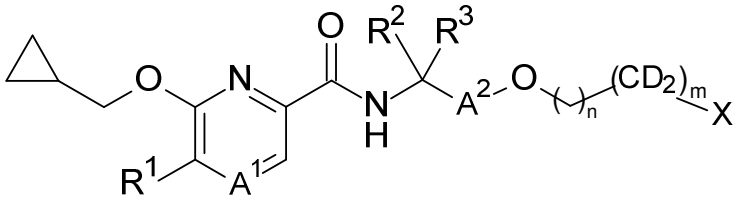
Claims

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 halogen;

n is 0 to 3; and

m is 0 or 1;

provided that m and n are not both 0 at the same time;

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, wherein X is fluorine.

7. A compound according to any one of claims 1 to 6, wherein n is 1, 2 or 3.

8. A compound according to any one of claims 1 to 7 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;

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

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

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

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

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

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

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

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

2-fluoro(2,2-dideuterio)ethyl 2-{[6-(cyclopropylmethoxy)-5-(pyrrolidin-1-yl)pyridine-2-carbonyl]amino}-2-ethylbutanoate;

6-(cyclopropylmethoxy)-N-[(2S)-1-{[fluoro(dideuterio)methyl]oxy}-4-methylpentan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-{[2-fluoro(2,2-dideuterio)ethyl]oxy}-4-methylpentan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-{[3-fluoro(3,3-dideuterio)propyl]oxy}-4-methylpentan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-{[fluoro(dideuterio)methyl]oxy}-3-methylbutan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-{[2-fluoro(2,2-dideuterio)ethyl]oxy}-3-methylbutan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-{[3-fluoro(3,3- dideuterio)propyl]oxy}-3-methylbutan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-{[fluoro(dideuterio)methyl]oxy}propan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-{[2-fluoro(2,2-dideuterio)ethyl]oxy}propan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-{[3-fluoro(3,3-dideuterio)propyl]oxy}propan-2-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-{[fluoro(dideuterio)methyl]oxy}-4-methylpentan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-{[2-fluoro(2,2-dideuterio)ethyl]oxy}-4-methylpentan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-{[3-fluoro(3,3-dideuterio)propyl]oxy}-4-methylpentan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-{[fluoro(dideuterio)methyl]oxy}-3-methylbutan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-{[2-fluoro(2,2-dideuterio)ethyl]oxy}-3-methylbutan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-{[3-fluoro(3,3-dideuterio)propyl]oxy}-3-methylbutan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-{[2-fluoro(2,2-dideuterio)ethyl]oxy}propan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[(2S)-1-{[3-fluoro(3,3- dideuterio)propyl]oxy}propan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

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

6-(cyclopropylmethoxy)-N-[3-({[2-fluoro(2,2-dideuterio)ethyl]oxy}methyl)pentan-3-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[3-({[3-fluoro(3,3-dideuterio)propyl]oxy}methyl)pentan-3-yl]-5-(pyrrolidin-1-yl)pyridine-2-carboxamide;

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

6-(cyclopropylmethoxy)-N-[3-({[2-fluoro(2,2-dideuterio)ethyl]oxy}methyl)pentan-3-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

6-(cyclopropylmethoxy)-N-[3-({[3-fluoro(3,3-dideuterio)propyl]oxy}methyl)pentan-3-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

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

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

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.

9. A compound according to any one of claims 1 to 8 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;

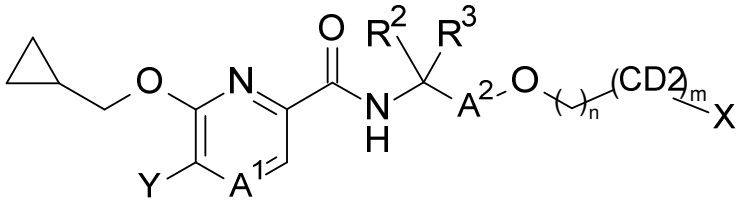
6-(cyclopropylmethoxy)-N-[(2S)-1-(fluoromethoxy)-4-methylpentan-2-yl]-5-(3-methoxyazetidin-1-yl)pyridine-2-carboxamide;

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.

10. A process for the preparation of a compound according to any one of claims 1 to 9, comprising one of the following steps:

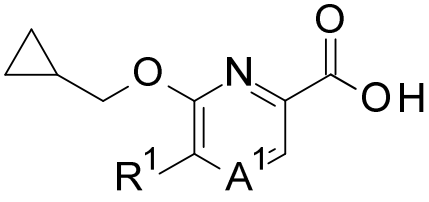
(a) the reaction of a compound of formula (A)



(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.

11. A compound according to any one of claims 1 to 9, when manufactured according to a process of claim 10.

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

13. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 9 and a therapeutically inert carrier.

14. The use of a compound according to any one of claims 1 to 9 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.

15. The use of a compound according to any one of claims 1 to 9 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.

16. A compound according to any one of claims 1 to 9 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.

17. A method 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, which method comprises administering an effective amount of a compound as defined in any one of claims 1 to 9 to a patient in need thereof.

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