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(71) Applicant(s)
Les Laboratoires Servier

(72) Inventor(s)
Chimenti, Stefano;Courchay, Christine;Dessinges, Aimee;Gellibert, Francoise;Goument, Bertrand;Konnert, Marc;Peglion, Jean-Louis;Poitevin, Christophe;Vilaine, Jean-Paul;Villeneuve, Nicole

(74) Agent / Attorney
Allens Patent & Trade Mark Attorneys, Deutsche Bank Place Corner Hunter and Phillip Streets, SYDNEY, NSW, 2000, AU

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(71) Déposant : **LES LABORATOIRES SERVIER** [FR/FR]; 35 rue de Verdun, F-92284 Suresnes Cedex (FR).

(72) Inventeurs : **CHIMENTI, Stefano**; 199, boulevard Voltaire, F-75011 Paris (FR). **COURCHAY, Christine**; 15, rue Jean Tassel, F-91430 Igny (FR). **DESSINGES, Aimée**; Appart. N° 47, 8, Bd du Général de Gaulle, F-92500 Rueil-Malmaison (FR). **GELLIBERT, Françoise**; 7, Chemin de la Croix de Bures, F-91440 Bures-sur-Yvette (FR). **GOUMENT, Bertrand**; 53, rue du Louvre, F-78220 Viroflay (FR). **KONNERT, Marc**; Bat E2, 30, rue Soeur Azélie, F-95170 Deuil-la-Barre (FR). **PEGLION, Jean-Louis**; 5, allée des Bégonias, F-78110 Le Vesinet (FR). **POITEVIN, Christophe**; 100, rue de Charonne, F-75011 Paris (FR). **VILAINE, Jean-Paul**; 21, rue des Vallées, F-92290 Chatenay Malabry (FR). **VILLENEUVE, Nicole**; 60, rue de la Chapelle, F-92500 Rueil Malmaison (FR).

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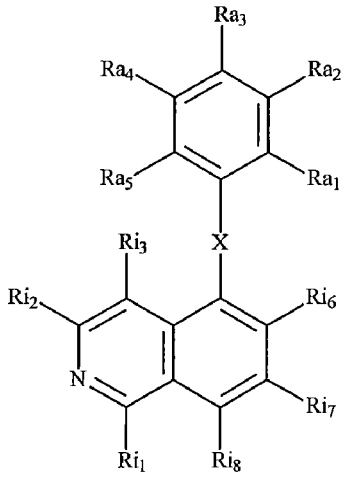
[Suite sur la page suivante]

(54) **Title** : DERIVATIVES OF 5-BENZYLISOQUINOLINE FOR THE TREATMENT OF CARDIOVASCULAR DISEASES

(54) **Titre** : DÉRIVÉS DE 5-BENZYLISOQUINOLÉINE POUR LE TRAITEMENT DE MALADIES CARDIOVASCULAIRES



(I)

(57) **Abstract** : The invention relates to novel isoquinoline derivatives of formula (I), to the synthesis thereof, and to the use of same in the prevention and/or treatment of pathologies resulting from the activation of the RhoA/ROCK pathway and the phosphorylation of the light chain of myosin. X represents a group -C(=0)-, -CH(OH)- or -CH_2-, and the other substituents represent various groups such as those defined in claim 1.

(57) **Abrégé** : L'invention concerne de nouveaux dérivés isoquinoléines de formule (I), leur synthèse et leur utilisation dans la prévention et/ou le traitement de pathologies qui résultent de l'activation de la voie RhoA/ROCK et de la phosphorylation de la chaîne légère de la myosine. X représente un groupement -C(=0)-, -CH(OH)- ou -CH_2-, et les autres substituants représentent des groupements variés tels que définis dans la revendication 1.

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ISOQUINOLINE COMPOUNDS, A PROCESS FOR THEIR PREPARATION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

LES LABORATOIRES SERVIER
35, RUE DE VERDUN
F-92284 SURESNES CEDEX

INVENTORS : Stefano CHIMENTI
Christine COURCHAY
Aimee DESSINGES
Françoise GELLIBERT
Bertrand GOUMENT
Marc KONNERT
Jean-Louis PEGLION
Christophe POITEVIN
Jean-Paul VILAINE
Nicole VILLENEUVE

The present invention relates to new isoquinoline compounds, to their synthesis and to their use in the prevention and/or treatment of pathologies which are the result of activation of the RhoA/ROCK pathway and phosphorylation of the myosin light chain.

Under the effect of agonists such as angiotensin II, 5-hydroxytryptamine or endothelin, the RhoA membrane protein, which belongs to the family of the small GTP-binding proteins, acquires the active GTP-bound configuration, under the control of specific adenyl nucleotide exchange factors. This active membrane form permits binding to the Rho-kinase protein and activation thereof.

Rho-kinase is a serine/threonine kinase with a molecular mass of 160 kdaltons and one of the many targets of the RhoA protein. Two isoforms of Rho-kinase, Rho-kinase β/ROCK β/p160ROCK or ROCK1 and Rho-kinase α/ROCK α or ROCK2, which are coded for by two different genes, have been identified. The two isoforms are expressed ubiquitously, ROCK2 especially in the vascular smooth muscle cells, the heart and the brain. ROCK1 is expressed preferentially on the non-nervous tissues such as the lungs, the liver, the spleen, the kidneys and the testicles. These two isoforms share 92% homology in their kinase domain. The activation of ROCK by RhoA-GTP leads to phosphorylation and inhibition of a myosin phosphatase regulatory subunit and thus allows the myosin light chain to be maintained in a phosphorylated state, independently of the intracellular Ca^{2+} concentration (a process known as Ca^{2+} sensitisation). Phosphorylation of the myosin light chain is responsible for increasing the contractility of the actin cytoskeleton, which is the result of sliding between the actin and myosin filaments.

Activation of the RhoA/ROCK pathway is involved in the following dysfunctions and the pathologies associated therewith:

- vasoconstriction by increase of the myogenic tone (Rattan et al, Pharmacological Sciences, 880 :1-10, 2011),
- formation of stress fibres and cellular contraction (Kaibuchi et al, Sciences, 275 : 1308, 1997),
- systemic arterial hypertension (Uehata et al, Nature, 389 : 990-993, 1997 ; Pacaud et al, P. Nat. Rev. Cardiol .,7(11) : 637-647, 2010),

- pulmonary arterial hypertension (Jankov et al, Am J Physiol Heart Circ Physiol, 299 :H1854-H1864, 2010 ; Fukumoto et al, Heart, 91 : 391-392, 2005) and associated pulmonary fibrosis (Duong-Quy et al, J. Fran. Viet. Pneu., 03(08) : 1-74, 2012),
- increase in intraocular pressure, retinopathy and glaucoma resulting therefrom (Acott et al, Curr Opin Ophtalmol, 23(2) : 135-43, 2012 ; Tanihara et al, Curr Eye Res, 36(10) : 964-70, 2011 ; Rossetti et al, Expert.Opin.Investig.Drugs, 20(7) :947-959, 2011 ; Chen et al, Clin. Ophtalmol, 5 : 667-677, 2011 ; Rao et al, J Glaucoma, 21 :530-538, 2012, Zhong et al, Int J Oncol, 43(5) :1357-67, 2013 ; Van de Velde, Acta Ophtalmologica, 91 : s252, 2013), dystrophy of the cornea due to proliferation of endothelial cells (Kinoshita et al, Cornea, 32(8) : 1167-1170, 2013),
- coronary artery vasospasm, angina pectoris, myocardial infarction (Kandabashi et al, Circulation, 101 : 1319-1323, 2000 ; Shimokawa et al, Am. J. Physiol. Heart Circ. Physiol, 301 : H287-H296, 2011),
- endothelial dysfunction by negative regulation of NO production and atherosclerosis (Shimokawa et al, Cardiovasc . Res. 51 : 169-177, 2001),
- aortic aneurysm, occlusion of the peripheral arteries (Shimokawa et al, Am J Physiol Heart Circ Physiol, 301 : H287-H296, 2011),
- erectile dysfunction (Chitaley et al, Int J Impot Res, 24(2) : 49-60, 2012),
- proliferation, mobility of the endothelial cells and angiogenesis (Imamura et al, Biochem, Biophys Res, 269(2) : 633-640, 2000),
- increased blood viscosity and fibrinogen level (Zhang et al, Central South Pharmacy, 3,035, 2008),
- differentiation of cardiac fibroblasts into myofibroblasts (Kalluri et al, J. Cell. Physiol. 225 :631-637, 2010 ; Sabbadini et al, Circ.Res., 82 : 303-312, 2009 ; Rohr, Heart Rhythm, 6(6) : 848-856, 2009),
- ventricular remodelling and cardiac fibrosis after myocardial infarction (Hattori et al, Circulation, 109 : 2234-2239, 2004 ; Krum et al, Am J Physiol Heart Circ Physiol, 294 : H1804-H1814, 2008 ; Entman et al, Cardiovasc.Res., 83 : 511-518, 2009 ; Liu et al, Toxicology Letters, 211 : 91-97, 2012) and heart failure (Kishi et al, Circulation, 111 : 2741-2747, 2005),

- proliferation of the smooth muscle cells and restenosis (Shimokawa et al, Am J Physiol Heart Circ Physiol, 301 : H287-H296, 2011),
- diabetes, hyperglycaemia, insulin resistance, diabetic nephropathies (Kikuchi et al, J. Endocrinol., 192 : 595-603, 2007 ; Kolavennu et al, Diabetes, 57 :714-723, 2008) and renal insufficiency, renal fibrosis, nephrosclerosis (Matsuoka et al, J Hypertens, 26(9) :1837-48, 2008),
- activation of the astrocytes of the liver and liver diseases such as cirrhosis, hepatitis and cancer (WO2000064478A1, 2000),
- differentiation of human dermal fibroblasts in cutaneous systemic sclerosis (Distler et al, Arthritis and Rheumatism, 58(8) : 2553-2564, 2008),
- post-radiotherapy intestinal fibrosis by differentiation of the smooth muscle cells (Vozenin-Brotons et al, Gut, 54(3) :336-343, 2005),
- adherence, migration, phagocytosis of the macrophages and inflammatory diseases (Schwartz et al, the EMBO Journal, 26 : 505-515, 2007 ; Doe et al, J.Pharmacol.Exp.Ther., 320 :89-98, 2007),
- cerebral vasospasm and ischaemia resulting therefrom with neurological dysfunction (Shibuya et al, J.Neurol.Science, 238 : 31-39, 2005),
- neuronal degeneration such as Alzheimer's disease (Zhou et al, Science, 302 : 1215-1217, 2003 ; Song et al, CNS Neurosci. Ther . 19, 603-610, 2013),
- neuropathic pain (Xiao et al, Brain, Behaviour and Immunity, 23(8) : 1083-88, 2009),
- neurological recovery after spinal cord injury (Hara et al, J. Neurosurg. 93 (suppl.1) :94-101, 2000 ; Dergham et al, J. Neurosci . 22, 6570-6577, 2002 ; Yamashita et al, Ther. Clin. Risk Manag., 4(3) : 605-615, 2008),
- cell proliferation and migration (Feng et al, Current Topics in Medical Chemistry, 9, 704-723, 2009 ; Utsunomiya et al, Biochemical and Biophysical Research Communication, 402 :725-730,2010),
- formation of metastases and development of cancer of the breast, lung, colon, brain, head and neck (Liu et al, Cancer Res, 69 : 8742-8751, 2009 ; Li et al, FEBS Lett. 580 : 4252-4260, 2006 ; Vishnubhotla et al, Lab.Invest. 87 : 1149-1158, 2007 ; Zohrabian et al, Anticancer Res. 29 : 119-123, 2009 ; Torre et al, Arch.

Otolaryngol. Head Neck Surg., 136 : 493-501, 2010 ; Ying et al, Mol.Cancer Ther., 5 : 2158-2164, 2006),

- activation of osteoclasts (migration) and of bone resorption (Hruska et al, J Biol chem, 278(31) : 29086-97, 2003),
- contraction of the bronchial smooth muscle cells, chronic broncho-pulmonary diseases and asthma (Mori et al, Am. J. Resp. Cell. Mol. Biol., 20(6) : 1190-1200, 1999 ; Kanaide et al, Br J Pharmacol, 132 : 111-118, 2001),
- increase of the SREBP (sterol response binding element) signalling pathway under the effect of shear stress and activation of the gene coding for the LDL receptor (Lin et al, Cir. Res., 92(12) : 1296-1304, 2003).

Accordingly, a compound which had the ability to inhibit Rho-kinase and phosphorylation of the myosin light chain might prevent or treat cardiovascular or non-cardiovascular diseases such as: systemic arterial hypertension, pulmonary arterial hypertension, glaucoma, retinopathies, degeneration of the optic nerve, pathologies of the cornea, coronary diseases such as angina, myocardial infarction, post-angioplasty restenosis, aortic aneurysm, occlusion of the peripheral arteries, atherosclerosis, cardiac fibrosis and heart failure, erectile dysfunction, broncho-obstructive pulmonary diseases such as asthma or respiratory distress syndrome in adults, post-radiation intestinal fibrosis, cutaneous systemic sclerosis, pulmonary fibrosis associated with pulmonary arterial hypertension, the prevention or treatment of hepatic diseases, renal fibrosis and glomerulo-sclerosis, diabetic nephropathies induced or not induced by hypertension, thrombotic diseases, cerebral vasospasm and resulting cerebral ischaemia, neuropathic pain, degenerative neuronal diseases such as Alzheimer's disease, inflammatory diseases, the development of cancer and its progression by metastases, osteoporosis, lipid metabolism.

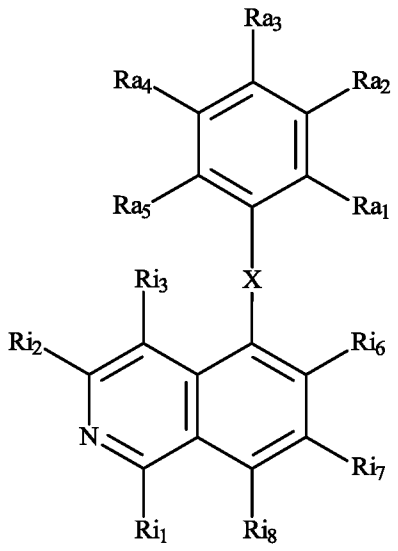
Rho-kinase inhibitors having an isoquinoline skeleton are described in several patent applications.

There may be mentioned, for example, application WO2005/035 503, which describes Rho-kinase inhibitors for the treatment of glaucoma.

Application EP 0 187 371 describes Rho-kinase inhibitors having an isoquinoline skeleton with a sulphonamide functional group for the treatment of glaucoma, and in particular Fasudil.

Mention may also be made of patent applications WO2007/000 240, WO2007/012 421, WO2007/012 422, WO2008/077 550, WO2008/077 552, WO2008/077 553, WO2008/077 554, WO2008/077 555, WO2008/077 556, WO2009/156 092, WO2009/156 099 and WO2009/156 100, which describe Rho-kinase inhibitors for use in the treatment of hypertension and glaucoma.

The present invention relates to compounds of formula (I)

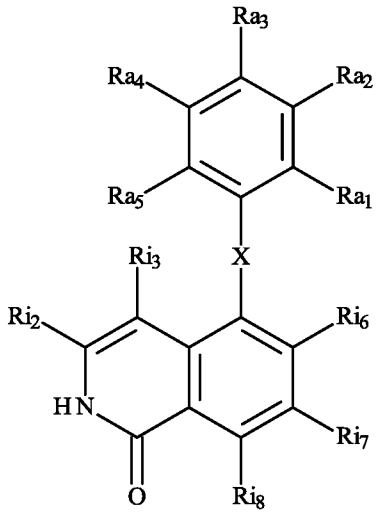


(I)

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 compounds 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 $(C_1\text{-}C_6)$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 $-O(C_1\text{-}C_6)$alkyl group or a $(C_1\text{-}C_6)$alkyl group,
- Ra_2 represents a hydrogen or halogen atom, a hydroxyl group, a $-O(C_1\text{-}C_6)$alkyl group, a $-(C_1\text{-}C_6)$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 $-O(C_1\text{-}C_6)$alkyl group, a $-(C_1\text{-}C_6)$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 $-O(C_1\text{-}C_6)$alkyl group, a $-(C_1\text{-}C_6)$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-2H-pyran-4-amine and 1-(tetrahydro-2H-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,

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

Among the pharmaceutically acceptable acids there may be mentioned, without implying any limitation, hydrochloric, hydrobromic, sulphuric, phosphoric, acetic, trifluoroacetic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, tartaric, maleic, citric, ascorbic, oxalic, methanesulphonic, para-toluenesulphonic, benzenesulphonic, camphoric, pamoic, 1,5-naphthalenedisulphonic acids.

The (C_1-C_6)alkyl groups can be linear or branched.

The hydrocarbon rings or the heterocycles present in the compounds of formula (I) of the present invention can be substituted by one or more halogen atoms and/or by one or more of the following groups: -NH_2, hydroxyl, -(C_1-C_6)alkyl, -O(C_1-C_6)alkyl, -NH(C_1-C_6)alkyl, -(C_1-C_6)alkyl-NH_2, -NH-C(=O)-(C_1-C_6)alkyl-NH_2.

When R' and R'' form together with the nitrogen carrying them a heterocycle, substituted or unsubstituted, having from 3 to 7 ring members, the heterocycle is preferably chosen from morpholine, pyrrolidine, piperidine and N-methylpiperidine.

When Ra_2 or Ra_3 represents a nitrogen-containing heterocycle having from 3 to 7 ring members, the heterocycle can be chosen from the following non-limiting list: aziridine, azetidine, imidazoline, pyrrolidine, piperidine, piperazine, imidazole, pyrrole, pyridine, pyrimidine, pyridazine, 1,2,3,4-tetrahydropyrimidine, hexahydropyrimidine, hexahydropyridazine.

One aspect of the invention relates to compounds of formula (I) wherein X represents a group -C(=O)-, their optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

Another aspect of the invention relates to compounds of formula (I) wherein Ri_1 represents a hydroxyl group, their optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

Another aspect of the invention relates to compounds of formula (I) wherein Ri_2 or Ri_3 represents a (C_1-C_6)alkyl group, more especially a methyl or ethyl group, their optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

Another aspect of the invention relates to compounds of formula (I) wherein Ri_2 and/or Ri_3 represent a hydrogen atom, their optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

Another aspect of the invention relates to compounds of formula (I) wherein Ri_6 and/or Ri_7 and/or Ri_8 represent a hydrogen atom, their optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

Another aspect of the invention relates to compounds of formula (I) wherein Ri_2, Ri_6, Ri_7 and Ri_8 each represent a hydrogen atom, their optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

Another aspect of the invention relates to compounds of formula (I) wherein Ra_1 and/or Ra_5 represent a hydrogen atom or a halogen atom, more especially a chlorine or fluorine atom, their optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

Another aspect of the invention relates to compounds of formula (I) wherein Ra_1 and Ra_5 each represent a fluorine atom, their optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

Another aspect of the invention relates to compounds of formula (I) wherein Ra_2 represents a hydrogen atom, their optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

Another aspect of the invention relates to compounds of formula (I) wherein Ra_3 and Ra_4 represent 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 $-CRy_1Ry_2NH(Ry_3)$, their optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

Another aspect of the invention relates to compounds of formula (I) wherein Ra_3 or Ra_4 represents a group $-CRy_1Ry_2NH(Ry_3)$, their optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

Another aspect of the invention relates to compounds of formula (I) wherein Ra_3 or Ra_4 represents a group $-CRy_1Ry_2NH(Ry_3)$ and:

- 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,

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

Another aspect of the invention relates to compounds of formula (I) wherein Ra_3 represents a group $-CRy_1Ry_2NH(Ry_3)$ and Ra_1 and Ra_2 form together with the carbon atoms carrying them a heterocycle having from 4 to 7 ring members, their optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

Preferably, such a heterocycle is chosen from tetrahydrofuran, 1,4-dioxane and tetrahydropyran.

Another aspect of the invention relates to compounds of formula (I) wherein Ra_3 represents a hydrogen atom and Ra_1 and Ra_2 form together with the carbon atoms carrying them a heterocycle having from 4 to 7 ring members, their optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

Preferably, such a heterocycle is chosen from tetrahydro-2H-pyran-4-amine and 1-(tetrahydro-2H-pyran-4-yl)methanamine.

Another aspect of the invention relates to compounds of formula (I) wherein Ra_2 and Ra_3 form together with the carbon atoms carrying them a hydrocarbon ring having from 4 to 7

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

Preferably, such a hydrocarbon ring is chosen from cyclopentane and its derivatives, more especially cyclopentanamine, N-cyclopentylglycinamide and 1-methylcyclopentanamine.

Another aspect of the invention relates to compounds of formula (I) wherein:

- 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-2H-pyran-4-amine or 1-(tetrahydro-2H-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,

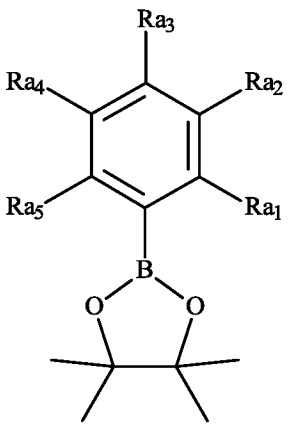
their optical isomers, where they exist, and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

Another aspect of the invention relates to compounds of formula (I) 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-((1R)-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-[(1S)-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(2H)-one and its addition salts with a pharmaceutically acceptable acid and hydrates thereof,
- 5-[4-(1-aminoethyl)-2-fluoro-3-methoxybenzoyl]isoquinolin-1(2H)-one and its optical isomers and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof,
- 5-({5-[(1R)-1-aminoethyl]-3,4-dihydro-2H-chromen-8-yl}carbonyl)isoquinolin-1(2H)-one and its addition salts with a pharmaceutically acceptable acid and hydrates thereof,
- 5-{4-[(1R)-1-aminoethyl]-2-methylbenzoyl}isoquinolin-1(2H)-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(2H)-one and its optical isomers and addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof,
- 5-{4-[(1R)-1-aminoethyl]-2,6-difluorobenzoyl}-4-methylisoquinolin-1(2H)-one and its addition salts with a pharmaceutically acceptable acid and hydrates thereof,

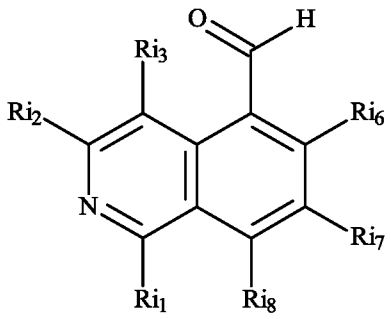
- 5-{3-[(1R)-1-aminoethyl]-2,6-difluorobenzoyl}isoquinolin-1(2H)-one and its addition salts with a pharmaceutically acceptable acid and hydrates thereof,
- 5-[(1-amino-4,6-difluoro-2,3-dihydro-1H-inden-5-yl)carbonyl]isoquinolin-1(2H)-one and its optical isomers and addition salts thereof with a pharmaceutically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

Another aspect of the invention relates to a process for the synthesis of compounds of formula (Ia), particular cases of compounds of formula (I) wherein X represents a group -C(=O), starting from a compound of formula (II):



(II)

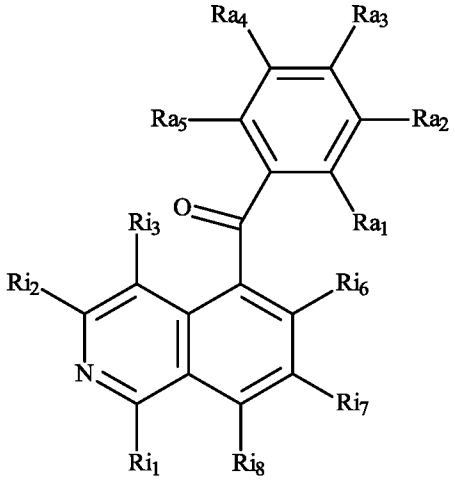
which is subjected to a coupling reaction with the compound of formula (III):



(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)

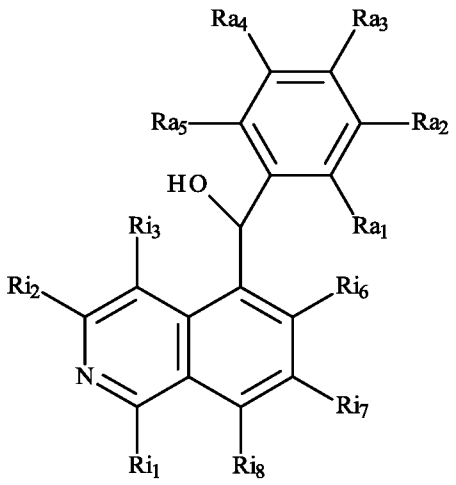
Among the rhodium and palladium catalysts which can be used to carry out the coupling reaction between the compound of formula (II) and the compound of formula (III) there may be mentioned, without implying any limitation, the following catalysts: ($[Rh(CH_2CH_2)_2Cl]_2$, Rh(acac)(coe)2 (coe = cyclooctene) and the tris(dibenzylidene-acetone)dipalladium/chloroform complex (Pd_2dba_3-$CHCl_3$).

Among the phosphines which can be used to carry out the coupling reaction between the compound of formula (II) and the compound of formula (III) there may be mentioned, without implying any limitation, tri-butylphosphine, 1,3-bis(diphenylphosphino)propane (dppp) and 1,1'-bis(diphenylphosphino)ferrocene (dppf).

Among the bases which can be used to carry out the coupling reaction between the compound of formula (II) and the compound of formula (III) there may be mentioned, without implying any limitation, potassium carbonate and potassium hydrogen carbonate.

Among the organic solvents which can be used to carry out the coupling reaction between the compound of formula (II) and the compound of formula (III) there may be mentioned, without implying any limitation, 1,4-dioxane, dimethoxyethane and toluene.

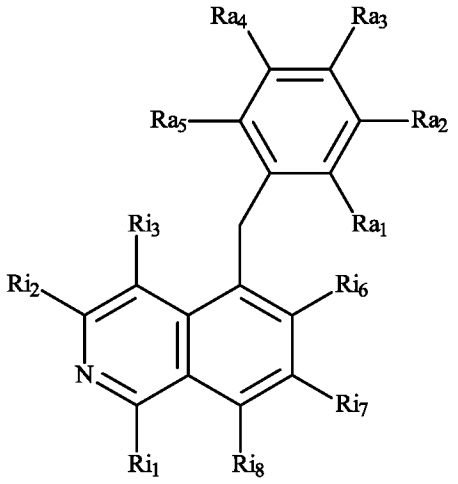
The compounds of formula (Ia) so obtained can then be converted into compounds of formula (Ib), particular cases of compounds of formula (I) wherein X represents -CH(OH)-, by a reduction reaction:



(Ib)

This reduction reaction can be carried out in the presence of hydride donors, such as sodium tetraborohydride ($NaBH_4$).

The compounds of formula (Ib) so obtained can then be converted into compounds of formula (Ic), particular cases of compounds of formula (I) wherein X represents $-CH_2-$, by a further reduction reaction, which can be carried out in the presence of trifluoroacetic acid and of triethylsilane:



(Ic)

The optically active forms of the compounds of formula (I) are obtained either starting from optically active forms of the compound of formula (III) or by separating the racemic forms of the compounds of formula (I) according to methods known in the literature.

The present invention relates also to pharmaceutical compositions comprising as active ingredient a compound of formula (I), or an addition salt thereof with a pharmaceutically acceptable acid, in combination with one or more inert, non-toxic, pharmaceutically acceptable excipients or carriers.

Among the pharmaceutical compositions according to the invention there may be mentioned more especially those that are suitable for oral, parenteral (intravenous, intramuscular or subcutaneous), per- or trans-cutaneous, nasal, rectal, perlingual, ocular or respiratory administration, especially tablets or dragées, sublingual tablets, gelatin capsules, capsules, suppositories, creams, ointments, dermal gels, injectable or drinkable preparations, aerosols, eye or nasal drops.

In addition to the compound of formula (I), the pharmaceutical compositions according to the invention comprise one or more excipients or carriers such as diluents, lubricants, binders, disintegrators, absorbents, colourings, sweeteners.

Examples of excipients or carriers which may be mentioned include:

- *for the diluents*: lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycerin,
- *for the lubricants*: silica, talc, stearic acid and its magnesium and calcium salts, polyethylene glycol,
- *for the binders*: aluminium and magnesium silicate, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and polyvinylpyrrolidone,
- *for the disintegrators*: agar, alginic acid and its sodium salt, effervescent mixtures.

The percentage of active ingredient of formula (I) in the pharmaceutical composition is preferably from 5% to 50% by weight.

The dosage used varies according to the age and weight of the patient, the administration route, the nature and severity of the disorder and the taking of any associated treatments, and ranges from 0.5 mg to 500 mg in one or more administrations per day.

The present invention also relates to a method for the treatment or prevention of pathologies which are the result of activation of the RhoA/ROCK pathway and phosphorylation of the myosin light chain in a subject, the method comprising administering to a subject in need thereof an effective amount of a compound according to the invention or a pharmaceutical composition according to the invention.

The present invention also relates to the use of a compound according to the invention or a pharmaceutical composition according to the invention in the manufacture of a medicament for the treatment or prevention of pathologies which are the result of activation of the RhoA/ROCK pathway and phosphorylation of the myosin light chain.

An aspect of the invention relates to 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.

A further aspect of the invention relates to the treatment or prevention of systemic arterial hypertension.

Another aspect of the invention relates to the treatment or prevention of glaucoma and pathologies of the cornea

A further aspect of the invention relates to 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.

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this specification.

The following examples illustrate the invention.

List of abbreviations used

AcOEt : ethyl acetate
Boc_2O : di-tert-butyl dicarbonate
DMF : dimethylformamide
DMSO : dimethyl sulphoxide
DTT : dithiothreitol
EDTA : ethylenediaminetetraacetic acid

EGTA	ethylenebis(oxyethylenenitrilo)tetraacetic acid
ESI :	electrospray ionization
eq. :	equivalent(s)
GC :	gas chromatography
Hepes :	4-(2-hydroxyethyl)-1-piperazineethanesulphonic acid
HRMS :	high resolution mass spectrometry
IR :	infrared
i.v. :	intravenous

KHMDS :	potassium hexamethyl-disilazane
LCMS :	liquid chromatography-mass spectrometry
LDA :	lithium diisopropylamide
m-CPBA :	meta-chloroperbenzoic acid
MS:	mass spectrometry
NEt_3:	triethylamine
TMSCN :	trimethylsilyl cyanide
SFC :	supercritical fluid chromatography
NMR :	nuclear magnetic resonance
tBuOK	potassium tert-butanoate
THF :	tetrahydrofuran
TMS :	tetramethylsilane
TMSCN	trimethylsilanecarbonitrile
Tris :	trishydroxymethylaminomethane or 2-amino-2-hydroxymethyl-1,3-propanediol

The presence of the symbol "*" next to a carbon atom in the chemical formulae emphasises that the carbon has a fixed absolute configuration, without the nature of that configuration having been identified.

The infrared spectra were recorded with the aid of a Bruker TENSOR 27 Fourier transform spectrometer in ATR mode .

The proton NMR spectra were recorded on Bruker DPX 400-B spectrometers. The chemical shifts are expressed in ppm and are determined relative to the TMS used as reference. The abbreviations used are:

- s : singlet
- d : doublet
- dd : doublet of doublets
- dt : doublet of triplets
- t : triplet
- td : triplet of doublets

- quad : quadruplet
- quint : quintuplet
- m : multiplet

The mass spectra are recorded on a TSQ 7000 spectrometer.

GC monitoring was carried out on a HPS-J&W Scientific column 0.53 x 15 m with an Agilent 4890 GC chromatograph with flame ionisation detection (FID).

HPLC monitoring was carried out on Acquity UPLC BEH C18 1.7 µm columns 2.1 x 30 mm on 1200 Agilent HPLC with diode array detector (DAD).

SFC : The analyses of enantiomeric purity are carried out on a UPC2 (Waters).

Thin layer chromatography (TLC) was carried out on MERCK 60F-254 silica plates.

The chromatographies were carried out with a MERCK 60 silica gel (0.040-0.063 mm) or with Interchim or Grace prepacked silica columns.

The reverse phase separations were carried out on Interchim FHP RP C18 15 µm columns 275 x 60 mm with UV detection.

Filtrations were carried out on Millipore filters of type GVHP (0.22 µm) for the organic phases and on Whatman GF/A filters cat. No1820-070 for the aqueous phases.

Preparation of compounds of the invention

Preparation of isoquinoline precursors

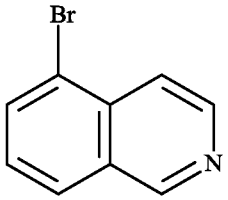
Protocol I : Preparation of 5-halo-isoquinoline intermediates

The following intermediates were prepared by bromation of commerical isoquinolines according to the protocol described by Brown, W. D. ; Gouliaev, A. H., Synthesis, **2002**, 1, 83-86 and Organic Syntheses, **2004**, 81, 98-104.

Intermediate 2 :

^{1}H NMR (300MHz-DMSO-d_6): δ 9.40 (s,1H), 8.70 (d,1H), 8.22 (d,1H), 8.18 (d,1H), 7.93 (d,1H), 7.65 (t,1H)

IR (cm^{-1}): 1621-1579, 819-629;



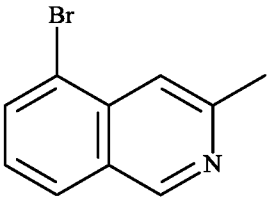
2

Intermediate 290 :

^{1}H NMR (400MHz-$CDCl_3$): δ 9.15 (s, 1H), 7.90 (2d, 2H), 7.80 (s, 1H), 7.35 (t, 1H), 2.75 (s, 3H)

IR (cm^{-1}): 1621-1584, 666

GC-EI (70 eV): M+. = 221.

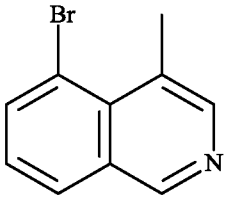


290

Intermediate 299 :

^{1}H NMR (400MHz-DMSO-d_6): δ 9.30 (s, 1H), 8.40 (s, 1H), 8.17 (t, 1H), 7.55 (t, 1H), 2.95 (s, 3H)

IR (cm^{-1}): 1609-1579



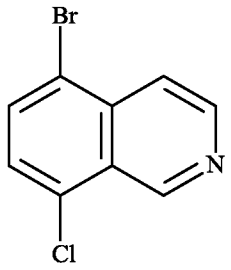
299

Intermediate **754** was prepared starting from intermediate **2** according to the following protocol:

To a solution of concentrated H_2SO_4 (48 mL) at ambient temperature there are added intermediate **2** (10 g, 48 mmoles), and then N-chlorosuccinimide (25 g, 187 mmoles). The mixture is heated at 80°C for 5 days. The reaction mixture is poured into an ice/water mixture (33 g/300 mL), and then a 28% NH_4OH solution is added to pH 8. The precipitate that forms is filtered off and then dissolved in AcOEt, the organic phase is dried over $MgSO_4$, concentration in vacuo yields intermediate **754** in the form of a beige solid (11 g), which can be used without additional treatment in the following step.

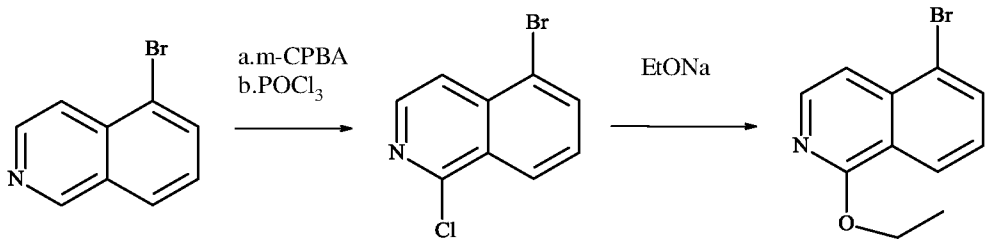
^{1}H NMR (300MHz-DMSO-d_6): δ 9.60 (s, 1H), 8.80 (d, 1H), 8.20 (d, 1H), 8.00 (d, 1H), 7.80 (d, 1H);

IR (cm^{-1}): 1607, 1568, 830, 631.



754

Protocol II : Preparation of 5-halo-1-alkoxyisoquinoline compounds



2 **123** **124**

Intermediate 123 :

To a solution of **2** (60 g, 288 mmoles) in methylene chloride (1.5 L) there are added (75 g, 436 mmoles) of 75% m-CPBA. The mixture is heated at 40°C for 20 hours. After HPLC monitoring and return to ambient temperature, 75 g of sodium thiosulphate are added in the course of 10 minutes, followed by 300 mL of water. The whole is decanted, the organic phase is washed with a 1N sodium hydroxide solution, and the organic phase is dried by

passage over $MgSO_4$. Evaporation under reduced pressure yields a white solid (42 g), which is used without additional treatment in the following step. A solution of the intermediate that forms (37 g, 165 mmoles) in methylene chloride (900 mL) and $POCl_3$ (37 mL) is stirred for 18 hours at 45°C. After HPLC and/or GC monitoring, the reaction mixture is concentrated in vacuo. The residue is treated carefully with water, and the aqueous phase is extracted with methylene chloride. The organic phase is washed carefully with a saturated $NaHCO_3$ solution and then with a saturated aqueous NaCl solution. Evaporation under reduced pressure yields intermediate **123** (33 g) in the form of a beige solid, which can be used without additional treatment in the following step.

^{1}H NMR (400MHz-$CDCl_3$): δ 8.35 (2d, 2H), 8.00 (2d, 2H), 7.55 (t, 1H)

GC-EI (70 eV): M+. = 241

Intermediate 124 :

To a solution of sodium ethoxide, prepared by adding sodium (10.3 g) to ethanol (323 mL), there is added intermediate **123** in portions (15 g, 62 mmoles). The mixture is heated for 2 hours. After HPLC monitoring and return to ambient temperature, the reaction mixture is poured into a mixture of water and ice (3 kg): the product precipitates. Filtration of the solid yields a solid which, by recrystallisation from acetonitrile, yields intermediate **124** (8.06 g).

^{1}H NMR (400MHz-DMSO-d_6): δ 8.20 (d, 1H), 8.15 (d, 1H), 8.10 (d, 1H), 7.55 (m, 1H), 7.45 (d, 1H), 4.55 (quad, 2H), 1.45 (t, 3H)

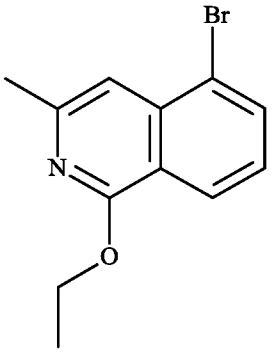
GC-EI (70 eV): $M^{+\cdot}$ = 251

This procedure was used to prepare intermediates **293** and **302**.

Intermediate 293 :

Obtained starting from intermediate **290** according to **protocol II**

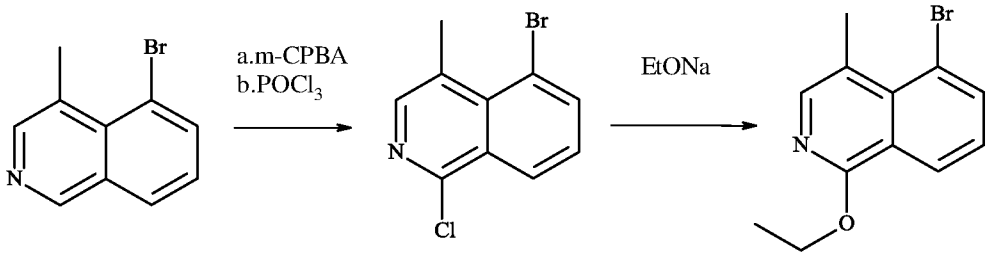
^{1}H NMR (400MHz-DMSO-d_6): δ 8.20 (td, 1H), 7.85 (dd, 1H), 7.35 (m, 1H), 7.30 (t, 1H), 4.55 (quad, 2H), 2.55 (s, 3H), 1.50 (t, 3H)



293

Intermediate 302 :

Obtained starting from **299** according to **protocol II**



299 **301** **302**

Intermediate 301 :

^{1}H NMR (400/500 MHz, dmso-d6): δ 8.29 (d, 1 H), 8.26 (d, 1 H), 8.22 (s, 1 H), 7.66 (m, 1 H), 2.94 (s, 3 H).

IR (cm^{-1}): 1603.

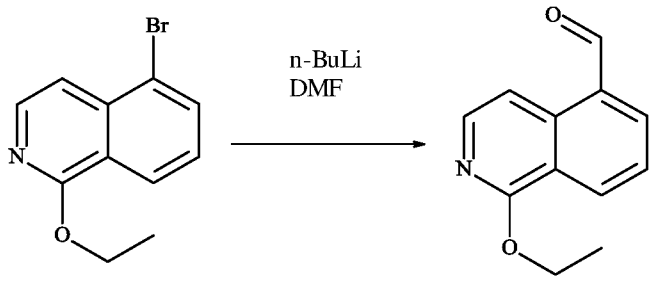
GC-EI (70 eV): M+. = 254.9

Intermediate 302 :

^{1}H NMR (400MHz-DMSO-d_6): δ 8.30 (dd, 1H), 8.10 (dd, 1H), 7.90 (broad s, 1H), 7.50 (t, 1H), 4.50 (quad, 2H), 2.80 (s, 3H), 1.40 (t, 3H)

Protocol III : Preparation of carbonylated isoquinoline intermediates according to a halogen-metal exchange reaction followed by formylation.

By way of example, the synthesis of intermediate **125** is described below:



124 **125**

Intermediate 125 :

A solution of intermediate **124** (21 g, 84 mmoles) in THF (106 mL) is added in the course of 35 minutes to a 2.5N solution of n-BuLi in hexane (67 mL, 168 mmoles) previously introduced into a THF/ethyl ether mixture (270 mL/270 mL) at -78°C. The reaction mixture is stirred for 1 hour at -78 C, and then a solution of DMF (10mL) in THF (30mL) previously cooled to -70 C is then introduced into the medium by means of a cannula in the course of 5 minutes. The reaction mixture is stirred for 35 minutes. Addition of 73 mL of ethanol and then 73 mL of a saturated aqueous NH_4Cl solution. Return to ambient temperature. The aqueous phase is extracted with ethyl ether and dried over $MgSO_4$, and evaporation under reduced pressure yields a yellow solid, which is purified on silica gel (eluant AcOEt/methylene chloride 10/90). Intermediate **125** (9 g) is obtained in the form of a yellow solid.

^{1}H NMR (400MHz ; DMSO-d_6): δ 10.41 (s, 1H), 8.53 (ddd, 1H), 8.44 (dd,1H), 8.41 (dd,1H), 8.19 (d,1H), 7.85 (dd,1H), 4.55 (quad, 2H), 1.45 (t, 3H).

IR (cm^{-1}): 1691.

This protocol was used to prepare the intermediates of the table below:

Int.	Obtained from	Nomenclature Analytical description
3	**2**	**isoquinoline-5-carbaldehyde** **^{1}H NMR** (300MHz ; DMSO-d_6): δ 10.50 (s, 1H), 9.50 (d, 1H), 8.90 (d,1H), 8.70 (d,1H), 8.50 (t and d,1H), 7.95 (dd,1H) **IR (cm^{-1})**: 1693-1679
294	**293**	**1-ethoxy-3-methyl-isoquinoline-5-carbaldehyde** **^{1}H NMR** (400MHz ; DMSO-d_6): δ 10.37 (s, 1H), 8.46 (d,1H), 8.34 (d,1H), 8.30 (s,1H), 7.73 (dd,1H), 4.53 (quad, 2H), 2.53 (s, 3H), 1.45 (t, 3H) **IR (cm^{-1})**: 1684
303	**302**	**1-ethoxy-4-methyl-isoquinoline-5-carbaldehyde** **^{1}H NMR** (400MHz ; DMSO-d_6): δ 10.90 (s, 1H), 8.50 (dd,1H), 8.20 (dd,1H), 8.00 (s,1H), 7.75 (t,1H), 4.50 (quad, 2H), 2.60 (s, 3H), 1.45 (t, 3H) **IR (cm^{-1})**: 1677
321	**299**	**4-methyl-isoquinoline-5-carbaldehyde** **^{1}H NMR** (400MHz ; DMSO-d_6): δ 10.90 (s, 1H), 9.20 (s,1H), 8.50 (s,1H), 8.25-8.20 (2d, 2H), 7.70 (t,1H), 2.80 (s, 3H)
755	**754**	**8-chloroisoquinoline-5-carbaldehyde** **^{1}H NMR** (400MHz ; DMSO-d_6): δ 10.50 (s, 1H), 9.70 (s, 1H), 9.00 (d, 1H), 8.40 (d, 1H), 8.35 (d, 1H), 8.10 (d 1H) **IR (cm^{-1})**: 1679

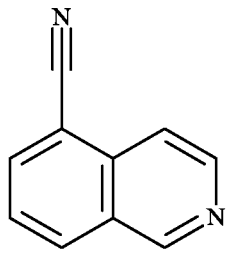
Protocol IV: Preparation of intermediate 655

Intermediate 653 :

To a solution (degassed with nitrogen) of intermediate **2** (45 g, 216 mmoles) in DMF (450 mL) there are added $Zn(CN)_2$ (30 g) and $Pd(PPh_3)_4$ (9.8 g). The mixture is heated at 100°C for 2 hours. After return to ambient temperature, the mixture is taken up in AcOEt (200 mL) and water (2 L). The mixture is brought to pH>8 by addition of a 20% aqueous NaOH solution. After addition of AcOEt (200 mL), the organic phase is recovered by decantation, filtered over Celite®, washed with a saturated aqueous NaCl solution and then dried over $MgSO_4$ before being concentrated in vacuo. The solid is ground and dried in vacuo and taken up in a 1N aqueous HCl solution (1 L), and the acidic aqueous phase is washed with AcOEt and then treated with a 20% aqueous NaOH solution, the precipitate that forms is collected and dissolved in methylene chloride. The solution is dried over $MgSO_4$, and evaporation in vacuo yields intermediate **653** in the form of a beige solid (24 g).

^{1}H NMR (400MHz; DMSO-d_6): δ 9.53 (s, 1H), 8.76 (d, 1H), 8.54 (d, 1H), 8.45 (d, 1H), 7.96 (d, 1H), 7.87 (t, 1H)

IR (cm^{-1}): 2226.



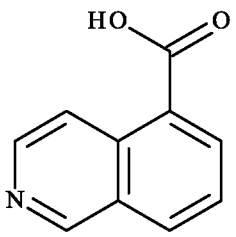
653

Intermediate 654 :

To a 37% HCl solution (137 mL) there is added intermediate **653**, and the mixture is heated at reflux for 20h. After return to ambient temperature, the precipitate is collected on a frit, washed with acetone and dried in an oven at 50°C in vacuo (10^{-2} mbar). The hydrochloride of intermediate **654** is obtained in the form of a white solid (33 g), which is used in the following step without additional purification.

^{1}H NMR (300MHz; DMSO-d_6): δ 10.00 (s, 1H), 9.20 (d, 1H), 8.00 (m, 3H), 8.10 (t, 1H)

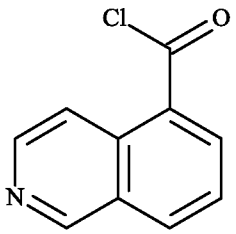
IR (cm^{-1}): 1695, 1214



654

Intermediate 655 :

Intermediate **654** (20 g, 95 mmoles) is added carefully to thionyl chloride (200 mL). The mixture is heated for 15 hours at 80°C. After return to ambient temperature, the mixture is filtered; (careful) concentration in vacuo of the filtrate yields the hydrochloride of **655** in the form of a brown solid, which is quickly used in the aromatic electrophilic substitution step (**Protocol XXIII**). The product can be analysed in its methyl ester form (by derivation from methanol).

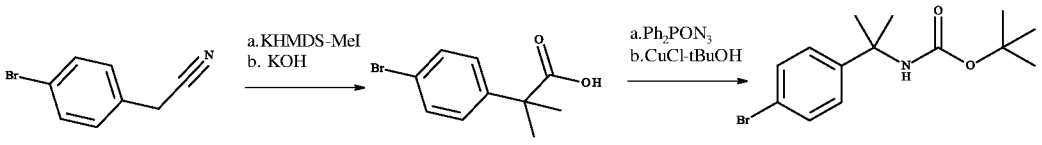


655

Preparation of phenyl precursors – general protocols

Protocol V : Preparation of amine intermediates starting from phenylacetonitrile intermediates

By way of example, the synthesis of intermediate **601** is described below:



599 **601**

Intermediate 599 :

Step 1

To a solution of KHMDS (50 g) in THF (300 mL) cooled to 0°C there is added slowly a solution of commercial (4-bromophenyl)acetonitrile (16 g, 81 mmoles) in THF (90 mL), the temperature being maintained below 3°C. The mixture is stirred for 40 minutes at 0°C, and then methyl iodide (11.7 mL) is added in the course of 50 minutes at a temperature below 8°C. The mixture is stirred at ambient temperature for 20 hours and then poured carefully into ice-water (1.5 L). The aqueous phase is extracted with Et_2O, and the organic phase is washed with a saturated aqueous NaCl solution, dried and concentrated in vacuo. The residue is chromatographed on silica gel (eluant CH_2Cl_2/cyclohexane (60/40)). The expected intermediate (13 g) is obtained in the form of a white solid.

^{1}H NMR (300MHz, $CDCl_3$): δ 7.52 (d, 2H), 7.36 (d, 2H), 1.75 (s, 6H)

IR (cm^{-1}): 2237

Step 2

A solution of the intermediate obtained above (5 g, 22 mmoles) and of KOH (2.4 g) in a mixture of ethanol (25 mL) and water (7.5 mL) is heated at reflux for 20 hours. The reaction mixture is concentrated in vacuo, and the residue is taken up with ethyl ether (100 mL) and water (60 mL). The aqueous phase (free of organic solvent) is cooled to 10°C and then acidified with a 37% HCl solution. The precipitate that forms is collected on a frit and dried in vacuo. Intermediate **599** (5.3 g) is obtained in the form of a white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ 9.00-8.00 (1H), 7.75 (d, 2H), 7.25 (d, 2H), 1.60 (s, 6H)
IR (cm^{-1}): 3347-2235, 1697

Intermediate 601 :

Step 1

To a solution of intermediate **599** (2.6 g, 10.7 mmoles) in toluene (60 mL) there are added NEt_3 (1.6 mL) and PhO_2PON_3 (2.3 mL). The resulting mixture is heated at reflux for 20 hours. After return to ambient temperature, a saturated aqueous $NaHCO_3$ solution is added. The organic phase is extracted with Et_2O, washed with a saturated aqueous NaCl solution, dried and concentrated in vacuo. The residue is chromatographed on silica gel (eluant CH_2Cl_2/cyclohexane (50/50)). The expected intermediate (1.8 g) is obtained in the form of a colourless oil.

^{1}H NMR (300MHz, $CDCl_3$): δ 7.50 (d, 2H), 7.35 (d, 2H), 1.70 (s, 6H)
IR (cm^{-1}): 2248

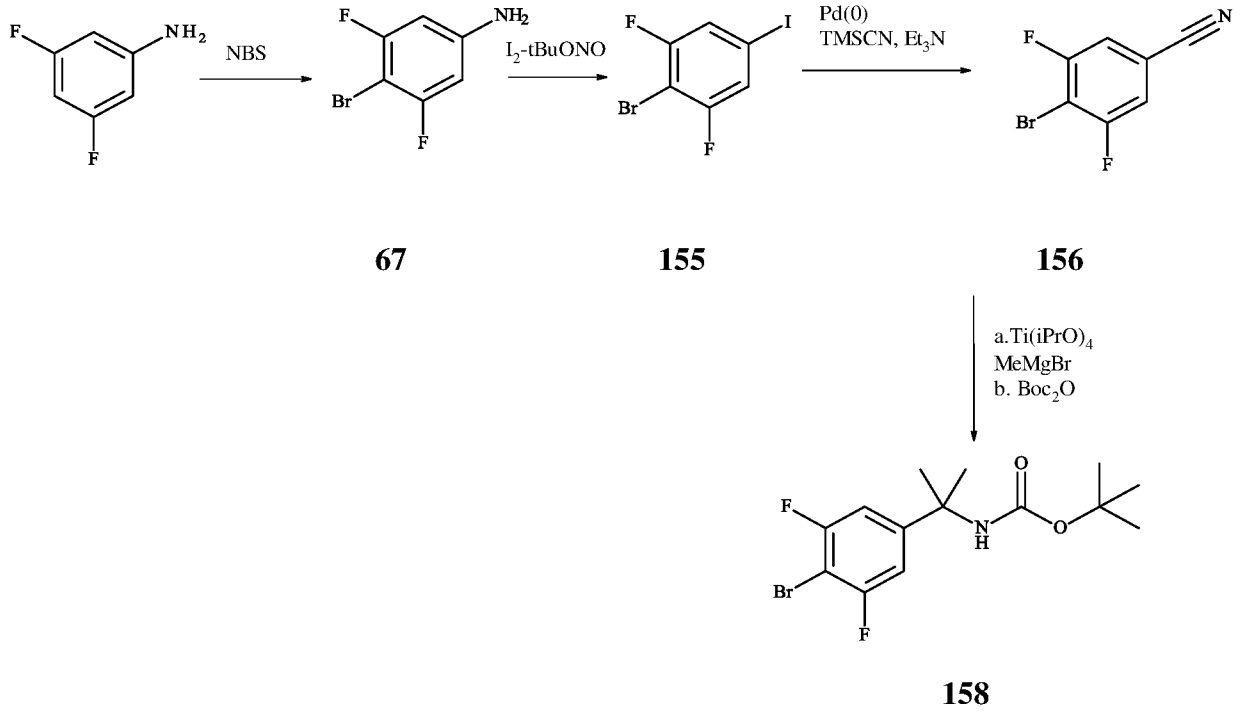
Step 2

To a mixture of tert-butanol (3.5 mL) and CuCl (0.74 g) in DMF (30 mL) there is added a solution of the intermediate obtained above (1.8 g, 7.5 mmoles) in DMF (10 mL). The mixture is stirred at ambient temperature for 5 hours. The reaction mixture is extracted with Et_2O. The organic phase is washed with a saturated NaCl solution, dried and concentrated in vacuo. The residue is chromatographed on silica gel (eluant CH_2Cl_2/AcOEt (100/0 to 95/5)). Intermediate **601** (1.2 g) is obtained in the form of a white solid.

^{1}H NMR (300 MHz; $CDCl_3$)**:** δ 7.45 (d, 2H); 7.30 (d, 2H) ; 4.90 (m, 1H) ; 1.60 (s, 6H) ; 1.35 (broad s, 9H)
IR (cm^{-1}) : 3265 ; 1698

Protocol VI : Preparation of protected amine intermediates starting from benzonitrile intermediates

By way of example, the synthesis of intermediate **158** (tert-butyl [2-(4-bromo-3,5-difluorophenyl)propan-2-yl]carbamate) is described below:



67 **155** **156**

158

Intermediate 67 :

2-Bromo-1,3-difluoro-5-aniline

To a solution of commercial 3,5-difluoronaniline (100 g, 770 mmoles) in DMF (310 mL) there is added a solution of N-bromosuccinimide (140 g, 786 mmoles) in DMF (310 mL) in the course of 40 minutes. The resulting solution is stirred at ambient temperature for 1½ hours. The whole is transferred to 8 L of water, which causes the desired intermediate to precipitate. The solid is filtered over a frit and then rinsed with copious amounts of water. The solid obtained is dried in the air for 48 hours : 148 g of the expected intermediate in the form of a white solid are obtained and used without additional treatment in the following step.

^{1}H NMR (400MHz, DMSO-d_6): δ 6.3 (2d, 2H), 3.90 (m, 2H)

IR (cm^{-1}): 3479-3392;

Intermediate 155 :

2-Bromo-1,3-difluoro-5-iodobenzene

Diiodine (365.48 g ; 1.44 moles) and tert-butyl nitrite (85 mL) are dissolved in acetonitrile (320 mL). A solution of the intermediate obtained above (100 g ; 0.48 mole) in acetonitrile

(210 mL) is added slowly to the reaction mixture (Tmax : 35°C). The mixture is stirred at ambient temperature for 50 minutes. An aqueous $Na_2S_2O_3$ solution is then added until the reaction mixture is discoloured. The aqueous phase is then extracted with Et_2O and then dried over $MgSO_4$ and concentrated under reduced pressure. The residue is purified by chromatography on silica (solid deposit (100 % cyclohexane)). Intermediate **155** (143 g) is obtained in the form of a yellow solid.

^{1}H NMR (400MHz, DMSO-d_6): δ 7.72 (d, 2H)

IR (cm^{-1}): 3080

Intermediate 156 :

4-Bromo-3,5-difluorobenzonitrile

To a solution of intermediate **155** (10 g, 31 mmoles) in triethylamine (63 mL) there are added TMSCN (6.2 mL) and then $Pd(PPh_3)_4$ (1.8 g). The reaction mixture is brought to 80°C, and 1.8 g of $Pd(PPh_3)_4$ are again added. The solution colours and a precipitate forms. After GC monitoring, the reaction mixture is returned to ambient temperature and then 50 mL of toluene are added. The mixture is filtered, and the filter is rinsed twice with 50 mL of toluene. The filtrate is treated with 300 mL of 1N HCl, and then with a saturated aqueous NaCl solution. Evaporation under reduced pressure yields 19 g of a solid. The residue is purified by chromatography on silica (solid deposit (100 % cyclohexane)). Intermediate **156** (5.6 g) is obtained in the form of a yellow solid.

^{1}H NMR (300MHz, DMSO-d_6): δ 7.98 (m, 2H)

IR (cm^{-1}): 2236, 1032; **GC-EI** (70 eV): 216.9

Intermediate 158 :

Step 1

To a solution of intermediate **156** (13.6 g, 62 mmoles) in ethyl ether (330 mL) there is added CH_3MgBr (3M in Et_2O) (65 mL, 195 mmoles). The mixture is stirred for 35 minutes at ambient temperature, and then $Ti(OiPr)_4$ (19 mL, 64 mmoles) is added. The reaction mixture is stirred overnight at ambient temperature and then treated carefully with a 20% aqueous NaOH solution (50 mL). The mixture was decanted in the presence of AcOEt and of a saturated aqueous NaCl solution, and the organic phase is dried over $MgSO_4$ and then

concentrated in vacuo. The residue is chromatographed on silica (eluant CH_2Cl_2/EtOH (100/0 to 95/05)). The expected intermediate **157** (6.2 g) is obtained in the form of an oil.

^{1}H NMR (400MHz, DMSO-d_6): δ 7.41 (d, 2H), 2.0 (broad s, 2H), 1.34 (s, 6H)

IR (cm^{-1}): 3375-3288, 1021.

Step 2

To a solution of the intermediate obtained above (4.2 g, 16.8 mmoles) in methylene chloride (80 mL) there is added carefully di-tert-butyl dicarbonate (3.56 g, 16.3 mmoles). The reaction mixture is stirred at ambient temperature for 3 days before being treated with a 1N HCl solution. The organic phase is dried and then concentrated in vacuo. The residue is chromatographed on silica gel using an eluant mixture CH_2Cl_2/cyclohexane (50/50 to 100/0). Intermediate **158** (4.3 g) is obtained in the form of an amorphous solid.

^{1}H NMR (300 MHz ; DMSO-d_6) **:** δ 7.13 (d, 2H) ; 6.85 (m, 1H) ; 1.50 (s, 6H) ; 1.30 (s, 9H)

IR (cm^{-1}) : 3318 ; 1683

Protocol VII : Preparation of ketones by Sandmeyer reaction

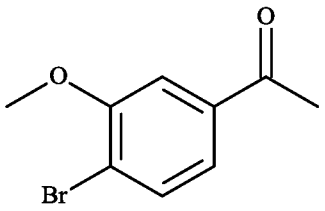
By way of example, the synthesis of intermediate **681** is described below:

Intermediate 681 :

To a mixture of commercial 4-bromo-3-methoxyaniline (10.2 g, 50.6 mmoles) in HCl_{cc}/H_2O (11/25 mL) previously cooled to -5°C there is added in portions $NaNO_2$ (3.48 g). The reaction mixture is stirred for 1h at 0°C before being transferred to a mixture of acetaldoxime (6.02 g), $CuSO_4$ (2.52 g), AcONa.3H_2O (36.64 g) in water (20.5 mL) at 0°C. The resulting mixture is stirred between 0°C and 10°C for 2h, and then 37% HCl (23 mL) is added and the mixture is refluxed for 2 hours. After return to ambient temperature, the mixture is extracted with heptane, and the organic phase is dried over $MgSO_4$. Evaporation of the organic phase in vacuo yields a residue, which is chromatographed on silica gel (eluant CH_2Cl_2/cyclohexane (50/50 to 90/10)). Intermediate **681** (5.9 g) is obtained in the form of an amorphous solid.

^{1}H NMR (400 MHz ; $CDCl_3$) **:** δ 7.55 (d, 1H) ; 7.50 (d, 1H) ; 7.40 (dd, 1H) ; 3.95 (s, 3H) ; 2.60 (s, 3H)

IR (cm^{-1}) : 1681



681

Protocol VIII : Obtaining ketones by reaction of a magnesium compound with benzonitriles

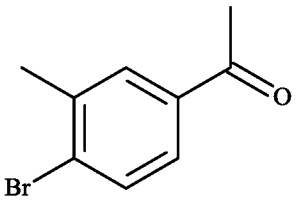
By way of example, the synthesis of intermediate **9** is described below:

Intermediate 9 :

At ambient temperature, methylmagnesium iodide (3 M in diethyl ether) (17 mL, 51 mmoles) is added dropwise to a solution of commercial 4-bromo-3-methylbenzonitrile (10 g, 51 mmoles) in diethyl ether (100 mL). The reaction mixture is heated at reflux for 16 hours. After return to ambient temperature, 60 mL of 6N hydrochloric acid are added, and the mixture is then heated at reflux for 6 hours. After cooling, the aqueous and organic phases are separated, and the aqueous phase is extracted with 40 mL of ethyl acetate. The organic phases are combined, washed with a saturated aqueous NaCl solution (2 x 40 mL), dried over $MgSO_4$ and then concentrated under reduced pressure. 4.5 g of intermediate **9** are obtained in the form of a brown oil.

^{1}H NMR (300MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.62 (s, 2H), 2.60 (s, 3H), 2.45 (s, 3H)

IR (cm^{-1}) : 1681



9

Protocol IX : Obtaining ketones by Weinreb reaction

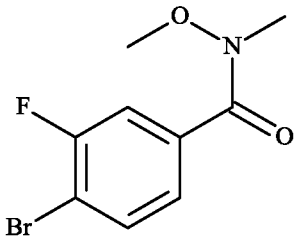
By way of example, the synthesis of intermediate **37** is described below:

Intermediate 36 :

To a suspension of commercial 4-bromo-3-fluoro-benzoic acid (5 g, 22.8 mmoles) in methylene chloride (70 mL) there are added DMF (0.1 mL) and then oxalyl chloride (2.1 mL). The mixture is stirred at ambient temperature for 4 hours, and then it is concentrated in vacuo. The residue is taken up in methylene chloride (220 mL), and N-methyl-methoxylamine hydrochloride is added thereto. The mixture is cooled to 5°C, and pyridine is added (4 mL). The mixture was stirred for 2 hours and then washed with a 2N aqueous HCl solution, and the organic phase is dried over $MgSO_4$ and then concentrated in vacuo. Intermediate **36** is obtained in the form of a solid (5.4 g).

^{1}H NMR (300MHz, DMSO-d_6): δ 7.85 (dd, 1H), 7.60 (dd, 1H), 7.40 (dd, 1H), 3.59 (s, 3H), 3.29 (s, 3H)

IR (cm^{-1}) : 1657



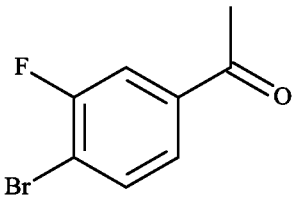
36

Intermediate 37 :

At -70°C, intermediate **36** (5.4 g, 20.6 mmoles) in solution in THF (75 mL) is treated with a solution of methylmagnesium bromide (3 M in diethyl ether) (8.1 mL, 24 mmoles). The mixture is stirred with return to ambient temperature for 3 hours before being poured into a 1N aqueous HCl solution at 0°C. The product is extracted with AcOEt, and the organic phase is washed with a saturated aqueous NaCl solution, dried over $MgSO_4$ and then concentrated in vacuo. Intermediate **37** is obtained in the form of a solid (3.6 g).

^{1}H NMR (300 MHz ; $CDCl_3$): δ 7.7-7.6 (m, 3H), 2.58 (s,3H)

IR (cm^{-1}) : 1679



37

Protocol X : Obtaining ketones by Stille reaction

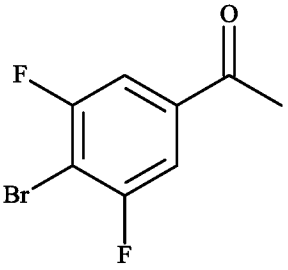
By way of example, the synthesis of compound **61** is described below:

Intermediate 61 :

To a solution, degassed with nitrogen, of 44 g (137 mmoles, 1 eq.) of intermediate **155** in 1.7 L of DMF there are added tri-butyl-(1-ethoxyvinyl)tin (65 mL, 179 mmoles) and then $PdCl_2(PPh_3)_2$ (13 g, 0.18 mmole). The mixture is heated at 80°C until the starting intermediate has disappeared (GC monitoring). After return to ambient temperature, the reaction mixture is decanted with 3 L of water and 1 L of Et_2O. The organic phase is dried over $MgSO_4$ and then concentrated. The residue so obtained is taken up in 300 mL of THF and stirred for 1 hour in the presence of a 1N aqueous HCl solution (100 mL). The mixture is then decanted in the presence of 1 L of Et_2O, and the organic phase is dried over $MgSO_4$. Evaporation under reduced pressure yields 56 g of an oil. The oil is chromatographed on silica gel (cyclohexane/methylene chloride 80/20 to 50/50). Intermediate **61** (27 g) is obtained in the form of a beige solid, which is used without additional treatment in the following step.

^{1}H NMR (300MHz, $CDCl_3$): δ 7.50 (d, 2H), 2.60 (s, 3H)

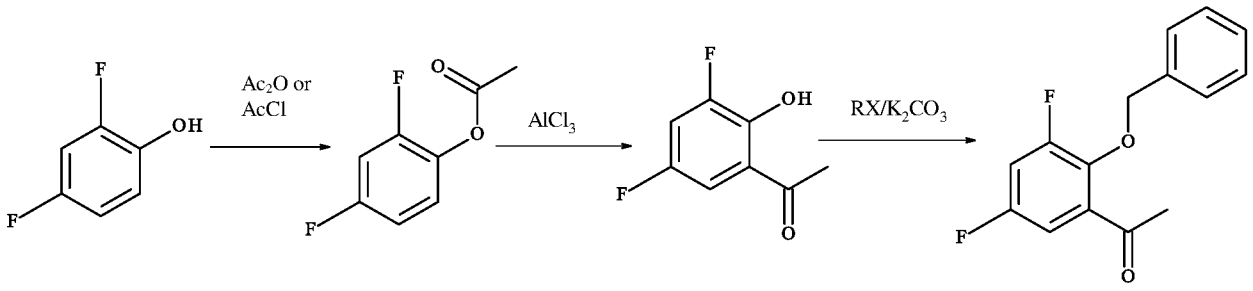
IR (cm^{-1}): 1694



61

Protocol XI : Obtaining ketones by Fries rearrangement

By way of example, the synthesis of intermediate **547** is described below:



362 **363** **547**

Intermediate 362 :

To a mixture of commercial 2,4-difluorophenol (15 g, 115 mmoles) and pyridine (10.2 mL) in methylene chloride (156 mL) there is added acetyl chloride (8.6 mL), the temperature being maintained below 30°C. The resulting mixture (formation of a precipitate) is stirred for 1 hour at ambient temperature before being hydrolysed. The mixture is decanted, and the organic phase is washed in succession with a 1N aqueous HCl solution and a saturated aqueous $NaHCO_3$ solution and is then dried over $MgSO_4$. Evaporation under reduced pressure yields intermediate **362** in the form of an oil (19.4 g), which is used in the following step.

^{1}H NMR (300MHz, $CDCl_3$): δ 7.10 (m, 1H), 6.90 (m, 2H), 2.30 (s, 3H)

IR (cm^{-1}) : 1770

Intermediate 363 :

A mixture of intermediate **362** (2 g, 11.6 mmoles) and $AlCl_3$ (2.8 g) is heated under argon at 150°C for 30 minutes. After return to ambient temperature, there are added carefully ice and then a 1N aqueous HCl solution. The mixture is decanted in the presence of toluene, and the organic phase is washed with water and then with a saturated aqueous NaCl solution. After drying, evaporation under reduced pressure yields intermediate **363** in the form of a solid (1.5 g).

^{1}H NMR (300MHz, $CDCl_3$): δ 12.00 (m, 1H), 7.25 (m, 1H), 7.10 (m, 1H), 2.65 (s, 3H)

IR (cm^{-1}) : 1651

Intermediate 547 :

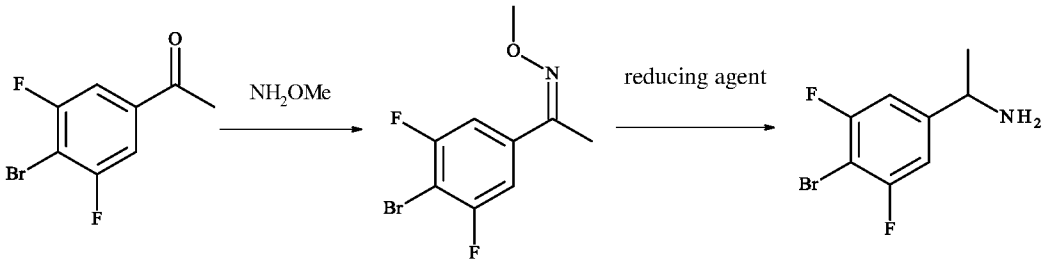
To a solution of intermediate **363** (15 g, 87 mmoles) in acetone (150 mL) there are added K_2CO_3 (24 g) and then benzyl bromide (10.8 mL, 91 mmoles). The mixture is stirred at ambient temperature for 24 hours. The salts are filtered off and the filtrate is evaporated off. The residue is taken up in Et_2O and then washed with water and with a saturated aqueous NaCl solution. After drying over $MgSO_4$, evaporation under reduced pressure yields intermediate **547** in the form of an oil (22.5 g).

^{1}H NMR (400MHz, $CDCl_3$): δ 7.40 (m, 5H), 7.15 (m, 1H), 7.00 (m, 1H), 5.10 (s, 2H), 2.50 (s, 3H)

IR (cm^{-1}) : 1687

Protocol XII : Conversion of ketones into racemic amines

By way of example, the synthesis of intermediate **48** is described below:



61 **62** **48**

Intermediate 62 :

To a mixture of 26 g (110 mmoles) of intermediate **61** in 53 mL of ethanol there are added 107 mL of water, 11.8 g (141 mmoles) of methoxylamine hydrochloride and 11.8 g (142 mmoles) of sodium acetate. The mixture is heated for 3 hours at 70°C. The mixture is returned to ambient temperature and then extracted with AcOEt (0.5 L) in the presence of a saturated aqueous NaCl solution. The organic phase is dried over $MgSO_4$. Evaporation under reduced pressure yields 27.7 g of the mixture of oximes **62** in the form of a light-brown solid, which is used without additional treatment in the following step.

IR (cm^{-1}) : 1025

Intermediate 48 :

At ambient temperature, 210 mL (210 mmoles, 2 eq.) of a 1M solution of BH_3.THF in THF are added in the course of 10 minutes to a solution of 27 g (105 mmoles, 1 eq.) of the mixture of oximes **62** in 114 mL of THF. The solution obtained is heated at 70°C for 2½ h. After HPLC monitoring, the mixture is returned to ambient temperature. A 2N solution of HCl in ether (2 eq.) is added carefully to the mixture. The mixture is heated for 1 h at 40°C. Filtration of the solid yields 11.8 g of the hydrochloride of intermediate **48**.

^{1}H NMR (400MHz ; DMSO-d_6): δ 8.65 (m, 3H), 7.53 (d, 2H), 4.46 (quad, 1H), 1.51 (d, 3H)

IR (cm^{-1}): 3200-2500

This procedure is used to prepare the racemic amines in the form of hydrochlorides or of free bases.

<u>Protocol XIIb : Alternative process for the conversion of ketones into racemic amines</u>

By way of example, the synthesis of intermediate **341** is described below:

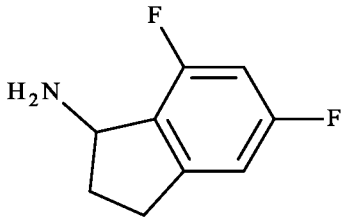
Intermediate 341 :

To a solution of commercial 5,7-difluoro-2,3-dihydro-1H-inden-1-one (6 g, 35 mmoles) in pyridine (60 mL) at ambient temperature there is added methoxylamine hydrochloride (3.0 g, 37 mmoles). The reaction mixture is stirred for 20 hours at ambient temperature. The pyridine is evaporated off in vacuo, and the residue is stirred in water (30 mL) for 1 hour and then collected on a frit. The solid is rinsed with water and then dried in vacuo at 50°C. The oxime intermediate is obtained in the form of a white solid (6.5 g), which is then reduced to intermediate **341** according to the process described for intermediate **48**.

^{1}H NMR (300MHz ; DMSO-d_6): δ 7.10 (m, 2H), 6.50 (m, 3H), 4.80 (m, 1H), 3.25 (m, 1H), 2.95 (m, 1H), 2.50 (m, 1H), 2.15 (m, 1H)

^{19}F NMR: -107.6, -110.8 (quad and dd, 2F)

IR (cm^{-1}): 3380-2500



341

Protocol XIII : Conversion of ketones into chiral tert-butanesulphinylamine intermediates

Bibliographical reference: John T. Colyer, Neil G. Andersen,* Jason S. Tedrow, Troy S. Soukup, and Margaret M. Faul. J. Org. Chem. **2006**, 71, 6859-6862

By way of example, the synthesis of intermediate **286** is described below:

Intermediate 286 :

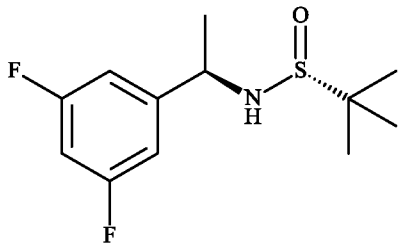
To a solution of commercial 1-(3,5-difluorophenyl)ethanone (20 g, 120 mmoles) in THF (332 mL) there are added in succession $Ti(OEt)_4$ (34 mL, 163 mmoles) and then (R)-(+)-2-methyl-2-propanesulphinamide (14.5 g, 119 mmoles). The mixture is heated for 24 hours at 70°C. The mixture, cooled to –40°C, is transferred by cannulation to a suspension of $NaBH_4$ (18.1 g; 374 mmoles) in THF (220 mL). The reaction mixture at ambient temperature is treated carefully with methanol (56 mL) and then diluted with AcOEt (300 mL) and an aqueous NaCl solution (700 mL). The resulting mixture is filtered over Celite®, which is rinsed with THF and AcOEt. The filtrate is decanted, and the organic phase is dried over $MgSO_4$. Evaporation under reduced pressure yields a white solid, which is purified on silica gel using an AcOEt/methylene chloride elution gradient 0/100 to 40/60. The diastereoisomer **286** (18 g) is isolated in the form of a white solid.

^{1}H NMR (400MHz; DMSO-d_6): δ 7.15 (m, 2H), 7.08 (m, 1H), 5.29 (d, 1H), 4.40 (m, 1H), 1.38 (d, 3H), 1.10 (s, 9H)

IR (cm^{-1}): 3146, 1043

GC-EI (70 eV): $M^{+\cdot}$= 261.1

Diastereoisomeric purity: de>99%



286

Protocol XIIIb : Alternative method for the preparation of chiral tert-butanesulphinylamine intermediates

The preparation of chiral tert-butanesulphinylamine intermediates can be broken down according to the sequence described for intermediate **331**.

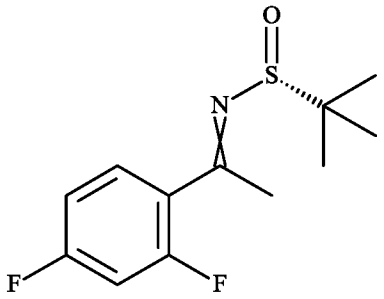
Intermediate 330 :

To a solution of commercial 1-(2,4-difluorophenyl)ethanone (4 g, 25.6 mmoles) in 80 mL of THF there are added in succession $Ti(OEt)_4$ (13.1 g, 46 mmoles) and then (R)-(+)-2-methyl-2-propanesulphinamide (3.1 g, 25 mmoles). The mixture is heated for 24 hours at 70°C. The reaction mixture, cooled to about 15°C, is poured into a saturated aqueous NaCl solution, and then ethyl acetate is added. After stirring (30 minutes), the mixture is filtered over Celite® and washed with 2 times 80 mL of ethyl acetate. The filtrate is decanted, and the organic phase is dried over $MgSO_4$, filtered and evaporated to dryness. The residue is purified by flash chromatography on silica (eluant: CH_2Cl_2/AcOEt : 95/5). Intermediate **330** (5.2 g) is obtained in the form of a yellow liquid.

^{1}H NMR (400MHz; DMSO-d_6): δ 7.80 (m, 1H), 7.40 (m, 1H), 7.20 (m, 1H), 2.70 (s, 3H), 1.20 (s, 9H)

IR (cm^{-1}): 1603, 1080

GC-EI (70 eV): $M^{+\cdot}$= 259.1



330

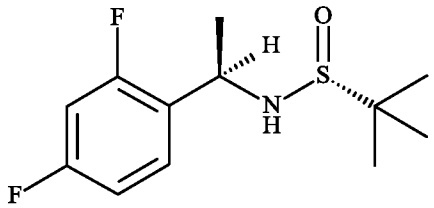
Intermediate 331 :

To a solution of intermediate **330** (2.5 g, 9.64 mmoles) in 50 mL of THF, cooled to -60°C, there is added $NaBH_4$ (366 mg, 9.64 mmoles). After return to ambient temperature, the reaction mixture is treated carefully with methanol and then concentrated in vacuo. The residue is taken up in water and extracted with ether. The organic phase is washed with a saturated aqueous NaCl solution and then dried over $MgSO_4$. The residue is purified by flash chromatography on silica (eluant: CH_2Cl_2/AcOEt : 80/20). Intermediate **331** is obtained (1.85 g) in the form of a white crystalline solid.

^{1}H NMR (300MHz; DMSO-d_6): δ 7.60 (m, 1H), 7.20 (m, 1H), 7.10 (m, 1H), 5.75 (d, 1H), 4.60 (quint, 1H), 1.4 (d, 3H), 1.1 (s, 9H)

IR (cm^{-1}): 3243, 1603, 853, 814

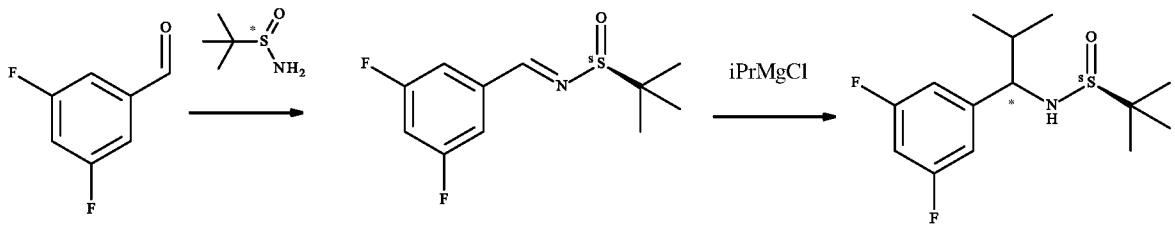
Diastereoisomeric purity: de>99%



331

<u>Protocol XIV: Conversion of commercial aldehydes into chiral tert-butanesulphinylamine intermediates</u>

By way of example, the synthesis of intermediate **497** N-[1-(3,5-difluorophenyl)-2-methylpropyl]-2-methylpropane-2-sulphinamide) is described below:



(495) **496** **497**

Intermediate 496 :

To a solution of (S)-(-)-2-methylpropane-2-sulphinamide (44.7 g, 368 mmoles) in methanol (500 mL) there is added at ambient temperature tBuOK (3.93 g). After 15 minutes' stirring at ambient temperature, commercial 3,5-difluoro-benzaldehyde (50 g, 0.35 mole) is added. The reaction mixture is stirred at ambient temperature for 1 hour and then it is hydrolysed with a saturated aqueous NH_4Cl solution. Evaporation of the methanol in vacuo allows a solid to crystallise, which solid is taken up in 300 mL of water, filtered and washed with water. The solid is dissolved in ether, washed with a saturated aqueous NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. Intermediate **496** (74.5 g) is obtained in the form of an oil, which crystallises.

^{1}H NMR (400MHz, DMSO-d_6): δ 8.58 (s, 1H), 7.70 (broad d, 2H), 7.50 (t, 1H), 1.25 (s, 9H)

IR (cm^{-1}): 1620, 1142,1078

Intermediate 497 :

To a solution of intermediate **496** (3 g, 12 mmoles) in THF (60 mL), cooled to -65°C, there is added a solution of isopropylMgBr (3M/ether) (9 mL, 27 mmoles) in the course of 20 minutes. After monitoring, the reaction mixture is hydrolysed at -40°C with a saturated aqueous NH_4Cl solution. The mixture is decanted in the presence of ethyl ether, and the organic phase is washed with a saturated NaCl solution, dried over $MgSO_4$ and then concentrated. Chromatography on silica (eluant CH_2Cl_2/AcOEt 99/1 to 85/15) yields intermediate **497** (2.7 g) in the form of an oil.

^{1}H NMR (400MHz, DMSO-d_6): δ 7.05 (m, 3H), 5.35 (d, 1H), 4.0 (t, 1H), 2.0 (m, 1H), 1.05 (s, 9H), 1.0-0.8 (2d, 6H)

IR (cm^{-1}): 3189, 1116, 1040

Protocol XV : Preparation of tert-butylcarbamate compounds

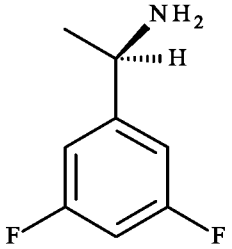
The chiral auxiliary was cleaved in an acidic medium according to the following protocol:

Intermediate 287 :

A solution of intermediate **286** (18 g, 69 mmoles) in ethyl ether (580 mL) is treated with hydrochloric acid in Et_2O (2M solution, 59 mL). The reaction mixture is stirred for 20 hours at ambient temperature. The precipitate is filtered over a frit and then dried in vacuo. The hydrochloride of **287** (11.5 g, ee > 99%) is obtained in the form of a white solid.

^{1}H NMR (300MHz, DMSO-d_6): δ 8.68 (broad s, 3H), 7.32 (m, 2H), 7.27 (m, 1H), 4.45 (quad, 1H), 1.50 (d, 3H)

IR (cm^{-1}): 3100-2500



287

The amines obtained are protected in the form of tert-butylcarbamates according to the procedure described for intermediate **158** (**protocol VI**).

When hydrochlorides are obtained, they are treated with 1N sodium hydroxide and the amines obtained are protected as indicated above.

Protocol XVI : Preparation of trifluoroacetamide compounds

By way of example, the procedure for preparing intermediate **17** is described below:

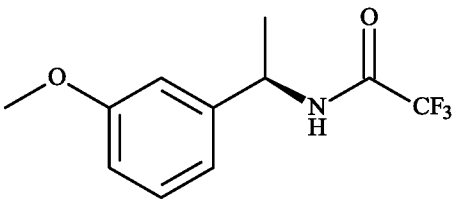
Intermediate 17 :

To a solution of commercial (R)-(+)-1-(3-methoxyphenyl)ethylamine (50 g, 330 mmoles) in methylene chloride (400 mL) at ambient temperature there is added slowly a solution of

trifluoroacetic anhydride (46 mL, 330 mmoles). The mixture is stirred at ambient temperature for 2½ hours. The reaction mixture is washed with a 1N aqueous HCl solution (400 mL). The whole is decanted, and the organic phase is dried by passage over $MgSO_4$. Evaporation under reduced pressure yields intermediate **17** (84 g) in the form of a solid, which is used without additional treatment in the following step.

^{1}H NMR (400 MHz, $CDCl_3$) **:** δ 7.30 (m, 1H), 6.90 (2d and s, 3H), 6.45 (broad s, 1H), 5.10 (m, 1H), 3.80 (s, 3H), 1.60 (d, 3H)

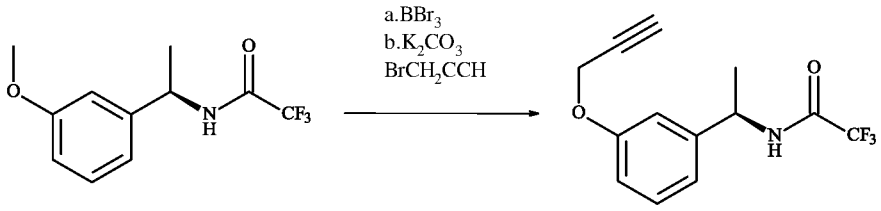
IR (cm^{-1}): 3293, 1696, 1612, 1588



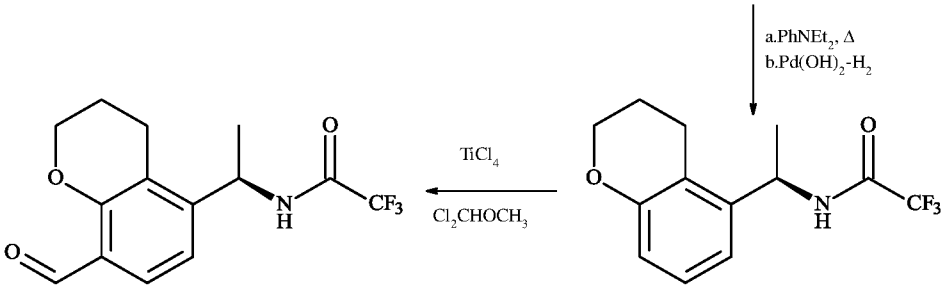
17

Protocol XVII

By way of example, the preparation of **94** is described below:



17 **90**



94 **93**

Intermediate 90 :

To a solution of intermediate **17** (65 g, 262 mmoles) in methylene chloride (800 mL) at -70°C there is added slowly a solution of BBr_3 (1M in CH_2Cl_2) (480 mL, 480 mmoles). The mixture is brought to ambient temperature over a period of 2 hours. After HPLC monitoring, the reaction mixture is cooled to –70°C and treated carefully with methanol (200 mL). The solution is concentrated in vacuo, the residue is taken up carefully in water (300 mL), and the mixture is treated with NaOAc until pH 4-5 is reached. The whole is decanted in the presence of methylene chloride (500 mL), and the organic phase is dried by passage over $MgSO_4$. Evaporation under reduced pressure yields intermediate **90** (64 g) in the form of a beige solid, which is used without additional treatment in the following step.

^{1}H NMR (300 MHz, DMSO-d_6) : δ 9.70 (m, 1H), 9.20 (s, 1H), 7.12 (t, 1H), 6.75 (s, 1H), 6.78 (m, 1H), 6.65 (dd, 1H), 4.90 (quint, 1H), 1.42 (d, 3H)

IR (cm^{-1}): 3298, 1702, 1153

Intermediate 93 :

Step 1

To a solution of intermediate **90** (21 g, 90 mmoles) in DMF (450 mL) there are added K_2CO_3 (15 g, 108 mmoles) and then propargyl bromide (11 mL, 98 mmoles). The mixture is stirred at 60°C for 4 hours. After HPLC monitoring, the reaction mixture, cooled to ambient temperature, is poured into a water/ice mixture (1 L/1 kg). The solid is filtered over a frit and washed with water. Drying in vacuo yields the expected intermediate (24 g) in the form of a beige solid, which is used without additional treatment in the following step.

^{1}H NMR (300 MHz, DMSO-d_6) : δ 9.70 (broad s, 1H), 7.28 (t, 1H), 6.92 (m, 3H), 5.00 (quad, 1H), 4.78 (s, 2H), 3.42 (t, 1H), 1.45 (d, 3H)

IR (cm^{-1}): 3301, 1693, 1158

Step 2

A suspension of the intermediate obtained above (5 g, 11 mmoles, 1 eq) in diethylaniline (7 mL) is heated in a microwave oven (CEM, DISCOVER, standard mode) for 40 minutes at 210°C. The reaction mixture is poured into a water/ice/AcOEt mixture (0.2 L/0.2 kg/0.2 L), with stirring, and is then treated with 12N HCl until a stable pH 1 is

reached, and the organic phase is washed with a saturated NaCl solution (1L) and then dried by passage over $MgSO_4$. Evaporation under reduced pressure yields an oil, which is chromatographed on silica gel using an eluant mixture CH_2Cl_2/cyclohexane (30/70 to 50/50). The mixture of two compounds **a and b** (2.3 g) is obtained in the form of a yellow oil (ratio **a/b** : 56/43).

Intermediate a :

^{1}H NMR (400 MHz, DMSO-d_6) : δ 9.90 (s, 1H), 7.15 (t, 1H), 6.9-6.7 (2d, 2H), 6.80 (d, 1H), 6.00 (m, 1H), 5.20 (m, 1H), 4.70 (m, 2H), 1.40 (d, 3H)

IR (cm^{-1}): 3284, 1692

Step 3

To a solution of **a/b** (7.1 g, 26.1 mmoles, 1 eq) in methanol (700 mL) there is added $Pd(OH)_2$ (2.9 g, 40% by weight). The resulting mixture is stirred at atmospheric pressure and at ambient temperature until the starting material has disappeared (GC monitoring). The reaction mixture is filtered. Evaporation under reduced pressure of the filtrate yields a mixture of intermediates **93a/93b** (5.8 g), which is used without additional treatment in the following step.

Intermediate 93a :

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.80 (d, 1H), 7.10 (t, 1H), 6.90 (broad d, 1H), 6.65 (broad d, 1H), 5.10 (quint, 1H), 4.10 (t, 2H), 2.85-2.6 (m, 2H), 1.95 (m, 2H), 1.40 (d, 3H)

IR (cm^{-1}): 3276, 1691, 1181

Intermediate 94 :

2,2,2-Trifluoro-N-[(1R)-1-(8-formyl-3,4-dihydro-2H-chromen-5-yl)ethyl]acetamide

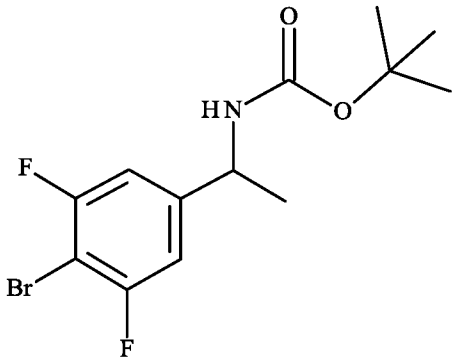
To a solution of **93a/93b** (2.58 g, 9.4 mmoles) in methylene chloride (40 mL) at 0°C there are added $TiCl_4$ (1.8 mL, 16 mmoles) and then Cl_2CHOMe (0.78 mL, 8.6 mmoles). The resulting mixture is stirred at ambient temperature for 20 hours and then poured into a water/ice mixture (250 mL/250 g). The whole is decanted in the presence of methylene chloride (500 mL), and the organic phase is dried by passage over $MgSO_4$. Evaporation under reduced pressure yields an oil, which is chromatographed on silica gel (eluant CH_2Cl_2/AcOEt (97/3)). Intermediate **94** (0.9 g) is obtained in the form of an oil.

^{1}H NMR (500MHz, $CDCl_3$): δ 10.30 (s, 1H), 10.00 (1H), 7.55 (d, 1H), 7.05 (d, 1H), 5.10 (quad, 1H), 4.28 (t, 2H), 2.9-2.78 (m, 2H), 2.05 (m, 2H), 1.40 (dd, 3H)

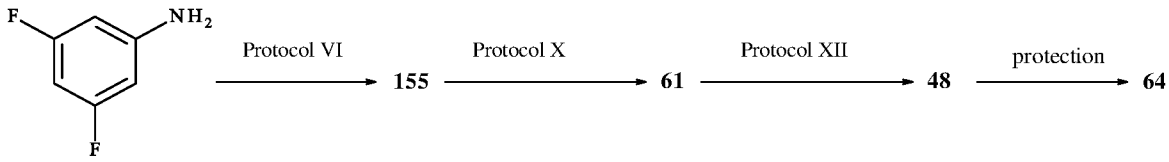
IR (cm^{-1}): 3303, 1716, 1660

Preparation of phenyl precursors - Examples

Intermediate 64 :



64



Obtained by protection of amine **48** according to the protocol described for intermediate **158**

^{1}H NMR (300MHz, $CDCl_3$): δ 6.90 (d, 2H), 4.70 (2m, 2H), 1.40 (m and d, 12H)

IR (cm^{-1}): 3420, 1680

Intermediates 145 and 146 :

Intermediate **64** (11 g) was chromatographed by high pressure chromatography on a chiral support (ChiralPak IC column, eluant heptane/THF 100/5, detection UV 270 nm) to give intermediates **145** (4 g) and **146** (4 g).

Intermediate 145 :

tert-Butyl [(1R)-1-(4-bromo-3,5-difluorophenyl)ethyl]carbamate

^{1}H NMR (400MHz, DMSO-d_6): 7.45 (broad d, 1H), 7.20 (d, 2H), 4.65 (m, 1H), 1.40 (s, 9H), 1.30 (d, 3H)

IR (cm^{-1}): 3368, 1678

Attribution of chirality carried out by IR-VCD on the basis of the infrared spectra of (1R)-1-(4-bromophenyl)ethanamine.

Intermediate 146 :

tert-Butyl [(1S)-1-(4-bromo-3,5-difluorophenyl)ethyl]carbamate

^{1}H NMR (300MHz, DMSO-d_6): 7.14 (m, 2H), 7.01 (m, 1H), 4.62 (m, 1H), 1.35 (s, 9H), 1.32 (d, 3H)

IR (cm^{-1}): 3366, 1678

Attribution of chirality carried out by IR-VCD on the basis of the infrared spectra of (1S)-1-(4-bromophenyl)ethanamine.

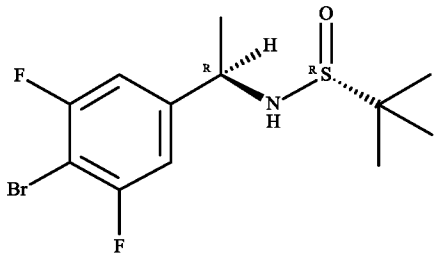
Intermediates **145** and **146** can also be obtained starting from intermediates **166** and **161**, respectively, using the conditions of **protocol XV**.

Intermediate 166 :

Obtained by reaction of intermediate **61** and (R)-(+)-2-methyl-2-propanesulphinamide according to **protocol XIIIb**

LC/MS : [M+H]+ measured 339

chemical purity 85%.



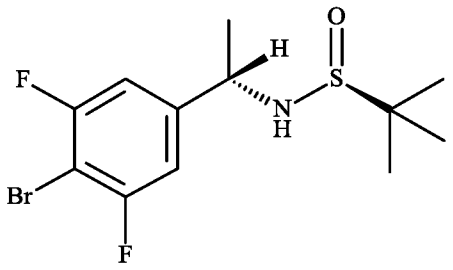
166

Intermediate 161 :

Obtained by reaction of intermediate **61** and (S)-(-)-2-methyl-2-propanesulphinamide according to **protocol XIIIb**

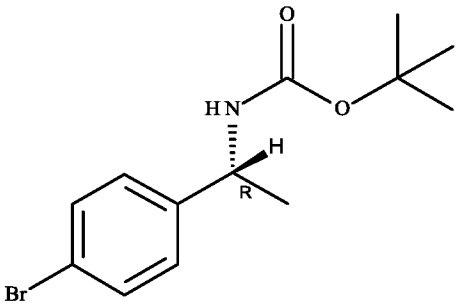
^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34 (d, 2H), 5.81 (d, 1H), 4.41 (quint, 1H), 1.38 (d, 3H), 1,12 (s, 9H)

IR (cm^{-1}): 3174



161

Intermediate 5 :



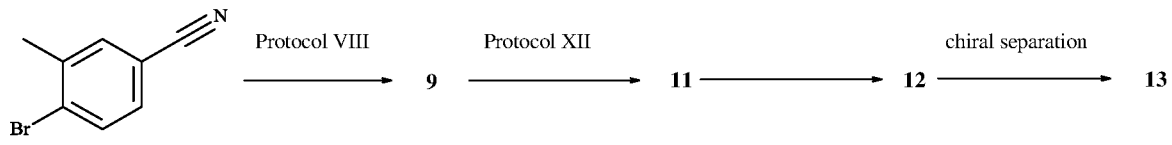
5

Obtained by protection of commercial (1R)-1-(4-bromophenyl)ethanamine according to the protocol described for intermdiate **158**

^{1}H NMR (300MHz, DMSO-d_6): δ 7.50 (d, 2H), 7.25 (d, 2H), 7.40 (d, 1H), 4.60 (m, 1H), 1.40 (s, 9H), 1.30 (d, 3H)

IR (cm^{-1}): 3373, 1681.

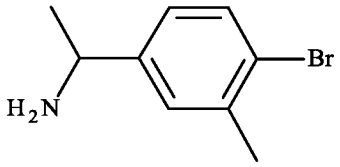
Intermediates 13 and 313 :



Intermediate 11 :

Obtained starting from intermediate **9** according to **protocol XII**

^{1}H NMR (300 MHz; $CDCl_3$) : 7.45 (d, 1H), 7.20 (d, 1H); 7.05 (dd, 1H); 4.05 (quad, 1H); 2.40 (s, 3H); 1.35 (d, 3H); 1.55 (m, 2H)



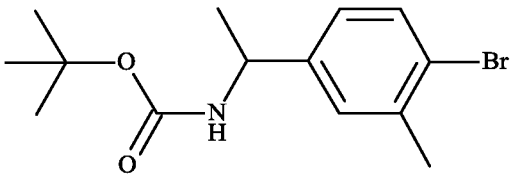
11

Intermediate 12 :

To a solution of intermediate **11** (28 g, 131 mmoles) in methylene chloride (1.4 L) at ambient temperature there is added a solution of di-tert-butyl dicarbonate (28 g, 131 mmoles) in methylene chloride (0.36 L). The reaction mixture is stirred for 3½ hours, and then a 1N aqueous HCl solution is added. The organic phase is dried over $MgSO_4$ and then concentrated in vacuo. The solid residue is stirred in pentane for 1 hour, and the solid is collected on a frit. Intermediate **12** is obtained in the form of a white solid.

^{1}H NMR (400MHz, DMSO-d_6): δ 7.50 (d, 1H), 7.37 (d, 1H), 7.26 (d, 1H), 7.05 (dd, 1H), 4.54 (m, 1H), 2.32 (s, 3H), 1.36 (s, 9H), 1.27 (d, 3H)

IR (cm^{-1}): 3374, 1684



12

Intermediate **12** (122 g) was then chromatographed by high pressure chromatography on a chiral support (ChiralPak (R,R) WHELK column, eluant iPrOH, detection : 220nm) to yield enantiomers **313** (48 g) and **13** (57 g).

Intermediate 313 :

α_D (589nM) = - 69.9 (c = 0.010 g/mL, MeOH) at 20°C

Optical purity: >99%, intermediate **13**< 1%.

Intermediate 13 :

^{1}H NMR (400MHz, DMSO-d_6): 7.50 (d, 1H), 7.37 (d, 1H), 7.26 (d, 1H), 7.05 (dd, 1H), 4.54 (m, 1H), 2.32 (s, 3H), 1.36 (s, 9H), 1.27 (d, 1H)

IR (cm^{-1}): 3374, 1684

α_D (589nM) = + 71.80 (c = 0.010 g/mL, MeOH) at 20°C

Optical purity: >99%, intermediate **313**< 1%

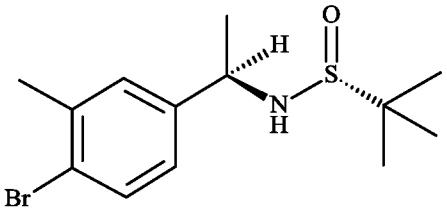
Intermediate **13** can also be obtained starting from intermediate **459** using the conditions of **protocol XV**.

Intermediate 459 :

Obtained by reaction of intermediate **9** and (R)-(+)-2-methyl-2-propanesulphinamide according to **protocol XIIIb**

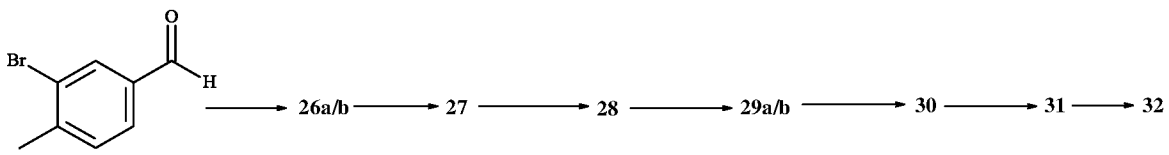
^{1}H NMR (400 MHz, DMSO-d_6): δ 7.50 (d, 1H), 7.35 (d, 1H), 7.15 (dd, 1H), 5.60 (d, 1H), 4.30 (quint, 1H), 2.30 (s, 3H), 1.40 (d, 3H), 1.10 (s, 9H)

IR (cm^{-1}) : 3207, 1052



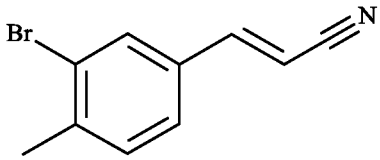
459

Intermediate 32 :

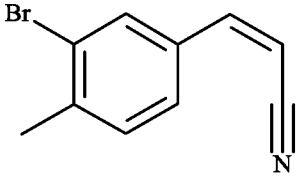


Intermediates 26a/b :

To a solution of sodium ethoxide prepared by adding sodium (9.1 g, 396 mmoles) to ethanol (400 mL) previously cooled to 0°C there is added $(EtO)_2POCH_2CN$ (63 mL, 396 mmoles). The resulting mixture is stirred at 0°C for 30 minutes, and then commercial 3-bromo-4-methylbenzaldehyde (77 g, 391 mmoles) is added slowly (approximately 20 minutes). The reaction mixture is stirred at ambient temperature until the starting material has disappeared, and it is then poured into water (4 L). The precipitate is filtered off over a frit, rinsed with water and dried in vacuo. The mixture of intermediates **26a/b** (mixture of the Z and E forms) is obtained (81 g) and used in the following step.



26a



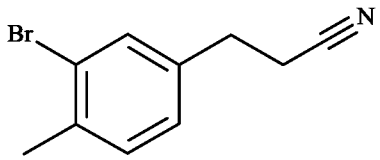
26b

Intermediate 27 :

To a solution of intermediates **26a/b** (75 g, 338 mmoles) in isopropanol (1 L) there is added $NaBH_4$ (51 g, 1.35 mole). The reaction mixture is heated at 90-100°C for 48 hours and stirred with return to ambient temperature for 2 days. The solvent is evaporated off, and the residue is taken up in water, neutralised carefully with concentrated HCl and extracted with AcOEt. The organic phase is washed in succession with water and with a saturated aqueous NaCl solution and is then dried over $MgSO_4$ and concentrated in vacuo. The oil is chromatographed on silica gel (methylene chloride 100%). Intermediate **27** (58 g) is obtained in the form of an oil.

^{1}H NMR (400 MHz ; $CDCl_3$) **:** δ 7.40 (d, 1H); 7.20 (d, 1H); 7.10 (dd, 1H); 2.90 (t, 2H); 2.60 (t, 2H); 2.40 (s, 3H)

IR (cm^{-1}) : 2247, 1040.



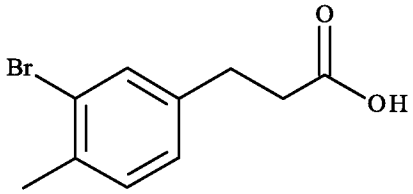
27

Intermediate 28 :

Intermediate **27**, treated according to the protocol described for intermediate **599** (**protocol V**), yields intermediate **28** (60 g).

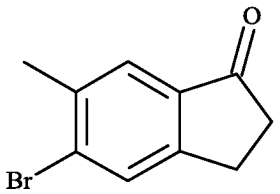
^{1}H NMR (400 MHz ; $CDCl_3$) **:** δ 11.0 (m, 1H); 7.40 (d, 1H); 7.15 (d, 1H); 7.00 (dd, 1H); 2.90 (t, 2H); 2.65 (t, 2H); 2.35 (s, 3H).

IR (cm^{-1}) : 3400, 2100, 1697.

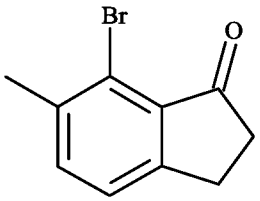


28

Intermediates 29a/b : To a mixture of P_2O_5 (14 g, 100 mmoles) and methanesulphonic acid (142 mL) previously heated at 60°C for 2 hours there is added intermediate **28** (12 g, 50 mmoles). The reaction mixture is stirred for 35 minutes at 60°C and is then poured carefully into ice. The mixture is extracted with AcOEt, and the organic phase is washed in succession with water, with a 4N aqueous NaOH solution, again with water and with a HCl solution. The organic phase is dried over $MgSO_4$ and concentrated in vacuo. The residue is solidified in isopropyl ether. The mixture of intermediates **29a/b** (5 g) obtained is used in the following step.



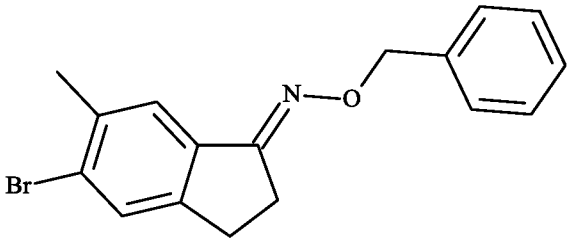
29a



29b

Intermediate 30 : The mixture of intermediates **29a/b** (5.2 g, 23 mmoles) is treated according to the protocol described for Example **341**, methoxylamine hydrochloride being replaced by o-benzylhydroxylamine hydrochloride. After treatment and chromatography (SiO_2, eluant : toluene/CH_2Cl_2 80/20), intermediate **30** (2.5 g) is obtained.

^{1}H NMR (300 MHz ; $CDCl_3$) **:** δ 7.55 (s, 1H); 7.50 (s, 1H); 7.4-7.25 (m, 5H); 5.20 (s, 2H); 2.90 (2m, 4H); 2.40 (s, 3H).

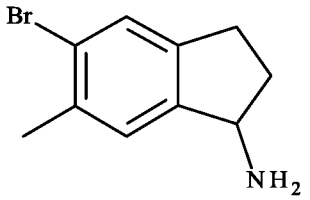


30

Intermediate 31:

Obtained starting from intermediate **30** according to the process described for intermediate **48** (**protocol XII**)

^{1}H NMR (300 MHz ; $CDCl_3$) : 7.40 (s, 1H), 7.20 (s, 1H) ; 4.30 (t, 1H); 2.90 (m, 1H) ; 2.75 (m, 1H); 2.50 (m, 1H); 2.40 (s, 3H) ; 1.70 (m, 1H); 1.50 (m, 2H)



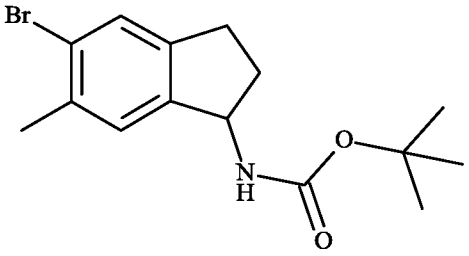
31

Intermediate 32 :

Obtained by protection of intermediate **31** according to the protocol described for intermediate **158** (**protocol VI**)

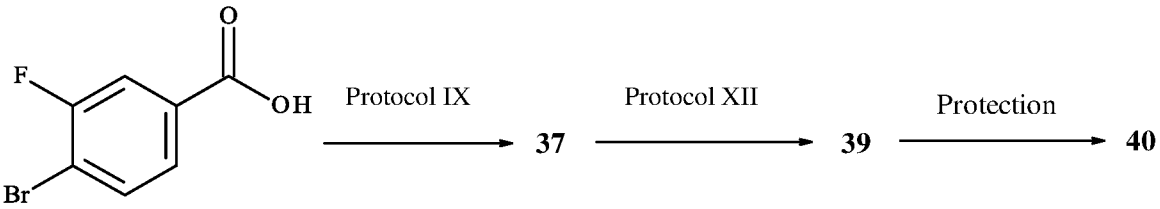
^{1}H NMR (400MHz, $CDCl_3$): δ 7.40 (s, 1H), 7.20 (s, 1H), 5.10 (quad, 1H), 4.70 (broad d, 1H), 2.90 (m, 1H), 2.80 (m, 1H), 2.55 (m, 1H), 2.40 (s, 3H), 1.80 (m, 1H), 1.50 (s, 9H)

IR (cm^{-1}): 3299, 1674



32

Intermediate 40 :



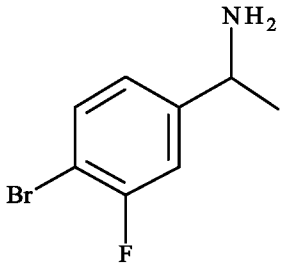
The synthesis of intermediate **37** is described by way of example for **protocol IX**.

Intermediate 39 :

Obtained starting from intermediate **37** according to **protocol XII**

^{1}H NMR (300MHz ; $CDCl_3$): 7.49 (t, 1H), 7.18 (dd, 1H), 7.01 (dd, 1H), 4.11 (quad, 1H), 1.50 (s, 2H), 1.35 (d, 3H)

IR (cm^{-1}): 3372, 3288



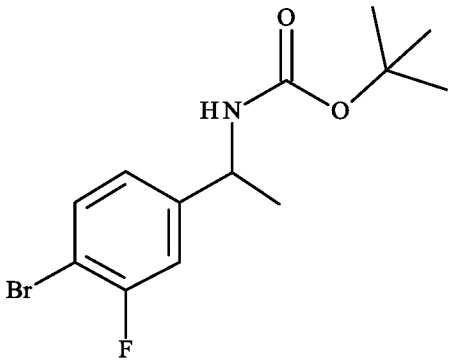
39

Intermediate 40 :

Obtained by protection of intermediate **39** according to the protocol described for intermediate **158** (**protocol VI**)

^{1}H NMR (300MHz, DMSO-d_6): δ 7.65 (t, 1H), 7.45 (d, 1H), 7.30 (dd, 1H), 7.09 (dd, 1H), 4.60 (m, 1H), 1.40 (s, 9H), 1.30 (d, 3H)

IR (cm^{-1}): 3365, 1678



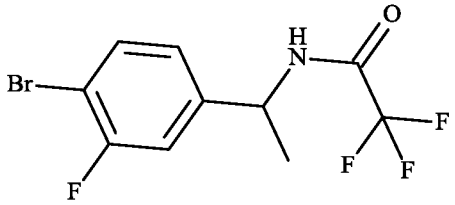
40

Intermediate 676:

Obtained starting from intermediate **39** according to **protocol XVI**

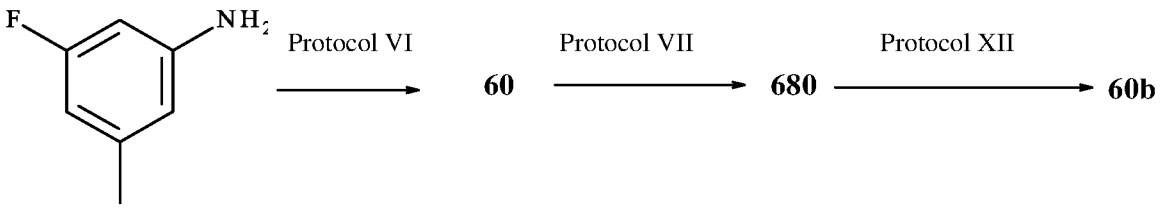
^{1}H NMR (300 MHz, DMSO-d_6) : δ 9.80 (d, 1H), 7.70 (dd, 1H), 7.40 (dd, 1H), 7.15 (dd, 1H), 5.00 (quint, 1H), 1.45 (d, 3H)

IR (cm^{-1}) : 3267, 1702, 1556, 1205, 1146



676

Intermediate 60b :



Intermediate 60 :

4-Bromo-3-fluoro-5-methylaniline

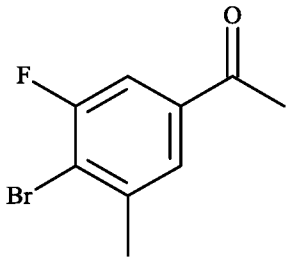
Obtained by bromation of commercial 3-fluoro-5-methylaniline according to the protocol described for intermediate **67** (**protocol VI**)

Intermediate 680 :

Obtained starting from 4-bromo-3-fluoro-5-methylaniline **60** according to **protocol VII**

^{1}H NMR (300 MHz ; $CDCl_3$) **:** δ 7.60 (dd, 1H); 7.50 (dd, 1H); 2.60 (s, 3H); 2.50 (broad s, 3H)

IR (cm^{-1}) : 1687



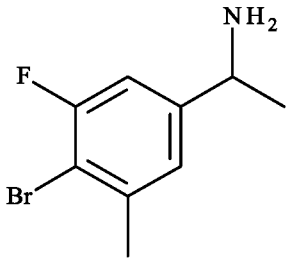
680

Intermediate 60b :

Obtained starting from intermediate **680** according to **protocol XII**

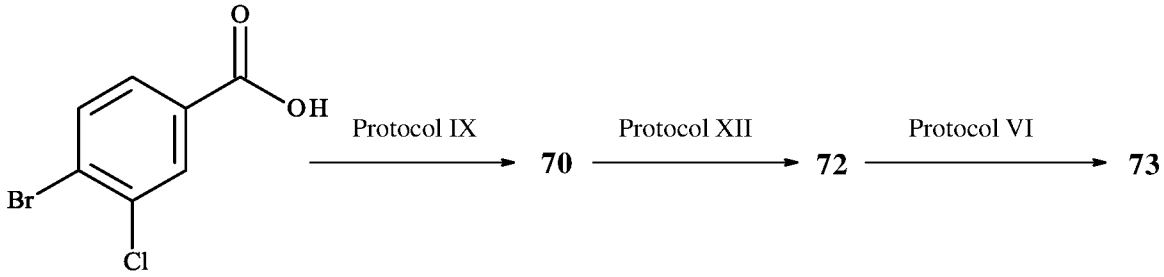
^{1}H NMR (300MHz ; DMSO-d_6): 7.20 (m, 2H), 3.90 (quad, 1H), 2.40 (s, 3H), 1.85 (m, 2H), 1.20 (d, 3H)

IR (cm^{-1}): 3650-3030



60b

Intermediate 73 :

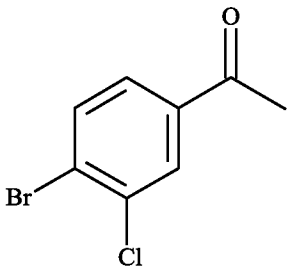


Intermediate 70 :

Obtained starting from commercial 4-bromo-3-chlorobenzoic acid and methylmagnesium bromide according to **protocol IX**

^{1}H NMR (400 MHz ; $CDCl_3$): δ 8.00 (d, 1H), 7.70 (d, 1H), 7.65 (dd, 1H), 2.60 (s,3H)

IR (cm-1): 1680



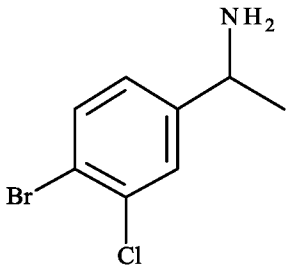
70

Intermediate 72 :

Obtained starting from intermediate **70** according to **protocol XII**

^{1}H NMR (400MHz ; $CDCl_3$): 7.55 (d, 1H), 7.50 (sd, 1H); 7.10 (dd, 1H ;) 4.10 (quad, 1H); 1.60 (m, 2H); 1.35 (d, 3H)

IR (cm^{-1}): 3650, 3000



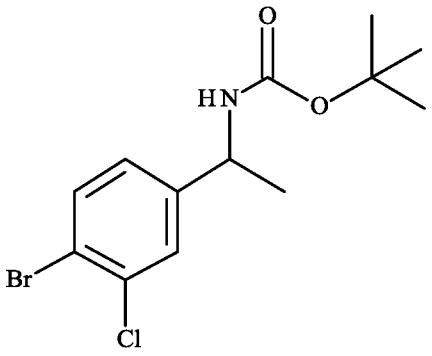
72

Intermediate 73 :

Obtained by protection of intermediate **72** according to the protocol described for intermediate **158** (**protocol VI**)

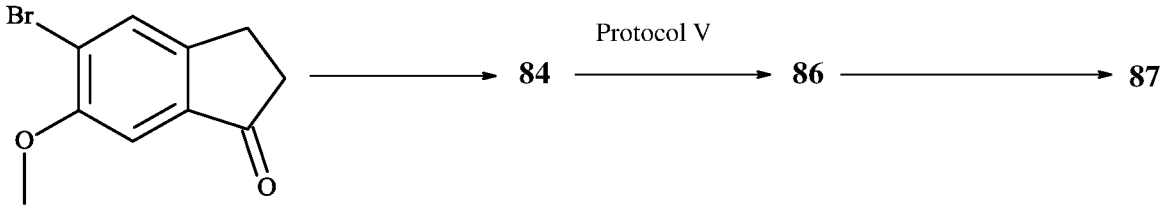
^{1}H NMR (300MHz, $CDCl_3$): δ 7.55 (d, 1H), 7.40 (sd, 1H), 7.05 (dd, 1H), 4.70 (m, 2H), 1.40 (m, 12H)

IR (cm^{-1}): 3365, 1681



73

Intermediate 87 :



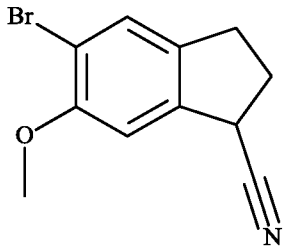
Intermediate 84 :

To a mixture of 5-bromo-6-methoxy-2,3-dihydro-1H-inden-1-one (10 g, 41 mmoles) and LiCN (0.27 g, 8.3 mmoles) in THF (105 mL) there is added $(Et_2O)_2POCN$ (9.5 mL, 62 mmoles). The mixture is stirred at ambient temperature for 5 hours and then concentrated in vacuo. The residue is taken up in AcOEt and washed with water and then with a saturated aqueous NaCl solution. The organic phase is dried over $MgSO_4$ and concentrated in vacuo. The residue is taken up in toluene (100 mL) and then treated with $BF_3.OEt_2$ (10.2 mL, 82.96 mmoles) for 5 hours. The mixture is washed with water and then with a saturated aqueous NaCl solution. The organic phase is dried over $MgSO_4$ and then concentrated in vacuo. Intermediate **83** (5-bromo-6-methoxy-3H-indene-1-carbonitrile) so

obtained (11.9 g) is used in the following step without additional purification. A solution of **83** (10 g, 41 mmoles) in THF (70 mL) is added in the course of 10 minutes to a mixture of $NaBH_4$ (4.7 g, 124 mmoles) in THF (100 mL), this addition is exothermic (Tmax 48°C). The mixture is heated at 50°C for 2½ hours and then cooled to about 0°C. A 4N HCl solution (30 mL) is added, followed by Et_2O (250 mL) and water (50 mL). The organic phase is extracted, dried over $MgSO_4$ and concentrated in vacuo. The residue is purified by chromatography on silica (eluant CH_2Cl_2/cyclohexane 50/50). Intermediate **84** (3 g) is obtained in the form of a yellow solid.

^{1}H NMR (300 MHz ; $CDCl_3$) : δ 7.45 (s, 1H) ; 6.95 (s, 1H), 4.05 (t, 1H), 3.90 (s, 3H), 3.0-2.9 (2m, 2H), 2.6-2.4 (2m, 2H)

IR (cm^{-1}) : 2238

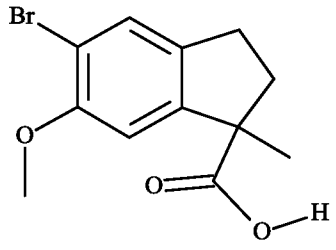


84

Intermediate 86 :

Obtained starting from intermediate **84** according to the protocol described for the preparation of intermediate **599** (**protocol V**)

^{1}H NMR (300 MHz ; DMSO-d_6) **:** δ 13.0-11.0 (m, 1H), 7.40 (s, 1H) ; 6.95 (s, 1H), 3.80 (s, 3H), 3.0-2.75 (m, 2H), 2.55 (m, 1H), 1.90 (m, 1H), 1.45 (s,3H).



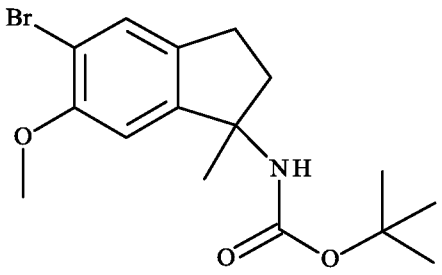
86

Intermediate 87 :

To a solution of tBuOH (18.3 mL) and Boc_2O (1.56 g, 7.1 mmoles) which has previously been heated for 2 hours at 90°C and then returned to ambient temperature there are added in succession intermediate **86** (2.31 g, 8 mmoles), NEt_3 (1.13 mL, 8 mmoles) and PhO_2PON_3 (1.75 mL). The mixture is heated at 90°C for 3 days and is then concentrated in vacuo. The residue is purified by chromatography on silica (eluant CH_2Cl_2 100%) to give intermediate **87** (1.5 g).

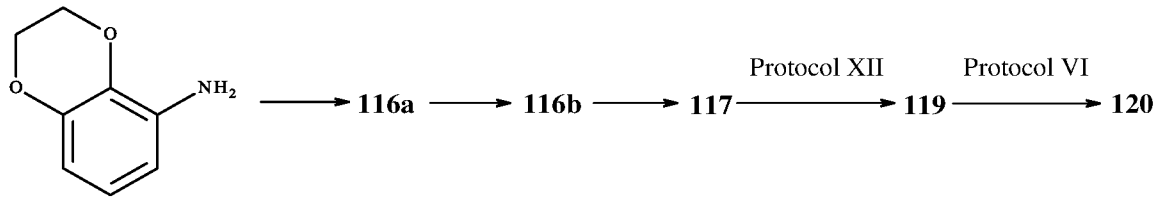
^{1}H NMR (300 MHz ; DMSO-d_6) : δ 7.35 (s, 1H) ; 7.00 (m, 1H), 6.95 (d, 1H), 3.80 (s, 3H), 2.85-2.65 (m, 2H), 2.45 (m, 1H), 2.00 (m, 1H), 1.40 (s, 3H), 1.30 (broad s, 9H)

IR (cm^{-1}) : 3356, 1694



87

Intermediate 120 :

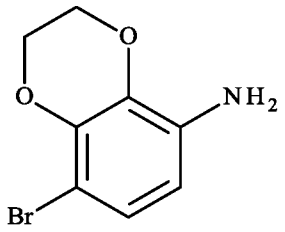


Intermediate 116a :

To a solution of 2,3-dihydro-1,4-benzodioxin-5-amine (40 g, 260 mmoles) in DMF (750 mL) cooled to -30°C there is added dropwise a solution of N-bromosuccinimide (47 g) in DMF (250 mL). The mixture is stirred for 1 hour and is then poured into a water/ice mixture (500 mL/500 g) ; the precipitate that forms is dissolved in methylene chloride. The organic phase is dried over $MgSO_4$ and then concentrated in vacuo. Intermediate **116a** is obtained in the form of a violet solid (30 g).

^{1}H NMR (400MHz, DMSO-d_6): δ 6.78 (d, 1H), 6.20 (d, 1H), 4.25 (m, 4H), 4.90 (s, 2H)

IR (cm^{-1}): 3480



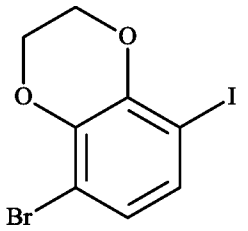
116a

Intermediate 116b :

To a mixture of intermediate **116a** (7 g, 30 mmoles) in water (20 mL) there is added HCl_{cc} (20 mL), the resulting mixture is cooled to 0°C, and a solution of $NaNO_2$ (2.2 g) in water (10 mL) is added. The mixture is stirred for 1½ h at 0°C, and then an aqueous KI solution (5 g in 7 mL) is added and the whole is heated gradually to 90°C. After return to ambient temperature, the mixture is poured into ice and the precipitate that forms is dissolved in AcOEt. The organic phase is washed with a 0.1N sodium thiosulphate solution, dried over $MgSO_4$ and then evaporated in vacuo. Intermediate **116b** is obtained in the form of a brown solid (7 g) (which can be chromatographed on silica gel (cyclohexane/methylene chloride 80/20 to 0/100)).

^{1}H NMR (400MHz, DMSO-d_6): δ 7.25 (d, 1H), 6.95 (d, 1H), 4.40 (s, 4H)

IR (cm^{-1}): 1734



116b

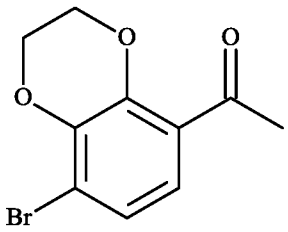
Intermediate 117 :

To a solution, degassed with nitrogen, of intermediate **116b** (15 g, 44 mmoles) in DMF (500 mL) there is added tri-butyl-(1-ethoxyvinyl)-tin (15 mL, 44 mmoles). The solution is brought to 70°C, and then $PdCl_2(PPh_3)_2$ (3.7 g) is added. The mixture is heated at 70°C until the starting intermediate has disappeared. After return to ambient temperature, the reaction mixture is treated in succession with 10 g of KF in water (1 L) and with ethyl

ether. The salts are filtered off, and the organic phase is concentrated in vacuo. The residue so obtained is dissolved in THF and stirred for 1 hour in the presence of 30 mL of a 1N aqueous HCl solution. The mixture is then decanted in the presence of 1 L of Et_2O, and the organic phase is dried over $MgSO_4$. Evaporation under reduced pressure yields an oil, which is chromatographed on silica gel using a cyclohexane/methylene chloride elution gradient (50/50 to 20/80). Intermediate **117** is obtained in the form of an orange solid (4.6 g).

^{1}H NMR (400MHz, DMSO-d_6): δ 7.2-7.1 (2d, 2H), 4.40 (s, 4H), 2.55 (s, 3H);7.25 (d, 1H), 6.95 (d, 1H), 4.40 (s, 4H)

IR (cm^{-1}): 1664

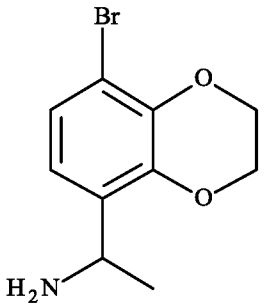


117

Intermediate 119 :

Obtained starting from intermediate **117** according to **protocol XII**

^{1}H NMR (400MHz ; DMSO-d_6): 7.08 (d, 1H), 6.95 (d, 1H), 4.30 (m, 4H), 4.20 (quad, 1H), 1.20 (d, 3H)



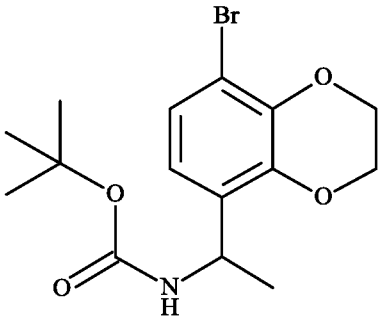
119

Intermediate 120 :

Obtained by protection of intermediate **119** according to the protocol described for intermediate **158** (**protocol VI**)

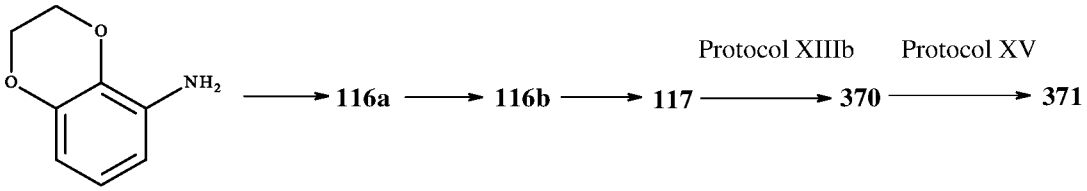
^{1}H NMR (400MHz, DMSO-d_6): δ 7.33 (d, 1H), 7.09 (d, 1H), 6.78 (d, 1H), 4.82 (m, 1H), 4.30 (m, 4H), 1.35 (s, 9H), 1.20 (d, 3H)

IR (cm^{-1}): 3368, 1684



120

Intermediate 371 :

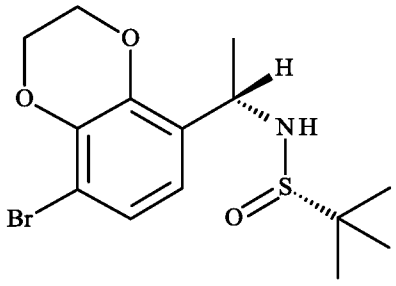


Intermediate 370 :

Obtained starting from intermediate **117** and (S)-(-)-2-methyl-2-propanesulphinamide according to **protocol XIIIb**

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.12 (d, 1H), 6.95 (d, 1H), 5.59 (d, 1H), 4.63 (m, 1H),4.32 (m, 4H), 1.33 (d, 3H), 1.10 (s, 9H)

IR (cm^{-1}) : 3500, 3000, 1056



370

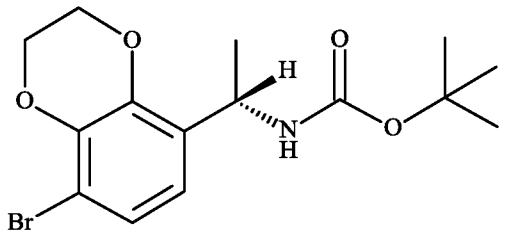
Intermediate 371 :

Obtained starting from intermediate **370** according to **protocol XV**

^{1}H NMR (400MHz, DMSO-d6): δ 7.35 (d, 1H), 7.09 (d, 2H), 6.79 (d, 2H), 4.85 (m, 1H), 4.33 (m, 4H), 1.37 (s, 9H), 1.21 (d, 3H)

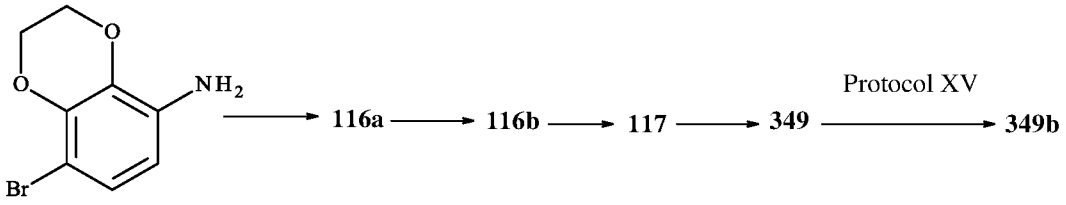
IR (cm^{-1}): 3260, 1695, 1676

Enantiomeric excess > 99%



371

Intermediate 349b :



Intermediate 349 :

To a solution of intermediate **117** (10.7 g, 41 mmoles) in 160 mL of THF there are added in succession $Ti(OEt)_4$ (30 mL, 143 mmoles) and then (R)-(+)-2-methyl-2-propanesulphinamide (5 g, 41 mmoles). The mixture is heated for 48 hours at 55°C. The mixture, cooled to –40°C, is transferred by cannulation to a suspension of $NaBH_4$ (3.1 g ; 82 mmoles) in 46 mL of THF. The reaction mixture, at ambient temperature, is treated carefully with methanol and then diluted with 300 mL of ethyl acetate and 700 mL of a saturated aqueous NaCl solution. The resulting mixture is filtered over Celite®, which is rinsed with THF and AcOEt. The filtrate is decanted, and the organic phase is dried by passage over $MgSO_4$. Evaporation under reduced pressure yields a white solid, which is

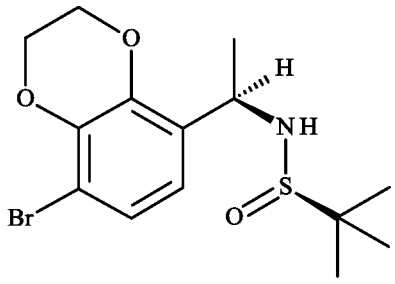
purified on silica using an AcOEt/methylene chloride elution gradient 0/100 to 40/60. The diastereoisomer **349** (7 g) is isolated in the form of a white solid.

^{1}H NMR (400MHz; DMSO-d_6): δ 7.12 (d, 1H), 6.95 (d, 1H), 5.59 (d, 1H), 4.63 (m, 1H), 4.32 (m, 4H), 1.33 (d, 3H); 1.10 (s, 9H)

IR (cm^{-1}): 3265, 1057

GC-EI (70 eV): $M^{+\cdot}$= 361

Diasteroisomeric purity: de>99%



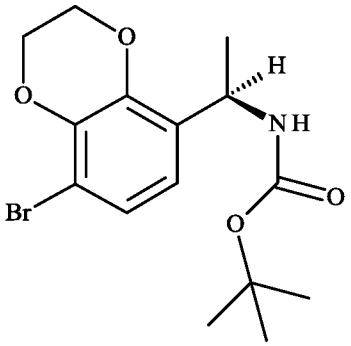
349

Intermediate 349b :

Obtained starting from intermediate **349** according to **protocol XV**

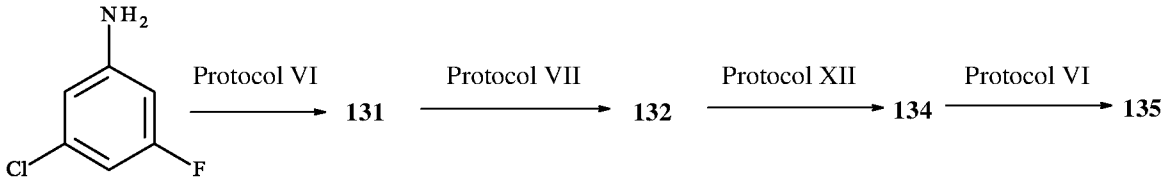
^{1}H NMR (400MHz, DMSO-d_6): δ 7.33 (broad d, 1H), 7.08 (d, 1H), 6.78 (d, 1H), 4.83 (m, 1H), 4.32 (broad m, 4H), 1.35 (broad s, 9H), 1.21 (d, 3H)

Enantiomeric excess > 99%



349b

Intermediate 135 :



Intermediate 131

4-Bromo-3-chloro-5-fluoroaniline

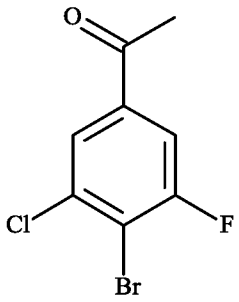
Obtained by bromation of commercial 3-chloro-5-fluoroaniline according to the protocol described for intermediate **67** (**protocol VI**)

Intermediate 132 :

Obtained starting from intermediate **131** according to **protocol VII**

^{1}H NMR (300MHz, $CDCl_3$) : δ 7.85 (s, 1H), 7.60 (d, 1H), 2.60 (s,3H)

IR (cm^{-1}) : 1692, 1206.



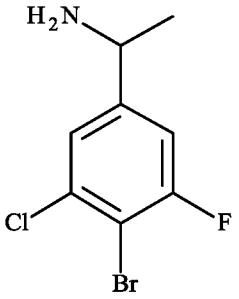
132

Intermediate 134 :

Obtained starting from intermediate **132** according to **protocol XII**

^{1}H NMR (300MHz ; $CDCl_3$): 7.30 (s, 1H), 7.05 (d, 1H) 4.10 (quad, 1H); 1.35 (d, 3H)

IR (cm^{-1}): 3600, 2500



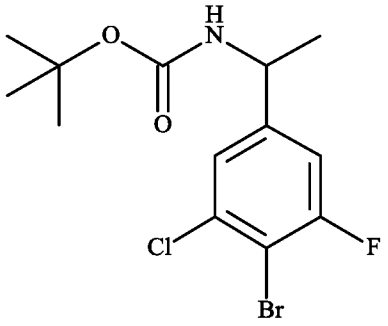
134

Intermediate 135 :

Obtained by protection of intermediate **134** according to the protocol described for intermediate **158** (**protocol VI**)

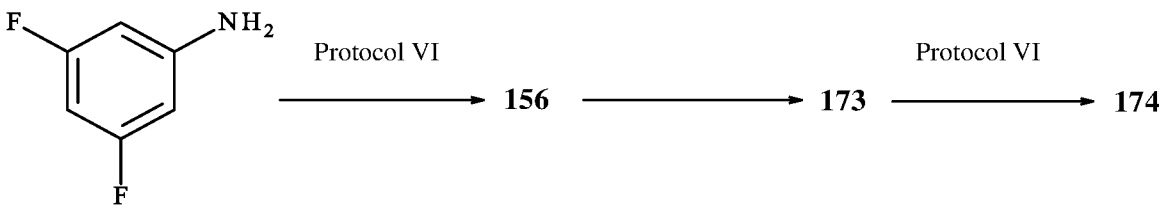
^{1}H NMR (400MHz, $CDCl_3$): δ 7.20 (s, 1H), 7.00 (d, 1H), 4.75 (broad s, 1H), 4.70 (m, 1H), 1.40 (s and d, 12H)

IR (cm^{-1}): 3367, 1682, 1163



135

Intermediate 174 :

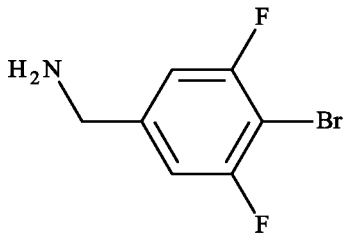


Intermediate 173 :

Intermediate **173** was prepared by reduction with BH_3.THF of intermediate **156** (4-bromo-3,5-difluorobenzonitrile).

^{1}H NMR (300MHz, DMSO-d_6): δ 8.60 (m, 3H), 7.50 (d, 2H), 4.05 (s, 2H)

IR (cm^{-1}): 3450-2400.



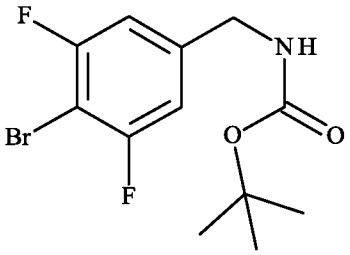
173

Intermediate 174 :

Obtained by protection of intermediate **173** according to the protocol described for intermediate **158** (**protocol VI**)

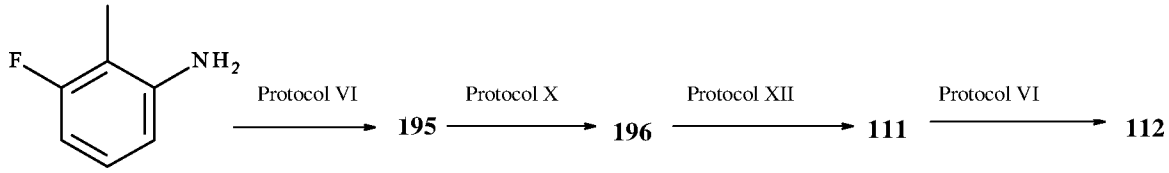
^{1}H NMR (300MHz, DMSO-d_6): δ 7.50 (t, 1H), 7.10 (d, 2H), 4.10 (d, 2H), 1.40 (s, 9H)

IR (cm^{-1}): 3323, 1681



174

Intermediate 112 :



Intermediate 195 :

1-Bromo-2-fluoro-4-iodo-3-methylbenzene

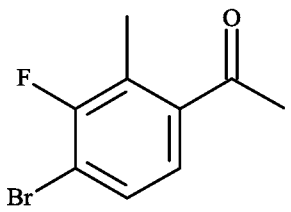
Obtained starting from commercial 3-fluoro-2-methylaniline according to the protocol described for intermediate **155** (**protocol VI**)

Intermediate 196 :

Obtained starting from intermediate **195** according to **protocol X**

^{1}H NMR (400MHz, $CDCl_3$): δ 7.45 (dd, 1H), 7.30 (d, 1H), 2.60 (s, 3H), 1.40 (s, 3H)

IR (cm^{-1}) : 1684



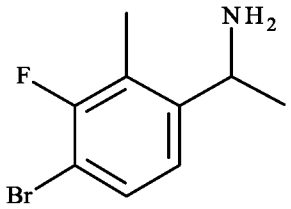
196

Intermediate 111 :

Obtained starting from intermediate **196** according to **protocol XII**

^{1}H NMR (400MHz ; $CDCl_3$): 7.40 (dd, 1H), 7.20 (d, 1H) ; 4.30 (quad, 1H) ; 2.30 (s, 3H), 1.60 (m, 2H) ; 1.30 (d, 3H)

IR (cm^{-1}): 3750, 2900



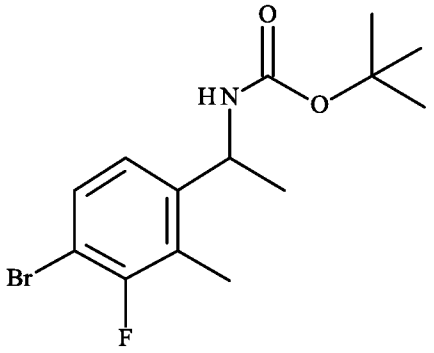
111

Intermediate 112 :

Obtained by protection of intermediate **111** according to the protocol described for intermediate **158** (**protocol VI**)

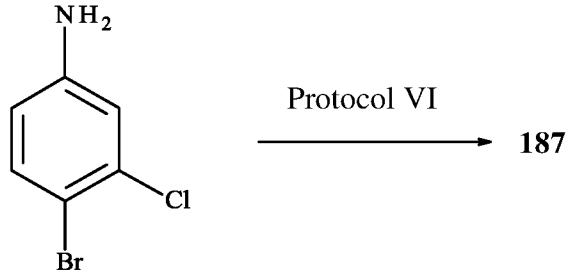
^{1}H NMR (300MHz, DMSO-d_6): δ 7.50 (dd, 1H), 7.10 (d, 1H), 4.75 (quint, 1H), 2.25 (m, 3H), 1.35 (m, 9H), 1.25 (d, 3H)

IR (cm^{-1}): 3301, 1690-1664



112

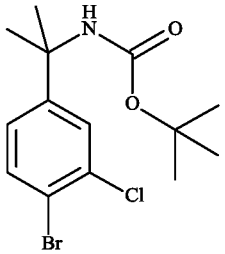
Intermediate 187 :



Obtained starting from commercial 4-bromo-3-chloroaniline according to **protocol VI**

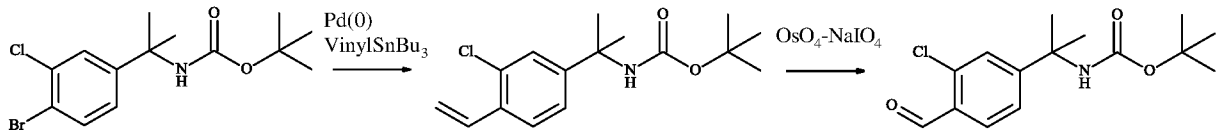
^{1}H NMR (400 MHz ; DMSO-d_6) **:** δ 7.70 (d, 1H) ; 7.50 (d, 1H) ; 7.30 (s, 1H) ; 7.20 (dd, 1H) ; 1.45 (s, 6H) ; 1.30 (s, 9H)

IR (cm^{-1}) : 3264-2972 ; 1698.



187

Intermediate 193 :



187 **192** **193**

Intermediate 192 :

To a solution (degassed with nitrogen) of intermediate **187** (12 g, 34 mmoles) in DMF (240 mL) there are added tri-butyl-vinyltin (10 mL, 34 mmoles) and $Pd(PPh_3)_4$ (2.47 g). The reaction mixture is heated at 100°C for 20h. After return to ambient temperature, the mixture is treated with a 10% aqueous KF solution, the resulting salts are filtered off, and the filtrate is extracted with ethyl acetate. The organic phase is washed with a saturated aqueous NaCl solution, dried over $MgSO_4$ and concentrated in vacuo. The residue is chromatographed on silica gel (eluant CH_2Cl_2 (100%)). Intermediate **192** (4.7 g) is obtained in the form of a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 7.60 (d, 1H), 7.36 (d, 1H), 7.30 (dd, 1H), 6.99 (dd, 1H), 6.85 (m, 1H), 5.82 (d, 1H), 5.40 (d, 1H), 1.52 (s, 6H), 1.31 (s, 9H)

IR (cm^{-1}) : 3327, 1689

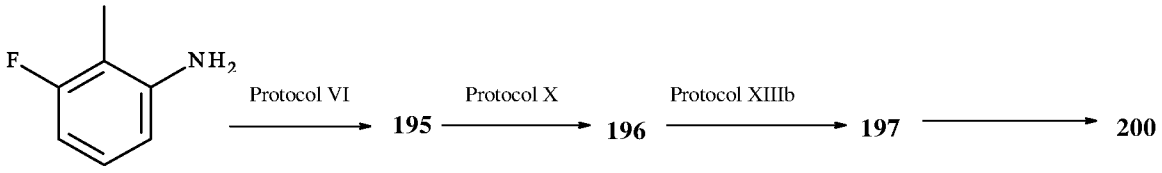
Intermediate 193 :

To a mixture of intermediate **192** (4.7 g, 15 mmoles) in dioxane (95 mL) and water (5 mL) there are added OsO_4 (2.5% by weight in butanol) (3.2 g), 2,6-lutidine (3.7 g, 31 mmoles) and $NaIO_4$ (13.6 g, 63 mmoles). The reaction mixture is stirred for 1h at ambient temperature. After addition of AcOEt and of a saturated NaCl solution, the solid is filtered off and the filtrate is extracted with ethyl acetate. The organic phase is washed with a saturated NaCl solution, dried over $MgSO_4$ and concentrated in vacuo. The residue is chromatographed on silica gel using a CH_2Cl_2 eluant (100). Intermediate **193** (4.2 g) is obtained in the form of a colourless oil.

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 10.40 (s, 1H), 7.81 (d, 1H), 7.50 (m, 2H), 7.40 (m, 1H), 1.50 (s, 6H), 1.35 (m, 9H)

IR (cm^{-1}) : 3350, 1688193

Intermediate 200 :



Intermediate 195 :

1-Bromo-2-fluoro-4-iodo-3-methylbenzene

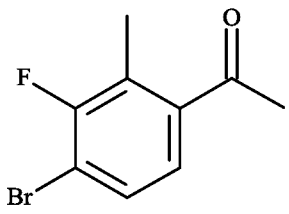
Obtained starting from commercial 3-fluoro-2-methylaniline according to the protocol described for intermediate **155** (**protocol VI**)

Intermediate 196 :

Obtained starting from intermediate **195** according to **protocol X**

^{1}H NMR (400MHz, $CDCl_3$): δ 7.45 (dd, 1H), 7.30 (d, 1H), 2.60 (s, 3H), 1.40 (s, 3H)

IR (cm^{-1}) : 1684



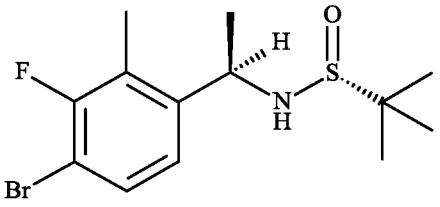
196

Intermediate 197 :

Obtained by reaction of intermediate **196** and (R)-(+)-2-methyl-2-propanesulphinamide according to **protocol XIIIb**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (m, 1H), 7.05 (d, 1H), 4.75 (m, 1H), 2.30 (d, 3H), 1.45 (d, 3H), 1.20 (s, 9H), 3.30 (m, 1H)

IR (cm^{-1}): 3378, 3290, 1620



197

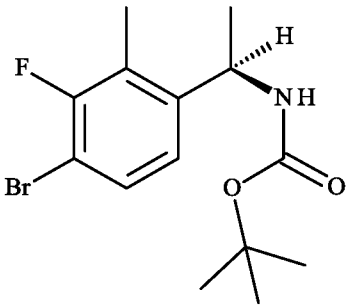
Intermediate 200 :

Obtained starting from intermediate **197** according to **protocol XV**

^{1}H NMR (400MHz, DMSO-d_6): δ 7.50 (2m, 2H), 7.10 (d, 1H), 4.75 (m, 1H), 2.25 (d, 3H), 1.35 (s, 9H), 1.25 (d, 3H)

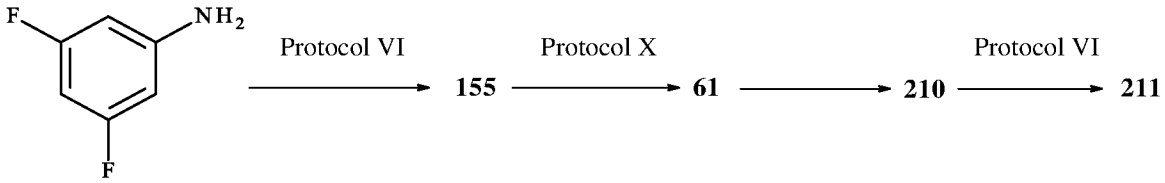
IR (cm^{-1}): 3373, 1681

Enantiomeric excess > 99%



200

Intermediate 211 :



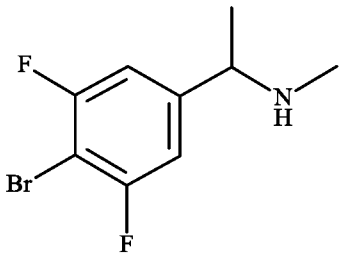
Intermediate 210 :

To a mixture of $TiOiPr_4$ (16 mL, 54 mmoles) in ethanol (70 mL) there are added NEt_3 (7.7 mL, 55.3 mmoles), methylamine hydrochloride (3.7 g, 54.8 mmoles) and intermediate **61** (7 g, 27.8 mmoles). The mixture is stirred at ambient temperature for 40 hours, and then $NaBH_4$ (1.56 g, 41.4 mmoles) is added in portions. After 20 hours' stirring, the reaction

mixture is poured carefully into a 2N aqueous NH_4OH solution, and the resulting precipitate is filtered off and rinsed with methylene chloride. The filtrate is decanted, the organic phase is washed with a 2N aqueous HCl solution, and the acidic phase is brought to basic pH by means of a 20% sodium hydroxide solution. The product is extracted with methylene chloride, the organic phase is dried over $MgSO_4$, and evaporation under reduced pressure yields an oil, which is purified on silica gel using a methylene chloride/ethanol elution gradient 100/0 to 95/5. Intermediate **210** is isolated in the form of an oil (1.5 g).

^{1}H NMR (400MHz; DMSO-d_6): δ 7.25 (d, 2H), 3.6 (q, 1H), 2.5-2.15 (m, 1H), 2.10 (s, 3H), 1.20 (d, 3H)

IR (cm^{-1}): 3280-3360



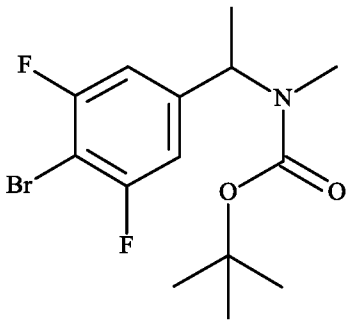
210

Intermediate 211 :

Obtained by protection of intermediate **210** according to the protocol described for intermediate **158** (**protocol VI**)

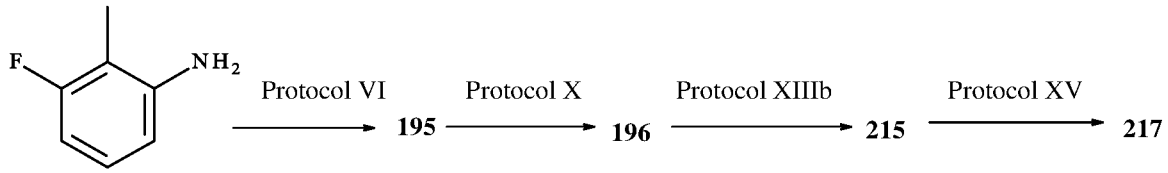
^{1}H NMR (400MHz, DMSO-d_6): δ 7.12 (m, 2H), 5.20 (broad s, 1H), 2.63 (s, 3H), 1.45 (d, 3H), 1.39 (broad s, 9H)

IR (cm^{-1}): 1686



211

Intermediate 217 :



Intermediate 195 :

1-Bromo-2-fluoro-4-iodo-3-methylbenzene

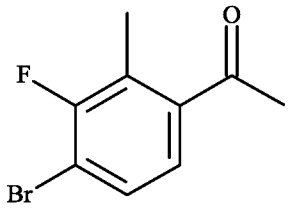
Obtained starting from commercial 3-fluoro-2-methylaniline according to the protocol described for intermediate **155** (**protocol VI**)

Intermediate 196 :

Obtained starting from intermediate **195** according to **protocol X**

^{1}H NMR (400MHz, $CDCl_3$): δ 7.45 (dd, 1H), 7.30 (d, 1H), 2.60 (s, 3H), 1.40 (s, 3H)

IR (cm^{-1}) : 1684



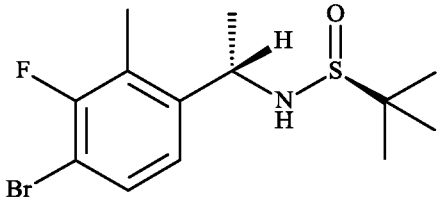
196

Intermediate 215 :

Obtained by reaction of intermediate **196** and (S)-(-)-2-methyl-2-propanesulphinamide according to **protocol XIIIb**

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.50 (dd, 1H), 7.25 (d, 1H), 5.70 (d, 1H), 4.55 (quint, 1H), 2.25 (d, 3H), 1.35 (d, 3H), 1.10 (s, 9H)

IR (cm^{-1}) : 3353, 3298, 1121



215

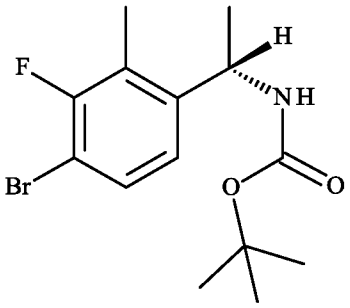
Intermediate 217 :

Obtained starting from intermediate **215** according to **protocol XV**

^{1}H NMR (400MHz, DMSO-d_6): δ 7.50 (t and m, 2H), 7.10 (d, 1H), 4.75 (m, 1H), 2.25 (d, 3H), 1.35 (s, 9H), 1.25 (d, 3H)

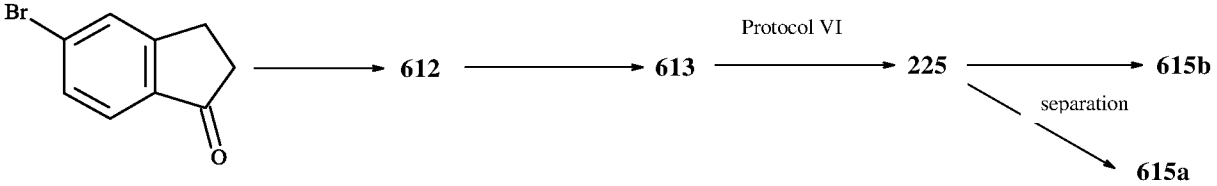
IR (cm^{-1}): 3373, 1681

Enantiomeric excess > 99%



217

<u>Intermediates 615a and 615b :</u>

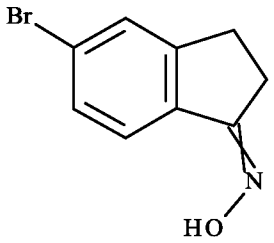


Intermediate 612 :

To a solution of commercial 5-bromo-2,3-dihydro-1H-inden-1-one (5 g, 23 mmoles) in ethanol (47 mL) there are added in succession hydroxylamine hydrochloride (3.1 g, 44 mmoles) and pyridine (9.5 mL). The reaction mixture is stirred for 8 hours at 80°C. The pyridine is evaporated off in vacuo, and the residue is taken up in water and then extracted with methylene chloride. After drying of the organic phase over $MgSO_4$ and concentration, intermediate **612** is obtained in the form of a solid (5.13 g), which is used without additional treatment in the following step.

^{1}H NMR (300MHz; DMSO-d_6): δ 11.0 (s, 1H), 7.60 (s, 1H), 7.45 (2d, 2H), 3.0-2.8 (2m, 4H)

IR (cm^{-1}): 3100



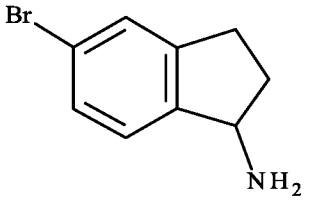
612

Intermediate 613 :

At 0°C, a mixture of **612** (0.5 g, 2.2 mmoles) and MoO_3 (0.42 g, 2.9 mmoles) in methanol (22 mL) is treated carefully with $NaBH_4$ (0.84 g, 2.2 mmoles), the temperature being maintained below 36°C. The reaction mixture is stirred for 1 hour at 0°C and then at ambient temperature for 18 hours before being concentrated in vacuo. The residue is taken up carefully in a 1N aqueous HCl solution and ethyl acetate, the salts are filtered off and the filtrate is decanted. The aqueous phase is rendered basic and then extracted with methylene chloride. After drying over $MgSO_4$ and concentration in vacuo, intermediate **613** is obtained (0.28 g).

^{1}H NMR (300MHz ; DMSO-d_6): δ 7.35 (s, 1H), 7.35 (d, 1H), 4.15 (t, 1H), 2.85-2.7 (m, 2H), 2.3-1.55 (m, 2H), 2.00 (m, 2H)

IR (cm^{-1}): 3400-3300



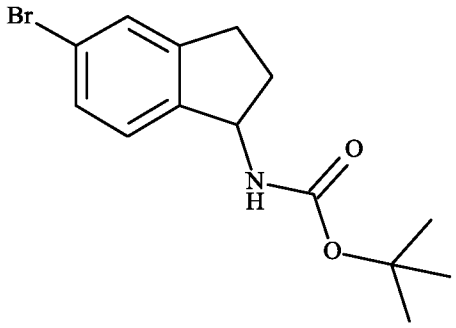
613

Intermediate 225 :

Obtained by protection of intermediate **613** according to the protocol described for intermediate **158** (**protocol VI**)

^{1}H NMR (400MHz, $CDCl_3$): δ 7.36 (broad s, 1H), 7.33 (broad d, 1H), 7.19 (d, 1H), 5.12 (quad, 1H), 4.69 (m, 1H), 2.93 (ddd, 1H), 2.82 (ddd, 1H), 2.57 (m, 1H), 1.79 (m, 1H), 1.48 (s, 9H)

IR (cm^{-1}): 3316, 1682



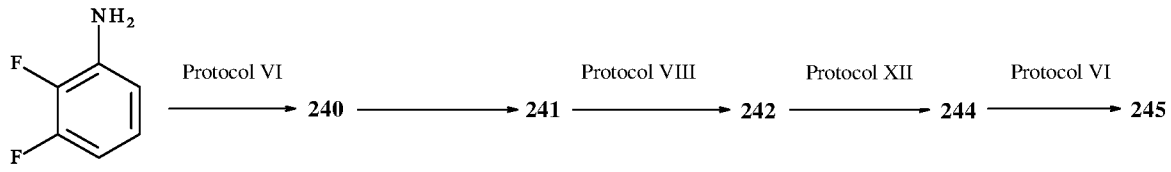
225

Intermediate **225** (18 g) was purified by high pressure chromatography on a chiral support (ChiralPak T101 column, eluant iPrOH/CH_3CN 10/90, detection: 275nm) to give enantiomers **615a** (9.8 g) and **615b** (7.4 g).

Intermediate 615a: α_D (589nM) = 76.78 (c = 0.011 g/mL, MeOH) at 20°C

Intermediate 615b: α_D (589nM) = -77.52 (c = 0.011 g/mL, MeOH) at 20°C

Intermediate 245 :



Intermediate 240 :

4-Bromo-2,3-difluorobenzonitrile

Obtained starting from commercial 2,3-difluoroaniline according to the protocol described for the preparation of intermediate **156** (**protocol VI**)

Intermediate 241 :

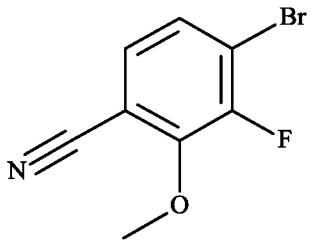
Obtained by treatment of intermediate **240** (0.5 g, 2.3 mmoles) in methanol (12 mL) at 0°C in the presence of sodium methoxide (0.25 g, 4.6 mmoles).

The reaction mixture is stirred for 72 hours at ambient temperature and then poured into water. The precipitate collected on a frit is dried in vacuo. Intermediate **241** (0.3 g) is obtained.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.30 (dd, 1H), 7.22 (d, 1H), 4.16 (s, 3H)

IR (cm^{-1}): 3091, 2233, 1674

GC-EI (70 eV): M+. = 229



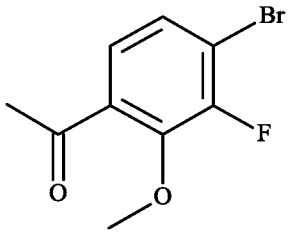
241

Intermediate 242 :

Obtained starting from intermediate **241** according to **protocol VIII**

^{1}H NMR (400 MHz ; DMSO-d_6) : δ 7.52 (dd, 1H), 7.39 (dd, 1H), 3.97 (s, 3H), 2.55 (s, 3H)

IR (cm^{-1}) : 1681



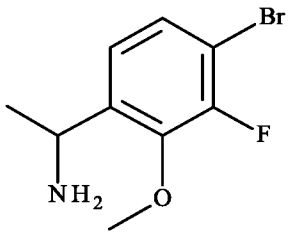
242

Intermediate 244 :

Obtained starting from intermediate **242** according to **protocol XII**

^{1}H NMR (400MHz ; DMSO-d_6): 8.45 (s, 3H), 7.55 (m, 1H), 7.35 (d, 1H), 4.60 (quad, 1H), 3.95 (s, 3H), 1.50 (d, 3H)

IR (cm^{-1}): 3170-2400



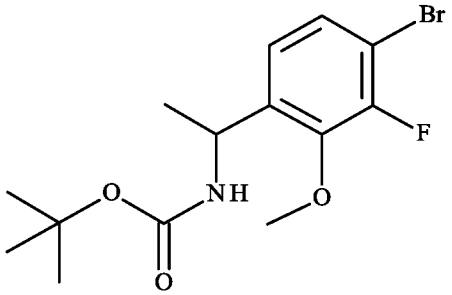
244

Intermediate 245 :

Obtained by protection of intermediate **244** according to the protocol described for intermediate **158** (**protocol VI**)

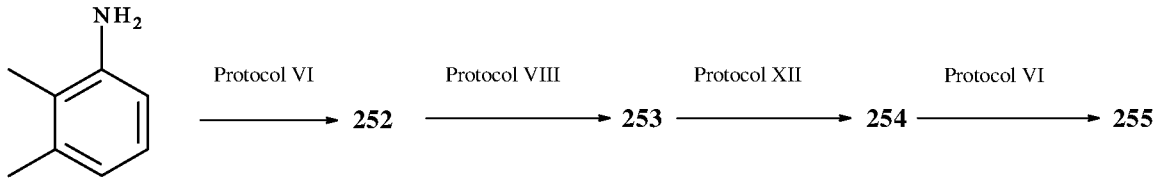
^{1}H NMR (300MHz, DMSO-d_6): δ 7.47 (broad d, 1H), 7.41 (dd, 1H), 7.10 (d, 1H), 4.88 (m, 1H), 3.90 (s, 3H), 1.36 (s, 9H), 1.25 (d, 3H)

^{19}F NMR: -125



245

Intermediate 255 :



Intermediate 252 :

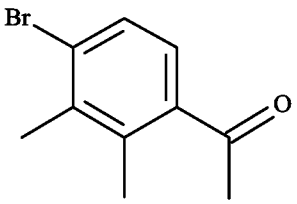
Obtained starting from commercial 2,3-dimethylaniline according to the procedure described for intermediate **156** (**protocol VI**)

Intermediate 253 :

Obtained starting from intermediate **252** according to **protocol VIII**

^{1}H NMR (300 MHz ; DMSO-d_6) : δ 7.55 (d, 1H), 7.40 (d, 1H), 2.55 (s, 3H), 2.40 (s, 3H), 2.30 (s, 3H)

IR (cm^{-1}): 1684



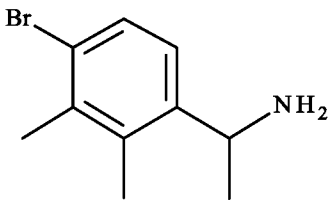
253

Intermediate 254 :

Obtained starting from intermediate **253** according to **protocol XII**

^{1}H NMR (400MHz ; DMSO-d_6): 8.45 (s, 3H), 7.55 (d, 1H), 7.35 (d, 1H), 4.60 (quad, 1H), 2.4-2.3 (2s, 6H), 1.45 (d, 3H)

IR (cm^{-1}): 3200, 2430

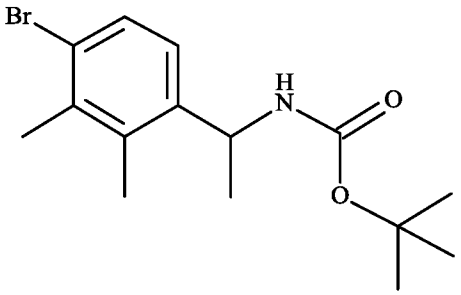


254

Intermediate 255 :

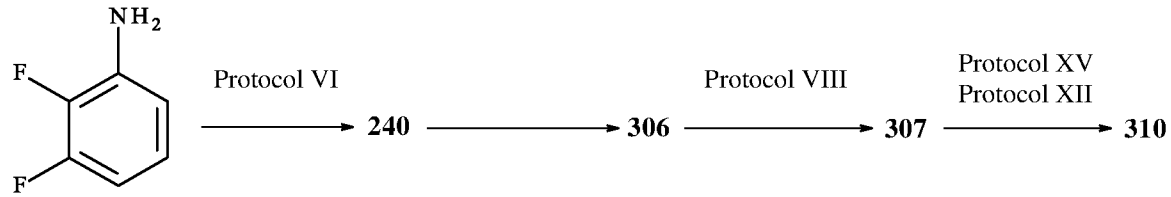
Obtained by protection of intermediate **254** according to the protocol described for intermediate **158** (**protocol VI**)

^{1}H NMR (300MHz, DMSO-d_6): δ 7.45 (dl, 1H), 7.41 (d, 1H), 7.10 (d, 1H), 4.81 (m, 1H), 2.35-2.28 (2s, 6H), 1.35 (s, 9H), 1.20 (d, 3H)



255

Intermediate 310 :



Intermediate 240 :

4-Bromo-2,3-difluorobenzonitrile

Obtained starting from commercial 2,3-difluoroaniline according to the protocol described for the preparation of intermediate **156** (**protocol VI**)

Intermediate 306 :

4-Bromo-2-ethoxy-3-fluorobenzonitrile

Obtained by treatment of intermediate **240** (0.5 g, 2.3 mmoles) in ethanol (12 mL) at 0°C in the presence of sodium ethoxide (0.31 g, 4.6 mmoles).

The reaction mixture is stirred for 72 hours at ambient temperature and then poured into water. The precipitate collected on a frit is dried in vacuo.

^{1}H NMR (400MHz, DMSO-d6): δ 7.60 (s, 2H), 4.35 (q, 2H), 1.35 (t, 3H)

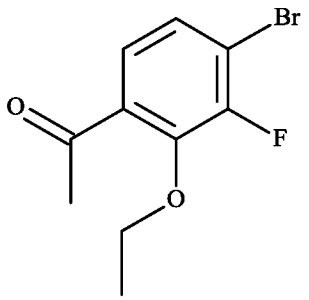
IR (cm^{-1}): 3085, 2237

Intermediate 307 :

Obtained starting from intermediate **306** according to **protocol VIII**

^{1}H NMR (300 MHz ; $CDCl_3$) : δ 7.33 (d, 1H), 7.28 (dd, 1H), 4.26 (quad, 2H), 2.62 (s, 3H), 1.45 (t, 3H)

IR (cm^{-1}) : 1685



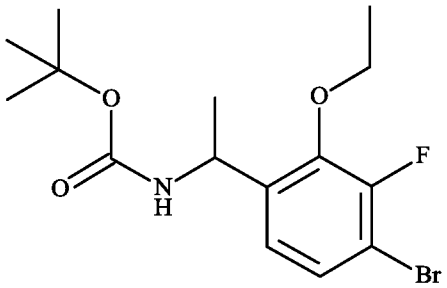
307

Intermediate 310 :

Obtained starting from intermediate **307** according to **protocol XV**, which intermediate **307** is converted beforehand into the amine (not isolated) according to **protocol XII**

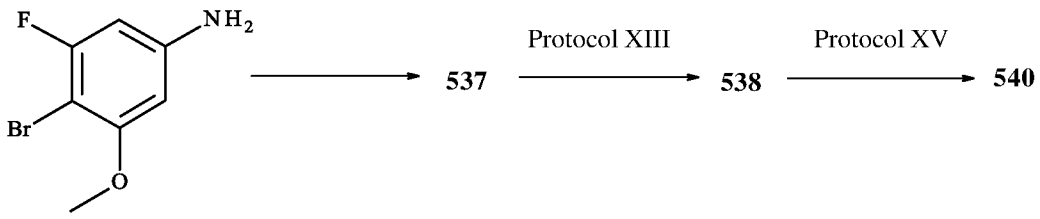
^{1}H NMR (400MHz, DMSO-d_6): δ 7.45 (d, 1H), 7.40 (dd, 1H), 7.10 (d, 1H), 4.90 (m, 1H), 4.10 (m, 2H), 1.35 (m, 12H), 1.20 (d, 3H)

IR (cm^{-1}): 3480-3280, 1694



310

Intermediate 540 :

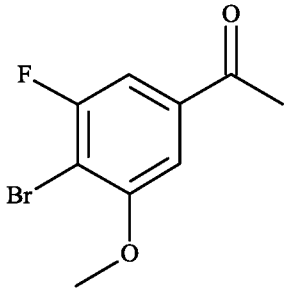


Intermediate 537 :

Obtained starting from 4-bromo-3-fluoro-5-methoxyaniline, prepared by bromation of 3-fluoro-5-methoxyaniline, according to the protocol described for intermediate **117**

^{1}H NMR (300MHz, DMSO-d_6): δ 7.55 (dd, 1H), 7.40 (d, 1H), 4.00 (s, 3H), 2.60 (s, 3H)

IR (cm^{-1}) : 1682, 1229



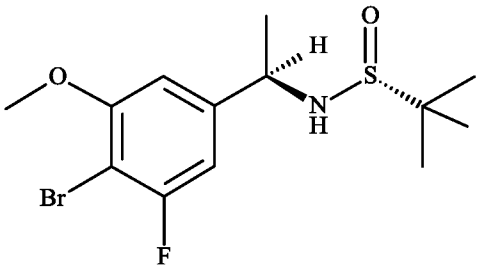
537

Intermediate 538 :

Obtained by reaction of intermediate **537** and (R)-(+)-2-methyl-2-propanesulphinamide according to **protocol XIII**

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.05-7.00 (2m, 2H), 5.75 (d, 1H), 4.38 (m, 1H), 3.88 (s, 3H), 1.39 (d, 3H), 1.12 (s, 9H)

IR (cm^{-1}) : 3265, 1058



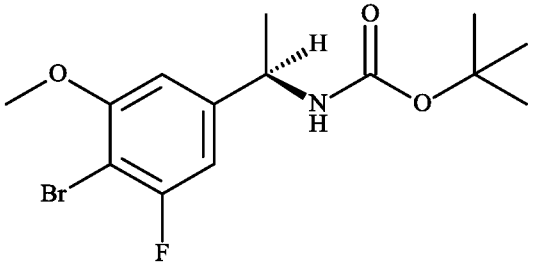
538

Intermediate 540 :

Obtained starting from intermediate **538** according to **protocol XV**

^{1}H NMR (400MHz, DMSO-d_6): δ 7.40 (d, 1H), 6.92 (broad s, 1H), 6.88 (dd, 1H), 4.6 (m, 1H), 3.87 (s, 3H), 1.35 (broad s, 9H), 1.3 (d, 3H)

Optical purity: > 99%



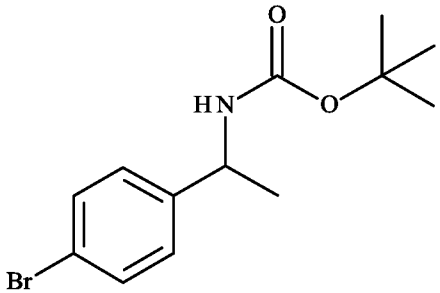
540

Intermediate 589 :

Obtained by protection of commercial 1-(4-bromophenyl)ethanamine according to the protocol described for intermediate **158** (**protocol VI**)

^{1}H NMR (300MHz, DMSO-d_6): δ 7.50 (d, 2H), 7.40 (d, 1H), 7.25 (d, 2H), 4.60 (m, 1H), 1.40 (s, 9H), 1330 (d, 3H)

IR (cm^{-1}): 3373, 1681



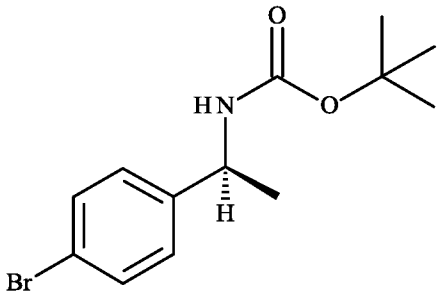
589

Intermediate 594 :

Obtained by protection of commercial (1S)-1-(4-bromophenyl)ethanamine according to the protocol described for intermediate **158** (**protocol VI**)

^{1}H NMR (300MHz, DMSO-d_6): δ 7.50 (d, 2H), 7.40 (d, 1H), 7.25 (d, 2H), 4.60 (m, 1H), 1.40 (s, 9H), 1.30 (d, 3H)

IR (cm^{-1}): 3373, 1681



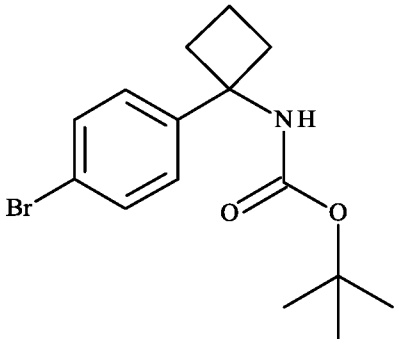
594

Intermediate 608 :

Obtained starting from (4-bromophenyl)acetonitrile according to **protocol V** in the presence of 1,3-dibromopropane in the first step

^{1}H NMR (300 MHz ; DMSO-d_6) **:** δ 7.65 (m, 1H) ; 7.50-7.30 (dd, 4H) ; 2.35 (m, 4H) ; 2.00-1.75 (m, 2H) ; 1.30 (m, 9H)

IR (cm^{-1}) : 3346, 1683



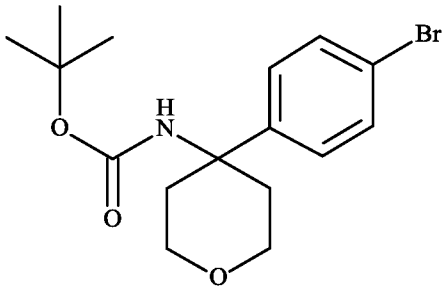
608

Intermediate 623 :

Obtained starting from (4-bromophenyl)acetonitrile according to **protocol V** in the presence of 1-bromo-2-(2-bromoethoxy)ethane in the first step

^{1}H NMR (300 MHz ; DMSO-d_6) **:** δ 7.50 (d, 2H); 7.30 (d, 2H); 3.75-3.55 (m, 4H); 2.20 (m, 2H); 1.85 (m, 2H); 1.30 (broad s, 9H)

IR (cm^{-1}) : 3255-3135, 1692



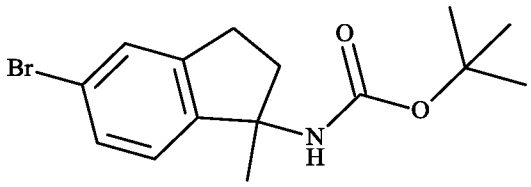
623

Intermediate 633 :

Obtained starting from commercial 5-bromoinden-1-one according to the procedure used to prepare intermediate **87**

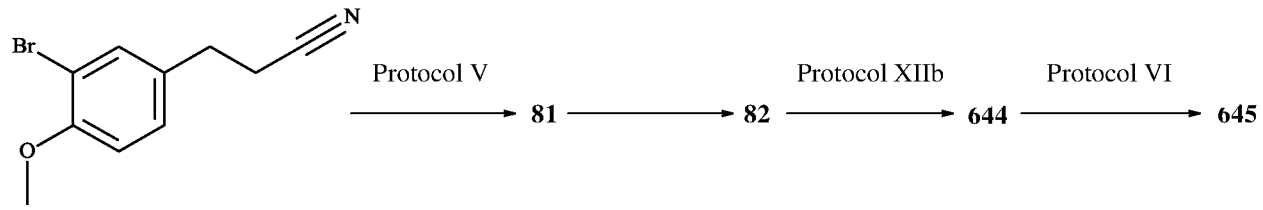
^{1}H NMR (400MHz, $CDCl_3$): δ 7.31 (d and s, 1H), 7.12 (d, 1H), 4.80 (s, 1H), 3.00 (m, 1H), 2.85 (m, 1H), 2.60 (m, 1H), 2.12 (m, 1H), 1.50 (s, 3H), 1.38 (s, 9H)

IR (cm-1): 3347, 1694



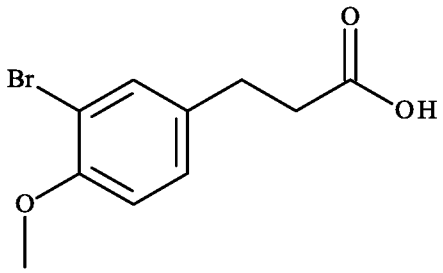
633

Intermediate 645 :



Intermediate 81 :

Obtained starting from commercial 3-(3-bromo-4-methoxyphenyl)propanenitrile according to the protocol described for obtaining intermediate **599** (**protocol V**)



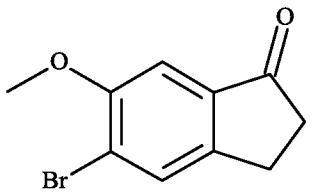
81

Intermediate 82 :

Intermediate **81** is stirred in the presence of PCl_5 (44 g, 211 mmoles) for 2½ hours, and then the mixture is carefully concentrated in vacuo. The residue, diluted in methylene chloride (960 mL) and cooled to 0°C, is treated with $AlCl_3$ (28 g, 211 mmoles). The reaction mixture is stirred for 2 hours at 15°C and then poured carefully into ice. The mixture is extracted with AcOEt, and the organic phase is washed in succession with water, with a 4N aqueous NaOH solution, again with water and with an HCl solution. The organic phase is dried over $MgSO_4$ and concentrated in vacuo. The residue is solidified in isopropyl ether. Intermediate **82** (39 g) is obtained in the form of a solid.

^{1}H NMR (300 MHz ; $CDCl_3$) **:** δ 7.70 (s, 1H); 7.20 (s, 1H); 3.92 (s, 3H); 3.06 (t, 2H); 2.70 (t, 2H).

IR (cm^{-1}) : 1698

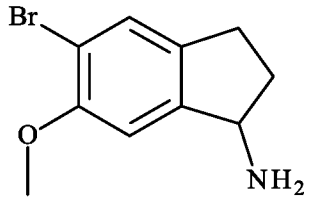


82

Intermediate 644 :

Obtained starting from intermediate **82** according to **protocol XIIb**

^{1}H NMR (300MHz ; $CDCl_3$): 7.35 (s, 1H); 6.90 (s, 1H), 4.30 (t, 1H); 3.90 (s, 3H), 2.85-2.7 (2m, 2H), 2.50 (m, 1H), 1.70 (m, 1H), 1.50 (m, 2H)



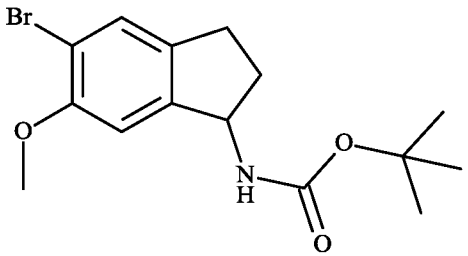
644

Intermediate 645 :

Obtained by protection of intermediate **644** according to the protocol described for intermediate **158** (**protocol VI**)

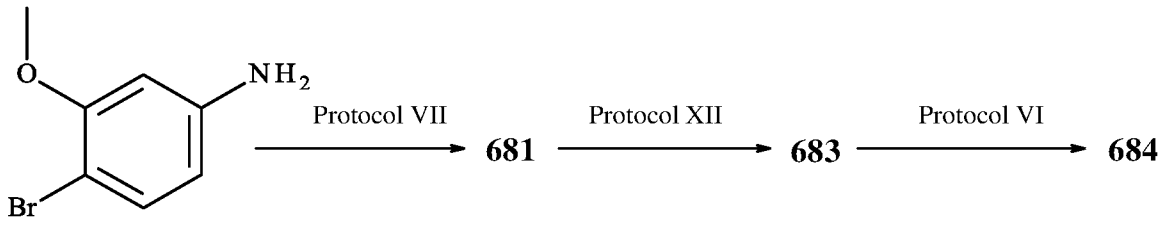
^{1}H NMR (300MHz, DMSO-d6): δ 7.35 (s, 1H), 6.90 (s, 1H), 4.90 (m, 1H), 3.80 (s, 3H), 2.9-2.6 (2m, 2H), 2.35 (m, 1H), 1.80 (m, 1H), 1.45 (s, 9H)

IR (cm^{-1}): 3309, 1682



645

Intermediate 684 :



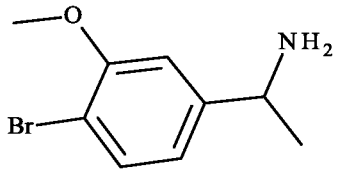
The synthesis of intermediate **681** is described in **protocol VII**

Intermediate 683 :

Obtained starting from intermediate **681** according to **protocol XII**

^{1}H NMR (300MHz ; $CDCl_3$): 7.40 (d, 1H), 7.15 (d, 1H); 6.90 (dd, 1H), 4.00 (quad, 1H) ; 3.85 (s, 3H), 1.90 (m, 2H), 1.20 (d, 3H)

IR (cm^{-1}): 3750, 3000



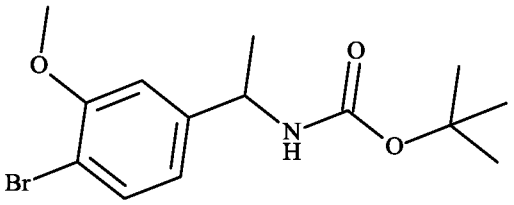
683

Intermediate 684 :

Obtained by protection of intermediate **683** according to the protocol described for intermediate **158** (**protocol VI**)

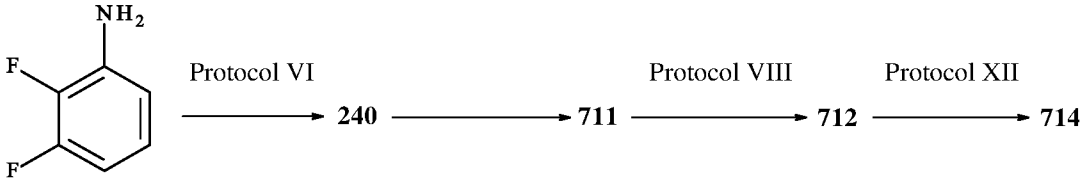
^{1}H NMR (400MHz, DMSO-d_6): δ 7.50 (d, 1H), 7.40 (d, 1H), 7.05 (d, 1H), 6.80 (dd, 1H), 4.60 (quint, 1H), 3.80 (s, 3H), 1.38 (m, 9H), 1.30 (d, 3H)

IR (cm^{-1}): 3286, 1690



684

Intermediate 714 :



Intermediate 240 :

4-Bromo-2,3-difluorobenzonitrile

Obtained starting from commercial 2,3-difluoroaniline according to the protocol described for the preparation of intermediate **156** (**protocol VI**)

Intermediate 711 :

4-Bromo-3-fluoro-2-(2-methylpropoxy)benzonitrile

Obtained starting from intermediate **240** (5 g, 23 mmoles) and isobutanol (2.1 mL, 23 mmoles) in DMF (100 mL) at 0°C in the presence of 60% sodium hydride in oil (0.92 g).

The reaction mixture is stirred for 72 hours at ambient temperature and then poured into water and extracted with ethyl ether. The organic phase is washed with water, dried over $MgSO_4$ and then concentrated. The residue is purified on silica gel (eluant cyclohexane/methylene chloride 70/30 to 0/100). Intermediate **711** (4.1 g) is obtained.

^{1}H NMR (400MHz, DMSO-d6): δ 7.60 (s, 1H), 4.10 (d, 2H), 2.05 (m, 1H), 1.00 (d, 6H)

IR (cm^{-1}): 2240

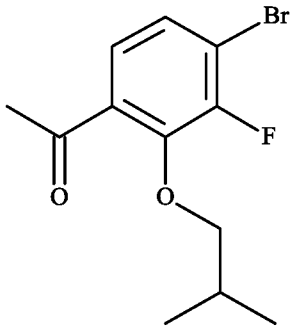
GC-EI (70 eV): M+. = 271

Intermediate 712 :

Obtained starting from intermediate **711** according to **protocol VIII**

^{1}H NMR (400 MHz ; DMSO-d_6) **:** δ 7.50 (m, 1H), 7.35 (dd, 1H), 3.90 (d, 2H), 2.55 (s, 3H), 2.05 (m, 1H), 1.00 (d, 6H)

IR (cm^{-1}) : 1686



712

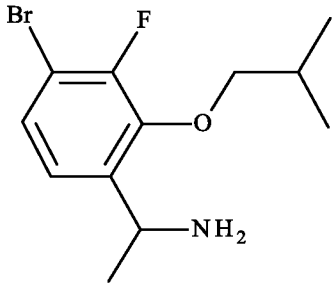
Intermediate 714 :

Obtained starting from intermediate **712** according to **protocol XII**

^{1}H NMR (400MHz ; DMSO-d_6): 8.70 (broad s, 3H), 7.55 (m, 1H), 7.45 (d, 1H), 4.60 (quad, 1H), 4.0-3.8 (2dd, 2H), 2.05 (m, 1H), 1.50 (d, 3H), 1.00 (d, 6H)

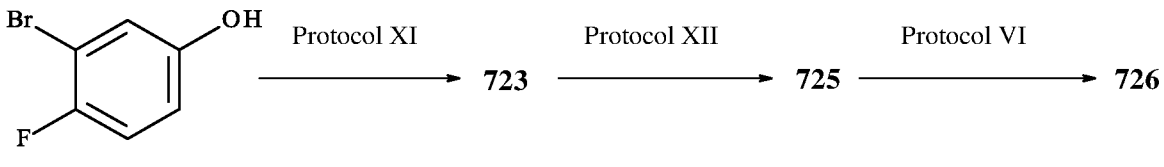
^{19}F NMR: -123 (1F)

IR (cm^{-1}): 3154, 2000



714

Intermediate 726 :



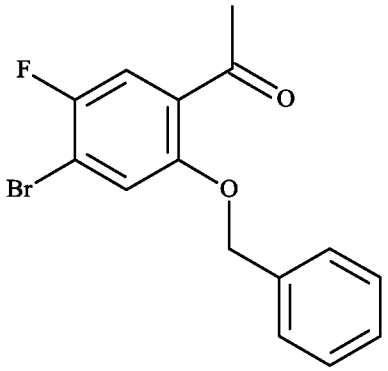
Intermediate 723 :

Obtained starting from commercial 3-bromo-4-fluorophenol according to **protocol XI**

^{1}H NMR (400MHz, DMSO-d6): δ 7.68 (d, 1H), 7.54 (d, 1H), 7.51 (d, 2H), 7.44 (t, 2H), 7.38 (t, 1H), 5.28 (s, 2H), 2.51 (s, 3H)

^{19}F NMR: -117.49 (1F)

IR (cm^{-1}) : 1662



723

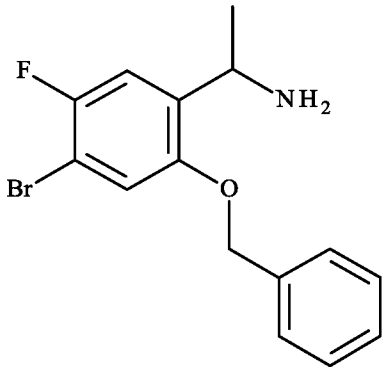
Intermediate 725 :

Obtained starting from intermediate **723** according to **protocol XII**

^{1}H NMR (300/400MHz: DMSO-d_6): 7.46 (d, 1H), 7.5-7.35 (m, 5H), 7.31 (d, 1H), 5.15 (2d, 2H), 4.26 (quad, 1H), 1.85 (broad s, 2H), 1.19 (d, 3H)

^{19}F NMR: -117.8 (dd, 1F)

IR (cm^{-1}): 3154, 2000.



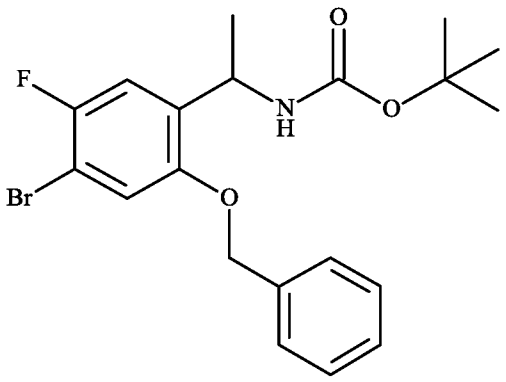
725

Intermediate 726 :

Obtained by protection of intermediate **725** according to the protocol described for intermediate **158** (protocol VI)

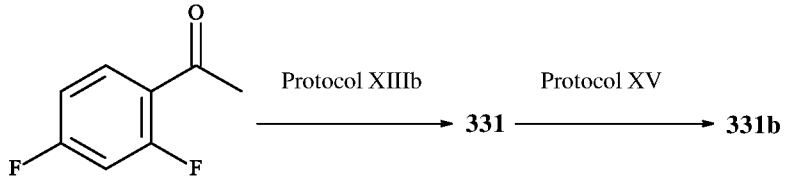
^{1}H NMR (300MHz, DMSO-d_6): δ 7.40 (m and d, 6H), 7.25 (d, 1H), 5.20 (s, 2H), 4.95 (m, 1H), 1.35 (broad s, 9H), 1.25 (d, 3H)

IR (cm^{-1}): 3303, 1675



726

Intermediate 331b :



The synthesis of intermediate 331 is described in **protocol XIIIb**.

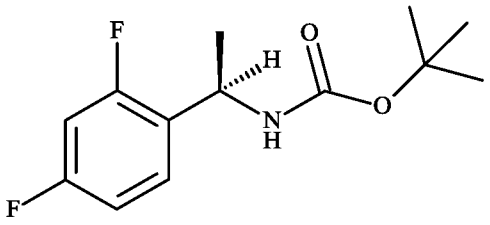
Intermediate 331b :

Obtained starting from intermediate **331** according to **protocol XV**

^{1}H NMR (400MHz, DMSO-d_6): δ 7.46 (broad d, 1H), 7.40 (m, 1H), 7.14 (m, 1H), 7.06 (m, 1H), 4.83 (m, 1H), 1.34 (broad s, 9H), 1.27 (d, 3H)

IR (cm^{-1}): 3373, 1678

Enantiomeric excess > 99%



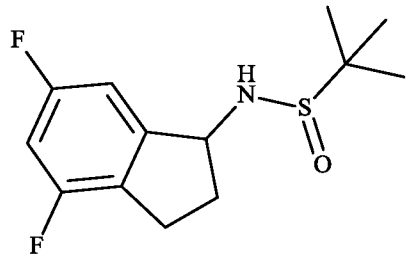
331b

Intermediate 234 :

Obtained by reaction of commercial 4,6-difluoro-2,3-dihydro-1H-inden-1-one and (+/-)-2-methyl-2-propanesulphinamide according to **protocol XIII**

^{1}H NMR (400/500MHz, DMSO-d_6): δ 7.28 (d, 1H), 7.04 (t, 1H), 5.90 (d, 1H), 4.78 (quad, 1H), 2.9-2.7 (2m, 2H), 2.45-1.98 (2m, 2H), 1.16 (s, 9H)

IR (cm^{-1}) : 3246



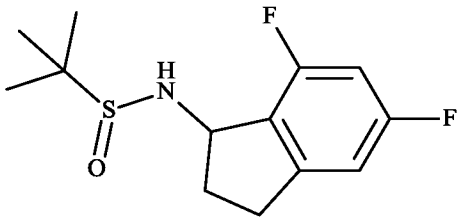
234

Intermediate 260 :

Obtained by reaction of commercial 5,7-difluoro-2,3-dihydro-1H-inden-1-one and (+/-)-2-methyl-2-propanesulphinamide according to **protocol XIII**

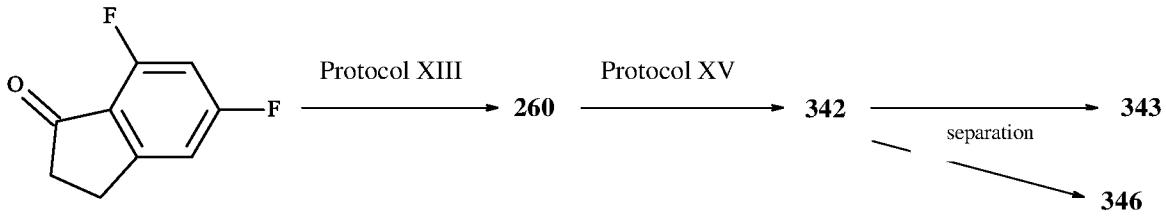
^{1}H NMR (400MHz, DMSO-d_6): δ 6.98 (m, 2H), 5.64 (d, 1H), 4.89 (m, 1H), 3.13 (m, 1H), 2.8 (m, 1H), 2.34 (m, 1H), 2.13 (m, 1H), 1.07 (s, 9H)

IR (cm^{-1}) : 3209, 1048



260

Intermediates 343 and 346 :

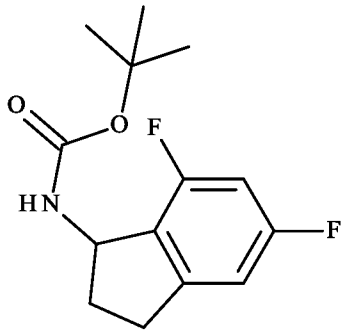


Intermediate 342 :

Obtained starting from intermediate **260** according to **protocol XV**

^{1}H NMR (400MHz, DMSO-d_6): δ 7.26 (d, 1H), 6.95 (m, 2H), 5.16 (quad, 1H), 3.00 (m, 1H), 2.77 (m, 1H), 2.38 (m, 1H), 1.87 (m, 1H), 1.41 (s, 9H)

IR (cm^{-1}): 3241, 1708-1680



342

Intermediate **342** (7.9 g) was purified by high pressure chromatography on a chiral support (ChiralPak IC column, eluant ethanol/n-heptane 10/90, detection: 260 nm) to give enantiomers **343** (3.7 g) and **346** (3.7 g).

Intermediate 343 :

optical purity (ChiralPak IC3 column: 3µm, 4.6x250mm, eluant ethanol/n-heptane 10/90, detection: 210 nm): >99%, intermediate **346**< 1%

IR (cm^{-1}): 3355, 1680

α_D (589nM) = + 60.7 (c = 0.013 g/mL, EtOH) at 20°C

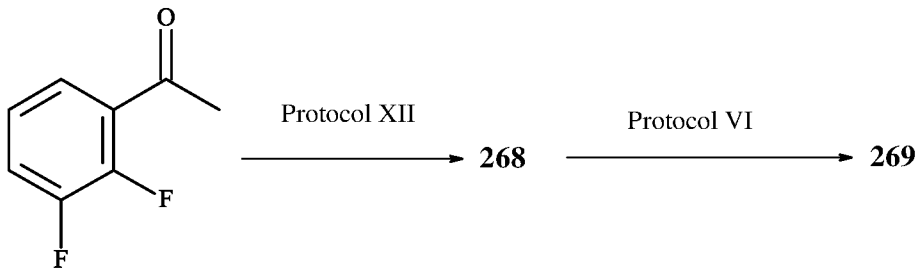
Intermediate 346 :

Optical purity (ChiralPak IC3 column: 3µm, 4.6x250mm, eluant ethanol/n-heptane 10/90, detection: 210 nm): >99%, intermediate **343**< 1%

IR (cm^{-1}): 3354, 1678

α_D (589nM) = - 60.7 (c = 0.013 g/mL, EtOH) at 20°C

Intermediate 269 :

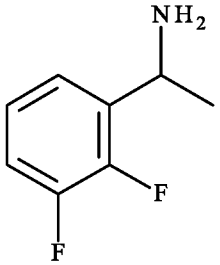


Intermediate 268 :

Obtained starting from commercial 1-(2,3-difluorophenyl)ethanone according to **protocol XII**

^{1}H NMR (400MHz ; DMSO-d_6): 7.40 (ddd, 1H), 7.25 (m, 1H), 7.20 (m, 1H), 4.30 (quad, 1H), 1.95 (m, 2H), 1.25 (d, 3H)

IR (cm^{-1}): 3750, 3000.



268

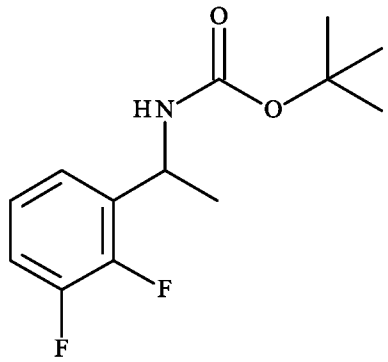
Intermediate 269 :

Obtained by protection of intermediate **268** according to the protocol described for intermediate **158** (**protocol VI**)

^{1}H NMR (400MHz, DMSO-d_6): δ 7.53 (d, 1H), 7.20 (m, 3H), 4.90 (m, 1H), 1.35 (m, 9H), 1.30 (d, 3H), **IR (cm^{-1})**: 3377, 1681

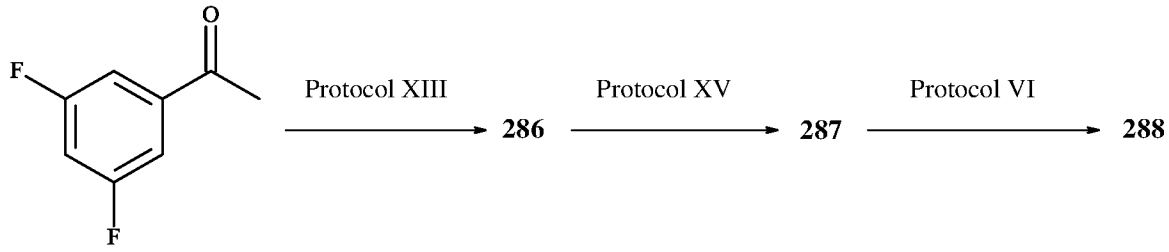
^{19}F NMR: -140, -146

GC-EI (70 eV) 257.1



269

Intermediate 288 :



The preparations of intermediates **286** and **287** are described in **protocols XIII** and **XV**, respectively.

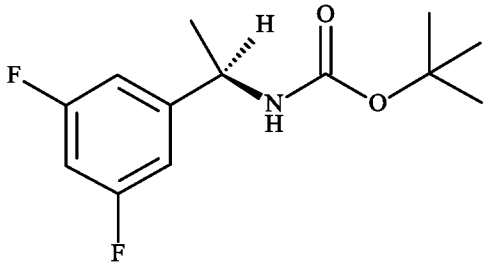
Intermediate 288 :

Obtained by protection of intermediate **287** according to the protocol described for intermediate **158** (**protocol VI**)

^{1}H NMR (300MHz, DMSO-d_6): δ 7.42 (d, 1H), 7.03 (m, 1H), 7.00 (m, 2H), 4.61 (m, 1H), 1.37 (s, 9H), 1.30 (d, 3H)

IR (cm^{-1}): 3369, 1682

α_D (589nM) = 58.22 (c = 0.0087 g/mL, methanol) at 20°C



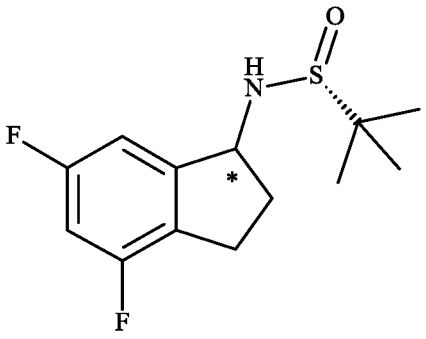
288

Intermediate 317 :

Obtained by reaction of commercial 4,6-difluoro-2,3-dihydro-1H-inden-1-one and (R)-(+)-2-methyl-2-propanesulphinamide according to **protocol XIIIb**

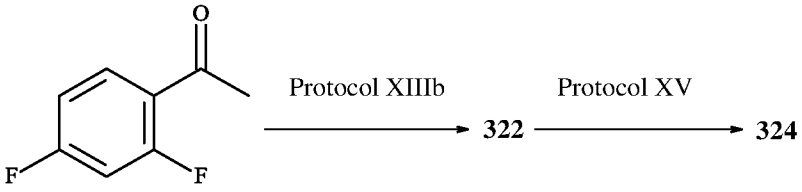
^{1}H NMR (400MHz, DMSO-d_6): δ 7.29 (d, 1H), 7.05 (t, 1H), 5.91 (d, 1H), 4.79 (m, 1H), 2.9-2.7 (m, 2H), 2.45-1.99 (m, 2H), 1.15 (s, 9H)

IR (cm^{-1}) : 3207



317

Intermediate 324 :

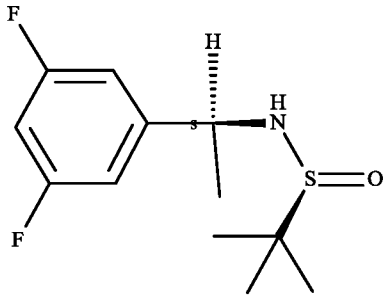


Intermediate 322 :

Obtained by reaction of commercial 3,5-difluoroacetophenone and (S)-(-)-2-methyl-2-propanesulphinamide according to **protocol XIIIb**

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.14 (d, 2H), 7.05 (tt, 1H), 4.40 (m, 1H), 3.80 (d, 1H), 1.38 (d, 3H), 1.13 (s, 9H)

IR (cm^{-1}) : 3125, 1624, 1598, 1117, 853, 699



322

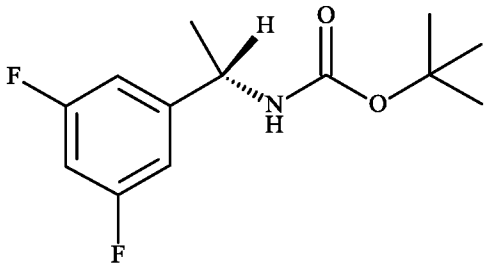
Intermediate 324 :

Obtained starting from intermediate **322** according to **protocol XV**

^{1}H NMR (400MHz, DMSO-d_6): δ 7.40 (d, 1H), 7.05 (m, 1H), 7.00 (m, 2H), 4.65 (m, 1H), 1.35 (broad s, 9H), 1.30 (d, 3H)

IR (cm^{-1}): 3364, 1683

Enantiomeric excess > 99%



324

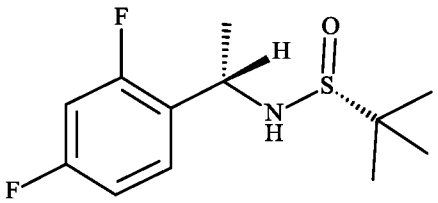
Intermediate 334 :

Obtained by reaction of commercial 1-(2,4-difluorophenyl)ethanone and (R)-(+)-2-methyl-2-propanesulphinamide and then reduction with L-selectride (1M in THF) according to **protocol XIII**

^{1}H NMR (300MHz, DMSO-d_6): δ 7.6 (m, 1H), 7.20 (m, 1H), 7.10 (m, 1H), 5.45 (d, 1H), 4.65 (quint, 1H), 1.5 (d, 3H), 1.10 (s, 9H)

IR (cm^{-1}) : 3214

^{19}F NMR: -111, -114 (2m)



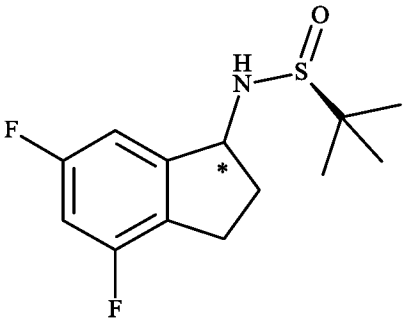
334

Intermediate 337 :

Obtained by reaction of commercial 4,6-difluoro-2,3-dihydro-1H-inden-1-one and (S)-(-)-2-methyl-2-propanesulphinamide according to **protocol XIIIb**

^{1}H NMR (400MHz, DMSO-d_6): δ 7.3 (dd, 1H), 7.05 (td, 1H), 5.95 (d, 1H), 4.80 (quad, 1H), 2.9-2.7 (m, 2H), 2.45-2.0 (m, 2H), 1.15 (s, 9H)

IR (cm^{-1}) : 3207



337

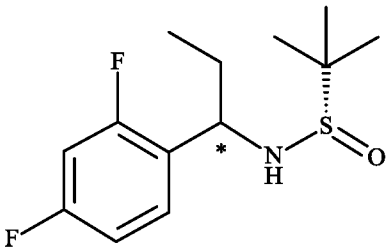
Intermediate 478 :

Obtained starting from N-[(2,4-difluorophenyl)methylidene]-2-methylpropane-2-sulphinamide (precursor of intermediate **334** before reduction) and EtMgCl according to **protocol XIV**

^{1}H NMR (300MHz, DMSO-d_6): δ 7.49 (m, 1H), 7.09 (m,1H), 5.44 (d, 1H), 4.39 (m, 1H), 4.37 (m, 1H), 1.9 (m, 1H), 1.71 (m, 1H), 1.07 (s, 9H), 0.81 (s, 3H)

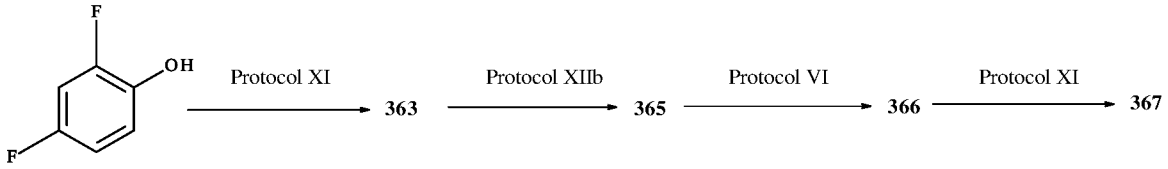
^{19}F NMR: -112.2, -115.4

IR (cm^{-1}): 3205, 1049



478

Intermediate 367 :



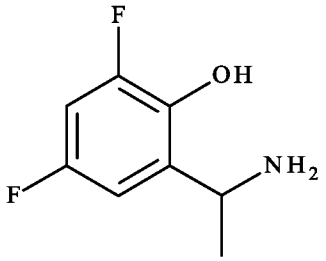
The preparation of intermediate **363** is described in **protocol XI**.

Intermediate 365 :

Obtained starting from intermediate **363** according to **protocol XIIb**

^{1}H NMR (400MHz ; DMSO-d_6): 7.00 (m, 1H), 6.80 (m, 1H), 7.00-5.0 (m, 3H), 4.20 (quad, 1H), 1.30 (d, 3H)

IR (cm^{-1}): 3300-2000



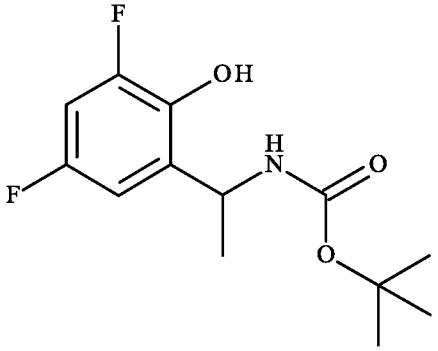
365

Intermediate 366 :

Obtained by protection of intermediate **365** according to the protocol described for intermediate **158** (**protocol VI**)

^{1}H NMR (400MHz, DMSO-d_6): δ 9.40 (m, 1H), 7.35 (d l, 1H), 7.05 (m, 1H), 6.90 (dd, 1H), 4.95 (quint, 1H), 2.39 (s, 3H), 1.35 (d, 9H), 1.20 (d, 3H)

IR (cm^{-1}): 3500, 2600, 1690, 1672.



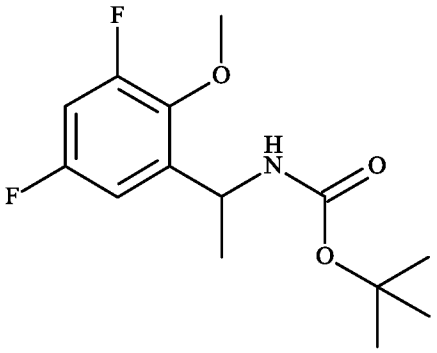
366

Intermediate 367 :

Obtained starting from intermediate **366** according to the protocol described for intermediate **384** (**Protocol XI**)

^{1}H NMR (400MHz, DMSO-d_6): δ 7.43 (d, 1H), 7.15 (m, 1H), 7.00 (m, 1H), 4.93 (m, 1H), 3.82 (s, 3H), 1.36 (s, 9H), 1.21 (d, 3H)

IR (cm^{-1}): 3368, 1681



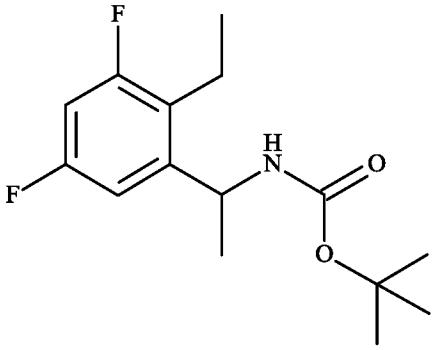
367

Intermediate 430 :

Obtained starting from intermediate **366** according to the protocol described for intermediate **562** (**Protocol XXI**)

^{1}H NMR (400MHz, DMSO-d_6): δ 7.50 (d, 1H), 7.05 (dd, 1H), 7.00 (td, 1H), 4.85 (quint, 1H), 2.70 (m, 1H), 2.60 (m, 1H), 1.35 (m, 9H), 1.30 (d, 3H), 1.15 (t, 3H)

IR (cm^{-1}): 3380, 1671



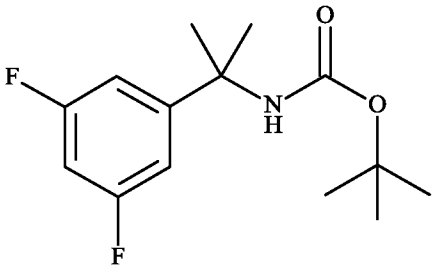
430

Intermediate 378:

Obtained starting from commercial 3,5-difluorobenzonitrile according to **protocol VI**

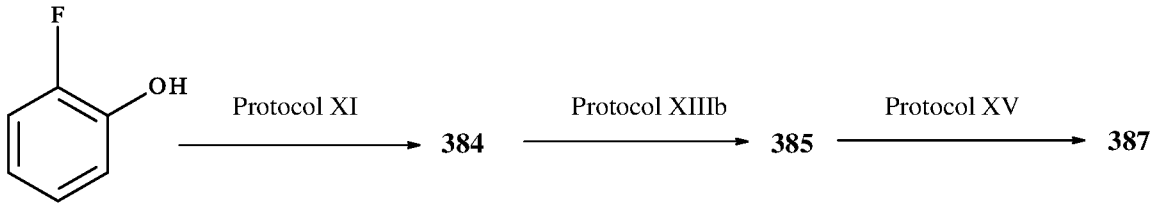
^{1}H NMR (400 MHz ; DMSO-d_6) **:** δ 7.28 (m, 1H) ; 7.00 (m, 1H) ; 6.98 (m, 2H) ; 1.48 (s, 6H) ; 1.30 (m, 9H)

IR (cm^{-1}): 3314 ; 1685 ; 1523



378

Intermediate 387:

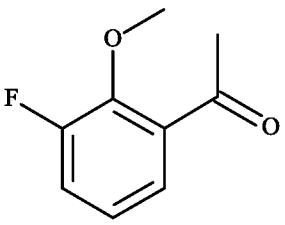


Intermediate 384 :

Obtained starting from commercial 2-fluorophenol according to **protocol XI**, in the presence of methyl iodide in the last step

^{1}H NMR (400MHz, DMSO-d_6): δ 7.50 (dd, 1H), 7.40 (dd, 1H), 7.20 (m, 1H), 3.90 (s, 3H), 2.55 (s, 3H)

IR (cm^{-1}) : 1685



384

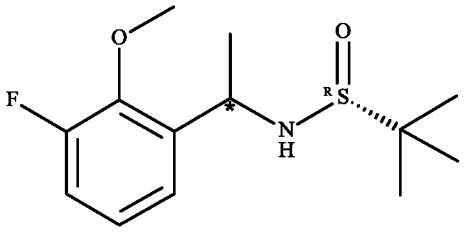
Intermediate 385 :

Obtained by reaction of intermediate **384** and (R)-(+)-2-methyl-2-propanesulphinamide according to **protocol XIIIb**

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.30 (d, 1H), 7.12 (m, 2H), 5.63 (d, 1H), 4.72 (m, 1H), 3.89 (d, 3H), 1.36 (d, 3H), 1.11 (s, 9H)

^{19}F NMR: -130.0

IR (cm^{-1}) : 3500, 3000, 1056



385

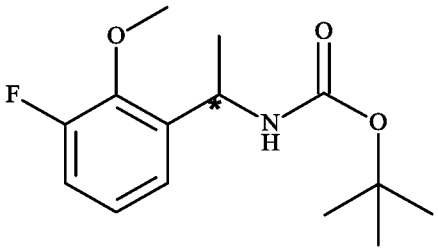
Intermediate 387 :

Obtained starting from intermediate **385** according to **protocol XV**

^{1}H NMR (400MHz, DMSO-d_6): δ 7.42 (broad d, 1H), 7.16 (broad d, 1H), 7.10 (m, 2H), 4.95 (m, 1H), 3.87 (s, 3H), 1.36 (s, 9H), 1.25 (d, 3H)

IR (cm^{-1}): 3346, 1695

Enantiomeric excess > 99%



387

<u>Intermediate 739 :</u>

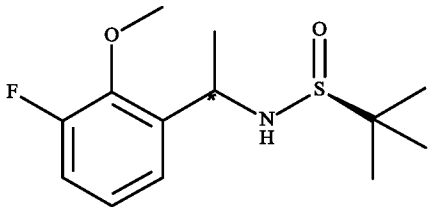
Intermediate 737 :

Obtained by reaction of intermediate **384** and (S)-(-)-2-methyl-2-propanesulphinamide according to **protocol XIIIb**

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.30 (d, 1H), 7.12 (m, 2H), 5.63 (d, 1H), 4.72 (m, 1H), 3.89 (d, 3H), 1.36 (d, 3H), 1.11 (s, 9H)

^{19}F NMR: -130.02

IR (cm^{-1}): 3219, 1050.



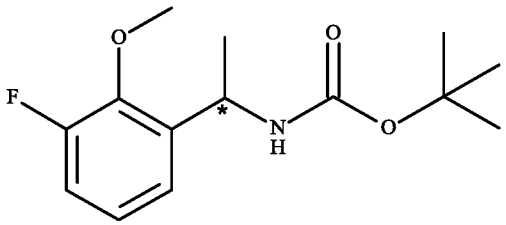
737

Intermediate 739 :

Obtained starting from intermediate **737**according to **protocol XV**

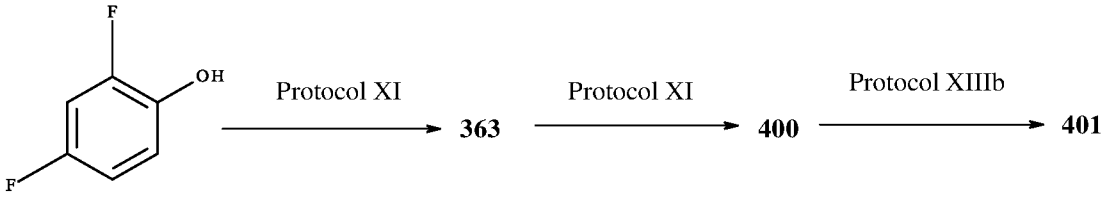
^{1}H NMR (300MHz, DMSO-d_6): δ 7.2-7.0 (m, 3H), 6.95 (m, 1H), 4.98 (quint, 1H), 3.90 (s, 3H), 1.35 (s, 9H), 1.30 (d, 3H)

IR (cm^{-1}): 3353, 1697



739

Intermediate 401:



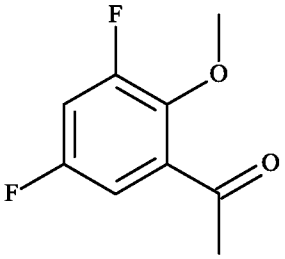
The preparation of intermediate **363** is described in **protocol XI**.

Intermediate 400 :

Obtained starting from intermediate **363** according to **protocol XI**, in the presence of methyl iodide in the last step

^{1}H NMR (400MHz, $CDCl_3$): δ 7.20 (ddd, 1H), 7.00 (ddd, 1H), 4.00 (s, 3H), 2.65 (s, 3H)

IR (cm^{-1}) : 1674



400

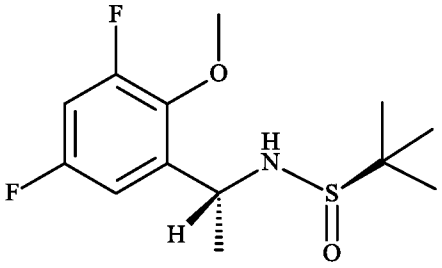
Intermediate 401 :

Obtained by reaction of intermediate **400** and (R)-(+)-2-methyl-2-propanesulphinamide according to **protocol XIIIb**

^{1}H NMR (400MHz, DMSO-d_6): δ 7.2 (m, 2H), 5.70 (s, 1H), 4.70 (quint, 1H), 3.85 (d, 3H), 1.35 (d, 3H), 1.10 (s, 9H)

IR (cm^{-1}): 3150

Diastereoisomeric purity: de>99%



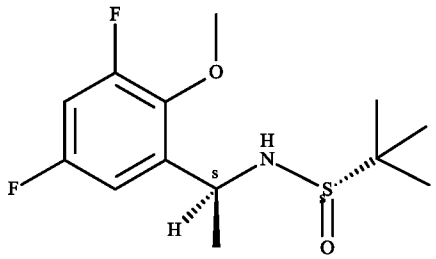
401

Intermediate 404:

Obtained by reaction of intermediate **400** and (S)-(-)-2-methyl-2-propanesulphinamide and then reduction with L-selectride (1M in THF) according to **protocol XIII**

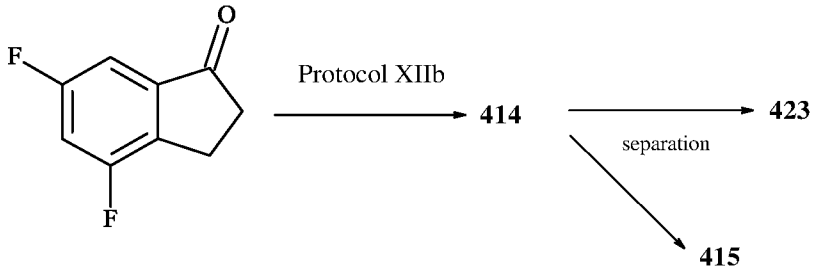
^{1}H NMR (400MHz, DMSO-d_6): δ 7.2 (m, 1H), 7.1 (ddd, 1H), 5.40 (d, 1H), 4.75 (quint, 1H), 3.85 (s, 3H), 1.4 (d, 3H), 1.10 (s, 9H)

IR (cm^{-1}): 3260



404

Intermediates 423 and 415:

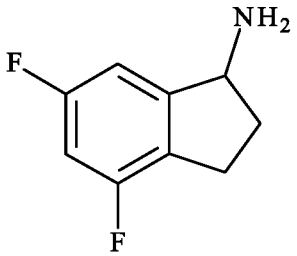


Intermediate 414 :

Obtained starting from commercial 4,6-difluoro-2,3-dihydro-1H-inden-1-one according to **protocol XIIb**

^{1}H NMR (400MHz ; DMSO-d_6): 8.85 (m, 3H), 7.50 (dd, 1H), 7.20 (td, 1H), 4.75 (t, 1H), 3.05 (m, 1H), 2.85 (m, 1H), 2.55 (m, 1H), 2.10 (m, 1H)

IR (cm^{-1}): 3450-2440



414

Intermediate **414** (11 g) was purified by high pressure chromatography on a chiral support (ChiralPak T304 column, eluant acetonitrile : 100 : detection 260nm) to give enantiomers **415** (5.2 g) and **423** (5.5 g).

Intermediate 415 :

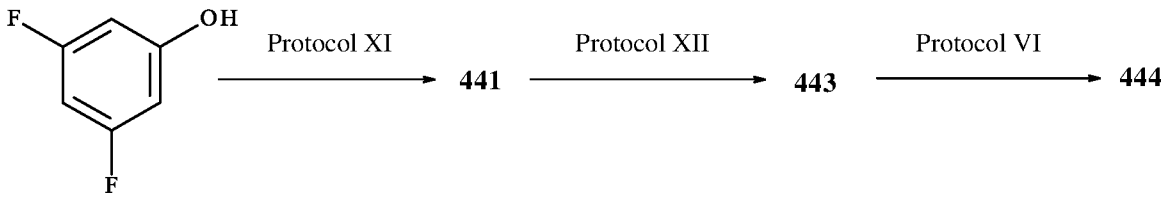
^{1}H NMR (400MHz, DMSO-d_6): 7.00 (td, 1H), 6.80 (dd, 1H), 5.00 (m, 1H), 2.90 (m, 1H), 2.70 (m, 1H), 2.40 (m, 1H), 1.90 (m, 1H), 1.40 (s, 9H)

Optical purity (SFC: Kromasil-3-amy coat 3µM column 4.6x250 mm; CO_2 / (ethanol/diethylamine:100/0.5): 80/20; Detection: 260nm):> 99%, intermediate **423**< 1%

Intermediate 423:

Optical purity (SFC: Kromasil-3-amy coat 3µM column 4.6x250 mm; CO_2 / (ethanol/diethylamine:100/0.5) : 80 / 20; Detection: 260nm) : > 99%, intermediate **415**< 1%.

<u>Intermediate 444 :</u>

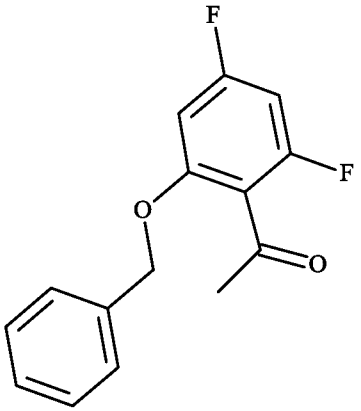


Intermediate 441 :

Obtained starting from commercial 3,5-difluorophenol according to **protocol XI**

^{1}H NMR (400MHz, DMSO-d6): δ 7.50-7.30 (m, 6H), 7.05 (d, 1H), 6.95 (t, 1H), 5.20 (s, 2H), 2.45 (s, 3H)

IR (cm^{-1}) : 1699



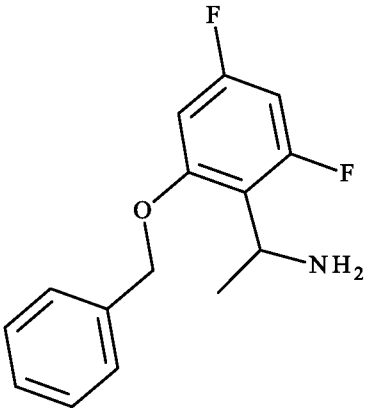
441

Intermediate 443 :

Obtained starting from intermediate **441** according to **protocol XII**

^{1}H NMR (400MHz ; DMSO-d_6): 8.30 (m, 3H), 7.50 (d, 2H), 7.40 (t, td, 3H), 7.00 (dd, 1H), 6.95 (td, 1H), 5.30 (s, 2H), 4.65 (quad, 1H), 1.50 (d, 3H)

IR (cm^{-1}): 3500-2450



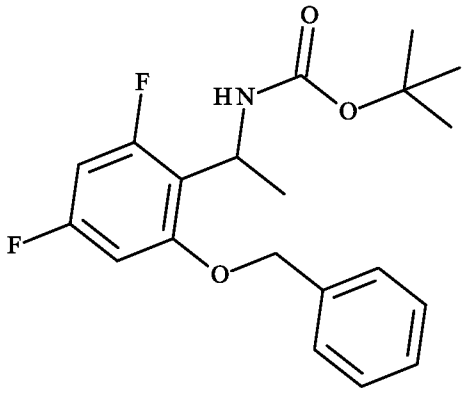
443

Intermediate 444 :

Obtained by protection of intermediate **443** according to the protocol described for intermediate **158** (**protocol VI**)

^{1}H NMR (400MHz, DMSO-d_6): δ 7.50 (d, 2H), 7.40 (t, 2H), 7.35 (td, 1H), 6.85 (dd, 1H), 6.80 (d, 1H), 6.75 (td, 1H), 5.20 (s, 2H), 5.10 (quint, 1H), 1.45-1.15 (m, 12H)

IR (cm^{-1}): 3475, 1709



444

Intermediate 558 :

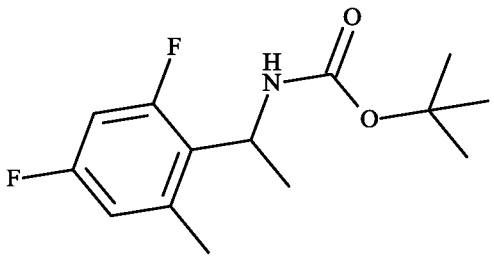
Obtained starting from intermediate **444** according to the following procedure:

6.3 g of intermediate **444** are engaged in a debenzylation reaction in the presence of 10% by mass of 10% Pd/C in ethyl acetate to obtain 4.5g of the phenolic intermediate **556**. The 4.5g of intermediate **556** yielded intermediate **557** (5.2 g of triflate) (flash chromatography on SiO_2, cyclohexane/methylene chloride gradient 10/90 to 100% methylene chloride). Intermediate **557** (4.3 g) was converted into intermediate **558** according to the following procedure:

A mixture of **557** (1 g, 2.47 mmoles), trimethyl-boroxine (0.62 g, 5 mmoles), K_2CO_3 (1.36 g, 9.8 mmoles) in 1,4-dioxane (10 mL) degassed by N_2 for 15 minutes is treated with $Pd(PPh_3)_4$ (0.57 g, 0.5 mmoles). The mixture is heated at reflux for 1 hour. After return to ambient temperature, the solid is filtered off and the filtrate is concentrated in vacuo. Intermediate **558** (0.55 g) is obtained after purification on silica (2.4 g of methyl obtained after flash chromatography on SiO_2, gradient methylene chloride 100% to methylene chloride/AcOEt 90/10).

^{1}H NMR (400MHz, DMSO-d_6): δ 7.24-6.95 (broad d and m, 1H), 6.95 (ddd, 1H), 6.86 (broad d, 1H), 4.85 (quint, 1H), 2.39 (s, 3H), 1.35 (d, 3H), 1.33-1.19 (2 broad s, 9H)

IR (cm^{-1}): 3468, 1705



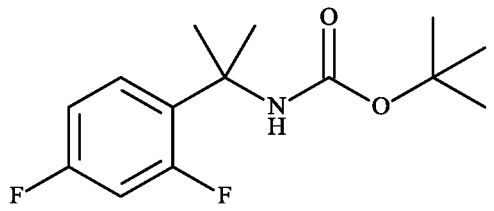
558

Intermediate 465 :

Obtained starting from commercial 2,4-difluorobenzonitrile according to **protocol VI**

^{1}H NMR (300 MHz; DMSO-d_6): δ 7.30 (m, 1H); 7.20 (m, 1H); 7.10 (m, 1H); 7.00 (m, 1H); 1.50 (s, 6H); 1.30 (m, 9H)

IR (cm^{-1}) : 3410; 1697; 1613; 1160; 848-700.



465

Intermediate 484 :

N-[(2,4-Difluorophenyl)methylidene]-(2S)-2-methylpropane-2-sulphinamide

Obtained by reaction of 2,4-difluorobenzaldehyde with (S)-(-)-2-methylpropane-2-sulphinamide according to **protocol XIV**

Intermediate 482 :

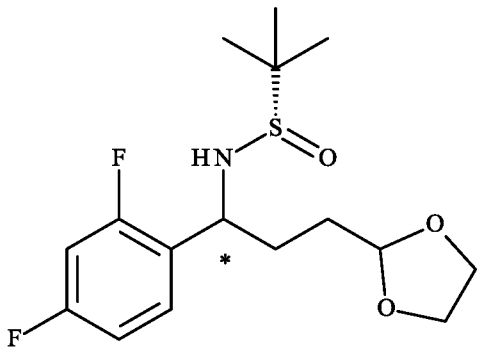
To a solution of N-[(2,4-difluorophenyl)methylidene]-(2S)-2-methylpropane-2-sulphinamide (5.1 g, 20 mmoles) in THF (30 mL), cooled to -60°C, there is added a solution of 2-(1,3-dioxolan-2-yl)ethyl-MgBr in methylene chloride (32 mL) prepared by reaction of magnesium (0.42 g) and 2-(2-bromoethyl)-1,3-dioxolane. The reaction mixture is stirred at -60°C for 20 minutes and is then hydrolysed at -40°C with a saturated aqueous

NH_4Cl solution. The mixture is decanted in the presence of ethyl ether, and the organic phase is washed with a saturated NaCl solution, dried over $MgSO_4$ and then concentrated. Chromatography on silica (eluant CH_2Cl_2/THF 95/5) yields 1.7 g of intermediate **482** in the form of an oil.

^{1}H NMR (300MHz, DMSO-d_6): δ 7.58 (m, 1H), 7.15 (m, 1H), 7.09 (m, 1H), 5.71 (d,NH), 4.78 (t, 1H), 4.45 (m, 1H), 3.85-3.73 (2m, 4H), 1.95-1.4 (m, 4H), 1.09 (s, 9H)

IR (cm^{-1}): 3230, 1048

Optical purity (SFC: AD 5µM column 4.6x250 mm; CO_2 / MeOH : 90 / 10; Detection: 260nm) : > 98.6%



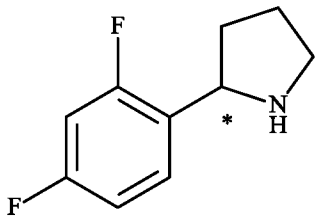
482

Intermediate 483 :

To a solution of intermediate **482** (5.2 g, 15 mmoles) in an EtOH/H_2O mixture (50 mL/50 mL) there are added trifluoroacetic acid (10 mL) and PtO_2 (0.5 g). The mixture is hydrogenated at atmospheric pressure and at ambient temperature for 22 hours. The catalyst is filtered off and the filtrate is concentrated. The residue is taken up in water and extracted with ethyl ether. The aqueous phase is brought to basic pH using a 10N NaOH solution. After extraction with ethyl ether, washing with a saturated aqueous NaCl solution and drying over $MgSO_4$, evaporation under reduced pressure yields intermediate **483** (2.2 g).

^{1}H NMR (300MHz, DMSO-d_6): δ 7.59 (m, 1H), 7.11 (m, 1H), 7.0 (m, 1H), 4.25 (m, 1H), 2.9 (m, 2H), 2.75 (broad s, NH), 1.72 (quint, 2H), 1.4 (m, 1H), 1.12 (m, 1H)

IR (cm^{-1}): 3286, 1097, 846



483

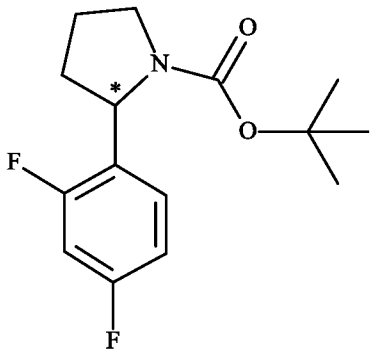
Intermediate 484 :

Obtained by protection of intermediate **483** according to the protocol described for intermediate **158** (**protocol VI**)

^{1}H NMR (300MHz, DMSO-d_6): δ 7.21 (dt, 1H), 7.09 (t, 1H), 7.00 (t, 1H), 4.94 (dd, 1H), 3.50 (t, 2H), 2.32 (m, 1H), 1.85 (quint, 2H), 1.73 (m, 1H), 1.23 (s, 9H)

IR (cm^{-1}): 1687, 1117

Enantiomeric excess > 99%



484

<u>Intermediate 521 :</u>

N-[(2,4-Difluorophenyl)methylidene]-(2R)-2-methylpropane-2-sulphinamide

Obtained by reaction of 2,4-difluorobenzaldehyde with (R)-(+)-2-methylpropane-2-sulphinamide according to **protocol XIV**.

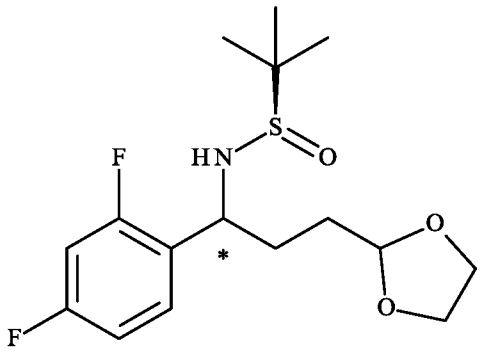
Intermediate **520**, the optical antipode of intermediate **483**, was obtained according to the protocol described for intermediate **483** starting from N-[(2,4-difluorophenyl)methylidene]-(2R)-2-methylpropane-2-sulphinamide, via intermediate **519**.

Intermediate 519 :

^{1}H NMR (400MHz, DMSO-d_6): δ 7.60 (m, 1H), 7.15 (m, 1H), 7.1 (m, 1H), 5.7 (d, 2H), 4.8 (m, 1H), 4.45 (m, 1H), 3.85-3.75 (2m, 4H), 1.95-1.6 (m, 4H), 1.1 (s, 9H)

IR (cm^{-1}): 3230, 1047

Optical purity (SFC: AD 5µM column 4.6x250 mm; CO_2/MeOH: 90/10; Detection: 260nm): > 99%.

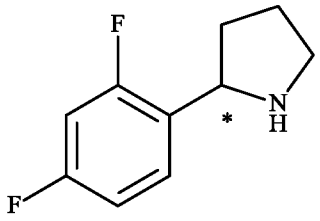


519

Intermediate 520 :

^{1}H NMR (300MHz, DMSO-d_6): δ 7.59 (m, 1H), 7.11 (m, 1H), 7.0 (m, 1H), 4.25 (m, 1H), 2.9 (m, 2H), 2.75 (broad s, NH), 1.72 (quint, 2H), 1.4 (m, 1H), 1.12 (m, 1H).

IR (cm^{-1}): 3286, 1097, 846.



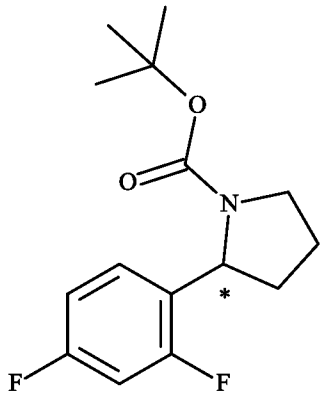
520

Intermediate 521 :

Obtained by protection of intermediate **520** according to the protocol described for intermediate **158**

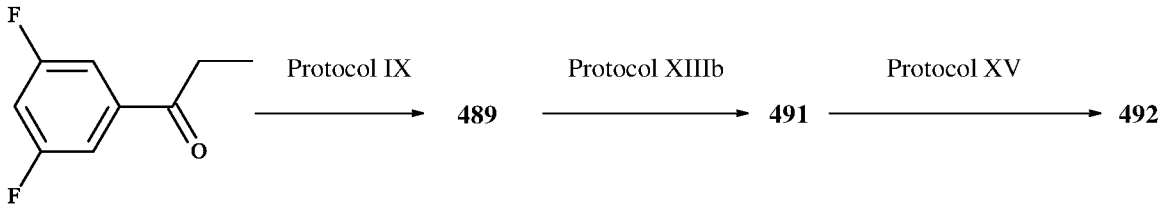
^{1}H NMR (400MHz, DMSO-d_6): δ 7.3-7.1 (2m, 1H), 7.05 (m, 1H), 5.0-4.85 (m, 1H), 3.6-3.35 (m, 2H), 2.32-1.7 (2m, 2H), 1.85 (m, 2H), 1.35-1.1 (2s, 9H)

IR (cm^{-1}): 1687



521

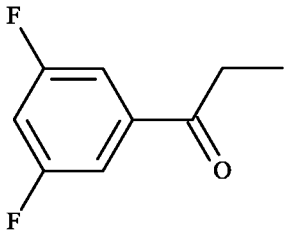
Intermediate 492 :



Intermediate 489 :

Obtained starting from commercial 3,5-difluorobenzoic acid and ethylmagnesium bromide according to **protocol IX**

GC-EI (70 eV): $M^{+\cdot}$ = 170.



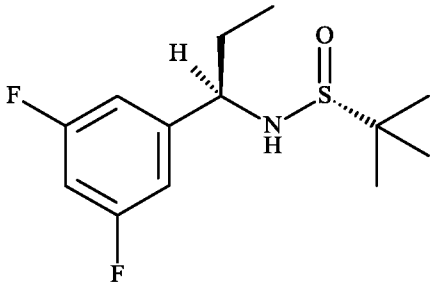
489

Intermediate 491 :

Obtained by reaction of intermediate **489** and (R)-(+)-2-methyl-2-propanesulphinamide according to **protocol XIIIb**

^{1}H NMR (400 MHz, DMSO-d6): δ 7.15 (dd, 2H), 7.05 (td, 1H), 5.70 (d, 1H), 4.10 (dd, 1H), 1.85-1.65 (m, 2H), 1.15 (s, 9H), 0.85 (t, 3H)

IR (cm^{-1}) : 3151, 1040



491

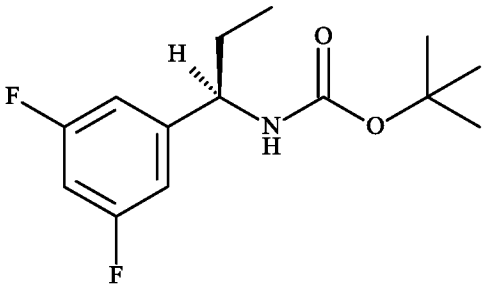
Intermediate 492 :

Obtained starting from intermediate **491** according to **protocol XV**

^{1}H NMR (400MHz, DMSO-d_6): δ 7.05 (td, 1H), 7.00 (broad d, 2H), 4.40 (m, 1H), 1.60 (quint, 2H), 1.35 (s, 9H), 0.80 (t, 3H)

IR (cm^{-1}): 3371, 1679

Enantiomeric excess > 99%



492

<u>Intermediate 499 :</u>

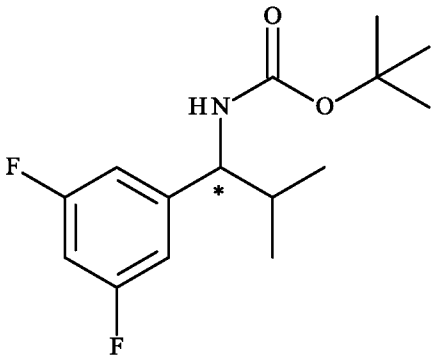
The preparation of intermediate **497** is described in **protocol XIV**.

Intermediate 499 :

Obtained starting from intermediate **497** according to **protocol XV**

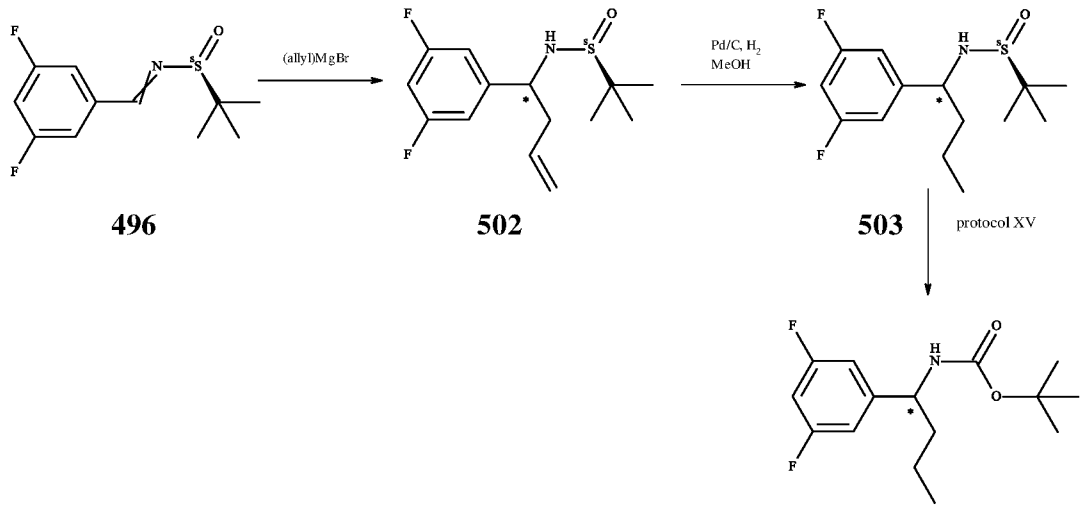
^{1}H NMR (400MHz, DMSO-d_6): δ 7.05 (m, 3H), 7.40 (d, 1H), 4.25 (t, 1H), 1.85 (m, 1H), 1.40-1.2 (s, 9H), 0.9-0.7 (2d, 6H)

IR (cm^{-1}): 3365, 1678, 1161



499

Intermediate 505 :



496 **502** **503** **505**

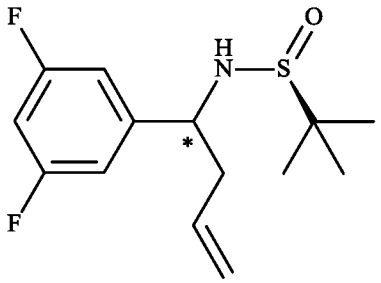
The preparation of intermediate **496** is described in **protocol XIV**.

Intermediate 502 :

Obtained starting from intermediate **496** and (allyl)MgBr according to **protocol XIV** (see preparation of intermediate **497**)

^{1}H NMR (400MHz, DMSO-d_6): δ 7.1 (m, 3H), 5.7 (m, 1H), 5.05 (m, 2H), 4.35 (quad, 1H), 2.65-2.45 (m, 2H), 1.1 (s, 9H)

IR (cm^{-1}): 3205, 1053.



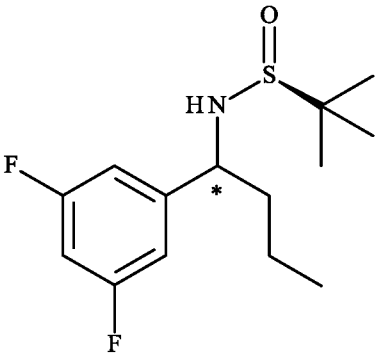
502

Intermediate 503 :

Obtained starting from intermediate **502** in the presence of 10% Pd/C in methanol under hydrogen for 2 days (2.9 g of intermediate **502** used, 2.9 g of intermediate **503** obtained).

^{1}H NMR (400MHz, DMSO-d6): δ 7.1 (d, 3H), 5.45 (d, 1H), 4.25 (quad, 1H), 1.85-1.6 (m, 2H), 1.35-1.15 (m, 2H), 1.1 (s, 9H), 1.85 (t, 3H)

IR (cm^{-1}): 3208, 1052



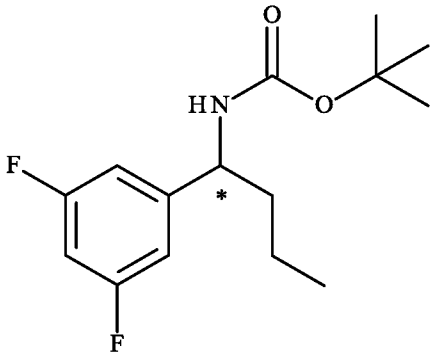
503

Intermediate 505 :

Obtained starting from intermediate **503** according to **protocol XV**

^{1}H NMR (400MHz, DMSO-d_6): δ 7.38 (d, 1H), 7.1-7.0 (m, 3H), 4.45 (quad, 1H), 1.55 (m, 2H), 1.35 (s, 9H), 1.4-1.3 (m, 2H), 0.85 (t, 3H)

IR (cm^{-1}): 3372, 1681



505

Intermediate 510 :

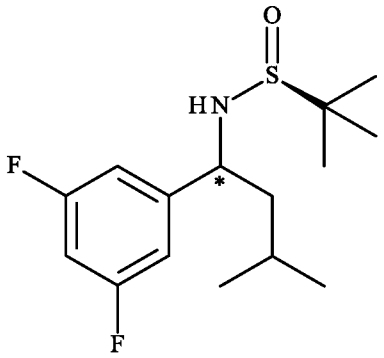
The preparation of intermediate **496** is described in **protocol XIV**.

Intermediate 508 :

Obtained starting from intermediate **496** and i-BuMgCl according to **protocol XIV**

^{1}H NMR (400MHz, DMSO-d_6): δ 7.1 (m, 3H), 5.45 (d, 1H), 4.3 (quad, 1H), 1.75-1.5 (m, 2H), 1.5 (m, 1H), 1.1 (s, 9H), 0.9 (2d, 6H)

IR (cm^{-1}): 3200, 1725, 1057



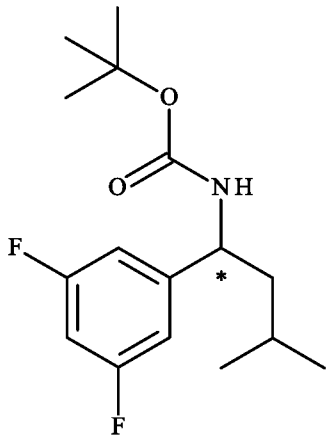
508

Intermediate 510 :

Obtained starting from intermediate **508** according to **protocol XV**

^{1}H NMR (400MHz, DMSO-d_6): δ 7.35 (broad d, 1H), 7.0 (m, 3H), 4.55 (m, 1H), 1.55 (m, 2H), 1.40 (s, 9H), 1.35 (m, 1H), 0.95 (d, 6H)

IR (cm^{-1}): 3367, 1681, 1253



510

Intermediate 526 :

Intermediate 525 :

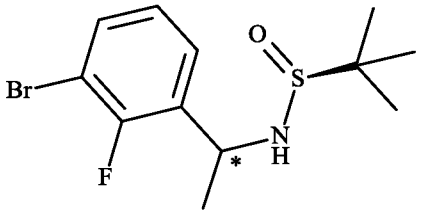
Obtained by reaction of (S)-2-methylpropane-2-sulphinamide with commercial 3-bromo-2-fluoro-benzaldehyde according to **protocol XIV**

Intermediate 526 :

Obtained by treatment with MeMgBr (3M/ether) of intermediate **525** according to **protocol XIV**

^{1}H NMR (400MHz, DMSO-d_6): δ 7.60-7.5 (m, 1H), 7.5 (m, 1H), 7.18 (m, 1H), 5.51 (d, 1H), 4.7 (m, 1H), 1.5 (d, 3H), 1.1 (s, 9H)

IR (cm^{-1}): 3206, 1048



526

Intermediate 550 :

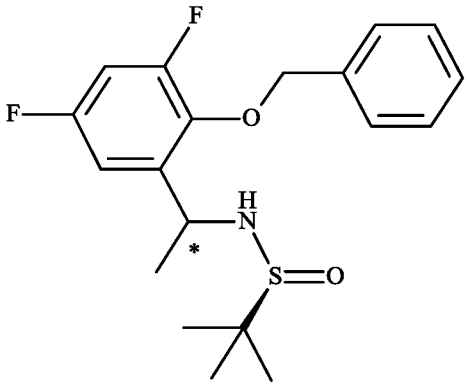
The preparation of intermediate **547** is described in **protocol XI**.

Intermediate 548 :

Obtained by reaction of intermediate **547** and (R)-(+)-2-methyl-2-propanesulphinamide according to **protocol XIII**

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.50-7.35 (m, 5H), 7.22 (td, 1H), 7.10 (dd, 1H), 5.42 (d, 1H), 5.05 (s, 2H), 4.75 (m, 1H), 1.35 (d, 3H), 1.10 (s, 9H)

IR (cm^{-1}): 3206



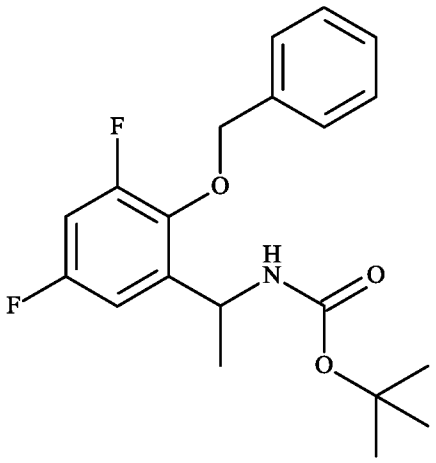
548

Intermediate 550 :

Obtained starting from intermediate **548** according to **protocol XV**

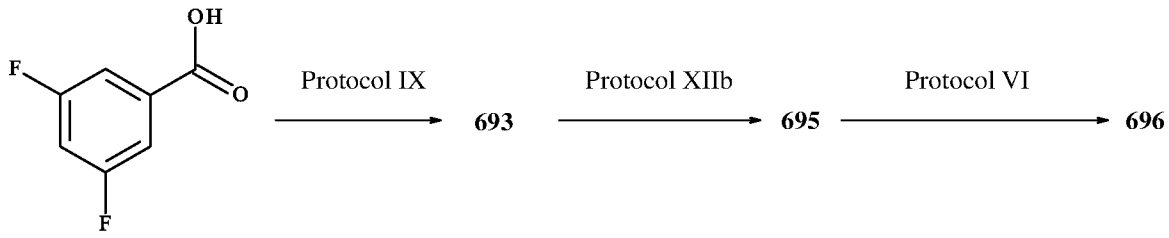
^{1}H NMR (400MHz, DMSO-d_6): δ 7.49 (m, 3H), 7.42 (t, 2H), 7.37 (t, 1H), 7.20 (m, 1H), 7.05 (m, 1H), 5.04 (m, 3H), 1.36 (s, 9H), 1.19 (d, 3H)

IR (cm^{-1}): 3329, 1699



550

Intermediate 696 :

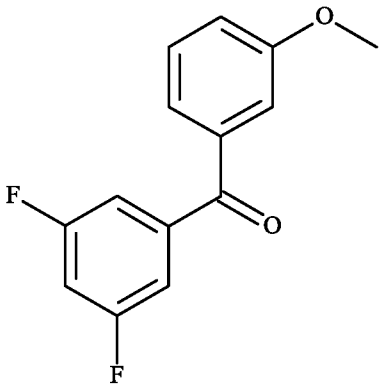


Intermediate 693 :

Obtained starting from commercial 3,5-difluorobenzoic acid and 3-methoxy-phenylmagnesium bromide according to **protocol IX**

^{1}H NMR (400 MHz ; DMSO-d_6): δ 7.60 (m, 1H), 7.50 (t, 1H), 7.40 (m, 2H), 7.30 (m, 3H), 3.85 (s, 1H)

IR (cm-1) : 1665



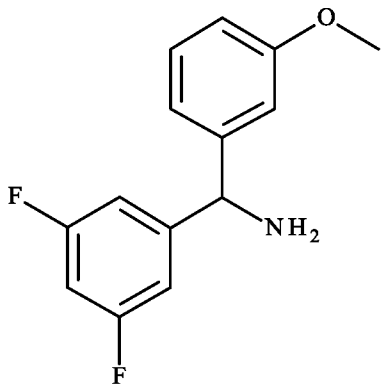
693

Intermediate 695 :

Obtained starting from intermediate **693** according to **protocol XIIb**

^{1}H NMR (300MHz; DMSO-d_6): 7.20 (t, 1H), 7.10 (m, 2H); 7.00 (m, 2H), 6.95 (d, 1H), 6.75 (dd, 1H), 5.05 (s, 1H), 3.75 (s, 3H), 2.35 (broad s, 2H)

IR (cm^{-1}): 3385-3309, 1594, 1254



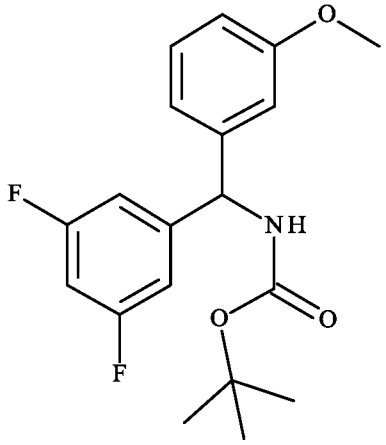
695

Intermediate 696 :

Obtained by protection of intermediate **695** according to the protocol described for intermediate **158** (**protocol VI**)

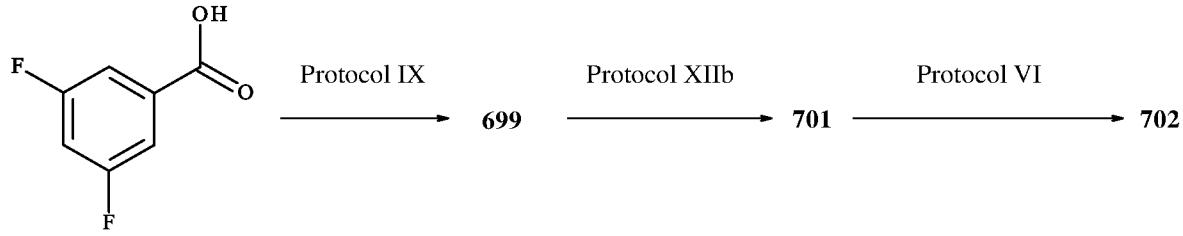
^{1}H NMR (300MHz, DMSO-d_6): δ 8.00 (broad d, 1H), 7.25 (t, 1H), 7.10 (m, 3H), 6.95 (m, 2H), 6.80 (dd, 1H), 5.70 (broad d, 1H), 3.75 (s, 3H), 1.40 (broad s, 9H)

IR (cm^{-1}): 3357, 1684, 1162



696

Intermediate 702 :

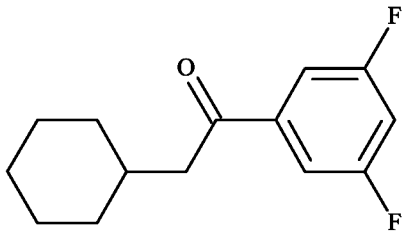


Intermediate 699 :

Obtained starting from commercial 3,5-difluorobenzoic acid and methyl-cyclohexylmagnesium bromide according to **protocol IX**

^{1}H NMR (400 MHz ; DMSO-d_6): δ 7.64 (m, 2H), 7.56 (tt, 1H), 2.90 (d, 2H), 1.83 (m, 1H), 1.6-1.1-0.99 (3m, 10H)

IR (cm-1): 1688



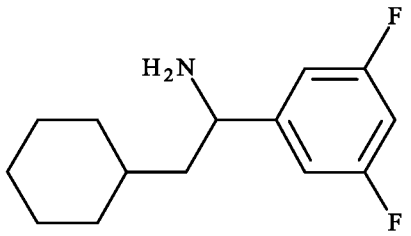
699

Intermediate 701 :

Obtained starting from intermediate **699** according to **protocol XIIb**

^{1}H NMR (400MHz ; DMSO-d_6): 8.57 (broad s, 3H), 7.35 (m, 2H); 7.28 (tt, 1H), 4.35 (dd, 1H), 1.85-1.67 (m, 3H), 1.6-0.88 (3m, 10H)

IR (cm^{-1}): 3200-2500, 1126.



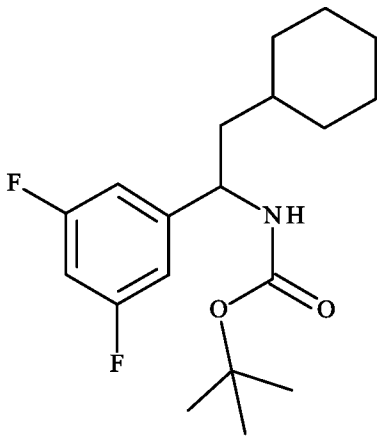
701

Intermediate 702 :

Obtained by protection of intermediate **701** according to the protocol described for intermediate **158** (**protocol VI**)

^{1}H NMR (400MHz, DMSO-d_6): δ 7.00 (m, 3H), 7.38 (d, 1H), 4.60 (m,1H), 1.78-1.55 (2m, 2H), 1.7-0.8 (m, 11H), 1.40 (s, 9H)

IR (cm^{-1}): 3280, 1677



702

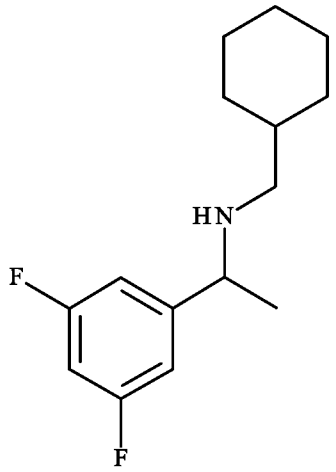
Intermediate 706 :

Intermediate 705 :

A solution of commercial 1-(3,5-difluorophenyl)ethanone (5 g, 32 mmoles) and cyclohexanemethylamine (3.6 g, 32 mmoles) in toluene (50 mL) is heated for 40 hours at reflux in an azeotropic assembly. The toluene is evaporated off and the residue is dissolved in ethanol (40 mL). The solution is cooled to 10°C, and then $NaBH_4$ (1.2 g, 32 mmoles) is added in portions; the reaction mixture is stirred for 2 hours, and $NaBH_4$ (0.12 g) is again added. After stirring for 30 minutes, a 3N aqueous HCl solution is added carefully, and the ethanol is evaporated off in vacuo. The residue is taken up in toluene (200 mL) and washed with a 40% aqueous NaOH solution. The organic phase is dried over $MgSO_4$, and evaporation under reduced pressure yields intermediate **705** (4.4 g), which is used without additional treatment in the following step.

^{1}H NMR (300MHz, DMSO-d_6): δ 7.00 (m, 3H), 3.70 (quad, 1H), 2.20 (dd,1H), 2.05 (dd, 1H), 1.80-1.70 (3m, 10H), 1.30 (m, 1H), 1.20 (d, 3H)

IR (cm^{-1}): 2922-2850, 1114



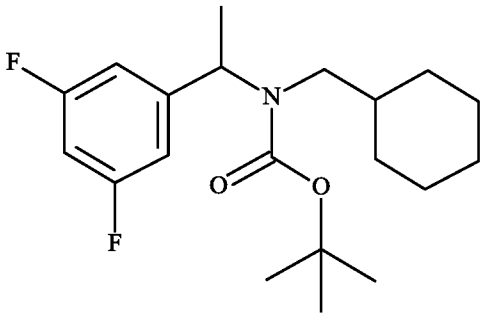
705

Intermediate 706 :

Obtained by protection of intermediate **705** according to the protocol described for intermediate **158** (**protocol VI**)

^{1}H NMR (300MHz, DMSO-d_6): δ 7.10 (tt, 1H), 6.95 (d, 2H), 4.90 (broad s,1H), 3.00 (broad s, 2H), 1.50 (d, 3H), 1.30 (broad s, 9H), 1.70-0.75 (2m, 11H). **19F NMR**: -110.7

IR (cm^{-1}): 1686, 1147



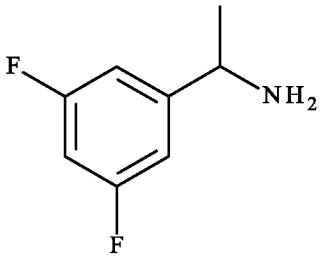
706

Intermediate 278 :

Obtained starting from intermediate **489** according to **protocol XII**

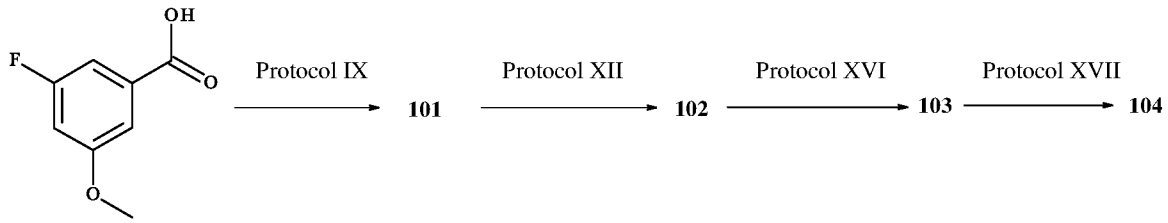
^{1}H NMR (400MHz ; $CDCl_3$): 6.88 (d, 2H); 6.65 (tt, 1H), 4.10 (quad, 2H) ; 1.53 (broad s, 2H), 1.35 (d, 3H)

IR (cm^{-1}): 3371, 3298



278

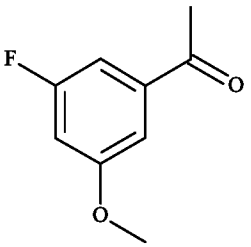
Intermediate 104 :



Intermediate 101:

Obtained starting from commercial 3-fluoro-5-methoxybenzoic acid and methyl-magnesium bromide according to **protocol IX**

^{1}H NMR ($CDCl_3$): δ 7.20 (s, 1H), 7.14 (d, 1H), 6.73 (d, 1H), 3.77 (s, 3H), 2.50 (s, 3H)



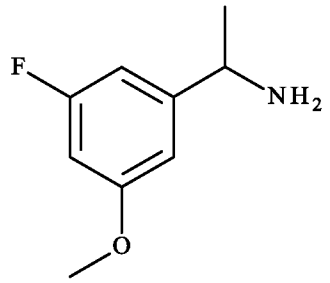
101

Intermediate 102 :

Obtained starting from intermediate **101** according to **protocol XII**

^{1}H NMR (300MHz ; DMSO-d_6): 6.75 (t and d, 2H), 6.60 (d and t, 1H), 3.90 (quad, 1H), 3.75 (s, 3H), 1.80 (m, 2H), 1.20 (d, 6H)

IR (cm^{-1}): 3750-2750



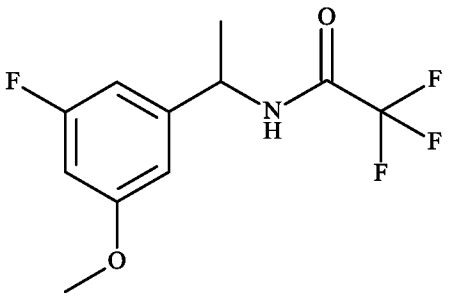
102

Intermediate 103 :

Obtained starting from intermediate **102** according to **protocol XVI**

^{1}H NMR (300 MHz, $CDCl_3$) : δ 6.60 (2m, 2H), 6.55 (t, 1H), 6.40 (m, 1H), 5.10 (quint, 1H), 3.80 (s, 3H), 1.55 (d, 3H)

IR (cm^{-1}) : 3240, 1694, 1627, 1595, 1558



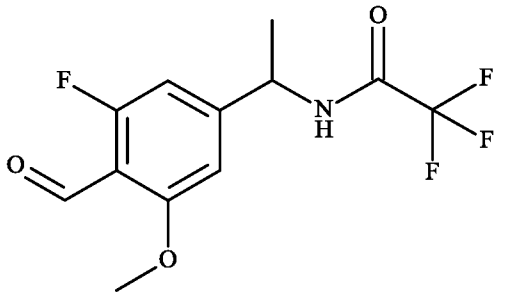
103

Intermediate 104 :

Obtained starting from intermediate **103** according to the procedure used to convert intermediate **93a** into intermediate **94** (**Protocol XVII**)

^{1}H NMR (500MHz, DMSO-d_6): 10.30 (s, 1H), 9.90 (1, 1H), 7.08 (d, 1H), 6.87 (d, 1H), 5.05 (m, 1H), 3.92 (s, 3H), 1.48 (dd, 3H)

IR (cm^{-1}): 3294, 1688



104

Intermediate 18 :

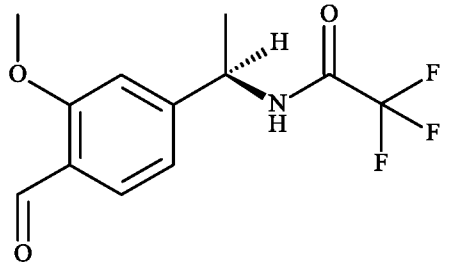
The preparation of intermediate **17** is described in **protocol XVI**.

Intermediate 18 :

Obtained starting from intermediate **17** according to the procedure used to convert intermediate **93a** into intermediate **94** (**Protocol XVII**)

^{1}H NMR (400MHz, DMSO-d_6): δ 10.31 (s, 1H), 9.94 (m, 1), 7.68 (d, 1H), 7.22 (broad s, 1H) 7.05 (broad d, 1H), 5.06 (quad, 1H), 3.93 (s, 3H), 1.48 (d, 3H)

IR (cm^{-1}): 3299, 1703, 1672



18

Intermediate 357 :

2,2,2-Trifluoro-N-[(1S)-1-(8-formyl-3,4-dihydro-2H-chromen-5-yl)ethyl]acetamide

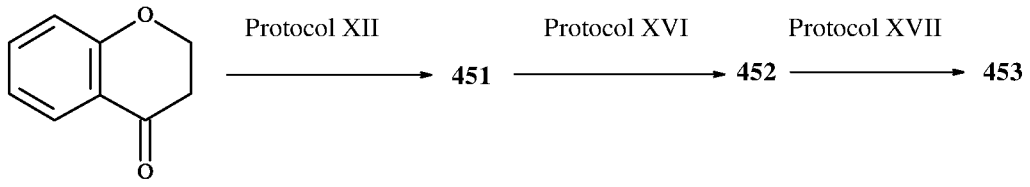
Obtained starting from (S)-(-)-1-(3-methoxyphenyl)ethylamine according to **protocols XVI** and **XVII**

^{1}H NMR (400MHz, DMSO-d_6): δ 10.30 (s, 1H), 10.00 (s, 1H), 7.55 (d, 1H), 7.05 (d, 1H), 5.12 (quad, 1H), 4.25 (t, 2H), 2.9-2.78 (m, 2H), 2.05 (m, 2H), 1.40 (d, 3H)

^{19}F NMR: -72 (dd, 1F)

IR (cm^{-1}): 3298, 1701, 1673.

Intermediate 453:

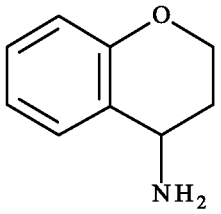


Intermediate 451 :

Obtained starting from commercial 2,3-dihydro-4H-chromen-4-one according to **protocol XII**

^{1}H NMR (300MHz ; DMSO-d_6): 8.70 (m, 3H), 7.60 (d, 1H), 7.25 (t, 1H), 6.95 (t, 1H), 6.85 (d, 1H), 4.50 (m, 1H), 4.25 (m, 2H), 2.20 (m, 2H)

IR (cm^{-1}): 3400-2250



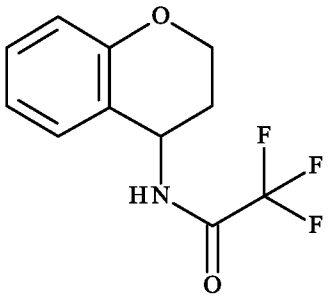
451

Intermediate 452 :

Obtained starting from intermediate **451** according to **protocol XVI**

^{1}H NMR (300 MHz, DMSO-d_6) : δ 9.90 (d, 1H), 7.20 (td, 1H), 7.10 (dd, 1H), 6.90 (td, 1H), 6.80 (d, 1H), 5.10 (m, 1H), 4.20 (m, 2H), 2.10 (2m, 2H)

IR (cm^{-1}) : 3266, 1699, 1546, 754, 711

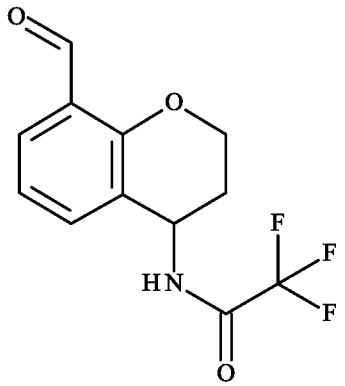


452

Intermediate 453 :

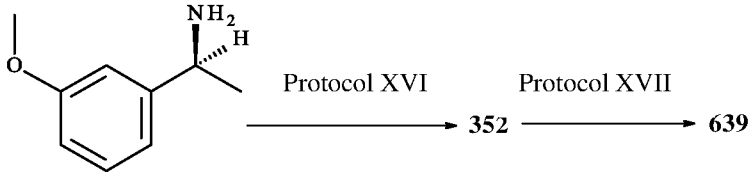
Obtained starting from intermediate **452** according to the procedure used to convert intermediate **93a** into intermediate **94** (**Protocol XVII**)

^{1}H NMR (500MHz, $CDCl_3$): 10.35 (s, 1H), 9.95 (s, 1H), 7.65 (dd, 1H), 7.45 (dd, 1H), 7.05 (t, 1H), 5.20 (m, 1H), 4.4-4.35 (2m, 2H), 2.20 (2m, 2H)



453

Intermediate 639:

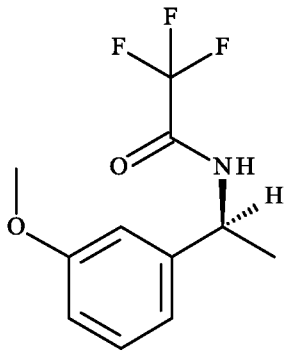


Intermediate 352 :

Obtained by protection of commercial (1S)-1-(3-methoxyphenyl)ethanamine according to **protocol XVI**

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.30 (m, 1H), 6.90 (d, 1H), 6.85 (m, 2H), 6.68 (m, 1H), 5.10 (quint, 1H), 3.80 (s, 3H), 1.58 (d, 3H)

IR (cm^{-1}) : 3294, 1697, 1151



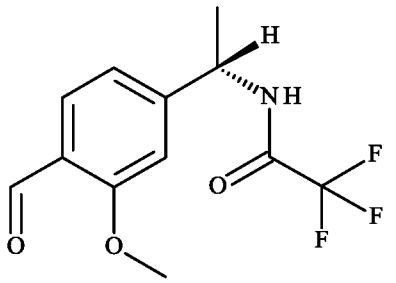
352

Intermediate 639 :

Obtained starting from intermediate **352** according to the procedure used to convert intermediate **93a** into intermediate **94** (**Protocol XVII**)

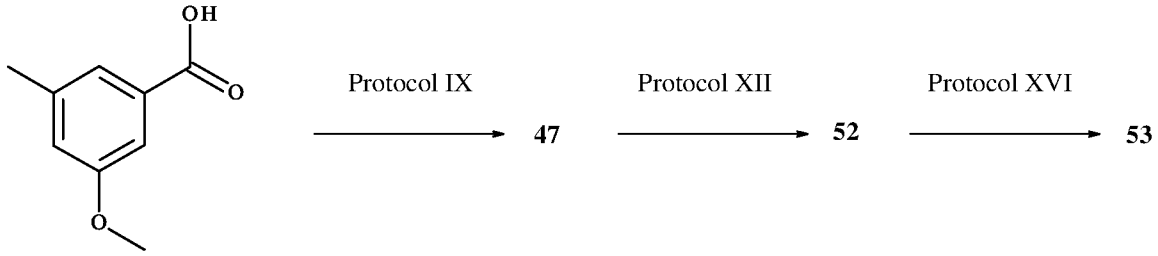
^{1}H NMR (500MHz, DMSO-d_6): 10.50 (s, 1H), 7.80 (d, 1H), 6.95 (dd, 1H), 6.90 (d, 1H), 6.60 (broad s, 1H), 5.18 (m, 1H), 3.95 (s, 3H), 1.60 (dd, 3H)

IR (cm^{-1}): 3324, 1692-1660



639

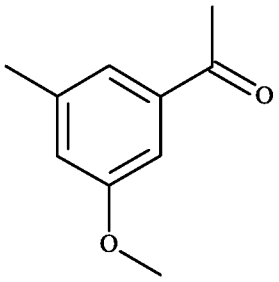
Intermediate 53:



Intermediate 47:

Obtained starting from commercial 3-methoxy-5-methylbenzoic acid and methylmagnesiumn bromide according to le **protocol IX**

^{1}H NMR ($CDCl_3$): δ 7.26 (s, 1H), 7.20 (s, 1H), 6.84 (s, 1H), 3.74 (s, 3H), 2.49 (s, 3H), 2.29 (s, 3H)



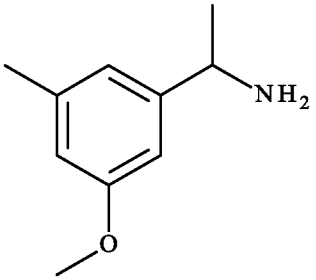
47

Intermediate 52 :

Obtained starting from intermediate **47** according to **protocol XII**

^{1}H NMR (400/500MHz ; DMSO-d_6): 6.72 (s, 1H), 6.56 (s, 1H), 3.90 (quad, 1H), 3.70 (s, 3H), 2.25 (s, 3H), 1.70 (s, 2H), 1.20 (s, 3H)

IR (cm^{-1}): 3750-2750



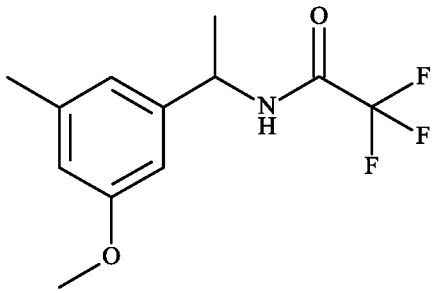
52

Intermediate 53 :

Obtained starting from intermediate **52** according to **protocol XVI**

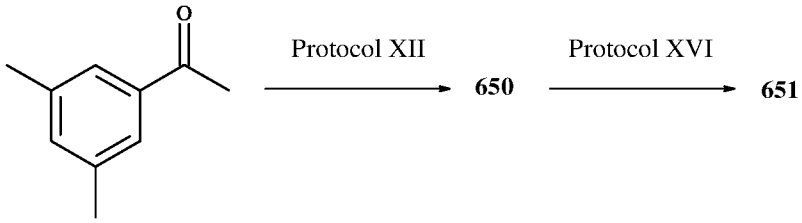
^{1}H NMR (400 MHz, DMSO-d_6) : δ 9.80 (d, 1H), 6.70-6.65 (3 broad s, 3H), 4.95 (quint, 1H), 3.70 (s, 3H), 2.25 (s, 3H), 1.40 (d, 3H)

IR (cm^{-1}) : 3295, 1694, 1596, 1558, 1185, 1152, 847-685



53

Intermediate 651 :

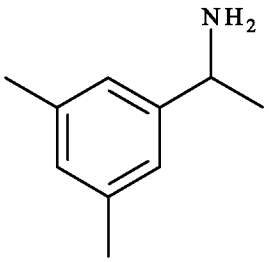


Intermediate 650 :

Obtained starting from commercial 1-(3,5-dimethylphenyl)ethanone according to **protocol XII**

^{1}H NMR (300MHz ; $CDCl_3$): 7.00 (m, 2H); 6.90 (m, 1H), 4.05 (quad, 1H) ; 2.30 (s, 6H), 1.50 (m, 2H), 1.35 (d, 3H)

IR (cm^{-1}): 3364, 3290



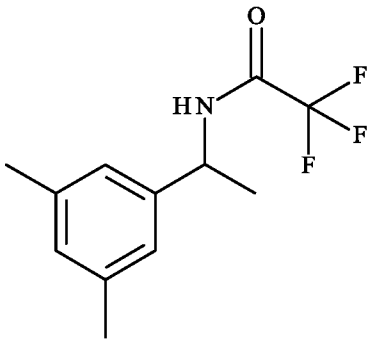
650

Intermediate 651 :

Obtained starting from intermediate **650** according to **protocol XVI**

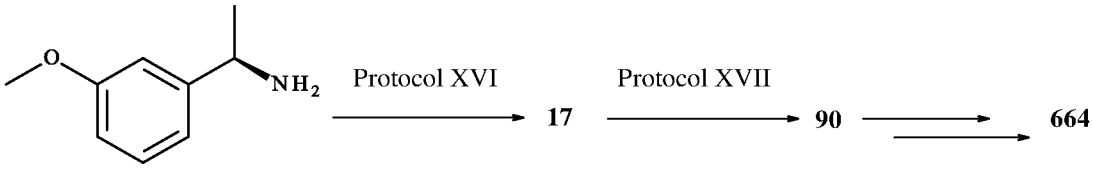
^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.98 (s, 1H), 6.92 (s, 2H), 6.40 (broad s, 1H), 5.05 (quint, 1H), 2.30 (s, 6H), 1.55 (d, 3H)

IR (cm^{-1}) : 3298, 1694, 1161



651

Intermediate 664:



Intermediate **664** was prepared starting from intermediate **90** (which was in turn prepared according to **Protocol XVII**, starting from intermediate **17**, which was prepared according to **protocol XVI**) according to the following sequence:

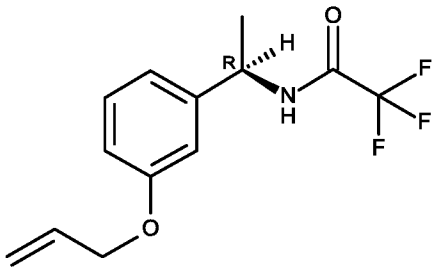
Intermediate 660 :

To a solution of intermediate **90** (1 g, 4.3 mmoles) in DMF (25 mL) there are added potassium carbonate (0.7 g) and then allyl bromide (0.4 mL, 4.5 mmoles). The mixture is stirred at ambient temperature for 5 hours and then poured into an ice/water mixture. After decantation in the presence of ethyl ether, the organic phase is dried over $MgSO_4$ and then

concentrated. The residue obtained is chromatographed on silica (eluant : CH_2Cl_2 100%), intermediate **660** (0.7 g) is obtained in the form of a solid.

^{1}H NMR (300MHz, DMSO-d_6): 9.70 (broad s, NH), 7.25 (t, 1H), 6.95-6.80 (m, 3H), 6.10-5.95 (m, 1H), 5.30 (2dd, 2H), 4.95 (quad, 1H), 4.55 (d, 2H), 1.45 (d, 3H)

IR (cm^{-1}): 3319, 1693, 1662, 1157



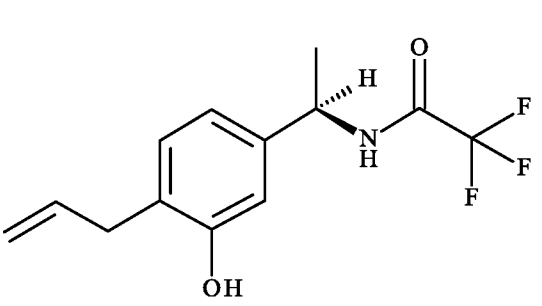
660

Intermediate 662 :

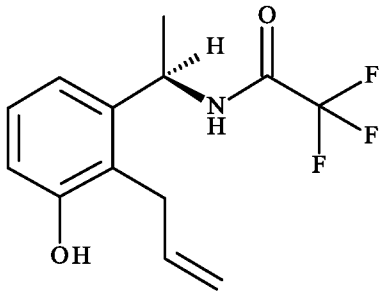
A mixture of intermediate **660** (0.7 g) in diethylaniline (7 mL) is heated at 210°C for 20 hours. The reaction mixture is washed with a 1N HCl solution and then extracted with methylene chloride. The organic phase is dried over $MgSO_4$ and then concentrated. The mixture of isomers **661** and **662** is chromatographed on silica (eluant : CH_2Cl_2 100%), isomer **662** (0.15 g) is obtained.

^{1}H NMR (300MHz, DMSO-d_6): 10.0-9.0 (2 broad s, NH-OH), 7.05 (t, 1H), 6.90 (d, 1H), 6.75 (d, 1H), 5.95 (m, 1H), 5.18 (quad, 1H), 4.90 (m, 2H), 3.45 (d, 2H), 1.40 (d, 3H)

IR (cm^{-1}): 3461, 3293, 1698, 1156



661



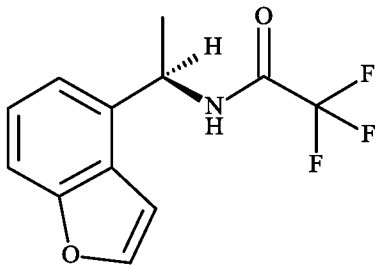
662

Intermediate 663 :

To a solution of intermediate **662** (2 g) in a mixture of 1,4-dioxane (90 mL) and water (30 mL) there are added in succession OsO_4 (2.5% in t-BuOH) (1.48 g), 2,6-lutidine (1.68 mL) and $NaIO_4$ (6 g). The reaction mixture is stirred at ambient temperature for 20 hours. After decantation by AcOEt, the organic phase is washed with water, with a 1N aqueous HCl solution and with a saturated aqueous NaCl solution, and the organic phase is dried over $MgSO_4$ and then concentrated. The residue (1 g), taken up in toluene (100 mL), was treated with para-toluenesulphonic acid (0.5 g). The reaction mixture is heated for 1 hour at reflux. The mixture is concentrated in vacuo and the residue is chromatographed on silica (eluant 100% CH_2Cl_2). Intermediate **663** (1 g) is obtained in the form of a white solid.

^{1}H NMR (300MHz, DMSO-d_6): 9.80 (d, 1H), 7.95 (d, 1H), 7.50 (broad d, 1H), 7.30 (t, 1H), 7.20 (broad d, 1H), 7.10 (broad d, 1H), 5.30 (quint, 1H), 1.55 (d, 3H)

IR (cm^{-1}): 3276, 1695



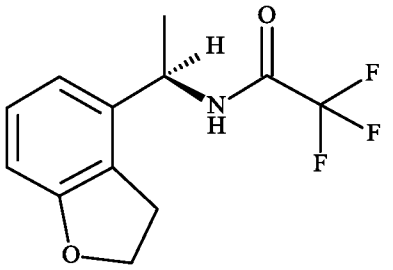
663

Intermediate 664 :

Intermediate **663** (0.9 g, 3.5 mmoles) in solution in ethanol (90 mL) is hydrogenated at atmospheric pressure and ambient temperature in the presence of $Pd(OH)_2$ (0.25 g). The catalyst is filtered off, and concentration of the filtrate yields intermediate **664** (0.8 g), which is used in the following step without additional purification.

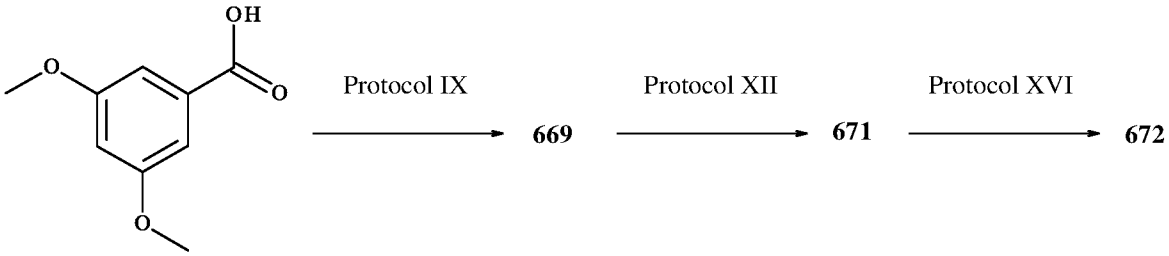
^{1}H NMR (300MHz, DMSO-d_6): 9.90 (broad s, NH), 7.10 (t, 1H), 6.82 (d, 1H), 6.66 (d, 1H), 4.93 (m, 1H), 4.52 (t, 1H), 3.20 (t, 2H), 1.45 (d, 3H).

IR (cm^{-1}): 3272, 1696



664

Intermediate 672

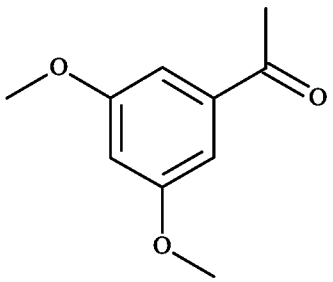


Intermediate 669 :

Obtained starting from commercial 3,5-dimethoxybenzoic acid and methylmagnesium bromide according to **protocol IX**

^{1}H NMR (300 MHz ; DMSO-d_6): δ 7.05 (d, 2H), 6.75 (m, 1H), 3.80 (s, 6H), 2.55 (s, 1H)

IR (cm-1): 1681



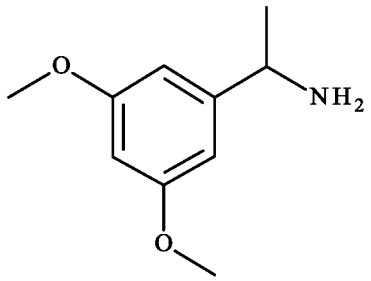
669

Intermediate 671 :

Obtained starting from intermediate **669** according to **protocol XII**

^{1}H NMR (300MHz ; $CDCl_3$): 6.50 (d, 2H); 6.32 (t, 1H), 4.02 (quad, 1H) ; 3.80 (s, 6H), 1.50 (s, 2H), 1.35 (d, 3H)

IR (cm^{-1}): 3359, 3295



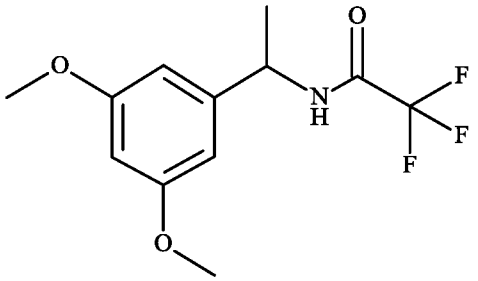
671

Intermediate 672 :

Obtained starting from intermediate **671** according to **protocol XVI**

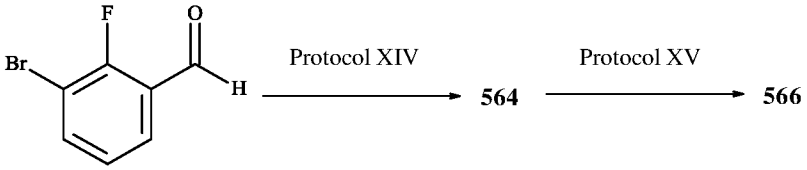
^{1}H NMR (300 MHz, DMSO-d_6) : δ 9.60 (d, 1H), 6.50 (d, 2H), 6.40 (t, 1H), 4.92 (m, 1H), 3.74 (s, 6H), 1.45 (d, 3H)

IR (cm^{-1}) : 3321, 1698, 1608, 1553, 1182-1144



672

Intermediate 566:



Intermediate 563:

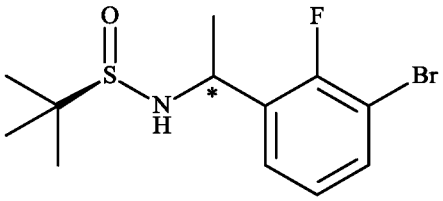
Obtained by reaction of (R)-2-methylpropane-2-sulphinamide with commercial 3-bromo-2-fluoro-benzaldehyde according to **protocol XIV**

Intermediate 564 :

Obtained by treatment with MeMgBr (3M/ether) of intermediate **563** according to **protocol XIV**

^{1}H NMR (400MHz, DMSO-d_6): δ 7.60-7.50 (2m, 2H), 7.16 (t, 1H), 5.53 (d, 1H), 4.7 (m, 1H), 1.48 (d, 3H), 1.09 (s, 9H)

IR (cm^{-1}): 3189, 1040



564

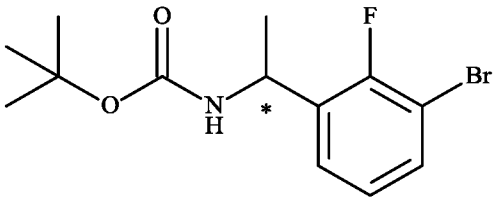
Intermediate 566 :

Obtained starting from intermediate **564** according to **protocol XV**

^{1}H NMR (400MHz, DMSO-d_6): δ 7.55 (2m, 2H), 7.36 (t, 1H), 7.15 (t, 1H), 4.85 (m, 1H), 1.35 (broad s, 9H), 1.3 (d, 3H)

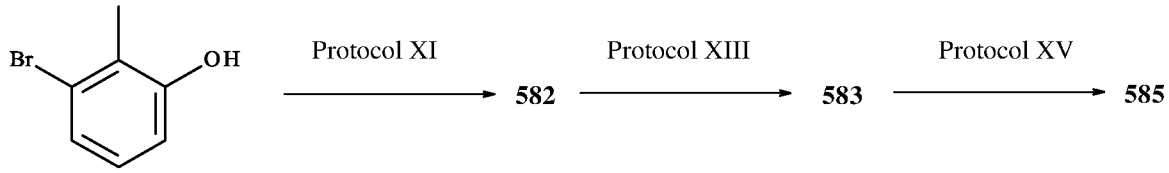
IR (cm^{-1}): 3360, 1676

α_D (589nM) = 35.09 (0.005 g/mL/MeOH) at 20°C



566

Intermediate 585:

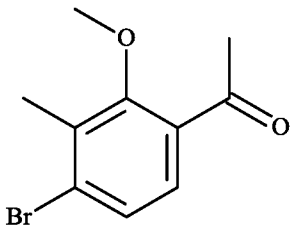


Intermediate 582 :

Obtained starting from commercial 3-bromo-2-methylphenol according to **protocol XI**, in the presence of methyl iodide in the last step

^{1}H NMR (400MHz, DMSO-d_6): δ 7.45 (d, 1H), 7.35 (d, 1H), 3.72 (s, 3H), 5.10 (s, 2H), 2.58 (s, 3H), 2.35 (s, 3H)

IR (cm^{-1}) : 1681



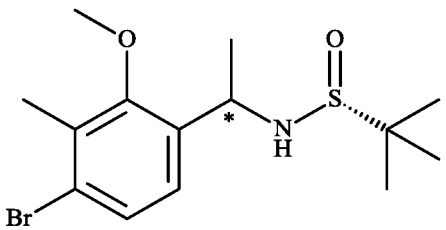
582

Intermediate 583 :

Obtained by reaction of intermediate **582** and (R)-(+)-2-methyl-2-propanesulphinamide according to **protocol XIII**

^{1}H NMR (400 MHz, DMSO-d6): δ 7.40 (d, 1H), 7.31 (d, 1H), 5.62 (d, 1H), 4.64 (m, 1H), 3.71 (s, 3H), 2.29 (s, 3H), 1.33 (d, 3H), 1.10 (s, 9H)

IR (cm^{-1}): 3215, 1009



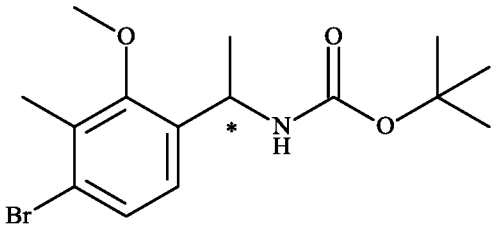
583

Intermediate 585 :

Obtained starting from intermediate **583** according to **protocol XV**

^{1}H NMR (400MHz, DMSO-d_6): δ 7.43 (d, 1H), 7.37 (d, 1H), 7.15 (d, 1H), 4.88 (m, 1H), 3.75 (s, 3H), 2.28 (s, 3H), 1.35 (broad s, 9H), 1.21 (d, 3H)

IR (cm^{-1}): 3353, 1695



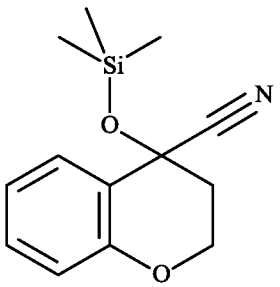
585

Intermediate 748 :

Intermediate 743 :

To a solution of commercial 2,3-dihydro-4H-chromen-4-one (20 g, 135 mmoles) in methylene chloride (400 mL) there are added ZnI_2 (0.8 g) and TMSCN (20 g, 201 mmoles). The reaction mixture is stirred at ambient temperature for 20 hours, and then the organic phase is washed with an aqueous $NaHCO_3$ solution (400 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Intermediate **743** is obtained (32 g) in the form of an oil, which is used in the following step.

^{1}H NMR (400MHz, $CDCl_3$): 7.47 (dd, 1H), 7.18 (dd, 1H), 6.88 (td, 1H), 6.75 (dd, 1H), 4.25 (m, 2H), 2.30 (m, 2H), 0.08 (s, 9H)



743

Intermediate 745 and **intermediate 746**:

To a solution of intermediate **743** (2.7 g, 11 mmoles) in THF (20 mL) there is added a solution of $LiAlH_4$ (1M/THF) (23 mmoles) diluted in THF (10 mL) and previously cooled to 0°C. The reaction mixture is stirred for 90 minutes at 5°C and is then treated in succession with water, with a 20% aqueous sodium hydroxide solution and with water. The salts are filtered off, the filtrate is washed with a saturated aqueous NaCl solution, and the organic phase is dried over $MgSO_4$ and then concentrated. The residue (2.4 g) obtained, dissolved in methylene chloride (20 mL), is treated with a solution of trifluoroacetic anhydride (2 mL) in methylene chloride (15 mL). The reaction mixture is stirred for 20 hours at ambient temperature and then concentrated in vacuo. The residue obtained is chromatographed on silica (eluant : cyclohexane/CH_2Cl_2 30/70 to 0/100). A mixture of intermediates **745** (exo) and **746** (endo) is obtained, which mixture is used in the following step.

Intermediate 745 :

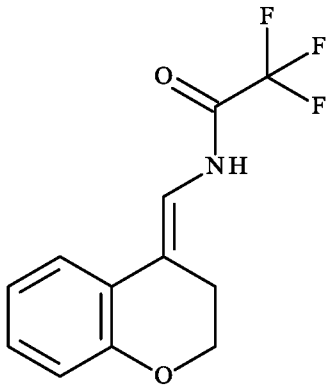
^{1}H NMR (400MHz, DMSO-d_6): 10.8 (s, 1H), 7.61 (d, 1H), 7.15 (m, 2H), 6.89 (t, 1H), 6.72 (d, 1H), 4.15 (t, 2H), 2.75 (t, 2H)

IR (cm^{-1}): 3350, 1693

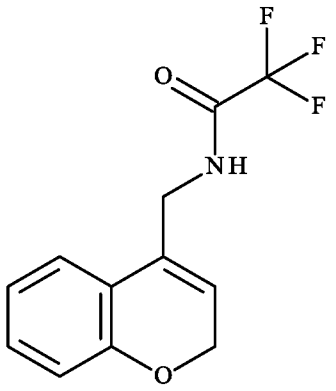
Intermediate 746 :

^{1}H NMR (400MHz, DMSO-d_6): 9.80 (s, 1), 7.22 (t, 1H), 7.15 (d, 1H), 6.92 (t, 1H), 6.80 (d, 1H), 5.75 (t, 1H), 4.75 (broad s, 2H), 4.2 (broad s, 2H)

IR (cm^{-1}): 3300, 1702, 1150



745



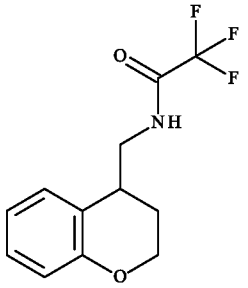
746

Intermediate 747 :

The mixture of intermediates **745** and **746** (12 g, 46 mmoles) in solution in ethanol (600 mL) is hydrogenated at atmospheric pressure and ambient temperature in the presence of 10% Pd/C (1.2 g). The catalyst is filtered off, and concentration of the filtrate yields compound **747** (10 g), which is used in **Protocol XVII** without additional purification.

^{1}H NMR (400MHz, DMSO-d_6): 9.70 (t, 1), 7.15 (d, 1H), 7.10 (t, 1H), 6.85 (t, 1H), 6.75 (d, 1H), 4.15-4.1 (m, 2H), 3.55-3.3 (m, 2H), 3.00 (m, 1H), 1.9-1.8 (m, 2H)

IR (cm^{-1}): 3300, 1702, 1150



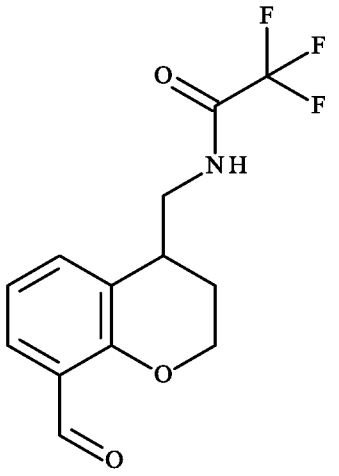
747

Intermediate 748 :

Obtained starting from intermediate **747** according to the procedure used to convert intermediate **93a** into intermediate **94** (**Protocol XVII**)

^{1}H NMR (300MHz, DMSO-d_6): 10.30 (s, 1H), 9.70 (m, 1), 7.57 (dd, 1H), 7.48 (m, 1H), 7.00 (t, 1H), 4.39 (m, 1H), 4.28 (m, 1H), 3.55 (m, 1H), 3.40 (m, 1H), 3.09 (m, 1H), 2.02 (m, 1H), 1.85 (m, 1H), 1.48 (d, 3H)

IR (cm^{-1}): 3300, 1700, 1672

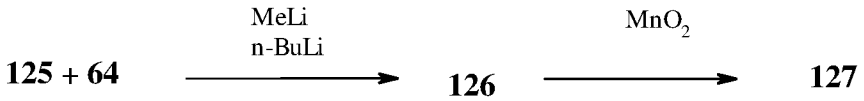


748

Coupling reactions yielding compounds of the invention

Protocol XX : Preparation of compounds of formula (I) wherein X represents -C(=O)

Compounds of formula (I) wherein X represents -C(=O) can be prepared by coupling reaction via a halogen-metal exchange according to the example of the synthesis of intermediate **127** :



Intermediate 126:

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)(hydroxy)methyl]-3,5-difluorophenyl}-ethyl)carbamate

To a solution of intermediate **64** (3 g, 8.92 mmoles) in 36 mL of THF previously cooled to –78°C there are added 5.5 mL (8.8 mmoles) of a 1.6N solution of MeLi in pentane, an internal temperature below –75°C being maintained. After 15 minutes' contact, 3.54 mL (8.8 mmoles) of a 2.5N solution of n-BuLi in hexane are added, the internal temperature being maintained below –75°C. After one hour's contact, a solution of intermediate **125** (1.9 g, 9.83 mmoles) in 80 mL of THF is added, the temperature being maintained below -75°C. The mixture is stirred at –78°C for 1 hour, and then a solution of THF with 20%

water is added to the mixture. After return to ambient temperature, the mixture is decanted in the presence of ethyl acetate and of a saturated NaCl solution. The organic phase is dried over $MgSO_4$. Evaporation under reduced pressure yields an oil, which is purified on silica gel (eluant AcOEt/methylene chloride 10/90). Intermediate **126** (2.05 g) is obtained in the form of a colourless amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.17-8.14 (m, 2H), 7.94 (m, 1H), 7.67 (dd, 1H), 7.38 (broad d, 1H), 7.18 (broad d, 1H), 6.95 (m, 2H), 6.52 (broad s, 1H), 6.34 (broad s, 1H), 4.57 (m, 1H), 1.41 (t, 3H), 1.24 (d, 3H), 4.49 (quad, 2H), 1.34-1.15 (2 broad s, 9H)

IR (cm^{-1}) : 3312, 1685, 1161, 1009, 855-804-757

Intermediate 127 :

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}ethyl)-carbamate

A solution of intermediate **126** (2.05 g, 4.47 mmoles) in 490 mL of methylene chloride is treated with 7.4 g (85 mmoles) of MnO_2, and the mixture is stirred for 20 hours. The mixture is filtered over Celite®, and the Celite® is rinsed with CH_2Cl_2 and then with AcOEt. Evaporation under reduced pressure yields 1.85 g of intermediate **127** in the form of a white solid, which can be used without additional treatment in the following step or can be purified on silica (eluant AcOEt/methylene chloride 5/95).

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.1-8.2 (dd, 2H), 8.05 (d, 1H), 7.7 (m, 1H), 7.55 (d, 1H), 7.20 (d, 2H), 4.75 (m, 1H), 4.55 (quad, 2H), 1.45 (t, 3H), 1.3-1.45 (d and s, 12H)

IR (cm^{-1}) : 3362-3309, 1675, 1523, 1255-1160, 856-811-788-752

This sequence was used to prepare the following intermediates:

Intermediate 7 :

tert-Butyl {1-[4-(isoquinolin-5-ylcarbonyl)phenyl]ethyl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **5 and 3**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.45 (s, 1H), 8.55 (d, 1H), 8.35 (d, 1H), 7.95 (d, 1H), 7.75 (m, 4H), 7.50 (d, 1H), 7.45 (d, 2H), 4.70 (m, 1H), 1.35 (s, 9H), 1.30 (d, 3H)

IR (cm^{-1}) : 1697, 1654

Intermediate 15 :

tert-Butyl {(1R)-1-[4-(isoquinolin-5-ylcarbonyl)-3-methylphenyl]ethyl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **13** and **3** :

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 9.46 (s, 1H), 8.61 (d, 1H), 8.39 (d, 1H), 8.17 (d, 1H), 7.82 (d, 1H), 7.75 (t, 1H), 7.47 (d, 1H), 7.32 (broad s, 1H), 7.28 (d, 1H), 7.20 (dl, 1H), 4.65 (m, 1H), 2.39 (s, 3H), 1.38 (s, 9H), 1.33 (d, 3H)

IR (cm^{-1}) : 3359, 1680, 1656

Intermediate 34 :

tert-Butyl [5-(isoquinolin-5-ylcarbonyl)-6-methyl-2,3-dihydro-1H-inden-1-yl]-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **32** and **3**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.45 (s, 1H), 8.60 (d, 1H), 8.35 (d, 1H), 8.20 (d, 1H), 7.80 (m, 1H), 7.70 (m, 1H), 7.20 (s, 1H), 7.15 (s, 1H), 7.10-6.90 (m, 1H), 5.00 (m, 1H), 2.90-2.60 (2m, 2H), 2.35 (m, 1H), 2.30 (s, 3H), 1.85 (m, 1H), 1.40 (s, 9H)

Intermediate 42 :

tert-Butyl [5-(isoquinolin-5-ylcarbonyl)-6-methyl-2,3-dihydro-1H-inden-1-yl]-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **40** and **3**:

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.45 (s, 1H), 8.62 (d, 1H), 8.42 (d, 1H), 8.20 (d, 1H), 7.95 (d, 1H), 7.78 (t, 1H), 7.68 (t, 1H), 7.52 (broad d, 1H), 7.32 (d, 1H), 7.25 (d, 1H), 4.71 (m, 1H), 1.35 (s, 9H), 1.35 (t, 3H)

Intermediate 51 :

tert-Butyl {1-[3,5-difluoro-4-(isoquinolin-5-ylcarbonyl)phenyl]ethyl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **64** and **3**:

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.50 (s, 1H), 8.70 (d, 1H), 8.63 (d, 1H), 8.50 (d, 1H), 8.10 (d, 1H), 7.80 (t, 1H), 7.52 (d, 1H), 7.25 (d, 2H), 4.70 (m, 1H), 1.40 (s, 9H), 1.35 (d, 3H)

IR (cm^{-1}) : 3360, 1684, 1667, 1634, 1248-1167, 862-824-761

Intermediate 60c :

tert-Butyl {1-[3-fluoro-4-(isoquinolin-5-ylcarbonyl)-5-methylphenyl]ethyl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of the carbamate of intermediate **60b** and **3**:

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.40 (s, 1H), 8.70 (m, 2H), 8.45 (d, 1H), 7.95 (dd, 1H), 7.80 (t, 1H), 7.45 (m, 1H), 7.20 (d, 1H), 7.10 (dd, 1H), 4.70 (m, 1H), 2.10 (s, 3H), 1.40 (broad s, 9H), 1.35 (d, 3H)

IR (cm^{-1}) : 3500-3080, 1695, 1664, 1619, 1516, 1164, 837-680

Intermediate 75 :

tert-Butyl {1-[3-chloro-4-(isoquinolin-5-ylcarbonyl)phenyl]ethyl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **73** and **3**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.40 (s, 1H), 8.70 (d, 1H), 8.50 (d, 1H), 8.45 (d, 1H), 7.90 (dd, 1H), 7.75 (t, 1H), 7.60 (d, 1H), 7.50 (broad s, 1H), 7.40 (dd, 1H), 4.70 (quint, 1H), 1.40 (m, 12H)

IR (cm^{-1}) : 3500-3060, 1695, 1664, 1600, 1510, 1163, 834-647

Intermediate 89 :

tert-Butyl [5-(isoquinolin-5-ylcarbonyl)-6-methoxy-1-methyl-2,3-dihydro-1H-inden-1-yl]carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **87** and **3**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.40 (s, 1H), 8.55 (d, 1H), 8.30 (broad d, 1H), 8.20 (d, 1H), 7.80 (broad d, 1H), 7.70 (t, 1H), 7.30 (s, 1H), 7.00 (s, 1H), 6.85 (m, 1H), 3.40 (s, 3H), 3.00-2.70 (m, 2H), 2.55 (m, 1H), 2.05 (m, 1H), 1.45 (s, 3H), 1.30 (s, 9H)

IR (cm^{-1}) : 3390-3240, 1702, 1654

Intermediate 114 :

tert-Butyl {1-[3-fluoro-4-(isoquinolin-5-ylcarbonyl)-2-methylphenyl]ethyl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **112** and **3**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.50 (s, 1H), 8.60 (d, 1H), 8.40 (d, 1H), 8.20 (d, 1H), 7.95 (d, 1H), 7.80 (t, 1H), 7.62 (d, 1H), 7.50 (t, 1H), 7.35 (d, 1H), 4.90 (m, 1H), 2.22 (s, 3H), 1.40 (s, 9H), 1.30 (d, 3H)

IR (cm^{-1}) : 3360, 1680, 1655, 1615, 1525

Intermediate 122 :

tert-Butyl {1-[8-(isoquinolin-5-ylcarbonyl)-2,3-dihydro-1,4-benzodioxin-5-yl]ethyl}-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **120** and **3**

^{1}H NMR (400/500 MHz, DMSO-d_6) **:** δ 9.40 (1H), 8.60 (1H), 8.35 (1H), 8.30 (1H), 7.92 (1H), 7.75 (1H), 7.45 (1H), 7.05-7.00 (2H), 4.95 (1H), 4.28-4.00 (4H), 1.40 (9H), 1.30 (3H)

IR (cm^{-1}) : 3358, 1677, 1246-1161-1058, 833-787-760

Intermediate 137 :

tert-Butyl {1-[3-chloro-5-fluoro-4-(isoquinolin-5-ylcarbonyl)phenyl]ethyl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **135** and **3**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.50 (s, 1H), 8.80 (d, 1H), 8.50 (d, 1H), 8.02 (d, 1H), 7.80 (t, 1H), 7.53 (d, 1H), 7.45 (s, 1H), 7.38 (d, 1H), 4.72 (m, 1H), 1.40 (broad s, 9H), 1.38 (d, 3H), 1.40 (s, 9H), 1.38 (d, 3H)

IR (cm^{-1}) : 3400, 1675, 1615-1569, 1245-1164, 837-761

Intermediate 160 :

tert-Butyl {2-[3,5-difluoro-4-(isoquinolin-5-ylcarbonyl)phenyl]propan-2-yl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **158** and **3**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 9.50 (s, 1H), 8.70 (d, 1H), 8.65 (d, 1H), 8.05 (broad d, 1H), 7.80 (t, 1H), 7.50 (d, 1H), 7.35 (broad s, 1H), 7.20 (d, 2H), 1.55 (s, 6H), 1.35 (broad s, 9H)

IR (cm^{-1}) : 3256, 3206, 1708, 1663, 1633

Intermediate 165 :

tert-Butyl [(1S)-1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}ethyl]-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **146** and **125**

^{1}H NMR (400/500 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (d, 1H), 8.15 (d, 1H), 8.05 (broad d, 1H), 7.70 (t, 1H), 7.55 (broad d, 1H), 7.25 (d, 2H), 4.75 (m, 1H), 4.55 (quad, 2H), 1.45 (t, 3H), 1.40 (s, 9H), 1.35 (d, 3H)

IR (cm^{-1}) : 3300, 1677, 1260

Intermediate 170 :

tert-Butyl [(1R)-1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}ethyl]-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **145** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (d, 1H), 8.15 (d, 1H), 8.05 (d, 1H), 7.75 (m, 1H), 7.55 (d, 1H), 7.25 (m, 2H), 4.75 (m, 1H), 4.55 (quad, 2H), 1.45 (t, 3H), 1.40 (s, 9H), 1.35 (d, 3H)

IR (cm^{-1}) : 3363, 1681

Intermediate 172 :

tert-Butyl (2-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}propan-2-yl)-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **158** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20-8.10 (dd, 2H), 8.00 (d, 1H), 7.75 (t, 1H), 7.35 (m, 1H), 7.20 (d, 2H), 4.55 (q, 2H), 1.50 (s, 6H), 1.45 (t, 3H), 1.35 (broad s, 9H)

IR (cm^{-1}) : 1712, 1682, 1670

Intermediate 176 :

tert-Butyl {4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluorobenzyl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **174** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.54 (dt, 1H), 8.19 (d, 1H), 8.14 (broad d, 1H), 8.05 (broad d, 1H), 7.71 (dd, 1H), 7.56 (t, 1H), 7.14 (m, 2H), 4.57 (quad, 2H), 4.24 (d, 2H), 1.46 (t, 3H), 1.41 (broad s, 9H)

IR (cm^{-1}) : 3327, 1673, 1251-1160, 1040

Intermediate 178 :

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3-fluoro-2-methylphenyl}ethyl)-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **112** and **125**

^{1}H NMR (400 MHz, DMSO-d6) **:** δ 8.45 (dt, 1H), 8.10 (d, 1H), 7.90 (d, 1H), 7.70 (m, 1H), 7.65 (m, 1H), 7.60 (d, 1H), 7.50 (t, 1H), 7.30 (d, 1H), 4.85 (m, 1H), 4.55 (q, 2H), 2.20 (s, 3H), 1.45 (t, 3H), 1.35 (s, 9H), 1.30 (d, 3H)

IR (cm^{-1}) : 3340, 1703, 1660.

Intermediate 180 :

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3-fluorophenyl}ethyl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **40** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.47 (d, 1H), 8.10 (d, 1H), 7.90 (d, 1H), 7.70 (t and m, 2H), 7.65 (d, 1H), 7.55 (broad d, 1H), 7.31 (d, 1H), 7.27 (d, 1H), 4.71 (quint, 1H), 4.55 (quad, 2H), 1.48 (t, 3H), 1.45 (d, 3H), 1.40 (s, 9H)

IR (cm^{-1}) : 3344, 1681, 1655

Intermediate 189 :

tert-Butyl {2-[3-chloro-4-(isoquinolin-5-ylcarbonyl)phenyl]propan-2-yl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **187** and **3**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 9.48 (s, 1H), 8.68 (d, 1H), 8.49 (d, 1H), 8.44 (broad d, 1H), 7.83 (broad d, 1H), 7.76 (t, 1H), 7.57 (d, 1H), 7.48 (broad s, 1H), 7.46 (broad d, 1H), 7.37 (broad s, 1H), 1.55 (s, 6H), 1.35 (broad s, 9H)

IR (cm^{-1}) : 3265, 1707-1657

Intermediate 202 :

tert-Butyl [(1R)-1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3-fluoro-2-methylphenyl}-ethyl]carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **200** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.44 (d, 1H), 8.10 (d, 1H), 7.85 (d, 1H), 7.70 (t, 1H), 7.66 (m, 1H), 7.60 (d, 1H), 7.50 (t, 1H), 7.35 (d, 1H), 4.85 (m, 1H), 4.55 (quad, 2H), 2.20 (s, 3H), 1.47 (t, 3H), 1.38 (s, 9H), 1.30 (d, 3H)

IR (cm^{-1}) : 3366, 1681, 1670, 1615-1572, 1291-1265-1251-1167, 808-781-755

Intermediate 213 :

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}ethyl)methyl-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **211** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (d, 1H), 8.20 (d, 1H), 8.05 (d, 1H), 7.71 (t, 1H), 7.15 (d, 2H), 5.30 (m, 1H), 4.59 (quad, 2H), 2.70 (s, 3H), 1.52 (d, 3H), 1.49 (t, 3H), 1.43 (s, 9H)

IR (cm^{-1}) : 1673, 1632, 1615

Intermediate 219 :

tert-Butyl [(1S)-1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3-fluoro-2-methylphenyl}-ethyl]carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **217** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.44 (d, 1H), 8.09 (d, 1H), 7.87 (dl, 1H), 7.69 (t, 1H), 7.67 (d, 1H), 7.62 (dl, 1H), 7.51 (t, 1H), 7.34 (d, 1H), 4.87 (m, 1H), 4.56 (quad, 2H), 2.21 (s, 3H), 1.46 (t, 3H), 1.37 (broad s, 9H), 1.29 (d, 3H)

IR (cm^{-1}) : 3362, 1738, 1681-1666, 1527, 1291-1165

Intermediate 227 :

tert-Butyl {(1S)-5-[(1-ethoxyisoquinolin-5-yl)carbonyl]-2,3-dihydro-1H-inden-1-yl}-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **615b** and **125**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 8.40 (d, 1H), 8.00 (d, 1H), 7.82 (d, 1H), 7.72 (t, 1H), 7.60 (s, 1H), 7.58 (d, 1H), 7.34 (d, 1H), 7.32 (d, 1H), 7.23 (d, 1H), 5.03 (m, 1H), 4.55 (quad, 2H), 2.90 (dd, 1H), 2.80 (dd, 1H), 2.38 (m, 1H), 1.85 (m, 1H), 1.42 (s, 9H)

IR (cm^{-1}) : 3330, 1708-1694, 1656, 1266-1244, 810-756

Intermediate 247 :

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3-fluoro-2-methoxyphenyl}-ethyl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **245** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.45 (d, 1H), 8.10 (d, 1H), 7.95 (d, 1H), 7.70 (m, 2H), 7.55 (d, 1H), 7.40 (m, 1H), 7.30 (d, 1H), 5.00 (m, 1H), 4.55 (quad, 2H), 3.85 (s, 3H), 1.45 (t, 3H), 1.35 (s, 9H), 1.30 (d, 3H)

IR (cm^{-1}) : 3341, 1702, 1666

Intermediate 257 :

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-2,3-dimethylphenyl}ethyl)-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **255** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.45 (d, 1H), 8.10 (d, 1H), 7.90 (d, 1H), 7.75 (d, 1H), 7.65 (m, 1H), 7.50 (d, 1H), 7.30 (d, 1H), 7.10 (d, 1H), 4.95 (m, 1H), 4.55 (quad, 2H), 2.30 (2s, 6H), 1.45 (t, 3H), 1.35 (s, 9H), 1.25 (d, 3H)

IR (cm^{-1}) : 3346, 1701, 1659

Intermediate 273 :

tert-Butyl [(1R)-1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3-methylphenyl}ethyl]-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **13** and **125**

^{1}H NMR (300/400 MHz, DMSO-d_6) **:** δ 8.42 (d, 1H), 8.06 (d, 1H), 7.75 (d, 1H), 7.70 (t, 1H), 7.60 (d, 1H), 7.45 (dl, 1H), 7.30 (broad s, 1H), 7.25 (d, 1H), 7.18 (broad d, 1H), 4.65 (quint, 1H), 4.55 (quad, 2H), 2.40 (s, 3H), 1.45 (t, 3H), 1.40 (broad s, 9H), 1.32 (d, 3H)

IR (cm^{-1}) : 3336, 1697, 1657

Intermediate 312 :

tert-Butyl (1-{2-ethoxy-4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3-fluorophenyl}ethyl)-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **310** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.45 (d, 1H), 8.10 (d, 1H), 7.90 (d, 1H), 7.70 (m, 2H), 7.55 (d, 1H), 7.35 (m, 1H), 7.30 (d, 1H), 5.00 (m, 1H), 4.55 (quad, 2H), 4.05 (m, 2H), 1.45 (t, 3H), 1.40 (s, 9H), 1.35 (d, 3H), 1.30 (d, 3H)

IR (cm^{-1}) : 3348, 1710, 1661

Intermediate 315 :

tert-Butyl [(1S)-1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3-methylphenyl}ethyl]-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **313** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.45 (d, 1H), 8.05 (d, 1H), 7.80 (d, 1H), 7.70 (m, 1H), 7.60 (d, 1H), 7.45 (d, 1H), 7.30 (s, 1H), 7.25 (d, 1H), 7.20 (dd, 1H), 4.65 (m, 1H), 4.55 (quad, 2H), 2.40 (s, 3H), 1.45 (t, 3H), 1.35 (s, 9H), 1.30 (d, 3H)

IR (cm^{-1}) : 3392-3355, 1685, 1649

Intermediate 351 :

tert-Butyl [(1R)-1-{8-[(1-ethoxyisoquinolin-5-yl)carbonyl]-2,3-dihydro-1,4-benzo-dioxin-5-yl}ethyl]carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **349b** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.41 (d, 1H), 8.07 (d, 1H), 7.85 (d, 1H), 7.77 (d, 1H), 7.65 (dd, 1H), 7.42 (d, 1H), 7.03 (d, 1H), 6.98 (d, 1H), 4.93 (m, 1H), 4.55 (quad, 2H), 4.25 (m, 2H), 4.02 (m, 2H), 1.45 (t, 3H), 1.38 (s, 9H), 1.26 (d, 3H)

IR (cm^{-1}) : 3346, 1703, 1656, 1614

Intermediate 373 :

tert-Butyl [(1S)-1-{8-[(1-ethoxyisoquinolin-5-yl)carbonyl]-2,3-dihydro-1,4-benzo-dioxin-5-yl}ethyl]carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **371** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.41 (d, 1H), 8.07 (d, 1H), 7.85 (d, 1H), 7.76 (d, 1H), 7.66 (dd, 1H), 7.43 (d, 1H), 7.03 (d, 1H), 6.98 (d, 1H), 4.93 (m, 1H), 4.55 (quad, 2H), 4.25 (m, 2H), 4.02 (m, 2H), 1.45 (t, 3H), 1.38 (s, 9H), 1.26 (d, 3H)

IR (cm^{-1}) : 3346, 1703, 1656, 1614

Intermediate 391 :

tert-Butyl [(1S)-1-{8-[(1-ethoxyisoquinolin-5-yl)carbonyl]-2,3-dihydro-1,4-benzodioxin-5-yl}ethyl]carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **13** and **294**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.36 (d, 1H), 7.69 (d, 1H), 7.56 (t, 1H), 7.51 (s, 1H), 7.44 (broad d, 1H), 7.30 (s, 1H), 7.24 (d, 1H), 7.18 (d, 2H), 4.64 (m, 1H), 4.54 (quad, 2H), 2.46 (s, 3H), 2.38 (s, 3H), 1.45 (t, 3H), 1.37 (broad s, 9H), 1.32 (d, 3H)

IR (cm^{-1}) : 3350, 1677, 1658

Intermediate 408 :

tert-Butyl [(1S)-1-{4-[(1-ethoxy-4-methylisoquinolin-5-yl)carbonyl]-3-methylphenyl}-ethyl]carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **313** and **301**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.40 (d, 1H), 7.85 (s, 1H), 7.70 (t, 1H), 7.60 (dd, 1H), 7.45 (d, 1H), 7.35 (s, 1H), 7.25 (d, 1H), 7.15 (dd, 1H), 4.65 (m, 1H), 4.50 (quad, 2H), 2.60 (s, 3H), 2.10 (s, 3H), 1.50 (t, 3H), 1.35 (m, 9H), 1.30 (d, 3H)

IR (cm^{-1}) : 3410, 1700, 1662

Intermediate 462 :

tert-Butyl [(1R)-1-{4-[(1-ethoxy-4-methylisoquinolin-5-yl)carbonyl]-3-methylphenyl}-ethyl]carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **13** and **302**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.40 (d, 1H), 7.85 (s, 1H), 7.70 (t, 1H), 7.60 (dd, 1H), 7.45 (d, 1H), 7.35 (s, 1H), 7.25 (d, 1H), 7.15 (dd, 1H), 4.65 (m, 1H), 4.50 (quad, 2H), 2.60 (s, 3H), 2.10 (s, 3H), 1.50 (t, 3H), 1.35 (m, 9H), 1.30 (d, 3H)

IR (cm^{-1}) : 3335, 1698, 1662

Intermediate 542 :

tert-Butyl [(1R)-1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3-fluoro-5-methoxyphenyl}-ethyl]carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **540** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.5 (d, 1H), 8.25 (d, 1H), 8.2 (d, 1H), 7.9 (d, 1H), 7.7 (t, 1H), 7.5 (d, 1H), 7.0 (s, 1H), 6.9 (d, 1H), 4.7 (m, 1H), 4.55 (quad, 2H), 3.7 (s, 3H), 1.45 (t, 3H), 1.4 (s, 9H), 1.35 (d, 3H).

IR (cm^{-1}) : 3389, 1680, 1168

Intermediate 591 :

tert-Butyl {1-[4-(isoquinolin-5-ylcarbonyl)phenyl]ethyl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **589** and **3**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.45 (s, 1H), 8.55 (d, 1H), 8.35 (d, 1H), 7.95 (d, 1H), 7.75 (m, 4H), 7.50 (d, 1H), 7.45 (d, 2H), 4.70 (m, 1H), 1.35 (s, 9H), 1.30 (d, 3H)

IR (cm^{-1}) : 1697, 1654

Intermediate 596 :

tert-Butyl {(1S)-1-[4-(isoquinolin-5-ylcarbonyl)phenyl]ethyl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **594** and **3**

^{1}H NMR (300 MHz, DMSO-d_6) : δ 9.45 (s, 1H), 8.55 (d, 1H), 8.35 (d, 1H), 7.95 (d, 1H), 7.75 (m, 4H), 7.50 (d, 1H), 7.45 (d, 2H), 4.70 (m, 1H), 1.35 (s, 9H), 1.30 (d, 3H)

IR (cm^{-1}) : 1697, 1654

Intermediate 603 :

tert-Butyl {2-[4-(isoquinolin-5-ylcarbonyl)phenyl]propan-2-yl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **601** and **3**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.50 (s, 1H), 8.55 (d, 1H), 8.35 (d, 1H), 7.90 (broad d, 1H), 7.80 (m, 2H), 7.75-7.5 (dd, 4H), 7.30 (m, 1H), 1.55 (s, 6H), 1.30 (m, 9H)

IR (cm^{-1}) : 1697, 1654

LCMS [M+H]+= 391

Intermediate 610 :

tert-Butyl {1-[4-(isoquinolin-5-ylcarbonyl)phenyl]cyclobutyl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **608** and **3**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.50 (s, 1H), 8.55 (d, 1H), 8.40 (d, 1H), 7.9-7.7 (m, 4H), 7.8-7.5 (dd, 4H), 2.40 (m, 4H), 2.05-1.8 (m, 2H), 1.30 (m, 9H)

IR (cm^{-1}) : 1697, 1654

LCMS [M+H]+= 403

Intermediate 617 :

tert-Butyl [(1R)-5-(isoquinolin-5-ylcarbonyl)-2,3-dihydro-1H-inden-1-yl]carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **615a** and **3**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.50 (s, 1H), 8.55 (d, 1H), 8.35 (d, 1H), 7.90 (d, 1H), 7.80 (dd, 1H), 7.80 (d, 1H), 7.65 (d and s, 2H), 7.35 (broad t, 1H), 5.05 (m, 1H), 2.9-2.8 (m, 2H), 2.4-1.85 (m, 2H), 1.45 (s, 9H)

IR (cm^{-1}) : 3300, 1692-1654

Optical purity (OJ-H column, eluant : n-propyl alcohol/heptane/diethylamine : 10/90/0.1, detection 270nm) : 99%.

Intermediate 619 :

tert-Butyl [(1S)-5-(isoquinolin-5-ylcarbonyl)-2,3-dihydro-1H-inden-1-yl]carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **615b** and **3**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.40 (s, 1H), 8.55 (d, 1H), 8.35 (d, 1H), 7.90 (d, 1H), 7.85 (d, 1H), 7.80 (d, 1H), 7.65 (m, 2H), 7.35 (d, 1H), 5.05 (m, 1H), 3.0-2.7 (2m, 2H), 2.41-1.9 (2m, 2H), 1.45 (s, 9H)

IR (cm^{-1}) : 3300, 1692-1654

Optical purity (OJ-H column, eluant : n-propyl alcohol/heptane/diethylamine 10/90/0.1, detection 270nm) : > 98%

Intermediate 625 :

tert-Butyl {4-[4-(isoquinolin-5-ylcarbonyl)phenyl]tetrahydro-2H-pyran-4-yl}-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **623** and **3**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 9.45 (s, 1H), 8.54 (d, 1H), 8.38 (d, 1H), 7.92 (d, 1H), 7.80 (d and t, 2H), 7.76/7.55 (2d, 4H), 7.40 (broad s, 1H, NH), 3.70 (m, 4H), 2.2/1.9 (2m, 4H), 1.35 (broad s, 9H)

IR (cm^{-1}) : 3300, 1708-1695, 1655

Intermediate 635 :

tert-Butyl [5-(isoquinolin-5-ylcarbonyl)-1-methyl-2,3-dihydro-1H-inden-1-yl]-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **633** and **3**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.40 (s, 1H), 8.55 (d, 1H), 8.35 (d, 1H), 7.90 (d, 1H), 7.80 (m, 2H), 7.60 (m, 2H), 7.35 (d, 1H), 7.20 (broad s, 1H, NH), 3.00-2.8 (m, 2H), 2.55-1.95 (2m, 2H), 1.40 (s, 3H), 1.30 (broad s, 9H)

IR (cm^{-1}) : 3340-3230, 1700, 1653, 1616

Intermediate 637 :

tert-Butyl {(1S)-1-[4-(isoquinolin-5-ylcarbonyl)-3-methylphenyl]ethyl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **313** and **3**

^{1}H NMR (400 MHz, DMSO-d_6)**:** δ 9.46 (s, 1H), 8.61 (d, 1H), 8.39 (d, 1H), 8.17 (d, 1H), 7.82 (d, 1H), 7.75 (t, 1H), 7.47 (d, 1H), 7.32 (broad s, 1H), 7.28 (d, 1H), 7.20 (dl, 1H), 4.65 (m, 1H), 2.39 (s, 3H), 1.38 (s, 9H), 1.33 (d, 3H)

Intermediate 647 :

tert-Butyl [5-(isoquinolin-5-ylcarbonyl)-6-methoxy-2,3-dihydro-1H-inden-1-yl]-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **645** and **3**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.30 (d, 1H), 8.55 (d, 1H), 8.30 (d, 1H), 8.25 (d, 1H), 7.80 (d, 1H), 7.70 (t, 1H), 7.35 (s, 1H), 7.10 (m, 1H, NH), 6.95 (s, 1H), 5.00 (m, 1H), 3.45 (s, 3H), 2.75-2.90 (2m, 2H), 2.40 (m, 1H), 1.90 (m, 1H), 1.45 (s, 9H)

IR (cm^{-1}) : 3400-3200, 1700, 1651

Intermediate 686 :

tert-Butyl {1-[4-(isoquinolin-5-ylcarbonyl)-3-methoxyphenyl]ethyl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **684** and **3**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 9.40 (s, 1H), 8.60 (d, 1H), 8.35 (d, 1H), 8.25 (d, 1H), 7.80 (d, 1H), 7.70 (t, 1H), 7.45 (d, 2H), 7.10 (s, 1H), 7.05 (d, 1H), 4.70 (tl, 1H), 3.50 (s, 3H), 1.40 (s, 9H), 1.35 (d, 3H)

IR (cm^{-1}) : 3400-3150, 1702-1656, 1607, 1243, 1164, 1032, 832-760

Intermediate 718 :

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3-fluoro-2-(2-methylpropoxy)-phenyl}ethyl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of the tert-butylcarbamate intermediate of **714** and **125**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 8.45 (d, 1H), 8.10 (d, 1H), 7.90 (d, 1H), 7.70 (t and m, 2H), 7.53 (d, 1H, NH), 7.34 (dd, 1H), 7.32 (d, 1H), 5.02 (m, 1H), 4.68 (quad, 2H), 3.78 (m, 2H), 2.03 (m, 1H), 1.46 (t, 3H), 1.36 (broad s, 9H), 1.30 (d, 3H), 0.98 (d, 6H)

IR (cm^{-1}) : 3354, 1704, 1662, 1264, 1161, 813, 759

Intermediate 728 :

tert-Butyl (1-{2-(benzyloxy)-4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-5-fluorophenyl}-ethyl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **726** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.46 (d, 1H), 8.09 (d, 1H), 7.90 (dl, 1H), 7.70 (dd, 1H), 7.66 (dl, 1H), 7.51 (dl, 1H, NH), 7.45-7.30 (m, 6H), 5.21 (dd, 2H), 5.08 (m, 1H), 4.58 (quad, 2H), 1.48 (t, 3H), 1.39 (s, 9H), 1.30 (d, 3H)

IR (cm^{-1}) : 3350, 1679, 1657, 1619

Intermediate 757 :

tert-Butyl [(1R)-1-{4-[(8-chloroisoquinolin-5-yl)carbonyl]phenyl}ethyl]carbamate

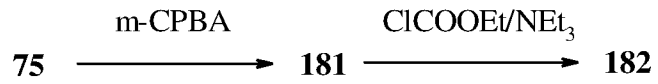
Obtained by oxidation of the intermediate resulting from the coupling of **5** and **755**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.70 (s, 1H), 8.68 (d, 1H), 7.95 (d, 1H), 7.90 (d, 1H), 7.88 (d, 1H), 7.77 (d, 2H), 7.53 (d, 1H, NH), 7.47 (d, 2H), 4.70 (quint, 1H), 1.36 (s, 9H), 1.32 (d, 3H)

IR (cm^{-1}) : 3378, 1674, 1669, 1245, 1168, 1062, 836

Intermediate 182 :

Obtained in two steps starting from intermediate **75**



Intermediate 181 :

tert-Butyl (1-{3-chloro-4-[(2-oxidoisoquinolin-5-yl)carbonyl]phenyl}ethyl)carbamate

Intermediate **75,** treated according to the protocol described for intermediate **123**, was converted into **181.**

MS (DEI 70 eV) = 426.1

Intermediate 182 :

tert-Butyl (1-{3-chloro-4-[(1-ethoxyisoquinolin-5-yl)carbonyl]phenyl}ethyl)carbamate

To a solution of intermediate **181** (1.1 g, 2.57 mmoles) in ethanol (680 mL), at ambient temperature, there are added in succession ethyl chloroformate (0.9 mL) and then, after 5 minutes, NEt_3 (1.9 mL). The reaction mixture is stirred for 10 minutes at ambient temperature, and then ethyl chloroformate (0.9 mL) is again added. After 10 minutes' stirring at ambient temperature, the reaction mixture is concentrated in vacuo. The residue is taken up in water and extracted in the presence of methylene chloride. The organic phase is dried over $MgSO_4$ and concentrated. By chromatography on silica (eluant CH_2Cl_2/AcOEt 100/0 to 90/10), intermediate **182** is obtained (0.5 g).

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.50 (d, 1H), 8.15 (d, 1H), 8.00 (d, 1H), 7.80 (d, 1H), 7.70 (m, 1H), 7.55 (d, 1H), 7.55 (broad s, 1H), 7.50 (s, 1H), 7.40 (d, 1H), 4.70 (m, 1H), 4.55 (quad, 2H), 1.45 (t, 3H), 1.40 (s, 9H), 1.35 (d, 3H)

IR (cm^{-1}) : 3336, 1694, 1668

This procedure was applied to prepare intermediate **191** obtained from intermediate **189** :

Intermediate 191 :

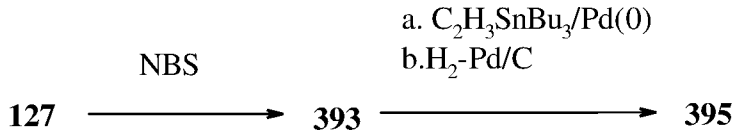
tert-Butyl (2-{3-chloro-4-[(1-ethoxyisoquinolin-5-yl)carbonyl]phenyl}propan-2-yl)-carbamate

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.48 (d, 1H), 8.15 (d, 1H), 7.96 (d, 1H), 7.78 (broad d, 1H), 7.69 (t, 1H), 7.54 (d, 1H), 7.46 (broad s, 1H), 7.45 (broad d, 1H), 7.36 (broad s, 1H), 4.57 (quad, 2H), 1.54 (s, 6H), 1.46 (t, 3H), 1.35 (broad s, 9H)

IR (cm^{-1}) : 3350, 1698, 1666, 1243-1159

Intermediate 395 :

Obtained in three steps starting from intermediate **127**



Intermediate 393 :

tert-Butyl (1-{4-[(4-bromo-1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}-ethyl)carbamate

To a solution of intermediate **127** (2.7 g, 5.9 mmoles) in DMF (65 mL) there is added N-bromosuccinimide (1 g, 6 mmoles). The reaction mixture is stirred at ambient temperature for 24 hours. The mixture is taken up in AcOEt and water, and the organic phase is washed with a saturated aqueous NaCl solution, dried over $MgSO_4$ and concentrated. By chromatography on silica (eluant CH_2Cl_2/AcOEt 100/0 to 95/5), intermediate **393** is obtained in the form of an amorphous solid (1.35 g).

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.43 (d, 1H), 8.31 (s, 1H), 7.86 (d, 1H), 7.74 (t, 1H), 7.52 (broad d, 1H), 7.16 (d, 2H), 4.69 (m, 1H), 4.56 (quad, 2H), 1.46 (t, 3H), 1.37 (broad s, 9H), 1.30 (d, 3H)

IR (cm^{-1}) : 3346, 1708, 1678

Intermediate 395 :

tert-Butyl (1-{4-[(1-ethoxy-4-ethylisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}-ethyl)carbamate

Step 1 :

To a solution, degassed with N_2, of intermediate **393** (1.6 g) in DMF (33 mL) there are added vinyl-tributyl-tin (0.89 mL) and $Pd(PPh_3)_4$ (56 mg). The mixture is heated at 100°C for 5 hours. After return to ambient temperature, the mixture is treated with a 10% aqueous KF solution, the salts are filtered off, and the filtrate is extracted with AcOEt. The organic

phase is dried over $MgSO_4$ and concentrated in vacuo. The expected product is obtained by chromatography on silica (eluant CH_2Cl_2/AcOEt 100/0 to 90/10) in the form of an amorphous solid (0.9 g).

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.45 (d, 1H), 8.09 (s, 1H), 7.85 (d, 1H), 7.70 (t, 1H), 7.51 (d, 1H), 7.13 (d, 2H), 6.61 (dd, 1H), 5.43 (d, 1H), 5.08 (d, 1H), 4.67 (m, 1H), 4.57 (quad, 2H), 1.46 (t, 3H), 1.37 (broad s, 9H), 1.30 (d, 3H)

IR (cm^{-1}) : 3344, 1710, 1673, 1631

Step 2 :

A solution of the intermediate obtained in step 1 above (0.94 g, 1.95 mmoles) in ethanol (90 mL) is hydrogenated at atmospheric pressure of H_2 and at ambient temperature in the presence of 10% Pd/C (0.2 g) for 24 hours. A fresh batch of 10% Pd/C is added, and the mixture is hydrogenated for a further 24 hours, the catalyst is then filtered off, and the filtrate is concentrated in vacuo. By chromatography on silica (eluant CH_2Cl_2/cyclohexane 20/80 to 100/0 then CH_2Cl_2/AcOEt 95/5), intermediate **395** is obtained in the form of an amorphous solid (0.5 g).

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 8.45 (d, 1H), 8.00 (s, 1H), 7.80 (d, 1H), 7.65 (t, 1H), 7.50 (broad d, 1H), 7.20 (d, 2H), 4.70 (m, 1H), 4.55 (quad, 2H), 2.65 (quad, 2H), 1.50 (t, 3H), 1.35 (broad s, 9H), 1.32 (d, 3H), 1.20 (t, 3H)

IR (cm^{-1}) : 3340, 1678

Intermediate **433** was obtained by chlorination (with N-chlorosuccinimide) of intermediate **170** or tert-butyl (1-{4-[(4-chloro-1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}-ethyl)carbamate.

Intermediate 433 :

tert-Butyl (1-{4-[(4-chloro-1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}-ethyl)carbamate

To a solution of **170** (1 g, 2.19 mmoles) in CH_3CN (30 mL) there is added N-chlorosuccinimide (0.3 g, 2.3 mmoles). The reaction mixture is heated at reflux for 24 hours, and then the solvent is evaporated off in vacuo. The residue is taken up in AcOEt and washed with water, and the organic phase is dried over $MgSO_4$ and concentrated. By

chromatography on silica (eluant CH_2Cl_2/AcOEt 98/2), intermediate **433** is obtained in the form of an amorphous solid (0.6 g).

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.43 (dd, 1H), 8.18 (s, 1H), 7.88 (d, 1H), 7.77 (t, 1H), 7.52 (d, 1H), 7.16 (d, 2H), 4.69 (m, 1H), 4.57 (quad, 2H), 1.47 (t, 3H), 1.38 (s, 9H), 1.31 (d, 3H)

IR (cm^{-1}) : 3350, 1712-1680

Intermediate 434 :

tert-Butyl [(1S)-1-{4-[(4-chloro-1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluoro-phenyl}ethyl]carbamate

Obtained starting from **165** according to the protocol described for the preparation of intermediate **433.**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.43 (dd, 1H), 8.18 (s, 1H), 7.88 (d, 1H), 7.77 (t, 1H), 7.52 (d, 1H), 7.16 (d, 2H), 4.69 (m, 1H), 4.57 (quad, 2H), 1.47 (t, 3H), 1.38 (s, 9H), 1.31 (d, 3H)

IR (cm^{-1}) : 3500-3400, 1679-1632

Intermediate 688 :

tert-Butyl {1-[3-hydroxy-4-(isoquinolin-5-ylcarbonyl)phenyl]ethyl}carbamate

Obtained in two steps, by treatment of intermediate **686** with BBr_3 in methylene chloride, and treatment of the phneol intermediate formed **687** in the presence of Boc_2O and NEt_3.

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 11.30, 9.50, 8.60, 8.40, 7.95, 7.90, 7.82, 7.50, 7.32, 6.97, 6.88, 4.62,1.40, 1.35

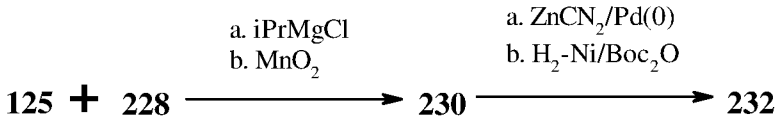
IR (cm^{-1}) : 3330, 1699

LCMS [M+H]+= 392

Intermediate 230 :

(4-Bromo-2,5-difluorophenyl)(isoquinolin-5-yl)methanone

Obtained by oxidation of intermediate **229** resulting from the coupling of **228** and **125** according to the following protocol:



Step 1 :

500 mg (1.83 mmoles) of 1,4-dibromo-2,5-difluorobenzene **228** are dissolved in 10 mL of anhydrous THF. The mixture is cooled to -50°C, under argon, and there is added dropwise 1 mL (2 mmoles, 1.1 eq.) of a 2M solution in THF of isopropylmagnesium chloride. The temperature is maintained between -50°C and -40°C. Stirring is carried out for 30 minutes at -50°C, and the progress of the reaction is monitored by HPLC (approximately 75%). There is then added, still at -50°C, a solution of 0.37 g (1.83 mmoles, 1 eq.) of **125** in 3 mL of anhydrous THF. The temperature is allowed to rise to -10°C. Monitoring of the reaction by HPLC shows the formation of 68% of the desired alcohol. Hydrolysis is carried out with 15 mL of 1N HCl. Extraction with 3 times 25 ml of ether is carried out, and the organic phase is washed with a saturated aqueous NaCl solution, dried over $MgSO_4$, filtered and evaporated to dryness. The residue obtained crystallises in dichloromethane. The solid is then filtered off and dried to give 280 mg of expected product in the form of a solid. The crystallisation liquors are evaporated to dryness and purified by flash chromatography on 40 g of silica, eluant : CH_2Cl_2-AcOEt gradient : 99-1 to 90-10 to give 200 mg of the purified intermediate.

^{1}H NMR (400/500 MHz, DMSO-d_6) **:** δ 8.18 (d, 1H), 8.01 (d, 1H), 7.73 (d, 1H), 7.61 (t, 1H), 7.67 (dd, 1H), 7.53 (d, 1H), 7.47 (dd, 1H), 6.51 (d, 1H) , 6.41 (d, 1H), 4.52 (quad, 2H), 1.45 (t, 3H).

IR (cm^{-1}) : 1621

Step 2 :

Oxidation with MnO_2 of the intermediate obtained above yields intermediate **230**:

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.50 (d, 1H), 8.13 (d, 1H), 8.01 (d, 1H), 7.93 (dd, 1H), 7.82 (d, 1H), 7.73 (dd, 1H), 7.70 (t, 1H), 4.58 (quad, 2H), 1.46 (t, 3H)

IR (cm^{-1}) : 3211, 1652

Intermediate 232 :

tert-Butyl [3-fluoro-4-(isoquinolin-5-ylcarbonyl)benzyl]carbamate

Obtained starting from **230** according to the following protocol:

Step 1 :

There are dissolved in 2 ml of anhydrous DMF, degassed with argon, 220 mg (0.558 mmole) of intermediate **230**. There are added to the solution, under argon, 11 mg (0.055 mmole, 0.1 eq.) of CuI, 92 mg (0.558 mmole, 1 eq.) of potassium iodide and 20 mg (0.11 mmole, 0.2 eq.) of phenanthroline. The whole is heated at 110°C for 18h. HPLC monitoring shows 90% conversion to the iodine-containing compound. There are then added 36 mg (0.0558 mmole, 1 eq.) of potassium cyanide, and heating is continued at 110°C for 3 hours. The conversion is incomplete and 20% of iodine-containing compound remain. A further 5 mg (0.077 mmole, 0.13 eq.) of KCN are added. Heating is carried out for a further 3 hours at 110°C. The reaction mixture is cooled and hydrolysed on 10 mL of water. The mixture is filtered, and the solid is rinsed 3 times with water. There are then added to the filtrate a 5% aqueous ammonia solution and ethyl acetate. A solid precipitates. It is filtered off and washed with ethyl acetate and water. The ethyl acetate phase is decanted and washed with water and then with a saturated aqueous NaCl solution. The organic phase is then dried over $MgSO_4$, filtered and evaporated to give 170 mg of a residue, which is purified by flash chromatography on 12 g of silica, eluant = CH_2Cl_2 100% to give 100 mg of the expected intermediate.

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (dd, 1H), 8.20 (d, 1H), 8.05 (m, 3H), 7.95 (dd, 1H), 7.70 (m, 1H), 4.60 (quad, 2H), 1.45 (t, 3H)

IR (cm^{-1}) : 2244, 1663

Step 2 :

Reduction of the intermediate obtained in step 1 according to the protocol described for intermediate **223** yields intermediate **232**

^{1}H NMR (400 MHz, DMSO-d_6)**:** δ 8.49 (d, 1H), 8.10 (d, 1H), 7.95 (d, 1H), 7.72 (d, 1H), 7.70 (t, 1H), 7.52 (m, 1H), 7.51 (m, 1H), 7.20 (m, 1H), 4.55 (quad, 2H), 4.22 (m, 2H), 1.45 (t, 3H), 1.40 (s, 9H)

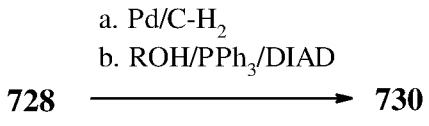
^{19}F NMR: -123, -117

IR (cm^{-1}) : 3351, 1676-1662.

Intermediate 730 :

tert-Butyl (1-{2-[2-(dimethylamino)ethoxy]-4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-5-fluorophenyl}ethyl)carbamate

Intermediate **730** was obtained in two steps starting from **728** :



Step 1 :

Intermediate **728** or tert-butyl (1-{2-(benzyloxy)-4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-5-fluorophenyl}ethyl)carbamate was converted into the corresponding phenolic compound according to the conditions described for obtaining compound **553** (intermediate of **555**).

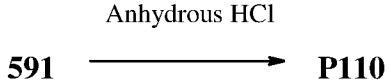
Step 2 :

The phenolic intermediate obtained above (1 g, 2.2 mmoles) is dissolved in THF and, in the presence of commercial dimethyl-ethanol-amine (0.22 mL), is treated with triphenylphosphine (0.87 g, 3.3 mmoles) and diisopropyl azodicarboxylate (0.65 mL, 3.3 mmoles). The reaction mixture was stirred at ambient temperature for 3 days. After concentration in vacuo, the residue is chromatographed on silica (eluant : CH_2Cl_2/EtOH 90/10), and the solid obtained is recrystallised from methanol. Intermediate **730** is obtained in the form of a solid (0.36 g).

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 8.45 (d, 1H), 8.10 (d, 1H), 7.90 (d, 1H), 7.70 (m, 2H), 7.55 (d, 1H, NH), 7.30 (d, 1H), 7.20 (d, 1H), 5.00 (quint, 1H), 4.60 (quad, 2H), 4.10 (t, 2H), 2.65 (m, 2H), 2.20 (s, 6H), 1.50 (t, 3H), 1.40 (broad s, 9H), 1.30 (d, 3H)

IR (cm^{-1}) : 3410, 1679, 1630, 1533, 1166

The ketone intermediates obtained by protocol **XX** were deprotected in an acidic medium to yield the final products, such as in the example of product **P110**:



Product P110 :

[4-(1-Aminoethyl)phenyl](isoquinolin-5-yl)methanone hydrochloride

To a solution of intermediate **591** (2.9 g, 7.7 mmoles) in Et_2O (60 mL) there is added a solution of 2N HCl in ether HC(30 mL). The resulting suspension is stirred at ambient temperature for 4 days. The precipitate collected on a frit is dried in vacuo, and product **P110** is obtained in the form of a white solid (2.05 g).

The 1-ethoxyisoquinolin-5-yl ketone intermediates were then deprotected according to one of the two examples described below for **P17** and **P68**:

Product P17 :

[4-(1-Aminoethyl)-2,6-difluorophenyl](1-hydroxyisoquinolin-5-yl)methanone hydrochloride

A mixture of 11.86 g (36 mmoles) of intermediate **127** in 710 mL of 4N HCl is heated at 80°C for 48h. After HPLC monitoring, the mixture is cooled to 0°C and the solid is filtered over a frit, which yields 8.2 g of product **P17** in the form of a white solid (1.1% of deamination product).

Product P68 :

5-{4-[(1R)-1-Aminoethyl]-2-methylbenzoyl}-3-methylisoquinolin-1(2H)-one methanesulphonate

A solution of intermediate **391** (0.7 g, 1.58 mmoles) in a 1,4-dioxane/water mixture (14 mL/4 mL) and of methanesulphonic acid (0.51 mmole) is heated at 80°C for 24 hours. The reaction mixture is concentrated in vacuo, and the residue is taken up in CH_3CN. The resulting solid is filtered off and dried in vacuo. Product **P68** is obtained in the form of a solid.

Product	**Obtained from**	**Nomenclature** **Analytical description**
P1	**7**	**{4-[(1R)-1-Aminoethyl]phenyl}(isoquinolin-5-yl)-methanone dihydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 9.80 (s, 1H), 8.75 (m,

		3H), 8.65 (2d, 2H), 8.20 (d, 1H), 8.15 (d, 1H), 8.00 (t, 1H), 7.88 (t, 2H), 7.75 (d, 2H), 4.50 (m, 1H), 1.55 (d, 3H) **IR (cm^{-1}) :** 3000-2000, 1650 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{17}N_2O$ $[M+H]^+$ 277.1341, measured 277.1357 **Optical purity** : (ADH 5µm column 4.6x250mm, eluant : EtOH/triethylamine 1000/1, detection : 265nm) : > 99%. (absence of **P111**)
P2	**15**	**{4-[(1R)-1-Aminoethyl]-2-methylphenyl}(isoquinolin-5-yl)methanone hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 9.88 (s, 1H), 8.74 (m, 4H), 8.68 (d, 1H), 8.59 (d, 1H), 8.04 (d, 1H), 7.98 (t, 1H), 7.62 (broad s, 1H), 7.48 (broad d, 1H), 7.42 (d, 1H), 4.46 (m, 1H), 2.43 (s, 3H), 1.56 (d, 3H) **IR (cm^{-1}) :** 3000-2000, 1654 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{19}N_2O$ $[M+H]^+$ 291.1497, measured 291.1525 **Optical purity** : (ADH 5µm column 4.6x250mm, eluant : EtOH/diethylamine 100/0.1, detection : 270nm) : > 99%. (absence of **P121**) **α_D** (589nM) = 7 (c = 0.004 g/mL, MeOH) at 20°C
P4	**34**	**(1-Amino-6-methyl-2,3-dihydro-1H-inden-5-yl)-(isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 9.85 (s, 1H), 8.88-8.55 (3d, 3H), 8.75 (m, 3H), 8.00 (d and t, 2H), 7.70 (s, 1H), 7.30 (s, 1H), 5.05 (m, 1H), 4.75 (m, 1H), 3.00-2.80 (2m, 2H), 2.40 (s, 3H), 2.50-2.02 (2m, 2H) **IR (cm^{-1}) :** 3100-2200, 1657 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{19}N_2O$ $[M+H]^+$ 303.1497, measured 303.1511

P5	**42**	**[4-(1-Aminoethyl)-2-fluorophenyl](isoquinolin-5-yl)-methanone dihydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 9.95 (s, 1H), 9.00 (broad s, 3H), 8.80 (2dd, 2H), 8.62 (d, 1H), 8.21 (dd, 1H), 8.05 (t, 1H), 7.80 (m, 1H), 7.72-7.58 (m, 2H), 7-6.50 (m, 1H), 4.60 (m, 1H), 1.60 (d, 3H) **IR (cm^{-1}) :** 3000-2000, 1663 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{16}F_1N_2O$ $[M+H]^+$ 295.1247, measured 295.1249
P6	**51**	**[4-(1-Aminoethyl)-2,6-difluorophenyl](isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 9.70 (s, 1H) 8.90 (d, 1H) 8.80 (d and m, 4H) 8.70 (d, 1H) 8.25 (d, 1H) 7.95 (t, 1H) 7.60 (d, 2H) 4.60 (sept, 1H) 1.60 (d, 3H) **IR (cm^{-1}) :** 3280-2000, 1673 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{15}F_2N_2O$ $[M+H]^+$ 313.1152, measured 313.1167
P8	**60c**	**[4-(1-Aminoethyl)-2-fluoro-6-methylphenyl]-(isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 9.90 (m, 1H), 9.10 (m, 1H), 8.80 (m, 4H), 8.70 (d, 2H), 8.60 (d, 1H), 8.00 (t, 1H), 7.50 (s and d, 2H), 4.50 (m, 1H), 2.30 (s, 3H), 1.60 (d, 3H) **IR (cm^{-1}) :** 3385-1900, 1660 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{18}F_1N_2O$ $[M+H]^+$ 309.1403, measured 309.1403
P11	**75**	**[4-(1-Aminoethyl)-2-chlorophenyl](isoquinolin-5-yl)-methanone dihydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 9.90 (s and d and m, 5H), 8.80 (d, 1H), 8.70 (d, 2H), 8.10 (d,1H), 8.00 (t, 1H), 7.90 (broad s, 1H), 7.70 (m, 2H), 4.55 (m, 1H), 1.60 (d, 3H) **IR (cm^{-1}) :** 3290-1910, 1663

		HRMS (ESI) : theoretical m/z for $C_{18}H_{16}Cl_1N_2O$ $[M+H]^+$ 310.0873, measured 310.0859
P12	**89**	**(1-Amino-6-methoxy-1-methyl-2,3-dihydro-1H-inden-5-yl)(isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 9.60 (s, 1H), 8.70 (m, 3H), 8.65 (d, 1H), 8.44 (d, 2H), 7.90 (d, 1H), 7.82 (t, 1H), 7.60 (s, 1H), 7.45 (s, 1H), 3.10-2.85 (m, 4H), 2.40-2.20 (m, 2H), 1.65 (s, 3H) **IR (cm^{-1}) :** 2800-2056, 1654 **HRMS (ESI) :** theoretical m/z for $C_{21}H_{21}N_2O_2$ $[M+H]^+$ 333.1603, measured 333.1616
P15	**114**	**[4-(1-Aminoethyl)-2-fluoro-3-methylphenyl]-(isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 9.95 (s, 1H), 8.80 (m, 4H), 8.25 (d, 1H), 8.52 (d, 1H), 8.10 (d, 1H), 7.95 (t, 1H), 7.65 (m, 2H), 4.70 (m, 1H), 2.78 (s, 3H), 1.55 (d, 3H) **IR (cm^{-1}) :** 3400-2200, 1668 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{18}FN_2O$ $[M+H]^+$ 309.1403, measured 309.1391
P16	**122**	**[8-(1-Aminoethyl)-2,3-dihydro-1,4-benzodioxin-5-yl]-(isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 9.90 (s, 1H), 8.75 (d, 1H), 8.70 (m, 6H), 8.15 (d, 1H), 8.00 (t, 1H), 7.25 (d, 1H), 7.20 (d, 1H), 4.60 (d, 1H), 4.30 (m, 2H), 4.05 (m, 2H), 1.55 (d, 3H) **IR (cm^{-1}) :** 3200-2400, 165 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{19}N_2O_3$ $[M+H]^+$ 335.1396, measured 335.1392
P17	**127**	**[4-(1-Aminoethyl)-2,6-difluorophenyl](1-hydroxy-isoquinolin-5-yl)methanone hydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 11.60 (broad s, 1H), 8.52 (dd, 1H), 8.50 (m, 3H), 7.90 (dd, 1H), 7.58 (t, 1H),

		7.40 (s, 2H), 7.50 (d, 2H), 4.53 (quad, 1H), 1.55 (d, 3H) **IR (cm^{-1}) :** 3000-2500, 1674 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{15}F_2N_2O_2$ $[M+H]^+$ 329.1102, measured 329.1102
P18	**137**	**[4-(1-Aminoethyl)-2-chloro-6-fluorophenyl]-(isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 10.80 (s, 1H), 9.05 (d, 1H), 8.70 (d, 1H), 8.85 (broad d, 4H), 8.20 (d, 1H), 7.95 (t, 1H), 7.80 (s, 1H), 7.75 (d, 1H), 4.55 (t, 1H), 1.60 (d, 3H) **IR (cm^{-1}) :** 3100-2400, 1675 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{15}ClFN_2O$ $[M+H]^+$ 329.0857, measured 329.0846
P24	**160**	**[4-(2-Aminopropan-2-yl)-2,6-difluorophenyl]-(isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 9.84 (s, 1H), 9.10 (m, 4H), 8.94 (d, 1H), 8.82 (d, 1H), 7.73 (d, 1H), 8.32 (d, 1H), 7.99 (t, 1H), 7.64 (d, 2H), 1.71 (s, 6H) **IR (cm^{-1}) :** 3200-2300, 1674. **HRMS (ESI) :** theoretical m/z for $C_{19}H_{17}F_2N_2O$ $[M+H]^+$ 327.1309, measured 327.129
P25	**165**	**{4-[(1S)-1-Aminoethyl]-2,6-difluorophenyl}(1-hydroxy-isoquinolin-5-yl)methanone hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.70 (s, 1H), 8.90 (broad s, 3H), 8.55 (d, 1H), 7.90 (d, 1H), 7.60 (m, 3H), 7.40 (s, 2H), 4.55 (quad, 1H), 1.60 (d, 3H) **IR (cm^{-1}) :** 3200-2300, 1673, 1631 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{15}F_2N_2O_2$ $[M+H]^+$ 329.1102, measured 329.1112 **Optical purity** (SFC: Chiralpak ID 3µM 4.6x250 mm ; eluant: CO_2/ (isopropanol/diethylamine:100/0.5) : 65 / 35 ; detection:255nm) :>99%. (absence of **P26**)

P26	**170**	**{4-[(1R)-1-Aminoethyl]-2,6-difluorophenyl}(1-hydroxy-isoquinolin-5-yl)methanone hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.70 (m, 1H), 8.80 (m, 3H), 8.55 (d, 1H), 7.90 (d, 1H), 7.55 (t and m, 3H), 7.40 (m, 2H), 4.55 (quad, 1H), 1.60 (d, 3H) **IR (cm^{-1}) :** 3500-3000, 2863, 1673 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{15}F_2N_2O_2$ $[M+H]^+$ 329.1102, measured 329.1119 **Optical purity** (SFC: Chiralpak ID 3µM 4.6x250 mm ; eluant: CO_2/ (isopropanol/diethylamine:100/0.5): 65 / 35 ; detection: 255nm) :>99%. (absence of **P25**) **[P26** in the form of methanesulphonate α_D (589nM) = +2.48 (c = 0.01 g/mL, MeOH) at 20°C
P27	**172**	**5-[4-(2-Aminopropan-2-yl)-2,6-difluorobenzoyl]-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 11.70 (m, 1H), 9.00 (m, 3H), 8.55 (dd, 1H), 7.90 (dd, 1H), 7.60 (t and d, 3H), 7.40 (m, 2H), 1.70 (broad s, 6H) **IR (cm^{-1}) :** 3400-2400, 1677, 1631 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{17}F_2N_2O_2$ $[M+H]^+$ 343.1258, measured 343.1271
P28	**176**	**[4-(Aminomethyl)-2,6-difluorophenyl](1-hydroxy-isoquinolin-5-yl)methanone hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.67 (broad s, 1H), 8.55 (broad s, 3H), 8.54 (dd, 1H), 7.88 (broad d, 1H), 7.58 (t, 1H), 7.50 (m, 2H), 7.40 (m, 2H), 4.16 (s, 2H) **IR (cm^{-1}) :** 3250-1950, 1671 **HRMS (ESI) :** theoretical m/z for $C_{17}H_{13}F_2N_2O_2$ $[M+H]^+$ 314.0867, measured 314.0865
P29	**178**	**5-[4-(1-Aminoethyl)-2-fluoro-3-methylbenzoyl]-isoquinolin-1(2H)-one hydrochloride**

		^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 11.60 (m, 1H), 9.00-8.50 (m, 3H), 8.45 (dd, 1H), 7.75 (dd, 1H), 7.70-7.55 (2m, 3H), 7.30 (m, 1H), 6.95 (d, 1H), 4.65 (quad, 1H), 2.25 (s, 3H), 1.55 (d, 3H) **IR (cm^{-1}) :** 3300-2000, 1668, 1629 **MS (DEI 70 eV) :** m/z measured for $C_{19}H_{18}FN_2O_2$ 324.10
P30	**180**	**5-[4-(1-Aminoethyl)-2-fluorobenzoyl]isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.56 (broad s, 1H), 8.60 (broad s, 3H), 8.46 (d, 1H), 7.76 (d, 1H), 7.73 (t, 1H), 7.60-7.50 (m, 3H), 7.30 (dd, 1H), 6.91 (d, 1H), 4.53 (quad, 1H), 1.55 (d, 3H) **IR (cm^{-1}) :** 3200-2400, 1684-1659, 1625 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{16}FN_2O_2$ $[M+H]^+$ 311.1196, measured 311.1205
P31	**182**	**5-[4-(1-Aminoethyl)-2-chlorobenzoyl]isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.62 (broad s, 1H), 8.58 (broad s, 3H), 8.49 (d, 1H), 7.80 (s, 1H), 7.66 (m, 3H), 7.55 (t, 1H), 7.37 (broad d 1H), 7.28 (d, 1H), 4.53 (quad, 1H), 1.56 (d, 3H) **IR (cm^{-1}) :** 3300-2500, 1661, 1631 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{16}ClN_2O_2$ $[M+H]^+$ 327.0900, measured 327.0902

P32	**191**	**5-[4-(2-Aminopropan-2-yl)-2-chlorobenzoyl]-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.63 (d, 1H), 8.82 (broad s, 3H), 8.49 (d, 1H), 7.81 (broad s, 1H), 7.68 (m, 3H), 7.55 (t, 1H), 7.38 (dd, 1H), 7.29 (d, 1H), 1.69 (s, 6H) **IR (cm^{-1}) :** 3500-2400, 1662-1651, 1623 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{18}ClN_2O_2$ $[M+H]^+$ 341.1057, measured 341.1062
P33	**202**	**5-{4-[(1R)-1-Aminoethyl]-2-fluoro-3-methylbenzoyl}-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.60 (d, 1H), 8.80-8.60 (m, 3H), 8.45 (d, 1H), 7.75 (d, 1H), 7.65-7.55 (m, 3H), 7.30 (m, 1H), 6.95 (d, 1H), 4.65 (m, 1H), 2.25 (s, 3H), 1.50 (d, 3H) **IR (cm^{-1}) :** 3500-2000, 1650-1630 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{18}FN_2O_2$ $[M+H]^+$ 325.1352, measured 325.1354. **Optical purity** (ASH 5µM column 4.6x250 mm ; eluant: EtOH/heptane/diethylamine:70/30/0.1; detection: 620nm) : >99%. (absence **P36**)
P34	**189**	**[4-(2-Aminopropan-2-yl)-2-chlorophenyl](isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (400 MHz, DMSO-d6) **:** δ 9.90 (s, 1H), 9.40-8.90 (m, 3H), 8.90 (d, 1H), 8.80 (d, 1H), 8.70 (broad d, 1H), 8.05 (dd, 1H), 7.95 (t, 1H), 7.90 (s, 1H), 7.75 (m, 2H), 1.70 (s 6H) **IR (cm^{-1}) :** 3200-2000, 1662 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{18}ClN_2O$ $[M+H]^+$ 325.1108, measured 325.1116
P35	**213**	**5-{2,6-Difluoro-4-[1-(methylamino)ethyl]benzoyl}-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.68 (s, 1H), 9.68

		(broad s, 2H), 8.54 (dd, 1H), 7.98 (broad d, 1H), 7.59 (m, 2H), 7.58 (t, 1H), 7.42 (m, 2H), 4.44 (quad, 1H), 2.47 (s, 3H), 1.61 (d, 3H) **IR (cm^{-1}) :** 3250-3200, 1672-1668, 1632 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{17}F_2N_2O_2$ $[M+H]^+$ 343.1258, measured 343.1258
P36	**219**	**5-{4-[(1S)-1-Aminoethyl]-2-fluoro-3-methylbenzoyl}-isoquinolin-1(2H)-one hydrochloride** **^1H NMR** (400 MHz, DMSO-d_6) **:** δ 11.50 (d, 1H), 8.57 (broad s, 3H), 8.46 (d, 1H), 7.73 (d, 1H), 7.59 (m, 2H), 7.58 (t, 1H), 7.30 (m, 1H), 6.92 (d, 1H), 4.65 (quad, 1H), 2.27 (s, 3H), 1.50 (d, 3H) **IR (cm^{-1}) :** 3500-2000, 1650-1630 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{18}FN_2O_2$ $[M+H]^+$ 325.1352, measured 325.1363. **Optical purity** (ASH 5µM column 4.6x250 mm; eluant: EtOH/ heptane/diethylamine: 70/30/0.1; detection: 620nm): >99%. (absence **P36**)
P37	**223**	**5-[4-(Aminomethyl)-2-fluorobenzoyl]isoquinolin-1(2H)-one hydrochloride** **^1H NMR** (400 MHz, DMSO-d_6) **:** δ 11.55 (d, 1H), 8.60 (m, 3H), 8.47 (d, 1H), 7.77 (d, 1H), 7.70 (t, 1H), 7.60-7.49 (m, 2H), 7.58 (t, 1H), 7.30 (m, 1H), 6.90 (d, 1H), 4.15 (s, 2H) **IR (cm^{-1}) :** 2970, 1680-1655, 1622 **HRMS (ESI) :** theoretical m/z for $C_{17}H_{14}FN_2O_2$ $[M+H]^+$ 297.1093, measured 297.1024
P39	**227**	**5-{[(1S)-1-Amino-2,3-dihydro-1H-inden-5-yl]-carbonyl}isoquinolin-1(2H)-one hydrochloride** **^1H NMR** (400 MHz, DMSO-d_6) **:** δ 11.50 (s, 1H), 8.55 (broad s, 3H), 8.40 (d, 1H), 7.78 (d, 1H), 7.70 (d, 1H), 7.65 (m, 2H), 7.60 (t, 1H), 7.20 (d, 1H), 6.40 (m, 1H),

		4.78 (t, 1H), 3.10-2.90 (m, 2H), 2.50-2.00 (m, 2H) **IR (cm^{-1}) :** 3300-2400, 1687-1665 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{17}N_2O_2$ $[M+H]^+$ 305.1290, measured 305.1311. **Optical purity** (ASH 5µM column 4.6x250 mm ; eluant: heptane/propanol/diethylamine:70/30/0.1; detection: 270nm) : >99%.
P40	**232**	**5-[4-(Aminomethyl)-2,5-difluorobenzoyl]isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.60 (s, 1H), 8.60 (broad s, 3H), 8.49 (d, 1H), 7.80 (d, 1H), 7.70-7.60 (m, 2H), 7.59 (t, 1H), 7.30 (m, 1H), 7.00 (d, 1H), 4.15 (s, 2H) **IR (cm^{-1}) :** 3200-2400, 1689-1658 **HRMS (ESI) :** theoretical m/z for $C_{17}H_{13}F_2N_2O_2$ $[M+H]^+$ 315.0945, measured 315.0934
P42	**247**	**5-[4-(1-Aminoethyl)-2-fluoro-3-methoxybenzoyl]-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 12.60 (s, 1H), 8.65 (broad s, 3H), 8.50 (d, 1H), 7.80 (d, 1H), 7.55 (m, 2H), 7.45 (m, 1H), 7.30 (d, 1H), 7.00 (d, 1H), 4.65 (q, 1H), 3.95 (s, 3H), 1.50 (d, 3H) **IR (cm^{-1}) :** 3359-2437, 1690, 1656 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{18}FN_2O_3$ $[M+H]^+$ 341.1031, measured 341.1318
P43	**257**	**5-[4-(1-Aminoethyl)-2,3-dimethylbenzoyl]isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d6) **:** δ 11.58 (broad d, 1H), 8.57 (m, 3H), 8.46 (d, 1H), 7.63 (d, 1H), 7.52 (m, 2H), 7.34 (dd, 1H), 7.22 (d, 1H), 7.18 (d, 1H), 4.71 (m, 1H), 2.31 (s, 3H), 2.20 (s, 3H), 1.51 (d, 3H) **IR (cm^{-1}) :** 3300-2400, 1642, 1626 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{21}N_2O_2$ $[M+H]^+$

		321.1603, measured 321.1594
P47	**273**	**5-{4-[(1R)-1-Aminoethyl]-2-methylbenzoyl}isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.60-11.50 (m, 1H), 8.60-8.40 (m, 3H), 8.45 (m, 1H), 7.65 (dd, 1H), 7.60 (m, 1H), 7.50 (m, 1H), 7.40 (dd, 1H), 7.35 (d, 1H), 7.30 (m, 1H), 6.90 (d, 1H), 4.45 (quad, 1H), 2.35 (s, 3H), 1.55 (d, 3H) **IR (cm^{-1}) :** 3500, 3300-1950, 1685, 1653 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{19}N_2O_2$ $[M+H]^+$ 307.1441, measured 307.1455 theoretical m/z for $C_{19}H_{16}NO_2$ $[M+H-NH_3]^+$ 290.1176, measured 290.1175 **Optical purity** : (AD 5µm column 4.6x250mm, eluant : EtOH/heptane/diethylamine 40/60/0.1, detection : 255nm) : > 99%, (absence of **P52**) α_D (589nM) = 5.7 (c = 0.01 g/mL, MeOH) at 20°C
P51	**312**	**5-[4-(1-Aminoethyl)-3-ethoxy-2-fluorobenzoyl]-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.60 (m, 1H), 8.70-8.30 (m, 3H), 8.50 (d, 1H), 7.80 (d, 1H), 7.65 (m, 1H), 7.50 (m, 1H), 7.40 (m, 1H), 7.30 (d, 1H), 6.95 (d, 1H), 4.70 (quad, 1H), 4.15 (q, 2H), 1.50 (d, 3H), 1.30 (t, 3H) **IR (cm^{-1}) :** 3200-2300, 1667, 1626 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{20}FN_2O_3$ $[M+H]^+$ 355.1489, measured 355.1489
P52	**315**	**5-{4-[(1S)-1-Aminoethyl]-2-methylbenzoyl}isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.60-11.50 (m, 1H), 8.60-8.40 (m, 3H), 8.45 (m, 1H), 7.65 (dd, 1H), 7.60-7.50 (2m, 2H), 7.40 (dd, 1H), 7.35 (d, 1H), 7.30 (m, 1H), 6.90 (d, 1H), 4.45 (quad, 1H), 2.35 (s, 3H), 1.55 (d, 3H)

		IR (cm^{-1}) : 3200-2340, 1652, 1615 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{19}N_2O_2$ $[M+H]^+$ 307.1447, measured 307.1455. **Optical purity** : (AD 5µm column 4.6x250mm, eluant : EtOH/heptane/diethylamine 40/60/0.1, detection : 255nm) : > 99%. (absence of **P47**)
P61	**351**	**5-({8-[(1R)-1-Aminoethyl]-2,3-dihydro-1,4-benzo-dioxin-5-yl}carbonyl)isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 11.50 (broad s, 1H), 8.45 (d, 1H), 8.38 (broad s, 3H), 7.72 (d, 1H), 7.52 (t, 1H), 7.29 (m, 1H), 7.18 (d, 1H), 7.09 (d, 1H), 7.05 (d, 1H), 4.59 (quad, 1H), 4.30 (m, 2H), 4.10 (m, 2H), 1.51 (d, 3H) **IR (cm^{-1}) :** 3211, 3100-2500, 1669, 1219, 1076, 777 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{19}N_2O_4$ $[M+H]^+$ 351.1345, measured 351.1341 **Optical purity** (SFC: Chiralpak IA 3µM 4.6x250 mm ; eluant: CO_2/(ethanol/butylamine:100/0.5) : 70 / 30 ; detection: 260nm) :>99%. (absence of **P64**) α_D (589nM) = -15.1 (c = 0.009 g/mL, MeOH) at 20°C
P64	**373**	**5-({8-[(1S)-1-Aminoethyl]-2,3-dihydro-1,4-benzo-dioxin-5-yl}carbonyl)isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.52 (m, 1H), 8.43 (d, 1H), 8.36 (m, 3H), 7.73 (d, 1H), 7.53 (t, 1H), 7.29 (broad d 1H), 7.16 (d, 1H), 7.08 (d, 1H), 7.05 (d, 1H), 4.58 (quad, 1H), 4.31 (m, 2H), 4.10 (m, 2H), 1.51 (d, 3H) **IR (cm^{-1}) :** 3221, 3200-2300, 1669 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{19}N_2O_4$ $[M+H]^+$ 351.1345, measured 351.1353. theoretical m/z for $C_{20}H_{19}N_2O_4$ $[M+H]^+$ 351.1345,

		measured 351.1353. **Optical purity** (SFC: Chiralpak IA 3µM 4.6x250 mm ; eluant: CO_2/(ethanol/butylamine:100/0.5) : 70 / 30 ; detection: 260nm) :>99%. (absence of **P61**) α_D (589nM) = 15.41 (c = 1, DMSO) at 20°C
P68	**391**	**5-{4-[(1R)-1-Aminoethyl]-2-methylbenzoyl}-3-methyl-isoquinolin-1(2H)-one methanesulphonate** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 8.40 (d, 1H), 7.60 (d, 1H), 7.50 (broad s, 1H), 7.45 (t, 1H), 7.40 (m, 2H), 6.80 (broad s, 1H), 4.50 (m, 1H), 2.40-2.20 (3s, 9H), 1.50 (d, 3H) **IR (cm^{-1}) :** 3400-2450, 1684, 1637, 1600, 1550, 1315, 1239, 1149, 825-681 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{21}N_2O_2$ $[M+H]^+$ 321.1603, measured 321.1591 theoretical m/z for $C_{40}H_{41}N_4O_4$ $[2M+H]^+$ 641.3128, measured 641.3080 theoretical m/z for $C_{40}H_{40}N_4NaO_4$ $[2M+Na]^+$ 663.2947, measured 663.2919 **Optical purity** (capillary electrophoresis: standard CE, phosphate buffer/HS α-cyclodextrin, detection 210nm) : >99%.
P74	**408**	**5-{4-[(1S)-1-Aminoethyl]-2-methylbenzoyl}-4-methyl-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (500 MHz, DMSO-d_6) : δ 11.62 (d, 1H), 8.61 (broad s, 3H), 8.44 (dd, 1H), 7.61 (d, 1H), 7.55 (t, 1H), 7.50 (dd, 1H), 7.42 (dd, 1H), 7.39 (d, 1H), 7.06 (d, 1H), 4.43 (quad, 1H), 2.63 (s, 3H), 1.89 (s, 3H), 1.52 (d, 3H) **IR (cm^{-1}) :** 3200-2000, 1677, 1645 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{21}N_2O_2$ [M+H]+ 321.1603, measured 321.1579.

		m/z measured for $C_{20}H_{20}N_2O_2$ [M]+ 320.20. **Optical purity** (SFC: (S,S) Whelk 5µM 4.6x250 mm ; eluant: CO_2/(ethanol/butylamine:100/0.5) : 75 / 25 ; detection: 255nm) :>99%. (absence of **P87**)
P87	**462**	**5-{4-[(1R)-1-Aminoethyl]-2-methylbenzoyl}-4-methyl-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.40 (broad s, 1H), 8.45 (broad s, 3H), 8.45 (dd, 1H), 7.60 (s, 1H), 7.56 (t, 1H), 7.50 (dd, 1H), 7.40 (2m, 2H), 7.06 (broad s, 1H), 4.42 (quad, 1H), 2.63 (s, 3H), 1.90 (s, 3H), 1.50 (d, 3H) **IR (cm^{-1}) :** 3000-2500, 1677, 1645 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{21}N_2O_2$ $[M+H]^+$ 321.1603, measured 321.1589, **Optical purity** (SFC: (S,S) Whelk 5µM 4.6x250 mm ; eluant: CO_2/(ethanol/butylamine:100/0.5) : 75 / 25 ; detection: 255nm) :>99%. (absence of **P74**)
P102	**542**	**5-{4-[(1R)-1-Aminoethyl]-2-fluoro-6-methoxy-benzoyl}isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.63 (m, 1H), 8.80-8.50 (m, 3H), 8.50 (d, 1H), 7.78 (d, 1H), 7.55 (t, 1H), 7.52 (d, 1H), 7.38 (dd, 1H), 7.35 (s, 1H), 7.18 (d, 1H), 4.49 (quad, 1H), 3.74 (s, 3H), 1.57 (d, 3H) **IR (cm^{-1}) :** 3300-2000, 1674, 1648, 1617 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{18}FN_2O_3$ $[M+H]^+$ 341.1301, measured 341.1292.
P110	**591**	**[4-(1-Aminoethyl)phenyl](isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 9.80 (s, 1H), 8.75 (m, 3H), 8.65 (2d, 2H), 8.20 (d, 1H), 8.15 (d, 1H), 8.00 (t, 1H), 7.88 (d, 2H), 7.75 (d, 2H), 4.50 (m, 1H), 1.55 (d, 3H)

		IR (cm^{-1}) : 3000-2500, 2051, 1665-1645, 1604, 819-746 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{16}N_2O$ $[M+H]^+$ 277.1341, measured 277.1356 theoretical m/z for $C_{18}H_{17}N_2O$ $[M+H-NH_3]^+$ 260.1075, measured 260.1078
P111	**596**	**{4-[(1S)-1-Aminoethyl]phenyl}(isoquinolin-5-yl)-methanone dihydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 9.80 (s, 1H), 8.75 (m, 3H), 8.65 (2d, 2H), 7.20 (d, 1H), 8.15 (d, 1H), 8.00 (t, 1H), 7.88 (d, 2H), 7.75 (d, 2H), 4.50 (m, 1H), 1.55 (d, 3H) **IR (cm^{-1}) :** 3000-2000, 1650 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{17}N_2O$ $[M+H]^+$ 277.1341, measured 277.1353 **Optical purity** : (ADH 5µm column 4.6x250mm, eluant : EtOH/ triethylamine 1000/1, detection : 265nm) : > 99%. (absence of **P1**)
P112	**603**	**[4-(2-Aminopropan-2-yl)phenyl](isoquinolin-5-yl)-methanone dihydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 10.00 (s, 1H), 9.00 (m, 3H), 8.70 (m, 2H), 8.30-8.20 (2d, 2H), 8.05 (t, 1H), 7.85 (dd, 4H), 1.70 (s, 6H) **IR (cm^{-1}) :** 2800, 1651 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{19}N_2O$ $[M+H]^+$ 291.1497, measured 291.1514
P113	**610**	**[4-(1-Aminocyclobutyl)phenyl](isoquinolin-5-yl)-methanone dihydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 9.95 (s, 1H), 9.00 (m, 3H), 8.70 (m, 2H), 8.25 (d, 1H), 8.20 (d, 1H), 8.05 (t, 1H), 7.85-7.75 (dd, 4H), 2.65 (m, 4H), 2.25-1.80 (m, 2H) **IR (cm^{-1}) :** 3000-2500, 1650 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{19}N_2O$ $[M+H]^+$ 303.1497, measured 303.1528

P114	**617**	**[(1R)-1-Amino-2,3-dihydro-1H-inden-5-yl](isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 9.90 (s, 1H), 8.90 (broad s, 3H), 8.68 (2d, 2H), 8.25 (d, 1H), 8.18 (d, 1H), 8.05 (t, 1H), 7.90 (d, 1H), 7.72 (m, 2H), 4.78 (m, 1H), 3.10 (m, 1H), 2.90 (m, 1H), 2.50 (m, 1H), 2.10 (m, 1H) **IR (cm^{-1}) :** 2484-2077, 2077-1955-1866, 1662-1651, 1607, 820-754 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{17}N_2O$ $[M+H]^+$ 289.1341, measured 289.1348 **Optical purity** (capillary electrophoresis: standard CE, phosphate buffer/HS α-cyclodextrin, detection 210nm) : >99%. (absence of **P115**)
P115	**619**	**[(1S)-1-Amino-2,3-dihydro-1H-inden-5-yl](isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 9.85 (s, 1H), 8.80 (broad s, 3H), 8.65 (m, 2H), 8.20 (d, 1H), 8.15 (d, 1H), 8.05 (m, 1H), 7.85 (d, 1H), 7.75 (m, 2H), 4.80 (m, 1H), 3.15-2.90 (2m, 2H), 2.55-2.05 (2m, 2H) **IR (cm^{-1}) :** 2725-2150, 2076, 1957, 1866, 1664, 1651, 1606-1590 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{17}N_2O$ $[M+H]^+$ 289.1341, measured 289.1364 **Optical purity** (capillary electrophoresis: standard CE, phosphate buffer/HS α-cyclodextrin, detection 210nm) : >99%. (absence of **P114**) α_D (589nM) = -12.83 (c = 0.013 g/mL, MeOH) at 20°C

P116	**625**	**[4-(4-Aminotetrahydro-2H-pyran-4-yl)phenyl]-(isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 9.80 (s, 1H), 8.95-8.75 (broad m, 3H), 8.67 (d, 1H), 8.63 (d, 1H), 8.21 (d, 1H), 8.15 (d, 1H), 8.00 (t, 1H), 7.88 (m, 4H), 3.92-3.40 (2m, 4H), 2.45-2.20 (2m, 4H) **IR (cm^{-1}) :** 3700-3200, 3300-1800, 1659 **HRMS (ESI) :** theoretical m/z for $C_{21}H_{21}N_2O_2$ $[M+H]^+$ 333.1603, measured 333.2
P117	**635**	**(1-Amino-1-methyl-2,3-dihydro-1H-inden-5-yl)-(isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 9.90 (s, 1H), 8.88 (broad s, 3H), 8.68 (m, 2H), 8.20 (d, 1H), 8.15 (d, 1H), 8.01 (t, 1H), 7.85 (d, 1H), 7.75 (m, 2H), 3.13 (m, 1H), 2.99 (m, 1H), 2.35 (m, 1H), 2.25 (m, 1H), 1.63 (s, 3H) **IR (cm^{-1}) :** 3200-2000, 1659 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{19}N_2O$ $[M+H]^+$ 303.1497, measured 303.1511
P118	**637**	**{4-[(1S)-1-Aminoethyl]-2-methylphenyl}(isoquinolin-5-yl)methanone hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 9.88 (s, 1H), 8.74 (m, 4H), 8.68 (d, 1H), 8.59 (d, 1H), 8.04 (d, 1H), 7.98 (t, 1H), 7.62 (broad s, 1H), 7.48 (broad d, 1H), 7.42 (d, 1H), 4.46 (m, 1H), 2.43 (s, 3H), 1.56 (d, 3H) **IR (cm^{-1}) :** 3468, 3000-2000, 1657 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{19}N_2O$ $[M+H]^+$ 291.1497, measured 291.1521 **Optical purity** : (ADH 5µm column 4.6x250mm, eluant : EtOH/diethylamine 100/0.1, detection : 270nm) : > 99%. (absence of **P2**)
P120	**647**	**(1-Amino-6-methoxy-2,3-dihydro-1H-inden-5-yl)-(isoquinolin-5-yl)methanone dihydrochloride**

		^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.70 (broad s, 1H), 8.90-8.60 (m, 3H), 8.65 (d, 1H), 8.60-8.50 (2m, 2H), 7.95 (d, 1H), 7.85 (t, 1H), 7.70 (s, 1H), 7.50 (s, 1H), 4.75 (m, 1H), 3.50 (s, 3H), 3.10 (m, 1H), 2.85 (m, 1H), 2.50 (m, 1H), 2.10 (m, 1H) **IR (cm^{-1}) :** 3600-3300, 3100-2000, 1647 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{19}N_2O_2$ $[M+H]^+$ 319.1447, measured 319.1432
P126	**688**	**[4-(1-Aminoethyl)-2-hydroxyphenyl](isoquinolin-5-yl)-methanone dihydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.03 (m, 1H), 9.87 (s, 1H), 8.72 (m, 3H), 8.69 (d, 1H), 8.64 (d, 1H), 8.38 (d, 1H), 8.14 (d, 1H), 8.00 (t, 1H), 7.52 (d, 1H), 7.18 (d(fine), 1H), 7.14 (dd(fine), 1H), 4.41 (m, 1H), 1.53 (d, 3H) **IR (cm^{-1}) :** 3600-2000, 1630 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{17}N_2O_2$ $[M+H]^+$ 293.1290, measured 293.1284
P132	**718**	**5-[4-(1-Aminoethyl)-2-fluoro-3-(2-methylpropoxy)-benzoyl]isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 12.60 (s, 1H), 8.50 (s, 3H), 8.50 (d, 1H), 7.80 (d, 1H), 7.60 (d, 1H), 7.55 (m, 1H), 7.45 (m, 1H), 7.35 (m, 1H), 7.00 (d, 1H), 4.70 (quad, 1H), 3.95-3.80 (m, 2H), 2.05 (m, 1H), 1.55 (d, 3H), 1.00 (d, 6H). **IR (cm^{-1}) :** 3220-2450, 1664, 1628 **HRMS (ESI) :** theoretical m/z for $C_{22}H_{24}FN_2O_3$ $[M+H]^+$ 383.1771, measured 383.1760
P141	**757**	**{4-[(1R)-1-Aminoethyl]phenyl}(8-chloroisoquinolin-5-yl)-1(2H)-one dihydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 9.76 (s, 1H), 8.72 (d, 1H), 8.68 (broad s, 1H), 8.02 (d, 1H), 7.98 (d, 1H), 7.92 (d, 1H), 7.87 (d, 1H), 7.71 (d, 2H), 4.53 (m, 1H), 1.54 (d,

		3H) **IR (cm^{-1}) :** 3200-2000, 1655-1643 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{15}ClN_2O$ $[M+H]^+$ 311.095, measured 311.093

Products **P9**, **P10**, **P22** and **P23** were obtained by separation of the corresponding racemic products:

Product **P6** in the form of the free base (3.4 g) was chromatographed by high pressure chromatography on a chiral support (OD column, eluant CH_3CN, detection : 255nm) to give, after salt formation, products **P9** and **P10**.

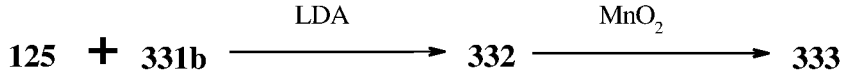
Product	Obtained from	Nomenclature Analytical description
P9	**P6**	**{4-[(1R)-1-Aminoethyl]-2,6-difluorophenyl}-(isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (300MHz ; DMSO-d6) **:** δ 9.79 (s, 1H); 8.90 (d, 1H); 8.85 (broad s, 3H); 8.80 (d, 1H); 8.70 (d, 1H); 8.27 (d, 1H); 7.96 (t, 1H); 7.61 (d, 2H); 4.57 (m, 1H); 1.59 (d, 3H) **IR (cm^{-1}) :** 3200-2200, 1668 **HRMS (ESI) :** m/z calculated for $C_{18}H_{14}F_2N_2O$ $[M+H]^+$; 313.1152 found 313.1140 **Optical purity** : (Kromasil Cellucoat column 4.6x250mm, eluant : heptane/EtOH/diethylamine 70/30/0.1, detection : 252nm) : > 99%. (absence of **P10**) α_D (589nM) = 2.49 (c = 0.008 g/mL, MeOH) at 20°C
P10	**P6**	**{4-[(1S)-1-Aminoethyl]-2,6-difluorophenyl}-(isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (300MHz ; DMSO-d6) **:** δ 9.79 (s, 1H); 8.90 (d, 1H); 8.85 (broad s, 3H); 8.80 (d, 1H); 8.70 (d, 1H); 8.27 (d, 1H); 7.96 (t, 1H); 7.61 (d, 2H); 4.57 (m, 1H); 1.59 (d, 3H) **IR (cm^{-1}) :** 3200-2200, 1670 **HRMS (ESI) :** m/z calculated for $C_{18}H_{14}F_2N_2O$ $[M+H]^+$; 313.1152 found 313.1141 **Optical purity** : (Kromasil Cellucoat column 4.6x250mm, eluant : heptane/EtOH/diethylamine 70/30/0.1, detection : 252nm) : > 99%. (absence of **P9**) α_D (589nM) = -2.2 (c = 0.008 g/mL, $CHCl_3$) at 20°C

Product **P11** in the form of the free base (1.8 g) was chromatographed by high pressure chromatography on a chiral support (AD column, eluant MeOH, detection : 295nm) to give, after salt formation, products **P22** and **P23**.

Product	**Obtained from**	**Nomenclature** **Analytical description**
P22	**P11**	**{4-[(1S)-1-Aminoethyl]-2-chlorophenyl}(isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (400MHz ; DMSO-d_6)**:** δ 9.90 (s, 1H); 9.90 (d and m, 4H); 8.80 (d, 1H); 8.70 (d, 2H); 8.10 (d, 1H); 8.00 (t, 1H); 7.90 (broad s, 1H); 7.70 (m, 2H); 4.55 (m, 1H); 1.60 (d, 3H) **IR (cm^{-1}) :** 3000-2500, 1661 **MS (DEI 70 eV) :** m/z measured for $C_{18}H_{15}Cl_1F_1N_2O$ 310.1 **Optical purity** : (ADH 5µm column 4.6x250mm, eluant : EtOH/heptane/diethylamine 70/30/0.1, detection : 235nm) : > 99%. (absence of **P23**)
P23	**P11**	**{4-[(1R)-1-Aminoethyl]-2-chlorophenyl}(isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (400MHz ; DMSO-d6)**:** δ 9.90 (s, 1H); 9.90 (d and m, 4H); 8.80 (d, 1H); 8.70 (d, 2H); 8.10 (d, 1H); 8.00 (t, 1H); 7.90 (broad s, 1H); 7.70 (m, 2H); 4.55 (m, 1H); 1.60 (d, 3H) **IR (cm^{-1}) :** 3000-2500, 1660 **MS (DEI 70 eV) :** m/z measured for $C_{18}H_{15}Cl_1F_1N_2O$ 310.1 **Optical purity** : (ADH 5µm column 4.6x250mm, eluant : EtOH/heptane/diethylamine 70/30/0.1, detection : 235nm) : > 99%. (absence of **P22**)

Protocol XXI : Alternative method for the preparation of compounds of formula (I) wherein X represents -C(=O)

Compounds of formula (I) wherein X represents -C(=O)- can also be prepared by coupling reaction via directed ortho-metalation according to the example of the synthesis of intermediate **333** below:



Intermediate 332 :

tert-Butyl [(1R)-1-{3-[(1-ethoxyisoquinolin-5-yl)(hydroxy)methyl]-2,4-difluoro-phenyl}ethyl]carbamate

To a solution of intermediate **331b** (35 g, 137 mmoles) in THF (700 mL), cooled to -78°C under a nitrogen atmosphere, there is added a 2N solution of LDA in heptane/THF/ethylbenzene (170 mL, 342 mmoles), the temperature being maintained below -75°C. The reaction mixture is stirred at -78°C for 30 minutes, and then a solution of intermediate **125** (28.8 g, 143 mmoles) in THF (330 mL) is added in the course of 1 hour, the temperature being maintained below -75°C. The reaction mixture is stirred for 30 minutes. The reaction mixture is hydrolysed with water and then allowed to return to ambient temperature. The THF is removed under reduced pressure. The aqueous phase is extracted with 2 x 350 mL of AcOEt, and then the organic phases are combined and evaporated in vacuo. The residue is purified by flash chromatography on silica (eluant = CH_2Cl_2/AcOEt : 70/30). Intermediate **332** (56.3 g) is obtained in the form of a yellowish solid.

^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.15 (m, 2H), 7.92 (d, 1H), 7.64 (t, 1H), 7.35 (m, 1H), 7.26 (m, 1H), 6.98 (m, 1H), 6.60 (s, 1H), 6.11 (broad s, 1H), 4.81 (m, 1H), 4.53 (quad, 2H), 1.42 (t, 3H), 1.38-1.22 (m, 12H), 1.35 (d, 3H).

^{19}F NMR: -119, -115

IR (cm^{-1}) : 3331, 1689, 1572, 1161

Intermediate 333 :

tert-Butyl [(1R)-1-{3-[(1-ethoxyisoquinolin-5-yl)carbonyl]-2,4-difluorophenyl}ethyl]-carbamate

Intermediate **332** is converted into intermediate **333** according to the protocol described for intermediate **127** (**Protocol XX**).

^{1}H NMR (300/400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.05 (d, 1H), 8.20 (m, 2H), 7.75 (t, 1H), 7.65 (quad, 1H), 7.55 (broad d, 1H), 7.30 (t, 1H), 4.85 (m, 1H), 4.55 (quad, 2H), 1.45 (t, 3H), 1.40 (m, 9H), 1.3 (d, 3H)

IR (cm^{-1}) : 3300, 1676, 1250

This sequence was used to prepare the following intermediates:

Intermediate 236 :

N-{5-[(1-Ethoxyisoquinolin-5-yl)carbonyl]-4,6-difluoro-2,3-dihydro-1H-inden-1-yl}-2-methylpropane-2-sulphinamide

Obtained by oxidation of the intermediate resulting from the coupling of **234** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.53 (d, 1H), 8.19 (2d, 2H), 8.00 (d, 1H), 7.71 (t, 1H), 7.48 (d, 1H), 6.01 (d, 1H), 4.89 (m, 1H), 4.58 (quad, 1H), 2.96-2.78 (m, 2H), 2.50-2.05 (m, 2H), 1.47 (t, 3H), 1.19 (s, 9H)

IR (cm^{-1}) : 3200, 1668

Intermediate 262 :

N-{6-[(1-Ethoxyisoquinolin-5-yl)carbonyl]-5,7-difluoro-2,3-dihydro-1H-inden-1-yl}-2-methylpropane-2-sulphinamide

Obtained by oxidation of the intermediate resulting from the coupling of **260** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (d, 1H), 8.15 (d, 1H), 8.00 (d, 1H), 7.70 (m, 1H), 7.25 (d, 1H), 5.75 (d, 1H), 4.95 (m, 1H), 4.55 (quad, 2H), 3.20-2.90 (2m, 2H), 2.40-2.20 (2m, 2H), 1.45 (t, 3H), 1.05 (s, 9H)

IR (cm^{-1}) : 3215, 1738, 1670.

Intermediate 271 :

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-2,3-difluorophenyl}ethyl)-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **269** and **125**

^{1}H NMR (300/400 MHz, DMSO-d_6) **:** δ 8.47 (d, 1H), 8.11 (d, 1H), 7.95 (d, 1H), 7.70 (t, 1H), 7.70 (d, 1H), 7.70 (broad d, 1H), 7.49 (t, 1H), 7.32 (t, 1H), 4.95 (quint, 1H), 4.55 (quad, 2H), 1.45 (t, 3H), 1.40 (broad s, 9H), 1.35 (d, 3H)

IR (cm^{-1}) : 3345, 1671, 1523

Intermediate 296 :

tert-Butyl [(1R)-1-{4-[(1-ethoxy-3-methylisoquinolin-5-yl)carbonyl]-3,5-difluoro-phenyl}ethyl]carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **288** and **294**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.50 (d, 1H), 8.05 (s, 1H), 8.00 (d, 1H), 7.65 (t, 1H), 7.55 (broad d, 1H), 7.15 (broad d, 2H), 4.75 (m, 1H), 4.55 (quad, 2H), 2.55 (s, 3H), 1.45 (t, 3H), 1.40 (s, 9H), 1.40 (d, 6H)

IR (cm^{-1}) : 3400, 1679, 1260

Intermediate 305 :

tert-Butyl [(1R)-1-{4-[(1-ethoxy-4-methylisoquinolin-5-yl)carbonyl]-3,5-difluoro-phenyl}ethyl]carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **288** and **303**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.45 (d, 1H), 8.00 (s, 1H), 7.80 (d, 1H), 7.65 (m, 1H), 7.55 (d, 1H), 7.20 (d, 2H), 4.75 (m, 1H), 4.55 (quad, 2H), 2.20 (s, 3H), 1.45 (t, 3H), 1.40 (s, 9H), 1.30 (t, 3H)

IR (cm^{-1}) : 3387, 1686, 1668

Intermediate 319 :

N-{5-[(1-Ethoxyisoquinolin-5-yl)carbonyl]-4,6-difluoro-2,3-dihydro-1H-inden-1-yl}-2-methylpropane-2-sulphinamide

Obtained by oxidation of the intermediate resulting from the coupling of **317** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.53 (d, 1H), 8.19 (2d, 2H), 8.00 (d, 1H), 7.71 (t, 1H), 7.48 (d, 1H), 6.01 (d, 1H), 4.89 (m, 1H), 4.58 (quad, 1H), 2.96-2.78 (m, 2H), 2.50-2.05 (m, 2H), 1.47 (t, 3H), 1.19 (s, 9H)

IR (cm^{-1}) : 3200, 1734, 1668, 1033

Intermediate 326 :

tert-Butyl [(1S)-1-{3,5-difluoro-4-[(4-methylisoquinolin-5-yl)carbonyl]phenyl}ethyl]-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **324** and **321**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 9.30 (s, 1H), 8.50 (s, 1H), 8.35 (d, 1H), 7.90 (d, 1H), 7.70 (m, 1H), 7.60 (d, 1H), 7.25 (d, 2H), 4.75 (m, 1H), 2.35 (s, 3H), 1.40 (s, 9H), 1.35 (d, 3H)

IR (cm^{-1}) : 3392, 1685, 1635

Intermediate 328 :

tert-Butyl [(1S)-1-{4-[(1-ethoxy-4-methylisoquinolin-5-yl)carbonyl]-3,5-difluoro-phenyl}ethyl]carbamate

Obtained starting from **326** according to the protocol described for **182**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.53 (d, 1H), 8.05 (s, 1H), 7.90 (broad d, 1H), 7.75 (t, 1H), 7.62 (broad d, 1H), 7.30 (m, 2H), 4.81 (quint, 1H), 4.64 (quad, 2H), 2.29 (s, 3H), 1.55 (t, 3H), 1.48 (broad s, 9H), 1.41 (d, 3H)

LCMS [M+H]+= 471.

Intermediate 336 :

N-[(1S)-1-{3-[(1-Ethoxyisoquinolin-5-yl)carbonyl]-2,4-difluorophenyl}ethyl]-2-methylpropane-2-sulphinamide

Obtained by oxidation of the intermediate resulting from the coupling of **334** and **125**

^{1}H NMR (300/400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.02 (dd, 2H), 8.00 (d, 1H), 7.75 (t, 2H), 7.35 (t, 1H), 5.55 (d, 1H), 4.7 (m, 1H), 4.55 (quad, 2H), 1.55 (d, 3H), 1.48 (t, 3H), 1.12 (s, 9H)

IR (cm^{-1}) : 1669, 1048

Intermediate 339 :

N-{5-[(1-Ethoxyisoquinolin-5-yl)carbonyl]-4,6-difluoro-2,3-dihydro-1H-inden-1-yl}-2-methylpropane-2-sulphinamide

Obtained by oxidation of the intermediate resulting from the coupling of **337** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.60 (ddd, 1H), 8.20 (d, 1H), 8.20 (dd, 1H), 8.00 (d, 1H), 7.75 (t, 1H), 7.50 (d, 1H), 6.05 (d, 1H), 4.90 (quad, 1H), 4.60 (quad, 2H), 3.00 (m, 1H), 2.80 (m, 1H), 2.50 (m, 1H), 2.05 (m, 1H), 1.50 (t, 3H), 1.20 (s, 9H)

IR (cm^{-1}) : 3240, 1667, 1633, 1605, 1568, 815, 758

Intermediate 345 :

tert-Butyl {(1R)-6-[(1-ethoxyisoquinolin-5-yl)carbonyl]-5,7-difluoro-2,3-dihydro-1H-inden-1-yl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **343** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (2d, 2H), 8.05 (d, 1H), 7.70 (t, 1H), 7.35 (d, 1H), 7.20 (d, 1H), 5.20 (quad, 1H), 4.60 (quad, 2H), 3.10 (m, 1H), 2.90 (m, 1H), 2.45 (m, 1H), 1.95 (m, 1H), 1.50 (t, 3H), 1.35 (s, 9H)

IR (cm^{-1}) : 3430, 1672, 1635, 1575, 1517, 1162

Intermediate 348 :

tert-Butyl {(1S)-6-[(1-ethoxyisoquinolin-5-yl)carbonyl]-5,7-difluoro-2,3-dihydro-1H-inden-1-yl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **346** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (2d, 2H), 8.05 (d, 1H), 7.70 (t, 1H), 7.35 (d, 1H), 7.20 (d, 1H), 5.20 (quad, 1H), 4.60 (quad, 2H), 3.10 (m, 1H), 2.90 (m, 1H), 2.45 (m, 1H), 1.95 (m, 1H), 1.50 (t, 3H), 1.35 (m, 9H)

IR (cm^{-1}) : 3430, 1673, 1636, 1575, 1517, 1162

Intermediate 369 :

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluoro-2-methoxyphenyl}-ethyl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **367** and **125**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (2d, 2H), 8.10 (d, 1H), 7.75 (t, 1H), 7.50 (d, 1H), 7.20 (d, 1H), 5.00 (m, 1H), 4.60 (quad, 2H), 3.90 (s, 3H), 1.45 (t, 3H), 1.40 (m, 9H), 1.30 (d, 3H)

^{19}F NMR: -118, -129

IR (cm^{-1}) : 3390, 1682, 1675, 1517, 1162, 851-738

Intermediate 375 :

tert-Butyl (1-{4-[(1-ethoxy-3-methylisoquinolin-5-yl)carbonyl]-3,5-difluoro-2-methoxyphenyl}ethyl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **367** and **294**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 8.50 (d, 1H), 8.05 (s, 1H), 8.05 (d, 1H), 7.65 (t, 1H), 7.50 (d, 1H), 7.20 (d, 1H), 5.00 (m, 1H), 4.55 (quad, 2H), 3.90 (s, 3H), 2.55 (s, 3H), 1.50 (t, 3H), 1.40 (m, 9H), 1.30 (d, 3H)

^{19}F NMR: -118, -129

IR (cm^{-1}) : 3400, 1679, 1665, 1616, 1571, 1520, 1148, 860-691

Intermediate 380 :

tert-Butyl (2-{4-[(1-ethoxy-4-methylisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}-propan-2-yl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **378** and **303**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.45 (m, 1H), 7.95 (s, 1H), 7.80 (m, 1H), 7.65 (t, 1H), 7.35 (m, 1H), 7.15 (d, 2H), 4.55 (quad, 2H), 2.20 (s, 3H), 1.50 (s, 6H), 1.45 (t, 3H), 1.35 (broad s, 9H)

IR (cm^{-1}) : 3310, 1718, 1688, 1627

Intermediate 389 :

tert-Butyl [1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3-fluoro-2-methoxyphenyl}-ethyl]carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **387** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.46 (d, 1H), 8.10 (d, 1H), 7.93 (d, 1H), 7.70 (m, 2H), 7.56 (d, 1H), 7.37 (dd, 1H), 7.30 (d, 1H), 4.99 (m, 1H), 4.57 (quad, 2H), 3.86 (s, 3H), 1.46 (t, 3H), 1.37 (s, 9H), 1.29 (d, 3H)

IR (cm^{-1}) : 3354, 1703, 1660

Intermediate 403 :

N-[(1R)-1-{4-[(1-Ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluoro-2-methoxyphenyl}-ethyl]-2-methylpropane-2-sulphinamide

Obtained by oxidation of the intermediate resulting from the coupling of **401** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (2d, 2H), 8.10 (d, 1H), 7.75 (t, 1H), 7.40 (dd, 1H), 5.80 (d, 1H), 4.75 (quint, 1H), 4.60 (quad, 2H), 3.90 (s, 3H), 1.50 (t, 3H), 1.40 (d, 3H), 1.15 (s, 9H)

IR (cm^{-1}) : 3245, 1668, 1617, 1569, 816, 757

Intermediate 406 :

N-[(1S)-1-{4-[(1-Ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluoro-2-methoxyphenyl}-ethyl]-2-methylpropane-2-sulphinamide

Obtained by oxidation of the intermediate resulting from the coupling of **404** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (2d, 2H), 8.10 (d, 1H), 7.75 (t, 1H), 7.30 (dd, 1H), 5.55 (d, 1H), 4.80 (quint, 1H), 4.60 (quad, 2H), 3.90 (s, 3H), 1.50 (t, 3H), 1.50 (d, 3H), 1.15 (s, 9H)

IR (cm^{-1}) : 3230, 1668, 1617, 1569, 815, 757

Intermediate 417 :

tert-Butyl {5-[(1-ethoxyisoquinolin-5-yl)carbonyl]-4,6-difluoro-2,3-dihydro-1H-inden-1-yl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **415** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (dd, 1H), 8.20 (2d, 2H), 8.00 (dd, 1H), 7.70 (t, 1H), 7.50 (d, 1H), 7.00 (d, 1H), 5.10 (m, 1H), 4.60 (quad, 2H), 3.00 (m, 1H), 2.80 (m, 1H), 2.45 (m, 1H), 1.95 (m, 1H), 1.45 (t, 3H), 1.45 (s, 9H)

IR (cm^{-1}) : 3385, 1680, 1662, 1569, 1511, 1162

Intermediate 425 :

tert-Butyl {5-[(1-ethoxyisoquinolin-5-yl)carbonyl]-4,6-difluoro-2,3-dihydro-1H-inden-1-yl}carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **423** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (dd, 1H), 8.20 (2d, 2H), 8.00 (dd, 1H), 7.70 (t, 1H), 7.50 (d, 1H), 7.00 (d, 1H), 5.10 (m, 1H), 4.60 (quad, 2H), 3.00 (m, 1H), 2.80 (m, 1H), 2.45 (m, 1H), 1.95 (m, 1H), 1.45 (t, 3H), 1.45 (s, 9H)

IR (cm^{-1}) : 3385, 1680, 1662, 1569, 1510

Intermediate 432 :

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-2-ethyl-3,5-difluorophenyl}-ethyl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **430** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.54 (d, 1H), 8.19 (d, 1H), 8.15 (d, 1H), 8.03 (d, 1H), 7.72 (dd, 1H), 7.60 (d, 1H), 7.25 (d, 1H), 4.94 (m, 1H), 4.57 (quad, 2H), 2.74 (m, 1H), 2.64 (m, 1H), 1.46 (t, 3H), 1.38 (s, 9H), 1.33 (d, 3H), 1.16 (t, 3H)

IR (cm^{-1}) : 3358, 1677, 1631

Intermediate 446 :

tert-Butyl (1-{6-(benzyloxy)-3-[(1-ethoxyisoquinolin-5-yl)carbonyl]-2,4-difluoro-phenyl}ethyl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **444** and **125**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 8.50 (d, 1H), 8.15 (d, 1H), 8.0 (m, 2H), 7.70 (t, 1H), 7.6-7.3 (m, 5H), 7.05 (d, 1H), 6.95 (m, 1H), 5.30 (s, 2H), 5.10 (m, 1H), 4.55 (quad, 2H), 1.45 (t, 3H), 1.30 (m, 12H)

^{19}F NMR: -112.5, -115.5

IR (cm^{-1}) : 3490, 1709

Intermediate 467 :

tert-Butyl (2-{3-[(1-ethoxyisoquinolin-5-yl)carbonyl]-2,4-difluorophenyl}propan-2-yl)-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **465** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.54 (d, 1H), 8.20 (s, 2H), 7.92 (d, 1H), 7.69 (t, 1H), 7.50 (m, 1H), 7.30 (broad s, 1H), 7.22 (t, 1H), 4.58 (quad, 2H), 1.55 (s, 6H), 1.45 (t, 3H), 1.30 (m, 9H)

^{19}F NMR:-117.2, -116.2

IR (cm^{-1}) : 3345, 1697, 1672

Intermediate 480 :

N-(1-{3-[(1-Ethoxyisoquinolin-5-yl)carbonyl]-2,4-difluorophenyl}propyl)-2-methylpropane-2-sulphinamide

Obtained by oxidation of the intermediate resulting from the coupling of **478** and **125**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 8.56 (d, 1H), 8.19 (2d, 2H), 7.99 (d, 1H), 7.72 (2m, 2H), 7.31 (t, 1H), 5.50 (d, 1H), 4.59 (quad., 2H), 4.40 (m, 1H), 1.92 (m, 1H), 1.78 (m, 1H), 1.48 (t, 3H), 1.08 (s, 9H), 0.87 (t, 3H)

IR (cm^{-1}) : 3197, 1670, 1264, 1050, 1018

Intermediate 486 :

tert-Butyl 2-{3-[(1-ethoxyisoquinolin-5-yl)carbonyl]-2,4-difluorophenyl}pyrrolidine-1-carboxylate

Obtained by oxidation of the intermediate resulting from the coupling of **484** and **125**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 8.45 (d, 1H), 8.17 (2d, 2H), 7.98 (d, 1H), 7.80 (t, 1H), 7.45 (m, 1H), 7.21 (t, 1H), 4.95 (m, 1H), 4.61 (quad, 2H), 3.52 (m, 2H), 2.33 (m, 1H), 1.89 (m, 2H), 1.80 (m, 1H), 1.48 (t, 3H), 1.29 (s, 9H)

IR (cm^{-1}) : 1694, 1674, 1159

Optical purity (SFC: ID 3µM column 4.6x250 mm; CO_2 / (isopropanol/n-butylamine:100/0.5) : 75 / 25; Detection: 254nm) : > 99%.

Intermediate 494 :

tert-Butyl [(1R)-1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}propyl]-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **492** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (d, 1H), 8.15 (d, 1H), 8.05 (broad d, 1H), 7.25 (d, 2H), 4.55 (m and quad, 3H), 1.7 (m, 2H), 1.45 (t, 3H), 1.4 (s, 9H), 0.9 (t, 3H)

Intermediate 501 :

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}-2-methyl-propyl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **499** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.54 (d, 1H), 8.19 (d, 1H), 8.11 (d, 1H), 8.05 (d, 1H), 7.71 (t, 1H), 7.22 (m, 2H), 4.58 (quad, 2H), 4.39 (t, 1H), 1.95 (m, 1H), 1.48 (t, 3H), 1.38 (broad s, 9H), 0.9-0.79 (2d, 6H)

^{19}F NMR: -113.1

IR (cm^{-1}) : 3354, 1678, 1633

Intermediate 507 :

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}butyl)-carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **505** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.15 (d, 1H), 8.2 (d, 1H), 8.05 (d, 1H), 7.7 (t, 1H), 7.45 (broad d, 1H), 7.2 (broad d, 2H), 4.6 (m, 1H), 4.58 (quad, 2H), 1.65 (m, 2H), 1.45 (t, 3H), 1.4 (broad s, 9H), 1.3 (m, 2H), 0.9 (t, 3H)

IR (cm^{-1}) : 3350, 1676, 1160

Intermediate 512 :

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}-3-methyl-butyl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **510** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.15 (dd, 1H), 8.05 (d, 1H), 7.7 (t, 1H), 7.25 (d, 2H), 4.65 (m, 1H), 4.55 (quad, 2H), 1.65-1.45 (m, 3H), 1.45 (t, 3H), 1.4 (s, 9H), 0.95 (2d, 6H)

IR (cm^{-1}) : 3380, 1681, 1673, 1663

Intermediate 523 :

tert-Butyl 2-{3-[(1-ethoxyisoquinolin-5-yl)carbonyl]-2,4-difluorophenyl}pyrrolidine-1-carboxylate

Obtained by oxidation of the intermediate resulting from the coupling of **521** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.56 (d, 1H), 8.18 (2d, 2H), 7.98 (d, 1H), 7.7 (t, 1H), 7.46 (m, 1H), 7.22 (m, 1H), 4.96 (m, 1H), 4.62 (quad, 2H), 3.52 (m, 2H), 2.35-1.8 (2m, 2H), 1.90 (m, 2H), 1.5 (t, 3H), 1.29 (s, 9H)

IR (cm^{-1}) : 1682, 1667

Optical purity (SFC: ID 3µM column 4.6x250 mm; CO_2 / (isopropanol/n-butylamine:100/0.5) : 75 / 25; Detection: 254nm) : > 99%.

Intermediate 528 :

N-(1-{3-[(1-Ethoxyisoquinolin-5-yl)carbonyl]-2-fluorophenyl}ethyl)-2-methyl-propane-2-sulphinamide

Obtained by oxidation of the intermediate resulting from the coupling of **526** and **125**

^{1}H NMR (300/400 MHz, DMSO-d_6) **:** δ 8.50 (broad d, 1H), 8.10 (d, 1H), 7.87 (broad d, 1H), 7.69 (dd, 1H), 7.71 (dd, 1H), 7.77 (td, 1H), 7.57 (td, 1H), 7.38 (t, 1H), 4.64 (quint., 1H), 4.56 (quad., 2H), 1.47 (d, 3H), 1.46 (t, 3H), 1.07 (s, 9H)

^{19}F NMR: -118

IR (cm^{-1}) : 1663, 1051, 3203

Intermediate 552 :

tert-Butyl (1-{2-(benzyloxy)-4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluoro-phenyl}ethyl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **550** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.56 (d, 1H), 8.2-8.16 (2d, 2H), 8.06 (d, 1H), 7.74 (t, 1H), 7.54 (d, 1H), 7.48 (d, 2H), 7.41 (t, 2H), 7.37 (t, 1H), 7.24 (d, 1H), 5.11 (AB, 2H), 5.12 (m, 1H), 4.58 (quad, 2H), 1.46 (t, 3H), 1.39 (broad s, 12H), 1.27 (d, 3H)

IR (cm^{-1}) : 3358, 1679

Intermediate 560 :

tert-Butyl (1-{3-[(1-ethoxyisoquinolin-5-yl)carbonyl]-2,4-difluoro-6-methylphenyl}-ethyl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **558** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.53 (d, 1H), 8.19-8.12 (2d, 2H), 7.96 (d, 1H), 7.69 (t, 1H), 7.33 (d, 1H), 7.11 (d, 1H), 4.88 (quint, 1H), 4.58 (quad, 2H), 2.49 (s, 3H), 1.46 (t, 3H), 1.36 (d, 3H), 1.33-1.25 (2 broad s, 9H)

IR (cm^{-1}) : 3340, 1705, 1670, 1258, 1162

Intermediate 698 :

tert-Butyl [{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}(3-methoxy-phenyl)methyl]carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **696** and **125**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (d, 1H), 8.15 (d, 1H), 8.05 (d, 1H), 7.70 (t, 1H), 7.35 (d, 2H), 7.25 (t, 1H), 7.00 (m, 2H), 6.85 (dd, 1H), 5.95 (m, 1H), 4.55 (quad, 2H), 3.75 (s, 3H), 1.45 (t, 3H), 1,40 (broad s, 9H)

IR (cm^{-1}) : 3342, 2980, 1675, 1632-1612, 1568, 1250, 1159

Intermediate 704 :

tert-Butyl (2-cyclohexyl-1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluoro-phenyl}ethyl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **702** and **125**

^{1}H NMR (300 MHz, DMSO-d_6) : δ 8.55 (d, 1H), 8.20 (d, 1H), 8.15 (d, 1H), 8.05 (d, 1H), 7.80 (d, 1H), 7.45 (dl, 1H, NH), 7.20 (d, 2H), 4.70 (m, 1H), 4.55 (quad., 2H), 1.85-0.90 (m, 13H), 1.45 (t, 3H), 1.40 (s, 9H)

IR (cm^{-1}) : 3359, 2924-2854, 1680-1634, 1616, 1526, 1252, 1164

Intermediate 708 :

tert-Butyl (cyclohexylmethyl)(1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluoro-phenyl}ethyl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **706** and **125**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 8.53 (d, 1H), 8.18 (d, 1H), 8.13 (d, 1H), 8.00 (d, 1H), 7.70 (t, 1H), 7.15 (m, 2H), 4.92 (m, 1H), 4.56 (quad., 2H), 3.10 (m, 2H), 1.75-0.75 (m, 11H), 1.58 (d, 3H), 1.45 (t, 3H), 1.30 (broad s, 9H)

IR (cm^{-1}) : 1674, 1632, 1254-1150, 957, 816, 757

Intermediate 710 :

tert-Butyl (1-{4-[(1-ethoxy-3-methylisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}-ethyl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of intermediate **278** and **294**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.50 (m, 1H), 8.05 (s, 1H), 8.00 (d, 1H), 7.60 (t, 1H), 7.50 (d, 1H), 7.20 (d, 2H), 4.75 (m, 1H), 4.55 (quad., 2H), 2.55 (s, 3H), 1.45 (t, 3H), 1.40 (broad s, 9H), 1.35 (d, 3H)

IR (cm^{-1}): 3349, 1672

Intermediate 732 :

tert-Butyl (2-{4-[(1-ethoxy-3-methylisoquinolin-5-yl)carbonyl]-3,5-difluoro-phenyl}propan-2-yl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **378** and **294**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.45 (d, 1H), 8.00 (s, 1H), 7.95 (d, 1H), 7.65 (t, 1H), 7.35 (m, 1H, NH), 7.20 (d, 2H), 4.55 (quad., 2H), 2.55 (s, 3H), 1.50 (s, 6H), 1.45 (t, 3H), 1.35 (broad s, 9H)

IR (cm^{-1}) : 3331, 1687, 1669

Intermediate 734 :

tert-Butyl (1-{4-[(1-ethoxy-3-methylisoquinolin-5-yl)carbonyl]-3,5-difluoro-2-methoxyphenyl}ethyl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **367** and **294**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 8.50 (d, 1H), 8.05 (s and d, 2H), 7.65 (t, 1H), 7.50 (d, 1H), 7.20 (d, 1H), 5.0 (m, 1H), 4.55 (quad, 2H), 3.90 (s, 3H), 2.55 (s, 3H), 1.50 (t, 3H), 1.40 (m, 9H), 1.30 (d, 3H)

^{19}F NMR: -118, -129

IR (cm^{-1}) : 3259, 1697-1663

Intermediate 741 :

tert-Butyl [1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3-fluoro-2-methoxyphenyl}-ethyl]carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **739** and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.50 (d, 1H), 8.10 (d, 1H), 7.95 (d, 1H), 7.70 (m, 2H), 7.55 (d, 1H, NH), 7.40 (d, 1H), 7.30 (dd, 1H), 5.00 (quint., 1H), 4.60 (quad., 2H), 3.85 (s, 3H), 1.50 (t, 3H), 1.35 (m, 9H), 1.30 (d, 3H)

IR (cm^{-1}) : 3410, 1709, 1665, 1616, 1570, 1265, 1160, 813, 757

Intermediates **448**, **546**, **555**, **562** and **730** were obtained starting from intermediates prepared using coupling protocol **XXI** and described above.

Intermediate 546 :

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-2-fluoro-3-methoxyphenyl}-ethyl)carbamate

Intermediate **546** was obtained by nuceophilic substitution reaction (MeONa/DMF) starting from intermediate **271**: 4.8 g (10.5 mmoles) of intermediate **271** are dissolved in 150 mL of DMF under a stream of nitrogen. 1.5 g (27.75 mmoles, 2.6 eq.) of powdered sodium methoxide are added in a single batch. Stirring is carried out at ambient temperature overnight. HPLC monitoring after 16h at ambient temperature shows only 40% of product formed. A further 1.5 g (27.75 mmoles, 2.6 eq.) of powdered sodium methoxide are added, and stirring is carried out for a further 6 hours. The mixture is hydrolysed by addition of ice-water. Extraction is carried out with 3 times 250 mL of ethyl acetate, and the organic phase is dried over $MgSO_4$ and then filtered and evaporated to dryness. 18 g of an oil still containing DMF are obtained. The residue is taken up in 200 mL of water and extracted with 5 times 200 mL of ether. The organic phase is dried over $MgSO_4$, filtered and evaporated to dryness. There are obtained 4.89 g of an orange oil, which is purified by flash chromatography on silica (eluant : CH_2Cl_2-AcOEt gradient: 99-1 to 90-10) to give 1.55 g of intermediate **546** in the form of a yellow meringue and 1.6 g of impure fractions.

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.44 (d, 1H), 8.11 (d, 1H), 7.84 (d, 1H), 7.80 (d, 1H), 7.68 (t, 1H), 7.35 (d, 1H), 7.25 (t, 1H), 4.94 (quint, 1H), 4.56 (quad, 2H), 3.49 (s, 3H), 1.45 (t, 3H), 1.38 (s, 9H), 1.36 (d, 3H)

^{19}F NMR:-137.1

IR (cm^{-1}) : 3342, 1701, 1664

Intermediate **554** was obtained starting from **552** according to the following sequence:

Intermediate 553 :

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluoro-2-hydroxyphenyl}-ethyl)carbamate

A solution of **552** (6.7 g, 12 mmoles) in an ethanol/AcOEt mixture (500 mL, 1/1) is hydrogenated at atmospheric pressure of H_2 and at 60°C in the presence of 10% Pd/C (0.2 g) for 7 hours. The catalyst is filtered off, and concentration of the filtrate yields intermediate **553** in the form of a solid (5.7 g).

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 9.88 (broad s, 1H), 8.53 (d, 1H), 8.19-8.13 (2d, 2H), 8.06 (d, 1H), 7.72 (t, 1H), 7.47 (broad d, 1H), 7.07 (d, 1H), 5.03 (quint, 1H), 4.57 (quad, 2H), 1.46 (t, 3H), 1.39 (broad s and d, 12H), 1.29 (d, 3H)

IR (cm^{-1}) : 3350, 3500-2600, 1675

Intermediate 554 :

6-{1-[(tert-Butoxycarbonyl)amino]ethyl}-3-[(1-ethoxyisoquinolin-5-yl)carbonyl]-2,4-difluorophenyl trifluoromethanesulphonate

A solution at 0°C of **553** (5.6 g, 11 mmoles) in pyridine (45 mL) is treated with triflic anhydride (3.36 g, 11 mmoles). The reaction mixture is stirred at ambient temperature for 2 hours and then cooled to 0°C again and treated with triflic anhydride (0.2 eq.) until conversion is complete. The pyridine is evaporated off in vacuo, and the residue is taken up in water and AcOEt. The organic phase is washed with a saturated NaCl solution, dried over $MgSO_4$ and then concentrated. By chromatography on silica (eluant CH_2Cl_2/AcOEt 100/0 to 95/5), intermediate **554** is obtained in the form of a solid (6.2 g).

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 8.59 (d, 1H), 8.23-8.19 (2d, 2H), 8.17 (d, 1H), 7.74 (t, 1H), 7.71 (broad d, 1H), 7.5 (d, 1H), 4.97 (quint, 1H), 4.57 (quad, 2H), 1.47 (t, 3H), 1.4 (d, 3H), 1.38 (broad s, 9H)

IR (cm^{-1}) : 3375, 1675

LCMS [M+H]+: 604

Intermediate **448** was obtained in two steps starting from intermediate **446 :** intermediate **446** was converted into phenol **447** according to the protocol described for obtaining **553.** The phenol **447** was treated with methyl iodide according to the protocol described for intermediate **93**.

Intermediate 448:

tert-Butyl (1-{3-[(1-ethoxyisoquinolin-5-yl)carbonyl]-2,4-difluoro-6-methoxyphenyl}-ethyl)carbamate

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.50 (d, 1H), 8.15 (d, 1H), 7.97 (2m, 2H), 7.69 (tt, 1H), 6.99 (d, 1H), 7.0-6.7 (broad s, 1H), 5.1-4.9 (m, 1H), 4.57 (quad, 2H), 3.92 (s, 3H), 1.45 (t, 3H), 1.4-1.3 (broad s, 12H)

IR (cm^{-1}) : 3455, 1707, 1163

Intermediate **554** was used to prepare intermediates **555** and **562:**

Intermediate 555 :

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluoro-2-methylphenyl}-ethyl)carbamate

A mixture of **554** (1 g, 1.65 mmoles), trimethyl-boroxine (0.42 g, 3.3 mmoles), K_2CO_3 (0.91 g, 6 mmoles) in 1,4-dioxane (15 mL) degassed with N_2 for 15 minutes is treated with $Pd(PPh_3)_4$ (0.38 g, 0.3 mmole). The mixture is heated at reflux for 1 hour. After return to ambient temperature, the solid is filtered off and the filtrate is concentrated in vacuo. By chromatography on silica (eluant CH_2Cl_2/AcOEt 100/0 to 50/50), 0.7 g of intermediate **555** is obtained.

^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.54 (d, 1H), 8.2-8.15 (2d, 2H), 8.03 (d, 1H), 7.72 (t, 1H), 7.59 (broad d, 1H), 7.21 (d, 1H), 4.9 (quint, 1H), 4.57 (quad, 2H), 2.22 (broad s, 3H), 1.46 (t, 3H), 1.38-1.26 (2 broad s, 9H), 1.3 (d, 3H)

IR (cm^{-1}): 3369, 1682-1672

LCMS [M+H]$^+$: 470

Intermediate **562** was obtained starting from intermediate **554** according to the sequence:

Intermediate 561 :

tert-Butyl (1-{2-ethenyl-4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}-ethyl)carbamate

To a solution, degassed with N_2, of intermediate **554** (1.g) in 1,4-dioxane (20 mL) there are added vinyl-tributyl-tin (0.58 g) and $Pd(PPh_3)_4$ (50 mg) and LiCl (0.2 g). The mixture is heated at 100°C for 2 hours. After return to ambient temperature, the mixture is treated with a 10% aqueous KF solution, the salts are filtered off and the filtrate is extracted with AcOEt. The organic phase is dried over MgSO4 and concentratd in vacuo. By chromatography on silica (eluant CH_2Cl_2/AcOEt 100/0 to 90/5), intermediate **561** is obtained in the form of an amorphous solid (0.7 g).

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.21-8.18 (2d, 2H), 8.09 (d, 1H), 7.72 (t, 1H), 7.62 (broad d, 1H), 7.28 (d, 1H), 6.73 (dd, 1H), 5.69 (d, 1H), 5.66 (d, 1H), 4.98 (quint, 1H), 4.57 (quad, 2H), 1.46 (t, 3H), 1.38-1.26 (2 broad s, 9H), 1.3 (d, 3H)

IR (cm^{-1}) : 3367, 1683-1670

Treatment of intermediate **561** according to the protocol described for intermediate **395** yielded **562**.

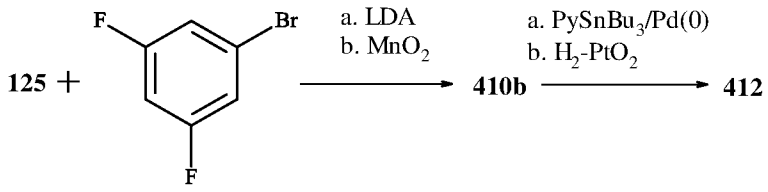
Intermediate 562:

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-2-ethyl-3,5-difluorophenyl}-ethyl)carbamate

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.54 (d, 1H), 8.2-8.15 (2d, 2H), 8.03 (d, 1H), 7.72 (t, 1H), 7.6 (broad d, 1H), 7.25 (d, 1H), 4.94 (quint, 1H), 4.57 (quad, 2H), 2.74-2.64 (2m, 2H), 1.46 (t, 3H), 1.38 (broad s, 9H), 1.33 (d, 3H), 1.16 t, 3H)

LCMS [M+H]+: 484

Intermediate **412** was obtained according to the following protocol:



Intermediate 410b :

(4-Bromo-2,6-difluorophenyl)(1-ethoxyisoquinolin-5-yl)methanone

Obtained by oxidation of the intermediate resulting from the coupling of 1-bromo-3,5-difluorobenzene and **125**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (m, 2H), 8.15 (d, 1H), 7.70 (m, 3H), 4.60 (quad, 2H), 1.45 (t, 3H)

IR (cm^{-1}) : 1668.

Intermediate 412 :

[2,6-Difluoro-4-(piperidin-2-yl)phenyl](1-ethoxyisoquinolin-5-yl)methanone

Step 1 :

To a solution, degassed with nitrogen, of intermediate **410b** (1.1 g) in anhydrous DMF (20 mL) there are added 2-(tributylstannyl)-pyridine (1 g, 2.7 mmoles) and $Pd(PPh_3)_4$ (500 mg, 0.43 mmole) . The reaction mixture is heated at 100°C for 20 hours and is then diluted with ethyl acetate and water. The organic phase is decanted, washed with water, dried over $MgSO_4$, filtered and evaporated in vacuo. The residue is purified by flash chromatography on silica (eluant : CH_2Cl_2-AcOEt gradient: 99-1 to 85-15). The expected intermediate (700 mg) is obtained in the form of a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.75 (dd, 1H), 8.56 (d, 1H), 8.21 (dd, 2H), 8.18 (m, 2H), 8.04 (d, 2H), 7.99 (td, 1H), 7.73 (t, 1H), 7.50 (dd, 1H), 4.58 (quad, 2H), 1.46 (t, 3H)

IR (cm^{-1}) : 1668

Step 2 :

To a solution of the intermediate obtained above (700 mg, 1.79 mmoles) in 45 mL of methanol there are added 0.4 mL of a concentrated 37% HCl solution and 140 mg of PtO_2. The reaction mixture is hydrogenated at ambient temperature and under atmospheric pressure of H_2 for 15 hours. The catalyst is filtered off and the filtrate is concentrated in vacuo. The residue is suspended in water and treated with a 10N aqueous sodium hydroxide solution and extracted with ethyl acetate. The organic phase is washed with water, dried over $MgSO_4$, filtered and evaporated in vacuo. The product is purified on

Phase Strategy RP 15 µm, eluant : water-acetonitrile-trifluoroacetic acid. After evaporation of the acetonitrile, the aqueous phase is rendered basic by addition of 10N sodium hydroxide and is then extracted with ethyl acetate. The organic phase is washed with water, dried over $MgSO_4$, filtered and evaporated in vacuo. Intermediate **412** (180 mg) is obtained in the form of an oil, which crystallises at ambient temperature.

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.54 (d, 1H), 8.20 (d, 1H), 8.14 (d, 1H), 8.01 (d, 1H), 7.72 (t, 1H), 7.30 (d, 2H), 4.57 (quad., 2H), 3.78 (m, 1H), 3.12 (m, 1H), 2.72 (m, 1H), 1.84 (m, 2H), 1.62 (m, 1H), 1.46 (t, 3H), 1.60-1.30 (m, 3H)

IR (cm^{-1}) : 1667

Products **P66** and **P134** were obtained starting from intermediates **380** and **732**, respectively, according to the procedure described for product **P68**.

The other ketone intermediates obtained by protocol **XXI** were deprotected in an acidic medium (4N HCl ou 2N HCl in ether) to yield the final products, according to the procedures described for products **P17** and **P110**.

Product	Obtained from	Nomenclature Analytical description
P41	**236**	**5-[(1-Amino-4,6-difluoro-2,3-dihydro-1H-inden-5-yl)carbonyl]isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.60 (s, 1H), 8.65 (m, 3H), 8.52 (d, 1H), 7.90 (d, 1H), 7.60 (d and t, 2H), 7.40 (s, 2H), 4.85 (m, 1H), 3.10 (m, 1H), 2.92 (m, 1H), 2.60 (m, 1H), 2.12 (m, 1H) **IR (cm^{-1}) :** 1687-1671, 1629 **HRMS (ESI)**: theoretical m/z for $C_{19}H_{15}F_2N_2O_2$ $[M+H]^+$ 341.1102, measured 341.1107
P44	**262**	**5-[(3-Amino-4,6-difluoro-2,3-dihydro-1H-inden-5-yl)carbonyl]isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.70 (s, 1H), 8.65 (broad s, 3H), 8.55 (d, 1H), 7.95 (d, 1H), 7.60 (m, 1H), 7.40 (2d, 2H), 7.30 (d, 1H), 4.90 (dd, 1H), 3.35-3.00 (2m, 2H), 2.55-2.20 (2m, 2H) **IR (cm^{-1})**: 3250-2480, 1687-1672 **HRMS (ESI):** theoretical m/z for $C_{19}H_{15}F_2N_2O_2$ $[M+H]^+$ 341.1102, measured 341.1107
P46	**271**	**5-[4-(1-Aminoethyl)-2,3-difluorobenzoyl]isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.60 (m, 1H), 9.00-8.50 (m, 3H), 8.50 (broad d, 1H), 7.85 (broad d, 1H), 7.65 (broad t, 1H), 7.60-7.50 (m, 2H), 7.30 (m, 1H), 7.00 (d, 1H), 4.70 (quad, 1H), 1.6 (d, 3H) **IR (cm^{-1}) :** 3200-1950, 1671, 1632 **HRMS (ESI)**: theoretical m/z for $C_{18}H_{15}F_2N_2O_2$ $[M+H]^+$ 329.1101, measured 329.1102
P49	**296**	**5-{4-[(1R)-1-Aminoethyl]-2,6-difluorobenzoyl}-3-methylisoquinolin-1(2H)-one hydrochloride**

		^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 11.80 (s, 1H), 8.75 (s, 3H), 8.50 (d, 1H), 7.85 (d, 1H), 7.55 (d, 2H), 7.50 (m, 1H), 7.30 (s, 1H), 4.55 (quad, 1H), 2.30 (s, 3H), 1.55 (d, 3H) **IR (cm^{-1}) :** 3237-2450, 1687-1672, 1622 **HRMS (ESI)**: theoretical m/z for $C_{19}H_{17}F_2N_2O_2$ $[M+H]^+$ 343.1258, measured 343.1256
P50	**305**	**5-{4-[(1R)-1-Aminoethyl]-2,6-difluorobenzoyl}-4-methylisoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.60 (s, 1H), 8.75 (s, 3H), 8.50 (d, 1H), 7.70 (d, 1H), 7.55 (m, 1H), 7.55 (m, 2H), 7.20 (s, 1H), 4.55 (quad, 1H), 1.95 (s, 3H), 1.55 (d, 3H) **IR (cm^{-1}) :** 3158, 3120-2432, 1676, 1633 **HRMS (ESI)**: theoretical m/z for $C_{19}H_{17}F_2N_2O_2$ $[M+H]^+$ 343.1258, measured 343.1274
P53	**319**	**5-[(1-Amino-4,6-difluoro-2,3-dihydro-1H-inden-5-yl)carbonyl]isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.60 (s, 1H), 8.65 (m, 3H), 8.52 (d, 1H), 7.90 (d, 1H), 7.60 (d, 1H), 7.60 (t, 1H), 7.40 (s, 2H), 4.85 (m, 1H), 3.10 (m, 1H), 2.92 (m, 1H), 2.60 (m, 1H), 2.12 (m, 1H) **IR (cm^{-1})** : 3600-2600, 1687, 1633 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{15}F_2N_2O_2$ $[M+H]^+$ 341.1101, measured 341.1101 **Optical purity** (SFC: AD 3µM column 4.6x250 mm ; eluant: CO_2 / (isopropanol/diethylamine:100/0.5) : 70 / 30 ; detection:255nm) : >99%. (absence of **P58**)
P55	**328**	**5-{4-[(1S)-1-Aminoethyl]-2,6-difluorobenzoyl}-4-methylisoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.50 (s, 1H), 8.65

		(m, 3H), 8.48 (dd, 1H), 7.70 (d, 1H), 7.50 (t, 1H), 7.50 (d, 2H), 7.15 (d, 1H), 4.55 (broad s, 1H), 1.99 (s, 3H), 1.55 (d, 3H) **^{19}F NMR:** -108.2 **IR (cm^{-1}) :** 3500-2500, 1680, 1632 **MS (DEI 70 eV)** : m/z 342,1
P56	**333**	**5-{3-[(1R)-1-Aminoethyl]-2,6-difluorobenzoyl}-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d$_6$) **:** δ 11.80 (broad s, 1H), 8.80 (broad s, 3H), 8.55 (d, 1H), 8.00 (d and dd, 2H), 7.60 (t, 1H), 7.40 (t and d, 3H), 4.62 (quad, 1H), 1.60 (d, 3H) **^{19}F NMR:** -112, -115 **IR (cm^{-1}) :** 3450-2480, 1668, 1619, 1589, 1273-1237 **HRMS (ESI)**: theoretical m/z for $C_{18}H_{15}F_2N_2O_2$ $[M+H]^+$ 329.1102, measured 329.1115 **Optical purity** (SFC: ID 5µM column 4.6x250 mm ; eluant: CO_2 / (isopropanol/n-butylamine:100/0.5): 75 / 25 ; detection: 254nm) : >99%. (absence of **P57**) α_D (589nM) = -3.09 (c = 0.0097 g/mL, DMSO) at 20°C
P57	**336**	**5-{3-[(1S)-1-Aminoethyl]-2,6-difluorobenzoyl}-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d$_6$): δ 11.80 (broad s, 1H), 8.80 (broad s, 3H), 8.60 (d, 1H), 8.00 (d and dd, 2H), 7.65 (t, 1H), 7.50 (t and d, 3H), 4.68 (quad, 1H), 1.62 (d, 3H) **^{19}F NMR:** -111, -115 **IR (cm^{-1})**: 3450-2480, 1674, 1612, 1589, 1262-1222 **HRMS (ESI) :** theoretical m/z for $C_{18}F_2H_{15}N_2O_2$ $[M+H]^+$ 329.1102, measured 329.1105 **Optical purity** (SFC: ID 5µM column 4.6x250 mm ; eluant: CO_2 / (isopropanol/n-butylamine:100/0.5) : 75 / 25 ; detection:254nm) : >99%.

		(absence of **P56**) α_D (589nM) = 3.43 (c = 1, DMSO) at 20°C
P58	**339**	**5-[(1-Amino-4,6-difluoro-2,3-dihydro-1H-inden-5-yl)carbonyl]isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.60 (s, 1H), 8.65 (m, 3H), 8.52 (d, 1H), 7.90 (d, 1H), 7.60 (d, 1H), 7.60 (t, 1H), 7.40 (s, 2H), 4.85 (m, 1H), 3.10 (m, 1H), 2.92 (m, 1H), 2.60 (m, 1H), 2.12 (m, 1H) **IR (cm^{-1}) :** 3410-2390, 1675, 1632, 1600, 879-740 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{15}F_2N_2O_2$ $[M+H]^+$ 341.1101, measured 341.1104 **Optical purity** (SFC: AD 3µM column 4.6x250 mm ; eluant: CO_2 / (isopropanol/ diethylamine:100/0.5) : 70/30; detection:255nm): >99%.(absence of **P53**)
P59	**345**	**5-{[(3R)-3-Amino-4,6-difluoro-2,3-dihydro-1H-inden-5-yl]carbonyl}isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.70 (m, 1H), 8.65 (m, 3H), 8.50 (d, 1H), 7.95 (d, 1H), 7.60 (t, 1H), 7.40 (2d, 2H), 7.30 (d, 1H), 4.90 (m, 1H), 3.30 (m, 1H), 3.00 (m, 1H), 2.55 (m, 1H), 2.20 (m, 1H) **IR (cm^{-1}) :** 3200-2300, 1657, 1628 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{15}F_2N_2O_2$ $[M+H]^+$ 341.1102, measured 341.1104 **Optical purity** (SFC: AD-H 3µM column 4.6x250 mm ; eluant: CO_2 / (methanol/butylamine:100/0.5) : 65 / 35 ; detection: 308nm) : >99%. (absence of **P60**) α_D (589nM) = -27.7 (c = 0.009 g/mL, MeOH) at 20°C□

P60	**348**	**5-{[(3S)-3-Amino-4,6-difluoro-2,3-dihydro-1H-inden-5-yl]carbonyl}isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.70 (m, 1H), 8.65 (m, 3H), 8.50 (d, 1H), 7.95 (d, 1H), 7.60 (t, 1H), 7.40 (2d, 2H), 7.30 (d, 1H), 4.90 (m, 1H), 3.30 (m, 1H), 3.00 (m, 1H), 2.55 (m, 1H), 2.2 (m, 1H) **IR (cm^{-1}) :** 3200-2300, 1657, 1627 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{15}F_2N_2O_2$ $[M+H]^+$ 341.1102, measured 341.1101 **Optical purity** (SFC: AD-H 3µM column 4.6x250 mm ; eluant: CO_2 / (methanol/butylamine:100/0.5) : 65 / 35 ; detection: 308nm) : >99%. (absence of **P59**)
P63	**369**	**5-[4-(1-Aminoethyl)-2,6-difluoro-3-methoxybenzoyl]-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 11.70 (m, 1H), 8.80 (m, 3H), 8.55 (d, 1H), 7.95 (d, 1H), 7.60 (dd, 1H), 7.60 (t, 1H), 7.40 (broad s, 2H), 4.70 (quad, 1H), 3.95 (s, 3H), 1.55 (d, 3H) **IR (cm^{-1}) :** 3410-2080, 1666, 1629, 1610, 1589, 832-702 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{17}F_2N_2O_3$ $[M+H]^+$ 359.1207, measured 359.1232
P65	**375**	**5-[4-(1-Aminoethyl)-2,6-difluoro-3-methoxybenzoyl]-3-methylisoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 11.70 (m, 1H), 8.70 (m, 3H), 8.50 (d, 1H), 7.95 (d, 1H), 7.65 (dd, 1H), 7.50 (t, 1H), 7.30 (s, 1H), 4.70 (quad, 1H), 3.90 (s, 3H), 2.30 (s, 3H), 1.55 (d, 3H) **IR (cm^{-1}) :** 3430-2250, 1666, 1632, 1595, 838-687 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{19}F_2N_2O_3$ $[M+H]^+$ 373.1364, measured 373.1365
P66	**380**	**5-[4-(2-Aminopropan-2-yl)-2,6-difluorobenzoyl]-4-**

		methylisoquinolin-1(2H)-one methanesulphonate **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.50 (d, 1H), 8.70-8.50 (m, 3H), 8.50 (d, 1H), 7.70 (d, 1H), 7.55 (t, 1H), 7.50 (d, 2H), 7.15 (broad d, 1H), 1.95 (broad s, 3H), 1.65 (s, 6H) **IR (cm^{-1}) :** 3300-2200, 1682, 1634, 1162, 1035 **HRMS (ESI) :** theoretical m/z for $C_{20}F_2H_{19}N_2O_2$ $[M+H]^+$ 357.1415, measured 357.1423 theoretical m/z for $C_{20}F_2H_{19}N_2O_2$ $[M+H-NH_3]^+$ 340.1149, measured 340.1142
P67	**389**	**5-{4-[-1-Aminoethyl]-2-fluoro-3-methoxybenzoyl}-isoquinolin-1(2H)-one hydrochloride, enantiomer 1** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.57 (d, 1H), 8.55 (m, 3H), 8.47 (d, 1H), 7.80 (d, 1H), 7.57 (t, 1H), 7.54 (d, 1H), 7.42 (dd, 1H), 7.31 (dd, 1H), 6.96 (d, 1H), 4.67 (quad, 1H), 3.93 (d, 3H), 1.52 (d, 3H) **IR (cm^{-1}) :** 3300-2500, 1665, 1627 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{18}FN_2O_3$ $[M+H]^+$ 341.1301, measured 341.1297; theoretical m/z for $C_{19}FH_{18}N_2O_3$ $[M+H-NH_3]^+$ 324.1036, measured 324.1014 **Optical purity** (AD-H 5µM column 4.6x250 mm ; eluant: EtOH/ CH_3CN/butylamine:95/5/0.1) ; detection: 260nm) : >99%. **α_D** (589nM) = -6.99 (c = 0.01 g/mL, MeOH) at 20°C

P70	**395**	**5-[4-(1-Aminoethyl)-2,6-difluorobenzoyl]-4-ethyl-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.60 (d, 1H), 8.75 (broad s, 3H), 8.47 (d, 1H), 7.70 (dd, 1H), 7.52 (t, 1H), 7.52 (d, 2H), 7.08 (d, 1H), 4.52 (broad s, 1H), 2.33 (quad, 2H), 1.55 (d, 3H), 1.10 (t, 3H) **^{19}F NMR:** -108.7 **IR (cm^{-1}) :** 3300-2000, 1676, 1631 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{19}F_2N_2O_2$ $[M+H]^+$ 357.1415, measured 357.1415
P72	**403**	**5-{4-[(1R)-1-Aminoethyl]-2,6-difluoro-3-methoxy-benzoyl}isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.70 (m, 1H), 8.55 (d, 1H), 8.55 (m, 3H), 7.95 (dd, 1H), 7.60 (t and dd, 2H), 7.40 (m, 2H), 4.70 (quad, 1H), 3.90 (s, 3H), 1.50 (d, 3H) **IR (cm^{-1}) :** 3300-2300, 1687, 1649, 1630, 1589 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{17}F_2N_2O_3$ $[M+H]^+$ 359.1207, measured 359.1189. **Optical purity** (SFC: ID 5µM column 4.6x250 mm ; eluant: CO_2 / (isopropanol/butylamine:100/0.5) : 70 / 30 ; detection: 256nm) : >99%. (absence of **P73**)
P73	**406**	**5-{4-[(1S)-1-Aminoethyl]-2,6-difluoro-3-methoxy-benzoyl}isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.70 (m, 1H), 8.60 (m, 3H), 8.55 (d, 1H), 7.95 (dd, 1H), 7.60 (t, 1H), 7.60 (dd, 1H), 7.40 (m, 2H), 4.70 (quad, 1H), 3.90 (s, 3H), 1.50 (d, 3H) **IR (cm^{-1}) :** 3300-2300, 1687, 1649, 1630, 1589 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{17}F_2N_2O_3$ $[M+H]^+$ 359.1207, measured 359.1215. **Optical purity** (ID 5µM column 4.6x250 mm ; eluant:

		CO_2/(isopropanol/butylamine :100/0.5) : 70 / 30 ; detection: 256nm) : >99%. (absence of **P72**)
P75	**412**	**5-[2,6-Difluoro-4-(piperidin-2-yl)benzoyl]isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.67 (broad s, 1H), 9.46 (m, 2H), 8.54 (d, 1H), 7.90 (d, 1H), 7.59 (m, 1H), 7.59 (m, 2H), 7.41 (m, 2H), 4.37 (dd, 1H), 3.39 (m, 1H), 3.03 (m, 1H), 2.02 (m, 1H), 2.00-1.50 (m, 5H) **IR (cm^{-1}) :** 3200-2400, 1673, 1632 **HRMS (ESI) :** theoretical m/z for $C_{21}H_{19}F_2N_2O_2$ $[M+H]^+$ 369.1415, measured 369.1415.
P80	**432**	**5-[4-(1-Aminoethyl)-3-ethyl-2,6-difluorobenzoyl]-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.70 (m, 1H), 8.80 (m, 3H), 8.50 (dd, 1H), 7.90 (dd, 1H), 7.75 (d, 1H), 7.60 (t, 1H), 7.40 (m, 1H), 7.40 (broad s, 2H), 4.65 (quad, 1H), 2.70 (m, 2H), 1.60 (d, 3H), 1.10 (t, 3H) **IR (cm^{-1}) :** 3500-2250, 1673-1624, 1594, 788-697 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{19}F_2N_2O_2$ $[M+H]^+$ 357.1415, measured 357.1396.
P81	**433**	**5-{4-[(1R)-1-Aminoethyl]-2,6-difluorobenzoyl}-4-chloroisoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 12.10-11.60 (broad s, 1H), 8.90-8.40 (broad s, 3H), 8.42 (d, 1H), 7.77 (d, 1H), 7.63 (t, 1H), 7.53 (s, 1H), 7.47 (m, 2H), 4.50 (quad, 1H), 1.51 (d, 3H) **IR (cm^{-1}) :** 3600-2400, 1671, 1648 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{14}ClF_2N_2O_2$ $[M+H]^+$ 363.0712, measured 363.0706. α_D (589nM) = 4.39 (c = 1, DMSO) at 20°C
P82	**434**	**5-{4-[(1S)-1-Aminoethyl]-2,6-difluorobenzoyl}-4-**

		chloroisoquinolin-1(2H)-one hydrochloride **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 12.10-11.60 (broad s, 1H), 8.90-8.40 (broad s, 3H), 8.42 (d, 1H), 7.77 (d, 1H), 7.63 (t, 1H), 7.53 (s, 1H), 7.47 (m, 2H), 4.50 (quad, 1H), 1.51 (d, 3H) **^{19}F NMR:** -107.2 **IR (cm^{-1}) :** 3600-2400, 1681, 1634 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{14}ClF_2N_2O_2$ $[M+H]^+$ 363.0712, measured 363.0701. α_D (589nM) = -4.4 (c = 1, DMSO) at 20°C
P85	**448**	**5-[3-(1-Aminoethyl)-2,6-difluoro-4-methoxybenzoyl]-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.60 (broad s, 1H), 8.50 (d, 1H), 8.29 (broad s, 3H), 7.93 (d, 1H), 7.58 (t, 1H), 7.37 (d, 1H), 7.23 (d, 1H), 7.23 (d, 1H), 4.60 (quad, 2H), 3.97 (s, 3H), 1.52 (d, 6H) **^{19}F NMR:** -109, -115 **IR (cm^{-1}) :** 3200-2600, 1674, 1650, 1625, 1144, 1052, 781 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{17}F_2N_2O_3$ $[M+H]^+$ 359.1207, measured 359.1212.
P88	**467**	**5-[3-(2-Aminopropan-2-yl)-2,6-difluorobenzoyl]-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.70 (s, 1H), 8.83 (broad s, 3H), 8.54 (d, 1H), 7.97 (d, 1H), 7.74 (m, 1H), 7.59 (t, 1H), 7.45 (2d, 2H), 7.40 (m, 1H), 1.70 (s, 6H) **^{19}F NMR :** -109.7, -112.6 **IR (cm^{-1}) :** 3200-2500, 1684, 1625 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{17}F_2N_2O_2$ $[M+H]^+$ 343.1258, measured 343.1265.
P90	**480**	**5-[3-(1-Aminopropyl)-2,6-difluorobenzoyl]isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.70 (broad s, 1H),

		8.54 (broad s, 3H), 8.53 (d, 1H), 7.93 (2m, 2H), 7.59 (t, 1H), 7.45 (t, 1H), 7.42 (s, 2H), 4.39 (dd, 1H), 2.01 (m, 1H), 1.88 (m, 1H), 0.82 (t, 3H) **IR (cm^{-1}) :** 3350-2500, 1675, 1630, 1026, 1006 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{17}F_2N_2O_2$ $[M+H]^+$ 343.1258, measured 343.1248 **Optical purity** (SFC: (S, S) Whelk 5µM column 4.6x250 mm ; eluant: CO_2 / (isopropanol/diethylamine:100/0.5) : 70 / 30 ; detection: 254nm) : >99%.
P91	**486**	**5-[2,6-Difluoro-3-(pyrrolidin-2-yl)benzoyl]isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.70 (broad s, 1H), 9.50 (broad s, 2H), 8.54 (d, 1H), 8.00 (d, 1H), 7.92 (m, 1H), 7.59 (t, 1H), 7.42 (m, 3H), 4.76 (dd, 1H), 3.30 (m, 2H), 2.38-2.13-1.99 (m, 4H) **IR (cm^{-1}) :** 3250-2400, 1687, 1667, 787 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{17}F_2N_2O_2$ $[M+H]^+$ 355.1258, measured 355.1267. **Optical purity** (SFC: ID 5µM column 4.6x250 mm ; eluant: CO_2 / (isopropanol/diethylamine:100/0.5) : 70 / 30 ; detection: 255nm) : >99%. (absence of **P99**)
P92	**494**	**5-{4-[(1R)-1-Aminopropyl]-2,6-difluorobenzoyl}-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.80 (broad s, 1H), 8.70 (m, 3H), 8.50 (d, 1H), 7.90 (d, 1H), 7.60 (t, 1H), 7.55 (d, 2H), 7.40 (m, 2H), 4.30 (dd, 1H), 2.05-1.85 (m, 2H), 0.85 (t, 3H) **IR (cm^{-1}) :** 3300-2100, 1670, 1624 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{17}F_2N_2O_2$ $[M+H]^+$ 343.1258, measured 343.1248.
P93	**501**	**5-[4-(1-Amino-2-methylpropyl)-2,6-difluorobenzoyl]-isoquinolin-1(2H)-one hydrochloride**

		^{1}H NMR (300-500 MHz, DMSO-d_6) **:** δ 11.67 (broad s, 1H), 8.61 (broad s, 3H), 8.54 (d, 1H), 7.90 (d, 1H), 7.59 (t, 1H), 7.49 (d, 2H), 7.39 (s, 2H), 4.13 (d, 1H), 2.21 (m, 1H), 1.06-0.81 (d, 6H) **IR (cm^{-1}) :** 3500-2500, 1626, 1524, 1480 **^{19}F NMR:** -111.3 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{19}F_2N_2O_2$ $[M+H]^+$ 357.1415, measured 357.1409.
P94	**507**	**5-[4-(1-Aminobutyl)-2,6-difluorobenzoyl]isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.70 (s, 1H), 8.80 (m, 3H), 8.55 (d, 1H), 7.90 (d, 1H), 7.60 (m, 3H), 7.40 (m, 2H), 4.35 (m, 1H), 1.90 (m, 2H), 1.25 (m, 2H), 0.90 (t, 3H) **IR (cm^{-1}) :** 3200, 2800, 1632 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{19}F_2N_2O_2$ $[M+H]^+$ 357.1415, measured 357.1422.
P95	**512**	**5-[4-(1-Amino-3-methylbutyl)-2,6-difluorobenzoyl]-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.70 (m, 1H), 8.75 (m, 3H), 8.55 (d, 1H), 7.90 (d, 1H), 7.60 (m, 3H), 7.40 (m, 2H), 4.40 (t, 1H), 1.85 (dd, 2H), 1.45 (m, 1H), 0.90 (2d, 6H) **IR (cm^{-1}) :** 3165, 2870, 1658, 1216 **HRMS (ESI):** theoretical m/z for $C_{21}H_{21}F_2N_2O_2$ $[M+H]^+$ 371.1571, measured 371.1576.
P99	**523**	**5-[2,6-Difluoro-3-(pyrrolidin-2-yl)benzoyl]isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.69 (d, 1H), 9.64 (m, 2H), 8.55 (broad d, 1H), 8.01 (d, 1H), 7.92 (m, 1H), 7.60 (t, 1H), 7.5-7.35 (m, 3H), 4.8 (dd, 1H), 3.3 (m, 2H), 2.38 (m, 1H), 2.2-2.05 (2m, 2H), 2.00 (m, 1H)

		IR (cm^{-1}) : 3300-2000, 1686, 1666 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{17}F_2N_2O_2$ $[M+H]^+$ 355.1258, measured 355.1266. **Optical purity** (SFC: ID 5µM column 4.6x250 mm ; eluant: CO_2 /(isopropanol/diethylamine:100/0.5) : 70 / 30 ; detection: 255nm) : >99%. (absence of **P91**)
P100	**528**	**5-[3-(1-Aminoethyl)-2-fluorobenzoyl]isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.57 (d, 1H), 8.48 (d, 1H), 7.96 (m, 1H), 7.80 (d, 1H), 7.66 (m, 1H), 7.55 (t, 1H), 7.50 (t, 1H), 7.30 (dd, 1H), 6.98 (d, 1H), 6.65 (m, 3H), 4.62 (quad, 1H), 1.55 (d, 3H) **IR (cm^{-1}) :** 3167, 3000-2000, 1664, 1630 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{16}FN_2O_2$ $[M+H]^+$ 311.1196, measured 311.1195. **Optical purity** (SFC: ID 3µM column 4.6x250 mm ; eluant: CO_2 /(isopropanol/diethylamine:100/0.5) : 70 / 30 ; detection: 253nm) : >99%. (absence of **P108**)
P104	**546**	**5-[4-(1-Aminoethyl)-3-fluoro-2-methoxybenzoyl]-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.57 (m, 1H), 8.59 (broad s, 3H), 8.46 (broad d, 1H), 7.71 (dd, 1H), 7.55 (t, 1H), 7.50 (dd, 1H), 7.42 (d, 1H), 7.32 (dd, 1H), 7.08 (d, 1H), 4.68 (quad, 1H), 3.57 (s, 3H), 1.57 (d, 3H) **IR (cm^{-1}) :** 3650-2400, 1678, 1651, 783, 752 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{18}FN_2O_3$ $[M+H]^+$ 341.1301, measured 341.1292
P105	**555**	**5-[4-(1-Aminoethyl)-2,6-difluoro-3-methylbenzoyl]-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6): δ 11.67 (broad s, 1H), 8.62 (broad s, 3H), 8.53 (dd, 1H), 7.88 (broad d, 1H), 7.59 (d, 1H), 7.58 (t, 1H), 7.41 (m, 2H), 4.69 (quad, 1H), 2.26

		(s, 3H), 1.53 (d, 3H). **IR (cm^{-1}) :** 3350-2000, 1672, 1626 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{17}F_2N_2O_2$ $[M+H]^+$ 343.1253, measured 343.1244
P106	**560**	**5-[3-(1-Aminoethyl)-2,6-difluoro-4-methylbenzoyl]-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.7 (m, 1H), 8.55 (m, 4H), 8.00 (d, 1H), 7.60 (t, 1H), 7.40 (m, 2H), 7.25 (d, 1H), 4.60 (m, 1H), 1.50 (m, 6H). **IR (cm^{-1}) :** 2859, 1622, 789-747-709 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{17}F_2N_2O_2$ $[M+H]^+$ 343.1253, measured 343.1246
P107	**562**	**5-[4-(1-Aminoethyl)-3-ethyl-2,6-difluorobenzoyl]-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.68 (broad s, 1H), 8.59 (broad s, 3H), 8.54 (broad d, 1H), 7.88 (broad d, 1H), 7.64 (d, 1H), 7.59 (t, 1H), 7.41 (m, 2H), 4.67 (quad, 1H), 2.70 (m, 2H), 1.55 (d, 3H), 1.13 (t, 3H) **IR (cm^{-1}) :** 3200-2500, 1674, 789 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{19}F_2N_2O_2$ $[M+H]^+$ 357.1409, measured 357.1403.
P128	**698**	**5-{4-[Amino(3-methoxyphenyl)methyl]-2,6-difluoro-benzoyl}isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 11.65 (broad s, 1H), 9.30 (broad s, 3H), 8.50 (d, 1H), 7.90 (d, 1H), 7.55 (m, 3H), 7.40 (m, 3H), 7.30 (s, 1H), 7.15 (d, 1H), 7.00 (dd, 1H), 5.75 (s, 1H), 3.80 (s, 3H) **IR (cm^{-1}) :** 3300-2400, 1661, 1627-1591, 1259, 783 **HRMS (ESI) :** theoretical m/z for $C_{24}H_{19}F_2N_2O_3$ $[M+H]^+$ 421.1364, measured 421.1346
P129	**704**	**5-[4-(1-Amino-2-cyclohexylethyl)-2,6-difluorobenzoyl]-isoquinolin-1(2H)-one hydrochloride**

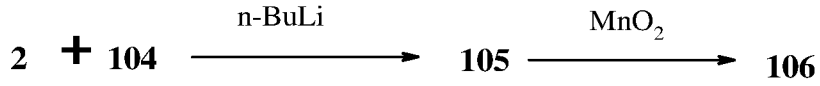
		^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 11.70 (broad s, 1H), 8.75 (m, 3H), 8.55 (d, 1H), 7.90 (d, 1H), 7.60 (m, 3H), 7.40 (m, 2H), 4.45 (m, 1H), 1.95-0.85 (3m, 13H) **IR (cm^{-1}) :** 3387, 3150-2600, 2923-2851, 1661-1631, 1591, 1260 **HRMS (ESI) :** theoretical m/z for $C_{24}H_{25}F_2N_2O_2$ $[M+H]^+$ 411.1884, measured 411.1869
P130	**708**	**5-(4-{1-[(Cyclohexylmethyl)amino]ethyl}-2,6-difluorobenzoyl)isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 8.50 (d, 1H), 7.85 (d, 1H), 7.55 (m, 3H), 7.35 (s, 2H), 4.45 (m, 1H), 2.75 (m, 1H), 2.60 (m, 1H), 1.75-0.90 (3m, 11H), 1.65 (d, 3H) **IR (cm^{-1}) :** 3163, 3019, 2921-2854, 2661, 1692-1673, 1634-1592, 1437, 1237 **HRMS (ESI) :** theoretical m/z for $C_{25}H_{27}F_2N_2O_2$ $[M+H]^+$ 425.2041, measured 425.2042
P131	**710**	**5-[4-(1-Aminoethyl)-2,6-difluorobenzoyl]-3-methylisoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.80-11.60 (m, 1H), 9.00-8.60 (m, 3H), 8.50 (dd, 1H), 7.85 (dd, 1H), 7.55 (d, 2H), 7.50 (t, 1H), 7.30 (broad s, 1H), 4.55 (quad, 1H), 2.30 (s, 3H), 1.55 (d, 3H) **IR (cm^{-1}) :** 3200-2300, 1672 **HRMS (ESI) :** theoretical m/z for $C_{19}F_2H_{17}N_2O_2$ $[M+H]^+$ 343.1258, measured 343.1268; theoretical m/z for $C_{19}H_{17}F_2N_2O_2$ $[M+H-NH_3]^+$ 326.0993, found 326.0991

P133	**730**	**5-{4-(1-Aminoethyl)-5-[2-(dimethylamino)ethoxy]-2-fluorobenzoyl}isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.70 (m, 1H), 10.80 (m, 1H), 8.60 (m, 3H), 8.50 (d, 1H), 7.80 (d, 1H), 7.60 (t, 1H), 7.60 (d, 1H), 7.40 (d, 1H), 7.35 (dd, 1H), 7.00 (t, 1H), 5.00 (quad, 1H), 4.45 (m, 2H), 3.60 (m, 2H), 2.85 (broad s, 6H), 1.55 (d, 3H) **IR (cm^{-1}) :** 3367, 2800-2300, 1655, 1627, 1481 **HRMS (ESI) :** theoretical m/z for $C_{22}H_{25}FN_3O_3$ $[M+H]^+$ 398.1880, measured 398.1881
P134	**732**	**5-[4-(2-Aminopropan-2-yl)-2,6-difluorobenzoyl]-3-methylisoquinolin-1(2H)-one methanesulphonate** **^{1}H NMR** (400 MHz, DMSO-d_6)**:** δ 11.80-11.60 (m, 1H), 8.50 (d, 1H), 8.50-8.30 (m, 3H), 7.85 (d, 1H), 7.55-7.45 (m, 3H), 7.30 (s, 1H), 2.30 (broad s, 3H), 1.70 (s, 6H) **IR (cm^{-1}) :** 3300-2000, 1675, 1632, 1176 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{19}F_2N_2O_2$ $[M+H]^+$ 357.1415, measured 357.1412
P135	**734**	**5-[4-(1-Aminoethyl)-2,6-difluoro-3-methoxybenzoyl]-3-methylisoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 11.70 (m, 1H), 8.70 (m, 3H), 8.50 (d, 1H), 7.95 (d, 1H), 7.65 (dd, 1H), 7.50 (t, 1H), 7.30 (s, 1H), 4.70 (quad, 1H), 3.90 (s, 3H), 2.30 (s, 3H), 1.55 (d, 3H) **IR (cm^{-1}) :** 3430-2250, 1666, 1632, 1595, 838-687 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{19}F_2N_2O_3$ $[M+H]^+$ 373.1364, measured 373.1365
P137	**741**	**5-{4-[-1-Aminoethyl]-2-fluoro-3-methoxybenzoyl}-isoquinolin-1(2H)-one hydrochloride, enantiomer 2** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.60 (d, 1H), 8.70 (broad s, 3H), 8.45 (d, 1H), 7.80 (d, 1H), 7.58 (t, 1H), 7.45 (dd, 1H), 7.42 (dd, 1H), 7.30 (dd, 1H), 6.95 (d, 1H), 4.68

		(quad, 1H), 3.93 (s, 3H), 1.55 (d, 3H) **IR (cm^{-1}) :** 3300-2200, 1664, 1621 **HRMS (ESI) :** theoretical m/z for $C_{19}FH_{18}N_2O_3$ $[M+H]^+$ 341.1301, measured 341.1298; theoretical m/z for $C_{19}H_{18}FN_2O_3$ $[M+H-NH_3]^+$ 324.1012, found 324.1036 **Optical purity** (AD-H 5µM column 4.6x250 mm ; eluant: EtOH/CH_3CN/butylamine:95/5/0.1) ; detection: 260nm) : >99%. (absence of **P67**) α_D (589nM) = 6.85 (c = 0.01 g/mL, MeOH) at 20°C

Protocol XXII : Alternative method for the preparation of compounds of formula (I) wherein X represents -C(=O)

Compounds of formula (I) wherein X represents -C(=O) can also be prepared by coupling reaction by halogen-metal exchange of a halo-isoquinoline compound according to the example of the synthesis of intermediate **106** :



Intermediate 105 :

2,2,2-Trifluoro-N-(1-{3-fluoro-4-[hydroxy(isoquinolin-5-yl)methyl]-5-methoxy-phenyl}ethyl)acetamide

To a solution of intermediate **2** (1 g, 4.8 mmoles) in anhydrous THF (15 mL), under N_2 and cooled to -78°C, there is added a solution of n-BuLi (2.5N/hexane) (2.1 mL), the temperature being maintained below -70°C. The resulting solution is stirred for 20 minutes at -78°C, and then a solution of intermediate **104** (1.3 g, 4.4 mmoles) in anhydrous THF (15 mL) is added, the temperature being maintained below -70°C. The reaction mixture is stirred for 1 hour at -78°C and then for 1½ h at -50°C, and it is then hydrolysed and extracted with AcOEt. The organic phase is washed with water, dried over $MgSO_4$ and evaporated in vacuo. The residue is purified by flash chromatography on silica (eluant : CH_2Cl_2 / AcOEt : gradient : 100/0 to 90/10). Intermediate **105** (1 g) is obtained.

^{1}H NMR (300 MHz, DMSO-d_6) : δ 9.80 (broad s, 1H), 9.27 (s, 1H), 8.42 (d, 1H), 8.14 (broad d, 1H), 8.00 (d, 1H), 7.75 (d, 1H), 7.71 (t, 1H), 6.94 (broad s, 1H), 6.70 (broad d, 1H), 6.65 (dl, 1H), 5.98 (d, 1H), 4.97 (m, 1H), 3.93 (s, 3H), 1.41 (2d, 3H).

IR (cm^{-1}) : 3400-3100, 1707, 1209-1183-1157, 733

Intermediate 106 :

2,2,2-Trifluoro-N-{1-[3-fluoro-4-(isoquinolin-5-ylcarbonyl)-5-methoxyphenyl]ethyl}-acetamide

To a solution of (0.68 g, 1.61 mmoles) of intermediate **105** in methylene chloride (100 mL) there is added MnO_2 (2.6 g, 30 mmoles). The mixture is stirred for 17 hours at ambient temperature, and then the MnO_2 is filtered off. Evaporation of the filtrate yields intermediate **106** (450 mg) in the form of a solid.

^{1}H NMR (300 MHz, DMSO-d_6) : δ 9.90 (m, 1H), 9.50 (s, 1H), 8.75 and 8.70 (2d, 2H), 8.45 (d, 1H), 8.00 (d, 1H), 7.80 (t, 1H), 7.10 (broad s, 1H), 7.00 (broad d, 1H), 5.10 (q, 1H), 3.70 (s, 3H), 1.50 (d, 3H)

IR (cm^{-1}) : 3125 (weak), 1717, 1677, 1621 and 1590, 1570, 1208-1095, 833-667

This sequence was used to prepare the following intermediates:

Intermediate 20 :

2,2,2-Trifluoro-N-{(1R)-1-[4-(isoquinolin-5-ylcarbonyl)-3-methoxyphenyl]ethyl}-acetamide

Obtained by oxidation of the intermediate resulting from the coupling of **18** and **2**

^{1}H NMR (300 MHz, DMSO-d_6) : δ 9.90 (broad s, 1H), 9.40 (s, 1H), 8.60 (d, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 7.80 (d, 1H), 7.42 (t, 1H), 7.50 (d, 1H), 7.15 (s, 1H), 7.10 (d, 1H), 5.10 (m, 1H), 3.53 (s, 3H), 1.50 (d, 3H)

IR (cm^{-1}): 3125, 1708, 1653, 1608, 1568, 1204-1181-1149, 831-760-734

Intermediate 96

2,2,2-Trifluoro-N-{(1R)-1-[8-(isoquinolin-5-ylcarbonyl)-3,4-dihydro-2H-chromen-5-yl]ethyl}acetamide

Obtained by oxidation of the intermediate resulting from the coupling of **94** and **2**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 10.00 (broad s, 1H), 9.50 (s, 1H), 8.60 (d, 1H), 8.35 (m, 2H), 7.85 (d, 1H), 7.70 (t, 1H), 7.35 (d, 1H), 7.10 (d, 1H), 5.15 (quad, 1H), 3.80 (t, 2H), 2.80 (2m, 2H), 1.85 (quint, 2H), 1.45 (d, 3H)

IR (cm^{-1}) : 3395, 1708, 1652, 1610, 1595, 1572 . 1200-1148, 830-700

Intermediate 264 :

N-[(1R)-1-{8-[(1-Ethoxyisoquinolin-5-yl)carbonyl]-3,4-dihydro-2H-chromen-5-yl}ethyl]-2,2,2-trifluoroacetamide

Obtained by oxidation of the intermediate resulting from the coupling of **94** and **124**

^{1}H NMR (300 MHz, DMSO-d_6) : δ 10.0 (m, 1H), 8.40 (d, 1H), 8.10 (d, 1H), 7.9-7.75 (2d, 2H), 7.65 (t, 1H), 7.35 (d, 1H), 7.10 (d, 1H), 5.15 (m, 1H), 4.55 (quad, 2H), 3.80 (m, 2H), 2.9-2.65 (m, 2H), 1.95-1.8 (m, 2H), 1.5-1.35 (d and t, 6H)

IR (cm-1) : 3294, 1724, 1700, 1656, 1100-1280

LCMS [M+H]+ = 472

Optical purity (SFC: IA 3µM column 4.6x250 mm; CO_2 / (ethanol/diethylamine:100/0.5) : 80 / 20; Detection: 215nm) : > 99%.

α_D (589nM) = +65.93 (c=0.010g/mL, MeOH, 20°C).

Intermediate 359 :

N-[(1S)-1-{8-[(1-Ethoxyisoquinolin-5-yl)carbonyl]-3,4-dihydro-2H-chromen-5-yl}ethyl]-2,2,2-trifluoroacetamide

Obtained by oxidation of the intermediate resulting from the coupling of **357** and **124**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 9.99 (s, 1H), 8.41 (d, 1H), 8.09 (d, 1H), 7.84 (d, 1H), 7.80 (d, 1H), 7.66 (dd, 1H), 7.36 (d, 1H), 7.09 (d, 1H), 5.16 (quad, 1H), 4.56 (quad, 2H), 3.80 (m, 2H), 2.87 (dt, 1H), 2.76 (dt, 1H), 1.88 (m, 2H), 1.47 (m, 6H)

IR (cm^{-1}) : 3286, 1702, 1651

Optical purity (SFC: IA 3µM column 4.6x250 mm; CO_2 / (ethanol/diethylamine:100/0.5) : 80 / 20; Detection: 215nm) : > 99%.

Intermediate 399 :

tert-Butyl (2-{3-chloro-4-[(1-ethoxy-4-methylisoquinolin-5-yl)carbonyl]phenyl}-propan-2-yl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **193** and **301**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.45 (d, 1H), 7.92 (s, 1H), 7.65 (d and t, 3H), 7.50 (d, 1H), 7.45 (dd, 1H), 7.38 (broad s, 1H), 4.52 (quad, 2H), 2.18 (s, 3H), 1.55 (s, 6H), 1.45 (t, 3H), 1.35 (broad s, 9H)

IR (cm^{-1}): 3313, 1684-1658

Intermediate 455 :

N-{8-[(1-Ethoxyisoquinolin-5-yl)carbonyl]-3,4-dihydro-2H-chromen-4-yl}-2,2,2-trifluoroacetamide

Obtained by oxidation of the intermediate resulting from the coupling of **453** and **124**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 9.95 (broad s, 1H), 8.42 (d, 1H), 8.10 (d, 1H), 7.90 (d, 1H), 7.82 (d, 1H), 7.67 (d, 1H), 7.41 (d, 1H), 7.38 (d, 1H), 7.09 (t, 1H), 5.15 (m, 1H), 4.57 (quad, 2H), 3.98 (t, 2H), 2.05 (m, 1H), 1.92 (m, 1H), 1.46 (t, 3H)

IR (cm^{-1}) : 3280, 1703, 1655

Intermediate 514 :

N-[(1R)-1-{8-[(1-Ethoxy-4-methylisoquinolin-5-yl)carbonyl]-3,4-dihydro-2H-chromen-5-yl}ethyl]-2,2,2-trifluoroacetamide

Obtained by oxidation of the intermediate resulting from the coupling of **94** and **302**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 10.00 (m, 1H), 7.85 (s, 1H), 7.60 (m, 2H), 7.50 (dd, 1H), 7.10 (d, 1H), 5.15 (quad, 1H), 4.50 (quad, 2H), 3.70 (t, 2H), 2.80 (m, 2H), 2.10 (s, 3H), 1.80 (m, 2H), 1.45 (t, 6H)

^{19}F NMR: -73, **IR (cm^{-1})** : 3270, 1722

Intermediate 544 :

N-[(1R)-1-{4-[(1-Ethoxyisoquinolin-5-yl)carbonyl]-3-methoxyphenyl}ethyl]-2,2,2-trifluoroacetamide

Obtained by oxidation of the intermediate resulting from the coupling of **18** and **124**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 10.00 (m, 1H), 8.4 (d, 1H), 8.05 (d, 1H), 7.8-7.75 (d and dd, 2H), 7.65 (dd, 1H), 7.5 (d, 1H), 7.15 (d, 1H), 7.05 (d, 1H), 5.01 (quad, 1H), 4.55 (quad, 2H), 3.5 (s, 3H), 1.5 (d, 3H), 1.45 (t, 3H)

IR (cm^{-1}) : 3290, 1698, 1651

Intermediate 641 :

2,2,2-Trifluoro-N-{(1S)-1-[4-(isoquinolin-5-ylcarbonyl)-3-methoxyphenyl]ethyl}-acetamide

Obtained by oxidation of the intermediate resulting from the coupling of **639** and **2**

^{1}H NMR (300 MHz, DMSO-d6) **:** δ 10.00 (broad s, 1H, NH), 9.45 (s, 1H), 8.60 (d, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 7.85 (d, 1H), 7.75 (t, 1H), 7.52 (d, 1H), 7.20 (s, 1H), 7.10 (d, 1H), 5.10 (m, 1H), 3.55 (s, 3H), 1.53 (d, 3H)

IR (cm^{-1}) : 3222, 1710, 1651, 1608, 1569

Intermediate 736 :

tert-Butyl (2-{3-chloro-4-[(1-ethoxy-3-methylisoquinolin-5-yl)carbonyl]phenyl}-propan-2-yl)carbamate

Obtained by oxidation of the intermediate resulting from the coupling of **397** and **293**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.42 (d, 1H), 7.85 (s, 1H), 7.70 (d, 1H), 7.60 (t, 1H), 7.52 (d, 1H), 7.45 (s and d, 2H), 7.35 (broad s, 1H, NH), 4.52 (quad, 2H), 2.50 (s, 3H), 1.55 (s, 6H), 1.45 (t, 3H), 1.30 (broad s, 9H)

IR (cm^{-1}) : 3259, 1697-1663

Intermediate 750 :

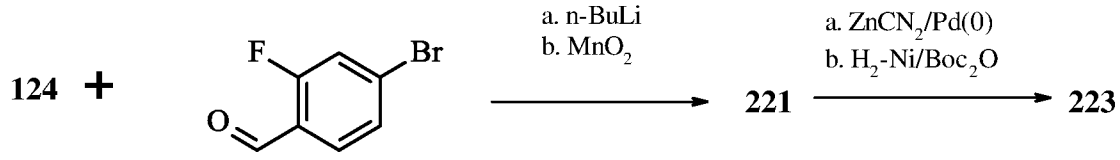
N-({8-[(1-Ethoxyisoquinolin-5-yl)carbonyl]-3,4-dihydro-2H-chromen-4-yl}methyl)-2,2,2-trifluoroacetamide

Obtained by oxidation of the intermediate resulting from the coupling of **748** and **125**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.65 (s, 1H, NH), 8.40 (d, 1H), 8.09 (d, 1H), 7.82 (d, 1H), 7.81 (dd, 1H), 7.65 (t, 1H), 7.40-7.37 (2d, 2H), 7.07 (t, 1H), 4.55 (quad., 2H), 3.83 (m, 2H), 3.55 (dd, 1H), 3.38 (dd, 1H), 3.08 (m, 1H), 1.87 (m, 1H), 1.70 (m, 1H), 1.47 (t, 3H)

IR (cm^{-1}) : 3307, 1709, 1653, 1568, 1277, 1155

Intermediate 221 was obtained by oxidation of **220** resulting from the coupling between 4-bromo-2-fluorobenzaldehyde and intermediate **124.**



Intermediate 221 :

(4-Bromo-2-fluorophenyl)(1-ethoxyisoquinolin-5-yl)methanone

Step 1 :

To a solution of intermediate **124** (2 g, 7.94 mmoles) in anhydrous THF (40 mL), cooled to -70°C, there is added, in the course of 20 minutes, a 2.5N solution of n-BuLi in hexane (3.2 mL, 8 mmoles). The resulting solution is stirred for 10 minutes at -70°C, and then a solution of commercial 4-bromo-2-fluoro-benzaldehyde (1.66 g, 8.17 mmoles) in THF (15 mL) is added in the course of 15 minutes. The reaction mixture is stirred at -70°C until the starting product has disappeared, and is hydrolysed with a saturated aqueous ammonium chloride solution. The organic phase is extracted with ethyl ether, washed with a saturated aqueous NaCl solution, dried over $MgSO_4$, filtered and evaporated in vacuo. By recrystallisation from acetonitrile, the expected intermediate (1.8 g) is obtained.

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.16 (d, 1H), 7.98 (d, 1H), 7.80 (d, 1H), 7.62 (t, 1H), 7.50 (d, 1H),7.42 (d, 1H), 7.38 (m, 2H), 6.52 (d, 1H), 6.32 (d, OH), 4.50 (quad., 2H), 1.40 (t, 3H)

IR (cm^{-1}) : 3252, 1620-1602-1571, 1209-1163, 1038, 867-801-755

Step 2 :

Oxidation of the intermediate obtained above in the presence of MnO_2 yields intermediate **221**.

^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.48 (d, 1H), 8.10 (d, 1H), 7.95 (d, 1H), 7.78 to 7.6 (m, 5H), 4.57 (quad, 2H), 1.45 (t, 3H)

IR (cm^{-1}) : 1650

Intermediate **223** was obtained starting from **221** :

Intermediate 222 :

4-[(1-Ethoxyisoquinolin-5-yl)carbonyl]-3-fluorobenzonitrile

To a solution of intermediate **221** (2 g, 5.34 mmoles) in DMF (10 mL), degassed with nitrogen, at ambient temperature, there are added $Zn(CN)_2$ (0.75 g, 6.41 mmoles) and $Pd(PPh_3)_4$ (0.31 g). The reaction mixture is heated at 100°C for 45 minutes and is then hydrolysed with water. The organic phase is extracted with ethyl acetate, washed 4 times with water and with a saturated aqueous NaCl solution, dried over $MgSO_4$, filtered and evaporated in vacuo. The residue is purified by flash chromatography on silica (eluant : CH_2Cl_2-AcOEt gradient: 100/0 to 95-5. The expected intermediate **222** (1.6 g) is obtained in the form of a solid.

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.51 (d, 1H), 8.17 (d, 1H), 8.08 (d, 1H), 7.99 (d, 1H), 7.94 (d, 1H), 7.89 (m, 2H), 7.70 (t, 1H), 4.58 (quad, 2H), 1.46 (t, 3H)

IR (cm^{-1}) : 1651, 2239

Intermediate 223 :

tert-Butyl {4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3-fluorobenzyl}carbamate

To a solution of intermediate **222** (250 mg, 0.78 mmole) in ethanol (5 mL) there are added di-tert-butyl dicarbonate (220 mg, 1.04 mmoles) and Raney nickel (200 mg). The mixture is hydrogenated at atmospheric pressure and ambient temperature for 18 hours and then heated at 70°C for 2½ hours. After cooling, the catalyst is filtered off. The filtrate is evaporated to dryness and purified by flash chromatography on silica (eluant : CH_2Cl_2-AcOEt gradient: 99-1 to 90-10). Intermediate **223** (190 mg) is obtained.

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.45 (d, 1H), 8.08 (d, 1H), 7.89 (d, 1H), 7.72 to 7.62 (m, 3H), 7.53 (t, 1H), 7.25 (dl, 1H), 7.16 (dl, 1H), 4.56 (quad., 2H), 4.23 (d, 2H), 1.46 (t, 3H), 1.40 (broad s, 9H)

IR (cm^{-1}) : 3360, 1740, 1683-1662, 1525, 1278-1159, 810-783-752

The ketone intermediates protected in the form of trifluoro-acetamides were deprotected in a basic medium according to the example of intermediate **56**.

Intermediate 21:

{4-[(1R)-1-Aminoethyl]-2-methoxyphenyl}(isoquinolin-5-yl)methanone

^{1}H NMR (300 MHz, DMSO-d_6) : δ 9.50 (s, 1H), 8.60 (d, 1H), 8.35 (d, 1H), 8.25 (d, 1H), 7.80 (d, 1H), 7.70 (t, 1H), 7.50 (d, 1H), 7.20 (d, 1H), 7.12 (d, 1H), 4.10 (quad, 1H), 3.52 (s, 3H), 2.10 (m, 2H), 1.35 (d, 3H)

IR (cm^{-1}) : 3344, 3277, 1646, 1609

Intermediate 265:

{5-[(1R)-1-Aminoethyl]-3,4-dihydro-2H-chromen-8-yl}(1-ethoxyisoquinolin-5-yl)methanone

Obtained starting from intermediate **264**

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 (d, 1H), 8.05 (d, 1H), 7.80 (m, 1H), 7.70 (m, 1H), 7.65 (t, 1H), 7.30 (d, 1H), 7.25 (d, 1H), 4.55 (q, 2H), 4.20 (q, 1H), 3.75 (m, 2H), 2.85-2.70 (2m, 2H), 2.30-1.90 (m, 2H), 1.80 (m, 2H), 1.25 (d, 3H), 1.45 (t, 3H)

IR (cm^{-1}): 3383, 3269, 1643

Intermediate 360 :

{5-[(1S)-1-Aminoethyl]-3,4-dihydro-2H-chromen-8-yl}(1-ethoxyisoquinolin-5-yl)methanone

^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.40 (d, 1H), 8.07 (d, 1H), 7.77 (m, 2H), 7.65 (dd, 1H), 7.32 (d, 1H), 7.27 (d, 1H), 4.56 (quad, 2H), 4.19 (quad, 1H), 3.75 (t, 2H), 2.85 (dt, 1H), 2.69 (dt, 1H), 1.83 (m, 4H), 1.47 (t, 3H), 1.24 (d, 3H)

IR (cm^{-1}) : 3387, 3290, 1643, 1612

Intermediate 456 :

(4-Amino-3,4-dihydro-2H-chromen-8-yl)(1-ethoxyisoquinolin-5-yl)methanone

^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.40 (d, 1H), 8.08 (d, 1H), 7.81 (d, 1H), 7.79 (d, 1H), 7.64 (t, 1H), 7.62 (dd, 1H), 7.31 (dd, 1H), 7.00 (t, 1H), 4.55 (quad, 2H), 3.94 (m, 1H), 3.90 (m, 1H), 3.83 (m, 1H), 2.04 (broad s, 2H), 1.90 (m, 1H), 1.64 (m, 1H), 1.45 (t, 3H)

IR (cm^{-1}): 3361, 3285, 1651, 1585, 1272, 1235, 807, 756

Intermediate 515 :

{5-[(1R)-1-Aminoethyl]-3,4-dihydro-2H-chromen-8-yl}(1-ethoxy-4-methylisoquinolin-5-yl)methanone

^{1}H NMR (500 MHz, DMSO-d_6) : δ 8.31 (d, 1H), 7.86 (s, 1H), 7.57 (t, 1H), 7.52 (d, 1H), 7.52 (d, 1H), 7.28 (d, 1H), 4.51 (quad, 2H), 4.17 (quad, 1H), 3.66 (m, 2H), 2.81 (m, 1H), 2.66 (m, 1H), 2.17 (s, 3H), 1.79 (m, 2H), 1.45 (t, 3H), 1.22 (d, 3H), 1.95 (broad s, 2H)

IR (cm^{-1}) : 3379, 3310, 1653

Intermediate 545 :

{4-[(1R)-1-Aminoethyl]-2-methoxyphenyl}(1-ethoxyisoquinolin-5-yl)methanone

^{1}H NMR (400 MHz, DMSO-d_6) : δ 8.39 (dt, 1H), 8.05 (d, 1H), 7.74 (dd, 1H), 7.70 (dd, 1H), 7.64 (dd, 1H), 7.45 (d, 1H), 7.18 (d, 1H), 7.10 (dd, 1H), 4.55 (quad, 2H), 4.05 (quad, 1H), 3.50 (s, 3H), 1.90 (broad s, 2H), 1.46 (t, 3H), 1.29 (d, 3H)

IR (cm^{-1}): 3365, 3300, 1657, 1245, 1033, 810, 788

Intermediate 751 :

[4-(Aminomethyl)-3,4-dihydro-2H-chromen-8-yl](1-ethoxyisoquinolin-5-yl)-methanone

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 (d, 1H), 8.05 (d, 1H), 7.78 (d, 1H), 7.78 (d, 1H), 7.62 (t, 1H), 7.45 (d, 1H), 7.30 (d, 1H), 6.98 (t, 1H), 4.53 (quad, 2H), 3.80 (m, 2H), 2.90-2.65 (2dd, 2H), 2.74 (m, 1H), 1.93-1.80 (2m, 2H), 1.50 (broad s, 2H), 1.48 (t, 3H)

IR (cm^{-1}) : 3381, 1654

Intermediates **223**, **265**, **360**, **399**, **456**, **515**, **545** and **751** were treated in an acidic medium to yield the final products, according to the procedures described for product **P17**.

Product	Obtained from	Nomenclature Analytical description
P3	**20**	**{4-[(1R)-1-Aminoethyl]-2-methoxyphenyl}(isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 9.90 (s, 1H), 8.75 (d, 1H), 8.56 (dl, 2H), 8.05 (dd, 1H), 8.00 (t, 1H), 7.65 (d, 1H), 7.55 (d, 1H), 7.30 (dd, 1H), 4.50 (m, 1H), 3.55 (s, 3H), 1.60 (d, 3H) **IR (cm-1):** 3300-1980, 1656 **HRMS (ESI) :** theoretical m/z for C19H19N2O2 [M+H]+ 307.1447, measured 307.1472 **Optical purity** (ADH 3µm column 4.6x250 mm ; eluant : CH_3CN/isopropanol/triethylamine) : 85/15/0.1 ; Detection: 325nm : >99%. (absence of **P119**) α_D (589nM) = 1.15 (c = 0.011 g/mL, MeOH) at 20°C
P13	**96**	**{5-[(1R)-1-Aminoethyl]-3,4-dihydro-2H-chromen-8-yl}(isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 9.80 (s, 1H), 8.70 (d, 1H), 8.60 (m, 5H), 8.05 (d, 1H), 7.90 (t, 1H), 7.50 (d, 1H), 7.30 (d, 1H), 4.55 (m, 1H), 3.80 (t, 2H), 2.80 (dd, 2H), 1.90 (m, 2H), 1.50 (d, 3H) **IR (cm^{-1}) :** 3000-2500, 1650 **HRMS (ESI) :** theoretical m/z for $C_{21}H_{21}N_2O_2$ $[M+H]^+$ 333.1603, measured 333.1593

P14	**106**	**[4-(1-Aminoethyl)-2-fluoro-6-methoxyphenyl]-(isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 9.76 (s, 1H), 8.98 (d, 1H), 8.79 (d, 1H), 8.76 (broad s, 3H), 8.65 (d, 1H), 8.13 (d, 1H), 7.93 (t, 1H), 7.42 (s, 1H), 7.23 (d, 1H), 4.51 (quint, 1H), 3.72 (s, 3H), 1.59 (d, 1H) **IR (cm^{-1}) :** 3000-2500, 1673 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{18}FN_2O_2$ $[M+H]^+$ 352.1352, measured 325.1352
P45	**265**	**5-({5-[(1R)-1-Aminoethyl]-3,4-dihydro-2H-chromen-8-yl}carbonyl)isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.60 (s, 1H), 8.80-8.30 (m, 3H), 8.40 (broad d, 1H), 7.65 (dd, 1H), 7.50 (t, 1H), 7.40 (d, 1H), 7.30 (2m, 2H), 7.10 (d, 1H), 4.50 (quad, 1H), 3.85 (m, 2H), 2.85-2.75 (2m, 2H), 1.90 (m, 2H), 1.50 (d, 2H) **IR (cm^{-1}) :** 3500-1950, 1632 **HRMS (ESI) :** theoretical m/z for $C_{21}H_{21}N_2O_3$ $[M+H]^+$ 349.1552, measured 349.1543. **αD 589nM** = -19.28 (c = 0.00688 g/mL, MeOH) at 21°C
P62	**359**	**5-({5-[(1S)-1-Aminoethyl]-3,4-dihydro-2H-chromen-8-yl}carbonyl)isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.50 (d, 1H), 8.48 (m, 3H), 8.41 (d, 1H), 7.66 (d, 1H), 7.51 (t, 1H), 7.38 (d, 1H), 7.27 (m, 2H), 7.09 (d, 1H), 4.54 (quad, 1H), 3.86 (t, 2H), 2.88 (m, 1H), 2.73 (m, 1H), 1.88 (m, 2H), 1.50 (d, 3H) **IR (cm-1)** : 3600-2300, 1632 **HRMS (ESI) :** theoretical m/z for C21H21N2O3 [M+H]+ 349.1552, measured 349.1564 **Optical purity** (SFC: AD 3µm column 4.6x250 mm ; Composition: CO_2 /(ethanol/n-butylamine:100/0.5) : 65/

		35 ; Detection:254nm : >99%. (absence of **P45**)
P71	**399**	**5-[4-(2-Aminopropan-2-yl)-2-chlorobenzoyl]-4-methylisoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) : δ 11.50 (d, 1H), 8.82 (m, 3H), 8.46 (m, 1H), 7.85 (d, 1H), 7.78 (d, 1H), 7.68 (dd, 1H), 7.52 (m, 2H), 7.14 (d, 1H), 1.96 (s, 3H), 1.67 (s, 6H). **IR (cm^{-1})** : 3300-2300, 1684, 1662 **HRMS (ESI)** : theoretical m/z for $C_{20}H_{20}ClN_2O_2$ [M+H]+ 355.1213, measured 355.1212; theoretical m/z for $C_{20}H_{20}ClN_2O_2$ [M+H-NH3]+ 338.0948, measured 338.0934
P86	**455**	**5-[(4-Amino-3,4-dihydro-2H-chromen-8-yl)carbonyl]-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) : δ 11.50 (broad s, 1H), 8.61 (broad s, 3H), 8.42 (d, 1H), 7.75 (2d, 2H), 7.50 (t, 1H), 7.45 (d, 1H), 7.29 (m, 1H), 7.12 (d + t, 2H), 4.55 (t, 1H), 4.10 (m, 1H), 4.00 (m, 1H), 2.20 (m, 1H), 2.05 (m, 1H) **IR (cm^{-1}) :** 3100-2700, 1686, 1667, 1237, 793, 761 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{17}N_2O_3$ [M+H]+ 321.1239, measured 321.1212.
P96	**514**	**5-({5-[(1R)-1-Aminoethyl]-3,4-dihydro-2H-chromen-8-yl}carbonyl)-4-methylisoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) : δ 11.35 (d, 1H), 8.50 (m, 3H), 8.36 (dd, 1H), 7.60 (d, 1H), 7.48 (t, 1H), 7.37 (dd, 1H), 7.29 (d, 1H), 7.03 (m, 1H), 4.53 (m, 1H), 3.78 (m, 2H), 2.82+2.71 (m, 2H), 1.91 (s, 3H), 1.82 (m, 2H), 1.49 (d, 3H). **IR (cm^{-1}) :** 3500-2300, 3350, 1635 **HRMS (ESI) :** theoretical m/z for $C_{22}H_{23}N_2O_3$ [M+H]+

		363.1709, measured 363.1706.
P103	**544**	**5-{4-[(1R)-1-Aminoethyl]-2-methoxybenzoyl}-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) : δ 11.50 (broad s, 1H), 8.46 (broad s, 3H), 8.41 (d, 1H), 7.63 (d, 1H), 7.52 (d, 1H), 7.51 (t, 1H), 7.41 (broad s, 1H), 7.21 (dl, 1H), 7.27 (m, 1H), 7.03 (d, 1H), 4.47 (quad, 1H), 3.61 (s, 3H), 1.56 (d, 3H) **IR (cm-1) :** 3300-2400, 1665, 1643, 1617, 794 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{19}N_2O_3$ [M+H]+ 323.1396, measured 323.1386.
P119	**641**	**{4-[(1S)-1-Aminoethyl]-2-methoxyphenyl}(isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) : δ 9.92 (s, 1H), 8.88 (broad s, 3H), 8.76 (dd, 1H), 8.70 (m, 2H), 8.10 (dd, 1H), 8.00 (t, 1H), 7.64 (d, 1H), 7.60 (d fine, 1H), 7.30 (dd, 1H), 4.50 (m, 1H), 3.55 (s, 3H), 1.60 (d, 3H) **IR (cm^{-1}) :** 3000-2000, 1656 **HRMS (ESI) :** theoretical m/z for C19H19N2O2 [M+H]+ 307.1447, measured 307.1447. **Optical purity** (ADH 3µm column 4.6x250 mm ; eluant : CH_3CN/isopropanol/triethylamine): 85/15/0.1 ; Detection: 325nm : >99%. (absence of **P3**)
P136	**736**	**5-[4-(2-Aminopropan-2-yl)-2-chlorobenzoyl]-3-methylisoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) : δ 11.66 (s, 1H), 8.80 (m, 3H), 8.43 (d, 1H), 7.81 (d, 1H), 7.69 (dd, 1H), 7.65 (d, 1H), 7.60 (d, 1H), 7.45 (t, 1H), 7.17 (broad s, 1H), 2.28 (s, 3H), 1.68 (s, 6H) **IR (cm^{-1})** : 3200-2300, 1639. **HRMS (ESI)** : theoretical m/z for C20H20ClN2O2 [M+H]+ 355.1213, measured 355.1212

P139	**750**	**5-{[4-(Aminomethyl)-3,4-dihydro-2H-chromen-8-yl]-carbonyl}isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) : δ 11.50 (s, 1H), 8.40 (d, 1H), 8.20 (m, 3H), 7.70 (d, 1H), 7.50 (t, 1H), 7.50 (d, 1H), 7.35 (d, 1H), 7.30 (dd, 1H), 7.05 (t, 1H), 7.05 (d, 1H), 3.95 (m, 2H), 3.25 (m, 1H), 3.20-3.05 (m, 2H), 2.00 (m, 2H) **IR (cm^{-1}) :** 3400, 3100, 2900-2800, 1647-1626 **HRMS (ESI) :** theoretical m/z for C20H19N2O3 [M+H]+ 335.1396, measured 335.1400

Protocol XXIII : Alternative method for the preparation of compounds of formula (I) wherein X represents -C(=O)

Compounds of formula (I) wherein X represents -C(=O) can be prepared by aromatic electrophilic substitution reaction.

By way of example, the synthesis of intermediate **54** is described below:

Intermediate 54 :

2,2,2-Trifluoro-N-{1-[3-hydroxy-4-(isoquinolin-5-ylcarbonyl)-5-methylphenyl]ethyl}-acetamide

To a mixture of **53** (8.7 g, 33 mmoles) and **655** (7.6 g, 33 mmoles) in methylene chloride (700 mL) at 30°C there is added $AlCl_3$ (8.8 g). The mixture is heated for 1 hour at 50°C and then, after return to ambient temperature, $AlCl_3$ (8.8 g) is again added. The mixture is heated at 50°C for 24 hours, and $AlCl_3$ (8.8 g) is again added. After heating for 24 hours at 50°C and for two days at ambient temperature, the mixture is hydrolysed carefully on a mixture of ice and water. The product is extracted with methylene chloride, and the organic phase is dried and then concentrated in vacuo. The product is purified by chromatography on silica (eluant CH_2Cl_2AcOEt 90/1). Intermediate **54** (3.8 g) is thus obtained.

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 9.50, 8.72, 8.70, 8.40, 7.90, 7.75, 6.80, 6.70, 4.97, 2.15, 1.50.

IR (cm^{-1}) : 3331, 3000-2500, 1692-1663, 1165

Compounds **652**, **656, 665** and **673** were obtained according to the same protocol.

Intermediate 652 :

2,2,2-Trifluoro-N-{1-[4-(isoquinolin-5-ylcarbonyl)-3,5-dimethylphenylethyl}-acetamide

Obtained by reaction of **655** with **651**

^{1}H NMR (300/500 MHz, DMSO-d_6) **:** δ 9.90 (broad s, 1H, NH), 9.48 (s, 1H), 8.85 (broad d, 1H), 8.72 (d, 1H), 8.45 (d, 1H), 7.82 (d, 1H), 7.75 (t, 1H), 7.15 (s, 2H), 5.03 (quad, 1H), 2.10 (s, 6H), 1.51 (d, 3H)

IR (cm^{-1}) : 3208, 1712, 1653, 1571, 1145, 1185, 1208

Intermediate 656 :

2,2,2-Trifluoro-N-{(1R)-1-[3-hydroxy-4-(isoquinolin-5-ylcarbonyl)phenyl]ethyl}-acetamide

Obtained by reaction of **655** with **17**

^{1}H NMR (300/500 MHz, DMSO-d_6) **:** δ 9.40 (s, 1H), 8.52 (d, 1H), 8.32 (d, 1H), 7.88 (m, 2H), 7.78 (t, 1H), 7.38 (d, 1H), 6.98 (s, 1H), 6.88 (d, 1H), 5.00 (quint, 1H), 1.78 (d, 3H)

IR (cm^{-1}) : 3295, 1707, 1629, 1147 broad

Intermediate 665 :

2,2,2-Trifluoro-N-{(1R)-1-[7-(isoquinolin-5-ylcarbonyl)-2,3-dihydro-1-benzofuran-4-yl]ethyl}acetamide

Obtained by reaction of **655** and **664**

^{1}H NMR (300MHz, DMSO-d_6) **:** δ 10.00 (NH), 9.40, 8.55, 8.30, 8.00, 7.88, 7.75, 7.45, 6.98, 5.00, 4.45, 3.20, 1.48

IR (cm^{-1}) : 3300, 1709, 1650, 1230-1150

Intermediate 673 :

2,2,2-Trifluoro-N-{1-[3-hydroxy-4-(isoquinolin-5-ylcarbonyl)-5-methoxyphenyl]-ethyl}acetamide

Obtained by reaction of **655** and **672**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 10.1-9.85 (m, 2H), 8.75 (d, 1H), 8.65 (d, 1H), 8.35 (t, 2H), 7.95 (d, 1H), 7.75 (t, 1H), 6.65-6.55 (2s, 2H), 4.98 (m, 1H), 3.60 (s, 3H), 1.50 (d, 3H)
IR (cm^{-1}) : 3287, 3120-1980,1706-1625

Intermediate 55 :

2,2,2-Trifluoro-N-{1-[4-(isoquinolin-5-ylcarbonyl)-3-methoxy-5-methylphenyl]ethyl}-acetamide

Obtained by reaction of methyl iodide with intermediate **54** according to the protocol described for intermediate **93** (**Protocol XVII**)

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.90 (broad s, 1H), 9.40 (s, 1H), 8.80 (d, 1H), 8.70 (d, 1H), 8.40 (broad d, 1H), 7.85 (broad d, 1H), 7.75 (t, 1H), 7.00 (broad s, 1H), 6.95 (broad s, 1H), 5.05 (quad, 1H), 3.60 (s, 3H), 2.10 (s, 3H), 1.50 (d, 3H)
IR (cm^{-1}) : 3215, 1724-1658, 1178

Intermediate 659 :

N-{(1R)-1-[3-Ethyl-4-(isoquinolin-5-ylcarbonyl)phenyl]ethyl}-2,2,2-trifluoro-acetamide

Obtained starting from **656** according to the sequence described for obtaining **562**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.80 (broad s, 1H, NH), 9.50 (s, 1H), 8.62 (d, 1H), 8.40 (d, 1H), 8.30 (d, 1H), 7.82 (d, 1H), 7.74 (t, 1H), 7.40 (s, 2H), 7.25 (m, 2H), 5.05 (quad., 1H), 2.70 (quad, 2H), 1.52 (d, 3H), 1.12 (t, 3H)
IR (cm^{-1}) : 3296, 1705, 1657

Intermediate 674 :

2,2,2-Trifluoro-N-{1-[4-(isoquinolin-5-ylcarbonyl)-3,5-dimethoxyphenyl]ethyl}-acetamide

Obtained by reaction of methyl iodide with intermediate **673** according to the protocol described for intermediate **93** (**Protocol XVII**)

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 9.90 (broad s, 1H, NH), 9.45 (s, 1H), 8.82 (d, 1H), 8.68 (d, 1H), 8.40 (d, 1H), 7.92 (d, 1H), 7.75 (t, 1H), 6.85 (s, 2H), 5.10 (quad., 1H), 3.65 (s, 6H), 1.52 (d, 3H)
IR (cm^{-1}) : 3233, 1726-1664, 1118, 852, 763, 614

The ketone intermediates protected in the form of trifluoro-acetamides were deprotected in a basic medium to yield the final products, according to the example of intermediate **56**.

Intermediate 56 :

[4-(1-Aminoethyl)-2-methoxyphenyl](isoquinolin-5-yl)methanone

To a solution of **55** (2.67 g, 6.41 mmoles) in methanol there is added a 1N NaOH solution (46 mL), and the reaction mixture is stirred at ambient temperature until conversion is complete. The solvent is evaporated off in vacuo, the residue is taken up in water (150 mL) and extracted with methylene chloride, and the organic phase is dried and then concentrated in vacuo. The residue is chromatographed on silica gel (eluant CH_2Cl_2/EtOH/NH_4OH 28% (95/05/0.5)). Intermediate **56** (0.8 g) is obtained in the form of an oil.

^{1}H NMR (300 MHz, DMSO-d_6)**:** δ 9.40 (s, 1H), 8.80 (d, 1H), 8.70 (d, 1H), 8.40 (dl, 1H), 7.85 (broad d, 1H), 7.70 (t, 1H), 7.00 (broad s, 1H), 6.95 (broad s, 1H), 4.00 (quad, 1H), 3.55 (s, 3H), 2.10 (s, 3H), 1.90 (m, 2H), 1.30 (d, 3H)

IR (cm^{-1}) : 3500-3250, 1654, 1610, 1571, 834-672

The intermediates obtained are converted into hydrochlorides by treatment with a 2N HCl solution in ethyl ether.

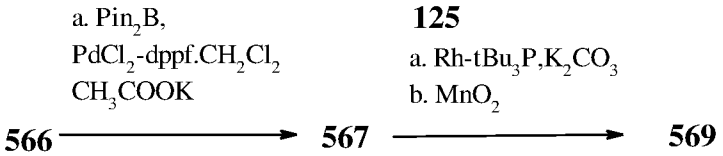
Product	Obtained from	Nomenclature Analytical description
P7	**56**	**[4-(1-Aminoethyl)-2-methoxy-6-methylphenyl]-(isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 9.80 (s, 1H), 9.10 (s, 1H), 8.80 (d, 1H), 8.70 (d, 1H), 8.65 (d, 1H), 8.00 (d, 1H), 7.98 (t, 1H), 7.35 (s, 1H), 7.12 (s, 1H), 4.40 (m, 1H), 3.60 (s, 3H), 2.20 (s, 3H), 1.60 (d, 3H) **IR (cm^{-1}) :** 2710-2076, 1667 **HRMS (ESI) :** m/z calculated for $C_{20}H_{20}N_2O_2$ $[M+H]^+$ 321.1603, found 321.1612
P121	**652**	**[4-(1-Aminoethyl)-2,6-dimethylphenyl](isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 9.80 (s, 1H), 9.10 (d, 1H), 8.85 (d, 1H), 8.68 (d, 1H), 8.60 (broad s, 3H), 7.96 (d, 1H), 7.90 (t, 1H), 7.38 (s, 2H), 4.40 (m, 1H), 2.10 (s, 6H), 1.58 (d, 3H) **IR (cm^{-1}) :** 3000-2000, 1659, 910-832 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{21}N_2O$ $M^{+\cdot}$304.1576, measured 304.2
P122	**659**	**{4-[(1R)-1-Aminoethyl]-2-ethylphenyl}(isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 9.80 (s, 1H), 8.78 (d, 1H), 8.65 (broad s, 3H), 8.65 (m, 2H), 7.95 (m, 2H), 7.65 (s, 1H), 7.48 (dd, 1H), 7.40 (d, 1H), 4.48 (m, 1H), 2.72 (quad, 2H), 1.58 (d, 3H), 1.18 (t, 3H) **IR (cm^{-1}) :** 3000-2000, 1662, 918-821 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{21}N_2O$ $M^{+\cdot}$304.1576, measured 304.2
P123	**665**	**{4-[(1R)-1-Aminoethyl]-2,3-dihydro-1-benzofuran-7-yl}(isoquinolin-5-yl)methanone dihydrochloride**

		^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 9.90 (s, 1H), 8.70 (2d, 2H), 8.40 (d, 1H), 8.20 (broad d, 1H), 8.00 (t, 1H), 7.60 (d, 1H), 7.30 (d, 1H), 4.40 (t and m, 3H), 3.30 (2m, 2H), 1.50 (d, 3H) **IR (cm^{-1}) :** 3250-2000, 1651, 1604, 833, 658 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{19}N_2O_2$ $[M+H]^+$ 319.1447, measured 319.1442
P124	**674**	**[4-(1-Aminoethyl)-2,6-dimethoxyphenyl](isoquinolin-5-yl)methanone dihydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 9.80 (s, 1H), 9.10 (d, 1H), 8.80 (d, 1H), 8.65 (broad d, 1H), 8.10 (broad d, 1H), 7.95 (t, 1H), 7.10 (s, 2H), 4.45 (quint, 1H), 3.70 (s, 6H), 1.60 (d, 3H) **IR (cm^{-1}) :** 3340, 1970, 1673, 1607, 1582, 831, 759 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{21}N_2O_3$ $[M+H]^+$ 337.1552, measured 337.1566

Protocol XXIV : Alternative method for the preparation of compounds of formula (I) wherein X represents -C(=O)

Compounds of formula (I) wherein X represents -C(=O) can be prepared by reaction of boronic intermediates with carbonylated intermediates, the intermediate alcohol obtained is then oxidised to the ketone, and the protecting group of the amine function is removed.

By way of example, the synthesis of intermediate **569** is described below:



Intermediate 567 :

tert-Butyl {1-[2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl}-carbamate

To a mixture of intermediate **566** (2 g, 6.2 mmoles), potassium acetate (1.2 g) and bis(pinacolato)diborane (1.75 g, 6.9 mmoles) in 1,4-dioxane degassed with nitrogen (20 mL), there is added $PdCl_2$-dppf.CH_2Cl_2 (0.15 g, 3%). The reaction mixture is heated at reflux for 4 hours. After return to ambient temperature, the mixture is hydrolysed, and then toluene is added. After filtration, the filtrate is washed with water and a saturated aqueous NaCl solution; the organic phase is dried over $MgSO_4$ and concentrated. The residue is chromatographed on silica gel using an iPr_2O/cyclohexane eluant mixture (10/90 to 100/0). Intermediate **567** (1.9 g) is obtained in the form of an oil.

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 7.50 (2m, 3H), 7.16 (t, 1H), 4.85 (m, 1H), 1.35 (broad s, 9H), 1.3 (s, 12H), 1.28 (d, 3H)

^{19}F NMR: -108.6

IR (cm^{-1}) : 3341, 1700, 1361

GC-EI (70 eV): M+. = 365.2

Intermediate 569 :

tert-Butyl (1-{3-[(1-ethoxyisoquinolin-5-yl)carbonyl]-2-fluorophenyl}ethyl)carbamate

Step 1 :

To a mixture of intermediate **567** (1.8 g, 4.9 mmoles), intermediate **125** (0.986 g, 4.9 mmoles) and K_2CO_3 (1.36 g, 9.8 mmoles) in dioxane (18 mL) degassed with argon, there are added bis(ethylene)rhodium(I) chloride dimer (38 mg) and tri-tert-butyl-phosphine as a 1M solution in toluene (0.196 mL). The reaction mixture is heated for 6 hours at 60 °C and then stirred for 3 days at ambient temperature. After hydrolysis and extraction with Et_2O, the organic phase is washed in succession with water to pH=7 and then with a saturated aqueous NaCl solution, dried over $MgSO_4$, filtered and evaporated in vacuo. The residue is purified by flash chromatography on silica (eluant : CH_2Cl_2-THF : 95-5) to give the expected intermediate (1.1 g) in the form of a beige solid.

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.15 (d, 1H), 7.95 (d, 1H), 7.80 (d, 1H), 7.60 (t, 1H), 7.50 (d, 1H), 7.45 (m, 1H), 7.30-7.15 (m, 1H), 7.10 (m, 1H), 6.53 (m, 1H), 6.18 (m, 1H), 4.85 (m, 1H), 4.50 (quad, 2H), 1.40 (t, 3H), 1.35 (broad s, 9H), 1.25 (d, 3H)

IR (cm^{-1}): 3315, 1683

Step 2 :

The intermediate obtained above is oxidised in the presence of MnO_2 (according to protocol described above) to give intermediate **569**.

^{1}H NMR (400 MHz, DMSO-d_6)**:** δ 8.47 (d, 1H), 8.1 (d, 1H), 7.89 (d, 1H), 7.75-7.6 (3m, 3H), 7.6-7.5 (2m, 2H), 7.37 (t, 1H), 4.85 (m, 1H), 4.57 (quad, 2H), 1.46 (t, 3H), 1.36 (broad s, 9H), 1.26 (d, 3H)

IR (cm^{-1}): 3348, 1680-1661

Intermediate 587 :

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)(hydroxy)methyl]-2-methoxy-3-methyl-phenyl}ethyl)carbamate

Obtained starting from **586** and **125** according to the same protocol.

^{1}H NMR (400 MHz, DMSO-d_6)**:** δ 8.15 (d, 1H), 7.95 (d, 1H), 7.61 (m, 2H), 7.36-7.29 (2 broad d, 1H), 7.34 (d, 1H), 7.14-7.11 (2d, 1H), 6.85-6.81 (m, 1H), 6.4 (s, 1H), 4.93 (m,

1H), 4.51 (quad, 2H), 3.73-3.69 (2s, 3H), 2.2 (broad s, 3H), 1.43 (t, 3H), 1.34 (broad s, 9H), 1.22-1.2 (2d, 3H)

IR (cm^{-1}): 3343, 1689

Intermediate **587** is oxidised in the presence of MnO_2 (according to protocol described above) to give intermediate **588**:

Intermediate 588 :

tert-Butyl (1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-2-methoxy-3-methylphenyl}-ethyl)carbamate

^1H NMR (400 MHz, DMSO-d_6) **:** δ 8.44 (d, 1H), 7.79 (d, 1H), 7.67 (t, 1H), 8.10 (d, 1H), 7.74 (d, 1H), 7.50 (broad d, 1H), 7.29 (d, 1H), 7.07 (d, 1H), 5.0 (m, 1H), 4.58 (quad, 2H), 3.80 (s, 3H), 2.27 (s, 3H), 1.46 (t, 3H), 1.36 (s, 9H), 1.27 (d, 3H)

IR (cm^{-1}) : 3352, 1708, 1660

The ketone intermediates obtained by protocol **XXIV** were deprotected in an acidic medium to yield the final product, according to the procedures described for products **P17** and **P110** when they are protected in the form of tert-butyl-carbamates.

Product	**Obtained from**	**Nomenclature** **Analytical description**
P108	**569**	**5-[3-(1-Aminoethyl)-2-fluorobenzoyl]isoquinolin-1(2H)-one hydrochloride** **^1H NMR** (400 MHz, DMSO-d_6) **:** δ 11.57 (d, 1H), 8.80-8.40 (m, 3H), 8.47 (d, 1H), 7.96 (td, 1H), 7.81 (d, 1H), 7.66 (td, 1H), 7.56 (t, 1H), 7.47 (t, 1H), 7.31 (dd, 1H), 6.98 (d, 1H), 4.62 (m, 1H), 1.54 (d, 3H) **IR (cm^{-1}) :** 3300-2000, 1663, 1615 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{16}FN_2O_2$ $[M+H]^+$ 311.1190, measured 311.1184. **Optical purity** (SFC: ID 3µM column 4.6x250 mm ; eluant: CO_2 / (isopropanol/diethylamine:100/0.5) : 70 /

		30 ; detection: 253nm) : >99%. (absence of **P100**)
P109	**588**	**5-[4-(1-Aminoethyl)-3-methoxy-2-methylbenzoyl]-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.58 (d, 1H), 8.51 (m, 3H), 8.46 (d, 1H), 7.66 (d, 1H), 7.55 (t, 1H), 7.55 (d, 1H), 7.32 (dd, 1H), 7.19 (d, 1H), 7.05 (d, 1H), 4.66 (quad, 1H), 3.79 (s, 3H), 2.25 (s, 3H), 1.53 (d, 3H) **IR (cm^{-1}) :** 3400-2300, 1681, 1650 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{21}N_2O_3$ $[M+H]^+$ 337.1547, measured 337.1541. theoretical m/z for $C_{20}H_{18}NO_3$ $[M+H-NH_3]^+$ 320.1281, measured 320.1277. m/z measured for $C_{20}H_{19}N_2O_3$ $[M-H]^-$ 335.30.

Protocol XXV : Preparation of compounds of formula (I) wherein X represents -CH(OH)-

Compounds of formula (I) wherein X represents -CH(OH)- can be synthesised according to **protocol XX**, without the final oxidation step.

Intermediate **147** was prepared starting from intermediate **3** and intermediate **145** according to the procedure described for obtaining product **P17**.

Intermediate 147 :

tert-Butyl [(1R)-1-{3,5-difluoro-4-[hydroxy(isoquinolin-5-yl)methyl]phenyl}ethyl]-carbamate

^{1}H NMR (300MHz, DMSO-d_6): 9.30 (s, 1H), 8.45 (d, 1H), 8.20 (d, 1H), 8.05 (broad d, 1H), 7.75 (t, 1H), 7.65 (broad d, 1H), 7.40 (broad d, 1H), 6.95 (d, 1H), 6.60 (d, 1H), 6.40 (d, 1H), 4.60 (quint, 1H), 1.35 (s, 9H), 1.20 (d, 3H)

Intermediate **147** (1.44 g) was chromatographed by high pressure chromatography on a chiral support (ChiralCell OJ column, eluant : n-propyl alcohol/heptane/diethylamine 10/90/0.1, detection 270nm) to give the two optical antipodes **148** (0.6 g) and **149** (0.53 g).

Intermediate 148 :

Optical purity (OJ-H column, eluant : n-propyl alcohol/heptane/diethylamine 10/90/0.1, detection 270nm) : >99%.

Intermediate 149 :

Optical purity (OJ-H column, eluant : n-propyl alcohol/heptane/diethylamine 10/90/0.1, detection 270nm) : 98%.

To a solution of intermediate **149** (0.5 g) in methylene chloride (30 mL) there is added in the course of 10 minutes TFA (1.7 mL). The reaction mixture is stirred at ambient temperature for 20h before being concentrated in vacuo. The residue is taken up in water and treated with 20% sodium hydroxide and extracted with methylene chloride, and the organic phase is dried over $MgSO_4$. Evaporation under reduced pressure yields intermediate **150** (0.25 g).

Intermediate 150 :

{4-[(1R)-1-Aminoethyl]-2,6-difluorophenyl}(isoquinolin-5-yl)methanol, enantiomer 1

Optical purity (capillary electrophoresis: standard CE, NaH_2PO_4 0.05M, pH2.5 - H_3PO_4cc/HS α-cyclodextrin, detection 233nm) : 99%.

Intermediate **148**, treated according to the protocol described for intermediate **150**, yielded intermediate **692** :

Intermediate 692 :

{4-[(1R)-1-Aminoethyl]-2,6-difluorophenyl}(isoquinolin-5-yl)methanol, enantiomer 2

Optical purity (capillary electrophoresis: standard CE, NaH_2PO_4 0.05M, pH2.5 - H_3PO_4cc/HS α-cyclodextrin, detection 233nm) : >99%.

Intermediate **151** was prepared starting from intermediate **3** and intermediate **146** according to the procedure described for obtaining product **P17**.

Intermediate 151 :

tert-Butyl [(1S)-1-{3,5-difluoro-4-[hydroxy(isoquinolin-5-yl)methyl]phenyl}ethyl]-carbamate

^{1}H NMR (300MHz, DMSO-d_6): 9.30 (s, 1H), 8.45 (d, 1H), 8.20 (d, 1H), 8.05 (broad d, 1H), 7.75 (t, 1H), 7.65 (broad d, 1H), 7.40 (broad d, 1H), 6.95 (d, 1H), 6.60 (d, 1H), 6.40 (d, 1H), 4.60 (quint, 1H), 1.35 (s, 9H), 1.20 (d, 3H)

Intermediate **151** (1.2 g) was chromatographed by high pressure chromatography on a chiral support (ChiralCell OJ column, eluant : n-propyl alcohol/heptane/diethylamine 10/100/0.1, detection 270nm) to give the two optical antipodes **152** (0.42 g) and **153** (0.59 g).

Intermediate 152 :

Optical purity (OJ-H column, eluant : ethanol/heptane/diethylamine 70/30/0.1 to 5/95/0.1, detection 275nm) : >98%

Intermediate 153 :

Optical purity (OJ-H column, eluant : ethanol/heptane/diethylamine 70/30/0.1 to 5/95/0.1, detection 275nm) : >99%.

Intermediate **153**, treated according to the protocol described for intermediate **150**, yielded intermediate **154** (0.25 g).

Intermediate 154 :

{4-[(1S)-1-Aminoethyl]-2,6-difluorophenyl}(isoquinolin-5-yl)methanol, enantiomer 1

Optical purity (capillary electrophoresis: standard CE, NaH_2PO_4 0.05M, pH2.5 - H_3PO_4cc/HS α-cyclodextrin, detection 233nm) : >99%.

Intermediates **150**, **154** and **692** are converted into hydrochlorides by treatment with a 2N solution of HCl in ethyl ether:

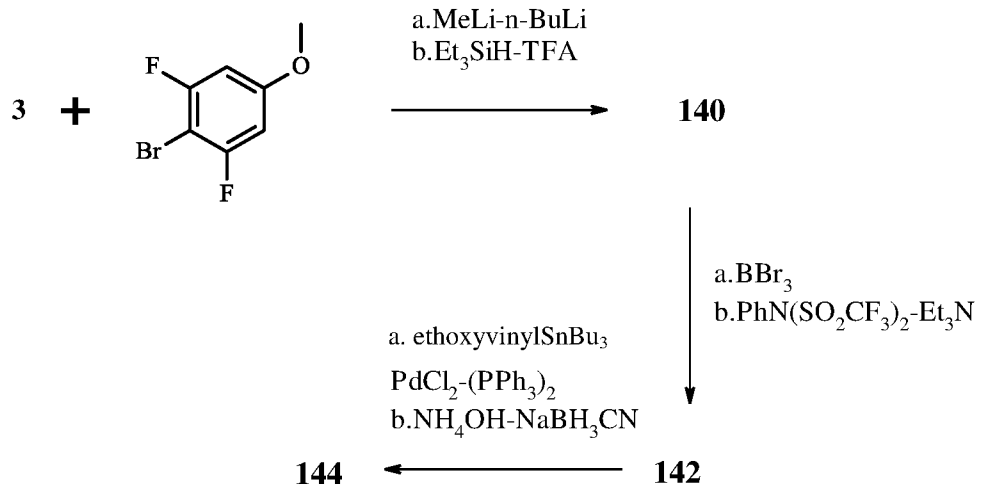
Product	**Obtained from**	**Nomenclature** **Analytical description**
P20	**150**	**{4-[(1R)-1-Aminoethyl]-2,6-difluorophenyl}-(isoquinolin-5-yl)methanol dihydrochloride, enantiomer 1** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 9.82 (s, 1H), 8.73 (m, 3H), 8.66 (d, 1H), 8.45 (m, 2H), 8.14 (d, 1H), 8.04 (t, 1H), 7.35 (d, 2H), 6.75 (s, 1H), 4.40 (m, 1H), 1.48 (d, 3H). **IR (cm^{-1}) :** 3231 **HRMS (ESI):** theoretical m/z for $C_{18}H_{17}F_2N_2O$ $[M+H]^+$ 315.1309, measured 315.1294. **Optical purity** (capillary electrophoresis: standard CE, NaH_2PO_4 0.05M, pH2.5 -H_3PO_4cc/HS α-cyclodextrin, detection 233nm) : 99%.
P21	**154**	**{4-[(1S)-1-Aminoethyl]-2,6-difluorophenyl}-(isoquinolin-5-yl)methanol dihydrochloride, enantiomer 1** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 9.78 (s, 1H), 8.68 (broad s, 3H), 8.65 (d, 1H), 8.44-8.41 (2d, 2H), 8.10 (d, 1H), 8.02 (t, 1H), 7.34 (d, 2H), 6.75 (s, 1H), 4.40 (m, 1H), 1.47 (d, 3H) **IR (cm^{-1}) :** 3300-1900 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{17}F_2N_2O$ $[M+H]^+$ 315.1309, measured 315.1297. **Optical purity** (capillary electrophoresis: standard CE, NaH_2PO_4 0.05M, pH2.5 -H_3PO_4cc/HS α-cyclodextrin, detection 233nm) : 99%.
P127	**692**	**{4-[(1R)-1-Aminoethyl]-2,6-difluorophenyl}-(isoquinolin-5-yl)methanol dihydrochloride,**

		enantiomer 2 **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 9.82 (s, 1H), 8.73 (m, 3H), 8.66 (d, 1H), 8.45 (m, 2H), 8.14 (d, 1H), 8.04 (t, 1H), 7.35 (d, 2H), 6.75 (s, 1H), 4.40 (m, 1H), 1.48 (d, 3H) **IR (cm^{-1}) :** 3231, 3200-2300 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{17}F_2N_2O$ $[M+H]^+$ 315.1309, measured 315.1309. **Optical purity** (capillary electrophoresis: standard CE, NaH_2PO_4 0.05M, pH2.5 -H_3PO_4cc/HS α-cyclodextrin, detection 233nm) : 99%.

Protocol XXVI : Preparation of compounds of formula (I) wherein X represents -CH_2-

Compounds of formula (I) wherein X represents -CH_2- can be synthesised according to the procedures described below:

By way of example, the synthesis of intermediate **144** (1-[3,5-difluoro-4-(isoquinolin-5-ylmethyl) phenyl] ethanamine) :



Intermediate 140 :

(5-(2,6-Difluoro-4-methoxybenzyl)isoquinoline)

Step 1 :

To a solution of commercial 4-bromo-3,5-difluoroanisole (25 g, 112 mmoles) in anhydrous THF (44 mL) cooled to -70°C there is added a 2.5 N solution of n-BuLi in cyclohexane (44 mL, 110 mmoles) in the course of 35 minutes. The resulting mixture is stirred at -70°C for 35 minutes, and then a solution (17 g, 108 mmoles) of intermediate **3** in THF (300 mL) is added, the temperature being maintained below -70°C. The reaction mixture is stirred for one hour at -70°C and then hydrolysed with water. The organic phase is extracted with Et_2O, dried over $MgSO_4$, filtered and evaporated in vacuo. The residue is purified on Lichroprep RP18 40-60 (CH_3CN/H_2O/TFA 95/5/0.1). The expected intermediate (15.7 g) is obtained in the form of a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.60 (s, 1H), 8.55 (dd, 1H), 8.35 (m, 1H), 8.25 (m, 1H), 7.85-7.95 (2m, 2H), 6.65-6.75 (d, 2H), 6.60 (s, 1H), 3.75 (s, 3H), 6.0-8.0 (m, 1H)

IR (cm^{-1}) : 3248, 1050-1200, 1705, 1666

Step 2 :

The intermediate obtained above (850 mg, 2.82 mmoles) dissolved in trifluoroacetic acid (35 mL) is treated with triethylsilane (4.5 mL, 28.2 mmoles) at ambient temperature. The resulting mixture is heated for 1 hour at 70°C. The reaction mixture is poured into a mixture of water and ice, and then a 40% aqueous sodium hydroxide solution is added. The organic phase is extracted with ethyl acetate and washed with water, dried over $MgSO_4$, filtered and evaporated in vacuo. The residue obtained is purified by flash chromatography on silica (eluant : CH_2Cl_2/AcOEt, gradient 100-0 to 70-30). Intermediate **140** (400 mg) is obtained in the form of a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.30 (s, 1H), 8.60 (d, 1H), 8.10 (d, 1H), 8.00 (d, 1H), 7.60 (t, 1H), 7.30 (d, 1H), 6.80 (d, 2H), 4.35 (s, 2H), 3.80 (s, 3H)

IR (cm^{-1}) : 1138

Intermediate 142 :

3,5-Difluoro-4-(isoquinolin-5-ylmethyl)phenyl trifluoromethanesulphonate

Step 1 :

To a solution of intermediate **140** (8 g, 20 mmoles) in methylene chloride (160 mL) cooled to -70°C there is added a 1N BBr_3/CH_2Cl_2 solution (48 mL, 48 mmoles). The reaction mixture is stirred for 2 days at ambient temperature. The reaction mixture is cooled to -70°C and treated with 50 mL of methanol in the course of 20 minutes and is then returned to ambient temperature and then concentrated in vacuo. The residue is heated at reflux in 160 mL of methanol for 1½ h and is then concentrated in vacuo. The expected intermediate (6.9 g) is obtained in the form of its hydrobromide.

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 10.35 (broad s, 1H), 9.80 (s, 1H), 8.77 (d, 1H), 8.60 (d, 1H), 8.35 (d, 1H), 7.89 (t, 1H), 7.69 (d, 1H), 6.54 (d, 2H), 4.41 (s, 2H)

IR (cm^{-1}) : 1647-1633, 2500-3100

Step 2 :

To a solution of the intermediate obtained above (500 mg, 1.8 mmoles) and triethylamine (1.8 g, 18 mmoles) in 35 mL of methylene chloride cooled to -78°C there is added N-phenyl-bistrifluoromethanesulphonimide (1 g, 2.8 mmoles) in the course of one minute. The reaction mixture is stirred for 1 hour at -78°C and a further 1 mL of Et_3N is added. After stirring for 1 hour at -78°C, the reaction mixture is hydrolysed at -78°C by addition of water. The organic phase is washed with a saturated aqueous NaCl solution, dried over $MgSO_4$, filtered and evaporated in vacuo. The residue is purified by flash chromatography on silica (eluant CH_2Cl_2-AcOEt: 100-0 to 80-20). There are obtained 230 mg of intermediate **142** in the form of an oil.

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.40 (s, 1H), 8.60 (d, 1H), 8.05 (m, 2H), 7.65 (m, 3H), 7.35 (m, 1H), 4.50 (s, 2H)

IR (cm^{-1}): 1427-1138, 1210

Intermediate 144 :

1-[3,5-Difluoro-4-(isoquinolin-5-ylmethyl)phenyl]ethanamine

Step 1 :

To a solution, degassed with nitrogen, of intermediate **142** (500 mg, 1.23 mmoles) in DMF (5 mL) there are added 60 mg (0.22 mmole) of triphenylphosphine, 15 mg (0.066 mmole) of $Pd(OAc)_2$, 160 mg (3.77 mmoles) of LiCl and 530 mg (1.46 mmoles) of (1-ethoxy-vinyl)-tributyltin. The mixture is heated at 70°C for 5 hours and then stirred overnight at ambient temperature. The mixture is treated with a 1N aqueous HCl solution and stirred at ambient temperature and is then rendered basic with a 28% NH_4OH solution. The organic phase is extracted with AcOEt and washed with an aqueous NaCl solution, dried over $MgSO_4$, filtered and evaporated to dryness. The residue is purified by flash chromatography on silica (eluant : CH_2Cl_2-AcOEt gradient : 100-0 to 90-10). The expected intermediate (150 mg) is obtained.

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.35 (s, 1H), 8.60 (d, 1H), 8.10 (d, 1H), 8.05 (d, 1H), 7.70 (d, 2H), 7.60 (t, 1H), 7.35 (d, 1H), 4.50 (s, 2H), 2.60 (s, 3H)

IR (cm^{-1}) : 1685, 1620, 1579, 1315, 860-831-761

Step 2 :

To a solution of the intermediate obtained above (650 mg, 2.18 mmoles) in 13 mL of methanol there are added ammonium acetate (2.4 g, 31 mmoles) and then 4 Å powdered molecular sieve. After 20 minutes, sodium cyanoborohydride (120 mg, 1.9 mmoles) is added. The reaction mixture is stirred overnight at ambient temperature. The solution is filtered to remove the molecular sieve, and then the filtrate is evaporated in vacuo. The residue is treated with 20% HCl to which ethyl acetate is added. The aqueous phase is decanted, rendered basic by addition of 20% NaOH and extracted twice with methylene chloride. The organic phase is then dried over $MgSO_4$, filtered and evaporated in vacuo. The residue is purified by flash chromatography on silica (eluant : CH_2Cl_2-EtOH gradient : 97-3 to 90-10). Intermediate **144** (260 mg) is obtained in the form of an oil.

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.40 (s, 1H), 8.60 (d, 1H), 8.10 (d, 1H), 8.00 (d, 1H), 7.60 (t, 1H), 7.35 (d, 1H), 7.15 (d, 2H), 4.45 (s, 2H), 3.95 (quad., 1H), 1.25 (d, 3H), 1.95 (m, 2H)

IR (cm^{-1}) : 1309, 3200-3400

Intermediate 530 :

N-[(1R)-1-{4-[(1-Ethoxyisoquinolin-5-yl)methyl]-3-methoxyphenyl}ethyl]-2,2,2-trifluoroacetamide

Obtained by dehydroxylation (according to the conditions described for intermediate **140**) of alcohol **677**, prepared by coupling of **676** and **3**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.2 (s, 1H), 8.1 (d, 1H), 8.00 (d, 1H), 7.55 (m, 1H), 7.5 (m, 1H), 7.4 (d, 1H), 7.05 (s, 1H), 6.8 (m, 2H), 5.0 (m, 1H), 4.5 (quad., 2H), 4.25 (s, 2H), 3.85 (s, 3H), 1.45 (m, 6H)

19F NMR: -73

Intermediate 678 :

2,2,2-Trifluoro-N-{1-[3-fluoro-4-(isoquinolin-5-ylmethyl)phenyl]ethyl}acetamide

Obtained by dehydroxylation (according to the conditions described for intermediate **140**) of alcohol **543**, prepared by coupling of **18** and **124**

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 9.80 (d, 1H), 9.30 (s, 1H), 8.50 (d, 1H), 8.00 (broad d, 1H), 7.95 (d, 1H), 7.60 (t, 1H), 7.55 (dd, 1H), 7.20 (dd, 1H), 7.15 (t, 1H), 7.05 (dd, 1H), 5.0 (quint., 1H), 4.40 (s, 2H), 1.40 (d, 3H)

IR (cm^{-1}): 3430, 3050, 1703, 1555

The ketone intermediates protected in the form of trifluoro-acetamides were deprotected in a basic medium to yield the final products, according to the example of intermediate **56**. The intermediates obtained are converted into hydrochlorides by treatment with a 2N HCl solution in ethyl ether.

Product	**Obtained from**	**Nomenclature** **Analytical description**
P19	**144**	**1-[3,5-Difluoro-4-(isoquinolin-5-ylmethyl)phenyl]-ethanamine dihydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 9.90 (s, 1H), 8.80 (m, 3H), 8.80 (d, 1H), 8.35 (d, 1H), 7.90 (t, 1H), 7.70 (d, 1H), 7.45 (d, 2H), 4.60 (s, 2H), 4.45 (m, 1H), 1.55 (d, 3H) **IR (cm^{-1}) :** 3000-2500 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{17}F_2N_2$ $[M+H]^+$ 299.1360, measured 299.1368
P101	**530**	**5-{4-[(1R)-1-Aminoethyl]-2-methoxybenzyl}-isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.29 (m, 1H), 8.38 (broad s, 3H), 8.11 (broad d, 1H), 7.44 (broad d, 1H), 7.40 (t, 1H), 7.28 (broad s, 1H), 7.16 (m, 1H), 6.94 (broad d, 1H), 6.88 (d, 1H), 6.56 (d, 1H), 4.34 (quad, 1H), 4.15 (s, 2H), 3.86 (s, 3H), 1.50 (d, 3H) **IR (cm^{-1}) :** 3300-2400, 3173, 1641, 1263, 1036, 782 **HRMS (ESI) :** theoretical m/z for $C_{19}H_{21}N_2O_2$ $[M+H]^+$ 309.1603, measured 309.1614.
P125	**678**	**1-[3-Fluoro-4-(isoquinolin-5-ylmethyl)phenyl]-ethanamine dihydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 9.80 (s, 1H), 8.70 (s,

		1H), 8.62 (broad s, 3H), 8.48 (d, 1H), 8.40 (dd, 1H), 7.90 (m, 2H), 7.48 (d, 1H), 7.28 (m, 2H), 4.58 (s, 2H), 4.38 (m, 1H), 1.50 (d, 3H) **IR (cm^{-1}) :** 2552-2505, 2083-1984-1855, 1645-1609, 877-839-815 **HRMS (ESI) :** theoretical m/z for $C_{18}H_{18}FN_2$ $[M+H]^+$ 281.1454, measured 281.1466

Protocol XXVII

When Ry_3 represents:

- 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, or
- a -O(C_1-C_3)alkyl group, or
- a cyclohexyl group, or
- a methylsulphonyl group,

the following protocols were used.

The final products were prepared starting from intermediates or final products described above:

Intermediate 418 :

(1-Amino-4,6-difluoro-2,3-dihydro-1H-inden-5-yl)(1-ethoxyisoquinolin-5-yl)methanone

To a solution of intermediate **417** (2.6 g, 5.5 mmoles) in methylene chloride (20 mL) there is added trifluoroacetic acid (2 times 2.07 mL). The mixture is stirred at ambient temperature for 18h and is then diluted with CH_2Cl_2 and treated with 1N sodium hydroxide. The organic phase is washed with water and then dried over $MgSO_4$ and concentrated in vacuo. Intermediate **418** (2 g) so obtained is used in the following step without additional purification.

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.50 (d, 1H), 8.20 (2d, 2H), 8.00 (d, 1H), 7.70 (t, 1H), 7.25 (d, 1H), 4.60 (quad, 2H), 4.30 (t and s, 1H), 2.90 (m, 1H), 2.70 (m, 1H), 2.45 (m, 1H), 2.30 (m, 2H), 1.75 (m, 1H), 1.45 (t, 3H)

IR (cm^{-1}) : 3390, 1667, 1633, 1567, 814-757

Intermediate 421 :

[4-(2-Aminopropan-2-yl)-2,6-difluorophenyl](1-ethoxyisoquinolin-5-yl)methanone

Obtained starting from **172** according to **protocol XXVII**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.50 (d, 1H), 8.2-8.1 (dd, 2H), 8.00 (dd, 1H), 7.75 (dd, 1H), 7.45 (d, 1H), 4.55 (quad, 2H), 2.05 (m, 1H), 2.70 (m, 2H), 1.45 (t, 3H), 1.40 (s, 6H)

IR (cm^{-1}) : 3371, 3302, 1668

Intermediate 426 :

(1-Amino-4,6-difluoro-2,3-dihydro-1H-inden-5-yl)(1-ethoxyisoquinolin-5-yl)-methanone

Obtained starting from **425** according to **protocol XXVII**

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.50 (d, 1H), 8.20 (2d, 2H), 8.00 (d, 1H), 7.70 (t, 1H), 7.25 (d, 1H), 4.60 (quad, 2H), 4.30 (t and s, 1H), 2.90 (m, 2H), 2.70 (m, 1H), 2.45 (m, 1H), 2.30 (m, 2H), 1.75 (m, 1H), 1.45 (t, 3H)

IR (cm^{-1}): 3390, 1666, 1633, 1567, 814-757

Intermediate 435 :

{4-[(1S)-1-Aminoethyl]-2,6-difluorophenyl}(1-ethoxyisoquinolin-5-yl)methanone

Obtained starting from **165** according to **protocol XXVII**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (d, 1H), 8.15 (d, 1H), 8.00 (d, 1H), 7.70 (t, 1H), 7.30 (d, 2H), 4.60 (quad, 2H), 4.05 (quad, 1H), 2.05 (m, 2H), 1.45 (t, 3H), 1.30 (d, 3H)

IR (cm^{-1}) : 3380, 3317, 1669, 1633

Intermediate 468 :

{4-[(1R)-1-Aminoethyl]-2,6-difluorophenyl}(1-ethoxyisoquinolin-5-yl)methanone

Obtained starting from **170** according to **protocol XXVII**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (d, 1H), 8.15 (d, 1H), 8.02 (d, 1H), 7.72 (t, 1H), 7.30 (d, 2H), 4.60 (quad, 2H), 4.05 (quad, 1H), 2.02 (m, 2H), 1.45 (t, 3H), 1.30 (d, 3H)

IR (cm^{-1}) : 3381, 3314, 1670

Intermediate 752 :

[4-(1-Aminoethyl)-2,6-difluorophenyl](1-ethoxyisoquinolin-5-yl)methanone

Obtained starting from **127** according to **protocol XXVII**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.54 (broad d, 1H), 8.19 (d, 1H), 8.13 (broad d, 1H), 8.02 (broad d, 1H), 7.72 (dd, 1H), 7.31 (m, 2H), 4.57 (quad, 2H), 4.06 (quad, 1H), 2.01 (broad s, 2H), 1.46 (t, 3H), 1.30 (d, 3H)

IR (cm^{-1}) : 3375-3310, 1671

LCMS [M+H]+= 356

The amines obtained were converted into amide intermediates according to the following protocols:

Intermediate 419 :

tert-Butyl [2-({5-[(1-ethoxyisoquinolin-5-yl)carbonyl]-4,6-difluoro-2,3-dihydro-1H-inden-1-yl}amino)-2-oxoethyl]carbamate

To a solution of **418** (0.8 g, 2.1 mmoles) in CH_3CN (16 mL) there are added in succession 1-hydroxybenzotriazole (0.03 g, 0.1 eq.), *N,N'*-dicyclohexylcarbodiimide (0.71 g), N-tert-butoxy-carbonyl-glycine (0.38 g). The mixture is stirred at ambient temperature for 3 days. The precipitate is filtered off and washed with CH_3CN, and the filtrate is concentrated in vacuo. The residue is chromatographed on silica gel using a CH_2Cl_2/AcOEt eluant: 80/20 to 60/40. Intermediate **419** (1.16 g) is obtained in the form of an amorphous solid.

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.35 (d, 1H), 8.20 (2d, 2H), 8.0 (d, 1H), 7.70 (t, 1H), 7.10 (d, 1H), 7.00 (t, 1H), 5.40 (quad, 1H), 4.60 (quad, 2H), 3.60 (d, 2H), 3.0 (m, 1H), 2.80 (m, 1H), 2.45 (m, 1H), 2.00 (m, 1H), 1.50 (t, 3H), 1.40 (m, 9H)

IR (cm^{-1}) : 3350, 1720, 1667,1586

Intermediate 427 :

tert-Butyl [2-({5-[(1-ethoxyisoquinolin-5-yl)carbonyl]-4,6-difluoro-2,3-dihydro-1H-inden-1-yl}amino)-2-oxoethyl]carbamate

Obtained according to the same protocol starting from **426**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.35 (d, 1H), 8.20 (2d, 2H), 8.0 (d, 1H), 7.70 (t, 1H), 7.10 (d, 1H), 7.00 (t, 1H), 5.40 (quad, 1H), 4.60 (quad, 2H), 3.60 (d, 2H), 3.0 (m, 1H), 2.80 (m, 1H), 2.45 (m, 1H), 2.00 (m, 1H), 1.50 (t, 3H), 1.40 (m, 9H)

IR (cm^{-1}) : 3350, 1720, 1667,1586

Intermediate 765 :

tert-Butyl (2-{[(1R)-1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}-ethyl]amino}-2-oxoethyl)carbamate

To a solution of **468** (1 g, 2.8 mmoles) in CH_2Cl_2 (20 mL) there are added in succession 1-hydroxybenzotriazole (0.37 g, 2.8 mmoles), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.59 g, 2.8 mmoles), N-tert-butoxy-carbonyl-glycine (0.49 g, 2.8 mmoles) and Et_3N (0.78 mL, 5.6 mmoles). The mixture is stirred at ambient temperature for 1h. The mixture is diluted with methylene chloride and washed with 1N sodium hydroxide, 1N HCl and water. The organic phase is dried over $MgSO_4$ and then concentrated in vacuo. Product **765** (1.1 g) is obtained in the form of a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.35 (d, 1H), 8.2 (dd, 2H), 8.15 (d, 1H), 8.02 (d, 1H), 7.70 (d, 1H), 7.25 (d, 2H), 7.0 (t, 1H), 5.02 (quint, 1H), 4.55 (quad, 2H), 3.58 (dd, 2H), 1.48 (t, 3H), 1.45 (d, 3H), 1.4 (s, 9H)

IR (cm^{-1}) : 3304, 1714, 1675, 1654

Intermediate 436 :

tert-Butyl (2-{[(1S)-1-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}-ethyl]amino}-2-oxoethyl)carbamate

Obtained according to the same protocol starting from **435**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.35 (d, 1H), 8.2-8.1 (dd, 2H), 8.05 (dd, 1H), 7.70 (dd, 1H), 7.25 (d, 2H), 5.00 (m, 1H), 4.55 (quad, 2H), 3.65-3.5 (m, 2H), 1.45 (t, 3H), 1.40 (d, 3H), 1.35 (s, 9H)

IR (cm^{-1}) : 3311, 1717, 1672, 1637

Intermediate 742 :

tert-Butyl {2-[(2-{4-[(1-ethoxyisoquinolin-5-yl)carbonyl]-3,5-difluorophenyl}propan-2-yl)amino]-2-oxoethyl}carbamate

Obtained according to the same protocol starting from **421**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (m, 1H), 8.20 (d, 1H), 8.15 (d, 1H), 8.00 (d, 1H), 7.75 (dd, 1H), 7.25 (d, 2H), 4.55 (quad, 2H), 3.55 (d, 2H), 1.60 (s, 6H), 1.45 (t, 3H), 1.35 (s, 9H)

IR (cm^{-1}) : 3500-3200, 1667

Intermediates **419**, **427**, **468**, **436**, **742** obtained were deprotected in an acidic medium to yield the final products, according to the procedure described for product **P17**.

The amides were also obtained by reaction according to the following protocols:

Intermediate 224 :

tert-Butyl {2-[(1-{3,5-difluoro-4-[(1-oxo-1,2-dihydroisoquinolin-5-yl)carbonyl]-phenyl}ethyl)amino]-2-oxoethyl}carbamate

To a solution, at -10°C, of N-tert-butoxy-carbonyl-glycine (0.48 g, 2.8 mmoles), Et_3N (0.38 mL, 2.7 mmoles) in THF (5 mL) treated with ethyl chloroformate (0.26 mL, 2.7 mmoles) there is added slowly a solution of **P17** (1 g, 2.7 mmoles) and Et_3N (0.42 mL, 3 mmoles) in a DMF/THF mixture (13 mL/7.6 mL). The mixture is stirred at ambient temperature for 20h. The reaction mixture is poured into water and extracted with AcOEt, dried and then concentrated. The residue is chromatographed on silica gel via a solid deposit using a CH_2Cl_2/EtOH eluant: 97/3. Product **224** (0.46 g) is obtained.

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 11.62 (m, 1H), 8.51 (d, 1H), 8.36 (d, 1H), 7.90 (d, 1H), 7.57 (t, 1H), 7.37 (m, 2H), 7.24 (m, 2H), 6.97 (t, 1H), 4.99 (quint, 1H), 3.58 (d, 1H), 1.38 (broad s, 12H)

IR (cm^{-1}) : 3305

LCMS [M+H]+= 485

Intermediate 320 :

tert-Butyl {(2S,3S)-1-[(1-{3,5-difluoro-4-[(1-oxo-1,2-dihydroisoquinolin-5-yl)-carbonyl]phenyl}ethyl)amino]-3-methyl-1-oxopentan-2-yl}carbamate

Obtained according to the same protocol starting from **P17** using N-tert-butoxy-carbonyl-(L)-isoleucine. Intermediate **320** was converted directly into **P55** by treatment according to the protocol described for **P17**.

Intermediate 392 :

tert-Butyl {2-[(1-{3,5-difluoro-4-[(1-oxo-1,2-dihydroisoquinolin-5-yl)carbonyl]-phenyl}ethyl)amino]-2-oxoethyl}methylcarbamate

Obtained according to the same protocol starting from **P17** using methyl-N-tert-butoxy-carbonyl-glycine

^{1}H NMR (300 MHz, DMSO-d_6) **:** δ 11.32 (m, 1H), 8.52 (d, 1H), 8.15 (broad d, 1H), 7.87 (d, 1H), 7.55 (t, 1H), 7.32 (dd, 2H), 7.21 (d, 2H), 5.03 (m, 1H), 3.83 (dd, 1H), 2.85 (s, 3H), 1.44 (d, 3H), 1.38 (s, 9H)

IR (cm^{-1}) : 3303, 3200-2500, 1699, 1672, 1660, 1632

Intermediate 420 :

tert-Butyl (2-{[(1S)-1-{3-methyl-4-[(1-oxo-1,2-dihydroisoquinolin-5-yl)carbonyl]-phenyl}ethyl]amino}-2-oxoethyl)carbamate

Obtained according to the same protocol starting from **P53** using N-tert-butoxy-carbonyl-glycine

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 11.50 (m, 1H), 8.40 (d, 1H), 8.35 (d, 1H), 7.65 (dd, 1H), 7.50 (t, 1H), 7.30 (d, 1H), 7.25 (d, 1H), 7.20 (m, 2H), 6.90 (t, 1H), 6.75 (d, 1H), 4.95 (m, 1H), 3.60 (d, 2H), 1.40 (s, 3H), 1.35 (m, 12H)

IR (cm^{-1}) : 3600-2500, 1695, 1633, 1505

LCMS [M+H]+= 463

The intermediates so obtained were deprotected in an acidic medium to yield the final products, according to the procedure described for product **P110** when they are protected in the form of tert-butyl-carbamates.

The amines obtained were converted into alkyl intermediates according to the following protocols:

Intermediate 469 :

{2,6-Difluoro-4-[(1R)-1-{[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino}ethyl]phenyl}-(1-ethoxyisoquinolin-5-yl)methanone

To a solution of **468** (1 g, 2.8 mmoles) in DMF (10 mL) there are added K_2CO_3 (1.2 g, 8.4 mmoles) and 2-(2-bromoethoxy)-tetrahydro-2H-pyran (0.46 mL, 3.08 mmoles). The mixture is heated at 80°C for 20h. The solvent is evaporated off in vacuo, the residue is taken up in water and extracted with methylene chloride, and the organic phase is dried over $MgSO_4$ and then concentrated in vacuo. The residue is chromatographed on silica gel using a CH_2Cl_2/EtOH eluant : 98-2. Product **469** (0.59 g) is obtained in the form of an oil.

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (d, 1H), 8.15 (d, 1H), 8.05 (d, 1H), 7.72 (d, 1H), 7.30 (d, 2H), 4.58 (quad and m, 3H), 3.85 (quad, 1H), 3.75-3.45 (2m, 2H), 3.68-3.45 (2m, 2H), 2.65-2.5 (m, 2H), 2.30 (m, 1H), 1.75-1.65 (2m, 2H), 1.50 (t and m, 7H), 1.30 (d, 3H)

IR (cm^{-1}) : 3333, 1674

Intermediate 437 :

{2,6-Difluoro-4-[(1S)-1-{[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino}ethyl]phenyl}-(1-ethoxyisoquinolin-5-yl)methanone

Obtained according to the same protocol starting from intermediate **435**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (d, 1H), 8.15 (d, 1H), 8.05 (d, 1H), 7.72 (d, 1H), 7.30 (d, 2H), 4.58 (quad and m, 3H), 3.85 (quad, 1H), 3.75-3.45 (2m, 2H), 3.68-3.45 (2m, 2H), 2.65-2.5 (m, 2H), 2.30 (m, 1H), 1.75-1.65 (2m, 2H), 1.50 (t and m, 7H), 1.30 (d, 3H)

IR (cm^{-1}) : 3328, 1671

Intermediate 285 :

[2,6-Difluoro-4-(1-{[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino}ethyl)phenyl](1-ethoxyisoquinolin-5-yl)methanone

This procedure was also used to prepare intermediate **285**, racemic mixture of intermediates **469** and **437**.

Intermediate 422 :

[2,6-Difluoro-4-(2-{[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]amino}propan-2-yl)-phenyl](1-ethoxyisoquinolin-5-yl)methanone

Obtained according to the same protocol starting from **421**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (d, 1H), 8.15 (d, 1H), 8.05 (d, 1H), 7.72 (t, 1H), 7.35 (d, 2H), 4.57 (quad and m, 3H), 3.75-3.45 (2m, 2H), 3.65-3.45 (2m, 2H), 2.48 (m, 2H), 2.30 (m, 1H), 1.8-1.4 (m, 4H), 1.6-1.45 (2m, 2H), 1.50 (t, 3H), 1.4 (s, 6H)

Intermediate 516 :

(2,6-Difluoro-4-{(1R)-1-[(2-methoxyethyl)amino]ethyl}phenyl)(1-ethoxyisoquinolin-5-yl)methanone

To a solution of **468** (1 g, 2.8 mmoles) in DMF (15 mL) there are added Et_3N (1.18 mL, 8.4 mmoles) and 2-bromoethyl methyl ether (0.29 mL, 3.1 mmoles). The mixture is heated at 70°C for 4 days. The mixture is decanted in the presence of water and of methylene chloride, and the organic phase is washed with water and then with a saturated NaCl solution. After drying over $MgSO_4$ and concentration in vacuo, the residue is chromatographed on silica gel using a CH_2Cl_2/AcOEt eluant : 50/50. Product **516** (0.46 g) is obtained in the form of an oil.

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (d, 1H), 8.15 (d, 1H), 8.05 (d, 1H), 7.75 (m, 1H), 7.30 (m, 2H), 4.6 (quad, 2H), 3.85 (m, 1H), 3.4 (t, 2H), 3.25 (s, 3H), 2.55 (m, 2H), 2.25 (s, 1H), 1.45 (t, 3H), 1.30 (d, 3H)

IR (cm^{-1}) : 3325

LCMS [M+H]+= 414

Optical purity (OJ-H column, eluant : methanol/diethylamine 100/0.1, detection 254nm) : >98.8%.

Intermediate 517 :

(2,6-Difluoro-4-{(1S)-1-[(2-methoxyethyl)amino]ethyl}phenyl)(1-ethoxyisoquinolin-5-yl)methanone

Obtained according to the same protocol starting from **435**

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.55 (d, 1H), 8.20 (d, 1H), 8.15 (d, 1H), 8.05 (d, 1H), 7.75 (m, 1H), 7.30 (m, 2H), 4.6 (quad, 2H), 3.85 (m, 1H), 3.4 (t, 2H), 3.25 (s, 3H), 2.55 (m, 2H), 2.25 (s, 1H), 1.45 (t, 3H), 1.30 (d, 3H)

IR (cm^{-1}) : 3325

LCMS [M+H]+= 414

Optical purity (OJ-H column, eluant : methanol/diethylamine 100/0.1, detection 254nm) : >99%.

Intermediate 753 :

[2,6-Difluoro-4-(1-{[2-(methylsulphonyl)ethyl]amino}ethyl)phenyl](1-ethoxy-isoquinolin-5-yl)methanone

To a solution of **752** (0.7 g, 2.09 mmoles) in 1,4-dioxane (7.5 mL) there are added diisopropyl-ethyl-amine (0.47 mL, 3.3 mmoles) and methyl-vinyl-sulphone (1.09 mL, 1.2 mmoles). The mixture is heated at 90°C for 8 days. The mixture is decanted in the presence of water and of methylene chloride, and the organic phase is washed with a saturated NH_4Cl solution and then with a saturated Na_2CO_3 solution. After drying over $MgSO_4$ and concentration in vacuo, the residue is chromatographed on silica gel using a CH_2Cl_2/EtOH eluant: 100/0 to 95/5. Product **753** (0.46 g) is obtained in the form of an oil.

^{1}H NMR (400 MHz, DMSO-d_6) **:** δ 8.53 (d, 1H), 8.20 (d, 1H), 8.12 (d, 1H), 8.06 (d, 1H), 7.72 (t, 1H), 7.30 (d, 2H), 4.58 (quad, 2H), 3.88 (quad, 1H), 3.23 (quad, 2H), 3.03 (s, 3H), 2.78 (t, 2H), 1.47 (t, 3H), 1.29 (d, 3H)

IR (cm^{-1}) : 3339, 1671, 1371, 1119

Intermediates **422**, **437**, **469**, **516**, **517**, **753** obtained were deprotected in an acidic medium to yield the final products, according to the procedure described for product **P17**.

Product	Obtained from	Nomenclature Analytical description
P38	**P17**	**N-(1-{3,5-Difluoro-4-[(1-oxo-1,2-dihydroisoquinolin-5-yl)carbonyl]phenyl}ethyl)glycinamide hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) : δ 10.70 (m, 1H), 9.20 (d, 1H), 8.55 (d, 1H), 8.20 (m, 3H), 7.90 (d, 1H), 7.60 (t, 1H), 7.40 (m, 2H), 7.35 (m, 2H), 5.05 (m, 1H), 3.70 (m, 2H), 1.45 (d, 3H) **IR (cm^{-1}) :** 3100-3000, 3000-2800, 1672 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{18}F_2N_3O_3$ $[M+H]^+$ 386.1316, measured 386.1315
P48	**285**	**5-(2,6-Difluoro-4-{1-[(2-hydroxyethyl)amino]ethyl}-benzoyl)isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.70-11.60 (s, 1H), 10.0-9.0 (2m, 2H), 8.55 (m, 1H), 8.00 (m, 1H), 7.77-7.55 (m, 3H), 7.40 (m, 2H), 5.5-5.0 (m, 1H), 4.55 (m, 1H), 3.70 (m, 2H), 2.95-2.80 (2m, 2H) **IR (cm^{-1}) :** 3350, 2844-2400, 1687-1674, 1633 **HRMS (ESI) :** theoretical m/z for $C_{10}H_{19}F_2N_2O_3$ $[M+H]^+$ 373.1364, measured 373.1362
P54	**P17**	**N-(1-{3,5-Difluoro-4-[(1-oxo-1,2-dihydroisoquinolin-5-yl)carbonyl]phenyl}ethyl)-L-isoleucinamide hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.65 (broad s, 1H), 9.25 (2d, 1H), 8.55 (d, 1H), 8.12 (unresolved peak, 3H), 7.90 (2d, 1H), 7.60 (2t, 1H), 5.10 (quint, 1H), 3.72 (m, 1H), 1.90 (m, 1H), 1.60-1.05 (m, 3H), 0.95-0.85 (m, 6H) **IR (cm^{-1}) :** 3600-2300, 1689, 1661, 1630 **HRMS (ESI) :** theoretical m/z for $C_{24}H_{26}F_2N_3O_3$ $[M+H]^+$ 442.194223, measured 442.1939
P69	**P17**	**N-(1-{3,5-Difluoro-4-[(1-oxo-1,2-dihydroisoquinolin-5-**

		yl)carbonyl]phenyl}ethyl)-N^2-methylglycinamide hydrochloride **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.70 (s, 1H), 9.15 (d, 1H), 8.80 (m, 2H), 8.52 (d, 1H), 7.90 (d, 1H), 7.60 (t, 1H), 7.40 (m, 2H), 7.30 (d, 2H), 5.05 (quint, 1H), 3.80 (AB, 2H), 2.60 (s, 3H), 1,45 (d, 3H) **IR (cm^{-1}) :** 3700-2000, 1689, 1672, 1632 **HRMS (ESI) :** theoretical m/z for $C_{21}H_{20}F_2N_3O_3$ $[M+H]^+$ 400.1473, measured 400.1456
P76	**419**	**N-{4,6-Difluoro-5-[(1-oxo-1,2-dihydroisoquinolin-5-yl)carbonyl]-2,3-dihydro-1H-inden-1-yl}glycinamide hydrochloride** **^{1}H NMR** (300 MHz, DMSO-d_6) **:** δ 11.60 (m, 1H), 8.90 (d, 1H), 8.50 (dd, 1H), 8.00 (m, 3H), 7.90 (d, 1H), 7.60 (t, 1H), 7.40 (m, 2H), 7.15 (d, 1H), 5.40 (quad, 1H), 3.65 (2d, 2H), 3 (m, 1H), 2.85 (m, 1H), 2.55 (m, 1H), 2.00 (m, 1H) **IR (cm^{-1}) :** 3300-2300, 3289, 1652, 1628, 1544 **HRMS (ESI) :** theoretical m/z for $C_{21}H_{18}F_2N_3O_3$ $[M+H]^+$ 398.1316, found 398.1304. Optical purity (SFC: AD 5µM column 4.6x250 mm ; eluant: CO_2 / (methanol/butylamine:100/0.5) : 65/35 ; detection: 255nm) : >99%. (absence of **P79**)
P77	**P53**	**N-[(1S)-1-{3-Methyl-4-[(1-oxo-1,2-dihydroisoquinolin-5-yl)carbonyl]phenyl}ethyl]glycinamide hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.50 (m, 1H), 9.00 (d, 1H), 8.45 (d, 1H), 8.10 (m, 3H), 7.65 (dd, 1H), 7.55 (t, 1H), 7.40 (d, 1H), 7.30 (m, 2H), 7.30 (m, 1H), 6.80 (d, 1H), 5.00 (quint, 1H), 3.60 (s, 2H), 2.40 (s, 3H), 1.40 (d, 3H) **IR (cm^{-1}) :** 3650-2080, 1675-1660, 1600, 1557, 832-688 **HRMS (ESI) :** theoretical m/z for $C_{21}H_{22}N_3O_3$ $[M+H]^+$

		364.1661, measured 364.1648
P78	**422**	**5-(2,6-Difluoro-4-{2-[(2-hydroxyethyl)amino]propan-2-yl}benzoyl)isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.70 (broad s, 1H), 9.80-9.30 (m, 2H), 8.55 (m, 1H), 8.00 (m, 1H), 7.65 (d, 2H), 7.60 (t, 1H), 7.40 (m, 2H), 5.25 (t, 1H), 3.65 (quad, 2H), 2.75 (m, 2H), 1.80 (broad s, 6H) **IR (cm^{-1}) :** 3500-2000, 1660, 1627 **HRMS (ESI) :** theoretical m/z for $C_{21}H_{21}F_2N_2O_3$ $[M+H]^+$ 387.1520, measured 387.1517.
P79	**427**	**N-{4,6-Difluoro-5-[(1-oxo-1,2-dihydroisoquinolin-5-yl)carbonyl]-2,3-dihydro-1H-inden-1-yl}glycinamide hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.60 (m, 1H), 9.10 (d, 1H), 8.50 (dd, 1H), 8.20 (m, 3H), 7.90 (d, 1H), 7.60 (t, 1H), 7.40 (m, 2H), 7.15 (d, 1H), 5.40 (quad, 1H), 3.65 (2d, 2H), 3.00 (m, 1H), 2.85 (m, 1H), 2.55 (m, 1H), 2.00 (m,1H) **IR (cm^{-1}) :** 3300-2300, 3289, 1652, 1628, 1544 **HRMS (ESI) :** theoretical m/z for $C_{21}H_{18}F_2N_3O_3$ $[M+H]^+$ 398.1316, measured 398.1334. **Optical purity** (SFC: AD 5µM column 4.6x250 mm ; eluant: CO_2 / (methanol/butylamine:100/0.5) : 65/35 ; detection: 255nm) : >99%. (absence of **P76**)
P83	**436**	**N-[(1S)-1-{3,5-Difluoro-4-[(1-oxo-1,2-dihydroisoquinolin-5-yl)carbonyl]phenyl}ethyl]-glycinamide hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.65 (broad s, 1H), 9.10 (d, 1H), 8.50 (dd, 1H), 8.30-7.90 (broad s, 3H), 7.90 (dd, 1H), 7.55 (t, 1H), 7.35 (dd, 2H), 7.30 (d, 2H), 5.05 (m, 1H), 3.65 (m, 2H), 1.45 (d, 3H)

		IR (cm^{-1}) : 3318, 3200-2500, 1692, 1674 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{18}F_2N_3O_3$ $[M+H]^+$ 386.1316, measured 386.1300. α_D (589nM) = -59.93 (c = 1, DMSO) at 20°C
P84	**437**	**5-(2,6-Difluoro-4-{(1S)-1-[(2-hydroxyethyl)amino]-ethyl}benzoyl)isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.70 (d, 1H), 8.53 (d, 1H), 7.99 (d, 1H), 7.60 (m, 3H), 7.41 (m, 2H), 5.24 (t, 1H), 4.53 (q, 1H), 3.69 (m, 2H), 2.95 (m, 1H), 2.80 (m, 1H), 1.63 (d, 3H) **IR (cm^{-1}) :** 3500-3200, 3200-2200, 1685, 1620 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{19}F_2N_2O_3$ $[M+H]^+$ 373.1364, measured 373.1350. α_D (589nM) = -1.7 (c = 0.01, DMSO) at 20°C
P89	**469**	**5-(2,6-Difluoro-4-{(1R)-1-[(2-hydroxyethyl)amino]-ethyl}benzoyl)isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.80 (broad s, 1H), 10.80-10.30 (2 broad s, 2H), 8.52 (d, 1H), 8.00 (d, 1H), 7.60 (d+t, 3H), 7.40 (d, 2H), 5.25 (t, 1H), 4.50 (m, 1H), 3.70 (m, 2H), 2.95-2.70 (m, 2H), 1.65 (d, 3H) **IR (cm^{-1}) :** 3500-2700, 3200-2700, 1685-1672 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{19}F_2N_2O_3$ $[M+H]^+$ 373.1364, measured 373.1348. α_D (589nM) = 1.29 (c = 1, DMSO) at 20°C

P97	**468**	**5-(2,6-Difluoro-4-{(1R)-1-[(2-methoxyethyl)amino]-ethyl}benzoyl)isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.66 (m, 1H), 9.67-9.38 (2m, 2H), 8.54 (dd, 1H), 7.98 (broad d, 1H), 7.58 (t, 1H), 7.56 (d, 2H), 7.42 (m, 2H), 4.50 (m, 1H), 3.60 (m, 2H), 3.30 (s, 3H), 3.05-2.90 (2m, 2H), 1.62 (d, 3H) **IR (cm^{-1}) :** 3500-2000, 1671, 1630 **HRMS (ESI) :** theoretical m/z for $C_{21}H_{21}F_2N_2O_3$ $[M+H]^+$ 387.1520, measured 387.1524. **Optical purity** (SFC: OZ-H 5µM column 4.6x250 mm ; eluant: CO_2 / (methanol/diethylamine:100/0.5) : 73/27 ; detection: 254nm) : 98.7%.
P98	**495**	**5-(2,6-Difluoro-4-{(1S)-1-[(2-methoxyethyl)amino]-ethyl}benzoyl)isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.68 (m, 1H), 9.90-9.56 (2m, 2H), 8.54 (dd, 1H), 7.99 (broad d, 1H), 7.61 (d, 2H), 7.57 (t, 1H), 7.42 (m, 2H), 4.51 (m, 1H), 3.63 (m, 2H), 3.30 (s, 3H), 3.05-2.90 (2m, 2H), 1.64 (d, 3H) **IR (cm^{-1}) :** 3500-2000, 1693, 1662, 1627 **HRMS (ESI) :** theoretical m/z for $C_{21}H_{21}F_2N_2O_3$ $[M+H]^+$ 387.1520, measured 387.1524. **Optical purity** (SFC: OZ-H 5µM column 4.6x250 mm ; eluant: CO_2 / (methanol/diethylamine:100/0.5) : 73/27 ; detection: 254nm) : >99%. (absence of **P97**)

P138	**742**	**N-(2-{3,5-Difluoro-4-[(1-oxo-1,2-dihydroisoquinolin-5-yl)carbonyl]phenyl}propan-2-yl)glycinamide hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 11.90-11.50 (m, 1H), 8.85 (m, 1H), 8.50 (dd, 1H), 8.20-7.85 (m, 3H), 7.90 (dd, 1H), 7.60 (dd, 1H), 7.40 (m, 2H), 7.25 (d, 2H), 3.65 (s, 2H), 1.65 (s, 6H) **IR (cm^{-1}) :** 3600-2000, 3303, 1672, 1628 **HRMS (ESI) :** theoretical m/z for $C_{21}H_{20}F_2N_3O_3$ $[M+H]^+$ 400.1473, measured 400.14518
P140	**753**	**5-[2,6-Difluoro-4-(1-{[2-(methylsulphonyl)ethyl]-amino}ethyl)benzoyl]isoquinolin-1(2H)-one hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 10.70 (m, 1H), 10.50-10.00 (m, 2H), 8.55 (d, 1H), 7.95 (d, 1H), 7.65 (d, 2H), 7.60 (t, 1H), 7.40 (m, 2H), 4.60 (m, 1H), 3.65 (m, 2H), 3.40-3.10 (m, 2H), 3.15 (s, 3H), 1.65 (d, 3H) **^{19}F NMR:** -111.7 **IR (cm^{-1}) :** 3100, 2800-2600, 1674-1634, 1276-1139 **HRMS (ESI) :** theoretical m/z for $C_{21}H_{21}F_2N_2O_4S$ $[M+H]^+$ 435.1190, measured 435.1152.
P142	**765**	**N-[(1R)-1-{3,5-Difluoro-4-[(1-oxo-1,2-dihydroiso-quinolin-5-yl)carbonyl]phenyl}ethyl]glycinamide hydrochloride** **^{1}H NMR** (400 MHz, DMSO-d_6) **:** δ 12.0-11.5 (m, 1H), 9.0 (d, 1H), 8.50 (dd, 1H), 7.90 (dd, 1H), 8.2-7.8 (m, 3H), 7.55 (t, 1H), 7.35 (dd, 2H), 7.30 (d, 2H), 5.05 (m, 1H), 3.65 (m, 2H), 1.45 (d, 3H) **IR (cm^{-1}) :** 3307, 3300-2000, 1691, 1673 **HRMS (ESI) :** theoretical m/z for $C_{20}H_{18}F_2N_3O_3$ $[M+H]^+$ 386.1316, measured 386.1300. **α_D** (589nM) **=** +62.5 (c = 1, DMSO) at 20°C

Pharmacological studies

ROCK1 enzymatic test

Evaluation of the effects of compounds on human ROCK1 activity quantified by measuring the phosphorylation of the substrate Ulight-RRRSLLE (PLK) using a human recombinant enzyme and the LANCE® detection method.

Experimental protocol

The test compound, the reference compound or water (control) is mixed with the enzyme (8.2 ng) in a buffer comprising 40 mM Hepes/Tris (pH 7.4), 0.8 mM EGTA/Tris, 8 mM $MgCl_2$, 1.6 mM DTT and 0.008% Tween 20.

The reaction is then started by adding 50 nM of Ulight-RRRSLLE (PLK) substrate and 1 μM of ATP, and the mixture is incubated for 30 minutes at ambient temperature. For the basal control measurements, the enzyme is excluded from the reaction mixture.

After the incubation, the reaction is stopped by adding 13 mM of EDTA. After 5 minutes, the anti-phospho-PLK antibody labelled with europium chelate is added. After a further 60 minutes, the fluorescence transfer is measured at lex=337 nm, lem=620 nm and lem=665 nm using a microplate reader (Envision, Perkin Elmer). The enzymatic activity is determined by dividing the signal measured at 665 nm by that measured at 620 nm (ratio).

The results are expressed in the form of a percentage inhibition of the control enzymatic activity. The standard reference inhibition compound is staurosporine, which is tested in each experiment at several concentrations in order to obtain an inhibition curve on the basis of which the value of the IC_{50} (concentration that induces 50% inhibition) is calculated.

Bibliographical reference

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Compound of formula (I)	ROCK1(h), IC_{50} (M)
P9	5.87E-09
P17	4.20E-09
P19	6.30E-08
P24	2.30E-08
P27	8.70E-09
P42	9.60E-09
P45	5.00E-09
P47	6.78E-09
P48	7.45E-09
P50	5.40E-09
P56	1.65E-08
P58	3.85E-09
P59	1.95E-09
P61	5.35E-09
P75	1.04E-08
P129	2.05E-08
P139	8.75E-08

Functional test (rat aorta)

Study of vascular reactivity on aortic segments of the rat.

After anaesthesia of the animal, the thoracic aorta is removed and immediately placed in a physiological saline solution (PSS). The proximal thoracic aorta is cleaned of adherent conjunctive tissue and 4 aortic rings (3-4 mm) are cut. The endothelium is removed mechanically without damaging the smooth muscle cells.

The rings without endothelium are placed in PSS medium in isolated organ baths maintained at 37°C in the presence of carbogen. The isometric tension of the rings is recorded by means of a force sensor. At their optimum tension, the rings are subjected to an equilibration period during which the physiological medium is replaced regularly.

The preparations are then contracted twice by means of a hyperpotassic solution (KCl 60 mM), each of the 2 contractions being followed by successive washings in order to return to the original tension. The absence of endothelium is verified after contraction by an α_1-adrenergic receptor agonist, phenylephrine (PHE, 10^{-6}M), followed by the addition of carbachol (10^{-5}M), a muscarinic receptor agonist, which induces a relaxation only in the presence of endothelium. The rings are then washed regularly with PSS for 60 minutes in order to remove the pharmacological agents.

The rings are recontracted with PHE (10^{-6}M) and then, after stabilisation of the contraction, the product or its solvent is added in cumulative concentrations, 5 concentrations are tested: 10^{-8}M, 10^{-7}M, 10^{-6}M, 10^{-5}M and $3x10^{-5}$M (if the product is dissolved in DMSO) or 10^{-4}M (if H_2O is the solvent of the product).

Analysis of the results

The contractile response is obtained in milligrams (mg). The results are expressed by the mean ± SEM of the contractile responses obtained on at least 2 rats. The variations in tension of each product are calculated as a percentage of the maximum contraction induced by PHE before the product is added, according to the formula:

% contraction B(t) = [x (mg) tension (compound) B(t) / y (mg) maximum tension (PHE) B] x100.

The concentration-response curves obtained are analysed and allow the IC_{50} value of each product to be determined (IC_{50}: concentration of product necessary to inhibit 50% of the maximum contraction induced by PHE), the estimation of the IC_{50} value of the concentration-response curves being obtained by non-linear regression.

Compound of formula (I)	**Relaxation (rat aorta+PHE), IC_{50} (M)**
P6	2.00E-07
P9	3.30E-08
P17	1.40E-08
P19	2.30E-07
P21	1.00E-06
P24	1.00E-08

P27	5.00E-08
P42	2.00E-07
P45	1.00E-07
P47	4.00E-08
P48	1.50E-07
P50	1.00E-07
P56	1.50E-07
P58	7.00E-08
P59	5.50E-07
P61	1.70E-07
P75	2.00E-07
P129	2.00E-06
P139	2.00E-06

Evaluation on the arterial pressure (SHR rats)

The effect of the ROCK inhibitors was tested by the reduction of the arterial pressure (AP) that they induce in spontaneously hypertensive rats (SHR) after intravenous (i.v.) and/or oral administration. In summary, the SHRs were anaesthetised with 2% isoflurane, and a telemetry probe (PAC40, Data Science International) was implanted in the abdominal aorta to record the AP and a polyethylene catheter was implanted in the jugular vein for the i.v. administration.

After recovery from the surgery (2 to 3 weeks), the AP was recorded continuously for 24 hours after adminstration of the ROCK inhibitors at doses of 1, 3, 10 and 30 mg/kg by the i.v. route and/or by the oral route. The effect on the AP was expressed as the percentage reduction relative to the basal arterial pressure before administration of the product.

Compound of formula (I)	SHR rat ΔAP% max, IV 3mg/kg	SHR rat ΔAP% max, PO 3mg/kg
P6	-73.4	-35.6
P9	-67	-53.7
P17	-72.8	-56.6
P19	-39.6	-
P24	-68.2	-52.5
P27	-69	-54
P42	-59.9	-12.3
P45	-60.6	-24
P47	-62.7	-26.4
P48	-67.3	-29.2
P50	-58	-16.8
P56	-54.7	-
P58	-65.1	-52.7
P59	-40.3	-
P61	-59	-
P75	-49.8	-12.4
P129	-30.2	-18.4

Pharmaceutical compositions

Tablets obtained by wet granulation

Constituents	Quantity %
Compound of formula (I)	10
Normal lactose powder	qs 100
Maize starch	20
PVP K30	7
Carboxymethyl potato starch, weakly cross-linked sodium salt	3
Colloidal silica	0.2
Magnesium stearate	0.5

Tablets obtained by direct compression

Constituents	Quantity %
Compound of formula (I)	10
Agglomerated lactose	qs 100
Microcrystalline cellulose	25
Carboxymethyl potato starch, weakly cross-linked sodium salt	3
Colloidal silica	0.2
Magnesium stearate	0.5

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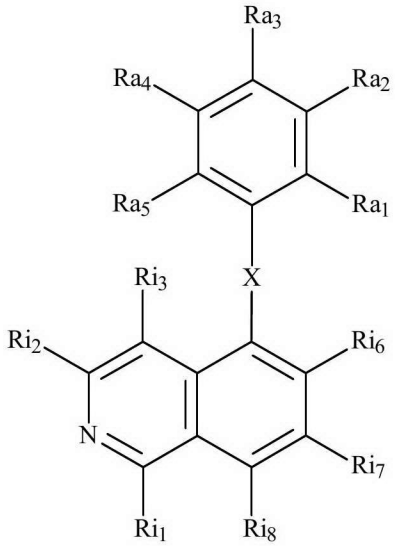
The claims defining the invention are as follows:

1. A compound of formula (I) :

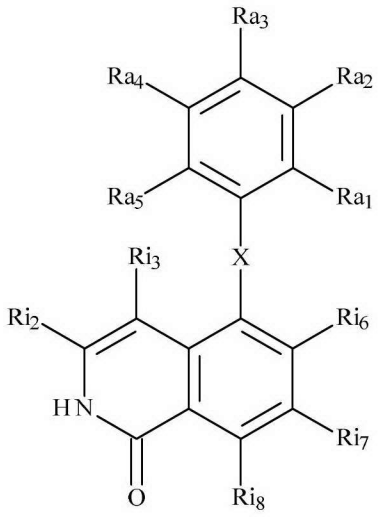


(I)

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:



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- 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. The compound of formula (I) according to claim 1, wherein 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. The compound of formula (I) according to either claim 1 or claim 2, wherein 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. The compound of formula (I) according to any one of claims 1 to 3, wherein 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. The compound of formula (I) according to any one of claims 1 to 4, wherein 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. The compound of formula (I) according to any one of claims 1 to 5, wherein 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. The compound of formula (I) according to claim 6, wherein:

- 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. The compound of formula (I) according to claim 1, wherein:

- 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. The 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.

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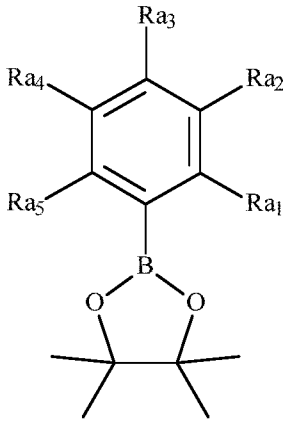
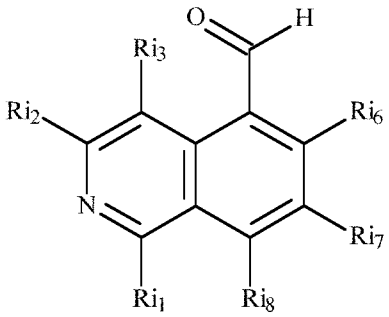
10. A process for the synthesis of compounds of formula (Ia), particular cases of compounds of formula (I) wherein X represents a group -C(=O), wherein the compounds of formula (Ia) are prepared starting from a compound of formula (II) :



(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) :

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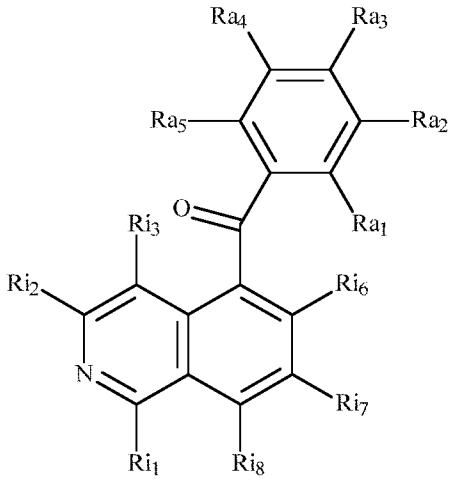
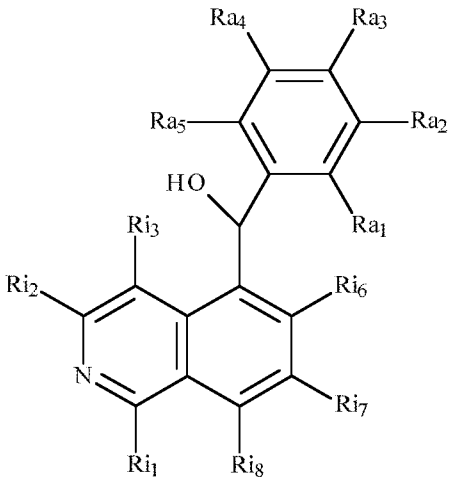


(Ia)

11. A process for the synthesis of compounds of formula (Ib), particular cases of the compounds of formula (I) wherein X represents a group -CH(OH)- :



(Ib)

wherein the compounds of formula (Ib) are prepared starting from compounds of formula (Ia) by a reduction reaction in the presence of sodium tetraborohydride.

12. A process for the synthesis of compounds of formula (Ic), particular cases of the compounds of formula (I) wherein X represents a group -CH_2-

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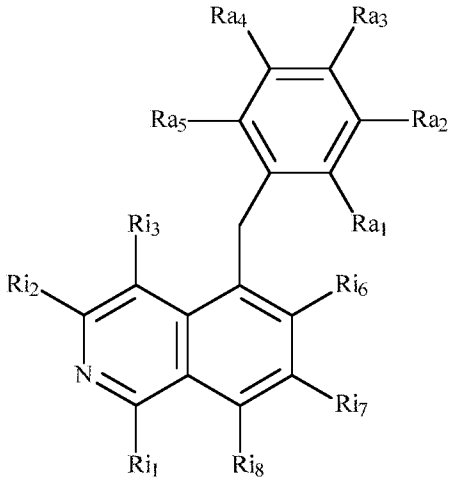

(Ic)

wherein the compounds of formula (Ic) are prepared starting from the compounds of formula (Ib) by a reduction reaction in the presence of trifluoroacetic acid and of triethylsilane.

13. A 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. A method for the treatment or prevention of pathologies which are the result of activation of the RhoA/ROCK pathway and phosphorylation of the myosin light chain in a subject, the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 9 or a pharmaceutical composition according to claim 13.

15. The method according to claim 14, for 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. The method according to claim 15, for the treatment or prevention of systemic arterial hypertension.

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17. The method according to claim 14, for the treatment or prevention of glaucoma and pathologies of the cornea.

18. The method according to claim 14, for 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.

19. Use of a compound according to any one of claims 1 to 9 or a pharmaceutical composition according to claim 13 in the manufacture of a medicament for the treatment or prevention of pathologies which are the result of activation of the RhoA/ROCK pathway and phosphorylation of the myosin light chain.