Design and Development of a Novel Chalcone Derivative as an Anticholinesterase Inhibitor for Possible Treatment of Dementia

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Background: Cognitive decline (e.g., memory loss), which mainly occurs in the elderly, is termed dementia. In the present study, we intended to explore the cholinesterase inhibitory activity of some novel synthesized chalcones, together with their effect on β-amyloid anti-aggregation.

Material/Methods: A novel class of chalcone derivatives have been synthesized and characterized by FT-IR, 1H-NMR, 13C-NMR, and mass and elemental analysis. These derivatives were later used for the determination of acetylcholinesterase (AChE) inhibitory and β-amyloid anti-aggregation activity.

Results: The results of the study showed that among the developed compounds, 8g inhibits AChE more prominently than BuChE, as suggested by a selectivity index (SI) of 2.88. Furthermore, the most potent compound, 8g, showed considerable action in inhibition of β-secretase and Aβ aggregation, but not as prominent as that of curcumin as a standard.

Conclusions: In conclusion, our study revealed a novel class of chalcone derivatives as a selective inhibitor of AChE with considerably action against β-secretase and Aβ aggregation. Our results may be useful in developing AD drug therapy and warrant further investigation to generate more advanced analogues.

MeSH Keywords: Alzheimer Disease • Cholinesterase Inhibitors • Chemistry Techniques, Synthetic

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Background

Cognitive decline (e.g., memory loss), mainly in the elderly, is termed dementia [1]. It is not as a disease, but rather is a phenomenon considered to be a collection of symptoms related to problem in thinking and memory, affecting the daily life of the individual [2,3]. According to the World Health Organisation (WHO), China has witnessed marked improvement in life expectancy as result of increased access to better healthcare facilities [4]. This has increased the number of dementia patients; in 2010, around 10 million people were suffering from dementia in China, as compared to just 3.68 million in 1990 [5]. The treatment and care for this huge number of patients is a huge economic burden, with a cost of 392.6 billion RMB (US$ 63.21 billion) per year for dementia patients in China alone [6]. Among the diagnosed cases of dementia, nearly 60–80% of cases have Alzheimer disease (AD) [7]. The etiology of AD is still a matter of investigation and not yet been fully elucidated [8]. The available literature suggests that AD may progress because of decrease in the level of acetyl choline, increase in β-amyloid plaques [9,10], and increase in oxidative stress, together with inflammation [11] and Tau-protein aggregation [12].

Although there is no definitive cure for dementia of the AD type, various pharmacological approaches have been utilized to offer symptomatic relief, for instance, acetylcholine replacement therapy [13], acetylcholine precursors [14], cholinergic agonists [15], and enhancement of acetylcholinesterase release and acetylcholinesterase inhibition [16]. Except for the acetylcholine esterase inhibitor (Achls), all of the above interventions have been associated with certain disadvantages that render them ineffective in treating AD [17]. Achls prevents degradation of Ach during its transport from one cell to another and increases the concentration of Ach, causing increase in the cholinergic neurotransmission in AD patients [18]. However, these inhibitors have been also associated with certain problems, such as toxicity, adverse effects, short half-life, and non-selective inhibition of Ach esterase (AChE) [19]. Thus, much interest has been focussed on the design and development of novel inhibitors of AChE that are devoid of these shortcomings.

Due to ease of synthesis and possibility of numerous structural diversity, chalcones have attracted the attention of medical chemists [20]. It is extensively reported to exhibit a wide array of bioactivities, such as antibacterial [21], anticancer [22], antimalarial [23], and antifungal [24] effects, particularly Achls. Various researchers have successfully developed numerous novel Achls belonging to the category of chalcones [25]. These analogues were also revealed to inhibit the amyloid beta (Aβ) self-assembly and the disassembly of preformed Aβ oligomers, suggesting its multifunctional role in treating symptoms of AD [26]. Encouraged by the above, in the present study we intended to enumerate the cholinesterase inhibitory effects of some novel synthesized chalcones together with their effect on β-amyloid anti-aggregation.

Material and Methods

Chemistry

The chemicals used in the present study were procured from Sigma Aldrich (USA). The spectra of 1H NMR and 13C NMR were recorded on a Bruker Avance 400 and a Bruker Avance 100 Spectrophotometer, respectively. The chemical shifts are expressed in parts per million (ppm), and coupling constants are expressed in Hertz (Hz). The low-resolution mass spectrum (MS) was recorded on a Waters ZQ LC/MS single quadrupole system equipped with an electrospray ionization (ESI) source. The elemental analysis of the final derivatives was performed using a Vario Elemental analyzer. The Thin-layer chromatography was performed on 0.25 mm Merck silica gel plates (60F254) and visualized under UV light.

General procedure for synthesis of (E)-1-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one. (3)

We dissolved 1-(4-hydroxyphenyl)ethanone, 1 (0.01 mol) and benzaldehyde, 2 (0.01 mol) in 50 mL ethanolic solution and stirred it for 30 min, followed by dropwise addition of aqueous sodium hydroxide (0.05 mol), followed by further stirring for 24 h. After completion of the reaction as monitored by TLC using the mobile phase as n-butanol: acetic acid: water (4: 3: 1), a crude product was obtained as (E)-1-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one, 3. The resultant solid was then filtered off, washed with water, dried, and re-crystallized from ethanol [27].

General procedure for synthesis of (E)-1-(4-(2-bromoethoxy)phenyl)-3-phenylprop-2-en-1-one (4)

A mixture of 3 (4.95 mmol) and K2CO3 (9.99 mmol) in DMF (10 mL) was stirred at 80°C for 1 h, then 1,2-dibromoethane (14.84 mmol) was added dropwise. The mixture was stirred until the TLC showed completion of the reaction. The reaction mixture was poured into water (20 mL) and was extracted with ETOAc (3×10 mL). The combined organic layers were dried over anhydrous Na2SO4 and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel by using petroleum ether and ethyl acetate (v/v=2: 1) as eluent to give 4 [28].

General procedure for synthesis of tert-butyl piperidin-4-ylcarbamate. (6)

A solution of the appropriate 2- (bromo alkyl)isindole-1,3-dione or 1-(bromo alkyl)-1H-indole (1 equiv),
4-amino-1-benzylpiperidine (5) (1 equiv) and TEA (1.2 equiv) in MeCN was refluxed for 4 h. After cooling, the product precipitated as the hydrobromide salt. This was collected by filtration, washed with MeCN, and dried in vacuo. The product was dissolved in 30 mL water, and then adjusted to basic pH by adding 25% NH₄OH solution. Then the product was extracted with DCM (3×30 mL) and dried over anhydrous Na₂SO₄ to afford the product.

**General procedure for synthesis of substituted 1-benzylpiperidin-4-amine. (7)**

A solution of the appropriate tert-butyl piperidin-4-ylcarbamate (6) and substituted benzyl bromide or chloride in THF was refluxed for 24 h. After completion of the reaction, the desired substituted 1-benzylpiperidin-4-amine was obtained by tert-butyloloxycarbonyl (BOC)-deprotection in 10% HCl solution in methanol.

**General procedure for synthesis of title compounds. (8a–h)**

A mixture of substituted 1-benzylpiperidin-4-amine (7) and (E)-1-(4-((1-(4-bromobenzyl)piperidin-4-yl)amino)-3-phenylprop-2-en-1-one (4) was dissolved in 1,4-dioxane. The mixture was refluxed for 48 h and monitored by TLC. The reaction mixture was poured into water (20 mL) and was extracted with EtOAc (3×20 mL), and the combined organic layers were dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give the title compounds 8 (a–h).

**E-(1-(4-(2-((1-(4-bromobenzyl)piperidin-4-yl)amino)ethoxy)phenyl)-3-phenylprop-2-en-1-one. (8c)**

Yield: 76%; MP: 212–213°C; MW: 519.47; R₂: 0.62; FT-IR (νₘₐₓ; cm⁻¹ KBr): 3189 (secondary N-H str), 1653 (C=O str), 1541, 1216 ppm; 1H-NMR (400 MHz, DMSO, TMS) δ ppm: 8.11-7.19 (m, 4H, Ar-H), 8.06-7.57 (m, 2H,Aliphatic-H), 7.59-7.29 (m, 9H, Ar-H), 4.12-2.96 (m, 4H, CH₂x2), 3.69 (s, 2H,Aliphatic-H), 2.63-1.46 (m, 9H, piperidine-H), 1.97 (s, 1H,NH); 13C-NMR (100 MHz, CDCl₃) δ ppm: 189.9, 165.3, 146.5, 137.7, 135.3, 131.3, 131.2, 129.7, 128.7, 128.4, 127.9, 121.7, 121.3, 114.8, 69.3, 64.8, 59.3, 51.9, 47.4, 30.8; Mass: 520.54 (M+1); Elemental analysis for C₂₇H₂₃BrN₂O₂: Calculated: C, 75.96; H, 6.81; N, 6.11; Found: C; 75.99; H, 6.78; N, 6.15.

**E-(1-(4-(2-((1-(4-nitrobenzyl)piperidin-4-yl)amino)ethoxy)phenyl)-3-phenylprop-2-en-1-one. (8e)**

Yield: 82%; MP: 224–225°C; MW: 485.57; R₂: 0.78; FT-IR (νₘₐₓ; cm⁻¹ KBr): 3197 (secondary N-H str), 3092 (Ar-H str), 2975 (Ali C-H str), 1529 (NO₂ str), 1484 (C=C of benzene), 1709 (C=O str), 789 cm⁻¹; 1H-NMR (400MHz, DMSO, TMS) δ ppm: 8.15-7.96 (m, 4H, NO₂,Ar-H), 8.11-7.18 (m, 4H, Ar-H), 8.06-7.58 (m, 2H,Aliphatic-H), 7.61-7.32 (m, 5H, Ar-H), 4.15-2.95 (m, 4H, CH₂x2), 3.67 (s, 2H,Aliphatic-H), 2.64-1.51 (m, 9H, piperidine-H), 1.96 (s, 1H,NH); 13C-NMR (100MHz, CDCl₃) δ ppm: 189.9, 165.3, 146.5, 145.2, 144.8, 135.3, 130.5, 129.7, 128.7, 128.5, 127.9, 127.9, 127.9, 127.9, 127.9, 127.9.
Yield: 75%; MP: 212–213°C; MW: 470.60; R
(4-((3,4-dichlorobenzyl)piperidin-4-yl)amino)
ethoxy)phenyl)-3-phenylprop-2-en-1-one. (8f)

Yield: 69%; MP: 228–229°C; MW: 454.60; R: 0.61; FT-IR (v\text{max},
cm^{-1}; 
KBr): 3198 (secondary N-H str), 3192 (C=O str), 1718 (C=O str), 775 cm^{-1}; 1\text{H}-NMR (400MHz, DMSO, TMS) δ ppm: 8.12-7.21 (m, 4H, NO2-Ar-H), 8.06-7.64 (m, 2H, Aliphatic-H), 7.59-7.14 (m, 9H, Ar-H), 4.12-2.95 (m, 4H, CH2), 3.68 (s, 2H, Aliphatic-H), 2.63-1.48 (m, 9H, piperidine-H), 2.63 (s, 3H, Ar-CH3); 1\text{3C}-NMR (100MHz, CDCl3) δ ppm: 189.8, 165.2, 145.2, 135.4, 135.1, 130.6, 130.1, 129.7, 128.7, 128.5, 128.4, 127.9, 121.4, 114.8, 68.4, 64.8, 59.3, 55.9, 31.7, 47.4, 30.8; Mass: 471.63 (M+1); Elemental analysis for C29H24N3O; Calculated: C, 76.63; H, 7.25; N, 5.98.

Yield: 69%; MP: 235-236°C; MW: 509.47; R: 0.68; FT-IR (v\text{max},
cm^{-1}; 
KBr): 3194 (secondary N-H str), 3192 (C=O str), 1842 (C=O of benzene), 1718 (C=O str), 775 cm^{-1}; 1\text{H}-NMR (400MHz, DMSO, TMS) δ ppm: 8.12-7.21 (m, 4H, NO2-Ar-H), 8.06-7.64 (m, 2H, Aliphatic-H), 7.59-7.14 (m, 9H, Ar-H), 4.12-2.95 (m, 4H, CH2), 3.68 (s, 2H, Aliphatic-H), 2.63-1.48 (m, 9H, piperidine-H), 2.63 (s, 3H, Ar-CH3); 1\text{3C}-NMR (100MHz, CDCl3) δ ppm: 189.7, 165.2, 145.2, 136.9, 135.1, 130.6, 130.1, 129.7, 128.7, 128.5, 128.4, 127.8, 121.3, 114.9, 69.4, 64.8, 59.5, 51.8, 47.5, 21.4, 30.7; Mass: 455.57 (M+1); Elemental analysis for C29H24N3O; Calculated: C, 79.26; H, 7.54; N, 6.16; Found: C, 79.29; H, 7.59; N, 6.12.

Yield: 69%; MP: 235-236°C; MW: 509.47; R: 0.68; FT-IR (v\text{max},
cm^{-1}; 
KBr): 3194 (secondary N-H str), 3192 (C=O str), 1842 (C=O of benzene), 1718 (C=O str), 775 cm^{-1}; 1\text{H}-NMR (400MHz, DMSO, TMS) δ ppm: 8.12-7.21 (m, 4H, NO2-Ar-H), 8.06-7.64 (m, 2H, Aliphatic-H), 7.59-7.14 (m, 9H, Ar-H), 4.12-2.95 (m, 4H, CH2), 3.68 (s, 2H, Aliphatic-H), 2.63-1.48 (m, 9H, piperidine-H), 2.63 (s, 3H, Ar-CH3); 1\text{3C}-NMR (100MHz, CDCl3) δ ppm: 189.7, 165.3, 159.2, 145.2, 136.9, 135.1, 130.6, 130.1, 129.7, 128.7, 128.5, 128.4, 128.3, 127.8, 121.4, 114.8, 69.4, 64.8, 59.3, 51.8, 47.5, 21.4, 30.7; Mass: 455.57 (M+1); Elemental analysis for C29H24N3O; Calculated: C, 79.26; H, 7.54; N, 6.16; Found: C, 79.29; H, 7.59; N, 6.12.

Biological activity

**AChe and BChE inhibition assay**

Acetylcholinesterase and butyrylcholinesterase were purchased from Sigma Aldrich and the other chemicals were obtained from Fluka. The compound solution was prepared in a mixture of DMSO (5 ml) and methanol (5 ml) and diluted in 0.1 M KH2PO4/K2HPO4 buffer (pH 8.0) to obtain final assay concentrations. All experiments were performed at controlled temperature and humidity in triplicate in a 96-well plate reader. Each well contained 50 µl of potassium phosphate buffer (KH2PO4/ K2HPO4, 0.1 M, pH 8), 25 µl sample dissolved in 50% methanol and 50% DMSO and 25 µl enzyme. They were preincubated for 15 min at room temperature, and then 125 µl DTNB (3 mM in buffer) was added and determined spectrometrically at 405 nm. The IC50 values were determined graphically using Graph Pad Prism [29].

**Self-mediated Aβ (1–42) aggregation assay**

For measuring the effect on self-mediated Aβ (1–42) aggregation, thioflavin T-based fluorometric assay was utilized. Initially, the stock solutions of 5 mM Ab (1–42) samples (GL Biochem, Shanghai) were prepared by dissolving in DMSO and freezing at −20°C. Experiments were conducted in the presence/absence of various concentration of title compounds; peptide was shaken in 50 mM phosphate buffer (pH 7.4) containing 100 mM NaCl at 37°C for 10 h (final Ab concentration 100 µM) and incubated. The experiments were performed in triplicate and the IC50 value for each inhibitor was calculated.

**β-secretase inhibition assay**

For this assay, a β-secretase fluorescence resonance energy transfer assay kit (P2985, PanVera) was utilized according to the manufacturer’s protocol. Due to cleavage catalyzed by β-Secretase, the weakly fluorescent substrate becomes highly fluorescent and the rate of proteolysis at the early stage accurately indicates the concentration of the active enzyme. The fluorescence signal was recorded at λem=585 nm (λexc=535 nm) by use of a microplate reader. The inhibition percentage corresponding to the presence of different concentrations of test compound were calculated by the following equation: 100×[(Fi/Fo)/100], where Fi and Fo are the fluorescence intensities obtained for the desired inhibitor, respectively. The IC50 values corresponding to the presence of different concentrations of title compounds; peptide was shaken in 50 mM phosphate buffer (pH 7.4) containing 100 mM NaCl at 37°C for 10 h (final Ab concentration 100 µM) and incubated. The experiments were performed in triplicate and the IC50 value for each inhibitor was calculated.
Table 1. In vitro inhibition of AChE and BuChE of compound 8(a–h).

| Code | AChE inhibition (IC\textsubscript{50} µM)* | BuChE inhibition (IC\textsubscript{50} µM)* | Selectivity Index (SI)** |
|------|---------------------------------|---------------------------------|------------------------|
| 8a   | 32.34±0.26                      | 21.72±0.11                      | 0.67                   |
| 8b   | 10.03±0.54                      | 9.45±0.25                       | 1.06                   |
| 8c   | 18.11±0.33                      | 28.42±0.42                      | 1.56                   |
| 8d   | 14.23±0.15                      | 26.50±0.28                      | 1.86                   |
| 8e   | 28.62±0.22                      | 25.01±0.31                      | 1.12                   |
| 8f   | 4.22±0.34                       | 9.45±0.25                       | 2.23                   |
| 8g   | 1.12±0.13                       | 3.23±0.12                       | 2.88                   |
| 8h   | 24.54±0.21                      | 26.11±0.18                      | 1.06                   |
| Donepezil | 0.02±0.006                      | 2.11±0.33                       | 105.5                  |

* Data are expressed as means ± standard deviation (SD) of at least three independent experiments; ** The selectivity index of inhibitor has been determined by BuChE/AChE.

Results and Discussion

Chemistry

Scheme 1: Synthesis of designed analogues of chalcones, 8 (a–h). Reagents and condition: EtOH, NaOH, stirring 24 h; (b) 1,2-di bromo ethane, K\textsubscript{2}CO\textsubscript{3}, DMF, 80°C; (c): BOC, O, TEA, THF, rt, 12 h; (d) 10% Pd/C, H\textsubscript{2}, methanol, 24 h; (e) substituted benzylic chloride or chloride, THF, reflux, 24 h; (f) 10% HCl in methanol, 24 h; (g) 1,4-dioxane, reflux, 48 h.

To obtain the designed chalcones, a cost-effective synthesis was devised, as presented in scheme 1. The synthesis was initially started with condensation of benzaldehyde (1) with 4-hydroxy acetophenone (2) under reflux in the presence of ethanol to yield compound 3. It was later allowed to undergo nucleophilic substitution reaction with 1,2-dibromoethane in DMF for 8 h at 80°C to furnish compound 4. In the next step, the synthesis has been aimed at development of substituted 4-amino-1-benzylpiperidines. The primary amine of benzyl-4-aminopiperidine was BOC-protected with the help of tert-butyloxy carbonyl in the presence of tetrahydrofuran to furnish a compound which then was debenzylated in the presence of methanol and alkylated with the corresponding substituted benzylic bromide in tetrahydrofuran. Compound 7 was obtained by means of BOC-deprotection in 10% alc HCl solution. The last step corresponds to etherification of compound 4 with 7 in the presence of KOH in DMF at 40°C, as indicated by TLC, for the appropriate time.

The structure of the title compound has been ascertained with the help of various spectroscopic analyses. It has been found that the FT-IR spectra of all title compounds 8(a–h) were characterized by the appearance of strong bands at 3198–3189 cm\textsuperscript{-1}, which is attributed to the N-H group. The band corresponds to the C-H benzene ring that appears at 3098–3082 cm\textsuperscript{-1}. Furthermore, another band at 2826 cm\textsuperscript{-1} is attributed to the stretching vibrations of the aromatic OCH\textsubscript{3} group. The CH\textsubscript{3} group of aromatic rings appears at 2982 cm\textsuperscript{-1}. Many strong absorption bands appear at 1718–1704 cm\textsuperscript{-1}, which confirm the existence of a C=O group. Another band at 1529 cm\textsuperscript{-1} is attributed to the stretching vibrations of the aromatic NO\textsubscript{2} group. Furthermore, another band at 1534–1510 cm\textsuperscript{-1} is attributed to the stretching vibrations of the aromatic Cl group. The \textsuperscript{1}H NMR spectra of title compounds 8(a–h) reveal a multiple corresponding to the phenyl ring at 8.11–7.18 ppm. The aliphatic CH\textsubscript{2} proton appears at 4.13–2.97 ppm. A resonance due to piperidine proton was found in the range of 2.65–1.45 ppm. The substituted benzene ring proton appeared as a singlet at 7.63–7.24 ppm. The CH\textsubscript{2}OH group of aromatic rings appears at 3.23–2.81 ppm. The band at 2826 cm\textsuperscript{-1} is attributed to the \textsuperscript{13}C NMR spectra of title compounds 8(a–h) reveal a multiple corresponding to the methylene group at 2.65–1.45 ppm. The CH\textsubscript{2}OH group of aromatic rings appears at 3.23–2.81 ppm. The band at 2826 cm\textsuperscript{-1} is attributed to the \textsuperscript{13}C NMR spectra of title compounds 8(a–h) reveal a multiple corresponding to the methylene group at 2.65–1.45 ppm. The CH\textsubscript{2}OH group of aromatic rings appears at 3.23–2.81 ppm.

Pharmacological activity

Due to involvement of choline esterase enzyme in the degradation of ACh in AD patients, the designed target compound was rigorously analyzed for the determination of inhibitory activity against AChE and BuChE. As presented in Table 1, the entire set of target compounds showed considerable inhibition of AChE and BuChE, with varying degrees of inhibition. Among the series, the most potent inhibition was in the compound 8g, which has the p-methyl as substituent on the piperidine against both of the tested enzymes (AChE and BuChE). The inhibitory activity showed that 8g inhibits AChE more prominently than BuChE, as interpreted with the help of

* Data are expressed as means ± standard deviation (SD) of at least three independent experiments; ** The selectivity index of inhibitor has been determined by BuChE/AChE.
a selectivity index (SI) of 2.88. The conversion of methyl to methoxy, as in the case of 8f, renders the compound approximately 3-fold less active against AChE and BuChE than the parent compound. The least activity was observed in compound 8a, which contains no substituent with IC_{50} of 32.34 µM against AChE, with improved inhibition against BuChE. With the introduction of an electron-withdrawing group, p-chloro led to marked improvement in the activity against AChE, with marginal improvement against BuChE. The activity against AChE was markedly reduced in compound 8c, with SI index of 1.56. The activity against ChE was further enhanced, together with mild improvement against BuChE, in the case of compound 8d. Compound 8e showed significant reduction in the inhibitory activity against AChE, with mild improvement in the case of BuChE, with SI of 0.87. The di-chloro-containing compound 8h showed drastic reduction in the activity as compared to its mono-chloro substituted derivative 8b, together with noticeable change in SI value. In comparison to the inhibitory activity of Donepezil, none of the synthesized compounds showed equal or better activity.

Results of the structure-activity relationship study suggest that the activity is greatly dependent on the type and nature of the substituents (Figure 1). On close inspection, the inhibitory activity of the compounds containing an electron-donating group showed much stronger activity than in the electron-withdrawing group. It was surprising to find that the di-chloro-substituted compound is less potent than the mono-chloro derivative.

**Table 2.** Compound 8g showed considerably affinity in inhibiting the β-secretase and Aβ aggregation.

| Compound | Aβ aggregation (IC_{50} µM)a | β-secretase (IC_{50} µM)** |
|----------|-----------------------------|--------------------------|
| 8g       | 18.21±2.3                   | 23.14±1.8                |
| Curcumin | 11.3±0.3                    | 6.1±0.8                  |

* Data are expressed as means ± standard deviation (SD) of at least three independent experiments.

The most potent compound, 8g, has been further evaluated to assess inhibitory activity against β-secretase and Aβ aggregation. This assay is important because current therapeutic approaches to treat AD have focussed on targeting the various pathways that leads to AD progression. Several studies confirmed that β-secretase plays a significant role in the cleavage of amyloid precursor, which leads to the production of Aβ peptide. Particularly, in the case of AD, this pathway is involved in cognitive decline and offers beneficial and symptomatic effects when targeted specifically. As presented in Table 2, compound 8g showed considerable action in inhibiting β-secretase and Aβ aggregation, but not as prominent as compared to curcumin as a standard.

**Conclusions**

A novel class of chalcone derivatives has been synthesized and characterized with the aid of various spectroscopic methods. Our results show that this novel class of chalcone derivative is a selective inhibitor of AChE, with considerable action against β-secretase and Aβ aggregation. This study demonstrates potential value in developing drugs against AD and warrants further investigation to generate more advanced analogues.

**Conflict of interest**

The authors have declared no conflict of interest.
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