Title: PYRIDINE DERIVATIVES AS SODIUM CHANNEL MODULATORS

Abstract: The present invention relates to compounds of the formula (I) and pharmaceutically acceptable salts and solvates thereof, to processes for the preparation of, intermediates used in the preparation of, and compositions containing such compounds and the uses of such compounds for the treatment of pain.
PYRIDINE DERIVATIVES AS SODIUM CHANNEL MODULATORS

This invention relates to pyridine derivatives. More particularly, this invention relates to 6-amino-5-aryl-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 Na\textsubscript{i.s} modulators.

The Na\textsubscript{i.s} 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, 257-262; Pain 1998, 78(2), 107-14. The Na\textsubscript{i.s} channel was previously known as SNS (sensory neurone specific) and PN3 (peripheral nerve type 3). The Na\textsubscript{i.s} 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\textsubscript{i.s} channel is the Na\textsubscript{i.B} channel, which is the cardiac sodium channel, with which it shares approximately 60% homology. The Na\textsubscript{i.B} 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\textsubscript{i.s} channel is not expressed anywhere other than subpopulations of DRG neurones. The Na\textsubscript{i.1.8} channels are thought to contribute to the process of DRG sensitisation and also to hyperexcitability due to nerve injury. Inhibitory modulation of the Na\textsubscript{i.1.8} channels is aimed at reducing the excitability of nociceptors, by preventing them from contributing to the excitatory process.

Studies have shown that Na\textsubscript{i.s} knock-out leads to a blunted pain phenotype, mostly to inflammatory challenges (A.N. Akopian et al., Nat. Neurosci. 1999, 2, 541-548) and that Na\textsubscript{i.s} knockdown reduces pain behaviours, in this case neuropathic pain (J. Lai et al., Pain, 2002, 95(1-2), 143-52). Coward et al. and Yiangou et al., have shown that Na\textsubscript{i.s} appears to be expressed in pain conditions (Pain, 2000, 85(1-2), 41-50 and FESS Lett. 2000, 11, 467(2-3), 249-52).


Several sodium channel modulators are known for use as anticonvulsants or antidepressants, such as carbamazepine, amitriptyline, lamotrigine and riluzole, all of which target brain tetrodotoxin-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\textsubscript{j,s} channel modulators that are good drug candidates. Preferred compounds should bind potently to the Na\textsubscript{j,β} channel and show functional activity as Na\textsubscript{j,β} 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.

The present invention therefore provides pyridine derivatives which are 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, causalgia, and conditions of lower urinary tract dysfunction.

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

![Pyridine derivative](image)

or a pharmaceutically acceptable salt or solvate thereof,

wherein;

R\textsuperscript{1} is hydrogen and

R\textsuperscript{2} is (C\textsubscript{1}-C\textsubscript{6})alkyl, optionally substituted with one or more substituents selected from hydroxy, (C\textsubscript{1}-C\textsubscript{6})alkoxy, halogen, halo(C\textsubscript{1}-C\textsubscript{6})alkyl and (C\textsubscript{3}-C\textsubscript{8})cycloalkyl; or

R\textsuperscript{1} and R\textsuperscript{2} may be taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered saturated or partially unsaturated heterocyclic ring optionally comprising one or two additional heteroatom ring members each independently selected from nitrogen, oxygen and sulphur, said ring
nitrogen atom optionally bearing a \((\text{CrC}_x)\)alkyl substituent and said ring sulphur atom optionally bearing 1 or 2 oxygen atoms;

\(X\) is sulphur or \(\text{NR}^3\);

\(\text{R}^3\) is hydrogen, \((\text{C}_r \text{C}_s)\)alkyl, or cyano; or, where \(\text{R}^1\) and \(\text{R}^2\) are not taken together to form a ring, \(\text{R}^1\) and \(\text{R}^2\) may be taken together with the N-C=N group to which they are attached to form a 5- or 6- membered aromatic or partially unsaturated heterocyclic ring optionally comprising one or two additional nitrogen atoms;

\(\text{R}^4\) is phenyl, naphthalenyl or azanaphthalenyl, each optionally substituted with one or more substituents \(\text{R}^5\); and each \(\text{R}^5\) is independently selected from halogen, \((\text{Ci-C}_6)\)alkoxy, \((\text{Ci-C}_6)\)alkyl, halo\((\text{CrC}_e)\)alkyl, cyano, cyclopropyl and methylcyclopropyl;

or where \(\text{R}^4\) is phenyl, two adjacent \(\text{R}^5\) groups may be taken together with the carbon atoms to which they are attached to form a 5- or 6-membered saturated or partially unsaturated heterocyclic ring comprising one or two heteroatom ring members each independently selected from nitrogen, oxygen and sulphur, said ring nitrogen atom optionally bearing a \((\text{Ci-C}_6)\)alkyl substituent and said ring sulphur atom optionally bearing 1 or 2 oxygen 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 haloalkyl include trifluoromethyl. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Specific examples of 5- or 6-membered saturated or partially unsaturated heterocyclic rings include pyrrolidinyl, piperidinyl, morpholiny1, thiomorpholiny1 and piperaziny1, (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 \(\text{R}^1\) is hydrogen and \(\text{R}^2\) is \((\text{C}_r \text{C}_s)\)alkyl or halo \((\text{C}_t \text{C}_\tau)\)alkyl; or \(\text{R}^1\) and \(\text{R}^2\) are taken together with the nitrogen atom to which they are attached to form a morpholine or piperazine ring; and \(X, \text{R}^3, \text{R}^4\) and \(\text{R}^5\) are as defined above.

In a preferred aspect (B), the invention provides a pyridine derivative of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein \(X\) is \(\text{NR}^3\) and \(\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4\) and \(\text{R}^5\) are as defined above, either in the broadest aspect or in a preferred aspect under (A).

In a preferred aspect (C), the invention provides a pyridine derivative of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein \(\text{R}^3\) is cyano, methyl or ethyl; and \(X, \text{R}^1, \text{R}^2, \text{R}^4\) and \(\text{R}^5\) are as defined above, either in the broadest aspect or in a preferred aspect under (A) or (B).
In a preferred aspect (D), the invention provides a pyridine derivative of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is phenyl, optionally substituted with one or more substituents R^5 wherein each R^6 is independently selected from halogen, (Cl-C_6)alkoxy, (C_1-C_6)alkyl, haloc(C_1-C_6)alkyl, cyano, cyclopropyl and methycyclopropyl; more preferably R^4 is phenyl substituted by from one to three substituents R^5; more preferably still each R^6 is halogen; most preferably R^4 is 2,5-dichlorophenyl or 2,3,5-trichlorophenyl; and X, R^1, R^2 and R^3 are each as defined above, either in the broadest aspect or in a preferred aspect under (A) (B) or (C).

Specific preferred pyridine derivatives according to the invention are those listed in the Examples section below and the pharmaceutically acceptable salts and solvates thereof.

The compounds of formula (I), being Na/<s>_16</s> 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 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, post herpetic 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 heightened 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, gastroesophageal 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 musculoskeletal disorders, including myalgia, fibromyalgia, spondylitis, seronegative (non-rheumatoid) arthropathies, non-articular rheumatism, dystrophinopathy, glycogenosis, polymyositis and pyomyositis;
• heart and vascular pain, including pain caused by angina, myocardial infarction, mitral stenosis, pericarditis, Raynaud's phenomenon, sclerodema 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 embolus, 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.

The compounds of the present invention are useful in the treatment of conditions of lower urinary tract dysfunction including but not exclusively restricted to overactive bladder, increased daytime frequency, nocturia, urgency, urinary incontinence (any condition in which there is an involuntary leakage of urine), including stress urinary incontinence, urge urinary incontinence and mixed urinary incontinence, overactive bladder with associated urinary incontinence, enuresis, nocturnal enuresis, continuous urinary

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, camyslate, 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;
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

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°, -COOK °, or -SO3Na°) or non-ionic (such as -NN+(CH3)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 (-NH₂ 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 (C₁-C₅)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 (-CH₃ -> -CH₂OH);

(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 (-NHR¹ -> -NH₂);

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

Compounds of formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. 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 /-lysine, or racemic, for example, (//-tartrate or d/-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, $^{12}$C and $^{14}$C, chlorine, such as $^{35}$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-labelled 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-labelled reagent in place of the non-labelled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. $D_2$O, $d_6$-acetone, $d_6$-DMSO.

Also within the scope of the invention are intermediate compounds 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).

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; film's; 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, H (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.


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.

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(\(d/-lactic\)-coglycolic)acid (PGLA) microspheres.

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.

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-heptfluoropropane, 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". The overall daily dose may be administered in a single dose or, more usually, as divided doses throughout the day.

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.
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 cellulotic 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.

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 91/11 172, WO 94/02518 and WO 98/55148.

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. 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 \( \text{Na}_\text{v},1.8 \) 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 Navi,\( \beta \) 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, naloxone, nalorphine, naltrexone, buprenorphine, butorphanol, nalbuphine or pentazocine;
- a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflunisal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mafenamic acid, meloxicam, nabumetone, naproxen, nimesulide, nitrofurinoprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolfenamic, or zomepirac;
- a barbiturate sedative, e.g. amobarbital, aprobarbital, butobarbital, butalbital, mephobarbital, methobarbital, methohexital, pentobarbital, phenobarbital, secobarbital, talbutal, theamylal or thiopental;
- a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;
- an \( \text{H}_1 \) antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;
- a sedative such as glutethimide, mepromamine, methaqualone or dichloralphenazone;
- a skeletal muscle relaxant, e.g. baclofen, carisoprodol, clorazapate, cyclobenzaprine, methocarbamol or orphenadrine;
- an NMDA receptor antagonist, e.g. dextromethorphan (\((\pm)-3\)-hydroxy-N-methylmorphinan) or its metabolite dextropropoxyphene (\((\pm)-3\)-hydroxy-N-methylmorphinan), ketamine, memantine, pyroloquinoline quinine, cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid, budipine, EN-3231 (MorphiDex\textsuperscript{\textregistered}, a combination formulation of morphine and dextromethorphan), topiramate, neramexane or perizinfotol including an NR2B antagonist, e.g. ifenprodil, traxoprodil or (-)-(R)-6-\( \text{H} \)2-[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]-1-hydroxymethyl-3,4-dihydro-2(1\( \text{H} \))-quinolinone;
- an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dextemetamidone, modafinil, or 4-amino-6,7-dimethoxy-2-(5-methane-sulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinaizoline;
- a tricyclic antidepressant, e.g. desipramine, imipramine, amitriptyline or nortriptyline;
- an anticonvulsant, e.g. carbamazepine, lamotrigine, topiramate or valproate;
- a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. \((\alpha R,9 R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,1\text{-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-}
[1,4]diazocino[2, 1-g][1,7]-naphthyridine-6-1 3-dione (TAK-637), 5-[[2R,3S]-2-\{(1 R)-1-[3,5-
bisOrifluoromethylJphenylJethoxy-S\(^{\wedge}\)fluorophenylH-morpholinyO-methyO-i\(^{-}\)dihydro-SH-i\(^{-}\)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, tropium chloride, darifenacin, solifenacin, temivine and ipratropium;
- a COX-2 selective inhibitor, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, etorcoixib, 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, raclopride, zipriactone,iperiden, palindore, eplivanserin, osanetant, rimonabant, meclinertant, Miraxion® or sarizotan;
- a vanilloid receptor agonist (e.g. resiferatoxin) 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-piperindinemethanol (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;
- 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-methyleneoxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione (IC-351 or tadafallif), 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-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo[4,3-c]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, (1\(\alpha\),3\(\alpha\),5\(\alpha\))(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-chlorophenox)-proline, (2S,4S)-4-(3-fluorobenzyl)-proline, [(1 R,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, (SS,SRJ-S-amino-5-methyl-octanoic
acid, (3S,5R)-3-amino-5-methyl-nonanoic acid, (SS,SRJ-S-amino-δ-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;
• a metabotropic glutamate subtype 1 receptor (mGluRI) antagonist;
• a serotonin reuptake inhibitor such as sertraline, sertraline metabolite demethylsertraline,
fluoxetine, norfluoxetine (fluoxetine desmethyl metabolite), fluvoxamine, paroxetine, citalopram,
citalopram metabolite desmethylicitalopram, escitalopram, d,l-fenfluramine, fenoxetin, ifoxetine,
cyanothiepin, 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-
desmethylenlafaxine, clomipramine, clomipramine metabolite demethylclomipramine,
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-[(2S)-2,4-difluorophenyl]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 prostanoid E2 subtype 4 (EP4) antagonist such as N-[(2-[2-(ethyl-4,6-dimethyl-1H-imidazol-4,5-c-)]pyridin-1-yl)phenyl]ethyl]amino]-carbonyl]-4,4-methylbenzenesulfonamide or 4-[(1S)-1-((5-chloro-2-(3-fluorophenyl)pyridin-3-yl)carbonyl]amino]ethylbenzoic acid;
• a leukotriene B4 antagonist; such as 1-(3-biphenyl-4-ylmethyl-4-hydroxy-chroman-7-yl)-
cyclopentenecarboxylic acid (CP-1 05696), 5-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-5E-
hexenyl]oxycine]-valeric acid (ONO-4057) or DPC-1 1870,
• 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.

Inasmuch as it may be 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 co-administration 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.

All of the pyridine derivatives of the formula (I) can be prepared by the procedures described in the general methods presented below 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, X, R¹, R², R³ and R⁴ are as previously defined for a pyridine derivative of the formula (I) unless otherwise stated.

According to a first process, when X is sulphur and R¹ is hydrogen, compounds of formula (I) may be prepared from compounds of formula (VIII), as illustrated by Scheme 1.

Scheme 1
wherein \( Y \) is a suitable leaving group, such as trifluoromethanesulfonyl, fluoro, chloro, bromo or iodo;

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

\( R^\alpha \) is a suitable ester group such as \((\text{C}_6\text{H}_5)\text{alkyl}, \text{benzyl}\);

\( M \) is hydrogen or an alkali metal; and

\( M^1 \) is a suitable coupling group such as a stannane, borane, metal or metalhalide.

Step i: 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 1,4-dioxan, at a temperature of from 25 to 50°C for about 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 treating 1.0 equivalent of a compound of formula (II) with an excess of acetic anhydride in 1,4-dioxan, at 50°C for 18 hours.

Step ii: 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 from 3 to 18 hours. Typical conditions comprise treating 1.0 equivalent of a compound of formula (III) with 2.0 to 6.0 equivalents of potassium permanganate, in water, at 80°C for 3 hours.

Step iii: Compounds of formula (V) can be prepared either as described in *J. Org. Chem.* 1996, 61, 4623-4633 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 from 18 to 72 hours. Removal of the amine protecting group (PG) occurs concomitantly under these conditions. Typical conditions comprise treating 1.0 equivalent of compound (IV) with an excess of methanol, in the presence of concentrated sulfuric acid, and heating under reflux for 48 hours.

Alternatively, compounds of formula (V) can be prepared from compounds of formula (III) by a combination of steps ii and iii. Typical conditions comprise treating 1.0 equivalent of a compound of formula (III) with 2.0 to 6.0 equivalents of potassium permanganate, in water, at 80°C for 3 hours.

Concentration *in vacuo* is followed by addition of methanol and concentrated sulfuric acid, and heating under reflux for 48 hours to yield the desired product.

Step iv: Compounds of formula (VI) can be prepared by reaction of compounds of formula (V) with an amine, NH₂R², in a suitable solvent, such as dichloromethane or a mixture of tetrahydrofuran/R ⁵OH, at a temperature of from 25°C to reflux, for from 18 to 72 hours. Typical conditions comprise treating 1.0 equivalent of compound (V) with 5.0 to 10.0 equivalents of NH₂R² in tetrahydrofuran/methanol, at a temperature of from 25 to 80°C for from 16 to 72 hours.

Step v: Compounds of formula (VII) can be prepared from compounds of formula (V) by a cross-coupling reaction with a compound of formula (IX), where M¹ 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, cesium carbonate, cesium fluoride or triethylamine, in a suitable solvent such as 1,4-dioxan or tetrahydrofuran, at a temperature of from 25°C to reflux, for from 1 to 18 hours. Typical conditions comprise reacting 1.0 equivalent of a compound of formula (V) with 1.0 to 1.1 equivalents of a suitable boronic acid, such as benzeneboronic acid or 2,3,5-trichlorobenzeneboronic acid, 3.2 to 3.3 equivalents of potassium fluoride, tBu(dibenzylideneacetone) dipalladium(O) (catalytic) or bis(tri-ferf-butylphosphine) palladium(O) (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 $\text{M}^1$ 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 compound of formula (VIII) may be prepared from a compound of formula (VI) by a cross-coupling reaction with a compound of formula (IX). The reaction conditions are as described above for process step v.

Alternatively, a compound of formula (VIII) may be prepared by reaction of a compound of formula (VII) with an amine, $\text{NH}_2\text{R}^2$. The reaction conditions are as described above for process step iv.

Step vi; A compound of formula (I) may be prepared by reaction of a compound of formula (VIII) with a suitable thiolating agent such as Lawesson's reagent (2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulphide) or phosphorous pentasulphide, in a suitable solvent such as toluene, dioxan or pyridine at a temperature of from 70 to 100°C for from 1 to 48 hours. Typical reaction conditions comprise treating a compound of formula (VIII) with 0.6 equivalents of phosphorous pentasulphide in pyridine at 100°C for 24 hours.

According to a second process, when $X$ is $\text{NR}^3$ and $\text{R}^3$ is cyano, compounds of formula (I) may be prepared from other compounds of formula (I) as illustrated by Scheme 2.

Scheme 2
wherein \( R^b \) is \((C_3 C_6) \) alkyl.

Step i: Compounds of formula \((I)\) may be prepared from other thioamide compounds of formula \((I)\) by reaction of the thioamide of formula \((I)\) with cyanamide and a suitable heavy metal salt such as mercury or lead salts in the presence of a suitable base in a suitable solvent. Typical reaction conditions comprise treating the thioamide of formula \((I)\) with cyanamide, mercury acetate and amine base in an organic solvent. Preferred reaction conditions comprise treating the thioamide of formula \((I)\) with 5 equivalents of cyanamide, 2.5 equivalents of mercury (II) acetate and 5 equivalents of diisopropylethylamine in acetonitrile at \( 5^\circ C \) for 16 hours.

Step ii: Compounds of formula \((I)\) may alternatively be prepared from thioamide compounds of formula \((I)\) by first alkylating the sulphur with an alkyl halide and a suitable base to provide a compound of formula \((X)\) according to reaction step (ii) of scheme 2. Typical reaction conditions comprise treating the thioamide of formula \((I)\) with methyl iodide or benzyl bromide and an alkali metal hydride in an organic solvent. Preferred reaction conditions comprise treating the thioamide of formula \((I)\) with 1.05 equivalents of sodium hydride and 1.02 equivalents of methyl iodide in tetrahydrofuran at room temperature.

Step iii: Subsequently the compound of formula \((X)\) may be reacted with cyanamide in a suitable solvent at a temperature of from 30 to \( 70^\circ C \), according to reaction step (iii) of scheme 2, to afford compounds of formula \((I)\). Preferred reaction conditions comprise treating a compound of formula \((X)\) with 1.1 equivalents of cyanamide in tetrahydrofuran at \( 70^\circ C \).

According to a third process, when \( X \) is \( NR^3 \), compounds of formula \((I')\) may be prepared from thioamide compounds of formula \((I)\) as illustrated by Scheme 3.

Scheme 3

\[
\text{D} \xrightarrow{i} \text{X} \xrightarrow{ii} \text{I'}
\]

wherein \( R^b \) is as defined above for Scheme 2.

Compounds of formula \((I')\) wherein \( X \) is \( NR^3 \) may be prepared from thioamide compounds of formula \((I)\) by first alkylating the sulphur using an alkyl halide and a suitable base according to reaction step (ii) of scheme 2. Typical reaction conditions comprise treating the thioamide compound of formula \((I)\) with
methyl iodide or benzyl bromide and an alkali metal hydride in an organic solvent. Preferred reaction
conditions comprise treating the thioamide compound of formula (I) with 1.05 equivalents of sodium
hydride and 1.02 equivalents of methyl iodide in tetrahydrofuran at room temperature.

The S-alkylated intermediate of formula (X) may then be reacted with ammonia or a primary or
secondary amine of formula NHR¹R² without further isolation. Typical reaction conditions comprise
treating the intermediate of formula (X) with an excess of amine in an organic solvent at a temperature of
from ambient temperature to the boiling point of the solvent. Preferred reaction conditions comprise
treating the intermediate of formula (X) with from 1 to 30 equivalents of amine (added as a solution) in
tetrahydrofuran at a temperature of from room temperature to 70°C for from 2 to 24 hours. Where the
amine is ammonia, preferred reaction conditions comprise the addition of ammonia as a solution in
methanol and conducting the reaction in THF at 70°C for 2 hours.

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 ferf-butoxycarbonyl group, this
may be readily interchanged with any suitable amine protecting group. Suitable protecting groups are
Wiley and Sons).

The present invention also relates to certain novel intermediate compounds as defined above, 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.

When preparing compounds of formula (I) in accordance with the invention, it is open to a person skilled
in the art to routinely select the form of the intermediates 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.

It will be appreciated that what the invention provides is as follows:

(i) a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof;
(ii) a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt
or solvate thereof;
(iii) a pharmaceutical composition including a compound of formula (I) or a pharmaceutically
acceptable salt or solvate thereof, together with a pharmaceutically acceptable excipient;
(iv) a compound of formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof,
for use as a medicament;
(v) a compound of formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use in the treatment of a disease or condition for which a Na\textsubscript{v,i}s channel modulator is indicated;

(vi) a compound of formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use in the treatment of pain.

(vii) the use of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament to treat a disease or condition for which a Na\textsubscript{v,i}s channel modulator is indicated;

(viii) the use of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of pain;

(ix) a method of treating a disease or condition for which a Na\textsubscript{v,β} 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;

(x) a method of treating pain 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;

(xi) certain novel intermediates disclosed herein; and

(xii) a combination of a compound of formula (I) and one or more further pharmacologically active compounds.

The invention is illustrated by the following representative Examples:

Example 1

[Chemical structure diagram]

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

Phosphorous pentasulphide (7.0 g, 31.5 mmol) was added to a solution of the amide of Preparation 5 (17.3 g, 52 mmol) in pyridine (200 mL) and the mixture heated at 100°C for 24 hours. The reaction was allowed to cool and the pyridine removed in vacuo. The residue was partitioned between water (750 mL) and ethyl acetate (500 mL). The layers were separated and the aqueous layer extracted with ethyl
acetate (2 x 300 mL). The combined organic extracts were washed with water (400 mL), brine (400 mL) dried (MgSO₄) and the solvent removed in vacuo. The crude product was purified by flash chromatography (20-35% EtOAc / heptane) to afford the title compound (13.6 g) as an orange yellow solid.

\[ ^1H \text{ NMR} (400\text{MHz}, d_6\text{-DMSO}) \delta: 3.17(d, 3H), 5.95(br s, 2H), 7.40-7.45(m, 2H), 7.65(d, 1H), 7.85 (d, 1H) \]

10.5 (br m, 1H)

MS: m/z APCI 346, 348 [MH⁺]

Example 2

6-Amino-N'-cyano-N-methyl-5-(2,3,5-trichlorophenyl)pyridine-2-carboximidamide

Sodium hydride (1.58 g of 60% NaH in mineral oil, 39.5 mmol) was added portionwise over 10 minutes to a solution of the thioamide of Example 1 (13 g, 37.5 mmol) in tetrahydrofuran (150 mL) with the reaction flask being cooled in a water bath. When effervescence had ceased, methyl iodide (2.38 mL, 38.2 mmol) was added and the reaction stirred at room temperature for 10 minutes. Cyanamide (1.73 g, 41.1 mmol) was added and the mixture heated at 70 °C for 5 hours before stirring at room temperature for a further 16 hours. The solvent was removed in vacuo and the residue partitioned between water (500 mL) and ethyl acetate (300 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (2 x 300 mL). The combined organic extracts were washed with brine (200 mL), dried (MgSO₄) and the solvent removed in vacuo. The crude product was purified by flash chromatography (50% EtOAc / heptane) and then recrystallised from isopropanol to afford the title compound (7.3 g) as a white solid.

\[ ^1H \text{ NMR} (400\text{MHz}, d_6\text{-DMSO}) \delta: 2.92(d, 3H), 6.12(br s, 2H), 7.22(d, 1H), 7.42 (d, 2H), 7.54(d, 1H), 7.85 (d, 1H) \]

9.05 (br m, 1H)

MS: m/z APCI 354, 356 [MH⁺]

Example 3

6-Amino-N,N'-dimethyl-5-(2,3,5-trichlorophenyl)-pyridine-2-carboxamidine
Method A
Sodium hydride (12 mg of 60% NaH in mineral oil, 0.30 mmol) was added to a solution of the thioamide of Example 1 (0.100 g, 1.04 mmol) in tetrahydrofuran (2 mL). After 5 minutes methyl iodide (0.018 mL, 0.294 mmol) was added and the reaction stirred at room temperature for 30 minutes. Methylamine (0.158 mL, 2M in THF, 0.32 mmol) was added and the mixture heated at 70°C for 2 hours. The reaction was allowed to cool and was partitioned between water (10 mL) and ethyl acetate (10 mL) and the layers separated. Upon standing, a solid precipitate formed in the aqueous phase. This was collected by filtration and dried to afford the title compound as a white solid (10 mg).

Method B
Sodium hydride (44 mg of 60% NaH in mineral oil, 1.06 mmol) was added to a solution of the thioamide of Example 1 (365 mg, 1.05 mmol) in tetrahydrofuran (10 mL). Once effervescence had ceased the reaction was stirred for a further 5 minutes at room temperature before the addition of methyl iodide solution (0.65 mL, 1:9 v/v in tetrahydrofuran, 1.05 mmol). The reaction was stirred at room temperature for 40 minutes and then methylamine solution (5 mL, 33% in ethanol, excess) was added and the reaction stirred at room temperature for 16 hours. The reaction was evaporated in vacuo and dichloromethane (20 mL) added to the residue. A white precipitate formed and was collected by filtration, the solid was washed with dichloromethane and dried to afford the title compound as a white solid (200 mg, 56%).

\(^1H\) NMR (400MHz, \(d_6\)-DMSO) \(\delta\): 2.80-3.0(br s, 6H), 6.30(br s, 2H), 7.00(m, 1H), 7.40 (s, 1H), 7.45(m, 2H), 7.90 (s, 1H)

MS: m/z APCI 343, 345 [MH]⁺

Example 4

6-(Methylimino-morpholin-4-yl-methyl)-3-(2,3,5-trichloro-phenyl)-pyridin-2-amine
Sodium hydride (6 mg of 60% NaH in mineral oil, 0.15 mmol) was added to a solution of the thioamide of Example 1 (0.05 g, 0.14 mmol) in tetrahydrofuran (1.5 mL). After 15 minutes methyl iodide (0.09 mL, 0.15 mmol) was added and the reaction stirred at room temperature for 20 minutes. Morpholine (0.025 mL, 0.29 mmol) was added and the mixture heated at 70 °C for 3 hours. The reaction was allowed to cool and was partitioned between water (10 mL) and ethyl acetate (10 mL), the layers were separated and the organic layer dried (MgSO₄) and the solvent removed in vacuo to afford a foam which was triturated with pentane and the resulting solid collected by filtration to afford the title compound as a yellow solid (8 mg).

\( ^1H \text{ NMR (400MHz, } d_\text{d}-\text{DMSO})\) \( \delta: 2.75(s, 3H), 3.10(m, 4H), 3.50(m, 4H), 6.00(br s, 2H), 6.45(d, 1H), 7.35(d, 1H), 7.40(d, 1H), 7.80(d, 1H) \)

MS: m/z APCI 399, 401 [MH]+

**Example 5**

6-Amino-N,N'-diethyl-5-(2,3,5-trichloro-phenyl)-pyridine-2-carboxamidine

Sodium hydride (6 mg of 60% NaH in mineral oil, 0.15 mmol) was added to a solution of the thioamide of Example 1 (0.05 g, 0.14 mmol) in tetrahydrofuran (1.5 mL). After 15 minutes methyl iodide (0.09 mL, 0.15 mmol) was added and the reaction stirred at room temperature for 20 minutes. Ethylamine (0.160 mL, 2M in THF, 0.32 mmol) was added and the mixture heated at 70 °C for 3 hours. The reaction was allowed to cool and was partitioned between water (10 mL) and ethyl acetate (10 mL), the layers were separated and the organic layer dried (MgSO₄) and the solvent removed in vacuo. The residue was purified by flash chromatography (CH₂Cl₂ / MeOH / NH₃) to afford the title compound as a yellow solid (2 mg).
Example 6

6-Amino-N-methyl-5-(2,3,5-trichloro-phenyl)-N'-(2,2,2-trifluoro-ethyl)-2-pyridine-2-carboxamidine

Sodium hydride (6 mg of 60% NaH in mineral oil, 0.15 mmol) was added to a solution of the thioamide of Example 1 (0.05 g, 0.14 mmol) in tetrahydrofuran (1.5 mL). After 20 minutes methyl iodide (0.09 mL, 0.15 mmol) was added and the reaction stirred at room temperature for 30 minutes. Trifluoroethylamine (0.023 mL, 0.29 mmol) was added and the mixture heated at 70°C for 3 hours. The reaction was allowed to cool and was partitioned between water (10 mL) and ethyl acetate (10 mL), the layers were separated and the organic layer dried (MgSO₄) and the solvent removed in vacuo. The residue was azeotroped with diethylether and triturated with pentane to afford the title compound as a buff solid (12 mg).

1H NMR (400MHz, d₆-DMSO) δ: 2.70(br s, 3H), 3.80(br m, 2H), 6.00(s, 2H), 6.60(d, 1H), 6.70(br s, 1H), 7.40(m, 2H), 7.80 (s, 1H).

LCMS: retention time 2.5 minutes m/z APCI 409, 411 [MH]⁺

Example 7

6-Amino-N-methyl-5-(2,3,5-trichloro-phenyl)-2-pyridine-2-carboxamidine

Sodium hydride (6 mg of 60% NaH in mineral oil, 0.15 mmol) was added to a solution of the thioamide of Example 1 (0.05 g, 0.14 mmol) in tetrahydrofuran (1.5 mL). After 15 minutes methyl iodide (0.09 mL, 0.15 mmol) was added and the reaction stirred at room temperature for 30 minutes. Ammonia solution (0.05 mL, 7N NH₃ in methanol, 0.35 mmol) was added and the mixture heated at 70°C for 2 hours. The reaction was allowed to cool and was partitioned between water (10 mL) and ethyl acetate (10 mL), the
layers were separated and the organic layer dried (MgSC\(_4\)) and the solvent removed in vacuo. The residue was triturated with pentane to afford the title compound as a pale yellow solid (15 mg).

\(^1\)H NMR (400MHz, d\(_6\)-DMSO) \(\delta\): 3.00(s, 3H), 6.20(br s, 2H), 7.35(d, 1H), 7.40(d, 1H), 7.60(d, 1H), 7.90 (d, 1H).

MS m/z APCI 329, 331 [MH]\(^+\)

The following Preparations illustrate the synthesis of certain intermediates used in the preparation of the preceding Examples:

Preparation 1

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

Acetic anhydride (21 ml, 223 mmol) was added to a solution of 2-amino-3-bromo-6-picoline (10 g, 53.46 mmol) in 1,4-dioxan (50 ml) 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 (150 mL). 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 (3x100 mL). The organic solutions were combined, washed with water, dried sulphate (MgSO\(_4\)) 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, 9.2 g.

\(^1\)H NMR (400MHz, CD\(_3\)OD) \(\delta\): 2.17(s, 3H), 2.49(s, 3H), 7.09(d, 1H), 7.94(d, 1H) LRMS: m/z APCI 231 [MH]\(^+\)

Microanalysis: C\(_8\)H\(_9\)BrN\(_2\)O requires: C 41.95; H 3.96 N 12.23; found C 41.92; H 3.91, N 12.16

Preparation 2

\[
6-Amino-5-bromo-pyridin e-2-carboxvlic acid methyl ester
\]

Potassium permanganate (144 g, 916 mmol) solution in water (1.4 L) was added dropwise over 45 minutes to a solution of the product of Preparation 1 (60 g, 262 mmol) in water (1.8 L) at 8°C. The mixture was stirred at 8°C for 3 hours and then sodium sulphite solution (200 mL, 1N aqueous, 200 mmol) was added dropwise and the mixture filtered through Arbocel® whilst still hot. The mixture was
concentrated in vacuo to 1 L total volume and then extracted with ethyl acetate (8 x 400 mL). The aqueous was then concentrated to dryness in vacuo and azeotroped with methanol (3 x 250 mL). The resulting off-white solid was slurried in methanol (800 mL) and concentrated sulphuric acid (30 mL) added dropwise. The mixture was heated at 80°C for 16 hours before filtering and evaporating to dryness in vacuo. The residue was dissolved in water (600 mL), basified with sodium bicarbonate solution and then extracted with ethyl acetate (3 x 400 mL). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo to afford the title compound as a white solid in 26% yield, 15.8g.

₁H NMR (400MHz, CD₃OD) δ: 3.90(s, 3H), 7.25(d, 1H), 7.88(d, 1H)

LRMS: m/z ES 232 [MH]⁺

Microanalysis: C₇H₉BrN₂O₂ 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

The product of Preparation 2 (1.0 g, 4.33 mmol), tri-tert-butylphosphine tetrfluoroborate (30 mg, 0.09 mmol), 2,3,5-trichlorobenzeneboronic acid (1.12 g, 4.98 mmol), potassium fluoride (0.805 g, 13.8 mmol) and tris(dibenzylideneacetone)dipalladium(0) (80 mg, 0.09 mmol) were combined and purged under nitrogen. Tetrahydrofuran (10 mL) was added and the reaction mixture was stirred under nitrogen for 16 hours at room temperature. The mixture was then concentrated in vacuo to afford a brown solid. The residue was slurried in water (15 mL) for 15 minutes and filtered to furnish a brown solid which was slurried in a mixture of ethyl acetate (15 mL) and diethylether (10 mL) for 1 hour. The suspension was filtered to afford a grey solid which was slurried in toluene (25 mL) and heated to reflux before filtering hot through Arbocel®. The filtrate was concentrated to dryness in vacuo to afford the title compound as a white solid in 70% yield, 1.0 g.

₁H NMR (400MHz, CD₃OD) δ: 3.94(s, 3H), 7.35(d, 1H), 7.48(m, 2H), 7.70(d, 1H) LRMS: m/z APCI 331 [MH]⁺

Microanalysis: C₁₃H₉Cl₃N₂O₂ requires: C 47.09; H 2.74 N 8.45; found C 47.05; H 2.80, N 8.51
Preparation 4
e-Amino-δ-bromo-pyridine-carboxylic acid methylamide

Methylamine (2M, in tetrahydrofuran, 43 mL, 86 mmol) was added to a suspension of the product of Preparation 2 (2.0 g, 8.66 mmol) in methanol (15 mL) and the mixture was stirred for 18 hours at room temperature. The reaction mixture was then concentrated in vacuo and the residue was triturated with a mixture of ethyl acetate (10 mL) and heptane (70 mL). The resulting solid was collected by filtration to afford the title compound as a pale solid (1.8 g).

1H NMR (400MHz, CD3OD) δ: 2.90(s, 3H), 7.20(d, 1H), 7.82(d, 1H)

LRMS: m/z APCI 231 [MH]+

Microanalysis: C7H8BrN3O requires: C 36.55; H 3.50; N 18.26; found C 36.50; H 3.47, N 18.12

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

Method 1
A solution of bis(tri-terf-butylphosphine) palladium(0) (135 mg, 0.27 mmol) in tetrahydrofuran (11 mL) was added to a mixture of the product of Preparation 4 (1.36 g, 5.92 mmol), potassium fluoride (1.14 g, 19.55 mmol), 2,3,5-trichlorobenzeneboronic acid (1.46 g, 6.51 mmol) and fr7s(dibenzyldieneacetone)dipalladium(0) (81 mg, 0.09 mmol) in tetrahydrofuran (27 mL) 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, 1.57 g.

Method 2
A suspension of the product of Preparation 3 (4 g, 12.1 mmol) in methylamine solution (50 mL, 2N in tetrahydrofuran, 100 mmol) was heated at 60°C for 48 hours before allowing to cool and evaporating to
dryness *in vacuo*. The residue was re-dissolved in methylamine solution (40 ml, 2N in tetrahydrofuran, 80 mmol) and heated at 80°C for 24 hours. The reaction mixture was concentrated *in vacuo* and triturated with diethyl ether to furnish the title compound as a white solid, 2.8 g, 76%.

$^1$H NMR (400 MHz, CD$_3$OD) δ: 2.94(s, 3H), 7.33(d, 1H), 7.41(dd, 2H), 7.68(d, 1H) LRMS: m/z APCI 330 [MH]$^+$

1. Microanalysis: C$_{13}$H$_{10}$Cl$_3$N$_3$O requires: C 47.23; H 3.05 N 12.71; found C 47.15; H 3.18, N 12.55

$^1$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: CDCl$_3$, deuterochloroform; d$_6$-DMSO, deuterodimethylsulphoxide; CD$_3$OD, deutermethanol; THF, tetrahydrofuran. ‘Ammonia’ refers to a concentrated solution of ammonia in water possessing a specific gravity of 0.88. Where thin layer chromatography (TLC) has been used it refers to silica gel TLC using silica gel 60 F$_{254}$ plates, R$_f$ is the distance travelled by a compound divided by the distance travelled by the solvent front on a TLC plate.

Microwave radiation was provided using the Emrys Creator or the Emrys Liberator, both supplied 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.

The ability of the pyridine derivatives of the formula (I) to inhibit the Na$_{v,1.8}$ channel may be measured using the assay described below.

**VIPR Assay for Navi compounds**

This screen is used to determine the effects of compounds on tetrodotoxin-resistant (TTX-R) sodium channels in Human Na$_{v,1.8}$ (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 voltagesensing 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$_{v,1.8}$) or veratridine (for the SHSY-5Y assay for TTX-S channels).

**Cell Maintenance:**
Human Na_{v1.8} cells are grown in T225 flasks, in a 5% CO₂ humidified incubator to about 70% confluence. Media composition consists of DMEM/F-12, 10% FCS and 300μg/ml Geneticin. They are 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-Na_{v1.8} cells (100μl per well) into poly-D-lysine coated plates prior to experimentation as follows: - 24 hours @ 3.5 x 10⁴ cells/well (3.5 x 10⁵ 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 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 below) to cells and incubate for 45 minutes at room temperature avoiding bright light.
3. Prepare Oxonol (DisBAC₂(3)) dye (see below):
4. Aspirate off Coumarin solution from the cells by washing in Na⁺ Free buffer.
5. Add 30μl compound then 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:

\[ Ri = \frac{(\text{Intensity } 460\text{nm, samples } 3-5 - \text{background } 460\text{nm, samples } 3-5)}{(\text{Intensity } 580\text{nm, samples } 3-5 - \text{background } 580\text{nm, samples } 3-5)} \]

\[ Rf = \frac{(\text{Intensity } 460\text{nm, samples } 25-30 - \text{background } 460\text{nm, samples } 25-30)}{(\text{Intensity } 580\text{nm, samples } 25-30 - \text{background } 580\text{nm, samples } 25-30)} \]

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) - 1OX stock

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<th>Mwt/Conc</th>
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<th>1X Conc (mM)</th>
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<tr>
<td>Hepes</td>
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<td>23.83g</td>
<td>100</td>
<td>10</td>
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<tr>
<td>dH₂O</td>
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<td>1L</td>
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Na+-Free Buffer pH 7.4 (adjust with 5M KOH) - 10X stock

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<td>Hepes</td>
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<tr>
<td>dH₂O</td>
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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.

<table>
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<tr>
<th>Coumarin (1mM)</th>
<th>Solution Concentration</th>
<th>Final Assay Concentration</th>
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<td>10µM</td>
<td>10µM</td>
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Oxonol (DiSBAC₄(3)): For 2 plates:

48µl Oxonol (5mM) + 12Oul Tartrazine (200mM) Vortex
8.0ml 2X Na+-Free Buffer Vortex
1.6µl Deltametherin (5mM) Vortex

Solution Concentration: Final Assay Concentration
All the compounds of the Examples were tested in the assay described above and were found to have an affinity for the Na\textsubscript{vL,s} channel of less than 5 \( \mu \text{M} \).

<table>
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<th>Example No.</th>
<th>Na\textsubscript{vL,s} IC50 (( \mu \text{M} ))</th>
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1. A compound of formula (I):

![Formula Image]

or a pharmaceutically acceptable salt or solvate thereof,
wherein;

R^1 is hydrogen and
R^2 is (C_1-C_6)alkyl, optionally substituted with one or more substituents selected from hydroxy, (C_1-C_6)alkoxy, halogen, halo(CrC_6)alkyl and (C_5-C_6)cycloalkyl; or
R^1 and R^2 may be taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered saturated or partially unsaturated heterocyclic ring optionally comprising one or two additional heteroatom ring members each independently selected from nitrogen, oxygen and sulphur, said ring nitrogen atom optionally bearing a (C_1-C_6)alkyl substituent and said ring sulphur atom optionally bearing 1 or 2 oxygen atoms;
X is sulphur or NR^3;
R^3 is hydrogen, (C_1-C_6)alkyl, or cyano; or, where R^1 and R^2 are not taken together to form a ring, R^1 and R^3 may be taken together with the N-C=N group to which they are attached to form a 5- or 6-membered aromatic or partially unsaturated heterocyclic ring optionally comprising one or two additional nitrogen atoms;
R^4 is phenyl, naphthalenyl or azanaphthalenyl, each optionally substituted with one or more substituents R^6; and
each R^6 is independently selected from halogen, (C_1-C_6)alkoxy, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, cyano, cyclopropyl and methycyclopropyl;
or where R^4 is phenyl, two adjacent R^6 groups may be taken together with the carbon atoms to which they are attached to form a 5- or 6-membered saturated or partially unsaturated heterocyclic ring comprising one or two heteroatom ring members each independently selected from nitrogen, oxygen and sulphur, said ring nitrogen atom optionally bearing a (C_1-C_6)alkyl substituent and said ring sulphur atom optionally bearing 1 or 2 oxygen atoms.

2. A compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is hydrogen and R^2 is (C_1-C_6)alkyl or halo (C_1-C_6)alkyl; or R^1 and R^2 are taken together with the nitrogen atom to which they are attached to form a morpholine or piperazine ring.
3. A compound of formula (I) according to claim 1 or claim 2, or a pharmaceutically acceptable salt or solvate thereof, wherein X is NR³.

4. A compound of formula (I) according to any one of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, wherein R³ is cyano or (C₉ C₆)alkyl.

5. A compound of formula (I) according to any one of claims 1 to 4, or a pharmaceutically acceptable salt or solvate thereof, wherein R⁴ is phenyl, optionally substituted with one or more substituents R⁵ wherein each R⁵ is independently selected from halogen, (CVC₉ Jalkoxy, (C₉ C₆)alkyl, halo(C₉ C₆)alkyl, cyano, cyclopropyl and methylcyclopropyl.

6. A compound of formula (I) according to any one of claims 1 to 5, or a pharmaceutically acceptable salt or solvate thereof, wherein each R⁵ is halogen.

7. A compound of formula (I) according to any one of claims 1 to 6, or a pharmaceutically acceptable salt or solvate thereof, wherein R⁴ is 2,5-dichlorophenyl or 2,3,5-trichlorophenyl.

8. A compound according to any one of claims 1 to 7, selected from:
6-Amino-5-(2,3,5-trichloro-phenyl)-pyridine-2-carbothioic acid methylamide;
6-amino-N'-cyano-N-methyl-5-(2,3,5-trichloro-phenyl)pyridine-2-carboximidamide;
6-Amino-N,N'-dimethyl-5-(2,3,5-trichloro-phenyl)-pyridine-2-carboxamidine;
6-(Methylimino-morpholin-4-yl-methyl)-3-(2,3,5-trichloro-phenyl)-pyridin-2-ylamine;
6-Amino-N,N'-diethyl-5-(2,3,5-trichloro-phenyl)-pyridine-2-carboxamidine;
6-Amino-N-methyl-5-(2,3,5-trichloro-phenyl)-N'-2,2,2-trifluoro-ethyl)-pyridine-2-carboxamidine; and
6-Amino-N-methyl-5-(2,3,5-trichloro-phenyl)-pyridine-2-carboxamidine; or a pharmaceutically acceptable salt or solvate thereof.

9. 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 8, together with one or more pharmaceutically acceptable excipients.

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

11. The use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in any one of claims 1 to 8, for the manufacture of a medicament for the treatment of a disease or condition for which a Naᵥ1.3 channel modulator is indicated.
12. The use according to claim 11 wherein the disease or condition is pain.

13. A method of treating a disease or condition for which a Navts 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 8 respectively.

14. A method according to claim 13 wherein the disease or condition is pain.

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 8, and another pharmacologically active agent.
**INTERNATIONAL SEARCH REPORT**

**International application No**

PCT/IB2007/000172

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D213/81  C07D213/83  C07D213/84  A61K31/4418  A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D  A61K  A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEMABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<tr>
<th>Category*</th>
<th>Citation of document, with indication where appropriate, of the relevant passages</th>
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<td>A</td>
<td>WO 98/38174 A (GLAXO GROUP LTD [GB]; COX BRIAN [GB]; NOBBS MALCOLM STUART [GB]; SHAH) 3 September 1998 (1998-09-03) page 1, line 3 - page 2, line 20 claims 1-12 -----</td>
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**Date of the actual completion of the International search**

4 May 2007

**Date of mailing of the international search report**

11/05/2007

**Name and mailing address of the ISA/Authorized officer**

European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk, Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016

Marzi, Elena

* Special categories of cited documents

- **A** document defining the general state of the art which is not considered to be of particular relevance
- **E** earlier document but published on or after the international filing date
- **L** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- **O** document referring to an oral disclosure, use, exhibition or other means
- **P** document published prior to the international filing date but later than the priority date claimed

- **T** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- **X** document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- **Y** document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- **A** document member of the same patent family
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<td>WO 2006/011050 A (PFIZER LTD [GB]; PFIZER [US]; LANE CHARLOTTE ALICE LOUISE [GB]; MAW GR) 2 February 2006 (2006-02-02) page 1, lines 6-13 page 3, line 27 - page 4, line 21 page 41; example 1 claims 1-15</td>
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This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:
   Although claims 13-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.
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<td>WO 9838174 A</td>
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| WO 2006011050 A                       | 02-02-2006      | AU 2005266090 A1        | 02-02-2006      |

Form PCT/ISA/210 (patent family astral) (April 2005)