Synthesis of tert-butyl 5-amino-4 - ((2- (dimethylamino) ethyl) (methyl) amino) -2- methoxyphenyl) Carbamate

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Abstract. Tert-Butyl 5-amino-4 - ((2-(dimethyl- amino) ethyl) (methyl) amino) -2- methoxyphenyl) carbamate (1) is an important intermediate in many biologically active compounds such as omisertinib (AZD9291). In this work, a rapid synthetic method for compound 1 was established. The compound 1 was synthesized from the commercially available 4-fluoro-2- methoxy-5-nitroaniline through three steps including acylation, nucleophilic substitution and reduction. The structures were confirmed by MS and 1HNMR. Furthermore, the synthetic method was optimized, and the total yield of the three steps was 81 %.

Introduction

AZD9291 is a novel oral, potent and selective third-generation irreversible inhibitor of both EGFR-sensitising and T790M resistance mutants[1-4]. It has a good therapeutic effect on non-small cell lung cancer (NSCLC) tumors, compared with the first-generation gefitinib and the second-generation erlotinib[5-11]. There are two synthetic methods documented for the synthesis of AZD9291[12]. They both have high reaction temperature, time consuming, low yield, harmful to environment and other shortcomings. However, the synthesis of AZD9291 with *tert*-butyl 5-amino-4 - ((2-(dimethyl- amino) ethyl) (methyl) amino) -2- methoxyphenyl) carbamate as the key intermediate has less reported[13]. In this study, we optimized the synthesis of compound 1, taking 4-fluoro-2methoxy- -5-nitroaniline[14] as a starting material. The final product compound 1 was obtained by acylation, nucleophilic substitution and reduction.

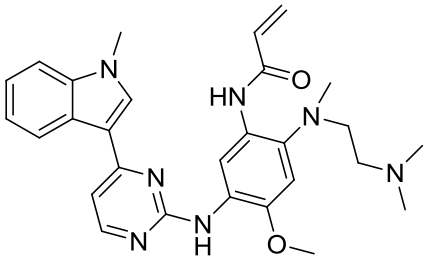


Fig. 1 Sructures of AZD9291

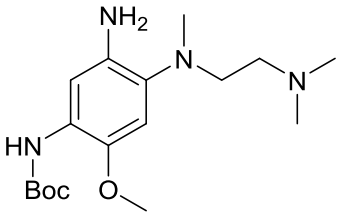
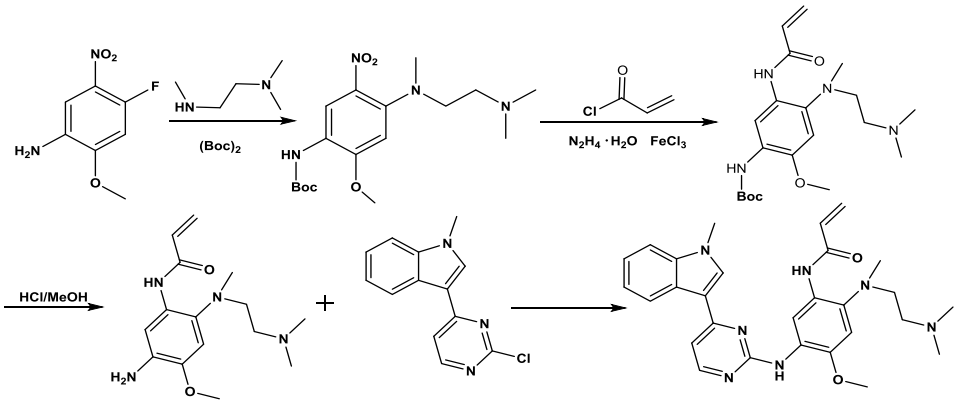


Fig. 2 Compound 1

In this study, we designed and optimized the synthetic methods for *tert*-butyl 5-amino-4 - ((2-(dimethylamino) ethyl) (methyl) amino) -2- methoxyphenyl) carbamate and make it more suitable for industrial production. The structures of AZD9291 and compound 1 were shown in Fig 1 and Fig 2, respectively.



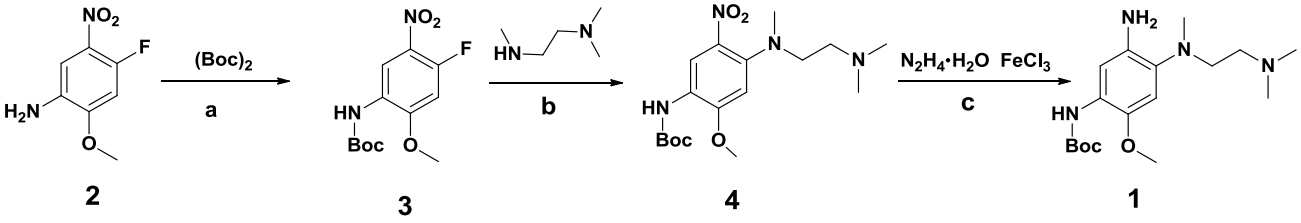
Scheme 1. The synthetic route of AZD9291

Materials and Methods

NMR spectra were performed using Bruker 300 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 2



Scheme 2. The synthetic route of compound 1

Reagents and conditions: (a) Boc_2O, triethylamine, DMAP (4-dimethylaminopyridine), 40 ℃. (b) N_1,N_1,N_2-trimethylethane-1,2-diamine, DIPEA (N,N-Diisopropylethylamine), 140 ℃. (c) 80% hydrazine hydrate, $FeCl_3$, activated carbon, 60 ℃ - 80 ℃.

(4-Fluoro-2-methoxy-5-nitro-phenyl)-carbamic acid *tert*--butyl ester (3)

A solution of 4-fluoro-2-methoxy-5-nitroaniline (4.0 g, 21.5 mmol), triethylamine (32.25 mmol) and DMAP (0.52 g, 4.3 mmol) in DCM (dichloromethane) (50 mL) was cooled to 0 - 5 ℃ in an ice/water bath. Boc_2O (9.4 g, 43.0 mmol) in DCM (30 mL) was added to the mixture slowly. The progress of the reaction was monitored by TLC. After completion of the reaction, extracted with DCM (300 mL*3), and the organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield product (5.5 g, 90%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ = 8.57 (s, 1H), 8.53 (s, 1H), 7.28 (s, 1H), 3.94 (s, 3H), 1.47 (s, 9H). MS (ESI): m/z 286.1[M+H] $^+$.

{4-[(2-Dimethylamino-ethyl)-methyl-amino]-2-methoxy-5-nitrophenyl}-carbamic acid *tert*-butyl ester (4)

N_1,N_1,N_2-Trimethylethane-1,2-diamine (2.7 g, 27.0 mmol) was added to a solution of (4-fluoro-2-methoxy-5-nitro-phenyl)-carbamic acid *tert*-butyl ester (6.3g, 22.0 mmol) and DIPEA (N,N-Diisopropylethylamine) (3.82 mL, 22.0 mmol) in DMA (N,N-Dimethylacetamide) (100 mL). The mixture was heated to 60 ℃ and stirred at this temperature for 2 h. Water (200 mL) was added to the reaction mixture, which was then extracted with DCM (50 mL*3). The combined extracts were dried over anhydrous sodium sulfate. The solvent was removed under vacuum to give product as an orange solid (7.5 g, 92%), ^{1}H NMR (400 MHz, DMSO) δ = 8.34 (s, 1H), 8.23 (s, 1H), 6.87 (s, 1H), 3.94 (s, 3H), 3.50 (t, J=6.8, 2H), 3.27 (t, J=6.7, 2H), 2.78 (d, J=8.3, 9H), 1.45 (s, 9H). MS (ESI): m/z 368.2[M+H]$^+$.

***tert*-butyl 5-amino-4 - ((2- (dimethylamino) ethyl) (methyl) amino) -2- methoxyphenyl) carbamate (1)**

A solution of {4-[(2-Dimethylamino-ethyl)-methyl-amino]-2-methoxy-5- nitrophenyl}-carbamic acid *tert*-butyl ester (2.5 g, 6.8 mmol) in ethanol, after heated to 60 ℃, $FeCl_3$ (0.5 g, 3.0 mmol) and activated carbon was added in such degree. Continue to heat to 80 ℃, 80% hydrazine hydrate (1.7 g, 34.0 mmol) was added to the reaction mixture. The resulting mixture was stirred at 80 ℃ for 1 h, and then cooled to r.t. The resulting filtrate was collected by filtration, washed with ethanol, the filtrate extracted with DCM (300 mL*3), and the organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give yellow oily liquid (2.5 g, 98%). ^{1}H NMR (400 MHz, DMSO) δ = 8.21 (s, 1H), 7.48 (s, 1H), 7.03 (s, 1H), 6.60 (s, 2H), 3.91 (s, 3H), 3.47 (t, J=6.8, 2H), 3.24(t, J=6.7, 2H), 2.75 (d, J=8.3, 9H), 1.42 (s, 9H). MS (ESI): m/z 338.2[M+H]$^+$.

Conclusions

In conclusion, *tert*-butyl 5-amino-4 - ((2- (dimethylamino) ethyl) (methyl) amino) -2-methoxyphenyl) carbamate was synthesized from the commercially available 4- fluoro-2-methoxy-5-nitroaniline through three steps including acylation, nucleophilic substitution and reduction. The synthetic method of compound 1 and the reactions conditions were optimized, the purity of the product was much higher. Its structure was confirmed by MS and ^{1}H NMR spectrum.

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