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A RESEARCH ON RATIONAL DESIGN OF QUINAZOLINE-BASED ACETYLCHOLINERASE INHIBITORS FOR ALZHEMER DISEASE TREATMENT: IN SILICO APPROACH

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Abstract: Alzheimer's disease (AD) poses a significant global health challenge with limited therapeutic options. Acetyl cholinesterase (Ache) inhibitors represent a cornerstone in AD treatment by enhancing cholinergic neurotransmission. Through in silico techniques, such as molecular docking and molecular dynamics simulations, a library of quinazoline derivatives was screened against the active site of AChE to predict binding affinities and interactions. Structural modifications were systematically explored to optimize inhibitor binding and pharmacokinetic properties. The computational results identified several promising candidates demonstrating potent inhibitory activity against Ache. These compounds exhibited favourable interactions within the enzyme's catalytic site, suggesting their potential efficacy in enhancing cholinergic neurotransmission.

Index Terms - Alzheimer's disease, neurotransmission, pharmacokinetic, enzyme's catalytic site.

I. INTRODUCTION

IN-SILICOS STRUCTURE-BASED DRUG DESIGN:

In-silico structure-based drug design (SBDD) is a sophisticated approach used in modern drug discovery that leverages computational techniques and molecular modeling to predict, analyze, and optimize the interactions between potential drug molecules and their target protein structures. This approach aims to accelerate the drug development process by providing insights into the binding mechanisms, potency, and selectivity of potential drug candidates before they are synthesized and tested in the laboratory. Drug design, often referred to as rational drug design or simply rational design, is the inventive process of finding new medications based on the knowledge of a biological target.

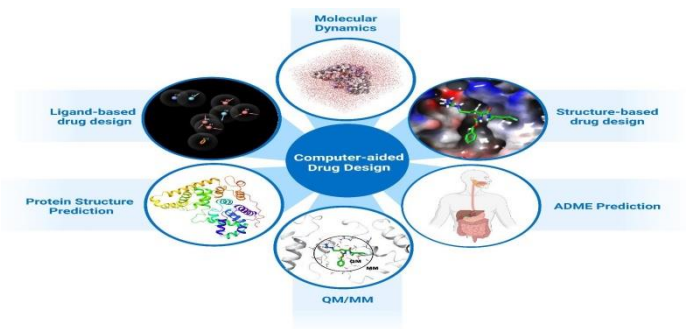

Figure1. In-silico-drug designing

The drug is most commonly an organic small molecule that activates sor inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient. In them basic sense, drug design involves the design of molecules that are complementary in shape and charge to the bimolecular target with which they interact and therefore will bind to it. Drug design frequently but not necessarily relies on computer modeling techniques. This type of modeling is sometimes referred to as computer-aided drug design. Finally, drug design that relies on the knowledge of the three-dimensional structure of the bimolecular target is known as structure-based drug design.

The phrase "drug design" is to some extent a misnomer. A more accurate term is ligand design (i.e., design of a molecule that will bind tightly to its target).Although design techniques for prediction of binding affinity are reasonably successful, there are many other properties, such as bioavailability, metabolic half-life, side-effects that first must be optimized before align and can be come safe and efficacious drug.

These other characteristics are often difficult to predict with rational design techniques. Nevertheless, due to high attrition rates, especially during clinical phases of drug development, more attention is being focused early in the drug design process on selecting candidate drugs whose physicochemical properties are predicted to result in fewer complications during development and hence more likely to lead to an-approved, marketed drug. Furthermore, in-vitro experiments complemented with computation methods are increasingly used in early drug discovery to select compounds with more favorable ADMET.

- **MOLECULAR MODELING:**

Molecular modeling is a powerful computational technique used to study the structure, behavior, and properties of molecules at the atomic level. It plays a crucial role in various scientific fields, including chemistry, biology, materials science and drug discovery. By simulating the interactions and motions of atoms and molecules, molecular modeling.

- **REPRESENTATION OF MOLECULES:**

In molecular modeling, molecules are typically represented as collections of atoms, each with its specific properties such as atomic mass, charge, and position. Different levels of representation, from simple ball-and-stick models to more complexes, detailed atomistic models.

- **ENERGY CALCULATION AND MINIMIZATION:**

One of the fundamental principles in molecular modeling is that molecules adopt conformations (arrangements of atoms) that minimize their energy. Various methods, such as molecular mechanics and quantum mechanics, are used to calculate the potential energy of a molecule based on its atomic positions. Researchers use energy minimization techniques to find stable conformations orto optimize molecular structures.

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- **DRUG DISCOVERY:**

Molecular modeling plays a vital role in drug discovery by predicting the interactions between drug candidates and

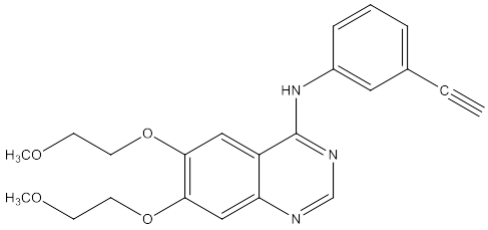
target molecules, helping to design more effective and specific drugs.

- **MOLECULAR DOCKING:**

Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand-protein docking is to predict the predominant binding mode(s) of aligand with a protein of known three-dimensional structures. Molecular docking algorithms calculate the energetically favorable binding poses and binding affinities of the drug candidates within the protein's binding site. These calculations take into account factors such as hydrogen bonding, hydrophobic interactions, and electrostatic forces.

- **TYPES OF MOLECULAR DOCKING:**
  A. Rigid docking,
  B. Semi-flexible docking, and Flexible docking

Table: 1. Designed Molecules, ADMET predicted analysis and Docking studies

Sr. No.	Code	Molecules	Lipinski Rule	Bioavailability Score	Log *P*	GI abs	BBB Permeation	Tox. Class	Glide Score
1.	Ref.	 *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine Chemical Formula: $C_{22}H_{23}N_3O_4$ Molecular Weight: 393.44	Yes	0.55	3.67	High	Yes	3	-8.52
2.	PR01	*N*-(6-(trifluoromethoxy)pyrimidin-4-yl)quinazolin-6-amine Chemical Formula: $C_{13}H_8F_3N_5O$ Molecular Weight: 307.23	Yes	0.55	2.32	High	Yes	5	-9.4
3.	PR02	*N*-(2,6-dichloropyrimidin-4-yl)quinazolin-6-amine Chemical Formula: $C_{12}H_7Cl_2N_5$ Molecular Weight: 292.12	Yes	0.55	2.30	High	Yes	4	-9.1
4.	PR03	*N*-(6-fluoropyrimidin-4-yl)quinazolin-6-amine Chemical Formula: $C_{12}H_8FN_5$ Molecular Weight: 241.22	Yes	0.55	1.82	High	Yes	4	-9
5.	PR04	*N*-(6-methylpyrimidin-4-yl)quinazolin-6-amine Chemical Formula: $C_{13}H_{11}N_5$ Molecular Weight: 237.26	Yes	0.55	2.02	High	Yes	4	-8.9
6.	PR05	6-(quinazolin-6-ylamino)pyrimidine-4-carbonitrile Chemical Formula: $C_{13}H_8N_6$ Molecular Weight: 248.24	Yes	0.55	1.63	High	No	4	-8.83
7.	PR06	2-chloro-6-(quinazolin-6-ylamino)pyrimidine-4-carbonitrile Chemical Formula: $C_{13}H_7ClN_6$ Molecular Weight: 282.69	Yes	0.55	1.89	High	No	4	-8
8.	PR07	*N*-(2-chloro-6-(3*H*-pyrrol-2-yl)pyrimidin-4-yl)quinazolin-6-amine Chemical Formula: $C_{16}H_{11}ClN_6$ Molecular Weight: 322.75	Yes	0.55	2.68	High	Yes	3	-10.5
9.	PR08	*N*-(2-chloro-6-(4*H*-imidazol-5-yl)pyrimidin-4-yl)quinazolin-6-amine Chemical Formula: $C_{15}H_{10}ClN_7$ Molecular Weight: 323.74	Yes	0.55	2.44	High	No	4	-7.36
10.	PR09	*N*-(2-fluoro-6-(4*H*-imidazol-5-yl)pyrimidin-4-yl)quinazolin-6-amine Chemical Formula: $C_{15}H_{10}FN_7$ Molecular Weight: 307.29	Yes	0.55	2.32	High	No	4	-9.8
11.	PR10	*N*-(6-(4*H*-imidazol-5-yl)-2-(trifluoromethoxy)pyrimidin-4-yl)quinazolin-6-amine Chemical Formula: $C_{16}H_{10}F_3N_7O$ Molecular Weight: 373.29	Yes	0.55	2.53	High	No	4	-10.6
12.	PR11	*N*-(6-chloro-2-(trifluoromethoxy)pyrimidin-4-yl)quinazolin-6-amine Chemical Formula: $C_{13}H_7ClF_3N_5O$ Molecular Weight: 341.68	Yes	0.55	2.30	High	No	5	-9.4

13.	PR12	*N*-(6-fluoro-2-(trifluoromethoxy)pyrimidin-4-yl)quinazolin-6-amine Chemical Formula: $C_{13}H_7F_4N_5O$ Molecular Weight: 325.22	Yes	0.55	2.14	High	No	5	-9.6
14.	PR13	*N*-(6-(pyridin-2-yl)pyrimidin-4-yl)quinazolin-6-amine Chemical Formula: $C_{17}H_{12}N_6$ Molecular Weight: 300.32	Yes	0.55	2.45	High	Yes	4	-9.3
15.	PR14	*N*-(2-chloro-6-(pyridin-2-yl)pyrimidin-4-yl)quinazolin-6-amine Chemical Formula: $C_{17}H_{11}ClN_6$ Molecular Weight: 334.76	Yes	0.55	2.79	High	Yes	4	-8.3
16.	PR15	*N*-(2-chloro-6-(pyridin-4-yl)pyrimidin-4-yl)quinazolin-6-amine Chemical Formula: $C_{17}H_{11}ClN_6$ Molecular Weight: 334.76	Yes	0.55	2.40	High	Yes	3	-7.2
17.	PR16	*N*-(2-chloro-6-methoxypyrimidin-4-yl)quinazolin-6-amine Chemical Formula: $C_{13}H_{10}ClN_5O$ Molecular Weight: 287.70	Yes	0.55	2.64	High	Yes	5	-9
18.	PR17	*N*-(2-fluoro-6-methoxypyrimidin-4-yl)quinazolin-6-amine Chemical Formula: $C_{13}H_{10}FN_5O$ Molecular Weight: 271.25	Yes	0.55	2.55	High	Yes	5	-9
19.	PR18	4-methoxy-6-(quinazolin-6-ylamino)pyrimidine-2-carbonitrile Chemical Formula: $C_{14}H_{10}N_6O$ Molecular Weight: 278.27	Yes	0.55	2.26	High	No	4	-7.56
20.	PR19	*N*-(6-methoxypyrimidin-4-yl)quinazolin-6-amine Chemical Formula: $C_{13}H_{11}N_5O$ Molecular Weight: 253.26	Yes	0.55	2.29	High	Yes	5	-7.9
21.	PR20	6-(quinazolin-6-ylamino)-*N*-(4-(trifluoromethoxy)benzyl)pyrimidine-4-carboxamide Chemical Formula: $C_{21}H_{15}F_3N_6O_2$ Molecular Weight: 440.38	Yes	0.55	3.10	High	No	3	-11.6
22.	PR21	*N*-(4-chlorobenzyl)-6-(quinazolin-6-ylamino)pyrimidine-4-carboxamide Chemical Formula: $C_{20}H_{15}ClN_6O$ Molecular Weight: 390.83	Yes	0.55	2.96	High	No	3	-11.2
23.	PR22	*N*-ethyl-6-(quinazolin-6-ylamino)pyrimidine-4-carboxamide Chemical Formula: $C_{15}H_{14}N_6O$ Molecular Weight: 294.31	Yes	0.55	2.40	High	No	3	-9.3
24.	PR23	*N*-(aminomethyl)-6-(quinazolin-6-ylamino)pyrimidine-4-carboxamide Chemical Formula: $C_{14}H_{13}N_7O$ Molecular Weight: 295.30	Yes	0.55	1.31	High	No	3	-9.21
25.	PR24	*N*-(hydroxymethyl)-6-(quinazolin-6-ylamino)pyrimidine-4-carboxamide Chemical Formula: $C_{14}H_{12}N_6O_2$ Molecular Weight: 296.28	Yes	0.55	1.33	High	No	4	-9.14

26.	PR25	6-(quinazolin-6-ylamino)-*N*-((trifluoromethoxy)methyl)pyrimidine-4-carboxamide Chemical Formula: $C_{15}H_{11}F_3N_6O_2$ Molecular Weight: 364.28	Yes	0.55	1.90	High	No	4	-10.3
27.	PR26	*N*-(methoxymethyl)-6-(quinazolin-6-ylamino)pyrimidine-4-carboxamide Chemical Formula: $C_{15}H_{14}N_6O_2$ Molecular Weight: 310.31	Yes	0.55	2.21	High	No	4	-9.3
28.	PR27	*N*-(cyanomethyl)-6-(quinazolin-6-ylamino)pyrimidine-4-carboxamide Chemical Formula: $C_{15}H_{11}N_7O$ Molecular Weight: 305.29	Yes	0.55	1.14	High	No	3	-9.5
29.	PR28	*N*-((dimethoxyamino)methyl)-6-(quinazolin-6-ylamino)pyrimidine-4-carboxamide Chemical Formula: $C_{16}H_{17}N_7O_3$ Molecular Weight: 355.35	Yes	0.55	2.77	High	No	3	-9.3
30.	PR29	*N*-((methoxyamino)methyl)-6-(quinazolin-6-ylamino)pyrimidine-4-carboxamide Chemical Formula: $C_{15}H_{15}N_7O_2$ Molecular Weight: 325.33	Yes	0.55	2.56	High	No	3	-9.6
31.	PR30	*N*-(6-(trifluoromethoxy)pyrimidin-4-yl)quinazolin-6-amine Chemical Formula: $C_{13}H_8F_3N_5O$ Molecular Weight: 307.23	Yes	0.55	2.32	High	Yes	5	-7.36

SELECTION OF NUCLEUS:

Quinazoline is a heterocyclic compound composed of two fused six-membered aromatic rings, containing nitrogen atoms at positions 1 and 3. Its diverse pharmacological activities have made it a prominent scaffold in medicinal chemistry. The nucleus of quinazoline serves as a fundamental building block for the synthesis of various biologically active molecules, including anticancer, antiviral, Neuroprotective, antimicrobial, and anti-inflammatory agents.

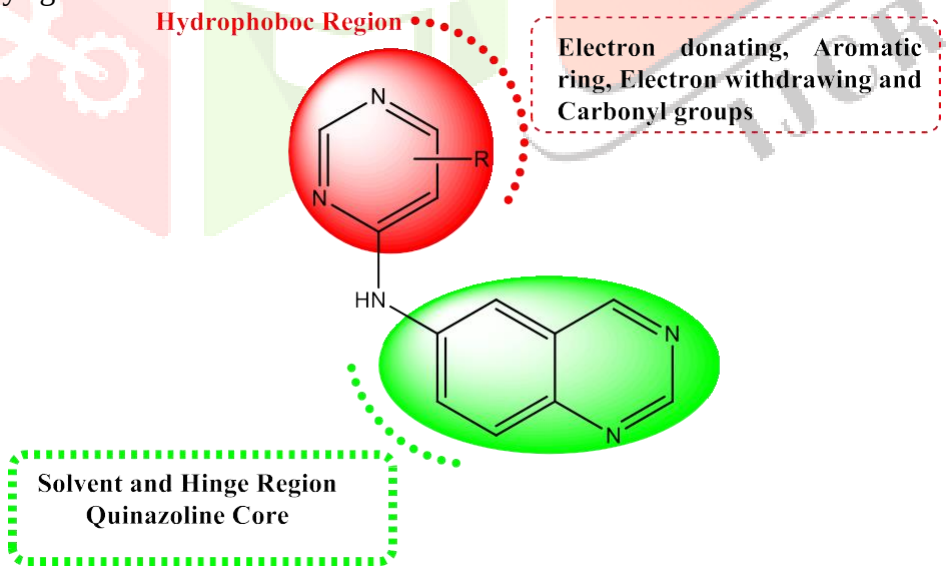


FIGURE 2 .SELECTION AND DESIGNING OF NUCLEUS

Due to its structural versatility and synthetic accessibility, researchers have extensively explored modifications to the quinazoline nucleus to enhance its pharmacological properties and develop novel therapeutic agents. This selection of the quinazoline nucleus represents a vital aspect of drug discovery and development, aiming to elucidate the structure-activity relationships essential for designing compounds with improved efficacy and reduced toxicity profiles. Int his review, we highlight recent advancements and strategies employed in the selection of the quinazoline nucleus, emphasizing its significance in the pursuit of innovative pharmaceuticals.

Results and Discussion:

Results:

The series of designed compound is subjected though the ADME & toxicity prediction and further screening of compounds for molecular docking. On completion of the molecular docking based screening process, the resulting conformations poses of the ligands in the binding site of 4EY6 were studied and per residue interaction pattern with in 15 areas from center of grid was studied. Based on glide score top scoring molecules were selected. Compounds which interact most appropriately to 4EY6. A network of hydrogen bonds between the reported inhibitors and GLY122, SER203, HIS447, PHE338,TRY286, PHE297, ASP274, PHE295, TYR124 and TRP286 was observed as well as hydrophobic interactions between the core of the ligands and surrounding lipophillic amino acid residues (eg, with ALA204,TYR124,SER203,GLY126andTYR341). Based on interaction pattern and knowledge based screening top 10 molecules out of 50 have good and docking score and interaction that could use for further studies.

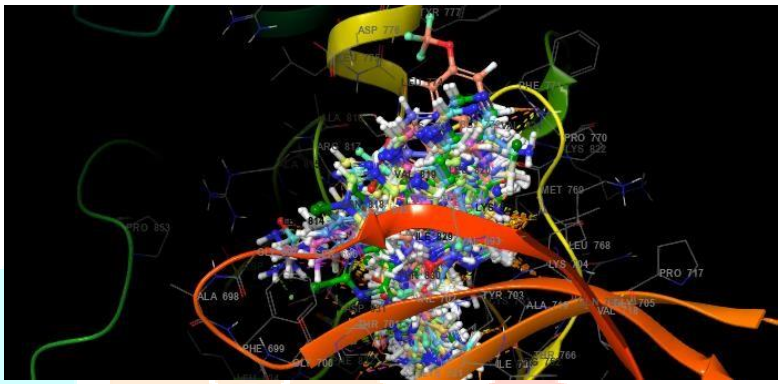


FIGURE 3. SUPERIMPOSED VIEW OF ALL THE DOCKED COMPOUNDS OF SERIES WITH MOLECULAR TARGET (4EY6)

Figure 4. Protein-LigandinteractionsofmoleculePR20

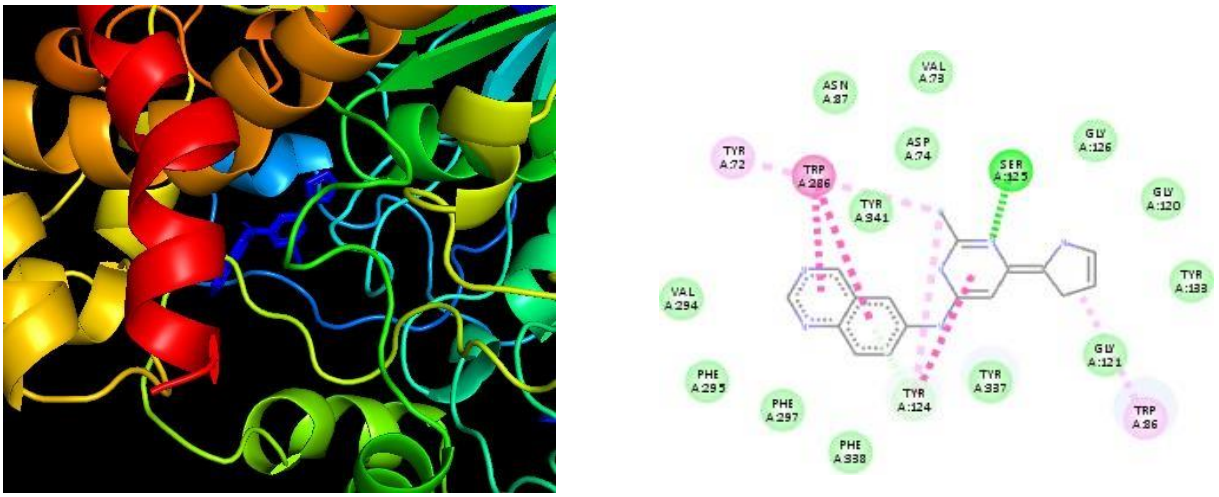


Figure 5.Protein-Ligand interactions of molecule PR07

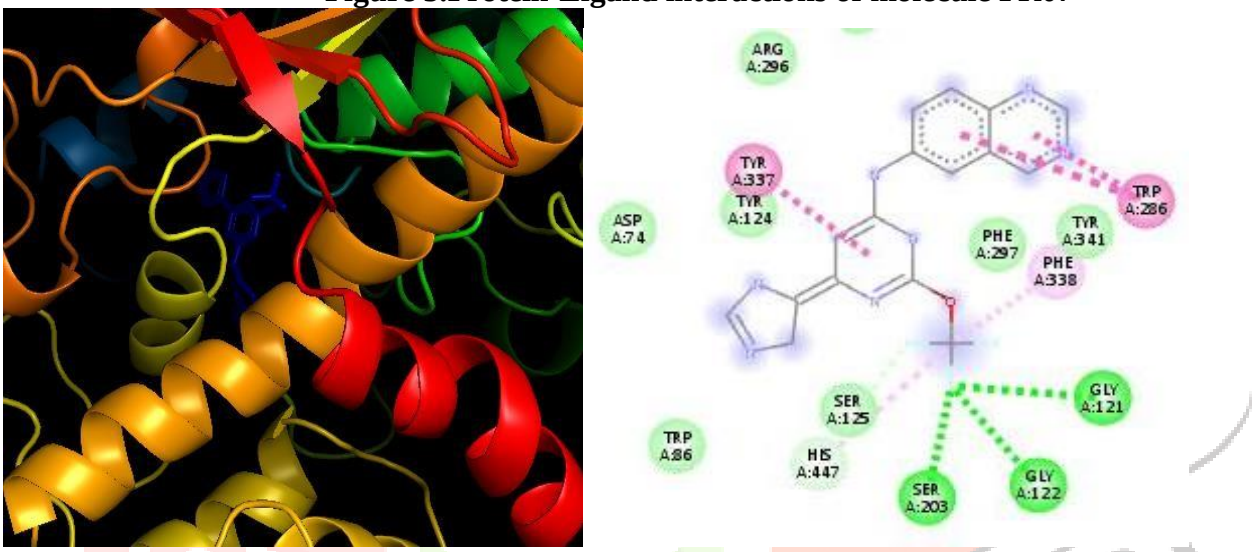


FIGURE 6.PROTEIN-LIGANDINTERACTIONSOFMOLECULEPR10

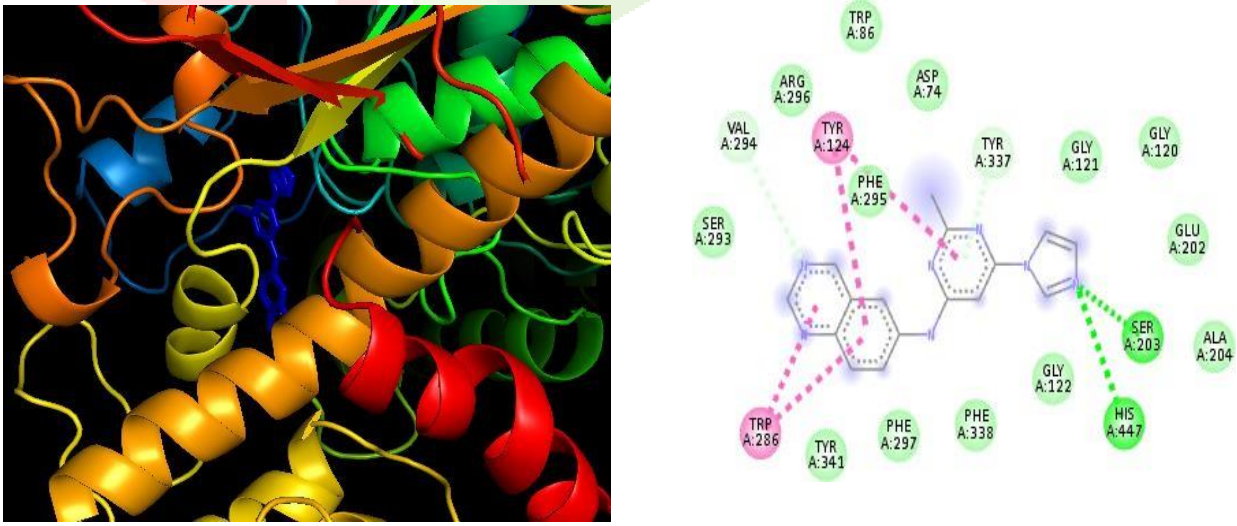


Figure7.Protein-Ligand interactions of molecule PR40

SUMMARY AND CONCLUSION:

Summary:

The rational design of quinazoline-based acetyl cholinesterase inhibitors for Alzheimer's disease treatment has been investigated through an in silico approach in this thesis. A comprehensive literature review highlighted the significance of acetyl cholinesterase inhibition in Alzheimer's disease pathologyand the potential of quinazoline-based compounds as therapeutic agents. Utilizing molecular modeling techniques, a diverse dataset of known inhibitors was analyzed to elucidate the structural features crucial for effective inhibition. Molecular docking and dynamics simulations predicted the binding modes and interactions between selected compounds and acetylcholinesterase, while quantitative structure-activity relationship modeling identified key molecular scriptors contributing to potency and selectivity. Computational optimization of compound structures aimed to enhance binding affinity and pharmacokinetic properties. Validation through in silico ADME prediction and virtual screening further supported the potential of the designed inhibitors. Analysis of structure-activity relationships provided insights into rational design strategies for future drug discovery efforts.

CONCLUSION:

The thesis has demonstrated the feasibility and utility of employing computational methods for the rational design of quinazoline-based acetyl cholinesterase inhibitors for Alzheimer's disease treatment. Through a systematic approach integrating molecular modeling, QSAR modeling, and computational optimization, novel compounds with enhanced binding affinity and potential therapeutic efficacy have been identified. The proposed guidelines for rational design of evaluable insights into the molecular mechanisms governing acetyl cholinesterase inhibition and provide a framework for the development to improved therapeutics.

Experimental validation and refinement of the designed compounds are warranted to translate these computational findings into clinically relevant treatments. Overall, this research contributes to the ongoing efforts in drug discovery and underscores the importance of computational approaches in addressing complex neurological disorders such as Alzheimer's d for Alzheimer's disease.

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