A. Aliabadi et al /J. Pharm. Sci. & Res. Vol. 9(9), 2017, 1598-1603

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Synthesis and Acetylcholinesterase Inhibitory Assessment of Benzamide Derivatives Incorporated Piperazine Moiety as Potential Anti-Alzheimer Agents

A. Aliabadi[a,b*], A. Mohammadi-Farani[a,c], J.R. Bistouni[b,d]

[a] *Pharmaceutical Sciences Research Center, School of Pharmacy, Kermanshah University of Medical Sciences, Kermanshah, Iran*
[b] *Department of Medicinal Chemistry, Faculty of Pharmacy, Kermanshah University of Medical Sciences, Kermanshah, Iran*
[c] *Department of Pharmacology and Toxicology, Faculty of Pharmacy, Kermanshah University of Medical Sciences, Kermanshah, Iran*
[d] *Students Research Committee, Kermanshah University of Medical Sciences, Kermanshah, Iran*

Abstract

Alzheimer's disease (AD) as a fatal neurodegenerative disorder is characterized by several symptoms such cognitive deficiency and memory loss as well as some behavioral, motor, language and learning abnormalities in geriatric people. One of the new approaches for combating the AD is fortifying the cholinergic neurotransmission. Inhibitors of the acetylcholinesterase such as donepezil are the efficacious drugs that administered currently in the market. In the current research, a new series of acetylcholinesterase inhibitors based on the benzamide substructure were synthesized and subsequently their anti-acetylcholinesterase activity was evaluated using Ellman's protocol. Compound **6f** with substitution of the chlorine atom at position *para* was the most active compound in these series (IC_{50} = 0.44±0.1 µM) compared to donepezil (6.4±0.8 µM).

Keywords: Synthesis, Benzamide derivatives, Acetylcholinesterase, Anti-Alzheimer

INTRODUCTION

Alzheimer's disease (AD) as a fatal neurodegenerative disorder is characterized by memory impairment and cognitive deficiency. Besides, behavioral, motor, language and learning abnormalities are also exerted in elderly people [1-3]. A wide range of approaches have been utilized to study the pathophysiology of the disease. But, the exact etiology of the disorder has not been revealed completely. Some parameters such as biometal dysfunction, oxidative stress, inflammation, aggregation of the amyloid β-peptide and cholinergic decline, are known as culprits of the AD [1, 4, 5]. Degeneration of the cholinergic neurons in some areas of the brain especially hippocampus and cortex could be the main cause of memory loss and cognition deficiency in AD patients. Acetylcholine is hydrolyzed by acetylcholinesterase (AChE) in the synaptic cleft. Inhibition of the AChE by some drugs like donepezil, rivastigmine and galanthamine (**Figure 1**) could enhance the half life of the acetylcholine. These drugs could improve the cognitive and psychological symptoms [6-8].

According to the obtained information from X-ray crystallography, it has been characterized that two distinct parts are observable in the active site of AChE. The first one is located at the bottom and is named catalytic anionic site (CAS) and the second one is peripheral anionic site (PAS) and is located in the entrance. The molecule of donepezil as potent AChE inhibitor is capable of binding to the both of the mentioned sections of the active site of the enzyme. The indanone ring is bond to the PAS, whereas the benzylpiperidne portion is bond to the CAS in protonated state [9, 10]. In continuation of our previous reports [6-8, 11], in the current study we embarked on the design and synthesis of novel benzamide-based anti-acetylcholinesterase bearing *N*-benzylpiperazine to block both PAS as well as CAS. In designed compounds the benzamide moiety mimics the aromatic feature of the indanone ring in donepezil (**Figure 2**). Piperidine ring has been replaced by piperazine as bioisoteric change and also has been appeared as *N*-benzylated same as donepezil.

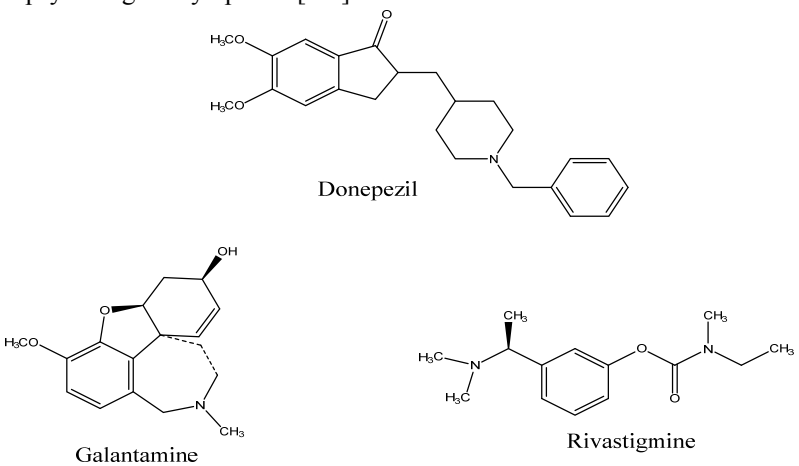


Figure 1. Structure of some acetylcholinesterase inhibitors in the market.

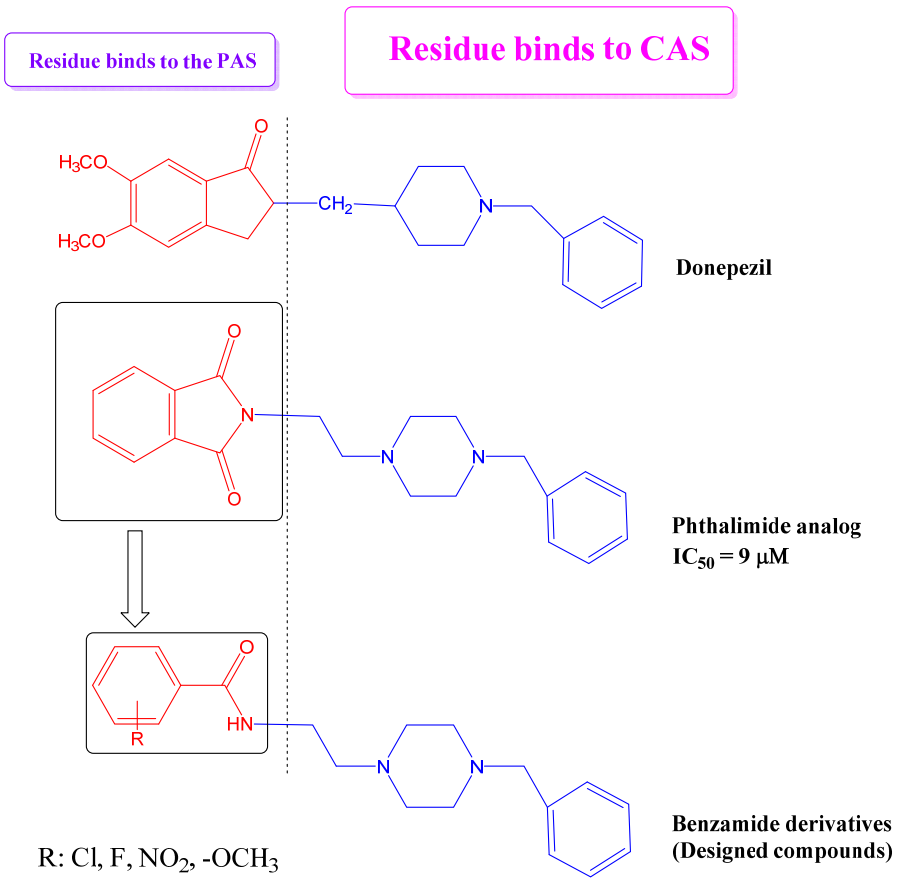
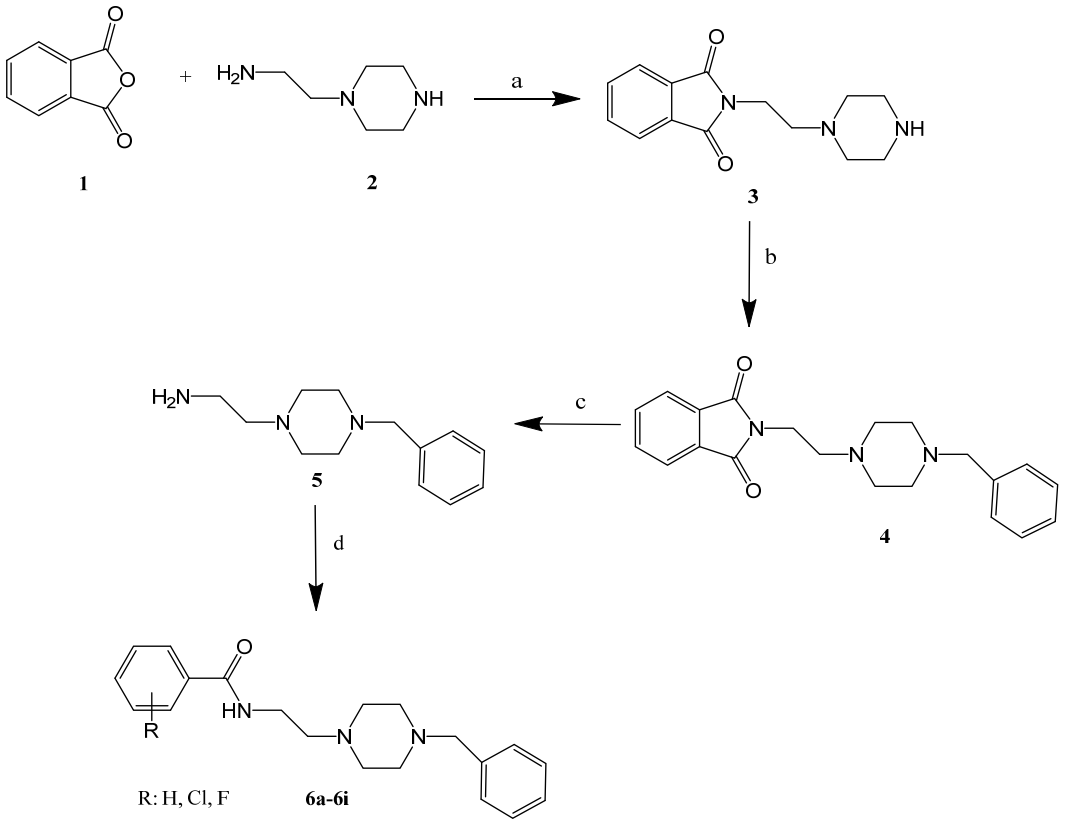


Figure 2. Structure of donepezil, phthalimide derivatives (previously reported compounds) and benzamide derivatives (new designed compounds).



Scheme 1. Synthetic pathway for preparation of compounds **6a-6i**. a) Et_3N, Toluene, reflux, 5 h; b) CH_3CN, Et_3N, reflux, 20 h; c) CH_3NH_2, Absolute EtOH, reflux 7h; d) EDC, HOBt, CH_3CN, rt, 20 h.

MATERIALS AND METHODS

Chemistry

The corresponding chemical reagents and starting materials were purchased from the commercial companies such as Merck and Sigma-Aldrich. The purification of the prepared compounds was carried out by column chromatography using ethyl acetate/petroleum ether. Spectroscopic methods were applied for characterization of the synthesized compounds. ^{1}H NMR spectra were acquired by Bruker 500 MHz in deutrated dimethylsulfoxide (DMSO-d_6) or chloroform ($CDCl_3$) and the obtained data were expressed as δ (ppm) compared to tetramethylsilane (TMS) as internal standard. Infrared (IR) spectra of the prepared compounds were obtained by Shimadzu 470 with preparing potassium bromide (KBr) disk. The mass spectra were run on a Finigan TSQ-70 spectrometer (Finigan, USA) at 70 eV. Melting points were determined using electrothermal 9001 melting point analyzer apparatus and are uncorrected.

Synthesis of of 2-(2-(Piperazin-1-yl)ethyl)isoindoline-1,3-dione **(3)**

The synthesis of compound **3** was carried out as reported previously (**scheme 1**) [7].

^{1}HNMR ($CDCl_3$, 400 MHz) δ (ppm): 2.37 (m, piperazine), 2.54 (m, piperazine), 3.22(t, phthalimide-CH_2-$\underline{CH_2}$-piperazine), 3.44(t, phthalimide-CH_2-CH_2-piperazine), 4.73 (NH, piperazine), 7.35-7.85(m, 4H, phthalimide). IR (KBr, cm-1)$\bar{\nu}$: 3380, 3157, 3111, 2924, 1730, 1681, 1521, 1489, 1458, 1328, 1303, 1186, 1143, 1035, 910, 750, 710. MS (*m/z*,%): 259(M^+, 10), 224(30), 174(30), 160(60), 149(85), 99(100), 70(70), 57(65), 41(40).

2-(2-(4-Benzylpiperazin-1-yl)ethyl)isoindoline-1,3-dione **(4)**

The synthesis of compound **4** was carried out as reported our previous literature [7].

^{1}HNMR ($CDCl_3$, 400 MHz) δ (ppm): 1.72 (brs,4H, piperazine), 2.98 (brs, 4H, piperazine), 3.42 (m,2H, phthalimide-CH_2-CH_2-piperazine), 4.20 (m, 2H, phthalimide-CH_2-CH_2-piperazine), 2.09 (s, 2H,-CH_2-benzyl), 7.42-8.01 (m, 5H, benzyl), 7.78 (q,2H, $H_{5,6}$-phthalimide), 7.90 (q, 2H, $H_{4,7}$-phthalimide). IR (KBr, cm-1)$\bar{\nu}$: 3095 (C-H, stretch, aromatic), 2924 (C-H, stretch, asymmetric, aliphatic), 2858 (C-H, stretch, symmetric, aliphatic), 1712 (C=O, stretch, phthalimide), 1639 (C=O, stretch, amide), 1465, 1246 (C-N, stretch).

2-(4-Benzylpiperazin-1-yl)ethan-1-amine **(5)**

3 g (8.60 mmol) of compound **4** was mixed with 2.97 ml (8.60 mmol) of methylamine 40% in 40 ml of absolute ethanol. The reaction mixture was refluxed for 7 h. Then, ethanol was evaporated using rotary evaporator and ethylacetate/water was added to the residue. Aqueous layer was discarded and the organic layer was washed two times by brine. Anhydrous sodium sulfate was added for dryness and subsequently filtered. Ethylacetate was removed under reduced pressure. The obtained oily product was washed by diethyl ether and treated with HCl to afford the corresponding hydrochloride salt. The obtained powder used for the next step without any extra purification [12].

IR (KBr, cm^{-1})$\bar{\nu}$: 3429, 2974, 2935, 1593, 1473. MS (*m/z*,%): 219 (M^+, weak), 176 (20), 99 (100), 87 (25), 70 (85), 56 (85), 42 (35).

General procedure for synthesis of N-(2-(4-Benzylpiperazin-1-yl)ethyl)benzamide **(6a-6i)**

In a flat bottom flask, equimolar quantities (0.91 mmol) of appropriate benzoic acid derivatives were mixed with equimolar quantities of *N*-ethyl-*N*-dimethylaminopropyl carbodiimide (EDC, 0.91 mmol) and hydroxybenzotriazole (HOBt, 0.91 mmol) in 20 ml acetonitrile. The reaction mixture were stirred at room temperature for 30 min. Then, equimolar quantity of compound **5** (0.91 mmol), was added to the reaction medium. Stirring was continued for 20 h. Consequently acetonitrile was evaporated under reduced pressure and ethylacetate/distilled water was added to the obtained residue. The aqueous layer was discarded and subsequently the organic layer was washed two times by brine. The organic layer was dried over anhydrous sodium sulfate. Sodium sulfate was filtered off. Lastly, the ethylacetate was evaporated using rotary evaporator apparatus and obtained precipitate was treated with n-hexane and diethyl ether. Column chromatography (EtOAC/Petroleum ether; 80:20) was utilized for more purification of the synthesized derivatives [13-16].

N-(2-(4-Benzylpiperazin-1-yl)ethyl)-4-nitrobenzamide **(6a)**

^{1}HNMR (DMSO-d_6, 500 MHz) δ (ppm): 0.87 (t, 4H, -CH_2, piperazine), 1.33 (t, 4H,-CH_2, piperazine), 2.09 (t, 2H, -CH_2-$C\underline{H_2}$-piperazine), 2.78 (t, 2H, -$C\underline{H_2}$-CH_2-piperazine), 4.09 (s, 2H, -CH_2-benzyl), 7.42-8.01 (m, 5H, benzyl), 7.58 (d, 2H, *J* = 10 Hz, $H_{2,6}$-4-nitrophenyl), 7.95 (d, 2H, *J* = 10 Hz, $H_{3,5}$-4-nitrophenyl), 13.45 (brs, NH). IR (KBr, cm^{-1}) ῡ: 3332, 3074, 1716, 1651, 1600, 1550, 1516, 1343, 1273. MS (*m/z*,%): 368 (M^+, 5), 312 (10), 248 (30), 176 (25), 162 (25), 150 (100), 137 (30), 104 (90), 92 (30), 76 (80), 50 (45).

N-(2-(4-Benzylpiperazin-1-yl)ethyl)-2-nitrobenzamide **(6b)**

^{1}HNMR (DMSO-d_6, 500 MHz) δ (ppm): 0.88 (t, 4H, -CH_2, piperazine), 1.33 (t, 4H,-CH_2, piperazine), 2.11 (t, 2H, -CH_2-$C\underline{H_2}$-piperazine), 2.77 (t, 2H, -$C\underline{H_2}$-CH_2-piperazine), 4.09 (s, 2H, -CH_2-benzyl), 7.62 (t, 1H, *J* = 7.5 Hz, H_4-2-Nitrophenyl), 7.68 (d, 1H, Benzyl), 7.79 (t, 1H, *J* = 7.5 Hz, H_5-2-Nitrophenyl), 7.85-90 (m, 3H, Benzyl), 8.01 (d, 1H, Benzyl), 8.33 (t, 1H, *J* = 7.5 Hz, H_6-2-Nitrophenyl), 8.57 (t, 1H, *J* = 7.5 Hz, H_3-2-Nitrophenyl), 13.47 (brs, NH). IR (KBr, cm^{-1}) ῡ: 3448, 3078, 2858, 1732, 1535, 1492, 1346. MS (*m/z*,%): 368 (M^+, 10), 357 (150), 339 (20), 312 (90), 283 (100), 269 (30), 257 (25), 167 (30), 135 (75), 95 (100), 76 (90), 63 (60).

N-(2-(4-Benzylpiperazin-1-yl)ethyl)-4-fluorobenzamide **(6c)**

^{1}HNMR (DMSO-d_6, 500 MHz) δ (ppm): 0.85 (t, 4H, -CH_2, piperazine), 1.30 (t, 4H,-CH_2, piperazine), 2.06 (t, 2H, -CH_2-$C\underline{H_2}$-piperazine), 2.74 (t, 2H, -$C\underline{H_2}$-CH_2-piperazine), 4.09 (s, 2H, -CH_2-benzyl), 7.30 (t, 2H, *J* = 10 Hz, $H_{2,6}$-4-Fluorophenyl), 7.44-7.48 (m, 3H, Benzyl), 7.56 (t, 1H, *J* = 10 Hz, Benzyl), 8.11 (d, 1H, *J* = 10 Hz, Benzyl), 8.32 (dd,

2H, *J* = 10 Hz, $H_{3,5}$-4-Fluorophenyl), 13.39 (brs, NH). IR (KBr, cm^{-1}) ῡ: 3492, 3074, 1774, 1600, 1500, 1238. MS (*m/z*,%): 341 (M^+, 30) , 281 (10), 257 (10), 135 (20), 123 (100), 109 (20, 95 (90), 83 (20), 75 (55), 64 (25),43 (55).

N-(2-(4-Benzylpiperazin-1-yl)ethyl)-2-chlorobenzamide
(6d)
^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm): 1.11 (m, 4H, piperazine), 1.34 (m, 4H, piperazine), 1.68 (t, -CO-CH_2-C<u>H</u>$_2$-piperazine), 1.93 (t, -CO-C<u>H</u>$_2$-CH_2-piperazine), 3.47 (s, CH_2-Benzyl), 7.42-7.71 (m, 5H, phenyl), 7.83-8.25 (m, 2-chlorophenyl), 13.38 (brs, NH). IR (KBr, cm^{-1}) ῡ: 3325, 2927, 2850, 1627, 1573, 1535, 1242. MS (*m/z*,%): 357(M^+, weak), 356 (10), 224 (80), 139 (80), 99 (90), 56 (100), 41 (70).

N-(2-(4-Benzylpiperazin-1-yl)ethyl)-3-chlorobenzamide
(6e)
^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm): 1.12 (m, 4H, piperazine), 1.33 (m, 4H, piperazine), 1.68 (t, 2H, -CO-CH_2-C<u>H</u>$_2$-piperazine), 1.93 (t, 2H, -CO-C<u>H</u>$_2$-CH_2-piperazine), 3.47 (s, 2H , -CH_2-phenyl), 7.42-7.77 (m, 5H, phenyl),7.86 (t, 1H, 3-chlorophenyl), 8.16-8.27 (m, 3H, 3-chlorophenyl), 10.15 (brs, NH). IR (KBr, cm^{-1}) ῡ: 3325, 3016, 2927, 2850, 1743, 1658, 1627, 1573, 1246. MS (*m/z*,%): 357 (M^+, 5), 300 (100), 283 (10), 273 (30), 245 (25), 228 (5), 217 (10),182 (30),162 (90).

N-(2-(4-Benzylpiperazin-1-yl)ethyl)-4-chlorobenzamide
(6f)
^{1}HNMR (DMSO-d_6, 500 MHz) δ (ppm): 0.83 (t, 4H, -CH_2, piperazine), 1.28 (t, 4H,-CH_2, piperazine), 2.07 (t, 2H, -CH_2-C<u>H</u>$_2$-piperazine), 2.75 (t, 2H, -C<u>H</u>$_2$-CH_2-piperazine), 4.10 (s, 2H, -CH_2-benzyl), 7.36-7.40 (m, 3H, Benzyl), 7.53 (d, 1H, *J* = 10 Hz, Benzyl), 7.59 (d, 2H, 4-Chlorophenyl), 8.10 (d, 1H, Benzyl), 8.21 (d, 2H, 4-Chlorophenyl). IR (KBr, cm^{-1}) ῡ: 3340, 3089, 2924, 2854, 1716, 165, 1593, 1485, 1246. MS (*m/z*, %): 359 (M^++2, 10), 357 (M^+, 3), 202 (5), 190 (30), 189 (100), 139 (40), 111 (15), 91 (95), 70 (30).

N-(2-(4-Benzylpiperazin-1-yl)ethyl)-2-methoxybenzamide
(6g)
^{1}HNMR (DMSO-d_6, 250 MHz) δ (ppm): 1.11 (t, 4H, piperazine), 1.33 (t, 4H, piperazine), 1.70 (t, 2H, -CH_2-CH_2-piperazine), 1.92 (t, 2H, -CH_2-CH_2-piperazine), 3.46 (s, 2H , -CH_2-phenyl), 7.14 (q, 2H, phenyl), 7.43 (t, 1H, 2-methoxyphenyl), 7.53 (m, 3H, phenyl), 7.69 (t, 1H, 2-methoxyphenyl), 8.10 (d,1H, 2-methoxyphenyl), 8.17 (d, 1H, 2-methoyphenyl). IR (KBr, cm^{-1}) ῡ: 3429, 3055, 2920, 1759, 1600, 1489, 1296. MS (*m/z*,%): 353 (M^+, 3), 281 (12), 211 (12), 135 (100), 123 (55), 105 (30), 92 (60), 77 (90), 63 (60).

N-(2-(4-Benzylpiperazin-1-yl)ethyl)-3-methoxybenzamide
(6h)
IR (KBr, cm^{-1}) ῡ: 3329, 3055, 1759, 1600, 1581, 1489, 1296. MS (m/z,%): 353 (M^+, 10), 316 (20), 244 (25), 224 (100),187 (25).

N-(2-(4-Benzylpiperazin-1-yl)ethyl)-4-methoxybenzamide
(6i)
^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm): 1.14 (m, 4H, -CH_2-piperazine), 1.35 (m, 4H, -CH_2- piperazine), 1.65 (t, 2H, -CO-CH_2-C<u>H</u>$_2$- piperazine), 1.89 (t, 2H, -CO-C<u>H</u>$_2$-CH_2-piperazine), 3.47 (s, 2H, -C<u>H</u>$_2$-phenyl), 7.07 (d, 2H, *J* = 10 Hz, $H_{3,5}$-4-Methoxyphenyl), 7.42-7.48 (m, 3H, phenyl), 7.53-7.56 (m, 1H, phenyl), 8.10 (d, 1H, phenyl), 8.24 (d, 2H, *J* = 10 Hz, $H_{2,6}$-4-Methoxyphenyl). IR (KBr, cm^{-1}) ῡ: 3441, 3062, 2978, 1770, 1600, 1573, 1246. MS (*m/z*,%): 353 (M^+, 2), 316 (15), 253 (15), 241 (20), 233 (15), 225 (30), 210 (12), 152 (85),136 (60),135 (100),119 (15),107 (30), 92 (60), 77 (55), 63 (30).

Ellman's test
The Ellman's test was performed according to the previously reported protocols (6-8, 11).

RESULTS AND DISCUSSION

Chemistry
All intermediate and final compounds were synthesized with accordance to the **scheme 1**. Compounds **3** and **4** were prepared according to the literature (6, 7, 11). Compound **5** were synthesized in the presence of methylamine from **4**. All final derivatives **6a-6i** were synthesized in the presence of DCC and HOBt in THF and the corresponding white to creamy powders were afforded with average yields. Spectroscopic techniques were applied for characterization and melting point for each compound was measured.

Anti-acetylcholinesterase activity
All bezamide-based derivatives that synthesized in the current project were evaluated for AChE activity. Various substituents such as Nitro, fluorine, chlorine and methoxy were introduced on the phenyl ring to investigate the role of the electronic effect at this position. Compound **6f** with substitution of the chlorine atom at position *para* was the most active compound in these series (IC_{50} = 0.44±0.1 μM) (**Table 2**). It is likely that chlorine atom with electron withdrawing activity as well as lipophilicity property enhanced the anti-acetylcholinesterase at this position. Position *para* was the best position for chlorine atom compared to other positions of the phenyl residue. It is notable to state that this compound was more active than donepezil as reference drug. Compound **6c** with fluorine moiety was also demonstrated more potency (IC_{50} = 4±0.6 μM) than donepezil (IC_{50} = 6.4±0.8). Compound **6a** with *para* substitution of the nitro moiety rendered a similar effect on the potency of AChE inhibition. Nitro group at position *para* of the phenyl residue showed a superior enhancement in activity in comparison with *ortho* position. According to the above mentioned information, all electron withdrawing groups such as Cl, F and nitro caused a remarkable and favorable increase in enzyme inhibitory activity. However, electron withdrawing effect is a suitable and effective parameter for enzyme inhibition. On the other hand, other factors like lipophilicity and size of the moiety in chlorine substituent fortified the enzyme inhibitory capability. It is likely that hydrophilic feature of the nitro moiety and small volume of the fluorine moiety are

detrimental factors for enzyme inhibition. While methoxy as an electron donating substituent was utilized at *para* position of the phenyl residue in compound **6i**, it caused a significant reduction in activity (IC_{50} = 27±3 μM). This evident confirmed the above conclusion that electron withdrawing moieties are beneficial for anti-acetylcholinesterase activity at position *para*. It was interesting that methoxy group exerted remakable potency when applied at position *meta*. As we know, the electron donating effect is minimal at this position whereas inducing electron withdrawing effects of the methoxy is in maximum herein.

As mentioned in the last paragraph of the introduction part the logic for design of the target compounds was according to the molecule of donepezil and also previously reported phthalimide derivatives [7]. Previously reported phthalimide-based compound with benzyl moiety on the piperazine residue (**Figure 2**) inhibited the AChE with IC_{50} = 9±2 μM. Displacement of the phthalimide group with benzamide group caused a significant enhancement in enzyme inhibitory potency especially as seen in compound **6f** (4-Cl, IC_{50} = 0.44±0.1 μM). Totally, conversion of the phthalimide group to the benzamide group caused a significant increase in enzyme inhibitory effect. It could be supposed that molecule in the benzamide region rotates more freely than phthalimide state. Therefore, more conformations could be considered for it to match the receptor.

Table 1. Physicochemical properties of synthesized compounds **6a-6i**.

Compound	(R)	Chemical formula	MW (g/mol)	mp (°C)	Yield (%)
3	-	$C_{14}H_{17}N_3O_2$	259	107	61
4	-	$C_{21}H_{23}N_3O_2$	349	229	52
5	-	$C_{13}H_{21}N_3$	219	77	28
6a	4-NO_2	$C_{20}H_{24}N_4O_3$	368	169	52
6b	2-NO_2	$C_{20}H_{24}N_4O_3$	368	162	59
6c	4-F	$C_{20}H_{24}FN_3O$	341	95	60
6d	2-Cl	$C_{20}H_{24}ClN_3$	257	203	62
6e	3-Cl	$C_{20}H_{24}ClN_3$	357	182	51
6f	4-Cl	$C_{20}H_{24}ClN_3$	357	101	42
6g	2-OCH_3	$C_{21}H_{27}N_3O_2$	353	101	39
6h	3-OCH_3	$C_{21}H_{27}N_3O_2$	353	96	48
6i	4-OCH_3	$C_{21}H_{27}N_3O_2$	353	150	45

Table 2. Enzymatic results of compounds **6a-6i** (IC_{50}±SD).

Compound	(R)	IC_{50}(μM)
6a	4-NO_2	6.9±0.4
6b	2-NO_2	23±1.2
6c	4-F	4±0.6
6d	2-Cl	9±0.5
6e	3-Cl	9.7±0.7
6f	4-Cl	0.44±0.1
6g	2-OCH_3	21±2
6h	3-OCH_3	7.2±0.6
6i	4-OCH_3	27±3
Donepezil	-	6.4±0.8

CONCLUSION

A new series of benzamide-based acetylcholinesterase inhibitors were synthesized and corresponding enzyme inhibitory effect was tested. The tested compounds demonstrated favorable anti-chloinesterase activity compared to donepezil as reference drug. Compound **6f** (IC_{50} = 0.44±0.1) could be considered as potential lead compound for development of new anti-Alzheimer drugs in the future.

CONFLICT OF INTERESTS

The authors have been declared no conflicts of interests.

ACKNOWLEDGEMENT

Authors are grateful from the research deputy of Kermanshah University of Medical Sciences for financial support (approved proposal No. 92398). This work was performed in partial fulfillment of the requirement for PharmD of Mr Javad Rezaei Bisotouni.

REFERENCES

[1] Mostofi, M., Mohammadi Ziarani, G., Mahdavi, M., Moradi, A., Nadri, H., Emami, S. et al., *Eur. J. Med. Chem*. 2015, *103*, 361-369.

[2] Qian, S., He, L., Mak, M., Han, Y., Ho, C.Y., Zuo, Z., *Int. J. Pharm*. 2014, *477*, 442-453.

[3] Akrami, H., Mirjalili, BF., Khoobi, M., Nadri, H., Moradi, A., Sakhteman, A., et al., *Eur. J. Med. Chem*. 2014, *84*, 375-381.

[4] Sukhorukov, A.Y.A., Nirvanappa, A.C., Swamy, J., Ioffe, S.L., Swamy, S.N., et al., *Bioorg. Med. Chem. Lett*. 2014, *24*, 3618-3621.

[5] Hu, Y., Zhang, J., Chandrashankra, O., Ip, F.C., Ip, N.Y., *Bioorg. Med. Chem. lett*. 2013, *21*, 676-683.

[6] Aliabadi, A., Foroumadi, A., Mohammadi-Farani, A., Mahvar, M.G., *Iran. J. Basic. Med. Sci*. 2013, *10*, 1049-1054.

[7] Mohammadi-Farani, A., Ahmadi, A., Nadri, H., Aliabadi, A., *Daru. J. Pharm. Sci*. 2013, *21*, 47-55.

[8] Rahmani-Khajouei, M., Mohammadi-Farani, A., Ghorbani, H., Aliabadi, A., *J. Rep. Pharm. Sci*. 2015, *4*, 148-157.

[9] Wang, B., Mai, Y.C., Li, Y., Hou, J.Q., Huang, S.L., *et al,. Eur. J. Med. Chem.* 2010, *45*, 1415-1423.

[10] Liu, S., Shang, R., Shi, L., Chi-Cheong Wan, D., Lin, H., *Eur. J. Med. Chem*. 2014, *81*, 237-244.

[11] Mohammadi-Farani, A., Abdi, N., Moradi, A., Aliabadi, A., *Iran J Basic Med Sci*. 2017, *20*, 59-66.

[12] Aliabadi, A., Shamsa, F., Ostad, S.N., Emami, S., Shafiee, A., et al., *Eur. J. Med. Chem.* 2010, *11*, 5384-5389.

[13] Mohammadi-Farani, A., Foroumadi, A., Kashani, M.R. and Aliabadi, A., *Iran J. Basic. Med. Sci.* 2014, *17*, 502-508.

[14] Aliabadi, A., Hasanvand, Z., Kiani, A., Mirabdali, S.S., *Iran. J. Pharm. Res.* 2013, *12*, 687-693.

[15] Aliabadi, A., Andisheh, S., Tyarani-Najaran, Z., Tayarani-Najaran, M., *Iran. J. Pharm. Res.* 2013, *12*, 267-271.

[16] Mohammadi-Farani, A., Heidarian, N., Aliabadi, A., *Iran. J. Pharm. Res.* 2014, *12*, 487-492.