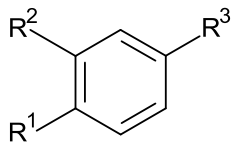
2009, 23(7), 2120-30), the brain (Zhang, M. et al. J Cereb Blood Flow Metab 2007, 27(7), 1387-96), the liver (Batkai, S. et al. Faseb J 2007, 21(8), 1788-800) and the kidney (Feizi, A. et al. Exp Toxicol Pathol 2008, 60(4-5), 405-10).

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 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)



(I)

wherein

R^1 is cyclopropyl, alkyl or haloazetidinyl;

R^2 iscyclopropylmethoxy, alkoxy, haloalkoxy, halopyridinyl, alkylpyrazolyl or halopyrrolidinyl;

provided that at least one of R^1 and R^2 is cyclopropyl or cyclopropylmethoxy;

R^3 is -C(O)-NH-C(R^4R^5)-R^6, -C(O)-R^7 or R^8;

R^4 and R^5 are independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkylsulfonylalkyl and alkyloxetanyl;

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

R^6 isaminocarbonyl, 5-methyl-1,2,4-oxadiazol-3-yl, hydroxyalkyl, thiazolyl, alkoxycarbonyl, carboxy, difluoroazetidinylcarbonyl, 5-amino-1,2,4-oxadiazol-3-yl, alkylaminocarbonyl or aminocarbonylalkyl;

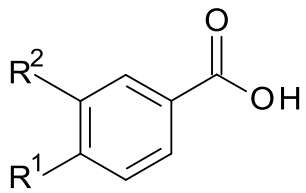
R^7 is (aminocarbonyl)(difluoro)pyrrolidinyl or (aminocarbonyl)azaspiro[2.4]heptyl; and

R^8 is 3-alkyl-1,2,4-oxadiazol-5-yl or 5-alkyl-1,2,4-oxadiazol-3-yl;

or a pharmaceutically acceptable salt or ester thereof.

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 (A)

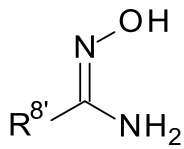


(A)

in the presence of H_2N-C(R^4R^5)-R^6, a coupling agent and a base, wherein R^2 is cyclopropylmethoxy, alkoxy or haloalkoxy;

(b) the reaction of a compound of formula (A) as defined above in the presence of H-R^7, a coupling agent and a base, wherein R^2 is cyclopropylmethoxy, alkoxy or haloalkoxy;

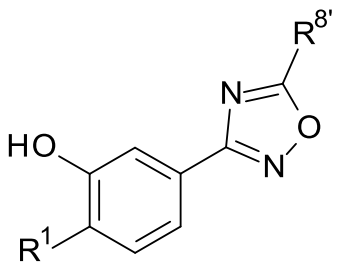
(c) the reaction of a compound of formula (A) as defined above in the presence of a compound of formula (B)



(B)

and carbonydiimidazole, wherein $R^{8'}$ is methyl or tert.-butyl; or

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



(C)

in the presence of $R^{2'}$-X, wherein $R^{2'}$ is cyclopropylmethyl, alkyl or haloalkyl, $R^{8'}$ is methyl or tert.-butyl and X is a leaving group.

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 in 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.

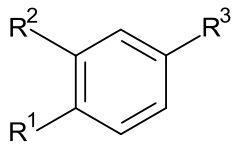
In the present description the term “alkyl”, alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, particularly a straight or branched-chain alkyl group with 1 to 6 carbon atoms and more particularly a straight or branched-chain alkyl group with 1 to 4 carbon atoms. Examples of straight-chain and branched-chain C_1-C_8 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, propyl, isopropyl, butyl 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. A particular example of “cycloalkyl” is cyclopropyl.

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,

Claims

1. A compound of formula (I)



(I)

wherein

R^1 is cyclopropyl, alkyl or haloazetidinyl;

R^2 is cyclopropylmethoxy, alkoxy, haloalkoxy, halopyridinyl, alkylpyrazolyl or halopyrrolidinyl;

provided that at least one of R^1 and R^2 is cyclopropyl or cyclopropylmethoxy;

R^3 is -C(O)-NH-C(R^4R^5)-R^6, -C(O)-R^7 or R^8;

R^4 and R^5 are independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkylsulfonylalkyl and alkyloxetanyl;

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

R^6 is aminocarbonyl, 5-methyl-1,2,4-oxadiazol-3-yl, hydroxyalkyl, thiazolyl, alkoxycarbonyl, carboxy, difluoroazetidinylcarbonyl, 5-amino-1,2,4-oxadiazol-3-yl, alkylaminocarbonyl or aminocarbonylalkyl;

R^7 is (aminocarbonyl)(difluoro)pyrrolidinyl or (aminocarbonyl)azaspiro[2.4]heptyl; and

R^8 is 3-alkyl-1,2,4-oxadiazol-5-yl or 5-alkyl-1,2,4-oxadiazol-3-yl;

or a pharmaceutically acceptable salt or ester thereof.

2. A compound according to claim 1, wherein R^1 is cyclopropyl.

3. A compound according to claim 1 or 2, wherein R^2 is cyclopropylmethoxy, alkoxy, haloalkoxy or halopyrrolidinyl.

4. A compound according to any one of claims 1 to 3, wherein R^2 is cyclopropylmethoxy, propyloxy, fluoroethoxy, trifluoroethoxy or difluoropyrrolidinyl.

5. A compound according to any one of claims 1 to 4, wherein R^4 and R^5 are independently selected from hydrogen, alkyl, cycloalkyl and cycloalkylalkyl.

6. A compound according to any one of claims 1 to 5, wherein R^4 and R^5 are independently selected from hydrogen, methyl, butyl, cyclopropyl and cyclopropylmethyl.

7. A compound according to any one of claims 1 to 6, wherein R^6 is aminocarbonyl, 5-methyl-1,2,4-oxadiazol-3-yl, hydroxyalkyl or alkylaminocarbonyl.

8. A compound according to any one of claims 1 to 7, wherein R^6 is aminocarbonyl, 5-methyl-1,2,4-oxadiazol-3-yl, hydroxymethyl or methylaminocarbonyl.

9. A compound according to any one of claims 1 to 8, wherein R^7 is (aminocarbonyl)(difluoro)pyrrolidinyl.

10. A compound according to any one of claims 1 to 9, wherein R^8 is 3-tert.butyl-1,2,4-oxadiazol-5-yl, 5-tert.butyl-1,2,4-oxadiazol-3-yl or 5-methyl-1,2,4-oxadiazol-3-yl.

11. A compound according to any one of claims 1 to 10 selected from

(R)-N-(1-amino-4-methyl-1-oxopentan-2-yl)-3-(cyclopropylmethoxy)-4-methylbenzamide;

3-(cyclopropylmethoxy)-4-methyl-N-[2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]benzamide;

4-cyclopropyl-3-(cyclopropylmethoxy)-N-[2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]benzamide;

N2-[4-cyclopropyl-3-(cyclopropylmethoxy)benzoyl]-L-leucinamide;

4-cyclopropyl-3-(cyclopropylmethoxy)-N-(1-hydroxy-2-methylpropan-2-yl)benzamide;

4-cyclopropyl-3-(cyclopropylmethoxy)-N-[2-(1,3-thiazol-2-yl)propan-2-yl]benzamide;

ethyl 2-[4-cyclopropyl-3-(cyclopropylmethoxy)benzamido]-2-ethylbutanoate;

2-[4-cyclopropyl-3-(cyclopropylmethoxy)benzamido]-2-ethylbutanoic acid;

4-cyclopropyl-3-(cyclopropylmethoxy)-N-[3-(3,3-difluoroazetidine-1-carbonyl)pentan-3-yl]benzamide;

3-(cyclopropylmethoxy)-4-(3,3-difluoroazetidin-1-yl)-N-[2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]benzamide;

N-[2-(5-amino-1,2,4-oxadiazol-3-yl)propan-2-yl]-3-(cyclopropylmethoxy)-4-(3,3-difluoroazetidin-1-yl)benzamide;

N2-[3-(cyclopropylmethoxy)-4-(3,3-difluoroazetidin-1-yl)benzoyl]-N-methyl-L-leucinamide;

3-(cyclopropylmethoxy)-4-(3,3-difluoroazetidin-1-yl)-N-[(2S)-1-hydroxy-4-methylpentan-2-yl]benzamide;

3-tert-butyl-5-[4-cyclopropyl-3-(cyclopropylmethoxy)phenyl]-1,2,4-oxadiazole;

N-[3-(2-amino-2-oxoethyl)oxetan-3-yl]-4-cyclopropyl-3-(cyclopropylmethoxy)benzamide;

N-[3-(2-amino-2-oxoethyl)-1,1-dioxothietan-3-yl]-4-cyclopropyl-3-(cyclopropylmethoxy)benzamide ;

1-[4-cyclopropyl-3-(cyclopropylmethoxy)benzoyl]-4,4-difluoro-L-prolinamide;

N-(3-carbamoylpentan-3-yl)-4-cyclopropyl-3-(cyclopropylmethoxy)benzamide;

N2-[4-cyclopropyl-3-(cyclopropylmethoxy)benzoyl]-N-methyl-L-leucinamide;

4-cyclopropyl-3-(cyclopropylmethoxy)-N-[(2S)-1-(methanesulfonyl)-2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]benzamide;

4-cyclopropyl-3-(cyclopropylmethoxy)-N-[(2R)-1-(methanesulfonyl)-2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]benzamide;

5-[4-cyclopropyl-3-(cyclopropylmethoxy)benzoyl]-5-azaspiro[2.4]heptane-6-carboxamide;

5-tert-butyl-3-[4-cyclopropyl-3-(2,2,2-trifluoroethoxy)phenyl]-1,2,4-oxadiazole;

5-tert-butyl-3-[4-cyclopropyl-3-(2,2-difluoroethoxy)phenyl]-1,2,4-oxadiazole;

4-cyclopropyl-N-[(2R)-1-cyclopropyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]-3-(2,2,2-trifluoroethoxy)benzamide;

4-cyclopropyl-N-[(2S)-1-cyclopropyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]-3-(2,2,2-trifluoroethoxy)benzamide;

N-[3-(2-amino-2-oxoethyl)-1,1-dioxo-thietan-3-yl]-4-cyclopropyl-3-(2,2,2-trifluoroethoxy)benzamide;

4-cyclopropyl-N-[(2R)-1-(methanesulfonyl)-2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]-3-(2,2,2-trifluoroethoxy)benzamide;

4-cyclopropyl-N-[(2S)-1-(methanesulfonyl)-2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]-3-(2,2,2-trifluoroethoxy)benzamide;

5-tert-butyl-3-[4-cyclopropyl-3-(2-fluoroethoxy)phenyl]-1,2,4-oxadiazole;

4-cyclopropyl-N-[(2R)-1-cyclopropyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]-3-(2,2-difluoroethoxy)benzamide;

4-cyclopropyl-N-[(2S)-1-cyclopropyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]-3-(2,2-difluoroethoxy)benzamide;

4-cyclopropyl-N-[(2R)-1-cyclopropyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]-3-(2-fluoroethoxy)benzamide;

4-cyclopropyl-N-[(2S)-1-cyclopropyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]-3-(2-fluoroethoxy)benzamide;

N-[(2S)-4-amino-2-cyclopropyl-4-oxobutan-2-yl]-4-cyclopropyl-3-(2,2,2-trifluoroethoxy)benzamide;

N-[(2R)-4-amino-2-cyclopropyl-4-oxobutan-2-yl]-4-cyclopropyl-3-(2,2,2-trifluoroethoxy)benzamide;

4-cyclopropyl-N-[(2S)-3,3-dimethyl-1-(methylamino)-1-oxobutan-2-yl]-3-[(propan-2-yl)oxy]benzamide;

4-cyclopropyl-N-[(2S)-1-cyclopropyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]-3-[(propan-2-yl)oxy]benzamide;

4-cyclopropyl-N-[(2S)-3,3-dimethyl-1-(methylamino)-1-oxobutan-2-yl]-3-(2-fluoroethoxy)benzamide;

1-[4-cyclopropyl-3-(2-fluoroethoxy)benzoyl]-4,4-difluoro-L-prolinamide;

4-cyclopropyl-N-[(2S)-3,3-dimethyl-1-(methylamino)-1-oxobutan-2-yl]-3-(2,2,2-trifluoroethoxy)benzamide;

1-[4-cyclopropyl-3-(2,2,2-trifluoroethoxy)benzoyl]-4,4-difluoro-L-prolinamide;

N-[(2S)-4-amino-2-cyclopropyl-4-oxobutan-2-yl]-4-cyclopropyl-3-[(propan-2-yl)oxy]benzamide;

N-[(2R)-4-amino-2-cyclopropyl-4-oxobutan-2-yl]-4-cyclopropyl-3-[(propan-2-yl)oxy]benzamide;

N-[(2R)-4-amino-2-cyclopropyl-4-oxobutan-2-yl]-4-cyclopropyl-3-(2-fluoroethoxy)benzamide;

3-tert-butyl-5-{4-cyclopropyl-3-[(propan-2-yl)oxy]phenyl}-1,2,4-oxadiazole;

3-tert-butyl-5-[4-cyclopropyl-3-(3,3-difluoropyrrolidin-1-yl)phenyl]-1,2,4-oxadiazole;

1-{4-cyclopropyl-3-[(propan-2-yl)oxy]benzoyl}-4,4-difluoro-L-prolinamide;

4-cyclopropyl-N-[(2R)-1-cyclopropyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]-3-[(propan-2-yl)oxy]benzamide;

4-cyclopropyl-N-[(2R)-1-cyclopropyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]-3-(6-fluoropyridin-3-yl)benzamide;

N-[(2S)-4-amino-2-cyclopropyl-4-oxobutan-2-yl]-4-cyclopropyl-3-(2,2,2-trifluoroethoxy)benzamide;

N-[(2R)-4-amino-2-cyclopropyl-4-oxobutan-2-yl]-4-cyclopropyl-3-(6-fluoropyridin-3-yl)benzamide;

N-[(2S)-4-amino-2-cyclopropyl-4-oxobutan-2-yl]-4-cyclopropyl-3-(6-fluoropyridin-3-yl)benzamide;

N-[(2S)-4-amino-2-cyclopropyl-4-oxobutan-2-yl]-4-cyclopropyl-3-(2-fluoroethoxy)benzamide;

1-[4-cyclopropyl-3-(1-methyl-1H-pyrazol-5-yl)benzoyl]-4,4-difluoro-L-prolinamide;

4-cyclopropyl-N-[(2S)-3,3-dimethyl-1-(methylamino)-1-oxobutan-2-yl]-3-(1-methyl-1H-pyrazol-5-yl)benzamide;

1-[4-cyclopropyl-3-(6-fluoropyridin-3-yl)benzoyl]-4,4-difluoro-L-prolinamide;

4-cyclopropyl-N-[(2S)-3,3-dimethyl-1-(methylamino)-1-oxobutan-2-yl]-3-(6-fluoropyridin-3-yl)benzamide;

4-cyclopropyl-N-[(2S)-1-cyclopropyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]-3-(1-methyl-1H-pyrazol-5-yl)benzamide;

4-cyclopropyl-N-[(2S)-1-cyclopropyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]-3-(6-fluoropyridin-3-yl)benzamide;

N-[(2R)-4-amino-2-cyclopropyl-4-oxobutan-2-yl]-4-cyclopropyl-3-(3,3-difluoropyrrolidin-1-yl)benzamide;

N-[(2S)-4-amino-2-cyclopropyl-4-oxobutan-2-yl]-4-cyclopropyl-3-(3,3-difluoropyrrolidin-1-yl)benzamide;

4-cyclopropyl-N-[(2R)-1-cyclopropyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]-3-(3,3-difluoropyrrolidin-1-yl)benzamide;

4-cyclopropyl-N-[(2S)-1-cyclopropyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]-3-(3,3-difluoropyrrolidin-1-yl)benzamide;

1-[4-cyclopropyl-3-(3,3-difluoropyrrolidin-1-yl)benzoyl]-4,4-difluoro-L-prolinamide;

4-cyclopropyl-3-(3,3-difluoropyrrolidin-1-yl)-N-[(2S)-3,3-dimethyl-1-(methylamino)-1-oxobutan-2-yl]benzamide;

4-cyclopropyl-N-[(5-methyl-1,2,4-oxadiazol-3-yl)(3-methyloxetan-3-yl)methyl]-3-(2,2,2-trifluoroethoxy)benzamide;

4-cyclopropyl-N-[(5-methyl-1,2,4-oxadiazol-3-yl)(3-methyloxetan-3-yl)methyl]-3-[(propan-2-yl)oxy]benzamide;

N-[3-amino-1-(3-methyloxetan-3-yl)-3-oxopropyl]-4-cyclopropyl-3-(2,2,2-trifluoroethoxy)benzamide; and

4-cyclopropyl-3-(2-fluoroethoxy)-N-[(5-methyl-1,2,4-oxadiazol-3-yl)(3-methyloxetan-3-yl)methyl]benzamide.

12. A compound according to any one of claims 1 to 11 selected from

N2-[4-cyclopropyl-3-(cyclopropylmethoxy)benzoyl]-L-leucinamide;

4-cyclopropyl-3-(cyclopropylmethoxy)-N-(1-hydroxy-2-methylpropan-2-yl)benzamide;

3-tert-butyl-5-[4-cyclopropyl-3-(cyclopropylmethoxy)phenyl]-1,2,4-oxadiazole;

N-[3-(2-amino-2-oxoethyl)oxetan-3-yl]-4-cyclopropyl-3-(cyclopropylmethoxy)benzamide;

N-[3-(2-amino-2-oxoethyl)-1,1-dioxothietan-3-yl]-4-cyclopropyl-3-(cyclopropylmethoxy)benzamide;

1-[4-cyclopropyl-3-(cyclopropylmethoxy)benzoyl]-4,4-difluoro-L-prolinamide;

5-tert-butyl-3-[4-cyclopropyl-3-(2-fluoroethoxy)phenyl]-1,2,4-oxadiazole;

N-[(2S)-4-amino-2-cyclopropyl-4-oxobutan-2-yl]-4-cyclopropyl-3-(2,2,2-trifluoroethoxy)benzamide;

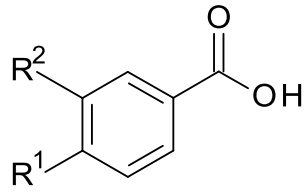
4-cyclopropyl-N-[(2S)-3,3-dimethyl-1-(methylamino)-1-oxobutan-2-yl]-3-[(propan-2-yl)oxy]benzamide;

4-cyclopropyl-N-[(2S)-1-cyclopropyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)propan-2-yl]-3-[(propan-2-yl)oxy]benzamide; and

N-[(2R)-4-amino-2-cyclopropyl-4-oxobutan-2-yl]-4-cyclopropyl-3-[(propan-2-yl)oxy]benzamide.

13. A process for the preparation of a compound according to any one of claims 1 to 12, comprising one of the following steps:

(a) The reaction of a compound of formula (A)

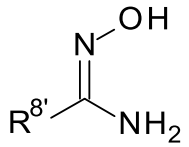


(A)

in the presence of H_2N-C(R^4R^5)-R^6, a coupling agent and a base, wherein R^2 is cyclopropylmethoxy, alkoxy or haloalkoxy;

(b) The reaction of a compound of formula (A) as defined above in the presence of H-R^7, a coupling agent and a base, wherein R^2 is cyclopropylmethoxy, alkoxy or haloalkoxy;

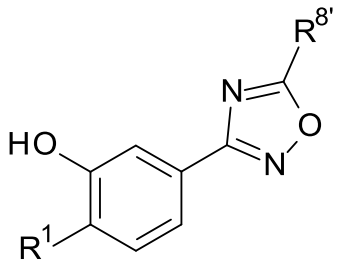
(c) The reaction of a compound of formula (A) as defined above in the presence of a compound of formula (B)



(B)

and carbonydiimidazole, wherein $R^{8'}$ is methyl or tert.-butyl; or

(d) The reaction of a compound of formula (C)



(C)

in the presence of $R^{2'}$-X, wherein $R^{2'}$ is cyclopropylmethyl, alkyl or haloalkyl, $R^{8'}$ is methyl or tert.-butyl and X is a leaving group.

14. A compound according to any one of claims 1 to 12 for use as therapeutically active substance.

15. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 12 and a therapeutically inert carrier.

16. The use of a compound according to any one of claims 1 to 12 in 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.

17. A compound according to any one of claims 1 to 12 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.