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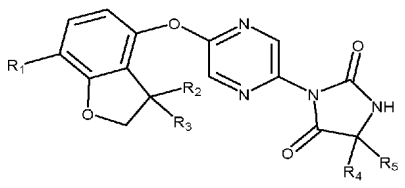

(I)

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KV3 MODULATORS

Technical field

This invention relates to novel compounds, pharmaceutical compositions containing them and their use in therapy, in particular in the prophylaxis or treatment of hearing disorders, including hearing loss and tinnitus, as well as schizophrenia, substance abuse disorders, pain and Fragile X syndrome.

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 repolarisation of the membrane. These biophysical properties ensure that the channels open towards the peak of the depolarising phase of the neuronal action potential to initiate repolarisation. Rapid termination of the action potential mediated by Kv3 channels allows the neuron to recover more quickly to reach sub-threshold membrane potentials from which further action potentials can be triggered. As a result, the presence of Kv3 channels in certain neurons contributes to their ability to fire at high frequencies (Rudy *et al.*, 2001). Kv3.1-3 subtypes are predominant in the CNS, whereas Kv3.4 channels are also found in skeletal muscle and sympathetic neurons (Weiser *et al.*, 1994). Kv3.1-3 channel subtypes are differentially expressed by sub-classes of interneurons in cortical and hippocampal brain areas (e.g. Chow *et al.*, 1999; 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.*, 2001).

Tetraethylammonium (TEA) has been shown to inhibit the channels at low millimolar concentrations (Rudy *et al.*, 2001), and blood-depressing substance (BDS) toxins from the sea anemone, *Anemonia sulcata* (Diochot *et al.*, 1998), have been shown to selectively inhibit Kv3 channels with high affinity (Yeung *et al.*, 2005).

Kv3 channels are important determinants of the function of the cerebellum, a region of the brain important for motor control (Joho *et al.*, 2009). 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 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) causes progressive myoclonic epilepsy (Muona et al., 2014). Mutations of the Kv3.3 gene (KCNC3) in humans have been associated with forms of spinocerebellar ataxia (SCA13) (Figueroa *et al.*, 2010).

Bipolar disorder, schizophrenia, anxiety, and epilepsy are serious disorders of the central nervous system that have been associated with reduced function of inhibitory interneurons and gamma-amino butyric acid (GABA) transmission (Reynolds *et al.*, 2004; Benes *et al.*, 2008; Brambilla *et al.*, 2003; Aroniadou-Anderjaska *et al.*, 2007; Ben-Ari, 2006). Parvalbumin positive basket cells that express Kv3 channels in the cortex and hippocampus play a key role in generating feedback inhibition within local circuits (Markram *et al.*, 2004). Given the relative dominance of excitatory synaptic input over inhibitory input to glutamatergic pyramidal neurons in these circuits, fast-firing of interneurons supplying inhibitory input is essential to ensure balanced inhibition. Furthermore, accurate timing of inhibitory input is necessary to sustain network synchronisation, for example, in the generation of gamma frequency field potential oscillations that have been associated with cognitive function (Fisahn *et al.*, 2005; Engel *et al.*, 2001). Notably, a reduction in gamma oscillations has been observed in patients with 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 who had not been taking antipsychotic drugs for at least 2 months before death (Yanagi *et al.*, 2014). Consequently, positive modulators of Kv3 channels might be expected to enhance the firing capabilities of specific groups of fast-firing neurons in the brain. These effects may be beneficial in disorders associated with abnormal activity of these neuronal groups. In addition, Kv3.2 channels have been shown to be expressed by neurons of the superchiasmatic nucleus (SCN) the main circadian pacemaker in the CNS (Schulz *et al.*, 2009).

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 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 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; Glait *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 tinnitus. Tinnitus may follow noise-induced hearing loss as a result of adaptive changes in central auditory pathways from brainstem to auditory cortex (Roberts *et al.*, 2010). Kv3.1 and/or Kv3.2 channels are expressed in many of these circuits and contribute to the function of GABAergic inhibitory interneurons that may control the function of these circuits.

It is known that Kv3.1 and/or Kv3.2 modulators have utility in the treatment of pain (WO2017/098254). In the broadest sense, pain can be grouped in to acute pain and chronic pain. Acute pain is defined as pain that is self-limited and generally requires treatment for no more than up to a few weeks, for example postoperative or acute musculoskeletal pain, such as fractures (US Food and Drug Administration, 2014). Chronic pain can be defined either as pain persisting for longer than 1 month beyond resolution of the initial trauma, or pain persisting beyond three months. There is often no clear cause of chronic pain, and a multitude of other health problems such as fatigue, depression, insomnia, mood changes and reduction in movement, often accompany chronic pain.

Chronic pain can be sub-divided in to the following groups: neuropathic pain, chronic musculoskeletal pain and miscellaneous chronic pain. Neuropathic pain usually accompanies tissue injury and is initiated or caused by damage to the nervous system (peripheral nervous system and/or central nervous system), such as amputation, stroke, diabetes, or multiple sclerosis. Chronic musculoskeletal pain can be a symptom of diseases such as osteoarthritis and chronic lower back pain and can occur following damage to muscle tissue as well as trauma to an area for example, fractures, sprains and dislocation. Miscellaneous chronic pain encompasses all other types of long term pain and includes non-neuropathic pain conditions such as cancer pain and fibromyalgia as well as headaches and tendinitis.

Chronic pain is a highly heterogeneous condition that remains amongst the most troublesome and difficult to manage of clinical indications (McCarberg *et al.*, 2008; Woolf, 2010; Finnerup *et al.*, 2015). Despite years of research and drug development, there has been little progress in identifying treatments that can match the opioids for efficacy without significant side effects and risk of dependence. Voltage-gated ion channels have been important targets for the management

of specific pain indications, in particular neuropathic pain states. Furthermore, genetic mutations in specific ion channels have been linked to some chronic pain disorders (Bennett *et al.*, 2014). Examples of voltage-gated ion channels that are being explored as pharmaceutical targets include: *Sodium channels (in particular NaV1.7)* – Sun *et al.*, 2014; Dib-Hajj *et al.*, 2013; *N-type calcium channels* – Zamponi *et al.*, 2015; *Kv7 potassium channels* – Devulder, 2010; Wickenden *et al.*, 2009; and *SLACK* – Lu *et al.*, 2015.

The hypothesis underlying these approaches is that chronic pain states are associated with increased excitability and/or aberrant firing of peripheral sensory neurons, in particular neurons involved in the transmission of painful sensory stimuli, such as the C-fibres of the dorsal root ganglia and specific circuits within the spinal cord (Baranauskas *et al.*, 1998; Cervero, 2009; Woolf *et al.*, 2011; Baron *et al.*, 2013). Animal models of neuropathic and inflammatory chronic pain provide the main support for this hypothesis, although demonstration of causality is still lacking (Cervero, 2009).

Drugs targeting hyperexcitability, such as sodium channel blockers (e.g. CNV1014802, lamotrigine, carbamazepine, and local anaesthetics), Kv7 positive modulators (e.g. flupertine and retigabine), and N-type calcium channel modulators (e.g. gabapentin, which interacts with the α2δ subunit of the N-type calcium channel, and ziconitide, derived from a cone snail toxin) show efficacy in models of inflammatory and/or neuropathic pain. However, amongst these drugs, there is mixed evidence for clinical efficacy, for example, balancing efficacy and increased burden of side effects on the central nervous system. The disparity between efficacy in animal models and efficacy in humans is likely to be due to a range of factors, but in particular, drug concentration achievable in humans (due to poor tolerability) and heterogeneity of human pain conditions are likely to be the main culprits. For pain indications, there is also a need to identify targets through which pain relief can be achieved with reduced tolerance or tachyphylaxis and reduced abuse liability and/or risk of dependence.

Thus, improving the pharmacological management of pain is focused on mechanisms that can deliver good efficacy with a reduced side-effect burden, reduced tolerance or tachyphylaxis, and reduced abuse liability and/or risk of dependence.

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 supress 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.

Dementia with Lewy Bodies (DLB) and Parkinson's disease (PD) are serious neurodegenerative disorders that are associated with the accumulation of the protein, alpha-synuclein in Lewy bodies, which leads to loss of connectivity and neuronal cell death. Symptoms of DLB include progressive cognitive deficits, in particular difficulties with planning and attention. Visual hallucinations are also common, occurring in approximately 60% of patients. PD is associated initially with motor deficits, primarily due to loss of dopamine neurons. While there are currently no studies directly linking Kv3 channels to DLB or PD, the location and role of Kv3 channels, in particular Kv3.1, in cortical and basal ganglia circuits suggests that modulators of these channels could improve symptoms of DLB or PD, either alone, or in combination with current treatments, such as acetyl-cholinesterase inhibitors for DLB or L-DOPA for PD.

Patent applications WO2011/069951, WO2012/076877, WO2012/168710, WO2013/175215, WO2013/083994, WO2013/182850, WO2017/103604, WO2018/020263 and WO2018/109484

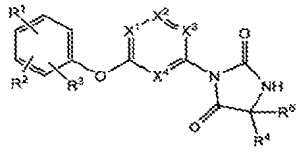
disclose compounds which are modulators of Kv3.1 and Kv3.2. Further, the utility of such compounds is demonstrated in animal models of seizure, hyperactivity, sleep disorders, psychosis, hearing disorders and bipolar disorders.

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.

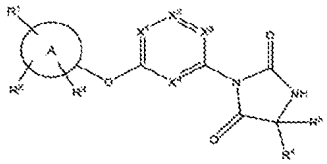
Patent application WO2017/098254 discloses that modulation of Kv3.1, Kv3.2 and/or Kv3.3 channels has been found to be beneficial in the prophylaxis or treatment of pain, in particular neuropathic or inflammatory pain.

Patent application WO2019/222816 discloses 'meta-linked' pyridinyl compounds of the general formula:



which are said to be modulators of Kv3.1 and/or Kv3.2 channels.

Patent application WO2020/000065 discloses 'meta-linked' diazine and triazine compounds of the general formula:



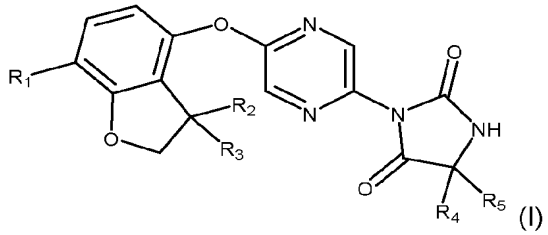
which are said to be modulators of Kv3.1 and/or Kv3.2 channels.

There remains a need for the identification of alternative modulators of Kv3.1, Kv3.2 and/or Kv3.3, 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 and/or Kv3.3 modulatory properties may be desirable e.g. compounds with 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 and/or Kv3.3 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:

R_1 is H or methyl;

R_2 and R_3 are both methyl, or R_2 and R_3, together with the carbon atom to which they are attached, are a spirocyclopropyl ring;

R_4 is methyl or ethyl;

R_5 is H or methyl;

or R_4 and R_5, together with the carbon atom to which they are attached, form a C_3-C_4 spiro carbocyclyl.

A compound of formula (I) may be provided in the form of a salt and/or solvate thereof. Suitably, the compound of formula (I) may be provided in the form of a pharmaceutically acceptable salt and/or solvate thereof and/or derivative 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 hearing disorders, including hearing loss and tinnitus, as well as schizophrenia, substance abuse disorders, pain or Fragile X syndrome.

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.

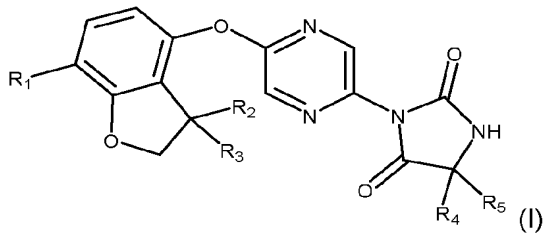
Also provided are pharmaceutical compositions containing a compound of formula (I) and a pharmaceutically acceptable carrier or excipient.

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

The present invention provides compounds of formula (I):



(I)

wherein:

R_1 is H or methyl;

R_2 and R_3 are both methyl, or R_2 and R_3, together with the carbon atom to which they are attached, are a spirocyclopropyl ring;

R_4 is methyl or ethyl;

R_5 is H or methyl;

or R_4 and R_5, together with the carbon atom to which they are attached, form a C_3-C_4 spiro carbocyclyl;

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

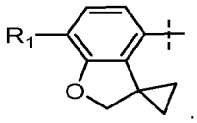
Embodiments set out below relating to relative stereochemistry and the nature of groups, including R_1, R_2, R_3, R_4, R_5, are envisaged as being independently, fully combinable with one another where appropriate to the circumstances (i.e. where chemically sensible) to form further embodiments of the invention. Such embodiments apply equally to intermediates which may be

of use in the synthesis of a compound of formula (I) e.g. compounds of formulae (II), (IV), (VI), (VII) and (XVI).

Compounds of formula (I) may optionally be provided in the form of a pharmaceutically acceptable salt and/or solvate. In one embodiment of the invention a compound of formula (I) is provided in the form of a pharmaceutically acceptable salt. In a second embodiment of the invention a compound of formula (I) is provided in the form of a pharmaceutically acceptable solvate. In a third embodiment of the invention a compound of formula (I) is not in the form of a salt or solvate.

In one embodiment, R_1 is H. In a second embodiment R_1 is methyl.

In one embodiment, R_2 is methyl and R_3 is methyl. In another embodiment, R_2 and R_3 are a spiro cyclopropyl such that that the following moiety is formed:

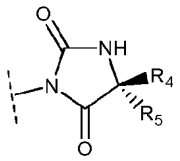


In one embodiment, R_4 is methyl. In a second embodiment, R_4 is ethyl.

In one embodiment, R_5 is hydrogen. In a second embodiment, R_5 is methyl.

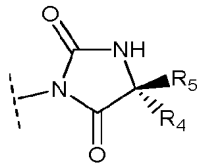
In one embodiment R_4 and R_5 are the same (i.e. methyl).

In embodiments wherein R_4 and R_5 are different, they may have the following stereochemical arrangement:



In this embodiment, for example, R_4 is methyl and R_5 is H, R_4 is ethyl and R_5 is H or R_4 is ethyl and R_5 is methyl.

In embodiments wherein R_4 and R_5 are different, they may alternatively have the following stereochemical arrangement:



In this embodiment, for example, R_4 is methyl and R_5 is H, R_4 is ethyl and R_5 is H or R_4 is ethyl and R_5 is methyl.

In one embodiment R_4 and R_5, together with the carbon atom to which they are attached, form a spirocyclopropyl.

In another embodiment R_4 and R_5, together with the carbon atom to which they are attached, form a spirocyclobutyl.

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

5,5-dimethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione;

3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-5,5-dimethyl-imidazolidine-2,4-dione;

(5R)-5-ethyl-5-methyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)imidazolidine-2,4-dione;

5,5-dimethyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)imidazolidine-2,4-dione;

(5R)-5-ethyl-5-methyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione;

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

5,5-dimethyl-3-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]imidazolidine-2,4-dione;

(5R)-5-ethyl-5-methyl-3-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]imidazolidine-2,4-dione;

(5R)-5-ethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione;

(5R)-5-ethyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)imidazolidine-2,4-dione;

(5R)-3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-5-ethyl-imidazolidine-2,4-dione;

(5R)-5-ethyl-3-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]imidazolidine-2,4-dione;

7-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]-5,7-diazaspiro[3.4]octane-6,8-dione;

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

In one embodiment, the compound of formula (I) is:

6-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]-4,6-diazaspiro[2.4]heptane-5,7-dione;

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

In one embodiment, the compound of formula (I) is:

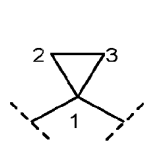
(5S)-5-ethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione;

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

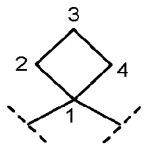
When the compound contains a C_{1-3}alkyl group, whether alone or forming part of a larger group, the alkyl group may be straight chain, branched or cyclic. Examples of C_{1-3}alkyl are methyl, ethyl, *n*-propyl, isopropyl and cyclopropyl. Reference to "propyl" includes n-propyl, isopropyl and cyclopropyl.

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

The term 'C_{3-4} spiro carbocyclyl' as used herein means a cyclic ring system containing 3 or 4 carbon atoms, namely a cyclopropyl or cyclobutyl 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 4 carbon atoms in the cyclic ring as follows:



C_3 spiro carbocyclyl



C_4 spiro carbocyclyl

It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art. Pharmaceutically acceptable salts include those described by Berge,

Bighley and Monkhouse J.Pharm.Sci. (1977) 66, pp 1-19. Such pharmaceutically acceptable salts include acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric, nitric or phosphoric acid and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. 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.

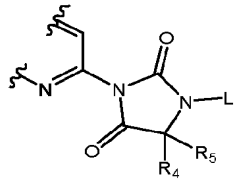
Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

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.

A pharmaceutically acceptable prodrug may be formed by functionalising the secondary nitrogen of the hydantoin, for example with a group "L" as illustrated below (wherein R_4 and R_5 are as described above):



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

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

b) $-PO(O^-)_2 \cdot 2M^+$,

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

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

e) $-CH(R^X)-PO(O^-)_2 \bullet 2M^+$,

f) $-CH(R^X)-PO(O^-)_2 \bullet D^{2+}$,

g) $-SO_3^- \bullet M^+$,

h) $-CH(R^X)-SO_3^- \bullet M^+$, and

i) $-CO-CH_2CH_2-CO_2 \bullet M^+$.

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 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 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 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 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) 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. ^{3}H, and 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. ^{2}H 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 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.

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. ^{2}H 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, 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 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.

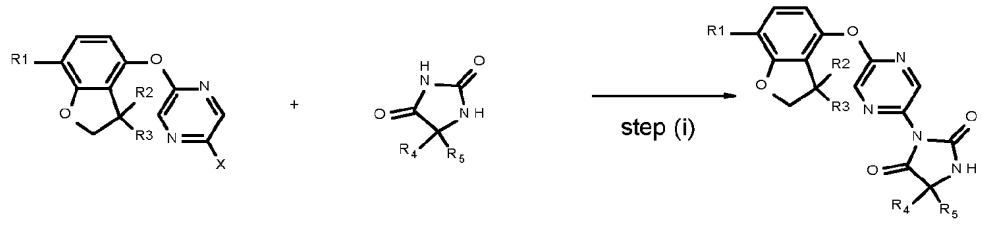
Patent applications WO2011/069951, WO2012/076877, WO2012/168710, WO2013/175215, WO2013/083994, WO2013/182850, WO2017/103604, WO2018/020263 and WO2018/109484 provide methods for the synthesis of intermediates which may be of use in the production of compounds of the present invention.

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 of formula (I), and salts and solvates thereof, may be prepared by the general methods outlined hereinafter. In the following description, the groups R_1, R_2, R_3, R_4 and R_5 have the meanings as previously defined for compounds of formula (I) unless otherwise stated.

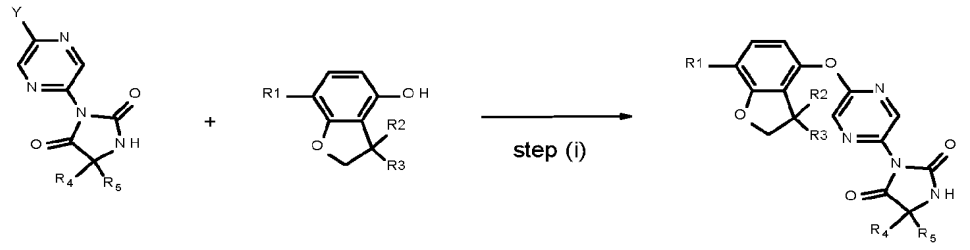
Scheme 1a



(II) (III) (I)

step (i): Compounds of formula (I) can be prepared by metal catalysed cross coupling reactions. In this reaction a halo-pyrazine derivative of formula (II) wherein typically X=Br and a hydantoin of formula (III) are reacted in the presence of a metal catalyst such as copper(I) oxide in a suitable solvent, *e.g.* in N,N-dimethylacetamide, with conventional heating or microwave heating.

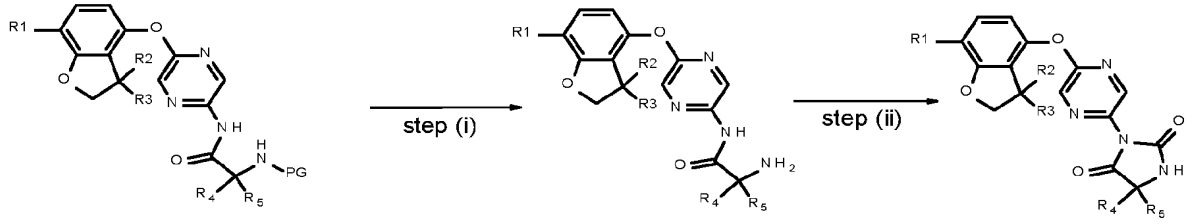
Scheme 1b



(IV) (V) (I)

Compounds of formula (I), wherein R_4 and R_5 are not H, can be prepared by nucleophilic aromatic substitution. In this reaction a halo-pyrazine derivative of formula (IV) wherein typically Y=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-dimethylformamide or in acetonitrile, with conventional heating or microwave heating.

Scheme 1c

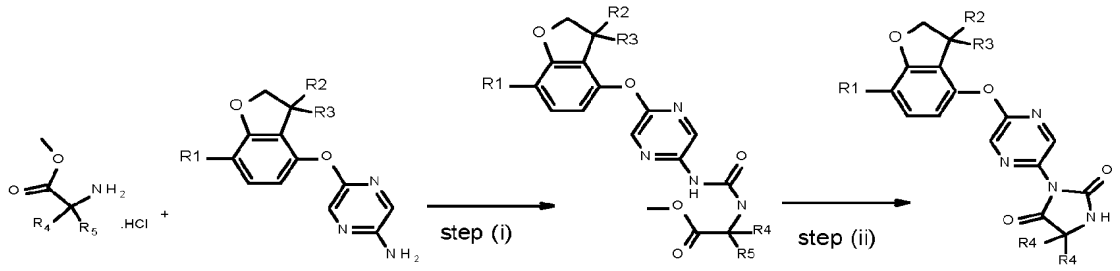


(VII) (VI) (I)

step (ii): Compounds of formula (I) can be prepared by cyclization of compounds of formula (VI) 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 0ºC in presence of a suitable base *e.g.* triethylamine. Alternatively compounds of formula (I) can be prepared by cyclization of compounds of formula (VI) 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.

step (i): Compounds of formula (VI) can be prepared by deprotection of compounds of formula (VII) wherein PG is a protecting group, suitably the protecting group is BOC, BOC may be removed in acidic conditions *e.g.* TFA in a suitable solvent *e.g.* dichloromethane at approximately 0ºC to room temperature.

Scheme 1d

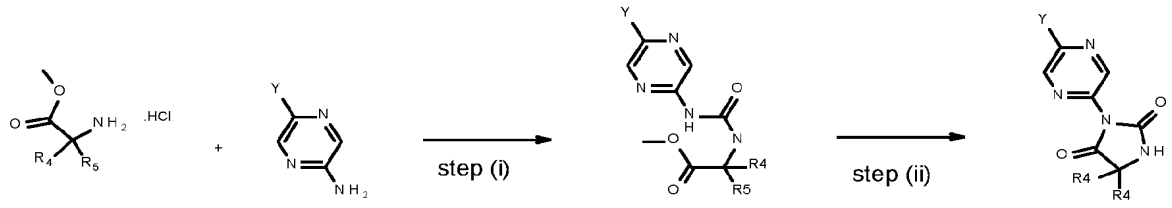


(IX) (XVI) (XVII) (I)

step (ii): Compounds of formula (I) can be prepared by reaction of ureas of formula (XVII) and a suitable base such as sodium methoxide in a suitable solvent such as methanol at temperature ranging from 0°C to room temperature.

step (i): Ureas of formula (XVII) can be prepared by reaction of anilines of formula (XVI) and amino esters (such as the hydrochloride salt) of formula (IX) 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 2a



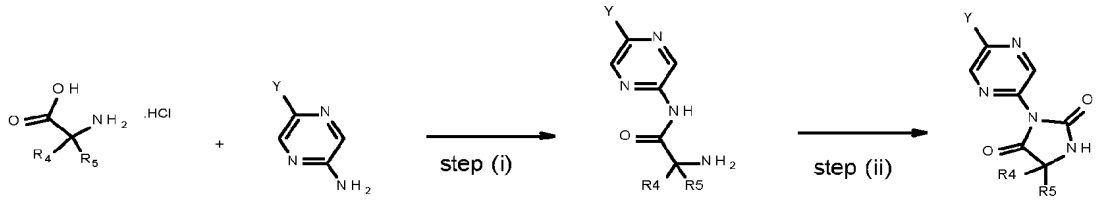
(IX) (X) (VIII) (IV)

step (ii): Compounds of formula (IV) can be prepared by reaction of ureas of formula (VIII) and a suitable base such as sodium methoxide in a suitable solvent such as methanol at temperature ranging from 0°C to room temperature.

step (i): Ureas of formula (VIII) can be prepared by reaction of commercially available halo-pyrazine derivative of formula (X), wherein typically Y=Cl, and amino esters (such as the hydrochloride salt) of formula (IX) 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 2b

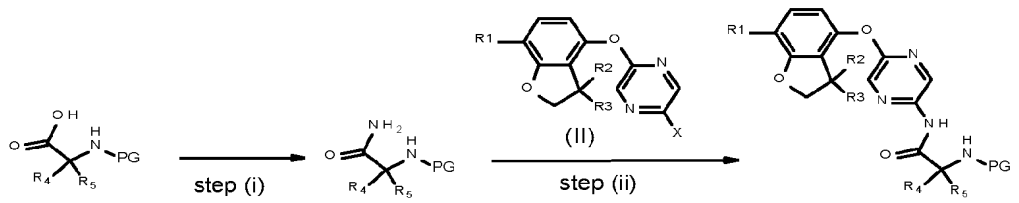


(XII) (X) (XI) (IV)

step (ii): Compounds of formula (IV) can be prepared by cyclization of compounds of formula (XI) 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 0ºC in presence of a suitable base *e.g.* triethylamine.

step (i): Compounds of formula (XI) can be prepared from anilines of formula (X), wherein typically Y=Cl, and amino acids (as free base or hydrochloride salt) of formula (XII) by amidic coupling in the presence of a coupling agent *e.g.* T3P in a suitable solvent such as ethyl acetate, acetonitrile or a mixture of them.

Scheme 3



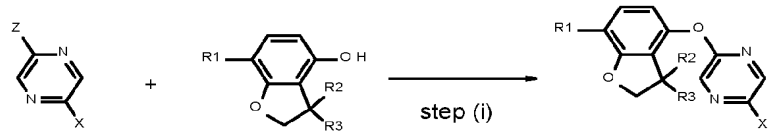
(XIV) (XIII) (VII)

step (ii): Compounds of formula (IV) can be prepared by metal catalysed cross coupling reactions. In this reaction a halo-pyrazine derivative of formula (II) wherein typically X=Br and an amide of formula (XIII) are reacted in the presence of a metal catalyst such as Tris(dibenzylideneacetone)dipalladium(0), a suitable ligand such as dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (XPhos) and a suitable base such as cesium carbonate in a suitable solvent, *e.g.* in 1,4-dioxane, with conventional heating or microwave heating. Alternatively in this reaction a halo-pyrazine derivative of formula (II) wherein typically X=Br and an amide of formula (XIII) are reacted in the presence of a metal catalyst such as copper(I) iodide, a suitable ligand such as N,N'-dimethylethane-1,2-diamine and a suitable base such

dipotassium carbonate in a suitable solvent, *e.g.* in 1-butanol, with conventional heating or microwave heating. A further alternative for the preparation of compounds of formula (IV) is to react a halo-pyrazine derivative of formula (II) wherein typically X=Br and an amide of formula (XIII) in the presence of a metal catalyst such as palladium (II) acetate, a suitable ligand such as 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.

step (i): Compounds of formula (XIII) can be prepared from N-protected (e.g. BOC) amino acids of formula (XIV) and an amine such as hexamethyldisilazane by amidic coupling in the presence of a base *e.g.* DIPEA and of a coupling agent *e.g.* HATU or TBTU in a solvent such as N,N-dimethylformamide.

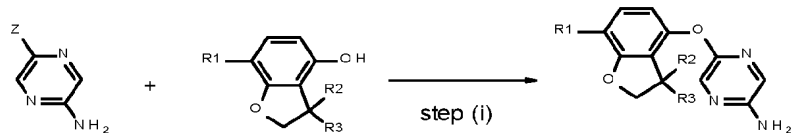
Scheme 4



(XV) (V) (II)

step (i): Compounds of formula (II) wherein typically X=Br can be prepared by nucleophilic aromatic substitution. In this reaction a halo-pyrazine derivative of formula (XV) wherein typically X=Z=Br and a phenol of formula (V) are reacted in the presence of a base such as potassium carbonate in a suitable solvent, *e.g.* in N,N-dimethylformamide, with conventional heating or microwave heating.

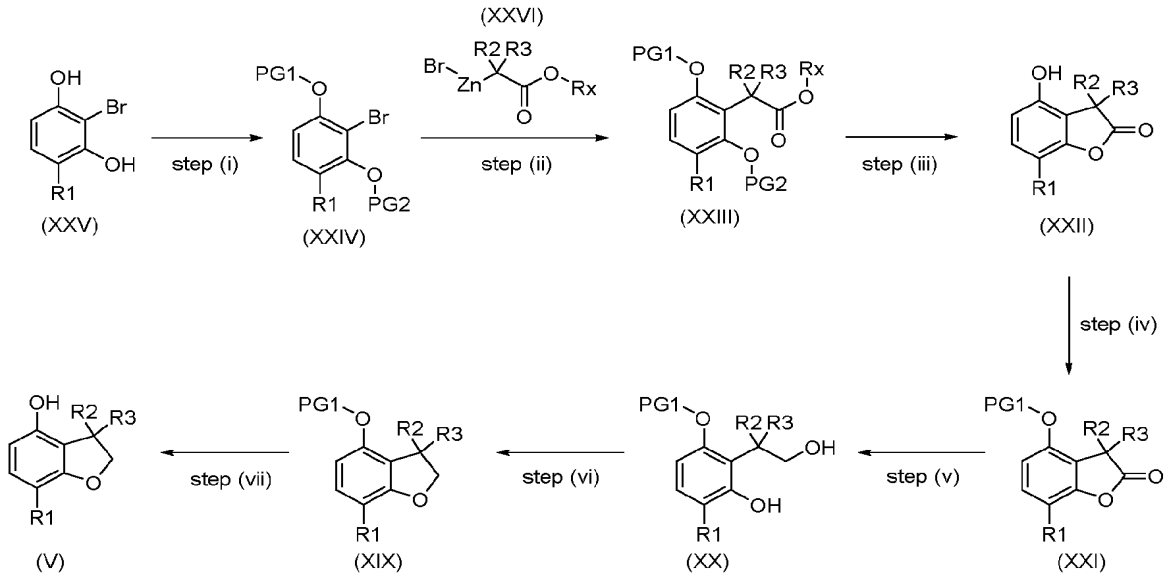
Scheme 5



(XVIII) (V) (XVI)

step (i): Anilines of formula (XVI) can be prepared by metal catalysed cross coupling reactions. In this reaction a halo-pyrazine derivative of formula (XVIII) wherein typically Z=Br and a phenol of formula (V) are reacted in the presence of a metal catalyst such as Copper(I)Iodide, a suitable ligand like picolinic acid, in a suitable solvent, *e.g.* in N,N-dimethylformamide or N,N-dimethylacetamide, with conventional heating or microwave heating optionally a suitable base such as potassium carbonate or caesium carbonate can be used.

Scheme 6



In Scheme 6 shown above, PG_1 and PG_2 represent suitable protecting groups. PG_1 in steps (i)=-(iii) may be different from PG_1 in Steps (iv)-(vii). Suitable protecting groups include benzyl. tetrahydropyranyl or methyloxymethyl. Suitably PG_2 is the same as PG_1, e.g. both are benzyl.

Description of the scheme wherein PG_1 and PG_2 are both benzyl

step (vii): Phenols of formula (V) can be prepared from the benzylated compounds of formula (XIX), by deprotection such as using a metal catalyst such as palladium on carbon and a hydrogen source such as hydrogen atmosphere or ammonium formate in a suitable solvent such as ethanol or methanol at a temperature ranging from room temperature to reflux.

step (vi): Benzylated compounds of formula (XIX) can be prepared from diols of formula (XX) using a base such as potassium tert-butoxide and a suitable solvent such as dimethyl carbonate at a temperature ranging from room temperature to reflux.

step (v): Diols of formula (XX) can be prepared from lactones of formula (XXI) using a reducing agent such as lithium aluminium hydride in a suitable solvent such as THF at a temperature ranging from 0ºC to room temperature.

step (iv): Lactones of formula (XXI) can be prepared from phenols of formula (XXII) using a benzylating agent such as benzyl bromide in presence of a base such as potassium carbonate in a suitable solvent such as acetonitrile or THF or a mixture thereof at a temperature ranging from room temperature to reflux.

step (iii): Phenols of formula (XXII) can be prepared from di-benzylated esters of formula (XXIII) wherein Rx is a suitable alkylic group such as methyl or ethyl, using a metal catalyst such as

palladium on carbon and a hydrogen source such as hydrogen atmosphere or ammonium formate in a suitable solvent such as ethanol or methanol at a temperature ranging from room temperature to reflux.

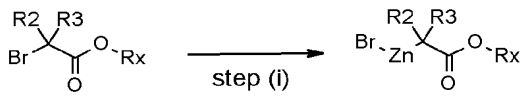
step (ii): Di-benzylated esters of formula (XXIII) wherein Rx is a suitable alkylic group such as methyl or ethyl can be prepared from di-benzylated bromo derivatives of formula (XXIV) by using pre-formed organozinc derivatives of formula (XXVI) wherein Rx is a suitable alkylic group such as methyl or ethyl in presence of a metal catalyst complex such as Bis(tri-tert-butylphosphine)palladium(0) in a suitable solvent such as THF or DMF or a mixture thereof at a temperature ranging from room temperature to reflux.

step (i): Di-benzylated bromo derivatives of formula (XXIV) can be prepared from commercially available derivatives of formula (XXV) using a benzylating agent such as benzyl bromide in presence of a base such as potassium carbonate in a suitable solvent such as acetonitrile or THF or acetone or a mixture thereof at a temperature ranging from room temperature to reflux.

When PG_1 and/or PG_2 are protecting groups such as tetrahydropyranyl or methyloxymethyl, usual protection/deprotection conditions apply:

- Protection conditions of phenols with tetrahydropyranyl include the reaction of a phenol with dihydro-2H-pyran in presence of a catalyst such C:Py •p-$MePhSO_3H$ in a suitable solvent such us dichloromethane at a temperature ranging from 0°C to reflux.
- Cleavage conditions for a tetrahydropyranyl protecting group from phenols include the reaction of a THP protected phenol in presence of an acid such as sulphuric acid or p-$MePhSO_3H$ or HCl in a suitable solvent such us methanol or ethanol at a temperature ranging from 0oC to reflux.
- Protection conditions of phenols with methyloxymethyl include the reaction of a phenol with chloromethyl methyl ether in presence of a base such us potassium carbonate in a suitable solvent such us tetrahydrofuran or acetonitrile at a temperature ranging from 0°C to reflux.
- Cleavage conditions for a methyloxymethyl protecting group from phenols include the reaction of a MOM protected phenol in presence of an acid such as sulphuric acid or p-$MePhSO_3H$ or HCl in a suitable solvent such us methanol or ethanol at a temperature ranging from 0°C to reflux.

Scheme 7



(XXVII) (XXVI)

Step (i): Organozinc derivatives of formula (XXVI) wherein Rx is a suitable alkylic group such as methyl or ethyl can be prepared by adding commercially available bromo esters of formula (XXVII) to a refluxing suspension of zinc (0) in presence of 1,2-dibromoethane and chlorotrimethylsilane in a suitable solvent such as THF.

Processes of the invention

According to further aspects of the present invention are provided processes for the preparation of compounds of formula (I) and derivatives thereof, as well as processes for preparing intermediates in the synthesis of compounds of formula (I).

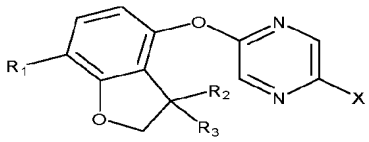
The processes of the invention are described above and include any individual step of a multi-step scheme.

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), (IV), (VI), (VII), (VIII), (XI), (XVI) and (XVII). Also of interest are intermediates of formulae (XIX) to (XXIV). Salts, such as pharmaceutically acceptable salts, of such intermediates are also provided by the present invention.

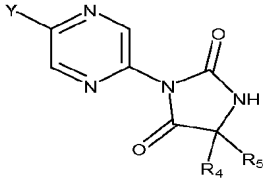
Intermediates of the invention therefore include:

- compounds of formula (II):



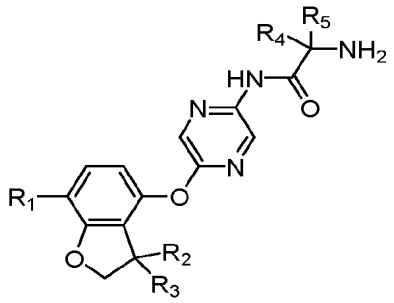
wherein R_1, R_2 and R_3 are as defined previously, X is halo, such as Br;

- compounds of formula (IV):



wherein R_1, R_2 and R_3 are as defined previously, Y is halo, such as Cl;

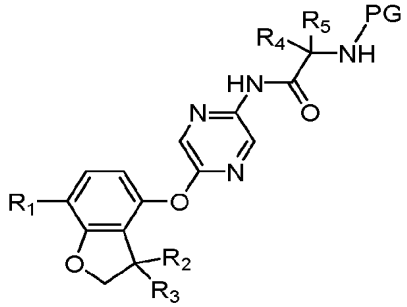
- compounds of formula (VI):



(VI)

wherein R_1, R_2, R_3, R_4 and R_5 are as defined previously;

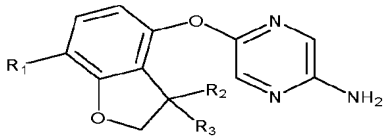
- compounds of formula (VII):



(VII)

wherein R_1, R_2, R_3, R_4 and R_5 are as defined previously, PG is a suitable protecting group such as BOC;

- compounds of formula (XVI):



wherein R_1, R_2 and R_3 are as defined previously.

Kv3.1, Kv3.2 and/or Kv3.3 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 and/or Kv3.3. 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 channels.

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 channels recombinantly expressed in mammalian cells.

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

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 pEC_{50} of the modulator is in the range of 4-7 (such as 5-6.5).

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 pEC_{50} of the modulator is in the range of 4-7 (such as 5-6.5).

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 Kv3.3 channels recombinantly expressed in mammalian cells. Suitably the pEC_{50} of the modulator is in the range of 4-7 (such as 5-6.5).

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 recombinantly 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 recombinantly 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 recombinantly 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 recombinantly 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 and/or Kv3.3 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 and/or Kv3.3 is required, for example those diseases and disorders mentioned herein below, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt and/or solvate (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 and/or Kv3.3 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.

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 in need thereof an effective amount of 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 of 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 photosensive, 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 Amnestic Disorder, Substance-Induced Psychotic Disorder, Substance-Induced Mood Disorder, Substance-Induced Anxiety Disorder, Substance-Induced Sexual Dysfunction, Substance-Induced Sleep Disorder and Hallucinogen Persisting Perception Disorder (Flashbacks); Alcohol-Related Disorders such as Alcohol Dependence (303.90), Alcohol Abuse (305.00), Alcohol Intoxication (303.00), Alcohol Withdrawal (291.81), Alcohol Intoxication Delirium, Alcohol Withdrawal Delirium, Alcohol-Induced Persisting Dementia, Alcohol-Induced Persisting Amnestic Disorder, Alcohol-Induced Psychotic Disorder, Alcohol-Induced Mood Disorder, Alcohol-Induced Anxiety Disorder, Alcohol-Induced Sexual Dysfunction, Alcohol-Induced Sleep Disorder and Alcohol-Related Disorder Not Otherwise Specified (291.9);

Amphetamine (or Amphetamine-Like)-Related Disorders such as Amphetamine Dependence (304.40), Amphetamine Abuse (305.70), Amphetamine Intoxication (292.89), Amphetamine Withdrawal (292.0), Amphetamine Intoxication Delirium, Amphetamine Induced Psychotic Disorder, Amphetamine-Induced Mood Disorder, Amphetamine-Induced Anxiety Disorder, Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder and Amphetamine-Related Disorder Not Otherwise Specified (292.9); Caffeine Related Disorders such as Caffeine Intoxication (305.90), Caffeine-Induced Anxiety Disorder, Caffeine-Induced Sleep Disorder and Caffeine-Related Disorder Not Otherwise Specified (292.9); Cannabis-Related Disorders such as Cannabis Dependence (304.30), Cannabis Abuse (305.20), Cannabis Intoxication (292.89), Cannabis Intoxication Delirium, Cannabis-Induced Psychotic Disorder, Cannabis-Induced Anxiety Disorder and Cannabis-Related Disorder Not Otherwise Specified (292.9); Cocaine-Related Disorders such as Cocaine Dependence (304.20), Cocaine Abuse (305.60), Cocaine Intoxication (292.89), Cocaine Withdrawal (292.0), Cocaine Intoxication Delirium, Cocaine-Induced Psychotic Disorder, Cocaine-Induced Mood Disorder, Cocaine-Induced Anxiety Disorder, Cocaine-Induced Sexual Dysfunction, Cocaine-Induced Sleep Disorder and Cocaine-Related Disorder Not Otherwise Specified (292.9); Hallucinogen-Related Disorders such as Hallucinogen Dependence (304.50), Hallucinogen Abuse (305.30), Hallucinogen Intoxication (292.89), Hallucinogen Persisting Perception Disorder (Flashbacks) (292.89), Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder, Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder and Hallucinogen-Related Disorder Not Otherwise Specified (292.9); Inhalant-Related Disorders such as Inhalant Dependence (304.60), Inhalant Abuse (305.90), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium, Inhalant-Induced Persisting Dementia, Inhalant-Induced Psychotic Disorder, Inhalant-Induced Mood Disorder, Inhalant-Induced Anxiety Disorder and Inhalant-Related Disorder Not Otherwise Specified (292.9); Nicotine-Related Disorders such as Nicotine Dependence (305.1), Nicotine Withdrawal (292.0) and Nicotine-Related Disorder Not Otherwise Specified (292.9); Opioid-Related Disorders such as Opioid Dependence (304.00), Opioid Abuse (305.50), Opioid Intoxication (292.89), Opioid Withdrawal (292.0), Opioid Intoxication Delirium, Opioid-Induced Psychotic Disorder, Opioid-Induced Mood Disorder, Opioid-Induced Sexual Dysfunction, Opioid-Induced Sleep Disorder and Opioid-Related Disorder Not Otherwise Specified (292.9); Phencyclidine (or Phencyclidine-Like)-Related Disorders such as Phencyclidine Dependence (304.60), Phencyclidine Abuse (305.90), Phencyclidine Intoxication (292.89), Phencyclidine Intoxication Delirium, Phencyclidine-Induced Psychotic Disorder, Phencyclidine-Induced Mood Disorder, Phencyclidine-Induced Anxiety Disorder and Phencyclidine-Related Disorder Not Otherwise Specified (292.9); Sedative-, Hypnotic-, or Anxiolytic-Related Disorders such as Sedative, Hypnotic, or Anxiolytic Dependence (304.10),

Sedative, Hypnotic, or Anxiolytic Abuse (305.40), Sedative, Hypnotic, or Anxiolytic Intoxication (292.89), Sedative, Hypnotic, or Anxiolytic Withdrawal (292.0), Sedative, Hypnotic, or Anxiolytic Intoxication Delirium, Sedative, Hypnotic, or Anxiolytic Withdrawal Delirium, Sedative-, Hypnotic-, or Anxiolytic-Persisting Dementia, Sedative-, Hypnotic-, or Anxiolytic- Persisting Amnestic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Psychotic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Mood Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Anxiety Disorder Sedative-, Hypnotic-, or Anxiolytic-Induced Sexual Dysfunction, Sedative-, Hypnotic-, or Anxiolytic-Induced Sleep Disorder and Sedative-, Hypnotic-, or Anxiolytic-Related Disorder Not Otherwise Specified (292.9); Polysubstance-Related Disorder such as Polysubstance Dependence (304.80); and Other (or Unknown) Substance-Related Disorders such as Anabolic Steroids, Nitrate Inhalants and Nitrous Oxide.

The compounds of 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.

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.

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.

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.

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.

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 channels are neuropathic pain and/or inflammatory pain.

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 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.

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 Kv3.1/Kv3.2/Kv3.3 modulator, such as a compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof to a subject in need thereof.

Administration of a Kv3.1/Kv3.2/Kv3.3 modulator 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 in pain experienced by the subject, a Kv3.1/Kv3.2/Kv3.3 modulator, such as 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 Kv3.1/Kv3.2/Kv3.3 modulator, such as a compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof may be administered to a subject in need thereof.

Treatment of the subject in need thereof may continue for as long as treatment is required, for example, 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 therapeutically effective amount of a Kv3.1/Kv3.2/Kv3.3 modulator, such as a compound of formula (I) or a pharmaceutically acceptable salt, solvate and/or derivative thereof, is administered to a subject in need thereof 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.

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 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 therapeutically effective amount of a Kv3.1/Kv3.2/Kv3.3 modulator, such as 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 receiving the Kv3.1/Kv3.2/Kv3.3 modulator 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 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 in need thereof 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 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, 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 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.

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 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 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 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 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, 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 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 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 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, 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 in need thereof an effective amount of 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 acceptable balance of desired benefits and undesired side effects.

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 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.

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, 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 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

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

Analytical Equipment

Starting materials, reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise stated. Unless otherwise stated, all compounds with chiral centres are racemic. Where reactions are described as having been carried out in a similar manner to earlier, more completely described reactions, the general reaction conditions used were essentially the same. Work up conditions used were of the types standard in the art, but may have been adapted from one reaction to another. The starting material may not necessarily have been prepared from the batch referred to. Compounds synthesised may have various purities, ranging from for example 85% to 99%. Calculations of number of moles and yield are in some cases adjusted for this.

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 µm 3 x 50 mm). Mobile phase: A: (H2O + 0.05% TFA by vol.) / B: (CH3CN + 0.05% TFA by vol). Gradient: t = 0 min 0% (B), from 0 to 95% (B) in 2.5 min, 95% (B)for 0.2 min, from 95 to 100% (B) in 0.2 min, 100% (B) for 0.4 min, from 100% to 0% (B) in 0.1 min. Stop time 4 min. Column T = 60°C. Flow rate: 1.5 ml/min. Mass range ES+: (100-1000 amu, F=60). UV detection wavelengths: DAD 1A = 220.8, DAD 1B = 254.8. The use of this methodology is indicated by "QC_3_MIN" in the analytic characterization of the described compounds.

Chiral control: LC/MS-ES+ under acidic conditions was performed on a CHIRALCEL® OD-H (250 x 4,6 mm - 5 um). Mobile phase: A: (H2O + 0.05% TFA by vol.) / B: (CH3CN + 0.05% 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 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.

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.

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).

Abbreviations

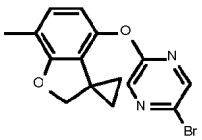
AIBN	azobisisobutyronitrile
BuLi	butyllithium
$CDCl_3$	deuterated chloroform
CCl_4	carbon tetrachloride
D_2O	deuterated water
DCM	dichloromethane
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
DMSO-d_6	deutrated dimethylsulfoxide
Et_2O	diethyl ether
EtOAc	ethyl acetate
h	hours
HATU	(O-7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluoro phosphate)
HCl	hydrogen chloride
K_2CO_3	potassium carbonate
MeCN /CH_3CN	acetonitrile
MeOH	methanol
MOM	methyloxymethyl

NaH	sodium hydride
Na_2SO_4	sodium sulphate
Na_2CO_3	sodium carbonate
NaOH	sodium hydroxide
NaOMe	sodium methoxide
NMR	Nuclear Magnetic Resonance
r.t.	room temperature
T3P	propylphosphonic anhydride
MTBE	Methyl *tert*-butyl ether
TBTU	Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
wt.	weight

Compound Examples

Intermediate 1

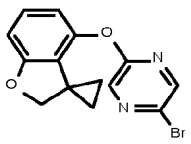
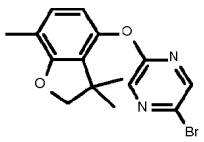
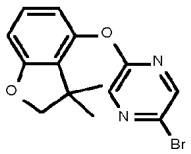
2-bromo-5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-pyrazine



A mixture of 7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-ol (Intermediate 156 WO2012076877, 1.11g, 6,30mmol), 2,5-dibromopyrazine (1.5g, 6,30mmol) and dipotassium carbonate (1.31g, 9.46mmol) in N,N-dimethylformamide (14mL) was stirred at 120°C for 3 hours. After cooling, the reaction mixture was diluted with MTBE (100 ml) and washed with brine (50 ml). Phases were separated and the aqueous layer was washed with MTBE (100ml) and EtOAc (100ml). All organic phases are collected, dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (Biotage System) on silica gel using a SNAP 100g as column and Cyclohexane: Ethyl acetate from 100:0 to 90:10 as eluent affording 2-bromo-5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-pyrazine (1.8g) as white solid.

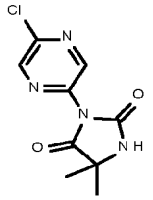
LC/MS: QC_3_MIN: Rt = 2.705 min; m/z 333 & 335 [M+H]+.

The following compounds were prepared using the foregoing methodology, replacing 7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-ol with the appropriate phenol. Final products were purified by flash-chromatography (Silica cartridge; Cyclohexane/EtOAc or other appropriate solvent system).

Int.	Structure	Name	Phenol	LCMS
2		2-bromo-5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrazine	spiro[2H-benzofuran-3,1'-cyclopropane]-4-ol (Intermediate 85 WO2012076877)	LC/MS: QC_3_MIN: Rt = 2.575 min; m/z 319 & 321 [M+H]+.
3		2-bromo-5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazine	3,3,7-trimethyl-2H-benzofuran-4-ol (Intermediate 184 WO2012076877)	LC/MS: QC_3_MIN: Rt = 2.365 min; m/z 335 & 337 [M+H]+.
4		2-bromo-5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazine	3,3-dimethyl-2H-benzofuran-4-ol (Intermediate 50 WO2012076877)	LC/MS: QC_3_MIN: Rt = 2.632 min; m/z 321 & 323 [M+H]+.

Intermediate 5 route 1

3-(5-chloropyrazin-2-yl)-5,5-dimethyl-imidazolidine-2,4-dione

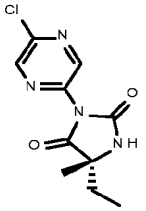


To a solution of bis(trichloromethyl) carbonate (950mg, 3.20mmol) in ethyl acetate (30mL) at 0°C a solution of 5-chloropyrazin-2-amine (0.75g, 5.79mmol)/N,N-diisopropylethylamine (6.05ml, 34.74mmol) in ethyl acetate (12mL) was added dropwise and the reaction mixture was stirred for 15 minutes at the same temperature. Maintaining the reaction mixture at 0°C, vacuum was applied (5 minutes) in order to remove the excess of phosgene. A solution of 4-(dimethylamino)pyridine (710mg, 5.81mmol) in ethyl acetate (8mL)/ dichloromethane (2mL) was added and the reaction mixture was stirred for 5 minutes at the same temperature. Then, methyl

2-amino-2-methyl-propanoate hydrochloride (1.4g, 9.1mmol) was added at 0°C and the reaction mixture was stirred for 30 minutes at the same temperature. The reaction was quenched with a solution 0.2 N of HCl (100 ml) and the two phases were separated. The organic layer was washed with brine (100 ml), dried over Na_2SO_4, filtered and evaporated affording the urea intermediate.

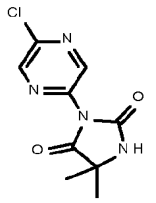
The urea was dissolved in dichloromethane (20mL) and at 0°C sodium methoxide (315mg, 5.83mmol) was added. The reaction mixture was stirred 15 minutes at the same temperature; the reaction was quenched with a saturated solution of NH_4Cl to allow the pH to reach 3-4. The mixture was extracted with ethyl acetate (50 ml); phases were separated, and the organic layer was washed with brine (50 ml), dried over Na_2SO_4, filtered and evaporated. The residue were purified by reverse phase flash chromatography (Biotage System) on C-18 phase using a SNAP 30g as column and Water:Acetonitrile from 95:5 to 40:60 as eluent. The appropriate fractions were combined and evaporated to dryness affording 3-(5-chloropyrazin-2-yl)-5,5-dimethyl-imidazolidine-2,4-dione (220mg) as a pale brown solid.
LC/MS: QC_3_MIN: Rt = 1.649 min; m/z 241 & 243 [M+H]+.

The following compounds were prepared using the foregoing methodology, replacing 2,2-dimethylglycine methyl ester hydrochloride with the appropriate amino ester hydrochloride. Final products were purified by flash-chromatography (Silica cartridge; Cyclohexane/EtOAc or other appropriate solvent system) or triturated in an appropriate solvent or crystallised from an appropriate solvent.

Int.	Structure	Name	Amino ester hydrochloride	LCMS
6		5R)-3-(5-chloropyrazin-2-yl)-5-ethyl-5-methyl-imidazolidine-2,4-dione	methyl (2R)-2-amino-2-methyl-butanoate hydrochloride	LC/MS: QC_3_MIN: Rt = 1.546 min; m/z 255 & 257 [M+H]+.

Intermediate 5 route 2

3-(5-chloropyrazin-2-yl)-5,5-dimethyl-imidazolidine-2,4-dione

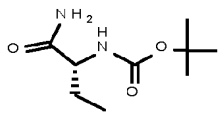


To a solution of 5-chloropyrazin-2-amine (500mg, 3.86mmol) and 2-amino-2-methyl-propanoic acid hydrochloride (646mg, 4.63mmol) in acetonitrile (10mL), Propylphosphonic anhydride solution ≥50 wt. % in ethyl acetate (3.68g, 5.78mmol) was slowly added at RT. The reaction mixture was stirred at 80°C for 6h. The reaction mixture was diluted with Ethyl Acetate (10ml) and an aqueous solution of NaOH 1 N was added, while the ph was allowed to reach ~8. The two phases were separated and the organic one was washed with brine (10ml), dried with Na_2SO_4, concentrated under vacuum and the crude was purified by Flash Chromatography on silica gel (BIOTAGE SYSTEM), using a SNAP 25g as column and DCM:MEOH from 99/1 to 90/10 as eluent, affording 2-amino-N-(5-chloropyrazin-2-yl)-2-methyl-propanamide (190mg) as yellow solid.
LC/MS: QC_3_MIN: Rt = 1.181 min; m/z 215 & 217 [M+H]+.

To a solution of 2-amino-N-(5-chloropyrazin-2-yl)-2-methyl-propanamide (190mg, 0.88mmol) and triethylamine (268mg, 2,6555mmol) in dichloromethane (5mL), at 0°C a solution of bis(trichloromethyl) carbonate (105,07mg,0,3541mmol) in dichloromethane (4mL) was slowly added. and the reaction mixture was stirred for 30 minutes at the same temperature. The reaction mixture was diluted in DCM (10mL), washed with an aqueous solution 0.2N of HCl (10mL) and Brine (10mL). The organic phases were concentrated under *vacuum* and the crude was purified by flash chromatography on silica gel (Biotage system) using a SNAP 25g as column and Chexane/EtOAc from 80/20 to 0/100 as eluent affording 3-(5-chloropyrazin-2-yl)-5,5-dimethyl-imidazolidine-2,4-dione (130mg) as white solid.
LC/MS: QC_3_MIN: Rt = 1.598 min; m/z 241 & 243 [M+H]+.

Intermediate 7

tert-butyl N-[(1R)-1-carbamoylpropyl]carbamate



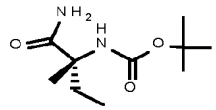
A mixture of [dimethylamino-(3-oxidotriazolo[4,5-b]pyridin-3-ium-1-yl)methylene]-dimethyl-ammonium tetrafluoroborate (1,1084g,3,4415mmol), N,N-diisopropylethylamine (0,7939g,6,1431mmol) and (2R)-2-(tert-butoxycarbonylamino)butanoic acid

(0,5000g,2,4601mmol) in dry N,N-dimethylformamide (8mL) was stirred at room temperature for 10 minutes. Hexamethyldisilazane (0,5960g,3,6928mmol) was added and the mixture stirred for 18h.

Reaction mixture was separated in MTBE (30 mL) and Brine (20 mL). The organic layer was dried with sodium sulphate, filtered and the solvent removed. The resulting oil triturated in MTBE (3 mL) and the resulting precipitate was washed with MTBE and dried via vacuum to give tert-butyl N-[(1R)-1-carbamoylpropyl]carbamate (0,3000g,1,4833mmol, 60,294 %) as a white solid.

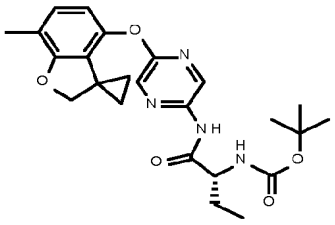
LC/MS: QC_3_MIN: m/z 147 [M-tBu+H]+.

The following compounds were prepared using the foregoing methodology, replacing (2R)-2-(tert-butoxycarbonilamino) butanoic acid with the appropriate protected amino-acid.

Int.	Structure	Name	Amino-acid	LCMS
8		tert-butyl N-[(1R)-1-carbamoyl-1-methyl-propyl]carbamate	(2R)-2-(tert-butoxycarbonylamino)-2-methyl-butanoic acid	LC/MS: QC_3_MIN: m/z 455 [2M+Na]+.

Intermediate 9 (route 1)

tert-butyl N-[(1R)-1-[[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]carbamoyl]propyl]carbamate



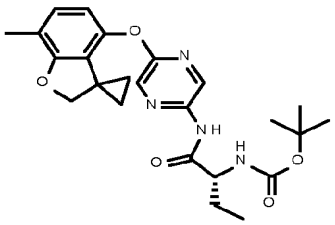
A mixture of 2-bromo-5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-pyrazine (Intermediate 1, 50mg, 0.15mmol), tert-butyl N-[(1R)-1-carbamoylpropyl]carbamate (Intermediate 7 , 46mg, 0.23mmol), Tris(dibenzylideneacetone)dipalladium(0) (10.3mg, 0.011mmol), dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (XPhos) (5.4mg, 0.011mmol) and cesium carbonate (73mg, 0.22mmol) in 1,4-dioxane (2mL) was stirred under an atmosphere of nitrogen at 80°C for 3h.

The reaction was partitioned between ethyl acetate and brine. The organic layer was separated, dried with sodium sulphate, filtered and evaporated to dryness. The residue was purified by

flash chromatography on silica gel (Biotage system) using a SNAP 10g column and cyclohexane and EtOAc from 100/0 to 0/100 as eluent. The appropriate fractions were combined and evaporated to dryness, affording tert-butyl N-[(1R)-1-[[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]carbamoyl]propyl]carbamate (10mg). LC/MS: QC_3_MIN: Rt = 2.696 min; m/z 455 [M+H]+.

Intermediate 9 (route 2)

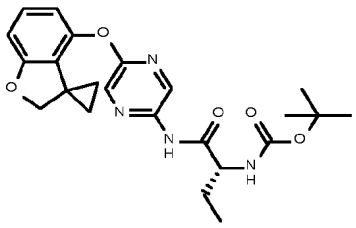
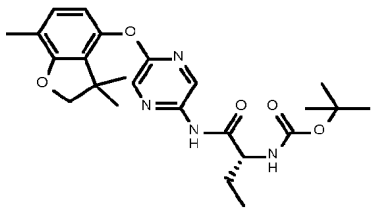
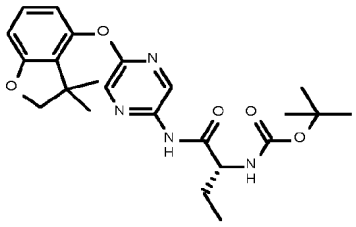
tert-butyl N-[(1R)-1-[[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]carbamoyl]propyl]carbamate



To a mixture of 2-bromo-5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-pyrazine (Intermediate 1, 16g, 48.0mmol), tert-butyl N-[(1R)-1-carbamoylpropyl]carbamate (Intermediate 7, 10g, 49.4mmol), cesium carbonate (24.16g, 74.17mmol) in 1,4-dioxane (150mL), after flushing with argon, diacetoxypalladium (0.555g, 2.47mmol) and (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (2.15g, 3.71mmol) were added. For three times cycle vacuum-argon was applied and the reaction mixture was stirred at 95°C for 1.5h. The reaction mixture was cooled using an external ice bath and then filtered under vacuum to remove cesium carbonate. The filtrate was collected, diluted with EtOAc (150ml) and washed with an aqueous saturated solution of NH_4Cl (100ml) and then with a n aqueous saturated solution of NaCl (100ml), dried with sodium sulphate, filtered and evaporated to dryness. The residue was purified by flash chromatography on silica gel (Biotage system) using 2x SNAP 100g column (200g silica) and cyclohexane/EtOAc from 0 to 40% as eluent affording tert-butyl N-[(1R)-1-[[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]carbamoyl]propyl]carbamate (16.8g) as yellow solid.

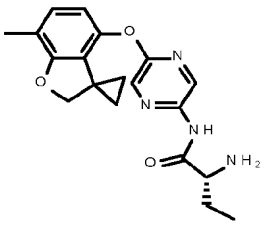
The following compounds were prepared using the foregoing methodology (either route 1 or route 2), replacing 2-bromo-5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-pyrazine (Intermediate 1) with the appropriate bromopyrazine. Final products were purified by flash-chromatography (Silica cartridge; Cyclohexane/EtOAc or other appropriate solvent system).

Int.	Structure	Name	bromopyrazine	LCMS

10		tert-butyl N-[(1R)-1-[(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)carbamoyl]propyl]carbamate	2-bromo-5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrazine (Intermediate 2)	LC/MS: QC_3_MIN: Rt = 2.246 min; m/z 441 [M+H]+.
11		tert-butyl N-[(1R)-1-[[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]carbamoyl]propyl]carbamate	2-bromo-5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazine (Intermediate 3)	LC/MS: QC_3_MIN: Rt = 2.309 min; m/z 457 [M+H]+.
12		tert-butyl N-[(1R)-1-[[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]carbamoyl]propyl]carbamate	2-bromo-5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazine (Intermediate 4)	LC/MS: QC_3_MIN: Rt = 2.366 min; m/z 443 [M+H]+.

Intermediate 13

(2R)-2-amino-N-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]butanamide

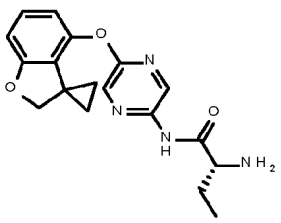
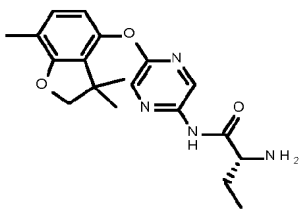
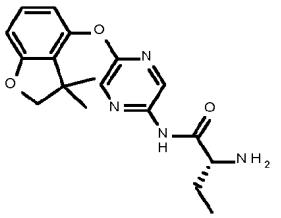


A mixture of tert-butyl N-[(1R)-1-[[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]carbamoyl]propyl]carbamate (Intermediate 9, 16mg, 0.035mmol) and 2,2,2-trifluoroacetic acid (0.50mL, 6.53mmol) in dichloromethane (2mL) was stirred at room temperature for 2h.

The reaction mixture was diluted with dichloromethane (20 ml) and a saturated solution of $NaHCO_3$ (aq) was added while the pH was allowed to reach 8. The phases were separated and the organic layer was washed with brine (20 ml), dried over Na_2SO_4, filtered and evaporated

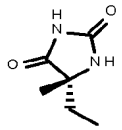
affording (2R)-2-amino-N-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]butanamide (13mg) that was used in the next step without further purification.
LC/MS: QC_3_MIN: Rt = 2.009 min; m/z 355 [M+H]+.

The following compounds were prepared using the foregoing methodology, replacing tert-butyl N-[(1R)-1-[[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]carbamoyl]propyl]carbamate (Intermediate 9) with the appropriate Boc amine.

Int.	Structure	Name	Boc amine	LCMS
14		(2R)-2-amino-N-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)butanamide	tert-butyl N-[(1R)-1-[(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)carbamoyl]propyl]carbamate (Intermediate 10)	LC/MS: QC_3_MIN: Rt = 1.675 min; m/z 342 [M+H]+.
15		(2R)-2-amino-N-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]butanamide	tert-butyl N-[(1R)-1-[[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]carbamoyl]propyl]carbamate (Intermediate 11)	LC/MS: QC_3_MIN: Rt = 1.756 min; m/z 357 [M+H]+.
16		(2R)-2-amino-N-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]butanamide	tert-butyl N-[(1R)-1-[[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]carbamoyl]propyl]carbamate (Intermediate 12)	LC/MS: QC_3_MIN: Rt = 1.673 min; m/z 343 [M+H]+.

Intermediate 17

(5R)-5-ethyl-5-methyl-imidazolidine-2,4-dione

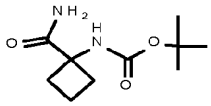


A mixture of tert-butyl N-[(1R)-1-carbamoyl-1-methyl-propyl]carbamate (Intermediate 8, 100mg,0,4624mmol) and potassium carbonate (191,71mg,1,3871mmol) in 1-butanol (5mL) was stirred under an atmosphere of nitrogen at 95°C overnight. After cooling, potassium carbonate was filtered off and the reaction mixture was diluted with ethyl acetate (30 ml) and washed with an aqueous 0.1N HCl solution (30 ml) and then with brine (30 ml). Phases were separated and

the organic layer was collected, dried over Na_2SO_4, filtered and evaporated affording (5R)-5-ethyl-5-methyl-imidazolidine-2,4-dione (60mg,0,4221mmol, 91,283 %).
LC/MS: QC_3_MIN: m/z 285 [2M+H]+.

Intermediate 18

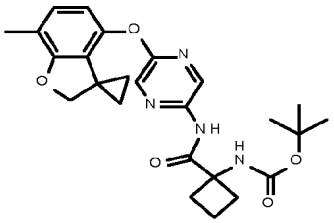
tert-butyl N-(1-carbamoylcyclobutyl)carbamate



Intermediate 18 was prepared using the methodology described for Intermediate 7, replacing (2R)-2-(tert-butoxycarbonylamino)butanoic acid with 1-(tert-butoxycarbonylamino)cyclobutanecarboxylic acid.
LC/MS: QC_3_MIN: m/z 159 [M-tBu+H]+.

Intermediate 19

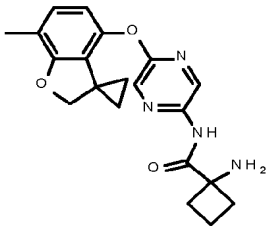
tert-butyl N-[1-[[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]carbamoyl]cyclobutyl]carbamate



A mixture of 2-bromo-5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-pyrazine (Intermediate 1, 50mg, 0.1501mmol), tert-butyl N-(1-carbamoylcyclobutyl)carbamate (Intermediate 18, 64mg, 0.2987mmol), dipotassium carbonate (62mg,0,4486mmol), copper(I) iodide (2.9mg,0.0152mmol) and N,N'-dimethylethane-1,2-diamine (0.0065mL,0.0601mmol) in 1-butanol (1mL) was stirred under an atmosphere of nitrogen at 95°C for 4h. After cooling, the reaction mixture was diluted with ethyl acetate (30 ml) and washed with an aqueous 0.1M HCl solution (30 ml) and then with brine (30 ml). Phases were separated, and the organic layer was collected, dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (Biotage System) on silica gel using a SNAP 10g as column and Cyclohexane: Ethyl acetate from 100:0 to 30:70 as eluent affording tert-butyl N-[1-[[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]carbamoyl]cyclobutyl]carbamate (18mg).
LC/MS: QC_3_MIN: Rt = 2.675 min; m/z 467 [M+H]+.

Intermediate 20

1-amino-N-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]cyclobutanecarboxamide

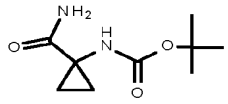


Intermediate 20 was prepared using the methodology described for Intermediate 13, replacing tert-butyl N-[(1R)-1-[[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]carbamoyl]propyl]carbamate (Intermediate 9) with tert-butyl N-[1-[[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]carbamoyl]cyclobutyl]carbamate (Intermediate 19).

LC/MS: QC_3_MIN: Rt = 1.979 min; m/z 367 [M+H]+.

Intermediate 21

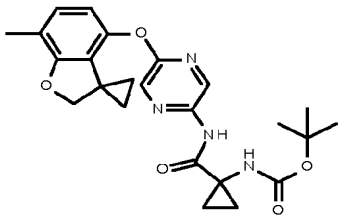
tert-butyl N-(1-carbamoylcyclopropyl)carbamate



Intermediate 21 was prepared using the methodology described for Intermediate 7, replacing (2R)-2-(tert-butoxycarbonylamino)butanoic acid with 1-(tert-butoxycarbonylamino)cyclopropanecarboxylic acid.

Intermediate 22

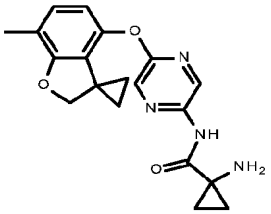
tert-butyl N-[1-[[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]carbamoyl]cyclopropyl]carbamate



A mixture of dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (12mg, 0.0252mmol), tert-butyl N-(1-carbamoylcyclopropyl)carbamate (Intermediate 21, 67mg, 0.3346mmol), Tris(dibenzylideneacetone)dipalladium(0) (22mg, 0.0240mmol), 2-bromo-5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-pyrazine (Intermediate 1, 79.518mg, 0.2387mmol) and caesium carbonate (116mg, 0.3560mmol) in 1,4-dioxane (1mL) were stirred under an atmosphere of nitrogen at 95°C for 2h. Additional tert-butyl N-(1-carbamoylcyclopropyl)carbamate (Intermediate 21, 67mg, 0.3346mmol) and Tris(dibenzylideneacetone)dipalladium(0) (22mg, 0.0240mmol) was added and the reaction mixture was stirred at 95°C under nitrogen for a further 2h, followed by the addition of a further dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (12mg, 0.0252mmol), Tris(dibenzylideneacetone)dipalladium(0) (22mg, 0.0240mmol) and caesium carbonate (58mg) and the mixture was stirred under nitrogen for a further 2h. The reaction mixture was then quenched with water (10mL), NH_4Cl (10mL) and extracted with ethyl acetate (20mL). The organic layer was then washed with brine (15mL), dried over Na_2SO_4, filtered, then concentrated in vacuo. The crude was purified by flash chromatography (Biotage System) on silica gel using a SNAP 10g as column and Cyclohexane:Ethyl acetate 90:10 to 70:30 as eluent to afford tert-butyl N-[1-[[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]carbamoyl]cyclopropyl]carbamate (55mg) as a yellow solid.
LC/MS: QC_3_MIN: Rt = 2.634 min; m/z 453 [M+H]+.

Intermediate 23

1-amino-N-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]cyclopropanecarboxamide

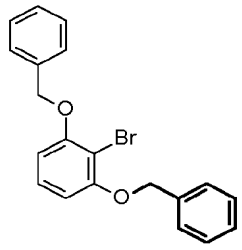


tert-butyl N-[1-[[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]carbamoyl]cyclopropyl]carbamate (Intermediate 22, 55mg, 0.1215mmol) was dissolved in dichloromethane (4mL) and cooled to 0 °C. 2,2,2-trifluoroacetic acid (1154.7mg, 10.026mmol) (0.8mL) was added dropwise and the reaction was stirred at room temperature for 1 hour. The reaction mixture was then cooled to 0 °C and $NaHCO_3$ was added until the pH reached 8. The mixture was then allowed to warm to room temperature and extracted with DCM (10mL). The

organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum to afford1-amino-N-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]cyclopropanecarboxamide (40mg) as a yellow oil.
LC/MS: QC_3_MIN: Rt = 1.935 min; m/z 353 [M+H]+.

Intermediate 24

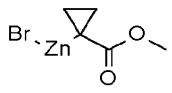
1,3-dibenzyloxy-2-bromo-benzene



To a solution of 2-bromobenzene-1,3-diol (20g,105.8mmol) in acetone (200mL), potassium carbonate (43.87g, 317.4mmol) was added followed by the addition of benzyl bromide (40.72g, 238.1mmol) (28ml) and the reaction mixture was refluxed for 1.5 hours. After cooling, the reaction mixture was filtered under vacuum and the filtrate was concentrated to dryness. The residue was diluted with ethyl acetate (100 ml) and washed with water (100 ml) and then with brine (100 ml). Phases were separated and the organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was suspended in isopropanol (8 volumes) and the mixture heated at 80°C and stirred for 1 hour at this temperature (to obtain a clear solution). Then, the mixture was allowed to reach room temperature (in 1h) and the obtained suspension was filtered. The solid was washed with ice cold isopropanol and then dried affording the title compound 1,3-dibenzyloxy-2-bromo-benzene (34g) as pale pink solid.
LC/MS: QC_3_MIN: Rt = 2.688 min.

Intermediate 25

bromo-(1-methoxycarbonylcyclopropyl)zinc

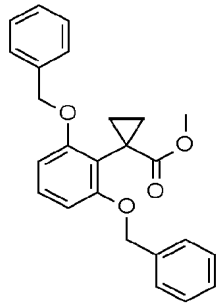


In a two-neck round-bottom flask activated zinc powder (6.84g,104.6mmol) was added and the powder was heated under vacuum. The system was put under argon and dry tetrahydrofuran (58mL) was added. Then, 1,2-dibromoethane (2.18g, 11.62mmol) was added and the mixture

was heated to reflux. Chlorotrimethylsilane (505mg, 4.65mmol) was added in a single portion and the mixture kept stirring at reflux temperature. A solution of methyl 1-bromocyclopropylcarboxylate (10.4g, 58.1mmol) in dry tetrahydrofuran (12mL) was slowly added at the same temperature and the reaction mixture was refluxed for 1.5h. The reaction mixture was cooled down to room temperature and the zinc was allowed to settle affording 70ml of a 0.83M (theoretical) solution of bromo-(1-methoxycarbonylcyclopropyl)zinc in THF which was used in the next step without further work up.

Intermediate 26

methyl 1-(2,6-dibenzyloxyphenyl)cyclopropanecarboxylate

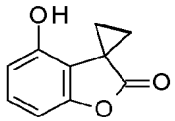


To a solution of 1,3-dibenzyloxy-2-bromo-benzene (Intermediate 24, 16g, 43.33mmol) and Bis(tri-tert-butylphosphine)palladium(0) (221mg, 0.43mmol) in N,N-dimethylformamide (150mL) pre-heated at 70 °C, a 0.83M (theoretical) solution of bromo-(1-methoxycarbonylcyclopropyl)zinc in THF (Intermediate 25, 60ml) was added (via cannulation) and the reaction mixture was stirred at the same temperature for 40 minutes. After cooling, the reaction mixture was concentrated under vacuum up to ~30 ml and the residue was diluted with ethyl acetate (450 ml) and washed twice with a 1N aqueous solution of HCl (2x100 ml) and then three times with ice cold brine (3x100ml). Phases were separated and the organic layer was filtered under vacuum on a Gooch filter assembled with filter paper and cellulose and washing with ethyl acetate. The filtrate was dried over Na_2SO_4, filtered and evaporated affording the title compound methyl 1-(2,6-dibenzyloxyphenyl)cyclopropanecarboxylate (15.5g) that was in the next step without further purification.

LC/MS: QC_3_MIN: Rt = 2.606 min; m/z 389 [M+H]+.

Intermediate 27

4-hydroxyspiro[benzofuran-3,1'-cyclopropane]-2-one



The reaction was performed in three different runs using about 20g of starting material each.

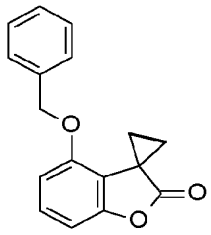
General procedure: to a mixture of methyl 1-(2,6-dibenzyloxyohenyl)cyclopropanecarboxylate (Intermediate 26, 20.4g, 52.52mmol) and palladium 5% wt. on carbon (1.02g) in ethanol (200ml), ammonium formate (16.56g, 262.6mmol) was added and the reaction mixture was stirred at 80°C for 1 hour. After cooling, the catalyst was filtered off on a cellulose pad and the filtrate was concentrated under vacuum up to ~20ml.

The residues coming from the 3 runs were put together and diluted with ethyl acetate (400ml) and washed twice with water (2x300 ml). The two phases were separated and the organic one was washed with brine (300 ml), dried with Na_2SO_4 and concentrated under vacuum affording 4-hydroxyspiro[benzofuran-3,1'-cyclopropane]-2-one (27.55g) (containing ~10-15% of the uncyclized methyl 1-(2,6-dihydroxyphenyl)cyclopropanecarboxylate intermediate) that was used in the next step without further purification.

LC/MS: QC_3_MIN: Rt = 1.707 min.

Intermediate 28

4-benzyloxyspiro[benzofuran-3,1'-cyclopropane]-2-one

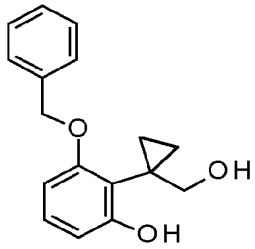


To a solution of 4-hydroxyspiro[benzofuran-3,1'-cyclopropane]-2-one (Intermediate 27, 28.5g,161.8mmol) (containing ~10-15% of the uncyclized methyl 1-(2,6-dihydroxyphenyl)cyclopropanecarboxylate intermediate) in acetonitrile (200mL)/tetrahydrofuran (50mL), potassium carbonate (33.54g, 242,7mmol) was added and the reaction mixture was stirred at 70°C for 1.5 hours. The reaction mixture was then cooled to room temperature and benzyl bromide (27.67g,161.8mmol) was slowly added. The reaction mixture was stirred at 60°C for 5 hours. After cooling, the reaction mixture was filtered under vacuum and the solid

discarded, the filtrate was concentrated up to 50 ml, diluted with ethyl acetate (250 ml) and washed twice with brine (2x100 ml). Phases were separated and the organic layer was dried over Na_2SO_4, filtered and evaporated affording the title compound 4-benzyloxyspiro[benzofuran-3,1'-cyclopropane]-2-one (42,4g) that was used in the next step without further purification.
LC/MS: QC_3_MIN: Rt = 2.389 min; m/z 267 [M+H]+.

Intermediate 29

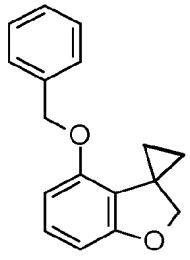
3-benzyloxy-2-[1-(hydroxymethyl)cyclopropyl]phenol



To a solution of 4-benzyloxyspiro[benzofuran-3,1'-cyclopropane]-2-one (Intermediate 28, 42.4g,159.2mmol) in dry tetrahydrofuran (300mL), a 1M solution of lithium aluminium hydride in THF (79.6ml, 79,6mmol) was slowly added at 0 °C and the reaction mixture was stirred at the same temperature for 30 minutes. The reaction was quenched with ice, water (400 ml) and an aqueous 1M solution of HCl (160 ml) and then diluted with ethyl acetate (700 ml). Phases were separated and the aqueous layer was back extracted with ethyl acetate (500 ml). The combined organic phases were washed with brine (600 ml), dried over Na_2SO_4, filtered and evaporated affording the title compound 3-benzyloxy-2-[1-(hydroxymethyl)cyclopropyl]phenol (43g) which was used in the next step without further purification.
LC/MS: QC_3_MIN: Rt = 2.148 min; m/z 271 [M+H]+, m/z 293 [M+Na]+, m/z 253 [M-OH]+.

Intermediate 30

4-benzyloxyspiro[2H-benzofuran-3,1'-cyclopropane]

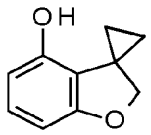


To a solution of 3-benzyloxy-2-[1-(hydroxymethyl)cyclopropyl]phenol (Intermediate 29, 43g, 159.1mmol) in dimethyl carbonate (430 mL), potassium tert-butoxide (35.7g, 318.1mmol) was slowly added and the reaction mixture was stirred at 85°C for 3.5 hours. The reaction mixture was cooled to room temperature, concentrated under vacuum up to 150mL, diluted with MTBE (400 ml) and washed with water (400 ml). Phases were separated and the aqueous layer was back extracted with MTBE (250 ml).The combined organic layers were washed with brine (350 ml), dried over Na_2SO_4, filtered and concentrated affording the title compound 4-benzyloxyspiro[2H-benzofuran-3,1'-cyclopropane] (40g) that was used in the next step without further purification.

LC/MS: QC_3_MIN: Rt = 2.457 min; m/z 253 [M+H]+.

Intermediate 31 (Intermediate 85 WO2012/076877)

1 spiro[2H-benzofuran-3,1'-cyclopropane]-4-ol



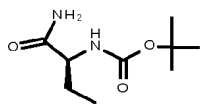
The reaction was done in two runs using 20g of starting material each.

To a mixture of 4-benzyloxyspiro[2H-benzofuran-3,1'-cyclopropane] (Intermediate 30, 20g, 79.27mmol) and ammonium formate (24.99g, 396.34mmol) in ethanol (160ml), palladium 5% wt. on carbon (2.0g) was added and the reaction mixture was stirred at 80°C for 10 minutes. After cooling, the catalyst was filtered off through a cellulose pad and the filtrate was concentrated under vacuum up to ~20 ml. The residues coming from the two reactions were combined and the mixture was diluted with ethyl acetate (300 ml) and washed three times with water (3x200 ml) and then with brine (200 ml). The two phases were separated and the organic one was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (Biotage System) on silica gel using Cyclohexane: Ethyl acetate from 99:1 to 85:15 as eluent affording spiro[2H-benzofuran-3,1'-cyclopropane]-4-ol (17,75g) as white solid.

LC/MS: QC_3_MIN: Rt = 1.723 min; m/z 163 [M+H]+.

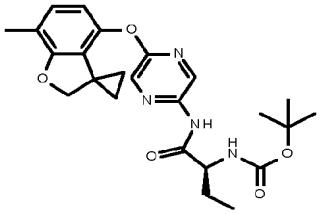
Intermediate 32

tert-butyl N-[(1S)-1-carbamoylpropyl]carbamate



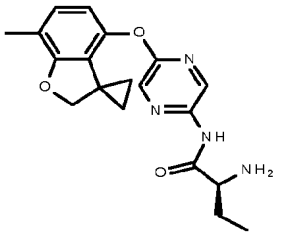
The title compound was synthesized following the same methodology used for the synthesis of Intermediate 7 replacing (2R)-2-(tert-butoxycarbonylamino)butanoic acid with (2S)-2-(tert-butoxycarbonylamino)butanoic acid
LC/MS: QC_3_MIN: m/z 147 [M-tBu+H]+, m/z 427 [2M+Na]+

Intermediate 33
tert-butyl N-[(1S)-1-[[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]carbamoyl]propyl]carbamate



The title compound was synthesized following the "route 1" methodology used for the synthesis of Intermediate 9 replacing tert-butyl N-[(1R)-1-carbamoylpropyl]carbamate (Intermediate 7) with tert-butyl N-[(1S)-1-carbamoylpropyl]carbamate (Intermediate 32).
LC/MS: QC_3_MIN: Rt = 2.65 min; m/z 455 [M+H]+.

Intermediate 34
(2S)-2-amino-N-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]butanamide

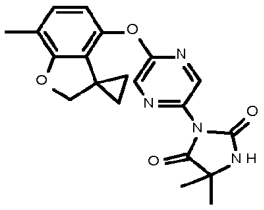


The title compound was synthesized following the same methodology used for the synthesis of Intermediate 13 replacing tert-butyl N-[(1R)-1-[[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]carbamoyl]propyl]carbamate (Intermediate 9) with tert-butyl

N-[(1S)-1-[[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]carbamoyl]propyl]carbamate (Intermediate 33)
LC/MS: QC_3_MIN: Rt = 1.98 min; m/z 355 [M+H]+.

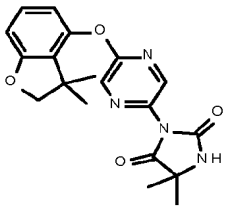
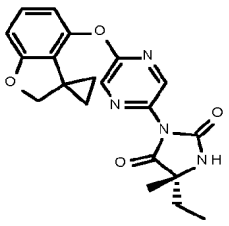
Example 1 route 1

5,5-dimethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione



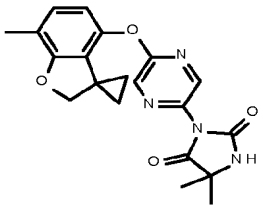
To a solution of 2-bromo-5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-pyrazine (Intermediate 1, 30mg, 0.069mmol) in N,N-dimethylacetamide (1mL) 5,5-dimethylimidazolidine-2,4-dione (44.4mg, 0.345mmol) and copper (I) oxide (5mg, 0.035mmol) were added. The flask was flushed with nitrogen gas and left stirring overnight at 135 °C. The reaction was diluted with EtOAc (10 mL) and first washed with an aqueous saturated solution of ammonium chloride (20 mL) and then brine (20 mL). The organic layer was collected, dried with sodium sulphate and evaporated to dryness. The residue was then purified using flash column chromatography using cyclohexane:ethyl acetate from 80:20 to 40:60 as eluent to afford 5,5-dimethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione (17mg) as a white solid.
^{1}H-NMR (400 MHz; DMSO-d6): δ ppm 8.72 (bs, 1H), 8.51 (d, 1H), 8.30 (d, 1H), 6.95 (dd, 1H), 6.53 (d, 1H), 4.46 (s, 2H), 2.14 (s, 3H), 1.42 (s, 6H), 1.07-1.14 (m, 2H),0.89-0.95 (m, 2H).

The following compounds were prepared using the foregoing methodology, replacing 2-bromo-5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxy-pyrazine (Intermediate 1) with the appropriate bromopyrazine and 5,5-dimethylimidazolidine-2,4-dione with the appropriate hydantoin. 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	Bromopyrazine	Hydantoin	LCMS/NMR
2		3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-5,5-dimethyl-imidazolidine-2,4-dione	2-bromo-5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazine (Intermediate 4)	5,5-dimethylimidazolidine-2,4-dione	LC/MS: QC_3_MIN: Rt = 2.288 min; m/z 369 [M+H]+. ^{1}H-NMR (500 MHz; DMSO-d6): δ ppm 8.73 (bs, 1H), 8.60 (d, 1H), 8.32 (d, 1H), 7.17 (dd, 1H), 6.70 (d, 1H), 6.66 (d, 1H), 4.23 (s, 2H), 1.42 (s, 6H), 1.28 (s, 6H).
3		(5R)-5-ethyl-5-methyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)imidazolidine-2,4-dione	2-bromo-5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-pyrazine (Intermediate 2)	(5R)-5-ethyl-5-methyl-imidazolidine-2,4-dione (Intermediate 17)	LC/MS: QC_3_MIN: Rt = 2.228 min; m/z 381 [M+H]+.

Example 1 route 2

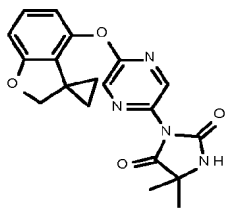
5,5-dimethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione

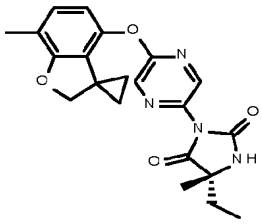
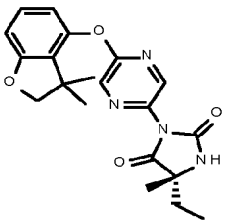
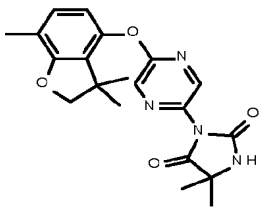


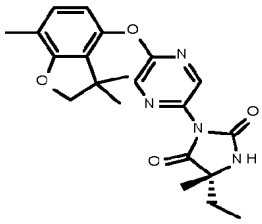
To a solution of 3-(5-chloropyrazin-2-yl)-5,5-dimethyl-imidazolidine-2,4-dione (Intermediate 5, 20mg, 0.083mmol) and 7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-ol (Intermediate 156 WO2012076877, 22mg, 0.125mmol) in acetonitrile (1mL), dipotassium carbonate (17.2mg,

0.12mmol) was added. The reaction mixture was stirred overnight at 60°C and then for 3h at 80°C. The reaction mixture was concentrated under vacuum and the crude was purified by flash chromatography on silica gel (BIOTAGE SYSTEM) using a SNAP 10g as column and Chexane/EtOAc from 80/20 to 20/80 as eluent. The fraction were still impure and they were purified by reverse chromatography using a SNAP C-18 as column and H2O/ACN from 95/5 to 5/95 as eluent affording 5,5-dimethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione (9.4mg) as a white solid.
LC/MS: QC_3_MIN: Rt = 2.224 min; m/z 381 [M+H]+.

The following compounds were prepared using the foregoing methodology, replacing 7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-ol with the appropriate phenol and use 3-(5-chloropyrazin-2-yl)-5,5-dimethyl-imidazolidine-2,4-dione (Intermediate 5) or replace it with the appropriate chloropyrazine 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).

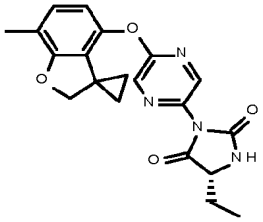
Ex.	Structure	Name	Phenol	Chloro-pyrazine intermediate	LCMS/NMR
4		5,5-dimethyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)imidazolidine-2,4-dione	spiro[2H-benzofuran-3,1'-cyclopropane]-4-ol (Intermediate 85, WO2012/076877)	3-(5-chloropyrazin-2-yl)-5,5-dimethyl-imidazolidine-2,4-dione (Intermediate 5)	LC/MS: QC_3_MIN: Rt = 2.085 min; m/z 367 [M+H]+. ^{1}H-NMR (500 MHz; DMSO-d6): δ ppm 8.73 (bs, 1H), 8.54 (d, 1H), 8.32 (d, 1H), 7.11 (dd, 1H), 6.71 (d, 1H), 6.62 (d, 1H), 4.46 (s, 2H), 1.42 (s, 6H), 1.12-1.16 (m, 2H), 0.92-0.97 (m, 5H).

5		(5R)-5-ethyl-5-methyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione	7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-ol (Intermediate 156 WO2012/076877)	5R)-3-(5-chloropyrazin-2-yl)-5-ethyl-5-methyl-imidazolidine-2,4-dione (Intermediate 6)	LC/MS: QC_3_MIN: Rt = 2.361 min; m/z 395 [M+H]+. ^{1}H-NMR (500 MHz; DMSO-d6): δ ppm 8.64 (bs, 1H), 8.48 (d, 1H), 8.25 (d, 1H), 6.91 (dd, 1H), 6.49 (d, 1H), 4.42 (s, 2H), 2.11 (s, 3H), 1.71-1.79 (m, 1H), 1.60-1.68 (m, 1H), 1.38 (s, 3H), 1.02-1.09 (m, 2H), 0.82-0.92 (m, 5H).
6		(5R)-3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-5-ethyl-5-methyl-imidazolidine-2,4-dione	3,3-dimethyl-2H-benzofuran-4-ol (Intermediate 50 WO2012/076877)	5R)-3-(5-chloropyrazin-2-yl)-5-ethyl-5-methyl-imidazolidine-2,4-dione (Intermediate 6)	LC/MS: QC_3_MIN: Rt = 2.008 min; m/z 383 [M+H]+.
7		5,5-dimethyl-3-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]imidazolidine-2,4-dione	3,3,7-trimethyl-2H-benzofuran-4-ol (Intermediate 184 WO2012/076877)	3-(5-chloropyrazin-2-yl)-5,5-dimethyl-imidazolidine-2,4-dione (Intermediate 5)	LC/MS: QC_3_MIN: Rt = 2.025 min; m/z 383 [M+H]+.

8		(5R)-5-ethyl-5-methyl-3-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]imidazolidine-2,4-dione	3,3,7-trimethyl-2H-benzofuran-4-ol (Intermediate 184 WO2012/076877)	(5R)-3-(5-chloropyrazin-2-yl)-5-ethyl-5-methyl-imidazolidine-2,4-dione (Intermediate 6)	LC/MS: QC_3_MIN: Rt = 2.111 min; m/z 397 [M+H]+.

Example 9 (route 1)

(5R)-5-ethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione

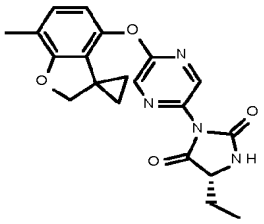


A mixture of (2R)-2-amino-N-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]butanamide (Intermediate 13, 13mg, 0.037mmol) and N,N-diethylethanamine (11mg, 0.11mmol) in dichloromethane (2mL) was cooled to 0°C. A solution of bis(trichloromethyl) carbonate (4,5mg, 0.015mmol) in dichloromethane (0.5mL) was added dropwise and the reaction mixture was stirred for 1 hour at the same temperature. Additional bis(trichloromethyl) carbonate (1.5mg) in dichloromethane (0.5mL) was added and stirring continued for 30 minutes. The mixture was allowed to warm to room temperature. The reaction mixture was diluted with dichloromethane (20 ml) and the organic phase was washed with an aqueous solution 0.1N HCl (20 ml) and then with brine (20 ml). Phases were separated and the organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by reverse phase chromatography using a SNAP C-18 column, eluting with water:acetonitrile from 90:10 to 0:100. The appropriate fractions were combined and evaporated to dryness, affording (5R)-5-ethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione (7.5mg) as a white solid.

LC/MS: QC_3_MIN: Rt = 2.305 min; m/z 381 [M+H]+. Enantiomeric purity was confirmed as >95% using Chiral Control method.

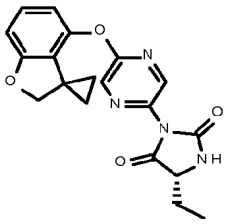
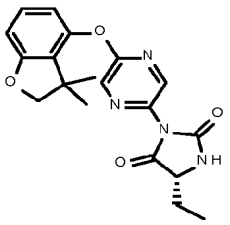
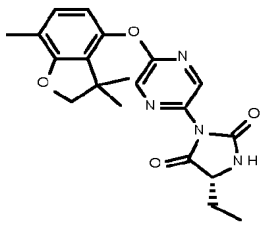
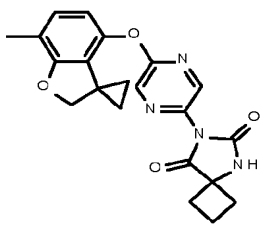
Example 9 (route 2)

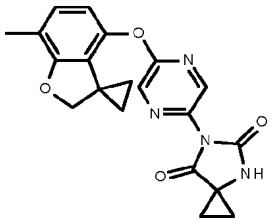
(5R)-5-ethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione



To a solution of (2R)-2-amino-N-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]butanamide (Intermediate 13, 21g, 59.26mmol) in ethyl acetate (500mL) 1-1'-carbonyldiimidazole (10.57g, 65.18mmol) was added in 5 portions of about 2g each, and stirred at room temperature for 4h. The reaction was quenched with ice and an aqueous 0.2N solution of HCl (250ml) was added. The two phases were separated and the organic layer was washed with an aqueous 0.2N solution of HCl (250ml) and with brine (200ml), then dried with sodium sulphate, filtered and evaporated to dryness. The crude was split into 4 aliquots of ~4.2g each and each aliquot was purified by flash chromatography on silica gel using a SNAP (100G) as column and Cyclohexane/Ethyl acetate from 80/20 to 20/80 as eluent. The desired fractions from each run were collected and the solvent evaporated to dryness. The obtained light-yellow solid was suspended in a solution of Cyclohexane/Ethyl acetate (1/1, 3volumes) (90ml) and stirred for 2h at 50°C. The mixture was then allowed to cool to room temperature and filtered under vacuum. The wet cake was washed with ice cold cyclohexane (15ml), the solid was collected and dried to afford the title compound (5R)-5-ethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione (13.6g) as a white solid.
^{1}H-NMR (500 MHz; DMSO-d6): δ ppm 8.69 (bs, 1H), 8.52 (d, 1H), 8.26 (d, 1H), 6.94 (d, 1H), 6.53 (d, 1H), 4.46 (s, 2H), 4.26-4.30 (m, 1H), 2.14 (s, 3H), 1.77-1.86 (m, 1H), 1.65-1.76 (m, 1H), 1.07-1.12 (m, 2H), 0.90-0.99 (m, 5H).

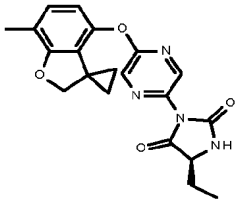
The following compounds were prepared using the foregoing methodology (either route 1 or route 2), replacing (2R)-2-amino-N-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]butanamide (Intermediate 13) with the appropriate butanamide. Final products were purified by flash-chromatography (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	Butanamide	LCMS/NMR
10		(5R)-5-ethyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)imidazolidine-2,4-dione	(2R)-2-amino-N-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)butanamide (Intermediate 14)	LC/MS: QC_3_MIN: Rt = 2.081 min; m/z 367 [M+H]+. Enantiomeric purity was confirmed as >95% using Chiral Control method. ^{1}H-NMR (500 MHz; DMSO-d6): δ ppm 8.70 (bs, 1H), 8.55 (d, 1H), 8.27 (d, 1H), 7.11 (dd, 1H), 6.71 (dd, 1H), 6.62 (dd, 1H), 4.46 (s, 2H), 4.27-4.31 (m, 1H), 1.76-1.87 (m, 1H), 1.65-1.76 (m, 1H), 1.11-1.17 (m, 2H), 0.92-0.98 (m, 5H).
11		(5R)-3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-5-ethyl-imidazolidine-2,4-dione	(2R)-2-amino-N-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]butanamide (Intermediate 16)	LC/MS: QC_3_MIN: Rt = 2.142 min; m/z 369 [M+H]+.
12		(5R)-5-ethyl-3-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]imidazolidine-2,4-dione	(2R)-2-amino-N-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]butanamide (Intermediate 15)	LC/MS: QC_3_MIN: Rt = 2.111 min; m/z 383 [M+H]+.
13		7-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]-5,7-diazaspiro[3.4]octane-6,8-dione	1-amino-N-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]cyclobutanecarboxamide (Intermediate 20)	LC/MS: QC_3_MIN: Rt = 2.309 min; 393 m/z [M+H]+.

14		6-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]-4,6-diazaspiro[2.4]heptane-5,7-dione	1-amino-N-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]cyclopropanecarboxamide	LC/MS: QC_3_MIN: Rt = 2.236 min; 379 m/z [M+H]+.

Example 15

(5S)-5-ethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione



The title compound was synthesized following the "route 1" methodology used for the synthesis of Intermediate 9 replacing (2R)-2-amino-N-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]butanamide (Intermediate 13) with (2S)-2-amino-N-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]butanamide (Intermediate 34)

LC/MS: QC_3_MIN: Rt = 2.29 min; m/z 381 [M+H]+.

Biological Examples

Biological Example 1: Measurement of Kv3.1, Kv3.2 and Kv3.3 channel modulation

The ability of the compounds of the invention to modulate the voltage-gated potassium channel subtypes 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

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 containing 5% CO_2 in air.

To assess compound effects on human Kv3.2 channels (hKv3.2), a stable cell line expressing human Kv3.2 channels (hKv3.2) 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). Cells are grown and maintained at 37 °C in a humidified environment containing 5% CO_2 in air.

To assess compound effects on human Kv3.1 channels (hKv3.1):

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, 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.

Cell preparation for IonWorks Quattro™ experiments

The day of the experiment, cells are removed from the incubator and the culture medium 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

Ionworks

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 (Rp) 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 -70mV to +40 mV (duration 50 ms) was applied to clamp later the voltage at -40 mV during 200ms

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.

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 50mg/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): $CaCl_2$ 0.90, KCl 2.67, KH_2PO_4 1.47, $MgCl.6H_2O$ 0.493, NaCl 136.9, Na_3PO_4 8.06, with a pH of 7.4.

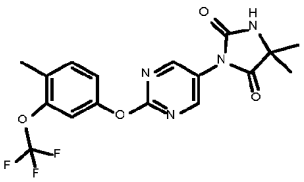
Compounds of use in the invention (or reference compounds such as *N*-cyclohexyl-*N*-[(7,8-dimethyl-2-oxo-1,2-dihydro-3-quinolinyl)methyl]-*N'*-phenylurea) are dissolved in dimethylsulfoxide (DMSO) at a stock concentration of 10 mM. These solutions are further diluted

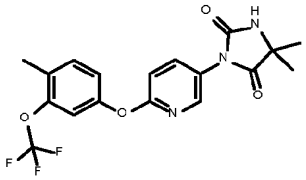
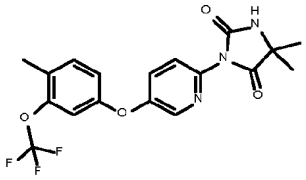
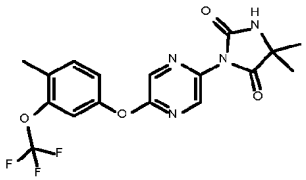
with DMSO using a Biomek FX (Beckman Coulter) in a 384 compound plate. Each dilution (1 µL) is transferred to another compound plate and external solution containing 0.05% pluronic acid (66 µL) is added. 3.5 µL from each plate containing a compound of the invention is added and incubated with the cells 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

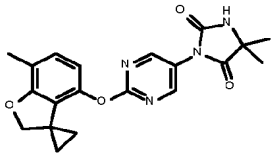
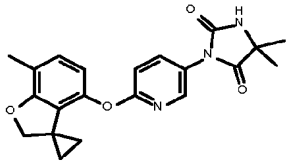
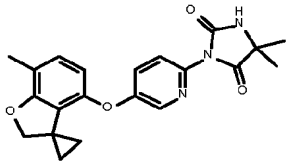
The recordings are analysed and filtered using both seal resistance (>20 MΩ) and peak current amplitude (>500 pA at the voltage step of 40 mV) in the absence of compound to eliminate unsuitable cells from further analysis. For hKv3.2 and hKv3.1 assays, paired comparisons of evoked currents between pre- 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 (50microM of *N*-cyclohexyl-*N*-[(7,8-dimethyl-2-oxo-1,2-dihydro-3-quinolinyl)methyl]-*N'*-phenylurea) and to the effect of a vehicle control (0.5% DMSO). The normalised data 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 (EC_{50}) 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).

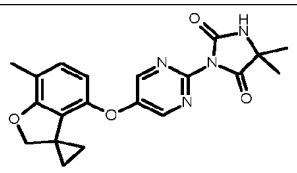
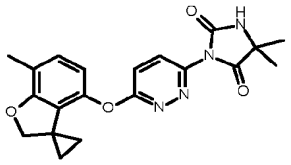
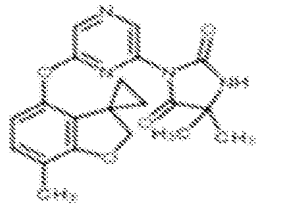
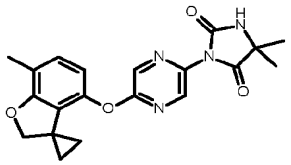
N-cyclohexyl-*N*-[(7,8-dimethyl-2-oxo-1,2-dihydro-3-quinolinyl)methyl]-*N'*-phenylurea is obtained from ASINEX (Registry Number: 552311-06-5).

Ex.	Compound	Kv3.1 pEC50	Kv3.1 max R%	Reference / LCMS
RE1		4.78	105	Ex57 WO2011/069951

Ex.	Compound	Kv3.1 pEC50	Kv3.1 max R%	Reference / LCMS
RE2		5.25	118	Ex45 WO2011/069951
RE3		4.89	79	LC/MS: QC_3_MIN: Rt = 2.376 min; m/z 396 [M+H]+.
RE4		<4.3	24	LC/MS: QC_3_MIN: Rt = 2.346 min; m/z 397 [M+H]+.

As shown by testing of RE1-RE4, the incorporation of a pyrazine ring can detrimentally impact the pEC50 and maxR of Kv3.1 modulators.

Ex.	Compound	Kv3.1 pEC50	Kv3.1 max R%	Reference / LCMS
RE5		5.14	158	Ex58 WO2012/076877
RE6		5.58	144	Ex70 WO2012/076877
RE7		5.56	130	Ex3 WO2017/103604

Ex.	Compound	Kv3.1 pEC50	Kv3.1 max R%	Reference / LCMS
RE8		4.98	42	LC/MS: QC_3_MIN: Rt = 2.224 min; m/z 381 [M+H]+.
RE9		<4.3	16	LC/MS: QC_3_MIN: Rt = 2.043 min; m/z 381 [M+H]+.
RE10		<4.3	22	LC/MS: QC_3_MIN: Rt = 2.29 min; m/z 381 [M+H]+.
1[+]		5.47	164	Example 1

[+] *n=10. For n=18,* pEC50 was 5.56 and maxR% 152

As shown by testing of RE5-RE9 as compared to Example 1, the incorporation of a para-pyrazine ring in Example 1 unexpectedly results in high pEC50 and high maxR in the Kv3.1 assay. RE10 shows that a meta-pyrazine central ring has greatly reduced pEC50 and maxR as compared to the para-pyrazine of Example 1.

Example	Kv3.1 pEC50	Kv3.1 max R%
1[+]	5.47	164
2	4.68	149
3	5.15	205
4	5.17	170
5	5.69	149
6	4.75	165

Example	Kv3.1 pEC50	Kv3.1 max R%
8	5.29	119
9[*]	5.88	172
10[$]	5.45	153
11	4.89	165
12	5.56	118
13	5.09	165

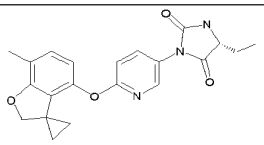
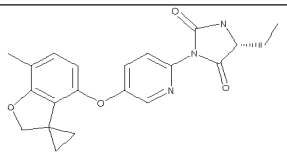
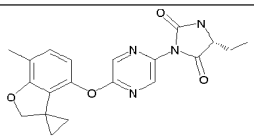
Example	Kv3.1 pEC50	Kv3.1 max R%
7	5.12	134

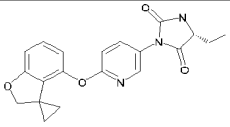
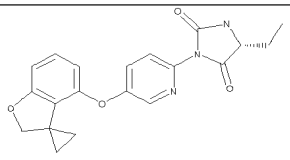
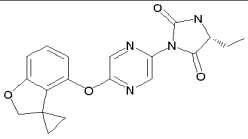
Example	Kv3.1 pEC50	Kv3.1 max R%
14	5.51	145
15	5.10	136

[+] *n=10. For n=18,* pEC50 was 5.56 and maxR% 152

[*] *n=4. For n=22,* pEC50 was 5.90 and maxR% 146

[$] *n=2. For n=26,* pEC50 was 5.63 and maxR% 147

Ex.	Compound	Kv3.1 pEC50	Kv3.1 max R%	Reference / LCMS
RE11		6.1	152	Ex62 WO2012/076877
RE12		5.6	149	Ex4 WO2017/102604
9		5.90	146	Example 9

Ex.	Compound	Kv3.1 pEC50	Kv3.1 max R%	Reference / LCMS
RE13		6.1	149	Ex15 WO2012/076877
RE14		5.2	150	Ex6 WO2017/102604
10		5.63	147	Example 10

All tested examples of the compounds of formula (I) are shown above and demonstrate good pEC50 and maxR properties in the Kv3.1 assay. Previous disclosures of Kv3.1 data for comparator compounds may differ slightly due to a lower number of measurements.

A secondary analysis of the data from the hKv3.1, hKv3.2 and hKv3.3 assays described in 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.

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

where:

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

Ymax is the plateau current;

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

Similarly, the effect of the compounds on the time taken for Kv3.1, Kv3.2 or Kv3.3 currents to decay on closing of the channels at the end of the -15mV depolarising voltage pulses can also be investigated. In this latter case, the magnitude of the effect of a compound on channel closing can be determined from the time constant (Tau_{deact}) of a non-linear fit of the decay of the current ("tail current") immediately following the end of the depolarising voltage pulse.

Kv3.1, Kv3.2 and Kv3.3 channels must activate and deactivate very rapidly in order to allow neurons to fire actions potentials at high frequency (Rudy *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

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, those compounds which markedly increase the value of Tau_{act} can reduce the ability of neurons in native tissues to fire at high frequency.

Biological Example 2: Determination of blood and brain tissue binding

Materials and Methods

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).

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 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 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.

Analysis

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

Afu=Buffer/Blood or Afu=CSF/Brain

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

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

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

Then:

%Binding = (1 -fucr) x 100

%Unbound = 100 -%Bound

Brain/Blood partition ratio (Kbb) Determination

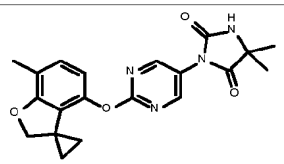
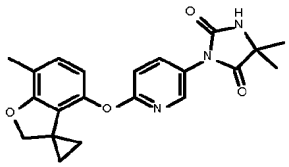
For compounds freely permeable across the blood/brain barrier (BBB), the unbound concentrations in blood and brain would be equivalent under steady-state distribution conditions. Therefore, the Kbb value could be calculated as:

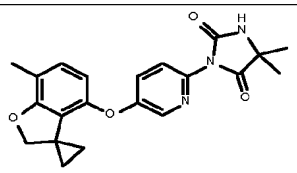
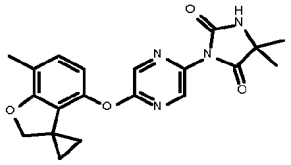
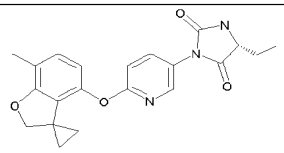
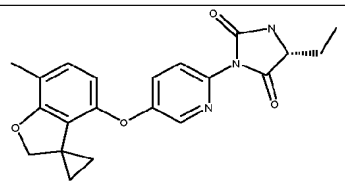
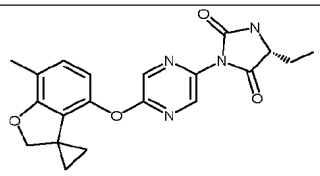
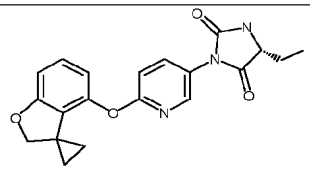
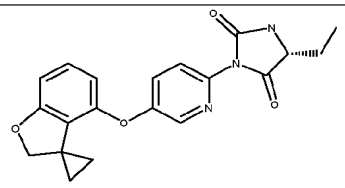
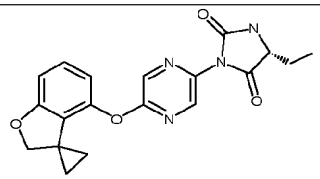
Fu(blood)/Fu(brain)

which is expected to be equivalent to the brain-to-blood concentration ratio (Ct(brain)/Ct(blood)) if efflux pump transporters are not involved.

Results

Examples 1, 9 and 10, and certain comparator compounds, were tested in the above described methodology to determine the brain fraction unbound. The results were as follows:

Ex.	Compound	Brain fraction unbound (%)
RE5		5.1
RE6		2.8

Ex.	Compound	Brain fraction unbound (%)
RE7		2.3*
1		4.3
RE11		2.1
RE12		1.9
9		3.0
RE13		6.2
RE14		5.8
10		8.7

* Supernatant diluted with 18% AcN in water

Pyrazine compounds of the invention, demonstrated an increased brain fraction unbound as compared to their pyridine comparator compounds.

Biological Example 3: 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 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 Isofluorane 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. 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. Blood and brain samples ar collected at a single timepoint of 0.5 h after dose administration for these animals. In all cases, blood samples are collected into potassium EDTA tubes.

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

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 (Cmax), integrated concentration over time (AUC), clearance (Clb), volume of distribution (Vss) and half-life (t1/2).

Oral dosing: Cmax, time of maximum concentration (Tmax), AUC, bioavailability (F%), fraction absorbed (Fa%), blood to brain ratio (AUC BB), and Fold-change in AUC BB in the presence of Elacridar.

Compounds of the invention may be expected to demonstrate good availability in brain tissue.

Biological Example 4: *In Vitro* Metabolic Stability Study in Human Hepatocytes

Methodology

The objective of this study was to determine metabolic stability in mixed gender human cryopreserved hepatocytes. Testosterone and 7−Hydroxycoumarin were used as positive controls for Phase I and Phase II metabolism, respectively.

Incubation medium was prepared by combining William's medium E, HEPES buffer 1 M and L-glutamine 200 mM in the following proportions: 88%, 10% and 2%, respectively (440 mL, 50 mL and 10 mL, respectively). The medium obtained was bubbled with carbogen (5% CO_2, 95% O_2) for 30 minutes prior to use. Cryopreserved hepatocytes were thawed and suspended in incubation medium pre−warmed at 37°C. Cells were centrifuged, re−suspended in medium and counted by means of a haemocytometer (Burker's chamber). Cell viability was measured using the Trypan Blue exclusion test.

Test compounds were separately dissolved in DMF to obtain 50 mM stock solutions that were further diluted in water/acetonitrile 50/50 (v/v) to obtain the corresponding 50 uM working solutions. Testosterone and 7−Hydroxy-Coumarin were dissolved in DMF in order to obtain a 50 mM Testosterone solution and 5 mM 7−Hydroxy-Coumarin solution. These solutions were then diluted in the incubation medium in order to obtain a 1 mM Testosterone working solution and a 500 uM 7−Hydroxy-Coumarin working solution.

10 uL of each working solution, i.e. 50 uM test compound, 1 mM Testosterone and 500 uM of 7−Hydroxy−Coumarin were added to 990 uL of $0.5x10^6$ cell suspensions in order to obtain the final concentrations of 0.5 uM, 10 uM and 5 uM, respectively. The concentration of the organic solvent in each incubation was constant and < 1% (v/v).

Test compounds were separately incubated at 0.5 uM for 0, 5, 10, 15, 20, 30, 45, 60, 90, 120, 150 and 180 min (12 time points) with mixed gender human cryopreserved hepatocytes at 37ºC in a 24 well plate. At each time point a robotic handling processor aspirated 50 uL of incubation mixture from each well and dispensed it into a refrigerated 96 well plate, containing 100 uL of acetonitrile with the corresponding internal standard 150 ng/mL to stop the reaction. Then an aliquot of water (120 uL) was added to equilibrate the organic solvent content at 37%. Samples were centrifuged (ca. 3500 g for 10 minutes) prior to LC MS/MS analysis.

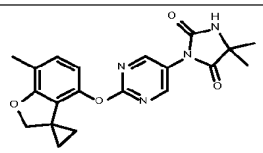
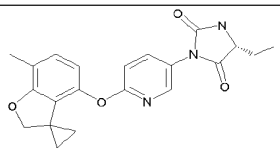
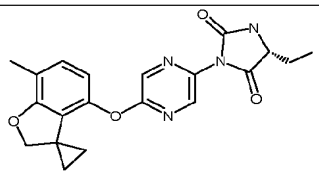
Positive controls, Testosterone and 7−Hydroxy−Coumarin, were incubated in single (n=1) at 10 and 5 uM, respectively, for 0, 5, 10, 15, 20, 30, 45, 60, 90, 120, 150 and 180 min (12 time points) with mixed gender human cryopreserved hepatocytes at the same conditions reported above for the test items, to demonstrate Phase I and Phase II metabolism in the hepatocytes systems. At each time point a robotic handling processor aspirated 50 uL of incubation mixture from each well and dispensed it into a refrigerated 96 well plate, containing 100 uL of acetonitrile with Rolipram as internal standard to stop the reaction. Then an aliquot of water (120 uL) was added to equilibrate the organic solvent content at 37%. Samples were centrifuged (ca. 3500 g for 10 minutes) prior to LC MS/MS analysis.

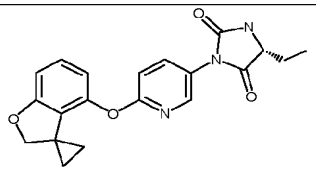
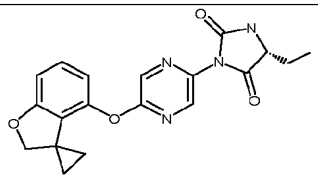
Metabolic stability was calculated from the peak area ratio of the remaining test compound with internal standard versus time.

The intrinsic clearance (CLint) was determined from the first order elimination constant k (min^{-1}) (obtained from GraphPad by plotting the natural logarithm of 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 Hn (120 for human).

$$CLint = k * \frac{V}{M} * \frac{Hn\ x10^6 cells}{g\ liver}$$

Values for CLint were expressed as mL/min/g liver.

Ex.	Compound	Rate constant k (min^{-1})	In vitro Cl_{int} (mL/min/g liver)
RE5		0.002	0.31
RE11		0.02	3.58
9		0.004	1.03

Ex.	Compound	Rate constant k (min^{-1})	In vitro Cl_{int} (mL/min/g liver)
RE13		0.009	2.16
10		0.003	0.70

Examples 9 and 10 demonstrate low clearance compared to pyridine comparator compounds RE11 and RE13.

Biological Example 5: Ames testing

Methodology

The objective of this *in vitro* study was to assess the potential of test articles to induce gene mutations *in vitro* in bacterial strains of *Salmonella typhimurium* (TA1535, TA1537, TA98 and TA100) and *Escherichia coli* WP2 *uvrA* (pKM101); test methodology was based on established procedures for bacterial mutagenicity testing, and assays were performed in the presence and absence of an exogenous mammalian oxidative metabolizing system (S9-mix).

The study was designed in accordance with national and international guidelines, to fulfil the requirements of regulatory authorities, for the toxicity testing of new drugs. The study design is in agreement with the following test guidelines:

- ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (CPMP/ICH/286/95, June 2009).
- ICH Topic S2 (R1) Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use. June 2012.

Bacterial strains

The following bacterial strains were used:

Species	Strain	Genotype
S. typhimurium	TA1535	hisG46 rfa Δ *uvrB*

Species	Strain	Genotype
S. typhimurium	TA1537	hisC3076 rfa Δ *uvrB*
S. typhimurium	TA98	hisD3052 rfa Δ *uvrB* (pKM101)
S. typhimurium	TA100	hisG46 rfa Δ *uvrB* (pKM101)
E. coli	WP2 *uvrA* (pKM101)	TrpE Ochre *uvrA* (pKM101)
Source	Molecular Toxicology Incorporated, Boone, NC, USA (MolTox™)	
Growth Phase	Late log phase	

The strains TA1535, TA100, and WP2 *uvrA* pKM101 detect base change mutations. The strains TA1537 and TA98 detect frameshift mutations.

Bacteria inocula were used to prepare fresh cultures in 10 mL of nutrient broth (NB2, containing ampicillin for the pKM101 plasmid containing strains *S. typhimurium* strains TA98 and TA100 and *E. coli* WP2 *uvrA* (pKM101) to maintain the plasmid copy number). Bacteria were cultured for 10-12 hours in a shaking incubator at 37±2°C to yield 1-2x10^9 cells/mL.

The bacteria suspension was added to the Top Agar (containing trace amounts of the amino acids required for auxotrophy) at a volume of 100 uL.

Mammalian Oxidative Metabolizing System

Phenobarbital, 5 6 Benzoflavone induced rat liver post mitochondrial fraction (S9) from Molecular Toxicology Incorporated, USA (MolTox™) was used as an exogenous oxidative metabolizing system. Batches of S9 fraction stored as frozen aliquots at approximately -80°C were thawed immediately prior to use. S9 mix was prepared by the addition of S9 (10% v/v) to a NADPH generating system, which included NADP (3.15 mg/mL), glucose 6 phosphate (1.5 mg/mL), and 2% v/v of a saline solution containing $MgCl_2$ (81.3 mg/mL) and KCl (123 mg/mL) in phosphate buffer pH 7.4. For treatment in the presence of S9 mix, S9 mix was used at a final volume of 500 uL/plate. For treatment in the absence of S9 mix, an equivalent volume of sterile phosphate buffer pH 7.4 was added in place of the S9 mix.

Positive Control Formulations

The following positive controls (supplied by MolTox™ through Trinova Biochem GmbH, Giessen, Germany and Sigma Aldrich, Milano, Italy) were used and formulated as follows:

Bacterial Strain	Positive Control	Conc. (µg/plate)	Vehicle (Solvent)	S9-mix

TA98	2-Nitrofluorene (2NF)	2	Dimethyl Sulfoxide (DMSO)	No
TA1535, TA100	Sodium Azide (NaAz)	2	H_2O	No
TA1537	ICR-191	1	DMSO	No
WP2 *uvrA* (pKM101)	4-Nitroquinoline-1-oxide (4NQO)	1	DMSO	No
TA98	Benzo[a]pyrene (B[a]P)	1.25	DMSO	Yes
TA1535, TA1537, TA100, WP2 *uvrA* (pKM101)	2-Aminoanthracene (2AAN)	5	DMSO	Yes

Positive controls were prepared from frozen (approximately -20°C) stock solutions and stored at ambient temperature during the use.

Test Articles

The test consisted of 4 replicate plates for vehicle (DMSO) controls and 2 replicate plates for the test article and positive controls, treated in the absence and in the presence of S9-mix. A range of test article concentrations starting from 5 ug/plate to 5000 ug/plate was tested, as follows:

Species	**Strain**	**Test Item Concentrations (ug/plate)**	**S9-mix**
S. typhimurium	TA1535, TA1537, TA98 and TA100	5, 15, 50, 150, 500, 1500 and 5000	No
E. coli	WP2 *uvrA* (pKM101)		
S. typhimurium	TA1535, TA1537, TA98 and TA100		Yes
E. coli	WP2 *uvrA* (pKM101)		

The vehicle, test article and positive control formulations were added to plates at a volume of 100 uL/plate.

Plate Treatment and Incubation

Top agar was supplemented with trace amounts of histidine and biotin, or tryptophan, aliquoted (2 mL/plate), and maintained at 46±2°C. The appropriate bacterial suspension was added to 2 mL of top agar followed by the test article, or vehicle/positive control solutions, and sterile phosphate buffer pH 7.4 or S9-mix. This final treatment mixture was poured over minimal agar plates (Vögel Bonner plates) and incubated in the dark for approximately 64 hours at 37±2°C.

Plate Scoring and Analysis

At the end of the incubation period, plates were evaluated (by visual examination) for test article precipitation. Plates were scored electronically for bacterial colony formation using the colony counter ProtoCOL3 Synbiosis. Where test article precipitation occurred, the bacterial colony count

for each strain was performed manually and halted at the lowest treatment concentration that did not interfere with the manual scoring.

The scoring was followed by the inspection of the plates for signs of toxicity (i.e. reduced growth/diminution of background lawn, the presence of pin dot/pseudorevertant colonies, and/or a reduction in colony numbers).

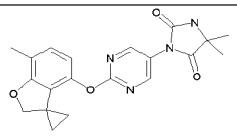
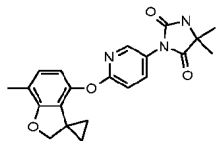
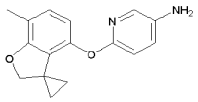
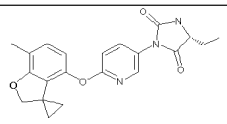
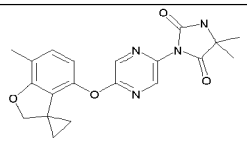
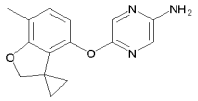
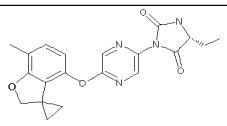
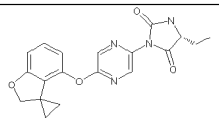
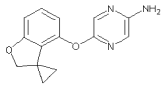
If the data for any treatment concentration show a response ≥2 times the concurrent vehicle control value for TA98, TA100, and WP2 uvrA (pKM101), or ≥3 times the concurrent vehicle control value for TA1535 and TA1537, in conjunction with a dose related response, the result should be considered positive. Results that only partially satisfy these criteria or where the data for any strain show a dose related response, but do not exceed the 2 or 3 fold threshold as detailed, are considered equivocal.

The following acceptance criteria were applied:

1. The highest concentration tested should be 5000 ug/plate, or limited by solubility of test item in the vehicle.
2. If the test item solubility is a limiting factor, the maximum concentration chosen for plate scoring would be the lowest concentration at which the test item precipitation is observed on treatment plates at the end of the incubation period and that does not interfere with the scoring.

If toxicity is a limiting factor, the maximum concentration evaluable for gene mutation would be the lowest concentration at which signs of significant bacterial toxicity are observed during plate scoring.

Results

Ex.	Compound	Ames Result	Aniline	Ames Result
RE5		Non-mutagenic	Not tested	Not tested
RE6		Non-mutagenic		Mutagenic for TA1535 in the presence of metabolic activation at 150 ug/plate
RE11		Non-mutagenic		
1		Non-mutagenic		Non-mutagenic
9		Non-mutagenic		
10		Non-mutagenic		Non-mutagenic

The aniline associated with RE6/RE11, which has been shown to be a degradant under certain conditions, was found to be mutagenic. This finding presents a risk in the future development of RE6/RE11 and also for compounds which could produce related anilines (e.g. (5R)-5-ethyl-3-(6-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxy-3-pyridyl)imidazolidine-2,4-dione, i.e. RE13). Compounds which may be distinguished on the basis of their associated anilines are advantageous.

Anilines for Examples 1, 9 and 10 are non-mutagenic, which may be expected to apply to other compounds of the invention which could produce related anilines.

Additional animal models

Patent applications WO2011/069951, WO2012/076877, WO2012/168710, WO2013/083994 WO2013/175215 and WO2013/182851 (all incorporated by reference for the purpose of illustrating the potential utility of the compounds and providing animal models for the testing of compounds) 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 and bipolar disorders.

Patent application WO2013/175211 (incorporated by reference for the purpose of illustrating the potential utility of the compounds and providing animal models for the testing of compounds) 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.

Glait et al 2018, Anderson et al 2018 and Chamber et al 2018 demonstrate the efficacy of a modulator of Kv3.1 and Kv3.2 in hearing associated models.

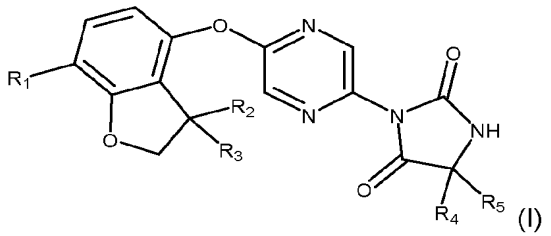
Patent application WO2017/098254 (incorporated by reference for the purpose of illustrating the potential utility of the compounds and providing animal models for the testing of compounds) demonstrates the efficacy of a compound which is a modulator of Kv3.1 and Kv3.2 in models of neuropathic and inflammatory pain.

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

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

Clauses of the invention:

Clause 1 - A compound of formula (I):



(I)

wherein:

R_1 is H or methyl;

R_2 and R_3 are both methyl, or R_2 and R_3, together with the carbon atom to which they are attached, are a spirocyclopropyl ring;

R_4 is methyl or ethyl;

R_5 is H or methyl;

or R_4 and R_5, together with the carbon atom to which they are attached, form a C_3-C_4 spiro carbocyclyl;

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

Clause 2 - The compound according to clause 1 wherein R_1 is H.

Clause 3 -. The compound according to clause 1 wherein R_1 is methyl.

Clause 4 - The compound according to any one of clauses 1 to 3, wherein R_2 and R_3 are a spiro cyclopropyl ring.

Clause 5 - The compound according to any one of clauses 1 to 3, wherein R_2 is methyl and R_3 is methyl

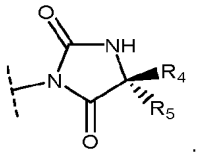
Clause 6 - The compound according to any one of clauses 1 to 5, wherein R_4 is methyl.

Clause 7 - The compound according to any one of clauses 1 to 5, wherein R_4 is ethyl.

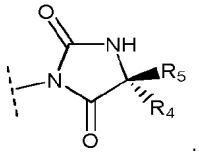
Clause 8 - The compound according to any one of clauses 1 to 7, wherein R_5 is H.

Clause 9 - The compound according to any one of clauses 1 to 7, wherein R_5 is methyl.

Clause 10 - The compound according to any one of clauses 1 to 9 wherein when R_4 and R_5 are different and they have the following stereochemical arrangement:



Clause 11 - The compound according to any one of clauses 1 to 9 wherein when R_4 and R_5 are different and they have the following stereochemical arrangement:



Clause 12 - The compound according to any one of clauses 1 to 5, wherein R_4 and R_5, together with the carbon atom to which they are attached, form a spirocyclopropyl.

Clause 13 - The compound according to any one of clauses 1 to 5, wherein R_4 and R_5, together with the carbon atom to which they are attached, form a spirocyclobutyl.

Clause 14 - The compound according to clause 1 selected from the group consisting of:
5,5-dimethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione;
3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-5,5-dimethyl-imidazolidine-2,4-dione;
(5R)-5-ethyl-5-methyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)imidazolidine-2,4-dione;
5,5-dimethyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)imidazolidine-2,4-dione;
(5R)-5-ethyl-5-methyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione;
(5R)-3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;
5,5-dimethyl-3-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]imidazolidine-2,4-dione;
(5R)-5-ethyl-5-methyl-3-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]imidazolidine-2,4-dione;
(5R)-5-ethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione;

(5R)-5-ethyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)imidazolidine-2,4-dione;
(5R)-3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-5-ethyl-imidazolidine-2,4-dione;
(5R)-5-ethyl-3-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]imidazolidine-2,4-dione;
7-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]-5,7-diazaspiro[3.4]octane-6,8-dione;
6-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]-4,6-diazaspiro[2.4]heptane-5,7-dione;
(5S)-5-ethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione;
or a salt and/or solvate thereof and/or derivative thereof.

Clause 15 - The compound according to clause 1 which is:
5,5-dimethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione.

Clause 16 - The compound according to clause 1 which is:
3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-5,5-dimethyl-imidazolidine-2,4-dione.

Clause 17 - The compound according to clause 1 which is:
(5R)-5-ethyl-5-methyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)imidazolidine-2,4-dione.

Clause 18 - The compound according to clause 1 which is:
5,5-dimethyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)imidazolidine-2,4-dione.

Clause 19 - The compound according to clause 1 which is:
(5R)-5-ethyl-5-methyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione.

Clause 20 - The compound according to clause 1 which is:

(5R)-3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-5-ethyl-5-methyl-imidazolidine-2,4-dione.

Clause 21 - The compound according to clause 1 which is:
5,5-dimethyl-3-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]imidazolidine-2,4-dione.

Clause 22 - The compound according to clause 1 which is:
(5R)-5-ethyl-5-methyl-3-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]imidazolidine-2,4-dione.

Clause 23 - The compound according to clause 1 which is:
(5R)-5-ethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione.

Clause 24 - The compound according to clause 1 which is:
(5R)-5-ethyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)imidazolidine-2,4-dione.

Clause 25 - The compound according to clause 1 which is:
(5R)-3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-5-ethyl-imidazolidine-2,4-dione.

Clause 26 - The compound according to clause 1 which is:
(5R)-5-ethyl-3-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]imidazolidine-2,4-dione.

Clause 27 - The compound according to clause 1 which is:
7-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]-5,7-diazaspiro[3.4]octane-6,8-dione.

Clause 28 - The compound according to clause 1 which is:
6-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]-4,6-diazaspiro[2.4]heptane-5,7-dione.

Clause 29 - The compound according to clause 1 which is:

(5S)-5-ethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione.

Clause 30 - The compound of formula (I) according to any one of clauses 1 to 29, or a pharmaceutically acceptable salt and/or solvate thereof.

Clause 31 - The compound according to any one of clauses 1 to 30 for use as a medicament.

Clause 32 - The compound according to clause 31 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 dementia and Parkinson's disease.

Clause 33 - The compound according to clause 31 for use in the prophylaxis or treatment of schizophrenia.

Clause 34 - The compound according to clause 31 for use in the prophylaxis or treatment of hearing disorders.

Clause 35 - The compound according to clause 31 for use in the prophylaxis or treatment of pain.

Clause 36 - The compound according to clause 31 for use in the treatment of Fragile X.

Clause 37 - 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 in need thereof an effective amount of a compound according to any one of clauses 1 to 30.

Clause 38 - A method for the prophylaxis or treatment of schizophrenia, comprising administering to a subject in need thereof a compound according to any one of clauses 1 to 30.

Clause 39 - A method for the prophylaxis or treatment of hearing disorders, comprising administering to a subject in need thereof a compound according to any one of clauses 1 to 30.

Clause 40 - A method for the prophylaxis or treatment of pain, comprising administering to a subject in need thereof a compound according to any one of clauses 1 to 30.

Clause 41 - A method for the treatment of Fragile X, comprising administering to a subject in need thereof a compound according to any one of clauses 1 to 30.

Clause 42 - Use of a compound according to any one of clauses 1 to 30 in the manufacture of a medicament 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.

Clause 43 - Use of a compound according to any one of clauses 1 to 30 in the manufacture of a medicament for the prophylaxis or treatment of schizophrenia.

Clause 44 - Use of a compound according to any one of clauses 1 to 30 in the manufacture of a medicament for the prophylaxis or treatment of hearing disorders.

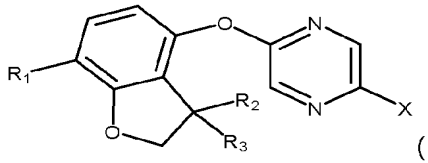
Clause 45 - Use of a compound according to any one of clauses 1 to 30 in the manufacture of a medicament for the prophylaxis or treatment of pain.

Clause 46 - Use of a compound according to any one of clauses 1 to 30 in the manufacture of a medicament for the treatment of Fragile X.

Clause 47 - A pharmaceutical composition comprising a compound of any one of clauses 1 to 30 and a pharmaceutically acceptable carrier or excipient.

Clause 48 - The compound according to any one of clauses 1 to 30 for use in combination with a further pharmaceutically acceptable active ingredient.

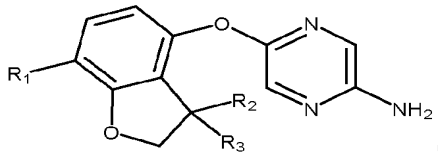
Clause 49 - A compound of formula (II) or (XVI):



(II),

wherein R_1, R_2 and R_3 are as defined in clause 1, X is halo, such as Br.

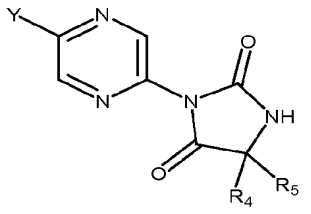
Clause 50 - A compound of formula (XVI):



(XVI),

wherein R_1, R_2 and R_3 are as defined in clause 1.

Clause 51 - A compound of formula (IV):



(IV)

wherein R_4 and R_5 are as defined in clause 1, Y is halo, such as Cl.

Clause 52 - A derivative of a compound of formula (I), or salt and/or solvate thereof, according to any one of clauses 1 to 30 functionalised via the secondary nitrogen

of the hydantoin or via the secondary nitrogen of the triazolone with a group L, wherein L is selected from the groups consisting of:

a) $-PO(OH)O^- \bullet M^+$, wherein M^+ is a pharmaceutically acceptable monovalent counterion,

b) $-PO(O^-)_2 \bullet 2M^+$,

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

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

e) $-CH(R^X)-PO(O^-)_2 \bullet 2M^+$,

f) $-CH(R^X)-PO(O^-)_2 \bullet D^{2+}$,

g) $-SO_3^- \bullet M^+$,

h) $-CH(R^X)-SO_3^- \bullet M^+$, and

i) $-CO-CH_2CH_2-CO_2 \bullet M^+$.

Clause 53 - The compound according to any one of clauses 1 to 36, which is in natural isotopic form.

Clause 54 - The compound, method, use, composition or derivative according to any one of clauses 1 to 48, 52 or 53, for oral administration.

Clause 55 - The compound, method, use, composition or derivative according to any one of clauses 1 to 48 or 52 to 54 for administration at 2 to 400 mg per day, such as 2 to 300 mg per day, especially 5 to 250 mg per day.

Clause 56 - The compound, method, use, composition or derivative according to any one of clauses 1 to 48 or 52 to 55 for administration once or twice per day.

Clause 57 - The compound according to clause 56 for administration once per day.

Clause 58 - The compound according to clause 56 for administration twice per day.

Clause 59 - The compound, method, use, composition or derivative according to any one of clauses 1 to 48 or 52 to 58 for administration for a period of at least three months.

Clause 60 - The compound, method, use, composition or derivative according to any one of clauses 1 to 48 or 52 to 58 for administration to a human subject.

Clause 61 - The compound, method, use, composition or derivative according to clause 60 for administration to a human adult, such as aged 18 to 65.

Clause 62 - The compound, method, use, composition or derivative according to clause 60 for administration to a human aged 66 years old or older.

Clause 63 - The compound, method, use, composition or derivative according to clause 60 to a human subject of less than 18 years of age, such as 4 to 17 years old.

Clause 64 - The compound, method, use, composition or derivative according to according to any one of clauses 1 to 48, 52, 53 or 59 to 63 wherein a compound of formula (I) or a pharmaceutically acceptable, salt, solvate and/or derivative thereof is delivered by a patch or implant.

References

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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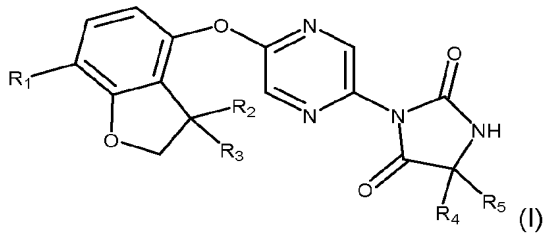
CLAIMS

1. A compound of formula (I):



(I)

wherein:

R_1 is H or methyl;

R_2 and R_3 are both methyl, or R_2 and R_3, together with the carbon atom to which they are attached, are a spirocyclopropyl ring;

R_4 is methyl or ethyl;

R_5 is H or methyl;

or R_4 and R_5, together with the carbon atom to which they are attached, form a C_3-C_4 spiro carbocyclyl;

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

2. The compound according to claim 1 wherein R_1 is H.

3. The compound according to claim 1 wherein R_1 is methyl.

4. The compound according to any one of claims 1 to 3, wherein R_2 and R_3 are a spiro cyclopropyl.

5. The compound according to any one of claims 1 to 3, wherein R_2 is methyl and R_3 is methyl

6. The compound according to any one of claims 1 to 5, wherein R_4 is methyl.

7. The compound according to any one of claims 1 to 5, wherein R_4 is ethyl.

8. The compound according to any one of claims 1 to 7, wherein R_5 is H.

9. The compound according to any one of claims 1 to 7, wherein R_5 is methyl.

10. The compound according to any one of claims 1 to 5, wherein R_4 and R_5, together with the carbon atom to which they are attached, form a spirocyclopropyl.

11. The compound according to any one of claims 1 to 5, wherein R_4 and R_5, together with the carbon atom to which they are attached, form a spirocyclobutyl.

12. The compound according to claim 1 selected from the group consisting of:
5,5-dimethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione;
3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-5,5-dimethyl-imidazolidine-2,4-dione;
(5R)-5-ethyl-5-methyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)imidazolidine-2,4-dione;
5,5-dimethyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)imidazolidine-2,4-dione;
(5R)-5-ethyl-5-methyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione;
(5R)-3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-5-ethyl-5-methyl-imidazolidine-2,4-dione;
5,5-dimethyl-3-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]imidazolidine-2,4-dione;
(5R)-5-ethyl-5-methyl-3-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]imidazolidine-2,4-dione;
(5R)-5-ethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione;
(5R)-5-ethyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)imidazolidine-2,4-dione;
(5R)-3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-5-ethyl-imidazolidine-2,4-dione;
(5R)-5-ethyl-3-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]imidazolidine-2,4-dione;
7-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]-5,7-diazaspiro[3.4]octane-6,8-dione;
6-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]-4,6-diazaspiro[2.4]heptane-5,7-dione;

(5S)-5-ethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione

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

13. The compound according to claim 1 which is:
5,5-dimethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione.

14. The compound according to claim 1 which is:
3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-5,5-dimethyl-imidazolidine-2,4-dione.

15. The compound according to claim 1 which is:
(5R)-5-ethyl-5-methyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)imidazolidine-2,4-dione.

16. The compound according to claim 1 which is:
5,5-dimethyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)imidazolidine-2,4-dione.

17. The compound according to claim 1 which is:
(5R)-5-ethyl-5-methyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione.

18. The compound according to claim 1 which is:
(5R)-3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-5-ethyl-5-methyl-imidazolidine-2,4-dione.

19. The compound according to claim 1 which is:
5,5-dimethyl-3-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]imidazolidine-2,4-dione.

20. The compound according to claim 1 which is:
(5R)-5-ethyl-5-methyl-3-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]imidazolidine-2,4-dione.

21. The compound according to claim 1 which is:
(5R)-5-ethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione.

22. The compound according to claim 1 which is:
(5R)-5-ethyl-3-(5-spiro[2H-benzofuran-3,1'-cyclopropane]-4-yloxypyrazin-2-yl)imidazolidine-2,4-dione.

23. The compound according to claim 1 which is:
(5R)-3-[5-[(3,3-dimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]-5-ethyl-imidazolidine-2,4-dione.

24. The compound according to claim 1 which is:
(5R)-5-ethyl-3-[5-[(3,3,7-trimethyl-2H-benzofuran-4-yl)oxy]pyrazin-2-yl]imidazolidine-2,4-dione.

25. The compound according to claim 1 which is:
7-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]-5,7-diazaspiro[3.4]octane-6,8-dione.

26. The compound according to claim 1 which is:
6-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]-4,6-diazaspiro[2.4]heptane-5,7-dione.

27. The compound according to claim 1 which is:
(5S)-5-ethyl-3-[5-(7-methylspiro[2H-benzofuran-3,1'-cyclopropane]-4-yl)oxypyrazin-2-yl]imidazolidine-2,4-dione.

28. The compound according to any one of claims 1 to 27 for use as a medicament.

29. The compound according to any one of claims 1 to 28 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 dementia and Parkinson's disease.

30. Use of a compound according to any one of claims 1 to 27 in the manufacture of a medicament 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.

31. 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 in need thereof an effective amount of a compound according to any one of claims 1 to 27.

32. A pharmaceutical composition comprising a compound according to any one of claims 1 to 27 and a pharmaceutically acceptable carrier or excipient.

33. The compound, use, method or composition according to any one of claims 1 to 32, wherein the compound is administered orally.

34. The compound, use, method or composition according to any one of claims 1 to 33, wherein the compound is administered at 2 to 400 mg per day, such as 2 to 300 mg per day, especially 5 to 250 mg per day.

35. The compound, use, method or composition according to any one of claims 1 to 34, wherein the compound is administered once or twice per day.

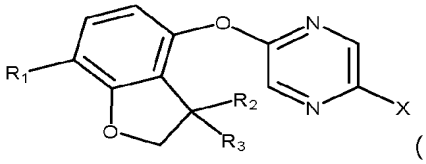
36. The compound, use, method or composition according to claim 35 wherein the compound is administered once per day.

37. The compound, use, method or composition according to claim 35 wherein the compound is administered twice per day.

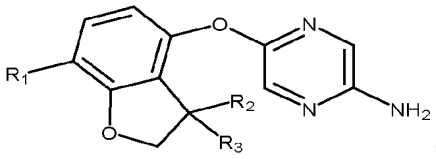
38. The compound, use, method or composition according to any one of claims 1 to 37, wherein the compound is administered for a period of at least three months.

39. The compound, use, method or composition according to any one of claims 1 to 32, wherein the compound 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.

40. A compound of formula (II) or (XVI):



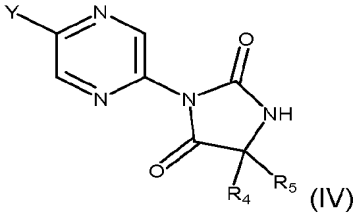
(II),



(XVI),

wherein R_1, R_2 and R_3 are as defined in claim 1, X is halo, such as Br.

41. A compound of formula (IV):



(IV)

wherein R_4 and R_5 are as defined in claim 1, Y is halo, such as Cl.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2020/050268

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/04 C07D405/12 C07D405/14 A61P25/00 A61P27/00
A61K31/497
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/076877 A1 (AUTIFONY THERAPEUTICS LTD [GB]; ALVARO GIUSEPPE [IT] ET AL.) 14 June 2012 (2012-06-14) cited in the application claims 1-43; examples 9, 10, 15, 64, 69, 70	1-41
E	WO 2020/079422 A1 (AUTIFONY THERAPEUTICS LTD [GB]) 23 April 2020 (2020-04-23) claims 1-34	1-33,40, 41

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/	Authorized officer
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1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2020/050268

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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A61K 31/497(2006.01)

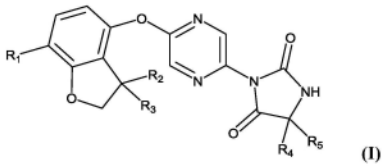
权利要求书4页 说明书75页

(54)发明名称

Kv3调节剂

(57)摘要

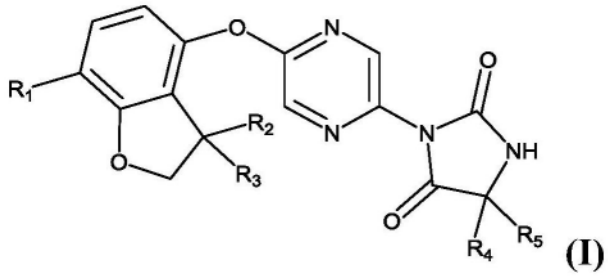
式(I)的化合物和相关方面。



(I)

CN 115066424 A

1.式(I)的化合物：



(I)

其中：

R_1为H或甲基；

R_2和R_3均为甲基，或R_2和R_3与所连接的碳原子一起为螺环丙基环；

R_4为甲基或乙基；

R_5为H或甲基；

或R_4和R_5与所连接的碳原子一起形成C_3-C_4螺碳环基；

或其盐和/或溶剂化物和/或衍生物。

2.权利要求1的化合物，其中R_1为H。

3.权利要求1的化合物，其中R_1为甲基。

4.权利要求1-3任一项的化合物，其中R_2和R_3为螺环丙基。

5.权利要求1-3任一项的化合物，其中R_2为甲基，且R_3为甲基。

6.权利要求1-5任一项的化合物，其中R_4为甲基。

7.权利要求1-5任一项的化合物，其中R_4为乙基。

8.权利要求1-7任一项的化合物，其中R_5为H。

9.权利要求1-7任一项的化合物，其中R_5为甲基。

10.权利要求1-5任一项的化合物，其中R_4和R_5与所连接的碳原子一起形成螺环丙基。

11.权利要求1-5任一项的化合物，其中R_4和R_5与所连接的碳原子一起形成螺环丁基。

12.权利要求1的化合物，选自：

5,5-二甲基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮；

3-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]-5,5-二甲基-咪唑烷-2,4-二酮；

(5R)-5-乙基-5-甲基-3-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)咪唑烷-2,4-二酮；

5,5-二甲基-3-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)咪唑烷-2,4-二酮；

(5R)-5-乙基-5-甲基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮；

(5R)-3-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]-5-乙基-5-甲基-咪唑烷-2,4-二酮；

5,5-二甲基-3-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]咪唑烷-2,4-二酮；

(5R)-5-乙基-5-甲基-3-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]咪唑烷-2,4-二酮；

(5R)-5-乙基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮；

(5R)-5-乙基-3-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)咪唑烷-2,4-二酮；

(5R)-3-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]-5-乙基-咪唑烷-2,4-二酮；

(5R)-5-乙基-3-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]咪唑烷-2,4-二酮；

7-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]-5,7-二氮杂螺[3.4]辛烷-6,8-二酮；

6-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]-4,6-二氮杂螺[2.4]庚烷-5,7-二酮；

(5S)-5-乙基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮；

或其盐和/或其溶剂化物和/或其衍生物。

13.权利要求1的化合物,其为：

5,5-二甲基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮。

14.权利要求1的化合物,其为：

3-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]-5,5-二甲基-咪唑烷-2,4-二酮。

15.权利要求1的化合物,其为：

(5R)-5-乙基-5-甲基-3-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)咪唑烷-2,4-二酮。

16.权利要求1的化合物,其为：

5,5-二甲基-3-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)咪唑烷-2,4-二酮。

17.权利要求1的化合物,其为：

(5R)-5-乙基-5-甲基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮。

18.权利要求1的化合物,其为：

(5R)-3-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]-5-乙基-5-甲基-咪唑烷-2,4-二酮。

19.权利要求1的化合物,其为：

5,5-二甲基-3-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]咪唑烷-2,4-二酮。

20.权利要求1的化合物,其为：

(5R)-5-乙基-5-甲基-3-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]咪唑烷-2,4-二酮。

21.权利要求1的化合物,其为:

(5R)-5-乙基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮。

22.权利要求1的化合物,其为:

(5R)-5-乙基-3-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)咪唑烷-2,4-二酮。

23.权利要求1的化合物,其为:

(5R)-3-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]-5-乙基-咪唑烷-2,4-二酮。

24.权利要求1的化合物,其为:

(5R)-5-乙基-3-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]咪唑烷-2,4-二酮。

25.权利要求1的化合物,其为:

7-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]-5,7-二氮杂螺[3.4]辛烷-6,8-二酮。

26.权利要求1的化合物,其为:

6-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]-4,6-二氮杂螺[2.4]庚烷-5,7-二酮。

27.权利要求1的化合物,其为:

(5S)-5-乙基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮。

28.权利要求1-27任一项的化合物,用作药物。

29.权利要求1-28任一项的化合物,用于预防或治疗疾病或病症,所述疾病或病症选自听力障碍、精神分裂症、抑郁症和情绪障碍、双相情感障碍、物质滥用障碍、焦虑症、睡眠障碍、听觉过敏和响度感知障碍、梅尼埃病、平衡障碍和内耳障碍、冲动控制障碍、人格障碍、注意力缺陷/多动障碍、孤独症谱群疾病、进食障碍、认知障碍、共济失调,疼痛例如神经性疼痛、炎性疼痛和混杂的疼痛,路易体痴呆和帕金森病。

30.权利要求1-27任一项的化合物在制备用于预防或治疗疾病或病症的药物中的用途,所述疾病或病症选自听力障碍、精神分裂症、抑郁症和情绪障碍、双相情感障碍、物质滥用障碍、焦虑症、睡眠障碍、听觉过敏和响度感知障碍、梅尼埃病、平衡障碍和内耳障碍、冲动控制障碍、人格障碍、注意力缺陷/多动障碍、孤独症谱群疾病、进食障碍、认知障碍、共济失调,疼痛例如神经性疼痛、炎性疼痛和混杂的疼痛,路易体痴呆和帕金森病。

31.用于预防或治疗疾病或病症的方法,所述疾病或病症选自听力障碍、精神分裂症、抑郁症和情绪障碍、双相情感障碍、物质滥用障碍、焦虑症、睡眠障碍、听觉过敏和响度感知障碍、梅尼埃病、平衡障碍和内耳障碍、冲动控制障碍、人格障碍、注意力缺陷/多动障碍、孤独症谱群疾病、进食障碍、认知障碍、共济失调,疼痛例如神经性疼痛、炎性疼痛和混杂的疼痛,路易体痴呆和帕金森病,该方法包含向有此需要的个体施用有效量的权利要求1-27任

一项的化合物。

32.药物组合物,包含权利要求1-27任一项的化合物和药学上可接受的载体或赋形剂。

33.权利要求1-32任一项的化合物、用途、方法或组合物,其中通过口服施用所述化合物。

34.权利要求1-33任一项的化合物、用途、方法或组合物,其中以2-400mg/天,例如2-300mg/天,尤其是5-250mg/天施用所述化合物。

35.权利要求1-34任一项的化合物、用途、方法或组合物,其中以每天1次或2次施用所述化合物。

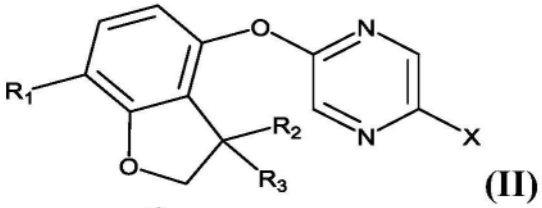
36.权利要求35的化合物、用途、方法或组合物,其中以每天1次施用所述化合物。

37.权利要求35的化合物、用途、方法或组合物,其中以每天2次施用所述化合物。

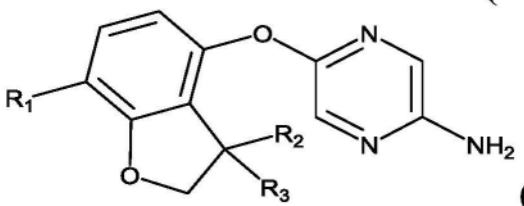
38.权利要求1-37任一项的化合物、用途、方法或组合物,其中将所述化合物施用至少3个月的时期。

39.权利要求1-32任一项的化合物、用途、方法或组合物,其中以2-400mg/天,例如2-300mg/天,尤其是5-250mg/天通过口服施用所述化合物,每天1次或2次。

40.式(II)或(XVI)的化合物:



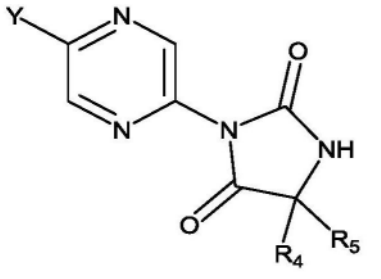
(II)



(XVI),

其中R_1、R_2和R_3如权利要求1中所定义,X为卤素,例如Br。

41.式(IV)的化合物:



(IV)

其中R_4和R_5如权利要求1中所定义,Y为卤素,例如Cl。

Kv3调节剂

技术领域

[0001] 本发明涉及新的化合物、包含它们的药物组合物及其在疗法中的用途，特别是在预防或治疗听力障碍(包括听力损失和耳鸣)以及精神分裂症、物质滥用障碍、疼痛和脆性X染色体综合征中的用途。

[0002] 发明背景

[0003] Kv3电压门控钾通道家族包括四个成员，Kv3.1、Kv3.2、Kv3.3和Kv3.4。Kv3通道通过将质膜去极化至比-20mV更正的电压而被激活；此外，通道在膜复极化时迅速失活。这些生物物理性质确保通道朝向神经元动作电位的去极化相的峰值打开以启动复极化。由Kv3通道介导的动作电位的快速终止允许神经元更快地恢复以达到亚阈值膜电位，从该亚阈值膜电位可以触发进一步的动作电位。作为结果，某些神经元中Kv3通道的存在有助于它们在高频下激发的能力(Rudy等人,2001)。Kv3.1-3亚型在CNS中占优势，而Kv3.4通道也在骨骼肌和交感神经元中发现(Weiser等人,1994)。Kv3.1-3通道亚型由皮质和海马脑区域(例如Chow等人,1999;Martina等人,1998;McDonald等人,2006;Chang等人,2007)、丘脑(例如Kasten等人,2007)、小脑(例如Sacco等人,2006;Puente等人,2010)和听觉脑干核(Li等人,2001)中的中间神经元的亚类所差异表达。

[0004] 已经显示，四乙基铵(TEA)在低毫摩尔浓度下抑制所述通道(Rudy等人,2001)，并且已经显示，来自海葵(海葵(Anemonia sulcata))的血液抑制物质(BDS)毒素(Diochot等人,1998)以高亲和力选择性地抑制Kv3通道(Yeung等人,2005)。

[0005] Kv3通道是小脑功能的重要决定因素，小脑是对运动控制重要的脑区域(Joho等人,2009)。其中缺失一种或多种Kv3亚型的小鼠的表征表明，Kv3.1的缺失导致运动活动增加、脑电图活动改变和碎片化睡眠模式(Joho等人,1999)。Kv3.2的缺失导致癫痫发作阈值的降低和改变的皮层脑电图活动(Lau等人,2000)。Kv3.3的缺失与轻度共济失调和运动缺陷相关(McMahon等人,2004)。Kv3.1和Kv3.3的双缺失产生严重的表型，其特征在于自发性癫痫发作、共济失调和对乙醇作用的敏感性增加(Espinosa等人,2001;Espinosa等人,2008)。Kv3.1基因(KCNC1)中的自发突变引起进行性肌阵挛性癫痫(Muona等人,2014)。人类Kv3.3基因(KCNC3)突变与脊髓小脑性共济失调(SCA13)的形式相关(Figueroa等人,2010)。

[0006] 双相性精神障碍、精神分裂症、焦虑和癫痫是中枢神经系统的严重障碍，其与抑制性中间神经元和γ-氨基丁酸(GABA)传递的功能降低相关(Reynolds等人,2004;Benes等人,2008;Brambilla等人,2003;Aroniadou-Anderjaska等人,2007;Ben-Ari,2006)。在皮质和海马中表达Kv3通道的鼠骨肌钙蛋白阳性篮状细胞在局部环路内产生反馈抑制中起关键作用(Markram等人,2004)。鉴于在这些回路中兴奋性突触输入相对于对谷氨酸能锥体神经元的抑制性输入的相对优势，提供抑制性输入的中间神经元的快速激发对于确保平衡抑制是必需的。此外，抑制性输入的准确定时对于维持网络同步是必要的，例如，在生成与认知功能相关联的γ频率场电位振荡中(Fisahn等人,2005;Engel等人,2001)。值得注意的是，在精神分裂症患者中观察到γ振荡的减少(Spencer等人,2004)，并且证据表明，在死亡前至少2个月未服用抗精神病药物的精神分裂症患者的背外侧前额叶皮质中是Kv3.1而不是

Kv3.2的表达减少(Yanagi等人,2014)。因此,可预期Kv3通道的正调节剂可增强脑中特定组的快速激发的神经元的激发能力。这些作用在与这些神经元组的异常活性相关的疾病中可能是有益的。此外,已经显示Kv3.2通道由CNS中的主要昼夜节律起搏器视上交叉核(SCN)的神经元表达(Schulz等人,2009)。

[0007] Kv3家族的电压门控离子通道在听觉脑干核中以高水平表达(Li等人,2001),其中它们允许将听觉信息从耳蜗传递到高级脑区域的神经元的快速激发。已经表明,听觉脑干神经元中Kv3.1和Kv3.3通道的磷酸化有助于对声音水平的快速生理适应,这可能在暴露于噪声期间起到保护作用(Desai等人,2008;Song等人,2005)。在听力受损小鼠中观察到中枢听觉神经元中Kv3.1通道表达的丧失(von Hehn等人,2004);此外,Kv3.1表达的下降可能与老年小鼠的听力损失有关(Jung等人2005),并且Kv3通道功能的损失也可能在噪声创伤诱导的听力损失之后出现(Pilati等人,2012)。此外,听觉脑干网络的病理可塑性可能有助于许多患有不同类型听力损失的人所经历的症状。最近的研究表明,Kv3.1通道功能和表达的调节在控制听觉神经元兴奋性中具有主要作用(Kaczmarek等人,2005;Anderson等人,2018;Glait等人,2018;Olsen等人,2018,Chambers等人,2017),表明这种机制可以解释引起耳鸣的一些可塑性变化。由于从脑干到听觉皮质的中枢听觉通路的适应性变化,噪声诱导的听力损失之后可能会出现耳鸣(Roberts等人,2010)。Kv3.1和/或Kv3.2通道在许多这些回路中表达,并且有助于可控制这些回路功能的GABA能抑制性中间神经元的功能。

[0008] 已知Kv3.1和/或Kv3.2调节剂可用于治疗疼痛(WO2017/098254)。在最广泛的意义上,疼痛可以分为急性痛和慢性痛。急性痛被定义为自限性疼痛,并且通常需要治疗不超过几周,例如术后或急性肌肉骨骼痛,例如骨折(美国食品和药品管理局,2014)。慢性痛可以定义为在初始创伤消退后持续超过1个月的疼痛,或持续超过3个月的疼痛。慢性痛通常没有明确的原因,并且许多其他健康问题如疲劳、抑郁、失眠、情绪变化和运动减少通常伴随慢性痛。

[0009] 慢性痛可以细分为以下组:神经性疼痛、慢性肌肉骨骼痛和混杂的慢性痛。神经性疼痛通常伴随组织损伤,并且由神经系统(外周神经系统和/或中枢神经系统)的损伤引发或引起,例如截肢、中风、糖尿病或多发性硬化。慢性肌肉骨骼痛可以是诸如骨关节炎和慢性腰背痛的疾病的症状,并且可以在肌肉组织损伤以及区域创伤(例如骨折、扭伤和脱位)后发生。混杂的慢性痛包括所有其他类型的长期疼痛,并且包括非神经性疼痛病症,例如癌症疼痛和纤维肌痛以及头痛和肌腱炎。

[0010] 慢性痛是高度不同种类的病症,其仍然是最麻烦和难以管理的临床适应证之一(McCarberg等人,2008;Woolf,2010;Finnerup等人,2015)。尽管有多年的研究和药物开发,但在确认可在功效上匹配阿片样物质且没有显著副作用和依赖性风险的治疗方面几乎没有进展。电压门控离子通道已经成为管理特定疼痛适应证、特别是神经性疼痛状态的重要靶标。此外,特定离子通道中的遗传突变与一些慢性疼痛病症有关(Bennett等人,2014)。正在作为药物靶标探索的电压门控离子通道的实例包括:钠通道(特别是NaV1.7)-Sun等人,2014;Dib-Hajj等人,2013;N-型钙通道-Zamponi等人,2015;Kv7钾通道-Devulder,2010;Wickenden等人,2009;和SLACK-Lu等人,2015。

[0011] 这些方法的潜在假设在于慢性疼痛状态与外周感觉神经元的兴奋性增加和/或异常放电相关,特别是参与疼痛感觉刺激的传递的神经元,例如背根神经节的C-纤维和脊髓

内的特定回路(Baranauskas等人,1998;Cervero,2009;Woolf等人,2011;Baron等人,2013)。神经性和炎性慢性痛的动物模型为该假设提供了主要支持,不过仍然缺乏因果关系的证明(Cervero,2009)。

[0012] 靶向于过度兴奋性的药物,例如钠通道阻滞剂(例如CNV1014802、拉莫三嗪、卡马西平和局部麻醉剂)、Kv7正调节剂(例如氟哌汀(flupertine)和瑞替加滨)和N-型钙通道调节剂(例如与N-型钙通道的α2δ亚单位相互作用的加巴喷丁和衍生自锥螺毒素的齐康尼肽(ziconitide))在炎性和/或神经性疼痛模型中显示出功效。然而,在这些药物中,存在临床功效的混合证据,例如平衡功效和增加的对中枢神经系统副作用负担。在动物模型中的功效和在人类中的功效之间的差异可能是由于一系列因素,但是特别地,在人类中可实现的药物浓度(由于差的耐受性)和人类疼痛状况的不同种类可能是主要的原因。对于疼痛适应证,还需要鉴定靶标,通过该靶标可以实现疼痛缓解,同时具有降低的耐受性或快速耐受性以及降低的滥用倾向和/或依赖性风险。

[0013] 因此,改善疼痛的药理学管理关注可以递送良好效力、具有降低的副作用负担、降低的耐受性或快速耐受性以及降低的滥用倾向和/或依赖性风险的机制。

[0014] 最近,Kv3.4通道已成为治疗慢性痛的关注靶标。Kv3.4通道在背根神经节的神经元上表达(Ritter等人,2012;Chien等人,2007),其中它们主要在感觉C-纤维上表达(Chien等人,2007)。Kv3通道也由脊髓中神经元的特定子集表达。具体地,已经在啮齿动物脊髓中鉴定了Kv3.1b(Deuchars等人,2001;Brooke等人,2002)、Kv3.3(Brooke等人,2006)和Kv3.4亚单位(Brooke等人,2004),不过,并不总是与涉及感觉处理的回路相关。Kv3通道可能形成脊髓神经元(包括运动神经元)的放电特性。

[0015] 此外,最近的研究显示在DRG伤害感受器中表达的Kv3.4通道对谷氨酸能突触传递具有显著影响(Muqeem等人,2018)。动物模型数据表明,在与对疼痛刺激的超敏反应相关的脊髓损伤后,DRG神经元中Kv3.4通道表面表达下调(Ritter等人,2015;Zemel等人,2017;Zemel等人,2018)。类似地,已经观察到在脊髓结扎后啮齿动物的DRG中存在Kv3.4表达的下调(Chien等人,2007)。后一项研究还表明,鞘内给予大鼠反义寡核苷酸以抑制Kv3.4的表达导致对机械刺激的超敏反应。已经表明,Kv3.4通道失活可能受到通道的蛋白激酶C依赖性磷酸化的影响,并且这种生理机制可能允许DRG神经元响应于疼痛刺激而改变其放电特征(Ritter等人,2012)。这些研究表明机械性异常性疼痛的出现与Kv3.4通道表达或功能的降低之间的因果关系。在这些研究的任何一个中都没有评估在SC或DRG神经元中Kv3.1、Kv3.2或Kv3.3的表达,并且在DRG神经元上没有明确证明这两种亚型的表达(尽管如上所述,它们在脊髓的特定区域内是丰富的)。上述报道的体内研究提供了调节Kv3.4作为治疗某些神经性疼痛状态的新方法的基本原理。

[0016] 路易体痴呆(DLB)和帕金森病(PD)是严重的神经变性疾病,其与路易体中的蛋白质α-突触核蛋白的蓄积相关,这导致连接性丧失和神经元细胞死亡。DLB的症状包括进行性认知缺陷,特别是计划和注意力困难。幻视也是常见的,发生在大约60%的患者中。PD最初与运动缺陷相关,主要是由于多巴胺神经元的损失。虽然目前还没有研究将Kv3通道直接与DLB或PD相关联,但Kv3通道,特别是Kv3.1在皮质和基底神经节回路中的位置和作用表明,这些通道的调节剂可以单独或与目前的治疗(例如用于DLB的乙酰胆碱酯酶抑制剂或用于PD的L-DOPA)组合来改善DLB或PD的症状。

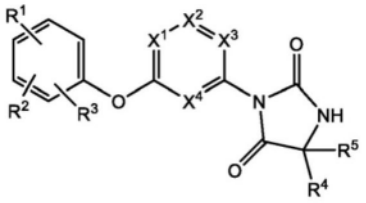
[0017] 专利申请WO2011/069951、WO2012/076877、WO2012/168710、WO2013/175215、WO2013/083994、WO2013/182850、WO2017/103604、WO2018/020263和WO2018/109484公开了作为Kv3.1和Kv3.2调节剂的化合物。此外，在癫痫发作、活动过度、睡眠障碍、精神病、听力障碍和双相性精神障碍的动物模型中证明了这类化合物的效用。

[0018] 专利申请WO2013/182851公开了某些化合物对Kv3.3通道的调节。

[0019] 专利申请WO2013/175211公开了已发现Kv3.1、Kv3.2和/或Kv3.3通道的调节有益于防止或限制由急性噪声暴露引起的永久性听力损失的建立。甚至在停止施用Kv3.1、Kv3.2和/或Kv3.3调节剂之后，也可以观察到这种预防的益处。

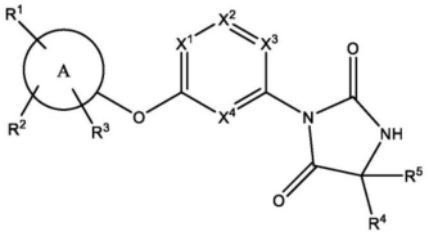
[0020] 专利申请WO2017/098254公开了已发现Kv3.1、Kv3.2和/或Kv3.3通道的调节有益于预防或治疗疼痛，特别是神经性疼痛或炎性疼痛。

[0021] 专利申请WO2019/222816公开了以下通式的‘间位连接的’吡啶基化合物：

[0022] 

[0023] 认为其为Kv3.1和/或Kv3.2通道的调节剂。

[0024] 专利申请WO2020/000065公开了以下通式的‘间位连接的’二嗪和三嗪化合物：

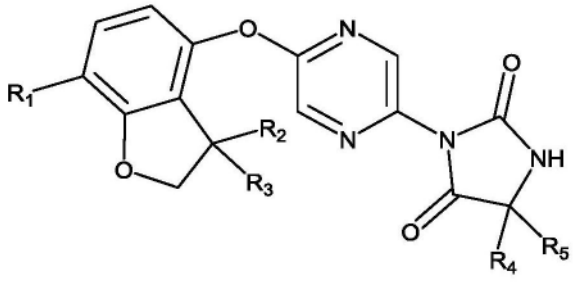
[0025] 

[0026] 认为其为Kv3.1和/或Kv3.2通道的调节剂。

[0027] 仍然需要鉴定Kv3.1、Kv3.2和/或Kv3.3的替代调节剂，特别是Kv3.1和/或Kv3.2的调节剂。此类调节剂可表现出高的体内效力、通道选择性、改善的安全性特征或期望的药代动力学参数，例如高的脑内利用度和/或低清除率，其降低了体内治疗效果所需的剂量。替代的调节剂可以通过具有不同的来自已知调节剂的代谢物而提供益处。具有平衡的Kv3.1、Kv3.2和/或Kv3.3调节性质的化合物可能是理想的，例如具有相同或相似程度的调节Kv3.1和Kv3.2的化合物。对于某些治疗适应证，还需要鉴定对Kv3.1、Kv3.2和/或Kv3.3通道具有不同调节作用的化合物，例如，改变通道门控或通道失活的动力学并且可以在体内作为通道的负调节剂起作用的化合物。

[0028] 发明概述

[0029] 本发明提供了式(I)的化合物：

[0030] 

(I)

[0031] 其中：

[0032] R_1为H或甲基；

[0033] R_2和R_3均为甲基，或R_2和R_3与所连接的碳原子一起为螺环丙基环；

[0034] R_4为甲基或乙基；

[0035] R_5为H或甲基；

[0036] 或R_4和R_5与所连接的碳原子一起形成C_3-C_4螺碳环基。

[0037] 式(I)的化合物可以以其盐和/或溶剂化物的形式提供。适合地，式(I)的化合物可以以其药学上可接受的盐和/或溶剂化物和/或其衍生物的形式提供。在本发明的一个实施方案中，式(I)化合物以药学上可接受的盐的形式提供。

[0038] 式(I)的化合物可以用作药物，特别是用于预防或治疗听力障碍，包括听力损失和耳鸣，以及精神分裂症、物质滥用障碍、疼痛或脆性X染色体综合征。

[0039] 此外，提供了预防或治疗听力障碍(包括听力损失和耳鸣)以及听力障碍(包括听力损失和耳鸣)以及精神分裂症、物质滥用障碍、疼痛或脆性X染色体综合征的方法。

[0040] 式(I)的化合物可用于制备用于预防或治疗听力障碍(包括听力损失和耳鸣)以及精神分裂症、物质滥用障碍、疼痛或脆性X染色体综合征的药物。

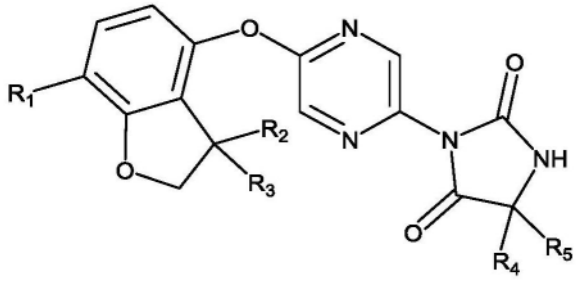
[0041] 还提供了药物组合物，其包含式(I)的化合物和药学上可接受的载体或赋形剂。

[0042] 还提供了制备式(I)的化合物和用于制备式(I)的化合物的新中间体的方法。

[0043] 还提供了式(I)的化合物的前药衍生物。

[0044] 发明详述

[0045] 本发明提供了式(I)的化合物：

[0046] 

(I)

[0047] 其中：

[0048] R_1为H或甲基；

[0049] R_2和R_3均为甲基，或R_2和R_3与所连接的碳原子一起为螺环丙基环；

[0050] R_4为甲基或乙基；

[0051] R_5为H或甲基；

[0052] 或R_4和R_5与所连接的碳原子一起形成C_3-C_4螺碳环基；

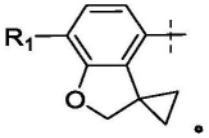
[0053] 或其药学上可接受的盐和/或溶剂化物和/或衍生物。

[0054] 以下所述的涉及基团(包括R_1、R_2、R_3、R_4、R_5)的相对立体化学和性质的实施方案被设想为在适宜情况下(即在化学上敏感的情况下)独立地、彼此完全可组合以形成本发明的另外的实施方案。这样的实施方案同样适用于以下中间体:其可用于合成式(I)的化合物,例如式(II)、(IV)、(VI)、(VII)和(XVI)的化合物。

[0055] 式(I)的化合物可以任选地以药学上可接受的盐和/或溶剂化物的形式提供。在本发明的一个实施方案中,式(I)化合物以药学上可接受的盐的形式提供。在本发明的第二个实施方案中,提供了药学上可接受的溶剂化物形式的式(I)的化合物。在本发明的第三个实施方案中,式(I)化合物不是盐或溶剂化物的形式。

[0056] 在一个实施方案中,R_1为H。在第二个实施方案中,R_1为甲基。

[0057] 在一个实施方案中,R_2为甲基,且R_3为甲基。在另一个实施方案中,R_2和R_3为螺环丙基,以便形成如下部分:

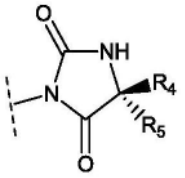
[0058] 

[0059] 在一个实施方案中,R_4为甲基。在第二个实施方案中,R_4为乙基。

[0060] 在一个实施方案中,R_5为氢。在第二个实施方案中,R_5为甲基。

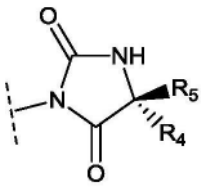
[0061] 在一个实施方案中,R_4和R_5相同(即,甲基)。

[0062] 在其中R_4和R_5不同的实施方案中,它们可以具有以下立体化学排列:

[0063] 

[0064] 在该实施方案中,例如,R_4为甲基且R_5为H,R_4为乙基且R_5为H,或R_4为乙基且R_5为甲基。

[0065] 在其中R_4和R_5不同的实施方案中,它们也可具有以下立体化学排列:

[0066] 

[0067] 在该实施方案中,例如,R_4为甲基且R_5为H,R_4为乙基且R_5为H,或R_4为乙基且R_5为甲基。

[0068] 在一个实施方案中,R_4和R_5与所连接的碳原子一起形成螺环丙基。

[0069] 在另一个实施方案中,R_4和R_5与所连接的碳原子一起形成螺环丁基。

[0070] 在一个实施方案中,式(I)的化合物选自:

[0071] 5,5-二甲基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮;

[0072] 3-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]-5,5-二甲基-咪唑烷-2,4-二酮;

[0073] (5R)-5-乙基-5-甲基-3-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)咪唑烷-2,4-二酮；

[0074] 5,5-二甲基-3-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)咪唑烷-2,4-二酮；

[0075] (5R)-5-乙基-5-甲基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮；

[0076] (5R)-3-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]-5-乙基-5-甲基-咪唑烷-2,4-二酮；

[0077] 5,5-二甲基-3-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]咪唑烷-2,4-二酮；

[0078] (5R)-5-乙基-5-甲基-3-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]咪唑烷-2,4-二酮；

[0079] (5R)-5-乙基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮；

[0080] (5R)-5-乙基-3-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)咪唑烷-2,4-二酮；

[0081] (5R)-3-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]-5-乙基-咪唑烷-2,4-二酮；

[0082] (5R)-5-乙基-3-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]咪唑烷-2,4-二酮；

[0083] 7-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]-5,7-二氮杂螺[3.4]辛烷-6,8-二酮；

[0084] 或其药学上可接受的盐和/或溶剂化物和/或其衍生物。

[0085] 在一个实施方案中，式(I)的化合物为：

[0086] 6-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]-4,6-二氮杂螺[2.4]庚烷-5,7-二酮；

[0087] 或其药学上可接受的盐和/或溶剂化物和/或其衍生物。

[0088] 在一个实施方案中，式(I)的化合物为：

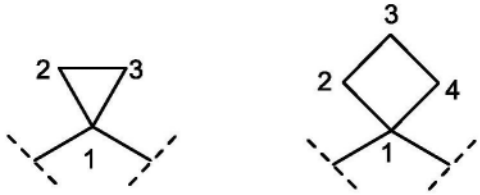
[0089] (5S)-5-乙基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮；

[0090] 或其药学上可接受的盐和/或溶剂化物和/或其衍生物。

[0091] 当化合物含有C_{1-3}烷基时，无论是单独的还是形成较大基团的一部分，烷基可以是直链、支链或环状的。C_{1-3}烷基的实例是甲基、乙基、正丙基、异丙基和环丙基。提及“丙基”包括正丙基、异丙基和环丙基。

[0092] 如本文所用的术语“卤代”或“卤素”是指氟、氯、溴或碘原子。卤素的具体实例是氟、氯和溴，例如氯或溴。

[0093] 如本文所用的术语‘C_{3-4}螺碳环基’指含有3或4个碳原子的环状环系统，即环丙基或环丁基，其中环状环系统经由螺中心连接至仲碳，使得仲碳是环状环中的3至4个碳原子其中之一，如下所示：

[0094] 

C_3螺碳环基 C_4螺碳环基

[0095] 应当理解,为了在药物中使用,式(I)化合物的盐应当是药学上可接受的。适合的药学上可接受的盐对于本领域技术人员来说是显而易见的。药学上可接受的盐包括由Berge、Bighley和Monkhouse J.Pharm.Sci.(1977)66,pp 1-19描述的那些。此类药学上可接受的盐包括与无机酸(例如盐酸、氢溴酸、硫酸、硝酸或磷酸)和有机酸(例如琥珀酸、马来酸、乙酸、富马酸、柠檬酸、酒石酸、苯甲酸、对甲苯磺酸、甲磺酸或萘磺酸)形成的酸加成盐。非药学上可接受的盐可用于例如分离式(I)的化合物,并且包括在本发明的范围内。

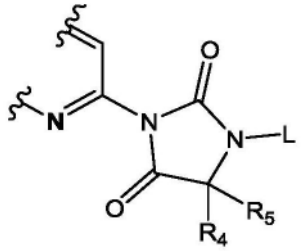
[0096] 式(I)化合物的某些可以与一当量或多当量的酸形成酸加成盐。本发明在其范围内包括所有可能的化学计量和非化学计量形式。

[0097] 式(I)的化合物可以以结晶或非结晶形式制备,并且如果是结晶,则可以任选地被溶剂化,例如作为水合物。本发明在其范围内包括化学计量的溶剂化物(例如水合物)以及含有可变量溶剂(例如水)的化合物。

[0098] 应当理解,本发明包括式(I)化合物的药学上可接受的衍生物,并且这些衍生物包括在本发明的范围内。

[0099] 如本文所用,“药学上可接受的衍生物”包括式(I)化合物的任何药学上可接受的酯或此类酯的盐,其在施用于接受者时能够提供(直接或间接)式(I)的化合物或其活性代谢物或残余物。

[0100] 药学上可接受的前药可以通过例如用如下所示例的基团“L”(其中R_4和R_5如上所述)官能化乙内酰脲的仲氮来形成:

[0101] 

[0102] 在本发明的一个实施方案中,式(I)的化合物通过乙内酰脲的仲氮被基团L官能化,其中L选自:

[0103] a)$-PO(OH)O^- \cdot M^+$,其中M^+为药学上可接受的一价抗衡离子,

[0104] b)$-PO(O^-)_2 \cdot 2M^+$,

[0105] c)$-PO(O^-)_2 \cdot D^{2+}$,其中D^{2+}为药学上可接受的二价抗衡离子,

[0106] d)$-CH(R^X)-PO(OH)O^- \cdot M^+$,其中$R^X$为氢或$C_{1-3}$烷基,

[0107] e)$-CH(R^X)-PO(O^-)_2 \cdot 2M^+$,

[0108] f)$-CH(R^X)-PO(O^-)_2 \cdot D^{2+}$,

[0109] g)$-SO_3^- \cdot M^+$,

[0110] h)$-CH(R^X)-SO_3^- \cdot M^+$,且

[0111] i)-CO-CH_2CH_2-CO_2•M^+。

[0112] 应当理解，本发明涵盖式(I)的所有异构体及其药学上可接受的衍生物，包括所有几何、互变异构和光学形式及其混合物(例如外消旋混合物)。当另外的手性中心存在于式(I)化合物中时，本发明的范围内包括所有可能的非对映异构体，包括其混合物。不同的异构体形式可以通过常规方法彼此分离或拆分，或者任何给定的异构体可以通过常规合成方法或通过立体特异性或不对称合成获得。

[0113] 本申请包括本文提供的本发明化合物的所有同位素形式，无论是以下形式：(i)其中给定原子序数的所有原子具有在自然界中占优势的质量数(或质量数的混合物)(在本文中称为“天然同位素形式”)或(ii)其中一个或多个原子被具有相同原子序数但质量数不同于在自然界中占优势的原子的质量数的原子替代(在本文中称为“非天然变体同位素形式”)。应当理解，原子可以作为质量数的混合物天然存在。术语“非天然变体同位素形式”还包括这样的实施方案，其中具有在自然界中较不常见的质量数的给定原子序数的原子的比例(在本文中称为“不常见同位素”)相对于天然存在的原子的比例增加，例如增加至>20％、>50％、>75％、>90％、>95％或>99％的水平(按该原子序数的原子数计)(后一实施方案称为“同位素富集的变体形式”)。术语“非天然变体同位素形式”还包括其中不常见同位素的比例相对于天然存在的比例已经降低的实施方案。同位素形式可包括放射性形式(即它们掺入放射性同位素)和非放射性形式。放射性形式典型地为同位素富集的变体形式。

[0114] 因此，化合物的非天然变体同位素形式可以含有一种或多种人工或不常见的同位素，例如在一个或多个原子中的氘(^{2}H或D)、碳-11(^{11}C)、碳-13(^{13}C)、碳-14(^{14}C)、氮-13(^{13}N)、氮-15(^{15}N)、氧-15(^{15}O)、氧-17(^{17}O)、氧-18(^{18}O)、磷-32(^{32}P)、硫-35(^{35}S)、氯-36(^{36}Cl)、氯-37(^{37}Cl)、氟-18(^{18}F)、碘-123(^{123}I)、碘-125(^{125}I)或与在自然界中在一个或多个原子中占优势的比例相比可以含有增加的比例的所述同位素。

[0115] 包含放射性同位素的非天然变体同位素形式可以例如用于药物和/或底物组织分布研究。放射性同位素氚，即^{3}H和碳-14，即^{14}C鉴于它们易于掺入和现成的检测手段，特别适用于该目的。掺入氘的非天然变体同位素形式，即^{2}H或D可以提供由更大的代谢稳定性引起的某些治疗优势，例如增加的体内半衰期或减少的剂量需求，因此在一些情况下可能是优选的。此外，可以制备非天然变体同位素形式，其掺入正电子发射同位素，例如^{11}C、^{18}F、^{15}O和^{13}N，并且可用于正电子发射断层扫描(PET)研究以检查底物受体占有率。

[0116] 在一个实施方案中，本发明的化合物以天然同位素形式提供。

[0117] 在一个实施方案中，本发明的化合物以非天然变体同位素形式提供。在一个具体实施方案中，非天然变体同位素形式是其中掺入氘(即^{2}H或D)的形式，其中在本发明化合物的一个或多个原子的化学结构中指定氢。在一个实施方案中，本发明化合物的原子为非放射性的同位素形式。在一个实施方案中，本发明化合物的一个或多个原子是放射性的同位素形式。适合地，放射性同位素是稳定的同位素。适合地，非天然变体同位素形式是药学上可接受的形式。

[0118] 在一个实施方案中，提供了本发明的化合物，其中化合物的单个原子以非天然变体同位素形式存在。在另一个实施方案中，提供了本发明的化合物，其中两个或更多个原子以非天然变体同位素形式存在。

[0119] 非天然同位素变体形式通常可以通过本领域技术人员已知的常规技术或通过本

文所述的方法制备，例如类似于所附实施例中描述的用于制备天然同位素形式的方法。因此，非天然同位素变体形式可以通过使用适当的同位素变体(或标记的)试剂替代实施例中使用的常规试剂来制备。由于式(I)化合物旨在用于药物组合物中，因此容易理解，它们各自优选以基本上纯的形式提供，例如至少60％纯，更适合地至少75％纯，优选至少85％，特别是至少98％纯(％是基于重量的重量％)。化合物的不纯制备物可用于制备药物组合物中使用的更纯形式。

[0120] 由于式(I)化合物旨在用于药物组合物中，因此容易理解，它们各自优选以基本上纯的形式提供，例如至少60％纯，更适合地至少75％纯，且优选至少85％，特别是至少98％纯(％是基于重量的重量％)。化合物的不纯制备物可用于制备药物组合物中使用的更纯的形式。

[0121] 通常，式(I)的化合物可以根据本领域技术人员已知的有机合成技术，以及通过下面阐述的代表性方法、实施例中的那些方法及其修改方法来制备。

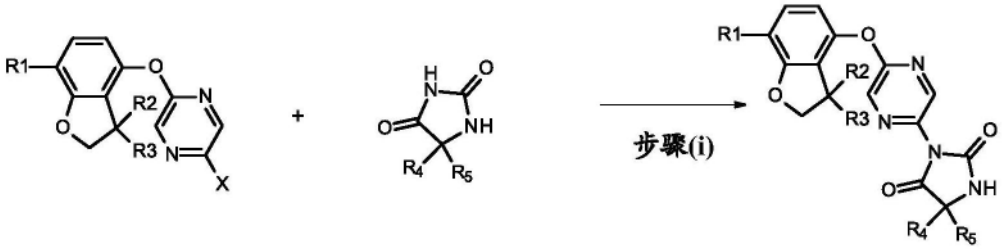
[0122] 专利申请WO2011/069951、WO2012/076877、WO2012/168710、WO2013/175215、WO2013/083994、WO2013/182850、WO2017/103604、WO2018/020263和WO2018/109484提供了用于合成可用于生产本发明化合物的中间体的方法。

[0123] 一般合成方案

[0124] 以下方案详述了本发明化合物的合成途径和合成此类化合物中的中间体。在以下方案中，反应性基团可以用保护基团保护并根据本领域技术人员众所周知的已建立的技术脱保护。

[0125] 式(I)的化合物及其盐和溶剂化物可以通过下文概述的一般方法制备。在以下描述中，基团R_1、R_2、R_3、R_4和R_5具有如上述对式(I)化合物所定义的含义，另有指出的除外。

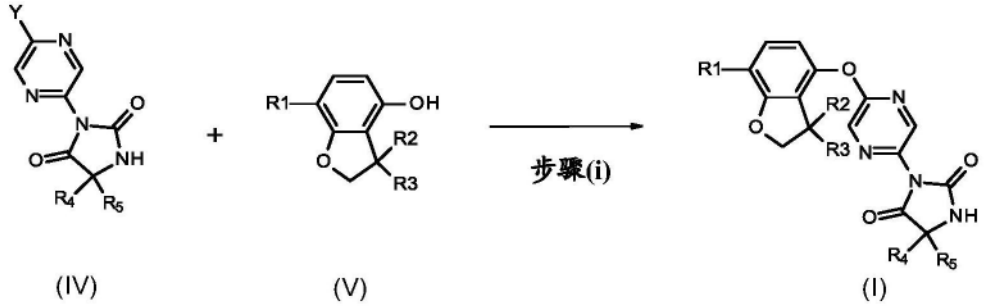
[0126] 方案1a

[0127] 

(II) (III) (I)

[0128] 步骤(i)：式(I)的化合物可以通过金属催化的偶联反应制备。在该反应中，式(II)的卤代-吡嗪衍生物，其中典型地X＝Br，与式(III)的乙内酰脲在金属催化剂例如氧化亚铜(I)存在下，在适合的溶剂例如在N,N-二甲基甲酰胺中，使用常规加热或微波加热反应。

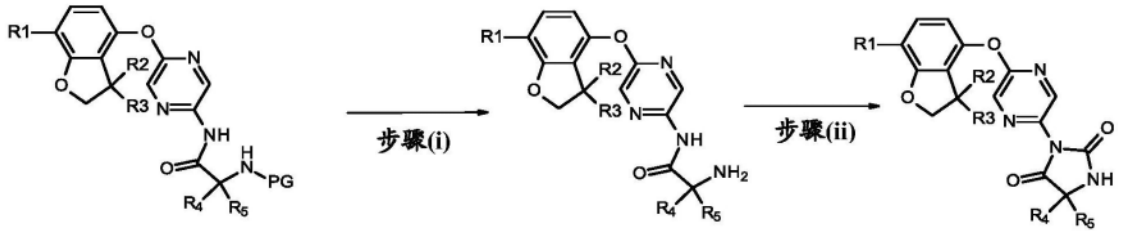
[0129] 方案1b

[0130] 

(IV) (V) (I)

[0131] 式(I)的化合物,其中R_4和R_5不为H,可以通过亲核芳香取代制备。在该反应中,式(IV)的卤代-吡嗪衍生物,其中典型的Y=Cl,与式(V)的苯酚在适合的碱,例如碳酸钾存在下,在适合的溶剂,例如在N,N-二甲基甲酰胺或乙腈中,使用常规的加热或微波加热反应。

[0132] 方案1c

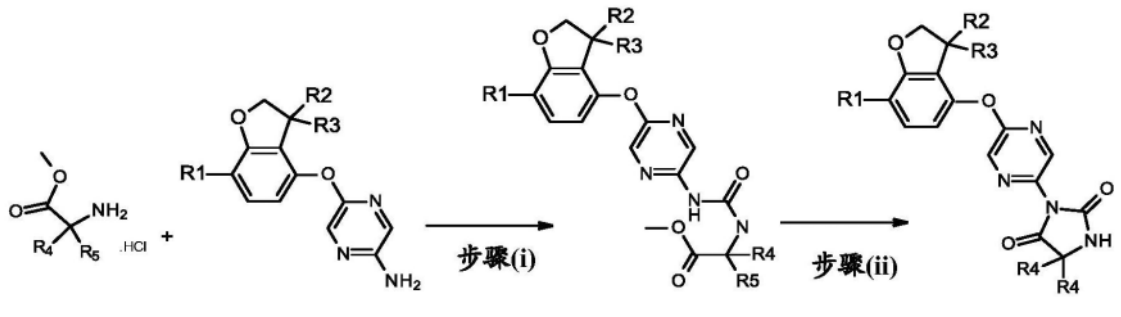
[0133] 

(VII) (VI) (I)

[0134] 步骤(ii):式(I)的化合物可以通过下列方式制备:在适合的溶剂例如二氯甲烷中,在适合的碱例如三乙胺存在下,用羰基化试剂(例如优选在相同溶剂中预稀释的并且在0℃二次加入的三光气)使式(VI)的化合物环化。或者,可以通过使用羰基化试剂例如羰基二咪唑,在适合的溶剂例如乙酸乙酯中,在碱例如三乙胺或DIPEA存在下使式(VI)的化合物环化制备式(I)的化合物。

[0135] 步骤(i):式(VI)的化合物可以通过使式(VII)的化合物脱保护制备,其中PG为保护基,适当地,保护基为BOC,可以在酸性条件下,例如TFA,在适合的溶剂,例如二氯甲烷中,在约0℃-室温下除去BOC。

[0136] 方案1d

[0137] 

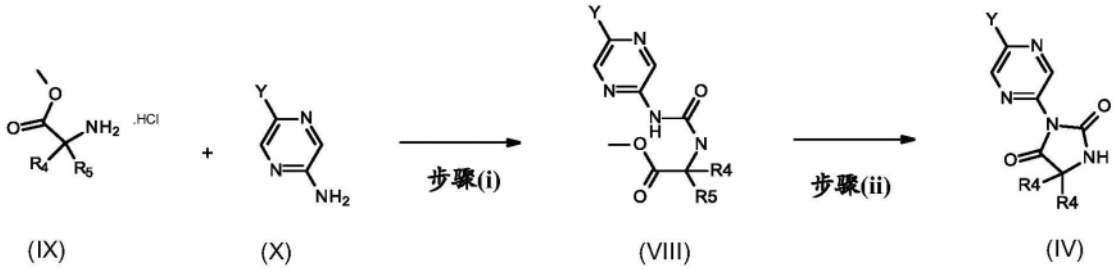
(IX) (XVI) (XVII) (I)

[0138] 步骤(ii):式(I)的化合物可以通过使式(XVII)的脲和适合的碱,例如甲醇钠在适合的溶剂,例如甲醇中,在0℃至室温的温度范围内反应来制备。

[0139] 步骤(i):式(XVII)的脲可以通过式(XVI)的苯胺和式(IX)的氨基酯(例如盐酸盐)在适合的溶剂例如二氯甲烷或乙酸乙酯中,在适合的碱例如三乙胺或二异丙基乙胺存在下,在0℃至室温的温度下与羰基化试剂例如三光气反应来制备,所述三光气优选在相同溶

剂中预稀释。

[0140] 方案2a

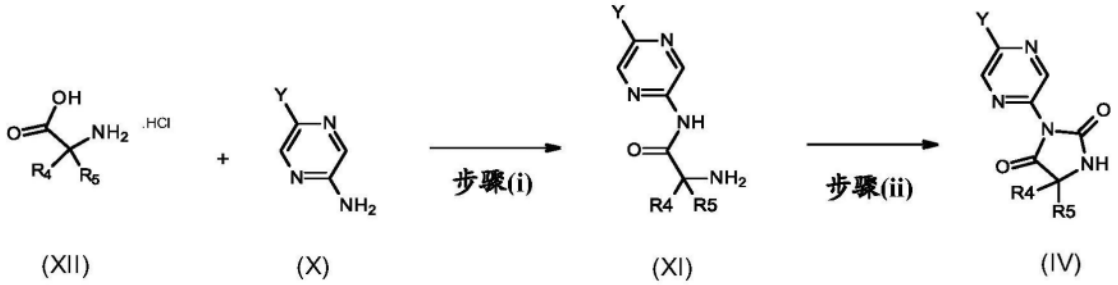
[0141] 

(IX) (X) (VIII) (IV)

[0142] 步骤(ii):式(IV)的化合物可以通过使式(VIII)的脲和适合的碱,例如甲醇钠在适合的溶剂,例如甲醇中,在0℃至室温的温度范围内反应来制备。

[0143] 步骤(i):式(VIII)的脲可以通过使商购的式(X)的卤代-吡嗪衍生物(其中典型地Y=Cl)和式(IX)的氨基酯(例如盐酸盐)在适合的溶剂例如二氯甲烷或乙酸乙酯中与羰基化试剂,例如三光气反应来制备,所述三光气优选在相同溶剂中,在适合的碱例如三乙胺或二异丙基乙胺存在下,在0℃至室温的范围的温度下预稀释。

[0144] 方案2b

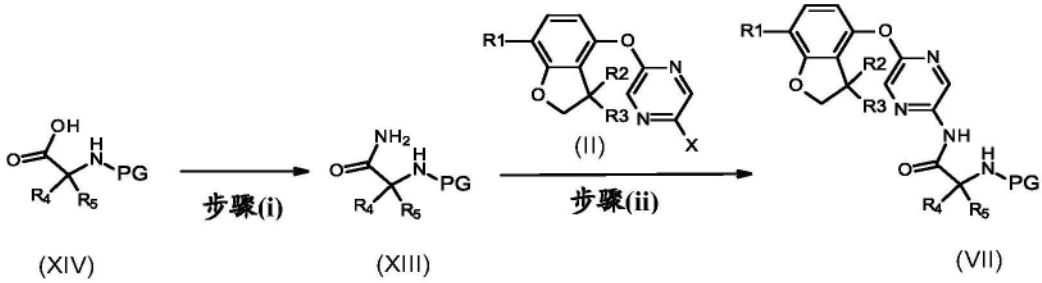
[0145] 

(XII) (X) (XI) (IV)

[0146] 步骤(ii):式(IV)的化合物可以通过在适合的溶剂例如二氯甲烷中,在适合的碱例如三乙胺存在下在0℃用羰基化试剂例如三光气环化式(XI)化合物来制备,所述羰基化试剂例如三光气优选在相同溶剂中预稀释并第二次加入。

[0147] 步骤(i):具有式(XI)的化合物可以由具有式(X)的苯胺(其中典型地Y=Cl)和具有式(XII)的氨基酸(作为游离碱或盐酸盐)通过在偶联剂(例如T3P)的存在下在适合的溶剂(如乙酸乙酯、乙腈或它们的混合物)中进行酰胺偶联来制备。

[0148] 方案3

[0149] 

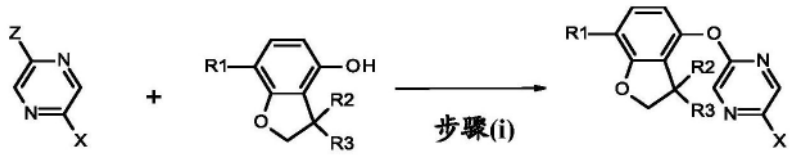
(XIV) (XIII) (II) (VII)

[0150] 步骤(ii):式(IV)的化合物可以通过金属催化的交叉偶联反应制备。在该反应中,在金属催化剂如三(二亚苄基丙酮)二钯(0)、适合的配体如二环己基-[2-(2,4,6-三异丙基苯基)苯基]膦(XPhos)和适合的碱例如碳酸铯的存在下,在适合的溶剂例如1,4-二噁烷中,用常规加热或微波加热,使式(II)的卤代-吡嗪衍生物(其中通常X=Br)和式(XIII)的酰胺

反应。或者，在该反应中，式(II)的卤代-吡嗪衍生物(其中典型地X＝Br)和式(XIII)的酰胺在金属催化剂如碘化亚铜(I)、适合的配体如N,N'-二甲基乙烷-1,2-二胺和适合的碱如碳酸钾存在下，在适合的溶剂中，例如在1-丁醇中，用常规加热或微波加热反应。制备式(IV)化合物的另一种方法是在金属催化剂如乙酸钯(II)、适合的配体例如Xantphos和适合的碱例如碳酸铯存在下，在适合的溶剂如1,4-二噁烷中，用常规加热或微波加热，使式(II)的卤代吡嗪衍生物(其中通常X＝Br)与式(XIII)的酰胺反应。

[0151] 步骤(i)：具有式(XIII)的化合物可以从具有式(XIV)的N-保护的(例如Boc)氨基酸和胺(例如六甲基二硅氮烷)通过在碱(例如DIPEA)和偶联剂(例如HATU或TBTU)的存在下在溶剂(例如N,N-二甲基甲酰胺)中进行酰胺偶联来制备。

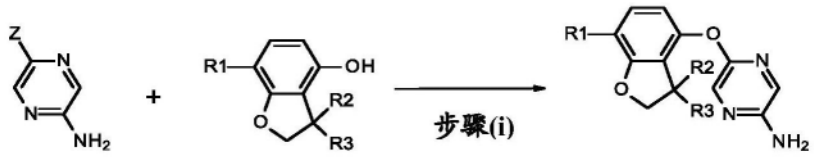
[0152] 方案4

[0153] 

(XV) (V) (II)

[0154] 步骤(i)：式(II)的化合物，其中典型地X＝Br，可以通过亲核芳族取代制备。在该反应中，式(XV)的卤代-吡嗪衍生物(其中典型地X＝Z＝Br)与式(V)的苯酚在碱例如碳酸钾存在下，在适合的溶剂中，例如在N,N-二甲基甲酰胺中，在常规加热或微波加热下反应。

[0155] 方案5

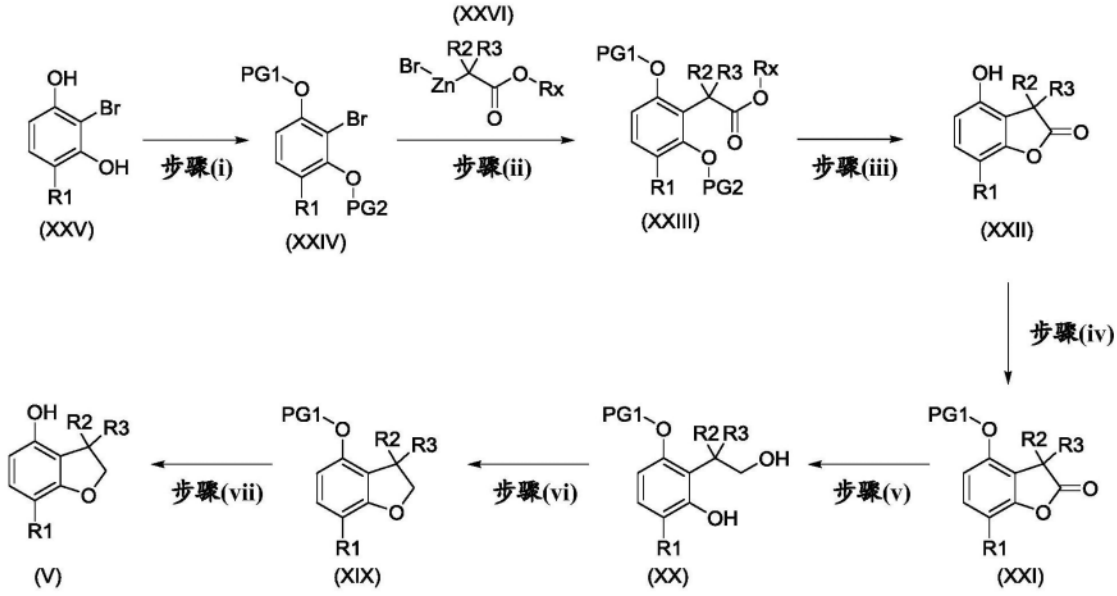
[0156] 

(XVIII) (V) (XVI)

[0157] 步骤(i)：式(XVI)的苯胺可以通过金属催化的交叉偶联反应制备。在该反应中，式(XVIII)的卤代-吡嗪衍生物(其中典型地Z＝Br)和式(V)的苯酚在金属催化剂例如碘化亚铜(I)、适合的配体如吡啶甲酸的存在下，在适合的溶剂例如N,N-二甲基甲酰胺或N,N-二甲基乙酰胺中，在常规加热或微波加热下反应，任选地，可以使用适合的碱，例如碳酸钾或碳酸铯。

[0158] 方案6

[0159]



[0160] 在上文所示的方案6中，PG_1和PG代表适合的保护基团。步骤(i)-(iii)中的PG_1可以不同于步骤(iv)-(vii)中的PG_1。适合的保护基包括苄基、四氢吡喃基或甲氧基甲基。适合地，PG_2与PG_1相同，例如两者均为苄基。

[0161] 其中PG_1和PG_2均为苄基的方案描述

[0162] 步骤(vii)：式(V)的苯酚可以由式(XIX)的苄基化化合物通过脱保护，例如使用金属催化剂例如钯/碳和氢源例如氢气氛或甲酸铵，在适合的溶剂例如乙醇或甲醇中，在室温至回流的温度范围内制备。

[0163] 步骤(vi)：式(XIX)的苄基化化合物可以由式(XX)的二醇，使用碱例如叔丁醇钾和适合的溶剂例如碳酸二甲酯，在室温至回流的温度范围内制备。

[0164] 步骤(v)：式(XX)的二醇可以由式(XXI)的内酯，使用还原剂例如氢化铝锂，在适合的溶剂如THF中，在0℃至室温的温度下制备。

[0165] 步骤(iv)：具有式(XXI)的内酯可以由具有式(XXII)的酚，使用苄基化剂例如苄基溴，在碱例如碳酸钾的存在下，在适合的溶剂例如乙腈或THF或其混合物中，在室温至回流的温度范围内制备。

[0166] 步骤(iii)：具有式(XXII)的苯酚可以由具有式(XXIII)的二苄基化酯(其中Rx为适合的烷基基团，例如甲基或乙基)，使用金属催化剂例如钯/碳和氢源例如氢气氛或甲酸铵，在适合的溶剂例如乙醇或甲醇中，在室温至回流的温度范围内制备。

[0167] 步骤(ii)：式(XXIII)的二苄基化酯(其中Rx为适合的烷基基团，例如甲基或乙基)可以由式(XXIV)的二苄基化溴衍生物通过使用预先形成的式(XXVI)的有机锌衍生物(其中Rx为适合的烷基基团，例如甲基或乙基)，在金属催化剂配合物例如双(三叔丁基膦)钯(0)的存在下，在适合的溶剂如THF或DMF或其混合物中，在室温至回流的温度范围内制备。

[0168] 步骤(i)：式(XXIV)的二苄基化溴衍生物可以由可商购的式(XXV)的衍生物，使用苄基化试剂例如苄基溴，在碱例如碳酸钾的存在下，在适合的溶剂如乙腈或THF或丙酮或其混合物中，在室温至回流的温度范围内制备。

[0169] 当PG_1和/或PG_2是保护基团如四氢吡喃基或甲氧基甲基时，适用通常的保护/脱保护条件：

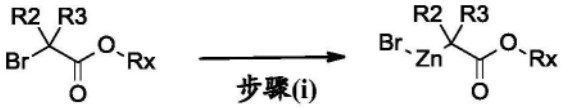
[0170] • 用四氢吡喃基保护苯酚的条件包括使苯酚与二氢-2H-吡喃在催化剂如C:Py • p-MePhSO$_3$H存在下，在适合的溶剂例如二氯甲烷中，在0℃至回流的温度下反应。

[0171] • 从苯酚中裂解四氢吡喃基保护基的条件包括使THP保护的苯酚在酸例如硫酸或p-MePhSO$_3$H或HCl存在下，在适合的溶剂如甲醇或乙醇中，在0℃至回流的温度下反应。

[0172] • 用甲氧基甲基保护苯酚的条件包括使苯酚与氯甲基甲基醚在碱如碳酸钾存在下，在适合的溶剂如四氢呋喃或乙腈中，在0℃至回流的温度下反应。

[0173] • 来自苯酚的甲氧基甲基保护基团的裂解条件包括使MOM保护的苯酚在酸例如硫酸或p-MePhSO$_3$H或HCl存在下，在适合的溶剂如甲醇或乙醇中，在0℃至回流的温度下反应。

[0174] 方案7

[0175] 

(XXVII) (XXVI)

[0176] 步骤(i)：式(XXVI)的有机锌衍生物，其中Rx为适合的烷基基团，例如甲基或乙基，可以通过将商购的式(XXVII)的溴酯在1,2-二溴乙烷和氯三甲基硅烷存在下，在适合的溶剂例如THF中添加至锌(0)的回流混悬液中制备。

[0177] 本发明的方法

[0178] 本发明的其他方面提供了用于制备式(I)的化合物及其衍生物的方法以及用于制备式(I)的化合物合成中的中间体的方法。

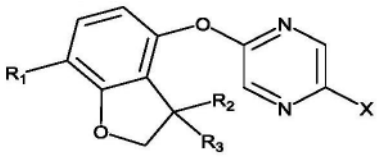
[0179] 本发明的方法如上所述且包括多-步骤方案的任一单个步骤。

[0180] 中间体

[0181] 本发明还涉及式(I)的化合物合成中的新的中间体。这类新的中间体包括式(II)、(IV)、(VI)、(VII)、(VIII)、(XI)、(XVI)和(XVII)的化合物。还关注式(XIX)-(XXIV)的中间体。本发明还提供了这类中间体的盐，例如药学上可接受的盐。

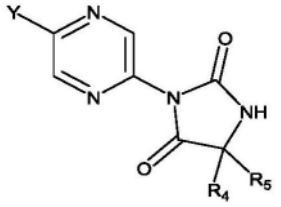
[0182] 因此，本发明的中间体包括：

[0183] -式(II)的化合物：

[0184] 

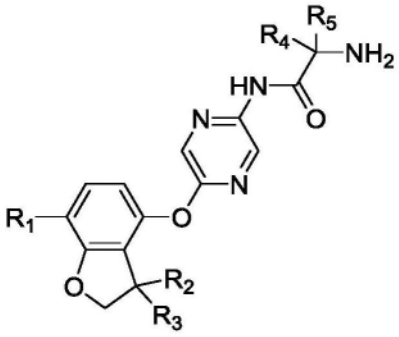
[0185] 其中R_1、R_2和R_3如上述所定义，X为卤素，例如Br；

[0186] -式(IV)的化合物：

[0187] 

[0188] 其中R_1、R_2和R_3如上述所定义，Y为卤素，例如Cl；

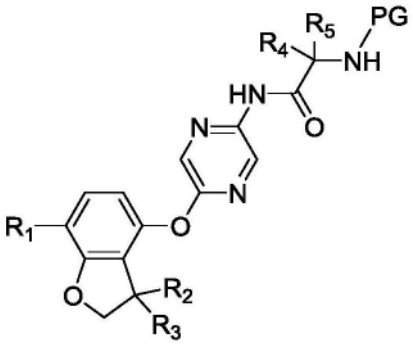
[0189] -式(VI)的化合物：

[0190] 

(VI)

[0191] 其中R_1、R_2、R_3、R_4和R_5如上述所定义；

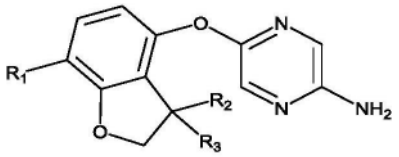
[0192] -式(VII)的化合物：

[0193] 

(VII)

[0194] 其中R_1、R_2、R_3、R_4和R_5如上述所定义，PG为适合的保护基，例如BOC；

[0195] -式(XVI)的化合物：

[0196] 

[0197] 其中R_1、R_2和R_3如上述所定义。

[0198] Kv3.1、Kv3.2和/或Kv3.3调节

[0199] 本发明的式(I)的化合物为Kv3.1的调节剂。式(I)的化合物也可以为Kv3.2和/或Kv3.3的调节剂。可以在生物学实施例1的测定中测试本发明的化合物，以确定它们对Kv3.1和/或Kv3.2和/或Kv3.3通道的调节特性。

[0200] 如本文所用的“调节剂”是指能够产生由在哺乳动物细胞中重组表达的人Kv3.1和/或人Kv3.2和/或人Kv3.3通道介导的全细胞电流的至少10％增强，且适合地至少20％增强的化合物。

[0201] 术语“Kv3.1、Kv3.2和/或Kv3.3”应被认为与“Kv3.1和/或Kv3.2和/或Kv3.3”含义相同，并且也可以称作“Kv3.1/Kv3.2/Kv3.3”。

[0202] 在一个实施方案中，调节剂能够产生由在哺乳动物细胞中重组表达的人Kv3.1通道介导的全细胞电流的至少10％增强，适合地至少20％增强。适合地，调节剂的pEC_{50}在4-7(例如5-6.5)的范围内。

[0203] 在一个实施方案中，调节剂能够产生由在哺乳动物细胞中重组表达的人Kv3.2通道介导的全细胞电流的至少10％增强，适合地至少20％增强。适合地，调节剂的pEC_{50}在4-7

(例如5-6.5)的范围内。

[0204] 在一个实施方案中,调节剂能够产生由在哺乳动物细胞中重组表达的人Kv3.3通道介导的全细胞电流的至少10%增强,适合地至少20%增强。适合地,调节剂的pEC_{50}在4-7(例如5-6.5)的范围内。

[0205] 在另一个实施方案中,调节剂能够产生由在哺乳动物细胞中重组表达的人Kv3.1和Kv3.2通道介导的全细胞电流的至少10%的增强,适合地至少20%的增强。

[0206] 在另一个实施方案中,调节剂能够产生由在哺乳动物细胞中重组表达的人Kv3.1和Kv3.3通道介导的全细胞电流的至少10%的增强,适合地至少20%的增强。

[0207] 在另一个实施方案中,调节剂能够产生由在哺乳动物细胞中重组表达的人Kv3.2和Kv3.3通道介导的全细胞电流的至少10%的增强,适合地至少20%的增强。

[0208] 在另一个实施方案中,所述调节剂能够产生由在哺乳动物细胞中重组表达的人Kv3.1、Kv3.2和Kv3.3通道介导的全细胞电流的至少10%增强,适合地至少20%增强。

[0209] 式(I)的化合物或其药学上可接受的盐和/或溶剂化物和/或衍生物可用于治疗或预防其中需要Kv3.1或Kv3.2或Kv3.1和Kv3.2通道调节剂的疾病或病症。如本文所用,Kv3.1或Kv3.2或Kv3.1和Kv3.2的调节剂是正或负改变这些通道性质的化合物。在本发明的一个特定方面,式(I)的化合物是正调节剂。可以在生物学实施例1的测定中测试本发明的化合物以确定它们的调节特性。

[0210] 在本发明的一个实施方案中,式(I)的化合物或其药学上可接受的盐和/或溶剂化物和/或衍生物对Kv3.1通道的调节比对Kv3.2通道的调节具有选择性。所谓选择性是指化合物对Kv3.1通道的活性是对Kv3.2通道的活性的至少2倍、5倍或10倍。化合物的活性通过其由Ec50值指示的效力适当地定量。

[0211] 在本发明的另一个实施方案中,式(I)的化合物或其药学上可接受的盐和/或其溶剂化物和/或其衍生物对Kv3.2通道的调节比对Kv3.1通道的调节具有选择性。同样,选择性是指化合物对Kv3.2通道的活性是对Kv3.1通道的活性的至少2倍、5倍或10倍。

[0212] 在本发明的一个具体的实施方案中,式(I)的化合物或其药学上可接受的盐和/或其溶剂化物和/或其衍生物显示出在Kv3.1和Kv3.2通道的调节之间相当的活性,例如一个通道的活性小于另一个通道的活性的2倍,例如小于1.5倍或小于1.2倍。

[0213] 在某些病症中,使用Kv3.3或Kv3.1或Kv3.3和Kv3.1的调节剂可能是有益的,所述调节剂在两个通道之间显示出特定的选择性分布。例如,化合物对Kv3.3通道的调节可以比对Kv3.1通道的调节具有选择性,表现出例如对Kv3.3通道的活性比对Kv3.1通道的活性至少2倍、5倍或10倍。

[0214] 在本发明的另一个实施方案中,式(I)的化合物或其药学上可接受的盐和/或其溶剂化物和/或其衍生物对Kv3.1通道的调节比对Kv3.3通道的调节具有选择性。同样,所谓选择性是指化合物例如,Kv3.1通道的活性比Kv3.3通道的至少2倍、5倍或10倍。

[0215] 在本发明的一个具体的实施方案中,化合物可以在Kv3.3和Kv3.1通道的调节之间表现出相当的活性,例如每个通道的活性小于另一个通道的活性的2倍,例如小于1.5倍或小于1.2倍。

[0216] 在某些病症中,使用Kv3.3或Kv3.2或Kv3.3和Kv3.2的调节剂可能是有益的,所述调节剂在两个通道之间显示出特定的选择性分布。化合物对Kv3.3通道的调节相对于对

Kv3.2通道的调节可以是选择性的，表现出例如对Kv3.3通道的活性比对Kv3.2通道的活性至少2倍、5倍或10倍。

[0217] 在本发明的另一个实施方案中，式(I)的化合物或其药学上可接受的盐和/或其溶剂化物和/或其衍生物对Kv3.2通道的调节比对Kv3.3通道的调节具有选择性。同样，所谓选择性是指化合物对Kv3.2通道的活性是对Kv3.3通道的活性的至少2倍、5倍或10倍。

[0218] 在另一个具体的实施方案中，化合物可以在Kv3.3和Kv3.2通道的调节之间表现出相当的活性，例如每个通道的活性小于另一个通道的活性的2倍，例如小于1.5倍或小于1.2倍。

[0219] 在本发明的另一个具体的实施方案中，化合物可以在Kv3.3、Kv3.2和Kv3.1通道的调节之间表现出相当的活性，例如每个通道的活性小于任何其它通道的活性的2倍，例如小于1.5倍或小于1.2倍。化合物的活性通过其由EC50值指示的效力适当地定量。

[0220] 治疗方法

[0221] 本发明还提供了式(I)的化合物或其药学上可接受的盐和/或溶剂化物(例如盐)和/或衍生物，其用于治疗或预防其中需要Kv3.1、Kv3.2和/或Kv3.3调节剂的疾病或病症，例如下文提及的那些疾病和病症。

[0222] 本发明提供了治疗或预防其中需要Kv3.1、Kv3.2和/或Kv3.3调节剂的疾病或病症的方法，例如下文提及的那些疾病或病症，所述方法包含向有此需要的个体施用有效量的式(I)的化合物或其药学上可接受的盐和/或溶剂化物(例如盐)和/或衍生物。

[0223] 本发明还提供了式(I)的化合物或其药学上可接受的盐和/或溶剂化物(例如盐)和/或衍生物在制备用于治疗或预防其中需要Kv3.1、Kv3.2和/或Kv3.3调节剂的疾病或病症的药物中的用途，所述疾病或病症例如下文提及的那些疾病和病症。

[0224] 在一个实施方案中，提供了式(I)的化合物或其药学上可接受的盐和/或其溶剂化物和/或其衍生物，用作药物。

[0225] 本文所用的术语“治疗”包括疾病状态或其症状的控制、缓解、减少或调节。

[0226] 术语“预防”在本文中用于指预防个体的疾病或病症的症状或预防患病个体的疾病或病症的症状的复发，并且不限于完全预防疾病。

[0227] 适合地，所述个体为人。

[0228] 可以通过调节Kv3.1和/或Kv3.2通道介导的疾病或病症可以选自以下列表。下面列出的疾病后的括号中的数字是指由美国精神病学协会出版的精神障碍诊断和统计手册第4版(DSM-IV)和/或国际疾病分类(International Classification of Diseases)第10版(ICD-10)中的分类代码。

[0229] 在本发明的一个实施方案中，式(I)的化合物或其药学上可接受的盐和/或溶剂化物和/其衍生物可以用于治疗或预防选自以下的疾病或病症：听力障碍、精神分裂症、抑郁症和情绪障碍、双相情感障碍、物质滥用障碍、焦虑症、睡眠障碍、听觉过敏和响度感知障碍、梅尼埃病、平衡障碍和内耳障碍、冲动控制障碍、人格障碍、注意力缺陷/多动障碍、孤独症谱群疾病、进食障碍、认知障碍、共济失调，疼痛例如神经性疼痛、炎性疼痛和混杂的疼痛，路易体痴呆和帕金森病。

[0230] 在本发明的一个实施方案中，式(I)的化合物或其药学上可接受的盐和/或溶剂化物和/其衍生物可以用于治疗或预防选自以下的疾病或病症：听力障碍(包括听力损失和耳

鸣)、精神分裂症、物质滥用障碍、疼痛(例如神经性疼痛、炎性疼痛和混杂的疼痛)、路易体痴呆和帕金森病。

[0231] 在本发明的一个实施方案中,式(I)的化合物或其药学上可接受的盐和/或溶剂化物和/其衍生物可以用于治疗或预防选自以下的疾病或病症:脆性X染色体、雷特障碍和阿尔茨海默病。

[0232] 本发明提供了用于预防或治疗选自以下的疾病或病症的方法:听力障碍、精神分裂症、抑郁症和情绪障碍、双相情感障碍、物质滥用障碍、焦虑症、睡眠障碍、听觉过敏和响度感知障碍、梅尼埃病、平衡障碍和内耳障碍、冲动控制障碍、人格障碍、注意力缺陷/多动障碍、孤独症谱群疾病、进食障碍、认知障碍、共济失调,疼痛例如神经性疼痛、炎性疼痛和混杂的疼痛,路易体痴呆和帕金森病,该方法包含向有此需要的个体施用有效量的式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物。

[0233] 本发明还提供了式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物在制备用于治疗或预防选自以下的疾病或病症的药物中的用途:听力障碍、精神分裂症、抑郁症和情绪障碍、双相情感障碍、物质滥用障碍、焦虑症、睡眠障碍、听觉过敏和响度感知障碍、梅尼埃病、平衡障碍和内耳障碍、冲动控制障碍、人格障碍、注意力缺陷/多动障碍、孤独症谱群疾病、进食障碍、认知障碍、共济失调,疼痛例如神经性疼痛、炎性疼痛和混杂的疼痛,路易体痴呆和帕金森病。

[0234] 在本发明的一个具体的实施方案中,提供了式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物,其用于治疗或预防听力障碍。听力障碍包括听神经病、听觉处理障碍、听力损失,其包括突发性听力损失、噪声性听力损失、物质诱导的听力损失以及60岁以上、65岁以上、70岁以上或75岁以上成年人的听力损失(老年性耳聋)和耳鸣。

[0235] 式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物可以具有治疗或预防梅尼埃病、平衡障碍和内耳障碍的用途。

[0236] 在本发明的一个具体的实施方案中,提供了式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物,其用于治疗或预防精神分裂症。精神分裂症包括偏执型(295.30)、紊乱型(295.10)、紧张型(295.20)、未分化型(295.90)和残留型(295.60)亚型;精神分裂症样精神障碍(295.40);情感性分裂症(295.70),包括双相型和抑郁型亚型;妄想症(297.1),包括色情狂型、夸张型、嫉妒型、迫害型、躯体型、混合型和不明型亚型;短暂性精神障碍(298.8);感应性精神障碍(297.3);由包括具有妄想和幻觉的亚型的一般医学病症引起的精神障碍;物质诱导的精神障碍,包括具有妄想(293.81)和幻觉(293.82)的亚型;和不明型精神障碍(298.9)。

[0237] 式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物可以具有治疗或预防抑郁症和情绪障碍的用途,包括严重抑郁发作、躁狂性发作、混合发作和轻躁狂发作;抑郁症,包括严重抑郁障碍、心境恶劣障碍(300.4)、未另外指明的抑郁症(311);双相性精神障碍,包括I型双相性精神障碍、II型双相性精神障碍(伴有轻躁狂发作的复发性重度抑郁发作)(296.89)、循环性精神障碍(301.13)和未另外指明的双相性精神障碍(296.80);其他情绪障碍,包括由一般医学病症引起的情绪障碍(293.83),其包括具有抑郁特征、具有重性抑郁样发作、具有躁狂特征和具有混合特征的亚型)、物质诱导的情绪

障碍(包括具有抑郁特征、具有躁狂特征和具有混合特征的亚型)和未另外指定的情绪障碍(296.90);季节性情感障碍。

[0238] 式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物可以具有治疗或预防癫痫的用途,(包括但不限于有关定位的癫痫、全身型癫痫、伴有全身性和局限性癫痫发作的癫痫等)、与伦诺克斯-加斯托综合征相关的癫痫发作、作为疾病或病症的并发症的癫痫发作(例如与脑病、苯丙酮尿症、幼年型戈谢病、Lundborg进行性肌阵挛性癫痫、中风、头部损伤、应激、激素变化、药物使用或戒断、酒精使用或戒断、睡眠剥夺、发热、感染等相关的癫痫发作)、特发性震颤、不宁腿综合征、部分性和全身性癫痫发作(包括强直性、阵挛性、强直-阵挛性、失张力性、肌阵挛性、失神型癫痫发作)、继发性全身性癫痫发作、颞叶癫痫、失神性癫痫(包括儿童期、青少年期、肌阵挛性、光诱发和模式诱发的)、严重癫痫性脑病(包括缺氧相关的和Rasmussen综合征)、发热惊厥、部分性癫痫持续状态、进行性肌阵挛性癫痫(包括翁-伦病和拉福拉病)、创伤后癫痫发作/癫痫(包括与头部损伤相关的那些)、简单反射性癫痫(包括光敏性、体感性和本体感受性、听源性和前庭性)、通常与癫痫相关的代谢障碍(如吡哆辛依赖性癫痫)、门凯卷发病、球形细胞脑白质营养不良)、因酒精和药物滥用(例如可卡因)导致的癫痫发作、与癫痫相关的皮质畸形(例如双皮质综合征或皮质下染色体异位),与癫痫发作或癫痫相关的染色体异常,例如部分单体性(15q)/安格尔曼综合征)。

[0239] 式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物可以具有治疗或预防物质相关性障碍的用途,包括物质应用所致精神障碍,例如物质依赖、物质渴求和物质滥用;物质诱导的障碍,例如物质中毒、物质戒断、物质诱导的谵妄、物质诱导的持续性痴呆、物质诱导的持续性遗忘症、物质诱导的感应性精神障碍、物质诱导的情绪障碍、物质诱导的焦虑性障碍、物质诱导的性功能障碍、物质诱导的睡眠障碍和致幻剂持久性知觉障碍(闪回);酒精相关性疾病,如酒精依赖(303.90)、酒精滥用(305.00)、酒精中毒(303.00)、戒酒(291.81)、酒精中毒性谵妄、戒酒性谵妄、酒精诱导的持续性痴呆、酒精诱导的持续性遗忘症、酒精诱导的感应性精神障碍、酒精诱导的情绪障碍、酒精诱导的焦虑症、酒精诱导的性功能障碍、酒精诱导的睡眠障碍和未另外说明的酒精相关性疾病(291.9);安非他明(或类安非他明)相关障碍,如安非他明依赖(304.40)、安非他明滥用(305.70)、安非他明中毒(292.89)、安非他明戒断(292.0)、安非他明中毒性谵妄、安非他明诱发的感应性精神障碍、安非他明诱发的情绪障碍、安非他明诱发的焦虑性障碍、安非他明诱发的性功能障碍、安非他明诱发的睡眠障碍和未另外指明的安非他明相关障碍(292.9);咖啡因相关障碍,例如咖啡因中毒(305.90)、咖啡因诱导的焦虑障碍、咖啡因诱导的睡眠障碍和未另外指明的咖啡因相关障碍(292.9);大麻相关障碍,例如大麻依赖(304.30)、大麻滥用(305.20)、大麻中毒(292.89)、大麻中毒谵妄、大麻诱发的精神障碍、大麻诱发的焦虑障碍和未另外说明的大麻相关障碍(292.9);可卡因相关障碍,如可卡因依赖(304.20)、可卡因滥用(305.60)、可卡因中毒(292.89)、可卡因戒断(292.0)、可卡因中毒性谵妄、可卡因诱导的精神障碍、可卡因诱导的情绪障碍、可卡因诱导的焦虑障碍、可卡因诱导的性功能障碍、可卡因诱导的睡眠障碍和未另外指明的可卡因相关障碍(292.9);迷幻剂相关疾病,例如迷幻剂依赖(304.50)、迷幻剂滥用(305.30)、迷幻剂中毒(292.89)、迷幻剂持续性感知障碍(闪回)(292.89)、迷幻剂中毒性谵妄、迷幻剂诱导的精神病性疾病、迷幻剂诱导的情绪障碍、迷幻

剂诱导的焦虑症和未另外说明的迷幻剂相关疾病(292.9);吸入剂相关疾病,如吸入剂依赖(304.60)、吸入剂滥用(305.90)、吸入剂中毒(292.89)、吸入剂中毒谵妄、吸入剂诱导的持续性痴呆、吸入剂诱导的精神病、吸入剂诱导的心境障碍、吸入剂诱导的焦虑症和未另外说明的吸入剂相关疾病(292.9);尼古丁相关疾病,例如尼古丁依赖(305.1)、尼古丁戒断(292.0)和未另外说明的尼古丁相关疾病(292.9);阿片样物质相关疾病,例如阿片样物质依赖(304.00)、阿片样物质滥用(305.50)、阿片样物质中毒(292.89)、阿片样物质戒断(292.0)、阿片样物质中毒性谵妄、阿片样物质诱导的精神病、阿片样物质诱导的心境障碍、阿片样物质诱导的性功能障碍、阿片样物质诱导的睡眠障碍和未另外说明的阿片样物质相关疾病(292.9);苯环利定(或苯环利定样)相关疾病,例如苯环利定依赖(304.60)、苯环利定滥用(305.90)、苯环利定中毒(292.89)、苯环利定中毒性谵妄、苯环利定诱导的精神病、苯环利定诱导的心境障碍、苯环利定诱导的焦虑症和未另外说明的苯环利定相关疾病(292.9);镇静剂-、催眠剂-或抗焦虑剂相关障碍,例如镇静剂、催眠剂或抗焦虑剂依赖(304.10),镇静剂、催眠剂或抗焦虑剂滥用(305.40)、镇静剂、催眠剂或抗焦虑剂中毒(292.89)、镇静剂、催眠剂或抗焦虑剂戒断(292.0)、镇静剂、催眠剂或抗焦虑剂中毒性谵妄、镇静剂、催眠剂或抗焦虑剂戒断谵妄、镇静剂、催眠剂或抗焦虑剂持续性痴呆、镇静剂、催眠剂或抗焦虑剂持续性遗忘障碍、镇静剂、催眠剂或抗焦虑剂诱发的精神障碍、镇静剂、催眠剂或抗焦虑剂诱发的情绪障碍、镇静剂、催眠剂或抗焦虑剂诱发的焦虑障碍、镇静剂、催眠剂或抗焦虑剂诱发的性功能障碍、镇静剂、催眠剂或抗焦虑剂诱发的睡眠障碍以及镇静剂、催眠剂或抗焦虑剂诱发的未另外说明的相关病症(292.9);多物质相关疾病,例如多物质依赖(304.80);和其他(或未知)物质相关障碍,例如促蛋白合成类固醇、硝酸盐吸入剂和一氧化二氮。

[0240] 式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物可以具有治疗或预防焦虑症的用途,包括惊恐发作;惊恐性障碍,包括恐怖性障碍不伴广场恐怖(300.01)和恐怖性障碍伴广场恐怖(300.21);广场恐怖症;广场恐怖不伴恐怖性病症史(300.22)、特异恐怖症(300.29,以前称为单纯恐怖症),包括动物型、自然环境型、血-注射-损伤型、情境类型和其他类型亚型)、社交恐怖症(社交焦虑症,300.23)、强迫症(300.3)、创伤后应激障碍(309.81)、急性应激障碍(308.3)、广泛性焦虑症(300.02)、由一般医学病症引起的焦虑症(293.84)、物质诱导的焦虑症、分离焦虑障碍(309.21)、具有焦虑的适应障碍(309.24)和未另外指明的焦虑症(300.00)。

[0241] 式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物可以具有治疗或预防睡眠障碍的用途,包括原发性睡眠障碍,例如睡眠异常,例如原发性失眠(307.42)、原发性嗜睡症(307.44)、发作性睡病(347)、与呼吸相关的睡眠障碍(780.59)、昼夜节律睡眠障碍(307.45)和未另外说明的睡眠障碍(307.47);原发性睡眠障碍,例如深眠状态,例如恶梦障碍(307.47)、夜惊症(307.46)、梦游症(307.46)和未另外指明的深眠状态(307.47);与另一种精神障碍相关的睡眠障碍,例如与另一种精神障碍相关的失眠(307.42)和与另一种精神障碍相关的睡眠过度(307.44);由于一般医学病症引起的睡眠障碍,特别是与例如神经障碍、神经性疼痛、不宁腿综合征、心脏和肺部疾病这样疾病相关的睡眠障碍;和物质诱导的睡眠障碍,包括失眠型、睡眠过度型、深眠状态型和混合型亚型;睡眠呼吸暂停和飞行时差反应综合征。

[0242] 式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物可以具有治疗或预防听觉过敏和响度感觉障碍,包括脆性X综合征和孤独症的用途。

[0243] 式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物可以具有治疗或预防冲动控制障碍的用途,包括:间歇性暴躁障碍(312.34)、偷窃癖(312.32)、病理性赌博(312.31)、纵火癖(312.33)、拔毛癖(312.39)、未另外指明的冲动控制障碍(312.3)、暴食、强迫性购买、强迫性性行为和强迫性囤积。

[0244] 式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物可以具有治疗或预防性功能障碍的用途,包括性欲障碍,例如性欲过低障碍(302.71)和性厌恶障碍(302.79);性唤起障碍,例如女性性唤起障碍(302.72)和男性勃起障碍(302.72);性欲障碍,例如女性性高潮障碍(302.73)、男性性高潮障碍(302.74)和早泄(302.75);性交疼痛障碍,例如性交困难(302.76)和阴道痉挛(306.51);未另外指明的性功能障碍(302.70);性欲倒错,例如露阴癖(302.4)、恋物癖(302.81)、摩擦癖(302.89)、恋童癖(302.2)、性受虐癖(302.83)、性虐待癖(302.84)、易装癖(302.3)、窥阴癖(302.82)和未另外说明的性欲倒错(302.9);性认同异常,例如儿童性身份障碍(302.6)和青少年或成人性身份障碍(302.85);和未另外指明的性功能障碍(302.9)。

[0245] 式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物可以具有治疗或预防人格障碍的用途,包括偏执型人格障碍(301.0)、分裂型人格障碍(301.20)、精神分裂型人格障碍(301,22)、反社会型人格障碍(301.7)、边缘型人格障碍(301,83)、表演型人格障碍(301.50)、自恋型人格障碍(301,81)、回避型人格障碍(301.82)、依赖型人格障碍(301.6)、强迫型人格障碍(301.4)和未另行指明的人格障碍(301.9)亚型。

[0246] 式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物可以具有治疗或预防注意力缺陷/多动障碍的用途,包括注意力缺陷/多动障碍组合型(314.01)、注意力缺陷/多动障碍-注意障碍为主型(314.00)、注意力缺陷/多动障碍多动-冲动型(314.01)和未另外指明的注意力缺陷/多动障碍(314.9)的亚型;多动障碍;破坏性行为障碍,例如行为障碍,包括儿童期发作型(321.81)、青少年发作型(312.82)和未明确的发作(312.89)的亚型,对立违抗性障碍(313.81)和未另外明确说明的破坏性行为障碍;和抽动性运动障碍,例如图雷特病(307.23)亚型。

[0247] 式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物可以具有治疗或预防孤独症谱群疾病的用途,包括孤独症(299.00)、阿斯伯格症(299.80)、雷特障碍(299.80)、童年瓦解性障碍(299.10)和未另外说明的广泛性障碍(299.80,包括非典型孤独症)。

[0248] 式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物可以具有治疗或预防进食障碍的用途,例如神经性厌食症(307.1),包括限制型和暴食/净化型亚型;神经性贪食症(307.51),包括净化型和非净化型亚型;肥胖症;强迫性进食障碍;暴食症;以及未另外指明的进食障碍(307.50)。

[0249] 式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物可以具有增强认知的用途,包括治疗其他疾病中的认知障碍,所述其他疾病例如精神分裂症、双相情感障碍、抑郁症、其他精神障碍和与认知缺损相关的精神病,例如阿尔茨海默病。

或者，式(I)的化合物或其药学上可接受的盐和/或溶剂化物可以具有预防认知缺损的用途，例如可能与疾病相关的认知缺损，所述疾病例如精神分裂症、双相情感障碍、抑郁症、其他精神障碍和与认知缺损相关的精神病，例如阿尔茨海默病。

[0250] 式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物可以具有治疗或预防共济失调，包括共济失调，特别是脊髓小脑性共济失调，尤其是与R420H、R423H或F448L突变相关的共济失调的用途。

[0251] 式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物可以具有治疗或预防疼痛的用途，包括伤害性疼痛、神经性疼痛、炎性疼痛或混杂的疼痛。

[0252] 伤害性疼痛代表对例如皮肤、肌肉、内脏器官、关节、肌腱或骨的组织的有害伤害或损伤的正常反应。构成本发明的一部分的伤害性疼痛的实例包括躯体痛：肌肉骨骼疼痛(关节疼痛、肌盘膜痛)或皮肤疼痛，其通常是良好局限性的；或内脏痛：中空器官或平滑肌。

[0253] 神经性疼痛是由躯体感觉神经系统中的原发病灶或疾病引发或引起的疼痛。感觉异常的范围从感知为感觉异常(麻木)的缺陷到超敏反应(痛觉过敏或异常性疼痛)和感觉迟钝(麻刺感和其他感觉)。构成本发明一部分的神经性疼痛的实例包括但不限于糖尿病性神经病、疱疹后神经痛、脊髓损伤疼痛、幻肢(截肢后)疼痛和脑卒中后中枢性疼痛。神经性疼痛的其他原因包括创伤、化疗和重金属暴露。

[0254] 炎性疼痛是由于在组织炎症部位释放的各种介质激活和致敏伤害性疼痛途径而发生的。在炎性疼痛中作为关键参与者涉及的介质为促炎细胞因子如IL-1-α、IL-1-β、IL-6和TNF-α、趋化因子、活性氧物质、血管活性胺、脂质、ATP、酸和由浸润性白细胞、血管内皮细胞或组织驻留肥大细胞释放的其他因子。构成本发明一部分的炎性疼痛的实例原因包括阑尾炎、类风湿性关节炎、炎性肠病和带状疱疹。

[0255] 混杂的疼痛是指不易分类的疼痛病症或障碍。目前对其潜在机制的理解仍然是初步的，不过，这些疾病的特定疗法是众所周知的；它们包括癌症疼痛、偏头痛和其他原发性头痛以及纤维肌痛类型的广泛疼痛。

[0256] 适当地，可以由Kv3.1和/或Kv3.2和/或Kv3.3通道的调节剂介导的特定疼痛适应证为神经性疼痛和/或炎性疼痛。

[0257] 疼痛是主观状况，并且在临床环境中倾向于通过患者的自我评估来测量。因此，可能难以测量和量化痛阈。对于慢性痛，典型地使用主观11分评定量表，其中0是无痛，且10是可想象的最严重疼痛。个体通常在给定时间段(通常为一天)内记录其最严重的疼痛。还记录最小平均基线评分，并且相对于基线测量对药物的响应，例如，可以观察到疼痛从基线评分减少至少10％、20％、30％、40％或50％。

[0258] 由于个体对药物的反应可能不同，因此并非所有个体都可能经历疼痛从基线评分的减轻。因此，适当地，在至少10％、20％、30％、40％、50％、60％、70％、80％、90％或所有测试个体中观察到减少。

[0259] 因此，在本发明的一个实施方案中，在将Kv3.1/Kv3.2/Kv3.3调节剂例如式(I)的化合物或其药学上可接受的盐、溶剂化物和/衍生物施用于有需要的个体时，观察到疼痛从基线评分降低至少10％、20％、30％、40％或50％。

[0260] Kv3.1/Kv3.2/Kv3.3调节剂的施用可以发生在预期的疼痛发作之前或疼痛发作之后。在预期疾病或病症的发展可能导致个体经历的疼痛增加的情况下，可以施用Kv3.1/

Kv3.2/Kv3.3调节剂，例如式(I)化合物或其药学上可接受的盐、溶剂化物和/或衍生物。在个体已经经历疼痛的情况下，可以向有此需要的个体施用Kv3.1/Kv3.2/Kv3.3调节剂，例如式(I)的化合物或其药学上可接受的盐、溶剂化物和/衍生物。

[0261] 只要需要治疗，则可以继续治疗有需要的个体，例如1天、1周、2周、3周、1个月、6个月、1年、超过1年、超过2年、超过5年或超过10年。因此，在本发明一个实施方案中，将治疗有效量的Kv3.1/Kv3.2/Kv3.3调节剂，例如式(I)的化合物或其药学上可接受的盐、溶剂化物和/衍生物施用于有此需要的个体持续1天至1个月、1周至3个月、1个月至6个月、3个月至1年或超过1年。

[0262] 个体中疼痛的减轻可以通过评估对外部刺激如机械或热(例如冷)刺激(如实验部分中所述)的反应来测量。减轻可以被认为是逆转百分比(通过测量受影响的疼痛部位与未受影响的疼痛部位的剂量药前和剂量后阈值来计算，例如在实验部分的数据分析下更详细地描述的)或通过测量受影响的疼痛部位的缩回阈值来计算。优选地，使用百分比逆转计算。

[0263] 因此，在本发明的一个实施方案中，在施用治疗有效量的Kv3.1/Kv3.2/Kv3.3调节剂，例如式(I)的化合物或其药学上可接受的盐、溶剂化物和/衍生物后，对疼痛(例如神经性疼痛或炎性疼痛)的敏感性逆转超过20％、超过30％、超过40％、超过50％、超过60％、超过70％、超过80％或超过90％。适当地，对疼痛的敏感性逆转超过80％或超过90％。

[0264] 接受Kv3.1/Kv3.2/Kv3.3调节剂的个体可经历后续益处，例如改善的功能、情绪、睡眠、生活质量、减少的工作时间中的一种或多种。

[0265] 在一个具体的实施方案中，式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物可以具有治疗或预防神经性疼痛的用途。

[0266] 在一个具体的实施方案中，式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物可以具有治疗或预防炎性疼痛的用途。

[0267] 在一个具体的实施方案中，式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或其衍生物可以具有治疗或预防混杂的疼痛的用途。

[0268] 在一个实施方案中，提供了式(I)的化合物，用于预防急性噪声性听力损失。

[0269] 在一个实施方案中，提供了预防急性噪声性听力损失的方法，包含向有此需要的个体施用式(I)的化合物。

[0270] 在一个实施方案中，提供了式(I)的化合物在制备用于预防急性噪声性听力损失的药物中的用途。

[0271] 急性噪声性听力损失可以由诸如暴露于响亮噪声或爆炸的事件引起。在这些情况下，当预期未来事件可能导致急性噪声性听力损失时，可以在该事件之前施用式(I)的化合物或其药学上可接受的盐、溶剂化物和/衍生物，以预防或减少急性噪音性听力损失。化合物(I)或其药学上可接受的盐、溶剂化物和/或衍生物的施用可以预防任何急性噪声性听力损失，或者可以降低急性噪声性听力损失的严重程度，或者可以减轻由急性噪声性听力损失引起的其他症状，例如耳鸣。

[0272] 将“急性听力损失”定义为在数小时或数天内迅速发生的听力损失。例如，听力损失可以在数分钟、数小时或数天的时间期限内发生(例如在至多1天的时间期限内，例如至多2天、3天、4天、5天、6天或7天)。急性听力损失典型地由暴露于响亮的声音或爆炸引起。由

暴露于大声或爆炸引起的听力损失在本文中称为“噪声性听力损失”。因此，“急性噪声性听力损失”是指由于暴露于响亮的声音或爆炸引起的在数小时或数天内快速发生的听力损失。

[0273] 急性听力损失的重要症状包括：

[0274] 1.听觉阈值的偏移，即在没有其他声音存在的情况下可以听到的纯音的最小声级的增加；

[0275] 2.耳鸣；以及

[0276] 3.中枢听觉处理的退化，例如听觉时间处理和/或语音理解受损。

[0277] “响亮的”噪声或爆炸可以是至少90dB，例如至少100dB、至少110dB、至少120dB或至少130dB。

[0278] 在一个实施方案中，式(I)的化合物或其药学上可接受的盐、溶剂化物和/或衍生物的施用可以在预期引起噪声性急性听力损失的事件之前开始。例如，式(I)化合物或其药学上可接受的盐、溶剂化物和/或衍生物的施用可以提前至多2周开始，例如在预期会引起噪声性急性听力损失的事件之前至多1周、6天、5天、4天、3天、2天、24h、12h、6h、5h、4h、3h、2h、1h、30分钟或至多15分钟开始。式(I)的化合物或其药学上可接受的盐、溶剂化物和/衍生物可以在预期引起噪音性急性听力损失的事件之前多次施用。

[0279] 在一个实施方案中，式(I)的化合物或其药学上可接受的盐、溶剂化物和/衍生物在潜在暴露于预期会引起急性噪声性听力损失的噪音或爆炸之前施用，用于预防或减少永久性耳鸣的发展；用于防止或减少听阈的永久偏移的发展；或用于防止或减少永久性退化的中枢听觉处理的发展，包括例如听觉时间处理和/或语音理解。

[0280] 可以理解，预先施用可以是在个体被认为处于暴露于预期会引起急性噪声性听力损失的噪声或爆炸的风险的情况下，并且不限于最终发生这种暴露的那些情况。

[0281] 在一个实施方案中，式(I)的化合物或其药学上可接受的盐、溶剂化物和/衍生物的施用在预期引起噪声性急性听力损失的事件期间开始。式(I)化合物或其药学上可接受的盐、溶剂化物和/或衍生物可以在预期会引起噪声性急性听力损失的事件期间多次施用。

[0282] 在一个实施方案中，式(I)的化合物或其药学上可接受的盐、溶剂化物和/衍生物最初在预期会引起急性噪声性听力损失的噪音或爆炸期间施用，用于预防或减少永久性耳鸣的发展；用于防止或减少听阈的永久偏移的发展；或用于防止或减少永久性退化的中枢听觉处理的发展，包括例如听觉时间处理和/或语音理解。

[0283] 在一个实施方案中，式(I)的化合物或其药学上可接受的盐、溶剂化物和/衍生物的施用在预期引起急性噪声性听力损失的事件之后开始。

[0284] 因此，在一个实施方案中，式(I)化合物或其药学上可接受的盐、溶剂化物和/或衍生物最初在预期会引起急性噪声性听力损失的噪音或爆炸之后施用，用于预防或减少永久性耳鸣的发展；用于防止或减少听阈的永久偏移的发展；或用于防止或减少永久性退化的中枢听觉处理的发展，包括例如听觉时间处理和/或语音理解。

[0285] 当式(I)的化合物在预期引起急性噪声性听力损失的事件之后施用时，这种施用通常在“急性期”期间进行，即在听力损失已经确定之前进行。

[0286] 在一个实施方案中，式(I)的化合物或其药学上可接受的盐、溶剂化物和/衍生物的施用可以在预期引起噪声性急性听力损失的事件后至多2个月开始，例如在预期引起急

性噪声性听力损失的事件后至多1个月、2周、1周、6天、5天、4天、3天、2天、24h、12h、6h、5h、4h、3h、2h、1h、30分钟或至多15分钟。式(I)化合物或其药学上可接受的盐、溶剂化物和/或衍生物可以在预期会引起噪声性急性听力损失的事件之后多次施用。

[0287] 式(I)的化合物或其药学上可接受的盐、溶剂化物和/衍生物可以在至多7天(例如,至多1天、至多2天、至多3天、至多4天、至多5天、至多6天或至多7天)、1-2周(例如,7-8天、7-9天、7-10天、7-11天、7-12天、7-13天或7-14天)、2-4周(例如,2-3周或2-4周)或1-2个月(例如,4-6周或4-8周)的期限内施用。

[0288] 式(I)的化合物或其药学上可接受的盐、溶剂化物和/衍生物最初可以在预期会引起急性噪声性听力损失的噪音或爆炸之前至多1天,例如至多2天、至多3天、至多5天、至多1周、至多2周或至多1个月施用,在暴露于预期会引起急性噪声性听力损失的噪声或爆炸之前的任何点开始的施用典型地在暴露于预期会引起急性噪声性听力损失的噪声或爆炸之后持续至多2个月,例如之后至多1个月、之后至多3周、之后至多2周、之后至多1周、之后至多5天、之后至多3天、之后至多2天或之后至多1天。

[0289] 在一个实施方案中,提供了式(I)的化合物或其药学上可接受的盐、溶剂化物和/或衍生物,其用于预防或减少听阈的永久偏移的发展,其中听阈的永久偏移被减少至少10dB,例如至少15dB、至少20dB、至少30dB、至少40dB或完全减少。

[0290] 药物组合物

[0291] 为了用于疗法,本发明的化合物通常作为药物组合物施用。本发明还提供了药物组合物,其包含式(I)的化合物或其药学上可接受的盐和/或溶剂化物(例如盐)和/或衍生物和药学上可接受的载体或赋形剂。

[0292] 在一个实施方案中,提供了药物组合物,其包含式(I)的化合物或其药学上可接受的盐和/或溶剂化物(例如盐)和/或衍生物,该药物组合物用于治疗或预防选自以下的疾病或病症:听力障碍、精神分裂症、抑郁症和情绪障碍、双相情感障碍、物质滥用障碍、焦虑症、睡眠障碍、听觉过敏和响度感知障碍、梅尼埃病、平衡障碍和内耳障碍、冲动控制障碍、人格障碍、注意力缺陷/多动障碍、孤独症谱群疾病、进食障碍、认知障碍、共济失调,疼痛例如神经性疼痛、炎性疼痛和混杂的疼痛,路易体痴呆和帕金森病。

[0293] 在另一个实施方案中,提供了用于预防或治疗选自以下的疾病或病症的方法:听力障碍、精神分裂症、抑郁症和情绪障碍、双相情感障碍、物质滥用障碍、焦虑症、睡眠障碍、听觉过敏和响度感知障碍、梅尼埃病、平衡障碍和内耳障碍、冲动控制障碍、人格障碍、注意力缺陷/多动障碍、孤独症谱群疾病、进食障碍、认知障碍、共济失调,疼痛例如神经性疼痛、炎性疼痛和混杂的疼痛,路易体痴呆和帕金森病,该方法包含向有此需要的个体施用有效量的药物组合物,所述组合物包含式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或衍生物。

[0294] 本发明还提供了包含式(I)的化合物或其药学上可接受的盐和/或其溶剂化物(例如盐)和/或衍生物的药物组合物在制备治疗或预防选自以下的疾病或病症的药物中的用途:听力障碍、精神分裂症、抑郁症和情绪障碍、双相情感障碍、物质滥用障碍、焦虑症、睡眠障碍、听觉过敏和响度感知障碍、梅尼埃病、平衡障碍和内耳障碍、冲动控制障碍、人格障碍、注意力缺陷/多动障碍、孤独症谱群疾病、进食障碍、认知障碍、共济失调,疼痛例如神经性疼痛、炎性疼痛和混杂的疼痛,路易体痴呆和帕金森病。

[0295] 式(I)的化合物或其药学上可接受的盐和/或其溶剂化物和/或其衍生物可以通过任意方便的方法施用,例如通过口服、肠胃外、口含、舌下、鼻、直肠或透皮施用,并相应调整药物组合物。其他可能的施用途径包括鼓室内和耳蜗内。

[0296] 当通过口服给予时,可以将具有活性的式(I)的化合物或其药学上可接受的盐和/或其溶剂化物和/或其衍生物配制成液体或固体,例如糖浆剂、混悬剂、乳剂、片剂、胶囊或锭剂。

[0297] 液体制剂通常由活性成分(例如式(I)的化合物或其药学上可接受的盐和/或溶剂化物(例如盐)和/或衍生物)在适合的液体载体(例如水性溶剂(如水、乙醇或甘油)或非水性溶剂(例如聚乙二醇或油))中的混悬液或溶液组成。该制剂还可以包含助悬剂、防腐剂、矫味剂和/或着色剂。

[0298] 片剂形式的组合物可以使用常规用于制备固体制剂的任意适合的药用载体制备,例如硬脂酸镁、淀粉、乳糖、蔗糖和纤维素。

[0299] 胶囊形式的组合物可以使用常规包封方法制备,例如包含活性成分(例如式(I)化合物或其药学上可接受的盐和/或溶剂化物(例如盐)和/或衍生物)的小丸可以使用标准载体制备,然后填充到硬明胶胶囊中;或者,分散体或混悬液可以使用适合的药用载体制备,例如水性树胶、纤维素、硅酸盐或油,然后将分散体或混悬液填充到软明胶胶囊中。

[0300] 典型的肠胃外组合物由活性成分(例如式(I)化合物或其药学上可接受的盐和/或溶剂化物(例如盐)和/或衍生物)在无菌水性载体或肠胃外可接受的油(例如聚乙二醇、聚乙烯吡咯烷酮、卵磷脂、花生油或芝麻油)中的溶液或混悬液组成。或者,可以将溶液冻干,然后在即将施用前用适合的溶剂重配。

[0301] 可以将用于经鼻施用的组合物便利地配制成气雾剂、滴剂、凝胶和粉末。气雾剂制剂典型地包含活性成分在药学上可接受的水性或非水性溶剂中的溶液或精细混悬液,并且通常以无菌形式以单剂量或多剂量存在于密封容器中,所述密封容器可以采取药筒或再填充的形式以与雾化装置一起使用。或者,密封容器可以为一次性分配装置,例如单剂量鼻吸入器或配备计量阀的气雾剂分配器。当剂型包含气雾剂分配器时,其包含推进剂,所述推进剂可以为压缩气体,例如空气,或有机推进剂,例如氟氯烃或氢氟烃。气雾剂剂型也可以采用泵-雾化器的形式。

[0302] 适于口含或舌下施用的组合物包括片剂、锭剂和软锭剂,其中将活性成分与载体例如糖和阿拉伯胶、黄蓍胶或明胶和甘油一起配制。

[0303] 用于直肠施用的组合物方便地为包含常规栓剂基质如可可脂的栓剂形式。

[0304] 适于透皮施用的组合物包括软膏、凝胶和贴剂。在一个实施方案中,组合物为单位剂量形式,例如片剂、胶囊或安瓿。

[0305] 根据施用方法的不同,组合物可以包含0.1%-100%重量,例如10-60%重量的活性物质。根据施用方法的不同,组合物可以包含0%-99%重量,例如40%-90%重量的载体。根据施用方法的不同,组合物可以包含0.05mg-1000mg,例如1.0mg-500mg的活性物质。根据施用方法的不同,组合物可以包含50mg-1000mg,例如100mg-400mg的载体。用于治疗上述病症的化合物的剂量将以通常的方式随病症的严重程度、患者的体重和其他类似因素的不同而变化。然而,作为一般性指导原则,适合的单位剂量可以为0.05mg-1000mg,更适合地是1.0mg-500mg,并且这样的单位剂量可以每天施用多于一次,例如每天两次或三次。这种疗

法可以延伸数周或数月。

[0306] 提供给个体的剂量典型地为安全有效的剂量,即,期望的益处和不期望的副作用的可接受的平衡。

[0307] 在另一个方面,本发明提供了包含式(I)化合物或其药学上可接受的盐、溶剂化物和/或衍生物(例如包含式(I)化合物或其药学上可接受的衍生物的组合)以及另外的一种或多种药学上可接受的活性成分的组合。

[0308] 本发明提供了式(I)的化合物,其用于与另外的一种或多种药学上可接受的活性成分组合使用。

[0309] 当化合物与其他治疗剂组合使用时,化合物可以通过任意便利的途径依次或同时施用。或者,化合物可以单独施用。

[0310] 上述组合可以便利地以药物制剂的形式使用,因此包含如上定义的组合以及药学上可接受的载体或赋形剂的药物制剂构成本发明的另一个方面。这类组合的各个成分可以在分开的或组合的药物制剂中依次或同时施用。组合的各个成分也可以通过相同或不同的途径分开施用。

[0311] 当式(I)化合物或其药学上可接受的衍生物与对相同疾病状态有活性的第二种治疗剂组合使用时,每种化合物的剂量可以与单独使用该化合物时的剂量不同。本领域技术人员将容易理解适当的剂量。

[0312] 适当地,式(I)的化合物或其药学上可接受的盐、溶剂化物和/或衍生物通过口服施用。

[0313] 适当地,式(I)的化合物或其药学上可接受的盐、溶剂化物和/或衍生物以每天2至400mg施用,例如每天2至300mg,尤其是每天5至250mg。

[0314] 适当地,将式(I)的化合物或其药学上可接受的盐、溶剂化物和/或衍生物每天施用一次或两次。

[0315] 适当地,将式(I)的化合物或其药学上可接受的盐、溶剂化物和/或衍生物施用至少三个月期限。

[0316] 理想地,式(I)的化合物或其药学上可接受的盐、溶剂化物和/或衍生物通过口服施用,每天一次或两次,每天2-400mg,例如每天2-300mg,特别是每天5-250mg。

[0317] 人类个体可以是成人,例如18至65岁。或者,人类个体可以是66岁或以上。可以将式(I)的化合物或其药学上可接受的盐、溶剂化物和/或衍生物施用于年龄小于18岁,例如4-17岁的人类个体。在进行性肌阵挛性癫痫和脆性X染色体综合征的情况下,对低于18岁的人类个体的施用可能具有特别的相关性。

[0318] 为了便利性和有助于患者的依从性,可以使用例如贴剂或植入物这样的递送技术在持续的时间期限内递送式(I)的化合物或其药学上可接受的盐、溶剂化物和/或衍生物,例如至少1周或至少4周。

[0319] 实验

[0320] 本发明通过如下所述的化合物来示例。以下实施例描述了本发明具体化合物的实验室合成,并不意味着以任何方式就化合物或方法而言限制本发明的范围。应当理解,尽管使用了特定的试剂、溶剂、温度和时间期限,但是存在可以用于产生类似结果的许多可能的等效替代方案。本发明意在包括这样的等效方案。

[0321] 分析仪器

[0322] 除非另有说明，否则起始材料、试剂和溶剂得自商业供应商，并且无需进一步纯化即可使用。除非另有说明，否则所有具有手性中心的化合物都是外消旋的。当反应被描述为已经以与先前更完整描述的反应类似的方式进行时，所使用的一般反应条件基本上相同。使用的后处理条件具有本领域的标准类型，但可以从一个反应到另一个反应进行调整。起始材料可以不一定已经由所提及的批次制备。合成的化合物可以具有不同纯度，例如85%-99%。在一些情况下，为此调整摩尔数和产率的计算。

[0323] HPLC-质谱(HPLC-MS)在与HPLC仪器Agilent 1100系列偶联的Agilent1100系列LC/MSD质谱仪上获取，以正电喷雾电离模式和酸性梯度条件操作。

[0324] 质量控制(3分钟方法)：在Zorbax SB C18柱(1.8μm 3×50mm)上在酸性条件下进行LC/MS-ES+。流动相:A:(H2O+0.05体积%TFA)/B:(CH3CN+0.05体积%TFA)。梯度:t＝0min 0%(B)，在2.5min内从0至95%(B)，95%(B)持续0.2min，在0.2分钟内从95至100%(B)，100%(B)持续0.4min，在0.1min内从100%至0%(B)。停止时间4min。柱T＝60℃。流速:1.5ml/min。质量范围ES+:(100-1000amu,F＝60)。UV检测波长:DAD 1A＝220.8,DAD 1B＝254.8。在所述化合物的分析表征中，该方法的应用由“QC_3_MIN”表示。

[0325] 手性控制：在CHIRALCEL®OD-H(250x4,6mm-5um)上在酸性条件下进行LC/MS-ES+。流动相:A:(H2O+0.05体积%TFA)/B:(CH3CN+0.05体积%TFA)。梯度:t＝0-6min 35%(B)，t＝6-40min从35%至50%(B)，t＝6-40min从50%至70%(B)，t＝45-50min从70%至35%(B)，t＝50-55min35%(B)。停止时间60min。柱T＝40℃。流速:1.0ml/min。UV检测波长:DAD 1A＝220.8,DAD 1B＝254.8。

[0326] 质子磁共振(NMR)光谱在Varian Instruments上在300、400、500或600MHz记录，或在Bruker Instruments上在400MHz记录。使用残留溶剂线作为内标，以ppm(δ)报告化学位移。分裂模式被设计为s(单峰)、br.s(宽单峰)、d(双峰)、t(三重峰)、q(四重峰)、dd(双联双峰)、dt(双联三重峰)和m(多重峰)。在25-60℃范围内的温度下记录NMR光谱。

[0327] 在f1和f2两者中使用3355Hz的光谱宽度以500ms的混合时间获取2D NMR NOESY实验。收集总计256个增量，用线性预测处理至1K，每个扫描8次。在两个维度上用正弦钟形偏移处理数据，并且在f1中用LB＝0.3Hz处理数据。在许多制备中，使用Biotage自动化快速色谱法(SP1和SP4)或Flash Master Personal系统进行纯化。

[0328] 快速色谱在230-400目硅胶(由Merck AG Darmstadt,Germany提供)或300-400目硅胶(由Sinopharm Chemical Reagent Co.,Ltd.提供)、Varian Mega BE-Si预填充柱、预填充Biotage硅胶柱(例如Biotage SNAP柱)上进行。

[0329] 缩写

[0330] AIBN 偶氮双异丁腈

[0331] BuLi 丁基锂

[0332] $CDCl_3$ 氘代氯仿

[0333] CCl_4 四氯化碳

[0334] D_2O 重水

[0335] DCM 二氯甲烷

[0336] DIPEA N,N-二异丙基乙胺

[0337] DMAP 4-二甲基氨基吡啶

[0338] DMF N,N-二甲基甲酰胺

[0339] DMSO 二甲亚砜

[0340] DMSO-d_6 氘代二甲亚砜

[0341] Et_2O 乙醚

[0342] EtOAc 乙酸乙酯

[0343] h 小时

[0344] HATU (O-7-氮杂苯并三唑-1-基)-N,N,N',N'-四甲基脲鎓六氟磷酸盐)

[0345] HCl 氯化氢

[0346] K_2CO_3 碳酸钾

[0347] MeCN/CH_3CN 乙腈

[0348] MeOH 甲醇

[0349] MOM 甲氧基甲基

[0350] NaH 氢化钠

[0351] Na_2SO_4 硫酸钠

[0352] Na_2CO_3 碳酸钠

[0353] NaOH 氢氧化钠

[0354] NaOMe 甲醇钠

[0355] NMR 核磁共振

[0356] r.t. 室温

[0357] T3P 丙基膦酸酐

[0358] MTBE 甲基叔丁基醚

[0359] TBTU 苯并三唑-1-基-N,N,N',N'-四甲基脲鎓四氟硼酸盐

[0360] TEA 三乙胺

[0361] TFA 三氟乙酸

[0362] THF 四氢呋喃

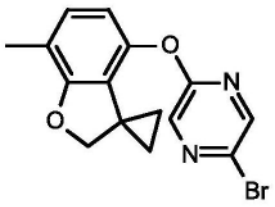
[0363] THP 四氢吡喃

[0364] wt. 重量

[0365] 化合物实施例

[0366] 中间体1

[0367] 2-溴-5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基-吡嗪

[0368] 

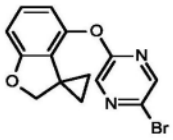
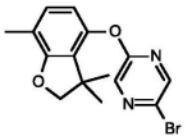
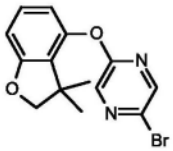
[0369] 将7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-醇(中间体156WO2012076877,1.11g,6,30mmol)、2,5-二溴吡嗪(1.5g,6,30mmol)和碳酸二钾(1.31g,9.46mmol)在N,N-二甲基甲酰胺(14mL)中的混合物在120℃搅拌3小时。冷却后,用MTBE(100ml)稀释该反应混合物,用

盐水(50ml)洗涤。分离各相,用MTBE(100ml)和EtOAc(100ml)洗涤水层。采集全部有机相,用Na_2SO_4干燥,过滤并蒸发。通过硅胶快速色谱法(Biotage系统)纯化残余物,使用SNAP 100g作为柱和环己烷:乙酸乙酯100:0-90:10作为洗脱剂,得到2-溴-5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基-吡嗪(1.8g),为白色固体。

[0370] LC/MS:QC_3_MIN:Rt＝2.705min;m/z 333&335[M+H]+。

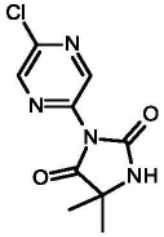
[0371] 使用上述方法,用适合的苯酚替代7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-醇制备下列化合物。通过快速色谱法(硅胶柱;环己烷/EtOAc或其他适合的溶剂系统)纯化终产物。

[0372]

中间体	结构	名称	苯酚	LCMS
2		2-溴-5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基-吡嗪	螺[2H-苯并呋喃-3,1'-环丙烷]-4-醇(中间体 85 WO2012076877)	LC/MS: QC_3_MIN: Rt = 2.575 min; m/z 319 & 321 [M+H]+.
3		2-溴-5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪	3,3,7-三甲基-2H-苯并呋喃-4-醇(中间体 184 WO2012076877)	LC/MS: QC_3_MIN: Rt = 2.365 min; m/z 335 & 337 [M+H]+.
4		2-溴-5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪	3,3-二甲基-2H-苯并呋喃-4-醇(中间体 50 WO2012076877)	LC/MS: QC_3_MIN: Rt = 2.632 min; m/z 321 & 323 [M+H]+.

[0373] 中间体5路线1

[0374] 3-(5-氯吡嗪-2-基)-5,5-二甲基-咪唑烷-2,4-二酮

[0375] 

[0376] 在0℃向碳酸二(三氯甲基)酯(950mg,3.20mmol)在乙酸乙酯(30mL)中的溶液中滴加5-氯吡嗪-2-胺(0.75g,5.79mmol)/N,N-二异丙基乙胺(6.05ml,34.74mmol)在乙酸乙酯(12mL)中的溶液,将该反应混合物在相同温度下搅拌15分钟。维持该反应混合物在0℃,施加真空(5分钟),以便除去过量的光气。加入4-(二甲基氨基)吡啶(710mg,5.81mmol)在乙酸乙酯(8mL)/二氯甲烷(2mL)中的溶液,将该反应混合物在相同温度下搅拌5分钟。然后在0℃加入2-氨基-2-甲基-丙酸甲酯盐酸盐(1.4g,9.1mmol),将该反应混合物在相同温度下搅拌

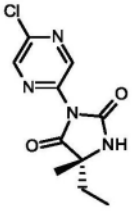
30分钟。用0.2N HCl溶液(100ml)使反应停止,分离两相。用盐水(100ml)洗涤有机层,用Na_2SO_4干燥,过滤,蒸发,得到脲中间体。

[0377] 将脲溶于二氯甲烷(20mL),在0℃加入甲醇钠(315mg,5.83mmol)。将该反应混合物在相同温度下搅拌15分钟;用饱和NH_4Cl溶液使pH达到3-4,以使反应停止。用乙酸乙酯(50ml)萃取该混合物;分离各相,用盐水(50ml)洗涤有机层,用Na_2SO_4干燥,过滤并蒸发。通过C-18相的反相快速色谱法(Biotage系统)纯化残余物,使用SNAP 30g作为柱和水:乙腈95:5-40:60作为洗脱剂。合并适合的流分,蒸发至干,得到3-(5-氯吡嗪-2-基)-5,5-二甲基-咪唑烷-2,4-二酮(220mg),为浅棕色固体。

[0378] LC/MS:QC_3_MIN:Rt＝1.649min;m/z 241&243[M+H]+。

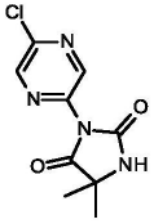
[0379] 使用上述方法,用适合的氨基酯盐酸盐替代2,2-二甲基甘氨酸甲酯盐酸盐制备下列化合物。通过快速色谱法(硅胶柱;环己烷/EtOAc或其他适合的溶剂系统)或在适合的溶剂中研磨或从适合的溶剂中结晶来纯化终产物。

[0380]

中间体	结构	名称	氨基酯盐酸盐	LCMS
6		5R)-3-(5-氯吡嗪-2-基)-5-乙基-5-甲基-咪唑烷-2,4-二酮	(2R)-2-氨基-2-甲基-丁酸甲酯盐酸盐	LC/MS: QC_3_MIN: Rt = 1.546 min; m/z 255&257 [M+H]+。

[0381] 中间体5路线2

[0382] 3-(5-氯吡嗪-2-基)-5,5-二甲基-咪唑烷-2,4-二酮

[0383] 

[0384] 在RT向5-氯吡嗪-2-胺(500mg,3.86mmol)和2-氨基-2-甲基-丙酸盐酸盐(646mg,4.63mmol)在乙腈(10mL)中的溶液中缓慢地加入在乙酸乙酯(3.68g,5.78mmol)中≥50重量%的丙基膦酸酐溶液。将该反应混合物在80℃搅拌6h。用乙酸乙酯(10ml)稀释该反应混合物,加入NaOH 1N水溶液,同时使ph达到～8。分离两相,用盐水(10ml)洗涤有机相,用Na_2SO_4干燥,真空浓缩,通过硅胶快速色谱法(Biotage系统)纯化粗产物,使用SNAP 25g作为柱和DCM:MEOH 99/1-90/10作为洗脱剂,得到2-氨基-N-(5-氯吡嗪-2-基)-2-甲基-丙酰胺(190mg),为黄色固体。

[0385] LC/MS:QC_3_MIN:Rt＝1.181min;m/z 215&217[M+H]+。

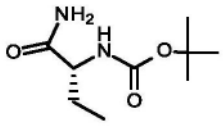
[0386] 在0℃向2-氨基-N-(5-氯吡嗪-2-基)-2-甲基-丙酰胺(190mg,0.88mmol)和三乙胺(268mg,2,6555mmol)在二氯甲烷(5mL)中的溶液中缓慢地加入碳酸二(三氯甲基)酯(105,07mg,0,3541mmol)在二氯甲烷(4mL)中的溶液,将该反应混合物在相同温度下搅拌30分钟。用DCM(10mL)稀释该反应混合物,用0.2N HCl水溶液(10mL)和盐水(10mL)洗涤。真空浓缩有

机相，通过硅胶快速色谱法(Biotage系统)纯化粗产物，使用SNAP 25g作为柱和环己烷/EtOAc 80/20-0/100作为洗脱剂，得到3-(5-氯吡嗪-2-基)-5,5-二甲基-咪唑烷-2,4-二酮(130mg)，为白色固体。

[0387] LC/MS:QC_3_MIN:Rt＝1.598min;m/z 241&243[M+H]+。

[0388] 中间体7

[0389] N-[(1R)-1-氨基甲酰基丙基]氨基甲酸叔丁酯

[0390] 

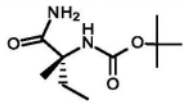
[0391] 将[二甲基氨基-(3-氧化三唑并[4,5-b]吡啶-3-鎓-1-基)亚甲基]-二甲基-铵四氟硼酸盐(1,1084g,3,4415mmol)、N,N-二异丙基乙胺(0,7939g,6,1431mmol)和(2R)-2-(叔丁氧基羰基氨基)丁酸(0,5000g,2,4601mmol)在干N,N-二甲基甲酰胺(8mL)中的混合物在室温搅拌10分钟。加入六甲基二硅氮烷(0,5960g,3,6928mmol)，将该混合物搅拌18h。

[0392] 使反应混合物在MTBE(30mL)和盐水(20mL)中分离。用硫酸钠干燥有机层，过滤，除去溶剂。将得到的油状物在MTBE(3mL)中研磨，用MTBE洗涤得到的沉淀，真空干燥，得到N-[(1R)-1-氨基甲酰基丙基]氨基甲酸叔丁酯(0,3000g,1,4833mmol,60,294%)，为白色固体。

[0393] LC/MS:QC_3_MIN:m/z 147[M-tBu+H]+。

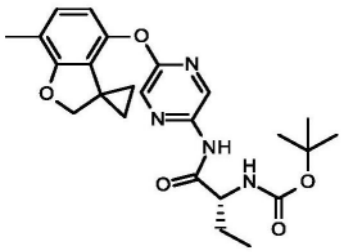
[0394] 使用上述方法，用适合的被保护的氨基酸替代(2R)-2-(叔丁氧基羰基氨基)丁酸制备下列化合物。

[0395]

中间体	结构	名称	氨基-酸	LCMS
8		N-[(1R)-1-氨基甲酰基-1-甲基-丙基]氨基甲酸叔丁酯	(2R)-2-(叔丁氧基羰基氨基)-2-甲基-丁酸	LC/MS: QC_3_MIN:m/z 455 [2M+Na]+.

[0396] 中间体9(路线1)

[0397] N-[(1R)-1-[[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]氨基甲酰基]丙基]氨基甲酸叔丁酯

[0398] 

[0399] 将2-溴-5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基-吡嗪(中间体1,50mg,0.15mmol)、N-[(1R)-1-氨基甲酰基丙基]氨基甲酸叔丁酯(中间体7,46mg,0.23mmol)、三(二亚苄基丙酮)二钯(0)(10.3mg,0.011mmol)、二环己基-[2-(2,4,6-三异丙基苯基)苯基]膦(phosphane)(XPhos)(5.4mg,0.011mmol)和碳酸铯(73mg,0.22mmol)在1,

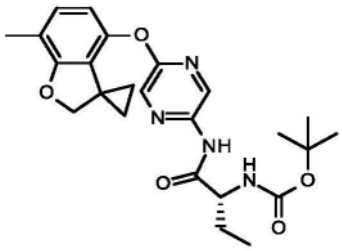
4-二噁烷(2mL)中的混合物在氮气气氛中在80℃搅拌3h。

[0400] 使该反应体系分配在乙酸乙酯与盐水之间。分离有机层,用硫酸钠干燥,过滤,蒸发至干。通过硅胶快速色谱法(Biotage系统)纯化残余物,使用SNAP 10g柱,使用环己烷和EtOAc 100/0-0/100作为洗脱剂。合并适合的流分,蒸发至干,得到N-[(1R)-1-[[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]氨基甲酰基]丙基]氨基甲酸叔丁酯(10mg)。

[0401] LC/MS:QC_3_MIN:Rt＝2.696min;m/z 455[M+H]+。

[0402] 中间体9(路线2)

[0403] N-[(1R)-1-[[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]氨基甲酰基]丙基]氨基甲酸叔丁酯

[0404] 

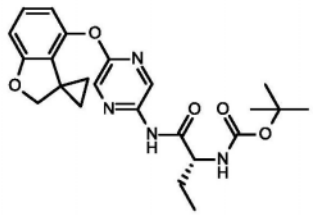
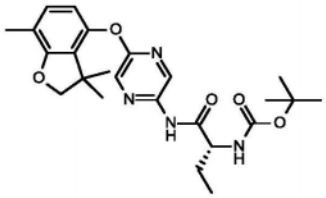
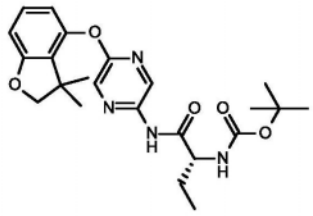
[0405] 在用氩气吹扫后,向2-溴-5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基-吡嗪(中间体1,16g,48.0mmol)、N-[(1R)-1-氨基甲酰基丙基]氨基甲酸叔丁酯(中间体7,10g,49.4mmol)、碳酸铯(24.16g,74.17mmol)在1,4-二噁烷(150mL)中的混合物中加入二乙酰氧基钯(0.555g,2.47mmol)和(5-二苯基膦基-9,9-二甲基-呫吨-4-基)-二苯基-膦(2.15g,3.71mmol)。施加3次真空-氩气循环,将该反应混合物在95℃搅拌1.5h。使用外部冰浴冷却该反应混合物,然后真空过滤以除去碳酸铯。采集滤液,用EtOAc(150ml)稀释,用饱和NH_4Cl水溶液(100ml)洗涤,然后用饱和NaCl水溶液(100ml)洗涤,用硫酸钠干燥,过滤,蒸发至干。通过硅胶快速色谱法(Biotage系统)纯化残余物,使用2x SNAP 100g柱(200g二氧化硅),使用环己烷/EtOAc 0-40%作为洗脱剂,得到N-[(1R)-1-[[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]氨基甲酰基]丙基]氨基甲酸叔丁酯(16.8g),为黄色固体。

[0406] 使用上述方法(路线1或路线2),用适合的溴吡嗪替代2-溴-5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基-吡嗪(中间体1)制备下列化合物。通过快速色谱法(硅胶柱;环己烷/EtOAc或其他适合的溶剂系统)纯化终产物。

[0407]

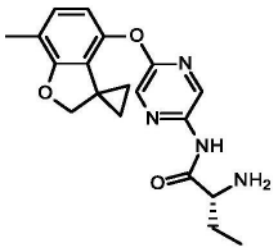
中间体	结构	名称	溴吡嗪	LCMS

[0408]

10		N-[(1R)-1-[(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)氨基甲酰基]丙基]氨基甲酸叔丁酯	2-溴-5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基-吡嗪(中间体 2)	LC/MS: QC_3_MIN: Rt = 2.246 min; m/z 441 [M+H]+。
11		N-[(1R)-1-[[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]氨基甲酰基]丙基]氨基甲酸叔丁酯	2-溴-5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪(中间体 3)	LC/MS: QC_3_MIN: Rt = 2.309 min; m/z 457 [M+H]+。
12		N-[(1R)-1-[[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]氨基甲酰基]丙基]氨基甲酸叔丁酯	2-溴-5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪(中间体 4)	LC/MS: QC_3_MIN: Rt = 2.366 min; m/z 443 [M+H]+。

[0409] 中间体13

[0410] (2R)-2-氨基-N-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]丁酰胺

[0411] 

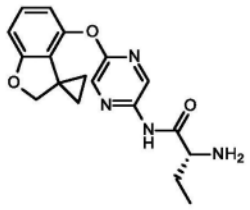
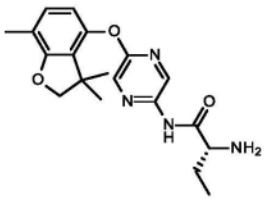
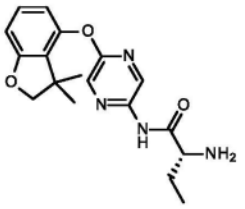
[0412] 将N-[(1R)-1-[[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]氨基甲酰基]丙基]氨基甲酸叔丁酯(中间体9,16mg,0.035mmol)和2,2,2-三氟乙酸(0.50mL,6.53mmol)在二氯甲烷(2mL)中的混合物在室温搅拌2h。

[0413] 用二氯甲烷(20ml)稀释该反应混合物,加入$NaHCO_3$饱和溶液(水溶液),同时使pH达到8。分离各相,用盐水(20ml)洗涤有机层,用Na_2SO_4干燥,过滤,蒸发,得到(2R)-2-氨基-N-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]丁酰胺(13mg),不经进一步纯化用于下一步。

[0414] LC/MS:QC_3_MIN:Rt=2.009min;m/z 355[M+H]+。

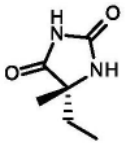
[0415] 使用上述方法，用适合的Boc胺替代N-[(1R)-1-[[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]氨基甲酰基]丙基]氨基甲酸叔丁酯(中间体9)制备下列化合物。

[0416]

中间体	结构	名称	Boc 胺	LCMS
14		(2R)-2-氨基-N-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)丁酰胺	N-[(1R)-1-[(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)氨基甲酰基]丙基]氨基甲酸叔丁酯(中间体 10)	LC/MS: QC_3_MIN: Rt = 1.675 min; m/z 342 [M+H]+。
15		(2R)-2-氨基-N-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]丁酰胺	N-[(1R)-1-[[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]氨基甲酰基]丙基]氨基甲酸叔丁酯(中间体 11)	LC/MS: QC_3_MIN: Rt = 1.756 min; m/z 357 [M+H]+。
16		(2R)-2-氨基-N-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]丁酰胺	N-[(1R)-1-[[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]氨基甲酰基]丙基]氨基甲酸叔丁酯(中间体 12)	LC/MS: QC_3_MIN: Rt = 1.673 min; m/z 343 [M+H]+。

[0417] 中间体17

[0418] (5R)-5-乙基-5-甲基-咪唑烷-2,4-二酮

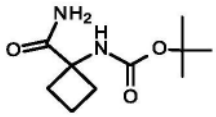
[0419] 

[0420] 将N-[(1R)-1-氨基甲酰基-1-甲基-丙基]氨基甲酸叔丁酯(中间体8,100mg,0,4624mmol)和碳酸钾(191,71mg,1,3871mmol)在1-丁醇(5mL)中的混合物在氮气气氛中在95℃搅拌过夜。冷却后，过滤出碳酸钾，用乙酸乙酯(30ml)稀释该反应混合物，用0.1N HCl水溶液(30ml)、然后用盐水(30ml)洗涤。分离各相，收集有机层，用Na_2SO_4干燥，过滤，蒸发，得到(5R)-5-乙基-5-甲基-咪唑烷-2,4-二酮(60mg,0,4221mmol,91,283%)。

[0421] LC/MS:QC_3_MIN:m/z 285[2M+H]+。

[0422] 中间体18

[0423] N-(1-氨基甲酰基环丁基)氨基甲酸叔丁酯

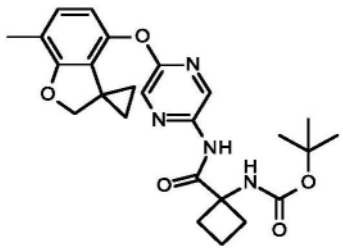
[0424] 

[0425] 使用对中间体7所述的方法，用1-(叔丁氧基羰基氨基)环丁烷甲酸替代(2R)-2-(叔丁氧基羰基氨基)丁酸制备中间体18。

[0426] LC/MS:QC_3_MIN:m/z 159[M-tBu+H]+。

[0427] 中间体19

[0428] N-[1-[[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]氨基甲酰基]环丁基]氨基甲酸叔丁酯

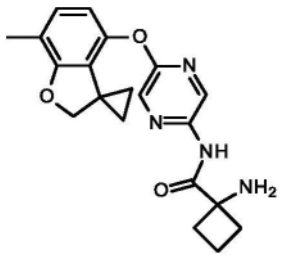
[0429] 

[0430] 将2-溴-5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基-吡嗪(中间体1,50mg,0.1501mmol)、N-(1-氨基甲酰基环丁基)氨基甲酸叔丁酯(中间体18,64mg,0.2987mmol)、碳酸二钾(62mg,0,4486mmol)、碘化亚铜(I)(2.9mg,0.0152mmol)和N,N'-二甲基乙-1,2-二胺(0.0065mL,0.0601mmol)在1-丁醇(1mL)中的混合物在氮气气氛中在95℃搅拌4h。冷却后，用乙酸乙酯(30ml)稀释该反应混合物，用0.1M HCl水溶液(30ml)、然后用盐水(30ml)洗涤。分离各相，收集有机层，用Na_2SO_4干燥，过滤，蒸发。通过硅胶快速色谱法(Biotage系统)纯化残余物，使用SNAP 10g作为柱和环己烷:乙酸乙酯100:0-30:70作为洗脱剂，得到N-[1-[[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]氨基甲酰基]环丁基]氨基甲酸叔丁酯(18mg)。

[0431] LC/MS:QC_3_MIN:Rt＝2.675min;m/z 467[M+H]+。

[0432] 中间体20

[0433] 1-氨基-N-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]环丁烷甲酰胺

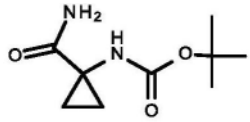
[0434] 

[0435] 使用对中间体13所述的方法，用N-[1-[[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]氨基甲酰基]环丁基]氨基甲酸叔丁酯(中间体19)替代N-[(1R)-1-[[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]氨基甲酰基]丙基]氨基甲酸叔丁酯(中间体9)制备中间体20。

[0436] LC/MS:QC_3_MIN:Rt＝1.979min;m/z 367[M+H]+。

[0437] 中间体21

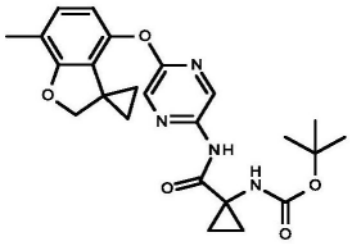
[0438] N-(1-氨基甲酰基环丙基)氨基甲酸叔丁酯

[0439] 

[0440] 使用对中间体7所述的方法,用1-(叔丁氧基羰基氨基)环丙烷甲酸替代(2R)-2-(叔丁羰基羰基氨基)丁酸制备中间体21。

[0441] 中间体22

[0442] N-[1-[[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]氨基甲酰基]环丙基]氨基甲酸叔丁酯

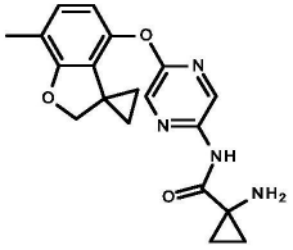
[0443] 

[0444] 将二环己基-[2-(2,4,6-三异丙基苯基)苯基]膦(12mg,0.0252mmol)、N-(1-氨基甲酰基环丙基)氨基甲酸叔丁酯(中间体21,67mg,0.3346mmol)、三(二亚苄基丙酮)二钯(0)(22mg,0.0240mmol)、2-溴-5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基-吡嗪(中间体1,79.518mg,0.2387mmol)和碳酸铯(116mg,0.3560mmol)在1,4-二噁烷(1mL)中的混合物在氮气气氛中在95℃搅拌2h。再加入N-(1-氨基甲酰基环丙基)氨基甲酸叔丁酯(中间体21,67mg,0.3346mmol)和三(二亚苄基丙酮)二钯(0)(22mg,0.0240mmol),将该反应混合物在95℃在氮气气氛中再搅拌2h,随后再添加二环己基-[2-(2,4,6-三异丙基苯基)苯基]膦(12mg,0.0252mmol)、三(二亚苄基丙酮)二钯(0)(22mg,0.0240mmol)和碳酸铯(58mg),将该混合物在氮气气氛中再搅拌2h。然后用水(10mL)、NH_4Cl(10mL)使该反应混合物淬灭,用乙酸乙酯(20mL)萃取。然后用盐水(15mL)洗涤有机层,用Na_2SO_4干燥,过滤,然后真空浓缩。通过硅胶快速色谱法(Biotage系统)纯化粗产物,使用SNAP 10g作为柱和环己烷:乙酸乙酯90:10-70:30作为洗脱剂,得到N-[1-[[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]氨基甲酰基]环丙基]氨基甲酸叔丁酯(55mg),为黄色固体。

[0445] LC/MS:QC_3_MIN:Rt＝2.634min;m/z 453[M+H]+。

[0446] 中间体23

[0447] 1-氨基-N-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]环丙烷甲酰胺

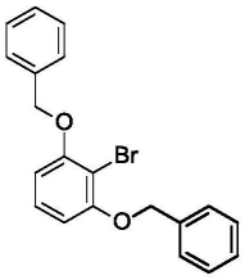
[0448] 

[0449] 将N-[1-[[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]氨基甲酰基]环丙基]氨基甲酸叔丁酯(中间体22,55mg,0.1215mmol)溶于二氯甲烷(4mL),冷却

至0℃。滴加2,2,2-三氟乙酸(1154.7mg,10.026mmol)(0.8mL),将该反应体系在室温搅拌1小时。然后将该反应混合物冷却至0℃,加入$NaHCO_3$,直至pH达到8。然后将该混合物温热至室温,用DCM(10mL)萃取。用Na_2SO_4干燥有机层,过滤,真空浓缩,得到1-氨基-N-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]环丙烷甲酰胺(40mg),为黄色油状物。LC/MS:QC_3_MIN:Rt=1.935min;m/z 353[M+H]+。

[0450] 中间体24

[0451] 1,3-二苄氧基-2-溴-苯

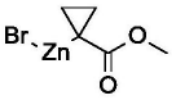
[0452] 

[0453] 向2-溴苯-1,3-二醇(20g,105.8mmol)在丙酮(200mL)中的溶液中加入碳酸钾(43.87g,317.4mmol),然后添加苄基溴(40.72g,238.1mmol)(28ml),将该反应混合物回流1.5小时。冷却后,真空过滤该反应混合物,将滤液浓缩至干。用乙酸乙酯(100ml)稀释残余物,用水(100ml)、然后用盐水(100ml)洗涤。分离各相,用Na_2SO_4干燥有机层,过滤,浓缩。将残余物混悬于异丙醇(8个体积),在80℃加热该混合物,在该温度下搅拌1小时(得到澄清溶液)。然后使该混合物达到室温(1h内),过滤得到的混悬液。用冰冷异丙醇洗涤固体,然后干燥,得到标题化合物1,3-二苄氧基-2-溴-苯(34g),为粉红色固体。

[0454] LC/MS:QC_3_MIN:Rt=2.688min。

[0455] 中间体25

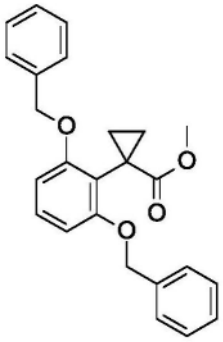
[0456] 溴-(1-甲氧基羰基环丙基)锌

[0457] 

[0458] 在双颈圆底烧瓶中加入活化的锌粉(6.84g,104.6mmol),真空加热该粉末。将该系统放入氩气气氛中,加入无水四氢呋喃(58mL)。然后加入1,2-二溴乙烷(2.18g,11.62mmol),将该混合物加热至回流。以一个批次加入氯三甲基硅烷(505mg,4.65mmol),将该混合物保持在回流温度下搅拌。在相同温度下缓慢地加入1-溴环丙基甲酸甲酯(10.4g,58.1mmol)在无水四氢呋喃(12mL)中的溶液,将该反应混合物回流1.5h。将该反应混合物冷却至室温,使锌沉降,得到70ml的0.83M(理论值)溴-(1-甲氧基氧基环丙基)锌在THF中的溶液,将其不经进一步后处理而用于下一步。

[0459] 中间体26

[0460] 1-(2,6-二苄氧基苯基)环丙烷甲酸甲酯

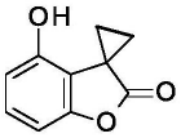
[0461] 

[0462] 在70℃向预热的1,3-二苄氧基-2-溴-苯(中间体24,16g,43.33mmol)和双(三-叔丁基膦)钯(0)(221mg,0.43mmol)在N,N-二甲基甲酰胺(150mL)中的溶液中加入0.83M(理论值)的溴-(1-甲氧基羰基环丙基)锌在THF中的溶液(中间体25,60ml)(通过插套管),将该反应混合物在相同温度下搅拌40分钟。冷却后,真空浓缩该反应混合物至～30ml,用乙酸乙酯(450ml)稀释残余物,用1N HCl水溶液洗涤两次(2x100ml),然后用冰冷盐水洗涤三次(3x100ml)。分离各相,使用配备滤纸和纤维素的Gooch滤器真空过滤有机层,用乙酸乙酯洗涤。用Na_2SO_4干燥滤液,过滤,蒸发,得到标题化合物1-(2,6-二苄氧基苯基)环丙烷甲酸甲酯(15.5g),将其不经进一步纯化用于下一步。

[0463] LC/MS:QC_3_MIN:Rt＝2.606min;m/z 389[M+H]+。

[0464] 中间体27

[0465] 4-羟基螺[苯并呋喃-3,1'-环丙烷]-2-酮

[0466] 

[0467] 该反应分三次不同运行进行,每次使用约20g起始材料。

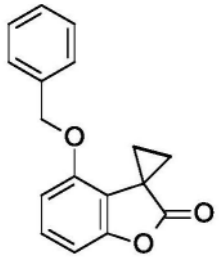
[0468] 通用方法:向1-(2,6-二苄氧基苯基)环丙烷甲酸甲酯(中间体26,20.4g,52.52mmol)和5%重量钯/碳(1.02g)在乙醇(200ml)中的混合物中加入甲酸铵(16.56g,262.6mmol),将该反应混合物在80℃搅拌1小时。冷却后,用纤维素垫过滤出催化剂,真空浓缩滤液至～20ml。

[0469] 将来自3次运行的残余物收集在一起,用乙酸乙酯(400ml)稀释,用水洗涤两次(2x300ml)。分离两相,用盐水(300ml)洗涤有机相,用Na_2SO_4干燥,真空浓缩,得到4-羟基螺[苯并呋喃-3,1'-环丙烷]-2-酮(27.55g)(包含约10-15%的未环化的1-(2,6-二羟基苯基)环丙烷甲酸甲酯中间体),不经进一步纯化用于下一步。

[0470] LC/MS:QC_3_MIN:Rt＝1.707min。

[0471] 中间体28

[0472] 4-苄氧基螺[苯并呋喃-3,1'-环丙烷]-2-酮

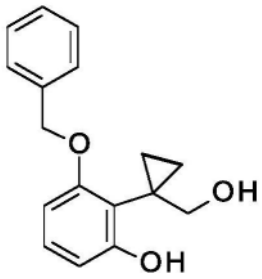
[0473] 

[0474] 向4-羟基螺[苯并呋喃-3,1'-环丙烷]-2-酮(中间体27,28.5g,161.8mmol)(包含～10-15%的未环化的1-(2,6-二羟基苯基)环丙烷甲酸甲酯中间体)在乙腈(200mL)/四氢呋喃(50mL)中的溶液中加入碳酸钾(33.54g,242,7mmol),将该反应混合物在70℃搅拌1.5小时。然后将该反应混合物冷却至室温,缓慢地加入苄基溴(27.67g,161.8mmol)。将该反应混合物在60℃搅拌5小时。冷却后,真空过滤该反应混合物,弃去固体,浓缩滤液至50ml,用乙酸乙酯(250ml)稀释,用盐水洗涤两次(2x100ml)。分离各相,用Na_2SO_4干燥有机层,过滤,蒸发,得到标题化合物4-苄氧基螺[苯并呋喃-3,1'-环丙烷]-2-酮(42,4g),不经进一步纯化用于下一步。

[0475] LC/MS:QC_3_MIN:Rt＝2.389min;m/z 267[M+H]+。

[0476] 中间体29

[0477] 3-苄氧基-2-[1-(羟甲基)环丙基]苯酚

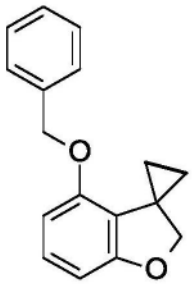
[0478] 

[0479] 在0℃向4-苄氧基螺[苯并呋喃-3,1'-环丙烷]-2-酮(中间体28,42.4g,159.2mmol)在无水四氢呋喃(300mL)中的溶液中缓慢地加入1M氢化铝锂的THF溶液(79.6ml,79,6mmol),将反应混合物在相同温度下搅拌30分钟。用冰、水(400ml)和1M HCl水溶液(160ml)使反应停止,然后用乙酸乙酯(700ml)稀释。分离各相,用乙酸乙酯(500ml)反萃取水层。用盐水(600ml)洗涤合并的有机相,用Na_2SO_4干燥,过滤,蒸发,得到标题化合物3-苄氧基-2-[1-(羟甲基)环丙基]苯酚(43g),将其不经进一步纯化用于下一步。

[0480] LC/MS:QC_3_MIN:Rt＝2.148min;m/z 271[M+H]+,m/z 293[M+Na]+,m/z 253[M-OH]+。

[0481] 中间体30

[0482] 4-苄氧基螺[2H-苯并呋喃-3,1'-环丙烷]

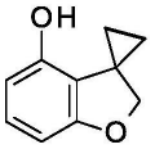
[0483] 

[0484] 向3-苄氧基-2-[1-(羟甲基)环丙基]苯酚(中间体29,43g,159.1mmol)在碳酸二甲酯(430mL)中的溶液中缓慢地加入叔丁醇钾(35.7g,318.1mmol),将该反应混合物在85℃搅拌3.5小时。将该反应混合物冷却至室温,真空浓缩至150mL,用MTBE(400ml)稀释,用水(400ml)洗涤。分离各相,用MTBE(250ml)反萃取水层。用盐水(350ml)洗涤合并的有机层,用Na_2SO_4干燥,过滤,浓缩,得到标题化合物4-苄氧基螺[2H-苯并呋喃-3,1'-环丙烷](40g),不经进一步纯化用于下一步。

[0485] LC/MS:QC_3_MIN:Rt＝2.457min;m/z 253[M+H]+。

[0486] 中间体31(中间体85WO2012/076877)

[0487] 1螺[2H-苯并呋喃-3,1'-环丙烷]-4-醇

[0488] 

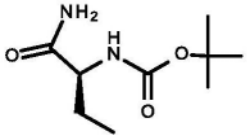
[0489] 该反应分两次进行,每次使用20g起始材料。

[0490] 向4-苄氧基螺[2H-苯并呋喃-3,1'-环丙烷](中间体30,20g,79.27mmol)和甲酸铵(24.99g,396.34mmol)在乙醇(160ml)中的混合物中加入5%重量钯/碳(2.0g),将该反应混合物在80℃下搅拌10分钟。冷却后,通过纤维素垫滤出催化剂,真空浓缩滤液至～20ml。将来自两个反应的残余物合并,将该混合物用乙酸乙酯(300ml)稀释,用水(3x200ml)洗涤三次,然后用盐水(200ml)洗涤。分离两相,用Na_2SO_4干燥有机相,真空浓缩。通过硅胶快速色谱法(Biotage系统)纯化残余物,使用环己烷:乙酸乙酯99:1-85:15作为洗脱剂,得到螺[2H-苯并呋喃-3,1'-环丙烷]-4-醇(17,75g),为白色固体。

[0491] LC/MS:QC_3_MIN:Rt＝1.723min;m/z 163[M+H]+。

[0492] 中间体32

[0493] N-[(1S)-1-氨基甲酰基丙基]氨基甲酸叔丁酯

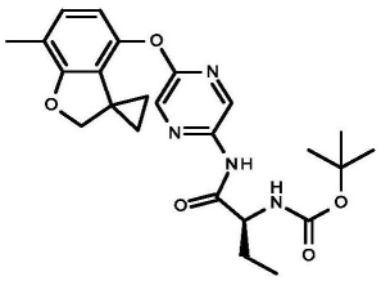
[0494] 

[0495] 按照与用于合成中间体7相同的方法,用(2S)-2-(叔丁氧基羰基氨基)丁酸替代(2R)-2-(叔丁氧基羰基氨基)丁酸合成标题化合物。

[0496] LC/MS:QC_3_MIN:m/z 147[M-tBu+H]+,m/z 427[2M+Na]+

[0497] 中间体33

[0498] N-[(1S)-1-[[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]氨基甲酰基]丙基]氨基甲酸叔丁酯

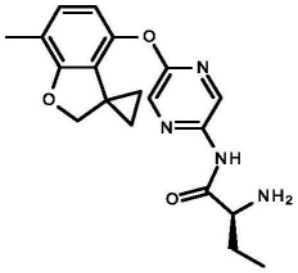
[0499] 

[0500] 按照用于合成中间体9的“路线1”方法，用N-[(1S)-1-氨基甲酰基丙基]氨基甲酸叔丁酯(中间体32)替代N-[(1R)-1-氨基甲酰基丙基]氨基甲酸叔丁酯(中间体7)合成标题化合物。

[0501] LC/MS:QC_3_MIN:Rt＝2.65min;m/z 455[M+H]+。

[0502] 中间体34

[0503] (2S)-2-氨基-N-[5-(7-甲基螺[2H-苯并呋喃-3,1’-环丙烷]-4-基)氧基吡嗪-2-基]丁酰胺

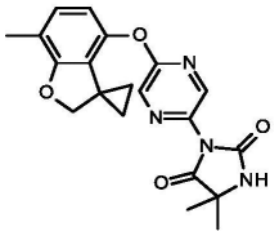
[0504] 

[0505] 按照与用于合成中间体13相同的方法，用N-[(1S)-1-[[5-(7-甲基螺[2H-苯并呋喃-3,1’-环丙烷]-4-基)氧基吡嗪-2-基]氨基甲酰基]丙基]氨基甲酸叔丁酯(中间体33)替代N-[(1R)-1-[[5-(7-甲基螺[2H-苯并呋喃-3,1’-环丙烷]-4-基)氧基吡嗪-2-基]氨基甲酰基]丙基]氨基甲酸叔丁酯(中间体9)合成标题化合物。

[0506] LC/MS:QC_3_MIN:Rt＝1.98min;m/z 355[M+H]+。

[0507] 实施例1路线1

[0508] 5,5-二甲基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1’-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮

[0509] 

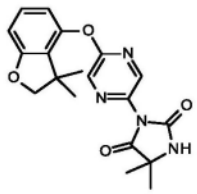
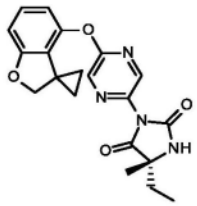
[0510] 向2-溴-5-(7-甲基螺[2H-苯并呋喃-3,1’-环丙烷]-4-基)氧基-吡嗪(中间体1,30mg,0.069mmol)在N,N-二甲基乙酰胺(1mL)中的溶液中加入5,5-二甲基咪唑烷-2,4-二酮(44.4mg,0.345mmol)和氧化亚铜(I)(5mg,0.035mmol)。用氮气吹扫烧瓶，在135℃保持搅拌过夜。用EtOAc(10mL)稀释该反应体系，首先用饱和氯化铵水溶液(20mL)、然后用盐水(20mL)洗涤。收集有机层，用硫酸钠干燥，蒸发至干。然后用快速柱色谱法纯化残余物，使用环己烷:乙酸乙酯80:20-40:60作为洗脱剂，得到5,5-二甲基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1’-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮(17mg)，为白色固体。

[0511] ^{1}H-NMR(400MHz;DMSO-d6):δppm 8.72(bs,1H),8.51(d,1H),8.30(d,1H),6.95(dd,1H),6.53(d,1H),4.46(s,2H),2.14(s,3H),1.42(s,6H),1.07-1.14(m,2H),0.89-0.95(m,2H)。

[0512] 使用上述方法，用适合的溴吡嗪替代2-溴-5-(7-甲基螺[2H-苯并呋喃-3,1’-环丙烷]-4-基)氧基-吡嗪(中间体1)并且使用适合的乙内酰脲替代5,5-二甲基咪唑烷-2,4-二酮制备下列化合物。通过快速色谱法(硅胶柱;环己烷/EtOAc或其他适合的溶剂系统)和/或

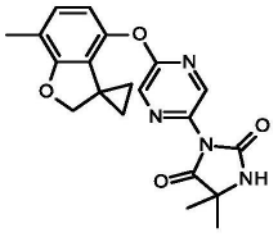
反相色谱法(C-18柱;水/乙腈或其他适合的溶剂系统)纯化终产物。

[0513]

实施例	结构	名称	溴吡嗪	乙内酰脲	LCMS/NMR
2		3-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]-5,5-二甲基-咪唑烷-2,4-二酮	2-溴-5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪(中间体4)	5,5-二甲基咪唑烷-2,4-二酮	LC/MS: QC_3_MIN: Rt = 2.288 min; m/z 369 [M+H]+. ^{1}H-NMR (500 MHz; DMSO-d6): δ ppm 8.73 (bs, 1H), 8.60 (d, 1H), 8.32 (d, 1H), 7.17 (dd, 1H), 6.70 (d, 1H), 6.66 (d, 1H), 4.23 (s, 2H), 1.42 (s, 6H), 1.28 (s, 6H).
3		(5R)-5-乙基-5-甲基-3-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)咪唑烷-2,4-二酮	2-溴-5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基-吡嗪(中间体2)	(5R)-5-乙基-5-甲基-咪唑烷-2,4-二酮(中间体17)	LC/MS: QC_3_MIN: Rt = 2.228 min; m/z 381 [M+H]+.

[0514] 实施例1路线2

[0515] 5,5-二甲基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮

[0516] 

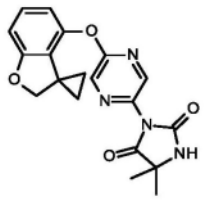
[0517] 向3-(5-氯吡嗪-2-基)-5,5-二甲基-咪唑烷-2,4-二酮(中间体5,20mg,0.083mmol)和7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-醇(中间体156,WO2012076877,22mg,0.125mmol)在乙腈(1mL)中的溶液中加入碳酸二钾(17.2mg,0.12mmol)。将该反应混合物在60℃搅拌过夜,然后在80℃搅拌3h。真空浓缩该反应混合物,通过硅胶快速色谱法(BIOTAGE SYSTEM)纯化粗产物,使用SNAP 10g作为柱和环己烷/EtOAc 80/20-20/80作为洗脱剂。流分仍然不纯,通过反相色谱法纯化它们,使用SNAP C-18作为柱和H2O/ACN 95/5-5/95作为洗脱剂,得到5,5-二甲基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮(9.4mg),为白色固体。

[0518] LC/MS:QC_3_MIN:Rt=2.224min;m/z 381[M+H]+。

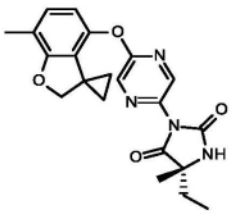
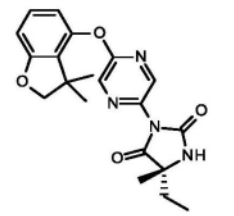
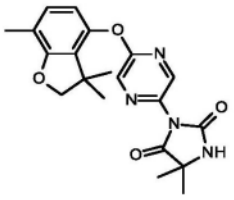
[0519] 使用上述方法,用适合的苯酚替代7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-醇并且使用3-(5-氯吡嗪-2-基)-5,5-二甲基-咪唑烷-2,4-二酮(中间体5)或使用适合的氯吡嗪

中间体替代它制备下列化合物。通过快速色谱法(硅胶柱;环己烷/EtOAc或其他适合的溶剂系统)和/或反相色谱法(C-18柱;水/乙腈或其他适合的溶剂系统)纯化终产物。

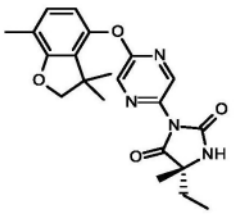
[0520]

实施例	结构	名称	苯酚	氯-吡嗪中间体	LCMS/NMR
4		5,5-二甲基-3-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)咪唑烷-2,4-二酮	螺[2H-苯并呋喃-3,1'-环丙烷]-4-醇(中间体 85、WO2012/076877)	3-(5-氯吡嗪-2-基)-5,5-二甲基-咪唑烷-2,4-二酮(中间体 5)	LC/MS: QC_3_MIN: Rt = 2.085 min; m/z 367 [M+H]+。^{1}H-NMR (500 MHz; DMSO-d6): δ ppm 8.73 (bs, 1H), 8.54 (d, 1H), 8.32 (d, 1H), 7.11 (dd, 1H), 6.71 (d, 1H), 6.62 (d, 1H),

[0521]

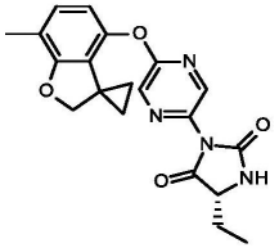
					4.46 (s, 2H), 1.42 (s, 6H), 1.12-1.16 (m, 2H), 0.92-0.97 (m, 5H).
5		(5R)-5-乙基-5-甲基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮	7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-醇(中间体 156 WO2012/076877)	5R)-3-(5-氯吡嗪-2-基)-5-乙基-5-甲基-咪唑烷-2,4-二酮(中间体 6)	LC/MS: QC_3_MIN: Rt = 2.361 min; m/z 395 [M+H]+。 ^{1}H-NMR (500 MHz; DMSO-d6): δ ppm 8.64 (bs, 1H), 8.48 (d, 1H), 8.25 (d, 1H), 6.91 (dd, 1H), 6.49 (d, 1H), 4.42 (s, 2H), 2.11 (s, 3H), 1.71-1.79 (m, 1H), 1.60-1.68 (m, 1H), 1.38 (s, 3H), 1.02-1.09 (m, 2H), 0.82-0.92 (m, 5H).
6		(5R)-3-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]-5-乙基-5-甲基-咪唑烷-2,4-二酮	3,3-二甲基-2H-苯并呋喃-4-醇(中间体 50 WO2012/076877)	5R)-3-(5-氯吡嗪-2-基)-5-乙基-5-甲基-咪唑烷-2,4-二酮(中间体 6)	LC/MS: QC_3_MIN: Rt = 2.008 min; m/z 383 [M+H]+。
7		5,5-二甲基-3-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]咪唑烷-2,4-二酮	3,3,7-三甲基-2H-苯并呋喃-4-醇(中间体 184 WO2012/076877)	3-(5-氯吡嗪-2-基)-5,5-二甲基-咪唑烷-2,4-二酮(中间体 5)	LC/MS: QC_3_MIN: Rt = 2.025 min; m/z 383 [M+H]+。

[0522]

8		(5R)-5-乙基-5-甲基-3-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]咪唑烷-2,4-二酮	3,3,7-三甲基-2H-苯并呋喃-4-醇(中间体 184 WO2012/076877)	(5R)-3-(5-氯吡嗪-2-基)-5-乙基-5-甲基-咪唑烷-2,4-二酮(中间体 6)	LC/MS: QC_3_MIN: Rt = 2.111 min; m/z 397 [M+H]+。

[0523] 实施例9(路线1)

[0524] (5R)-5-乙基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮

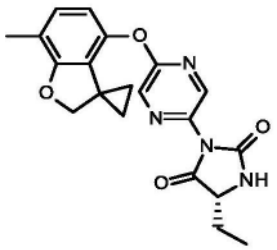
[0525] 

[0526] 将(2R)-2-氨基-N-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]丁酰胺(中间体13,13mg,0.037mmol)和N,N-二乙基乙胺(11mg,0.11mmol)在二氯甲烷(2mL)中的混合物冷却至0℃。滴加碳酸二(三氯甲基)酯(4,5mg,0.015mmol)在二氯甲烷(0.5mL)中的溶液,将该反应混合物在相同温度下搅拌1小时。再加入在二氯甲烷(0.5mL)中的碳酸二(三氯甲基)酯(1.5mg),持续搅拌30分钟。将该混合物温热至室温。用二氯甲烷(20ml)稀释该反应混合物,用0.1N HCl水溶液(20ml)、然后用盐水(20ml)洗涤有机相。分离各相,用Na_2SO_4干燥有机层,过滤,蒸发。通过反相色谱法纯化残余物,使用SNAP C-18柱,用水:乙腈90:10-0:100洗脱。合并适合的流分,蒸发至干,得到(5R)-5-乙基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮(7.5mg),为白色固体。

[0527] LC/MS:QC_3_MIN:Rt＝2.305min;m/z 381[M+H]+。使用手性控制方法将对映异构体纯度证实为>95%。

[0528] 实施例9(路线2)

[0529] (5R)-5-乙基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮

[0530] 

[0531] 向(2R)-2-氨基-N-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]丁酰胺(中间体13,21g,59.26mmol)在乙酸乙酯(500mL)中的溶液中分5批加入1,1'-羰基二咪唑(10.57g,65.18mmol),每批约2g,在室温搅拌4h。用冰使该反应体系淬灭,加入0.2N HCl水溶液(250ml)。分离两相,用0.2N HCl水溶液(250ml)和盐水(200ml)洗涤有机层,然后用硫酸钠干燥,过滤,蒸发至干。将粗产物分成4个各自～4.2g等分部分,通过硅胶快速色谱法纯化每个等分部分,使用SNAP(100G)作为柱和环己烷/乙酸乙酯80/20-20/80作为洗脱剂。收集来自每次运行的期望的流分,蒸发溶剂至干。将得到的淡黄色固体混悬于环己烷/乙酸乙酯的溶液(1/1,3个体积)(90ml),在50℃搅拌2h。然后使该混合物冷却至室温,真空过滤。用冰冷的环己烷(15ml)洗涤湿饼状物,收集固体,干燥,得到标题化合物(5R)-5-乙基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二

酮(13.6g),为白色固体。

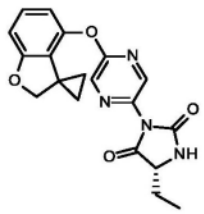
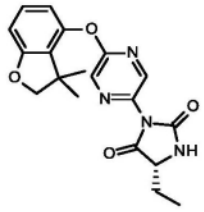
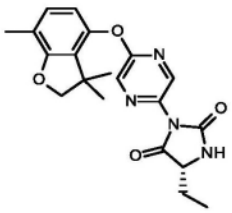
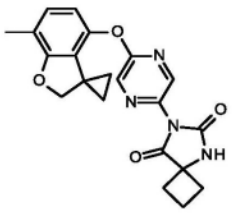
[0532] ^{1}H-NMR(500MHz;DMSO-d6):δppm 8.69(bs,1H),8.52(d,1H),8.26(d,1H),6.94(d,1H),6.53(d,1H),4.46(s,2H),4.26-4.30(m,1H),2.14(s,3H),1.77-1.86(m,1H),1.65-1.76(m,1H),1.07-1.12(m,2H),0.90-0.99(m,5H)。

[0533] 使用上述方法(路线1或路线2),用适合的丁酰胺替代(2R)-2-氨基-N-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]丁酰胺(中间体13)制备下列化合物。通过快速色谱法(硅胶柱;环己烷/EtOAc或其他适合的溶剂系统)和/或反相色谱法(C-18柱;水/乙腈或其他适合的溶剂系统)纯化终产物。

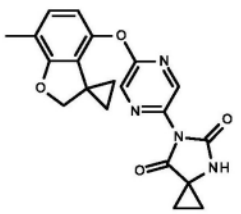
[0534]

实施例	结构	名称	丁酰胺	LCMS/NMR

[0535]

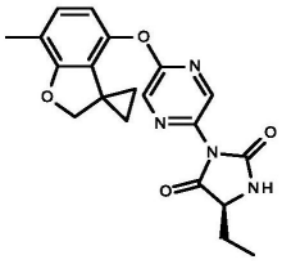
10		(5R)-5-乙基-3-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)咪唑烷-2,4-二酮	(2R)-2-氨基-N-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)丁酰胺(中间体 14)	LC/MS: QC_3_MIN: Rt = 2.081 min; m/z 367 [M+H]+。使用手性控制方法证实对映体纯度为> 95%。^{1}H-NMR (500 MHz; DMSO-d6): δ ppm 8.70 (bs, 1H), 8.55 (d, 1H), 8.27 (d, 1H), 7.11 (dd, 1H), 6.71 (dd, 1H), 6.62 (dd, 1H), 4.46 (s, 2H), 4.27-4.31 (m, 1H), 1.76-1.87 (m, 1H), 1.65-1.76 (m, 1H), 1.11-1.17 (m, 2H), 0.92-0.98 (m, 5H).
11		(5R)-3-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]-5-乙基-咪唑烷-2,4-二酮	(2R)-2-氨基-N-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]丁酰胺(中间体 16)	LC/MS: QC_3_MIN: Rt = 2.142 min; m/z 369 [M+H]+。
12		(5R)-5-乙基-3-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]咪唑烷-2,4-二酮	(2R)-2-氨基-N-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]丁酰胺(中间体 15)	LC/MS: QC_3_MIN: Rt = 2.111 min; m/z 383 [M+H]+。
13		7-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]-5,7-二氮杂螺[3.4]辛烷-6,8-二酮	1-氨基-N-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]环丁烷甲酰胺 (中间体 20)	LC/MS: QC_3_MIN: Rt = 2.309 min; 393 m/z [M+H]+。

[0536]

14		6-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]-4,6-二氮杂螺[2.4]庚烷-5,7-二酮	1-氨基-N-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]环丙烷甲酰胺	LC/MS: QC_3_MIN: Rt = 2.236 min; 379 m/z [M+H]+.

[0537] 实施例15

[0538] (5S)-5-乙基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮

[0539] 

[0540] 按照“路线1”方法,用(2S)-2-氨基-N-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]丁酰胺(中间体34)替代(2R)-2-氨基-N-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]丁酰胺(中间体13)合成标题化合物。

[0541] LC/MS:QC_3_MIN:Rt=2.29min;m/z 381[M+H]+。

[0542] 生物学实施例

[0543] 生物学实施例1:Kv3.1、Kv3.2和Kv3.3通道调节的测定

[0544] 本发明化合物调节电压门控钾通道亚型Kv3.3/Kv3.2/Kv3.1的能力可以使用以下测定法来测定。可以使用类似的方法研究本发明化合物调节其它通道亚型的能力。

[0545] 细胞生物学

[0546] 为了评估化合物对人Kv3.3通道(hKv3.3)的作用,用pBacMire_KCNC-3载体转染中国仓鼠卵巢(CHO)-K1细胞产生表达人Kv3.3通道的稳定细胞系。将细胞在补充有10%胎牛血清(Gibco)、1X非必需氨基酸(Invitrogen)和遗传霉素(G418)400ug/mL的DMEM/F12(Gibco)中培养。使细胞在37℃下在空气中包含5%CO_2的加湿环境中生长并维持。

[0547] 为了评估化合物对人Kv3.2通道(hKv3.2)的作用,通过用pCIH5-hKv3.2载体转染CHO-K1细胞来产生表达人Kv3.2通道(hKv3.2)的稳定细胞系。在补充有10%胎牛血清、1X非必需氨基酸(Invitrogen)和500ug/ml潮霉素-B(Invitrogen)的DMEM/F12培养基中培养细胞。使细胞在37℃下在空气中包含5%CO_2的加湿环境中生长并维持。

[0548] 为了评估化合物对人Kv3.1通道(hKv3.1)的作用:

[0549] 通过用具有人Kv3.1(NM_004976.4)的表达载体转染HEK-293细胞来产生人胚肾(HEK)-HKv3.1细胞系。用补充有10%热灭活的FBS、2mM L-谷氨酰胺、1%青霉素-链霉素和0.6mg/ml遗传霉素(G418)的MEM中培养细胞。使用包含G418选择抗生素(0.6mg/ml)的MEM扩增培养基,在T175cm2培养瓶中在37℃与5%CO_2下扩增HEK-hKV3.1B细胞。每3-4天使细胞脱

粘附，使用DPBS洗涤两次，然后用TrypLE使细胞离壁，以2-4×10^6个细胞/瓶的密度重新铺板。

[0550] 用于IonWorksQuattro™实验的细胞制备

[0551] 在本实验的当天，从温育箱中取出细胞并除去培养基。用5ml不含钙和镁的Dulbecco PBS(DPBS)洗涤细胞，并通过加入3ml依地酸(Versene)(Invitrogen,Italy)脱粘附，然后在37℃下短暂温育5分钟。轻敲培养瓶以使细胞离壁，加入10ml包含钙和镁的DPBS以制备细胞悬浮液。然后将细胞悬浮液置于15ml离心管中，并以1200rpm离心2min。离心后，除去上清液，并使用5mL移液管将细胞沉淀重悬于4mL包含钙和镁的DPBS中以分散沉淀。然后校正细胞悬浮液体积以得到用于测定的约300万个细胞/ml的细胞浓度。

[0552] 将添加到细胞中的所有溶液预温热至37℃。

[0553] 电生理学

[0554] Ionworks

[0555] 实验在室温下进行，使用具有PatchPlate™ PPC的IonWorks Quattro™平面阵列电生理学技术(Molecular Devices Corp.)。使用微型计算机(Dell Pentium 4)进行刺激方案和数据收集。通过在每个孔上施加10mV电压阶跃来确定平面电极孔电阻(Rp)。这些测量在细胞添加之前进行。在细胞添加和密封形成之后，通过施加从-80mV至-70mV的电压阶跃持续160ms来进行密封测试。此后，将两性霉素-B溶液添加到电极的胞内表面以实现胞内进入。将细胞保持在-70mV。在所有实验中，通过施加50ms超极化(10mV)前脉冲以诱发漏电流，然后在测试脉冲之前在维持电位下进行20ms期限来进行漏扣除。

[0556] 对于hKV3.2和hKV3.1，从-70mV的维持电位测定，施加-15mV的第一测试脉冲100ms，并且在-70mV的100ms之后施加+40mV的第二脉冲50ms。然后将细胞在-100mV下维持100ms，并施加从-70mV至+40mV(持续时间50ms)的另一脉冲以在200ms期间将电压钳位在-40mV。

[0557] 对于hKV3.3测定，从-70mV的维持电位开始，施加第一测试脉冲至0mV，持续500ms，并且在-70mV下再施加100ms，施加第二脉冲至40mV，持续200ms。这些较长的测试脉冲用于研究hKV3.3通道的失活。测试脉冲方案可以在不存在(加入前读数)和存在(加入后读数)测试化合物的情况下进行。可以通过添加化合物、然后温育3分钟来分隔加入前读数和加入后读数。

[0558] 溶液和药物

[0559] 胞内溶液包含如下(以mM计)：葡萄糖酸钾100、KCl 54、$MgCl_2$ 3.2，HEPES 5，用KOH调节至pH 7.3。将两性霉素-B溶液制备成在DMSO中的50mg/mL储备溶液，并在胞内溶液中稀释至0.1mg/mL的最终工作浓度。外部溶液是Dulbecco磷酸缓冲盐水(DPBS)且包含如下(以mM计)：$CaCl_2$ 0.90，KCl 2.67，KH_2PO_4 1.47，$MgCl.6H_2O$ 0.493，NaCl 136.9，Na_3PO_4 8.06，具有pH 7.4。

[0560] 将用于本发明的化合物(或参比化合物例如N-环己基-N-[(7,8-二甲基-2-氧代-1,2-二氢-3-喹啉基)甲基]-N'-苯基脲)以10mM的储备浓度溶于二甲亚砜(DMSO)。使用Biomek FX(Beckman Coulter)在384孔化合物板中将这些溶液进一步用DMSO稀释。将每个稀释液(1μL)转移到另一个化合物板中，并加入包含0.05％普流尼克酸(66μL)的外部溶液。加入3.5μL来自每个板的包含本发明化合物，并在IonWorksQuattro™实验期间与细胞一起

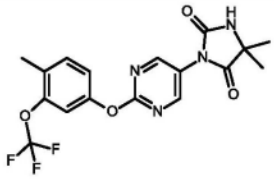
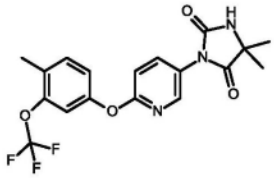
温育。最终测定稀释度为200，并且最终化合物浓度在50μM-50nM的范围内。

[0561] 数据分析

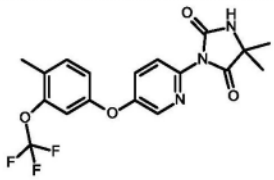
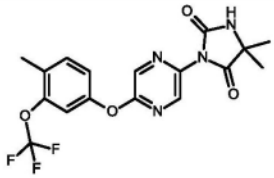
[0562] 在化合物不存在下，使用密封电阻(>20MΩ)和峰值电流振幅(>500pA，在40mV的电压阶跃下)分析和过滤记录，以从进一步分析中消除不适合的细胞。对于hKV3.2和hKV3.1测定，使用对-15mV电压阶跃测量的药物添加前后之间的诱发电流的配对比较来确定每种化合物的正调节作用。测量Kv3通道介导的外向电流，由在-15mV电压脉冲的最后10ms内的电流的平均振幅减去在-15mV阶跃之前的10ms期限内-70mV的平均基线电流来确定。然后将加入测试化合物后的这些Kv3通道电流与加入化合物前记录的电流进行比较。将数据对参比化合物(50uM N-环己基-N-[(7,8-二甲基-2-氧代-1,2-二氢-3-喹啉基)甲基]-N'-苯基脲)的最大作用和溶媒对照(0.5%DMSO)的作用进行归一化。使用ActivityBase或Excel软件分析归一化的数据。通过使用ActivityBase中的四参数逻辑函数拟合浓度-响应数据来确定将电流由参比化合物产生的最大增加而增加50%所需的化合物浓度(EC_{50})。对于hKV3.3测定，考虑到在0mV测试脉冲(500ms)的持续时间内峰值电流和电流衰减(失活)，针对0mV阶跃测量药物添加前后之间的诱发电流的配对比较。

[0563] N-环己基-N-[(7,8-二甲基-2-氧代-1,2-二氢-3-喹啉基)甲基]-N'-苯基脲得自ASINEX(登记号:552311-06-5)。

[0564]

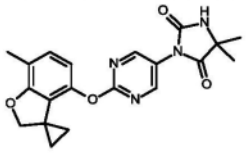
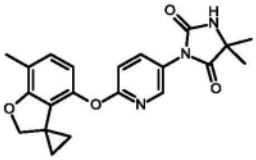
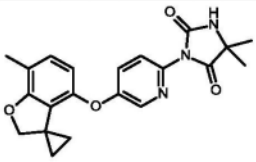
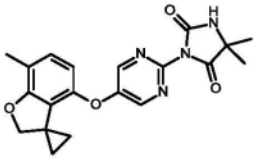
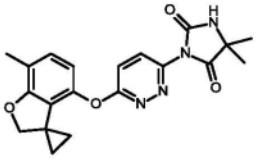
实施例	化合物	Kv3.1 pEC50	Kv3.1 max R%	参考文献/ LCMS
RE1		4.78	105	Ex57 WO2011/069951
RE2		5.25	118	Ex45 WO2011/069951

[0565]

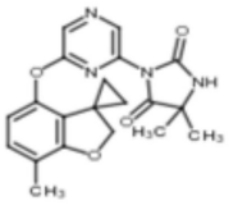
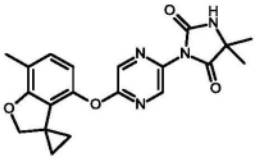
实施例	化合物	Kv3.1 pEC50	Kv3.1 max R%	参考文献/ LCMS
RE3		4.89	79	LC/MS: QC_3_MIN: Rt = 2.376 min; m/z 396 [M+H]+.
RE4		<4.3	24	LC/MS: QC_3_MIN: Rt = 2.346 min; m/z 397 [M+H]+.

[0566] 正如RE1-RE4的测试所示，吡嗪环的掺入可不利地影响Kv3.1调节剂的pEC50和maxR。

[0567]

实施例	化合物	Kv3.1 pEC50	Kv3.1 max R%	参考文献/ LCMS
RE5		5.14	158	Ex58 WO2012/076877
RE6		5.58	144	Ex70 WO2012/076877
RE7		5.56	130	Ex3 WO2017/103604
RE8		4.98	42	LC/MS: QC_3_MIN: Rt = 2.224 min; m/z 381 [M+H]+.
RE9		<4.3	16	LC/MS: QC_3_MIN: Rt = 2.043 min; m/z 381 [M+H]+.

[0568]

实施例	化合物	Kv3.1 pEC50	Kv3.1 max R%	参考文献/ LCMS
RE10		<4.3	22	LC/MS: QC_3_MIN: Rt = 2.29 min; m/z 381 [M+H]+.
1^{+}		5.47	164	实施例 1

[0569] $^{+}$n＝10.对于n＝18,pEC50为5.56,且maxR％152

[0570] 正如与实施例1相比RE5-RE9测试的所示,在实施例1中掺入对-吡嗪环令人意外地导致Kv3.1测定中的高pEC50和高maxR。RE10显示,与实施例1的对-吡嗪相比,间-吡嗪中心环具有大大降低的pEC50和maxR。

[0571]

实施例	Kv3.1 pEC50	Kv3.1 max R%
1+	5.47	164
2	4.68	149
3	5.15	205
4	5.17	170
5	5.69	149
6	4.75	165
7	5.12	134

实施例	Kv3.1 pEC50	Kv3.1 max R%
8	5.29	119
9*	5.88	172
10$	5.45	153
11	4.89	165
12	5.56	118
13	5.09	165
14	5.51	145
15	5.10	136

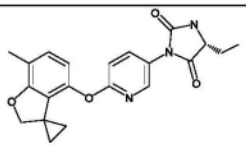
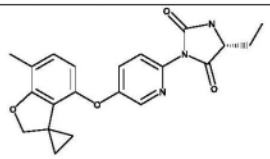
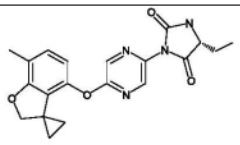
[0572] +n＝10.对于n＝18,pEC50为5.56,且maxR％152

[0573] *n＝4.对于n＝22,pEC50为5.90,且maxR％146

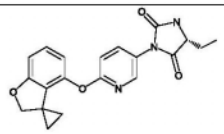
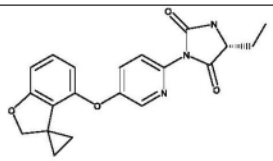
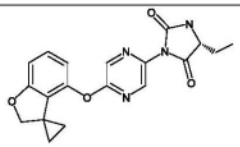
[0574] $n＝2.For n＝26,pEC50为5.63,且maxR％147

[0575]

实施例	化合物	Kv3.1 pEC50	Kv3.1 max R%	参考文献/ LCMS

RE11		6.1	152	Ex62 WO2012/076877
RE12		5.6	149	Ex4 WO2017/102604
9		5.90	146	实施例 9

[0576]

实施例	化合物	Kv3.1 pEC50	Kv3.1 max R%	参考文献/ LCMS
RE13		6.1	149	Ex15 WO2012/076877
RE14		5.2	150	Ex6 WO2017/102604
10		5.63	147	实施例 10

[0577] 式(I)化合物的所有测试实施例如上所示,并且在Kv3.1测定中显示出良好的pEC50和maxR特性。在先公开的参比化合物的Kv3.1数据可能由于测量次数较少而略有不同。

[0578] 其中所述的hKV3.1、hKV3.2和hKV3.3测定的数据的二次分析可用于研究化合物对从去极化电压脉冲开始的电流上升速率的影响。化合物的作用等级可以根据时间常数(Tau_{act})确定,(Tau_{act})使用下面给出的等式从在-15mV去极化电压脉冲开始之后的Kv3.1、Kv3.2和Kv3.3电流的上升的非线性拟合获得。

[0579] $Y = (Y0-Ymax)*exp(-K*X)+Ymax$

[0580] 其中:

[0581] Y0为去极化电压脉冲开始时的电流值;

[0582] Ymax为坪值电流;

[0583] K为速率常数,且Tau_{act}为激活时间常数,其为K的倒数。

[0584] 类似地,也可以研究化合物对在-15mV去极化电压脉冲结束时通道闭合时Kv3.1、Kv3.2或Kv3.3电流衰减所花费的时间的影响。在后一种情况下,化合物对通道关闭的影响的等级可以根据在去极化电压脉冲结束后即刻的电流(“尾电流”)衰减的非线性拟合的时

间常数(Tau_{deact})确定。

[0585] Kv3.1、Kv3.2和Kv3.3通道必须非常快速地激活和失活,以便使神经元以高频率释放动作电位(Rudy等人,2001)。激活的减慢可能延迟动作电位复极化的启动;失活的减慢可能产生超极化电流,其降低神经元的兴奋性并延迟神经元可以释放进一步的动作电位之前的时间。这两种对通道激活和失活的减慢作用一起可能导致神经元高频放电的能力降低而不是促进。因此,对Kv3.1和/或Kv3.2和/或Kv3.3通道具有这种减慢作用的化合物将有效地表现为通道的负调节剂,导致神经元放电减慢。对于WO2011/069951中公开的某些化合物,已经显示了后一种作用,其中Tau_{act}的显著增加可以从使用电生理学技术在体外大鼠脑皮质中的"快速放电"的中间神经元进行的记录中观察到。加入相关化合物降低了神经元响应于300Hz的去极化脉冲串而放电的能力。

[0586] 因此,尽管某些化合物可以在重组细胞测定中被鉴定为正调节剂,但是显著增加Tau_{act}值的那些化合物可以降低天然组织中神经元高频放电的能力。

[0587] 生物学实施例2:血液和脑组织结合的测定

[0588] 材料和方法

[0589] 将在使用K3-EDTA作为抗凝血剂的实验周中采集的Sprague Dawley大鼠全血用等渗磷酸盐缓冲液1:1(v/v)稀释。将在-20℃下冷冻储存的Sprague Dawley大鼠全脑解冻并在1:2(w/v)的人工脑脊液(CSF)中均化。

[0590] 将适量的测试化合物溶于DMSO中,得到10毫摩尔溶液。然后使用在MilliQ水中的50%乙腈制备进一步的稀释液,以获得166.7微摩尔工作溶液。该工作溶液用于掺入血液以在全血中获得0.5微摩尔的终浓度。类似地,该工作溶液用于掺入脑样品以在全脑中获得5微摩尔的终浓度。从这些掺加的血液和脑制品中,立即提取对照样品(n=3),并用于计算测试品的初始收率。

[0591] 将150uL不含化合物的缓冲液(用于血液的等渗磷酸盐缓冲液或用于脑的人造CSF缓冲液)分配到一个半孔中,并将150uL掺加(血液或脑)的基质加载到另一个半孔中,其中两个半孔通过半透膜分隔开。在37℃下平衡5h后,将50uL透析的基质(血液或脑)加入50uL相应的不含化合物的缓冲液中,对于缓冲液反之亦然,使得缓冲液与基质(血液或脑)的体积保持相同。然后用300uL含有咯利普兰(正电离模式的对照)或双氯芬酸(负电离模式的对照)作为内标的乙腈通过蛋白质沉淀提取样品,并以3000rpm离心10min。收集上清液(100uL),用在MilliQ水中的27%ACN(200uL)稀释,然后注入HPLC-MS/MS或UPLC-MS/MS系统中以测定存在的测试化合物的浓度。

[0592] 分析

[0593] 然后使用以下公式确定血液和脑组织结合:

[0594] Afu=缓冲液/血液或Afu=CSF/脑

[0595] 其中Afu=未结合的表观分数;缓冲液=在缓冲液隔室中测定的分析物/内标比;血液=在血液隔室中测定的分析物/内标比;脑=在脑隔室中测定的分析物/内标比。

[0596] $$Fucr = \frac{1/D}{[(1/Afu - 1)+1/D]}$$

[0597] 其中:fucr=校正的未结合分数;D=基质稀释因子(血液D=2,脑D=3)。

[0598] 然后：

[0599] 结合%＝(1-fucr)x100

[0600] 未结合%＝100-结合%

[0601] 脑/血液分配比(Kbb)测定

[0602] 对于可自由透过血/脑屏障(BBB)的化合物，血液和脑中的未结合浓度在稳态分布条件下应当是相等的。因此，Kbb值可以计算为：

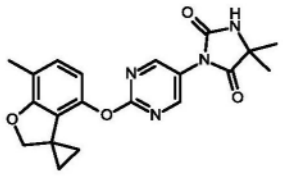
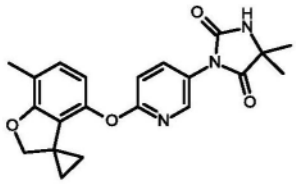
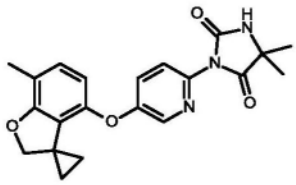
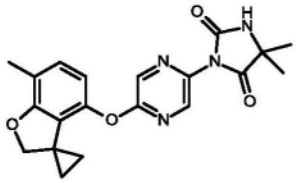
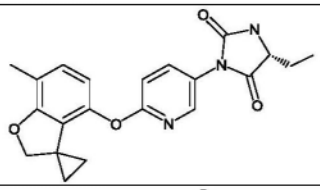
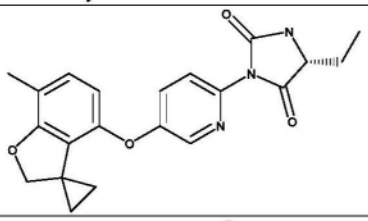
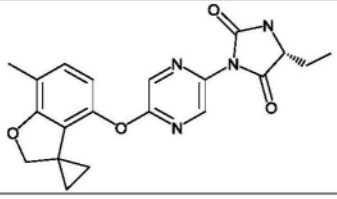
[0603] Fu(血液)/Fu(脑)

[0604] 如果不涉及流出泵转运蛋白，则预期其等于脑与血液中浓度比(Ct(脑)/Ct(血液))。

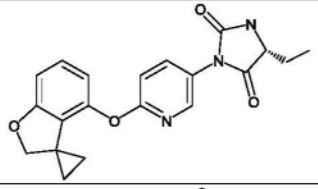
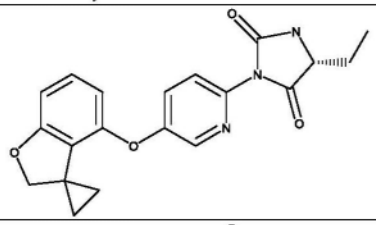
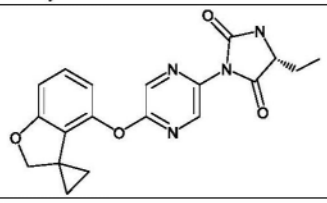
[0605] 结果

[0606] 用上述方法测试实施例1、9和10以及某些参比化合物，以确定未结合的脑分数。结果如下：

[0607]

实施例	化合物	未结合的脑分数(%)
RE5		5.1
RE6		2.8
RE7		2.3*
1		4.3
RE11		2.1
RE12		1.9
9		3.0

[0608]

实施例	化合物	未结合的脑分数(%)
RE13		6.2
RE14		5.8
10		8.7

[0609] *用18%AcN的水溶液稀释的上清液

[0610] 本发明的吡嗪化合物与它们的吡啶参比化合物相比显示出增加的未结合的脑分数。

[0611] 生物学实施例3:体内药代动力学参数的测定

[0612] 材料和方法

[0613] 向成年雄性大鼠(Charles River,Italy)口服给予1mg/kg(5ml/kg,在5%v/v DMSO中,0.5%w/v HPMC水溶液)和静脉内给予0.5mg/kg(2ml/kg,在5%v/v DMSO中40%w/v PEG400盐水溶液)的测试化合物。口服施用后,在深度异氟烷麻醉下从每只大鼠的门静脉和心脏采集血样(每个时间点1只大鼠)。静脉内施用后,从每只大鼠的侧尾静脉采集系列血样。另一组大鼠(每种测试化合物n=1)在如上口服施用1mg/kg测试化合物之前不久接受PgP转运抑制剂依克立达(3mg/kg)的单次静脉内施用。在这些动物的剂量施用后0.5h的单个时间点采集血液和脑样品。在所有情况下,将血样采集入EDTA钾管中。

[0614] 可以使用基于乙腈沉淀蛋白质、然后用优化的分析方法进行HPLC/MS-MS分析的方法测定血液和脑样品的测试化合物浓度。

[0615] 分析

[0616] 使用WinNonlin Professional 4.1版,使用非隔室药代动力学模型分析口服或静脉内给药后不同时间点的血液(表示为ng/mL)和脑(表示为ng/g)中测试化合物的浓度。导出以下参数:

[0617] 静脉内给药:随时间的最大浓度(Cmax)、随时间的积分浓度(AUC)、清除率(Clb)、分布体积(Vss)和半衰期(t1/2)。

[0618] 口服给药:Cmax、达到最大浓度的时间(Tmax)、AUC、生物利用度(F%)、吸收分数(Fa%)、血脑比(AUC BB)和在依克立达存在下AUC BB的倍数变化。

[0619] 可以预期本发明的化合物在脑组织中显示出良好的利用度。

[0620] 生物学实施例4:体外人肝细胞中的代谢稳定性

[0621] 方法

[0622] 本研究的目的在于确定混合性别的人冷冻保存肝细胞的代谢稳定性。睾酮和7-羟基香豆素分别用作I期和II期代谢的阳性对照。

[0623] 通过将William培养基E、HEPES缓冲液1M和L-谷氨酰胺200mM以以下比例合并来制备温育培养基:分别为88%、10%和2%(分别为440mL、50mL和10mL)。将获得的培养基用氧和5%二氧化碳的混合气(5%CO_2,95%O_2)起泡30分钟,然后使用。将冷冻保存的肝细胞解冻并在37℃混悬于预温热的温育培养基中。将细胞离心,重新混悬于培养基中并通过血细胞计数器(Burker室)计数。使用台盼蓝排除试验测量细胞存活力。

[0624] 将测试化合物分别溶于DMF中以获得50mM储备溶液,将其在水/乙腈50/50(v/v)中进一步稀释以获得相应的50uM工作溶液。将睾酮和7-羟基-香豆素溶于DMF中,以获得50mM睾酮溶液和5mM 7-羟基-香豆素溶液。然后将这些溶液在温育培养基中稀释,以获得1mM睾酮工作溶液和500uM 7-羟基-香豆素工作溶液。

[0625] 将10uL的每种工作溶液,即50uM测试化合物、1mM睾酮和500uM的7-羟基-香豆素加入到990uL的0.5x10^6细胞混悬液中,以便分别得到0.5uM、10uM和5uM的终浓度。每次温育中有机溶剂的浓度是恒定的并且<1%(v/v)。

[0626] 将测试化合物以0.5uM与混合性别的人冷冻保存的肝细胞在37℃下在24孔板中分别温育0、5、10、15、20、30、45、60、90、120、150和180min(12个时间点)。在每个时间点,机器人处理处理器从每个孔中吸出50μL温育混合物,并将其分配到冷冻的96孔板中,所述96孔板包含100μL乙腈和相应的内标150ng/mL以终止反应。然后加入等分的水(120μL)以使有机溶剂含量平衡在37%。在LC MS/MS分析之前,将样品离心(约3500g,10分钟)。

[0627] 将阳性对照睾酮和7-羟基-香豆素分别以10μM和5μM单独(n=1)与混合性别的人冷冻保存的肝细胞在上文报告的测试项目的相同条件下温育0、5、10、15、20、30、45、60、90、120、150和180min(12个时间点),以证明肝细胞系统中的I相和II相代谢。在每个时间点,机器人处理处理器从每个孔中抽吸50μL温育混合物,将其分配到冷冻的96孔板中,所述96孔板包含100μL含有咯利普兰作为内标的乙腈,以终止反应。然后加入等分的水(120μL)以使有机溶剂含量平衡在37%。在LC MS/MS分析之前将样品离心(约3500g,10分钟)。

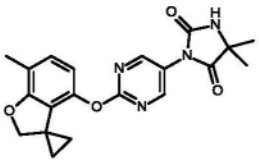
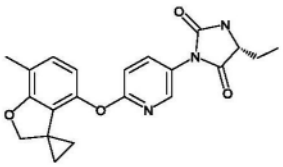
[0628] 由剩余测试化合物与内标物的峰面积比例相对于时间计算代谢稳定性。

[0629] 使用温育的实际体积V(mL)、温育中肝细胞的量M(百万个细胞)和每g肝脏的肝细胞数量Hn(对于人为120),按照一级消除常数k(min^{-1})(通过绘制剩余测试品与内标的峰面积比例的自然对数相对于时间的曲线,从GraphPad获得)确定固有清除率(Clint)。

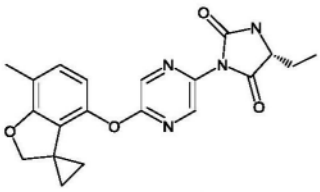
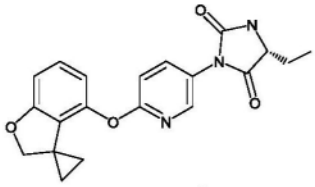
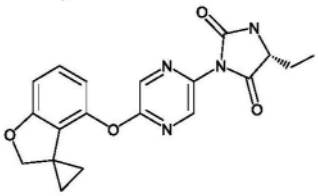
[0630] $$CLint = k * \frac{V}{M} * \frac{Hn\ x10^6 cells}{g\ liver}$$

[0631] CLint的值表示为mL/min/g肝脏。

[0632]

实施例	化合物	速率常数 k (min^{-1})	体外 Cl_{int} (mL/min/g 肝)
RE5		0.002	0.31
RE11		0.02	3.58

[0633]

实施例	化合物	速率常数 k (min^{-1})	体外 Cl_{int} (mL/min/g 肝)
9		0.004	1.03
RE13		0.009	2.16
10		0.003	0.70

[0634] 与吡啶参比化合物RE11和RE13相比,实施例9和10显示出低清除率。

[0635] 生物学实施例5:Ames测试

[0636] 方法

[0637] 该体外研究目的在于评估测试品在鼠伤寒沙门菌(Salmonella typhimurium)(TA1535、TA1537、TA98和TA100)和大肠杆菌(Escherichia coli)WP2 uvrA(pKM101)的细菌菌株中体外诱导基因突变的潜能;测试方法基于细菌诱变性测试的既定方法,并且在外源性哺乳动物氧化代谢系统(S9-混合物)存在和不存在下进行测定。

[0638] 该研究根据国家和国际指南设计,以满足监管机构对新药毒性测试的要求。研究设计符合以下测试指南:

[0639] • ICH guideline M3(R2)on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (CPMP/ICH/286/95,2009年6月)。

[0640] • ICH Topic S2(R1)Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use。2012年6月。

[0641] 细菌菌株

[0642] 使用如下细菌菌株：

[0643]

物种	菌株	基因型
鼠伤寒沙门菌 *(S. typhimurium)*	TA1535	hisG46 rfa Δ *uvrB*
鼠伤寒沙门菌	TA1537	hisC3076 rfa Δ *uvrB*
鼠伤寒沙门菌	TA98	hisD3052 rfa Δ *uvrB* (pKM101)
鼠伤寒沙门菌	TA100	hisG46 rfa Δ *uvrB* (pKM101)
大肠杆菌(E. coli)	WP2 *uvrA* (pKM101)	TrpE Ochre *uvrA* (pKM101)
来源	Molecular Toxicology Incorporated, Boone, NC, USA (MolTox™)	
生长期	晚对数期	

[0644] 菌株TA1535、TA100和WP2 uvrA pKM101检测碱基变化突变。菌株TA1537和TA98检测移码突变。

[0645] 细菌接种物用于在10mL营养肉汤培养基(NB2，包含氨苄青霉素，用于包含pKM101质粒的菌株鼠伤寒沙门菌菌株TA98和TA100以及大肠杆菌WP2 uvrA(pKM101)，以维持质粒拷贝数)中制备新鲜培养物。将细菌在37±2℃的振荡培养箱中培养10-12小时，以产生1-2x10^9个细胞/mL。

[0646] 将细菌混悬液以100μL的体积加入到TOP琼脂(包含营养缺陷型所需的痕量氨基酸)中。

[0647] 哺乳动物氧化代谢系统

[0648] 使用来自Molecular Toxicology Incorporated,USA(MolTox™)的苯巴比妥,56苯并黄酮诱导的大鼠肝线粒体后部分(S9)作为外源性氧化代谢系统。在约-80℃下以冷冻等分试样储存的S9部分批次在使用前立即解冻。通过将S9(10％v/v)添加到NADPH产生系统中来制备S9混合物，所述NADPH产生系统包括NADP(3.15mg/mL)、葡萄糖-6-磷酸(1.5mg/mL)和2％v/v的在pH 7.4的磷酸盐缓冲液中含有$MgCl_2$(81.3mg/mL)和KCl(123mg/mL)的盐水溶液。对于在S9混合物存在下的处理，以500μl/板的最终体积使用S9混合物。对于不存在S9混合物的处理，加入等体积的无菌磷酸盐缓冲液pH 7.4替代S9混合物。

[0649] 阳性对照制备物

[0650] 使用以下阳性对照(由Moltox™通过Trinova Biochem GmbH,Giesen,Germany和Sigma Aldrich,Milano,Italy提供)并如下配制：

[0651]

细菌菌株	阳性对照	浓度(μg/板)	媒介物(溶剂)	S9-混合物
TA98	2-硝基芴(2NF)	2	二甲亚砜(DMSO)	无
TA1535, TA100	叠氮化钠(NaAz)	2	H_2O	无
TA1537	ICR-191	1	DMSO	无
WP2 *uvrA*(pKM101)	4-硝基喹啉-1-氧化物(4NQO)	1	DMSO	无
TA98	苯并[a]芘(B[a]P)	1.25	DMSO	有
TA1535, TA1537, TA100, WP2 *uvrA* (pKM101)	2-氨基蒽(2AAN)	5	DMSO	有

[0652] 由冷冻(约-20℃)储备溶液制备阳性对照,并在使用期间在环境温度下储存。

[0653] 测试品

[0654] 测试由4个用于媒介物(DMSO)对照的重复板和2个用于测试品和阳性对照的重复板组成,在不存在和存在S9-混合物的情况下进行处理。如下测试从5μg/板开始至5000μg/板的测试品浓度范围:

[0655]

物种	菌株	测试品浓度(ug/板)	S9-混合物
鼠伤寒沙门菌(S. typhimurium)	TA1535、TA1537、TA98 和 TA100	5、15、50、150、500、1500 和 5000	无
大肠杆菌(E. coli)	WP2 *uvrA*(pKM101)		
鼠伤寒沙门菌	TA1535、TA1537、TA98 和 TA100		有
大肠杆菌	WP2 *uvrA*(pKM101)		

[0656] 将媒介物、测试品和阳性对照制剂以100μl/板的体积加入板中。

[0657] 板处理和温育

[0658] Top琼脂补充有痕量的组氨酸和生物素或色氨酸,等分试样(2mL/板),并维持在46±2℃。将适当的细菌悬浮液加入到2mL顶层琼脂中,然后加入测试品或媒介物/阳性对照溶液和无菌磷酸盐缓冲液pH 7.4或S9-混合物。将该最终处理混合物倾倒在最小琼脂板(**Vögel**Bonner板)上,并在37±2℃下在黑暗中温育约64小时。

[0659] 板评分和分析

[0660] 在温育期结束时,评估板的测试品沉淀(通过目视检查)。使用菌落计数器ProtoCOL3 Synbiosis对板进行细菌菌落形成的电子评分。在测试品沉淀发生的情况下,细菌菌落计数对于每个菌株手动进行并在不干扰手动评分的最低处理浓度下停止。

[0661] 评分后,检查板的毒性迹象(即背景菌苔的生长减少/缩小、针点/假逆转菌落的存在和/或菌落数量的减少)。

[0662] 如果任何处理浓度的数据显示TA98、TA100和WP2 UVRA(PKM101)的响应是同时媒

介物对照值的≥2倍或TA1535和TA1537的响应是同时媒介物对照值的≥3倍，结合剂量相关的响应，则结果应被认为是阳性的。仅部分满足这些标准或任何菌株的数据显示剂量相关反应但不超过详述的2或3倍阈值的结果被认为是不明确的。

[0663] 应用以下验收标准：

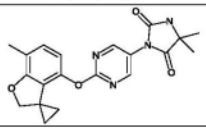
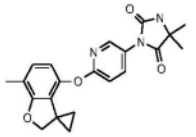
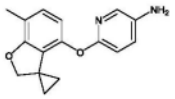
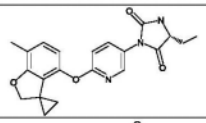
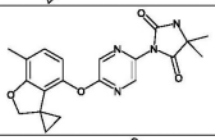
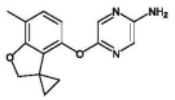
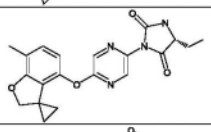
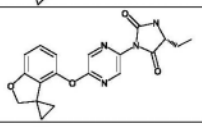
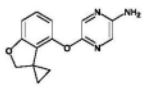
[0664] 1.测试的最高浓度应为5000μg/板或受测试项目在媒介物中的溶解度限制。

[0665] 2.如果测试项目溶解度是限制因素，则选择用于板评分的最大浓度是在温育期结束时在处理板上观察到测试项目沉淀时的最低浓度，并且该浓度不干扰评分。

[0666] 如果毒性是限制因素，则可评估基因突变的最大浓度是在平板评分期间观察到显著细菌毒性迹象时的最低浓度。

[0667] 结果

[0668]

实施例	化合物	Ames 结果	苯胺	Ames 结果
RE5		非致诱变的	未测试	未测试
RE6		非致诱变的		对于 TA1535，在 150 ug/板在代谢活化存在下具有致诱变作用
RE11		非致诱变的		
1		非致诱变的		非致诱变的
9		非致诱变的		
10		非致诱变的		非致诱变的

[0669] 发现与RE6/RE11相关的苯胺(其在某些条件下显示为降解物)是致诱变的。该发现提示将来开发RE6/RE11以及可能产生相关苯胺的化合物(例如(5R)-5-乙基-3-(6-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基-3-吡啶基)咪唑烷-2,4-二酮，即RE13)中存在风险。可根据其相关的苯胺区分的化合物是有利的。

[0670] 实施例1、9和10的苯胺是非致突变性的，其可预期适用于可产生相关苯胺的本发明的其它化合物。

[0671] 另外的动物模型

[0672] 专利申请WO2011/069951、WO2012/076877、WO2012/168710、WO2013/083994、WO2013/175215和WO2013/182851(为了示例说明化合物的潜在效用和提供用于化合物测试的动物模型的目的，全部通过引用并入)证明了作为Kv3.1和Kv3.2的调节剂的化合物在癫痫发作、多动、睡眠障碍、精神病、听力障碍和双相性精神障碍的动物模型中的活性。

[0673] 专利申请WO2013/175211(为了示例说明化合物的潜在效用和提供用于测试化合

物的动物模型的目的，通过引用并入)证明了作为Kv3.1和Kv3.2的调节剂的化合物在栗鼠类急性噪声诱导的听力损失模型中的功效，并且还评估了化合物在中枢听觉处理缺陷模型和耳鸣模型中的功效。

[0674] Glait等人2018,Anderson等人2018和Chamber等人2018证明了Kv3.1和Kv3.2调节剂在听力相关模型中的功效。

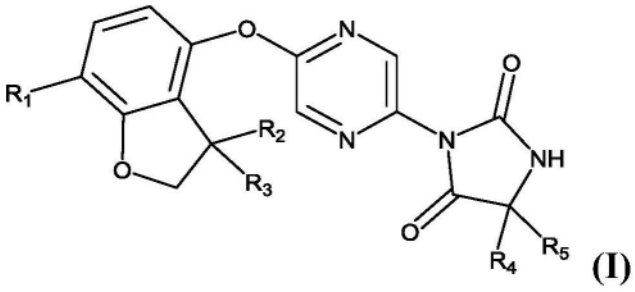
[0675] 专利申请WO2017/098254(为了示例说明化合物的潜在效用和提供用于测试化合物的动物模型的目的，通过引用并入)证明了作为Kv3.1和Kv3.2的调节剂的化合物在神经性疼痛和炎性疼痛模型中的功效。

[0676] 在整个说明书和随后的权利要求书中，除非上下文另有要求，否则词语“包含”以及诸如“含有”和“包括”的变化形式将被理解为暗示包括所述整数、步骤、整数组或步骤组，但不排除任何其他整数、步骤、整数组或步骤组。

[0677] 本申请包括说明书和权利要求书，其可以用作关于任何后续申请的优先权的基础。这样的后续申请的权利要求可以涉及本文描述的任何特征或特征的组合。它们可以采取产品、组合物、方法或用途权利要求的形式，并且可以包括例如但不限于以下权利要求。

[0678] 本发明的方案：

[0679] 方案1-式(I)的化合物：

[0680] 

(I)

[0681] 其中：

[0682] R_1为H或甲基；

[0683] R_2和R_3均为甲基，或R_2和R_3与所连接的碳原子一起为螺环丙基环；

[0684] R_4为甲基或乙基；

[0685] R_5为H或甲基；

[0686] 或R_4和R_5与所连接的碳原子一起形成C_3-C_4螺碳环基；

[0687] 或其盐和/或溶剂化物和/或衍生物。

[0688] 方案2-方案1的化合物其中R_1为H。

[0689] 方案3-方案1的化合物，其中R_1为甲基。

[0690] 方案4-方案1-3任一项的化合物，其中R_2和R_3为螺环丙基环。

[0691] 方案5-方案1-3任一项的化合物，其中R_2为甲基，且R_3为甲基。

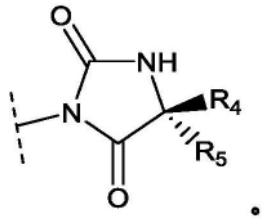
[0692] 方案6-方案1-5任一项的化合物，其中R_4为甲基。

[0693] 方案7-方案1-5任一项的化合物，其中R_4为乙基。

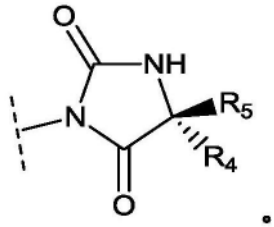
[0694] 方案8-方案1-7任一项的化合物，其中R_5为H。

[0695] 方案9-方案1-7任一项的化合物，其中R_5为甲基。

[0696] 方案10-方案1-9任一项的化合物，其中当R_4和R_5不同时，它们具有如下立体化学排列：

[0697] 

[0698] 方案11-方案1-9任一项的化合物，其中当R_4和R_5不同时，它们具有如下立体化学排列：

[0699] 

[0700] 方案12-方案1-5任一项的化合物，其中R_4和R_5与所连接的碳原子一起形成螺环丙基。

[0701] 方案13-方案1-5任一项的化合物，其中R_4和R_5与所连接的碳原子一起形成螺环丁基。

[0702] 方案14-方案1的化合物，选自：

[0703] 5,5-二甲基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮；

[0704] 3-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]-5,5-二甲基-咪唑烷-2,4-二酮；

[0705] (5R)-5-乙基-5-甲基-3-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)咪唑烷-2,4-二酮；

[0706] 5,5-二甲基-3-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)咪唑烷-2,4-二酮；

[0707] (5R)-5-乙基-5-甲基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮；

[0708] (5R)-3-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]-5-乙基-5-甲基-咪唑烷-2,4-二酮；

[0709] 5,5-二甲基-3-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]咪唑烷-2,4-二酮；

[0710] (5R)-5-乙基-5-甲基-3-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]咪唑烷-2,4-二酮；

[0711] (5R)-5-乙基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮；

[0712] (5R)-5-乙基-3-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)咪唑烷-2,4-二酮；

[0713] (5R)-3-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]-5-乙基-咪唑烷-2,4-二酮；

[0714] (5R)-5-乙基-3-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]咪唑烷-2,4-二酮；

[0715] 7-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]-5,7-二氮杂螺[3.4]辛烷-6,8-二酮；

[0716] 6-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]-4,6-二氮杂螺[2.4]庚烷-5,7-二酮；

[0717] (5S)-5-乙基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮；

[0718] 或其盐和/或其溶剂化物和/或其衍生物。

[0719] 方案15-方案1的化合物，其为：

[0720] 5,5-二甲基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮。

[0721] 方案16-方案1的化合物，其为：

[0722] 3-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]-5,5-二甲基-咪唑烷-2,4-二酮。

[0723] 方案17-方案1的化合物，其为：

[0724] (5R)-5-乙基-5-甲基-3-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)咪唑烷-2,4-二酮。

[0725] 方案18-方案1的化合物，其为：

[0726] 5,5-二甲基-3-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)咪唑烷-2,4-二酮。

[0727] 方案19-方案1的化合物，其为：

[0728] (5R)-5-乙基-5-甲基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮。

[0729] 方案20-方案1的化合物，其为：

[0730] (5R)-3-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]-5-乙基-5-甲基-咪唑烷-2,4-二酮。

[0731] 方案21-方案1的化合物，其为：

[0732] 5,5-二甲基-3-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]咪唑烷-2,4-二酮。

[0733] 方案22-方案1的化合物，其为：

[0734] (5R)-5-乙基-5-甲基-3-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]咪唑烷-2,4-二酮。

[0735] 方案23-方案1的化合物，其为：

[0736] (5R)-5-乙基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮。

[0737] 方案24-方案1的化合物，其为：

[0738] (5R)-5-乙基-3-(5-螺[2H-苯并呋喃-3,1'-环丙烷]-4-基氧基吡嗪-2-基)咪唑烷-2,4-二酮。

[0739] 方案25-方案1的化合物，其为：

[0740] (5R)-3-[5-[(3,3-二甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]-5-乙基-咪唑烷-2,4-二酮。

[0741] 方案26-方案1的化合物，其为：

[0742] (5R)-5-乙基-3-[5-[(3,3,7-三甲基-2H-苯并呋喃-4-基)氧基]吡嗪-2-基]咪唑烷-2,4-二酮。

[0743] 方案27-方案1的化合物，其为：

[0744] 7-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]-5,7-二氮杂螺[3.4]辛烷-6,8-二酮。

[0745] 方案28-方案1的化合物，其为：

[0746] 6-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]-4,6-二氮杂螺[2.4]庚烷-5,7-二酮。

[0747] 方案29-方案1的化合物，其为：

[0748] (5S)-5-乙基-3-[5-(7-甲基螺[2H-苯并呋喃-3,1'-环丙烷]-4-基)氧基吡嗪-2-基]咪唑烷-2,4-二酮。

[0749] 方案30-方案1-29任一项的式(I)的化合物或其药学上可接受的盐和/或溶剂化物。

[0750] 方案31-方案1-30任一项的化合物，用作药物。

[0751] 方案32-方案31的化合物，用于预防或治疗选自以下的疾病或病症：听力障碍、精神分裂症、抑郁症和情绪障碍、双相情感障碍、物质滥用障碍、焦虑症、睡眠障碍、听觉过敏和响度感知障碍、梅尼埃病、平衡障碍和内耳障碍、冲动控制障碍、人格障碍、注意力缺陷/多动障碍、孤独症谱群疾病、进食障碍、认知障碍、共济失调，疼痛例如神经性疼痛、炎性疼痛和混杂的疼痛，路易体痴呆和帕金森病。

[0752] 方案33-方案31的化合物，用于预防或治疗精神分裂症。

[0753] 方案34-方案31的化合物，用于预防或治疗听力障碍。

[0754] 方案35-方案31的化合物，用于预防或治疗疼痛。

[0755] 方案36-方案31的化合物，用于治疗脆性X染色体。

[0756] 方案37-用于预防或治疗选自以下的疾病或病症的方法：听力障碍、精神分裂症、抑郁症和情绪障碍、双相情感障碍、物质滥用障碍、焦虑症、睡眠障碍、听觉过敏和响度感知障碍、梅尼埃病、平衡障碍和内耳障碍、冲动控制障碍、人格障碍、注意力缺陷/多动障碍、孤独症谱群疾病、进食障碍、认知障碍、共济失调，疼痛例如神经性疼痛、炎性疼痛和混杂的疼痛，路易体痴呆和帕金森病，该方法包含向有此需要的个体施用有效量的方案1-30任一项的化合物。

[0757] 方案38-用于预防或治疗精神分裂症的方法，包含向有此需要的个体施用方案1-30任一项的化合物。

[0758] 方案39-用于预防或治疗听力障碍的方法，包含向有此需要的个体施用有效量的方案1-30任一项的化合物。

[0759] 方案40-用于预防或治疗疼痛的方法，包含向有此需要的个体施用有效量的方案1-30任一项的化合物。

[0760] 方案41-用于治疗脆性X染色体的方法，包含向有此需要的个体施用方案1-30任一项的化合物。

[0761] 方案42-方案1-30任一项的化合物在制备用于预防或治疗选自以下的疾病或病症的药物中的用途：听力障碍、精神分裂症、抑郁症和情绪障碍、双相情感障碍、物质滥用障碍、焦虑症、睡眠障碍、听觉过敏和响度感知障碍、梅尼埃病、平衡障碍和内耳障碍、冲动控制障碍、人格障碍、注意力缺陷/多动障碍、孤独症谱群疾病、进食障碍、认知障碍、共济失调，疼痛例如神经性疼痛、炎性疼痛和混杂的疼痛，路易体痴呆和帕金森病。

[0762] 方案43-方案1-30任一项的化合物在制备用于预防或治疗精神分裂症的药物中的用途。

[0763] 方案44-方案1-30任一项的化合物在制备用于预防或治疗听力障碍的药物中的用途。

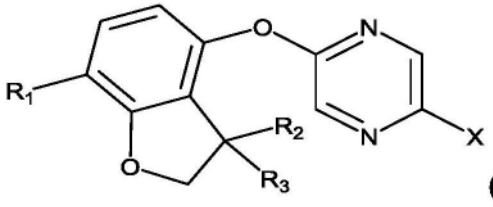
[0764] 方案45-方案1-30任一项的化合物在制备用于预防或治疗疼痛的药物中的用途。

[0765] 方案46-方案1-30任一项的化合物在制备用于治疗脆性X染色体的药物中的用途。

[0766] 方案47-药物组合物，包含方案1-30任一项的化合物和药学上可接受的载体或赋形剂。

[0767] 方案48-方案1-30任一项的化合物，用于与另一种药学上可接受的化学成分组合。

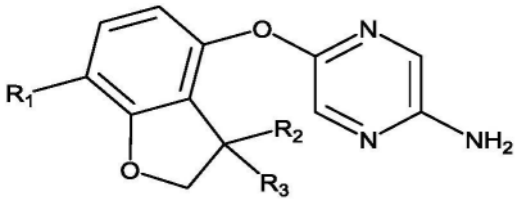
[0768] 方案49-式(II)或(XVI)的化合物：

[0769] 

(II),

[0770] 其中R_1、R_2和R_3如方案1中所定义，X为卤素，例如Br。

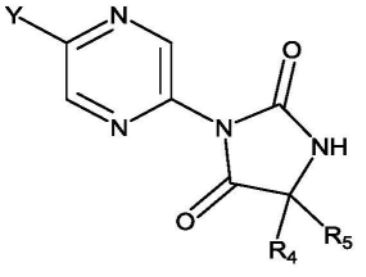
[0771] 方案50-式(XVI)的化合物：

[0772] 

(XVI),

[0773] 其中R_1、R_2和R_3如方案1中所定义。

[0774] 方案51-式(IV)的化合物：

[0775] 

(IV)

[0776] 其中R_4和R_5如方案1中所定义，Y为卤素，例如Cl。

[0777] 方案52-方案1-30任一项的式(I)的化合物的衍生物或其盐和/或溶剂化物，通过

用基团L使乙内酰脲的仲氮或的三唑酮的仲氮官能化，其中L选自：

[0778] a)-PO(OH)O^- • M^+，其中M^+为药学上可接受的一价抗衡离子，

[0779] b)-PO(O^-)$_2$ • $2M^+$，

[0780] c)-PO(O^-)$_2$ • D^{2+}，其中D^{2+}为药学上可接受的二价抗衡离子，

[0781] d)-CH(R^X)-PO(OH)O^- • M^+，其中R^X为氢或C_{1-3}烷基，

[0782] e)-CH(R^X)-PO(O^-)$_2$ • $2M^+$，

[0783] f)-CH(R^X)-PO(O^-)$_2$ • D^{2+}，

[0784] g)-SO_3^- • M^+，

[0785] h)-CH(R^X)-SO_3^- • M^+，和

[0786] i)-CO-CH_2CH_2-CO_2 • M^+。

[0787] 方案53-方案1-36任一项的化合物，其为天然同位素形式。

[0788] 方案54-方案1-48、52或53任一项的化合物、方法、用途、组合物或衍生物，用于口服施用。

[0789] 方案55-方案1-48或52-54任一项的化合物、方法、用途、组合物或衍生物，用于以2-400mg/天，例如2-300mg/天，尤其是5-250mg/天施用。

[0790] 方案56-方案1-48或52-55任一项的化合物、方法、用途、组合物或衍生物，用于每天一次或两次施用。

[0791] 方案57-方案56的化合物，用于每天施用一次。

[0792] 方案58-方案56的化合物，用于每天施用两次。

[0793] 方案59-方案1-48或52-58任一项的化合物、方法、用途、组合物或衍生物，用于施用至少3个月的期限。

[0794] 方案60-方案1-48或52-58任一项的化合物、方法、用途、组合物或衍生物，用于向人类个体施用。

[0795] 方案61-方案60的化合物、方法、用途、组合物或衍生物，用于向年龄在18-65岁的成年人施用。

[0796] 方案62-方案60的化合物、方法、用途、组合物或衍生物，用于向年龄在66岁或以上的人施用。

[0797] 方案63-方案60的化合物、方法、用途、组合物或衍生物，用于向低于18岁、例如4-17岁年龄的人类个体施用。

[0798] 方案64-方案1-48、52、53或59-63任一项的化合物、方法、用途、组合物或衍生物，其中式(I)的化合物或其药学上可接受的盐、溶剂化物和/或衍生物通过贴剂或植入物递送。

[0799] 参考文献

[0800] 本说明书中引用的所有出版物，包括但不限于专利和专利申请，通过引用并入本文，如同每个单独的出版物被具体和单独地指出通过引用并入本文，如同完全列出一样。

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Abstract

A compound of formula (I) and related aspects.