

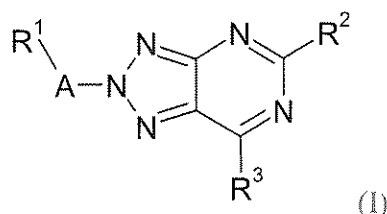
Recent data indicates that endocannabinoids and their receptors, in particular CB2 might be involved in pre-conditioning and contribute to prevent reperfusion injury by downregulation of the inflammatory response (Pacher, P. et al. Br J Pharmacol 2008, 153(2), 252-62). Specifically, recent studies using 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 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 ~~invention-disclosure~~ bind to and modulate the CB2 receptor and have lower CB1 receptor activity.

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



wherein

A is alkylene, hydroxyalkylene, $-\text{CH}_2\text{C}(\text{O})-$, $-\text{C}(\text{O})-$, $-\text{SO}_2-$ or absent;

R^1 is hydrogen, alkyl, haloalkyl, hydroxyl, alkoxy, haloalkoxy, phenyl, halophenyl, alkoxyphenyl, haloalkylphenyl, haloalkoxyphenyl, cyanophenyl, hydroxyalkoxyphenyl, alkylsulfonylphenyl, alkylsulfonylaminophenyl,

(halo)(haloalkyl)phenyl, (halo)(alkoxy)phenyl, cyano, cycloalkyl, cycloalkylalkoxy, amino, heterocyclyl, alkylheterocyclyl, hydroxyheterocyclyl, alkylheterocyclyl, heteroaryl, haloheteroaryl, alkylheteroaryl, (alkyl)(alkylsulfonyl)heteroaryl, (halo)(alkylamino)heteroaryl, haloalkylheteroaryl, cycloalkylheteroaryl or nitrobenzo[1,2,5]oxadiazolylaminoheteroaryl, wherein heterocyclyl is a three to eight membered carbocyclic ring comprising at least one nitrogen or oxygen atom, and wherein heteroaryl is pyridinyl, pyrazolyl, oxadiazolyl, furazanyl, tetrazolyl, triazolyl or oxypyridinyl;

R^2 is alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkoxyalkyl, cycloalkylalkoxy, haloalkoxy, alkoxy or alkylamino;

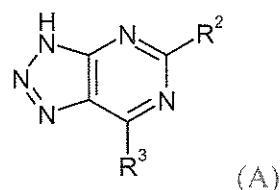
R^3 is halogen or $-NR^4R^5$;

one of R^4 and R^5 is hydrogen or alkyl and the other one is alkyl or cycloalkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached form heterocyclyl or substituted heterocyclyl, wherein heterocyclyl is morpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, 2-oxa-6-azaspiro[3.3]heptyl, azetidiny, thiazolidinyl, thiomorpholinyl, dioxothiomorpholinyl, oxazepanyl, 2-oxa-6-azaspiro[3.4]octyl, 6-oxa-1-azaspiro[3.3]heptyl, 2-oxa-5-aza-spiro[3.4]octyl, isoxazolidinyl, aziridinyl or dioxoisothiazolidinyl and wherein substituted heterocyclyl is heterocyclyl substituted with one to four substituents independently selected from alkyl, halogen, hydroxyl, alkoxy, hydroxyalkyl, carboxyl, alkoxyalkyl, cyano and alkylcarbonylamino;

or a pharmaceutically acceptable salt or ester thereof.

In a second 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 R^1-A-X and a base, or in the presence of R^1-A-OH under Mitsunobu conditions, wherein A and R^1 to R^3 are defined herein and wherein X is halogen or SO_2 .

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

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

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

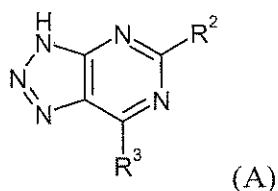
In a sixth aspect, there is provided a compound as defined herein for the preparation of a medicament for the treatment or prophylaxis of pain, atherosclerosis, age-related macular degeneration, diabetic retinopathy, glaucoma, diabetes mellitus, inflammation, inflammatory bowel disease, ischemia-reperfusion 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, stroke, transient ischemic attack or uveitis.

In a seventh aspect, there is provided a compound as defined herein for the treatment or prophylaxis of 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, myocardial infarction, systemic sclerosis, thermal injury, burning, hypertrophic scars, keloids, gingivitis pyrexia, liver cirrhosis or tumors, regulation of bone mass, neurodegeneration, stroke, transient ischemic attack or 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-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 more particularly methyl, ethyl, propyl, isopropyl, isobutyl, tert.-butyl and isopentyl. Particular examples of alkyl are methyl, ethyl and tert.-butyl.

In the present description the term “alkylene”, alone or in combination, signifies a straight-chain or branched-chain alkylene group with 1 to 8 carbon atoms, particularly a

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 R^1 -A-X and a base, or in the presence of R^1 -A-OH under Mitsunobu conditions, wherein A and R^1 to R^3 are defined according to any one of claims 1 to 12 and wherein X is halogen or SO_2 .

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.
18. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 14 and a therapeutically inert carrier.

~~19. The use of 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, 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, stroke, transient ischemic attack or uveitis.~~

2019. 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, 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, stroke, transient ischemic attack or uveitis.

2120. 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, 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, stroke, transient ischemic attack or uveitis.

~~22. A method for the treatment or prophylaxis of 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, myocardial infarction, systemic sclerosis, thermal injury, burning, hypertrophic scars, keloids, gingivitis pyrexia, liver cirrhosis or tumors, regulation of bone mass, neurodegeneration, stroke, transient ischemic attack or uveitis, which method comprises administering an effective amount of a compound as defined in any one of claims 1 to 14 to a patient in need thereof.~~
