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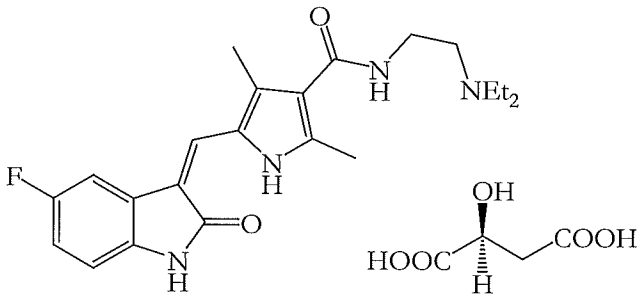
(54) Title: NOVEL PROCESS

(57) Abstract: The present invention relates to novel processes for the preparation of sunitinib and salts thereof, in particular sunitinib (2S)-2-hydroxybutanedioate. The invention further relates to novel intermediates, their use in the preparation of sunitinib or salts thereof and to processes for the preparation of said intermediates. The invention also relates to compositions comprising sunitinib or its pharmaceutically acceptable salts.

Novel Process

Field of the invention

The present invention relates to novel intermediates useful in the preparation of sunitinib (VII) and salts thereof, in particular sunitinib L-malate (IV), to processes for preparing said intermediates, sunitinib (VII) and its salts, and to sunitinib and its salts, in particular sunitinib L-malate (IV), prepared using said processes. The invention also relates to compositions comprising sunitinib (VII) or its pharmaceutically acceptable salts prepared via said novel intermediates.



(IV)

Sunitinib is a multi-targeted receptor tyrosine kinase (RTK) inhibitor approved as the malate salt by the FDA for the treatment of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST). There is thus considerable interest in the development of new processes for the preparation of sunitinib and its salts.

Background of the invention

There are several processes disclosed in the prior art for the preparation of sunitinib base (VII) and its malate salt. These processes generally involve the condensation of a pyrrole derivative and a 2-oxindole derivative in the presence of a base to form sunitinib free base (VII). The free base (VII) is then converted into the malate salt by treating the free base (VII) with malic acid.

(1) US 6573293, US 2006/0009510 and J. Org. Chem., 2003, vol. 68(16), pages 6447-6450 describe the condensation of an appropriate pyrrole derivative with a 2-

oxindole derivative in the presence of pyrrolidine or potassium hydroxide as a base to afford sunitinib free base (VII).

(2) WO 03/070725 and US 7119209 describe a three component condensation, comprising reacting an appropriate pyrrole derivative with a 2-oxindole derivative and the additional step of reacting an amine with the pyrrole substituted indolinone to form sunitinib free base (VII).

(3) US 7125905 and US 7435832 describe a process for the preparation of sunitinib malate from sunitinib free base (VII) and malic acid.

(4) Another approach for the preparation of sunitinib base (VII) is described in WO 2010/001167 where N-[2-(diethylamino)ethyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide and 5-fluoro-3-formyl-2-oxindole are condensed in the presence of an acid catalyst.

(5) An approach for the direct preparation of sunitinib malate is described in WO 2009/150523 and involves the condensation of the malic acid salt of N-[2-(diethylamino)ethyl]-5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxamide and 5-fluoro-2-oxindole (5-fluoro-1,3-dihydroindol-2-one) in the presence of an organic amine.

There are also several patents and patent applications describing various approaches to synthesizing the key pyrrole derivatives disclosed above.

With the exception of WO 2009/150523, the above prior art processes involve the isolation of sunitinib base (VII) before conversion to a salt thereof. However, the inventors have found several drawbacks in working with sunitinib base (VII):

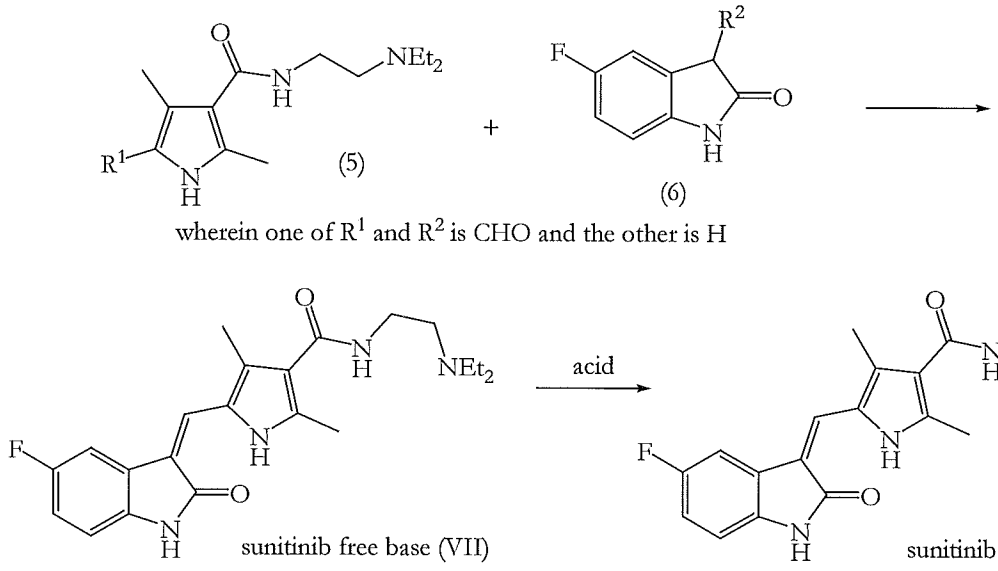
(1) Due to the low solubility profile of sunitinib base (VII) in a significant number of typically used organic solvents, large amounts of solvent and high temperatures are required for purification of the sunitinib base (VII). This is particularly disadvantageous on an industrial scale, where the base (VII) may require several

purification steps to meet the quality specifications required for human consumption.

(2) Typically sunitinib base (VII) is a powder having a very fine particle nature. This makes processing such a powder difficult, particularly on an industrial scale.

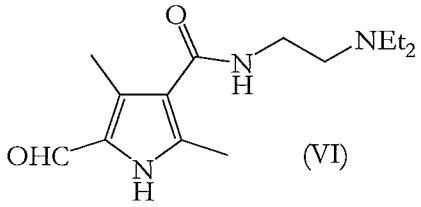
(3) Conversion of sunitinib base (VII) to sunitinib malate involves the addition of a solution comprising malic acid to the sunitinib base (VII). The aforementioned problems of solubility of the base (VII) in commonly used solvents mean that the initial reaction mass is a suspension. Sunitinib malate salt also has very poor solubility in common solvents. However, compared to sunitinib base (VII), the corresponding malate salt is much easier to filter and is amenable to purification. Thus the complete formation of the sunitinib malate salt during this step is difficult to judge due to the heterogeneous nature of the reaction mass during the reaction.

The prior art processes all require the presence of a carbonyl group either on the pyrrole derivative or the oxindole derivative. Scheme 1 shows a generalised scheme for preparing sunitinib malate according to the prior art.

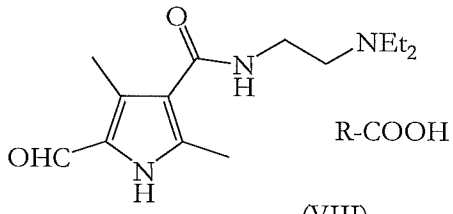


Scheme 1

The inventors have found that the use of pyrrole intermediates with these carbonyl groups results in unreacted carbonyl pyrrole derivatives (VI) and (VIII) as contaminants.



(VI)



(VIII)

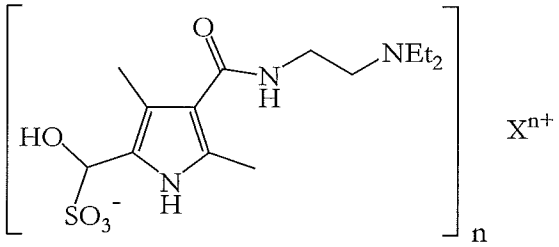
In view of the importance of pyrrole substituted indolinones such as sunitinib in the treatment of cancer, there is a great need for developing an improved and commercially feasible process for the preparation of sunitinib and its salts. In particular there is a need for a process that results in pure sunitinib or a salt thereof, in particular sunitinib malate, without the presence of aldehyde contaminants (VI) and (VIII) or the need for a further purification step. There is also a need for a one pot process that results in a sunitinib salt, wherein sunitinib base (VII) does not need to be isolated separately. Any new process should be advantageous in terms of cost and operability in manufacturing, and result in sunitinib or a salt thereof having high purity.

Summary of the invention

In order to overcome the problems associated with the prior art, in particular handling sunitinib base (VII) and preparing particularly pure sunitinib salts such as sunitinib malate, the inventors have found that when a sulphite intermediate (I) is reacted with 5-fluoro-2-oxindole (II), or when a sulphite intermediate (IIa) is reacted with pyrrole derivative (Ia), preferably in the presence of an amine derived or ammonium derived salt, particularly pure sunitinib or a salt thereof comprising undetectable amounts of compounds (VI) and (VIII) is obtained.

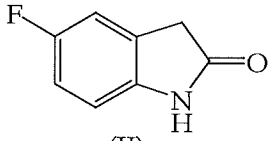
Accordingly, there is provided in a first aspect of the invention a process for preparing sunitinib (VII) or a salt thereof comprising:

either reacting a pyrrole derivative (I)



(I)

with 5-fluoro-2-oxindole (II)

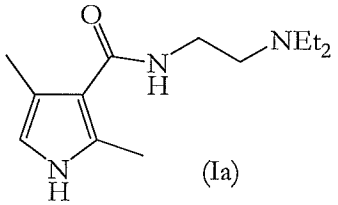


(II)

,

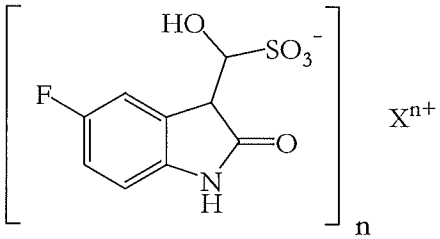
wherein X is a suitable cation and n is 1, 2 or 3;

or reacting pyrrole derivative (Ia)



(Ia)

with a 5-fluoro-2-oxindole derivative (IIa)

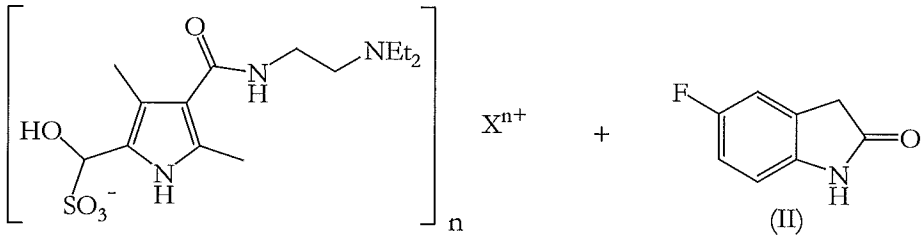


(IIa)

,

wherein X is a suitable cation and n is 1, 2 or 3.

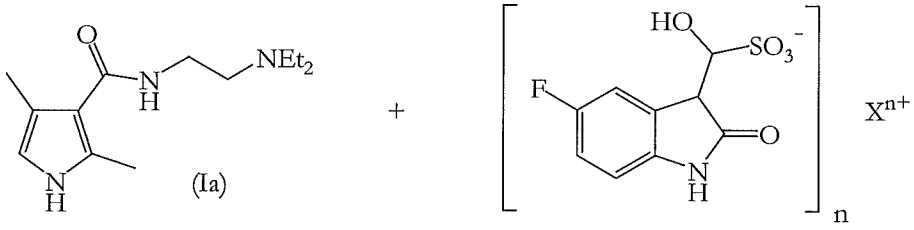
Scheme 2 shows a generalised scheme for preparing sunitinib or a salt thereof according to the invention. Route A relates to preparing sunitinib acid addition salts by adding an amine derived or ammonium derived salt of the acid to the reaction mixture. Route B relates to the preparation of sunitinib acid addition salts by preparing sunitinib base (VII) and subsequent in situ addition of the desired acid.



(I), wherein X is a suitable cation and n is 1, 2 or 3

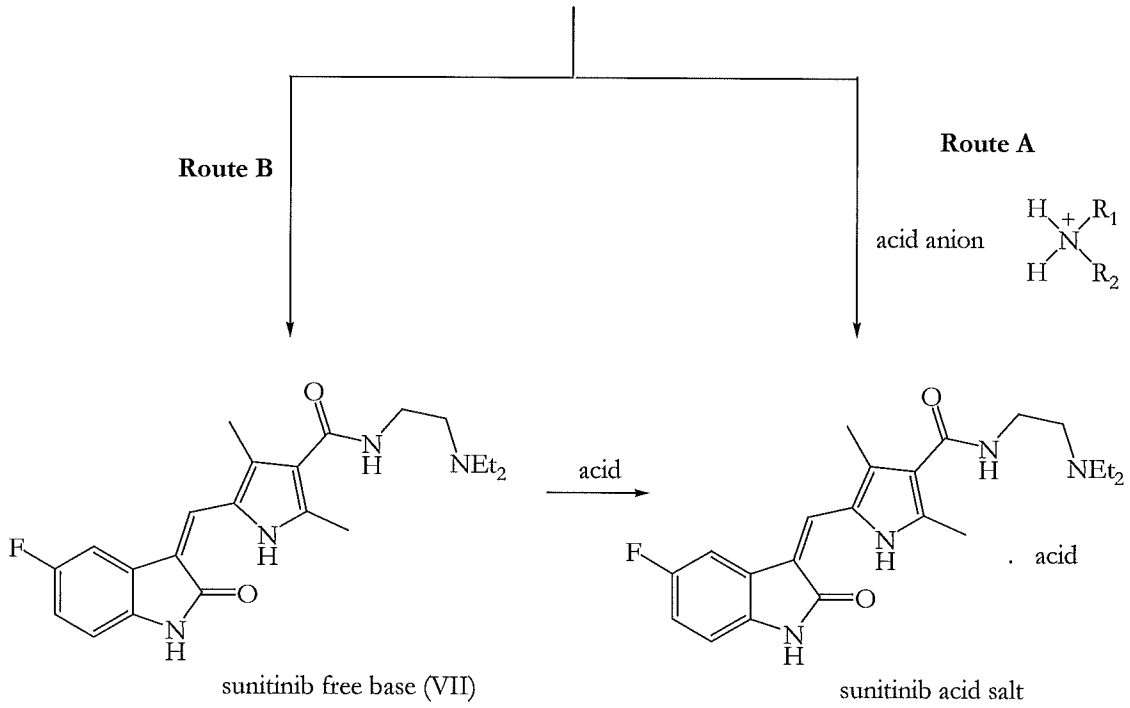
(II)

OR



(Ia)

(IIa), wherein X is a suitable cation and n is 1, 2 or 3



sunitinib free base (VII)

sunitinib acid salt

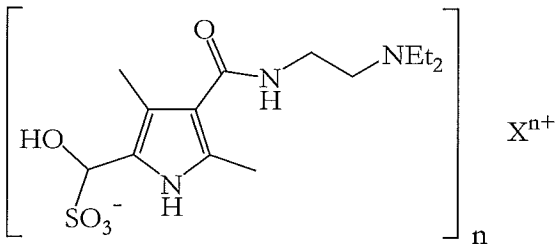
Scheme 2

In a preferred embodiment of the first aspect of the invention, the inventors have found that when sulphite intermediate (I) is reacted with 5-fluoro-2-oxindole (II), preferably in

the presence of an amine derived or ammonium derived salt, particularly pure sunitinib or a salt thereof comprising undetectable amounts of compounds (VI) and (VIII) is obtained.

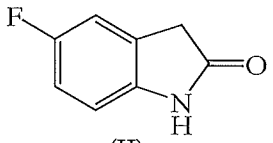
Accordingly, in a preferred embodiment of the first aspect of the invention, there is provided a process for preparing sunitinib (VII) or a salt thereof comprising:

reacting a pyrrole derivative (I)



(I)

with 5-fluoro-2-oxindole (II)



(II)

,

wherein X is a suitable cation and n is 1, 2 or 3.

In preferred embodiments, a process for preparing an acid addition salt of sunitinib is provided comprising adding an acid to the reaction mixture. The acid may comprise an inorganic acid for example selected from the group comprising HCl, HBr, HNO_3, H_3PO_4, H_2SO_4 and $HClO_4$. Alternatively the acid may comprise an organic acid, preferably the organic moiety of the organic acid is a straight or branched chain, substituted or unsubstituted alkyl, alkenyl, allyl, aryl or arylalkyl group, or a heteroatom-substituted straight or branched chain alkyl or aryl group. In particularly preferred embodiments, the organic acid is selected from the group comprising sulfonic acids, mono-, di- and tri-carboxylic acids. In particularly preferred embodiments, the organic acid is selected from the group comprising acetic acid, formic acid, oxalic acid, D-malic acid, L-malic acid, DL-malic acid, maleic acid, methane sulfonic acid, ethane sulfonic acid, p-toluene sulfonic acid, salicylic acid, tartaric acid, citric acid, succinic acid and malonic acid. Preferably the acid is L-malic acid and the resulting salt is sunitinib L-malate (IV).

Alternatively, in particularly preferred embodiments, acid addition salts of sunitinib may be prepared by adding an amine derived or ammonium derived salt of the acid to the reaction mixture. In a preferred embodiment, the acid moiety is an inorganic acid for example selected from the group comprising HCl, HBr, HNO_3, H_3PO_4, H_2SO_4 and $HClO_4$. In an alternative embodiment, the acid moiety is an organic acid, preferably the organic moiety of the organic acid is a straight or branched chain, substituted or unsubstituted alkyl, alkenyl, allyl, aryl or arylalkyl group, or a heteroatom-substituted straight or branched chain alkyl or aryl group. In particularly preferred embodiments, the organic acid is selected from the group comprising sulfonic acids, mono-, di- and tri-carboxylic acids. In particularly preferred embodiments, the organic acid is selected from the group comprising acetic acid, formic acid, oxalic acid, D-malic acid, L-malic acid, DL-malic acid, maleic acid, methane sulfonic acid, ethane sulfonic acid, p-toluene sulfonic acid, salicylic acid, tartaric acid, citric acid, succinic acid and malonic acid. Most advantageously the acid is L-malic acid.

Examples of organic acids, wherein the organic moiety of the organic acid is a straight or branched chain, substituted or unsubstituted alkyl group, are acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, malic acid, tartaric acid, citric acid, methane sulfonic acid, ethane sulfonic acid, trifluoroacetic acid, chloroacetic acid, glycine, pyruvic acid, thioglycolic acid, histidine, phenylalanine and thioacetic acid. Examples of organic acids, wherein the organic moiety of the organic acid is a straight or branched chain, substituted or unsubstituted alkenyl group, are maleic acid and fumaric acid. Examples of organic acids, wherein the organic moiety of the organic acid is a straight or branched chain, substituted or unsubstituted allyl group, are acrylic acid and methacrylic acid. Examples of organic acids, wherein the organic moiety of the organic acid is a straight or branched chain, substituted or unsubstituted aryl group, are benzoic acid, p-toluene sulfonic acid, salicylic acid, 3-pyridine-acetic acid and pyrazole-3-carboxylic acid. Examples of organic acids, wherein the organic moiety of the organic acid is a straight or branched chain, substituted or unsubstituted arylalkyl group, are phenyl acetic acid and 4-hydroxy phenyl acetic acid. Examples of organic acids, wherein the organic moiety of the organic acid is a heteroatom-substituted straight or branched chain alkyl group, are oxalic acid, malonic acid, succinic acid, malic acid, tartaric acid, citric acid, trifluoroacetic acid, chloroacetic acid, glycine, pyruvic acid, thioglycolic acid, histidine and phenylalanine. Examples of organic acids, wherein the organic moiety of the organic acid is a heteroatom-substituted straight or

branched chain aryl group, are salicylic acid, 3-pyridine-acetic acid and pyrazole-3-carboxylic acid.

In particularly preferred embodiments, when an amine derived or ammonium derived acid addition salt is added to the reaction mixture, the amine or ammonium moiety is selected from the group comprising primary amines and secondary amines, preferably the amine or ammonium moiety is selected from the group comprising cyclic amines, allyl amines, arylalkyl amines, heteroalkyl amines, alkyl amines, alkenyl amines, alkynyl amines and aryl amines.

Examples of primary amines are alkyl amines and aryl amines. Examples of secondary amines are dialkyl amines, alkyl aryl amines, diaryl amines and alkyl arylalkyl amines. Examples of cyclic amines are pyrrolidine and piperidine. Examples of arylalkyl amines are alkyl arylalkyl amines such as N-methyl benzyl amine. Examples of heteroalkyl amines are 2-amino-pyrrolidine and N,N-dimethyl ethylene diamine. Examples of alkyl amines are ethyl amine, dimethyl amine, diethyl amine, dipropyl amine, dibutyl amine and dicyclohexyl amine.

In the most advantageous embodiments, the amine or ammonium derived acid addition salt is a malate salt, preferably selected from the group comprising 2-(N,N-diethylamino)ethyl ammonium malate, 2-(N,N-diethylamino)ethyl ammonium dimalate, diammonium malate, dipyrrolidine malate, di-(n-propyl ammonium) malate, and di-(diisopropyl ammonium) malate.

In a preferred embodiment according to the first aspect of the invention, X is a metal cation, preferably an alkali metal or an alkaline earth metal cation. Advantageously the metal cation is either sodium or potassium, most advantageously sodium.

In a preferred embodiment according to the first aspect of the invention, the sunitinib or salt thereof is isolated. In particularly preferred embodiments, the sunitinib or salt thereof is further purified by recrystallisation from a C_1-C_6 alcohol : water mixture, preferably the C_1-C_6 alcohol : water mixture has a v/v ratio of about 4:1. Most preferably the C_1-C_6 alcohol is n-butanol.

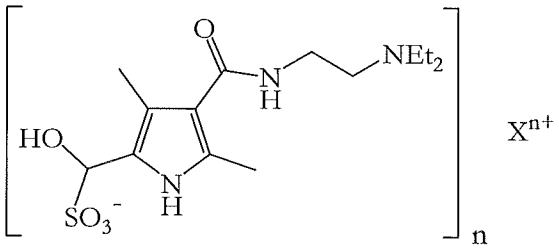
In certain preferred embodiments of a process according to the first aspect of the invention, the reaction is carried out at a temperature of between about 0°C to about 50°C, preferably at between about 20°C to about 40°C, most preferably at between about 25°C to about 35°C.

In further preferred embodiments of a process according to the first aspect of the invention, the process is carried out in an organic solvent system, preferably the organic solvent system comprises acetonitrile and methanol. Advantageously the v/v ratio of acetonitrile : methanol is from about 5:1 to about 1:5. Most advantageously the v/v ratio of acetonitrile : methanol is about 3:2.

In further advantageous embodiments according to the first aspect of the invention, the reaction mixture has a pH of between 4.0 to 7.0, preferably between 4.0 to 6.0, most preferably between 4.0 to 5.0.

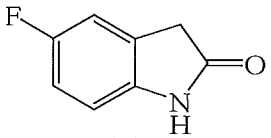
A most preferred embodiment according to the first aspect of the invention provides a process for preparing sunitinib malate comprising:

reacting a pyrrole derivative (I)



(I)

with 5-fluoro-2-oxindole (II)



(II)

in the presence of malic acid or an amine derived or ammonium derived malic acid salt; and

isolating the sunitinib malate;

wherein X is a suitable cation and n is 1, 2 or 3.

In this most preferred embodiment, preferably the malic acid or malic acid salt used is L-malic acid or an L-malic acid salt, such that the process provides sunitinib L-malate (IV).

In this most preferred embodiment, preferably the amine derived or ammonium derived malic acid salt is selected from the group comprising 2-(N,N-diethylamino)ethyl ammonium malate, 2-(N,N-diethylamino)ethyl ammonium dimalate, diammonium malate, dipyrrolidine malate, di-(n-propyl ammonium) malate, and di-(diisopropyl ammonium) malate. Preferably the amine derived or ammonium derived malic acid salt is 2-(N,N-diethylamino)ethyl ammonium dimalate.

In this most preferred embodiment, preferably X is sodium.

In this most preferred embodiment, preferably the sunitinib malate is further purified by recrystallisation from a n-butanol : water mixture having a v/v ratio of about 4:1.

In this most preferred embodiment, preferably the temperature of the reaction is between 25°C to 35°C.

In this most preferred embodiment, preferably the process is carried out in an organic solvent system comprising acetonitrile and methanol having a v/v ratio of acetonitrile : methanol of about 3:2.

In this most preferred embodiment, preferably the pH of the reaction mixture is between 4 to 6.

In any process of the first aspect of the present invention, preferably the sunitinib or salt thereof is obtained in a yield of 60% or more, preferably 70% or more, preferably 80% or more, from the pyrrole derivative (I) and/or the 5-fluoro-2-oxindole (II), or from the pyrrole derivative (Ia) and/or the 5-fluoro-2-oxindole derivative (IIa).

In any process of the first aspect of the present invention, preferably the sunitinib or salt thereof is obtained on a commercial scale, preferably in batches of 0.5kg or more, 1kg or more, 10kg or more, 100kg or more, 500kg or more, or 1000kg or more.

A second aspect of the present invention provides sunitinib or a salt thereof prepared by a process according to the first aspect of the present invention, having a purity as determined by HPLC of at least 97%, preferably at least 99%, preferably at least 99.5%, most preferably at least 99.8%. In particularly preferred embodiments, the sunitinib salt is sunitinib malate, preferably sunitinib L-malate (IV).

A third aspect of the present invention provides sunitinib or a salt thereof comprising less than 3% of compound (VI) and/or compound (VIII), preferably less than 1%, advantageously less than 0.1%, most advantageously less than 0.01%. In particularly preferred embodiments, the sunitinib salt is sunitinib malate, preferably sunitinib L-malate (IV).

Preferably the process according to the first aspect of the invention provides sunitinib or a salt thereof having a polymorphic purity such that the presence of other polymorphic forms is undetectable. Preferably the sunitinib or salt thereof according to the second or third aspect of the invention or prepared by a process according to the first aspect of the invention has a polymorphic purity of at least 97%, preferably at least 99%, preferably at least 99.5%, most preferably at least 99.8%, preferably as determined by XRPD. Preferably the sunitinib free base (VII) is in polymorphic form I as defined in WO 2010/023473. Preferably the sunitinib salt is sunitinib L-malate (IV) in polymorphic form I as defined in US 7435832.

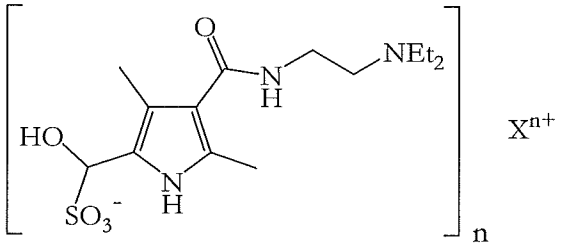
Preferably the sunitinib or salt thereof according to the second or third aspect of the invention or prepared by a process according to the first aspect of the invention is suitable for use in medicine, preferably for treating a protein kinase mediated disorder, preferably for treating a cell proliferative disorder, preferably for treating renal cell carcinoma (RCC) or gastrointestinal stromal tumor (GIST).

A fourth aspect of the present invention provides a pharmaceutical composition comprising sunitinib or a salt thereof according to the second or third aspect of the invention or prepared by a process according to the first aspect of the invention, and one or more pharmaceutically acceptable excipients. Most preferably the sunitinib salt is sunitinib malate, preferably sunitinib L-malate (IV). Preferably the composition is for use in the treatment of a protein kinase mediated disorder, in certain embodiments the disorder is a cell proliferative disorder, and in further embodiments the disorder is one of renal cell carcinoma (RCC) or gastrointestinal stromal tumor (GIST).

A fifth aspect of the present invention provides use of sunitinib or a salt thereof according to the second or third aspect of the invention or prepared by a process according to the first aspect of the invention, or use of a pharmaceutical composition according to the fourth aspect of the invention, in the manufacture of a medicament for treating a protein kinase mediated disorder. Preferably the medicament is suitable for treating a cell proliferative disorder, preferably renal cell carcinoma (RCC) or gastrointestinal stromal tumor (GIST).

A sixth aspect of the present invention provides a method of treating a protein kinase mediated disorder, comprising administering to a patient in need thereof a therapeutically effective amount of sunitinib or a salt thereof according to the second or third aspect of the invention or prepared by a process according to the first aspect of the invention, or a therapeutically effective amount of a pharmaceutical composition according to the fourth aspect of the invention. Preferably the method is suitable for treating a cell proliferative disorder, preferably renal cell carcinoma (RCC) or gastrointestinal stromal tumor (GIST). Preferably the patient is a mammal, preferably a human.

A seventh aspect of the invention provides a pyrrole derivative (I)



(I)

,

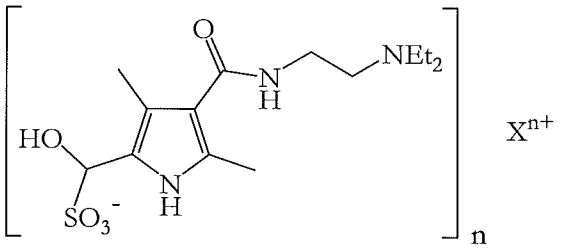
wherein X is a suitable cation and n is 1, 2 or 3.

In a preferred embodiment according to the seventh aspect of the invention, X is a metal cation, preferably an alkali metal or an alkaline earth metal cation. Advantageously the metal cation is either sodium or potassium, most advantageously sodium.

Preferably the pyrrole derivative (I) has a purity as determined by HPLC of at least 97%, preferably at least 99%, preferably at least 99.5%, most preferably at least 99.8%.

Preferably the pyrrole derivative (I) comprises less than 3% of compound (VI) and/or compound (VIII), preferably less than 1%, advantageously less than 0.1%, most advantageously less than 0.01%.

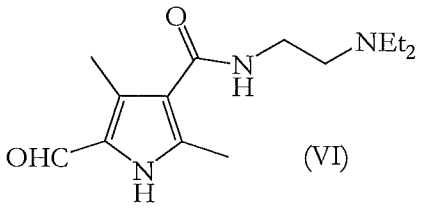
An eighth aspect of the invention provides a process for preparing a pyrrole derivative (I):



(I)

,

wherein X is a suitable cation and n is 1, 2 or 3, the process comprising reacting aldehyde (VI):



(VI)

with a bisulphite anion of formula HSO_3^-.

In a preferred embodiment according to the eighth aspect of the invention, X is a metal cation, preferably an alkali metal or an alkaline earth metal cation. Advantageously the metal cation is either sodium or potassium, most advantageously sodium.

Preferably the bisulphite anion is provided by mixing a metabisulphite salt in the reaction mixture. Preferably the metabisulphite salt is a salt of an alkali metal or an alkaline earth metal. Advantageously the salt is an alkali metal metabisulphite salt, preferably sodium or potassium metabisulphite, most preferably the alkali metal metabisulphite is sodium metabisulphite $Na_2S_2O_5$.

Alternatively a bisulphite salt could be used, preferably an alkali metal or alkaline earth metal bisulphite salt. Advantageously the salt is an alkali metal bisulphite salt, preferably sodium or potassium bisulphite, most preferably the alkali metal bisulphite is sodium bisulphite $NaHSO_3$.

Preferably the bisulphite anion is used in an amount of 1 to 5 equivalents, preferably 1 to 3 equivalents, relative to the aldehyde (VI).

In certain preferred embodiments of a process according to the eighth aspect of the invention, the reaction occurs in an aqueous C_1-C_5 alcohol solvent system. Preferably the C_1-C_5 alcohol is ethanol.

In further preferred embodiments, the reaction occurs at a temperature in the range of -10°C to reflux of the alcohol. Most preferably the reaction occurs at a temperature in the range of 10°C to 30°C.

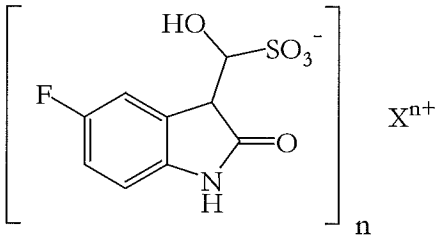
In further advantageous embodiments according to the eighth aspect of the invention, the reaction mixture has a pH of between 4.0 to 7.0, preferably between 4.0 to 6.0, most preferably between 4.0 to 5.0.

In certain preferred embodiments, the pyrrole derivative (I) is further isolated, preferably by filtration.

In the process of the eighth aspect of the present invention, preferably the pyrrole derivative (I) is obtained in a yield of 60% or more, preferably 70% or more, preferably 80% or more, from the aldehyde (VI).

In the process of the eighth aspect of the present invention, preferably the pyrrole derivative (I) is obtained on a commercial scale, preferably in batches of 0.1kg or more, 0.5kg or more, 1kg or more, 10kg or more, 100kg or more, 500kg or more, or 1000kg or more.

A ninth aspect of the invention provides a 5-fluoro-2-oxindole derivative (IIa)



(IIa)

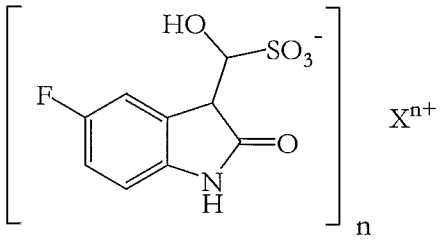
,

wherein X is a suitable cation and n is 1, 2 or 3.

In a preferred embodiment according to the ninth aspect of the invention, X is a metal cation, preferably an alkali metal or an alkaline earth metal cation. Advantageously the metal cation is either sodium or potassium, most advantageously sodium.

Preferably the 5-fluoro-2-oxindole derivative (IIa) has a purity as determined by HPLC of at least 97%, preferably at least 99%, preferably at least 99.5%, most preferably at least 99.8%.

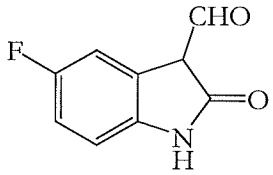
A tenth aspect of the invention provides a process for preparing a 5-fluoro-2-oxindole derivative (IIa):



(IIa)

,

wherein X is a suitable cation and n is 1, 2 or 3, the process comprising reacting aldehyde (IIb):



(IIb)

with a bisulphite anion of formula HSO_3^-.

In a preferred embodiment according to the tenth aspect of the invention, X is a metal cation, preferably an alkali metal or an alkaline earth metal cation. Advantageously the metal cation is either sodium or potassium, most advantageously sodium.

Preferably the bisulphite anion is provided by mixing a metabisulphite salt in the reaction mixture. Preferably the metabisulphite salt is a salt of an alkali metal or an alkaline earth metal. Advantageously the salt is an alkali metal metabisulphite salt, preferably sodium or potassium metabisulphite, most preferably the alkali metal metabisulphite is sodium metabisulphite $Na_2S_2O_5$.

Alternatively a bisulphite salt could be used, preferably an alkali metal or alkaline earth metal bisulphite salt. Advantageously the salt is an alkali metal bisulphite salt, preferably sodium or potassium bisulphite, most preferably the alkali metal bisulphite is sodium bisulphite $NaHSO_3$.

Preferably the bisulphite anion is used in an amount of 1 to 5 equivalents, preferably 1 to 3 equivalents, relative to the aldehyde (IIb).

In certain preferred embodiments of a process according to the tenth aspect of the invention, the reaction occurs in an aqueous C_1-C_5 alcohol solvent system. Preferably the C_1-C_5 alcohol is ethanol.

In further preferred embodiments, the reaction occurs at a temperature in the range of -10°C to reflux of the alcohol. Most preferably the reaction occurs at a temperature in the range of 10°C to 30°C.

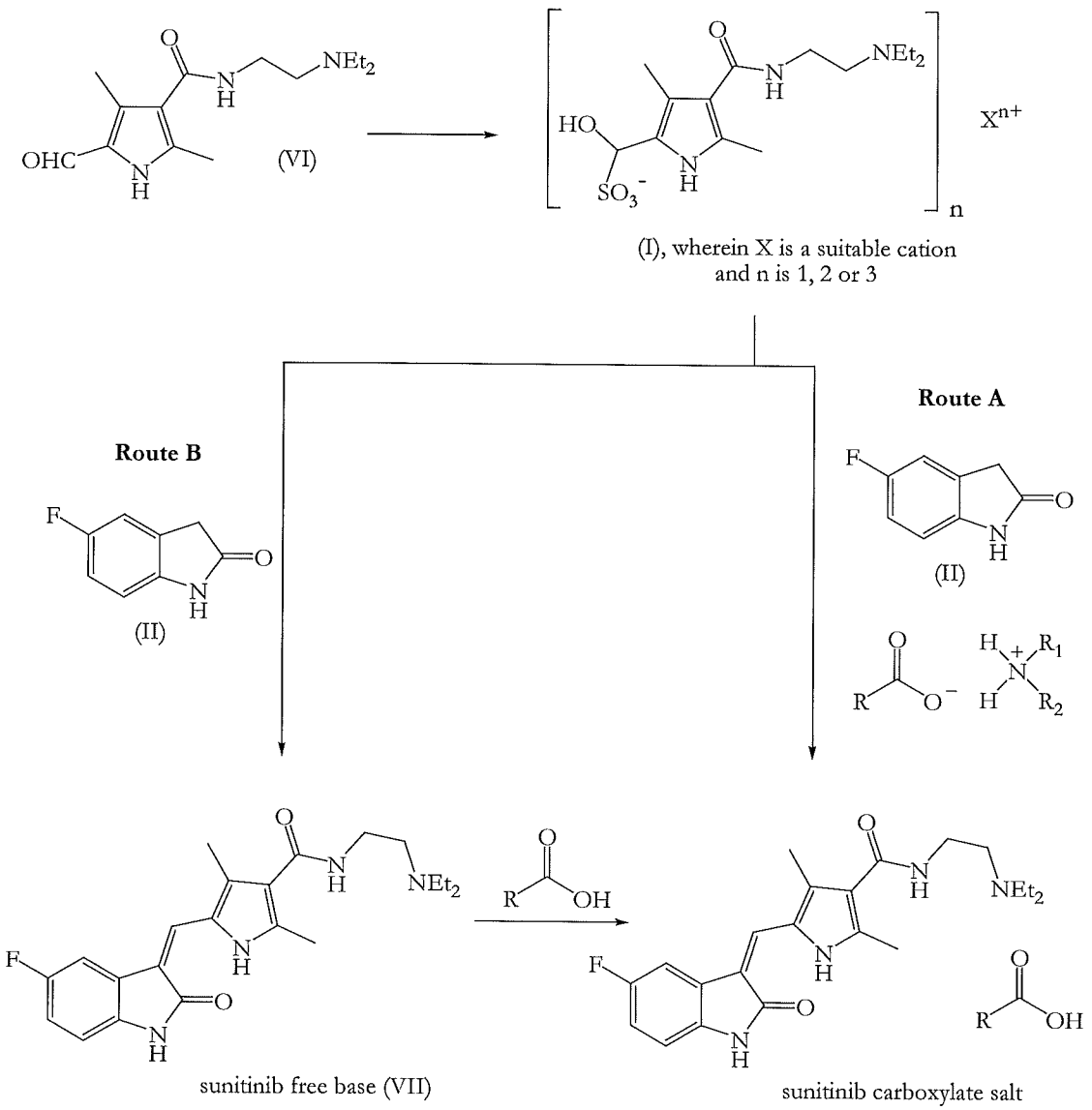
In further advantageous embodiments according to the tenth aspect of the invention, the reaction mixture has a pH of between 4.0 to 7.0, preferably between 4.0 to 6.0, most preferably between 4.0 to 5.0.

In certain preferred embodiments, the 5-fluoro-2-oxindole derivative (IIa) is further isolated, preferably by filtration.

In the process of the tenth aspect of the present invention, preferably the 5-fluoro-2-oxindole derivative (IIa) is obtained in a yield of 60% or more, preferably 70% or more, preferably 80% or more, from the aldehyde (IIb).

In the process of the tenth aspect of the present invention, preferably the 5-fluoro-2-oxindole derivative (IIa) is obtained on a commercial scale, preferably in batches of 0.1kg or more, 0.5kg or more, 1kg or more, 10kg or more, 100kg or more, 500kg or more, or 1000kg or more.

Scheme 3 shows a generalised scheme for preparing sunitinib or a salt thereof via pyrrole derivative (I) according to the invention. Route A relates to preparing sunitinib acid addition salts by adding an amine derived or ammonium derived salt of the acid to the reaction mixture, in this case the acid moiety is a carboxylic acid. Route B relates to the preparation of sunitinib acid addition salts by preparing sunitinib base (VII) and subsequent in situ addition of the desired acid, in this case a carboxylic acid.



Scheme 3

Brief description of the drawings

Figure 1 shows a XRP diffractogram of sunitinib L-malate (IV) in polymorphic form I as disclosed in US 7435832. Sunitinib L-malate (IV) in polymorphic form I has an X-ray diffraction pattern comprising peaks at 13.2, 19.4, 24.2 and 25.5 ± 0.2 degrees 2-theta. Preferably sunitinib L-malate (IV) in polymorphic form I has an X-ray diffraction pattern comprising peaks at 13.2, 19.4, 21.3, 22.1, 24.2 and 25.5 ± 0.2 degrees 2-theta.

Figure 2 shows a differential scanning calorimetry (DSC) trace of sunitinib L-malate (IV) in polymorphic form I as disclosed in US 7435832. Sunitinib L-malate (IV) in polymorphic form I has an endothermic peak at about 198°C ± 2°C, when a rate of heating of 10°C/min is used.

Figure 3 shows a XRP diffractogram of sunitinib free base (VII) in polymorphic form I as disclosed in WO 2010/023473. Sunitinib free base (VII) in polymorphic form I has an X-ray diffraction pattern comprising peaks at 4.48 and 8.88 ± 0.2 degrees 2-theta. Preferably sunitinib free base (VII) in polymorphic form I has an X-ray diffraction pattern comprising peaks at 4.48, 7.07, 8.88, 10.57, 11.38, 12.78, 13.51, 14.95, 16.41, 18.86, 19.61, 20.58, 21.59, 22.53, 22.87, 23.09, 25.68, 27.22, 28.07, 29.19, 32.61, 34.09, 36.00, 41.93 and 44.00 ± 0.2 degrees 2-theta.

Figure 4 shows a differential scanning calorimetry (DSC) trace of sunitinib free base (VII) in polymorphic form I as disclosed in WO 2010/023473. Sunitinib free base (VII) in polymorphic form I has an endothermic peak at about 244°C ± 2°C, when a rate of heating of 10°C/min is used.

Detailed description of the invention

For the purposes of the present invention, an "alkyl" group is defined as a monovalent saturated hydrocarbon, which may be straight-chained or branched, or be or include cyclic groups. An alkyl group may optionally include one or more heteroatoms N, O or S in its carbon skeleton. Examples of alkyl groups are methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl and *n*-pentyl groups. Preferably an alkyl group is straight-chained or branched, and does not include any heteroatoms in its carbon skeleton. Preferably an alkyl group is a C_1-C_{12} alkyl group, preferably a C_1-C_6 alkyl group. An "alkylene" group is similarly defined as a divalent alkyl group.

An "alkenyl" group is defined as a monovalent hydrocarbon, which comprises at least one carbon-carbon double bond, which may be straight-chained or branched, or be or include cyclic groups. An alkenyl group may optionally include one or more heteroatoms N, O or S in its carbon skeleton. Examples of alkenyl groups are vinyl, allyl, but-1-enyl and but-2-enyl

groups. Preferably an alkenyl group is straight-chained or branched, and does not include any heteroatoms in its carbon skeleton. Preferably an alkenyl group is a C_2-C_{12} alkenyl group, preferably a C_2-C_6 alkenyl group. An "alkenylene" group is similarly defined as a divalent alkenyl group.

An "alkynyl" group is defined as a monovalent hydrocarbon, which comprises at least one carbon-carbon triple bond, which may be straight-chained or branched, or be or include cyclic groups. An alkynyl group may optionally include one or more heteroatoms N, O or S in its carbon skeleton. Examples of alkynyl groups are ethynyl, propargyl, but-1-ynyl and but-2-ynyl groups. Preferably an alkynyl group is straight-chained or branched, and does not include any heteroatoms in its carbon skeleton. Preferably an alkynyl group is a C_2-C_{12} alkynyl group, preferably a C_2-C_6 alkynyl group. An "alkynylene" group is similarly defined as a divalent alkynyl group.

An "aryl" group is defined as a monovalent aromatic hydrocarbon. An aryl group may optionally include one or more heteroatoms N, O or S in its carbon skeleton. Examples of aryl groups are phenyl, naphthyl, anthracenyl and phenanthrenyl groups. Preferably an aryl group does not include any heteroatoms in its carbon skeleton. Preferably an aryl group is a C_4-C_{14} aryl group, preferably a C_6-C_{10} aryl group. An "arylene" group is similarly defined as a divalent aryl group.

For the purposes of the present invention, a "heteroatom" is defined as N, O, S, F, Cl, Br or I, preferably as N, O or S.

For the purposes of the present invention, where a combination of groups is referred to as one moiety, for example, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl, the last mentioned group contains the atom by which the moiety is attached to the rest of the molecule. Preferably the groups, where a combination of groups is referred to as one moiety, comprise 4-18 carbon atoms. A typical example of an arylalkyl group is benzyl.

For the purposes of this invention, an optionally substituted group may be substituted with one or more of -F, -Cl, -Br, -I, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, -SH, $-NH_2$, -CN, $-NO_2$,

-COOH, $-R^x-O-R^y$, $-R^x-S-R^y$, $-R^x-SO-R^y$, $-R^x-SO_2-R^y$, $-R^x-SO_2-OR^y$, $-R^xO-SO_2-R^y$, $-R^x-SO_2-N(R^y)_2$, $-R^x-NR^y-SO_2-R^y$, $-R^xO-SO_2-OR^y$, $-R^xO-SO_2-N(R^y)_2$, $-R^x-NR^y-SO_2-OR^y$, $-R^x-NR^y-SO_2-N(R^y)_2$, $-R^x-N(R^y)_2$, $-R^x-N(R^y)_3^+$, $-R^x-P(R^y)_2$, $-R^x-Si(R^y)_3$, $-R^x-CO-R^y$, $-R^x-CO-OR^y$, $-R^xO-CO-R^y$, $-R^x-CO-N(R^y)_2$, $-R^x-NR^y-CO-R^y$, $-R^xO-CO-OR^y$, $-R^xO-CO-N(R^y)_2$, $-R^x-NR^y-CO-OR^y$, $-R^x-NR^y-CO-N(R^y)_2$, $-R^x-CS-R^y$, $-R^x-CS-OR^y$, $-R^xO-CS-R^y$, $-R^x-CS-N(R^y)_2$, $-R^x-NR^y-CS-R^y$, $-R^xO-CS-OR^y$, $-R^xO-CS-N(R^y)_2$, $-R^x-NR^y-CS-OR^y$, $-R^x-NR^y-CS-N(R^y)_2$ or $-R^y$, or a bridging substituent such as -O-, -S-, $-NR^y-$ or $-R^x-$, or a π-bonded substituent such as =O, =S or $=NR^y$. In this context, $-R^x-$ is independently a chemical bond, a C_1-C_{10} alkylene, C_2-C_{10} alkenylene or C_2-C_{10} alkynylene group. $-R^y$ is independently hydrogen, unsubstituted C_1-C_6 alkyl or unsubstituted C_4-C_{10} aryl. Optional substituent(s) are not taken into account when calculating the total number of carbon atoms in the parent group substituted with the optional substituent(s). Preferably a substituted group comprises 1, 2 or 3 substituents, preferably 1 or 2 substituents, preferably 1 substituent.

Any optional substituent may be protected. Suitable protecting groups for protecting optional substituents are known in the art, for example from "Protective Groups in Organic Synthesis" by T.W. Greene and P.G.M. Wuts (Wiley-Interscience, 3rd edition, 1999).

As used herein the term "solvent system" should be taken to mean one of the following:

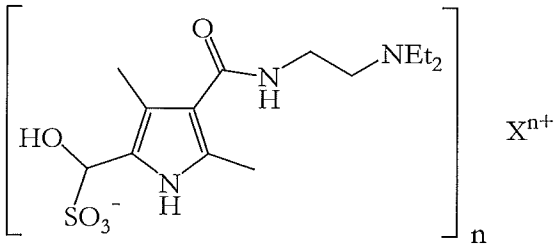
(1) a single organic solvent

(2) a combination of two or more organic solvents in various proportions

(3) a combination of water and one or more organic solvents in various proportions

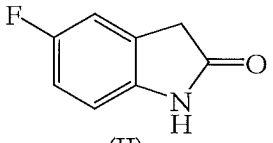
The inventors have found that utilising a novel sulphite pyrrole derivative (I) in the condensation reaction with a 2-oxindole, in particular 5-fluoro-2-oxindole (II), provides an alternative route to preparing pure sunitinib or a salt thereof, in particular sunitinib L-malate (IV). Accordingly, there is provided in a first aspect of the invention a process for preparing sunitinib or a salt thereof comprising:

reacting a pyrrole derivative (I)



(I)

with 5-fluoro-2-oxindole (II)



(II)

,

wherein X is a suitable cation and n is 1, 2 or 3.

In a preferred embodiment according to the first aspect of the invention, X is a metal cation, preferably an alkali metal or an alkaline earth metal cation. Advantageously the metal cation is either sodium or potassium, most advantageously sodium.

In a preferred embodiment of a process according to the first aspect of the invention, when an acid addition salt of sunitinib is prepared, the acid may be an inorganic acid, preferably selected from the group comprising HCl, HBr, HNO_3, H_3PO_4, H_2SO_4 and $HClO_4$. In an alternative embodiment, the acid is an organic acid, preferably the organic moiety of the organic acid is a straight or branched chain, substituted or unsubstituted alkyl, alkenyl, allyl, aryl or arylalkyl group, or a heteroatom-substituted straight or branched chain alkyl or aryl group. In particularly preferred embodiments, the organic acid is selected from the group comprising sulfonic acids, mono-, di- and tri-carboxylic acids. In particularly preferred embodiments, the organic acid is selected from the group comprising acetic acid, formic acid, oxalic acid, D-malic acid, L-malic acid, DL-malic acid, maleic acid, methane sulfonic acid, ethane sulfonic acid, p-toluene sulfonic acid, salicylic acid, tartaric acid, citric acid, succinic acid and malonic acid.

The inventors have found that when an acid addition salt derived from an organic amine or ammonium or derivatives thereof and an organic or inorganic acid is added to a reaction mass containing pyrrole derivative (I) and 5-fluoro-2-oxindole derivative (II), the resulting

corresponding sunitinib salt is obtained wherein the salt moiety is obtained from the acid of the initial organic amine or ammonium salt. The resulting sunitinib salt has surprisingly high purity and high quantitative yield. The reaction requires relatively reduced reaction times and most surprisingly the reaction can be carried out ambient temperatures. This aspect is not taught or even suggested in the prior art, which teaches reaction temperatures of greater than about 70°C. The process of the invention utilising salts derived from organic amines or ammonium and carboxylic acid derivatives results in a simpler, more cost effective, one pot process for the preparation of sunitinib salts, in particular sunitinib malate. The process of the present invention may also be used to prepare sunitinib base (VII) by simple condensation of pyrrole derivative (I) and 5-fluoro-2-oxindole derivative (II). The base (VII) may then be utilised conventionally to prepare acid addition salts, such as sunitinib L-malate (IV), by adding the desired acid, such as L-malic acid, to the reaction mixture.

In a preferred embodiment of a process according to the first aspect of the invention, when an acid addition salt of sunitinib is prepared using an amine derived or ammonium derived acid addition salt, the acid moiety may be an inorganic acid, preferably selected from the group comprising HCl, HBr, HNO_3, H_3PO_4, H_2SO_4 and $HClO_4$. In an alternative embodiment, the acid moiety is an organic acid, preferably the organic moiety of the organic acid is a straight or branched chain, substituted or unsubstituted alkyl, alkenyl, allyl, aryl or arylalkyl group, or a heteroatom-substituted straight or branched chain alkyl or aryl group. In particularly preferred embodiments, the organic acid is selected from the group comprising sulfonic acids, mono-, di- and tri-carboxylic acids. In particularly preferred embodiments, the organic acid is selected from the group comprising acetic acid, formic acid, oxalic acid, D-malic acid, L-malic acid, DL-malic acid, maleic acid, methane sulfonic acid, ethane sulfonic acid, p-toluene sulfonic acid, salicylic acid, tartaric acid, citric acid, succinic acid and malonic acid.

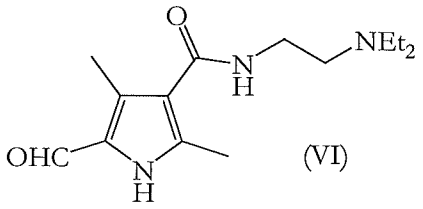
In a preferred embodiment of a process according to the first aspect of the invention, when an acid addition salt of sunitinib is prepared using an amine derived or ammonium derived acid addition salt, the amine or ammonium moiety is selected from the group comprising primary amines and secondary amines, preferably the amine or ammonium moiety is selected from the group comprising cyclic amines, allyl amines, arylalkyl amines,

heteroalkyl amines, alkyl amines, alkenyl amines, alkynyl amines and aryl amines. Most preferably the amine derived or ammonium derived acid addition salt is a malate salt selected from the group comprising 2-(N,N-diethylamino)ethyl ammonium malate, 2-(N,N-diethylamino)ethyl ammonium dimalate, diammonium malate, dipyrrolidine malate, di-(n-propyl ammonium) malate, and di-(diisopropyl ammonium) malate. Most preferably the amine derived or ammonium derived malate salt is 2-(N,N-diethylamino)ethyl ammonium dimalate.

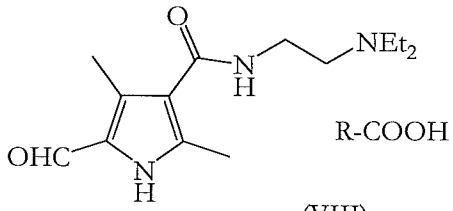
The amine derived or ammonium derived salt of the acid can be prepared by simply mixing the appropriate organic amine or ammonia or derivatives thereof and the appropriate acid in a solvent system and isolating the resulting salt either by filtration or by evaporation of the solvent system. The isolated salts were characterized by spectroscopic techniques to confirm that salts were actually prepared and the solution was not just a physical mixture of the organic amine or ammonia or derivatives thereof and the acid. The amine or ammonium derived acid salts are most preferably prepared using equimolar stoichiometry of the acid and the amine or ammonium moiety. Alternatively the acid and the amine or ammonium moiety may be used in a ratio of from about 1:2 to about 2:1. The amine or ammonium moieties and the acid moieties are preferably combined in a C_1-C_5 alcoholic solvent. Most preferably the alcoholic solvents are selected from the group comprising methanol, ethanol, propanol, isopropanol, butanol, pentanol and mixtures thereof. In preferred embodiments the reaction proceeds at a temperature of between about 10°C to about 80°C, preferably between about 20°C to about 50°C, and most preferably between about 25°C to about 35°C.

It should be noted that in the preparation of the amine or ammonium derived acid salts the different stoichiometry of the organic amine or ammonium moieties and the acid moieties results in the preparation of different salts. For example, 1 equivalent of 2-(N,N-diethylamino)ethyl amine reacted with 1 equivalent of malic acid results in 2-(N,N-diethylamino)ethyl ammonium malate, whereas 2-(N,N-diethylamino)ethyl ammonium dimalate is obtained when 1 equivalent of 2-(N,N-diethylamino)ethyl amine is reacted with 2 equivalents of malic acid.

The inventors have also found that sunitinib and salts thereof prepared using pyrrole derivative (I) do not comprise any detectable by-products normally associated with sunitinib preparation, in particular compounds (VI) and (VIII):



(VI)



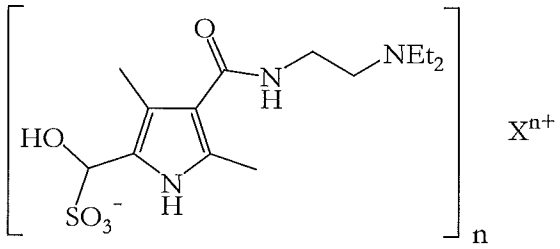
(VIII)

The prior art processes all require the presence of a carbonyl group either on the pyrrole derivative or the oxindole derivative. The inventors have found that use of pyrrole intermediates with these carbonyl groups results in unreacted carbonyl pyrrole derivatives (VI) and (VIII) as contaminants. The processes of the invention do not require these carbonyl intermediates. Indeed the absence of formyl intermediates (VI) and (VIII) was confirmed by spectroscopic analysis (IR, ^{1}H-NMR, HPLC) of the reaction mixture. The compounds (VI) and (VIII) were not detected at any point during the condensation reaction of the sulphite pyrrole derivative (I) and the 5-fluoro-2-oxindole derivative (II).

The preparation of sunitinib base (VII) or sunitinib acid addition salts from the corresponding pyrrole derivative (I) is preferably achieved under the influence of an amine derived or ammonium derived salt of the acid. This salt catalyses the condensation of the pyrrole derivative (I) and 5-fluoro-2-oxindole (II) under acidic pH. Typically the pH of the condensation reaction is between about 4.0-7.0, more preferably between about 4.0-5.5. As the pyrrole derivative (I) is prepared under the same pH conditions as the condensation reaction, the pyrrole derivative (I) remains intact and does not revert back to the corresponding aldehyde precursor (VI) during the reaction.

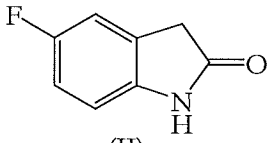
A most advantageous embodiment of the first aspect of the invention provides a process for the preparation of sunitinib malate, preferably sunitinib L-malate (IV), comprising:

reacting a pyrrole derivative (I)



(I)

with 5-fluoro-2-oxindole (II)



(II)

in the presence of malic acid or an amine derived or ammonium derived malic acid salt; and

isolating the sunitinib malate, preferably sunitinib L-malate (IV);

wherein X is a suitable cation and n is 1, 2 or 3.

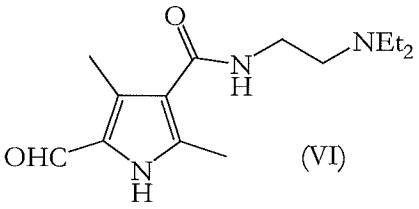
In any process of the first aspect of the present invention, the resulting sunitinib or salt thereof may be isolated by any means available to the skilled person. The inventors have found filtering the sunitinib or salt thereof to be particularly advantageous. The filtered solid may then be washed with a solvent, preferably an organic solvent. The most advantageous embodiments comprise washing with C_1-C_6 aliphatic alcohols, such as methanol or ethanol.

The washed or unwashed solid may then be allowed to dry or preferably is dried under vacuum. The conditions for drying are easily obtainable by the skilled person, but the inventors have found drying under vacuum at 55-60°C for between about 3 to 4 hours to be particularly advantageous.

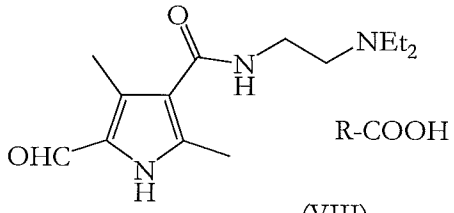
If required the isolated sunitinib or salt thereof may be further purified by recrystallisation from an organic solvent and/or water. The inventors have found a mixture of a C_1-C_6 alcohol and water in a v/v ratio of between 1:4 to 4:1, preferably about 4:1, preferably

wherein the C_1-C_6 alcohol is n-butanol, to be particularly advantageous in further purifying the sunitinib or salt thereof.

A second aspect of the invention provides sunitinib or a salt thereof prepared by a process according to the invention, having a purity as determined by HPLC of at least 97%, preferably at least 99%, preferably at least 99.5%, most preferably at least 99.8%. Preferably the sunitinib or salt thereof does not comprise compound (VI) or compound (VIII):



(VI)



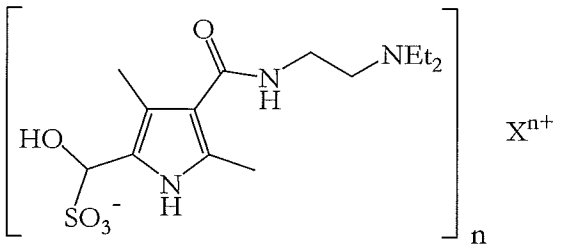
(VIII)

It is interesting to note that when one equivalent each of the pyrrole derivative (I) was treated with the L-malic acid salt of N,N-diethylethylenediamine, the corresponding expected malate salt could not be formed and isolated. However when 5-fluoro-2-oxindole (II) was added to the same reaction and the reaction continued, sunitinib L-malate (IV) was obtained.

Further, when one equivalent each of the aldehyde compound (VI), sunitinib free base (VII) and the L-malic acid salt of N,N-diethylethylenediamine were reacted together, sunitinib L-malate (IV) was preferentially obtained. Similarly, when one equivalent of the pyrrole derivative (I), sunitinib free base (VII) and the L-malic acid salt of N,N-diethylethylenediamine were reacted together, sunitinib L-malate (IV) was preferentially obtained.

A fourth aspect of the present invention provides a pharmaceutical composition comprising sunitinib or a salt thereof and one or more pharmaceutically acceptable excipients. A pharmaceutically acceptable excipient refers to an inert substance added to a pharmaceutical composition to further facilitate administration of a compound. Examples of excipients without limitation include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

A seventh aspect of the invention provides a pyrrole derivative (I)



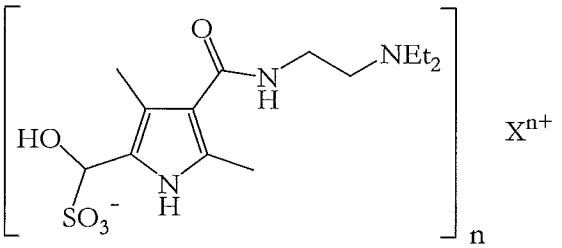
(I)

,

wherein X is a suitable cation and n is 1, 2 or 3.

In a preferred embodiment according to the seventh aspect of the invention, the cation is a metal cation, preferably an alkali metal or an alkaline earth metal cation. Advantageously the metal cation is either sodium or potassium, most advantageously sodium.

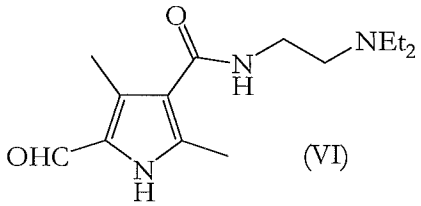
A particularly preferred aspect of the invention provides a process for preparing a pyrrole derivative (I):



(I)

,

wherein X is a suitable cation and n is 1, 2 or 3, the process comprising reacting aldehyde (VI):



(VI)

with a bisulphite anion of formula HSO_3^-.

Preferably the bisulphite anion is provided by mixing a metabisulphite salt in the reaction mixture. Preferably the metabisulphite salt is a salt of an alkali metal or an alkaline earth

metal. Advantageously the salt is an alkali metal metabisulphite salt, preferably sodium or potassium metabisulphite, most preferably the alkali metal metabisulphite is sodium metabisulphite $Na_2S_2O_5$.

Alternatively a bisulphite salt could be used, preferably an alkali metal or alkaline earth metal bisulphite salt. Advantageously the salt is an alkali metal bisulphite salt, preferably sodium or potassium bisulphite, most preferably the alkali metal bisulphite is sodium bisulphite $NaHSO_3$.

In certain preferred embodiments, the reaction occurs in an aqueous C_1-C_5 alcohol solvent system, preferably the C_1-C_5 alcohol is ethanol.

In further preferred embodiments, the reaction occurs at a temperature in the range of -10°C to reflux of the alcohol. Most preferably the reaction occurs at a temperature in the range of 10°C to 30°C.

In further advantageous embodiments, the reaction mixture has a pH of between 4.0 to 7.0, preferably between 4.0 to 6.0, most preferably between 4.0 to 5.0.

The resulting pyrrole derivative (I) may be isolated by any means available to the skilled person. The inventors have found filtering the pyrrole derivative (I) to be particularly advantageous. The filtered solid may then be washed with a solvent, preferably an organic solvent. The most advantageous embodiments comprise washing with C_1-C_6 aliphatic alcohols, such as methanol or ethanol, and/or water.

The washed or unwashed solid may then be allowed to dry or preferably is dried under vacuum. The conditions for drying are easily obtainable by the skilled person, but the inventors have found drying under vacuum at between about 30°C to 50°C, most preferably about 40°C, until no weight change is detected, preferably for between about 3 to 4 hours, to be particularly advantageous.

The details of the invention, its objects and advantages are explained hereunder in greater detail in relation to non-limiting examples.

Examples

The process of the invention will be illustrated by the preparation of sunitinib L-malate (IV) and the preparation of sunitinib free base (VII).

Example 1: Preparation of 2-(N,N-diethylamino)ethyl ammonium L-malate

2-(N,N-Diethylamino)ethyl amine (2g, 1 equivalent) was added to methanol (10ml) at 25-30°C under stirring, followed by the addition of L-malic acid (2.31g, 1 equivalent). A clear solution was formed which progressively became turbid. After further stirring for 1 hour, the methanol was removed under vacuum to afford a dark yellow oil.

Yield = 4.2g (97%)

^{1}H-NMR (DMSO-d_6): 0.98 (t, 6H), 2.27 (t, 1H), 2.30-2.54 (m, 7H), 2.83 (t, 2H), 3.86 (dd, 1H).

Example 2: Preparation of the sodium salt of pyrrole derivative (I)

N-[2-(Diethylamino)ethyl]-5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxamide (2g, 0.0075 mol) was added to ethanol (30ml, 15vol) under stirring and cooled to 10-15°C. A solution of sodium bisulphite (2.1g, 0.0202mol) in water (4ml, 2vol) was added dropwise to the above solution over a time period of 15 to 20 minutes, whilst maintaining the temperature below 20°C. The temperature of the reaction mixture was reduced and maintained at about 10°C and the reaction mixture was stirred for a further 1 to 2 hours. The resulting precipitate was filtered and washed with ethanol (10ml, 5vol) followed by water (4ml, 2vol). The solid obtained was then dried in a vacuum oven at 40°C to obtain the title compound.

Yield = 2.1g (79%)

IR (KBr, cm^{-1}): 3376 (N-H str.), 3298 (O-H str.) 2976 & 2943 (ali C-H str.), 1609 (C-O str.), 1533, 1511, 1438, 1381, 1341, 1254, 1171, 1061, 1025, 980, etc.

^{1}H-NMR (DMSO-d_6): 2.04 (s, 3H, -C<u>H</u>$_3$), 2.28 (s, 3H, -C<u>H</u>$_3$), 2.50 (m, 6H, 2 x -CH$_2$-C<u>H</u>$_3$), 3.34 (m, 8H, 4 x -C<u>H</u>$_2$-), 4.87 (d, 1H, >C<u>H</u>-OH), 5.52 (d, 1H, -OH, D_2O exchangeable), 6.92 (s, 1H, >NH, D_2O exchangeable), 10.07 (bs, 1H, >NH, D_2O exchangeable).

Example 3: Preparation of sunitinib L-malate (IV) using the sodium salt of pyrrole derivative (I)

The sodium salt of pyrrole derivative (I) (10g, 0.028mol), 5-fluoro-2-oxindole (II) (4.3g, 0.028mol) and 2-(N,N-diethylamino)ethyl ammonium L-malate (10.5g, 0.042mol, 1.5 equivalent) were added to acetonitrile : methanol (60ml:40ml, 6vol:4vol) at 25-30°C. A clear solution was obtained within 5 minutes. After stirring for 3 hours at 25-30°C, a yellow solid progressively precipitated out of the solution. The yellow solid was isolated by filtration, washed with methanol (50ml, 5vol) and dried under vacuum at 55-60°C for 3-4 hours.

Yield = 10g (67%)

Chemical Purity (HPLC) > 99%

Polymorphic Purity (XRPD) > 99% (other polymorphic forms below detection limit)

IR (KBr, cm^{-1}): 3326 (broad, N-H str.), 3231 (broad, O-H str.), 3063, 2927, 1671 (>C=O str.), 1654, 1636, 1577, 1475, etc.

^{1}H-NMR (DMSO-d_6): 1.12 (t, 6H, J=7.14Hz, 2 x -CH_2-C$\underline{H}_3$), 2.36 (m, 2H, -C$\underline{H}_2$-COOH), 2.44 (s, 3H, -C$\underline{H}_3$), 2.46 (s, 3H, -C$\underline{H}_3$), 2.55 (m, 1H, -C$\underline{H}$OH-COOH), 2.92 (m, 6H, 3 x -C$\underline{H}_2$-), 4.02 (m, 2H, -C$\underline{H}_2$-), 6.86 (m, 1H, vinyl proton), 6.94 (t, 1H, J=10.22Hz, aromatic ortho position), 7.64 (bs, 1H, -CON$\underline{H}$-, D_2O exchangeable), 7.73 (s, 1H, aromatic ortho position), 7.78 (d, 1H, J=9.42Hz, aromatic meta position), 10.92 (s, 1H, -CON$\underline{H}$-, D_2O exchangeable), 13.73 (s, 1H, pyrrole -N$\underline{H}$-, D_2O exchangeable).

^{13}C-NMR (DMSO-d_6): 9.69 (2C, 2 x -CH_2-$\underline{C}H_3$, DEPT), 10.68 (1C, -$\underline{C}H_3$, DEPT), 13.46 (1C, -$\underline{C}H_3$, DEPT), 35.01 (1C, -$\underline{C}H_2$-, DEPT), 40.89 (1C, -$\underline{C}H_2$-, DEPT), 46.81 (2C, 2 x -$\underline{C}H_2$-, DEPT), 50.57 (1C, -$\underline{C}H_2$-, DEPT), 66.40 (1C, vinyl carbon, DEPT), 106.06 (1C, d, aromatic ortho position, DEPT), 110.08 (1C, d, aromatic ortho position, DEPT), 112.60 (1C, d, aromatic meta position, DEPT), 115.04 (1C, -$\underline{C}$HOH-COOH), 124.91 (1C, d, aromatic =$\underline{C}$F-, DEPT), 119.90-136.96 (5C, 4 x Ar-C + =$\underline{C}$ indole ring), 159.86 (1C, -$\underline{C}$ONH-), 169.52 (1C, -$\underline{C}$ONH-), 172.21 (1C, -$\underline{C}$OOH), 176.06 (1C, -$\underline{C}$OOH).

Mass (m/z): (M+1) 399 (100%), [(M+2) +1] 401 (14%).

This solid was further purified by dissolving in n-butanol : water (4:1, 20vol) at 50-60°C and cooling to 25-30°C.

Recrystallisation Yield = 80%

Chemical Purity (HPLC) > 99.5%

Polymorphic Purity (XRPD) > 99% (other polymorphic forms below detection limit)

The structure of sunitinib L-malate (IV) was confirmed by NMR and HPLC retention time with standard sample. XRPD and DSC analysis indicated polymorphic form I as shown in Figures 1 and 2. Sunitinib L-malate (IV) polymorphic form I was obtained before and after recrystallisation.

Example 4: Preparation of sunitinib free base (VII) using the sodium salt of pyrrole derivative (I)

The sodium salt of pyrrole derivative (I) (10g, 0.028mol) and 5-fluoro-2-oxindole (II) (4.3g, 0.028mol) were added to acetonitrile : methanol (60ml:40ml, 6vol:4vol) at 25-30°C. A clear solution was obtained within 5 minutes. After stirring for 3 hours at 25-30°C, a yellow solid progressively precipitated out of the solution. The yellow solid was isolated by filtration, washed with methanol (50ml, 5vol) and dried under vacuum at 55-60°C for 3-4 hours.

Yield = 9.0g (80%)

Chemical Purity (HPLC) > 99%

Polymorphic Purity (XRPD) > 99% (other polymorphic forms below detection limit)

IR (KBr, cm^{-1}): 3276 (broad, N-H str.), 3063, 2966, 2925, 2807, 1675 (>C=O str.), 1560, 1475, etc.

^{1}H-NMR (DMSO-d_6): 0.97 (t, 6H, J=7.08Hz, 2 x -CH_2-CH_3), 2.42 (s, 3H, -CH_3), 2.44 (s, 3H, -CH_3), 2.47-2.56 (m, 6H, 3 x -CH_2-), 3.25-3.31 (m, 2H, -CO-NH-CH_2-), 6.83-6.87 (m, 1H, vinyl proton), 6.90-6.94 (t, 1H, J=5.9Hz, aromatic ortho position), 7.43-7.47 (t, 1H, J=5.6Hz, aromatic meta position), 7.74-7.78 (dd, 1H, J=5.9Hz, aromatic ortho position), 7.72 (s, 1H, aliphatic amide -NH-, D_2O exchangeable), 10.90 (s, 1H, pyrrole -NH-, D_2O exchangeable), 13.68 (s, 1H, indole -NH-, D_2O exchangeable).

^{13}C-NMR (DMSO-d_6): 10.64 (1C, -CH_3, DEPT), 11.92 (2C, 2 x -CH_2-CH_3, DEPT), 13.38 (1C, -CH_3, DEPT), 37.02 (1C, -CH_2-, DEPT), 46.55 (2C, 2 x -CH_2-, DEPT), 51.69 (1C, -CH_2-, DEPT), 105.90 (1C, d, aromatic ortho position, DEPT), 110.10 (1C, d, aromatic ortho position, DEPT), 112.45 (1C, d, aromatic meta position, DEPT), 124.94 (1C, vinyl carbon, DEPT), 127.22 (1C, d, aromatic =C-F, DEPT), 114.62-159.84 (5C, 4 x Ar-C + =C indole ring), 164.60 (1C, >CO), 169.63 (1C, >CO).

Mass (m/z): (M+1) 399 (100%), [(M+2) +1] 401 (14%).

The structure of sunitinib free base (VII) was confirmed by NMR and HPLC retention time with standard sample. XRPD and DSC analysis indicated polymorphic form I as shown in Figures 3 and 4.

Example 5: Preparation of 2-(N,N-diethylamino)ethyl ammonium di-L-malate

Into 10ml of methanol at 25-30°C, 2-(N,N-diethylamino)ethyl amine (2g, 1 equivalent) was added followed by the addition of L-malic acid (4.62g, 2 equivalent) under stirring. A clear solution was observed. After stirring for 1 hour, the solvent was removed under vacuum on a rotary evaporator to afford a dark yellow oil.

Yield = 6.5g (98%)

^{1}H-NMR (DMSO-d_6): 0.98 (t, 6H), 2.33 (dd, 2H), 2.40-2.67 (m, 8H), 2.65 (t, 2H), 4.04 (dd, 2H).

Example 6: Preparation of diammonium L-malate

Into 10ml of methanol at 25-30°C, ammonia (10% methanolic solution 5ml, 2 equivalent) was added followed by the addition of L-malic acid (2g, 1 equivalent). A clear solution was observed. A white solid progressively precipitated out. The solution was stirred for 1 hour and the white solid filtered and dried under vacuum on a rotary evaporator.

Yield = 2.4g (96%)

^{1}H-NMR (DMSO-d_6): 2.27 (dd, 1H), 2.48-2.54 (m, 1H), 3.86 (dd, 1H).

Example 7: Preparation of di-(diisopropyl ammonium) L-malate

Into 10ml of methanol at 25-30°C, diisopropyl amine (3g, 2 equivalent) was added followed by the addition of L-malic acid (2g, 1 equivalent). A clear solution was observed. After stirring for 1 hour, the solvent was removed under vacuum on a rotary evaporator to afford a dark yellow oil.

Yield = 4.9g (98%)

^{1}H-NMR (DMSO-d_6): 1.07 (d, 12H), 1.09 (d, 12H), 2.30 (dd, 1H), 2.65 (dd, 1H), 3.05- 3.13 (m, 4H), 3.80-3.84 (dd, 1H).

Example 8: Preparation of dipyrrolidine L-malate

Into 10ml of methanol at 25-30°C, pyrrolidine (2.1g, 2 equivalent) was added followed by the addition of L-malic acid (2g, 1 equivalent). A clear solution was observed after 15

minutes. After stirring for 1 hour, the solvent was removed under vacuum on a rotary evaporator to afford a light yellow oil.

Yield = 4g (98%)

^{1}H-NMR (DMSO-d_6): 1.78 (t, 8H), 2.01-2.09 (dd, 1H), 2.37-2.43 (dd, 1H), 3.01-3.16 (t, 8H), 3.87-3.91 (m, 1H).

Example 9: Preparation of di-(n-propyl ammonium) L-malate

Into 10ml of methanol at 25-30°C, n-propyl amine (1.76g, 2 equivalent) was added followed by the addition of L-malic acid (2g, 1 equivalent). A clear solution was observed. After stirring for 1 hour, the solvent was removed under vacuum on a rotary evaporator to afford a light yellow oil.

Yield = 3.5g (95%)

^{1}H-NMR (DMSO-d_6): 0.85-0.90 (t, 6H), 1.47-1.55 (m, 4H), 2.05-2.13 (dd, 1H), 2.39-2.46 (dd, 1H), 2.63-2.68 (t, 4H), 3.84-3.89 (t, 1H).

XRPDs were recorded on a Bruker D8 Advance Instrument, using Cu α-radiation as the X-ray source, with a 2θ range of from 3 to 50°, a step-size of 0.5° and a time/step of 1sec.

DSCs were recorded on a Perkin Elmer Pyris 6, with a temperature range of from 25°C to 280°C and a rate of heating of 10°C/min.

HPLC purities were determined using:

HPLC Machine: Waters

Column: Inertsil ODS 3V (250 x 4.6mm), 5 µm

Mobile Phase: 0.05 M ammonium acetate : methanol + 0.05% acetic acid

Diluent: buffer : methanol (60:40 v/v)

Flow Rate: 1.0 ml/min

Wavelength: 235 nm

Auto-Sampler Temperature: 15 ± 2°C

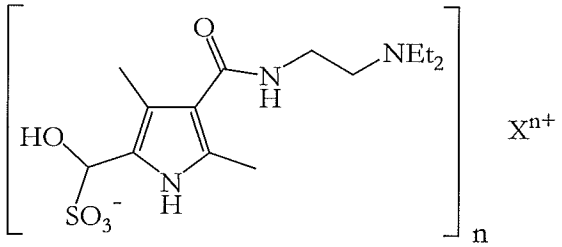
The foregoing description and examples have been set forth merely to illustrate the invention and are not intended to be limiting. Since modifications of the described embodiments incorporating the spirit and substance of the invention may occur to persons

skilled in the art, the invention should be construed broadly to include all variations within the scope of the appended claims and equivalents thereof.

Claims

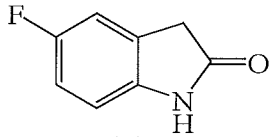
1. A process for preparing sunitinib (VII) or a salt thereof comprising:

either reacting a pyrrole derivative (I)



(I)

with 5-fluoro-2-oxindole (II)



(II)

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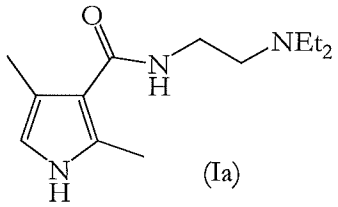
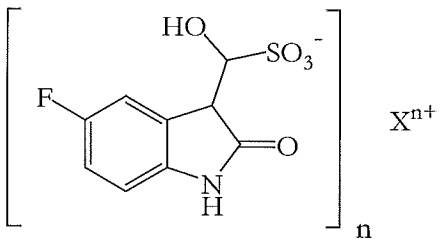
wherein X is a suitable cation and n is 1, 2 or 3;

or reacting pyrrole derivative (Ia)



(Ia)

with a 5-fluoro-2-oxindole derivative (IIa)



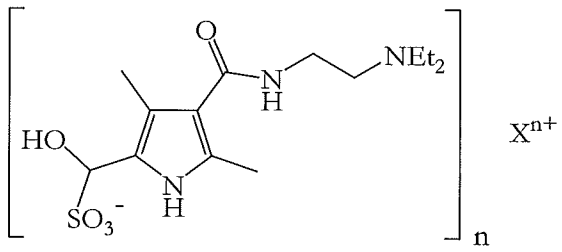
(IIa)

,

wherein X is a suitable cation and n is 1, 2 or 3.

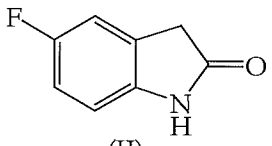
2. A process according to claim 1, comprising:

reacting a pyrrole derivative (I)



(I)

with 5-fluoro-2-oxindole (II)



(II)

,

wherein X is a suitable cation and n is 1, 2 or 3.

3. A process according to claim 1 or 2 for preparing an acid addition salt of sunitinib, comprising adding an acid to the reaction mixture.

4. A process according to claim 1 or 2 for preparing an acid addition salt of sunitinib, comprising adding an amine derived or ammonium derived salt of the acid to the reaction mixture.

5. A process according to claim 3 or 4, wherein the acid is an inorganic acid.

6. A process according to claim 5, wherein the inorganic acid is selected from the group comprising HCl, HBr, HNO_3, H_3PO_4, H_2SO_4 and $HClO_4$.

7. A process according to claim 3 or 4, wherein the acid is an organic acid.

8. A process according to claim 7, wherein the organic moiety of the organic acid is selected from the group comprising a straight or branched chain, substituted or unsubstituted alkyl, alkenyl, allyl, aryl or arylalkyl group, or a heteroatom-substituted straight or branched chain alkyl or aryl group.

9. A process according to claim 7 or 8, wherein the organic acid is selected from the group comprising sulfonic acids, mono-, di- and tri-carboxylic acids.

10. A process according to claim 9, wherein the organic acid is selected from the group comprising acetic acid, formic acid, oxalic acid, D-malic acid, L-malic acid, DL-malic acid, maleic acid, methane sulfonic acid, ethane sulfonic acid, p-toluene sulfonic acid, salicylic acid, tartaric acid, citric acid, succinic acid and malonic acid.

11. A process according to claim 10, wherein the organic acid is L-malic acid.

12. A process according to claim 4, wherein the amine or ammonium moiety is selected from the group comprising primary amines and secondary amines.

13. A process according to claim 12, wherein the amine or ammonium moiety is selected from the group comprising cyclic amines, allyl amines, arylalkyl amines, heteroalkyl amines, alkyl amines, alkenyl amines, alkynyl amines and aryl amines.

14. A process according to claim 4, wherein the amine derived or ammonium derived acid addition salt is a malate salt.

15. A process according to claim 14, wherein the amine derived or ammonium derived acid addition salt is a malate salt selected from the group comprising 2-(N,N-diethylamino)ethyl ammonium malate, 2-(N,N-diethylamino)ethyl ammonium dimalate, diammonium malate, dipyrrolidine malate, di-(n-propyl ammonium) malate, and di-(diisopropyl ammonium) malate.

16. A process according to any preceding claim, wherein X is a metal cation.

17. A process according to claim 16, wherein X is an alkali metal or an alkaline earth metal cation.

18. A process according to claim 17, wherein X is either sodium or potassium.

19. A process according to claim 18, wherein X is sodium.

20. A process according to any preceding claim, wherein the sunitinib or salt thereof is isolated.

21. A process according to claim 20, wherein the sunitinib or salt thereof is further purified by recrystallisation from:

(i) a C_1-C_6 alcohol : water mixture; and/or

(ii) a C_1-C_6 alcohol : water mixture, wherein the C_1-C_6 alcohol : water mixture has a v/v ratio of about 4:1; and/or

(iii) a n-butanol : water mixture; and/or

(iv) a n-butanol : water mixture, wherein the n-butanol : water mixture has a v/v ratio of about 4:1.

22. A process according to any preceding claim, wherein the process is carried out at a temperature of between about 25°C to about 35°C.

23. A process according to any preceding claim, wherein the process is carried out in:

(i) an organic solvent system; and/or

(ii) an organic solvent system comprising acetonitrile and methanol; and/or

(iii) an organic solvent system comprising acetonitrile and methanol, wherein the v/v ratio of acetonitrile : methanol is from about 5:1 to about 1:5; and/or

(iv) an organic solvent system comprising acetonitrile and methanol, wherein the v/v ratio of acetonitrile : methanol is about 3:2.

24. A process according to any preceding claim, wherein the reaction mixture has a pH of:

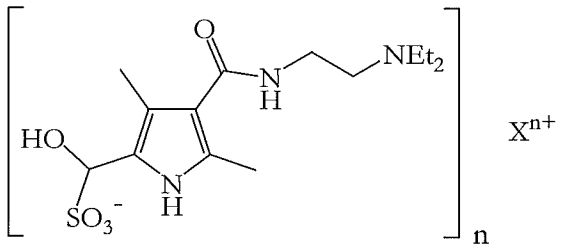
(i) between 4 to 7; and/or

(ii) between 4 to 6; and/or

(iii) between 4 to 5.

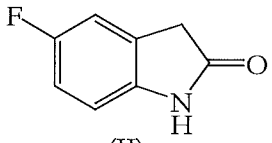
25. A process for preparing sunitinib malate comprising:

reacting a pyrrole derivative (I)



(I)

with 5-fluoro-2-oxindole (II)



(II)

in the presence of malic acid or an amine derived or ammonium derived malic acid salt; and

isolating the sunitinib malate;

wherein X is a suitable cation and n is 1, 2 or 3.

26. A process according to claim 25, wherein the malic acid or malic acid salt used is L-malic acid or an L-malic acid salt.

27. A process according to claim 25 or 26, wherein the amine derived or ammonium derived malic acid salt is selected from the group comprising 2-(N,N-diethylamino)ethyl ammonium malate, 2-(N,N-diethylamino)ethyl ammonium dimalate, diammonium malate, dipyrrolidine malate, di-(n-propyl ammonium) malate, and di-(diisopropyl ammonium) malate.

28. A process according to claim 27, wherein the amine derived or ammonium derived malic acid salt is 2-(N,N-diethylamino)ethyl ammonium dimalate.

29. A process according to any one of claims 25 to 28, wherein X is sodium.

30. A process according to any one of claims 25 to 29, wherein the sunitinib malate is further purified by recrystallisation from a n-butanol : water mixture having a v/v ratio of about 4:1.

31. A process according to any one of claims 25 to 30, wherein the temperature of the reaction is between 25°C to 35°C.

32. A process according to any one of claims 25 to 31, wherein the process is carried out in an organic solvent system comprising acetonitrile and methanol having a v/v ratio of acetonitrile : methanol of about 3:2.

33. A process according to any one of claims 25 to 32, wherein the pH of the reaction mixture is between 4 to 6.

34. Sunitinib or a salt thereof prepared by a process according to any one of claims 1 to 33, having a purity as determined by HPLC of at least 97%.

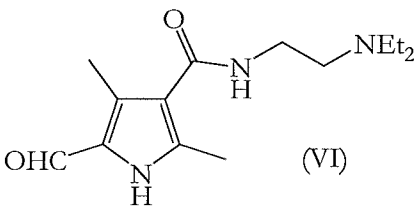
35. Sunitinib or a salt thereof according to claim 34, having a purity as determined by HPLC of:

(i) at least 99%; and/or

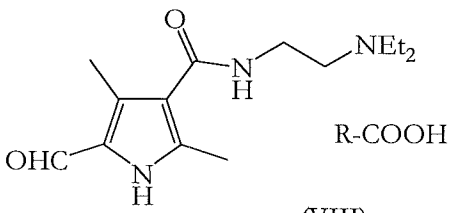
(ii) at least 99.5%; and/or

(iii) at least 99.8%.

36. Sunitinib or a salt thereof, comprising less than 3% of compound (VI) and/or compound (VIII):



(VI)



(VIII)

37. Sunitinib or a salt thereof according to claim 36, comprising:

(i) less than 1% of compound (VI) and/or compound (VIII); and/or

(ii) less than 0.1% of compound (VI) and/or compound (VIII); and/or

(iii) less than 0.01% of compound (VI) and/or compound (VIII).

38. A sunitinib salt according to any one of claims 34 to 37, wherein the salt is sunitinib malate or sunitinib L-malate (IV).

39. Sunitinib or a salt thereof according to any one of claims 34 to 38 or prepared by a process according to any one of claims 1 to 33, for:

(i) use in medicine; and/or

(ii) treating a protein kinase mediated disorder; and/or

(iii) treating a cell proliferative disorder; and/or

(iv) treating renal cell carcinoma (RCC) or gastrointestinal stromal tumor (GIST).

40. A pharmaceutical composition comprising sunitinib or a salt thereof according to any one of claims 34 to 39 or prepared by a process according to any one of claims 1 to 33, and one or more pharmaceutically acceptable excipients.

41. A pharmaceutical composition according to claim 40, wherein the sunitinib salt is sunitinib malate or sunitinib L-malate (IV).

42. A pharmaceutical composition according to claim 40 or 41, for use in the treatment of:

(i) a protein kinase mediated disorder; and/or

(ii) a cell proliferative disorder; and/or

(iii) renal cell carcinoma (RCC) or gastrointestinal stromal tumor (GIST).

43. Use of sunitinib or a salt thereof according to any one of claims 34 to 39 or prepared by a process according to any one of claims 1 to 33, or use of a pharmaceutical composition according to any one of claims 40 to 42, in the manufacture of a medicament for treating a protein kinase mediated disorder.

44. Use according to claim 43, wherein the medicament is for treating:

(i) a cell proliferative disorder; and/or

(ii) renal cell carcinoma (RCC) or gastrointestinal stromal tumor (GIST).

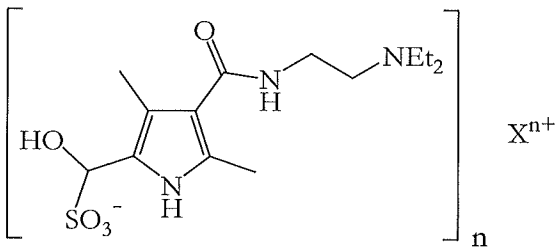
45. A method of treating a protein kinase mediated disorder, comprising administering to a patient in need thereof a therapeutically effective amount of sunitinib or a salt thereof according to any one of claims 34 to 39 or prepared by a process according to any one of claims 1 to 33, or a therapeutically effective amount of a pharmaceutical composition according to any one of claims 40 to 42.

46. A method according to claim 45, wherein the method is for treating:

(i) a cell proliferative disorder; and/or

(ii) renal cell carcinoma (RCC) or gastrointestinal stromal tumor (GIST).

47. A pyrrole derivative (I)



(I)

,

wherein X is a suitable cation and n is 1, 2 or 3.

48. A pyrrole derivative (I) according to claim 47, wherein X is a metal cation.

49. A pyrrole derivative (I) according to claim 48, wherein X is an alkali metal or an alkaline earth metal cation.

50. A pyrrole derivative (I) according to claim 49, wherein X is either sodium or potassium.

51. A pyrrole derivative (I) according to claim 50, wherein X is sodium.

52. A pyrrole derivative (I) according to any one of claims 47 to 51, having a purity as determined by HPLC of:

(i) at least 97%; and/or

(ii) at least 99%; and/or

(iii) at least 99.5%; and/or

(iv) at least 99.8%.

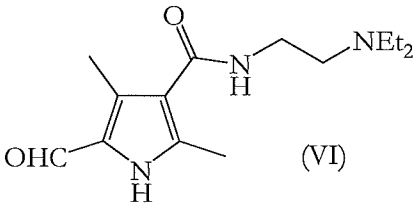
53. A pyrrole derivative (I) according to any one of claims 47 to 52, comprising:

(i) less than 3% of compound (VI) and/or compound (VIII); and/or

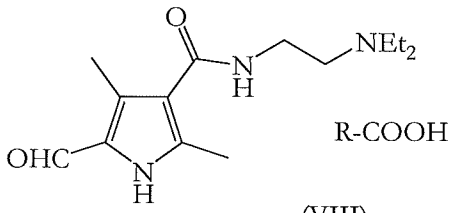
(ii) less than 1% of compound (VI) and/or compound (VIII); and/or

(iii) less than 0.1% of compound (VI) and/or compound (VIII); and/or

(iv) less than 0.01% of compound (VI) and/or compound (VIII).



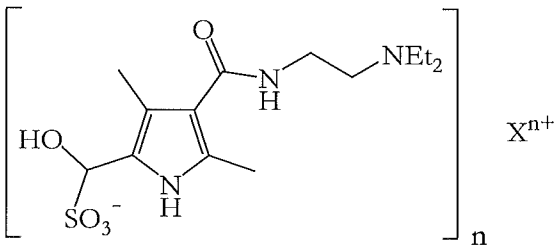
(VI)



R-COOH

(VIII)

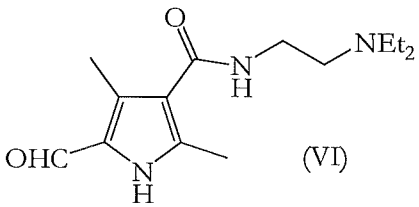
54. A process for preparing a pyrrole derivative (I):



(I)

,

wherein X is a suitable cation and n is 1, 2 or 3, the process comprising reacting aldehyde (VI):



(VI)

with a bisulphite anion of formula HSO_3^-.

55. A process according to claim 54, wherein X is:

(i) a metal cation; and/or

(ii) an alkali metal or an alkaline earth metal cation; and/or

(iii) either sodium or potassium; and/or

(iv) sodium.

56. A process according to claim 54 or 55, wherein the bisulphite anion is provided by mixing a metabisulphite salt in the reaction mixture.

57. A process according to claim 56, wherein the metabisulphite salt is:

(i) a salt of an alkali metal or an alkaline earth metal; and/or

(ii) sodium or potassium metabisulphite; and/or

(iii) sodium metabisulphite $Na_2S_2O_5$.

58. A process according to claim 54 or 55, wherein the bisulphite anion is provided by mixing a bisulphite salt in the reaction mixture.

59. A process according to claim 58, wherein the bisulphite salt is:

(i) a salt of an alkali metal or an alkaline earth metal; and/or

(ii) sodium or potassium bisulphite; and/or

(iii) sodium bisulphite $NaHSO_3$.

60. A process according to any one of claims 54 to 59, wherein the reaction occurs in:

(i) an aqueous C_1-C_5 alcohol solvent system; and/or

(ii) an aqueous ethanol solvent system.

61. A process according to any one of claims 54 to 60, wherein the reaction mixture has a pH of:

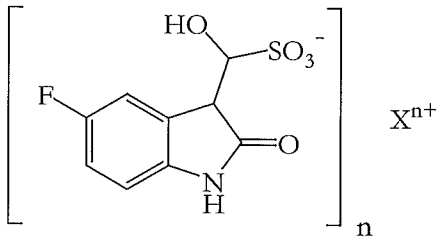
(i) between 4 to 7; and/or

(ii) between 4 to 6; and/or

(iii) between 4 to 5.

62. A process according to any one of claims 54 to 61, wherein the pyrrole derivative (I) is further isolated.

63. A 5-fluoro-2-oxindole derivative (IIa)



(IIa)

,

wherein X is a suitable cation and n is 1, 2 or 3.

64. A 5-fluoro-2-oxindole derivative (IIa) according to claim 63, wherein X is a metal cation.

65. A 5-fluoro-2-oxindole derivative (IIa) according to claim 64, wherein X is an alkali metal or an alkaline earth metal cation.

66. A 5-fluoro-2-oxindole derivative (IIa) according to claim 65, wherein X is either sodium or potassium.

67. A 5-fluoro-2-oxindole derivative (IIa) according to claim 66, wherein X is sodium.

68. A 5-fluoro-2-oxindole derivative (IIa) according to any one of claims 63 to 67, having a purity as determined by HPLC of:

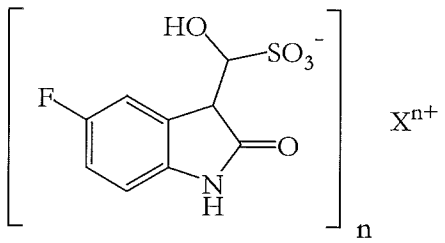
(i) at least 97%; and/or

(ii) at least 99%; and/or

(iii) at least 99.5%; and/or

(iv) at least 99.8%.

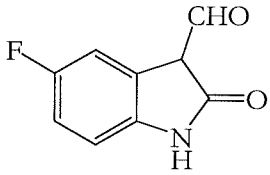
69. A process for preparing a 5-fluoro-2-oxindole derivative (IIa):



(IIa)

,

wherein X is a suitable cation and n is 1, 2 or 3, the process comprising reacting aldehyde (IIb):



(IIb)

with a bisulphite anion of formula HSO_3^-.

70. A process according to claim 69, wherein X is:

(i) a metal cation; and/or

(ii) an alkali metal or an alkaline earth metal cation; and/or

(iii) either sodium or potassium; and/or

(iv) sodium.

71. A process according to claim 69 or 70, wherein the bisulphite anion is provided by mixing a metabisulphite salt in the reaction mixture.

72. A process according to claim 71, wherein the metabisulphite salt is:

(i) a salt of an alkali metal or an alkaline earth metal; and/or

(ii) sodium or potassium metabisulphite; and/or

(iii) sodium metabisulphite $Na_2S_2O_5$.

73. A process according to claim 69 or 70, wherein the bisulphite anion is provided by mixing a bisulphite salt in the reaction mixture.

74. A process according to claim 73, wherein the bisulphite salt is:

(i) a salt of an alkali metal or an alkaline earth metal; and/or

(ii) sodium or potassium bisulphite; and/or

(iii) sodium bisulphite $NaHSO_3$.

75. A process according to any one of claims 69 to 74, wherein the reaction occurs in:

(i) an aqueous C_1-C_5 alcohol solvent system; and/or

(ii) an aqueous ethanol solvent system.

76. A process according to any one of claims 69 to 75, wherein the reaction mixture has a pH of:

(i) between 4 to 7; and/or

(ii) between 4 to 6; and/or

(iii) between 4 to 5.

77. A process according to any one of claims 69 to 76, wherein the pyrrole derivative (I) is further isolated.

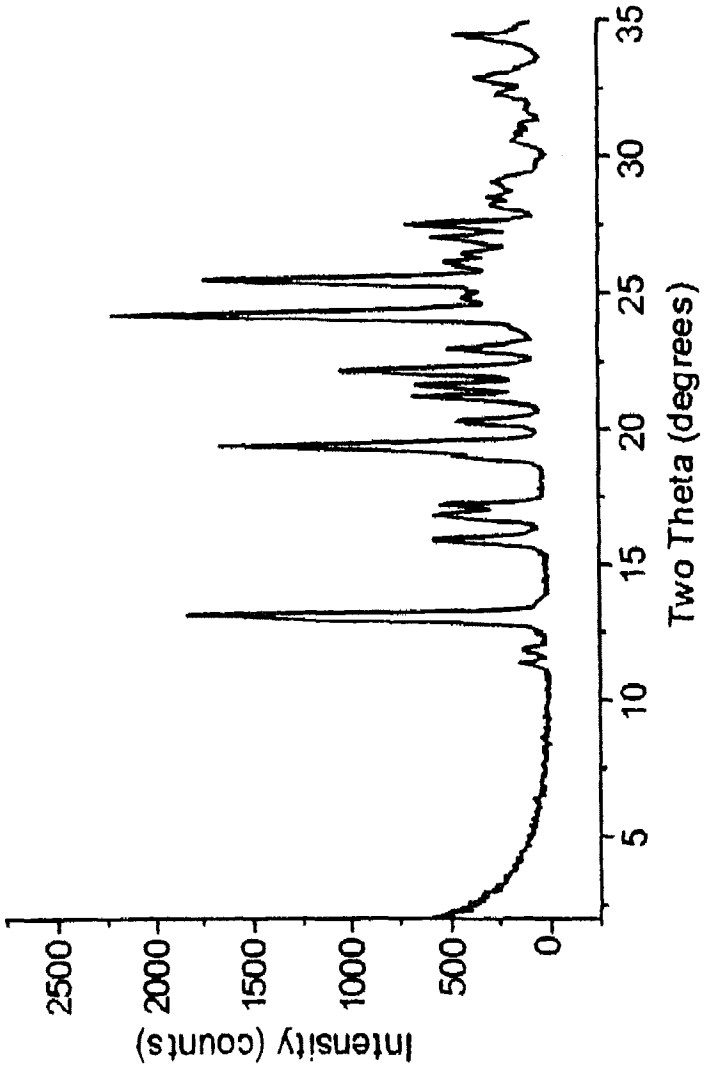

Intensity (counts)
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
Two Theta (degrees)

Figure 1

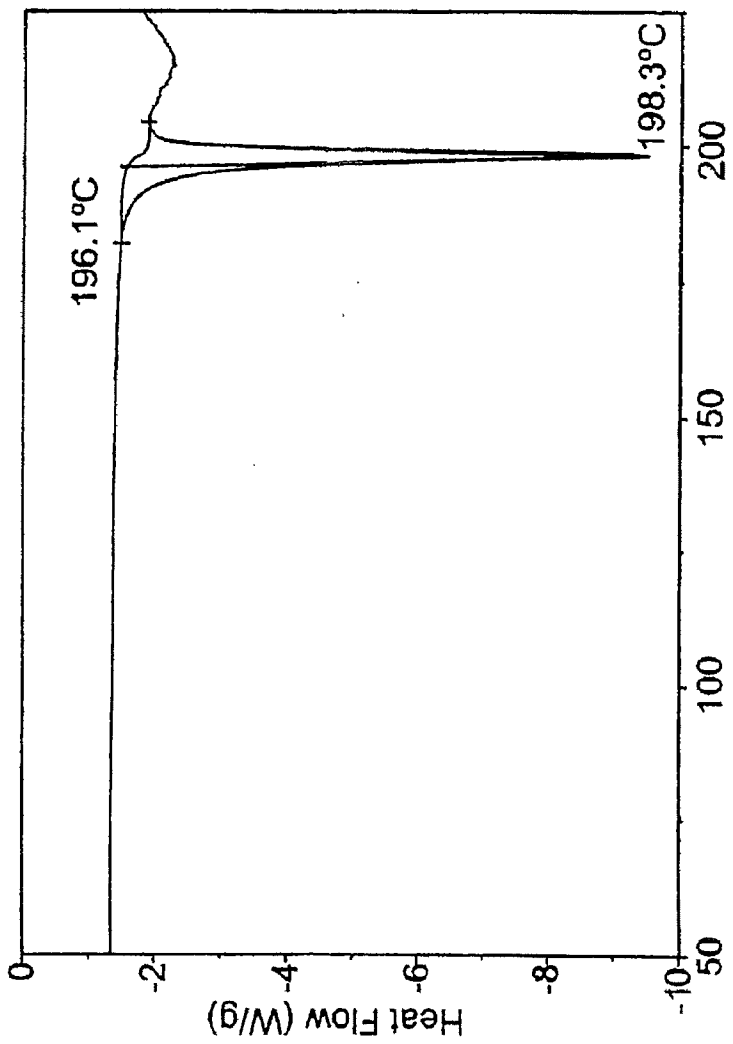

196.1°C
198.3°C
Heat Flow (W/g)
0
-2
-4
-6
-8
-10
50
100
150
200
Temperature (°C)

Figure 2

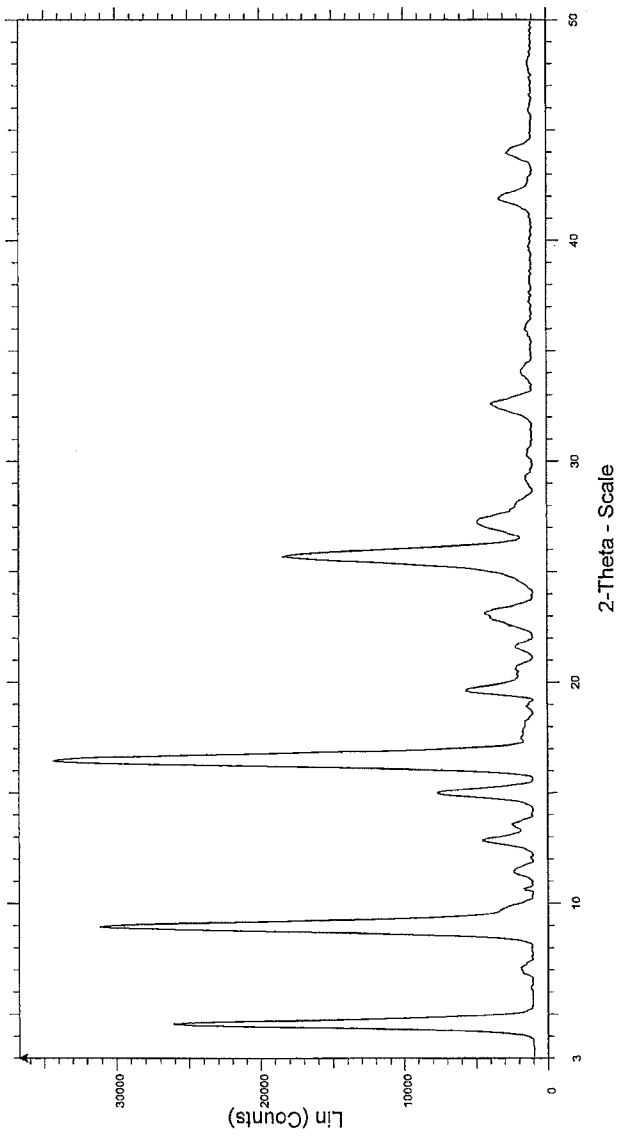


Figure 3

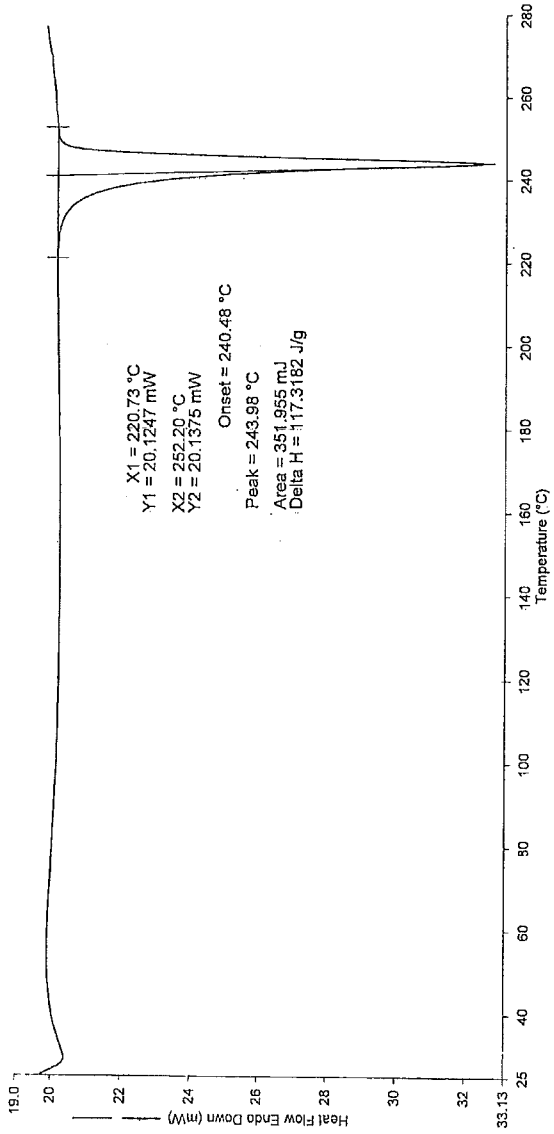

X1 = 220.73 °C
Y1 = 20.1247 mW
X2 = 252.20 °C
Y2 = 20.1375 mW
Onset = 240.48 °C
Peak = 243.98 °C
Area = 351.955 mJ
Delta H = 117.3182 J/g
Heat Flow Endo Down (mW)
Temperature (°C)
19.0
20
22
24
26
28
30
32
33.13
25
40
60
80
100
120
140
160
180
200
220
240
260
280

Figure 4