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Screening the cholinesterase inhibitory potential of some (1E, 4E)-1.5-diphenylpenta-1.4-dien-3-one derivatives

Acelya Mavideniz, Amirhossein Fallah, Foroogh Koshravi, Farimah Ahdno, Mehmet Arter, Tugba Ercetin, Mustafa Fethi Sahin, Hayrettin Ozan Gulcan*

Eastern Mediterranean University, Faculty of Pharmacy, Famagusta, North Cyprus, Mersin 10 Turkey.

Abstract

α,β-unsaturated ketones are particularly important scaffolds to be utilized in diverse organic reactions including the synthesis of many heterocyclics. Regarding their reactivities as electrophiles, their nature to be utilized as drug candidates are quite limited, although there are natural molecules with diverse pharmacological activities whivh are known to have α,β-unsaturated functionalization. Within this preliminary and random drug-screening based medicinal chemistry study, some (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one derivatives were synthesized and their structures were identified employing chromatographic and spectral methods. The potential of the compounds to inhibit acetylcholinesterase and butyrylcholinesterase enzymes was measured employing modified Ellman's method. Although the compounds were not found to be potent inhibitors in comparison to current drugs, their activity spectra and selectivity properties displayed their availability to be utilized as important scaffolds for further design of similar α,β-unsaturated systems.

Keywords

Acetylcholinesterase, butyrylcholinesterase, α,β-unsaturated ketones.

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***Corresponding author:** Ozan Gulcan, email: ozan.gulcan@emu.edu.tr

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INTRODUCTION

Alzheimer's disease (AD) is one of the life-threatening central nervous system diseases affecting ten millions of people worldwide (Selkoe 2001). The major symptoms of the disease include mainly the progressive cognitive decline, also referred to as dementia. Although dementia can appear throughout the scope of various disease states, AD related dementia is the major form (Whitehouse *et al.* 1982). The pathophysiology of the disease is quite complex involving diverse oxidative stress, and neurodegeneration related mechanisms (Kumar and Singh 2015).

So far, numerous scientific research studies have been conducted to discover the exact pathophysiology and epidemiology of AD. However, no single biochemical pathway has solely been attributed to be involved within the generation of the disease. It is known that cholinesterase system, particularly the action of acetylcholine on some muscarinic and nicotinic receptors, is an important tool of cognition, involving personal characteristics, recognition, learning, and daily activities (Ferreira-Vieira *et al.* 2016). Using this information, cholinesterase inhibition mechanism has been suggested to the clinic through the end of the last century to overcome with dementia related symptoms of AD. Indeed, acetylcholine hydrolyzing enzymes, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), have been targeted and clinically used current drugs have been obtained. Donepezil, rivastigmine, and galantamine are the currently used cholinesterase inhibitor drugs used for the treatment of cognition symptoms of AD (Deardorff WJ *et al.* 2015). Based on the pharmacokinetic and pharmacodynamic variances among these drugs, there has been a continuous interest on the discovery of novel cholinesterase inhibitor molecules. Regarding this point, within this preliminary random screening base study, we have synthesized some (1E, 4E)-1,5-diphenylpenta-1,4-dien-3-one derivatives and screened their potential to inhibit AChE and BuChE. Within the scope of Organic Chemistry II lectures in Eastern Mediterranean University, pharmacy students exploit from Aldol reaction to learn and practice the synthesis of (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one. Since the methodology employs the reaction between benzaldehyde and acetone, we have used several substituted benzaldehyde derivatives. The title compounds are shown in Figure 1.

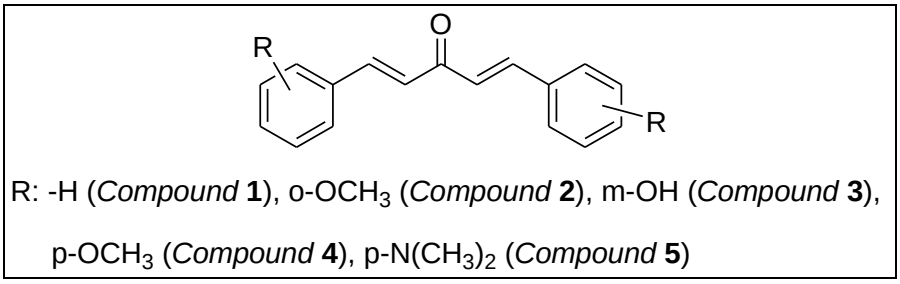

Figure 1: The title compounds synthesized.

MATERIALS AND METHODS

Benzaldehyde, o-anisaldehyde, p-anisaldehyde, 3-hydroxybenzaldehyde, 4-dimethylaminobenzaldehyde, acetone, sodium hydroxide and ethanol were obtained from Sigma Aldrich (CA, USA). Purities of the chemicals were more than 99% as stated on their labels. Therefore, no other purification was conducted on the reagents.

Synthesis of the title compounds

For a typical reaction, 62.5 mmol of sodium hydroxide was dissolved in water-ethanol solution (55:45) in a 100 ml reaction flask. 24.5 mmol of the benzaldehyde derivative and 12.9 mmol of acetone was added to the solution. The reaction was stirred at room temperature for 15 min. The precipitate formed was filtered off and washed with acidified aqueous.

Structure identification and characterization

The reactions were monitored employing Thin Layer Chromatography (TLC) (Alugram Xtra SIL G/UV_{254} 0,2 mm silica gel 60 with fluorescent indicator from Germany) with an n-hexane ; ethyl acetate (1:1) mobile phase. The infrared spectra of the compounds were obtained with a Shimadzu FT-IR Prestige Infrared Spectrophotometer. The ^{1}H-NMR and ^{13}CNMR spectra of the compounds were obtained using a Bruker 400 NMR Spectrophotometer. Trimethylsilane was used as internal standard and DMS-d6 as solvent.

(1E,4E)-1,5-diphenylpenta-1,4-dien-3-one (**compound 1**): Yield 85%, solid yellow crystals, mp 125°C (uncorrected data). IR, 3055 (ArC-H), 1648 (-C=O). ^{1}HNMR, 7.87 ppm (d, HC=CH-Ar), 7.81 ppm (dd, Ar-H, o), 7.48 ppm (dd, Ar-H, m), 7.42 ppm (s, Ar-H, p), 7.38 ppm (d, -CH=CH-Ar). ^{13}CNMR, 188ppm (C=O).

(1E,4E)-1,5-bis(2-methoxyphenyl)penta-1,4-dien-3-one (**compound 2**): Yield 87%, solid pale yellow crystals, mp 134°C (uncorrected data). IR, 3027 (ArC-H), 1668 (-C=O). ^{1}HNMR, 7.93 ppm (d, -CH=CH-Ar), 7.81 ppm (d, Ar-H, o), 7.42 ppm (t, Ar-H, p), 7.28 ppm (d, Ar-H, m), 7.09ppm (d, Ar-H, o′), 7.09ppm (d, -CH=CH-Ar). ^{13}CNMR, 188ppm (C=O).

(1E,4E)-1,5-bis(3-hydroxyphenyl)penta-1,4-dien-3-one (**compound 3**): Yield 89%, solid brown crystals, mp 136°C (uncorrected data). 3075 (ArC-H), 1620 (-C=O). ^{1}HNMR, 9.74 ppm (s, Ar-O<u>H</u>), 7.79 ppm (d, -CH=<u>CH</u>-Ar), 7.35 ppm (t, Ar-H, m), 7.31 ppm (d, Ar-H, o), 7.28 ppm (d, -<u>CH</u>=CH-Ar), 7.25 ppm (d, Ar-H, p), 6.95 ppm (d, Ar-H, o). ^{13}CNMR, 188ppm (C=O).

(1E,4E)-1,5-bis(4-methoxyphenyl)penta-1,4-dien-3-one (**compound 4**): Yield 81%, solid yellow crystals, mp 128°C (uncorrected data). 3033 (ArC-H), 1648 (-C=O). ^{1}HNMR, 7.73 ppm (d, -CH=<u>CH</u>-Ar), 7.68 ppm (d, Ar-H, o), 7.16 ppm (d, -<u>CH</u>=CH-Ar), 6.99 ppm (d, Ar-H, m), 3.79 ppm (s, Ar-O<u>CH_3</u>). ^{13}CNMR, 188ppm (C=O).

(1E,4E)-1,5-bis(4-(dimethylamino) phenyl)penta-1,4-dien-3-one (**compound 5**): Yield 85%, solid orange crystals, mp 141°C (uncorrected data). 3038 (ArC-H), 1634 (-C=O).). ^{1}HNMR, 9.69 ppm (s, N-H), 7.69 ppm (d, -CH=<u>CH</u>-Ar), 7.60 ppm (d, Ar-H, o), 7.05 ppm (d, -<u>CH</u>=CH-Ar), 6.74 ppm (d, Ar-H, m), 3.48 ppm (s, N-<u>CH_3</u>). ^{13}CNMR, 188ppm (C=O).

Determ*ination of AChE and BChE inhibitory activities*

The modified spectrophotometric method of Ellman was used to determine AChE and BuChE inhibitory activities of 5 compounds synthesized (Gulcan *et al.* 2014). The enzymes used for cholinesterase activity studies were, electric eel AChE (eeAChE) (Sigma) and equine BuChE (Sigma). Acetylthiocholine iodide and butyrylthiocholine chloride (Sigma, St. Louis, MO, USA) were employed as substrates of the reaction. 5, 5´-Dithio-bis (2-nitrobenzoic) acid (DTNB, Sigma, St. Louis, MO, USA) was used for the measurement of the cholinesterase activity. 50 mM Tris HCl buffer (pH 8.0), 6.8 mM DTNB, 2 µl of sample solutions and 10 µl of AChE/BChE solution were added in a 96-well microplate. The reaction was then initiated with the addition of 10 µl of acetylthiocholine iodide/butyrylthiocholine chloride. The hydrolysis of acetylthiocholine iodide/butyrylthiocholine chloride was monitored by the formation of the yellow 5-thio-2-nitrobenzoate anion as a result of the reaction of DTNB with thiocholines, catalyzed by enzymes at a wavelength of 412 nm utilizing a 96-well microplate reader (Varioskan Flash, Thermo Scientific, USA) and incubated for 15 min at 27°C. The measurements and calculations were evaluated by using SkanIt Software 2.4.5 RE for Varioskan Flash software. Percentage of inhibition of AChE and BuChE were determined by comparison of the rates of reaction of samples relative to blank sample (methanol) using the formula (E-S)/E x 100, where E is the activity of enzyme without the test sample and S is the activity of enzyme with the test sample. The experiments were

done in triplicate. Donepezil hydrochloride and rivastigmine were used as reference compound. The percent inhibition at 100 and 50 µM was obtained for each test compound with standard compounds.

RESULTS AND DISCUSSION

The general synthetic scheme of the title compounds is shown in the Figure 2. Employing the general synthetic scheme (1E, 4E)-1,5-diphenylpenta-1,4-dien-3-one derivatives were synthesized. Following the structure identification studies, the compounds were screened for their potential to inhibit AChE and BuChE enzymes. The results obtained are displayed the Table 1.

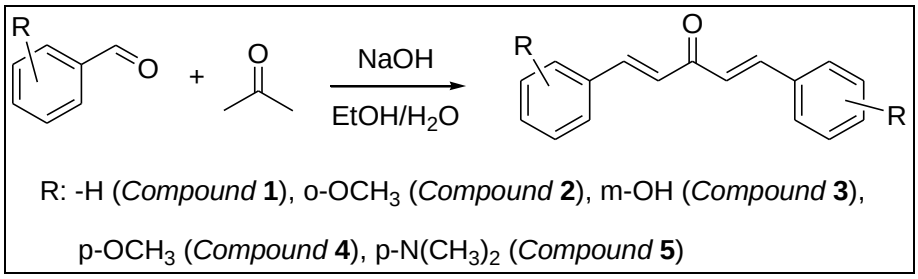

Figure 2: The general synthetic scheme and the title compounds.

Table 1: The potential the title compounds to inhibit AChE and BuChE enzymes.

Compounds	% Inhibition (AChE) 50µM	% Inhibition (AChE) 100µM	% Inhibition (BuChE) 50µM	% Inhibition (BuChE) 100µM
Compund 1	36.54 ± 0.33	54.2 ± 0.23	45.90 ± 0.29	58.6 ± 0.41
Compund 2	11.1 ± 0.04	25.6 ± 0.09	21.52 ± 0.04	36.85 ± 0.04
Compund 3	29.77 ± 0.36	45.04 ± 0.37	49.65 ± 0.31	68.11 ± 0.72
Compund 4	29.01 ± 0.12	44.37 ± 0.28	25.76 ± 0.13	39.37 ± 0.91
Compund 5	14.51 ± 0.07	24.75 ± 0.14	18.31 ± 0.08	39.66 ± 0.21
Rivastigmine	65.02 ± 0.11	76.12 ± 0.06	78.31 ± 0.03	83.61 ± 0.09
Donepezil	91.20 ± 0.17	94.19 ± 0.10	83.75 ± 0.04	88.22 ± 0.62

According to the results, the title compounds were not found to be superior to the currently used drugs donepezil and rivastigmine, which were already used as references in this study. However, each title compound displayed activity for both AChE and BuChE. Although it is not apparent for each title molecule, a tendency for more inhibition of BuChE particularly for compounds 2 , 3, and 5, was identified, it is noteworthy to state that it is very critical to identify IC_{50}s of the title compounds to

further proof this observation. Besides, the results were primitive to describe a structure activity relationship study. In other words, the (1E, 4E)-1,5-diphenylpenta-1,4-dien-3-one main moiety was obtained important for activity, but no net result was observed depending on the substitutions followed. From this point of view, the results of the study indicated that this scaffold stands a good candidate to design novel (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one derivative potent cholinesterase inhibitors. However, more data related to the number of more substitutions and concomitant IC_{50} are needed to explore both the molecule-receptor interactions and a concessive structure activity relationship studies.

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