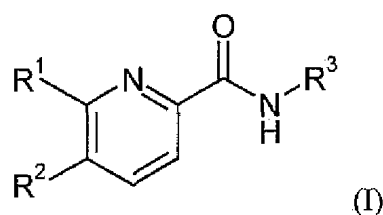


In one aspect, there is provided a compound of formula (I)



wherein

R¹ is halogen, cycloalkylalkoxy, haloalkoxy, alkylsulfonylor alkylsulfinyl;

5 R² is halogen, cycloalkyl, haloalkyl, haloalkoxy, haloazetidinyll or cycloalkyloxy;

R³ is -C(R⁴R⁵)-C(R⁶R⁷)-C(O)-R⁸;

R⁴ and R⁵ are independently selected from hydrogen, alkyl, phenyl, phenylalkyl, cycloalkyl, tetrahydropyranyl, haloalkyl and halophenyl;

10 or R⁴ and R⁵ together with the carbon atom to which they are attached form cycloalkyl, oxetanyl, thiethanyl, 1,1-dioxo-1λ6-thiethanyl, azetidinyll, haloazetidinyll, 2-oxa-spiro[3.3]heptyll, tetrahydrofuranyl, pyrrolidinyl, oxopyrrolidinyl, 1,1-dioxo-1λ6-isothiazolidinyl, 1,1-dioxo-tetrahydro-1λ6-thiophenyl, tetrahydrothiophenyl, tetrahydropyranyl, piperidinyl, oxopiperidinyl, tetrahydrothiopyranyl, 2-oxo-[1,3]oxazinanyl, 1,1-dioxo-1λ6-[1,2]thiazinanyllor 2-oxo-hexahydro-pyrimidinyl;

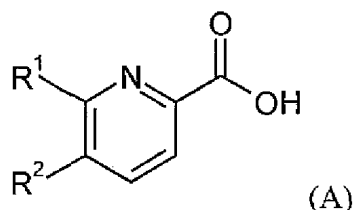
15 R⁶ and R⁷ are independently selected from hydrogen and alkyl;

or one of R⁴ and R⁵ and one of R⁶ and R⁷, together with the carbon atoms to which they are attached, form cycloalkyl, and the other ones are both hydrogen at the same time; and

R⁸ is -NH₂, alkoxy, alkylamino or hydroxyl;

20 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 the reaction of a compound of formula (A)



in the presence of R³-NH₂, an amide coupling agent and a base;

5 wherein R¹ to R³ are as defined herein.

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

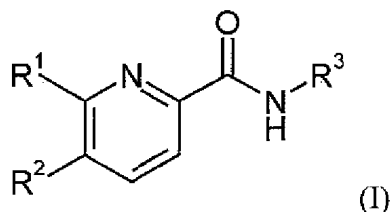
In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a therapeutically inert carrier.

10 In another aspect, there is provided the 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
15 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, amyotrophic lateral
20 sclerosis, 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
25 disease, ischemia-reperfusion injury, acute liver failure, liver fibrosis, lung fibrosis, kidney fibrosis, systemic fibrosis, acute allograft rejection, chronic allograft nephropathy, diabetic

Claims

1. A compound of formula (I)



wherein

5 R^1 is halogen, cycloalkylalkoxy, haloalkoxy, alkylsulfonyl or alkylsulfinyl;

R^2 is halogen, cycloalkyl, haloalkyl, haloalkoxy, haloazetidiny or cycloalkyloxyl;

R^3 is $-C(R^4R^5)-C(R^6R^7)-C(O)-R^8$;

R^4 and R^5 are independently selected from hydrogen, alkyl, phenyl, phenylalkyl, cycloalkyl, tetrahydropyranyl, haloalkyl and halophenyl;

10 or R^4 and R^5 together with the carbon atom to which they are attached form cycloalkyl, oxetanyl, thiethanyl, 1,1-dioxo-1 λ 6-thiethanyl, azetidiny, haloazetidiny, 2-oxa-spiro[3.3]heptyl, tetrahydrofuranyl, pyrrolidiny, oxopyrrolidiny, 1,1-dioxo-1 λ 6-isothiazolidiny, 1,1-dioxo-tetrahydro-1 λ 6-thiophenyl, tetrahydrothiophenyl, tetrahydropyranyl, piperidiny,
15 oxopiperidiny, tetrahydrothiopyranyl, 2-oxo-[1,3]oxazinanyl, 1,1-dioxo-1 λ 6-[1,2]thiazinanyl or 2-oxo-hexahydro-pyrimidinyl;

R^6 and R^7 are independently selected from hydrogen and alkyl;

or one of R^4 and R^5 and one of R^6 and R^7 , together with the carbon atoms to which they are attached, form cycloalkyl, and the other ones are both hydrogen at the
20 same time; and

R^8 is $-NH_2$, alkoxy, alkylamino or hydroxyl;

or a pharmaceutically acceptable salt or ester thereof.

2. A compound according to claim 1, wherein R¹ is cycloalkylalkoxy or haloalkoxy,.
3. A compound according to claim 1 or 2, wherein R¹ is cyclopropylmethoxy or pentafluoropropoxy.
- 5 4. A compound according to any one of claims 1 or 3, wherein R² is cycloalkyl or haloazetidiny.
5. A compound according to any one of claims 1 or 4, wherein one of R⁴ and R⁵ is hydrogen or alkyl, and the other one is independently selected from alkyl, haloalkyl, phenyl, cycloalkyl and tetrahydropyranyl.
- 10 6. A compound according to any one of claims 1 or 5, wherein one of R⁴ and R⁵ is hydrogen or methyl, and the other one is independently selected from methyl, trifluoromethyl, phenyl, cyclohexyl, cyclopropyl and tetrahydropyranyl.
7. A compound according to any one of claims 1 or 6, wherein R⁴ and R⁵ together with the carbon atom to which they are attached form oxetanyl, 1,1-dioxo-1λ6-thiethanyl, 15 piperidiny, cycloalkyl, or thiethanyl.
8. A compound according to any one of claims 1 or 7, wherein R⁶ and R⁷ are both hydrogen at the same time.
9. A compound according to any one of claims 1 or 8, wherein one of R⁴ and R⁵ and one of R⁶ and R⁷, together with the carbon atoms to which they are attached, form 20 cyclohexyl, and the other ones are both hydrogen at the same time.
10. A compound according to any one of claims 1 or 9, wherein R⁸ is -NH₂ or ethoxy.
11. A compound according to any one of claims 1 to 10 selected from

{3-[(5-Cyclopropyl-6-cyclopropylmethoxy-pyridine-2-carbonyl)-amino]-oxetan-3-yl}-acetic acid ethyl ester;

- tert*-Butyl 3-({[6-(cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)pyridin-2-yl]carbonyl}amino)-5-methylhexanoate;
- 3-{[6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carbonyl]-amino}-3-phenyl-propionic acid ethyl ester;
- 5 3-{[6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carbonyl]-amino}-3-methyl-butyric acid ethyl ester;
- 6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (1,1-dimethyl-2-methylcarbamoyl-ethyl)-amide;
- 10 6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (1-methylcarbamoylmethyl-hexyl)-amide;
- 6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (1-methylcarbamoylmethyl-3-phenyl-propyl)-amide;
- (-)-5-Cyclopropyl-6-cyclopropylmethoxy-pyridine-2-carboxylic acid (1-carbamoylmethyl-pentyl)-amide;
- 15 (+)-5-Cyclopropyl-6-cyclopropylmethoxy-pyridine-2-carboxylic acid (1-carbamoylmethyl-pentyl)-amide;
- 2-[({[6-(Cyclopropylmethoxy)-5-(3,3-difluoroazetidin-1-yl)pyridin-2-yl]carbonyl}amino)methyl]-4-methylpentanoic acid;
- 20 5-Cyclopropyl-6-cyclopropylmethoxy-pyridine-2-carboxylic acid (rel-(1S,2R)-2-carbamoyl-cyclohexyl)-amide;
- 5-Cyclopropyl-6-cyclopropylmethoxy-pyridine-2-carboxylic acid ((R)-1-carbamoylmethyl-2-methyl-propyl)-amide;
- 5-Cyclopropyl-6-cyclopropylmethoxy-pyridine-2-carboxylic acid ((S)-1-carbamoylmethyl-2-methyl-propyl)-amide;
- 25 (+)-cis-5-Cyclopropyl-6-cyclopropylmethoxy-pyridine-2-carboxylic acid (2-carbamoyl-cyclohexyl)-amide;

- 6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (3-carbamoylmethyl-tetrahydro-thiophen-3-yl)-amide;
- 6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (4-carbamoylmethyl-piperidin-4-yl)-amide;
- 5 6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (4-carbamoylmethyl-2-oxo-piperidin-4-yl)-amide;
- 6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (5-carbamoylmethyl-2-oxo-[1,3]oxazinan-5-yl)-amide;
- 10 6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (4-carbamoylmethyl-1,1-dioxo-hexahydro-1 λ^6 -thiopyran-4-yl)-amide;
- 6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (4-carbamoylmethyl-1,1-dioxo-1 λ^6 -[1,2]thiazinan-4-yl)-amide;
- 6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (3-carbamoylmethyl-6-oxo-piperidin-3-yl)-amide;
- 15 6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (5-carbamoylmethyl-2-oxo-hexahydro-pyrimidin-5-yl)-amide;
- 6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (3-carbamoylmethyl-1,1-dioxo-hexahydro-1 λ^6 -thiopyran-3-yl)-amide;
- 20 6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (5-carbamoylmethyl-2-oxo-[1,3]dioxan-5-yl)-amide;
- 6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (3-carbamoylmethyl-tetrahydro-pyran-3-yl)-amide;
- 6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (3-carbamoylmethyl-piperidin-3-yl)-amide;
- 25 6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (3-carbamoylmethyl-tetrahydro-thiopyran-3-yl)-amide; and
- 6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (5-carbamoylmethyl-1,1-dioxo-1 λ^6 -[1,2]thiazinan-5-yl)-amide.

12. A compound according to any one of claims 1 to 13 selected from
- 3-{[6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carbonyl]-amino}-3-phenyl-propionic acid ethyl ester;
- 5 (+)-cis-5-Cyclopropyl-6-cyclopropylmethoxy-pyridine-2-carboxylic acid (2-carbamoyl-cyclohexyl)-amide;
- (+)-5-Cyclopropyl-6-cyclopropylmethoxy-pyridine-2-carboxylic acid (2-carbamoyl-1-cyclohexyl-ethyl)-amide;
- 5-Cyclopropyl-6-cyclopropylmethoxy-pyridine-2-carboxylic acid (3-carbamoylmethyl-oxetan-3-yl)-amide;
- 10 6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (3-carbamoylmethyl-oxetan-3-yl)-amide;
- (+)-5-Cyclopropyl-6-cyclopropylmethoxy-pyridine-2-carboxylic acid (2-carbamoyl-1-cyclopropyl-ethyl)-amide;

5-Cyclopropyl-6-cyclopropylmethoxy-pyridine-2-carboxylic acid [2-carbamoyl-1-(tetrahydro-pyran-4-yl)-ethyl]-amide;

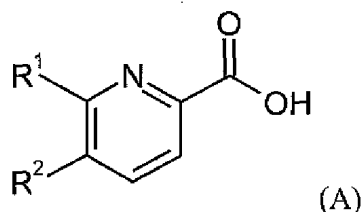
6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (2-carbamoyl-1,1-dimethyl-ethyl)-amide;

5 5-Cyclopropyl-6-(2,2,3,3,3-pentafluoro-propoxy)-pyridine-2-carboxylic acid (3-carbamoylmethyl-oxetan-3-yl)-amide;

6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (1-carbamoylmethyl-2,2,2-trifluoro-ethyl)-amide; and

10 6-Cyclopropylmethoxy-5-(3,3-difluoro-azetidin-1-yl)-pyridine-2-carboxylic acid (3-carbamoylmethyl-1,1-dioxo-1λ6-thietan-3-yl)-amide.

13. A process for the preparation of a compound according to any one of claims 1 to 12, comprising the reaction of a compound of formula (A)



in the presence of R³-NH₂, an amide coupling agent and a base;

- 5 wherein R¹ to R³ are as defined in any one of claims 1 to 10.
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.
- 10 16. The use of a compound according to any one of claims 1 to 12 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,
- 15 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, amyotrophic lateral sclerosis, stroke, transient ischemic attack or uveitis.

- 5 17. A compound according to any one of claims 1 to 12 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,
10 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, amyotrophic lateral sclerosis,
15 stroke, transient ischemic attack or uveitis.
