

ORIGINAL RESEARCH

Synthesis and acetylcholinesterase (AChE) inhibitory activity of some *N*-substituted-5-chloro-2(3*H*)-benzoxazolone derivatives

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ABSTRACT: Alzheimer's disease is a progressive neurodegenerative disorder of the central nervous system. Acetylcholinesterase inhibition is one of the proposed mechanisms for treatment of Alzheimer's disease. Currently, acetylcholinesterase inhibitors such as tacrine, donepezil, rivastigmine and galantamine are applied in different stages of Alzheimer's disease treatment. In recent years, various heterocyclic systems have been used as a skeleton to discover new acetylcholinesterase inhibitors. On the other hand, it is known that the benzoxazolone heterocyclic structure exhibited a wide range of biological activities. In this study, a series *N*-substituted-5-chloro-2(3*H*)-benzoxazolone derivatives were synthesized and evaluated their acetylcholinesterase inhibitory activity. These compounds were synthesized by Mannich reaction of 5-chloro-2(3*H*)-benzoxazolone with the appropriated amines. The acetylcholinesterase inhibitory activity of the title compounds was determined by colorimetric Ellman's method. The preliminary screening results indicated that 5-chloro-2-(3*H*)-benzoxazolone scaffold demonstrated different inhibition range against acetylcholinesterase enzyme depending on the structural differences.

KEY WORDS: acetylcholinesterase Inhibitory activity, 2(3*H*)-benzoxazolone, mannich reaction, Ellman's method, synthesis.

INTRODUCTION

Alzheimer's disease (AD), characterized by a progressive memory loss, decline in language skills and other cognitive impairments, is an age-related neurodegenerative disorder, affecting approximately 36 million people worldwide (1). The etiology of AD is still elusive and multiple factors, such as amyloid β deposits, τ -protein aggregation, oxidative stress and low levels of acetylcholine (ACh). In the past decade, treatment strategies for AD have mainly been aimed at improving cholinergic neurotransmission in brain, which was mostly based on the "cholinergic hypothesis". According to this hypothesis, impairment in the cholinergic function is of critical importance in AD especially the brain areas dealing with learning, memory, behaviour and emotional responses that include the neocortex

and the hippocampus. Brain atrophy is the most obvious clinical finding in AD in which the levels of acetylcholine are decreased due to its rapid hydrolysis by acetylcholinesterase (AChE) enzyme. Therefore, a promising treatment strategy for AD has been the use of acetylcholinesterase inhibitors (AChEIs) (1-4). Currently, only four acetylcholinesterase inhibitors namely, tacrine (5), donepezil (6), rivastigmine (7) and galantamine (8) have been approved by the US Food and Drug Administration. Thus, the development of effective new agents as acetylcholinesterase inhibitors is needed.

In recent years, several natural and synthetic compounds have been tested acetylcholinesterase inhibitory potency. These compounds are comprising a diverse group of chemical structures.

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2(3*H*)-Benzoxazolone, as one of the most versatile heterocyclic ring, produce diverse compounds with a wide range of biological activities such as anti-HIV (9), anticancer (10), analgesic (11), anti-inflammatory (12), antinociceptive (13), antimicrobial (14), anticonvulsant (15), antimalarial (16), human leukocyte MPO chlorinating inhibitor activity (17) In addition, some benzoxazole compounds have been reported as β -amyloid imaging agents of AD patients [18]. Moreover, benzoxazolone scaffold is the ring isoster of indanone pharmacophore of donepezil which is one of the most important AChEIs.

AChE has a narrow and hydrophobic gorge. There are lots of aromatic amino acid residues both on the entrance and inside this of the enzyme gorge. On the other hand, basic side chains and a free amino group are an integral part of the structure of several reported acetylcholinesterase inhibitors and it is known that this nitrogen atom plays an important role in enzyme-inhibitor interaction (19).

In the light of these findings, a series of *N*-substituted-2(3*H*)-benzoxazolone derivatives containing aromatic or aliphatic basic amine groups on the side chain were designed to evaluate their acetylcholinesterase inhibitory activity.

MATERIALS AND METHODS

Chemistry

Melting points were determined on an Electrothermal IA 9100 (Electrothermal, Essex, U.K.) melting point apparatus and are uncorrected. The IR spectra of compounds were recorded on a Perkin Elmer FT-IR (ATR) Spectrometer 100 (Perkin Elmer Inc., Massachusetts, USA). The ^1H NMR spectra were recorded on a Varian As 400 Mercury Plus NMR (Varian Inc., Palo Alto, CA, USA) spectrometer using CDCl_3 as solvent. Chemical shifts were reported in parts per million (δ). *J* values were given in Hz. Mass spectra (APCI-MS) were measured on a Thermo MSQ Plus LC/MS (Thermo Scientific Inc., San Jose, CA, USA). Microwave irradiation synthesis of the compounds was conducted on Milestone MicroSYNTH (Milestone S.r.l., Sorisole, Italy) microwave apparatus.

General procedure for the synthesis of compound 1a

Compound 1a was synthesized by modification of the procedure described in the literature (20). 2-Amino-4-chlorophenol (0.01 mol), urea (0.05 mol) and 37% HCl (2.5 ml) were irradiated (300 W, 140 °C) for 15 min in a microwave reactor. After completion of reaction (by monitoring with TLC), water (10 ml) was added to the reaction mixture and stirred at room temperature for 1 h. The resulting precipitate was filtered and washed with water. After drying, the precipitate was crystallized from ethanol-water (1:1) to yield 5-chloro-2(3*H*)-benzoxazolone (1a).

General procedure for the synthesis of the compounds 1-11

The title compounds were prepared by Mannich reaction conditions. For this purpose, 5-chloro-2(3*H*)-benzoxazolone (0.002 mol) was dissolved in methanol (5 ml). Appropriate amines (0.002 mol) and 37 % formalin (0.0025 mol) were added to this solution. The mixture was stirred vigorously for 3h at room temperature. The resulting precipitate was filtered and washed with cold methanol. The crude product was crystallized from methanol to yield the target compounds.

3,3'-((ethylazanediy)bis(methylene))bis(5-chlorobenzoxazol-2(3*H*)-one) (1)

Yield 29%; mp 147°C; IR ν_{maks} (FT/ATR): 2968, 2161, 2031, 1769, 1606, 1479 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.09-7.14 (4H, m, Benzoxazolone-H), 7.00 (2H, d, *J*=1.6 Hz, Benzoxazolone-H), 4.90 (4H, s, 2x CH_2), 2.92 (2H, q, *J*=7.2 Hz, CH_2CH_3), 1.78 (2H, t, *J*=7.2 Hz, CH_2CH_3) ppm; MS (APCI) *m/z* (%): 239 (8) [$\text{M}+\text{H}-169$] $^+$, 202 (17), 102 (15), 58 (100), 45(16).

3,3'-((phenethylazanediy)bis(methylene))bis(5-chlorobenzoxazol-2(3*H*)-one) (2)

Yield 24%; mp 154.1°C; IR ν_{maks} (FT/ATR): 3062, 2862, 2161, 1769, 1607, 1478 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.03-7.16 (9H, m, Ar-H), 6.87-6.88 (2H, m, Ar-H), 4.90 (4H, s, 2x CH_2), 3.14 (2H, t, *J*=7.0 Hz, N- CH_2CH_2 -Phenyl), 2.79 (2H, t, *J*=6.8 Hz, N- CH_2CH_2 -Phenyl) ppm; MS (APCI) *m/z* (%): 328 (29) [$\text{M}+\text{H}-157$] $^+$, 315(83), 317 (2), 157 (100), 145 (13), 65 (89).

3,3'-(((4-chlorophenethyl)azanediy)bis(methylene))bis(5-chlorobenzoxazol-2(3*H*)-one) (3)

Yield 38%; mp 190°C; IR ν_{maks} (FT/ATR): 2859, 2161, 2034, 1767, 1609, 1480 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.11-7.12 (4H, m, Benzoxazolone-H), 7.02 (2H, d, *J*= 8.2 Hz, Phenyl-H), 6.91 (2H, d, *J*= 8.2 Hz, Phenyl-H), 6.86 (2H, t, *J*=1.2 Hz, Benzoxazolone-H), 4.91 (4H, s, 2x CH_2), 3.11 (2H, t, *J*=7.0 Hz, N- CH_2CH_2 -Phenyl), 2.76 (2H, t, *J*=6.8 Hz, N- CH_2CH_2 -Phenyl) ppm; MS (APCI) *m/z* (%): 349 (15), 351 (7), 244 (30), 246 (10), 212 (18), 214 (8), 168 (100), 139 (95), 103 (17).

3,3'-(((3,4-dimethoxyphenethyl)azanediy)bis(methylene))bis(5-chlorobenzoxazol-2(3*H*)-one) (4)

Yield 35%; mp 164°C; IR ν_{maks} (FT/ATR): 2839, 2160, 2032, 1763, 1608, 1479 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.07-7.12 (4H, m, Benzoxazolone-H), 6.87 (2H, d, *J*= 1.6 Hz, Benzoxazolone-H), 6.59 (1H, d, *J*= 8.2 Hz, Phenyl-H), 6.55 (1H, dd, *J*=1.6; 8.2 Hz, Phenyl-H), 6.48 (1H, d, *J*=1.6 Hz, Phenyl-H), 4.81 (4H, s, 2x CH_2), 3.79 (6H, s, 2x OCH_3), 3.12 (2H, t, *J*=6.6 Hz, N- CH_2CH_2 -Phenyl), 2.71 (2H, t, *J*=6.8 Hz, N- CH_2CH_2 -Phenyl) ppm; MS (APCI) *m/z* (%): 206 (100) [$\text{M}+\text{H}-2\times 169$] $^+$, 194(37), 165 (30), 238 (15), 270 (14).

5-chloro-3-((phenylamino)methyl)benzoxazol-2(3*H*)-one (5)

Yield 84%; mp 190°C; IR ν_{maks} (FT/ATR): 3398, 3066, 2161, 2032, 1750, 1604, 1479 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.19-7.25 (2H, m, Phenyl-H), 7.10-7.11 (1H, m, Phenyl-H), 7.07-7.08 (2H, m, Phenyl-H), 6.81-6.85 (3H, m, Benzoxazolone-H), 5.30 (2H, d, *J*=7.0 Hz, CH_2), 4.64 (1H, t, *J*=6.8 Hz, NH) ppm; MS (APCI) *m/z* (%): 274 (1) [$\text{M}+\text{H}$] $^+$, 106 (100), 94(10).

5-chloro-3-((naphthalen-1-ylamino)methyl)benzoxazol-2(3*H*)-one (6)

Yield 55%; mp 173°C; IR ν_{maks} (FT/ATR): 3436, 2160, 2033, 1760, 1606, 1479 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.77-7.85 (2H, m, Naphthalene-H), 7.44-7.49 (2H, m, Naphthalene-H), 7.32-7.37 (2H, m, Naphthalene-H), 7.11 (1H, d, *J*=2.0 Hz, Naphthalene-H), 6.98-7.07 (3H, m, Benzoxazolone-H), 5.47 (2H, d, *J*=6.6 Hz, CH_2), 5.28 (1H, t, *J*=6.8 Hz, NH) ppm; MS (APCI) *m/z* (%): 325 (1) [$\text{M}+\text{H}$] $^+$, 188 (20), 168 (9), 156 (100), 129 (10).

5-chloro-3-((quinolin-8-ylamino)methyl)benzo[d]oxazol-2(3H)-one (7)

Yield 74 %; mp 137.3°C; IR ν_{maks} (FT/ATR): 2161, 1774, 1609, 1483 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): δ 8.75 (1H, dd, $J=1.6$; 6.4 Hz, quinoline-H), 8.06 (1H, dd, $J=1.6$; 8.2 Hz, quinoline-H), 7.38-7.44 (2H, m, quinoline-H), 7.29 (1H, d, $J=2.0$ Hz, quinoline-H), 7.15-7.19 (3H, m, Benzoxazolone-H), 7.02-7.08 (2H, m, quinoline-H and NH), 5.54 (2H, d, $J=7.4$ Hz, CH_2) ppm; MS (APCI) m/z (%): 326 (83) $[\text{M}+\text{H}]^+$, 328 (29) $[\text{M}+\text{H}+2]^+$, 157 (100), 145 (13), 65 (89).

5-chloro-3-(pyrrolidin-1-ylmethyl)benzo[d]oxazol-2(3H)-one (8)

Yield 12 %; mp 93°C; IR ν_{maks} (FT/ATR): 2976, 2802, 2161, 2032, 1777, 1606, 1482 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): δ 7.12 (1H, d, $J=2.0$ Hz, Benzoxazolone-H), 7.09-7.10 (2H, m, Benzoxazolone-H), 4.73 (2H, s, CH_2), 2.73-2.78 (4H, m, Pyrrolidine-H), 1.78-1.82 (4H, m, Pyrrolidine-H) ppm; MS (APCI) m/z (%): 204 (35) $[\text{M}+\text{H}-49]^+$, 202 (100), 84 (76), 72 (42), 65 (34).

5-chloro-3-(piperidin-1-ylmethyl)benzo[d]oxazol-2(3H)-one (9)

Yield 59 %; mp 118°C; IR ν_{maks} (FT/ATR): 2938, 2918, 2161, 2032, 1773, 1610 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): δ 7.09-7.11 (3H, m, Benzoxazolone-H), 4.59 (2H, s, CH_2), 2.62-2.64 (4H, m, Piperidine-H), 1.56-1.62 (4H, m, Piperidine-H), 1.40-1.45 (2H, m, Piperidine-H) ppm; MS (APCI) m/z (%): 130 (15) $[\text{M}+\text{H}-137]^+$, 100 (10), 98 (100), 86 (10).

3,3'-(piperazine-1,4-diylbis(methylene))bis(5-chlorobenzoxazol-2(3H)-one) (10)

Yield 23%; mp 236 °C; IR ν_{maks} (FT/ATR): 2916, 2849, 2160, 2032, 1762, 1605 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): δ 7.04-7.10 (6H, m, Benzoxazolone-H), 4.59 (4H, s, $2\times\text{CH}_2$), 2.65-2.78 (8H, m, Piperazine-H) ppm; MS (APCI) m/z (%): 143 (100) $[\text{M}+\text{H}-169, -111, -28]^+$, 111 (50), 99 (32).

5-chloro-3-((4-methylpiperazin-1-yl)methyl)benzo[d]oxazol-2(3H)-one (11)

Yield 23 %; mp 151°C; IR ν_{maks} (FT/ATR): 2944, 2796, 2160, 2033, 1772, 1614 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): δ 7.09-7.10 (3H, m, Benzoxazolone-H), 4.61 (2H, s, CH_2), 2.71-2.73 (4H, m, Piperazine-H), 2.42-2.47 (4H, m, Piperazine-H), 2.27 (3H, s, CH_3) ppm; MS (APCI) m/z (%): 113 (100) $[\text{M}+\text{H}-169]^+$, 98 (5), 70 (28).

Biological activity

Acetylcholinesterase E.C.3.1.1.7., Type VI-S, from *Electric Eel*, 500 units was purchased from Sigma-Aldrich (Steinheim, Germany). 5,5'-Dithiobis(2-nitrobenzoic acid) (DTNB)-Ellman's reagent, buffer compounds (potassium dihydrogen phosphate, potassium hydroxide), sodium hydrogen carbonate and acetylthiocholine iodide (ATC) used as a substrate were obtained from Fluka (Buchs, Switzerland). Spectrophotometric measurements were performed on a Shimadzu UV/160-A Spectrophotometer.

Acetylcholinesterase activity assay

enzyme activity was investigated using a slightly modified colorimetric Ellman's method (21), using tacrine as standart drug. As the product of the enzymatic hydrolysis, the thiocholine, does not possess a significant chromophore for UV detec-

tion, the evaluation of enzyme activity was performed using a specific chromogenic reagent, DTNB.

Stock solutions of the potential inhibitor compounds were prepared in 2% DMSO, which were diluted with aqueous assay medium to a final content of organic solvent lower than 0.2%. The enzyme activity was determined in the presence of 10^{-3} and 10^{-4} M concentrations of an inhibitor, in order to obtain inhibition of AChE activity between 0 and 100 %. Each experiment was assayed in triplicate. Prior to use, all solutions were adjusted to 20 °C. Enzyme solution (2.5 units/mL, 100 μL) and inhibitor solution (100 μL) were added into a cuvette containing the phosphate buffer (3.0 mL, 0.1 M; pH=8.0). After 5 min incubation, required aliquots of the DTNB solution (0.01 M, 100 μL) and of the acetylthiocholine iodide (0.075 M, 20 μL) were added. After a rapid and immediate mixing, the absorption was measured at 412 nm. The relative enzyme activity was calculated according to the literature (22).

RESULTS AND DISCUSSION**Chemistry**

In this study, eleven *N*-substituted-5-chloro-2(3H)-benzoxazolone derivatives have been synthesized to evaluate acetylcholinesterase inhibitory activity. The target compounds were prepared by a two-step synthesis. In the first step, 5-chloro-2(3H)-benzoxazolone was prepared by reacting 2-amino-4-chlorophenol with urea using microwave-assisted method. In the second step, this intermediate was reacted with aliphatic and aromatic amines to furnish the mono and bis Mannich bases as target compounds under Mannich reaction condition. The synthetic pathway is given in Figure 1. The structures of the synthesized compounds were confirmed by spectral IR, $^1\text{H NMR}$, and AP-MS analysis.

According to the literature survey, compounds **5**, **8**, **9** and **10** are reported derivatives (23-25) and **11** is listed substance in the literature with the CAS registry numbers 1222770-26-4, but corresponding scientific reference data are not available for this compound.

In the IR spectra, the C=O stretching bands of 2(3H)-benzoxazolone groups were observed between 1750 and 1777 cm^{-1} and those bands were the confirmative signals for the constructed functional groups in the title compounds. On the other hand, N-H stretching bands of the compounds **5** and **6** were detected at 3398 and 3436 cm^{-1} , respectively (26, 27).

$^1\text{H NMR}$ spectra of the title compounds were consistent with expected resonance signals in term of chemical shifts and integrations (26). The methylene-proton signals of compounds **1-4**, **8-11** were observed as a singlet signal at δ 4.59-4.91 ppm, whereas corresponding signals of compounds **5**, **6** and **7** were detected as doublet at δ 5.30-5.54 ppm resulting from vicinal coupling between methylene protons and N-H proton. In addition, N-H proton signals of the compounds **5** and **6** were observed as triplet signals with 6.8 Hz coupling constants at δ 4.43 and 5.28 ppm, respectively. For compound **7**, it was detected as multiplet signal at δ 7.02-7.08 ppm.

The structure of the title compounds was further verified by AP-MS data. According to APCI-MS analysis, only compounds

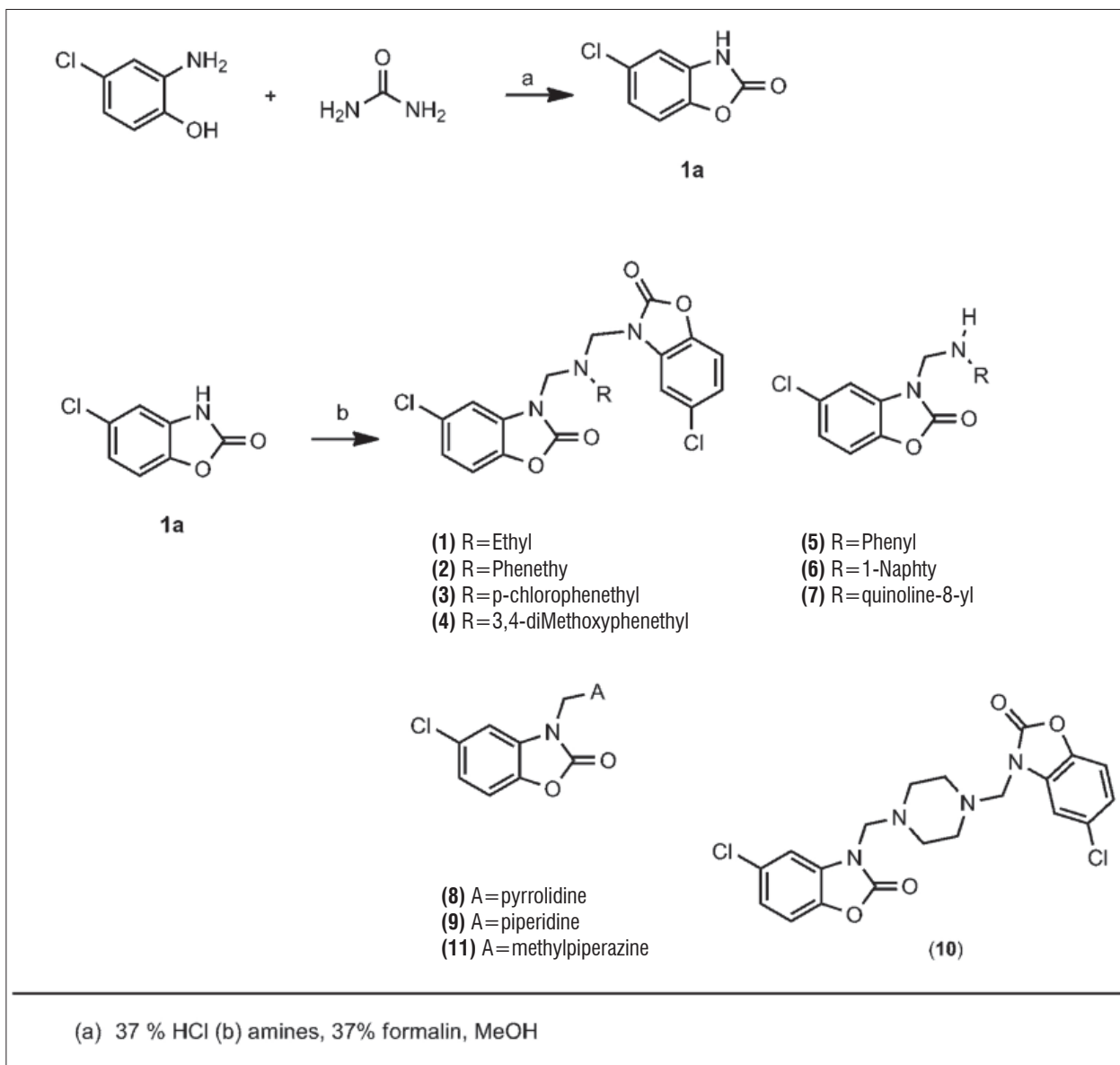


FIGURE 1. Synthesis of the compounds 1-11.

5, 6 and 7 bearing aromatic amine group have produced stable $[M+H]^+$ ions. The rest of the compounds having aliphatic amine group have not yielded corresponding $[M+H]^+$ ions. Those compounds have produced m/z $[M+H\text{-different fragments}]^+$ ions, evidencing for the removal of one or two 5-chloro-2(3H)-benzoxazolone structure in the initial compounds.

Acetylcholinesterase Inhibitory Activity

Inhibitor potencies of the final compounds against AChE from *electric eel* were evaluated by the spectroscopic method as described in the literature (21). This test is based on the reaction of 5,5'-dithio-bis-(2-nitrobenzoic) acid (DTNB or Ellman's reagent) with the sulfhydryl group of acetylthiocholine enzyme to produce as a yellow-colored product, i.e. 2-nitro-5-thiobenzoic acid. Changes of absorbance recorded at 412 nm determine the activity of the tested compounds. The AChEI activity results are summarized in Table 1.

TABLE 1. % Inhibition values of title compounds against acetylcholinesterase enzyme.

Compound	Inhibition %	
	10^{-3} M	10^{-4} M
1	75.51	18.90
2	74.17	7.55
3	80.32	25.03
4	78.70	25.45
5	73.94	26.06
6	75.23	15.41
7	81.84	22.25
8	74.79	14.92
9	75.20	27.33
10	80.27	33.70
11	69.90	15.25
Tacrine	99.98	99.10

The initial acetylcholinesterase inhibitory activity screening results indicated that all tested compounds exhibited AChEI activity with different ratio as shown in Table 1. According to the results, (69.90-81.84%) inhibition range of title compounds at 10^{-3} M concentration decreased to (7.55 and 33.07 %) inhibition range at 10^{-4} M concentration against AChE enzyme. All tested compounds have lower anti-AChE activity in comparison to the reference compound, tacrine. Considering both concentrations, the most active compound in the series was compound **10** with 80.27 % and 33.7% inhibition at 10^{-3} M and 10^{-4} M concentrations, respectively.

In *N*-phenethylamine series which are bis 5-chloro-2(3*H*)-benzoxazolone derivatives, introduction of the substituents to phenyl ring on the side chain seems to enhance anti-AChE activity at both concentrations.

Among the mono 5-chloro-2(3*H*)-benzoxazolone derivatives **5**, **6** and **7** bearing benzene, naphthalene and quinoline rings on the side chain, respectively, the most potent compound at 10^{-4} M concentration was compound **5**. Considering the compounds **6** and **7** carrying isosteric rings (naphthalene and quinoline) on the side chain, compound **7** displayed higher activity in comparison to compound **6**. It can be speculated that nitrogen atom of quinoline ring favoured the interaction of the molecule with binding side of AChE enzyme.

When compared the mono 5-chloro-2(3*H*)-benzoxazolone compounds **8**, **9** and **11** bearing pyrrolidine, piperidine and

4-methylpiperazine rings as aliphatic heterocyclics on the side chain, compound **9** was observed more potent than compounds **8** and **11**. According to this result, the replacement of the pyrrolidine ring with piperidine homolog resulted in approximately two-fold increase in AChE inhibitory activity at 10^{-4} M concentration, Interestingly, compound **10** which is bis 5-chloro-2(3*H*)-benzoxazolone derivative of compound **11**, exhibited higher activity than mono counterpart and it is the most active compound in the series at 10^{-4} M concentration. This result indicated that one more time addition of aromatic heterocyclic 5-chloro-2(3*H*)-benzoxazolone structure to the side chain improve the inhibitory activity.

In conclusion, the preliminary activity screening results have demonstrated that *N*-substituted-5-chloro-2(3*H*)-benzoxazolone template has acetylcholinesterase inhibitory activity and can serve as a starting structure for further studies to design new effective acetylcholinesterase inhibitors.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

Bazı *N*-süstitüe-5-kloro-2(3*H*)-benzoksazon türevi bileşiklerin sentezi ve asetilkolinesteraz inhibitör aktiviteleri

ÖZET: Alzheimer hastalığı merkezi sinir sisteminin progresif dejeneratif bir bozukluğudur. Asetilkolinesteraz inhibisyonu, Alzheimer hastalığının tedavisi için önerilen mekanizmalardan birisidir. Günümüzde takrin, donepezil, rivastigmin ve galantamin gibi asetilkolinesteraz inhibitörleri Alzheimer hastalığı tedavisinin farklı aşamalarında uygulanmaktadır. Son yıllarda birçok heterosiklik sistem yeni asetilkolinesteraz inhibitörlerinin keşfi için iskelet yapı olarak kullanılmaktadır. Diğer yandan benzoksazon heterosiklik yapısının geniş bir biyolojik aktivite sergilediği bilinmektedir. Bu çalışmada, bir grup *N*-süstitüe-5-kloro-2 (3*H*)-benzoksazon türevi bileşik sentezlenmiş ve asetilkolinesteraz inhibitör aktiviteleri değerlendirilmiştir. Bileşikler, 5-kloro-2(3*H*)-benzoksazon ile uygun aminlerin Mannich reaksiyonu ile hazırlanmıştır. Bileşiklerin asetilkolinesteraz inhibitör aktiviteleri kolorimetrik Ellman metodu ile tespit edilmiştir. Ön tarama sonuçları 5-kloro-2(3*H*)-benzoksazon iskeletinin yapısal farklılığa bağlı olarak asetilkolinesteraz enzimine karşı farklı oranlarda inhibisyona sahip olduğunu göstermiştir.

ANAHTAR SÖZCÜKLER: asetilkolinesteraz inhibitör aktivite, 2(3*H*)-benzoksazon, mannich reaksiyonu, Ellman metodu, sentez.

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