Synthesis of (E)-N, N-dimethyl-N'-(4-(4-nitrophenoxy) picolinoyl) formohydrazonamide

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Abstract: (*E*)-*N*, *N*-dimethyl-*N*'-(4-(4-nitrophenoxy) picolinoyl) formohydrazonamide (8) is considered as an important intermediate of many antitumor drugs. Compound 8 was synthesized from 6-chloropyrimidine-4-amine by three steps nucleophilic substitution. The structures of the intermediates were confirmed by MS. Furthermore, the synthetic method was optimized.

1. Introduction

With the change of people's lifestyle and the aggravation of environmental pollution, malignant tumors have become the number one killer of serious threats to human health, killing more than 7 million people every year and making them one of the biggest public health problems in the world.[1-2] Cancer has become a serious burden on the society and family, especially the mental and physical pain caused to the patients themselves is huge.[3] The current state of chemotherapy is far from satisfactory due to theirs serious side effects and acquired drug resistance.[4] This has led to a continuing demand for safer, more effective anti-tumor drugs. Tumorigenesis is a multistage complex process in which the activation of proto-oncogenes and the inactivation of inhibitory genes are important molecular bases for tumorigenesis. c-Met is a prototypical member of the Ron subfamily of the receptor tyrosine kinase (RTK) family and is the only known recipient of high affinity for hepatocyte growth factor (HGF).[5-6] Since c-Met kinase was first discovered in 1984, research and reports on the biological function of HGF / c-Met signaling pathway and its pathological relationship with diseases have appeared exponentially.[7-8] c-Met is a receptor tyrosine kinase that is activated by binding to its natural ligand hepatocyte growth factor (HGF / SF). HGF combined with c-Met can induce a variety of complex signal transduction pathways, and lead to cell proliferation, movement, migration and survival. These cell activities are important in normal development and wound healing, but can lead to cancer when the pathway is deregulated. [9-11] recent studies have shown that c-Met is overexpressed in most tumor cells and exhibits high levels of autophosphorylation. c-Met kinase can promote the proliferation of tumor cells, regulate the migration of tumor cells, increase the invasion ability of tumor cells and induce the generation of tumor neovascularization.[12-13] At present, c-Met kinase has become an important target for anti-tumor drug research. Part of the highly potent and selective small molecule inhibitors are shown in Figure 1. [14-17] Compound 1 is cabozatinib, which has been on the market. It is a multi-target small molecule inhibitor of Lok, and has good efficacy on many kinds of tumors. This study designed and optimized the synthetic route and method of (*E*)-*N*, *N*-dimethyl-*N*'-(4-(4-nitrophenoxy) picolinoyl) formohydrazonamide (8). The structures and the synthetic route were shown in Figure 2.

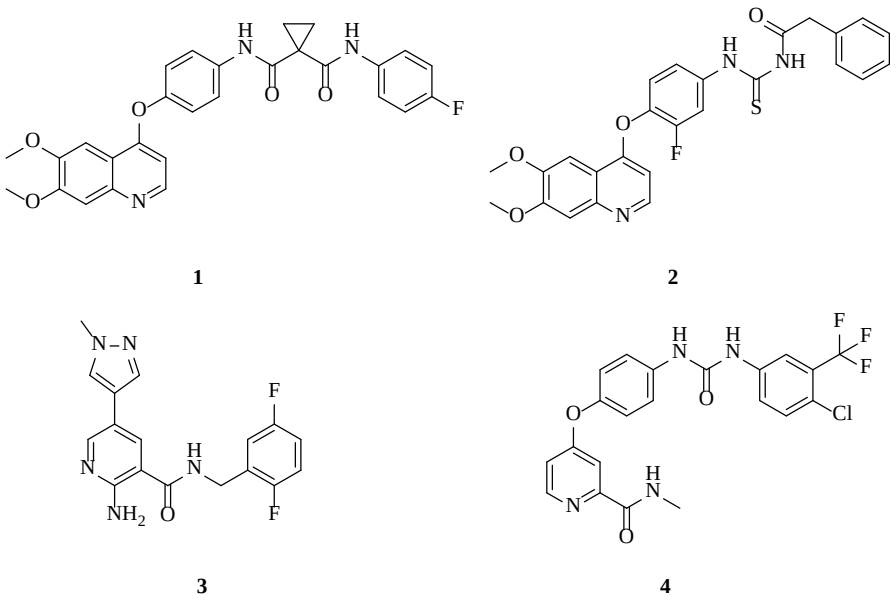

Figure 1. Some representative c-Met inhibitors bearing the intermediate.

2. Materials and Methods

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

3. Synthesis of compounds

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

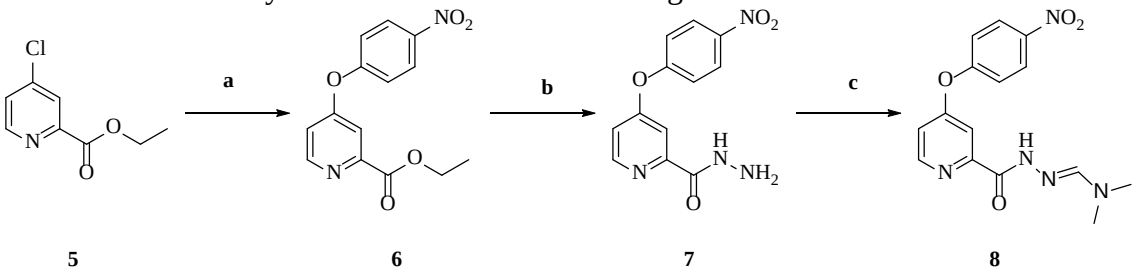

Figure 2. The synthetic route.

Reagents and conditions: (a) 4-nitrophenol, chlorobenzene 130 ºC, 12 h; (b) $NH_2NH_2 \cdot H_2O$, DCM, rt, 2 h; (c) DMF-DMA, CH_3CN, 50 ºC, 3 h

3.1 Synthesis of ethyl 4-(4-nitrophenoxy) picolinate (6)

A solution of ethyl 4-chloropicolinate (5) (10.0 g, 0.054 mol), 4-nitrophenol (11.3 g, 0.080 mol) and chlorobenzene (100 mL) was stirred at 130 ºC for 12 h. After cooling to room temperature, the mixture was concentrated under vacuum. The residue was dissolved in DCM (100 mL), and then extracted with saturated aqueous K_2CO_3 (3×100 mL). The extracting solution was concentrated and dried to obtain yellow solid ethyl 4-(4-nitrophenoxy) picolinate (6) (8.5 g). Yield 54.7%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (d, J = 5.5 Hz, 1H), 8.34 (d, J = 9.2 Hz, 2H), 7.65 (d, J = 2.5 Hz, 1H), 7.45 (d, J = 9.1 Hz, 2H), 7.38 (dd, J = 5.5, 2.5 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.0 Hz, 3H). MS (ESI): m/z $[M + H]^+$ 288.26.

3.2 Synthesis of 4-(4-nitrophenoxy) picolinohydrazide (7)

Appropriate 80% hydrazine hydrate (25 mL) was added slowly to a stirred solution of ethyl 4-(4-nitrophenoxy) picolinate (6) (5.8 g, 0.020 mol) and DCM (100 mL) at room temperature. TLC indicated that the reaction had gone to completion after 2 h. The reaction was then washed with brine (3×100 mL). Organic layer was concentrated and dried to obtain yellow solid 4-(4-nitrophenoxy) picolinohydrazide (**7**) (3.8 g). Yield 69.5%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.59 (d, *J* = 5.6 Hz, 1H), 8.35 (d, *J* = 9.2 Hz, 2H), 7.52 (d, *J* = 2.3 Hz, 1H), 7.45 (d, *J* = 9.2 Hz, 2H), 7.31 (dd, *J* = 5.6, 2.6 Hz, 1H), 4.58 (d, *J* = 4.3 Hz, 2H). MS (ESI): m/z [M + H] $^+$ 274.24.

3.3 Synthesis of (*E*)-*N*, *N*-dimethyl-*N*'-(4-(4-nitrophenoxy) picolinoyl) formohydrazonamide (8)

A mixture of 4-(4-nitrophenoxy) picolinohydrazide **(7)** (3.00 g, 0.011 mol), CH_3CN (20 mL), and DMF-DMA (3.94 g, 0.033 mol) were added into the flask and stirred in 50 ºC for 2 h. The mixture was concentrated under vacuum. The residue was washed with water, filtered, and dried to obtain yellow solid (*E*)-*N*, *N*-dimethyl-*N*'-(4-(4-nitrophenoxy) picolinoyl) formohydrazonamide (8) (2.52 g). Yield 69.6%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.59 (d, *J* = 5.5 Hz, 1H), 8.35 (d, *J* = 9.1 Hz, 2H), 8.05 (s, 1H), 7.53 (d, *J* = 2.6 Hz, 1H), 7.46 (d, *J* = 9.1 Hz, 2H), 7.30 (dd, *J* = 5.4, 2.6 Hz, 1H), 2.82 (s, 6H).MS (ESI): m/z [M + H]$^+$ 314.30.

4. Conclusions

In conclusion, (*E*)-*N*, *N*-dimethyl-*N*'-(4-(4-nitrophenoxy) picolinoyl) formohydrazonamide was synthesized by three steps nucleophilic substitution of ethyl 4-chloropicolinate. The synthetic method of the intermediate and the reaction conditions were optimized, the yield of the product was much higher. The structure of intermediate was confirmed by MS spectrum.

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