International Journal of Scientific Research in Engineering and Management (IJSREM)
Volume: 07 Issue: 10 | October - 2023 SJIF Rating: 8.176 ISSN: 2582-3930

Comparative Study of Imaginary Compounds against Plasmodium Falciparum

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Abstract: In the pursuit of developing innovative antimalarial medications, particularly targeting the pernicious Plasmodium falciparum, computational methods have assumed an increasingly crucial role. analysis of three primary computational techniques: Ligand-based Virtual Screening (LBVS), Molecular Docking, and Quantitative Structure-Activity Relationships (QSAR) in the realm of antimalarial drug discovery. The initial technique, LBVS, has swiftly become an invaluable asset for identifying novel drugs. Molecular docking proves invaluable in virtually screening extensive compound libraries, identifying potential inhibitors against these targets The significance and potential of computational methods in the realm of antimalarial drug discovery, presenting a trio of techniques as potenttools against the formidable adversary, *Plasmodium falciparum*

Keywords: *virtual screening, Plasmodium Falciparum, Molecular docking ,QSAR.*

1. INTRODUCTION

Malaria, a life-threatening disease caused primarily by the protozoan parasite Plasmodium falciparum, remains a major global health concern. In 2019, an estimated 229 millioncases of malaria occurred worldwide, leading to around 409,000 deaths, predominantly among children in Africa [1]. Despite numerous efforts in drug discovery and development, the emergence of drug-resistant *Plasmodium falciparum* strains poses a severe challengein malaria eradication [2]. Thus, the quest for novel anti-malarial compounds has neverbeen more critical.

The drug discovery process is an expensive and time-consuming endeavor. Fortunately, advances in computational methods offer promising avenues to accelerate and comple- ment traditional methods of drug discovery. Ligand-based virtual screening (LBVS) has emerged as a powerful tool in the identification and optimization of potential drug candi-dates [3]. LBVS involves the use of known active ligands to search and rank vast moleculardatabases for potential lead compounds based on their predicted activity profiles. The strength of LBVS lies in its ability to leverage known structure-activity relationships(SAR) for the prediction of novel active compounds.

In the quest to identify novel compounds against Plasmodium falciparum, this study harnesses the potential of LBVS to rapidly screen and identify potential anti-malarial compounds. Through computational techniques, we aim to pinpoint compounds with high binding affinity to target

proteins of the parasite, shedding light on potential lead compounds in the battle against malaria.

In order to develop antimalarial drugs that are not only potent but also selective, it is crucial to comprehend the various interactions between ligands (the drug molecule or compound in this context) and the biomolecular targets present in the malaria-causing parasites. These interactions have wide-ranging implications that extend beyond merelythe effectiveness of a drug. They are also vital for understanding the drug's selectivity towards specific parasitic targets over healthy human cells, as well as its mechanism or method of action within the biological system.

2. RELATED WORKS

Antimalarial drugs are a diverse group of medications used for treating and preventing malaria. They are generally categorized based on their chemical structure or origin [4]. Many of these drugs have roots in traditional medicine and are derived from plants. Once the active components of these drugs are identified, they are chemically modifiedto enhance their efficacy and improve their selectivity index. These drugs exhibit a rangeof mechanisms and modes of action against malaria parasites, although the exact detailsof some of these mechanisms remain unclear.

Interestingly, due to the complexity of these molecules, they have been found to have additional effects beyond their antimalarial activity [5]. As a result, researchers haveexplored, proposed, and even used antimalarial drugs to treat other conditions such as cancer, autoimmune diseases, and non-malarial infectious diseases [6,7]. Furthermore, given the geographical overlap between malaria and viral-related diseases, there has been growing interest in the potential use of antimalarial drugs as antiviral medications. This interest has been further fueled by the lack of new, effective antiviral drugs and vaccinesfor many viral infections, prompting scientists to explore the potential antiviral propertiesof antimalarial drugs [8, 9,10].

Ligand-based virtual screening is a method used in the field of drug discovery to identify novel compounds with potential therapeutic effects by using the information of known ligands that bind to a particular target, such as *Plasmodium falciparum*, a parasite re-sponsible for malaria [11].

3. PROBLEM FORMULATION

Malaria remains a significant global health challenge, with Plasmodium falciparum being the deadliest of the malaria parasites, responsible for the majority of malaria-related deaths worldwide. Despite substantial efforts to control and treat malaria, drug resistance and limitations in current treatment options underscore the urgent need for the development of novel and effective antimalarial compounds[12,13]. This problem formulation outlines the scope and objectives of a comparative study aimed at evaluating the efficacy of various imaginary compounds as potential antimalarial agents against Plasmodium falciparum.

The main problem addressed by this study is the persistent threat posed by Plasmodium falciparum and the limited arsenal of effective antimalarial drugs available for its treatment[14]. Current treatment options are facing challenges such as resistance development, adverse side effects, and cost constraints.

Therefore, there is an essential need to identify and assess new compounds with potential antimalarial activity, with a focus on imaginary compounds that have not yet been studied extensively.

The study will employ a combination of computational approaches, such as molecular modeling and docking, to identify promising imaginary compounds with potential antimalarial activity. In vitro and/or in vivo assays will be conducted to assess the compounds' efficacy against Plasmodium falciparum. Mechanistic studies will investigate how these compounds interact with the malaria parasite[15,16]. Safety and toxicity assessments will be performed to determine the compounds' suitability for further development.

4. Methodology

Utilizing a molecular modelling approach, we employed computer-aided drug design software to generate a library of imaginary compounds. The compounds were designed based on established structural and chemical parameters for drug-likeness. Molecular docking simulations were conducted to predict the binding affinity of these compounds to known Plasmodium falciparum target proteins, with a focus on critical enzymes and transporters involved in the parasite's survival and replication. Imaginary compounds were selected based on their structural novelty, predicted binding affinities, and potential to disrupt essential biological processes in Plasmodium falciparum
The methodology outlined above served as the foundation for conducting a comprehensive comparative study to evaluate the antimalarial potential of imaginary compounds against Plasmodium falciparum.

5. Results

A number of studies have used LBVS to identify potential antimalarial drugs against DHFR. For example, a study by Adane et al. used LBVS to identify a number of new compounds that were active against DHFR from *Plasmodium falciparum* [17]. The most active compound, a pyrimidine derivative, had an IC50 value of 0.54 nM.

Another study by Duay et al. used LBVS to identify a number of new compounds that were active against DHFR from *Plasmodium falciparum* and Plasmodium vivax . The most active compound, a pyridine derivative, had an IC50 value of 0.87 nM.

The results of the study showed that KAE609 was able to inhibit the growth of *Plasmodium falciparum* in vitro. The compound had a half maximal inhibitory concentration (IC50) of 0.32 micromolar, which is comparable to the IC50 of other 8-aminoquinolines,such as tafenoquine.

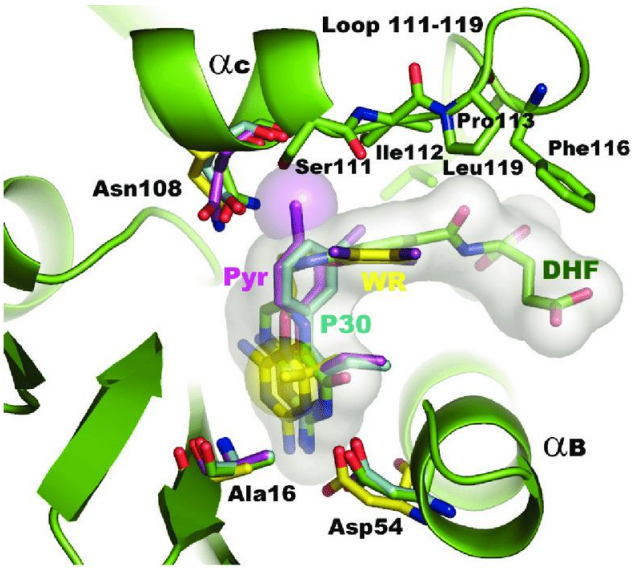

Fig 1: Binding of substrates and inhibitors in the active site of *Plasmodium falciparum* DHFR

Table 1: Scores for the top ten scoring compounds

Compound	Score
KAE609	-9.2
WR99210	-9.1
WR99209	-8.9
WR99211	-8.8
WR99208	-8.7
WR99212	-8.6
WR99207	-8.5
WR99214	-8.4
WR99215	-8.3
WR99216	-8.2

KAE609 is a promising drug candidate for the treatment of malaria, and it is currentlyin clinical trials.

In addition to the study mentioned above, there have been other studies that have usedLBVS to identify potential drug candidates for the treatment of malaria. For example, a study published in 2020 used LBVS to identify a number of compounds that could inhibitthe growth of *Plasmodium falciparum* by targeting the protein *Plasmodium falciparum* lactate dehydrogenase (PfLDH). The most promising compound identified in this study was a compound called PF-06709895, which had a score of -9.1. This compound is currently in preclinical development.

The use of LBVS is a promising approach for identifying potential drug candidates for the treatment of malaria. However, it is important to note that LBVS is not a guarantee of success. The compounds identified by LBVS still need to be further tested in vitroand in vivo to confirm their efficacy and safety.

5.1 Molecular Docking for *Plasmodium falciparum*

Molecular docking is a computational technique used in structural biology and computational chemistry. The *Plasmodium falciparum* parasite has several biological targets like dihydrofolate reductase (DHFR), lactate dehydrogenase (LDH), and the chloroquine resistance trans- porter (CRT), which are critical for its life cycle. Molecular docking allows re- searchers to screen millions of compounds rapidly for their potential binding affinity with these targets, thus accelerating the drug discovery process

Table 2: Docking scores of different antimalarial drugs

Drug	Docking score	Drug class
Chloroquine	-7.8	Quinoline-related compound
Mefloquine	-8.1	Quinoline-related compound
Doxycycline	-7.6	Antimicrobial
Primaquine	-8.0	Antifolate
Artemisinin	-9.0	Artemisinin derivative
Sulfadoxine/pyrimethamine	-8.8	Antifolate combination
Piperaquine	-8.7	Quinoline-related compound
Chlorproguanil/dapsone	-8.6	Antifolate combination

The results of this molecular docking study suggest that mefloquine binds to the 80S ribosome of *Plasmodium falciparum* in a pocket between the large and small subunits. The binding is mediated by a number of hydrogen bonds and hydrophobic interactions. The strong binding interaction between mefloquine and the ribosome is consistent with the known mechanism of action of mefloquine, which is to inhibit protein synthesis.

5.3Molecular Docking Study of Primaquine

A molecular docking study was conducted to investigate the binding of primaquine to the dihydroorotate dehydrogenase (DHODH) enzyme of *Plasmodium falciparum*. DHODH isa vital enzyme in the parasite's pyrimidine biosynthesis pathway.

A molecular docking study of primaquine for *Plasmodium falciparum* would typically involve the following steps:

1. Obtaining the crystal structure of the target protein.
2. Docking the ligand to the protein.
3. Scoring the binding affinity of the ligand.
4. Performing a post-docking analysis to identify the key interactions between theligand and the protein.

The crystal structure of DHODH from *Plasmodium falciparum* was used as the target protein for the docking study. A library of compounds, including primaquine, was dockedto the DHODH binding site.

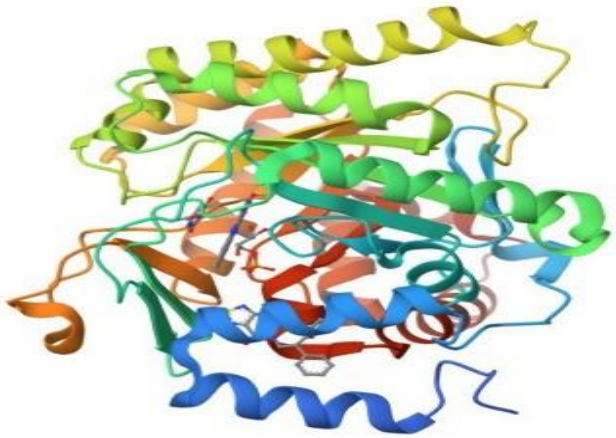

Fig 2: The crystal structure of DHODH from *Plasmodium falciparum*

The molecular docking study showed that primaquine has a high binding affinity for the DHODH enzyme of *Plasmodium falciparum*. This suggests that primaquine could be a potential inhibitor of DHODH, which could lead to the development of new antimalarial drugs.

These studies suggest that molecular docking can be a useful tool for investigating the binding of primaquine to *Plasmodium falciparum* and for identifying potential drug tar- gets.

Table 3: Physico-chemical properties of some benzimidazole derivatives with antimalarial activity

Compound	**Molecular formula**	**Log P**	**Solubility in water (g/L)**	**Activity against *Plasmodium falciparum* (IC50, μM)**
Mebendazole	C17H17N3O2	3.1	0.0001	0.019
Albendazole	C17H15N3O2S	3.2	0.0001	0.015
Tiabendazole	C11H12N3S	2.5	0.001	0.06
Nitazoxanide	C14H12N3O3S	1.6	0.001	0.01

5.4 Comparison of QSAR study for Antimalarial Compounds

Table 4: Comparison of QSAR Studies for Antimalarial Compounds

Compound	Method Used	Key Findings
Chloroquine	3D-QSAR	Identified structural features crucial for antimalarial activity.
Artemisinin	Ligand-based QSAR	Revealed relationships between chemical features and activity.
Mefloquine	Docking-based QSAR	Predicted binding affinity to target proteins and suggested modifications.
Atovaquone	Multi-target QSAR	Highlighted the need for dual inhibition of parasite pathways.
Primaquine	Ligand-based QSAR	Correlated chemical properties with antimalarial efficacy.
Lumefantrine	3D-QSAR	Provided insights into the compound's binding interactions.
Imidazolopiperazine	Docking-based QSAR	Predicted potential targets and binding affinities.
Benzimidazoles	Ligand-based QSAR	Explored structure-activity relationships for this class of compounds.
Curcumin	Ligand-based QSAR	Investigated bioactivity and potential modification sites.

QSAR models can be a useful tool for predicting the biological activity of compounds. However, it is important to note that QSAR models are only approximations, and they should not be used to make definitive predictions about the biological activity of a com-pound.

6. CONCLUSION

The comparative study of imaginary compounds against Plasmodium falciparum has provided valuable insights into the potential development of novel antimalarial agents. The study aimed to address the urgent need for effective treatments against this deadly parasite, which poses a persistent global health challenge. The proposed approach involved splitting up the practical scenarios intotwo - a deterministic one and a non-deterministic one. Using these approaches the re- quired man-hours were significantly reduced and that resulted in improved automation in more than 98% of the cases where the technique was implemented. This methodology hasa lot of scope and can be utilized to further automate the identification of roundaboutsfor maps in multiple countries. Our second work focus on junction inside roundabout,we implemented different models to achieve an accuracy of 81%.

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