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(54) **2, 3, 6 - TRIAMINO SUBSTITUTED PYRIDINES AS KV7 (KCNQ) CHANNEL MODULATORS**

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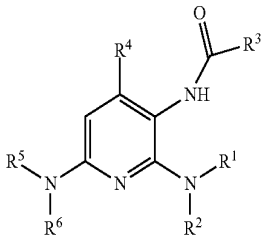
(57) **ABSTRACT**

The present application relates to novel substituted aminopyridine derivatives, to their use in therapy, to pharmaceutical compositions comprising the derivatives, to the use of said derivatives in the manufacture of a medicament, and to therapeutic methods comprising the administration of the derivatives. The present derivatives are useful for treating a disorder responsive to activation of K_v7 channels. Due to the distribution of K_v7 channels within the organism, K_v7 channel modulators are considered potentially useful for the treatment or alleviation of conditions as diverse as CNS disorders, psychiatric disorders, CNS damage caused by trauma, stroke or neurodegenerative illness or diseases, a variety of neuronal hyperexcitability disorders and conditions, epilepsy, pain, neuropathic pain, migraine, tension type headache, learning and cognitive disorders, motion and motor disorders, multiple sclerosis, cardiac disorders, heart failure, cardio-myopathia, inflammatory diseases, ophthalmic conditions, deafness, progressive hearing loss, tinnitus, obstructive or inflammatory airway diseases, for inducing or maintaining bladder control including the treatment or prevention of urinary incontinence.



2, 3, 6 - TRIAMINO SUBSTITUTED PYRIDINES AS KV7 (KCNQ) CHANNEL MODULATORS

TECHNICAL FIELD

[0001] The present invention relates to novel substituted aminopyridine derivatives, to their use in therapy, to pharmaceutical compositions comprising the derivatives, to the use of said derivatives in the manufacture of a medicament, and to therapeutic methods comprising the administration of the derivatives. The present derivatives are useful for treating a disorder, disease or a condition of a subject, which disorder, disease or condition is responsive to activation of K_v7 channels.

BACKGROUND ART

[0002] Potassium (K^+) channels are structurally and functionally diverse families of K^+-selective channel proteins, which are ubiquitous in cells, indicating their central importance in regulating a number of key cell functions. While widely distributed as a class, K^+ channels are differentially distributed as individual members of this class or as families.

[0003] Recently a new family of potassium channels, the KCNQ channels, now also designated K_v7, of which $K_v7.1$-$K_v7.5$ have currently been characterised, has attracted attention as target for therapeutic development.

[0004] Due to the distribution of K_v7 channels within the organism, K_v7 channel modulators are considered potentially useful for the treatment or alleviation of conditions as diverse as CNS disorders, psychiatric disorders, CNS damage caused by trauma, stroke or neurodegenerative illness or diseases, a variety of neuronal hyperexcitability disorders and conditions, epilepsy, pain, neuropathic pain, migraine, tension type headache, learning and cognitive disorders, motion and motor disorders, multiple sclerosis, cardiac disorders, heart failure, cardio-myopathia, inflammatory diseases, ophthalmic conditions, deafness, progressive hearing loss, tinnitus, obstructive or inflammatory airway diseases, for inducing or maintaining bladder control including the treatment or prevention of urinary incontinence.

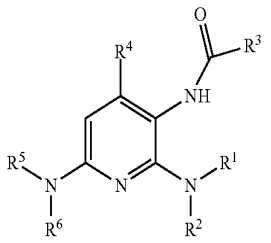
[0005] WO2006/092143 (Lundbeck A/S) discloses substituted pyridine derivatives useful as openers of the KCNQ family potassium ion channels. This document does no disclose or suggest any cyclic amine substituents in the 2-position. Neither does it disclose or suggest any heteroaryl moieties represented by R3.

SUMMARY OF THE INVENTION

[0006] The present invention discloses novel substituted aminopyridine compounds having medical utility for combating disorders, diseases or conditions responsive to activation of K_v7 channels.

[0007] In one embodiment the present invention provides compounds of Formula (I)

(I)



a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof, wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined below.

[0008] In another embodiment the invention provides pharmaceutical compositions comprising a therapeutically effective amount of a compound of the invention, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof or a pharmaceutically-acceptable addition salt thereof.

[0009] In another embodiment the invention relates to the use of a compound of the invention, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof, for the manufacture of a pharmaceutical composition.

[0010] In another embodiment the invention relates to the use of a compound of the invention, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to activation of K_v 7 channels.

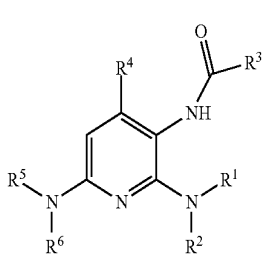
[0011] In another embodiment the invention provides a method of treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to activation of K_v 7 channels, which method comprises the step of administering to such a living animal body in need thereof, a therapeutically effective amount of a compound of the invention, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof.

[0012] Another embodiment of the invention is the provision of compounds with optimal pharmacodynamic and/or pharmacokinetic properties such as kinetic behaviour, bioavailability, solubility, efficacy and/or adverse effects.

[0013] Other embodiments of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

[0014] In one embodiment the present invention provides compounds of Formula (I)



(I)

a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof, wherein

R^1 and R^2, together with the nitrogen to which they are attached, form a heterocyclic ring selected from pyrrolidinyl, 2,5-dihydro-1H-pyrrol-1-yl, azetidinyl, thiazolidinyl, piperidinyl, piperazinyl and morpholinyl, which pyrrolidinyl, azetidinyl, piperidinyl, piperazinyl and morpholinyl is optionally substituted one or more times with a substituent selected from the group consisting of halo and trifluoromethyl;

R^3 represents a heterocyclic ring selected from furanyl and pyrrolyl which furanyl and pyrrolyl is optionally substituted one or more times with substituents selected from C_{1-6}-alkyl, C_{1-6}-alkoxy, halo and trifluoromethyl;

R^4 represents C_{1-6}-alkyl; and

R^5 and R^6, together with the nitrogen to which they are attached, form a heterocyclic ring selected from morpholinyl and 1,4-oxazepanyl.

[0015] In another embodiment of the invention, in formula (I), R^1 and R^2, together with the nitrogen to which they are attached, represent pyrrolidinyl, which is optionally substituted one or more times with a substituent selected from the group consisting of halo and trifluoromethyl. In another embodiment R^1 and R^2, together with the nitrogen to which they are attached, represent pyrrolidinyl. In another embodiment R^1 and R^2, together with the nitrogen to which they are attached, represent pyrrolidinyl, which is substituted one or two times with a substituent selected from the group consisting of halo and trifluoromethyl. In another embodiment R^1 and R^2, together with the nitrogen to which they are attached, represent pyrrolidinyl, substituted one time with a substituent selected from the group consisting of halo and trifluoromethyl. In another embodiment R^1 and R^2, together with the nitrogen to which they are attached, represent pyrrolidinyl substituted one time with halo. In another embodiment R^1 and R^2, together with the nitrogen to which they are attached, represent pyrrolidinyl substituted one time with trifluoromethyl. In another embodiment R^1 and R^2, together with the nitrogen to which they are attached, represent pyrrolidinyl substituted two times with a substituent selected from the group consisting of halo and trifluoromethyl. In another embodiment R^1 and R^2, together with the nitrogen to which they are attached, represent pyrrolidinyl substituted two times with halo.

[0016] In another embodiment of the invention, in formula (I), R^1 and R^2, together with the nitrogen to which they are attached, represent 2,5-dihydro-1H-pyrrol-1-yl.

[0017] In another embodiment of the invention, in formula (I), R^1 and R^2, together with the nitrogen to which they are attached, represent azetidinyl which is optionally substituted one or more times with a substituent selected from the group consisting of halo and trifluoromethyl.

[0018] In another embodiment of the invention, in formula (I), R^1 and R^2, together with the nitrogen to which they are attached, represent thiazolidinyl.

[0019] In another embodiment of the invention, in formula (I), R^1 and R^2, together with the nitrogen to which they are attached, represent piperidinyl, which is optionally substituted one or more times with a substituent selected from the group consisting of halo and trifluoromethyl.

[0020] In another embodiment of the invention, in formula (I), R^1 and R^2, together with the nitrogen to which they are attached, represent piperazinyl which is optionally substituted one or more times with a substituent selected from the group consisting of halo and trifluoromethyl.

[0021] In another embodiment of the invention, in formula (I), R^1 and R^2, together with the nitrogen to which they are attached, represent morpholinyl, which is optionally substituted one or more times with a substituent selected from the group consisting of halo and trifluoromethyl. In another embodiment R^1 and R^2, together with the nitrogen to which they are attached, represent morpholinyl. In another embodiment R^1 and R^2, together with the nitrogen to which they are attached, represent morpholinyl substituted one or two times with a substituent selected from the group consisting of halo and trifluoromethyl.

[0022] In another embodiment of the invention, in formula (I), R^3 represents furanyl which is optionally substituted one or more times with substituents selected from C_{1-6}-alkyl, C_{1-6}-alkoxy, halo and trifluoromethyl. In another embodiment R^3 represents furanyl. In another embodiment R^3 represents furanyl, which is substituted one time with a substituent selected from C_{1-6}-alkyl, C_{1-6}-alkoxy, halo and trifluoromethyl. In another embodiment R^3 represents furanyl which is substituted one time with C_{1-6}-alkyl, such as methyl. In another embodiment R^3 represents furanyl which is substituted one time with halo. In another embodiment R^3 represents furanyl which is substituted one time with C_{1-6}-alkoxy. In another embodiment R^3 represents furanyl which is substituted one time with trifluoromethyl.

[0023] In another embodiment of the invention, in formula (I), R^3 represents furanyl, which is substituted two times with substituents selected from C_{1-6}-alkyl, C_{1-6}-alkoxy, halo and trifluoromethyl. In another embodiment R^3 represents furanyl which is substituted two times with C_{1-6}-alkyl. In another embodiment R^3 represents furanyl which is substituted two times with C_{1-6}-alkoxy. In another embodiment R^3 represents furanyl which is substituted two times with halo. In another embodiment R^3 represents furanyl which is substituted two times with fluoro. In another embodiment R^3 represents furanyl which is substituted two times with trifluoromethyl.

[0024] In another embodiment of the invention, in formula (I), R^3 represents pyrrolyl which is optionally substituted one or more times with substituents selected from C_{1-6}-alkyl, C_{1-6}-alkoxy, halo and trifluoromethyl. In another embodiment R^3 represents pyrrolyl which is optionally substituted one or more times with substituents selected from C_{1-6}-alkyl and halo.

[0025] In another embodiment of the invention, in formula (I), R^4 represents C_{1-6}-alkyl. In another embodiment R^4 rep-

resents methyl. In another embodiment R^4 represents ethyl. In another embodiment R^4 represents iso-propyl.

[0026] In another embodiment of the invention, in formula (I), R^5 and R^6, together with the nitrogen to which they are attached, form a heterocyclic ring which is morpholinyl. In another embodiment R^5 and R^6, together with the nitrogen to which they are attached, form a heterocyclic ring which is 1,4-oxazepanyl.

[0027] In another embodiment of the invention, in formula (I), R^1 and R^2, together with the nitrogen to which they are attached, represent pyrrolidinyl, which is optionally substituted one or more times with halo; R^3 represents furanyl which is optionally substituted one or more times with C_{1-6}-alkyl; R^4 represents C_{1-6}-alkyl; and R^5 and R^6, together with the nitrogen to which they are attached, form a heterocyclic ring which is morpholinyl.

[0028] In another embodiment of the invention, in formula (I), R^1 and R^2, together with the nitrogen to which they are attached, represent pyrrolidinyl, which is optionally substituted one or more times with halo; R^3 represents furanyl which is optionally substituted one or more times with C_{1-6}-alkyl; R^4 represents C_{1-6}-alkyl; and R^5 and R^6, together with the nitrogen to which they are attached, form a heterocyclic ring which is 1,4-oxazepanyl.

[0029] In another embodiment of the invention the compound of the invention is 3-Methyl-furan-2-carboxylic acid [2-((R)-3-fluoro-pyrrolidin-1-yl)-4-methyl-6-[1,4]oxazepan-4-yl-pyridin-3-yl]-amide; or a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof.

[0030] In another embodiment of the invention the compound of the invention is 3-Methyl-furan-2-carboxylic acid [2-((R)-3-fluoro-pyrrolidin-1-yl)-4-methyl-6-[1,4]oxazepan-4-yl-pyridin-3-yl]-amide; or a pharmaceutically-acceptable salt thereof, or an N-oxide thereof.

[0031] In another embodiment of the invention the compound of the invention is 3-Methyl-furan-2-carboxylic acid [2-((R)-3-fluoro-pyrrolidin-1-yl)-4-methyl-6-[1,4]oxazepan-4-yl-pyridin-3-yl]-amide.

[0032] In another embodiment of the invention the compound of the invention is 3-Methyl-furan-2-carboxylic acid [2-((R)-3-fluoro-pyrrolidin-1-yl)-4-methyl-6-morpholin-4-yl-pyridin-3-yl]-amide or a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof.

[0033] In another embodiment of the invention the compound of the invention is 3-Methyl-furan-2-carboxylic acid [2-((R)-3-fluoro-pyrrolidin-1-yl)-4-methyl-6-morpholin-4-yl-pyridin-3-yl]-amide or a pharmaceutically-acceptable salt thereof, or an N-oxide thereof.

[0034] In another embodiment of the invention the compound of the invention is 3-Methyl-furan-2-carboxylic acid [2-((R)-3-fluoro-pyrrolidin-1-yl)-4-methyl-6-morpholin-4-yl-pyridin-3-yl]-amide.

DEFINITION OF TERMS

[0035] As used throughout the present specification and appended claims, the following terms have the indicated meaning:

[0036] The term "C_{1-6}-alkyl" as used herein means a saturated, branched or straight hydrocarbon group having from 1-6 carbon atoms, e.g. C_{1-3}-alkyl, C_{1-4}-alkyl, C_{1-6}-alkyl, C_{2-6}-alkyl, C_{3-6}-alkyl, and the like. Representative examples are methyl, ethyl, propyl (e.g. prop-1-yl, prop-2-yl (or iso-propyl)), butyl (e.g. 2-methylprop-2-yl (or tert-butyl), but-1-yl, but-2-yl), pentyl (e.g. pent-1-yl, pent-2-yl, pent-3-yl), 2-methylbut-1-yl, 3-methylbut-1-yl, hexyl (e.g. hex-1-yl), and the like.

[0037] The term "halo" or "halogen" means fluorine, chlorine, bromine or iodine.

[0038] The term "hydroxy" shall mean the radical —OH.

[0039] The term "amino" shall mean the radical —NH_2.

[0040] The term "trihalomethyl" means trifluoromethyl, trichloromethyl, and similar trihalo-substituted methyl groups.

[0041] The term "C_{1-6}-alkoxy" as used herein refers to the radical —O—C_{1-6}-alkyl. Representative examples are methoxy, ethoxy, propoxy (e.g. 1-propoxy, 2-propoxy), butoxy (e.g. 1-butoxy, 2-butoxy, 2-methyl-2-propoxy), pentoxy (1-pentoxy, 2-pentoxy), hexoxy (1-hexoxy, 3-hexoxy), and the like.

[0042] The term "hydroxy-C_{1-6}-alkyl" as used herein refers to alkyl substituted one or more times at any carbon atom(s) with hydroxyl. Representative examples are hydroxymethyl, hydroxyethyl (e.g. 1-hydroxyethyl, 2-hydroxyethyl) and the like.

[0043] The term "C_{1-6}-alkoxy-C_{1-6}-alkyl" as used herein refers to an C_{1-6}-alkyl-O—C_{1-6}-alkyl group, wherein the C_{1-6}-alkyl and C_{1-6}-alkyl-O— are as defined above. Representative examples are methoxy-methyl, methoxy-ethyl, ethoxy-methyl, and ethoxy-ethyl.

[0044] The term "optionally substituted" as used herein means that the groups in question are either unsubstituted or substituted with one or more of the substituents specified. When the group(s) in question is/are substituted with more than one substituent the substituents may be the same or different.

[0045] Certain of the defined terms may occur more than once in the structural formulae, and upon such occurrence each term shall be defined independently of the other.

[0046] The term "treatment" as used herein means the management and care of a patient for the purpose of combating a disease, disorder or condition. The term is intended to include the delaying of the progression of the disease, disorder or condition, the alleviation or relief of symptoms and complications, and/or the cure or elimination of the disease, disorder or condition. The patient to be treated is preferably a mammal, in particular a human being.

[0047] The terms "disease", "condition" and "disorder" as used herein are used interchangeably to specify a state of a patient which is not the normal physiological state of man.

[0048] The term "medicament" as used herein means a pharmaceutical composition suitable for administration of the pharmaceutically active compound to a patient.

[0049] The term "pharmaceutically acceptable" as used herein means suited for normal pharmaceutical applications, i.e. giving rise to no adverse events in patients etc.

[0050] The term "effective amount" as used herein means a dosage which is sufficient in order for the treatment of the patient to be effective compared with no treatment.

[0051] The term "therapeutically effective amount" of a compound as used herein means an amount sufficient to cure, alleviate or partially arrest the clinical manifestations of a given disease and its complications. An amount adequate to accomplish this is defined as "therapeutically effective amount". Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. It will be understood that deter-

mining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician or veterinary.

Pharmaceutically Acceptable Salts

[0052] The compounds of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the compounds of the invention.

[0053] Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived from sulphuric acid, the formate derived from formic acid, the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulphonate derived from benzensulphonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycollate derived from glycolic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulphonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphtalene-2-sulphonic acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

[0054] Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

[0055] Examples of pharmaceutically acceptable cationic salts of a chemical compound of the invention include, without limitation, the sodium, the potassium, the calcium, the magnesium, the zinc, the aluminium, the lithium, the choline, the lysine, and the ammonium salt, and the like, of a chemical compound of the invention containing an anionic group. Such cationic salts may be formed by procedures well known and described in the art.

[0056] Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate, the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate derived, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art.

[0057] Examples of pharmaceutically acceptable cationic salts of a chemical compound of the invention include, without limitation, the sodium, the potassium, the calcium, the magnesium, the zinc, the aluminium, the lithium, the choline, the lysine, and the ammonium salt, and the like, of a chemical compound of the invention containing an anionic group. Such cationic salts may be formed by procedures well known and described in the art.

Steric Isomers

[0058] The compounds of the present invention may exist in (+) and (−) forms as well as in racemic forms (±). The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

[0059] Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

[0060] Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by Jaques J, Collet A, & Wilen S in "*Enantiomers, Racemates, and Resolutions*", John Wiley and Sons, New York (1981)

[0061] Optical active compounds can also be prepared from optical active starting materials.

Methods of Preparation

[0062] The compounds of the present invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

[0063] Also one compound of the invention can be converted to another compound of the invention using conventional methods.

[0064] The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Biological Activity

[0065] The compounds of the invention have been found useful as modulators of the K_v 7 (KCNQ) potassium channels. At present five such channels are known, i.e. the $K_v7.1$ (KCNQ1) channel, the $K_v7.2$ (KCNQ2) channel, the $K_v7.3$ (KCNQ3) channel, the $K_v7.4$ (KCNQ4) channel, and the $K_v7.5$ (KCNQ5) channel, and heteromeric combinations hereof. Moreover, the modulatory activity may be inhibitory (i.e. inhibitory activity) or stimulatory (i.e. activating activity).

[0066] The modulatory activity may be determined using conventional methods, e.g. binding or activity studies, known in the art, e.g. as described in WO 2004/080377 (NeuroSearch A/S) or as described in the working examples.

[0067] In one aspect of the invention, the compounds of the invention show stimulating activity at $K_v7.2$, $K_v7.3$, $K_v7.4$ and/or $K_v7.5$ potassium channels, and heteromeric combinations hereof. Compounds of the invention are selective, e.g. showing $K_v7.2$, $K_v7.2$+$K_v7.3$, and/or $K_v7.4$ potassium channel activation.

[0068] Accordingly, the compounds of the invention are considered useful for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of a K_v7 potassium channel.

[0069] Due to the distribution of KCNQ channels within the organism, KCNQ channel modulators are considered useful for the treatment or alleviation of conditions as diverse as an affective disorder, a neuro-physiological disorder, an anxiety disorder, depression, a bipolar disorder, a sleep disorder, addiction, an eating disorder, a phobia, a neurodegenerative disorder, Parkinson's disease, a mood disorder, a psychotic disorder, a compulsive behaviour, mania, psychosis, schizophrenia, dementia, Alzheimer's disease, epilepsy, Lennox-Gastaut, convulsions, seizures, seizure disorders, absence seizures, general seizures, partial seizures, vascular spasms, hypertension, coronary artery spasms, tremor, muscle spasms, myasthenia gravis, a motor neuron disease, motion and motor disorders, a tic disorder, a Parkinson-like motor disorder, essential tremors, multiple sclerosis, amyelotrophic lateral sclerosis (ALS), multiple system atrophy, corticobasal degeneration, HIV associated dementia, Huntington's disease, Pick's disease, torsades de pointes, functional bowel disorders, CNS damage caused by trauma, stroke or neurodegenerative illness or diseases, ataxia, myokymia, spasticity, myopathy, learning and cognitive disorders, memory dysfunction, memory impairment, age-associated memory loss, Down's syndrome, pain, acute or chronic pain, mild pain, moderate or severe pain, neuropathic pain, central pain, pain related to diabetic neuropathy, to postherpetic neuralgia, to peripheral nerve injury, somatic pain, visceral pain or cutaneous pain, pain caused by inflammation or by infection, postoperative pain, phantom limb pain, neuronal hyperexcitability disorders, peripheral nerve hyperexcitability, chronic headache, migraine, migraine-related disorders, tension-type headache, heart failure, cardiac disorders, cardio-myopathia, cardiac arrhythmia, cardiac ischaemia, long QT syndrome, inflammatory diseases or conditions, inflammatory bowel disease, Crohn's disease, ulcerative colitis, Creutzfeld-Jacobs disease, an obstructive or inflammatory airway disease, asthma, an airway hyper reactivity, pneumoconiosis, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis, byssinosis, chronic obstructive pulmonary disease (COPD), excerbation of airways hyper reactivity, cystic fibrosis, hearing impairment or hearing loss, progressive hearing loss, tinnitus, a drug-dependence or drug-addiction disorder, hyperactive gastric motility, ophthalmic conditions, erectile dysfunction, fibromylgia, for inducing or maintaining bladder control, nocturia, bladder spasms, overactive bladder (OAB), bladder outflow obstruction, interstitial cystitis (IC) (also called painfull bladder syndrome) and urinary incontinence.

[0070] In another embodiment the disease, disorder or condition contemplated according to the invention is an anxiety disorder such as panic disorder, agoraphobia, phobias, social anxiety disorder, obsessive-compulsive disorder and post-traumatic stress disorder. In another embodiment the disease, disorder or condition contemplated according to the invention is anxiety.

[0071] In one embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of a disease, disorder or adverse condition of the CNS. In another embodiment, the disease, disorder or condition is an affective disorder, a neuro-physiological disorder, an anxiety disorder, depression, a bipolar disorder, a sleep disorder, addiction, an eating disorder, a phobia, a neurodegenerative disorder, a mood disorder, a psychotic disorder, mania, psychosis or schizophrenia. In another embodiment the compounds of the invention are useful for the treatment or alleviation of schizophrenia. In another embodiment the compounds of the invention are useful for the treatment or alleviation of depression. In another embodiment the compounds of the invention are useful for the treatment or alleviation of bipolar disorder. In another embodiment the compounds of the invention are useful for the treatment or alleviation of mania. In another embodiment the compounds of the invention are useful for the treatment or alleviation of psychosis.

[0072] In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of a CNS damage caused by trauma or by a spinal cord damage, stroke, traumatic brain injury, a neurodegenerative illness or disease, dementia, Alzheimer's disease, a motor neuron disease, Parkinson's disease, a Parkinson-like motor disorder, multiple sclerosis, amyelotrophic lateral sclerosis (ALS), multiple system atrophy, HIV associated dementia, Huntington's disease, Pick's disease, torsades de pointes, tremor, muscle spasms, myasthenia gravis.

[0073] In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of, a compulsive behaviour, epilepsy, Lennox-Gastaut, convulsions, seizures, seizure disorders, absence seizures, general seizures, partial seizures, vascular spasms or hypertension. In another embodiment the compounds of the invention are useful for the treatment or alleviation of a compulsive behaviour. In another embodiment the compounds of the invention are useful for the treatment or alleviation of epilepsy. In another embodiment the compounds of the invention are useful for the treatment or alleviation of seizures.

[0074] In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of pain, including acute and chronic pain, mild pain, moderate or even severe pain of acute, chronic or recurrent character, as well as postoperative pain, phantom limb pain, chronic headache, post therapeutic neuralgia, neuropathic pain, central pain, or pain related to diabetic neuropathy, to postherpetic neuralgia, to peripheral nerve injury or drug addiction, migraine and migraine-related disorders and to tension-type headache. In another embodiment the pain is somatic pain, incl. visceral pain or cutaneous pain, or pain caused by inflammation or by infection. In another embodiment the pain is neuropathic, e.g. caused by injury to the central or peripheral nervous system, e.g. due to tissue trauma, infection, diabetes, an autoimmune disease, arthritis or neuralgia.

[0075] In another embodiment the compounds of the invention are useful for the treatment or alleviation of pain. In another embodiment the compounds of the invention are useful for the treatment or alleviation of neuropathic pain.

[0076] In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of addiction, e.g. drug addiction, drug abuse, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction or alcoholism, or withdrawal symptoms caused by the termination of abuse of chemical substances, in particular opioids, heroin, cocaine and morphine, benzodiazepines and benzodiazepine-like drugs, and alcohol.

[0077] In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of a learning and cognitive disorder, memory dysfunction, memory impairment, age-associated memory loss or Down's syndrome. In another embodiment the compounds of the invention are useful for the treatment or alleviation of cognition.

[0078] In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of chronic headache, migraine, migraine-related disorders or tension-type headache. In another embodiment the compounds of the invention are considered useful for treatment or alleviation of migraine. In another embodiment the compounds of the invention are useful for the treatment or alleviation of chronic headache. In another embodiment the compounds of the invention are useful for the treatment or alleviation of tension-type headache.

[0079] In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of a disease, disorder or condition associated with the heart or skeletal muscle, heart failure, cardiomyopathia, cardiac arrhythmic, cardiac ischaemia or long QT syndrome.

[0080] In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of an inflammatory disease or condition, inflammatory bowel disease, Crohn's disease, ulcerative colitis or Creutzfeld-Jacobs disease.

[0081] In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of asthma, an obstructive or inflammatory airway disease, an airway hyper reactivity, a pneumoconiosis such as aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis, a chronic obstructive pulmonary disease (COPD), excerbation of airways hyper reactivity or cystic fibrosis. In another embodiment the compounds of the invention are considered useful for treatment or alleviation of asthma.

[0082] In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of progressive hearing loss or tinnitus.

[0083] In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of an ophthalmic disorder, a drug-dependence or drug-addiction disorder or hyperactive gastric motility.

[0084] In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of nocturia, bladder spasms, overactive bladder (OAB), interstitial cystitis (IC) and urinary incontinence. In another embodiment the compounds of the invention are considered useful for treatment or alleviation of urinary incontinence.

Pharmaceutical Compositions

[0085] Viewed from one aspect the invention relates to the use of a compound of the invention, or a pharmaceutically-acceptable addition salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of K_v7 channels.

[0086] Viewed from another aspect, the invention provides pharmaceutical compositions comprising a therapeutically-effective amount of a compound of the invention, or a pharmaceutically-acceptable addition salt thereof, together with at least one pharmaceutically-acceptable carrier or diluent, for the treatment, prevention or alleviation of a disease or a disorder or a condition that is responsive to modulation of K_v7 channels.

[0087] While a compound for use according to the invention may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

[0088] In another embodiment, the invention provides pharmaceutical compositions comprising a compound of the invention, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

[0089] The pharmaceutical composition of the invention may be administered by any convenient route which suite the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition may be prepared by the skilled person using standard and conventional techniques appropriate for the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

[0090] Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, pulmonal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, intraperitoneal, intravenous, intraarterial, intracerebral, intraocular injection or infusion) administration, or those in a form suitable for administration by inhalation or insufflation, including powders and liquid aerosol administration, or by sustained release systems. Suitable examples of sustained release systems include semipermeable matrices of solid hydrophobic polymers containing the compound of the invention, which matrices may be in form of shaped articles, e.g. films or microcapsules.

[0091] The chemical compound of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof. Such forms include solids, and in particular tablets, filled capsules, powder and pellet forms, and liquids, in particular aqueous or non-aqueous solutions, suspensions, emulsions, elixirs, and capsules filled with the same, all for oral use, suppositories for rectal administration, and sterile injectable solutions for parenteral use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such

unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

[0092] The chemical compound of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a chemical compound of the invention or a pharmaceutically acceptable salt of a chemical compound of the invention.

[0093] For preparing pharmaceutical compositions from a chemical compound of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

[0094] In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component.

[0095] In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

[0096] The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

[0097] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.

[0098] Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[0099] Liquid preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

[0100] The chemical compound according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

[0101] Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents, as desired.

[0102] Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

[0103] Also included are solid form preparations, intended for conversion shortly before use to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. In addition to the active component such preparations may comprise colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0104] For topical administration to the epidermis the chemical compound of the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

[0105] Compositions suitable for topical administration in the mouth include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[0106] Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions may be provided in single or multi-dose form.

[0107] Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

[0108] Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch compounds such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

[0109] In compositions intended for administration to the respiratory tract, including intranasal compositions, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

[0110] When desired, compositions adapted to give sustained release of the active ingredient may be employed.

[0111] The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0112] Tablets or capsules for oral administration and liquids for intravenous administration and continuous infusion are preferred compositions.

[0113] Further details on techniques for formulation and administration may be found in the latest edition of *Remington's Pharmaceutical Sciences* (Maack Publishing Co., Easton, Pa.).

[0114] The actual dosage depends on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, e.g. from about 1 to about 100 mg, or from about 1 to about 10 mg, are suitable for therapeutic treatments.

[0115] The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 μg/kg i.v. and 1 μg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 μg/kg to about 10 mg/kg/day i.v., and from about 1 μg/kg to about 100 mg/kg/day p.o.

Methods of Therapy

[0116] In another aspect the invention provides a method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease, disorder or condition is responsive to activation of K_v7 channels, and which method comprises administering to such a living animal body, including a human, in need thereof an effective amount of a compound of the invention.

[0117] The preferred medical indications contemplated according to the invention are those stated above.

[0118] It is at present contemplated that suitable dosage ranges are 0.1 to 2000 milligrams daily, 10-1000 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

[0119] A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.005 mg/kg i.v. and 0.01 mg/kg p.o. The upper limit of the dosage range is about 30 mg/kg i.v. and 500 mg/kg p.o. Preferred ranges are from about 0.001 to about 100 mg/kg i.v. and from about 0.1 to about 30 mg/kg p.o.

Examples

[0120] The following examples and general procedures refer to intermediate compounds and final products for general Formula (I) identified in the specification and in the synthesis schemes. The preparation of the compounds of general Formula (I) of the present invention is described in detail using the following examples. Occasionally, the reaction may not be applicable as described to each compound included within the disclosed scope of the invention. The compounds for which this occurs will be readily recognised by those skilled in the art. In these cases the reactions can be successfully performed by conventional modifications known to those skilled in the art, which is, by appropriate protection of interfering groups, by changing to other conventional reagents, or by routine modification of reaction conditions. Alternatively, other reactions disclosed herein or otherwise conventional will be applicable to the preparation of the corresponding compounds of the invention. In all preparative methods, all starting materials are known or may easily be prepared from known starting materials.

DMSO: Dimethylsulfoxide

DIPEA: Diisopropylethylamine

[0121] EtOAc: Ethyl acetate

THF: Tetrahydrofuran

TEA: Triethylamine

[0122] min: minutes

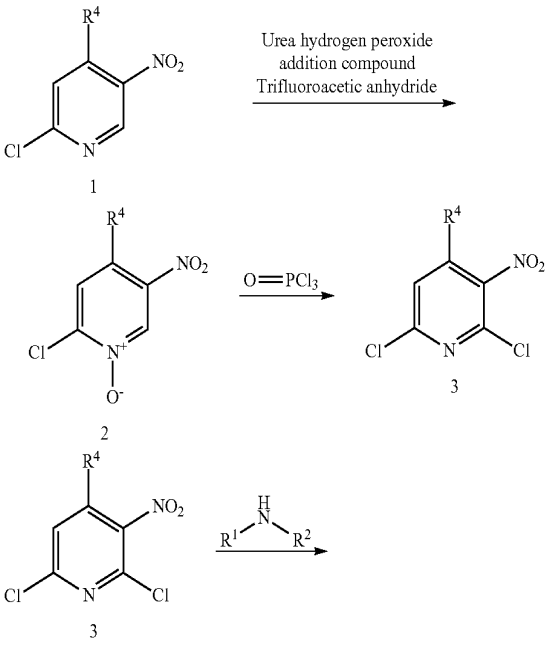
hrs: hours

rt: room temperature (ca. 19-22° C.)

Preparative Example

[0123]

Scheme 1:



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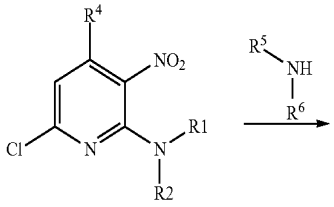

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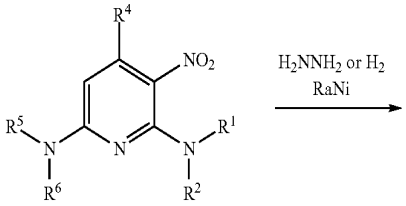

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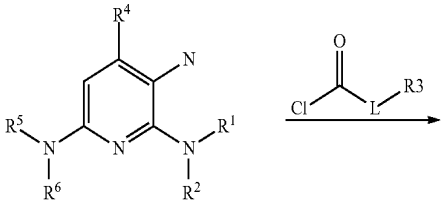
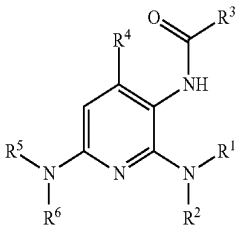
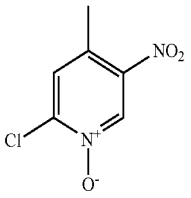




6

2-Chloro-4-methyl-5-nitro-pyridine 1-oxide (Intermediate compound)

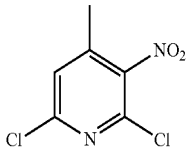
[0124]



[0125] To a solution of 2-chloro-4-methyl-5-nitropyridine (10 g; 58 mmol) and urea hydrogen peroxide (ca. 12 g; 2.1 eq) in 100 mL DCM at 0° C. was added trifluoroacetic anhydride (1.6 mL; 2 eq) in a dropwise manner at a pace that allowed the reaction mixture to slowly reach room temperature. The reaction mixture was stirred for 3 h after which the bright yellow reaction mixture was added one aliquot water and stirred for another 20 min. The DCM layer was separated and the remaining aqueous layer extracted with DCM (3×150 mL). The combined organic fractions were washed with sat. $NaHCO_3$(aq), dried over Na_2SO_4, filtered and concentrated in vacuo yielding 9.7 g of crude material as a yellow solid. (purity ~87% (GC-MS)) The solid was taken as such for the next step

2,6-Dichloro-4-methyl-3-nitro-pyridine (Intermediate compound)

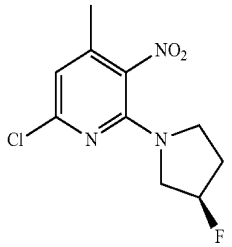
[0126]



[0127] Crude 2-chloro-4-methyl-5-nitro-pyridine 1-oxide (see previous reaction; 9.7 g; 51.4 mmol) was dissolved in 50 mL $POCl_3$ and stirred at 80° C. overnight. The reaction mixture was poured out on 500 g ice (very exothermic!) and was stirred for 1 h in order to quench all $POCl_3$. The mixture was extracted with EtOAc (3×150 mL). The combined organic layers were washed with sat. $NaHCO_3$(aq), brine, dried over Na_2SO_4, filtered and evaporated to dryness to yield 8.73 g of crude material as a brownish liquid. (purity ~80% (GC-MS))

6-Chloro-2-((R)-3-fluoro-pyrrolidin-1-yl)-4-methyl-3-nitro-pyridine (Intermediate compound)

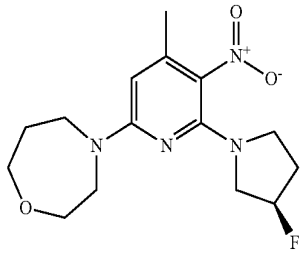
[0128]



[0129] To a solution of 2,6-dichloro-4-methyl-3-nitropyridine (6.5 g; 31.4 mmol) and TEA (10 g; 3 eq) in acetonitrile (200 ml) was added (R)-(−)-3-fluoropyrrolidine hydrochloride (4.75 g; 1.2 eq). The mixture was stirred for 4 h at rt, after which the reaction mixture was quenched with sat $NaHCO_3$ (aq) (300 ml), diluted with water and EtOAc. The layers were separated and the waterlayer was extracted with EtOAc (3×150 mL) until no UV (254 nm) active material was extracted). The combined organic layers were washed with brine and dried over Na_2SO_4(s). Filtration and in vacuo concentration resulted in a quantitative yield 8.36 g of the title compound as a yellow/orange oil.

4-[6-((R)-3-Fluoro-pyrrolidin-1-yl)-4-methyl-5-nitro-pyridin-2-yl]-[1,4]oxazepane (Intermediate compound)

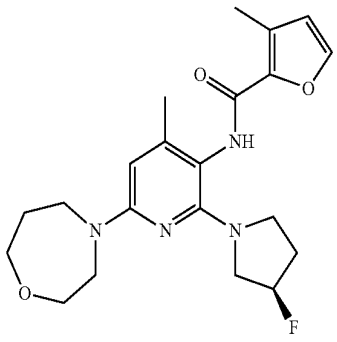
[0130]



[0131] To a solution of 6-chloro-2-((R)-3-fluoro-pyrrolidin-1-yl)-4-methyl-3-nitro-pyridine (2.1 g; 8 mmol), homomorpholine hydrochloride (1.67, 1.5 eq) in DMSO was added TEA (~3.5 ml, 3 eq) and the mixture was heated to 110° C. in the MW for 4 hrs. The complete rxm was poured out in water and extracted with EtOAc (×3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to yield 1.94 g (73%) of the title compound as red oil that solidifies upon standing. The compound was used as such in the next step.

3-Methyl-furan-2-carboxylic acid [2-((R)-3-fluoro-pyrrolidin-1-yl)-4-methyl-6-[1,4]oxazepan-4-yl-pyridin-3-yl]-amide (Compound 1.1)

[0132]



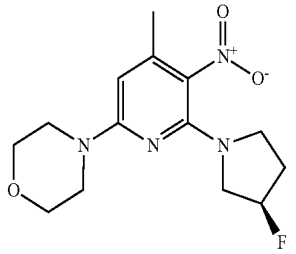
[0133] To a slurry of 4-[6-((R)-3-Fluoro-pyrrolidin-1-yl)-4-methyl-5-nitro-pyridin-2-yl]-[1,4]oxazepane (300 mg; 0.92 mmol) in oxygen-free and dry THF (15 mL) was added RaNi (2 mL) and hydrazine (136 μl; 3 eq) while purging with argon to keep reagents under an inert atmosphere. The mixture was stirred at rt. for 30 min after which additional hydrazine was added and stirring at rt. was continued.

[0134] After an additional 30 min the complete rxm was filtered over a syringe filter into a solution of 3-methylfuran-2-carbonyl chloride (145 mg; 1.05 eq) in dry and oxygen-free THF and this mixture was stirred at rt over the weekend. The rxm was concentrated in vacuo and purified first by reverse phase column chromatography (10-95% MeOH in H_2O, loaded with MeOH) and then by straight phase column chromatography (10-50% Ethyl acetate in heptane, loaded with DCM) to yield 159 mg (43%) of the title compound as a white solid. Mp 93-96° C.

[0135] LC-ESI-HRMS of [M+H]: 403.21324 Da. (Calc.) 403.213999 Da, (found).

4-[6((R)-3-Fluoro-pyrrolidin-1-yl)-4-methyl-5-nitro-pyridin-2-yl]-morpholine (Intermediate compound)

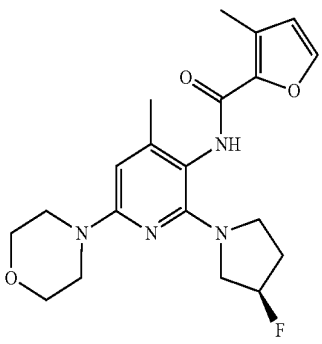
[0136]



[0137] A solution of 6-chloro-2-((R)-3-fluoro-pyrrolidin-1-yl)-4-methyl-3-nitro-pyridine (6.5 g; 25 mmol), morpholine (3.27 g; 1.5 eq) and TEA (7.67 ml; 3 eq) in DMSO (40 ml) was heated in the microwave at 110° C. for 3 hrs. The mixture was quenched with sat $NaHCO_3$(aq) (700 mL), diluted with water (300 mL) and EtOAc (250 mL). The layers were separated and the water layer was extracted with EtOAc (2×250 mL; until no UV (254 nm) active material was extracted). The combined organic layers were washed with brine and dried over Na_2SO_4(s). Filtration and in vacuo concentration, resulted in 7.65 g orange solid. The crude compound was purified by flash chromatography (silica 60A; particle size 20-40 micron; 270 g; loaded with the use of (SOLUTE SORBENT HN-M; ca 1:10) using 4-40% EtOAc in heptane as eluent) to yield pure title compound (6.7 g; 86%) as an orange crystalline solid.

3-Methyl-furan-2-carboxylic acid [2-((R)-3-fluoro-pyrrolidin-1-yl)-4-methyl-6-morpholin-4-yl-pyridin-3-yl]-amide (Compound 1.2)

[0138]



[0139] Under an argon atmosphere, Raney-Nickel (ca 10 ml of a 50% slurry in water) was carefully rinsed with dry THF to remove the bulk of water. After precipitation of the Raney Ni in the glass flask, the THF layer was removed with a pipet (this was repeated 4 times). Finally, fresh THF (dry

and oxygenfree; 100 mL) and 4-[6-((R)-3-fluoro-pyrrolidin-1-yl)-4-methyl-5-nitro-pyridin-2-yl]-morpholine (6.68 g; 21.5 mmol) was dissolved and the mixture was flushed with argon for several minutes and then flushed with H_2(g). The reaction mixture was stirred in a H_2 (g) atmosphere until the solution was no longer yellow (ca. 2 h). The reaction mixture was filtered through a 0.4 μm filter disk while keeping it under a argon atmosphere at all times. The mixture was cooled in an ice-bath for ca 15 min after which DIPEA (3.34 g; 1.2 eq) was added followed by a solution of 3-methylfuran-2-carbonyl chloride (3.53 g; 1.1 eq) in pre-Ar(g)-flushed and dry THF (ca 5 ml).

[0140] The reaction mixture was quenched with sat $NaHCO_3$ (aq) [200 ml], diluted with water (200 mL) and EtOAc (200 mL). The layers were separated and the water-layer was extracted with EtOAc (2×150 mL; until no UV (254 nm) active material was extracted). The combined organic layers were washed with brine and dried over Na_2SO_4(s). Filtration and in vacuo concentration resulted in 8.01 g. the crude product was purified by flash chromatography (silica 60A; particle size 20-40 micron; 230 g; and 7-100% EtOAc in heptane as the eluent) to yield pure title compound (5.65 g; 68%) as a white solid. Mp 165-166° C.

[0141] LC-ESI-HRMS of $[M+H]^+$: 389.19768 Da. (Calc.) 389.198349 (found).

Pharmacological Methods

[0142] In a standard patch-clamp set-up, e.g. as outlined in International Patent Publication WO 2004/080377, using HEK293 cell lines stably expressing the human K_v7_2+3 channels, the compounds of the invention were found to be activators of the channels at various concentrations at various degrees.

[0143] The effect obtained by these channel activators is described as a percentage increase in baseline current at a given concentration. The baseline current is defined as 100%, and an increase in current is expressed relative to this, i.e. an increase from 1 nA to 1.2 nA is reported as 120%.

TABLE 1

Test Compound	I_K(%) conc. 0.03 μM, −30 mV, 20 ms	I_K(%) conc. 0.3 μM, −30 mV, 20 ms
1.1		293 (n = 2)
1.2	136	428 (n = 5)

FLIPR-Based Characterization of K_v7.2+3 Modulators

[0144] This experiment determines the ability of a test compound to modulate the activity of K_v7.2+3 channels heterologously expressed in human HEK293 cells. The ability is determined relative to retigabine. The activity is determined using a standard thallium (I) sensitive assay, e.g. using a fluorometric method in a Fluorescent Image Plate Reader (FLIPR) as described below in more detail.

[0145] Full concentration/response curves are generated and EC_{50} values are calculated based on max values. EC_{50} values (Effective Concentration) represent the concentration of the test substance, at which 50% of the channel activity is obtained when compared to retigabine control responses. Maximal response determined relative to the reference (retigabine) response is calculated.

Methods

Cell Culture

[0146] Human HEK293 cells over-expressing human K_v7.2+3 are grown in culture medium (DMEM supplemented with 10% foetal bovine serum), in polystyrene culture flasks (175 mm^2) in a humidified atmosphere of 5% CO_2 in air, at 37° C. Cell confluence should be 80-90% on day of plating. Cells are rinsed with 4 ml of PBS (phosphate buffered saline) and incubated 2 min with 1 ml of Trypsin-EDTA. After addition of 25 ml of culture medium cells are re-suspended by trituration with a 25 ml pipette.

[0147] The cells are seeded at a density of ~3×10^6 cells/ml (25 μl/well) in blackwalled, clear bottom, 384-well plates pre-treated with 0.01 g/l poly-D-lysin (20 μl/well for ≧30 min). Plated cells were allowed to proliferate for 24 h before loading with dye.

Loading with BTC-AM

[0148] BTC-AM (50 mg, Invitrogen) is added 25.5 μl DMSO. The BTC-AM stock solution (2 mM) is diluted to a final concentration of 2 μM in Cl^- free assay buffer (in mM: 140 Na^--gluconate, 2.5 K^+-gluconate, 6 $Ca2^+$-gluconate, 1 Mg^{2+} gluconate, 5 glucose, 10 HEPES, pH 7.3) containing 2 μM ouabain, 2 mM amaranth and 1 mM tartrazine.

[0149] The culture medium is aspirated from the wells, the cells are washed thrice in Cl^- free assay buffer, and 25 μl of the BTC-AM loading solution is added to each well. The cells are incubated at 37° C. for 60 min.

Tl^+ Influx Measurements

[0150] After the loading period, the Tl^+-sensitive BTC fluorescence signal is measured over time using a FLIPR.

FLIPR Settings/Parameters

[0151] Temperature: Room temp.

[0152] First addition: 12 μl test or control compound after 15 sec at a rate of 30 μl/sec and starting height of 20 μl

[0153] Second addition: 12 μl stimulus buffer (Cl^- free assay buffer supplemented with 1 mM Tl_2SO_4, 5 mM K_2SO_4 as well as the quenchers amaranth (2 mM) and tartrazine (1 mM)) is added after an additional 3 minutes at a rate of 30 μl/sec and starting height of 30 μl

[0154] Reading intervals: First sequence—3 sec×5, 2 sec×24 and 5 sec×25

[0155] Second sequence—1 sec×5, 2 sec×24 and 5 sec×36

Addition plates (compound plate and stimulus plate) are placed in positions 2 and 3, respectively. Cell plates are placed in position 1 and run using the "KCNQ (two additions)" program. FLIPR will then take the appropriate measurements in accordance with the interval settings above. Fluorescence obtained after stimulation is corrected for the mean basal fluorescence (in Cl^- free assay buffer).

Analysis

Characterization of Active Substances

[0156] Full concentration/response curves are generated and EC_{50} values ("Effective Concentration"; the concentration at which 50% of the channel activity is obtained when compared to retigabine control responses) are calculated

based on peak values. Maximal response determined relative to the reference (retigabine) response is calculated.

TABLE 2

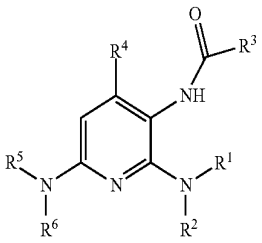
Test Compound	EC_{50} (μM)	Efficacy (%)
1.1	1.2	98
1.2	0.19	98

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not to be limited as by the appended claims.

[0157] The features disclosed in the foregoing description, in the claims and/or in the accompanying drawings, may both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

1-17. (canceled)

18. A compound of Formula (I)



(I)

a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically acceptable addition salt thereof, or an N-oxide thereof, wherein

R^1 and R^2, together with the nitrogen to which they are attached, form a heterocyclic ring selected from pyrrolidinyl, 2,5-dihydro-1H-pyrrol-1-yl, azetidinyl, thiazolidinyl, piperidinyl, piperazinyl and morpholinyl, which pyrrolidinyl, azetidinyl, piperidinyl, piperazinyl and morpholinyl is optionally substituted one or more times with a substituent selected from the group consisting of halo and trifluoromethyl;

R^3 represents a heterocyclic ring selected from furanyl and pyrrolyl which furanyl and pyrrolyl is optionally substituted one or more times with substituents selected from C_{1-6}-alkyl, C_{1-6}-alkoxy, halo and trifluoromethyl;

R^4 represents C_{1-6}-alkyl; and

R^5 and R^6, together with the nitrogen to which they are attached, form a heterocyclic ring selected from morpholinyl and 1,4-oxazepanyl.

19. The compound according to claim **18**, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically acceptable addition salt thereof, or an N-oxide thereof, wherein R^1 and R^2 together with the nitrogen to which they are attached is pyrrolidinyl which is optionally substituted one or more times with halo.

20. The compound according to any one of the claims **18-19**, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically acceptable addition salt thereof, or an N-oxide thereof, wherein R^3 represents furanyl which is optionally substituted with C_{1-6}-alkyl.

21. The compound according to claim **18**, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically acceptable addition salt thereof, or an N-oxide thereof, wherein R^4 represents C_{1-6}-alkyl.

22. The compound according to claim **18**, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically acceptable addition salt thereof, or an N-oxide thereof, wherein R^5 and R^6, together with the nitrogen to which they are attached, represents morpholinyl.

23. The compound according to claim **18**, which is:

3-Methyl-furan-2-carboxylic acid [2-((R)-3-fluoro-pyrrolidin-1-yl)-4-methyl-6-[1,4]oxazepan-4-yl-pyridin-3-yl]-amide;

or a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically acceptable addition salt thereof, or an N-oxide thereof.

24. The compound according to claim **18**, which is:

3-Methyl-furan-2-carboxylic acid [2-((R)-3-fluoro-pyrrolidin-1-yl)-4-methyl-6-morpholin-4-yl-pyridin-3-yl]-amide;

or a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically acceptable addition salt thereof, or an N-oxide thereof.

25. A pharmaceutical composition comprising a therapeutically effective amount of the compound according to claim **18**, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically acceptable addition salt thereof, or an N-oxide thereof.

26. A method of treatment or prevention of a disease or a disorder or a condition, which disorder, disease or condition is responsive to activation of K_v7 channels, which method comprises the step of administering to such a living animal body in need thereof, a therapeutically effective amount of the compound according to claim **18**, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically acceptable addition salt thereof, or an N-oxide thereof.

27. The method according to claim **26**, wherein the disease, disorder or condition is pain, bipolar disorders, mania, psychosis, depression, anxiety or schizophrenia.

28. The method according to claim **26**, wherein the disease, disorder or condition is a compulsive behaviour, epilepsy, Lennox-Gastaut, convulsions, seizures, seizure disorders, absence seizures, general seizures, partial seizures, vascular spasms or hypertension.

29. The method according to claim **26**, wherein the disease, disorder or condition is pain, mild, moderate or severe pain, acute, chronic or recurrent pain, neuropathic pain, pain caused by migraine, chronic headache, migraine, migraine-related disorders, tension-type headache, postoperative pain, phantom limb pain, neuropathic pain, central pain, pain related to diabetic neuropathy, to post therapeutic neuralgia, or to peripheral nerve injury.

30. The method according to claim **26**, wherein the disease, disorder or condition is bladder control, nocturia, bladder spasms, overactive bladder (OAB), bladder outflow obstruction, interstitial cystitis (IC) or urinary incontinence.

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