Abstract:

A process for preparation of sunitinib malate is provided, which comprises condensing an indole intermediate with formyl amide intermediate. A process for preparation of crystalline form I of sunitinib malate is also provided, which uses methyl isobutyl ketone as solvent.

Formula I

![Chemical Structure](image)
FIELD OF THE INVENTION

The present invention relates to an industrially advantageous process for the preparation of sunitinib of formula I,

![Formula I](image)

and its pharmaceutically acceptable salts thereof.

The present invention also provides novel salts of sunitinib and preparation thereof. The present invention further provides an efficient process for the preparation of form I of sunitinib malate.

BACKGROUND OF THE INVENTION

Sunitinib of formula I, is a tyrosine kinase inhibitor (TKI) that targets and blocks the signaling pathways of multiple selected receptor tyrosine kinases (RTKs) and is chemically known as N-[2-(diethyl amino)ethyl]-5-[(2)-(5-fluoro-1,2-dihydro-2-oxo-3 \( H \)-indol-3-ylidene)methyl]-2,4-dimethyl-\( H \)-pyrrole-3-carboxamide.

![Formula I](image)

It is indicated for the treatment of abnormal cell growth in mammals, particularly in humans and marketed in the United States under the trade name SUTENT® by Pfizer, Inc. SUTENT® is approved by the FDA for the treatment of metastatic malignant gastrointestinal stromal tumor (GIST) and for the treatment of advanced metastatic renal cell carcinoma (MRCC).

Sunitinib has been first disclosed in US patent 6,573,293, (referred herein as US ‘293). US ‘293 patent discloses synthesis of sunitinib by the following reaction scheme:
Sunitinib thus prepared is washed with ethanol, slurried in ethanol, isolated from the slurry by filtration, again washed with ethanol, and dried for 130 hours under vacuum to give an orange solid. Process involves the use of pyrrolidine for the condensation which is very expensive reagent. Further patent is silent about the purity of the sunitinib and also its conversion to sunitinib malate. US patent 7,119,209 exemplifies preparation of sunitinib by activating carboxylic group of 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid with imidazole moiety to form 4-(imidazole-1-carbonyl)-3,5-dimethyl-1H-pyrrole-2-carbaldehyde followed by reaction of resulting intermediate with N,N-diethyl ethylenediamine, and 5-fluorooxindole in acetonitrile in presence of triethylamine to give sunitinib as shown below:

Process involves protection of carboxylic group prior to condensation reaction which adds an extra step to the process, hence makes the process lengthy. Process involves use of organic base such as triethylamine for condensation.

US patent 7,435,832 discloses process for the preparation of sunitinib L-malate by adding malic acid to the solution of sunitinib base in methanol and then methanol is evaporated under reduced pressure resulting in poorly orange solid. A further solvent like acetonitrile is then added to the product to
obtain the slurry which is heated and then cooled to obtain the crystal form 1. The patent also
discloses two polymorphs of sunitinib malate referred to as form I and form II. It is found that
process results in low yield of desired product, therefore not attractive to utilize at industrial scale
US patent application 2006/0009510 discloses process for preparation of sunitinib by preparing
formyl amide intermediate by reacting 4-(2-diethylamino-ethylcarbamoyl)-3,5-dimethyl-lH-pyrrole-2-carboxylic acid tert-butyl ester with sulfuric acid in methanol followed by condensation with 5-fluorooxindole in acetonitrile in the presence of Vilsmeier reagent (chloromethylenedimethylammonium chloride). The synthesis is as given below:

![Chemical Structure]

Process employs the use of Vilsmeier reagent which is highly corrosive in nature, reacts violently
with water and produce toxic fumes of hydrogen chloride, thus unsuitable for use in the industrial scale.
US patent application 2009/247767 discloses a process for the preparation of sunitinib by the
following method:
In above process, condensation reaction of 5-fluorooxoindole is carried out with 5-formyl indole-3-carboxylic acid derivative followed by activation of carboxylic group prior to condensation with N,N-diethyl ethylenediamine to form sunitinib.

PCT publication WO 2009/150523 discloses a process for the preparation of sunitinib malate without isolating sunitinib by condensation of malate salt of 5-formyl-2,4-lH-pyrrole-3-carboxylic acid-(2-diethylaminoethyl) amide with 5-fluorooxoindole in an organic solvent in presence of an organic amine like pyrrolidine which is then crystallized using water: isopropanol.

PCT publication WO 2009/15701 discloses a process for the preparation of sunitinib by reacting 5-formyl-2,4-lH-pyrrole-3-carboxylic acid-(2-diethylaminoethyl) amide with 5-fluorooxoindole in a solvent optionally employing a catalyst to give sunitinib, which is then converted to sunitinib malate by refluxing with L-malic acid and a suitable solvent. Several catalysts such as inorganic bases, quaternary ammonium compound, Lewis acid, organic base, para-toluene sulfonic acid; and the like have been disclosed which can be used to hasten reaction, but examples are found using
only basic catalyst such as pyrrolidine, piperidine, sodium bicarbonate, potassium hydroxide, ammonia, sodium methoxide, tert-butyl ammonium hydroxide and potassium fluoride.

PCT publication WO 2010/001 167 discloses a process for the preparation of sunitinib by employing different strategy as shown below:

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Process involves condensation of 5-fluoro-2-oxo-2,3-dihydro-lH-indole-3-carbaldehyde with 2,4-dimethyl-lH-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide to give sunitinib. Sunitinib prepared by the above process is having purity only 93.87% as exemplified. Sunitinib base of such low purity is not suitable for the further synthesis of final product i.e. sunitinib malate as purity of the intermediate as well as final compound is important in the field of pharmaceutical chemistry.

PCT publication WO 2010/055082 discloses a process for preparation of sunitinib malate by refluxing 5-formyl-2,4-lH-pyrrole-3-carboxylic acid-(2-diethylaminoethyl) amide with 5-fluoro-1,3-dihydro-indol-2-one in organic solvent in presence of organic base selected from linear amines, cyclic amines (preferably organic base used is pyrrolidine) followed by addition of malic acid to form sunitinib malate. Pyrrolidine is an expensive reagent, highly toxic, causes skin irritation and therefore not suitable for use at industrial scale.

Chinese patent application CN 101497607 A discloses a process for preparation of sunitinib by amidation of 2,4-dimethyl-lH-pyrrole-3-carboxylic acid with N^N-diethyl ethylenediamine using Vilsmeier-Haack reagent followed by condensation with 5-fluoroindolin-2-one in organic solvent in the presence of inorganic or organic base.

Most of the prior art processes involves condensation of 5-formyl-2,4-lH-pyrrole-3-carboxylic acid-(2-diethylaminoethyl) amide with 5-fluoro-1,3-dihydro-indol-2-one for preparation of sunitinib in the presence of reagents like pyrrolidine, inorganic or organic bases or Vilsmeier reagent. Pyrrolidine is an expensive reagent, highly toxic causes skin irritation; Vilsmeier reagent is highly
corrosive in nature, reacts violently with water and produce toxic fumes of hydrogen chloride, thus uses of these reagents are unsuitable for industrial scale. We have not found any references wherein said condensation is carried out using acidic reagents as condensing agent. Further prior art processes are time consuming and difficult to carry out as they involve many steps and also not suitable for synthesis of API because the final product is not obtained in desired purity.

There are several polymorphs known in prior art for sunitinib malate, but form I of sunitinib malate has been found to have more thermodynamic stability, higher crystallinity and lower hygroscopicity. Various processes are known for preparation of sunitinib malate form I, which are incorporated herein as reference.

PCT publication WO 2010/004339 discloses a process for preparation of sunitinib L-malate by mixing sunitinib with suitable solvents like acetone, methanol or ethyl acetate followed by adding malic acid to yield crystal form I of sunitinib malate.

PCT publication WO 2010/01 1834 discloses a process for preparation of sunitinib L-malate by dissolving sunitinib in solvents like pyridine, dioxane, butyl acetate, ethyl acetate, N-methyl pyrrolidone or toluene, N-methyl pyrrolidone or propanol, dimethylacetamide or n-propanol followed by adding L-malic acid to form crystal form I of sunitinib malate. This application also discloses another method for the preparation of sunitinib malate through acid addition salt of sunitinib wherein in acid is selected from acetic acid, formic acid, ascorbic acid, benzoic acid, succinic acid, n-butyric acid, propionic acid and boric acid.

PCT publication WO 2010/041134 discloses a process for preparation of sunitinib malate by reacting 5-formyl-2,4-1H-pyrrole-3-carboxylic acid-(2-diethylaminoethyl) amide with 5-fluoro-1,3-dihydro-indol-2-one in butanol in the presence of pyrrolidine followed by addition of acetic acid to reaction mixture to directly form sunitinib acetate without isolating sunitinib base. Sunitinib acetate thus formed is then reacted with L-malic acid in n-butanol to form sunitinib malate which is crystallized using water: isopropanol.

PCT publication WO 2010/049449 exemplifies synthesis of sunitinib salts using different acids selected from D-tartaric acid, L-tartaric acid and citric acid. Patent is completely silent about the conversion of above sunitinib salts to sunitinib malate which is active ingredient for drug product.

PCT publication WO 2010/076805 discloses a process for preparation of sunitinib L-malate by refluxing sunitinib base, L-malic acid in a solvent like dimethylsulfoxide to obtain a clear solution followed by adding antisolvent or mixture of antisolvents selected from acetone, methyl tert-butyl ether and isopropyl acetate to give crystal form I of sunitinib malate.
As solubility of sunitinib is very less in organic solvents, so it is very challenging to prepare form I of sunitinib L-malate in pure form consistently. Prior art methods may not give reproducible results and also necessitate the optimization of experimental conditions along with that of the selection of solvents. Numerous factors effect crystallization conditions, and they are well known to one of skill in the art. The discovery of new process to prepare polymorph of sunitinib L-malate provides opportunities to improve the characteristics of pharmaceutical product.

In view of above, there is an urgent need to develop an industrially advantageous and cost effective process for the preparation of sunitinib and its malate salt. Thus, present invention fulfills the need in of the art and provides a process for the preparation of sunitinib wherein use of expensive and hazardous reagent such as pyrrolidine or Vilsmeier reagent is avoided and proved to be simple, efficient and industrially advantageous. Present invention also provides efficient and improved process for the synthesis of crystalline form I of sunitinib malate, wherein form I can be prepared in pure form without contamination of other forms, consistently.

**OBJECTIVE OF THE INVENTION**

The principal objective of present invention is to provide an industrially advantageous and cost effective process for the synthesis of sunitinib and pharmaceutically acceptable salts thereof.

Another object of the present invention is to provide an industrially advantageous process for the preparation of sunitinib which circumvent the use of expensive reagent such as pyrrolidine.

Another object of the present invention is to provide an industrially advantageous process for the preparation of sunitinib which circumvent the use of corrosive reagent such as Vilsmeier reagent.

Another object of the present invention is to provide novel acid addition salts of sunitinib.

Yet another object of present invention is to provide an efficient process for preparation of crystalline form I of sunitinib L-malate.

**SUMMARY OF THE INVENTION**

Accordingly, present invention provides an improved and industrially advantageous process for the preparation of sunitinib of formula I,

![Formula I](image)

and pharmaceutically acceptable salts thereof. More particularly, the present invention provides improved processes for preparation of sunitinib and its L-malate salt.
According to one embodiment, present invention provides an improved process for the preparation of sunitinib and pharmaceutically acceptable salts thereof, comprising the steps of:

a) condensing indole intermediate of formula II,

![Formula II](image)

with formyl amide intermediate of formula III,

![Formula III](image)

in the presence of a suitable condensing reagent in a suitable solvent;

b) optionally, neutralizing the product obtained in step a) with a suitable base; and

c) isolating sunitinib from the reaction mixture.

According to another embodiment, the present invention provides a process for the preparation of crystalline form I of sunitinib malate, comprising the steps of:

a) providing sunitinib in methyl isobutyl ketone or a mixture of methyl isobutyl ketone with other solvents;

b) adding L-malic acid to the above mixture and stirred for sufficient period of time to give form I of sunitinib malate;

c) isolating form I of sunitinib malate therefrom.

According to another embodiment, the present invention provides a process for preparation of form I of sunitinib malate, comprising the steps of:

a) condensing indole intermediate of formula II,

![Formula II](image)

with formyl amide intermediate of formula III,

![Formula III](image)

in the presence of a suitable condensing reagent in a suitable solvent;

b) optionally, neutralizing the product obtained in step a) with a suitable base;

c) isolating sunitinib from the reaction mixture;
d) treating sunitinib with malic acid in a suitable solvent; and
e) isolating sunitinib malate form 1.

According to another embodiment, the present invention provides novel salt of sunitinib with protic acid selected from hydrochloric acid, hydrobromic acid, oxalic acid, lavulinic acid, salicylic acid, phosphoric acid, sulfuric acid, picric acid.

According to another embodiment, the present invention provides a process for preparation of sunitinib with enhanced purity using novel salts.

According to another embodiment, the present invention provides sunitinib hydrochloride salt in isolated form, both in amorphous as well as crystalline.

According to yet another embodiment, present invention provides crystalline sunitinib hydrochloride.

According to yet another embodiment, present invention provides crystalline sunitinib hydrobromide.

According to one another embodiment, the present invention provides sunitinib hydrobromide salt in isolated from, both in amorphous as well as crystalline.

According to another embodiment, the present invention provides sunitinib phosphate in isolated form, both in amorphous as well as crystalline.

According to another embodiment, the present invention provides sunitinib salicylate in isolated form, both in amorphous as well as crystalline.

20 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: shows X-ray powder diffraction pattern of sunitinib hydrochloride

Figure 2: shows X-ray powder diffraction pattern of sunitinib hydrobromide

DETAILED DESCRIPTION OF THE INVENTION

Accordingly, the present invention provides a process for the preparation of sunitinib of formula I and pharmaceutically acceptable salts thereof by the condensation of indole intermediate of formula II with formyl amide intermediate of formula III using a suitable condensing reagent.

Generally, process involves reaction of indole intermediate of formula II with formyl amide intermediate of formula III in the presence of a suitable condensing reagent at a temperature of 10 to 150 °C for few minutes to several hours, preferably till completion of condensation reaction.

Suitable condensing reagent can be selected from protic acid such as hydrochloric acid, hydrobromic acid, oxalic acid, lavulinic acid, salicylic acid, phosphoric acid, sulfuric acid, picric acid and the like; phenols, substituted phenol; acid salts such as sodium bisulfite; ammonium picrate and the like. Protic acid employed for the reaction can be used as such or in mixture with a suitable solvent.
selected from alcohol such as methanol, ethanol, iso-propanol; ester such as ethyl acetate; ketone such as acetone, methyl isobutyl ketone, methyl ethyl ketone; ether such as isopropyl ether, methyl tert-butyl ether; halogenated solvent such as dichloromethane, chloroform and the like. Source of hydrochloric acid is not limited to aqueous hydrochloric acid, concentrated hydrochloric acid, solution of hydrogen chloride in suitable solvent selected from C_{1-10} alcohols like methanol, ethanol, isopropanol; C_{4-12} ester like ethyl acetate, C_{3-12} ketones like acetone, C_{4-12} ethers like isopropyl ether; aliphatic halogenated hydrocarbon like dichloromethane and the like. Solution of hydrogen chloride can be prepared by purging dry hydrogen chloride gas in a solvent. Similarly other acid can be employed as aqueous, concentrated or in mixture with solvents or any other suitable source of acid can be used for the condensation reaction. Reaction can be carried out in a suitable solvent which can be selected from C_{1-10} alcohol such as methanol, ethanol, isopropanol, n-butanol; C_{3-12} ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone; halogenated solvent such as dichloromethane, chloroform; C_{4-12} ether such as 1,2-dimethoxy ethane, 1,4-dioxane, diethyl ether, isopropyl ether, methyl tertiary butyl ether, tetrahydrofuran, 2-methyl tetrahydrofuran, cyclopentyl methyl ether, C_{4-12} ester such as ethyl acetate and the like or mixture thereof. Quantity of the condensing reagent used for the reaction can vary up to 6 mol equivalent. Preferably protic acid can be employed in catalytic amount or stoichiometric amount. Usually reaction can be carried out at ambient temperature to reflux temperature. It generally takes 2 hours for completion of reaction. Reaction monitoring can be performed by suitable chromatography techniques such as high performance liquid chromatography (HPLC), ultra pressure liquid chromatography (UPLC), thin layer chromatography (TLC) or gas chromatography (GC) and the like. After completion of the reaction, desired product can be isolated from the reaction mixture or insitu proceeded for further reaction. Specifically, desired product can be isolated from the reaction mixture by cooling reaction mixture and/or diluting the reaction mixture. Dilution can be performed by adding suitable solvent selected from alcoholic solvent such as methanol, ethanol, isopropanol, n-butanol and the like or mixture thereof or mixture with other solvents which includes halogenated solvents such as dichloromethane; ether such as tetrahydrofuran, methyl tertiary butyl ether; ketone; nitrile such as acetonitrile and the like. Resulting product can be isolated from the resulting mixture by using suitable techniques such as filtration, centrifugation and the like.

Product obtained from the reaction can be sunitinib free base or sunitinib salt depending upon the nature as well as on the quantity of condensing reagent used for the reaction. Whenever reaction is carried out using catalytic amount of condensing reagent such as protic acid, reaction mass can be optionally washed with a suitable base to remove extra acid, if present, to give sunitinib free base.
Alternatively, reaction can be carried out using stoichiometric to 6 mol equivalent of protic acid which yields corresponding sunitinib salts, which form other novel part of the invention.

Present invention provides novel salts of sunitinib with a protic acid selected from hydrochloric acid, hydrobromic acid, oxalic acid, lavulinic acid, salicylic acid, phosphoric acid, sulfuric acid, picric acid and the like, preferably sunitinib hydrochloride, sunitinib hydrobromide. Novel salts of sunitinib as described by the present invention can be amorphous or crystalline.

Sunitinib salt can be characterized by suitable spectroscopic techniques such as Infra-red spectroscopy (IR), nuclear magnetic spectroscopic (H-NMR and/or 13C-NMR), mass analysis, melting point and the like. Polymorphic nature of the sunitinib salt can be checked by the differential scanning calorimetric (DSC) and/or powder X-ray diffraction pattern (PXRD) and the like.

Sunitinib hydrochloride shows the powder X-ray diffraction pattern as shown in Figure 1. Sunitinib hydrochloride having a melting point falling in a range of 275 to 285 °C. Sunitinib hydrobromide is also analyzed by powder X-ray diffraction technique which displays X-ray diffraction pattern as shown in Figure 2. Sunitinib hydrobromide having a melting point falling in a range of 288 to 298 °C. Similarly, polymorphic nature and other characteristic of sunitinib salts can be characterized by any suitable technique in known in the art.

Sunitinib salts can be direct product of condensation reaction or can be alternatively prepared by the reaction of sunitinib free base with a suitable acid.

According to another embodiment, present invention provides a process for the preparation of sunitinib salt by reaction of sunitinib free base with a suitable acid.

Generally, sunitinib free base is treated with a suitable acid at a temperature of 10 °C to boiling point of the solvent system for a time period sufficient for the salt formation. Suitable acid can be selected from but not limited to hydrochloric acid, hydrobromic acid, oxalic acid, lavulinic acid, salicylic acid, phosphoric acid, sulfuric acid, picric acid and the like. Acid employed for the salt formation can be used as such or in mixture with a suitable solvent selected from alcohol, ester, ketone, ether, halogenated solvent, and the like. Source of hydrochloric acid is not limited to aqueous hydrochloric acid, concentrated hydrochloric acid, solution of hydrogen chloride in suitable solvent selected from Ci-io alcohols like methanol, ethanol, isopropanol,; C₄₋₁₂ ester like ethyl acetate, C₃₋₁₂ ketones like acetone, C₄₋₁₂ ethers like isopropyl ether; aliphatic halogenated hydrocarbon like dichloromethane and the like. Solution of hydrogen chloride can be prepared by purging dry hydrogen chloride gas in a solvent. Similarly other acid can be employed as aqueous, concentrated or in mixture with solvents or any other suitable source of acid can be used for the salt formation. Salt formation can be carried
out in the presence of a suitable solvent which includes water, alcohols, ketones, ethers, aliphatic or aromatic hydrocarbon, solvent, halogenated solvent, nitriles, esters and the like or mixture thereof. Sunitinib salt thus prepared can be isolated from the reaction mixture or can be in situ neutralized to form sunitinib free base. Preferably, sunitinib salt can be isolated from the reaction mixture by suitable techniques such as filtration, centrifugation, decantation and the like.

Sunitinib salt thus prepared by the process of present invention can be in isolated form or can be used in situ without isolation for the neutralization reaction with a suitable base to provide pure sunitinib.

Generally, process involves neutralization of sunitinib salt with a suitable base at a temperature of 0 to 30 °C for 0.5 hours to several hours, preferably at a temperature of 10 to 25 °C to 1 to 3 hours, more preferably till completion of the neutralization. Suitable base used for the neutralization can be organic or inorganic base. Sunitinib salts to be neutralized can be acid salt of sunitinib with acid selected from but not limited to protic acid selected from hydrochloric acid, hydrobromic acid, oxalic acid, lavulinic acid, salicylic acid, phosphoric acid, sulfuric acid, picric acid and the like. Suitable base employed for the neutralization reaction can be selected from any base known in the art that can serve the purpose of neutralization and can be selected depending upon nature and amount of acid to be neutralized. Specifically suitable base includes but not limited to organic bases such as ammonia, triethylamine, diisopropylethylamine and the like; or inorganic base can be selected from alkali or alkaline metal hydroxides, carbonates, bicarbonate, alkoxide thereof such as lithium, sodium and potassium hydroxide, carbonates, bicarbonate, alkoxide and the like. After completion of neutralization, sunitinib can be isolated from the reaction mixture or can be reacted in situ with malic acid to form sunitinib malate. Preferably sunitinib can be isolated from the reaction mixture by suitable techniques such as filtration, centrifugation and the like.

Sunitinib thus prepared can be optionally purified to enhance the purity and/or to minimize the impurities present in it. Any suitable purification method can be employed for purification of sunitinib, preferably sunitinib can be crystallized or slurry washed in a suitable solvent. Specifically, sunitinib can be stirred in a suitable solvent at a temperature of 0 to 150 °C for 1 to 48 hours. Preferably reaction mixture can be stirred at a temperature of 25 to 80 °C for 12 hours. Suitable solvent includes C₄₋₆ alcohol such as methanol, ethanol, n-butanol, isopropanol and the like or mixture thereof or mixture with other solvent selected from C₄₋₆ ether such as tetrahydrofuran, 2-methyl tetrahydrofuran, methyl tertiary butyl ether; halogenated solvents such as dichloromethane; ketone such as methyl isobutyl ketone; nitrile such as acetonitrile and the like. Thereafter, purified
product can be recovered from the resulting mixture using suitable techniques such as filtration, centrifugation and the like.

Sunitinib thus prepared can be converted to sunitinib malate by any method known in the art. Preferably sunitinib is converted to sunitinib malate crystalline form I.

Sunitinib can be converted to crystalline form I of sunitinib malate using methyl isobutyl ketone or a mixture of methyl isobutyl ketone with other solvents which forms another novel feature of the invention.

Generally, the process involves reaction of sunitinib in a solvent with malic acid at a temperature of 0 to 150 °C for 1 to 48 hours. Preferably, salt formation can be carried out at a temperature from 15 °C to 100 °C for 1 to 24 hours, more preferably at a temperature of 20 to 75 °C for 1 to 6 hours. Suitable solvent used for the salt formation can be selected from methyl isobutyl ketone or a mixture of methyl isobutyl ketone with other solvents which are not limited to methanol, methyl tertiary butyl ether, 2-methyl tetrahydrofuran, ethyl acetate and the like or mixture thereof. Malic acid used for the reaction is preferably L-malic acid. Sufficient amount of malic acid can be added to the reaction mixture so that whole of the sunitinib reacts with malic acid. After completion of salt formation, sunitinib malate crystalline form I can be isolated using suitable techniques such as filtration, centrifugation and the like.

Starting materials of formulae II and III used in present invention can be prepared by prior art method or can be procured from commercial sources. Preferably, formyl amide intermediate of formula III can be prepared by the method as described herein for reference.

Formyl amide intermediate of formula III can be prepared by the amidation of 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid of formula,

![Chemical structure](attachment:image)

using N,N-diethylaminoethylamine in the presence of a coupling agent.

Specifically, process involves amidation of 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid with N,N-diethylaminoethylamine in the presence of coupling agent at a temperature of -20 to 120 °C for 1 to 24 hours, preferably till completion of reaction. Coupling agent used for the reaction can be 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride with or without additives such as hydroxybenzotriazole and the like. Preferably, process involves addition of a suitable base in addition to coupling agent. Suitable base can be selected from organic base such as tertiary amine such as triethylamine, diisopropyl ethyl amine and the like; or inorganic base can be selected from
alkali or alkaline metal hydroxide, carbonates, bicarbonates, silyl amide or hydride thereof such as lithium carbonate, sodium carbonate, potassium carbonate, lithium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydride, lithium hydride, potassium bis(trimethyl)silylamide, sodium bis(trimethyl)silylamide, lithium bis(trimethyl)silylamide, lithium bicarbonate and the like. Solvent employed for the reaction is not critical and can be selected from ether such as tetrahydrofuran, 2-methyl terahydrofuran, methyl tert-butyl ether, isopropyl ether, dioxane, 1,2-dimethoxyethane and the like or mixture thereof. Usually, reaction mixture is stirred for 2 to 18 hours at temperature of 0 to 100 °C. Reaction completion can be monitored by HPLC, TLC, UPLC or GC. After completion of reaction, a suitable base is added to the reaction mixture followed by extraction with water immiscible solvent, in which desired product has more solubility. Suitable base can be selected from alkali metal carbonate or bicarbonate thereof such as sodium bicarbonate, sodium carbonate and the like. Water immiscible solvent used for extraction can be selected from halogenated solvent such as dichloromethane; alcohols such as methanol, ethanol, iso-propanol, n-butanol or mixture thereof in any suitable proportions. Resulting organic solvent can be optionally washed with water followed by solvent removal by any suitable technique known in the art such as distillation, evaporation and the like, to give desired product.

Resulting compound can be optionally purified to enhance purity and/or to remove impurity in the product. Any suitable purification method can be employed such as slurry wash, crystallization, base acid treatment and the like.

Specifically, formyl intermediate of formula III can be stirred with a suitable solvent at a temperature of -10 to 120 °C for 10 minutes to 8 hours. Solvent can be selected from ether such as methyl tert-butyl ether, isopropyl ether; aliphatic hydrocarbon such as cyclohexane, n-heptane and the like. Product can be isolated from the mixture by removal of solvent using suitable techniques such as filtration, centrifugation and the like.

Alternatively, formyl intermediate of formula III can be purified by treatment with a base followed by extraction using water immiscible solvent.

Specifically, process involves treatment of formyl intermediate of formula III in a solvent with a suitable base at a temperature of -10 to 120 °C followed by addition of water immiscible solvent. Reaction mixture is stirred for 10 minutes to 8 hours. Preferably, reaction mixture is stirred for 1 to 3 hours. Solvent used can be selected from water and the like. Suitable base employed can be selected from alkali or alkaline metal carbonate or bicarbonate such as sodium bicarbonate, potassium bicarbonate and the like. Water immiscible solvent selected from halogenated solvent such as dichloromethane; alcohol such as methanol, ethanol, iso-propanol, n-butanol or mixture
thereof in any suitable proportion. Purified product can be isolated from the mixture by solvent removal using suitable techniques such as distillation, evaporation and the like.

Purification of intermediate of formula III by either of process as described herein can be optionally repeated individually or combined with other till the product of desired purity achieved.

Further, 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid can be prepared by any method known in art, specifically by the hydrolysis of corresponding ester intermediate of formula,

\[ \text{OR} \]

wherein \( R \) is selected from alkyl group such as methyl, ethyl and the like.

Specifically, process involves treatment of ester intermediate in a solvent with a suitable base at a temperature of 0 to 120 °C for few minutes to several hours, preferably till completion of hydrolysis.

Suitable base employed for the reaction include alkali metal hydroxide, carbonates, bicarbonate such as potassium hydroxide, sodium hydroxide and the like. Solvent used can be selected from water, alcohol such as methanol, ethanol, ethanol, iso-propanol, n-butanol and the like or mixture thereof. After completion of reaction, reaction mixture can be optionally cooled to 5 °C to ambient temperature followed by washing with water immiscible solvent selected from ester such as ethyl acetate; ether such as isopropyl ether, methyl tert-butyl ether; aromatic hydrocarbon such as toluene; halogenated solvent such as dichloromethane and the like. 5-Formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid can be isolated from resulting aqueous layer by acidification using suitable acid. Acid can be selected from hydrochloric acid, phosphoric acid, sulfuric acid, hydrobromic acid, carboxylic acid, alkane sulfonic acid and the like. Product, thus precipitated, can be isolated from the mixture by a suitable techniques such as filtration, centrifugation and the like.

Acid intermediate, thus prepared, can be optionally purified using base-acid treatment to enhance purity of product and/or to remove impurities.

Specifically, process involves treatment of acid intermediate with a suitable base at a temperature of 0 to 120 °C for 30 minutes to 10 hours, preferably till clear solution is obtained. Solvent employed for the reaction is not critical and can be selected from water; alcohol such as methanol and the like. Suitable base can be selected from alkali or alkaline metal hydroxide such as potassium hydroxide, sodium hydroxide and the like. Reaction mixture is charcoalized and then acidified to precipitate acid intermediate. Purified product can be isolated from the mixture using suitable techniques such as filtration, centrifugation and the like.
Major advantage realized in the present invention is that it avoids the use of expensive and toxic reagents during preparation of sunitinib and employs use of acidic reagents which proved to be highly effective as well as economically suitable for the industrial synthesis of sunitinib. Present invention also provides novel salts of sunitinib which are highly advantageous in yielding pure sunitinib free base. Further present invention provides an efficient process for preparation of pure sunitinib malate form I consistently.

Having described the invention with reference to certain preferred aspects, other aspects will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples describing in detail by the preparation of the compounds of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

**Examples:**

Example 1: Preparation of 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid

To a stirred suspension of 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid ethyl ester (1.0 kg, 5.122 mol) in aqueous methanol (5.8 L containing 5.0L water & 0.8L methanol), potassium hydroxide (1.15 kg, 20.5 mol) was added at ambience, and the reaction mixture was heated to 75-85 °C for 6 hours. After completion of reaction, reaction mixture was cooled to ambient temperature and washed with ethyl acetate (2 x 2.5 L) followed by layer separation. Aqueous layer was cooled to 0-5 °C and quenched with 2 N hydrochloric acid till pH 4-5. The resulting solid was filtered, washed with demineralized water (2 x 2.5 L) and suck dried. Demineralized water (5 L) was added to the obtained solid and mixture was cooled to 0-5 °C followed by addition of potassium hydroxide (1.5 kg, 26.75 mol) to obtain clear solution. Activated carbon (0.15 kg) was added to the solution at 0-5 °C and then mixture was heated to 25-30 °C. Mixture was stirred for 30 minutes, filtered through celite, washed with demineralized water (0.5 L). All aqueous filtrates were combined, cooled to 0-5 °C and quenched with 2N hydrochloric acid (4 L). The solid, thus formed, was filtered, washed with demineralized water (2 x 2.5 L) and dried in vacuum to give 0.788 kg of title compound having purity of 99.4 % by HPLC.

Example 2: Preparation of 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide

To a stirred slurry of 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (1.0 kg, 5.98 mol), hydroxybenzotriazole (0.969 kg), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (1.6 kg, 8.34 mol) in tetrahydrofuran (15L) at 25-30 °C, triethylamine (1.162 kg, 11.48 mol) was added and mixture was stirred for 30 minutes. N,N-diethyl ethylenediamine (1.902 kg, 16.37 mol) was added
to resulting mixture at 25-30 °C and stirred for 5-6 hours at 25-30 °C. After completion of reaction, reaction mixture was cooled to ambient followed by addition of saturated 15 % sodium bicarbonate solution (10 L ) till pH = 9-10. Resulting product was extracted with a mixture of dichloromethane-methanol (5% methanol, 3 x 10 L). The organic layers were combined, washed with demineralized water (2 x 5L). Solvent was distilled off from resulting organic layer. Methyl tert-butyl ether (5 L) was added to resulting product and stirred at 45-50 °C for 30 minutes. Mixture was cooled to ambient temperature and resulting product was filtered. Filtered solid was washed with methyl tert-butyl ether (5L) and dried. Water (10 L) was added to thus obtained solid followed by addition of sodium bicarbonate (568 g), and a mixture of dichloromethane-methanol (10% methanol, 10 L).

Resulting mixture was stirred at ambient temperature for 1 hour. The organic layer was separated, washed with demineralised water (2 x 5 L) and distilled off. Cyclohexane (5 L) was added to the crude mass, stirred for 30 minutes, filtered and dried in vacuum oven at 75-80 °C for 24 hours to give 0.524 kg of title compound having purity 99.83 % by HPLC.

**Example 3: Preparation of sunitinib**

**Method A**: A mixture of 5-fluoro-1,3-dihydro-indol-2-one (1 g), 5-formyl-2,4-dimethyl-l H-pyrrole-3-carboxylic acid-(2-diethylaminoethyl) amide (1.8 g), methanol (20 ml) and methanolic hydrochloride (10 %, 0.3 ml) was refluxed for 2 hours, followed by cooling to room temperature. The reaction mixture was diluted with methanol (20 ml). Reaction mixture was filtered and washed with methanol (10 ml). Resulting product was neutralized with aqueous ammonia (25 %, 3 ml) and stirred for 30 minutes. The product thus obtained was filtered, washed with water (10 ml) and dried to give the 2.1 g of the title compound having purity 99 % by HPLC.

**Method B**: A mixture of 5-fluoro-1,3-dihydro-indol-2-one (1 g), 5-formyl-2,4-dimethyl-l H-pyrrole-3-carboxylic acid-(2-diethylaminoethyl) amide (1.8 g), methanol (20 ml) and aqueous hydrobromide (47 %, 0.1 ml) was refluxed for 2 hours, followed by cooling to room temperature. The reaction mixture was diluted with methanol (20 ml). Reaction mixture was filtered and washed with methanol (10 ml). Resulting product was neutralized with aqueous ammonia (25 %, 3 ml) and stirred for 30 minutes. The product thus obtained was filtered, washed with water (10 ml) and dried to give the 2.0 g of the title compound having purity 97.6 % by HPLC.

**Method C**: A mixture of 5-fluoro-1,3-dihydro-indol-2-one (5 g), 5-formyl-2,4-dimethyl-l H-pyrrole-3-carboxylic acid-(2-diethylaminoethyl) amide (9.18 g), sodium bisulfite (6.9 g) and ethanol (50 ml) was refluxed for 24 hours followed by cooling to room temperature. The reaction mixture was diluted with ethanol (20 ml). Solid thus obtained was filtered, washed with ethanol (20 ml) and dried to give 10.2 g of the title compound having purity 98 % by HPLC.
Example 4: Preparation of sunitinib

Step I: Preparation of sunitinib hydrochloride

A mixture of 5-fluoro-1,3-dihydro-indol-2-one (1 g), 5-formyl-2,4-dimethyl-1'H'-pyrrole-3-carboxylic acid-(2-diethylarninoethyl) amide (1.8 g), methanol (20 ml) and methanolic hydrochloride (10 %, 4 ml) was refluxed for 2 hours, followed by cooling to room temperature. The reaction mixture was diluted with methanol (20 ml). Solid thus obtained was filtered, washed with methanol (10 ml) and dried to give 2.5 g of title compound.

Step II: Preparation of sunitinib

Resulting hydrochloride salt was neutralized with aqueous ammonia (25 %, 5 ml) and stirred for 30 minutes. The product thus obtained was filtered, washed with water (10 ml) and dried to give 2.2 g of the title compound having purity 98.8 % by HPLC.

Example 5: Preparation of sunitinib

Step I: Preparation of sunitinib hydrobromide

A mixture of 5-fluoro-1,3-dihydro-indol-2-one (1 g), 5-formyl-2,4-dimethyl-1'H'-pyrrole-3-carboxylic acid-(2-diethylaminoethyl) amide (1.8 g), methanol (20 ml) and aqueous hydrobromide (47 %, 1.7 ml) was refluxed for 2 hours, followed by cooling to room temperature. The reaction mixture was diluted with methanol (20 ml). Solid thus obtained was filtered, washed with methanol (10 ml) and dried to give 2.5 g of title compound.

Step II: Preparation of sunitinib

Resulting hydrobromide salt was neutralized with aqueous ammonia (25 %, 5 ml) and stirred for 30 minutes. The product thus obtained was filtered, washed with water (10 ml) and dried to give the 2.3 g of the title compound having purity 97.2 % by HPLC.

Example 6: Preparation of sunitinib hydrochloride

Method A: To a stirred slurry of sunitinib free base (1 g) in demineralised water (10 ml), concentrated hydrochloric acid was added and mixture was stirred for 15 hours at ambient temperature. Resulting product was filtered, washed with water and dried in air oven at 50 °C for 4 hours to give 1 g of the title compound having melting point: 279-28 1.7 °C.

Method B: To a stirred solution of 2N hydrochloric acid (5 ml), sunitinib free base (2 g) was added and stirred for 2 hours at ambient temperature. Resulting product was filtered, washed with methanol (3 ml) and dried to give 2.2g of title compound having purity 97.12 % by HPLC.

Example 7: Preparation of sunitinib hydrobromide

Method A: To a stirred slurry of sunitinib free base (1 g) in demineralised water (10 ml), concentrated hydrobromic acid was added and mixture was stirred for 15 hours at ambient temperature. Resulting
product was filtered, washed with water and dried to give 1 g of the title compound having melting point: 293.4-295 °C.

**Method B**: To a stirred solution of 48% hydrobromic acid (5 ml) and water (1 ml), sunitinib free base (2 g) was added and stirred for 2 hours at room temperature. Solid thus obtained was filtered, washed with methanol (3 ml) and dried to give 2.3 g of title compound having purity 96.05 % by HPLC.

**Example 8: Preparation of sunitinib phosphate**

To a stirred slurry of sunitinib free base (2 g) in methyl isobutyl ketone (15 ml), phosphoric acid (0.044 g) was added and stirred for 2 hours at 50 °C. The precipitate was then filtered, washed with methyl isobutyl ketone (3 ml) to give 2.4 g of title compound having purity 98.97 % by HPLC.

**Example 9: Preparation of sunitinib salicylate**

To a slurry of sunitinib free base (2 g) in methyl isobutyl ketone (15 ml), salicylic acid (0.76 g) was added and stirred for 2 hours at 50 °C. Solid thus obtained was filtered, washed with methyl isobutyl ketone (3 ml) to give 2.5 g of title compound having purity 94.65 % by HPLC.

**Example 10: Purification of sunitinib**

Sunitinib (5 g) was slurred with ethanol (50 ml) for 2 hours at 60-70° C, followed by cooling to room temperature. Resulting product was filtered and dried to give 4.6 g of title compound having purity 99.6 % by HPLC.

**Example 11: Preparation of crystalline form I of sunitinib L-malate**

**Method A**: Sunitinib (1.3 g) was taken in methyl isobutylketone (39 ml) and L-Malic acid (0.472 g) was added to the above mixture. Reaction mixture was stirred for 3 hours at room temperature. The product thus obtained was filtered and dried to give 1.3 g of title compound having purity 99.6 % by HPLC.

**Method B**: Sunitinib (1 g) was added to a stirred mixture of methyl isobutylketone (10 ml) and methyl tertiary butyl ether (10 ml) followed by addition of L-malic acid (0.360 g). Reaction mixture was stirred for 2 hours at room temperature. The product thus obtained was filtered and dried to give 1.2 g of title compound.

**Method C**: Sunitinib (1 g) was added to a mixture of methyl isobutylketone (10 ml) and ethyl acetate (10 ml) followed by addition of L-malic acid (0.360 g). Reaction mixture was stirred for 2 hours at room temperature. The product thus obtained was filtered and dried to give 1.1 g of title compound.

**Method D**: To a mixture of sunitinib (1 kg) in methyl isobutylketone (15 L), L-Malic acid (359 g) was added and heated to 50-55 °C for 2 hours. Resulting product was filtered and washed with ethanol (2 x 5 L). Solid, thus obtained, was dried in vacuum at 75-80 °C (150mmHg) to give 1.27 kg of title compound.
We Claim:

1. A process for the preparation of crystalline form I of sunitinib malate of formula I,

\[
\begin{align*}
\text{F} & \quad \text{H}_3\text{C} \\
\text{HN} & \quad \text{O} \\
\text{HN} & \quad \text{CH}_3 \\
\end{align*}
\]

Formula I

comprising the steps of:

a) providing sunitinib in methyl isobutyl ketone or a mixture of methyl isobutyl ketone with other solvents;

b) adding L-malic acid to the above mixture and stirred for sufficient period of time to give form I of sunitinib malate;

c) isolating form I of sunitinib malate there from.

2. The process according to claim 1, wherein in step a) solvent is selected from methanol, methyl tertiary butyl ether, 2-methyl tetrahydrofuran, ethyl acetate and the like or mixture thereof.

3. The process according to claim 1, wherein step b) is stirred at a temperature of 15 to 100 °C for 1 to 24 hours.

4. The process according to claim 3, wherein stirring is preferably carried out at a temperature of 20 to 75 °C for 1 to 6 hours.

5. A process for the preparation of sunitinib or pharmaceutically acceptable salts thereof, comprising the steps of:

a) condensing an indole intermediate of formula II,

\[
\begin{align*}
\text{F} & \quad \text{N} \\
\end{align*}
\]

Formula II

with formyl amide intermediate of formula III,

\[
\begin{align*}
\text{O} & \quad \text{H}_3\text{C} \\
\text{HN} & \quad \text{N} \\
\text{HN} & \quad \text{CH}_3 \\
\end{align*}
\]

Formula III

in the presence of a suitable condensing reagent;

b) optionally, neutralizing the product obtained in step a) with a suitable base; and

c) isolating sunitinib from the reaction mixture.
6. The process according to claim 5, wherein in step a) condensing agent is selected from protic acid, phenols, substituted phenols, or acid salts.

7. The process according to claim 6, wherein protic acid is selected from hydrochloric acid, hydrobromic acid, oxalic acid, lavulinic acid, salicylic acid, phosphoric acid, sulfuric acid, picric acid and the like.

8. The process according to claim 6, wherein acid salt is selected from sodium bisulfite; ammonium picrate and the like.

9. The process according to claim 6, wherein acid is used as such or in mixture with a suitable solvent selected from alcohol such as methanol, ethanol, iso-propanol; ester such as ethyl acetate; ketone such as acetone, methyl isobutyl ketone, methyl ethyl ketone; ether such as isopropyl ether, methyl tert-butyl ether; halogenated solvent such as dichloromethane, chloroform and the like.

10. The process according to claim 5, wherein in step b) suitable base is selected from organic base or inorganic base such as alkali or alkaline metal hydroxides, carbonates, bicarbonate, alkoxide thereof.

11. The process according to claim 10, wherein in organic base is selected from such as ammonia, triethylamine, diisopropylethylamine and the like.

12. The process according to claim 10, wherein in inorganic base is selected from such as alkali or alkaline metal hydroxides, carbonates, bicarbonate, alkoxide thereof.

13. Protic acid salts of sunitinib.

14. The compound according to claim 13, wherein protic acid is selected from hydrochloric acid, hydrobromic acid, oxalic acid, lavulinic acid, salicylic acid, phosphoric acid, sulfuric acid, picric acid and the like.

15. The compound according claim 13, wherein compound is amorphous.

16. The compound according claim 13, wherein compound is amorphous.

17. The compound according to claim 14, wherein protic acid is hydrochloric acid.

18. The compound according to claim 14, wherein protic acid is hydrobromic acid.

19. The compound according to claim 14, wherein protic acid is salicylic acid.

20. The compound according to claim 14, wherein protic acid is phosphoric acid.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

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: C07D403/06, A61K31/404, A61P35/00

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 practicable, search terms used)

WPI, EPODOC, CNPAT, CNKI, CAPLUS, REGISTRY, CA: sunitinib, indol+, malate, malic acid, crystal+, methyl isobutyl ketone,
Rii: 108-10-1, 557795-19-4, 326914-13-0, 356068-86-5, 56341^11-4

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>CN1439005A (SUGEN, INC., et al.) 27 Aug. 2003(27.08.2003) the last paragraph of page 17 to the first paragraph of page 18 in the description, example 80</td>
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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
  "E " Earlier application or patent but published on or after the international filing date
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Date of the actual completion of the international search: 20 Feb. 2012(20.02.2012)

Date of mailing of the international search report: 15 Mar. 2012 (15.03.2012)

Name and mailing address of the ISA/CN
The State Intellectual Property Office, the P.R.China
6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088
Facsimile No. 86-10-62019451

Form PCT/ISA /210 (second sheet) (July 2009)

Authorized officer
DAI, Nianzhen
Telephone No. (86-10)82246692
### DOCUMENTS CONSIDERED TO BE RELEVANT

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This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☑ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.
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Form PCT/ISA/210 (patent family annex) (July 2009)
Continuation of: Box No. III   Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

The international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention").

This International Searching Authority found multiple inventions in this international application, as follows:

I: Claims 1-4 are directed to processes for preparation of crystalline form I of sunitinib malate.
II: Claims 5-12 are directed to processes for preparation of sunitinib or pharmaceutically acceptable salts thereof.
III: Claims 13-20 are directed to salts of sunitinib.

The technical feature in common among the above-mentioned three groups of the inventions is sunitinib. However, sunitinib is well-known in the art and can not become a novel and inventive contribution over the prior art. So, the above-mentioned three groups of the inventions are not linked by the same or corresponding special technical features and do not meet the requirements of unity of invention as defined in Rule 13.1.

Continuation of: CLASSIFICATION OF SUBJECT MATTER:
C07D403/06(2006.01)i
A61K3 1/404(2006.01)i
A61P35/00(2006.01)i