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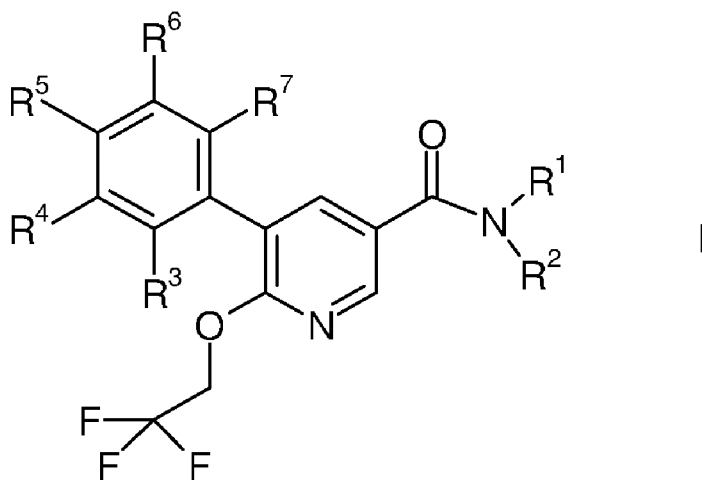
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(54) Title: PROCESS FOR THE PREPARATION OF NICOTINAMIDE DERIVATIVES

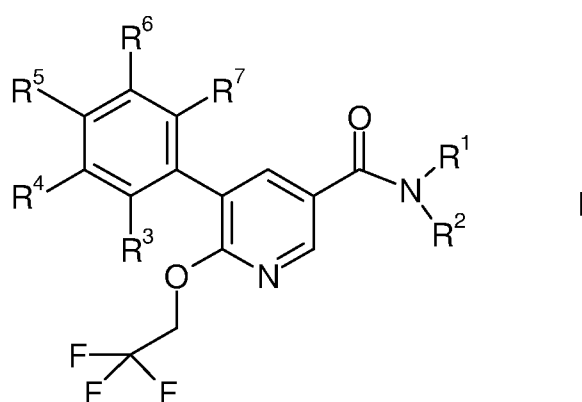


(57) Abstract: The present invention relates to a process for the preparation of nicotinamide derivatives of the formula (I) R^1 to R^7 are as defined in the and to pharmaceutically acceptable salts thereof. The compounds of formula (I) are useful for the treatment and / or prophylaxis of diseases which are associated with the modulation of cannabinoid 1 receptors (CB 1 receptors) as described in the PCT Publ. WO 2006/106054.

PROCESS FOR THE PREPARATION OF NICOTINAMIDE DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of nicotinamide derivatives of the formula



5 wherein

R^1 is selected from the group consisting of lower hydroxyalkyl, cycloalkyl which is unsubstituted or substituted by hydroxy or lower hydroxyalkyl, and from $-\text{CH}_2-\text{CR}^8\text{R}^9$ -cycloalkyl,

R^8 is hydrogen or lower alkyl;

10 R^9 is hydrogen, hydroxy or lower alkoxy;

R^2 is hydrogen;

or R^1 and R^2 together with the nitrogen atom they are attached to form a piperidinyl ring or a morpholinyl ring;

R^3 and R^7 are hydrogen or halogen;

15 R^4 , R^5 and R^6 independently from each other are selected from the group consisting of hydrogen, lower alkyl, lower halogenalkyl, lower halogenalkoxy, cyano and halogen

and pharmaceutically acceptable salts thereof.

The compounds of formula I are useful for the treatment and / or prophylaxis of diseases which are associated with the modulation of cannabinoid 1 receptors (CB1 receptors) as described in the PCT Publ. WO 2006/106054.

BACKGROUND OF THE INVENTION

5 The PCT Publ. WO 2006/106054 discloses various synthetic approaches to the nicotinamide derivatives of formula I in the respective schemes 1 to 7.

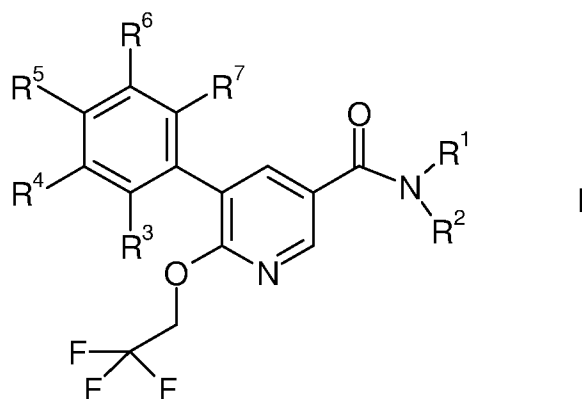
However, it was found that the overall yield of the above mentioned synthetic approaches were low to moderate based on low yielding reaction steps, formation of several by-products, unselective reactions and incomplete conversions and due to the need of chiral preparative HPLC.

10 Object of the invention therefore was to find an alternative synthetic approach which can be applied on a technical scale and which allows to obtain the product in an excellent yield and purity and without the need of chromatographical purification steps.

The object could be achieved with the process of the present invention as outlined below.

DETAILED DESCRIPTION OF THE INVENTION

15 The process for the preparation of nicotinamide derivatives of the formula



wherein

R^1 is selected from the group consisting of lower hydroxyalkyl, cycloalkyl which is unsubstituted or substituted by hydroxy or lower hydroxyalkyl,
 20 and from $-CH_2-CR^8R^9$ -cycloalkyl,

R^8 is hydrogen or lower alkyl;

R^9 is hydrogen, hydroxy or lower alkoxy;

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R^2 is hydrogen;

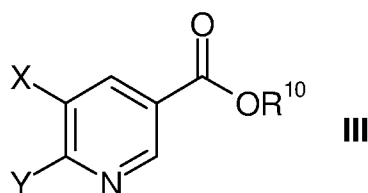
or R^1 and R^2 together with the nitrogen atom they are attached to form a piperidinyl ring or a morpholinyl ring;

R^3 and R^7 are hydrogen or halogen;

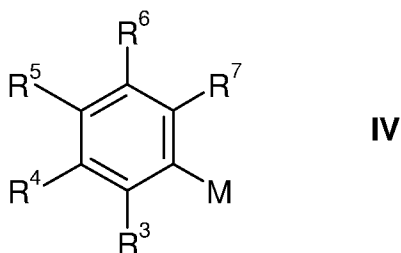
5 R^4 , R^5 and R^6 independently from each other are selected from the group consisting of hydrogen, lower alkyl, lower halogenalkyl, lower halogenalkoxy, cyano and halogen

and pharmaceutically acceptable salts thereof comprises

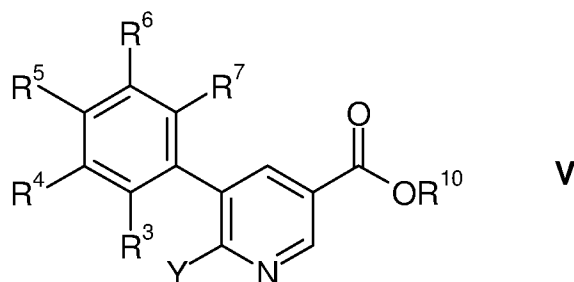
a) coupling a 5,6-dihalogenated nicotinic acid derivative of the formula



10 wherein X and Y stand for a halogen atom and R^{10} is hydrogen or lower alkyl
with an aryl metal species of the formula

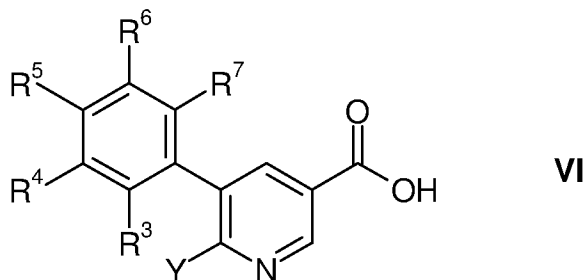


wherein R^3 to R^7 are as defined herein before and M means boronic acid or a boronic acid ester, in the presence of a Pd catalyst under basic conditions to form a 5-aryl substituted nicotinic
15 acid derivative of the formula



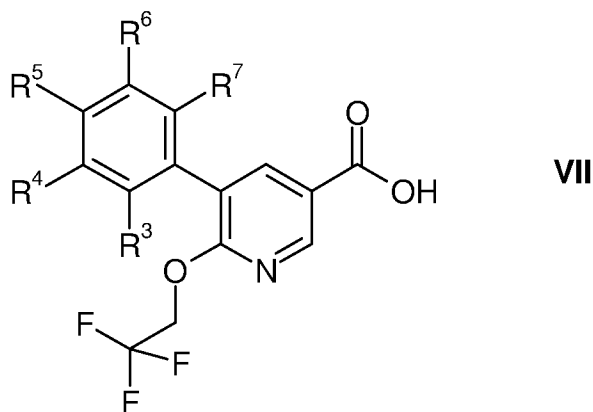
wherein Y, R^3 , R^4 , R^5 , R^6 , R^7 and R^{10} are as defined herein before;

b) optionally hydrolyzing a 5-aryl substituted nicotinic acid derivative of the formula V wherein R^{10} is lower alkyl with a base to form a 5-aryl substituted nicotinic acid derivative of the formula



5 wherein Y, R^3 , R^4 , R^5 , R^6 and R^7 are as defined herein before;

c) introducing the trifluoroethoxy group into the 5-aryl substituted nicotinic acid derivative of the formula VI to form a 6-trifluoroethoxy substituted nicotinic acid derivative of formula



10

wherein

R^3 , R^4 , R^5 , R^6 and R^7 are as defined herein before;

and

d) forming the nicotinamide derivative of formula I by reacting the 6-trifluoroethoxy substituted nicotinic acid derivative of formula VII with an amine of the formula



wherein

R¹ and R² are as defined herein before.

The following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The term “pharmaceutically acceptable salts” embraces salts of the compounds of formula I with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, fumaric acid, succinic acid, tartaric acid, methanesulphonic acid, salicylic acid, p-toluenesulphonic acid and the like, which are non toxic to living organisms. Preferred salts with acids are formates, maleates, citrates, hydrochlorides, hydrobromides and methanesulfonic acid salts, with hydrochlorides being especially preferred.

The term “lower alkyl” refers to a branched or straight-chain monovalent alkyl radical of one to seven carbon atoms, preferably one to four carbon atoms. This term is further exemplified by radicals such as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, isobutyl, t-butyl, n-pentyl, 3-methylbutyl, n-hexyl, 2-ethylbutyl and the like, but particularly methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, isobutyl and t-butyl and even more particularly methyl and ethyl.

The term “lower alkoxy” refers to a group R'-O, wherein R' is lower alkyl as defined above. Preferred are C₁₋₇-alkoxy groups, even more preferred C₁₋₄-alkoxy groups. Examples of lower alkoxy are methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, i-butoxy or t-butoxy.

The term “lower hydroxyalkyl” refers to lower alkyl groups as defined above wherein at least one of the hydrogen atoms of the lower alkyl group is replaced by a hydroxy group. Preferred are C₁₋₇-hydroxyalkyl groups, even more preferred C₁₋₄-hydroxyalkyl groups. Examples of lower hydroxyalkyl groups are 2-hydroxybutyl or 3-hydroxy-2,2-dimethylpropyl.

The term “lower halogenalkyl” refers to lower alkyl groups as defined above wherein at least one of the hydrogen atoms of the lower alkyl group is replaced by halogen as defined below. Preferred are C₁₋₇-halogenalkyl groups, even more preferred are C₁₋₄-halogenalkyl groups.

The term “lower halogenalkoxy” refers to lower alkoxy groups as defined above wherein at least one of the hydrogen atoms of the lower alkoxy group is replaced by halogen as defined below. Preferred are C₁₋₇-halogenalkoxy groups, even more preferred are C₁₋₄-halogenalkoxy groups.

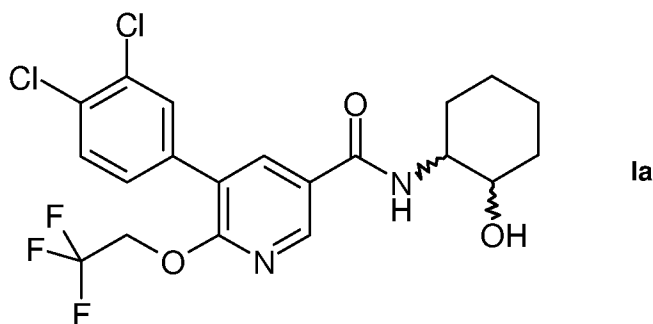
The term “cycloalkyl” refers to a monovalent carbocyclic radical of three to seven, preferably three to five carbon atoms. This term is further exemplified by radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, with cyclohexyl being especially preferred.

The term “halogen” refers to fluorine, chlorine, bromine and iodine. Preferred “halogen” groups are specifically exemplified hereinafter.

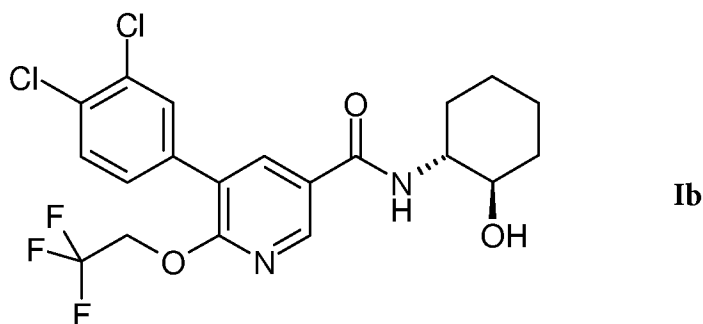
In a particular embodiment the present invention relates to the preparation of nicotinamide derivatives of the formula I wherein R¹ is cycloalkyl unsubstituted or substituted by hydroxy or lower hydroxyalkyl, R², R³, R⁴ and R⁷ are hydrogen and R⁵ and R⁶ are halogen.

In a further particular embodiment the present invention relates to the preparation of nicotinamide derivatives of the formula I wherein R¹ is 2-hydroxy-cyclohexyl, R², R³, R⁴ and R⁷ are hydrogen and R⁵ and R⁶ are chlorine.

In a still further particular embodiment the present invention relates to the preparation of the optical isomers of 5-(3,4-dichloro-phenyl)- *N*-2-hydroxy-cyclohexyl-6-(2,2,2-trifluoro-ethoxy)-nicotinamide of the formula .

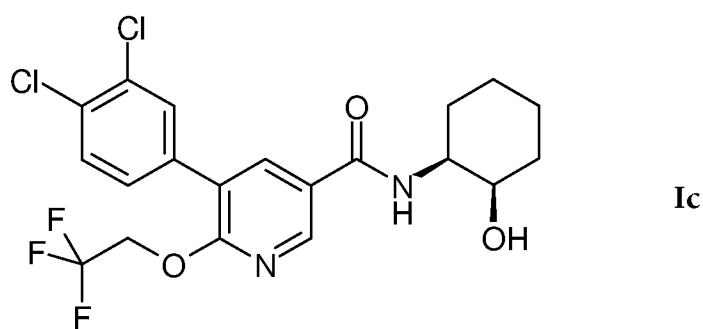


particularly to the isomer 5-(3,4-dichloro-phenyl)- *N*-((1*R*,2*R*)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide of the formula



and the isomer 5-(3,4-Dichloro-phenyl)- *N*-((1*S*,2*R*)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide of the formula

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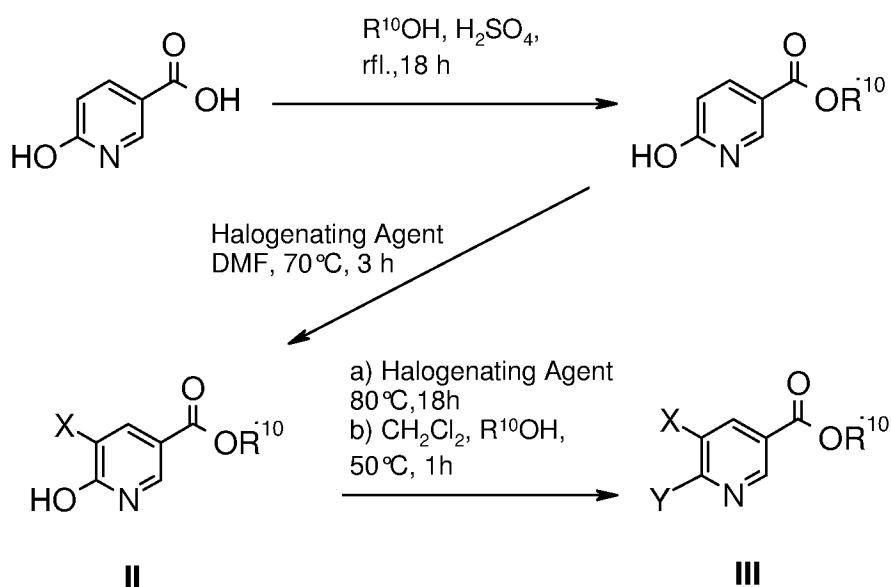
and to pharmaceutically acceptable salts of the isomers, whereby the isomer of the formula Ib is particularly preferred.

Step a

- 5 Step a) requires coupling a 5,6-dihalogenated nicotinic acid derivative of the formula III with an aryl metal species of the formula IV in the presence of a Pd catalyst under basic conditions to form a 5-aryl substituted nicotinic acid derivative of the formula V.

The 5,6-dihalogenated nicotinic acid derivative of the formula III are either commercially available or can be manufactured according to the following schemes:

10 Scheme 1



The esterification in the first step is advantageously performed with methanol (R^{10} being methyl). This reaction is well known in the literature (see e.g. PCT Publ. WO97/00864 or Oila et al., Tetrahedron Letters 46(6), 967-969(2005)).

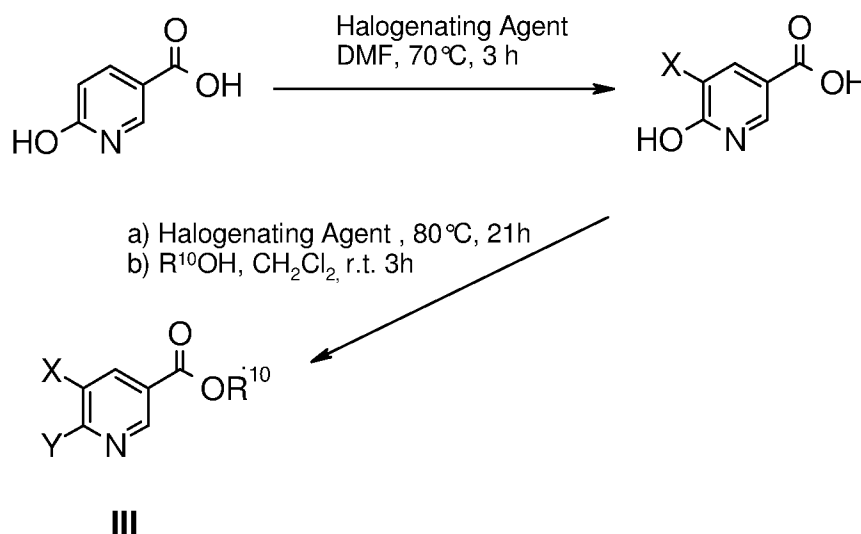
The halogenation in the ortho position of the hydroxy group which is characterizing the second step is also known in the literature (see e.g. Meana et al., Synlett (11), 1678-1682(2003) or Weller et al.; J Org Chem 1983, 48 (25), 4873).

In a particular embodiment the halogenation is a iodination (X being I) preferably using
5 iodosuccinimide as iodinating agent.

The substitution of the hydroxy group by a halogen in the third step to form the 5,6-dihalogenated nicotinic acid derivative of formula III as a rule is a chlorination which can be effected with phosphorous oxychloride as described in the literature mentioned above.

Scheme 2

10

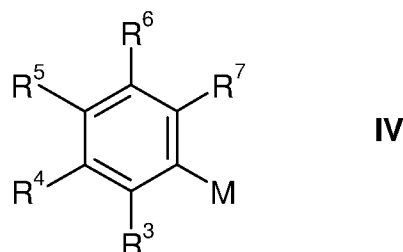


The halogenation in the ortho position of the hydroxy group in the first step is known in the literature (see e.g. Meana et al., Synlett (11), 1678-1682(2003) or Weller et al.; J Org Chem 1983, 48 (25), 4873). In a particular embodiment the halogenation is a iodination (X being I)
15 preferably using iodosuccinimide as iodinating agent.

The substitution of the hydroxy group by a halogen in the second step to form the 5,6-dihalogenated nicotinic acid derivative of formula III as a rule is a chlorination which can be effected with phosphorous oxychloride and the optional subsequent esterification can preferably be effected with methanol (R¹⁰ being methyl). This reaction is also described in the literature
20 (see e.g. Signor et al; Gazz Chim Ital 1963, 93, 65 or Wozniak et al.; J Heterocycl Chem 1978, 15, 731).

In a particular embodiment of the present invention the 6-chloro-5-iodo-nicotinic acid methyl ester is selected as advantageous representative for the 5,6-dihalogenated nicotinic acid derivative of formula III.

The subsequent coupling of the 5,6-dihalogenated nicotinic acid derivative of the formula
5 III is performed with an aryl metal species of formula



wherein R³, R⁴ and R⁷ particularly are hydrogen and R⁵, R⁶ are halogen, more particularly wherein R³, R⁴ and R⁷ are hydrogen and R⁵ and R⁶ are chlorine and wherein M is as above.

3,4-dichlorophenylboronic acid was found to be a favorable aryl metal species of formula
10 IV.

Pd-catalysts which have been found suitable for the coupling can be selected from palladium(II)acetate/triphenylphosphine mixtures, palladium(II)chloride-dppf (1,1'-bis(diphenylphosphino)ferrocene) or palladium(II)chloride bis(triphenylphosphino).

The basic conditions necessary for the coupling can be achieved with the presence of a
15 base selected from a tertiary amine or an alkali carbonate, preferably with sodium carbonate.

As a rule the reaction can be performed in the presence of an organic solvent, such as in aromatic hydrocarbon like toluene, or toluene/water, DMF, methanol, methanol/water at a reaction temperature of 20°C to 110°C, preferably of 70°C to 90°C.

The resulting 5-aryl substituted nicotinic acid derivative of the formula V can be isolated
20 following methods known to the skilled in the art.

Step b)

Step b) optionally requires hydrolyzing a 5-aryl substituted nicotinic acid derivative of the formula V wherein R¹⁰ is lower alkyl with a base to form a 5-aryl substituted nicotinic acid derivative of the formula VI.

Advantageously the 5-aryl substituted nicotinic acid derivative of formula V obtained in step a) is not isolated and in situ subjected to the hydrolysis in step b) for the formation of the 5-aryl substituted nicotinic acid derivative of formula VI.

5 In a preferred embodiment the 5-aryl substituted nicotinic acid derivative of formula V is the 6-Chloro-5-(3,4-dichloro-phenyl)-nicotinic acid methylester which is hydrolyzed to form the 6-Chloro-5-(3,4-dichloro-phenyl)-nicotinic acid as 5-aryl substituted nicotinic acid derivative of the formula VI.

The hydrolysis can usually be performed with a base selected from an alkali hydroxide, in a mixture of a suitable organic solvent such as tetrahydrofuran and water.

10 Suitably alkali hydroxides are selected from lithium-, sodium- or potassium hydroxide. Preferably an aqueous solution of lithium hydroxide is used.

The reaction is as a rule performed in the same organic solvent as used for the previous coupling step at a reaction temperature of 0°C to 60°C, preferably of 10°C to 30°C.

15 The 5-aryl substituted nicotinic acid derivative of formula VI can be isolated following methods known to the skilled in the art e.g. by acidifying the reaction mixture, by exchanging the solvent towards a lower boiling solvent like ethanol and by filtering off the crystals obtained.

Step c)

20 Step c) requires introducing the trifluoroethoxy group into the 5-aryl substituted nicotinic acid derivative of the formula VI to form a 6-trifluoroethoxy substituted nicotinic acid derivative of formula VII.

In a preferred embodiment the 6-trifluoroethoxy substituted nicotinic acid derivative of formula VII obtained in step c) is the 5-(3,4-Dichloro-phenyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinic acid.

25 The introduction of the trifluoroethoxy group in this step can be effected with 2,2,2-trifluoroethanol in the presence of a base and an organic solvent at a reaction temperature between 20°C to 150°C, particularly between 60°C and 100°C.

Suitable bases are alkali hydroxides, such as lithium-, sodium- or potassium hydroxide, preferably lithium hydroxide or organic base selected from Diazabicycloundecen or from Triazabicyclodecene.

30 Suitable organic solvents are for instance tetrahydrofuran, DMF or NMP.

The isolation of the 6-trifluoroethoxy substituted nicotinic acid derivative of formula VII from the reaction mixture can follow methods known to the skilled in the art via extractive work up and crystallization due to solvent exchange.

Step d)

- 5 Step d) requires forming the nicotinamide derivative of formula I by reacting the 6-trifluoroethoxy substituted nicotinic acid derivative of formula VII with an amine of the formula VIII.

Particularly an amine of formula VIII is selected, wherein R^1 is cycloalkyl unsubstituted or substituted by hydroxy or lower hydroxyalkyl and R^2 is hydrogen, even more particular wherein
10 R^1 is 2-hydroxy cyclohexyl and R^2 is hydrogen.

Reactions for forming an amide bond are well known in the art.

As a rule a coupling agent is employed to affect the transition.

Suitable coupling agents are oxalyl chloride, N,N'-carbonyl-diimidazole (CDI), N,N'-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
15 hydrochloride (EDCI), 1-[bis(dimethylamino)-methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate (HATU), 1-hydroxy-1,2,3-benzotriazole (HOBT) and O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) .

Advantageously oxalyl chloride is used as coupling agent to form the respective acid chloride of the 6-trifluoroethoxy substituted nicotinic acid derivative of formula VII.

- 20 The acid chloride formation can take place in the presence of a suitable organic solvent like tetrahydrofuran or methyl tetrahydrofuran at a reaction temperature of 0°C to 120°C.

Thereafter the coupling with the amine of formula VIII can take place, usually in the presence of a base and an organic solvent at a reaction temperature of 10°C to 30°C.

- 25 Suitable bases are alkali hydroxides, such as lithium-, sodium- or potassium hydroxide, preferably an aqueous solution of sodium hydroxide is used.

As a rule the same solvent as used for the acid chloride formation is used for the coupling with the amine.

- 30 Isolation of the desired nicotinamide derivative of formula I can happen following methods known to the skilled in the art, e.g. by crystallization of the product in a suitable solvent such as in ethanol.

EXAMPLES

Abbreviations:

DMF N,N-dimethylformamide

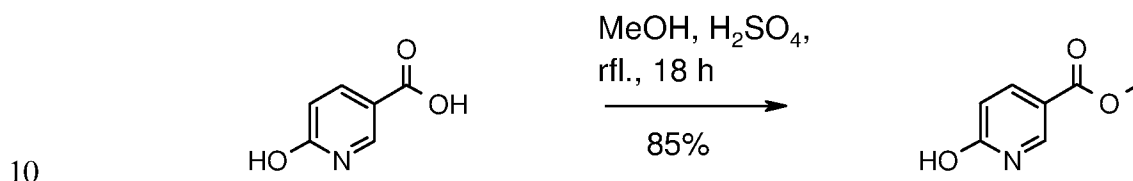
DMSO Dimethylsulfoxide

5 NMP N-methylpyrrolidone

THF Tetrahydrofuran

Example 1

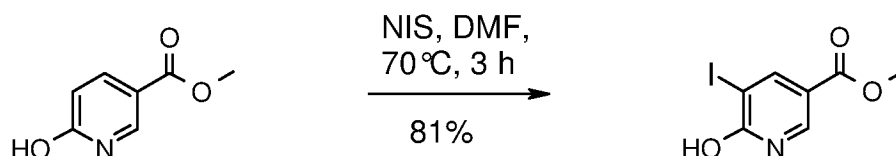
6-Hydroxy-nicotinic acid methyl ester



A suspension of 5-hydroxynicotinic acid (200 g, 1438 mmol) in methanol (1.0 l) was treated drop wise over 25 min with sulfuric acid (84 ml, 1505 mmol, exothermic!), heated to reflux and stirred at this temperature for 18 h. The yellow solution was cooled to ca. 30°C and
15 the solvent evaporated under reduced pressure (ca. 50-100 mbar) until a residual volume of ca. 600 ml. The solvent of the formed suspension was exchanged by water keeping the volume of ca. 600 ml. The suspension was stirred for 1 h at room temperature. The crystals were filtered, washed with water (50 ml) and dried to isolate the product in 68% yield. MS (GC_Split): 153 (M, 64%), 122 (100%), 94 (36), 66 (14).

20 Example 2

6-Hydroxy-5-iodo-nicotinic acid methyl ester

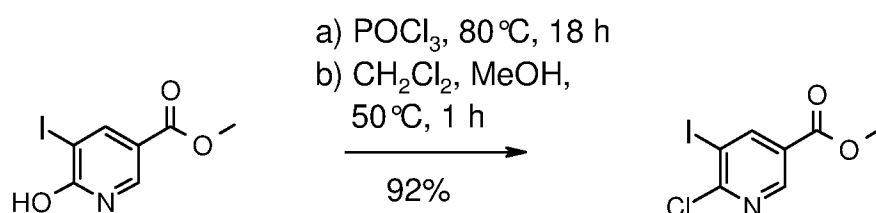


25 A solution of 6-hydroxy-nicotinic acid methyl ester (100.0 g, 653.0 mmol) and N-Iodosuccinimide (162.0 g, 720.1 mmol) in DMF (500 ml) was heated to 70°C and stirred for 3 h.

The reaction mixture was cooled within 20 min to room temperature and treated within 30 min with a solution of sodium thiosulfate (30.0 g, 189.7 mmol) in water (600 ml). The formed suspension was stirred for 30 min at room temperature, the crystals filtered, washed with water (500 ml) and dried to isolate the desired product in 81% yield. MS (pos): 302 ($M+H^+$, 5%), 280 ($M+H^+$, 100%).

Example 3

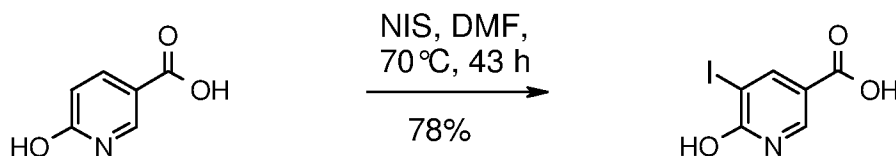
6-Chloro-5-iodo-nicotinic acid methyl ester



To a suspension of 6-hydroxy-5-iodo-nicotinic acid methyl ester (150.0 g, 538.0 mmol) in acetonitrile was added at room temperature phosphorus oxychloride (123.0 g, 805.0 mmol). The suspension was heated to reflux and stirred for 18 h. After cooling to 50 °C, methanol (70.1 g, 2.19 mol) was added and the reaction mixture was stirred at this temperature for 1 h. The formed suspension was cooled to room temperature and treated with water (1.1 l). The crystals were filtered, washed with water (600 ml) and dried to isolate the product in 92% yield. MS (GC-Split): 297 (M, 84%), 266 (100), 238 (36), 111 (56).

Example 4

6-Hydroxy-5-iodo-nicotinic acid



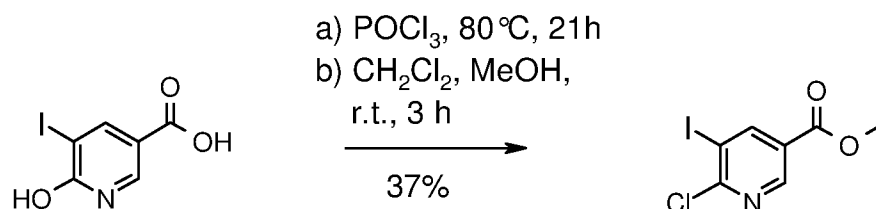
A solution of 6-hydroxy-nicotinic acid (1.0 g, 7.2 mmol) and N-Iodosuccinimide (1.8 g, 7.9 mmol) in DMF (8.0 ml) was heated to 70 °C and stirred for 4 h. The reaction mixture was cooled to room temperature and the suspension treated with a solution of sodium thiosulfate 0.1 N (50.0 ml, 5.0 mmol) and water (15 ml). The formed suspension was stirred for 3 days at room

temperature, the crystals filtered, washed with water and dried to isolate the desired product in 78% yield. MS (mixed scan): 264 ($M-H^-$, 100%).

Example 5

6-Chloro-5-iodo-nicotinic acid methyl ester

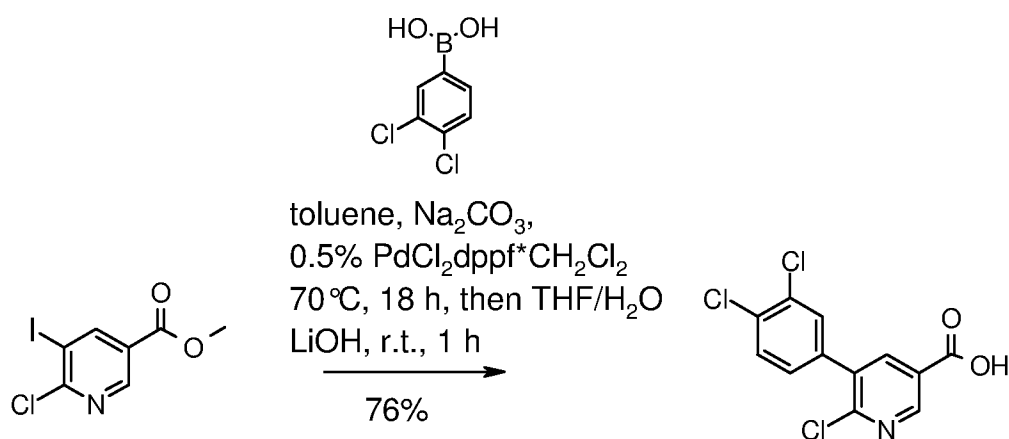
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To a suspension of 6-hydroxy-5-iodo-nicotinic acid (200.0 mg, 755 μ mol) in toluene (1.0 ml) was added at room temperature phosphorus oxychloride (289.0 mg, 1.9 mmol). The suspension was heated to 80 °C and stirred for 21 h. After cooling to room temperature, methanol (101 μ l, 2.49 mmol) was added and the reaction mixture was stirred at this temperature for 3 h. The reaction mixture was treated with toluene (10 ml) and extracted 3 times with water (total 30 ml) to isolate after evaporation of the organic solvent the crude product in 37% yield. MS (GC-Split): 297 (M, 84%), 266 (100), 238 (36), 111 (56).

15 Example 6

6-Chloro-5-(3,4-dichloro-phenyl)-nicotinic acid



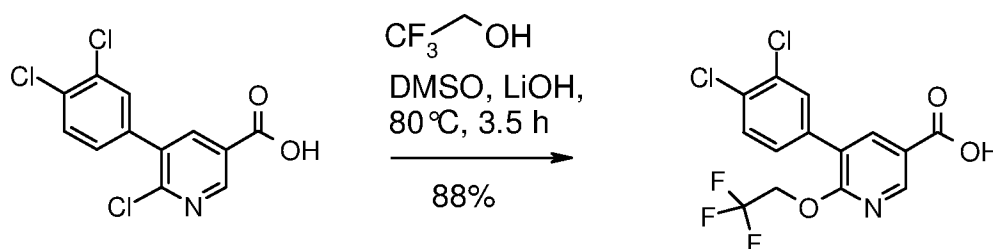
20 A suspension of 6-chloro-5-iodo-nicotinic acid methyl ester (20.0 g, 67.2 mmol), 3,4-dichlorophenylboronic acid (13.3 g, 69.9 mmol) and 1,1'-bis(diphenylphosphino)ferrocene palladium(II) dichloride dichloromethane complex (275.0 mg, 336 μ mol) in toluene (120 ml)

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was treated at room temperature with a solution of sodium carbonate (14.3 g, 134.0 mmol) in water (60.0 ml). The suspension was heated to 70°C and stirred for 18 h. After cooling to 60°C the phases were separated and the organic phase was washed at 60°C with water (60 ml). The combined organic phase was treated with a solution of lithium hydroxide monohydrate (5.7 g, 136 mmol) in water (65 ml) and stirred for 2 h at 60°C. The solution was cooled to room temperature, treated with water (60 ml) and within 10 min with HCl (18.0 ml, 138 mmol). The solvent of the formed suspension was exchanged under constant volume with ethanol (ca. 400 ml) at 45°C and 100 to 250 mbar and stirred for 17 h at room temperature. The crystals were filtered, washed with water (100 ml) and dried to isolate the product in 76% yield. MS (pos): 306 (M+H⁺, 31%), 304 (M+H⁺, 85%), 302 (M+H⁺, 100%).

Example 7

5-(3,4-Dichloro-phenyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinic acid

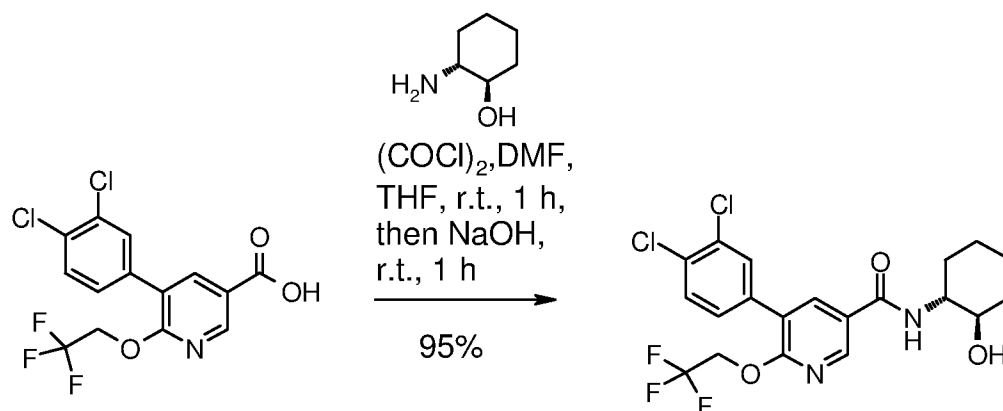


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A suspension of 6-chloro-5-(3,4-dichloro-phenyl)-nicotinic acid (70.0 g, 231.4 mmol) in DMSO (350.0 ml) was treated at room temperature in one part with LiOH (14.1 g, 578.5 mmol, exothermic -> 31°C). To the suspension was added within 10 min 2,2,2-trifluoroethanol (46.2 g, 462.8 mmol, exothermic -> 35°C). The reaction mixture was heated to 80°C and stirred for 4 h. After cooling to room temperature, water (700 ml) was added within 15 min, followed by the addition of dicalite (35.0 g). The suspension was stirred over night, filtered and the residue washed with water (140 ml). To the filtrate THF (560 ml) was added and within 15 min HCl 25% (75.0 ml, 575.3 mmol) to adjust the pH < 2. After stirring for 5 min at room temperature the phases were separated, the organic phase was treated with THF (160 ml) and filtered over QuadraPureTM MPA (Sigma Aldrich) (0.7 g) and washed with THF (50 l). The solvent of the mixture was exchanged with ethanol (700 ml) keeping the volume constant. The formed suspension was stirred for 1 h at 0°C, filtered and the crystals washed with ethanol (70 ml). After drying the product was isolated in 88% yield. MS (TurboSpray): 366 (M-H, 65%), 364 (M-H, 100%).

Example 8

5-(3,4-Dichloro-phenyl)-N-((1R,2R)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide



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To a solution of 5-(3,4-dichloro-phenyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinic acid (600 g, 1.64 mmol) in a mixture of THF (3.6 l) and DMF (4.0 ml) was added at room temperature within 1 h oxalyl chloride (215.0 ml, 2.46 mol). The reaction mixture was stirred for 1 h at room temperature (acid chloride formation).

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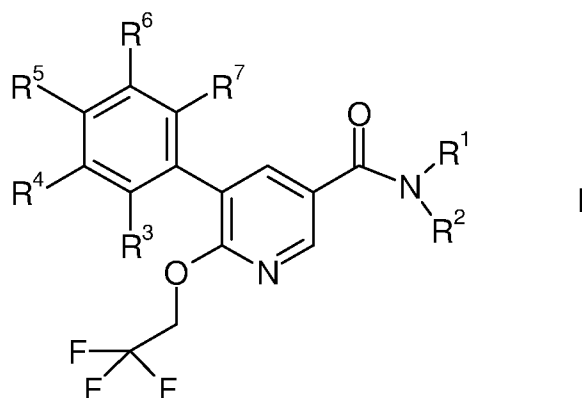
A solution of (1R,2R)-2-aminocyclohexanol hydrochloride (298.0 g, 1.97 mol) in a mixture of THF (2.4 l) and water (2.4 l) was treated at room temperature with NaOH (759.0 ml, 8.19 mmol) and stirred for 1 h. The biphasic mixture was heated to ca. 38°C, treated at this temperature within 45 min with the above described acid chloride and stirred for 45 min at ca. 38°C. After addition of ethanol (2.19 l) and stirring for 5 min, water (4.8 l) was added. The mixture was heated to 60°C and the organic solvent exchanged with ethanol (9.6 l) under reduced pressure keeping the total volume constant. The formed suspension was stirred for 3 h at room temperature, filtered and the crystals washed with a mixture of ethanol (2.1 l) and water 2.1 l followed by water (3.0 l). After drying the product was isolated in 95% yield. MS (TurboSpray): 465 (M+H⁺, 70%), 463 (M+H⁺, 100%).

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20

Claims

1. Process for the preparation of nicotinamide derivatives of the formula



5 wherein

R^1 is selected from the group consisting of lower hydroxyalkyl, cycloalkyl which is unsubstituted or substituted by hydroxy or lower hydroxyalkyl, and $-CH_2-CR^8R^9$ -cycloalkyl,

R^8 is hydrogen or lower alkyl;

10 R^9 is hydrogen, hydroxy or lower alkoxy;

R^2 is hydrogen;

or R^1 and R^2 together with the nitrogen atom they are attached to form a piperidinyl ring or a morpholinyl ring;

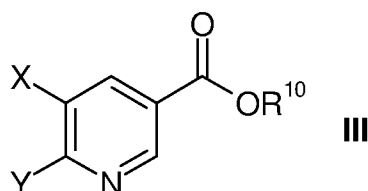
R^3 and R^7 are hydrogen or halogen;

15 R^4 , R^5 and R^6 independently from each other are selected from the group consisting of hydrogen, lower alkyl, lower halogenalkyl, lower halogenalkoxy, cyano and halogen

and pharmaceutically acceptable salts thereof comprising

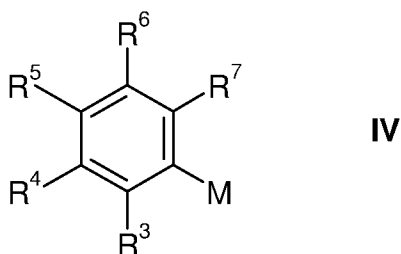
a) coupling a 5,6-dihalogenated nicotinic acid derivative of the formula

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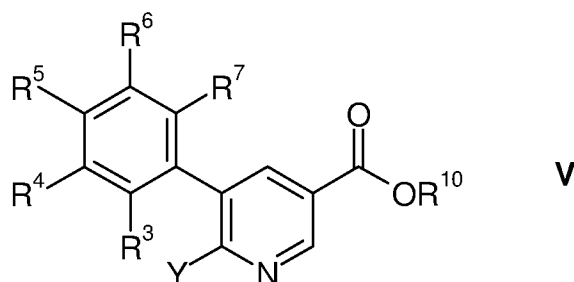


wherein X and Y stand for a halogen atom and R¹⁰ is hydrogen or lower alkyl

with an aryl metal species of the formula

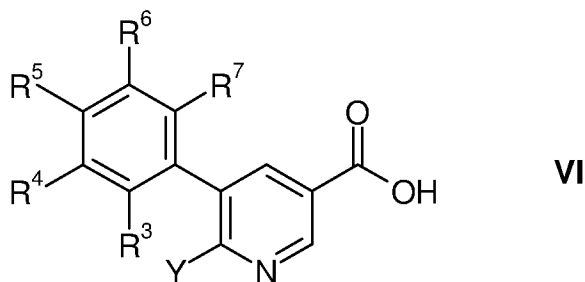


- 5 wherein R³ to R⁷ are as defined herein before and M means boronic acid or a boronic acid ester, in the presence of a Pd catalyst under basic conditions to form a 5-aryl substituted nicotinic acid derivative of the formula



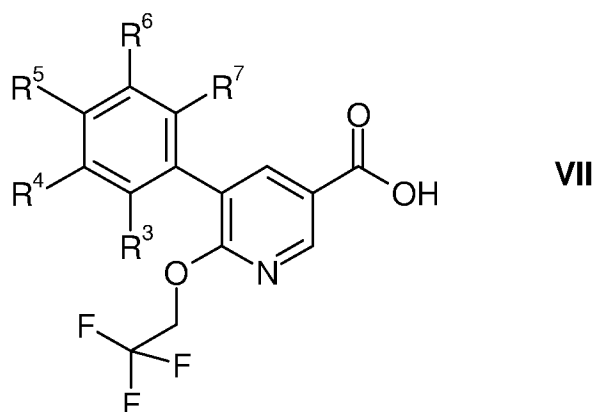
wherein Y, R³, R⁴, R⁵, R⁶, R⁷ and R¹⁰ are as defined herein before;

- 10 b) optionally hydrolyzing a 5-aryl substituted nicotinic acid derivative of the formula V wherein R¹⁰ is lower alkyl with a base to form a 5-aryl substituted nicotinic acid derivative of the formula



wherein Y, R³, R⁴, R⁵, R⁶ and R⁷ are as defined herein before;

c) introducing the trifluoroethoxy group into the 5-aryl substituted nicotinic acid derivative of the formula VI to form a 6-trifluoroethoxy substituted nicotinic acid derivative of formula



5

wherein

R^3 , R^4 , R^5 , R^6 and R^7 are as defined herein before;

and

d) forming the nicotinamide derivative of formula I by reacting the 6-trifluoroethoxy substituted nicotinic acid derivative of formula VII with an amine of the formula

10



wherein

R^1 and R^2 are as defined herein before.

2. Process according to claim 1, wherein the coupling in step a) is performed with an aryl metal species of formula IV, wherein R^3 , R^4 and R^7 are hydrogen and R^5 and R^6 are halogen.

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3. Process according to claim 2, wherein the coupling in step a) is performed with an aryl metal species of formula IV, wherein R^3 , R^4 and R^7 are hydrogen and R^5 and R^6 are chlorine.

4. Process according to claim 1, wherein the coupling in step a) is performed with a Pd catalyst selected from complexes of palladium(II)acetate/triphenylphosphine mixtures, palladium(II)chloride-dppf (1,1'-bis(diphenylphosphino)ferrocene) or palladium(II)chloride bis(triphenylphosphino).

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5. Process according to claim 1, wherein the basic conditions for the coupling in step a) are achieved with the presence of a base selected from a tertiary amine or an alkali carbonate.

6. Process according to any one of claims 2 to 5, wherein the coupling in step a) is performed in the presence of an organic solvent at a reaction temperature of 20°C to 110°C.

5 7. Process according to claim 1, wherein the hydrolysis in step b) is performed with an alkali hydroxide.

8. Process according to claim 1, wherein the 5-aryl substituted nicotinic acid derivative of formula V obtained from step a) is not isolated and in situ subjected to the hydrolysis in step b) for the formation of the 5-aryl substituted nicotinic acid derivative of formula VI.

10 9. Process according to claim 1, wherein the introduction of the trifluoroethoxy group in step c) is effected with 2,2,2-trifluoroethanol in the presence of a base and an organic solvent at a reaction temperature between 20°C to 150°C.

10. Process according to claim 9, wherein the base is selected from an inorganic base selected from an alkali hydroxide or from an organic base selected from Diazabicycloundecen or
15 from Triazabicyclodecene.

11. Process according to claim 1, wherein the amide formation in step d) is performed with an amine of the formula VIII, wherein R¹ is cycloalkyl unsubstituted or substituted by hydroxy or lower hydroxyalkyl and R² is hydrogen.

12. Process according to claim 11, wherein the amide formation in step d) is performed
20 with an amine of the formula VIII, wherein R¹ is 2-hydroxy cyclohexyl and R² is hydrogen.

13. Process according to claims 11 or 12, wherein the amide formation is effected in the presence of a coupling agent and an organic solvent at a reaction temperature of 0°C to 120°C.

14. Process according to claim 13, wherein the coupling agent is selected from oxalyl chloride, N,N'-carbonyl-diimidazole (CDI), N,N'-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), 1-[bis(dimethylamino)-methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate (HATU), 1-hydroxy-1,2,3-benzotriazole (HOBT) and O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) .
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/068197

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D213/82 A61K31/455
ADD.

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)

C07D

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/040651 A1 (HOFFMANN LA ROCHE [CH]; ANDJELKOVIC MIRJANA [CH]; BENARDEAU AGNES [FR]) 10 April 2008 (2008-04-10) examples 5, 8	1-14
A,P	----- WO 2011/029827 A1 (HOFFMANN LA ROCHE [CH]; ROEVER STEPHAN [DE]; WRIGHT MATTHEW [CH]) 17 March 2011 (2011-03-17) page 3; compound Ia schemes 1 and 2 example 3 -----	1-14



Further documents are listed in the continuation of Box C.



See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search

30 November 2011

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06/12/2011

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/068197

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