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RESEACH ARTICLE

MOLECULAR DOCKING AND DRUG KINETICS ASSESSMENT FOR STRUCTURE-BASED DRUG DESIGN OF NEW PIPERAZINE-CONTAINING HYDRAZONE DERIVATIVES AS EFFECTIVE ACETYLCHOLINESTERASE INHIBITORS FOR ALZHEIMER'S DISEASE

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Abstract

Background: Alzheimer's disease (AD), a progressive neurodegenerative disorder affecting cognitive functions, remains a critical medical challenge with limited treatment options and significant side effects. This study explores the potential of novel piperazine-containing hydrazone derivatives as acetylcholinesterase inhibitors, targeting a key enzymatic pathway implicated in AD progression. **Methods:** A structure-based drug design approach was adopted to identify and synthesize hydrazone derivatives. The study utilized the protein target 4EY7, recognized for its relevance in AD, with molecular docking and pharmacokinetic evaluations to optimize compound interaction and binding efficiency. **Results:** Fifteen hydrazone derivatives demonstrated enhanced binding interactions, stability, and superior drug-like properties compared to the reference compound. A lead compound with a binding energy of -27.23 kcal/mol showed the highest affinity and pharmacological promise, surpassing the reference compound, galantamine, in molecular docking analyses. **Conclusion:** The findings suggest that these hydrazone derivatives represent a promising class of multifunctional inhibitors with potential therapeutic applications in AD. Further investigations are warranted to validate their efficacy and safety in preclinical and clinical settings.

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

Introduction

The elderly are most affected by Alzheimer's disease (AD), a chronic neurodegenerative disorder linked to dementia and cognitive impairment(Ajala, Eltayb, et al., 2024; Borisovskaya et al., 2014; Mohamed & Rao, 2011) However, a thorough explanation of the mechanism of sickness is still pending. Numerous investigations have shown that neuro-inflammation is a significant factor in the pathophysiology of neurodegenerative disorders in the brain, which isinked to amyloid-beta (A) deposition (Ahmad et al., 2019; Leong et al., 2020) . Therefore, the inflammatory process in neurodegeneration requires that this link be broken right away (Adewale et al., 2022; Ajala et al., 2022; Behl et al., 2021; Jellinger, 2010; Kaya et al., 2016; Pathak et al., 2018).

According to recent research, molecules with the hydrazone moiety have a wide range of biological functions (Adewale et al., 2022; Ajala, Eltayb, et al., 2024; Ajala et al., 2022; Bilen et al., 2022; Kaya et al., 2016) . As possible therapies for Alzheimer's disease,

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pharmacologically active hydrazone derivatives with anti-neuroinflammatory properties are now being researched (Ajala et al., 2022; Kaya et al., 2016) . 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 (Adewale et al., 2022; Ajala et al., 2025; Ajala, Uzairu, et al., 2024).

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 (Amat-Ur-Rasool & Ahmed, 2015; Marucci et al., 2021; Nadri et al., 2013; R Saxena M., 2019).

In order to better understand how and where the inhibitor binds in 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 (Cheung et al., 2012) . Structure validation tools known as PROCHECK have been used to discover further and verify receptor characteristics software (ebi.ac.uk/Thornton-srv/software/PROCHECK/).

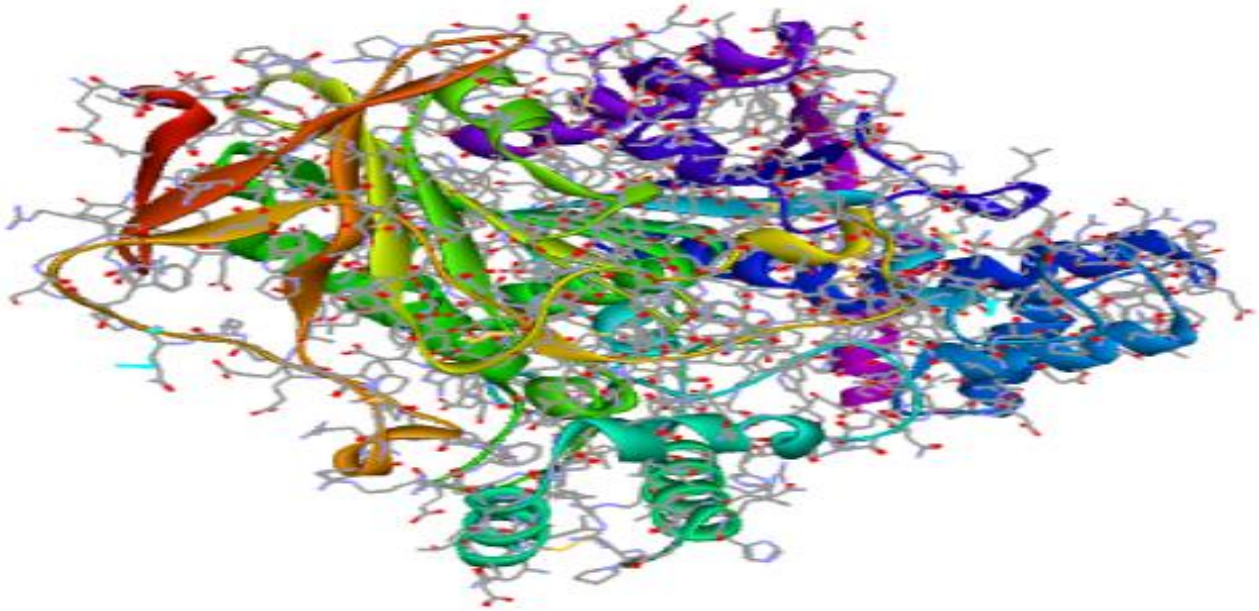


Figure 1: A cleaned and recovered receptor

Screening of Compounds

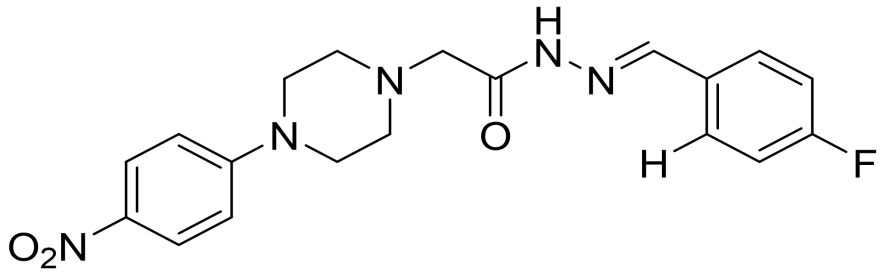
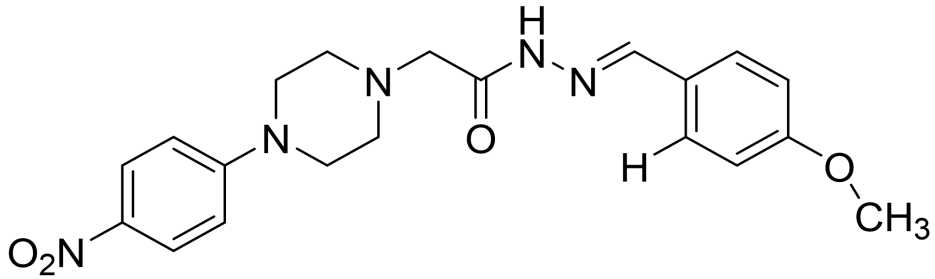
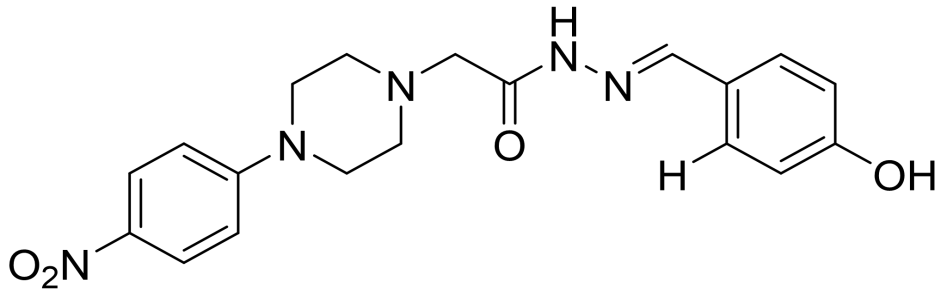
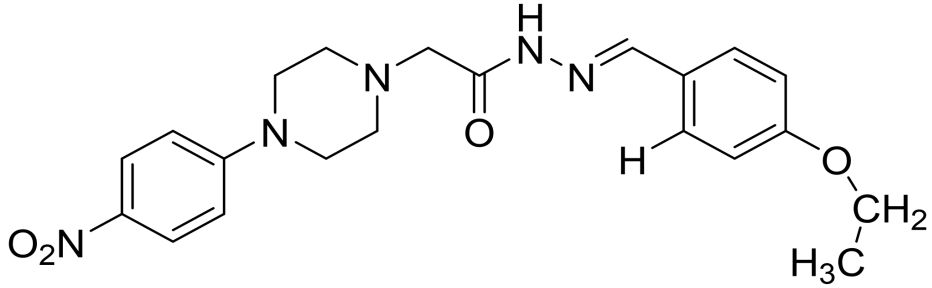
Table 1(Kaya et al., 2016) and the binding scores for the hydrazone compounds were taken from the literature. The structures were created using ChemDraw Professional version 16.0 and saved as SD files. On the Spartan '14 interphase, it was first seen in 2D before being transformed to 3D. Energy minimisation 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 (Ajala et al., 2022) . 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 (Rufa'i, Abdulganiyyu, et al., 2025) .

The greatest binding interaction with the receptor, known as the binding affinity (kcal mol-1), is used by ICM Pro to classify ligands(Rufa'i, Abdalla, et al., 2025) .

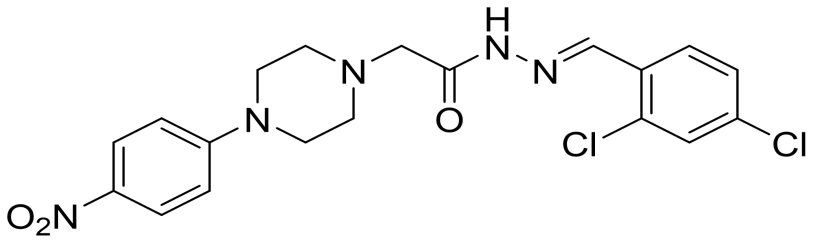
Compound Screening

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 (Abdulganiyyu et al., 2024; Ajala, Uzairu, et al., 2024; Akinbo et al., 2024) . The developed compounds' pharmacokinetics, drug-likeness, and physicochemical characteristics were investigated.

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

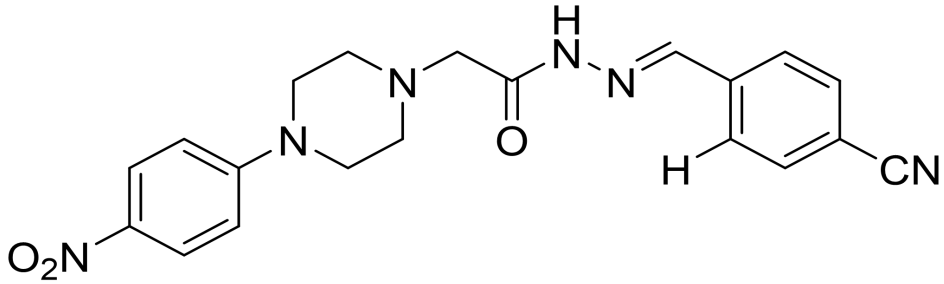
S/No	Molecule	ΔG (kcalmol^{-1})
1	 (*E*)-*N*'-(4-fluorobenzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)acetohydrazide	-20.18
2	 (*E*)-*N*'-(4-methoxybenzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)acetohydrazide	-15.27
3	 (*E*)-*N*'-(4-hydroxybenzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)acetohydrazide	-14.32
4	 (*E*)-*N*'-(4-ethoxybenzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)acetohydrazide	-15.44

5 -10.75



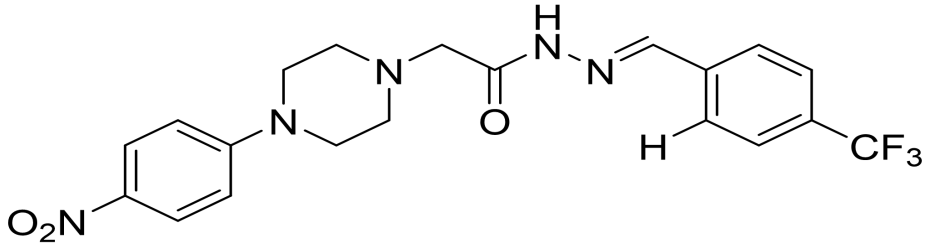
(*E*)-*N*'-(2,4-dichlorobenzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)acetohydrazide

6 -14.87



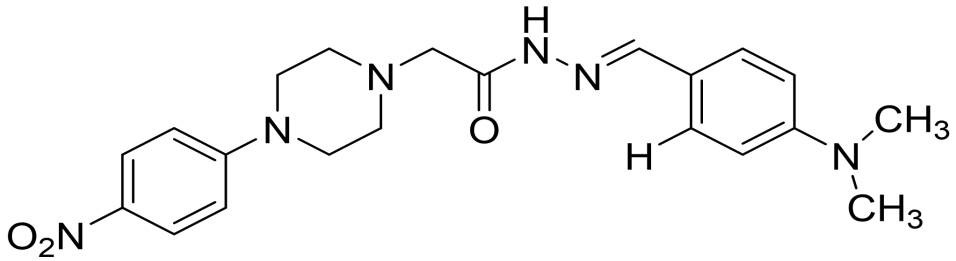
(*E*)-*N*'-(4-cyanobenzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)acetohydrazide

7 -18.99



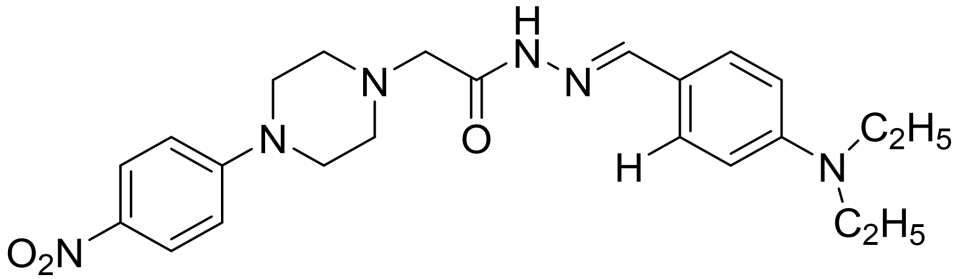
(*E*)-2-(4-(4-nitrophenyl)piperazin-1-yl)-*N*'-(4-(trifluoromethyl)benzylidene)acetohydra

8 -14.05



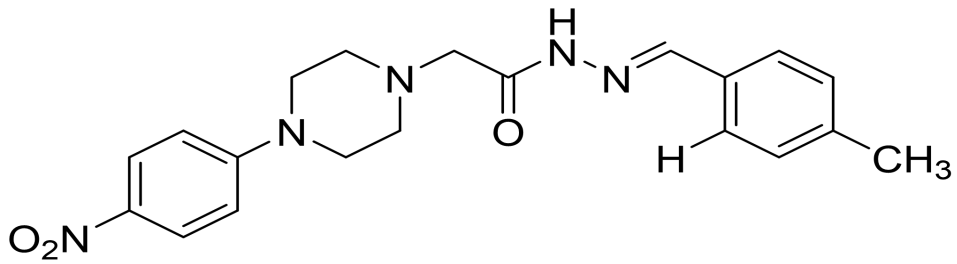
(*E*)-*N*'-(4-(dimethylamino)benzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)acetohydr

9 -19.25



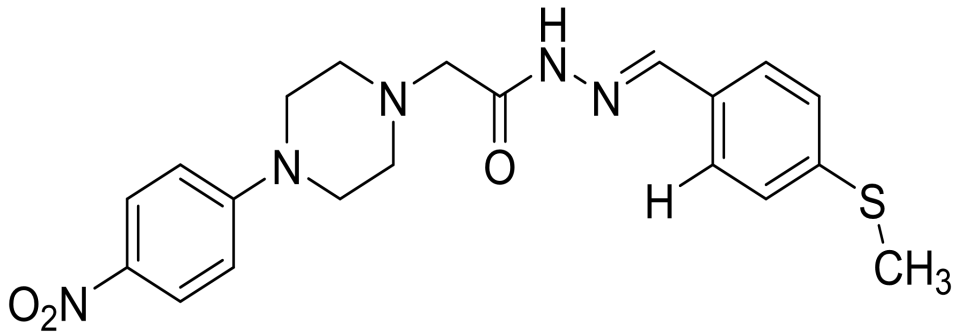
(*E*)-*N*'-(4-(diethylamino)benzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)acetohydrazi

10 -10.77



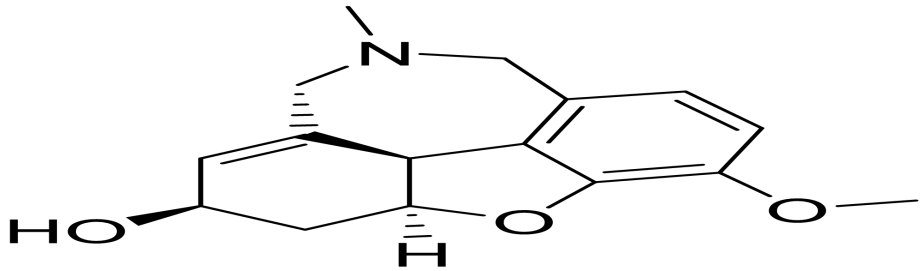
(*E*)-*N*'-(4-methylbenzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)acetohydrazide

11 -15.71



(*E*)-*N*'-(4-(methylthio)benzylidene)-2-(4-(4-nitrophenyl)piperazin-1-yl)acetohydrazid

-14.74



(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

Reference Compound: Galantamine

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

Every molecule in the literature was docked with the target (4EY7). The molecules with the best interaction had the lowest binding scores. Several hydrazone derivatives with better binding scores and interactions may be made using this template. The pharmacokinetic assessment and drug-like characteristics of the proposed compounds were further examined. The Glide module will be used in the Schrodinger suite to execute the docking validation methodology.

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

Figure 3displays 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 residue, 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.

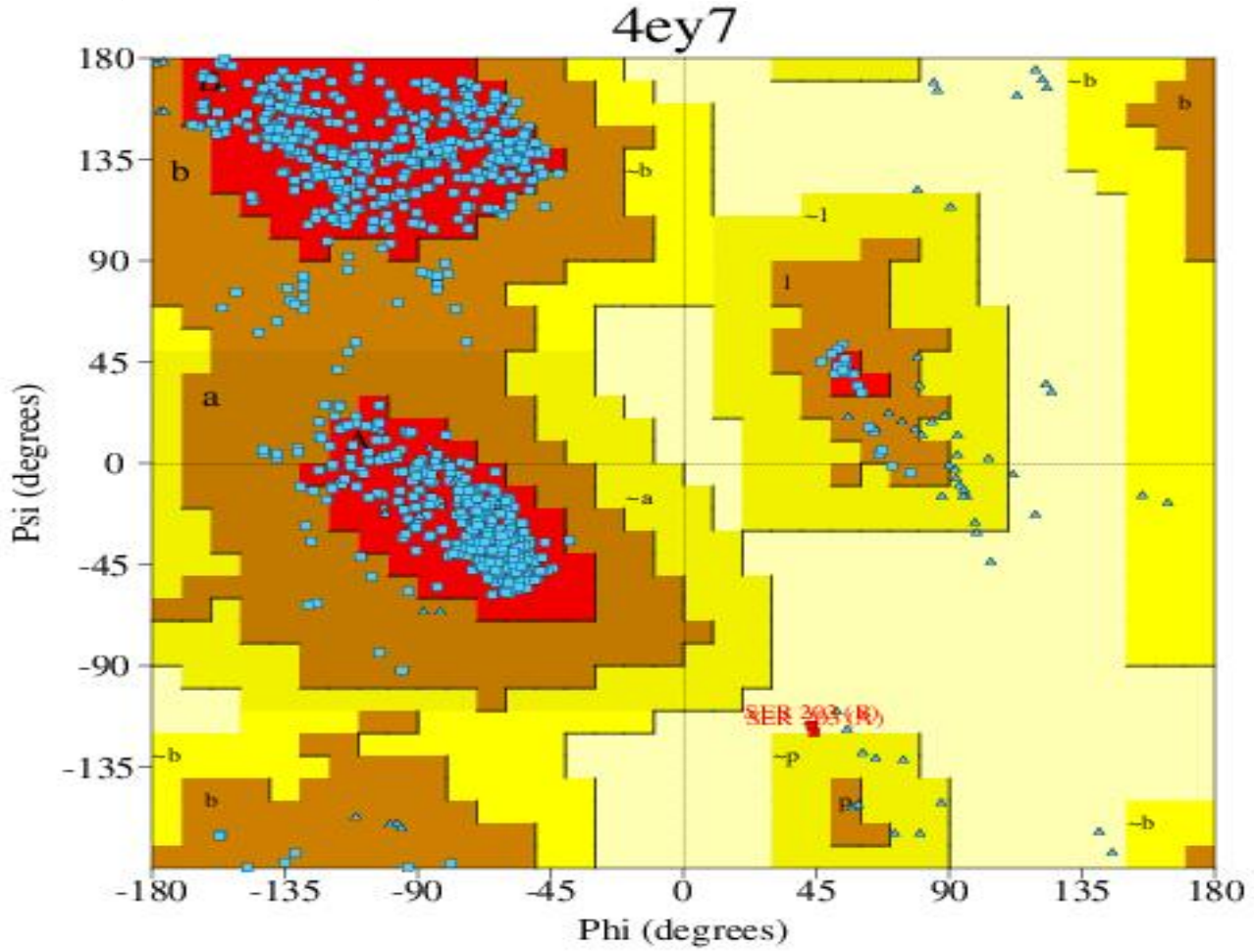


Figure 2: Ramachandran plot of Protein Target

Ligand Used for this study

most 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 (Figure 3) to design several hydrazone derivatives.

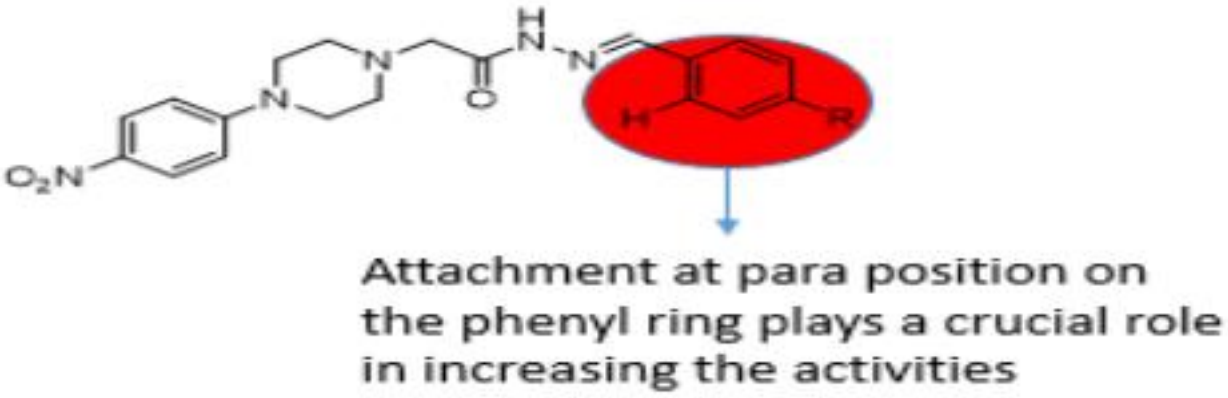


Figure 3: 2D Structure of the template compound

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 found using molecular docking, which helps predict molecules in a short period. 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 (Akinbo et al., 2024).

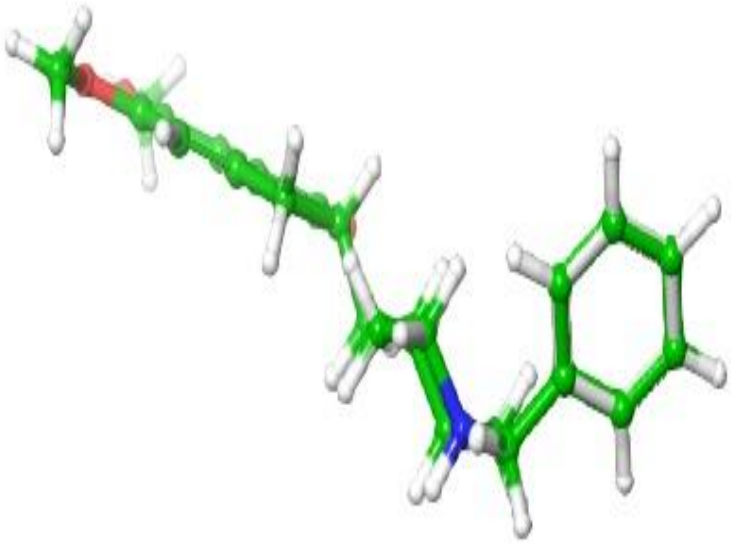
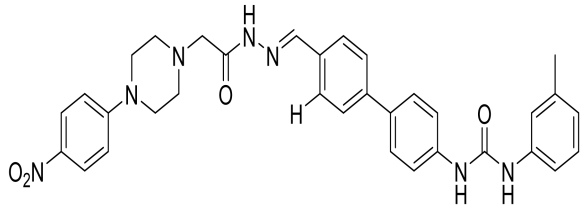
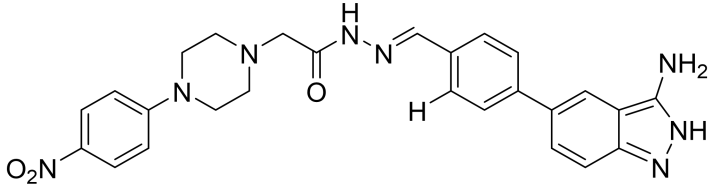
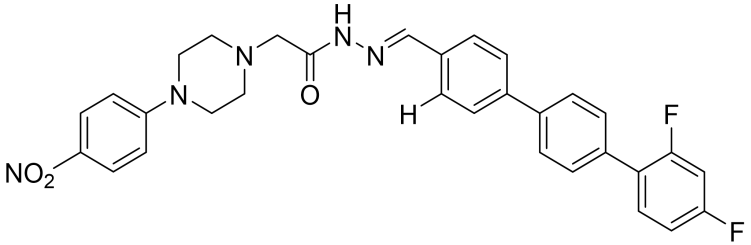
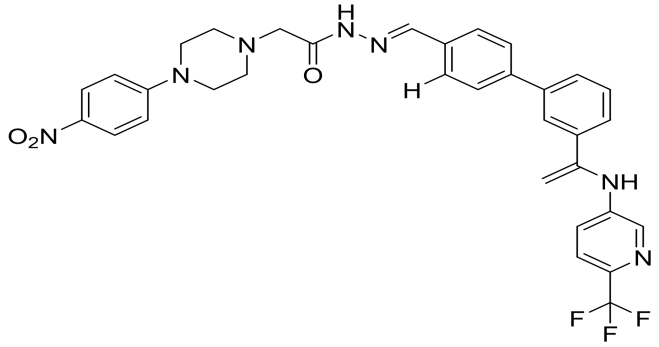


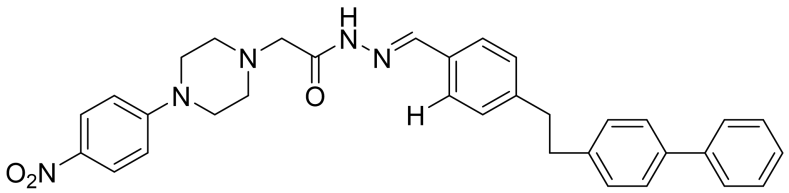
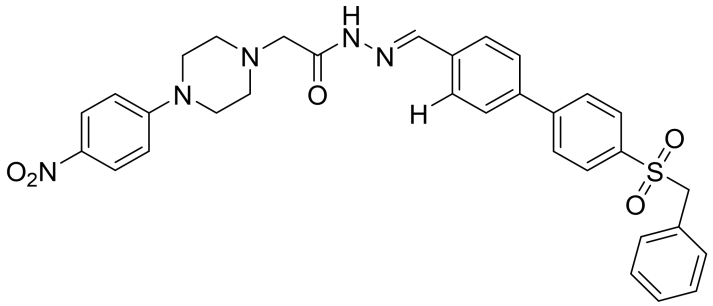
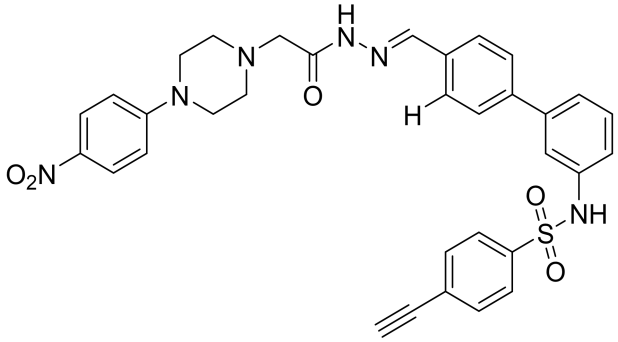
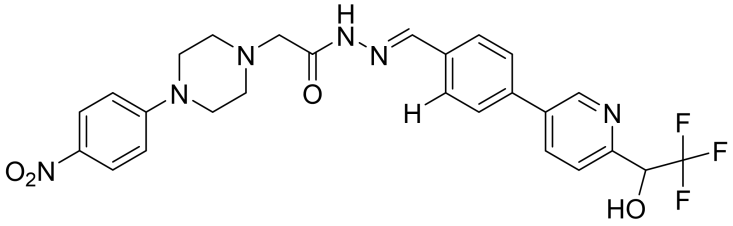
Figure 4: Superimposition of the co-crystal ligand (green) was superimposed with its docked Compound (white), revealing a significant RMSD of 0.1943 Å

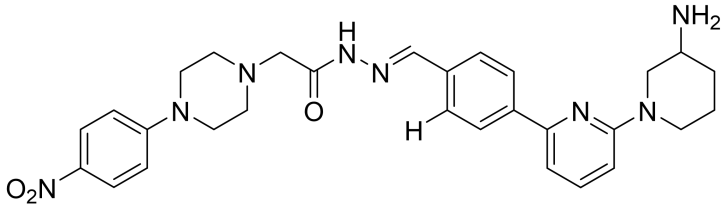
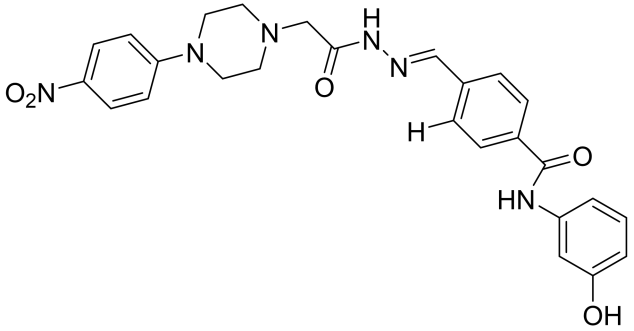
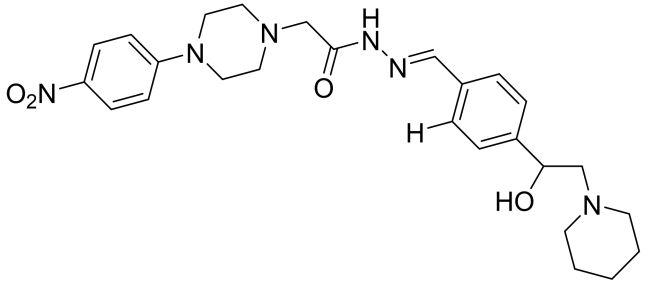
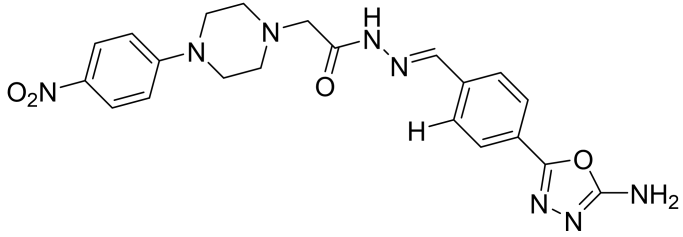
As seen in Table 2, fifteen compounds with lower binding scores and better interactions than the Template were produced by creating many hydrazone derivatives. The affinity of fifteen hydrazone derivatives for the human receptor (PDB ID: 4EY7) is shown in Table 2. Numerous linkages and the active site's highly conserved residues that bind to receptors are shown in Table 2, which supports the exceptional drugability potential of our designed compounds.

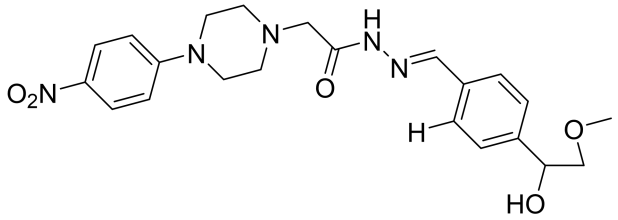
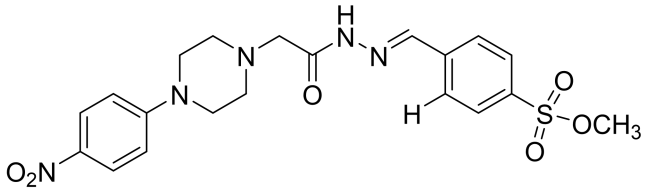
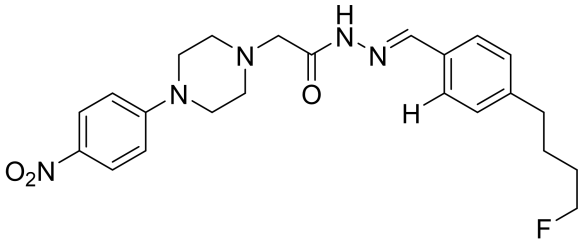
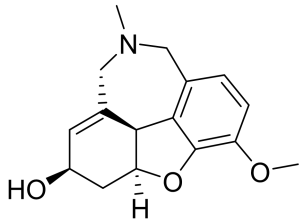
The dimensions of the docked compounds (3D and 2D) are shown in Figure 5. We can find strong inhibitors of this enzyme by molecularly docking these structures to the target's active site. The molecular docking data showed that the reference inhibitor (i.e., the Template) had higher interactions with the receptor than any developed compounds. Consequently, these compounds could block the receptors under study.

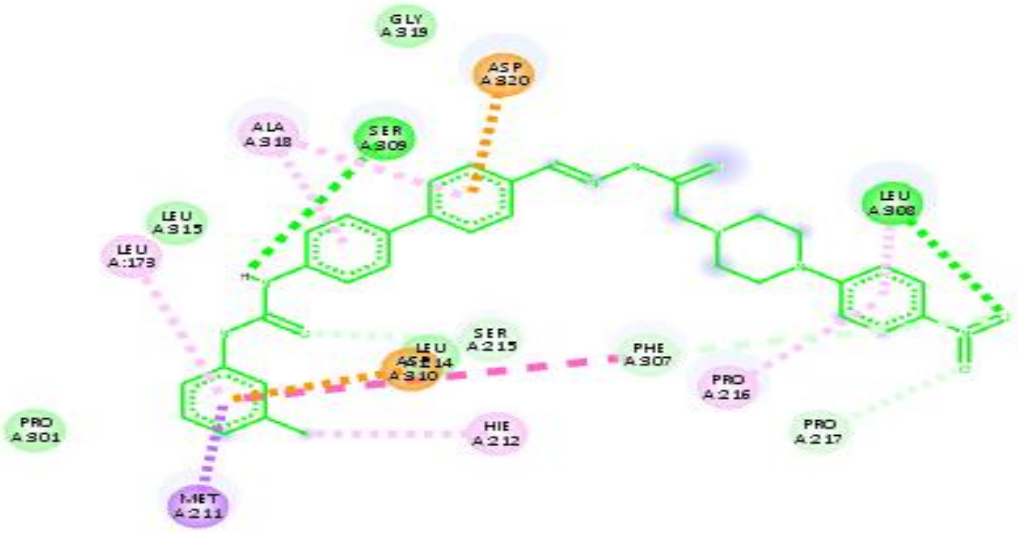
Table 2: Structures, Binding interaction of designed and reference compounds with receptor (4EY7)

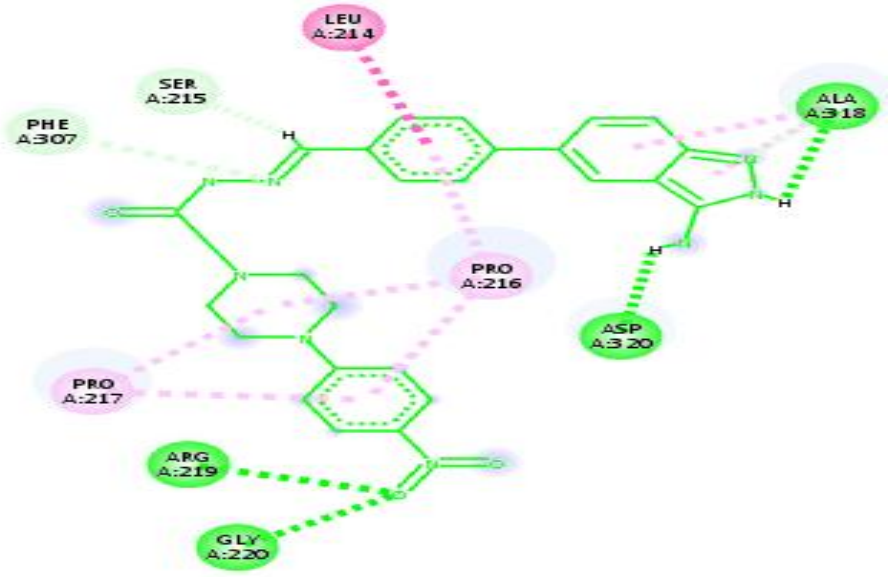
S/No		ΔG (kcal mol^{-1})	nHB and Residue	nAmide-π Stacked and Residue	nπ-Alkyl and Residue
D1		-21.46	2 and LEU308, SER309	1 and PHE307	5 and LEU173, ALA318, HIE212, PRO216, LEU308
D2		-22.79	4 and ALA318, ASP320, ARG219, GLY220	LEU214	2 and PRO217, PRO216
D3		-22.16	1 and SER309,	2 and LEU214, PHE307	5 and MET211, ALA308, LEU315, PRO216, PRO217
D4		-23.04	2 and SER218, LEU308	2 and PHE307, LEU214	4 and LEU315, PRO216, PRO217, LEU173

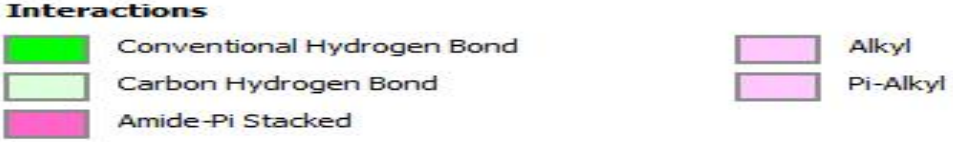
D5		-22.31	2 and LEU308, SER215	2 and SER309, PHE307	3 and ALA308, ALA314, PRO217
D6		-22.70	2 and LEU308, ASP320	2 and PHE307, LEU214	2 and ALA318, PRO216
D7		-25.93	2 and PHE307, ASP310	2 and LEU214, HIE212	5 and LEU315, ARG177, PRO217, LEU308, PRO216
D8		-27.23	3 and THR311, ASP306, ASP320	1 and SER309	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
REFERENCE (Galantamine)		-14.74	1 and LEU308	1 and LEU214	2 and PRO216, ALA318

S/No	2D Structures of ligand interactions
1	

2	



3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LEU A 308
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ASP A 320
PRO A 216
PRO A 301
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ASP A 310
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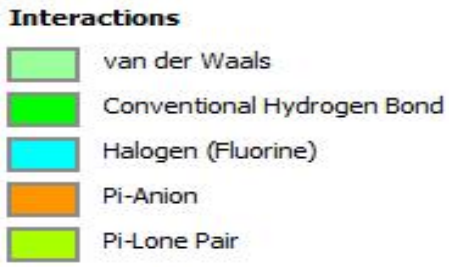
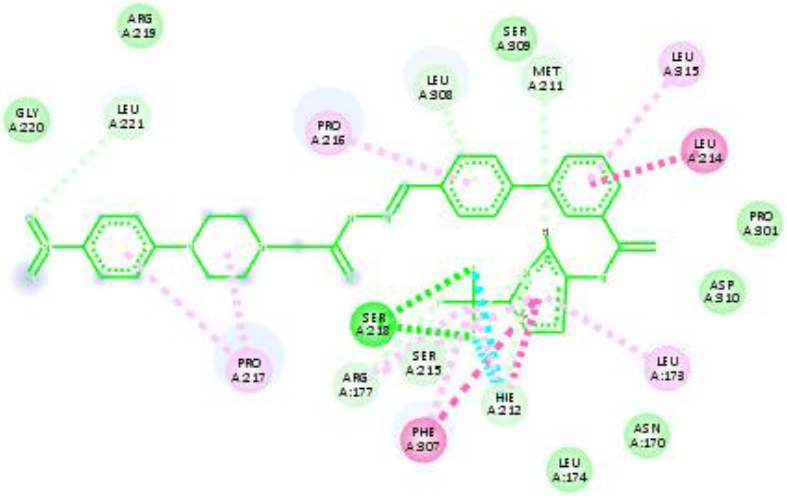
SER A 309
PRO A 217
ASP A 306


Interactions
van der Waals
Conventional Hydrogen Bond
Halogen (Fluorine)
Pi-Anion
Pi-Lone Pair
Pi-Pi Stacked
Amide-Pi Stacked
Alkyl
Pi-Alkyl

4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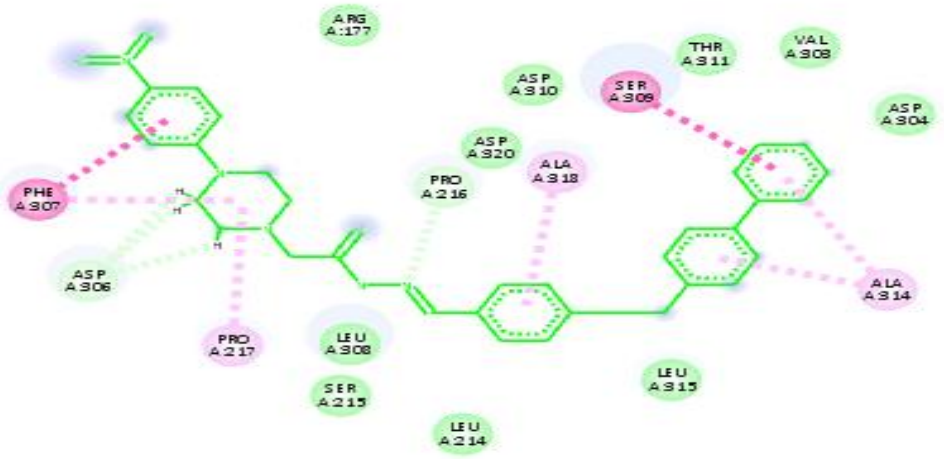
SER A 218
SER A 215
LEU A:173
ARG A:177
HIE A 212
PHE A 307
ASN A:170
LEU A:174
PRO A 217


Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Halogen (Fluorine)
Pi-Donor Hydrogen Bond
Pi-Pi Stacked
Pi-Pi T-shaped
Amide-Pi Stacked
Alkyl
Pi-Alkyl

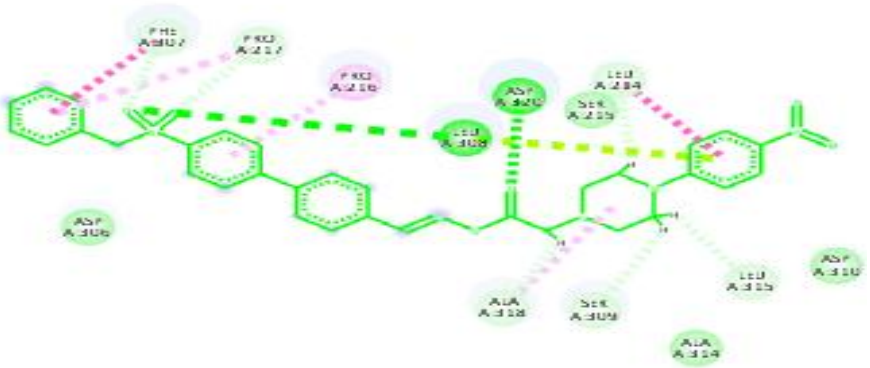
5



Interactions

- van der Waals
- Carbon Hydrogen Bond
- Pi-Pi Stacked
- Amide-Pi Stacked
- Alkyl
- Pi-Alkyl

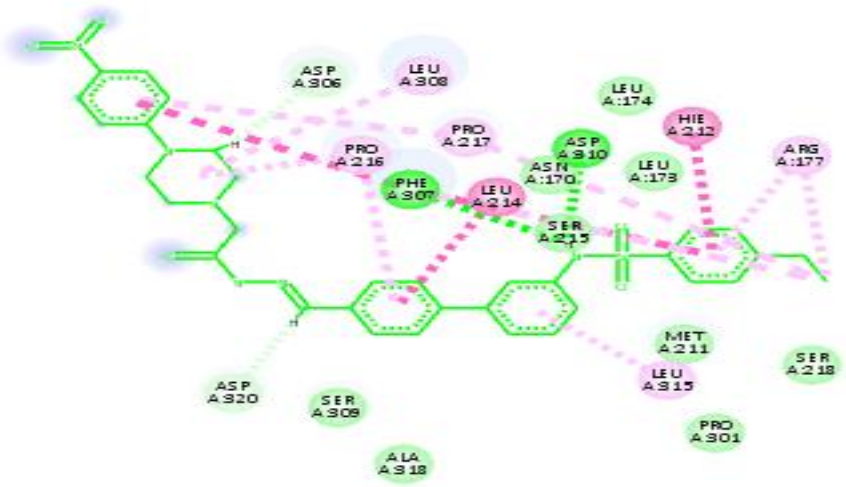
6



Interactions

- van der Waals
- Conventional Hydrogen Bond
- Carbon Hydrogen Bond
- Pi-Lone Pair
- Pi-Pi Stacked
- Amide-Pi Stacked
- Alkyl
- Pi-Alkyl

7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PRO A:217
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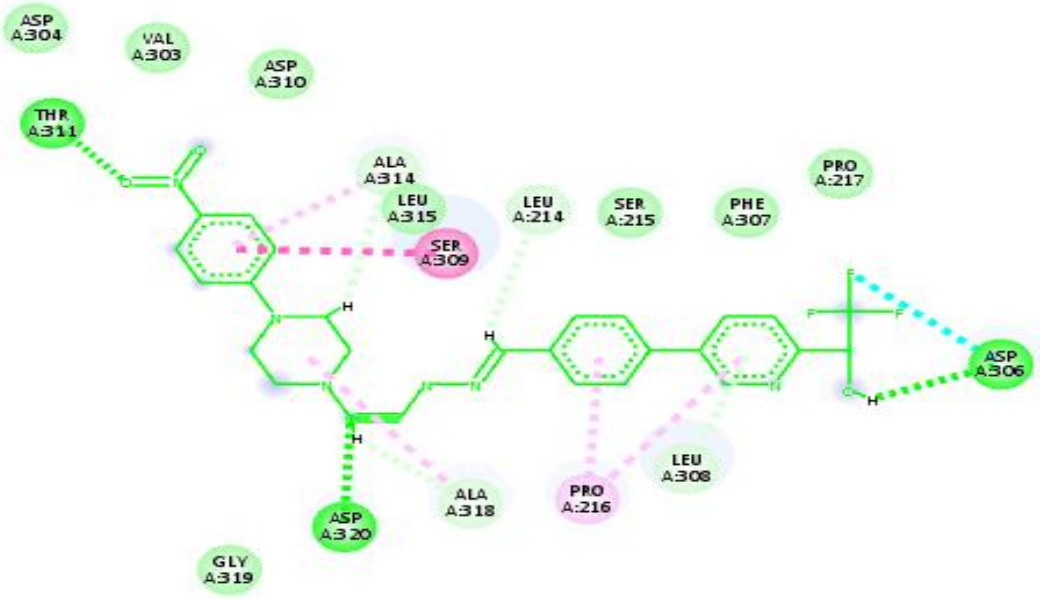
PHE A:307
LEU A:214
SER A:215
MET A:211
SER A:218
LEU A:315
ASP A:320
SER A:309
PRO A:301
ALA A:318


Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Pi Stacked
Pi-Pi T-shaped
Amide-Pi Stacked
Alkyl
Pi-Alkyl

8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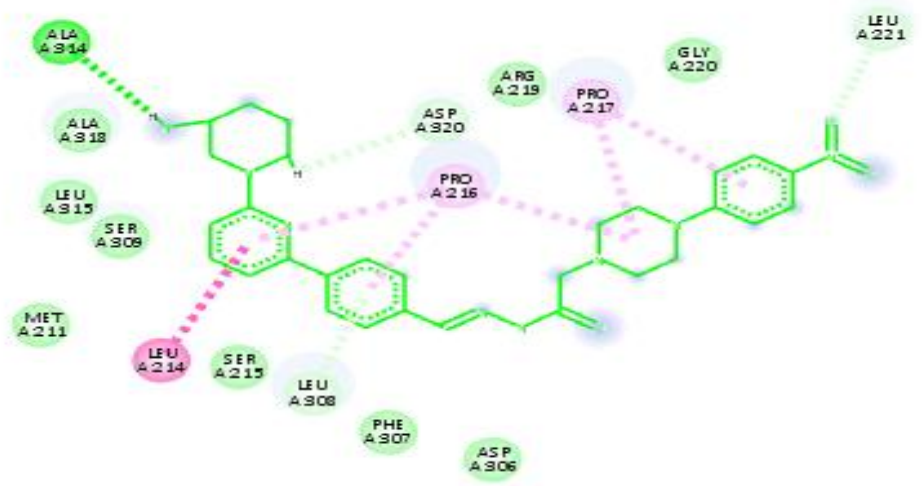
PHE A:307
PRO A:217
ASP A:306
LEU A:308
PRO A:216
ALA A:318
ASP A:320
GLY A:319


Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Halogen (Fluorine)
Pi-Donor Hydrogen Bond
Amide-Pi Stacked
Alkyl
Pi-Alkyl

9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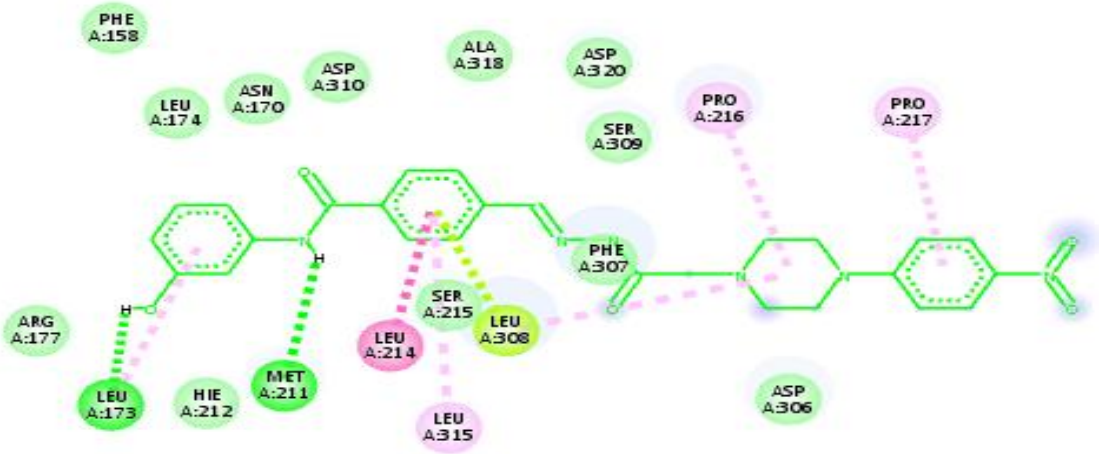
ASP A:306
ASP A:320
PRO A:216
ARG A:219
PRO A:217
GLY A:220
LEU A:221


Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Donor Hydrogen Bond
Amide-Pi Stacked
Alkyl
Pi-Alkyl

10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MET A:211
LEU A:214
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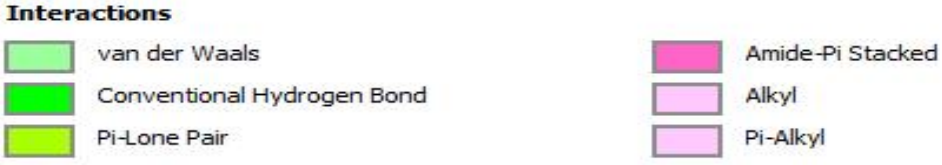
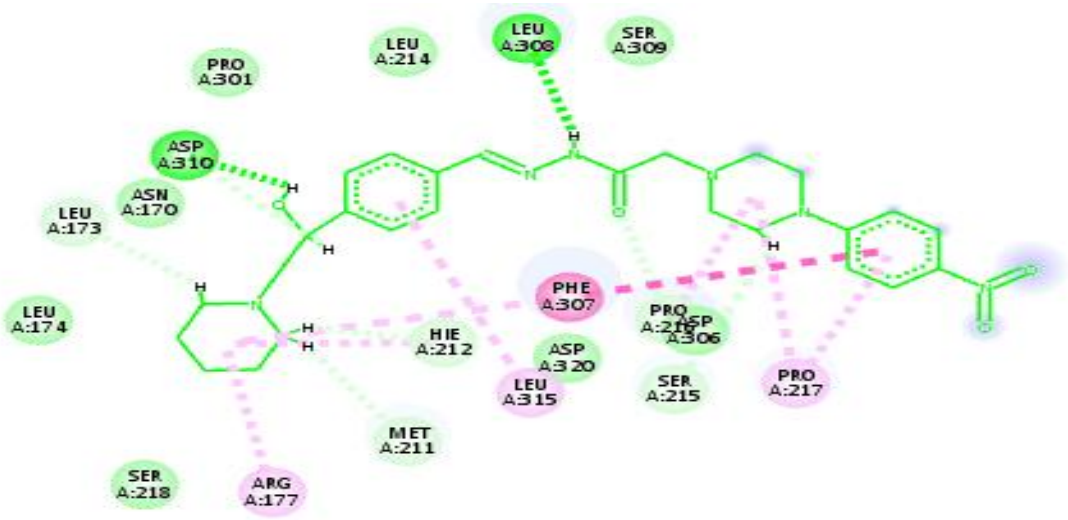
ASP A:306


Interactions
van der Waals
Conventional Hydrogen Bond
Pi-Lone Pair
Amide-Pi Stacked
Alkyl
Pi-Alkyl

11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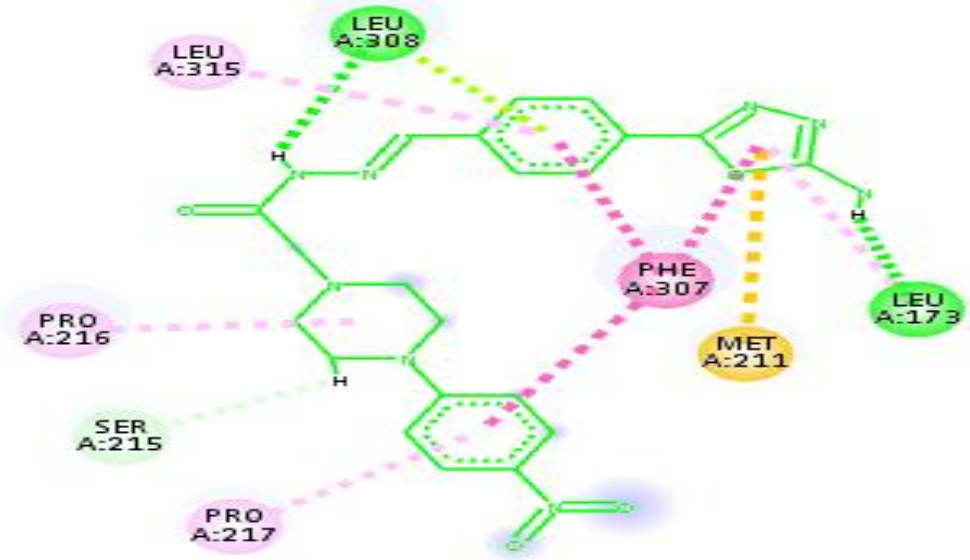
PRO A:216
ASP A:306
HIE A:212
ASP A:320
LEU A:315
SER A:215
PRO A:217
MET A:211
SER A:218
ARG A:177


Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Pi Stacked
Alkyl
Pi-Alkyl

12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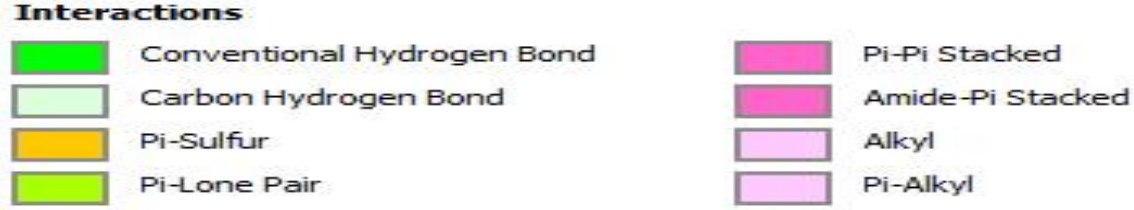
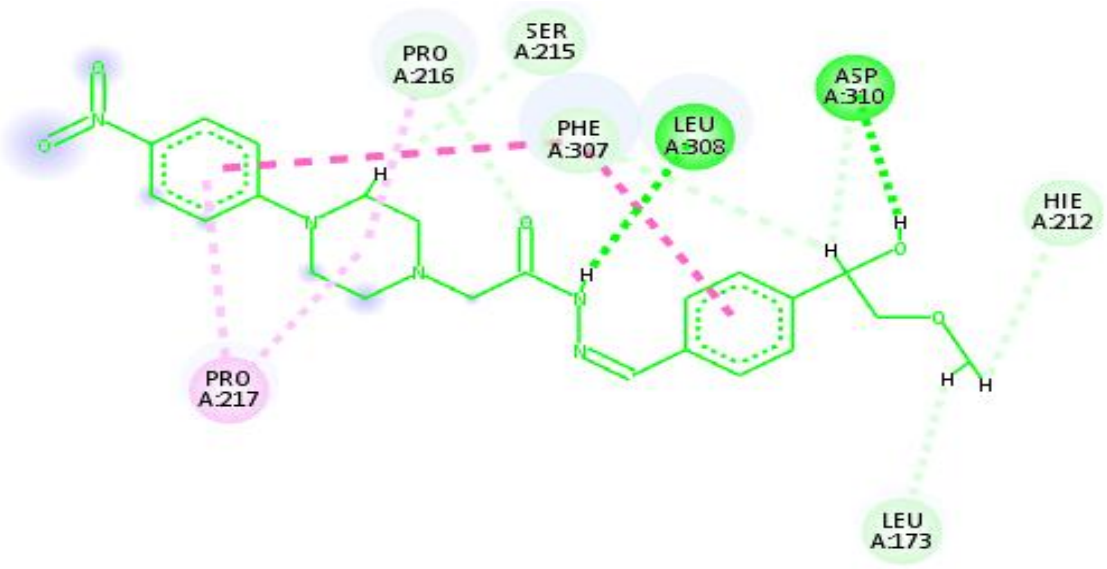
PRO A:217


Interactions
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Sulfur
Pi-Lone Pair
Pi-Pi Stacked
Amide-Pi Stacked
Alkyl
Pi-Alkyl

13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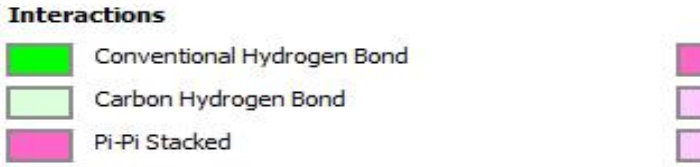
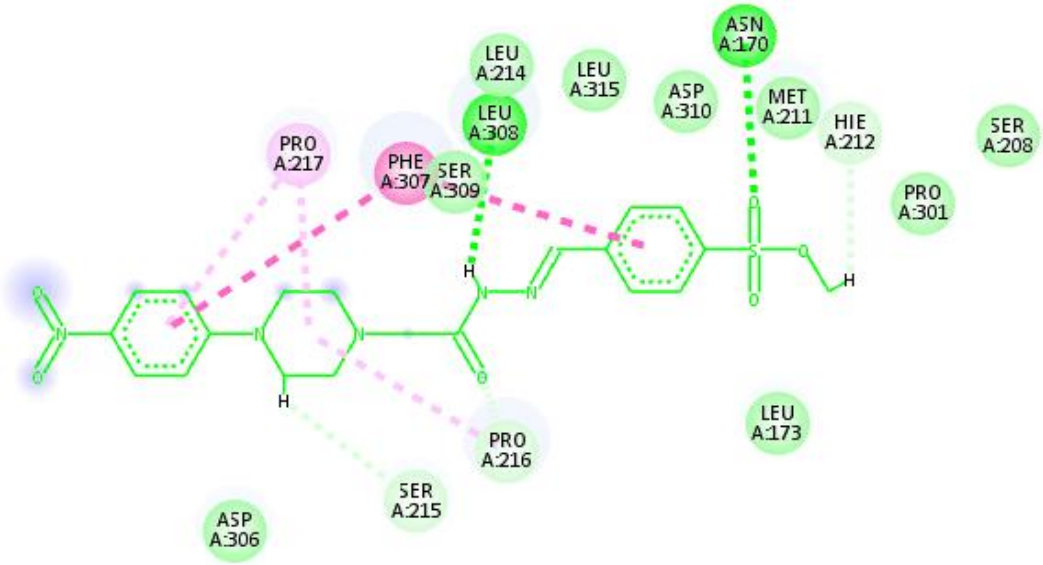

Interactions
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Pi Stacked
Amide-Pi Stacked
Alkyl
Pi-Alkyl

14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PRO A:217
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SER A:309
PRO A:301
LEU A:173
PRO A:216
SER A:215
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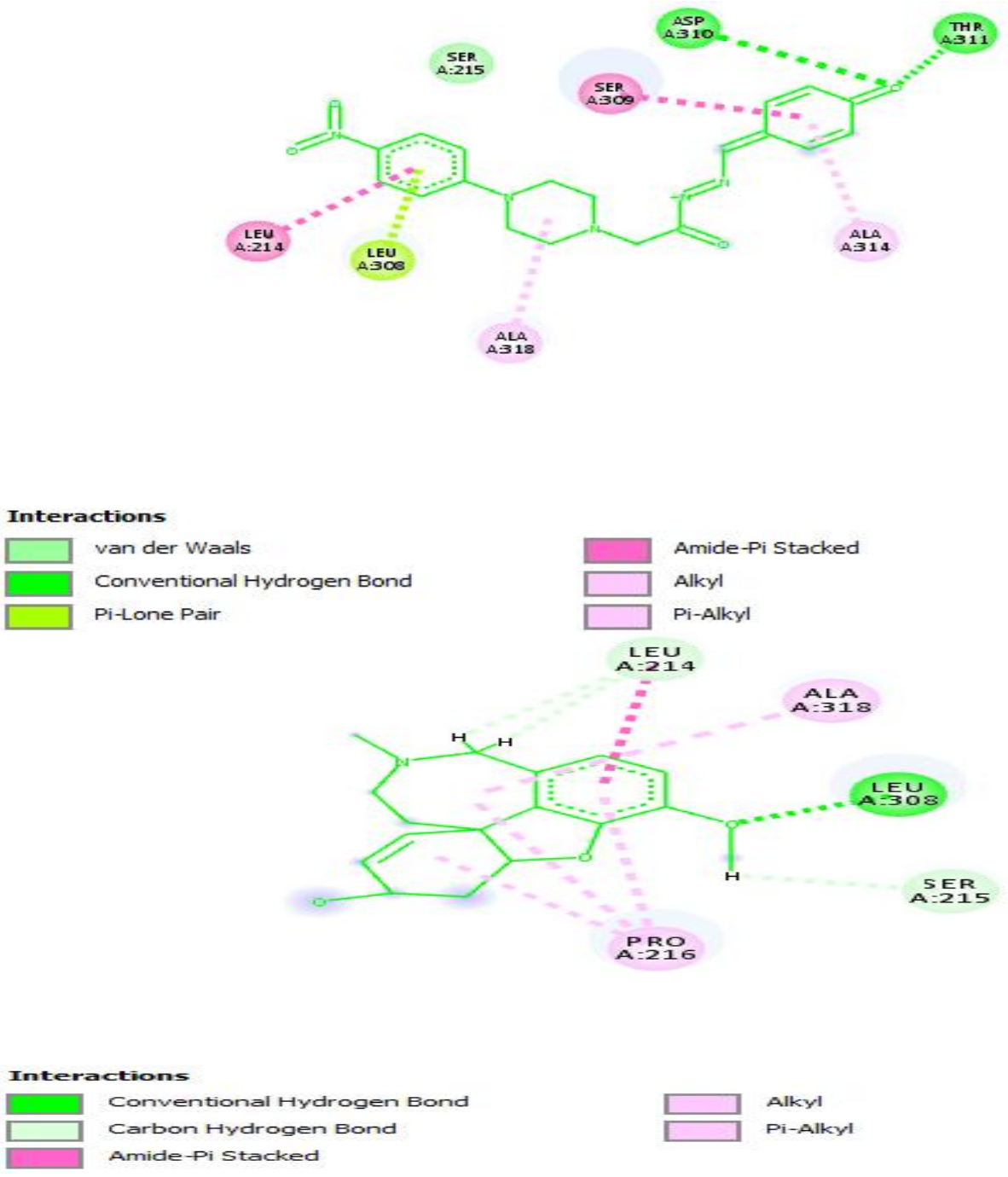
Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Pi Stacked
Amide-Pi Stacked
Alkyl
Pi-Alkyl

15



Reference Compound Galantamine

Figure 5: 2D Visualisation of Binding Interactions of Designed Compounds and Reference Compounds

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. (Daina et al., 2017)

The other four Pfizer Ro5 are included in Table 4, including (Egan et al., 2000; Middleton et al., 2005; Veber et al., 2002) , and all of the compounds that Ghose (Ghose et al., 1999; X Mahaman Y. A. R., 2019) authorised, including Teague's stringent leadlike criteria (Teague et al., 1999) . 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 (Alam & Khan, 2018; Belal, 2018; Cheng et al., 2012; Flores-Holguín et al., 2021; Moroy et al., 2012).

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 (Fedi et al., 2021) . According to the study's results, all of the produced ligands had values 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(Neumaier et al., 2021).

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 compound has the potential to be a useful drug.

Cconclusion

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.

An 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).

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	Reference
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
	P	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes
Toxicity	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

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