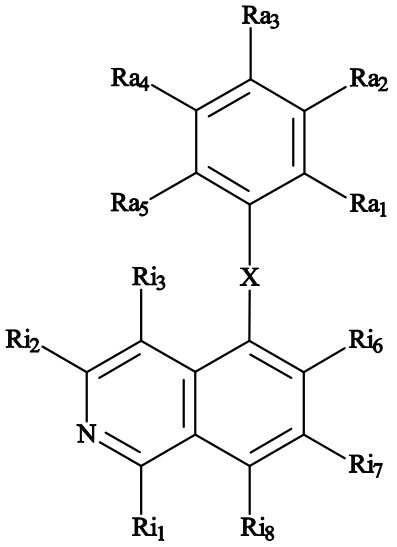
CLAIMS

1. Compound of formula (I) :

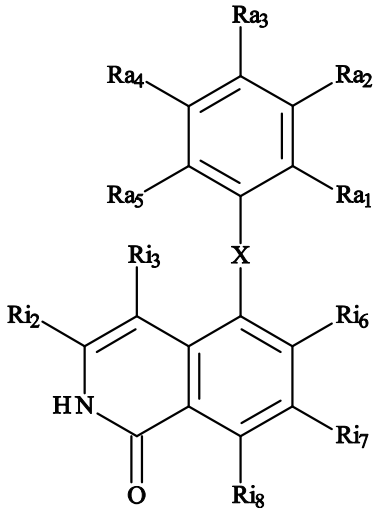


(I)

wherein:

- X represents a group -C(=O), -CH(OH)- or -CH_2-,
- Ri_1 represents a hydrogen atom or a hydroxyl group,

it being understood that the compound of formula (I) wherein Ri_1 represents a hydroxyl group may be represented by the following tautomeric form:



- Ri_2 and Ri_3, which may be identical or different, each represent a hydrogen atom, a (C_1-C_6)alkyl group or a halogen atom,

- Ri_6, Ri_7 and Ri_8, which may be identical or different, each represent a hydrogen atom or a halogen atom,
- Ra_1 and Ra_5, which may be identical or different, each represent a hydrogen or halogen atom, a -O(C_1-C_6)alkyl group or a (C_1-C_6)alkyl group,
- Ra_2 represents a hydrogen or halogen atom, a hydroxyl group, a -O(C_1-C_6)alkyl group, a -(C_1-C_6)alkyl group, a nitrogen-containing heterocycle having from 3 to 7 ring members, or a group -O-$(CH2)_m$-NR'R'',
- Ra_3 represents a hydrogen atom, a -O(C_1-C_6)alkyl group, a -(C_1-C_6)alkyl group, a nitrogen-containing heterocycle having from 3 to 7 ring members, or a group -$CRy_1Ry_2NH(Ry_3)$,
- Ra_4 represents a hydrogen or halogen atom, a -O(C_1-C_6)alkyl group, a -(C_1-C_6)alkyl group, or a group -$CRy_1Ry_2NH(Ry_3)$,

it being understood that:

- Ra_1, Ra_2, Ra_3, Ra_4 and Ra_5 may not simultaneously represent a hydrogen atom,
- Ra_3 and Ra_4 may not simultaneously represent a group -$CRy_1Ry_2NH(Ry_3)$,
- Ra_1 and Ra_2 can form together with the carbon atoms carrying them a heterocycle having from 4 to 7 ring members chosen from tetrahydrofuran, 1,4-dioxane, tetrahydropyran, tetrahydro-2*H*-pyran-4-amine and 1-(tetrahydro-2*H*-pyran-4-yl)methanamine, and
- Ra_2 and Ra_3 can form together with the carbon atoms carrying them a hydrocarbon ring having from 4 to 7 ring members chosen from cyclopentane, cyclopentanamine, *N*-cyclopentylglycinamide and 1-methylcyclopentanamine,

- m is an integer the value of which is fixed at 1, 2 or 3,
- R' and R'', which may be identical or different, each represent -(C_1-C_6)alkyl groups or form together with the nitrogen atom carrying them a heterocycle having from 3 to 7 ring members,
- Ry_1 represents a hydrogen atom, a -(C_1-C_6)alkyl group, a -CH_2-cyclohexyl group, or a 3-methoxyphenyl group,
- Ry_2 represents a hydrogen atom or a -(C_1-C_6)alkyl group,
- Ry_3 represents:
  - a hydrogen atom,

- a group –C(=O)-CHRy_4-NHRy_5 wherein Ry_4 represents a hydrogen atom or a (C_1-C_6)alkyl group and Ry_5 represents a hydrogen atom or a methyl group, or
- a -(C_1-C_6)alkyl group which can be substituted by a hydroxyl group, a -O(C_1-C_3)alkyl group, a cyclohexyl group or a methylsulphonyl group,

or Ry_1 and Ry_2 form together with the carbon atom carrying them a cyclopropane, cyclobutane or tetrahydropyran group,

or Ry_2 and Ry_3 form together with the carbon and nitrogen atoms carrying them, respectively, a pyrrolidine or piperidine group,

its optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

2. Compound of formula (I) according to claim 1, characterised in that X represents a group -C(=O), its optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

3. Compound of formula (I) according to either claim 1 or claim 2, characterised in that Ri_1 represents a hydroxyl group, it being understood that said compound may be represented in its tautomeric form, its optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

4. Compound of formula (I) according to any one of claims 1 to 3, characterised in that Ri_2, Ri_6, Ri_7 and Ri_8 each represent a hydrogen atom, its optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

5. Compound of formula (I) according to any one of claims 1 to 4, characterised in that Ra_1 and Ra_5 each represent a fluorine atom, its optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

6. Compound of formula (I) according to any one of claims 1 to 5, characterised in that Ra_3 or Ra_4 represents a group -CRy_1Ry_2NH(Ry_3), its optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

7. Compound of formula (I) according to claim 6, characterised in that:

- Ry_1 represents a hydrogen atom or a -(C_1-C_6)alkyl group,
- Ry_2 represents a -(C_1-C_6)alkyl group,
- Ry_3 represents a hydrogen atom,

its optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

8. Compound of formula (I) according to claim 1, characterised in that:

- X represents a group -C(=O)-,
- Ri_1 represents a hydrogen atom or a hydroxyl group,
- Ri_2, Ri_6, Ri_7 and Ri_8 each represent a hydrogen atom and Ri_3 represents a hydrogen atom or a (C_1-C_6)alkyl group,
- Ra_1 and Ra_5, which may be identical or different, each represent a hydrogen or fluorine atom or a (C_1-C_6)alkyl group,
- Ra_2 represents a hydrogen atom or a -(C_1-C_6)alkyl group,
- Ra_3 represents a hydrogen atom, a piperidine group or a group -$CRy_1Ry_2NH(Ry_3)$,
- Ra_4 represents a hydrogen atom or a group -$CRy_1Ry_2NH(Ry_3)$, it being understood that Ra_3 and Ra_4 may not simultaneously represent a group -$CRy_1Ry_2NH(Ry_3)$, and that:
    - when Ra_3 represents a group -$CRy_1Ry_2NH(Ry_3)$, Ra_1 and Ra_2 can form together with the carbon atoms carrying them a tetrahydrofuran, 1,4-dioxane or tetrahydropyran group, or
    - when Ra_3 represents a hydrogen atom, Ra_1 and Ra_2 can form together with the carbon atoms carrying them a tetrahydro-2*H*-pyran-4-amine or 1-(tetrahydro-2*H*-pyran-4-yl)methanamine group, or
    - Ra_2 and Ra_3 can form together with the carbon atoms carrying them a cyclopentanamine or 1-methylcyclopentanamine group,
- Ry_1 represents a hydrogen atom, a -(C_1-C_6)alkyl group or a -CH_2-cyclohexyl group,
- Ry_2 represents a hydrogen atom or a -(C_1-C_6)alkyl group,
- Ry_3 represents a hydrogen atom or a -(C_1-C_6)alkyl group which can be substituted by a hydroxyl group,

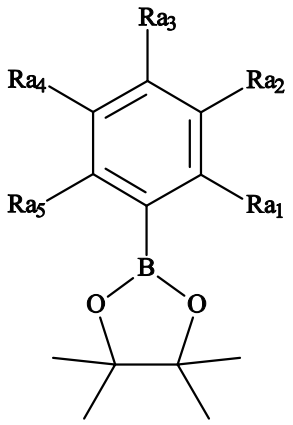
its optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

9. Compound of formula (I) according to claim 1 chosen from:

- [4-(1-aminoethyl)-2,6-difluorophenyl](isoquinolin-5-yl)methanone and its optical isomers and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof,
- [4-((1*R*)-1-aminoethyl)-2,6-difluorophenyl](isoquinolin-5-yl)methanone and its addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof,
- [4-(1-aminoethyl)-2,6-difluorophenyl](1-hydroxyisoquinolin-5-yl)methanone and its optical isomers and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof,
- 1-[3,5-difluoro-4-(isoquinolin-5-ylmethyl)phenyl]ethanamine and its optical isomers and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof,
- {4-[(1*S*)-1-aminoethyl]-2,6-difluorophenyl}(isoquinolin-5-yl)methanol and its addition salts with a pharmaceutically acceptable acid and hydrates thereof,
- [4-(2-aminopropan-2-yl)-2,6-difluorophenyl](isoquinolin-5-yl)methanone and its addition salts with a pharmaceutically acceptable acid and hydrates thereof,
- 5-[4-(2-aminopropan-2-yl)-2,6-difluorobenzoyl]isoquinolin-1(2*H*)-one and its addition salts with a pharmaceutically acceptable acid and hydrates thereof,
- 5-[4-(1-aminoethyl)-2-fluoro-3-methoxybenzoyl]isoquinolin-1(2*H*)-one and its optical isomers and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof,
- 5-({5-[(1*R*)-1-aminoethyl]-3,4-dihydro-2*H*-chromen-8-yl}carbonyl)isoquinolin-1(2*H*)-one and its addition salts with a pharmaceutically acceptable acid and hydrates thereof,
- 5-{4-[(1*R*)-1-aminoethyl]-2-methylbenzoyl}isoquinolin-1(2*H*)-one and its addition salts with a pharmaceutically acceptable acid and hydrates thereof,
- 5-(2,6-difluoro-4-{1-[(2-hydroxyethyl)amino]ethyl}benzoyl)isoquinolin-1(2*H*)-one and its optical isomers and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof,
- 5-{4-[(1*R*)-1-aminoethyl]-2,6-difluorobenzoyl}-4-methylisoquinolin-1(2*H*)-one and its addition salts with a pharmaceutically acceptable acid and hydrates thereof,
- 5-{3-[(1*R*)-1-aminoethyl]-2,6-difluorobenzoyl}isoquinolin-1(2*H*)-one and its addition salts with a pharmaceutically acceptable acid and hydrates thereof,

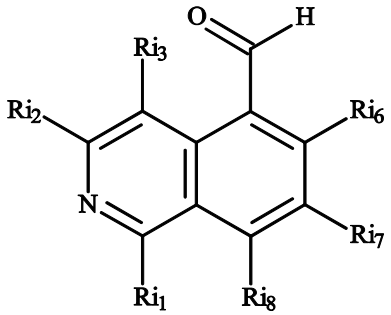
- 5-[(1-amino-4,6-difluoro-2,3-dihydro-1*H*-inden-5-yl)carbonyl]isoquinolin-1(2*H*)-one and its optical isomers and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof,
- 5-{[(3*R*)-3-amino-4,6-difluoro-2,3-dihydro-1*H*-inden-5-yl]carbonyl}isoquinolin-1(2*H*)-one and its addition salts with a pharmaceutically acceptable acid and hydrates thereof,
- 5-({8-[(1*R*)-1-aminoethyl]-2,3-dihydro-1,4-benzodioxin-5-yl}carbonyl)isoquinolin-1(2*H*)-one and its addition salts with a pharmaceutically acceptable acid,
- 5-[2,6-difluoro-4-(piperidin-2-yl)benzoyl]isoquinolin-1(2*H*)-one and its optical isomers and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof,
- 5-[4-(1-amino-2-cyclohexylethyl)-2,6-difluorobenzoyl]isoquinolin-1(2*H*)-one and its optical isomers and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof,
- 5-{[4-(aminomethyl)-3,4-dihydro-2*H*-chromen-8-yl]carbonyl}isoquinolin-1(2*H*)-one and its optical isomers and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

10. Process for the synthesis of compounds of formula (Ia), particular cases of compounds of formula (I) according to claim 1 wherein X represents a group -C(=O), characterised in that the compounds of formula (Ia) are prepared starting from a compound of formula (II) :



(II)

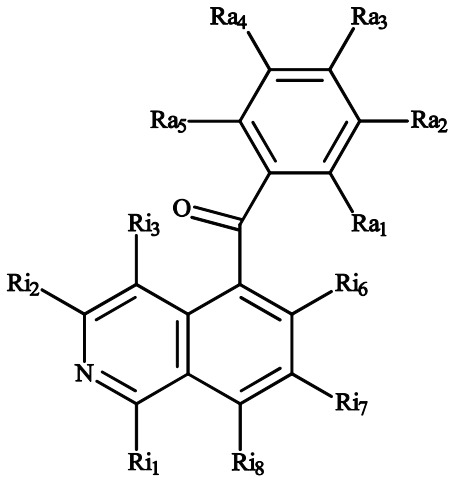
which is subjected to a coupling reaction with the compound of formula (III) :



(III)

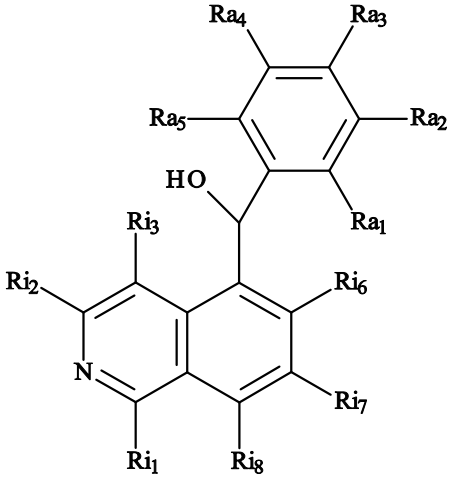
in the presence of a rhodium or palladium catalyst, of a phosphine and of a base in an organic solvent,

to yield the compound of formula (Ia) :



(Ia)

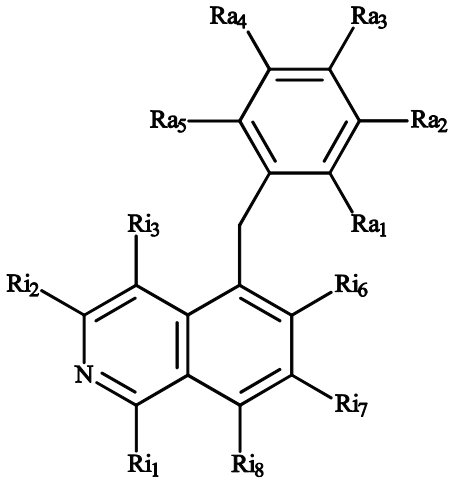
11. Process for the synthesis of compounds of formula (Ib), particular cases of the compounds of formula (I) according to claim 1 wherein X represents a group -CH(OH)- :



(Ib)

characterised in that the compounds of formula (Ib) are prepared starting from compounds of formula (Ia) according to claim 10 by a reduction reaction in the presence of sodium tetraborohydride.

12. Process for the synthesis of compounds of formula (Ic), particular cases of the compounds of formula (I) according to claim 1 wherein X represents a group -CH_2-



(Ic)

characterised in that the compounds of formula (Ic) are prepared starting from the compounds of formula (Ib) according to claim 11 by a reduction reaction in the presence of trifluoroacetic acid and of triethylsilane.

13. Pharmaceutical composition comprising as active ingredient a compound of formula (I) according to any one of claims 1 to 9, in combination with one or more inert, non-toxic, pharmaceutically acceptable excipients or carriers.

14. Pharmaceutical composition according to claim 13, for use in the treatment or prevention of pathologies which are the result of activation of the RhoA/ROCK pathway and phosphorylation of the myosin light chain.

15. Pharmaceutical composition according to claim 14, for use in the treatment or prevention of systemic arterial hypertension, pulmonary arterial hypertension, angina, myocardial infarction, post-angioplasty restenosis, aortic aneurysm, occlusion of the peripheral arteries, atherosclerosis, cardiac fibrosis and heart failure.

16. Pharmaceutical composition according to claim 15, for use in the treatment or prevention of systemic arterial hypertension.

17. Pharmaceutical composition according to claim 14, for use in the treatment or prevention of glaucoma and pathologies of the cornea.

18. Pharmaceutical composition according to claim 14, for use in the treatment or prevention of erectile dysfunction, broncho-obstructive pulmonary diseases, post-radiation intestinal fibrosis, cutaneous systemic sclerosis, pulmonary fibrosis associated with pulmonary arterial hypertension, hepatic diseases, renal fibrosis and glomerulo-sclerosis, diabetes, hyperglycaemia, insulin resistance, diabetic nephropathies induced or not induced by hypertension, thrombotic diseases, cerebral vasospasm and resulting cerebral ischaemia.