Synthesis of 2-chloro-N, N-diethyl-7-fluoroquinazolin-4-amine

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Abstract. 7-fluoroquinazoline-2, 4-diol is an important intermediate of small molecule anticancer drugs. In this work, a rapid synthetic method for target compounds was established. Compound (4) was synthesized from 2-amino-4-fluoro benzoic acid and urea through three steps including cyclization, chlorination and nucleophilic substitution. The structure of the target compound was confirmed by H NMR and MS spectrum. Furthermore, the synthetic method was optimized. The total yield of the three steps was 51%.

1. Introduction

7-fluoroquinazoline-2, 4-diol (1) is an important intermediate for the synthesis of EGFR inhibitors. EGFR inhibitors are targeted therapies targeting at EGFR, which block the biological function of EGFR, thereby blocking the biological behavior of tumor cells. Because of its high specificity, high efficiency and low toxicity, EGFR inhibitors have been widely used in the clinical treatment of cancer [1]. Therefore, design and synthesis of 7-fluoroquinazoline-2, 4-diol (1) derivative as small molecule inhibitors played a great role in the study of anticancer drugs. In recent years, many molecules contained the 7-fluoroquinazoline-2, 4-diol (1) had been reported. For example, 4-((3-chloro-4-fluorophenyl)amino)-7-methoxyquinazolin-6-ol (2) [2-4], N-(4-bromo-2-fluorophenyl)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-amine (3) [5-7], (S)-N4-(3-chloro-4-fluorophenyl)-7-((tetrahydrofuran-3-yl)oxy) quinazoline-4,6-diamine (4**)** [8-10].

The Structures of the intermediate active compounds were shown in Fig. 1

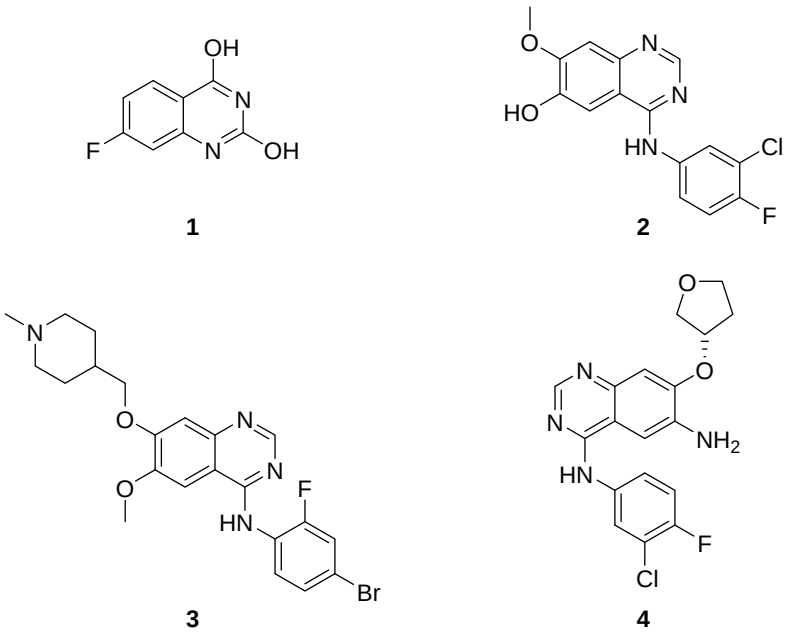


Figure 1. Structures of the intermediate active compounds containing the intermediate

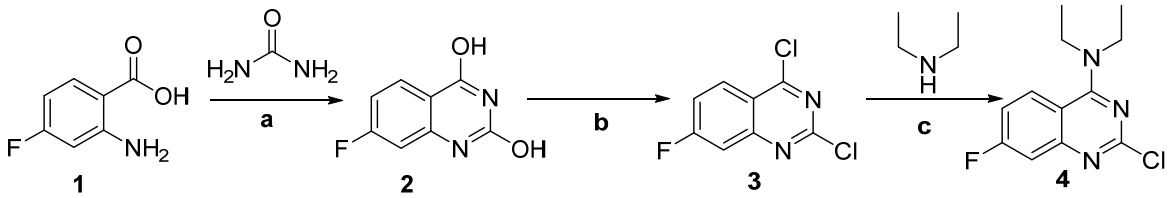
In this study, we synthesized 2-chloro-N, N-diethyl-7-fluoroquinazolin-4-amine, taking 2-amino-4-fluoro benzoic acid as a starting material. The final product was obtained by cyclization, chlorination and nucleophilic substitution, which make it more suitable for industrial production. The reaction contains feature of simple steps, mild conditions, and post-treatment application prospects.

2. Materials and methods

NMR spectra were performed using Bruker 400 MHz spectrometers (Bruker Bioscience, Billerica, MA, USA) with TMS 210 as an internal standard. Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC–MS (Agilent, Palo Alto, CA, USA). 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).

3. Synthesis of compounds

The structures and the synthetic route were shown in Scheme 1



Scheme 1. The synthetic route of compound 4

Reagents and conditions: (a) 100°C, 12 h; (b) $POCl_3$, 110°C reflux, 6 h; (c) toluene, 8 h.

4. Preparation for 7-fluoroquinazoline-2, 4-diol (2)

To the mixture of 2- amino -4- fluoro benzoic acid (10 g, 0.064 mol) and urea (26 g, 0.43 mol), in three flasks (250 mL). After stirring for 12h with mechanical agitation at 160°C, the reaction was complete by TLC analysis. Slightly cool down, a saturated aqueous $NaHCO_3$ solution was added, and adding 10%

NaOH solution (10 g of NaOH in 100 mL of water). Filtration, the filter cake was transferred to a beaker, slowly adding the dilute HCl solution and stir the 10 min. Filtration, the filter cake was washed with saturated aqueous $NaHCO_3$ solution, dried to obtain a white solid (75%). 1H NMR (400 MHz, DMSO-d6) δ 11.33 (s, 1H), 11.24 (s, 1H), 7.92 (dd, J = 8.8, 6.0 Hz, 1H), 7.00 (td, J = 8.7, 2.5 Hz, 1H), 6.87 (dd, J = 10.0, 2.6 Hz, 1H).

5. Preparation for 2, 4-dichloro-7-fluoroquinazoline (3)

A mixture of 7-fluoroquinazoline-2,4-diol (2) (2 g, 11 mmol), $POCl_3$ (10 mL) and DMF (6 d) was heated and stirred for 6 h at 110^{o}C, and the reaction was monitored by TLC. The mixture was concentrated under reduced pressure to afford product as viscous oil. Then, the mixture was transferred to a beaker, ice water acetate was added slowly with stirring. Filtration, the filter cake was washed with ice-water, dried to obtain a brown solid (2.05 g, 85.4%).

6. Preparation for 2-chloro-N, N-diethyl-7-fluoroquinazolin-4-amine (4)

Ethylene diamine (2 mL) was added to flask with toluene (15 mL), Stirred and slowly added 2, 4-dichloro-7-fluoroquinazoline (2 g, 9.2 mmol) to the solution. Stirred for 8 h at room temperature and the reaction was monitored by TLC. The reaction liquid was concentrated under a reduced pressure to obtain white solid. Then, added the right amount of water and ultrasonic agitation. Filtration, the filter cake was washed with water, dried to obtain a brown solid (1.86 g, 79.5%). 1H NMR (400 MHz, DMSO-d6) δ 8.05 (dt, J = 9.1, 4.9 Hz, 1H), 7.49 – 7.40 (m, 1H), 7.39 – 7.33 (m, 1H), 3.36 (d, J = 4.1 Hz, 4H), 1.32 (q, J = 7.1, 5.2 Hz, 6H).

7. Conclusion

In general, 2-chloro-N, N-diethyl-7-fluoroquinazolin-4-amine (4) was optimized by three steps including cyclization, chlorination and nucleophilic substitution. Due to optimization of the synthesis conditions of the target compound 4, the purity of the product was higher. Its structure was confirmed by ^{1}HNMR spectrum.

Acknowledgments

We gratefully acknowledge the generous support provided by The National Natural Science Funds of China (No.21662014), Outstanding Youth Foundation of Jiangxi, Natural Science Foundation of Jiangxi, China(20171BCB23078), Natural Science Foundation of Jiangxi, China (20171ACB21052 &20181ACB20025, 20181BBG70003), Innovative Research Team of Jiangxi Science & Technology Normal University(2017CXTD002).

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