JOTCS A
Journal of the Turkish Chemical Society
Section: A
Chemistry

TURKISH CHEMICAL SOCIETY

Exploring Promising Multi-targeted Drug Candidate for Alzheimer's Disease from Compounds Based on Benzalaniline with 1,3,4-Oxadiazole Skeleton: An *In Silico* Modeling and Docking Study

Rahul Kizhakeveedu[1], Devi Thamizhamban[1*], Hariraj Narayanan[2]

[1]Chettinad School of Pharmaceutical Sciences, Chettinad Hospital and Research Institute, CARE, Kelambakkam-603103, Tamil Nadu, India.
[2]Department of Pharmaceutical Sciences, Government Medical College Kannur, 670503, Kerala, India.

Abstract: In general, oxadiazole and benzalaniline derivatives have shown promising activity against a variety of diseases. Combining these two scaffolds into a single drug candidate is a strategy that has garnered increasing interest in multi-targeted drug discovery. This study aims to identify potential ligands from benzalaniline derivatives containing 1,3,4-oxadiazole, targeting various proteins associated with Alzheimer's disease through molecular modeling and docking studies. *In silico* ADME screening was also performed to predict drug-likeness and blood-brain barrier (BBB) permeability, using the QikProp tool from the Schrodinger suit 2023-1 (Maestro 13.5.128). The crystallographic structure of the molecular targets was obtained from the PDB database, specifically Acetylcholinesterase (PDB ID: 4EY7), Butyrylcholinesterase (PDB ID: 4BDS), Monoamine Oxidase (PDB ID: 2V60), and BACE-1 (PDB ID: 7B1P). The designed ligands demonstrated strong affinity with key amino acid residues and their drug-likeness. Along with BBB permeability, it highlights their potential as inhibitors for these targets. In particular, chloro substitution on benzalaniline, combined with hydroxyl aromatic substitution on oxadiazole, exhibited favorable binding affinity with the four receptors selected for this study. A ligand with 3-Chloro and 3'-hydroxy substitution (R139) displayed a strong binding affinity for acetylcholinesterase, with a docking score of -10.247. When the chloro group was positioned at the second site (R114), it was more effective against butyrylcholinesterase, yielding a docking score of -7.723. Furthermore, a ligand with 3-chloro and 4'-hydroxy substitution showed a superior binding score (-10.545) with MAO-B. All proposed compounds fell within the acceptable ADME range (BBB permeability: QPPMDCK value >500; QPlog BB 3 to 1.2). Based on the data presented in this study, the suggested ligands should be considered as potential inhibitors.

Keywords: 1,3,4-Oxadiazole, Benzalaniline, Multi-targeted drug discovery, Alzheimer's disease.

Submitted: March 18, 2024. **Accepted:** August 29, 2024.

Cite this: Kizhakeveedu R, Thamizhamban D, Narayanan H. Exploring Promising Multi-targeted Drug Candidate for Alzheimer's Disease from Compounds Based on Benzalaniline with 1,3,4-Oxadiazole Skeleton: An *In Silico* Modeling and Docking Study. JOTCSA. 2024;11(4): 1473-82.

DOI: https://doi.org/10.18596/jotcsa.1454468

***Corresponding author's E-mail:** devrajmphd@gmail.com

1. INTRODUCTION

Oxadiazole is a compound containing two nitrogen atoms and oxygen atoms in a five-membered ring (1). It exists in several isomeric forms, with 1,2,4-Oxadiazole being the most common. Oxadiazoles have a variety of applications in medicinal chemistry and agrochemicals due to their electronic and physicochemical properties (2). In medicinal chemistry, these compounds exhibit promising activity against cancer, microbial infections, and neurodegenerative disorders. Additionally, they possess anti-inflammatory and antioxidant properties (3).

Bioisosteric replacement is a technique used in drug design to enhance the activity of the original compound. This method is commonly applied in drug discovery to optimize biological activity, selectivity, and safety. Aza-resveratrol is an analog of resveratrol, in which one of the carbon atoms in the structure is replaced by a nitrogen atom (4).

Due to its improved bioavailability and pharmacological properties, this bioisostere-containing molecule may be a promising therapeutic candidate. These aza compounds demonstrate anti-inflammatory and antioxidant properties, as well as the pot-

ential to treat neurological diseases. Resveratrol, a polyphenol found in berries, grapes, and peanuts, is produced by plants in response to fungal infections and injury. As a result, it functions as a phytoalexin, contributing to plant defense. Because of this, resveratrol is believed to offer similar protective benefits in humans (5). Researchers have discovered various benefits of resveratrol in human health, including its anti-aging properties, which keep it under continued scientific investigation.

The nitrogen aton in aza-resveratrol forms a hydrogen bond, which enhances its solubility in aqueous media, thereby improving its bioavailability and therapeutic potential (6). Aza derivatives also exhibit greater stability and a longer shelf life than resveratrol. However, further research is needed to fully understand their pharmacological Properties and to demonstrate their efficacy in humans. Aza-resveratrol primarily consists of benzalaniline (6).

The neurodegenerative process in Alzheimer's disease is both complicated and multifaceted (7), with cognitive decline being the primary symptom. Several pathological mechanisms contribute to the disease. The major factors include oxidative stress, inflammation of the brain, and the accumulation of beta-amyloid and tau protein (Figure 1) (8). Since no single clinical issue can be effectively targeted to treat Alzheimer’s disease, a multifaceted approach is necessary.

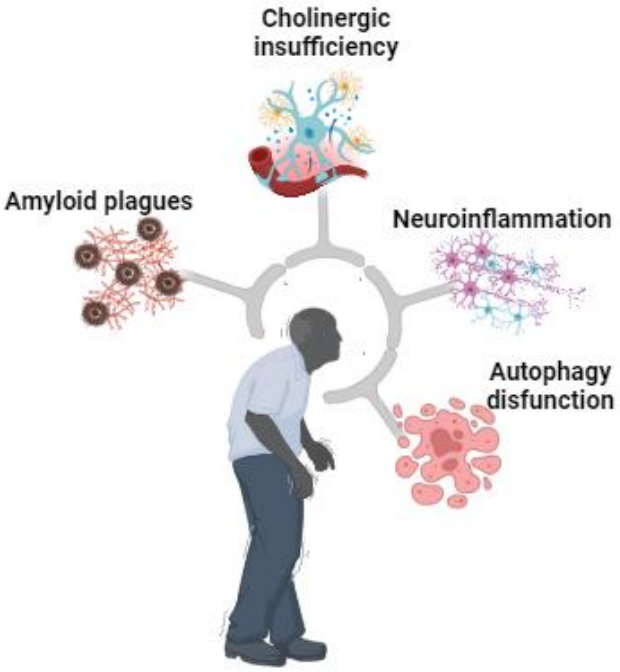


Figure 1: Multiple disease mechanisms of Alzheimer’s Disease.

Multi-targeted drug candidates, i.e., compounds that target various pathways in disease-related processes, are crucial in the development of Alzheimer’s Disease treatments (9,10). Such drugs offer more therapeutic benefits than single-target approaches (11). To prevent the accumulation of tau and amyloid-beta proteins, reduce neuronal inflammation, and promote neuronal survival in Alzheimer’s Disease, the creation of a multi-targeted drug is essential (12). Given that Alzheimer's disease is influenced by multiple clinical factors, this strategy may prove effective. Additionally, by applying these realistic strategies, it may be possible to reduce dosage, toxicity risk, and drug-drug interactions.

Multi-targeted drugs represent an important and effective strategy in the development of new treatments due to their ability to address different pathological processes simultaneously (13). Combining different scaffolds into a single drug framework, known as scaffold hybridization or scaffold merging, is another approach to developing potent and effective drugs (9). This strategy aims to create compounds that incorporate the beneficial properties of both scaffolds, leading to increased potency and efficacy. Scaffold merging can be achieved by covalently linking the two scaffolds (11).

The challenges of bioavailability, toxicity, and selectivity associated with individual scaffolds can be addressed through the fusion of two or more compounds (14). This approach optimizes the pharmacokinetic and pharmacodynamic profiles of the drug and may improve therapeutic outcomes (15). Additionally, scaffold hybridization creates compounds that not only target multiple pathways but are also less likely to lead to drug-resistant (16). A promising strategy for developing new drug candidates for Alzheimer's disease involves the hybridization of oxadiazole with benzalaniline (Figure 2).

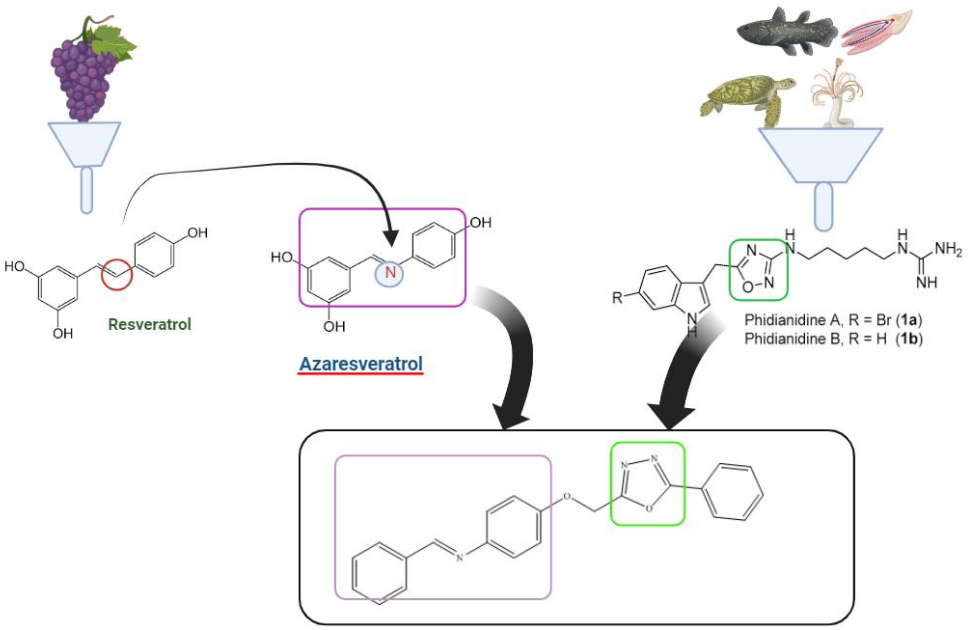


Figure 2: Hybridization of two scaffolds-new strategies for drug discovery.

2. MATERIALS AND METHODS

2.1. Materials

For our study, we utilized the Schrodinger Maestro software suite (2023-1, Maestro 13.5.128) and various biological databases, including the Protein Data Bank (PDB). The tools employed include the 2D sketcher for ligand preparation, Glide for molecular docking, LigPrep for generating flexible and accurate 3D molecular models, SiteMap for predicting binding sites, and QikProp for rapid ADME predictions of compounds. The Protein Data Bank, the only global repository of structural data on biological macromolecules, contains structural information obtained through techniques such as NMR and X-ray crystallography.

2.2. Protein Preparation

The crystal structure of recombinant human acetylcholinesterase in complex with donepezil (PDB ID: 4EY7) at 2.35 A°, human butyrylcholinesterase in complex with tacrine (PDB ID: 4BDS) at 2.1 A°, human beta-secretase (BACE1) (PDB ID: 7B1P) at 1.77 A°, and human MAO B (PDB ID: 2V60) at 2 A° were downloaded from the Protein Data Bank (PDB) and used to model the protein structure in this study. The protein structures were preprocessed and refined using the protein preparation wizard tool from Schrodinger software, version 13.5.128. This process included assigning bond orders, adding missing hydrogen atoms, setting zero-order for metals, creating disulfide bonds, and deleting water molecules beyond 5 A°. The possible ionization states were generated, and the most stable state was selected. Protein structure minimization was performed using the OPLS3e force field (17).

2.3. Preparation of Ligands

The structures of the chemical compounds were designed using the 2D sketch tool in Schrodinger Maestro, version 13.5.128. These ligands were then processed through the LigPrep module in the Schrodinger suite 2023-1. This process involved converting the 2D ligand structures to 3D, optimizing stereochemistry and ionization states, generating tautomeric variations, and performing energy minimization and geometric optimization. Chirality was corrected, missing hydrogens were added, bond orders were adjusted, and charged groups were neutralized. Ionization and tautomeric states were generated using the Epik module. The compounds were then minimized using the OPLS3e force field (18).

2.4. Receptor Grid Generation

Grid generation involves creating a 3D grid of points within the receptor protein (19), representing potential binding sites for a ligand. This helps in calculating interaction energies. The co-crystallized ligands of acetylcholinesterase, butyrylcholines-terase, and beta-secretase enzymes were retained and used for grid preparation (20). This was done using the receptor grid generation tool in Schrodinger. However, in the case of MAO, the sitemap tool was used to identify the largest binding pocket.

2.5. Glide Ligand Docking and ADME Prediction

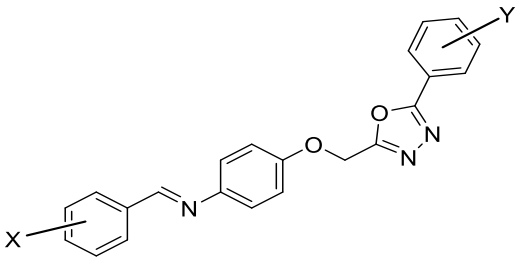
The *in-silico* ADME properties, including BBB permeability and drug-likeness, of the proposed compounds were determined using the Qikprop module in Schrodinger Maestro, Version 13.1.141. Glide docking of the proposed compounds was performed using the previously created receptor grid and the ligand molecules. Positive interactions between the ligand molecules and the receptor were recorded using the Glide ligand docking program. All these calculations were carried out in extra precision (XP) mode, which provides more accuracy compared to other modes (21). QikProp is a module in Schrodinger software that predicts various physicochemical and pharmacokinetic properties of ligand molecules. These predictions include:

1. Property prediction: Molecular weight, log P, polar surface area, hydrogen bond donors, and

acceptors, in line with lead-likeness property prediction (Lipinski's Rule of Five).
2. Pharmacokinetic properties: Oral bioavailability, blood-brain barrier penetration, and CYP450 metabolism. These predictions are useful for prioritizing compounds based on their pharmacokinetic profiles.
3. Lipophilic Efficiency: This module calculates the balance between a compound's lipophilic properties and its potency, helping to identify compounds with optimal hydrophobicity.

3. RESULTS AND DISCUSSION

Based on the availability of chemicals and information gathered from the literature, 150 ligands (R1-R150) were designed using the 2D sketch tool in Schrodinger software (Figure 3). These ligands were then subjected to ligand preparation. ADME properties are crucial in the development of anti-Alzheimer's drugs, as they influence the drug's efficacy, safety, and pharmacokinetic profile. The ADME properties of the synthesized compounds can be predicted *in-silico* using the Qikprop module in the Schrödinger suite 2023-1.



X = ***Ortho, Meta, Para*-Cl,**
***Ortho, Meta, Para*- CH3**

Y = **o-Cl; m-Cl; p-Cl;**
o-CH_3; m-CH_3; p-CH_3
o-Br; m-Br; p-Br
o-F; m-F; p-F
o-OH; m-OH; p-OH
2,3-dihydroxy; 2,4-dihydroxy; 3,4-dihydroxy;
3,5-dihydroxy; 3,4,5-trihydroxy; 2,3,4-trihydroxy
2-methoxy; 3-methoxy; 4-methoxy; 2-CHO

Figure 3: Ligands R1 to R150.

The computed dipole moment of the molecules ranges from 2.535 to 8.006. The total solvent-accessible surface area (SASA) is between 485.52 and 767.341. The hydrophobic components (FOSA) of SASA, i.e., saturated carbon and attached hydrogen, are in the range of 34.228 and 405.756, while the hydrophilic component (FISA) of SASA is in the range of 32 and 216.885. The π component (PISA) of SASA is in the range of 115.719 to 513.439. The number of hydrogen bonds donated by the solute to water molecules in aqueous solution ranges from 0 to 3, while the number of hydrogen bonds formed by the solute from water molecules is between 4.25 and 6.5. The predicted octanol/water partition coefficient values for the compounds are in the range of 1.717 to 6.216. Prediction for binding to human serum albumin (QPlogKhsa) range from -0.372 to 0.98. Some violations of Lipinski's rule of five were observed, with the number of violations ranging from 0 to 1. Out of the 150 compounds, only 57 obey Lipinski's rule. Many of the compounds show human oral absorption percentage between 50 % and 100%. Two parameters were used to predict the blood-brain permeability of the ligands: QplogBB and QPPMDCK. The QPlogBB values for all the compounds fall within the accepted range of -3.00 to 1.2, and the QPPMDCK values are greater than 25 (values below 25 indicate poor permeability, while values above 500 are considered excellent). These results suggest that all the compounds exhibit BBB permeability. Based on the drug-likeness properties and strong BBB permeability, 12 compounds were selected for docking studies (Figure 4). The detailed ADME properties of these 12 compounds are presented in Table 1.

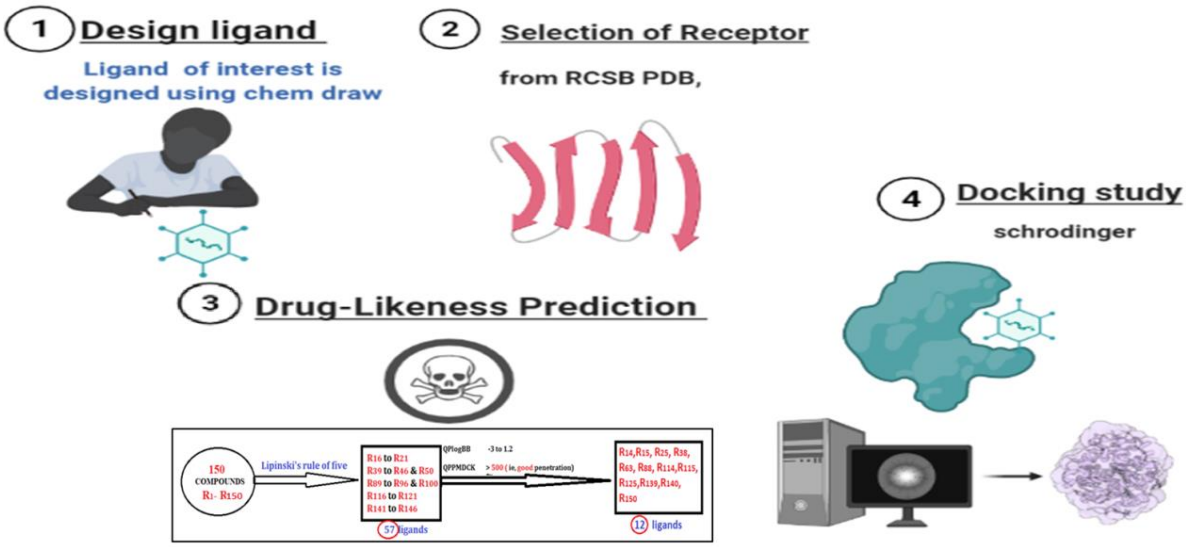


Figure 4: Workflow of the computational study.

Advanced molecular docking using Schrodinger Maestro, version 13.5.128, was conducted to determine the binding affinities of the compounds towards four key receptors involved in Alzheimer's disease. The docking protocol for ligand docking included the following steps: (1) protein preparation with Protein Preparation Wizard, (2) ligand preparation with LigPrep, (3) site prediction with SiteMap, (4) grid generation with the receptor grid generation tool, and (5) ligand docking with Glide.

Predicting the protein binding sites is represented as a group of points called site points (22). Based on the ligand-binding sites, grids were created, with details provided in Table 2 and Figure 5. Ligand docking searches for the best fit and potential interactions between a ligand and the receptor grid. The grid serves as the search area, containing information about the force field surrounding the receptor protein (23).

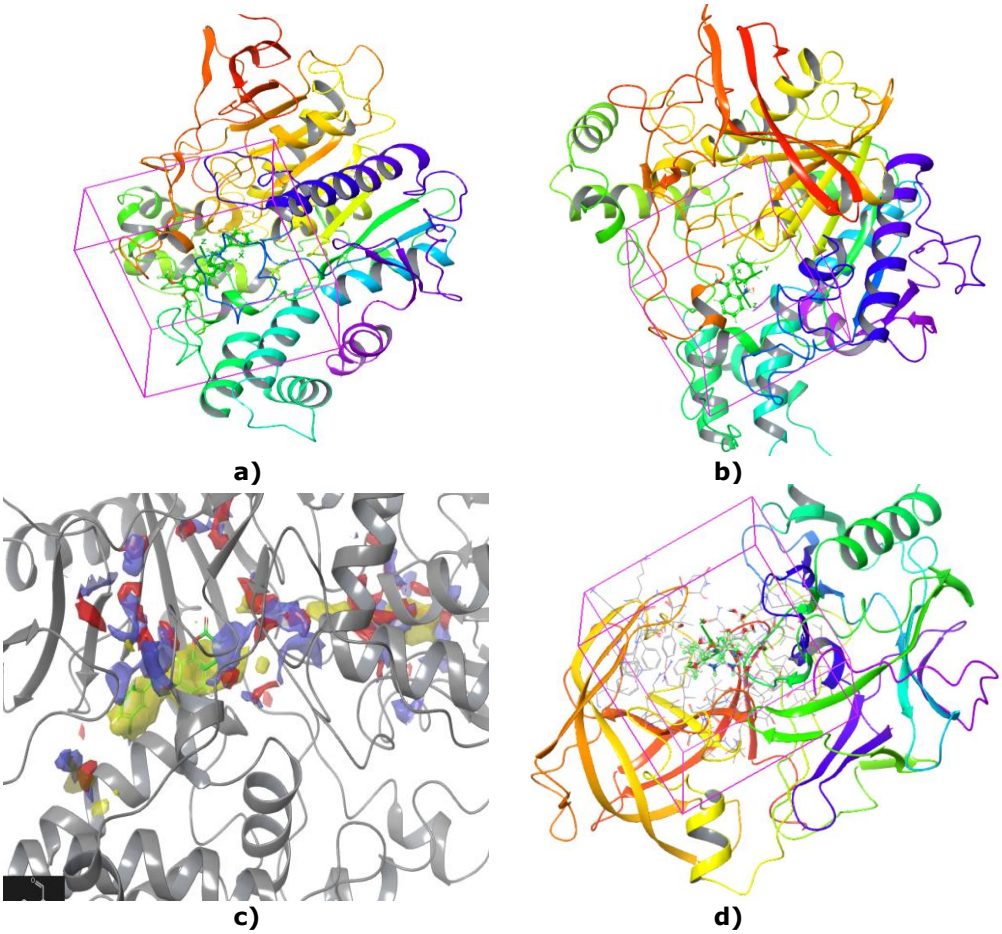


Figure 5: a) 4EY7 with grid box; b) 4BDS with grid box; c) 2V60 with site map; d) 7B1P with grid box.

Table 1: ADME properties of compounds.

Ligands	Dipole	SASA	HB Donor	HB Acceptor	QPlogPo/w	QPlogBB	QPPMDCK	Rule of five (violations)
R14	3.411	734.296	1	5	4.983	-1.095	802.237	0
R15	3.605	734.296	1	5	4.983	-1.095	802.237	0
R25	7.22	742.301	0	6.25	4.651	-0.955	1037.661	0
R38	5.124	721.235	1	5	4.843	-0.999	526.02	0
R63	5.024	727.676	1	5	4.877	-1.011	526.02	0
R88	5.357	736.187	1	5	4.907	-1.036	523.193	0
R114	5.194	730.92	1	5	4.922	-1.12	685.391	0
R115	3.457	730.92	1	5	4.922	-1.12	685.39	0
R125	7.928	737.078	0	6.25	4.587	-0.963	908.692	0
R139	4.013	734.836	1	5	4.986	-1.097	802.234	0
R140	4.078	734.836	1	5	4.986	-1.097	802.234	0
R150	7.649	740.673	0	6.25	4.651	-0.939	1063.453	0
Recommended range	**1 - 12.5**	**300-1000**	**0.0-6.0**	**2 - 20**	**-2 -6.5**	**-3 – 1.2**	**<25 poor >500 good**	**Max 4**

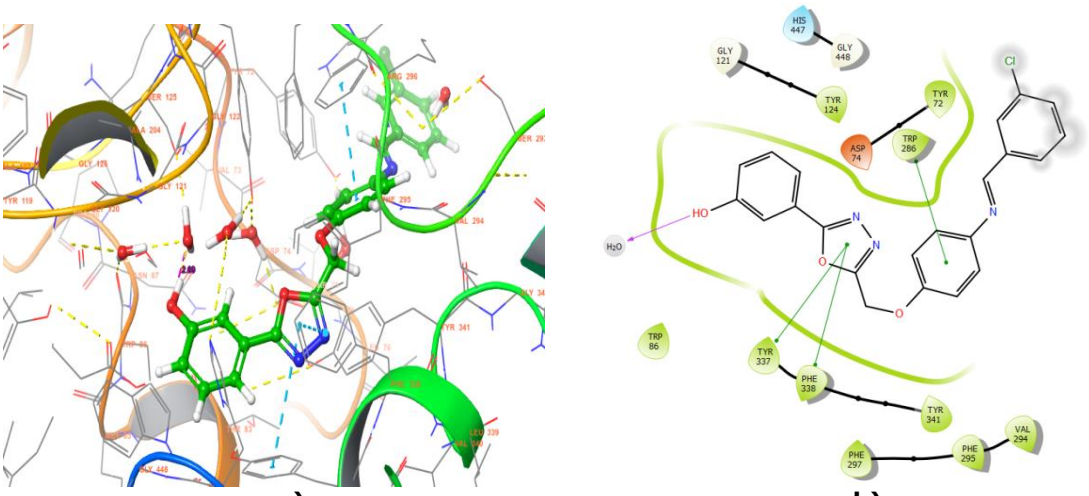
Table 2: Grid box dimensions.

Receptors	Xcent	Ycent	Zcent	Xrange	Yrange	Zrange
4EY7	-14.029	-43.997	27.959	27.782	27.782	27.782
4BDS	133.238	116.200	41.060	21.641	21.641	21.641
2V60	53.794	148.823	21.943	50.345	50.345	50.345
7B1P	29.174	74.215	19.706	24.284	24.284	24.284

The ligands were docked to the receptors, and the results indicated that compound R139 exhibited a strong affinity for acetylcholinesterase compared to other derivatives. In contrast, compounds R114, R88, and R140 demonstrated higher Glide scores with butyrylcholinesterase, BACE-1, and MAO-B, respectively. These variations can be attributed to the different positions of similar functional groups. The findings are detailed in Table 3 and are illustrated by 2D and 3D representations (Figures 6, 7, 8, and 9) of the docked ligands. A hydrogen bond (bond length 2.69 A°) was formed between R139 and a water molecule within the binding site of acetylcholinesterase, highlighting the significance of water molecules within the $3A^{\circ}$ region and their influence on ligand binding in the active site. Additionally, R139 interacts with the amino acid residues TYR 337, PHE 338, and TRP 286 through pi-pi interactions. For butyrylcholinesterase, the ligand R114 exhibited strong affinity, forming a pi-pi bond with PHE 329 and TRP 82 and a hydrogen bond with TYR 332 (bond length 2.06). R88 showed a greater affinity for BACE-1 compared to other ligands, displaying a pi-pi interaction with TYR 71, a hydrogen bond (bond length 2.68) with a water molecule in the binding pocket, and an additional hydrogen bond (bond length 2.09) with ASP 32, involving the oxygen of oxadiazole ring and the benzal aniline nucleus. Moreover, R140 exhibited improved interaction with MAO-B. Chlorine and hydroxyl substitutions vary in position across these four ligands, suggesting that these substitutions are necessary; receptor affinities are affected by their positions. The results are summarized in Table 4. The bioavailability of all four ligands, as predicted using SwissADME, is similar, with each ligand showing a bioavailability score of 0.55.

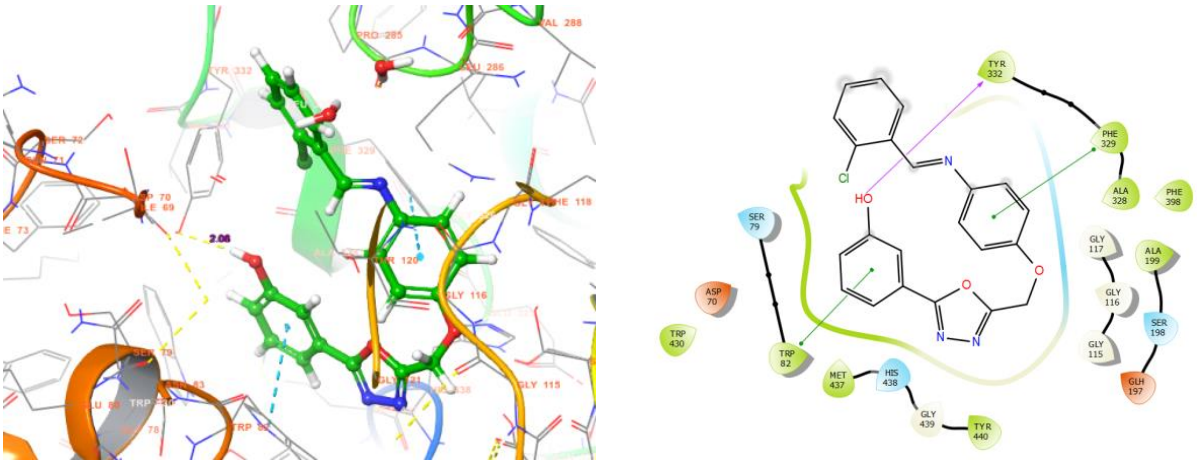
Table 3: Docking studies for compounds.

Ligands	Acetylcholinesterase (PDB ID: 4EY7)		Butyrylcholinesterase (PDB ID: 4BDS)		β Secretase (PDB ID: 7B1P)		MAO-B (PDB ID: 2V60)	
	Docking Score	Glide Score	Docking Score	Glide Score	Docking Score	Glide Score	Docking Score	Glide Score
R14	-7.484	-7.485	-7.314	-7.315	-4.181	-4.182	-7.230	-7.231
R15	-7.600	-7.609	-6.817	-6.826	-2.972	-5.451	-6.906	-6.915
R25	-9.199	-9.199	-6.645	-6.645	-2.702	-2.702	-8.750	-8.750
R38	-9.956	-9.985	-6.808	-6.837	-3.144	-3.173	-6.538	-6.567
R63	-9.994	-10.023	-5.652	-5.681	-2.620	-2.649	-8.135	-8.164
R88	-9.283	-9.311	-4.762	-6.571	-5.185	-5.213	-9.575	-9.604
R114	-9.240	-9.242	-7.723	-7.724	-2.860	-2.861	-7.248	-7.249
R115	-9.176	-9.185	-6.642	-6.651	-2.456	-2.465	-9.158	-11.637
R125	-9.351	-9.351	-6.829	-6.829	-2.901	-2.901	-5.868	-5.868
R139	-10.247	-10.248	-6.828	-6.829	-3.862	-3.863	-8.014	-8.015
R140	-9.398	-9.407	-4.555	-4.564	-3.049	-3.058	-10.545	-10.555
R150	-9.190	-9.190	-7.300	-7.300	-2.192	-2.192	-9.728	-9.728
Ligands having High affinity	**R139**		**R114**		**R88**		**R140**	



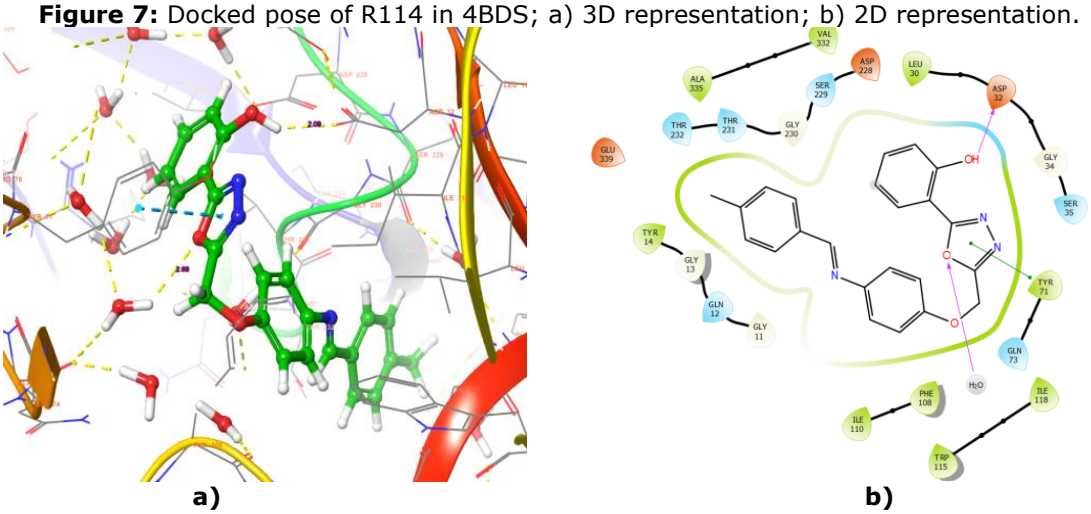
a) **b)**

Figure 6: Docked pose of R139 in 4EY7; a)3D representation; b) 2D representation.



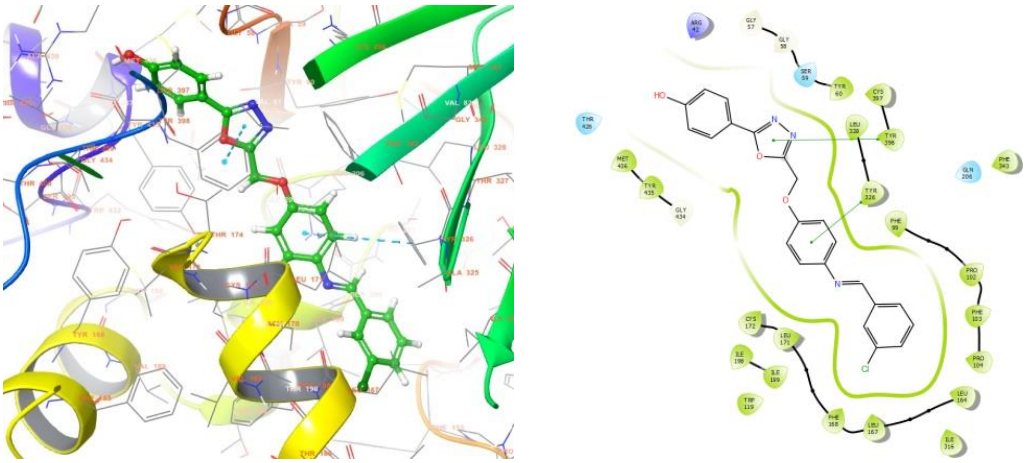
a) **b)**

Figure 7: Docked pose of R114 in 4BDS; a) 3D representation; b) 2D representation.



a) **b)**

Figure 8: Docked pose of R88 in 7B1P; a) 3D representation; b) 2D representation.

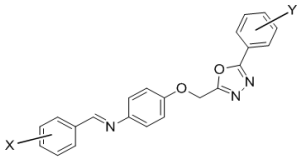


a) **b)**

Figure 9: Docked pose of R140 in 2V60; a- 2d representation; b- 2D representation.

Table 4: Summary of result.

Basic structure



Ligand	X	Y'	Affinity with
R 139	3-Cl	3'-OH	Acetylcholinesterase (4EY7)
R114	2-Cl	3'-OH	Butyrylcholinesterase (4BDS)
R140	3-Cl	4'-OH	MAO β (2V60)
R88	4-CH3	1'-OH	BASE (7B1P)

4. CONCLUSION

A computer-based approach was used to identify potential drug candidates for treating Alzheimer's disease, focusing specifically on a group of chemical compounds known as 1,3,4-oxadiazole derivatives with benzal aniline. These compounds were validated through docking simulations, which demonstrated their ability to effectively bind to the active sites of four different receptors in the brain that are known to play a role in Alzheimer's disease. This *in-silico* approach helped to identify promising lead compounds for further investigation. In this study, we conclude that a series of chloro-substituted benzal aniline compounds combined with hydroxyl aromatic-substituted 1,3,4-oxadiazole showed inhibitory activity against the four key receptors. Specifically, R139, R114, R88, and R140 demonstrated significant anti-Alzheimer activity. The ADME analysis also confirmed that all these ligands possess the necessary ADME properties required for anti-Alzheimer's activity. With further testing and refinement, these candidates may serve as promising drug treatments for Alzheimer's disease in the future.

5. CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding this publication.

6. ACKNOWLEDGMENT

The authors express their gratitude to Shahin Muhammed, Assistant Professor at the College of Pharmaceutical Sciences, Government Medical College Kannur, for providing the necessary facilities to conduct this study.

7. REFERENCES

1. Bajaj S, Asati V, Singh J, Roy PP. 1,3,4-Oxadiazoles: An emerging scaffold to target growth factors, enzymes and kinases as anticancer agents. Eur J Med Chem [Internet]. 2015 Jun 5;97:124–41. Available from: <URL>.

2. Vaidya A, Pathak D, Shah K. 1,3,4-oxadiazole and its derivatives: A review on recent progress in anticancer activities. Chem Biol Drug Des [Internet]. 2021 Mar 27;97(3):572–91. Available from: <URL>.

3. Qadir T, Amin A, Sharma PK, Jeelani I, Abe H. A review on medicinally important heterocyclic compounds. Open Med Chem J [Internet]. 2022 Apr 28;16(1):e187410452202280. Available from: <URL>.

4. Deacon RMJ. A novel approach to discovering treatments for Alzheimer's disease. J Alzheimers Dis Park. 2014;4(2):142–5.

5. Lizard G, Latruffe N, Vervandier-Fasseur D. Aza-

and Azo-stilbenes: Bio-isosteric analogs of resveratrol. Molecules [Internet]. 2020 Jan 30;25(3):605. Available from: <URL>.

6. Siddiqui A, Dandawate P, Rub R, Padhye S, Aphale S, Moghe A, et al. Novel aza-resveratrol analogs: Synthesis, characterization and anticancer activity against breast cancer cell lines. Bioorg Med Chem Lett [Internet]. 2013 Feb 1;23(3):635–40. Available from: <URL>.

7. Alanazi FK, Radwan AA, Aou-Auda H. Molecular scaffold and biological activities of anti-alzheimer agents. Trop J Pharm Res [Internet]. 2022 Apr 28;21(2):439–51. Available from: <URL>.

8. Melchiorri D, Merlo S, Micallef B, Borg JJ, Dráfi F. Alzheimer's disease and neuroinflammation: will new drugs in clinical trials pave the way to a multi-target therapy? Front Pharmacol [Internet]. 2023 Jun 2;14:1196413. Available from: <URL>.

9. Kumar N, Kumar V, Anand P, Kumar V, Ranjan Dwivedi A, Kumar V. Advancements in the development of multi-target directed ligands for the treatment of Alzheimer's disease. Bioorg Med Chem [Internet]. 2022 May 1;61:116742. Available from: <URL>.

10. Hasan AH, Abdulrahman FA, Obaidullah AJ, Alotaibi HF, Alanazi MM, Noamaan MA, et al. Discovery of novel coumarin-schiff base hybrids as potential acetylcholinesterase inhibitors: Design, synthesis, enzyme inhibition, and computational studies. Pharmaceuticals [Internet]. 2023 Jul 6;16(7):971. Available from: <URL>.

11. Alcaro S, Bolognesi ML, García-Sosa AT, Rapposelli S. Editorial: Multi-Target-Directed Ligands (MTDL) as challenging research tools in drug discovery: from design to pharmacological evaluation. Front Chem [Internet]. 2019 Feb 18;7:448718. Available from: <URL>.

12. Alarcón-Espósito J, Mallea M, Rodríguez-Lavado J. From hybrids to new scaffolds: the latest medicinal chemistry goals in multi-target directed ligands for alzheimer's disease. Curr Neuropharmacol [Internet]. 2021 May 27;19(6):832–67. Available from: <URL>.

13. Ibrahim M, Gabr M. Multitarget therapeutic strategies for Alzheimer's disease. Neural Regen Res [Internet]. 2019 Mar 1;14(3):437–40. Available from: <URL>.

14. Cummings J, Zhou Y, Lee G, Zhong K, Fonseca J, Cheng F. Alzheimer's disease drug development pipeline: 2023. Alzheimer's Dement Transl Res Clin Interv [Internet]. 2023 Apr 25;9(2):e12179. Available from: <URL>.

15. Choubey PK, Tripathi A, Tripathi MK, Seth A, Shrivastava SK. Design, synthesis, and evaluation of N-benzylpyrrolidine and 1,3,4-oxadiazole as multitargeted hybrids for the treatment of Alzheimer's disease. Bioorg Chem [Internet]. 2021 Jun 1;111:104922. Available from: <URL>.

16. Wang Y, Sun Y, Guo Y, Wang Z, Huang L, Li X. Dual functional cholinesterase and MAO inhibitors for the treatment of Alzheimer's disease: synthesis, pharmacological analysis and molecular modeling of homoisoflavonoid derivatives. J Enzyme Inhib Med Chem [Internet]. 2015 Mar 23;31(3):389–97. Available from: <URL>.

17. Remya C, Dileep KV, Koti Reddy E, Mantosh K, Lakshmi K, Sarah Jacob R, et al. Neuroprotective derivatives of tacrine that target NMDA receptor and acetyl cholinesterase – Design, synthesis and biological evaluation. Comput Struct Biotechnol J [Internet]. 2021 Jan 1;19:4517–37. Available from: <URL>.

18. Mehta S, Pathak SR. In silico drug design and molecular docking studies of novel coumarin derivatives as anticancer agents. Asian J Pharm Clin Res [Internet]. 2017 Apr 1;10(4):335–40. Available from: <URL>.

19. Tantoso E, Wahab HA, Chan HY. Molecular docking: An example of grid enabled applications. New Gener Comput [Internet]. 2004 Jun;22(2): 189–90. Available from: <URL>.

20. Ali SK, Hamed AR, Soltan MM, El-Halawany AM, Hegazy UM, Hussein AA. Kinetics and molecular docking of vasicine from Adhatoda vasica : An acetylcholinesterase inhibitor for Alzheimer's disease. South African J Bot [Internet]. 2016 May 1;104:118–24. Available from: <URL>.

21. Friesner RA, Murphy RB, Repasky MP, Frye LL, Greenwood JR, Halgren TA, et al. Extra precision glide: Docking and scoring incorporating a model of hydrophobic enclosure for protein−ligand complexes. J Med Chem [Internet]. 2006 Oct 1;49(21):6177–96. Available from: <URL>.

22. Ban T, Ohue M, Akiyama Y. Multiple grid arrangement improves ligand docking with unknown binding sites: Application to the inverse docking problem. Comput Biol Chem [Internet]. 2018 Apr 1;73:139–46. Available from: <URL>.

23. Pissurlenkar R, Shaikh M, Iyer R, Coutinho E. Molecular mechanics force fields and their applications in drug design. Antiinfect Agents Med Chem [Internet]. 2009 Apr 1;8(2):128–50. Available from: <URL>.