Synthesis of ethyl 4-(2-fluoro-4-nitrophenoxy) picolinate

Jintian Dai, Jianqing Zhang, Meng Liu, Yan Zhang, Han Zhang, Qidong Tang, Pengwu Zheng*

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

Abstract. Cancer has seriously affected people's production and life. The appearance of anti-cancer drugs has brought good news to people. Ethyl 4-(2-fluoro-4-nitrophenoxy) picolinate is an important basic skeleton of a small molecule inhibitor of c-Met and a major intermediate in cancer therapy. A rapid and efficient method for the synthesis of compound 8 was established. Compound 8 was synthesized from picolinic acid by acylation and substitution. These steps were weight gain reaction. The synthesis method was optimized and the structure was confirmed by hydrogen NMR spectroscopy.

1. Introduction

Cancer [1] is a deadly disease with increasing morbidity and mortality, which seriously endangers the normal life and health of human beings. The main causes of cancer [2] are abnormal mutations in genes that control cell proliferation, metabolism, death and DNA repair. The interstitial epithelial transformation factor (MET) gene, located in the long arm of human chromosome 7, contains 21 exons and is a receptor tyrosine kinase for hepatocyte growth factor (HGF) [3, 4]. Binding of MET to HGF activates RAS-MAPK and PI3K-AKT signaling pathways involved in tumorigenosis and metastasis. c-MET is a transmembrane receptor with self-phosphorylation activity encoded by the MET gene, which is a key factor in embryonic development, organ regeneration and wound healing. Abnormal forms of the MET gene are mutated, amplified, rearranged, and overexpressed. MET rearrangement is very rare in lung cancer. Abnormal activation of c-Met signaling pathway is involved in the formation, metastasis and invasion of various malignant tumors. Therefore, c-Met has attracted great attention as an anticancer drug target, which has led to a large number of studies on abnormal activation of c-Met kinase inhibitors in order to block the c-Met signaling pathway [5, 6].

4-(2-fluorophenoxy)pyridine is a common basic skeleton in many C-Met-related small molecule inhibitors that have emerged in recent years. We list some anticancer drugs that have this skeleton. The structure of these compounds is shown in Figure 1. *N*-(4-(4-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)phenoxy)pyridin-2-yl)acetamide [7], *N*-(4-(2-fluoro-4-((3-(4-fluorophenyl)-4-oxo-1,4-dihydro-1,6-naphthyridin-5-yl)amino)phenoxy)pyridin-2-yl)cyclopropanecarboxamide [8], *N*-(3-fluoro-4-((2-(4-(4-methylpiperazin-1-yl)-4*H*-1,2,4-triazol-3-yl)pyridin-4-yl)oxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide [9], *N*-(4-((2-amino-3-chloropyridin-4-yl)oxy)-3-fluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide [10] are small molecules with a 4-(2-fluorophenoxy)pyridine backbone. The synthesis route in the literature is flawed. These reaction temperatures are high, the reaction time is too long, and the byproducts are harmful to the environment.

In addition, ethyl 4-(2-fluoro-4-nitrophenoxy)picolinate is an important intermediate in many tumor inhibitors, such as lung cancer and colon cancer. During the experiment, the synthesis of ethyl 4-(2-fluoro-4-nitrophenoxy)picolinate was optimized to make it more suitable for industrial production. The operation time is short, the effect is obvious, and the quality is good, the temperature is controllable.

* Corresponding author: Zhengpw@126.com

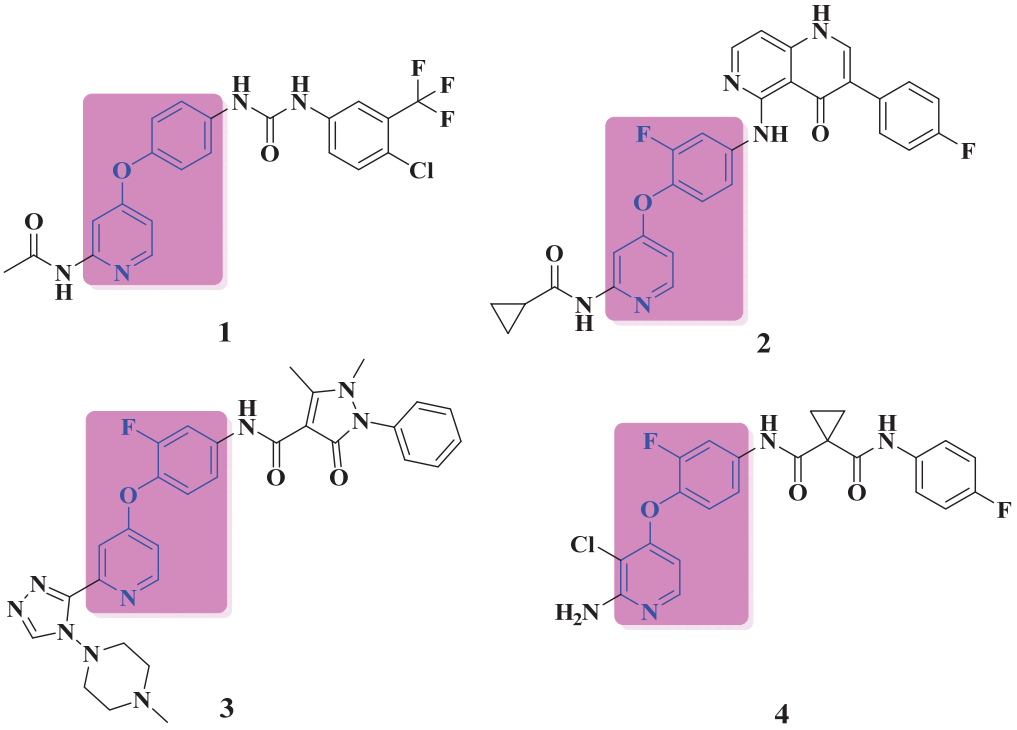

Figure 1. Anticancer drugs containing the 4-(2-fluorophenoxy) pyridine skeleton

2. Materials and methods

All reagents and solvents purchased do not require further purification. Nuclear magnetic resonance (^{1}H NMR) spectra of the compounds were recorded using tetramethylsilane (TMS) as internal standard by Bruker 400 MHz spectrometer (Bruker Bioscience, Billerica, MA, USA). Mass spectra were obtained in ESI mode on Agilent 1100 LC-MS (Agilent, Palo Alto, California, USA). Thin layer analysis was performed using silica gel plate GF254 (Qingdao Haiyang Chemical Industry, China).

3. Synthesis of compounds

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

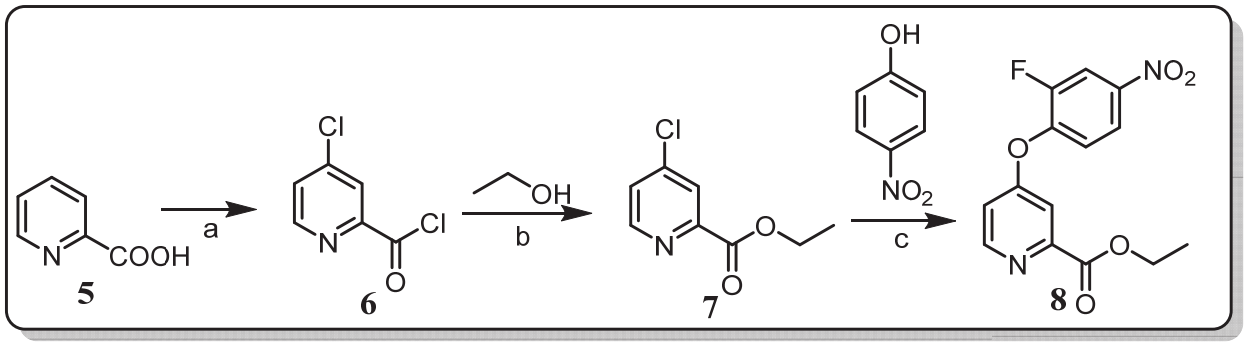

Figure 2. The synthetic route of compounds 6-8

Reagents and conditions: (a) DMF, sulfoxide chloride, 80 °C, 1.5 h; (b) triethylamine, dichloromethane, ethanol, rt, 0.5 h; (c) KI, chlorobenzene, 2-fluoro-4-nitrophenol, 120 °C, 5 h

4. 4-chloropicolinoyl chloride (6)

Picolinic acid (3 g) was put it into a round-bottomed flask with $SOCl_2$ (8-10 mL) as solvent. After the addition, the reaction solution turned green. The reaction solution was heated in an oil bath to 80 °C, and DMF was added after half an hour. The point plate observed that the reaction liquid was cooled at the end of the reaction, then the solvent $SOCl_2$ was removed by spin evaporation to obtain yellow oily liquid **6**. The final recorded yield was 3.42 g, and the actual yield was 79.7%.

* Corresponding author: Zhengpw@126.com

5. ethyl 4-chloropicolinate (7)

Triethylamine (3.75 g, 1.2 mol) and ethanol (3.58 g, 4 mol) were weighed into a beaker where long stirred bars were present, CH_2Cl_2 (20 mL) was used as a solvent, and this part was used as a reaction system 1. Compound **6** was dissolved with methylene chloride as reaction system 2. Reaction system 2 was dropped into reaction system 1 (drop by drop), and the white gas produced during the reaction was blown off with an ear wash ball. Reaction half an hour to process, appropriate amount of saturated sodium bicarbonate solution was added to the reaction solution and extracted with methylene chloride. After extraction, yellow oily liquid **7** was concentrated. The theoretical value is 3.59 g, the yield is 71.3%, and the measured value is 2.56 g.

6. ethyl 4-(2-fluoro-4-nitrophenoxy) picolinate (8)

KI (0.20 g, 0.1 mol) and 2-fluoro-4-nitrophenol (3.69 g, 1.7 mol) were added to the reaction bottle with chlorobenzene (12 mL) as solvent, and the reaction was placed in 120 ℃ oil bath for 5 hours. After the reaction was stopped, the reaction solution was poured into a certain amount of petroleum ether while hot (chlorobenzene was removed) and repeated for 3 times, and the supernatant was discarded. An appropriate amount of sodium hydroxide solution was added to the collected crude product, extracted with methylene chloride, finally concentrated to obtain compound **8**. The theoretical value is 4.23 g, the yield is 69.3%, and the measured value is 2.93 g.

7. ethyl 4-(2-fluoro-4-nitrophenoxy) picolinate (8)

Light yellow solid. The yield was 66.4%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (d, J = 5.5 Hz, 1H), 8.42 – 8.31 (m, 2H), 7.67 (d, J = 2.5 Hz, 1H), 7.48 (d, J = 2.2 Hz, 1H), 7.41 (dd, J = 5.5, 2.5 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H).

8. Conclusion

In general, the production rate of chlorine atoms on the pyridine ring is relatively low, and the chlorine atoms may be replaced in other positions on the ring, resulting in the difficulty in the establishment of the basic skeleton behind, and finally, we can't get the intermediate we want. The optimization of the synthesis method is beneficial to shorten the reaction time, maintain the mild reaction temperature and small byproducts, so as to improve the yield of target compound **8**. Its structure was confirmed by hydrogen ^{1}H NMR spectroscopy.

Acknowledgments

We gratefully acknowledge the generous support provided by Natural Science Foundation of Jiangxi, China (No. 20192ACBL21009), National Natural Science Foundation of China (NSFC No. 81660572; NSFC No. 81803369), Natural Science Foundation of Jiangxi Province (20171BAB215071), Top-notch talent project of Jiangxi Science& Technology Normal University (2016QNBJRC002), and Jiangxi Provincial Key Laboratory of Drug Design and Evaluation (20171BCD40015). Thanks to the Special Innovation Fund of Jiangxi Science and Technology Normal University (YC2021-S747).

References

1. Torre, L.A., Siegel, R.L., Ward, E.M., et al.Global Cancer Incidence and Mortality Rates and Trends--An Update [J]. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, 2016, 25(1): 16-27.
2. Graham, T.A., Sottoriva, A.Measuring cancer evolution from the genome [J]. The Journal of pathology, 2017, 241(2): 183-191.
3. Fu, J., Su, X., Li, Z., et al.HGF/c-MET pathway in cancer: from molecular characterization to clinical evidence [J]. Oncogene, 2021, 40(28): 4625-4651.
4. Zhao, Y., Ye, W., Wang, Y.D., et al.HGF/c-Met: A Key Promoter in Liver Regeneration [J]. Frontiers in pharmacology, 2022, 13: 808855.
5. Wang, Q., Yang, S., Wang, K., et al.MET inhibitors for targeted therapy of EGFR TKI-resistant lung cancer [J]. Journal of hematology & oncology, 2019, 12(1): 63.
6. Zhao, S., Wu, W., Jiang, H., et al.Selective Inhibitor of the c-Met Receptor Tyrosine Kinase in Advanced Hepatocellular Carcinoma: No Beneficial Effect With the Use of Tivantinib? [J]. Frontiers in immunology, 2021, 12: 731527.
7. Machado, V.A., Peixoto, D., Costa, R., et al.Synthesis, antiangiogenesis evaluation and molecular docking studies of 1-aryl-3-[(thieno[3,2-b]pyridin-7-ylthio)phenyl]ureas: Discovery of a new substitution pattern for type II VEGFR-2 Tyr kinase

inhibitors [J]. Bioorganic & medicinal chemistry, 2015, 23(19): 6497-6509.

8. Wang, M.S., Zhuo, L.S., Yang, F.P., et al.Synthesis and biological evaluation of new MET inhibitors with 1,6-naphthyridinone scaffold [J]. European journal of medicinal chemistry, 2020, 185: 111803.
9. Gu, W., Dai, Y., Qiang, H., 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 [J]. Bioorganic chemistry, 2017, 72: 116-122.
10. Zhuo, L.S., Xu, H.C., Wang, M.S., et al.2,7-naphthyridinone-based MET kinase inhibitors: A promising novel scaffold for antitumor drug development [J]. European journal of medicinal chemistry, 2019, 178: 705-714.