Synthesis of 7-chloro-6-fluoro-1-(4-fluorophenyl)-4-oxo-1, 4-dihydro-1, 8-naphthyridine-3-carboxylic acid

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Abstract. 7-chloro-6-fluoro-1-(4-fluorophenyl)-4-oxo-1, 4-dihydro-1, 8-naphthyridine-3-carboxylic acid is an important intermediate for the many biologically active anticancer drugs. In this research, a rapid and efficient synthesis of compounds 7 was established. Compound 7 consisting of methyl (Z)-2-(2, 5-dichloro-6-fluoronicotinoyl)-3-(4-fluorophenyl) (methyl) amino acrylate was synthesized by two steps including substitution and hydrolysis. The synthesis method was optimized, and structure was confirmed by 1H NMR and MS spectrum. The synthesis method is optimized. The total yield of the two steps is 63.69%.

1. Introduction
Cancer is named malignant tumor, which is the second leading cause of death after global cardiovascular disease [1]. The incidence of primary liver cancer is the fourth most common malignant tumor in China, and the tumor mortality rate is even more the third [2-3]. More than 85% of tumor patients belonged to non-small cell lung cancer, which most of patients had developed to the advanced stage of cancer when they were discovered [4]. An important target for anti-tumor therapy is the receptor tyrosine kinase c-Met, which is related to tumor resistance by affecting tumor invasion, metastasis and neovascularization [5]. The ligand for c-Met is HGF, and abnormal activation of Met kinase was found in a variety of malignancies. Met Excessive activation not causes tumorigenesis, development and metastasis, but closely relates to drug resistance of anti-tumor therapy. Therefore, research on HGF/c-Met signaling pathway play an important target for anti-tumor.

Recently, some research have reported on small molecules against cancer containing methyl (Z)-2-(2-chlorobenzoyl)-3-(dimethylamino) acrylate. Moreover, the design and synthesis of this compound derivative as a small molecule inhibitor has been played in the anticancer drugs. The structures of these compounds as shown Fig.1, dimethyl 2-(2-chlorophenyl)-4-hydroxynaphthalene-1,3-dicarboxylate [6], methyl(Z)-2-(3-(3-chloro-2-fluorobenzyl)-2,6-difluorobenzoyl)-3-(ethylamino)acrylate [7], N-4-((2-ethylcarbamoyl)pyridin-4-yl)oxy)phenyl)-2-oxo-1-phenyl-1 [8], 2-dihydro-1,8-naphthyridine-3-carboxamide [9], N-4-((6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1 [10], 1-dicarboxamideMostsyntheticmethodsformethyl(Z)-2-(2-chlorobenzoyl)-3-(dimethylamino)acrylate have been reported, and there are defects in the synthetic route in the literature, including substitution reactions and aldol condensation reactions. While the product and reaction temperature was high and by-products was harmful to the environment.

In addition, methyl (Z)-2-(2-chlorobenzoyl)-3-(dimethylamino) acrylate is an important intermediate for many tumors inhibitor such as breast cancer and Lung cancer. During the experiment, 1-(N, N-dimethyl) amine-2-(o-chlorobenzoyl)-methyl acrylate was optimized and designed to be more in line...
with industrial production. The operation not takes less time but the effect is more obvious, moreover, the quality is better and the temperature is controlled.

![Figure 1. Active compound containing an intermediate](image)

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.

![Scheme 1. The synthetic route of compounds 7](image)

Reagents and conditions: (a) K$_2$CO$_3$, toluene, CS$_2$CO$_3$, 150°C; (b) 1, 4 dioxane, water, NaOH, 85°C.
4. Methyl 7-chloro-6-fluoro-1-(4-fluorophenyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate(6)
Methyl 2-(2, 5-dichloro-6-fluoronicotinoyl)-3-((4-fluo rophenyl) (methyl) amino) acrylate 1.15 g in toluene (8-10 mL), slowly adding K$_2$CO$_3$ (0.4 g, 0.003 mol), CS$_2$CO$_3$ (0.9 g, 0.003 mol), at 150°C, the reaction was judged by TLC, for 24 hours to observe the reaction completely. Post-treatment: The reaction solution was cooled to room temperature, suction filtered, the residue was washed with dichloromethane, and the filtrate was concentrated. The yield was 1 g, and the actual yield was 81%, which was 0.81 g.

5. 7-chloro-6-fluoro-1-(4-fluorophenyl)-4-oxo-1, 4-dihydro-1, 8-naphthyridine-3-carboxylic acid (7)
The product methyl 7-chloro-6-fluoro-1-(4-fluorophenyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate obtained in the previous step is directly adding an appropriate amount of 1,4 dioxane (8-10 mL), add a certain proportion of NaOH (0.37g) and an appropriate amount of water (2 mL), and the reaction time at 85°C is 10 h. Post-treatment: The reaction was completed, spin-dried, an appropriate amount of saturated brine was added, and the mixture was adjusted to pH 3-4 with HCl in a beaker, and filtered to give an orange-red solid. The theoretical value was 0.77 g, the yield was 81%, and the actual value was 0.63 g.

6. 7-chloro-6-fluoro-1-(4-fluorophenyl)-4-oxo-1, 4-dihydro-1, 8-naphthyridine-3-carboxylic acid (7)
Orange solid. The yield was 65.6%. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 15.16 (d, $J = 7.2$ Hz, 1H), 8.63 (s, 1H), 8.04 (d, $J = 10.5$ Hz, 1H), 7.64 (d, $J = 4.4$ Hz, 2H), 7.41 (s, 2H).

7. Conclusion
Typically, 7-chloro-6-fluoro-1-(4-fluorophenyl)-4-oxo-1, 4-dihydro-1, 8-naphthyridine-3-carboxylic acid are synthesized by two steps including substitution and hydrolysis. The optimization of the synthesis method is instrumental for shorting reaction time, maintaining mild temperature as well as the small by-products and then the yield of the target compound 7 is high. Its structure was confirmed by $^1$H NMR.

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References
[1] Obstetrics and Gynecology Branch of Chinese Medical Association Obstetrics and Gynecology Branch. Guidelines for prevention and treatment of postpartum hemorrhage [J]. Chinese Journal of Obstetrics and Gynecology, 2014, 49 (9): 641 - 646.
[2] Shirasu N, Yamada H, Shibaguchi H, et al. Molecular Characterization of a fully Human Chimeric T-cell Antigen Receptor for Tumor Associated Antigen EPCAM [J]. Journal of Biomedicine Biotechnology, 2012, (6): 853-879.
[3] Guest RD, Hawkins RE, Kirillova N, et al. The role of extracellular spacer regions in the optimal design of Chimeric immune receptors: evaluation of four different scFrs and antigens [J]. Journal of Immunotherapy, 2005 28 (3): 203 - 211.
[4] Zhou Ning, Liang Ailing, et al. Advances in research on EGFR-KTI resistance mechanism and its countermeasures in non-small cell tumors [J]. Guangdong Medical Journal, 2013 35 (19): 3109 - 3117.
[5] Maroun CR, Rowlands T. The Met receptor tyrosine kinase: a key player in oncogenesis and drug resistance [J]. Pharmacol Ther, 2014, 142 (3): 316 - 338.

[6] Gao, Hongyin, and L. Kurti. "TRANSITION METAL FREE METHODS OF SYNTHESIS OF BIARYL COMPOUNDS.", 2017, 837 (19): 20 - 26.

[7] Mohareb, Rafat M., F. O. A. Farouk, and W. W. Wardakhan. "Uses of dimedone for the synthesis of new heterocyclic derivatives with anti-tumor, c-Met, tyrosine, and Pim-1 kinases inhibitions." Medicinal Chemistry Research 2018, 27 (8): 1984 - 2003.

[8] Li, Sai, et al. "ChemInform Abstract: Synthesis and Antitumor Activity of Novel 4-(2-Fluorophenoxy)quinoline Derivatives Bearing the 4-Oxo-1,4-dihydroquinoline-3-carboxamide Moiety." Archiv Der Pharmazie 2013, 346 (7): 521 - 533.

[9] Duan, Y, et al. "Discovery of novel 2-substituted-4-phenoxy pyridine derivatives as potential antitumor agents." Bioorganic & Medicinal Chemistry Letters 2017, 28 (3): 12 - 16.

[10] Lien, V. T., J. Klaveness, and D. E. Olberg. "One-step synthesis of [18 F] cabozantinib for use in positron emission tomography imaging of c-Met." Journal of Labelled Compounds & Radiopharmaceuticals 2017, 39 (6): 30 - 39.