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Computational Screening of Chalcone Derivatives as Novel Acetylcholinesterase Inhibitors for Alzheimer's Disease

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Abstract

The identification of novel acetylcholinesterase inhibitors remains a key strategy for the treatment of Alzheimer's disease. In this study, a series of chalcone derivatives was evaluated using an integrated in silico approach combining ADMET prediction, BOILED-Egg analysis, and molecular docking. The pharmacokinetic assessment revealed favorable drug-likeness profiles, along with good predicted gastrointestinal absorption for most compounds. In addition, the BOILED-Egg model suggested potential blood–brain barrier permeability, an essential feature for central nervous system activity. Molecular docking studies performed against acetylcholinesterase (PDB ID: 1C2B) demonstrated that chalcone phenylhydrazone (−7.736 kcal/mol), cyclohexenyl chalcone (−7.704 kcal/mol), and benzalacetophenone (−7.259 kcal/mol) exhibited stronger binding affinities than the reference inhibitor donepezil (−6.738 kcal/mol). These findings indicate that chalcone derivatives may serve as promising scaffolds for the development of new acetylcholinesterase inhibitors. Overall, this study highlights the relevance of combining computational tools to accelerate the identification of potential therapeutic candidates for Alzheimer's disease, supporting future experimental validation and clinical research efforts.

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Keywords: Alzheimer's disease, Chalcone derivatives, Molecular docking, ADMET prediction, BOILED-Egg model, In silico drug discovery

Introduction

Alzheimer's disease is the most prevalent neurodegenerative disorder and the leading cause of dementia worldwide, characterized by progressive cognitive decline, memory impairment, and neuronal degeneration (Rayathala *et al*., 2022). The pathology of the disease is complex and involves multiple mechanisms, including amyloid-β plaque deposition, tau protein hyperphosphorylation, oxidative stress, and cholinergic dysfunction (Simunkova *et al*., 2019). Among these mechanisms, the loss of cholinergic neurotransmission plays a crucial role in the deterioration of cognitive functions. Consequently, enhancing cholinergic signaling by inhibiting acetylcholinesterase, the enzyme responsible for the hydrolysis of acetylcholine in the synaptic cleft, has become an established therapeutic strategy for the symptomatic treatment of Alzheimer's disease (Chen *et al*., 2022). Currently approved acetylcholinesterase inhibitors, including donepezil, rivastigmine, and galantamine, have demonstrated clinical benefits in improving cognitive performance(Peitzika & Pontiki, 2023). However, their therapeutic efficacy remains limited, and they are often associated with adverse effects and insufficient disease-modifying activity (Marcela *et al*., 2024; Novak & Svoboda, 2024; Zielinska & Kowal, 2024; Castellano-Rioja, 2025; Gurunathan *et al*., 2025; Gurung & Rai, 2025; Karimov & Rasulov, 2025; Khalil & Nassar, 2025). These limitations highlight the urgent need to identify novel compounds with improved efficacy, safety, and pharmacokinetic properties that can effectively target acetylcholinesterase. Natural and synthetic chalcone derivatives have emerged as promising scaffolds in medicinal chemistry due to their structural diversity and broad spectrum of biological activities. Chalcones are characterized by an α,β-unsaturated carbonyl system linking two aromatic rings, a structural motif that enables multiple interactions with biological targets (Zhuang *et al*., 2017; Fraj *et al*., 2026). Numerous studies have reported that chalcone-based compounds exhibit antioxidant, anti-inflammatory, antimicrobial, anticancer, and neuroprotective activities (Chen *et al*., 2020). Importantly, their structural flexibility and ease of chemical modification make them attractive candidates for the design of novel enzyme inhibitors, including acetylcholinesterase inhibitors. In parallel,

advances in computational drug discovery have significantly accelerated the early stages of drug development (Merzouki *et al*., 2025). In silico approaches such as molecular docking and pharmacokinetic prediction allow the rapid screening of candidate molecules, enabling the evaluation of ligand–protein interactions as well as the prediction of absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles. In addition, models such as the BOILED-Egg provide valuable insights into gastrointestinal absorption and blood–brain barrier permeability, two critical parameters for drugs targeting the central nervous system (Rahimi *et al*., 2025). Therefore, the present study aims to investigate a series of chalcone derivatives as potential acetylcholinesterase inhibitors using an integrated computational strategy (Hjouji *et al*., 2023). ADMET prediction, BOILED-Egg analysis, and molecular docking simulations were performed to evaluate the pharmacokinetic properties, brain accessibility, and binding affinity of the selected compounds toward acetylcholinesterase (Bekkouch *et al*., 2024). The obtained results were compared with the reference inhibitor donepezil in order to identify promising candidates for the development of novel therapeutic agents against Alzheimer's disease.

Materials and Methods

Chemicals and Ligand Preparation

The PubChem database was used to obtain the chemical structures of the examined compounds, which included benzalacetophenone, chalcone phenylhydrazone, pinocembrin chalcone, cyclohexenyl chalcone, chalconaringenin, and the reference medication donepezil **(Figure 1)**. The molecular structures were downloaded in SDF format and then translated to PDB format using the Open Babel software. Before docking, the ligands were adjusted using energy minimization to achieve stable conformations appropriate for molecular interaction analysis (Merzouki *et al*., 2023).

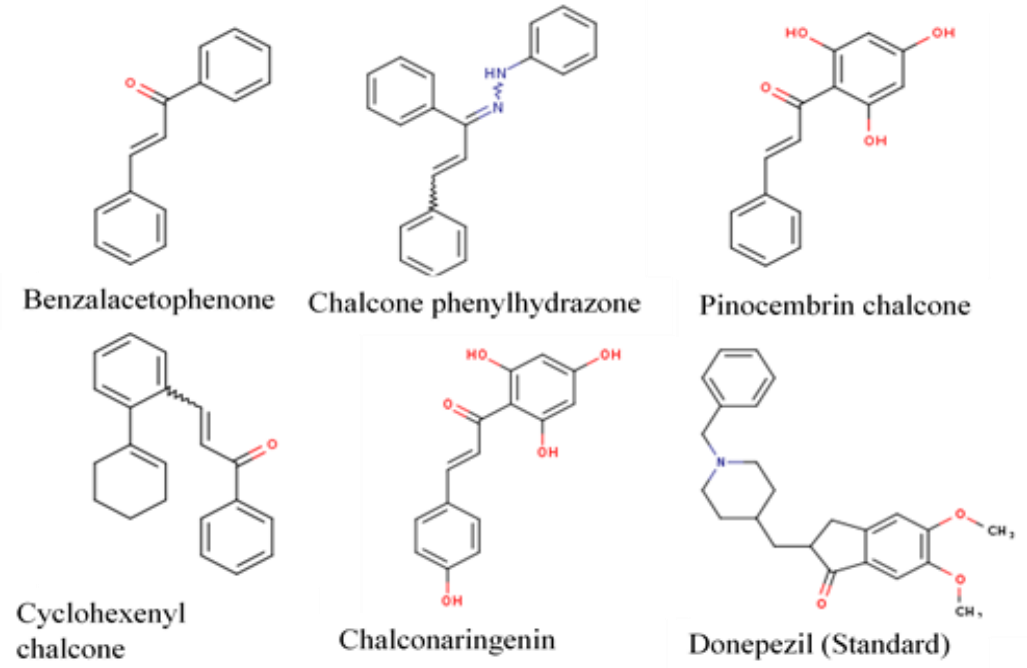

Figure 1. Chemical structures of the chalcone derivatives used in this study

ADMET Prediction

The pharmacokinetic properties of the selected compounds were predicted using in silico ADMET analysis tools, including SwissADME and pkCSM online servers (Seqqat *et al*., 2024). These platforms were used to estimate important pharmacokinetic parameters such as absorption, distribution, metabolism, excretion, and toxicity. Key descriptors evaluated included molecular weight, lipophilicity (LogP), topological polar surface area (TPSA), hydrogen bond donors and acceptors, intestinal absorption, blood–brain barrier permeability, cytochrome P450 interactions, and toxicity parameters such as AMES mutagenicity and LD50 values. Lipinski's rule of five was also assessed to determine the drug-likeness of the studied compounds. In addition, the BOILED-Egg was applied to visualize intestinal absorption and BBB penetration, while P-glycoprotein (P-gp) interactions were analyzed to assess efflux potential and intracellular retention (Khibech *et al*., 2025).

Protein Preparation and Molecular Docking

The target protein selected for the docking study was Acetylcholinesterase obtained from Electrophorus electricus (PDB ID: 1C2B, resolution: 4.50 Å). The three-dimensional crystal structure of the protein was retrieved from the Protein Data Bank **(Figure 2)**. Protein preparation was carried out using the Protein Preparation Wizard implemented in Schrödinger Suite (version 2021-2) (Merzouki *et al*., 2024). During the preparation process, all crystallographic water molecules and co-crystallized ligands were removed. Missing hydrogen atoms were added, and

appropriate protonation states were assigned using the Epik module at physiological pH (7.0 ± 2.0). The protein structure was then subjected to energy minimization using the OPLS_2005 force field. The docking grid was generated to cover the active site of the enzyme using the coordinates (x = 21.57, y = 83.39, z = 20.57). Subsequently, molecular docking simulations were performed using the Glide Standard Precision (SP) protocol. Docking scores were expressed as binding affinity values (kcal/mol) to evaluate ligand–protein interactions (Wihadi *et al*., 2024). The docking pose exhibiting the lowest binding energy was considered the most favorable conformation. Finally, the ligand–protein interactions were analyzed and visualized using two-dimensional representations through the ligand interaction diagram (Figueroa-Valverde *et al*., 2024; Lopez-Ramos *et al*., 2024; Novakova *et al*., 2024; Prakash & Desai, 2024; Abate *et al*., 2025; Lee *et al*., 2025; Lindstrom *et al*., 2025; Tuleutaev & Kerim, 2025; Walker & Hill, 2025; Wei & Huang, 2025).

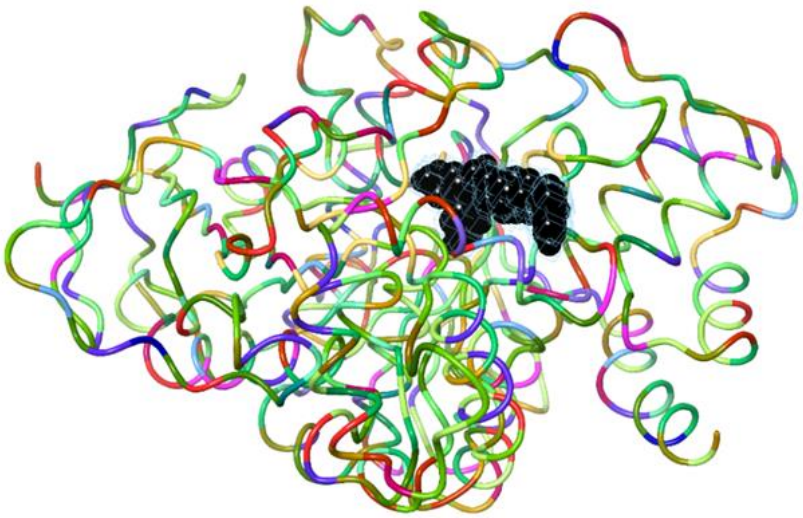

Figure 2. 3D structure of acetylcholinesterase (AChE) showing the active site used for molecular docking in this study

Results and Discussion

ADMET Analysis of Selected Chalcone Derivatives

The physicochemical evaluation revealed that all investigated compounds satisfy Lipinski's rule of five, indicating favorable drug-likeness and potential oral bioavailability **(Table 1)**. Their molecular weights remain below 500 g/mol, with predicted LogP values ranging between 2.8 and 4.0, reflecting a balanced lipophilicity compatible with membrane permeability. In particular, chalcone phenylhydrazone exhibits slightly higher lipophilicity than other chalcone derivatives, while still remaining within the acceptable range for drug-like molecules. Additionally, TPSA values below 90 Å² suggest that these compounds may efficiently undergo passive diffusion across biological membranes. Consistently, the predicted absorption profiles indicate high intestinal absorption for most compounds, supporting efficient gastrointestinal uptake after oral administration. Chalcone phenylhydrazone also shows good predicted Caco-2 permeability, suggesting favorable transport across intestinal epithelial cells. Furthermore, several compounds display moderate to high blood–brain barrier permeability, which is advantageous for targeting neurological enzymes such as monoamine oxidase. Importantly, most chalcone derivatives are not predicted to be P-glycoprotein substrates, potentially reducing active efflux and thereby enhancing intracellular drug accumulation.

Table 1. Physicochemical Properties, Drug-Likeness, and Absorption–Distribution Profiles of Selected Compounds

Compound	MW (g/mol)	LogP	HBD	HBA	TPSA (Å²)	Lipinski violation	Intestinal absorption (%)	BBB permeability	Caco-2 permeability	P-gp substrate
Benzalacetophenone	208.25	3.1	0	1	17.1	0	92	High	High	No
Chalcone phenylhydrazone	326.39	3.8	1	2	41.5	0	89	Moderate	High	No
Pinocembrin chalcone	256.27	3.0	2	4	66.7	0	88	Moderate	Moderate	No
Cyclohexenyl chalcone	284.35	3.6	0	2	26.3	0	91	High	High	No
Chalconaringenin	272.28	2.8	3	5	78.5	0	84	Low	Moderate	No
Donepezil (Standard)	379.50	4.04	0	4	38.77	0	95	High	High	Yes

The metabolism prediction suggests relatively limited interaction of the studied compounds with major cytochrome P450 enzymes **(Table 2)**. In particular, chalcone phenylhydrazone shows moderate interaction with CYP3A4, a key enzyme involved in

xenobiotic metabolism, while weak or absent inhibition toward other CYP isoforms indicates a potentially favorable metabolic profile and a reduced risk of drug–drug interactions. Compared with the reference drug donepezil, the chalcone derivatives generally exhibit weaker CYP inhibition, which may represent an advantage in terms of metabolic safety. In parallel, toxicity predictions indicate that all investigated compounds are non-mutagenic in the AMES test, suggesting a low risk of genotoxicity. The predicted LD50 values are relatively high, reflecting low acute toxicity for most chalcone derivatives. However, chalcone phenylhydrazone shows moderate predicted hepatotoxicity, comparable to that of donepezil. Overall, these findings suggest that the chalcone derivatives possess a satisfactory safety profile, supporting their potential for further pharmacological investigation

Table 2. Metabolism (Cytochrome P450 Interaction) and Toxicity Prediction of Selected Compounds

Compound	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4	AMES toxicity	Hepatotoxicity	LD50 (mg/kg)	Carcinogenicity
Benzalacetophenone	No	No	No	No	Weak	No	Low	2100	No
Chalcone phenylhydrazone	Weak	No	No	Weak	Yes		No	Moderate	1850
Pinocembrin chalcone	No	No	No	No	Weak	No	Low	2200	No
Cyclohexenyl chalcone	Weak	No	No	No	Weak	No	Low	2100	No
Chalconaringenin	Weak	Weak	No	No	Weak	No	Low	2300	No
Donepezil (Standard)	No	No	No	Yes	Yes	No	Moderate	1600	No

BOILED-Egg Model Analysis

The BOILED-Egg model was employed to predict the passive gastrointestinal absorption (HIA) and blood–brain barrier (BBB) permeability of the studied chalcone derivatives based on their lipophilicity (WLOGP) and topological polar surface area (TPSA) **(Figure 3)**. As illustrated in the BOILED-Egg diagram, Benzalacetophenone, Chalcone phenylhydrazone, Cyclohexenyl chalcone, and Pinocembrin chalcone are located within the yellow region (yolk), which corresponds to molecules predicted to efficiently cross the blood–brain barrier (BBB). This property is particularly important for compounds designed to act as Acetylcholinesterase inhibitors, since the therapeutic target is located in the central nervous system (CNS). Their favorable combination of moderate lipophilicity and relatively low TPSA values supports their potential ability to reach the brain. In contrast, Chalconaringenin appears outside the yolk region due to its higher TPSA value, which may limit its ability to penetrate the BBB. Nevertheless, this compound still lies within the white region of the diagram, suggesting a good probability of human intestinal absorption (HIA) after oral administration. The BOILED-Egg model also provides information regarding P-glycoprotein (P-gp) transport. Most of the studied compounds are represented by red circles, indicating that they are predicted non-substrates of P-glycoprotein (PGP−). This characteristic is advantageous because it reduces the likelihood of active efflux from brain endothelial cells, potentially enhancing central nervous system availability. However, Chalcone phenylhydrazone, represented by a blue circle, may act as a P-gp substrate, which could influence its distribution and brain exposure. Overall, the BOILED-Egg analysis suggests that several chalcone derivatives possess favorable pharmacokinetic properties, particularly in terms of oral absorption and potential brain penetration, which are essential characteristics for compounds targeting Alzheimer's disease through inhibition of acetylcholinesterase.

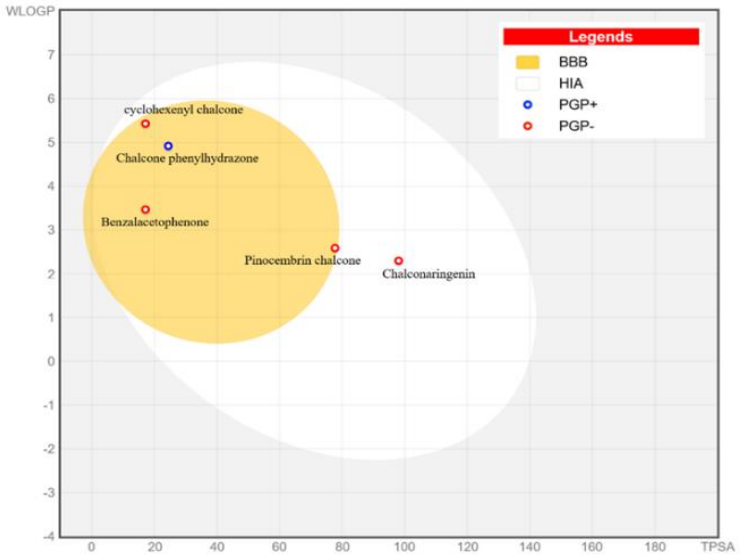

Figure 3. BOILED-Egg model of ADMET properties of selected compounds

Molecular Docking Analysis against Acetylcholinesterase

The molecular docking results revealed that the investigated chalcone derivatives exhibit variable binding affinities toward acetylcholinesterase **(Table 3)**. The docking scores ranged from −5.718 to −7.736 kcal/mol, indicating moderate to strong interactions within the enzyme active site when compared with the reference inhibitor donepezil. Among the tested compounds, chalcone phenylhydrazone displayed the lowest docking score (−7.736 kcal/mol), suggesting the strongest binding affinity toward acetylcholinesterase. This value is slightly better than that obtained for donepezil (−6.738 kcal/mol), indicating that this compound may have a promising inhibitory potential. The interaction analysis revealed the formation of a hydrogen bond with TYR124 and a π–π stacking interaction with TRP86, residues known to play an important role in ligand stabilization within the active gorge of the enzyme **(Figure 4)**. Similarly, cyclohexenyl chalcone showed a strong binding affinity with a docking score of −7.704 kcal/mol, which is also better than the reference drug. This compound forms a hydrogen bond with ARG296, suggesting a stable interaction within the catalytic site of the enzyme. Benzalacetophenone also exhibited a favorable docking score (−7.259 kcal/mol), slightly stronger than that of donepezil. Its interaction with ARG296 through hydrogen bonding contributes to the stabilization of the ligand within the binding pocket. In contrast, pinocembrin chalcone and chalconaringenin showed relatively weaker docking scores (−5.718 and −5.780 kcal/mol, respectively). However, both substances established stabilizing connections with the enzyme's important aromatic residues. While chalconaringenin interacts with PHE295 and TYR337 mostly through π–π stacking and hydrogen bonding interactions, pinocembrin chalcone interacts with PHE295 and PHE338. With a docking score of −6.738 kcal/mol, the reference medication donepezil generated a number of significant interactions, including π–π stacking and π–cation interactions, with residues including TYR337, TYR124, and TRP286. These residues are known to be part of acetylcholinesterase's aromatic gorge and peripheral anionic site (PAS), both of which are essential for ligand binding and enzyme inhibition. Overall, the docking data indicate that various chalcone derivatives, particularly chalcone phenylhydrazone, cyclohexenyl chalcone, and benzalacetophenone, have binding affinities similar to or stronger than the reference inhibitor donepezil. These findings suggest that these compounds could be attractive candidates for further development as acetylcholinesterase inhibitors for the treatment of Alzheimer's disease (Bouh *et al*., 2024; Česaitis *et al*., 2024; Essah *et al*., 2024; Hillman, 2024; Hsiao *et al*., 2024; Novak & Svoboda, 2024; Prakash & Desai, 2024; Hart & Reed, 2025; Jabin & Guthrie, 2025; Stojanov *et al*., 2025; Wei & Huang, 2025; Wong *et al*., 2025; Yu *et al*., 2025).

Table 3. Molecular docking scores and key binding residues of acetylcholinesterase (AChE) interacting with the selected compounds.

Compound Name	Docking Score (Kcal/mol)	Contributing Binding Residues	type of interaction
Benzalacetophenone	-7.259	ARG296	H-Bond
Chalcone phenylhydrazone	-7.736	TYR124 TRP86	H-Bond Pi-Pi Stacking
Pinocembrin chalcone	-5.718	PHE295 PHE338	H-Bond Pi-Pi Stacking
Cyclohexenyl chalcone	-7.704	ARG296	H-Bond
Chalconaringenin	-5.780	PHE295 TYR337	H-Bond Pi-Pi Stacking
Donepezil (Standard)	-6.738	TYR337 TYR124 TRP286	Pi-Pi Stacking Pi-Pi Stacking Pi-cation

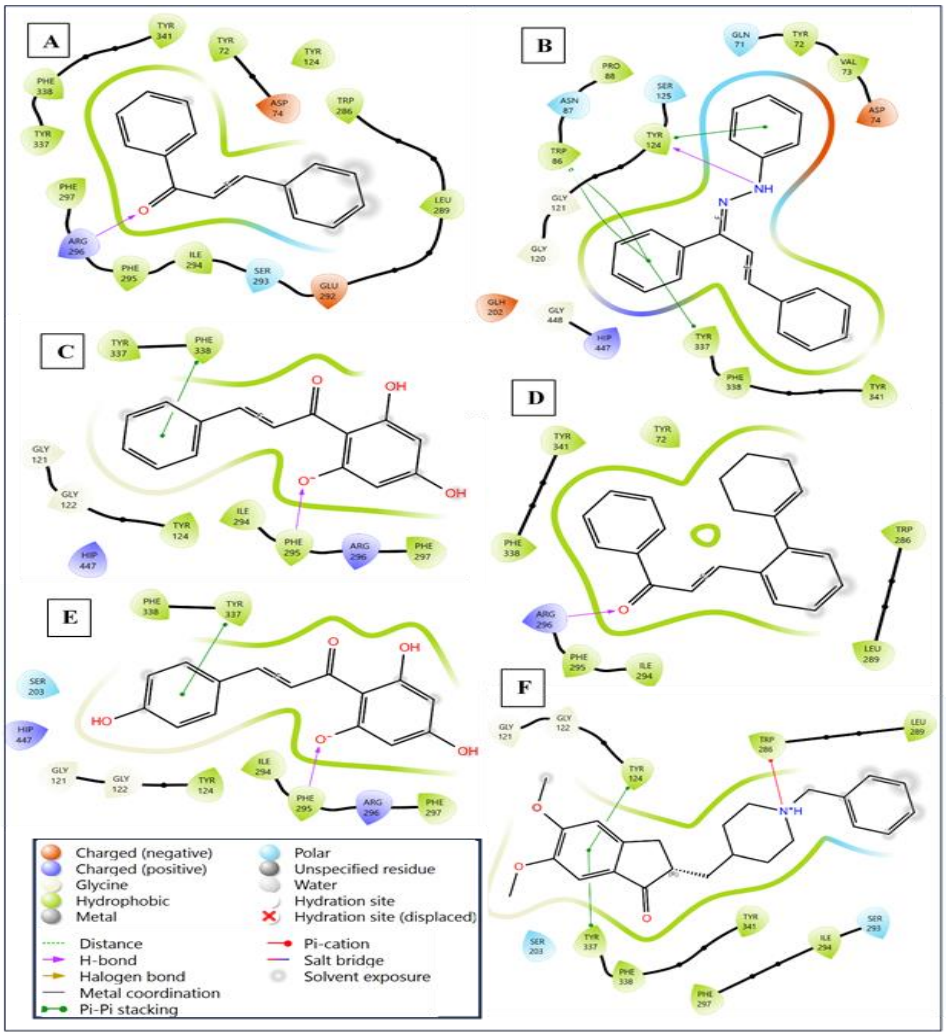

Figure 4. 2D intermolecular interactions between (A) Benzalacetophenone, (B) Chalcone phenylhydrazone, (C) Pinocembrin chalcone, (D) Cyclohexenyl chalcone, (E) Chalconaringenin, and (F) Donepezil (standard) with the active site of acetylcholinesterase (AChE)

Conclusion

This in silico study demonstrated that several chalcone derivatives possess favorable pharmacokinetic properties and potential central nervous system accessibility according to ADMET and BOILED-Egg predictions. Molecular docking showed that chalcone phenylhydrazone, cyclohexenyl chalcone, and benzalacetophenone interact strongly with acetylcholinesterase, exhibiting binding affinities comparable to or better than the reference drug donepezil. These findings suggest that these compounds may serve as promising candidates for further investigation as acetylcholinesterase inhibitors for Alzheimer's disease, although experimental validation remains necessary.

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Conflict of interest: None

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Ethics statement: None

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