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Synthesis and cholinesterase inhibitory activity studies of some piperidinone derivatives

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Abstract: A series of α,β-unsaturated carbonyl based piperidinone derivatives were synthesized and evaluated for their abilities to inhibit AChE and BuChE. All compounds exhibited AChE and BuChE inhibitory activity in different ratios. Among the series, compound **1d**, (1-benzyl-3,5-bis(4-nitrobenzylidene)piperidine-4-one), was found to be the most potent derivative against AChE (IC_{50}= 12.55 µM) and compound **1g**, (1-benzyl-3,5-bis(4-chlorobenzylidene)piperidine-4-one) showed the best anti-BuChE activity (IC_{50}= 17.28 µM). The derivatives exhibited selectivity on AChE enzyme with respect to BuChE. Only compound **1g**, bearing chlorine substituents, demonstrated as a dual inhibitor of cholinesterases. Taken together, these results indicated that α,β-unsaturated carbonyl based piperidinone scaffold might be a promising drug candidate for further anti-AD drug development.

Keywords: Acetylcholinesterase inhibitors; butyrylcholinesterase inhibitors; piperidinone; Alzheimer's disease.

1. Introduction

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disorder associated with loss of cholinergic neurons in the brain which results in memory loss, cognitive deficiency and learning disabilities. It is the most common type of dementia among elderly people. According to the World Alzheimer's Report 2016, more than 47 million people worldwide are suffering from dementia and the number of affected patients is estimated to increase to 131.5 million by 2050.[1] The exact origin of the disease is still unclear and several factors are considered to play important roles in AD pathogenesis. Inhibition of the enzyme acetylcholinesterase (AChE), which is responsible for the degradation of the neurotransmitter acetylcholine (ACh) at synaptic clefts, is the most widely accepted hypothesis. AChE is the predominant ACh hydrolyzing enzyme while butyrylcholinesterase (BuChE) which also plays an important role in cholinergic neurotransmission acts as a co-regulator of the ACh degradation. To date, ChE inhibitors, such as tacrine, donepezil, galantamine and rivastigmine, are the main FDA-approved drugs for the symptomatic treatment of AD (Scheme 1). Thus, inhibition of AChE and BuChE considered as valuable therapeutic targets for the treatment of AD.

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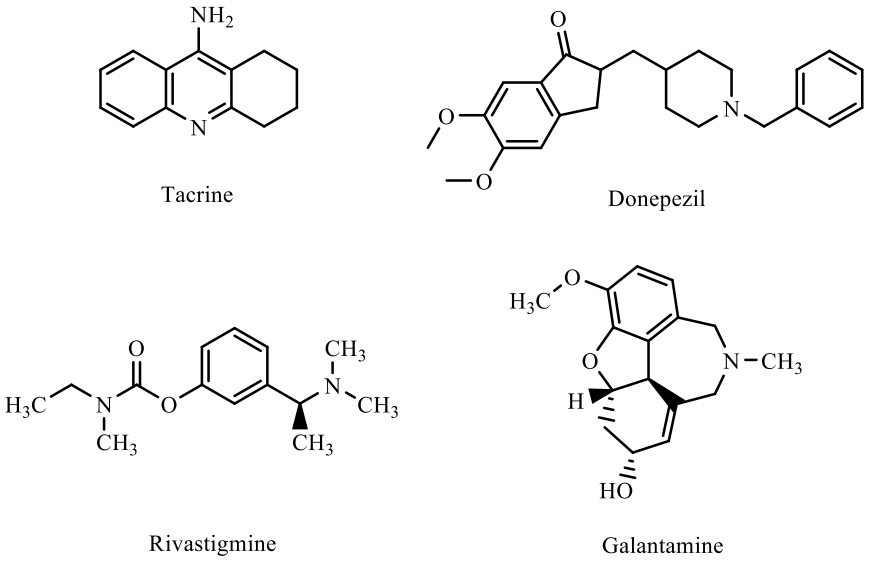


Scheme 1. FDA-approved ChE inhibitors for the treatment of Alzheimer's disease

The crystal structure of both AChE and BuChE indicates that they have two main substrate-binding sites: the peripheral anionic site (PAS) located near the entrance of the gorge and the catalytic active site (CAS) located at the bottom of the gorge.[2,3] The main difference between two enzymes is associated with acyl binding site of CAS. BuChE has a larger region than of AChE which allows bulkier ligands binding.

Several studies have been indicated that chalcone derivatives and curcumin-like compounds having an α,β-unsaturated carbonyl moiety have a variety of pharmacological activities.[4-9] Recent studies also showed that they have the capacity of inhibiting AChE and BuChE enzymes and could be promising candidates for the management of AD.[10] 4-piperidinone moieties were found to be potent inhibitors of AChE.[11,12] Especially, bis-piperidinone derivatives showed high ChE inhibitory potencies.[12] According to the docking results in the literature, one of the phenyl moiety attached to the piperidinone core was interacted with acyl binding pocket, the other was interacted with PAS of the AChE enzyme.[12] On the other hand, donepezil is the most popular AChE inhibitor and several donepezil analogs have been reported to show more potent effects on inhibiting AChE. *N*-benzylpiperidine fragment of donepezil was known to interact with CAS of the AChE enzyme and provides the possibility for stronger interaction. Moreover, a protonable amine group is necessary for cation-π interactions with the aromatic amino acids of the catalytic center of the AChE. In this regard, presence of *N*-benzylpiperidine moiety contributes to inhibitory potency and has also been used to develope potent AChE inhibitors.

Based on the mentioned reports, in the current study, a series of α,β-unsaturated carbonyl based piperidinone analogs were designed, synthesized, and investigated for their *in vitro* anti-Alzheimer activities. All synthesized compounds were prepared by the Claisen-Schmidt condensation of *N*-benzyl-4-piperidinone with a series of aromatic aldehydes having different substituents at *para* position.

2. Experimental

2.1. Chemistry

Melting points of the synthesized compounds were taken on a Stuart SMP30 (Staffordshire, ST15 OSA, U.K.) and are uncorrected. IR spectra were registered using an attenuated total reflectance (ATR) unit on a Perkin-Elmer 100 FT-IR spectrometer and wave numbers are expressed in cm^{-1}. ^1H NMR spectra of the compounds were recorded in deutero-chloroform($CDCl_3$) on a Varian AS 400 Mercury Plus NMR spectrometer (Palo Alto, CA, U.S.A.) at 400 MHz. Chemical shifts are given in ppm (δ) and peak multiplicities are reported as follow: s (singlet), d (doublet), m (multiplet).

Elemental analyses for C, H, and N were performed using Leco TruSpec Micro (Leco, St. Joseph, MI). All chemicals, reagents and solvents were bought from commercial suppliers; Sigma-Aldrich and Fluka Companies. Chemical purities of the final compounds were checked by analytical thin layer chromatography (TLC) on Merck silica gel plates (Kieselgel 60 F254 /UV 254 nm).

*2.1.1. General Procedure for the Synthesis of Compounds **1a-h***

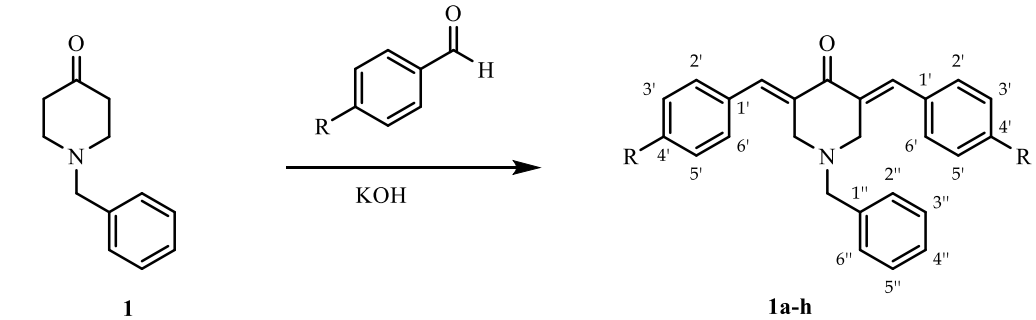
The synthesis of 4-piperidinone derivatives were realized in a simple ‘‘one-pot’’ method (Scheme 2).[13-16] In the ‘‘one-pot’’ synthesis, 1-benzyl-4-piperidinone (5 mmol) and corresponding aromatic aldehyde (10 mmol) were dissolved in 30 mL of methanol at 0 °C (ice bath). To this reaction mixture, 30% solution of KOH (2 mL) was added dropwise. Then, the reaction mixture was allowed to stir at room temperature for 3-5 h. The obtained yellow compound was filtered and washed with cold methanol several times. Crude product was then crystallized from ethyl acetate to obtain pure product.

2.2. Biological Activity Assays

2.2.1. Acetylcholinesterase/Butyrylcholinesterase Activity

AChE (E.C. 3.1.1.7., VI-S type, from Electric eel), BuChE (E.C. 3.1.1.8, from equine serum), *S*-butyrylthiocholine iodide (BTC) were bought from Sigma-Aldrich chemical company (MO, USA). 5,5-Dithiobis(2-nitrobenzoic acid) (DTNB), acetylthiocholine iodide (ATC), potassium dihydrogen phosphate, potassium hydroxide and sodium hydrogen carbonate were obtained from Fluka (Bachs, Switzerland). Absorption was measured using a Shimadzu 160-A UV-Vis spectrophotometer.

Inhibitory capacity of compounds **1a-h** on AChE and BuChE enzymes were evaluated through the use of a slightly modified colorimetric method of Ellman et al.[17,18] Rivastigmine and galantamine were used as the reference drugs. Prior to use, the temperature was adjusted at 25 °C. 100 µL of enzyme solution and 100 µL of inhibitor solution were mixed in 3 mL phosphate buffer 0.1 M at pH 8.0. After 5 min of preincubation, 100 µL of DTNB solution and 20 µL of substrate (0.075 M ATC or BTC) were added. Then, AChE/BuChE inhibitory activities were spectrophotometrically measured at 412 nm. The activities of the enzymes were measured at least five different concentrations of the inhibitor (between 10^{-2} and 10^{-8}) to inhibit the enzymes between 0 and 100%. All assays were performed in triplicate. The IC_{50} values and the selectivity results of the inhibitors were summarized in Table 1.



1

1-benzyl-4-piperidinone

1a-h

R

a= H
b= CH_3
c= OCH_3
d= NO_2
e= CN
f= F
g= Cl
h= Br

Scheme 2. Synthesis pathway of the final compounds

Table 1. *In vitro* AChE and BuChE inhibitory activities of the final compounds

Compound	IC_{50} ± S.E.M. (μM)[a]		Selectivity AChE/BuChE
	***ee*AChE**	***eq*BuChE**	
1a	23.75 ± 0.91	59.96 ± 2.12	0.40
1b	18.45 ± 0.79	38.32 ± 2.85	0.48
1c	16.27 ± 0.80	43.88 ± 1.96	0.37
1d	12.55 ± 0.75	42.53 ± 2.81	0.30
1e	20.20 ± 0.96	33.25 ± 2.33	0.61
1f	16.31 ± 0.38	18.78 ± 1.13	0.87
1g	18.04 ± 0.74	17.28 ± 0.80	1.04
1h	22.92 ± 0.14	26.76 ± 3.51	0.86
Galantamine	0.43 ± 0.03	14.92 ± 0.57	0.02
Rivastigmine	10.87 ± 0.24	5.13 ± 0.18	2.12

[a] Data are means ± standard error of the main of triplicate independent experiments.
The IC_{50} values were calculated by using GraphPad 5 software.

3. Results and Discussion

3.1. Chemistry

In the current study, eight piperidinone derivatives were prepared according to the given literatures[13-16] The synthesis of the compounds was accomplished by the Claisen-Schmidt condensation of *N*-benzyl-4-piperidinone with a series of aromatic aldehydes. The synthetic pathway is given in Scheme 2.

The desired piperidinone analogues were prepared by using a simple ‘’one-pot’’ method. *N*-benzyl-4-piperidinone was used as the starting material. Corresponding benzaldehyde bearing a substituent at *para* position (methyl, methoxy, chlorine, bromine, fluorine, nitro and nitrile) or nonsubstituted benzaldehyde was stirred with the starting material in the presence of KOH using methanol as solvent. The obtained crude products were purifed by crystallization from ethyl acetate to achieve pure target compounds **1a-h** in excellent yields.

All synthesized compounds were confirmed by spectrophotometric techniques (IR and ^{1}H NMR), elemental analyses and melting points. ^{1}H NMR spectra of the title compounds were consistent with expected resonance signals in terms of chemical shifts and integrations. The purity levels of compounds were determined by elemental analyses (C, H, N), and the results were within ±0.4% of the calculated values.

The IR spectra of the final compounds showed the appearance of a characteristic stretching band for α,β-unsaturated C=O in the range of 1672-1658 cm^{-1}.[19] C=C stretching bands were observed between 1629-1440 cm^{-1}. Aliphatic C-H stretching bands were recorded between 2989-2803 cm^{-1} and =C-H stretching bands were observed between 3082-3007 cm^{-1}. In the IR spectra of compound **1d**, the intense absorbtion bands appeared at 1514 cm^{-1} and 1343 cm^{-1} were attributed to asymmetric and symmetric vibrations of nitro substituent, respectively, which are confirmative values with the literature survey.[19] Additionally, C≡N characteristic stretching vibration was detected at 2227 cm^{-1} in the spectra of compound **1e** as expected.

The NMR data of the final compounds were recorded in $CDCl_3$. According to the ^{1}H NMR spectra, the aromatic and aliphatic proton signals were observed in the expected regions with expected integrations and splittings.[19] The proton signal due to the =CH groups integrating for two protons were

recorded as a singlet between δ 7.81-7.70 ppm. The aromatic proton signals of nonsubstituted benzyl ring connected to piperidinone nitrogen were detected in the range of δ 7.28-7.15 ppm integrating five protons with expected multiplicities. In the spectra of nitro (**1d**), nitrile (**1e**), chloro (**1g**) and bromo (**1h**) containing derivatives, aromatic protons at 3'-, 5'- positions of benzylidene ring were resonated as a doublet signal at δ 8.22-7.34 ppm integrating for four protons while the signal of protons at 2'-, 6'- positions were observed at δ 7.45-7.18 ppm. The relatively shifted to the downfield region of the 3'-, 5'- protons were due to the withdrawing effect of nitro, nitrile, chloro and bromo atoms. On the otherhand, for methoxy (**1c**) and fluoro (**1f**) containing derivatives, the signal resonated between at δ 7.09-6.90 ppm were attributed to 3'-, 5'- protons and the other signal relatively shifted to the downfield region at δ 7.34-7.29 ppm were attributed to 2'-, 6'- protons due to the electron donating effects of these substituents.[19] These proton signals of compounds **1a** and **1b** were observed in the region of δ 7.40-7.24 ppm as multiplet signal. In the aliphatic region, signals integrating for four protons at δ 3.87-3.79 ppm were attributed to piperidinone protons as expected. Methylene protons attached to piperidinone nitrogen showed a singlet signal between δ 3.72-3.70 ppm. The presence of methyl group protons of compound **1b** and methoxy group protons of compound **1c** were confirmed by a singlet signal in the aliphatic region at δ 2.37 and 3.82 ppm, respectively.[19]

The structure of the final compounds was further verified by elemental analyses (C, H, N). The analytical results for the elements were within ±0.4% of the theoretical values. All final compounds were reported in the literature[16,20-22], but their AChE and BuChE activity results were reported for the first time with this study.

*1-benzyl-3,5-dibenzylidenepiperidin-4-one (**1a**):*Yield 81%; mp 163.1 ºC. IR V_{max}(cm^{-1}) 3060, 3042, 3014, 1670, 1614, 1583, 1488, 1443, 1297, 1261, 1186, 1026, 932, 765, 734, 687. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (2H, s, N-CH_2), 3.87 (4H, s, piperidinone-H), 7.15-7.24 (5H, m, H-2'', H-3'', H-4'', H-5'', H-6''), 7.31-7.40 (10H, m, H-2', H-3', H-4', H-5', H-6'), 7.81 (2H, s, =CH) ppm. Anal. calcd. for $C_{26}H_{23}NO$. 0.2H_2O: C, 84.61; H, 6.39; N, 3.80. Found: C, 84.65; H, 6.36; N, 3.53.

*1-benzyl-3,5-bis(4-methylbenzylidene)piperidin-4-one (**1b**):* Yield 83%; mp 178.5 ºC. IR V_{max}(cm^{-1}) 3078, 3021, 2985, 2910, 2814, 1671, 1614, 1577, 1559, 1508, 1451, 1264, 1178, 999, 929, 814, 740, 726, 697. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (6H, s, CH_3), 3.71 (2H, s, N-CH_2), 3.86 (4H, s, piperidinone-H), 7.17-7.22 (5H, m, H-2'', H-3'', H-4'', H-5'', H-6''), 7.24-7.27 (8H, m, H-2', H-3', H-5', H-6'), 7.78 (2H, s, =CH) ppm. Anal. calcd. for $C_{28}H_{27}NO$. 0.1H_2O: C, 85.07; H, 6.94; N, 3.54. Found: C, 84.89; H, 6.85; N, 3.58.

*1-benzyl-3,5-bis(4-methoxybenzylidene)piperidin-4-one (**1c**):* Yield 79%; mp 172.9 ºC. IR V_{max}(cm^{-1}) 3064, 3028, 3007, 2969, 2889, 2835, 1668, 1597, 1576, 1508, 1453, 1440, 1259, 1168, 1023, 932, 828, 731, 693. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (2H, s, N-CH_2), 3.82 (6H, s, OCH_3), 3.85 (4H, s, piperidinone-H), 6.90 (4H, d, *J*= 8.7 Hz, H-3', H-5'), 7.18-7.26 (5H, m, H-2'', H-3'', H-4'', H-5'', H-6''), 7.31 (4H, d, *J*= 8.6 Hz, H-2', H-6'), 7.77 (2H, s, =CH) ppm. Anal. calcd. for $C_{28}H_{27}NO_3$: C, 79.03; H, 6.40; N, 3.29. Found: C, 78.82; H, 6.39; N, 3.26.

*1-benzyl-3,5-bis(4-nitrobenzylidene)piperidin-4-one (**1d**):* Yield 81%; mp 199.4 ºC. IR V_{max}(cm^{-1}) 3060, 3028, 2989, 2907, 2825, 1666, 1597, 1514, 1343, 1189, 1109, 857, 745, 699. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (2H, s, N-CH_2), 3.82 (4H, s, piperidinone-H), 7.20-7.28 (5H, m, H-2'', H-3'', H-4'', H-5'', H-6''), 7.45 (4H, d, *J*= 8.8 Hz, H-2', H-6'), 7.79 (2H, s, =CH), 8.22 (4H, d, *J*= 8.8 Hz, H-3', H-5') ppm. Anal. calcd. for $C_{26}H_{21}N_3O_5$. 0.1H_2O: C, 68.29; H, 4.67; N, 9.19. Found: C, 68.09; H, 4.93; N, 8.85.

*1-benzyl-3,5-bis(4-cyanobenzylidene)piperidin-4-one (**1e**):* Yield 74%; mp 221.1 ºC. IR V_{max}(cm^{-1}) 3057, 3028, 2971, 2903, 2227, 1658, 1629, 1601, 1573, 1503, 1411, 1251, 1188, 1005, 979, 830, 748, 703. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (2H, s, N-CH_2), 3.80 (4H, s, piperidinone-H), 7.21-7.25 (5H, m, H-2'', H-3'', H-4'', H-5'', H-6''), 7.38 (4H, d, *J*= 8.2 Hz, H-2', H-6'), 7.65 (4H, d, *J*= 8.4 Hz, H-3', H-5'), 7.75 (2H, s, =CH) ppm. Anal. calcd. for $C_{28}H_{21}N_3O$. 1.2H_2O: C, 76.94; H, 5.40; N, 9.61. Found: C, 76.55; H, 5.36; N, 9.24.

*1-benzyl-3,5-bis(4-fluorobenzylidene)piperidin-4-one (**1f**):* Yield 73%; mp 162.9 ºC. IR V_{max}(cm^{-1}) 2987, 2896, 1670, 1617, 1603, 1581, 1507, 1455, 1235, 1190, 1004, 924, 828, 749, 700. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (2H, s, N-CH_2), 3.82 (4H, s, piperidinone-H), 7.03-7.09 (4H, m, H-3', H-5'), 7.20-7.27 (5H, m, H-2", H-3", H-4", H-5", H-6"), 7.29-7.34 (4H, m, H-2', H-6'), 7.76 (2H, s, =CH) ppm. Anal. calcd. for $C_{26}H_{21}F_2NO$: C, 77.79; H, 5.27; N, 3.49. Found: C, 77.44; H, 5.38; N, 3.25.

*1-benzyl-3,5-bis(4-chlorobenzylidene)piperidin-4-one (**1g**):* Yield 87%; mp 167 ºC. IR V_{max}(cm^{-1}) 3082, 3060, 3021, 2982, 2900, 2803, 1672, 1616, 1579, 1488, 1262, 1185, 1089, 999, 930, 823, 733, 695. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (2H, s, N-CH_2), 3.80 (4H, s, piperidinone-H), 7.23-7.26 (9H, m, H-2", H-3", H-4", H-5", H-6", H-2', H-6'), 7.34 (4H, d, *J*= 8.5 Hz, H-3', H-5'), 7.73 (2H, s, =CH) ppm. Anal. calcd. for $C_{26}H_{21}Cl_2NO$: C, 71.90; H, 4.87; N, 3.22. Found: C, 71.78; H, 5.02; N, 2.97.

*1-benzyl-3,5-bis(4-bromobenzylidene)piperidin-4-one (**1h**):* Yield 78%; mp 172 ºC. IR V_{max}(cm^{-1}) 2982, 2900, 1672, 1617, 1576, 1557, 1485, 1451, 1261, 1184, 1069, 1001, 928, 819, 731, 695. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (2H, s, N-CH_2), 3.79 (4H, s, piperidinone-H), 7.18 (4H, d, *J*= 8.4 Hz, H-2', H-6'), 7.24-7.28 (5H, m, H-2", H-3", H-4", H-5", H-6"), 7.50 (4H, d, *J*= 8.4 Hz, H-3', H-5'), 7.70 (2H, s, =CH) ppm. Anal. calcd. for $C_{26}H_{21}Br_2NO$: C, 59.68; H, 4.05; N, 2.68. Found: C, 59.92; H, 4.34; N, 2.47.

3.2. Biological Activity Evaluation

The target compounds **1a-h** were evaluated for their *in vitro* cholinesterase inhibitory activity against AChE and BuChE enzymes by modified Ellman's spectrophotometric method.[17,18] Rivastigmine and galantamine were used as the reference standards and the results were summarized in Table 1 as IC_{50} values.

Different substituents such as methyl, methoxy, nitro, nitrile, fluorine, chlorine and bromine were introduced into *para* positions of both benzylidene rings in order to investigate their effect on the inhibitory potency. According to the AChE results, all compounds exhibited inhibitory activity in the range of 12.55-23.75 μM. Compound **1d** bearing nitro substituent showed the highest activity with an IC_{50} value of 12.55 μM which is comparable to the standard drug rivastigmine (IC_{50}= 10.87 μM) and also exhibited the highest selectivity for AChE over BuChE in the series. The compounds having substitutions at *para* position of benzylidene groups (**1b**, **1c**, **1d**, **1e**, **1f**, **1g** and **1h**) were found to be more potent against AChE enzyme in comparison to that without any substitution (**1a**). This result suggested that insertion of a substituent to this position appeared to improve the AChE inhibitory activity. In addition, regarding the derivatives bearing halogens, the order of the inhibitory potency (**1f**, **1g**, **1h**) was observed as: flourine > chlorine > bromine.

In comparison to AChE, all compounds, generally were found to be less potent against BuChE enzyme and they showed moderate to weak BuChE inhibition with IC_{50} values in the range of 17.28-59.96 μM. Halogen containing derivatives (**1f**, **1g**, **1h**) displayed the highest BuChE activity within the series. This indicated that the presence of a halogen atom on benzylidene moiety has a positive influence on BuChE inhibition. Moreover, the compounds having halogen substituent (**1f**, **1g**, **1h**) exhibited dual inhibitor of AChE and BuChE, possessing a selectivity index 0.87, 1.04 and 0.86, respectively. Compound **1g**, chlorine bearing derivative, showed the best inhibitory activity with an IC_{50} value of 17.28 μM, followed by fluorine derivative **1f** with an IC_{50} value of 18.78 μM. Among the tested compounds, compound **1a**, nonsubstituted analogue, demonstrated the weakest BuChE activity. Therefore, it seems that introduction of a substituent into *para* position of benzylidene groups improved the anti-BuChE potency.

4. Conclusion

A series of α,β-unsaturated carbonyl based bis-piperidinone derivatives, having potencies of interacting with CAS and PAS of the enzyme, were synthesized and assayed for their AChE and BuChE inhibitory activities. The biological assays revealed that the compounds were able to inhibit both AChE and BuChE in different ratios. The synthesized derivatives generally were found to be more potent against AChE rather than BuChE. Among the series, compound **1d**, having nitro substituent displayed the best anti-AChE activity (IC_{50}= 12.55 μM) with a selectivity for AChE

whereas compound **1g**, having chlorine substituent showed the best anti-BuChE activity with a dual inhibition (BuChE IC_{50}= 17.28 μM, AChE IC_{50}= 18.04 μM). Based on the data, the introduction of a substituent on benzylidene moieties into *para* positions resulted in improvement on both AChE and BuChE potencies when compared with nonsubstituted analogues. Besides, the insertion of a halogen provided an increase on BuChE inhibition. However, no correlation was established between the inhibitory potency on AChE/BuChE and the electron withdrawing or donating effects of the substituents. On the basis of these findings, it can be stated that these bis-derivatives might prove to be promising scaffolds for the development of new potent anti-AD drugs. This work is still under progress in our laboratory.

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Supporting Information

Supporting information accompanies this paper at http://www.acgpubs.org/journal/organic-communications

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References

[1] Prince, M.; Comas-Herrera, A.; Knapp, M.; Guerchet, M.; Karagiannidou, M. World Alzheimer Report 2016. Improving healthcare for people living with dementia: Coverage, quality and costs now and in the future, Alzheimer's Disease International, London. https://www.alz.co.uk/research/WorldAlzheimerReport2016.pdf.

[2] Nicolet, Y.; Lockridge, O.; Masson, P.; Fontecilla-Camps, J.C.; Nachon, F. Crystal structure of human butyrylcholinesterase and of its complexes with substrate and products. *J. Biol. Chem.* **2003**, *278*, 41141-41147.

[3] Dvir, H.; Silman, I.; Harel, M.; Rosenberry, T.L.; Sussman, J.L. Acetylcholinesterase: from 3D structure to function. *Chem. Biol. Interact.* **2010**, *187*, 10-22.

[4] Lal, J.; Gupta, S.K.; Thavaselvam, D.; Agarwal, D.D. Design, synthesis, synergistic antimicrobial activity and cytotoxicity of 4-aryl substituted 3,4-dihydropyrimidinones of curcumin. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2872-2876.

[5] Magerramov, A.M.; Kurbanova, M.M.; Abdinbekova, R.T.; Rzaeva, I.A.; Farzaliev, V.M.; Allakhverdiev, M.A. Synthesis and antioxidative properties of some 3,4-dihydropyrimidin-2(1*H*)ones(-thiones). *Russ. J. Appl. Chem.* **2006**, *79*, 787-790.

[6] Feng, R.; Lu, Y.; Bowman, L.L.; Qian, Y.; Castranova, V.; Ding, M. Inhibition of activator protein-1, NF-kB, and MAPKs and induction of phase 2 detoxifying enzyme activity by chlorogenic acid. *J. Biol. Chem.* **2005**, *280*, 27888-27895.

[7] Bukhari, S.N.A.; Tajuddin, Y.; Benedict, V.J.; Lam, K.W.; Jantan, I.; Jalil, J.; Jasamai, M. Synthesis and evaluation of chalcone derivatives as inhibitors of neutrophils' chemotaxis, phagocytosis and production of reactive oxygen species. *Chem. Biol. Drug. Des.* **2014**, *83*, 198-206.

[8] Bukhari, S.N.; Jantan, I.; Jasamai, M. Anti-inflammatory trends of 1,3-diphenyl-2-propen-1-one derivatives. *Mini Rev. Med. Chem.* **2013**, *13*, 87-94.

[9] Bukhari, S.N.; Jasamai, M.; Jantan, I. Synthesis and biological evaluation of chalcone derivatives. *Mini Rev. Med. Chem.* **2012**, *12*, 1394-1403.

[10] Hasan, A.; Khan, M.; Sher, M.; Maharvi, G.M.; Nawaz, S.A.; Choudhary, M.I.; Atta-Ur-Rahman, Supuran, C.T. Synthesis and inhibitory potential towards acetylcholinesterase, butyrylcholinesterase and lipoxygenase of some variably substituted chalcones. *J. Enzyme Inhib. Med. Chem.* **2005**, *20*, 41-47.

[11] Bukhari, S.N.A.; Jantan, I.; Masand, V.H.; Mahajan, D.T.; Sher, M.; Naeem-ul-Hassan, M.; Amjad, M.W. Synthesis of α,β-unsaturated carbonyl based compounds as acetylcholinesterase and

butyrylcholinesterase inhibitors: Characterization, molecular modeling, QSAR studies and effect against amyloid β-induced cytotoxicity. *Eur. J. Med. Chem.* **2014**, *83*, 355-365.
[12] Kia, Y.; Osman, H.; Kumar, R.S.; Murugaiyah, V.; Basiri, A.; Perumal, S.; Wahab, H.A.; Bing, C.S. Synthesis and discovery of novel piperidone-grafted mono- and bis-spirooxindole-hexahydropyrrolizines as potent cholinesterase inhibitors. *Bioorg. Med. Chem*. **2013**, *21(7)*,1696-1707.
[13] Gregory, M.; Dandavati, A.; Lee, M.; Tzou, S.; Savagian, M.; Brien, K.A.; Satam, V.; Patil, P.; Lee, M. Synthesis, cytotoxicity, and structure-activity insight of NH- and *N*-methyl-3,5-bis-(arylidenyl)-4-piperidones. *Med. Chem. Res.* **2013**, *22*, 5588-5597.
[14] Huber, I.; Zupko, I.; Kovacs, I.J.; Minorics, R.; Gulyas-Fekete, G.; Maasz, G.; Perjesi, P. Synthesis and antiproliferative activity of cyclic arylidene ketones: A direct comparison of monobenzylidene and dibenzylidene derivatives. *Monatsh. Chem.* **2015**, *146*, 973-981.
[15] Anthwalab, A.; Singh, K.; Rawat, M.S.M.; Tyagi, A.K.; Aggarwal, B.B.; Rawat, D.S. C5-curcuminoid-dithiocarbamate based molecular hybrids: Synthesis and anti-inflammatory and anticancer activity evaluation. *RSC Adv*. **2014**, *4*, 28756-28764.
[16] Kumar, N.; Sun, G.; Ni, N.; Chen, W.; Calderon Molina A.D.; Wang, B.; Rawat, D.S. Synthesis and cytotoxicity evaluation of C5-curcuminoids. *Chemistry & Biology Interface.* **2013**, *3(3)*, 164-186.
[17] Ellman, G.L.; Courtney, K.D.; Andres, VJr.; Feather-Stone, R.M. A new and rapid colorimetric determination of acetylcholinesterase activity. *Biochem. Pharmacol.* **1961**, *7(2)*, 88-95.
[18] Kapkova, P.; Stiefl, N.; Sürig, U.; Engels, B.; Baumann, K.; Holzgrabe, U. Synthesis, biological activity and docking studies of new acetylcholinesterase inhibitors of the bispyridinium type. *Arch. Pharm. Pharm. Med. Chem.* **2003**, *336*, 523-540.
[19] Hesse, M.; Meier, H.; Zeeh, B. Spectroscopic methods in organic chemistry, 2nd ed., Enders, D.; Noyori, R.; Trost, B.M. (Eds.). Georg Thieme Verlag Stuttgart, New York, USA, 1997.
[20] Buu-Hoi, N.P.; Roussel, O.; Jacquignon, P. Condensation of aromatic and heterocyclic aldehydes with γ-piperidones; relation between structure and choleretic activity of the products of this reaction. *Bulletin de la Societe Chimique de France*. **1964**, *12*, 3096-3099.
[21] Han, Z.G.; Tu, S.J.; Jiang, B.; Yan, S.; Zhang, X.H.; Wu, S.S.; Hao, W.J.; Cao, X.D.; Shi, F.; Zhang, G.; Ma, N. An efficient and chemoselective synthesis of 1,6-naphthyridines and pyrano[3,2-c]pyridines under microwave irradiation. *Synthesis* **2009**, *10*, 1639-1646.
[22] Martinez-Cifuentes, M.; Weiss-Lopez, B.; Araya-Maturana, R.A computational study of structure and reactivity of *N*-substitued-4-piperidones curcumin analogues and their radical anions. *Molecules* **2016**, *21(12)*, 1658-1667.