Synthesis of tert-butyl 4-((2-methoxy-4-(methoxycarbonyl) phenoxy) methyl) piperidine-1-carboxylate

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Abstract. Tert-butyl 4-((2-methoxy-4-(methoxycarbonyl) phenoxy) methyl) piperidine-1-carboxylate (1) is the key intermediate of Vandetanib. It was synthesized from piperidin-4-ylmethanol (2) through three steps Including acylation, sulfonation and substitution. The structures and the synthetic route were determined by MS and 1HNMR.And the synthetic method was optimized. The total yield of the three steps was 20.2%.

1. Introduction

Cancer is a widespread, complex, and lethal disease. It is a group of different diseases characterized by uncon-trolled cellular growth, tissue damage, invasion and metastases [1]. In 2008, 7.6 million people died of cancer (around 13% of all deaths), and this number is projected to increase with an estimated 13.1 million in 2030. According to an estimate from the American Cancer Society, a total of 1 638 910 new cancer cases and 577 190 deaths from cancer could occur in the United States this year [2]. Despite the efforts to discover and develop small molecule anticancer drugs in the last decade [3-6], development of new antitumor agents with improved tumor selectivity, efficiency, and safety remains desirable. Recently, a number of new quinoline derivatives with excellent antitumor activity have been reported [7-16]. Vandetanib (a) is one of the quinoline derivatives and a kind of tryrosine kinase inhibitors. It is a potent inhibitor of VEGF RTK and also has some activity against epidermal growth factor (EGF) RTK [17]. It inhibits the effects of VEGF and is of interest for its antiangiogenic and/or vascular permeability effect [18]. It was approved for the treatment of metastatic medullary thyroid cancer (MTC) by U. S. Food and Drug Administration (FDA) on June 4, 2011.

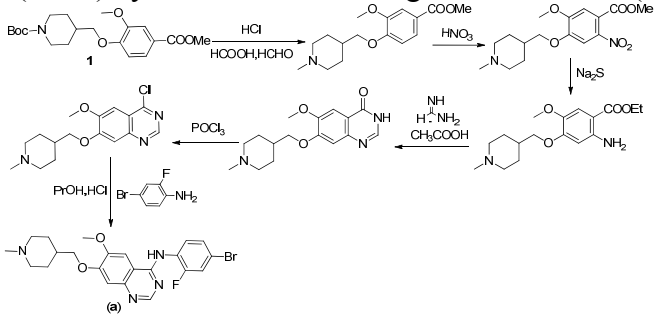


Fig. 1 Structures of compounds and synthetic route of Vandetanib

Vandetanib was synthesized from Tert-butyl 4-((2-methoxy-4-(methoxycarbonyl) phenoxy) methyl) piperidine-1-carboxylate **(1)** through six steps including deprotection, nitration, reduction, cyclization, chlorination and substitution. So it aslo provide a vital role in the subsequent rection. Sructures of compounds and synthetic route of Vandetanib were shown in Fig.1.

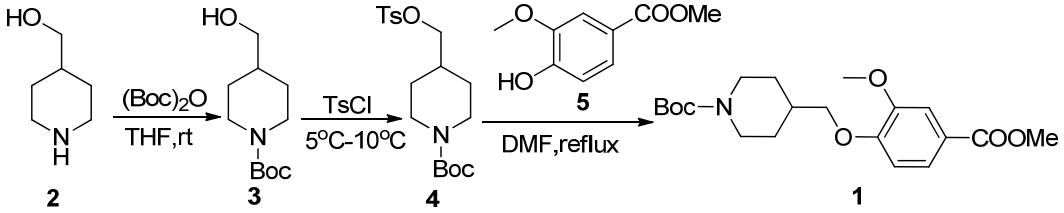
2. Materials and methods

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). 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 1

3.1 Tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate(3)

4-Hydroxymethylpiperidine(2)(2.7g,23.5mmol) and di-tert-butyldicarbonate(5.12g,23.5mmol) were dissolved in THF(30mL) and the solution was stired 8 hours at room temperature.The mixture was concentrated in vacuo and the residue was dissolved in ether.The either solution was washed with water and then with brine,and dried over sodium sulfate.Evaporation of the solvents and gave a residue of 4.0g tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate. yield:85.0%. ESI-MS m/z:216.3$(M+H)^+$.

3.2 Tert-butyl 4-((tosyloxy)methyl)piperidine-1-carboxylate(4)

The compound **3**(2.55g,12.6mmol) was dissolved in pyridine(20mL) and the solution was cooled to 0^{o}C.P-Toluenesulfonyl chloride(2.38g,12.6mmol) was then added to the solution and the mixture was stired at 5 ^{o}C for 10 hours.The mixture was pured into water and extracted into ethyl acetate.The ethylacetate extract was washed with 5 percent HCl,with water,and with brine.The ethyl acetate was then dried over sodium sulfate and then evaporated.Crystallization from actate-hexane gave tert-butyl 4-((tosyloxy)methyl)piperidine-1-carboxylate 2.09g. yield:45.1%.m.p.71 ^{o}C -72 ^{o}C. ESI-MS m/z:370.5$(M+H)^+$.

3.3 Tert-butyl 4-((2-methoxy-4-(methoxycarbonyl)phenoxy)methyl)piperidine-1-carboxylate(1)

Methyl 4-hydroxy-3-methoxybenzoate(5)(0.91g,5mmol) and tert-butyl 4-((tosyloxy) methyl) piperidine-1-carboxylate (4) (2.0g,5.5mmol) were dissolved in DMF(5mL).Then potassium carbonate(0.14g,10mmol) was added into the reaction system,then heated to 153 ^{o}C and stirred for 10 hours. After cooling to room temperature, the mixture was pured into water and extracted into ethyl acetate. The ethyl acetate was then dried over sodium sulfate and then evaporated. We can get 0.97g *tert*-butyl 4-((2-methoxy-4- (methoxycarbonyl) phenoxy) methyl) piperidine-1-carboxylate (1). yield: 51.2%. M.p.75 ^{o}C -76 ^{o}C .ESI-MS m/z: 380.4$(M+H)^+$. ^{1}HNMR, δ 1.13(m, 2H); 1.44(s, 9H); 1.64(d, 2H); 1.75(m, 2H); 2.44(s, 3H); 2.55(m, 2H); 3.84(d, 2H); 4.12(s, 2H); 7.34(d, 2H); 7.80(d, 2H).

4. Conclusions

In conclusion, the compound 1 is a key intermediate of Vandetanib. It was synthesized from 4-Hydroxymethylpiperidine (2) through three steps including acylation, sulfonation and substitution. The synthetic method of compound 1 and the reactions conditions were optimized, after recrystallization, the purity of the product was higher. Its structure was confirmed by MS spectrum and ^{1}HNMR.

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