

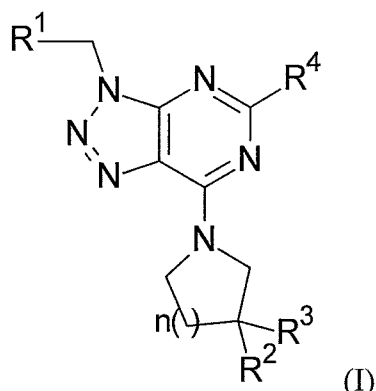
psychosis, oncology, encephalitis, malaria, allergy, immunological disorders, arthritis, gastrointestinal disorders, psychiatric disorders rheumatoid arthritis, psychosis and allergy.

The interest in CB2 receptor ligands has been steadily on the rise during the last decade (currently 30-40 patent applications/year). Evidence from different sources support
5 the view that lipid endocannabinoid signaling through CB2 receptors represents an aspect of the mammalian protective armamentarium (Pacher, P. *Prog Lipid Res* 2011, 50, 193). Its modulation by either selective CB2 receptor agonists or inverse agonists/antagonists (depending on the disease and its stage) holds unique therapeutic potential in a huge number of diseases. For CB2 inverse agonists/antagonists therapeutic opportunities have
10 been demonstrated for many pathological conditions including pain (Pasquini, S. *J Med Chem* 2012, 55(11): 5391), neuropathic pain (Garcia-Gutierrez, M.S. *Br J Pharmacol* 2012, 165(4): 951), psychiatric disorders (Garcia-Gutierrez, M.S. *Br J Pharmacol* 2012, 165(4): 951), psychosis (Garcia-Gutierrez, M.S. *Br J Pharmacol* 2012, 165(4): 951), osteoporosis and inflammation (Sophocleous, A. *Calcif Tissue Int* 2008, 82(Suppl. 1):Abst
15 OC18), psychiatric diseases and psychosis (Garcia-Gutierrez, M.S. *Br J Pharmacol* 2012, 165(4): 951), oncology (Preet, A. *Cancer Prev Res* 2011, 4: 65), encephalitis and malaria (Zimmer, A. WO 2011045068), allergy and inflammation (Ueda, Y. *Life Sci* 2007, 80(5): 414), encephalitis and malaria (Zimmer, WO 2011045068), asthma (Lunn, C.A. *J Pharmacol Exp Ther* 2006, 316(2): 780), immunological disorders (Fakhfour, G.
20 *Neuropharmacology* 2012, 63(4): 653), rheumatoid arthritis (Chackalamannil, S. US 7776889), arthritis (Lunn, C.A. *J Pharmacol Exp Ther* 2006, 316(2): 780), and gastrointestinal disorders (Barth, F. FR 2887550).

The compounds of the invention bind to and modulate the CB2 receptor and have lower CB1 receptor activity.

25 The compounds of the invention contain functional groups such as sulfonyl fluoride, isothiocyanate, thiol, azide and methyldisulfanyl which can optionally be used to form a covalent bond with the CB2 receptor. Such small organic molecules as covalent modifiers can be used for the detection and localisation of the target, for imaging, and for therapeutic use (compare e.g. Adebayo A Adeniyi, Ramesh Muthusamy & Mahmoud ES Soliman,
30 *Expert Opin. Drug Discov.* (2016) 11(1):79-90).

In one aspect, there is provided a compound of formula (I)



wherein

R¹ is a ring selected from phenyl and [1,2,5]oxadiazolyl wherein said ring is substituted with one substituent selected from halosulfonyl, halosulfonylalkyl, isothiocyanatoalkyl, isothiocyanato, aminoalkyldisulfanylalkyl, hydroxyalkyldisulfanylalkyl, hydroxyalkyldisulfanyl, aminoalkyldisulfanyl, halogen, alkyl, pyridinyldisulfanylalkyl, benzotriazolysulfonylalkyl, dihydroxyalkyldisulfanylalkyl and pyridinyldisulfanyl and optionally further substituted with cyano;

R² and R³ are independently selected from hydrogen, hydroxyl, halogen, thiohydroxyl, thiohydroxyazetidiny, azido, isothiocyanato and alkyldisulfanyl;

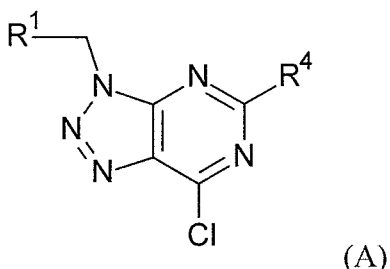
provided that at least one of R¹, R² and R³ is a group comprising sulfonyl, isothiocyanato, disulfanyl, thiohydroxyl or azido;

R⁴ is alkyl or phenylhaloalkyl; and

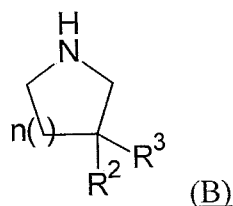
n is 0 or 1;

or a pharmaceutically acceptable salt or ester thereof.

In another aspect, there is provided a process for the manufacture of a compound as defined herein comprising the reaction of a compound of formula (A)



in the presence of a compound of formula (B)



and a base, wherein R^1 to R^4 and n are as defined herein.

5 In another aspect, there is provided a compound as defined herein, when manufactured according to a process as defined herein.

In another aspect, there is provided a compound as defined herein for use as therapeutically active substance.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a therapeutically inert carrier.

10 In another aspect, there is provided use of a compound as defined herein for the preparation of medicaments for the treatment or prophylaxis of pain, neuropathic pain, atherosclerosis, age-related macular degeneration, diabetic retinopathy, glaucoma, diabetes mellitus, inflammation, inflammatory bowel disease, ischemia-reperfusion injury, acute liver failure, liver fibrosis, lung fibrosis, kidney fibrosis, systemic fibrosis, acute allograft rejection, chronic allograft nephropathy, diabetic nephropathy, glomerulonephropathy, 15 cardiomyopathy, heart failure, myocardial ischemia/infarction, systemic sclerosis, thermal injury, burning, hypertrophic scars, keloids, gingivitis pyrexia, liver cirrhosis or tumors, regulation of bone mass, neurodegeneration, stroke, transient ischemic attack, uveitis, asthma, osteoporosis, psychiatric diseases, psychosis, oncology, encephalitis, malaria, 20 allergy, immunological disorders, arthritis, gastrointestinal disorders, rheumatoid arthritis or allergy.

In another aspect, there is provided a compound as defined herein for use in the treatment or prophylaxis of pain, neuropathic pain, atherosclerosis, age-related macular degeneration, diabetic retinopathy, glaucoma, diabetes mellitus, inflammation, 25 inflammatory bowel disease, ischemia-reperfusion injury, acute liver failure, liver fibrosis, lung fibrosis, kidney fibrosis, systemic fibrosis, acute allograft rejection, chronic allograft nephropathy, diabetic nephropathy, glomerulonephropathy, cardiomyopathy, heart failure, myocardial ischemia/infarction, systemic sclerosis, thermal injury, burning, hypertrophic scars, keloids, gingivitis pyrexia, liver cirrhosis or tumors, regulation of bone mass, 30 neurodegeneration, stroke, transient ischemic attack, uveitis, asthma, osteoporosis,

psychiatric diseases, psychosis, oncology, encephalitis, malaria, allergy, immunological disorders, arthritis, gastrointestinal disorders, rheumatoid arthritis or allergy.

In the present description the term “alkyl”, alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, particularly a
5 straight or branched-chain alkyl group with 1 to 6 carbon atoms and more particularly a straight or branched-chain alkyl group with 1 to 4 carbon atoms. Examples of straight-chain and branched-chain C₁-C₈ alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls and the

12. A compound according to any one of claims 1 to 9 for use as therapeutically active substance.
13. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 9 and a therapeutically inert carrier.
- 5 14. The use of a compound according to any one of claims 1 to 9 for the preparation of medicaments for the treatment or prophylaxis of pain, neuropathic pain, atherosclerosis, age-related macular degeneration, diabetic retinopathy, glaucoma, diabetes mellitus, inflammation, inflammatory bowel disease, ischemia-reperfusion injury, acute liver failure, liver fibrosis, lung fibrosis, kidney fibrosis, systemic
10 fibrosis, acute allograft rejection, chronic allograft nephropathy, diabetic nephropathy, glomerulonephropathy, cardiomyopathy, heart failure, myocardial ischemia/infarction, systemic sclerosis, thermal injury, burning, hypertrophic scars, keloids, gingivitis pyrexia, liver cirrhosis or tumors, regulation of bone mass, neurodegeneration, stroke, transient ischemic attack, uveitis, asthma, osteoporosis,
15 psychiatric diseases, psychosis, oncology, encephalitis, malaria, allergy, immunological disorders, arthritis, gastrointestinal disorders, rheumatoid arthritis or allergy.
15. A compound according to any one of claims 1 to 9 for use in the treatment or
20 prophylaxis of pain, neuropathic pain, atherosclerosis, age-related macular degeneration, diabetic retinopathy, glaucoma, diabetes mellitus, inflammation, inflammatory bowel disease, ischemia-reperfusion injury, acute liver failure, liver fibrosis, lung fibrosis, kidney fibrosis, systemic fibrosis, acute allograft rejection, chronic allograft nephropathy, diabetic nephropathy, glomerulonephropathy, cardiomyopathy, heart failure, myocardial ischemia/infarction, systemic sclerosis,
25 thermal injury, burning, hypertrophic scars, keloids, gingivitis pyrexia, liver cirrhosis or tumors, regulation of bone mass, neurodegeneration, stroke, transient ischemic attack, uveitis, asthma, osteoporosis, psychiatric diseases, psychosis, oncology, encephalitis, malaria, allergy, immunological disorders, arthritis, gastrointestinal disorders, rheumatoid arthritis or allergy.
- 30 ~~16. A method for the treatment or prophylaxis of pain, neuropathic pain, atherosclerosis, age-related macular degeneration, diabetic retinopathy, glaucoma, diabetes mellitus, inflammation, inflammatory bowel disease, ischemia-reperfusion injury, acute liver failure, liver fibrosis, lung fibrosis, kidney fibrosis, systemic fibrosis, acute allograft rejection, chronic allograft nephropathy, diabetic nephropathy,~~
35 ~~glomerulonephropathy, cardiomyopathy, heart failure, myocardial ischemia/infarction, systemic sclerosis, thermal injury, burning, hypertrophic scars,~~

keloids, gingivitis pyrexia, liver cirrhosis or tumors, regulation of bone mass, neurodegeneration, stroke, transient ischemic attack, uveitis, asthma, osteoporosis, psychiatric diseases, psychosis, oncology, encephalitis, malaria, allergy, immunological disorders, arthritis, gastrointestinal disorders, rheumatoid arthritis or allergy, which method comprises administering an effective amount of a compound as defined in any one of claims 1 to 9 to a patient in need thereof.

1716. The use of a compound according to any one of claims 1 to 9 for the detection or the imaging of the CB2 receptor.

18. The invention as hereinbefore described.
