- NO_2;
- methylenedioxy;
- ethylenedioxy;
- cycloalkyl, preferably C_3-C_6 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 according to scheme 1:

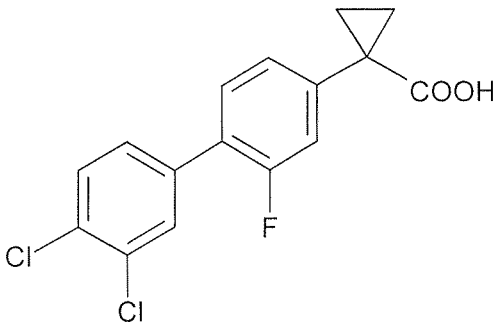
i) reacting a compound of formula (IV) wherein X' is chlorine, bromine, iodine or a triflate group (CF_3SO_3), preferably bromine~~bromide~~, with 1,2-dibromoethane to form a compound of formula (V);

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

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



Any compound of formula (IV), with X' selected from the group consisting of chlorine, bromine~~bromide~~, iodine and a CF_3SO_3 group (triflate), which is commercially available, may be used as starting material.

Preferably, the compound wherein X' is bromine~~bromide~~ is used as starting 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 as ethanol or acetonitrile or mixtures thereof with water.

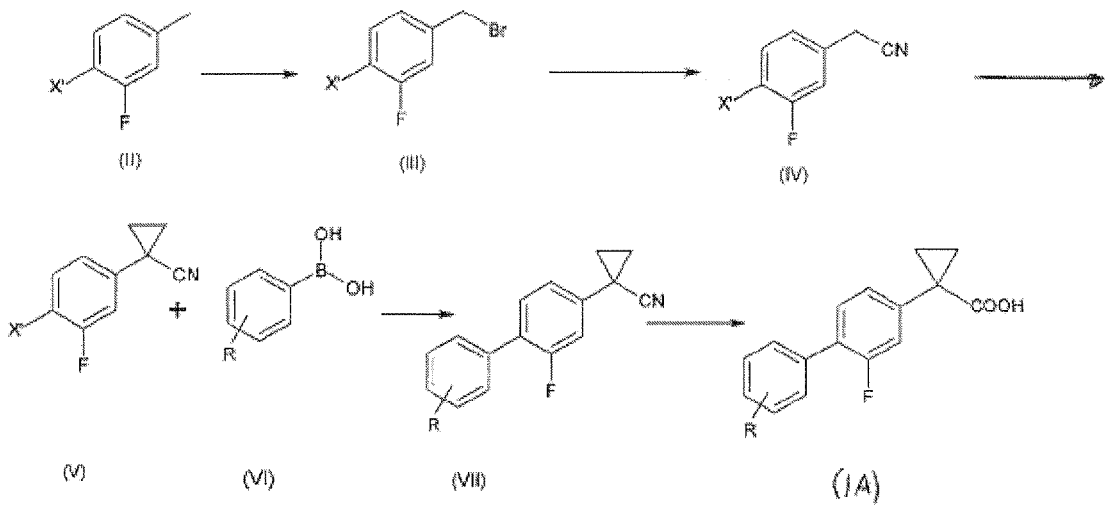
Preferably, said cyclopropanation step is carried out as a phase transfer catalysis reaction in the presence of concentrated NaOH and tetrabutylammonium chloride (TBAC) or tetrabutylammonium bromide (TBAB). The concentration of NaOH can advantageously range from 30 to 50% w/v.

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%, 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 with a phenyl boronic acid of formula (VI) 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; OR_1 or $NHCOR_1$ wherein R_1 is selected from the group consisting of



SCHEME 2

In order to obtain compound (IV), a compound of formula (II), with X' selected from the group consisting of chlorine, bromine~~bromide~~, iodine and a CF_3SO_3 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 $PhCOOO_2$.

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 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 (III).

Generally, the compound of formula (IV), which is preferably 4-bromo-3-fluoro-benzylnitrile, 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 to standard procedures.

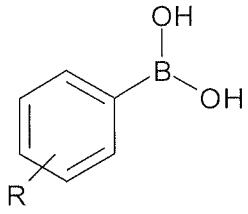
Accordingly, the present invention also concerns a process for the preparation of a compound of formula (IA) with R as defined above, and pharmaceutically acceptable salts thereof, said process comprising the following steps according to scheme 2:

i) submitting a compound of formula (II), wherein X' is chlorine, bromine, iodine or a triflate group (CF_3SO_3), preferably <u>bromine</u>~~bromide~~, to radical brominaton to form a compound of formula (III);

ii) transforming the compound of formula (III) into the corresponding nitrile derivative of formula (IV);

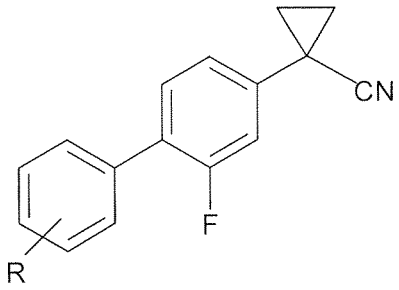
iii) reacting a compound of formula (IV) with 1,2-dibromoethane to form a compound of formula (V);

coupling a compound of formula (V) with a compound a formula (VI) wherein R is defined as above, to form a compound of formula



(VI)

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



(VII)

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 bromine~~bromide~~.

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

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 $Pd(OCOCH_3)_2$ and triphenylphosphine (PPh_3).

5. The process as claimed in claim 4 wherein the palladium catalyst is a 1:2 w/w mixture of $Pd(OCOCH_3)_2$ 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),