Method Optimization for Synthesis of Trisubstitued Quinazoline Derivatives

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Abstract

A series of new 4-anilinoquinazoline derivatives ***(IV-XVI)*** were synthesized in convenient pathway with desirable yields. 4-Aminoquinazoline derivatives corresponding Erlotinib are more active compounds for inhibition of the epidermal growth factor receptor (EGFR) which are used as anticancer agents. Although these categories of compounds have widespread clinical use, most of the reported syntheses protocol for them require multistep and low-yielding reaction pathways. Here we tried a new method with only 3 or 4 steps to prepare 4-anilinoquinazoline derivatives. We synthesized our new compounds in two parts (part I with 3 steps and part II with 4 steps). In the first step of part I, we used *ortho*-diflouro or *ortho*-dimethoxy anthranilic acid to get the quinazoline ring with a carbonyl group at its 4 position. Then, in the second and third steps of this part, we replaced the carbonyl group of quinazoline ring by chlorine and amine group respectively ***(IV-X)***. In part II, we used dichloro anthranilic acid to get the quinazoline ring with a carbonyl group at its 4 position. In these cases, after synthesis of the quinazoline ring we could etherify it via its substitutions on the starting anthranilic acid ***(XI-XVI)***, in order to mimic the erlotinib structure as a tyrosine kinase inhibitor. The next steps of this part (replacing the carbonyl group by chlorine and then by amine) were the same as part I. Our new compounds contain different substitutions at *orto* (6,7*)* or *meta* (5,7) positions of the quinazoline ring.

Keywords: 4–aminoquinazoline, Erlotinib, anti-cancer, EGFR

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1. Introduction

Quinazoline derivatives are an important class of compounds in medicinal chemistry. They show a wide variety of biological activities such as antimicrobial, antifungal, antiviral, insecticidal activity, antihypertension, antiinflammation, antiallergic, antidepressant, anticonvulsant, analgesic, antitumor and anticancer [1-13]. Quinazolines which are substituted at C-4, C-6 and C-7 have emerged as one of the most important classes of quinazoline-based EGFR inhibitors. EGFR is over expressed in several human tumours including prostate, breast, ovarian and non-small cell lung cancers and is an attractive target for the design and development of anticancer compounds [14]. Several small molecules of these compounds have been introduced like Gefitinib and Erlotinib (Fig. 1).

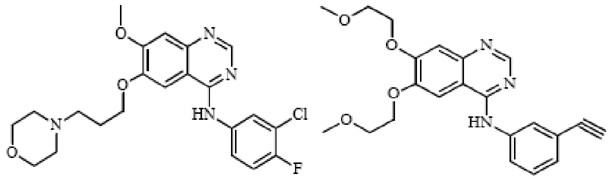


Figure 1: Structure of Gefitinib ***1*** and Erlotinib ***2***

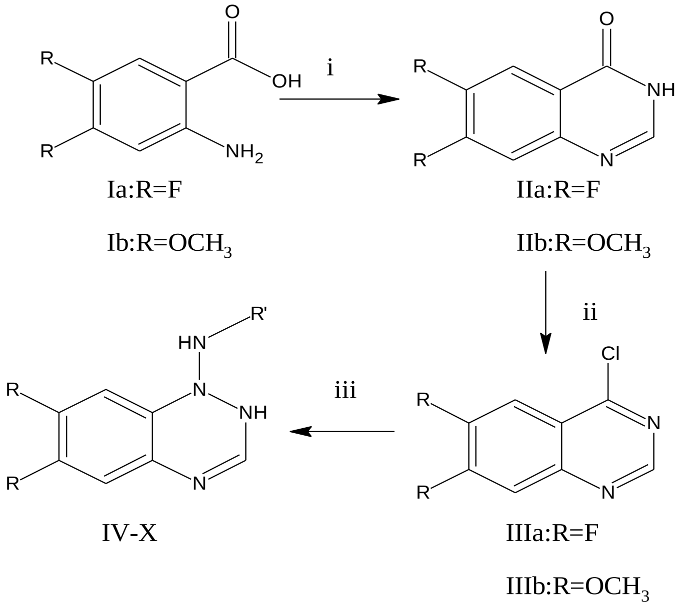
As a part of our on-going research program on quinazoline synthesis, which may serve as leads for designing novel antitumor referred to Erlotinib, we were particularly interested in tri-substituted quinazoline in different positions like 4,5,6 or 4,5,7.

Several methods have been reported for synthesis of 4-aminoquinazolinones. Synthetic sequence of specific example starts from different reagents such as benzoic acid, benzoate [15], aniline derivatives [16] and aminobenzonitrile [17]. Synthetic methods for elaboration of this simple ring structure are however, time consuming, tedious and often low yielding. In this study, we used different di-substituted 2-aminobenzoic acids (anthranilic acids) as starting materials for synthesis of di-substituted 4-aminoquinazolines. We reported a short synthetic method with low toxic reagents and also optimized time and yield of the reactions. Hopefully, our new compounds could be good candidates for inhibition of EGFR like Erlotinib.

2. Experimental

All solvents and reagents were purchased from Fluka or Merck chemical companies. Melting points were determined with a Thermo Scientific Electrothermal digital apparatus (Thermo Fisher Scientific Inc.). IR spectra were recorded on a Bruker optical beampath vertex 70 using KBr pellet technique. ^{1}H NMR was recorded on a Bruker 250 ultra-shield (250 MHz) in CDCl$_3$ or DMSO-d6 and chemical shifts were reported in *ppm* (d). TLC was performed on the glass-backed silica gel sheets (Silica Gel 60 GF$_{254}$) and visualized in UV light (254 nm).

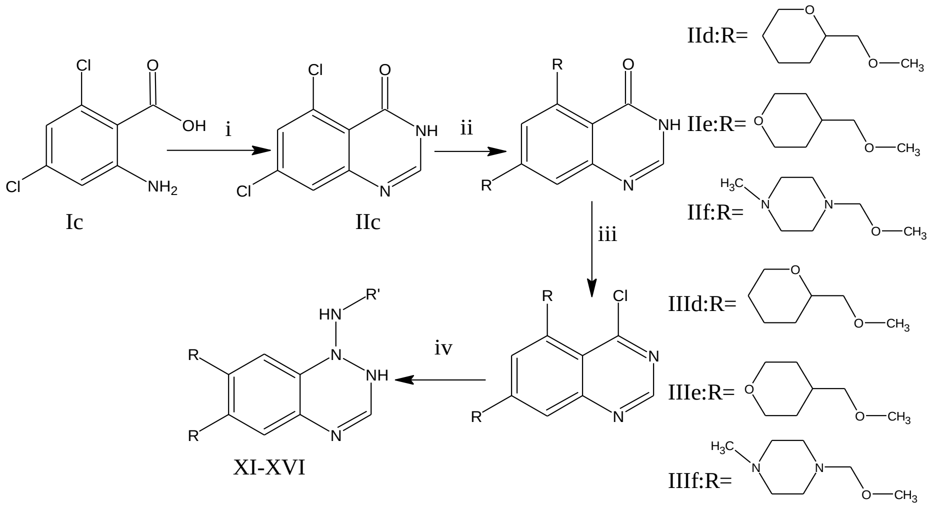
In part I, in order to synthesize 4-aminoquinazoline derivatives, two starting materials ***(Ia, Ib)*** were used to prepare the quinazoline ring. These starting material were reacted with formamide under microwave (MW) irradiation condition to allow desired quinazoline ring cyclization (Scheme 1). Then, the ketone group in position 4 of the quinazoline ring was changed to chlorine with thionyl chloride under reflux condition. In the final step, aniline derivatives were attached to the ring via the chlorine atom using 2-propanol and DMF (Scheme 1).



i:Formamide, MW, ii:$SOCl_2$,DMF,reflux, iii:aniline derivatives, iPrOH,DMF,reflux

Scheme 1: Synthesis of 6, 7-disubstited 4-aminoquinazoline derivatives

In part II, we used ***Ic*** as our starting material. In this case, after closing the quinazoline ring, in the second step two *meta* chlorine substituents were replaced by ether moiety using different alcohol under NaH condition and DMF. The next two steps were the same as the part I (Scheme 2).



i:Formamide, MW, ii:NaH,ROH,DMF,reflux, iii:$SOCl_2$,DMF,reflux, iv:aniline derivatives, iPrOH,DMF,reflux

Scheme 2: Synthesis of 5, 7-disubstited4-aminoquinazoline derivatives

General procedure for the synthesis of compounds ***(IIa-IIb)***

2-Aminobenzoic acid derivative (***Ia-Ib***, 10 mmol) was reacted with excess formamide (10 ml) under MW irradiation condition for 25 min. After the reaction was over, 100 ml of boiling water was added drop wise to the reaction mixture to dissolve the excess of formamide. The yellow solid was filtered and recrystallized in ethanol.

6, 7-difluoroquinazolin-4(3H)-one ***(IIa)*****:** 52%, Mp: 263-265°C

6, 7-dimethoxyquinazolin-4(3H)-one ***(IIb)*****:** 56%. Mp: 217-219°C

General procedure for the synthesis of compounds ***(IIIa-IIIb)***

Quinazolin-4(3H)-one (***IIa-IIb***, 10 mmol) was added to thionyl chloride (10 mL) and acetonitrile (10 mL), and the mixture was heated to reflux for 4 h. Most of the excess of thionyl chloride was then removed under reduced pressure, and the yellow residue was dissolved in chloroform (10 mL), washed with a saturated solution of sodium carbonate (2 ×20 mL), and dried using Na_2SO_4. The chloroform was then removed under reduced pressure to give pale yellow powder, which was recrystallized from ethyl acetate.

General procedure for the synthesis of compounds ***(IV-X)***

To a stirring solution of compound ***IIIa-IIIb*** (2 mmol) in isopropanol (3ml), aniline derivatives (2 mmol) was added and refluxed. After cooling the reaction mixture, solvent was evaporated and yellow solid crystallised from methanol.

6,7-difluoro-N-phenylquinazolin-4-amine ***(IV)***

IR, $\tilde{\nu}$ /cm^{-1}: 3344(NH), ^{1}HNMR (DMSO-d_6), δ: 7.078-7.431 (m, 7H, H_{Ar}), 8.011 (s,1H,H-2 quinazoline)-8.415 (s,1H,NH), ^{13}CNMR (DMSO-d_6):δ 107.6, 113.7, 11398, 118.87,120.41, 128.22, 143.66, 146.92, 152.81, 156.33, 159.95, 169.95.

2-(6,7-difluoroquinazolin-4-ylamino)benzonitrile ***(V)***

IR, $\tilde{\nu}$ /cm^{-1}: 3408(NH),2216(CN), ^{1}HNMR (DMSO-d_6), δ: 7.492-7.926 (m, 6H, H_{Ar}), 8.168 (dd, 2H, NH, H-2 quinazoline), ^{13}CNMR (DMSO-d_6), δ: 102.46, 197.72, 116.73, 125.63, 128.22, 134.35, 135.11, 140.66, 152.67, 152.75, 153.94, 156.98, 157.02, 166.11, 168.51.

N-(2,5-diethoxyphenyl)-6,7-difluoroquinazolin-4-amine ***(VI)***

IR, $\tilde{\nu}$ /cm^{-1}:3424 (NH), 1259(C-O)**,** ^{1}HNMR (DMSO-d_6): 1.677(S, 6H, OCH_3),3.857(m,4H, CH_2), 6.949-7.551 (m, 5H, H_{Ar}), 7.719 (s,1H,H-2 quinazoline), 8.122 (s,1H,NH), ^{13}CNMR (DMSO-d_6): 28.36, 67.71, 97.55, 107.09, 107.25, 130.14, 130.23, 133.3, 133.46, 133.85, 137.17, 156.65, 157.01, 157.09, 157.25, 160.14, 163.68, 170.12.

N-(5-chloro-2-methoxyphenyl)-6,7-difluoroquinazolin-4-amine ***(VII)***

IR, $\tilde{\nu}$ /cm^{-1}: 3437 (NH), ^{1}HNMR (DMSO-d_6): 3.351(s,3H,CH_3), *7.194-7.811 (m, 5H,* H_{Ar}*), 8.168*(s,1H,H-2 quinazoline), *8.523* (s,1H,NH).

N-(2-chloro-6-methylphenyl)-6,7-difluoroquinazolin-4-amin ***(VIII)***

IR, $\tilde{\nu}$ /cm^{-1} :3368 (NH), 1255(C-O), ^{1}HNMR (DMSO-d_6), 2.477(s,3H,OCH_3), 7.686-7.999 (m, 5H, H_{Ar}), 8.035-8.122 (, 2H, NH, NCHN), ^{13}CNMR (DMSO-d_6), δ: 58.02, 120.46, 113.71, 114.01, 115.6, 147.19, 147.37, 151.06, 152.24, 156.05, 159.96, 167.71, 170.46.

*2-(6,7-dimethoxyquinazolin-4-ylamino) benzonitrile **(IX)***

IR, /cm–1 :3535 (NH),2217(CN), 1024(C-O), ^{1}HNMR (DMSO-d6), 3.029-3.068(m,6H,OCH_3), 7.258-7.676 (m, 6H, H_{Ar}), 8.107(s,1H,H-2 quinazoline), 8.507(s,1H, NH), ^{13}CNMR (DMSO-d6), 56.15, 102.48, 102.70, 105.41, 108.12, 115.96, 122.01, 12207, 143.84, 143.87, 144.55, 149.07, 152.11, 152.62, 154.96, 156.39, 160.38, 164.16.

*N-(2, 5-diethoxyphenyl)-6, 7-dimethoxyquinazolin-4-amine **(X)***

IR, /cm–1: 3535 (NH),1255(C-O), ^{1}HNMR (DMSO-d6), 2.481(m,6H,OCH_3), 3.462-3.586(m,6H,OCH_3), 4.258(m,4H,CH_2), 7.399-7.410 (m, 3H, H_{Ar}),7.682-7.731 (m, 2H,HAr), 8.010 (s,1H,H-2 quinazoline), 8.432 (s,1H, NH), ^{13}CNMR (DMSO-d_6), δ: 28.41, 56.35, 100.23, 100.34, 108.45,108.48, 108.70, 116.04, 144.27, 148.73, 148.76, 148.95, 150.14, 154.87, 157.94, 163.85, 167.71.

*Synthesis of 5,7-dichloroquinazolin-4(3H)-one **(IIc)***

A solution of 2-amino-4,6-dichlorobenzoic acid (***Ic,*** 7.004g, 34 mmol) in formamide (40 ml) was stirred for 20 min at room temperature, then the reaction mixture was irradiated for 10 min under microwave condition (500w). The light yellow product was obtained, filtered, washed with water and recrystallized from hot ethanol, 67%. Mp: 224-226˚C.

*General procedure for the synthesis of compound **(IId-IIf)***

A mixture of NaH (0.5 g, 21 mmol) and desired alcohol (21 mmol) was stirred and heated (30°C) for 20 min. The reaction mixture was poured in to solution of ***IIc*** (10 mmol) in DMF (10 ml) and heated under reflux for 7 h. The product was extracted with ethyl acetate and then solvent was removed under reduced pressure and recrystallized from chloroform.

*5,7-bis((tetrahydro-2H-pyran-2-yl)methoxy)quinazolin-4(3H)-one **(IId):*** 80%

*5,7-bis((tetrahydro-2H-pyran-4-yl)methoxy) quinazolin-4(3H)-one **(IIe):*** 80%

*5,7-bis(2-(4-methylpiperazin-1-yl)ethoxy)quinazoline-4(3H)-one **(IIf):*** 75%

*General procedure for the synthesis of compound **(IIId-IIIf)***

The ***IId-IIf*** (8 mmol) in DMF (10 ml) was stirred for 30 min and thionyl chloride (8 mmol, 0.5 ml) was poured and heated under reflux (150°C) for 20 h. After cooling the solution, solvent was evaporated under reduced pressure and product recrystallized from chloroform.

*General procedure for the synthesis of compound **(XI-XVI)***

To a stirring solution of compound ***IIId-IIIf*** (2 mmol) in DMF (3 ml) 2-aminobenzonitrile (2 mmol) was added and refluxed for 20 h. After cooling the reaction mixture, product was extracted as yellowish liquid from ethyl acetate. Solvent evaporated and the product obtained from chloroform.

*2-(5,7-bis((tetrahydro-2H-pyran-2-yl)methoxy)quinazolin-4-ylamino)benzonitrile**(XI)***

IR, $\tilde{\nu}$ /cm^{-1}: 3402(NH), 2223(CN),1502(C-O), ^{1}HNMR ($CDCl_3$): δ =0.76 -0.87 (4H, <u>CH2</u>-CH2-CH2-O); 1.18-1.38 (8H, CH2-<u>CH_2</u>-CH2-O); 3.80 -4.15(10H, <u>CH2</u>-O); 7.06 -7.65 (6H, H_{Ar}); 7.64 (s,1H,H-2 quinazoline), *7.75 (s,1H, NH),* ^{13}CNMR ($CDCl_3$): δ =29.18 -35.97, 60.59-90.76 , 95.93-130.0, 146.5 ,172.7 , 174.0.

*3-(5,7-bis((tetrahydro-2H-pyran-2yl)methoxy)quinazolin-4-ylamino)benzonitrile**(XII)***

IR, $\tilde{\nu}$ /cm^{-1}: 3358(NH), 1145(C-O), ^{1}HNMR (400MHz,$CDCl_3$): δ=0.71-0.89 tetrahydropyran (4H, CH2-CH2-CH2-O); 1.16-1.39 (8H, CH2-CH_2-CH2-O); 3.94-4.30 (10H, CH2-O); 6.65-7.32 (6H, HAr); 7.47 (s,1H,H-2 quinazoline), 7.64 (s,1H, NH), ^{13}CNMR (80 MHz, $CDCl_3$): δ =11.33 - 38.73, 68.19-77.39, 96.02-134.40, 149.64.

N(5-chloro-2-methoxyphenyl)-5,7-bis((tetrahydro-2H-pyran-2yl)methoxy)quinazolin-4-amine ***(XIII)***

^{1}HNMR ($CDCl_3$): δ =0.85 (4H, CH2-CH2-CH2-O); 1.51 (8H, CH_2-CH_2-CH_2-O); 3.86 (13H, CH_2-O and O-CH_3); 6.78-7.26 (5H,H_{Ar});7.80 ((broad peak), 1H, NH);8.44 (s, 1H,N-CH-N),^{13}CNMR (80 MHz, $CDCl_3$): δ =56.0 , 76.72-77.36 , 110.83-127.53(11C, C_{Ar}); 146.32 , 158.60,160.89.

*2-(5,7-bis((tetrahydro-2H-pyran-4-yl)methoxy)quinazolin-4-ylamino)benzonitrile**(XIV)***

IR, $\tilde{\nu}$ /cm^{-1}:3368 (NH),2215(CN), 1261(C-O), ^{1}HNMR (400MHz,$CDCl_3$): δ =0.76-0.89 (2H, CH2-CH2-CH2-O); 1.12-1.68 (8H, CH2-CH_2-CH2-O); 4.19-4.43 (12H, CH2-O); 6.67-7.72 (6H, HAr); 7.44 (s,1H,H-2 quinazoline), 7.64 (s,1H, NH), ^{13}CNMR (80 MHz, $CDCl_3$): δ =10.97 - 38.72, 68.19-77.36, 115.14-134.03, 146.94, 159.49.

*3-(5,7-bis((tetrahydro-2H-pyran-4-yl)methoxy)quinazolin-4-ylamino)benzonitrile**(XV)***

IR, $\tilde{\nu}$ /cm^{-1}: 3382 (NH),2229(CN), 1077(C-O), ^{1}HNMR ($CDCl_3$): δ =0.76-1.38 (10H, CH2-CH2-CH2-O); 4.10-4.59(12H, CH2-O); 6.62-7.50 (6H_{Ar}); 7.88 (s,1H,H-2 quinazoline), 8.29 *(s,1H, NH)* , ^{13}CNMR ($CDCl_3$): δ =23.39 -31.43, 68.51-77.08, 117.43-130.0, 174.86, 160.28.

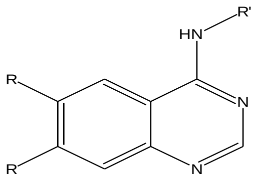
N-(5-Chloro-2-methoxyphenyl)-5,7-bis((4-methylpiperazin-1-yl)methoxy)quinazolin-4-amine ***(XVI)***

IR, $\tilde{\nu}$ /cm^{-1}: 3388 (NH), 1215(C-O), ^{1}HNMR (400MHz,$CDCl_3$): δ 1.30 (,6H, CH3-N), 2.45-2.63 (16H, N-CH2-CH2-N); 3.06 (t, 4H, N-CH2-CH2-O); 3.78 (s, 3H, O-CH3), 6.77-7.89 (5H, CH aromatic), 7.36 (s,1H,H-2 quinazoline), 8.61(*s,1H, NH),* ^{13}CNMR (80 MHz, $CDCl_3$): δ =29.67 - 59.18, 77.18, 110.64-134.27, 159.05; 161.61, 174.64.

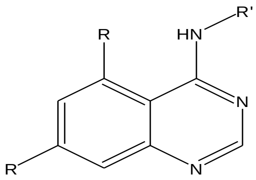
3. Results and Discussion

Target compounds ***(IV-XVI)*** were achieved in three steps as shown in Scheme 1 or four steps as shown in scheme 2 using anthranilic acids derivatives as starting materials (***Ia, Ib*** and ***Ic***). Substituted 2-aminobenzoicacids reacted with formamide to give substituted quinazoline-4(3H) ones (***IIa, IIb*** and ***IIc***), that chlorinated by thionyl chloride. Then, the chloride atoms in position 4 are replaced with aniline derivatives. The access to a series of diether analogues was achieved via the reaction of compound 5,7-dichloroquinazolin-4(3H)-one ***(IIIa)*** with different alcohols under NaH condition (Table 1).

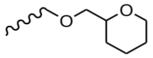
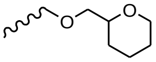
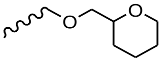
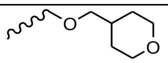
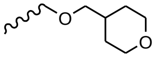
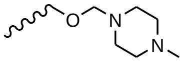
Table 1: Results for synthesis of compounds ***(IV-XVI)***



IV-X



XI-XVI

entry	R	R′	Time (h)	Yield (%)	MP (℃)
IV	F	ph	4	65	197-199
V	F	2-CN-Ph	2	75	262-264
VI	F	2,5-OEt-Ph	3	75	114-116
VII	F	5-Cl-2-OMe-Ph	4	65	224-226
VIII	F	2-Cl-6-Me-Ph	4	70	255-257
IX	OCH_3	2-CN-Ph	4	67	245-247
X	OCH_3	2,5-OEt-Ph	8	73	249-251
XI		2-CN-Ph	20	40	oily
XII		3-CN-Ph	20	46	129-131
XIII		5-Cl-2-OMe-Ph	20	40	oily
XIV		2-CN-Ph	20	48	oily
XV		3-CN-Ph	20	43	oily
XVI		5-Cl-2-OMe-Ph	20	53	<41

The IR spectra of ***(IV-XVI)*** showed the expected two bands corresponding different bonds for υ(NH) in the region of 3100–3600 cm^{-1} and for υ(C-O) about 1100-1300 cm^{-1}. The NMR spectral data of synthesized compounds were consistent with the assigned structures. Since recently a new MW-attempted improvement of quinazoline synthetic method was reported [18], even though once again reduced synthetic steps were required to perform quinazoline formation with new starting material and desirable substituted. All of the alcohols and some aniline derivatives were selected from text and potent compound [19]. We will continue our research about the biological activity of target compounds and investigate QSAR of them in a future program. In comparison to previous work that most of them use expensive and toxic reagents with long pathway [20-23], we receive the main products in minimum steps. Although other advantages of our method are the use of cheaper and easily available starting materials, good yields are the main advantage.

4. Conclusion

We have developed a convenient microwave assisted synthesis of 4-amino 5,7or 6,7-disubstituted (3H)-quinazolinones. The method offers several advantages including good yields, at least comparable with those obtained with other literature methods (20-50%) [24-26], cleaner products, an easy experimental work up procedure.

Acknowledgement

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