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(71) Applicant (for all designated States except US): **NATCO PHARMA LIMITED** [IN/IN]; "Natco House", Road No.2, Banjara Hills, Hyderabad 500 033, Andhra Pradesh (IN).

(71) Applicants and

(72) Inventors: **KOMPELLA, Amala** [IN/IN]; Natco Pharma Limited, Natco House, Road No.2, Banjara Hills, Hyderabad 500 033 (IN). **RACHAKONDA, Sreenivas** [IN/IN]; Natco House, Road No.2, Banjara Hills, Hyderabad 500 033 (IN). **ADIBHATLA KALI SATYA, Bhujanga rao** [IN/IN]; Natco Pharma Limited, Natco House, Road No.2, Banjara Hills, Hyderabad 500 033, Andhra Pradesh (IN). **VENKAIAH CHOWDARY, Nannapaneni** [IN/IN]; Natco Pharma Limited, "Natco House", Road No.2, Banjara Hills, Hyderabad 500 033, Andhra Pradesh (IN).

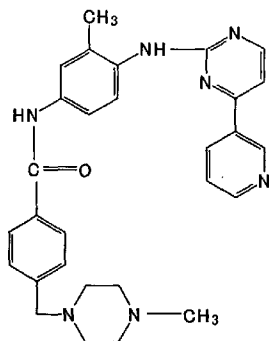
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(54) Title: A PROCESS FOR THE PREPARATION OF HIGHLY PURE IMATINIB BASE



(I)

(57) Abstract: A novel process for the preparation of highly pure (>99.8%) imatinib base of Formula (I) is disclosed. Highly pure imatinib base of this invention is suitable for conversion to pharmaceutically acceptable salts.

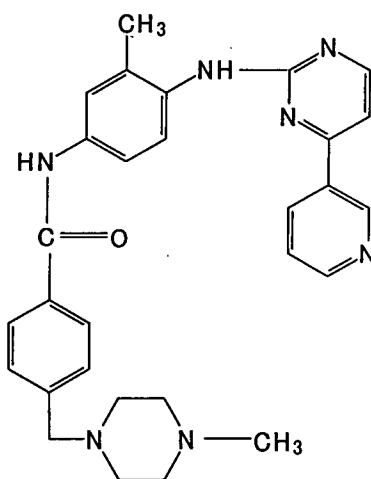
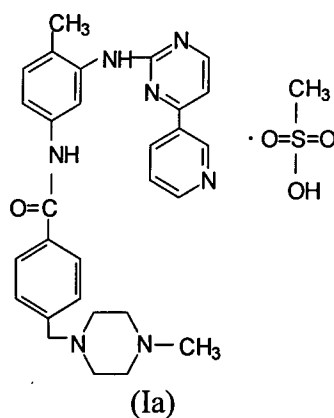
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A PROCESS FOR THE PREPARATION OF HIGHLY PURE IMATINIB BASE

Field of the invention:

- 5 The present invention relates to an improved and novel process for the preparation of highly pure (>99.8) (Imatinib) of formula (I) and its pharmaceutically acceptable salts and process for preparation thereof

Back ground of the invention :



Imatinib mesylate which is the methane sulfonate salt of N-{5-[4-(4-methylpiperazino-
methyl)- benzoylamido]-2-methylphenyl}-4- (3-pyridyl) 2-pyrimidine-amine having the
Formula I (a) I is approved under the trademark "Gleevec ®" by the US Food and Drug
Administration for the treatment of Chronic Myelogenous Leukemia before and after the

failure of interferon alpha. It has also been approved for the treatment of patients with kit (CD117) positive unresectable and / or metastatic malignant Gastro Intestinal Stromal Tumors (GISTs). It has also been approved for the treatment of pediatric patients with philadelphia chromosome positive (Ph+) Chronic Myeloid Leukemia (CML) in chronic phase.

The preparation of N-{5-[4-(4-methylpiperazino-methyl)- benzoylamido]-2-methylphenyl}-4-(3-pyridyl) 2-pyrimidine-amine (Imatinib) of Formula (I) and the use thereof especially as an antitumour agent is described in EP0564 409, (Ciba-Geigy corp.) which was published on 6th October 1993 and in US 55211584 (Assignee : Ciba-Geigy corp; Title : Pyrimidine derivatives and process for the preparation thereof) which was published on 28th May 1996 and in equivalent applications in numerous other countries. However, the purity aspects of imatinib base are not discussed here.

The preparation of Imatinib mesylate I(a) and the use thereof especially as an antitumour agent is described in WO99/03854, (Assignee : Novartis). This application describes two polymorphic forms of imatinib mesylate, the α -form and the β -form, WO 2005/075454 describes acid addition salts of imatinib such as tartrate, citrate, malate, fumarate, etc., which are prepared by treatment of imatinib base with the corresponding acid.

In EP 0564409 and in its equivalent US 55211584 the following route is described (Scheme-1)

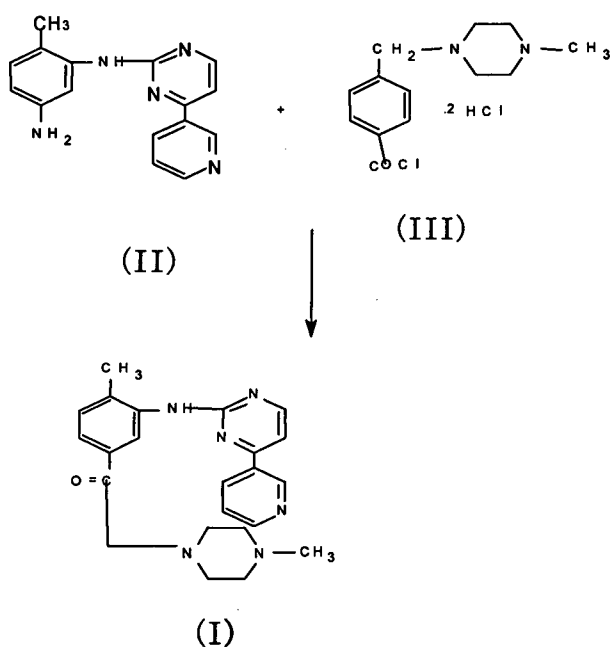
Scheme -I :

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A solution of N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidineamine of the formula (II) and 4-(4-methyl-piperazinomethyl)benzoyl chloride of the formula (III) taken in pyridine are stirred under nitrogen at room temperature for 23 hours. The resulting reaction mixture is concentrated under high vacuum; water is added and the mixture is filtered. After drying at 80°C under high vacuum, the crude product is made into slurry with methylene chloride & methanol and filtered to yield Imatinib of the formula (I). Chromatographic separation is used to obtain further crop of product.

After implementing the process described in the patent mentioned as per the scheme indicated, the following are the difficulties encountered and draw backs noticed.

- i) the yield of compound of formula (I) is low (50%) making the process non economical and the purity of the product is only 97%
- ii) column chromatography is necessary to isolate product of formula (I) in pure form and column chromatography technique becomes unpractical on commercial scale.
- iii) usage of the obnoxious and foul smelling chemical pyridine as a solvent and its distillation for work-up makes this process to be abandoned on bulk scale.

Imatinib base is the precursor of the salt forms of imatinib. As such, there is a need for imatinib base of high purity which may be conveniently used as a precursor in the preparation of highly pure imatinib mesylate for therapeutic application.

It is observed that pharmaceutical salts of Imatinib, when prepared from imatinib of lower purity do not meet the pharmaceutically acceptable quality. There is therefore an unfulfilled need to provide industrially feasible process for the preparation of pharmaceutically acceptable salts of imatinib from less pure imatinib.

To overcome the problem, the inventors have tried to prepare high purity imatinib base through acid addition salts of imatinib of lower purity. When the base is liberated from the acid addition salts, imatinib of higher purity results.

It is surprisingly found by the inventors that when the impure imatinib is reacted with maleic acid it selectively forms the corresponding acid addition salt, leaving behind the other related substances and impurities which are otherwise difficult to remove by the conventional methods. The maleic acid salt of imatinib is further converted to highly pure imatinib base which in turn is converted into other pharmaceutically acceptable salts with high purity.

Summary of the invention:

The main object of the present invention is to provide an improved process for the preparation of highly pure (>99.8%) imatinib base and/or its pharmaceutically acceptable salts.

- 5 Another object of the invention is to provide a process for preparation of highly pure (>99.8%) imatinib and/or its pharmaceutically acceptable salts using maleic acid salt of Imatinib.

10 Accordingly in the present invention highly pure Imatinib and its pharmaceutically acceptable salts are prepared by

i. preparing imatinib base by the condensation of N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidine amine of the formula (II) and 4-(4-methyl-piperazinomethyl)benzoyl chloride of the formula (III) in presence of potassium hydroxide base and isolation of crude imatinib base

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ii. Treatment of impure Imatinib with hydrochloric acid and again liberation of imatinib of purity g 99.5%

iii. Treating Imatinib with maleic acid yields maleic acid addition salt of Imatinib

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iv) neutralizing maleic acid salts and isolating Imatinib of purity 99.99% and

v) converting highly pure Imatinib to other pharmaceutically acceptable salts

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Detailed description of the invention:

30 Thus in accordance with the present invention preparation of Imatinib and its pharmaceutically acceptable salts comprise the following steps.

i. condensation of N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidine amine and 4-(4-methyl-piperazinomethyl)benzoyl chloride of the formula (III) chloroform to yield Imatinib

- 5 ii. Treatment of impure Imatinib with hydrochloric acid and again liberation of imatinib of purity 99.5%
- iii. Treating crude Imatinib with maleic acid yielding maleic acid addition salt of Imatinib
- iv. Converting Imatinib maleic acid addition salt to highly pure(>99.8)Imatinib

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In a specific embodiment, the present invention provides a process for the preparation of Imatinib and its pharmaceutically acceptable salts, which involve

i. Cooling suspension of 4-(4-methyl-piperazinomethyl)benzoyl chloride of the formula (III) in chloroform at temperature of 5-15°C

15 ii. Addition of 5-15 moles of potassium hydroxide flakes preferably 10-12 moles of potassium hydroxide flakes to the above suspension and stirring the mixture for 30-40 minutes

iii. raising reaction mass temperature to 25-30°C and addition of -(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidine amine of the formula (II)

20 iv. Addition of 30% aqueous potassium hydroxide solution to the reaction mass over a period of 1 hour to 6 hours preferably over 3-4 hours

Separation of organic layer and washing of organic layer with water.

Carbon treatment of the chloroform layer

25 vii. Suspension of chloroform layer into DM water and adjusting P^H to 3.0 to 4.0 with diluted hydrochloric acid.

viii. Washing the reaction mass with Chloroform

ix. Adjusting the aqueous layer P^H to 9.0 to 12.0 and extraction with chloroform.

x. Concentration of the organic layer and addition of ethyl acetate.

30 xi. Isolation of the precipitated imatinib base of purity 99.5%

Further reacting the resultant base of of Imatinib with maleic acid by

- i. Suspension of the imatinib base in a short chain alcohol such as methanol, ethanol, propanol or mixture thereof,
- 5 ii. Adding maleic acid directly or as a solution in short chain alcohol, Maintaining the reaction mixture at room temperature of the solvent for about 30 min to 2 hrs
- iii. Removal of the alcohol under vacuum and triturating the syrup with acetone
- iv. Isolating the precipitated product and drying the product at 40 to 60°C, preferably at 50 to 60°C affording pure Imatinib as an acid addition salt of maleic acid.

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The novel Imatinib maleic acid addition salt thus prepared is identified and characterized by chemical analysis, IR, NMR & Mass spectra. This acid addition salt is further converted to Imatinib by

- 15 i) Neutralizing Imatinib maleate with a base such as organic amines, alkali hydroxides, alkali carbonates, alkali bicarbonates and ammonia, in a mixture of water and water immiscible solvent
- ii) Separating the layers,
- 20 iii) Washing the organic layer with water,
- iv) Concentrating the organic layer under vacuum affording Imatinib of purity 99.99% by HPLC

- 25 The required N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidine amine and 4-(4-methyl-piperazinomethyl)benzoyl chloride of the formula (III) can be prepared by the prior art processes

The details of the inventions are given in the Examples which are provided for illustration
30 only and therefore the Examples should not be construed to limit the scope of the invention.

EXAMPLES

Example-1 : Process for the preparation highly pure imatinib of the formula (I)

Step-1 : Condensation of N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidine amine of the formula (II) and 4-(4-methyl-piperazinomethyl)benzoyl chloride of the formula (III) :

Into the reactor a suspension of 50L of chloroform and 13.0 Kgs of 4-(4-methyl-piperazinomethyl)benzoyl chloride(III) is charged and cooled to 5-10°C. 50 kgs of potassium hydroxide pellets are charged slowly during 1-2 hours. It is stirred for 30 minutes and 25 Kg of amine of formula (II) is charged to the reaction mass. Aqueous 30% solution of potassium hydroxide (500L) is added slowly during four hours at 25-35°C. Organic layer is separated from the reaction mass and is washed with 3 x 400 L DM water .. Carbon treatment is given to the chloroform layer and is suspended in 350L DM water and dilute Hydrochloric acid is added slowly during 30 minutes to a p^H of 3-4. Aqueous layer is washed with 3x100L of chloroform. Aqueous layer is basified with sodium hydroxide solution to a pH of 9-12 and extracted with 1x350L chloroform. Organic layer is dried over anhydrous sodium sulfate and the solvent distilled off under vacuum to a residual volume of 7-10L . 25L of Ethyl acetate is charged and stirred for 15 minutes at 25-35°C. The product of the formula (I) is centrifuged and washed with 10 L Ethyl Acetate. It is dried in oven at 60-70°C

Dry wt. : 35 Kg

Purity by HPLC : 99.5%

Step – II : Preparation of Imatinib maleate :

Imatinib (5kgs, purity 99.5%) is suspended in methanol (25L) at room temperature. Maleic Acid solution (1.1kgs in 10L methanol) is added to the above solution over 30 min at room temperature. Reaction mass temperature is raised to reflux and maintained for about 2-3 hrs. The reaction mass is slowly cooled to 0°C and maintained for about 1 hr at 0°C. The precipitated material is filtered and washed with 5L of methanol. The product is dried at 60-70°C under vacuum to constant weight.

Dry weight : 5.5 kg

melting point : 166-170 °C

Step – III : Preparation of highly pure Imatinib from Imatinib maleate :
Imatinib maleate (5.5kgs) is suspended in DM water(50L). Aqueous sodium hydroxide
5 solution is added over a period of 30 min to a pH of 9-12 and extracted with
chloroform(2x50L). Organic layer is washed with DM water and the solvent distilled off
under vacuum to a residual volume of 5L . Ethyl acetate(50L) is charged to the residue and
stirred for 30 minutes. The precipitated product is filtered and washed with ethyl acetate. The
product is dried at temperature of 60-70°C till constant weight.

10 Dry weight of Imatinib : 4.7 kgs

Purity: 99.99% (by HPLC)

Advantages of the invention:

- 15 1) The Imatinib is produced in more than 99.8% purity.
2) The process can be used for commercial preparation of Imatinib salts of
pharmaceutical grade.

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WE CLAIM :

1) Novel process for the preparation of Imatinib base comprising

- i. Cooling suspension of 4 -(4-methyl-piperazinomethyl)benzoyl chloride of the formula (III)
5 in chloroform at temperature of 5-15°C
 - ii. Addition of 5-15 moles of potassium hydroxide flakes preferably 10-12 moles of potassium hydroxide flakes to the above suspension and stirring this at for 30-40 minutes
 - iii. raising reaction mass temperature to 25-30°C and addition of -(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidine amine of the formula (II)
 - 10 iv. Addition of 30% aqueous potassium hydroxide solution to the reaction mass over a period of 1 hour to 6 hours preferably over 3-4 hours
- Separation of organic layer and washing of organic layer with water.
- Carbon treatment of the chloroform layer
- vii. Suspension of chloroform layer into DM water and adjusting P^H to 3.0 to 4.0 with
15 diluted hydrochloric acid .
 - viii. Washing the reaction mass with Chloroform
 - ix. Adjusting the aqueous layer P^H to 9.0 to 12.0 and extraction with chloroform .
 - x. Concentration of the organic layer and addition of ethyl acetate.
 - xi. Isolation of the precipitated imatinib base of purity 99.5%

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2) Novel process for the preparation of highly pure (>99.8) Imatinib and its pharmaceutically acceptable acid addition salts comprising of the following steps

- i. Suspension of the imatinib base of purity 99.5% in a short chain alcohol such as methanol, ethanol, propanol or mixture thereof,
- 25 ii. Adding maleic acid directly or as a solution in short chain alcohol, Maintaining the reaction mixture at room temperature for about 30 min to 2 hrs
- iii. Removal of the alcohol under vacuum and triturating the syrup with acetone
- iv. Isolating the precipitated product and drying the product at 40 to 60 °C, preferably at 50 to 60°C affording the pure Imatinib as an acid addition salt of maleic acid

v. Neutralizing Imatinib maleate with a base such as organic amines, alkali hydroxides, alkali carbonates, alkali bicarbonates and ammonia, in a mixture of water and water immiscible solvent

Separating the layers,

5 vi. Washing the organic layer with water

vii. Concentration of the organic layer and addition of ethyl acetate.

viii. Isolation of the precipitated imatinib base of purity 99.99%

3. The acid addition salt 'Imatinib maleate' as a novel pharmaceutically acceptable salt of imatinib.

10 4. Imatinib base of high purity (> 99.8%)

5. A novel method of preparing highly pure (> 99.8%) Imatinib essentially as herein described with reference to example 1 .

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2007/000178

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 A61K31/505

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

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 2006/149061 A1 (ANLI HUANG [CN] ET AL) 6 July 2006 (2006-07-06)	1-3,5
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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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

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Lauro, Paola

INTERNATIONAL SEARCH REPORT

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