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An Evaluation of the Pharmacokinetics and Virtual Screening of Highly Effective Hybrid Compounds for Alzheimer's Disease

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Receptor
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ABSTRACT

Alzheimer's disease remains challenging due to complex etiology and limited therapies. Hybrid multitarget drugs show promise. This study applies computer-aided drug design to assess 25 hybrids against key AD proteins. Virtual screening, molecular docking, simulations, and pharmacokinetic analyses identified compounds with high binding affinities, supporting further development and clinical translation. The top-performing compounds were further analysed using LIGPLOT+ V 2.2.7 for 2D interaction mapping and PyMol V 2.5 for 3D visualisation of ligand-receptor interactions. Additionally, pharmacokinetic properties, including ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiles, were predicted to assess the therapeutic potential of these compounds as anti-AD agents. Out of the 25 compounds screened, ten exhibited significant interactions with the protein targets, showing high binding affinities based on their docking scores. Notable compounds, such as compound 3 (-37.41 kcal/mol), compound 19 (-35.68 kcal/mol), and compound 20 (-36.88 kcal/mol), demonstrated superior binding energy compared to the reference compound, which had a docking score of -26.30 kcal/mol. The amino acids ASN349, PHE168, and SER67 were identified as key residues involved in hydrogen and hydrophobic bonding with the ligands. These interactions are critical as they play roles in neurotransmitter production, including dopamine and norepinephrine, which are implicated in treating and managing A.D. symptoms. Pharmacokinetic and ADMET-ox predictions further supported the therapeutic potential of all the screened compounds, suggesting favourable drug-like properties and minimal toxicity. While in-silico results are encouraging, further in-vitro and in-vivo validation is needed. These findings lay a solid foundation for developing multitargeted therapies for Alzheimer's disease.

INTRODUCTION

Alzheimer's disease (A.D.) 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 [1]. It primarily affects elderly individuals and is characterised by these neurodegenerative symptoms [2]. Despite extensive research into A.D.'s pathophysiology, the disease remains incurable. However, certain mechanisms, such as intracellular neurofibrillary tangles (NFTs) and the accumulation of extracellular β-amyloid (Aβ) plaques are recognised as playing a role in its development [3]. Currently, treatment options are severely limited, with only three acetylcholinesterase (AChE) inhibitors (donepezil, rivastigmine,

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and galantamine) and and one N-methyl-D-aspartate (NMDA) receptor antagonist, memantine, which have been approved for clinical use [4]. However, despite their initial efficacy, recent data indicate that all AChE inhibitors were subsequently withdrawn or had restricted use due to their association with dose-dependent hepatotoxicity, which posed significant safety concerns for long-term administration [5].

The complexity of A.D. necessitates the development of bioactive compounds with multitarget capabilities to potentially mitigate or reverse the damage associated with the disease. The multifactorial nature of Alzheimer's disease renders single-target therapies insufficient, thereby positioning multitarget directed ligands (MTDLs), particularly hybrid compounds, as a more promising strategy [6]. Hybrid compounds can concurrently target multiple bioactive sites, while minimizing toxicity and lowering preclinical trial costs [7,8]. The design of hybrid molecules presents advantages compared to traditional methods by addressing multiple mechanisms, resulting in expedited and more economical outcomes [1]. As such, hybrid compounds have emerged as promising anti-Alzheimer's agents [9]. To address the ongoing damage caused by A.D, we employed computational-aided drug design in this study.

Computational methods are essential for in-silico screening, simulation, and pharmacokinetic predictions of potential therapeutic inhibitors for Alzheimer's disease [10]. Because of its function in producing low-resolution simulation structures of antagonist-bound A2A adenosine receptors and its adaptability in investigating different protein designs, the fusion G-protein-coupled receptor (GPCR) was chosen as the protein target for this study [11,12]. The receptor is a perfect subject for this investigation because it is specific to Homo sapiens and has never undergone any mutations [11]. To evaluate their potential as therapeutic agents against Alzheimer's disease, this research will virtual screen powerful but non-toxic hybrid compounds, run molecular simulations on the compounds that pass the screening, and then predict the drug-like properties of these compounds.

METHODS

A previously reported research of synthesised anti-Alzheimer hybrid compounds were screened [13]. Twenty-five identified therapeutic hybrid inhibitors were utilized with potential efficacy against Alzheimer's disease. The compounds' chemical structures were illustrated using ChemDraw Professional V. 16.0. The file was saved in the SD Mol format, which is then processed using the Spartan'14 software. Then these structures were imported and underwent conversion from two-dimensional to three-dimensional formats and the energy were subsequently minimized to enhance stability and structural integrity. Utilizing a previously documented method, the three-dimensional structures are optimized and computed in Spartan software. Table 1 presents the 2D hybrid structures along with their IUPAC identifications as reported in the literature.

Table 1. Hybrid molecular structures, along with their IUPAC names.

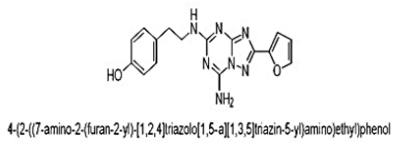
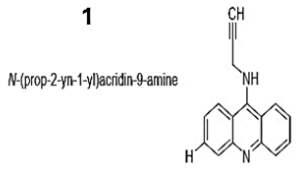
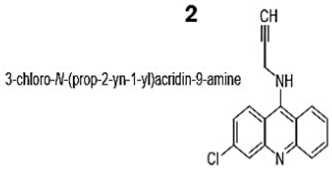
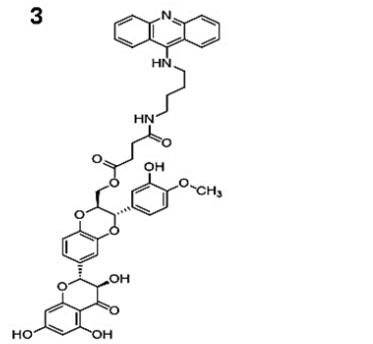
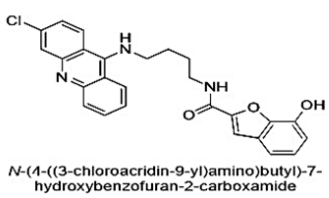
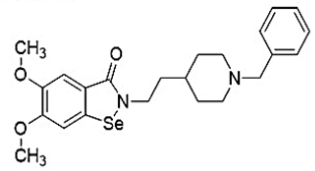
Starting / Reference	**1**
	
4-[2-((7-amino-2-(furan-2-yl)-[1,2,4]triazolo[1,5-a][1,3,5]triazin-5-yl)amino)ethyl]phenol	*N*-(prop-2-yn-1-yl)acridin-9-amine
2	**3**
	
3-chloro-*N*-(prop-2-yn-1-yl)acridin-9-amine	((2*S*,3*S*)-3-(3-hydroxy-4-methoxyphenyl)-6-((2*R*,3*R*)-3,5,7-trihydroxy-4-oxochroman-2-yl)-2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)methyl 4-((4-(acridin-9-ylamino)butyl)amino)-4-oxobutanoate
4	**5**
	
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

Table 1. Hybrid molecular structures, along with their IUPAC names.-continue

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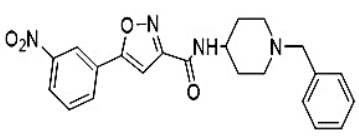
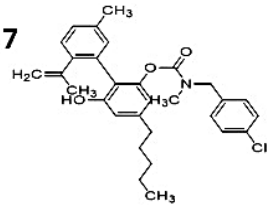
6



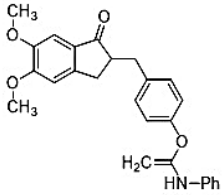
N-(1-benzylpiperidin-4-yl)-5-(3-nitrophenyl)isoxazole-3-carboxamide

7



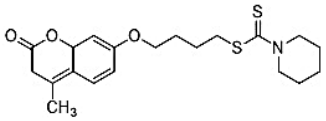
6-hydroxy-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-[1,1'-biphenyl]-2-yl (4-chlorobenzyl)(methyl)carbamate

8



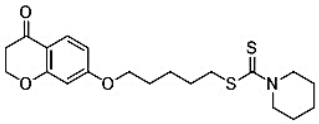
5,6-dimethoxy-2-(4-((1-(phenylamino)vinyl)oxy)benzyl)-2,3-dihydro-1*H*-inden-1-one

9



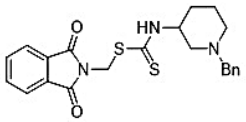
4-((4-methyl-2-oxo-3,8a-dihydro-2*H*-chromen-7-yl)oxy)butyl piperidine-1-carbodithioate

10



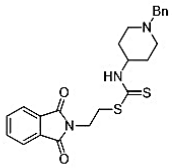
5-((4-oxochroman-7-yl)oxy)pentyl piperidine-1-carbodithioate

10



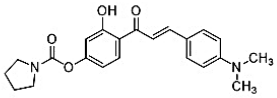
(1,3-dioxoisoindolin-2-yl)methyl (1-benzylpiperidin-3-yl)carbamodithioate

11



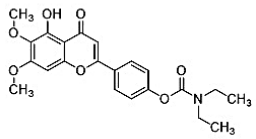
2-(1,3-dioxoisoindolin-2-yl)ethyl (1-benzylpiperidin-4-yl)carbamodithioate

12



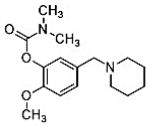
(*E*)-4-(3-(4-(dimethylamino)phenyl)acryloyl)-3-hydroxyphenyl pyrrolidine-1-carboxylate

13



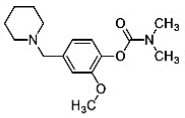
4-(5-hydroxy-6,7-dimethoxy-4-oxo-4*H*-chromen-2-yl)phenyl diethylcarbamate

14



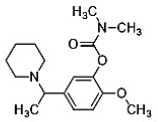
2-methoxy-5-(piperidin-1-ylmethyl)phenyl dimethylcarbamate

15



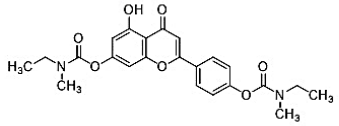
2-methoxy-4-(piperidin-1-ylmethyl)phenyl dimethylcarbamate

16



2-methoxy-5-(1-(piperidin-1-yl)ethyl)phenyl dimethylcarbamate

17



2-(4-((ethyl(methyl)carbamoyl)oxy)phenyl)-5-hydroxy-4-oxo-4*H*-chromen-7-yl ethyl(methyl)carbamate

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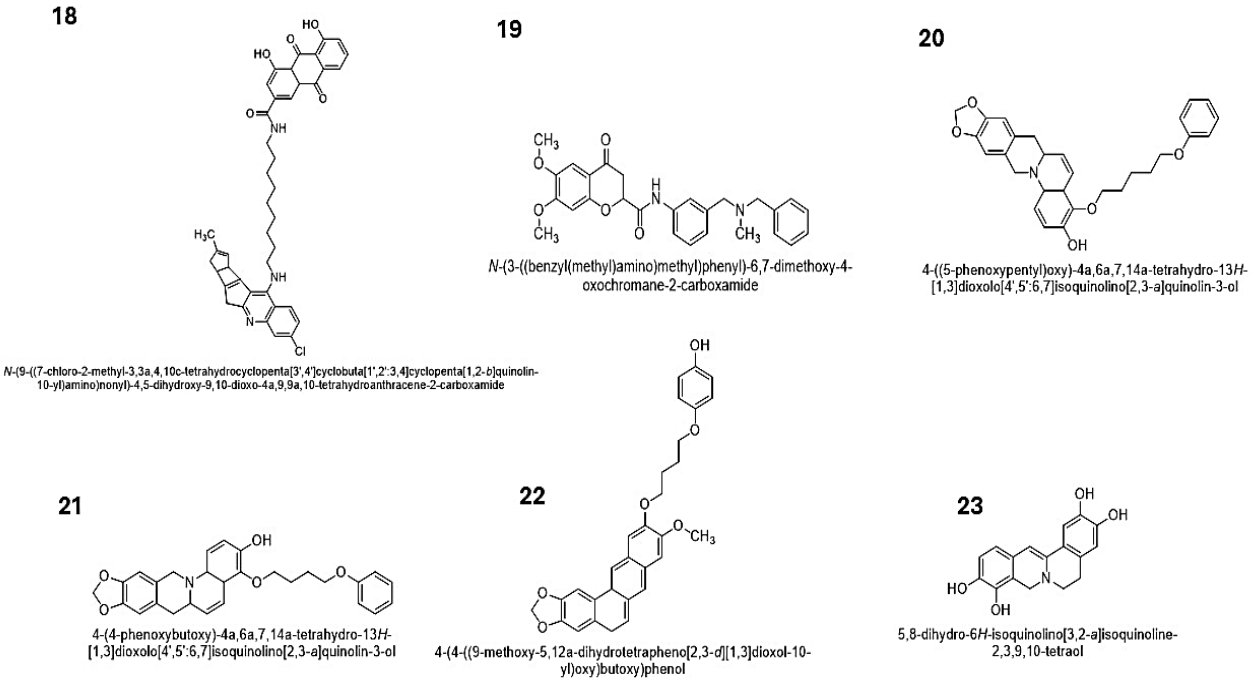
Table 1. Hybrid molecular structures, along with their IUPAC names.-continue



Protein target retrieval, preparation, and Ramachandran Plot Analysis

The fusion G-protein-coupled receptor (GPCR) protein target's raw structure was acquired from the Protein Data Bank (PDB) (www.rcsb.org), as illustrated in Figure 1. The receptor was prepared with the PyMOL Molecular Graphics System V. 2.5.4, facilitating the analysis of various fusion protein designs. This process yielded structures including the antagonist-bound A2A adenosine receptor at a resolution of 3.4 Å and the unliganded Smoothened receptor at 3.7 Å. This research utilized established methodologies to elucidate the structures of small membrane proteins and GPCRs [8]. 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 [14,15].

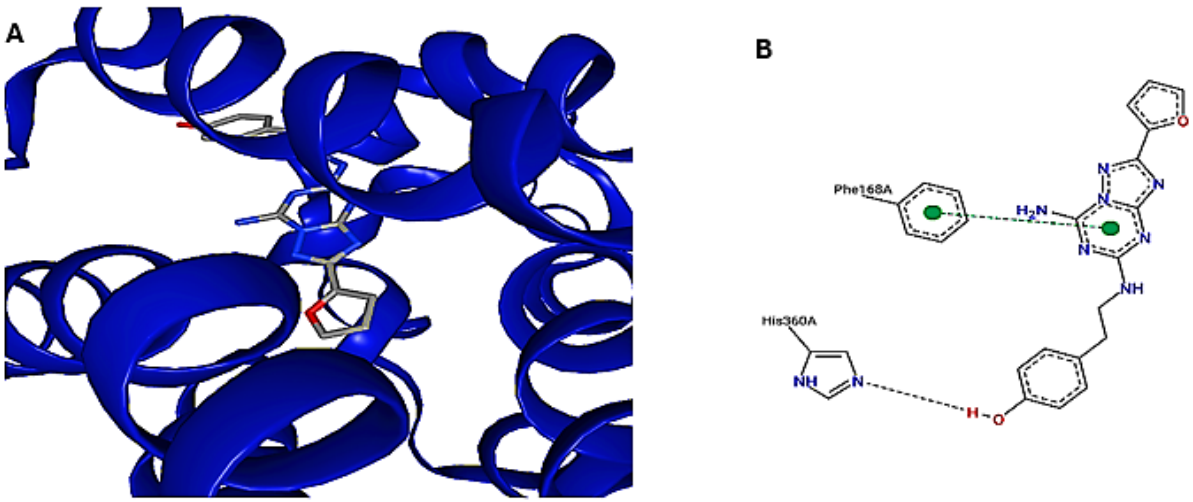


Fig. 1. **a**) Prepared protein target in complex **b**) antagonist ligand (ZM241385) structure.

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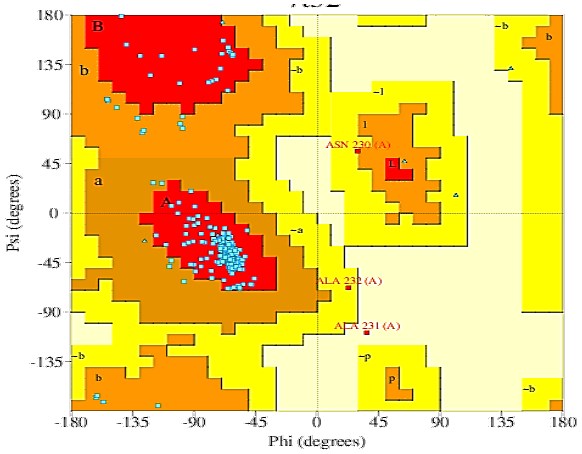

Fig. 2. Ramachandran plot of Adenosine 2A receptor.

Docking Studies and Inhibitor Screening

An excellent docking tool, ICM-Pro has received widespread acclaim [16,17] and was utilized to dock hybrid compounds to the protein target after embedded ligands, including the reference antagonist inhibitor, were removed in this study [18]. In the early stage of the molecular docking simulations, the binding site was determined using a 40 × 40 × 40 grid box along the x, y, and z axes. As shown in **Fig.** 3, this grid covered the whole enzyme with a spacing of 0.570 Å. The interactions between the lowest energy conformations, such as hydrophobic, hydrogen-bonding, and electrostatic interactions, were studied using LIGPLOT+ V 2.2.7.

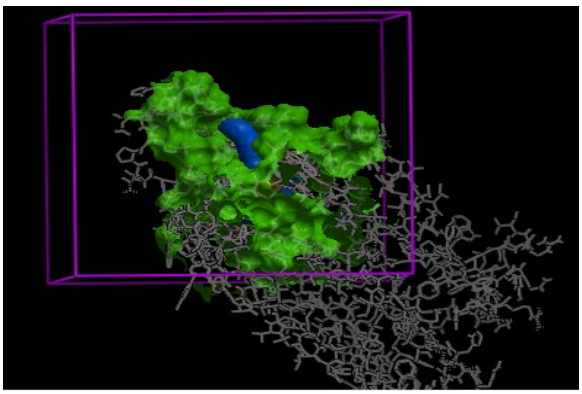

Fig. 3. Active site of the receptor (colour: blue).

Predicting the Pharmacokinetics of Selected Chemicals

SwissADME, a web-based tool, was used to assess the pharmacokinetic potential of the in-silico screened compounds [19]. This choice was informed by the observation that certain compounds exhibited superior docking scores and binding affinities compared to reference compounds [20,21]. Pharmacokinetic predictions included key ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) parameters, known for their effectiveness in providing reliable kinetics data across various molecules [22]. Additionally, radar plots and the BOILED-egg model were employed to ensure comprehensive and statistically sound predictions [23,24].

RESULTS

Statistical and Structural Analysis of the Ramachandran 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. 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 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 [4]. 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}, VAL^{84}, 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}

Two- and three-dimensional views of the referenced and screened compounds are displayed in **Fig. 4**. All of the compounds that were screened share residues that form hydrophobic and hydrogen bonds, according to a Keenan analysis of the images. Along with the aforementioned bond, the amino acids SER67, PHE168, and ASN349 also interact with the ligands.

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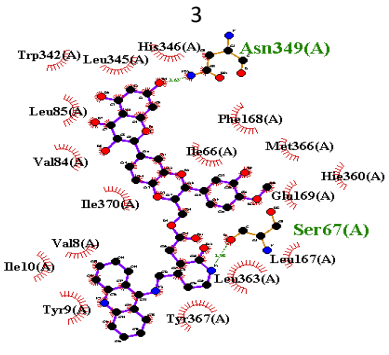

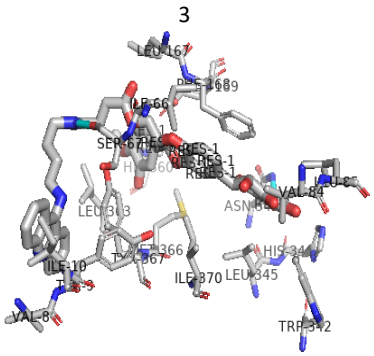

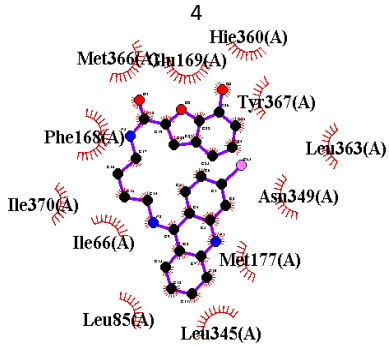

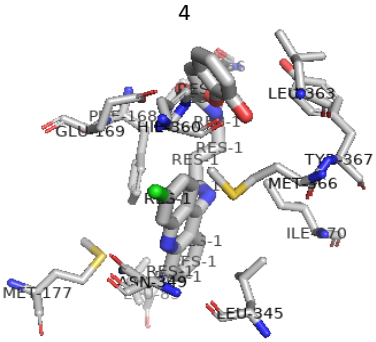

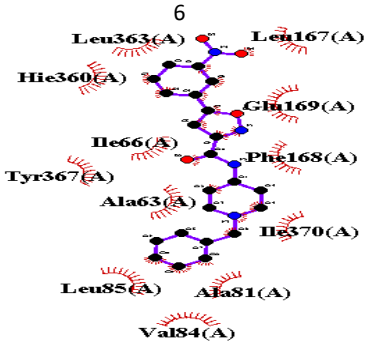

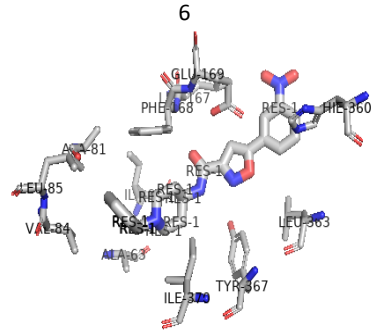

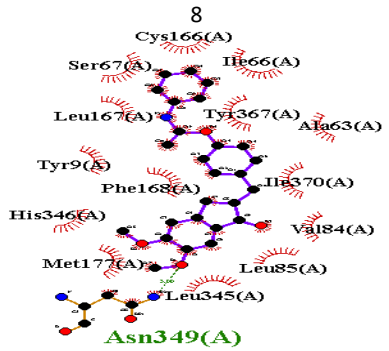

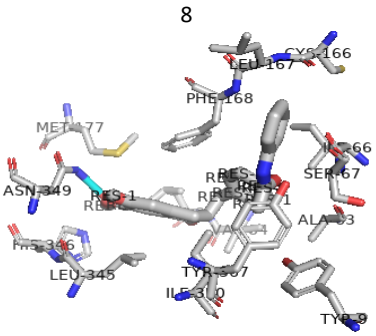

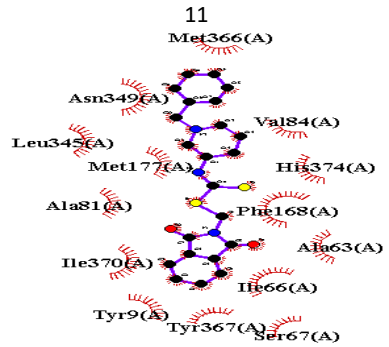

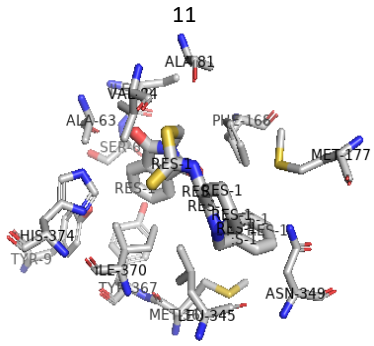

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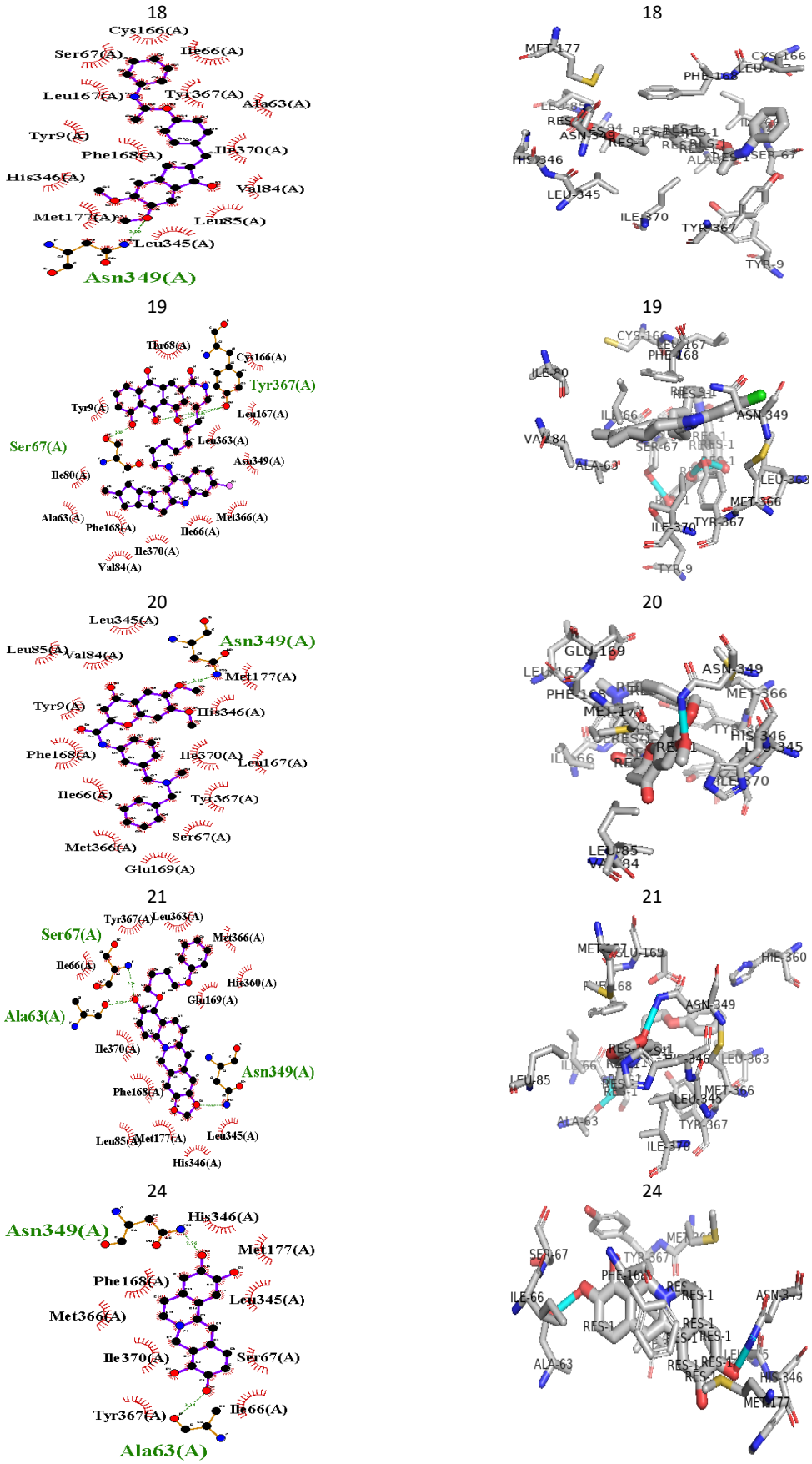

Fig. 4. The Ligplot and PyMol-generated two- and three-dimensional representations of the receptor and the screened compound interactions, respectively.-continue.

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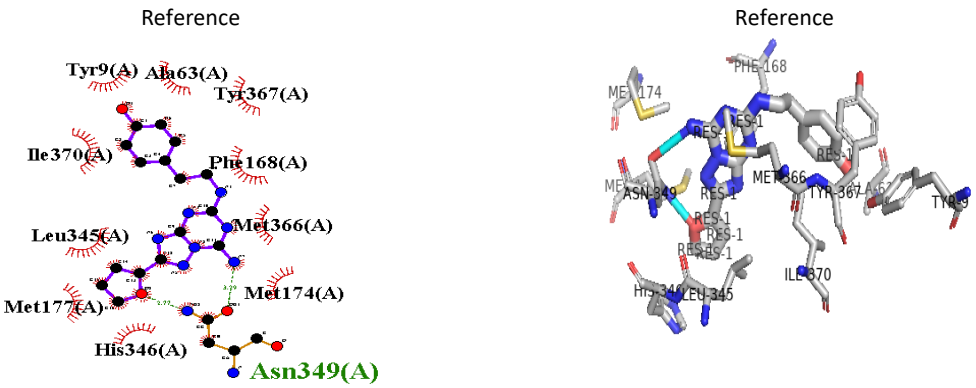

Fig. 4. The Ligplot and PyMol-generated two- and three-dimensional representations of the receptor and the screened compound interactions, respectively.-continue.

The inhibitors' efficacy and therapeutic potential in the treatment of Alzheimer's disease

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 [25].

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 A.D. are active [26]. This inhibitor may cross the central nervous system and blood-brain barrier, improving cell survival [27].

Sixth inhibitor (6)

With a docking score of -28.17 kcal/mol, compound six has very strong inhibitory action against A.D. 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 (Kaplan [28]. This chemical can preserve spinal function while reducing or eliminating cognitive impairment [29]. Compound six can, therefore, function as a chemotherapeutic anti-Alzheimer drug with a healthier potency and anti-amyloid properties.

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 A.D. by inhibiting β-amyloid aggregation and concurrently interacting with the catalytic and peripheral anionic active sites ([30–32]. Reduce neurotoxicity and have a high permeability, making them a good pharmacological option for Alzheimer's disease therapy [33,34].

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 A.D. as evaluated and possesses qualities of an attractive therapeutic candidate [35,36].

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 C.A.S. and P.A.S., making it a potent suppressor of acetylcholinesterase compounds [37]

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 [38].

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. It also shows antioxidant action and can prevent beta-amyloid aggregation [39]. 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. 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 A.D. and has distinct properties. Along with being a powerful antioxidant and neuroprotectant, they are able to pass the blood-brain barrier. The activating effect of the benzylamine was due to the alkyl group attached to the second position in the parent structure.

A caveat to this study that employs molecular docking to predict the binding affinity of ligands to the active site of the target protein is that we have not employed molecular dynamics simulation (MDS) to assess the stability and behavior of the docked complexes over time [40]. It is well known that docking provides a static representation based on scoring functions that may not consider protein flexibility, interactions with water, or contributions to entropy [41]; thus, the predicted interactions is incomplete. We are currently utilizing MDS in to gain a clearer understanding of the behavior and interactions of ligand-receptor complexes in real-world conditions of which the results will be published in the near future.

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The selected substances' capacity for neuroprotection

Hybridization is a relatively new and improved theory in the field of computer-aided drug design and development that proposes combining different bioactive components found in chemical compounds in order to increase bonding and medicinal benefits [42]. These substances can target several targets and are less harmful [43]. According to Teixeira et al. [44] neurotoxicity, oxidative stress, and reactive oxygen species production are the main suspects in A.D. physiology. However, because of their bioactive composition, hybrid compounds are multitargeted and have intrinsic capabilities to prevent or treat A.D. or protein aggregation, which typically leads to the formation of A.D.

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 [26,32]. However, regarding radical scavenging and unambiguous activity, hybrid compounds (oxidised, alkenylated, and amidated forms) are more active than the parent compounds [45]. As a result, they are multitargeted against diseases, including A.D.

Pharmacokinetic characteristics and anticipated medicinal properties

We utilized SwissADME, an online tool, to forecast and assess essential pharmacokinetic properties and verify adherence to Lipinski's Rule of Five. This enabled us to ascertain the drug-like and therapeutic properties of the hybrid compounds. **Table 4** presents the anticipated values for the octanol-water partition coefficient (log Po/w), blood-brain barrier (BBB) permeability, calculated lipophilicity (clogP), molecular weight (MW), lipophilic characteristics, and skin permeability (log Kp) to identify compounds potentially effective as anti-Alzheimer's agents. All compounds satisfy the molecular weight criterion of less than 500 Da, except for compound 3, which has a value of 829.85 g/mol, exceeding the limit and indicating reduced oral bioavailability.

All tested compounds, with the exception of compound 3, exhibit a Topological Polar Surface Area (TPSA) within the favorable range of 20–130 Å². This indicates that they may be effectively absorbed in the intestines [46]. **Table 4** indicates that all tested compounds, with the exception of the reference drug (log Po/w = 5.38), possess log Po/w values below the threshold of 5.0. This indicates that the membrane is permeable and can function in lipid environments [47]. The compounds that were nearly screened exhibit favorable characteristics for traversing the blood-brain barrier (BBB), being absorbed by the human intestine (HIA), and permeating the skin (log Kp). This indicates that they may serve as effective oral anti-Alzheimer's medications that target the brain [48–50].

BOILED-egg plots and radar plots

Fig. 5 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 **Fig. 6** 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 [52]. The best chemicals for brain disorders are those found in the yolk region since they may enter the intestinal tract [53].

Table 4. 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

Similarity to drugs and medicinal chemistry

The expected descriptors of the screened compounds are displayed in **Table** 5. 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 5** 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 [51].

Table 5. 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

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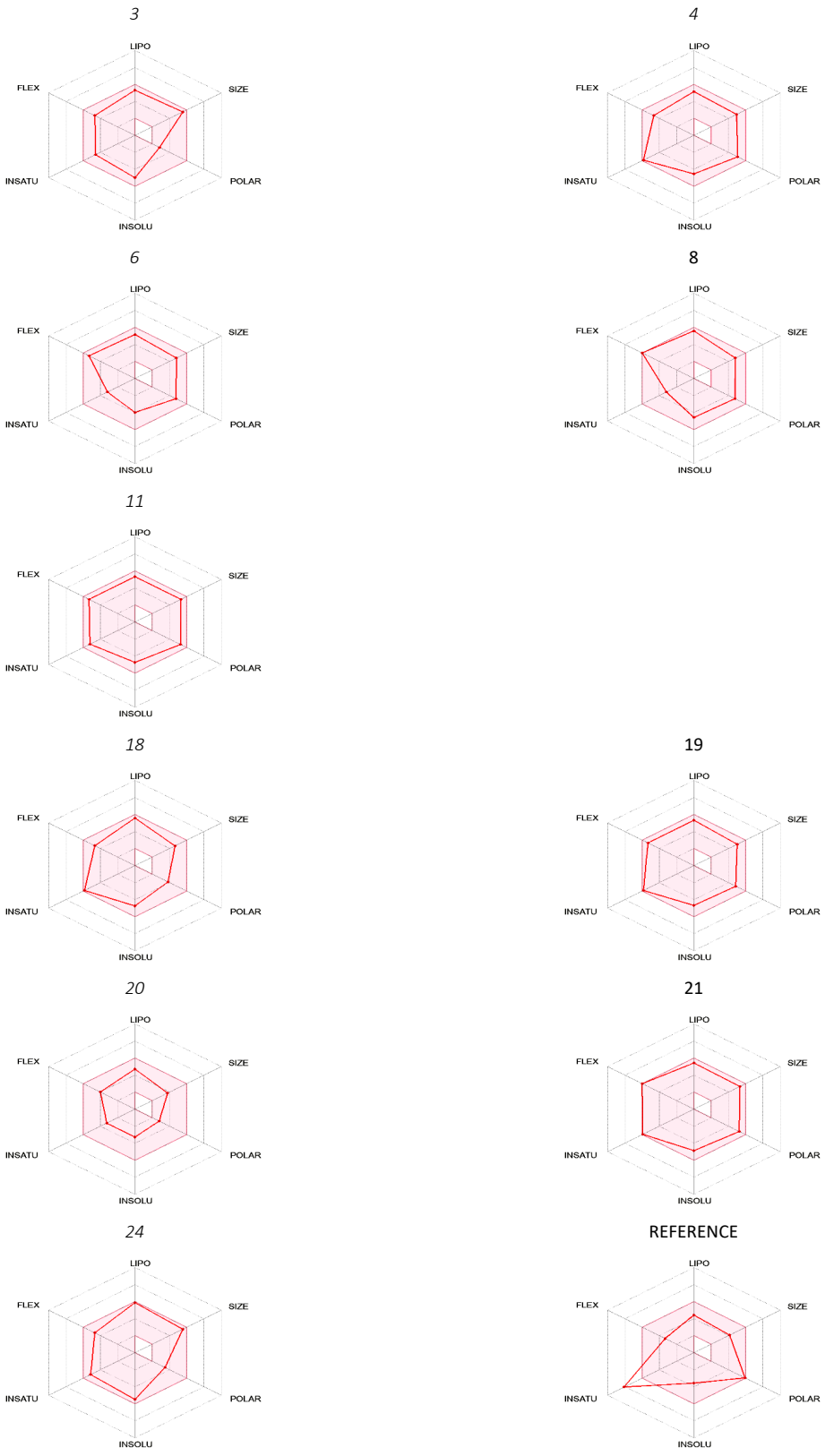

Fig. 5. Bioavailability Radar plots of the screened PLE-derived compounds and reference compound, illustrating six key physicochemical properties. Compounds falling within the pink area are predicted to have optimal oral bioavailability, supporting their potential as drug-like candidates.

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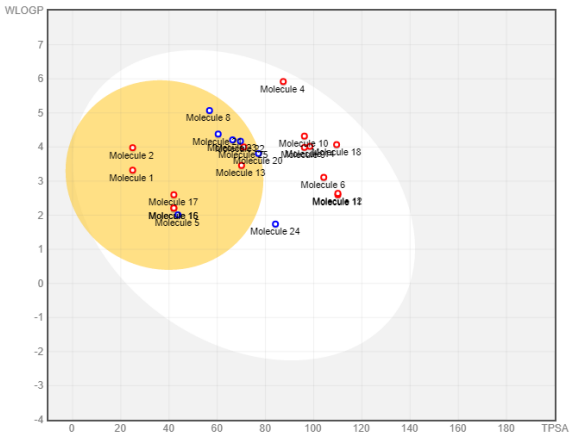

Fig. 6. An illustration of a BOILED-egg plot of the evaluated compounds. The graph illustrates the anticipated passive absorption of compounds into the brain, which is dependent upon their lipophilicity and polarity. Compounds within the yolk region are anticipated to traverse the blood-brain barrier (BBB) and is also anticipated to highly absorbed in the gastrointestinal tract. This renders these compounds to be suitable candidates for targeting the central nervous system (CNS). Conversely, compounds in the white (albumen) region, although is absorbed by the human intestine, is unable to traverse the blood-brain barrier (BBB). The yolk region indicates the compounds most likely to be utilized for addressing neurological issues.

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 used for 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 good molecules, including in-vitro and in-vivo tests.

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