

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.

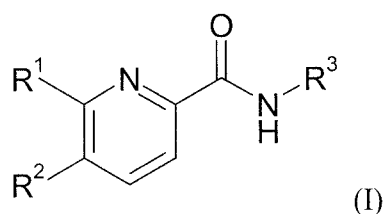
Recent data indicates that endocannabinoids and their receptors, in particular CB2
5 might be involved in pre-conditioning and contribute to prevent reperfusion injury by downregulation of the inflammatory response (Pacher, P. et al. *Br J Pharmacol* 2008, 153(2), 252-62). Specifically, recent studies 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),
10 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
15 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*
20 (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 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,
25 153(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)



wherein

R^1 is halogen, cycloalkylalkoxy, haloalkoxy, alkylsulfonyl, alkylsulfinyl,
5 halophenylalkyl, alkylsulfanyl, oxanylalkoxy, halophenyl or oxolanylalkoxy;

R^2 is halogen, cycloalkyl, haloalkyl, haloalkoxy, haloazetidiny, cycloalkyloxy,
halocycloalkyl, hydroxycycloalkyl, hydroxyazetidiny, hydroxyoxetanyl or halooxetanyl;

R^3 is (alkyl)(oxo)pyrrolidiny or $-C(R^4R^5)-C(R^6R^7)-C(O)-R^8$;

R^4 and R^5 are independently selected from hydrogen, alkyl, phenyl, phenylalkyl,
10 cycloalkyl, tetrahydropyranyl, haloalkyl, halophenyl and oxolanyl;

or R^4 and R^5 together with the carbon atom to which they are attached form
cycloalkyl, oxetanyl, thiethanyl, 1,1-dioxo-1 λ 6-thiethanyl, azetidiny, haloazetidiny, 2-
oxa-spiro[3.3]heptyl, tetrahydrofuranyl, pyrrolidiny, oxopyrrolidiny, 1,1-dioxo-1 λ 6-
isothiazolidiny, 1,1-dioxo-tetrahydro-1 λ 6-thiophenyl, tetrahydrothiophenyl,
15 tetrahydropyranyl, piperidiny, oxopiperidiny, tetrahydrothiopyranyl, 2-oxo-
[1,3]oxazinanyl, 1,1-dioxo-1 λ 6-[1,2]thiazinanyl, 2-oxo-hexahydro-pyrimidiny, 1,1-dioxo-
hexahydro-1 λ 6-thiopyranyl, 2-oxo-[1,3]dioxanyl, 1,1-dioxothianyl,
alkylcarbonylpiperidiny, alkylcarbonylazetidiny, phenylalkyloxycarbonylazetidiny,
oxolanyl, or phenylalkyloxycarbonylpyrrolidiny;

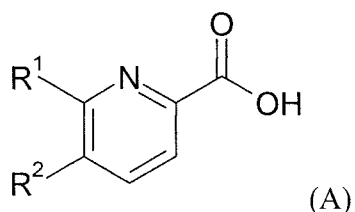
20 R^6 and R^7 are independently selected from hydrogen and alkyl;

or one of R^4 and R^5 and one of R^6 and R^7 , together with the carbon atoms to which
they are attached, form cycloalkyl, and the other ones are both hydrogen at the same time;
and

R^8 is $-NH_2$, alkoxy, alkylamino or hydroxyl;

25 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 the reaction of a compound of formula (A)



in the presence of R³-NH₂, an amide coupling agent and a base;

5 wherein R¹ to R³ are as defined herein.

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.

10 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.

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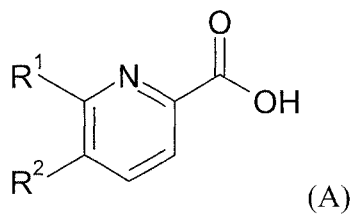
In another aspect, there is provided a compound as defined herein for the treatment or prophylaxis of pain, atherosclerosis, age-related macular degeneration, diabetic retinopathy, glaucoma, retinal vein occlusion, retinopathy of prematurity, ocular ischemic syndrome, geographic atrophy, diabetes mellitus, 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

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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
5 uveitis.

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 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-
10 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 isomeric octyls, particularly methyl, ethyl, propyl, butyl and pentyl. Particular examples of alkyl are methyl, ethyl, isopropyl, butyl, isobutyl, tert.-butyl and pentyl.

15. A process for the preparation of a compound according to any one of claims 1 to 14, comprising the reaction of a compound of formula (A)



in the presence of R³-NH₂, an amide coupling agent and a base;

- 5 wherein R¹ to R³ are as defined in any one of claims 1 to 12.
16. A compound according to any one of claims 1 to 14, when manufactured according to a process of claim 15.
17. A compound according to any one of claims 1 to 14 for use as therapeutically active substance.
- 10 18. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 14 and a therapeutically inert carrier.
- 15 19. The use of a compound according to any one of claims 1 to 14 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.

- 5 20. A compound according to any one of claims 1 to 14 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,
10 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,
15 stroke, transient ischemic attack or uveitis.
