Advances in Biological Sciences Research (ABSR), volume 6
2017 2nd International Conference on Biological Sciences and Technology (BST 2017)

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

He-hua XIONG, Jia ZHI, Yin-mei ZHUANG, Meng-zi CHEN, Yin-hua XIONG[1,a] and Qi-dong TANG[1,b,*]

School of Pharmacy, Jiangxi Science & Technology Normal University, Nanchang 330013, China

[a]axiongyhfriend@126.com, [b]tangqidongcn@126.com,

*Corresponding author

Keywords: 4-(4-aminophenoxy)-*N*-propylpicolinamide, Synthesis.

Abstract. 4-(4-aminophenoxy)-*N*-propylpicoliamide 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*H*-pyrazole derivatives were prepared. The structure was confirmed by MS and ^{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.

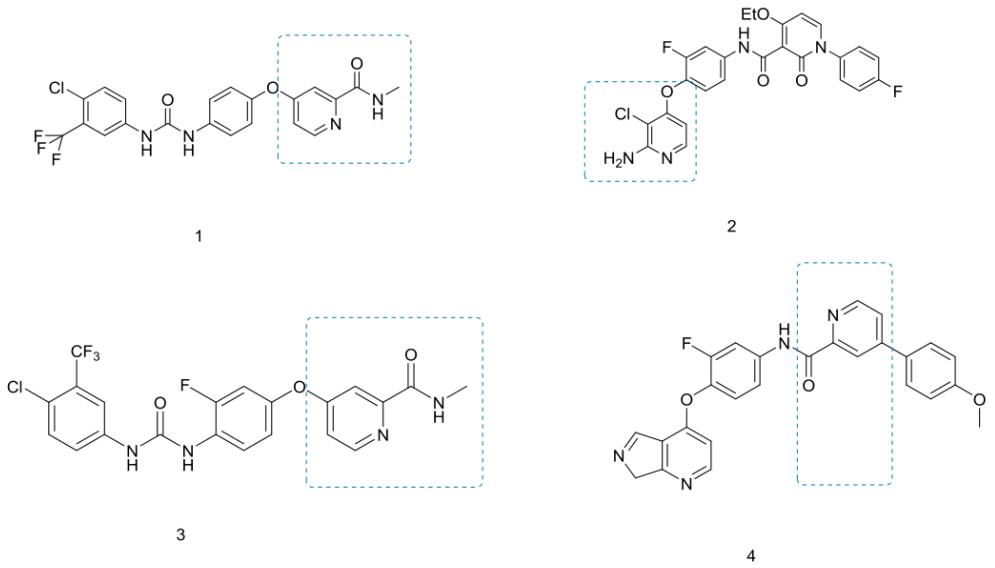


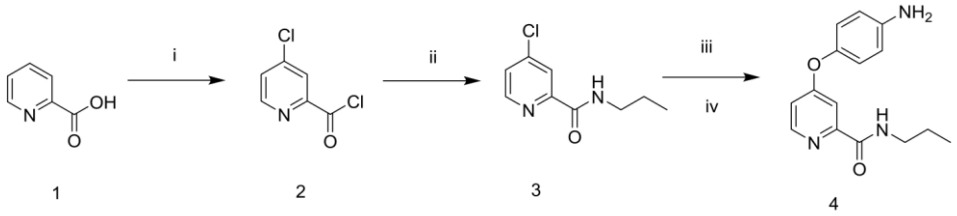
Fig.1. Structure of small molecule inhibitors.

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].



Scheme 1. The synthetic route of compound 4

Reagents and conditions: (i) NaBr, $SOCl_2$,85 ℃, reflux, 1 h; (ii) CH_3NH_2, CH_2Cl_2, 80 ℃, 2 h. (iii) KI, DMSO, 0 ℃. (iv) *p*-aminophenol, Potassium *tert*-butoxide, N_2, 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 ℃, dilute $SOCl_2$ and phosphorus oxychloride was added slowly with stirring maintaining the temperature at 50 ℃, raise the temperaturethe to 85 ℃. 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.

Synthesis of 4-chloro-N-propylpicolinamide 3

The CH_2CI_2 (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 ℃ for 20 minutes followed by the addition of propylamine (30 %) , the reaction was stirred at 0 ℃ 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 Na_2SO_4 and concentrated under a reduced pressure to afford 4-(4-aminophenoxy)- *N*- propylpicolinamide as a yellow viscous oil, yield : 86.5%. ^{1}H NMR (400 MHz, DMSO-d_6)) 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 ^{1}H NMR spectrum.

Acknowledgments

We gratefully acknowledge the generous support provided by National Natural Science Foundation of China (NSFC No. 81660572), Natural Science Foundation of Jiangxi Province (20171BAB215071), and Top-notch talent project of Jiangxi Science & Technology Normal University (2016QNBJRC002).

References

[1] Helleberg, Marie, et al. "Mortality attributable to smoking among HIV-1–infected individuals: a nationwide, population-based cohort study." Clinical Infectious Diseases 56.5 (2012): 727-734.

[2] Chien, Tiffany, Anjali Doshi, and Tal Danino. "Advances in Bacteria Cancer Therapies using Synthetic Biology." Current Opinion in Systems Biology (2017).

[3] Zhu, Yuan, et al. "Smad3 mutant mice develop metastatic colorectal cancer." Cell 94.6 (1998): 703-714.

[4] Paez, J. Guillermo, et al. "EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy." Science304.5676 (2004): 1497-1500.

[5] Semenza, Gregg L. "Targeting HIF-1 for cancer therapy." Nature reviews cancer 3.10 (2003): 721-732.

[6] Zhang, Jianming, Priscilla L. Yang, and Nathanael S. Gray. "Targeting cancer with small molecule kinase inhibitors." Nature Reviews Cancer 9.1 (2009): 28-39.

[7] Taldone, Tony, et al. "Targeting Hsp90: small-molecule inhibitors and their clinical development." Current opinion in pharmacology 8.4 (2008): 370-374.

[8] Zhao, Wei, et al. "Sorafenib induces apoptosis in HL60 cells by inhibiting Src kinase-mediated STAT3 phosphorylation." Anti-cancer drugs 22.1 (2011): 79-88.

[9] Zhang, Dengyou, et al. "Discovery of novel 2-aminopyridine- 3-carboxamides as c-Met kinase inhibitors." Bioorganic & medicinal chemistry 20.17 (2012): 5169-5180.

[10] Wang, Xiaoqiang, et al. "Design, synthesis and biological evaluation of novel 4-(2-fluorophenoxy) quinoline derivatives as selective c-Met inhibitors." Bioorganic & medicinal chemistry 25.3 (2017): 886-896.

[11] Qiang, Hao, et al. "Design, synthesis and biological evaluation of 4-aminopyrimidine-5-cabaldehyde oximes as dual inhibitors of c-Met and VEGFR-2." Bioorganic & medicinal chemistry24.16 (2016): 3353-3358.

[12] Gu, Weijie, et al. "Discovery of novel 2-substituted-4-(2-fluorophenoxy) pyridine derivatives possessing pyrazolone and triazole moieties as dual c-Met/VEGFR-2 receptor tyrosine kinase inhibitors." Bioorganic Chemistry 72 (2017): 116-122.