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ONE-POT CONVERSION OF 2-NITROBENZONITRILES TO QUINAZOLIN-4(3*H*)-ONES AND SYNTHESIS OF GEFITINIB AND ERLOTINIB HYDROCHLORIDE

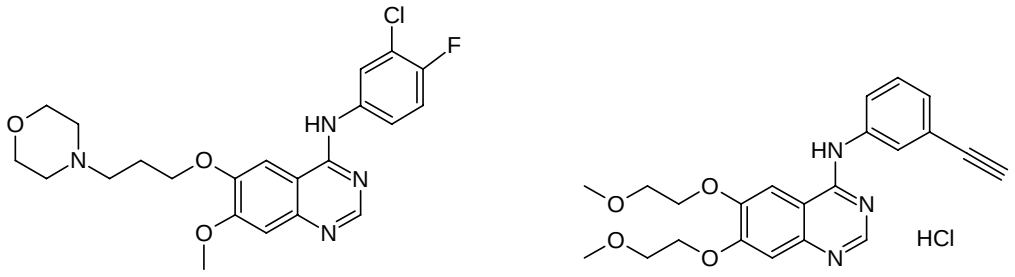
Venkateshappa Chandregowda, Gudapati Venkateswara Rao, and Goukanapalli Chandrasekara Reddy*

Vittal Mallya Scientific Research Foundation, P.O. Box 406, K. R. Road, Bangalore-560004, India .Tel: +91-80-26611664. Fax: +91-80-26612806.
E-mail: gcreddy@vmsrf.org

Abstract- A simple and efficient one-pot conversion of 2-nitrobenzonitriles to quinazolin-4(3*H*)-ones involving reduction, formylation, hydrolysis and cyclization is reported. These quinazolinones have been used for making in economical way the anticancer drug molecules gefitinib (Iressa®) and erlotinib HCl (Tarceva®).

INTRODUCTION

In nature, the quinazoline skeleton is widely found in alkaloids and in many biologically active compounds[1]. This class of compounds have been demonstrated to possess a variety of biological activities such as fungicidal, antihypertensive, antimicrobial, anticancer and anti-inflammatory.[2a-e] Of particular importance is, two drugs by name gefitinib (Iressa®,**1**) & erlotinib hydrochloride (Tarceva®,**2**) (Figure 1),



1 **2**

Figure 1. Structures of gefitinib (**1**) and erlotinib.HCl (**2**)

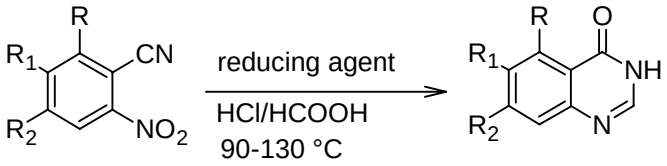
which have central quinazoline moiety are potent inhibitors of epidermal growth factor receptor-tyrosine kinase enzymes[3] and which are recently approved by US FDA for the treatment of non-small-cell lung

cancer.[4] Evidently, quinazolin-4(3*H*)-ones are interesting synthetic targets for medicinal chemists and researchers. A simple and efficient synthesis of quinazolin-4(3*H*)-ones facilitates generation of synthones for making various biologically-active compounds. However, the traditional synthetic methods for the preparation of quinazolin-4(3*H*)-ones and its derivatives[5,6] typically involve either the Meerwein cyclization, the Bischler cyclization, Grignard reaction, cyclization of acylanthranilinonitriles or Niementowski condensation involving fusion at high temperatures or moisture sensitive conditions. Other methods of synthesis include treatment of phosphoranes with NaH/CH_3CN[7a] and pyrolysis of Schiff bases derived from 3-amino-1,2,3-triazin-4-one in paraffin oil at 300 ºC.[7b] All these literature synthetic methods for elaboration of this simple ring structure are, however, time consuming, tedious and often low yielding. Further, the conventional processes for the synthesis of gefitinib[8,9] i.e. 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxy]quinazoline (**1**), starts reacting 4-(3-chloro-4-fluoroanilino)-6-hydroxy-7-methoxyquinazoline with 3-morpholinopropyl chloride using potassium carbonate in solvent like DMF. As per this method, preparation of 4-(3-chloro-4-fluoroanilino)-6-hydroxy-7-methoxyquinazoline involves making of 6-hydroxy-7-methoxyquinazolin-4(3*H*)-one by selective demethylation of 6,7-dimethoxyquinazolin-4(3*H*)-one (**4a**) (Table 1) using methanesulphonic acid and L-methionine. **4a** was in turn prepared[10] by reacting 4,5-dimethoxyantranilic acid and formamide at 190 ºC. A large excess of methanesulphonic acid has been used (about 1:11 molar ratio of substrate v/s methanesulphonic acid) in conjunction with methionine which acts as the nucleophile in demethylation of **4a**. Then protection of 6-hydroxy group has been done which requires a large excess of acetic anhydride (about 1:14 molar ratio of substrate v/s acetic anhydride). In case of [6,7-bis-(2-methoxyethoxy)-quinazolin-4-yl]-(3-ethynylphenyl)amine hydrochloride (erlotinib·HCl) (**2**)**,** the method employed comprises,[11] preparation of 6,7-bis(2-methoxyethoxy)quinazolin-4(3*H*)-one (**4f**) (Table 1), which in turn was prepared, starting from 3,4-dihydroxybenzoic acid involving series of reactions, costly reagents like platinum oxide and flammable gas like hydrogen, high temperature reaction conditions in making quinazoline skeleton and then reacting **4f** with $SOCl_2$ to get 4-chloro-6,7-bis-(2-methoxyethoxy)-quinazoline (**12**) followed by reaction with 3-ethynylaniline under basic conditions to get a free base [6,7-bis-(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)amine. Erlotinib·HCl (**2**) has been obtained in a separate reaction involving titration of free base with 1M HCl. Final products (**1** and **2**) were obtained in pure form, only after subjecting to column chromatography. Thus, in view of above industrial difficulties in constructing quinazoline skeleton and synthesis of compounds of pharmacological interest, we have now developed a highly efficient, economical and industrially viable process for the preparation of quinazolin-4(3*H*)-ones (Scheme 1) involving reductive formylation followed by cyclization in situ from 2-nitrobenzonitriles under mild reaction conditions and then synthesized gefitinib (**1**) (Scheme 2) and erlotinib·HCl (**2**) (Scheme 3).

RESULTS AND DISCUSSION

The synthesis of quinazolin-4(3*H*)-one (**4**) was performed by reacting suitably substituted *ortho*-nitrobenzonitriles (**3**) with reducing agent, HCl and formic acid (Table 1). 2-Nitrobenzonitrlies (Table 1) were synthesized from commercially available suitably substituted aldehydes in a highly efficient way as per procedure adopted under Scheme 2.

Scheme 1



3 **4**

We have studied the suitability of various reducing agents (Na_2S/HCl, Zn/HCl, Sn/HCl, Fe/HCl, and $N_2H_4.H_2O/FeCl_3$) with 4,5-dimethoxy-2-nitrobenzonitrile (**3a**) and cyclization insitu using formic acid. Sodium sulfide method gave low yields of 6,7-dimethoxyquinazoline-4(3*H*)-one (**4a**) (may be due to the evaporation of H_2S during the reaction), the use of Zn/HCl method gave moderate yields (70%). Though, the use of Fe/HCl & Sn/HCl methods gave high yields (>90%) with shorter reaction times (2-3 h), Fe and Sn salts which are formed during reaction pose effluent disposal problems. Hence we used hydrazine hydrate method which also gave high yields of the product (>81-91%). Suitability of this method in presence of various substituents on the aromatic ring of 2-nitrobenzonitriles has been demonstrated (Table1)

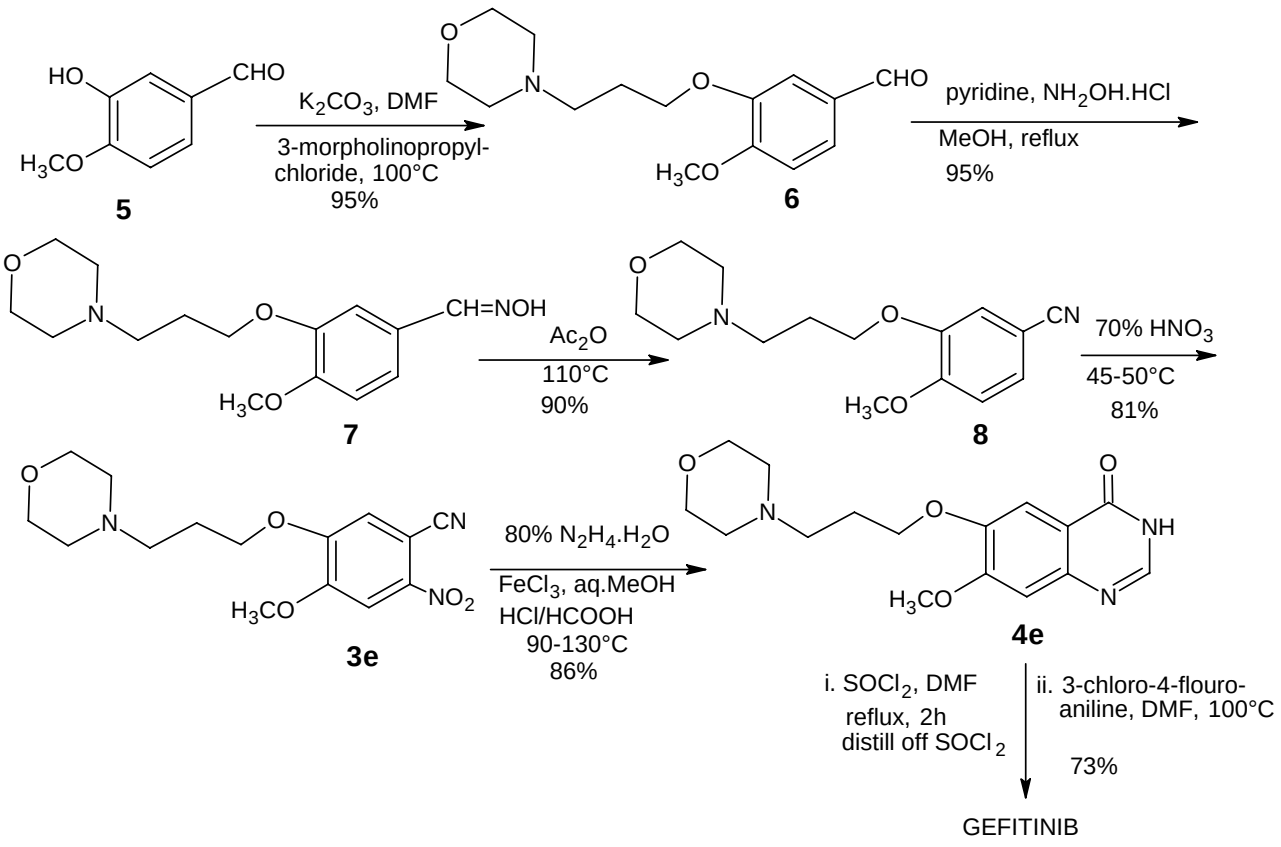
Table1. Yields of quinazolones from *ortho*-nitrobenzonitriles

Reactant	Product	R	R1	R2	Yield (%)
3a	**4a**	H	OMe	OMe	85
3b*	**4b**	H	H	H	80
3c	**4c**	H	------- methylinedioxy--------		91
3d	**4d**	H	OMe	*N*-morpholinopropoxy	86
3e	**4e**	H	*N*-morpholinopropoxy	OMe	86
3f	**4f**	H	2-methoxyethoxy	2-methoxyethoxy	81
3g*	**4g**	CH_3	H	H	91
3h*	**4h**	H	H	CF_3	81
3i	**4i**	H	OMe	*N*-piperidinyl propoxy	86

* Obtained as such from commercial sources

Synthesis of gefitinib (**1**) involved the construction of key intermediate 7-methoxy-6-[3-(4-morpholinyl)propoxy]quinazolin-4(3*H*)-one (**4e**) (Scheme 2), which was prepared in highly efficient way from commercially available isovanillin (**5**). Reaction of **5** with 3-morpholinopropyl chloride gave compound (**6**), which on further reacting with pyridine/$NH_2OH.HCl$ and dehydration of the resulting oxime (**7**) using acetic anhydride at 110°C yielded compound (**8**). The desired regioisomer 4-methoxy-5-[3-(4-morpholinyl)propoxy]-2-nitrobenzonitrile (**3e**) was obtained by nitration of compound (**8**) in 70% HNO_3 at 45-50 °C. The one-pot preparation of **4e** from **3e** involved reduction, formylation, hydrolysis and cyclization using 80% hydrazine hydrate/ferric chloride and HCl/HCOOH at 90-130 °C in 60% overall yield. Further, compound (**4e**) was reacted with $SOCl_2$ at reflux temperature followed by treating with 3-chloro-4-flouroaniline in DMF at 100 °C yielded gefitinib (**1**). We have synthesized **1** from **4e** in one step without isolating 4-chloro-7-methoxy-6-[3-(4-morpholinyl)propoxy]quinazoline. The crude material **1** was purified by crystallization technique without resorting to chromatographic procedures to get **1** in 73% yield from **4e** with 51% of overall yield starting from isovanillin.

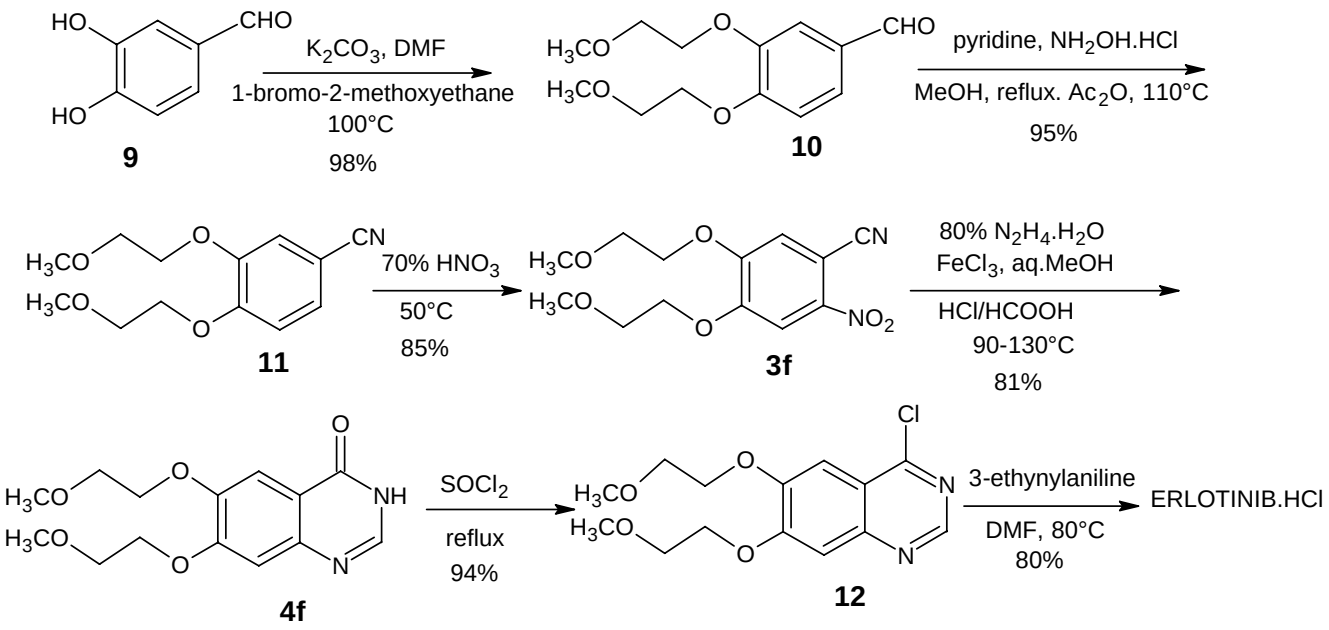
Scheme 2



In a similar way erlotinib HCl (**2**) was synthesized from 6,7-bis-(2-methoxyethoxy)quinazolin-4(3*H*)-one (**4f**) (Scheme 3), which in turn was prepared in efficient way from commercially available 3,4-dihydroxy

benzaldehyde (**9**) in 57% yield. Further, the compound (**4f**) was reacted with thionyl chloride at reflux temperature to get 4-chloro-6,7-bis-(2-methoxyethoxy)quinazoline (**12**), this on treatment with 3-ethynylaniline in DMF without using external base yielded erlotinib·HCl (**2**) with purity >99% by HPLC. The compound (**2**) was obtained in hydrochloride form, from compound (**12**) without titrating with external hydrochloric acid with overall yield of 42% from 3,4-dihydroxybenzaldehyde (**9**) and 75% yield from **4f**.

Scheme 3



In conclusion we have developed a novel one-pot synthesis of quinazolinones from 2-nitrobenzonitriles. This work surveyed various reducing agents for reduction of 2-nitrobenzonitriles and found hydrazine hydrate was best. This work also describes two commercially viable alternative processes for making gefitinib (**1**) and erlotinib·HCl (**2**)

EXPERIMENTAL

All the starting materials and reagents were obtained from commercial source and were used without further purification. ^{1}H NMR spectra were recorded in $CDCl_3$ / DMSO-d_6 at 200 MHz on a Bruker A G Spectrometer. All the chemical shift values are reported in δ units and down field from TMS as internal standard. Mass spectra were recorded using GCMS-QP2010S (Direct probe) on Q-TOF micro ™ APS MAX 0/6Asystem. HPLC analysis was done using Shimadzu CLASS VP using the column conditions: ODS-3V 4.6×250mm, particle size 5µ, λ=254nm, flow rate 1mL/min, mobile phase: (40:60) buffer: acetonitrile, buffer-1% ammonium acetate. Melting points were recorded using melting point apparatus Acro Steel Pvt. Ltd.

General procedure for the synthesis of substituted quinazolin-4(3*H*)-ones (4a-i). To a stirred suspension of **3a** (200g, 0.96 mol) in Water-Methanol (1:3, 2L) with catalytic amount of anhyd. $FeCl_3$ (1g), was added 80% hydrazine hydrate (180mL, 4.50 mol) slowly over a period of 1h at reflux temperature. Stirring was continued for about 2h., then the reaction mixture was concentrated under vacuum and to the residue was added water (500mL), 35% HCl (600mL) and 85% formic acid (800mL), raised temperature of the reaction mixture to 130°C, stirred for about 3h, distilled off excess HCl and formic acid. The residue obtained was dissolved in water (1L) and pH of the reaction mass was adjusted to 7.0 with $NaHCO_3$, The resulting precipitate was filtered, washed with water and dried the material at 60-70 °C to yield **4a** (170g) in 85% yield. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.86 (s, 3H), 3.90 (s, 3H), 7.12 (s, 1H), 7.43 (s, 1H), 7.97 (s, 1H), 12.03 (brs, 1H). MS: M/Z 206(M^+), 191, 120.

4, 5-Dimethoxy-2-nitrobenzonitrile (3a). 3,4-dimethoxybenzonitrlie[12] (163g, 1mol) was added to 70% nitric acid (326mL) at 35 °C in 1h. Quenched the reaction mass in ice water, filtered and air dried to yield yellow solid **3a** (195g, 94% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.02 (s, 3H), 4.04 (s, 3H), 7.21 (s, 1H), 7.80 (s, 1H). MS: M/Z 208 (M^+), 178, 150, 104, 76.

3,4-Methylenedioxy-2-nitrobenzonitrile (3c). Using 3,4-methylenedioxybenzonitrile and following the procedure described for **3a, 3c** was obtained in 94% yield. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.27 (s, 2H), 7.19 (s, 1H), 7.74 (s, 1H). : M/Z 192(M^+), 162, 88, 61, 53.

General procedures for the preparation of (3d, e, f & i). 4-Methoxy-5-[3-(4-morpholinyl)propoxy]-2-nitrobenzonitrile (3e). To a stirred solution of isovanillin (**5**) (225g, 1.48 mol) and potassium carbonate (400g, 2.9 mol) in DMF (1.35L) was added 3-morpholinopropyl chloride (340g, 1.7 mol), the reaction mixture was heated to 100 °C and stirred for about 3h cooled to room temperature, filtered the solids, concentrated DMF to get 4-methoxy-3-[3-(4-morpholinyl)propoxy]benzaldehyde (**6**) (391.5g). To the above obtained aldehyde was added methanol (2L), pyridine (205g, 2.6mol) and hydroxylamine hydrochloride (195g, 2.8 mol) at 25 °C. The reaction mixture was heated to reflux, stirred for about 1h, cooled to room temperature filtered and air dried to yield 4-Methoxy-3-[3-(4-morpholinyl)propoxy]-benzaldoxime (**7**) (391g). To this material was added acetic anhydride (800mL) and heated to 110 °C, stirred for 3h quenched in water adjusted pH of the reaction mixture to 8 with sodium bicarbonate, extracted the material into dichloromethane (3x500mL), washed organic layer with water, dried over calcium chloride and on evaporation yielded 4-methoxy-3-[3-(4-morpholinyl)propoxy]benzonitrile (**8**) (349g). Compound (**8**) was dissolved in acetic acid (500mL) and added slowly to a stirred solution of 70% nitric acid at 45-50 °C (maintaining temperature at 45-50 °C is very crucial) in 8h quenched the reaction mass in ice, basified to pH 8 with ammonia solution, filtered the solid and air dried to get **3e**

(329g, 70% overall yield). ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.15-2.18 (m, 2H), 3.14-3.69 (m, 8H), 3.90-4.04 (m, 2H), 3.99 (s, 3H), 4.30 (t, J=5.7Hz, 2H), 7.73 (s, 1H), 7.91 (s, 1H) MS: M/Z 321(M^+), 100.

5-Methoxy-4-[3-(4-morpholinyl)propoxy]-2-nitrobenzonitrile (3d). Using vanillin as starting material and following the procedure described for **3e, 3d** was obtained in 70% overall yield. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.00-2.14 (m, 2H), 2.44-2.57 (m, 6H), 3.70-3.74 (m, 4H), 3.99 (s, 3H), 4.24 (t, J=6.4Hz, 2H), 7.19 (s, 1H), 7.82 (s, 1H). MS: M/Z 321(M^+), 100.

4,5-Bis-(2-methoxyethoxy)-2-nitrobenzonitrile (3f). Using 3,4-dihydroxybenzaldehyde and 2-bromo-methoxyethane as starting materials and following the procedure described for **3e, 3f** was obtained in 75% overall yield. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.45 (s, 6H), 3.80-3.84 (m, 4H), 4.26-4.33 (m, 4H), 7.28 (s, 1H), 7.85 (s, 1H) MS: M/Z 296(M^+), 59.

5-Methoxy-4-[(3-piperidin-1-yl-propoxy)]-2-nitrobenzonitrile (3i). Using vanillin and 3-piperidin-1-yl-propylchloride as starting materials and following the procedure described for **3e, 3i** was obtained in 70% overall yield. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.47-1.59 (m, 6H), 2.03 (brs, 2H), 2.50-2.70 (m, 6H), 3.97 (s, 3H), 4.25 (t, J= 5.7Hz, 2H), 7.71 (s, 1H), 7.87 (s, 1H). MS: M/Z 319(M^+), 98

Quinazoline-4(3*H*)-one (4b). Following the procedure described for **4a, 3b** gave **4b** in 80% yield. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.53 (t, J= 7.5Hz, 1H), 7.67 (d, J=8.0Hz, 1H), 7.82 (t, J= 7.5Hz, 1H), 8.01 (s, 1H), 8.12 (d, J= 8.0Hz, 1H), 12.25 (brs, 1H, -NHC=O /-N=COH). MS: M/Z 146(M^+), 118, 91, 73.

6, 7-Methylenedioxyquinazoline-4(3*H*)-one (4c). Following the procedure described for **4a, 3c** gave **4c** in 91% yield. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 6.20 (s, 2H), 7.12 (s, 1H), 7.41 (s, 1H), 7.98 (s, 1H), 12.18 (brs, 1H, -NHC=O/-N=COH) MS: M/Z 190(M^+), 163, 134, 105, 77.

6-Methoxy-7-[3-(4-morpholinyl)propoxy]quinazoline-4(3*H*)-one (4d). Following the procedure described for **4a, 3d** gave **4d** in 86% yield. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.06 (m, 2H), 2.54 (m, 6H), 3.66 (m, 4H), 3.96 (s, 3H, -OMe), 4.25 (m, 2H), 7.24 (s, 1H), 7.52 (s, 1H), 8.03 (s, 1H), 12.07 (brs, 1H, -NHC=O/-N=COH) MS: M/Z 319(M^+), 288, 100.

7-Methoxy-6-[-3-(4-morpholinyl)propoxy]quinazoline-4(3*H*)-one (4e). Following the procedure described for **4a, 3e** gave **4e** in 86% yield. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.94 (m, 2H), 2.40 (m, 6H), 3.58 (m, 4H), 3.90 (s, 3H, -OMe), 4.09 (m, 2H), 7.14 (s, 1H), 7.43 (s, 1H), 7.98 (s, 1H), 11.98 (brs, 1H, -NHC=O/-N=COH). MS: M/Z 319(M^+), 288, 100.

6,7-Bis-(2-methoxyethoxy)quinazoline-4(3*H*)-one (4f). Following the procedure described for **4a, 3f**

gave **4f** in 81% yield. ^{1}H NMR (D_2O, 200 MHz) δ 3.38 (s, 6H, 2 x -OMe), 3.77 (m, 4H), 3.98 (m, 4H), 6.44 (s, 1H), 6.86 (s, 1H), 7.75 (s, 1H) MS: M/Z 294(M^+), 204, 178, 59.

5-Methylquinazoline-4(3*H*)-one (4g). Following the procedure described for **4a, 3g** gave **4g** in 91% yield. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.78 (s, 3H, CH3), 7.25 (d, J=7.2Hz, 1H), 7.46 (d, J=7.8Hz, 1H), 7.62 (t, J=7.8Hz, 1H), 7.99 (s, 1H), 12.02(brs, 1H, -NHC=O /-N=COH). MS: M/Z 160(M^+), 131, 104, 90, 77.

7-Trifluoromethylquinazoline-4(3*H*)-one (4h). Following the procedure described for **4a, 3h** gave **4h** in 81% yield. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.82 (d, J=8Hz, 1H), 7.99 (s, 1H), 8.25 (s, 1H), 8.33 (d, J=8Hz, 1H), 12.64 (brs, 1H, -NHC=O/-N=COH) MS: M/Z 214(M^+), 160, 145, 73.

6-Methoxy-7-(3-piperidin-1-yl-propoxy)quinazoline-4(3*H*)-one (4i). Following the procedure described for **4a, 3i** gave **4i** in 86% yield. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.44 (m, 6H), 1.90 (m, 2H), 2.37 (m, 6H), 3.86 (s, 3H, -OMe), 4.13 (m, 2H), 7.11 (s, 1H), 7.43 (s, 1H), 7.97(s, 1H). MS: M/Z 317(M^+), 124, 98.

4-(3-Chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxy]quinazoline (1). To **4e** (200g, 0.62mol) was added thionyl chloride (1.2L) and DMF (20mL), refluxed for about 2 h, distilled off excess thionyl chloride. Then to this reaction mixture was added 1.2L of DMF and 3-chloro-4-fluoro aniline (63g, 1.43mol) the reaction mixture was heated to 100 ºC, stirred for about 1h. Then quenched the reaction mixture in water, adjusted the pH to 8.0 with ammonia solution and extracted with ethyl acetate (3x500mL). Organic layer was washed with water, dried over anhydrous sodium sulphate and concentrated. The crude material obtained was recrystallized from ethyl acetate and then with methanol to get 206g (73% yield) of off-white crystalline compound (**1**). mp 193-195 ºC. HPLC purity>99%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.11 (m, 2H), 2.46-2.59 (m, 6H), 3.74 (dd, J=4.5Hz & 4.4Hz, 4H), 3.98 (s, 3H), 4.17 (t, J=6.5Hz, 2H), 7.09 (s, 1H), 7.16 (t, J=8.8Hz, 1H), 7.26 (s, 1H), 7.34 (brs, 1H, exchangeable with D_2O), 7.50-7.58 (m, 1H), 7.84-7.88 (m, 1H), 8.66 (s, 1H). MS M/Z 446(M+). Anal. Calcd for $C_{22}H_{24}N_4O_3ClF$: C, 59.19; H, 5.38; N, 12.55. Found: C, 59.17; H, 5.21; N, 12.33.

4-Chloro-6,7-bis-(2-methoxyethoxy)quinazoline (12). To a stirred solution of **4f** (200g, 0.68mol) and thionyl chloride (1.2L) was added DMF (20mL). The reaction mixture was refluxed for about 2h. Distilled off excess thionyl chloride, dissolved the residue in dichloromethane (750mL), washed the organic layer with water & dil. $NaHCO_3$ solution and dried over calcium chloride. On evaporation of organic layer yielded **12** (200g, 94% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.50 (s, 6H), 3.89 (dd, J= 4.4Hz & 4.8Hz, 4H), 4.34 (dd, J= 4.4Hz & 4.8Hz, 4H), 7.33 (s, 1H), 7.42 (s, 1H), 8.85 (s, 1H).

[6,7-Bis-(2-methoxyethoxy)quinazolin-4-yl]-(3-ethynylphenyl)amine hydrochloride (2). To **12** (200g, 0.64mol) in DMF (2L) was added 3-ethynyl aniline(75g, 0.64mol) and the reaction contents were stirred at 80 °C for about an hour. Then cooled the reaction mixture to 10 °C, filtered and dried to get the crystalline substance **2** (220g, 80%), mp 228-230 °C. Purity by HPLC >99%. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.36 (s, 6H), 3.77 (m, 4H), 4.29 (s, 1H), 4.32-4.38 (m, 4H), 7.38-7.55 (m, 3H), 7.78 (d, J=8.0Hz, 1H), 7.88 (s, 1H), 8.38 (s, 1H), 8.86 (s, 1H), 11.42 (s, 1H). Anal. Calcd for $C_{22}H_{24}N_3O_4Cl$: C, 61.32; H, 5.85; N, 9.75. Found: C, 61.45; H, 5.62; N, 9.60. Chloride assay by potentiometric method 98.82%

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