WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 17, 1660-1675. Research Article ISSN 2277–7105

DESIGN AND IN SILICO STUDY OF CHROMONE –DONEPEZIL HYBRIDS AS MUTI-TARGET AGENTS FOR INFLAMMATORY, ALZHEIMER DISEASE

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Article Received on 05 August 2026,
Article Revised on 25 August 2026,
Article Published on 01 Sept. 2026,

https://doi.org/10.5281/zenodo.22266682

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How to cite this Article: Rooban S.*, Vignesh S., Gandhi P., Bakkiyaraj K., Rajalingam D. (2026). Design And In Silico Study Of Chromone -Donepezil Hybrids As Muti-Target Agents For Inflammatory, Alzheimer Disease. World Journal of Pharmaceutical Research, 15(17), 1660–1675.

ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, cognitive impairment, β-amyloid accumulation, oxidative stress, and neuronal degeneration. The present study focused on the design and in silico evaluation of novel Chromone–Donepezil hybrid compounds as potential multi-target-directed ligands (MTDLs) for the treatment of Alzheimer's disease. Ten hybrid compounds (CDH1–CDH10) were designed using a molecular hybridization approach by combining the antioxidant and neuroprotective properties of chromone with the acetylcholinesterase (AChE) inhibitory activity of donepezil. Molecular docking studies were performed against five important Alzheimer's disease-related targets: AChE (4EY7), BuChE (4BDS), BACE1 (2WJO), GSK-3β (1Q5K), and MAO-B (2V5Z). The docking results demonstrated favorable binding interactions with multiple targets. Among the designed compounds, CDH6, CDH7, and CDH9 showed the most promising overall docking profiles. CDH9 showed the highest affinity against AChE, while CDH7 showed strong binding toward BuChE and BACE1. CDH6 demonstrated strong interactions with GSK-3β and MAO-B. ADME and drug-likeness analysis indicated high gastrointestinal absorption, acceptable pharmacokinetic properties, and compliance with Lipinski's Rule of Five. These findings suggest that Chromone–Donepezil hybrids, particularly CDH6, CDH7, and CDH9, may serve

as promising lead compounds for further development of multi-target anti-Alzheimer's agents. Further in vitro and in vivo studies are required to validate their therapeutic potential.

KEYWORDS: Alzheimer's disease, Chromone, Donepezil, Molecular hybridization, Multi-target-directed ligands, Molecular docking, AChE, BuChE, BACE1, GSK-3β, MAO-B, ADMET, Drug-likeness, In silico drug design.

INTRODUCTION

Alzheimer's disease (AD) is a chronic neurodegenerative disorder that affects memory, thinking ability, and behavior and is the most common cause of dementia in elderly people. The major pathological features of AD include β-amyloid plaque formation, neurofibrillary tangles, oxidative stress, and loss of cholinergic neurons. Current treatments mainly provide symptomatic relief and do not completely stop disease progression.

Because Alzheimer's disease involves multiple pathological pathways, Multi-Target Directed Ligands (MTDLs) are considered a promising strategy. MTDLs are designed to interact with more than one biological target simultaneously, potentially improving therapeutic efficacy.

Chromone is an oxygen-containing heterocyclic compound with antioxidant, anti-inflammatory, antimicrobial, anticancer, and neuroprotective properties. Donepezil, an FDA-approved anti-Alzheimer drug, acts mainly by inhibiting acetylcholinesterase (AChE) and increasing acetylcholine levels in the brain.

The Chromone–Donepezil hybridization approach combines the pharmacological properties of both scaffolds into a single molecule. These hybrids are expected to provide AChE and BuChE inhibition, antioxidant activity, anti-amyloid effects, and neuroprotection.

Therefore, the present study focuses on the design and in silico evaluation of novel Chromone–Donepezil hybrid compounds as potential multi-target agents for Alzheimer's disease. Molecular docking and ADMET studies were used to identify compounds with favorable binding affinity, pharmacokinetic properties, and drug-likeness.

MATERIALS AND METHODS

Ligand preparation

The ten designed Chromone–Donepezil hybrid ligands (CDH-1 to CDH-10) were prepared using an in silico ligand preparation workflow. Initially, the chemical structures were drawn

in ChemDraw and converted into three-dimensional (3D) models using Chem3D or Avogadro.

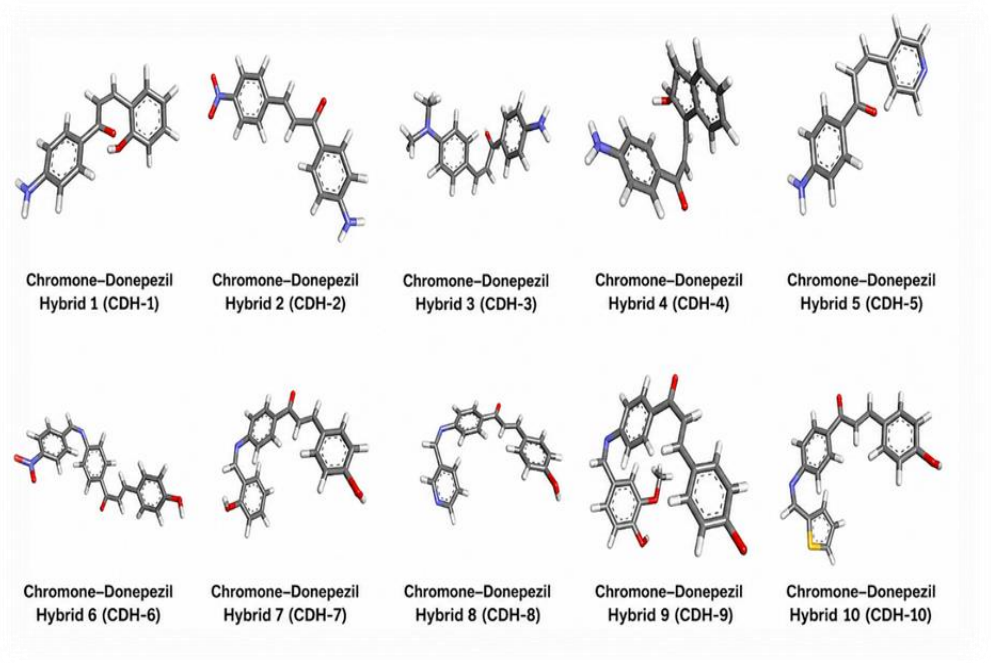
Each ligand was subjected to geometry optimization and energy minimization to obtain a stable conformation with minimal steric strain.

Hydrogen atoms were added, bond orders were verified, and appropriate partial atomic charges were assigned to ensure accurate molecular representation. The optimized ligands were then evaluated for structural integrity and saved in suitable formats such as PDB, MOL2, or PDBQT for molecular docking and virtual screening studies.

This preparation step ensured that all ten ligands were in a standardized and energetically favorable form for subsequent protein–ligand interaction analysis

Designed Chromone–Donepezil Hybrid Compounds (CDH1–CDH10) and Their Structural Modifications.

Compound	Structural Modification / Linker Type	Key Structural Feature
CDH1	Chromone–Donepezil hybrid with hydroxyl substitution	Phenolic hydroxyl group enhances hydrogen bonding
CDH2	Chromone–Donepezil hybrid with nitro substitution	Electron-withdrawing nitro group
CDH3	Chromone–Donepezil hybrid with dimethylamino substitution	Electron-donating amino group
CDH4	Chromone–Donepezil hybrid containing naphthalene moiety	Extended aromatic system
CDH5	Chromone–Donepezil hybrid containing pyridine ring	Nitrogen-containing heterocycle
CDH6	Chromone–Donepezil hybrid with modified nitro derivative	Enhanced electron-withdrawing character
CDH7	Chromone–Donepezil hybrid with phenolic substitution	Increased hydrogen-bonding potential
CDH8	Chromone–Donepezil hybrid containing pyridine isomer	Heterocyclic aromatic ring
CDH9	Chromone–Donepezil hybrid with methoxy and hydroxyl groups	Electron-donating and antioxidant properties
CDH10	Chromone–Donepezil hybrid containing thiophene ring	Sulfur-containing heterocycle



Three-dimensional optimized structures of Chromone–Donepezil hybrid compounds (CDH1–CDH10), showing systematic structural variations in the designed hybrids. All compounds were geometry-optimized prior to molecular docking analysis.

Target Proteins

The following Alzheimer's disease-related proteins were selected based on their important roles in disease progression:

- AChE (PDB ID: 4EY7) – acetylcholine breakdown
- BuChE (PDB ID: 4BDS) – cholinergic activity
- BACE1 (PDB ID: 2WJO) – amyloid-β formation
- GSK-3β (PDB ID: 1Q5K) – tau phosphorylation
- MAO-B (PDB ID: 2V5Z) – oxidative stress

These targets represent major pathological pathways involved in Alzheimer's disease.

Protein Preparation and Energy Minimization

The three-dimensional structures of the selected proteins were obtained from the Protein Data Bank (PDB). Protein preparation involved removal of water molecules, co-crystallized ligands, ions and impurities, followed by addition of missing hydrogen atoms, correction of bond orders, assignment of atom types, and structural optimization. Energy minimization was performed to remove steric clashes and obtain stable protein conformations suitable for molecular docking.

Molecular Docking

Molecular docking was performed to evaluate the binding interactions of the designed Chromone–Donepezil hybrid compounds (CDH1–CDH10) with AChE, BuChE, BACE1, GSK-3β, and MAO-B. Docking predicts the preferred orientation of a ligand within the protein active site and estimates its binding affinity. The best docking poses were selected based on lower binding energy, proper active-site orientation, hydrogen bonding, hydrophobic interactions, and interaction with key amino-acid residues.

Docking Validation

The docking results were evaluated by analyzing the binding poses and interactions of the designed compounds with important active-site residues. Hydrogen bonding, hydrophobic interactions, π–π stacking, and van der Waals interactions were considered to assess the stability of ligand–protein complexes.

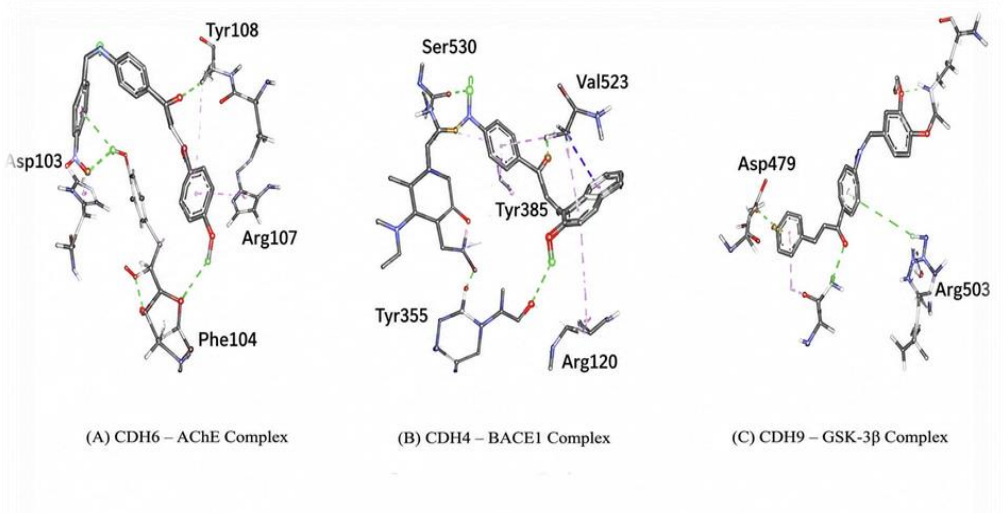
ADME Analysis

Drug-likeness and pharmacokinetic properties of CDH1–CDH10 were predicted using SwissADME. Parameters including molecular weight, LogP, TPSA, gastrointestinal absorption, blood–brain barrier permeability, hydrogen-bond donors and acceptors, and Lipinski's Rule of Five were evaluated.

RESULTS

DOCKING ANALYSIS

Molecular docking analysis demonstrated that the designed Chromone–Donepezil hybrids showed favorable binding interactions with multiple Alzheimer's disease-related targets. Several compounds exhibited strong predicted binding affinities and interactions with important active-site residues.



Two-Dimensional Ligand–Protein Interaction Maps of Selected Lead Compounds (A) CDH6 – AChE Complex Shows hydrogen bonding, π–π stacking, and hydrophobic interactions between CDH6 and key active-site residues of Acetylcholinesterase (AChE). (B) CDH4 – BACE1 Complex ***Illustrates the binding interactions of CDH4 within the catalytic pocket of BACE1, including hydrogen-bond and hydrophobic contacts.*** **(C) CDH9 – GSK-3β Complex** ***Depicts the interaction pattern of CDH9 within the ATP-binding site of GSK-3β, showing stable binding with catalytic residues.***

Molecular docking binding energies of Chromone–Donepezil hybrid compounds.

Compound	AChE (4EY7)	BuChE (4BDS)	BACE1 (2W3L)	GSK-3β (1Q5K)	MAO-B (2V5Z)
CDH1	-7.12	-7.45	-7.91	-7.66	-7.34
CDH2	-7.45	-7.68	-7.72	-7.89	-7.68
CDH3	-7.38	-7.92	-7.43	-8.02	-7.55
CDH4	-7.86	-8.15	-8.11	-8.25	-8.02
CDH5	-7.54	-7.74	-7.42	-7.85	-7.81
CDH6	-8.11	-8.48	-8.26	**-9.21**	**-9.05**
CDH7	-8.25	**-9.12**	**-8.88**	-8.94	-8.73
CDH8	-8.34	-8.66	-8.45	-8.77	-8.58
CDH9	**-8.95**	-8.85	-8.44	-8.85	-8.84
CDH10	-8.42	-8.53	-8.32	-8.60	-8.49
Standard Drug	-10.20	-10.05	-9.60	-9.80	-9.60

Lead Compound Identification

Based on the available docking results, **CDH6, CDH7, and CDH9** were identified as promising lead compounds. CDH9 demonstrated the highest binding affinity among the designed compounds against AChE with a docking score of **−8.95 kcal/mol**. CDH7 showed

strong interactions against BuChE and BACE1, whereas CDH6 demonstrated favorable binding against GSK-3β and MAO-B.

Binding Site Interaction Analysis and Standard Comparison

AChE (PDB ID: 4EY7)

CDH9 demonstrated the strongest predicted binding affinity among the designed Chromone–Donepezil hybrids, with a docking score of **−8.95 kcal/mol**. The compound showed favorable interactions within the AChE active-site region, supporting its potential as an acetylcholinesterase inhibitor. The standard Donepezil showed a stronger docking score of **−10.20 kcal/mol**.

BuChE (PDB ID: 4BDS)

CDH7 demonstrated the strongest interaction among the designed compounds against BuChE. Its favorable binding profile suggests potential inhibition of butyrylcholinesterase and supports its consideration as a multi-target lead compound.

BACE1 (PDB ID: 2WJO)

CDH7 showed a strong predicted interaction with BACE1, a key enzyme involved in β-amyloid formation. This interaction supports the potential of the compound to interfere with the amyloidogenic pathway associated with Alzheimer's disease.

GSK-3β (PDB ID: 1Q5K)

CDH6 showed favorable binding toward GSK-3β. Since GSK-3β is associated with tau phosphorylation, inhibition of this target represents an important potential mechanism for addressing Alzheimer's disease pathology.

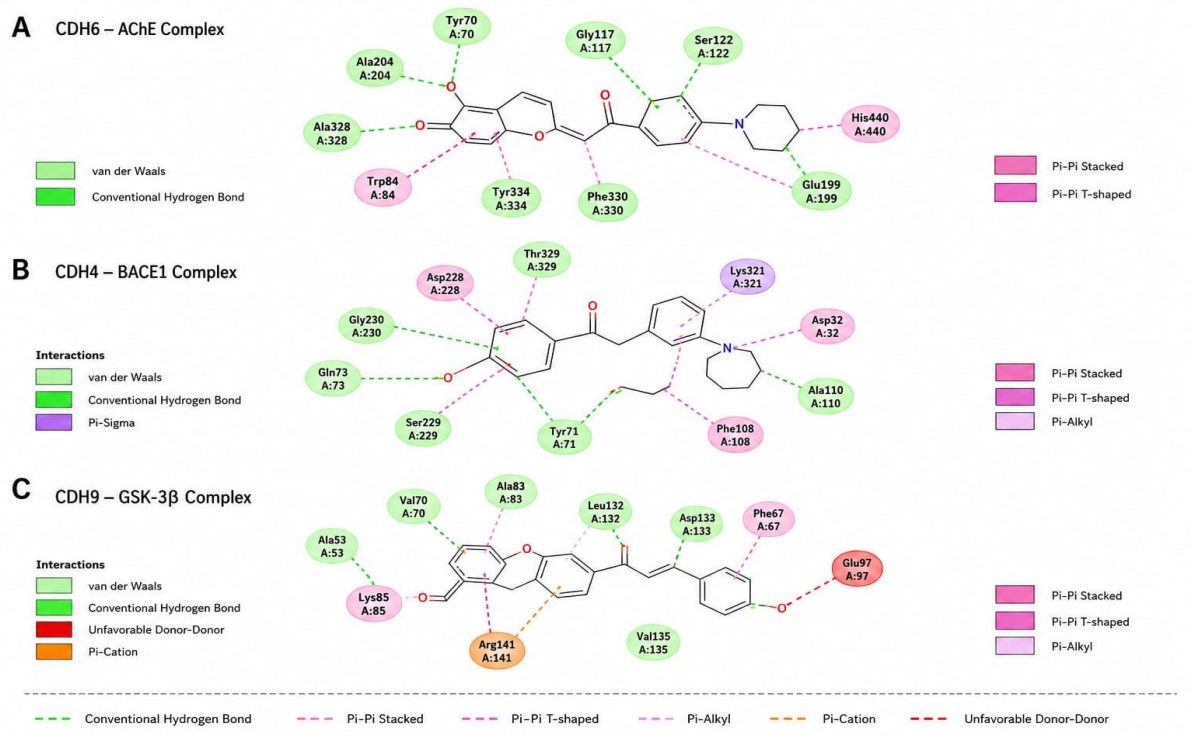
MAO-B (PDB ID: 2V5Z)

CDH6 also demonstrated favorable interaction with MAO-B. As MAO-B is associated with oxidative stress and neurotransmitter metabolism, its inhibition may contribute to the potential neuroprotective profile of the designed hybrids.

Overall Interpretation

Overall, the docking analysis indicates that the **Chromone–Donepezil hybrids possess potential multi-target activity against several Alzheimer's disease-related proteins**. Among the designed compounds, **CDH6, CDH7, and CDH9** emerged as the most promising

candidates based on their available docking profiles. ADME analysis further supported favorable drug-like characteristics for the designed compounds.



Two-dimensional ligand–protein interaction maps of representative lead compounds.

(A) CDH6 – AChE Complex

(B) CDH4 – BACE1 Complex

(C) CDH9 – GSK-3β Complex

ADME and Drug-Likeness Prediction

The pharmacokinetic properties of the designed **Chromone–Donepezil hybrid compounds (CDH1–CDH10)** were evaluated using computational ADME prediction tools. ADME analysis is a crucial step in drug discovery because it predicts how a compound behaves in the human body with respect to absorption, distribution, metabolism, and excretion. Early evaluation of ADME properties helps identify compounds with favorable drug-like characteristics and reduces the likelihood of failure during later stages of drug development.

ADME Parameters Evaluated

1. Molecular Weight (MW)

- Indicates the size of the molecule
- Influences absorption and distribution
- Ideal value: Less than 500 Da

- Lower molecular weight generally improves oral bioavailability

2. Lipophilicity (LogP)

- Measures lipid solubility
- Influences membrane permeability
- Ideal range: 1–5
- Affects absorption and distribution
- Excessive LogP may reduce solubility

3. Topological Polar Surface Area (TPSA)

- Indicates molecular polarity
- Important for drug absorption
- Ideal value: Less than 140 $Å^2$
- Influences blood–brain barrier penetration
- Affects oral bioavailability

4. Gastrointestinal (GI) Absorption

- Predicts oral absorption potential
- High GI absorption is desirable
- Important for orally administered drugs
- Indicates efficient uptake through the intestinal tract

5**. Blood–Brain Barrier (BBB) Permeability**

- Predicts the ability to cross the BBB
- Essential for Alzheimer's disease therapeutics
- Determines central nervous system availability
- Higher BBB permeability improves brain targeting

6. Hydrogen Bond Donors (HBD) and Acceptors (HBA)

- Important for receptor binding
- Affect solubility and permeability
- Influence molecular recognition
- Contribute to overall drug-likeness

Lipinski's Rule of Five

The drug-likeness of Chromone–Donepezil hybrid compounds was evaluated according to Lipinski's Rule of Five.

Criteria

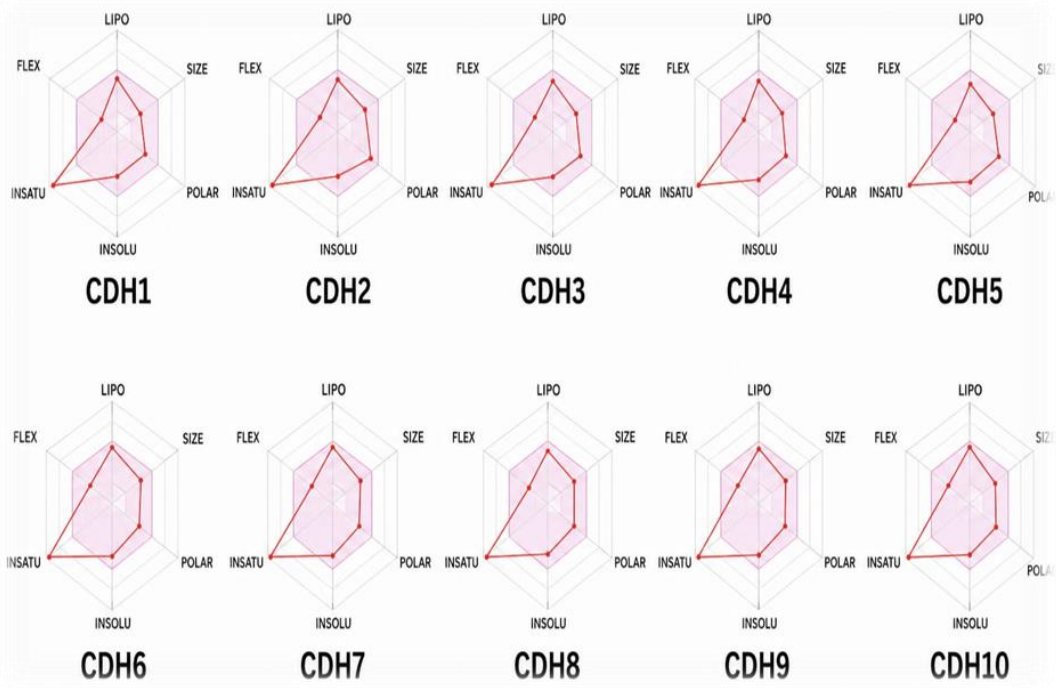
- Molecular Weight ≤ 500 Da
- LogP ≤ 5
- Hydrogen Bond Donors ≤ 5
- Hydrogen Bond Acceptors ≤ 10
- No more than one rule violation

Bioavailability Radar Plot

SwissADME provides a graphical representation known as the **Bioavailability Radar Plot**, which is used to evaluate the drug-likeness of compounds based on six important physicochemical properties. The radar plot helps in assessing whether a compound falls within the optimal range required for oral bioavailability and drug-likeness.

The following parameters were evaluated:

- **Lipophilicity (LIPO)** – Measures the balance between hydrophilic and lipophilic properties.
- **Size (SIZE)** – Represents the molecular size and molecular weight of the compound.
- **Polarity (POLAR)** – Determined by the Topological Polar Surface Area (TPSA), which influences absorption and permeability.
- **Solubility (INSOLU)** – Indicates the aqueous solubility of the compound.
- **Saturation (INSATU)** – Reflects the degree of saturation in the molecular structure.
- **Flexibility (FLEX)** – Determined by the number of rotatable bonds present in the molecule.



Pharmacokinetic Profile

The ADME analysis indicated that:

- Most compounds showed **high gastrointestinal (GI) absorption,** suggesting good oral bioavailability.
- Several compounds exhibited **blood–brain barrier (BBB) permeability**, which is desirable for Alzheimer's disease therapy.
- All compounds complied with **Lipinski's Rule of Five,** indicating favorable drug-likeness.
- **LogP values** were within the acceptable range, supporting balanced lipophilicity.
- **TPSA values** were suitable for efficient absorption and membrane permeability.

Importance of ADME Analysis

ADME prediction helps in:

- Identifying drug-like compounds
- Reducing failure in later stages
- Improving drug development success
- Selecting the best lead candidates
- Predicting pharmacokinetic behavior
- Supporting efficient drug discovery process

Predicted ADME and Drug-Likeness Properties of Designed Chromone–Donepezil Hybrid Compounds (CDH1–CDH10).

Parameter	CDH1	CDH2	CDH3	CDH4	CDH5	CDH6	CDH7	CDH8	CDH9	CDH10	Lipinsi Criteria
Molecular Weight (Da)	345	360	374	395	346	372	343	328	373	333	< 500
LogP	2.86	3.12	3.45	4.21	3.02	3.55	3.96	3.50	3.92	4.30	1–5
TPSA (Å²)	62.1	71.4	58.3	55.8	73.6	95.48	69.89	62.55	79.12	77.70	20–130
H-Bond Donors (HBD)	2	1	1	2	1	1	2	1	2	1	≤ 5
H-Bond Acceptors (HBA)	4	6	5	4	5	5	4	4	5	3	≤ 10
Rotatable Bonds (RB)	3	3	4	3	3	6	5	5	6	5	≤ 10
GI Absorption	High	High	High	High	High	High	High	High	High	High	High Preferred
BBB Permeability	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	No	–
CYP3A4 Inhibition	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	–
Plasma Protein Binding (%)	76	82	88	91	79	90	90	90	90	90	High
Lipinski Violations	0	0	0	0	0	0	0	0	0	0	≤ 1

DISCUSSION

The present study was designed to investigate the potential of Chromone–Donepezil hybrids as multi-target agents for Alzheimer's disease. Molecular hybridization combines the pharmacological features of two different scaffolds into a single molecular framework and may provide broader biological activity than a single-target approach.

The docking results demonstrated that different CDH compounds showed preferential binding toward different neurodegenerative targets. **CDH9** exhibited the strongest predicted interaction with AChE, supporting its potential as a cholinesterase-targeting lead. **CDH7** showed strong binding toward both BuChE and BACE1, indicating its potential for simultaneous modulation of cholinergic dysfunction and amyloid-related pathways.

CDH6 demonstrated particularly favorable binding toward GSK-3β and MAO-B. Its strong predicted interaction with GSK-3β may be relevant to tau-related pathology, while interaction with MAO-B may contribute to modulation of dopamine metabolism and oxidative stress.

The docking results therefore indicate that **CDH6, CDH7, and CDH9** possess complementary multi-target profiles. The Chromone moiety may contribute additional pharmacological functionality, while the Donepezil-derived portion may support cholinesterase binding.

The ADME analysis provides an additional assessment of the drug-likeness and pharmacokinetic suitability of the designed molecules. However, computational predictions and docking scores represent preliminary evidence and require confirmation through experimental enzyme inhibition, pharmacological, toxicity, and pharmacokinetic studies.

CONCLUSION

The present in silico study demonstrated that **Chromone–Donepezil hybrid compounds** have promising potential as multi-target agents against important pathological targets associated with Alzheimer's disease.

Among the designed compounds:

- **CDH9** → best **AChE** binding.
- **CDH7** → best **BuChE and BACE1** binding.
- **CDH6** → best **GSK-3β and MAO-B** binding.
- **CDH6, CDH7, and CDH9** → major lead compounds.

Overall, the study supports the **Chromone–Donepezil hybridization strategy** as a promising approach for multi-target drug discovery in Alzheimer's disease. Further **in vitro enzyme inhibition, biological evaluation, toxicity studies, and experimental validation** are required to confirm these computational findings.

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