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(54) Title: A PROCESS FOR PREPARING 2-HYDROXY-3-[5-(MORPHOLIN-4-YLMETHYL)PYRIDIN-2-YL]LH-INDOLE-5-CARBONITRILE AS A FREE BASE OR SALTS THEREOF

(57) Abstract: The present invention relates to a new process for the manufacture of the compound 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]H-indole-5-carbonitrile as a free base and pharmaceutically acceptable salts thereof, particularly the 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]H-indole-5-carbonitrile citrate, to the use of said compounds for the manufacturing of a medicament for the treatment of cognitive disorders, Alzheimer disease, dementias, chronic and acute neurodegenerative diseases, bipolar disorders, schizophrenia, diabetes, hair loss etc. and to new intermediates as well as a robust condition for catalytic cyanation for the preparation of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]H-indole-5-carbonitrile as a free base and pharmaceutically acceptable salts thereof, and to a new intermediate prepared in said process suitable for large scale manufacturing of said compounds. The invention also relates to a new use in cyanation reaction of palladium catalysts.



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NEW PROCESS

5 FIELD OF THE INVENTION

The present invention relates to a new process for the manufacture of the compound 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1*H*-indole-5-carbonitrile as a free base and pharmaceutically acceptable salts thereof and to new intermediates prepared therein
10 suitable for large scale manufacturing of said compounds. The invention also relates to a new robust process for large scale cyanation to produce 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1*H*-indole-5-carbonitrile under mild conditions. The invention also relates to the use of new palladium catalysts for metal-catalysed cyanation of aryl halides.

15 BACKGROUND OF THE INVENTION

2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1*H*-indole-5-carbonitrile as a free base and pharmaceutically acceptable salts thereof are known and useful because they possess pharmacological activity by showing inhibiting effect on GSK3 (WO 03/082853).
20 This compound could be used to treat cognitive disorders, Alzheimer disease, dementias, chronic and acute neurodegenerative diseases, bipolar disorders, schizophrenia, diabetes, hair loss and all the listed disorders described in WO 03/082853, which hereby are incorporated into this specification by reference.

25 WO 03/082853 discloses a process for the preparation of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1*H*-indole-5-carbonitrile as a free base and the hydrochloride salt thereof. In said process 5-cyanooxindole is reacted with a 2-halopyridin-*N*-oxide derivative in an inert organic solvent such as tetrahydrofuran, dioxane, dimethylformamide or *N*-methylpyrrolidin-2-one. The presence of a base is advantageous for the coupling. A
30 temperature range of 0-130°C was disclosed.

The N-oxide could be removed with phosphorus trichloride in a suitable solvent such as methylene chloride, toluene or ethyl acetate to furnish 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1*H*-indole-5-carbonitrile. In the disclosed process the 5-cyano-oxindole is expensive and is not available as a commercial bulk substance. At the temperature for the coupling, 130°C, the starting 5-cyanooxindole decomposes. The use of *N*-oxides on large scale is of concern due to their potential explosive properties. Purification to achieve a pharmaceutically acceptable quality material could only be achieved by column chromatography. This purification technique is not the most practical or economical for large-scale manufacture. In addition, upon scale up low yields were obtained.

WO 03/082853 discloses the preparation of 5-bromo-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1*H*-indol-2-ol which was prepared analogously as 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1*H*-indole-5-carbonitrile however using 5-bromooxindole instead of 5-cyanooxindole.

The catalytic transformation of an aryl halide into an aryl nitrile is a very attractive method, which is evident by the large number of publications in the field (Tetrahedron Lett. 1999, 40, 8193; Tetrahedron Lett. 2000, 41, 3271; Tetrahedron Lett. 2004, 45, 1441; Synlett. 2003, 2237.; Org. Lett. 2004, 3723; J. Organomet. Chem. 2004, 689, 4576; Tetrahedron Lett. 2005, 46, 1815; EP 0771786; DE 10113976). However, despite much effort the reaction is still known for being notoriously difficult to perform on large scale due to robustness problems. Another problem is the long reaction times at elevated temperature that is usually required which may lead to product decomposition.

The new use of catalysts for the cyanation of aryl halides described in the present invention have been earlier disclosed as catalysts for other applications in the following literature: di- μ -bromobis(tri-tert-butylphosphine)dipalladium(I) ([BrPdP(t-Bu)₃]₂) in Angew. Chem. Int. Ed. 2002, 41, 4746; J. Organomet. Chem. 2000, 600, 198; the combination of tris(dibenzylideneacetone)dipalladium(0) or bis(dibenzylideneacetone)palladium(0) and

bis(tri-*tert*-butylphosphine)palladium(0) ($\text{Pd}_2(\text{dba})_3$ or $\text{Pd}(\text{dba})_2$ and $\text{Pd}[\text{P}(\text{t-Bu})_3]_2$) in J. Am. Chem. Soc. 2000, 122, 4020; J. Am. Chem. Soc. 2001, 123, 12905, the combination of tris(dibenzylideneacetone)dipalladium(0) or bis(dibenzylideneacetone)palladium(0) and 1,2,3,4,5-pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene in J. Org. Chem. 2002, 67, 5553; J. Am. Chem. Soc. 2003, 125, 11176, WO 02/11883, and the combination of tris(dibenzylideneacetone)-dipalladium(0) or bis(dibenzylideneacetone)palladium(0) and tri-*ortho*-tolylphosphine in Angew. Chem. Int. Ed., 1995, 34, 1348, and bis(tri-*tert*-butylphosphine)palladium(0) ($\text{Pd}[\text{P}(\text{t-Bu})_3]_2$) in J. Am. Chem. Soc. 2001, 123, 2719, a combination of tris(dibenzylideneacetone)dipalladium(0) or bis(dibenzylideneacetone)-palladium(0) and a 2-(dialkylphosphino)biphenyl, where the alkyl is a bulky group, in J. Am. Chem. Soc. 1998, 120, 9722; J. Am. Chem. Soc. 1999, 121, 9550; J. Am. Chem. Soc. 2003, 125, 6653; US 6,307,087.

In summary, there is a need for a more convenient and more economically efficient process for the manufacturing of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1*H*-indole-5-carbonitrile as a free base and pharmaceutically acceptable salts thereof, especially with regard to large-scale production where factors like costs, manufacturing time, robustness and safety are vital for commercial application. The present invention provides for such a process.

BRIEF DESCRIPTION OF THE INVENTION

The present invention is directed to a new process for manufacturing of the compound (2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1*H*-indole-5-carbonitrile as a free base and pharmaceutically acceptable salts thereof, particularly the citrate salt.

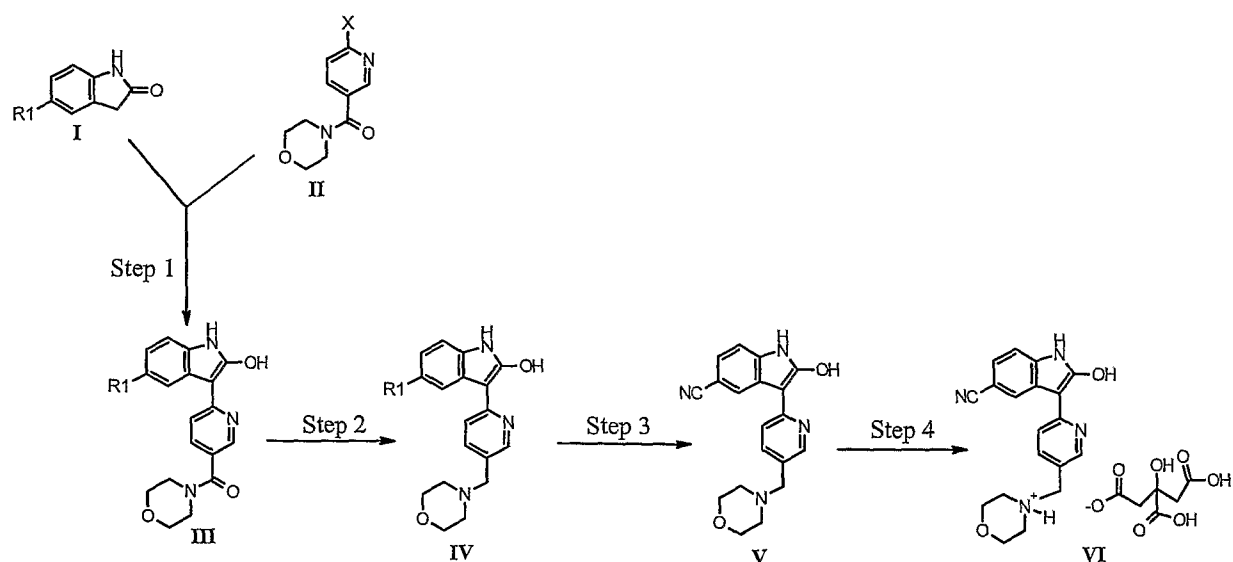
Further, it provides for a new process to prepare compounds, which are useful as intermediates in the preparation of such pharmaceutically active compounds, example of such new intermediates are [6-(5-halo-2-hydroxyl-1*H*-indol-3-yl)-pyridin-3-yl]-morpholin-4-yl-methanone, in particular [6-(5-bromo-2-hydroxyl-1*H*-indol-3-yl)-pyridin-3-yl]-

morpholin-4-yl-methanone. The invention also relates to a new robust process for large scale cyanation to produce 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1*H*-indole-5-carbonitrile under mild conditions.

5 DETAILED DESCRIPTION OF THE INVENTION

A general outline of the new manufacturing process is as follows, wherein R1 is halogen, where halogen is chloro, bromo or iodo, and X is halogen, where halogen is chloro, bromo or iodo.

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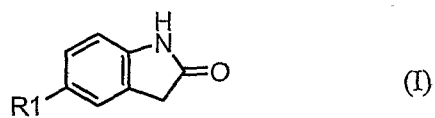


In the above scheme, preferably R1 is bromo and X is chloro.

The new manufacturing process of the present invention may be described in the following way:

15 A process for the preparation of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1*H*-indole-5-carbonitrile as a free base and pharmaceutically acceptable salts thereof, by

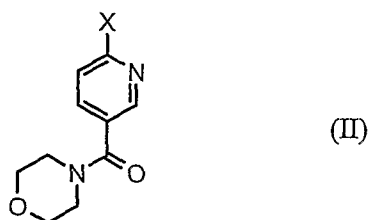
a) reacting a compound of formula (I) wherein R1 is halogen, where the halogen is chloro,



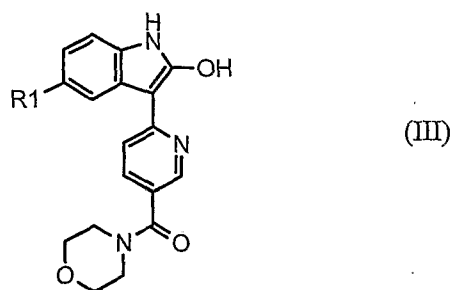
bromo or iodo

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with a compound of formula (II) wherein X is halogen, where the halogen is chloro, bromo or iodo



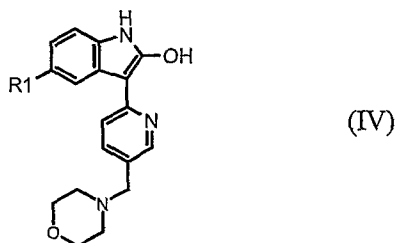
10 in the presence of a base and a solvent to obtain a compound of formula (III) wherein R1 is halogen, where the halogen is chloro, bromo or iodo



15 followed by,

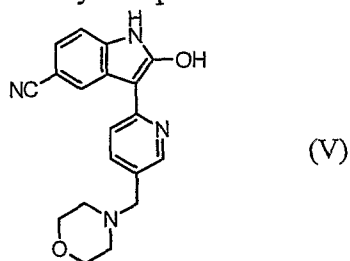
- b) i) selective reduction of the compound of formula (III) with a reducing agent in the presence of a solvent, and
ii) decomplexation to form of compounds of formula (IV) wherein R1 is halogen, where halogen is chloro, bromo or iodo

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followed by,

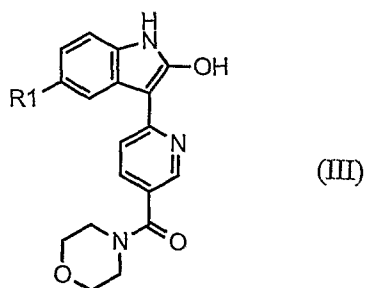
- c) cyanation of the compound of formula (IV) with a cyanide source, a metal catalyst and optionally with an additive, in the presence of a solvent to obtain a compound of formula (V), 2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile, which
10 either is isolated, or followed by
d) treating the compound of formula (V) with a suitable acid in the presence of a solvent to obtain the corresponding pharmaceutically acceptable salt.



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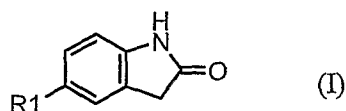
In step 1 (process step a above and in claim 1) of the manufacturing process a compound of formula (III)

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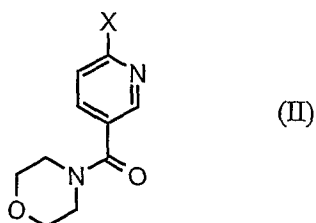
wherein R1 is halogen, where halogen is chloro, bromo or iodo, is prepared by reacting compounds of formula (I), wherein R1 is halogen, where halogen is chloro, bromo or iodo,

5



with a compound of formula (II) wherein X is a halogen, where the halogen is chloro, bromo or iodo

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A step 1 using a compound of formula (I) wherein R1 is bromo and a compound of formula (II) wherein X is chloro is particularly suitable.

The starting compound of formula (I) wherein R1 is bromo may be prepared in a known manner described in the prior art, e.g. reacting oxindole with bromine and potassium bromide (J. Am. Chem. Soc, 1945, 67, 1656). The chloro analogue may be synthesized as disclosed in the prior art (Synthesis, 1991, 10, 871) and the iodo analogue

20

may be synthesized as disclosed in the prior art (Heterocyclic Communications, 1997, 3(3), 207).

The starting compound of formula (II) wherein X is chloro may be prepared in a known
5 manner described in the prior art, e.g. formation of the acid chloride of 6-chloronicotinic acid and subsequent reaction with morpholine (Ann. Pharm. Fr. 1977, 35(5-6), 197). The other halogen analogue of compound of formula (II) could be prepared by someone skilled in the art starting from the corresponding 6-halonicotinic acid i.e. 6-fluoro- (J. Med. Chem., 1990, 33(6), 1667, 6-bromo- (Synthesis, 2003, 4, 551), 3394, 6-iodo-nictonic acid
10 (J. Am. Chem. Soc, 1950, 72, 1032), respectively.

Step 1 is performed in a solvent and in the presence of a base.

The solvent may be selected from the group comprising of ethers such as tetrahydrofuran, methyltetrahydrofuran, diethyleneglycol dimethyl ether or 1,4-dioxane, or a polar aprotic
15 solvent such as *N,N*-dimethylacetamide, *N*-methyl-2-pyrrolidinone, dimethylformamide, dimethylsulfoxide, 1,3-dimethyl-tetrahydro-2(1H)-pyrimidinone or mixtures thereof. The preferred solvents are polar aprotic solvents, particularly preferred is *N*-methyl-2-pyrrolidinone.

20 The total amount of solvents used in the coupling process step 1, may vary between 2 to 100 (v/w) volume parts per weight of starting material, preferably between 3-30 (v/w) volume parts per weight of starting material.

A suitable base may be an organic amine base such as diazabicyclo[5.4.0]undec-7-ene, or alkali metal salts such as sodium carbonate; or alkali metal hydrides such as sodium
25 hydride and lithium hydride; alkali metal alkoxides as lithium *tert*-butoxide; or alkali metal amides such as potassium bis(trimethylsilyl) amide, lithium diisopropylamide or sodium amide. The preferred base is lithium hydride.

The amount of base used in the coupling process step a) may vary between 1 to 5 mole equivalents of compound of formula (I).

The preferred equivalent of base ranges from 2 to 3 mole equivalents of compound of formula (I).

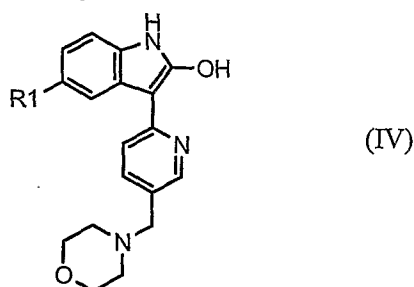
5 The temperature of the coupling step a) may be between -100°C to +180°C, preferably between room temperature and +140°C.

The mole equivalent of compound of formula (II) compared to compound of formula (I) may be between 1 and 5 mole equivalents, preferably between 1 and 2.5 mole equivalents.

10 The work up may be performed by methods known by someone skilled in the art, for example by quenching with water, ammonium chloride either as a solid or as a solution in water of varying concentration or by an organic or inorganic acid. Other protic solvents of low molecular weight could also be used as quenching agent e.g. methanol, ethanol, propanol or butanol, or mixtures thereof as long as the pH is adjusted by the addition of an
15 acid.

The compound of formula (III) obtained in step 1 has a chromatographic purity of at least 90%, preferably more than 95%.

20 Step 2 (process step b above and in claim 1) of the manufacturing process of a compound of formula (IV) wherein the R1 is halogen, where halogen is chloro, bromo or iodo



is carried out in two stages, (i) the selective reduction of the compound of formula (III),
25 wherein the R1 is halogen, where halogen is chloro, bromo or iodo, with a reducing agent followed by (ii) decomplexation reaction.

Stage i) The reducing agent used for the formation of compound (IV) may be selected from the group comprising of boranes e.g. borane tetrahydrofuran complex, borane dimethyl-

5 sulphide complex, borane-morpholine complex and borane-*N,N*-diethylaniline.
Preferred reducing agents are borane tetrahydrofuran complex or borane dimethylsulphide complex, particularly preferred is borane tetrahydrofuran complex.

The mole equivalent of the reducing agent compared to compound of formula (III) may be between 1 and 5 mole equivalents, preferably between 3 and 4 mole equivalents.

10

A suitable polar, aprotic solvent in step 2), stage i) is preferably ethers such as tetrahydrofuran, 2-methyl tetrahydrofuran, dioxane, or diethyleneglycol dimethyl ether, or mixtures thereof. The preferred solvent is tetrahydrofuran.

15 The total amount of solvents may vary between 1 to 100 (v/w) volume parts per weight of starting material, preferably between 5 to 20 (v/w) volume parts per weight of starting material.

The temperature used in process step 2), stage i) may be between -100°C to +100°C. The
20 temperature is preferably kept between -10°C to +40°C. The formed borane complex of compound of formula (IV) is usually not isolated.

Stage ii) The decomplexation reaction of the formed borane complex of the compound of formula (IV) may be performed by quenching with either an inorganic acid e.g.
25 hydrochloric acid, sulphuric acid, phosphoric acid or an organic acid e.g. acetic acid, or a protic solvent which includes water, methanol, ethanol, propanol, butanol or triethanolamine, or mixture thereof.

The acids may be used in the gas or fluid phase and may optionally be mixed with water and/or any of the protic solvents mentioned above.

The reagent for free basing of the salt of compound of formula (IV) is selected from aqueous hydroxides such as sodium hydroxide, lithium hydroxide or other inorganic bases such as sodium hydrogen carbonate, potassium carbonate, or organic bases such as amines e.g. triethylamine, diisopropylamine or ammonia optionally in combination with water
5 and/or a protic solvent, preferably one of the protic solvent mentioned above.

The preferred quench agent for step 2, stage ii) is water and/or methanol.

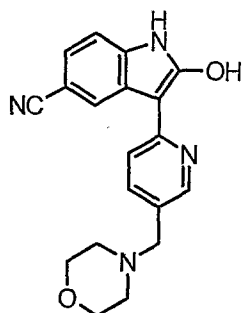
The temperature used in process step 2, stage ii) may be between -10°C to +150°C, preferably between room temperature and +80°C.

10 Compounds of formula (IV) are normally obtained with a purity of at least 85%.

Compounds of formula (IV) may optionally be further purified by recrystallisation from a mixture of an organic solvent using a hydrocarbon as antisolvent to obtain a purity of at least 95%.

15 Suitable solvents for crystallisation may include polar solvents such as dimethylsulphoxide, *N*-methylpyrrolidinone, 1,4-dioxane and a hydrocarbon solvent such as toluene, cumene, xylenes, ligroin, petroleum ether, halobenzenes, heptanes, hexanes, octanes, cyclohexanes, cycloheptanes, or mixtures thereof.

20 Step 3 (process step c above and in claim 1), the cyanation reaction, of the manufacturing process of a compound of formula (V), 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile



(V)

is carried out by reacting compounds of formula (IV) wherein the R1 is halogen, where the halogen is chloro, bromo or iodo, with a metal catalyst, a cyanide source in a suitable solvent and optionally in the presence of additive(s).

5 The catalyst is based on a metal where the metal may be selected from the group comprising of palladium, nickel or copper, or mixtures thereof, preferably palladium, or alternatively it may be based on the combination of a metal and a ligand where the metal may be palladium, nickel or copper, or mixtures thereof, preferably palladium, and where the ligand may be a tertiary phosphine or di-phosphine, secondary or tertiary amine or di-
10 amine, a tertiary arsine or a *N*-heterocyclic carbene, or combinations thereof. Preferably the ligand is selected from tri-*tert*-butylphosphine, tri-*ortho*-tolylphosphine or 1,2,3,4,5-pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene. A preferred source of palladium is a complex between palladium and dibenzylideneacetone. The catalyst is preferably selected from the group comprising of di- μ -bromobis(tri-*tert*-butylphosphine)dipalladium(I) ([BrPdP(t-Bu)₃]₂), a combination of tris(dibenzylideneacetone)di-palladium(0) or
15 bis(dibenzylideneacetone)palladium(0) and tri-*tert*-butylphosphine, a combination of tris(dibenzylideneacetone)dipalladium(0) or bis(dibenzylideneacetone)palladium(0) and tri-*ortho*-tolylphosphine, a combination of tris(dibenzylideneacetone)dipalladium(0) or bis(dibenzylideneacetone)palladium(0) and 1,2,3,4,5-pentaphenyl-1'-(di-*tert*-
20 butylphosphino)ferrocene, bis(tri-*tert*-butylphosphine)palladium(0) (Pd[P(t-Bu)₃]₂), a combination of tris(dibenzylideneacetone)dipalladium(0) or bis(dibenzylideneacetone)palladium(0) and bis(tri-*tert*-butylphosphine)palladium(0) (Pd[P(t-Bu)₃]₂), bis(tri-*ortho*-tolylphosphine)palladium(0) (Pd[P(o-tol)₃]₂), a combination of tris(dibenzylideneacetone)dipalladium(0) or bis(dibenzylideneacetone)palladium(0) and a 2-(dialkyl-
25 phosphino)biphenyl, where the alkyl is a bulky group, which may be selected from *tert*.butyl or cyclohexyl but not limited thereto. The most preferred catalyst is (di- μ -bromobis(tri-*tert*-butylphosphine)dipalladium(I) ([BrPdP(t-Bu)₃]₂).

The mole equivalents of the catalyst compared to compound of formula IV may be from
30 0.0001 to 0.1 mole equivalents, preferably between 0.001 to 0.05 mole equivalents.

When the ligand is tri-*tert*-butylphosphine or 1,2,3,4,5-pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene or a 2-(dialkylphosphino)biphenyl the ligand to metal ratio may be from 0.5:1 to 2:1 but preferably from 0.9:1 to 1.2:1. When the ligand is tri-*ortho*-tolylphosphine the ligand to metal ratio may be from 1:1 to 4:1 but preferably from 1.8:1 to 2.5:1.

The source of cyanide may be selected by a person skilled in the art of organic synthesis. Examples of cyanide sources so far used in cyanation are inorganic salts or organic compounds.

Inorganic salts used include sodium cyanide, potassium cyanide, zinc cyanide, lithium cyanide, copper cyanide, calcium cyanide and tetrapotassium hexacyanoferrate(II).

Examples of organic compounds that can be used as cyanide sources are acetone cyanohydrin or other cyanohydrins. The preferred cyanide source is zinc cyanide.

The mole equivalents of the cyanide ions compared to compound of formula IV may be between 1 and 3 mole equivalents, preferably between 1 and 2 mole equivalents.

The reaction may be performed in a solvent selected from the group comprising of polar aprotic solvents e.g. *N,N*-dialkylamides such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidinone and dimethylsulphoxide, ethers such as tetrahydrofuran or 1,4-dioxane, ketones such as acetone or methyl *iso*-butyl ketone, nitriles such as acetonitrile or propionitrile, or mixtures thereof. The preferred solvent is *N,N*-dimethylformamide.

The total volume of solvents used may vary between 1 to 100 (v/w) volume parts per weight of starting material. Preferably between 2 to 40 (v/w) volume parts per weight of starting material.

The reaction is performed by adding the cyanide source to a preheated mixture of the other reaction components in the reaction medium under inert conditions, which means under an atmosphere of inert gases such as nitrogen, argon or helium, preferably nitrogen, excluding air/oxygen.

5

The temperature of the reaction may be between room temperature and +150°C, preferably between +35°C and +80°C.

The additives may be selected from the group comprising of zinc-dust, acetic acid or a metal acetate such as zinc acetate, lithium acetate, sodium acetate, potassium acetate or magnesium acetate, a base such as sodium carbonate, potassium carbonate, an oxide such as calcium oxide or magnesium oxide or an amine such as *N,N'*-dimethyl ethylenediamine, triethylamine, ethylenediamine, or mixtures thereof. The reaction may be carried out without the additive also. The preferred additive is zinc-dust as such or zinc dust in combination with zinc acetate. The mole equivalent of the additive may be from 0 to 1.0 equivalents, preferably between 0 to 0.5 mole equivalents.

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The new improved cyanation reaction is more advantageous than prior known cyanation reactions since it can be performed in relatively short time under mild conditions such as low temperatures, which is particularly valuable in large scale manufacturing processes of complex and/or sensitive molecules.

20

Compound of formula (V) may be purified by a sequence where the reaction mixture is treated with a metal scavenger e.g. an extractive metal chelating agent, an organo-functionalised polysiloxane or polymer, activated carbon, or mixtures thereof. The amount of metal scavenger to compound of formula (V) may be between 10% (w/w) and 100%(w/w), preferably between 10% (w/w) to 40% (w/w). A satisfactory purity of the compound of formula (V) is in the range of 96 to 99%, preferably at least 98%.

25

The solid product is then obtained by precipitation by adding water or an aqueous solution of a metal chelating agent selected from the group comprising of ethylenediamine-tetraacetic acid, oxalic acid, citric acid or one of their metal salts e.g. sodium, potassium, calcium salts, or mixtures thereof.

5

In step 4 (process step d above and in claim 1), the salt formation, of the manufacturing process of the compound (VI), 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile citrate salt, is performed by mixing the compound (V) with citric acid in the presence of a solvent.

10

The equivalent of citric acid may vary between 1 and 3 mole equivalents, preferably between 1 to 1.5 mole equivalent.

15

The reaction of step 4 may be performed in a solvent, suitable solvents are ethers such as 1,4-dioxane, diethyl ether or alcohols such as methanol, ethanol, propanol, or ketones such as acetone, isobutylmethylketone, or acetates such as ethyl acetate, butylacetate, or organic acids such as acetic acid, or mixtures thereof, optionally using water as an additive.

20

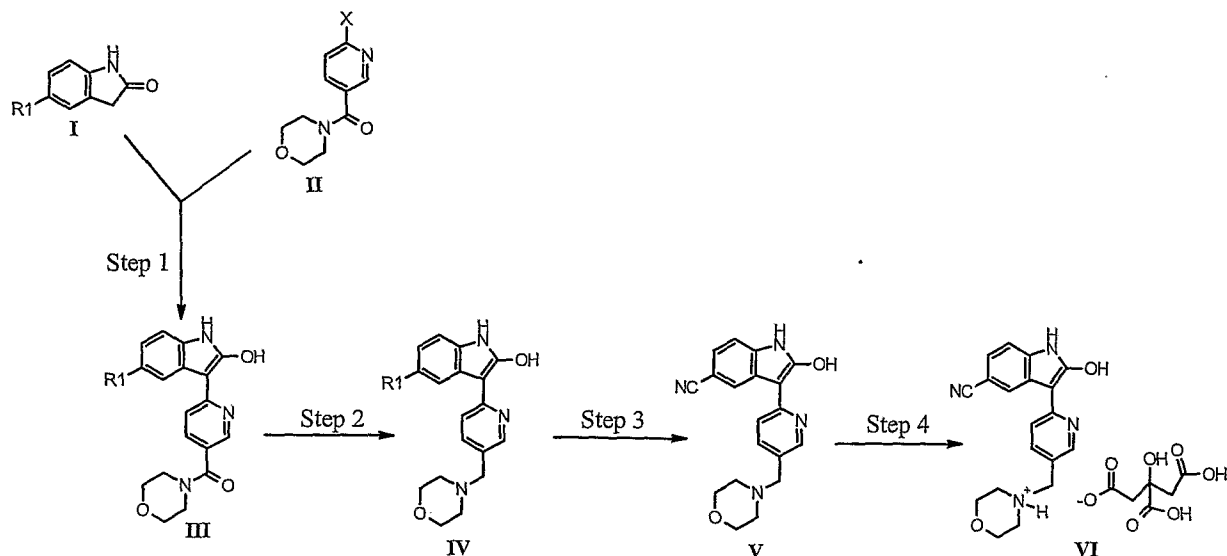
The total volume of solvents used may vary between 1 (v/w) to 100 (v/w) volume parts per weight of starting material, preferably between 10 (v/w) and 45 (v/w) volumes parts per weight of starting material.

The temperature of the reaction may be between -30 and 150°C, preferably between -5°C and 100°C.

25

Pure compound of formula (VI), 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile citrate, may be obtained by crystallising with or without an additive in suitable solvents to obtain a crystalline solid having a purity of about 95% and preferably about 98%.

The new synthetic route for the manufacture of (2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1*H*-indole-5-carbonitrile as a free base is performed as described in the three Steps 1 to 3 below, preferably wherein R1 is bromo and X is chloro.



- 5 The new synthetic route for the manufacture of (2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1*H*-indole-5-carbonitrile citrate is performed as described in the four Steps 1 to 4 above, preferably wherein R1 is bromo and X is chloro.

For the manufacture of pharmaceutically acceptable salts of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1*H*-indole-5-carbonitrile other than the citrate salt it is suitable to use Step 1 to 3 in the new synthetic route described above followed by a conventional salt formation step known by a skilled person working in the area.

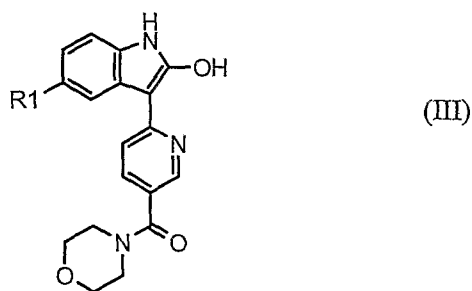
In this specification, unless otherwise stated, the term "room temperature" means a temperature between 18°C and 25°C, the term "halogen" refers to fluoro, chloro, bromo or iodo and the term "large scale" means a manufacturing scale in the range of about 10 gram to 1 ton.

The above-mentioned solvents may be used as pure solvents, or mixtures with other solvents in the steps in question.

The skilled person will appreciate that the different reaction steps need different reaction times.

5 The new large scale manufacturing process is more advantageous than the known processes with respect to commercial potential, safety, yield, and robustness. In a process of the present invention the use of potential explosive intermediates such as pyridine-N-oxides is avoided.

10 The present invention is also directed to new intermediates, namely intermediates of the compound of formula (III)



15

wherein R1 is halogen, where halogen is chloro, bromo or iodo. Especially preferred new intermediate is the compound of the formula (III) where R1 is bromo.

20

Another object of the present invention relates to the use of the compound of formula (III), wherein R1 is halogen, where halogen is chloro, bromo or iodo, preferably where the halogen is bromo, as an intermediate for the manufacturing of a pharmaceutically active compound.

25

Yet another object of the present invention relates to the use of the compound of formula (III), wherein R1 is halogen, where halogen is chloro, bromo or iodo, preferably where the halogen is bromo, as an intermediate for the manufacturing of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile and pharmaceutically acceptable salts thereof, particularly the citrate salt thereof.

30

Yet another object of the present invention is the selective reduction of the amide functional group in compounds of formula (III), wherein R1 is halogen, where halgen is chloro, bromo or iodo, preferably where the halogen is bromo, to form compounds of formula (IV) wherein R1 is halogen, where halgen is chloro, bromo or iodo, preferably
5 where the halogen is bromo.

Yet another object of the present invention is the catalytic cyanation of compounds of formula (IV), wherein R1 is halogen, where the halogen is chloro, bromo or iodo,
10 preferably where the halogen is bromo, under mild reaction conditions on a large scale manufacturing process.

Yet another object of the present invention is the development of a robust process for the catalytic cyanation of compounds of formula (IV) where the source of cyanide is added to
15 a preheated mixture of compound of formula (IV), wherein R1 is halogen, where the halogen is chloro, bromo or iodo, preferably where the halogen is bromo, the catalyst and optional additive(s) in an appropriate solvent.

Yet another object of the present invention is the catalytic cyanation of compounds of formula (IV), wherein the R1 may be halogen, where the halogen is chloro, bromo or iodo
20 for the manufacture 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1*H*-indole-5-carbonitrile and pharmaceutically acceptable salts thereof, particularly the citrate salt thereof.

25 Yet another object of the present invention is the use of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1*H*-indole-5-carbonitrile and pharmaceutically acceptable salts thereof, particularly the citrate salt thereof prepared according to a process described above under step a, b, c and optionally d for the manufacturing of a medicament for the treatment of cognitive disorders, Alzheimer's disease, dementias, chronic and acute

neurodegenerative diseases, bipolar disorders, schizophrenia, diabetes, hair loss and all the listed disorders described in WO 03/082853.

Another object of the present invention is the new use in catalytic cyanation of aryl halides of prior disclosed Pd-catalyst such as di- μ -bromobis(tri-*tert*-butylphosphine)dipalladium(I) ([BrPdP(t-Bu)₃]₂), the combination of tris(dibenzylideneacetone)dipalladium(0) or bis(dibenzylideneacetone)palladium(0) and tri-*ortho*-tolylphosphine, the combination of tris(dibenzylideneacetone)dipalladium(0) or bis(dibenzylideneacetone)palladium(0) and 1,2,3,4,5-pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene, bis(tri-*tert*-butylphosphine)-palladium(0) (Pd[P(t-Bu)₃]₂), the combination of tris(dibenzylideneacetone)dipalladium(0) or bis(dibenzylideneacetone)palladium(0) and bis(tri-*tert*-butylphosphine)palladium(0) (Pd₂(dba)₃ or Pd(dba)₂ and Pd[P(t-Bu)₃]₂), and bis(tri-*ortho*-tolylphosphine)palladium(0) (Pd[P(o-tol)₃]₂).

The present invention is described in more detail in the following non-limiting Examples.

Preparation of the compound of formula (III), where R1 is bromo.

Synthesis of [6-(5-bromo-2-hydroxyl-1H-indol-3-yl)-pyridin-3-yl]-morpholin-4-yl-methanone

Example 1

To a solution of 5-bromooxindole (40g, 188.6mmol) in *N*-methylpyrrolidinone (340mL) at room temperature was added lithium hydride (3.00g, 377.3mmol) and (6-chloro-pyridin-3-yl)-morpholin-4-yl methanone (85.5g, 377.3mmol). The resulting solution was heated to 120°C for 14 h. The reaction mixture was then cooled to an inner temperature of 50°C and divided into two portions. Portion 1: Saturated aqueous ammonium chloride (591 mL) was added over 1 h at 50°C. The resulting orange coloured slurry was stirred at 50°C for 1 h then cooled to 5°C over 3 h. The solid was filtered off, washed with water (4x80mL), methanol (2x30mL) and toluene (30mL). Vacuum drying gave 27.54g, 73% yield of [6-(5-

bromo-2-hydroxyl-1H-indol-3-yl]-pyridin-3-yl]-morpholin-4-yl-methanone having a purity of at least 90% according to HPLC. Portion 2: Aqueous ammonium chloride (400 mL, 5% w/v) was added over 1 h at 50°C. The resulting orange coloured slurry was stirred at 50°C for 1 h then cooled to 5°C over 3 h. The solid was filtered off, washed with water
5 (4x80mL), methanol (2x30mL) and toluene (30mL). Vacuum drying gave 33.6g, 88% yield of [6-(5-bromo-2-hydroxyl-1H-indol-3-yl)-pyridin-3-yl]-morpholin-4-yl-methanone (combined yield of 80%) having a purity of at least 90% according to HPLC ¹H NMR (*d6*-DMSO, 400 MHz) δ 14.9 (br s, 1 H), 10.62 (s, 1 H), 8.31 (d, J = 1.4Hz, 1 H), 7.76 (m, 2 H), 7.64 (d, J = 1.56, 1H), 7.05 (dd, J = 1.84, 8.20 Hz, 1 H), 6.84 (d, J = 8.16 Hz, 1 H), 3.6
10 (dd, J = 4.68, 8.8 Hz, 8 H), 3.31 (br m, 2 H) ppm; ¹³C NMR (*d6*-DMSO, 400MHz) δ 168.6, 148.4, 141.7, 135.8, 132.9, 126.9, 121.8, 121.6, 118.0, 117.9, 112.1, 109.9, 85.0, 66.3, 66.1, 58.4, 52.8, 40.1, 39.9, 39.7, 39.3, 39.1, 38.8 ppm; MS (ES) *m/z* [M⁺+1]⁺ 404.

Example 2

15 [6-(5-Bromo-2-hydroxyl-1H-indol-3-yl)-pyridin-3-yl]-morpholin-4-yl-methanone.
To a solution of 5-bromooxindole (4.0 kg, 18.86 mol) in *N*-methylpyrrolidinone (68L) under nitrogen was added lithium hydride (300g, 37.73 mol) and (6-chloro-pyridin-3-yl)-morpholin-4-yl methanone (8.54 kg, 37.73 mol). The resulting suspension was heated to an internal temperature of 120°C and kept there for 12 h. The reaction mixture was cooled to
20 50°C and saturated aqueous ammonium chloride solution (119L) was added over 2 h at such a rate that the internal temperature was kept in the range of 50°C. The resulting suspension was stirred for 1 h at 50°C and then cooled down to an inner temperature of 15°C over 4 h and held there for 5 h. The solid was filtered and the filter cake washed with water (3x16 L), then with cooled (5°C) methanol (2 x 6L) and washed with cooled (5°C)
25 TBME (6 L). Vacuum drying at 45°C for 24 h gave 6.387 kg, 84% yield of [6-(5-bromo-2-hydroxyl-1H-indol-3-yl)-pyridin-3-yl]-morpholin-4-yl-methanone having a purity of at least 90 %. ¹H NMR (*d6*-DMSO, 400 MHz) δ 14.85 (br s, 1 H), 10.50 (s, 1 H), 8.05 (s, 1 H), 7.75 (dd, J = 1.84, 9.08Hz, 1H), 7.65 (br d, J = 9.0, 1H), 7.58 (d, J = 1.44Hz, 1 H), 7.00 (dd, J = 1.88, 8.16 Hz, 1 H), 6.82 (d, J = 8.20Hz), 3.57 (d, J = 2.80Hz, 4 H), 3.35 (s, 2 H),
30 2.37 (s, 4H) ppm; ¹³C NMR (*d6*-DMSO, 400MHz) δ 168.6, 148.4, 141.7, 135.8, 132.9,

126.9, 121.8, 121.6, 118.0, 117.9, 112.1, 109.9, 99.5, 84.9, 79.1, 67.0, 58.4, 52.8, 40.1, 39.9, 39.7, 39.5, 39.3, 39.1, 38.8 ppm; MS (ES) m/z $[M^+ + 1]^+$ 404.

Preparation of the compound of formula (IV) where R1 is bromo.

5 Synthesis of 5-Bromo-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indol-2-ol

Example 3

5-Bromo-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indol-2-ol, large scale, quench with methanol/water

10 A suspension of [6-(5-Bromo-2-hydroxyl-1H-indol-3-yl)-pyridin-3-yl]-morpholin-4-yl-methanone (12.9 kg, 32.1 mol) in tetrahydrofuran (104 L) under nitrogen was cooled to -1°C. A solution of borane-tetrahydrofuran complex (1M, 84.7 kg, 96.9 mol) was added over 2 h keeping the internal temperature between 0 and 2°C. The mixture was stirred at 1°C for 5 h and it was then allowed to warm to room temperature over 5 h and stirred there
15 for an additional 11 h. The resulting solution was cooled to -1°C and mixed with water/methanol (5.5 L/20.9 L) within 55 min keeping the inner temperature below 2°C. After 1 h at 3°C the mixture was heated to 60°C for 3 h. The solvent (135 L) was then distilled off at 60°C and the resulting suspension was cooled to an inner temperature of 40°C before mixing with water (65 L). The resulting suspension was stirred at 40°C for 5 h
20 and then cooled to an inner temperature of 3°C over 5 h and held there for 2h. After filtration the precipitate was washed with water (2x 32.3L), isopropanol (2x32.3L) and methyl-tert-butyl ether (32.3 L). Drying gave 5.78kg (46% yield) of 5-bromo-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indol-2-ol with a purity of at least 90% by HPLC.
¹H NMR (*d6*-DMSO, 400 MHz) δ 14.85 (br s, 1 H), 10.50 (s, 1 H), 8.05 (s, 1 H), 7.75 (dd, J= 1.84, 9.08Hz, 1H), 7.65 (br d, J= 9.0, 1H), 7.58 (d, J = 1.44Hz, 1 H), 7.00 (dd, J = 1.88, 8.16 Hz, 1 H), 6.82 (d, J= 8.20Hz), 3.57 (d, J= 2.80Hz, 4 H), 3.35 (s, 2 H), 2.37 (s, 4H)
25 ppm; ¹³C NMR (*d6*-DMSO, 400MHz) δ 168.6, 148.4, 141.7, 135.8, 132.9, 126.9, 121.8, 121.6, 118.0, 117.9, 112.1, 109.9, 99.5, 84.9, 79.1, 67.0, 58.4, 52.8, 40.1, 39.9, 39.7, 39.5, 39.3, 39.1, 38.8 ppm; MS (ES) m/z $[M^+ + 1]^+$ 388.

Example 4

5-Bromo-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indol-2-ol, quenched with triethanolamine. Recrystallisation with dioxane/isooctane.

[6-(5-Bromo-2-hydroxyl-1H-indol-3-yl)-pyridin-3-yl]-morpholin-4-yl-methanone

5 (5 g, 0.012 mol) was suspended in tetrahydrofuran (40mL) and the suspension was cooled to -30°C. A solution of borane-tetrahydrofuran complex in tetrahydrofuran (1 M, 37.3mL, 0.037 mol) was then added over 15 min keeping the internal temperature below -5°C. The mixture was then allowed to warm to room temperature and stirred for an additional 15 h. The resulting solution was cooled to -15°C and a solution of triethanolamine (8.3 mL, 10 0.062 mol) in water (25 mL) was added the reaction mixture was then heated to 60°C and stirred for 15h. The resulting suspension was concentrated to 20ml then cooled to 0°C and water (30ml) added. The precipitate was filtered and washed with water (3x30 mL), isopropanol (2x25 mL). Vacuum drying gave 3.34g of 5-bromo-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indol-2-ol with a purity of at least 85%.

15 Recrystallisation: The crude precipitate (3.34g) was dissolved in dioxane (50ml) at 100 °C. To the hot solution was then added isooctane (30ml) and the suspension allowed to cool to room temperature over night. Filtration of the precipitate and washing with isooctane (15ml) and tert-butylmethyl ether (10ml) gave 2.74g, 57% yield of 5-bromo-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indol-2-ol with a purity of at least 95%. HPLC. ¹H
20 NMR (*d6*-DMSO, 400 MHz) δ 14.85 (br s, 1 H), 10.50 (s, 1 H), 8.05 (s, 1 H), 7.75 (dd, J= 1.84, 9.08Hz, 1H), 7.65 (br d, J= 9.0, 1H), 7.58 (d, J = 1.44Hz, 1 H), 7.00 (dd, J = 1.88, 8.16 Hz, 1 H), 6.82 (d, J= 8.20Hz), 3.57 (d, J= 2.80Hz, 4 H), 3.35 (s, 2 H), 2.37 (s, 4H) ppm; ¹³C NMR (*d6*-DMSO, 400MHz) δ 168.6, 148.4, 141.7135.8, 132.9, 126.8, 121.8, 121.6, 118.0, 117.9, 112.1, 109.9, , 84.9, 66.3, 66.1, 58.4, 52.8, 40.1, 39.9, 39.7, 39.3, 39.1,
25 38.8 ppm; MS (ES) *mz* [M⁺+1] 388.

Preparation of the compound of formula (V).

Synthesis of 2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile

Example 5

2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile using di- μ -bromobis(tri-*tert*-butylphosphine)dipalladium(I) with zinc dust

5-Bromo-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indol-2-ol (2.00 g, 5.151 mmol),
5 zinc-dust (40.8 mg, 0.618 mmol) and di- μ -bromobis(tri-*tert*-butylphosphine)dipalladium(I)
(50 mg, 0.064 mmol) were added to a 50 mL schlenk tube with a magnetic stir bar. The
schlenk tube was sealed with a rubber septum and then evacuated and re-filled with
nitrogen gas twice. Degassed dimethylformamide (14 mL) was then added with a syringe.
The mixture was then heated under stirring to 50°C and kept there for 4 minutes before
10 zinc cyanide (339 mg, 2.83 mmol) was charged against a positive flow of nitrogen. The
mixture was stirred at 50°C for 3 h at which point of HPLC (high performance liquid
chromatography) analysis showed 100% conversion and then cooled to room temperature
and filtered through a sintered glass filter. 3-Mercaptopropyl functionalized silica (0.3 g)
was then added to the filtrate and the mixture was stirred at 40°C over night and then
15 filtered. The filtrate was heated to 60°C and tetrasodiummethylenediamine tetra acetate (25
mL of a 0.30 M solution in water) was added over 5 minutes to give a bright yellow
precipitate. The mixture was cooled to room temperature and filtered. The precipitate was
washed with 25 mL of water and then dried under vacuum at 40°C to give 1.23 g, 71%
yield of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile. ¹H
20 NMR (*d*₆-DMSO, 400 MHz) δ 14.79 (broad s, 1H), 10.86 (broad s, 1H), 8.08 (s, 1H), 7.95
(s, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.27 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H),
3.57 (t, *J* = 4.4 Hz, 4H), 3.36 (s, 2H), 2.36 (broad s, 4H) ppm; ¹³C NMR (*d*₆-DMSO,
400MHz) δ 168.8, 148.6, 141.8, 137.0, 136.1, 125.4, 123.9, 122.3, 121.1, 118.8, 118.3,
108.7, 101.3, 84.6, 66.1, 58.4, 52.8 ppm; MS (ES) *m/z* [*M*⁺+1] 335.

25

Example 6

2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile using bis-(dibensylideneacetone)palladium(0) and tri-*tert*-butylphosphine

5-Bromo-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indol-2-ol (1.00 g, 2.57 mmol),
30 zinc-dust (25.5 mg, 0.386 mmol) and bis(dibensylideneacetone)palladium(0) (37 mg, 0.064

mmol) were added to a 10 mL schlenk tube with a magnetic stir bar. The schlenk tube was sealed with a rubber septum and then evacuated and re-filled with nitrogen gas twice. Degassed dimethylformamide (7 mL) was then added with a syringe followed by tri-*tert*-butylphosphine (65 μ L of a 20% w/v solution in toluene, 0.064 mmol). The mixture was then heated under stirring to 50°C and kept there for 4 minutes before zinc cyanide (169 mg, 1.42 mmol) was charged against a positive flow of nitrogen. The mixture was stirred at 50°C for 3 h at which point HPLC analysis showed 100% conversion and then cooled to room temperature and filtered through a sintered glass filter. 3-Mercaptopropyl functionalized silica (0.3 g) was then added to the filtrate and the mixture was stirred at 40°C over night and then filtered. The filtrate was heated to 60°C and tetrasodium-ethylenediamine tetra acetate (25 mL of a 0.30 M solution in water) was added over 5 minutes to give a bright yellow precipitate. The mixture was cooled to room temperature and filtered. The precipitate was washed with 10 mL of water and then dried under vacuum at 40°C to give 0.63 g, 73% yield of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile. Characterisation data were in accordance with example 5.

Example 7

2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile using bis(dibenzylideneacetone)palladium(0) and tri-*ortho*-tolylphosphine.

5-Bromo-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indol-2-ol (1.00 g, 2.57 mmol), zinc-dust (25.5 mg, 0.386 mmol), bis(dibenzylideneacetone)palladium(0) (74 mg, 0.128 mmol) and tri-*ortho*-tolylphosphine (79.6 mg, 0.258 mmol) were added to a 10 mL schlenk tube with a magnetic stirbar. The schlenk tube was sealed with a rubber septum and then evacuated and re-filled with nitrogen gas twice. Degassed dimethylformamide (7 mL) was then added with a syringe. The mixture was then heated under stirring to 50°C and kept there for 12 minutes before zinc cyanide (169 mg, 1.42 mmol) was charged against a positive flow of nitrogen. The mixture was stirred at 50°C for 3 h at which point of HPLC analysis showed 100% conversion and then cooled to room temperature and filtered through a sintered glass filter. 3-Mercaptopropyl functionalized silica (0.3 g) was then added to the filtrate and the mixture was stirred at 40°C over night and then filtered. The

filtrate was heated to 60°C and tetrasodiummethylenediamine tetra acetate (25 mL of a 0.30 M solution in water) was added over 5 minutes to give a bright yellow precipitate. The mixture was cooled to room temperature and filtered. The precipitate was washed with 10 mL of water and then dried under vacuum at 40°C to give 0.59g, 69% yield of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile. Characterisation data were in accordance with example 5.

Example 8

2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile using bis(dibenzylideneacetone)palladium(0) and 1,2,3,4,5-pentaphenyl-1'-(di-tert-butylphosphino)ferrocene.

5-Bromo-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indol-2-ol (0.100 g, 0.257 mmol), zinc-dust (2.0 mg, 0.031 mmol), bis(dibenzylideneacetone)palladium(0) (7.4 mg, 0.0128 mmol) and 1,2,3,4,5-pentaphenyl-1'-(di-tert-butylphosphino)ferrocene (9.2 mg, 0.0128 mmol) were added to a 10 mL schlenk tube with a magnetic stirbar. The schlenk tube was sealed with a rubber septum and then evacuated and re-filled with nitrogen gas twice. Degassed dimethylformamide (0.7 mL) was then added with a syringe. The mixture was then heated under stirring to 50°C and kept there for 5 minutes before zinc cyanide (17 mg, 0.14 mmol) was charged against a positive flow of nitrogen. The mixture was stirred at 50°C for 2 h at which point of HPLC analysis showed 100% conversion and then cooled to room temperature and filtered through a sintered glass filter. 3-Mercaptopropyl functionalized silica (0.03 g) was then added to the filtrate and the mixture was stirred at 40°C over night and then filtered. The filtrate was heated to 60°C and tetrasodium-ethylenediamine tetra acetate (1.5 mL of a 0.30 M solution in water) was added over 5 minutes to give a bright yellow precipitate. The mixture was cooled to room temperature and filtered. The precipitate was washed with 1 mL of water and then dried under vacuum at 40°C to give 0.042g, 49% yield of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile. Characterisation data were in accordance with example 5.

Example 9

2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile using bis(dibenzylideneacetone)palladium(0) and 2-(dicyclohexylphosphino)biphenyl.

5-Bromo-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indol-2-ol (0.100 g, 0.257 mmol),
5 zinc-dust (2.0 mg, 0.031 mmol), bis(dibenzylideneacetone)palladium(0) (7.4 mg, 0.0128
mmol) and 2-dicyclohexylphosphinobiphenyl (4.6 mg, 0.0128 mmol) were added to a 10
mL schlenk tube with a magnetic stirbar. The schlenk tube was sealed with a rubber
septum and then evacuated and re-filled with nitrogen gas twice. Degassed
dimethylformamide (0.7 mL) was then added with a syringe. The mixture was then heated
10 under stirring to 50°C and kept there for 5 minutes before zinc cyanide (17 mg, 0.14 mmol)
was charged against a positive flow of nitrogen. The mixture was stirred at 50°C for 2 h at
which point of HPLC analysis showed 100% conversion and then cooled to room
temperature and filtered through a sintered glass filter. 3-Mercaptopropyl functionalized
silica (0.03 g) was then added to the filtrate and the mixture was stirred at 40°C over night
15 and then filtered. The filtrate was heated to 60°C and tetrasodiummethylenediamine tetra
acetate (25 mL of a 0.30 M solution in water) was added over 5 minutes to give a bright
yellow precipitate. The mixture was cooled to room temperature and filtered. The
precipitate was washed with 10 mL of water and then dried under vacuum at 40°C to give
0.030g, 35% yield of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-
20 carbonitrile. Characterisation data were in accordance with example 5.

Example 10

2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile using bis(tri-tert-butylphosphine)palladium(0)

25 5-Bromo-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indol-2-ol (0.100 g, 0.257 mmol),
zinc-dust (2.0 mg, 0.031 mmol,) and bis(tri-tert-butylphosphine)palladium(0) (6.7 mg,
0.013 mmol) were added to a 10 mL schlenk tube with a magnetic stirbar. The schlenk
tube was sealed with a rubber septum and then evacuated and re-filled with nitrogen gas
twice. Degassed dimethylformamide (0.7 mL) was then added with a syringe. The mixture
30 was then heated under stirring to 50°C and kept there for 5 minutes before zinc cyanide (17

mg, 0.14 mmol) was charged against a positive flow of nitrogen. The mixture was stirred at 50°C for 2 h at which point of HPLC analysis showed 100% conversion and then cooled to room temperature and filtered through a sintered glass filter. 3-Mercaptopropyl functionalized silica (0.03 g) was then added to the filtrate and the mixture was stirred at 40°C over night and then filtered. The filtrate was heated to 60°C and tetrasodium-ethylenediamine tetra acetate (1.5 mL of a 0.30 M solution in water) was added over 5 minutes to give a bright yellow precipitate. The mixture was cooled to room temperature and filtered. The precipitate was washed with 10 mL of water and then dried under vacuum at 40°C to give 0.035g, 41% yield of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile. Characterisation data were in accordance with example 5.

Example 11

2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile using a combination of bis(dibenzylideneacetone)palladium(0) and bis(tri-*tert*-butylphosphine)palladium(0)

5-Bromo-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indol-2-ol (0.100 g, 0.257 mmol), zinc-dust (2.0 mg, 0.031 mmol), bis(dibenzylideneacetone)palladium(0) (7.4 mg, 0.013 mmol) and bis(tri-*tert*-butylphosphine)palladium(0) (6.7 mg, 0.013 mmol) were added to a 10 mL schlenk tube with a magnetic stirbar. The schlenk tube was sealed with a rubber septum and then evacuated and re-filled with nitrogen gas twice. Degassed dimethylformamide (0.7 mL) was then added with a syringe. The mixture was then heated under stirring to 50°C and kept there for 5 minutes before zinc cyanide (17 mg, 0.14 mmol) was charged against a positive flow of nitrogen. The mixture was stirred at 50°C for 2 h at which point of HPLC analysis showed 100% conversion and then cooled to room temperature and filtered through a sintered glass filter. 3-Mercaptopropyl functionalized silica (0.03 g) was then added to the filtrate and the mixture was stirred at 40°C over night and then filtered. The filtrate was heated to 60°C and tetrasodiummethylenediamine tetra acetate (1.5 mL of a 0.30 M solution in water) was added over 5 minutes to give a bright yellow precipitate. The mixture was cooled to room temperature and filtered. The precipitate was washed with 10 mL of water and then dried under vacuum at 40°C to give

0.030g, 35% yield of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile. Characterisation data were in accordance with example 5.

Example 12

5 2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile using bis(tri-tert-butylphosphine)palladium(0), addition of zinc cyanide from the beginning
5-Bromo-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indol-2-ol (0.192 g, 0.505 mmol), zinc-dust (6 mg, 0.09 mmol), zinc cyanide (32 mg, 0.53 mmol) and bis(tri-tert-butylphosphine)palladium(0) (6.4 mg, 0.013 mmol) were added to a 10 mL schlenk tube
10 with a magnetic stirbar. The schlenk tube was sealed with a rubber septum and then evacuated and re-filled with nitrogen gas twice. Degassed dimethylformamide (1.5 mL) was then added with a syringe. The mixture was then stirred at 55°C for 1 h at which point HPLC analysis showed only starting material and no product.

15

Example 13

2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile, large scale
5-Bromo-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indol-2-ol (6.673 kg) and zinc-dust (0.134 kg) was mixed with dimethylformamide (80 L) and the slurry stirred at room
20 temperature. The mixture was purged with nitrogen until the oxygen level was below 0.02 mg/L. Di- μ -bromobis(tri-tert-butylphosphine)dipalladium(I) (0.168 kg) was added to the slurry and the vessel was made inert by evacuation and refilling with nitrogen. The mixture was heated to 40°C and zinc cyanide (1.109 kg) was added to the suspension in one portion and the system was made inert again. The resulting mixture was heated to an inner
25 temperature of 50°C and stirred for 3 h. HPLC indicated full conversion at this point. The reaction mixture was filtered at an inner temperature of 50°C and the filter cake was washed with dimethylformamide (3 L), mercaptopropyl functionalised silica (1.458 kg, 25%w/w) was added to the filtrate and the mixture was stirred for 82 h at an inner temperature of 50°C. The scavenger was filtered off and the filtrate was concentrated in
30 vacuo. After 62 L (~ 60%) of the dimethylformamide had been removed, aqueous

ethylenediamine tetraacetic acid tetrasodium salt solution (0.3 M, 142 L) was added at an inner temperature of 40°C and the resulting mixture was stirred for 1 h keeping the inner temperature at 40°C. The mixture was cooled to 1°C over 5 h and the product was filtered off. Drying under vacuum at 50°C gave 5.2 kg, 90% yield of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile with a purity of a least 90% by HPLC. MS (ES) m/z [$M^+ + 1$] 335.

Preparation of the compound of formula (VI).

Synthesis of 2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile citrate

Example 14

2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile citrate salt

2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile (5.14 kg, 15.4 mol) was suspended in ethanol (54 L) at room temperature. The suspension was heated to an inner temperature of 70°C and a solution of citric acid (3.424 kg, 17.82 mol, 1.300 eq) in water (103 L) was added keeping the inner temperature above 65°C. The mixture was heated to reflux. After this the resulting solution was mixed with activated charcoal (0.412 kg) and reflux continued for 3.5 h after which the reaction mixture was clear filtered at 83°C followed by cooling to room temperature over 20 h. After filtration the precipitate was washed twice with a cold mixture of ethanol/water (6.9 L/13.7 L).

Drying under vacuum at 50°C gave 6.648 kg, 82.2% yield of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile citrate having a purity of at least 98%.

The palladium content was less than 1 ppm and the zinc content was lower than 10 ppm.

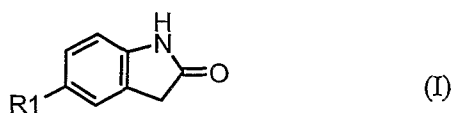
^1H NMR (d_6 -DMSO, 400 MHz) δ 14.7 (br s, 1 H), 11.55 (s, 1 H), 10.98 (s, 1H), 8.31 (s, 1 H), 8.08 (br d, $J = 1.84\text{Hz}$, 1H), 8.02 (s, 1H), 7.90 (br d, $J = 8.92\text{Hz}$, 1 H), 7.31 (d, $J = 8.0\text{Hz}$, 1 H), 7.02 (d, $J = 8.0\text{Hz}$), 4.28 (s, 2 H), 3.97 (m, 2 H), 3.94 (m, 2H), 3.35 (m, 9H), 3.32 (m, 2H) ppm; ^{13}C NMR (d_6 -DMSO, 400MHz) δ 168.9, 148.5, 142.7, 139.8, 137.5, 126.4, 124.9, 124.8, 120.9, 119.4, 118.4, 113.3, 109.0, 101.6, 85.7, 63.1, 55.5, 50.3, 40.1, 39.9, 39.7, 39.2, 39.0, 38.8 ppm; MS (ES) m/z [$M^+ + 1$] 335.

CLAIMS

1. A process for the preparation of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile as a free base and pharmaceutically acceptable salts thereof, by

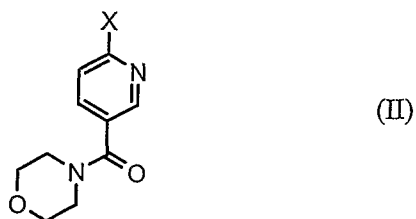
5

a) reacting a compound of formula (I) wherein R1 is halogen, where the halogen is chloro, bromo or iodo



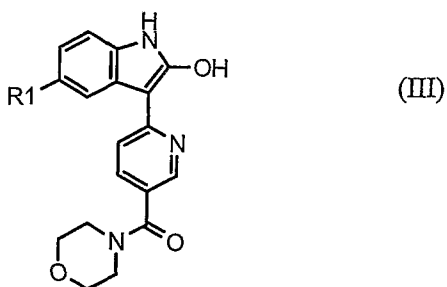
with a compound of formula (II) wherein X is halogen, where the halogen is chloro, bromo or iodo

10



in the presence of a base and a solvent to obtain a compound of formula (III) wherein R1 is halogen, where the halogen is chloro, bromo or iodo

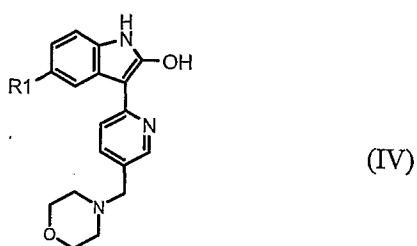
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followed by,

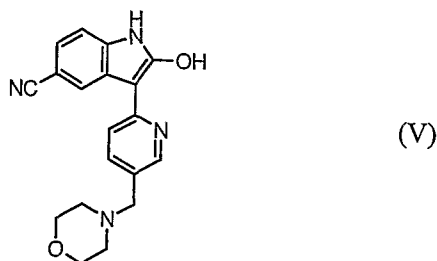
b) i) selective reduction of the compound of formula (III) with a reducing agent in the presence of a solvent, and

ii) decomplexation to form of compounds of formula (IV) wherein R1 is halogen, where
5 halogen is chloro, bromo or iodo



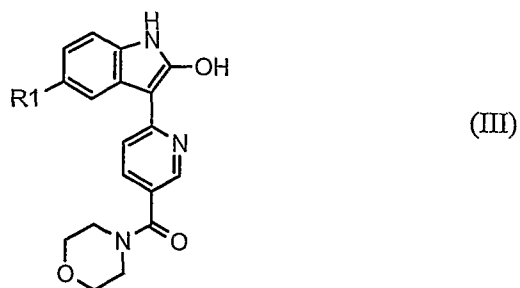
followed by

c) cyanation of the compound of formula (IV) with a cyanide source, a metal catalyst and
10 optionally with an additive, in the presence of a solvent to obtain a compound of formula (V), 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile, which either is isolated, or followed by

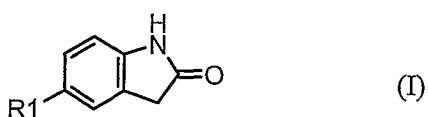


d) treating the compound of formula (V) with a suitable acid in the presence of a solvent to
15 obtain the corresponding pharmaceutically acceptable salt.

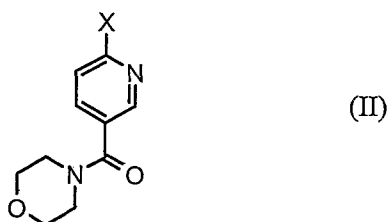
2. A process for the preparation of compound of formula (III) wherein R1 is halogen, where the halogen is chloro, bromo or iodo



by reacting compound of formula (I) wherein R1 is halogen, where the halogen is chloro,
 5 bromo or iodo



with a compound of formula (II) wherein X is halogen, where the halogen is chloro, bromo
 10 or iodo



in the presence of a base and a solvent.

15 3. A process according to any one of claims 1 to 2 wherein R1 is bromo.

4. A process according to any one of claims 1 to 2 wherein X is chloro.

5. A process according to any one of claims 1 to 4 wherein the base is selected from the group comprising organic amine bases, alkali metal salts, alkali metal hydrides or alkali metal amides.

5

6. A process according to claim 5 wherein the base is lithium hydride.

7. A process according to any one of claims 1 to 6 wherein the solvent is selected from the group comprising ethers, polar aprotic solvents, dimethylsulfoxide, or mixtures thereof.

10

8. A process according to claim 7 wherein the solvent is a polar aprotic solvent.

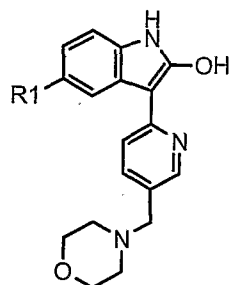
9. A process according to claim 8 wherein the solvent is N-methyl-2-pyrrolidinone.

15 10. A process according to any one of claims 1 to 9 wherein the temperature range of the reaction is between -100°C and $+180^{\circ}\text{C}$.

11 A process according to claim 10 wherein the temperature range is between room temperature and $+140^{\circ}\text{C}$.

20

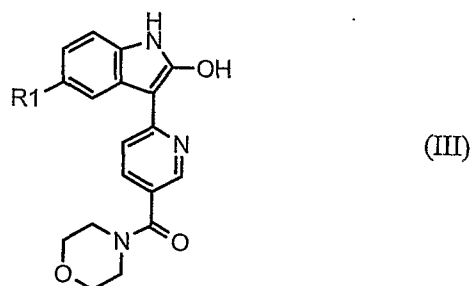
12. A process for the preparation of compound of formula (IV) wherein R1 is halogen, where the halogen is chloro, bromo or iodo



(IV)

by

i) selective reduction of compound of formula (III) wherein R1 is halogen, where the halogen is chloro, bromo or iodo



(III)

5 with a reducing agent in the presence of a solvent, followed by
ii) decomplexation.

13. A process according to any one of claims 1bi) and 12 wherein the reducing agent is selected from the group comprising of boranes.

10

14. A process according to claim 13 wherein the borane is borane dimethylsulphide complex.

15. A process according to claim 13 wherein the borane is borane tetrahydrofuran
5 complex,

16. A process according to any one of claims 1bi) and 12 to 15 wherein the solvent is a polar aprotic solvent.

0 17. A process according to claim 16 wherein the solvent is tetrahydrofuran.

18. A process according to any one of claims 1bi) and 12 to 17 wherein the temperature range of the reaction is between -10°C and $+40^{\circ}\text{C}$.

19. A process according to any one of claims 1bii) and 12 wherein the decomplexation reaction is performed by quenching with an inorganic acid, an organic acid, a protic solvent or water, or mixtures thereof.

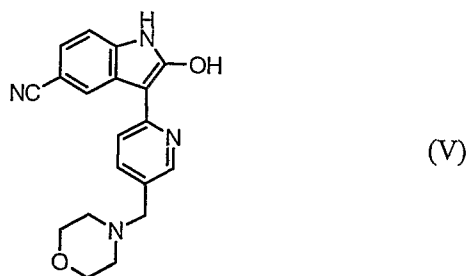
5 20. A process according to claim 19 wherein the quench agent is water and/or methanol.

21. A process according to any one of claims 19 to 20 wherein the temperatures range of the reaction is between room temperature and +80°C.

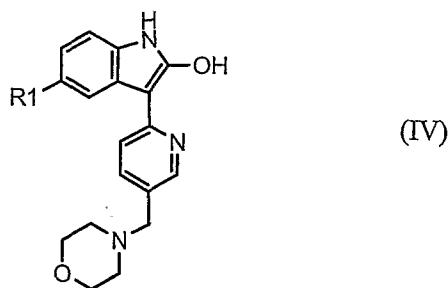
10 22. A process according to any one of claims 1b)ii) and 19 to 21 wherein the base used for free basing is selected from the group comprising an inorganic or organic base optionally in combination with water and/or a protic solvent.

15 23. A process according to any one of claims 1b) and 12 to 22 wherein R1 is halogen, where the halogen is bromo.

24. A process for the preparation of 2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile of formula (V)



20 by cyanation of a compound of formula (IV) wherein R1 is a halogen, where halogen is chloro, bromo or iodo



with a cyanide source, a metal catalyst and optionally with additives in the presence of a solvent.

5

25. A process according to claim 24 wherein the cyanide source is zinc cyanide.

26. A process according any one of claims 1c) and 24 wherein the metal catalyst is selected a metal or a combination of a metal and a ligand.

10

27. A process according to claim 26 wherein the metal is palladium.

28. A process according to claim 27 wherein the ligand is tri-*tert*-butylphosphine, tri-*ortho*-tolylphosphine or 1,2,3,4,5-pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene.

15

29. A process according to any one of claims 1c) and 24 to 28 wherein the source of palladium is a complex between palladium and dibenzylideneacetone.

20

30. A process according to any one of claims 1c) and 24 to 29 wherein the metal catalyst is selected from the group comprising of di- μ -bromobis(tri-*tert*-butylphosphine)dipalladium(I), a combination of tris(dibenzylideneacetone)dipalladium(0) or bis(dibenzylideneacetone)palladium(0) and tri-*tert*-butylphosphine, a combination of tris(dibenzylideneacetone)dipalladium(0) or bis(dibenzylideneacetone)palladium(0) and tri-*ortho*-tolylphosphine, a combination of tris(dibenzylideneacetone)dipalladium(0) or

bis(dibenzylideneacetone)palladium(0) and 1,2,3,4,5-pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene, bis(tri-*tert*-butylphosphine)palladium(0), a combination of tris(dibenzylideneacetone)dipalladium(0) or bis(dibenzylideneacetone)palladium(0) and bis(tri-*tert*-butylphosphine)palladium(0).

5

31. A process according to 30 wherein the catalyst is (di- μ -bromobis(tri-*tert*-butylphosphine) dipalladium(I).

32. A process according any one of claims 1c) and 26 to 31 wherein the ligand to metal ratio is from 0.5:1 to 2:1 for reaction using the ligands tri-*tert*-butylphosphine or 1,2,3,4,5-pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene.

10

33. A process according to claim 32 wherein the ligand to metal ratio is from 0.9:1 to 1.2:1.

15

34. A process according any one of claims 1c) and 26 to 30 wherein the ligand to metal ratio is from 1:1 to 4:1 for reactions using tri-*ortho*-tolylphosphine as ligand.

20

35. A process according to claim 34 wherein the metal to ligand ratio is from 1.8:1 to 2.5:1.

36. A process according to any one of claims 1c) and 24 to 35 wherein the additive is zinc-dust.

25

37. A process according to any one of claims 1c) and 24 claim 36 wherein the solvent is selected from *N,N*-dimethylformamide, *N*-methylpyrrolidinone and *N,N*-dimethylacetamide.

38. A process according to claim 37 wherein the solvent is *N,N*-dimethylformamide.

30

39. A process according to claims 1c) and 24 to 38 where the source of cyanide is added to a preheated mixture of the other reaction components in the appropriate solvent under inert conditions.

5 40. A process according to any one of claims 1c) and 24 to 39 wherein the temperature range for the reaction is between room temperature and +150°C.

41. A process according to claim 40 wherein the temperatures range for the reaction is between +35°C and +80°C.

10

42. A process according to any one of claims 1c) and 24 to 41 wherein compound (V) is isolated by addition of water or an aqueous solution of a metal chelating compound such as ethylenediamine-tetraacetic acid, oxalic acid, citric acid or one of their metal salts.

15 43. A process according to claim 1d) for the preparation of a 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile pharmaceutically acceptable salt by reacting
2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile with a suitable acid in a solvent.

20

44. A process according to claim 1d) for the preparation of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile citrate by reacting
2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile with citric acid in a solvent.

25

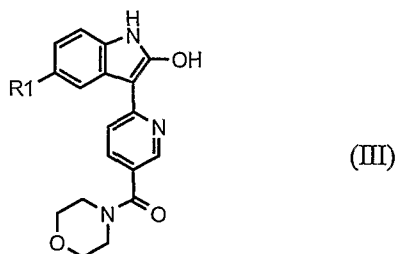
45. A process according to claim 44 wherein the solvent is selected from a group comprising ethers, alcohols, ketones, acetates or organic acids, or mixture thereof, optionally using water as an additive.

46. A process according to claim 45 wherein the solvent is a mixture of ethanol and water or acetic acid.

47. A process according to any one of claims 43 to 46 wherein the temperatures range is
5 between
-5°C and +100°C.

48. A process according to any one of claims 1c) and 24 to 47 wherein R1 is halogen, where the halogen is bromo.

10 49. A compound of formula (III) wherein R1 is halogen, where the halogen is chloro, bromo or iodo



15 50. A compound according to claim 49 wherein R1 is bromo.

51. Use of the compound of formula (III) according to any one of claims 49 to 51 as an
20 intermediate for the manufacturing of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile and pharmaceutically acceptable salts thereof.

52. The use of the compound of formula (III) according to claim 51 as an intermediate for
25 the manufacturing of a 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile citrate salt.

53. The use of 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]1H-indole-5-carbonitrile citrate prepared according to a process defined in any one of claims 1 to 52 for the manufacturing of a medicament for the treatment of cognitive disorders, Alzheimer disease, dementias, chronic and acute neurodegenerative diseases, bipolar disorders, schizophrenia, diabetes, hair loss.

54. Use of compounds which are di- μ -bromobis(tri-*tert*-butylphosphine)dipalladium(I) ($[\text{BrPdP}(\text{t-Bu})_3]_2$), the combination of tris(dibenzylideneacetone)dipalladium(0) or bis(dibenzylideneacetone)palladium(0) and tri-*ortho*-tolylphosphine, the combination of tris(dibenzylideneacetone)dipalladium(0) or bis(dibenzylideneacetone)palladium(0) and 1,2,3,4,5-pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene, bis(tri-*tert*-butylphosphine)palladium(0), the combination of tris(dibenzylideneacetone)dipalladium(0) or bis(dibenzylideneacetone)palladium(0) and bis(tri-*tert*-butylphosphine)palladium (0) as catalysts in cyanation of aryl halidees.

55. Use of a compound according to claim 54 which is di- μ -bromobis(tri-*tert*-butylphosphine)-dipalladium(I).

56. Use of a compound according to claim 54 which is the combination of tris(dibenzylideneacetone)dipalladium(0) or bis-dibenzylideneacetone palladium(0) and 1,2,3,4,5-pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene.

57. Use of a compound according to claim 54 which is the combination of combination of tris(dibenzylideneacetone)dipalladium(0) or bis-dibenzylideneacetone palladium(0) and tri-*ortho*-tolylphosphine.

58. Use of a compound according to claim 54 which is the combination of tris(dibenzylideneacetone)-dipalladium(0) or bis-(dibenzylideneacetone)palladium(0) and bis-tri-*tert*-butylphosphine-palladium.

59. Use of compounds as described in any one of claims 54 to 58 as catalysts in cyanation of aryl halides where the source of cyanide is added to a preheated mixture of the other reaction components in the appropriate solvent under inert conditions.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2007/000088

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

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)

IPC: C07D, A61K, A61P

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

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03082853 A1 (ASTRAZENECA AB), 9 October 2003 (09.10.2003)	2-11,43-53
A	---	1
X	EP 1554266 B1 (CLARIANT LIFE SCIENCE MOLECULES (ITALIA) S.P.A.), 20 July 2005 (20.07.2005)	12-23
X	WO 0026187 A1 (SYNTHON B.V.), 11 May 2000 (11.05.2000)	12-23
A	US 20040215020 A1 (FOGUET, RAFAEL), 28 October 2004 (28.10.2004)	12-23

 Further documents are listed in the continuation of Box C. See patent family annex.

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Date of the actual completion of the international search

25 May 2007

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2007/000088

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 1012618 A (STERLING DRUG INC.), 8 December 1965 (08.12.1965)	12-23
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X	MALIGRES, PETER E. et al, "A highly catalytic robust palladium catalyzed cyanation of aryl bromides", Tetrahedron Letters, 1999, vol. 40, page 8193 - page 8195	24-42,54-59
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X	DE 10113976 A1 (DEGUSSA AG), 26 Sept 2002 (26.09.2002)	24-42,54-59
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X	EP 0771786 A1 (ELI LILLY AND COMPANY), 7 May 1997 (07.05.1997)	24-42,54-59
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X	WO 0211883 A1 (YALE UNIVERSITY), 14 February 2002 (14.02.2002)	24-42,54-59
	--	

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