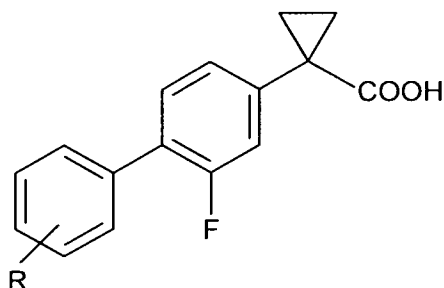


PROCESS FOR THE PREPARATION OF DERIVATIVES OF 1-(2-HALOBIPHENYL-4-YL)-CYCLOPROPANECARBOXYLIC ACID

TECHNICAL FIELD

The invention relates to a process for the preparation of compounds of formula (IA):



(IA)

The compounds are useful for prevention and/or treatment of neurodegenerative diseases such as Alzheimer's disease.

BACKGROUND OF THE INVENTION

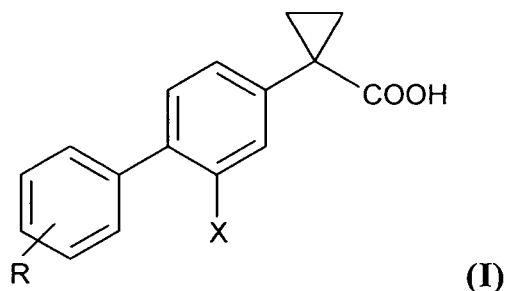
Alzheimer's disease is a neurodegenerative disorder characterized from a histopathologic point of view by a diffuse presence of extracellular and perivascular neuritic plaques and intracellular neurofibrillary tangles in the cerebral parenchyma of Alzheimer patients.

Neuritic plaques are mainly composed of aggregates of a protein with 39-43 amino acid residues known as β -amyloid (β A), and, depending on the numbers of amino acids, $A\beta_{39}$, $A\beta_{40}$, $A\beta_{42}$ and $A\beta_{43}$.

Compounds have been reported which can reduce the production of the most neurotoxic isoform of β -amyloid, namely the form containing 42 amino acids ($A\beta_{42}$), through their interaction with a macromolecular/multiprotein enzymatic complex with aspartyl-protease activity, known as γ -secretase.

WO 2004/074232 discloses derivatives of 1-(2-halobiphenyl-4-yl)-cyclopropanecarboxylic acid of formula (I) capable of modulating γ -secretase

activity without affecting other important metabolic processes such as cyclooxygenase-enzymes activity.



R is defined below, and X is preferably fluorine.

5 The key intermediate step of the preparation of said compounds is the Suzuki reaction between a suitable phenylboronic acid or an ester thereof with a 3,4-dihalo-cyclopropanecarboxylic acid, preferably a 3-fluoro-4-halo-cyclopropanecarboxylic acid.

10 In WO 2004/074232, 3-fluoro-4-halo-cyclopropanecarboxylic acid may be obtained starting from 3-fluoro-4-halo-toluene which is transformed into the corresponding benzyl bromide by radical bromination in carbon tetrachloride (CCl₄); the resulting bromide is transformed into the 3-fluoro-4-halophenylacetonitrile; the latter is reacted with 1,2-dibromoethane to give the corresponding 3-fluoro-4-halo-phenylcyclopropanenitrile which is finally
15 hydrolyzed to the desired 3-fluoro-4-halo-cyclopropanecarboxylic.

However, the process described in WO 2004/074232 provides a low overall yield (12-14%) and suffers from severe restrictions for the industrial use.

20 In particular, the final Suzuki coupling reaction has a poor yield and the resulting product is difficult to purify by crystallization without a loss of yield. Silica gel chromatography has been used for such purification, but scale-up of silica gel chromatography is tedious and requires large volumes of solvents.

Moreover, the radical bromination step used for the preparation of the benzyl bromide derivative gives a significant amount of the *bis*-halogenated side-product, detrimental to its yield, and involves the use of CCl₄ which is highly toxic

and also both ozone-depleting and a greenhouse gas.

The present invention concerns a process for the preparation of derivatives of 1-(2-halobiphenyl-4-yl)-cyclopropanecarboxylic acid of formula (IA), wherein the halogen atom is fluorine, which does not have all the aforementioned
5 drawbacks.

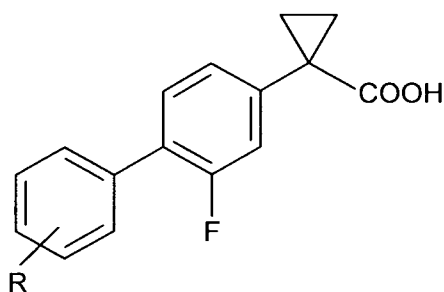
The object of the present invention is mainly achieved by carrying out the Suzuki reaction on the nitrile derivative before the hydrolysis to the corresponding carboxylic acid derivative.

Moreover, different conditions for ameliorating the yield of the other steps
10 have been introduced, in particular the radical bromination step.

The process of the invention turned out to be more efficient, especially for large scale production, providing higher yield of the compounds of formula (IA) in high chemical purity without the need for a chromatographic purification step

SUMMARY OF THE INVENTION

15 The present invention concerns a process for the preparation of a compound of formula (IA)



(IA)

wherein R represents one or more groups independently selected from:

- 20
- halogen atoms, preferably chlorine;
 - CF_3 ;
 - $\text{CH}=\text{CH}_2$;
 - CN ;
 - CH_2OH

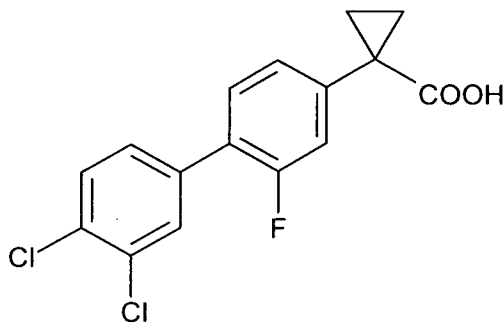
- NO₂;
 - methylenedioxy;
 - ethylenedioxy;
 - cycloalkyl, preferably C₃-C₆ cycloalkyl;
 - 5 - phenyl;
 - OR₁ or NHCOR₁ wherein R₁ is selected from CF₃, alkenyl, alkynyl, benzyl; and phenyl;
 - SR₂, SOR₂ or COR₂ wherein R₂ is alkyl;
- and pharmaceutically acceptable salts thereof,

10 said process comprising the following steps according to scheme 1:

- i) reacting a compound of formula (IV) wherein X' is chlorine, bromine, iodine or a triflate group (CF₃SO₃), preferably bromide, with 1,2-dibromoethane to form a compound of formula (V);
- ii) coupling a compound of formula (V) with a compound a formula
15 (VI) wherein R is as defined above to form a compound of formula (VII); and
- iii) hydrolyzing a compound of formula (VII) to obtain a compound of formula (I)

20 Preferably, the invention provides a process for the preparation of a compound of formula (IA) wherein R is chlorine.

More preferably, the invention provides a process for the preparation of 1-(3',4'-dichloro-2-fluoro[1,1'-biphenyl]-4-yl)-cyclopropanecarboxylic acid of formula



Said compound has also been referred to with the code CHF 5074.

The invention also concerns a process for preparing a pharmaceutical composition, said process comprising steps (i)–(iii) and an additional step comprising admixing of one or more pharmaceutically acceptable excipients.

5 **DEFINITIONS**

The term “halogen atoms” includes fluorine, chlorine, bromine, and iodine.

“Alkyl” means straight chain or branched C₁–C₄ alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl,

10 “Alkenyl” means straight chain or branched C₂–C₆ alkenyl, such as vinyl, 1-propenyl, 2-propenyl, 1-butenyl, isobutenyl, or straight-or branched-pentenyl and hexenyl. The term “alkynyl” is to be construed in an analogous manner.

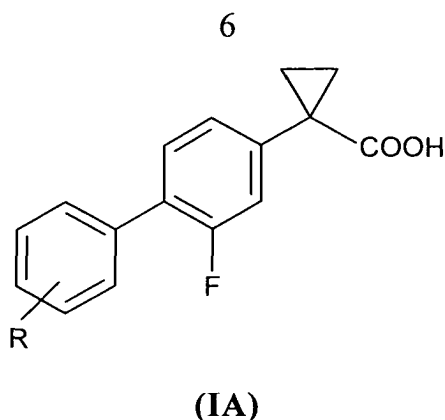
“Cycloalkyl” means a cyclic non-aromatic hydrocarbon group
15 containing from 3 to 8 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

“Saturated heterocyclic” means a saturated heterocyclic group having at least 4 carbon atoms and at least one heteroatom, preferably from one to four heteroatoms selected from nitrogen, oxygen and sulphur. Examples include
20 piperidyl or tetrahydrofuryl.

The term “pharmaceutically acceptable salts” refer to salts obtained by reacting the main compound, in acid form, with an inorganic or organic base to form a salt approved for human use, e. g., sodium, potassium, calcium, magnesium, and ammonium salts.

25 **DETAILED DESCRIPTION OF THE INVENTION**

The present invention provides a process for the preparation of a compound of formula (IA) wherein R is as defined above,
said process comprising the steps of Scheme 1.

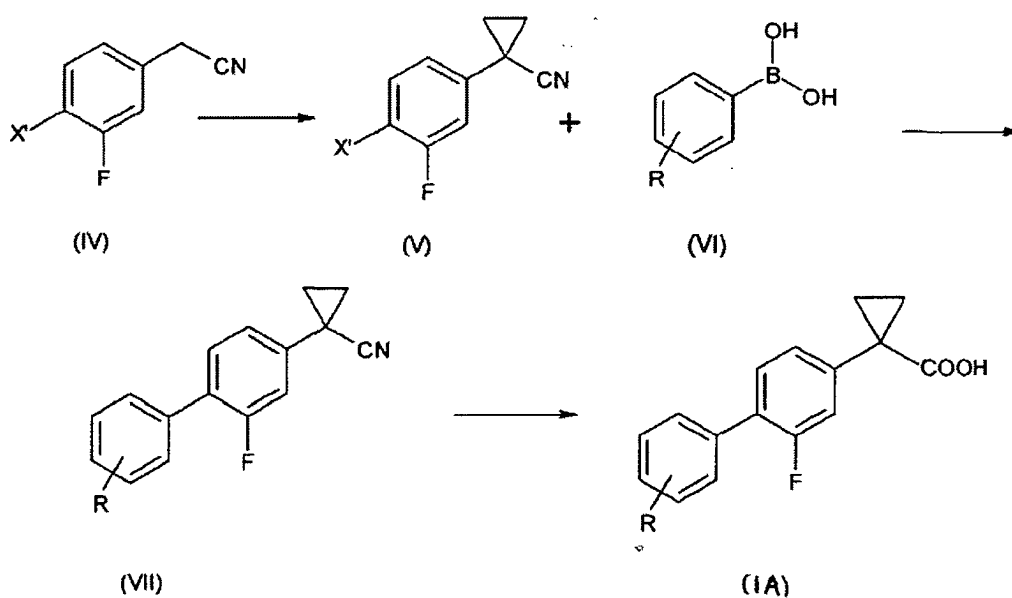


When R is cycloalkyl, it is optionally substituted by one or more groups independently selected from alkyl, CF₃, OH and oxo groups.

5 Preferably the cycloalkyl group is C₃-C₆ cycloalkyl.

When R is phenyl, it is optionally substituted by one or more groups independently selected from halogen atoms, CF₃, OCF₃, OH, alkyl and a saturated heterocyclic.

10 The saturated heterocyclic group is preferably a monocyclic ring having 5 or 6 atoms and one or two nitrogen atoms or one nitrogen atom and one oxygen atom such as pyrrolidine, imidazolidine and isoxazolidine.



Any compound of formula (IV), with X' selected from the group consisting of chlorine, bromide, iodine and a CF₃SO₃ group (triflate), which is commercially available, may be used as starting material.

Preferably, the compound wherein X' is bromide is used as starting
5 material.

In the first step (step i), the compound of formula (IV) is reacted with 1,2-dibromoethane to form a compound of formula (V) wherein X' is as defined above.

Advantageously, step (i) may be conducted in an organic solvent such
10 as ethanol or acetonitrile or mixtures thereof with water.

Preferably, said cyclopropanation step is carried out as a phase transfer catalysis reaction in the presence of concentrated NaOH and tetrabutylammonium chloride (TBAC) or tetrabutylammonium bromide (TBAB). The concentration of NaOH can advantageously range from 30 to
15 50% w/v.

The temperature in step (i) may be preferably maintained from about 20°C to about 50°C.

Generally, the compound of formula (V), which is preferably 4-bromo-3-fluorophenylcyclopropanenitrile, is obtained with a yield higher than 80%,
20 preferably equal to or higher than 90%

Optionally, the obtained compound may be further purified by crystallisation before its use in the following step of the process according to standard procedures.

In the second step (step ii), the compound of formula (V), is reacted
25 with a phenyl boronic acid of formula (VI) wherein R represents one or more groups independently selected from halogen atoms, preferably chlorine; CF₃; CH=CH₂; CN; CH₂OH; NO₂; methylenedioxy; ethylenedioxy; cycloalkyl; phenyl; OR₁ or NHCOR₁ wherein R₁ is selected from the group consisting of

CF₃, alkenyl, alkynyl; benzyl; phenyl; SR₂, SOR₂ and COR₂ wherein R₂ is alkyl.

Preferably, the reaction, known as Suzuki reaction or Miyaura-Suzuki reaction, is carried out using 4-bromo-3-fluoro-phenylcyclopropanenitrile as the compound of formula (V) and 3,4-dichloro-phenylboronic acid as the compound of formula (VI).

Said reaction, which relies on a palladium catalyst, may also be carried out using alkyl boronic esters instead of boronic acids.

Advantageously, any palladium catalyst such as, for example, tetrakis(triphenylphosphine)palladium [Pd(PPh)₃], palladium on activated charcoal also known as Palladium on Carbon (Pd/C), palladium on alumina, or a mixture of Pd(OCOCH₃)₂ and PPh₃ may be used as catalyst.

Advantageously, step (ii) may be conducted in the presence of an organic solvent such as ethanol, acetone, tetrahydrofuran (THF), isopropyl alcohol, N-methylpyrrolidone (NMP), dioxane and mixtures thereof with water. A combination of organic solvents may also be used.

Preferably, when Pd(PPh)₃ or a mixture of Pd(OCOCH₃)₂ and PPh₃ is used, the reaction is carried out in the presence of N-methylpyrrolidone (NMP) or a mixture of dioxane/water 2:1.

Otherwise, when Pd/C is used, the preferred solvent is ethanol.

Step (ii) is advantageously conducted in the presence of from 1 to 4 equivalent of a base.

Bases which may be advantageously used include Na₂CO₃, K₂CO₃, K₃PO₄, Cs₂CO₃, NaOH. and KOH. The preferred bases are Na₂CO₃, K₂CO₃ or K₃PO₄.

Optionally, additives such as triphenylphosphine (P(Ph)₃), polymethylhydrosiloxane (PMHS), tetrabutylammonium bromide (TBAB), 1,4-diazabicyclo[2.2.2]octane (DABCO), or NaI may be added to the reaction

medium.

Generally, the reaction is carried out at the temperature from 80 to 140°C, preferably at 110°.

Advantageously, step (ii) may be conducted using a equimolar amount
5 of the compound (VI) with respect to compound (V), or with a slight molar excess.

Generally, a compound of formula (VI) is obtained with a yield higher than 60%, preferably higher than 70%, more preferably higher than 80%.

The compound of formula (VI) is preferably 3',4'-dichloro-2-fluoro-4-
10 cyanomethyl-biphenyl.

The preferred conditions of step (ii) are:

- solvent: NMP;
- base: 4 equivalents K_3PO_4 in powder form;
- catalyst: a 1:2 w/w mixture of $Pd(OCOCH_3)_2$ and PPh_3 .
- 15 - temperature: 110°C.

In these conditions, 3',4'-dichloro-2-fluoro-4-cyanomethyl-biphenyl is obtained with a yield higher than 90%.

Optionally, the obtained compound may be further purified by crystallisation before its use in the following step of the process according to
20 standard procedures.

In the third step (step iii), a compound of formula (VII) is hydrolysed to obtain the desired compound of formula (IA) according to well known methods. Preferably, the hydrolysis is conducted in a mixture of methanol and water in the presence of a strong base, preferably KOH under reflux.

25 Generally, the compound of formula (IA), which is preferably 1-(3',4'-dichloro-2-fluoro[1,1'-biphenyl]-4-yl)-cyclopropanecarboxylic acid, is obtained with a yield higher than 65%.

The compound of formula (IA) may be washed, filtered and isolated by

various well known techniques.

Said compound may be further purified by crystallisation according to standard procedures and is obtained with a high chemical purity, e.g. higher than 95% without using final purification by chromatography.

5 Crystallization from a mixture of n-heptane and isopropyl alcohol is particularly preferred.

The obtained compound (IA) may be further transformed into the corresponding pharmaceutically acceptable salts according to various known techniques.

10 In an alternative embodiment, when NMP is used as solvent for the reaction of step (ii), the compound of formula (IA) in the form of alkaline salt may be obtained by direct precipitation in a basic aqueous solution, without isolation of the intermediate compound (VII).

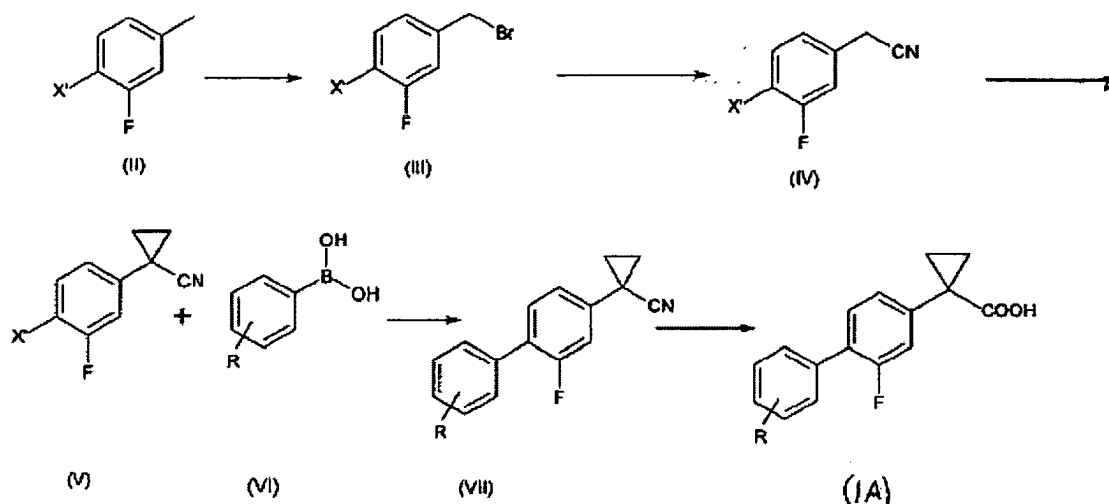
15 This is possible as it has been found that all the impurities of step (II) do not contain groups than can be salified in the water phase.

This allows an increase of the yield of the overall process.

The alkaline salt can be converted to the free acid form according to known methods.

20 The overall yield is generally at least 30%, preferably equal to or higher than 40% more preferably higher than 50%.

In a particular aspect, the process of the invention may further comprise the steps of preparing the compound (IV) starting from the commercially available compound (II) according to Scheme 2.



SCHEME 2

In order to obtain compound (IV), a compound of formula (II), with X' selected from the group consisting of chlorine, bromide, iodine and a CF₃SO₃ group (triflate) is submitted to radical bromination to form a compound of formula (III).

Advantageously the radical bromination is conducted with N-bromosuccinimide (NBS) in the presence of a catalytic amount of benzoyl peroxide [PhCOO]₂ and acetonitrile as a solvent.

Generally, the reaction is carried out at the solvent reflux temperature.

Preferably, in order to minimise the formation of dibrominated product, said step is conducted with a slight excess of NBS, preferably 1.05 mole equivalents to 1 mole equivalents of compound (II), and in the presence of 0.04 equivalents of PhCOOO₂.

Generally, the compound of formula (III), which is preferably 3-fluoro-4-bromo-benzyl bromide, is obtained with a yield higher than 85%, preferably higher than 90%.

The compound of formula (III), optionally further purified by crystallisation according to standard procedures, is then transformed into the

corresponding nitrile derivative of formula (IV) using sodium cyanide or another suitable salt.

Advantageously, said transformation is conducted in an organic solvent such as ethanol or acetonitrile, preferably ethanol, keeping the temperature
5 from about 20°C to about 60°C, preferably between about 40°C and about 50°C.

Preferably, the reaction is conducted with a molar excess of sodium cyanide, advantageously from 1.2 mole equivalent to 1.0 mole equivalent of sodium cyanide, preferably 1.05 mole equivalent to 1 equivalent of compound
10 (III).

Generally, the compound of formula (IV), which is preferably 4-bromo-3-fluoro-benzyl nitrile, is obtained with a yield higher than 50%.

Optionally, the obtained compound (IV), before of being subjected to the steps described above may be further purified by crystallisation according
15 to standard procedures.

Accordingly, the present invention also concerns a process for the preparation of a compound of formula (IA) with R as defined above, and pharmaceutically acceptable salts thereof, said process comprising the following steps according to scheme 2:

- 20 i) submitting a compound of formula (II), wherein X' is chlorine, bromine, iodine or a triflate group (CF₃SO₃), preferably bromide, to radical bromination to form a compound of formula (III);
- ii) transforming the compound of formula (III) into the corresponding nitrile derivative of formula (IV);
- 25 iii) reacting a compound of formula (IV) with 1,2-dibromoethane to form a compound of formula (V);
- iv) coupling a compound of formula (V) with a compound a formula (VI) wherein R is defined as above, to form a compound of formula

(VII); and

- v) hydrolyzing a compound of formula (VII) to obtain a compound of formula (IA).

The compounds of formula (IA) obtained by the processes of the invention may be used in the preparation of pharmaceutical compositions for the treatment and/or the prevention of neurodegenerative diseases such as Alzheimer's disease.

Said pharmaceutical compositions, preferably for the oral use, comprise at least one compound of formula (IA) in admixture with pharmaceutically acceptable excipients and/or carriers, for example those described in Remington's Pharmaceutical Sciences Handbook, XVII Ed., Mack Pub., N.Y., U.S.A..

The invention is illustrated in greater detail in the following Examples.

Example 1

Preparation of 4-bromo-3-fluorobenzyl bromide (III)

A solution of 4-bromo-3-fluorotoluene (21.5 g, 0.114 moles) in acetonitrile (200 ml) is added with N-bromosuccinimide, (NBS; 21.2 g, 0.119 moles). The mixture is refluxed, added with dibenzoyl peroxide (1.4 g, 0.004 moles), refluxed for 3 hour, then cooled at room temperature and extracted with water. The aqueous phase is discarded, the organic phase is washed with brine, dried over sodium sulphate and concentrated under vacuum to give an oil (27.1 g, 90% yield).

Example 2

Preparation of 4-bromo-3-fluorophenylacetonitrile (IV)

A solution of 4-bromo-3-fluorobenzyl bromide (27 g, 0.1 moles) in ethanol (200 ml) is added with NaCN (5.4 g, 0.11 moles) and refluxed for 3 hours. The mixture is concentrated under vacuum; the resulting residue is taken up with water, then extracted with ethyl acetate. The organic phase is

washed with brine, dried over sodium sulfate and concentrated under vacuum to give a dark oil (12.1 g, 56% yield).

Example 3

Preparation of 4-bromo-3-fluorophenylcyclopropanenitrile (V)

5 A solution of 4-bromo-3-fluorophenylacetonitrile (1g, 4.6 mmoles) in toluene (4 ml) is added with 0.6 ml (7 mmoles) of 1,2-dibromoethane, a 50% NaOH aqueous solution (4 ml) and tetrabutylammonium bromide (0.32 g, 1 mmoles). The mixture is kept under stirring at room temperature for 4 hours, then diluted with water and extracted with ethyl acetate. The organic phase is
10 recovered and solvent is eliminated under vacuum to give a brown solid, which is subjected to silica gel chromatography purification, to afford an orange to yellow product in the solid form (1 g, yield 90%).

Example 4

15 **Preparation of 1-(3',4'-dichloro-2-fluoro[1,1'-biphenyl]-4-yl)-cyclopropanenitrile (VI)**

In a flask in inert atmosphere, 3,4-dichlorophenylboronic acid (374 mg, 1 eq), Pd(OAc)₂ (44 mg, 0.1 eq), PPh₃ (105 mg, 0.2 eq) and fine mesh K₃PO₄ (1.6 g, 4 eq) are added to 4-bromo-3-fluorophenylcyclopropanenitrile (470 mg, 1 eq).

20 5 mL of previously degassed N-methylpyrrolidone (NMP) are added at room temperature.

The reaction mixture is heated at 110° C for 2 hours to reach completion (monitored by ¹⁹F NMR), then diluted with ethyl acetate, and washed with water.

25 The organic phase is recovered and the solvent evaporated to give a rose-violet powder (700 mg). To the solid, a water:acetone 1:1 v/v mixture (40 ml) is added, then the suspension is heated to reflux under stirring to obtain a solution. After evaporation of acetone, a solid light violet product is

obtained (560 mg, yield 95%).

Example 5

Preparation of 1-(3',4'-dichloro-2-fluoro[1,1'-biphenyl]-4-yl)-cyclopropane carboxylic acid (IA)

5 1-(3',4'-dichloro-2-fluoro[1,1'-biphenyl]-4-yl)-cyclopropanenitrile (14.3 g, 0.047 mol) is dissolved in a mixture of methanol (143 ml) and water (71.5 ml), potassium hydroxide (35.1 g, 0.563 mol) is added portionwise, and the mixture is refluxed for 48 hours.

10 The reaction mixture is cooled and poured in a solution of aqueous hydrogen chloride 36% (57 ml) in water (57 ml) at 20-25°C. The suspension is stirred and filtered; the solid is repeatedly washed with water and dried at 40°C under vacuum. The crude product is dissolved in refluxing 2-propanol (178 ml), the solution is added with activated carbon (0.3 g), stirred at reflux and filtered, concentrated and added with n-heptane (116 ml). The hot solution
15 is cooled to 0-5°C and the crystallized solid is filtered, washed with 2-propanol and dried at 40°C under vacuum.

 The compound 1-(3',4'-dichloro-2-fluoro[1,1'-biphenyl]-4-yl)-cyclopropanecarboxylic acid is obtained as a white powder (10.3 g, 68% yield).

20 HPLC-UV purity (255 nm): 99.8%

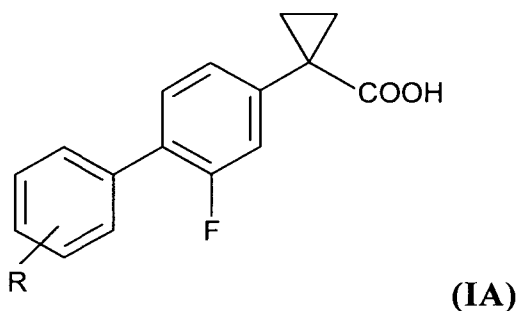
¹H NMR (DMSO-d₆, 300 MHz): 12.51 (bs, 1H); 7.78 (m, 2H); 7.54 (m, 2H); 7.30 (m, 2H); 1.48 (m, 2H); 1.22 (m, 2H)

 MS (ESI⁺, 40 V): 323 (M⁺); 279.

 Melting range: 199-200°C.

CLAIMS

1. A process for the preparation of a compound of formula (IA)

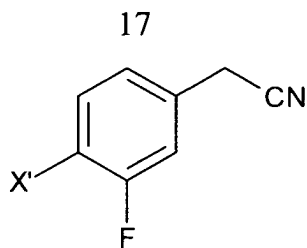


wherein R represents one or more groups independently selected from:

- halogen atoms;
- CF_3 ;
- $\text{CH}=\text{CH}_2$;
- CN ;
- CH_2OH
- NO_2 ;
- methylenedioxy;
- ethylenedioxy;
- cycloalkyl;
- phenyl;
- OR_1 or NHCOR_1 wherein R_1 is selected from CF_3 , alkenyl, alkynyl; benzyl; and phenyl;
- SR_2 , SOR_2 or COR_2 wherein R_2 is alkyl; and

pharmaceutically acceptable salts thereof,
said process comprising the following steps:

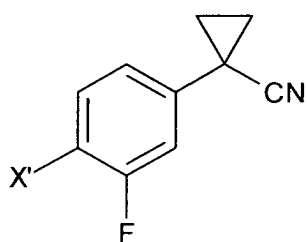
- (i) reacting a compound of formula (IV)



(IV)

wherein X' is selected from chlorine, bromine, iodine and a triflate group (CF₃SO₃) with 1,2-dibromoethane to form a compound of formula (V)

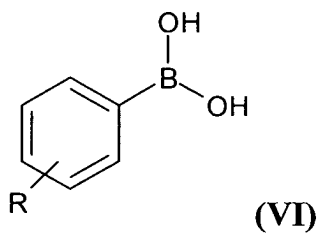
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(V)

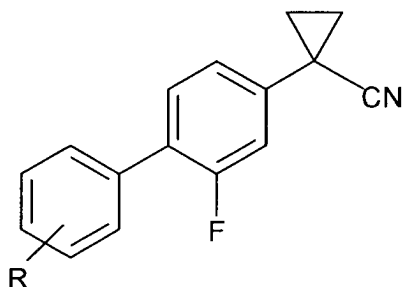
- (ii) coupling a compound of formula (V) with a compound of formula (VI)

10



(VI)

wherein R is as defined above to form a compound of formula (VII);



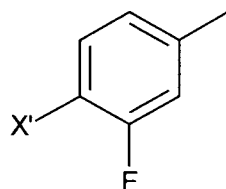
(VII)

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- iii) hydrolyzing a compound of formula (VII) to obtain a compound

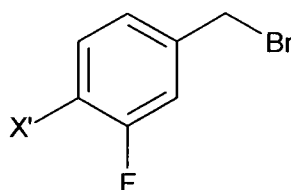
of formula (IA).

2. The process as claimed in claim 1, wherein X' is bromide.
3. The process as claimed in claim 1 or 2 further comprising the steps of isolating and crystallising the compound of formula (IA).
- 5 4. The process as claimed in any one of claims 1 to 3 wherein step (ii) is conducted in the presence of a palladium catalyst selected from tetrakis(triphenylphosphine)palladium, palladium on activated charcoal, palladium on alumina, and a mixture of $\text{Pd}(\text{OCOCH}_3)_2$ and triphenylphosphine (PPh_3).
- 10 5. The process as claimed in claim 4 wherein the palladium catalyst is a 1:2 w/w mixture of $\text{Pd}(\text{OCOCH}_3)_2$ and PPh_3 .
6. The process as claimed in any of the preceding claims further comprising the steps of i) submitting a compound of formula (II),



(II)

wherein X' is as defined above, to radical bromination to form a compound of formula (III);



(III)

- ii) transforming the compound of formula (III) into the corresponding nitrile derivative of formula (IV).
7. The process as claimed in claim 6, wherein the bromination step is conducted with N-bromosuccinimide in the presence of a catalytic amount of

benzoyl peroxide using acetonitrile as a solvent.

8. The process as claimed in any one of the preceding claims wherein the compound of formula (1A) is 1-(3',4'-dichloro-2-fluoro[1,1'-biphenyl]-4-yl)-cyclopropanecarboxylic acid.
- 5 9. The process for preparation of a pharmaceutical composition comprising steps (i) –(iii) of claim 1 and an additional step comprising admixture of one or more pharmaceutically acceptable excipients.