Synthesis of 4-(4-aminophenoxy)-N-propylpicolinamide
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Abstract. 4-(4-aminophenoxy)-N-propylpicolinamide 4 is an important intermediate for the synthesis of many biologically active compounds. The compound 4-(4-aminophenoxy)-N-propylpicolinamide was obtained by three simple steps to synthesis from picolinic acid. In this paper, three novel 3-phenyl-1\textsubscript{H}-pyrazole derivatives were prepared. The structure was confirmed by MS and \textsuperscript{1}H NMR. Furthermore, the synthetic method was optimized. The total yield of the target product was 80%.

Introduction
Cancer is one of the most serious diseases that threaten human life. Fast-paced life, high pressure work and disorganized lifestyle all increase our chances of getting cancer. In the same time the changing of the environment make the kinds of cancers more complex and changeable [1-3]. Traditional cancer treatment is mainly based on surgery, radiotherapy and chemotherapy. However, Most of the cancers are not obvious in the earlier stage, absolute cure is not easy for traditional therapies, and the toxic side-effect is too harmful to recover [4-5]. In recent years, with the progress of molecular biology research, molecular targeted therapy has become a hot spot as a new biological treatment method. Compared with traditional chemotherapeutic drugs, antitumor therapy designed for specific molecular target of tumor has the advantages of strong specificity, obvious curative effect and less damage to normal tissues [6-7]. 4-chloropyridine derivatives are important intermediates for many small molecule inhibitors, all of which have good pharmacokinetic activity. There are many signaling pathways in our body that affect the growth, metastasis, proliferation and proliferation of cancer cells. Small molecule inhibitors can prevent cell growth by combining with small signaling pathways and promote cell apoptosis. Part of the highly potently and selectively small molecule inhibitors are shown in Figure 1, those compounds content the fraction of 4-(4-aminophenoxy)-N-propylpicolinamide all have great curative effect. Our synthetic 4-(4-aminophenoxy)-N-propylpicolinamide 4 derivatives are an essential integral part of many similar small molecule inhibitors. There are many reported synthesis methods, most exist in shortcomings of long synthetic route, low yield, and harmful to the environment [8-9]. To solve those problems, this study designed and optimized the synthetic route and method of 4-(4-aminophenoxy)-N-propylpicolinamide derivatives. The 4-(4-aminophenoxy)-N-propylpicolinamide 4 was synthesized from 4-chloropicolinic acid main via nucleophilic substitution reaction. Make it more suitable for industrial production.
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).

Synthesis of Compounds

The structures and the synthetic route were shown in Scheme 1 [10-12].

Reagents and conditions: (i) NaBr, SOCl₂, 85 °C, reflux, 1 h; (ii) CH₃NH₂, CH₂Cl₂, 80 °C, 2 h. (iii) KI, DMSO, 0 °C. (iv) p-aminophenol, Potassium tert-butoxide, N₂, rt.

Synthesis of 4 - chloropicolinoyl Chloride 2

To the mixture of NaBr (0.42 g, 0.004 mol) and picolinic acid (5.00 g, 0.04 mol), in chlorobenzene (40 mL). After stirring for 0.5 h at 50 °C, dilute SOCl₂ and phosphorus oxychloride was added slowly with stirring maintaining the temperature at 50 °C, raise the temperature to 85 °C. Reaction was complete by TLC analysis, filtration, take filtrate, the filtrate was concentrated under reduced pressure to afford product as yellow viscous oil and was used for next step without further purification. yield 94.0 %. MS (ESI): m/z [M+H] + 174.96.

Fig.1. Structure of small molecule inhibitors.
Synthesis of 4-chloro-N-propylpicolinamide 3

The CH₂Cl₂ (30 mL) was transferred to a beaker and 4-chloropicolinoyl chloride (3.00 g, 0.017 mol) was added slowly with stirring at a temperature below 0 °C for 20 minutes followed by the addition of propylamine (30 %), the reaction was stirred at 0 °C for 4.5 hours. The reaction was completed by TLC analysis. The reaction mixture was added to the right amount of water and extracted with ethyl acetate extraction 2-3 times. The organic phase was taken and then concentrated under reduced pressure to give the product as a yellow viscous oil, yield : 89 %. MS (ESI): m/z [M+H] + 198.06.

Synthesis of 4-(4-aminophenoxy)-N-propylpicolinamide 4

Under nitrogen protection, 2 p-aminophenol (2.50g, 0.023mol) and potassium tert-butoxide (3.39 g, 0.03 mol) were mixed and stirred for 1.5-2 h at room temperature, this is solution A. At the same time, KI (0.33 g, 0.002mol) and 4-chloro-N-propylpicolinamide (3.00 g, 0.015mol) were dissolved in DMSO (30 mL) and stirred at room temperature for 30 minutes, this is solution B. Then the reaction solution B was slowly added to the reaction solution A and stirred at room temperature for 3-4 h. The reaction was completed by TLC analysis. The reaction solution was added to NaCl and extracted with ethyl acetate. The organic layer was dried over by anhydrous Na₂SO₄ and concentrated under a reduced pressure to afford 4-(4-aminophenoxy)-N-propylpicolinamide as a yellow viscous oil, yield : 86.5%. 1H NMR (400 MHz, DMSO-d₆) δ 8.76 (s, 1H), 8.46 (d, J = 4.9 Hz, 1H), 7.35 (s, 1H), 7.03 (dd, J = 29.1, 20.4 Hz, 2H) 6.65 (d, J = 5.9 Hz, 1H), 6.49 (dd, J = 36.0, 10.6 Hz, 2H), 5.52 (s, 2H), 3.21 (d, J = 6.8 Hz, 2H), 1.51 (dd, J = 14.3, 7.2 Hz, 2H), 0.84 (t, J = 7.3 Hz, 3H). MS (ESI): m/z [M+H] + 271.13.

Conclusions

In conclusion, the compound 4 4-(4-aminophenoxy)-N-propylpicolinamide was prepared by nucleophilic substitution reaction through three steps. The synthetic method and the reaction’s conditions was optimized, the yield of the product was higher than others, and making it more suitable for industrial production. It structure was confirmed by MS and 1H NMR spectrum.

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References


