Synthesis of phenol analogues containing 3-alkyl substituted acrylamide

Cilong Chu, Zixuan Rao and Shan Xu*

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

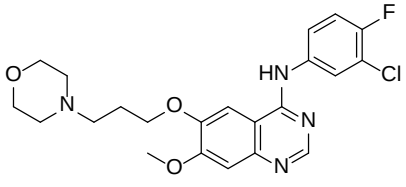
*Corresponding author: shanxu9891@126.com

Keywords: 3-alkyl substituted acrylamidophenol, Synthesis

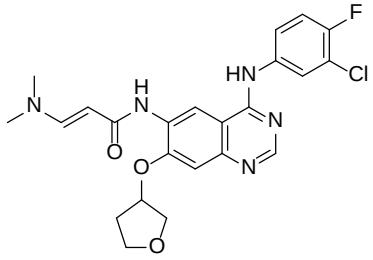
Abstract: 3-alkyl substituted acrylamidophenol analogues are important intermediates of small molecule antitumor drugs. A rapid and high yield synthetic method for 3-alkyl substituted acrylamidophenol analogues was established in this work. The target compound was synthesized from commercially available 3-nitrophenol through reduction and nucleophilic substitution reactions. The structure of the target product was confirmed by ^{1}HNMR. In addition, the synthesis steps were optimized, and the total yield of the two steps was up to 83%.

1. Introduction

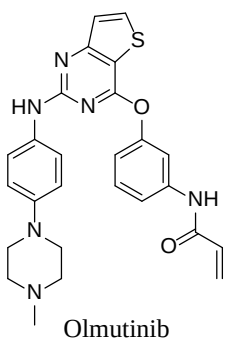
With the development of molecular biology, more and more clinical data indicate that the epidermal growth factor receptor (EGFR) encoded of protein tyrosine kinase family is mutated by proto-oncogenes and their family-related genes. It is the main cause of tumor development in patients with lung cancer, especially in non-small cell lung cancer (NSCLC). Therefore, EGFR has become a popular target for the treatment of non-small cell lung cancer. In fact, many compounds that inhibit the EGFR pathway have been discovered and used clinically for years, such as Gefitinib, Afatinib and Olmutinib [1] (Fig. 1). Olmutinib is an irreversible EGFR tyrosine kinase inhibitor (TKI), for the treatment of patients with locally advanced or met-astatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer. In addition, it was approved by the Korean Ministry of Food and Drug Safety in 2016 [2]. Olmutinib possesses potent inhibition against cell lines of H1975 (L858R and T790M) and HCC827 (exon 19 deletion) [3-5]. In addition, it has a low potency for NSCLC cell line H358 harboring wild-type EGFR (GI_{50} of 2225 nM) [6, 7]. In the *in vivo* studies of xenograft models with grafts of H1975 and HCC827, Olmutinib was active against the tumors without showing any side effects.



Gefitinib



Afatinib



Olmutinib

Fig.1 Typical EGFR inhibitors.

Therefore, finding new small molecule compounds based on the mechanism of lead drugs has become a research hotspot. In structural analysis of existing third-generation EGFR inhibitors such as Osimertinib, Rociletinib and Olmutinib [8, 9] (Figure. 2), we found that all third-generation EGFR inhibitors possess the structure of acrylamide. Through computer-aided drug design, we found that the acrylamide part forms a covalent bond with C797S, and there is still much room left in this part. Combining the structures of Dacamitinib, Nazartinib and (Figure. 3), we identified the transformation direction of Olmutinib intermediate 3-acrylamidephenol, so we used (*E*)-hex-2-enoic acid and (*E*) -4-methylpent-2-enoic acid to increase the carbon chain length of the acrylamide moiety.

In this paper, *m*-nitrophenol was used as a raw material to explore a fast and high-yield synthetic route. After reduction reaction and nucleophilic substitution reaction, a 3-alkyl substituted acrylamide phenol analog was obtained with a yield of 95%, which was more suitable for industrial production. The synthetic route was shown in Figure. 4,

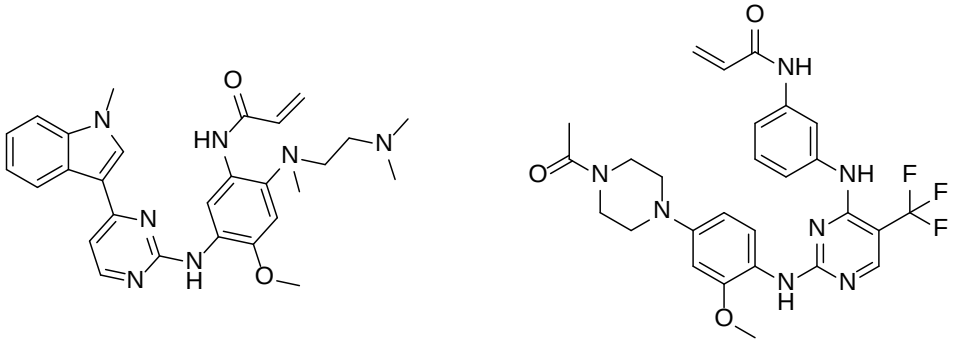


Fig. 2 Third generation EGFR inhibitors.

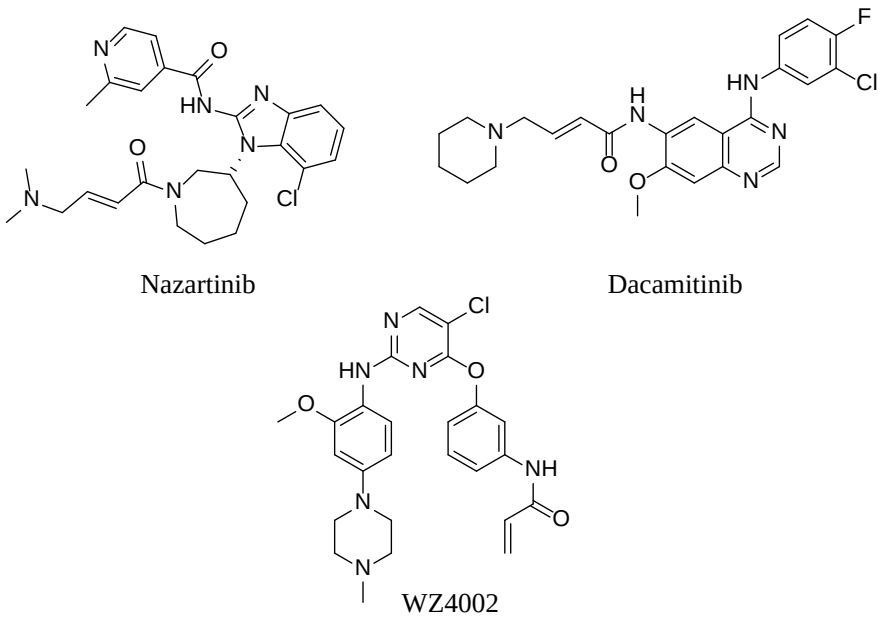


Fig 3. EGFR inhibitors with alkyl substituted acrylamide structure.

2. Materials and Methods

^{1}NMR spectra were performed using Bruker 300 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). Elemental analysis was determined on a Carlo-Erba 1106. Elemental analysis instrument (Carlo Erba, Milan, Italy). 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 Fig.4.

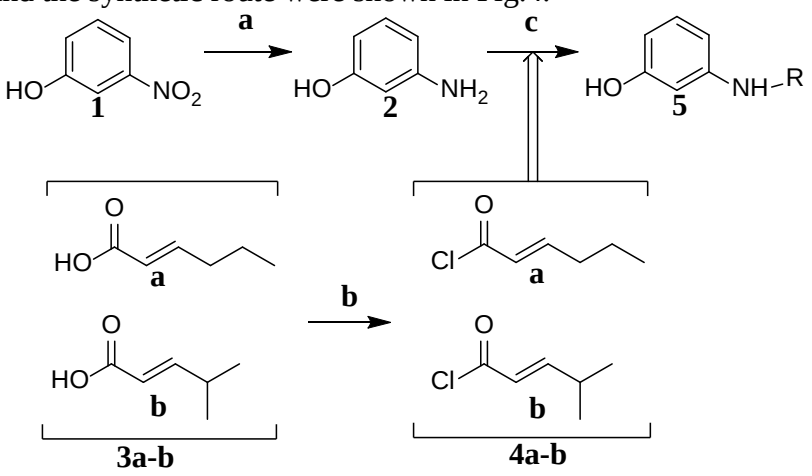


Fig 4. The synthetic route.

Reagents and conditions: (a) $FeCl_3 \cdot 6H_2O$, hydrazine hydrate, activated carbon, ethanol, 3 h, rt; (b) Oxalyl chloride, DMF, DCM, 0.25 h, rt; (c)DIPEA, DCM, 0.5 h, 0 ℃.

3.1 Preparation for m-aminophenol (2)

M-nitrophenol (10 mmol), $FeCl_3.6H_2O$ (10 mmol) and activated carbon (70 mmol) were heated in ethanol at reflux until 80 ℃ for 0.5 h. Add hydrazine hydrate to the mixture and heat to reflux for 2.5 h. The mixture was suction filtered while hot. The filter cake was washed with methanol. The filtrate was spin-dried to give *m*-aminophenol as a gray solid, with a yield of 87.4% MS (ESI): m/z $[M+H]^+$110.06. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 1H), 6.77 (t, *J* = 7.8 Hz, 1H), 5.98 (dd, *J* = 25.3, 8.4 Hz, 3H), 5.26 (s, 1H), 3.39 (s, 1H).

3.2 Preparation for alkyl substituted acryloyl chloride (4 a-b)

(*E*)-Hex-2-enoic acid, (*E*)-4-methylpent-2-enoic acid (25 mmol), oxalyl chloride (23 mmol) was dissolved in DCM, and DMF was added.

3.3 Preparation for 3-acrylamide alkyl substituted phenol (5 a-b)

M-aminophenol (10 mmol) and DIPEA (15 mmol) were dissolved in DCM and stirred at 0 ℃ for 0.25 h. 4 a-b was slowly added to the mixture. 5a MS (ESI): m/z $[M+H]^+$ 206.11. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 9.37 (s, 1H), 7.33(d, *J* = 5.7 Hz, 2H), 7.10 (s, 1H), 6.66 (d, *J* = 7.5 Hz, 1H), 6.18 (s, 1H), 5.89 (s, 1H), 2.04 (s, 2H), 1.37 (d, *J* = 12.3 Hz, 2H), 0.93 (s, 3H). 5b MS (ESI): m/z $[M+H]^+$ 206.11. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.71(s, 1H), 9.37 (s, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), 7.24 (t, *J* = 2.0 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.62 (dt, *J* = 7.5, 2.0 Hz, 1H), 6.45 (s, 1H), 6.29 (s, 1H), 2.21 (s, 1H), 1.10 (d, *J* = 8.2, 6H).

4. Conclusion

In summary, 3-acrylamidoalkyl-substituted phenol analogs were synthesized from a commercially available *m*-nitrophenol as a raw material through reduction reaction and nucleophilic substitution reaction. Its structure was confirmed by ^{1}HNMR spectrum. The purity of the product was high.

Acknowledgement

We gratefully acknowledge the generous support provided by The Project Supported by National Natural Science Foundation of China (21967009), Youth Top Talent Support Program of Jiangxi Science & Technology Normal University (2019QNBJRC008), Science and Technology Project Founded by the Education Department of Jiangxi Province, China (GJJ180628), Key Laboratory of Molecular Targeted Anticancer Drug Design and Evaluation of Nanchang (2019-NCZDSY-007).

References

[1] Yarden, Y, et al. The EGFR family and its ligands in human cancer: signalling mechanisms and therapeutic opportunities [J]. European journal of cancer, 2001, 37(4): 3-8.

[2] Patel H, et al. Recent updates on third generation EGFR inhibitors and emergence of fourth generation EGFR inhibitors to combat C797S resistance [J]. Eur. J. Med. Chem, 2017, 142: 32−47.

[3] R. Pirker, et al. Third-generation epidermal growth factor receptor tyrosine kinase inhibitors in advanced nonsmall cell lung cancer [J]. Curr. Opin. Oncol, 2016, 28(2): 115-121.

[4] A. Tartarone, et al. Clinical approaches to treat patients with non-small cell lung cancer and epidermal growth factor receptor tyrosine kinase inhibitor acquired resistance [J]. Ther. Adv. Respir. Dis, 2015, 9(5): 242-250.

[5] J.C. Yang, et al. Second and third-generation epidermal growth factor receptor tyrosine kinase inhibitors in advanced nonsmall cell lung cancer [J]. Curr. Opin. Oncol, 2015, 27(2): 94-101.

[6] H. Cheng, et al. Recent progress on third generation covalent EGFR inhibitors [J]. Biorg. Med. Chem. Lett., 2016, 26(8): 1861-1868.

[7] S. Wang, et al. Third-generation inhibitors targeting EGFR T790M mutation in advanced non-small cell lung cancer [J]. J. Hematol. Oncol. 2016, 9: 34.

[8] P.A. Janne, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer [J]. N. Engl. J. Med. 2015, 372(18): 1689-1699.

[9] S.V. Liu, et al. emerging protein kinase inhibitors for non-small cell lung cancer [J]. Expert Opin. Emerg. Drugs, 2014, 19(3): 51-65.