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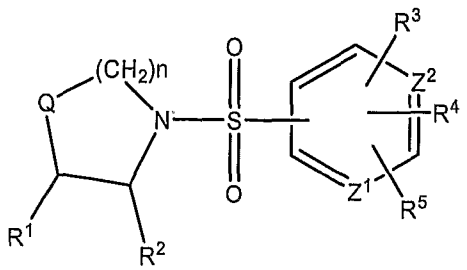
(54) **Title:** SULFONAMIDE COMPOUNDS



(I)

(57) **Abstract:** This invention provides the compounds of formula (I): or a pharmaceutically acceptable salt thereof, wherein Q is CH_2 or the like; Z^1 is CR^a or the like; Z^2 is CR^b or the like; R^1 and R^2 are each independently hydrogen or the like, R^a, R^b, R^3, R^4 and R^5 are each independently hydrogen or the like and n is 1 or the like. These compounds are useful for the treatment of disease conditions caused by overactivation of N type calcium channel such as pain or the like in mammalian. This invention also provides a pharmaceutical composition comprising the above compound.

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SULFONAMIDE COMPOUNDS

Technical Field

This invention relates to novel sulfonamide compounds and to their use in therapy. These compounds are particularly useful as antagonists of the N-type calcium channel, and are thus useful for the treatment of pain, neuralgia, neuropathies, nerve injury, burns, migraine, carpal tunnel syndrome, fibromyalgia, neuritis, sciatica, pelvic hypersensitivity, bladder disease, inflammation, or the like in mammals, especially humans. The present invention also relates to a pharmaceutical composition comprising the above compounds.

Background Art

N-type calcium channel (NTCC) is a member of voltage-sensitive calcium channel. NTCC is located presynaptically in afferent C- and A- fiber terminals of spinal lamina I and II where they may play a major role in the control of neuropeptides and glutamate released from nociceptive nerve fibers (J. Pain 7: S13-30, 2006). In addition, postsynaptic expression of NTCC and their contribution to the depolarization-induced calcium influx in spinal lamina I neuron were demonstrated (Eur. J. Neuroscience 19: 103-111, 2004). These observations suggest that the inhibition of NTCC of spinal cord can decrease neuronal activity by reducing neurotransmitter release as well as by postsynaptic depression of the excitability of the second-order neurons. Indeed, intrathecal injection of NTCC-selective blocker, ziconotide (Prialt), has been shown to have potent anti-allodynic effect in humans when assessed on a variety of complex pain states, such as nerve injury and various neuropathies including those arising from cancer or AIDS (Pharmacotherapy 25: 1084-1094, 2005, The Journal of the American Medical Association 291: 63-70, 2004). These results provide the ultimate evidence that blockade of NTCC is the promised mechanism of pain treatment in humans.

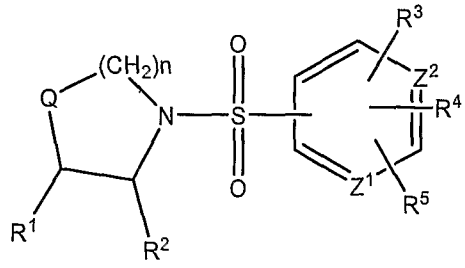
International Patent Publication Number WO2005068448 discloses a variety of sulfonamide derivatives as an antagonist for N-type calcium channels.

It would be desirable if there were provided improved N-type calcium channels antagonist with a good half-life. Other potential advantages include less toxicity, good absorption, good solubility, low protein binding affinity, less drug-drug interaction, a reduced inhibitory activity at HERG channel, reduced QT prolongation and good metabolic stability.

Brief Disclosure of the Invention

It has now been found that sulfonamide compounds are potent N-type calcium channels antagonists. The compounds of the present invention may show less toxicity, good absorption, good half-life, good solubility, low protein binding affinity, less drug-drug interaction, a reduced inhibitory activity at the HERG channel, reduced QT prolongation and good metabolic stability.

The present invention provides a compound of the following formula (I):



(I)

or a pharmaceutically acceptable salt thereof;

wherein Q is CH_2, O or S;

Z^1 is CR^a or N; Z^2 is CR^b or N;

R^1 and R^2 are each independently hydrogen, halogen, hydroxy, oxo, thio, amino, cyano, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, -Het-L, -Het-A, -X-L, -X-A, -L-Y, -L-Het-Y, -L-X-Y, (C_6-C_{10})aryl, 5- to 10-membered heteroaryl or $-CONH_2$, or R^1 and R^2, together with the carbons to which R^1 and R^2 are attached, form (C_3-C_{10})carbocycle or 5- to 10- membered heterocycle,

wherein X is -CO-, -CO-O-, $-CONR^6$-, -O-CO-, $-NR^6$-CO- or $-NR^6$-CO- or $-NR^6$-CO-NR^6-, wherein R^6 is hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

Het is -O-, -S- or $-NR^6$-, wherein R^6 is as defined above;

A is (C_6-C_{10})aryl, 5- to 10- membered heteroaryl, (C_3-C_{10})carbocyclyl or 5- to 10- membered heterocyclyl;

L is (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl moiety;

Y is (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_6-C_{10})aryl, 5- to 10- membered heteroaryl, (C_3-C_{10})carbocyclyl, 5- to 10- membered heterocyclyl or –L-A;

R^a, R^b, R^3, R^4 and R^5 are each independently hydrogen, halogen, hydroxy, thio, amino, cyano, nitro, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, mono(C_1-C_6)alkylamino or di(C_1-C_6)alkylamino; and

n is 1 or 2;

wherein said alkyl, alkenyl and alkynyl in R^a, R^b, R^1, R^2, R^3, R^4 and R^5 are optionally substituted by 1 to 3 substituents each independently selected from halogen, hydroxy, amino or thio;

said aryl, heteroaryl, carbocyclyl and heterocyclyl groups and moieties in R^1 and R^2 are optionally substituted by 1 to 3 substituents each independently selected from halogen, hydroxy, amino, thio, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, -mono(C_1-C_6)alkylamino, -di(C_1-C_6)alkylamino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, halo(C_1-C_6)alkylthio, hydroxy(C_1-C_6)alkyl, (C_3-C_{10})carbocyclyl, 5- to 10- membered heterocyclyl, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl, -(C_1-C_6)alkyl-S-(C_1-C_6)alkyl, -(C_1-C_6)alkyl-mono(C_1-C_6)alkylamino, -(C_1-C_6)alkyl-di(C_1-C_6)alkylamino, -CO-(C_1-C_6)alkyl, -CO-O-(C_1-C_6)alkyl, -CO-mono(C_1-C_6)alkylamino, -CO-di(C_1-C_6)alkylamino, -(C_1-C_6)alkyl-(C_3-C_{10})carbocyclyl or -(C_1-C_6)alkyl-(C_6-C_{10})aryl;

provided that when Q is CH_2 and n is 2, at least one of Z^1 and Z^2 is N.

Detailed Description of the Invention

As used herein, the term "**halogen**" means fluoro, chloro, bromo or iodo, preferably fluoro or chloro.

As used herein, the term "**(C_1-C_4)alkyl**" and "**(C_1-C_6)alkyl**" means straight or branched chain saturated monovalent hydrocarbon radicals having the required number of carbon atoms, including, but not limited to methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *secondary*-butyl, *tert*-butyl and 2-methylbutyl groups. Preferred groups are methyl, ethyl, *n*-propyl, *n*-butyl, *tert*-butyl and 2-methylbutyl groups.

As used herein, the term "**(C_2-C_6)alkenyl**" means straight or branched (C_2-C_6)alkenyl. Typically, alkenyl is saturated except for one double bond. Typically, it is ethenyl, propenyl or butenyl. Preferably it is ethenyl. Divalent alkenyl can be attached via the same carbon atom, via adjacent carbon atoms or via non-adjacent carbon atoms.

As used herein, the term "**(C_2-C_6)alkynyl**" means straight or branched (C_2-C_6)alknyl. Typically,

alkynyl is saturated except for one triple bond. Typically, it is ethynyl, propynyl or butynyl. Divalent alkynyl can be attached via the same carbon atom, via adjacent carbon atoms or via non-adjacent carbon atoms.

As used herein, the term **"(C_6-C_{10})aryl"** means typically phenyl or naphthyl. Preferably, it is phenyl.

As used herein, the term **"5- to 10-membered heteroaryl"** means 5- to 10-membered aromatic ring containing at least one heteroatom, for example 1 to 4 heteroatoms, selected from O, S or N. Preferred 5- to 10-membered heteroaryl are 5- to 6- membered heteroaryl. Examples include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl.

As used herein, the term **"(C_3-C_{10})carbocyclyl"** means non-aromatic saturated or unsaturated hydrocarbon ring, having from 3 to 10 carbon atoms, preferably 3 to 6 carbon atoms. Typically, carbocyclyl is saturated, for example (C_3-C_6)cycloalkyl. Examples include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

As used herein, the term **"5- to 10-membered heterocyclyl"** means non aromatic, saturated or unsaturated (C_5-C_{10})carbocyclic ring in which one or more, for example 1, 2 or 3, of the carbon atoms are replaced by a heteroatom selected from N, O or S. Examples include pyrrolidinyl, imidazolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, dioxolanyl, dithiolanyl, oxazolidinyl, thiazolidinyl, piperidinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, dioxanyl, dithianyl, morpholinyl and thiomorpholinyl.

As used herein, the term **"(C_1-C_6)alkoxy"** means (C_1-C_6)alkyl-O- wherein (C_1-C_6)alkyl radical is as defined above, including, but not limited to methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-butoxy. Preferred groups are methoxy, ethoxy, *n*-propoxy, *n*-butoxy and *tert*-butoxy.

As used herein, the terms **"(C_1-C_6)alkylthio"** means (C_1-C_6)alkyl-S- wherein (C_1-C_6)alkyl radical is as defined above, including, but not limited to methylthio, ethylthio, propylthio and butylthio. Preferred groups are methylthio and methylthio groups.

As used herein, the term **"halo(C_1-C_6)alkyl"** means (C_1-C_6)alkyl radical as defined above which is substituted by one or more halogen as defined above including, but not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2,2,2-trifluoro-1,1-dimethylethyl, 2,2,2-trichloroethyl, 3-fluoropropyl, 4-fluorobutyl, chloromethyl, trichloromethyl, iodomethyl, bromomethyl and 4,4,4-trifluoro-3-methylbutyl. Preferred groups are fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl and 2,2,2-trifluoro-1,1-dimethylethyl.

As used herein, the term **"halo(C_1-C_6)alkoxy"** means (C_1-C_6)alkoxy radical as defined above which is substituted by one or more halogen as defined above including, but not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, trichloromethoxy and bromomethoxy.

As used herein, the term **"halo(C_1-C_6)alkylthio"** means (C_1-C_6)alkylthio as defined above which is substituted by one or more halogen atoms as defined above. Typically, it is substituted by 1, 2 or 3 said halogen including, but not limited to, fluoromethylthio, difluoromethylthio and trifluoromethylthio.

As used herein, the term **"hydroxy(C_1-C_6)alkyl"** means (C_1-C_6)alkyl radical as defined above which is substituted by at least one hydroxy group including, but not limited to, hydroxymethyl, hydroxyethyl, hydroxy *n*-propyl, hydroxy *iso*-propyl (e. g. 2-hydroxy-1,1-dimethylethyl), hydroxy *n*-butyl, hydroxy *iso*-butyl, hydroxy *secondary*-butyl and hydroxy *tert*-butyl. Preferred groups are hydroxymethyl, hydroxyethyl,

hydroxy *n*-propyl, hydroxy *iso*-propyl (e. g. 2-hydroxy-1,1-dimethylethyl) and hydroxy *n*-butyl.

As used herein, the term **"-mono(C_1-C_6)alkylamino"** and **"-di(C_1-C_6)alkylamino"** include, but not limited to, methylamino, ethylamino, *n*-propylamino, *iso*-propylamino, *n*-butylamino, *iso*-butylamino, *secondary*-butylamino, *tert*-butylamino. Preferred alkylamino groups are methylamino, ethylamino, *n*-propylamino, *n*-butylamino, dimethylamino, diethylamino, methylethylamino, di *n*-propylamino, methyl *n*-propylamino, ethyl *n*-propylamino, di *iso*-propylamino, di *n*-butylamino, methyl *n*-butylamino, di *iso*-butylamino, di *secondary*-butylamino and di *tert*-butylamino.

As used herein, the term **"-(C_1-C_6)alkyl-O-(C_1-C_6)alkyl"** includes, but not limited to, methoxymethyl, ethoxymethyl and ethoxyethyl.

As used herein, the term **"-(C_1-C_6)alkyl-S -(C_1-C_6)alkyl"** include, but not limited to, methylthiomethyl, ethylthioethyl, propylthiomethyl and butylthiomethyl.

As used herein, the term **"-(C_1-C_6)alkyl-mono(C_1-C_6)alkylamino"** and **"-(C_1-C_6)alkyl-di(C_1-C_6)alkylamino"** include, but not limited to, methylaminomethyl, ethylaminoethyl, dimethylaminomethyl and diethylaminomethyl.

As used herein, the term **"-CO-(C_1-C_6)alkyl"** includes, but not limited to, -CO-CH_3, -CO-CH_2-CH_3 and -CO-CH_2-CH_2-CH_3.

As used herein, the term **"-CO-O-(C_1-C_6)alkyl"** includes, but not limited to, -CO-O-CH_3, -CO-O-CH_2-CH_3 and -CO-O-CH_2-CH_2-CH_3.

As used herein, the term **"-CO-mono(C_1-C_6)alkylamino"** and **"-CO-di(C_1-C_6)alkylamino"** include, but not limited to, -CO-NH-CH_3, -CO-N(CH_3)$_2$ and -CO-NH-CH_2-CH_3.

As used herein, the term **"-(C_1-C_6)alkyl-(C_3-C_{10})carbocyclyl"** includes, but not limited to, cyclopropylmethyl, cyclobutylethyl, cyclopentylmethyl and cyclohexylethyl.

As used herein, the term **"-(C_1-C_6)alkyl-(C_6-C_{10})aryl"** includes, but not limited to, phenylmethyl and naphthylethyl.

Preferably Q is O or CH_2; more preferably O.

Preferably when Q is CH_2, then Z^1 is N and Z^2 is CR^b or N; more preferably when Q is CH_2, then Z^1 is N and Z^2 is CR^b.

Preferably R^1 and R^2 are each independently hydrogen, (C_1-C_4)alkyl, -L-Y, -L-Het-Y, -L-X-Y, phenyl or heteroaryl selected from 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, tetrazolyl or pyridyl, provided that at least one of R^1 and R^2 is hydrogen, or R^1 and R^2, together with the carbons to which R^1 and R^2 are attached, form indane;

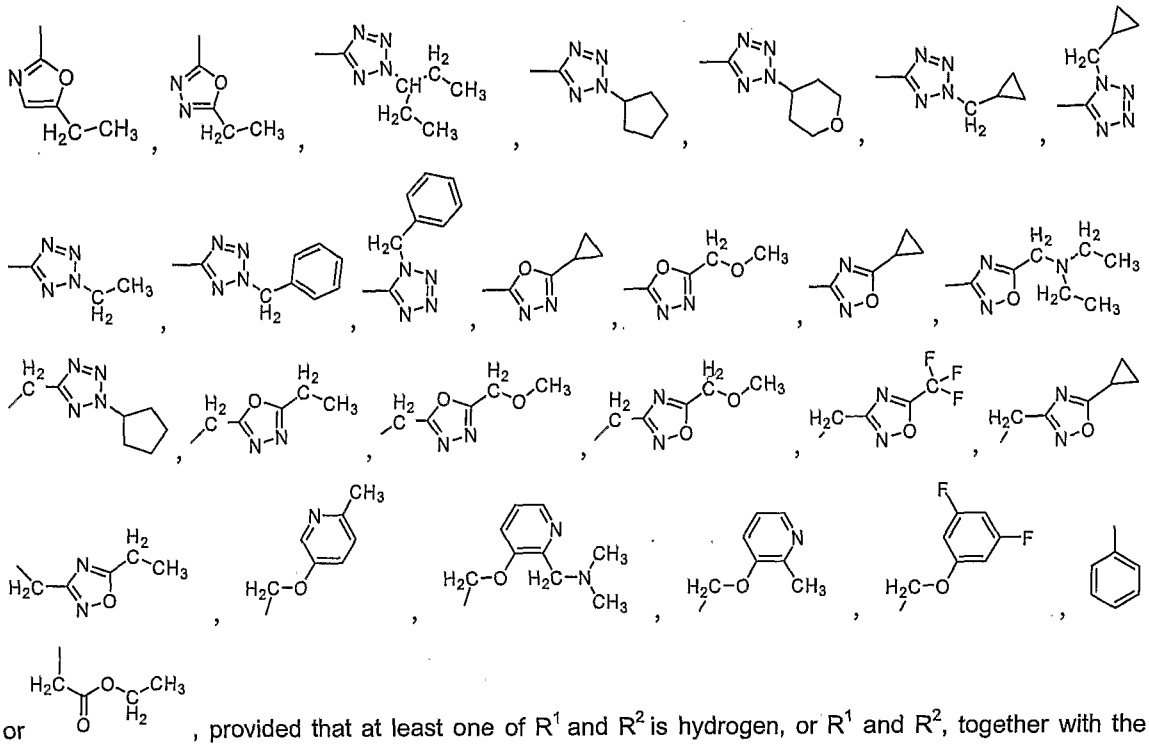
wherein X is -CO-O-; Het is -O-; L is (C_1-C_4)alkyl moiety;

Y is (C_1-C_6)alkyl, phenyl or heteroaryl selected from 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, tetrazolyl or pyridyl;

wherein said alkyl in R^1 and R^2 are optionally substituted by 1 to 3 substituents each independently selected from halogen or hydroxy;

said phenyl and heteroaryl groups and moieties in R^1 and R^2 are optionally substituted by 1 to 2 substituents each independently selected from fluorine, chloride, (C_1-C_6)alkyl, amino, -N(CH_3)$_2$, -N(C_2H_5)$_2$, -N(CH_3)(C_2H_5), trifluoromethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydro-2H-pyranyl, -CH_2-O-CH_3, -CH_2-O-C_2H_5, -CH_2-N(CH_3)$_2$, -CH_2-N(C_2H_5)$_2$, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl or phenylmethyl; more preferably R^1 and R^2 are

each independently hydrogen,



or , provided that at least one of R^1 and R^2 is hydrogen, or R^1 and R^2, together with the carbons to which R^1 and R^2 are attached, form indane.

Preferably R^a, R^b, R^3, R^4 and R^5 are each independently hydrogen, halogen or trifluoromethyl; more preferably hydrogen, fluorine, chlorine or trifluoromethyl; most preferably hydrogen, chlorine or trifluoromethyl.

Preferably R^6 is hydrogen.

Preferably n is 2.

Preferred compounds of the invention include those in which each variable in formula (I) is selected from the preferred groups for each variable.

Specific preferred compounds of the invention are those listed in the Examples section below and the pharmaceutically acceptable salts thereof.

The compounds of formula (I), being NTCC antagonists, are potentially useful in the treatment of a range of disorders, particularly the treatment of acute cerebral ischemia, pain, chronic pain, acute pain, nociceptive pain, neuropathic pain, inflammatory pain, post herpetic neuralgia, neuropathies, neuralgia, diabetic neuropathy, HIV-related neuropathy, nerve injury, rheumatoid arthritic pain, osteoarthritic pain, burns, back pain, visceral pain, cancer pain, dental pain, headache, migraine, carpal tunnel syndrome, fibromyalgia, neuritis, sciatica, pelvic hypersensitivity, pelvic pain, menstrual pain, bladder disease, such as incontinence, micturition disorder, renal colic and cystitis, inflammation, such as burns, rheumatoid arthritis and osteoarthritis, neurodegenerative disease, such as stroke, post stroke pain and multiple sclerosis, pulmonary disease, such as asthma, cough, chronic obstructive pulmonary disease (COPD) and broncho constriction, gastrointestinal disorders, such as gastroesophageal reflux disease (GERD), dysphagia, ulcer, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), colitis and Crohn's disease, ischemia, such as cerebrovascular ischemia, emesis, such as cancer chemotherapy-induced

emesis, and obesity, or the like in mammals, especially humans. The treatment of pain, particularly neuropathic 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, postherpetic neuralgia), carpal tunnel syndrome, back pain, headache, cancer pain, arthritic pain and chronic post-surgical pain.

When a substantial injury occurs to body tissue, *via* disease or trauma, the characteristics of nociceptor activation are altered and there is sensitisation in the periphery, locally around the injury and centrally where the nociceptors terminate. These effects lead to a 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 intervertabral 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 includes functional bowel disorder (FBD) and inflammatory bowel disease (IBD). These GI disorders include a wide range of disease states that are currently only moderately controlled, including, in respect of FBD, gastro-esophageal reflux, dyspepsia, irritable bowel syndrome (IBS) and functional abdominal pain syndrome (FAPS), and, in respect of IBD, Crohn's disease, ileitis and ulcerative colitis, all of which regularly produce visceral pain. Other types of visceral pain include the pain associated with dysmenorrhea, cystitis and pancreatitis and pelvic pain.

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

Other types of pain include:

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

The present invention provides a pharmaceutical composition including a compound of formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable excipient. The composition is preferably useful for the treatment of the disease conditions defined above.

The present invention further provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use as a medicament.

Further, the present invention provides a method for the treatment of the disease conditions defined above in a mammal, preferably a human, which includes administering to said mammal a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Yet further, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of the disease conditions defined above.

Yet further, the present invention provides a combination of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, and another pharmacologically active agent.

In this specification, especially in "General Synthesis" and "Examples", the following abbreviations

can be used:

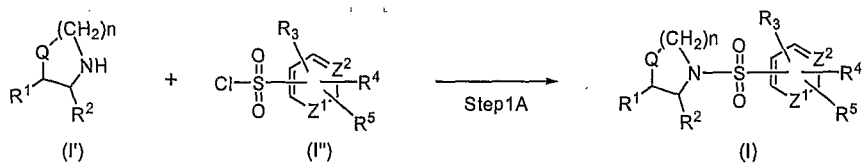
BEP	2-bromo-1-ethylpyridinium tetrafluoroborate
BOP	benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
CDI	2-chloro-1,3-dimethylimidazolinium chloride
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DME	1,2-dimethoxyethane, dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
EDC	1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrogen chloride
NaOAc	sodium acetate
EtOH	ethanol
HOBt	1-hydroxybenzotriazole
MeOH	methanol
NMP	N-methyl-2-pyrroliidone
THF	tetrahydrofuran

General Synthesis

The compounds of formula I of the present invention may be prepared according to known preparation methods, or the general procedures or preparation methods illustrated in the following reaction schemes. Unless otherwise indicated, R^1 through R^5 and Q, Z^1, Z^2 and n in the reaction schemes and discussion that follow are defined as above. R^{iii}, R^{iv} and R^v in the reaction schemes and discussion are each independently selected from halogen, hydroxy, amino, thio, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, -mono(C_1-C_6)alkylamino, -di(C_1-C_6)alkylamino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, halo(C_1-C_6)alkylthio, hydroxy(C_1-C_6)alkyl, (C_3-C_{10})carbocyclyl, 5- to 10- membered heterocyclyl, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl, -(C_1-C_6)alkyl-S-(C_1-C_6)alkyl, -(C_1-C_6)alkyl-mono(C_1-C_6)alkylamino, -(C_1-C_6)alkyl-di(C_1-C_6)alkylamino, -CO-(C_1-C_6)alkyl, -CO-O-(C_1-C_6)alkyl, -CO-mono(C_1-C_6)alkylamino, -CO-di(C_1-C_6)alkylamino, -(C_1-C_6)alkyl-(C_3-C_{10})carbocyclyl or -(C_1-C_6)alkyl-(C_6-C_{10})aryl. The term "protecting group", as used hereinafter, means a hydroxy or amino protecting group which is selected from typical hydroxy or amino protecting groups described in Protective Groups in Organic Synthesis edited by T. W. Greene *et al.* (John Wiley & Sons, 1999).

All starting materials in the following general syntheses may be commercially available or obtained by conventional methods known to those skilled in the art.

Scheme 1:



This illustrates the preparation of compounds of formula (I).

Step 1A:

A compounds of formula (I) may be prepared by the reaction of a compound of formula (I') and a

compound of formula (I"). The coupling of the amine and the sulphonyl chloride may be performed at 0 °C to room temperature in a suitable solvent, such as toluene or dichloromethane, pyridine, lutidine, collidine, in the presence of a base, for example triethylamine, N- ethylmorpholine or diisopropylethylamine. When R^1 and/or R^2 are hydroxy or amino, or they are substituted by hydroxy or amino, the hydroxy or the amino are protected with a protecting group according to conventional methods. Both a compound of formula (I') and a compound of formula (I") are either known compounds or can be prepared by the skilled person using known methods or according to the following schemes.

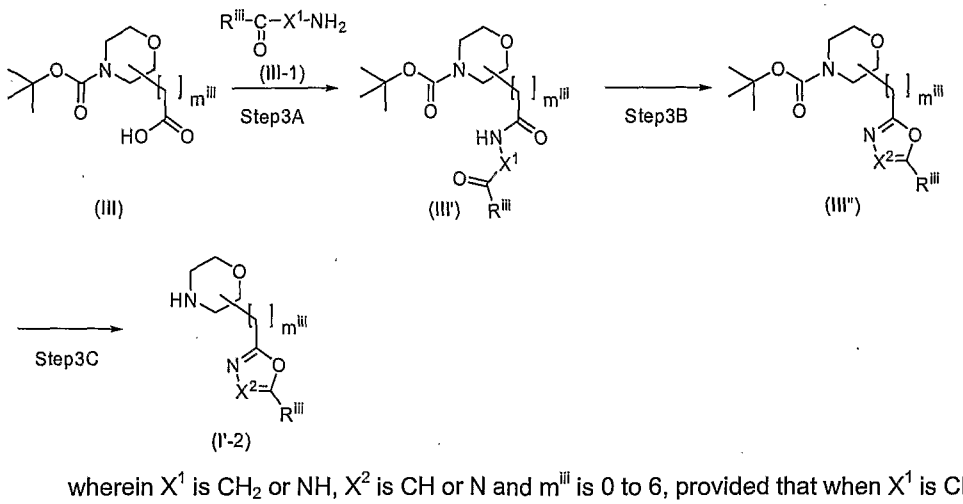
Scheme 2:

This illustrates the preparation of compounds of formula (I").

Step 2A:

In this step, a compounds of formula (I") may be prepared by the reaction of a compound of formula (II). The reaction may be carried out by bubbling chlorine into the solution. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include dioxane, acetic acid, CH_3CN or tert-buthyl alcohol. This reaction can be carried out for 30 minutes to 24 hours, usually 60 minutes to 10 hours.

Scheme 3:



wherein X^1 is CH_2 or NH, X^2 is CH or N and m^{iii} is 0 to 6, provided that when X^1 is CH_2, then X^2 is CH and when X^1 is NH, then X^2 is N.

This illustrates the preparation of compounds of formula (I'-2).

Step 3A:

In this Step, a compound of formula (III') can be prepared by the coupling reaction of a compound of formula (III) with a compound of formula (III-1) in the presence or absence of a coupling reagent in an inert solvent. When R^{iii} is hydroxy, then the hydroxy is protected with a protecting group according to conventional methods. Suitable coupling reagents are those typically used in peptide synthesis including,

for example, diimides (e.g., DCC, EDC, 2-ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline, BEP, CDI, BOP, diethyl azodicarboxylate-triphenylphosphine, diethylcyanophosphate, diethylphosphorylazide, 2-chloro-1-methylpyridinium iodide, N, N'-carbonyldiimidazole , benzotriazole-1-yl diethyl phosphate, ethyl chloroformate or isobutyl chloroformate). The reaction can be carried out in the presence of a base such as HOBt, N,N-diisopropylethylamine, N-methylmorpholine or triethylamine. The amide compound of formula (III') can be formed via an acylhalide, which can be obtained by the reaction with halogenating agents such as oxalylchloride, phosphorus oxychloride or thionyl chloride. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: acetone; nitromethane; DMF; NMP; sulfolane; DMSO; 2-butanone; acetonitrile; halogenated hydrocarbons such as DCM, dichloroethane or chloroform; and ethers such as THF or 1,4-dioxane. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -20 °C to 100 °C, more preferably from about 0 °C to 60 °C. The time required for the reaction can also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of 5 minutes to 1 week, more preferably 30 minutes to 24 hours, will usually suffice.

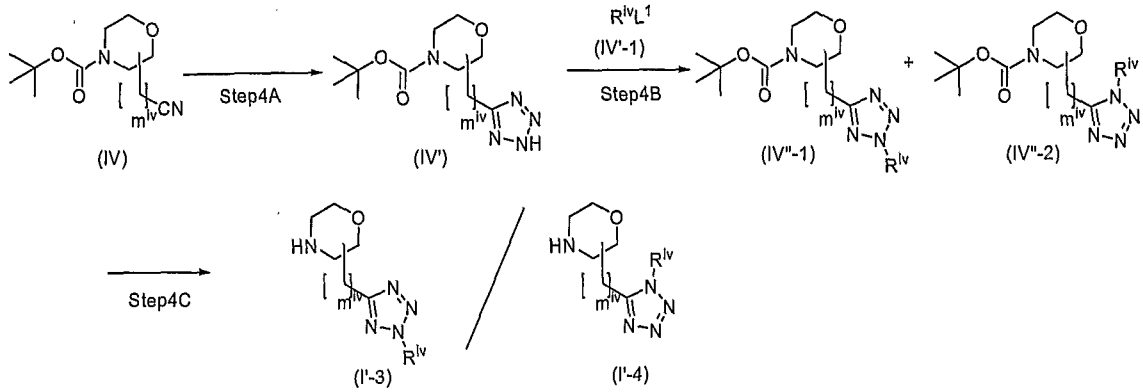
Step 3B:

In this Step, a compound of formula (III") can be prepared by cyclization of a compound of formula (III') in a solvent. The cyclization can be carried out by conventional procedures. In a typical procedure, the cyclization may be accomplished by heating in a solvent. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Suitable solvents include, for example, neat solvent such as $POCl_3$ or $SOCl_2$. This reaction can be carried out for 30 minutes to 24 hours, usually 60 minutes to 10 hours.

Step 3C:

In this Step, a compound of formula (I'-2) can be prepared by hydrolysis of a compound of formula (III") in a solvent. The hydrolysis may be carried out by conventional procedures. In a typical procedure, the hydrolysis may be carried out under the basic condition, e.g. in the presence of sodium hydroxide, potassium hydroxide or lithium hydroxide. Suitable solvents include, for example, alcohols such as MeOH, EtOH, propanol, butanol, 2-methoxyethanol or ethylene gylcol; ethers such as THF, DME or 1,4-dioxane; amides such as DMF or hexamethylphosphorictriamide; or sulfoxides such as DMSO. This reaction may be carried out at a temperature in the range from -20 to 100°C, usually from 20°C to 65°C for 30 minutes to 24 hours, usually 60 minutes to 10 hours. The hydrolysis may also be carried out under an acid condition, e.g. in the presence of hydrogen halides, such as hydrogen chloride and hydrogen bromide; sulfonic acids, such as p-toluenesulfonic acid and benzenesulfonic acid; pyridium p-toluenesulfonate; and carboxylic acid, such as acetic acid and trifluoroacetic acid.

Scheme 4:



wherein m^{iv} is 0 to 6 and L^1 is a suitable leaving group, for example halogen atoms, such as chlorine, bromine and iodine; sulfonic esters such as TfO (triflates), MsO (mesylates), TsO (tosylates); and the like.

This illustrates the preparation of compounds of formula (I'-3) and (I'-4).

Step 4A:

In this step, a compound of formula (IV') can be prepared by heating a compound of formula (IV) with NaN_3 and NH_4Cl in a solvent. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: acetone; nitromethane; DMF; NMP; sulfolane; DMSO; 2-butanone; acetonitrile; halogenated hydrocarbons such as DCM, dichloroethane or chloroform; and ethers such as THF or 1,4-dioxane. This reaction can be carried out for 30 minutes to 24 hours, usually 60 minutes to 10 hours.

Step 4B:

In this step, a compound of formula (IV"-1) and (IV"-2) can be prepared by alkylation of a compound of formula (IV') with an alkylating agent of the formula (IV'-1) in the presence of a base in a reaction-inert solvent. Examples of suitable solvents include: tetrahydrofuran, diethylether, toluene, ethylene glycol dimethylether and 1,4-dioxane. Examples of suitable bases include: lithium bis(trimethylsilyl)amide; sodium bis(trimethylsilyl)amide; potassium bis(trimethylsilyl)amide; metal amide such as sodium amide or lithium diisopropylamide; and alkali metal hydride, such as potassium hydride or sodium hydride. If desired, this reaction may be carried out in the presence or absence of an additive such as *N,N'*-dimethylpropyleneurea (DMPU), hexamethylphosphoramide (HMPA), or *N,N,N',N'*-tetramethylethylenediamine (TMEDA). This reaction may be carried out at a temperature in the range from –100 °C to 200 °C, usually from –80 °C to 100 °C, for from 5 minutes to 72 hours, usually from 30 minutes to 36 hours.

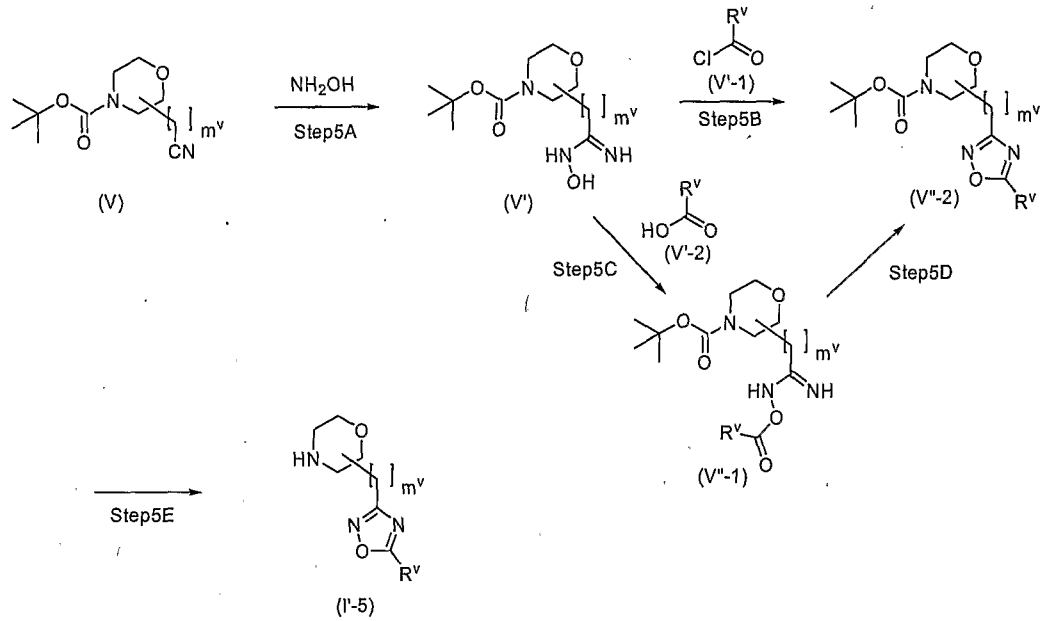
Subsequently, the mixture of the compounds of formula (IV"-1) and (IV"-2) can be separated by chromatography, such as HPLC.

Step 4C:

In this Step, a compound of formula (I'-3) and (I'-4) can be prepared by hydrolysis of a compound of formula (IV"-1) and (IV"-2) respectively in a solvent. The hydrolysis may be carried out by conventional procedures. In a typical procedure, the hydrolysis carried out under the basic condition, e.g. in the

presence of sodium hydroxide, potassium hydroxide or lithium hydroxide. Suitable solvents include, for example, alcohols such as MeOH, EtOH, propanol, butanol, 2-methoxyethanol or ethylene gylcol; ethers such as THF, DME or 1,4-dioxane; amides such as DMF or hexamethylphosphorictriamide; or sulfoxides such as DMSO. This reaction may be carried out at a temperature in the range from -20 to 100°C, usually from 20°C to 65°C for 30 minutes to 24 hours, usually 60 minutes to 10 hours. The hydrolysis may also be carried out under an acid condition, e.g. in the presence of hydrogen halides, such as hydrogen chloride and hydrogen bromide; sulfonic acids, such as p-toluenesulfonic acid and benzenesulfonic acid; pyridium p-toluenesulfonate; and carboxylic acid, such as acetic acid and trifluoroacetic acid.

Scheme 5:



wherein m^v is 0 to 6.

This illustrates the preparation of compounds of formula (I'-5).

Step 5A:

In this Step, a compound of formula (V') can be prepared by refluxing of a compound of formula (V) with hydroxyamine hydrochloride in a solvent. The refluxing may be carried out by conventional procedures. In a typical procedure, the refluxing can be performed in the presence of an inorganic base such as sodium carbonate. A suitable solvent is a protic solvent including, for example, alcohols such as MeOH, EtOH, propanol or butanol.

Step 5B:

In this Step, a compound of formula (V"-2) can be prepared by acylation and cyclization of a compound of formula (V') with a compound of formula (V'-1) in a solvent. The acylation may be carried out by conventional procedures. In a typical procedure, the acylation can be carried out in the presence of organic base such as triethylamine.

The cyclization can be carried out by conventional procedures. In a typical procedure, the cyclization may be accomplished by heating in a solvent. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed,

provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Suitable solvents include, for example, neat solvent such as pyridine. This reaction can be carried out for 30 minutes to 24 hours, usually 60 minutes to 10 hours.

Step 5C:

In this Step, a compound of formula (V"-1) can be prepared by the coupling reaction of a compound of formula (V') with a compound of formula (V'-2) in the presence or absence of a coupling reagent in an inert solvent. Suitable coupling reagents are those typically used in peptide synthesis including, for example, diimides (e.g., DCC, EDC, 2-ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline, BEP, CDI, BOP, diethyl azodicarboxylate-triphenylphosphine, diethylcyanophosphate, diethylphosphorylazide, 2-chloro-1-methylpyridinium iodide, N, N'-carbonyldiimidazole , benzotriazole-1-yl diethyl phosphate, ethyl chloroformate or isobutyl chloroformate. The reaction can be carried out in the presence of a base such as HOBt, N,N-diisopropylethylamine, N-methylmorpholine or triethylamine. The amide compound of formula (V"-1) can be formed via an acylhalide, which can be obtained by the reaction with halogenating agents such as oxalylchloride, phosphorus oxychloride or thionyl chloride. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: acetone; nitromethane; DMF; NMP; sulfolane; DMSO; 2-butanone; acetonitrile; halogenated hydrocarbons such as DCM, dichloroethane or chloroform; and ethers such as THF or 1,4-dioxane. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -20 °C to 100 °C, more preferably from about 0 °C to 60 °C. The time required for the reaction can also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of 5 minutes to 1 week, more preferably 30 minutes to 24 hours, will usually suffice.

Step 5D:

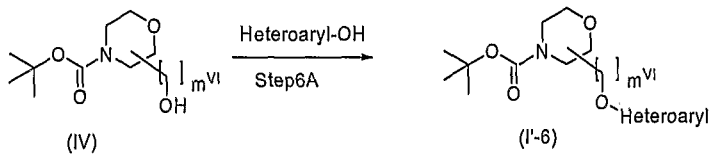
In this Step, a compound of formula (V"-2) can be prepared by cyclization of a compound of formula (V"-1) in a solvent. The cyclization can be carried out by conventional procedures. In a typical procedure, the cyclization may be accomplished by heating in a solvent. Suitable solvents include, for example, neat solvent such as NaOAc or EtOH. This reaction can be carried out for 30 minutes to 24 hours, usually 60 minutes to 10 hours.

Step 5E:

In this Step, a compound of formula (I'-5) can be prepared by hydrolysis of a compound of formula (V"-2) in a solvent. The hydrolysis may be carried out by conventional procedures. In a typical procedure, the hydrolysis is carried out under the basic condition, e.g. in the presence of sodium hydroxide, potassium hydroxide or lithium hydroxide. Suitable solvents include, for example, alcohols such as MeOH, EtOH, propanol, butanol, 2-methoxyethanol or ethylene gylcol; ethers such as THF, DME or 1,4-dioxane; amides such as DMF or hexamethylphosphorictriamide; or sulfoxides such as DMSO. This reaction may be carried out at a temperature in the range from -20 to 100°C, usually from 20°C to 65°C for 30 minutes to 24

hours, usually 60 minutes to 10 hours. The hydrolysis may also be carried out under an acid condition, e.g. in the presence of hydrogen halides, such as hydrogen chloride and hydrogen bromide; sulfonic acids, such as p-toluenesulfonic acid and benzenesulfonic acid; pyridium p-toluenesulfonate; and carboxylic acid, such as acetic acid and trifluoroacetic acid.

Scheme 6:



(IV) (I'-6)

wherein m^{VI} is 0 to 6 and heteroaryl is as defined above.

This illustrates the preparation of compounds of formula (I'-6).

Step 6A:

In this Step, a compound of formula (I'-6) can be prepared by Mitsunobu Reaction (Bulletin of the Chemical Society of Japan 1967, 40, 2380) of a compound of formula (IV) with Heteroaryl-OH in a solvent. When heteroaryl is substituted by hydroxy, the hydroxy is protected with a protecting group according to conventional methods. Mitsunobu Reaction can be carried out by conventional procedures. In a typical procedure, Mitsunobu Reaction may be carried out under the basic condition, e.g. in the presence of Diethylazodicarboxylate (DEAD) and triphenylphosphine (Ph_3P) in a solvent. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: acetone; nitromethane; DMF; NMP; sulfolane; DMSO; 2-butanone; acetonitrile; halogenated hydrocarbons such as DCM, dichloroethane or chloroform; and ethers such as THF or 1,4-dioxane. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting material or reagent used. However, in general, we find it convenient to carry out the reaction at a temperature of from -20 °C to 100 °C, more preferably from about 0 °C to 60 °C. The time required for the reaction can also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of 5 minutes to 1 week, more preferably 30 minutes to 24 hours, will usually suffice.

Method for assessing biological activities

NTCC antagonist assay

Inhibition of NTCC activity was determined by cell-based fluorescent Ca^{2+} influx assay which uses extra-cellular high-K^+ stimulation to modulate the membrane potential of the cell.

Rat CaV2.2, $CaV\alpha_2\delta_1$ and $CaV\beta_3$ transfected tsA201 cells were used in the assay. Cells were maintained in Dulbecco's Modified Eagle's Medium (DEME) supplemented with 10% Fatal Bovine Serum (FBS), 5 μg/mL blasticidin, 25 μg/mL zeocin and 25 μg/mL hygromycin.

Cells were harvested and seeded in black-sided clear bottom 384-well plate at density of 5,000 cells/well

and cultured overnight. Cells were then incubated with 4 μM Fluo-4 AM (Molecular Probes) in DMEM at 37°C for 1 hour. Cells were washed three times with vEarle's balanced salt solution (1.8 mM $CaCl_2$, 0.8 mM $MgCl_2$, 5.6 mM Glucose, 20 mM HEPES, 117 mM NaCl, 26 mM $NaHCO_3$, 1 mM NaH_2PO_4). In the experiments to examine the inhibition by blockers, cells were incubated with blocker for 5 min, followed by addition of depolarizing Earle's Balanced Salt Solution (EBSS) (1.8 mM $CaCl_2$, 0.8 mM $MgCl_2$, 5.6 mM Glucose, 20 mM HEPES, 117 mM KCl, 26 mM $NaHCO_3$, 1 mM NaH_2PO_4) to depolarize the cells and open the voltage-gated calcium channel. Calcium influx image was measured using FDSS6000 (Hamamatsu photonics, Japan).

Determination of antagonist activity

Inhibition of channel activity was calculated based on the comparison of fluorescence intensity in a presence of a blocker with that of a control response in the absence of compound. The calculation of IC_{50} value was decided using curve-fit program (Model:Sigmoidal-600 or 601) of Excel Fit™.

Chronic Constriction Injury Model (CCI Model)

Male Sprague-Dawley rats (270-300 g; B.W., Charles River, Tsukuba, Japan) were used. The chronic constriction injury (CCI) operation was performed according to the method described by Bennett and Xie (Bennett, G.J. and Xie, Y.K. Pain, 33:87-107, 1988). Briefly, animals were anesthetized with sodium pentobarbital (64.8 mg/kg, i.p.) and the left common sciatic nerve was exposed at the level of the middle of the thigh by blunt dissection through biceps femoris. Proximal to the sciatic's trifurcation was freed of adhering tissue and 4 ligatures (4-0 silk) were tided loosely around it with about 1 mm space. Sham operation was performed as same as CCI surgery except for sciatic nerve ligation. Two weeks after surgery, mechanical allodynia was evaluated by application of von Frey hairs (VFHs) to the plantar surface of the hind paw. The lowest amount of force of VFH required to elicit a response was recorded as paw withdrawal threshold (PWT). VFH test was performed at 0.5, 1 and 2 hr post-dosing. Experimental data were analyzed using Kruskal-Wallis test followed by Dunn's test for multiple comparisons or Mann-Whitney U-test for paired comparison.

Caco-2 permeability

Caco-2 permeability was measured according to the method described in Shiyin Yee, *Pharmaceutical Research,* 763 (1997).

Caco-2 cells were grown on filter supports (Falcon HTS multiwell insert system) for 14 days. Culture medium was removed from both the apical and basolateral compartments and the monolayers were preincubated with pre-warmed 0.3 ml apical buffer and 1.0 ml basolateral buffer for 0.75 hour at 37°C in a shaker water bath at 50 cycles/min. The apical buffer consisted of Hanks Balanced Salt Solution, 25 mM D-glucose monohydrate, 20 mM MES Biological Buffer, 1.25 mM $CaCl_2$ and 0.5 mM $MgCl_2$ (pH 6.5). The basolateral buffer consisted of Hanks Balanced Salt Solution, 25 mM D-glucose monohydrate, 20 mM HEPES Biological Buffer, 1.25 mM $CaCl_2$ and 0.5 mM $MgCl_2$ (pH 7.4). At the end of the preincubation, the media was removed and test compound solution (10μM) in buffer was added to the apical compartment. The inserts were moved to wells containing fresh basolateral buffer and incubated for 1 hr. Drug concentration in the buffer was measured by LC/MS analysis.

Flux rate (F, mass/time) was calculated from the slope of cumulative appearance of substrate on the receiver side and apparent permeability coefficient (P_{app}) was calculated from the following equation.

P_{app} (cm/sec) = (F * VD) / (SA * MD)

where SA is surface area for transport (0.3 cm^2), VD is the donor volume (0.3ml), MD is the total amount of drug on the donor side at t = 0. All data represent the mean of 2 inserts. Monolayer integrity was determined by Lucifer Yellow transport.

Human dofetilide binding

Cell paste of HEK-293 cells expressing the HERG product can be suspended in 10-fold volume of 50 mM Tris buffer adjusted at pH 7.5 at 25 °C with 2 M HCl containing 1 mM $MgCl_2$, 10 mM KCl. The cells were homogenized using a Polytron homogenizer (at the maximum power for 20 seconds) and centrifuged at 48,000g for 20 minutes at 4°C. The pellet was resuspended, homogenized and centrifuged once more in the same manner. The resultant supernatant was discarded and the final pellet was resuspended (10-fold volume of 50 mM Tris buffer) and homogenized at the maximum power for 20 seconds. The membrane homogenate was aliquoted and stored at -80°C until use. An aliquot was used for protein concentration determination using a Protein Assay Rapid Kit and ARVO SX plate reader (Wallac). All the manipulation, stock solution and equipment were kept on ice at all time. For saturation assays, experiments were conducted in a total volume of 200 µl. Saturation was determined by incubating 20 µl of [^{3}H]-dofetilide and 160 µl of membrane homogenates (20-30 µg protein per well) for 60 min at room temperature in the absence or presence of 10 µM dofetilide at final concentrations (20 µl) for total or nonspecific binding, respectively. All incubations were terminated by rapid vacuum filtration over polyetherimide (PEI) soaked glass fiber filter papers using Skatron cell harvester followed by two washes with 50 mM Tris buffer (pH 7.5 at 25 °C). Receptor-bound radioactivity was quantified by liquid scintillation counting using Packard LS counter.

For the competition assay, compounds were diluted in 96 well polypropylene plates as 4-point dilutions in semi-log format. All dilutions were performed in DMSO first and then transferred into 50 mM Tris buffer (pH 7.5 at 25 °C) containing 1 mM $MgCl_2$, 10 mM KCl so that the final DMSO concentration became equal to 1%. Compounds were dispensed in triplicate in assay plates (4 µl). Total binding and nonspecific binding wells were set up in 6 wells as vehicle and 10 µM dofetilide at final concentration, respectively. The radioligand was prepared at 5.6x final concentration and this solution was added to each well (36 µl). The assay was initiated by addition of YSi poly-L-lysine Scintillation Proximity Assay (SPA) beads (50 µl, 1 mg/well) and membranes (110 µl, 20 µg/well). Incubation was continued for 60 min at room temperature. Plates were incubated for a further 3 hours at room temperature for beads to settle. Receptor-bound radioactivity was quantified by counting Wallac MicroBeta plate counter.

I_{HERG} assay

HEK 293 cells which stably express the HERG potassium channel were used for electrophysiological study. The methodology for stable transfection of this channel in HEK cells can be found elsewhere (Z.Zhou et al., 1998, Biophysical Journal, 74, pp230-241). Before the day of experimentation, the cells were harvested from culture flasks and plated onto glass coverslips in a standard Minimum Essential Medium (MEM) medium with 10% Fetal Calf Serum (FCS). The plated cells were stored in an incubator at 37°C maintained in an atmosphere of 95%O_2/5%CO_2. Cells were studied between 15-28hrs after harvest.

HERG currents were studied using standard patch clamp techniques in the whole-cell mode. During the experiment the cells were superfused with a standard external solution of the following composition (mM); NaCl, 130; KCl, 4; $CaCl_2$, 2; $MgCl_2$, 1; Glucose, 10; HEPES, 5; pH 7.4 with NaOH.

Whole-cell recordings was made using a patch clamp amplifier and patch pipettes which have a resistance of 1-3MOhm when filled with the standard internal solution of the following composition (mM); KCl, 130; MgATP, 5; $MgCl_2$, 1.0; HEPES, 10; EGTA 5, pH 7.2 with KOH. Only those cells with access resistances below 15MΩ and seal resistances >1GΩ was accepted for further experimentation. Series resistance compensation was applied up to a maximum of 80%. No leak subtraction was done. However, acceptable access resistance depended on the size of the recorded currents and the level of series resistance compensation that can safely be used. Following the achievement of whole cell configuration and sufficient time for cell dialysis with pipette solution (>5min), a standard voltage protocol was applied to the cell to evoke membrane currents. The voltage protocol is as follows. The membrane was depolarized from a holding potential of -80mV to +40mV for 1000ms. This was followed by a descending voltage ramp (rate 0.5mV $msec^{-1}$) back to the holding potential. The voltage protocol was applied to a cell continuously throughout the experiment every 4 seconds (0.25Hz). The amplitude of the peak current elicited around -40mV during the ramp was measured. Once stable evoked current responses were obtained in the external solution, vehicle (0.5% DMSO in the standard external solution) was applied for 10-20 min by a peristalic pump. Provided there were minimal changes in the amplitude of the evoked current response in the vehicle control condition, the test compound of either 0.3, 1, 3, 10μM was applied for a 10 min period. The 10 min period included the time which supplying solution was passing through the tube from solution reservoir to the recording chamber via the pump. Exposing time of cells to the compound solution was more than 5min after the drug concentration in the chamber well reached the attempting concentration. There was a subsequent wash period of a 10-20min to assess reversibility. Finally, the cells were exposed to high dose of dofetilide (5μM), a specific IKr blocker, to evaluate the insensitive endogenous current.

All experiments were performed at room temperature (23 ± 1°C). Evoked membrane currents were recorded on-line on a computer, filtered at 500-1KHz (Bessel -3dB) and sampled at 1-2 KHz using the patch clamp amplifier and a specific data analyzing software. Peak current amplitude, which occurred at around -40mV, was measured off line on the computer.

The arithmetic mean of the ten values of amplitude was calculated under vehicle control conditions and in the presence of drug. Percent decrease of I_N in each experiment was obtained by the normalized current value using the following formula: $I_N = (1- I_D/I_C)x100$, where I_D is the mean current value in the presence of drug and I_C is the mean current value under control conditions. Separate experiments were performed for each drug concentration or time-matched control, and arithmetic mean in each experiment is defined as the result of the study.

Drug-drug interaction assay

This method essentially involves determining the percent inhibition of product formation from fluorescence probe at 3μM of the each compound.

More specifically, the assay is carried out as follows. The compounds were pre-incubated with recombinant CYPs, 100 mM potassium phosphate buffer and fluorescence probe as substrate for 5min. Reaction was started by adding a warmed NADPH generating system, which consist of 0.5 mM NADP (expect; for 2D6 0.03 mM), 10 mM $MgCl_2$, 6.2 mM DL-Isocitric acid and 0.5 U/ml Isocitric Dehydrogenase (ICD). The assay plate was incubated at 37°C (expect; for 1A2 and 3A4 at 30°C) and taking fluoresce reading every minutes over 20 to 30min.

Data calculations were preceded as follows;

1. The slope (Time vs. Fluorescence units) was calculated at the linear region
2. The percentage of inhibition in compounds was calculated by the equation

$\{(v_o - v_i) / v_o\} \times 100 =$ % inhibition

Wherein

v_o = rate of control reaction (no inhibitor)

v_i = rate of reaction in the presence of compounds.

Table 1. Condition for drug-drug interaction assay.

	1A2	2C9	2C19	2D6	3A4
Substrate	Vivid blue (Aurora)	MFC (Gentest)	Vivid blue (Aurora)	AMMC (Gentest)	Vivid red (Aurora)
Substrate (μM)	10	30	10	1	2
Enzyme (pmol)	50	50	5	50	5
EX./Em(λ)	408/465	408/535	408/465	400/465	530/595

Half-life in human liver microsomes (HLM)

Test compounds (1 μM) were incubated with 3.3 mM $MgCl_2$ and 0.78 mg/mL HLM (HL101) in 100 mM potassium phosphate buffer (pH 7.4) at 37°C on the 96-deep well plate. The reaction mixture was split into two groups, a non-P450 and a P450 group. NADPH was only added to the reaction mixture of the P450 group. An aliquot of samples of P450 group was collected at 0, 10, 30, and 60 min time point, where 0 min time point indicated the time when NADPH was added into the reaction mixture of P450 group. An aliquot of samples of non-P450 group was collected at -10 and 65 min time point. Collected aliquots were extracted with acetonitrile solution containing an internal standard. The precipitated protein was spun down in centrifuge (2000 rpm, 15 min). The compound concentration in supernatant was measured by LC/MS/MS system.

The half-life value was obtained by plotting the natural logarithm of the peak area ratio of compounds/ internal standard versus time. The slope of the line of best fit through the points yields the rate of metabolism (k). This was converted to a half-life value using following equations:

Half-life = ln 2 / k

Mono-Iodoacetate (MIA)-induced OA model

Male 6-weeks-old Sprague-Dawley (SD, Japan SLC or Charles River Japan) rats were anesthetized with pentobarbital. Injection site (knee) of MIA was shaved and cleaned with 70% ethanol. Twenty-five μl of MIA solution or saline was injected in the right knee joint using a 29G needle. The effect of joint damage on the weight distribution through the right (damaged) and left (untreated) knee was assessed using an incapacitance tester (Linton Instrumentation, Norfolk, UK). The force exerted by each hind limb was measured in grams. The weight-bearing (WB) deficit was determined by a difference of weight loaded on each paw. Rats were trained to measure the WB once a week until 20 days post MIA-injection. Analgesic effects of compounds were measured at 21 days after the MIA injection. Before the compound administration, the "pre value" of WB deficit was measured. After the administration of compounds, attenuation of WB deficits was determined as analgesic effects.

Complete Freund's adjuvant (CFA) induced thermal and mechanical hyperalgesia in rats

Thermal hyperalgesia

Male 6-week-old SD rats were used. Complete Freund's adjuvant (CFA, 300 μg of *Mycobacterium*

Tuberculosis H37RA (Difco, MI) in 100 µL of liquid paraffin (Wako, Osaka, Japan)) was injected into the plantar surface of hind paw of the rats. Two days after CFA-injection, thermal hyperalgesia was determined by method described previously (Hargreaves et al., 1988) using the plantar test apparatus (Ugo-Basil, Varese, Italy). Rats were adapted to the testing environment for at least 15 min prior to any stimulation. Radiant heat was applied to the plantar surface of hind paw and paw withdrawal latencies (PWL, seconds) were determined. The intensity of radiant heat was adjusted to produce the stable PWL of 10 to 15 seconds. The test compound was administered in a volume of 0.5 mL per 100 g body weight. PWL were measured after 1, 3 or 5 hours after drug administration.

Mechanical hyperalgesia

Male 4-week-old SD rats were used. CFA (300 µg of *Mycobacterium Tuberculosis* H37RA (Difco, MI) in 100 µL of liquid paraffin (Wako, Osaka, Japan)) was injected into the plantar surface of hind paw of the rats. Two days after CFA-injection, mechanical hyperalgesia was tested by measuring paw withdrawal threshold (PWT, grams) to pressure using the analgesy-Meter (Ugo-Basil, Varese, Italy). The animals were gently restrained, and steadily increasing pressure was applied to the dorsal surface of a hind paw via a plastic tip. The pressure required to elicit paw withdrawal was determined. The test compound was administered in a volume of 0.5 mL per 100 g body weight. PWT were measured after 1, 3 or 5 hours after drug administration.

The compounds of the examples were tested in the NTCC antagonist assay described above. The IC_{50} values are presented in the following table.

Table 2

Example #	IC_{50}(nM)
1	70
2	68
3	366
4	48
5	131
6	187
7	339
8	149
9	294
10	341
11	429
12	95
13	305
14	89
15	104

Example #	IC_{50}(nM)
16	322
17	168
18	395
19	147
20	261
21	276
22	278
23	229
24	335
25	375
26	452
27	95
28	91
29	110

Drug Substance

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 acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, 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, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

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

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

A pharmaceutically acceptable salt of a compound of formula (I) may be readily prepared by mixing together solutions of the compound of formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the salt may vary from completely ionized to almost non-ionized.

The compounds of the invention may exist in both 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.

Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionized, partially ionized, or non-ionized. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

Hereinafter all references to compounds of formula (I) include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

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

As stated, the invention includes all polymorphs of the compounds of formula (I) as hereinbefore defined.

Also within the scope of the invention are so-called 'prodrugs' of the compounds of formula (I). 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:

(i) where the compound of formula (I) contains a carboxylic acid functionality (-COOH), an ester thereof, for example, replacement of the hydrogen with $(C_1$-$C_8)$alkyl;

(ii) where the compound of formula (I) contains an alcohol functionality (-OH), an ether thereof, for example, replacement of the hydrogen with (C_1-C_6)alkanoyloxymethyl; and
(iii) where the compound of formula (I) contains a primary or secondary amino functionality (-NH_2 or -NHR where R is not H), an amide thereof, for example, replacement of one or both hydrogens with (C_1-C_{10})alkanoyl.

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

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

Compounds of formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of formula (I) contains an alkenyl or alkenylene group, geometric *cis*/*trans* (or Z/E) isomers are possible. Where the compound contains, for example, a keto or oxime group or an aromatic moiety, tautomeric isomerism ('tautomerism') can occur. It follows that a single compound may exhibit more than one type of isomerism.

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

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

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, an acid or base such as tartaric acid or 1-phenylethylamine. 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% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art - see, for example, "Stereochemistry of Organic Compounds" by E L Eliel (Wiley, New York, 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 usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S. Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

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

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, or spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

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

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

ORAL ADMINISTRATION

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

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol,

polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

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

For tablet dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60 wt% 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 wt% to 25 wt%, preferably from 5 wt% to 20 wt% 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 wt% to 5 wt% of the tablet, and glidants may comprise from 0.2 wt% to 1 wt% 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 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the tablet.

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

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

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

The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X).

Solid formulations for oral administration may be formulated to be immediate and/or modified controlled 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 Verma *et al*, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

PARENTERAL ADMINISTRATION

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include .intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular 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 powdered 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 use with needle-free injection administration comprise a compound of the invention in powdered form in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

Formulations for parenteral administration may be formulated to be immediate and/or modified controlled release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated 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 PGLA microspheres.

TOPICAL ADMINISTRATION

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. 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 controlled release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

INHALED/INTRANASAL ADMINISTRATION

The compounds of the invention can also be administered intranasally or by inhalation, typically in

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

The pressurized 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 HPMC), 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 controlled release using, for example, poly(DL-lactic-coglycolic acid (PGLA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 1 µg to 10mg of the compound of formula (I). The overall daily dose will typically be in the range 1 µg to 10 mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

RECTAL/INTRAVAGINAL ADMINISTRATION

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

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

targeted and programmed release.

OTHER TECHNOLOGIES

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

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

DOSAGE

For administration to human patients, the total daily dose of the compounds of the invention is typically in the range 0.1 mg to 3000 mg, preferably from 1mg to 500mg, depending, of course, on the mode of administration. For example, oral administration may require a total daily dose of from 0.1 mg to 3000 mg, preferably from 1mg to 500mg, while an intravenous dose may only require from 0.1 mg to 1000 mg, preferably from 0.1mg to 300mg. The total daily dose may be administered in single or divided doses.

These dosages are based on an average human subject having a weight of about 65kg 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 NTCC antagonist 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 NTCC antagonist, particularly a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined above, may be administered simultaneously, sequentially or separately in combination with one or more agents selected from:

- an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine or pentazocine;
- a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin or zomepirac;
- a barbiturate sedative, e.g. amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobartital, secobarbital, talbutal, theamylal or thiopental;

- a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;
- an H_1 antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;
- a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone;
- a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphrenadine;
- an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinine, cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid, budipine, EN-3231 (MorphiDex®, a combination formulation of morphine and dextromethorphan), topiramate, neramexane or perzinfotel including an NR2B antagonist, e.g. ifenprodil, traxoprodil or (–)-(R)-6-{2-[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]-1-hydroxyethyl-3,4-dihydro-2(1H)-quinolin one;
- an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dexmetatomidine, modafinil, or 4-amino-6,7-dimethoxy-2-(5-methane-sulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;
- a tricyclic antidepressant, e.g. desipramine, imipramine, amitriptyline or nortriptyline;
- an anticonvulsant, e.g. carbamazepine, lamotrigine, topiratmate or valproate;
- a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (αR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1 ,4]diazocino[2,1-g][1,7]-naphthyridine-6-13-dione (TAK-637), 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-met hyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), aprepitant, lanepitant, dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2S,3S);
- a muscarinic antagonist, e.g oxybutynin, tolterodine, propiverine, tropsium chloride, darifenacin, solifenacin, temiverine and ipratropium;
- a COX-2 selective inhibitor, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, or lumiracoxib;
- a coal-tar analgesic, in particular paracetamol;
- a neuroleptic such as droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonepiprazole, blonanserin, iloperidone, perospirone, raclopride, zotepine, bifeprunox, asenapine, lurasidone, amisulpride, balaperidone, palindore, eplivanserin, osanetant, rimonabant, meclinertant, Miraxion® or sarizotan;
- a vanilloid receptor agonist (e.g. resinferatoxin) or antagonist (e.g. capsazepine);
- a beta-adrenergic such as propranolol;
- a local anaesthetic such as mexiletine;
- a corticosteroid such as dexamethasone;

- a 5-HT receptor agonist or antagonist, particularly a 5-$HT_{1B/1D}$ agonist such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan;
- a 5-HT_{2A} receptor antagonist such as R(+)-alpha-(2,3-dimethoxy-phenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (MDL-100907);
- a cholinergic (nicotinic) analgesic, such as ispronicline (TC-1734), (E)-N-methyl-4-(3-pyridinyl)-3-buten-1-amine (RJR-2403), (R)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594) or nicotine;
- Tramadol®;
- a PDEV inhibitor, such as 5-[2-ethoxy-5-(4-methyl-1-piperazinyl-sulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione (IC-351 or tadalafil), 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil), 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 4-[(3-chloro-4-methoxybenzyl)amino]-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide, 3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide;
- an alpha-2-delta ligand such as gabapentin, pregabalin, 3-methylgabapentin, (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (2S,4S)-4-(3-chlorophenoxy)proline, (2S,4S)-4-(3-fluorobenzyl)-proline, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (3R,4R,5R)-3-amino-4,5-dimethyl-heptanoic acid, (3R,4R,5R)-3-amino-4,5-dimethyl-octanoic acid, (2*S*)-2-Amino-4-ethyl-2-methylhexanoic acid and (2S)-2-aminomethyl-5-ethyl-heptanoic acid;
- a cannabinoid;
- metabotropic glutamate subtype 1 receptor (mGluR1) antagonist;
- a serotonin reuptake inhibitor such as sertraline, sertraline metabolite demethylsertraline,

fluoxetine, norfluoxetine (fluoxetine desmethyl metabolite), fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine, dapoxetine, nefazodone, ericlamine and trazodone;

- a noradrenaline (norepinephrine) reuptake inhibitor, such as maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, buproprion, buproprion metabolite hydroxybuproprion, nomifensine and viloxazine (Vivalan®), especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular (S,S)-reboxetine;
- a dual serotonin-noradrenaline reuptake inhibitor, such as venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine, milnacipran and imipramine;
- an inducible nitric oxide synthase (iNOS) inhibitor such as S-[2-[(1-iminoethyl)amino]ethyl]-L-homocysteine, S-[2-[(1-iminoethyl)-amino]ethyl]-4,4-dioxo-L-cysteine, S-[2-[(1-iminoethyl)amino]ethyl]-2-methyl-L-cysteine, (2S,5Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-5-heptenoic acid, 2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)-butyl]thio]-5-chloro-3-pyridinecarbonitrile; 2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chlorobenzonitrile, (2S,4R)-2-amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol, 2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl) butyl]thio]-6-(trifluoromethyl)-3 pyridinecarbonitrile, 2-[[(1R,3S)-3- amino-4-hydroxy- 1 -(5-thiazolyl)butyl]thio]-5-chlorobenzonitrile, N-[4-[2-(3-chlorobenzylamino)ethyl]phenyl]thiophene-2-carboxamidine, or guanidinoethyldisulfide;
- an acetylcholinesterase inhibitor such as donepezil;
- a prostaglandin E_2 subtype 4 (EP4) antagonist such as *N*-[({2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl}amino)-carbonyl]-4-methylbenzenesulfonamide or 4-[(1*S*)-1-({[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;
- a leukotriene B4 antagonist; such as 1-(3-biphenyl-4-ylmethyl-4-hydroxy-chroman-7-yl)-cyclopentanecarboxylic acid (CP-105696), 5-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-5E- hexenyl]oxyphenoxy]-valeric acid (ONO-4057) or DPC-11870,
- a 5-lipoxygenase inhibitor, such as zileuton, 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone (ZD-2138), or 2,3,5-trimethyl-6-(3-pyridylmethyl),1,4-benzoquinone (CV-6504);
- a sodium channel blocker, such as lidocaine;
- a 5-HT3 antagonist, such as ondansetron;

and the pharmaceutically acceptable salts and solvates thereof.

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

Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I) in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

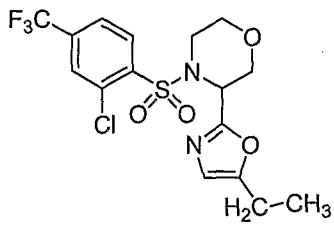
The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically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

Examples

The invention is illustrated in the following non-limiting examples in which, unless stated otherwise: all operations were carried out at room or ambient temperature, that is, in the range of 18-25 °C; evaporation of solvent was carried out using a rotary evaporator under reduced pressure with a bath temperature of up to 60 °C; reactions were monitored by thin layer chromatography (TLC) and reaction times were given for illustration only; the structure and purity of all isolated compounds were assured by at least one of the following techniques: TLC (Merck silica gel 60 F_{254} precoated TLC plates), mass spectrometry or nuclear magnetic resonance spectra (NMR). Yields were given for illustrative purposes only. Flash column chromatography was carried out using Merck silica gel 60 (230-400 mesh ASTM) or Fuji Silysia amino bounded silica (Chromatorex, 30-50 μM) or Biotage amino bounded silica (35-75 μm, KP-NH) or Biotage silica (32-63 μm, KP-Sil). The purification using HPLC was perfomed by the following apparatus and conditions. Apparatus: UV-trigger preparative HPLC system, Waters (Column: XTerra MS C18, 5 um, 19 x 50 mm or 30 x 50 mm), Detector: UV 254 nm Conditions: CH_3CN/0.05% HCOOH aqueous solution or CH_3CN/0.01% NH_3 aqueous solution; 20ml/min (19 x 50 mm) or 40ml/min (30 x 50 mm) at ambient temperature. Microwave apparatus used in the reaction was Emrys optimizer (Personal chemistry). Optical rotation was measured by P-1020 (Jasco). Low-resolution mass spectral data (EI) were obtained on a Integrity (Waters) mass spectrometer. Low-resolution mass spectral data (ESI) were obtained on a ZMD (Micromass) mass spectrometer. NMR data were determined at 270 MHz (JEOL JNMLA 270 spectrometer) or 300 MHz (JEOL JNMLA300 spectrometer) using deuterated chloroform (99.8% D) or DMSO (99.9% D) as solvent unless indicated otherwise, relative to tetramethylsilane (TMS) as internal standard in parts per million (ppm); conventional abbreviations used were: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br. = broad, etc. Chemical symbols have their usual meanings; L (liter(s)), ml (milliliter(s)), g (gram(s)), mg (milligram(s)), mol (moles), mmol (millimoles), eq. (equivalent(s)), quant. (quantitative yield), sat.(saturated), aq (aqua).

EXAMPLE 1

4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-3-(5-ethyl-1,3-oxazol-2-yl)morpholine



Step 1. *tert*-Butyl 3-{[(2-hydroxybutyl)amino]carbonyl}morpholine-4-carboxylate

To dichloromethane (3.0 ml) solution of 4-(tert-butoxycarbonyl)morpholine-3-carboxylic acid (1.7 g, 7.5 mmol, WO20030350761) were added 1-aminobutan-2-ol (1.00 g, 11.3 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.20 g, 11.3 mmol), triethylamine (3.1 mL, 23 mmol), and 1-hydroxybenzotriazole hydrate (1.00 g, 7.5 mmol) at room temperature successively and the mixture was stirred for 14 hours. Aqueous sodium bicarbonate was added to the mixture and the mixture was extracted with dichloromethane and washed with brine. The extract was combined and dried over magnesium sulfate and concentrated in vacuo. The residual oil was purified by silica gel column chromatography (dichloromethane/methanol 9:1) to afford 2.0 g (87%) of the title compound as a white solid.

^{1}H-NMR (270MHz, $CDCl_3$) δ: 6.47 (1H, brs), 4.61-4.29 (2H, m), 3.99-3.75 (2H, m), 3.74-3.36 (4H, m), 3.31-3.01 (2H, m), 2.51 (1H, brs), 1.60-1.34 (2H, m), 1.48 (9H, s), 0.96 (3H, t, J = 8.0 Hz).

ESIMS m/z: 303 ($M + H^+$).

Step 2. *tert*-Butyl 3-{[(2-oxobutyl)amino]carbonyl}morpholine-4-carboxylate

To a dichloromethane (5.0 mL) solution of *tert*-butyl 3-{[(2-hydroxybutyl)amino]carbonyl}morpholine-4-carboxylate (0.6 g, 2.0 mmol, EXAMPLE1, Step 1) were added aqueous sodium bicarbonate (2.0 mL), sodium hypochlorite (2.0 mL), potassium bromide (60.0 mg, 0.5 mmol), and 2,2,6,6-tetramethyl-1-piperidinyloxy (32.0 mg, 0.2 mmol) at 0 °C successively and the mixture was stirred for 1 hour. The mixture was extracted with dichloromethane, washed with brine, dried over magnesium sulfate, and *concentrated in vacuo*. The residual oil was purified by silica gel column chromatography (dichloromethane/methanol 25:1) to afford 0.6 g (quant.) of the title compound as a colorless oil.

^{1}H-NMR (270MHz, $CDCl_3$) δ: 6.77 (1H, brs), 4.52 (1H, d, J = 11.2 Hz), 4.52 (1H, m), 4.35-4.03 (2H, m), 4.03-3.73 (2H, m), 3.55 (1H, dd, J = 4.0, 11.9 Hz), 3.47 (1H, dt, J = 2.6, 11.9 Hz), 3.24 (1H, m), 2.49 (2H, q_{AB}, J = 7.3 Hz), 1.51 (9H, s), 1.13 (3H, t, J = 7.3 Hz). ESIMS m/z: 301 ($M + H^+$).

Step3. 4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-3-(5-ethyl-1,3-oxazol-2-yl)morpholine

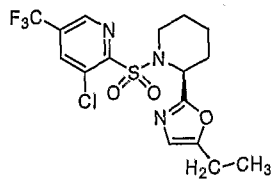
A mixture of *tert*-butyl 3-{[(2-oxobutyl)amino]carbonyl}morpholine-4-carboxylate (600.0 mg, 2.0 mmol, EXAMPLE 1, Step 3) and phosphorus oxychloride (8.0 mL) was refluxed for 2 hours. After being concentrated *in vacuo*, the residual oil was poured into ice carefully. The solution was adjusted pH to 14 using 2*N* aqueous sodium hydroxide. The resulting mixture was extracted with dichloromethane, washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residual oil was purified by silica gel column chromatography (dichloromethane/methanol 19:1) to afford a crude 3-(5-ethyl-1,3-oxazol-2-yl)morpholine (600 mg) as a dark brown viscous oil. The crude mixture of 3-(5-ethyl-1,3-oxazol-2-yl)morpholine (600 mg) was dissolved with pyridine (2 mL) and 2-chloro-4-(trifluoromethyl)benzenesulfonyl chloride (150 mg, 0.5 mmol) was added to the mixture. After being stirred at room temperature for 2 hours, the mixture was concentrated *in vacuo* and the residual mixture was dissolved with dichloromethane. The organic layer was washed with 2*N* hydrochloric acid and brine, dried over magnesium sulfate and concentrated *in vacuo*. The residual oil was purified by preparative silica gel TLC (hexane/ethyl acetate 1:1) and preparative HPLC (acetonitrile-water 4-96, basic condition) to afford 6.7 mg (yield 1%) of the title compound as a white solid.

^{1}H-NMR (270MHz, $CDCl_3$) δ: 8.20 (1H, d, J = 8.1 Hz), 7.76 (1H, s), 7.61 (1H, d, J = 8.1 Hz), 6.58 (1H,

s), 5.03 (1H, s), 4.38 (1H, d, J = 11.7 Hz), 4.02-3.86 (2H, m), 3.86-3.52 (3H, m), 2.51 (2H, q_{AB}, J = 7.3 Hz), 1.16 (3H, t, J = 7.3 Hz).

EXAMPLE 2

(2*S*)-2-(5-Ethyl-1,3-oxazol-2-yl)-1-{[4-(trifluoromethyl)phenyl]sulfonyl}piperidine



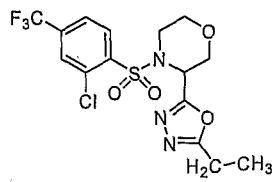
Step1. (2*S*)-2-(5-Ethyl-1,3-oxazol-2-yl)-1-{[4-(trifluoromethyl)phenyl]sulfonyl}piperidine

A solution of 3-chloro-5-(trifluoromethyl)pyridine-2-thiol (430 mg, 2.0 mmol, *Heterocycles* 1984, *22*, 117) in concentrated hydrochloric acid (2.6 mL) and water (0.8 mL) was cooled to 0 °C. Chlorine was bubbled into the solution for 30 minutes at 0 °C. Ice-water was added to the mixture and the mixture was extracted with cold ether. The extract was washed with cold aqueous sodium bicarbonate, dried over magnesium sulfate and concentrated with a stream of nitrogen at 0 °C to afford crude 3-chloro-5-(trifluoromethyl)pyridine-2-sulfonyl chloride as a viscous oil. To the residual oil was added an ice-cold pyridine (3.0 mL) solution of (2*S*)-2-(5-ethyl-1,3-oxazol-2-yl)piperidine (180.0 mg, 1.0 mmol, WO2005068448). After being stirred at 0 °C for 1.5 hours, the mixture was concentrated *in vacuo*. The residual oil was dissolved with dichloromethane. The mixture was washed with 2*N* hydrochloric acid and brine. The extract was dried over magnesium sulfate and concentrated *in vacuo* to afford an oil. The residual oil was purified by silica gel column chromatography (hexane/ethyl acetate 4:1) and preparative HPLC (acetonitrile-water 4-96, basic condition) to give 53 mg (12%) of the title compound as a white solid.

^{1}H-NMR (300MHz, $CDCl_3$) δ:8.57 (1H, s), 8.07 (1H, s), 6.54 (1H, s), 5.33 (1H, d, J = 4.4 Hz), 4.00 (1H, d, J = 13.2 Hz), 3.54-3.40 (1H, m), 2.49 (2H, q_{AB}, J = 7.3 Hz), 2.27-1.58 (6H, m), 1.15 (3H, t, J = 7.3 Hz). ESIMS: m/z 423 ($M + H^+$).

EXAMPLE 3

4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-3-(5-ethyl-1,3,4-oxadiazol-2-yl)morpholine



Step1. *tert*-Butyl 3-[(2-propionylhydrazino)carbonyl]morpholine-4-carboxylate

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.46 g, 2.4 mmol) was added to a mixture of 4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid (0.46 g, 2.0 mmol), hydrazine hydrate (0.11 mL, 2.2 mmol), triethylamine (1.4 mL, 10 mmol), and 1-hydroxybenzotriazole hydrate (0.37 g, 2.4 mmol) in dichloromethane (20 mL). After being stirred at room temperature for 16 hours, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.58 g, 3.0 mmol) and propionic acid (0.22 mL, 3.0 mmol) were added to the mixture. The mixture was stirred at room temperature for 6 hours, and concentrated *in vacuo*. The residual oil was purified by silica gel column chromatography (dichloromethane/methanol 15:1) to afford 0.44 g (73%) of the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 9.15-8.67 (2H, br); 4.74-4.33 (2H, m); 4.11-3.20 (5H, br); 3.16-2.26 (2H, m); 1.50 (9H, s); 1.38-1.14 (3H, m). ESIMS m/z: 300 ($M-H^-$).

Step 2. *N'*-Propionylmorpholine-3-carbohydrazide hydrochloride

The mixture of *tert*-butyl 3-[(2-propionylhydrazino)carbonyl]morpholine-4-carboxylate (0.44 g, 1.5 mmol, EXAMPLE 3 Step 1) and 4*N* hydrogen chloride in ethyl acetate was stirred at room temperature for 30 minutes. The mixture was cooled to 0 °C and filtered, and the precipitate was dried to give 0.26 g (73%) the title compound as a white solid.

^{1}H NMR (dimethylsulfoxide-d_6) δ: 10.53 (1H, s); 10.05 (1H, s); 4.32-3.52 (7H, m); 3.19 (2H, br), 2.28-2.05 (2H, m); 1.02 (3H, t, J = 7.3 Hz). ESIMS: m/z 202 ($M+H^+$), 200 ($M-H^-$).

Step 3. 4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-*N'*-propionylmorpholine-3-carbohydrazide

To a mixture of *N'*-propionylmorpholine-3-carbohydrazide hydrochloride (71 mg, 0.30 mmol, EXAMPLE 3, Step 2) and triethylamine (0.13 mL, 0.90 mmol) in dichloromethane (3.0 mL) was added 2-chloro-4-(trifluoromethyl)benzenesulfonyl chloride (84 mg, 0.30 mmol). After being stirred at room temperature for 16 hours, aqueous sodium hydrogen carbonate (10 mL) was added to the mixture. The mixture was extracted with dichloromethane (50 mL). The extract was dried over magnesium sulfate and filtered and concentrated *in vacuo*. The residual solid was purified by preparative HPLC (column: XTerra MS C18, 5 um, 20 x 50 mm, A:0.01% aqueous ammonia. B:acetonitrile, gradient 4-96%B, flow rate 20 mL/minute, run time 7 minutes) to give 20 mg (15%) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$) δ: 9.27 (1H, br); 8.41 (1H, br), 8.27 (1H, d, J = 8.6 Hz), 7.83 (1H, s); 7.69 (1H, d, J = 8.6 Hz), 4.56-3.29 (7H, m); 2.30 (2H, q, J = 7.9 Hz); 1.18 (3H, t, J = 7.3 Hz).

ESI MS: m/z 443 ($M+H^+$), 441 ($M-H^-$).

Step 4. 4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-3-(5-ethyl-1,3,4-oxadiazol-2-yl)morpholine

Phospholic trichloride (38 μL) was added to a solution of 4-{[2-chloro-4-(trifluoromethyl)phenyl]sulfonyl}-*N'*-propionylmorpholine-3-carbohydrazide (18 mg, 41 μmol, EXAMPLE 3, Step 3) in acetonitrile (0.60 mL). The mixture was heated at 90 °C and stirred for 2 hours. After cooling to room temperature, aqueous sodium hydrogen carbonate (10 mL) was added to the mixture. The mixture was extracted with ethyl acetate (30 mL x 2) and washed with brine. The extracts were combined and dried over sodium sulfate and concentrated *in vacuo*. The residual oil was purified by preparative HPLC (column: XTerra MS C18, 5 um, 20 x 50 mm, A:0.01% aqueous ammonia. B:acetonitrile, gradient 4-96%B, flow rate 20 mL/minute, run time 7 minutes) to give the title compound (3.1 mg, yield 18%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 8.24 (1H, d, J = 8.6 Hz), 7.79 (1H, s); 7.65 (1H, d, J = 8.6 Hz); 5.21 (1H, d, J = 3.3 Hz); 4.37 (1H, d, J = 11.9 Hz); 3.96 (1H, dd, J = 3.3, 11.9 Hz); 3.87-3.47 (3H, m); 2.80 (2H, q, J = 7.9 Hz); 1.33 (3H, t, J = 7.9 Hz). ESI MS: m/z 426 ($M+H^+$).

EXAMPLE 4-29

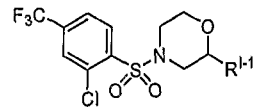
Genenal Procedure

In a 4ml vial, 2-chloro-4-(trifluoromethyl)benzene-1-sulfonyl chloride (61 mg, 0.22 mmol) was dissolved in 0.9 ml of *N,N*-dimethylacetamide, and a solution of the corresponding amine (0.2 mmol) and *N,N*-diisopropylethylamine (43 μl, 0.25 mmol) in 0.8 ml of *N,N*-dimethylacetamide was added to the sulfonyl chloride solution. The mixture was agitated by shaking at room temperature for 6 hours and the mixture was concentrated to dryness by vacuum centrifuge. The resulting solid was purified with

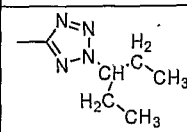
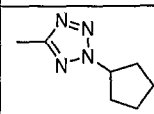
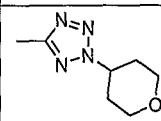
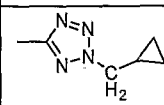
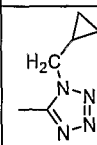
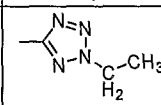
reverse-phase preparative HPLC (0.05 % trifluoroacetic acid-acetonitrile) to give the title compound.

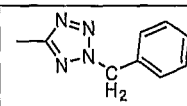
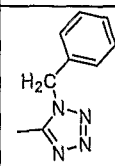
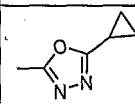
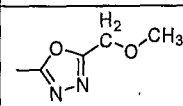
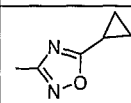
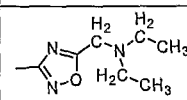
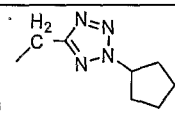
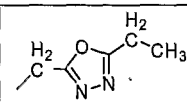
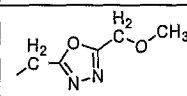
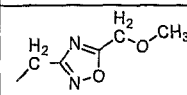
Analytical condition for LCMS

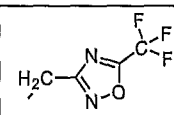
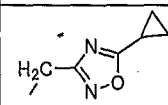
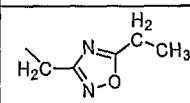
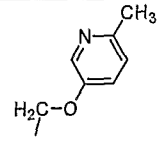
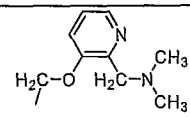
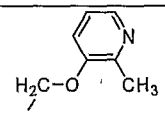
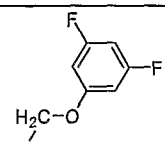
Column Xterra C18 4.6 mm x 50 mm, Flow rate 2.0 mL/minute; Mobile phase 5% MeOH/95% 0.05% HCO_2H in H_2O programmed over 1.0 minute to 95% MeOH/5% 0.05% HCO_2H in H_2O. Hold for 1.5 minutes. Wave length 210-400 nm. MS detector ESI cone 15 Volts.

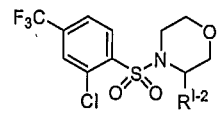


(I-1)

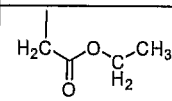
EXAMPLE	Compound name Physical data	R^{I-1} in formula (I-1)
4	4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-[2-(1-ethylpropyl)-2*H*-tetrazol-5-yl]morpholine LCMS retention time: 1.56 minutes. ESIMS: m/z 468 ($M+H^+$).	
5	4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-(2-cyclopentyl-2*H*-tetrazol-5-yl)morpholine LCMS retention time: 1.56 minutes. ESIMS: m/z 466 ($M+H^+$).	
6	4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-[2-(tetrahydro-2*H*-pyran-4-yl)-2*H*-tetrazol-5-yl]morpholine LCMS retention time: 1.48 minutes. ESIMS: m/z 482 ($M+H^+$).	
7	4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-[2-(cyclopropylmethyl)-2*H*-tetrazol-5-yl]morpholine LCMS retention time: 1.52 minutes. ESIMS: m/z 452 ($M+H^+$).	
8	4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-[1-(cyclopropylmethyl)-1*H*-tetrazol-5-yl]morpholine LCMS retention time: 1.49 minutes. ESIMS: m/z 452 ($M+H^+$).	
9	4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-(2-ethyl-2*H*-tetrazol-5-yl)morpholine LCMS retention time: 1.47 minutes. ESIMS: m/z 426 ($M+H^+$).	

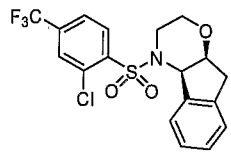
10	2-(2-Benzyl-2*H*-tetrazol-5-yl)-4-{[2-chloro-4-(trifluoromethyl)phenyl]sulfonyl}morpholine LCMS retention time: 1.52 minutes. ESIMS: m/z 488 ($M+H^+$).	
11	2-(1-Benzyl-1*H*-tetrazol-5-yl)-4-{[2-chloro-4-(trifluoromethyl)phenyl]sulfonyl}morpholine LCMS retention time: 1.51 minutes. ESIMS: m/z 488 ($M+H^+$).	
12	4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)morpholine LCMS retention time: 1.53 minutes. ESIMS: m/z 438 ($M+H^+$).	
13	4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]morpholine LCMS retention time: 1.47 minutes. ESIMS: m/z 442 ($M+H^+$).	
14	4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)morpholine LCMS retention time: 1.53 minutes. ESIMS: m/z 438 ($M+H^+$).	
15	*N*-{[3-(4-{[2-chloro-4-(trifluoromethyl)phenyl]sulfonyl}morpholin-2-yl)-1,2,4-oxadiazol-5-yl]methyl}-*N*-ethylethanamine LCMS retention time: 1.21 minutes. ESIMS: m/z 483 ($M+H^+$).	
16	4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-[(2-cyclopentyl-2*H*-tetrazol-5-yl)methyl]morpholine LCMS retention time: 1.56 minutes. ESIMS: m/z 480 ($M+H^+$).	
17	4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-[(5-ethyl-1,3,4-oxadiazol-2-yl)methyl]morpholine LCMS retention time: 1.50 minutes. ESIMS: m/z 440 ($M+H^+$).	
18	4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-{[5-(methoxymethyl)-1,3,4-oxadiazol-2-yl]methyl}morpholine LCMS retention time: 1.46 minutes. ESIMS: m/z 456 ($M+H^+$).	
19	4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-{[5-(methoxymethyl)-1,2,4-oxadiazol-3-yl]methyl}morpholine LCMS retention time: 1.47 minutes. ESIMS: m/z 456 ($M+H^+$).	

20	4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-{[5-(difluoromethyl)-1,2,4-oxadiazol-3-yl]methyl}morpholine LCMS retention time: 1.49 minutes. ESIMS: m/z 462 ($M+H^+$).	
21	4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-[(5-cyclopropyl-1,2,4-oxadiazol-3-yl)methyl]morpholine LCMS retention time: 1.52 minutes. ESIMS: m/z 452 ($M+H^+$).	
22	4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-[(5-ethyl-1,2,4-oxadiazol-3-yl)methyl]morpholine LCMS retention time: 1.50 minutes. ESIMS: m/z 440 ($M+H^+$).	
23	4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-{[(6-methylpyridin-3-yl)oxy]methyl}morpholine LCMS retention time: 1.26 minutes. ESIMS: m/z 451 ($M+H^+$).	
24	1-{3-[(4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}morpholin-2-yl)methoxy]pyridin-2-yl}-*N,N*-dimethylmethanamine LCMS retention time: 1.15 minutes. ESIMS: m/z 494 ($M+H^+$).	
25	4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-{[(2-methylpyridin-3-yl)oxy]methyl}morpholine LCMS retention time: 1.24 minutes. ESIMS: m/z 451 ($M+H^+$).	
26	4-{[2-Chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-[(3,5-difluorophenoxy)methyl]morpholine LCMS retention time: 1.61 minutes. ESIMS: m/z 472 ($M+H^+$).	



(I-2)

EXAMPLE	Compound name Physical data	R^{I-2} in formula (I-2)
27	(3*R*)-4-{[2-chloro-4-(trifluoromethyl)phenyl]sulfonyl}-3-phenylmorpholine LCMS retention time: 1.57 minutes. ESIMS: m/z 406 ($M+H^+$).	
28	Ethyl (4-{[2-chloro-4-(trifluoromethyl)phenyl]sulfonyl}morpholin-3-yl)acetate LCMS retention time: 1.51 minutes. ESIMS: m/z 416 ($M+H^+$).	

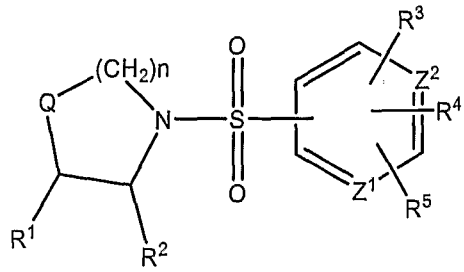


EXAMPLE 29

EXAMPLE	Compound name Physical data
29	(4a*R*,9a*S*)-4-{[2-chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2,3,4,4a,9,9a-hexahydroindeno[2,1-*b*][1,4]oxazine LCMS retention time: 1.51 minutes. ESIMS: m/z 416 ($M+H^+$).

CLAIMS

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof;

wherein Q is CH_2, O or S;

Z^1 is CR^a or N; Z^2 is CR^b or N;

R^1 and R^2 are each independently hydrogen, halogen, hydroxy, oxo, thio, amino, cyano, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, -Het-L, -Het-A, -X-L, -X-A, -L-Y, -L-Het-Y, -L-X-Y, (C_6-C_{10})aryl, 5- to 10- membered heteroaryl or $-CONH_2$, or R^1 and R^2, together with the carbons to which R^1 and R^2 are attached, form (C_3-C_{10})carbocycle or 5- to 10- membered heterocycle,

wherein X is -CO-, -CO-O-, $-CONR^6$-, -O-CO-, $-NR^6$-CO- or $-NR^6$-CO- or $-NR^6$-CO-NR^6-, wherein R^6 is hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

Het is -O-, -S- or $-NR^6$-, wherein R^6 is as defined above;

A is (C_6-C_{10})aryl, 5- to 10- membered heteroaryl, (C_3-C_{10})carbocyclyl or 5- to 10- membered heterocyclyl;

L is (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl moiety;

Y is (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_6-C_{10})aryl, 5- to 10- membered heteroaryl, (C_3-C_{10})carbocyclyl, 5- to 10- membered heterocyclyl or -L-A,

R^a, R^b, R^3, R^4 and R^5 are each independently hydrogen, halogen, hydroxy, thio, amino, cyano, nitro, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, mono(C_1-C_6)alkylamino or di(C_1-C_6)alkylamino; and

n is 1 or 2;

wherein said alkyl, alkenyl and alkynyl in R^a, R^b, R^1, R^2, R^3, R^4 and R^5 are optionally substituted by 1 to 3 substituents each independently selected from halogen, hydroxy, amino or thio;

said aryl, heteroaryl, carbocyclyl and heterocyclyl groups and moieties in R^1 and R^2 are optionally substituted by 1 to 3 substituents each independently selected from halogen, hydroxy, amino, thio, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, -mono(C_1-C_6)alkylamino, -di(C_1-C_6)alkylamino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, halo(C_1-C_6)alkylthio, hydroxy(C_1-C_6)alkyl, (C_3-C_{10})carbocyclyl, 5- to 10- membered heterocyclyl, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl, -(C_1-C_6)alkyl-S-(C_1-C_6)alkyl, -(C_1-C_6)alkyl-mono(C_1-C_6)alkylamino, -(C_1-C_6)alkyl-di(C_1-C_6)alkylamino, -CO-(C_1-C_6)alkyl, -CO-O-(C_1-C_6)alkyl, -CO-mono(C_1-C_6)alkylamino, -CO-di(C_1-C_6)alkylamino, -(C_1-C_6)alkyl-(C_3-C_{10})carbocyclyl or -(C_1-C_6)alkyl-(C_6-C_{10})aryl;

provided that when Q is CH_2 and n is 2, then at least one of Z^1 and Z^2 is N.

2. A compound according to claim 1, wherein R^1 and R^2 are each independently hydrogen, halogen, (C_1-C_6)alkyl, -L-Y, -L-Het-Y, -L-X-Y, (C_6-C_{10})aryl or 5- to 10- membered heteroaryl, provided that at least one of R^1 and R^2 is hydrogen, or R^1 and R^2, together with the carbons to which R^1 and R^2 are attached, form (C_3-C_{10})carbocycle or 5- to 10- membered heterocycle,

wherein X is -CO-, -CO-O- or -O-CO-;

Het is -O- or -S-;

L is (C_1-C_6)alkyl moiety;

Y is (C_1-C_6)alkyl, (C_6-C_{10})aryl, 5- to 10- membered heteroaryl, (C_3-C_{10})carbocyclyl or 5- to 10- membered heterocyclyl;

wherein said alkyl in R^1 and R^2 are optionally substituted by 1 to 3 substituents each independently selected from halogen or hydroxy;

said aryl, heteroaryl, carbocyclyl and heterocyclyl in R^1 and R^2 are optionally substituted by 1 to 3 substituents each independently selected from halogen, hydroxy, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, -mono(C_1-C_6)alkylamino, -di(C_1-C_6)alkylamino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxy(C_1-C_6)alkyl, (C_3-C_{10})carbocyclyl, 5- to 10- membered heterocyclyl, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl, -(C_1-C_6)alkyl-mono(C_1-C_6)alkylamino, -(C_1-C_6)alkyl-di(C_1-C_6)alkylamino, -CO-(C_1-C_6)alkyl, -CO-O-(C_1-C_6)alkyl, -(C_1-C_6)alkyl-(C_3-C_{10})carbocyclyl or -(C_1-C_6)alkyl-(C_6-C_{10})aryl.

3. A compound according to claim 1 or 2, wherein R^1 and R^2 are each independently hydrogen, (C_1-C_6)alkyl, -L-Y, -L-Het-Y, -L-X-Y, (C_6-C_{10})aryl or 5- to 10- membered heteroaryl, provided that at least one of R^1 and R^2 is hydrogen, or R^1 and R^2, together with the carbons to which R^1 and R^2 are attached, form (C_3-C_{10})carbocycle or 5- to 10- membered heterocycle,

wherein X is -CO-O-;

Het is -O-;

L is (C_1-C_6)alkyl moiety;

Y is (C_1-C_6)alkyl, (C_6-C_{10})aryl or 5- to 10- membered heteroaryl;

wherein said alkyl in R^1 and R^2 are optionally substituted by 1 to 3 substituents each independently selected from halogen or hydroxy;

said aryl, heteroaryl, carbocyclyl and heterocyclyl groups and moieties in R^1 and R^2 are optionally substituted by 1 to 2 substituents each independently selected from halogen, amino, (C_1-C_6)alkyl, -mono(C_1-C_6)alkylamino, -di(C_1-C_6)alkylamino, halo(C_1-C_6)alkyl, (C_3-C_{10})carbocyclyl, 5- to 10- membered heterocyclyl, -(C_1-C_6)alkyl-O-(C_1-C_6)alkyl, -(C_1-C_6)alkyl-mono(C_1-C_6)alkylamino, -(C_1-C_6)alkyl-di(C_1-C_6)alkylamino, -(C_1-C_6)alkyl-(C_3-C_{10})carbocyclyl or -(C_1-C_6)alkyl-(C_6-C_{10})aryl.

4. A compound according to any one of claims 1 to 3, wherein R^1 and R^2 are each independently hydrogen, (C_1-C_6)alkyl, -L-Y, -L-Het-Y, -L-X-Y or phenyl or heteroaryl selected from thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, pyridyl or pyrimidinyl, provided that at least one of R^1 and R^2 is hydrogen, or R^1 and R^2, together with the carbons to which R^1 and R^2 are attached, form indane or tetraline;

wherein X is -CO-O-;

Het is –O-;

L is (C_1-C_4)alkyl moiety;

Y is (C_1-C_4)alkyl, phenyl or heteroaryl selected from thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, pyridyl or pyrimidinyl;

wherein said alkyl in R^1 and R^2 are optionally substituted by 1 to 3 substituents each independently selected from halogen or hydroxy;

said phenyl and heteroaryl groups and moieties in R^1 and R^2 are optionally substituted by 1 to 2 substituents each independently selected from fluorine, chloride, amino, (C_1-C_6)alkyl, -$N(CH_3)_2$, -$N(C_2H_5)_2$, -$N(CH_3)(C_2H_5)$, -CF_3, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydro-2H-pyranyl, -CH_2-O-CH_3, -CH_2-O-C_2H_5, -$(CH_2)_2$-O-CH_3, -$(CH_2)_2$-O-C_2H_5, -CH_2-$N(CH_3)_2$, -$(CH_2)_2$-$N(CH_3)_2$, -CH_2-$N(C_2H_5)_2$, -$(CH_2)_2$-$N(C_2H_5)_2$, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopropylethyl, cyclobutylethyl, cyclopentylethyl, cyclohexylethyl, phenylmethyl or phenylethyl.

5. A compound according to any one of claims 1 to 4, wherein R^a, R^b, R^3, R^4 and R^5 are each independently hydrogen, halogen, hydroxy, amino, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, -mono(C_1-C_6)alkylamino or -di(C_1-C_6)alkylamino;

wherein said alkyl in R^a, R^b, R^3, R^4 and R^5 are optionally substituted by 1 to 3 substituents each independently selected from halogen or hydroxy.

6. A compound according to any one of claims 1 to 5, wherein R^a, R^b, R^3, R^4 and R^5 are each independently hydrogen, halogen or (C_1-C_6)alkyl;

wherein said alkyl in R^a, R^b, R^3, R^4 and R^5 are optionally substituted by 1 to 3 substituents each independently selected from halogen or hydroxy.

7. A compound according to any one of claims 1 to 6, wherein Z^1 is CR^a, Z^2 is CR^b, Q is O and n is 2.

8. A compound according to any one of claims 1 to 6, wherein Z^1 is N, Z^2 is CR^b, Q is CH_2 and n is 2.

9. A compound according to any one of claims 1 to 8, wherein the compound is selected from the group consisting of:

4-{[2-chloro-4-(trifluoromethyl)phenyl]sulfonyl}-3-(5-ethyl-1,3-oxazol-2-yl)morpholine,

(2*S*)-2-(5-ethyl-1,3-oxazol-2-yl)-1-{[4-(trifluoromethyl)phenyl]sulfonyl}piperidine,

4-{[2-chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-[2-(1-ethylpropyl)-2*H*-tetrazol-5-yl]morpholine,

4-{[2-chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)morpholine,

4-{[2-chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)morpholine,

(3*R*)-4-{[2-chloro-4-(trifluoromethyl)phenyl]sulfonyl}-3-phenylmorpholine and

4-{[2-chloro-4-(trifluoromethyl)phenyl]sulfonyl}-3-(5-ethyl-1,3,4-oxadiazol-2-yl)morpholine;

and pharmaceutically acceptable salts thereof.

10. A pharmaceutical composition including a compound of the formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 9, together with a pharmaceutically acceptable excipient.

11. A use of a compound of the formula (I) or a pharmaceutically acceptable salt or composition

thereof, as defined in any one of claims 1 to 9, for the manufacture of a medicament to treat a disease for which a N type calcium channel antagonist is indicated.

12. A use according to claim 11 wherein the disease is selected from acute cerebral ischemia, pain, chronic pain, neuropathic pain, inflammatory pain, post herpetic neuralgia, neuropathies, neuralgia, diabetic neuropathy, HIV-related neuropathy, nerve injury, rheumatoid arthritic pain, osteoarthritic pain, burns, back pain, visceral pain, cancer pain, dental pain, headache, migraine, carpal tunnel syndrome, fibromyalgia, neuritis, sciatica, pelvic hypersensitivity, pelvic pain, menstrual pain; bladder disease such as incontinence, micturition disorder, renal colic and cystitis; inflammation such as burns, rheumatoid arthritis and osteoarthritis; neurodegenerative disease such as stroke, post stroke pain and multiple sclerosis; pulmonary disease such as asthma, cough, chronic obstructive pulmonary disease (COPD) and broncho constriction; gastrointestinal disease such as gastroesophageal reflux disease (GERD), dysphagia, ulcer, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), colitis and Crohn's disease; ischemia such as cerebrovascular ischemia; emesis such as cancer chemotherapy-induced emesis, and obesity.

13. A method of treatment of a mammal, including a human being, to treat a disease for which a N type calcium channel antagonist is indicated, including treating said mammal with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt or composition thereof, as defined in any one of claims 1 to 9.

14. A combination of a compound of the formula (I) or the pharmaceutical acceptable salt as defined in any one of claims 1 to 9, and another pharmacologically active agent.

15. A pharmaceutical composition including a compound of the formula (I) or the pharmaceutical acceptable salt as defined in any one of claims 1 to 9, and another pharmacologically active agent.