(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 November 2007 (15.11.2007)

PCT

(10) International Publication Number
WO 2007/129188 A1

(51) International Patent Classification:
C07D 213/24 (2006.01) *A61P 29/00* (2006.01)
A61K 31/435 (2006.01)

(21) International Application Number:
PCT/IB2007/001143

(22) International Filing Date: 27 April 2007 (27.04.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/799,614 10 May 2006 (10.05.2006) US

(71) Applicant *(for JP only)*: **PFIZER JAPAN INC.** [JP/JP]; Shinjuku Bunka Quint Bldg., 3-22-7, Yoyogi, Shibuya-ku,, Tokyo 151-8589 (JP).

(71) Applicant *(for all designated States except JP, US)*: **PFIZER INC.** [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HANAZAWA, Takeshi** [JP/JP]; Pfizer Japan Inc., Pfizer Global Research and Development, Nagoya Laboratories, 2, Aza 5 Gochi, Taketoyo-cho, Chita-gun, Aichi 470-2393 (JP). **NAGAYAMA, Satoshi** [JP/JP]; Pfizer Japan Inc., Pfizer Global Research and Development, Nagoya Laboratories, 2, Aza 5 Gochi, Taketoyo-cho, Chita-gun, Aichi 470-2393 (JP). **NAKAO, Kazunari** [JP/JP]; Pfizer Japan Inc., Pfizer Global Research and Development, Nagoya Laboratories, 2, Aza 5 Gochi, Taketoyo-cho, Chita-gun, Aichi 470-2393 (JP). **SHISHIDO, Yuji** [JP/JP]; Pfizer Japan Inc., Pfizer Global Research and Development, Nagoya Laboratories, 2, Aza 5 Gochi, Taketoyo-cho, Chita-gun, Aichi 470-2393 (JP). **TANAKA, Hirotaka** [JP/JP]; Pfizer Japan Inc., Pfizer Global Research and Development, Nagoya Laboratories, 2, Aza 5 Gochi, Taketoyo-cho, Chita-gun, Aichi 470-2393 (JP).

(74) Agent: **GROVER, F., Fuller, Jr.**; C/o DROUIN, Stéphane, Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** CYCLOPROPANECARBOXAMIDE COMPOUND

(57) **Abstract:** This invention relates to novel substituted N-(N-sulfonylaminoarylmethyl)cyclopropanecarboxamide compound and to their use in therapy. This invention provides 2-(6-tert-butylpyridin-3-yl)-N-((1R)-1-{3,5-difluoro-4-[(methylsulfonyl)amino]phenyl}ethyl)-2-methylcyclopropanecarboxamide, or a pharmaceutically acceptable salt or solvate thereof. This compound is particularly useful as an antagonist of the VR1 (Type I Vanilloid) receptor, and is 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 compound.

WO 2007/129188 A1

CYCLOPROPANECARBOXAMIDE COMPOUND

Technical Field

This invention relates to novel substituted N-(N-sulfonylaminoarylmethyl)cyclopropanecarboxamide compound and to their use in therapy. This compound is particularly useful as an antagonist of the VR1 (Type I Vanilloid) receptor, and is 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 compound.

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 (Aδ- and C-) fibers, 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.

International Patent Application Number WO-A-2005003084 discusses 4-(methylsulfonylamino)phenyl analogues which are stated to have activity as VR1 antagonists.

International Patent Application Number WO200216318 discloses a variety of sulfonylaminobenzylthiourea derivatives and N-sulfonylaminobenzyl-2-phenoxyacetamide derivatives as modulators for vanilloid receptor.

International Patent Application Number WO2006098554 discloses a variety of thioamide derivatives as modulators for vanilloid receptor.

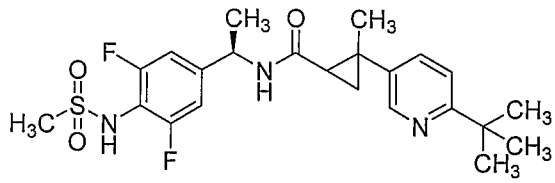
International Patent Application Number WO2004047738 discloses a variety of arylcyclopropylcarboxylic amides as potassium channel openers.

It would be desirable if there were provided improved VR1 selective antagonist 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 a difluoro substituted N-(N-sulfonylaminoarylmethyl)-cyclopropanecarboxamide compound is a potent VR1 antagonist with analgesic activity when given by systemic administration. The compound of the present invention may show less toxicity, good absorption, good half-life, good solubility, low protein binding affinity, less drug-drug interaction, a reduced inhibitory activity at HERG channel, reduced QT prolongation and good metabolic stability.

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



(I)

Detailed Description of the Invention

The compound of formula (I), being a VR1 antagonist, is potentially useful in the treatment of a range of disorders, particularly the treatment of acute cerebral ischemia, pain, chronic pain, acute pain, nociceptive pain, neuropathic pain, inflammatory pain, post herpetic neuralgia, neuropathies, neuralgia, diabetic neuropathy, HIV-related neuropathy, nerve injury, rheumatoid arthritic pain, osteoarthritic pain, burns, back pain, visceral pain, cancer pain, dental pain, headache, migraine, carpal tunnel syndrome,

fibromyalgia, neuritis, sciatica, pelvic hypersensitivity, pelvic pain, menstrual pain, bladder disease, such as incontinence, micturition disorder, renal colic and cystitis, inflammation, such as burns, rheumatoid arthritis and osteoarthritis, neurodegenerative disease, such as stroke, post stroke pain and multiple sclerosis, pulmonary disease, such as asthma, cough, chronic obstructive pulmonary disease (COPD) and broncho constriction, gastrointestinal disorders, such as gastroesophageal reflux disease (GERD), dysphagia, ulcer, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), colitis and Crohn's disease, ischemia, such as cerebrovascular ischemia, emesis, such as cancer chemotherapy-induced emesis, and obesity, or the like in mammals, especially humans. The treatment of pain, particularly neuropathic pain, is a preferred use.

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

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

neuropathic pain (e.g. painful diabetic neuropathy, postherpetic neuralgia), carpal tunnel syndrome, back pain, headache, cancer pain, arthritic pain and chronic post-surgical pain.

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

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

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

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

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

The inflammatory process is a complex series of biochemical and cellular events, activated in response to tissue injury or the presence of foreign substances, which results in swelling and pain (Levine and Taiwo, 1994, Textbook of Pain, 45-56). Arthritic pain is the most common inflammatory pain. Rheumatoid disease is one of the commonest chronic inflammatory conditions in developed countries and

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

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

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

Other types of pain include:

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

The 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.

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.

General Synthesis

The compound of the present invention may be prepared by a variety of processes well known for

the preparation of compound of this type, for example as shown in Example 1.

Method for assessing biological activities:

Human VR1 antagonist assay

VR1 antagonistic activity can be determined by the Ca^{2+} 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 the human VR1 gene, which is usually a silent gene or doesn't produce a detectable level of VR1 receptors, is also available to obtain appropriate cells. Such genetic modification method is described in detail; Nat. Biotechnol., 19, pp440-445, 2001.

The cells that express human VR1 receptors are maintained in a 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 may be done by following procedures.

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

Capsaicin stimulation assay:

The capsaicin-induced changes in the intracellular calcium concentration are 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 $MgSO_4$, 1.8 mM $CaCl_2$, 11 mM

D-Glucose, 25 mM HEPES, 0.96 mM Na_2HPO_4, pH 7.3) are 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 a capsaicin solution, which gives 300 nM in assay mixture, is automatically added to the assay plate by the FDSS 6000.

Acid stimulation assay:

The Acid-induced changes in the intracellular calcium concentration are 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) are 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 are automatically added the stimulating solution (HBSS supplemented with MES, final assay buffer pH5.8) by the FDSS 6000. The IC_{50} values of VR1 antagonists are 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 (λex = 340 nm/ 380 nm, λem = 510 - 520 nm) is initiated at 1 minute prior to the addition of capsaicin solution or acidic buffer and continued for 5 minute. The IC_{50} values of VR1 antagonists are determined from the half of the increase demonstrated by buffer control samples after agonist stimulation. Example 1 showed 18.8 nM as IC_{50} value of VR1 antagonists.

Chronic Contriction Injury Model (CCI Model):

Male Sprague-Dawley rats (270-300 g; B.W., Charles River, Tsukuba, Japan) are used. The chronic constriction injury (CCI) operation is performed according to the method described by Bennett and Xie (Bennett, G.J. and Xie, Y.K. Pain, 33:87-107, 1988). Briefly, animals are anesthetized with sodium pentobarbital (64.8 mg/kg, i.p.) and the left common sciatic nerve is exposed at the level of the middle of the thigh by blunt dissection through biceps femoris. An area proximal to the sciatic's trifurcation is freed of adhering tissue and 4 ligatures (4-0 silk) are tied loosely around it with about 1 mm space. A sham operation is performed as same as CCI surgery except for sciatic nerve ligation. Two weeks after surgery,

mechanical allodynia is 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 is recorded as paw withdrawal threshold (PWT). VFH test is performed at 0.5, 1 and 2 hr post-dosing. Experimental data are analyzed using Kruskal-Wallis test followed by Dunn's test for multiple comparisons or Mann-Whitney U-test for paired comparison.

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 µL of MES buffered HBSS (pH 6.5) containing 10 µM 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 cm X 10^{-6}/sec and the membrane retention value. The Example 1 showed 10.2 x 10^{-6} cm/sec.

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 are 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 is resuspended, homogenized and centrifuged once more in the same manner. The resultant supernatant is discarded and the final pellet is resuspended (10-fold volume of 50 mM Tris buffer) and homogenized at the maximum power for 20 seconds. The membrane homogenate is aliquoted and stored at -80°C until use. An aliquot is used for protein concentration determination using a Protein Assay Rapid Kit and ARVO SX plate reader (Wallac). throughout the entire

procedure, the stock solution and equipment are kept on ice at all time. For saturation assays, experiments are conducted in a total volume of 200 µl. Saturation is determined by incubating 20 µl of [^{3}H]-dofetilide and 160 µl of membrane homogenates (20-30 µg protein per well) for 60 min at room temperature in the absence or presence of 10 µM dofetilide at final concentrations (20 µl) for total or nonspecific binding, respectively. All incubations are 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 is quantified by liquid scintillation counting using Packard LS counter.

For the competition assay, compounds are diluted in 96 well polypropylene plates as 4-point dilutions in semi-log format. All dilutions are 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 can become equal to 1%. Compounds are dispensed in triplicate in assay plates (4 µl). Total binding and nonspecific binding wells are set up in 6 wells as vehicle and 10 µM dofetilide at final concentration, respectively. The radioligand is prepared at 5.6x final concentration and this solution is added to each well (36 µl). The assay is initiated by addition of YSi poly-L-lysine Scintillation Proximity Assay (SPA) beads (50 µl, 1 mg/well) and membranes (110 µl, 20 µg/well). Incubation is continued for 60 min at room temperature. Plates are incubated for a further 3 hours at room temperature for beads to settle. Receptor-bound radioactivity is quantified by counting with a Wallac MicroBeta plate counter. Example 1 showed more than 10 uM as IC_{50} in the condition of HPLC solubility of 19µM at 30µM.

I_{HERG} assay

HEK 293 cells which stably express the HERG potassium channel are 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 are 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 are stored in an incubator at 37°C maintained in an atmosphere of 95%O_2/5%CO_2. Cells are studied between 15-28hrs after harvest.

HERG currents are studied using standard patch clamp techniques in the whole-cell mode. During the experiment the cells are superfused with a standard external solution of the following composition (mM); NaCl, 130; KCl, 4; $CaCl_2$, 2; $MgCl_2$, 1; Glucose, 10; HEPES, 5; pH 7.4 with NaOH. Whole-cell recordings is made using a patch clamp amplifier and patch pipettes which have a resistance of 1-3MOhm when filled with the standard internal solution of the following composition (mM); KCl, 130; MgATP, 5; $MgCl_2$, 1.0; HEPES, 10; EGTA 5, pH 7.2 with KOH. Only those cells with access resistances below 15MΩ and seal resistances >1GΩ are accepted for further experimentation. Series resistance compensation is applied up to a maximum of 80%. No leak subtraction is done. However, acceptable access resistance depends 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 is applied to the cell to evoke membrane currents. The voltage protocol is as follows. The membrane is depolarized from a holding potential of -80mV to +40mV for 1000ms. This is followed by a descending voltage ramp (rate 0.5mV $msec^{-1}$) back to the holding potential. The voltage protocol is 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 is measured. Once stable evoked current responses are obtained in the external solution, vehicle (0.5% DMSO in the standard external solution) is applied for 10-20 min by a peristalic pump. Provided there are minimal changes in the amplitude of the evoked current response in the vehicle control condition, the test compound of either 0.3, 1, 3, 10μM is applied for a 10 min period. The 10 min period includes the time which supplying solution is passing through the tube from the solution reservoir to the recording chamber via the pump. Exposure time of cells to the compound solution is more than 5min after the drug concentration in the chamber well reaches the attempting concentration. There is a subsequent wash period of a 10-20min to assess reversibility. Finally, the cells are exposed to a high dose of dofetilide (5μM), a specific IKr blocker, to evaluate the insensitive endogenous current.

All experiments are performed at room temperature (23 ± 1°C). Evoked membrane currents are recorded on-line on a computer, filtered at 500-1KHz (Bessel -3dB) and sampled at 1-2KHz using the

patch clamp amplifier and a specific data analyzing software. Peak current amplitude, which occurred at around -40mV, is measured off line on the computer.

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

Drug-drug interaction assay

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

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

Data calculations are performed as follows;

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

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

   Wherein

   v_o = rate of control reaction (no inhibitor)

   v_i = rate of reaction in the presence of compounds.

Table 1. Condition for drug-drug interaction assay.

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

Example 1 showed O% inhibition against 1A2, 2C9, 2D6 at 3uM, and 1% inhibition against 3A4 at 3uM.

Intrinsic Clearance in human liver microsomes (HLM)

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:

Cl_{int} (μl/min/mg protein) = (k x incubation volume) / Protein concentration

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

Example 1 showed 21.0μL/min/mg as intrinsic clearance (Cl_{int}).

Mono-Iodoacetate (MIA)-induced OA model

Male 6-weeks-old Sprague-Dawley (SD, Japan SLC or Charles River Japan) rats are anesthetized with pentobarbital. The injection site (knee) of MIA is shaved and cleaned with 70% ethanol. Twenty-five μl of MIA solution or saline is 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 is assessed using an incapacitance tester (Linton Instrumentation, Norfolk, UK). The force exerted by each hind limb is measured in grams. The weight-bearing (WB) deficit is determined by a difference of weight loaded on

each paw. Rats are trained to measure the WB once a week until 20 days post MIA-injection. Analgesic effects of compounds are measured at 21 days after the MIA injection. Before the compound administration, the "pre value" of WB deficit is measured. After the administration of compounds, attenuation of WB deficits is determined as analgesic effects.

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

Thermal hyperalgesia

Male 6-week-old SD rats ware used. Complete Freund's adjuvant (CFA, 300 μg of *Mycobacterium Tuberculosis* H37RA (Difco, MI) in 100 μL of liquid paraffin (Wako, Osaka, Japan)) is injected into the plantar surface of hind paw of the rats. Two days after CFA-injection, thermal hyperalgesia is determined by method described previously (Hargreaves et al., 1988) using the plantar test apparatus (Ugo-Basil, Varese, Italy). Rats are adapted to the testing environment for at least 15 min prior to any stimulation. Radiant heat is applied to the plantar surface of hind paw and paw withdrawal latencies (PWL, seconds) are determined. The intensity of radiant heat is adjusted to produce the stable PWL of 10 to 15 seconds. The test compound is administered in a volume of 0.5 mL per 100 g body weight. PWL are measured after 1, 3 or 5 hours after drug administration.

Mechanical hyperalgesia

Male 4-week-old SD rats are used. CFA (300 μg of *Mycobacterium Tuberculosis* H37RA (Difco, MI) in 100 μL of liquid paraffin (Wako, Osaka, Japan)) is injected into the plantar surface of hind paw of the rats. Two days after CFA-injection, mechanical hyperalgesiais tested by measuring paw withdrawal threshold (PWT, grams) to pressure using the analgesy-Meter (Ugo-Basil, Varese, Italy). The animals are gently restrained, and steadily increasing pressure is applied to the dorsal surface of a hind paw via a plastic tip. The pressure required to elicit paw withdrawal is determined. The test compound is administered in a volume of 0.5 mL per 100 g body weight. PWT are 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, ethanol. The term 'hydrate' is employed when said solvent is water.

Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionized, partially ionized, or non-ionized. For a review of such

complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

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

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

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

Also within the scope of the invention are so-called 'prodrugs' of the compounds of formula (I). Thus certain derivatives of compounds of formula (I) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in 'Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T Higuchi and W Stella) and 'Bioreversible Carriers in Drug Design', Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association).

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

Some examples of prodrugs in accordance with the invention include:

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

(ii) where the compound of formula (I) contains an alcohol functionality (-OH), an ether thereof, for example, replacement of the hydrogen with $(C_1$-$C_6)$alkanoyloxymethyl; and

(iii) where the compound of formula (I) contains a primary or secondary amino functionality ($-NH_2$ or -NHR where $R \neq H$), an amide thereof, for example, replacement of one or both hydrogens with $(C_1$-$C_{10})$alkanoyl.

Further examples of replacement groups in accordance with the foregoing examples and examples

of other prodrug types may be found in the aforementioned references.

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

Compounds of formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers.

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

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

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

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

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

Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art - see, for example, "Stereochemistry of Organic Compounds" by E L Eliel (Wiley, New York, 1994).

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

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

Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

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

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

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

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or

amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, or spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

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

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

ORAL ADMINISTRATION

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

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

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

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

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

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

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

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

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

Exemplary tablets contain up to about 80% drug, from about 10 wt% to about 90 wt% binder, from

about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

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

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

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

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

PARENTERAL ADMINISTRATION

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

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

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation,

may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents. Formulations for use with needle-free injection administration comprise a compound of the invention in powdered form in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

Formulations for parenteral administration may be formulated to be immediate and/or modified controlled release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

TOPICAL ADMINISTRATION

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999).

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

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

INHALED/INTRANASAL ADMINISTRATION

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

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

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

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

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

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin

sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

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

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

RECTAL/INTRAVAGINAL ADMINISTRATION

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

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

OTHER TECHNOLOGIES

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

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and

gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

DOSAGE

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

These dosages are based on an average human subject having a weight of about 65kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

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

A 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, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide,

nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin or zomepirac;

- a barbiturate sedative, e.g. amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobartital, secobarbital, talbutal, theamylal or thiopental;
- a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;
- an H_1 antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;
- a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone;
- a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphrenadine;
- an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinine, cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid, budipine, EN-3231 (MorphiDex®, a combination formulation of morphine and dextromethorphan), topiramate, neramexane or perzinfotel including an NR2B antagonist, e.g. ifenprodil, traxoprodil or (–)-(R)-6-{2-[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]-1-hydroxyethyl-3,4-dihydro-2(1H)-quinolin one;
- an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dexmetatomidine, modafinil, or
  4-amino-6,7-dimethoxy-2-(5-methane-sulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;
- a tricyclic antidepressant, e.g. desipramine, imipramine, amitriptyline or nortriptyline;
- an anticonvulsant, e.g. carbamazepine, lamotrigine, topiratmate or valproate;
- a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g.

(αR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]-naphthyridine-6-13-dione (TAK-637), 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), aprepitant, lanepitant, dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2S,3S);

- a muscarinic antagonist, e.g oxybutynin, tolterodine, propiverine, tropsium chloride, darifenacin, solifenacin, temiverine and ipratropium;
- a COX-2 selective inhibitor, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, or lumiracoxib;
- a coal-tar analgesic, in particular paracetamol;
- a neuroleptic such as droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonepiprazole, blonanserin, iloperidone, perospirone, raclopride, zotepine, bifeprunox, asenapine, lurasidone, amisulpride, balaperidone, palindore, eplivanserin, osanetant, rimonabant, meclinertant, Miraxion® or sarizotan;
- a vanilloid receptor agonist (e.g. resinferatoxin) or antagonist (e.g. capsazepine);
- a beta-adrenergic such as propranolol;
- a local anaesthetic such as mexiletine;
- a corticosteroid such as dexamethasone;
- a 5-HT receptor agonist or antagonist, particularly a 5-$HT_{1B/1D}$ agonist such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan;
- a 5-HT_{2A} receptor antagonist such as R(+)-alpha-(2,3-dimethoxy-phenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (MDL-100907);
- a cholinergic (nicotinic) analgesic, such as ispronicline (TC-1734), (E)-N-methyl-4-(3-pyridinyl)-3-buten-1-amine (RJR-2403),

(R)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594) or nicotine;

- Tramadol®;
- a PDEV inhibitor, such as

5-[2-ethoxy-5-(4-methyl-1-piperazinyl-sulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil),

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione (IC-351 or tadalafil),

2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil),

5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one,

5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one,

5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one,

4-[(3-chloro-4-methoxybenzyl)amino]-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide,

3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide;

- an alpha-2-delta ligand such as gabapentin, pregabalin, 3-methylgabapentin,

(1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid,

(3S,5R)-3-aminomethyl-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid,

(3S,5R)-3-amino-5-methyl-octanoic acid, (2S,4S)-4-(3-chlorophenoxy)proline,

(2S,4S)-4-(3-fluorobenzyl)-proline, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid,

3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one,

C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine,

(3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid,

(3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid,

(3S,5R)-3-amino-5-methyl-octanoic acid, (3R,4R,5R)-3-amino-4,5-dimethyl-heptanoic acid,

(3R,4R,5R)-3-amino-4,5-dimethyl-octanoic acid, (2*S*)-2-Amino-4-ethyl-2-methylhexanoic acid and

(2S)-2-aminomethyl-5-ethyl-heptanoic acid;

- a cannabinoid;
- metabotropic glutamate subtype 1 receptor (mGluR1) antagonist;
- a serotonin reuptake inhibitor such as sertraline, sertraline metabolite demethylsertraline, fluoxetine, norfluoxetine (fluoxetine desmethyl metabolite), fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine, dapoxetine, nefazodone, cericlamine and trazodone;
- a noradrenaline (norepinephrine) reuptake inhibitor, such as maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, buproprion, buproprion metabolite hydroxybuproprion, nomifensine and viloxazine (Vivalan®), especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular (S,S)-reboxetine;
- a dual serotonin-noradrenaline reuptake inhibitor, such as venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine, milnacipran and imipramine;
- an inducible nitric oxide synthase (iNOS) inhibitor such as

S-[2-[(1-iminoethyl)amino]ethyl]-L-homocysteine,

S-[2-[(1-iminoethyl)-amino]ethyl]-4,4-dioxo-L-cysteine,

S-[2-[(1-iminoethyl)amino]ethyl]-2-methyl-L-cysteine,

(2S,5Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-5-heptenoic acid, 2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)-butyl]thio]-5-chloro-3-pyridinecarbonitrile;

2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chlorobenzonitrile,

(2S,4R)-2-amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol,

2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl) butyl]thio]-6-(trifluoromethyl)-3 pyridinecarbonitrile, 2-[[(1R,3S)-3- amino-4-hydroxy- 1 -(5-thiazolyl)butyl]thio]-5-chlorobenzonitrile, N-[4-[2-(3-chlorobenzylamino)ethyl]phenyl]thiophene-2-carboxamidine, or guanidinoethyldisulfide;

- an acetylcholinesterase inhibitor such as donepezil;
- a prostaglandin E_2 subtype 4 (EP4) antagonist such as *N*-[({2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl}amino)-carbonyl]-4-methylbenzenesulfonamide or 4-[(1*S*)-1-({[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;
- a leukotriene B4 antagonist; such as 1-(3-biphenyl-4-ylmethyl-4-hydroxy-chroman-7-yl)-cyclopentanecarboxylic acid (CP-105696), 5-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-5E- hexenyl]oxyphenoxy]-valeric acid (ONO-4057) or DPC-11870,
- a 5-lipoxygenase inhibitor, such as zileuton, 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone (ZD-2138), or 2,3,5-trimethyl-6-(3-pyridylmethyl),1,4-benzoquinone (CV-6504);
- a sodium channel blocker, such as lidocaine;
- a 5-HT3 antagonist, such as ondansetron;

and the pharmaceutically acceptable salts and solvates thereof.

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

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

example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

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

In this specification, especially in "Examples", the following abbreviations can be used:

Co(TPP)	5, 10, 15, 20 tetraphenyl-21H, 23H porphine Co(II)
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
EtOH	ethanol
MeOH	methanol
THF	tetrahydrofuran
TFA	trifluoroacetic acid

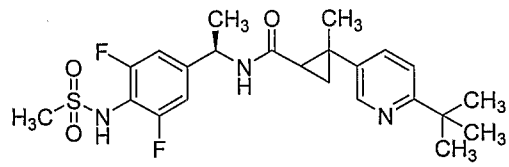
Examples

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 are given for illustration only; melting points (mp) given are 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 F_{254} precoated TLC plates), mass spectrometry, nuclear magnetic resonance spectra (NMR), infrared red absorption spectra (IR) or microanalysis. Yields are 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 uM) or Biotage amino bounded silica (35-75 μm, KP-NH) or Biotage silica (32-63 μm, KP-Sil). The purification using HPLC was

perfomed by the following apparatus and conditions. Apparatus : UV-trigger preparative HPLC system, Waters (Column: XTerra MS C18, 5 um, 19 x 50 mm or 30 x 50 mm), Detector: UV 254 nm Conditions : CH_3CN/0.05% HCOOH aqueous solution or CH_3CN/0.01% NH_3 aqueous solution; 20ml/min (19 x 50 mm) or 40ml/min (30 x 50 mm) at ambient temperature. Microwave apparatus used in the reaction was Emrys optimizer (Personal chemistry). Optical rotation was measured by P-1020 (Jasco). Low-resolution mass spectral data (EI) were obtained on a Integrity (Waters) mass spectrometer. Low-resolution mass spectral data (ESI) were obtained on a ZMD (Micromass) mass spectrometer. NMR data was 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 are: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br. = broad, etc. IR spectra were measured by a Shimazu 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).

Example 1

2-(6-TERT-BUTYLPYRIDIN-3-YL)-N-((1*R*)-1-{3,5-DIFLUORO-4-[(METHYLSULFONYL)AMINO]PHENYL}ETHYL)-2-METHYLCYCLOPROPANECARBOXAMIDE



1A) N-(4-BROMO-2,6-DIFLUOROPHENYL)METHANESULFONAMIDE

To a solution of 4-bromo-2,6-difluoroaniline (3.0 g, 14.4 mmol) in pyridine (20 ml) was added methanesulfonyl chloride (2.23 ml, 28.8 mmol) at room temperature. Then the mixture was stirred at 50 °C for 6 hours. After cooing to room temperature, the mixture was concentrated *in vacuo*. The resulting residue was dissolved in THF (40 ml). To this solution was added 2M sodium hydroxide

aqueous solution (40 ml) and the reaction was stirred at room temperature for 4 hours. The mixture was acidified with 2M HCl aqueous solution and extracted with EtOAc. The organic layer was washed with 2M HCl aqueous solution and brine, dried over sodium sulfate and concentrated *in vacuo*, to give the title compound (4.05 g, 98%) as an orange solid.

^{1}H NMR (270 MHz, $CDCl_3$) δ 3.22 (3H, s), 6.08 (1H, br s), 7.17-7.24 (2H, m).

MS (ESI) m/z 286 $(M + H)^+$,284 $(M - H)^-$.

1B) *N*-(4-ACETYL-2,6-DIFLUOROPHENYL)METHANESULFONAMIDE

A test tube suitable for microwave use was charged with palladium (II) acetate (12 mg, 0.05 mmol), 1,3-bis(diphenylphosphino)propane (43 mg, 0.11 mmol), the compound of Example 1A (500 mg, 1.75 mmol), *n*-butyl vinyl ether (1.1 ml, 8.75 mmol), and potassium carbonate (290 mg, 2.10 mmol) in DMF (4.8 ml) – water (1.2 ml). The mixture was subjected to microwave irradiation at 100 °C with stirring for 30 minutes. The mixture was diluted with THF, acidified with concentrated HCl aqueous solution and stirred at room temperature for 14 hours. The mixture was partitioned between EtOAc and water. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography, eluting with gradually from hexane/EtOAc (2:1) to hexane/EtOAc (1:1), to give the title compound (214 mg, 49%) as a white solid.

^{1}H NMR (270 MHz, $CDCl_3$) δ 2.59 (3H, s), 3.32 (3H, s), 7.55-7.63 (2H, m). A signal due to NH was not observed. MS (ESI) m/z 248 $(M - H)^-$.

1C) *N*-[4-((1*R*)-1-{[(*R*)-*TERT*-BUTYLSULFINYL]AMINO}ETHYL)-2,6-DIFLUOROPHENYL]METHANESULFONAMIDE

To a solution of the compound of Example 1B (270 mg, 1.1 mmol) and titanium(IV) ethoxide (2 ml) in THF(2 ml) was added (*R*)-(+)-2-methyl-2-propanesulfininamide (131mg, 1.1 mmol) under a nitrogen atmosphere and the mixture was stirred for 18 hours at 70 °C. After cooling to –20 °C, sodium borohydride (123 mg, 3.2 mmol) was added to the mixture. The mixture was warmed to room temperature and stirred for 16 hours, then quenched with MeOH and water, and the resulting white precipitate was filtered off. The filtrate was concentrated *in vacuo* to furnish the title compound (423 mg,

100%) as a yellow solid.

^{1}H NMR (270 MHz, $CDCl_3$) δ 1.18 (9H, s), 1.40 (3H, d, J = 6.6 Hz), 2.92 (3H, s), 3.84-3.85 (1H, m), 4.30-4.38 (1H, m), 6.87 (2H, d, J = 8.6 Hz). A signal due to NH was not observed.

1D) *N*-{4-[(1*R*)-1-AMINOETHYL]-2,6-DIFLUOROPHENYL}METHANESULFONAMIDE HYDROCHLORIDE

A mixture of the compound of Example 1C (423 mg, 1.1 mmol) and HCl-MeOH (10%, 10 ml) was stirred at room temperature for 24 hours and then concentrated *in vacuo*. Diethyl ether and MeOH were added to precipitate the amine hydrochloride. The precipitate was then filtered and washed with diethyl ether to furnish the title compound (290 mg, 94%) as a yellow solid.

^{1}H NMR (270 MHz, DMSO-d_6) δ 1.51 (3H, d, J = 6.6 Hz), 3.08 (3H, s), 4.44 (1H, br s), 7.44-7.47 (2H, m), 8.67 (2H, br s), 9.67 (1H, s). MS (ESI) m/z 249 $(M - H)^-$.

1E) 2-*TERT*-BUTYL-5-ISOPROPENYLPYRIDINE

To a suspension of (methyl)triphenylphosphonium bromide (15.5 g, 43.5 mmol) in THF (50 ml) was added a suspension of potassium tert-butoxide (4.88 g, 43.5 mmol) in THF (25 ml) dropwise at 0°C over 1hour. After the mixture was stirred at room temperature for 1 hour, a solution of 1-(6-*tert*-butylpyridin-3-yl)ethanone in THF (25 ml) was added dropwise at 0°. Then the mixture was stirred at room temperature for 1 hour. The reaction was quenched with acetone (5ml), evaporated, diluted with EtOAc-hexane (1:3) (500ml). The formed precipitate was removed by filtration and filtrate was concentrated, purified through silica gel column chromatography eluting with EtOAc-hexane (1:20) to furnish the title compound as colorless oil (5.26 g, 90%).

^{1}H NMR ($CDCl_3$) δ ppm 1.37 (9H, s), 2.15 (3H, s), 5.12 (1H, s), 5.39 (1H, s), 7. 31 (1H, d, J = 7.9 Hz), 7.68 (1H, dd, J = 2.0, 7.9 Hz) 8.68 (1H, d, J = 2.0 Hz)

1F) ETHYL 2-(6-*TERT*-BUTYLPYRIDIN-3-YL)-2-METHYLCYCLOPROPANECARBOXYLATE

To a toluene (60 ml) solution of 2-*tert*-butyl-5-isopropenylpyridine (5.96 g, 34 mmol), Co(TPP) (0.69 g, 1.0 mmol) and 1-methyl-1H-imidazole (8.37 g, 102 mmol), ethyl diazoacetate (5.4 g, 48 mmol) was added and the mixture was stirred for 5 minutes at room temperature followed by additional stirring for 1 hour at 80 °C.

Then, evaporation of the solvent and purification by silica gel column chromatography, eluting with gradually from hexane to hexane/EtOAc (30:1), gave the title compound (3.51 g, 39 % as trans-form) as white solids.

^{1}H NMR ($CDCl_3$) δ ppm 1.30 (3H, t, J = 7.3 Hz), 1.35 (9H, s), 1.37-1.50 (2H, m), 1.53 (3H, s), 1.93 (1H, dd, J = 5.9, 8.6 Hz), 4.19 (2H, q, J = 7.3 Hz), 7.28 (1H, d, J= 8.6 Hz), 7.51 (1H, dd, J = 2.6, 8.6 Hz), 8.51 (1H, dt, J = 2.5 Hz). MS (ESI) : m/z 248 $(M + H)^+$.

1G) 2-(6-*TERT*-BUTYLPYRIDIN-3-YL)-2-METHYLCYCLOPROPANECARBOXYLIC ACID (RACEMIC)

To a THF (25 ml) solution of the compound of Example 1F (3.51 g, 13.4 mmol), 2M sodium hydroxide aqueous solution (14 ml) and MeOH (25 ml) were added and the mixture was stirred for 16 hours at room temperature. After the reaction was completed, the basic mixture was washed with diethyl ether, and the separated aqueous layer was neutralized with 2M HCl aqueous solution to pH 5~6 and the whole was extracted with EtOAc followed by evaporation to afford 3.22 g (quant.) of racemic 2-(6-*tert*-butylpyridin-3-yl)-2-methylcyclopropanecarboxylic acid as white solids.

^{1}H NMR ($CDCl_3$) δ ppm 1.37 (9H, s), 1.45-1.60 (2H, m), 1.60 (3H, s), 1.96-2.01 (1H, m), 7.30 (1H, d, J = 8.1 Hz), 7.56 (1H, dd, J= 2.2, 8.1 Hz), 8.58 (1H, d, J = 2.2 Hz).

MS (ESI) m/z 232 $(M - H)^-$.

1H) 2-(6-*TERT*-BUTYLPYRIDIN-3-YL)-2-METHYLCYCLOPROPANECARBOXYLIC ACID (SINGLE ISOMER)

Racemic 2-(6-*tert*-butylpyridin-3-yl)-2-methylcyclopropanecarboxylic acid was separated by Daicel Chiralpak AD-H (20 x 250 mm), eluting with n-hexane/EtOH/TFA/diethylamine=95/5/0.05/0.05 at column temperature of 40 °C. The title compound was given as a later fraction (retention time was 2.9 min).

1I)

2-(6-TERT-BUTYLPYRIDIN-3-YL)-N-((1*R*)-1-{3,5-DIFLUORO-4-[(METHYLSULFONYL)AMINO]PHENYL}ETHYL)-2-METHYLCYCLOPROPANECARBOXAMIDE

To an acetonitrile (10 ml) solution of the compound of Example 1H (244 mg, 1.05 mmol), the compound of Example 1D (300 mg, 1.05 mmol) and HBTU (476 mg, 1.26 mmol) was added triethylamine (0.44 ml, 3.14

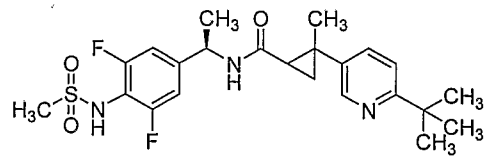
mmol) and the mixture was stirred for 1 hour at room temperature. Then the reaction was concentrated and the crude residue was purified by column chromatography on silica gel with acetone-hexane (1:2) to give a white solid, which was recrystallized from EtOAc-hexane to furnish the title compound as a white solid (356 mg, 73%).

^{1}H NMR (DMSO-d_6): δ 1.25-1.45 (17H, m), 1.94-2.00 (1H, m), 3.05 (3H, s), 4.92-5.01 (1H, m), 7.14 (2H, d, J = 8.8 Hz), 7.36 (1H, d, J = 8.1 Hz), 7.61 (1H, d, J = 8.1 Hz), 8.51 (1H, s), 8.66 (1H, d, J = 7.5 Hz), 9.49 (1H, s).

MS (ESI) m/z 464 $(M-H)^-$, 466 $(M+H)^+$.

CLAIMS

1. A compound of the formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof, as defined in Claim 1, for use as a medicament.

3. A pharmaceutical composition including a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof, as defined in Claim 1, together with a pharmaceutically acceptable excipient.

4. A pharmaceutical composition including a compound of the formula (I) or a pharmaceutically acceptable salt or solvate thereof, as defined in Claim 1, together with a pharmaceutically acceptable excipient, for treatment of a disease for which an VR1 antagonist is indicated.

5. A pharmaceutical composition according to Claim 4, wherein the disease is selected from acute cerebral ischemia, pain, chronic pain, acute pain, nociceptive pain, neuropathic pain, inflammatory pain, post herpetic neuralgia, neuropathies, neuralgia, diabetic neuropathy, HIV-related neuropathy, nerve injury, rheumatoid arthritic pain, osteoarthritic pain, burns, back pain, visceral pain, cancer pain, dental pain, headache, migraine, carpal tunnel syndrome, fibromyalgia, neuritis, sciatica, pelvic hypersensitivity, pelvic pain, menstrual pain, bladder disease, such as incontinence, micturition disorder, renal colic and cystitis, inflammation, such as burns, rheumatoid arthritis and osteoarthritis, neurodegenerative disease, such as stroke, post stroke pain and multiple sclerosis, pulmonary disease, such as asthma, cough, chronic obstructive pulmonary disease (COPD) and broncho constriction, gastrointestinal disorders, such as gastroesophageal reflux disease (GERD), dysphagia, ulcer, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), colitis and Crohn's disease, ischemia, such as cerebrovascular ischemia, emesis, such as cancer chemotherapy-induced emesis and obesity.

6. A use of a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, as defined in Claim 1, for the manufacture of a medicament to treat a disease for which an VR1 antagonist is indicted.

7. A use according to Claim 6 where the disease is selected from acute cerebral ischemia, pain, chronic pain, acute pain, nociceptive pain, neuropathic pain, inflammatory pain, post herpetic neuralgia, neuropathies, neuralgia, diabetic neuropathy, HIV-related neuropathy, nerve injury, rheumatoid arthritic pain, osteoarthritic pain, burns, back pain, visceral pain, cancer pain, dental pain, headache, migraine, carpal tunnel syndrome, fibromyalgia, neuritis, sciatica, pelvic hypersensitivity, pelvic pain, menstrual pain, bladder disease, such as incontinence, micturition disorder, renal colic and cystitis, inflammation, such as burns, rheumatoid arthritis and osteoarthritis, neurodegenerative disease, such as stroke, post stroke pain and multiple sclerosis, pulmonary disease, such as asthma, cough, chronic obstructive pulmonary disease (COPD) and broncho constriction, gastrointestinal disorders, such as gastroesophageal reflux disease (GERD), dysphagia, ulcer, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), colitis and Crohn's disease, ischemia, such as cerebrovascular ischemia, emesis, such as cancer chemotherapy-induced emesis and obesity.

8. A method of treatment of a mammal, including a human being, to treat a disease for which an VR1 antagonist is indicated, 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 Claim 1.

9. A method according to Claim 8 where the disease is selected from acute cerebral ischemia, pain, chronic pain, acute pain, nociceptive pain, neuropathic pain, inflammatory pain, post herpetic neuralgia, neuropathies, neuralgia, diabetic neuropathy, HIV-related neuropathy, nerve injury, rheumatoid arthritic pain, osteoarthritic pain, burns, back pain, visceral pain, cancer pain, dental pain, headache, migraine, carpal tunnel syndrome, fibromyalgia, neuritis, sciatica, pelvic hypersensitivity, pelvic pain, menstrual pain, bladder disease, such as incontinence, micturition disorder, renal colic and cystitis, inflammation, such as burns, rheumatoid arthritis and osteoarthritis, neurodegenerative disease, such as stroke, post stroke pain

and multiple sclerosis, pulmonary disease, such as asthma, cough, chronic obstructive pulmonary disease (COPD) and broncho constriction, gastrointestinal disorders, such as gastroesophageal reflux disease (GERD), dysphagia, ulcer, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), colitis and Crohn's disease, ischemia, such as cerebrovascular ischemia, emesis, such as cancer

10. A combination of a compound of the formula (I), as defined in Claim 1, and another pharmacologically active agent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2007/001143

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/24 A61K31/435 A61P29/00

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

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, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/047738 A (SQUIBB BRISTOL MYERS CO [US]) 10 June 2004 (2004-06-10) claim 1	1-10
A	SZALLASI A ET AL: "Vanilloid receptor TRPV1 antagonists as the next generation of painkillers. Are we putting the cart before the horse?" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 47, no. 11, 3 April 2004 (2004-04-03), pages 2717-2723, XP002400521 ISSN: 0022-2623 the whole document	1-10

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 September 2007	08/10/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Baston, Eckhard

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2007/001143

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2006/097817 A1 (PFIZER JAPAN INC [JP]; PFIZER [US]; HANAZAWA TAKESHI [JP]; HIRANO MISA) 21 September 2006 (2006-09-21) claim 1	1-10
T	WESTWAY, S.M.: "The Potential of Transient Receptor Potential Vanilloid Type 1 Channel Modulators for the Treatment of Pain" JOURNAL OF MEDICINAL CHEMISTRY, vol. 50, 2007, pages 2589-2596, XP002452089 the whole document	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2007/001143

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004047738 A	10-06-2004	AU 2003295781 A1	18-06-2004
		EP 1565190 A2	24-08-2005
WO 2006097817 A1	21-09-2006	NL 1031385 C2	05-03-2007
		NL 1031385 A1	20-09-2006