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(54) **Title:** AN IMPROVED PROCESS FOR THE PREPARATION OF NILOTINIB AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

(57) **Abstract:** The present invention relates to an improved process for the preparation of nilotinib and pharmaceutically acceptable salts thereof, with high purity and yields.

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AN IMPROVED PROCESS FOR THE PREPARATION OF NILOTINIB AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

PRIORITY:

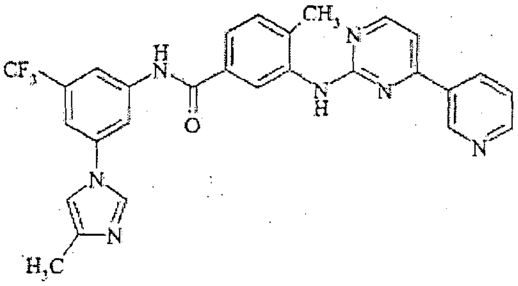
This application claims the benefit under Indian Provisional Application No. 5653/CHE/2013, filed on December 9, 2013, the content of which is incorporated by reference herein.

FIELD OF THE INVENTION:

The present invention relates to an improved process for the preparation of Nilotinib and pharmaceutically acceptable salts thereof, with high purity and yields. The present invention also relates to pharmaceutical composition comprising them.

BACKGROUND OF THE INVENTION:

Nilotinib is chemically known as 4-methyl-N-[3-(4-methyl-lH-imidazol-l-yl)-5-(trifluoromethyl)phenyl]-3-[[4-(3-pyridinyl)-2-pyrimidmyl]ammo]-benzamide and represented by the following structural Formula-I:

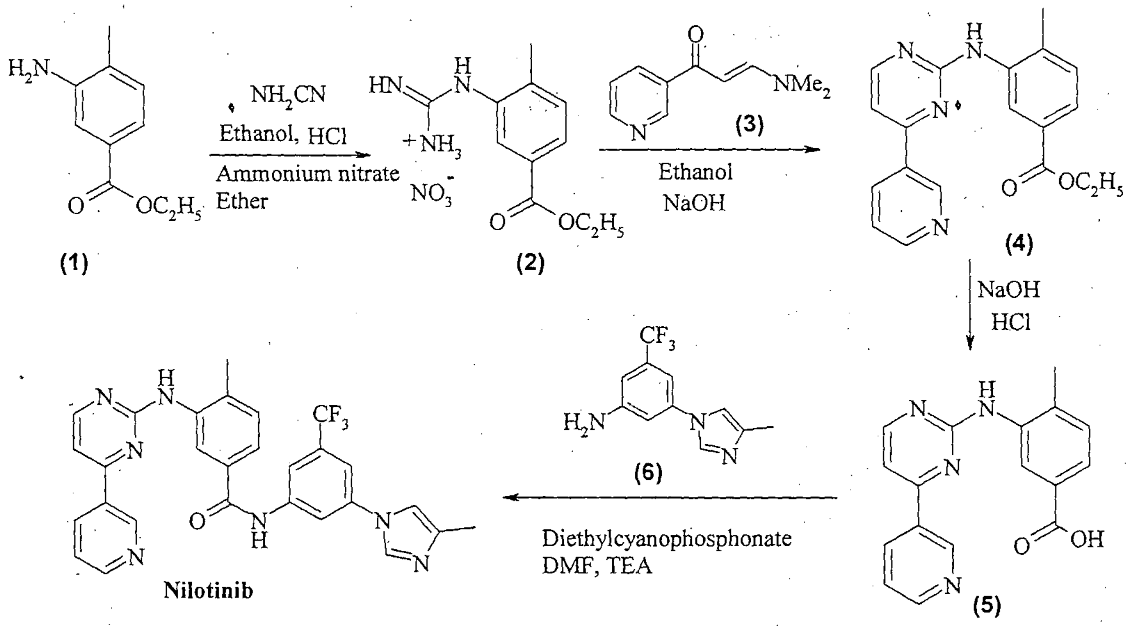


Formula-I

Nilotinib 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. Nilotinib is administrated as a hydrochloride salt in the form of capsules that are marketed in the USA and the EU under the name Tasigna®.

US 7169791 discloses Nilotinib and process for its preparation. The disclosed process involves reaction of ethyl-3-amino-4-methyl benzoate **(1)** with cyanamide in presence of hydrochloric acid in ethanol followed by treating with aqueous ammonium nitrate provides 3-[(Aminoiminomethyl)amino]-4-methyl-benzoic acid ethylester mononitrate **(2)**; which on further treatment with 3-(dimethylamino)-l-(pyridine-3-yl)prop-2-en-l-one **(3)** in presence of a sodium hydroxide in ethanol provides 4-Methyl-3-{[4-(3-

pyridinyl)-2-pyrimidinyl]amino} benzoic acid ethylester **(4)**; this ethyl ester compound **(4)** was hydrolyzed using sodium hydroxide in ethanol solvent; the obtained 4-Methyl-3-{[4-(3-pyridinyl)-2-pyrimidinyl]amino} benzoic acid **(5)** coupled with 5-trifluoro methyl-3-[4-methyl-H1-imidazolyl]aniline **(6)** in presence of diethylcyanophosphate and a base, triethylamine in dimethylformamide to provide nilotinib. The said process represented in the following scheme:



The process disclosed in US 7169791 has the following disadvantageous; a) isolation of intermediates requires number of operations like extraction, azeotropic distillation and washings makes it time consuming and costly; b) involves the usage of expensive reagent like diethylcyanophosphonate; c) yields and purity of Nilotinib obtained by this process are low and inconsistent and requires repeated extractions for isolation of the same; hence this process is not suitable for commercial scale.

International patent publcation WO 2010/009402 discloses a process which involves reaction of 4-methyl-3-{[4-(pyridin-3-yl) pyrimidin-2-yl] amino} benzoic acid with 5-trifluoromemyl-3-[4-memyl-Hl-imidazolyl]aniline in the presence of thionyl chloride in N-methylpyrrolidine solvent to provide nilotinib. The usage of highly reactive thionylchloride in this process makes it difficult to handle and carried out in commercial scale.

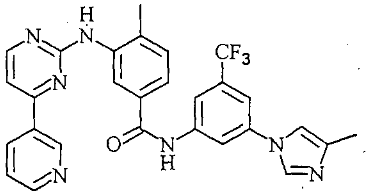
Chinese patent publication CN 103288804 discloses a process for the preparation of nilotinib, which involves the condensation of 4-methyl-3-{[4-(pyridin-3-yl) pyrimidin-2-yl]amino}benzoic acid with 5-trifluoromethyl-3-[4-methyl-Hl-imidazolyl] aniline in presence of (Benzotriazol-l-yloxy)tris(dimethylamino) phosphonium hexafluoro phosphate (BOP) and 1,8-Diazabicyclo[5.4.0]undec-7-ene in dimethylformamide. The use of BOP reagent in general discouraged because coupling reactions using BOP liberates HMPA (Hexamethylphosphoramide) which is carcinogenic; hence not suitable for industrial scale operations.

Still there is a need in the art to provide an alternate process for the preparation of nilotinib, which avoids the problems allied with the prior art processes.

SUMMARY OF THE INVENTION:

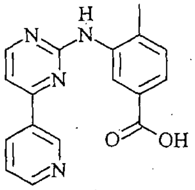
Accordingly, the present invention provides an industrially feasible and cost effective process for the preparation of nilotinib and pharmaceutically acceptable acid addition salts thereof, in high product purity and yield using low cost and easy to handle reagents.

In one aspect, the present invention provides an improved process for the preparation of nilotinib of Formula I or pharmaceutically acceptable salts thereof,



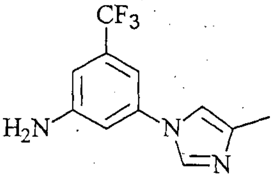
Formula I

comprising; reacting 4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}benzoic acid of Formula II



Formula II

with 5-trifluoromethyl-3-[4-methyl-Hl-imidazolyl] aniline of Formula III

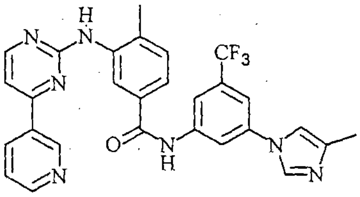


Formula III

in presence of a coupling agent and an additive in a suitable solvent to obtain nilotinib of Formula I.

In another aspect, the present invention provides an improved process for the preparation of nilotinib of Formula I or pharmaceutically acceptable salts thereof, comprising: reacting 4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}benzoic acid of Formula II with 5-trifluoromethyl-3-[4-methyl-Hl-imidazolyl]aniline of Formula III in presence of a coupling agent and an additive in a suitable solvent to obtain nilotinib of Formula I; wherein the coupling agent is selected from the group comprising carbonyl-diimidazole (CDI), carbonyl-di(l,2,4-triazole), l-ethyl-3-(-3-dimethyl aminopropyl) carbodiimide (EDC) and dicyclohexylcarbodiimide (DCC) and the like; and the additive is selected from the group comprising hydroxy benzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole(HO At), 6-chloro- 1-hydroxy- 1H-benzotriazole(Cl-HOBt), hydroxypyridines (HOPy), imidazole or its salts, l,8-diazabicyclo[5.4.0] undec-7-en (DBU), tertiary amines or its salts and the like.

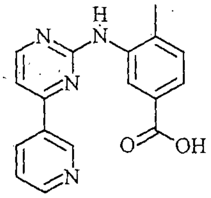
In another aspect, the present invention provides an improved process for the preparation of nilotinib of Formula I or pharmaceutically acceptable salts thereof,



Formula I

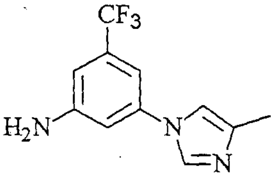
comprising;

a) reacting 4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}benzoic acid of Formula II



Formula II

with 5-trifluoromethyl-3-[4-memyl-Hl-imidazolyl]amline of Formula III



Formula III

in presence of a coupling agent and an additive in a suitable solvent, *

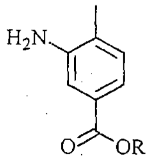
b) adding suitable base to the reaction mass of step a),

c) isolating the nilotinib of Formula-I, and

d) optionally converting the nilotinib of Formula I in to its pharmaceutically acceptable salt thereof.

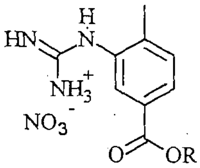
In another aspect, the present invention provides an improved process for the preparation of nilotinib of Formula I and pharmaceutically acceptable salt thereof, which comprises:

a) reacting alkyl-3-amino-4-methylbenzoate of Formula IV -



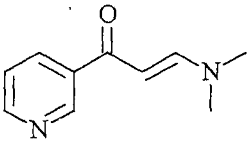
Formula IV, wherein R is C_{1-4} alkyl;

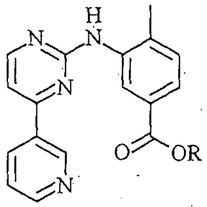
with cyanamide and a suitable nitrate source to provide nitrate salt compound of Formula V,



Formula V, wherein R is C_{1-4} alkyl;

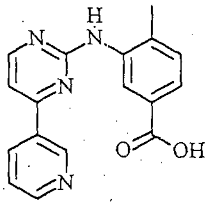
b) condensing the nitrate salt compound of Formula V with dimethyl amino compound of Formula VI in a high boiling solvent and a base to provide ester compound of Formula VII,





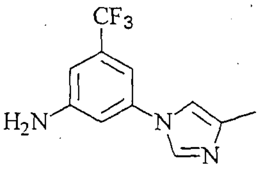
Formula VI Formula VII, wherein R is C_{1-4} alkyl;

c) hydrolyzing the ester compound of Formula VII using suitable base to provide 4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}benzoic acid of Formula II,



Formula II

d) reacting the 4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}benzoic acid of Formula II with 5-trifluoromethyl-3-[4-methyl-H 1-imidazolyl]aniline of Formula III



Formula III

in presence of a coupling agent and an additive in a suitable solvent,

e) adding a suitable base to the reaction mass of step d),
f) isolating the nilotinib of Formula-I, and
g) optionally converting the nilotinib of Formula I in to its pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides one pot process for the preparation of **4**-methyl **-3-{[4** -(pyridin **-3**-yl)pyrimidin-2-yl] amino} benzoic acid Formula II, which ^comprises condensing the nitrate salt compound of Fprmula V with dimethyl amino compound of Formula VI in a high boiling solvent and a base followed by in-situ hydrolysis of the obtained ester compound of Formula VII to provide Formula II.

In another aspect, the present invention provides a process for the preparation of **4**-methyl **-3-{[4** -(pyridin **-3**-yl)pyrimidin-2-yl] amino} benzoic acid of Formula II, which comprises reacting the nitrate salt compound of Formula V with dimethyl amino compound of Formula VI in a high boiling solvent followed by treatment with a suitable base to provide Formula II.

In another aspect, the present invention provides a process for the purification of nilotinib of Formula I, which comprises

a) suspending or mixing nilotinib with one or more suitable solvent,
b) optionally heating the reaction mass to provide the solution,
c) cooling the reaction mass to less than 25°C; and
d) isolating the pure nilotinib.

DETAILED DESCRIPTION OF THE INVENTION:

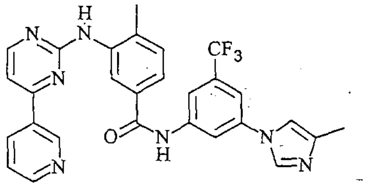
As used herein the term "additive" refers to the chemical substance which added along with coupling agent to enhance the rate of reaction and improves the formation of product.

The inventors achieved an improved and commercially viable process for preparation of nilotinib and its pharmaceutically acceptable salt thereof having desired purity, which ameliorates the problems in the art.

The inventors of the present invention have found that nilotinib or pharmaceutically acceptable salts thereof in pure form may be obtained by incorporating the process modifications such as use of an additive along with coupling agent in the reaction between an acid compound of Formula II and an amine compound of Formula III leads to complete conversion of the raw materials, which makes the. process substantially minimize the formation of undesired process impurities such as unreacted Formula II & Formula III, thereby yields and purity of nilotinib substantially increased.

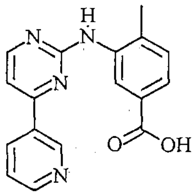
It has been observed by the present inventors that during the synthesis of nilotinib by coupling 54rifluoromethyl-3-[4-methyl-Hl-imidazolyl]aniline with 4-methyl-3-{[4-(pyridin-3-yl)pyrimidm-2-yl]amino}benzoic acid in presence of diethylcyano-phosphonate or propylphosphoric anhydride and triethylamine in dimethylformamide as per the process disclosed in US 7169791, the reaction was not get completed within 12 hours. Thereby the product was not extracted completely in solvents, for example ethyl acetate even after repeated extractions due to the presence of unreacted starting materials present in high quantity. Further found that those unreacted reactants are carry forwarded in to final nilotinib as impurities, which are referred to as acid impurity and amine impurity.

In one embodiment, the present invention provides an improved process for preparation of nilotinib of Formula I or pharmaceutically acceptable salts thereof,



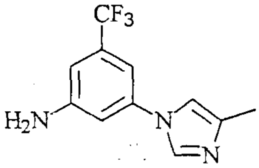
Formula I

comprising; reacting 4-methyl-3-{[4-(^yridin-3-yl)pyrimidin-2-yl]amino}benzoic acid of Formula II



Formula II

with 5-trifluoromethyl-3-[4-methyl-Hl -imidazolyl]aniline of Formula III



Formula III

in presence of a coupling agent and an additive in a suitable solvent to obtain nilotinib of Formula I.

The starting material of Formula II and Formula III are known in the art and can be prepared by any known method, for example Formula II can be synthesized as per the procedure described herein below and compound of Formula III can be obtained from commercially available sources.

In another embodiment, the suitable coupling agent used herein for the reaction of Formula II with Formula III is selected from the group comprising carbonyldiimidazole (CDI), carbonyl-di(l,2 ,4-triazole), l-ethyl-3-(-3-dimethylamino propyl)carbodiimide (EDC) and dicyclohexylcarbodiimide (DCC) and the like; preferably carbonyldiimidazole (CDI).

In another embodiment, the suitable additive used herein for the reaction of Formula II with Formula III is selected from the group comprising hydroxybenzotriazole (HOBt), l-hydroxy-7-azabenzotriazole (HOAt), 6-chloro-l -hydroxy-1H,-benzotriazole (Cl-HOBt), hydroxypyridines (HOPy), imidazole or its salts, 1,8-diazabicycle[5.4.0] undec-7-en (DBU), tertiary amines or its salts such as triethyl amine hydrochloride or diisopropylethylamine hydrochloride and the like or mixtures thereof; preferably imidazole or its salts thereof, and more preferably imidazole hydrochloride.

In a preferred embodiment, the suitable coupling agent used herein is carbonyldiimidazole and the suitable additive is imidazole hydrochloride.

The inventors of the present invention have surprisingly found that use of an additive along with coupling agent improved the rate of reaction, thereby relatively better product yields and purity obtained. Further the present inventors isolating the product directly from the reaction mass and avoiding repeated extractions as compared to prior art processes.

In another embodiment, the solvent used for the reaction of Formula II with Formula III is selected from the group comprising dimethyl formamide, dimethyl acetamide, N-methyl pyrrolidin-2-one, dimethylsulfoxide and the like and mixtures thereof; preferably N-methyl pyrrolidin-2-one.

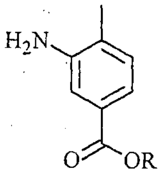
In another embodiment, the ratio of coupling agent and additive is in the ratio of about 1:2 to 2:1, preferably in the ratio of 1:1.15.

The reaction temperature should be sufficient to effect the coupling reaction. Typically the reaction temperature may be from about ambient temperature to about reflux temperature. Preferably the reaction temperature is about 30°C to about 120°C, more preferably about 95°C to about 105°C. The reaction time may be from about 0.5 hours to about 32 hours, preferably about 24 hours, depending upon the coupling agent, additive, solvent and temperature chosen.

After completion of coupling reaction, the resultant nilotinib of Formula I can be isolated by adding a suitable base in to the resultant reaction mass followed by isolating the product by known methods. The base used herein is selected from the group comprising inorganic base such as sodium hydroxide, potassium hydroxide, lithium hydroxide and the like; sodium carbonate, potassium carbonate and the like; sodium bicarbonate, potassium bicarbonate and the like; organic bases such as triethyl amine, diisopropyl amine, diisopropyl ethyl amine and the like; and mixtures thereof: Then, the precipitated product can be isolated by known methods, for example filtration.

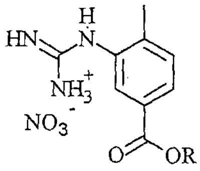
In another embodiment, the present invention provides an improved process for the preparation of nilotinib of Formula I or pharmaceutically acceptable salts thereof, which comprises:

a) reacting alkyl-3-amino-4-methylbenzoate of Formula Iv



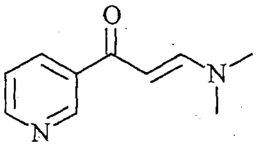
Formula TV, wherein R is C_{1-4} alkyl;

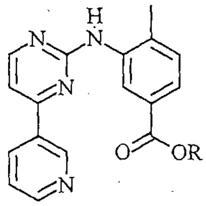
with cyanamide and a suitable nitrate source to provide nitrate salt compound of Formula V,



Formula V, wherein R is C_{1-4} alkyl;

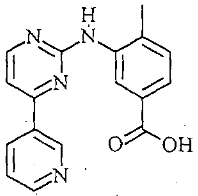
b) condensing the nitrate salt compound of Formula V with dimethyl amino compound of Formula VI in a high boiling solvent and a base to provide ester compound of Formula VII,





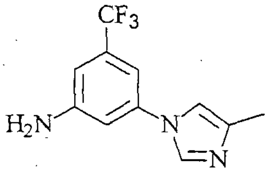
Formula VI Formula VII, wherein R is C_{1-4} alkyl;

c) hydrolyzing the ester compound of Formula VII using suitable base to provide 4-methyl-3-{[4-^yridin-3-yl)pyrimidin-2-yl]amino}benzoic acid of Formula II,



Formula II

d) reacting the 4-methyl-3-{[4-(pyridin-3-yl)pyrirnidin-2-yl]amino} benzoic acid of Formula II with 5-trifluoromethyl-3-[4-methyl-Hl -imidazolyl] aniline of Formula III



Formula III

in presence of a coupling agent and an additive in a suitable solvent,

e) adding a suitable base to the reaction mass of step d),

f) isolating the nilotinib of Formula-I, and

g) optionally converting the nilotinib of Formula I in to its pharmaceutically acceptable salt thereof.

The step a) of reacting alkyl-3-amino-4-methylbenzoate of Formula-IV, wherein R is C_{1-4} alkyl, preferably methyl with cyanamide is carried out with a nitrate source and a suitable acid in a suitable solvent. Preferably, the suitable solvent used is selected from the group consisting of alcohols such as methanol, ethanol, isopropanol, n-butanol and isobutanol and the like and mixtures thereof; more preferably ethanol; the nitrate source is sodium nitrate and the acid is hydrochloric acid.

The step a) reaction is carried out at a temperature of about 45°C to about reflux temperature for a period of about 4 to 12 hours, preferably at about 80°C to about 85°C for 6 hours.

The step b) of condensing a nitrate salt compound of Formula V with dimethyl amino compound of Formula VI is carried out in a high boiling solvent and a base to obtain ester compound of Formula VII, wherein R is C_{1-4} alkyl, preferably methyl.

Preferably, the high boiling solvent is selected from alcohols such as 1-propanol, n-butanol, isobutanol, n-pentanol and the like and mixtures thereof; more preferably n-butanol and the base is selected from the group consisting of alkali metal hydroxides like sodium hydroxide, potassium hydroxide, lithium hydroxide and the like; alkali metal carbonates like sodium carbonate, potassium carbonate and the like; alkali metal bicarbonates like sodium bicarbonate, potassium bicarbonate and the like and mixtures thereof; preferably sodium hydroxide.

The step b) reaction can be carried out at a suitable temperature for sufficient period @f time to effect the condensation. Typically the reaction carried out at a temperature of about ambient temperature to about reflux temperature for the period of 5-16 hours. Preferably the reaction temperature is about 45°C to about reflux temperature; more preferably at reflux temperature.

The resultant reaction mass containing compound of Formula VII can be further processed directly in the same reaction vessel to form compound of Formula II. Alternatively, the solvent from the organic layer may be concentrated under vacuum to get the residue by any methods known in the art, at the end of the reaction. For example distillation, evaporation, rotational drying (such as with the Buchi Rotavapor), and the like, preferably distillation under vacuum.

Preferably, the ester compound of Formula VII in step b) is not isolated as a solid and hydrolyzed in-situ using suitable base to corresponding acid of Formula II in a one pot reaction.

The suitable base used herein for hydrolysis of Formula VII may be selected from the group consisting of alkali metal hydroxides like sodium hydroxide, potassium hydroxide, lithium hydroxide and the like and mixtures thereof; preferably sodium hydroxide.

The hydrolysis reaction may be carried out in a same solvent as used for step b) reaction or in another solvent; preferably both the step b) and step c) reactions are carried out in a same solvent system.

The hydrolysis reaction is suitably carried out at about ambient temperature to about reflux temperature of the solvent; preferably at reflux temperature.

The resultant compound of Formula II is further converted into nilotinib of Formula I by a procedure described as above.

Reported process for the preparation of 4-Methyl-3-{[4-(3-pyridmyl)-2-pyrimidinyl] amino} benzoic acid Formula II involves reaction of 3-[(aminoimino methyl) amino]-4-methyl-benzoic acid ethyl ester mononitrate with 3-(dimethylamino)-l-(pyridine-3-yl)prop-2-en-l-one, sodium hydroxide in ethanol at reflux temperature for a period of about 68 hrs. The isolation of product involves many stages, which includes solvent evaporation, product extractions in to organic solvent such as ethyl acetate, and solvent evaporation to obtain product as residue. The residue obtained is crystallized with diethyl ether to provide the ethyl ester compound of Formula VII, which on hydrolysis to form compound of Formula II. The hydrolysis of the ethyl ester compound of Formula VII also -involves many steps after ester hydrolysis, which involves repeated number of washing with water, followed by azeotropic distillation to remove the water present in the compound and finally washing with diethyl ether. The disclosed process for the preparation of Formula II involves number of workup process makes it time consuming and not-viable for commercial scale.

In contrast, the present invention utilizes simple work up methods that avoids multiple solvent extractions and cumbersome distillations, thereby substantially decreasing the manufacturing time cycle.

In another embodiment, the present invention provides one pot process for the preparation of 4-memyl-3-{[4-(pyridm-3-yl)pyrirnidin-2-yl] amino}benzoic acid of Formula II, which comprises condensing the nitrate salt compound of Formula V with dimethyl amino compound of Formula VI in a high boiling solvent and a base followed by followed by hydrolysis of the ester compound of Fprmula VII in a one pot reaction.

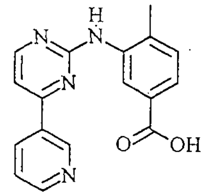
Preferably, the high boiling solvent is selected from alcohols such as 1-propanol, n-butanol, isobutanol, n-pentanol and the like and mixtures thereof; more preferably n-butanol and the base is selected from the group comprising of alkali metal hydroxides like sodium hydroxide, potassium hydroxide, lithium hydroxide and the like; alkali metal carbonates like sodium carbonate, potassium carbonate and the like; alkali metal bicarbonates like sodium bicarbonate, potassium bicarbonate and the like and mixtures thereof; preferably sodium hydroxide.

The reaction of Formula V with Formula VI can be carried out at a suitable temperature of about ambient temperature to about reflux temperature, preferably at about 120°C to about 125°C for sufficient period of time, preferably for 5-16 hours.

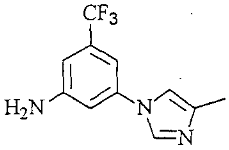
After completion of the condensation reaction of Formula V with Formula VI, the resultant reaction mass comprising ester compound of Formula VII may be cooled to room temperature and then hydrolyzed by treating it with a suitable base selected from the group comprising alkali metal hydroxides like sodium hydroxide, potassium hydroxide, lithium hydroxide and the like and mixtures thereof; preferably sodium hydroxide, at a temperature of about 45°C to about 125°C for a period of about 20 mins to about 8 hours. Then, the reaction mass may be cooled to room temperature and neutralized with a suitable acid such as hydrochloric acid to precipitate out the compound of Formula II.

The present inventors surprisingly found that the usage of higher boiling alcohol ^solvents at reflux temperature reduces the time cycle to 12 hours from 68 hours for the reaction of Formula V with Formula VI as compared to the prior art process reported in US 7169791.

The repetition of the process disclosed in the '791 patent resulted in a final nilotinib product containing about 0.5% of acid impurity and 1% of amine impurity. In contrast, the process herein described arrives at a nilotinib with substantially lower levels of such impurities. The acid and amine impurities are represented by the following structural formula.



"Acid Impurity"



"Amine Impurity"

In another embodiment, the present invention provides a process for the purification of nilotinib of Formula I, comprising

a) suspending or mixing nilotinib with one or more suitable solvent,
b) optionally heating the mass to provide the solution,
c) cooling the reaction mass to less than 25°C; and
d) isolating the pure nilotinib.

The one or more suitable solvent used in step a) includes alcohols, ketones or mixture thereof. The alcohols used herein include, but are not limited to methanol, ethanol, isopropanol, n-propanol, n-butanol and the like; ketones used herein include, but are not limited to acetone, methylethylketone, methylisobutylketone and the like and mixtures thereof; preferably acetone.

Optionally, the reaction mass of step b) may be heated to obtain a solution at a temperature from about ambient temperature to about reflux temperature, preferably from about 25°C to about 75°C.

Then the resultant suspension or solution may be cooled to less than 25°C and isolating the product by conventional techniques known in the art, for example filtration. Typically, if stirring is involved, the temperature during stirring can range from about 0°C to about 20°C.

In another embodiment, the present invention provides a process for the purification of nilotinib of Formula I, comprising slurrying or washing the nilotinib of Formula I with one or more suitable solvent at a suitable temperature of about 25°C to about 35°C. The suitable solvent used for slurrying or washing is selected from water, methanol, ethanol, isopropanol, n-propanol, n-butanol, acetone, methylethylketone, methyl isobutylketone and the like and mixtures thereof; preferably acetone.

The resulted pure nilotinib further converted into its pharmaceutically acceptable acid addition salts, preferably nilotinib hydrochloride in accordance with the procedures reported in the art, preferably by treating nilotinib as obtained by the process described above with hydrochloric acid in methanol solvent to obtain nilotinib hydrochloride.

In another embodiment, the present invention provides nilotinib or pharmaceutically acceptable salts thereof, particularly nilotinib hydrochloride as obtained by the process described above having purity of at least about 98%, as measured by HPLC; preferably at least about 99%, as measured by HPLC; and more preferably at least about 99.5%, as measured by HPLC.

In another embodiment, the present invention provides nilotinib or its pharmaceutically acceptable salts thereof obtained by the process described above having less than 0.1% of amine impurity, as measured by HPLC, preferably less than 0.05% as measured by HPLC; and less than 0.1% of acid impurity, as measured by HPLC; preferably less than 0.05%, as measured by HPLC.

In another embodiment, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of nilotinib or pharmaceutically acceptable salts thereof, particularly mlotinib hydrochloride of the invention with at least one pharmaceutically acceptable carrier or other excipient.

The purity of nilotinib or pharmaceutically acceptable salts thereof was analyzed using high performance liquid chromatography ("HPLC") with the conditions are tabulated below:

Column	Inertsil ODS-3V, 250 X 4.6, 5 µ
Column/Sample temperature	30 °C
Mobile phase	Mobile Phase-A: Buffer Mobile Phase-B: Acetonitrile
Buffer	0.02M K_2HPO_4, pH 2.5 with Ortho phosphoric acid
Diluent	Buffer : Acetonitrile (1:1)
Flow rate	1 ml / min
Wavelength	210 nm
Injection Volume	10 µl
Elution	Gradient

The following examples are provided by way of illustration only, and are not intended to be limiting of the present invention. Further, the present invention covers all the possible combinations of particular and preferred embodiments indicated herein.

EXAMPLES

EXAMPLE-1: Preparation of 3-(dimethylamino)-l-(pyridine-3-yl)prop-2-en-l-one

3-Acetylpyridine (44.1 g) and dimethylformamide dimethylacetal (112.8 g) was charged to a round bottom flask at 25-35°C under nitrogen atmosphere. The reaction mass was heated to 78-80°C and stirred for 2 hrs. Then the reaction mass was concentrated under vacuum at below 60°C. Diisopropylether (200 mL) was added to the reaction mass and stirred for an hour. Filtered the reaction mass and washed with mixture of diisopropylether and hexane. The compound obtained was dried under vacuum to get the title compound (60.2 g).

EXAMPLE-2: Preparation of 3-[(Aminoiminomethyl)amino]-4-methyl-benzoic acid methylestermononitrate.

Methyl-3-amino-4-methyl benzoate (50 g), cyanamide (42 g) was added to ethanol (300 mL) in a round bottom flask at 25-35°C. Concentrated hydrochloric acid (21.2 mL) was added to the reaction mass in a drop-wise manner at 25-35°C under nitrogen atmosphere. The reaction mass was heated to 80-85°C and stirred for 6 hours. Then the reaction mass was concentrated under vacuum at less than 50°C, then cooled to 25-35°C. Water (350 mL) was added to the reaction mass, cooled to 0-5°C and stirred for 15 mins. Aqueous sodium nitrate solution (51.5 g in 135 ml of DM water) was added to the reaction mass at 0-5°C in 45 mins. The precipitate formed was filtered, washed with DM water, acetone followed by methyl *tert*-butylether (MTBE), and dried under vacuum at 50-55°C to provide the title compound (47.5 g).

EXAMPLE-3: Preparation of 4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino} benzoic acid.

3-[(Aminoiminomethyl)amino]-4-methyl-benzoic acid methylester mononitrate (10 g), 3-(Dimethylamino)-l-(pyridine-3-yl)prop-2-en-l-one (7.3 g), sodium hydroxide (1.7 g) was added to 1-butanol (100 mL) in a round bottom flask under nitrogen atmosphere. The reaction mass was heated to reflux temperature and stirred for 12 hrs. Then the reaction mass was cooled to 25-35°C and IN sodium hydroxide solution (1.5 g in 37 mL of DM water) was added to it over a period of 20 min. The reaction mass was heated to reflux temperature (120-125°C) and then cooled to 25-35°C. IN hydrochloric acid (3.3 mL in 37 mL of DM water) was added to the reaction mass at 25-35°C and stirred for an hour. The material formed was filtered, washed with DM water and then dried under vacuum at 50-55°C to provide the title compound (8.7 g).

EXAMPLE-4: Preparation of Nilotinib

4-Memyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}benzoic acid (lOg), carbonyl diimidazole (6.9 g) and imidazole hydrochloride (5.1 g) was added to N-methyl pyrrolidin-2-one (200 mL) in a round bottom flask under nitrogen atmosphere at room temperature and stirred for 60 mins. The reaction mass was heated to 50-55°C and stirred for an hour. 5-trifluoromethyl-3-[4-methyl-Hl-imidazolyl] aniline (11.8 g) was added to the reaction mass at 50-55°C under nitrogen atmosphere. The reaction mass was further heated to 95-105°C and stirred for 24 hrs. After completion of reaction, the reaction mass was cooled to 25-35°C, 5% sodium hydroxide solution was added to it and stirred for 1.5 hrs. The precipitated solid was filtered, washed with water followed by acetone and then dried under vacuum at 50-55°C to get the title compound (9.1 g).

Purity by HPLC: 99.84%; Amine impurity: 0.04%; Acid impurity: 0.03%

EXAMPLE-5: Preparation of Nilotinib HC1 monohydrate

Nilotinib (2 g), concentrated hydrochloric acid (0.35 mL) were added to methanol (20 mL) in a round bottom flask at 25-35°C under nitrogen atmosphere. The reaction mass was heated to 50-55°C and stirred for an hour. The reaction mass was initially cooled to 25-35°C, stirred for 3 hrs, then further cooled to 0-5°C and stirred for an hour. The obtained precipitate was filtered, washed with chilled methanol and dried under -vacuum at 50-55°C to get the title compound (1.8 g).

Purity by HPLC: 99.96%; Acid impurity: 0.01%; Amine impurity: Not detected

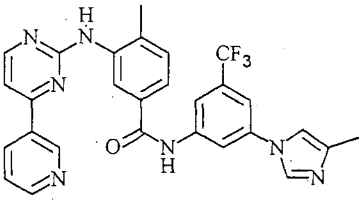
EXAMPLE-6: Purification of Nilotinib

Nilotinib (10 g) was added to acetone (100 mL) in a round bottom flask at 25-35°C. The reaction mass was stirred for 10 mins at 25-35°C. Then the reaction mass was filtered, washed with acetone and dried under vacuum at 50-55°C to get the title compound(9 g).

Purity by HPLC: 99.93%; Amine impurity: 0.02%; Acid impurity: 0.02%

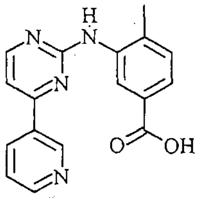
WE CLAIM:

Claim 1: An improved process for the preparation of Nilotinib of Formula I or pharmaceutically acceptable salts thereof,



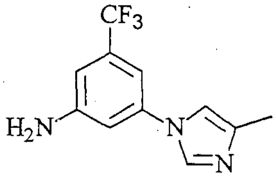
Formula I

comprising: reacting 4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}benzoic acid of Formula II



Formula II

with 5-trifluoromethyl-3-[4-methyl-Hl-imidazolyl]aniline of Formula III



Formula III

in presence of a coupling agent and an additive in a suitable solvent.

Claim 2: The process of claim 1, wherein the coupling agent is selected from the group comprising carbonyldiimidazole (CDI), carbonyl-di(l,2,4-triazole), l-ethyl-3-(-3-dimethylaminopropyl)carbodiimide (EDC) and dicyclohexyl- carbodiimide (DCC).

Claim 3: The process of claim 1, wherein the additive is selected from the group comprising hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), 6-chloro-1-hydroxy-1H-benzotriazole (Cl-HOBt), hydroxypyridines (HOPy), imidazole or its salts, 1,8-diazabicycle[5.4.0] undec-7-en (DBU) and tertiary amines or its salts.

Claim 4: The process of claim 1, wherein the coupling agent is carbonyldiimidazole (CDI) and the additive is imidazole hydrochloride.

Claim 5: The process of claim 1, wherein the ratio of coupling agent and the additive is about 1:2 to 2:1.

Claim 6: The process of claim 1, wherein the suitable solvent is selected from the group comprising dimethyl formamide, dimethyl acetamide, N-methyl pyrrolidin-2-one and dimethylsulfoxide and mixtures thereof.

Claim 7: The process of claim 6, wherein the suitable solvent is N-methyl pyrrolidin-2-one.

Claim 8: The process of claim 1, wherein the reaction is carried out at a temperature of about 25°C to about reflux temperature.

Claim 9: The process of claim 1, further comprising the steps of:

a) adding suitable base to the reaction mass obtained according to claim 1,
b) isolating the nilotinib, and
c) converting the nilotinib in to pharmaceutically acceptable salts thereof.

Claim 10: The process of claim 9, wherein the suitable base is inorganic base or organic base.

Claim 11: The process of claim 10, wherein the inorganic base is selected from the group comprising sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate and mixtures thereof.

Claim 12: The process of claim 10, wherein the organic base is selected from the group comprising triethyl amine, diisopropyl amine, diisopropyl ethyl amine and mixtures thereof.

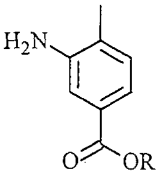
Claim 13: The process of claim 9, wherein the suitable base is sodium hydroxide.

Claim 14: The process of claim 9, wherein the pharmaceutically acceptable salt is hydrochloride salt.

Claim 15: An improved process for the preparation of Nilotinib of Formula I or .pharmaceutically acceptable salts thereof, comprising reacting 4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}benzoic acid of Formula II with 5-trifluoromethyl-3-[4-methyl-Hl-imidazolyl] aniline of Formula III in presence of a carbonyldiimidazole (CDI) and imidazole hydrochloride in N-methyl pyrrolidin-2-one.

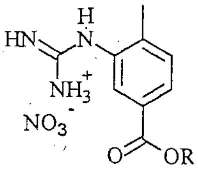
Claim 16: An improved process for the preparation of nilotinib of Formula I or pharmaceutically acceptable salts thereof, which comprises:

a) reacting alkyl-3-amino-4-methylbenzoate of Formula IV



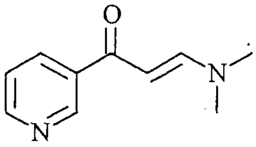
Formula IV, wherein R is C_{1-4} alkyl;

with cyanamide and a suitable nitrate source to provide nitrate salt compound of Formula V,

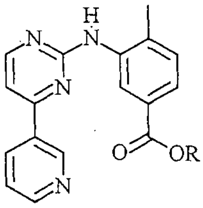


Formula V, wherein R is C_{1-4} alkyl;

b) condensing the nitrate salt compound of Formula V with dimethyl amino compound of Formula VI in a high boiling solvent and a base to provide ester compound of Formula VII,

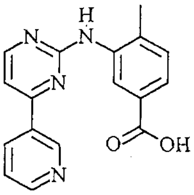


Formula VI



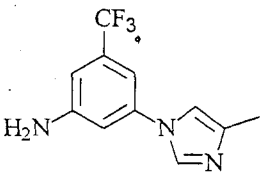
Formula VII, wherein R is C_{1-4} alkyl;

c) hydrolyzing the ester compound of Formula VII using suitable base to provide 4-methyl-3-{[4-(pyridm-3-yl)pyrimidin-2-yl]amino}benzoic acid of Formula II,



Formula II

d) reacting the 4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}benzoic acid of Formula II with 5-trifluoromethyl-3-[4-methyl-Hl-imidazolyl]aniline of Formula III



Formula III

in presence of a coupling agent and an additive in a suitable solvent,

e) adding a suitable base to the reaction mass of step d),

f) isolating the nilotinib of Formula-I, and

g) optionally converting the nilotinib of Formula I in to its pharmaceutically acceptable salt thereof.

Claim 17: The process of claim 16, wherein the nitrate source of step a) is sodium nitrate.

Claim 18: The process of claim 16, wherein the high boiling solvent is selected from 1-propanol, n-butanol, isobutanol, n-pentanol and mixtures thereof.

Claim 19: The process of claim 18, wherein the high boiling solvent is n-butanol.

Claim 20: The process of claim 16, wherein the step b) and step c) are carried out in a one pot reaction.

Claim 21: The process of claim 16, wherein the suitable base of step b) is selected from sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate and mixtures thereof.

Claim 22: The process of claim 21, wherein the suitable base is sodium hydroxide.

Claim 23: The process of claim 16, wherein the suitable base of step c) is selected from sodium hydroxide, potassium hydroxide, lithium hydroxide and mixtures thereof.

Claim 24: The process of claim 23, wherein the suitable base is sodium hydroxide.

Claim 25: The process of claim 16, wherein the coupling agent is selected from the group comprising carbonyldiimidazole (CDI), carbonyl-di(l,2,4-triazole), l-ethyl-3-(-3-dimethylaminopropyl)carbodiimide(EDC) and dicyclohexyl- carbodiimide (DCC).

Claim 26: The process of claim 16, wherein the additive is selected from the group comprising hydroxybenzotriazole (HOBt), l-hydroxy-7-azabenzotriazole (HOAt), 6-chloro-1-hydroxy-IH-benzotriazole (Cl-HOBt), hydroxypyridines (HOPy), imidazole or its salts, l,8-diazabicycle[5.4.0] undec-7-en (DBU) and tertiary amines or its salts.

Claim 27: The process of claim 16, wherein in the coupling agent is carbonyldiimidazole (CDI) and the additive is imidazole hydrochloride.

Claim 28: The process of claim 16, wherein the suitable solvent of step d) is selected from the group comprising dimethyl formamide, dimethyl acetamide, N-methyl pyrrolidin-2-one, dimethylsulfoxide and mixtures thereof.

Claim 29: The process of claim 28, wherein the suitable solvent is N-methyl pyrrolidin-2-one.

Claim 30: The process of claim 16, wherein the suitable base of step e) is selected from the group comprising inorganic bases such as sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate and mixtures thereof; organic bases such as triethyl amine, diisopropyl amine, diisopropyl ethyl amine and mixtures thereof.

Claim 31: An improved process for the preparation of 4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}benzoic acid of Formula II, which comprises condensing the nitrate salt compound of Formula V with dimethyl amino compound of Formula VI in a high boiling solvent and a base followed by hydrolysis of the ester compound of Formula VII in a one pot reaction.

Claim 32: The process of claim 31, wherein in the high boiling solvent is selected from 1-propanol, n-butanol, isobutanol, n-pentanol and mixtures thereof.

Claim 33: The process of claim 31, wherein the high boiling solvent is n-butanol.

Claim 34: The process of claim 31, wherein the base is selected from sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate and mixtures thereof.

Claim 35: The process of claim 34, wherein the base is sodium hydroxide.

Claim 36: The process of claim 31, wherein the hydrolysis is carried out in presence of a base.

Claim 37: The process of claim 36, wherein the base is selected from the group comprising sodium hydroxide, potassium hydroxide, lithium hydroxide and mixtures thereof.

Claim 38: The process of claim 37, wherein the base is sodium hydroxide.

Claim 39: A process for the purification of nilotinib of Formula-1, comprising;

a) suspending or mixing nilotinib with one or more suitable solvent,
b) optionally heating the reaction mass to provide the solution,
c) cooling the reaction mass to less than 25°C; and
d) isolating the pure nilotinib.

Claim 40: The process of claim 39, wherein in the one or more suitable solvent is selected from alcohols such as methanol, ethanol, isopropanol, n-propanol, n-butanol; ketones such as acetone, methylethylketone, methylisobutylketone; and mixtures thereof.

Claim 41: The process of claim 40, wherein the one or more suitable solvent is acetone.

Claim 42: A process for purification of nilotmib of Formula- 1, comprising slurrying or washing the nilotinib of formula I with a suitable solvent; wherein the suitable solvent is selected from the group comprising water, methanol, ethanol, isopropanol, n-propanol, n-butanol, acetone, methylethylketone, methyl isobutylketone and mixtures thereof,

Claim 43: The process of claim 42, wherein the suitable solvent is acetone.

Claim 44: Nilotinib hydrochloride, obtained according to process of claims 1-43 having purity greater than about 99%.

Claim 45: Nilotinib hydrochloride, obtained according to process of claims 1-43 having less than 0.1% of amine impurity, as measured by HPLC, and less than 0.1% of acid impurity, as measured by HPLC.