

(halo)(haloalkyl)phenyl, (halo)(alkoxy)phenyl, cyano, cycloalkyl, cycloalkylalkoxy, amino, heterocyclyl, alkylheterocyclyl, hydroxyheterocyclyl, alkylheterocyclyl, heteroaryl, haloheteroaryl, alkylheteroaryl, (alkyl)(alkylsulfonyl)heteroaryl, (halo)(alkylamino)heteroaryl, haloalkylheteroaryl, cycloalkylheteroaryl or nitro-benzo[1,2,5]oxadiazolylaminoheteroaryl, wherein heterocyclyl is a three to eight membered carbocyclic ring comprising at least one nitrogen or oxygen atom, and wherein heteroaryl is pyridinyl, pyrazolyl, oxadiazolyl, furazanyl, tetrazolyl, triazolyl or oxypyridinyl;

R² is alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkoxyalkyl, cycloalkylalkoxy, haloalkoxy, alkoxy or alkylamino;

R³ is halogen or -NR⁴R⁵;

one of R⁴ and R⁵ is hydrogen or alkyl and the other one is alkyl or cycloalkyl;

or R⁴ and R⁵ together with the nitrogen atom to which they are attached form heterocyclyl or substituted heterocyclyl, wherein heterocyclyl is morpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, 2-oxa-6-azaspiro[3.3]heptyl, azetidiny, thiazolidinyl, thiomorpholinyl, dioxothiomorpholinyl, oxazepanyl, 2-oxa-6-azaspiro[3.4]octyl, 6-oxa-1-azaspiro[3.3]heptyl, 2-oxa-5-aza-spiro[3.4]octyl, isoxazolidinyl, aziridinyl or dioxoisothiazolidinyl and wherein substituted heterocyclyl is heterocyclyl substituted with one to four substituents independently selected from alkyl, halogen, hydroxyl, alkoxy, hydroxyalkyl, carboxyl, alkoxyalkyl, cyano and alkylcarbonylamino; wherein,

“alkyl”, alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms;

“alkylene”, alone or in combination, signifies a straight-chain or branched-chain alkylene group with 1 to 8 carbon atoms;

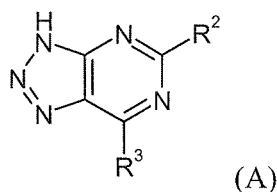
“cycloalkyl”, alone or in combination, signifies a cycloalkyl ring with 3 to 8 carbon atoms and particularly a cycloalkyl ring with 3 to 6 carbon atoms;

“alkoxy”, alone or in combination, signifies a group of the formula alkyl-O-;

or a pharmaceutically acceptable salt or ester thereof.

In a second aspect, there is provided a process for the preparation of a compound as defined herein comprising the reaction of a compound of formula (A)

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in the presence of R¹-A-X and a base, or in the presence of R¹-A-OH under Mitsunobu conditions, wherein A and R¹ to R³ are defined herein and wherein X is halogen or SO₂.

~~In a third aspect, there is provided a compound as defined herein, when manufactured according to a process as defined herein.~~

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

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

In a ~~sixth~~ fifth aspect, there is provided 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, 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 a ~~seventh~~ sixth aspect, there is provided a compound as defined herein 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 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 and tert.-butyl.

- 5 In the present description the term “alkylene”, alone or in combination, signifies a straight-chain or branched-chain alkylene group with 1 to 8 carbon atoms, particularly a

independently selected from alkyl, halogen, hydroxyl, alkoxy, hydroxyalkyl, carboxyl, alkoxyalkyl, cyano and alkylcarbonylamino; wherein,

“alkyl”, alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms;

“alkylene”, alone or in combination, signifies a straight-chain or branched-chain alkylene group with 1 to 8 carbon atoms;

“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;

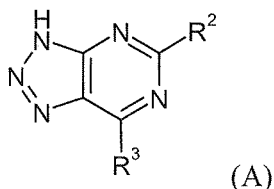
“alkoxy”, alone or in combination, signifies a group of the formula alkyl-O-;

or a pharmaceutically acceptable salt or ester thereof.

2. A compound according to claim 1, wherein A is alkylene, -CH₂C(O)- or absent.
3. A compound according to claim 1 or 2, wherein A is alkylene.
4. A compound according to any one of claims 1 to 3, wherein A is methylene, ethylene or -CH(CH₃)-.
5. A compound according to any one of claims 1 to 4, wherein R¹ is alkyl, haloalkyl, hydroxyl, alkoxy, phenyl, halophenyl, alkoxyphenyl, haloalkylphenyl, haloalkoxyphenyl, cyanophenyl, cycloalkyl, heterocyclyl, haloheteroaryl or alkylheteroaryl, wherein heterocyclyl is oxetanyl, and wherein heteroaryl is pyridinyl or furazanyl.
6. A compound according to any one of claims 1 to 5, wherein R¹ is alkyl, haloalkyl, hydroxyl, alkoxy, phenyl, halophenyl, alkoxyphenyl, haloalkylphenyl, haloalkoxyphenyl, cyanophenyl, cycloalkyl, oxetanyl, pyridinyl, halopyridinyl or alkylfurazanyl.
7. A compound according to any one of claims 1 to 6, wherein R¹ is trifluoromethyl, phenyl, chlorophenyl, bromophenyl, cyanophenyl, cyclohexyl, pyridinyl, chloropyridinyl, methylfurazanyl or trifluoromethylphenyl.
8. A compound according to any one of claims 1 to 7, wherein R² is alkyl.
9. A compound according to any one of claims 1 to 8, wherein R² is tert.-butyl.
10. A compound according to any one of claims 1 to 9, wherein R³ is -NR⁴R⁵.

11. A compound according to any one of claims 1 to 10, wherein R⁴ and R⁵ together with the nitrogen atom to which they are attached form morpholinyl, halopyrrolidinyl or hydroxypyrrolidinyl.
- 5 12. A compound according to any one of claims 1 to 11, wherein R⁴ and R⁵ together with the nitrogen atom to which they are attached form morpholinyl, difluoropyrrolidinyl or hydroxypyrrolidinyl.
13. A compound according to any one of claims 1 to 12 selected from

15. A process for the preparation of a compound according to any one of claims 1 to 14 comprising the reaction of a compound of formula (A)



in the presence of R^1 -A-X and a base, or in the presence of R^1 -A-OH under Mitsunobu conditions, wherein A and R^1 to R^3 are defined according to any one of claims 1 to 12 and wherein X is halogen or SO_2 .

~~16. A compound according to any one of claims 1 to 14, when manufactured according to a process of claim 15.~~

~~17~~16. A compound according to any one of claims 1 to 14 for use as therapeutically active substance.

~~18~~17. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 14 and a therapeutically inert carrier.

~~19~~18. The use of a compound according to any one of claims 1 to 14 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.

5 | 2019. A compound according to any one of claims 1 to 14 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,
10 gingivitis pyrexia, liver cirrhosis or tumors, regulation of bone mass, neurodegeneration,
stroke, transient ischemic attack or uveitis.
