Synthesis of Cinnamic Acid Derivatives

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Abstract. Quinazoline derivatives have been shown to be biologically active such as afatinib. The cinnamic acid derivative is an important part of the quinazoline derivative which exerts its activity. And Cinnamic acid derivatives were prepared by the benzaldehyde derivatives and malonic acids. In this paper, four cinnamic acid derivatives were prepared. The structure was confirmed by MS and ^{1}H NMR. In addition, this method not only saved the reaction time, but also improved the purity of the product. The yield of the step was about 90%.

Introduction

In a number of studies, it has been found that some viral transfer gene expression products have tyrosine kinase (PTK) activity [1]. Therefore, PTK has become an important breakthrough in studying the mechanism of oncogenes and exploring the treatment of tumor diseases. Among them, the more important subfamilies are the epidermal growth factor receptor (EGFR) family [2]. Abnormal expression of epidermal growth factor in cancer cells is an important target for tumor therapy. Studies have shown that EGFR inhibitors are quinazoline structures [3].

Quinazoline derivatives are wildly found in many natural alkaloids, it is a kind of heterocyclic compound bearing important biological activity such as N-(3-bromophenyl)-1H-imidazo[4,5-g]quinazolin-8-amine (2) [4], afatinib (3) [5], (R,E)-N-(4-((3-chloro-4-fluorophenyl)amino)-7-((tetrahydrofuran-3-yl)oxy)quinazolin-6-yl)-3-(2,3, 4-trimethoxyphenyl)acrylamide (4) [6]. These compounds have a very good antibacterial, anticancer, antispasmodic, malaria and anti-inflammatory effect, so they have an extremely important application prospect in biology, medicine and pesticide [7-9]. In a word, quinoline is a dominant skeleton structure, as a supporting structure, connecting different properties of the pharmacological groups, with a variety of biological macromolecules, resulting in a variety of biological activity, especially in the field of anti-tumor drug research, quinoline Class played an important role [9]. In addition, as early as 2000, Lamazz [11] synthesized benzimidazole and quinoline compounds on human HT-29 cell inhibitory activity reached a level of micro-mol.

The cinnamic acid derivative is an important part of the quinazoline derivative which exerts its activity. There are many synthetic methods of cinnamic acid derivatives have been reported, but most of the synthetic methods there are still deficiencies. In this paper, the synthetic methods of cinnamic acid derivatives were summarized and optimized. We prepared four kinds of cinnamic derivatives making it more suitable for industrial production. The structures of representative cinnamic derivatives were shown in Fig. 1.

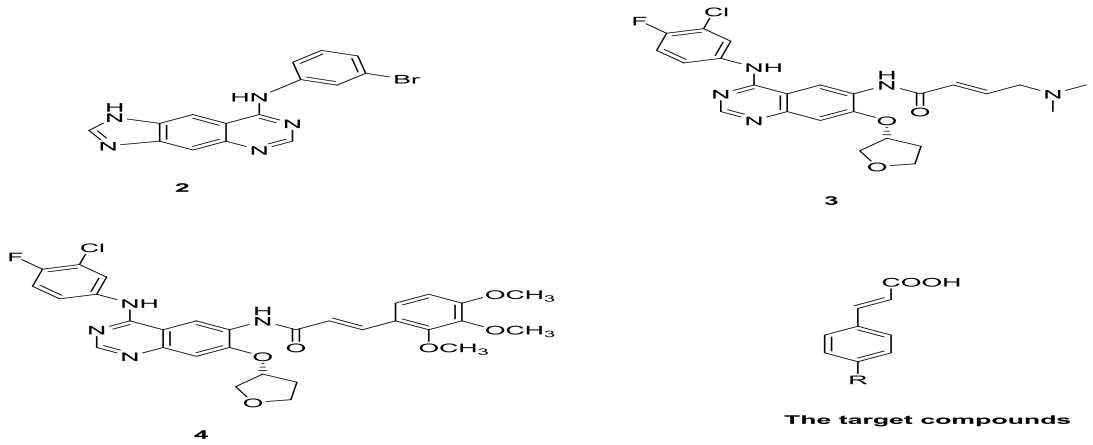


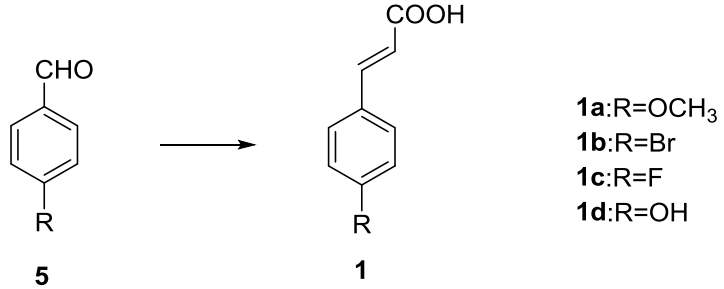
Figure 1. Structure of representative cinnamic derivatives

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).

Synthesis of Compounds

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



Scheme 1. The synthetic route of compound **1a-1d**

Reagents and conditions: malonic acid; pyridine; piperidine; 110℃; 1.5 h

(E)-3-(4-methoxyphenyl) acrylic acid (1a)

To a 25 ml round bottom flask was added p-bromobenzaldehyde (0.50 g, 3.72 mmol), pyridine (6.0 ml), 2 drops of piperidine and malonic acid (0.38 g, 3.68 mmol). The above round bottom flask was placed in an oil bath and reacted at 110 °C for 1.5 h. Next, the reaction was complete by TLC analysis. Dilute hydrochloric acid to adjust the pH to 5, filtration, washing with water to get the product. (0.45 g, 90.0%) ESI -MS m/z: 179.0 [M+H] +. 1H NMR (400 MHz, DMSO) δ 12.25 (s, 1H), 7.64 (d, J = 5.3 Hz, 1H), 7.63 (s, 1H), 7.54 (d, J = 16.0 Hz, 1H), 6.98 (s, 1H), 6.95 (s, 1H), 6.38 (d, J = 16.0 Hz, 1H), 3.79 (s, 3H).

(E)-3-(4-bromophenyl) acrylic acid (1b)

The experimental procedure was the same as for compound 1a. (0.43 g, 86.0%) ESI -MS m/z: 228.0 [M+H] +. 1H NMR (400 MHz, DMSO) δ 12.50 (s, 1H), 7.67 (s, 1H), 7.65 (s, 1H), 7.62 (s, 1H), 7.59 (d, J = 5.7 Hz, 1H), 7.54 (s, 1H).

(E)-3-(4-fluorophenyl) acrylic acid (1c)

The experimental procedure was the same as for compound 1a. (0.44 g, 88.5%) ESI -MS m/z: 167.1 [M+H] +. 1H NMR (400 MHz, DMSO) δ 12.44 (s, 1H), 7.77 (dd, J = 8.1, 5.9 Hz, 1H), 7.59 (d, J = 16.1 Hz, 1H), 7.25 (t, J = 8.7 Hz, 1H), 6.52 (s, 1H), 6.48 (s, 1H).

(E)-3-(4-hydroxyphenyl) acrylic acid (1d)

The experimental procedure was the same as for compound 1a. (0.45 g, 89.3%) ESI -MS m/z: 165.1 [M+H] +. 1H NMR (400 MHz, DMSO) δ 12.16 (s, 1H), 9.98 (s, 1H), 7.52 (s, 1H), 7.51 (s, 1H), 7.50 (s, 1H), 7.47 (s, 1H), 6.78 (d, J = 8.3 Hz, 2H), 6.28 (d, J = 15.9 Hz, 1H).

Conclusions

In summary, four cinnamic acid derivatives were prepared by the reaction of substituted benzaldehydes and malonic acid. The synthesis method and reaction conditions of cinnamic acid dervatives were optimized. The purity of the product was higher than before and it was more suitable for industrial production. Its structure was confirmed by MS and 1H NMR spectrum.

Acknowledgments

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