

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.

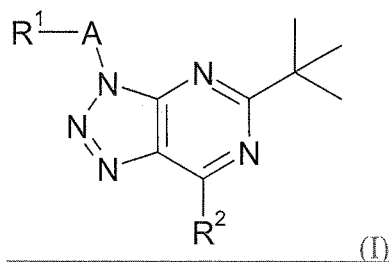
Recent data indicates that endocannabinoids and their receptors, in particular CB2 might be involved in pre-conditioning and contribute to prevent reperfusion injury by downregulation of the inflammatory response (Pacher, P. et al. Br J Pharmacol 2008, 153(2), 252-62). Specifically, recent studies using 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 alkyl, hydroxyalkyl, -CH₂C(O)-, -C(O)-, -SO₂- or absent;

5 R¹ is hydrogen, alkyl, haloalkyl, hydroxyl, alkoxy, haloalkoxy, phenyl, halophenyl, alkoxyphenyl, haloalkylphenyl, haloalkoxyphenyl, (halo)(haloalkyl)phenyl, cyanophenyl, hydroxyalkoxyphenyl, alkylsulfonylphenyl, alkylsulfonylaminophenyl, cyano, cycloalkyl, cycloalkylalkoxy, amino, (alkylsulfonyl)(alkyl)[1,2,4]triazolyl, (halo)(dialkylamino)pyridinyl,
 10 (alkyl)(oxy)pyridinyl, nitro-benzo[1,2,5]oxadiazolylaminopyridinyl, heterocyclyl, alkylheterocyclyl, hydroxyheterocyclyl, alkylheterocyclyl, heteroaryl, haloheteroaryl, alkylheteroaryl, cycloalkylheteroaryl or haloalkylheteroaryl, wherein heterocyclyl is a three to eight membered carbocyclic ring comprising at least one nitrogen or oxygen atom, and wherein
 15 heteroaryl is pyridinyl, pyrazolyl, oxadiazolyl, furazanyl, tetrazolyl or triazolyl;

R² is halogen or -NR³R⁴ or -OR⁵;

one of R³ and R⁴ is hydrogen or alkyl and the other one is alkyl or cycloalkyl;

or R³ and R⁴ together with the nitrogen atom to which they are attached form
 20 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, dioxoisothiazolidinyl or oxopyrrolidinyl and wherein
 25 substituted heterocyclyl is heterocyclyl substituted with one to four substituents independently selected from alkyl, halogen, hydroxyl, alkoxy, hydroxyalkyl, carboxyl, alkoxyalkyl, cyano, alkylamino, dialkylamino,

4b

alkylcarbonylamino, alkylcarbonyl(alkylamino), phenyl, alkoxy carbonyl, aminoalkyl, alkylpyrazolyl or alkylisoxazolyl;

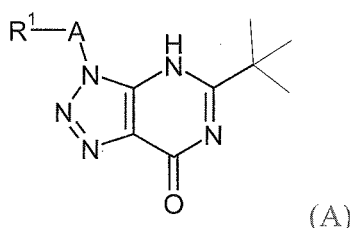
R⁵ is alkyl, cycloalkyl, cycloalkylalkyl, haloalkyl or oxetanyl;

or a pharmaceutically acceptable salt or ester thereof;

- 5 with the proviso that 3-[(2-chlorophenyl)methyl]-5-(1,1-dimethylethyl)-7-(4-morpholinyl)-3H-1,2,3-triazolo[4,5-d]pyrimidine and N-cyclopropyl-5-(1,1-dimethylethyl)-3-(phenylmethyl)-3H-1,2,3-triazolo[4,5-d]pyrimidin-7-amine are excluded.

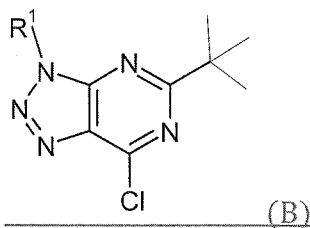
In a second aspect, there is provided a process for the preparation of a compound as defined above comprising:

- 10 (a) the reaction of a compound of formula (A), a tautomer thereof or a mixture of tautomers thereof



in the presence of a halogenation reagent and optionally with a base; or

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



15 in the presence of NHR³R⁴ and optionally with a base;

wherein A, R¹, R³ and R⁴ are as defined above.

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

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

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

In a sixth aspect, there is provided use of a compound as defined above 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 above 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

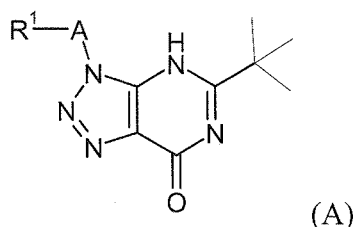
In the present description the term “alkyl”, alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, particularly a straight or branched-chain alkyl group with 1 to 6 carbon atoms and more particularly a straight or branched-chain alkyl group with 1 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

(S)-1-(5-tert-butyl-3-(2-(methylsulfonyl)benzyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)-3-methylpyrrolidin-3-ol; and

(R)-1-(5-tert-butyl-3-(2-(methylsulfonyl)benzyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl)-3-methylpyrrolidin-3-ol.

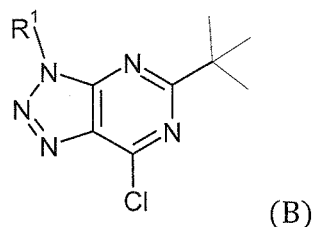
- 5 13. A process for the preparation of a compound according to any one of claims 1 to 12 comprising:

(a) the reaction of a compound of formula (A), a tautomer thereof or a mixture of tautomers thereof



- 10 in the presence of a halogenation reagent and optionally with a base; or

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



in the presence of NHR^3R^4 and optionally with a base;

wherein A, R^1 , R^3 and R^4 are defined according to any one of claims 1 to 10.

- 15 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.
- 20 ~~17. The use of 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, 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.~~

1817. 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, 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.

1818. 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, 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.

~~20. 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 12 to a patient in need thereof.~~