(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
02 July 2020 (02.07.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/136671 A1

(51) International Patent Classification:
C07D 405/04 (2006.01)

(21) International Application Number:
PCT/IN2019/050930

(22) International Filing Date:
17 December 2019 (17.12.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
201841049252 27 December 2018 (27.12.2018) IN

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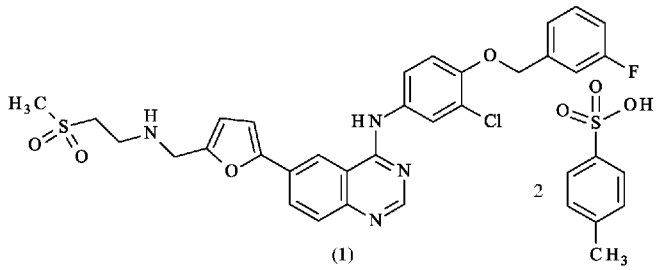
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report (Art. 21(3))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

(54) Title: IMPROVED PROCESS FOR THE PREPARATION OF LAPATINIB BASE AND IT'S ANHYDROUS DITOSYLATE SALT



(1)

(57) **Abstract:** The present invention relates to an improved, high yielding and industrially viable process for the preparation of high pure Lapatinib of formula (1). The present invention involves simple crystallization techniques avoiding column chromatographic techniques and the process conditions can be easily adopted for scale-up studies.

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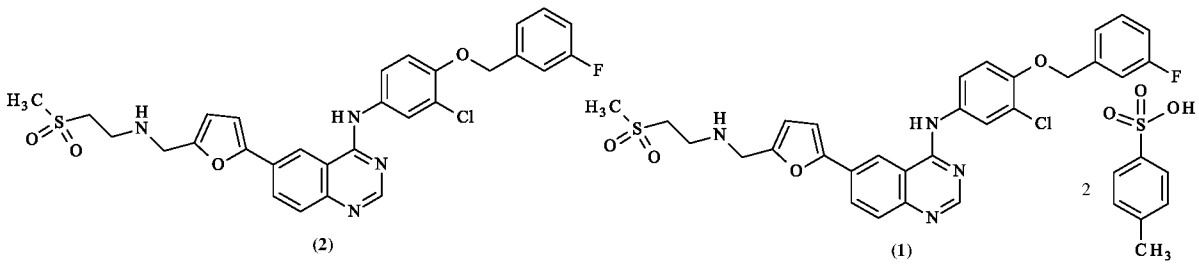
IMPROVED PROCESS FOR THE PREPARATION OF LAPATINIB BASE AND IT'S ANHYDROUS DITOSYLATE SALT

Field of the invention:

The present invention relates to an improved, high yielding and industrially viable process for the preparation of highly pure Lapatinib and its anhydrous ditosylate salt. The present invention can be easily adopted for scale-up studies.

Background of the Invention:

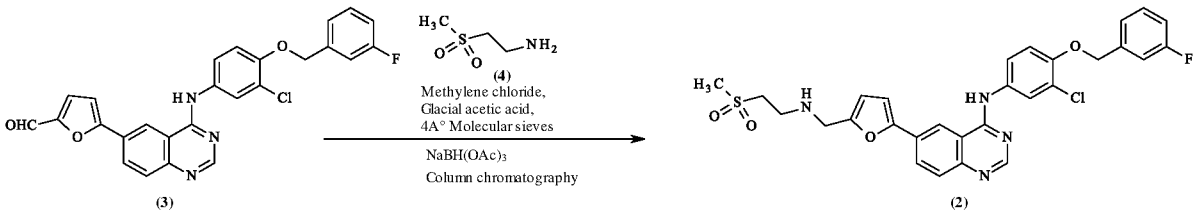
Lapatinib is a 4-anilinoquinazoline kinase inhibitor. The chemical name of Lapatinib ditosylate is *N*-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl)-6-[5-[(2-methylsulfonylethylamino)methyl)-2-furanyl]-4-quinazolinamine, ditosylate of formula (1) as depicted below.



Lapatinib of formula (2) is marketed as Lapatinib ditosylate monohydrate of formula (6) under the brand name TYKERB®. Lapatinib used as an orally active drug for breast cancer and other solid tumors. It is a dual tyrosine kinase inhibitor which interrupts the HER2/neu and epidermal growth factor receptor (EGFR) pathways. It is used in combination therapy for HER2-positivebreast cancer.

The process for the preparation of Lapatinib of formula (2), is first disclosed in US6727256 (scheme-1). According to this process, the aldehyde of formula (3) on reaction with 2-methanesulfonylethylamine of formula (4) in the presence of catalytic amount of glacial acetic acid in dichloromethane medium, followed by reduction in the

presence of sodium triacetoxyborohydride ($NaBH(OAc)_3$) affords Lapatinib of formula (2) as an organic residue, which is further purified by column chromatography.



Scheme-1

The disclosed process could be more efficient and commercially viable, if the following disadvantages are avoided.

a) Condensation of aldehyde of formula (3) with amine of formula (4) under acidic condition may lead to reversible reaction and form aldehyde of formula (3) which also can undergo reduction with sodium triacetoxyborohydride resulting unwanted impurities.

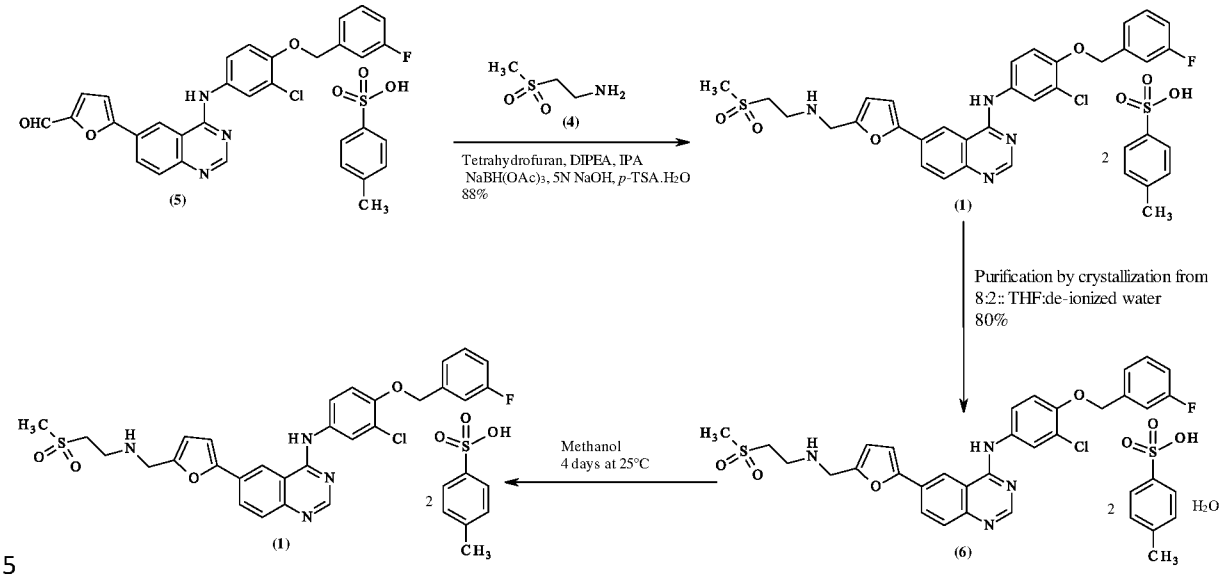
b) Usage of expensive and highly unstable reducing agent like sodium triacetoxyborohydride.

c) Commercially impracticable column chromatography as Lapatinib is a large volume product.

d) Huge volumes of organic solvents, energy and time consuming while doing column purification.

In another patent, US7157466, process for the preparation of ditosylate salts of Lapatinib of formula (1) as shown in Scheme-2. According to this patent, tosylate salt of aldehyde of formula (5) is reacted with 2-(methylsulfone)ethylamine of formula (4) in tetrahydrofuran in the presence of diisopropylethylamine (DIPEA) and the resulting solution is subjected to reduction in the presence of sodium triacetoxyborohydride ($NaBH(OAc)_3$) at room temperature. Later the reaction mixture is basified to pH 10-11 using addition of 5N sodium hydroxide and the resulting organic layer is treated with *para* toluenesulfonic acid monohydrate (*p*-TSA.H_2O) to afford Lapatinib ditosylate

anhydrous. Thereafter Lapatinib ditosylate anhydrate is purified via Lapatinib ditosylate monohydrate of formula (6) by crystallization from ~ 20% aqueous tetrahydrofuran followed by trituration in methanol for 4 days to afford Lapatinib ditosylate anhydrous of formula (1).



Scheme-2

The disclosed process has following drawbacks.

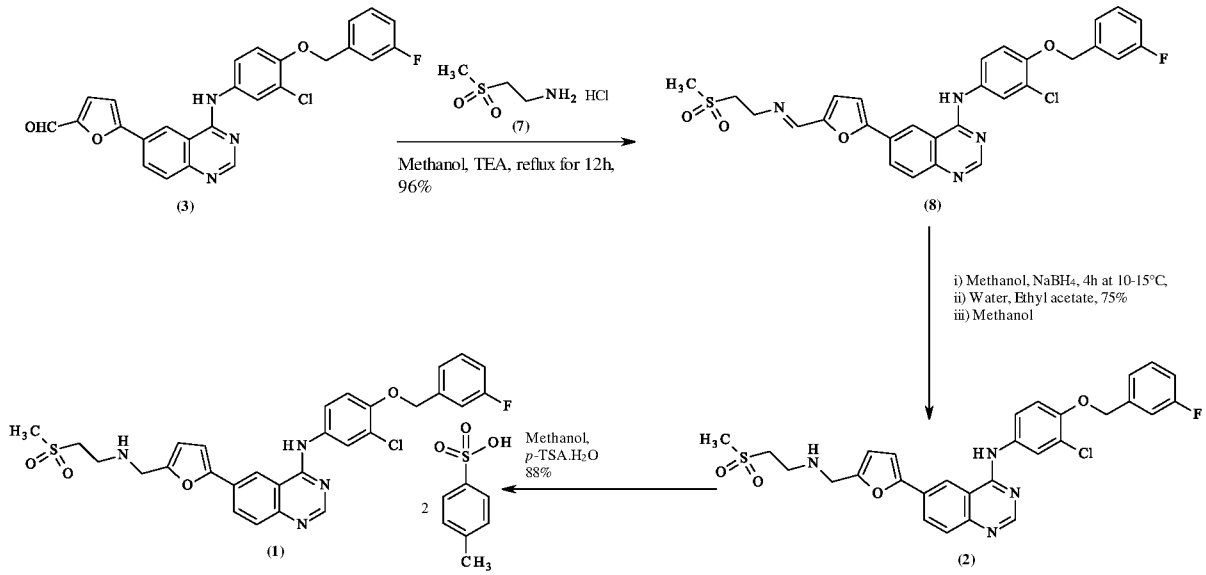
a) Usage of expensive and unstable reducing agent like sodium triacetoxyborohydride.

b) Tosylate salt of aldehyde may not give any additional advantage for the imine formation reaction. Moreover, *p*-toluenesulfonic acid is removed as organic waste.

c) Prolonged trituration (for four days) in methanol to afford Lapatinib ditosylate anhydrous of formula (1) is a time taking process.

In another patent, US8664389, as depicted in scheme-3, aldehyde of formula (3) is condensed with 2-(methylsulfone)ethylamine hydrochloride of formula (7) in the presence of triethylamine in methanol medium at reflux temperature to afford imine intermediate of formula (8). Later imine intermediate of formula (8) is reduced in the

presence of sodium borohydride in methanol medium at 10-15°C to afford Lapatinib base of formula (2) in crude form which is further purified from methanol to afford pure Lapatinib base of formula (2). Thereafter, Lapatinib base of formula (2) is converted to Lapatinib ditosylate salt of formula (1) using *para* toluenesulfonic acid monohydrate in methanol medium to afford pure Lapatinib ditosylate of formula (1).



Scheme-3

In spite of having prior art methods for the preparation of compound of formula (1), there is a need to have simple, cost effective, high yielding and commercially viable process for the preparation of Lapatinib ditosylate anhydrous of formula (1) on large scale operations since, the above shortcomings may affect the commercial production of Lapatinib ditosylate anhydrous of formula (1).

Object of the present invention:

Accordingly, commercially viable process is developed by addressing the below drawbacks like:

a) Avoid highly unstable and expensive reducing agent, sodium triacetoxyborohydride ($NaBH(OAc)_3$) for the reduction process.

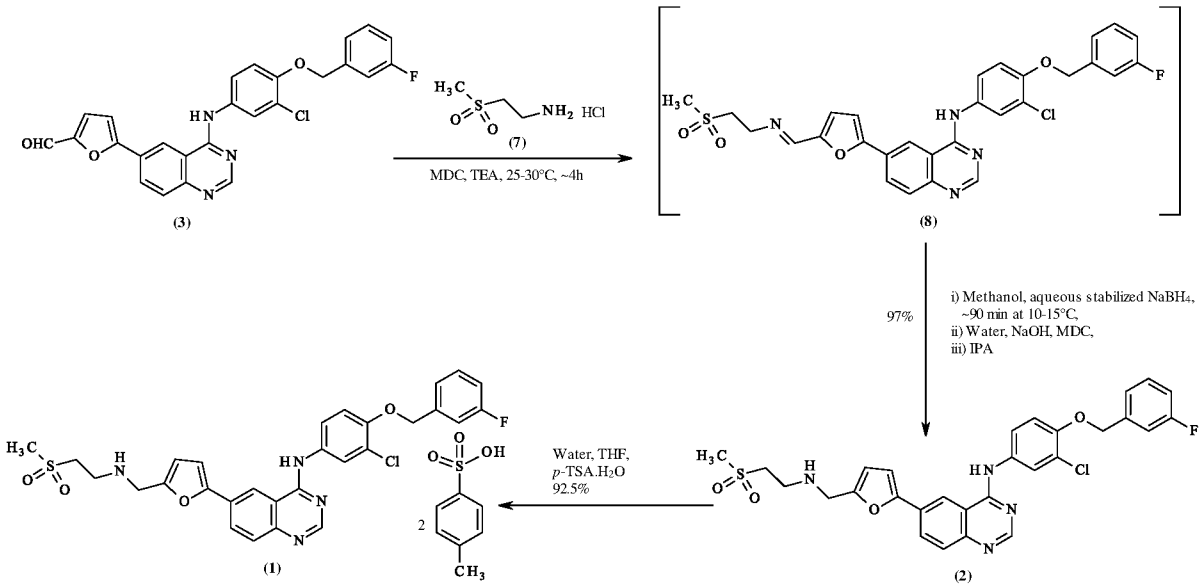
b) To overcome the non-homogeneous mixture during reduction of imine of formula (8).
c) Avoid additional purification of Lapatinib base of formula (2)
d) Avoid column purification in the process.
e) Avoid prolonged cycle time.
f) Incorporate appropriate process controls.
g) Avoid tosylate salt of aldehyde of formula (5) in the process which may affect the atom economy.
h) Improve the overall yield of Lapatinib ditosylate anhydrous of formula (1)

Keeping in view of the above drawbacks associated with the prior art processes disclosed for the preparation of Lapatinib ditosylate anhydrous of formula (1), the inventors of the present invention have developed a simple, economical, high yielding and commercially viable process for commercial production of Lapatinib ditosylate anhydrous of formula (1) by modifying the process.

Accordingly, the main objective of the present invention is to provide an improved process for the preparation of compound of formula (1) as shown in scheme-4, which comprises simple, economical, high yielding and commercially viable process which surpasses the above mentioned limitations, thereby imine formation under homogeneous conditions in the presence of base which could avoid the reversible reaction thereby controlling the unwanted impurities. Apart from that, replacing expensive and unstable reducing agent, sodium triacetoxyborohydride with stabilized aqueous sodium borohydride solution for the reduction of imine of formula (8) under homogeneous conditions in organic solvent mixture medium, in this manner increase the overall yield and quality of Lapatinib base of formula (2).

Accordingly, another main objective of the present invention is to provide an improved process for the preparation of compound of formula (1), which comprises Lapatinib ditosylate salt formation in aqueous tetrahydrofuran medium.

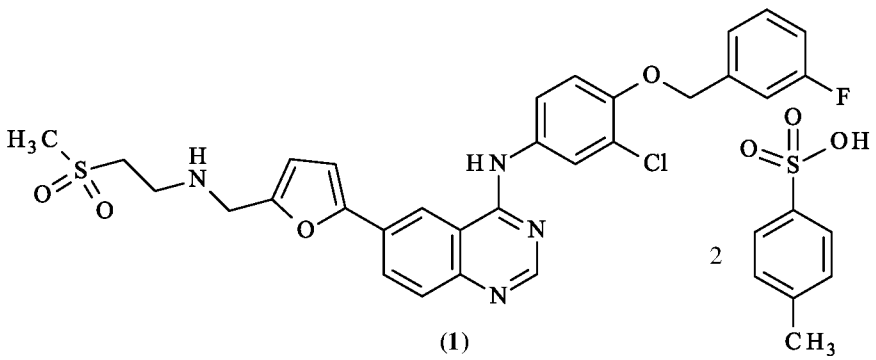
Accordingly, one more main objective of the present invention is to provide an improved process for the preparation of compound of formula (1), which comprises isolation of Lapatinib tosylate in anhydrous form by simple trituration from tetrahydrofuran.



Scheme-4

Summary of the present invention:

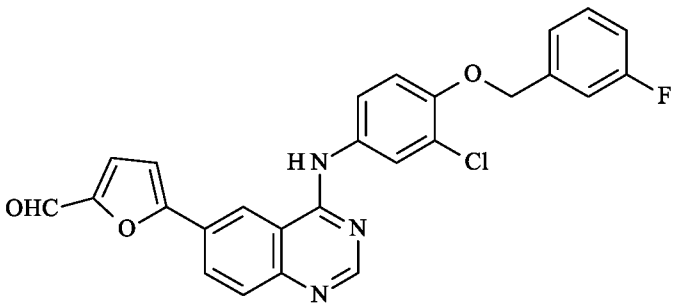
One aspect of the present invention is to provide a process for the preparation of Lapatinib ditosylate anhydrous of formula (1),



Formula (1)

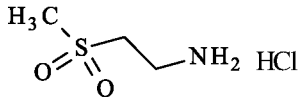
comprising the steps of:

(i) condensing aldehyde of formula (3)



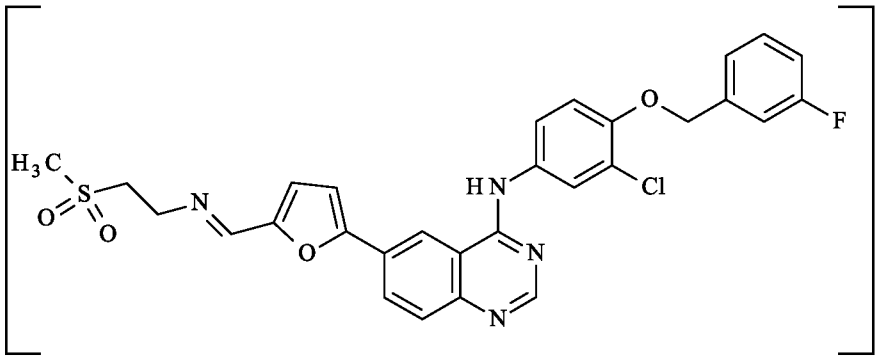
Formula (3)

with 2-(Methylsulfonyl)ethylamine hydrochloride of formula (7)



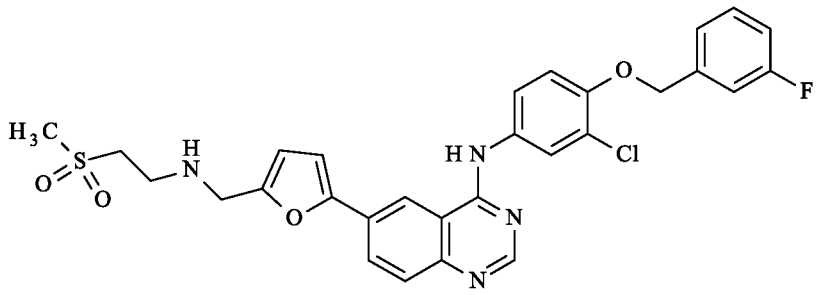
Formula (7)

in the presence of an organic base in organic solvent medium to afford imine of formula (8),



Formula (8)

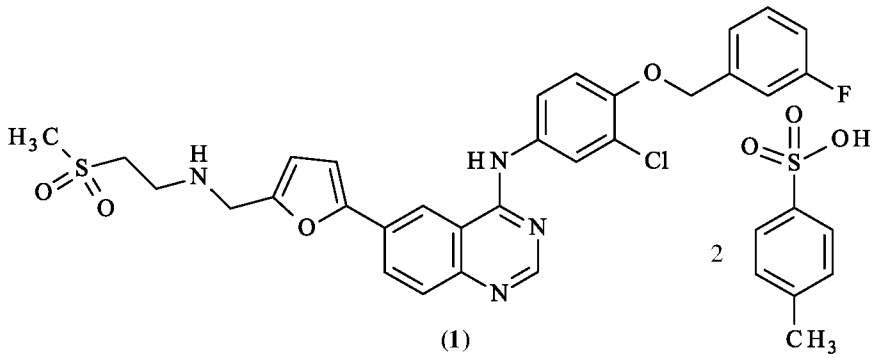
which in-turn subjected to reduction with stabilized aqueous reducing agent solution in organic solvent mixture medium to afford Lapatinib base of formula (2),



Formula (2)

Optionally Lapatinib base of formula (2) is purified by crystallization / trituration in an organic solvent medium to afford pure Lapatinib base of formula (2),

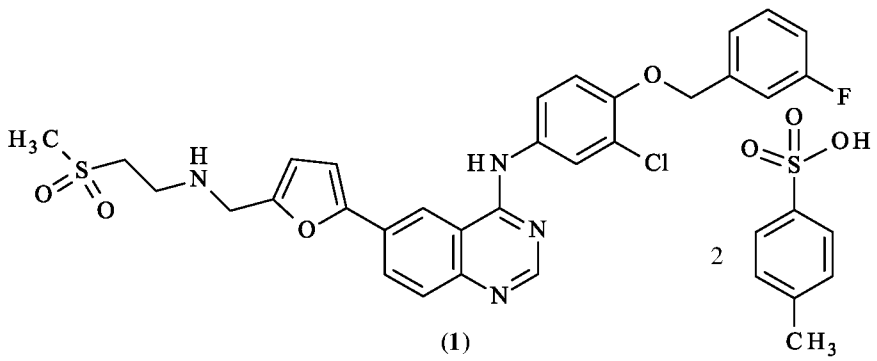
(ii) reacting Lapatinib base of formula-(2) with *para* toluenesulfonic acid monohydrate in aqueous-tetrahydrofuran to obtain anhydrous Lapatinib ditosylate,



(1)

Formula (1)

optionally Lapatinib ditosylate anhydrous of formula (1) is purified in tetrahydrofuran to afford pharmaceutically pure Lapatinib ditosylate anhydrous of formula (1).



(1)

Formula (1)

Detailed Description of the Present Invention:

One embodiment of the present invention is to provide a process for the preparation of Lapatinib ditosylate anhydrous of compound of formula (1), comprising the steps of:

(i) condensing aldehyde of formula (3) with 2-(Methylsulfonyl)ethylamine hydrochloride of formula (7) in the presence of an organic base in organic solvent medium to afford compound of formula (8) which in-turn subjected to reduction

with stabilized aqueous reducing agent solution in organic solvent mixture medium to afford Lapatinib base of formula (2),

optionally Lapatinib base of formula (2) is purified by crystallization / trituration in an organic solvent medium to afford pure Lapatinib base of formula (2),

(ii) reacting Lapatinib base of formula-(2) with *para* toluenesulfonic acid monohydrate in aqueous-tetrahydrofuran to obtain anhydrous Lapatinib ditosylate(1),

optionally Lapatinib ditosylate anhydrous of formula (1) is purified from an organic solvent medium to afford pharmaceutically pure Lapatinib ditosylate anhydrous formula (1).

In step (i), the organic base used for condensation of aldehyde of formula-(3) with 2-(Methylsulfonyl)ethylamine hydrochloride of formula (7) is triethylamine.

In step (i), the organic solvent used during condensation of aldehyde of formula (3) with 2-(Methylsulfonyl)ethylamine Hydrochloride of formula (7) is dichloromethane.
In step (i), the temperature at which condensation of aldehyde of formula (3) with 2-(Methylsulfonyl)ethylamine Hydrochloride of formula (7) is selected from 0-40°C preferably at 25-30°C.

In step (i), Imine of formula (8) is reduced in the presence of stabilized aqueous sodium borohydride solution.

In step (i), the organic solvent mixture medium used for reduction of imine of formula (8) is selected from dichloromethane, methanol, isopropyl alcohol, ethanol or mixture thereof preferably in dichloromethane-methanol mixture.

In step (i), the temperature at which reduction of imine of formula (8) in the presence of aqueous sodium borohydride in dichloromethane-methanol mixture is selected from 0-40°C, preferably, at 5-20°C.

In step (i), Lapatinib base of formula (2) is optionally purified by crystallization / trituration in an organic solvent medium in isopropyl alcohol, ethanol, methanol, ethylacetate, tetrahydrofuran or any other suitable organic solvent medium preferably isopropyl alcohol.

In step (ii), the solvent medium used for the conversion of Lapatinib base of formula (2) to its Lapatinib ditosylate of formula (1) by treating it with *para* toluenesulfonic acid monohydrate is selected from water, aqueous tetrahydrofuran, aqueous isopropyl alcohol, aqueous methanol, aqueous ethanol, aqueous tertiary butanol, or mixture thereof preferably aqueous tetrahydrofuran.

In step (ii), Lapatinib ditosylate of formula (1) is isolated in anhydrous form in tetrahydrofuran.

Advantages of the Present Invention:

(i) As the imine of formula (8) is in homogeneous solution under basic conditions, the possibility of reversible reaction is minimized which avoid formation of unwanted impurities.

(ii) The process of the present invention requires commercially viable stabilized aqueous sodium borohydride solution as reducing agent.

(iii) The process of the present invention discloses direct isolation of Lapatinib ditosylate in anhydrous form.

(iv) The purity of the isolated Lapatinib base of formula (2) is ~99% which is sufficient to convert to its pharmaceutical grade ditosylate salt of Lapatinib of formula (1) in anhydrous form.

(v) The process of the present invention successfully avoids chromatographic purification technique from the process.

(vi) Lapatinib ditosylate anhydrous of formula (1) from the present invention has having HPLC purity more than 99.5%.

(vii) The process of the present invention is commercially viable and industrially applicable and cost effective.

(viii) The overall yield of Lapatinib ditosylate anhydrous of formula (1) is >89% from aldehyde of formula (3).

According to the Present invention, N-(3-chloro-4-(3-fluorobenzyloxy)anilino)-6-quinazolinyl)-furan-2-carbaldehyde(4) is prepared according to prior art process.

The Present invention is further illustrated in detail with reference to following examples. It is desired that the examples be considered in all respect as illustrative and are not intended to limit the scope of the invention in any way.

Example-1: Preparation of Lapatinib base (2):

N-(3-chloro-4-(3-fluorobenzyloxy)anilino)-6-quinazolinyl)-furan-2-carbaldehyde (4) (100g; 0.211 mole) was reacted with 2-methanesulfonylethylamine HC1 (7) (47.2g; 0.295 mole) in the presence of triethylamine (42.7g; 0.421 mole) in dichloromethane at 25-30°C under N_2 atmosphere and monitored progress of the reaction by HPLC. After completion of reaction, methanol followed by cold aqueous stabilized sodiumborohydride solution (20.0g; 0.527 mole) were added, maintained at 10-15°C and monitored progress of the reaction by HPLC. The reaction mass was treated with DM water and aqueous sodium hydroxide, separated the organic layer and concentrated. The concentrated mass was treated with IPA at reflux temperature, filtered, washed with IPA and dried at 60-65°C to obtain pure Lapatinib base (118.9g; 97%); HPLC: ~99%

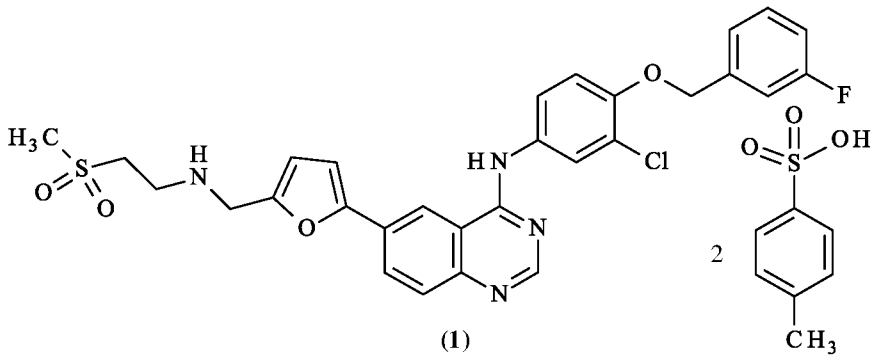
Example-2: Lapatinib ditosylate anhydrous (1)

To the solution of Lapatinib base (75g; 0.129 mole) in aqueous THF (2.25L), *p*-TSA (54g; 0.283 mole) dissolved in aqueous THF (150 mL) was added at ambient temperature, heated to 57.5±2.5°C. The resulting solution was treated with carbon activated, filtered and washed. The filtrate was cooled to 0-5°C, maintained for 3-4h, filtered the product, washed and dried at 75-80°C under vacuum to obtain pure Lapatinib ditosylate anhydrous product (110.5g; 92.5%)

HPLC purity: >99.5%

We Claim:

1. A process for the preparation of compound of formula (1),

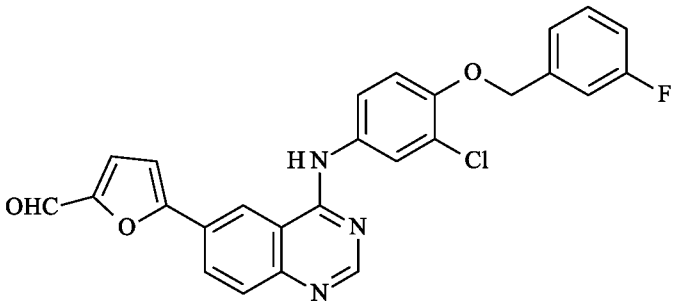


(1)

Formula (1)

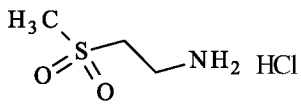
comprising the steps of

(i) condensing aldehyde of formula (3)



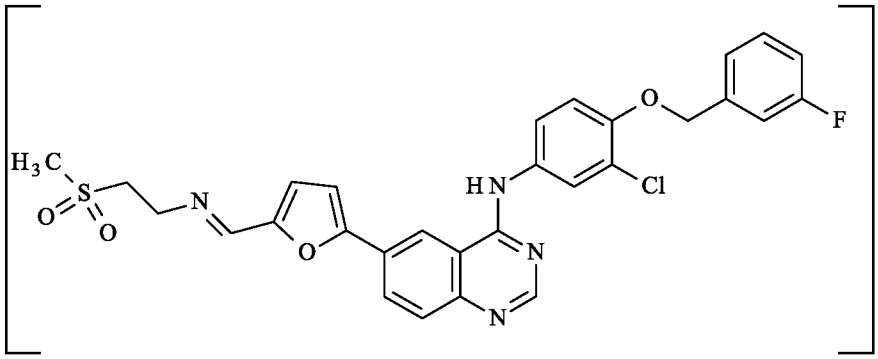
Formula (3)

with 2-(Methylsulfonyl)ethylamine hydrochloride of formula (7)



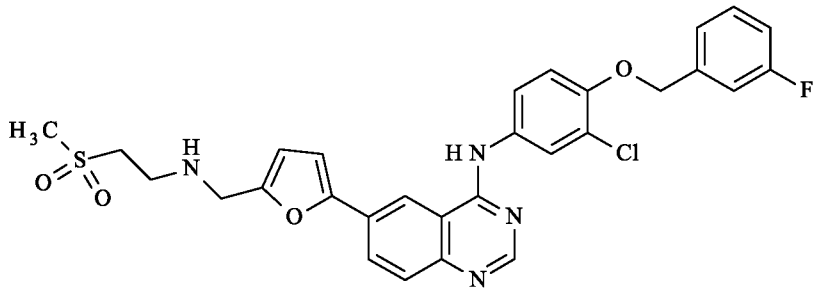
Formula (7)

in the presence of an organic base in organic solvent medium to afford compound of formula (8),



Formula (8)

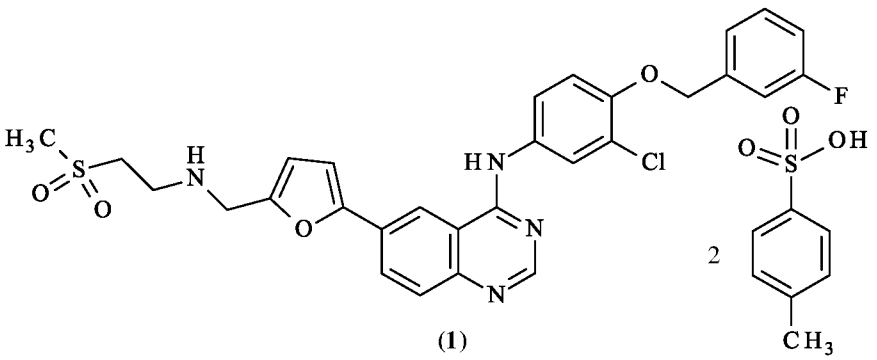
which in-turn subjected to reduction with stabilized aqueous reducing agent solution in organic solvent mixture medium to afford Lapatinib base of formula (2),



Formula (2)

Optionally Lapatinib base of formula (2) is purified by crystallization / trituration in an organic solvent medium to afford pure Lapatinib base of formula (2),

(ii) reacting Lapatinib base of formula-(2) with *para* toluenesulfonic acid monohydrate in aqueous-tetrahydrofuran to obtain anhydrous Lapatinib ditosylate,



(1) Formula (1)

optionally Lapatinib ditosylate anhydrous of formula (1) is purified in an organic solvent medium to afford pharmaceutically pure Lapatinib ditosylate anhydrous of formula (1).

2. The process according to claim 1, wherein in step (i), aldehyde of formula-(3) is condensed with 2-(Methylsulfonyl)ethylamine Hydrochloride of formula (7) in the presence of triethylamine in dichloromethane.

3. The process according to claim 1 and 2, wherein in step (i), imine of formula (8) is reduced in the presence of aqueous stabilized sodium borohydride solution.

4. The process according to claim 1, wherein in step (i), the organic solvent mixture medium used for reduction of imine of formula (8) is selected from dichloromethane, methanol, isopropyl alcohol, ethanol or mixture thereof.

5. The process according to claim 1, wherein the solvent used for purification in step (i), Lapatinib base of formula (2) is selected from isopropyl alcohol, ethanol, methanol, ethylacetate, tetrahydrofuran.

6. The process according to claim 1, wherein in step (ii), solvent medium used in the preparation of Lapatinib ditosylate of formula (1) is selected from water, aqueous tetrahydrofuran, aqueous isopropyl alcohol, aqueous methanol, aqueous ethanol, aqueous tertiary butanol, or mixture thereof.

7. The process according to claim 1, wherein in step (ii), the solvent used for the purification of anhydrous Lapatinib ditosylate of formula (1) is tetrahydrofuran.

8. A process for the preparation of anhydrous Lapatinib ditosylate (1) comprising the steps of:
   a) reacting N-(3-chloro-4-(3-fluorobenzyloxy)anilino)-6-quinazolinyl)-furan-2-carbaldehyde(3) with 2-methanesulfonylethylamine HC1(7) in presence of triethylamine and solvent to get N-{3-chloro-4-[(fluorobenzyloxy] phenyl}-6-[5-({[2-methanesulphonyl)ethyl]imino}methyl)-2-furyl]-4-quinazolinamine(8),
   b) reducing the N-{3-chloro-4-[(fluorobenzyloxy]phenyl}-6-[5-({[2-methane-sulphonyl)ethyl]imino}methyl)-2-furyl]-4-quinazolinamine (8) with sodium borohydride in presence of dichloromethane-methanol mixture to obtain Lapatinib free base (2),
   c) crystalizing the Lapatinib base from isopropanol to get pure Lapatinib base (2),
   d) reacting Lapatinib base of formula-(2) by dissolving or suspending in tetrahydrofuran/water medium with p-toluenesulfonic acid monohydrate to obtain anhydrous Lapatinib ditosylate of formula-(1).
   e) Optionally purifying the anhydrous Lapatinib ditosylate of formula (1) is purified using organic solvent.

9. The process according to claim 8, wherein in step-a) the solvent is selected from dichloromethane, dichloroethane and chlorobenzene.

10. The process according to claim 8, wherein the solvent used for the purification of anhydrous Lapatinib ditosylate of formula (1) is tetrahydrofuran.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2019/050930

A. CLASSIFICATION OF SUBJECT MATTER
C07D405/04 Version=2020.01

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

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

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

TotalPatent One, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2012/0245351A1; NATCO PHARMA LIMITED (IN); 27 September 2012 (27.09.2012)(page 8 scheme C; claims 1, 16, 17, 23, 29, 30; para [0046], [0083])	1-10
Y	US8530701 B2; NEWRON PHARMACEUTICALS, S.P.A. (IT); 10 September 2013 (10.09.2013)(column 22 lines 26-40; column 27 lines 10-15)	1-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
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"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
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
02-03-2020	02-03-2020
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Dr. Shahida Umar Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2019/050930

Citation	Pub.Date	Family	Pub.Date
US 2012/0245351 A1	27-09-2012	WO 2011039759 A1	07-04-2011
US 8530701 B2	10-09-2013	WO 2009074478 A1	18-06-2009
		EP 2229351 A1	22-09-2010
		CN 101896456 A	24-11-2010
		JP 2011506375 A	03-03-2011