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SYNTHESIS, STRUCTURAL STUDIES AND ACETYLCHOLINESTERASE INHIBITION ACTIVITY OF SOME (*E*)-2-METHOXY-3-NITRO-4-(3-OXO-3-ARYLPROP-1-EN-1-YL)PHENYL ACETATES

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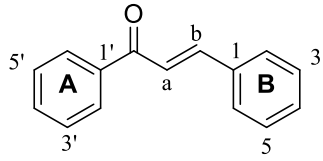
Abstract. A semi-synthetic process from vanillin (isolated from vanilla) was developed to obtain new esters with potential inhibitory activity against the acetylcholinesterase (AchE.). 2-Nitrovanillin was synthesized from vanillin by esterification, nitration, and hydrolysis reactions. Four chalcones were synthesized by acid-catalyzed condensation reaction of 2-nitrovanillin and methyl aryl ketone. The identity of 2-nitrovanillin and four chalcones was confirmed by thin-layer chromatography compared with the known compounds. Subsequent esterification of the chalcones with acetic anhydride yielded four new derivatives of (*E*)-2-methoxy-3-nitro-4-(3-oxo-3-(aryl)prop-1-en-1-yl)phenyl acetate. The structures of the four new compounds were elucidated by ^{1}H NMR and ^{13}C NMR spectra. The four compounds were evaluated for their inhibitory activity against AChE. and three of them exhibited significant activity.

Keywords: vanillin, chalcone, acetate, acetylcholinesterase.

1. Introduction

The chalcones are *α, β* - unsaturated ketones (1,3-diaryl-2-propen-1-one) containing the reactive ketoethylenic group (- CO – CH= CH –), and the phenyl ring attached to the carbonyl group is defined to be the ring A, and the other benzene ring is named as the ring B [1]. The structure of chalcone shows the ring A and ring B as follows:



Chalcones and their derivatives are polyphenolic compounds of the flavonoid family. They occur in many plants as metabolic precursors of other flavonoids and

isoflavonoids [2]. The presence of an *α, β-unsaturated* carbonyl system in chalcone makes it biologically active. Some substituted chalcones and their derivatives have been reported to possess some interesting biological properties such as antibacterial [3], [4], antifungal [5], insecticidal [6], anaesthetic [7], analgesic, ulcerogenic [8], antimalarial [1], [7], [8], anti-tuberculosis [9] activities, antidiabetic [10], anticancer [1], [11], [12], anti-inflammatory [1], antioxidant [1], antimicrobial activity [1], cancer prevention and neuroprotective properties [12]. Among the numerous pharmacological activities explored for chalcone derivatives, the development of novel chalcone analogs for the treatment of Alzheimer's disease (AD) has attracted significant interest [13], [14]. Because chalcones possess numerous advantages, such as a smaller molecular size, they provide opportunities for further structural modification to alter physicochemical properties, improve cost-effectiveness, and employ convenient synthetic methodologies. Various chemical reactions have been reported for the synthesis of chalcones, including the Suzuki, Heck, Wittig, Julia–Kocienski olefination, as well as cross-coupling reactions [15]. The most common method is the Claisen–Schmidt condensation of acetophenone derivatives with benzaldehyde derivatives in the presence of both acid and base catalysts. Recently, some chalcones have also been synthesized by using microwave irradiation [16], which maximizes product yield, minimizes by-products, and allows the use of environmentally friendly solvents.

Vanillin is a natural compound widely used as a flavoring agent in the food industry. Numerous biologically active derivatives have been prepared from vanillin, such as chalcone [17], [18], azomethine [19], thiazolidine-2-one heterocycle [20], quinoline heterocycle [21]. Some chalcones synthesized from vanillin exhibit good inhibitory activity against acetylcholinesterase [18]. In the previous report, some chalcones from 2-nitrovanillin were synthesized and structurally identified [17]. In this paper, some acetate derivatives of chalone from 2-nitrovanillin and their inhibitory activity against acetylcholinesterase (AchE.) are presented.

2. Content

2.1. Experiments

2.1.1. Chemicals and laboratory equipment

**** Chemicals***

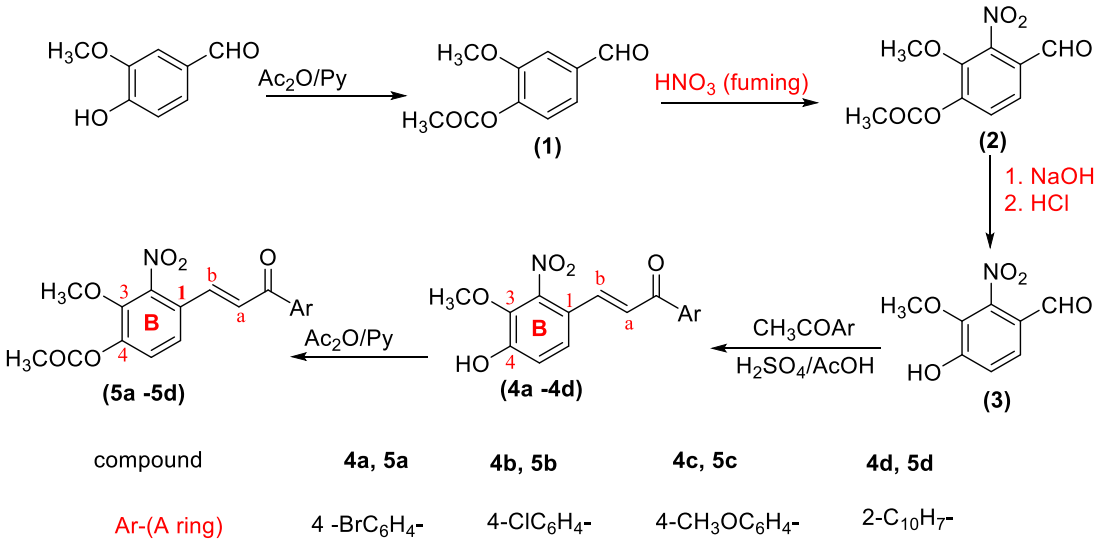
Vanillin (100%, Xin Hua perfume), pyridine (Py) AR (Xilong), H_2SO_4 AR (Xilong), NaOH AR (Xilong), HCl AR (Xilong), ethanol (AR, Guangdong Guanghua), acetone AR (Xilong), acetic acid AR (Xilong), *p*-bromacetophenone (98%,9-Ding chem), and 2-acetonaphtalenene (98%, Aladin) were purchased from China. *P-chloroacetophenone* (97%, Sigma-Aldrich) and *p*-methoxyacetophenone (99%, Sigma-Aldrich) were purchased from the USA. $NaNO_3$ (Duc Giang), *n*-hexane, and ethyl acetate were bought from Vietnam. Acetic anhydride ($(CH_3CO)_2O$, RG, Scharlau) was obtained from Spain.

**** Laboratory equipment***

Thin-layer chromatography (TLC) was carried out on pre-coated silica gel 60 F_{254} (Sigma-Aldrich). Column chromatography was carried out on silica gel 60 (Merck).

TLC spots were visualized under UV light at 254 nm and 365 nm. ^{1}H NMR spectra were recorded on a Bruker Avance 600 MHz Instrument, and ^{13}C NMR spectra were recorded on a Bruker Avance 125 MHz Instrument, using $CDCl_3$ as a solvent. Mass spectra were acquired using a Dionex Ultimate UHPLC system coupled with a Q Exactive Orbitrap mass spectrometer (Thermo Scientific) via electrospray ionization (ESI-MS).

2.1.2. Synthesis of some derivatives of chalcones from vanillin



Scheme 1. Synthesize some acetate derivatives of chalcones from vanillin

2.1.3. Synthesis of chalcone derivatives from vanillin

Chalcones **4a – 4d** were synthesized from vanillin according to reference [17]. Intermediate products (**1**), (**2**), (**3**), and chalcones **4a - 4d** were tested by TLC and compared with standards, Scheme 1.

2.1.4. Synthesis of acetate derivatives

General procedure

Chalcone (1 mmol), acetic anhydride ($(CH_3CO)_2O$, 0.5 ml), and pyridine (0.2 ml) were dissolved in acetone (5 ml). The reaction mixture was stirred at room temperature for 120 min, then poured into a beaker containing ice water (200 g) and stirred until a precipitate appeared. The precipitate was filtered and washed with cold water on a Buchner funnel until neutral. The crude product was dried and recrystallized with acetone. The structure of the product was elucidated by ^{1}H NMR, ^{13}C NMR spectra, and HRMS.

Compound *(E)-4-(3-(4-bromophenyl)-3-oxoprop-1-en-1-yl)-2-methoxy-3-nitrophenyl acetate* ***(5a)*** was obtained as white crystals, recrystallized with ethanol, yield = 92%.

^{1}H NMR (500 MHz, $CDCl_3$, δ (ppm), J (Hz)): 3.94 (3H, s), 2.39 (3H, s), 7.57 (1H, d, J = 16 Hz), 7.37 (1H, d, J = 16 Hz), 7.31 (1H, d, J = 8.5 Hz), 7.49 (1H, d, J = 8.5 Hz), 7.65 (2H, dd, J = 6.5 Hz, J = 2 Hz), 7.82 (2H, dd, J = 6.5, J = 2 Hz).

^{13}C NMR (125 MHz, $CDCl_3$, δ (ppm)): 20.8, 167.9, 62.6, 188.3, 122.6, 126.0, 126.1, 126.6, 128.6, 130.1, 132.1, 136.1, 136.2, 144.4, 145.4, 146.1.

Compound *(E)-4-(3-(4-chlorophenyl)-3-oxoprop-1-en-1-yl)-2-methoxy-3-nitrophenyl acetate (**5b**)* was obtained as purple crystals, recrystallized with ethanol, yield = 94%.

^{1}H NMR (500 MHz, $CDCl_3$, δ (ppm), J (Hz)): 3.94 (3H, s), 2.39 (3H, s), 7.57 (1H, d, J = 16 Hz), 7.38 (1H, d, J = 16 Hz), 7.31 (1H, d, J = 8.5 Hz), 7.49 (1H, d, J = 8.5 Hz), 7.48 (2H, d, J = 8.5 Hz), 7.91 (2H, d, J = 8.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$, δ (ppm)): 20.8, 168.0, 62.8, 188.2, 122.6, 126.0, 126.1, 126.7, 129.1, 130.1, 135.6, 136.2, 139.9, 144.4, 145.4, 146.8.

HRMS *m/z* $[M+H]^+$, Calcd. for $C_{18}H_{14}ClNO_6$: 376.0584 (^{35}Cl); found: 376.0576; calcd. 378.0554 (^{37}Cl), found: 378.0544.

Compound *(E)-2-methoxy-4-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)-3-nitrophenyl acetate (**5c**)* was obtained as light purple crystals, recrystallized with ethanol, yield = 90%.

^{1}H NMR (500 MHz, $CDCl_3$, δ (ppm), J (Hz)): 3.93 (3H, s), 2.38 (3H, s), 7.54 (1H, d, J = 16 Hz), 7.43 (1H, d, J = 16 Hz), 6.98 (2H, dd, J = 7 Hz, J = 2 Hz), 7.30 (1H, d, J = 8.5 Hz), 7.49 (1H, d, J = 8.5 Hz), 7.97 (2H, d, J = 7 Hz), 3.89 (3H, s).

^{13}C NMR (125 MHz, $CDCl_3$, δ (ppm)): 20.8, 168.0, 62.7, 187.6, 114.1, 122.6, 125.9, 126.5, 127.3, 130.3, 131.1, 134.8, 144.3, 145.0, 146.0, 163.9.

HRMS (m/z) $[M+H]^+$: Calcd. for $C_{19}H_{17}NO_7$, 372.1083; found, 372.1074.

Compound *(E)-2-methoxy-4-(3-(naphthalen-2-yl)-3-oxoprop-1-en-1-yl)-3-nitrophenyl acetate (**5d**)* was obtained as a purple crystal, recrystallized with ethanol, yield = 89%.

^{1}H NMR (500 MHz, $CDCl_3$, δ (ppm), J (Hz)): 3.95 (3H, s), 2.39 (3H, s), 7.63 (1H, d, J = 14 Hz), 7.58 (1H, d, J = 14 Hz), 7.33 (1H, d, J = 8.5 Hz), 7.56 (1H, d, J = 8.5), 7,59 (1H, m), 7,62 (1H, m), 7,90 (1H, d, J = 8 Hz), 7.94 (1H, d, J = 8.5 Hz), 7.99 (1H, d, J = 7.5 Hz), 8.04 (1H, dd, J = 9 Hz, J = 2 Hz), 8.48 (1H, d, J = 1 Hz).

^{13}C NMR (125 MHz, $CDCl_3$, δ (ppm)): 20.8, 168.0, 62.8, 189.3, 122.6, 124.3, 126.0, 126.4, 127.0, 127.4, 127.9, 128.7, 128.8, 129.7, 130.5, 132.5, 134.7, 135.6, 135.7, 144.4, 145.2.

HRMS (m/z) $[M+H]^+$: Calcd. for $C_{22}H_{17}NO_6$, 392.1134; found, 392.1122.

2.1.3. Acetylcholinesterase inhibitory activity assay

Acetylcholinesterase enzyme (AChE.) inhibitory activity of the synthesized compounds was assayed by the spectrophotometric method developed by Ellman *et al.* with slight modifications [22]-[24].

The experiment was performed in a 96-well plate with a total volume of 200 µL: Add each solution in turn: tris-HCl buffer solution (pH=8), test sample, and 0.25 IU/mL enzyme solution to each well of the 96-well plate. The mixture of these solutions was mixed well and incubated for 15 min at 25 ^{o}C. Then, 2.4 mM DTNB (5-5'-dithiobis-2-nitrobenzoic acid) reagent solution and 2.4 mM ATCI (acetylthiocholine iodide) substrate solution were added to the mixture and mixed well. Continue to incubate the mixture for 15 minutes at 25 ^{0}C and measure the absorbance at 412 nm. Each test sample was repeated 3 times. The reference substance was donepezil. Experimental data were compiled and processed using statistical methods commonly used in biomedicine with the help of Microsoft Excel 2007 software. The AChE inhibitory activity of the test sample was calculated according to the following formula:

$$\% I = \{[(A_{0E} - A_0) - (A_c - A_{0C})]/(A_{0E} - A_0)\}*100\% \quad (1)$$

where I is the percent inhibition of acetylcholinesterase; A_{0E} is the absorbance value of the control blank sample with enzyme; A_0 is the absorbance value of the blank sample; Ac is the absorbance value of the tested sample; A_{0C} is the absorbance value of the blank test sample.

IC_{50} is the concentration of the test substance that inhibits 50% of the enzyme activity, calculated by Table curve software based on the % inhibition. Evaluate the activity of the test substance by comparing it with the reference substance. Experimental results are expressed as the average value plus/minus the standard deviation, denoted by ± SD. In which the standard deviation (SD) is calculated according to the formula as follows:

$$SD = \sqrt{\frac{\Sigma(X_i - \bar{X})^2}{n-1}} \quad (2)$$

2.2. Results and discussion

2.2.1. Synthesis and structure determination of acetate derivatives

The intermediates and two chalcones, **4a** and **4b,** were tested by thin-layer chromatography, and the R_f of the products coincided with the R_f of known compounds.

Acetate derivatives **5a-5d** were obtained by the esterification reaction between chalcones **4a-4d** with $(CH_3CO)_2O$, with high yields from 89% to 92%.

**** ^{1}H NMR spectrum***

^{1}H-NMR spectrum of **5a** is presented in Figure 1.

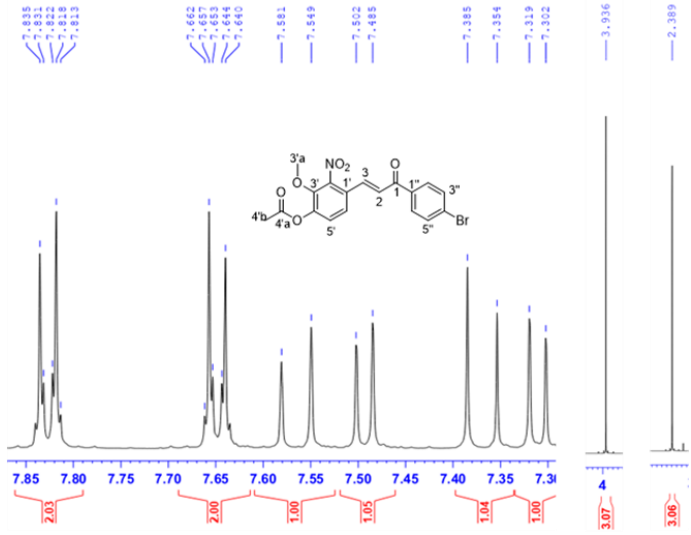


Figure 1. ^{1}H NMR spectrum of compound 5a

The ^{1}H NMR spectra of compounds **5a -5d** have spectral peaks consistent with the expected proton resonances (number of peaks, chemical shifts, spectral peak intensities, and multiplicities). In particular, the signal corresponding to the –OH proton of the chalcone moiety was absent. Instead, characteristic signals for the protons of the CH_3-group at 4'b position appeared at 2.38-2.39 ppm.

Figure 1 shows the ^{1}H NMR spectrum of compound **5a,** showing 8 spectral peaks. A characteristic singlet at δ 3.94 ppm (3H, s) corresponds to the –OCH_3 group. A typical singlet at δ 2.39 ppm (3H, s) is assigned to the CH_3COO- group, which has δ = 2.39 ppm (3H, s). Four signals in the range δ 7.31–7.82 ppm correspond to aromatic protons.

Two doublets at δ 7.57 ppm (1H, d, J = 16 Hz) and δ 7.37 ppm (1H, d, J = 16 Hz) are assigned to alkene protons, with the large coupling constant (J = 16 Hz) indicating a trans configuration.

Compounds **5b- 5d** exhibited ^{1}H NMR signals consistent with their proposed structures. The –OCH_3 groups resonated at δ = 3.94 ppm (3H, s) (**5b**), δ =3.93 ppm (3H, s) and 3.89 ppm (3H, s) (**5c**), δ = 3.95 ppm (3H, s) (**5d**). The typical peak for the resonance signal of the CH_3COO- group has δ = 2.39 ppm (3H, s) (**5b**), δ = 2.38 ppm (3H, s) (**5c**), δ = 2.39 ppm (3H, s) (**5d**). The peaks represent resonance signals of aromatic protons with δ ranging from 7.31 ppm to 7.91 ppm for 4 peaks of **5b**, from 6.98 ppm to 7.97 ppm for 4 peaks of **5c**, and 7.33 ppm to 7.48 ppm for 9 peaks of **5d**. The 2 peaks represent resonance signals of alkene protons with δ=7.57 (1H, d, J = 16 Hz) and 7.38 (1H, d, J = 16 Hz) of **5b**, δ= 7.54 (1H, d, J = 16 Hz) and 7.43 (1H, d, J = 16 Hz) of **5c**, δ=7.63 (1H, d, J = 14 Hz) and 7.58 (1H, d, J = 14 Hz) of **5d**. The large coupling constants (J = 14–16 Hz) confirmed the trans (E) configuration of the olefinic protons.

Thus, the ^{1}H NMR spectra confirmed the structures of compounds **5a-5d** as acetate derivatives of chalcones **4a-4d**.

**** ^{13}C NMR spectrum***

The ^{13}C-NMR spectrum of compound **5a** is presented in Figure 2.

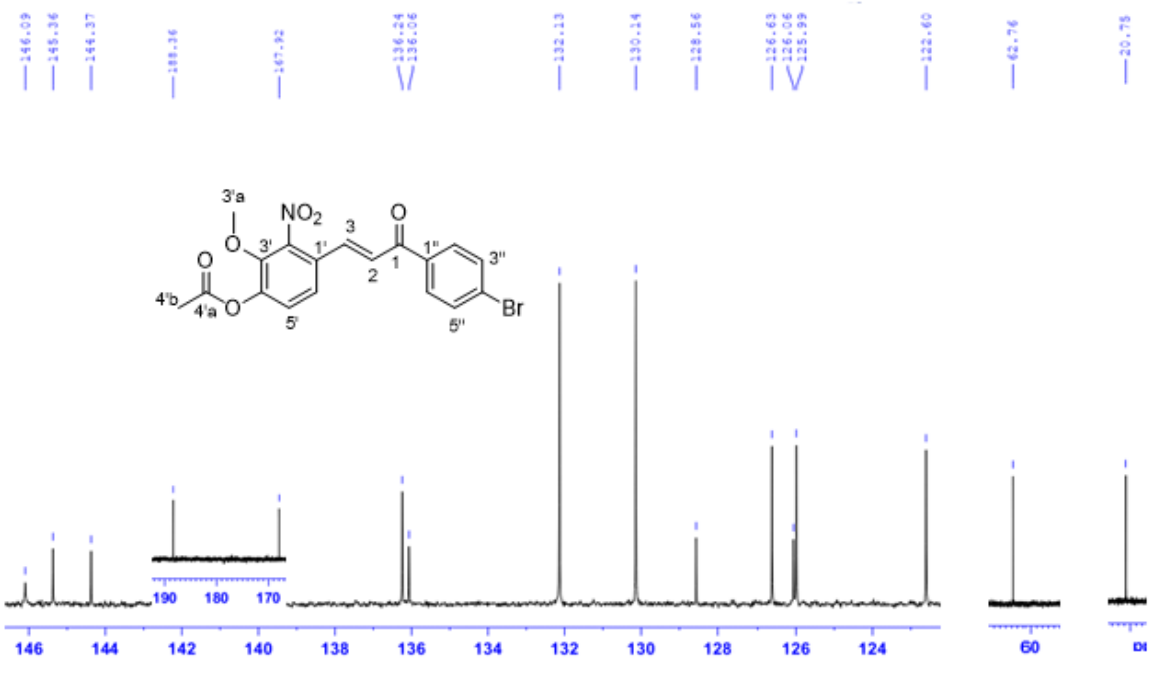


Figure 2. ^{13}C NMR spectrum of compound 5a

Figure 2 is the ^{13}C-NMR spectrum of compound **5a** with 16 peaks representing 16 carbons, in which the peak with δ = 20.8 ppm is the resonance signal of the carbon of group CH_3COO- at position 4'b, the peak with δ = 62.8 ppm is the resonance signal of the carbon of group -OCH_3 at position 3'a. In addition, there are 12 peaks with chemical shifts in the region from 122.6 ppm to 146.1 ppm, which are the resonance signals of aromatic carbons of the two phenyl moieties and alkenes. The peak with δ = 167.9 ppm is the resonance signal of carbon of group -COO- at 4'a position, and the peak with δ = 188.4 ppm is the resonance signal of carbon of group -CO- at 1 position. These peaks are consistent with the expected formula of compound **5a**.

Similar to compound **5a**, compounds **5b-5d** also have spectral peaks consistent with the expected formulas.

The results of the ^{13}C NMR spectral analysis confirmed that the 4 formed compounds are aryl acetate derivatives of chalcones **4a-4d**.

**** HRMS spectra***

The MS spectra of compound **5b** are presented in Figure 3.

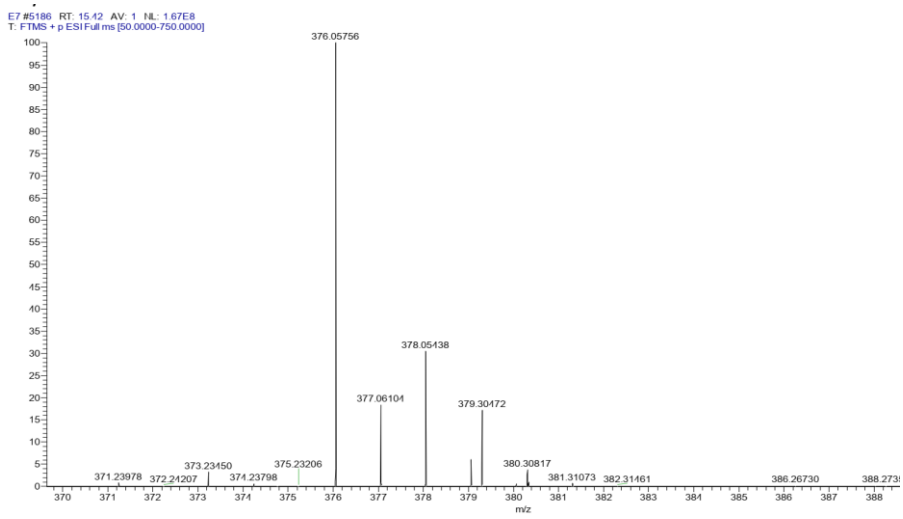


Figure 3. Mass spectrum of compound 5b

Figure 3 shows the mass spectrum of compound **5b.** A peak was observed at m/z 376.0576, which corresponds to the calculated value of 376.0584 for $[M+H]^+$ (^{35}Cl) of $C_{18}H_{14}ClNO_6$. Another peak was observed at m/z 378.0544, matching the calculated value of 378.0554 for $[M+H]^+$ (^{37}Cl) of the same compound.

Similar to compound **5b**, compounds **5c** and **5d** also exhibited spectral peaks consistent with the $[M+H]^+$ ion. For compound **5c**, a peak was observed at m/z 372.1074, closely matching the calculated value of 372.1083 for $[M+H]^+$ of $C_{19}H_{17}NO_7$. For compound **5d,** a peak was observed at m/z 392.1122, corresponding to the calculated value of 392.1134 for $[M+H]^+$ of $C_{22}H_{17}NO_6$.

Thus, based on the reaction diagram and the results of ^{1}H NMR, and ^{13}C NMR spectra, it has been confirmed that compound **5a** is (*E*)-4-(3-(4-bromophenyl)-3-oxoprop-1-en-1-yl)-2-methoxy-3-nitrophenyl acetate, compound **5b** is (*E*)-4-(3-(4-chlorophenyl)-3-oxoprop-1-en-1-yl)-2-methoxy-3-nitrophenyl acetate, compound **5c** is (*E*)-2-

methoxy-4-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)-3-nitrophenyl acetate and compound **5d** is (*E*)-2-methoxy-4-(3-(naphthalen-2-yl)-3-oxoprop-1-en-1-yl)-3-nitrophenyl acetate.

2.2.2. Acetylcholinesterase inhibitory activity

Inhibitory activities against AChE of the 4 ester derivatives **5a -5d** were determined by the Ellman's method, with doneperil as a reference compound. The IC_{50} values for AChE inhibition are indicated in Table 1.

Table 1. Acetylcholinesterase inhibitory activity of esters

Compound	IC_{50} (µg/mL)	Compound	IC_{50} (µg/mL)
4a	*42.23 ± 2.15*	**5a**	> 128
4b	> 128	**5b**	62.31 ± 0.64
4c	> 128	**5c**	32 ± 0.24
4d	32 ± 0.25	**5d**	2.7 ± 0.18
Donepezil	0.024 ± 0.009		

Five out of eight synthesized compounds exhibited acetylcholinesterase (AChE) inhibitory activity. Of these, two chalcones, **4a**, **4d,** and two esters, **5b-5c,** showed moderate inhibitory activity against acetylcholinesterase with their IC_{50} values of 42.23 ± 2.15 *µg/mL*, 32±0.25 *µg/mL*, 62.31±0.64 *µg/mL,* and 32±0.24 *µg/mL*, respectively. Especially, compound **5d** showed strong inhibition of acetylcholinesterase (IC_{50} = 2.7±0.18 *µg/mL*). Thus, when the HO-group was replaced by the CH_3COO- group at position 4 in the ring B, the AchE inhibitory activity increased significantly (3 compounds increased activity compared to the original substance). In the chalcone series and the acetate series of chalcone, the ring A (Ar-) is naphthyl, which has the highest AchE. Inhibitory activity. According to [14]: "For a promising drug candidate for AD, penetration ability through the blood-brain barrier (BBB) is essential". The structural modifications to the chalcone are also made by the consideration of BBB permeability". The highly active compounds all showed that they had lipophilic groups in the rings A and B, which increased the ability to penetrate the blood-brain barrier, leading to increased AChE inhibitory activity.

3. Conclusions

Four chalcones were synthesized from 2-nitrovanillin by condensation reactions. The chalcone compounds and intermediates were confirmed by thin-layer chromatography and compared with the standard compounds. Four new acetate derivatives were synthesized by acetylation reaction between $(CH_3CO)_2O$ and each chalcone of 2-nitrovanillin in high yields (from 89% to 94%). ^1H NMR and ^{13}C NMR spectra confirmed the structures of the obtained acetate derivatives. The two chalcones and three acetate derivatives showed good inhibitory activity against acetylcholinesterase with IC_{50} *(µg/mL)* of: 42.23 ± 2.15 *µg/mL*, 32±0.25 *µg/mL*, 62.31±0.64 (**5b**), 32±0.24 (**5c**), and 2.7±0.18 (**5d**). When the rings A and B of chalones and derivatives are lipophilic substituents, there is a tendency to increase AchE inhibitory activity.

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