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Research paper

Novel ferulic amide derivatives with tertiary amine side chain as acetylcholinesterase and butyrylcholinesterase inhibitors: The influence of carbon spacer length, alkylamine and aromatic group

Haoran Liu [a], Linbo Liu [a], Xiaohui Gao [b], Yingzi Liu [c, *], Wanjun Xu [c], Wei He [c], Hong Jiang [c], Jingjing Tang [a], Haoqun Fan [a], Xinhua Xia [b]

[a] College of Chemistry and Chemical Engineering, Hu'nan University, Changsha 410082, China
[b] College of Pharmacy, Hu'nan University of Chinese Medicine, Changsha 410208, China
[c] College of Medicine, Hu'nan Normal University, Changsha 410013, China

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ABSTRACT

Based on our recent investigations on chalcone derivatives as AChE inhibitors, a series of ferulic acid (FA) tertiary amine derivatives similar to chalcone compounds were designed and synthesized. The results of bioactivity evaluation revealed that most of new synthesized compounds had comparable or more potent AChE inhibitory activity than the control drug Rivastigmine. The alteration of carbon chain linking tertiary amine groups and ferulic acid scaffold markedly influenced the inhibition activity against AChE. Among them the inhibitory activity of compound **6d** (IC_{50}: 0.71 ± 0.09 μmol/L) and **6e** (IC_{50}: 1.11 ± 0.17 μmol/L) was equal to 15-fold and 9-fold than that of Rivastigmine against AChE (IC_{50}: 10.54 ± 0.86 μmol/L), respectively. Moreover, compound **6d** shows the highest selectivity for AChE over butyrylcholinesterase(BuChE) (ratio: 18.3). The kinetic study suggested that compound **6d** revealed a mixed-type inhibition against AChE. The result of molecular docking showed that compound **6d** combines to AChE with three amino acid sites(Trp84, Tyr334 and Trp279), while combines to BuChE with two amino acid sites (Tyr67 and Gly66) in enzyme domains, respectively. Compound **6d** might act as a potential agent for the treatment of Alzheimer's diseases (AD).

1. Introduction

Chalcone, a special natural product containing α,β-unsaturated carbonyl group, is thought as a reasonable scaffold to develop novel drugs via structure modification [1–3]. AChE inhibitors from natural products or their derivatives are considered as possible new resources for the treatment of Alzheimer's diseases (AD). In our laboratory more than one hundred Mannich base derivatives originated from natural products were screening for the bioactivity in inhibiting AChE in the past several years. Fortunately Flavokawain Mannich base derivatives containing chalcone scaffold were discovered with potent AChE inhibiting effect two years ago [4]. Afterwards, a lot of chalcone nitrogen-containing derivatives were synthesized and confirmed as potent AChE inhibitors in our further investigations [5–7]. According to these results, it seemed that the presence of an α,β-unsaturated carbonyl group in chalcone scaffold was essential for AChE inhibitory activity.

Ferulic acid, a natural product containing α,β-unsaturated carbonyl group, had versatile application prospects in medicine [8–10]. In the present investigation, a series of ferulic acid benzamide derivatives coupled with tertiary amines side chain were synthesized, and evaluated the biological activity in inhibiting AChE and BuChE. In order to explore whether the benzamide groups were essential for the bioactivity, some ferulic acid ester or free ferulic acid derivatives were synthesized and evaluated, compared with that of ferulic acid benzamide derivatives (Fig. 1). For the purpose of exploring the inhibition profile and mechanism, enzyme kinetic and molecular docking studies were carried out.

2. Results and discussion

2.1. Chemistry

In the beginning the amide derivative of ferulic acid (compound

* Corresponding author.
E-mail address: liuyingzi111@sina.com (Y. Liu).

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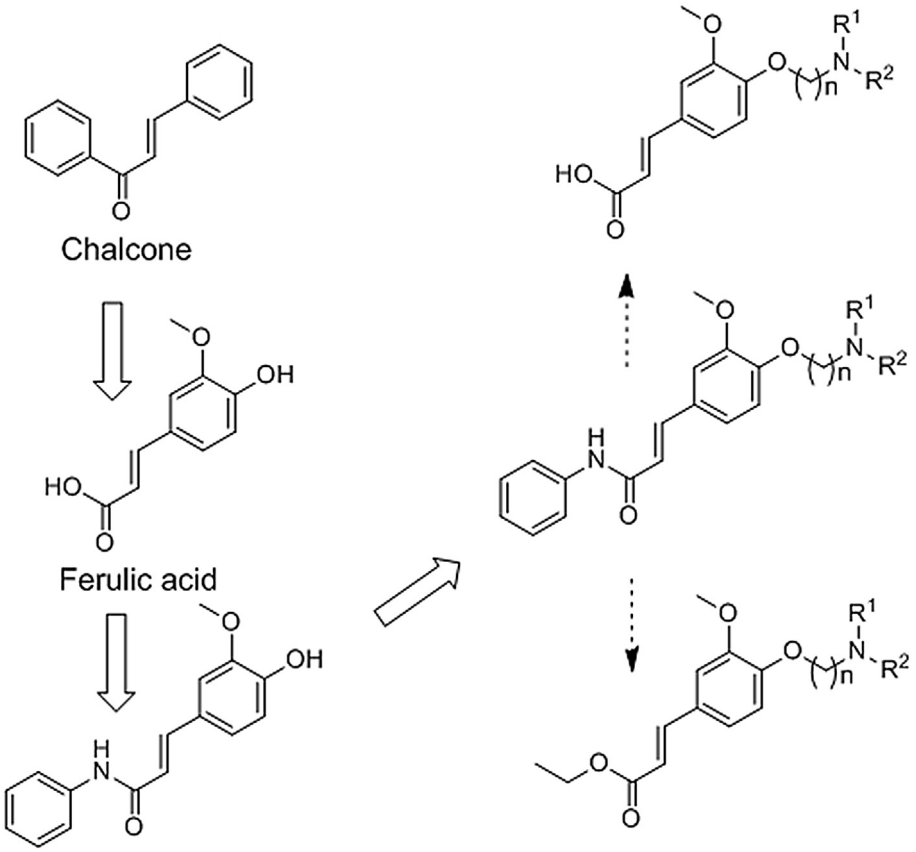

Fig. 1. Design strategy of the ferulic acid derivatives.

5) was planned to synthesize from ferulic acid and phenylamine directly, but only poor-yield product was gained. Then it was synthesized from ferulic acid chloride as the intermediate, but the impurity of the final product is not easy to remove. So new synthesis route was applied to prepared acetyl ferulic acid(compound **2**) firstly [11], and then acetyl ferulic acid chloride (compound **3**) was synthesized as an intermediate to gain compound **4** with previous reported method [12,13]. Finally, the acetyl group was hydrolyzed by ammonium hydroxide at room temperature to achieve compound **5** with a good yield. The synthesis route above is summarized in Scheme 1.

Compounds **2b-2e** were generated by compound **5** with four commercially available compounds (chloroethyldimethylamine hydrochloride, chloroethyldiethylamine hydrochloride, chloroethylpiperidine hydrochloride, or chloroethylpyrrolidine hydrochloride) in the presence of K_2CO_3 and NaI. Then compounds **3b-8e** were synthesized from compounds **3a-8a** which were prepared from compound **5** with different dibromoalkanes (Scheme 1).

In order to further investigate the influence of benzamide group in inhibiting AChE, the derivatives of four compounds possessing higher AChE inhibitory activity (compounds **6c, 7c, 6d** and **6e**) were synthesized by removing benzamide group or introducing ethyl ester group,respectively (Scheme 2).

The final products were purified by silica gel chromatography. The structures of the compounds were characterized by proton nuclear magnetic resonance spectroscopy (^{1}H NMR, ^{13}C NMR), infrared spectrum (IR) and mass spectrum (MS). Representative ^{1}H and ^{13}C NMR spectra were outlined in Supplement Materials.

2.2. In vitro inhibition against AChE and BuChE

The half maximal inhibitory concentration (IC_{50} values) of new synthesized compounds in inhibiting AChE and BuChE as well as the selectivity for AChE were shown in Table 1. The results revealed that all of test compounds showed perfect inhibition activity against AChE and BuChE, compared to compound **5** (IC_{50} > 500 μmol/L).

The variation of the spacer linking ferulic acid scaffold and terminal amine groups dramatically influenced the anticholinesterase activity (Table 1). The compounds with six methylenes spacer showed better inhibition activity against AChE (**6b**: 8.40 ± 0.09; **6c**: 1.83 ± 0.22; **6d**: 0.71 ± 0.09; **6e**: 1.11 ± 0.17 μmol/L) than the others. The inhibitory activity against AChE also markedly changed with the alteration of tertiary amine groups. For compounds with the same methylene spacer, most compounds containing piperidine group have more potent inhibition activity against AChE than other derivatives. But for those compounds with eight or ten methylenes spacer, the compounds containing dimethylamine or diethylamine group (compounds **7c** and **8b**) possessed higher activity than the others (Table 1).

Among new synthesized compounds, nine compounds showed better inhibitory activity (IC_{50} = 0.71–8.40 μmol/L) than the control drug Rivastigmine (IC_{50}: 10.54 μmol/L). The most promising compound **6d** (IC_{50}: 0.71 ± 0.09 μmol/L) and **6e** (IC_{50}: 1.11 ± 0.17 μmol/L) possessed 15-fold or 9-fold of inhibitory activity against AChE than that of Rivastigmine, respectively. Moreover, compound **6d** showed the highest selectivity for AChE over BuChE (IC_{50}: 12.97 ± 0.13 μmol/L; ratio: 18.3).

Among new synthesized compounds, compounds **6c, 7c, 6d** and