

- 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

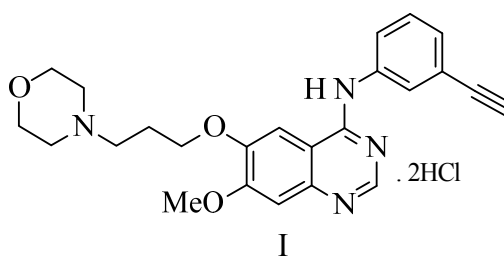
5

Summary:

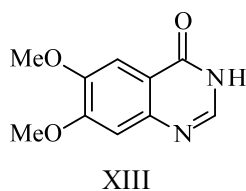
According to biological test reports, N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy) quinazolin-4-amine dihydrochloride of formula-I is found to be a promising small molecule having inhibitory effect against EGF-type receptor
 10 tyrosine kinase enzymes and Erb group receptors like Erb-2, Erb-3,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

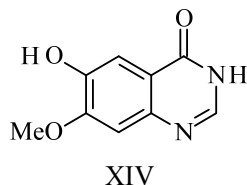
In one aspect, the present disclosure refers to a process for the preparation of N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine
 20 dihydrochloride of formula-I comprising the steps of :



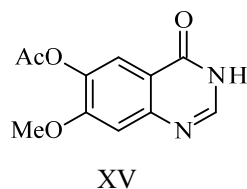
- i) selective demethylation of 6,7-dimethoxy-quinazoline-4(3H)-one of formula-XIII



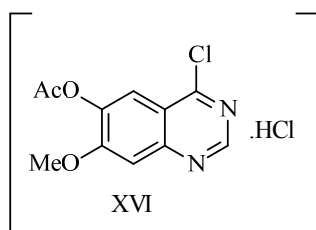
using de-methylating agent to get 6-hydroxy-7-methoxy-quinazoline-4(3H)-one of formula-XIV,



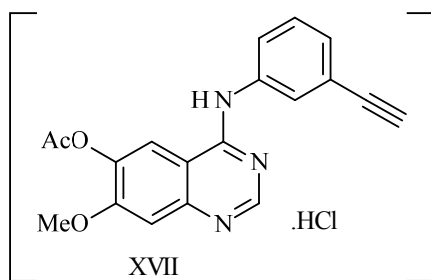
ii) protecting 6-hydroxy-7-methoxy-quinazoline-4(3H)-one of formula-XIV using acylating agent to get 6-acetoxy-7-methoxy-quinazoline-4(3H)-one of formula-XV,



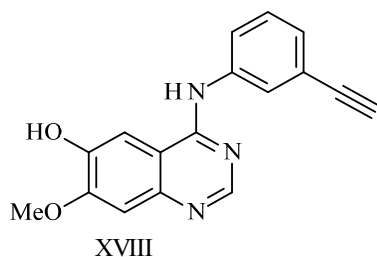
iii) chlorination of 6-acetoxy-7-methoxy-quinazoline-4(3H)-one of formula-XV with chlorinating agent in the presence of catalyst in an organic solvent to get (4-chloro-7-methoxy-quinazolin-6-yl) acetate hydrochloride of compound of formula-XVI,



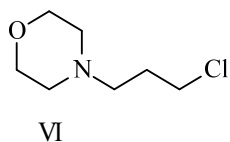
which is reacted in-situ with 3-ethynylaniline of formula-III in alcoholic solvent medium to get [4-(3-ethynylanilino)-7-methoxy-quinazolin-6-yl] acetate hydrochloride of formula-XVII,



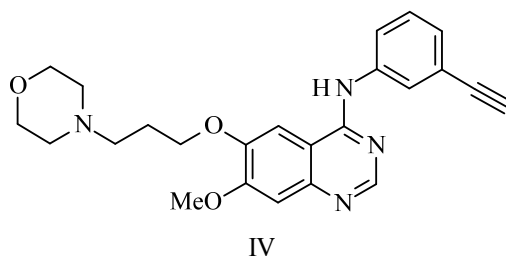
which is further subjected to de-protection of acetoxy moiety using aqueous alcoholic medium to get 4-(3-ethynylanilino)-7-methoxy-quinazolin-6-ol of formula-XVIII,



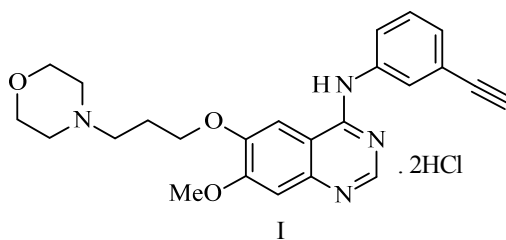
- 5 iv) condensing 4-(3-ethynylanilino)-7-methoxy-quinazolin-6-ol of formula-XVIII with 3-morpholinopropyl chloride of formula-VI,



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

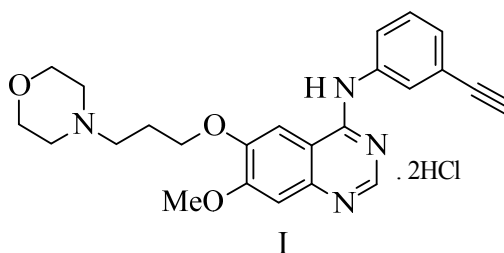


- v) converting N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine of formula-IV to dihydrochloride salt of formula-I using hydrochloric acid gas dissolved in organic solvent medium,

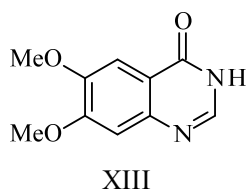


v) optionally purification of N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy) quinazolin-4-amine dihydrochloride of formula-I from alcoholic solvent or organic solvent mixture.

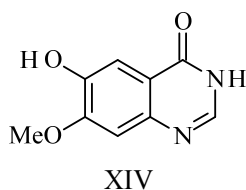
- 5 In another aspect, the present disclosure refers to a process for the preparation of N-(3-ethynylphenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine dihydrochloride of formula-I comprising the steps of :



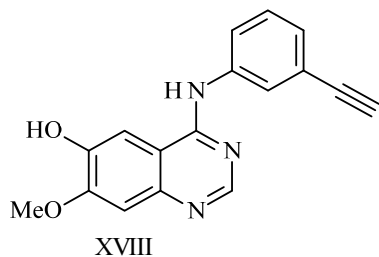
- i) selective demethylation of 6,7-dimethoxy-quinazoline-4(3H)-one of formula-
10 XIII



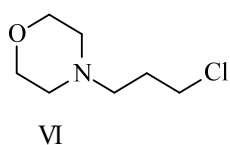
using de-methylating agent to get 6-hydroxy-7-methoxy-quinazoline-4(3H)-one of formula-XIV,



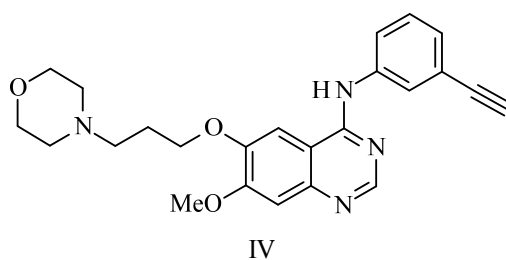
- 15 ii) converting 6-hydroxy-7-methoxy-quinazoline-4(3H)-one of formula-XIV to 4-(3-ethynylanilino)-7-methoxy-quinazolin-6-ol of formula-XVIII,



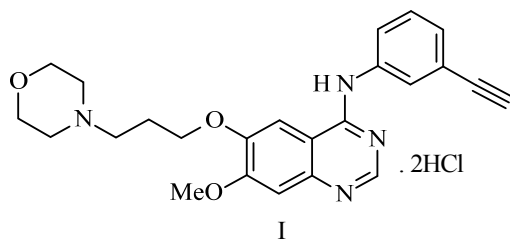
iii) condensing 4-(3-ethynylanilino)-7-methoxy-quinazolin-6-ol of formula-XVIII with 3-morpholinopropyl chloride of formula-VI,



- 5 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 dihydrochloride salt of formula-I using
10 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
15 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.

- 5 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.

The present disclosure also provides an improved process for the preparation of compound of formula-I by avoiding cumbersome work-up procedures.

5 The present disclosure also provides an improved process for the preparation of compound of formula-I by improving process timelines by avoiding isolation of intermediates wherever possible.

The present disclosure also provides an improved process for the preparation of compound of formula-I with improved overall yield of compound of formula-I.

10

Accordingly, the present disclosure provides for the preparation of compound of formula I, wherein present process uses readily and cheaply available 6, 7-dimethoxyquinazoline-4(3H)-one of formula-XIII as starting material to make the compound of formula-I. Compound of formula-XIII is commercially available or can be readily prepared from veratrole.

15

Accordingly, the present disclosure provides a process for the preparation of compound of formula (I) comprising the steps of:

- 20 a) selective demethylation of 6, 7-dimethoxyquinazoline-4(3H)-one of formula-XIII using DL-Methionine-sulfuric acid medium to get 6-hydroxy-7-methoxyquinazoline-4(3H)-one of formula-XIV,
- b) acetylation of 6-hydroxy-7-methoxyquinazoline-4(3H)-one of formula-XIV in acetic anhydride medium to get 6-acetoxy-7-methoxyquinazoline-4(3H)-one of formula-XV,
- 25 c) reacting 6-acetoxy-7-methoxy-quinazoline-4(3H)-one of formula-XV with thionyl chloride in the presence of DMF in chloroform to get 6-acetoxy-4-chloro-7-methoxyquinazoline hydrochloride of formula-XVI as in-situ intermediate,
- d) reacting 6-acetoxy-4-chloro-7-methoxyquinazoline hydrochloride of formula-XVI in-situ with 3-ethynylaniline of formula-III in isopropanol