Asian Journal of Chemistry; Vol. 38, No. 11 (2026), 3107-3114
ASIAN JOURNAL OF CHEMISTRY
https://doi.org/10.14233/ajchem.2026.36542

Coumarin-Piperidine Derivatives as Acetylcholinesterase Inhibitors: Design, *In silico*, Synthesis and Evaluation

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Received: 9 July 2026 *Accepted*: 31 October 2026 *Published online*: 13 November 2026 AJC-22542

A library of 70 coumarin–piperidine derivatives (**Cop1-Cop70**) was designed and subjected to molecular docking studies against acetylcholinesterase (AChE; PDB ID: 4EY7) using the Schrödinger software suite. Based on their docking scores, 24 compounds with scores more than -9.50 kcal/mol were selected for ADME prediction using SwissADME. Fourteen derivatives were predicted to cross the blood–brain barrier and were selected for chemical synthesis. The selected compounds were synthesized through cyclization and amide coupling reactions and characterized using FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry and elemental analysis (CHN). Molecular docking analysis provided insights into the predicted binding modes and interactions of the derivatives within the AChE active site. Their inhibitory activity was further assessed using an AChE inhibition assay. Among the synthesized compounds, **Cop54** exhibited the highest inhibitory activity, with 72.41% inhibition of AChE. These findings identify **Cop54** as a promising lead for further investigation and provide a basis for the development of coumarin–piperidine derivatives as potential AChE inhibitors for Alzheimer's disease research.

Keywords: Acetylcholinesterase (AChE), Coumarin, Alzheimer's disease, Molecular docking.

INTRODUCTION

Coumarin is an important heterocyclic scaffold in medicinal chemistry, owing to its stable conjugated ring system, favourable solubility in many organic solvents and widespread occurrence in natural products [1,2]. 4-Hydroxycoumarin serves as a valuable building block in organic synthesis, while its derivatives have been investigated for a broad range of pharmacological activities, such as anticoagulant, antifungal, antibacterial, antiprotozoal, insecticidal, antimycobacterial, antimutagenic, anti-inflammatory, HIV protease inhibitory and monoamine oxidase (MAO) inhibitory effects [3]. Coumarin derivatives have gained interest as potential acetylcholinesterase (AChE) inhibitors. Their planar, aromatic ring system may facilitate interactions with the peripheral anionic site (PAS) of AChE through π–π stacking with aromatic amino acid residues, contributing to ligand recognition and binding [4]. Coumarin derivatives have been reported to exhibit anticancer [5-7], anticonvulsant [8], antimicrobial [9], anticholinesterase [10], antidiabetic [11], antitubercular [12] and monoamine oxidase inhibitory activities [13].

Coumarin–piperidine hybrids have attracted interest in medicinal chemistry due to the combination of two pharmacologically relevant structural units within a single molecular framework [14]. Structural modifications involving *N*-benzylpiperidine substitution and suitable linker groups have yielded derivatives with promising acetylcholinesterase (AChE) and monoamine oxidase-B (MAO-B) inhibitory activities, along with favourable predicted properties for central nervous system (CNS) drug development [15].

The disruption of cholinergic neurotransmission is closely associated with the cognitive deficits observed in Alzheimer's disease (AD), making AChE an important molecular target for inhibitor development [16,17]. Although established drugs such as donepezil, rivastigmine and galantamine are used to manage AD symptoms, their therapeutic limitations warrant

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the exploration of structurally distinct AChE inhibitors [18]. The architecture of AChE offers opportunities for molecular design through its catalytic active site (CAS) and peripheral anionic site (PAS), which accommodate ligands through different binding interactions. Targeting these regions through appropriate structural modifications may provide new methods to modulating enzyme activity [19-23].

The presence of a piperidine moiety in donepezil, an established AChE inhibitor, further supports its relevance in the design of cholinesterase-targeting compounds [24]. Combining these two structural motifs offers an opportunity to develop hybrid molecules with modified molecular architecture and potential AChE inhibitory properties. In this context, 6-chloro-2-oxo-2*H*-chromene-3-carboxylic acid was employed as a functionalized coumarin precursor for the construction of new derivatives [25].

The present work describes the design of 70 coumarin–piperidine derivatives (**Cop1-Cop70**) and their computational screening against acetylcholinesterase (AChE) (PDB ID: 4EY7) using the Schrödinger software suite. Twenty-four compounds with docking scores more than -9.50 kcal/mol were subjected to ADME prediction using SwissADME, from which 14 derivatives with favourable predicted blood-brain barrier permeability was selected for synthesis. The target com-pounds were synthesized through cyclization and amide coupling reactions and characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry and elemental analysis. Their inhibitory activity was examined using an *in vitro* AChE assay.

EXPERIMENTAL

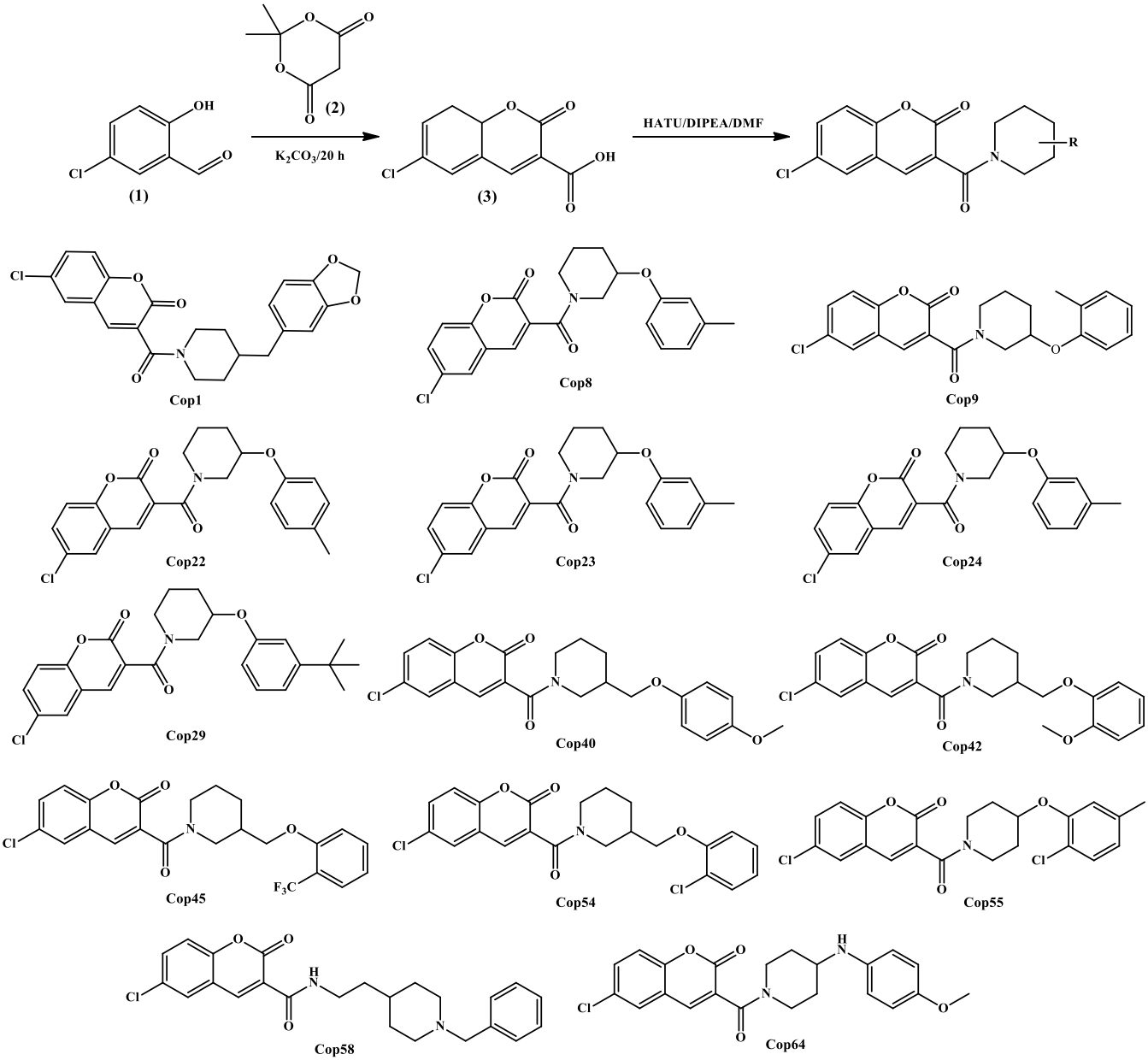
All solvents and reagents were of analytical grade and purchased from Merck, Avra Synthesis, Enamine and Spectrochem (India). Melting points were determined using a Gallen Kamp apparatus (SSI/MPA/5314) with capillary tubes and are reported uncorrected. Reaction progress was monitored by thin-layer chromatography (TLC) using precoated Merck silica gel aluminium sheets (CAS No. 112926-00-8), with spots visualized under UV light or in an iodine chamber. FT-IR spectra were recorded using a Bruker TENSOR 27 spectrophotometer employing the KBr pellet technique. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were acquired using a Bruker NMR spectrometer with deuterated solvents. Spectral processing was performed using TopSpin 7.1 software. LC-MS spectra were recorded using an Agilent mass spectrometry system equipped with an electrospray ionization (ESI) source. The percentage yields of the synthesized compounds were calculated based on the initial reactant quantities (1.0 mmol each).

Synthesis: Selected coumarin–piperidine derivatives were synthesized through a two-step procedure. In the first step, Meldrum's acid (1 equiv.) was added to a stirred aqueous solution of 5-chloro-2-hydroxybenzaldehyde (1 equiv.) at 0 ºC followed by the addition of 20% aqueous K_2CO_3 (0.1 equiv.). The reaction mixture was stirred vigorously at room temperature for 20 h, with the reaction progress monitored by TLC. After completion, the mixture was acidified with 2 N HCl to obtain a white precipitate, which was collected by filtration, washed with cold water, dried and recrystallized from ethyl acetate to yield 6-chloro-2-oxo-2*H*-chromene-3-carboxylic acid. In the second step, the resulting intermediate (1 equiv.) was dissolved in DMF and cooled to 0 ºC. HATU (1.5 equiv.) and DIPEA (3 equiv.) were added and the mixture was stirred for 5 min before adding the appropriate substituted piperidine derivative (1.1 equiv.). The reaction was continued at room temperature for 12 h and monitored by TLC. After completion, the mixture was quenched with crushed ice and extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried over anhydrous sodium sulphate and concentrated under reduced pressure (**Scheme-I**). The crude products were purified by silica gel column chromatography (100-200 mesh) using methanol in DCM (2-10%) as eluent to obtain the desired coumarin–piperidine derivatives.

3-(4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)piperidine-1-carbonyl)-6-chloro-2*H*-chromen-2-one (Cop1): White solid; yield: 90.40%; R_f: 0.60; m.p.: 168-170 ºC; elemental analysis of $C_{23}H_{19}ClNO_5$ (*m.w.* 425.86): calcd. (found) %: C, 65.02 (64.44); H, 4.51 (4.69); N, 3.30 (3.31); FT-IR (KBr, ν_{max}, cm^{-1}): 3035 (arom. H), 2848 (aliph. C–H), 1720 (lactone keto), 1660 (–$CONH_2$ amide), 1570 (C=C), 1100 (C–O–C of dioxole ring), 745 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.50 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.76 (s, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 5.95 (s, 2H), 4.45 (bd, *J* = 13.0 Hz, 1H), 3.55 (bd, *J* = 13.0 Hz, 1H), 3.00 (bt, 1H), 2.75 (bt, 1H), 2.47 (d, *J* = 6.8 Hz, 2H), 1.70-1.82 (m, 1H), 1.58-1.68 (m, 2H), 1.08-1.22 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.5, 158.2, 154.1, 147.6, 145.8, 142.1, 138.0, 133.8, 130.6, 125.8, 125.2, 122.2, 117.8, 116.8, 109.5, 108.3, 101.0, 47.1, 42.1, 41.8, 37.8, 32.2, 31.6 MS: *m/z* 426 (M^+); found: *m/z* 425 $(M–H)^+$.

6-Chloro-3-(3-(*m*-tolyloxy)piperidine-1-carbonyl)-2*H*-chromen-2-one (Cop8): White solid; yield: 87.90%; R_f: 0.41; m.p.: 172-174 ºC; elemental analysis of $C_{22}H_{20}ClNO_4$ (*m.w.* 397.85): calcd. (found) %: C, 66.42 (66.44); H, 5.07 (5.09); N, 3.52 (3.54); FT-IR (KBr, ν_{max}, cm^{-1}): 3050 (arom. H), 2952 (aliph. C–H), 1705 (lactone keto), 1678 (–$CONH_2$ amide), 1603 (C=C), 1242 (Ar–O–C *str.*), 722 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.90 (d, *J* = 2.4 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.49 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 6.78 (m, 3H), 4.79 (m, 1H), 4.01 (m, 1H), 3.63 (m, 1H), 3.32 (m, 2H), 2.28 (s, 3H), 2.02 (m, 1H), 1.93 (m, 1H), 1.60 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2, 160.8, 157.1, 153.8, 142.1, 139.2, 137.8, 130.4, 129.5, 125.6, 123.8, 122.1, 117.8, 116.4, 112.5, 72.7, 44.0, 38.9, 31.2, 30.4, 21.3; MS: calcd. *m/z* 397.85; found: *m/z* 397.98.

6-Chloro-3-(3-(*o*-tolyloxy)piperidine-1-carbonyl)-2*H*-chromen-2-one (Cop9): White product; yield: 83.70%; R_f: 0.38; m.p.: 165-167 ºC; elemental analysis of $C_{22}H_{20}ClNO_4$ (*m.w.* 397.85): calcd. (found) %: C, 66.42 (66.44); H, 5.07 (5.09); N, 3.52 (3.55); FT-IR (KBr, ν_{max}, cm^{-1}): 3042 (arom. H), 2942 (aliph. C–H), 1725-1718 (lactone keto), 1682 (–$CONH_2$ amide), 1590 (C=C), 1230 (Ar–O–C *str.*); ^{1}H NMR (400 MHz, DMSO-d_6): δ: 1.60 (m, 2H) 1.93 (bs, 1H) 2.02 (bs, 1H), 3.32 (m, 2H) 3.63 (bs, 1H) 4.01 (m, 1H) 4.79 (m, 1H) 7.34 (m, 1H), 7.39 (m, 1H) 7.48 (m, 3H) 7.70 (dd, *J* = 8.0 Hz, 1H) 7.89 (dd, *J* = 4.0 Hz, 1H) 8.17 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6):



Scheme-I: Synthetic procedure for the preparation of compounds

δ 162, 157, 141, 128, 112, 44; MS: calcd. *m/z* 397.85; found: *m/z* 397.97.

6-Chloro-3-(3-(*p*-tolyloxy)piperidine-1-carbonyl)-2*H*-chromen-2-one (Cop22): White product; yield: 86.40%; R_f: 0.67; m.p.: 181-183 ºC; elemental analysis of $C_{22}H_{20}ClNO_4$ (*m.w*. 397.85): calcd. (found) %: C, 66.42 (66.45); H, 5.07 (5.11); N, 3.55 (3.59); FT-IR (KBr, ν_{max}, cm^{-1}): 3050 (arom. H), 2930 (aliph. C–H), 1708 (lactone keto), 1680 (–$CONH_2$ amide), 1585 (C=C), 1200 (Ar–O–C), 742 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.90 (d, *J* = 2.4 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.49 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 4.79 (m, 1H), 4.01 (m, 1H), 3.63 (m, 1H), 3.32 (m, 2H), 2.24 (s, 3H), 2.02 (m, 1H), 1.93 (m, 1H), 1.60 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2, 160.8, 155.0, 153.8, 142.1, 137.8, 130.4, 130.1, 129.8, 125.6, 123.8, 122.1, 117.8, 115.8, 72.7, 44.0, 38.9, 31.2, 30.4, 20.2; MS: calcd. *m/z* 397.85; found: *m/z* 397.81.

6-Chloro-3-(3-(*m*-tolyloxy)piperidine-1-carbonyl)-2*H*-chromen-2-one (Cop23): White solid; yield: 85.31%; R_f: 0.26; m.p.: 148-150 ºC; elemental analysis of $C_{22}H_{20}ClNO_4$ (*m.w*. 397.85): calcd. (found) %: C, 66.42 (66.46); H, 5.07 (5.08); N, 3.55 (3.61); FT-IR (KBr, ν_{max}, cm^{-1}): 3035 (arom. H), 2940 (aliph. C–H), 1710 (lactone keto), 1670 (–$CONH_2$ amide), 1602 (C=C), 1230 (Ar–O–C), 755 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.48-7.52 (m, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.81 (s, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 4.44 (m, 1H), 4.05 (m, 1H), 3.51 (m, 2H), 2.30 (s, 3H), 2.15 (m, 1H), 1.73-1.85 (m, 3H), 1.59 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.4, 157.7, 157.4, 152.6, 142.2, 139.6, 132.7, 129.8, 128.8, 125.7, 122.3, 121.7, 118.8,

117.3, 113.5, 71.3, 49.7, 45.3, 42.0, 29.7, 22.9, 21.6; MS: calcd. *m/z* 397.85; found: *m/z* 397.81.

6-Chloro-3-(3-(*o*-tolyloxy)piperidine-1-carbonyl)-2*H*-chromen-2-one (Cop24): White solid; yield: 91.20%; R_f: 0.49; m.p.: 154-156 ºC; elemental analysis of $C_{22}H_{20}ClNO_4$ (*m.w*. 397.85): calcd. (found) %: C, 66.42 (66.46); H, 5.07 (5.08); N, 3.55 (3.61); FT-IR (KBr, ν_{max}, cm^{-1}): 3044 (arom. H), 2965 (C–H aliph.), 1722 (lactone keto), 1683 (–$CONH_2$ amide), 1596 (C=C), 1229 (Ar–O–C), 759 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.90 (d, *J* = 2.4 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.49 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 6.78 (m, 3H), 4.79 (m, 1H), 4.01 (m, 1H), 3.63 (m, 1H), 3.32 (m, 2H), 2.28 (s, 3H), 2.02 (m, 1H), 1.93 (m, 1H), 1.60 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2, 160.8, 157.1, 153.8, 142.1, 139.2, 137.8, 130.4, 129.5, 125.6, 123.8, 122.1, 117.8, 116.4, 112.5, 72.7, 44.0, 38.9, 31.2, 30.4, 21.3; MS: calcd. *m/z* 397.85; found: *m/z* 398.07.

3-(3-(3-(*tert*-Butyl)phenoxy)piperidine-1-carbonyl)-6-chloro-2*H*-chromen-2-one (Cop29): White solid; yield: 79.80%; R_f: 0.56; m.p.: 160-152 ºC; elemental analysis of $C_{25}H_{26}ClNO_4$ (*m.w*. 439.94): calcd. (found) %: C, 68.25 (68.48); H, 5.07 (5.11); N, 3.19 (3.21); FT-IR (KBr, ν_{max}, cm^{-1}): 3063 (arom. H), 2968 (C–H aliph., *tert*-butyl), 1722 (lactone keto), 1670 (–$CONH_2$ amide), 1605 (aryl C=C), 1110 (aryl-O-C), 735 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.90 (d, *J* = 2.4 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.49 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.20-7.10 (m, 1H), 6.95-6.75 (m, 3H), 4.79 (m, 1H), 4.01 (m, 1H), 3.63 (m, 1H), 3.32 (m, 2H), 2.02 (m, 1H), 1.93 (m, 1H), 1.60 (m, 2H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2, 160.8, 156.8, 153.8, 152.2, 142.1, 137.8, 130.4, 129.2, 125.6, 123.8, 122.1, 118.5, 117.8, 114.2, 112.5, 72.7, 44.0, 38.9, 34.5, 31.5, 31.2, 30.4; MS: calcd. *m/z* 439.94; found: *m/z* 439.98.

6-Chloro-3-(3-((4-methoxyphenoxy)methyl)piperidine-1-carbonyl)-2*H*-chromen-2-one (Cop40): White product; yield: 84.21%; R_f: 0.20; m.p.: 156-158 ºC; elemental analysis of $C_{23}H_{22}ClNO_5$ (*m.w*. 427.88): calcd. (found) %: C, 64.56 (64.66); H, 5.18 (5.21); N, 3.27 (3.31); FT-IR (KBr, ν_{max}, cm^{-1}): 3055 (arom. H), 2952 (C–H aliph.), 1710 (lactone keto), 1660 (–$CONH_2$ amide), 1590 (C=C), 1250 (Ar–O–CH_3/Ar–O–CH_2), 1015 (C–O–C), 745 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.90 (d, *J* = 2.4 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.49 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.92 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 4.02 (m, 2H), 3.72 (s, 3H), 3.65 (m, 2H), 3.32 (m, 2H), 2.75 (m, 1H), 1.92 (m, 2H), 1.45 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.5, 160.2, 153.8, 152.9, 142.1, 137.8, 130.5, 129.2, 125.6, 123.8, 122.1, 118.2, 115.4, 114.8, 112.5, 70.5, 55.6, 50.2, 45.4, 36.2, 27.4, 23.8; MS: calcd. *m/z* 427.88; found: *m/z* 427.92.

6-Chloro-3-(3-((2-methoxyphenoxy)methyl)piperidine-1-carbonyl)-2*H*-chromen-2-one (Cop42): White solid; yield: 90.00%; R_f: 0.56; m.p.: 162-164 ºC; elemental analysis of $C_{23}H_{22}ClNO_5$ (*m.w*. 427.88): calcd. (found) %: C, 64.56 (64.60); H, 5.18 (5.23); N, 3.27 (3.35); FT-IR (KBr, ν_{max}, cm^{-1}): 3040 (arom. H), 2950 (C–H aliph.), 1730 (lactone keto), 1660 (–$CONH_2$ amide), 1600 (C=C), 1225 (Ar–O–CH_3/Ar–O–CH_2), 1028 (C–O–C), 742 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.41 (s, 1H, COOH), 4.65 (s, 2H, -CH_2), 6.92-7.34 (m, 8H, Ar-H), 7.36 (s, 1H, isoxazole -CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172, 162, 133, 126,114, 98, 66; MS: calcd. *m/z* 427.88; found: *m/z* 427.95.

6-Chloro-3-(3-((4-fluorophenoxy)methyl)piperidine-1-carbonyl)-2*H*-chromen-2-one (Cop46): White powder; yield: 66.80%; R_f: 0.42; m.p.: 170-172 ºC; elemental analysis of $C_{22}H_{19}ClFNO_4$ (*m.w*. 415.85): calcd. (found) %: C, 63.54 (63.58); H, 4.16 (4.66); N, 3.37 (3.42); FT-IR (KBr, ν_{max}, cm^{-1}): 3069 (arom. H), 2955 (aliph. C–H), 1710 (lactone keto), 1653 (–$CONH_2$ amide), 1600 (C=C), 1254 (Ar–O–CH_2), 1032 (C–O–C), 752 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.41 (s, 1H, COOH), 4.65 (s, 2H, -CH_2), 6.92- 7.34 (m, 8H, Ar-H), 7.36 (s, 1H, isoxazole -CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ: 172, 162, 133, 128, 126, 114, 98, 66; MS: calcd. *m/z* 415.85; found: *m/z* 415.88.

6-Chloro-3-(3-((2-chlorophenoxy)methyl)piperidine-1-carbonyl)-2*H*-chromen-2-one (Cop54): White solid; yield: 91.20%; R_f: 0.64; m.p.: 180-182 ºC; elemental analysis of $C_{22}H_{19}Cl_2NO_4$ (*m.w*. 432.30): calcd. (found) %: C, 61.12 (61.18); H, 4.43 (4.45); N, 3.24 (3.30); FT-IR (KBr, ν_{max}, cm^{-1}): 3060 (Ar–H), 2962 (aliph. C–H), 1738 (lactone keto), 1670 (–$CONH_2$ amide), 1605 (C=C), 1258-1255 (Ar–O–CH_2), 1016 (C–O–C), 742 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.90 (d, *J* = 2.4 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.49 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.20-7.10 (m, 1H), 6.95-6.75 (m, 3H), 4.79 (m, 1H), 4.01 (m, 1H), 3.63 (m, 1H), 3.32 (m, 2H), 2.02 (m, 1H), 1.93 (m, 1H), 1.60 (m, 2H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2, 160.8, 156.8, 153.8, 152.2, 142.1, 137.8, 130.4, 129.2, 125.6, 123.8, 122.1, 118.5, 117.8, 114.2, 112.5, 72.7, 44.0, 38.9, 34.5, 31.5, 31.2, 30.4; MS: calcd. *m/z* 432.30; found: *m/z* 432.36.

6-Chloro-3-(4-(2-chloro-5-methylphenoxy)piperidine-1-carbonyl)-2*H*-chromen-2-one (Cop55): White solid; yield: 92.70%; R_f: 0.66; m.p.: 178-180 ºC; elemental analysis of $C_{22}H_{19}Cl_2NO_4$ (*m.w*. 432.30): calcd. (found) %: C, 61.12 (61.22); H, 4.43 (4.44); N, 3.24 (3.28); FT-IR (KBr, ν_{max}, cm^{-1}): 3005 (Ar–H), 2852 (aliph. C–H), 1706 (lactone keto),1646 (amide keto), 1570 (C=C), 1215 (Ar–O–CH_2), 1012 (C–O–C), 690 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.90 (d, *J* = 2.4 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.49 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 6.85 (s, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 4.79 (m, 1H), 4.01 (m, 1H), 3.63 (m, 1H), 3.32 (m, 2H), 2.28 (s, 3H), 2.02 (m, 1H), 1.93 (m, 1H), 1.60 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2, 160.8, 154.2, 153.8, 142.1, 137.8, 137.0, 130.6, 130.4, 126.5, 125.6, 123.8, 122.5, 117.8, 116.5, 115.2, 72.7, 44.0, 38.9, 31.2, 30.4, 21.0; MS: calcd. *m/z* 432.30; found: *m/z* 432.33.

***N*-(2-(1-Benzylpiperidin-4-yl)ethyl)-6-chloro-2-oxo-2*H*-chromene-3-carboxamide (Cop58):** White solid; yield: 92.32%; R_f: 0.39; m.p.: 162-164 ºC; elemental analysis of $C_{24}H_{25}ClN_2O_3$ (*m.w*. 424.92): calcd. (found) %: C, 67.84 (67.88); H, 5.93 (5.95); N, 6.59 (6.61); FT-IR (KBr, ν_{max}, cm^{-1}): 3230 (N–H), 3055 (arom. H), 2960 (C–H aliph.), 1718 (lactone keto gap.), 1670 (–$CONH_2$ amide), 1600 (C=C arom.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.82 (t, *J* = 5.6 Hz, 1H), 8.75 (s, 1H9), 7.92 (d, *J* = 2.4 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.55 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.35-7.22 (m, 5H), 3.48 (s, 2H), 3.32 (q, *J* = 6.8 Hz, 2H), 2.82 (d, *J* = 11.6 Hz, 2H), 1.95

(t, *J* = 11.6 Hz, 2H), 1.62 (m, 2H), 1.48 (m, 3H), 1.25 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.8, 160.5, 154.2, 148.5, 138.2, 134.2, 130.8, 129.2, 128.4, 127.0, 125.6, 122.3, 118.0, 117.2, 62.2, 53.2, 38.5, 34.2, 32.8, 32.1, 31.5; MS: calcd. *m/z* 424.92; found: *m/z* 424.98.

6-Chloro-3-(4-((4-methoxyphenyl)amino)piperidine-1-carbonyl)-2*H*-chromen-2-one (Cop64): White product; yield: 90.16%; R_f: 0.52; m.p.: 152-154 ºC; elemental analysis of $C_{22}H_{21}ClN_2O_4$ (*m.w*. 412.87): calcd. (found) %: C, 63.99 (64.05); H, 5.13 (5.23); N, 6.79 (6.85); FT-IR (KBr, ν_{max}, cm^{-1}): 3320 (N–H), 3062 (arom. H), 2955 (C–H aliph.), 1720 (lactone keto), 1665 (–$CONH_2$ amide), 1602 (C=C arom.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.12 (s, 1H), 7.90 (d, *J* = 2.4 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.50 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.59 (d, *J* = 8.8 Hz, 2H), 5.12 (d, *J* = 8.0 Hz, 1H), 4.30 (m, 1H), 3.64 (s, 3H), 3.45-3.35 (m, 3H), 3.19-2.94 (m, 1H), 1.99-1.87 (m, 2H), 1.32-1.30 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 164.39, 162.77, 157.79, 157.61, 152.56, 151.19, 142.19, 141.27, 140.86, 132.58, 132.52, 128.97, 128.35, 126.73, 120.29, 120.22, 118.74, 115.14, 114.37, 55.77, 49.74, 45.71, 38.70, 38.17, 34.83, 32.58, 31.64; MS: calcd. *m/z* 412.87; found: *m/z* 413.08.

Molecular docking: A structure-based virtual screening method was used to evaluate the design coumarin-piperidine derivatives as potential AChE inhibitors. A library of 70 compounds was prepared for molecular docking. The crystal structure of AChE (PDB ID: 4EY7) was retrieved from the Protein Data Bank and prepared using Schrödinger software. The two-dimensional ligand structures were converted into three-dimensional geometries and prepared using ChemDraw Ultra 8.0 before docking. Molecular docking was performed using the Glide module in standard precision (SP) mode, and the docking scores were used to rank the compounds. The binding poses were examined for key interactions with the enzyme active site, such as hydrogen bonding, π–π stacking and hydrophobic interactions. Based on their docking scores and binding interactions, compounds with favourable predicted binding profiles were selected for further ADME evaluation and experimental studies [26,27].

ADME studies: SwissADME software was employed to study the pharmacokinetic profile and physico-chemical investigation of 24 compounds selected based on their favourable docking scores (more than -9.5 kcal/mol) against Alzheimer's disease targets. All molecules were assessed for compliance with Lipinski's Rule of Five, which recommends molecular weight <500 g/mol, not more than 5 hydrogen bond donors, less than 10 hydrogen bond acceptors and a log P ≤ 5 for optimal drug-likeness [28].

AChE inhibition assay: The AChE inhibitory activity of the synthesized coumarin-piperidine derivatives was evaluated using the Ellman spectrophotometric method [29-31]. Acetylthiocholine iodide and 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB) were used as the substrate and chromogenic reagent, respectively. Lyophilized electric eel AChE was dissolved in 0.2 M phosphate buffer (pH 7.4) to prepare an enzyme solution with an activity of 2.5 U/mL. Human erythrocyte AChE (≥500 U/mg protein) was diluted in 20 mM HEPES buffer (pH 8.0) to obtain an enzyme solution with an activity of 0.25 U/mL. The test compounds were dissolved in analytical-grade DMSO. For the assay, 100 µL of 0.3 mM DTNB in phosphate buffer (pH 7.4), 50 µL of test compound solution and 50 µL of enzyme solution were added to each well of a 96-well microplate. The enzymatic hydrolysis of acetylthiocholine was monitored by measuring the formation of the yellow 5-thio-2-nitrobenzoate anion, generated through the reaction of DTNB with thiocholine released during substrate hydrolysis. Absorbance was recorded at 412 nm at 1 min intervals for 10 min using a microplate reader. Donepezil was used as the reference inhibitor. The percentage inhibition was calculated relative to the control, and dose-response curves were plotted as percentage inhibition *versus* the logarithm of compound concentration. For compounds exhibiting at least 50% inhibition after 4 min of reaction, the concentration required to produce 50% inhibition (IC_{50}) was estimated using Microsoft Excel.

RESULTS AND DISCUSSION

The selected coumarin–piperidine derivatives were synthesized according to **Scheme-I**. Briefly, 5-chloro-2-hydroxybenzaldehyde (**1**) was reacted with Meldrum's acid (**2**) in the presence of K_2CO_3 for 16-20 h to obtain 6-chloro-2-oxo-2*H*-chromene-3-carboxylic acid (**3**). The resulting intermediate was coupled with the appropriate substituted piperidine derivatives using HATU and DIPEA in DMF to obtain the target compounds. The FT-IR spectra showed characteristic absorption bands associated with the functional groups present in the molecular structures. Bands in the 3300-3200 cm^{-1} region were assigned to N–H stretching, where applicable, while aromatic and aliphatic C–H stretching vibrations appeared in the 3100-2900 and 2900-2800 cm^{-1}, respectively. Strong carbonyl absorption bands were observed between 1745 and 1700 cm^{-1}, while aromatic C=C stretching vibrations appeared in the 1600-1450 cm^{-1} region. Bands in the 900-690 cm^{-1} region were attributed to aromatic C–H bending. Substituent-related absorptions were observed in the fingerprint region, with C–Cl, C–F, CF_2 and CF_3 vibrations appearing within their characteristic spectral ranges. The ^{1}H NMR showed signals corresponding to aromatic and aliphatic protons within the reported chemical shift range of δ 1.60-8.17 ppm. The signals between δ 7.03 and 8.17 ppm were mainly attributed to aromatic and olefinic protons, while the aliphatic proton signals were observed at comparatively lower chemical shifts. The ^{13}C NMR spectra showed resonances at δ 168-164 ppm are due to the amide carbonyl carbon, whereas signals at δ 154-150 ppm, assigned to oxygen-bearing aromatic or heterocyclic carbons. Signals in the δ 57-52 ppm and δ 47-41 ppm regions were assigned to oxygen- and nitrogen-associated aliphatic carbons, respectively, while the remaining aliphatic carbon signals appeared between δ 33 and 18 ppm. The mass spectra showed molecular ion-related peaks corresponding to the expected molecular masses of the synthesized compounds. These spectral findings support the proposed structures of the synthesized derivatives.

Docking results: The 70 designed coumarin-piperidine derivatives were subjected to molecular docking against acetylcholinesterase (AChE; PDB ID: 4EY7) and the ligands were ranked according to their docking scores. Twenty-four

compounds with scores more than -9.50 kcal/mol were selected for further evaluation. Their docking scores ranged from -9.6 to -11.6 kcal/mol, with **Cop4**, **Cop9**, **Cop22**, **Cop44**, **Cop45**, **Cop46** and **Cop54** exhibiting scores below -10.0 kcal/mol (Table-1). These scores point to favourable predicted interactions between the selected compounds and the AChE binding site. Analysis of the 2D interaction diagrams revealed hydrogen bonding with residues such as Ser203, His447, Glu234, Tyr124, Trp286 and Phe295, along with π–π stacking and hydrophobic contacts (Fig. 1). These interactions may contribute to ligand recognition and binding within the active site gorge. The 3D docking poses further showed that the selected coumarin derivatives occupied the AChE binding site gorge with favourable ligand orientations and no apparent steric clashes. The presence of interactions with catalytic and peripheral site residues provides a structural basis for examining the AChE inhibitory potential of these compounds. Among the selected derivatives, **Cop54** is of particular interest in view of its subsequent *in vitro* AChE inhibition result.

TABLE-1
BINDING ENERGIES OF COMPOUNDS
HAVING HIGHEST SCORE AGAINST TARGET

Compound	Docking score (kcal/mol) AChE (4ey7)	Compound	Docking score (kcal/mol) AChE (4ey7)
Cop1	-9.6	**Cop32**	-9.7
Cop4	-10.2	**Cop34**	-9.9
Cop8	-9.8	**Cop35**	-9.9
Cop9	-10.3	**Cop40**	-9.6
Cop14	-9.6	**Cop42**	-9.9
Cop16	-9.8	**Cop44**	-10.2
Cop17	-9.7	**Cop45**	-11.6
Cop22	-10.1	**Cop46**	-10.0
Cop23	-9.8	**Cop54**	-10.5
Cop24	-9.8	**Cop55**	-9.6
Cop29	-9.6	**Cop58**	-9.7
Cop31	-9.8	**Cop64**	-9.6

***In silico* ADME prediction:** The pharmacokinetic properties of the 24 selected coumarin–piperidine derivatives were evaluated using SwissADME (Table-2). The predicted profiles covered oral bioavailability, topological polar surface area (TPSA), synthetic accessibility and aqueous solubility. The blood-brain barrier (BBB) permeability predictions identified 10 compounds as unlikely to cross the BBB; these compounds were excluded from further synthesis (highlighted in red in Table-2). The remaining 14 derivatives showed favourable predicted BBB permeability and were prioritized for synthesis and subsequent biological evaluation. This screening strategy combined molecular docking results with early ADME assessment to narrow the compound library before experimental work. The predicted BBB permeability provides a preliminary basis for selecting compounds intended for CNS related research, although actual brain penetration and pharmacokinetic behaviour require experimental confirmation.

***In vitro* AChE inhibition assay:** The synthesized coumarin–piperidine derivatives were evaluated for human acetylcholinesterase (hAChE) inhibition at concentrations ranging from 1 to 5 μg/mL. The compounds displayed different levels of concentration-dependent inhibitory activity. **Cop54** was the most active derivative, exhibiting 72.41% inhibition at 1 μg/mL and 84.98% at 5 μg/mL. Its inhibition remained above 50% at the lowest tested concentration, suggesting an IC_{50} below 1 μg/mL. **Cop64** showed the next highest activity, with inhibition increasing from 56.03% at 1 μg/mL to 67.73% at 5 μg/mL. Its IC_{50} is likewise expected to be below 1 μg/mL. **Cop55** showed an estimated IC_{50} of approximately 1.1 μg/mL, followed by **Cop58** (2.9 μg/mL), Cop24 (3.8 μg/mL), **Cop29** (4.0 μg/mL) and Cop42 (4.3 μg/mL). **Cop1**, **Cop8**, **Cop9**, **Cop22**, **Cop23**, **Cop40** and **Cop46** did not reach 50% inhibition at 5 μg/mL, placing their IC_{50} values above the highest tested concentration.

The preliminary structure–activity relationship (SAR) analysis points to a possible contribution of oxygen-linked aromatic substituents (–O–Ar) to hAChE inhibition. Their aromatic surfaces may favour π–π interactions within the

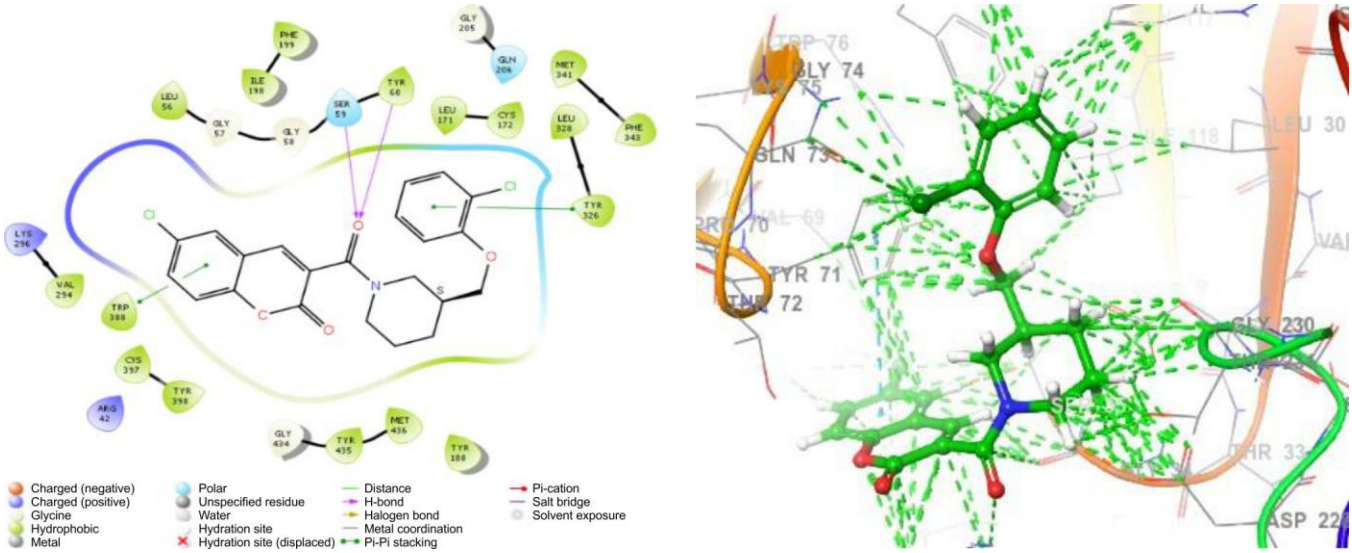


Fig. 1. 2D and 3D image of compound **Cop54** against AChE (4EY7)

TABLE-2
SWISSADME STUDY OF SELECTED 24 COMPOUNDS

Comp	M.W. < 500 (g/mol)	TPSA $(A)^2$ < 130	H BA <-10	H BD <-5	Log $P_{o/w}$ <-5	Bioavailability score	Synthetic accessibility	Water solubility	Lipinski violations	Blood-brain barrier permeability
Cop1	425.86	68.98	5	0	3.93	0.55	3.35	-5.58	No	Yes
Cop4	463.88	50.52	6	0	4.04	0.55	3.48	-6.64	No	No
Cop8	397.85	59.75	4	0	3.70	0.55	3.70	-5.48	No	Yes
Cop9	397.85	59.75	4	0	3.68	0.55	3.65	-5.48	No	Yes
Cop14	439.93	59.75	4	0	3.98	0.55	3.94	-6.86	No	No
Cop16	449.85	50.52	6	0	3.80	0.55	3.72	-6.33	No	No
Cop17	449.85	50.52	6	0	3.81	0.55	3.72	-6.33	No	No
Cop22	397.85	59.75	4	0	3.75	0.55	3.60	-5.48	No	Yes
Cop23	397.85	59.75	4	0	3.70	0.55	3.61	-5.48	No	Yes
Cop24	397.85	59.75	4	0	3.70	0.55	3.61	-5.48	No	Yes
Cop29	439.93	59.75	4	0	3.98	0.55	3.94	-6.46	No	Yes
Cop31	449.85	50.52	6	0	3.80	0.55	3.72	-6.33	No	No
Cop32	449.85	50.52	6	0	3.81	0.55	3.72	-6.33	No	No
Cop34	467.82	68.98	8	0	3.59	0.55	3.66	-6.25	No	No
Cop35	467.82	68.98	8	0	4.01	0.55	3.70	-6.25	No	No
Cop40	427.88	68.98	5	0	3.86	0.55	3.77	-5.38	No	Yes
Cop42	427.88	68.98	5	0	3.87	0.55	3.78	-5.38	No	Yes
Cop44	465.85	59.75	7	0	3.32	0.55	3.80	-6.17	No	No
Cop45	465.85	59.75	7	0	3.65	0.55	3.86	-6.17	No	No
Cop46	415.84	59.75	5	0	3.81	0.55	3.64	-5.47	No	Yes
Cop54	432.30	59.75	4	0	3.81	0.55	3.66	-5.91	No	Yes
Cop55	432.30	59.75	4	0	3.93	0.55	3.19	-6.08	No	Yes
Cop58	424.92	62.55	4	1	3.95	0.55	3.45	-5.69	No	Yes
Cop64	412.87	71.78	4	1	3.48	0.55	3.11	-5.26	No	Yes

enzyme gorge, while the oxygen atoms may participate in hydrogen-bond interactions where suitable residues are positioned. Fluorine and chlorine substitution may further influence activity through changes in lipophilicity and electronic distribution. The differences in inhibitory activity among the derivatives indicate that both substituent identity and molecular orientation may influence enzyme recognition. **Cop54** and **Cop64** emerged as the most active compounds, with **Cop55** showing the next best activity. **Cop54** is particularly noteworthy in view of its favourable docking profile and highest observed inhibition. Further concentration-dependent assays, particularly below 1 μg/mL, are required to establish accurate IC_{50} values and examine the proposed SAR.

Conclusion

In the present study, 70 coumarin-piperidine derivatives were designed and screened computationally against acetylcholinesterase (AChE). Molecular docking and SwissADME predictions were used to select 14 compounds for synthesis and biological evaluation. The synthesized derivatives were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, LC-MS and elemental analysis. Their *in vitro* evaluation revealed differences in AChE inhibitory activity, with **Cop54** exhibiting the highest inhibition (72.41% at 1 μg/mL and 84.98% at 5 μg/mL) followed by **Cop64** and **Cop55**. The favourable docking profile of **Cop54**, together with its observed inhibitory activity, which identifies it as a promising lead for further investigation. The preliminary structure-activity findings point to a possible influence of aromatic ether substituents and halogen substitution on AChE inhibition.

ACKNOWLEDGEMENTS

Two of the authors, A.G. and S.B., are grateful to MM College of Pharmacy, Maharishi Markandeshwar (Deemed to be university) for providing laboratory facilities of the Central instrumental laboratory and consistent support.

CONFLICT OF INTEREST

The authors declare that there is no conflicts of interest regarding the publication of this article.

DECLARATION OF AI-ASSISTED TECHNOLOGIES

During the preparation of this manuscript, the authors used an AI-assisted tool(s) to improve the language and no data, results or scientific conclusions were generated by AI. All analyses, interpretations and conclusions are the authors' own. The authors reviewed and edited the content and take full responsibility for the published work.

REFERENCES

1. M.M. Abdou, R.A. El-Saeed and S. Bondock, *Arab. J. Chem.*, **12**, 88 (2019); https://doi.org/10.1016/j.arabjc.2015.06.012.
2. J.C. Jung and O.S. Park, *Molecules*, **14**, 4790 (2009); https://doi.org/10.3390/molecules14114790
3. S. Singla and P. Piplani, *Bioorg. Med. Chem.*, **24**, 4587 (2016); https://doi.org/10.1016/j.bmc.2016.07.061
4. Z. Radić, E. Reiner and P. Taylor, *Mol. Pharmacol.*, **39**, 98 (1991); https://doi.org/10.1016/S0026-895X(25)10932-2

5. A.H. Halawa, M.M. Elaasser, A.M. El Kerdawy, A.M. Abd El-Hady, H.A. Emam and A.M. El-Agrody, *Med. Chem. Res.*, **26**, 2624 (2017); https://doi.org/10.1007/s00044-017-1961-3
6. H. Elshaflu, T.R. Todorović, M. Nikolić, A. Lolić, A. Višnjevac, S. Hagenow, J.M. Padrón, A.T. García-Sosa, I.S. Djordjević, S. Grubišić, H. Stark and N.R. Filipović, *Front Chem.*, **6**, 247 (2018); https://doi.org/10.3389/fchem.2018.00247
7. D.H. Elnaggar, N.A. Abdel Hafez, H.R. Rashdan, N.A. Abdelwahed, H.M. Awad and K.A. Ali, *Mini Rev. Med. Chem.*, **19**, 1717 (2019); https://doi.org/10.2174/1389557519666190722123422
8. P. Rawat and S.M. Verma, *Drug Des. Devel. Ther.*, **10**, 2779 (2016); https://doi.org/10.2147/DDDT.S111266
9. M. Mashhadinezhad, M. Mamaghani, M. Rassa and F. Shirini, *ChemistrySelect*, **4**, 4920 (2019); https://doi.org/10.1002/slct.201900405
10. M.B. Tehrani, Z. Rezaei, M. Asadi, H. Behnammanesh, H. Nadri, F. Afsharirad, A. Moradi, B. Larijani, M. Mohammadi-Khanaposhtani and M. Mahdavi, *Chem. Biodivers.*, **16**, e1900144 (2019); https://doi.org/10.1002/cbdv.201900144
11. R. Soni, S.D. Durgapal, S.S. Soman and J.J. Georrge, *Arab. J. Chem.*, **12**, 701 (2019); https://doi.org/10.1016/j.arabjc.2016.11.011
12. W. Zhao, B. Wang, Y. Liu, L. Fu, L. Sheng, H. Zhao, Y. Lu and D. Zhang, *Eur. J. Med. Chem.*, **189**, 112075 (2020); https://doi.org/10.1016/j.ejmech.2020.112075
13. K. Takao, U. Shiori, H. Kamauchi and Y. Sugita, *Bioorg. Chem.*, **87**, 594 (2019); https://doi.org/10.1016/j.bioorg.2019.03.042
14. N. Naeem, B. Shakoor, A. Sadiq, S.Y. Al Nami, A. Hossan and E.U. Mughal, *RSC Adv.*, **16**, 31257 (2026); https://doi.org/10.1039/D6RA01594H
15. L. Pisani, M. Catto, G. Muncipinto, O. Nicolotti, A. Carrieri, M. Rullo, A. Stefanachi, F. Leonetti and C. Altomare, *Front Chem.*, **10**, 1002547 (2022); https://doi.org/10.3389/fchem.2022.1002547
16. M. Goedert and M.G. Spillantini, *Science*, **314**, 777 (2006); https://doi.org/10.1126/science.1132814
17. H.Y. Zhang, *FEBS Lett.*, **579**, 5260 (2005); https://doi.org/10.1016/j.febslet.2005.09.006
18. S.K. Yusufzai, M.S. Khan, O. Sulaiman, H. Osman and D.N. Lamjin, *Chem. Cent. J.*, **12**, 128 (2018); https://doi.org/10.1186/s13065-018-0497-z
19. R. Orioli, F. Belluti, S. Gobbi, A. Rampa and A. Bisi, *Molecules*, **29**, 3514 (2024); https://doi.org/10.3390/molecules29153514
20. P. Anand, B. Singh and N. Singh, *Bioorg. Med. Chem.*, **20**, 1175 (2012); https://doi.org/10.1016/j.bmc.2011.12.042
21. M.B. Youdim, D. Edmondson and K.F. Tipton, *Nat. Rev. Neurosci.*, **7**, 295 (2006); https://doi.org/10.1038/nrn1883
22. G. Wolber and T. Langer, *J. Chem. Inf. Model.*, **45**, 160 (2005); https://doi.org/10.1021/ci049885e
23. G. Kryger, I. Silman and J.L. Sussman, *Structure*, **7**, 297 (1999); https://doi.org/10.1016/S0969-2126(99)80040-9
24. P. Sharma, A. Tripathi, P.N. Tripathi, S.K. Prajapati, M.K. Tripathi, A. Seth, P. Srivastava, V. Tiwari, S. Krishnamurthy and S.K. Shrivastava, *Eur. J. Med. Chem.*, **167**, 510 (2019); https://doi.org/10.1016/j.ejmech.2019.02.030
25. M.S. El-Gaby, M.A. Zahran, M.M. Ismail and Y.A. Ammar, *Farmaco*, **55**, 227 (2000); https://doi.org/10.1016/S0014-827X(00)00008-2
26. S. Kumar, G. Singh, M. Chhikara, S. Shukla, R. Khatri, M.O. Dar, A. Lather and T. Hooda, *Scr. Med.*, **56**, 463 (2025); https://doi.org/10.5937/scriptamed56-54329
27. D. Singh, P. Kumar, A. Kumar, V.V. Bhosale, K. Sharma, D. Kumar, R. Khatri, T. Hooda and A. Lather, *Turk. J. Chem.*, **49**, 325 (2025); https://doi.org/10.55730/1300-0527.3732
28. A. Daina, O. Michielin and V. Zoete, *Sci. Rep.*, **7**, 42717 (2017); https://doi.org/10.1038/srep42717
29. G.L. Ellman, K.D. Courtney, V. Andres Jr. and R.M. Featherstone, *Biochem. Pharmacol.*, **7**, 88 (1961); https://doi.org/10.1016/0006-2952(61)90145-9
30. S. Shukla, S. Sharma, N. Vasudeva and T. Hooda, *Indian J. Pharm. Educ. Res.*, **58**, 503 (2024); https://doi.org/10.5530/ijper.58.2.56
31. S. Shukla, S. Sharma, N. Vasudeva and T. Hooda, *Indian J. Pharm. Educ. Res.*, **58**, 595 (2024); https://doi.org/10.5530/ijper.58.2.66