Study on synthesis of naringenin derivatives and cholinesterase inhibitory activity in marine Chinese medicine

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Abstract: This paper describes the design and synthesis of a series of chalcone derivatives based on naringenin as the lead compound. The compounds were evaluated for their activities against AChE and BuChE using principles of new drug design. The intermediate benzopyran-3-formaldehyde was synthesized from commercial ortho-hydroxybenzaldehyde and acrolein using K_2CO_3 as a catalyst. The target compounds were obtained through the Claisen-Schmidt reaction of benzopyran-3-formaldehyde and substituted acetophenone. The inhibitory effects of the chalcone compounds against AChE and BuChE were determined using Ellman's method. Eight compounds showed certain inhibitory activities against AChE and BuChE, with compound **2d** exhibiting higher activity against cholinesterase. Molecular docking studies revealed that **2d** had a significant interaction with AChE and BuChE. This study suggested that chalcone compounds, including coumarin, might provide a potential pathway for discovering new anti-AD precursors.

Keywords: Ipomoea pes-caprae; Naringenin; Chalcone derivatives; Synthesis; Cholinesterase inhibitors

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1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by cognitive impairment, memory loss, and changes in language, emotions, behavior, and other functions. It is the leading cause of dementia[1–3]. Globally, nearly 50 million people suffer from AD, and this number is expected to increase to 115 million by 2050[4]. Although several main stream theories have been proposed, the pathogenesis of AD remains unclear and cannot fully explain the complex pathological phenomena associated with the disease. Currently, cholinesterase inhibitors are the primary drugs used to treat AD. Cholinesterase (ChE) is an essential enzyme involved in the normal functioning of the nervous system, and it is responsible for the metabolism of various biochemical reactions and the breakdown of cholinester. Two known ChE enzymes are acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE)[5]. ChE inhibitors block the action of the enzymes responsible for acetylcholine breakdown, enhancing brain cholinergic neurotransmission and providing symptomatic relief[6,7].

Ipomoea pes-caprae (Linn.) Sweet, also known as saddle vine or two-leaf sweet potato, is a sweet potato plant belonging to the family Convolvulaceae. It is a typical marine traditional Chinese medicine that thrives on the shoreline in coastal regions of southern China[8–10]. Previous studies have reported that I. pes-caprae possesses various pharmacological properties, including antibacterial, anti-inflammatory, analgesic, anti-tumor, anti-collagenase, antioxidant, and immunological modulation effects[11–14]. I. pes-caprae contains numerous active ingredients, with 117 chemicals, mainly phenolic acids, terpenoids, steroids, flavonoids, coumarins, resin glycosides, and volatile components, identified from the leaves, roots,

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and aboveground sections of the plant[15–23]. Naringenin, a flavonoid compound, was isolated from the caulis cauliflower in our study. Chalcone compounds are a type of flavonoid that occurs naturally. Recent research has discovered novel chalcone compounds with AChE and BuChE inhibitory activity and antioxidant effects, making them potential candidates for the treatment of AD[24–27]. Coumarin is a heterocyclic compound with a coumarin core structure that has been found to have AChE inhibitory activity. We have isolated coumarin compounds from Caulis in our previous studies[28–32]. Based on this research, we used naringenin as the lead compound to obtain the chalcone structure by ring-opening, and we replaced the A ring of chalcone with the coumarin ring. We linked the two active structures together to design and synthesize eight chalcones containing coumarin (the design strategy and synthetic route are shown in Fig. 1), and we used the improved Ellman's method[33] to determine the effect of the target compound on AChE and BuChE.

2. Experimental

2.1. General

First, the commercial 2-hydroxybenzaldehyde and acrolein were catalyzed by K_2CO_3 to form the intermediate of benzopyran-3-formaldehyde (**1**). Then, benzopyran-3-formaldehyde and substituted acetophenone were reacted with Claisen Schmidt to obtain the target compound.

2.2. General procedure for the synthesis of benzopyran-3-formaldehyde (1)

In an 80 mL solution of 1,4-dioxane, 8.5 g (0.07 mol) of *o*-hydroxybenzaldehyde and 15 g of K_2CO_3 were dissolved. The mixture was agitated and refluxed for 40 min for activation, then cooled to room temperature. The reaction was allowed to proceed at room temperature for 6 h, followed by the gradual addition of 5.88 g (0.105 mol) of acrolein in an ice bath. The reaction process was monitored using thin-layer chromatography (developing solvent: petroleum ether–ethyl acetate, v/v, 8:1).

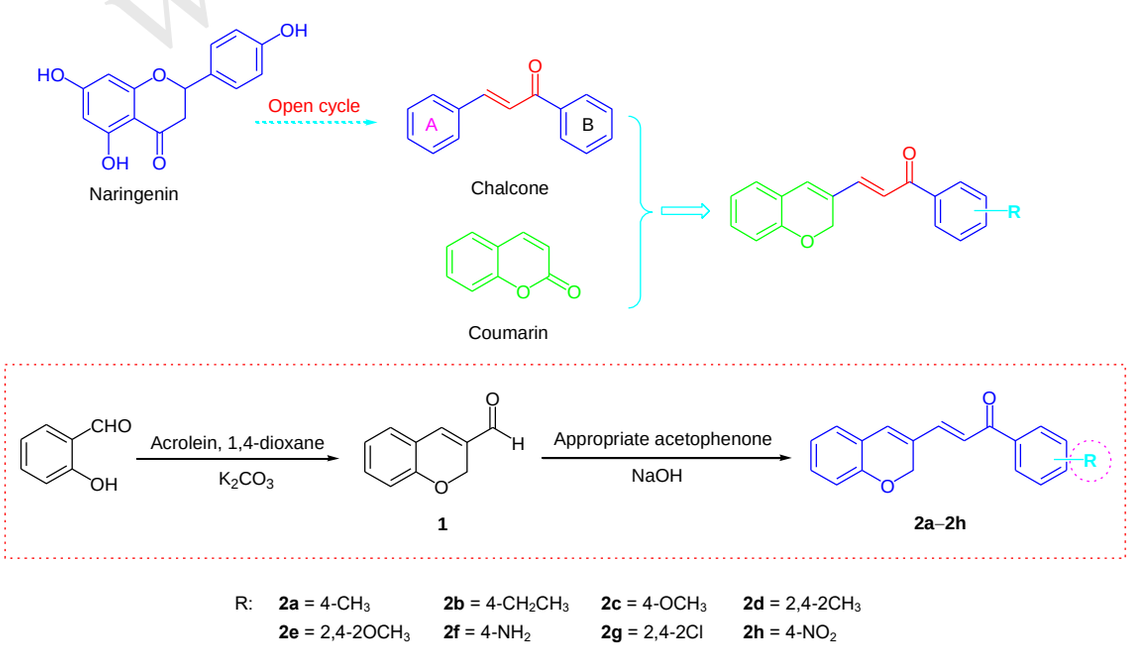

Figure 1. Design strategy and the synthetic route for chalcone compound.

Table 1. The relevant physical data of Chalcone derivatives **2a**–**2h**.

Compound	R	Mp (ºC)	Yield (%)	Formula	Recrystallization solvent
2a	4-CH_3	116.3–117.1	57.3	$C_{19}H_{16}O_2$	EtOH
2b	4-CH_2CH_3	128.7–129.4	64.5	$C_{20}H_{18}O_2$	EtOH
2c	4-OCH_3	121.5–122.8	49.7	$C_{19}H_{16}O_3$	EtOH
2d	3,4-2CH_3	134.7–135.3	60.2	$C_{20}H_{18}O_2$	EtOH
2e	3,4-2OCH_3	119.2–120.8	55.9	$C_{20}H_{18}O_2$	EtOH
2f	4-NH_2	128.6–129.6	48.5	$C_{18}H_{15}NO_2$	EtOH
2g	3,4-2Cl	132.4–133.5	49.9	$C_{18}H_{12}Cl_2O_2$	EtOH
2h	4-NO_2	171.1–172.2	53.7	$C_{18}H_{13}NO_4$	EtOH

After the reaction, dioxane was removed, and 20 mL of distilled water was added to initiate the third extraction with ether. The organic layer was filteredand dried with the appropriate amount of anhydrous sodium sulfate, and the ether was removed. The intermediate was crystallized to yield 9.45 g of benzopyran-3-formaldehyde, with an estimated yield of 84.3%.

2.3. General procedure for the synthesis of chalcone derivatives 2a–2h

Briefly, 0.64 g (4 mmol) of intermediate benzopyran-3-formaldehyde and 5.2 mmol of different substituted acetophenones were added to a round bottom flask. Next, 20 mL of absolute ethanol and 8 mL of 3.5 M NaOH solution were added, and the mixture was stirred overnight at room temperature. Thin-layer chromatography was used to track the reaction process during the reaction. After the reaction, the reaction solution was poured into ice water to obtain yellow or orange sediment, which was then filtered. Finally, the filter cake was recrystallized with ethanol to obtain chalcone derivatives **2a**–**2h**. The relevant physical data of chalcone derivatives **2a**–**2h** can be found in Table 1.

2.4. Structural characteristics of chalcone derivatives 2a–2h

The ^{1}H and ^{13}C NMR, and MS spectra of the compounds are available in the Supporting Information.

(*E*)-3-(2*H*-Benzopyran-3-yl)-1-(4-methyl)propyl-2-en-1-one (**2a**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.89–7.11 (m, 4H, -C_6H_4), 7.56 (d, 1H, J = 15 Hz, =CH), 7.13 (d, 1H, J = 15 Hz, =CH), 7.10–6.83 (m, 4H, -C_6H_4), 6.96 (s, 1H, =CH), 5.11 (s, 2H, -CH_2), 2.45 (s, 3H, -CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 189.54, 154.59, 143.72, 141.29, 135.53, 131.99, 130.94, 129.36, 129.07, 128.56, 128.10, 121.98, 121.81, 120.59, 115.85, 65.29, 21.70. MS *m/z* 277.33 (M+1).

(*E*)-3-(2*H*-Benzopyran-3-yl)-1-(4-ethyl)propyl-2-en-1-one (**2b**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.97–7.12 (m, 4H, -C_6H_4), 7.48 (d, 1H, J = 15 Hz, =CH), 7.08 (d, 1H, J = 15 Hz, =CH), 6.95–6.81 (m, 4H, -C_6H_4), 6.93 (s, 1H, =CH), 5.13 (s, 2H, -CH_2), 2.71 (q, 2H, -CH_2), 1.26 (t, 2H, -CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 193.56, 159.39, 154.51, 145.66, 136.52, 135.68, 134.44, 133.60, 133.02, 126.96, 126.61, 125.98, 120.57, 69.97, 45.71, 45.43, 45.16, 44.88, 44.60, 44.32, 44.04, 33.59, 20.22. MS *m/z* 291.36 (M+1).

(*E*)-3-(2*H*-Benzopyran-3-yl)-1-(4-methoxyphenyl) propyl-2-en-1-one (**2c**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.99–7.39 (m, 4H, -C_6H_4), 7.75 (d, 1H, J = 15 Hz, =CH), 7.53 (d, 1H, J = 15 Hz, =CH), 7.12–6.97 (m, 4H, -C_6H_4), 6.99 (s, 1H, =CH), 5.16 (s, 2H, -CH_2), 3.89 (s, 3H, -OCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 188.30, 163.48, 153.68, 141.38, 131.56, 131.19, 130.77, 130.23, 129.53, 128.81, 128.13, 127.58, 124.31, 121.27, 120.12, 117.42, 65.28, 55.56. MS *m/z* 293.33 (M+1).

(*E*)-3-(2*H*-Benzopyran-3-yl)-1-(2,4-dimethylphenyl) propyl-2-en-1-one (**2d**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.11–7.23 (m, 3H, -C_6H_3), 7.31 (d, 1H, J = 15 Hz, =CH), 7.22 (d, 1H, J = 15 Hz, =CH), 7.09–6.64 (m, 4H, -C_6H_4) , 7.07 (s, 1H, =CH), 5.00 (s, 2H, -CH_2), 2.53 (s, 3H, -CH_3), 2.51 (s, 3H, -CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 196.37, 145.54, 138.99, 135.69, 129.21, 129.15, 128.30, 127.99, 127.23, 126.15, 125.56, 61.87, 42.22, 40.94, 40.67, 40.39, 40.11, 39.83, 39.55, 39.28, 29.80. MS *m/z* 291.36 (M+1).

(*E*)-3-(2*H*-Benzopyran-3-yl)-1-(2,4-dimethoxyphenyl) propyl-2-en-1-one (**2e**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.96–7.10 (m, 3H, -C_6H_3), 7.33 (d, 1H, J = 15 Hz, =CH), 7.18 (d, 1H, J = 15 Hz, =CH), 6.92 (s, 1H, =CH), 6.92–6.55 (m, 4H, -C_6H_4), 5.03 (s, 2H, -CH_2), 3.91 (s, 3H, -OCH_3), 3.86 (s, 3H, -OCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 189.12, 164.41, 160.49, 154.42, 138.47, 132.59, 130.70, 130.66, 129.65, 128.05, 126.30, 122.18, 121.81, 121.65, 115.72, 105.93, 98.54, 65.23, 55.90, 55.70, 40.97, 40.68, 40.40, 40.13, 39.85, 39.57, 39.30. MS *m/z* 323.35 (M+1).

(*E*)-3-(2*H*-Benzopyran-3-yl)-1-(4-aminophenyl)propyl-2-en-1-one (**2f**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.58 (s, 2H, -NH_2), 8.06–7.14 (m, 3H, -C_6H_3), 7.40 (d, 1H, J = 15 Hz, =CH), 7.08 (d, 1H, J = 15 Hz, =CH), 6.99–6.63 (m, 4H, -C_6H_4), 6.89 (s, 1H, =CH), 5.12 (s, 2H, -CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 186.18, 154.48, 153.66, 138.95, 131.20, 130.58, 130.36, 130.04, 128.06, 122.39, 121.83, 121.62, 115.75, 113.38, 65.33, 40.95, 40.67, 40.39, 40.11, 39.83, 39.56, 39.27. MS *m/z* 278.32 (M+1).

(*E*)-3-(2*H*-Benzopyran-3-yl)-1-(2,4-Dichlorophenyl) propyl-2-en-1-one (**2g**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.34–7.17 (m, 4H, -C_6H_4), 7.55 (d, 1H, J = 15 Hz, =CH), 7.14 (d, 1H, J = 15 Hz, =CH), 7.03–6.81 (m, 3H, -C_6H_3), 6.89 (s, 1H, =CH), 5.14 (s, 2H, -CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 188.09, 154.83, 150.06, 142.77, 133.22, 131.33, 129.89, 128.51, 123.88, 121.94, 120.78, 115.89, 65.13, 40.96, 40.70, 40.41, 40.13, 39.85, 39.58, 39.30. MS *m/z* 332.19 (M+1).

(*E*)-3-(2*H*-Benzopyran-3-yl)-1-(4-nitrophenyl)propyl-2-en-1-one (**2h**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.00–7.10 (m, 4H, -C_6H_4), 7.54 (d, 1H, J = 15 Hz, =CH), 6.94–6.46 (m, 4H, -C_6H_4), 6.92 (s, 1H, =CH), 6.87 (d, 1H, J = 15 Hz, =CH), 5.04 (s, 2H, -CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 191.83, 154.70, 143.46, 137.44, 136.42, 133.26, 131.90, 131.42, 130.67, 130.03, 128.98, 128.50, 127.60, 124.84, 121.93, 115.89, 64.92, 40.96, 40.68, 40.40, 40.13, 39.85, 39.57, 39.29. MS *m/z* 308.30 (M+1).

2.5. Anticholinergic activity analysis

The improved Ellman's method was utilized to determine the inhibitory activity of AChE and BuChE, as described by Hostalkova et al. in 2019. For the AChE inhibition test, 96-well plates were filled with 100 μL of 0.1 M phosphate buffer (KH_2PO_4/K_2HPO_4, pH 7.4), 20 μL of 0.2 U/mL AChE, 20 μL of 0.001 M thioacetylcholine iodide (ATCI), and 20 μL of test compounds in various concentrations. The plates were then incubated at 37 °C for 15 min. Subsequently, 20 μL of 5,5-dithiodinitrobenzoic acid (DTNB) was added, and the absorbance at 412 nm was measured with a microplate reader. Three measurements were taken for each concentration, and the compound's inhibition rate was calculated using formula (1).

$$\text{Inhibition rate} = (1 - A_0/A_c) \times 100 \quad (1)$$

(A_0: The absorbance measured by the microplate reader when there is an inhibitor; A_c: the absorbance measured by the microplate reader when there is no inhibitor.)

2.6. Molecular docking analysis

Molecular simulations and docking tests were performed using the Vina (Simina) docking program. The crystal structure of human ChE protein was obtained from the protein crystal database, with a resolution of 5 Å (10–10 m). The initial structure of the ChE protein crystal was subjected to default parameters, and the optimized protein crystal structure was simulated with compound **2d**.

2.7. Statistical analysis

The results of the statistical analysis were presented as mean ± SD, and SPSS 22.0 was used for data analysis. To assess differences among groups, a one-way analysis of variance (ANOVA) was performed after testing for homogeneity of variance.

3. Results and discussion

3.1. Chemistry

Using salicylaldehyde as the starting material and 1,4-dioxane as the reaction solvent, acrolein undergoes a Michael addition reaction, followed by further intramolecular Aldol addition and elimination reaction to obtain the corresponding benzopyran-3-formaldehyde. Subsequently, benzopyran-3-formaldehyde and various substituted acetophenones undergo Claisen-Schmidt condensation under alkaline conditions to yield various chalcone derivatives with yields ranging from 48.5% to 64.5%. Detailed information regarding the NMR characterization of the compound structures can be found in the supporting information.

3.2. Biological activity

In this study, the antiChE drug Donepezil was utilized as the control, and the improved Ellman's method was employed to evaluate the inhibitory activity of chalcone compounds on AChE and BuChE. The results, which are presented in Table 2, revealed that eight chalcone compounds exhibited specific AChE and BuChE inhibitory actions. Of these, compound **2d** displayed the most potent inhibition on AChE and BuChE, with IC_{50} values of 30.52 ± 0.76 and 25.44 ± 1.02 μM, respectively. Structural analysis suggested that the inhibitory activity of the enzyme was influenced by various B ring substituents, and the methyl relative inhibitory activity was superior, particularly for the 2,4-methyl substituted compounds.

The inhibitory activity of four substitutions on AChE was ranked in the order **2h** > **2b** > **2c** > **2a** > **2f**, while the order of inhibitory activity of four substitutions on BuChE was **2b** > **2h** > **2c** > **2a** > **2f**. For double substitution on AChE, the order of inhibitory activity

Table 2. Inhibitory effects of AChE and BuChE by chalcone compounds.

Compound	IC_{50} for AChE (μM)	IC_{50} for BuChE (μM)	Selectivity index (IC_{50} (AChE)/IC_{50} (BuChE))
2a	79.31 ± 1.09	64.40 ± 1.01	1.23
2b	46.02 ± 0.59	30.06 ± 1.12	1.53
2c	60.80 ± 1.56	52.45 ± 1.71	1.16
2d	30.52 ± 0.76	25.44 ± 1.02	1.20
2e	99.02 ± 1.05	80.41 ± 0.90	1.23
2f	108.08 ± 0.89	84.07 ± 1.57	1.29
2g	98.55 ± 0.77	83.14 ±1.25	1.19
2h	42.07 ± 1.09	37.11 ± 0.98	1.13
Donepezil	45.04 ± 0.86	29.18 ± 0.64	1.54

was **2d** > **2g** > **2e**, and the order of inhibitory activity on BuChE was **2d** > **2e** > **2g**. In short, the introduction of 2-methyl improved the inhibition ability of AChE and BuChE, with BuChE showing superior inhibition compared to AChE. The effect of different substituents on enzyme activity was shown by the inhibitory order of AChE, which was **2d** > **2h** > **2b** > **2c** > **2a** > **2g** > **2e** > **2f**. Additionally, the sequence of the inhibitory activity of 4-position substitution on BuChE was **2d** > **2b** > **2h** > **2c** > **2a** > **2e** > **2g** > **2f**. In summary, the introduction of 2-methyl improved the inhibition ability of AChE and BuChE, especially for BuChE.

3.3. Molecular docking

Using AutoDockVina software, we investigated the binding sites of **2d** with AchE and BuChE. As illustrated in Figure 2, the oxygen atom of the aldehyde group formed a hydrogen bond with the AChE complex through the amino acid residue PHE-295, and the benzene ring formed π-π conjugation with amino acids TRP-286, TYR-341, and TYR-337. In the complex with BuChE, **2d** interacted by forming π-π bonds with amino acid residues TRP-82, TRP-231, and TYR-332. Additionally, the binding free energies of **2d** with AChE and BuChE were –12.1 and –9.8 kJ/mol, respectively. These results demonstrated the high binding activity and stable structure of both complexes. Therefore, based on the findings of our molecular docking studies and enzyme inhibitory activities for both AChE and BuChE, we concluded that **2d** was a dual inhibitor of AChE and BuChE and deserved further research.

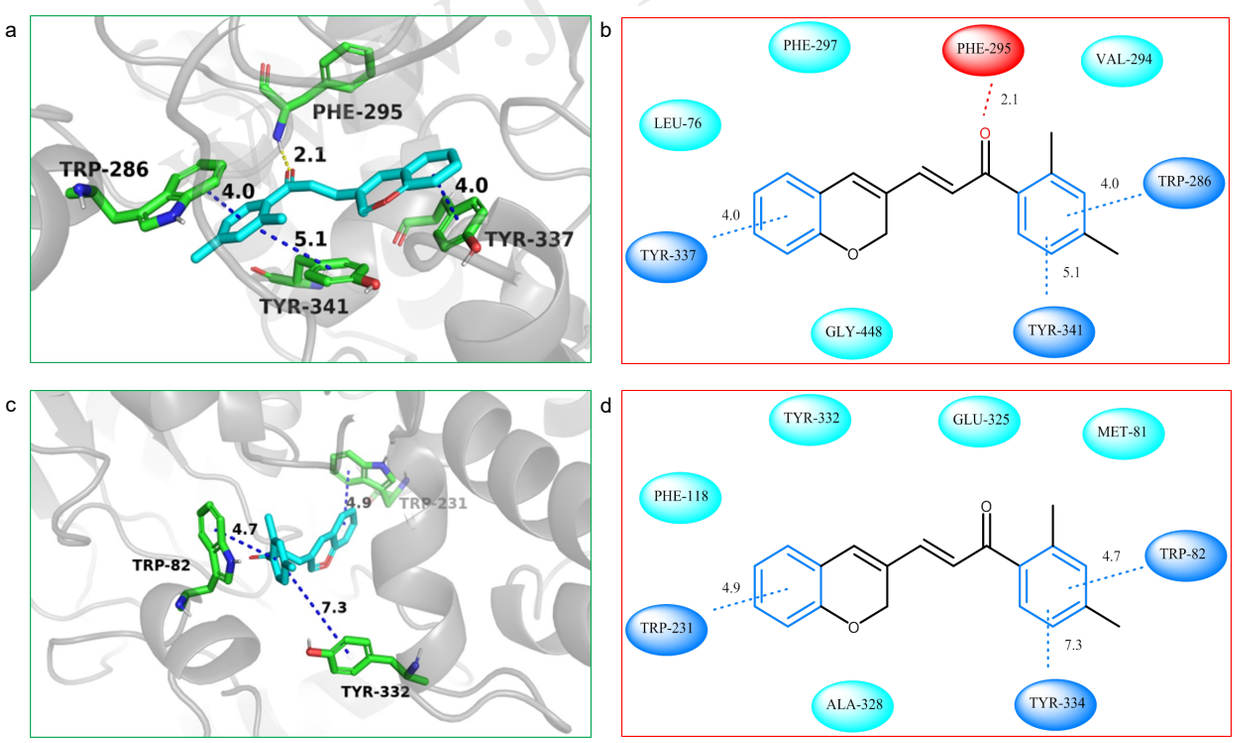

Figure 2. 2d docked with AchE molecules (a and b); **2d** docked with BuChE molecules (c and d).

4. Conclusions

This study employed naringenin, a substance isolated from a traditional Chinese medicine sourced from the sea, as the lead compound. Using the new drug design principle, we designed and synthesized eight novel chalcone derivatives containing coumarin and evaluated their AChE and BuChE inhibitory activities *in vitro*. Our experimental findings revealed that all eight compounds showed inhibitory effects against AChE and BuChE, with compound **2d** exhibiting particularly strong ChE inhibition. Furthermore, our molecular docking results demonstrated that **2d** exhibited significant interaction with both AChE and BuChE, suggesting that it might have potential efficacy in treating AD.

In conclusion, our experimental study indicated that chalcone compounds with coumarin might serve as a promising approach for discovering new lead compounds with potential anti-AD properties. However, further studies are necessary to investigate the absorption, distribution, metabolism, excretion, and toxicity of these compounds *in vivo*, as well as their blood-brain barrier penetration effect, derivative action mechanism, structural optimization, and quantitative structure-activity relationship.

Supporting Information

The ^{1}H and ^{13}C NMR spectra of compounds. The Supporting Information is available free of charge *via* the Internet at http://www.jcps.ac.cn.

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海洋中药厚藤中柚皮素(naringenin)衍生物合成及胆碱酯酶抑制活性研究

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摘要: 本文以柚皮素(naringenin)为先导化合物, 采用新药设计的原理, 设计合成一系列查尔酮衍生物并对其进行AChE和BuChE的抑制活性研究。市售的邻羟基苯甲醛与丙烯醛在K_2CO_3催化下生成苯并吡喃-3-甲醛中间体。苯并吡喃-3-甲醛与取代的苯乙酮经过Claisen-Schmidt反应得到目标化合物。采用改进的Ellmańs法测定查尔酮化合物对AChE和BuChE的抑制活性。8个化合物均显示出一定的抑制AChE和BuChE的活性, 其中化合物**2d**显示出比较高的抑制胆碱酯酶的活性。分子对接结果表明, **2d**与AChE和BuChE有明显的相互作用. 本实验研究表明具有香豆素的查尔酮化合物可能是发现具有潜在抗AD新先导物的一个途径。

关键词: 厚藤; 柚皮素; 查尔酮衍生物; 合成; 胆碱酶抑制剂