Synthesis of Pyridinium Pyrimidines C-Met Small Molecule Inhibitors

Hehua Xiong, Fu Peng, Fajuan Tian, Qidong Tang* and Pengwu Zheng*

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

*zhengpw@126.com, tangqidongcn@126.com, a18296154955@163.com

Abstract. Cancer has gradually become a serious threat to human health, and molecular targeted therapy has largely broken through the shortcomings of traditional treatment methods. C-met has been found to be overexpressed in a variety of cancer cells, and inhibition of its signaling pathway can effectively inhibit the occurrence of cancer. To explore the structure-activity relationship of the pyridinium pyrimidine c-met small molecule inhibitors, we synthesized the final compound A.

1. Introduction
The number of new global cancer cases in 2014 was about 14 million, according to the World Health Organization. It is estimated that the estimated number of deaths will rise from 8.2 million to 13 million in the next 20 years [1]. In recent years, with the in-depth study of the analytical signaling pathway, it has been revealed that the receptor tyrosine kinase (RTK) family regulates the transduction pathways of various cellular processes, including cell proliferation, differentiation, migration, metabolism, and cell cycle control [2-6]. Abnormal activation, disorder, genetic alteration or mutation of RTK is closely related to the development of cancer and many other diseases [7]. The pharmacological inhibition of these receptor tyrosine kinases has been recognized as an emerging strategy for targeted cancer therapy over the past 20 years. The discovery and development of novel small molecule receptor tyrosinase inhibitors has become a hot topic [8-10]. Among them, c-Met receptor tyrosine kinase was found to be highly expressed in malignant tumors, and excessive signaling of its signaling pathway is involved in tumor cell growth, invasion, metastasis and apoptosis, and may interact with signaling pathways. C-Met kinase acts as a target for antigens. [11-13].

A portion of potent and selective c-met small molecule inhibitors is shown in Figure 1 [14-17]. These compounds containing pyrrolopyrimidine fragments have a good inhibitory effect. In order to investigate the structure-activity relationship of small pyrimidine inhibitors, we synthesized a small molecule inhibitor A of c-met with pyrrolopyrimidine as the core.
2. 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).

3. Synthesis of Compounds
The structures and the synthetic route were shown in Scheme 1.

Reagents and conditions (i) THF, CH3I, NaH, rt; (ii) diphenyl ether, KI, 135 °C, reflux, 6 h; (iii) methanol: ethanol = 1:1, active C, FeCl₃·6H₂O, hydrazine hydrate (80%), 85 °C, reflux. (iv)DMF, triethylamine, dichloromethane, oxalyl chloride,rt.
4. Synthesis of 4-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidine 2

Compound 1 was dissolved in tetrahydrofuran, sonicated until Compound 1 was completely dissolved, and stirred under ice bath for 10 minutes. Sodium cyanide was added in portions to the reaction solution. The reaction was completed by stirring at room temperature for 0.5 hours. Finally add potassium iodide and stirring at room temperature. The reaction was completed by TLC analysis. The reaction mixture was suction filtered, and the filtrate was evaporated to dryness to afford compound 2 as a white solid. Yield: 90 %. MS (ESI): m/z [M+H] +167.03

5. Synthesis of 4-(2-fluoro-4-nitrophenoxy)-7-methyl-7H-pyrrolo[2,3-d]pyrimidine 3

The compound was dissolved in diphenyl ether at 100 °C, then the system was warmed to 135 °C and condensed and refluxed. After adding KI, the mixture was stirred at a constant temperature for 0.5 hour. Then 2-fluoro-4-nitrophenol was added at 135 °C and stirring was continued until the reaction was completed. The reaction was completed by TLC analysis. The reaction mixture was added to an appropriate amount of water and extracted with ethyl acetate for 2-3 times. The combined organics were concentrated and evaporated to dryness crystals MS (ESI): m / z [M + H] + 288.07

6. Synthesis of 3-fluoro-4-((7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)aniline 4

Compound 3, active C and FeCl3·6H2O were dissolved in a solution of absolute ethanol to methanol in a ratio of 1:1. And then adjust the temperature to 85 °C. After the mixture was refluxed for 0.5 hour, hydrazine hydrate was added dropwise and stirring was continued until the reaction was completed. The reaction was completed by TLC analysis. Heat, the filtrate was collected and concentrated under reduced pressure to give compound 4 as a green solid, yield 98%.m / z [M + H] + 258.26

7. Synthesis of 1-(4-chlorophenyl)-N-(3-fluoro-4-((7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamide A

A 50 mL round bottom flask was taken, compound 4 was dissolved in dichloromethane, and 2 drops of triethylamine were added to the reaction solution to form a reaction solution A. Another 50 mL round bottom flask was taken, namely, compound 5 was dissolved in dichloromethane. 1 drop of DMF was added to form a reaction liquid B in the reaction liquid, and an appropriate amount of oxalyl chloride was added until the reaction liquid had no bubbles. Finally, the reaction liquid B was added dropwise to the reaction liquid A. The reaction was completed by TLC analysis. The reaction solution was directly vacuum-dried and recrystallized to give a light gray compound A. 1H NMR (400 MHz, DMSO d6) δ 11.82 (s, 1H), 9.17 (s, 1H), 8.60 (d, J = 5.7 Hz, 2H), 8.35 (s, 1H), 7.98 (d, J = 12.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 2H), 7.54 (d, J = 10.9 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.45 (s, 1H), 7.44 – 7.39 (m, 1H), 6.62 (d, J = 2.4 Hz, 1H), 3.84 (s, 3H). Yield 80%. 1H NMR (400 MHz, DMSO) δ 11.82 (s, 1H), 9.17 (s, 1H), 8.60 (d, J = 5.7 Hz, 2H), 8.35 (s, 1H), 7.98 (d, J = 12.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 2H), 7.54 (d, J = 10.9 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.45 (s, 1H), 7.44 – 7.39 (m, 1H), 6.62 (d, J = 2.4 Hz, 1H), 3.84 (s, 3H).m / z [M + H] + 540.94

8. Conclusion

The pyrrolopyrimidine small molecule c-met inhibitor A has been synthesized and may contribute to the further development of the activity-activity relationship of the pyridopyrimidine inhibitor. The step refining and high yield synthetic route can further promote the synthesis of pyridinium pyrimidine small molecule inhibitors. Its structure was confirmed by MS and 1H NMR spectrum.

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