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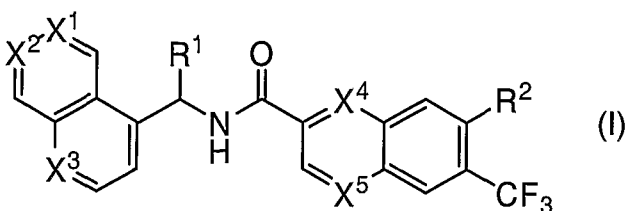
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(54) Title: SUBSTITUTED N-BICYCLICALKYL BICYCLIC CARBOXYAMIDE COMPOUNDS



(57) Abstract: This invention provides compounds of the formula (I): and their use for the treatment of disease conditions caused by overactivation of the VR1 receptor such as pain, or the like in mammal. The invention also provides pharmaceutical compositions comprising the above compounds.

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SUBSTITUTED N-BICYCLICALKYL BICYCLIC CARBOXYAMIDE COMPOUNDS**Technical Field**

This invention relates to novel substituted N-bicyclic alkyl bicyclic-carboxamide compounds and to their use in therapy. These compounds are particularly useful as antagonists of the VR1 (Type I Vanilloid) receptor, 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

The Vanilloid receptor 1 (VR1) is a ligand gated non-selective cation channel. It is believed to be a member of the transient receptor potential super family. VR1 is recognized as a polymodal nociceptor that integrates multiple pain stimuli, e.g., noxious heat, protons, and vanilloids (European Journal of Physiology 451:151-159, 2005). A major distribution of VR1 is in the sensory (A δ - and C-) fibres, which are bipolar neurons having somata in sensory ganglia. The peripheral fibers of these neurons innervate the skin, the mucosal membranes, and almost all internal organs. It is also recognized that VR1 exists in bladder, kidney, brain, pancreas, and various kinds of organs. A body of studies using VR1 agonists, e.g., capsaicin or resiniferatoxin, have suggested that VR1 positive nerves are thought to participate in a variety of physiological responses, including nociception (Clinical Therapeutics. 13(3): 338-395, 1991, Journal of Pharmacology and Experimental Therapeutics 314:410-421, 2005, and Neuroscience Letter 388: 75-80, 2005). Based on both the tissue distribution and the roles of VR1, VR1 antagonists would have good therapeutic potential.

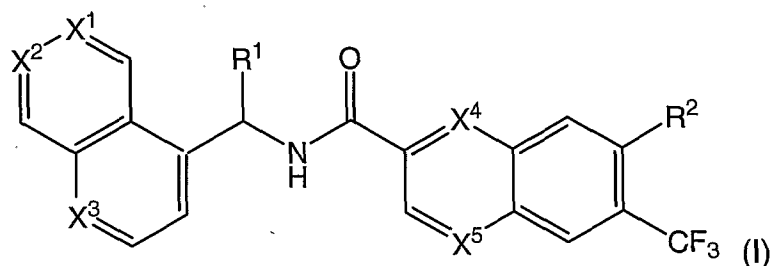
WO2004014377 discloses a variety of 4-hydroxyquinoline derivatives as matrix metalloproteinase inhibitors. WO2002030426 discloses a variety of naphthalenyl carboxamide derivatives and quinoline carboxamide derivatives as inhibitors of HIV integrase and inhibitors of HIV replication.

It would be desirable if there were provided improved VR1 selective antagonists with enhanced binding activity with the VR1 receptor by systemic administration and 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 certain substituted carboxamide derivatives are potent VR1 antagonists with analgesic activity by systemic administration.

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



wherein,

one of X^1 , X^2 and X^3 is N, and the others are CH;

X^4 is N and X^5 is CH, or X^4 and X^5 are CH, or X^4 is CH and X^5 is N;

R^1 is hydrogen or C_1 - C_4 alkyl;

R^2 is hydrogen or halogen;

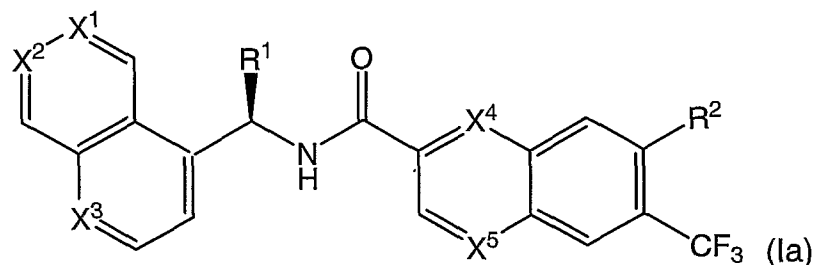
or a pharmaceutically acceptable salt or solvate thereof.

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 terms "**(C_1 - C_4)alkyl**" mean straight or branched chain saturated radicals having the required number of carbon atoms, including methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *secondary*-butyl and *tert*-butyl.

A preferred subgroup of compound of formula (I) includes compounds of formula (Ia)



wherein R^1 is C_1 - C_4 alkyl.

In a preferred embodiment, R^1 is hydrogen, methyl or ethyl; most preferably R^1 is hydrogen or methyl.

In a preferred embodiment, R^2 is hydrogen, fluoro or chloro.

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In a preferred embodiment, X¹ is N, and X² and X³ are both CH. (Isoquinolin-8-yl)

In a preferred embodiment, X² is N, and X¹ and X³ are both CH. (Isoquinolin-5-yl)

In a preferred embodiment, X³ is N, and X¹ and X² are both CH. (Quinolin-4-yl)

In a preferred embodiment, X⁴ is N, and X⁵ is CH. (Quinolin-2-yl)

In a preferred embodiment, X⁵ is N, and X⁴ is CH. (Quinolin-3-yl)

In a preferred embodiment, X⁴ and X⁵ are both CH. (Naphthyl)

Preferably the bicyclic moiety of the left hand (amine) side in formula (I) is isoquinolin-5-yl, isoquinolin-8-yl or quinolin-4-yl. Preferably the bicyclic moiety on the right hand (carboxylic acid) side in formula (I) is quinolin-2-yl, quinolin-3-yl or naphthalene.

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 and solvates thereof.

The compounds of formula (I), being VR1 antagonists, are potentially useful in the treatment of a range of disorders, particularly the treatment of pain, including 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 and menstrual pain; bladder disease, such as urinary incontinence, lower urinary tract symptoms, 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; diseases of the respiratory tree that have a contribution to symptoms or pathology arising from the sensory afferent nervous system, such as cough, bronchoconstriction, irritation, inflammation and other pathways in diseases of the lower airway such as asthma and COPD as well as those of the upper airway, such as allergic rhinitis and chronic sinusitis; 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 and acute cerebral ischemia; emesis, such as cancer chemotherapy-induced emesis; diabetes and obesity; or the like in mammals, especially humans. The treatment of pain, particularly inflammatory 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 intervertebral discs or abnormalities of the lumbar 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, myocardial 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.

Urinary incontinence (any condition in which there is an involuntary leakage of urine), includes stress urinary incontinence, urge urinary incontinence and mixed urinary incontinence, overactive bladder with associated urinary incontinence, enuresis, nocturnal enuresis, continuous urinary incontinence, and situational urinary incontinence such as incontinence during sexual intercourse.

Lower urinary tract symptoms comprise three groups of urinary symptoms, which may be defined as storage (irritative), voiding (obstructive) and post-micturition symptoms. Storage symptoms comprise urgency, frequency, nocturia, urgency incontinence and stress incontinence, which can be associated with overactive bladder

(OAB) and benign prostatic hyperplasia (BPH). Voiding symptoms comprise hesitancy, poor flow, intermittency, straining and dysuria. Post-micturition symptoms comprise terminal dribbling, post-void dribbling and a sense of incomplete emptying.

Over Active Bladder (OAB) is defined as urgency, with or without urge incontinence, usually with frequency and nocturia [Abrams et al., *Neurourology and Urodynamics* 21:167-178 (2002)]. Prevalence of OAB in men and women is similar, with approximately 16% of the population of the USA suffering from the condition [Stewart et al, *Prevalence of Overactive Bladder in the United States: Results from the NOBLE Program; Abstract Presented at the 2nd International Consultation on Incontinence, July 2001, Paris, France*]. OAB includes OAB Wet and OAB Dry. The terms OAB Wet and OAB Dry describe OAB patients with or without urinary incontinence, respectively. Until recently, the cardinal symptom of OAB was believed to be urinary incontinence. However, with the advent of the new terms this is clearly not meaningful for the large number of sufferers who are not incontinent (i.e. OAB Dry patients). Thus, a recent study from Liberman et al [*'Health Related Quality of Life Among Adults with Symptoms of Overactive Bladder: Results From A US Community-Based Survey'; Urology* 57(6), 1044-1050, 2001] examined the impact of all OAB symptoms on the quality of life of a community-based sample of the US population. This study demonstrated that individuals suffering from OAB without any demonstrable loss of urine have an impaired quality of life when compared with controls.

BPH is a chronically progressive disease that can lead to complications such as acute urinary retention, recurrent urinary tract infections, bladder stones and renal dysfunction. The prevalence and average severity of LUTS associated with BPH in men increases with age. BPH leads to an increase in prostate volume, creating urethral and bladder outflow obstruction as well as secondary changes in bladder function. The effects of this are manifested by both storage (irritative) and voiding (obstructive) symptoms.

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

The present invention further provides a compound of formula (I), or a

pharmaceutically acceptable salt or solvate thereof, for use in the treatment of the disease conditions defined above.

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 or solvate thereof.

Yet further, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate 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 or solvate 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-dimethylimidazolium chloride
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DME	1,2-dimethoxyethane, dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
EDC	1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrogen chloride
EtOAc	ethyl acetate
EtOH	ethanol
HOBt	1-hydroxybenzotriazole
MeOH	methanol
NMP	<i>N</i> -methyl-2-pyrrolidone
THF	tetrahydrofuran
TFA	trifluoroacetic acid

General Synthesis

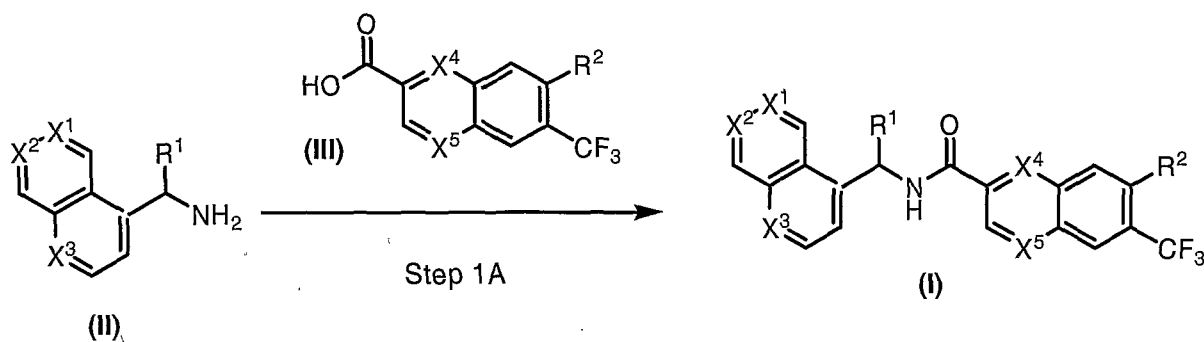
The compounds of the present invention may be prepared by a variety of

processes well known for the preparation of compounds of this type, for example as shown in the following reaction Schemes.

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

A compound of formula (I) may be prepared according to scheme 1 below.

Scheme 1

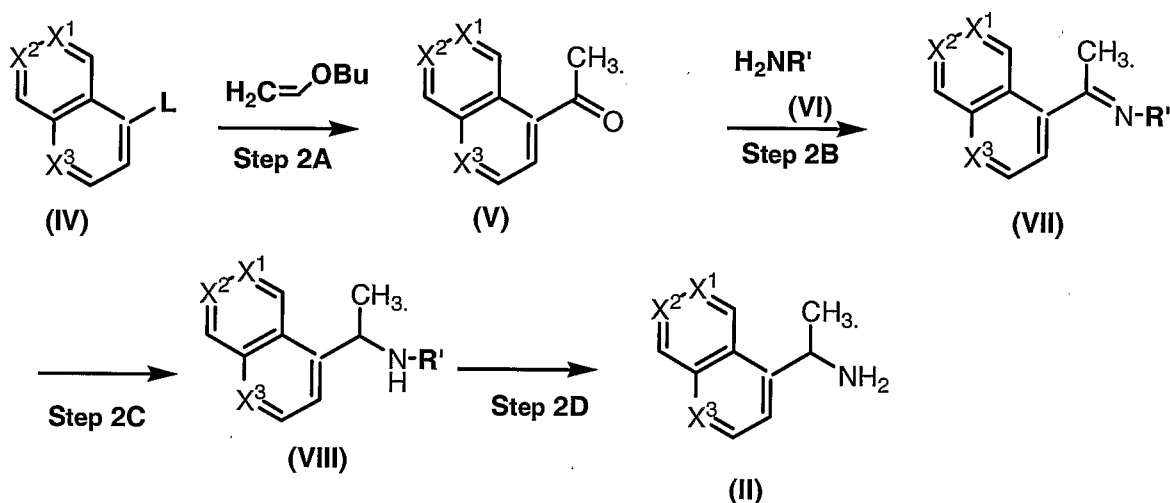


Step 1A : In this Step, an amide compound of formula (I) can be prepared by the coupling reaction of an amine compound of formula (II) with an acid compound of formula (III) in the presence or absence of a coupling reagent in an inert solvent. Suitable coupling reagents are those typically used in peptide 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 (I) can also be formed via the reaction of a compound of formula (II) with an acylhalide, which is obtained by the reaction of a compound of formula (III) 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 $-20\text{ }^{\circ}\text{C}$ to $100\text{ }^{\circ}\text{C}$, more preferably from about $0\text{ }^{\circ}\text{C}$ to $60\text{ }^{\circ}\text{C}$. 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.

When R^2 is methyl, a compound of formula (II) may be prepared from a compound of formula (IV), as illustrated by scheme.2.

Scheme 2:



wherein L is a suitable leaving group, and R' is *t*-butylsulfinyl, phenethyl, NH_2 , benzyl or diphenylmethyl.

Step 2A: In the above formula, a compound of formula (V) can be prepared by a coupling reaction of a compound of formula (IV) with 1-(vinyl)butane under basic conditions in the presence of a transition metal catalyst and additives in a solvent. Examples of suitable solvents include: protic solvents such as water, alcohols such as MeOH or EtOH, and co-solvents of water or alcohols as protic solvents mixed with THF, 1,4-dioxane, DMF or acetonitrile. This reaction can be carried out in the presence of a suitable catalyst. There is likewise no particular restriction on the nature of the catalyst used, and any catalysts commonly used in reactions of this type can equally be used here. Examples of such catalysts include: tetrakis(triphenylphosphine)-palladium, bis(triphenylphosphine)palladium(II) chloride, copper(0), copper(I) acetate, copper(I) bromide, copper(I) chloride, copper(I) iodide, copper(I) oxide, copper(II)

trifluoromethanesulfonate, copper(II) acetate, copper(II) bromide, copper(II) chloride, copper(II) iodide, copper(II) oxide, copper(II) trifluoromethanesulfonate, palladium(II) acetate, palladium(II) chloride, bisacetonitriledichloropalladium(0), bis(dibenzylideneacetone)palladium(0), tris(dibenzylideneacetone)dipalladium(0) or [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride. Preferred catalysts are tetrakis(triphenylphosphine)-palladium, bis(triphenylphosphine)palladium(II) chloride, palladium(II) acetate, palladium(II) chloride, bisacetonitriledichloropalladium(0), bis(dibenzylideneacetone)palladium(0), tris(dibenzylideneacetone)dipalladium(0) or [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride. This reaction can be carried out in the presence of a suitable additive agent. Examples of such additive agents include: triphenylphosphine, tri-*tert*-butylphosphine, 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane, 1,1'-bis(diphenylphosphino)ferrocene, tri-2-furylphosphine, tri-*o*-tolylphosphine, 2-(dichlorohexylphosphino)biphenyl or triphenylarsine. This reaction can be carried out in the presence of bases such as potassium carbonate, sodium carbonate or cesium carbonate. The reaction can be carried out at a temperature of from 0 °C to 200 °C, more preferably from 20 °C to 120 °C. Reaction time is, in general, from 5 minutes to 48 hours, more preferably 30 minutes to 24 hours will usually suffice.

Step 2B: In this step, a compound of formula (VII) can be prepared by coupling reaction of a compound of formula (V) with an amine of formula (VI) in the presence of a dehydration reagent and/or HCl-MeOH and/or Lewis Acid. A preferred dehydration reagent includes sodium sulfate, magnesium sulfate, calcium sulfate or methylformate. Examples of suitable solvents include: THF; 1,4-dioxane; DMF; acetonitrile; alcohols such as MeOH or EtOH; halogenated hydrocarbons such as DCM, 1,2-dichloroethane, chloroform or carbon tetrachloride; or acetic acid. Reaction temperature is generally in the range of from 0 to 200 °C, preferably in the range of from 100 °C to 140 °C. Reaction time is, in general, from 1 minute to a day, preferably from 5 minutes to 1 hour. If necessary, microwave conditions may be applied to the reaction.

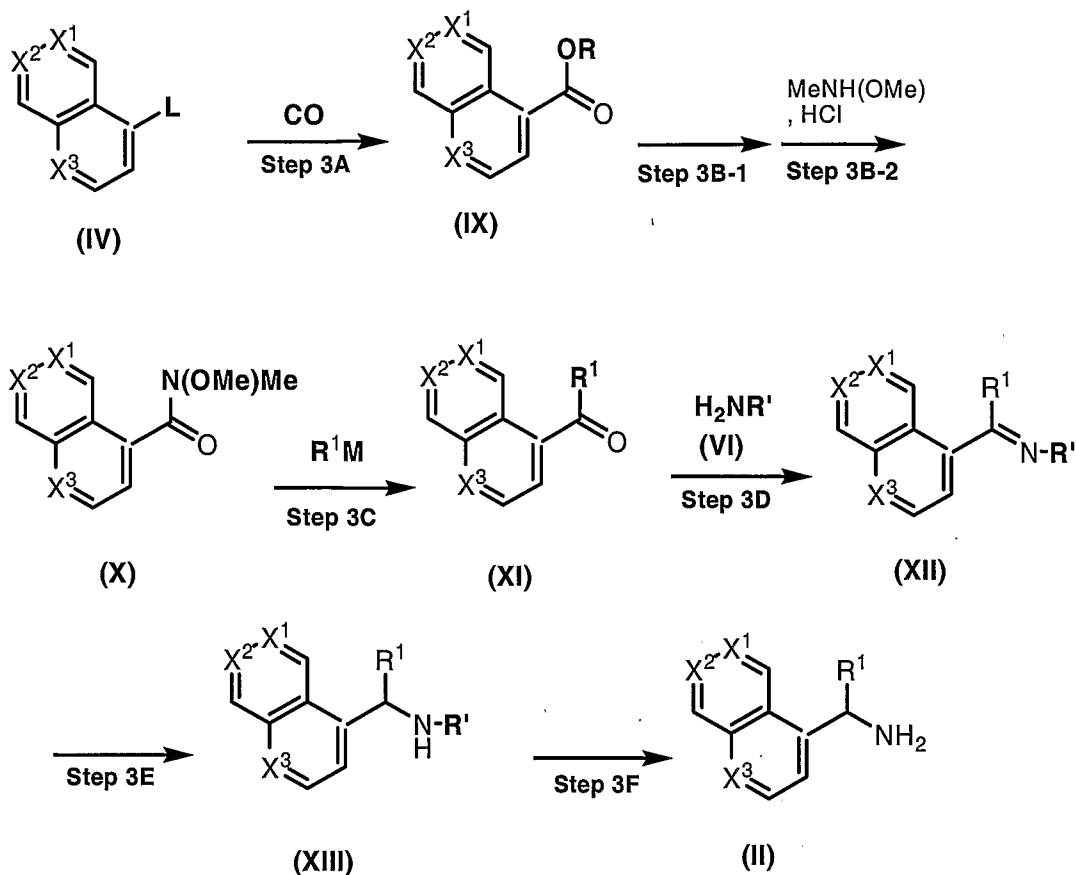
Step 2C: In this step, a compound of formula (VIII) can be prepared by reduction of a compound of formula (VII). This reaction may be carried out in the presence of a suitable reducing agent such as diboran, boran-methyl sulfide complex, sodium borohydride, lithium borohydride, sodium borohydride, or lithium aluminum hydride, in an inert solvent selected from THF and diethyl ether. Reaction temperature is generally in the range of from -100 to 250 °C, preferably in the range of from 0 °C to the reflux

temperature, but if necessary, lower or higher temperatures can be employed. Reaction time is, in general, from 1 minute to a day, preferably from 20 minutes to 5 hours, however shorter or longer reaction times, if necessary, can be employed. The reduction may also be carried out under known hydrogenation conditions such as in the presence of a metal catalyst such as Raney nickel catalysts in the presence or absence of hydrazine, palladium catalysts or platinum catalysts under hydrogen atmosphere. This reaction may be carried out in an inert solvent such as MeOH, EtOH, and THF in the presence or absence of hydrogen chloride. If necessary, this reduction may be carried out under pressure in the range from about 0.5 to 10 kg/cm², preferably in the range from 1 to 6 kg/cm². Examples of suitable solvents are similar to those mentioned in Step 2B.

Step 2D: In this Step, a compound of the formula (II) can be prepared by deprotection and/or salt formation of a compound of formula (VIII) under acidic conditions in an inert solvent using the method described by D. Cogan *et. al* (Journal of American Chemical Society, 1999, 121, pp268-269). Suitable acids include, for example, but not limited to hydrogen chloride, hydrogen bromide, trifluoromethane sulfonic acid, acetic acid or p-toluenesulfonic acid. The reaction may be also carried out under known hydrogenation conditions such as in the presence of a metal catalyst such as palladium-carbon catalyst or platinum catalysts under hydrogen atmosphere. This reaction may be carried out in an inert solvent such as MeOH, EtOH, and THF in the presence or absence of hydrogen chloride. If necessary, this reduction may be carried out under pressure in the range from about 0.5 to 10 kg/cm², preferably in the range from 1 to 6 kg/cm². Reaction temperature is generally in the range of from -100 °C to 250 °C, preferably in the range of from 0 °C to the reflux temperature, but if necessary, lower or higher temperatures can be employed. Reaction time is, in general, from 1 minute to 2 days, preferably from 20 minutes to 24 hours.

Alternatively, a compound of formula (II) may be prepared as illustrated in Scheme 3.

Scheme 3:



wherein R is C_1 - C_2 alkyl; R^1 is t-butylsulfanyl, phenethyl, NH_2 , benzyl or diphenylmethyl; and M is a suitable metal such as lithium, or MgZ , wherein Z is halogen.

Step 3A: In this Step, a compound of formula (IX) may be prepared by reacting a compound of formula (IV) with carbon monoxide and an alcohol (e.g. MeOH or EtOH) in the presence of a catalyst and/or base in an inert solvent. Examples of suitable catalysts include palladium reagents, such as palladium acetate or palladium dibenzylacetone. Examples of suitable bases include N,N-diisopropylethylamine, N-methylmorpholine or triethylamine. If desired, this reaction may be carried out in the presence or absence of an additive such as 1,1'-bis(diphenylphosphino)ferrocene, triphenylphosphine or 1,3-bis-(diphenylphosphino)propane (DPPP). 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; sulfolane; DMSO; NMP; 2-butanone; acetonitrile; halogenated hydrocarbons such as DCM, dichloroethane or chloroform; or 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 150°C , more preferably from about 50°C to 80°C . The time required for the reaction may 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 from 30 minutes to 24 hours, more preferably from 1 hour to 10 hours, will usually suffice.

Step 3B-1: In this Step, an acid compound may be prepared by hydrolysis of a compound of formula (IX) in a solvent. The hydrolysis may be carried out by conventional procedures. In a typical procedure, the hydrolysis is carried out under basic conditions in the presence of water. Suitable bases include, for example, sodium hydroxide, potassium hydroxide or lithium hydroxide. Suitable solvents include, for example, alcohols such as MeOH, EtOH, propanol, butanol, 2-methoxyethanol or ethylene glycol; ethers such as THF, DME or 1,4-dioxane; amides such as DMF or hexamethylphosphorotriamide; 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 from 30 minutes to 24 hours, usually from 60 minutes to 10 hours. The hydrolysis may also be carried out under acidic conditions, 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. Suitable solvents include, for example, alcohols such as MeOH, EtOH, propanol, butanol, 2-methoxyethanol, and ethylene glycol; ethers such as THF, DME and 1,4-dioxane; amides such as DMF and hexamethylphosphorotriamide; and 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 from 30 minutes to 24 hours, usually from 60 minutes to 10 hours.

Step 3B-2: In this step, an amide compound of formula (X) can be prepared from the product of 3B-1 by the same procedure as described in Step 1.

Step 3C: In this Step, a compound of formula (XI) can be prepared by reaction of a compound of formula (X) with an organometallic reagent R^1M . R^1M can be prepared from a halide compound of R^1 . For example, R^1M , in which M represents MgZ, can be generated by stirring Mg and R^1Z , dibromoethane and I_2 at a temperature in the range of

from 30 to 80 °C. This reaction may be carried out in the presence of an organometallic reagent or a metal. Examples of suitable organometallic reagents include alkylolithiums such as n-butyllithium, sec-butyllithium or tert-butyllithium; aryllithiums such as phenyllithium or lithium naphthylide. Examples of suitable metals include magnesium. Preferred inert solvents include, for example, hydrocarbons, such as hexane; ethers, such as diethyl ether, diisopropyl ether, DME, THF or 1,4-dioxane; or mixtures thereof. Reaction temperature is generally in the range of from -100 to 50 °C, preferably in the range of from -100 °C to room temperature. Reaction time is, in general, from 1 minute to a day, preferably from 1 hour to 10 hours.

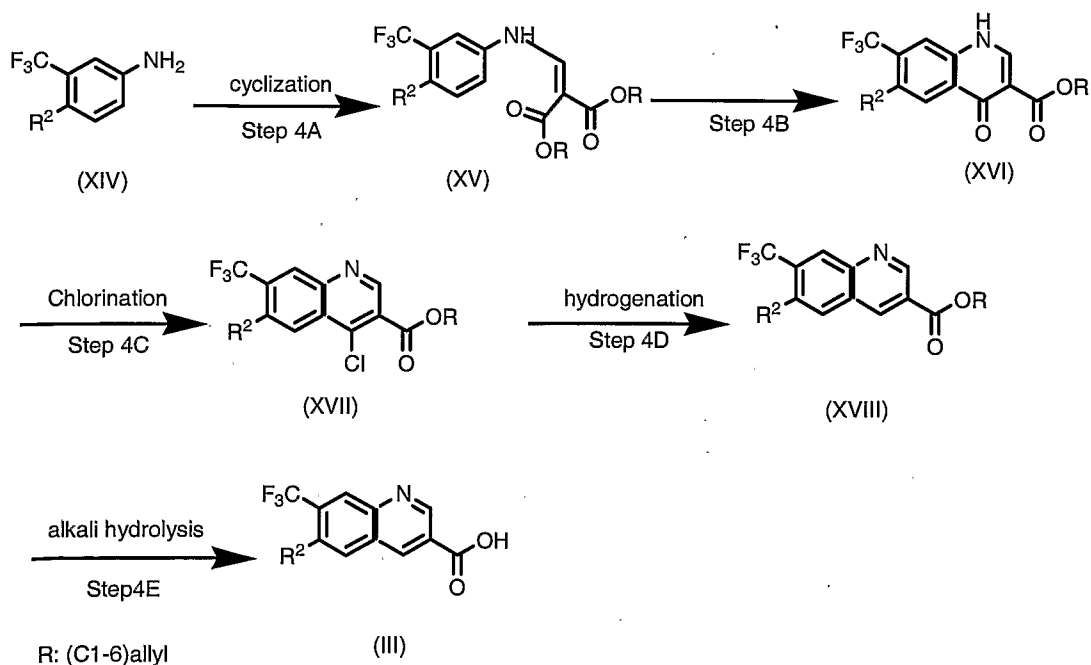
Step 3D: In this step, a compound of formula (XII) can be prepared by coupling reaction of a compound of formula (XI) with an amine of formula (VI) by the method described in Step 2B above.

Step 3E: In this Step, a compound of formula (XIII) can be prepared from a compound of formula (XII) by the method described in Step 2C above.

Step 3F: In this step, a compound of the formula (II) can be prepared from a compound of formula (XIII) by the method described in Step 2D above.

A compound of formula (III) may be prepared by the process illustrated in Scheme 4.

Scheme 4



Step 4A: In this Step, a compound of formula (XV) can be prepared by N-substituted acrylation of a compound of formula (XIV) with dialkyl alkoxy methylenemalonate in a

reaction inert solvent or without solvent. Examples of suitable solvents include alcohols such as MeOH, EtOH, propanol, butanol, 2-methoxyethanol, and ethylene glycol; and ethers such as THF, DME, and 1,4-dioxane. The reaction can be carried out at a temperature in the range from 50°C to 150°C for from 30 minutes to 24 hours, usually from 60 minutes to 3 hours.

Step 4B: In this Step, a compound of formula (XVI) can be prepared by thermal cyclization of a compound of formula (XV) in a reaction inert solvent. Examples of suitable solvents include ethers such as phenyl ether. This reaction can be carried out at a temperature in the range from 200 to 300°C for from 30 minutes to 24 hours, usually 250°C for from 30 minutes to 5 hours. (Journal of Medicinal chemistry, 1998, Vol 41, No25, pp4918-4926.

Step 4C: In this Step, a compound of formula (XVII) can be prepared by chlorination of a compound of formula (XVI). The reaction is carried out under chlorination conditions with a chlorination reagent in a reaction inert solvent or without solvent. Examples of suitable solvents include THF; 1,4-dioxane; DMF; acetonitrile; halogenated hydrocarbons, such as DCM, 1,2-dichloroethane, chloroform or carbon tetrachloride; and acetic acid. Examples of suitable halogenating reagents include phosphorus oxyhalide such as phosphorus oxychloride; and phosphorus oxybromide. The reaction can be carried out at a temperature of from 0 °C to 200 °C, more preferably from ambient temperature to 150 °C. Reaction times are, in general, from 5 minutes to 48 hours, more preferably from 30 minutes to 6 hours will usually suffice.

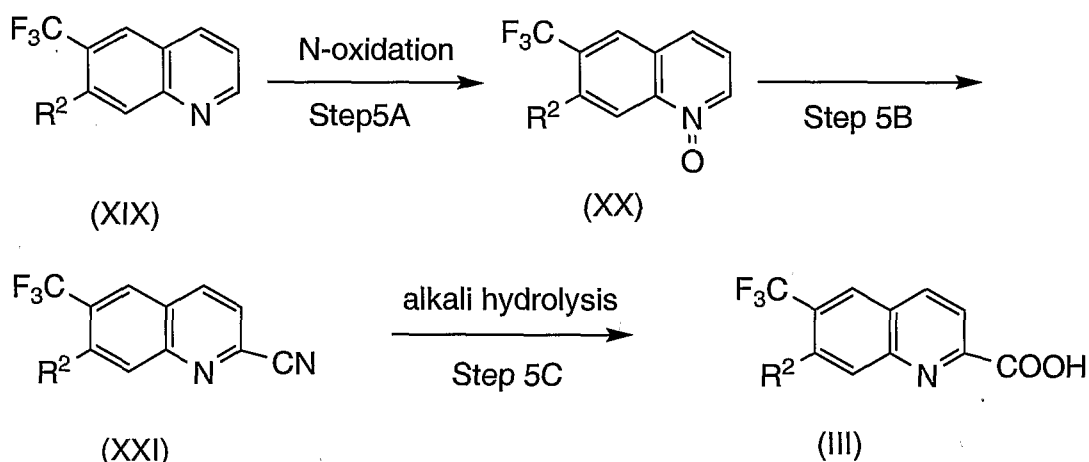
Step 4D: In this Step, a dehalogenated compound of formula (XVIII) can be prepared by hydrogenation of a compound of formula (XVII) in a solvent. Hydrogenation reaction is carried out under, for example, known hydrogenolysis conditions in the presence of a metal catalyst under a hydrogen atmosphere or in the presence of hydrogen sources such as formic acid or ammonium formate in a reaction inert solvent. If desired, the reaction may be carried out under basic conditions, for example, in the presence of triethylamine. Preferred reagents are selected from, for example, nickel catalysts such as Raney nickel, palladium-carbon, palladiumhydroxide-carbon, platinumoxide, platinum-carbon, ruthenium-carbon, rhodium-aluminumoxide and tris[triphenylphosphine] rhodiumchloride. Examples of suitable reaction inert aqueous or non-aqueous organic solvents include alcohols, such as MeOH, EtOH; ethers, such as THF or 1,4-dioxane; acetone; dimethylformamide; halogenated hydrocarbons, such as DCM, dichloroethane or chloroform; and acetic acid; or mixtures thereof. The reaction can be carried out at a

temperature in the range from 20°C to 100°C, preferably in the range from 20°C to 60°C. Reaction times are, in general, from 10 minutes to 48 hours, preferably from 30 minutes to 24 hours. This reaction can be carried out under hydrogen atmosphere at a pressure ranging from 1 to 100 atm, preferably from 1 to 10 atm. The preferred conditions are the use of 5 or 10% palladium-carbon at from 20 to 25°C for 1 to 24 hours under hydrogen atmosphere using a balloon.

Step 4E: In this Step, an acid compound of formula (III) can be prepared by hydrolysis of a compound of formula (XVIII) in a solvent by the method as described in Step 3B-1.

Alternatively, a compound of formula (III) may be prepared by the process illustrated in Scheme 5.

Scheme 5:



Step 5A: In this Step, a N-oxide compound of formula (XX) can be prepared by oxidation of a compound of formula (XIX) in a reaction inert solvent. The oxidation reaction may be carried out in the absence or presence of an additive agent in a reaction inert solvent. Examples of preferred oxidation reagents include meta-chloroperoxybenzoic acid (mCPBA), hydrogen peroxide and peracetic acid. Examples of preferred reaction inert solvents include halogenated hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride and dichloroethane; ethers, such as diethyl ether, diisopropyl ether, DME, THF and 1,4-dioxane; acetonitrile; acetic acid; and water; or mixtures thereof. Reaction temperatures are generally in the range from 0°C to 250°C, more preferably in the range from 0°C to 100°C. Reaction times are, in general, from 1 minute to 10 days, more preferably from 20 minutes to 6 hours. This reaction may be carried out in the presence of a suitable catalyst. There is likewise no particular restriction on the nature of the catalyst used, and any catalyst commonly used in reactions of this type may equally be used here. Examples of such catalysts include

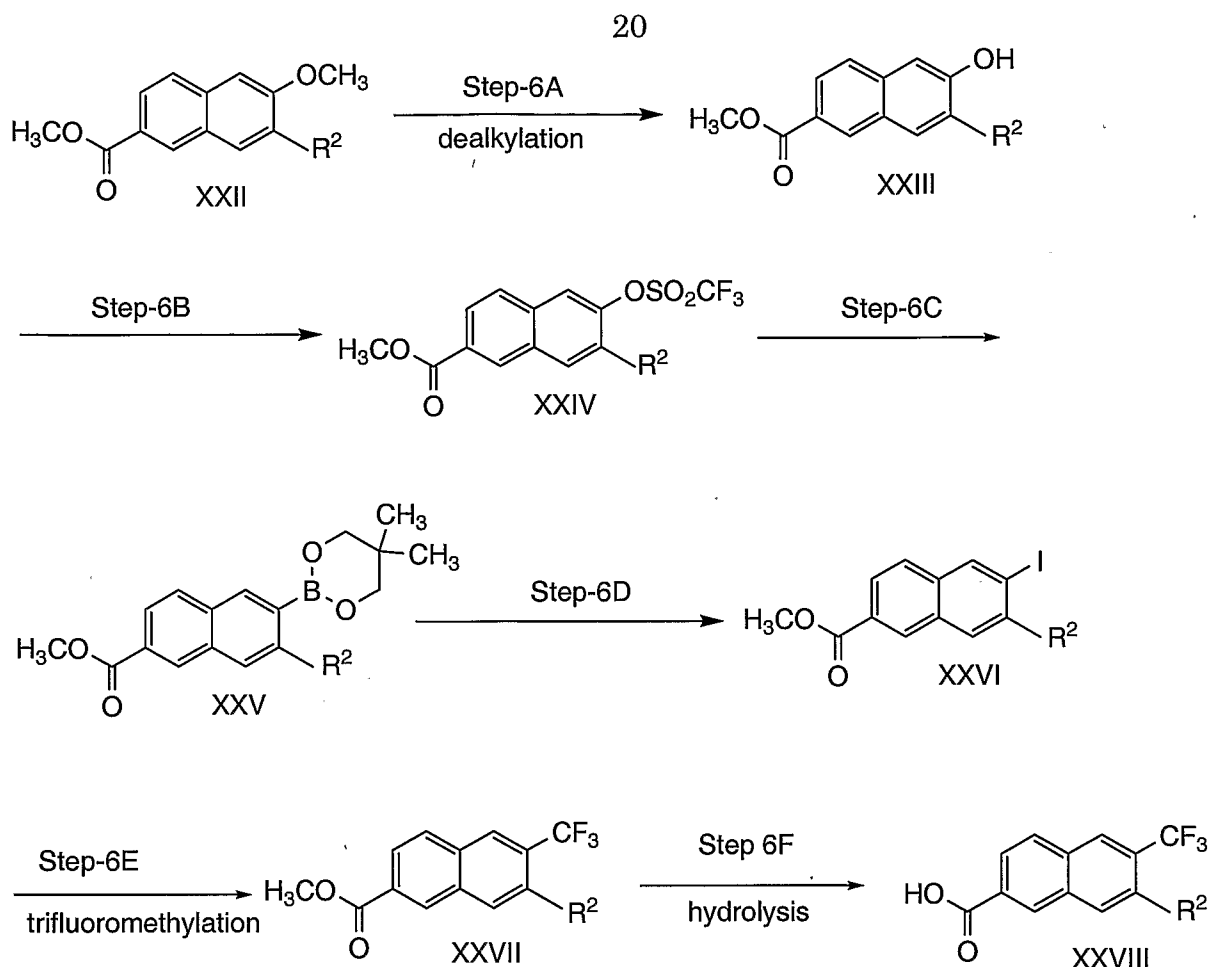
methyltrioxorhenium(VII), tungstic acid and sodium tungstate dehydrate.

Step 5B: In this Step, a cyano compound of formula (XXI) can be prepared by cyanation of a compound of formula (XX) in a reaction inert solvent. Examples of preferred cyanation reagents include trimethylsilanecarbonitrile (TMSCN), the combination of trimethylchlorosilane and sodium cyanide, and the combination of acylating agents such as N,N-dimethylcarbamoyl chloride with trimethylsilanecarbonitrile (TMSCN). A preferred cyanation reagent is trimethylsilanecarbonitrile (TMSCN) in the presence of a base such triethylamine in a reaction inert solvent. Examples of preferred reaction inert solvents include halogenated hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride and dichloroethane; ethers, such as diethyl ether, DME, THF and 1,4-dioxane; acetonitrile; DMF; DMSO; or mixtures thereof. Reaction temperatures are generally in the range from 0 °C to 250 °C, more preferably in the range from 0 °C to 100 °C. Reaction times are, in general, from 1 minute to 10 days, more preferably from 20 minutes to 24 hours.

Step 5C: In this Step, an acid compound of formula (III) can be prepared by hydrolysis of a cyano compound of formula (XXI) in a solvent. The hydrolysis can be carried out by conventional procedures. In a typical procedure, the hydrolysis may be carried out under basic conditions, e.g. in the presence of sodium hydroxide, potassium hydroxide or lithium hydroxide. Examples of suitable solvents include alcohols such as MeOH, EtOH, propanol, butanol, 2-methoxyethanol, and ethylene glycol; ethers such as THF, DME, and 1,4-dioxane; amides such as DMF and hexamethylphosphorictriamide; and sulfoxides such as DMSO. Preferable solvents are MeOH, EtOH, propanol, THF, DME, 1,4-dioxane, DMF and DMSO. This reaction can be carried out at a temperature in the range from -20 to 150 °C, usually from 20 °C to 100 °C for 30 minutes to 24 hours, usually 60 minutes to 10 hours.

When X⁴ and X⁵ are both CH, a compound of formula (III) may be prepared by the process illustrated in Scheme 6.

Scheme 6



Step-6A

In this Step, a compound of formula (XXIII) can be prepared by O-dealkylation of a compound of formula (XXII). The reaction is carried out under O-dealkylation conditions with a dealkylating reagent in a reaction inert solvent or without solvent. Examples of suitable solvents include halogenated hydrocarbons, such as dichloromethane, 1,2-dichloroethane, chloroform or carbon tetrachloride. Examples of suitable dealkylating reagents include boron halides, such as boron trichloride and boron tribromide. The reaction can be carried out at a temperature of from 0 °C to 200 °C, more preferably from ambient temperature to 60 °C. Reaction times are, in general, from 5 minutes to 48 hours, more preferably 30 minutes to 6 hours will usually suffice.

Step-6B

In this step, a compound of formula (XXIV) can be prepared by trifluoromethane sulfonation reaction of a compound of formula (XXIII) using trifluoromethane sulfonic acid anhydride under basic conditions in an inert solvent. A preferred base is selected from, for example, but not limited to: an alkali or alkaline earth metal hydroxide, alkoxide, carbonate, halide or hydride, such as sodium hydroxide, potassium hydroxide, sodium

methoxide, sodium ethoxide, potassium *tert*-butoxide, sodium carbonate, potassium carbonate, potassium fluoride, sodium hydride or potassium hydride; or an amine such as triethylamine, tributylamine, diisopropylethylamine, 2,6-lutidine, pyridine or dimethylaminopyridine. Examples of suitable solvents include: toluene; xylene; DME; DMSO; THF; 1,4-dioxane; DMF; acetonitrile; halogenated hydrocarbons, such as DCM, 1,2-dichloroethane, chloroform or carbon tetrachloride; and diethylether. Reaction temperatures are generally in the range of from -78°C to 200°C , preferably in the range of from 0°C to room temperature. Reaction times are, in general, from 1 minute to a day, preferably from 1 hour to 20 hours.

Step-6C

In this step, a compound of formula (XXV) can be prepared by palladium catalyzed reaction of a compound of formula (XXIV) using a suitable boron reagent in an inert solvent. Examples of suitable solvents include: THF; 1,4-dioxane; DMF; acetonitrile; alcohols, such as methanol or ethanol; halogenated hydrocarbons, such as DCM, 1,2-dichloroethane, chloroform or carbon tetrachloride; and diethylether; in the presence or absence of an aqueous base such as aqueous KOH, NaOH, LiOH or K_2CO_3 . Suitable boron reagents include, for example, pinacolborane and bis(neopentyl glycolato)diboron. Examples of suitable transition metal catalysts include: tetrakis(triphenylphosphine)-palladium, bis(triphenylphosphine)palladium(II) chloride, copper(0), copper(I) acetate, copper(I) bromide, copper(I) chloride, copper(I) iodide, copper(I) oxide, copper(II) trifluoromethanesulfonate, copper(II) acetate, copper(II) bromide, copper(II) chloride, copper(II) iodide, copper(II) oxide, copper(II) trifluoromethanesulfonate, palladium(II) acetate, palladium(II) chloride, bis(acetonitrile)dichloropalladium(0), bis(dibenzylideneacetone)palladium(0), tris(dibenzylideneacetone)dipalladium(0) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride. Preferred catalysts are tetrakis(triphenylphosphine)-palladium, bis(triphenylphosphine)palladium(II) chloride, palladium(II) acetate, palladium(II) chloride, bis(acetonitrile)dichloropalladium(0), bis(dibenzylideneacetone)palladium(0), tris(dibenzylideneacetone)dipalladium(0) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride. This reaction can be carried out in the presence of a suitable additive agent. Examples of such additive agents include: triphenylphosphine, tri-*tert*-butylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, tri-2-furylphosphine, tri-*o*-tolylphosphine, 2-(dichlorohexylphosphino)biphenyl, triphenylarsine, tetrabutylammonium chloride,

tetrabutylammonium fluoride, lithium acetate, lithium chloride, triethylamine, potassium acetate, potassium sodium methoxide, sodium hydroxide, carbonate, sodium bicarbonate and/or sodium iodide. The reaction can be carried out at a temperature of from 0 °C to 200 °C, more preferably from 20 °C to 120 °C. Reaction times are, in general, from 5 minutes to 96 hours, more preferably from 30 minutes to 24 hours.

Step-6D

In this step, a compound of formula (XXVI) can be prepared by iodination of a compound of formula (XXV). This reaction was carried out according to the method described in Synthesis, 2005, No4, pp 0547-0550.

Step-6E

In this step, a trifluoromethyl compound of formula (XXVII) can be prepared from a compound of formula (XXVI) by trifluoromethylation using a trifluoromethyl anion source in an inert solvent. Examples of suitable solvents include: THF; 1,4-dioxane; DMF; acetonitrile; and halogenated hydrocarbons, such as DCM, 1,2-dichloroethane, chloroform or carbon tetrachloride. Examples of suitable trifluoromethyl anion source reagents include for example, the combination of CF₂Cl₂(or CF₂Br₂)/Zn or Cd/CuI, ICF₂SO₂F/Cu, FSO₂CF₂CO₂Me./CuI, CF₃CO₂Na/CuI and Cl₂CF₂CO₂Me/KF/CuI. The reaction can be carried out at a temperature of from 0 °C to 200 °C, more preferably from 20 °C to 120 °C. Reaction times are, in general, from 5 minutes to 96 hours, more preferably from 30 minutes to 24 hours.

Step-6F

In this step, a trifluoromethyl compound of formula (XXVIII) can be prepared from a compound of (XXVII) by alkali hydrolysis as disclosed in Step 3B-1.

The various general methods described above may be useful for the introduction of the desired groups at any stage in the stepwise formation of the required compound, and it will be appreciated that these general methods can be combined in different ways in such multi-stage processes. The sequence of the reactions in multi-stage processes should of course be chosen so that the reaction conditions used do not affect groups in the molecule which are desired in the final product.

Method for assessing biological activities

Human VR1 antagonist assay

VR1 antagonistic activity can be determined by the Ca²⁺ imaging assay using human VR1 highly expressing cells. The cells that highly express human VR1 receptors are obtainable from several different conventional methods. The one

standard method is cloning from human Dorsal Root Ganglion (DRG) or kidney according to the methods such as described in the journal article; Nature, 389, pp816-824, 1997. Alternatively VR1 receptors highly expressing human keratinocytes are also known and published in the journal article (Biochemical and Biophysical Research Communications, 291, pp124-129, 2002). In this article, human keratinocytes demonstrated VR1 mediated intracellular Ca^{2+} increase by addition of capsaicin. Furthermore, the method to up regulate human VR1 gene, which is usually a silent gene or don't produce detectable level of VR1 receptors, is also available to obtain propriety cells. Such genetic modification method was described in detail; Nat. Biotechnol., 19, pp440-445, 2001.

The cells that express human VR1 receptors were maintained in culture flask at 37 °C in an environment containing 5% CO_2 until use in the assay. The intracellular Ca^{2+} imaging assay to determine VR1 antagonistic activities were done by following procedures.

The culture medium was removed from the flask and fura-2/AM fluorescent calcium indicator was added to the flask at a concentration of 5 μM in the medium. The flask was placed in CO_2 incubator and incubated for 1 hour. Then the cells expressing the human VR1 receptors were detached from the flask follow by washing with phosphate buffer saline, PBS(-) and re-suspended in assay buffer. The 80 μl of aliquot of cell suspension (3.75×10^5 cells/ml) was added to the assay plate and the cells were spun down by centrifuge (950 rpm, 20 °C, 3 minutes).

The compounds of the examples were tested in the Human VR1 antagonist assay described above. The IC_{50} values are presented in the following table.

Table 1

Example #	IC_{50} (nM)	Example #	IC_{50} (nM)
1	67.8	7	820
2	295	8	68
3	207	9	27.6
4	1150	10	785
5	10700	11	482
6	1410	Capsazepine (control)	237-455

Capsaicin stimulation assay

The capsaicin-induced changes in the intracellular calcium concentration were

monitored using FDSS 6000 (Hamamatsu Photonics, Japan), a fluorometric imaging system. The cell suspension in Krebs-Ringer HEPES (KRH) buffer (115 mM NaCl, 5.4 mM KCl, 1 mM MgSO₄, 1.8 mM CaCl₂, 11 mM D-Glucose, 25 mM HEPES, 0.96 mM Na₂HPO₄, pH 7.3) were pre-incubated with varying concentrations of the test compounds or KRH buffer (buffer control) for 15 minutes at room temperature under the dark condition. Then capsaicin solution, which gives 300 nM in assay mixture, was automatically added to the assay plate by the FDSS 6000.

Acid stimulation assay

The Acid-induced changes in the intracellular calcium concentration were monitored using FDSS 6000 (Hamamatsu Photonics, Japan), a fluorometric imaging system. The cell suspension in resting buffer (HBSS supplemented with 10mM HEPES, pH 7.4) were pre-incubated with varying concentrations of the test compounds or resting buffer (buffer control) for 15 minutes at room temperature under the dark condition. The cells were automatically added the stimulating solution (HBSS supplemented with MES, final assay buffer pH5.8) by the FDSS 6000. The IC₅₀ values of VR1 antagonists were determined from the half of the increase demonstrated by buffer control samples after acidic stimulation.

Determination of antagonist activity

The monitoring of the changes in the fluorescence signals ($\lambda_{ex} = 340 \text{ nm} / 380 \text{ nm}$, $\lambda_{em} = 510 - 520 \text{ nm}$) was initiated at 1 minute prior to the addition of capsaicin solution or acidic buffer and continued for 5 minute. The IC₅₀ values of VR1 antagonists were determined from the half of the increase demonstrated by buffer control samples after agonist stimulation.

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 tied 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 CaCl₂ and 0.5 mM MgCl₂ (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 CaCl₂ and 0.5 mM MgCl₂ (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.

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

where SA is surface area for transport (0.3 cm²), 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.

Parallel artificial membrane permeation assay (PAMPA)

Experiments were performed in 96-well acceptor and donor plates. Such 96-well system was described in *Journal of Medicinal Chemistry*, 1998, vol.41, No.7, 1007-1010. 4% phosphatidylcholine and 1% stearic acid in dodecane were used as artificial membrane material. The acceptor plate (96 well hydrophobic filter plate (MAIP N45, Millipore)) was prepared by adding 5 µL of artificial membrane material on the top of the filter and the plate was filled with 250 µL of 2-(N-morpholino)ethanesulfonic acid (MES)

buffered Hank's balanced salt solution (HBSS) (pH 6.5). The donor plate (Transport Receiver plate (MATRNPS50, Millipore)) was filled with 300 μ L of MES buffered HBSS (pH 6.5) containing 10 μ M of the test compounds. The acceptor plate was placed onto the donor plate to form a "sandwich" and was incubated at 30°C for 2.5 hours. After the incubation period, acceptor, donor and initial donor solution (reference) were analyzed via LC-MS/MS. Data were reported as the effective permeability value in $\text{cm} \times 10^6/\text{sec}$ and the membrane retention value.

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 μ l. Saturation was determined by incubating 20 μ l of [^3H]-dofetilide and 160 μ l of membrane homogenates (20-30 μ g protein per well) for 60 min at room temperature in the absence or presence of 10 μ M dofetilide at final concentrations (20 μ l) 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 μ l). Total binding and nonspecific binding wells were set up in 6 wells as vehicle and 10 μ M dofetilide at final concentration, respectively. The radioligand was prepared at 5.6x final concentration and this solution was added to

each well (36 μ l). The assay was initiated by addition of YSi poly-L-lysine Scintillation Proximity Assay (SPA) beads (50 μ l, 1 mg/well) and membranes (110 μ l, 20 μ g/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.

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%O₂/5%CO₂. 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; CaCl₂, 2; MgCl₂, 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 1-3M Ω when filled with the standard internal solution of the following composition (mM); KCl, 130; MgATP, 5; MgCl₂, 1.0; HEPES, 10; EGTA 5, pH 7.2 with KOH. Only those cells with access resistances below 15M Ω and seal resistances >1G Ω 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 peristaltic 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, 10 μ M 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 (5 μ M), a specific IKr blocker, to evaluate the insensitive endogenous current.

All experiments were performed at room temperature (23 \pm 1 $^{\circ}$ 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: $I_N = (1 - I_D/I_C) \times 100$, 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 3 μ M 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 MgCl₂, 6.2 mM DL-Isocitric acid and 0.5 U/ml Isocitric Dehydrogenase (ICD). The assay plate was incubated at 37 $^{\circ}$ C (expect; for 1A2 and 3A4 at 30 $^{\circ}$ 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

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

Wherein

v_o = rate of control reaction (no inhibitor)

v_i = rate of reaction in the presence of compounds.

Table 2. 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

Intrinsic Clearance

Test compounds (1 μM) were incubated with 1 mM MgCl_2 , 1 mM NADP^+ , 5 mM isocitric acid, 1U/mL isocitric dehydrogenase and 0.8 mg/mL HLM(human liver microsomes) in 100 mM potassium phosphate buffer (pH 7.4) at 37°C on a number of 384-well plates. At several time points, a plate was removed from the incubator and the reaction was terminated with two incubation volumes of acetonitrile. The compound concentration in supernatant was measured by LC/MS/MS system. The intrinsic clearance value (Cl_{int}) was calculated using following equations:

$$\text{Cl}_{\text{int}} (\mu\text{l}/\text{min}/\text{mg protein}) = (k \times \text{incubation volume}) / \text{Protein concentration}$$

$$k (\text{min}^{-1}) = - \text{slope of } \ln(\text{concentration vs. time})$$

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% EtOH. 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 μ g of *Mycobacterium Tuberculosis* H37RA (Difco, MI) in 100 μ L 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 μ g of *Mycobacterium Tuberculosis* H37RA (Difco, MI) in 100 μ L 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.

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, EtOH. 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 (C₁-C₈)alkyl;
- (ii) where the compound of formula (I) contains an alcohol functionality (-OH), an ether thereof, for example, replacement of the hydrogen with (C₁-C₆)alkanoyloxymethyl; and
- (iii) where the compound of formula (I) contains a primary or secondary amino functionality (-NH₂ or -NHR where R is not H), an amide thereof, for example, replacement of one or both hydrogens with (C₁-C₁₀)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).

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 ²H and ³H, carbon, such as ¹¹C, ¹³C and ¹⁴C, chlorine, such as ³⁶Cl, fluorine, such as ¹⁸F, iodine, such as ¹²³I and ¹²⁵I, nitrogen, such as ¹³N and ¹⁵N, oxygen, such as ¹⁵O, ¹⁷O and ¹⁸O, phosphorus, such as ³²P, and sulphur, such as ³⁵S. 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.* ^3H , 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.* ^2H , 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, EtOH, 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 tableting. 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, EtOH, aqueous EtOH, 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 1 μ g to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1 μ l to 100 μ l. A typical formulation may comprise a compound of formula (I), propylene glycol, sterile water, EtOH 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 μ g to 10mg of the compound of formula (I). The overall daily dose will typically be in the range 1 μ g 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 VR1 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 VR1 antagonist, particularly a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined above, may be administered simultaneously, sequentially or separately in combination with one or more agents selected from:

- an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine or pentazocine;
- a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflusal, 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, phenobarbital, secobarbital, talbutal, theamylal or thiopental;
- a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;
- an H₁ antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;

- a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone;
- a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphrenadine;
- an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinine, cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid, budipine, EN-3231 (MorphiDex®, a combination formulation of morphine and dextromethorphan), topiramate, neramexane or perzinfotel including an NR2B antagonist, e.g. ifenprodil, traxoprodil or (–)-(R)-6-{2-[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]-1-hydroxyethyl-3,4-dihydro-2(1H)-quinolinone};
- an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dexmetatomidine, modafinil, or 4-amino-6,7-dimethoxy-2-(5-methane-sulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;
- a tricyclic antidepressant, e.g. desipramine, imipramine, amitriptyline or nortriptyline;
- an anticonvulsant, e.g. carbamazepine, lamotrigine, topiramate or valproate;
- a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (αR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]-naphthyridine-6-13-dione (TAK-637), 5-[[2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), aprepitant, lanepitant, dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2S,3S);
- a muscarinic antagonist, e.g. oxybutynin, tolterodine, propiverine, tropsium chloride, darifenacin, solifenacin, temiverine and ipratropium;
- a COX-2 selective inhibitor, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, or lumiracoxib;
- a coal-tar analgesic, in particular paracetamol;

- a neuroleptic such as droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonopiprazole, blonanserin, iloperidone, perospirone, raclopride, zotepine, bifeprunox, asenapine, lurasidone, amisulpride, balaperidone, palindore, eplivanserin, osanetant, rimonabant, meclinetant, Miraxion® or sarizotan;
- a vanilloid receptor agonist (e.g. resiniferatoxin) 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 ispronidine (TC-1734), (E)-N-methyl-4-(3-pyridinyl)-3-buten-1-amine (RJR-2403), (R)-5-(2-azetidylmethoxy)-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-azetidyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidyl)-2,6-dihydro-7H-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, (1 α ,3 α ,5 α)(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, (2S)-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, cericlamine and trazodone;
- a noradrenaline (norepinephrine) reuptake inhibitor, such as maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, bupropion, bupropion metabolite hydroxybupropion, 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-carboxamide, or
 guanidinoethyldisulfide;

- an acetylcholinesterase inhibitor such as donepezil;
- a prostaglandin E₂ 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-[(1S)-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 be desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for 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

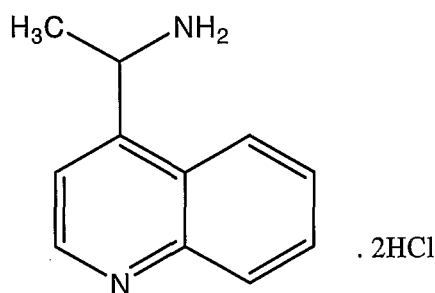
The invention is illustrated in the following non-limiting examples in which, unless stated otherwise: all operations were carried out at room or ambient temperature, that is, in the range of 18-25 °C; evaporation of solvent was carried out using a rotary evaporator under reduced pressure with a bath temperature of up to 60 °C; reactions were monitored by thin layer chromatography (TLC) and reaction times were given for illustration only; melting points (mp) given were uncorrected (polymorphism may result in different melting points); the structure and purity of all isolated compounds were assured by at least one of the following techniques: TLC (Merck silica gel 60 F₂₅₄ precoated TLC plates), mass spectrometry, nuclear magnetic resonance spectra (NMR), infrared red absorption spectra (IR) or microanalysis. 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 performed by the following apparatus and conditions. Apparatus : UV-trigger preparative HPLC system, Waters (Column: XTerra MS C18, 5 µm, 19 x 50 mm or 30 x 50 mm), Detector: UV 254 nm Conditions : CH₃CN/0.05% HCOOH aqueous solution or CH₃CN/0.01% NH₃ 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. IR spectra were measured by a Shimadzu infrared spectrometer (IR-470). Chemical symbols have their usual meanings; bp (boiling point), mp (melting point), 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). In the following Examples, "Me" means methyl and "Et" means ethyl.

Preparations

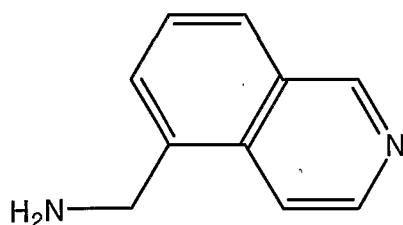
The following Preparations illustrate the preparation of certain Amine and Carboxylic Acid intermediates used to prepare the Examples herein below.

Amine 1: 1-Quinolin-4-ylethanamine, dihydrochloride



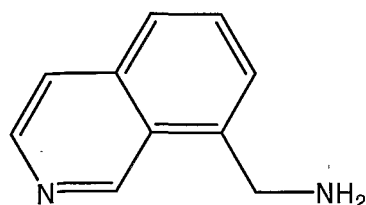
1-Quinolin-4-ylethanamine dihydrochloride can be prepared by the method described in Journal of the Chemical Society, Perkin Transactions 2, (1999), (11), pp 2415-2418.

Amine 2: 1-Isoquinolin-5-ylmethanamine hydrochloride



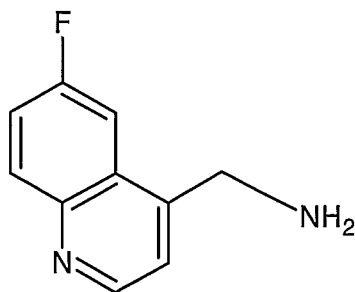
1-Isoquinolin-5-ylmethanamine was synthesized as described in WO 2001070229.

Amine 3: 1-isoquinolin-8-ylmethanamine



1-Isoquinolin-8-ylmethanamine was synthesized as described in WO 2001070229.

Amine 4: 1-(6-Fluoroquinolin-4-yl)methanamine dihydrochloride



Step 4-A) 6-fluoroquinoline-4-carbonitrile

A mixture of 4-chloro-6-fluoroquinoline (APOLLO) (1120 mg, 6.17 mmol), zinc cyanide (1450 mg, 12.3 mmol) and palladium (0) tetrakis(triphenylphosphine) (713 mg, 0.617 mmol) in dry DMF (15 ml) was treated with microwave conditions (160°C, 30 min). The mixture was diluted with ethyl acetate and filtered through a pad of celite. To the filtrate was added toluene (ca. 20 ml) and the organic layer was washed with water (x2), brine, dried and concentrated in vacuo to give crude product. The crude product was purified by column chromatography on silica gel (ca. 250 g), eluting with hexane-ethyl acetate (3:1), to give the title compound (880 mg, white solid).

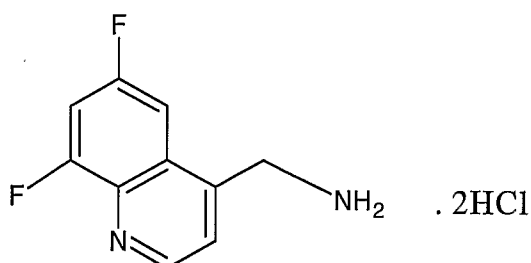
¹H NMR (270 MHz, CDCl₃) δ 7.60-7.70 (1H, m), 7.75-7.79 (1H, m), 7.81-7.87 (1H, m), 8.20 - 8.28 (1H, m), 9.00-9.05 (1H, m).

Step 4-B) 1-(6-fluoroquinolin-4-yl)methanamine dihydrochloride

A solution of the product of step 4-A (880 mg, 5.11 mmol) in 10% hydrochloric methanol (10 ml) and methanol (30 ml) was hydrogenated over 20% palladium hydroxide (150 mg) under balloon pressure (room temperature) for 6 hours. The mixture was diluted with methanol and the catalyst was filtered through a pad of celite pad (the filter cake was washed with methanol). The filtrate and washings were evaporated in vacuo to give crude product as white solid, which was recrystallized from methanol-diisopropyl ether to give the title compound (376 mg, slightly yellow solid).

¹H NMR (270 MHz, DMSO-*d*₆) δ 4.62-4.73 (2H, m), 7.86-7.967 (2H, m), 8.14-8.22 (1H, m), 8.30-8.39 (1H, m), 9.02 (2H, br, s), 9.12-9.17 (1H, m). MS (ESI) *m/z* 177 (M + H)⁺.

Amine 5: 1-(6,8-Difluoroquinolin-4-yl)methanamine dihydrochloride

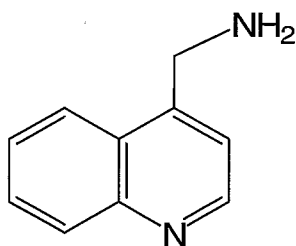


Step 5-A: 6,8-difluoroquinoline-4-carbonitrile

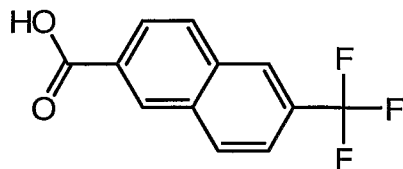
A mixture of 4-chloro-6,8-difluoroquinoline (APOLLO) (1000 mg, 5.01 mmol), zinc cyanide (1180 mg, 10.0 mmol) and palladium (0) tetrakis(triphenylphosphine) (579 mg, 0.501 mmol) in dry DMF (15 ml) was treated in the same procedure as described in Step 4-A. The crude product was purified by column chromatography on silica gel (ca. 250 g), eluting with hexane-ethyl acetate (3:1), to give the title compound (787 mg, yellow solid). ^1H NMR (270 MHz, CDCl_3) δ 7.37-7.50 (1H, m), 7.65-7.75 (1H, m), 7.83-7.90 (1H, m), 9.05 - 9.10 (1H, m).

Step 5-B: 1-(6,8-difluoroquinolin-4-yl)methanamine dihydrochloride

A solution of the product of step 5-A (787 mg, 4.14 mmol) in 10% hydrochloric methanol (10 ml) and methanol (30 ml) was treated in the same procedure as described in Step 4-B. The filtrate and washings were evaporated in vacuo to give crude product as a white solid, which was recrystallized from methanol-diisopropyl ether to give the title compound (1030 mg, slightly yellow solid). ^1H NMR (270 MHz, CDCl_3) δ 4.51-4.62 (m, 2H), 7.78-7.97 (3H, m), 8.85-9.05 (3H, m). MS (ESI) m/z 195 (M + H) $^+$.

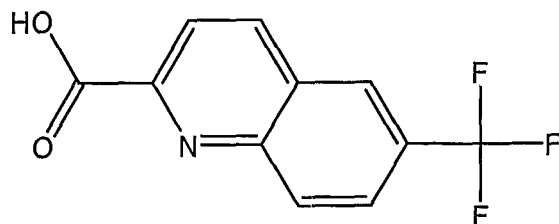
Amine 6: 1-quinolin-4-ylmethanamine

1-Quinolin-4-ylmethanamine can be prepared by the method described in Yakugaku Zasshi (1952), 72, pp 167-172.

Carboxylic acid 1: 6-(trifluoromethyl)-2-naphthoic acid

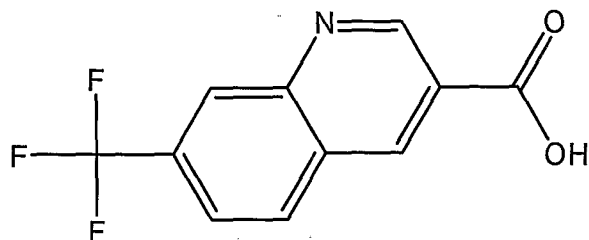
Carboxylic acid 1 was synthesized following the procedure described in Synthesis (2005), (5), pp 791-797.

Carboxylic acid 2: 6-(trifluoromethyl)quinoline-2-carboxylic acid



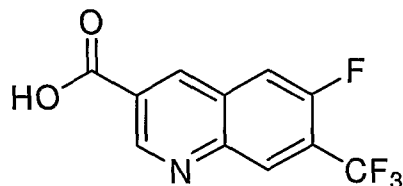
Carboxylic acid 2 was synthesized following the procedure described in WO 2005033082 A2.

Carboxylic acid 3: 7-(trifluoromethyl)quinoline-3-carboxylic acid



Carboxylic acid 3 was synthesized following the procedure described in Journal of Medicinal Chemistry (1979), 22(7), pp 816-823.

Carboxylic acid 4: 6-Fluoro-7-(trifluoromethyl)quinoline-3-carboxylic acid



Step 4-1: Ethyl 6-fluoro-4-hydroxy-7-(trifluoromethyl)quinoline-3-carboxylate

A mixture of 3-trifluoromethyl-4-fluoroaniline (15 g, 84 mmol, purchased from Wako) and diethylethoxymethylene malonate (22.8 mL, 113 mmol) was heated slowly as follows; 60 °C for 10 minutes, 90 °C for 15 minutes, 140 °C for 90 minutes. After EtOH was removed *in vacuo*, the residue was solidified upon standing. This solid was added portionwise to boiling diphenyl ether (278 mL) at 250 °C, and the resulting dark yellow solution was stirred at this temperature for 90 minutes. After being cooled to room temperature, the white solid began to precipitate out. This solid material was filtered, and washed with ethyl acetate-hexanes 2:1 (ca. 500 mL) to give the crude title compound as a white solid (3.38 g, 13 % yield). This crude product was used for the next step without further purification. ¹H NMR (270 MHz, DMSO-d₆) δ ppm 1.30 (3H, t, J= 7.3 Hz), 4.25 (2H, q, J= 7.3 Hz), 7.98-8.16 (1H, m), 8.73 (1H, s), 12.59 (1H, br s). MS (ESI) m/z 302 (M - H)⁻, 304 (M + H)⁺.

Step 4-2: Ethyl 4-chloro-6-fluoro-7-(trifluoromethyl)quinoline-3-carboxylate

A mixture of the product of Step 4-1 (3.38 g, 11.1 mmol) and phosphorous oxychloride

(20.8 mL, 223 mmol) was heated under reflux for 120 minutes. After phosphorous oxychloride was removed *in vacuo*, the residue was diluted in dichloromethane and poured into crushed ice-25 % ammonia water mixture portionwise. The aqueous layer was extracted with dichloromethane 3 times. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was chromatographed on a column of silica gel, eluting with ethyl acetate-hexane (1:5), to give the title compound (3.38 g, 94 %) as a white solid. $^1\text{H NMR}$ (270 MHz, CDCl_3) δ ppm 1.48 (3H, t, $J=7.3$ Hz), 4.54 (2H, q, $J=7.3$ Hz), 8.19 (1H, d, $J=11.2$ Hz), 8.49 (1H, d, $J=6.6$ Hz), 8.25 (1H, s). MS (ESI) m/z 322 ($M + H$) $^+$.

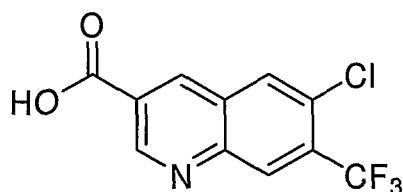
Step 4-3: Ethyl 6-fluoro-7-(trifluoromethyl)quinoline-3-carboxylate

A mixture of the product of Step 4-2 (3.38 g, 10.5 mmol), 5 % palladium on activated carbon (338 mg), triethylamine (2.93 mL, 21.0 mmol) and ethanol (50 mL) was hydrogenated (1 atm, balloon) at room temperature for 90 minutes. The reaction mixture was filtered over a pad of celite, and the filtrate was evaporated. The residue was chromatographed on a column of silica gel, eluting with ethyl acetate-hexane (1:10 to 1:5), to give the title compound (2.94 g, 97 %) as yellow solid. $^1\text{H NMR}$ (270 MHz, CDCl_3) δ ppm 1.48 (3H, t, $J=7.3$ Hz), 4.51 (2H, q, $J=7.3$ Hz), 7.72 (1H, d, $J=9.9$ Hz), 8.51 (1H, d, $J=7.3$ Hz), 8.84 (1H, br s), 9.51 (1H, br s). MS (ESI) m/z 288 ($M + H$) $^+$.

Step 4-4: 6-Fluoro-7-(trifluoromethyl)quinoline-3-carboxylic acid

To a solution of the product of Step 4-3 (2.94 g, 10.2 mmol) in ethanol (4 ml) was added 2N aqueous sodium hydroxide (10.2 mL, 20.5 mmol) at room temperature. The mixture was stirred at 60 °C for 2 hours. Then the reaction mixture was neutralized to pH 5~6 by 2N aqueous hydrochloride. The formed precipitate was collected and washed with water to furnish the title compound (2.52 g, 95 %) as a white solid. $^1\text{H NMR}$ (270MHz, $\text{DMSO}-d_6$) δ ppm 8.32 (1H, d, $J=11.2$ Hz), 8.51 (1H, d, $J=7.3$ Hz), 9.01 (1H, s), 9.42 (1H, s). MS (ESI) : m/z 260 ($M + H$) $^+$ 258 ($M - H$) $^+$.

Carboxylic acid 5: 6-Chloro-7-(trifluoromethyl)quinoline-3-carboxylic acid



Step 5-1: Ethyl 6-chloro-4-hydroxy-7-(trifluoromethyl)quinoline-3-carboxylate

The title compound was prepared by the procedure described in Step 4-1 using 3-trifluoromethyl-4-chloroaniline instead of 3-trifluoromethyl-4-fluoroaniline.

^1H NMR (270 MHz, $\text{DMSO-}d_6$) δ ppm 1.30 (3H, t, $J= 7.3$ Hz), 4.25 (2H, q, $J= 7.3$ Hz), 8.16 (1H, s), 8.73 (1H, s), 12.60 (1H, br s). MS (ESI) m/z 318 (M - H) $^-$, 320 (M + H) $^+$.

Step 5-2: Ethyl 4-bromo-6-chloro-7-(trifluoromethyl)quinoline-3-carboxylate

A mixture of the product of Step 5-1 (2.00 g, 6.26 mmol), phosphorous oxybromide (5.38 g, 18.8 mmol) and N,N-dimethylformamide (40 mL) was stirred at 70 °C for 2 hours. After phosphorous oxychloride was removed *in vacuo*, the residue was diluted in dichloromethane and poured onto crushed ice carefully. The mixture was diluted with saturated aqueous sodium bicarbonate (300 mL) and extracted with dichloromethane 3 times (total 150 mL). The combined organic extracts were dried over sodium sulfate and concentrated. The residue was chromatographed on a column of silica gel, eluting with ethyl acetate-hexane (1:5), to give the title compound (2.15 g, 90 %) as a white solid.

^1H NMR (270 MHz, CDCl_3) δ ppm 1.48 (3H, t, $J= 7.3$ Hz), 4.54 (2H, q, $J= 7.3$ Hz), 8.53 (1H, s), 8.56(1H, s), 9.14 (1H, s). MS (ESI) m/z 384, 382 (M + H) $^+$.

Step 5-3: Ethyl 6-chloro-7-(trifluoromethyl)quinoline-3-carboxylate

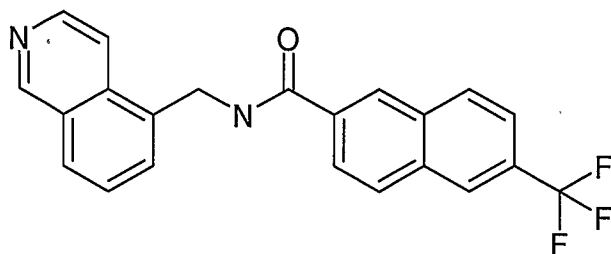
A mixture of the product of step 5-2 (2.15 g, 5.63 mmol), 5 % palladium on activated carbon (215 mg), triethylamine (1.57 mL, 11.30 mmol) and ethanol (56 mL) was hydrogenated (1 atm, balloon) at room temperature for 55 minutes. The reaction mixture was filtered over a pad of celite, and the filtrate was evaporated. The residue was chromatographed on a column of silica gel, eluting with ethyl acetate-hexane (1:10 to 1:5), to give a mixture of the title compound and ethyl 7-(trifluoromethyl)quinoline-3-carboxylate (des-diCl derivative). The mixture was recrystallized from hexane (50 mL) to give the title compound (0.61 g, 35 %) as a white solid. ^1H NMR (270 MHz, CDCl_3) δ ppm 1.48 (3H, t, $J= 7.3$ Hz), 4.52 (2H, q, $J= 7.3$ Hz), 8.10 (1H, s), 8.57 (1H, s), 8.81 (1H, d, $J= 2.0$ Hz), 9.53 (1H, d, $J= 2.0$ Hz). MS (ESI) m/z 304 (M + H) $^+$.

Step 5-4: 6-Chloro-7-(trifluoromethyl)quinoline-3-carboxylic acid

The title carboxylic acid was prepared by the procedure described in step 4-4 to give the title compound (595 mg, quant) as a white solid. ^1H NMR (270MHz, $\text{DMSO-}d_6$) δ ppm 8.57 (1H, s), 8.67 (1H, s), 9.09 (1H, d, $J= 2.0$ Hz), 9.44 (1H, d, $J= 2.0$ Hz). MS (ESI) : m/z 276 (M + H) $^+$ 274 (M - H) $^+$.

Examples

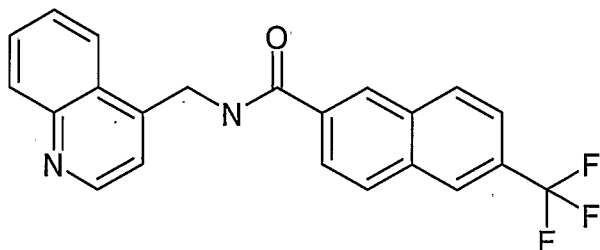
Example 1: N-(Isoquinolin-5-ylmethyl)-6-(trifluoromethyl)-2-naphthamide



To a DMF (7 ml) solution of Amine 2 (53 mg, 0.23 mmol) were added Carboxylic Acid 1 (50 mg, 0.210 mmol), HBTU (118 mg, 0.31 mmol) and trimethylamine (105 mg, 1.04 mmol) and the mixture was stirred for 3 hours at room temperature. The reaction was quenched with water and the product was extracted with EtOAc. Then, evaporation and purification gave a brown oil which was further purified by silica gel column chromatography, eluting with hexane-ethyl acetate (1:2), to afford the title compound (53.5 mg, 67.6%) as a white solid. $^1\text{H-NMR}$ (270 MHz, $\text{DMSO-}d_6$) δ 5.02 (2H, d, $J=5.3$ Hz), 7.72-7.66 (1H, m), 7.85-7.81 (2H, m), 8.14-8.07 (3H, m), 8.29-8.23 (2H, m), 8.63-8.50 (3H, m), 9.41-9.36 (2H, m). MS (ESI) : m/z 379 ($\text{M} - \text{H}$) $^-$, 381 ($\text{M} + \text{H}$) $^+$.

Examples 2 to 11 were prepared according to the process disclosed in example 1, using the appropriate starting material.

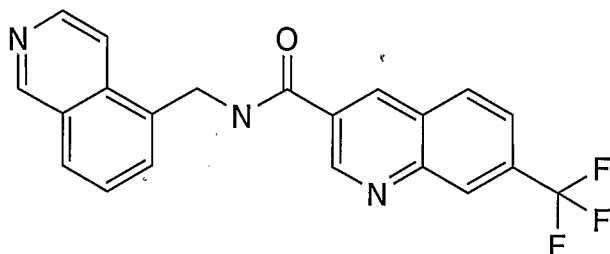
Example 2 : N-(Quinolin-4-ylmethyl)-6-(trifluoromethyl)-2-naphthamide



Example 2 was prepared from Amine 1 and Carboxylic Acid 1.

$^1\text{H NMR}$ (270 MHz, $\text{DMSO-}d_6$) δ 5.05-5.11 (2H, m), 7.48-7.53 (1H, m), 7.64-7.89 (3H, m), 8.05-8.20 (2H, m), 8.24-8.34 (3H, m), 8.52 (1H, br,s), 8.68 (1H, br,s), 8.86-8.91(m, 1H), 9.44-9.53 (1H, m). MS (ESI) m/z 379 ($\text{M} - \text{H}$) $^-$, 381 ($\text{M} + \text{H}$) $^+$

Example 3 : N-(Isoquinolin-5-ylmethyl)-7-(trifluoromethyl)quinoline-3-carboxamide

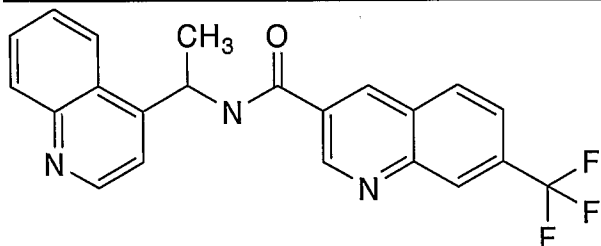


Example 3 was prepared from Amine 2 and Carboxylic Acid 3.

$^1\text{H-NMR}$ (270 MHz, $\text{DMSO-}d_6$) δ 5.04 (2H, d, $J=5.3$ Hz), 7.70 (1H, t, $J=7.6$ Hz), 7.86 (1H, d, $J=6.6$ Hz), 8.14-8.08 (3H, m), 8.30 (1H, d, $J=8.6$ Hz), 8.59 (1H, d, $J=5.9$ Hz), 8.64 (1H, s), 9.08 (1H, d, $J=2.0$ Hz), 9.37 (1H, s), 9.48 (1H, d, $J=2.0$ Hz), 9.54 (1H, t, $J=5.6$ Hz).

MS (ESI) : m/z 380 ($\text{M} - \text{H}$) $^-$, 382 ($\text{M} + \text{H}$) $^+$.

Example 4: *N*-(1-Quinolin-4-ylethyl)-7-(trifluoromethyl)quinoline-3-carboxamide

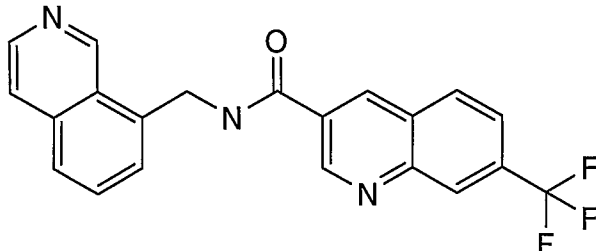


Example 4 was prepared from Amine 1 and Carboxylic Acid 3.

$^1\text{H-NMR}$ (270 MHz, $\text{DMSO-}d_6$) δ 1.68 (3H, d, $J=7.3$ Hz), 6.07-5.97 (1H, m), 7.66 (1H, d, $J=4.6$ Hz), 7.71 (1H, d, $J=7.0$ Hz), 7.80 (1H, t, $J=8.2$ Hz), 7.99 (1H, dd, $J=8.6, 2.0$ Hz), 8.08 (1H, d, $J=7.9$ Hz), 8.34 (1H, d, $J=7.9$ Hz), 8.40 (1H, d, $J=8.6$ Hz), 8.47 (1H, s), 8.90 (1H, d, $J=4.6$ Hz), 9.05 (1H, d, $J=2.0$ Hz), 9.45 (1H, d, $J=2.6$ Hz), 9.57 (1H, d, $J=7.3$ Hz).

MS (ESI) : m/z 394 ($\text{M} - \text{H}$) $^-$, 396 ($\text{M} + \text{H}$) $^+$.

Example 5: *N*-(Isoquinolin-8-ylmethyl)-7-(trifluoromethyl)quinoline-3-carboxamide

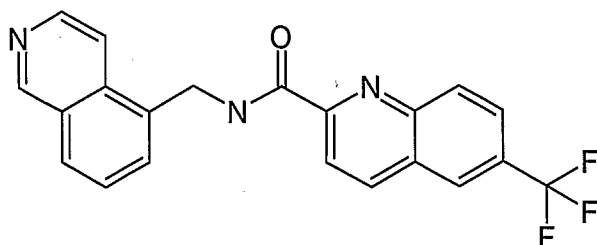


Example 5 was prepared from Amine 3 and Carboxylic Acid 3

LC-MS: Retention time: 2.28 min. MS (ESI) m/z 382 ($\text{M} + \text{H}$) $^+$

HPLC condition: Waters (Column: Xterra PrepMS C18, 3.5 μm , 4.6x50mm), Detector: photodiodearray (210- 400 nm) Conditions: water / MeOH / 1% NH_3 aqueous solution; 2.0 ml/min at 40°C.

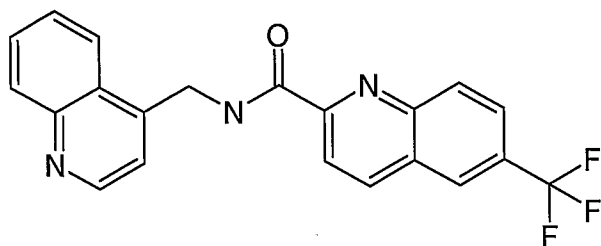
Example 6: *N*-(Isoquinolin-5-ylmethyl)-6-(trifluoromethyl)quinoline-2-carboxamide



Example 6 was prepared from Amine 2 and Carboxylic Acid 2

$^1\text{H-NMR}$ (270 MHz, $\text{DMSO-}d_6$) δ 5.04 (2H, d, $J=5.9$ Hz), 7.68 (1H, t, $J=7.6$ Hz), 7.82 (1H, d, $J=6.6$ Hz), 8.13-8.06 (2H, m), 8.19 (1H, d, $J=5.9$ Hz), 8.35-8.31 (2H, m), 8.58 (1H, d, $J=5.9$ Hz), 8.66 (1H, s), 8.81 (1H, d, $J=8.6$ Hz), 9.35 (1H, s), 9.70 (1H, t, $J=6.3$ Hz). MS (ESI) : m/z 380 ($\text{M} - \text{H}$) $^-$, 382 ($\text{M} + \text{H}$) $^+$.

Example 7: *N*-(Quinolin-4-ylmethyl)-6-(trifluoromethyl)quinoline-2-carboxamide

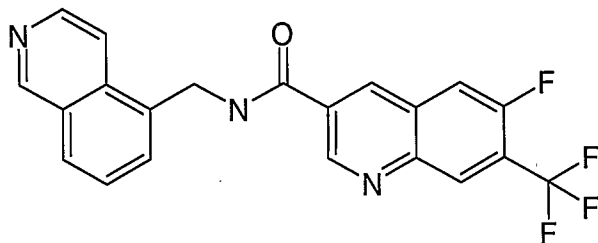


Example 7 was prepared from Amine 1 and Carboxylic Acid 2

$^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 270 MHz) δ 5.11 (2H, d, $J= 5.9$ Hz), 7.47 (1H, d, $J= 4.6$ Hz), 7.69 (1H, t, $J= 7.9$ Hz), 7.81 (1H, t, $J= 7.9$ Hz), 8.08 (1H, d, $J= 7.9$ Hz), 8.15 (1H, d, $J= 7.3$ Hz), 8.29-8.42 (3H, m), 8.68 (1H, s), 8.78-8.90 (2H, m), 9.80 (1H, t, $J= 6.6$ Hz). MS(ESI): m/z 382 ($\text{M}+\text{H}$) $^+$, 380 ($\text{M}-\text{H}$) $^+$.

Example 8:

6-Fluoro-*N*-(isoquinolin-5-ylmethyl)-7-(trifluoromethyl)quinoline-3-carboxamide

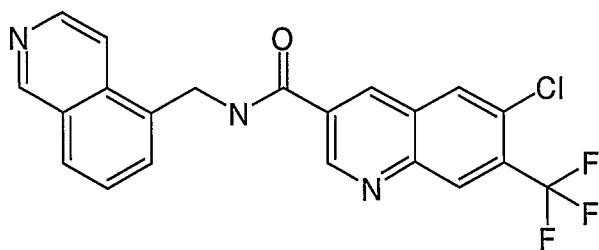


Example 8 was prepared from Amine 2 and Carboxylic Acid 4

$^1\text{H-NMR}$ (270 MHz, $\text{DMSO-}d_6$) δ 5.03 (2H, d, $J=5.3$ Hz), 7.69 (1H, t, $J=7.6$ Hz), 7.85 (1H, d, $J=6.6$ Hz), 8.08 (1H, s), 8.11 (1H, s), 8.27 (1H, d, $J=11.2$ Hz), 8.54 (1H, d, $J=7.3$ Hz), 8.59 (1H, d, $J=5.9$ Hz), 8.96 (1H, d, $J=2.0$ Hz), 9.36 (1H, s), 9.43 (1H, d, $J=2.6$ Hz), 9.61 (1H, t, $J=5.9$ Hz). MS (ESI): m/z 398 ($\text{M} - \text{H}$) $^-$, 400 ($\text{M} + \text{H}$) $^+$.

Example 9:

6-Chloro-*N*-(isoquinolin-5-ylmethyl)-7-(trifluoromethyl)quinoline-3-carboxamide

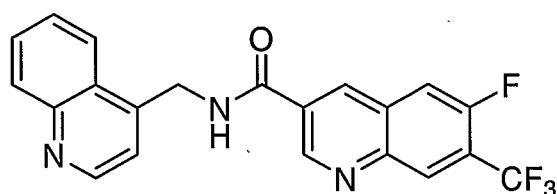


Example 9 was prepared from Amine 2 and Carboxylic Acid 5.

$^1\text{H-NMR}$ (270 MHz, $\text{DMSO-}d_6$) δ 5.03 (2H, d, $J=5.3$ Hz), 7.69 (1H, t, $J=7.6$ Hz), 7.85 (1H, d, $J=6.7$ Hz), 8.11-8.08 (2H, m), 8.60-8.57 (3H, m), 8.95 (1H, d, $J=2.0$ Hz), 9.36 (1H, s), 9.47 (1H, d, $J=2.6$ Hz), 9.61 (1H, t, $J=5.6$ Hz). MS (ESI): m/z 414 (M-H), 416 (M+H) $^+$.

Example 10:

6-Fluoro-N-(quinolin-4-ylmethyl)-7-(trifluoromethyl)quinoline-3-carboxamide

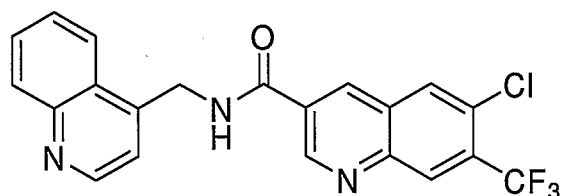


Example 10 was prepared from Amine 6 and Carboxylic Acid 4.

$^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 270 MHz) δ 5.10 (2H, d, $J=5.3$ Hz), 7.55 (1H, d, $J=4.0$ Hz), 7.70 (1H, t, $J=7.3$ Hz), 7.82 (1H, t, $J=8.6$ Hz), 8.09 (1H, d, $J=7.9$ Hz), 8.28 (1H, s), 8.31 (1H, d, $J=4.0$ Hz), 8.57 (1H, d, $J=6.6$ Hz), 8.88 (1H, d, $J=4.0$ Hz), 9.01 (1H, br s), 9.47 (1H, br s), 9.71 (1H, t, $J=5.9$ Hz). MS(ESI): positive 400 (M+H) $^+$, negative 398 (M-H) $^+$.

Example 11:

6-Chloro-N-(quinolin-4-ylmethyl)-7-(trifluoromethyl)quinoline-3-carboxamide

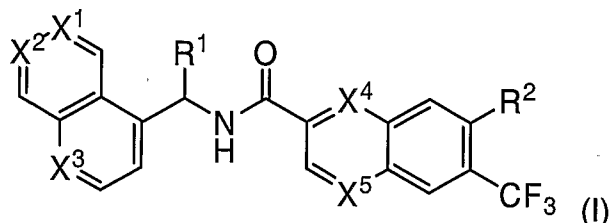


Example 11 was prepared from Amine 6 and Carboxylic Acid 5.

$^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 270 MHz) δ 5.10 (2H, d, $J=5.9$ Hz), 7.55 (1H, d, $J=4.0$ Hz), 7.70 (1H, t, $J=6.6$ Hz), 7.82 (1H, t, $J=6.6$ Hz), 8.09 (1H, d, $J=7.9$ Hz), 8.29 (1H, d, $J=7.9$ Hz), 8.59 (2H, s), 8.89 (1H, d, $J=4.6$ Hz), 9.01 (1H, d, $J=2.0$ Hz), 9.51 (1H, d, $J=2.0$ Hz), 9.71 (1H, t, $J=5.3$ Hz). MS(ESI): positive 416 (M+H) $^+$, negative 414 (M-H) $^+$

CLAIMS

1. A compound of the formula (I):



wherein,

one of X¹, X² and X³ is N, and the others are CH;

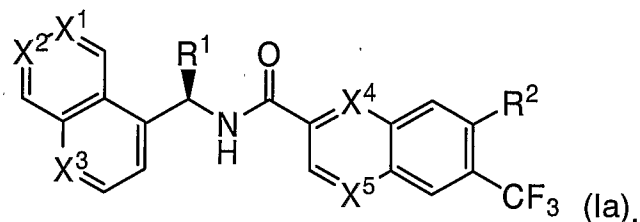
X⁴ is N and X⁵ is CH, or X⁴ and X⁵ are CH, or X⁴ is CH and X⁵ is N;

R¹ is hydrogen or C₁-C₄ alkyl;

R² is hydrogen or halogen;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound of formula (I), according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is C₁-C₄ alkyl and the compound is of the formula (Ia):



3. A compound according to claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, where R¹ is hydrogen, methyl or ethyl.

4. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt or solvate thereof, where R² is hydrogen, fluoro or chloro.

5. A compound according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is selected from the group consisting of:

N-(isoquinolin-5-ylmethyl)-6-(trifluoromethyl)-2-naphthamide,

N-(quinolin-4-ylmethyl)-6-(trifluoromethyl)-2-naphthamide,

N-(isoquinolin-5-ylmethyl)-7-(trifluoromethyl)quinoline-3-carboxamide,

N-(1-quinolin-4-ylethyl)-7-(trifluoromethyl)quinoline-3-carboxamide,

N-(isoquinolin-8-ylmethyl)-7-(trifluoromethyl)quinoline-3-carboxamide,

N-(isoquinolin-5-ylmethyl)-6-(trifluoromethyl)quinoline-2-carboxamide,

N-(quinolin-4-ylmethyl)-6-(trifluoromethyl)quinoline-2-carboxamide,

6-fluoro-*N*-(isoquinolin-5-ylmethyl)-7-(trifluoromethyl)quinoline-3-carboxamide,

6-chloro-*N*-(isoquinolin-5-ylmethyl)-7-(trifluoromethyl)quinoline-3-carboxamide,

6-fluoro-N-(quinolin-4-ylmethyl)-7-(trifluoromethyl)quinoline-3-carboxamide, and
6-chloro-N-(quinolin-4-ylmethyl)-7-(trifluoromethyl)quinoline-3-carboxamide.

6. A pharmaceutical composition including a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof, as defined in any one of claims 1 to 5, together with a pharmaceutically acceptable excipient.

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

8. Use of a compound of the formula (I), or a pharmaceutically acceptable salt or solvate or composition thereof, as defined in any one of claims 1 to 6, for the manufacture of a medicament for the treatment of a disease for which a VR1 antagonist is indicated.

9. A use according to claim 8, wherein the disease is selected from pain, including 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 and menstrual pain; bladder disease, such as urinary incontinence, lower urinary tract symptoms, 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; diseases of the respiratory tree that have a contribution to symptoms or pathology arising from the sensory afferent nervous system, such as cough, bronchoconstriction, irritation, inflammation and other pathways in diseases of the lower airway such as asthma and COPD as well as those of the upper airway, such as allergic rhinitis and chronic sinusitis; 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 and acute cerebral ischemia; emesis, such as cancer chemotherapy-induced emesis; diabetes and obesity.

10. A method of treating a disease for which a VR1 antagonist is indicated, in a mammal, including a human being, including treating said mammal with an effective amount of a compound of the formula (I), or with a pharmaceutically acceptable salt, solvate or composition thereof, as defined in any one of claims 1 to 6.

11. A combination of a compound of the formula (I) or a pharmaceutical acceptable salt or solvate thereof, as defined in any one of claims 1 to 5, and another pharmacologically active agent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2008/000125

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D215/14 C07D217/04 C07D401/12 A61K31/44 A61P25/00

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

B. FIELDS SEARCHED

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

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

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

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/069792 A (JANSSEN PHARMACEUTICA NV [BE]) 19 August 2004 (2004-08-19) cited in the application page 1, line 20 - page 1, line 25; claims	1-11

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed
- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search 19 June 2008	Date of mailing of the international search report 01/07/2008
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Schmid, Arnold
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2008/000125

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2008/000125

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		CA 2514940 A1	19-08-2004
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