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Research Article

Structure-Based Virtual Screening and Molecular Docking of Dual Inhibitors of Plasmodium Falciparum Prolyl-tRNA Synthetase

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ABSTRACT

Malaria is a disease caused by Plasmodium parasites, which remains a global problem including in Indonesia. One of the main types of parasites that cause malaria is Plasmodium falciparum which currently shows a tendency to be resistant to artemisinin-based combination therapy (ACT). This highlights the need to discover of more effective new drugs. This study aims to discover new drug candidates capable of overcoming ACT resistance using a computational approach. The methods used include structure-based pharmacophore modeling using the Pharmit webserver, virtual screening using the ChemDiv database, molecule docking using AutoDock Vina, and evaluation of ADME parameters using the SwissADME webserver. The molecular target used was the prolyl-tRNA synthetase enzyme (PDB ID: 4YDQ) with halofuginone as the reference compound. The pharmacophore screening successfully identified 312 hit compounds. Molecular docking using AutoDock Vina showed that 164 compounds had better binding affinity than halofuginone. Evaluation of ADME parameters showed that 11 compounds met the pharmacokinetic and toxicity criteria. Among them, ChemDiv-1481-0030 compound showed a binding affinity value of -10.6 kcal/mol with an 80% similarity in residue interactions compared to halofuginone. These results show that ChemDiv-1481-0030 has potential as an antimalarial drug candidate that works through the mechanism of inhibiting the PfPRS enzyme.

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1. Introduction

Malaria is an infectious disease caused by the *Plasmodium* parasite, which is transmitted to humans through the bite of *Anopheles* mosquitoes and is one of the leading causes of morbidity and mortality globally. One species of *Plasmodium* is *P. falciparum*, which has the highest level of virulence and contributes most to deaths caused by malaria. Based on a 2023 report by the World Health Organization (WHO, 2023) there were an estimated 249 million cases of malaria worldwide in 2022, with 608,000 deaths. Indonesia is an endemic country with varying levels of prevalence between regions. According to a national report, there were 443,530 recorded cases of malaria in 2022. Most of these cases are concentrated in eastern Indonesia, such as the provinces of Papua and West Papua, which account for about 94% of the total national malaria cases, even though these two provinces only represent about 2% of Indonesia's total population (Kemenkes, 2023).

Malaria caused by *Plasmodium falciparum* infection is generally treated using artemisinin-based combination therapy or ACT (Dondorp et al., 2010). Based on several studies the effectiveness of this therapy has declined due to the emergence of resistance to ACT. Various studies have confirmed the resistance case emerging in Southeast Asia (Noedl et al., 2008; Wongsrichanalai & Meshnick, 2008). The decline in therapeutic response in some patients is thought to be related to the longer duration of drug use even though patients received appropriate therapy. These findings emphasize the need to develop new treatment strategies that can overcome drug resistance while ensuring the safety and effectiveness of malaria treatment (Biamonte et al., 2013).

One strategy that can be used in the development of antimalarial drugs is the exploration of bioactive compounds from natural sources. During World War II, a research conducted by American scientists have successfully isolated an alkaloid compound with strong antimalarial activity known as febrifugin (Rangel & Llinás, 2021). This compound comes from the *Dichroa febrifuga* plant which has long been used traditionally in the treatment of malaria in China. Although it shows high antimalarial potential the use of febrifugin is limited by the emergence of side effects such as gastrointestinal disorders and liver toxicity (Jiang et al., 2005; Linder et al., 2007). There is a derivative of febrifugin called halofuginone which has undergone chemical modification to reduce its toxicity without diminishing its biological activity. Halofuginone shows effectiveness as an antimalarial agent through the mechanism of inhibiting the prolyl-tRNA synthetase (PfPRS) enzyme in *Plasmodium* parasites without damaging the PRS found in humans (Pines & Spector, 2015). Prolyl-tRNA synthetase (PRS) is one of the essential enzymes in the protein biosynthesis process that catalyzes the binding of proline amino acids to specific tRNA. The crucial role of PRS in cell survival makes it a potential molecular target in drug development (Keller et al., 2012). However, the use of halofuginone as an antimalarial therapeutic agent still requires further study regarding its safety in humans. Administration of halofuginone at high doses has been reported to cause significant side effects (Jiang et al., 2005).

Identifying new compounds that are effective, safe, and capable of overcoming drug resistance is a major challenge. Computational or *in silico* approaches are efficient strategies for accelerating the discovery of new drugs. Various studies have been carried out to design novel compounds which could potentially act as potent PfPRS enzyme, mostly catered for the potential allosteric binding site (Doshi et al., 2020; Nyamai & Tastan Bishop, 2020; Yuniarta et al., 2023). This study focuses on the discovery of potential inhibitors targeting febrifugine-halofuginone binding site using structure-based virtual screening approach which relies on the availability of three-dimensional structure of PfPRS enzyme (Jain et al., 2015). The process is carried out by filtering compounds contained in a database using a less costly

method (i.e. pharmacophore-based screening and ADMET evaluation) and then assessing the interactions of these compounds with target protein (Cosconati et al., 2010).

2. Materials and Methods

2.1 Material

Protein Structure

The three-dimensional (3D) structure of *Plasmodium falciparum* Prolyl-tRNA Synthetase (PfPRS) was retrieved from the Protein Data Bank (RCSB PDB: Homepage) with PDB ID: 4YDQ and used as the target protein in this study.

Compound Databases

Candidate compounds in .mol or .mol2 format were obtained from the ChemDiv database, attached to Pharmit webserver (https://pharmit.csb.pitt.edu) . Decoy compounds for validation were retrieved in 3D format from the Directory of Useful Decoys Enhanced (DUD-E) database (https://dude.docking.org/).

Hardware

All computational analyses were performed on an Acer Aspire E5-473G laptop equipped with an Intel® Core™ i3-4210U processor, 4 GB RAM, 1 TB HDD storage, and NVIDIA® GeForce® 920M graphics, running Windows 10 Home with internet access.

Software and Web Servers

Molecular docking simulations were conducted using AutoDock Vina version 1.2, with structure preparation performed in AutoDock Tools and visualization carried out using BIOVIA Discovery Studio Visualizer. In addition, the following web-based tools were used: Pharmit (https://pharmit.csb.pitt.edu), Protein Data Bank (https://www.rcsb.org), PubChem (https://pubchem.ncbi.nlm.nih.gov), Directory of Useful Decoys Enhanced (DUD-E) (https://dude.docking.org/), and SwissADME (http://www.swissadme.ch) for pharmacophore modeling, compound retrieval, decoy generation, and ADME prediction.

2.2 Methods

Pharmacophore modeling and validation

Pharmacophore modeling and validation ware performed using the Pharmit webserver (https://pharmit.csb.pitt.edu) (Sunseri & Koes, 2016). The three-dimensional (3D) structure of the Plasmodium falciparum Prolyl-tRNA Synthetase (PfPRS) with PDB code 4YDQ (Jain et al., 2015) was obtained from the Protein Data Bank database (www.rcsb.org) and uploaded to the Pharmit web server for pharmacophore identification, followed by a minimum of five pharmacophore combinations. The generated models were then validated by screening active reference compounds and decoy compounds obtained from the DUD-E webserver (https://dude.docking.org/) (Mysinger et al., 2012) based on known potent febrifugine and halofuginone analogs (Jain et al., 2015). The best pharmacophore model was selected based on its ability to retrieve the highest number of active compounds with the lowest number of decoy hits. Model performance was evaluated using the Goodness of Hit (GH) Score to evaluate the model's ability to discriminate between active and inactive compounds and the model was declared valid if the GH Score obtained was >0.5 (Güner, 2000). The GH Score was calculated using the following formula:

$$\text{GH Score: } (\frac{3}{4}\,\text{YoA} + \frac{1}{4}\,\text{Se})\,\text{Sp}$$

Explanation:

YoA (Yield of Active): Percentage of active compound yield

Se : Sensitivity

Sp : Specificity

Pharmacophore and drug-likeness-based screening of candidate compounds

Screening of candidate compounds was performed using the Pharmit webserver with a previously validated pharmacophore model. Subsequently, the screening process was carried out by applying Lipinski's Rule of Five (Lipinski et al., 1997) and Veber's Rule parameters (Veber et al., 2002).

Molecular docking

Before the docking simulation, both the protein and ligand structures are prepared, where the PfPRS structure is separated from its natural ligand using Biovia Discovery Studio Visualizer software. Docking validation is then carried out using AutoDock Vina (Eberhardt et al., 2021) by redocking the natural ligand into the active site of the protein, followed by determining the position and dimensions of the gridbox to cover the binding area with the appropriate x, y, and z coordinates. The docking validation was considered valid if the RMSD value obtained was below 2 Å. Further validation was carried out by performing docking on reference compounds and decoys using the batch docking method to produce binding affinity values, which were then evaluated through ROC curve analysis that included AUC (Area Under the Curve) and BED-ROC (Boltzmann-Enhanced Discrimination of Receiver Operating Characteristic) values. The method was declared valid if the AUC and BED-ROC values each surpassed 0.50 (Truchon & Bayly, 2007). The next step was to dock the molecules using the batch docking method against candidate compounds obtained from previous step using the same batch docking protocol. The docking results were then analyzed and compounds that showed higher binding affinity than the reference compound were selected as potential candidates.

ADMET evaluation of candidate compounds

The SwissADME webserver (www.swissadme.ch/index.php) (Daina et al., 2017) was used to evaluate candidate compounds based on pharmacokinetic and toxicity parameters. The parameters used include predictions of gastrointestinal absorption (GI absorption), potential interactions between the compound and cytochrome P450 enzymes, the presence of PAINS (Pan-Assay Interference Compounds) structures (Baell & Holloway, 2010) and the identification of toxicophore functional groups based on Brenk's rule criteria (Brenk et al., 2008).

Visual evaluation of candidate compounds

Visual analysis was performed on the best compounds obtained using BIOVIA Discovery Studio Visualizer. This stage produced a visualization of the interaction between the candidate compound ligand and the target protein as well as a two-dimensional (2D) diagram representation showing the relationship between amino acid residues and ligands which provided an overview of the mechanism of ligand binding to the receptor.

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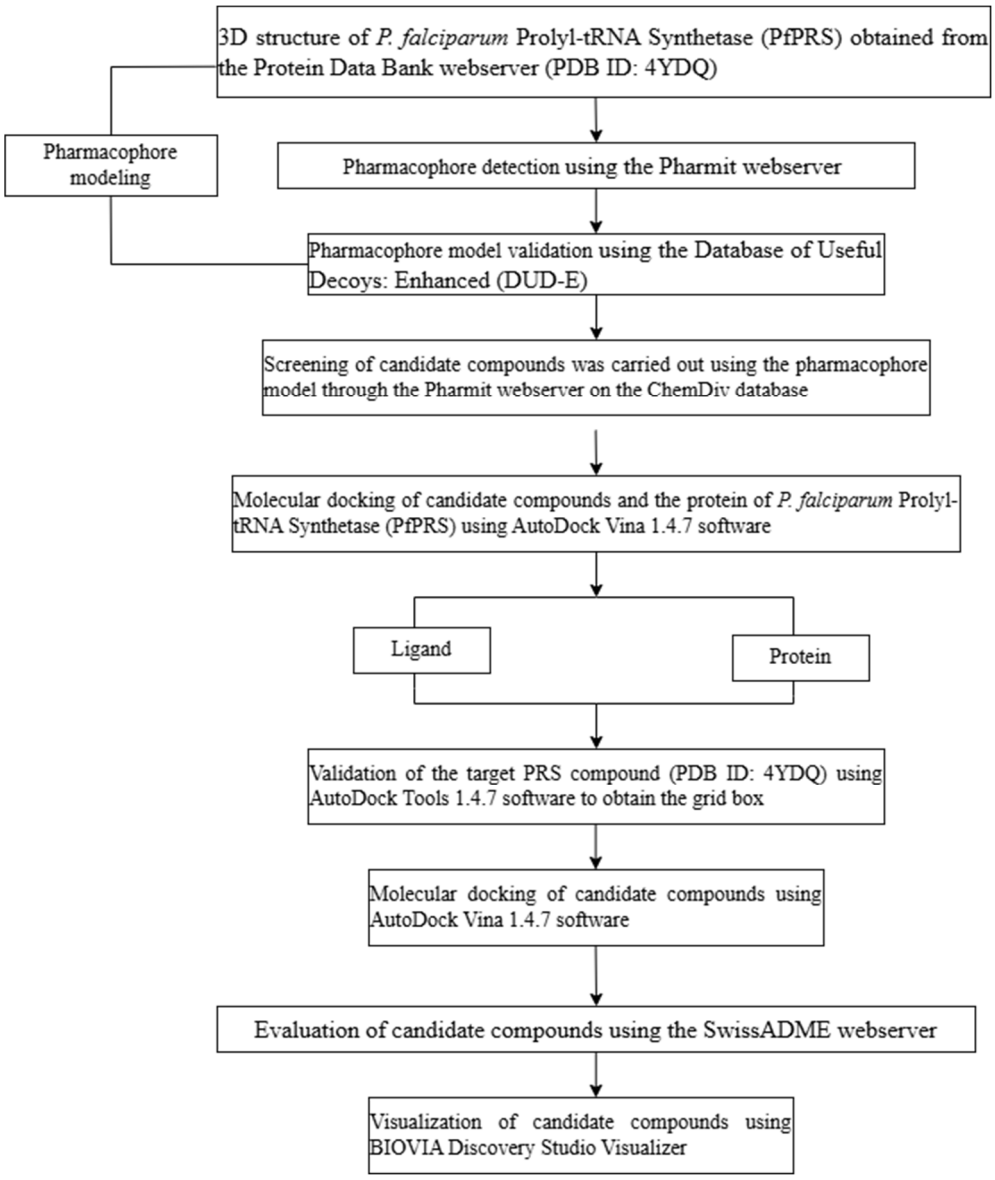

Figure 1. Workflow of virtual screening in this study

3. Results and Discussions

Pharmacophore modelling and validation

The study began with the creation of a pharmacophore model using the Pharmit web server based on the 3D structure of the *Plasmodium falciparum* Prolyl-tRNA synthetase (PfPRS; PDB ID: 4YDQ) protein. An analysis was first conducted on the structure of the reference compound halofuginone to identify key interactions. The position of halofuginone in the active site is maintained by hydrogen interactions involving the piperidine ring. The nitrogen atom in this structure interacts with residues Thr359 and Glu361 while its hydroxyl group forms a hydrogen bond with Thr478. This combination of interactions contributes significantly to the binding of halofuginone to the active site of the enzyme. Based on these interactions several pharmacophore model combinations with a maximum of five active features were compiled to represent the binding pattern during the virtual screening process (Jain et al., 2015).

The obtained pharmacophore model was validated using a dataset of active compounds and decoy compounds obtained from the DUD-E webserver consisting of 404 compounds, where 4 were active compounds and 400 were decoy compounds. The selection of the best model was based on its ability to recognize active compounds with minimal recognition of decoy compounds (Widyasari et al., 2022). The selection of the model was also based on the GH Score value which is one of the parameters of model effectiveness with a value >0.5 indicating a good model quality (Arba et al., 2020). Model 17 was selected as the best model because it was able to identify 3 active compounds without recognizing decoys and produced a GH score of 0.9375 indicating excellent identification capabilities, in particular for the febrifugin-halofuginone like scaffold which is used as training set data. This model consists of five pharmacophore features namely two aromatic features, two hydrogen donors, and one hydrogen acceptor as shown in **Figure 2.**

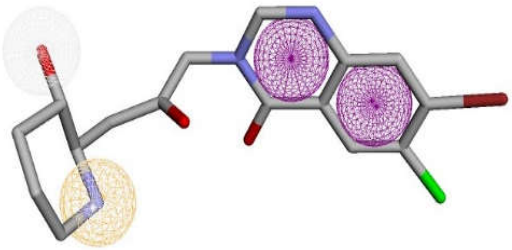

Figure 2. Visualization of selected pharmacophore combinations

Pharmacophore and drug-likeness-based screening of candidate compounds

Compound screening was performed using the Pharmit webserver with selected pharmacophore models against the ChemDiv database. Compound screening was performed based on Lipinski's Rule of Five parameters applied to evaluate the potential oral bioavailability of compounds. The parameters used include molecular weight ≤500 Da to support membrane permeability, logP value ≤5 to maintain water and lipid solubility balance, and the number of hydrogen bond acceptors (HBA ≤10) and donors (HBD ≤5) to ensure that the compounds are not too polar so that they can still penetrate biological membranes (Lipinski et al., 1997). Veber Rules parameters were also used to assess oral absorption efficiency by considering rotatable bonds ≤10, which reflect molecular flexibility and a topological polar surface area (TPSA) value ≤140 Å² to ensure that the polarity of the compound remains optimal and does not inhibit lipid membrane penetration (Veber et al., 2002). This screening yielded 312 compounds predicted to bind to the Plasmodium falciparum Prolyl tRNA Synthetase (PfPRS) protein.

Molecular docking

Before the structure-based screening process commenced, method validation was performed by redocking natural ligands to the active site of the protein using AutoDock Vina 1.5.7. This stage aimed to ensure that the docking method used was appropriate and to determine the position and size of the gridbox to cover the entire active site of the protein. The gridbox serves to limit the search space for ligand conformations during the docking process (Fatimah et al., 2020). The natural ligand used was halofuginone, which was first separated from the protein and then redocked to determine whether it could rebind at the same position or at a site close to its original position. The method is considered valid if the Root Mean Square Deviation (RMSD) value was < 2 Å. The RMSD value obtained was 1.121 Å. This validation was also reinforced by the visualization of the redocking results shown in **Figure 3**, which shows the overlapping positions between the ligands before and after docking, indicating that the docking

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method has a good level of accuracy because the orientation of the predicted ligands is almost identical to the position of the natural ligands (Agistia et al., 2013). The gridbox center was determined at coordinates X: 181.303; Y: 10.000; and Z: 31.087 to ensure that the docking process was focused on the active site of the protein.

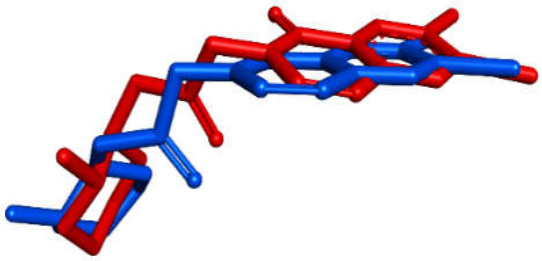

Figure 3. Ligand position after redocking

Method validation is used to assess the ability of the method to identify active and inactive compounds based on docking scores. A total of 404 compounds from previous validation set were used in this process. This process is carried out by docking molecules to reference compounds and decoy compounds using a batch docking approach in which all compounds are docked simultaneously to the same target protein. Method evaluation is performed using the Area Under the Curve (AUC) parameter from the ROC curve and the BED-ROC (Boltzmann-Enhanced Discrimination of Receiver Operating Characteristic) value. The ROC curve shows the relationship between the true positive rate (TPR) and the false positive rate (FPR). A model is said to have good identification capabilities if the ROC graph shows a high value and is close to the upper left corner (Yuniarta et al., 2023). BED-ROC (Boltzmann-Enhanced Discrimination of Receiver Operating Characteristic) is used as one of the validation parameters that focuses on the ability of the method to identify active compounds especially in the early stages of the screening process (Braga & Andrade, 2013), Based on the results shown in **Figure 4.** and **Table 1.** the method used produced an AUC value of 0.995 and a BED-ROC of 0.909 indicating that the method is valid and effective in distinguishing active compounds from inactive compounds. Similarly, this result reflects the method capability to better rank febrifugine-halofuginone scaffold-based compounds.

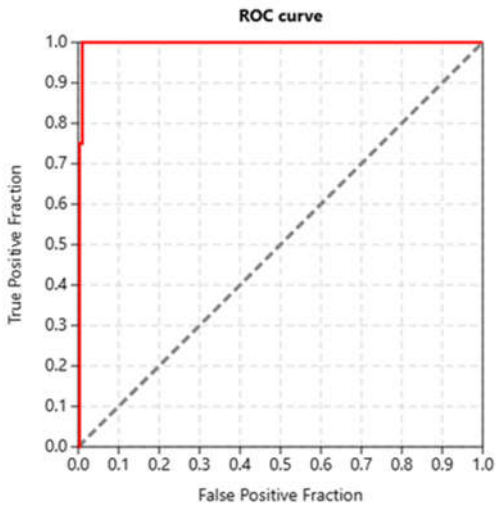

Figure 4. ROC curve

Table 1. AUC and BEDROC values

AUC ROC	BEDROC
0,995	0,909

From the docking results, the binding affinity values of the hit compounds toward the PfPRS protein were further analyzed. (Widyasari et al., 2022). Compounds with a binding affinity value lower than that of the reference compound halofuginone (−9.7 kcal/mol) were selected as potential candidates. Based on the docking analysis results 164 candidate compounds that met these criteria were obtained.

ADMET evaluation of candidate compounds

The evaluation was performed using the SwissADME webserver based on four main parameters. The first parameter was gastrointestinal absorption where only compounds with high absorption rates were selected due to their potential for good bioavailability (Lipinski et al., 1997). The second parameter involves predicting interactions with cytochrome P450 (CYP450) enzymes with the selection criterion being compounds that are not inhibitors to minimize the risk of drug interactions and toxicity (Durán-Iturbide et al., 2020). PAINS evaluation was used to eliminate compounds that could potentially produce false positives in biological tests. The final parameter was Brenk Rules which were used to detect the presence of toxicophores causing toxicity (Baell & Holloway, 2010). Based on these four criteria, out of 164 candidate compounds only 11 compounds met all evaluation parameters and were deemed suitable for the next stage of analysis.

Visualization of candidate compounds

The analysis of interactions between ligands and receptors was performed using BIOVIA Discovery Studio Visualizer to identify the types and characteristics of the bonds formed. Common interactions found in ligand-receptor complexes include hydrogen bonds, electrostatic interactions, van der Waals interactions, and hydrophobic interactions (Arwansyah & Hasrianti, 2014). The similarity of amino acid residues involved in the formation of hydrogen bonds between candidate compounds and reference compounds is used as an indicator of biological activity similarity (Naufa et al., 2021). The visualization results in **Figure 5.** show that the left side represent the natural ligands form hydrogen bonds with residues Glu361, Thr359, Arg390, Thr478, and His480. This interaction profile is used as a reference in evaluating the similarity of amino acid residues involved in candidate compound binding. Meanwhile the right side shows ChemDiv-1481-0030 compound shows the highest similarity to the reference compound at 80% through interactions with the same four residues namely Thr359, Arg390, Thr478, and His480. This degree of similarity indicates that ChemDiv-1481-0030 has a binding pattern similar to that of the reference ligand. The interactions formed at these residues are dominated by hydrogen bonds that are formed through hydroxyl, guanidino, and imidazole groups as hydrogen donors and acceptors with orientations influenced by the chirality of L-amino acids in the binding pocket (Donald Voet, 2011).

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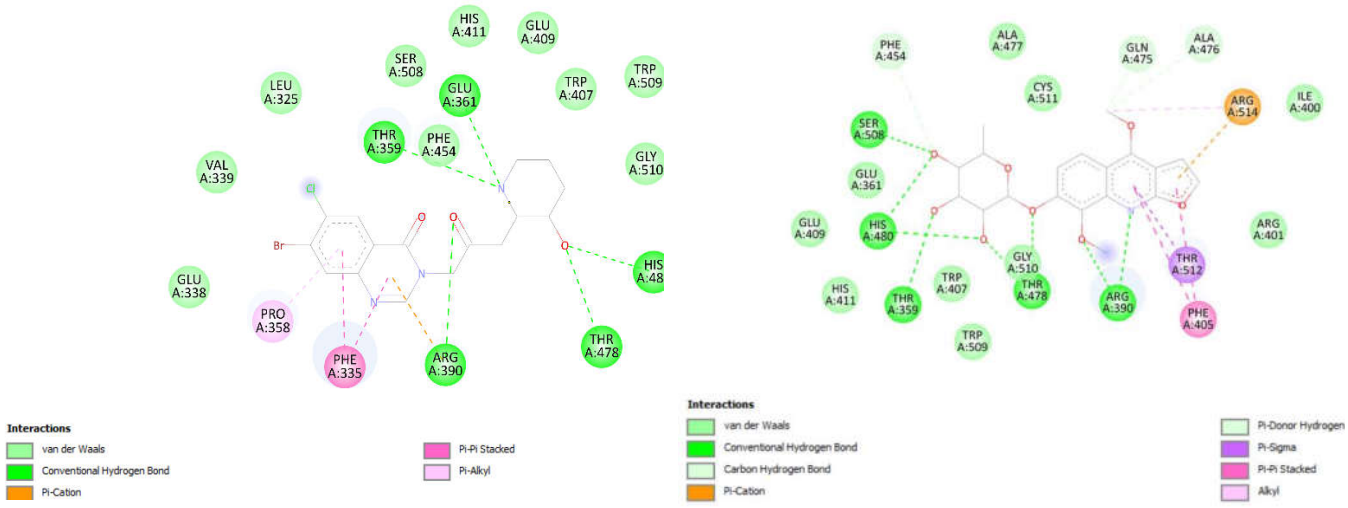

Figure 5. (left) Interaction of the PfPRS receptor with its natural ligand (halofuginone); (right) Interaction of the PfPRS receptor with the compound Chemdiv-1481-0030.

Advanced molecular docking was performed to confirm the suitability of the binding mode or pose obtained from docking with the reference compound. This second stage focused on the selected candidate compound, ChemDiv-1481-0030, using a smaller grid box size (40 × 40 × 40) to restrict the search space and concentrate the docking process on a more specific binding region (Fatimah et al., 2020). The interaction of ChemDiv-1481-0030 with the PfPRS protein was compared with the reference compound as shown in the left side of **Figure 6**. This compound formed hydrogen bonds with three key residues namely Arg390, Thr478, and His480. Compared to the first docking stage one residue (Thr359) is no longer involved but this difference is not significant because the main residues still interact and the ligand is close to the active site of PfPRS (Jain et al., 2015; Kitchen et al., 2004; Naufa et al., 2021). The binding pose evaluation was performed by comparing the binding positions of ChemDiv-1481-0030 and halofuginone as shown in the right side of **Figure 6.** ChemDiv-1481-0030 exhibits a position and orientation that overlaps with halofuginone indicating similar affinity and binding patterns at the active site of the target protein. The similarity in position and interaction suggests that ChemDiv-1481-0030 has the potential to be a competitive inhibitor of PfPRS supporting the insilico prediction as an antimalarial candidate (Jain et al., 2015; Meng et al., 2011). Visualization results show differences in orientation in the proline-like cyclic chain indicating structural flexibility that may be caused by the presence of a single connecting bond that allows rotation. Structural optimization through rigidification, such as the addition of a ring system or double bonds is necessary to improve the stability of the ligand orientation (Lawson et al., 2018; Lv et al., 2019).

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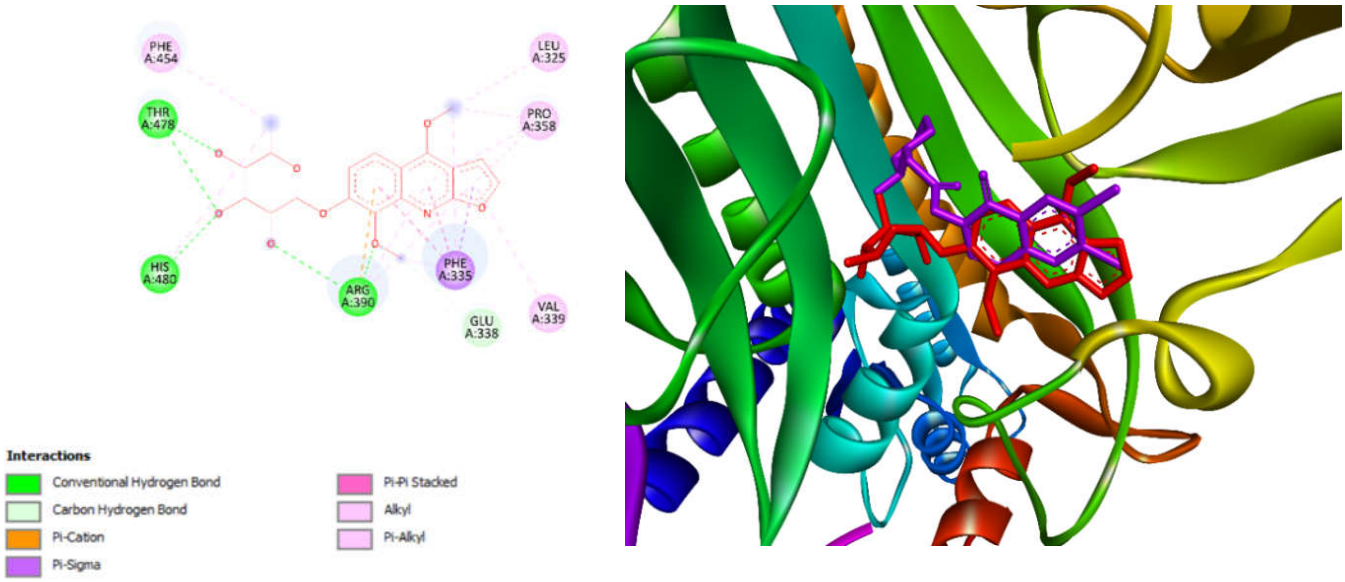

Figure 6. (left) Interaction of proteins with the compound Chemdiv-1481-0030 obtained from the second docking simulation using a smaller grid box size (40 × 40 × 40); (right) Protein complex with halofuginone and Chemdiv compound 1481-0030 within the active site under the same docking condition.

4. Conclusions

The structure-based virtual screening and molecular docking approaches in silico successfully identified PfPRS inhibitor candidates. The compound ChemDiv-1481-0030 was selected as the best candidate with the highest interaction similarity (80%) to halofuginone and met the pharmacokinetic and toxicity criteria. These findings demonstrate that the methods used are effective in identifying initial antimalarial candidates with potential for further development.

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6. Author contributions

TAY: conceptualization, supervision, writing, review, and editing; IIA: data curation and analysis, and writing; HS: data curation; TMF: supervision, writing, and review.

7. Conflict of interest

The authors declare no conflict of interest.

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