

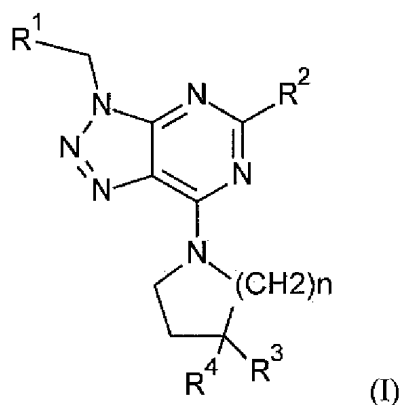
1387-96), the liver (Batkai, S. et al. *Faseb J* 2007, 21(8), 1788-800) and the kidney (Feizi, A. et al. *Exp Toxicol Pathol* 2008, 60(4-5), 405-10).

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 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

R¹ is haloalkyl, halophenyl, alkoxyphenyl, alkyl-1,2,5-oxadiazolyl, haloalkylphenyl, alkylsulfonylphenyl, halopyridinyl or alkyltetrazolyl;

R² is cycloalkyl, isopropyl, alkenyl, piperidinyl, alkylamino, azetidiny, pyrrolidinyl, cycloalkylamino, alkyloxetanylamino, morpholinyl, (cycloalkyl)(alkyl)amino, haloalkyloxy, alkoxy, cycloalkylalkoxy, cycloalkyloxy, oxetanyloxy,

alkyloxetanylalkyloxy, alkynyloxy, alkoxyalkoxy, hydroxyalkyloxy, alkylsulfanyl, haloalkylsulfanyl, alkylsulfonyl, hydroxyalkylsulfanyl, hydroxyalkylsulfonyl or alkoxyalkylsulfonyl;

R^3 and R^4 are independently selected from hydrogen, halogen, hydroxyl, alkylcarbonylamino and alkyl, provided that R^3 and R^4 are not both hydrogen at the same time; and

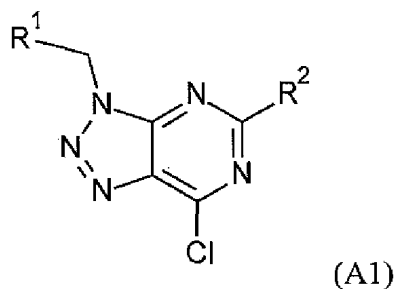
n is 1 or 2;

or a pharmaceutically acceptable salt or ester thereof;

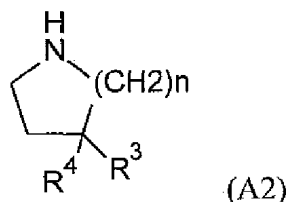
provided that (S)-1-[3-(4-Methoxy-benzyl)-5-(2,2,2-trifluoro-ethoxy)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-7-yl]-pyrrolidin-3-ol is excluded.

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 (A1)

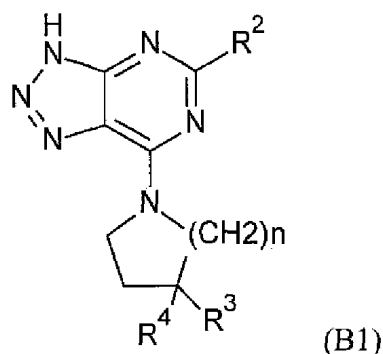


in the presence of a compound of formula (A2)



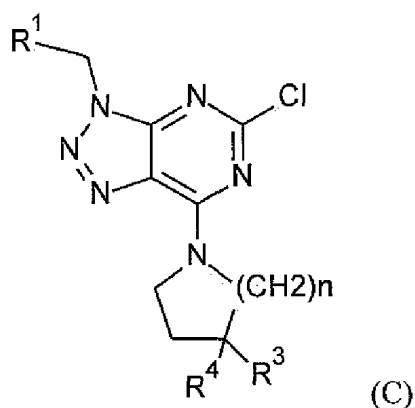
wherein R^2 is isopropyl, cycloalkyl or alkenyl and R^1 , R^3 , R^4 and n are as defined herein;

(b) the reaction of a compound of formula (B1)



in the presence of R^1CH_2X wherein X is a halogen, a hydroxyl or a sulfonate group, wherein R^2 is isopropyl, cycloalkyl or alkenyl and wherein R^3 to R^4 and n are as defined
 5 herein;

(c) the reaction of a compound of formula (C1)



in the presence of R^2-H wherein R^2 is piperidinyl, alkylamino, azetidiny, pyrrolidinyl, cycloalkylamino, alkyloxetanylamino, morpholinyl, (cycloalkyl)(alkyl)amino, haloalkyloxy, alkoxy, cycloalkylalkoxy, cycloalkyloxy, oxetanyloxy, alkyloxetanylalkoxy, alkynyloxy, alkoxyalkoxy, hydroxyalkyloxy, alkylsulfanyl, haloalkylsulfanyl, alkylsulfonyl, hydroxyalkylsulfanyl, hydroxyalkylsulfonyl or alkoxyalkylsulfonyl and wherein R^1 , R^3 , R^4 and n are as defined herein.
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In another aspect, there is provided a compound as defined herein for use as
 15 therapeutically active substance.

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

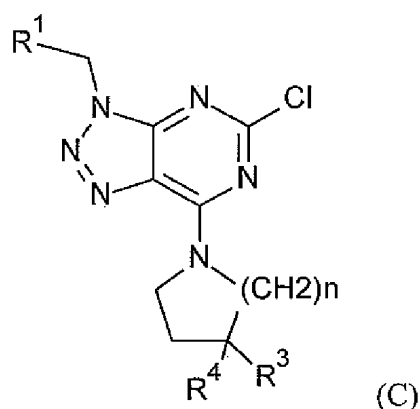
In another aspect, there is provided use of a compound as defined herein for the preparation of a medicament for the treatment or prophylaxis of pain, atherosclerosis, age-related macular degeneration, diabetic retinopathy, glaucoma, diabetes mellitus, inflammation, inflammatory bowel disease, ischemia-reperfusion 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 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. Particular examples of alkyl are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert.-butyl, and neopentyl.

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 and cyclobutyl.

The term “alkenyl”, alone or in combination, signifies a straight-chain or branched hydrocarbon residue comprising an olefinic bond and up to 8, preferably up to 6, particularly preferred up to 4 carbon atoms. Examples of alkenyl groups are ethenyl, 1-propenyl, 2-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl and isobutenyl. A
5 preferred example is 2-propenyl.



in the presence of R²-H wherein R² is piperidinyl, alkylamino, azetidiny, pyrrolidinyl, cycloalkylamino, alkyloxetanyl amino, morpholinyl, (cycloalkyl)(alkyl)amino, haloalkyloxy, alkoxy, cycloalkylalkoxy, cycloalkyloxy, oxetanyloxy, alkyloxetanylalkyloxy, alkynyloxy, alkoxyalkoxy, hydroxyalkyloxy, alkylsulfanyl, haloalkylsulfanyl, alkylsulfonyl, hydroxyalkylsulfanyl, hydroxyalkylsulfonyl or alkoxyalkylsulfonyl and wherein R¹, R³, R⁴ and n are as defined in any one of claims 1 to 8.

12. A compound according to any one of claims 1 to 10 for use as therapeutically active substance.
13. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 10 and a therapeutically inert carrier.
14. The use of a compound according to any one of claims 1 to 10 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.
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15. A compound according to any one of claims 1 to 10 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.
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