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Synthesis, docking and acetylcholinesterase inhibitory evaluation of (*E*)-3-(4-(diethylamino) phenyl)-1-phenylprop-2-en-1-one derivatives with probable anti-Alzheimer effects

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Alzheimer's disease (AD) as form of senile dementia is a cognitive and neurodegenerative disorder as well as behavioral and psychological problems in the geriatric people. The disease is characterized by memory deficit as well as decline in daily activities. The deficiency of the cholinergic system is one the main causes of the disease. Some medications such as donepezil are capable of enhancement of the acetylcholine neurotransmitter via the inhibition of the acetylcholinesterase (AChE) enzyme. According to the positive background of the chalcone derivatives in inhibition of AChE, a new series of chalcone derivatives were synthesized using aldol condensation procedure and their enzyme inhibitory potency were assessed by Ellman's test. Some of the tested derivatives demonstrated superior activity than donepezil (IC_{50} = 0.41 ± 0.09 µM) especially methoxylated compounds **3h** (2-OCH_3, IC_{50} = 0.1 ± 0.02 µM), **3i** (3-OCH_3, IC_{50} = 0.12 ± 0.03 µM) and **3j** (4-OCH_3, IC_{50} = 0.39 ± 0.04 µM). Compound **3b** (3-Cl, IC_{50} = 0.13 ± 0.03 µM) also possessed higher activity than donepezil. Molecular docking investigation also confirmed an effective hydrogen bonding interaction of **3h** with AChE. In conclusion, the synthesized compounds could be suggested as new anti-acetylcholinesterase lead compounds.

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Introduction

Alzheimer's disease (AD) as cognitive and neurodegenerative disorder produces a progressive dementia in the elderly people. The disease is characterized by memory deficiency as well as decline in daily activities. Besides, patients suffer from the behavioral and psychological problems such anxiety, depression and etc. [1-3]. Various parameters have been recognized that are involved in etiology of AD. The principal factors are oxidative stress, biometals dysfunctions, deposit of abnormal proteins such as amyloid beta-peptide (Aβ) and τ-protein, and degeneration of cholinergic neurons in the brain [1, 4, 5]. Currently in-used medications that administered for the treatment of AD in the clinic are acetylcholinesterase (AChE) inhibitors such as donepezil, rivastigmine and galantamine. The AChE inhibitors improve the cognitive and behavioral symptoms of the disease. AChE is an enzyme responsible for degradation of the acetylcholine in synaptic cleft. These drugs enhance the half-life of acetylcholine in the synaptic cleft of cholinergic nerves. In fact, the cholinergic hypothesis states that reduction in activity of cholinergic neurotransmission due to degeneration of cholinergic neurons is the reason for memory loss in AD patients [6-8]. Hence, in recent years medicinal chemists and pharmacologists try to design and discover new chemical entities for treatment of AD. They focused on the cholinergic drugs as mentioned above. The data obtained from the X-ray crystallography revealed that AChE has two distinct portions for binding to the ligands [9- 12]. The first one has been located at the bottom and is called catalytic anionic site (CAS) and the second portion has been located at the entrance and is nominated peripheral anionic site. The molecules that engage both of these locations are capable to producing a robust inhibition of the AChE. Some molecules such as donepezil could bind simultaneously to both CAS as well as PAS [13, 14].

In continuation of our previous reports on the development of new acetylcholinesterase inhibitors [6-14], we decided to design and synthesize some chalcone-based derivatives. In the recent years, several reports have been shown the efficacy of chalcone-based compounds towards the inhibition of AChE (**Figure 1**) [1, 15-17].

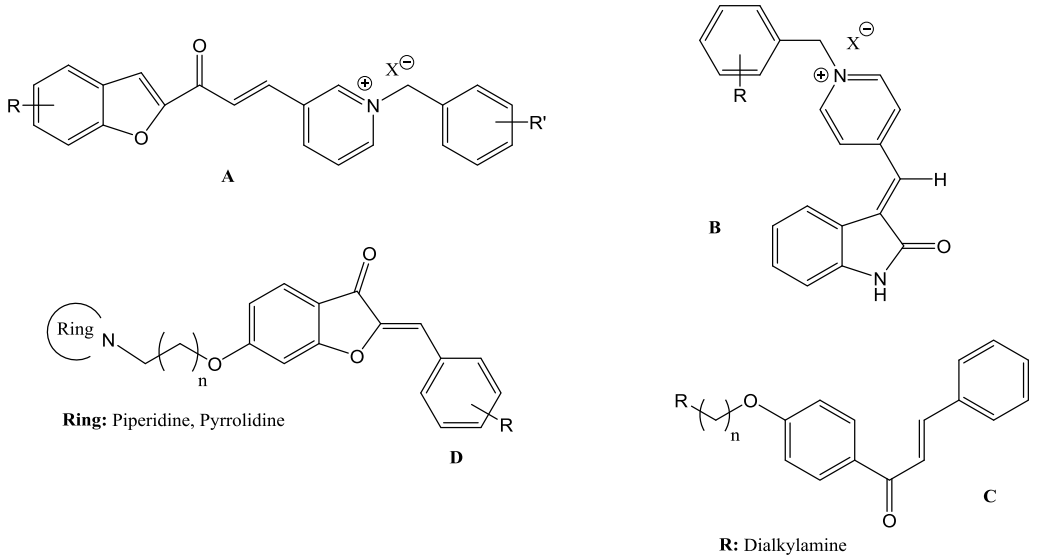


Fig. 1. Some chalcone-based acetylcholinesterase inhibitors.

In fact, because of the presence of aromatic (phenyl) ring and carbonyl group in chalcone derivatives, these types of molecules have similar pharmacophoric portions like donepezil. Phenyl ring of the benzoyl portion mimic the indanone residue of the donepezil. In designed molecules in the current project, the diethylamino moiety has same effect like piperidine ring as tertiary amino group (**Figure 2**).

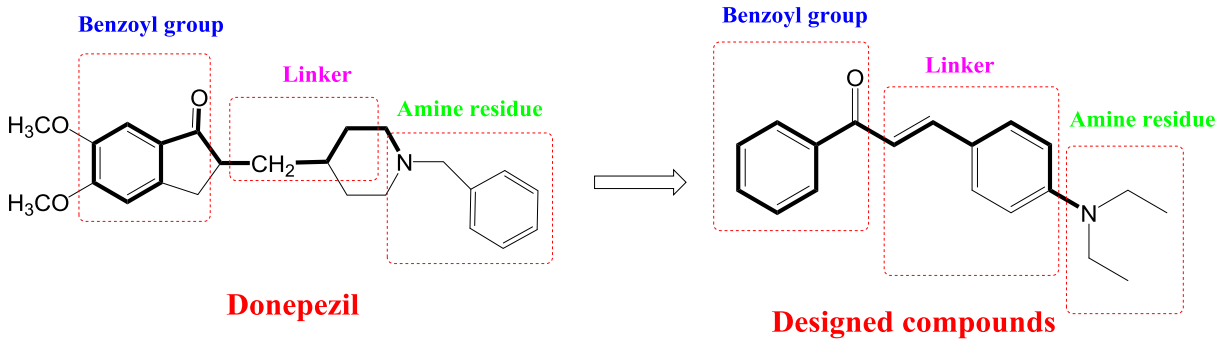


Fig. 2. Structure of donepezil and designed compounds with chalcone strucrure.

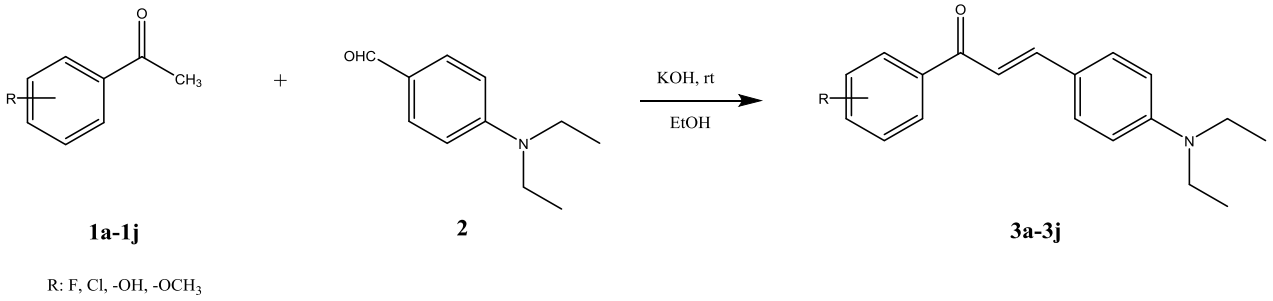
Materials and Methods

Chemistry

The corresponding chemical reagents and starter 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 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.

General procedure for synthesis of compounds 3a-3j

0.5 g (2.8 mmol) of 4-diethylaminobenzaldehyde and various derivatives of acetophenone (**1a-1j**) were stirred in the presence of potassium hydroxide equivalently in methanol overnight (**scheme 1**). The reaction was done at room temperature. Thin layer chromatography (TLC) was applied to determine the reaction end. Then, cold water and crushed ice were added to the reaction medium. The obtained precipitate was filtered and dried. Diethyl ether and *n*-hexane were utilized to wash the collected powders [18].



Scheme 1. Synthetic pathway for compounds **3a-3j**.

Enzymatic assay

All synthesized derivatives were tested towards acetylcholinesterase enzyme using Ellman's protocol as reported previously [6-8]. Ellman test was applied to investigate the capability of the synthesized compounds toward the inhibition of the acetylcholinesterase enzyme. Lyophilized powder of acetylcholinesterase from electric eel source (AChE, E.C. 3.1.1.7, Type V-S, 1000 unit) was purchased from Sigma-Aldrich (Steinheim, Germany). 5,5'-Dithiobis-(2-nitrobenzoic acid, DTNB), potassium dihydrogen phosphate (KH_2PO_4), dipotassium hydrogen phosphate (K_2HPO_4), potassium hydroxide (KOH), sodium hydrogen carbonate ($NaHCO_3$), and acetylthiocholine iodide were purchased from Fluka (Buchs, Switzerland). Spectrophotometric measurements were run on a Cecil BioAquarius CE 7250 Double Beam Spectrophotometer.

Compounds **3a-3j** were dissolved in a mixture of 20 ml distilled water and 5 ml methanol and then diluted in 0.1 M KH_2PO_4/K_2HPO_4 buffer (pH 8.0) to yield a final concentration range. According to the literature, the Ellman test was performed for assessment of the anticholinesterase activity of intended compounds *in vitro*. To achieve 20-80% inhibition of AChE activity five different concentrations of each compound were tested. Compounds **3a-3j** were added to the assay solution and preincubated at 25 ^{0}C with the enzyme for 15 min followed by adding 0.075 M of acetylthiocholine iodide. After rapid and immediate mixing the change of absorption was measured at 412 nm.

The blank reading contained 3 ml buffer, 200 µl water, 100 µl DTNB and 20 µl substrate. The reaction rates were calculated, and the percent inhibition of test compounds was determined. Each concentration was analyzed in triplicate, and IC_{50} values were determined graphically from inhibition curves (log inhibitor concentration vs percent of inhibition).

Docking

Docking study of all ligands was carried out using ArgusLab 4.0 software.[19] The target ligands were built in arguslab workspace and were energy minimized using AM1 as semiemperical method. The pdb files of acetyl cholinesterase in complex with donepezil (pdb code: 1EVE) was downloaded from brookhaven protein databank.[21, 22] The docking process was done for all ligands in the workspace of ArgusLab software after defining the related groups for each ligand as well as protein. The binding site of donepezil was defined as binding site for searching the best pose and conformation for all ligands. Binding mode and related interactions of ligands with acetyl cholinesterase enzyme were explored in Molegro molecular viewer software [23].

Results and Discussion

Chemistry

All synthesized derivatives were characterized using spectroscopic techniques such as ^{1}HNMR, IR and MS. Besides, melting points for each compound was also measured.

(*E*)-1-(2-Chlorophenyl)-3-(4-(diethylamino) phenyl) prop-2-en-1-one (3a)

^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm): 0.95 (t, 3H, *J* = 7.5 Hz, -$CH_2C\underline{H}_3$), 4.10 (d, 1H, *J* = 15 Hz, -CO-C<u>H</u>=CH-), 4.27 (q, 2H, -C<u>H</u>$_2CH_3$), 4.40 (d, 1H, *J* = 15 Hz, -CO-CH=C<u>H</u>-), 7.57 (m, 4H, aromatic), 7.75 (m, 4H, aromatic). IR (KBr, cm^{-1}) ῡ: 2970 (stretch, C-H, aliphatic), 1670 (stretch, C=O).

(*E*)-1-(3-Chlorophenyl)-3-(4-(diethylamino) phenyl) prop-2-en-1-one (3b)

^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm): 0.89 (t, 3H, -$CH_2C\underline{H}_3$), 3.06 (q, 2H, -C<u>H</u>$_2$-CH_3), 6.17 (d, 2H, *J* = 7.5 Hz, $H_{3,5}$-diethylamino), 6.42 (d, 2H, *J* = 7.5 Hz, $H_{2,6}$-diethylamino), 6.96 (t, 1H, *J* = 7.5 Hz, H_5-3-chlorophenyl), 7.01 (d, 1H, *J* = 8.5 Hz, -CO-C<u>H</u>=CH-), 7.11 (d, 1H, *J* = 8.5 Hz, -CO-CH=C<u>H</u>-), 7.19 (d, 1H, *J* = 8.5 Hz, $H_{2,6}$-2-chlorophenyl), 7.40 (d, 1H, *J* = 8.5 Hz, $H_{3,5}$-2-chlorophenyl), 7.54 (s, 1H, (d, 1H, *J* = 8.5 Hz, $H_{2,6}$-2-chlorophenyl). IR (KBr, cm^{-1}) ῡ: 2970 (stretch, C-H, aliphatic), 1674 (stretch, C=O).

(*E*)-1-(4-Chlorophenyl)-3-(4-(diethylamino) phenyl) prop-2-en-1-one (3c)

IR (KBr, cm^{-1}) ῡ: 3035 (stretch, C-H, aromatic), 2970 (stretch, C-H, aliphatic), 1674 (stretch, C=O). MS (*m/z*, %): 315 (M^++2, 12), 313 (30), 298 (100), 139 (40), 111 (25).

(*E*)-3-(4-(Diethylamino) phenyl)-1-(2-fluorophenyl)prop-2-en-1-one (3d)

IR (KBr, cm^{-1}) ῡ: 2970 (stretch, C-H, aliphatic), 1627 (stretch, C=O). MS (*m/z*, %): 297 (M^+, 25), 282 (40), 272 (100), 228 (55), 180 (20), 154 (25), 126 (60).

(*E*)-3-(4-(Diethylamino) phenyl)-1-(4-fluorophenyl) prop-2-en-1-one (3e)

^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm): 1.26 (t, 3H, -$CH_2C\underline{H}_3$), 3.46 (q, 2H, -C<u>H</u>$_2CH_3$), 6.61 (d, 2H, $H_{3,5}$-diethylamino), 7.20 (t, 2H, *J* = 8.5 Hz , $H_{2,6}$-4-fluorophenyl), 7.33 (d, 1H, *J* = 15 Hz, -COC<u>H</u>=CH-), 7.57 (d, 2H, $H_{2,6}$-diethylamino), 7.82 (d, 1H, *J* = 15 Hz, -COCH=C<u>H</u>-), 8.07 (t, 2H, *J* = 8.5 Hz , $H_{3,5}$-4-fluorophenyl). IR (KBr, cm^{-1}) ῡ: 2974 (stretch, C-H, aliphatic), 1680 (stretch, C=O). MS (*m/z*, %): 297 (M^+, 15), 282 (30), 272 (100), 228 (35), 180 (30), 154 (15), 126 (40).

(*E*)-3-(4-(Diethylamino) phenyl)-1-(3-hydroxyphenyl) prop-2-en-1-one (3f)

^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm): 0.95 (t, 3H, -CH_2CH_3), 4.12 (d, 1H, *J* = 15 Hz, -CO-C<u>H</u>=CH-), 4.27 (q, 2H, -C<u>H</u>$_2CH_3$), 4.43 (d, 1H, *J* = 15 Hz, -CO-CH=C<u>H</u>-), 7.57 (m, 4H, aromatic), 7.75 (m, 4H, aromatic). IR (KBr, cm^{-1}) ῡ: 2500-3500 (broad, stretch, OH), 1658 (stretch, C=O).

(*E*)-3-(4-(Diethylamino) phenyl)-1-(4-hydroxyphenyl) prop-2-en-1-one (3g)

^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm): 0.91 (t, 3H, -CH_2CH_3), 3.13 (brs, -O<u>H</u>), 4.19 (d, 1H, *J* = 15 Hz, -CO-C<u>H</u>=CH-), 4.22 (q, 2H, -C<u>H</u>$_2CH_3$), 4.24 (d, 1H, *J* = 15 Hz, -CO-CH=C<u>H</u>-), 7.53 (m, 4H, aromatic), 7.70 (m, 4H, aromatic). IR (KBr, cm^{-1}) ῡ: 2931-3500 (broad, stretch, OH), 1631 (stretch, C=O). MS (*m/z*, %): 295 (M^+, weak), 234 (60), 139 (60), 130 (50), 121 (90), 91 (100), 65 (70), 43 (60).

(*E*)-3-(4-(Diethylamino) phenyl)-1-(2-methoxyphenyl) prop-2-en-1-one (3h)

IR (KBr, cm^{-1}) ῡ: 3043 (stretch, C-H, aromatic), 2974 (stretch, C-H, aliphatic), 1666 (stretch, C=O), 1597 (C=C, aromatic). MS (*m/z*, %): 309 (M^+, 30), 294 (100), 158 (25), 135 (15).

(*E*)-3-(4-(Diethylamino) phenyl)-1-(3-methoxyphenyl) prop-2-en-1-one (3i)

^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm): 0.90 (t, 3H, -$CH_2C\underline{H}_3$), 3.08 (q, 2H, $C\underline{H}_2CH_3$), 3.76 (s, 3H, -OCH_3), 6.17 (d, *J* = 8.5 Hz, 1H, CO-CH=C<u>H</u>-), 6.46 (d, *J* = 8.5 Hz, 1H, CO-C<u>H</u>=CH-), 6.6-7.02 (m, 5H, aromatic, 7.10-7.16 (m, 3H, aromatic). IR (KBr, cm^{-1}) ῡ: 2970 (stretch, C-H, aliphatic), 1670 (stretch, C=O).

(*E*)-3-(4-(Diethylamino) phenyl)-1-(4-methoxyphenyl) prop-2-en-1-one (3j)

^{1}HNMR ($CDCl_3$, 500 MHz) δ (ppm): 1.25 (t, 3H, -$CH_2C\underline{H}_3$), 3.46 (q, 3H, -$C\underline{H}_2CH_3$), 3.93 (d, 3H, -OCH_3), 6.71 (d, 2H, *J* = 8.5 Hz, $H_{3,5}$-diethylaminophenyl), 7.01 (d, 2H, *J* = 15 Hz, $H_{3,5}$-4-methoxyphenyl), 7.36 (d, 2H, *J* = 8.5 Hz, -CO-C<u>H</u>=CH-), 7.57 (d, 2H, *J* = 8.5 Hz, $H_{2,6}$-diethylaminophenyl), 7.81 (d, 2H, *J* = 8.5 Hz, -CO-CH=C<u>H</u>-), 8.06 (d, 2H, *J* = 15 Hz, $H_{2,6}$-4-methoxyphenyl). IR (KBr, cm^{-1}) ῡ: 3070 (stretch, CH, aromatic), 2970 (stretch, C-H, aliphatic), 1643 (stretch, C=O). MS (*m/z*, %): 309 (M^+, 50), 294 (100), 158 (15), 135 (20).

Enzymatic assay

All synthesized derivatives **3a-3j** were tested against acetylcholinesterase using Ellman's protocol and obtained results were compared to donepezil as reference anti-acetylcholinesterase drug. Fortunately, some of the tested derivatives demonstrated superior activity than donepezil (IC_{50} = 0.41 ± 0.09 μM) especially methoxylated compounds (**3h**, **3i**, **3j**). Compound **3b** (3-Cl) also possessed higher activity (IC_{50} = 0.13 ± 0.03 μM) than donepezil. Compound **3h** with *ortho* substitution of the methoxy moiety produced the most potency in this series (IC_{50} = 0.1 ± 0.02 μM). It is likely that methoxy moiety causes hydrogen bonding interaction with the active site of the enzyme. This moiety exerted a remarkable enzyme inhibitory effects while moved to other positions. The methoxy moiety caused lower inhibitory potency towards the acetylcholinesterase at positions *meta* and *para* in comparison with *ortho*. It is probable that *meta* and *para* positioning of the methoxy substituent decreases the exact and proper orientation for hydrogen bonding. It is likely also the other properties of the methoxy moiety such lipophilicity and steric effect maybe important factors for enhancement of the potency at position *ortho*.

The best position of the phenyl residue for chlorine atom was found position *meta*. Electron withdrawing, lipophilicity and steric effects are the outstanding features of the chlorine. Movement of this moiety to the other positions of the phenyl ring reduced the enzyme inhibitory activity especially at *para* position. None of the fluorine and hydroxyl moieties caused favorable anti-acetylcholinesterase effect. According to the mentioned information, we conclude that electronic, steric and lipophilicity for the substituet at position *ortho* are important parameters. The fluorine moiety with a pure electron withdrawing effect and devoid of any steric effect was not capable to potentiate the activity.

Comparison of the inhibitory effects of the synthesized chalcone-based derivatives with other chalcone derivatives as anti-acetylcholinesterase showed that current compounds that presented in this research were more potent than compounds have been presented in the previous literatures [15-

17]. Indeed, the obtained pharmacophore in this project was more active towards the inhibition of acetyl cholinesterase. The α, β-unsaturation system of the chalcone may help the proper orientation and conformation of the carbonyl group and tertiary amine moiety.

Docking

According to the **Figure 3**, compound **3h** with 2-methoxy group participated in hydrogen bonding interaction via carbonyl moiety into the active site of AChE. This hydrogenic interaction potentiates the enzyme inhibitory activity of compound **3h**.

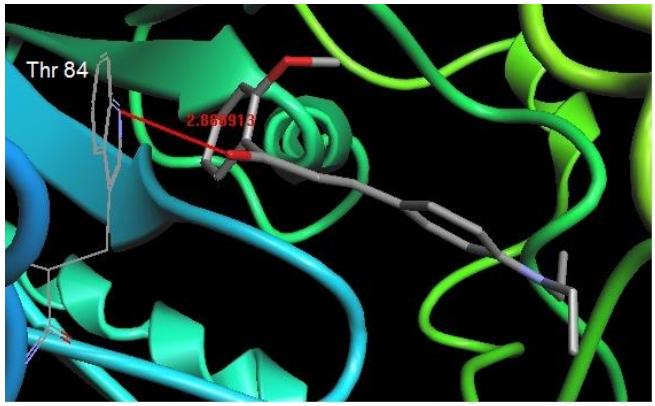


Fig. 3. Hydrogen bonding of carbonyl moiety of compound **3h** with Thr 84 is observable in the active site of the AChE.

Conclusion

A new series of chemical entities based on the chalcone substructure were synthesized and evaluated as acetylcholinesterase inhibitors. Based on the obtained results, the investigated derivatives were potent AChE inhibitors and can be proposed as potential anti-Alzheimer lead compounds.

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Conflict of Interests

Authors certify that there is no actual or potential conflict of interest in relation to this article.

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