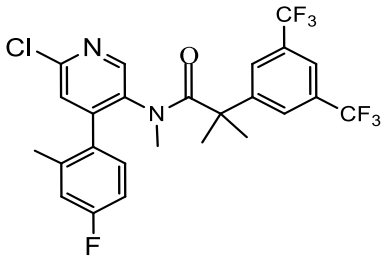
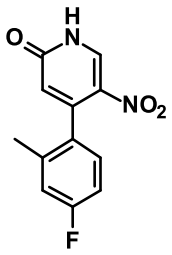
Claims

1. A process for preparing Compound (IX),



(IX)

said process comprising the following step i) reaction of 4-chloro-5-nitropyridin-2(1H)-one with 4-fluoro-2-methylphenyl boronic acid catalyzed by a palladium complex in the presence of a base to obtain 4-(4-fluoro-2-methylphenyl)-5-nitropyridin-2(1H)-one (III):



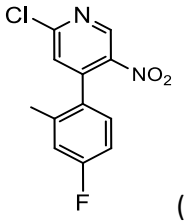
(III).

2. The process according to claim 1, wherein

- said palladium complex is selected from palladium acetate, tetrakis(tri-phenylphosphine)palladium, bis(triphenylphosphine)palladium(II) dichloride, and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride, phosphine palladium complex;
- said base is selected from potassium carbonate, cesium carbonate, triethylamine, potassium phosphate, sodium t-butoxide, potassium t-butoxide or a mixture thereof; and
- step i) takes place in an organic solvent selected from acyclic or cyclic ethers, toluene, dimethylformamide, N-methyl-2-pyrrolidone, acetonitrile or mixtures thereof.

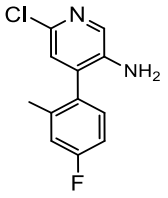
3. The process according to claim 1 or 2, wherein step i) is followed by

ii) reacting 4-(4-fluoro-2-methylphenyl)-5-nitropyridin-2(1H)-one (III) obtained in step i) with $POCl_3$ to obtain 2-chloro-4-(4-fluoro-2-methylphenyl)-5-nitropyridine (IV):


(IV).

4. The process according to claim 3, wherein step ii) is followed by

iii) comprising the reduction of said 2-chloro-4-(4-fluoro-2-methylphenyl)-5-nitropyridine (IV) by catalytic hydrogenation to obtain 6-chloro-4-(4-fluoro-2-methylphenyl)pyridin-3-amine of formula (V) or salts thereof:


(V),

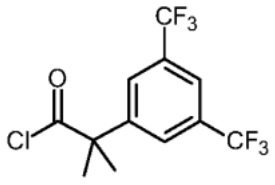
wherein

- said catalytic hydrogenation is carried out in the presence of catalysts selected from palladium or platinum on carbon and
- the salts of compound (V) are selected from maleate, hydrochloride, hydrobromide, phosphate, acetate, fumarate, salicylate, sulphate, citrate, lactate, mandelate, tartrate or methanesulphonate.

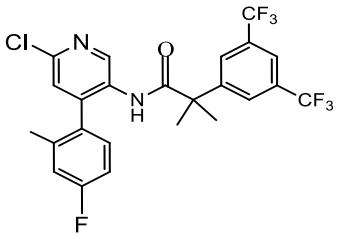
5. The process according to claim 4, wherein the salt of compound(V) is hydrochloride.

6. The process according to claim 4 or 5, wherein step iii) is followed by step

iv) reacting 6-chloro-4-(4-fluoro-2-methylphenyl)pyridin-3-amine (V) or a salt thereof obtaining in step iii) with 2-(3,5-bis(trifluoromethyl)phenyl)-2-methylpropanoyl chloride (VI)


(VI),

to obtain 2-(3,5-bis(trifluoromethyl)phenyl)-N-(6-chloro-4-(4-fluoro-2-methylphenyl)pyridin-3-yl)-2-methyl-propanamide of formula (VII):



(VII),

wherein step iv) takes place in dichloromethane in the presence of an organic base, selected from pyridine, triethylamine, diisopropylamine, N,N-diisopropylethylamine, 2,6-lutidine or a mixture thereof at a temperature at a temperature of 0-5°C.

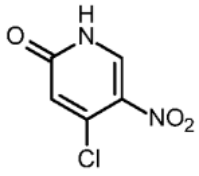
7. The process according to claim 6, wherein step iv) is followed by step

v) reacting 2-(3,5-bis(trifluoromethyl)phenyl)-N-(6-chloro-4-(4-fluoro-2-methylphenyl)pyridin-3-yl)-2-methyl-propanamide (VII) obtained by step iv) with a methyl halide of formula (VIII) CH3X, wherein X is selected from chlorine, bromide or iodine, in the presence of a base to obtain Compound (IX),
wherein step v) takes place in an organic base selected from pyridine, triethylamine, diisopropylamine, N,N-diisopropylethylamine, 2,6-lutidine or in an inorganic base selected from potassium carbonate, cesium carbonate, potassium phosphate, sodium t-butoxide, potassium t-butoxide or a mixture thereof.

8. The process according to claim 7, wherein the base is cesium carbonate.

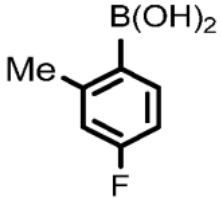
9. The process according to any one of claims 1-8, said process comprising the following steps:

i) reaction of 4-chloro-5-nitropyridin-2(1H)-one (I)



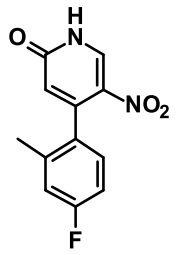
(I)

with 4-fluoro-2-methylphenyl boronic acid (II)



(II)

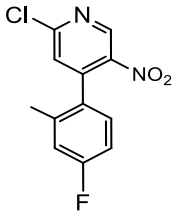
catalyzed by a palladium complex in the presence of a base to obtain 4-(4-fluoro-2-methylphenyl)-5-nitropyridin-2(1H)-one of structure (III):



(III);

followed by

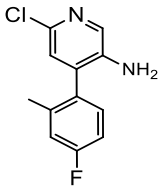
ii) reacting 4-(4-fluoro-2-methylphenyl)-5-nitropyridin-2(1H)-one (III) obtained in step i) with $POCl_3$ to obtain 2-chloro-4-(4-fluoro-2-methylphenyl)-5-nitropyridine (IV):



(IV);

followed by

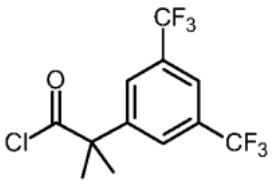
iii) reduction of 2-chloro-4-(4-fluoro-2-methylphenyl)-5-nitropyridine (IV) by catalytic hydrogenation to obtain 6-chloro-4-(4-fluoro-2-methylphenyl)pyridin-3-amine of formula (V) or salts thereof:



(V);

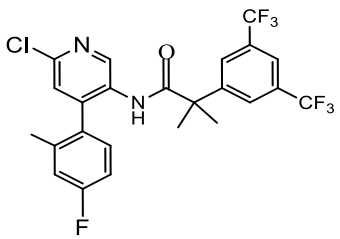
followed by

iv) reacting 6-chloro-4-(4-fluoro-2-methylphenyl)pyridin-3-amine (V) or a salt thereof obtaining in step iii) with 2-(3,5-bis(trifluoromethyl)phenyl)-2-methylpropanoyl chloride (VI)



(VI)

to obtain 2-(3,5-bis(trifluoromethyl)phenyl)-N-(6-chloro-4-(4-fluoro-2-methylphenyl)pyridin-3-yl)-2-methyl-propanamide of formula (VII):

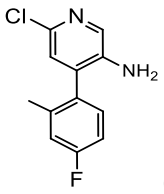


(VII);

followed by

v) reacting 2-(3,5-bis(trifluoromethyl)phenyl)-N-(6-chloro-4-(4-fluoro-2-methylphenyl)pyridin-3-yl)-2-methyl-propanamide (VII) with a methyl halide of formula (VIII) CH3X in the presence of cesium carbonate to obtain Compound (IX).

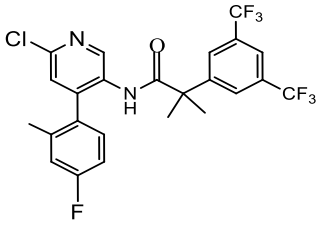
10. A salt of compound (V):



(V),

wherein the salts are selected from maleate, hydrochloride, hydrobromide, phosphate, acetate, fumarate, salicylate, sulphate, citrate, lactate, mandelate, tartrate or methanesulphonate.

11. A compound of formula (VII):



(VII).