

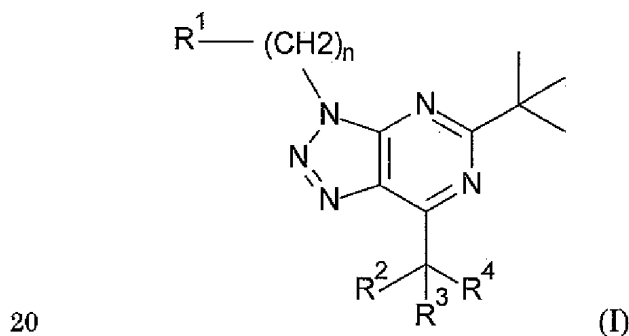
1387-96), the liver (Batkai, S. et al. *Faseb J* 2007, 21(8), 1788-800) and the kidney (Feizi, A. et al. *Exp Toxicol Pathol* 2008, 60(4-5), 405-10).

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
5 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
10 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.
15 *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)



wherein

n is 0, 1 or 2;

R¹ is phenyl, halophenyl, alkylsulfonylphenyl, alkyltetrazolyl, alkyloxadiazolyl, halohydroxyalkyl, oxolanyl, oxetanyl, haloalkyl, halopyridinyl or alkyloxetanyl;

25 R² is hydrogen, hydroxyl, halogen or haloalkyl; and

R³ and R⁴ are independently selected from alkyl; or

R^3 and R^4 , together with the carbon atom to which they are attached, form cycloalkyl, thiethanyl, haloalkylcycloalkyl or oxothietanyl;

or

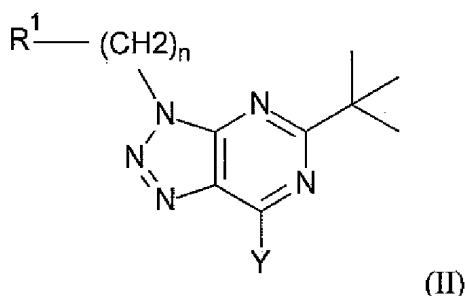
R^2 is absent; and

- 5 R^3 and R^4 , together with the carbon atom to which they are attached, form alkylphenyl, halophenyl, alkoxyphenyl, halopyridinyl, alkylpyridinyl, alkylpyrazolyl, phenyl, alkyloxazolyl, pyrazolyl, imidazolyl, benzyltriazolyl or cycloalkenyl;

or a pharmaceutically acceptable salt or ester thereof.

- 10 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 (II)



- 15 in the presence of $B(OH)_2CR^2R^3R^4$ or $B(OR)_2CR^2R^3R^4$ in the presence of a base and a palladium catalyst, wherein n and R^1 to R^4 are as defined herein, Y is chloride or bromide and $B(OR)_2$ is 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl; or

(b) the reaction of a compound of formula (II) as defined above in the presence of n-butyllithium followed by the addition of $R^3C(O)R^4$, wherein R^3 and R^4 are as defined herein.

- 20 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 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, 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 another aspect, there is provided a compound as defined herein for use in 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. Particular examples of alkyl are methyl, ethyl, isopropyl, butyl, isobutyl, tert.-butyl and pentyl. Methyl, ethyl, tert.-butyl and isobutyl are particular examples of "alkyl" in the compound of formula (I).

The term “cycloalkyl”, alone or in combination, signifies a cycloalkyl ring with 3 to 8 carbon atoms and particularly a cycloalkyl ring with 3 to 6 carbon atoms. Examples of cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, cycloheptyl and cyclooctyl. Particular examples of “cycloalkyl” are cyclopropyl, cyclobutyl, cyclopentyl,
5 cyclohexyl and cycloheptyl.

The term “cycloalkenyl”, alone or in combination, refers to a cycloalkyl group as defined above wherein one or more carbon-carbon single bond is replaced by a carbon-

(b) the reaction of a compound of formula (II) as defined above in the presence of n-butyllithium followed by the addition of $R^3C(O)R^4$, wherein R^3 and R^4 are as defined in any one of claims 1 to 6.

10. A compound according to any one of claims 1 to 8, when manufactured according to
5 a process of claim 9.
11. A compound according to any one of claims 1 to 8 for use as therapeutically active substance.
12. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 8 and a therapeutically inert carrier.
- 10 13. The use of a compound according to any one of claims 1 to 8 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
15 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 14. A compound according to any one of claims 1 to 8 for use in 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,
25 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.