Research Article

In-Silico Optimization of Galanthamine Derivatives: Towards Next-Generation Neuroprotective Agents

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Abstract

This investigation delineates the drug–receptor interactions of galantamine derivatives through advanced molecular docking methodologies, underscoring their relevance in contemporary medicinal chemistry. Ten structurally novel galantamine analogues, incorporating the indanone ring system, were synthesized and rigorously characterized via spectral analysis. Docking simulations against human acetylcholinesterase (AChE, PDB ID: 1dx6) revealed consistently favorable binding energies and pronounced affinity for the enzyme's catalytic pocket, with several derivatives surpassing the inhibitory potential of the parent compound. Critical interactions with residues including Trp86, Tyr124, Ser203, Glu202, Tyr337, Phe338, His447, and Tyr449 were elucidated, emphasizing the indispensability of flexible docking in capturing physiologically relevant conformations. The findings highlight the therapeutic promise of structural modifications to galantamine, particularly in enhancing pharmacological efficacy for Alzheimer's disease management. By obstructing the peripheral anionic site of AChE, these analogues may attenuate amyloid-β aggregation, a cardinal pathological hallmark of neurodegeneration. Computational modeling thus emerges as a cost-efficient and predictive paradigm for rational drug design, enabling the prioritization of candidate molecules prior to labor-intensive experimental validation. Collectively, the synthesized galantamine derivatives constitute compelling lead scaffolds for the development of next-generation AChE inhibitors with augmented neuroprotective activity. While subsequent in-vitro and in-vivo investigations remain imperative to substantiate therapeutic utility, this work establishes a robust foundation for the strategic advancement of cholinesterase-targeted interventions in neurodegenerative disorders.

Keywords: - Galantamine, Molecular Docking, 2D-3D Modeling, Acetylcholineesterase (AChE).

Introduction

Computational chemistry and physics provide powerful tools to study molecules and reactions using quantum mechanical approaches and computer simulations [01-05]. Since molecules are more complex than atoms, specialized programs have been developed to analyze their structures and properties [06]. These simulations allow researchers to calculate molecular properties and predict reaction mechanisms without relying solely on experimental methods [07, 08]. In drug design, this approach reduces costs and accelerates the discovery process by identifying promising compounds before laboratory testing [09-10].

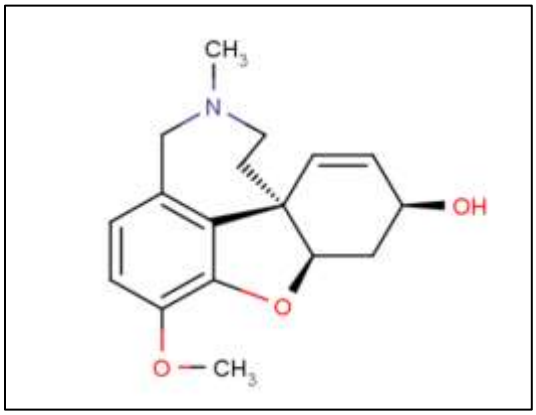
Molecular docking has emerged as one of the most important techniques in computer-aided drug design [11, 12]. It evaluates how well a molecule binds to a target protein, helping researchers screen millions of compounds efficiently [13]. Since it is impractical to test each compound experimentally, docking provides a strategic infrastructure for identifying the most effective candidates [14]. It also guides chemists in modifying molecules to improve their binding affinity and therapeutic potential, making it a cornerstone of modern drug discovery [15].

Galantamine (GAL), an alkaloid derived from plants such as Galanthus caucasicus and Galanthus woronowii, is a notable example of a drug studied through computational and experimental methods [16, 17, 18]. GAL fits into the acetylcholinesterase (AChE) binding gorge but is too short to fully occupy it [19]. Importantly, it interacts with the peripheral anionic site (PAS), which is linked to amyloid beta (Aβ) aggregation and plaque formation in Alzheimer's disease [20]. By blocking PAS, GAL can reduce Aβ aggregation, offering therapeutic benefits in neurodegenerative conditions [21].

Historically, GAL was first marketed under the brand name Nivalin and used to treat conditions such as myasthenia gravis, myopathy, and residual poliomyelitis paralysis [22]. Its ability to cross the blood-brain barrier and modulate cholinergic function led to its study in Alzheimer's disease during the 1980s [23]. By 2000, GAL was approved for clinical use in Europe, the United States, and Asia, marking a significant milestone in neuropharmacology [24,25].

This progression highlights how computational modeling and docking research complement experimental chemistry in advancing drug design and therapeutic innovation [26].

Fig1.1 Galantamine Structure.



Acetylcholinesterase (AChE) is a critical enzyme in the central nervous system, responsible for breaking down acetylcholine (ACh), a neurotransmitter essential for neuronal communication [27,28]. In Alzheimer's disease (AD), abnormal overexpression of AChE and the accumulation of β-amyloid plaques contribute to progressive neuronal damage [29, 30]. This dual role of AChE—both in neurotransmitter regulation and in plaque formation makes it a prime therapeutic target in AD research and treatment strategies [31].

Currently, four major AChE inhibitors tacrine, donepezil, galantamine, and rivastigmine are approved for AD therapy [32]. While these drugs can improve cognitive function by increasing acetylcholine levels, they suffer from limitations such as poor absorption and adverse side effects [33]. This has prompted researchers to explore natural compounds from medicinal plants, including alkaloids, flavonoids, tannins, and saponins, which show promising biological activity and may offer safer alternatives [34].

Molecular docking plays a pivotal role in this search for new inhibitors [35]. By simulating how bioactive molecules interact with the AChE binding pocket, docking studies provide insights into binding modes, pharmacophoric features, and potential modifications to enhance activity [36]. This computational approach allows rapid screening of thousands of compounds, narrowing down candidates before experimental validation [37]. It is particularly valuable in identifying natural products with structural features that can be optimized for therapeutic use [38].

In the research described, ten known derivatives of AChE inhibitors were examined through molecular docking to predict their binding mechanisms and pharmacophoric conformations [39]. Beyond evaluating existing molecules, the study also synthesized and designed novel inhibitors with improved structural features for stronger inhibitory action [40]. Such work demonstrates how computational modeling, combined with medicinal chemistry, accelerates the discovery of next-generation AChE inhibitors that may overcome current drug limitations and provide more effective treatment options for Alzheimer's disease [41].

Experimental Work

1. Software for Docking

Auto-dock 1.5.7 was selected as the primary docking software due to its efficiency, accuracy, and ability to handle flexible docking protocols [42]. It enables the prediction of ligand binding modes within the receptor's active site by calculating binding affinities and orientations [43]. This makes it particularly suitable for evaluating galantamine derivatives against acetylcholinesterase [44].

The program uses a scoring function to estimate binding energies, allowing researchers to compare the inhibitory potential of different compounds [45,46]. Its automated algorithms reduce computational time while maintaining reliability, making it a standard tool in computational drug design [47].

2. 2D Structure Drawing

ChemDraw Ultra 14.0 was employed to construct the 2D chemical structures of the synthesized galantamine derivatives [48]. This software provides a precise representation of molecular frameworks, ensuring accuracy in bond lengths, angles, and stereochemistry [49].
By generating clear 2D depictions, ChemDraw facilitates communication of structural information and serves as the foundation for subsequent 3D modelling [50]. These diagrams are essential for verifying synthetic pathways and documenting compound identity [51].

3. 3D Structure Generation
Discovery Studio was used to convert the 2D structures into 3D configurations, which are necessary for docking simulations [52-55]. The software applies molecular mechanics and force-field calculations to generate realistic conformations [56].
This step ensures that the ligands adopt spatial orientations compatible with receptor binding. Accurate 3D models are critical for predicting interactions such as hydrogen bonding, hydrophobic contacts, and steric complementarity [57].

4. Protein Data Source
The Protein Data Bank (PDB) served as the repository for acetylcholinesterase crystal structures [58]. Researchers accessed the enzyme's 3D coordinates in PDB format, ensuring standardized and validated structural data [59].
Using experimentally determined protein structures enhances the reliability of docking studies [60]. It provides a biologically relevant framework for simulating ligand binding and evaluating pharmacophoric interactions [61].

5. Protein Preparation
Before docking, proteins were prepared by removing water molecules and undesirable ligands using Discovery Studio [62]. This step prevents interference with binding simulations and ensures that only relevant residues participate in ligand interactions [63].
Protein preparation also involves energy minimization and optimization of side-chain orientations. Such refinements improve docking accuracy by replicating physiological conditions more closely [64].

6. Active Site Residues
Key residues in the acetylcholinesterase active siteTrp86, Tyr124, Ser203, Glu202, Tyr337, Phe338, His447, and Tyr449 were identified as critical for ligand binding. These amino acids form the catalytic and peripheral binding regions of the enzyme [65-66].
Understanding these residues allows researchers to predict how galantamine derivatives interact with the enzyme. Strong contacts with these sites often correlate with enhanced inhibitory activity [67].

7. Flexible Docking
Flexible docking was performed to allow side chains of active site residues to move during simulations. This accounts for protein flexibility, which is essential for capturing realistic binding conformations [68].
Rigid docking often oversimplifies interactions, while flexible docking provides a dynamic view of ligand–protein binding. This enhances predictive accuracy and reflects physiological binding mechanisms [69].

8. Docking Grid Parameters
The docking grid was defined to enclose the co-crystallized ligand and flexible residues. Its center was set at X = 8.2, Y = 61.5, Z = -23.8, with dimensions of 17 × 17 × 17 Å.
This grid ensures that docking simulations focus on the enzyme's active pocket. Proper grid sizing is crucial to capture all relevant interactions while avoiding unnecessary computational overhead [70].

Results And Discussion

1. Molecular Docking Analysis
The docking analysis provided insights into how galantamine derivatives interact with acetylcholinesterase (AChE). By retrieving the enzyme's 3D structure from the Protein Data Bank, researchers ensured that the simulations

were based on experimentally validated data. The chosen protein (PDB ID: 1dx6) is a well-studied crystal structure of human AChE, making it suitable for comparative analysis.
During docking, amino acids within the active pocket were observed to bind on both sides of the derivatives, confirming strong ligand–receptor interactions. Energy minimization of the protein further stabilized the docking environment, allowing the active sites to align favorably with the ligands. This step was crucial for ensuring realistic binding orientations.

2. Flexible Docking Significance

The interaction of ligands with the binding pocket caused notable rearrangements in amino acid positions. This highlighted the importance of flexible docking, where side chains of residues are allowed to rotate freely. Such flexibility mimics physiological conditions more accurately than rigid docking.
By enabling dynamic movement of residues, flexible docking captured subtle conformational changes that enhance binding affinity. This approach provided a more reliable calibration of the docking procedure, ensuring that the predicted orientations of ligands reflected realistic biological interactions.

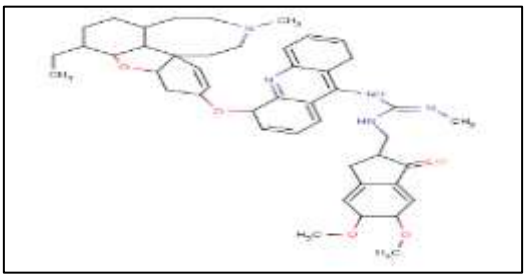
3. Validation of Docking Process

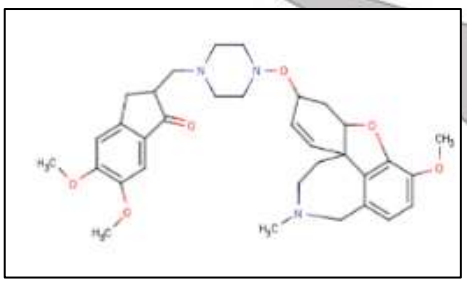
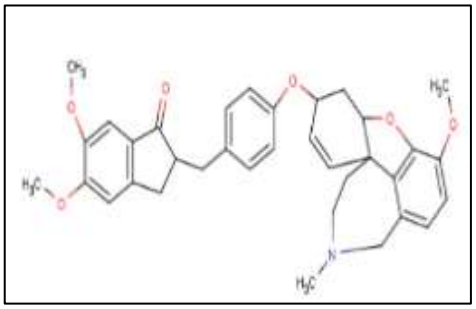
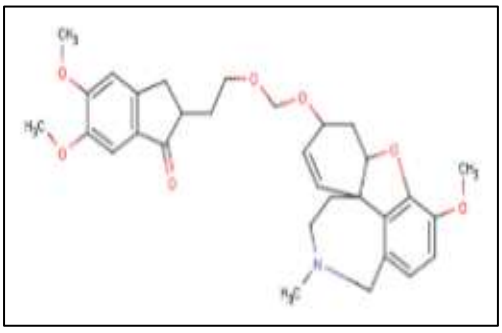
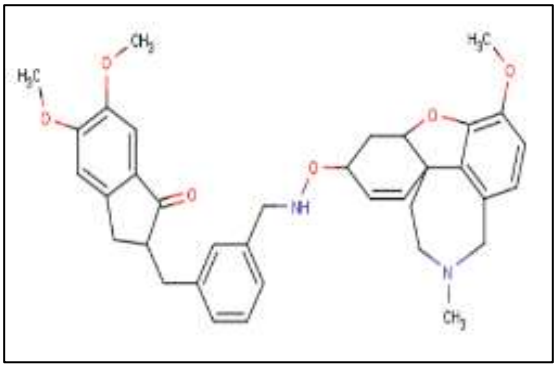
Validation was achieved by redrawing the native ligand in 2D, converting it into 3D, and selecting the best conformer. This ligand was then docked using Autodock Vina to confirm the accuracy of the docking protocol. The theoretical interaction closely resembled the crystal structure, reinforcing the reliability of the computational approach.
This validation step is essential in molecular docking studies, as it demonstrates that the software and parameters can reproduce known binding patterns. Once validated, the same protocol can be confidently applied to novel derivatives.

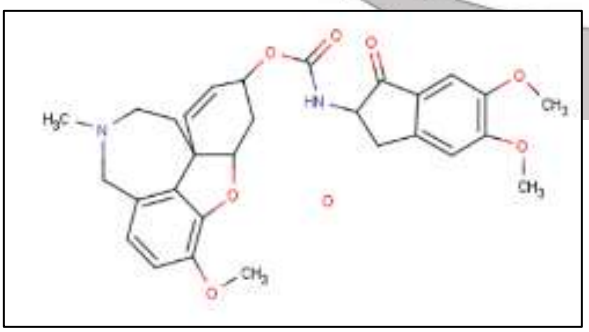
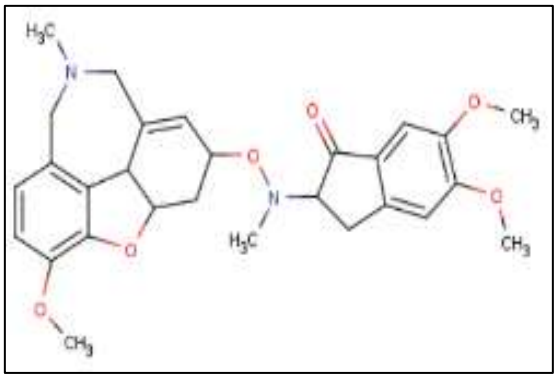
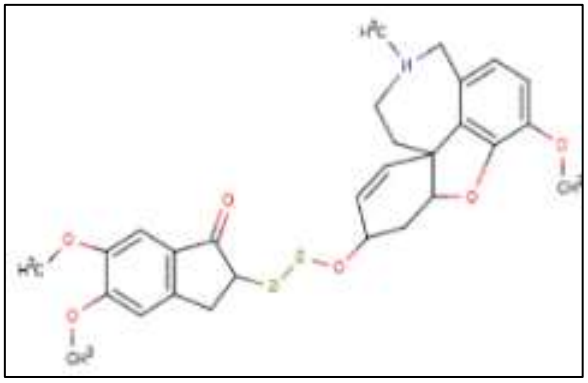
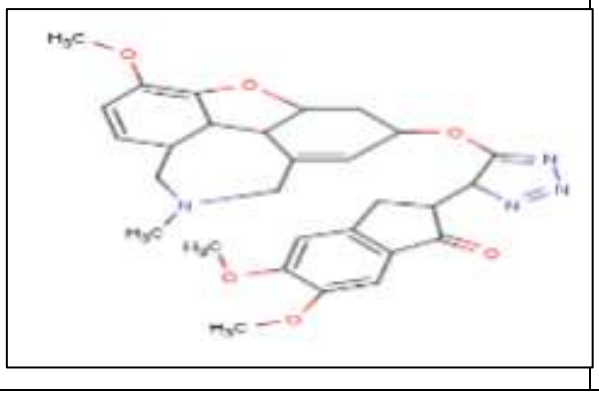
4. Docking of Galantamine Derivatives

Ten galantamine derivatives were subjected to docking simulations using Autodock. Each compound's binding energy was recorded, providing a quantitative measure of inhibitory potential. Lower binding energy values indicated stronger affinity for the enzyme's active site.
The comparative analysis revealed that several derivatives exhibited enhanced binding compared to galantamine itself. These results suggest that structural modifications can improve inhibitory activity, offering promising leads for drug development against Alzheimer's disease.

Table no 01- Derivatives of Galathamine

SR. NO	IUPAC Name	Structure	Binding Energy
1	(E)-1-[(5,6-dimethoxy-1-oxo-2,3,5,6-tetrahydro-1H- inden-2-yl)methyl]-3-[5-({10-ethyl-4-methyl-12-oxa-4 azatetracyclo[9.6.1.$0^{1,13}$.$0^{7,18}$]octadec-16-en-15-yl}oxy)-1,5-dihydroacridin-9-yl]-2-methylguanidine		-10.13

2	5,6-dimethoxy-2-{[4-({9-methoxy-4-methyl-11-oxa-4-azatetracyclo[8.6.1.0^{1,12}.0^{6,17}]heptadeca- 6,8,10(17),15-tetraen-14-yl}oxy)piperazin-1- yl]methyl}-2,3-dihydro-1H-inden-1-o		-11.39
3	5,6-dimethoxy-2-{[4-({9-methoxy-4-methyl-11-oxa-4-azatetracyclo[8.6.1.0^{1,12}.0^{6,17}]heptadeca- 6,8,10(17),15-tetraen-14-yl}oxy)phenyl]methyl}-2,3- dihydro-1H-inden-1-one		-11.04
4	5,6-dimethoxy-2-{2-[({9-methoxy-4-methyl-11-oxa-4-azatetracyclo[8.6.1.0^{1,12}.0^{6,17}]heptadeca-6,8,10(17),15-tetraen-14-yl}oxy)methoxy]ethyl}-2,3- dihydro-1H-inden-1-one		-9.73
5	5,6-dimethoxy-2-[(3-{[({9-methoxy-4-methyl-11-oxa-4-azatetracyclo[8.6.1.0^{1,12}.0^{6,17}]heptadeca-6(17),7,9,15-tetraen-14-yl}oxy)amino]methyl}phenyl)methyl]-2,3-dihydro-1H- inden-1-one		-10.38

6	9-methoxy-4-methyl-11-oxa-4-azatetracyclo[8.6.1.0^{1,12}.0^{6,17}]heptadeca- 6(17),7,9,15-tetraen-14-yl N-(5,6-dimethoxy-1-oxo- 2,3-dihydro-1H-inden-2-yl)carbamate		-9.91
7	5,6-dimethoxy-2-[({12-methoxy-7-methyl-16-oxa-7-azatetracyclo[11.2.1.0^{5,15}.0^{9,14}]hexadeca-4,9(14),10,12-tetraen-3-yl}oxy)(methyl)amino]-2,3- dihydro-1H-inden-1-one		-10.37
8	5,6-dimethoxy-2-[({9-methoxy-4-methyl-11-oxa-4-azatetracyclo[8.6.1.0^{1,12}.0^{6,17}]heptadeca-6,8,10(17),15-tetraen-14-yl}oxy)disulfanyl]-2,3- dihydro-1H-inden-1-one		-10.54
9	5,6-dimethoxy-2-[5-({12-methoxy-7-methyl-16-oxa-7-azatetracyclo[11.2.1.0^{5,15}.0^{9,14}]hexadeca-4,10,12-trien-3-yl}oxy)-4H-1,2,3-triazol-4-yl]-2,3- dihydro-1H-inden-1-one		-10.46

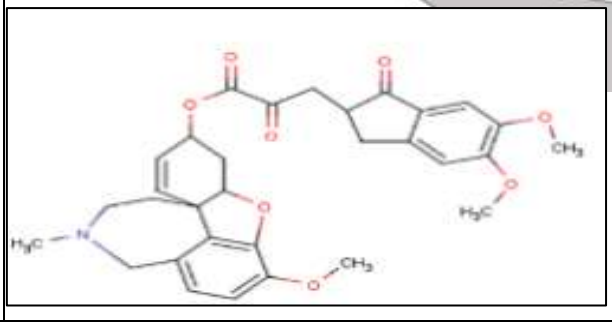
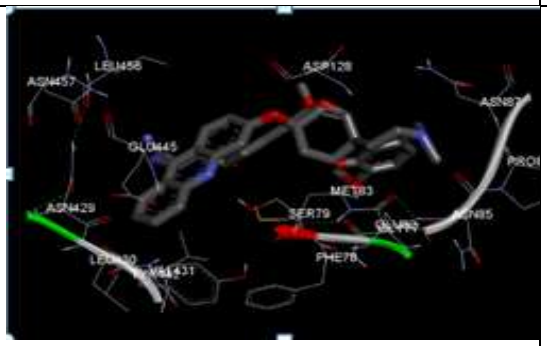
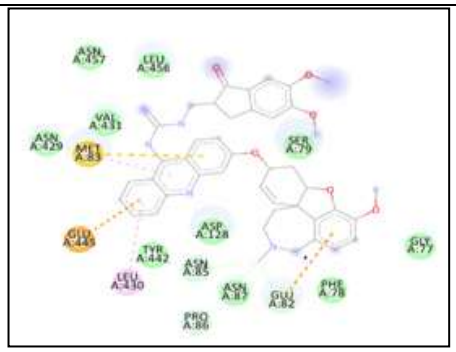
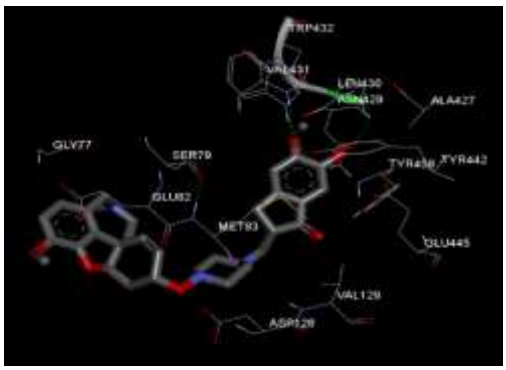
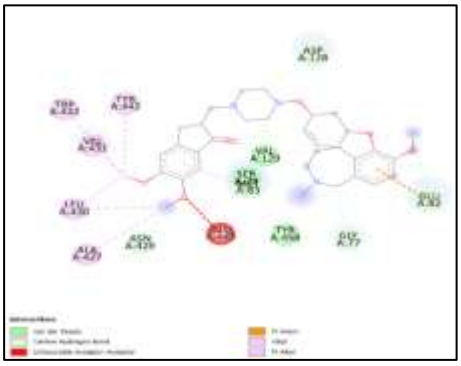
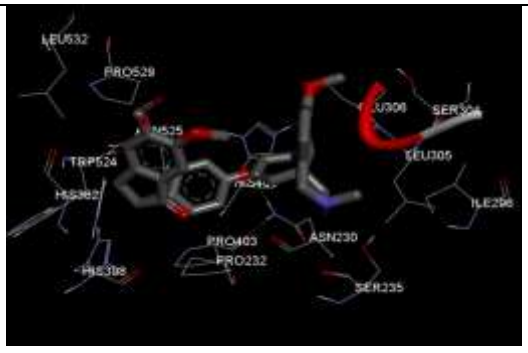
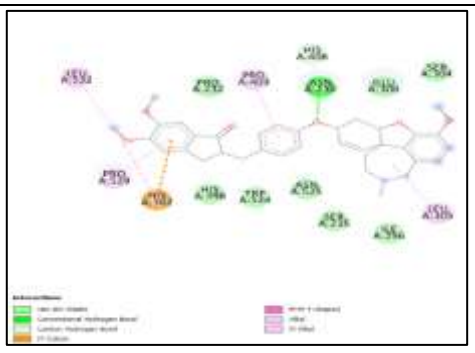
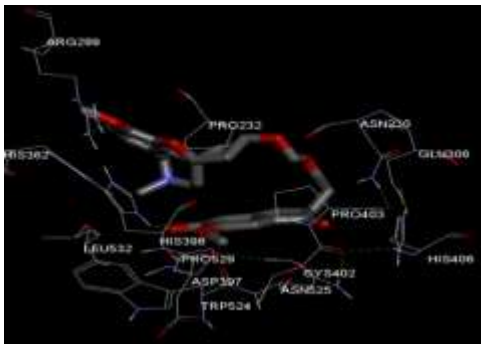
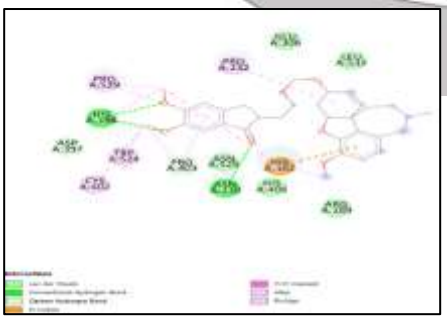
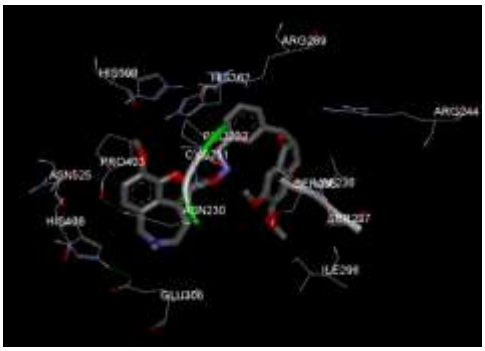
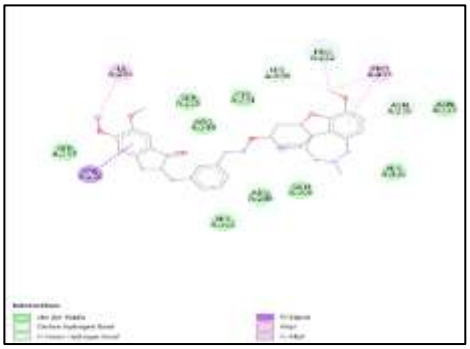
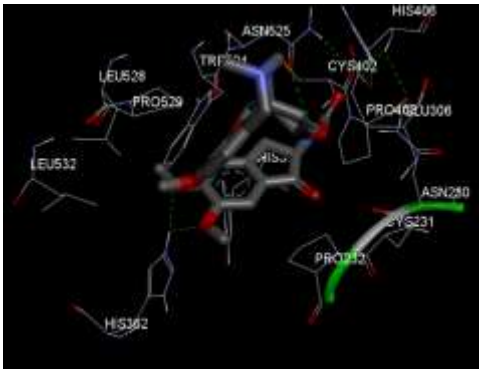
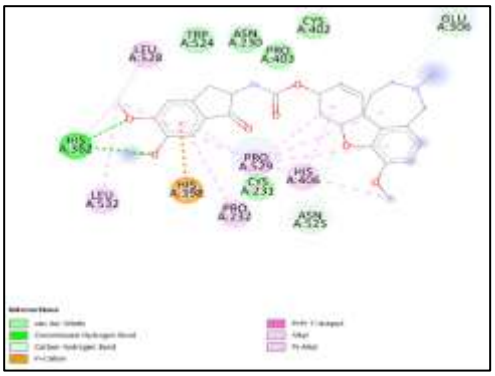
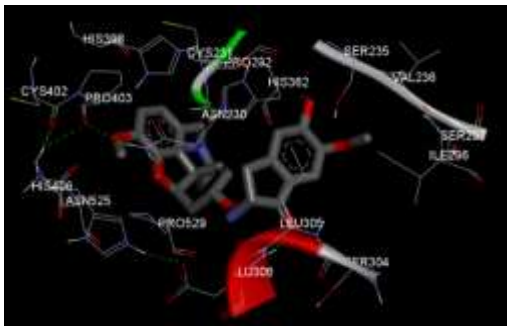
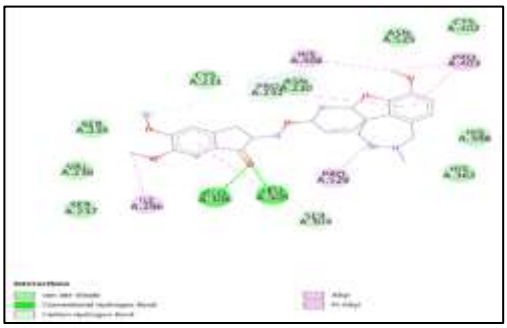
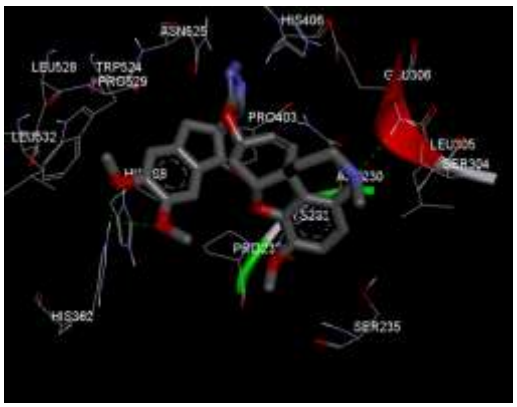
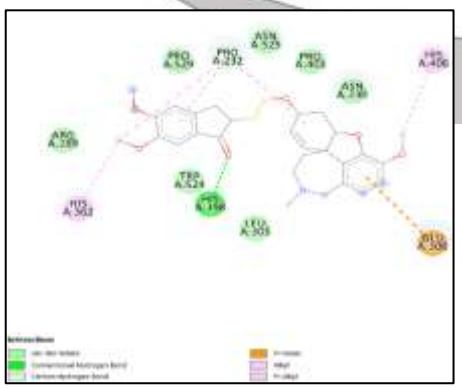
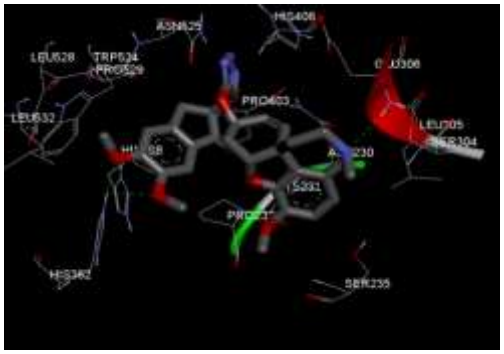
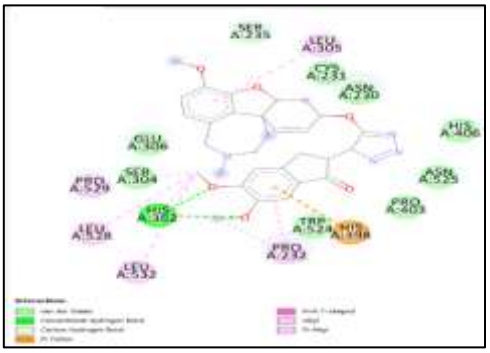
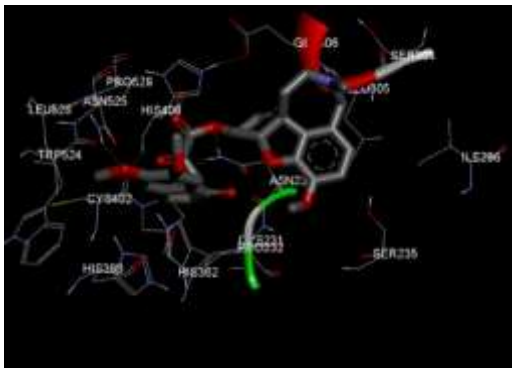
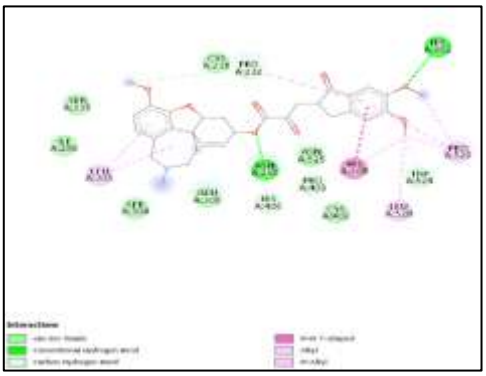
10	9-methoxy-4-methyl-11-oxa-4-azatetracyclo[8.6.1.0^{1,12}.0^{6,17}]heptadeca- 6,8,10(17),15-tetraen-14-yl 3-(5,6-dimethoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)-2-oxopropanoate		-11.40

Table no 02- 2D and 3D images of docked compound

Sr. No.	3D Images	2D Images
1.		
2.		
3.		

4.		
5		
6.		
7.		

8.		
9.		
10.		

Conclusion

The present molecular docking investigation unequivocally demonstrates that galantamine derivatives incorporating the indanone ring system possess robust inhibitory potential against acetylcholinesterase (AChE). All synthesized compounds exhibited substantial affinity for the enzyme's catalytic pocket, accompanied by favorable binding energies. These findings strongly suggest that the structural modifications introduced into galantamine confer enhanced pharmacological activity, positioning these analogues as promising candidates for therapeutic development. Docking simulations further underscore the capacity of structural alterations to augment galantamine's pharmacological effectiveness in the treatment of Alzheimer's disease. By optimizing binding interactions within the active site of AChE, these derivatives may surpass the efficacy of the parent compound. Importantly, their ability to obstruct the peripheral anionic site could mitigate amyloid-β aggregation, a pathological hallmark of neurodegeneration. This dual mechanism of action highlights the therapeutic promise of rationally designed galantamine analogues. The study also reinforces the strategic utility of computational docking as a cost-effective and predictive methodology in drug discovery. By enabling rapid screening of candidate molecules, docking circumvents the limitations of labor-intensive in-vitro assays at early stages of research.

Moreover, it provides valuable insights into drug–receptor interactions, guiding structural optimization and prioritization of lead compounds. This computational paradigm thus serves as a cornerstone for modern medicinal chemistry and rational drug design. Although further in-vitro and in-vivo validation remains imperative, the synthesized galantamine derivatives represent compelling lead molecules for the development of next-generation anti-Alzheimer therapeutics. Their strong binding affinities and favorable docking profiles establish a robust foundation for translational research. Ultimately, this work contributes to the advancement of cholinesterase-targeted interventions, offering new avenues for the design of neuroprotective agents capable of addressing the unmet clinical needs in neurodegenerative disorders.

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