

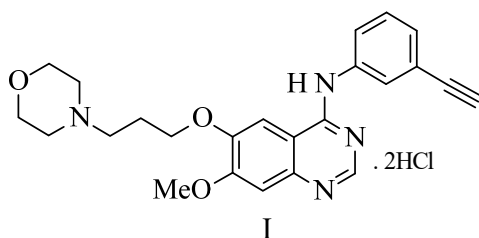
- c) The overall yield of formula-I is only about 10%
- d) Process demands corrosive reagents like nitric acid, hydrogen peroxide and pyrophoric catalyst like Raney Ni.
- e) Process involves cumbersome work-up procedures

**Summary:**

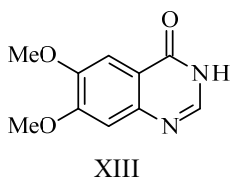
According to biological test reports, N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy) quinazolin-4-amine dihydrochloride of formula-I is found to be a promising small molecule having inhibitory effect against EGF-type receptor tyrosine kinase enzymes and Erb group receptors like Erb-2, Erb-3, and Erb-4 tyrosine kinase sensitive cancers.

Keeping in view of the difficulties in commercialization of the known process, we aimed to develop a simple, economically, environmentally friendly process for the commercial production of N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy) quinazolin-4-amine dihydrochloride of formula-I.

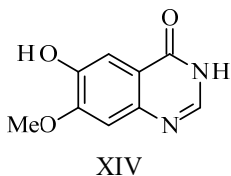
In another aspect, the present disclosure refers to a process for the preparation of N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine dihydrochloride salt of formula-I comprising the steps of :



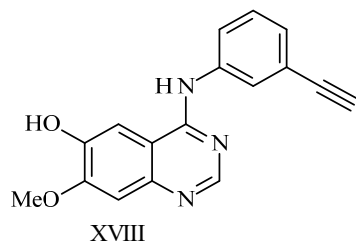
i) selective demethylation of 6,7-dimethoxy-quinazoline-4(3H)-one of formula-XIII



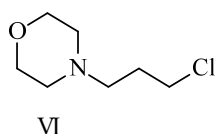
using a de-methylating agent to get 6-hydroxy-7-methoxy-quinazoline-4(3H)-one of formula-XIV,



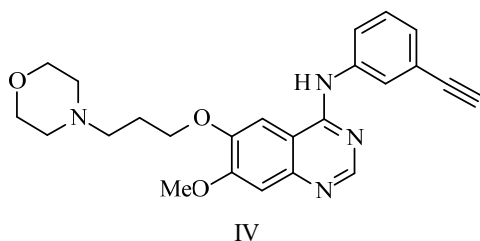
ii) converting 6-hydroxy-7-methoxy-quinazoline-4(3H)-one of formula-XIV to 4-(3-ethynylanilino)-7-methoxy-quinazolin-6-ol of formula-XVIII,



iii) condensing 4-(3-ethynylanilino)-7-methoxyquinazolin-6-ol of formula-XVIII with 3-morpholinopropyl chloride of formula-VI,



in dimethylformamide-potassium carbonate medium to get N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine of formula-IV,



iv) converting N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine of formula-IV to N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine dihydrochloride salt of formula-I using hydrochloric acid or hydrochloric acid gas dissolved in organic solvent medium.

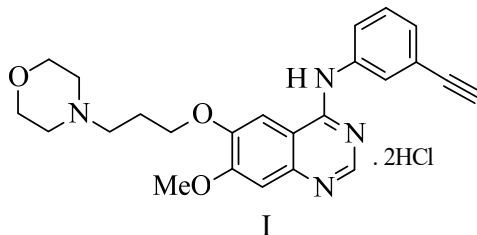
The present disclosure provides an alternate & improved process for preparing compound of formula-I. In particular, the process according to the present disclosure provides improved yield of the compound of formula-I.

The present disclosure provides an improved process for the preparation of compound of formula-I by avoiding expensive reactants like Isovanillin in the process.

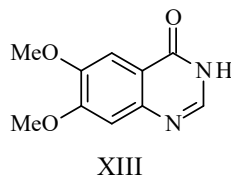
The present disclosure also provides an improved process for the preparation of compound of formula-I by avoiding pyrophoric catalysts like Raney Nickel, high pressure reactions in the process.

**We Claim:**

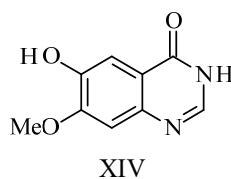
1. A process for the preparation of N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine dihydrochloride salt of formula-I comprising the steps of:



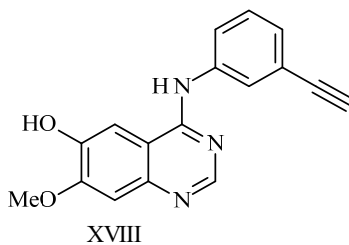
i) selective demethylation of 6,7-dimethoxy-quinazoline-4(3H)-one of formula-XIII



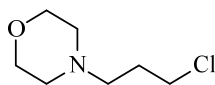
using a de-methylating agent to get 6-hydroxy-7-methoxy-quinazoline-4(3H)-one of formula-XIV,



ii) converting 6-hydroxy-7-methoxy-quinazoline-4(3H)-one of formula-XIV to 4-(3-ethynylanilino)-7-methoxy-quinazolin-6-ol of formula-XVIII,

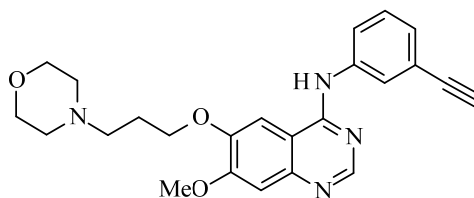


iii) condensing 4-(3-ethynylanilino)-7-methoxy-quinazolin-6-ol of formula-XVIII with 3-morpholinopropyl chloride of formula-VI,



VI

in dimethylformamide-potassium carbonate medium to get N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine of formula-IV,



IV

iv) converting N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine of formula-IV to N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine dihydrochloride salt of formula-I using hydrochloric acid or hydrochloric acid gas dissolved in organic solvent medium.

2. The process according to claim 1, wherein, in step (i):

(a) the de-methylating agent employed is selected from the group consisting of DL-Methionine-sulfuric acid mixture, aqueous hydrobromic acid and a pyridine hydrochloride medium,

(b) the temperature at which de-methylation is performed is from 25-100°C, and

(c) a base selected from the group consisting of aqueous ammonia, aqueous sodium hydroxide, aqueous potassium hydroxide, or any other equivalent inorganic base is employed.

3. The process according to claim 1, wherein, in step (iii),

(a) potassium carbonate is employed in the condensation step,

(b) dimethylformamide is employed in the condensation step,

(c) the temperature at which the condensation is performed is in the range of 20-100°C preferably at 60-70°C,

(d) purification of the resulting N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine of formula-IV by crystallization is  
5 conducted using methanol, ethanol, isopropyl alcohol, cyclohexane, toluene, n-heptane, methyl t-butyl ether, isopropyl ether, or mixtures thereof.

4. The process according to claim 1, wherein, in step (iv),

(a) the conversion step is conducted using hydrochloric acid or dry hydrochloric acid gas dissolved in methanol, ethanol, isopropyl alcohol, acetone, or  
10 ethylacetate,

(b) the organic solvent medium employed for dihydrochloride salt formation is selected from the group consisting of methanol, ethanol, and isopropyl alcohol,

(c) the isolated product of N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy) quinazolin-4-amine dihydrochloride of formula-I is  
15 characterized by:

(1) FT-IR ( $\lambda$ , cm<sup>-1</sup>): 3406 (N-H str); 3063, 3000 (Aromatic -C-H str); 2943, 2838 (Aliphatic -C-H str); 2623 (br, due to HCl salt); 2100 (-C≡C- str); 1633 (-C=N- str); 1438 (N-H bending); 1282 (-C-N str); 1219, 1159, 1002 (-C-O str)

(2) <sup>1</sup>HNMR (DMSO-d<sub>6</sub>; 400 MHz,  $\delta$  ppm): 2.33-2.35 (m, 2H); 3.12 (br, m, 2H); 3.29-3.34 (br, m, 2H); 3.48-3.51 (br, m, 2H); 3.80-3.85 (m, 2H); 3.96-4.0 (m, 5H); 4.28 (s, 1H), 4.38-4.41 (t, 2H); 7.39-7.41 (m, 2H); 7.47-7.51 (t, 1H); 7.83-7.85 (d, 1H); 7.92 (m, 1H); 8.61 (m, 1H); 8.86 (s, 1H); 11.04 (s, 1H), 11.72 & 15.40 (br, s, 2H)  
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(3) <sup>13</sup>CNMR (DMSO-d<sub>6</sub>; 100 MHz;  $\delta$  ppm): 22.72, 15.10, 53.48, 56.49, 63.17, 67.28, 81.21, 82.94, 99.95, 105.64, 107.35, 121.90, 125.28, 127.54, 129.00, 129.17, 135.85, 137.33, 148.73, 148.93, 156.32, 158.13  
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(4) DSC: Peak observed at 279.55°C

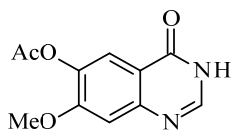
(5) PXRD (2 $\theta$ ,  $^{\circ}$ ): 5.76, 6.76, 7.13, 7.64, 9.81, 12.62, 13.50, 13.97, 14.23, 15.27, 15.77, 17.22, 20.30, 20.60, 21.44, 22.42, 22.95, 24.81, 25.82, 27.37, 28.10, 28.53, 29.60, 30.75, 32.42, 34.15 ( $\pm 0.2^{\circ}$ ).

5            5. The process according to claim 1, further comprising the step of:  
v) purification of N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy) quinazolin-4-amine dihydrochloride of formula-I from alcoholic solvent or organic solvent mixture.

10           6. The process according to claim 1, wherein, in step (v), the purification is by crystallization from an organic solvent or organic solvent mixture selected from the group consisting of methanol, ethanol, isopropyl alcohol, cyclohexane, toluene, n-heptane, methyl t-butyl ether, isopropyl ether, and mixtures thereof.

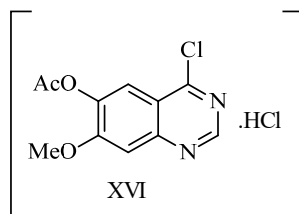
15           7. The process according to claim 1, wherein, in step ii, converting 6-hydroxy-7-methoxy-quinazoline-4(3H)-one of formula-XIV to 4-(3-ethynylanilino)-7-methoxy-quinazolin-6-ol of formula-XVIII comprises:

ii-a) protecting the 6-hydroxy-7-methoxy-quinazoline-4(3H)-one of formula-XIV using an acylating agent to get 6-acetoxy-7-methoxy-quinazoline-4(3H)-one of formula-XV,

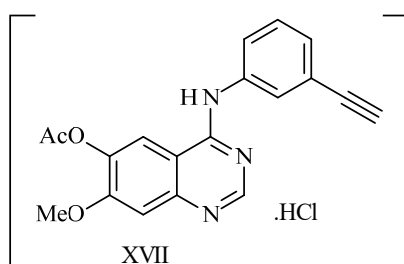


XV , and

20           ii-b) chlorination of 6-acetoxy-7-methoxy-quinazoline-4(3H)-one of formula-XV with a chlorinating agent in the presence of a catalyst in an organic solvent to get (4-chloro-7-methoxy-quinazolin-6-yl) acetate hydrochloride of compound of formula-XVI,



which is reacted in-situ with 3-ethynylaniline in an alcoholic solvent medium to get [4-(3-ethynylanilino)-7-methoxy-quinazolin-6-yl] acetate hydrochloride of formula-XVII,



5

which is further subjected to de-protection of acetoxymoiety using aqueous alcoholic medium to get 4-(3-ethynylanilino)-7-methoxy-quinazolin-6-ol of formula-XVIII.

8. The process according to claim 7, wherein, in step (ii-a),
  - 10 (a) the acylating agent is selected from the group consisting of acetic anhydride and acetyl chloride,
  - (b) an organic solvent selected from the group consisting of methylene chloride and chloroform medium is employed,
  - (c) the temperature at which the acylation is performed is in the range
    - 15 of 0-150°C,
    - (d) optionally 6-acetoxy-7-methoxy-quinazolin-4(3H)-one of formula-XV is obtained by crystallization from dimethylformamide.

9. The process according to claim 7, wherein, in step (ii-b),
  - 20 (a) the chlorinating agent is selected from the group consisting of oxalyl chloride, phosphorous oxychloride, and thionyl chloride,
  - (b) the catalyst is selected from the group consisting of dimethylformamide and pyridine,

(c) the organic solvent is selected from the group consisting of methylene chloride and chloroform,

(d) a base selected from the group consisting of sodium bicarbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, sodium carbonate, and potassium carbonate is employed during work-up,

(e) wet compound of formula-XVI is condensed with 3-ethynylaniline in isopropyl alcohol medium to get [4-(3-ethynylanilino)-7-methoxy-quinazolin-6-yl] acetate hydrochloride of formula-XVII,

(f) the temperature at which the condensation is performed is at room temperature or at reflux temperature,

(g) de-protection of the acetoxy moiety is performed with an aqueous base solution wherein the base is selected from the group consisting of potassium hydroxide and sodium hydroxide,

(h) the aqueous alcoholic medium employed in de-protection of [4-(3-ethynylanilino)-7-methoxy-quinazolin-6-yl] acetate hydrochloride of formula-XVII comprises methanol or isopropyl alcohol,

(i) the temperature at which de-protection is carried out is in the range of 25-70°C preferably at 40-50°C.

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