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In silico screening, molecular dynamic simulation, and pharmacokinetic studies of new Schiff base derivatives from 2-(3-benzoylphenyl) propionic acid as tyrosyl-tRNA synthetase inhibitor

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Abstract: Bacterial resistance is a major problem in hospitals and the community. Thus, much antibacterial research has focused on discovering new chemical agents and bacterial targets. Computational and structure-based design methods are used for the improvement of drug discovery. This work developed new Schiff base compounds from 2-(3-benzoylphenyl) propionic acid. The unique compounds were categorized as S and S(1-6). They were examined in silico for antibacterial activity on the tyrosyl-tRNA synthetase enzyme. Dynamic simulation and pharmacokinetic studies were also studied theoretically. In silico, experiments, including SwissADME studies, are utilized to predict the pharmacokinetics of newly designed compounds. The docking studies were done using GOLD Suite (v. 2021.3.0) software showed the binding of compounds with the enzyme tyrosyl-tRNA synthetase, finally, dynamic simulation studies of compound [S2] using the Desmond modules of the Schrodinger 2023 software. Since all compounds meet Lipinski's rule requirements, the new agents are expected to be given orally. Docking experiments showed that compound [S2] bound to tyrosyl-tRNA synthetase had the greatest PLP fitness value (89.02) compared to the reference ligand (79.71). Simulations of the compound [S2] with the enzyme pocket revealed stable variations with RMSD values below 3Å during the simulation period. Based on docking, compound [S2] is deemed a promising agent as a tyrosyl-tRNA synthetase inhibitor, with stable variations during dynamic simulation and RMSD and RMSF values within the normal range.

Keywords: Tyrosyl-tRNA synthetase, Molecular dynamic simulation, Swiss ADME.

1. Introduction

Drug development is a crucial and highly significant process in the pharmaceutical industry. Several computational techniques have significantly decreased the duration and expenses associated with drug discovery [1]. Computer-aided drug design (CADD) has helped generate therapeutically relevant small compounds for over 30 years. They are either structure-based or ligand-based approaches [2]. CADD uses computational approaches to predict drug receptor interactions to determine if a chemical will bind to a target and with what affinity [3]. This activity prediction method is the most widely utilized for limiting the number of probable pharmaceutical compounds in a large library. This strategy saves money and time while producing high quality leads for high-throughput screening. Academic and commercial pharmaceutical companies use this multi-disciplinary method to improve efficacy and reduce side effects [3,4].

Currently, many active molecules are available to combat microbial infection; however, most of them are largely ineffective due to the resistance that microorganisms have developed to antibiotics. To combat antibiotic resistance, there is a pressing need to develop new antimicrobial medications [5]. The focus of research for the development of antibacterial drugs is on the enzymes aminoacyl-tRNA synthetase (AaRS). Inhibiting these enzymes

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hinders protein production, thereby reducing bacterial growth in both in vitro and in vivo conditions. These enzymes have the ability to identify and bind certain amino acids and then attach these amino acids to their corresponding tRNA molecules during the process of protein synthesis. [6,7]. Blocking one of the twenty AARSs in the cell prevents the associated tRNA from translating into protein. This results in the failure of protein synthesis and the subsequent inhibition of cell development [8,9]. AaRSs are classified into Class I and Class II, which comprise ten aaRSs each and are structurally and evolutionarily distinct classes of aaRSs. The primary basis for the classification is the catalytic domain's structure [10,11]. Tyrosyl-tRNA synthetase (TyrRS) is an aaRS enzymes that plays a crucial role in the production of proteins in bacteria by ligating particular amino acids to their corresponding tRNA molecules. Since these enzymes are necessary for the synthesis of proteins, any blockage of an enzyme in the cell would result in the cessation of protein synthesis and the arrest of cell growth [8,12]. TyrRS inhibitors have therefore drawn a lot of interest as a novel class of antibacterial drugs. TyrR is classified as a class I synthetase enzyme [13]. In addition to advancing our basic knowledge of this class of vital enzymes, research on aminoacyl-tRNA synthetases will aid in the fight against bacterial infections [14]. Mupirocin, a substance derived from Pseudomonas fluorescens, is the only aaRS inhibitor licensed by the US Food and Drug Administration [15]. With the help of modern technology, it is possible to gather a huge number of different aminoacyl-tRNA synthetases, particularly those derived from virulent strains like S. aureus, and utilize them in high-throughput chemical library screening to produce new inhibitors [16].

Docking software is a valuable tool for screening thousands of compounds for affinity towards a given therapeutic target or pathogen Specifically, the drug discovery process now employs virtual screening for protein structure and molecule docking, which are effective techniques for lead discovery and highly supportive tools [17]. This is an attempt to remove the element of chance from the drug development process because molecular docking analysis of drug-receptor binding is necessary for biological activity [18]. By identifying the ideal active sites in proteins, determining the optimal geometry of the ligand-receptor complex, and computing the energy of interaction for various ligands to design the new lead moiety for research, molecular docking aids in the understanding of the interaction between the receptor protein and ligand [19].

The goal of the current work is to create new Schiff base compounds (S) and S (1-6) using 2-(3-benzoylphenyl) propionic acid as a starting material. These compounds will then be evaluated in silico as anti-bacterial agents against the tyrosyl-tRNA synthetase enzyme (PDB code: 1JIJ) through docking studies using the GOLD suite program (v.2021.3.0), and their absorption, distribution, metabolism, and excretion (ADME) will be examined using the SwissADME server. Furthermore, the molecular dynamic simulation of the best-docked compound (S2) was done.

2. Computational Method

2.1. In-silico ADME/Pharmacokinetic Predictions

The SwissADME website was used to determine the physicochemical properties of our developed compounds as well as their pharmacokinetic or ADME (Absorption, Distribution, Metabolism, and Excretion) investigations. Using ChemAxon's Marvin JS, the chemical structure of freshly developed compounds was drawn and subsequently transformed into the SMILE name. The lipophilicity and polarity of new compounds are assessed using BOILLED EGG [20].

2.2. Molecular docking studies

Docking examinations were carried out utilizing the Cambridge Crystallographic Data Center's (CCDC) using GOLD [Genetic Optimization for Ligand Docking] program (v.2021.3.0) under a full license. With the ability to predict a compound's affinity, interaction with receptors and most importantly, biological activity, molecular docking studies are a useful tool in the creation of novel drugs. The CCDC GOLD Suite (v. 2021.3.0) comes with the Hermes visualizer program (v. 2021.3.0), which helps with input file preparation for GOLD docking. Additionally, view the receptors, ligands, active site, bond length computation, interaction type (H-bond, hydrophobic, etc.), pose prediction, and obtain photos.

2.3. Ligands Preparation and Protein Receptor

The chemical structure of our ligands was drawn using ChemDraw Professional (v.16.0) software. Energy minimization for our compounds was carried out using Chem3D (v.16.0) by applying the MM2 force field. The newly designed ligands were docked with the 3D structure of S. aureus tyrosyl-tRNA synthetase enzyme (PDB code: 1JIJ) complexes with a potent inhibitor. The receptors were loaded into the Hermes module of GOLD from the protein data bank (PDB), and re-docking of the co-crystalized ligands was done primarily.

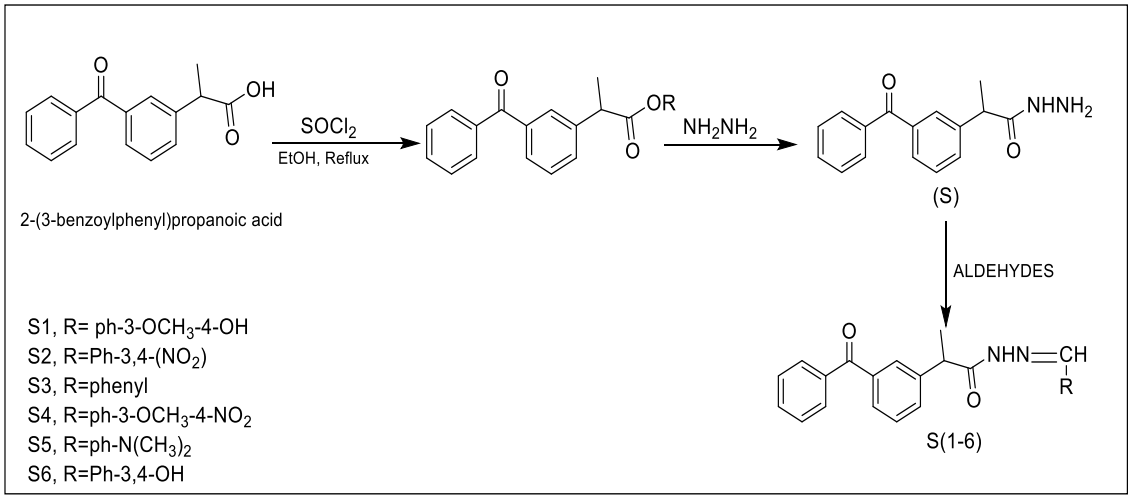
2.4. Molecular Docking Protocol

The receptors are prepared for the docking process using the Hermes visualizer program in the CCDC GOLD package. The active site is determined based on the site of contact with the initial ligand. The protein-binding site includes all protein residues within a 10-angstrom radius of the reference ligand for the docking procedure.

All parameters utilized in the docking process have been set as default values. 10 poses were generated, the top-ranked solution was set as default, and early termination was disabled. The Chemscore kinase is used as a configuration template. The piecewise linear potential (ChemPLP) serves as a scoring function. The results were ultimately saved as mol.2 files. This includes details on the optimal binding method, the free energy of binding, and the docked positions. The results were analyzed precisely to determine the optimal binding and interaction between our ligand design and the amino acid residues of the tyrosyl-tRNA synthetase enzyme.

2.5. Molecular dynamic simulation

Molecular dynamics simulations (MDS) were carried out on the derivative with the highest docking score using the Desmond modules of the Schrodinger 2023 software, employing the OPLS4 force field [21]. To achieve a system with a balanced charge for the protein-ligand complex, sodium ions were introduced, and a solution containing 0.15 M sodium chloride (NaCl) was included to replicate the natural environment. The system was generated using the TIP3P solvent model [22]. The simulation was conducted for a duration of 50 nanoseconds, with trajectory recording occurring at intervals of 50 picoseconds. The NPT ensemble class was employed, with the system energy being set to 1.2. The simulation was configured to run at a pressure of 1.01325 bar and a temperature of 300 K. To generate the simulation interaction diagram, the simulated system was assessed following a period of relaxation [23].



Scheme 1. Hypothesized synthetic pathway of newly designed compounds [S] and [S (1-6)].

3. Results and discussion

3.1. Chemical Synthesis

The new analogs were designed by converting the starting compound [2-(3-benzoylphenyl) propionic acid] into an intermediate hydrazine derivative compound [S] to get the new Schiff base compounds [S (1-6)] by adding different aldehydes. The targeted compounds were designed based on a research article [24]. The assumed synthesis pathway for the intermediate hydrazine derivative compound [S] and the final compounds [S (1-6)] is shown below in scheme-1.

3.2. ADME Results Interpretation

The physicochemical and ADME properties of the suggested compounds were predicted using computer-based methods on the SwissADME server [20]. It is a cheap way to find out about the ADME properties before biological screening and production, and it can be used to get rid of ligands that are not right for a certain pharmacokinetic profile [25]. These features include the topological polar surface area (TPSA), which is used to assess a drug's ability to enter cells. Compounds with TPSA<140Å are highly bioavailable and permeable. According to the findings, the compounds have a TPSA that falls between (58.53 and 150.17) Å. All of the compounds, however, satisfied the conventional lipophilicity requirement (log Po/w). The molar solubility in water (log S) ranges from poorly soluble to moderately soluble. The molar refractivity (MR) of the compound frequently serves as a proxy for the molecule's size and polarizability. The intended compounds range from (76.61–124.52), which is within the usual range (40–130). According to Lipinski's "rule of five" (RO5), a compound must have a molecular mass of at least 500 Daltons, ≤ 5 H-bond donors, ≤ 10 H-bond acceptors, and an octanol-water partition coefficient (log P value) of at least 5. If not, it might have low permeability and bioavailability [26]. According to the findings, every designed compound complies with the Rule of Five. Every ligand had a bioavailability score of 0.55. The pharmacokinetic properties of the produced drugs are displayed in Table-1. The boiled egg of the compounds [S and S1- S6] are labeled from (1-7) respectively showed that these compounds are passively absorbed from the gastrointestinal tract, and substances [S, S3, and S5] passively cross the blood-brain barrier. P-glycoprotein does not cause the molecules S, S1, and S6 to leave the cells of the central nervous system (CNS), but it does cause the molecules S2, S4, and S6 to leave the CNS.

3.3. Interpretation the Results of Molecular Docking Studies

Gold is a genetic algorithm specifically created for docking versatile ligands into binding regions of proteins. It is effective in predicting positions and produces exceptional outcomes for virtual screening [27,28]. The GOLD suite comprises supplementary software components such as Hermes, CSD Python, Mercury, ConQuest, Mogul, and more.

Table 1. Pharmacokinetic characteristics of new developed compounds

comp.	M.Wt (g/mol)	Bioavailability	Log P o/w	TPSA(Å)	MR	H.acceptor	Log S	H.donor	Lipinski violation
S	268.31	0.55	1.82	72.19	76.61	3	-2.95	2	Yes; 0 violation
S1	416.47	0.55	3.11	87.99	120.20	5	-4.92	2	Yes; 0 violation
S2	446.41	0.55	1.78	150.17	124.52	7	-5.15	1	Yes; 0 violation
S3	356.42	0.55	2.21	58.53	106.88	3	-4.92	1	Yes; 0 violation
S4	431.44	0.55	2.86	113.58	122.19	6	-5.16	1	Yes; 0 violation
S5	399.48	0.55	3.38	61.77	121.08	3	-5.26	1	Yes; 0 violation
S6	388.42	0.55	2.64	98.99	110.92	5	-4.75	3	Yes; 0 violation

Energy optimization techniques were used to find a stable and lowest-energy arrangement by modifying the structure's geometry. Docking experiments Analyze molecular interactions between the active binding site of the tyrosyl-tRNA synthetase enzyme and proposed drugs to estimate binding energies and selectivity. The proposed compounds and the reference ligand (SB-219383) [13] were tested to see if they could inhibit the tyrosyl-tRNA synthetase enzyme. This was done by seeing how well they could bind to the active sites during complex formation. Table-2 shows the pharmacophore fitness of the compounds docked on the tyrosyl-tRNA synthetase enzyme. The GOLD software calculates the hydrogen bonding distance between selected ligands and a specific protein, ensuring that all bond lengths are equal to or less than 3 angstroms [29]. The docking results indicate that the proposed compounds have favorable binding energies with the active pocket of the receptor and are likely to show promising activity with the tyrosyl-tRNA synthetase enzyme.

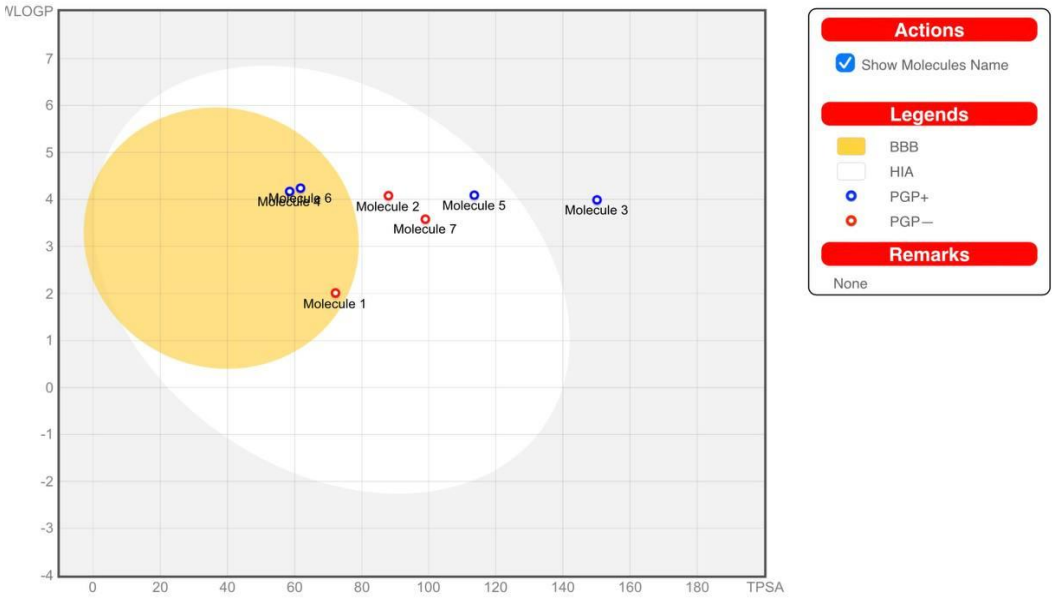


Figure 1. BOILED-EGG for designed compounds [S and S1- S6]. The compounds are labeled from 1-7 respectively. **Yellow ovule (yolk**): These are molecules expected to passively permeate through blood-brain barriers. **White ovule (white):** Are molecules expected to **be passively absorbed** by the GIT. **PGP+: Blue dots** are for molecules expected to be Evaluated by the P-glycoprotein (P-gp) from the CNS**. PGP-: Red dots** are for molecules expected **not** to be Evaluated by the P-glycoprotein (P-gp) from the CNS.

Table-2 The Binding Energies of new designed Derivatives Docked with enzyme *S.aureus tyrosyl-tRNA synthetase* (pdb code: 1JIJ

Compound	binding energy (PLP fitness)	Amino acid included in H-bonding	**Amino acid included in a short contacts**
S	75.75	GLN174, TYR170, TYR36	PRO53(4),ALA39, GLN196, TYR170, TYR36, ASP80(4)
S1	79.32	TYR36, GLY38, GLY193	GLY38,HIS50, GLY49,PRO53, GLY193
S2	**89.02**	TYR170, GLY38, GLY193,TYR36, GLN174	TYR170, THR75, GLY38, GLN196, GLY193,TYR36
S3	73.93	GLY38, GLY193	GLY38, PRO53(2),GLY49, HIS50
S4	**82.31**	GLY193(2), TYR170, GLN174	PRO53**,** GLY38, GLY193(5),
S5	74.53	GLY193	GLY38, GLY193
S6	76.83	GLY38,THR75	HIS50,GLN196, GLY38,THR75
Ligand (SB-219383)	**79.71**	ASP195(2), ASP40,GLY49, GLY38, ASP195(4), GLY193, ASP80, TYR170, GLN174	PRO53**,** GLY38, GLY49, ASP40, ASP195(2), GLY193(3),ASP80, TYR170,GLN174

*Number in brackets refer to the number of bonds.

This is because they form hydrogen bonds with the amino acid residues in the enzyme's active site, along with additional brief contacts.

Compound [S2] had the greatest Piece-wise linear potential (PLP) fitness value of (89.02) when interacting with the tyrosyl-tRNA synthetase enzyme, forming hydrogen bonds with amino acids TYR170, GLY38, GLY193, and TYR36 as shown in Table-2. The other highest PLP value (82.31) was for compound [S4] bonds with amino acids GLY193 (2), TYR170, GLN174 by hydrogen bonds at the active site. Other ligands Show lower binding energies and engage in hydrogen bonding with certain amino acids. Finally, the standard ligand gives a PLP fitness value of 79.71, concluding that compounds [S2, and S4] is very promising agents on this type of enzyme. Figure-2 Show H-bond and short contact interaction profile

for binding of compounds [S] and reference ligand, with the enzyme and the 2D model of best docked compound at the active site showed in Figure-3.

3.4. Molecular Dynamics Results

Molecular dynamics simulations (MD) are widely recognized as a top tool in the fields of chemistry, biophysics, pharmacology, and biochemistry for evaluating and calculating the biological properties of molecules [27]. The simulation utilized Newton's equations of motion to analyze the chemical system's behavior over a specified period and predict the interaction of the biological ligand based on force field calculations.

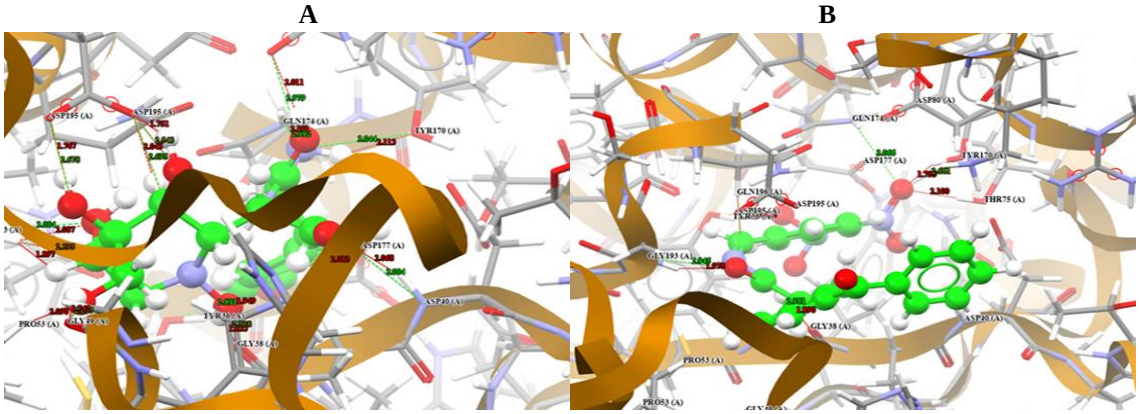


Figure-2 Show H-bond and short contact interaction profile for binding with the enzyme *S.aureus tyrosyl-tRNA synthetase* (pdb code: 1JIJ) **(A)** ***3D*** structure of reference ligand binding with the enzyme complex. **(B)** ***3D*** structure for compound [S2] binding with the enzyme complex.

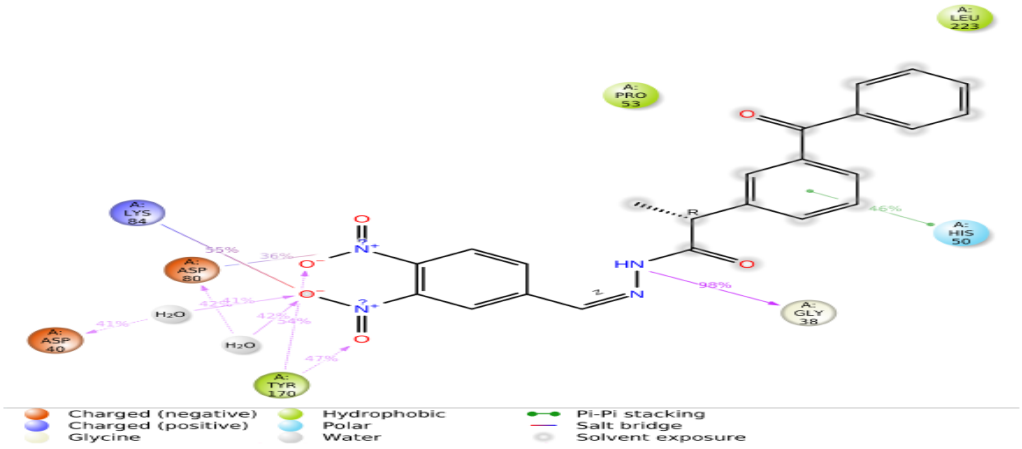


Figure-3 ***2D*** model for compound [S2] showing amino acid residues in the active site.

MD simulation offers a comprehensive and efficient analysis of the structural changes and fluctuations occurring over time in a complex generated by a ligand and receptor [30]. Figure-4 illustrates the dynamic simulation of the selected chemical compound [S2] with the greatest docking score and binding affinity with S. aureus enzyme tyrosyl-tRNA synthetase as the receptor. The Root Mean Square Deviation (RMSD) is a metric used to assess the average changes in position, displacement, and orientation of a chosen ligand (molecule) within a defined period in comparison to a reference (receptor) [31].

The RMSD plot above illustrates the interaction of the selected complex and provides insight into its conformational structure during the simulated time range. The RMSD analysis can indicate the stability of amino acid fluctuations during the simulation period near the structure of the liganded molecule. The receptor pocket fluctuations during the simulation duration for the complex were well within the permitted time limitations. This finding indicates that the variations are between 1-3 Å, which is thought a satisfactory outcome based on prior reports. If modifications exceed this range, it suggests that the receptor is undergoing significant conformational changes during the simulation

process [31]. Additionally, the RMSD values of the complex demonstrate increased stability around constant values when the receptor-ligand variations converge toward the end of the simulation period. The RMSF of almost all residues of protein was obtained below 0.2 nm, showing the good stability of the protein as shown in Figure-5

The amino acids enclosed within the receptor pocket remained attached to the ligand throughout the simulation, each contributing to the stability of the binding in a unique way. This resulted in a stable complex interaction due to the distinctive structure of the designed molecule, as shown in

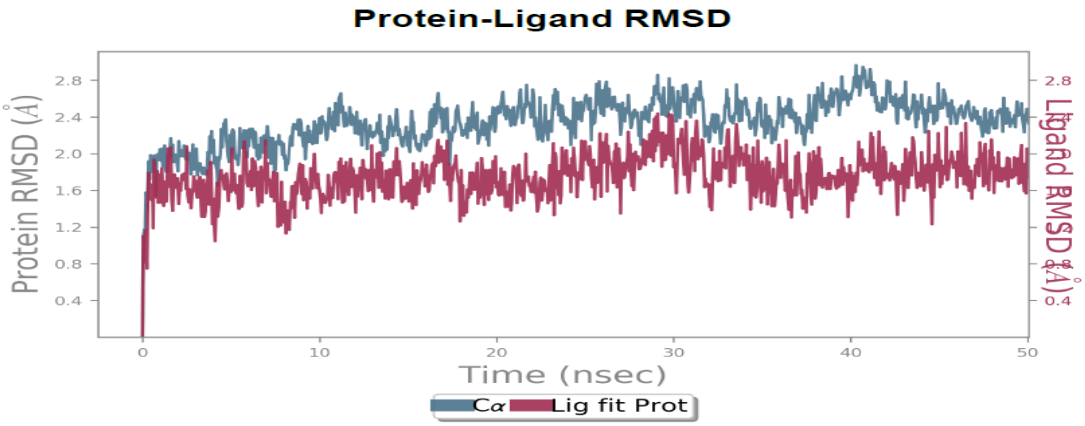


Figure 4. the RMSD of complex (Ligand and receptor).Compound [S2] with the *S.aureus* enzyme tyrosyl-tRNA synthetase.

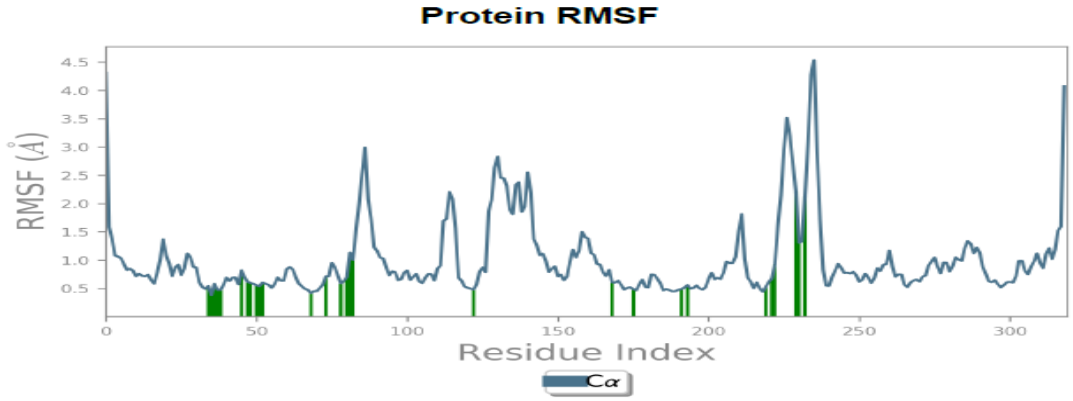


Figure 5. RMSF of Cα backbone of 1JIJ bound with [S2]-ligand.

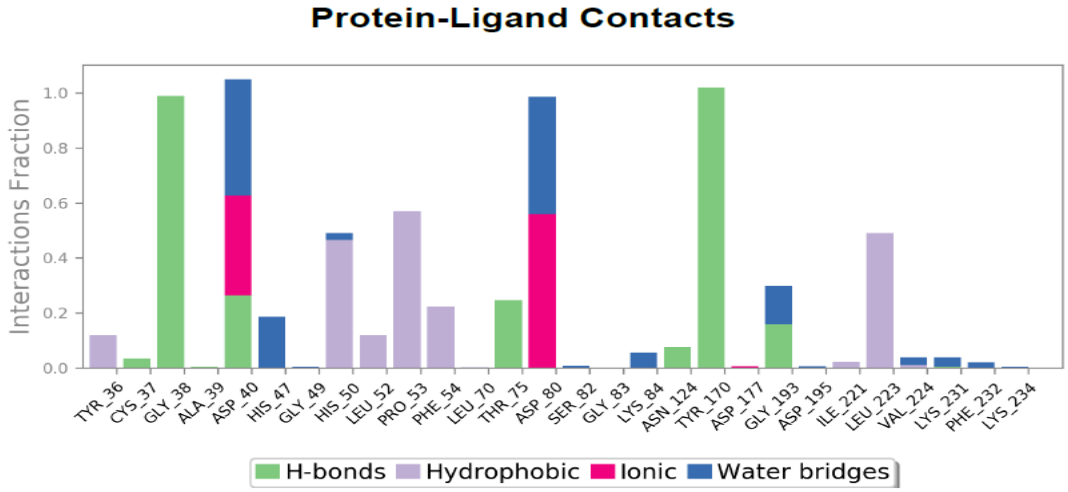


Figure 6. The interactions of amino acids inside active pocket 1jij with the ligand during molecular dynamics simulation time. Compound [S2] with the *S.aureus* enzyme tyrosyl-tRNA synthetase.

4. Conclusions

A new series of Schiff bases designed successfully, denoted as S and S (1-6), were developed from 2-(3-benzoylphenyl) propionic acid. In silico, experiments such as ADME studies were utilized to predict the pharmacokinetics of newly designed compounds. The results show that all the compounds meet Lipinski's rule requirements, indicating their potential for oral administration. Using GOLD Suite software for docking studies found that compound [S2] binds best to the enzyme tyrosyl-tRNA synthetase, giving it the highest PLP fitness value (89.02) compared to the standard ligand (79.71). Finally, studies of dynamic simulations of compound [S2] with the enzyme pocket showed that the complex had stable fluctuations during the simulation time with an RMSD value less than 3Å. The RMSD and RMSF analyses confirmed that the protein and compound [S2] complex were stable in an aqueous environment. Prove that compound [S2] is a promising agent as a tyrosyl-tRNA synthetase inhibitor.

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