JOBIMB, 2024, Vol 12, No 2, 37-43
https://doi.org/10.54987/jobimb.v12i2.1016

JOURNAL OF BIOCHEMISTRY, MICROBIOLOGY AND BIOTECHNOLOGY

Website: http://journal.hibiscuspublisher.com/index.php/JOBIMB/index

JOBIMB VOL 12 NO 2 2024
Bacterial acrylamidase

Molecular Docking and Drug Kinetics Assessment for Structure-Based Drug Design of New Piperazine-Containing Hydrazone Derivatives as Effective Alzheimer Inhibitors

Ibrahim Abdulganiyyu Akinbo[1,2]*, Maimuna Shehu Rufa'i[1], Abduljelil Ajala[3] and Abass Sambo[4]

[1]Department of Public and Environmental Health, Federal University Dutse, Ibrahim Aliyu Way Bye-Pass, Dutse, 720223, Jigawa State, Nigeria.
[2]Department of Science Laboratory Technology, College of Science and Technology, Jigawa State Polytechnic, Dutse, PMB 7040, Nigeria.
[3]Department of Chemistry, Faculty of Physical Sciences, Ahmadu Bello University, Samaru Main Campus, 810211, Kaduna, Nigeria.
[4]Ministry of Higher Education, Science and Technology, Block B Q2, New Secretariat Complex, 3-Arm Zone, Dutse, Jigawa State, Nigeria.

*Corresponding author:
Ibrahim Abdulganiyyu Akinbo,
Department of Public and Environmental Health,
Federal University Dutse,
Ibrahim Aliyu Way Bye-Pass,
720223 Dutse,
Jigawa State,
Nigeria.
Email: aaibrahim@fud.edu.ng

HISTORY

Received: 29th Sep 2024
Received in revised form: 21st Nov 2024
Accepted: 15th Dec 2024

KEYWORDS

Alzheimer's Disease
Computer-aided drug design
Complex mechanism
Binding energy
Pharmacokinetics

ABSTRACT

The neurodegenerative condition known as Alzheimer's disease (AD) impairs cognitive function and produces dementia in older people. The disease's precise mechanism is still a mystery. Four drugs are available. However, they all have a long list of adverse effects and only help people with their warning signs. Medicinal chemists are searching for ways to treat this disease. There is discussion about creating and using a new class of multifunctional small molecule inhibitors. The hydrazone scaffold was used to create a wide range of chemicals. This is because hydrazone derivatives may disrupt the self-assembly of amyloid beta (A), one of the factors that cause fibrils and oligomers. They may also reverse the effects of harmful compounds like free radicals on effective therapeutic agents like medications that penetrate the central nervous system. Structure-based drug design methods were used in this investigation. A protein target (code ID 4EY7) was selected based on published literature research and factors like a lower resolution value (2.35), no mutation, Homo sapiens, and the X-ray diffraction technique. Fifteen Hydrazone derivatives with increased interactions, higher binding scores, and improved drug-like properties and drug kinetic parameters were designed using the protein target, engineered to interact with compounds of interest (a lead compound with a higher binding energy). Promising pharmacotherapeutic drugs for AD treatment may be developed using the results of these investigations.

INTRODUCTION

The elderly are most affected by Alzheimer's disease (AD), a chronic neurodegenerative disorder linked to dementia and cognitive impairment [1]. However, a thorough explanation of the mechanism of sickness is still pending. Numerous investigations have shown that a significant factor in the pathophysiology of neurodegenerative disorders in the brain is neuro-inflammation linked to amyloid-beta (A) deposition [2]. Therefore, the inflammatory process in neurodegeneration requires that this link be broken right away [3]. According to recent research, molecules with the hydrazone moiety have a wide range of biological functions [4]. As possible therapies for Alzheimer's disease, pharmacologically active hydrazone derivatives with anti-neuroinflammatory properties are now being researched [5]. These results led to the creation of a new class of hydrazone derivatives. With structure-based drug design, this set of investigations supports the creation of innovative and effective drugs for treating Alzheimer's disease [6]. Current research aims to find possible hydrazine compounds that may be used as therapeutic possibilities. Using structure-based drug design, drug properties, molecular docking, and enhanced bonding with the Human Acetylcholinesterase receptor (4EY7), which is known to complete the pertinent complex for the treatment of AD—the derivatives of hydrazone were found [7-8].

In order to better understand how and where the inhibitor binds to AD, this study aimed to perform molecular docking of hydrazone with human acetylcholinesterase to analyse the binding orientation and affinities of hydrazone. Additionally, a lead compound that could be used to create powerful, non-toxic hydrazone derivatives with the lowest binding energy that will be assessed for pharmacokinetics and drug-likeness properties was obtained.

MATERIALS AND PROCEDURE

Several methods have been used to identify, synthesise, and test the best hydrazone compounds that may block the Human AChE receptor (4EY7). 4EY7 is a promising target protein for the therapy of AD because of its functioning, which may prevent brain-related disorders.

Retrieval and Cleaning of Receptors

The receptor's crystallography, which was established in the literature, was gathered from the PDB (rcsb.org) and had the following features: no mutation, a lower resolution value (2.35Å), Homo sapiens, and the X-ray diffraction technique [9]. Structure validation tools known as PROCHECK have been used to discover further and verify receptor characteristics software (ebi.ac.uk/Thornton-srv/software/PROCHECK/). A picture of the cleaned and recovered
the receptor is shown in **Fig. 1**.

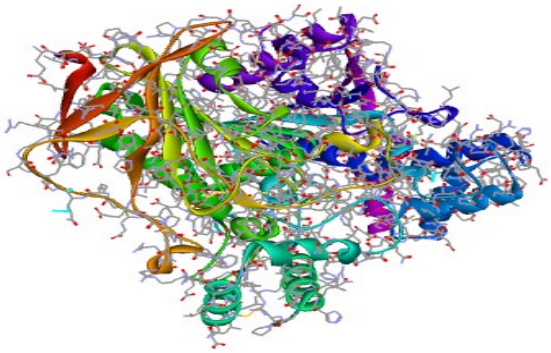


Fig. 1. Human AChE receptor (4EY7) with a resolution value (2.35Å).

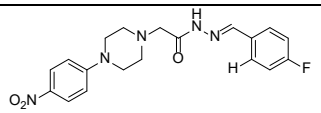
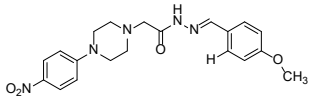
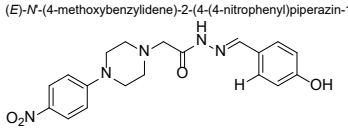
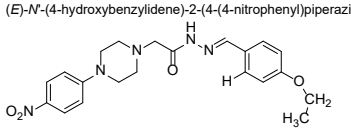
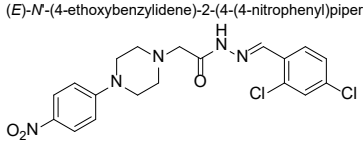
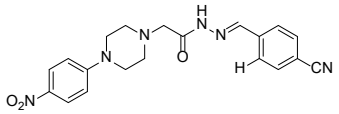
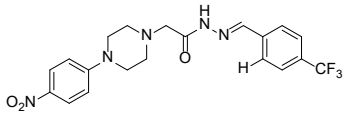
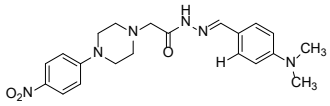
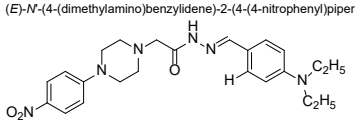
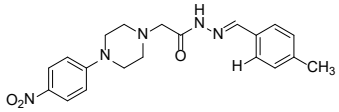
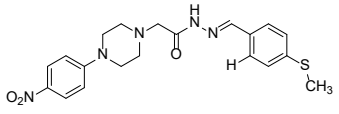
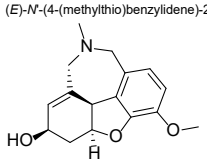
Screening of Compounds

Table 1 [10] and the binding scores for the hydrazone compounds were taken from the literature. The structures were created using ChemDraw Professional version 16.0 and saved as SD files. On the Spartan '14 interphase, it was first seen in 2D before being transformed to 3D. Energy minimisation was applied to the 3D molecules. Geometrical optimisation computations were carried out using a basis set of 6-31G** and DFT at the B3LYP level [11]. Until they could be further examined, the chemicals were stored in a PDB file. ICM Pro, based on docking, was used to screen ligand molecules virtually [12]. The greatest binding interaction with the receptor, known as the binding affinity (kcal mol-1), is used by ICM Pro to classify ligands [13].

Compound Screening

For the creation of hydrazone derivatives, the molecule with the lowest scores, the strongest binding interaction, and the best stability was selected as a template [14]. The developed compounds' pharmacokinetics, drug-likeness, and physicochemical characteristics were investigated.

Table 1. Hydrazone compounds with IUPAC names and data set docking scores.

S/No	Molecule	ΔG (kcalmol^{-1})
1	 (*E*)-*N*'-(4-fluorobenzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)acetohydrazide	-20.18
2	 (*E*)-*N*'-(4-methoxybenzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)acetohydrazide	-15.27
3	 (*E*)-*N*'-(4-hydroxybenzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)acetohydraz	-14.32
4	 (*E*)-*N*'-(4-ethoxybenzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)acetc	-15.44
5	 (*E*)-*N*'-(2,4-dichlorobenzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)acetohydraz	-10.75
6	 (*E*)-*N*'-(4-cyanobenzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)acet	-14.87
7	 (*E*)-2-(4-(4-nitrophenyl)piperazin-1-yl)-*N*'-(4-(trifluoromethyl)benzylidene)aceto	-18.99
8	 (*E*)-*N*'-(4-(dimethylamino)benzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)acetohydı	-14.05
9	 (*E*)-*N*'-(4-(diethylamino)benzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)aceto	-19.25
10	 (*E*)-*N*'-(4-methylbenzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)acetohydraz	-10.77
11	 (*E*)-*N*'-(4-(methylthio)benzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)acetohydra	-15.71
	 (2*R*,3a*S*,3a^1*S*)-5-methoxy-9-methyl-3,3a,3a^1,8,9,10-hexahydro-2*H*-4-oxa-9-azacyclohepta[*def*]fluoren-2-ol	-14.74
	Reference Compound: Galantamine	

Verification, investigation of docking analysis, and validation Protocol for Docking

The docking analysis and validation were then performed using the Glide module in the Schrodinger suite to recognize potential inhibitors targeting 4EY7. The protein was prepared through energy minimization, protonation adjustments, and removal of unnecessary water molecules, while ligands from the literature were optimized for stereochemistry, ionization, and energy using LigPrep. Docking was carried out with High Throughput Virtual Screening (HTVS), Standard Precision (SP), and Extra Precision (XP) modes to rank ligands based on binding affinity and interactions. Validation involved re-docking the co-crystallized ligand of 4EY7 to ensure protocol reliability, with an RMSD ≤ 2.0 Å confirming accuracy.

Ligand-protein interactions, including hydrogen bonds, hydrophobic contacts, and π-π stacking, were visualized and compared to key active site residues. Hydrazone derivatives with superior binding scores were identified and further optimized as templates for enhanced interactions. The pharmacokinetic properties and drug-likeness of the proposed compounds were evaluated using QikProp, focusing on absorption, distribution, metabolism, excretion, and toxicity (ADMET) parameters, alongside compliance with Lipinski's Rule of Five and Veber's criteria. This integrated approach combining docking, validation, and ADMET analysis provided a robust framework for identifying lead compounds with potential therapeutic applications.

Identification and Kinetics of Drug Properties (Pharmacokinetics)

Using preadmet.qsarhub.com/ and molinspiration.com/cgi-bin/properties, the ligands' pharmacological characteristics were determined. The hydrogen acceptor, hydrogen donor, molecular weight, number of rotatable bonds, clog P, and drug-likeness were all examined using Lipinski's Ro5. The blood-brain barrier and medication absorption in human intestines have also been studied using the Topological Polar Surface Area.

RESULTS AND DISCUSSION

Analysis and plot of receptors

Fig. 2 displays the protein target model's Ramachandran predicted plot, whose quality was evaluated using the PROCHECK online application. The model's non-glycine and non-proline residues exhibited dihedral angles in the most preferred and additionally permitted areas. The generously permitted portions had no residues, whereas the ones that were forbidden had 0.2% residues. The optimal zone had 787 residues, and the plotted value was 90.9%. 77 residues, or 8.9% of the total, were found in the authorised zone. Proline and glycine residue counts were 92 and 100, respectively. The Ramachandran plot showed a suitable proportion distribution of protein residues, indicating that the predicted model was of high enough quality to match the protein stereochemistry in the final model.

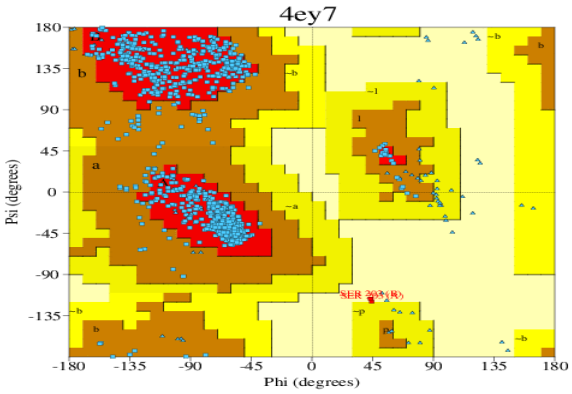


Fig. 2. Ramachandran plot of Protein Target.

Ligand Design and Screening

All of the novel piperazine-containing hydrazone compounds from the literature were docked, with molecule 1 having the lowest binding score of -20.18 kcal mol-1 (See **Table 1**) and used as a template (**Fig. 3**) to design several hydrazone derivatives.

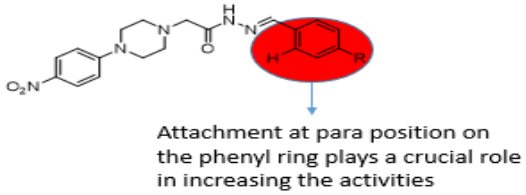


Fig. 3. 2D Structure of the template compound.

Verification and Inquiry of Docking Analysis and Validation Docking Protocol

The most effective way for a ligand and its receptor (therapeutic target) to interact was using molecular docking, which helps predict molecules quickly. As a docking process validation, the co-crystallised ligand and target from the PDB file were re-docked before the compounds were analysed to see whether the approach was appropriate for this research specifically. According to re-docking analysis, the superimposed ligand's Root mean square deviation (RSMD), as displayed in **Fig. 4** and acquired using the Schrodinger suite's Glide module, has a threshold value of 0.1943Å < 2Å, demonstrating the high quality of the docking protocol and confirming the dependability of the molecular docking process [23].

A caveat is no to rely solely on binding energy (kcal/mol) in docking studies to assess drug candidates, which has its limitations, including a neglect of protein and ligand flexibility, issue of solvent effects, entropic contributions, and the relatively dynamic nature of biomolecular interactions. Docking often oversimplifies the scoring functions and inadvertently fails to address the biological relevance or stability.

What is needed is to incorporate Molecular Dynamics Simulations (MDS) to overcome these drawbacks by providing dynamic insights, accounting for solvent interactions, refining binding free energy through MM-PBSA/GBSA, and evaluating complex ligand target stability. MDS filters false positives and offers a mechanistic understanding of key interactions, making it an essential complement to docking for accurate and reliable drug candidate evaluation [24].

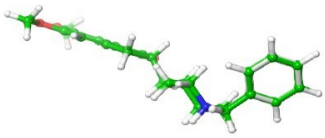


Fig. 4. Superimposition of the co-crystal ligand (green) was superimposed with its docked compound (white), revealing a significant RMSD of 0.1943 Å.

As seen in **Table 2**, fifteen compounds with lower binding scores and better interactions than the Template were produced by creating many hydrazone derivatives. The affinity of fifteen hydrazone derivatives for the human receptor (PDB ID: 4EY7) is shown in **Table 2**. Numerous linkages and the active site's highly conserved residues that bind to receptors are shown in **Table 2**, which supports the exceptional drugability potential of our designed compounds. The dimensions of the docked compounds (3D and 2D) are shown in **Fig. 5**. We can find potent inhibitors of this enzyme by molecularly docking these structures to the target's active site. The molecular docking data showed that the reference inhibitor (i.e., the Template) had higher interaction energies with the receptor than any developed compounds. Consequently, these compounds could block the receptors under study.

Determining the Drug's Kinetics and Properties

During drug development, the kinetics and properties of the drug are helpful for cautious and effective bonding exposure. To help determine those above, the doses of the marketed drugs were also established. Pharmacokinetic files provide professionals with pertinent data. **Table 3** displays the identification of drug properties and kinetics. All of the developed compounds passed the SwissADME web server filters, and the server indicated that they were drug-like. On ascertain if the created compounds complied with Pfizer's five-point criteria, they were posted on molinspiration.com.

The other four Pfizer Ro5 are included in **Table 4**, including Muegee [16], Veber [17], Egan [18], and all of the compounds that Ghose [19] authorised, including Teague's stringent leadlike criteria [20]. The molecules that were created showed promise as drugs. After going through the enzyme filter, compound D8 was predicted to be an AD inhibitor since it had the highest score of all the ligands, -27.23 kcal/mol.

However, compound D8 established three (3) hydrogen bonds with the protein, outperforming the reference medication regarding binding affinity and interaction. Galantamine, the reference drug employed, had a binding affinity of -14.74 kcal/mol with one (1) hydrogen bond interaction. The likelihood that the ligand would be active increases with the score. As seen in **Table 4**, it was predicted that all of our drug candidates would be disease inhibitors due to the significance of this filter's prediction. According to the data shown in **Table 4**, none of the developed compounds broke more than two of Pfizer's rules of five [15].

Table 2. Structures, Binding interaction of designed and reference compounds with receptor (4EY7).

S/No	ΔG (kcal mol^{-1})	nHB and Residue	nAmide-π Stacked and Residue	nπ-Alkyl and Residue
D1	-21.46	2 and LEU308, SER309	1 and PHE307	5 and LEU173, ALA318, HIE212, PRO216, LEU308
D2	-22.79	4 and ALA318, ASP320, ARG219, GLY220	LEU214	2 and PRO217, PRO216
D3	-22.16	1 and SER309,	2 and LEU214, PHE307	5 and MET211, ALA308, LEU315, PRO216, PRO217
D4	-23.04	2 and SER218, LEU308	2 and PHE307, LEU214	4 and LEU315, PRO216, PRO217, LEU173
D5	-22.31	2 and LEU308, SER215	2 and SER309, PHE307	3 and ALA308, ALA314, PRO217
D6	-22.70	2 and LEU308, ASP320	2 and PHE307, LEU214	2 and ALA318, PRO216
D7	-25.93	2 and PHE307, ASP310	2 and LEU214, HIE212	5 and LEU315, ARG177, PRO217, LEU308, PRO216
D8	-27.23	3 and THR311, ASP306, ASP320	1 and SER309	1 and PRO216
D9	-21.72	1 and ALA314	1 and LEU214	2 and PRO216, PRO217
D10	-20.44	2 and LEU173, MET211	1 and LEU214	3 and PRO216, LEU315, PRO217
D11	-20.93	2 and ASP310, LEU308	1 and PHE307	3 and PRO217, LEU315, ARG177
D12	-20.22	2 and LEU308, LEU173	1 and PHE307	3 and PRO216, LEU315, PRO217
D13	-20.46	2 and LEU308, ASP310	1 and PHE307	1 and PRO217
D14	-20.81	2 and LEU308, ASN170	1 and PHE307	1 and PRO217
D15	-20.86	2 and ASP310, THR311	2 and SER309, LEU214	2 and ALA318, ALA314
REFERE	-14.74	1 and LEU308	1 and LEU214	2 and PRO216, ALA318

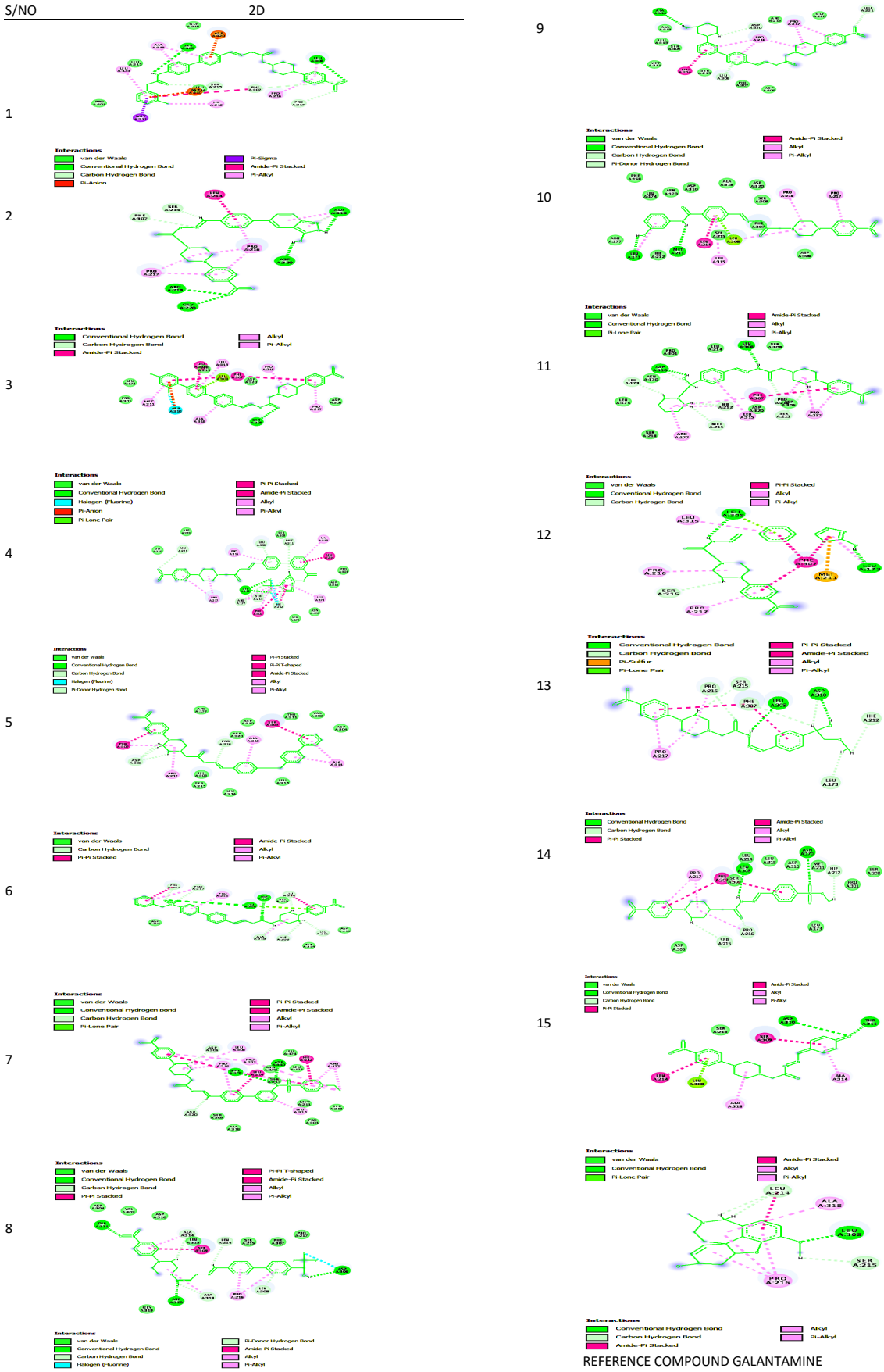


Fig. 5. 2D Visualisation of binding interactions of designed compounds and reference compounds.

Table 3. Physicochemical properties of reference and designed compounds.

Molecule	MW <600	Rot bonds ≤11	HBA ≤10	HBD ≤5	TPSA ≤140	Consensus Log P <5
1	591.66	12	6	3	134.89	3.63
2	498.54	8	6	3	118.46	2.25
3	555.57	9	7	1	93.76	4.68
4	629.63	7	9	2	118.68	4.65
5	547.65	8	5	1	93.76	4.58
6	597.68	9	7	1	106.28	3.7
7	522.69	9	7	2	115.31	3.45
8	542.51	10	10	2	126.88	2.74
9	542.63	9	7	2	135.91	2.11
10	494.59	10	7	2	117.23	1.85
11	400.70	8	8	3	111.9	1.94
12	450.45	8	8	2	138.7	1.06
13	441.48	10	7	2	123.22	1.11
14	445.49	9	8	1	129.12	0.83
15	461.49	9	8	1	125.51	1.23
Reference	273.33	1	4	1	41.93	1.59

Table 4. Drug-likeness analysis and reference of Designed compounds.

S/No	LV	GV	VV	EV	MV	BS	PAINS	BA	SA	EI	BS
1	2	3	1	1	1	0.17	1	3	3.30	Yes	0.58
2	1	2	1	1	0	0.55	1	3	3.68	Yes	0.70
3	1	2	0	0	1	0.55	1	3	3.95	Yes	0.36
4	1	4	1	1	2	0.55	1	3	3.42	Yes	0.73
5	1	3	1	0	1	0.55	1	3	3.08	Yes	1.10
6	1	3	1	1	1	0.55	1	3	3.36	Yes	0.44
7	2	3	2	1	2	0.17	1	4	3.41	Yes	0.57
8	1	2	0	0	0	0.55	1	3	3.24	No	0.11
9	2	3	0	1	0	0.17	1	3	3.59	No	0.14
10	0	2	0	0	0	0.55	1	3	3.23	yes	0.35
11	1	0	1	1	0	0.55	1	4	3.48	Yes	0.35
12	1	0	0	1	0	0.55	1	3	3.30	Yes	0.40
13	1	0	1	0	0	0.17	1	4	3.10	Yes	0.61
14	1	0	0	0	1	0.55	1	3	3.54	Yes	0.81
15	1	0	1	0	1	0.55	1	3	3.44	Yes	0.49
Reference	0	0	0	0	0	0.55	0	1	4.07	No	-0.03

The fifteen developed compounds' predictable values for several aspects of their pharmacokinetics and pharmacological characteristics are shown in **Table 5**. Absorption, distribution, metabolism, excretion, and toxicity were all incorporated in the model under investigation. **Table 5** shows the suggested ligands' intestinal absorption. The pharmaceutical industry uses the in-vitro CaCo-2 device for drug development and as a model to forecast oral medication absorption. A chemical is deemed extremely permeable if its model value exceeds 70 [21]. According to the study's results, all of the produced ligands had values of more than 70, which suggests that they have a high permeability towards Caco-2 cells.

A substance's degree of dispersion is determined by its distribution capacity (V), which is not the same as its physiological volume. Since a chemical is bound to bodily water, its real distribution volume cannot be more than that of physical water. The amount of free drug in plasma that may percolate and become ready to interact with the pharmacological target is the percentage of unbound drug. All of our produced compounds have VDss greater than 0.50, which indicates that the drug will be distributed throughout the tissue.

Finally, BBB penetration values reveal if a substance may cross the BBB, as seen in **Table 5**. In the central nervous system (CNS), a molecule is regarded as highly absorbing if its BBB value is more than 2.0 and as having intermediate absorption if its value is between 2.0 and 0.1 [22]. A chemical or its metabolite(s) is mostly eliminated from the body by metabolism and excretion. The findings indicated that the proposed compounds had modest absorption to the central nervous system. Substance metabolism is the chemical or enzymatic transformation of the parent substance into one or more readily excretable metabolites, with renal or biliary clearance being the main excretion route. According to **Table 5**, none of our compounds are substrates of the renal organic cation transporter 2 (total clearance) (OCT2), and all have excellent renal elimination (0.5–8.4 mL/min/kg). Lastly, toxicity testing verified the safety of every chemical created. Lastly, **Table 5** demonstrates that any of the above compounds has the potential to be a useful drug.

Table 5. Pharmacokinetic and toxicity analysis of designed and reference compounds.

	Models	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Ref
Absorption	A	0.60	0.74	0.68	0.51	0.83	0.74	1.18	0.96	0.53	0.72	0.64	0.95	0.37	0.06	0.24	1.37
	B	86.33	89.21	88.96	91.92	90.01	88.85	82.41	80.54	81.37	93.24	97.75	90.22	73.99	72.29	67.94	94.38
	C	-3.74	-2.74	-2.85	-2.74	-2.66	-2.74	-3.94	-2.77	-2.78	-2.80	-3.88	-2.77	-2.74	-2.74	-2.85	-3.03
Distribution	D	0.71	0.71	0.65	0.59	0.58	0.92	1.35	0.54	0.90	1.12	0.50	0.55	0.59	0.58	0.01	0.71
	E	0.24	0.34	0.22	0.37	0.21	0.23	0.15	0.12	0.15	0.32	0.33	0.17	0.39	0.07	0.24	0.58
	F	0.71	1.21	0.60	1.11	0.17	0.75	0.79	1.05	0.67	0.646	0.748	1.107	-0.94	-0.90	-1.02	0.25
	G	-1.08	-1.83	-1.99	-1.11	-1.07	-1.44	-1.51	-1.55	-1.64	-2.98	-1.89	-1.61	-3.00	-3.15	-3.16	-2.81
Metabolism	H	Yes	Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	Yes
	I	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
	J	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes
	K	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No	No	No	No	Yes
	L	Yes	Yes	No	Yes	No	No	Yes	Yes	No	No	No	No	Yes	No	No	Yes
	M	Yes	Yes	No	No	No	No	No	Yes	No	Yes	No	No	No	No	No	Yes
	N	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No
Excretion	O	0.57	0.71	0.62	0.87	0.54	0.88	0.92	1.76	0.67	1.67	0.81	1.52	0.17	0.42	0.45	0.15
Toxicity	P	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes
	Q	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes
	R	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes
	T	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes

A; $CaCO_3$ (log Papp in 10^{-6} cm/s), B; Human Intestinal Absorption (% Absorbed), C; Skin permeability (log Kp), D; VD_{ss} (human) (log L/kg), E; Fraction unbound (human) (Fu), F; BBB permeability (log BB), G; CNS permeability (log PS), H; CYP2D6 substrate, I; CYP3A4 substrate, J; CYP1A2 inhibitor, K; CYP2C19 inhibitor, L; CYP2C9 inhibitor, M; CYP2D6 inhibitor, N; CYP3A4 inhibitor, O; Total clearance (log ml/min/kg), P; Renal OCT2 substrate (Yes/No), Q; AMEX toxicity (Yes/No), R; Human ether-a-go-go-related gene inhibition, S; Carcinogens (mol/kg), T; Hepatotoxicity

CONCLUSION

This research developed hydrazone analogues, which were shown to be acetylcholinesterase inhibitors for Alzheimer's disease, using structure-based drug design. These methods provide crucial direction for creating new, powerful hydrazone derivatives with reduced Gibb's free energy (kcal/mol). With a docking score of -20.18 kcal mol-1, the lead Compound (also known as the Template) emerged victorious as the molecule with the greatest interaction and stability. Fifteen new Alzheimer's inhibitors with improved interactions, docking scores, drug-likeness, and drug kinetics were therefore designed using it. With the most powerful compound, 8, scoring 27.23 kcal mol-1 with the 4EY7 receptor, the docking study revealed significant active site residues involved in the binding interactions of all the suggested compounds. It demonstrated the dependability and safety of the created compounds.

ABBREVIATIONS LIST

Alzheimer's disease, or AD SA: Accessibility Synthetic, BS: Bioavailability Score, BA: Brenk alerts, The following infractions are listed: GV: Ghose, LV: Lipinski, EV: Egan, VV: Veber, and MV: Muegge. HIA: Absorption via the human gut, BBB: penetration of the blood-brain barrier, Enzyme Inhibitor (EI) and Bioactivity Score (BS)

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

Not applicable

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

FUNDING

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCE

1. Rosenberg A, Mangialasche F, Ngandu T, Solomon A, Kivipelto M. Multidomain interventions to prevent cognitive impairment, Alzheimer's disease, and dementia: From FINGER to World-Wide FINGERS. J Prev Alzheimers Dis. 2020;7(1):29-36.
2. Ozben T, Ozben S. Neuro-inflammation and anti-inflammatory treatment options for Alzheimer's disease. Clin Biochem. 2019;72:87-9.
3. Newcombe EA, Camats-Perna J, Silva ML, Valmas N, Huat TJ, Medeiros R. Inflammation: the link between comorbidities, genetics, and Alzheimer's disease. J Neuroinflammation. 2018;15(1):1-26.
4. Ramos-Inza S, Aydillo C, Sanmartín C, Plano D. Thiazole moiety: an interesting scaffold for developing new antitumoral compounds. In: Heterocycles-synthesis and biological activities. IntechOpen; 2019.
5. AlFadly ED, Elzahhar PA, Tramarin A, Elkazaz S, Shaltout H, Abu-Serie MM, et al. Tackling neuroinflammation and cholinergic deficit in Alzheimer's disease: Multi-target inhibitors of cholinesterases, cyclooxygenase-2 and 15-lipoxygenase. Eur J Med Chem. 2019;167:161-86.
6. Cummings JL, Tong G, Ballard C. Treatment combinations for Alzheimer's disease: current and future pharmacotherapy options. J Alzheimers Dis. 2019;67(3):779-94.
7. Zerroug E, Belaidi S, Chtita S. Artificial neural network-based quantitative structure–activity relationships model and molecular docking for virtual screening of novel potent acetylcholinesterase inhibitors. J Chin Chem Soc. 2021;68(8):1379-99.
8. Pascoini AL, Federico LB, Arêas ALF, Verde BA, Freitas PG, Camps I. In silico development of new acetylcholinesterase inhibitors. J Biomol Struct Dyn. 2019;37(4):1007-21.
9. Cheung J, Rudolph MJ, Burshteyn F, Cassidy MS, Gary EN, Love J, et al. Structures of human acetylcholinesterase in complex with pharmacologically important ligands. J Med Chem. 2012;55(22):10282-6.
10. Kaya B, Özkay Y, Temel HE, Kaplancıklı ZA. Synthesis and biological evaluation of novel piperazine containing hydrazone derivatives. J Chem. 2016;2016:1-8.
11. Mohdee V, Parasuk V, Pancharoen U. Synergistic effect of thiourea and HCl on palladium(II) recovery: An investigation on chemical structures and thermodynamic stability via DFT. Arab J Chem. 2021;14(7):103196.
12. Bhowmick S, Saha A, AlFaris NA, ALTamimi JZ, ALOthman ZA, Aldayel TS, et al. Identification of potent food constituents as SARS-CoV-2 papain-like protease modulators through advanced pharmacoinformatics approaches. J Mol Graph Model. 2022;111:108113.
13. Arthur DE, Uzairu A. Molecular docking studies on the interaction of NCI anticancer analogues with human phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit. J King Saud Univ Sci. 2019;31(4):1151-66.
14. Azimi F, Ghasemi JB, Azizian H, Najafi M, Faramarzi MA, Saghaei L, et al. Design and synthesis of novel pyrazole-phenyl semicarbazone derivatives as potential α-glucosidase inhibitor: kinetics and molecular dynamics simulation study. Int J Biol Macromol. 2021;166:1082-95.
15. Xiong G, Wu Z, Yi J, Fu L, Yang Z, Hsieh C, et al. ADMETlab 2.0: an integrated online platform for accurate and comprehensive predictions of ADMET properties. Nucleic Acids Res. 2021;49(W1):W5-W14.
16. Muegge I, Heald SL, Brittelli D. Simple selection criteria for drug-like chemical matter. J Med Chem. 2001;44(12):1841-6.
17. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. J Med Chem. 2002;45(12):2615-23.
18. Egan WJ, Merz KM, Baldwin JJ. Prediction of drug absorption using multivariate statistics. J Med Chem. 2000;43(21):3867-77.
19. Ghose AK, Viswanadhan VN, Wendoloski JJ. A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases. J Comb Chem. 1999;1(1):55-68.
20. Teague SJ, Davis AM, Leeson PD, Oprea T. The design of leadlike combinatorial libraries. Angew Chem Int Ed Engl. 1999;38(24):3743-8.
21. Volpe DA. Advances in cell-based permeability assays to screen drugs for intestinal absorption. Expert Opin Drug Discov. 2020;15(5):539-49.
22. Aswathy L, Jisha RS, Masand VH, Gajbhiye JM, Shibi IG. Design of novel amyloid β aggregation inhibitors using QSAR, pharmacophore modeling, molecular docking and ADME prediction. In Silico Pharmacol. 2018;6(1):1-19.
23. Halim SA, Sikandari AG, Khan A, Wadood A, Fatmi MQ, Csuk R, et al. Structure-based virtual screening of tumor necrosis factor-α inhibitors by cheminformatics approaches and bio-molecular simulation. Biomolecules. 2021;11(2):329.
24. Abd Shukor MS, Abd Shukor MY. Molecular docking and dynamics studies show: Phytochemicals from Papaya leaves extracts as potential inhibitors of SARS–CoV–2 proteins targets and TNF–alpha and alpha thrombin human targets for combating COVID-19. AIMS Mol Sci. 2023;10(3):213-62.