

Preferably, the compounds of the present invention are potent antagonists at Trk receptors, and have a suitable PK profile to enable once daily dosing.

- 5 The compounds of the present invention are potentially useful in the treatment of a range of disorders where a Trk antagonist is indicated, particularly pain indications. Depending on the disease and condition of the patient, the term "treatment" as used herein may include one or more of curative, palliative and prophylactic treatment.
- 10 According to the invention a compound of the present invention may be useful to treat any physiological pain such as inflammatory pain, nociceptive pain, neuropathic pain, acute pain, chronic pain, musculo-skeletal pain, on-going pain, central pain, heart and vascular pain, head pain, orofacial pain. Other pain conditions which may be treated include intense acute pain and chronic pain conditions which may involve the same pain pathways driven by pathophysiological processes and as such cease to provide a
- 15 protective mechanism and instead contribute to debilitating symptoms associated with a wide range of disease states.

Pain is a feature of many trauma and disease states. When a substantial injury, via disease or trauma, to body tissue occurs the characteristics of nociceptor activation are altered, this leads to hypersensitivity at

20 the site of damage and in nearby normal tissue. In acute pain the sensitivity returns to normal once the injury has healed. However, in many chronic pain states, the hypersensitivity far outlasts the healing process and is normally due to nervous system injury due to maladaptation of the afferent fibres (Woolf & Salter 2000 Science 288: 1765-1768). Clinical pain is present when discomfort and abnormal sensitivity feature among the patient's symptoms. There are a number of typical pain subtypes: 1) spontaneous pain

25 which may be dull, burning, or stabbing; 2) pain responses to noxious stimuli are exaggerated (hyperalgesia); 3) pain is produced by normally innocuous stimuli (allodynia) (Meyer et al., 1994 Textbook of Pain 13-44). Pain can be divided into a number of different areas because of differing pathophysiology, these include nociceptive, inflammatory, neuropathic pain among others. 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,

30 Cancer pain have both nociceptive and neuropathic components.

NOCICEPTIVE 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 sensitise the

35 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 the sharp and stabbing pain sensations, whilst unmyelinated C fibres transmit at a slower rate and convey the dull or aching pain. Moderate to severe acute nociceptive pain is a prominent feature of, but is not limited to

40 pain from strains/sprains, post-operative pain (pain following any type of surgical procedure),

posttraumatic pain, burns, myocardial infarction, acute pancreatitis, and renal colic. Also cancer related acute pain syndromes commonly due to therapeutic interactions such as chemotherapy toxicity, immunotherapy, hormonal therapy and radiotherapy. Moderate to severe acute nociceptive pain is a prominent feature of, ~~but is not limited to,~~ cancer pain which may be tumour related pain, (e.g. bone pain, headache and facial pain, viscera pain) or associated with cancer therapy (e.g. postchemotherapy syndromes, chronic postsurgical pain syndromes, post radiation syndromes), back pain which may be due to herniated or ruptured intervertebral discs or abnormalities of the lumbar facet joints, sacroiliac joints, paraspinal muscles or the posterior longitudinal ligament.

10 NEUROPATHIC PAIN

According to the invention a compound of the present invention can potentially be used to treat neuropathic pain and the symptoms of neuropathic pain including hyperalgesia, allodynia and ongoing pain. Neuropathic pain is defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system (IASP definition). 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,~~ Diabetic neuropathy, Post herpetic neuralgia, Back pain, Cancer neuropathy, HIV neuropathy, Phantom limb pain, Carpal Tunnel Syndrome, chronic alcoholism, hypothyroidism, trigeminal neuralgia, uremia, or vitamin deficiencies. 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 patients 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, or paroxysmal and abnormal evoked pain, such as hyperalgesia (increased sensitivity to a noxious stimulus) and allodynia (sensitivity to a normally innocuous stimulus).

INTENSE ACUTE PAIN AND CHRONIC PAIN

Intense acute pain and chronic pain may involve the same pathways driven by pathophysiological processes and as such cease to provide a protective mechanism and instead contribute to debilitating symptoms associated with a wide range of disease states. Pain is a feature of many trauma and disease states. When a substantial injury, via disease or trauma, to body tissue occurs the characteristics of nociceptor activation are altered. There is sensitisation in the periphery, locally around the injury and centrally where the nociceptors terminate. This leads to hypersensitivity at the site of damage and in nearby normal tissue. In acute pain these mechanisms can be useful and allow for the repair processes to take place and the hypersensitivity returns to normal once the injury has healed. However, in many chronic pain states, the hypersensitivity far outlasts the healing process and is normally due to nervous system injury. This injury often leads to maladaptation of the afferent fibres (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. There are a number of typical pain subtypes: 1) spontaneous pain which may be dull, burning,

chemicals or infective particles for example micro-organisms. Inflammatory conditions can be either acute or chronic inflammation or both.

Inflammatory pain can result from an inflammatory condition due to an inflammatory disease such as inflammatory joint diseases, inflammatory connective tissue diseases, inflammatory autoimmune diseases, inflammatory myopathies, inflammatory digestive system diseases, inflammatory air way diseases, cellular immune inflammation diseases, hypersensitivities and allergies, vascular inflammation diseases, non-immune inflammatory disease, synovitis, villonodular synovitis, arthralgias, ankylosing spondylitis, spondyloarthritis, spondyloarthropathy, gout, Pagets disease, periarticular disorders such as bursitis, rheumatoid disease, rheumatoid arthritis and osteoarthritis, rheumatoid arthritis or osteoarthritis. Rheumatoid arthritis in particular, represents ongoing inflammation associated with severe pain. Arthritic pain is a form of inflammatory pain and arises from inflammation in a joint which causes both peripheral sensitization and central sensitization. Under inflammatory conditions the nociceptive system is activated by normally innocuous and nonpainful mechanical stimuli. Additionally when the joint is at rest pain is present and appears as spontaneous pain and hyperalgesia (augmented pain response on noxious stimulation and pain on normally nonpainful stimulation). Inflammatory processes in peripheral tissues lead to central sensitization in the spinal cord, which contributes to hyperalgesia and allodynia typically associated with inflammatory pain. Other types of inflammatory pain include inflammatory bowel diseases (IBD).

OTHER TYPES OF PAIN

Other types of pain include but are not limited to:

- Musculo-skeletal disorders including but not limited to myalgia, fibromyalgia, spondylitis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, dystrophinopathy, Glycogenolysis,

- polymyositis, pyomyositis;

- Central pain or 'thalamic pain' as defined by pain caused by lesion or dysfunction of the nervous system including but not limited to central post-stroke pain, multiple sclerosis, spinal cord injury, Parkinson's disease and epilepsy;

- Heart and vascular pain including but not limited to angina, myocardical infarction, mitral stenosis, pericarditis, Raynaud's phenomenon, scleredoma, scleredoma, skeletal muscle ischemia;

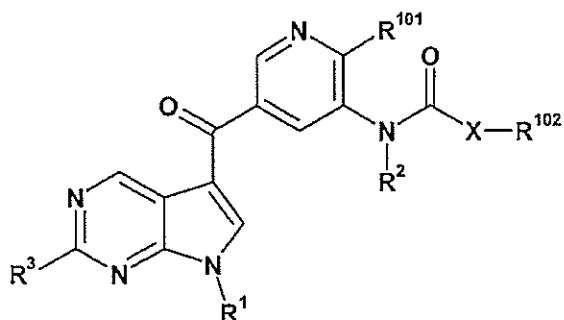
- Visceral pain, and gastrointestinal disorders. The viscera encompasses the organs of the abdominal cavity. These organs include the sex organs, spleen and part of the digestive system. Pain associated with the viscera can be divided into digestive visceral pain and non-digestive visceral pain. Commonly encountered gastrointestinal (GI) disorders include the functional bowel disorders (FBD) and the

- inflammatory bowel diseases (IBD). These GI disorders include a wide range of disease states that are currently only moderately controlled, including – for FBD, gastro-esophageal reflux, dyspepsia, the irritable bowel syndrome (IBS) and functional abdominal pain syndrome (FAPS), and – for IBD, Crohn's disease, ileitis, and ulcerative colitis, which all regularly produce visceral pain. Other types of visceral pain include the pain associated with dysmenorrhea, pelvic pain, cystitis and pancreatitis;

Head pain including but not limited to migraine, migraine with aura, migraine without aura cluster headache, tension-type headache. Orofacial pain including but not limited to dental pain, temporomandibular myofascial pain, tinnitus, hot flushes, restless leg syndrome and blocking development of abuse potential. Further pain conditions may include, back pain (e.g. chronic lower back pain), cancer pain, complex regional syndrome, HIV-related neuropathic pain, post-operative induced neuropathic pain, post-stroke pain, spinal cord injury pain, traumatic nerve injury pain, diabetic peripheral neuropathy, moderate / severe interstitial cystitis pain, irritable bowel syndrome pain, moderate / severe endometriosis pain, moderate / severe pelvic pain, moderate / severe prostatitis pain, moderate / severe osteoarthritis pain, post-herpetic neuralgia, rheumatoid arthritis pain, dysmenorrhea pain, pre-emptive post-operative pain, trigeminal neuralgia, bursitis, dental pain, fibromyalgia or myofascial pain, menstrual pain, migraine, neuropathic pain (including painful diabetic neuropathy), pain associated with post-herpetic neuralgia, post-operative pain, referred pain, trigeminal neuralgia, visceral pain (including interstitial cystitis and IBS) and pain associated with AIDS, allodynia, burns, cancer, hyperalgesia, hypersensitisation, spinal trauma and/or degeneration and stroke.

DETAILED DESCRIPTION

Emodiment 1 of the invention is a compound of Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein

R¹ is

H, or

C₁₋₅ alkyl optionally substituted by up to 3 substituents independently selected from OH, CON(R⁵R⁶),

SO₂R⁷, SR⁷, OR⁷, CH₂OH, CO₂R⁵, SONR⁷R⁷, NR⁷SO₂R⁵, CN, NO₂ and R⁸, or

a ring system selected from C₃₋₅ cycloalkyl, propellanyl, or a 4-6 membered saturated heterocyclyl ring, which ring system has up to 3 ring hetero-atoms selected from N, O and S, and which ring system is optionally substituted by up to 3 substituents independently selected from methyl, OH, CON(R⁵R⁶), SO₂R⁷, OR⁷, CH₂OH, CO₂R⁵, SONR⁷R⁷, NR⁷SO₂R⁵, CN, NO₂ and R⁸;

R² is H or methyl;

In addition to the active ingredient, a pharmaceutical composition of the invention may further comprise one or more additional pharmaceutically active agents.

Controlled- or sustained-release formulations of a pharmaceutical composition of the invention may be made using conventional technology.

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As used herein, "parenteral administration" of a pharmaceutical composition includes any route of administration characterized by physical breaching of a tissue of a subject and administration of the pharmaceutical composition through the breach in the tissue. Parenteral administration thus includes, ~~but is not limited to,~~ administration of a pharmaceutical composition by injection of the composition, by application of the composition through a surgical incision, by application of the composition through a tissue-penetrating non-surgical wound, and the like. In particular, parenteral administration is contemplated to include, ~~but is not limited to,~~ subcutaneous, intraperitoneal, intramuscular, intrasternal injection, and kidney dialytic infusion techniques.

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15 Formulations of a pharmaceutical composition suitable for parenteral administration comprise the active ingredient combined with a pharmaceutically acceptable carrier, such as sterile water or sterile isotonic saline. Such formulations may be prepared, packaged, or sold in a form suitable for bolus administration or for continuous administration. Injectable formulations may be prepared, packaged, or sold in unit dosage form, such as in ampules or in multi-dose containers containing a preservative. Formulations for
20 parenteral administration include, ~~but are not limited to,~~ suspensions, solutions, emulsions in oily or aqueous vehicles, pastes, and implantable sustained-release or biodegradable formulations as discussed below. Such formulations may further comprise one or more additional ingredients including, ~~but not limited to,~~ suspending, stabilizing, or dispersing agents. In one embodiment of a formulation for parenteral administration, the active ingredient is provided in dry (i.e. powder or granular) form for
25 reconstitution with a suitable vehicle (e.g. sterile pyrogen-free water) prior to parenteral administration of the reconstituted composition.

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A composition of the present invention can be administered by a variety of methods known in the art. The route and/or mode of administration vary depending upon the desired results. The active compounds can be prepared with carriers that protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems.

Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are described by e.g., Sustained and Controlled Release Drug Delivery Systems, J. R.

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Robinson, ed., Marcel Dekker, Inc., New York, (1978). Pharmaceutical compositions are preferably manufactured under GMP conditions.

The pharmaceutical compositions may be prepared, packaged, or sold in the form of a sterile injectable aqueous or oily suspension or solution. This suspension or solution may be formulated according to the
40 known art, and may comprise, in addition to the active ingredient, additional ingredients such as the

dispersing agents, wetting agents, or suspending agents described herein. Such sterile injectable formulations may be prepared using a non-toxic parenterally-acceptable diluent or solvent, such as water or 1,3-butane diol, for example. Other acceptable diluents and solvents include, ~~but are not limited to,~~ Ringer's solution, isotonic sodium chloride solution, and fixed oils such as synthetic mono- or di-glycerides. Other parentally-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form, in a liposomal preparation, or as a component of a biodegradable polymer system. Compositions for sustained release or implantation may comprise pharmaceutically acceptable polymeric or hydrophobic materials such as an emulsion, an ion exchange resin, a sparingly soluble polymer, or a sparingly soluble salt.

The precise dosage administered of each active ingredient will vary depending upon any number of factors, including ~~but not limited to,~~ the type of animal and type of disease state being treated, the age of the animal, and the route(s) of administration.

The following non-limiting Preparations and Examples illustrate the preparation of compounds and salts of the present invention.

GENERAL EXPERIMENTAL

The Preparations and Examples that follow illustrate the invention but do not limit the invention in any way. All starting materials are available commercially or described in the literature. All temperatures are in °C. Flash column chromatography was carried out using Merck silica gel 60 (9385). Thin layer chromatography (TLC) was carried out on Merck silica gel 60 plates (5729). "R_f" represents the distance travelled by a compound divided by the distance travelled by the solvent front on a TLC plate. Melting points were determined using a Gallenkamp MPD350 apparatus and are uncorrected. NMR was carried out using a Varian-Unity Inova 400MHz NMR spectrometer or a Varian Mercury 400MHz NMR spectrometer. Mass spectroscopy was carried out using a Finnigan Navigator single quadrupole electrospray mass spectrometer or a Finnigan aQa APCI mass spectrometer.

Where it is stated that compounds were prepared in the manner described for an earlier Preparation or Example, the skilled person will appreciate that reaction times, number of equivalents of reagents and reaction temperatures may be modified for each specific reaction, and that it may nevertheless be necessary or desirable to employ different work-up or purification conditions.

The invention is illustrated by the following non-limiting examples in which the following abbreviations and definitions are used:

The Preparations and Examples that follow illustrate the invention but do not limit the invention in any way. All starting materials are available commercially or described in the literature. All temperature are in °C. Flash column chromatography was carried out using Merck silica gel 60 (9385) or Redisep silica. NMR was carried out using a Varian Mercury 400MHz NMR spectrometer or a Jeol ECX 400MHz NMR.

~~All publications cited in this application are each herein incorporated by reference in their entirety.~~

Although the invention has been described above with reference to the disclosed embodiments, those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention. It should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims.

N-(5-([2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl)pyridin-3-yl)-2-[4-(trifluoromethyl)phenyl]acetamide;

N-(5-([2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl)pyridin-3-yl)-2-(4-chlorophenyl)acetamide;

N-(5-([2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl)pyridin-3-yl)-2-[4-(trifluoromethyl)phenyl]acetamide;

N-(5-([2-Amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl)pyridin-3-yl)-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

and

N-(5-([7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl)pyridin-3-yl)-2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)acetamide;

or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising a compound of the formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of the preceding claims 1 to 20, and a pharmaceutically acceptable carrier.

22. A compound of the formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 20, for use as a medicament.

23. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 20 for use in the treatment of a disease for which an Trk receptor antagonist is indicated.

24. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 20 for use in the treatment of pain.

25. The use of a compound of the formula (I) or a pharmaceutically acceptable salt or composition thereof, as defined in any one of claims 1 to 20, for the manufacture of a medicament to treat a disease for which an Trk receptor antagonist is indicated.

26. The use of a compound of the formula (I) or a pharmaceutically acceptable salt or composition thereof, as defined in any one of claims 1 to 20, for the manufacture of a medicament to treat pain.

27. A compound or salt according to any one of claims 1 to 20 for use in a medical treatment in combination with a further drug substance.

N-(5-{{2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl}pyridin-3-yl)-2-[4-(trifluoromethyl)phenyl]acetamide;

N-(5-{{2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl}pyridin-3-yl)-2-(4-chlorophenyl)acetamide;

N-(5-{{2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl}pyridin-3-yl)-2-[4-(trifluoromethyl)phenyl]acetamide;

N-(5-{{2-Amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl}pyridin-3-yl)-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

and

N-{5-[(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)acetamide;

or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising a compound of the formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of the preceding claims 1 to 20, and a pharmaceutically acceptable carrier.

22. A compound of the formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 20, for use as a medicament.

23. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 20 for use in the treatment of a disease for which an Trk receptor antagonist is indicated.

24. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 20 for use in the treatment of pain.

25. The use of a compound of the formula (I) or a pharmaceutically acceptable salt or composition thereof, as defined in any one of claims 1 to 20, in the manufacture of a medicament for the treatment of pain.

26. The use of a compound of the formula (I) or a pharmaceutically acceptable salt or composition thereof, as defined in any one of claims 1 to 20, for the manufacture of a medicament for the treatment of cancer.

27. A compound or salt according to any one of claims 1 to 20 for use in a medical treatment in combination with a further drug substance.