Abdulganiyyu et al. J Biomed & App Sci FUD (2025) 4:1
www.jobas.fud.edu.ng
ISSN: 2814-3221 (print), ISSN: 2955-0874 (online)

JOBASFUD

Journal of Biomedical and Applied Sciences

RESEACH ARTICLE

Computational Analysis of Potent Hybrid Compounds for Alzheimer's Disease; Virtual Screening, Molecular Dynamic Simulation, and Pharmacokinetic Evaluation

Ibrahim A. Abdulganiyyu [1, *], Abduljelil Ajala[2], Maimuna Shehu Rufai[1], Balogun Joshua Babalola[3], Balogun Sadia Ufeli [4], Nazifi Abbas[3]. Ibrahim Sani Ahmad[1]. Jamil Dauda Usman[5]. Kabiru M. Aujara[6], Abbas Sambo[7]

[1] Department of Public and Environmental Health, Federal University Dutse,
[2]Department of Chemistry, Faculty of Physical Sciences, Ahmadu Bello University, Zaria, Nigeria.
[3]Department of Biological Sciences Federal University Dutse
[4]Department of Human Anatomy Federal University Dutse
[5]Department of Human Physiology Federal University Dutse
[6]Department of Science Laboratory Technology, Jigawa State Polytechnic Dutse
[7] Ministry of Higher Education Science and Technology Dutse, Jigawa State.

Abstract

Background: Alzheimer's disease (AD) is a complex neurodegenerative disorder lacking effective therapeutic solutions. Hybrid molecules with multitarget potential are gaining attention as viable candidates to slow or halt AD progression. Computational-aided drug design offers a cost-effective and efficient method to identify promising drug leads with desirable pharmacological traits. This study investigates hybrid compounds as potential inhibitors of key AD-related proteins using virtual screening, molecular docking, and pharmacokinetic profiling. **Methods:** Twenty-five hybrid compounds were selected for virtual screening through molecular docking against critical AD-associated enzymes and receptors. Docking scores were used to assess binding affinities and interaction strengths. Top-performing candidates were analysed using LIGPLOT+ v2.2.7 for 2D interaction maps and PyMOL v2.5 for 3D structural visualization. Furthermore, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) predictions were conducted to evaluate drug-likeness and safety profiles. **Results**: Out of the 25 compounds screened, ten exhibited notable binding affinities. Compounds 3 (-37.41 kcal/mol), 19 (-35.68 kcal/mol), and 20 (-36.88 kcal/mol) outperformed the reference compound (-26.30 kcal/mol) in docking scores. Key residues such as ASN349, PHE168, and SER67 were identified as critical for hydrogen bonding and hydrophobic interactions, potentially influencing neurotransmitter pathways involving dopamine and norepinephrine. ADMET predictions further indicated favourable pharmacokinetic properties and minimal toxicity. **Conclusion:** The study identified several promising hybrid molecules with strong in-silico inhibitory activity against AD-related targets. Their favorable binding profiles and pharmacokinetics highlight their potential as anti-AD agents. These findings provide a strong foundation for future in-vitro and in-vivo investigations aimed at validating their clinical relevance in Alzheimer's therapy

Keywords: Alzheimer's Disease, Hybrid inhibitors, Receptor, Docking, Pharmacokinetic

INTRODUCTION

Alzheimer's disease (AD) is a major form of global brain dysfunction, manifesting through behavioural changes, including cognitive decline, memory loss, reduced mindfulness, and overall deterioration of mental health (Calabrò et al., 2021; Thies & Bleiler, 2013) . It primarily affects elderly individuals and is characterised by these neurodegenerative symptoms (Iskusnykh et al.,

* Corresponding Author: Ibrahim A. Abdulganiyyu,
Tel: +238154766430
E-mail: aaibrahim@fud.edu.ng

2024; Ueha et al., 2024). Despite extensive research into AD's pathophysiology, the disease remains incurable. However, certain mechanisms, such as the accumulation of extracellular β-amyloid (Aβ) plaques and intracellular neurofibrillary tangles (NFTs), are recognised as playing a role in its development(Gulisano et al., 2019; Naik et al., 2025; Neațu et al., 2024).

Currently, treatment options are severely limited, with only three acetylcholinesterase (AChE) inhibitors (rivastigmine, donepezil, and galantamine) and one N-Methyl-D-Aspartate receptor (NMDA) antagonist (memantine) approved for use (Marucci et al., 2021; Singh et al., 2024).

However, all AChE inhibitors were later withdrawn due to dose-dependent hepatotoxicity (Kaur Gulati et al., 2022; Saify & Sultana, 2014).

Given the complex nature of AD, there is an urgent need to develop bioactive compounds with multitarget capabilities that can potentially mitigate or reverse the damage caused by the disease. Due to the multifactorial nature of AD, single-target therapies have proven inadequate, making multitarget directed ligands (MTDLs), especially hybrid compounds, a more promising approach (Spinelli et al., 2025; Yoo et al., 2025).

These hybrid compounds can simultaneously target multiple bioactive sites while minimising toxicity and reducing the cost of preclinical trials (Doostmohammadi et al., 2024; Shaaban et al., 2025).

The method of designing hybrid molecules offers advantages over conventional approaches by targeting multiple mechanisms, leading to faster and more cost-effective results (Clifton et al., 2017; Sampath Kumar et al., 2020a; Soltan et al., 2021).

As such, hybrid compounds have emerged as promising anti-Alzheimer's agents ((González et al., 2019; Núnez et al., 2019)). This study employed computational-aided drug design to address the ongoing damage caused by AD. Computational methods have been highlighted in the literature as vital for in-silico screening, simulation, and (Agamah et al., 2020; Ejeh et al., 2021) of potential therapeutic inhibitors for AD. The structure of the fusion G-protein-coupled receptor (GPCR) was selected as the protein target for this research due to its versatility in exploring various protein designs and its role in generating structures of antagonist-bound A2A adenosine receptors at low resolution during simulations(Addis et al., 2024; Keri & Barth, 2018; Lee et al., 2018).

Moreover, the receptor's lack of mutations and its specificity to Homo sapiens make it an ideal target for this study(Schöneberg & Liebscher, 2021).

This study screened the potent, non-toxic hybrid compounds virtually, perform molecular simulations on the selected compounds, and predict their drug-like properties to assess their potential as therapeutic agents against Alzheimer's disease.

Methodology

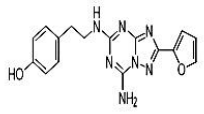
A previously reported study on synthesised anti-Alzheimer hybrid compounds was adopted in this study(Jana et al., 2018; Orioli et al., 2024; K. Wang et al., 2021).

Twenty-five identified therapeutic hybrid inhibitors with potentials against AD were employed in this research. The chemical structures of the compounds were drawn with the aid of ChemDraw Professional *v*. 16.0. It was saved in SD Mol file format recognised by Spartan'14, a bioinformatics software.

The imported structures were converted from two-dimensional (2D) to three-dimensional (3D) and minimised for better and more stable structures.

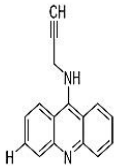
The 3D structures undergo optimisation and calculation in Spartan software using a method previously reported (Omolara, 2018). Figur 1s shows the 2D hybrid structures with their IUPAC identification from the literature.

Starting / Reference



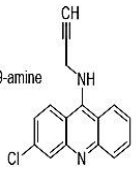
4-(2-((7-amino-2-(furan-2-yl)-[1,2,4]triazolo[1,5-a][1,3,5]triazin-5-yl)amino)ethyl)phenol

1



N-(prop-2-yn-1-yl)acridin-9-amine

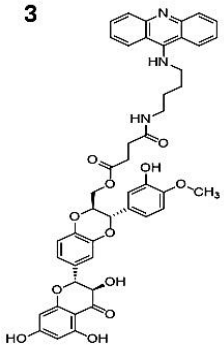
2



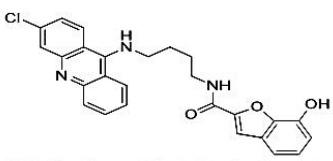
3-chloro-*N*-(prop-2-yn-1-yl)acridin-9-amine

((2*S*,3*S*)-3-(3-hydroxy-4-methoxyphenyl)-6-((2*R*,3*R*)-3,5,7-trihydroxy-4-oxochroman-2-yl)-2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)methyl 4-((4-(acridin-9-ylamino)butyl)amino)-4-oxobutanoate

3



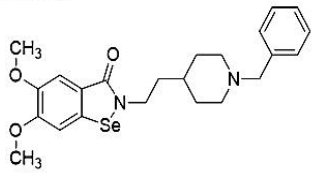
4



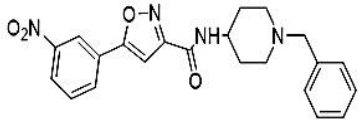
N-(4-((3-chloroacridin-9-yl)amino)butyl)-7-hydroxybenzofuran-2-carboxamide

2-(2-(1-benzylpiperidin-4-yl)ethyl)-5,6-dimethoxybenzo[*d*][1,2]selenazol-3(2*H*)-one

5

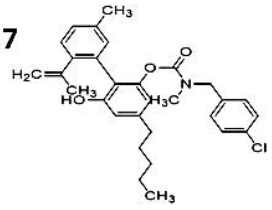


6



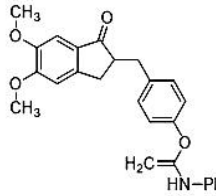
N-(1-benzylpiperidin-4-yl)-5-(3-nitrophenyl)isoxazole-3-carboxamide

7



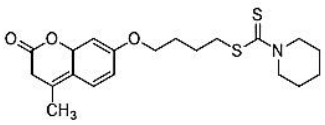
6-hydroxy-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-[1,1'-biphenyl]-2-yl (4-chlorobenzyl)(methyl)carbamate

8



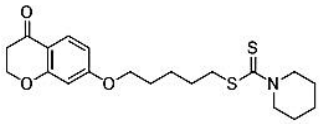
5,6-dimethoxy-2-(4-((1-(phenylamino)vinyl)oxy)benzyl)-2,3-dihydro-1*H*-inden-1-one

9



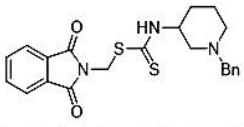
4-((4-methyl-2-oxo-3,8a-dihydro-2*H*-chromen-7-yl)oxy)butyl piperidine-1-carbodithioate

10



5-((4-oxochroman-7-yl)oxy)pentyl piperidine-1-carbodithioate

10



(1,3-dioxoisoindolin-2-yl)methyl (1-benzylpiperidin-3-yl)carbamodithioate

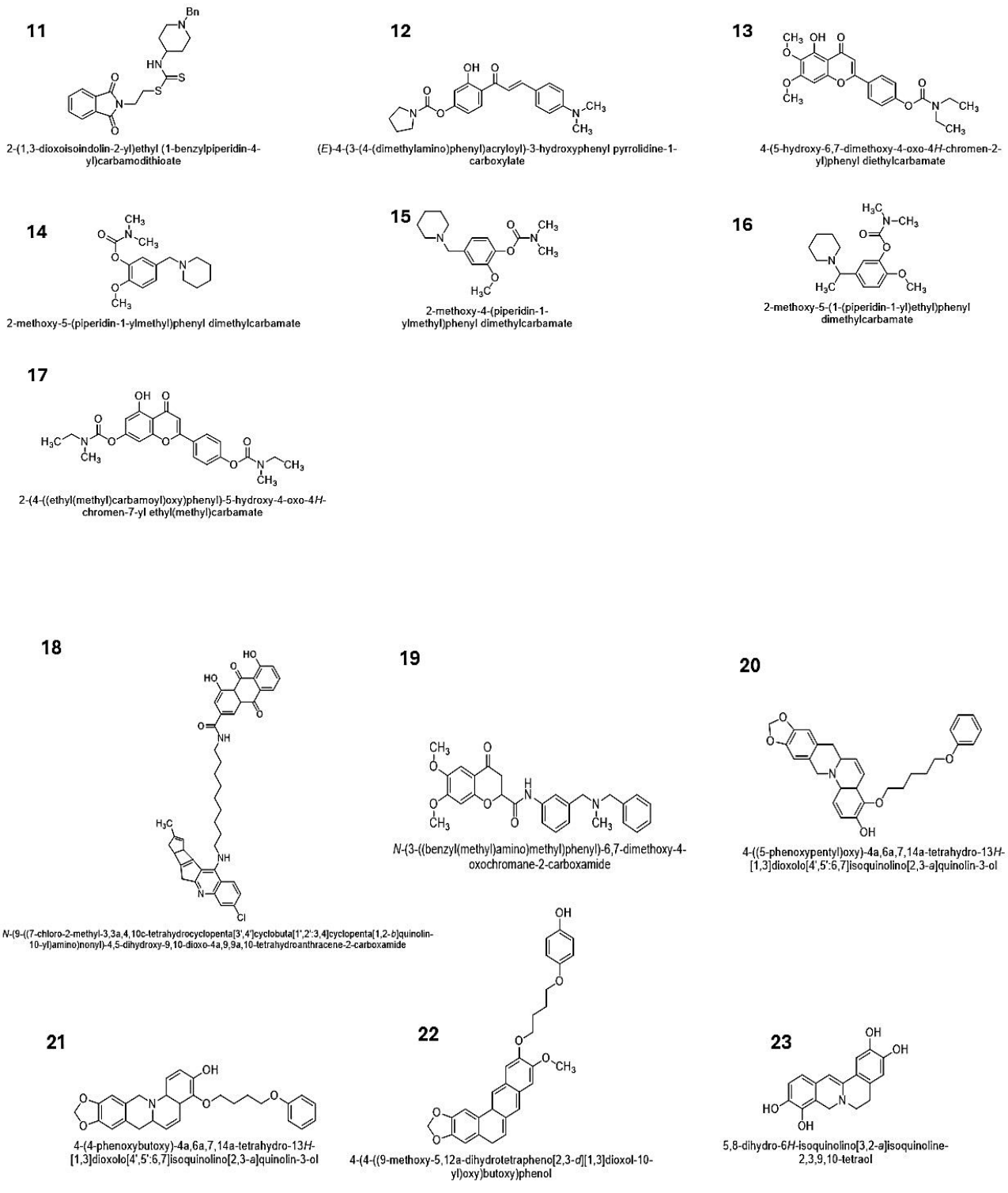


Figure 1s: Hybrid molecular structures, along with their IUPAC names

2.1 ***Protein Target Retrieval, Preparation, and Ramachandran Plot Analysis;***

The raw structure of the fusion G-protein-coupled receptor (GPCR) protein target was obtained from the Protein Data Bank (PDB) (*www.rcsb.org*), as shown in Figure 1. The receptor was prepared using PyMOL Molecular Graphics System *v*. 2.5.4, enabling analysis of different fusion protein designs, resulting in structures such as the antagonist-bound A2A adenosine receptor at a resolution of 3.4 Å and the unliganded Smoothened receptor at 3.7 Å. This study applied previously established methodologies to resolve small membrane proteins and GPCR structures (Maeda & Schertler, 2013; M. Zhang et al., 2024) . Figure 2 illustrates the 2D Ramachandran plot for the adenosine A2A receptor, representing amino acid conformations within the protein and providing structural insights into the target. The Ramachandran plot also informs the design of unnatural biocatalysts and protein-based therapeutic agents (Gunasekaran et al., 1996; Hooft et al., 1997; Lakshmi, Ramakrishnan, et al., 2014; Lakshmi, Sinduja, et al., 2014).

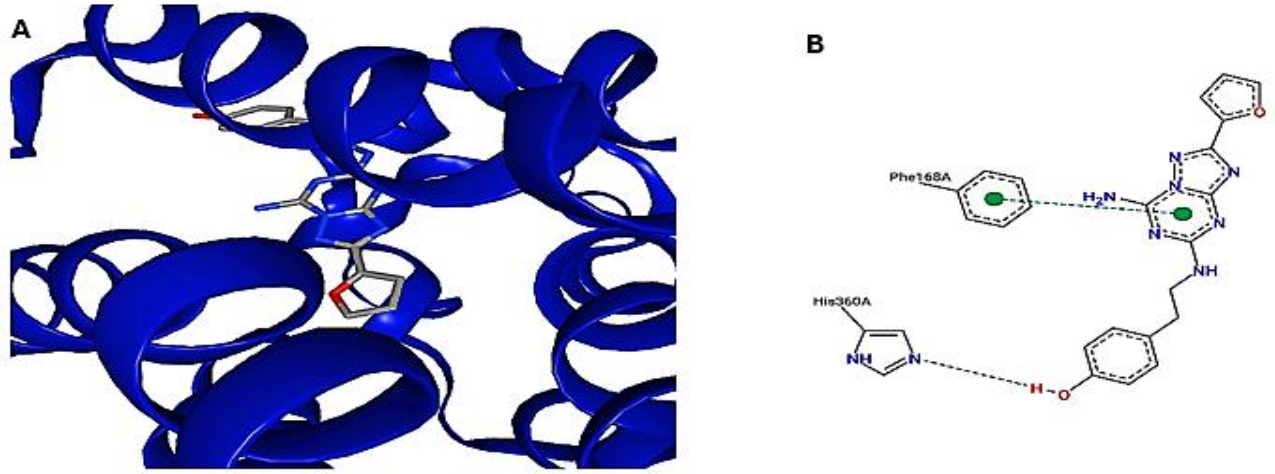


Figure 1: **a**) Prepared protein target in complex PDB ID: 5IU4 **b**) antagonist ligand (ZM241385) structure

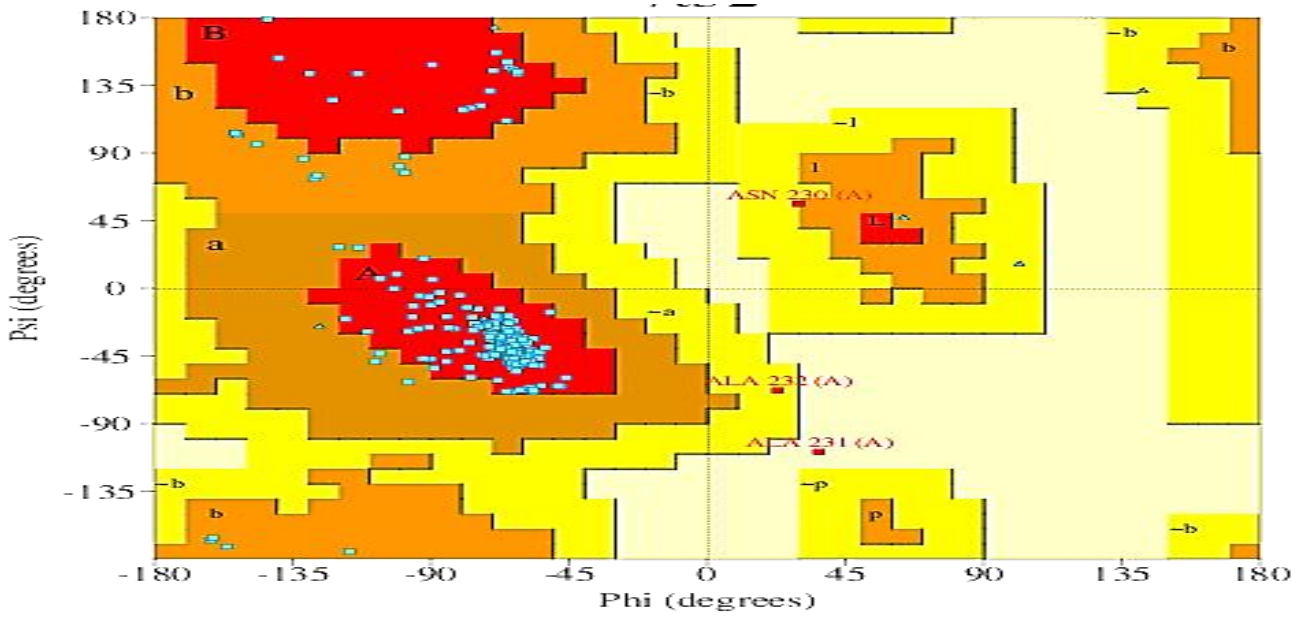


Figure 2: Ramachandran plot of Adenosine 2A receptor

Docking Studies and Inhibitor Screening

ICM-Pro has been recognised as a highly effective docking tool (Goswami et al., 2024; Mathur et al., 2024; Neves et al., 2012) and was used in this study to dock hybrid compounds to the protein target following the removal of embedded ligands, including the reference antagonist inhibitor(Mandal & Mandal, 2024; Meng et al., 2012; Mishra et al., 2024). Binding site determination was carried out with a grid box size of 40 × 40 × 40 along the x, y, and z axes at the start of molecular docking simulations. This grid encompassed the entire enzyme at a spacing of 0.570 Å, as depicted in Figure 3. LIGPLOT+ V 2.2.7 was used to examine the lowest energy conformations and their interactions, including hydrophobic, hydrogen-bonding, and electrostatic interactions.

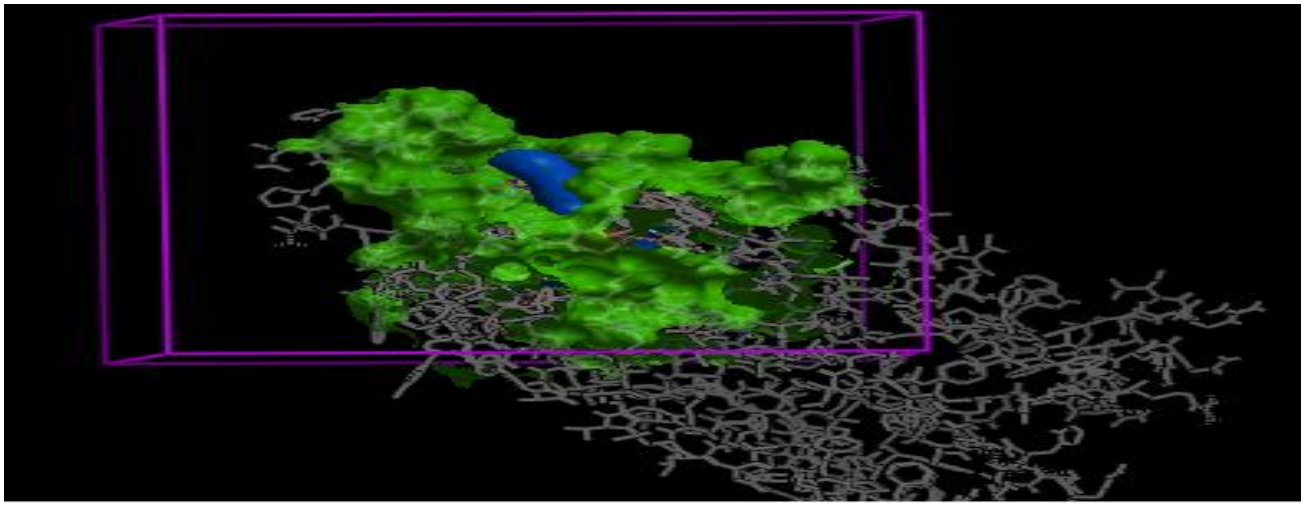


Figure 3: Active site of the receptor (colour: blue)

Results and Discussion

Pharmacokinetic Prediction of Screened Compounds

SwissADME, a web-based tool, was used to assess the pharmacokinetic potential of the *in-silico* screened compounds (Ajala et al., 2024, 2025; Daina et al., 2017). This choice was informed by the observation that certain compounds exhibited superior docking scores and binding affinities compared to reference compounds (Abdullahi et al., 2024; Elsaman et al., 2025).

Pharmacokinetic predictions included key ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) parameters, known for their effectiveness in providing reliable kinetics data across various molecules (Sucharitha et al., 2022; Thomas-Brown et al., 2023; White, 2017). Additionally, radar plots and the BOILED-egg model were employed to ensure comprehensive and statistically sound predictions(Daina & Zoete, 2016).

Mechanical Interpretation of the Ramachandran Statistical Plot

Table 2 presents the two dihedral angles for each amino acid residue. The Ramachandran plot, with a resolution model of 2Å, yields a favourable Rama-Z score, effectively highlighting the conformational diversity within the protein. Glycine stands out in the plot due to its lack of a side chain, allowing it to occupy a larger region due to its adaptable conformation.

Certain areas are intensely shaded in the plot, with the most favourable regions shown in red, comprising over ninety percent of residues. This indicates the core φ-ψ values for optimal amino acid positioning where the symbols φ (phi) and ψ (psi) refer to torsion angles (also called dihedral angles) in the backbone of a polypeptide or protein. These are fundamental in determining the secondary structure (like α-helices and β-sheets) of proteins. Phi torsion angle: The angle around the bond between the nitrogen (N) and the alpha carbon (Cα) while Psi torsion angle is the angle around the bond between the alpha carbon (Cα) and the carbonyl carbon (C'). In a

biological context, the plot is valuable for visualising the psi and phi angles in amino acid residues, as represented by the dihedral Ramachandran model. Additionally, the forbidden regions help prevent steric clashes between atoms. Overall, the protein used in this study demonstrates excellent quality with 100 percent favourable conformational scoring.

Table 2: Ramachandran statistical plot

PROCHECK Computed parameters statistics plots of Ramachandran		
Stereo-chemical Parameter	Calculated values	
	No of residue	Percentage
Present residue at the most favoured region [A, B, L]	320	93.6
Additionally, allowed region Residue [a, b, l, p]	19	5.6
Generously allowed residue [~a, ~b, ~l, ~p]	2	0.6
Disallowed regions residue [XX]	1	0.3
Non-residues (Glycine and proline)	342	100

The results of the simulation and virtual screening of a few chosen compounds are displayed in Table 3. Ten compounds (3, 4, 6, 8, 11, 18, 19, 20, 21, and 24) were found to have better interactions and lower docking scores than the reference compound See Figure 1s after close examination. These substances feature superior amino acid chains, hydrophobic interactions, and hydrogen bonding.

As shown in Table 3 findings, different locations within the tested compounds were identified using LIGPLOT+ software. All virtual screening inhibitors shared a few residue sites after closely examining the binding sites and the reference molecule. These residues include ASN349, PHE168, and SER67, previously documented in a study by (Abdulganiyyu et al., 2019; Akinbo, Ajala, et al., 2024; Akinbo, Rufa'i, et al., 2024) . It is implied that the suggested compounds may be used as anti-Alzheimer disease agents since the tested inhibitors share a residue location with the cited substance.

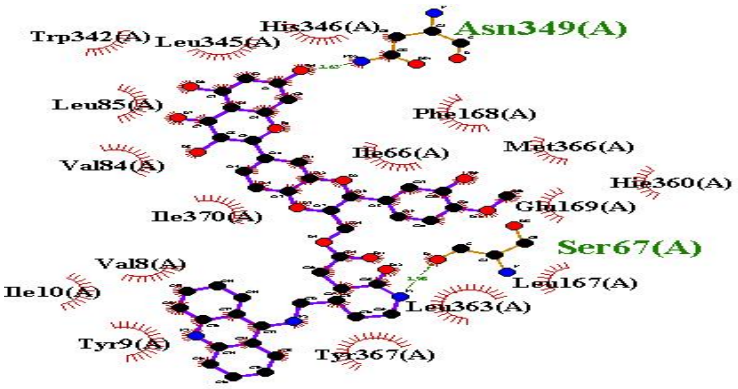
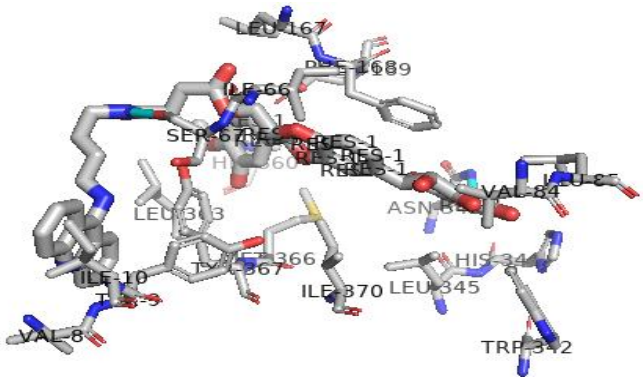
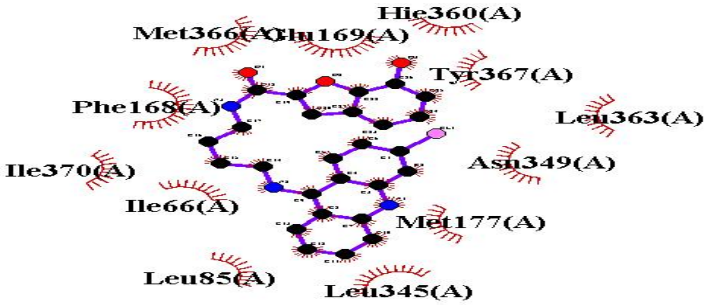
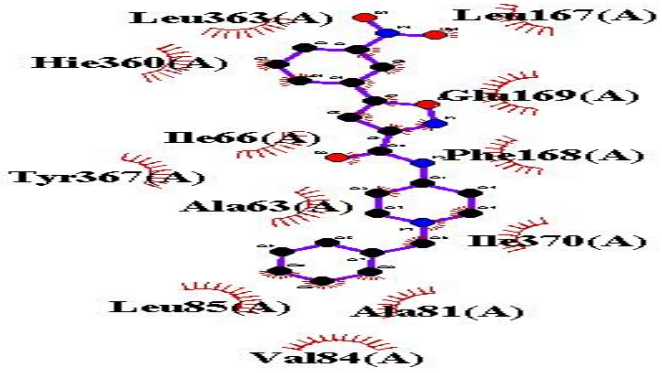
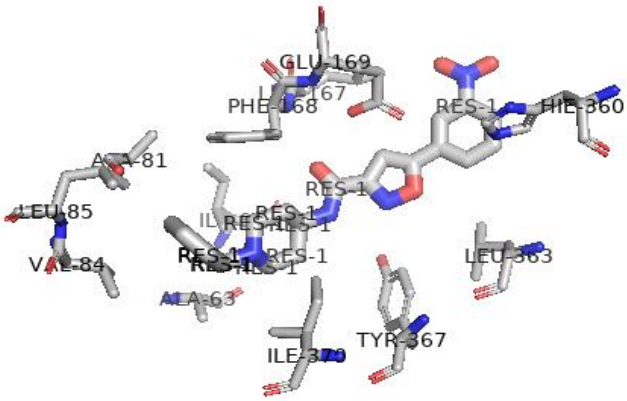
Table 3: Docking scores of screened compounds

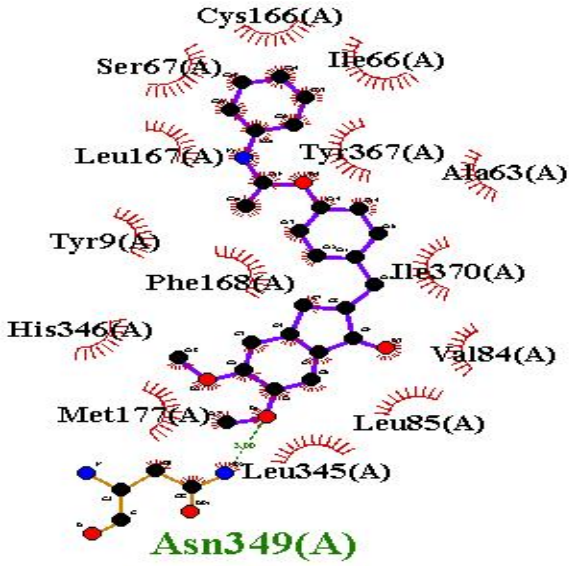
Compound Identity	Gibb's free energy (kcal/mol)	Residues predicted sites
3	-37.41	TRP^{342}, LEU^{345}, HIS^{346}, ASN^{349}, LEU^{85}, VAL^{84}, ILE^{370}, VAL^{8}, ILE^{10}, TYR^{9}, TYR^{367}, LEU^{363}, LEU^{167}, SER^{67}, GLE^{169}, HIS^{360}, MIT^{366}, ILE^{66}, and PHE^{168}
4	-30.94	HIE^{360}, MET^{366}, GLU^{169}, PHE^{168}, TYR^{367}, ILE^{370}, ILE^{66}, LEU^{85}, LEU^{345}, MET^{177}, ASN^{349}, LEU^{363}, SER^{67}
6	-28.17	LEU^{363}, HIE^{360}, ILE^{66}, TYR^{367}, ALA^{63}, LEU^{85}, VA^{L84}, ALA^{81}, ILE370, PHE^{168}, GLU^{169}, LEU^{167}
8	-29.41	CYS^{166}, SER^{67}, LEU^{167}, TYR^{9}, PHE^{168}, HIS^{346}, MET^{177}, ASN^{349}, LEU^{345}, LEU^{85}, VAL^{184}, ILE^{370}, ALA^{63},TYR^{367}, ILE^{66}
11	-26.56	MET^{366}, ASN^{349}, LEU^{345}, MET^{177}, ALA^{81}, ILE^{370}, TYR^{9}, TYR^{367}, SER^{67}, ILE^{66}, ALA^{63}, PHE^{168}, HIS^{374}, VAL^{84}
18	-27.46	CYS^{166}, SER^{67}, LEU^{167}, TYR^{9}, PHE^{168}, HIS^{346}, MET^{177}, ASN^{349}, LEU^{345}, LEU^{85}, VAL^{84}, ILE^{370}, ALA^{63}, TYR^{367}, ILE^{66}
19	-35.68	THR^{68}, TYR^{9}, SER^{67}, ILE^{80}, ALA^{63}, PHE^{168}, VAL^{84}, ILE^{370}, ILE^{66}, MET^{366}, ASN^{349}, LEU^{363}, LEU^{167}, TYR^{367}, CYS^{166}
20	-36.88	LEU^{345}, LEU^{85}, VAL^{84}, TYR^{9}, PHE^{168}, ILE^{66}, MET^{366}, GLU^{169}, SER^{67}, TYR^{367}, LEU^{167}, ILE^{370}, HIS^{346}, MET^{177}, ASN^{349}
21	-29.60	TYR^{367}, SER^{67}, ILE^{66}, ALA^{63}, ILE^{370}, PHE^{168}, LEU^{85}, MET^{177}, HIS^{346}, LUE^{345}, ASN^{349}, GLU^{169}, HIE^{360}, MET^{366}
24	-27.87	ASN^{349}, PHE^{168}, MET^{366}, ILE^{370}, TYR^{367}, ALA^{63}, ILE^{66}, SER^{67}, LEU^{345}, MET^{177}, HIS^{346}
Reference	-26.30	TYR^{9}, ILE^{370}, LEU^{345}, MET^{177}, HIS^{346}, ASN^{349}, MET^{174}, MET^{366}, PHE^{168}, TYR^{367}, ALA^{63}

Table 4 shows the screened and referenced compounds' two- and three-dimensional views. A Keenan study of the

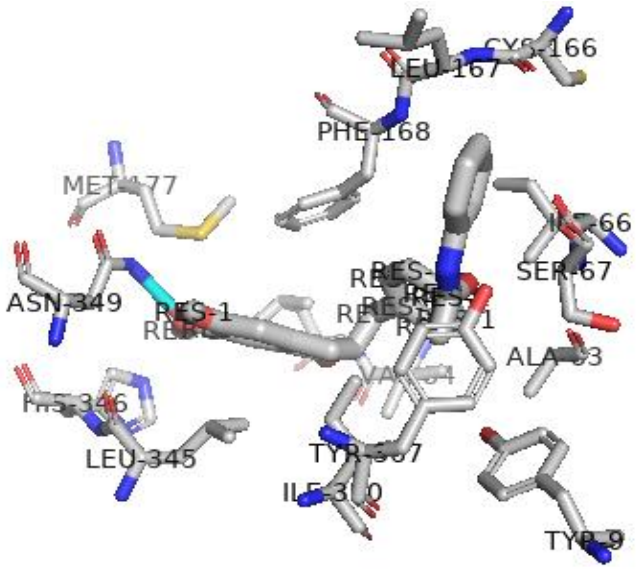
images shows common residues in all the screened compounds that form hydrogen and hydrophobic bonds. The amino acids ASN349, PHE168, and SER67 interact with the ligands via the abovementioned bond.

Table 4: Two- and three-dimensional views of the screened compound interactions and the receptor prepared by Ligplot and PyMol, respectively.

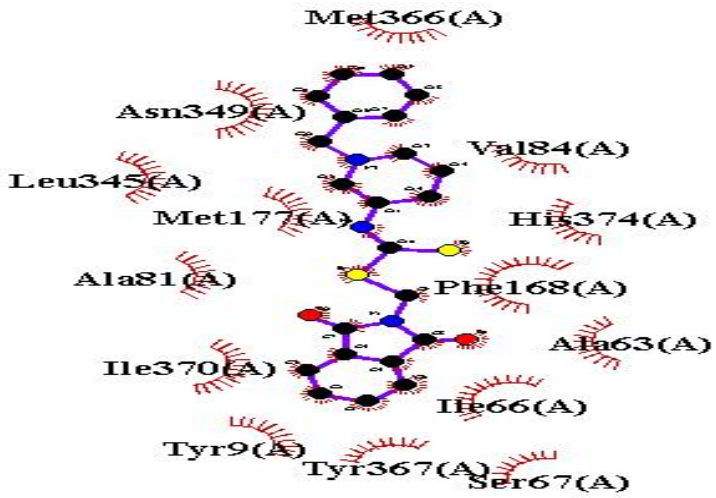
3	3
	
4	4
	
6	6
	


Cys166(A)
Ser67(A)
Ile66(A)
Leu167(A)
Tyr367(A)
Ala63(A)
Tyr9(A)
Phe168(A)
Ile370(A)
His346(A)
Val84(A)
Met177(A)
Leu85(A)
Leu345(A)
Asn349(A)

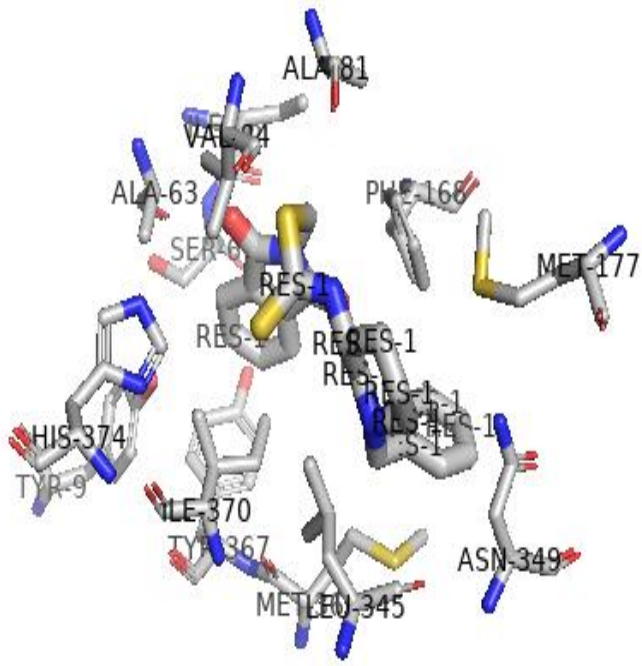
8


CYS-166
LEU-167
PHE-168
MET-177
SER-67
ASN-349
LEU-345
TYR-9

8

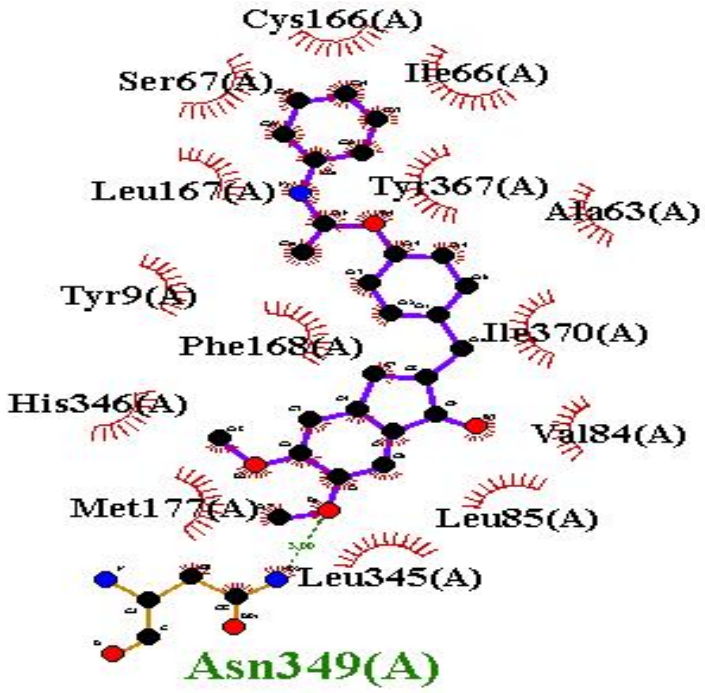

Met366(A)
Asn349(A)
Val84(A)
Leu345(A)
Met177(A)
His374(A)
Ala81(A)
Phe168(A)
Ala63(A)
Ile370(A)
Ile66(A)
Tyr9(A)
Tyr367(A)
Ser67(A)

11

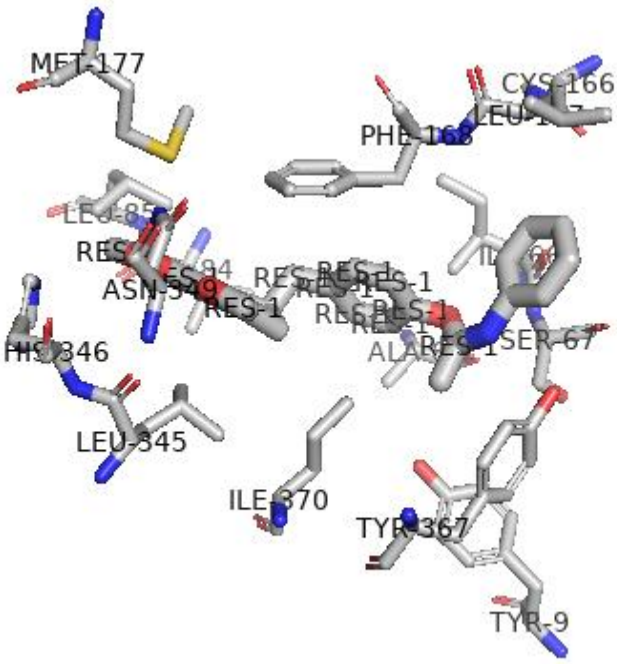

ALA-81
ALA-63
MET-177
HIS-374
TYR-9
ILE-370
ASN-349
LEU-345

11

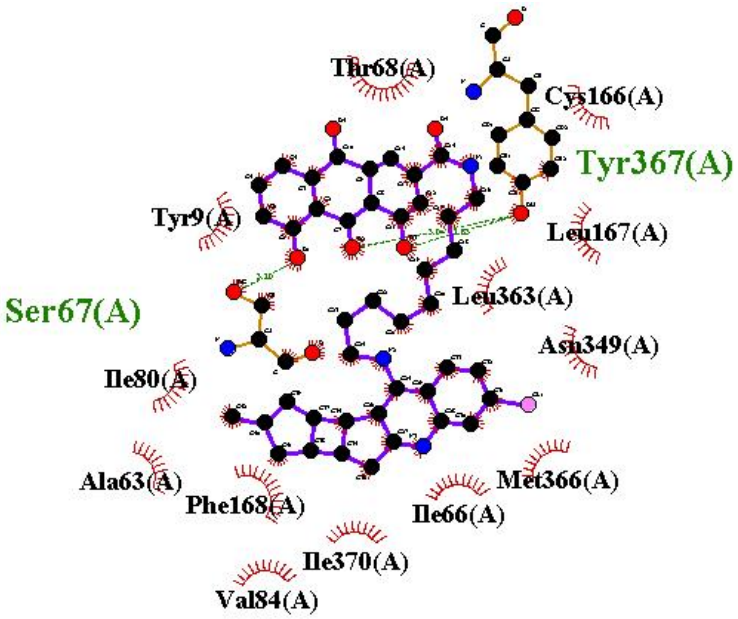
18


Cys166(A)
Ser67(A)
Ile66(A)
Leu167(A)
Tyr367(A)
Ala63(A)
Tyr9(A)
Phe168(A)
Ile370(A)
His346(A)
Val84(A)
Met177(A)
Leu85(A)
Leu345(A)
Asn349(A)

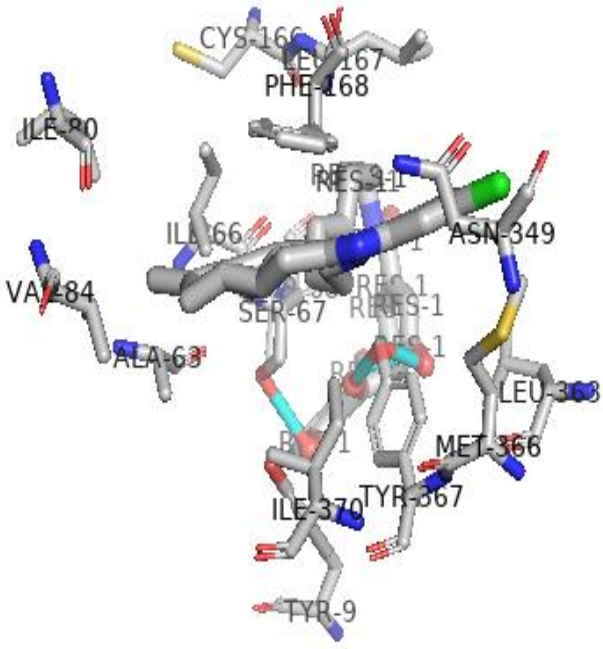
18


MET-177
CYS-166
PHE-168
LEU-345
ILE-370
TYR-367
TYR-9
SER-67

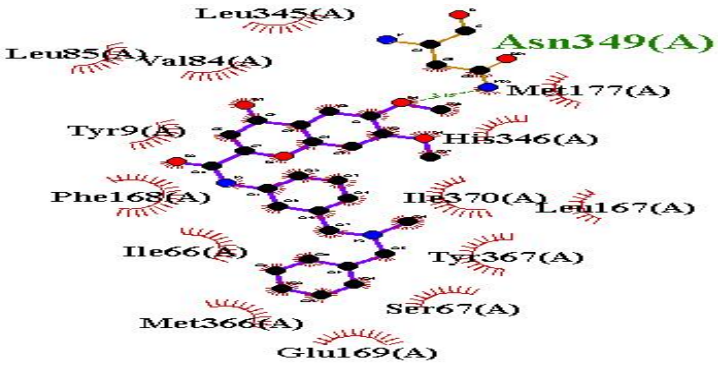
19


Thr68(A)
Cys166(A)
Tyr367(A)
Tyr9(A)
Leu167(A)
Leu363(A)
Ser67(A)
Asn349(A)
Ile80(A)
Ala63(A)
Met366(A)
Phe168(A)
Ile66(A)
Ile370(A)
Val84(A)

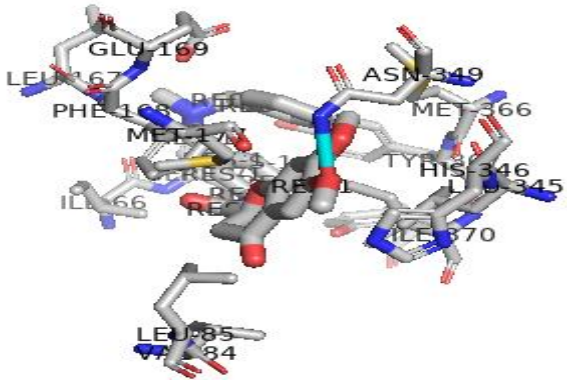
19


CYS-166
PHE-168
ASN-349
SER-67
ALA-63
MET-366
TYR-367
TYR-9

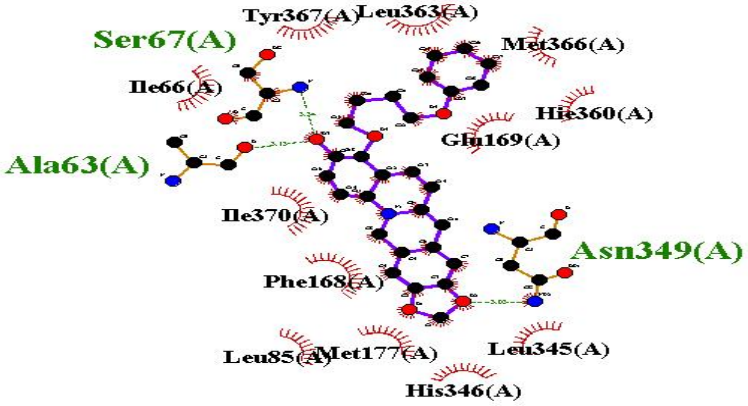
20



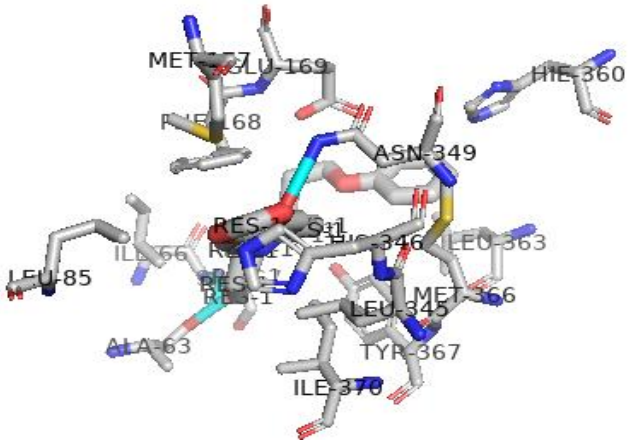
20



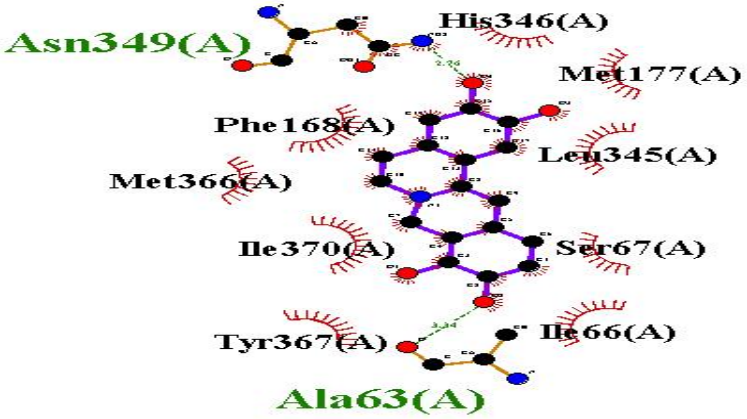
21



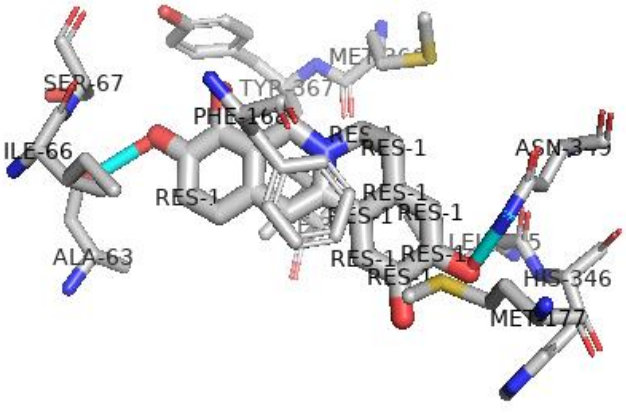
21



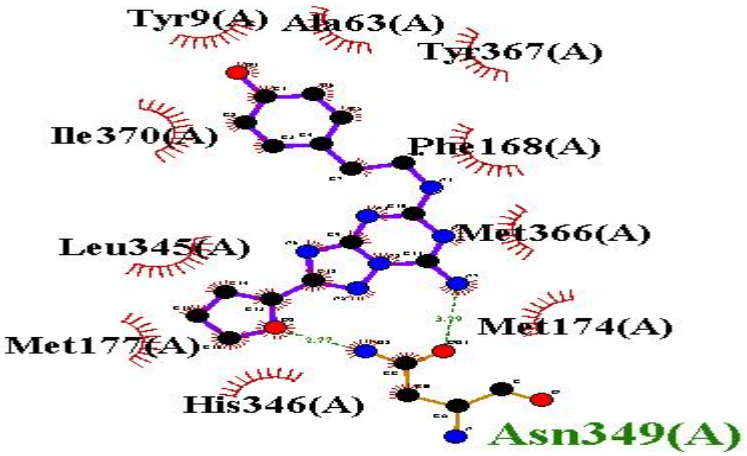
24



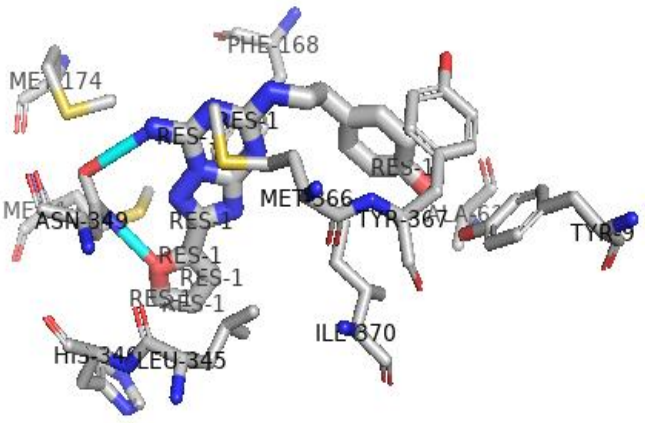
24



Reference



Reference



3.2 Potency and therapeutic ability of the screened inhibitors against Alzheimer's Disease

a. The third inhibitor (3)

With a docking score of -37.41 kcal/mol, molecule three (3) has the lowest among these 10 inhibitors. This inhibitor has nineteen amino acids that bind with the ligand. The chemical, which is a combination of tetrahydroacridine and silibinin, has intriguing qualities that make it a promising anti-Alzheimer drug, including neuro-protective, anti-inflammatory, anticancer, and hepatoprotective effects (Czarnecka et al., 2020; Kouli et al., 2018; Xie et al., 2015).

b. The fourth inhibitor (4)

These compounds' thirteen amino acids interact with the ligand in various ways. This compound's docking score in the complex is -30.94 kcal/mol. When a cholinesterase inhibitor and ebselen are combined, the molecule acts as an anti-βAmyloid aggregator, which is how it and a multitarget-directed ligand (MTDL) against AD are active (Cen et al., 2018; Z. Luo et al., 2013; Y. Wang et al., 2016) This inhibitor may cross the central nervous system and blood-brain barrier, improving cell survival (Porkka et al., 2008).

c. Sixth inhibitor (6)

With a docking score of -28.17 kcal/mol, compound six has very strong inhibitory action against AD Its twelve amino acids interact with the ligand in various ways. It is distinguished by its capacity to penetrate the blood-brain barrier and its non-dangerous neurological protection (Kadry et al., 2020; S. Zhang et al., 2022). This chemical can preserve spinal function while reducing or eliminating cognitive impairment (Kadry et al., 2020; Merlini et al., 2019) . Compound six can, therefore, function as a chemotherapeutic anti-Alzheimer drug with a healthier potency and anti-amyloid properties.

d. The eighth inhibitor (8)

Compound 8 has a docking score of -29.41 kcal/mol and 15 residues or amino acids that interact differently with the ligand to increase activity. A strong inhibitor that can block the protein that causes AD by inhibiting β-amyloid aggregation and concurrently interacting with the catalytic and peripheral anionic active sites (Chen et al., 2014; Inestrosa et al., 1996; L. Luo et al., 2017) . Reduce

neurotoxicity and have a high permeability, making them a good pharmacological option for Alzheimer's disease therapy(Chen et al., 2021; L. Luo et al., 2017) .

e. Eleventh inhibitor (11)

This molecule has a docking score of -26.56 kcal/mol and contains 14 amino acids that create various interactions with the ligand. Through its capacity to penetrate the blood-brain barrier and unfold the protein that causes beta-amyloid aggregation, this hybrid exhibits a unique potential inhibitory function against AD as evaluated and possesses qualities of an attractive therapeutic candidate (Dabur et al., 2022; Giorgetti et al., 2018).

f. The 18th inhibitor (18)

An alkaloid molecule that isoquinoline and has a docking value of -27.46 kcal/mol. This molecule interacts in various ways with the complex's fifteen amino acids. This hybrid possesses a kinetic model with inhibitory action among both Catalytic Active Site (C.A.S.) and Peripheral Anionic Site (P.A.S)., making it a potent suppressor of acetylcholinesterase compounds(Luque & Muñoz-Torrero, 2023; Naskar & Gour, 2023).

g. Nineteen Inhibitors (19)

By forming distinct contacts with 15 amino acid groups, inhibitor 19 provides more information about its active binding location. The docking score for this inhibitor is -35.68 kcal. Mol. It is a structured combination of berberine and benzene derivatives that may block the agent that causes Alzheimer's disease (Jiang et al., 2011).

h, With a docking value of -36.88 kcal/mol, inhibitor twenty (20) combines berberine and hydroquinone derivatives that form 15 distinct contacts, including hydrophobic and hydrogen interactions with 15 amino acid groups. Because it comes from natural sources, this molecule can potentially decrease cellulo-multifaceted toxicity in Alzheimer's. Additionally, this reveals an antioxidant action and can prevent beta-amyloid aggregation (Abbas et al., 2025; Zivari-Ghader et al., 2024).

i. Inhibitors 21 and 24 Inhibitor 21 had a docking score of -29.62 kcal/mol and had fourteen interactions with the amino acid group. A well-structured hybrid with polyphenolic properties inhibits beta-amyloid aggregation and prevents neuronal toxicity, making it a promising therapeutic candidate(Ding et al., 2023; Fang et al., 2024).

j. Finally, compound 24 has a docking score of -27.87 kcal/mol because eleven amino acid groups have various interactions with the ligand, including hydrophobic and hydrogen bonding. A new hybrid class that has substantial inhibitory action to treat AD and has distinct properties. They also can cross the blood-brain barrier, are neuroprotectant, and are highly antioxidant. The benzylamine demonstrated inhibitory activity because of the alkyl group affixed to position two in the parent structure(Chioua et al., 2012; Hatami et al., 2023).

3.3 The selected substances' capacity for neuroprotection.

The combination of various bioactive components found in chemical compounds with improved bonding and medicinal benefits is known as hybridisation, and it is a recent and improved hypothesis in computer simulation drug design and development (Sampath Kumar et al., 2020b) . These substances can target several targets and are less harmful (Löscher, 2021) . According to Chignon et al. (2018) and Teixeira et al. (2019), neurotoxicity, oxidative stress, and reactive oxygen species production are the main suspects in AD physiology (Jomova et al., 2023; Kamaljeet et al., 2024; Teixeira et al., 2019) . However, because of their bioactive composition, hybrid compounds are multitargeted and have intrinsic capabilities to prevent or treat AD or protein aggregation, which typically leads to the formation of AD. Following docking research, the best hybrid compounds were chosen because they have certain characteristics that make them potentially useful as anti-Alzheimer and neuroprotective drugs (Islam et al., 2022; Ismaili & do Carmo Carreiras, 2018; Mirza et al., 2022) . However, regarding radical scavenging and unambiguous activity, hybrid compounds (oxidised, alkenylated, and amidated forms) are more active than the parent compounds (Rimbach et al., 2003). As a result, they are multitargeted against diseases, including AD.

3.4.Pharmacokinetic characteristics and anticipated medicinal properties.

A web-based program called SwissADM was used to forecast and take advantage of the crucial pharmacokinetics characteristics and validate the Pfizer rule of five to determine these hybrid compounds' medicinal and drug-ability. Predicted factors such as the blood-brain barrier (BBB), the octanol-water partition coefficient, clog P, the lipophilic character, molecular weight, clog P, and skin penetration are displayed in Table 5 to indicate potential drug candidates as anti-Alzheimer disease agents.

Every chemical compound's Molecular Weight (M.W.) is within the limit except for compound 3, which has a value of 829.85 g/mol. Additionally, every screened compound's Topological Polar Surface Area (TPSA) is under the threshold limit of "20 < (TPSA) < 130 Å2". This indicates that other than compound 3, all tested compounds are orally bioactive. A consensus-based forecasting model known as the water-octanol ratio Except for the reference compound with a water-octanol ratio of 5.38, all of the screened compounds' log po/w ratios, as displayed in Table 5, are below the 5.0 criterion. As a result, all of these compounds' lipid environments are perfectly acceptable for consideration as potential therapeutic possibilities.

As shown in Table 5, the highly predictive human intestinal absorption (HIA), penetrating the BBB, and improved permeability indicate that the virtual screened compounds are effective anti-Alzheimer disease agents. This is supported by the predictions of HIA, BBB, and log Kp.

Table 5: Predicted physicochemical, lipophilicity, solubility, and pharmacokinetics parameters

I.D.	M.W. ≤ 500	nRB <	HBA ≤ 10	HBD ≤ 5	MR	TPSA < 130	CLog P ≤ 5	nV	HIA	BBB	SP
3	829.85	16	13	6	223.76	215.23	4.74	1	High	Yes	-6.97
4	459.92	8	4	3	132.3	87.39	4.94	0	High	Yes	-4.7
6	406.43	7	6	1	116.98	104.19	2.66	0	High	Yes	-6.25
8	415.48	8	4	1	121.42	56.79	4.71	0	High	Yes	-4.71
11	425.57	7	3	1	127.74	110.04	3.31	0	High	Yes	-6.1
18	440.45	9	7	1	118.74	109.52	3.28	0	High	Yes	-6.15
19	704.25	13	6	4	201.77	128.62	3.45	0	High	Yes	-5.41
20	460.52	9	6	1	129.8	77.1	3.50	0	High	Yes	-6.56
21	459.53	7	6	1	132.64	60.39	4.01	0	High	Yes	-5.71
24	297.31	0	4	4	87.23	84.16	1.75	0	High	Yes	-6.44
Refe	337.34	5	6	6	91.31	127.39	5.38	3	Low	No	-6.80

MW = Molecular weight, nRB = number Rotatable bond, HBA =Hydrogen bond acceptor, HBD= Hydrogen bond donor, MR = Molecular refractivity, TPSA= Total polar surface area, C = Consensus, nv = number of Violations, HIA = Human Intestinal Absorption, BBB= Blood brain Barrier, SP = Skin Permeation

3.5 Similarity to drugs and medicinal chemistry

The expected descriptors of the screened compounds are displayed in Table 6. All compounds, except the referred molecule, complied with Lipinski RO5 and other drug-likeness standards. This indicates that the evaluated compounds are viable therapeutic candidates and can undergo additional clinical testing. Additionally, Table 6 shows that the threshold values for metrics such as the PAINS, Brenk, and Lead-likeness fall within the limit, suggesting that the compounds may be extremely effective anti-Alzheimer agents. Since the mentioned substance has most of the threshold's limit fallout, it cannot be used orally or subjected to additional clinical testing.

Table 6: Drug-likeness and Medicinal Chemistry

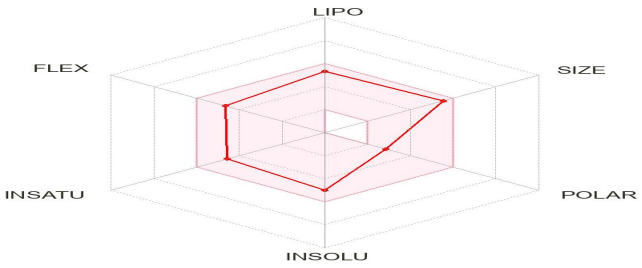
	3	4	6	8	11	18	19	20	21	24	Ref
Ghose	0	0	0	0	0	0	0	0	0	0	2
Veber	0	0	0	0	0	0	0	0	0	0	0
Egan	0	0	0	0	0	0	0	0	0	0	1
Muegge	0	0	0	0	0	0	0	0	0	0	1
BS	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.17
PAINS	0	0	0	0	0	0	0	0	0	0	1
Brenk	0	0	0	0	0	0	0	0	0	0	2
L.L.	0	0	0	0	0	0	0	0	0	0	3
SA	1.79	1.97	3,.17	3.83	3.48	3.96	3.83	3.73	3.21	3.22	6.62
Lipinski	0	0	0	0	0	0	0	0	0	0	1

BS= Bioavailability score, LL= Lead-likeness, Synthetic Accessibility =SA?

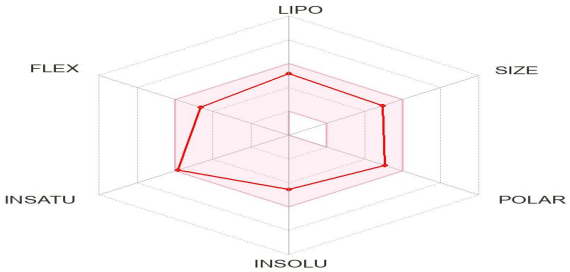
3.6 BOILED-egg plots and radar plots

Figure 4 displays the radar bioavailability of the screened bioactive compounds 3, 4, 6, 8, 11, 18, 19, 20, 21, and 24. The pink zone defines a therapeutic active substance as a physicochemical space. The preferred compound's off-shoot in-saturation at the radar zenith suggests that it is not orally active, yet all tested compounds are bioavailable based on the radar plots. The screened compounds are depicted in Figure 5 as BOILED-egg, an egg's yolk and albumen. Human Intestinal Absorption and Gastro are the compounds that belong to the albumen region and the yolk area, respectively. The best chemicals for brain disorders are those found in the yolk region since they may enter the intestinal tract.

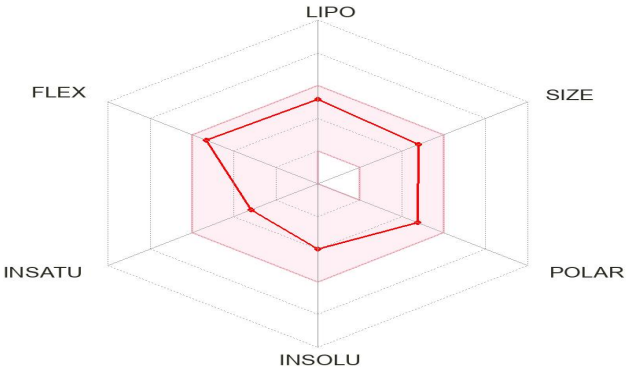
3


LIPO
SIZE
POLAR
INSOLU
INSATU
FLEX

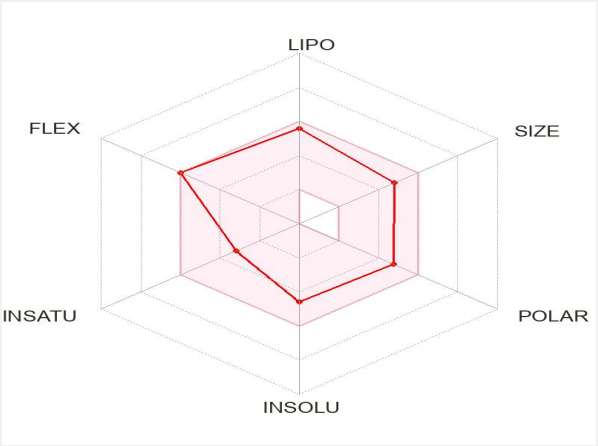
4

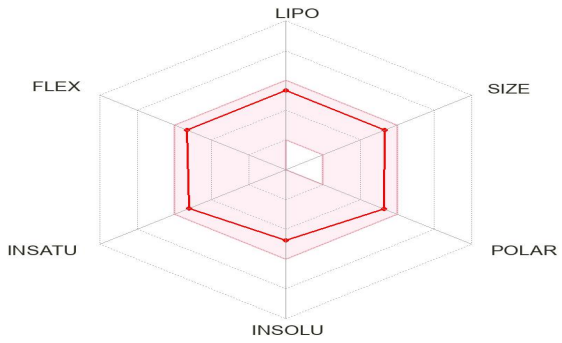

LIPO
SIZE
POLAR
INSOLU
INSATU
FLEX

6


LIPO
SIZE
POLAR
INSOLU
INSATU
FLEX

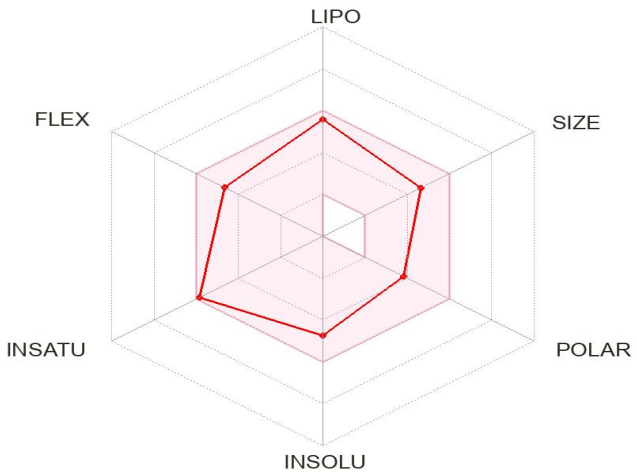
8


LIPO
SIZE
POLAR
INSOLU
INSATU
FLEX

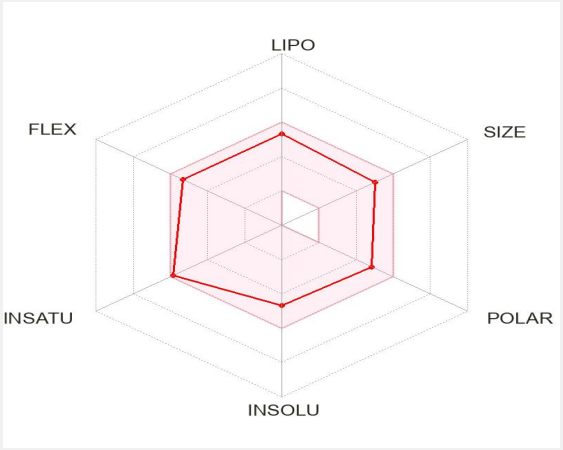

LIPO
SIZE
POLAR
INSOLU
INSATU
FLEX

11

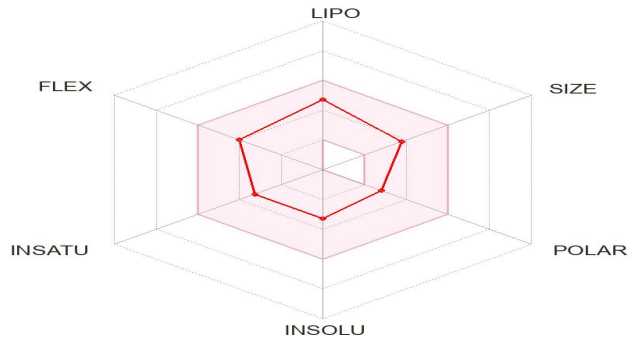
18



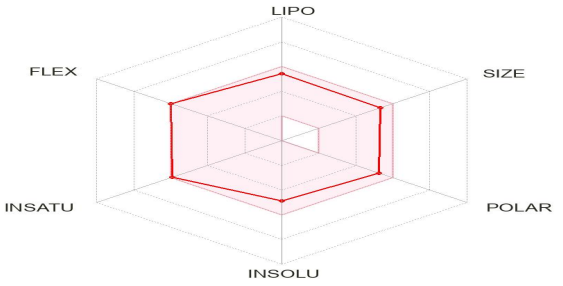
19



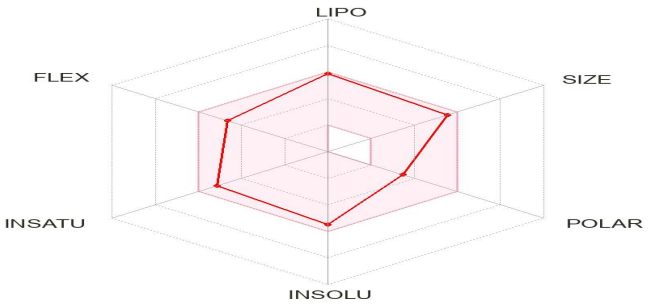
20



21



24



Reference

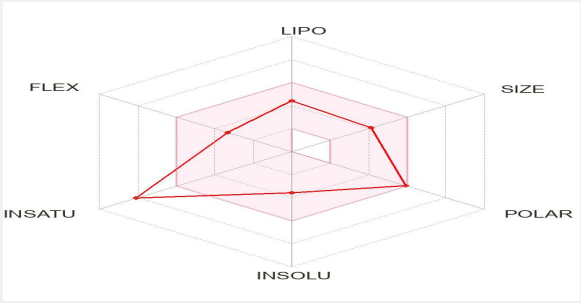


Figure 4. Radar Bioavailability of the screened compounds and reference compound

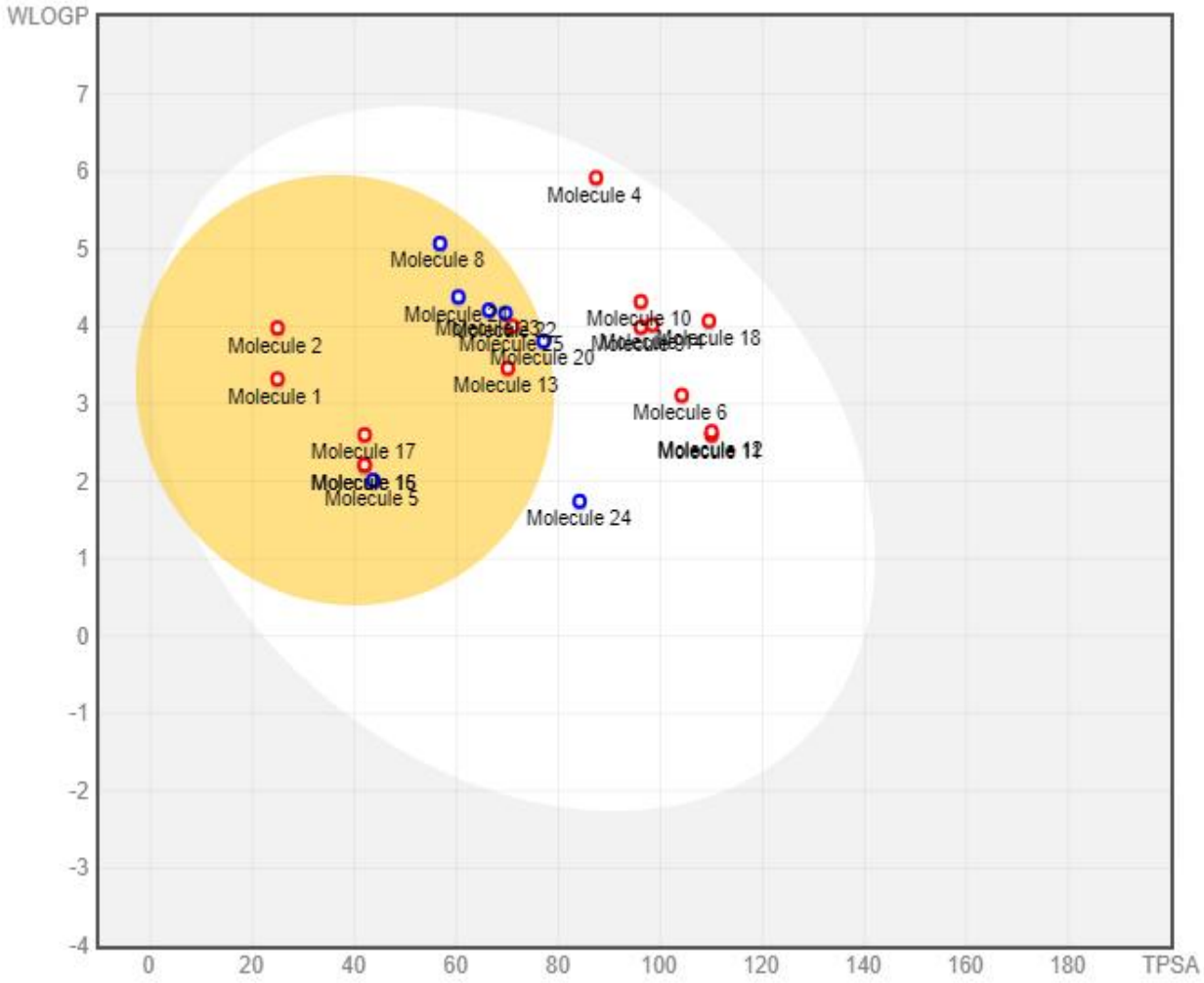


Figure 5: BIOLED-egg

4 Conclusion

A specific receptor with the identification number 7T32 retrieved from the protein database was used to screen 25 hybrid medicinal compounds identified in the literature against Alzheimer's disease, an incurable condition. With docking values and a better-docked image than the reference compound, ten of these compounds—three, four, six, eight, eleven, eighteen, twenty, twenty-one, and twenty-four—have strong protein-ligand interactions. Good interactions between the compounds and various amino acid groups, including hydrogen and hydrophobic bonds, provide further information on the ligands' capacity to cure. These medicinal substances can disrupt several biochemical pathways causing infection and prevent the folding of certain proteins that may cause cognitive dysfunction. They can also control many molecular targets. ADMET-ox predictions were made *in silico* for these chemicals. These substances were discovered to have outstanding pharmacokinetic properties, which means they may be more effective anti-Alzheimer disease agents. However, since this study was conducted using computer-aided drug design, neuroscientists may do more research on these potentially efficacious molecules, including *in-vitro* and *in-vivo* tests.

Acknowledgments

The authors are grateful to the technical personnel of the Drug Design and Molecular Modeling laboratory, Faculty of Basic Medical Sciences, Federal University Dutse, for their hard work and assistance during the project.

Conflicts of interest: None declared by the authors

Funding: Self-funded by the Authurs

Authors contributions

AAI: Conceptualization, , Project administration, Data curation, Writing – original draft, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Validation, VisualizationAA: Data curation, Writing – review & editing. MSR: Formal analysis, Funding acquisition, Investigation, Methodology BJB: Funding acquisition, Investigation, Methodology, Resources, BSU: Data curation, Formal analysis, Funding acquisition. NA: Resources, Software, Validation, Visualization ISA: Data curation, Formal analysis, Funding acquisition JDU: Project administration, Data curation, Writing – review & editing. KMA: Visualization, Writing – review & editing.

Article History

Received: 05th December, 2024.

Accepted: 13th June 2025.

Published online: 27th March 2026.

REFERENCE

Abbas, K., Mustafa, M., Alam, M., Habib, S., Ahmad, W., Adnan, M., Hassan, M. I., & Usmani, N. (2025). Multi-target approach to Alzheimer's disease prevention and treatment: antioxidant, anti-inflammatory, and amyloid- modulating mechanisms. *Neurogenetics*, *26*, 39. https://doi.org/10.1007/s10048-025-00821-y

Abdulganiyyu, I. A., Sani, M.-A. M. A., Separovic, F., Marco, H., & Jackson, G. E. G. E. (2019). Phote-HrTH (Phormia terraenovae Hypertrehalosaemic Hormone), the Metabolic Hormone of the Fruit Fly: Solution Structure and Receptor Binding Model. *Australian Journal of Chemistry*, *73*(3), 202–211. https://doi.org/10.1071/CH19461

Abdullahi, S. H., Moin, A. T., Uzairu, A., Umar, A. B., Ibrahim, M. T., Usman, M. T., Nawal, N., Bayil, I., & Zubair, T. (2024). Molecular docking studies of some benzoxazole and benzothiazole derivatives as VEGFR-2 target inhibitors: In silico design, MD simulation, pharmacokinetics and DFT studies. *Intelligent Pharmacy*, *2*, 232–250. https://doi.org/10.1016/j.ipha.2023.11.010

Addis, P., Bali, U., Baron, F., Campbell, A., Harborne, S., Jagger, L., Milne, G., Pearce, M., Rosethorne, E. M., Satchell, R., Swift, D., Young, B., & Unitt, J. F. (2024). Key aspects of modern GPCR drug discovery. In *SLAS Discovery* (Vol. 29, pp. 1–22). Society for Laboratory Automation and Screening (SLAS). https://doi.org/10.1016/j.slasd.2023.08.007

Agamah, F. E., Mazandu, G. K., Hassan, R., Bope, C. D., Thomford, N. E., Ghansah, A., & Chimusa, E. R. (2020). Computational/in silico methods in drug target and lead prediction. *Briefings in Bioinformatics*, *21*, 1663–1675. https://doi.org/10.1093/bib/bbz103

Ajala, A., Asipita, O. H., Michael, A. T., Tajudeen, M. T., Abdulganiyyu, I. A., & Ramu, R. (2025). Therapeutic exploration potential of adenosine receptor antagonists through pharmacophore ligand-based modelling and pharmacokinetics studies against Parkinson disease. *In Silico Pharmacology*, *13*, 17. https://doi.org/10.1007/s40203-025-00305-9

Ajala, A., Eltayb, W. A., Abatyough, T. M., Ejeh, S., El fadili, M., Otaru, H. A., Edache, E. I., Abdulganiyyu, A. I., Areguamen, O. I., Patil, S. M., & Ramu, R. (2024). In-silico screening and ADMET evaluation of therapeutic MAO-B inhibitors against Parkinson disease. *Intelligent Pharmacy*, *2*(4). https://doi.org/10.1016/j.ipha.2023.12.008

Akinbo, I. A., Ajala, A., Rufai, M. S., Baiwa, F. I., Kurawa, M. M., Jackson, G. E., Ismaila, S. S., Babalola, B. J., Ufeli, B. S., Adamu, L. H., Mustapha, A., Yahaya, N., Abba, J. E., Hussaini, H., Kazaure, M. B., & Garba, A. (2024). Theoretical examination of molecular docking, pharmacokinetics and in-silico design of specific tacrine derivatives as anti-Alzheimer agents. *Dutse Journal of Pure and Applied Sciences*, *10*, 187–201. https://doi.org/10.4314/dujopas.v10i3a.18

Akinbo, I. A., Rufa'i, M. S., Ajala, A., & Sambo, A. (2024). Molecular Docking and Drug Kinetics Assessment for Structure-Based Drug Design of New Piperazine-Containing Hydrazone Derivatives as Effective Alzheimer Inhibitors. *Journal of*

Biochemistry, Microbiology and Biotechnology, *12*, 37–43. https://doi.org/10.54987/jobimb.v12i2.1016

Calabrò, M., Rinaldi, C., Santoro, G., & Crisafulli, C. (2021). The biological pathways of Alzheimer disease: a review. *AIMS Neuroscience*, *8*(1). https://doi.org/10.3934/Neuroscience.2021005

Cen, J., Guo, H., Hong, C., Lv, J., Yang, Y., Wang, T., Fang, D., Luo, W., & Wang, C. (2018). Development of tacrine-bifendate conjugates with improved cholinesterase inhibitory and pro-cognitive efficacy and reduced hepatotoxicity. *European Journal of Medicinal Chemistry*, *144*, 128–136. https://doi.org/10.1016/j.ejmech.2017.12.005

Chen, X., Drew, J., Berney, W., & Lei, W. (2021). Neuroprotective natural products for alzheimer's disease. In *Cells* (Vol. 10). MDPI. https://doi.org/10.3390/cells10061309

Chen, X., Wehle, S., Kuzmanovic, N., Merget, B., Holzgrabe, U., König, B., Sotriffer, C. A., & Decker, M. (2014). Acetylcholinesterase inhibitors with photoswitchable inhibition of β-amyloid aggregation. *ACS Chemical Neuroscience*, *5*, 377–389. https://doi.org/10.1021/cn500016p

Chioua, M., Sucunza, D., Soriano, E., Hadjipavlou-Litina, D., Alcázar, A., Ayuso, I., Oset-Gasque, M. J., González, M. P., Monjas, L., Rodríguez-Franco, M. I., Marco-Contelles, J., & Samadi, A. (2012). α-aryl-N-alkyl nitrones, as potential agents for stroke treatment: Synthesis, theoretical calculations, antioxidant, anti-inflammatory, neuroprotective, and brain-blood barrier permeability properties. *Journal of Medicinal Chemistry*, *55*(1). https://doi.org/10.1021/jm201105a

Clifton, S. M., Kang, C., Li, J. J., Long, Q., Shah, N., & Abrams, D. M. (2017). Hybrid Statistical and Mechanistic Mathematical Model Guides Mobile Health Intervention for Chronic Pain. *Journal of Computational Biology*, *24*, 675–688. https://doi.org/10.1089/cmb.2017.0059

Czarnecka, K., Girek, M., Wójtowicz, P., Kręcisz, P., Skibiński, R., Jończyk, J., Łątka, K., Bajda, M., Walczak, A., Galita, G., Kabziński, J., Majsterek, I., Szymczyk, P., & Szymański, P. (2020). New tetrahydroacridine hybrids with dichlorobenzoic acid moiety demonstrating multifunctional potential for the treatment of alzheimer's disease. *International Journal of Molecular Sciences*, *21*. https://doi.org/10.3390/ijms21113765

Dabur, M., Loureiro, J. A., & Pereira, M. C. (2022). The current state of amyloidosis therapeutics and the potential role of fluorine in their treatment. In *Biochimie* (Vol. 202, pp. 123–135). Elsevier B.V. https://doi.org/10.1016/j.biochi.2022.08.003

Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports*, *7*(January), 1–13. https://doi.org/10.1038/srep42717

Daina, A., & Zoete, V. (2016). A BOILED-Egg To Predict Gastrointestinal Absorption and Brain Penetration of Small Molecules. *ChemMedChem*, 1117–1121. https://doi.org/10.1002/cmdc.201600182

Ding, H., Li, Z., Luo, K., Gong, Q., & Tian, X. (2023). Application of biomarker-derived fluorescent probes for the detection of Alzheimer's disease. In *TrAC - Trends in Analytical Chemistry* (Vol. 169). Elsevier B.V. https://doi.org/10.1016/j.trac.2023.117369

Doostmohammadi, A., Jooya, H., Ghorbanian, K., Gohari, S., & Dadashpour, M. (2024). Potentials and future perspectives of multi-target drugs in cancer treatment: the next generation anti-cancer agents. In *Cell Communication and Signaling* (Vol. 22). BioMed Central Ltd. https://doi.org/10.1186/s12964-024-01607-9

Ejeh, S., Uzairu, A., Shallangwa, G. A., & Abechi, S. E. (2021). Computational insight to design new potential hepatitis C virus NS5B polymerase inhibitors with drug-likeness and pharmacokinetic ADMET parameters predictions. *Future Journal of Pharmaceutical Sciences*, *7*(1). https://doi.org/10.1186/s43094-021-00373-6

Elsaman, T., Awadalla, M. K. A., Mohamed, M. S., Eltayib, E. M., & Mohamed, M. A. (2025). Identification of Microbial-Based Natural Products as Potential CYP51 Inhibitors for Eumycetoma Treatment: Insights from Molecular Docking, MM-GBSA Calculations, ADMET Analysis, and Molecular Dynamics Simulations. *Pharmaceuticals*, *18*. https://doi.org/10.3390/ph18040598

Fang, S., Zhang, K., Liu, D., Yang, Y., Xi, H., Xie, W., Diao, K., Rao, Z., Wang, D., & Yang, W. (2024). Polyphenol-based polymer nanoparticles for inhibiting amyloid protein aggregation: recent advances and perspectives. In *Frontiers in Nutrition* (Vol. 11). Frontiers Media SA. https://doi.org/10.3389/fnut.2024.1408620

Giorgetti, S., Greco, C., Tortora, P., & Aprile, F. A. (2018). Targeting amyloid aggregation: An overview of strategies and mechanisms. In *International Journal of Molecular Sciences* (Vol. 19). MDPI AG. https://doi.org/10.3390/ijms19092677

González, J. F., Alcántara, A. R., Doadrio, A. L., María, J., González, J. F., & Alcántara, A. R. (2019). Developments with multi-target drugs for Alzheimer ' s disease : an overview of the current discovery approaches current discovery approaches. *Expert Opinion on Drug Discovery*, *14*(9), 879–891. https://doi.org/10.1080/17460441.2019.1623201

Goswami, V., Patel, D., Rohit, S., Chaube, U., & Patel, B. (2024). Homology modeling, binding site identification, molecular docking and molecular dynamics simulation study of emerging and promising drug target of Wnt signaling – Human Porcupine enzyme. *Results in Chemistry*, *7*. https://doi.org/10.1016/j.rechem.2024.101482

Gulisano, W., Maugeri, D., Baltrons, M. A., Fà, M., Amato, A., Palmeri, A., D'Adamio, L., Grassi, C., Devanand, D. P., Honig, L. S., Puzzo, D., & Arancio, O. (2019). Role of Amyloid-β and Tau Proteins in Alzheimer's Disease: Confuting the Amyloid Cascade. *Journal of Alzheimer's Disease*, *68*(1). https://doi.org/10.3233/jad-189015

Gunasekaran, K., Ramakrishnan, C., & Balaram, P. (1996). Disallowed Ramachandran Conformations of Amino Acid Residues in Protein Structures. *Journal of Molecular Biology*, *264*(1), 191–198. https://doi.org/10.1006/jmbi.1996.0633

Hatami, M., Mortazavi, M., Baseri, Z., Khani, B., Rahimi, M., & Babaei, S. (2023). Antioxidant Compounds in the Treatment of Alzheimer's Disease: Natural, Hybrid, and Synthetic Products. In *Evidence-based Complementary and Alternative Medicine* (Vol. 2023). https://doi.org/10.1155/2023/8056462

Hooft, R. W., Sander, C., & Vriend, G. (1997). Objectively judging the quality of a protein structure from a Ramachandran plot. *Computer Applications in the Biosciences : CABIOS*, *13*(4), 425–430. http://www.ncbi.nlm.nih.gov/pubmed/9283757

Inestrosa, N. C., Alvarez, A., Pérez, C. A., Moreno, R. D., Vicente, M., Linker, C., Casanueva, O. I., Soto, C., & Garrido, J. (1996). Acetylcholinesterase accelerates assembly of amyloid-β-peptides into Alzheimer's fibrils: Possible role of the peripheral site of the enzyme. *Neuron*, *16*, 881–891. https://doi.org/10.1016/S0896-6273(00)80108-7

Iskusnykh, I. Y., Zakharova, A. A., Kryl'skii, E. D., & Popova, T. N. (2024). Aging, Neurodegenerative Disorders, and Cerebellum. In *International Journal of Molecular Sciences* (Vol. 25, Issue 2). https://doi.org/10.3390/ijms25021018

Islam, F., Khadija, J. F., Harun-Or-Rashid, M., Rahaman, M. S., Nafady, M. H., Islam, M. R., Akter, A., Emran, T. Bin, Wilairatana, P., & Mubarak, M. S. (2022). Bioactive Compounds and Their Derivatives: An Insight into Prospective Phytotherapeutic Approach against Alzheimer's Disease. In *Oxidative Medicine and Cellular Longevity* (Vol. 2022). Hindawi Limited. https://doi.org/10.1155/2022/5100904

Ismaili, L., & do Carmo Carreiras, M. (2018). Multicomponent Reactions for Multitargeted Compounds for Alzheimer`s Disease. *Current Topics in Medicinal Chemistry*, *17*(31). https://doi.org/10.2174/1568026618666180112155424

Jana, S., Ganeshpurkar, A., & Singh, S. K. (2018). *Multiple 3D-QSAR modeling, e-pharmacophore, molecular docking, and in vitro study to explore novel AChE inhibitors †*. https://doi.org/10.1039/c8ra08198k

Jiang, H., Wang, X., Huang, L., Luo, Z., Su, T., Ding, K., & Li, X. (2011). Benzenediol-berberine hybrids: Multifunctional agents for Alzheimer's disease. *Bioorganic and Medicinal Chemistry*, *19*, 7228–7235. https://doi.org/10.1016/j.bmc.2011.09.040

Jomova, K., Raptova, R., Alomar, S. Y., Alwasel, S. H., Nepovimova, E., Kuca, K., & Valko, M. (2023). Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging. In *Archives of Toxicology* (Vol. 97, pp. 2499–2574). Springer Science and Business Media Deutschland GmbH. https://doi.org/10.1007/s00204-023-03562-9

Kadry, H., Noorani, B., & Cucullo, L. (2020). A blood–brain barrier overview on structure, function, impairment, and biomarkers of integrity. In *Fluids and Barriers of the CNS* (Vol. 17). BioMed Central Ltd. https://doi.org/10.1186/s12987-020-00230-3

Kamaljeet, Singh, S., Gupta, G. D., & Aran, K. R. (2024). Emerging role of antioxidants in Alzheimer's disease: Insight into physiological, pathological mechanisms and management. *Pharmaceutical Science Advances*, *2*, 100021. https://doi.org/10.1016/j.pscia.2023.100021

Kaur Gulati, H., Choudhary, S., Kumar, N., Ahmed, A., Bhagat, K., Vir Singh, J., Singh, A., Kumar, A., Singh Bedi, P. M., Singh, H., & Mukherjee, D. (2022). Design, Synthesis, biological investigations and molecular interactions of triazole linked tacrine glycoconjugates as Acetylcholinesterase inhibitors with reduced hepatotoxicity. *Bioorganic Chemistry*, *118*. https://doi.org/10.1016/j.bioorg.2021.105479

Keri, D., & Barth, P. (2018). Reprogramming G protein coupled receptor structure and function. In *Current Opinion in Structural Biology* (Vol. 51, pp. 187–194). Elsevier Ltd. https://doi.org/10.1016/j.sbi.2018.07.008

Kouli, A., Torsney, K. M., & Kuan, W.-L. (2018). Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis Parkinson's Disease: Etiology, Neuropathology, and PathogenesisKouli, A. (2018). Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis. 3–26. *Parkinson's Disease: Pathogenesis and Clinical Aspects*.

Lakshmi, B., Ramakrishnan, C., Archunan, G., Sowdhamini, R., & Srinivasan, N. (2014). Investigations of Ramachandran disallowed conformations in protein domain families. *International Journal of Biological Macromolecules*, *63*, 119–125. https://doi.org/10.1016/j.ijbiomac.2013.10.032

Lakshmi, B., Sinduja, C., Archunan, G., & Srinivasan, N. (2014). Ramachandran analysis of conserved glycyl residues in homologous proteins of known structure. *Protein Science : A Publication of the Protein Society*, *23*(6), 843–850. https://doi.org/10.1002/pro.2468

Lee, Y., Basith, S., & Choi, S. (2018). Recent Advances in Structure-Based Drug Design Targeting Class A G Protein-Coupled Receptors Utilizing Crystal Structures and Computational Simulations. In *Journal of Medicinal Chemistry*. https://doi.org/10.1021/acs.jmedchem.6b01453

Löscher, W. (2021). Single-Target Versus Multi-Target Drugs Versus Combinations of Drugs With Multiple Targets: Preclinical and Clinical Evidence for the Treatment or Prevention of Epilepsy. *Frontiers in Pharmacology*, *12*, 730257. https://doi.org/10.3389/fphar.2021.730257

Luo, L., Li, Y., Qiang, X., Cao, Z., Xu, R., Yang, X., Xiao, G., Song, Q., Tan, Z., & Deng, Y. (2017). Multifunctional thioxanthone derivatives with acetylcholinesterase, monoamine oxidases and β-amyloid aggregation inhibitory activities as potential agents against Alzheimer's disease. *Bioorganic and Medicinal Chemistry*, *25*, 1997–2009. https://doi.org/10.1016/j.bmc.2017.02.027

Luo, Z., Sheng, J., Sun, Y., Lu, C., Yan, J., Liu, A., Luo, H. Bin, Huang, L., & Li, X. (2013). Synthesis and evaluation of multi-target-directed ligands against Alzheimer's disease based on the fusion of donepezil and ebselen. *Journal of Medicinal Chemistry*, *56*, 9089–9099. https://doi.org/10.1021/jm401047q

Luque, F. J., & Muñoz-Torrero, D. (2023). Acetylcholinesterase: A Versatile Template to Coin Potent Modulators of Multiple Therapeutic Targets. *Accounts of Chemical Research*. https://doi.org/10.1021/acs.accounts.3c00617

Maeda, S., & Schertler, G. F. X. (2013). Production of GPCR and GPCR complexes for structure determination. In *Current Opinion in Structural Biology* (Vol. 23, pp. 381–392). https://doi.org/10.1016/j.sbi.2013.04.006

Mandal, M., & Mandal, S. (2024). Discovery of multitarget-directed small molecule inhibitors from Andrographis paniculata for Nipah virus disease therapy: Molecular docking, molecular dynamics simulation and ADME-Tox profiling. *Chemical Physics Impact*, *8*. https://doi.org/10.1016/j.chphi.2024.100493

Marucci, G., Buccioni, M., Ben, D. D., Lambertucci, C., Volpini, R., & Amenta, F. (2021). Efficacy of acetylcholinesterase inhibitors in Alzheimer's disease. In *Neuropharmacology* (Vol. 190). Elsevier Ltd. https://doi.org/10.1016/j.neuropharm.2020.108352

Mathur, N., Sai Chandragiri, S., Sarita, Shandily, S., Mukeshbhai Santoki, K., Navinchandra Vadhavana, N., Shah, S., & Chandra, M. (2024). In Silico Docking: Protocols for Computational Exploration of Molecular Interactions. In *Unravelling Molecular Docking - From Theory to Practice [Working Title]*. IntechOpen. https://doi.org/10.5772/intechopen.1005527

Meng, X.-Y., Zhang, H.-X., Mezei, M., & Cui, M. (2012). Molecular Docking: A Powerful Approach for Structure-Based Drug Discovery. *Current Computer Aided-Drug Design*, *7*, 146–157. https://doi.org/10.2174/157340911795677602

Merlini, M., Rafalski, V. A., Rios Coronado, P. E., Gill, T. M., Ellisman, M., Muthukumar, G., Subramanian, K. S., Ryu, J. K., Syme, C. A., Davalos, D., Seeley, W. W., Mucke, L., Nelson, R. B., & Akassoglou, K. (2019). Fibrinogen Induces Microglia-Mediated Spine Elimination and Cognitive Impairment in an Alzheimer's Disease Model. *Neuron*, *101*, 1099-1108.e6. https://doi.org/10.1016/j.neuron.2019.01.014

Mirza, F. J., Zahid, S., Amber, S., Sumera, S., Jabeen, H., Asim, N., & Ali Shah, S. A. (2022). Multitargeted Molecular Docking and Dynamic Simulation Studies of Bioactive Compounds from Rosmarinus officinalis against Alzheimer's Disease. *Molecules*, *27*. https://doi.org/10.3390/molecules27217241

Mishra, C. B., Shalini, S., Gusain, S., Kumar, P., Kumari, S., Choi, Y. S., Kumari, J., Moku, B. K., Yadav, A. K., Prakash, A., Jeon, R., & Tiwari, M. (2024). Multitarget action of Benzothiazole-piperazine small hybrid molecule against Alzheimer's disease: In silico, In vitro, and In vivo investigation. *Biomedicine and Pharmacotherapy*, *174*. https://doi.org/10.1016/j.biopha.2024.116484

Naik, R. A., Rajpoot, R., Koiri, R. K., Bhardwaj, R., Aldairi, A. F., Johargy, A. K., Faidah, H., Babalghith, A. O., Hjazi, A., Alsanie, W. F., Alamri, A. S., Alhomrani, M., Alsharif, A., Shkodina, A., & Singh, S. K. (2025). Dietary supplementation and the role of phytochemicals against the Alzheimer's disease: Focus on polyphenolic compounds. In *The journal of prevention of Alzheimer's disease* (Vol. 12, p. 100004). https://doi.org/10.1016/j.tjpad.2024.100004

Naskar, S., & Gour, N. (2023). Realization of Amyloid-like Aggregation as a Common Cause for Pathogenesis in Diseases. In *Life* (Vol. 13). Multidisciplinary Digital Publishing Institute (MDPI). https://doi.org/10.3390/life13071523

Neațu, M., Covaliu, A., Ioniță, I., Jugurt, A., Davidescu, E. I., & Popescu, B. O. (2024). Monoclonal Antibody Therapy in Alzheimer's Disease. In *Pharmaceutics* (Vol. 16, Issue 1). https://doi.org/10.3390/pharmaceutics16010060

Neves, M. A. C., Totrov, M., & Abagyan, R. (2012). Docking and scoring with ICM: The benchmarking results and strategies for

improvement. *Journal of Computer-Aided Molecular Design*, *26*, 675–686. https://doi.org/10.1007/s10822-012-9547-0

Núnez, P., Poza, J., Gómez, C., Rodríguez-González, V., Hillebrand, A., Tola-Arribas, M. A., Cano, M., & Hornero, R. (2019). Characterizing the fluctuations of dynamic resting-state electrophysiological functional connectivity: Reduced neuronal coupling variability in mild cognitive impairment and dementia due to Alzheimer's disease. *Journal of Neural Engineering*, *16*(5). https://doi.org/10.1088/1741-2552/ab234b

Omolara, A. (2018). Computational modelling Procedures for Geometry Optimization, Kinetic and Thermodynamic Calculations using Spartan Software - A Review. *Archives of Organic and Inorganic Chemical Sciences*, *1*. https://doi.org/10.32474/aoics.2018.01.000123

Orioli, R., Belluti, F., Gobbi, S., Rampa, A., & Bisi, A. (2024). Naturally Inspired Coumarin Derivatives in Alzheimer's Disease Drug Discovery: Latest Advances and Current Challenges. In *Molecules* (Vol. 29). Multidisciplinary Digital Publishing Institute (MDPI). https://doi.org/10.3390/molecules29153514

Porkka, K., Koskenvesa, P., Lundán, T., Rimpiläinen, J., Mustjoki, S., Smykla, R., Wild, R., Luo, R., Arnan, M., Brethon, B., Eccersley, L., Hjorth-Hansen, H., Höglund, M., Klamova, H., Knutsen, H., Parikh, S., Raffoux, E., Gruber, F., Brito-Babapulle, F., … Lee, F. Y. F. (2008). Dasatinib crosses the blood-brain barrier and is an efficient therapy for central nervous system philadelphia chromosome positive leukemia. *Blood*, *112*, 1005–1012. https://doi.org/10.1182/blood-2008-02-140665

Rimbach, G., De Pascual-Teresa, S., Ewins, B. A., Matsugo, S., Uchida, Y., Minihane, A. M., Turner, R., Vafeiadou, K., & Weinberg, P. D. (2003). Antioxidant and free radical scavenging activity of isoflavone metabolites. *Xenobiotica*, *33*, 913–925. https://doi.org/10.1080/0049825031000150444

Saify, Z. S., & Sultana, N. (2014). Role of acetylcholinesterase inhibitors and alzheimer disease. In *Drug Design and Discovery in Alzheimer's Disease* (pp. 387–425). Elsevier Inc. https://doi.org/10.1016/B978-0-12-803959-5.50007-6

Sampath Kumar, H. M., Herrmann, L., & Tsogoeva, S. B. (2020a). Structural hybridization as a facile approach to new drug candidates. In *Bioorganic and Medicinal Chemistry Letters* (Vol. 30, Issue 23). https://doi.org/10.1016/j.bmcl.2020.127514

Sampath Kumar, H. M., Herrmann, L., & Tsogoeva, S. B. (2020b). Structural hybridization as a facile approach to new drug candidates. In *Bioorganic and Medicinal Chemistry Letters* (Vol. 30). Elsevier Ltd. https://doi.org/10.1016/j.bmcl.2020.127514

Schöneberg, T., & Liebscher, I. (2021). Mutations in g protein–coupled receptors: Mechanisms, pathophysiology and potential therapeutic approaches. *Pharmacological Reviews*, *73*, 89–119. https://doi.org/10.1124/pharmrev.120.000011

Shaaban, A. E., Ali, A. R., Ayyad, S. N., & Badria, F. A. (2025). Multi-target directed ligands inspired natural products as an effective approach for the treatment of complex chronic health disorders. In *Bioorganic Chemistry* (Vol. 154). Academic Press Inc. https://doi.org/10.1016/j.bioorg.2024.108075

Singh, B., Day, C. M., Abdella, S., & Garg, S. (2024). Alzheimer's disease current therapies, novel drug delivery systems and future directions for better disease management. In *Journal of Controlled Release* (Vol. 367, pp. 402–424). Elsevier B.V. https://doi.org/10.1016/j.jconrel.2024.01.047

Soltan, O. M., Shoman, M. E., Abdel-Aziz, S. A., Narumi, A., Konno, H., & Abdel-Aziz, M. (2021). Molecular hybrids: A five-year survey on structures of multiple targeted hybrids of protein kinase inhibitors for cancer therapy. In *European Journal of Medicinal Chemistry* (Vol. 225). Elsevier Masson s.r.l. https://doi.org/10.1016/j.ejmech.2021.113768

Spinelli, R., Sanchís, I., & Siano, A. (2025). Fighting Alzheimer's naturally: Peptides as multitarget drug leads. *Bioorganic & Medicinal Chemistry Letters*, 130305. https://doi.org/10.1016/j.bmcl.2025.130305

Sucharitha, P., Ramesh Reddy, K., Satyanarayana, S. V., & Garg, T. (2022). Absorption, distribution, metabolism, excretion, and toxicity assessment of drugs using computational tools. In *Computational Approaches for Novel Therapeutic and Diagnostic Designing to Mitigate SARS-CoV2 Infection: Revolutionary Strategies to Combat Pandemics*. https://doi.org/10.1016/B978-0-323-91172-6.00012-1

Teixeira, J. P., de Castro, A. A., Soares, F. V., da Cunha, E. F. F., & Ramalho, T. C. (2019). Future therapeutic perspectives into the Alzheimer's disease targeting the oxidative stress hypothesis. In *Molecules* (Vol. 24). MDPI AG. https://doi.org/10.3390/molecules24234410

Thies, W., & Bleiler, L. (2013). Alzheimer's Disease Fact Sheet. *Alzheimer's & Dementia*, *9*(2).

Thomas-Brown, P. G., Ruddock, P. L., & Gossell-Williams, M. (2023). Pharmacokinetics. In *Pharmacognosy: Fundamentals, Applications, and Strategies, Second Edition* (pp. 559–577). Elsevier. https://doi.org/10.1016/B978-0-443-18657-8.00008-6

Ueha, R., Cotaoco, C., Kondo, K., & Yamasoba, T. (2024). Management and Treatment for Dysphagia in Neurodegenerative Disorders. In *Journal of Clinical Medicine* (Vol. 13, Issue 1). https://doi.org/10.3390/jcm13010156

Wang, K., Shi, J., Zhou, Y., He, Y., Mi, J., Yang, J., Liu, S., Tang, X., Liu, W., Tan, Z., & Sang, Z. (2021). Design, synthesis and evaluation of cinnamic acid hybrids as multi-target-directed agents for the treatment of Alzheimer's disease. *Bioorganic Chemistry*, *112*. https://doi.org/10.1016/j.bioorg.2021.104879

Wang, Y., Wang, H., & Chen, H. (2016). AChE Inhibition-based Multi-target-directed Ligands, a Novel Pharmacological Approach for the Symptomatic and Disease-modifying Therapy of Alzheimer's Disease. *Current Neuropharmacology*, *14*, 364–375. https://doi.org/10.2174/1570159x14666160119094820

White, R. E. (2017). Role of ADME/PK in Drug Discovery, Safety Assessment, and Clinical Development. In *Comprehensive Medicinal Chemistry III* (Vols. 4–8, pp. 1–33). Elsevier Inc. https://doi.org/10.1016/B978-0-12-409547-2.12364-9

Xie, S. S., Lan, J. S., Wang, X. B., Jiang, N., Dong, G., Li, Z. R., Wang, K. D. G., Guo, P. P., & Kong, L. Y. (2015). Multifunctional tacrine-trolox hybrids for the treatment of Alzheimer's disease with cholinergic, antioxidant, neuroprotective and hepatoprotective properties. *European Journal of Medicinal Chemistry*, *93*. https://doi.org/10.1016/j.ejmech.2015.01.058

Yoo, J., Lee, J., Ahn, B., Han, J., & Lim, M. H. (2025). Multi-target-directed therapeutic strategies for Alzheimer's disease: controlling amyloid-β aggregation, metal ion homeostasis, and enzyme inhibition. In *Chemical Science*. Royal Society of Chemistry. https://doi.org/10.1039/d4sc06762b

Zhang, M., Chen, T., Lu, X., Lan, X., Chen, Z., & Lu, S. (2024). G protein- coupled receptors (GPCRs): advances in structures, mechanisms, and drug discovery. In *Signal Transduction and Targeted Therapy* (Vol. 9). Springer Nature. https://doi.org/10.1038/s41392-024-01803-6

Zhang, S., Gan, L., Cao, F., Wang, H., Gong, P., Ma, C., Ren, L., Lin, Y., & Lin, X. (2022). The barrier and interface mechanisms of the brain barrier, and brain drug delivery. In *Brain Research Bulletin* (Vol. 190, pp. 69–83). Elsevier Inc. https://doi.org/10.1016/j.brainresbull.2022.09.017

Zivari-Ghader, T., Valioglu, F., Eftekhari, A., Aliyeva, I., Beylerli, O., Davran, S., Cho, W. C., Beilerli, A., Khalilov, R., & Javadov, S. (2024). Recent progresses in natural based therapeutic materials for Alzheimer's disease. In *Heliyon* (Vol. 10). Elsevier Ltd. https://doi.org/10.1016/j.heliyon.2024.e26351