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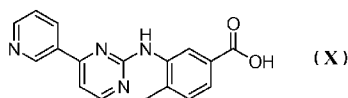
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(54) Title: PREPARATION OF NILOTINIB AND INTERMEDIATES THEREOF



(57) Abstract: N-(3-Bromo-5-trifluoromethylphenyl)-4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide is an intermediate of Nilotinib. Processes for preparing this intermediate from a compound of formula (X) is described.



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PREPARATION OF NILOTINIB AND INTERMEDIATES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

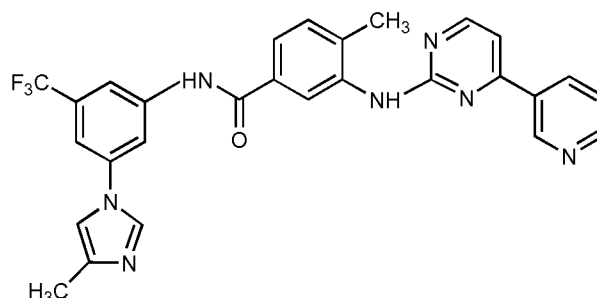
[0001] This application claims the benefit of U.S. Provisional Patent Application Serial. Nos. 61/117,478, filed November 24, 2008; 61/161,670, filed March 19, 2009; 61/171,706, filed April 22, 2009; 61/168,822, filed April 13, 2009; and PCT/US2009/051001, filed July 17, 2009, which are incorporated herein by reference.

FIELD OF INVENTION

[0002] The present invention is directed to preparation of Nilotinib and intermediates thereof.

BACKGROUND OF THE INVENTION

[0003] Nilotinib, 4-methyl-N-[3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-benzamide, having the following formula

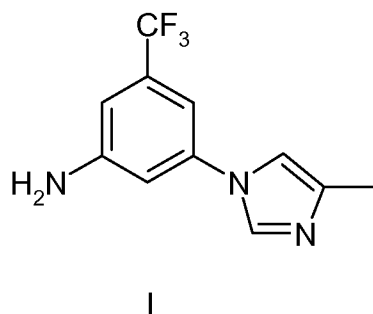


is a tyrosine kinase inhibitor used for the treatment of drug-resistant chronic myelogenous leukemia (CML), and in particular, for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myeloid leukemia (CML) in adult patients whose disease has progressed on or who cannot tolerate other therapies that included imatinib.

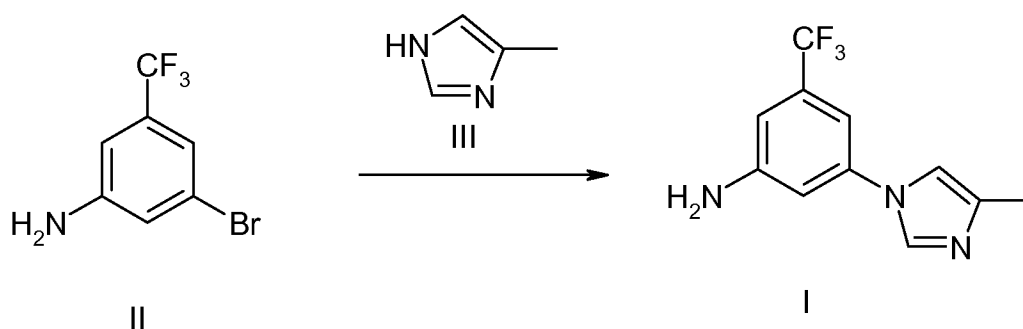
[0004] Nilotinib is administered as a hydrochloride salt in forms of capsules that are marketed in the USA and the EU under the name Tasigna®.

[0005] US patent no. 7,169,791 ("US '791") and its parallel PCT publication WO 2004/005281, the journal article in Synthesis, 2007, vol 14, pp 2121-2124, as well as PCT publication nos.: WO 2006/135640, WO 2006/135641 ("WO '641"), WO 2007/018325

and WO 2007/017734, report processes for preparing Nilotinib intermediate, 3-(trifluoromethyl)-5-(4-methyl-1H-imidazole-1-yl)-benzeneamine of formula I

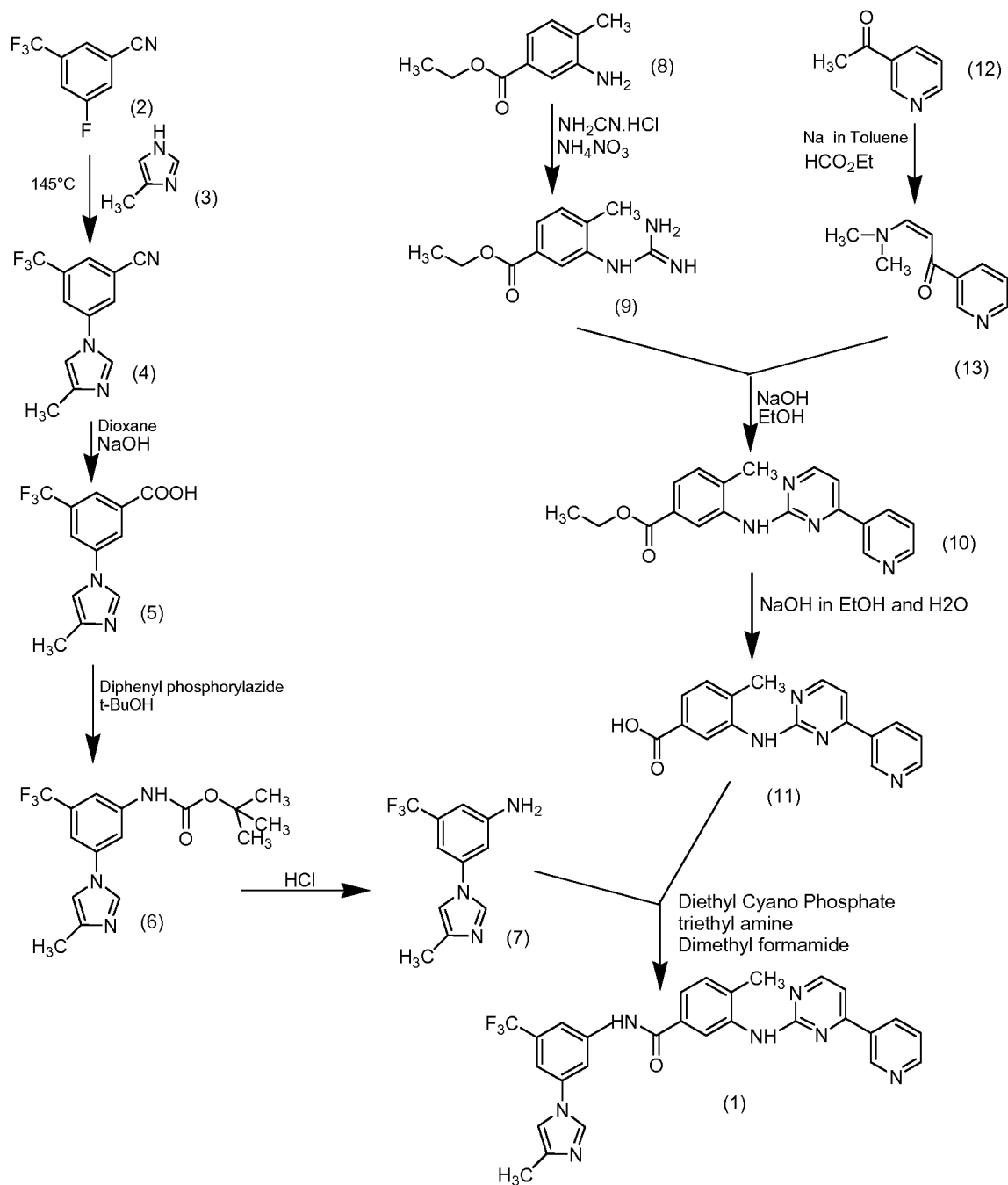


by reacting 3-bromo-5-trifluoromethylaniline of formula II and 4-methylimidazole of formula III in the presence of a non-alkaline hydroxide inorganic base, such as potassium carbonate, cesium carbonate and sodium hydride, a copper (I) salt, such as copper iodide and a complexing amine ligand, such as ethylene diamine. The process can be illustrated by the following scheme:



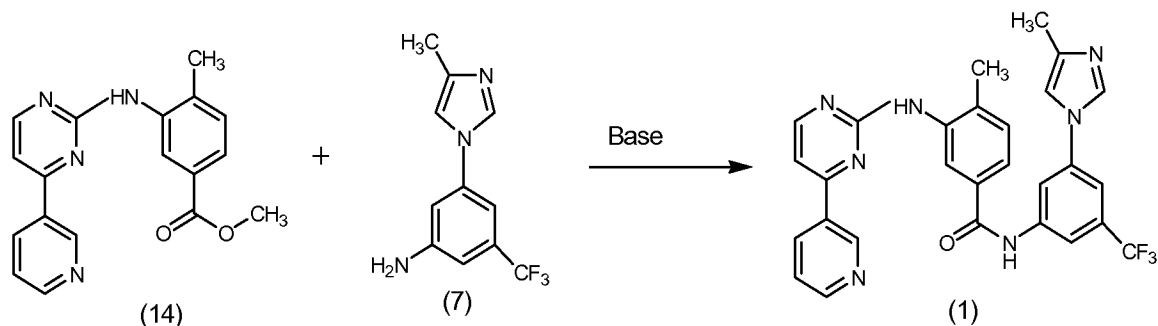
Scheme 1

[0006] US '791 describes processes for preparing Nilotinib and its different intermediates, using di-ethyl cyano phosphate, as described in the following scheme:



Scheme 2

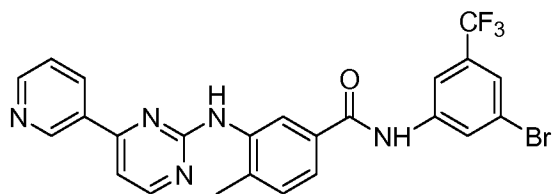
[0007] WO '641 further describes a process for preparing Nilotinib according to the following scheme:

**Scheme 3**

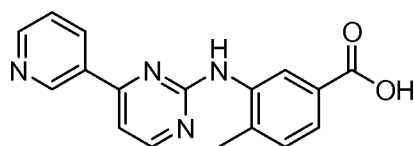
[0008] There is a need in the art for improved processes for preparing Nilotinib and its intermediates. The present invention provides improved processes for preparing Nilotinib and its intermediate, N-(3-Bromo-5-trifluoromethylphenyl)-4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide.

SUMMARY OF THE INVENTION

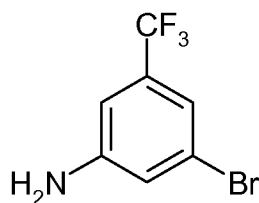
[0009] In one embodiment, the present invention provides a process for preparing N-(3-Bromo-5-trifluoromethylphenyl)-4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide, a Nilotinib intermediate of formula IV, having the following structure:

**IV**

comprising: combining a compound of formula X having the following structure:

**X**

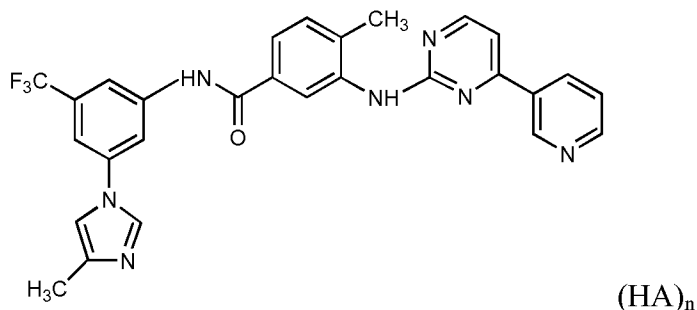
with a solvent selected from the group consisting of: an aromatic hydrocarbon, a C₄-C₆ cyclic or aliphatic ether, a chlorinated solvent, DMA, DMF, DMSO and N-methyl-pyrrolidone ("NMP"); a compound selected from the group consisting of: thionyl chloride ("SOCl₂"), thionyl bromide, oxalyl chloride, oxalyl bromide, phosphorous trichloride, phosphorous tribromide, phosphorous pentachloride, phosphorous pentabromide, C₁-C₅ carboxylic acid and activated reagent such as C₁-C₈ chloroformate and weinreb amide; and a compound of formula II having the following structure:



II

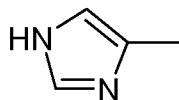
and heating the combination to obtain the compound of formula IV.

[0010] In another embodiment, the present invention provides processes for preparing Nilotinib or a salt thereof of the following formula



wherein, n is either 0 or 1, and HA is an acid, preferably, HCl, from a Nilotinib intermediate of formula IV prepared according to the above process.

[0011] In yet another embodiment, the present invention provides a process for preparing Nilotinib comprising: combining compound of formula IV, a solvent selected from the group consisting of: NMP, DMSO and DMF, an iodine salt selected from the group consisting of CuI, NaI, KI and combination thereof, and N,N-dimethyl ethylene diamine to obtain a reaction mixture; heating the reaction mixture; adding 8-hydroxyquinoline, an iodine salt selected from the group consisting of CuI, NaI, KI and combination thereof, a compound of formula III, having the following structure:



III

and a base selected from the group consisting of: DMAP, DBU, K₂CO₃, Cs₂CO₃, Na₂CO₃, KHCO₃, and NaHCO₃; and heating to obtain Nilotinib.

DETAILED DESCRIPTION OF THE INVENTION

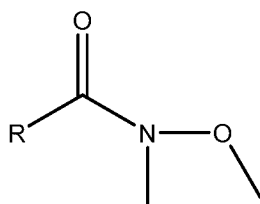
[0012] As used herein, the term "room temperature" refers to a temperature of about 15°C to about 30°C, more preferably, to a temperature of about 20°C to about 25°C.

[0013] As used herein, the term "reduced pressure" refers to a pressure of about 10 mbar to about 50 mbar.

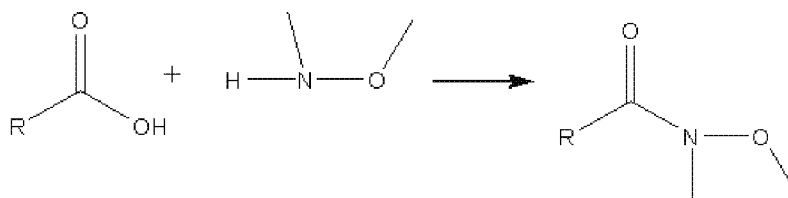
[0014] As used herein, the term "aromatic hydrocarbon" refers to a compound containing a six-carbon ring containing three double bonds that is normally liquid at about 25°C. Toluene is a preferred aromatic hydrocarbon solvent of the present invention. Other aromatic hydrocarbons useful in the practice of the present invention include benzene and the xylenes.

[0015] As used herein, the term "chlorinated solvent" refers to C₁-C₆ chlorinated hydrocarbon. Preferred chlorinated solvents are selected from the group consisting of: carbon tetrachloride, dichloromethane (CH₂Cl₂), dichloroethane, chlorobenzene and chloroform.

[0016] As used herein, the term "weinreb amide" has the same meaning as the term is used by those of ordinary skill in the art, and refers to a compound having the following structure:

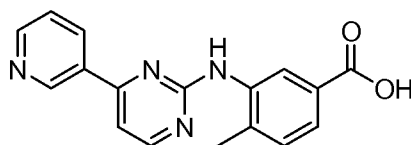


Typically, a weinreb amide is formed using *N,O*-Dimethylhydroxylamine in amide coupling reactions, according to the following scheme:

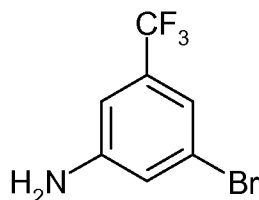


[0017] As used herein, the term "quantitative yield" refers to yield of about 90% to about 100%, preferably, to yield of about 95% to about 100%.

[0018] The present invention provides a process for preparing the Nilotinib intermediate of formula IV comprising: combining a compound of formula X having the following structure:

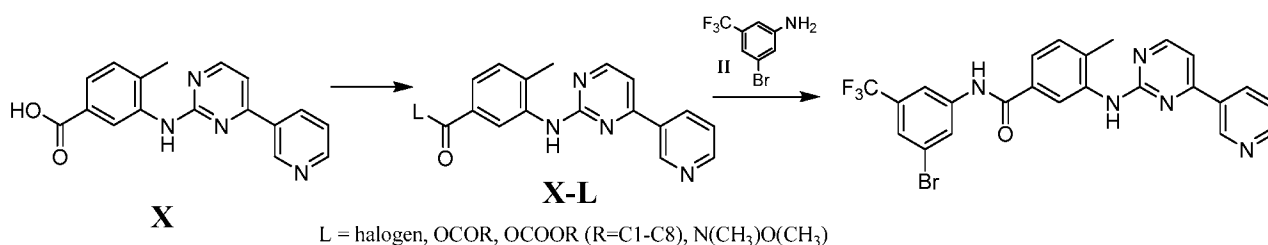
**X**

with a solvent selected from the group consisting of: an aromatic hydrocarbon, a C₄-C₆ cyclic or aliphatic ether, a chlorinated solvent, dimethylacetamide ("DMA"), dimethyl formamide ("DMF"), dimethylsulfoxide ("DMSO") and N-methyl-pyrrolidone ("NMP"); a compound selected from the group consisting of: thionyl chloride ("SOCl₂"), thionyl bromide, oxalyl chloride, oxalyl bromide, phosphorous trichloride, phosphorous tribromide, phosphorous pentachloride, phosphorous pentabromide, C₁-C₅ carboxylic acid and activated reagent such as C₁-C₈ chloroformate or weinreb amide; and a compound of formula II having the following structure:

**II**

and heating the combination to obtain the compound of formula IV.

[0019] The process can be illustrated, for example, by the following scheme:

**Scheme 4**

[0020] Typically, the process is done in the absence of a base.

[0021] Preferably, the aromatic hydrocarbon is toluene.

[0022] Preferably, the C₄-C₆ cyclic or aliphatic ether is selected from the group consisting of: tetrahydrofuran ("THF"), methyl tert-butyl ether ("MTBE") and methyl-THF, more preferably, the C₄-C₆ cyclic ether is THF.

[0023] Preferably, the chlorinated solvent is selected from the group consisting of: dichloromethane, dichloroethane, chlorobenzene and chloroform, more preferably, the chlorinated solvent is dichloromethane.

[0024] Preferably, the solvent is NMP.

[0025] Preferably, the compound selected from the group consisting of: thionyl chloride ("SOCl₂"), thionyl bromide, oxalyl chloride, oxalyl bromide, phosphorous trichloride, phosphorous tribromide, phosphorous pentachloride, phosphorous pentabromide C₁-C₅ carboxylic acid and activated reagent such as C₁-C₈ chloroformate or weinreb amide, is SOCl₂.

[0026] Preferably, the compound selected from the group consisting of: thionyl chloride ("SOCl₂"), thionyl bromide, oxalyl chloride, oxalyl bromide, phosphorous trichloride, phosphorous tribromide, phosphorous pentachloride, phosphorous pentabromide, C₁-C₅ carboxylic acid and activated reagent such as C₁-C₈ chloroformate or weinreb amide is added dropwise.

[0027] Preferably, the process for preparing the Nilotinib intermediate of formula IV comprises: combining a compound of formula X with a solvent selected from the group consisting of: an aromatic hydrocarbon, a C₄-C₆ cyclic or aliphatic ether, a chlorinated solvent, DMA, DMF, DMSO and NMP; adding a compound selected from the group consisting of: SOCl₂, thionyl bromide, oxalyl chloride, oxalyl bromide, phosphorous trichloride, phosphorous tribromide, phosphorous pentachloride, phosphorous pentabromide, C₁-C₅ carboxylic acid and activated reagent such as C₁-C₈ chloroformate or weinreb amide; adding a compound of formula II; and heating to obtain the compound of formula IV.

[0028] Preferably, prior to the addition of the compound of formula II, a heating step is performed. Preferably, the heating is to a temperature of about 55°C to about 65°C, more preferably, to about 60°C. Typically, the heating is done while stirring. The stirring may be done for about 1 hour to about 3 hours. Preferably, the stirring is done for about 2.5 hours.

[0029] Preferably, the heating is done at a temperature of about 60°C to about 120°C, more preferably, at about 90°C. Preferably, the heating is done for about 2 hours to about 16 hours, more preferably, for about 3 hours.

[0030] Preferably, the compound of formula IV is obtained in a quantitative yield.

[0031] The obtained compound of formula IV may be further recovered. The recovery can be done, for example by adding water; heating; adding a base selected from the group consisting of inorganic bases, organic C₂-C₅ secondary and tertiary amines, pyridine, 4-dimethylaminopyridine ("DMAP"), 2,3,4,6,7,8,9,10-Octahydropyrimidol[1,2-

a]azepine ("DBU") and (1,4-diazabicyclo(2.2.2)octane) ("DABCO"); cooling; filtering; washing; and drying.

[0032] Preferably, the heating is done to a temperature of about 60°C to about 120°C, more preferably, to about 80°C. Preferably, the base is inorganic base selected from the group consisting of: alkali metal hydroxide, alkali metal hydride, alkali metal carbonate, alkali metal bicarbonate and alkali metal alkoxide, more preferably, the base is selected from the group consisting of NaOH, KOH, LiOH, K₂CO₃, Na₂CO₃, NaHCO₃, NaH and Cs₂CO₃, most preferably the base is NaOH.

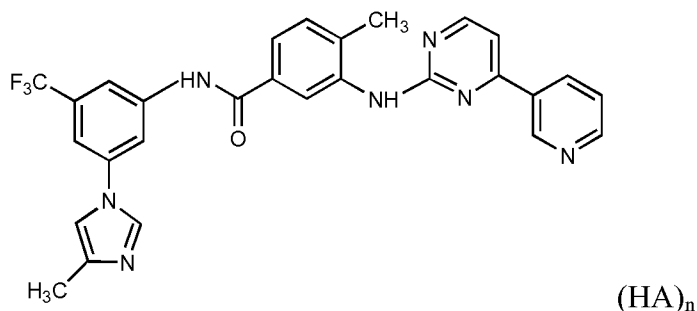
[0033] Preferably, the base is added until obtaining a pH of about 8 to about 12, more preferably, of about 12. Preferably, the cooling is to about 0°C to about 40°C, more preferably, to about 25°C. Preferably, the cooling is done for about 1 hour to about 8 hours, more preferably, for about 2 hours. After the cooling and prior to the filtering, a maintaining step may be done.

[0034] Preferably, the maintaining is done at a temperature of about 0°C to about 40°C, more preferably, at about 25°C. Preferably, the maintaining step is done for about 30 minutes to about 3 hours, more preferably, for about 45 minutes. Typically, the maintaining is done while stirring. Preferably, the filtering is done under reduced pressure.

[0035] Preferably, the washing is done with water. The drying may be done under vacuum. Preferably, the drying is done at a temperature of about 50°C to about 110°C, more preferably, at about 70°C. Optionally, slurring with a solvent selected from the group consisting of: aromatic hydrocarbon, a C₄-C₆ cyclic or aliphatic ether, a chlorinated solvent, DMA, DMF, DMSO and NMP, is done prior to the drying step.

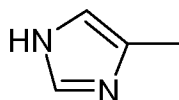
[0036] Preferably, the slurring is done with a solvent selected from the group consisting of: C₄-C₆ cyclic or aliphatic ether selected from the group consisting of: THF, MTBE and methyl-THF, more preferably, with MTBE. Typically, the slurring step is done at about room temperature. Preferably, the slurring is done for about 1 hour to about 5 hours, more preferably, for about 3 hours. The slurring is followed by additional filtering and washing steps. Preferably, the additional washing is done with a solvent selected from the group consisting of: aromatic hydrocarbon, a C₄-C₆ cyclic or aliphatic ether, a chlorinated solvent, chlorobenzene and chloroform, DMA, DMF, DMSO and NMP, more preferably, with C₄-C₆ cyclic or aliphatic ether selected from the group consisting of: THF, MTBE and methyl-THF, most preferably, with MTBE.

[0037] The present invention provides a process for preparing Nilotinib or a salt thereof of the following formula



wherein, n is either 0 or 1, and HA is an acid, preferably, HCl, from a Nilotinib intermediate of formula IV prepared according to the above process. This process can be done according to the process described below.

[0038] The present invention provides a process for preparing Nilotinib comprising: combining a compound of formula IV, a solvent selected from the group consisting of: NMP, DMSO and DMF an iodine salt selected from the group consisting of CuI, NaI, KI and combination thereof, and N,N-dimethyl ethylene diamine to obtain a reaction mixture; heating the reaction mixture; adding 8-hydroxyquinoline, an iodine salt selected from the group consisting of CuI, NaI, KI and combination thereof, a compound of formula III, having the following structure:



III

and a base selected from the group consisting of: DMAP, DBU, K₂CO₃, Cs₂CO₃, Na₂CO₃, KHCO₃, and NaHCO₃; and heating to obtain Nilotinib.

[0039] Preferably, the solvent is NMP.

[0040] Preferably, the base is DBU.

[0041] Preferably, the heating is to a temperature of about 90°C to about 125°C, more preferably, to a temperature of about 120°C. Preferably, the heating, prior to the addition of 8-hydroxyquinoline, is done for about 6 hours to about 24 hours, more preferably, for about 24 hours.

[0042] Typically, following the reaction mixture heating and prior to the addition of 8-hydroxyquinoline, a cooling step is performed. Preferably, the cooling is to a temperature of about 50°C to about 60°C, more preferably, to a temperature of about 60°C.

[0043] Preferably, the heating done after the base addition, is for a period of about 16 hours to about 72 hours, more preferably, for about 22.5 hours, to obtain a reaction mixture containing Nilotinib. Typically, while heating, the reaction is monitored by HPLC. The monitoring may be done by measuring the decrease in the amount of the compound of formula IV.

[0044] Typically, the reaction is done under nitrogen environment.

[0045] Preferably, the process for preparing Nilotinib comprises: combining compound of formula IV, CuI, NaI, NMP and N,N-dimethyl ethylene diamine to obtain a reaction mixture; heating the reaction mixture; cooling; adding 8-hydroxyquinoline, CuI, a compound of formula III and DBU; and heating to obtain Nilotinib.

[0046] The obtained Nilotinib may be recovered from the reaction mixture. The recovery may be done by treating the reaction mixture with an aqueous solution of NaHCO₃ and water to obtain a second reaction mixture; filtering; washing and drying to obtain crude Nilotinib. Preferably, the addition of NaHCO₃ and water is done at a temperature of about 20°C to about 30°C, more preferably, at about 25°C. Preferably, the washing is done with water. Preferably, the drying is under vacuum. The obtained crude Nilotinib may be further purified.

[0047] Having thus described the invention with reference to particular preferred embodiments and illustrative examples, those in the art can appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the invention as disclosed in the specification. The Examples are set forth to aid in understanding the invention but are not intended to, and should not be construed to limit its scope in any way.

EXAMPLES

Example 1: Preparation of compound of formula IV

[0048] To 500mL glass reactor was added the compound of formula 4-methyl-3-{{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}benzoic acid of formula X (20.0 g, 0.06 mol), and N-Methyl-pyrrolidone (100 mL). SOCl₂ (6.5 mL, 0.09 mol) was then added dropwise over 10 minutes. The resulted mixture was heated to 60°C, and was stirred at 60°C for 2.5 h. A compound of formula II (17.3 g, 0.07 mol) was added and the reaction mixture was stirred and heated to 90°C for 3 h. After completion of the reaction, water (100 mL) was added and the solution was heated to 80°C. NaOH 47% solution (16 mL) was added until pH 12. Then, the suspension was cooled to 25°C in 2 h and stirred at this temperature for

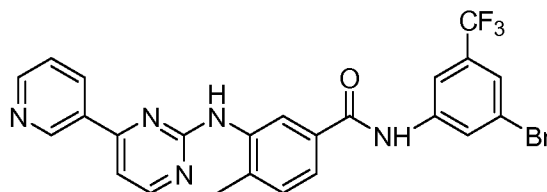
45minutes, filtered under reduced pressure at 25°C, and washed with 120 mL H₂O in portions to yield a beige solid. This material was slurried in MTBE (164 mL) at RT for 3 h, filtered, washed with MTBE (3x33 mL), and dried under vacuum at 70°C to obtain 32 g of compound IV with quantitative yield.

Example 2: Preparation of Nilotinib

[0049] The compound of formula IV (29.96 g, 57 mmol), NaI (17.2 g, 11.4 mmol), CuI (1.6 g, 8 mmol) and N,N-Dimethylethylenediamine (1.9 mL, 17 mmol) and NMP (150mL) were mixed under N₂ atmosphere. The formed mixture was heated to 120°C for 24h. The temperature of the above mixture was decreased to 60°C. 8-Hydroxyquinoline (2.5 g, 17 mmol), CuI (1.6 g, 8 mmol), the compound of formula III (6.6 g, 80 mmol) and DBU (13.0 g, 85 mmol) were added to the above mixture under N₂ atmosphere. The formed mixture was heated to 120°C for 22.5h. After the reaction was completed (detected by the consumption of the compound of formula IV, HPLC), the reaction solution was dropped to a solution of saturated NaHCO₃ (21.5 mL) and water (430 mL) at 25±5°C. The mixture was then filtered, and the filter cake was washed with water. 39.4 g of crude Nilotinib was obtained after drying in vacuum oven at 70°C.

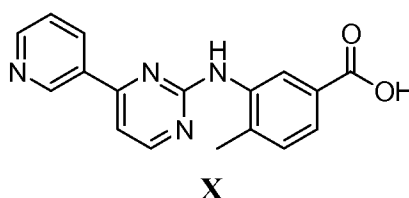
What is claimed is:

1. A process for preparing the N-(3-Bromo-5-trifluoromethylphenyl)-4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide having the following structure:



comprising: combining

a compound of formula X



with a solvent selected from the group consisting of: an aromatic hydrocarbon, a C₄-C₆ cyclic or aliphatic ether, a chlorinated solvent, DMA, DMF, DMSO and N-methylpyrrolidone ("NMP");

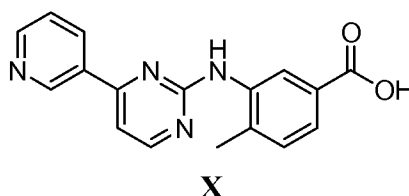
a compound selected from the group consisting of thionyl chloride, thionyl bromide, oxalyl chloride, oxalyl bromide, phosphorous trichloride, phosphorous tribromide, phosphorous pentachloride, phosphorous pentabromide, C₁-C₅ carboxylic acid, C₁-C₈ chloroformate and weinreb amide;

and 3-bromo-5- trifluoromethylaniline; and

heating the combination to form N-(3-Bromo-5-trifluoromethylphenyl)-4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide.

2. The process of claim 1, wherein the process is done in the absence of a base.
3. The process of claim 1, wherein the solvent is toluene.
4. The process of claim 1, wherein the solvent is selected from the group consisting of: tetrahydrofuran, methyl tert-butyl ether and methyl-THF.
5. The process of claim 1, wherein the solvent is selected from the group consisting of: dichloromethane chlorobenzene and chloroform.
6. The process of claim 1, wherein the solvent is NMP.
7. The process of claim 1, wherein the compound is SOCl₂.
8. The process of claim 1, wherein the compound is added dropwise.
9. The process of claim 1, wherein the process comprises:

combining a compound of formula X



with a solvent selected from the group consisting of: an aromatic hydrocarbon, a C₄-C₆ cyclic or aliphatic ether, a chlorinated solvent selected from the group consisting of dichloromethane, dichloroethane, chlorobenzene and chloroform, DMA, DMF, DMSO and N-methyl-pyrrolidone ("NMP");

adding a compound selected from the group consisting of thionyl chloride, thionyl bromide, oxalyl chloride, oxalyl bromide, phosphorous trichloride, phosphorous tribromide, phosphorous pentachloride, phosphorous pentabromide, C₁-C₅ carboxylic acid, C₁-C₈ chloroformate and weinreb amide;

adding 3-bromo-5- trifluoromethylaniline; and

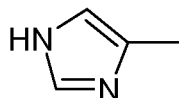
heating to form N-(3-Bromo-5-trifluoromethylphenyl)-4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide.

10. The process of claim 9, wherein prior to the addition of 3-bromo-5-trifluoromethylaniline, a heating step is performed.
11. The process of claim 10, wherein the heating is to a temperature of about 55°C to about 65°C.
12. The process of claim 1, wherein the heating is to a temperature of about 60°C to about 120°C.
13. The process of claim 12, wherein the heating is to a temperature of about 90°C.
14. The process of claim 1, wherein the obtained N-(3-Bromo-5-trifluoromethylphenyl)-4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide is recovered.
15. A process for preparing Nilotinib or salt thereof comprising converting N-(3-Bromo-5-trifluoromethylphenyl)-4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide of claim 1 to Nilotinib or a salt thereof.
16. A process for preparing Nilotinib comprising:

combining N-(3-Bromo-5-trifluoromethylphenyl)-4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide; a solvent selected from the group consisting of: NMP, DMSO and DMF; an iodine salt selected from the group consisting of CuI, NaI, KI and combination thereof; and N,N-dimethyl ethylene diamine to obtain a reaction mixture;

heating the reaction mixture;

adding 8-hydroxyquinoline; an iodine salt selected from the group consisting of CuI, NaI, KI and combinations thereof; a compound of formula III having the following structure:



III

and a base selected from the group consisting of: DMAP, DBU, K₂CO₃, Cs₂CO₃, Na₂CO₃, KHCO₃, and NaHCO₃; and

heating to obtain Nilotinib.

17. The process of claim 16, wherein the solvent is NMP.
18. The process of claim 16, wherein the base is DBU.
19. The process of claim 16, wherein the heating is to a temperature of about 90°C to about 125°C.
20. The process of claim 19, wherein the heating is to a temperature of about 120°C.
21. The process of claim 16, wherein following the reaction mixture heating and prior to the addition of 8-hydroxyquinoline, a cooling step is done.
22. The process of claim 21, wherein the cooling is to a temperature of about 50°C to about 60°C.
23. The process of claim 16, wherein the process comprises: combining N-(3-Bromo-5-trifluoromethylphenyl)-4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide, CuI, NaI, NMP and N,N-dimethyl ethylene diamine to obtain a reaction mixture; heating the reaction mixture; cooling; adding 8-hydroxyquinoline, CuI, a compound of formula III and DBU; and heating to obtain Nilotinib.
24. The process of claim 16, wherein the Nilotinib is recovered from the reaction mixture.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/065676

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04

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

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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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"&" document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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International application No

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