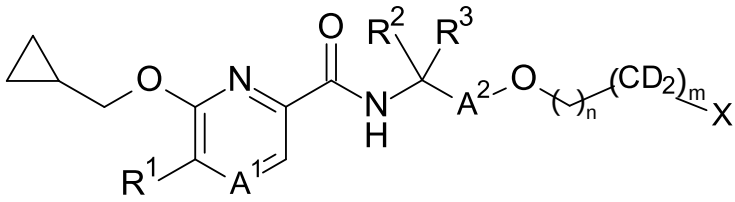
been demonstrated for many pathological conditions including pain (Pasquini, S. J Med Chem 2012, 55(11): 5391), neuropathic pain (Garcia-Gutierrez, M.S. Br J Pharmacol 2012, 165(4): 951), psychiatric disorders (Garcia-Gutierrez, M.S. Br J Pharmacol 2012, 165(4): 951), psychosis (Garcia-Gutierrez, M.S. Br J Pharmacol 2012, 165(4): 951), osteoporosis and inflammation (Sophocleous, A. Calcif Tissue Int 2008, 82(Suppl. 1):Abst OC18), psychiatric diseases and psychosis (Garcia-Gutierrez, M.S. Br J Pharmacol 2012, 165(4): 951), oncology (Preet, A. Cancer Prev Res 2011, 4: 65), encephalitis and malaria (Zimmer, A. WO 2011045068), allergy and inflammation (Ueda, Y. Life Sci 2007, 80(5): 414), encephalitis and malaria (Zimmer, WO 2011045068), asthma (Lunn, C.A. J Pharmacol Exp Ther 2006, 316(2): 780), immunological disorders (Fakhfouri, G. Neuropharmacology 2012, 63(4): 653), rheumatoid arthritis (Chackalamannil, S. US 7776889), arthritis (Lunn, C.A. J Pharmacol Exp Ther 2006, 316(2): 780), and gastrointestinal disorders (Barth, F. FR 2887550).

The compounds of the invention 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 alkoxyazetidinyl, dihaloazetidinyl or pyrrolidinyl;

R^2 and R^3 are independently selected from hydrogen and alkyl;

A^1 is -CH- or nitrogen;

A^2 is -CH_2- or carbonyl;

X is fluorine;

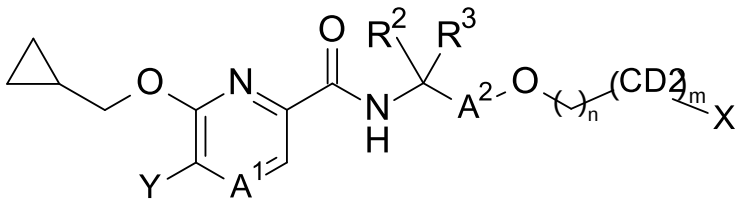
n is 1 to 3; and

m is 0;

or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a process for the preparation of a compound as defined herein, comprising one of the following steps:

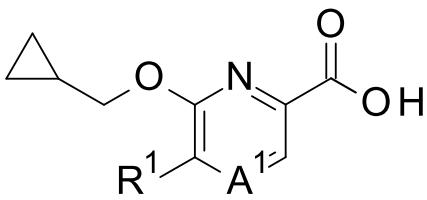
(a) the reaction of a compound of formula (A)



(A)

in the presence of R^1-H, a palladium catalyst and a base;

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



(B)

in the presence of NH_2-C(R^2R^3)-A^2-O-$(CH_2)_n$-$(CD_2)_m$-X, a coupling agent and a base;

wherein A^1, A^2, X, R^1-R^3, m and n are as defined herein and Y is halogen.

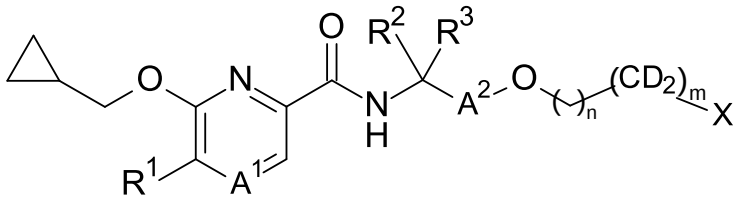
In another aspect, there is provided a compound as defined herein for use as therapeutically active substance.

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,

Claims

1. A compound of formula (I)



(I)

wherein

R^1 is alkoxyazetidinyl, dihaloazetidinyl or pyrrolidinyl;

R^2 and R^3 are independently selected from hydrogen and alkyl;

A^1 is -CH- or nitrogen;

A^2 is $-CH_2-$ or carbonyl;

X is fluorine;

n is 1 to 3; and

m is 0;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R^1 is methoxyazetidinyl, difluoroazetidinyl or pyrrolidinyl.

3. A compound according to claim 1 or 2, wherein R^2 and R^3 are independently selected from hydrogen, ethyl and butyl.

4. A compound according to any one of claims 1 to 3, wherein R^2 and R^3 are both ethyl at the same time, or one of R^2 and R^3 is hydrogen and the other one is butyl.

5. A compound according to any one of claims 1 to 4, wherein A^1 is -CH-.

6. A compound according to any one of claims 1 to 5 selected from

fluoromethyl 2-{[6-(cyclopropylmethoxy)-5-(3-methoxyazetidin-1-yl)pyridine-2-carbonyl]amino}-2-ethylbutanoate;

2-fluoroethyl 2-{[6-(cyclopropylmethoxy)-5-(3-methoxyazetidin-1-yl)pyridine-2-carbonyl]amino}-2-ethylbutanoate;

3-fluoropropyl 2-{[6-(cyclopropylmethoxy)-5-(3-methoxyazetidin-1-yl)pyridine-2-carbonyl]amino}-2-ethylbutanoate;

fluoromethyl 2-{[6-(cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)pyridine-2-carbonyl]amino}-2-ethylbutanoate;

2-fluoroethyl 2-{[6-(cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)pyridine-2-carbonyl]amino}-2-ethylbutanoate;

3-fluoropropyl 2-{[6-(cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)pyridine-2-carbonyl]amino}-2-ethylbutanoate;

3-fluoropropyl 2-{[6-(cyclopropylmethoxy)-5-(pyrrolidin-1-yl)pyridine-2-carbonyl]amino}-2-ethylbutanoate;

fluoromethyl 2-{[6-(cyclopropylmethoxy)-5-(pyrrolidin-1-yl)pyridine-2-carbonyl]amino}-2-ethylbutanoate;

2-fluoroethyl 2-{[6-(cyclopropylmethoxy)-5-(pyrrolidin-1-yl)pyridine-2-carbonyl]amino}-2-ethylbutanoate;

fluoromethyl N-[6-(cyclopropylmethoxy)-5-(3-methoxyazetidin-1-yl)pyridine-2-carbonyl]-L-leucinate;

2-fluoroethyl N-[6-(cyclopropylmethoxy)-5-(3-methoxyazetidin-1-yl)pyridine-2-carbonyl]-L-leucinate;

3-fluoropropyl N-[6-(cyclopropylmethoxy)-5-(3-methoxyazetidin-1-yl)pyridine-2-carbonyl]-L-leucinate;

fluoromethyl N-[6-(cyclopropylmethoxy)-5-(pyrrolidin-1-yl)pyridine-2-carbonyl]-L-leucinate;

2-fluoroethyl N-[6-(cyclopropylmethoxy)-5-(pyrrolidin-1-yl)pyridine-2-carbonyl]-L-leucinate;

3-fluoropropyl N-[6-(cyclopropylmethoxy)-5-(pyrrolidin-1-yl)pyridine-2-carbonyl]-L-leucinate;

6-(cyclopropylmethoxy)-N-[(2S)-1-(fluoromethoxy)-4-methylpentan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2R)-1-(2-fluoroethoxy)-4-methylpentan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-(2-fluoroethoxy)-4-methylpentan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-(3-fluoropropoxy)-4-methylpentan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-(fluoromethoxy)-3-methylbutan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-(2-fluoroethoxy)-3-methylbutan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-(3-fluoropropoxy)-3-methylbutan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-(fluoromethoxy)propan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-(2-fluoroethoxy)propan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-(3-fluoropropoxy)propan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-(fluoromethoxy)-4-methylpentan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)-N-[(2S)-1-(2-fluoroethoxy)-4-methylpentan-2-yl]pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2R)-1-(2-fluoroethoxy)-4-methylpentan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-(2-fluoroethoxy)-4-methylpentan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-(3-fluoropropoxy)-4-methylpentan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-(fluoromethoxy)-3-methylbutan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-(2-fluoroethoxy)-3-methylbutan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-(3-fluoropropoxy)-3-methylbutan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-(2-fluoroethoxy)propan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-(3-fluoropropoxy)propan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-{3-[(fluoromethoxy)methyl]pentan-3-yl}-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-{3-[(2-fluoroethoxy)methyl]pentan-3-yl}-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-{3-[(3-fluoropropoxy)methyl]pentan-3-yl}-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-{3-[(fluoromethoxy)methyl]pentan-3-yl}-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-{3-[(2-fluoroethoxy)methyl]pentan-3-yl}-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-{3-[(3-fluoropropoxy)methyl]pentan-3-yl}-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

fluoromethyl 2-{[6-(cyclopropylmethoxy)-5-(3-methoxyazetidin-1-yl)pyrazine-2-carbonyl]amino}-2-ethylbutanoate;

2-fluoroethyl 2-{[6-(cyclopropylmethoxy)-5-(3-methoxyazetidin-1-yl)pyrazine-2-carbonyl]amino}-2-ethylbutanoate;

3-fluoropropyl 2-{[6-(cyclopropylmethoxy)-5-(3-methoxyazetidin-1-yl)pyrazine-2-carbonyl]amino}-2-ethylbutanoate;

6-(cyclopropylmethoxy)-5-(3-fluoro-3-methylazetidin-1-yl)-N-(3-(3-fluoropropylcarbamoyl)pentan-3-yl)picolinamide;

ethyl 2-{[6-(cyclopropylmethoxy)-5-(3-methoxyazetidin-1-yl)pyridine-2-carbonyl]amino}-2-ethyl-4-fluorobutanoate;

ethyl 2-{[6-(cyclopropylmethoxy)-5-(3-methoxyazetidin-1-yl)pyridine-2-carbonyl]amino}-2-ethyl-3-fluorobutanoate;

ethyl 2-{[6-(cyclopropylmethoxy)-5-(3-methoxyazetidin-1-yl)pyridine-2-carbonyl]amino}-2-ethyl-4-fluorobutanoate; and

ethyl 2-{[6-(cyclopropylmethoxy)-5-(3-methoxyazetidin-1-yl)pyridine-2-carbonyl]amino}-2-ethyl-3-fluorobutanoate.

7. A compound according to any one of claims 1 to 6 selected from

2-fluoroethyl 2-{[6-(cyclopropylmethoxy)-5-(3-methoxyazetidin-1-yl)pyridine-2-carbonyl]amino}-2-ethylbutanoate;

3-fluoropropyl 2-{[6-(cyclopropylmethoxy)-5-(3-methoxyazetidin-1-yl)pyridine-2-carbonyl]amino}-2-ethylbutanoate;

2-fluoroethyl N-[6-(cyclopropylmethoxy)-5-(3-methoxyazetidin-1-yl)pyridine-2-carbonyl]-L-leucinate;

2-fluoroethyl N-[6-(cyclopropylmethoxy)-5-(pyrrolidin-1-yl)pyridine-2-carbonyl]-L-leucinate;

6-(cyclopropylmethoxy)-N-[(2S)-1-(fluoromethoxy)-4-methylpentan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-(2-fluoroethoxy)-4-methylpentan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

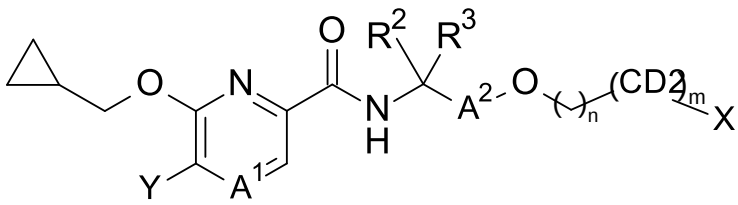
6-(cyclopropylmethoxy)-N-[(2S)-1-(fluoromethoxy)-4-methylpentan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)-N-[(2S)-1-(2-fluoroethoxy)-4-methylpentan-2-yl]pyridine-2-carboxamide; and

6-(cyclopropylmethoxy)-N-[(2S)-1-(2-fluoroethoxy)-4-methylpentan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide.

8. A process for the preparation of a compound according to any one of claims 1 to 7, comprising one of the following steps:

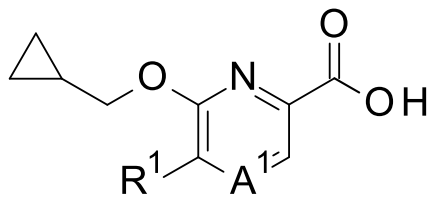
(a) the reaction of a compound of formula (A)



(A)

in the presence of R^1-H, a palladium catalyst and a base;

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



(B)

in the presence of NH_2-C(R^2R^3)-A^2-O-$(CH_2)_n$-$(CD_2)_m$-X, a coupling agent and a base;

wherein A^1, A^2, X, R^1-R^3, m and n are as defined in any one of claims 1 to 7 and Y is halogen.

9. A compound according to any one of claims 1 to 7 for use as therapeutically active substance.

10. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 7 and a therapeutically inert carrier.

11. The use of a compound according to any one of claims 1 to 7 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.

12. A compound according to any one of claims 1 to 7 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.

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