reperfusion. It describes the intriguing phenomenon in which transient non-lethal ischemia and reperfusion of one organ or tissue confers resistance to a subsequent episode of "lethal" ischemia reperfusion injury in a remote organ or tissue. The actual mechanism through which transient ischemia and reperfusion of an organ or tissue confers protection is currently unknown although several hypotheses have been proposed.

The humoral hypothesis proposes that the endogenous substance (such as adenosine, bradykinin, opioids, CGRP, endocannabinoids, Angiotensin I or some other as yet unidentified humoral factor) generated in the remote organ or tissue enters the blood stream and activates its respective receptor in the target tissue and thereby recruiting the various intracellular pathways of cardioprotection implicated in ischemic preconditioning.

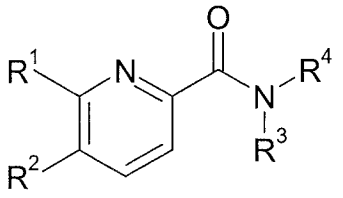
Recent data indicates that endocannabinnoids and their receptors, in particular CB2 might be involved in pre-conditioning and contribute to prevent reperfusion injury by downregulation of the inflammatory response (Pacher, P. et al. Br J Pharmacol 2008, 153(2), 252-62). Specifically, recent studies using CB2 tool agonists demonstrated the efficacy of this concept for reducing the I/R injury in the heart (Defer, N. et al. Faseb J 2009, 23(7), 2120-30), the brain (Zhang, M. et al. J Cereb Blood Flow Metab 2007, 27(7), 1387-96), the liver (Batkai, S. et al. Faseb J 2007, 21(8), 1788-800) and the kidney (Feizi, A. et al. Exp Toxicol Pathol 2008, 60(4-5), 405-10).

Moreover, over the last few years, a growing body of literature indicates that CB2 can also be of interest in sub-chronic and chronic setting. Specific upregulation of CB1 and CB2 has been shown to be associated in animal models of chronic diseases associated with fibrosis (Garcia-Gonzalez, E. et al. Rheumatology (Oxford) 2009, 48(9), 1050-6; Yang, Y. Y. et al. Liver Int 2009, 29(5), 678-85) with a relevant expression of CB2 in myofibroblasts, the cells responsible for fibrosis progression.

Activation of CB2 receptor by selective CB2 agonist has in fact been shown to exert anti-fibrotic effect in diffuse systemic sclerosis (Garcia-Gonzalez, E. et al. Rheumatology (Oxford) 2009, 48(9), 1050-6) and CB2 receptor has emerged as a critical target in experimental dermal fibrosis (Akhmetshina, A. et al. Arthritis Rheum 2009, 60(4), 1129-36) and in in liver pathophysiology, including fibrogenesis associated with chronic liver diseases (Lotersztajn, S. et al. Gastroenterol Clin Biol 2007, 31(3), 255-8; Mallat, A. et al. Expert Opin Ther Targets 2007, 11(3), 403-9; Lotersztajn, S. et al. Br J Pharmacol 2008, 153(2), 286-9).

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

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



(I)

wherein

R^1 iscycloalkylalkoxy, halophenyl, tetrahydrofuranylalkoxy, halophenylalkyl, haloalkyloxy, alkylsulfonyl, tetrahydropyranylalkoxy or halogen;

R^2 isalkyl, pyrrolidinyl, cycloalkyl, haloazetidinyl, haloalkyl, cycloalkylalkoxy, haloalkyloxy, halocycloalkyl, hydroxycycloalkyl or halooxetanyl;

one of R^3 and R^4 is alkyl, cycloalkyl, haloalkyl or hydroxyalkyl and the other one is alkyl, alkyloxyalkyl, (haloazetidinyl)(cycloalkyloxy)pyridinylcarbonyloxyalkyl, haloalkylcycloalkyl, hydroxyalkyl, phenylalkyl, alkoxycarbonylalkyl, carboxyalkyl, alkylaminocarbonylalkyl, (alkyloxadiazolyl)(cycloalkylalkyl)alkyl, (alkyloxadiazolyl)(cycloalkyl)alkyl, pyridazinylalkyl, aminocarbonylalkyl, alkyloxadiazolylalkyl, alkyltetrazolylalkyl, formyl, phenyl, dialkylpyrazolyl, alkylcarbonylpiperidinyl or cycloalkylalkyl;

or R^3 and R^4 together with the nitrogen atom to which they are attached form heterocyclyl or substituted heterocyclyl;

wherein heterocyclyl is 6-oxa-1-aza-spiro[3.3]heptyl, oxazolidinyl, morpholinyl, pyrrolidinyl, piperazinyl, 2-oxa-5-aza-spiro[3.4]octyl, piperidinyl, 6-aza-bicyclo[3.2.1.]octyl, imidazolidinyl, 4-aza-spiro[2.4]heptyl, 2-aza-bicyclo[2.2.1]heptyl, 2-thia-5-aza-bicyclo[2.2.1]heptyl, 2,5-diazabicyclo[2.2.1]heptyl, 2-oxa-5-aza-bicyclo[2.2.1]heptyl, hexahydro-furo[2,3-c]pyrrolyl, 2-thia-6-aza-spiro[3.3]heptyl, 1,8-diaza-spiro[4.5]decyl, 1-oxa-7-aza-spiro[4.4]nonyl, 5-oxa-2-aza-spiro[3.4]octyl, 8-oxa-3-aza-bicyclo[3.2.1]octyl, 3-oxa-8-aza-bicyclo[3.2.1]octyl, thiomorpholinyl, thiazolidinyl, 5-aza-spiro[3.4]octyl, azetidinyl, 5-aza-spiro[2.4]heptyl, 3-aza-bicyclo[3.1.0]hexyl or 5-aza-spiro[2.4]heptyl, 1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrolyl; and

wherein substituted heterocyclyl is heterocyclyl substituted with one to four substituents independently selected from alkyl, oxo, hydroxyl, carboxyl, alkylcarbonylamino, alkyloxyalkyl, hydroxyalkyl, aminocarbonyl, halogen, phenylalkyl,

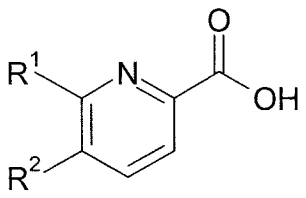
phenyl, alkoxycarbonyl, cycloalkylalkyl, phenylalkoxycarbonyl, cycloalkyl, halohydroxyalkyl and haloalkyl;

provided that R^3 and R^4 together with the nitrogen atom to which they are attached don't form unsubstituted piperidinyl, unsubstituted thiomorpholinyl or hydroxyalkylpyrrolidinyl;

or a pharmaceutically acceptable salt or ester thereof.

In another aspect, there is provided a process for the preparation of a compound as defined herein comprising one of the following steps:

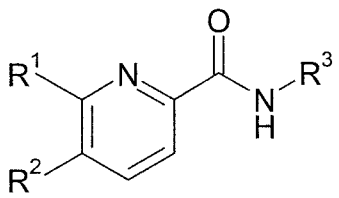
(a) the reaction of a compound of formula (A)



(A)

in the presence of NHR^3R^4, an amide bond forming coupling agent and a base; or

(b) the reaction of a compound of formula (B)



(B)

with a compound of formula R^4-X;

wherein R^1 to R^4 are as defined herein and X is a leaving group.

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.

In another aspect, there is provided the use of a compound as defined herein for the preparation of a medicament for the treatment or prophylaxis of pain, atherosclerosis, age-related macular degeneration, diabetic retinopathy, glaucoma, retinal vein occlusion, retinopathy of prematurity, ocular ischemic syndrome, geographic atrophy, 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, myocardial infarction, systemic sclerosis, thermal injury, burning, hypertrophic scars, keloids, gingivitis pyrexia, liver cirrhosis or tumors, regulation of bone mass, neurodegeneration, amyotrophic lateral sclerosis, stroke, transient ischemic attack or uveitis.

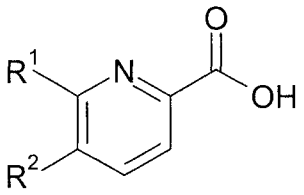
In another aspect, there is provided a compound as defined herein for the treatment or prophylaxis of pain, atherosclerosis, age-related macular degeneration, diabetic retinopathy, glaucoma, retinal vein occlusion, retinopathy of prematurity, ocular ischemic syndrome, geographic atrophy, diabetes mellitus, 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, myocardial infarction, systemic sclerosis, thermal injury, burning, hypertrophic scars, keloids, gingivitis pyrexia, liver cirrhosis or tumors, regulation of bone mass, neurodegeneration, amyotrophic lateral sclerosis, stroke, transient ischemic attack or uveitis.

3-[6-(Cyclopropylmethoxy)-5-(1-fluorocyclobutyl)pyridine-2-carbonyl]-1,1-dioxo-1,3-thiazolidine-4-carboxamide; and

5-[6-(Cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)pyridine-2-carbonyl]-5-azaspiro[2.4]heptane-6-carboxamide.

13. A process for the preparation of a compound according to any one of claims 1 to 12 comprising one of the following steps:

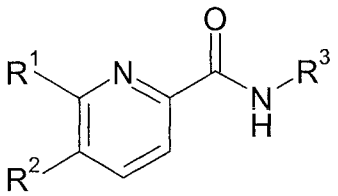
(a) the reaction of a compound of formula (A)



(A)

in the presence of NHR^3R^4, an amide bond forming coupling agent and a base; or

(b) the reaction of a compound of formula (B)



(B)

with a compound of formula R^4-X;

wherein R^1 to R^4 are as defined in any one of claims 1 to 10 and X is a leaving group.

14. A compound according to any one of claims 1 to 12, when manufactured according to a process of claim 13.

15. A compound according to any one of claims 1 to 12 for use as therapeutically active substance.

16. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 12 and a therapeutically inert carrier.

17. The use of a compound according to any one of claims 1 to 12 for the preparation of a medicament for the treatment or prophylaxis of pain, atherosclerosis, age-related macular degeneration, diabetic retinopathy, glaucoma, retinal vein occlusion, retinopathy of prematurity, ocular ischemic syndrome, geographic atrophy, 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, myocardial infarction, systemic sclerosis, thermal injury, burning, hypertrophic scars, keloids, gingivitis pyrexia, liver cirrhosis or tumors, regulation of bone mass, neurodegeneration, amyotrophic lateral sclerosis, stroke, transient ischemic attack or uveitis.

18. A compound according to any one of claims 1 to 12 for the treatment or prophylaxis of pain, atherosclerosis, age-related macular degeneration, diabetic retinopathy, glaucoma, retinal vein occlusion, retinopathy of prematurity, ocular ischemic syndrome, geographic atrophy, 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, myocardial infarction, systemic sclerosis, thermal injury, burning, hypertrophic scars, keloids, gingivitis pyrexia, liver cirrhosis or tumors, regulation of bone mass, neurodegeneration, amyotrophic lateral sclerosis, stroke, transient ischemic attack or uveitis.

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