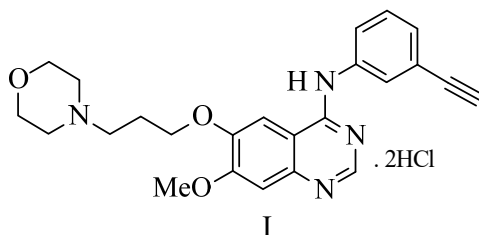
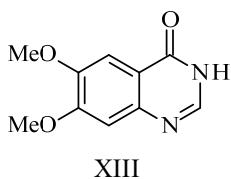


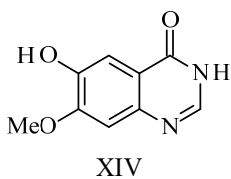
In ~~another one~~ aspect, the present disclosure refers to a process for the preparation of N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine dihydrochloride ~~salt~~ of formula-I comprising the steps of :



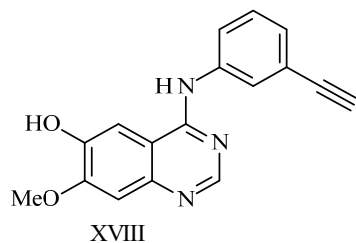
~~ia~~) selective demethylation of 6,7-dimethoxy-quinazoline-4(3H)-one of formula-XIII



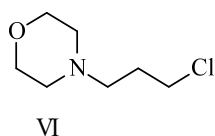
using ~~a~~ de-methylating agent to get 6-hydroxy-7-methoxy-quinazoline-4(3H)-one of formula-XIV,



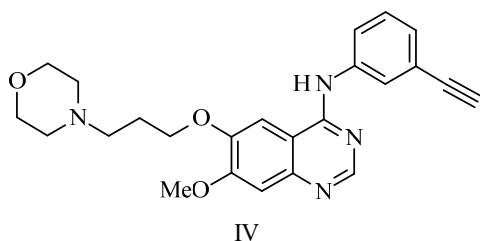
~~ib~~) converting 6-hydroxy-7-methoxy-quinazoline-4(3H)-one of formula-XIV to 4-(3-ethynylanilino)-7-methoxy-quinazolin-6-ol of formula-XVIII,



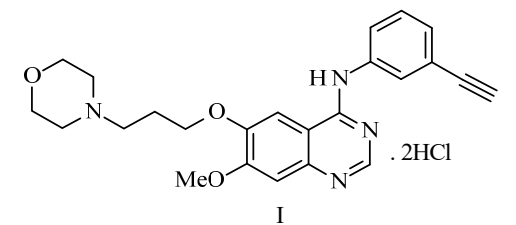
iii) condensing 4-(3-ethynylanilino)-7-methoxy-quinazolin-6-ol of formula-XVIII with 3-morpholinopropyl chloride of formula-VI,



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



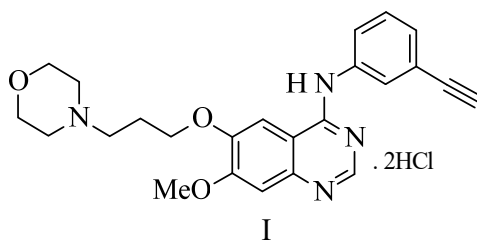
iv) converting N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine of formula-IV to ~~N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine~~ dihydrochloride salt of formula-I using hydrochloric acid ~~or hydrochloric acid~~ gas dissolved in organic solvent medium



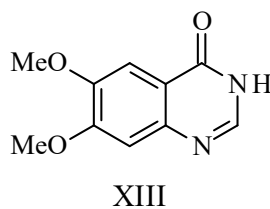
The present disclosure provides an alternate & improved process for preparing compound of formula-I. In particular, the process according to the present disclosure provides improved yield of the compound of formula-I.

We Claim:

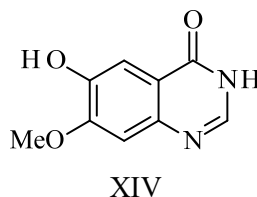
1. A process for the preparation of N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine dihydrochloride ~~salt~~ of formula-I comprising the steps of:



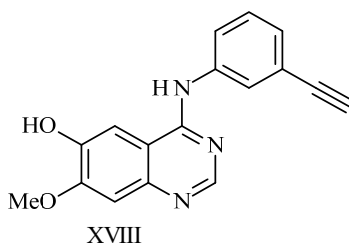
5 ~~ia~~) selective demethylation of 6,7-dimethoxy-quinazoline-4(3H)-one of formula-XIII



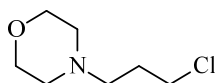
10 using a de-methylating agent to get 6-hydroxy-7-methoxy-quinazoline-4(3H)-one of formula-XIV,



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

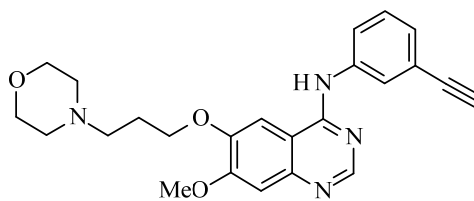


15 ~~ic~~) condensing 4-(3-ethynylanilino)-7-methoxy-quinazolin-6-ol of formula-XVIII with 3-morpholinopropyl chloride of formula-VI,



VI

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

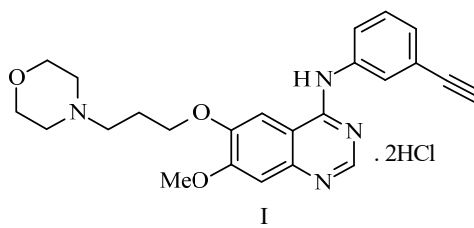


IV

5

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

10

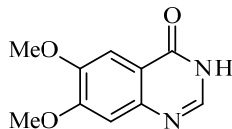


I

2. A process according to claim 1 comprising the steps of:

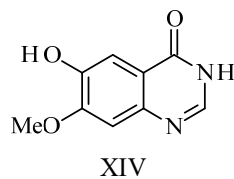
i) selective demethylation of 6,7-dimethoxy-quinazoline-4(3H)-one of

15 formula-XIII

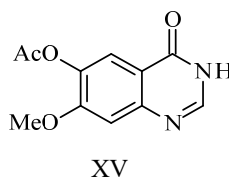


XIII

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

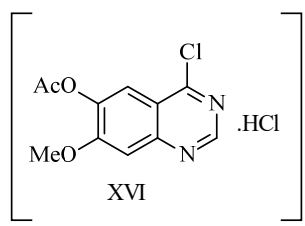


ii) protecting 6-hydroxy-7-methoxy-quinazoline-4(3H)-one of formula-XIV using acylating agent to get 6-acetoxy-7-methoxy-quinazoline-4(3H)-one of formula-XV,



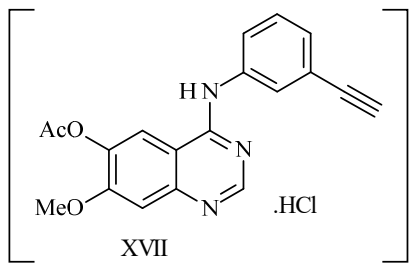
5

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



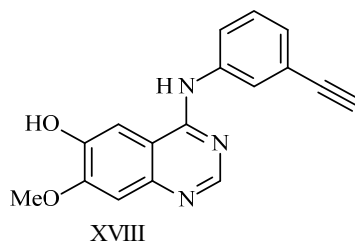
10

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

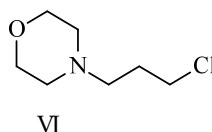


15

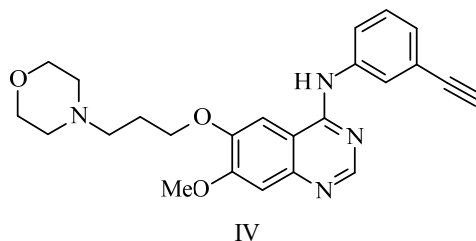
which is further subjected to de-protection of acetoxy moiety using aqueous alcoholic medium to get 4-(3-ethynylanilino)-7-methoxy-quinazolin-6-ol of formula-XVIII,



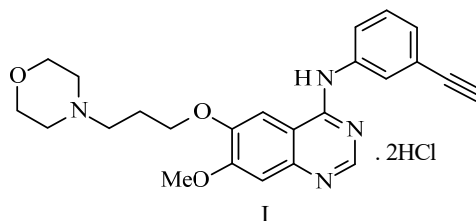
iv) condensing 4-(3-ethynylanilino)-7-methoxy-quinazolin-6-ol of formula-XVIII with 3-morpholinopropyl chloride of formula-VI,



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



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



15 vi) optionally purification of N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy) quinazolin-4-amine dihydrochloride of formula-I from alcoholic solvent or organic solvent mixture.

23. ~~The A~~ process according to claim 12, wherein, in step (i),^{2,3}

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

(b) the temperatures s at which de-methylation ~~is performed~~ is can be from
5 25-100°C, ~~and~~

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

4. A process according to claim 2, wherein step (ii),

10 (a) The acylating agent can be selected from acetic anhydride, or acetyl chloride,

(b) an organic solvent is employed in step (ii), said organic solvent being selected from methylene chloride or chloroform medium,

(c) the temperature at which the acylation in step (ii) can be performed is in
15 the range of 0-150°C,

(d) optionally in step (ii) 6-acetoxy-7-methoxy-quinazoline-4(3H)-one of formula-XV can be obtained by crystallization from dimethylformamide.

5. A process according to claim 2, wherein step (iii),

(a) chlorination of 6-acetoxy-7-methoxy-quinazoline-4(3H)-one of formula-
20 XV is performed with chlorinating agent selected from oxalyl chloride, phosphorous oxychloride, or thionyl chloride,

(b) the catalyst used in chlorination of 6-acetoxy-7-methoxy-quinazoline-4(3H)-one of formula-XV in step (iii) is selected from dimethylformamide or pyridine,

(c) the solvent employed in chlorination of 6-acetoxy-7-methoxy-quinazoline-4(3H)-one of formula-XV in step (iii) is selected from methylene chloride or chloroform
25

(d) a base is employed in step (iii) during work-up, said base being selected from sodium bicarbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, sodium carbonate, or potassium carbonate,

5 (e) in step (iii) of the present invention, the wet product of (4-chloro-7-methoxy-quinazolin-6-yl) acetate hydrochloride of compound of formula-XVI is condensed further with 3-ethynylaniline of formula-III in isopropyl alcohol medium to get [4-(3-ethynylanilino)-7-methoxy-quinazolin-6-yl] acetate hydrochloride of formula-XVII,

10 (f) The temperature at which the condensation is performed in step (iii) is at room temperature or at reflux temperature,

(g) de-protection of the resulting compound of [4-(3-ethynylanilino)-7-methoxy-quinazolin-6-yl] acetate hydrochloride of formula-XVII is performed with an aqueous base solution wherein the base is selected from potassium hydroxide or sodium hydroxide,

15 (h) an organic solvent is employed in de-protection of [4-(3-ethynylanilino)-7-methoxy-quinazolin-6-yl] acetate hydrochloride of formula-XVII, said organic solvent being selected from methanol or isopropyl alcohol,

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

20 36. The A process according to claim 12, wherein, in step (iv),

(a) a base is employed in the condensation step of 4-(3-ethynylanilino)-7-methoxy-quinazolin-6-ol of formula-XVIII with 3-morpholinopropyl chloride of formula-VI, said base being potassium carbonate is employed in the condensation step,

25 (b) a solvent is employed in condensation of 4-(3-ethynylanilino)-7-methoxy-quinazolin-6-ol of formula-XVIII with 3-morpholinopropyl chloride of formula-VI, said solvent being dimethylformamide is employed in the condensation step,

- (c) the temperature at which ~~the~~ condensation of 4-(3-ethynylanilino)-7-methoxy-quinazolin-6-ol of formula-XVIII with 3-morpholinopropyl chloride of formula-VI 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 is purified by crystallization ~~is conducted using from an organic solvent or organic solvent mixture selected from~~ methanol, ethanol, isopropyl alcohol, cyclohexane, toluene, n-heptane, methyl t-butyl ether, isopropyl ether, or its mixtures ~~thereof~~.
47. The A process according to claim 12, wherein, in step (iv),
- (a) ~~the conversion step is conducted~~ N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholino propoxy)quinazolin-4-amine of formula-IV is optionally converted to N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy) quinazolin-4-amine dihydrochloride of formula-I using hydrochloric acid or dry hydrochloric acid gas dissolved in methanol, ethanol, isopropyl alcohol, acetone, or ethylacetate,
- (b) the organic solvent ~~medium~~ employed for ~~di~~hydrochloride salt formation is selected from ~~the group consisting of~~ methanol, ethanol, ~~and/or~~ isopropyl alcohol,
- (c) the isolated product of N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy) quinazolin-4-amine dihydrochloride of formula-I is characterized by having following physical and crystal characteristics
- (1i) FT-IR (λ , cm⁻¹): 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)
- (2ii) ¹HNMR (DMSO-d₆; 400 MHz, δ 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)
- (3iii) ¹³CNMR (DMSO-d₆; 100 MHz; δ 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

(4iv) DSC: Peak observed at 279.55°C

(5v) PXRD (2θ, °): 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 (±0.2°).

5 8. A process according to claim 2, wherein, in step (vi),

 (a) N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy)
quinazolin-4-amine dihydrochloride of formula-I can be purified by crystallization
from an organic solvent or organic solvent mixture selected from methanol,
ethanol, isopropyl alcohol, cyclohexane, toluene, n-heptane, methyl t-butyl ether,
10 isopropyl ether or its mixture.

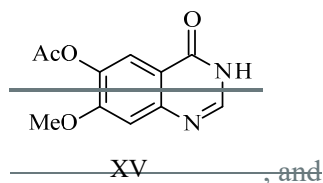
 9. A process according to claim 1, wherein de-methylating agent
employed can be selected from DL-Methionine-sulfuric acid mixture, aqueous
hydrobromic acid or pyridine hydrochloride medium.

 5. ~~The process according to claim 1, further comprising the step of:~~
15 ~~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.~~

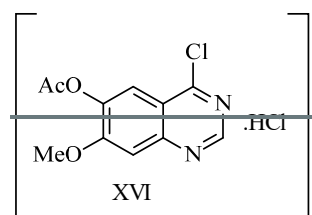
 6. ~~The process according to claim 1, wherein, in step (v), the~~
~~purification is by crystallization from an organic solvent or organic solvent mixture~~
20 ~~selected from the group consisting of methanol, ethanol, isopropyl alcohol,~~
~~cyclohexane, toluene, n-heptane, methyl t-butyl ether, isopropyl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

 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-~~
25 ~~ethynylanilino)-7-methoxy quinazolin-6-ol of formula XVIII comprises:~~

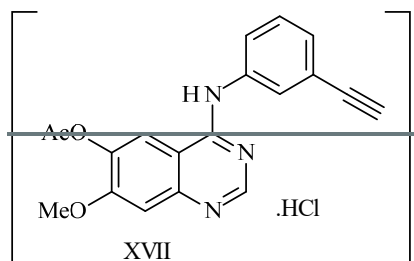
 ii a) ~~protecting the 6-hydroxy 7-methoxy quinazoline-4(3H)-one of~~
~~formula XIV using an acylating agent to get 6-acetoxy 7-methoxy quinazoline-~~
~~4(3H)-one of formula XV,~~



- ii-b) chlorination of 6-acetoxy-7-methoxyquinazolin-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-methoxyquinazolin-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-methoxyquinazolin-6-yl] acetate hydrochloride of formula XVII;



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

8. The process according to claim 7, wherein, in step (ii a),
- (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 of 0-150°C;

(d) — ~~optionally 6-acetoxy-7-methoxy-quinazoline-4(3H)-one of formula XV is obtained by crystallization from dimethylformamide.~~

9. — ~~The process according to claim 7, wherein, in step (ii-b),~~

(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.~~