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

3-(2-chloro-5-fluoropyrimidin-4-yl)-1-methyl-1*H*-indole

Wen-sheng ZOU[1, a], Hong ZHANG[1], Shuang JIA[1], Wu-fu ZHU[1,a] and Shan XU[1,b,*]

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

[a]zhuwufu-1122@163.com, [b]shanxu9891@126.com

*Corresponding author

Keywords: 3-(2-chloro-5-fluoropyrimidin-4-yl)-1-methyl-1*H*-indole, synthesis

Abstract: 3-(2-chloro-5-fluoropyrimidin-4-yl)-1-methyl-1*H*-indole is an important intermediate in many bioactive compounds, such as osimertinib. In this task, a new intermediate is synthesized (a fluorine attached to the pyrimidine ring). The compound is synthesized from commercially available 1*H*-indole through two-step substitution. The structures and the synthetic route were determined by MS and ^{1}HNMR.And the synthetic method was optimized. The method for synthesizing 3-(2-chloro-5-fluoropyrimidin-4-yl) -1-methyl-1*H*-indole has low environmental pollution and high purity of the synthesized product.

Introduction

Tumor is a new organism formed by various kinds of tumorigenic factors under the action of various tumorigenic factors [1-2]. Localized cells lose their normal regulation of their growth at the gene level resulting in abnormal proliferation and differentiation [3].Once a new organism is formed, it does not stop growing due to the etiological factor, and its growth is not affected by the normal physiological regulation of the body [4]. It destroys the normal tissues and organs, which is especially noticeable in malignant tumors. Although efforts have been made to find and develop small molecule anticancer drugs in the past decade, it is still urgent to develop new antitumor drugs with good tumor selectivity, high efficiency and safety [5-7].

Many 3-(2-chloro-5-fluoropyrimidin-4-yl)-1-methyl-1*H*-indole derivatives which exhibited potential biological activities, such as (*E*)-*N*-(4-((3-chloro -4-fluorophenyl)amino)-7-((tetrahydrofuran-3-yl)oxy)quinazolin-6-yl)-3-(dimethylam ino)acrylamide(Afatinib, compound 1)[8], *N*-(4- ((3-chloro-4- fluorophenyl) amino)-7-(3 -morpholinopropoxy)quinazolin-6-yl)acrylamide (Canertinib compound **2**)[9], (*E*)-*N*-(4-((3-chloro-4-fluorophenyl)amino) -7-methoxyquinazolin- 6-yl)-4-(piperidin- 1-yl)but-2-enamide(Dacamitinib compound **3**)[10]. Therefore, 3-(2-chloro-5-fluoropyrimidin-4-yl)-1-methyl-1H-indole is a very important intermediate.

The second generation of EGFR-TKI is represented by Afatinib (compound 1) and Dacomitinib (compound 3) [11]. Both are irreversible inhibitors of EGFR and HER2. In addition to competitively occupying the ATP binding site on EGFR, the therapeutic mechanism can also alkylate or covalently bind with the specific amino acid residues in the vicinity of the opening of the EGFR binding pocket so as to achieve irreversible inhibition of EGFR. With the continuous use of the first generation of reversible EGFR-TKI, increasingly prominent drug resistance becomes an unavoidable problem. The T790M mutation is the most common cause of resistance to EGFR-TKI therapy and about 50% of clinically resistant patients have the EGFR T790M mutation.

Irreversible EGFR-TKI can cope with the problems caused by the above mutations by covalent binding, dramatically increase drug concentration and provide a sustained blocking effect, and prolong the inhibition of tumor cells. In addition, the first generation of EGFR-TKI brought some problems such as the obvious skin toxicity (acne-like rash). The second generation of EGFR-TKI in this area has been better improved.

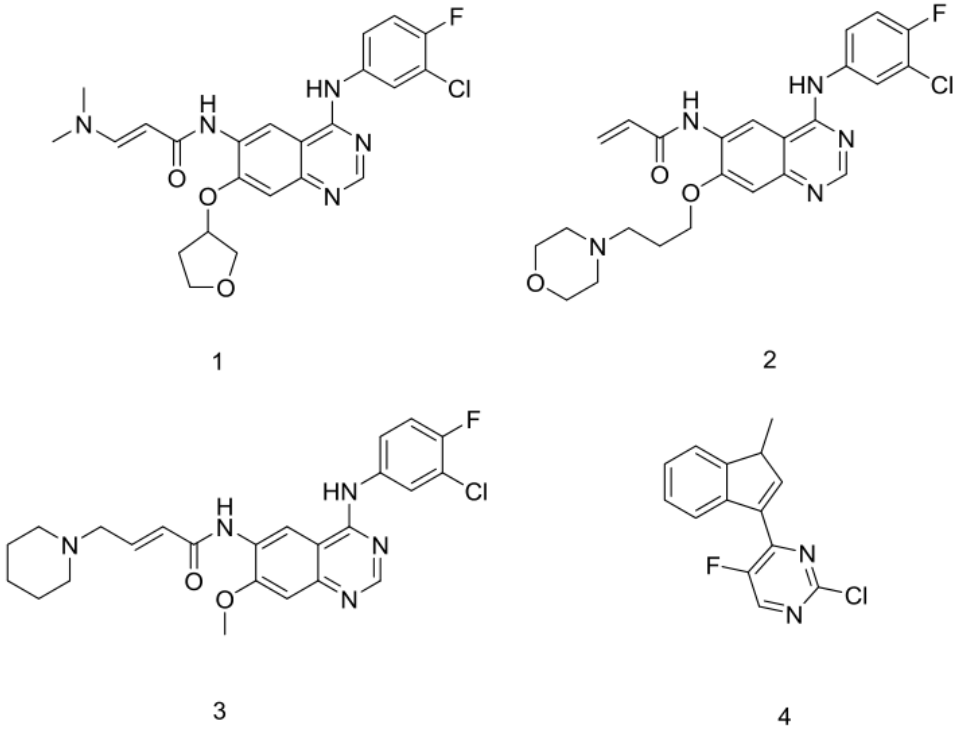
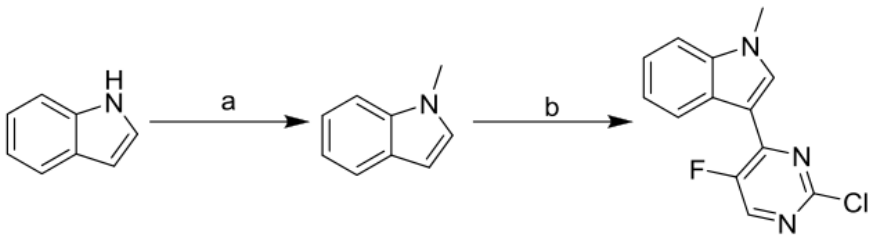


Fig.1Structures of some drugs or active compounds

Chemistry

The structures and the synthetic route were shown in Scheme 1.



Scheme1. The synthetic route of target Compound

Reagents and conditions:(a)Tetrahydrofuran, methyl iodide, sodium hydride, ice bath; (b) 2,4-dichloro-1-fluorobenzene, ethylene glycol dimethyl ether, anhydrous aluminum trichloride, 80℃.

Synthesis of 1-methyl-1H-indole

1*H*-indole (0.5 g, 0.0043mol) was dissolved in tetrahydrofuran (15 mL) first. Ice bath and sodium hydride(0.5 g, 0.021 mol) were slowly added under stirring, stirred at room temperature for 30 minutes, and then slowly dropped methyl iodide(1.5 g, 0.011 mol) in an ice bath, stirred at room temperature to complete consumption of the reactants. The combined reaction solution was dried under reduced pressure to

recover most of the solvent extracted with water and dichloromethane (with an equal volume of solvent). 1-methyl-1H-indole (0.51 g, 0.0039mol) was obtained. Yield 90.7%. ^{1}H NMR (400 MHz, DMSO) δ 7.51 (d, 0H), 7.28 (d, 0H), 7.18 (dd, *J* = 8.7 Hz, 1H), 7.06 (dd, 0H), 6.84 (dd, 0H), 3.81 (d, 1H).

Synthesis of 3-(2-chloro-5-fluoropyrimidin-4-yl)-1-methyl-1H-indole

2,4-dichloro-5-fluoropyrimidine(8.0 g, 0.0479 mol) was dissolved in ethylene glycol dimethyl ether(150ml), heated to 80 degrees Celsius under the protection of nitrogen, rapidly adding anhydrous aluminum chloride(6.4 g, 0.048 mol) as well as nitrogen methylindole (6.3 g, 0.048 mol), and stirring was continued to the raw materials Consumed. The reaction mixture was added to a mixed solvent of water: methanol 5: 2, stirred for 30 minutes and filtered off to obtain an off-white solid (6.5 g, 0.0219 mol). Yield 45.68%. ^{1}H NMR (400MHz, DMSO) δ 8.60 (s,1H), 7.95 (d,1H), 7.60 (s, 1H), 7.50 (d, 1H), 7.36 (t, 1H), 7.29 (t, 1H), 3.85 (s, 3H).

Conclusion

In conclusion, the desired compound 3-(2-chloro-5-fluoropyrimidin-4-yl) -1-methyl -1*H*-indole was synthesized from the commercially available 1H-indole by a two-step substitution reaction. The structure of the fluorine substituent attached to the pyrimidine ring has not been done before, and a more safe and effective anticancer drug may be synthesized on the basis of this structure. Therefore, the synthesis of the intermediate structure is of great significance.

Acknowledgment

We gratefully acknowledge the generous support provided by The National Natural S cience Funds (No. 21162014,81460527), The Project Supported by Natural Science F oundation of Jiangxi, China (20171BAB215073, 20171BAB205101); Natural Science Funds for Distinguished Young Scholar of Jiangxi Province, China (20171BCB2307 8); Key projects of the youth fund, Natural Science Funds of Jiangxi Province (20171 ACB21052); Jiangxi Provincial Key Laboratory of Drug Design and Evaluation (2017 1BCD40015) Graduate Students' Science and Technology Innovation Project of Jiang xi Science & Technology Normal University.

References

[1] Ostman A, Pietras K. Introduction to tumor-stroma interactions. Experimental Cell Research, 2013, 319(11):1595-1595.

[2] Kumar Mahto M, Yellapu N K, Kilaru R B, et al. Molecular designing and in silico evaluation of darunavir derivatives as anticancer agents. Bioinformation, 2014, 10(4): 221-6.

[3] Dayyani F, Gallick G E, Logothetis C J, et al. Novel therapies for metastatic castrate-resistant prostate cancer. Journal of the National Cancer Institute, 2011, 103(22): 1665-1675.

[4] Owyang S Y, Zhang M, Walkup G A, et al. The effect of CT26 tumor-derived TGF-β on the balance of tumor growth and immunity. Immunology Letters, 2017, 191: 47-54.

[5] Aly R M, Serya R A T, El-Motwally A M, et al. Novel quinoline-3-carboxamides (Part 2): Design, optimization and synthesis of quinoline based scaffold as EGFR inhibitors with potent anticancer activity. Bioorganic Chemistry, 2017, 75: 368-392.

[6] Tong C W S, Wu W K K, Loong H H F, et al. Drug combination approach to overcome resistance to EGFR tyrosine kinase inhibitors in lung cancer. Cancer Letters, 2017, 405: 100-110.

[7] Mend B A, Delavar M, Darroudi M. CdO-NPs; synthesis from 1D new nano Cd coordination polymer, characterization and application as anti-cancer drug for reducing the viability of cancer cells. Journal of Molecular Structure, 2017, 1134: 599-605.

[8] Patel H, Pawara R, Ansari A, et al. Recent updates on third generation EGFR inhibitors and emergence of fourth generation EGFR inhibitors to combat C797S resistance. European Journal of Medicinal Chemistry, 2017.

[9] Cai J, Sun M, Ge X, et al. EGFR tyrosine kinase inhibitors differentially affect autophagy in head and neck squamous cell carcinoma. Biochemical and Biophysical Research Communications, 2017, 486(4): 1027-1033.

[10] Assouline P, Léger-Ravet M B, Saffroy R, et al. Métastases mammaires des cancers bronchopulmonaires avec mutation de l'EGFR. Revue des Maladies Respiratoires, 2017, 34(1): 61-65.

[11] Cai J, Sun M, Ge X, et al. EGFR tyrosine kinase inhibitors differentially affect autophagy in head and neck squamous cell carcinoma. Biochemical and Biophysical Research Communications, 2017, 486(4): 1027-1033.