Synthesis of 4-((7-methoxy-6-nitroquinazolin-4yl) oxy) aniline

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Abstract: 4-((7-methoxy-6-nitroquinazolin-4-yl) oxy) aniline, is common to find in the synthesis process of many antitumor drugs. An efficient synthetic method with high yield for compound 9 was established in this work. The target product was synthesized from 7-fluoro-6-nitroquinazolin-4-ol (5) through three steps including chlorination and nucleophilic substitution reactions. The structure of the compound 9 was confirmed by ^{1}H NMR and MS spectrum and the total yield of the three steps was high up to 61.7%.

1. Introduction

Since cancer is still a serious threat to human health, and traditional treatment methods such as radiotherapy and chemotherapy are not effective enough, molecular targeted therapy has become a hot spot in drug research and development in recent years.

Growth factors are important mediators in cell apoptosis and their respective receptors trigger signal transduction pathways [1]. Growth factor signaling pathways play a fundamental role in regulating cell functions, including cell proliferation, differentiation and survival [2]. Receptor tyrosine kinase HER-2 is a member of the epidermal growth factor receptor (EGFR) family [3, 4]. The overactivity of this family leads to the overexpression of receptors, which leads to the overexpression of mutant growth factors, thereby improperly driving cell functions, such as proliferation, differentiation, migration and angiogenesis [5, 6]. The overexpression or amplification of HER-2 receptor can be seen in a variety of cancers, including breast, gastric, pancreatic, and bladder cancer [7, 8]. Consequently, the EGFR family is a major target of anticancer agents. Inhibitors of the EGFR and HER-2 have emerged as promising anticancer agents [9].

Some effective small molecule targeted inhibitors of the EGFR have already been developed and applied in clinical practice. For example, N-(3-chloro-4-(pyridin-2-ylmethoxy)phenyl)-7-methoxy-6-nitroquinazolin-4-amine (1) [10], (E)-N-(4-((3-chloro-4-(pyridin-2-ylmethoxy)phenyl)amino)-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)but-2-enamide (2) [11, 12], N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-(((2-(methylsulfonyl)ethyl)amino)methyl)furan-2-yl)quinazolin-4-amine (3) [13], N-(4-((3-chloro-4-fluorophenyl)amino)-7-(3-morpholinopropoxy)quinazolin-6-yl)acrylamide (4) [14, 15]. The structures of these compounds are shown in Fig.1.

It is not difficult to find that the structure of these inhibitors all contains a similar 4-phenylamine. Therefore, optimize the synthesis method of this intermediate product and increase the yield, which is very valuable for the synthesis of relevant anti-tumor drugs. In this paper, we have established an efficient synthetic method for the synthesis of 4-((7-methoxy-6-nitroquinazolin-4-yl) oxy) aniline (9).

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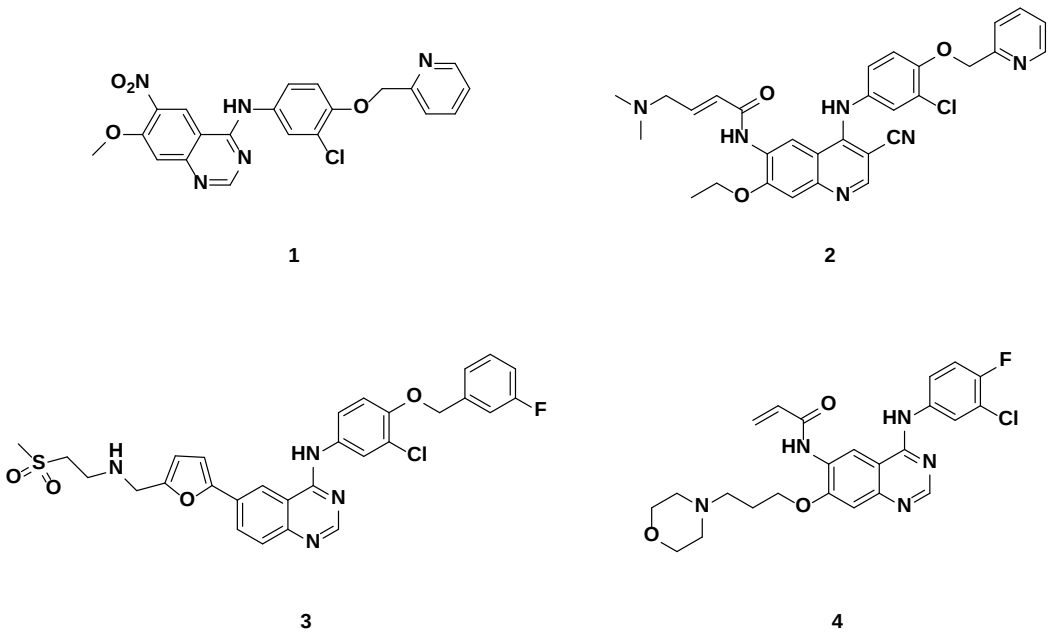

Figure 1. Inhibitors containing 4-phenylamine structure

2. Materials and methods

^{1}H 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 (Qingdao Haiyang Chemical, China).

3. Synthesis of compounds

The structures and the synthetic route were shown in Figure 2.

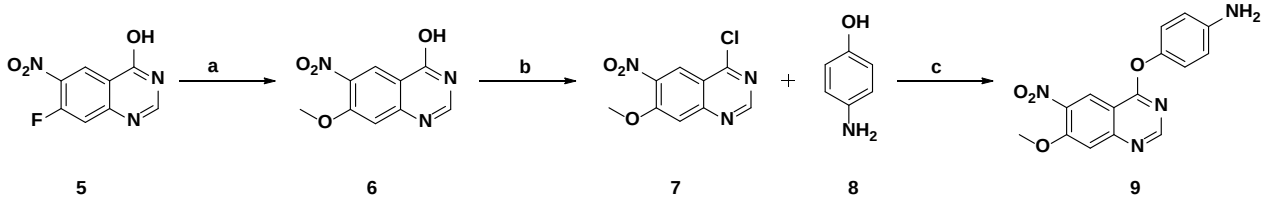

Figure 2. The synthetic route of compound 9

3.1 Reagents and conditions

(a) KOH, Methanol, 80 ºC,1 h; (b) DMF, $SOCl_2$, 90 ºC, 5 h; (c) *p*-nitrophenol, THF, potassium tert-butoxide, N_2, r.t., 0.5 h.

4. Preparation for 7-methoxy-6-nitroquinazolin-4-ol (6)

KOH (9.4 g, 0.1690 mol) was dissolved in water (6.0 mL) then mixed with 7-fluoro-6-nitroquinazolin-4-ol (5) (7.0 g, 0.0338 mol) and methanol. The mixture was stirred at 80 ºC for 1 h. After the reaction cooled to room temperature, poured the reactants into water, then suctioned and dried to obtain the solid of 7-methoxy-6-nitroquinazolin-4-ol (6) (6.5 g, 92%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.51 (s, 1H), 8.52 (s, 1H), 8.23 (s, 1H), 7.42 (s, 1H), 4.04 (s, 3H).

5. Preparation for 4-chloro-7-methoxy-6-nitroquinazoline (7)

7-methoxy-6-nitroquinazolin-4-ol (6) (6.5 g, 0.0295 mol) was dissolved with $SOCl_2$ and added a drop of DMF, refluxed reaction at 90 ºC for 5 h. After the reaction cooled to room temperature, evaporated the solvent and poured it into water. Then suctioned and dried to obtain the solid of 4-chloro-7-methoxy-6-nitroquinazoline (7) (5.6 g, 86%).

6. Preparation for 4-((7-methoxy-6-nitroquinazolin-4-yl) oxy) aniline (9)

The mixture of *p*-aminophenol (3.8 g, 0.0351 mol), THF and potassium tert-butoxide (4.2 g, 0.0468 mol) were stirred in ice bath for 0.5 h with the nitrogen gas in the same time. Then added the 4-chloro-7-methoxy-6-nitroquinazoline (**7**) (5.6 g, 0.0234 mol) in THF into the flask stirred in room temperature for 0.5 h. Filtration, the filter cake was washed by ethyl acetate, then extracted with DCM (3×100 mL) and sodium hydroxide solution. Evaporated the solvent and dried to obtain the solid of 4-((7-methoxy-6-nitroquinazolin-4-yl) oxy) aniline (**9**) (6.2 g, 78%). ESI-MS m/z: [M + H] + 312.09. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.76 (s, 1H), 7.68 (s, 1H), 6.96 (d, J = 8.8 Hz, 2H), 6.62 (d, J = 8.8 Hz, 2H), 5.12 (s, 2H), 4.09 (s, 3H).

7. Conclusions

In summary, the synthesis process of 4-((7-methoxy-6-nitroquinazolin-4yl) oxy) aniline (9) from 7-fluoro-6-nitroquinazolin-4-ol (5) have three steps including chlorination and nucleophilic substitution reactions. The synthesis method is convenient and quick, with high yield up to 78.3%. The structure of compound **9** was confirmed by MS and ^{1}H NMR spectrum.

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