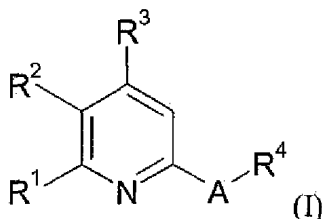


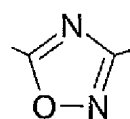
The compounds of the disclosure bind to and modulate the CB2 receptor and have lower CB1 receptor activity.

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

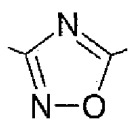


5 wherein

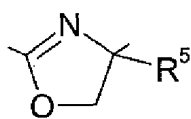
A is A1, A2, A3, A4, A5, A6, A7 or A8



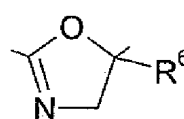
A1



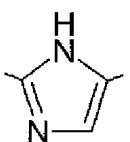
A2



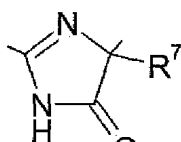
A3



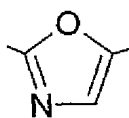
A4



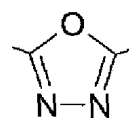
A5



A6



A7



A8

;

R^1 is hydrogen or halogen;

R^2 is halogen, cycloalkyl, haloazetidiny, 6-oxa-1-aza-spiro[3.3]heptyl or
10 alkylsulfonyl;

R^3 is-OR⁸, pyrrolidiny, halopyrrolidiny, hydroxypyrrolidiny, morpholiny,
cycloalkylsulfonyl, alkoxyazetidiny, 2-oxa-6-aza-spiro[3.3]heptyl or 2-oxa-7-
azaspiro[3.4]heptyl;

R^4 is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cycloalkyl,
15 hydroxycycloalkyl, alkylcycloalkyl, aminocarbonylcycloalkyl, phenyl, phenylalkyl,
alkyloxetanyl, azetidiny or aminooxetanyl;

R^5 is hydrogen, alkyl or alkyloxadiazolyl;

or R^4 and R^5 , together with the carbon atom to which they are attached, form
cycloalkyl;

R⁶ is alkyl;

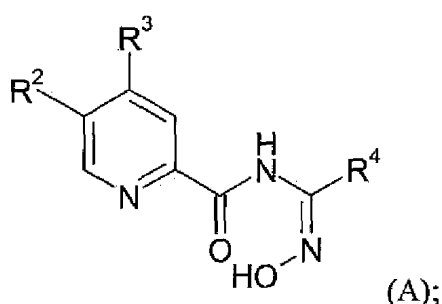
R⁷ is alkyl; and

R⁸ is haloalkyl, alkoxyalkyl, cycloalkylalkyl, haloalkyl, halophenyl, oxetanyl, oxetanylalkyl, alkyloxetanylalkyl, tetrahydrofuranyl, tetrahydrofuranylalkyl, alkylsulfonylphenyl, alkylpyrrolidinyl, alkylpyrrolidinylalkyl, azetidiny, morpholinylalkyl, tetrahydropyranyl, pyrrolidinylalkyl, piperidinyl, piperidinylalkyl, alkylpiperidinylalkyl, alkylpiperidinyl, dialkylaminoalkyl, pyridinylalkyl, halooxetanylalkyl, dialkyloxazolylalkyl, alkyloxazolylalkyl, halopyridinylalkyl or morpholinyl;

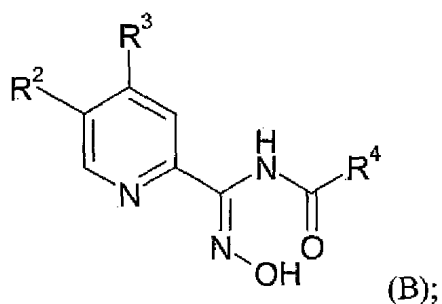
or a pharmaceutically acceptable salt or ester thereof.

10 In another aspect, there is provided a process for the manufacture of a compound of formula (I) as defined herein comprising one of the following steps:

(a) the heating of a compound of formula (A)

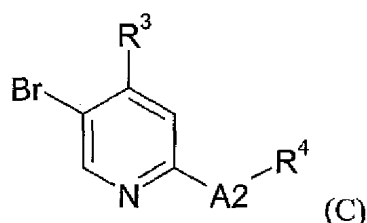


(b) the heating of a compound of formula (B)



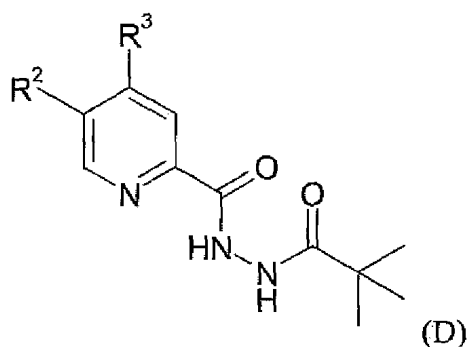
15

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



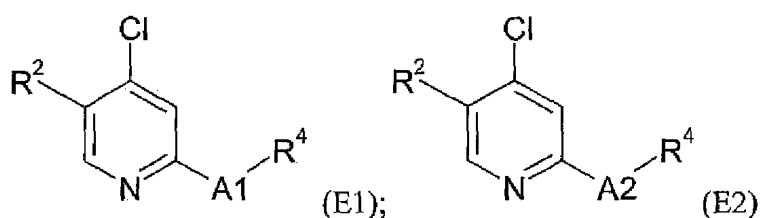
in the presence of haloazetidine or 6-oxa-1-aza-spiro[3.3]heptane, a base and a palladium catalyst;

(d) the reaction of a compound of formula (D)



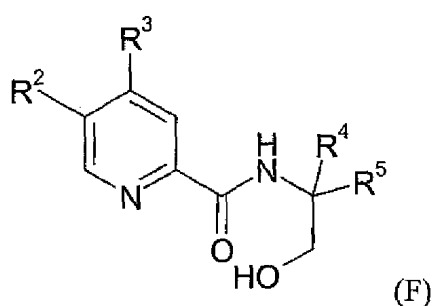
5 in the presence of trifluoromethanesulfonic anhydride and triphenylphosphine oxide;

(e) the reaction of a compound of formula (E1) or (E2)



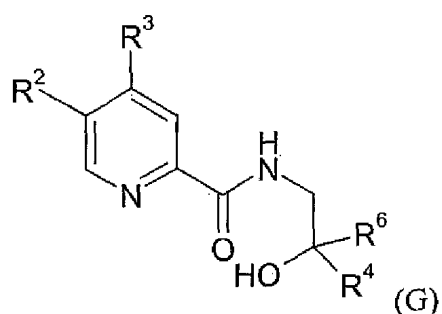
in the presence of HOR, haloazetidine, 6-oxa-1-aza-spiro[3.3]heptane or HSO_2R and a base;

10 (f) the heating of a compound of formula (F)



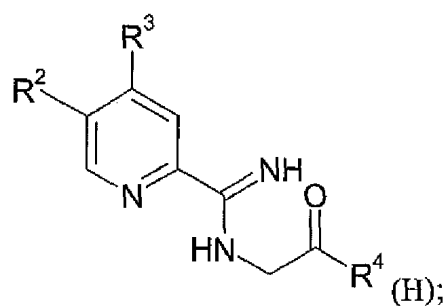
in the presence of Burgess reagent;

(g) the heating of a compound of formula (G)



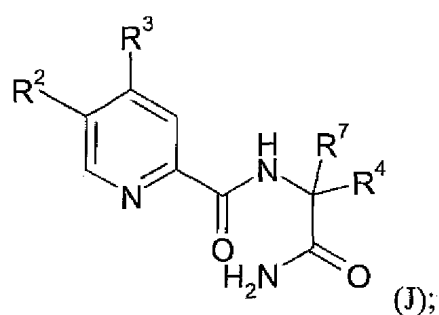
in the presence of methanesulfonic acid;

(h) the heating of a compound of formula (H)

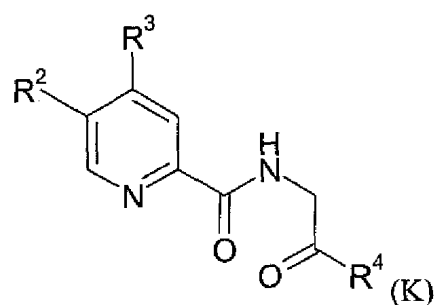


5

(j) the heating of a compound of formula (J)



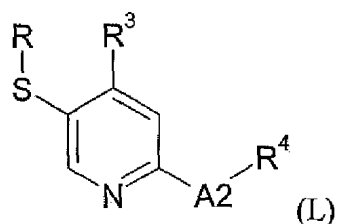
(k) the reaction of a compound of formula (K)



10

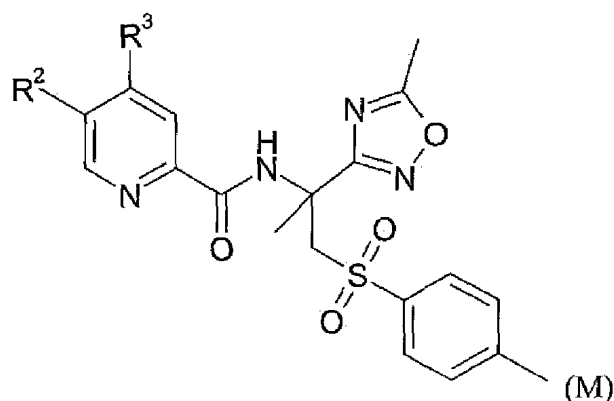
in the presence of hexachloroethane, a base and a phosphine;

(l) the reaction of a compound of formula (L)



in the presence of an oxidizing agent;

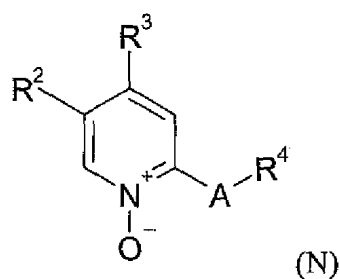
(m) the heating of a compound of formula (M)



5

in the presence of a base;

(n) the reaction of a compound of formula (N)



in the presence of a chlorinating agent and DMF; or

10 (o) the reaction of a compound of formula (C) as defined above in the presence of HSR and a base, and then an oxidation agent;

wherein A, A₁ to A₈ and R¹ to R⁴ are as defined herein and wherein R is alkyl.

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, 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, amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's disease, Parkinson's disease, 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, 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, amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's disease, Parkinson's disease, 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, isopropyl, isobutyl and tert.-butyl, in particular methyl, ethyl and tert.-butyl.

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, cyclopentyl and
5 cyclohexyl, in particular cyclopropyl and cyclohexyl.

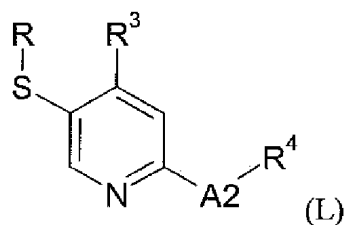
The term "alkoxy", alone or in combination, signifies a group of the formula alkyl-O- in which the term "alkyl" has the previously given significance, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert-butoxy. Particular "alkoxy" are methoxy, ethoxy and butoxy, and in particular methoxy and butoxy.

10 The term "oxy", alone or in combination, signifies the -O- group.

The terms "halogen" or "halo", alone or in combination, signifies fluorine, chlorine, bromine or iodine and particularly fluorine, chlorine or bromine, more particularly fluorine and chlorine. The term "halo", in combination with another group, denotes the substitution of said group with at least one halogen, particularly substituted with one to five halogens,
15 particularly one to four halogens, i.e. one, two, three or four halogens. A particular "halogen" is fluorine.

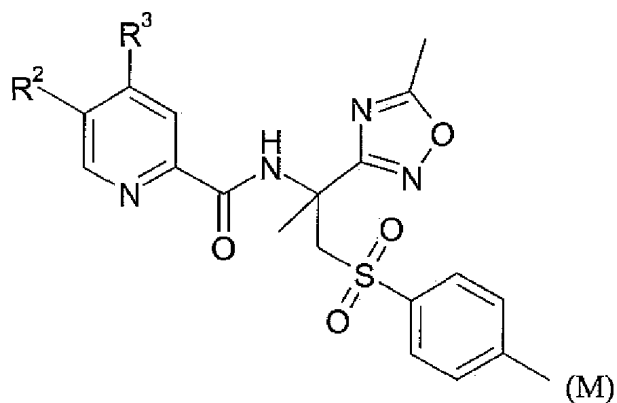
The term "haloalkyl", alone or in combination, denotes an alkyl group substituted with at least one halogen, particularly substituted with one to five halogens, particularly one to three halogens. Particular "haloalkyl" are trifluoroethyl, trifluoromethyl,
20 trifluoropropyl and difluoroethyl, more particularly trifluoroethyl and difluoroethyl.

A particular "halophenyl" is fluorophenyl. A particular haloazetidiny is difluoroazetidiny, in particular 3,3-difluoro-azetidin-1-yl. A particular halopyrrolidiny is



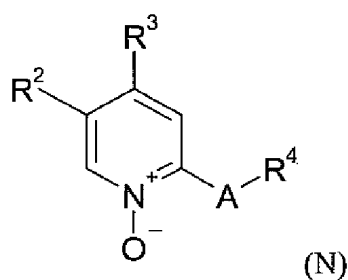
in the presence of an oxidizing agent;

(m) the heating of a compound of formula (M)



5 in the presence of a base;

(n) the reaction of a compound of formula (N)



in the presence of a chlorinating agent and DMF; or

10 (o) the reaction of a compound of formula (C) as defined above in the presence of HSR and a base, and then an oxidation agent;

wherein A, A1 to A8 and R¹ to R⁴ are as defined in any one of claims 1 to 14 and wherein R is alkyl.

18. A compound according to any one of claims 1 to 16 for use as therapeutically active substance.

19. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 16 and a therapeutically inert carrier.
20. The use of a compound according to any one of claims 1 to 16 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, amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's disease, Parkinson's disease, stroke, transient ischemic attack or uveitis.
21. A compound according to any one of claims 1 to 16 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, amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's disease, Parkinson's disease, stroke, transient ischemic attack or uveitis.
