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"In Silico Molecular Docking and ADME Prediction Studies for the Design of Novel Antimalarial Agents"

Afsar Ahmed[1], Shalini Singh[2]

[1,2]*QSAR & Cheminformatics Laboratory, Department of Chemistry, Bareilly College, M.J.P. Rohilkhand University, Bareilly, U.P. India*

***Abstract*--**

***Objective*--Malaria continues to pose a severe threat as one of the most lethal infectious diseases, despite extensive efforts aimed at its control. The emergence of resistance to treatment within Plasmodium presents a major challenge for existing anti-malarial drugs. Currently, the rise and dissemination of resistance to antimalarial medications have become a notable concern globally. There is a challenge in identifying natural substances that can lead to the creation of new antimalarial drugs. An effective approach to tackle this problem is the synthesis of new compounds or the modification of existing anti-malarial treatments. Molecular docking analyses and computational design play a key role in the innovation and adaptation of anti-malarial medications.**

Based on its docking score and the interactions between the protein and ligand, the molecules were selected and subsequently subjected to pharmacokinetic studies to identify key medicinal parameters. The molecule that was docked using docking tools was ranked based on the binding score, and a high-quality relationship model was identified with Plasmodium PIR Protein Ectodomain among the top-scoring molecules. The selected molecules also exhibited optimal pharmacokinetic properties.

***Keywords*-- Ectodomain, docking, Plasmodium falciparum, malaria, pharmacokinetic drug resistance.**

I. INTRODUCTION

Despite years of attempts to combat and manage malaria, it remains a widespread and lethal infectious disease, particularly in developing nations across Africa, Asia, and South America[1-2]. The illness is triggered by a parasite belonging to the genus Plasmodium. The primary species of Plasmodium include Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium knowlesi, and Plasmodium malariae. P. falciparum being responsible for the majority of deaths [3-4]. Among the five types of Plasmodium parasites that lead to malaria in humans, *Plasmodium falciparum* is the most harmful species with the highest potential for developing drug resistance[5-6].

Recent findings from the WHO indicate that since the year 2000, around 2.2 billion malaria cases and 12.7 million deaths have been prevented, but malaria continues to pose a significant global health challenge, especially in the WHO African Region. The most recent World malaria report from WHO estimates 263 million malaria cases and 597,000 deaths globally in 2023. This amounts to roughly 11 million additional cases in 2023 compared to 2022, while the death toll remained nearly unchanged. About 95% of the fatalities occurred in the WHO African Region, where many individuals at risk still do not have access to necessary services for preventing, detecting, and treating the disease[7]. Currently, artemisinin-based combination therapies (ACTs) are the primary treatment recommended by the World Health Organization (WHO) for uncomplicated falciparum malaria in all countries where it is endemic. Regrettably, there have been reports of the emergence and spread of artemisinin (ART)-resistant P. falciparum in Southeast Asian countries such as Thailand, as well as in many other regions where malaria is endemic, including parts of Africa [8-10]. Curcumin [1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], also known as diferuloyl methane, is a major hydrophobic polyphenol derived from the rhizome (turmeric) of the herb *Curcuma longa*. Turmeric has been widely reported as a principal component of traditional remedies for treating malaria and fever in India, Nigeria, and Samoa (Odugbemi et al., 2007; Uhe, 1974; Shankar & Venugopal, 1999). Curcumin is chemically classified as a bis-α,β-unsaturated β-diketone that exhibits keto-enol tautomerism. In recent years, it has generated considerable scientific interest due to its wide range of therapeutic properties, including antioxidant, anti-inflammatory, antimicrobial, and anticarcinogenic activities (Aggarwal & Harikumar, 2009; Kunnumakkara, Anand, & Aggarwal, 2008; Ahsan et al., 1999; Dubey et al., 2008; Liang et al., 2008). It also demonstrates hepatoprotective and nephroprotective effects, suppresses thrombosis, protects against myocardial infarction, and possesses hypoglycemic and antirheumatic properties.

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The clinical symptoms of malaria are associated with blood-stage parasites and linked to a large-scale infection of erythrocytes [11]. In order to provide amino acids for the synthesis of parasite proteins and to create the space necessary for the parasite to grow and multiply within the erythrocyte, intraerythrocytic malaria parasites break down approximately 60–80% of hemoglobin in an acidic food vacuole. Eventually, this toxic heme hinders the parasite's resilience[12]. The parasite uses a 200 KDa protein complex that includes histo-aspartic proteases, cysteine falcipain-2 (FP-2), aspartate (plasmepsin II and IV), and a specific enzyme (heme detoxification protein) that converts toxic heme to "hemozoin" as a survival strategy [13]. This mechanism protects the parasite against oxidative damage caused by reactive oxygen species (ROS). In this intricate process, FP-2, a member of the papain family, functions as a cysteine protease during the erythrocytic phase of P. falciparum, located in the food vacuole where it degrades the hemoglobin molecule. The FP-2 gene is situated on chromosome 11. FP-2 is produced consistently during the erythrocytic stages of the parasite's lifecycle, with notably higher levels of expression observed during the trophozoite stage [14-15]. The absence of a highly effective vaccine for malaria prevention, along with the prevalent use of multidrug-resistant P. falciparum, has created an urgent demand for the discovery of lead compounds and the development of new alternative antimalarial medications to potentially circumvent issues associated with drug resistance [16-18]. The identification of new or novel drug targets, along with the development of antimalarial drugs possessing unique modes of action, may provide a viable solution to combat drug resistance in malaria and help reduce malaria-related mortality. As malaria is a highly studied disease, several potential drug targets have already been proposed in research. These targets can be further explored and validated through experimental studies for drug development.

II. Materials And Method

2.1 Collection of protein and ligands datasets

The crystal structure of the *Plasmodium* PIR protein ectodomain (PDB ID: 6ZYV) was obtained in PDB format from the Protein Data Bank (https://www.rcsb.org/structure/6ZYV). The ligand used in the study was drawn using ChemSketch, a chemical drawing program available at https://www.acdlabs.com/resources/free-chemistry-software-apps/chemsketch-freeware/.

2.2 Preparation of target protein

The crystal structure of the *Plasmodium* PIR protein ectodomain (PDB ID: 6ZYV), with a resolution of 2.15 Å, was obtained in PDB format from the Protein Data Bank. This structure contains three chains: A, B, and C. For docking studies, the protein structures were prepared by assigning hydrogens and polarities and by calculating Gasteiger charges. Subsequently, the structures were converted from PDB to PDBQT format using the AutoDock tool (mgltools).

2.3 Preparation of ligand

Derivatives of pyridylvinylquinoline-triazole were drawn using ChemSketch software (https://blog.acdlabs.com/acdlabs/rss.xml) and saved in MOL format. These molecules were then used for docking studies. Using Open Babel and custom PERL scripts, all ligand molecules were subsequently converted from MOL format to PDB format.

2.4 Molecular docking

To identify potential hit compounds for further drug discovery research, molecular docking studies were performed using all ligands from the organic chemical library against the *Plasmodium* PIR protein ectodomain. In this study, AutoDock version 4.2 was employed for the docking investigations. AutoDock uses a semi-empirical free energy force field and applies the Lamarckian Genetic Algorithm (LGA) for docking simulations.The docking grid, which encompassed the entire binding site of the *Plasmodium* PIR protein ectodomain, was manually defined by visualizing the protein structure. Prior to importing the designed derivatives, the cavity detection wizard was used to identify the potential binding sites. The Autodock Vina program further assisted in the docking studies. Molecular docking experiments helped determine the orientation and interactions between the protein target and the proposed derivatives of pyridylvinylquinoline-triazole. Figure 1 presents the ribbon diagram of the *Plasmodium falciparum* PIR protein ectodomain bound to a derivative of pyridylvinylquinoline-triazole. Molecular docking was conducted on the *Plasmodium* PIR protein ectodomain using a self-developed PERL script. Fig. 1 shows Ribbon diagram of *Plasmodium* PIR protein ectodomain 6 with the Derivatives of pyridylvinylquinoline triazole. The docking grid was defined with dimensions X = 40, Y = 40, and Z = 40, centered at coordinates X = 12.644, Y = 11.143, and Z = 166.461.

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Key residues within the binding site included ILE C:73, LEU C:66, VAL C:11, ALA C:91, GLU C:71, and MET C:69, along with several adjacent residues (Fig. 2). An organic ligand library was systematically docked into the active site to identify potential compounds for further drug development. This approach aimed to validate the *Plasmodium* PIR protein ectodomain as a promising drug target in malaria. Furthermore, pharmacokinetic properties of the top-ranked ligands were evaluated to prioritize candidates with favorable ADME profiles for subsequent experimental validation.

2.5 Drug-likeness and ADME prediction

The pharmacokinetic properties and drug-likeness of the suggested derivatives were evaluated online using the SwissADME tool (http://www.swissadme.ch). The assessment of drug-likeness was based on Lipinski's Rule of Five, which provides baseline standards for evaluating the oral bioavailability of novel molecular entities [19].According to Lipinski's rule, a compound is more likely to exhibit good absorption and permeability if it meets the following criteria: no more than five hydrogen bond donors**,** no more than ten hydrogen bond acceptors**,** a molecular weight below 500 Da**,** and a logP (iLogP) value not exceeding 5. In addition to Lipinski's parameters, other important factors associated with poor absorption were also considered, such as the number of rotatable bonds (nRotb) and topological polar surface area (TPSA)**,** with poor absorption often indicated when TPSA is less than 140 **Å²** [20]. Furthermore, several pharmacokinetic characteristics were evaluated, including molar refractivity (MR)**,** logarithm of skin permeability (logKp)**,** blood-brain barrier (BBB) penetration**,** permeability glycoprotein (P-gp) substrate status, and gastrointestinal (GI) absorption. These parameters help predict the in vivo behavior of the compounds and their potential as drug candidates[20].

III. Result And Discussion

3.1 Analysis of docking

Molecular docking was performed with all ligands, and it was deemed successful, as each ligand was positioned within the receptor's active site. The twelve molecules with the highest estimated free energy of binding (EFEB) scores were selected for further analysis. The EFEB values of these selected molecules ranged from -11.2 to -8.7 [Table 2]. Protein-ligand complexes of the top-scoring molecules were examined to analyze binding interactions, the orientation of the docked compounds, and the interacting residues within the active site.

The top-ranked molecule, ligand1, showed substantial interactions with active site residues ILE C:73, MET C:69, VAL ILE C:73 and LEU C:66 [Figure 2]. Ligand2, which had the second-highest EFEB score, formed hydrogen bonds with LYS B:13, CYS B:21, and ASP B:20 [Figure 3]. These same residues—LYS B:13, CYS B:21, and ASP B:20—also displayed strong interactions with ligand3.All other selected compounds exhibited good patterns of hydrogen bonding and hydrophobic interactions as well.

3.2 Molecular parameters

The physicochemical characteristics were determined, revealing that the molecular weight of each chosen molecule was below 500 Da except ligand5. Each of the molecules listed in [Table 3] exhibited a log P value of less than 5. Additionally, all selected molecules had less than 5 hydrogen bond donors and equal or less 10 hydrogen bond acceptors, as indicated in [Table 3]. Compared to larger molecules, drug molecules with molecular weights around 500 Da are more easily transported, dispersed, and absorbed.[21]

3.3 Drug-likeness and ADME prediction

The Lipinski rule of five (Ro5) is commonly used to assess the drug-likeness of chemical compounds and potential drugs. According to this rule, pharmaceutical-grade compounds should have a molecular weight (MW) of less than 500 g/mol, a logarithm of the partition coefficient (logP) below 5, fewer than five hydrogen bond donors (HBDs), and fewer than ten hydrogen bond acceptors (HBAs) [22]. Additionally, studies have shown that pharmacological flexibility and membrane permeability are associated with a topological polar surface area (TPSA) of no more than 140 Å² and a total of ten or fewer rotatable bonds (RotB). Compounds that fulfill these criteria have demonstrated improved bioavailability and favorable pharmacokinetic properties [23–26].Low molecular weight (MW) molecules are light and can easily penetrate cell membranes. Compounds with a molecular weight below 500 Da (MW < 500) are generally better absorbed orally [27], whereas those with MW > 500 Da are typically absorbed through alternative pathways, such as membrane transport [28]. As shown in [Table 3], all the analyzed compounds had molecular weights below 500 Da except ligand5. The implicit logP (IlogP) represents the octanol/water partition coefficient of a molecule in two immiscible solvents, reflecting how the molecule dissolves in both solvents while maintaining its neutral state. Initially, IlogP was used in pharmacological and medicinal research.

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It plays a vital role in drug absorption through the oral route [27] and facilitates interactions between drugs and their biological targets [29]. Octanol, due to its combined hydrophilic and lipophilic nature, was considered a good mimic of phospholipid membrane properties [30]. According to Lipinski's rule of five, the predicted IlogP values for the compounds (Table 3) ranged between 3.13 and 4.42, all below the threshold of Ro5. This suggests that the synthesized derivatives are likely to exhibit good absorption. Regarding hydrogen bond acceptors (HBAs), they are defined as heteroatoms with at least one bonded hydrogen atom. According to Lipinski's rule of five (Ro5), the total number of hydrogen bond acceptors (HBAs), which includes nitrogen (N) and oxygen (O) atoms, should be less than 10 [27]. As shown in [Table 2], the selected compounds had HBA values ranging from 5 to 7, which is below the Ro5 threshold. Hydrogen bond donors (HBDs) are defined as any heteroatom with a formal positive charge—including the bonded oxygens—excluding pyrrole nitrogen, halogens, sulfur, heterochromatic oxygen, and higher oxidation states of nitrogen, phosphorus, and sulfur. Ro5 further states that the total number of hydrogen bond donors (OH and NH groups) should be five or fewer. As indicated in [Table 3], all compounds met this criterion with HBD values below 5. Both HBA and HBD are considered critical, as they influence oral absorption and interactions with other compounds and macromolecules [27]. Topological Polar Surface Area (TPSA), which is calculated by adding together all the polar fragments (such as oxygen, nitrogen, and their associated hydrogens) on a molecule's surface, is a widely used descriptor in medicinal chemistry [31]. TPSA is primarily used to predict drug transport properties, including intestinal absorption and blood-brain barrier (BBB) penetration [32–33]. It has gained popularity in virtual screening and ADME (Absorption, Distribution, Metabolism, and Excretion) property prediction [34]. A TPSA value of less than 60 $Å^2$ is generally considered indicative of good blood-brain barrier penetration [35]. The TPSA values of the proposed derivatives (Table 3) were found to be greater than 60 $Å^2$, with the exception of Ligand10 and Ligand11. This indicates that, while most derivatives may not effectively cross the blood-brain barrier, Ligand10 and Ligand11 show potential for BBB penetration due to their lower TPSA values (Table 4). However, all derivatives exhibit good intestinal absorption, as their TPSA values remain below 140 $Å^2$. Additionally, the total number of rotatable bonds (RBN) reflects the number of bonds within a molecule that are capable of freely rotating.

Rotatable bonds are defined as single non-ring bonds attached to non-terminal heavy atoms (i.e., non-hydrogen atoms). It has been observed that molecules with less than 10 rotatable bonds tend to have better oral bioavailability [36]. For the designed compounds, the number of rotatable bonds was found to be less than 10, suggesting excellent potential for oral availability. In the in silico ADME studies, several pharmacokinetic properties of the designed compounds were evaluated, including molar refractivity (MR), skin permeability (log Kp), blood-brain barrier (BBB) penetration, gastrointestinal (GI) absorption, permeability glycoprotein (P-gp) substrate properties, and inhibition of cytochrome P450 (CYP450) enzymes—specifically CYP1A2, CYP2C9, and CYP2C19. Molar refractivity (MR) is defined as the reciprocal of the volume of a mole of a substance and is closely related to the total polarizability of that mole. It provides valuable information about the electronic polarizability of specific ions in solution [37]. High MR values are often associated with favorable oral bioavailability and intestinal absorption in drug candidates. Permeability, which predicts absorption, distribution, metabolism, and excretion (ADME) characteristics, is a critical factor in therapeutic development.Skin permeability (Kp) specifically measures a molecule's ability to penetrate the outer layer of the skin [40]. It is frequently used in safety assessments to evaluate the potential for dermal absorption of a compound [41]. The acceptable range for the log Kp value of a drug is typically between -8.0 and -1.0 [42]. It was observed that the log Kp values of all the designed compounds (Table 4) fell within the acceptable range of -8.0 to -1.0, indicating suitable skin permeability. The blood-brain barrier (BBB), a specialized microvascular endothelial layer surrounding the central nervous system (CNS), serves as both a structural and chemical barrier that restricts the entry of many drugs into the brain. As a result, the effectiveness of newly developed drugs for treating brain-related conditions is often limited. Insufficient BBB penetration presents a significant challenge in the development of therapeutic agents for central nervous system disorders, as many promising compounds fail to reach therapeutic concentrations in brain tissue [43–44].Some of the proposed derivatives (Table 4) exhibited blood-brain barrier (BBB) permeability, which limits their usefulness in treating cerebral malaria, as such permeability is unnecessary or even undesirable for this condition. The ATP-binding cassette transporter known as permeability glycoprotein (P-gp) plays a key role in primary active efflux via carrier-mediated transport.

P-gp binds various substrates and is widely distributed throughout the body, including in the small intestine, blood-brain barrier capillaries, and several essential organs such as the liver and kidneys [45–46]. Cytochrome P450 (CYP) enzymes are a class of proteins responsible for the biosynthesis and metabolism of numerous endogenous and exogenous compounds. These enzymes have been identified in a broad range of organisms, including microorganisms, plants, animals, and even some viruses. Cytochrome P450 (CYP) enzymes derive their name from their cellular location ("cyto"), the presence of heme pigment ("chrome"), and the characteristic absorption peak at 450 nm observed when the heme is bound to carbon monoxide [47–48]. These heme-containing enzymes form a superfamily known as CYPs, which are responsible for the metabolism of a wide range of xenobiotic and endogenous compounds in humans.There are approximately 50 CYP enzyme isoforms, with five major isoforms—CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4—accounting for over 90% of oxidative metabolic activity [49]. Inhibition of these enzymes can lead to impaired drug metabolism and potential drug-drug interactions. Therefore, evaluating the inhibitory potential of drug candidates against specific CYP isoforms is a critical step in the drug development process. The inhibitory activity of the suggested derivatives against three key CYP isoforms—CYP1A2, CYP2C9, and CYP2C19—is summarized in Table 4.

IV. Conclusion

Pharmacokinetic and molecular docking studies were performed on twelve (12) substituted derivatives of pyridylvinylquinoline triazole using SwissADME, AutoDock Vina, and MGL Tools. This study represents a digitally driven and environmentally friendly approach to drug design, aligning with the principles of green chemistry, as no hazardous components were involved. The pharmacokinetic profiles of the compounds were found to be favorable, with none of the derivatives violating Lipinski's Rule of Five.

The compounds' biological activity may be attributed to hydrogen bonding and other hydrophobic interactions between the molecules and their targets. Given their excellent pharmacokinetic properties, the proposed derivatives show strong potential for use in the treatment of malaria.

Declaration

Ethics approval and consent to participate

Not applicable (as no human or animal subject was used in the investigation)

Consent for publication

Not applicable (as no human subject was used in the study)

Availability of data and material

The data used in this study are available and will be provided by the corresponding author on a reasonable request

Competing interests

Not declared.

Funding Statement

This research work not received any specific fund from any funding agency,

Author's contributions

Afsar Ahmed: Conceived and designed; Analyzed and interpreted the data; Wrote the paper. Shalini Singh Conceived and designed t; Contributed , analysis tools or data.

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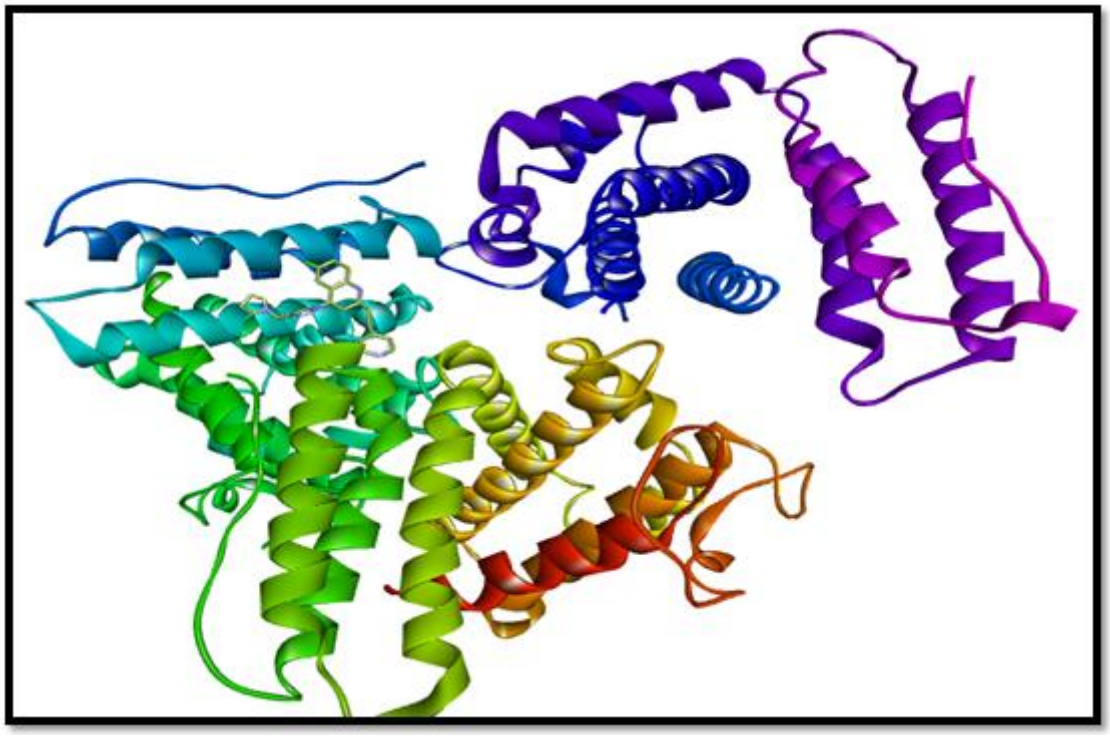

Fig. 1 Ribbon diagram of *Plasmodium* PIR protein ectodomain with the Derivatives of pyridylvinylquinoline triazole.

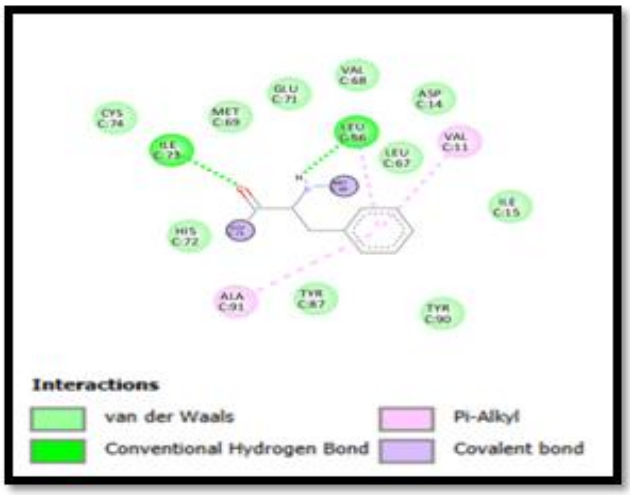

Fig. 2. Showing Interaction of Ligand1 with Residues

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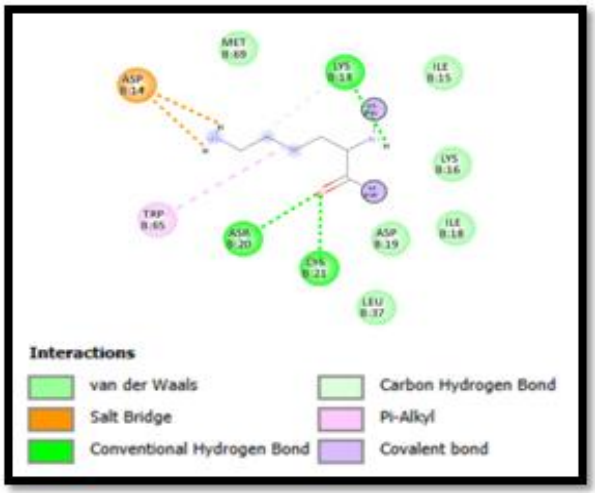
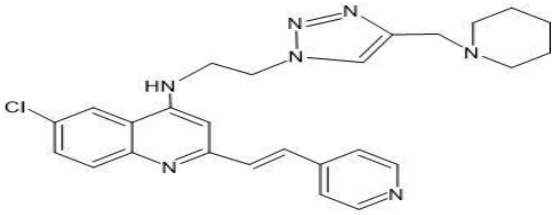
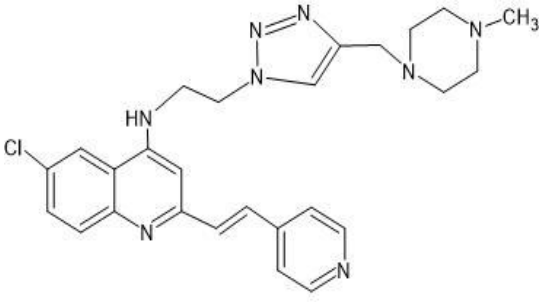


Fig. 3. Showing Interaction of Ligand2 with Residues

Table1
Structures, of the designed Derivatives of pyridylvinylquinoline triazole.

S.No.	Structure
Ligand 1.	
Ligand 2	

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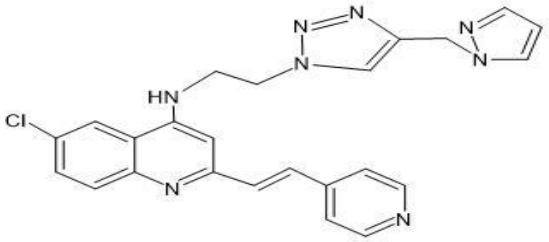
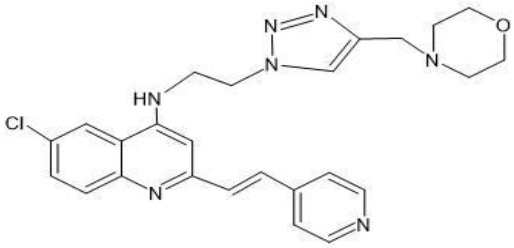
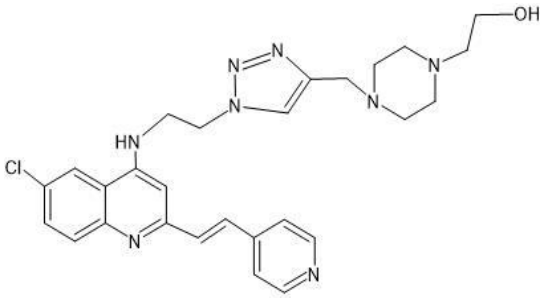
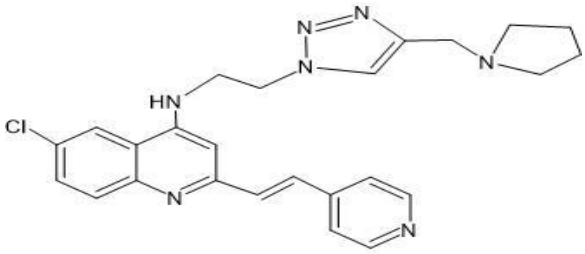
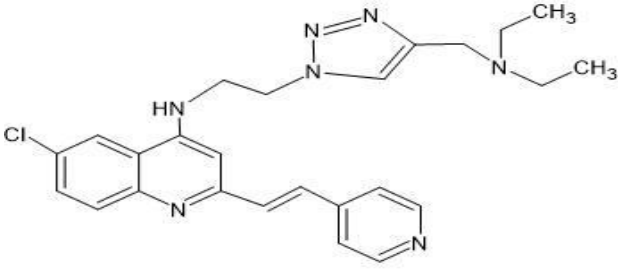
Ligand 3 
Ligand 4. 
Ligand 5. 
Ligand 6. 
Ligand 7. 

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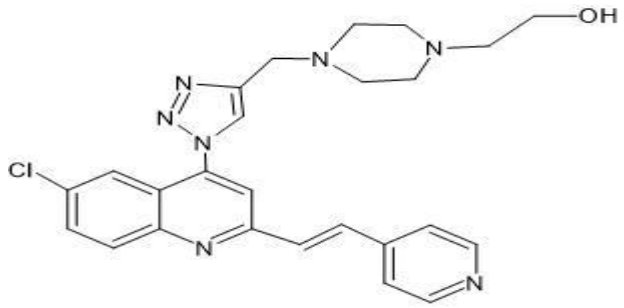
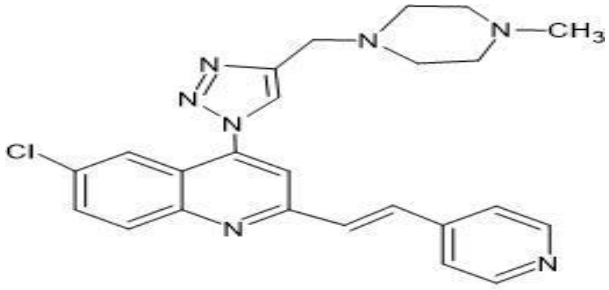
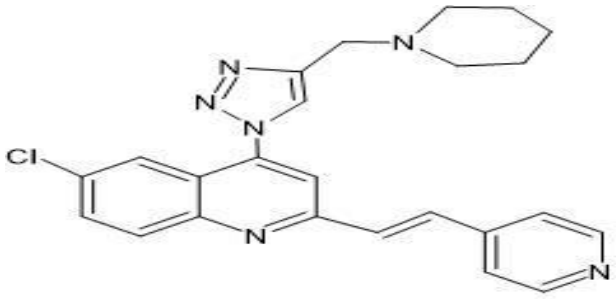
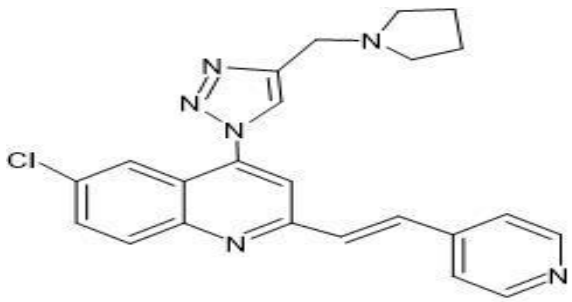
Ligand 8. 
Ligand 9. 
Ligand 10. 
Ligand 11 

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Ligand 12

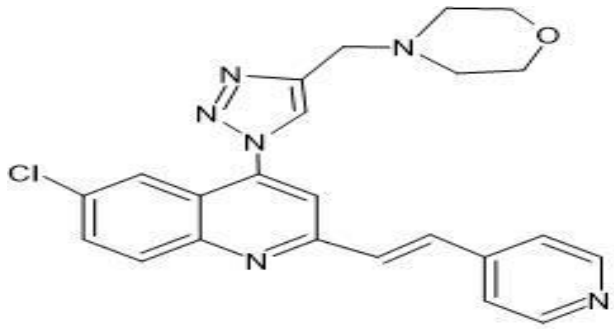

Table 2:
Binding affinity of selected potential molecules

S.No.	Binding affinity ((kcal/mol	Hydrogen Bonding	Hydrophobic interaction
Ligand 1	-11.3	ILE C:73, LEU C:66	7
Ligand 2	-11.0	LYS B:13, CYS B:21, ASP B:20	7
Ligand 3	-10.7	LYS B:13, CYS B:21, ASP B:20	7
Ligand 4	-10.6	CYS C:42, TYR C:41, HIS C:127, ASN C:121	10
Ligand 5	-10.6	CYS C:42, TYR C:41, HIS C:127, ASN C:121	10
Ligand 6	-10.1	ILE A:98, LEU A:99, ALA A;91	8
Ligand 7	-10.1	ASP A:204, GLU B:170, LYS B:162	5
Ligand 8	-9.1	ILE C:18, ASP C:19	7
Ligand 9	-9.1	LYS A:241	14
Ligand 10	-8.9	ASN B:187	4
Ligand 11	- 8.7	LYS A:241	7
Ligand 12	- 8.7	ASN A:214	9

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Table 3:
Lipinski's and Veber parameters of the designed Derivatives of pyridylvinylquinoline triazole.

S.No.	. Molecular weight	LogP	Hydrogen rotatable bonds	Hydrogen acceptors	Hydrogen donors	Lipinski#violations	TPSA
Ligand 1	474	4.42	8	5	1	0	71.76
Ligand 2	489.02	4.15	8	6	1	0	75.0
Ligand 3	456.93	3.13	8	5	1	0	86.34
Ligand 4	475.97	4.08	8	6	1	0	80.99
Ligand 5	519.04	4.21	10	7	2	0	95.23
Ligand 6	459.97	4.17	8	5	1	0	71.76
Ligand 7	461.99	4.24	10	5	1	0	71.76
Ligand 8	475.97	4.13	7	7	1	0	83.2
Ligand 9	445.95	4.09	5	6	0	0	62.97
Ligand 10	430.97	3.91	5	5	0	0	59.73
Ligand 11	416.91	4.0	5	5	0	0	59.73
Ligand 12	432.91	3.89	5	6	0	0	68.96

Table 4
Pharmacokinetics properties of the designed Derivatives of pyridylvinylquinoline triazole.

S.No.	logKp (cm/s)	GI Absorption	BBB Permeant	P-gp Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor
Ligand 1	-6.24	High	Yes	Yes	No	Yes	Yes
Ligand 2	-5.49	High	Yes	Yes	No	Yes	Yes
Ligand 3	-7.7	High	No	Yes	No	Yes	Yes
Ligand 4	-7.12	High	No	Yes	No	Yes	Yes
Ligand 5	-7.74	High	No	Yes	No	Yes	Yes
Ligand 6	-6.41	High	Yes	Yes	Yes	Yes	Yes
Ligand 7	-6.25	High	Yes	Yes	Yes	Yes	No
Ligand 8	-7.44	High	No	Yes	No	No	Yes
Ligand 9	-6.78	High	Yes	Yes	Yes	No	Yes
Ligand 10	-5.95	High	Yes	Yes	Yes	Yes	Yes
Ligand 11	-6.12	High	Yes	Yes	Yes	Yes	No
Ligand 12	-6.82	High	Yes	Yes	Yes	No	Yes

gastrointestinal (GI) absorption, log of skin permeability (logKp), blood-brainbarrier (BBB) penetration, Molar refractivity (MR), permeabilityglycoprotein(Pgp)substrate , cytochrome P450 (CYP450) enzymes:CYP1A2,CYP2C9, and CYP2C19 inhibitors

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