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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 December 2007 (06.12.2007)

PCT

(10) International Publication Number
WO 2007/138613 A2

(51) International Patent Classification:
C07D 239/94 (2006.01)

(21) International Application Number:
PCT/IN2007/000101

(22) International Filing Date: 12 March 2007 (12.03.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
904/CHE/2006 25 May 2006 (25.05.2006) IN

(71) Applicant *(for all designated States except US)*: **VITTAL MALLYA SCIENTIFIC RESEARCH FOUNDATION** [IN/IN]; P.B.No.406, K.R.Road, Banglore 560 004 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CHANDREGOWDA, Venkateshappa** [IN/IN]; Vittal Mallya Scientific Research Foundation, P.B.No.406, K.R.Road, Banglore 560 004 (IN). **RAO, Gudapati Venkateswara** [IN/IN]; Vittal Mallya Scientific Research Foundation, P.B.No.406, K.R.Road, Banglore 560 004 (IN). **KUSH, Anil Kumar** [IN/IN]; Vittal Mallya Scientific Research Foundation, P.B.No.406, K.R.Road, Banglore 560 004 (IN). **REDDY, Goukanapalli Chandrasekara** [IN/IN]; Vittal Mallya Scientific Research Foundation, P.B.No.406, K.R.Road, Banglore 560 004 (IN).

(74) Agents: **ANAND, Pravin** et al.; Anand and Anand Advocates, B-41, Nizamuddin East, New Delhi 110 013 (IN).

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

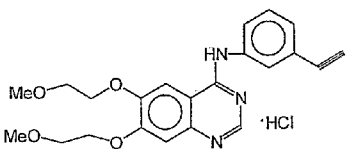
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to the identity of the inventor (Rule 4.17(i))*
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** A PROCESS FOR SYNTHESIS OF [6,7-BIS-(2-METHOXYETHOXY)-QUINAZOLIN-4-YL]-(3-ETHYNYLPHENYL)AMINE HYDROCHLORIDE



(I)

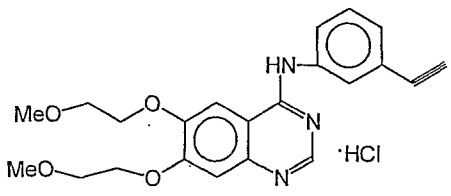
(57) **Abstract:** The present invention provides a process for synthesizing [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)amine hydrochloride (Erlitinib Hydrochloride) having the formula (I) comprising reacting 3,4-dihydroxy benzaldehyde with bromo derivative of ethyl methyl ether to obtain 3,4-bis(2-methoxyethoxy)benzaldehyde having formula (III). This is converted to give 3,4- bis (2-methoxyethoxy)-benzonitrile which on furthur nitration we obtain 4,5- bis (2-methoxyethoxy)-2-nitrobenzonitrile which on nitro reduction we get 2-amino-4,5-bis(2-methoxyethoxy)benzonitrile. Formylation of this compound yields N'-[2-cyano-4,5-bis(2methoxyethoxy)phenyl]-N,N-dimethylformamidine. Coupling of this formamidine with 3-ethynyl aniline gives erlotinib free base. On furthur treatment of this free base with methanolic/ethanolic hydrochloric acid gives us erlotinib hydrochloride.

WO 2007/138613 A2

A PROCESS FOR SYNTHESIS OF [6,7-BIS-(2-METHOXYETHOXY)-QUINAZOLIN-4-YL]-(3-ETHYNYLPHENYL)AMINE HYDROCHLORIDE

FIELD OF INVENTION

The present invention relates to a process for synthesis of [6,7-bis-(2-methoxyethoxy) - quinazolin -4- yl]-(3-ethynylphenyl)amine hydrochloride of the formula I.



I

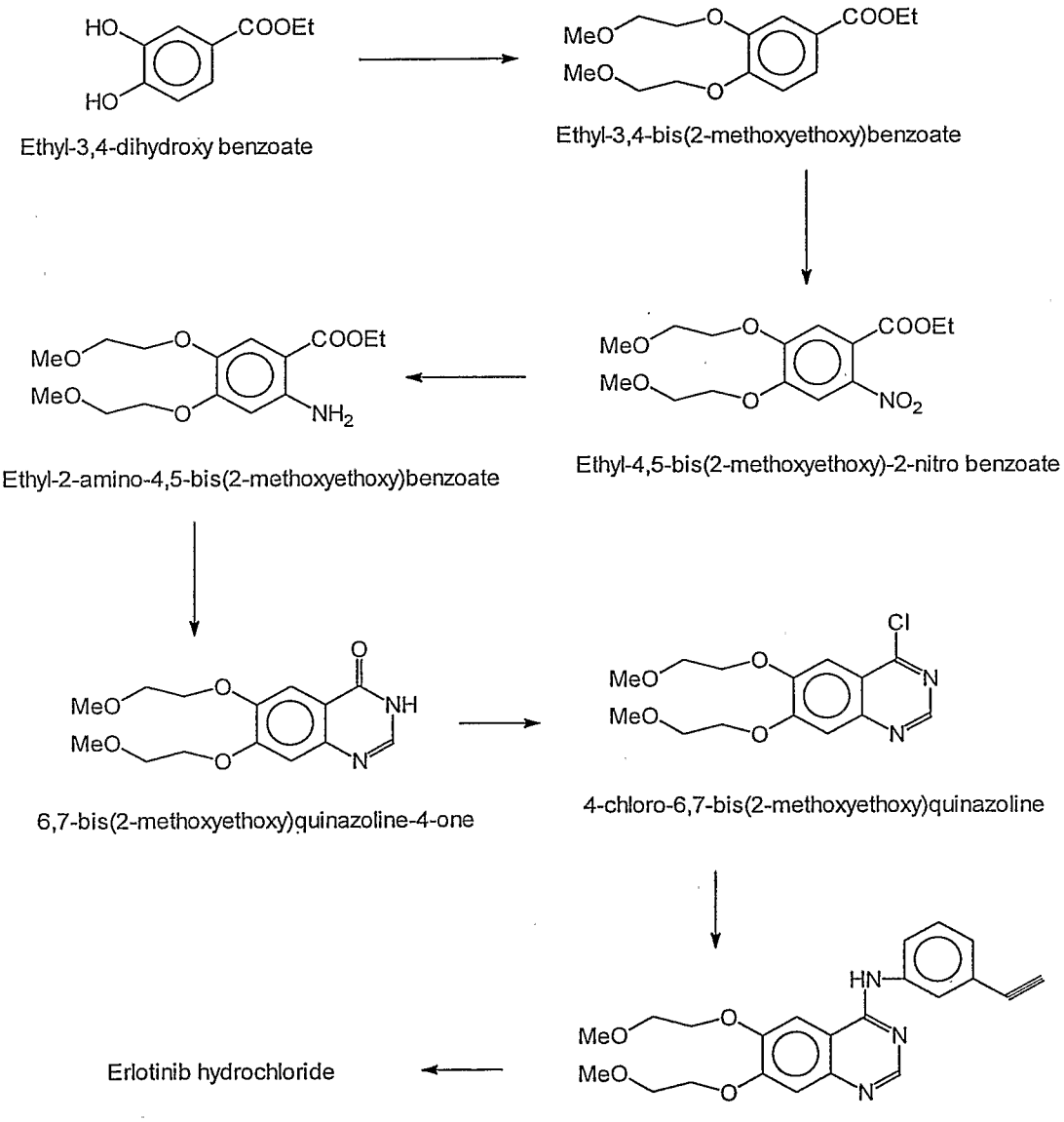
It is a low molecular weight compound used in the treatment of proliferative neoplastic and malignant diseases including multiple forms of solid tumors and psoriasis. It inhibits epidermal growth factor- receptor tyrosine kinase (EGFR-TKI). Receptor protein tyrosine kinases play a key role in signal transduction pathways that regulates cell division and differentiation. Over expression of certain growth factor receptor tyrosine kinases such as epidermal growth factor receptor (EGFR) as well as human epidermal growth factor receptor (HER-2) leads to cancer. Protein kinase inhibitors particularly phosphorylation inhibitors, have become important targets for selective cancer therapies (Bioorganic & Medicinal chemistry Letters 12, 2893-2897 (2002). Further, it exhibits significant anti-tumor activity in a broad range of solid tumor xenografts in vivo. Clinical toxicology studies have demonstrated good oral bio-availability and in long term oral administration it was well tolerated.

Description of prior art:

As known process for the synthesis of erlotinib hydrochloride , there can be mentioned a method comprising preparation of 6,7-bis(2-methoxyethoxy)quinazolone and then reacting 4-chloro-6,7-bis(2-methoxyethoxy)quinazoline with 3-ethynylaniline under basic conditions such as pyridine or using excess aniline in solvents like isopropanol (US patent No. 5,747,498, May 5, 1998), followed by silica gel column chromatographic purification as a free base erlotinib and titration of free base with IM HCl to yield erlotinib hydrochloride in 71% final step yield. Further preparation of 4-chloro-6,7-bis-(2-methoxyethoxy)quinazoline involved many independent steps like alkylation of ethyl 3,4-dihydroxybenzoate using 2-bromoethylmethyl ether and potassium carbonate, followed by nitration with nitric acid / acetic acid which yielded ethyl 4,5-bis (2-methoxyethoxy)-2-nitrobenzoate. The resulting nitro compound was then reduced to ethyl-2-amino- 4,5-bis-(2-methoxyethoxy)benzoate by hydrogenation in presence of PtO_2 with a yield of about 88%. This step involved handling of a combustible gas like hydrogen as well as costly catalyst such as PtO_2. Further cyclization of ethyl-2-amino-4,5-bis-(2-methoxyethoxy)benzoate has been achieved using ammonium formate and formaldehyde at a high temperature of 160-165°C yielding 6,7-bis-(2-methoxyethoxy)-quinazolone. Treatment of 6,7-bis(2-methoxyethoxy)-quinazolinone with oxalylchloride / phosphorousoxychloride in presence of suitable solvent yielded 4-chloro-6,7-bis-(2-methoxyethoxy)-quinazoline with yields of 92% and 56% respectively. Thus multiple steps are involved with usage of several costly reagents like platinum oxide, flammable gas like hydrogen and at very high reaction temperatures. Further the penultimate step product namely [6,7-bis-(2-methoxyethoxy)-

quinazolin-4-yl]-(3-ethynylphenyl)amine is purified by silica column chromatography . All these steps not only push the manufacturing cost to a higher side but also take more time. Thus this known method involves various industrial difficulties.

The steps of the process given in US Patent 5,747,498 are:

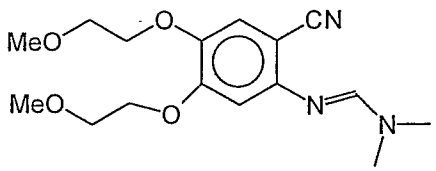


Summary of the Invention

In view of problems as described in above process, there is provided a process in the present invention a more efficient and convergent process for the synthesis of [6,7-bis-(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl)amine hydrochloride (scheme-1) having the above formula I by substantially reducing the number of steps and also intermediates that must be isolated. Further the present invention has significant advantage in terms of cost and time. In present invention, processes are provided for the preparation of key intermediates that must be used in the synthesis of compound of formula I.

One of the objectives of the present invention is to provide a simple and convergent process for preparation of Erlotinib hydrochloride.

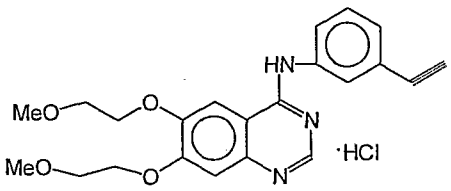
According to another objective of this invention there is provided a novel compound of the formula VIII which is an intermediate for the preparation of the compound of formula I and a process for its preparation.



VIII

DETAILS OF THE INVENTION

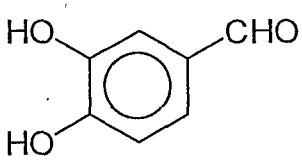
To obviate the disadvantages of the prior art, the present invention provides a process for the synthesis of [6,7-bis-(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl)amine hydrochloride having the formula I,



I

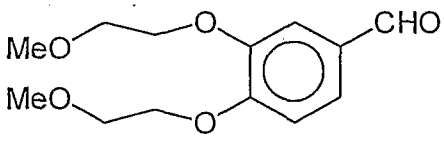
comprising

a) reacting 3,4-dihydroxy benzaldehyde having formula II



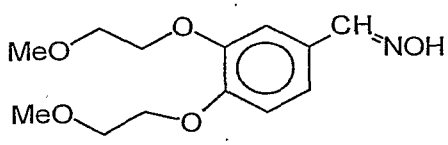
II

with substituted ethylmethyl ether in presence of an inert solvent and a base to obtain 3,4-bis(2-methoxyethoxy) benzaldehyde having formula III,



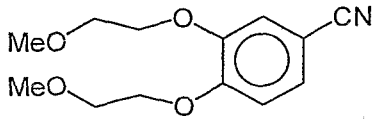
III

b) converting compound of the formula III in presence of a base and an organic solvent into 3,4-bis(2-



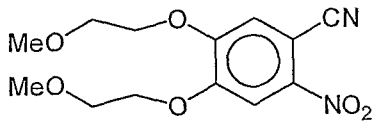
IV

methoxyethoxy)benzaldoxime of the formula IV and dehydrating the said compound to obtain 3,4-bis(2 methoxyethoxy)benzonitrile having formula V



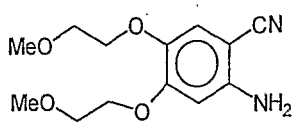
V

c) nitrating the compound of the formula V with nitrating agent to obtain 4,5-bis(2-methoxyethoxy)-2-nitrobenzonitrile having the formula VI



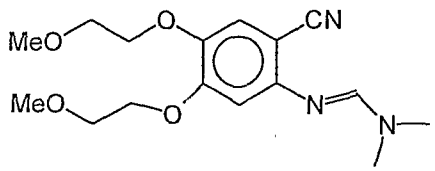
VI

d) subjecting the compound of the formula VI to nitro reduction to get 2-amino-4,5-bis(2methoxyethoxy)benzonitrile having the formula VII



VII

e) formylating of the compound of formula VII with a formylating agent in the presence of a derivative of formic acid to give N'-[2-cyano-4,5-bis(2methoxyethoxy)pheny]-N,N-dimethylformamidine of formula VIII



VIII

f) coupling the compound of the formula VIII with an aniline derivative in the presence of a acid catalyst to obtain [6,7-bis-(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl)-amine (erlotinib free base) .

g) treatment of the erlotinib free base with a polar solvent containing hydrochloric acid to obtain the compound of formula (I)

The compound of formula (I) of above process is purified by recrystallisation from solvents to get the compound of acceptable purity.

The inert solvent in step (a) is an aprotic solvent selected from aliphatic ketones and substituted amides, preferably dimethyl formamide .

The substitution of the ethylmethylether in step (a) is chloro, bromo, iodo, hydroxy or a methoxy group preferably bromo derivative.

The base in step (a) is alkali or alkaline earth carbonate and hydroxide preferably sodium and potassium carbonate.

The reaction mixture in step (a) is maintained at a temperature from ambient to reflux temperature preferably from 80^0 C to 100^0 C .

The solvent in step (b) is aliphatic alcohol preferably methanol or isopropanol.
The base in step (b) is organic or inorganic bases wherein the organic base is pyridine, dimethylaminopyridine, or triethylamine and the inorganic base is sodium acetate or ammonium acetate; the organic base used preferably is pyridine.

The dehydration in step (b) is carried out in the presence of thionyl chloride, phosphorous oxy chloride, propionic anhydride or acetic anhydride ; preferably acetic anhydride.

The reaction in step (b) is from ambient to reflux temperature from 50^0 C to 120^0 C ; preferably reaction is carried out at $110\ ^0$C .
The nitrating agent in step (c)can be selected from nitric acid /sulphuric acid and potassium nitrate.

The nitro reduction in step (d) is carried out in the presence of suitable catalyst on an inert carrier and in an inert solvent or in the presence of an inorganic reducing agent .

The reduction of the nitro group in step (d) is carried out in the presence of the catalyst selected from palladium ,platinum or iron , inert carrier is carbon,and the inert solvent is selected from water, ethanol, methanol or acetic acid or the

inorganic reducing agent used in step (d) is sodium dithionate at a temperature in the range from 30 to 50 ^{0}C conveniently at 30 ^{0} C ..

The fomylating agent used in step (e) is N,N-dimethylformamide dimethyl acetal in the presence of a polar aprotic solvent , an aromatic solvent or a dipolar aprotic solvents , preferably N,N dimethyl formamide at a temperature range from 20 to 140 ^{0}C. , preferably at 115 ^{0}C.

The process in step (e) wherein the

- polar aprotic solvent is tetrahydrofuran, 1,4 dioxane
- aromatic solvent used is toluene
- a dipolar aprotic solvent used is N,N- dimethylacetamide

The aniline derivative coupled to the compound of formula VIII in step (f) in one pot procedure is a 3-ethynyl aniline in the presence of acid catalyst at a temperature range from 30^{0}C to 140^0 C preferably at 130^0 C.

The acid catalyst is selected from trifluroacetic acid , formic acid , preferably acetic acid.

The polar solvent used in step (h) is selected from methanolic hydrochloric acid or ethanolic hydrochloric acid.

The process of the present invention provides the following distinct advantages over the prior art.

(a) Reduction in the number of steps:

The usage of costly reducing agent like platinum oxide in reducing nitro compound and higher temperatures used in cyclization of 2-amino-4,5-bis-(2-methoxyethoxy)benzoate are reported in US patent 5,747,498. Further 4-

chloro-6,7–bis(2-methoxyethoxy)quinazoline is coupled with suitably substituted aniline in the presence of additional base and isolated erlotinib as a free base and purified it by silica column chromatography. All these steps involve several independent operations including usage of flammable hydrogen gas and subjecting to silica column chromatographic purifications. In contrast, according to the processes of present invention erlotinib free base preparation is accomplished in one go from N'-[2-cyano-4, 5-bis (2-methoxyethoxy) phenyl]-N, N-dimethylformamidine without using corrosive chemicals like $POCl_3/SOCl_2$ and purified by crystallization techniques alone.

The process of preparation of 6,7-bis-(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl)amine hydrochloride , is herein described with reference to the following examples:

EXAMPLES

a) 3,4-bis (2-methoxyethoxy) benzaldehyde:

To 3, 4-dihydroxy benzaldehyde of the formula II (25g, 0.1811 mole), potassium carbonate (60g, 0.4347 mole) in N, N-dimethyl formamide (120ml) was added 2-bromoethylmethyl ether (50.4g, 0.3625 mole). The mixture was stirred at 100°C for 2 hours, cooled to room temperature, filtered inorganics. The clear filtrate was concentrated under vacuum and the residue was dissolved in methylene chloride, washed with water and dried over calcium chloride. Evaporation yielded 3,4-bis (2-methoxyethoxy) benzaldehyde of formula III (45g, 98%).

NMR spectrum ($CDCl_3$): δ 3.46 (s, 6H), 3.81(m, 4H), 4.22 (m, 4H), 7.00(d, 1H), 7.43(s, 1H), 7.45(d, 1H) and 9.83(s, 1H).

b) 3,4- bis (2-methoxyethoxy) benzonitrile:

To 3,4-bis(2-methoxyethoxy) benzaldehyde of the formula III (45g, 0.177 mole)and hydroxylamine hydrochloride (45g, 0.6521mole), in methanol (200ml) was added pyridine (52ml, 0.6521mole). This reaction mixture was stirred at reflux temperature for about 3 hours. Methanol was concentrated under vacuum and the residue was dissolved in ethyl acetate, washed the organic layer with water and dil. HCl, dried over anhydrous sodium sulphate. To the residue obtained after evaporation of ethylacetate was added acetic anhydride (75ml) and heated to 110°C for 4 hours, then cooled the reaction mixture to room temperature, quenched in water and adjusted the P^H to 8 with sodium bicarbonate and extracted with methylene chloride. Organic layer was washed with water and dried over calcium chloride. On evaporation of the solvent, a brown liquid i.e. 3,4- bis (2-methoxyethoxy) benzonitrile (42g, 95%) of the formula V.

NMR ($CDCl_3$): δ 3.45 (s, 6H), 3.79(m, 4H), 4.18(m, 4H), 6.93(d, 1H), 7.14(d, 1H) and 7.26(dd, 1H)

c) 4,5-bis(2-methoxyethoxy)-2-nitrobenzonitrile:

To 70% nitric acid (84ml) maintained at 40°C was added 3,4-bis(2-methoxyethoxy) benzonitrile (42g) of the formula V slowly over a period of 2 hours under stirring. After complete addition of the compound, stirring continued for further an hour, quenched the reaction mass in ice-water, filtered, washed the precipitate with water and dried the material at 50°C to get yellow solid i.e. 4,5-bis(2-methoxyethoxy)-2-nitrobenzonitrile of the formula VI (44.5g, 90%); m.p. 139-143°C.

NMR ($CDCl_3$): δ 3.45 (s, 6H), 3.82(m, 4H), 4.30(m, 4H), 7.28(s, 1H) and 7.85(s, 1H).

(d) Synthesis of 2-amino-4, 5-bis (2-methoxyethoxy) benzonitrile:

To 4,5-bis (2-methoxyethoxy)-2-nitrobenzonitrile(10 g) was added acetic acid (75ml) and water(75ml), stirred the reaction mass for about 10 min, added Iron powder (7g) in portions over a period of 2hrs, Stirred the reaction mixture for about ½ hr at 30°C adjusted P^H of the reaction mass to 7. Extracted the material into ethylacetate, the organic layer was dried over sodium sulfate and concentrated to yield crystalline yellow solid, Which was further recrystallized from methanol (6g)

mp 74-77 °C

^{1}HNMR ($CDCl_3$): δ 3.43(s, 6H), 3.73(m, 4H), 4.08(m, 4H), 4.20(brs, 2H), 6.25(s, 1H), 6.90(s, 1H)

e) Synthesis of N'-[2-cyano-4,5-bis (2-methoxyethoxy) phenyl]-N, N-dimethylformamidine:

To a solution of DMF(12ml) and N,N-dimethylformamide dimethylacetal(DMA, 6ml, 0.045 moles) was added 2-amino-4,5-bis(2-methoxyethoxy)benzonitrile(6g, 0.0225moles) and refluxed for about 3hrs, concentrated excess DMF-DMA to obtain light brown liquid(6.5g)

^{1}HNMR ($CDCl_3$): δ 3.06(s, 6H), 3.44(s, 6H), 3.75(m, 4H), 4.13(m, 4H), 6.48(s, 1H), 7.02(s, 1H), 7.55(s, 1H)

(f) [6, 7-bis-(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl) amine:

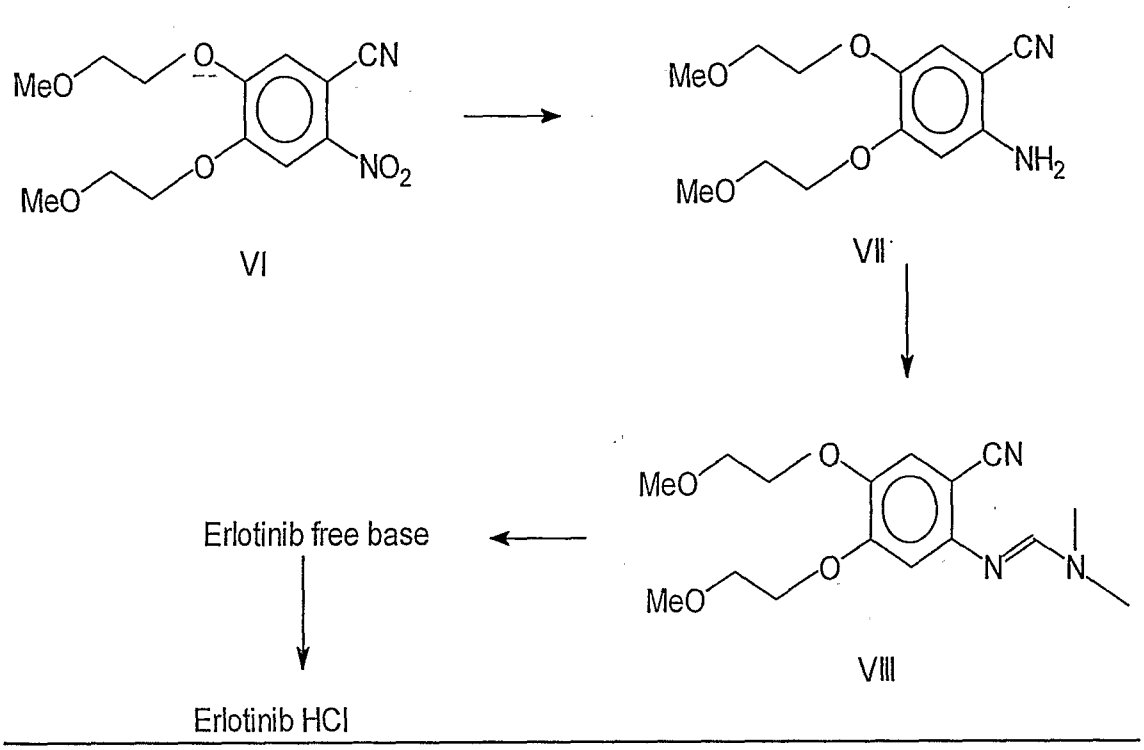
To N'-[2-cyano-4,5-bis(2-methoxyethoxy)phenyl]-N,N-dimethylformamidine(6.5g, 0.0202 moles) was added 3-ethynylaniline(2.37g, 0.0202 moles) and acetic acid(25ml) heated the reaction mixture to 125°C, stirred the reaction mixture for about 3hrs, quenched in ice water, neutralized with sodium bicarbonate, extracted the product into ethyl acetate, the organic layer was dried over sodium sulfate and concentrated to yield crude material which was further crystallized from ethyl acetate to get off-white crystalline compound(6.0g) having the mp 149-153 °C.

(g) [6,7-bis-(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl) amine hydrochloride (Erlotinib hydrochloride):

To a stirred solution of Erlotinib (6g) in methanol (50ml) was passed dry hydrochloric acid stirred the reaction mass for about 1/2hr the solid precipitated was filtered to get the white crystalline material of erlotinib hydrochloride (6g) having the mp 228-230 °C

UV, IR, NMR spectral data together with elemental analysis is in complete agreement with those of standard substance of erlotinib Hydrochloride.

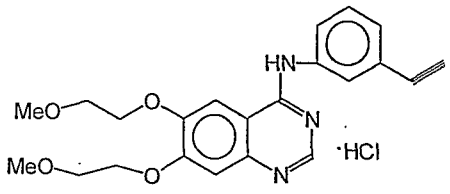
Scheme-1:



In our copending application 1483/CHE/2005 we have described the process for preparing 6,7-bis-(2methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl)amine hydrochloride (erlotinib hydrochloride)

We claim

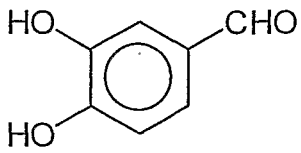
1. A process for the synthesis of [6,7-bis(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)amine hydrochloride having formula (I)



I

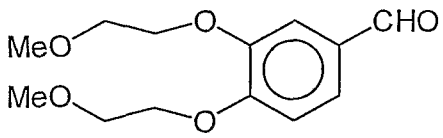
comprising

a) reacting 3,4-dihydroxy benzaldehyde having formula II



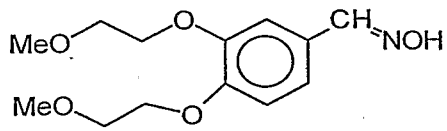
II

with substituted ethylmethyl ether in presence of an inert solvent and a base to obtain 3,4-bis(2-methoxyethoxy) benzaldehyde having formula III,



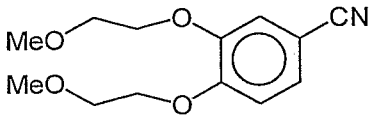
III

b) converting compound of the formula III in presence of a base and an organic solvent into 3,4-bis(2-



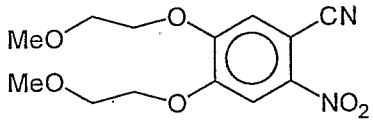
IV

methoxyethoxy)benzaldoxime of the formula IV and dehydrating the said compound to obtain 3,4-bis(2 methoxyethoxy)-benzonitrile having formula V



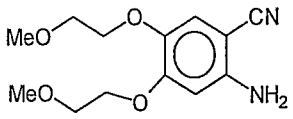
V

c) nitrating the compound of the formula V with nitrating agent to obtain 4,5-bis(2-methoxyethoxy)-2-nitrobenzonitrile having the formula VI



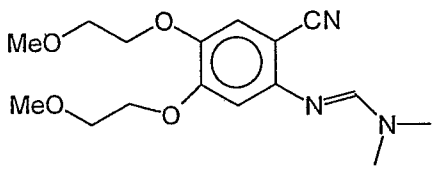
VI

d) subjecting the compound of the formula VI to nitro reduction to get 2-amino-4,5-bis(2methoxyethoxy)benzonitrile having the formula VII



VII

e) formylating of the compound of formula VII with a formylating agent in the presence of a derivative of formic acid to give N'-[2-cyano-4,5-bis(2mehtoxyethoxy)pheny]-N,N-dimethylformamidine of formula VIII



VIII

f) coupling the compound of the formula VIII with an aniline derivative in the presence of acidic catalysts to obtain [6,7-bis-(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl)-amine (erlotinib free base) .

g) treatment of the erlotinib free base with a polar solvent containing hydrochloric acid to obtain the compound of formula (I)

2. The process as claimed in claim 1 wherein the compound of formula (I) is purified by recrystallisation from polar solvents to get the compound of acceptable purity.

3. The process as claimed in claim 1, wherein the inert solvent in step (a) is an aprotic solvent selected from aliphatic ketones and substituted amides, preferably dimethyl formamide.

4. The process as claimed in claim 1, wherein the substitution of the ethylmethylether in step (a) is chloro, bromo, iodo, hydroxy or a methoxy group preferably bromo derivative.

5. The process as claimed in claim 1, wherein the base in step (a) is alkali or alkaline earth carbonate and hydroxide preferably sodium and potassium carbonate.

6. The process as claimed in claim 1, wherein the reaction mixture in step (a) is maintained at a temperature from ambient to reflux temperature preferably from 80^0 C to 100^0 C.

7. The process as claimed in claim 1, wherein the solvent in step (b) is aliphatic alcohol preferably methanol or isopropanol.

8. The process as claimed in claim 1, wherein the base in step (b) is organic or inorganic bases wherein the organic base is pyridine, dimethylaminopyridine, or triethylamine and the inorganic base is sodium acetate or ammonium acetate; the organic base used preferably is pyridine.

9. The process as claimed in claim 1, wherein the dehydration in step (b) is carried out in the presence of thionyl chloride, phosphorous oxy chloride, propionic anhydride or acetic anhydride ; preferably acetic anhydride.

10. The process as claimed in claim 1, wherein the reaction in step (b) is from ambient to reflux temperature from 50^0 C to 120^0 C ; preferably reaction is carried out at $110\ ^0$C .

11. The process as claimed in claim 1, wherein the nitrating agent in step (c) is nitric acid

12. The process as claimed in claim 1, wherein the reaction in step (c) is carried out in the temperature range from 25^0 C to 50^0 C ; preferably at 45^0 C .

13. The process as claimed in claim 1 wherein the nitro reduction in step (d) is carried out in the presence of suitable catalyst on an inert carrier and in an inert solvent or in the presence of an inorganic reducing agent .

14. The process as claimed in claim 1 under step (d) wherein the catalyst is selected from palladium ,platinum or iron or the inorganic reducing agent sodium dithionate and the solvent is selected from water, ethanol, methanol or acetic acid at a temperature in the range from 30 to 50 ^{0}C conveniently at 30 ^{0}C .

15. The process as claimed in claim 1, wherein the fomylating agent used in step (e) is N,N-dimethylformamide dimethyl acetal in the presence of a polar aprotic solvent , an aromatic solvent or a dipolar aprotic solvents , preferably N,N dimethyl formamide at a temperature range from 20 to 140 ^{0}C. , preferably at 115 ^{0}C.

16. The process as claimed in step (e) wherein the

- polar aprotic solvent is tetrahydrofuran, 1,4 dioxane
- aromatic solvent used is toluene
- a dipolar aprotic solvent used is N,N- dimethylacetamide

17. The process as claimed in claim 1, wherein the aniline derivative coupled to the compound of formula VIII in step (f) in one pot procedure is a 3-ethynyl aniline in the presence of acid catalyst at a temperature range from 30^0C to 140^0 C preferably at 130^0 C.

18. The process as claimed in step (f) wherein the acidic catalyst is selected from trifluroacetic acid , formic acid , preferably acetic acid.

19. The process as claimed in claim 1 wherein the polar solvent used in step (g) is selected from methanolic hydrochloric acid or ethanolic hydrochloric acid.

20. The process of preparation of 6,7-bis-(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl)amine hydrochloride , is substantially as herein described with reference to the foregoing examples.

21. [6,7-bis-(2-methoxyethoxy)-quinazolin–4–yl]-(3-ethynylphenyl)amine hydrochloride wherever prepared by the process as claimed in any of the preceding claims