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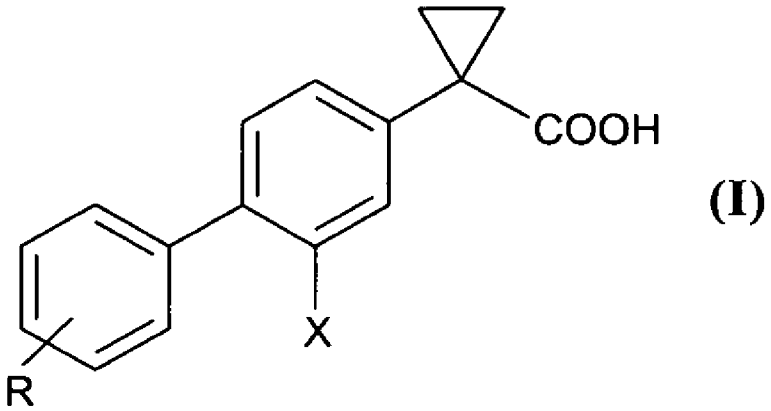
(54) Title: PROCESS OF PREPARING DERIVATIVES OF l-(2-HALOBIPHENYL-4-YL)-CYCLOPROPANECARBOXYLIC ACID



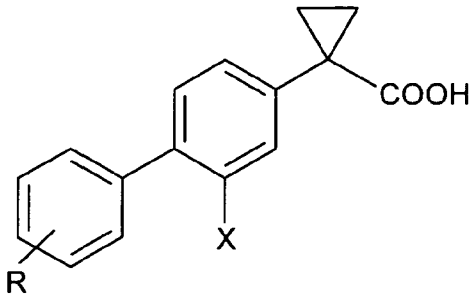
(I)

(57) Abstract: The invention relates to a process for preparing a compound according to formula (I). The invention also relates to useful intermediates in the process.

PROCESS OF PREPARING DERIVATIVES OF l-(2-HALOBIPHENYL-4-YL)-CYCLOPROPANECARBOXYLIC ACID

TECHNICAL FIELD

The invention relates to a process for preparing a compound according to formula (I):



(I)

The invention also relates to useful intermediates in the process.

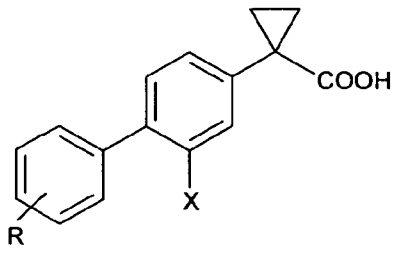
BACKGROUND OF THE INVENTION

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 (βA), and, depending on the numbers of amino acids, $A\beta_{39}$, $A\beta_{40}$, $A\beta_{42}$ and $A\beta_{43}$.

In the art, 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.

In particular WO 2004/074232 discloses derivatives of l-(2-halobiphenyl-4-yl)-cyclopropanecarboxylic acid of general formula (I)



(I)

wherein X and R are defined below,

capable of modulating γ-secretase activity without affecting other important metabolic processes such as cyclooxygenase-enzymes activity.

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.

In WO 2004/074232, 3,4-dihalo-cyclopropanecarboxylic acid is obtained starting from 3,4-dihalo-toluene which is transformed into the corresponding benzyl bromide by radical bromination in carbon tetrachloride (CCl_4); the resulting bromide is transformed into the 3,4-dihalophenylacetonitrile; the latter one is reacted with 1,2 dibromoethane to give the corresponding 3,4-dihalophenylcyclopropanenitrile which is finally hydrolyzed to the desired 3,4-dihalo-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.

For example, the radical bromination step gives rise to a significant amount of the bis-halogenated side-product, detrimental to its yield, and involves the use of CCl_4 which is highly toxic, ozone-depleting and a greenhouse gas.

In addition, the final Suzuki coupling reaction provides a poor yield and the resulting product is difficult to purify by crystallization without a loss of yield. For example, silica gel chromatography has been used for such purification, but scale-up of silica gel chromatography is tedious and requires

large volumes of solvents.

Therefore it is an object of the present invention to provide a process for the preparation of derivatives of l-(2-halobiphenyl-4-yl)-cyclopropanecarboxylic acid of formula (I) alternative to the one disclosed in WO 2004/074232 and which does not have all the aforementioned drawbacks.

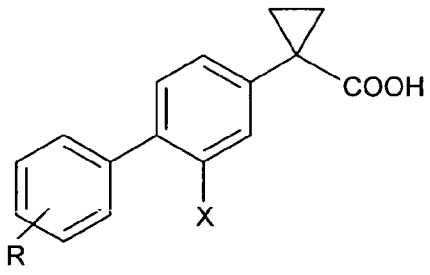
The object of the present invention is achieved by carrying out the Suzuki reaction as the first step.

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

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

SUMMARY OF THE INVENTION

The subject-matter of the present invention is a process for preparing a compound of general formula (I) or salts thereof



(I)

wherein

X is a halogen atom, preferably fluorine;

R represents one or more groups independently selected from:

- halogen atoms, preferably chlorine;
- CF_3;
- $CH=CH_2$;
- CN;

- CH_2OH;
- NO_2;
- methylenedioxy;
- ethylenedioxy;
- cycloalkyl, preferably C_3-C_6 cycloalkyl;
- phenyl;
- OR_1 or NHCORi wherein R_1 is selected from the group consisting of CF_3, alkenyl, alkynyl; benzyl; and phenyl;
- SR_2, SOR_2 or COR_2 wherein R_2 is alkyl;

said process comprising the following steps according to scheme 1:

(i) reacting a compound of formula (II) wherein X is defined as above and X' is chlorine, bromine, iodine or a triflate group (CF_3SO_3) with a compound of formula (III) wherein R is defined as above to form a compound of formula (IV);

(ii) submitting a compound of formula (IV) to radical bromination to form a compound of formula (V);

iii) transforming a compound of formula (V) into the corresponding nitrile derivative of formula (VI);

iv) reacting a compound of formula (VI) with 1,2-dibromoethane to form a compound of formula (VII); and

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

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.

The invention is also directed to the compound (VII), which has been obtained as stable intermediate of the reaction described above.

The invention is further directed to a process for preparing a

pharmaceutical composition, said process comprising steps (i) –(v) and an additional step (vi) comprising admixture of one or more pharmaceutically acceptable excipients.

DEFINITIONS

The terms used in the specification have the following meanings:

"Halogen atoms" includes fluorine, chlorine, bromine, and iodine.

"Alkyl" means straight chain or branched C_1-C_4 alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl,

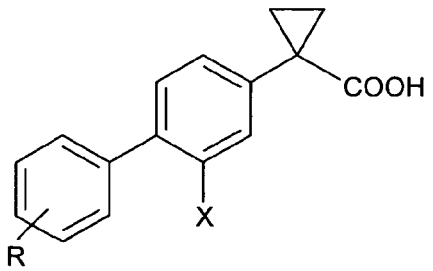
"Alkenyl" means straight chain or branched C_2-C_6 alkenyl, such as vinyl, 1-propenyl, 2-propenyl, 1-butenyl, isobutenyl, or straight-or branched-pentenyl and hexenyl. The term "alkynyl" is to be construed in an analogous manner.

"Cycloalkyl" means a cyclic non-aromatic hydrocarbon group containing 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 one to four heteroatoms selected from nitrogen, oxygen and sulphur. Examples include piperidyl or tetrahydrofuryl.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a process for preparing a compound of general formula (I) according to the scheme 1



(I)

wherein

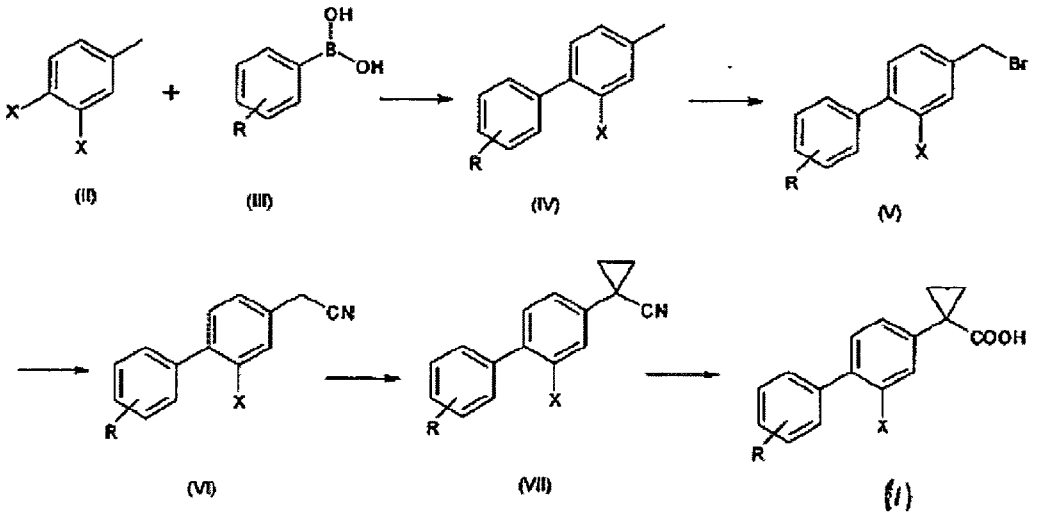
X and R are as defined above.

When R is cycloalkyl, said ring is optionally substituted with one or more groups independently selected from alkyl, CF_3, OH and oxo groups.

Preferably the cycloalkyl group is C_3-C_6 cycloalkyl.

When R is phenyl, said ring is optionally substituted with one or more groups independently selected from halogen atoms, CF_3, OCF_3, OH, alkyl and a saturated heterocyclic.

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.



SCHEME 1

In the first step (step i), a compound having formula (II), wherein X is a halogen atom, preferably fluorine and X' is selected from the group consisting of chlorine, bromine, iodine and a CF_3SO_3 group (triflate), is reacted with a phenyl boronic acid of formula (III) wherein R represents one or more groups independently selected from halogen atoms, preferably chlorine; CF_3; $CH=CH_2$; CN; CH_2OH; NO_2; methylenedioxy; ethylenedioxy; cycloalkyl; phenyl; ORi or $NHCOR_1$ wherein Ri is selected from the group consisting of

CF_3, alkenyl, alkynyl; benzyl; phenyl; SR_2, SOR_2 and COR_2 wherein R_2 is alkyl.

The compounds of formula (II) and (III) are commercially available or may be prepared according to methods well known to the skilled person.

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

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 tetrakis(triphenylphosphine)palladium [$Pd(PPh)_3$], palladium on activated charcoal also known as Palladium on Carbon (Pd on C), palladium on alumina may be used as catalyst.

Preferably Pd on C is used as it is less expensive and easier to handle.

Generally, step (i) is conducted in the presence of an organic solvent. Organic solvents which may be advantageously used include ethanol, acetone, tetrahydrofuran (THF), isopropyl alcohol, N-methylpyrrolidone (NMP), dioxane and mixtures thereof with water.

A combination of organic solvents may also be used.

Advantageously, the reaction is carried out at the solvent refluxing temperature.

When $Pd(PPh)_3$ is used, the preferred solvent is a mixture of dioxane/water 2:1 v/v, while, when Pd/C is used, the preferred solvent is ethanol.

Preferably, step (i) is conducted in the presence of a base.

Bases which may be advantageously used include Na_2CO_3, K_2CO_3, K_3PO_4, Cs_2CO_3, NaOH, and KOH. The preferred base is Na_2CO_3.

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.

Preferably, step (i) is conducted with a slight molar excess of the compound (III) with respect to compound (II).

The preferred conditions for conducting the reaction of step (i) are reported as follows:

- solvent: 20 volumes ethanol;
- base: 2 equivalents Na_2CO_3;
- catalyst: 13% w/w Pd on C 10%.
- temperature: reflux.

Usually, a compound of formula (IV) is obtained with a yield higher than 70%, preferably higher than 80%.

The compound of formula (IV) is preferably 3',4'-dichloro-2-fluoro-4-methyl-biphenyl.

In the second step (step ii), a compound of formula (IV) is submitted to radical bromination to form a compound of formula (V) wherein X and R are defined as above.

Compound (IV) may be as a crude product or may be previously crystallised according to standard procedures.

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 refluxing temperature.

Preferably, in order to minimise the formation of dibrominated product, step (ii) is conducted with a slight excess of NBS, preferably 1.05 mole

equivalents to 1 mole equivalent of compound (IV), and in the presence of 0.04 equivalent OfPhCOOO$_2$.

Generally the compound of formula (V), which is preferably 3',4'-dichloro-2-fluoro-4-bromomethyl-biphenyl, is obtained in a yield higher than 85%, preferably higher than 90%.

Optionally, the compound of formula (V) may be further purified by crystallisation according to standard procedures.

In the third step (step iii) a compound of formula (V) is transformed into the corresponding nitrile derivative of formula (VI) wherein X and R are defined as above.

Sodium cyanide or other suitable salts may be used.

Advantageously step (iii) is conducted in an organic solvent such as ethanol or acetonitrile, preferably ethanol.

The temperature used in step (iii) is preferably from about 20°C to about 60°C, more preferably between about 40°C and about 50°C.

Preferably, step (iii) is conducted with a molar excess of sodium cyanide. Advantageously between 1.2 mole equivalent and 1.0 mole equivalent of sodium cyanide, and preferably 1.05 mole equivalent to 1 equivalent of compound (V) is used.

Generally the compound of formula (VI), which is preferably 3',4'-dichloro-2-fluoro-4-cyanomethyl-biphenyl, is obtained in a yield higher than 50%, preferably of about 55-60%.

Optionally, said compound may be further purified by crystallisation according to standard procedures, preferably by slurring in ethanol.

In the fourth step (iv), a compound of formula (VI) is reacted with 1,2-dibromoethane to form a compound of formula (VII) wherein X and R are defined as above.

Advantageously step (iv) is conducted in an organic solvent such 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 30% NaOH and tetrabutylammonium chloride (TBAC) or tetrabutylammonium bromide (TBAB).

The temperature in step (iv) is preferably maintained from about 20^0C to about 50°C.

Generally the compound of formula (VII), which is preferably l-(3',4'-dichloro-2-fluoro[l,r-biphenyl]-4-yl)-cyclopropanenitrile, is obtained with a yield higher than 60%, preferably of about 65-70%.

Optionally, said compound may be further purified by crystallisation according to standard procedures, preferably using n-heptane as crystallization solvent.

In the fifth step (step v), a compound of formula (VII) is hydrolysed to obtain the desired compound of formula (I) according to methods well known to the person skilled in the art.

Preferably the hydrolysis is conducted in a mixture of methanol and water in the presence of a strong base, preferably KOH under reflux.

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

The compound of formula (I) may be washed, filtered and isolated by various techniques known in the art.

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.

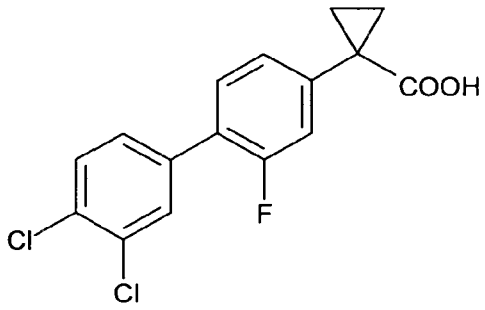
Crystallization from a mixture of n-heptane and isopropyl alcohol is especially preferred.

The overall yield of the process is usually at least 20%, preferably equal

to or higher than 25%, more preferably higher than 30%.

In a preferred embodiment, the invention provides a process for the preparation of a compound of formula (I) wherein X is fluorine and R is chlorine.

In a more preferred embodiment, the invention provides a process for preparing l-(3',4'-dichloro-2-fluoro[l,l'-biphenyl]-4-yl)-cyclopropane-carboxylic acid having formula (Ia)



(Ia)

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

Pharmaceutically acceptable salts include those in which the acidic function is reacted with an appropriate base to form, e. g., sodium, potassium, calcium, magnesium, and ammonium salts.

The compounds of formula (I) obtained by the process 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 (I) 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 3',4'-dichloro-2-fluoro-4-methyl-biphenyl

3-Fluoro-4-bromotoluene (50 g, 0.265 mol) and 3,4-dichlorophenylboronic acid (53 g, 0.278 mol) are dissolved in ethanol (970 ml) and sodium carbonate (56.1 g, 0.529 mol) is added. Palladium 10% on charcoal (6.6 g) is added, and the mixture is refluxed for 4 hours under nitrogen atmosphere. The reaction mixture is cooled, filtered and concentrated, isopropyl acetate (250ml) is added, and then the solution is concentrated again. The residue is dissolved in isopropyl acetate (250 ml) and IM sodium hydroxide (250ml). The organic phase is separated, washed with water (125 ml), neutralized with hydrogen chloride 3 M, washed with brine (250ml) and concentrated.

The residue is added with acetonitrile/water 1/1 v/v (150 ml), heated to 40^0C to dissolution and then cooled to 0-5^0C, and stirred for 30 min at this temperature.

The compound 3',4'-dichloro-2-fluoro-4-methyl-biphenyl crystallizes as a powder, which is filtered, washed with acetonitrile/water 1/1 v/v (25 ml) and dried at $4O^0$C (56 g, 86% yield).

HPLC-UV purity (210 nm): 95.0%

^{1}H NMR (DMSO-d6, 300 MHz): 7.73 (m, 2H); 7.49 (m. 2H); 7.14 (m, 2H); 2.36 (s, 3H)

Example 2

Preparation of 3',4'-dichloro-2-fluoro-4-bromomethyl-biphenyl

3',4'-Dichloro-2-fluoro-4-methyl-biphenyl (29 g, 0.114 mol), N-bromosuccinimide (21.2 g, 0.119 mol), benzoyl peroxide (1.4 g, 0.004 mol) are dissolved in acetonitrile (190 ml).

The mixture is refluxed for 3 hours, then cooled, added with a solution of sodium sulphite (2.2 g) in water (54 ml), stirred for 30 min and then left to

stand to separate the phases.

The lower aqueous phase is separated and extracted with dichloromethane (29 ml).

The upper phase is concentrated under vacuum, added with water (10 ml), and dichloromethane (58 ml) and stirred. The organic phases are separated and combined, washed twice with water (29 ml), and concentrated under vacuum.

The compound 3',4'-dichloro-2-fluoro-4-bromomethyl-biphenyl is isolated as an orange oil (35.7 g, 94% yield).

HPLC-UV purity (250 nm): 77.1%

^{1}H NMR (DMSO-d6, 300 MHz): 7.87-7.12 (m, 6H); 4.76 (s, 2H)

Example 3

Preparation of 3',4'-dichloro-2-fluoro-4-cyanomethyl-biphenyl

3',4'-Dichloro-2-fluoro-4-bromomethyl-biphenyl (35.0 g, 0.105 mol) and sodium cyanide (5.4 g, 0.1 10 mol) are dissolved in a mixture of ethanol (228 ml) and water (25 ml), then heated at 50°C for 3 hours. The solution is concentrated under vacuum and the residue is suspended in ethanol/water 1/1 v/v (35 ml) and cooled at 0-5^{0}C for 30 min.

The obtained solid is filtered and dried at 40^{0}C under vacuum. The crude product is suspended in ethanol (56 ml) at 20-25^{0}C for 30min, filtered and dried at 40^{0}C under vacuum.

The compound 3\4'-dichloro-2-fluoro-4-cyanomethyl-biphenyl is obtained as a light brown powder (16.8 g, 57% yield).

HPLC-UV purity (250 nm): 92.3%.

^{1}H NMR (DMSO-d6, 300 MHz): 7.78 (m, 2H); 7.60 (m, 2H); 7.34 (m, 2H); 4.14 (s, IH).

Example 4

Preparation of l-(3',4'-dichloro-2-fluoro[l,l'-biphenyl]-4-yl)-

cyclopropanenitrile

3',4'-Dichloro-2-fluoro-4-cyanomethyl-biphenyl (9.0 g, 0.032 tnol), 1,2-dibromomethane (9.0 g, 0.048 mol), tetrabutylammonium chloride (1.2 g, 0.043 mol), toluene (60 ml) and water (9 ml) are loaded in a reactor.

Sodium hydroxide 30% aq. (60 g, 0.45 mol) is dropped over 30 min at 20-25 ^{0}C and the reaction mixture is stirred for 6 hours. The organic phase is separated, and washed in sequence with water (12 ml), hydrogen chloride 3 M aq. (36 ml) and finally water (12 ml).

The solution is concentrated, then n-heptane (18 ml) is added at 80^{0}C.

The solution is cooled to 0-5°C and stirred for 30 min.

The product crystallized from the solution is filtered, washed with cold n-heptane (5 ml) and dried at 40^{0}C under vacuum.

The compound l-(3',4'-dichloro-2-fluoro[l,r-biphenyl]-4-yl)-cyclopropanenitrile is obtained as a yellow powder (6.4 g, 65% yield).

HPLC-UV purity (250 nm): 98.2%.

^{1}H NMR (DMSO-d6, 300 MHz): 7.78 (m, 2H); 7.60 (m, 2H); 7.30 (m, 2H); 1.84 (m, 2H); 1.63 (m, 2H).

Example 5

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

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.

The reaction mixture is cooled and poured in a solution of aqueous hydrogen chloride 36% (57 ml) in water (57 ml) at 20-25 ^{0}C. The suspension is stirred and filtered; the solid is repeatedly washed with water and dried at 40^{0}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 is cooled to 0-5°C and the crystallized solid is filtered, washed with 2-propanol and dried at 40^{0}C under vacuum.

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

HPLC-UV purity (255 nm): 99.8%

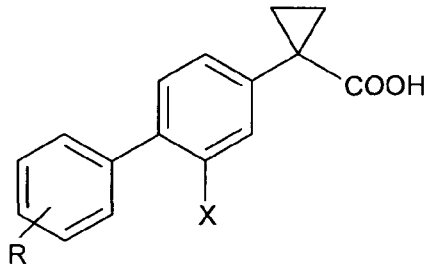
^{1}H NMR (DMSO-d6, 300 MHz): 12.51 (bs, IH); 7.78 (m, 2H); 7.54 (m, 2H); 7.30 (m, 2H); 1.48 (m, 2H); 1.22 (m, 2H).

MS (ESr, 40 V): 323 (NT); 279.

Melting range: 199-200^{0}C.

CLAIMS

1. A process for preparing a compound of general formula (I) and salts thereof



(I)

wherein

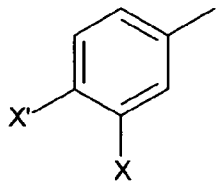
X is a halogen atom;

R represents one or more groups independently selected from:

- halogen atoms;
- CF_3;
- $CH=CH_2$;
- CN;
- CH_2OH
- NO_2;
- methylenedioxy;
- ethylenedioxy;
- cycloalkyl;
- phenyl;
- OR_1 or NHCORi wherein R_1 is selected from the group consisting of CF_3, alkenyl, alkynyl; benzyl; and phenyl;
- SR_2, SOR_2 or COR_2 wherein R_2 is alkyl;

said process comprising the following steps:

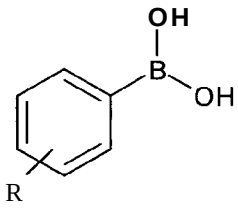
(i) reacting a compound of formula (II)



(II)

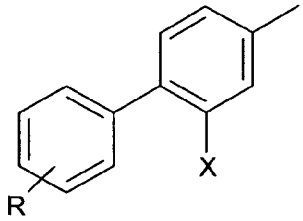
wherein X is defined as above and X' is selected from the group consisting of chlorine, bromine, iodine and a triflate group (CF_3SO_3)

with a compound of formula (III)



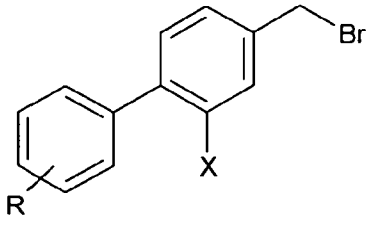
(HI)

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



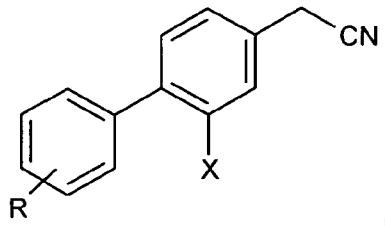
(IV)

(ii) submitting a compound of formula (IV) to radical brominaton to form a compound of formula (V);



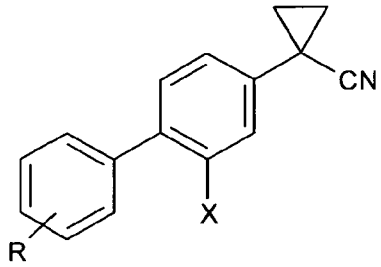
(V)

iii) transforming a compound of formula (V) into the corresponding nitrile derivative of formula (VI);



(VI)

iv) reacting a compound of formula (VI) with 1,2-dibromoethane to form a compound of formula (VII); and



(VII)

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

2. The process as claimed in claim 1, further comprising the steps of isolating and crystallising the compound of formula (I).

3. The process according to claim 2, wherein crystallisation is carried out by using a mixture of n-heptane and isopropyl alcohol.

4. The process as claimed in claim 1 or 2, wherein step (i) is conducted in the presence of a palladium catalyst selected from the group consisting of tetrakis(triphenylphosphine)palladium, palladium on activated charcoal, and palladium on alumina.

5. The process as claimed in claim 3 or 4, wherein the palladium catalyst is palladium on activated charcoal.

6. The process as claimed in any one of the preceding claims 1 to 3, wherein step (ii) is conducted with N-bromosuccinimide in the presence of a catalytic amount of benzoyl peroxide using acetonitrile as a solvent.

7. The process as claimed in any one of the preceding claims, wherein X is fluorine and R is a halogen atom.

8. The process as claimed in claim 7, wherein the halogen atom is chlorine.

9. The process as claimed in any one of the preceding claims comprising the following steps:

(i) reacting 4-bromo-3-fluoro-toluene with 3,4-dichlorophenylboronic acid to form 3',4'-dichloro-2-fluoro-4-bromomethyl-biphenyl;

(ii) submitting 3',4'-dichloro-2-fluoro-4-bromomethyl-biphenyl to radical bromination to form 3',4'-dichloro-2-fluoro-4-bromomethyl-biphenyl;

iii) transforming 3',4'-dichloro-2-fluoro-4-bromomethyl-biphenyl into the corresponding 3',4'-dichloro-2-fluoro-4-cyanomethyl-biphenyl;

iv) reacting 3',4'-dichloro-2-fluoro-4-cyanomethyl-biphenyl with 1,2-dibromoethane to form l-(3',4'-dichloro-2-fluoro[l,l'-biphenyl]-4-yl)-cyclopropanenitrile; and

v) hydrolyzing l-(3',4'-dichloro-2-fluoro[l,r-biphenyl]-4-yl)-cyclopropanenitrile to obtain l-(3',4'-dichloro-2-fluoro[l,l '-biphenyl]-4-yl)-cyclopropanecarboxylic acid.

10. A compound of formula (VII), wherein

X is a halogen atom; and

R represents one or more groups independently selected from the group consisting of halogen atoms; CF_3; $CH=CH_2$; CN; CH_2OH; NO_2; methylenedioxy; ethylenedioxy; cycloalkyl; phenyl; ORi or $NHCOR_1$ wherein R_1 is selected from the group consisting of CF_3, alkenyl, alkynyl; benzyl; and phenyl; and SR_2, SOR_2 or COR_2 wherein R_2 is alkyl.

11. The compound as claimed in claim 10, which is l-(3',4'-dichloro-2-fluoro[1,1'-biphenyl]-4-yl)-cyclopropanenitrile.

12. The process for preparing a pharmaceutical composition comprising steps (i) - (v) of claim 1 and an additional step (vi) comprising admixture of one or more pharmaceutically acceptable excipients.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/003288

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C51/09 C07C17/14 **C07C17/26** **C07C253/14** **C07C255/35**
C07C57/62 **C07C25/18**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal , CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document with indication, where appropriate of the relevant passages	Relevant to claim No
Y	**WO 2004/074232 A (CHIESI FARMA SPA [IT]; RAVEGLIA LUCA [IT]; PERETTO ILARIA [IT]; RADAEL) 2 September 2004 (2004-09-02) cited in the application schemes** 1,2 **and 3 examples 1,2**	1-7,12
Y	PERETTO, I. **ET. AL: "Synthesis and** Biological **Activity of** Flurbiprofen **Analogues as** Selective **Inhibitors of beta-Amyloid Secretion" JOURNAL OF MEDICINAL** CHEMISTRY, vol. **48, no.** 18, **2005, pages 5705-5720, XP002508517 schemes** 2,3,4 **and 5**	1-7,12

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[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

"L' document which may throw doubts on prtonty claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

"p* document published prior to the international filing date but later than the prtonty date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

1X- document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve-an inventive step when the document is taken alone

1Y' document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docu¬ments, such combination being obvious to a person skilled in the art

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of lhe international search report
10 September 2009	**17/09/2009**

Name and mailing address of the ISA'	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Fax (+31-70) 340-3016	**Del anghe, Patrick**

Form PCT/ISA/210 (second sheet) (April 200B)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/003288

C(Conβnuatlon). DOCUMENTS CONSIDERED TO BE RELEVANT

Category"	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	WO 2006/133559 A (MERCK FROSST CANADA LTD [CA]; OBALLA RENATA [CA]) 21 December 2006 (2006-12-21) example 13 _____	10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/003288

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004074232 A	02-09-2004	AT 409176 T	15-10-2008
		AU 2004213145 A1	02-09-2004
		CA 2514384 A1	02-09-2004
		DK 1594833 T3	15-12-2008
		EP 1594833 A1	16-11-2005
		ES 2312964 T3	01-03-2009
		HK 1087398 A1	12-06-2009
		JP 2006518351 T	10-08-2006
		KR 20050104369 A	02-11-2005
		PT 1594833 E	03-12-2008
		SI 1594833 T1	31-12-2008
		US 2007060752 A1	15-03-2007
WO 2006133559 A	21-12-2006	AU 2006257670 A1	21-12-2006
		CA 2610659 A1	21-12-2006
		EP 1893562 A1	05-03-2008
		JP 2008546651 T	25-12-2008