PYRIDINE DERIVATIVES

This invention relates to pyridine derivatives. More particularly, this invention relates to 6-amino-2-aminocarbonyl-5-phenyl-pyridine derivatives and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives.

The pyridine derivatives of the present invention are sodium channel modulators and have a number of therapeutic applications, particularly in the treatment of pain.

More particularly, the pyridine derivatives of the invention are selective $Na_{V1.8}$ modulators. They show an affinity for the $Na_{V1.8}$ channel which is greater than their affinity for the tetrodotoxin-sensitive sodium channels (TTX-S). Preferred pyridine derivatives of the invention show at least a 5-fold selectivity for the $Na_{V1.8}$ channel as compared with the tetrodotoxin-sensitive sodium channels.

The $Na_{V1.8}$ channel is a voltage-gated sodium channel which is expressed in nociceptors, the sensory neurones responsible for transducing painful stimuli. The rat channel and the human channel have been cloned in 1996 and 1998 respectively (*Nature* 379 (1996), pp. 257-262; *Pain* 1998 Nov;78(2):107-14). The $Na_{V1.8}$ channel was previously known as SNS (sensory neurone specific) and PN3 (peripheral nerve type 3). The $Na_{V1.8}$ channel is atypical in that it shows resistance to the blocking effects of the puffer fish toxin tetrodotoxin and it is believed to underlie the slow-voltage-gated and tetrodotoxin-resistant (TTX-R) sodium currents recorded from dorsal root ganglion neurones. The closest molecular relative to the $Na_{V1.8}$ channel is the $Na_{V1.5}$ channel, which is the cardiac sodium channel, with which it shares approximately 60% homology. The $Na_{V1.8}$ channel is expressed most highly in the 'small cells' of the dorsal root ganglia (DRG). These are thought to be the C- and A-delta cells which are the putative polymodal nociceptors, or pain sensors. Under normal conditions, the $Na_{V1.8}$ channel is not expressed anywhere other than subpopulations of DRG neurones. The $Na_{V1.8}$ channels are thought to contribute to the process of DRG sensitisation and also to hyperexcitability due to nerve injury. Inhibitory modulation of the $Na_{V1.8}$ channels is aimed at reducing the excitability of nociceptors, by preventing them from contributing to the excitatory process.

Studies have shown that $Na_{V1.8}$ knock-out leads to a blunted pain phenotype, mostly to inflammatory challenges (A.N. Akopian *et al.*, *Nat. Neurosci.* **2** (1999), 541-548) and that $Na_{V1.8}$ knockdown reduces pain behaviours, in this case neuropathic pain (J. Lai *et al.*, *Pain,* 2002 Jan;95(1-2):143-52). Coward *et al.* and Yiangou *et al.*, have shown that $Na_{V1.8}$ appears to be expressed in pain conditions (*Pain.* 2000 Mar;85(1-2):41-50 and FEBS Lett. 2000 Feb 11;467(2-3):249-52).

The $Na_{V1.8}$ channel has also been shown to be expressed in structures relating to the back and tooth pulp and there is evidence for a role in causalgia, inflammatory bowel conditions and multiple sclerosis (Bucknill *et al.*, *Spine.* 2002 Jan 15;27(2):135-40: Shembalker *et al.*, *Eur J Pain.* 2001;5(3):319-23: Laird *et al.*, *J Neurosci.* 2002 Oct 1;22(19):8352-6: Black *et al.*, *Neuroreport.* 1999 Apr 6;10(5):913-8 and *Proc. Natl. Acad. Sci. USA* **97** (2000), pp. 11598-11602).

Several sodium channel modulators are known for use as anticonvulsants or antidepressants, such as carbamazepine, amitriptyline, lamotrigine and riluzole, all of which target brain tetradotoxin-sensitive (TTX-S) sodium channels. Such TTX-S agents suffer from dose-limiting side effects, including dizziness, ataxia and somnolence, primarily due to action at TTX-S channels in the brain.

It is an objective of the invention to provide new $Na_{V1.8}$ channel modulators that are good drug candidates. Preferred compounds should bind potently to the $Na_{V1.8}$ channel whilst showing little affinity for other sodium channels, particularly the TTX-S channels, and show functional activity as $Na_{V1.8}$ channel modulators. They should be well absorbed from the gastrointestinal tract, be metabolically stable and possess favourable pharmacokinetic properties. They should be non-toxic and demonstrate few side-effects. Furthermore, the ideal drug candidate will exist in a physical form that is stable, non-hygroscopic and easily formulated.

In particular, the pyridine derivatives of the present invention are selective for the $Na_{V1.8}$ channel over the tetradotoxin-sensitive (TTX-S) sodium channels, leading to improvements in the side-effect profile.

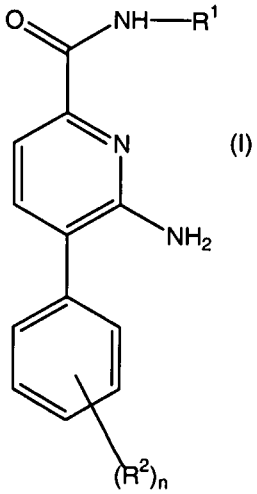
The pyridine derivatives of the present invention are therefore potentially useful in the treatment of a wide range of disorders, particularly pain, acute pain, chronic pain, neuropathic pain, inflammatory pain, visceral pain, nociceptive pain including post-surgical pain, and mixed pain types involving the viscera, gastrointestinal tract, cranial structures, musculoskeletal system, spine, urogenital system, cardiovascular system and CNS, including cancer pain, back and orofacial pain.

Other conditions that may be treated with the pyridine derivatives of the present invention include multiple sclerosis, neurodegenerative disorders, irritable bowel syndrome, osteoarthritis, rheumatoid arthritis, neuropathological disorders, functional bowel disorders, inflammatory bowel diseases, pain associated with dysmenorrhea, pelvic pain, cystitis, pancreatitis, migraine, cluster and tension headaches, diabetic neuropathy, peripheral neuropathic pain, sciatica, fibromyalgia and causalgia.

WO-A-96/18616 discloses pyridine derivatives useful as nitric oxide synthase inhibitors.

6-Amino-N-methyl-5-(2,3,5-trichlorophenyl)nicotinamide has been disclosed as a modulator of tetrodotoxin-sensitive (TTX-S) sodium channels (Gordon Conference, New London, USA, August 2000).

The invention therefore provides a pyridine derivative of the formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 is $(C_1\text{-}C_6)$alkyl optionally substituted with Het^1, Het^2 or $(C_3\text{-}C_7)$cycloalkyl, wherein said Het^1, Het^2 and $(C_3\text{-}C_7)$cycloalkyl are optionally substituted on a ring carbon atom by one or more substituents each independently selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy and halo$(C_1\text{-}C_4)$alkyl;

each R^2 is independently selected from fluoro, chloro, bromo and iodo;

n is 1, 2 or 3;

Het^1 is a 5- or 6-membered saturated or partially unsaturated heterocyclic group comprising one or two heteroatom ring members each independently selected from nitrogen, oxygen and sulphur, said ring nitrogen atom optionally bearing a $(C_1\text{-}C_4)$alkyl substituent and said ring sulphur atom optionally bearing 1 or 2 oxygen atoms; and

Het^2 is a 5- or 6-membered heteroaryl group comprising either (a) from 1 to 4 nitrogen atoms or (b) one oxygen or one sulphur atom and 0, 1 or 2 nitrogen atoms.

In the above definitions, halo means fluoro, chloro, bromo or iodo. Alkyl, and alkoxy groups, containing the requisite number of carbon atoms, can be unbranched or branched. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Examples of alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Examples of haloalkyl include trifluoromethyl.

Specific examples of Het^1 include tetrahydrofuranyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, morpholinyl, thiomorpholinyl and piperazinyl, (optionally substituted as specified above).

Specific examples of Het^2 include thienyl, furanyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl (optionally substituted as specified above).

In a preferred aspect (A), the invention provides a pyridine derivative of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is as defined above, and R^2 is chloro.

In a preferred aspect (B), the invention provides a pyridine derivative of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is as defined above, either in its broadest aspect or in a preferred aspect under (A) and n is 3; more preferably, the R^2 groups are in the 2, 3 and 5-positions on the phenyl ring.

In a further preferred aspect (C), the invention provides a pyridine derivative of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 and n are as defined above, either in the broadest aspect or in a preferred aspect under (A) or (B), and R^1 is $(C_1$-$C_6)$alkyl, optionally substituted with piperidinyl, imidazolyl, morpholinyl, piperazinyl or pyrrolidinyl; more preferably R^1 is methyl, ethyl or propyl, optionally substituted with piperidinyl, imidazolyl, morpholinyl, piperazinyl or pyrrolidinyl; most preferably R^1 is methyl.

Individual preferred R^1 groups are methyl; 2-(piperidin-1-yl)ethyl; 3-(pyrrolidin-1-yl)propyl; 3-(morpholin-4-yl)propyl; 2-(pyrrolidin-1-yl)ethyl; and 3-(imidazol-1-yl)propyl.

Specific preferred pyridine derivatives according to the invention are those listed below:

6-Amino-5-(2,3,5-trichloro-phenyl)-pyridine-2-carboxylic acid methylamide;

6-Amino-5-(2,3,5-trichloro-phenyl)-pyridine-2-carboxylic acid (2-piperidin-1-yl-ethyl)-amide;

6-Amino-5-(2,3,5-trichloro-phenyl)-pyridine-2-carboxylic acid (3-pyrrolidin-1-yl-propyl)-amide;

6-Amino-5-(2,3,5-trichloro-phenyl)-pyridine-2-carboxylic acid (3-morpholin-4-yl-propyl)-amide;

6-Amino-5-(2,3,5-trichloro-phenyl)-pyridine-2-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide;

6-Amino-5-(2,3,5-trichloro-phenyl)-pyridine-2-carboxylic acid (3-imidazol-1-yl-propyl)-amide; and
the pharmaceutically acceptable salts and solvates thereof.

A particularly preferred pyridine derivative according to the invention is 6-Amino-5-(2,3,5-trichloro-phenyl)-pyridine-2-carboxylic acid methylamide or a pharmaceutically acceptable salt or solvate thereof.

The compounds of formula (I), being $Na_{V1.8}$ channel modulators, are potentially useful in the treatment of a range of disorders. The treatment of pain, particularly chronic, inflammatory, neuropathic, nociceptive and visceral pain, is a preferred use.

Physiological pain is an important protective mechanism designed to warn of danger from potentially injurious stimuli from the external environment. The system operates through a specific set of primary sensory neurones and is activated by noxious stimuli *via* peripheral transducing mechanisms (see Millan, 1999, Prog. Neurobiol., 57, 1-164 for a review). These sensory fibres are known as nociceptors and are characteristically small diameter axons with slow conduction velocities. Nociceptors encode the intensity, duration and quality of noxious stimulus and by virtue of their topographically organised projection to the spinal cord, the location of the stimulus. The nociceptors are found on nociceptive nerve fibres of which there are two main types, A-delta fibres (myelinated) and C fibres (non-myelinated). The activity generated by nociceptor input is transferred, after complex processing in the dorsal horn, either directly, or via brain stem relay nuclei, to the ventrobasal thalamus and then on to the cortex, where the sensation of pain is generated.

Pain may generally be classified as acute or chronic. Acute pain begins suddenly and is short-lived (usually in twelve weeks or less). It is usually associated with a specific cause such as a specific injury and is often sharp and severe. It is the kind of pain that can occur after specific injuries resulting from surgery, dental work, a strain or a sprain. Acute pain does not generally result in any persistent psychological response. In contrast, chronic pain is long-term pain, typically persisting for more than three months and leading to significant psychological and emotional problems. Common examples of chronic pain are neuropathic pain (e.g. painful diabetic neuropathy,

postherpetic neuralgia), carpal tunnel syndrome, back pain, headache, cancer pain, arthritic pain and chronic post-surgical pain.

When a substantial injury occurs to body tissue, *via* disease or trauma, the characteristics of nociceptor activation are altered and there is sensitisation in the periphery, locally around the injury and centrally where the nociceptors terminate. These effects lead to a hightened sensation of pain. In acute pain these mechanisms can be useful, in promoting protective behaviours which may better enable repair processes to take place. The normal expectation would be that sensitivity returns to normal once the injury has healed. However, in many chronic pain states, the hypersensitivity far outlasts the healing process and is often due to nervous system injury. This injury often leads to abnormalities in sensory nerve fibres associated with maladaptation and aberrant activity (Woolf & Salter, 2000, Science, 288, 1765-1768).

Clinical pain is present when discomfort and abnormal sensitivity feature among the patient's symptoms. Patients tend to be quite heterogeneous and may present with various pain symptoms. Such symptoms include: 1) spontaneous pain which may be dull, burning, or stabbing; 2) exaggerated pain responses to noxious stimuli (hyperalgesia); and 3) pain produced by normally innocuous stimuli (allodynia - Meyer et al., 1994, Textbook of Pain, 13-44). Although patients suffering from various forms of acute and chronic pain may have similar symptoms, the underlying mechanisms may be different and may, therefore, require different treatment strategies. Pain can also therefore be divided into a number of different subtypes according to differing pathophysiology, including nociceptive, inflammatory and neuropathic pain.

Nociceptive pain is induced by tissue injury or by intense stimuli with the potential to cause injury. Pain afferents are activated by transduction of stimuli by nociceptors at the site of injury and activate neurons in the spinal cord at the level of their termination. This is then relayed up the spinal tracts to the brain where pain is perceived (Meyer et al., 1994, Textbook of Pain, 13-44). The activation of nociceptors activates two types of afferent nerve fibres. Myelinated A-delta fibres transmit rapidly and are responsible for sharp and stabbing pain sensations, whilst unmyelinated C fibres transmit at a slower rate and convey a dull or aching pain. Moderate to severe acute nociceptive pain is a prominent feature of pain from central nervous system

trauma, strains/sprains, burns, myocardial infarction and acute pancreatitis, post-operative pain (pain following any type of surgical procedure), posttraumatic pain, renal colic, cancer pain and back pain. Cancer pain may be chronic pain such as tumour related pain (e.g. bone pain, headache, facial pain or visceral pain) or pain associated with cancer therapy (e.g. postchemotherapy syndrome, chronic postsurgical pain syndrome or post radiation syndrome). Cancer pain may also occur in response to chemotherapy, immunotherapy, hormonal therapy or radiotherapy. Back pain may be due to herniated or ruptured intervertebral discs or abnormalities of the lumber facet joints, sacroiliac joints, paraspinal muscles or the posterior longitudinal ligament. Back pain may resolve naturally but in some patients, where it lasts over 12 weeks, it becomes a chronic condition which can be particularly debilitating.

Neuropathic pain is currently defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system. Nerve damage can be caused by trauma and disease and thus the term 'neuropathic pain' encompasses many disorders with diverse aetiologies. These include, but are not limited to, peripheral neuropathy, diabetic neuropathy, post herpetic neuralgia, trigeminal neuralgia, back pain, cancer neuropathy, HIV neuropathy, phantom limb pain, carpal tunnel syndrome, central post-stroke pain and pain associated with chronic alcoholism, hypothyroidism, uremia, multiple sclerosis, spinal cord injury, Parkinson's disease, epilepsy and vitamin deficiency. Neuropathic pain is pathological as it has no protective role. It is often present well after the original cause has dissipated, commonly lasting for years, significantly decreasing a patient's quality of life (Woolf and Mannion, 1999, Lancet, 353, 1959-1964). The symptoms of neuropathic pain are difficult to treat, as they are often heterogeneous even between patients with the same disease (Woolf & Decosterd, 1999, Pain Supp., 6, S141-S147; Woolf and Mannion, 1999, Lancet, 353, 1959-1964). They include spontaneous pain, which can be continuous, and paroxysmal or abnormal evoked pain, such as hyperalgesia (increased sensitivity to a noxious stimulus) and allodynia (sensitivity to a normally innocuous stimulus).

The inflammatory process is a complex series of biochemical and cellular events, activated in response to tissue injury or the presence of foreign substances, which results in swelling and pain (Levine and Taiwo, 1994, Textbook of Pain, 45-56).

Arthritic pain is the most common inflammatory pain. Rheumatoid disease is one of the commonest chronic inflammatory conditions in developed countries and rheumatoid arthritis is a common cause of disability. The exact aetiology of rheumatoid arthritis is unknown, but current hypotheses suggest that both genetic and microbiological factors may be important (Grennan & Jayson, 1994, Textbook of Pain, 397-407). It has been estimated that almost 16 million Americans have symptomatic osteoarthritis (OA) or degenerative joint disease, most of whom are over 60 years of age, and this is expected to increase to 40 million as the age of the population increases, making this a public health problem of enormous magnitude (Houge & Mersfelder, 2002, Ann Pharmacother., 36, 679-686; McCarthy et al., 1994, Textbook of Pain, 387-395). Most patients with osteoarthritis seek medical attention because of the associated pain. Arthritis has a significant impact on psychosocial and physical function and is known to be the leading cause of disability in later life. Ankylosing spondylitis is also a rheumatic disease that causes arthritis of the spine and sacroiliac joints. It varies from intermittent episodes of back pain that occur throughout life to a severe chronic disease that attacks the spine, peripheral joints and other body organs.

Another type of inflammatory pain is visceral pain which includes pain associated with inflammatory bowel disease (IBD). Visceral pain is pain associated with the viscera, which encompass the organs of the abdominal cavity. These organs include the sex organs, spleen and part of the digestive system. Pain associated with the viscera can be divided into digestive visceral pain and non-digestive visceral pain. Commonly encountered gastrointestinal (GI) disorders that cause pain include functional bowel disorder (FBD) and inflammatory bowel disease (IBD). These GI disorders include a wide range of disease states that are currently only moderately controlled, including, in respect of FBD, gastro-esophageal reflux, dyspepsia, irritable bowel syndrome (IBS) and functional abdominal pain syndrome (FAPS), and, in respect of IBD, Crohn's disease, ileitis and ulcerative colitis, all of which regularly produce visceral pain. Other types of visceral pain include the pain associated with dysmenorrhea, cystitis and pancreatitis and pelvic pain.

It should be noted that some types of pain have multiple aetiologies and thus can be classified in more than one area, e.g. back pain and cancer pain have both nociceptive and neuropathic components.

Other types of pain include:

- pain resulting from musculo-skeletal disorders, including myalgia, fibromyalgia, spondylitis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, dystrophinopathy, glycogenolysis, polymyositis and pyomyositis;
- heart and vascular pain, including pain caused by angina, myocardical infarction, mitral stenosis, pericarditis, Raynaud's phenomenon, scleredoma and skeletal muscle ischemia;
- head pain, such as migraine (including migraine with aura and migraine without aura), cluster headache, tension-type headache mixed headache and headache associated with vascular disorders; and
- orofacial pain, including dental pain, otic pain, burning mouth syndrome and temporomandibular myofascial pain.

The pyridine derivatives of formula (I) are also expected to be useful in the treatment of multiple sclerosis.

The invention also relates to therapeutic use of the pyridine derivatives of formula (I) as agents for treating or relieving the symptoms of neurodegenerative disorders. Such neurodegenerative disorders include, for example, Alzheimer's disease, Huntington's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis. The present invention also covers treating neurodegenerative disorders termed acute brain injury. These include but are not limited to: stroke, head trauma, and asphyxia. Stroke refers to a cerebral vascular disease and may also be referred to as a cerebral vascular accident (CVA) and includes acute thromboembolic stroke. Stroke includes both focal and global ischemia. Also, included are transient cerebral ischemic attacks and other cerebral vascular problems accompanied by cerebral ischemia. These vascular disorders may occur in a patient undergoing carotid endarterectomy specifically or other cerebrovascular or vascular surgical procedures in general, or diagnostic vascular procedures including cerebral angiography and the like. Other incidents are head trauma, spinal cord trauma, or injury from general anoxia, hypoxia,

hypoglycemia, hypotension as well as similar injuries seen during procedures from embole, hyperfusion, and hypoxia. The instant invention would be useful in a range of incidents, for example, during cardiac bypass surgery, in incidents of intracranial hemorrhage, in perinatal asphyxia, in cardiac arrest, and status epilepticus.

A skilled physician will be able to determine the appropriate situation in which subjects are susceptible to or at risk of, for example, stroke as well as suffering from stroke for administration by methods of the present invention.

Pharmaceutically acceptable salts of the compounds of formula (I) include the acid addition and base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, 2002).

Pharmaceutically acceptable salts of compounds of formula (I) may be prepared by one or more of three methods:

(i) by reacting the compound of formula (I) with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula (I) or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) by converting one salt of the compound of formula (I) to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

The compounds of the invention may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term 'amorphous' refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterised by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when

heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterised by a phase change, typically first order ('melting point').

The compounds of the invention may also exist in unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

A currently accepted classification system for organic hydrates is one that defines isolated site, channel, or metal-ion coordinated hydrates - see Polymorphism in Pharmaceutical Solids by K. R. Morris (Ed. H. G. Brittain, Marcel Dekker, 1995). Isolated site hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic molecules. In channel hydrates, the water molecules lie in lattice channels where they are next to other water molecules. In metal-ion coordinated hydrates, the water molecules are bonded to the metal ion.

When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content will be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

Also included within the scope of the invention are multi-component complexes (other than salts and solvates) wherein the drug and at least one other component are present in stoichiometric or non-stoichiometric amounts. Complexes of this type include clathrates (drug-host inclusion complexes) and co-crystals. The latter are typically defined as crystalline complexes of neutral molecular constituents which are bound together through non-covalent interactions, but could also be a complex of a neutral molecule with a salt. Co-crystals may be prepared by melt crystallisation, by recrystallisation from solvents, or by physically grinding the components together - see

Chem Commun, 17, 1889-1896, by O. Almarsson and M. J. Zaworotko (2004). For a general review of multi-component complexes, see J Pharm Sci, 64 (8), 1269-1288, by Haleblian (August 1975).

The compounds of the invention may also exist in a mesomorphic state (mesophase or liquid crystal) when subjected to suitable conditions. The mesomorphic state is intermediate between the true crystalline state and the true liquid state (either melt or solution). Mesomorphism arising as the result of a change in temperature is described as 'thermotropic' and that resulting from the addition of a second component, such as water or another solvent, is described as 'lyotropic'. Compounds that have the potential to form lyotropic mesophases are described as 'amphiphilic' and consist of molecules which possess an ionic (such as $-COO^-Na^+$, $-COO^-K^+$, or $-SO_3^-Na^+$) or non-ionic (such as $-N^-N^+(CH_3)_3$) polar head group. For more information, see Crystals and the Polarizing Microscope by N. H. Hartshorne and A. Stuart, 4th Edition (Edward Arnold, 1970).

Hereinafter all references to compounds of formula I include references to salts, solvates, multi-component complexes and liquid crystals thereof and to solvates, multi-component complexes and liquid crystals of salts thereof.

The compounds of the invention include compounds of formula (I) as hereinbefore defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of formula (I).

As indicated, so-called 'prodrugs' of the compounds of formula (I) are also within the scope of the invention. Thus certain derivatives of compounds of formula (I) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in Pro-drugs as

Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and Bioreversible Carriers in Drug Design, Pergamon Press, 1987 (Ed. E. B. Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (I) with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in Design of Prodrugs by H. Bundgaard (Elsevier, 1985).

Some examples of prodrugs in accordance with the invention include where the compound of formula (I) contains a primary or secondary amino functionality ($-NH_2$ or -NHR where R ≠ H), an amide thereof, for example, a compound wherein, as the case may be, one or both hydrogens of the amino functionality of the compound of formula (I) is/are replaced by (C_1-C_{10})alkanoyl.

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

Moreover, certain compounds of formula (I) may themselves act as prodrugs of other compounds of formula (I).

Also included within the scope of the invention are metabolites of compounds of formula (I), that is, compounds formed *in vivo* upon administration of the drug. Some examples of metabolites in accordance with the invention include

(i) where the compound of formula (I) contains a methyl group, an hydroxymethyl derivative thereof ($-CH_3$ -> $-CH_2OH$):

(ii) where the compound of formula (I) contains an alkoxy group, an hydroxy derivative thereof (-OR -> -OH);

(iii) where the compound of formula (I) contains a secondary amino group, a primary derivative thereof (-NHR^1 -> -NH_2);

(iv) where the compound of formula (I) contains a phenyl moiety, a phenol derivative thereof (-Ph -> -PhOH); and

(v) where the compound of formula (I) contains an amide group, a carboxylic acid derivative thereof (-$CONH_2$ -> COOH).

Compounds of formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of formula (I) contains an alkenyl or alkenylene group, geometric *cis/trans* (or Z/E) isomers are possible. Where structural isomers are interconvertible *via* a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds of formula (I) containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula (I), including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, *d*-lactate or *l*-lysine, or racemic, for example, *dl*-tartrate or *dl*-arginine.

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate

(or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

When any racemate crystallises, crystals of two different types are possible. The first type is the racemic compound (true racemate) referred to above wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. The second type is the racemic mixture or conglomerate wherein two forms of crystal are produced in equimolar amounts each comprising a single enantiomer.

While both of the crystal forms present in a racemic mixture have identical physical properties, they may have different physical properties compared to the true racemate. Racemic mixtures may be separated by conventional techniques known to those skilled in the art - see, for example, Stereochemistry of Organic Compounds by E. L. Eliel and S. H. Wilen (Wiley, 1994).

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula I wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in 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.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, 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.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

Also within the scope of the invention are intermediate compounds of formulae (V), (VI) and (VII) as defined below, all salts, solvates and complexes thereof and all solvates and complexes of salts thereof as defined hereinbefore for compounds of formula (I). The invention includes all polymorphs of the aforementioned species and crystal habits thereof.

The compounds of formula (I) should be assessed for their biopharmaceutical properties, such as solubility and solution stability (across pH), permeability, *etc.*, in order to select the most appropriate dosage form and route of administration for treatment of the proposed indication.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term 'excipient' is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in Remington's Pharmaceutical Sciences, 19th Edition (Mack Publishing Company, 1995).

ORAL ADMINISTRATION

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, and/or buccal, lingual, or sublingual administration by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid, semi-solid and liquid systems such as tablets; soft or hard capsules containing multi- or nano-particulates, liquids, or powders; lozenges (including liquid-filled); chews; gels; fast dispersing dosage forms; films; ovules; sprays; and buccal/mucoadhesive patches.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules (made, for example, from gelatin or hydroxypropylmethylcellulose) and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986, by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 weight % to 80 weight % of the dosage form, more typically from 5 weight % to 60 weight % of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 weight % to 25 weight %, preferably from 5 weight % to 20 weight % of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 weight % to 10 weight %, preferably from 0.5 weight % to 3 weight % of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 weight % to about 90 weight % binder, from about 0 weight % to about 85 weight % diluent, from about 2 weight % to about 10 weight % disintegrant, and from about 0.25 weight % to about 10 weight % lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in Pharmaceutical Dosage Forms: Tablets, Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

Consumable oral films for human or veterinary use are typically pliable water-soluble or water-swellable thin film dosage forms which may be rapidly dissolving or mucoadhesive and typically comprise a compound of formula (I), a film-forming polymer, a binder, a solvent, a humectant, a plasticiser, a stabiliser or emulsifier, a viscosity-modifying agent and a solvent. Some components of the formulation may perform more than one function.

The compound of formula (I) may be water-soluble or insoluble. A water-soluble compound typically comprises from 1 weight % to 80 weight %, more typically from 20 weight % to 50 weight %, of the solutes. Less soluble compounds may comprise a greater proportion of the composition, typically up to 88 weight % of the solutes. Alternatively, the compound of formula (I) may be in the form of multiparticulate beads.

The film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and is typically present in the range 0.01 to 99 weight %, more typically in the range 30 to 80 weight %.

Other possible ingredients include anti-oxidants, colorants, flavourings and flavour enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants and taste-masking agents.

Films in accordance with the invention are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper. This may be done in a drying oven or tunnel, typically a combined coater dryer, or by freeze-drying or vacuuming.

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Pharmaceutical Technology On-line, 25(2), 1-14, by Verma *et al* (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

PARENTERAL ADMINISTRATION

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a suspension or as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and semi-solids and suspensions comprising drug-loaded poly(*dl*-lactic-coglycolic)acid (PGLA) microspheres.

TOPICAL ADMINISTRATION

The compounds of the invention may also be administered topically, (intra)dermally, or transdermally to the skin or mucosa. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol.

Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958, by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (*e.g.* Powderject™, Bioject™, *etc.*) injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

INHALED/INTRANASAL ADMINISTRATION

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler, as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane, or as nasal drops. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1µg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1µl to 100µl. A typical formulation may comprise a compound of formula (I), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, PGLA. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the

invention are typically arranged to administer a metered dose or "puff" containing from 1 µg to 20 mg of the compound of formula (I). The overall daily dose will typically be in the range 1 µg to 100 mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

RECTAL/INTRAVAGINAL ADMINISTRATION

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

OCULAR/AURAL ADMINISTRATION

The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, gels, biodegradable (*e.g.* absorbable gel sponges, collagen) and non-biodegradable (*e.g.* silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for

example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

OTHER TECHNOLOGIES

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

KIT-OF-PARTS

Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I) in accordance

with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

DOSAGE

For administration to human patients, the total daily dose of the compounds of the invention is typically in the range 0.1 mg to 1000 mg depending, of course, on the mode of administration. For example, oral administration may require a total daily dose of from 1 mg to 1000 mg, while an intravenous dose may only require from 0.1 mg to 100 mg. The total daily dose may be administered in single or divided doses and may, at the physician's discretion, fall outside of the typical range given herein.

These dosages are based on an average human subject having a weight of about 60kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

For the avoidance of doubt, references herein to "treatment" include references to curative, palliative and prophylactic treatment.

A $Na_{V1.8}$ channel modulator may be usefully combined with another pharmacologically active compound, or with two or more other pharmacologically active compounds, particularly in the treatment of pain. For example, a $Na_{V1.8}$ channel modulator, particularly a compound of formula (I), or a pharmaceutically acceptable salt or solvate

thereof, as defined above, may be administered simultaneously, sequentially or separately in combination with one or more agents selected from:

- an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine or pentazocine;
- a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin or zomepirac;
- a barbiturate sedative, e.g. amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobartital, secobarbital, talbutal, theamylal or thiopental;
- a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;
- an H_1 antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;
- a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone;
- a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphrenadine;
- an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinine, cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid, budipine, EN-3231 (MorphiDex®, a combination formulation of morphine and dextromethorphan), topiramate, neramexane or perzinfotel including an NR2B antagonist, e.g. ifenprodil, traxoprodil or (–)-(R)-6-{2-[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]-1-hydroxyethyl-3,4-dihydro-2(1H)-quinolinone;

- an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dexmetatomidine, modafinil, or 4-amino-6,7-dimethoxy-2-(5-methane-sulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;
- a tricyclic antidepressant, e.g. desipramine, imipramine, amitriptyline or nortriptyline;
- an anticonvulsant, e.g. carbamazepine, lamotrigine, topiratmate or valproate;
- a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (αR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]-naphthyridine-6-13-dione (TAK-637), 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), aprepitant, lanepitant, dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2S,3S);
- a muscarinic antagonist, e.g oxybutynin, tolterodine, propiverine, tropsium chloride, darifenacin, solifenacin, temiverine and ipratropium;
- a COX-2 selective inhibitor, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, or lumiracoxib;
- a coal-tar analgesic, in particular paracetamol;
- a neuroleptic such as droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonepiprazole, blonanserin, iloperidone, perospirone, raclopride, zotepine, bifeprunox, asenapine, lurasidone, amisulpride, balaperidone, palindore, eplivanserin, osanetant, rimonabant, meclinertant, Miraxion® or sarizotan;
- a vanilloid receptor agonist (e.g. resinferatoxin) or antagonist (e.g. capsazepine);
- a beta-adrenergic such as propranolol;
- a local anaesthetic such as mexiletine;
- a corticosteroid such as dexamethasone;
- a 5-HT receptor agonist or antagonist, particularly a 5-$HT_{1B/1D}$ agonist such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan;
- a 5-HT_{2A} receptor antagonist such as R(+)-alpha-(2,3-dimethoxy-phenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (MDL-100907);

- a cholinergic (nicotinic) analgesic, such as ispronicline (TC-1734), (E)-N-methyl-4-(3-pyridinyl)-3-buten-1-amine (RJR-2403), (R)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594) or nicotine;
- Tramadol®;
- a PDEV inhibitor, such as 5-[2-ethoxy-5-(4-methyl-1-piperazinyl-sulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione (IC-351 or tadalafil), 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil), 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 4-[(3-chloro-4-methoxybenzyl)amino]-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide, 3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide;
- an alpha-2-delta ligand such as gabapentin, pregabalin, 3-methylgabapentin, (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (2S,4S)-4-(3-chlorophenoxy)proline, (2S,4S)-4-(3-fluorobenzyl)-proline, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (3R,4R,5R)-3-amino-4,5-dimethyl-heptanoic acid and (3R,4R,5R)-3-amino-4,5-dimethyl-octanoic acid;
- a cannabinoid;
- metabotropic glutamate subtype 1 receptor (mGluR1) antagonist;

- a serotonin reuptake inhibitor such as sertraline, sertraline metabolite demethylsertraline, fluoxetine, norfluoxetine (fluoxetine desmethyl metabolite), fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine, dapoxetine, nefazodone, cericlamine and trazodone;
- a noradrenaline (norepinephrine) reuptake inhibitor, such as maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, buproprion, buproprion metabolite hydroxybuproprion, nomifensine and viloxazine (Vivalan®), especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular (S,S)-reboxetine;
- a dual serotonin-noradrenaline reuptake inhibitor, such as venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine, milnacipran and imipramine;
- an inducible nitric oxide synthase (iNOS) inhibitor such as S-[2-[(1-iminoethyl)amino]ethyl]-L-homocysteine, S-[2-[(1-iminoethyl)-amino]ethyl]-4,4-dioxo-L-cysteine, S-[2-[(1-iminoethyl)amino]ethyl]-2-methyl-L-cysteine, (2S,5Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-5-heptenoic acid, 2-[[(1R,3S)-3-amino-4- hydroxy-1-(5-thiazolyl)-butyl]thio]-5-chloro-3-pyridinecarbonitrile; 2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chlorobenzonitrile, (2S,4R)-2-amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol, 2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl) butyl]thio]-6-(trifluoromethyl)-3 pyridinecarbonitrile, 2-[[(1R,3S)-3- amino-4-hydroxy- 1 -(5-thiazolyl)butyl]thio]-5-chlorobenzonitrile, N-[4-[2-(3-chlorobenzylamino)ethyl]phenyl]thiophene-2-carboxamidine, or guanidinoethyldisulfide;
- an acetylcholinesterase inhibitor such as donepezil;
- a prostaglandin E_2 subtype 4 (EP4) antagonist such as *N*-[({2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl}amino)-carbonyl]-4-methylbenzenesulfonamide or 4-[(1*S*)-1-({[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;
- a leukotriene B4 antagonist; such as 1-(3-biphenyl-4-ylmethyl-4-hydroxy-chroman-7-yl)-cyclopentanecarboxylic acid (CP-105696), 5-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-5E- hexenyl]oxyphenoxy]-valeric acid (ONO-4057) or DPC-11870,

- a 5-lipoxygenase inhibitor, such as zileuton, 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone (ZD-2138), or 2,3,5-trimethyl-6-(3-pyridylmethyl),1,4-benzoquinone (CV-6504);
- a sodium channel blocker, such as lidocaine;
- a 5-HT3 antagonist, such as ondansetron;

and the pharmaceutically acceptable salts and solvates thereof.

Such combinations offer significant advantages, including synergistic activity, in therapy.

The ability of the pyridine derivatives of the formula (I) to inhibit the $Na_{V1.8}$ channel may be measured using the assay described below.

VIPR Assay for Nav1.8 compounds

Abstract:

This screen is used to determine the effects of compounds on tetrodotoxin-resistant (TTX-R) sodium channels in Human Nav1.8 (HEK293) expressing cell line, utilising the technology of Aurora's fluorescent Voltage/Ion Probe Reader (VIPR). This experiment is based on FRET (Fluorescence Resonance Energy Transfer) and uses two fluorescent molecules. The first molecule, Oxonol ($DiSBAC_2(3)$), is a highly fluorescent, negatively charged, hydrophobic ion that "senses" the trans-membrane electrical potential. In response to changes in membrane potential, it can rapidly redistribute between two binding sites on opposite sides of the plasma membrane. The voltage dependent redistribution is transduced into a ratiometric fluorescent readout via a second fluorescent molecule (Coumarin (CC2-DMPE)) that binds specifically to one face of the plasma membrane and functions as a FRET partner to the mobile voltage-sensing ion. To enable the assay to work, the channels have to be pharmacologically held in the open state. This is achieved by treating the cells with either deltamethrin (for $Na_{V1.8}$) or veratridine (for the SHSY-5Y assay for TTX-S channels).

Cell Maintenance:

Human Nav1.8 cells were grown in T225 flasks, in a 5% CO2 humidified incubator to about 70% confluence. Media composition consisted of DMEM/F-12, 10% FCS and 300µg/ml Geneticine. They were split using cell dissociation fluid 1:5 to 1:20, depending on scheduling needs, and grown for 3-4 days before the next split.

PROTOCOL:

Day One:

Plate-out HEK-Nav1.8 cells (100µl per well) into poly-D-lysine coated plates prior to experimentation as follows: - 24 hours @ 3.5 x 10^4 cells/well (3.5 x 10^5 cells/ml) or using the technology of Select.

Day Two: *VIPR Assay:*

1. Equilibrate buffers at room temperature for 2 hours or at 37°C for 30 minutes prior to experimentation.
2. Prepare Coumarin dye (see below) and store in dark. Prime with the plate washer with Na+ Free buffer and wash cells twice, Note: Plate washer deposits ~30µl residual buffer per well. Add 100µL Coumarin (CC2-DMPE) solution (see appendix) to cells and incubate for 45 minutes at room temperature avoiding bright light.
3. Prepare Oxonol ($DiSBAC_2(3)$) dye (see below):
4. Aspirate off Coumarin solution from the cells by washing in Na+ Free buffer.
5. Add 30µl compound (refer to addition plates). Add 30µl Oxonol solution to the cells and incubate for 45 minutes at room temperature in the dark (total well volume ~90µl).
6. Once the incubation is complete, the cells are ready to be assayed using the VIPR for sodium addback membrane potential.

The data was analyzed and reported as normalised ratios of intensities measured in the 460nm and 580nm channels. The process of calculating these ratios was performed as follows. An additional plate contained control solution with the same DisBAC2(3) concentrations as used in the cell plates, however no cells were included in the background plate. Intensity values at each wavelength were averaged for sample points 5-7 (initial) and 44-49 (final). These averages were subtracted from intensity values averaged over the same time periods in all assay wells. The initial ratio obtained from samples 3-8 (Ri) and the final ratio obtained from samples 45-50 (Rf) are defined as:

Ri = (Intensity 460nm, samples 3-5 - background 460nm, samples 3-5) / (Intensity 580nm, samples 3-5 - background 580nm, samples 3-5)

Rf = (Intensity 460nm, samples 25-30 - background 460nm, samples 25-30) / (Intensity 580nm, samples 25-30 - background 580nm, samples 25-30)

Final data are normalised to the starting ratio of each well and reported as Rf/Ri. This analysis is performed using a computerised specific programme designed for VIPR generated data.

Rf/Ri ratio values are plotted using Excel Labstats (curve fit) or analysed via ECADA to determine an IC50 value for each compound.

Na+-Addback Buffer pH 7.4 (adjust with 5M NaOH) – **10X stock**

Component:	Mwt/Conc^{n}:	weight/volume	**10X** Conc. (mM)	**1X** Conc. (mM):
NaCl	58.44	93.5g	1600	**160**
KCL	74.55	3.35g	45.0	**4.5**
CaCl2	1M solution	20ml	20.0	**2**
MgCl2	203.31	2.03g	10.0	**1**
Hepes	238.3	23.83g	100	**10**
dH2O		**1L**		

Na+-Free Buffer pH 7.4 (adjust with 5M KOH) – **10X stock**

Component:	Mwt/Conc^{n}:	weight/volume	**10X** Conc. (mM)	**1X** Conc (mM):
Choline	139.6	223.36g	**1600**	**160**
CaCl2	1M solution	1ml	**1.0**	**0.1**
MgCl2	203.31	2.03g	**10.0**	**1.0**
Hepes	238.3	23.83g	**100**	**10**
dH2O		**1L**		

1X Na+ Free Buffer: - 400ml 10X + 3600ml dH2O

2X Na+ Free Buffer: - 100ml 10X + 400ml dH2O

1X Na+ Addback Buffer:- 50ml 10X Na+ Addback + 450ml dH2O

Coumarin (CC2-DMPE): For 2 plates: -

First mix 220µl Coumarin (1mM) + 22µl Pluronic (20%) in a tube + 22ml **1X Na+-Free Buffer**, gently vortex.

	Solution Conc^n:	Final Assay Conc^n
Coumarin (1mM)	10µM	10µM

Oxonol (DiSBAC$_2$(3)): For 2 plates:-

48µl Oxonol (5mM) + 120ul Tartrazine (200mM)	Vortex
8.0ml **2X Na+-Free Buffer**	Vortex
1.6µl Deltametherin (5mM)	Vortex

	Solution Conc^n:	Final Assay Conc^n
Oxonol (5mM)	30µM	10µM
Deltametherin (5mM)	1µM	330nM
Tartrazine (200mM)	3mM	1.0mM

TTX-S Assay

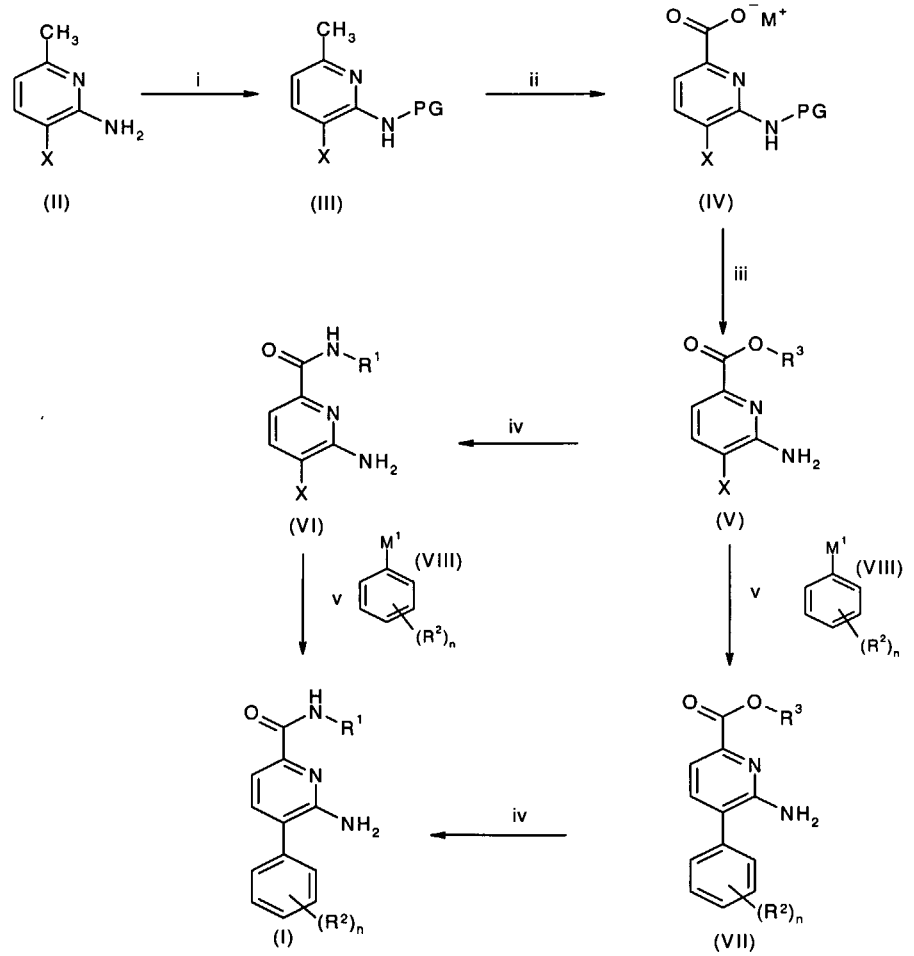
The TTX-S assay was performed in the native SHSY-5Y cell line. These cells express a number of tetrodotoxin-sensitive voltage-gated sodium channels including $Na_{V1.2}$, $Na_{V1.3}$ and $Na_{V1.7}$. The procedure detailed above for the $Na_{V1.8}$ assay was followed with the exception that veratridine was substituted for deltamethrin in the assay as an opener of the sodium channels, at a final assay concentration of 50µM.

All of the pyridine derivatives of the formula (I) can be prepared by the procedures described in the general methods presented below or by the specific methods described in the Examples section and the Preparations section, or by routine modifications thereof. The present invention also encompasses any one or more of these processes for preparing the pyridine derivatives of formula (I), in addition to any novel intermediates used therein.

In the following general methods, R^1, R^2 and n are as previously defined for a pyridine derivative of the formula (I) unless otherwise stated.

According to a first process, pyridine derivatives of formula (I) may be prepared from compounds of formulae (VI) or (VII), as illustrated by Scheme1.

Scheme 1



wherein X is a suitable leaving group, such as trifluoromethanesulfonyl, fluoro, chloro, bromo, iodo;

PG is a suitable protecting group, such as tert-butoxycarbonyl, N-benzyloxycarbonyl, tert-butylcarbonyl or methylcarbonyl;

R^3 is a suitable ester group such as (C_1-C_6)alkyl, benzyl;

M is hydrogen or an alkali metal; and

M^1 is a suitable coupling group such as a stannane, borane or boronic acid, metal or metalhalide.

Compounds of formula (III) can be prepared from compounds of formula (II) by reaction with a suitable acid chloride or anhydride, optionally in the presence of an acid acceptor, in a suitable solvent such as dichloromethane or dioxan, at a temperature of from 25 to 50°C for 5-18 hours. PG is suitably tert-butoxycarbonyl, N-benzyloxycarbonyl, tert-butylcarbonyl or methylcarbonyl, preferably tert-butylcarbonyl or methylcarbonyl, and most preferably methylcarbonyl.

When PG is methylcarbonyl, typical conditions are analogous to those described in *Bioorg. Med. Chem.* 9, 2061–2071, 2001 and comprise of 1.0 equivalent of compound (II) and an excess of acetic anhydride in dioxan, at 50°C for 18 hours.

Compounds of formula (IV) can be prepared from compounds of formula (III) by oxidation with a suitable oxidising agent, such as potassium permanganate or sodium dichromate, in a suitable solvent, such as water or water with pyridine, at a temperature of from 65 to 75°C for 3-18 hours. Typical conditions comprise 1.0 equivalent of compound (III) and 2.0-6.0 equivalents of potassium permanganate, in a mixture of water and pyridine, at 75°C for 18 hours.

Compounds of formula (V) can be prepared either as described in *J. Org. Chem.* 61, 4623-4633, 1996 or from compounds of formula (IV) by alkylation with a suitable alcohol in the presence of a suitable acid, such as concentrated hydrochloric acid or concentrated sulfuric acid, heated under reflux for 18-72 hours. Removal of the amine protecting group (PG) occurs concomitantly under these conditions. Typical conditions comprise of 1.0 equivalent of compound (IV) and an excess of methanol, in the presence of concentrated sulfuric acid, heated under reflux for 48 hours.

Alternatively, compounds of general formula (V) can be prepared from compounds of general formula (III) by combination of steps ii and iii. Typical conditions comprise of 1.0 equivalent of compound (III) and 2.0-6.0 equivalents of potassium permanganate, in a mixture of water and pyridine, at 75°C for 18 hours. Concentration *in vacuo* is

followed by addition of methanol and concentrated sulfuric acid, heated under reflux for 48 hours to yield the desired product.

Compounds of formula (VI) can be prepared by reaction of compounds of formula (V) with an amine, NH_2R^1, in a suitable solvent, such as dichloromethane or a mixture of tetrahydrofuran/R^3OH, at a temperature of from 25°C to reflux, for 18-72 hours. Typical conditions comprise of 1.0 equivalent of compound (V) and 5.0-10.0 equivalents of NH_2R^1 in tetrahydrofuran/methanol, at 25-80°C for 18-72 hours.

Alternatively, this reaction can also be carried out at elevated temperature using a microwave. Typical conditions comprise of 1.0 equivalent of compound (V) and 5.0-10.0 equivalents of NH_2R^1 in tetrahydrofuran/methanol, at 130°C for 30 minutes, followed by stirring at room temperature for 72 hours.

Compounds of formula (VII) can be prepared from compounds of formula (V) by a cross-coupling reaction with a compound of formula (VIII), where M^1 is suitably trialkyl stannane, dihydroxy borane, dialkoxy borane, lithium, halomagnesium, or halozinc, and preferably dihydroxy borane, in the presence of an appropriate catalyst system (e.g. a palladium or nickel catalyst) and an excess of a suitable base, such as potassium carbonate, potassium fluoride or triethylamine, in a suitable solvent such as dioxan or tetrahydrofuran, at a temperature of from 25°C to reflux, for 1-18 hours. Typical conditions comprise of 1.0 equivalent of compound (V), 1.0-1.1 equivalents of a suitable boronic acid such as benzeneboronic acid or 2,3,5-trichlorobenzeneboronic acid, 3.2-3.3 equivalents of potassium fluoride, *tris*(dibenzylideneacetone) dipalladium(0) (catalytic), and bis(tri-*tert*-butylphosphine) palladium(0) (catalytic) in tetrahydrofuran, under ambient conditions for 18 hours.

Those skilled in the art will appreciate that the type of catalyst that is employed will depend on factors such as the nature of the M^1 group, the substrate employed etc. Examples of such coupling reactions include the so-called "Suzuki" conditions, "Stille" conditions or "Negishi" conditions as described in "Metal Catalysed cross-coupling reactions", edited by F. Diederich, Wiley-VCH 1998 and references therein.

A pyridine derivative of formula (I) may be prepared from a compound of formula (VI) by a cross-coupling reaction with a compound of formula (VIII). The reaction conditions are as described above for process step v.

Alternatively, a pyridine derivative of formula (I) may be prepared by reaction of a compound of formula (VII) with an amine, NH_2R^1. The reaction conditions are as described above for process step iv.

Referring to the general methods above, it will be readily understood to the skilled person that where protecting groups are present, these will be generally interchangeable with other protecting groups of a similar nature, e.g. where an amine is described as being protected with a *tert*-butoxycarbonyl group, this may be readily interchanged with any suitable amine protecting group. Suitable protecting groups are described in 'Protective Groups in Organic Synthesis' by T. Greene and P. Wuts (3rd edition, 1999, John Wiley and Sons).

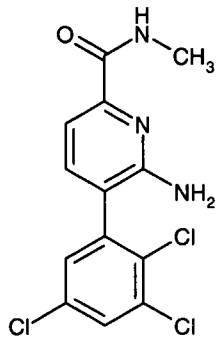
The present invention also relates to novel intermediate compounds of formulae (V), (VI) and (VII) as defined above, all salts, solvates and complexes thereof and all solvates and complexes of salts thereof as defined hereinbefore for pyridine derivatives of formula (I). The invention includes all polymorphs of the aforementioned species and crystal habits thereof.

When preparing pyridine derivatives of formula (I) in accordance with the invention, it is open to a person skilled in the art to routinely select the form of compound of formulae (V), (VI) or (VII) which provides the best combination of features for this purpose. Such features include the melting point, solubility, processability and yield of the intermediate form and the resulting ease with which the product may be purified on isolation.

The following Examples illustrate the preparation of pyridine derivatives of the formula (I).

Example 1

6-Amino-5-(2,3,5-trichloro-phenyl)-pyridine-2-carboxylic acid methylamide



A solution of bis(tri-*tert*-butylphosphine)palladium(0) (135mg, 0.27mmol) in tetrahydrofuran (11mL) was added to a mixture of the product of preparation 4 (1.36g, 5.92mmol), potassium fluoride (1.14g, 19.55mmol), 2,3,5-trichlorobenzeneboronic acid (1.46g, 6.51mmol) and *tris*(dibenzylideneacetone)dipalladium(0) (81mg, 0.09mmol) in tetrahydrofuran (27mL) and the reaction mixture was stirred under nitrogen for 18 hours at room temperature. The mixture was then filtered through Arbocel® and washed with tetrahydrofuran. The filtrate was concentrated *in vacuo* and purified by column chromatography on silica gel, eluting with heptane:ethyl acetate, 50:50, to afford the title compound as a white solid in 80% yield, 1.57g.

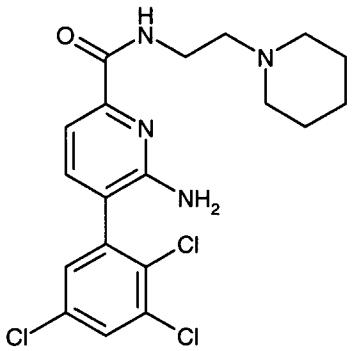
^{1}H NMR (400MHz, CD_3OD) δ: 2.94(s, 3H), 7.33(d, 1H), 7.41(dd, 2H), 7.68(d, 1H)

LRMS: m/z APCI 330 $[M+H]^+$

Microanalysis: $C_{13}H_{10}Cl_3N_3O$ requires: C 47.23; H 3.05 N 12.71; found C 47.15; H 3.18, N 12.55

Example 2

6-Amino-5-(2,3,5-trichloro-phenyl)-pyridine-2-carboxylic acid (2-piperidin-1-yl-ethyl)-amide



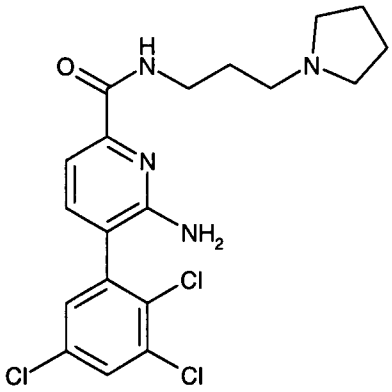
A solution of 1-(2-aminoethyl)piperidine (0.60g, 4.71mmol) in tetrahydrofuran (2.4mL) was added to a suspension of the product of preparation 3 (0.16g, 0.47mmol) in methanol (4mL) and tetrahydrofuran (2mL) and the mixture was heated at 50°C for 72

hours. The reaction mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol, 90:10 to afford the title compound as a yellow solid in 92% yield, 0.19g.

^{1}H NMR (400MHz, CD_3OD) δ: 1.45-1.54(m, 2H), 1.60-1.69(m, 4H), 2.53-2.66(m, 6H), 3.58(t, 2H), 7.33(d, 1H), 7.42(dd, 2H), 7.69(d, 1H) LRMS: m/z APCI 427 $[M+H]^+$ Microanalysis: $C_{19}H_{21}Cl_3N_4O$ 0.5 H_2O requires: C 52.25; H 5.08 N 12.83; found C 52.52; H 4.96, N 12.87

Example 3

6-Amino-5-(2,3,5-trichloro-phenyl)-pyridine-2-carboxylic acid (3-pyrrolidin-1-yl-propyl)-amide

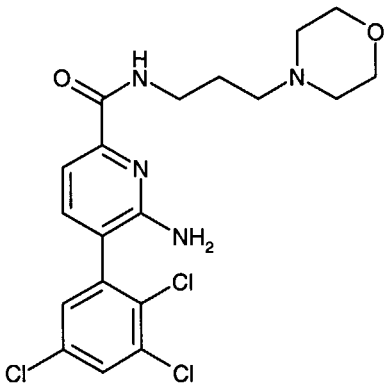


The title compound was prepared from the product of preparation 3 and 1-(3-aminopropyl)pyrrolidine, using a method analogous to that of example 2. The crude compound was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 ammonia, 90:10:1, followed by trituration with diethyl ether to afford the desired product in 60% yield, 61.5mg.

^{1}H NMR (400MHz, CD_3OD) δ: 1.81-1.92(m, 6H), 2.65-2.75(m, 6H), 3.44-3.50(m, 2H), 7.33(d, 1H), 7.42(dd, 2H), 7.70(d, 1H) LRMS: m/z APCI 427 $[M+H]^+$ Microanalysis: $C_{19}H_{21}Cl_3N_4O$ 0.5 H_2O requires: C 52.25; H 5.08 N 12.83; found C 52.02; H 4.86, N 12.61

Example 4

6-Amino-5-(2,3,5-trichloro-phenyl)-pyridine-2-carboxylic acid (3-morpholin-4-yl-propyl)-amide

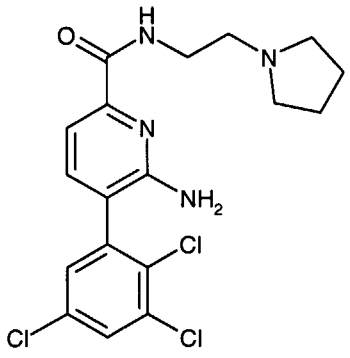


A solution of 2-(4-morpholino)propylamine (87mg, 0.6mmol) in methanol (0.5mL) was added to a solution of the product of preparation 3 (20mg, 0.06mmol) in tetrahydrofuran (0.5mL) and the mixture was stirred at room temperature for 72 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol, 90:10, to afford the title compound in 71% yield, 19mg.

^{1}H NMR (400MHz, CD_3OD) δ: 1.80-1.88(m, 2H), 2.43-2.53(m, 6H), 3.45(m, 2H), 3.65(m, 4H), 7.33(d, 1H), 7.42(dd, 2H), 7.70(d, 1H) LRMS: m/z APCI 443 $[M+H]^+$

Example 5

6-Amino-5-(2,3,5-trichloro-phenyl)-pyridine-2-carboxylic acid (2-pyrrolidin-1-yl-ethyl)-amide



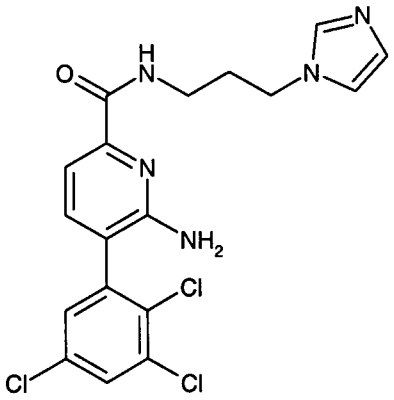
A mixture of the product of preparation 3 (20mg, 0.06mmol) and 1-(2-aminoethyl)pyrrolidine (69mg, 0.6mmol) in tetrahydrofuran (0.5mL) and methanol (0.5mL) was placed in a microwave tube and heated in a microwave for 30 minutes at 130°C. The mixture was then stirred at room temperature for 72 hours before the

solvent was evaporated under reduced pressure. Purification by column chromatography on silica gel, eluting with dichloromethane:methanol, 90:10, afforded the title compound in 88% yield, 22mg.

^{1}H NMR (400MHz, CD_3OD) δ: 1.80-1.90(m, 4H), 2.65(m, 4H), 2.75(t, 2H), 3.59(m, 2H), 7.34(d, 1H), 7.42(dd, 2H), 7.69(d, 1H) LRMS: m/z APCI 413 $[M+H]^+$

Example 6

6-Amino-5-(2,3,5-trichloro-phenyl)-pyridine-2-carboxylic acid (3-imidazol-1-yl-propyl)-amide

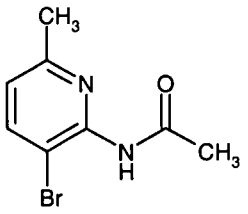


1-(3-Aminopropyl)imidazole (0.28mL, 2.42mmol) was added to a solution of the product of preparation 3 (122.6mg, 0.37mmol) in tetrahydrofuran (4mL) and methanol (0.5mL) and the mixture was heated at 65^{0}C for 18 hours and at 75°C for 72 hours. The reaction mixture was then concentrated *in vacuo* and purified by column chromatography on silica gel, eluting with dichloromethane:methanol:0.88 ammonia, 90:10:0.1, followed by trituration in dichloromethane/diethyl ether to afford the title compound as a white solid in 70% yield, 110mg.

^{1}H NMR (400MHz, CD_3OD) δ: 2.11(m, 2H), 3.42(m, 2H), 4.12(m, 2H), 6.97(s, 1H), 7.20(s, 1H), 7.34(d, 1H), 7.43(dd, 2H), 7.69(d, 1H), 7.72(d, 1H) LRMS: m/z APCI 424 $[M+H]^+$ Microanalysis: $C_{18}H_{16}Cl_3N_5O$ 0.25 H_2O requires: C 50.37; H 3.87 N 16.32; found C 50.36; H 3.84, N 16.15

Preparation 1

N-(3-Bromo-6-methyl-pyridin-2-yl)-acetamide



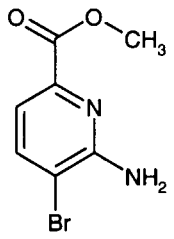
Acetic anhydride (21mL, 223mmol) was added to a solution of 2-amino-3-bromo-6-picoline (10g, 53.46mmol) in dioxan (50mL) and the mixture was stirred at 50°C for 18 hours. The solvent was then evaporated under reduced pressure and the residue was diluted with saturated sodium hydrogen carbonate solution (150mL). The precipitate was filtered off, washed with water and re-dissolved in dichloromethane, and the filtrate was neutralised to pH7 with saturated sodium hydrogen carbonate solution and extracted with dichloromethane (3x100mL). The organic solutions were combined, washed with water, dried over magnesium sulfate and concentrated *in vacuo* to give a white solid. Purification of the solid by column chromatography on silica gel, eluting with ethyl acetate:heptane, 75:25, afforded the title compound as a white solid in 75% yield, 9.2g.

^{1}H NMR (400MHz, CD_3OD) δ: 2.17(s, 3H), 2.49(s, 3H), 7.09(d, 1H), 7.94(d, 1H)

LRMS: m/z APCI 231 $[M+H]^+$ Microanalysis: $C_8H_9BrN_2O$ requires: C 41.95; H 3.96 N 12.23; found C 41.92; H 3.91, N 12.16

Preparation 2

6-Amino-5-bromo-pyridine-2-carboxylic acid methyl ester



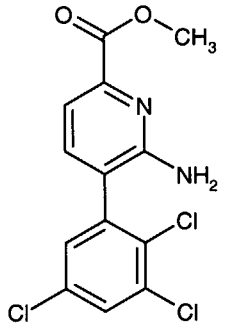
Potassium permanganate (9.77g, 61.81mmol) was added portionwise to a solution of the product of preparation 1 (4.8g, 20.95mmol) in water (100mL) and pyridine (8 drops) and the mixture was heated at 75°C for 18 hours. Further potassium permanganate (3.31g, 61.81mmol) was then added to the mixture and stirring continued at 75°C for 18 hours. The reaction mixture was then filtered through Celite® and the filtrate was washed with ethyl acetate (6x50mL). The aqueous solution was concentrated *in vacuo* to give a pale yellow solid that was azeotroped with toluene (5x50mL) at 50°C to afford the crude potassium salt as an intermediate. The

intermediate was then dissolved in methanol (400mL) and heated under reflux. Concentrated sulphuric acid (5mL) was added to the mixture and heating continued for 2 days. The solvent was then evaporated under reduced pressure and the residue was basified to pH8 with a saturated sodium hydrogen carbonate solution (150mL) and extracted with dichloromethane (3x50mL). The combined organic solutions were dried over magnesium sulfate and concentrated *in vacuo* to afford the title compound as a pale yellow solid in 34% yield, 1.65g.

^{1}H NMR (400MHz, CD_3OD) δ: 3.90(s, 3H), 7.25(d, 1H), 7.88(d, 1H) LRMS: m/z ES 233 $[M+H]^+$ Microanalysis: $C_7H_7BrN_2O_2$ requires: C 36.39; H 3.05 N 12.12; found C 36.24; H 3.08, N 11.94

Preparation 3

6-Amino-5-(2,3,5-trichloro-phenyl)-pyridine-2-carboxylic acid methyl ester

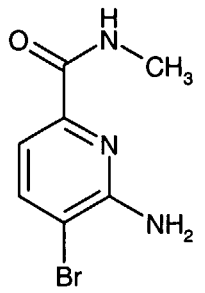


A solution of bis(tri-*tert*-butylphosphine)palladium(0) (9.3mg, 0.18mmol) in tetrahydrofuran (2mL) was added to a mixture of the product of preparation 2 (0.21g, 0.90mmol), potassium fluoride (0.17g, 2.86mmol), 2,3,5-trichlorobenzeneboronic acid (0.21g, 0.95mmol) and *tris*(dibenzylideneacetone)dipalladium(0) (9.3mg, cat.) in tetrahydrofuran (4mL) and the reaction mixture was stirred under nitrogen for 18 hours at room temperature. The mixture was then diluted with diethyl ether, filtered through Arbocel® and washed with further diethyl ether. The filtrate was concentrated *in vacuo* and purified by column chromatography on silica gel, eluting with heptane:ethyl acetate, 66:33, to afford the title compound as a white solid in 83% yield, 0.25g.

^{1}H NMR (400MHz, CD_3OD) δ: 3.94(s, 3H), 7.35(d, 1H), 7.48(m, 2H), 7.70(d, 1H) LRMS: m/z APCI 331 $[M+H]^+$ Microanalysis: $C_{13}H_9Cl_3N_2O_2$ requires: C 47.09; H 2.74 N 8.45; found C 47.05; H 2.80, N 8.51

Preparation 4

6-Amino-5-bromo-pyridine-2-carboxylic acid methylamide



Methylamine (2M, in tetrahydrofuran, 36.8mL, 73.64mmol) was added to a suspension of the product of preparation 2 (1.70g, 7.36mmol) in methanol (10mL) and the mixture was stirred for 18 hours at room temperature. The reaction mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on silica gel, eluting with ethyl acetate:heptane, 75:25, to afford the title compound as a solid in 96% yield, 1.63g.

^{1}H NMR (400MHz, CD_3OD) δ: 2.90(s, 3H), 7.20(d, 1H), 7.82(d, 1H) LRMS: m/z APCI 231 $[M+H]^+$ Microanalysis: $C_7H_8BrN_3O$ requires: C 36.55; H 3.50 N 18.26; found C 36.50; H 3.47, N 18.12

^{1}H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The mass spectra (m/z) were recorded using either electrospray ionisation (ESI) or atmospheric pressure chemical ionisation (APCI). The following abbreviations have been used for common solvents: CD_3OD, deuteromethanol; THF, tetrahydrofuran. 'Ammonia' refers to a concentrated solution of ammonia in water possessing a specific gravity of 0.88.

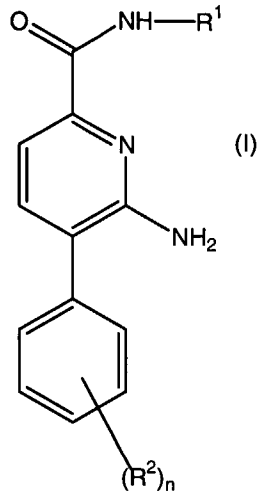
Microwave radiation was provided using the Emrys Creator or the Emrys Liberator, both suplied by Personal Chemistry Ltd. The power range is 15-300W at 2.45GHz. The actual power supplied varies during the course of the reaction to maintain a constant temperature.

All the compounds of the Examples have been tested in the assay described on pages 34-38 and found to have an affinity for the $Na_{V1.8}$ channel of less than 10μM. In particular, Examples 1 and 7 had binding affinities of 2.04 and 5.48 μM respectively.

All the compounds of the Examples have been found to have at least a 2-fold selectivity for the $Na_{V1.8}$ channel over the TTX-S sodium channels, using the test method described on page 38.

CLAIMS

1. A compound of the formula:



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is $(C_1\text{-}C_6)$alkyl optionally substituted with Het^1, Het^2 or $(C_3\text{-}C_7)$cycloalkyl, wherein said Het^1, Het^2 and $(C_3\text{-}C_7)$cycloalkyl are optionally substituted on a ring carbon atom by one or more substituents each independently selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy and halo$(C_1\text{-}C_4)$alkyl;

each R^2 is independently selected from fluoro, chloro, bromo and iodo;

n is 1, 2 or 3;

Het^1 is a 5- or 6-membered saturated or partially unsaturated heterocyclic group comprising one or two heteroatom ring members each independently selected from nitrogen, oxygen and sulphur, said ring nitrogen atom optionally bearing a $(C_1\text{-}C_4)$alkyl substituent and said ring sulphur atom optionally bearing 1 or 2 oxygen atoms; and

Het^2 is a 5- or 6-membered heteroaryl group comprising either (a) from 1 to 4 nitrogen atoms or (b) one oxygen or one sulphur atom and 0, 1 or 2 nitrogen atoms.

2. A compound according to claim 1, wherein each R^2 is chloro.

3. A compound according to claim 1 or claim 2, wherein n is 3.

4. A compound according to claim 3, wherein the R^2 groups are in the 2, 3 and 5-positions on the phenyl ring.

5. A compound according to any one of claims 1 to 4, wherein R^1 is $(C_1\text{-}C_6)$alkyl, optionally substituted with piperidinyl, imidazolyl, morpholinyl, piperazinyl or pyrrolidinyl.

6. A compound according to any one of claims 1 to 5, wherein R^1 is methyl.

7. A pharmaceutical composition including a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof, as defined in any one of claims 1 to 6, together with one or more pharmaceutically acceptable excipients.

8. A compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in any one of claims 1 to 6, for use as a medicament.

9. The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate or composition thereof, as defined in any one of claims 1 to 6 and 7 respectively, for the manufacture of a medicament for the treatment of a disease or condition for which a $Na_{V1.8}$ channel modulator is indicated.

10. The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate or composition thereof, as defined in any one of claims 1 to 6 and 7 respectively, for the manufacture of a medicament for the treatment of disease or condition selected from the group consisting of pain, acute pain, chronic pain, inflammatory pain, neuropathic pain, visceral pain, nociceptive pain, multiple sclerosis, neurodegenerative disorder, irritable bowel syndrome, osteoarthritis, rheumatoid arthritis, neuropathological disorders, functional bowel disorders, inflammatory bowel diseases, pain associated with dysmenorrhea, pelvic pain, cystitis, pancreatitis, migraine, cluster and tension headaches, diabetic neuropathy, sciatica, fibromyalgia and causalgia.

11. The use according to claim 10, wherein the disease or condition is selected from the group consisting of pain, acute pain, chronic pain, neuropathic pain, peripheral neuropathic pain and osteoarthritis.

12. A method of treating a disease or condition for which a $Na_{V1.8}$ channel modulator is indicated in a mammal, including a human, including administering to a mammal requiring such treatment an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate or composition thereof, as defined in any one of claims 1 to 6 and 7 respectively.

13. A method of treating a disease or condition selected from the group consisting of pain, acute pain, chronic pain, inflammatory pain, neuropathic pain, visceral pain, nociceptive pain, multiple sclerosis, neurodegenerative disorder, irritable bowel syndrome, osteoarthritis, rheumatoid arthritis, neuropathological disorders, functional bowel disorders, inflammatory bowel diseases, pain associated with dysmenorrhea, pelvic pain, cystitis, pancreatitis, migraine, cluster and tension headaches, diabetic neuropathy, sciatica, fibromyalgia and causalgia, including administering to a mammal requiring such treatment an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate or composition thereof, as defined in any one of claims 1 to 6 and 7 respectively.

14. A method according to claim 13, wherein the disease or condition is selected from the group consisting of pain, acute pain, chronic pain, neuropathic pain, peripheral neuropathic pain and osteoarthritis.

15. A combination of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in any one of claims 1 to 6, and another pharmacologically active agent.