Synthesis of 2-(4-((6-bromo-3-nitroquinolin-4-yl)amino)phenyl)-2-methylpropanenitrile

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Abstract. 2-(4-((6-bromo-3-nitroquinolin-4-yl)amino)phenyl)-2-methylpropanenitrile (**7**) is an important intermediate in many PI3K/mTOR inhibitors. The compound **5** was synthesized from 6-bromoquinolin-4-ol (**1**) and 2-(4-nitrophenyl)acetonitrile (**4**) through five steps including nitration, chlorination, alkylation, reduction and substitution. These structures were confirmed by ¹HNMR and MS spectrum. The synthetic method of **7** was optimized and can be used to synthesize the derivatives of NVP-BEZ235.

Introduction

Tumor molecular targeted therapy has become more and more popular in cancer treatment. The PI3K-Akt-mTOR signaling pathway was composed of Phosphoinositide 3-kinase, PAKT/PKB and mTOR. This pathway controlled many important biological processes in the development of tumor^[1]. Currently, there are many kinds of inhibitors. PI3K inhibitors bearing quinoline is a kind of important compound to treat cancer. Novartis has developed a series of quinoline PI3K/mTOR inhibitors (Fig.1) and most of them showed extent antitumor activity. The compound NVP-BBD130 is one of the typical representatives^[2]. It acts on PI3K, PI3K beta, gamma, delta and mTOR. NVP-BBD130 was optimized to get NVP-BEZ235. It also works on PI3K/mTOR^[3-4], and it can obviously reduce the mTOR activated kinase p70S6K phosphorylation level^[5]. The associated application of NVP-BEZ235 in solid tumor and some of the blood system tumor was reported, including combination with chemotherapy drugs, combination with other molecular targeted drugs as well as combination therapy with radiotherapy and so on^[6-10].

Fig.1 Structures of NVP-BBD130 and the representative compounds in study

2-(4-((6-bromo-3-nitroquinolin-4-yl)amino)phenyl)-2-methylpropanenitrile is a key intermediate for the synthesis of quinoline inhibitors. Compound **7** was synthesized from 6-bromo-4-chloro-3-nitroquinoline (**3**) and 2-(4-aminophenyl)-2-methylpropanenitrile (**6**) (Fig.2). In this paper, we summarized and optimized the synthetic methods of compound **1**.

Materials and methods

All melting points were obtained on a Büchi Melting Point B-540 apparatus (Büchi Labortechnik, Flawil, Switzerland) and were uncorrected. 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).

Synthesis of compounds

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

Preparation for 6-bromo-3-nitroquinolin-4-ol (2)

The solution of compound 1 5g (22 mmol) in 250mL propionic acid was stirred and the mixture of 12mL nitric acid and 13mL propionic acid was added dropwise for 1h at rt. Raise the temperature to 125°C. Then the mixture was reacted for 2 h and filtered by solid. The solid was washed with saturated NaHCO₃ solution for 1h at 0°C, filtration, the filtrate was dried to obtain a yellow powdery solid (3.54g 59.03%)^[3]. ESI-MS *m/z*: 268.9(M-H)⁻

Preparation for 6-bromo-4-chloro-3-nitroquinoline (3)

The solution of compound 2 3.54g(13mmol) in 100 mL POCl₃ was stirred and 4 drops DMF was added into the solution. Then the mixture was reacted for 2h at 110°C. The solution was concentrated under reduced pressure to afford a yellow solid. The solid was washed with saturated NaHCO₃ solution for 1h at 0°C, filtration, the filtrate was dried to obtain a milk white solid (3.22g 85%). ESI-MS *m/z*: 287.5[M - H]⁻

Preparation for 2-methyl-2-(4-nitrophenyl)propanenitrile (5) 2-(4-nitrophenyl)acetonitrile (4) 10g(61mmol) was first dissolved in 260 mL DMF, 60% NaH 9.76g(244mmol) was added into solution and was stirred for 1h at 0°C. Then, the mixture CH₃I 21.66g(153mmol) of 10 mL DMF was added dropwise, the mixture solution was reacted for 3h and filter by filtrate. The filtrate mixed with ice water was stirred for 1h, precipitation, filtration by green solid (10.58 90.21%). ESI-MS *m/z*: 190.1 [M - H]⁻

Preparation for 2-(4-aminophenyl)-2-methylpropanenitrile (6)

A mixture of compound 5 10.58g(55.6mmol), 500mL EtOH was stirred for 0.5 h. FeCl₃ 3.0g, activated carbon 10.03g were added into the solution and raise the temperature to 80°C. 80% hydrazine hydrate 34.75g(556mmol) was added dropwise and refluxed for 1h. The mixture was then filtered, washed with EtOH. The filtrate was dried by anhydrous sodium sulfate for 1 day, filtration, the filtrate was concentrated under reduced pressure to afford a yellow oil (6.71g 74.84%). ESI-MS *m/z*: 161.4 [M - H]⁺

Preparation for 2-(4-((6-bromo-3-nitroquinolin-4-yl)amino)phenyl)-2-Methylpropanenitrile (7)

The mixture of compound **3** 3.22g(11.2mmol), 100 mL acetic acid was stirred for 1h at room temperature. Compound **6** 2.44g(12.3mmol) was added dropwise into the solution. The mixture was refluxed for 1h, filtration, filter cake was dried to obtain yellow solid (2.3g 50%). ESI-MS m/z : 411.0[M - H]⁻, ¹H NMR(400 MHz, DMSO) δ 9.00 (s, 1H), 8.64 (s, 1H), 7.91 (s, 1H), 7.85 (d, 1H), 7.72 (d, 1H), 7.38 (d, 2H), 7.02 (d, 2H), 1.63 (s, 6H).

Conclusions

In conclusion, one novel compound **7** was synthesized from 6-bromoquinolin-4-ol and 2-(4-nitrophenyl)acetonitrile through five steps. The synthetic route can be used to synthesize 2-(4-((6-bromo-3-nitroquinolin-4-yl)amino)phenyl)-2-methylpropane-nitrile.

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