

Synthesis of N-(3-chloro-4-fluorophenyl)-6-nitro-7-((tetrahydrofuran-3-yl)oxy) quinazolin-4-amine

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Abstract. Afatinib (1) exhibited potential biological activities in medicine. There are shortcomings in the synthesis route of afatinib in the literature, the product yield is low and the post-processing is complicated. Therefore, in this paper, the two-step synthetic route of afatinib was optimized. The two-step reaction is discussed the reaction reagent and the feed ratio on the reaction yield were investigated. The optimized reaction conditions are as follows: n (compounds 4): n (4-chloro-7-fluoro-6-nitro-quinazolineand) = 1:1.2; n (compounds 5): n ((S)-tetrahydrofuran-3-ol): n (60 percent NaH) = 1:2.3:3. The improved process has the advantages of mild reaction conditions, simple operation and low cost. The structures were confirmed by ¹H NMR.

Introduction

Lung cancer treatment has evolved significantly during the past decade but this disease remains the leading cause of cancer-associated mortality worldwide[1]. Non-small cell lung cancer (NSCLC) accounts for almost 85% of all lung cancer cases and can be divided in squamous cell lung cancer and non-squamous cell lung cancer (mainly adenocarcinoma and large cell carcinoma)[2-3]. It is now well established that NSCLC can be further more classified to different subtypes according to the oncogenic events that drive carcinogenesis at a molecular level[4-5]. The two oncogenic events that currently have an impact in clinical practice are activating mutations of the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) gene rearrangement[6-7].

In recent years, many quinazoline derivatives were reported as EGFR signal transduction pathway inhibitors, afatinib (Fig. 1) which is a powerful, irreversible tyrosine kinase inhibition of EGFR, with IC₅₀ value (half-maximal inhibitory concentration) of 0.5nM, exhibits potent anti-tumor activity against non small-cell lung cancer(NSCLC), and was approved by the FDA for the treatment of patients with metastatic NSCLC in 2013[8]. In the literature, there are shortcomings in the synthesis route of afatinib (Fig. 2)[9-10], such as , the product yield is low and the post-processing is complicated. Therefore, in this paper, discussed of reaction step (d) and (e) that synthetic methods and routes, the two-step reaction is discussed the reaction reagent and the feed ratio on the reaction yield were investigated.

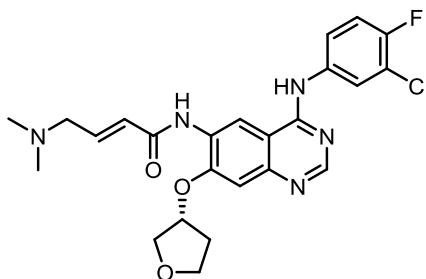


Figure 1. Structures of afatinib

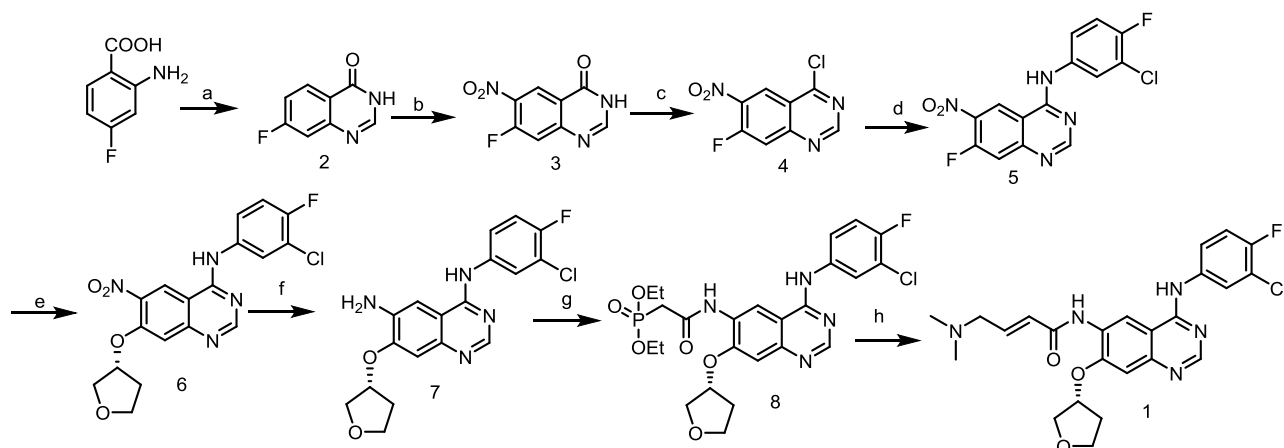


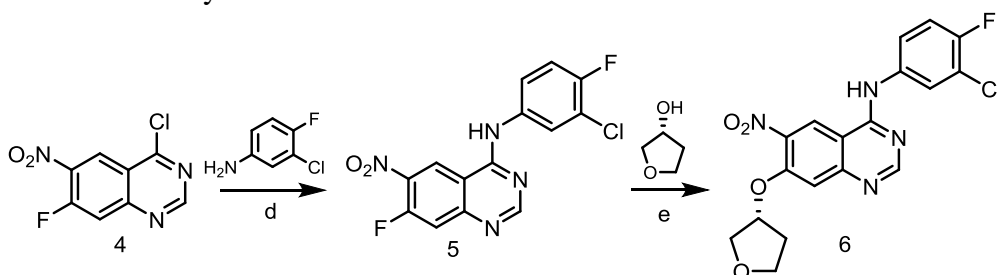
Figure 2. Synthesis of afatinib

Materials and Methods

NMR spectra were performed using Bruker 400 MHz spectrometers (Bruker Bioscience, Billerica, MA, USA) with TMS as an internal standard. Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC–MS (Agilent, Palo Alto, CA, USA). Elemental analysis was determined on a Carlo-Erba 1106 Elemental analysis instrument (Carlo Erba, Milan, Italy). All the materials were obtained from commercial suppliers and used without purification, unless otherwise specified. Yields were not optimized. TLC analysis was carried out on silica gel plates GF254 (Qindao Haiyang Chemical, China).

Synthesis of Compounds

The structures and the synthetic route were shown in Scheme 1.



Scheme 1. The synthetic route of compounds 5 and 6

Reagents and Conditions: (d) Acetonitrile, Isopropanol, r. t, 1.5 h; (e) Tetrahydrofuran, 60 percent NaH, r. t, 1 h.

***N*-(3-chloro-4-fluorophenyl)-7-fluoro-6-nitroquinazolin-4-amine (5).** A solution of 4-chloro-7-fluoro-6-nitro-quinazoline and (10.0 g, 0.0440 mol) and 4-chloro-3-trifluoromethyl-phenylamine (7.7 g, 0.0528 mol) in isopropanol (100 mL), then triethylamine (5.3 g, 0.0528 mol) was added drop-wise at room temperature. The reaction mixture then was stirred at room temperature for 1.5 h, after completion of the reaction (monitored by TLC). The reaction mixture was poured onto water (500 mL), the mixture was then filtered, the filter cake was washed with water, residue was dried to obtain a powdery solid. We can get 14.1 g *N*-(3-chloro-4-fluorophenyl)-7-fluoro-6-nitroquinazolin-4-amine (5). yield: 95.2%. M.p. 261.4 °C -262.5 °C. ¹H NMR (400 MHz, DMSO) δ 10.43 (s, 1H), 9.51 (d, *J* = 7.8 Hz, 1H), 8.68 (s, 1H), 8.08 (d, *J* = 6.4 Hz, 1H), 7.79 (d, *J* = 5.2 Hz, 1H), 7.76 (s, 1H), 7.45 (t, *J* = 9.0 Hz, 1H).

***N*-(3-chloro-4-fluorophenyl)-6-nitro-7-((tetrahydrofuran-3-yl)oxy)quinazolin-4-amine (6).** To the mixture of potassium 60 percent NaH (5.0 g, 0.1257 mol), anhydrous THF (300 mL), (*S*)-tetrahydrofuran-3-ol (8.5 g, 0.0964 mol) was added drop-wise at room temperature. The mixture was stirred at room temperature for 1h. a solution of

N-(3-chloro-4-fluorophenyl)-7-fluoro-6-nitroquinazolin-4-amine (14.1 g, 0.0419 mol) in anhydrous THF (200 mL) was added via a dropping funnel over 1h (the dropping funnel was rinsed with 15 mL of THF) at room temperature and the reaction mixture was stirred at room temperature for 0.5 h, the reaction was monitored by TLC. The solution was concentrated under a reduced pressure and the residue was poured into water with stirring yielding a precipitate, then the mixture was filtered and washed with ice-water and ethanol, dried to afford (*S*)-*N*-(3-chloro-4-fluorophenyl)-6-nitro-7-((tetrahydrofuran-3-yl)oxy)quinazolin-4-amine (6) as yellow solid (16.7 g, 98.5%). m.p. 210.1-211.0°C. ¹H NMR (400 MHz, DMSO) δ 10.10 (d, *J* = 11.8 Hz, 1H), 9.16 (d, *J* = 13.2 Hz, 1H), 8.62 (d, *J* = 13.4 Hz, 1H), 8.13 (d, *J* = 6.8 Hz, 1H), 7.75 (s, 1H), 7.45 – 7.35 (m, 2H), 5.40 (s, 1H), 3.99 – 3.79 (m, 4H), 2.34 (dd, *J* = 13.8, 6.2 Hz, 1H), 2.04 (d, *J* = 5.6 Hz, 1H).

Results and Discussion

Effect of Feed Ratio on Yield in Synthetic Route of Compounds 5. The ratio of 4-chloro-7-fluoro-6-nitro-quinazoline and to compounds 4 was varied, and the data shown in Table 1 were obtained. From Table 1, it can be seen that with the increase of the amount of 4-chloro-7-fluoro-6-nitro-quinazoline, the yield increases, when the ratio of n (compounds 4): n (4-chloro-7-fluoro-6-nitro-quinazoline) = 1:1.2 was maximized and increased again 4-chloro-7-fluoro-6-nitro-quinazoline, cannot improve the product yield, so choice the ratio of n (compounds 4): n (4-chloro-7-fluoro-6-nitro-quinazoline) = 1:1.2.

Table 1 Effect of feed ratio on yield				
Yield/%	n (compounds 4): n (4-chloro-7-fluoro-6-nitro-quinazoline)			
	1:1.1	1:1.2	1:1.3	1:1.4
	83.1%	95.2%	95.3%	95.5%

Effect of Reagent on Yield in Synthetic Route of Compounds 5. Synthesis of *N*-(3-chloro-4-fluorophenyl)-6-nitro-7-((tetrahydrofuran-3-yl)oxy)quinazolin-4-amine, the reagents used potassium tert-butoxide in the literature, but the reaction have some shortcomings, such as reaction time is long, the post-processing is complex and the yield is not high. Therefore, the authors intend to use 60 percent NaH instead of potassium tert-butoxide as the reagent. The data is shown in Table 2.

Table 2 Effect of reagent		
reagent	reaction time	yield
potassium tert-butoxide	5 h	82.1%
60 percent NaH	2.5 h	98.5%

Effect of Feed Ratio on Yield in Synthetic Route of Compounds 6. The ratio of (*S*)-tetrahydrofuran-3-ol and 60 percent NaH to compounds 5 was varied, and the data shown in Table 3 were obtained. From Table 3, it can be seen that with the increase of the amount of (*S*)-tetrahydrofuran-3-ol and 60 percent NaH, the yield increases, when the ratio of n (compounds 4): n ((*S*)-tetrahydrofuran-3-ol): n (60 percent NaH) = 1:2.3:3 was maximized and increased again (*S*)-tetrahydrofuran-3-ol and 60 percent NaH, cannot improve the product yield, so choice the ratio of n (compounds 5): n ((*S*)-tetrahydrofuran-3-ol): n (60 percent NaH) = 1:2.3:3.

Table 3 Effect of feed ratio on yield						
Yield/%	n (compounds 5): n ((<i>S</i>)-tetrahydrofuran-3-ol): n (60 percent NaH)					
	1:2:2.5	1:2:3	1:2.3:3	1:2.3:3.5	1:2.6:3	1:2.6:3.5
	78.1%	87.8%	98.5%	91.5%	93.5%	95.5%

Conclusions

In conclusion, discussed of reaction step d and reaction step e that synthetic methods and routes, the two-step reaction is discussed the reaction reagent and the feed ratio on the reaction yield were investigated. The synthetic method of N-(3-chloro-4-fluorophenyl)-7-fluoro-6-nitroquinazolin-4-amine and N-(3-chloro-4-fluorophenyl)-6-nitro-7-((tetrahydrofuran-3-yl)oxy)quinazolin-4-amine and the reactions conditions were optimized. after optimized, the yield of target compound was higher. Its structure was confirmed by ¹H NMR.

Acknowledgments

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