Original Article

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A rapid and convenient method for synthesis of anilinoquinazoline: an improved synthesis of erlotinib derivatives

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Abstract

4-Anilinoquinazolines have been widely studied as anticancer agents. Despite the widespread use of this class of compounds, the reported syntheses of 4-anilinoquinazolines require multistep and low-yielding reaction pathways. In this study, a novel strategy to prepare 4-anilinoquinazoline derivatives based on the cyclization of anthranilic acid is described. By using dichloroanthranilic acid, the quinazoline ring was etherified in order to mimic the erlotinib structure as a tyrosine kinase inhibitor. The new compounds contain different substitutions at the meta-positions of the quinazoline ring instead of the ortho-positions of erlotinib. Ten new 4-anilinoquinazoline derivatives were sysnthesized (21-30) in only 4 steps with desirable yields.

Keywords: Anilinoquinazolines, EGFR, Erlotinib, *S*ynthesis.

1. Introduction

Over the past decade, the synthesis of heterocyclic compounds has become one of the most important aspects of medicinal chemistry(1). Among the nitrogen-containing compounds the quinazoline nucleus is a very attractive and useful scaffold in medicinal and pharmaceutical chemistry; it can be found as a pharmacophore in a wide variety of biologically active compounds, such as anticancer, diuretic, anti-inflammatory, anticonvulsant, antibacterial, antiviral, antiplasmodial and antihypertensive compounds(1-5). Quinazoline ring is also a key intermediate for the production of therapeutic agents such as prazosin, bunazosin, doxazosin, erlotinib, gefitinib and imatinib(6).

4-Anilinoquinazolines (gefitinib and erlotinib) (Figure 1) have been widely studied as anticancer agents for their strong ability to inhibit several receptor tyrosine kinases, such as epidermal growth factor receptor (EGFR) or VEGFR-2, often overexpressed or deregulated in many solid tumors(7-10). Among the growth factor receptor kinases that have been identified as an important factor in cancer, is epidermal growth factor receptor (EGFR) kinase (also known as erb-B1 or HER-1) and the related human epidermal growth factor receptor HER-2 (also known as erbB-2)(11).EGFR plays an essential role in normal cell growth, cell division and differentiation which is involved in tumor proliferation and survival(12,13).

Upon ligand binding, the EGFR becomes activated by dimerization which leads to subsequent activation of EGFR tyrosine kinase (TK) activity, initiating receptor-mediated signal transduction, cell mitogenesis and cell transformation(14). Activation of EGFR may be because of overexpression and mutations resulting in constitutive activation, or autocrine expression of the ligand. EGFR and HER-2 over expression is seen in breast cancer, ovarian cancer, lung cancer and prostate

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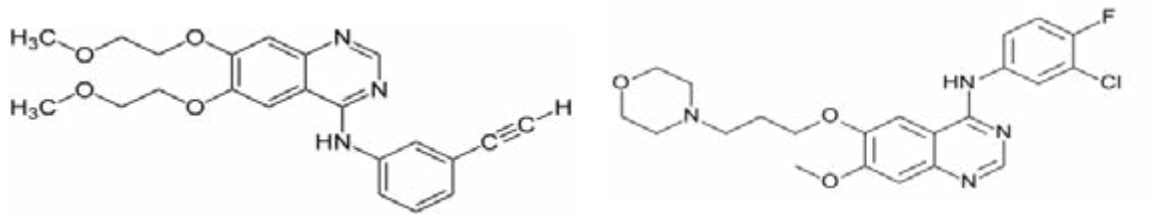


erlotinib gefitinib

Figure 1. Chemical structure of erlotinib and gefitinib.

cancers. Inhibiting the kinase activity of EGFR and/or HER-2 after binding of its cognate ligand is regarded as a promising approach for innovative therapeutic strategies in cancer treatment(11).

Erlotinib (N-(3-ethynylphenyl)-6,7-bis (2-methoxyethoxy)- 4-quinazolinamine) is a novel orally available low molecular weight quinazoline amine that acts as a potent and reversible inhibitor of EGFR-TK activity (Figure 1). The mechanism of action of erlotinib is competitive inhibition of ATP binding to the TK domain of the receptor, which leads to inhibition of EGFR auto-phosphorylation(15, 16).

The reported syntheses methods for this category of compounds require multi-step procedures and suffer from long reaction time, high toxicity of the reagents and use of extreme and drastic conditions(1, 6, 17-19). Therefore development of alternative protocols is critically needed.

The interest in this heterocyclic compound, prompted us to set up a short and efficient route toward erlotinib derivatives, consisting of building the entire quinazoline ring starting from 2-amino-4,6-dicholorobenzoic acid. This method uses formamide under microwave irradiation to-initiate the formation of quinazoline ring in 25-35 minutes. Then, NaH was used for etherification of the chlorine atoms in meta positions of quinazoline ring. In the next step, the oxo group in quinazoline ring was replaced with chlorine with thionyl chloride which was then reacted with aniline moiety in the final step.

The advantages of our method, compared with those previously reported (20-23) is the use of inexpensive and easily available starting materials, good yields, and also the reduction of the number of the steps required for the synthesis of the target molecule. In this study, we have synthesized ten new derivatives of erlotinib in only 4 steps with good yields and without the use of any expensive or toxic reagents.

2. Materials and methods

All chemicals and solvents were of analytical grade and were used without further purification. Analytical TLC was performed on precoated silica gel plates (Merck 60F254, 0.25 mm). Preparative column chromatography was performed using silica gel 60 (0.063–0.100 mm; Merck). Microwave assisted reactions were performed in closed devices with the temperature monitored and automatic control of the power. Melting points were determined on an Electrothermal 9100 digital melting point apparatus. The IR spectra were recorded on a Brucker-Vertex 70 spectrometer. The 1H NMR spectra were recorded on a Brucker 250 MHZ with TMS as an internal standard. Mass spectra were taken on a 7000 triple quadrapole.

2.1. Chemistry

In the first step, the starting anthranilic acid (2-Amino-4,6-dicholorobenzoic acid) was submitted to cyclization with formamide under microwave condition to obtain the primary quinazoline backbone. In the second step, two *meta* chlorines of quinazoline ring were etherified with different alkoxy or morpholine moiety. In the next step, the oxo group at position 4 of the quinazoline ring was substituted by chlorine through a chlorination reaction with $SOCl_2$, which were then converted to the final 4-anilinoquinazoline with the desirable aniline derivatives.

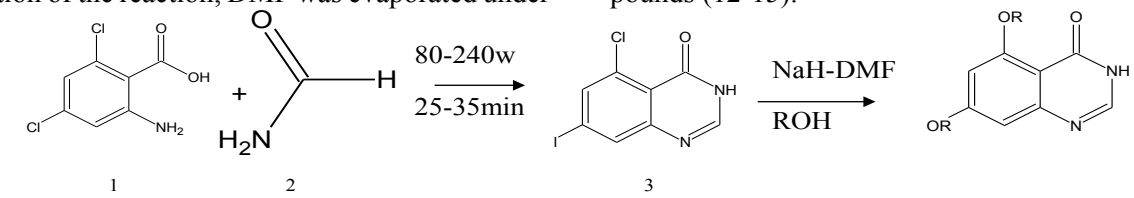
2.2. General procedure for Synthesis of 4-anilinoquinazolines

2-Amino-4,6-dicholorobenzoic acid (1, 1

g, 4.85 mmol) reacted with formamide (2, 12ml, 0.28mol) and converted to the quinazoline ring under microwave irradiation. The unreacted formamide was removed with distilled water and the resulting quinazoline (3) was recrystallized from hot ethanol.

In the next step, two meta chlorine atoms of quinazoline ring were substituted by ether moieties using DMF, selected alcohols (4-7) and NaH. At first, NaH was added to the alcohol in DMF under reflux condition and stirred at room temperature for 15-25 min. Then, the resulting mixture was added to (3) at reflux conditions. After completion of the reaction, DMF was evaporated under vacuum and the remaining base was neutralized with acetic acid to get the etherified compounds (8-11).

Then, the oxo group of the quinazoline ring was replaced with chlorine using thionyl chloride under reflux condition. The etherified compounds (8-11) were stirred in DMF at 100 °C, $SOCl_2$ was added dropwise to the resulting clear solution and then refluxed. After completion of the reaction, the remaining solvents (DMF and unreacted thionyl chloride) were evaporated under vacuum in the presence of saturated bicarbonate in the collector of the rotary evaporator to get the chlorinated compounds (12-15).

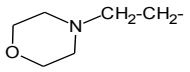


1 2 3

4) R= CH_3-O-CH_2-CH_2-

5) R= CH_3-O-CH_2-CH_2-CH_2-

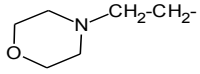
6) R= CH_3-O-CH_2-CH(CH_3)-

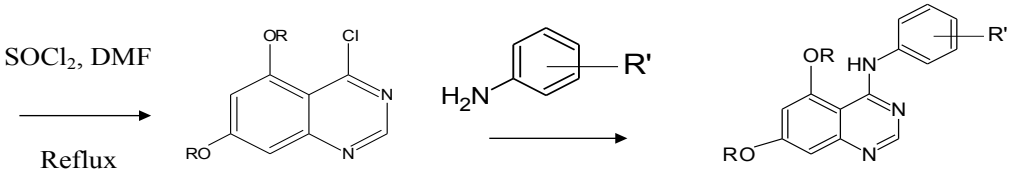
7) R= 

8) R= CH_3-O-CH_2-CH_2-

9) R= CH_3-O-CH_2-CH_2-CH_2-

10) R= CH_3-O-CH_2-CH(CH_3)-

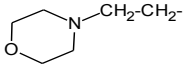
11) R= 



12) R= CH_3-O-CH_2-CH_2-

13) R= CH_3-O-CH_2-CH_2-CH_2-

14) R= CH_3-O-CH_2-CH(CH_3)-

15) R= 

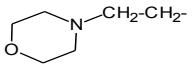
16) R'= H

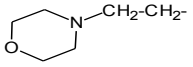
17) R'= 2-CN

18) R'= 3-CN

19) R'= 2-methyl-5-Chloro

20) R'= 2,5-diethoxy

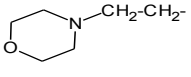
21) R'= H, R= 

22) R'= 2-CN, R= 

23) R'= 2-CN, R= CH_3-O-CH_2-CH_2-

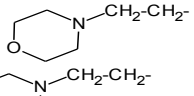
24) R'= 2-CN, R= CH_3-O-CH_2-CH_2-CH_2-

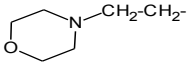
25) R'= 2-CN, R= CH_3-O-CH_2-CH(CH_3)-

26) R'= 3-CN, R= 

27) R'= 3-CN, R=CH_3-O-CH_2-CH_2-CH_2-

28) R'= 3-CN, R= CH_3-O-CH_2-CH(CH_3)-

29) R'= 2-methyl-5-Chloro, R= 

30) R'= 2,5-diethoxy, R= 

Scheme 1. Synthesis of 4-anilinoquinazolines.

In the final step, prepared aniline derivatives (16-20) were attached to the 4-chloroquinazoline ring via the chlorine atom by 2-propanol and DMF. Compounds (12-15) were stirred in DMF and 2-propanol at 100 °C. An aniline derivative was added to the resulting clear solution and refluxed. The crude products were filtered, washed and crystallized to get the final compounds (21-30) (Scheme 1).

3. Results

5,7-di(2-morpholinoethoxy)-4-quinazolinyl(phenyl)amine, M.W.=479.65(21)

^{1}H NMR ($CDCl_3$, 250MHz) δ(ppm):2.40 (t,J=5 8H, cyclic N-CH_2-CH_2-O),2.85 (t,J=10 4H,N-CH_2-CH_2-O), 3.72(t,J=7.5 8H, cyclic N-CH_2-CH_2-O), 4.32(t,J=5 4H, N-CH_2-CH_2-O), 5.47(s(broad peak), 1H, NH); 6.59 (d, 2H, CH aromatic); 6.77-6.83 (m, 2H, CH aromatic); 7.17(s,2H,CH aromatic); 7.39(s, 1H, CH aromatic); 8.48(s, 1H, N-CH-N).

m/z(%):478(7.3);401(17.3);287(28.6);172(42.6);114(100);77(38.6)

2-[5,7-di(2-morpholinoethoxy)-4-quinazolinyl]aminobenzonitrile, M.W.=504.58(22)

1H NMR ($CDCl_3$, 250MHz) δ (ppm): 2.13 (t, J=5, 8H cyclic, N-CH_2-CH_2-O), 2.66(t, J=7.5 4H, N-CH_2-CH_2-O), 3.51 (t, J=10, 8H, cyclic N-CH_2-CH_2-O), 4.06 (t, J=5 4H, N-CH_2-CH_2-O), 6.60 (s, 2H, CH aromatic) 6.81 (s, 1H, CH aromatic), 7.20 (s, 1H, CH aromatic), 7.31-7.34 (m, 2H, CH aromatic), 8.37 (s, 1H, N-CH-N)

m/z(%): 503 (23.3) ;401(17.6); 287 (21.5) 173(65.7) ;114 (100); 102 (56.8);

2-[5,7-di(2-methoxyethoxy)-4-quinazolinyl]aminobenzonitrile, M.W.=394.428(23)

1H-NMR ($CDCl_3$, 250 MHz): δ= 1.11 (t, J=15, 4H, Methoxy-CH2), 3.29 (t, J=2.5, 4H, O-CH_2), 3.56 (s, 6H, O-CH_3), 7.30 (s, 1H, Ha), 7.50 (s, 1H, Hb), 7.59-7.75 (m, 4H, aniline), 8.25 (s, 1H, Hc), 8.72 (s, 1H, NH).

m/z(%): 392 (M-2, 7), 275 (20), 201 (13), 128 (100), 116 (23), 65.6%, mp=254 °C

2-[5,7-di(3-methoxypropoxy)-4-quinazolinyl]aminobenzonitrile, M.W.=420.481 (24)

1H-NMR ($CDCl_3$, 250 MHz): δ= 1.34-1.52 (m, 4H, CH_2-CH_2-CH_2), 1.62 (t, J=10, 4H, Methoxy-CH_2), 3.01 (t, J=17, 4H, O-CH_2), 3.48 (s, 6H, O-CH_3), 7.1 (s, 1H, Ha), 7.42 (s, 1H, Hb), 7.61-7.68 (m, 4H, aniline), 8.14 (s, 1H, Hc), 8.42 (s, 1H, NH).

m/z(%): 420 (M+, 10), 306 (12), 216 (100), 130 (38),116 (57), 89 (38)

C23 H26 N4O4 ,M.W=420.481, 47%, Mp 272-274 °C, 62%, mp=265 °C

2-[5,7-di(2-methoxy-1-methylethoxy)-4-quinazolinyl]aminobenzonitrile, M.W.=420.481(25)

1H-NMR ($CDCl_3$, 250 MHz): δ= 1.23 (d, J=17, 6H, CH-CH_3), 2.02-2.16 (m, 2H, CH), 3.31 (s, 6H, OCH_3), 4.84 (d, J=7, 4H, methoxy-CH_2), 7.58 (s, 1H, Ha), 7.63 (s, 1H,Hb), 8.08-8.72 (m, 4H, aniline), 8.8 (s, 1H, Hc), 8.99 (s, 1H, NH).

m/z(%): 420 (M+, 7), 304 (1), 215 (100), 130 (14), 115 (19), 86 (43), 47%, mp=273 °C

3-[5,7-di(2-morpholinoethoxy)-4-quinazolinyl]aminobenzonitrile, M.W.=504.58(26)

1H NMR ($CDCl_3$, 250MHz) δ (ppm): 2.13 (t, J=5.4 Hz, 8H cyclic, N-CH_2-CH_2-O), 2.66 (t, J=7.2 Hz, 4H, N-CH2-CH2-O), 3.51 (t, J=9.8 Hz, 8H, cyclic N-CH_2-CH_2-O), 4.06 (t, J=5.1 Hz, 4H, N-CH_2-CH_2-O), 6.66-6.69 (m, 2H, CH aromatic), 6.81 (s, 1H, CH aromatic), 7.20 (s, 1H, CH aromatic), 7.31-7.34 (m, 2H, CH aromatic), 8.37 (s, 1H, N-CH-N)

m/z(%): 503(18.5) ;401(23.5) ;287(13.7) ;172(100);113.7(90.4) ;102 (34.2)

3-[5,7-di(3-methoxypropoxy)-4-quinazolinyl]aminobenzonitrile, M.W.=420.481 (27)

1H-NMR ($CDCl_3$, 250 MHz): δ= 1.28-1.37 (m, 4H, CH_2-CH_2-CH_2), 2.07 (t, J=10, 4H, Methoxy-CH_2), 2.76 (t, J=17, 4H, O-CH_2), 3.32 (s, 6H, O-CH_3), 7.01 (s, 1H, Ha), 7.76 (s, 1H, Hb), 8.02-8.07 (m, 4H, aniline), 8.32 (s, 1H, Hc), 8.81 (s, 1H, NH).

m/z(%): 419(M-1, 13),306 (17),215 (100), 127 (51), 116 (33), 86 (38), 55.5%, mp=265 °C

3-[5,7-di(2-methoxy-1-methylethoxy)-4-quinazolinyl]aminobenzonitrile, M.W.=420.481 (28)

1H-NMR ($CDCl_3$, 250 MHz): δ = 1.15 (d, J=7, 6H, CH-CH_3), 2.14-2.15 (m, 2H, CH), 3.32 (s, 6H, OCH_3), 4.64 (d, J=17, 4H, methoxy-CH_2), 6.88 (s, 1H, Ha), 7.16 (s, 1H,Hb), 7.58-7.63 (m, 4H, aniline), 8.07 (s, 1H, Hc), 8.77 (s, 1H, NH)

m/z(%): 418 (M-2, 1), 306 (1) , 215 (100), 128 (25), 116 (56), 88 (30), 55%, mp=273 °C

2-chloro-6-methylphenyl[5,7-di(2-morpholinoethoxy)-4-quinazolinyl]amine, M.W.=528.54(29)

1H NMR ($CDCl_3$, 250MHz) δ(ppm): 2.06 (s, 3H, CH_3), 2.39 (t, J=7.5 Hz, 8H, cyclic N-CH_2-

CH_2-O), 2.78 (t, J=12.1 Hz, 4H, N-CH_2-CH_2-O), 3.61 (t, J=5.4 Hz, 8H, cyclic N-CH_2-CH_2-O), 4.14 (t, J=6 Hz, 4H, N-CH_2-CH_2-O), 5.13 (s (br.s), 1H, NH), 6.45 (s, 1H, CH aromatic), 6.50-6.51 (m, 1H, CH aromatic); 6.68 (s, 1H, CH aromatic); 6.91 (d, J=5.2 Hz, 1H, CH aromatic), 7.21 (s, 1H, CH aromatic), 8.69 (s, 1H, N-CH-N)

m/z(%): 525(15.6); 400.6(13.6);286(16.4) 173(29.3);114(100);125(38.7);

2,5-diethoxyphenyl[5,7-di(2-morpholinoethoxy)-4-quinazolinyl]amine, M.W.=567(30)

1H NMR ($CDCl_3$, 250MHz) δ(ppm):1.28 (t, J=5، 6H, O-CH_2- CH_3), 2.31 (t, J=5، 8H, cyclic N-CH_2- CH_2-O), 2.86 (t, J=7.5، 4H, N-CH_2-CH_2-O), 3.73 (t, J=5 8H, cyclic N-CH_2- CH_2-O) 4.07-4.22 (m, 8H, CH_2) 5.14 (s (br.s), 1H, NH), 5.87 (s, 1H, CH aromatic); 6.24 (d, 1H, CH aromatic), 6.42 (d, 1H, CH aromatic) 6.82 (s, 1H, CH aromatic), 7.22 (s, 1H, CH aromatic); 8.36 (s, 1H, N-CH-N).

m/z(%): 567(17.5) ;450(12.6); 400(9.6); 287(43.6)173(54.4); 114(100);29(18.5);

4. Conclusions

In this study, we have developed a novel synthetic strategy to 4-anilinoquinazoline based on the oxidation of quinazoline intermediates. The efficiency of this approach was evaluated through the synthesis of well-known tyrosine kinases inhibitors, achieved them with overall yields that are higher or at least comparable with those obtained with other methods presented in the literature (20-50%) (24-26). Moreover, this method used simple work-up procedures and could lead to 6,7-differently substituted derivatives such as gefitinib or vandetanib with excellent overall yields. This strategy may represent a valid alternative to anthranilic acid based synthesis of 4-anilinoquinazolines in order to obtain not only known drugs but also novel compounds in the field of tyrosine kinase inhibitors.

Acknowledgement

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Conflict of interest

None declared.

5. References

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