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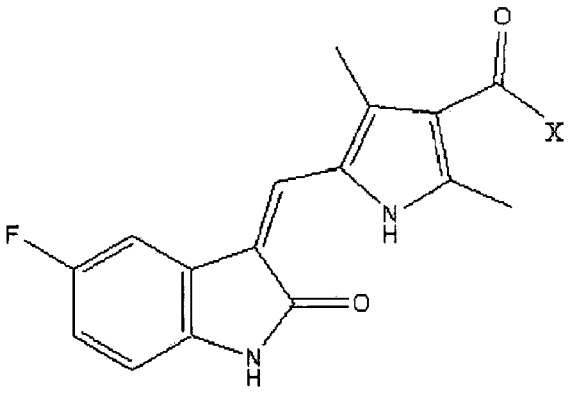
(54) **Title**: PROCESSES FOR PREPARING SUNITINIB AND SALTS THEREOF



(I)

(57) **Abstract**: Methods for preparing sunitinib or salts thereof are described using novel intermediates of formula (I); wherein X is either Cl or imidazole.

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PROCESSES FOR PREPARING SUNITINIB AND SALTS THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

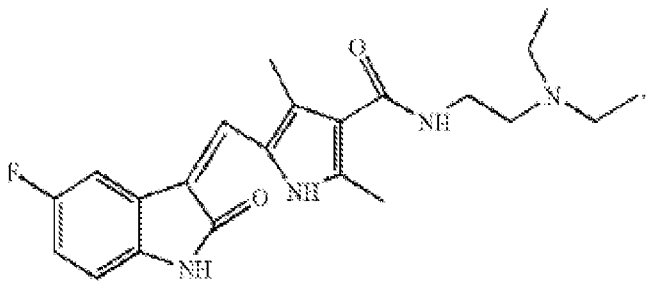
[0001] This application claims the benefit of U.S. Provisional Patent Application Ser. Nos. 61/113,044, filed November 10, 2008; 61/097,592, filed September 17, 2008; 61/094,341, filed September 4, 2008; 61/088,998, filed August 14, 2008; 61/082,681, filed July 22, 2008; 61/082,405, filed July 21, 2008; and 61/041,103, filed March 31, 2008.

FIELD OF INVENTION

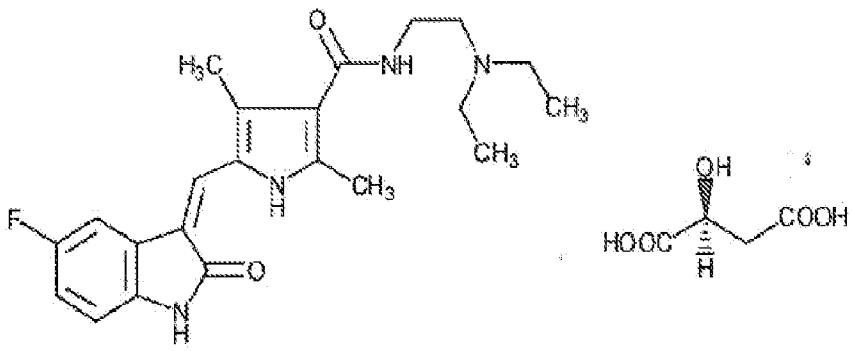
[0002] The present invention relates to a process for the preparation of Sunitinib and salt thereof.

BACKGROUND OF THE INVENTION

[0003] Sunitinib base ("Sunitinib") of the following formula:



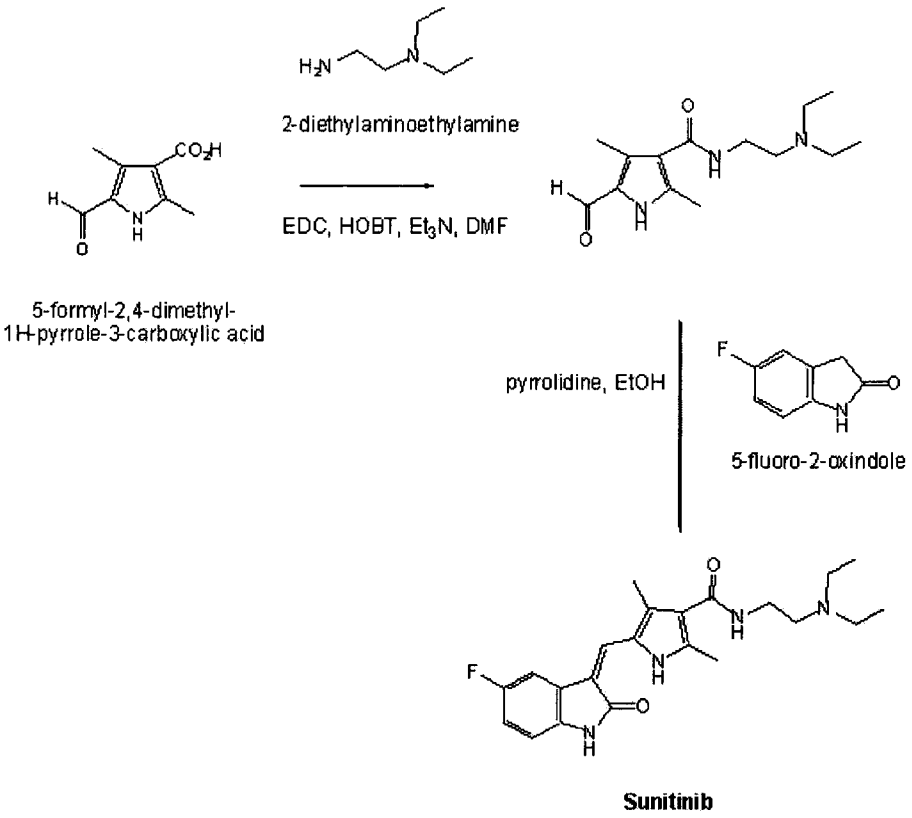
is an intermediate for Sunitinib salts, such as Sunitinib malate of the following formula:



[0004] Sunitinib malate is marketed under the trade name Sutent® by Pfizer. It is an oral, multi-targeted tyrosine kinase inhibitor used for treatment of various types of cancer.

[0005] Sunitinib and salts thereof, process of preparation thereof and the use of these salts are disclosed in US patent No. 6,573,293 B2 ("US '293").

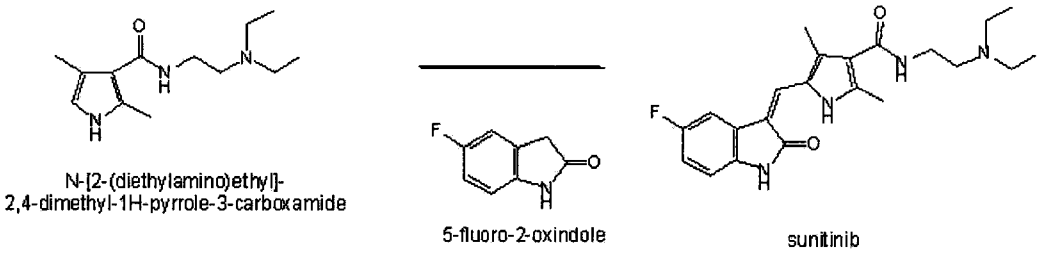
[0006] The preparation of Sunitinib disclosed in US '293 is done by amidation of 5-formyl-2, 4-1*H*-pyrrole-3-carboxylic acid to obtain 5-formyl-2, 4-1*H*-pyrrole-3-carboxylic acid (2-diethylaminoethyl) amide in a yield of 43%. The obtained amide is then condensed with 5-fluoro-1, 3-dihydro-indol-2-one in EtOH in the presence of pyrrolidine, obtaining Sunitinib. The process can be illustrated in the following scheme:



Scheme 1

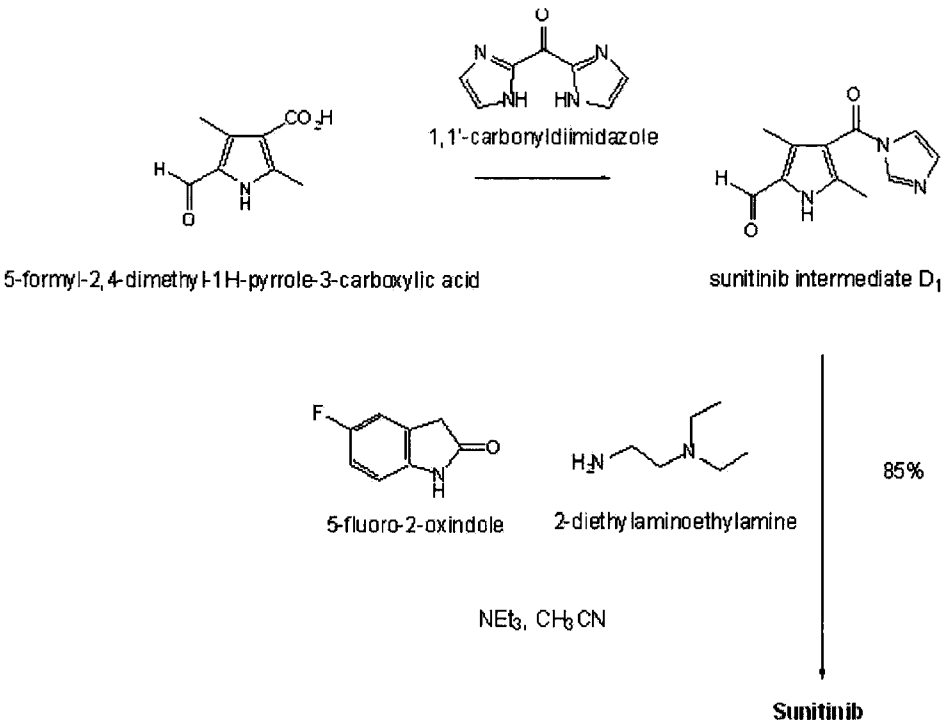
[0007] The amidation reaction in US '293 is performed on an activated carboxylic acid derivative. According to Journal of Organic Chemistry, 2003, 68, 6447, this reaction leads also to the formation of by-products. In addition, the amide coupling reagents, which are used in US '293 are toxic, dangerous and expensive reagents.

[0008] US 2006/0009510 (US '510) and Journal of Organic Chemistry, 2003, 68, 6447 disclose an alternative synthesis for the preparation of Sunitinib by reacting N-[2-(diethylamino) ethyl]-2, 4-dimethyl-1H-pyrrole-3-carboxamide with 5-fluoro-2-oxindole, in a yield of 74%, in the presence of acetonitrile and Vislmeier reagent, as described in the following scheme:



Scheme 2

[0009] US Patent No. 7,119,209 also discloses an alternative process for the preparation of Sunitinib by first activation of the pyrrole moiety as imidazole derivative, which is then used in the second step for the in situ preparation of the amide, as described in the following scheme:

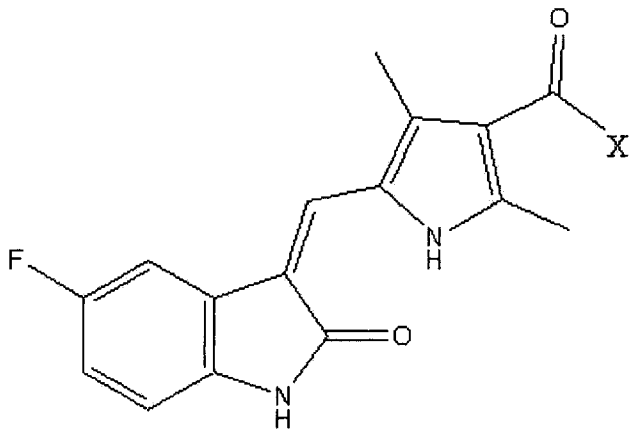


Scheme 3

[0010] There is a need in the art for an improved process for the preparation of Sunitinib and salts thereof which is also suitable for industrial scale.

SUMMARY OF THE INVENTION

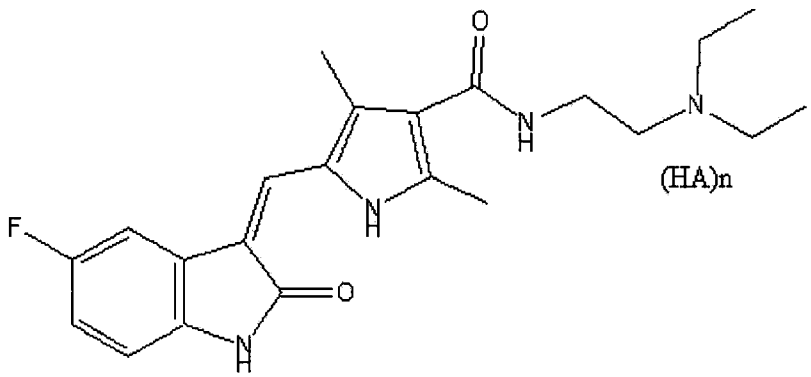
[0011] In one embodiment, the present invention encompasses 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-3Z-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carbonyl substitute of the following formula 1;



1

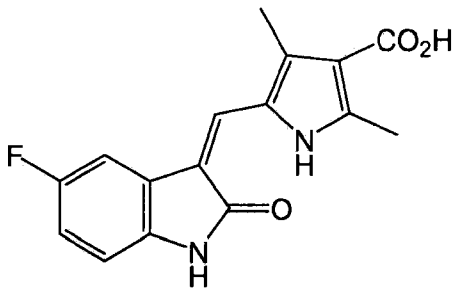
wherein X is either Cl or imidazole.

[0012] In another embodiment, the present invention encompasses the preparation of sunitinib and salts thereof of the following formula:



from the compound of formula 1, wherein n is either 0 or 1, HA is a diacid, preferably, malic acid.

[0013] In another embodiment, the present invention encompasses a process for preparing 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3Z-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carbonyl substitute of formula 1 comprising reacting 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 of the following structure:

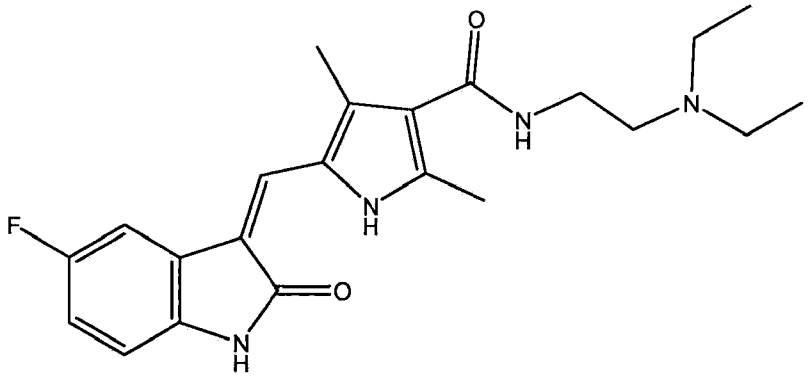


4

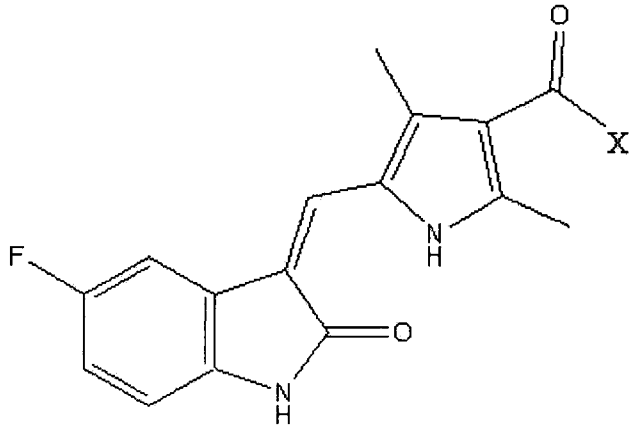
either with chlorinating agent or with 1, 1- carbonyldiimidazole.

[0014] In another embodiment, the present invention encompasses a process for preparing sunitinib and salts thereof comprising preparing 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3Z-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carbonyl substitute of formula 1 according to the process of the present invention, and converting it to sunitinib and salts thereof. Preferably, the sunitinib salt is sunitinib malate.

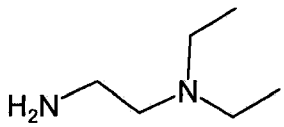
[0015] In another embodiment, the present invention encompasses a process for preparing sunitinib having the following structure:



comprising reacting the compound of formula 1:



with 2-diethylaminoethylamine of formula 3 of the following structure



3

[0016] In yet another embodiment, the present invention encompasses a process for preparing sunitinib salts comprising, preparing sunitinib according to the process of the present invention, and converting it to sunitinib salt. Preferably, the sunitinib salt is sunitinib malate.

BRIEF DESCRIPTION OF THE FIGURES

[0017] Figure 1 shows a powder XRD pattern of crystalline Form 1 of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4.

[0018] Figure 2 shows a FTIR spectrum of crystalline Form 1 of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4.

[0019] Figure 3 shows a powder XRD pattern of crystalline Form 2 of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4.

[0020] Figure 4 shows a FTIR spectrum of crystalline Form 2 of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4.

[0021] Figure 5 shows a powder XRD pattern of crystalline Form 3 of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4.

[0022] Figure 6 shows a FTIR spectrum of crystalline Form 3 of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4.

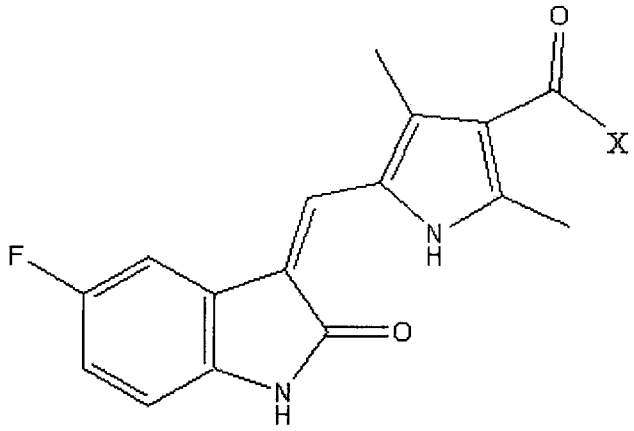
[0023] Figure 7 shows a powder XRD pattern of crystalline Form 4 of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4.

[0024] Figure 8 shows a FTIR spectrum of crystalline Form 4 of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4.

[0025] Figure 9 shows a PXRD pattern of pyrrolidinium salt of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid.

DETAILED DESCRIPTION OF THE INVENTION

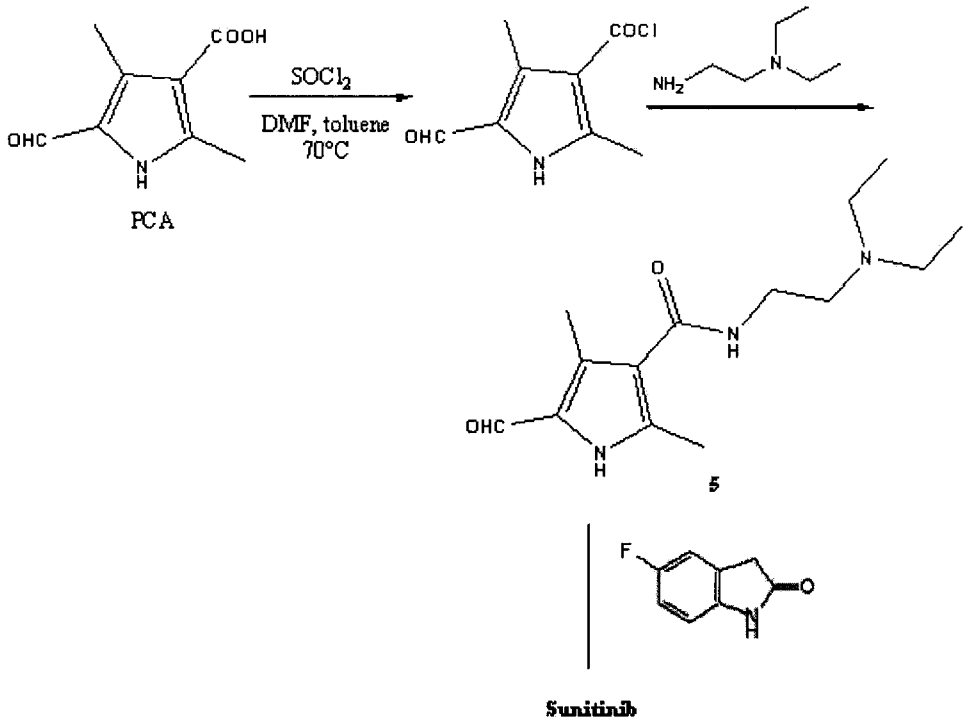
[0026] The present invention offers processes for the preparation of sunitinib and salts thereof. Preferred embodiments of the invention are capable of achieving higher yields compared to known processes, such as via a new intermediate of the following structure:



1

wherein X is either Cl or imidazole. The preparation of the compound of formula 1, is performed by first conducting a condensation reaction providing the carboxylic acid of formula 4, and then chlorinating it or reacting it with 1, 1- carbonyldiimidazole to obtain 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-3Z-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carbonyl substitute of the following formula 1. Then, the obtained formula 1 is reacted with 2-diethylaminoethylamine of formula 3. Preferably, Sunitinib is produced in a yield of about 80% or greater, preferably at least 82%, and/or purity of at least 99.5% when X is Cl. Preferably, Sunitinib is produced in a yield of about 90% or greater, preferably at least 93%, and/or purity of at least 98% when X is imidazole.

[0027] However, when the chlorination is done before the condensation reaction, as described in the following scheme:



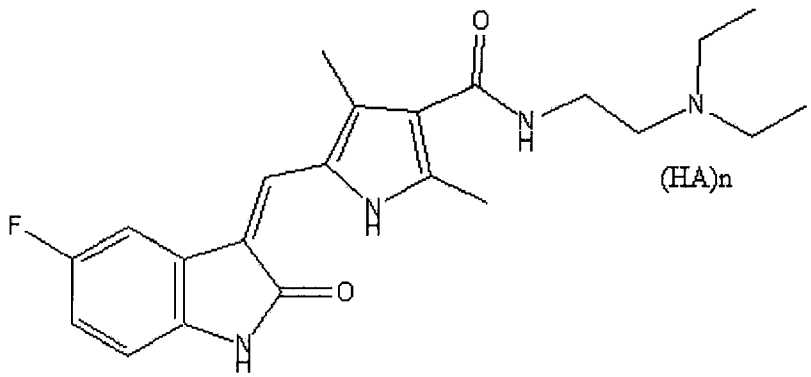
about 48% of the starting PCA remains unreacted. See example 12. In addition, when the process is further continued, by performing the amidation reaction on the mixture containing PCA and its chlorinated derivatives, the compound of formula 5 is formed in a very low yield (3%). See example 12.

[0028] When X is Cl, the compound of formula 1 refers to 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-3Z-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carbonyl chloride, designated formula 1a. 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3Z-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carbonyl chloride can be characterized by data selected from a group consisting of ^{1}H NMR (DMSO-d6, 400 MHz, 298 K): δ13.84 (s, 1H), 11.03 (s, 1H), 7.78 (dd, J 9.4,2.5 Hz, 1H), 7.69 (s, 1H), 6.90 (ddd, J 9.4,8.5,2.5, 1H), 6.83 (dd, J 8.5,4.6. 1H), 2.51 (s, 3H), 2.48 (s, 3H); ^{13}C-NMR (DMSO-d6, 100.6 MHz, 298 K): δ 170.0, 166.6, 158.7, 141.3, 135.2, 133.8, 127.4, 126.5, 125.1, 116.1, 114.7, 113.1; FTIR: 3168, 3043, 1739, 1676, 1570, 1480,1421,1329, 1195, 1151, 1037, 821, 800; MS: m/z 301, which correspond to (M+H)+ and combination thereof.

[0029] When X is imidazole, the compound of formula 1 refers to 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-3Z-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-(carbonyl-1-imidazole), designated formula 1b. 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3Z-

ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-(carbonyl- 1-imidazole) can be characterized by data selected from a group consisting of ^{1}H NMR (DMSO-d6, 400 MHz, 298 K): δ 13.99 (s, 1H), 11.03 (s, 1H), 8.18 (s, 1H), 7.78 dd, J 9.3,2.5 Hz, 1H), 7.75 (s, 1H), 7.64 (m, 1H), 7.13 (bs, 1H), 6.96 (td, J 9.0,2.5 Hz, 1H), 6.85 (dd, J 8.4,4.5 Hz, 1H), 2.31 (s, 3H), 2.30 (s, 3H); ^{13}C-NMR (DMSO-d6, 100.6 MHz, 298 K): δ 170.0, 162.8, 158.8, 127.1, 117.7, 113.7, 110.8, 107.0, 13.8, 10.9; FTIR: 3106, 3047, 2829, 1658, 1570, 1478,1416,1334, 1200, 1153, 867, 803; GC/MS: at m/z 350, the ion has 2 main fragmentations m/z 283 and m/z 68 and combination thereof.

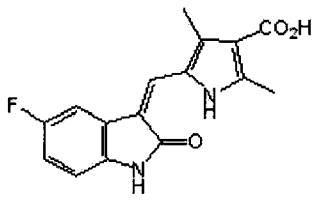
[0030] The compound of formula 1 can be used to prepare sunitinib and salts thereof having the following structure:



wherein, n is either 0 or 1, HA is a diacid, preferably, malic acid.

[0031] When n is 0, the above formula corresponds to sunitinib base ("Sunitinib"). When n is 1, the above formula corresponds to sunitinib salt, preferably, sunitinib malate.

[0032] Initially, the process comprises the preparation of formula 1. The process can be illustrated by the following scheme:



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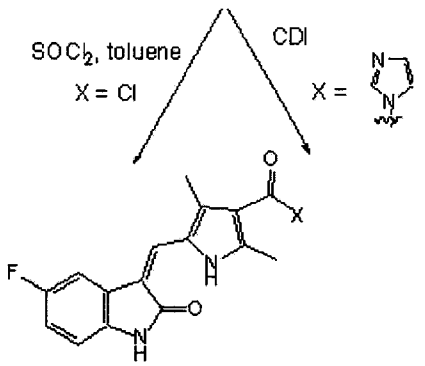
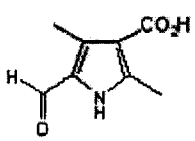


1
X= Cl or imidazole

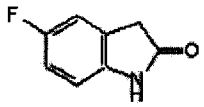
Scheme 5

wherein, the carboxylic moiety reacts with chlorinating agent or with 1, 1-carbonyldiimidazole ("CDI"). The process comprises reacting 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 either with chlorinating agent or with 1, 1- carbonyldiimidazole. Preferably, the chlorinating agent is either thionylchloride or oxalylchloride, more preferably, thionylchloride.

[0033] In one embodiment, 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 is prepared by a process comprising reacting 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (PCA) of the formula:



and 5-fluoro-1, 3-dihydro-indol-2-one (FDI) of the formula:



and pyrrolidone, and adjusting the pH to acidic pH at a temperature of about 25°C to about 70°C to obtain a suspension.

[0034] Preferably, the reaction comprises combining 5-formyl-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid (PCA), 5-fluoro-1, 3-dihydro-indol-2-one (FDI) and the solvent to obtain a mixture. Preferably, this mixture is combined with pyrrolidine and a second amount of solvent to obtain a suspension.

[0035] Preferably, the solvent is selected from a group consisting of ethanol, methanol and mixture thereof.

[0036] Preferably, the suspension is stirred for a period of about 5 minutes to about 20 minutes, more preferably, for a period of about 10 minutes to about 15 minutes to obtain a solution.

[0037] Further, the solution may then be heated to facilitate the reaction. Preferably, heating is done to a temperature of about 40°C to about 70°C more preferably, of about 45°C to about 55°C, most preferably, at about 50°C.

[0039] Preferably, heating is done for a period of about 0.5 hours to about 16 hours, more preferably, for a period of about 2 hours to about 6 hours; preferably the pyrrolidinium salt of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid forms and precipitates.

[0040] Optionally, the precipitated pyrrolidinium salt of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid can be recovered.

[0041] The recovery of pyrrolidinium salt of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid may be done by cooling and filtering the suspension, washing the precipitate and drying. Preferably, cooling is done to a temperature of about 30°C to about 15°C, more preferably, to a temperature of about 25°C to about 20°C, most preferably, to a temperature of about 25°C. Preferably, the washing is done with methanol.

[0042] The recovered pyrrolidinium salt of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid may be crystalline. Preferably, it is characterized by a PXRD pattern having peaks at about

5.1, 10.2, 11.5, 13.7, 15.4, 19.5, 21.7, 22.1, 25.5 and 28.0 deg. 2theta ± 0.2 deg and a PXRD pattern as depicted in figure 9.

[0043] The recovered pyrrolidinium salt of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid can then be converted to 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 by adjusting the pH to acidic pH at a temperature of about 25°C to about 70°C, preferably, 40°C to about 60°C to obtain a suspension.

[0044] A preferred process comprises suspending the pyrrolidinium salt of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid in a solvent, preferably water, and heating the suspension to the above temperature prior to adjustment of the pH.

[0045] More preferably, the adjustment of the pH is done at a temperature of about 45°C to about 50°C. Most preferably, the adjustment of the pH is done at a temperature of about 50°C.

[0046] Typically, the adjustment of the pH is provided by addition of a mineral acid. Preferably, the mineral acid is HCl. The adjustment of the pH provides an acidic pH, preferably, the pH is to about 0 to about 5.0, more preferably, to about 1.0 to about 3.0.

[0047] Preferably, the adjustment of the pH at the above temperature provides a suspension from which 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 is recovered easily due to enhanced filterability.

[0048] The recovered 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 can be washed and dried. The washing is done with a solvent and water. Preferably, the washing in the recovery step is done first with the solvent and then with water. Preferably, the solvent in the recovery step is either ethanol or methanol. Preferably, the drying is done at a temperature of about 60°C to about 80°C. Preferably, the drying is conducted for a period of about 16 hours.

[0049] In a preferred embodiment, the obtained 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 is crystalline. Reported herein are four crystalline forms of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4.

[0050] The first crystalline form of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 is characterized by data selected from a group consisting of PXRD pattern having peaks at about 5.0, 7.0, 7.6, 10.0, 10.7, 13.7, 15.0, 19.6, 22.7, 24.1, 25.5, 27.1 and 30.2 deg. 2theta ± 0.2 deg. 2theta and PXRD pattern as depicted in Figure 1.

[0051] The first crystalline form of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 may be further characterized by FTIR spectrum as depicted in Figure 2 .

[0052] The second crystalline form of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 is characterized by data selected from a group consisting of PXRD pattern having peaks at about 5.0, 6.9, 7.5, 8.1, 9.9, 13.6, 14.9, 19.5 and 27.1 deg. 2theta ± 0.2 deg. 2theta and PXRD pattern as depicted in Figure 3.

[0053] The second crystalline form of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 may be further characterized by FTIR spectrum as depicted in Figure 4.

[0054] The third crystalline form of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 is characterized by data selected from a group consisting of PXRD pattern having peaks at about 4.8, 6.9, 7.4, 9.8, 10.6, 13.6, 14.8 and 27.1 deg. 2theta ± 0.2 deg. 2theta and PXRD pattern as depicted in Figure 5.

[0055] The third crystalline form of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 may be further characterized by FTIR spectrum as depicted in Figure 6.

[0056] The forth crystalline form of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 is characterized by data selected from a group consisting of PXRD pattern having peaks

at about 5.0, 7.0, 7.6, 8.1, 9.9, 13.0, 13.7, 14.9, 20.0, 24.1, 25.5, 27.1 and 30.2 deg. 2theta ± 0.2 deg. 2theta and PXRD pattern as depicted in Figure 7.

[0057] The forth crystalline form of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 may be further characterized by FTIR spectrum as depicted in Figure 8.

[0058] The above described crystalline forms of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4, can be used to prepare 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3Z-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carbonyl substitute of formula 1.

[0059] As described before the process comprises reacting 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 either with chlorinating agent or with 1, 1- carbonyldiimidazole ("CDI").

[0060] When X is Cl, the compound of formula 1 refers to 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-3Z-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carbonyl chloride, designated formula 1a.

[0061] When X is imidazole, the compound of formula 1 refers to 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-3Z-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-(carbonyl-1-imidazole), designated formula 1b.

[0062] When 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3Z-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carbonyl chloride, designated formula 1a, is prepared, a preferred process comprises reacting 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 with thionyl chloride in the presence or absence of a catalyst. Preferably, the catalyst is DMF.

[0063] Preferably, the mole ratio between 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 and thionyl chloride is of about 1:1.3 to about 1:1.8 respectively, more preferably, of about 1:1.4.

[0064] Preferably, the mole ratio between 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 and DMF is of about 1:0.1 to about 1:0.3, more preferably, of about 1: 0.2.

[0065] When 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3Z-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-(carbonyl- 1-imidazole) (designated formula 1b) is prepared, a

preferred process comprises reacting 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 with CDI.

[0066] Typically, both reactions are done in the presence of a solvent. Preferably, the reaction with thionyl chloride is done in the presence of a solvent selected from a group consisting of: an aromatic hydrocarbon, cyclic ether and mixtures thereof.

[0067] Preferably, the aromatic hydrocarbon is C_6-C_9 aromatic hydrocarbon, more preferably, is selected from the group consisting of chlorobenzene, and toluene, most preferably, toluene. Preferably, the cyclic ether is C_4-C5 cyclic ether, more preferably, is either tetrahydrofuran or methyl-tetrahydrofuran.

[0068] Preferably, the reaction with CDI is done in the presence of a polar aprotic solvent. Preferably, the polar aprotic solvent is selected from a group consisting of 1-methyl-2-pyrrolidone, dimethylsulfoxide, dimethylformamide dioxane and tetrahydrofuran, more preferably, 1-methyl-2-pyrrolidone.

[0069] Typically, the above reactions are maintained for a sufficient time at a given temperature to allow the formation of the compound of formula 1. Preferably, the reactions are maintained with stirring. Preferably, the reactions are maintained at a temperature of about room temperature to about reflux. Preferably, the reaction with thionyl chloride is done at temperature of about 40°C to about 80°C, more preferably, at a temperature of about 65°C to about 75°C, most preferably, of about 70°C. Preferably, the reaction with CDI is done at about room temperature, more preferably, at about 20°C to about 25°C.

[0070] The above reactions are preferably maintained for a period of about 4 hours to about overnight. Preferably, the reaction with thionyl chloride is maintained for a period of about 3 hours to about 5 hours, more preferably, for a period of about 4 hours. Preferably, the reaction with CDI is maintained for overnight, for about 12 to about 24 hours, or for about 15 to about 18 hours.

[0071] The above reactions result in a suspension comprising 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-3Z-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carbonyl substitute of formula 1.

[0072] The precipitated 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3Z-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carbonyl substitute of formula 1 can then be recovered. The recovery may be done, for example, by cooling the heated

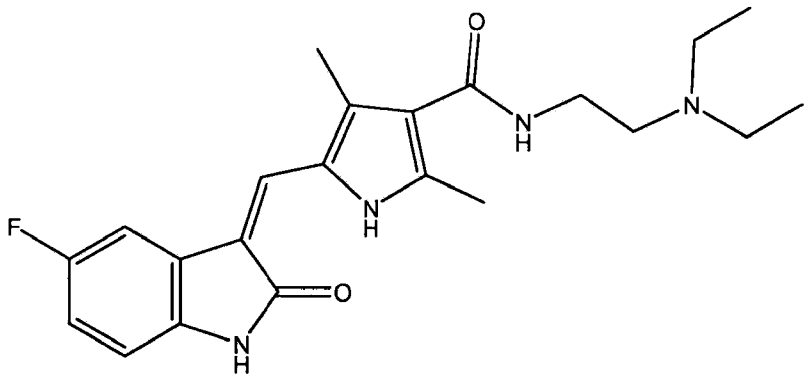
suspension, filtering it, washing and drying under vacuum. Preferably, drying is done at a temperature of about 50°C to about 60°C, preferably, for about 10 hours to about 18 hours.

[0073] Preferably, in the reaction with thionyl chloride the recovery process includes cooling to about room temperature. Preferably, the cooling is done for a period of about 1 hour to about 3 hours, more preferably for a period of about 2 hours.

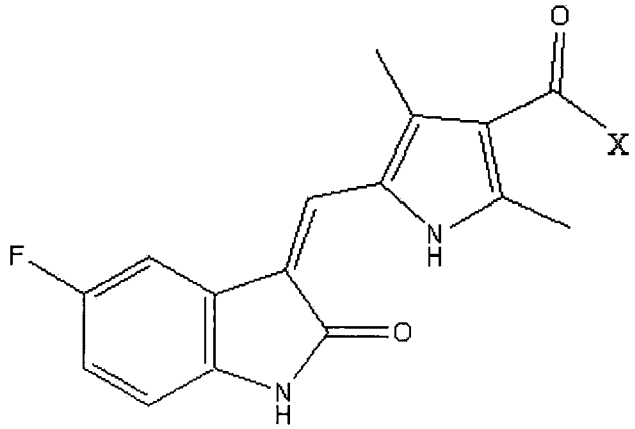
[0074] The obtained 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-3Z-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carbonyl substitute of formula 1 is preferably recovered in high yield. For example, when X is Cl, the obtained 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-3Z-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carbonyl chloride of formula 1a is preferably recovered in yield of at least 97.8%. When X is imidazole, the obtained 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-3Z-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-(carbonyl- 1-imidazole of formula 1b is preferably recovered in a yield of at least 95%.

[0075] 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3Z-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carbonyl substitute of formula 1 can be converted to sunitinib and salts thereof, as shown below.

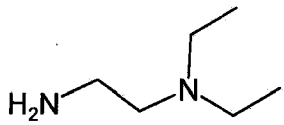
[0076] In one embodiment, the conversion to sunitinib having the following structure



comprises reacting the compound of formula 1 having the following formula:



with 2-diethylaminoethylamine of formula 3 having the following structure:



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wherein X is either Cl or imidazole. Typically, this reaction occurs in the presence of a solvent.

[0077] When X is imidazole the reaction is preferably done in the presence of a solvent selected from a group consisting of 1-methyl-2-pyrrolidone, dimethysulfoxide, dimethylformamide, dioxane and tetrahydrofuran, more preferably tetrahydrofuran.

[0078] When X is Cl the reaction is preferably done in the presence of a solvent selected from the group consisting of toluene, 2-methyl tetrahydrofuran, tetrahydrofuran, dimethylformamide and 1-methyl-2-pyrrolidone. More preferably, in the presence of 2-methyl tetrahydrofuran as a solvent.

[0079] When X is imidazole, the reaction comprises combining a solution comprising diethylenediamine of formula 3 and the solvent and reacting this solution with 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3Z-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-(carbonyl- 1-imidazole), designated formula 1b.

[0080] Typically, excess of thionyl chloride can be removed by distillation, prior to the reaction with diethylenediamine of formula 3.

[0081] Preferably, the distillation is done at a temperature of about 40°C to about 60°C, more preferably at about 50°C. Preferably, distillation is done under vacuum.

[0082] Typically, both reactions are maintained, preferably under stirring to allow the formation of sunitinib. Preferably, the reactions are maintained for a period of about 1 hour to about 24 hours, more preferably, for about 1 hour to about 5 hours. Preferably, the reactions are maintained at a temperature of about room temperature to about 70°C.

[0083] Preferably, when X is Cl the reaction is done for a period of about 0.5 to about 3 hours. More preferably, for a period of about 1 hour. Preferably, the reaction is done at a temperature of about 25°C to about 80°C, more preferably at about 40°C.

[0084] Preferably, when X is imidazole the reaction is done for a period of about 18 hours to about 24 hours. Preferably, the reaction is done at a temperature of about 40°C to about 80°C, more preferably at about 70°C.

[0085] The obtained sunitinib can then be recovered. The recovery process of sunitinib may comprise adding water to the reaction mixture to precipitate Sunitinib, filtering off the precipitated sunitinib, washing and drying.

[0086] Preferably, when X is Cl the recovery further comprises concentrating the obtained suspension, prior to the filtration, providing a new suspension.

[0087] Preferably, the concentration is done by evaporating some of the solvent at a temperature of about 40°C to about 60°C, more preferably 50°C. Preferably, the evaporation is done under vacuum.

[0088] To increase the yield, the obtained new suspension is stirred, preferably, for a period of about 1 hour to about 3 hours, more preferably for about 2 hours.

[0089] Preferably, drying is done at a temperature of about 50°C to about 80°C, more preferably at about 50°C to about 60°C. Preferably, drying is done for period of about 4 hours to about overnight, more preferably, for about 10 hours to about 16 hours.

[0090] Preferably, when X is Cl the drying is done at a temperature of about 70°C to about 80°C, more preferably at about 80°C. Preferably, the drying is done for a period of about 10 hours to about 16 hours.

[0091] Preferably, when X is imidazole the drying is done at a temperature of about 40°C to about 65°C, more preferably, at about 60°C. Preferably, drying is done for a period of about 1 hour to about 4 hours.

[0092] Typically, the recovered sunitinib can then be converted to sunitinib salt, preferably, to sunitinib malate. The conversion can be done by reacting sunitinib base with an acid, preferably, malic acid. When the acid is malic acid, the conversion can be done, for example, according to the process disclosed in U.S. publication No. 2003/0069298, hereby incorporated by reference.

[0093] Optionally, sunitinib can be purified prior to the conversion to sunitinib salt. Preferably, the purification comprises acidifying sunitinib to obtain sunitinib salt, and then converting it back to sunitinib by reacting the salt with a base.

[0094] The process comprises dissolving Sunitinib in a mixture of water with an acid to obtain sunitinib salt. Preferably, the acid is an inorganic acid, more preferably, hydrochloric acid. Then, said solution is extracted either with ketone, preferably, methyl-isobutyl ketone or with 2-Methyl THF, providing a two-phase system. Typically, the phases are separated and a base is added to the aqueous phase providing sunitinib. Preferably, when the reaction is performed in 2-Methyl THF, the extraction is done with 2-Methyl THF.

[0095] Preferably, the base is aqueous ammonia. Preferably, the aqueous phase is basified to a pH of about 8 to about 9, more preferably, to a pH of about 8.5, to obtain a suspension comprising a precipitation of sunitinib in forms of crystals.

[0096] The crystalline sunitinib can then be recovered. The recovery process may comprise filtering off the precipitated sunitinib, washing and drying. Preferably, drying is done at a temperature of about 70°C to about 80°C. Preferably, drying is done for a period of about 10 hours to about 16 hours.

EXAMPLES

[097] PXRD

[098] XRD diffraction was performed on X-Ray powder diffractometer: PanAlytical X'pert Pro powder diffractometer, CuKα radiation, λ = 1.541874 Å. X'Celerator detector active length (2 theta) = 2.122 mm, laboratory temperature 22-25°C, zero background sample-holders. Prior to analysis the samples were gently ground by means of mortar and pestle in order to obtain a fine powder. The ground

sample was adjusted into a cavity of the sample holder and the surface of the sample was smoothed by means of a cover glass slide.

FTIR

[099] FTIR spectra were collected by means of a spectrometer Nicolet Nexus. ATR technique was used for the measurement with the following settings:

[0100] Range: 4000 - 550 cm^{-1}

[0101] Number of sample scans: 64

[0102] Resolution: 4.000

[0103] Apodization: Happ-Genzel

[0104] Sample gain: 8.0

[0105] Final format: Absorbance

[0106] The empty ATR crystal was measured as a background under the same conditions as were the samples. The resulting record was then subtracted automatically from the spectra of the samples.

Example 1: Preparation of sunitinib via 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-3Z-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carbonyl chloride

[0107] 31.2 g of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-3Z-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid, obtained as described in US 7125905, were refluxed under stirring for 4 hours in one liter flask with 310 g of toluene, 15 g of thionyl chloride and 1 g of dimethylformamide.

[0108] The stirred suspension was cooled at room temperature for 2 hours and filtered; the cake was washed with 50 g of toluene and dried at 50° under vacuum overnight.

[0109] Yield was 32. 4 g (97.8%) of a compound corresponding by NMR and MS to the expected structure.

[0110] 20 g of diethylendiamine were dissolved in one liter flask with 300 g of tetrahydrofuran; about 200 g of solvent were distilled away at 50° under vacuum.

[0111] 20 g of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3Z-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carbonyl chloride, prepared as above, were added under stirring and solution obtained was left for one hour to react without more heating. 300 g of water were added and suspension was evaporated at 50° under vacuum to

eliminate most of organic solvent. After stirring 2 hours at room temperature the suspension was filtered, washed with 100 g of water and dried at 50° under vacuum overnight, obtaining 23.5 g of crude Sunitinib.

Purification

[0112] Crude material was dissolved with 560 g of water and 190 g of 1 M Hydrochloric acid, extracted with 200 g of methyl-isobutyl ketone.

[0113] Clarified aqueous phase was basified under stirring with concentrated aqueous ammonia to pH 8.5 and after 2 hours the suspension was filtered and crystals were washed with 100 g of water.

[0114] Product was dried at 50° under vacuum overnight obtaining 20.5 (82% yield, 99.6% purity by HPLC) of sunitinib.

Example 2: Preparation of Sunitinib via 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-3Z-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-(carbonyl-1-imidazole)

[0115] 4.6 g of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-3Z-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid, obtained as described in US7125905, were stirred for 4 hours in 0.1 liter flask with 46 g of 1-methyl-2-pyrrolidone and 3 g of 1,1'-carbonyldiimidazole (CDI), after this time 0.7 g of CDI were added and reaction was left stirring overnight.

[0116] 46 g of water were added under stirring and after 1 hour the suspension was filtered and the cake washed with water.

[0117] Product was dried at 60° under vacuum obtaining 5.1 g (95% yield); NMR and MS confirmed the expected structure.

[0118] 1 g of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3Z-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-(carbonyl-1-imidazole), prepared as above, was added to 10 g of 1-methyl-2-pyrrolidone and 0.5 g of diethylendiamine under stirring and the mixture was left for one day to react at 70°.

[0119] 10 g of water were added and after 2 hour at room temperature the suspension was filtered, the cake was washed with water and was dried at 60° under vacuum for 4 hours to constant weight.

[0120] 1.06 g of crude product (93% yield, 98% purity by HPLC) was obtained.

Example 3: Conversion of Sunitinib to Sunitinib Malate (according to Example 1, Preparation A of U.S. publication No. 2003/0069298)

Preparation of the Anhydrous Crystal Form I of the L-Malice Acid Salt of N-[2-(Diethylamino) ethyl]-5-[(5fluoro-1, 2-dihydro-2-oxo-3H-indol-- 3-ylidene) methyl]-2, 4-dimethyl-1H-pyrrole-3-carboxamide.

Preparation A:

[0121] N-[2-(Diethylamino)ethyl]-5-[(5-fluoro-1,2-dihydro-2- -oxo-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (130 mg, 0.326 mMol) was added to 20 mL methanol, and the mixture was stirred. L-malic acid (47.2 mg, 0.352 mMol) was added, resulting in rapid dissolution of all the solids. The methanol was removed under reduced pressure to produce a poorly crystalline orange solid. Acetonitrile (5 mL) was added, and the slurry was stirred and heated for about 10 minutes. Stirring was continued while the slurry was allowed to cool to room temperature. The crystals were filtered and dried, resulting in 149 mg of solids (86% yield).

Example 4- preparation of crystalline form 1 of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4

[0122] In a reactor under nitrogen atmosphere, 450 g of PCA (1.0 eq), 447.6 g of FDI (1.1 eq) and 9 L of absolute ethanol were loaded and vigorously stirred at room temperature. Then 229.95 g of pyrrolidine (1.2 eq) with 447 mL of ethanol were added and the suspension was stirred 10-15 minutes to dissolution.

[0123] The mixture was then heated to 50 °C and stirred at this temperature for 8 hours (precipitation of the product occurs during the heating). Then the mixture was neutralized with 1860 g of hydrochloric acid 2 $mol.L^{-1}$ and the suspension was kept at 50 °C for 2 hours.

[0124] After this step, the mixture was cooled to room temperature for 2 hours and then the solid was filtered on gooch P3 and washed with 2.7 L of ethanol. The filtered product was washed with 13.5 L of water. It was dried at 80°C overnight under vacuum yielding 777 g of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid derivative with 96.1% total yield.

Example 5- preparation of crystalline form 2 of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4

[0125] In a reactor under nitrogen atmosphere, 277 g of PCA (1.0 eq), 275.5 g of FDI (1.1 eq) and 5.54 L of absolute ethanol were loaded and vigorously stirred at room temperature. Then 141.54 g of pyrrolidine (1.2 eq) with 275 mL of ethanol were added and the suspension was stirred 10-15 minutes to dissolution.

[0126] Then the mixture was heated to 50 °C and stirred at this temperature for 8 hours (precipitation of the product occurs during the heating).

[0127] The mixture was neutralized with 1144 g of hydrochloric acid 2 $mol.L^{-1}$ and the suspension was kept at 50 °C for 2 hours.

[0128] After this step, the mixture was cooled to room temperature for 2 hours and then the solid was filtered on gooch P3 and washed with 1.66 L of ethanol. The filtered product was washed with 8.3 L of water. It was dried at 80 °C overnight under vacuum yielding 448 g of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid derivative with 90.0% total yield.

Example 6- preparation of crystalline form 3 of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4

[0129] In a reactor under nitrogen atmosphere, 23 g of PCA (1.0 eq). 26.3 g of FDI (1.265 eq) and 633 mL of absolute ethanol were loaded and vigorously stirred at room temperature. Then 26 g of pyrrolidine (3 eq) were added and the suspension was stirred 10-15 minutes to dissolution.

[0130] The mixture was then heated to reflux and stirred at this temperature for 6 hours (precipitation of the product occurs during the heating).

[0131] Then the mixture was cooled to room temperature and the solid was filtered on gooch P3 and washed with 100 mL of ethanol. The obtained product was loaded again into the reactor and it was suspended into 200 mL of a mixture acetone/water 40/60 and 17.3 g of HCl 37% were added. The suspension was stirred for 2 hours at 25 °C and then filtered on gooch P3 washing the solid with 200 mL of water. It was dried at 60 °C for a night under vacuum yielding 32.6 g of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid derivative.

Example 7- preparation of crystalline form 4 of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4

[0132] In a reactor under nitrogen atmosphere, 20 g of PCA (1.0 eq). 19.9 g of FDI (1.1 eq) and 400 mL of absolute ethanol were loaded and vigorously stirred at room temperature. Then 11.9 mL of pyrrolidine (1.2 eq) were added and the suspension was stirred 10-15 minutes to dissolution.

[0133] The mixture was then heated to 50 °C and stirred at this temperature for 6hours (precipitation of the product occurs during the heating).

[0134] Then the temperature was maintained at 50 °C and 68 mL of HCl 2 $mol.L^{-1}$ were slowly added up to pH 1.5 - 3.0. The suspension was stirred for 2 hours at 50 °C and then filtered on gooch P3 washing the solid with 2x50 mL of ethanol. It was dried at 60 °C for a night under vacuum, loaded again into the filter and washed with 3x150 mL of water.

[0135] The orange solid was dried in oven under vacuum at 60 °C for 16 hours yielding 27 g of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid derivative.

Example 8- preparation of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 in methanol

[0136] In a reactor under nitrogen atmosphere 5g of 5-formyl-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid (PCA) (1.0eq), 4.97g of 5-fluoro-1, 3-dihydro-indol-2-one (FDI) (1.1eq) and 75ml of methanol were loaded and vigorously stirred at room temperature. Then 2.97ml of pyrrolidine (1.2eq) were added and the suspension was stirred 10-15 minutes to dissolution.

[0137] The mixture was then heated to 50°C and stirred at this temperature for 2-3 hours (precipitation of the product occurs during the heating).

[0138] Then, maintaining the temperature at 50°C, 20ml of HCl 2M were slowly added up to pH 1.5-3.0. The suspension was stirred for 1 hour at 50°C and then filtered on gooch P3 washing the solid with 2x12.5ml of methanol and with 3x50ml of water.

[0139] The obtained product was dried at 60°C for a night under vacuum yielding 8.4g of Sunitinib carboxylic acid derivative.

Example 9- Preparation of Sunitinib via Sunitinib carboxylic acid derivative

[0140] In a 500 ml reactor, 15.0 g of Sunitinib carboxylic acid derivative (Compound 4) were suspended into 300ml of toluene (ratio 20/1.0 v/w. starting material) under vigorous stirring at room temperature. 0.755 g. of dimethylformamide (ratio 0.2/1.0 w/w) was added to the mixture.

[0141] The temperature was set at 70°C and at this temperature, 5.1 g. of thionyl chloride (ratio 1.4/1.0 w/w) were dropped in a range of sixty minutes. The reaction was kept at 70°C for 7 hours under stirring.

[0142] Then 140 ml of solvent were distilled to remove excess of thionyl chloride from the suspension and the reaction filtered on gooch P3 washing with 3v/w of toluene. The wet solid (sunitinib acyl chloride derivative) was re-loaded into the reactor and 300ml Methyl-tetrahydrofuran loaded and stirred. Then the reaction mixture was heated to 70°C and 6.35g of 2-diethylamino-ethylamine (ratio 1.1/1.0 w/w starting material) were dropped in five minutes at 70°C. After one hour the reaction was completed and 150 ml of water and HCl 2N until pH 2 were added to the suspension.

[0143] The mixture was filtered using a decalite pad to obtain a clarified phase. The two phases were separated at 50°C and the organic phase discarded. The aqueous phase was washed once more with 300ml of Methyl-tetrahydrofuran at 50°C under stirring. The two phases separated again and the organic phase discarded. The aqueous phase was then basified to pH 8.5 with 5% ammonia solution at 50 °C. After one hour stirring, the suspension was filtered on gooch P3 and the wet solid dried at 60°C under vacuum overnight.

[0144] 15.9 g. of sunitinib base were obtained with a purity of NLT 99.5% by HPLC.

Example 10- preparation of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid

[0145] In a reactor under nitrogen atmosphere 10g of 5-formyl-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid (PCA) (1.0eq), 9.94g of 5-fluoro-1, 3-dihydro-indol-2-one (FDI) (1.1eq) and 150ml of methanol were loaded and vigorously stirred at room temperature. Then 5.94ml of pyrrolidine (1.2eq) was added and the suspension was stirred 10-15 minutes to dissolution. The mixture was then heated to 50°C and stirred

at this temperature for 2-3 hours (precipitation of the product occurred during the heating).

[0146] The pyrrolidinium salt of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid thus obtained was cooled to 25°C, filtered on gooch P3 and washed with 50ml of methanol. The wet solid (24g) was then loaded again into the reactor and suspended into 150ml of water and the mixture heated to 50°C.

[0147] Then, maintaining the temperature at 50°C, 23ml of HCl 2M was slowly added up to pH 1.5-3.0. The suspension was stirred for 1 hour at 50°C and then filtered on gooch P3 washing the solid with 2x50ml of water.

[0148] The obtained product was dried at 75°C for a night under vacuum yielding 15.5g of 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid.

Example 11- Preparation of Sunitinib via Sunitinib carboxylic acid derivative

[0149] In a 500 ml reactor, 15.0 g. of Sunitinib carboxylic acid derivative (Compound 4) was suspended into 300ml of toluene (ratio 20/1.0 v/w. starting material) under vigorous stirring at room temperature. 0.755 g. of dimethylformamide (ratio 0.2/1.0 mol of SM) were added to the mixture.

[0150] The temperature was set at 70°C and at this temperature, 5.1 g. of thionyl chloride (ratio 1.4/1.0 mol of SM) were dropped in a range of sixty minutes. The reaction was kept at 70°C for 7 hours under stirring.

[0151] Then 140 ml of solvent were distilled to remove excess of thionyl chloride from the suspension and the reaction was filtered on gooch P3 was washed with 3v/w of toluene. The wet solid (sunitinib acyl chloride derivative) was re-loaded into the reactor and 225ml Methyl-tetrahydrofuran were loaded under stirring. Then the reaction mixture was heated to 40°C and 6.35g of 2-diethylamino-ethylamine (ratio 1.1/1.0 w/w starting material) were dropped in five minutes at 40°C. After one hour the reaction was completed and 225 ml of water and HCl 2N until pH 2 were added to the suspension.

[0152] The mixture was filtered using a decalite pad to obtain a clarified phase. The two phases were separated at 40°C and the organic phase was discarded. The aqueous phase was washed once more with 225ml of Methyl-tetrahydrofuran at

40°C under stirring. The two phases were separated again and the organic phase was discarded.

[0153] The aqueous phase was then basified to pH 8.5 with 5% ammonia solution at 40°C. After one hour stirring, the suspension was filtered on gooch P3 and the wet solid was dried at 80°C under vacuum overnight.

[0154] 16.5 g. of sunitinib base were obtained (83% yield) with a purity of NLT 99.5% by HPLC.

Comparative Example 12- unsuccessful chlorination of pyrrole carboxylic acid with thionylchloride

[0155] In a 100 ml reactor, 5.0 g. of PCA were suspended into 75ml of toluene under vigorous stirring at room temperature. 15 ml of toluene are thus distilled at 50°C under vacuum reaching a final volume of 50ml (10 volumes on weight SM).

[0156] At 50°C, 0.44 g. of dimethylformamide (ratio 0.2/1.0 mol of SM) and 5g of thionyl chloride (ratio 1.4/1.0 mol of SM) were added to the mixture.

[0157] The reaction was kept at 50°C for 3 hours under stirring. The HPLC control reveals still 48% unreacted pyrrole and no changing with respect to the control done after 2 hours. The reaction looks very dark with a presence of a lot of tars.

[0158] Then 15ml of solvent were distilled to remove excess of thionyl chloride from the suspension and then other 15ml are added to reach the starting 75ml of toluene.

[0159] Maintaining at 50°C, 3.83g of N, N'-diethylaminoethylamine (ratio 1.1/1.0 w/w starting material) were dropped in five minutes. After one hour the reaction was completed and 50 ml of water and HCl 2N until pH 2 were added to the suspension.

[0160] The precipitate was filtered and the two phases separated, the aqueous phase was basified with NaOH 2M to pH 9.0 and extracted with 70ml of dichloromethane. Difficult separation is observed, the extraction is done with a volume of 200ml of water and 500ml of dichloromethane.

[0161] The aqueous phase once more extracted with another 500ml of dichloromethane. The organic phase is then evaporated to residue and triturated with a mixture hexane/ethylether 3:1.

[0162] The obtained solid is filtered on gooch P3 and dried in oven under vacuum at 35°C, 0.25g of the desired product are obtained (3%yield, 80% purity).

Example 13 - chlorination

[0163] In a 100 ml reactor, 6.0g of Sunitinib Carboxylic acid derivative were suspended into 60ml of toluene under vigorous stirring at room temperature. 30 ml of toluene are thus distilled at 50°C under vacuum reaching a final volume of 60ml (10 volumes on weight SM).

[0164] At 70°C, 1.24 ml of dimethylformamide (ratio 0.8/1.0 mol of SM) and 9.72ml of thionyl chloride (ratio 6.5/1.0 mol of SM) were added to the mixture. The reaction was kept at 70°C for 8 hours under stirring then it is cooled to room temperature and filtered on gooch P3, washed with 20ml of toluene and the obtained solid used as is.

[0165] 3g of the solid is suspended in 20ml of Me-THF and, at 50°C, 1.45ml of N, N'-diethylaminoethylamine (ratio 1.1/1.0 w/w starting material) were dropped in five minutes. After one hour the reaction was completed. Sunitinib was obtained.

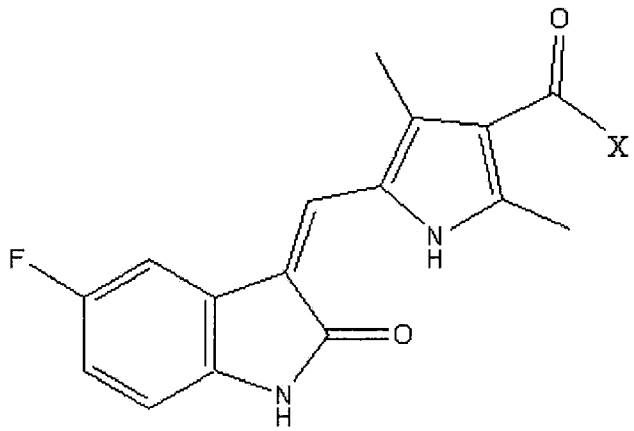
Example 14 - chlorination

[0166] In a 100 ml reactor, 6.0g of Sunitinib Carboxylic acid derivative were suspended into 60ml of toluene under vigorous stirring at room temperature. 30 ml of toluene are thus distilled at 50°C under vacuum reaching a final volume of 60ml (10 volumes on weight SM).

[0167] At 40°C, 0.31ml of dimethylformamide (ratio 0.2/1.0 mol on SM) and 1.75ml of thionyl chloride (ratio 1.2/1.0 mol on SM) were added to the mixture. The reaction was kept at 40°C for 7 hours and it is checked by HPLC. Formula 1 (when X is Cl) was obtained.

What is Claimed is:

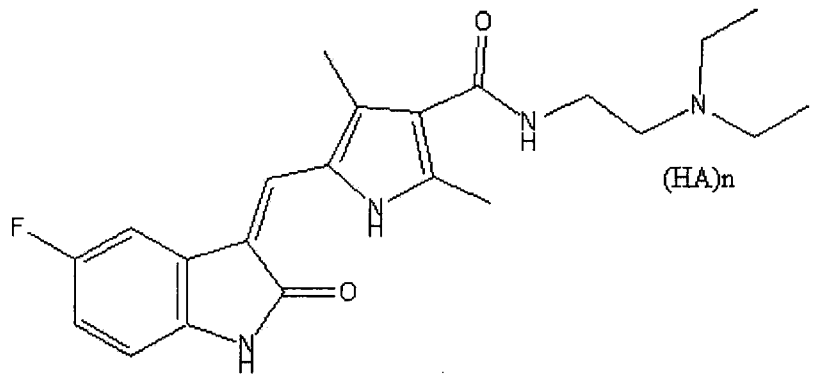
1. A compound of the following formula 1:



1

wherein X is either Cl or imidazole.

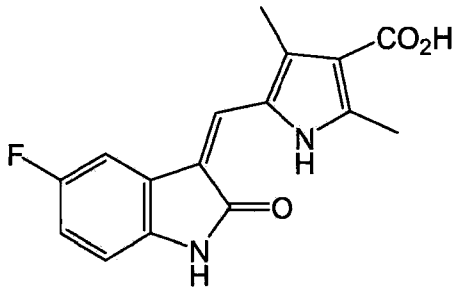
2. The use of the compound of claim 1 for the preparation of sunitinib or a salt thereof having the following structure:



wherein n is 0 or 1 and HA is a diacid.

3. The use of claim 2, wherein n is 1 and HA is malic acid.

4. A process for the preparation of the compound of any of claims 1-3, comprising reacting 5-(5-fluoro-2-oxo-1, 2-dihydro-indol-(3Z)-ylidenemethyl)-2, 4-dimethyl-1H-pyrrole-3-carboxylic acid (compound 4)



4

either with a chlorinating agent or with 1, 1- carbonyldiimidazole.

5. The process of claim 4, wherein compound 4 reacts with a chlorinating agent selected from the group consisting of thionyl chloride and oxalyl chloride.

6. The process of claim 5, wherein the chlorinating agent is thionyl chloride.

7. The process of any of claims 4-6, further comprising DMF.

8. The process of any of claims 4-7, wherein the mole ratio between 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 and thionyl chloride is about 1:1.3 to about 1:1.8 respectively.

9. The process of any of claims 4-8, wherein mole ratio between 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid of formula 4 and DMF is of about 1:0.1 to about 1:0.3.

10. The process of any of claims 4-9, wherein compound 4 reacts with thionyl chloride in the presence of a solvent selected from a group consisting of an aromatic hydrocarbon and a cyclic ether.

11. The process of claim 10, wherein the solvent is a C_6-C_9 aromatic hydrocarbon.

12. The process of any of claims 10-11, wherein the solvent is selected from the group consisting of chlorobenzene and toluene.

13. The process of claim 10, wherein the solvent is a C_4-C_5 cyclic ether.

14. The process of claim 13, wherein the cyclic ether is either tetrahydrofuran or methyl-tetrahydrofuran.

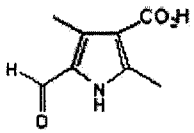
15. The process of claim 4, wherein compound 4 reacts with CDI in the presence of a polar aprotic solvent selected from a group consisting of 1-methyl-2-pyrrolidone, dimethylsulfoxide, dimethylformamide dioxane and tetrahydrofuran.

16. The process of claim 15, wherein the solvent is 1-methyl-2-pyrrolidone.

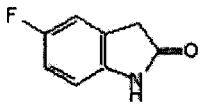
17. The process of any of claims 4-14, wherein the reaction with thionyl chloride is done at temperature of about 40°C to about 80°C.

18. The process of any of claims 4-17, further comprising the step of recovering the compound of formula 1.

19. The process of any of claims 4-18, wherein the compound of formula 4 is prepared by a process comprising reacting 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (PCA) of the formula:

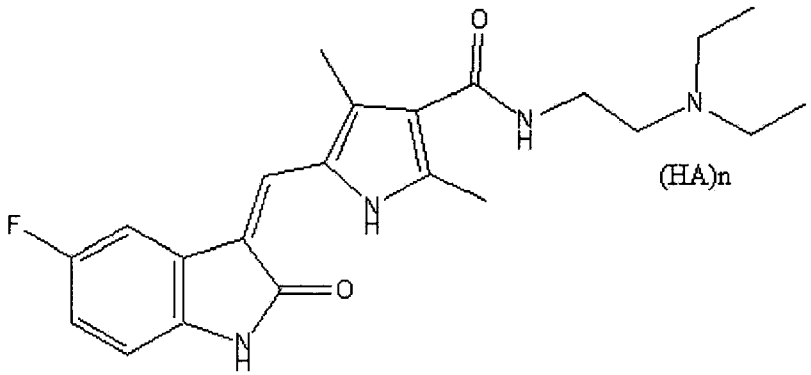


and 5-fluoro-1, 3-dihydro-indol-2-one (FDI) of the formula:



in the presence of pyrrolidine, and adjusting the pH to acidic pH at a temperature of about 25°C to about 70°C to obtain a suspension containing compound 4.

20. A process for preparing sunitinib or a salt thereof having the following structure:



wherein n is either 0 or 1 and HA is a diacid, comprising

preparing the compound of formula 1 according to any of claims 4-19, and converting it to sunitinib or a salt thereof.

21. The process of claim 20, wherein the converting step comprises reacting the compound of formula 1 with 2-diethylaminoethylamine.

22. The process of any of claims 20-21, wherein X is Cl in the compound of formula 1 and the reaction occurs in the presence of a solvent selected from the group consisting of toluene, 2-methyl tetrahydrofuran, tetrahydrofuran and 1-methyl-2-pyrrolidone.

23. The process of claim 22, wherein the solvent is 2-methyl tetrahydrofuran.

24. The process of any of claims 20-21, wherein X is imidazole in the compound of formula 1 and the reaction occurs in the presence of a solvent selected from a group consisting of 1-methyl-2-pyrrolidone, dimethysulfoxide, dimethylformamide, dioxane and tetrahydrofuran.

25. The process of claim 24, wherein the solvent is 1-methyl-2-pyrrolidone.

26. The process of any of claims 20-25, further comprising the step of recovering sunitinib or a salt thereof.

FIG. 1

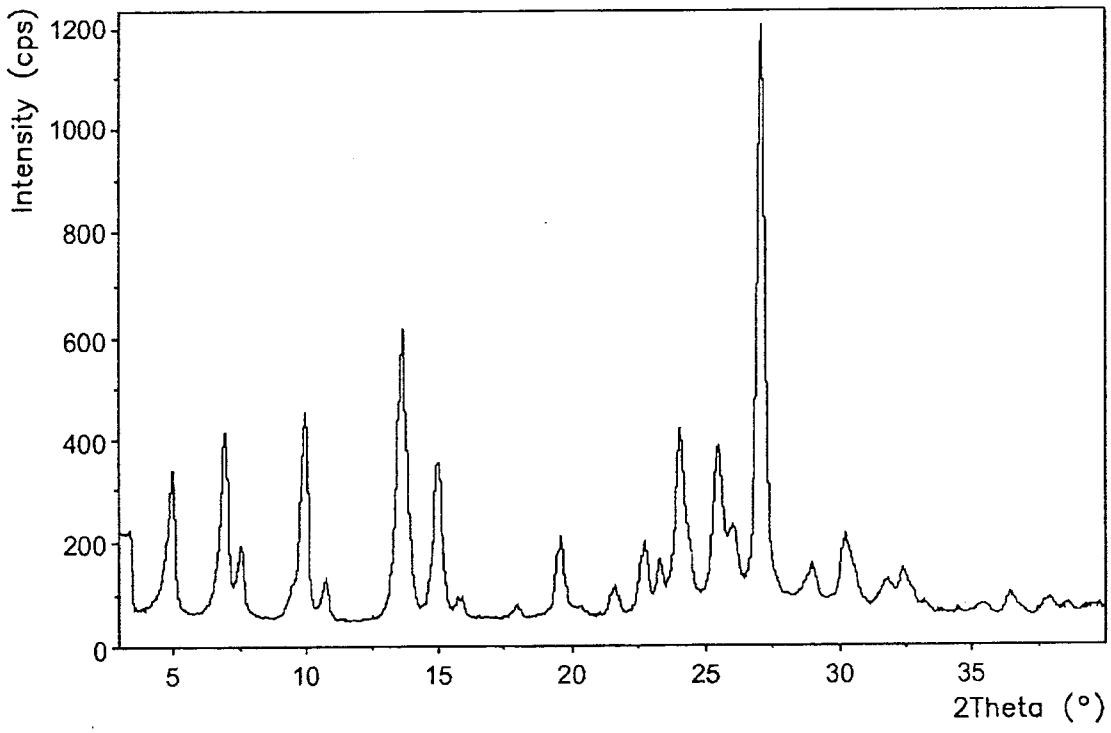

Intensity (cps)
1200
1000
800
600
400
200
0
5
10
15
20
25
30
35
2Theta (°)

FIG. 2

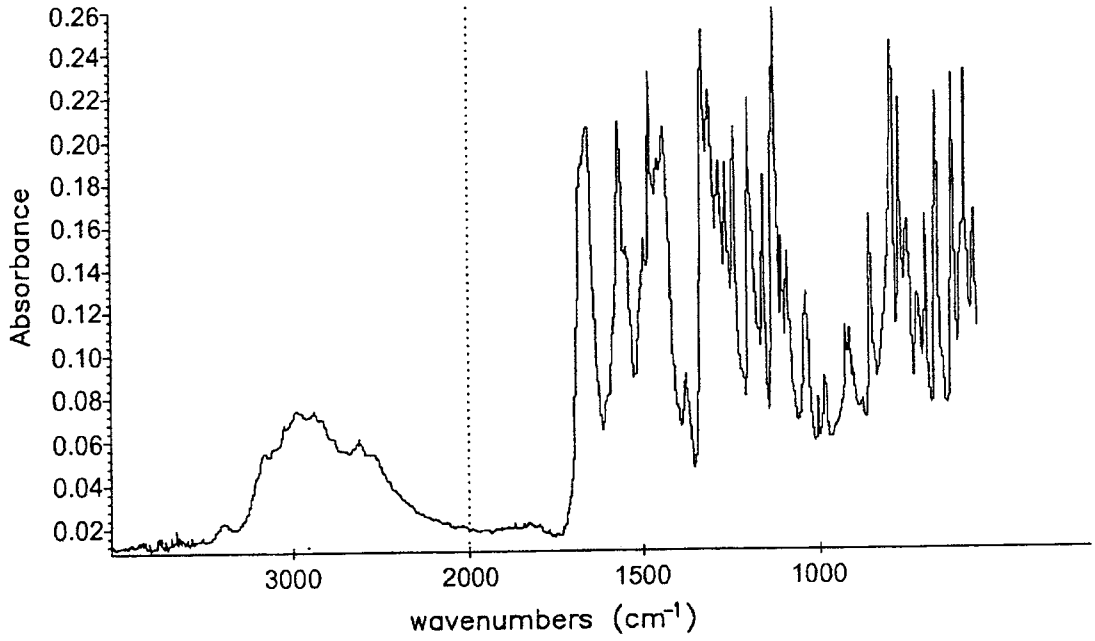

0.26
0.24
0.22
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
Absorbance
3000
2000
1500
1000
wavenumbers (cm-1)

FIG. 3

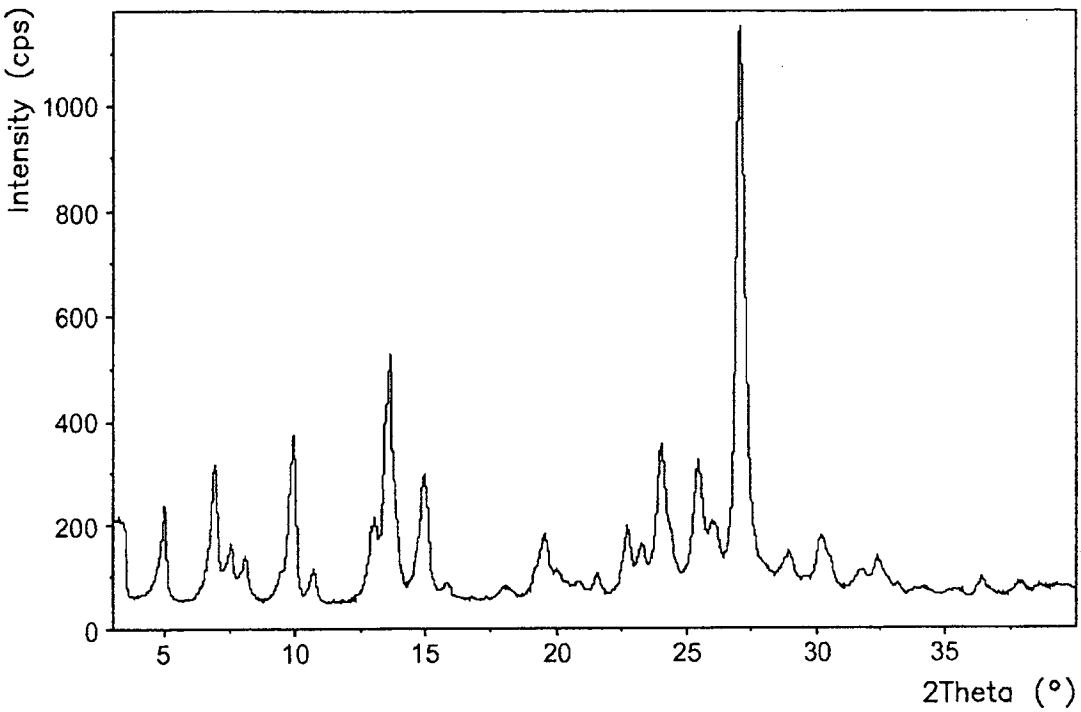


FIG. 4

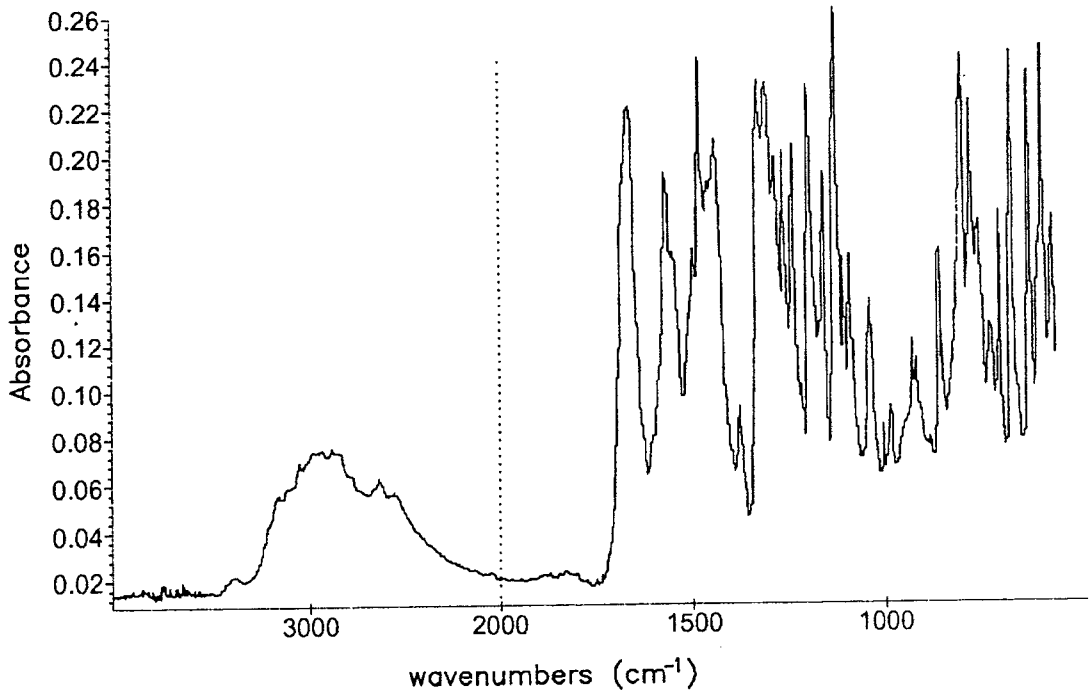

0.26
0.24
0.22
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
Absorbance
3000
2000
1500
1000
wavenumbers (cm-1)

FIG. 5

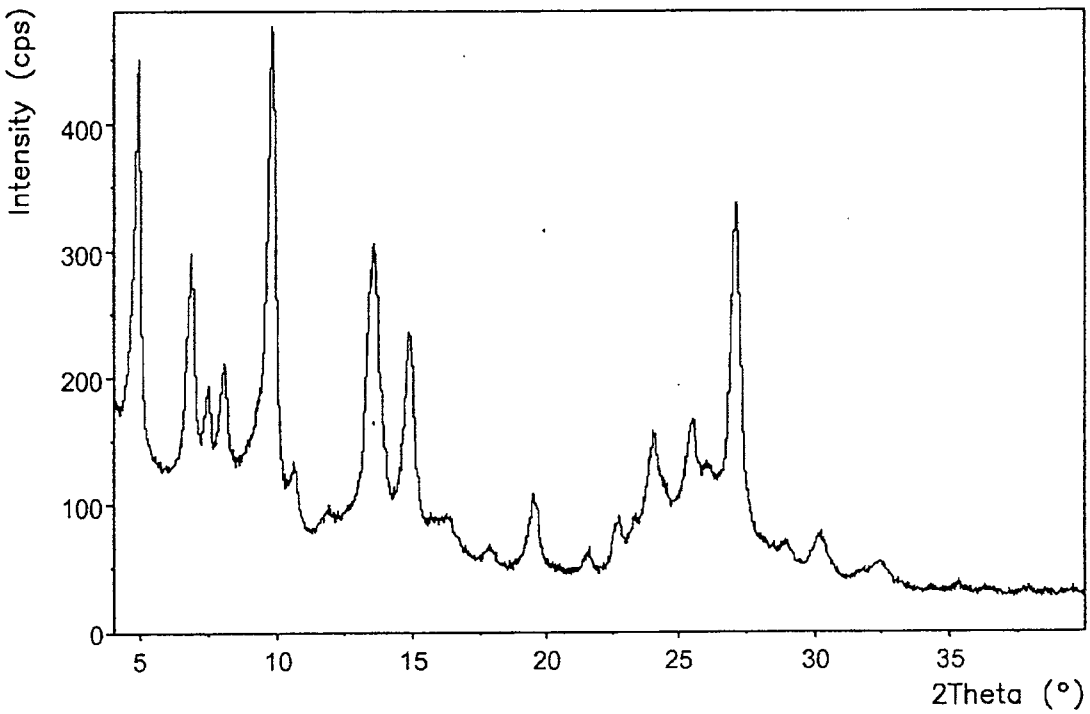


FIG. 6

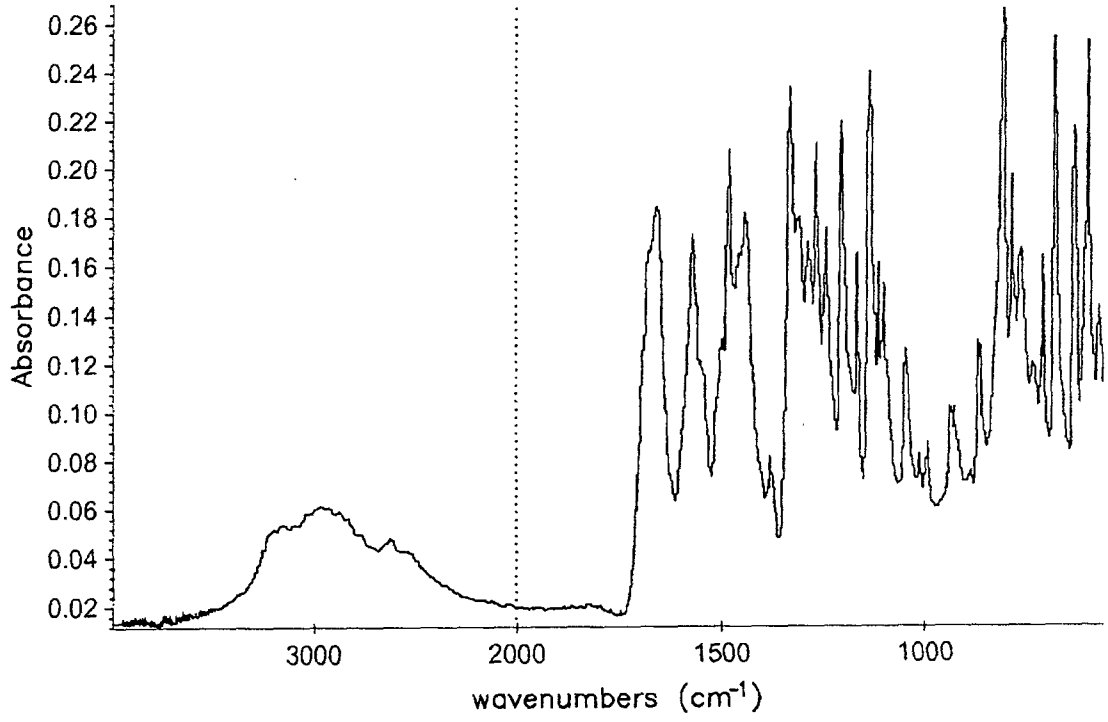

Absorbance
0.26
0.24
0.22
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
3000
2000
1500
1000
wavenumbers (cm-1)

FIG. 7

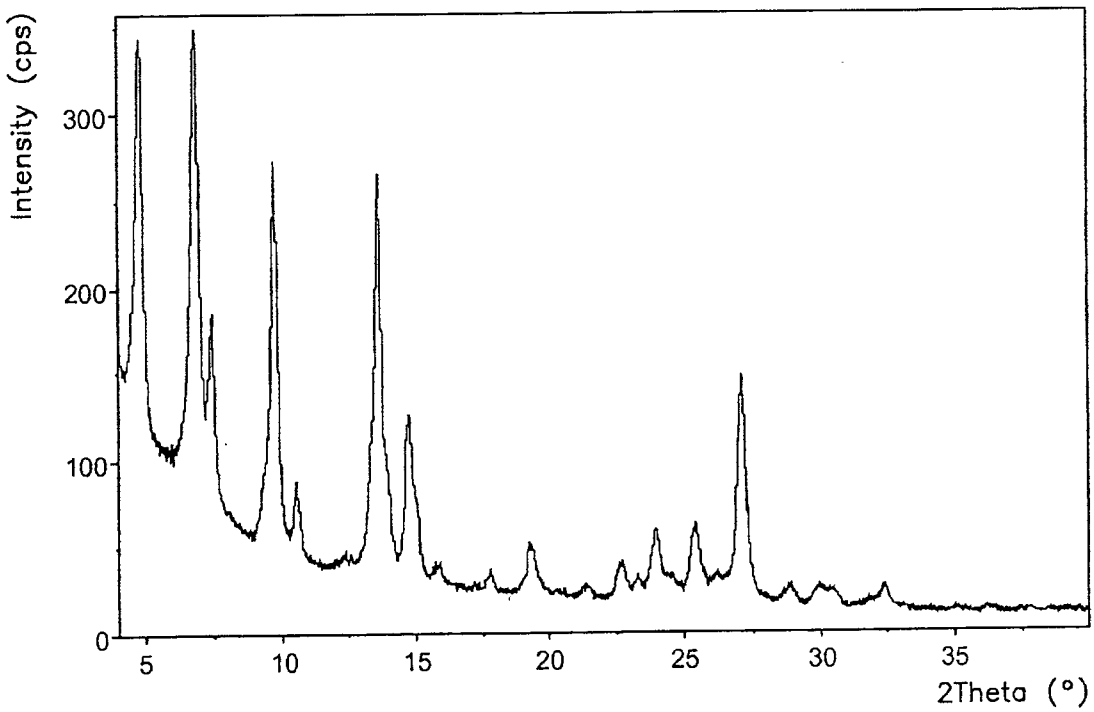


FIG. 8

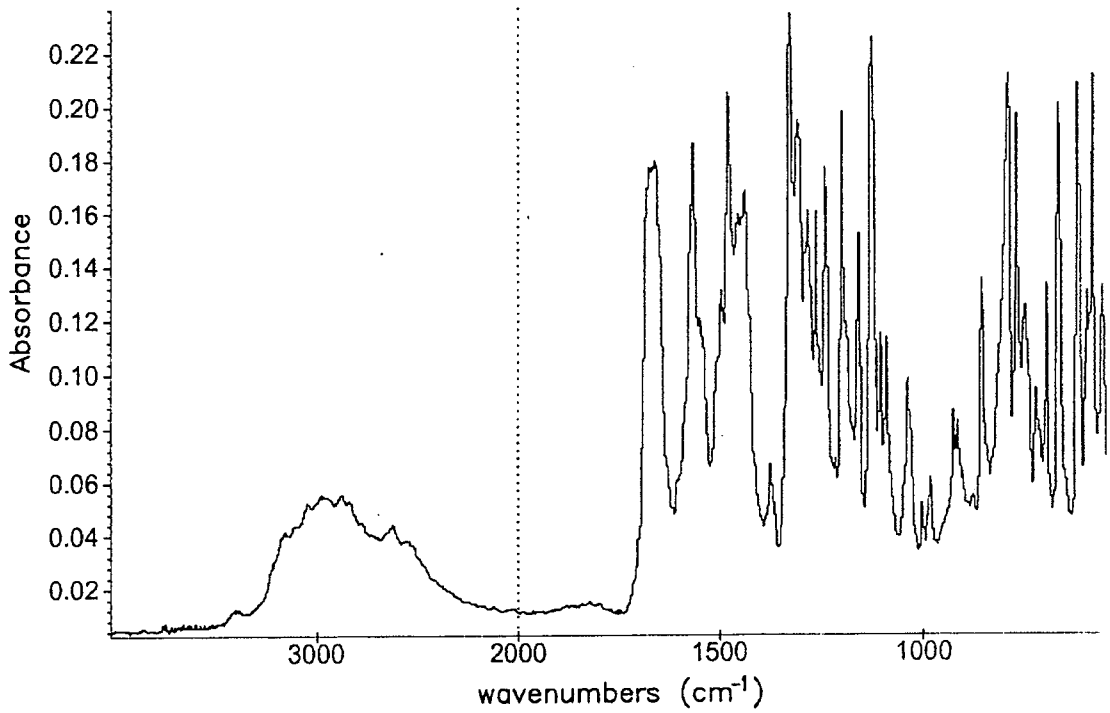
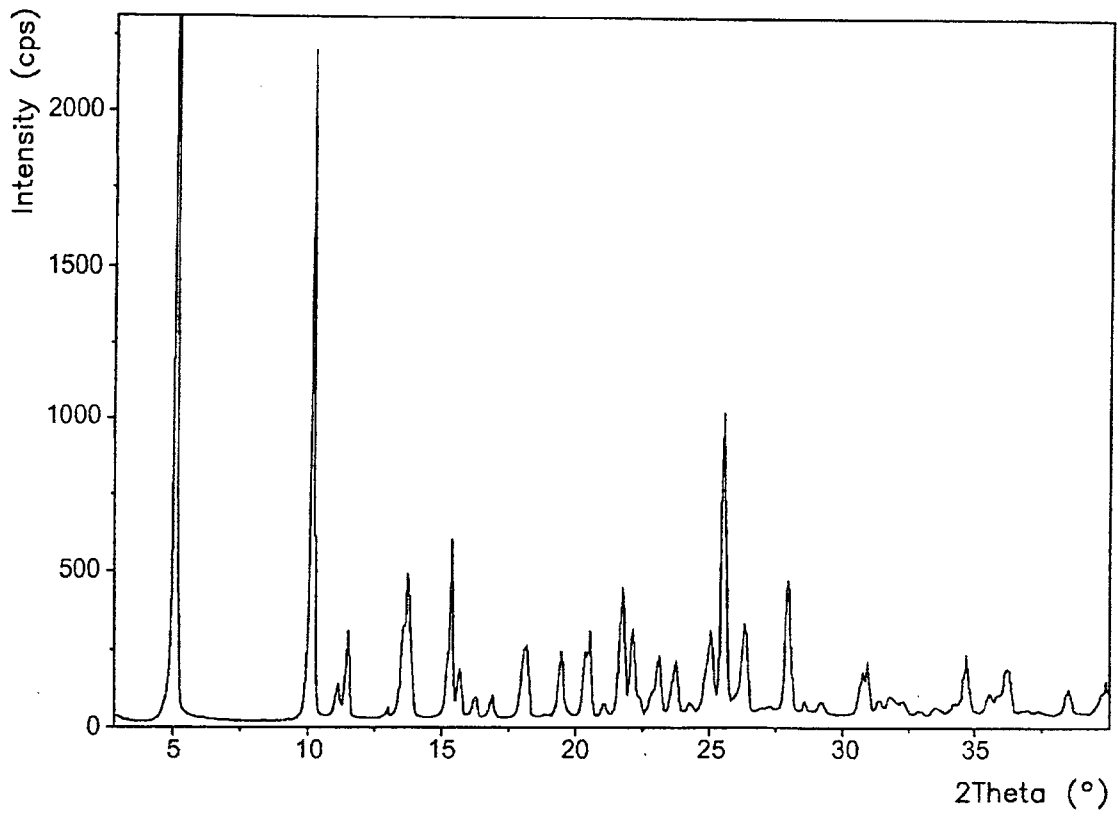

Absorbance
0.22
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
3000
2000
1500
1000
wavenumbers (cm-1)

FIG. 9



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/038934

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/06 A61K31/404 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SUN L ET AL: "Discovery of 5-[5-fluoro-2-oxo-1,2-dihydroindol-(3Z)-ylidenemethyl] 2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)ami de, a novel tyrosine kinase inhibitor targeting vascular endothelial and platelet-derived growth factor receptor tyrosine kinase" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 46, no. 7, 27 March 2003 (2003-03-27), pages 1116-1119, XP009070151 ISSN: 0022-2623 scheme 2, example 12b ----- -/--	1-26

[X] Further documents are listed in the continuation of Box C.

[X] 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 document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 July 2009	07/08/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sáez Díaz, R

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/038934

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2003/229229 A1 (JIN QINGWU [US] ET AL) 11 December 2003 (2003-12-11) cited in the application claim 1; example 1	1-26
E	WO 2009/067674 A (TEVA PHARMA [IL]; TEVA PHARMA [US]; GAVENDA ALES [CZ]; BIGATTI ETTORE) 28 May 2009 (2009-05-28) page 36; example 25	1-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/038934

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003229229 A1	11-12-2003	US 2005171357 A1	04-08-2005
WO 2009067674 A	28-05-2009	WO 2009067686 A2	28-05-2009