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Computational insights into the inhibitory potential of dihydroorotate dehydrogenase by natural compounds in *Artocarpus champeden* as antimalarial agents

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Abstract: *Plasmodium falciparum* dihydroorotate dehydrogenase (*Pf*DHODH) is a crucial target for the development of antimalarial drugs, as it plays a significant role in inhibiting the growth of parasites by disrupting the production of pyrimidines in the bloodstream. *Artocarpus champeden* is known to contain prenylated flavonoids with potential antimalarial activity. This study aims to explore the chemical interactions of active compounds found in *A. champeden* through an *in silico* approach. Nine compounds were docked into *Pf*DHODH (PDB ID: 6I55), and their stability was subsequently assessed using molecular dynamics simulations. Molecular docking results indicated that compounds **C1**, **C5** and **C6** emerged as the most promising candidates, exhibiting binding affinities of –37.80, –35.28 and –34.44 kJ/mol, respectively. His185 and Arg265 were found to be key binding residues, interacting with these compounds in a manner similar to DZB, the control ligand. A 50-ns molecular dynamics simulation further confirmed the stability of these compounds throughout the simulation. Moreover, the examination of hydrogen bond occupancy demonstrated that compound **C1** consistently engaged in hydrogen bonding interactions with His185 and Arg265 throughout the simulation.

Keywords: molecular docking; molecular dynamics; *Plasmodium falciparum*; malaria; natural product.

INTRODUCTION

Plasmodium falciparum (*Pf*) is a species of *Plasmodium* that significantly contributes to high malaria-related mortality.[1] Globally, the incidence of malaria remained relatively stable from 2020 to 2022, with a slight increase observed in

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2023, reaching from 5.86 to 60.4 cases per 1,000 population. The majority of these cases occur in Africa (89.7 %), with the highest numbers reported in Ethiopia (4.5 million cases), Madagascar (2.7 million), Pakistan (1.6 million), Nigeria (1.4 million) and the Republic of Congo (600,000 cases).[2] Concurrently, data from the World Health Organization (WHO) indicate that the Southeast Asian region accounts for approximately 4 million malaria cases, with India and Indonesia significantly contributing to malaria-related mortality and representing 88 % of total cases in the region. In Indonesia, national reports documented 73.5 thousand malaria cases, with approximately 20 deaths reported in 2025.[3]

The development and synthesis of 4-aminoquinoline analogs culminated in the identification of chloroquine as a first-line drug for malaria treatment.[4] Chloroquine had long been established as effective agent in malaria therapy. However, in the early 1960s, resistance to chloroquine was first documented in several malaria-endemic countries.[5] To address this issue, the WHO recommended the use of combination therapies with different mechanisms of action to suppress resistance rates. Artemisinin-based combination therapies (ACTs) demonstrated efficacy in mitigating and reducing malaria cases between 2000 and 2015.[6] Artemisinin and its derivatives – including artemether, artesunate and dihydro artemisinin (DHA) – are commonly combined with piperaquine, mefloquine or amodiaquine, as recommended by the WHO.[7] However, recent data indicate that resistance to ACTs has emerged in several regions of Southeast Asia, particularly in the Greater Mekong subregion.[8] The increasing resistance to existing treatments highlights the urgent need for the discovery and development of new antimalarial compounds.

Artocarpus champeden, known as Cempedak in Indonesia, has been scientifically validated to possess a diverse array of biological activities, including diuretic,[9] antifungal[10] and antidiabetic effects.[11] An *in vitro* study on the dichloromethane extract of its stem bark demonstrated significant antimalarial activity against the Pf 3D7 strain, with an IC_{50} value of 0.99 µg/mL.[12] The methanol extract of the stem bark exhibited the most potent antimalarial efficacy,[13] with IC_{50} values of 4.23 and 16.58 µg/mL against the 3D7 and G-2300 strains, respectively, after 48 h of incubation. Previous studies have explored the active compounds responsible for its antimalarial effects, identifying flavonoid derivatives as contributors to the inhibition of the *Pf* 3D7 strain, with IC_{50} values ranging from 0.001 to 75 µmol/L.[12,14] Heteroflavone C, a prenylated flavonoid, demonstrated potent activity (IC_{50} of 0.001 µmol/L) compared to artoindonesianin E. This non-prenylated flavonoid has an IC_{50} of 75 µmol/L. Despite several studies showing the antimalarial potential of *A. champeden*, the inhibitory mechanism of its active compounds remains inadequately understood. Therefore, comprehensive research is needed to elucidate the molecular mechanisms underlying its antimalarial activity.

The *de novo* biosynthesis of pyrimidine, a precursor for DNA and RNA synthesis, is critical for the survival of *Plasmodium*.[15] As a result, this pathway has emerged as a significant target in antimalarial drug development. Dihydroorotate dehydrogenase (DHODH) is an enzyme that catalyzes the oxidation of dihydroorotate (DHO) to orotate (ORO). Additionally, DHODH is located in the mitochondria, where it operates as part of the electron transport chain *via* cytochrome oxidase.[16] Atovaquone, a naphthoquinone derivative, has been scientifically proven to inhibit DHODH and is widely used as an antimalarial drug. However, its efficacy is constrained by issues of selectivity and specificity related to the lipophilic nature of the DHODH active site.[17] To improve its effectiveness, atovaquone is combined with proguanil, resulting in a synergistic antimalarial therapy.[18]

The presence of prenylated flavonoids in *A. champeden* suggests their potential as a DHODH inhibitor. The prenyl substituent on flavonoid compounds is thought to enhance their hydrophobic properties, thereby increasing interactions with the lipophilic binding site of DHODH. In this study, the potential of prenylated flavonoids in *A. champeden* was evaluated using an *in silico* approach. Molecular docking analysis was performed to assess the binding energy and chemical interactions between active compounds and the DHODH binding site. Furthermore, molecular dynamics simulations were conducted to evaluate the stability of the formed complexes and to identify the most suitable compounds based on prior analyses.

EXPERIMENTAL

Instrumentation

The computational analysis was conducted on a personal computer (PC) operating on Windows 10, equipped with an Intel Core i9-13900H processor. The software used in this study included ChemDraw Professional 16, Chem3D 16, AutoDock Vina with AutoDock tools, Open Babel, Discovery Studio Client 2021 (version 21.1.0.20298) and GROMACS.

Ligand preparation

The prenylated flavonoid compounds found in *Artocarpus champeden* was obtained from a previous study.[12] The 2D structure was drawn using ChemDraw Professional 16 and subsequently converted into a 3D structure using Chem3D 16. Geometry optimization was performed using the MM2 force field, with a minimum RMS gradient of 0.01. Following this optimization, the structure was saved in PDB format. For the preparation of the 3D structure, hydrogen atoms and Gasteiger charges were added using AutoDock Tools before saving it in PDBQT format.

Protein receptor preparation

The structure of *Plasmodium falciparum* dihydroorotate dehydrogenase (*Pf*DHODH) was used as the receptor and retrieved from the RCSB Protein Data Bank (PDB ID: 6I55). Water molecules and the native ligand were removed using Biovia Discovery Studio Client 2021, after which the structure was saved in PDB format. Subsequently, polar hydrogen atoms and Kollman charges were added to the receptor using AutoDock Tools (ADT). The prepared receptor was then saved in PDBQT format.

Molecular docking

Molecular docking is a computational method used to assess the binding energy and chemical interactions between a ligand and a protein receptor. Validating the docking protocol is a crucial step to ensure the reliability of the analysis of the tested compounds. This validation process was carried out by redocking the native ligand with the receptor, followed by superimposition to compare their conformations. The docking protocol is considered reliable if the *RMSD* value is below 2 Å.[19]

Molecular docking was performed at the binding site using a grid center located at (*x*, *y*, *z*) coordinates of 16.083, 22.654 and 35.024, respectively, with a box size of 18 Å in each dimension (*x*, *y*, *z*). After validating the docking protocol, the compounds being tested are docked onto the receptor using the predetermined grid center and box size. The lowest binding energy is indicative of a stable ligand-receptor complex. Additionally, the chemical interactions of the tested compounds are compared to those of the native ligand at the receptor's binding site.

Molecular dynamics

The molecular dynamics simulation was conducted on the three best compounds to evaluate their stability within the ligand-receptor complex. The simulation was performed using GROMACS 2023 software.[20] The protein topology was prepared using the General AMBER99SB force field,[21] while the acpype module with GAFF2 was used to generate the ligand topology.[22] The system was solvated in water molecules using the TIP3P model within a dodecahedron box.[23] To neutralize the system, sodium and chloride ions were added.

Energy minimization was carried out using the steepest descent method, followed by equilibration under NPT conditions for 1000 ps. Subsequently, the equilibrated system was further stabilized under NVT conditions at 300 K for the same duration. A 50-ns production simulation was then performed using the mdrun module. The simulation trajectory was analyzed and visualized using the mgrace package to evaluate *RMSD*, *RMSF*, radius of gyration (*Rg*), solvent-accessible surface area (*SASA*) and hydrogen bonding throughout the simulation.

RESULTS AND DISCUSSION

Molecular docking

Validating the docking protocol is a crucial step to ensure that the method yields valid and reliable data. The validation process involved redocking the DZB compound, which is the native ligand, into the receptor of *Pf*DHODH. The results of validation showed a low *RMSD* value of 0.46 Å, indicating the reliability of the docking procedure. The superimposition of the redocked ligand with the native ligand is presented in Fig. 1.

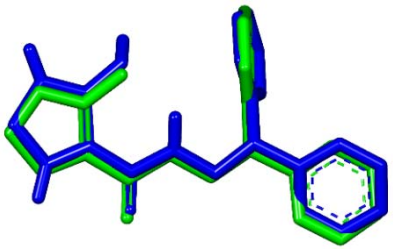
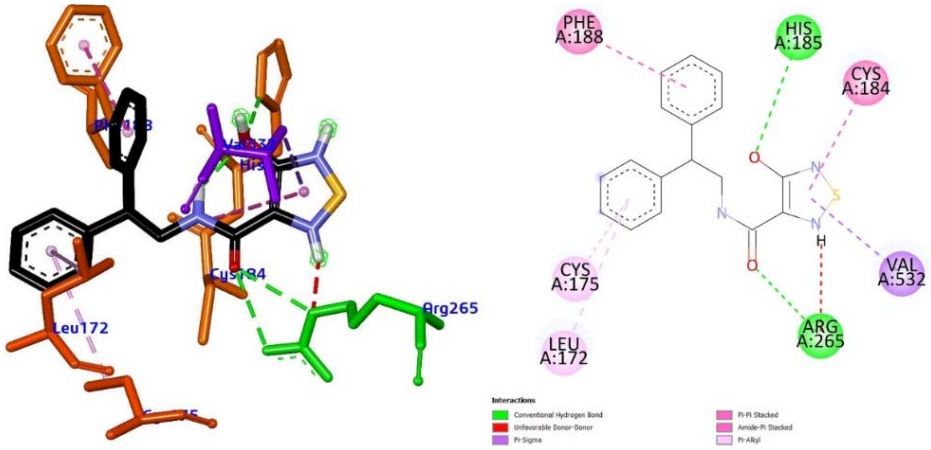


Fig. 1. Superimpose the re-docking ligand (green) onto the native ligand (blue).[24]

The DZB compound, acting as a native ligand, interacted with amino acids at the binding site of *Pf*DHODH (Fig. 2). The hydrophilic interaction of DZB within the binding site was facilitated by the hydroxyl group on the thiadiazole ring, which formed a hydrogen bond with His185. Additionally, the carbonyl group interacted with Arg265. Both of these amino acids are essential as catalytic residues in the oxidation reaction, converting flavin mononucleotide (FMN) to $FMNH_2$.[16] Moreover, the hydrophobic region of *Pf*DHODH, which includes Leu172, Cys175 and Phe188, interacted with the dibenzyl moiety of DZB through π–π stacking and π–alkyl interactions. The hydrophobic residues Cys184 and Val532 in *Pf*DHODH were also involved in interactions with the thiadiazole ring of DZB.



a) b)

Fig. 2. Chemical interaction of DZB in the binding pocket of *Pf*DHODH (PDB ID: 6i55): a) 3D visualization and b) 2D visualization.

Nine prenylated flavonoid compounds from *Artocarpus champeden* were predicted to have antimalarial activity, particularly as inhibitors of *Pf*DHODH (Fig. 3). The molecular docking results for each compound are presented in Table I. The findings indicate that prenylated flavonoids effectively interact with *Pf*DHODH. Four compounds – **C1**, **C2**, **C5** and **C8** – demonstrated high binding affinities of –37.80, –35.28, –35.28 and –37.38 kJ/mol, respectively. These values indicate stronger interaction compared to that of DZB (–34.44 kJ/mol), suggesting enhanced binding strength. Among these four compounds, hydrophilic interactions with the catalytic residues His185 and Arg265 were observed in **C1**, **C5** and **C8**. These interactions are believed to contribute to their greater binding stability relative to DZB.

Compound **C2** has a binding energy similar to that of compound **C5**; however, it does not establish hydrophilic interactions with the catalytic residues His185 and

Arg265. The stability of the **C2**–*Pf*DHODH complex relies solely on hydrophobic interactions, particularly through π–sigma interactions with Leu172. Therefore, compounds **C1**, **C5** and **C8** were identified as potential inhibitors in this study. Chemical interactions are crucial in determining a compound's efficacy as an inhibitor. The chemical interactions of these three compounds are illustrated in Fig. 4. Compound **C1** exhibited a hydrogen bond interaction with Arg265 *via* the hydroxyl group substituted at the meta position of ring B of the flavonoid, with a binding distance of 2.81 Å, which is shorter than the interaction observed in the DZB compound. Additionally, hydrophobic interactions with residues Leu172, Cys175, Cys184 and Val532 were identified. Furthermore, the presence of a prenyl substituent on ring C of the flavonoid enhanced the π–sigma interactions with Phe188, contributing to increased complex stability.

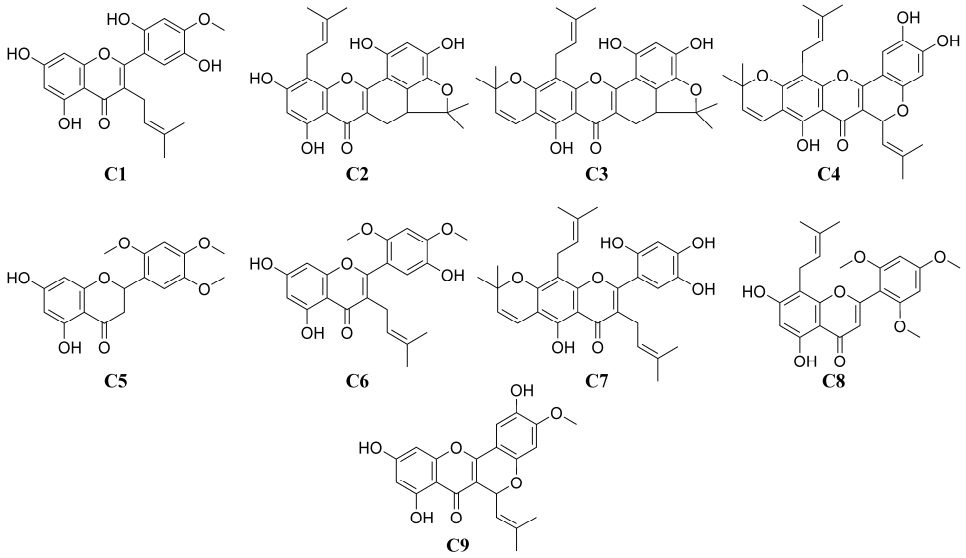


Fig. 3. Prenylated flavonoids in *Artocarpus champeden*.

Compound **C5** forms a hydrogen bond with His185 through a hydroxyl group attached to ring A of the flavonoid. Although the bond distance of 2.80 Å is slightly longer than the interaction observed in the DZB compound, this bond still contributes to the stability of the **C5** complex. Additionally, this stability is further reinforced by hydrophobic interactions between Leu172 and Cys175 with the methoxy group on ring B of the flavonoid. In contrast to compounds **C1** and **C8**, compound **C5** does not interact with Arg265, which explains its slightly lower binding energy compared to these two compounds. Furthermore, an analysis of the influence of the prenyl substituent revealed that compound **C5**, which lacks a prenyl group, was unable to form hydrophobic interactions with Phe188. This

absence of interaction contributes to the differences in complex stability when compared to compounds **C1** and **C8**.

TABLE I. Binding energy and interactions of prenylated flavonoid compounds

ID Compound (ID PubChem)	Binding energy kJ/mol	Interaction		
		Hydrogen bond	Distance, Å	Hydrophobic
DZB	–34.44	His185	2.76	Leu172, Cys175, Cys184,
		Arg265	4.39	Phe188, Val532
C1	–37.80	Tyr168	2.44	Leu172, Cys175, Cys184,
(163106267)		His185	3.46	Phe188, Phe227, Leu531,
		Arg265	2.81	Val532, Met536
C2	–35.28	Tyr168	2.92	Leu172, Leu187, Leu191,
(145950438)		Cys175	3.31	Leu197, Pro198, Met536
		Leu531	2.44	
		Gly535	2.55	
C3	–27.72	Val532	2.39	Leu172, Cys175 (pi-sulfur),
(14557102)				Ile179, Ile183, Cys184,
				Phe188, Phe227, Met536
				(pi-sulfur)
C4	–27.72	Cys175	4.00	Leu172, Ile179, Ile183,
(5316250)				Leu187, Cys184 (pi-sulfur),
				Met536
C5	–35.28	His185	2.80	Tyr168, Phe171, Leu172,
(nf)				Cys175, Cys184, Leu187,
				Val532, Met536
C6	–34.44	Tyr168	2.73	Leu172, Cys175, Cys184,
(5320437)				His185, Phe188, Leu531,
				Val532, Met536
C7	–33.18			Phe171, Leu172, Cys175,
(14557105)				Ile179, Cys184 (pi-sulfur),
				His185 (van der Waals),
				Leu187
C8	–37.38	Tyr168	3.78	Leu172, Cys175, Cys184,
(not found)		His185	2.59	Leu187, Phe188, Leu191,
		Arg265	2.72	Phe227, Leu531, Val532,
				Met536
C9	–34.02	Cys175	3.31	Tyr168, Phe171, Leu172,
(101415464)				Cys184 (pi-sulfur), Leu187,
				Leu191

Compound **C8** demonstrated an interaction pattern distinct from the previous compounds. While its binding energy is slightly lower than that of compound **C2**, its interaction pattern closely mimics that of the native ligand. The two hydroxyl groups on ring A of the flavonoid are crucial for forming hydrogen bonds with His185 and Arg265, with bond distances of 2.59 and 2.72 Å, respectively. These

distances are shorter than those observed in both DZB and compound **C2**, suggesting a stronger interaction with the active site of *Pf*DHODH.

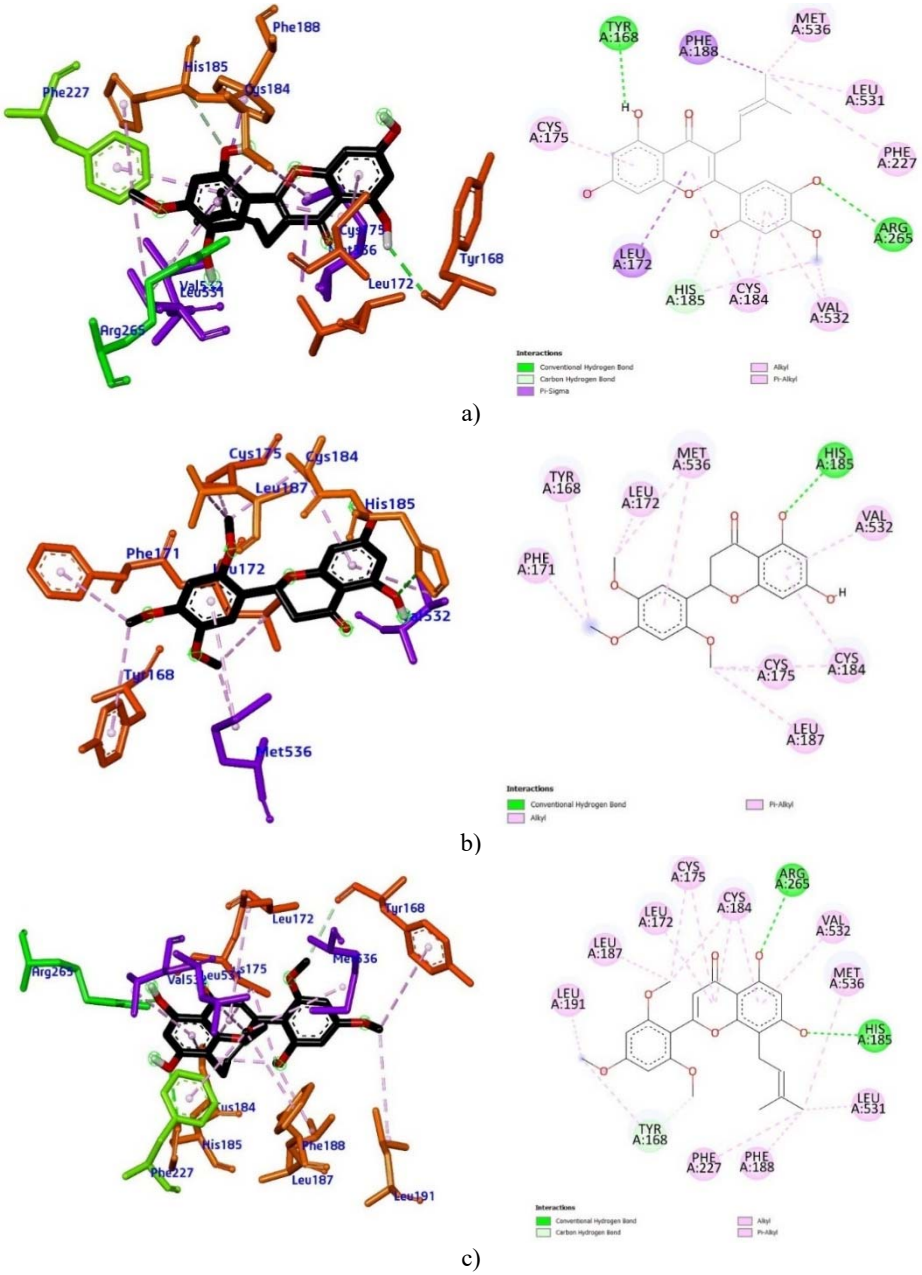


Fig. 4. The 3D and 2D visualization of chemical interaction for the three best compounds: a) **C1**, b) **C5** and c) **C8**.

In addition to hydrophilic interactions, hydrophobic interactions also contribute to stabilizing the **C8**–*Pf*DHODH complex. The amino acid residues Leu172, Cys184 and Val532 participated in π–alkyl interactions, while Cys175 was further stabilized by alkyl interactions from the methoxy group attached on ring B of the flavonoid. Notably, the presence of a prenyl substituent enhanced additional hydrophobic interactions with Phe188 through alkyl interactions.

The molecular docking analysis of the three selected compounds emphasized the critical role of the prenyl substituent in enhancing hydrophobic interactions with the binding site of *Pf*DHODH. The absence of this substituent was associated with a decline in the binding affinity of the compound to the target protein. Although lower binding energy indicates greater stability of the complex, it is important to note that molecular docking is performed using a rigid protein structure, which necessitates further validation. Therefore, the stability of these complexes should be further analyzed through molecular dynamics simulation.

Molecular dynamics

The three most effective compounds identified through molecular docking were further evaluated for their complex stability using molecular dynamics simulation over a period of 50 ns. To assess the stability of the complexes, the root mean square deviation (*RMSD*) of the protein backbone throughout the simulation was analyzed, as shown in Fig. 5a. The mean *RMSD* values for the protein backbone in complexes **C1**, **C5** and **C8** were 0.132, 0.145 and 0.139 nm, respectively. These low *RMSD* values indicate that the conformational changes in the protein during the simulation, resulting from interactions with the ligand, were minimal.[24] Among the tested compounds, complex **C1** exhibited the highest stability, which is associated with its effective binding at the active site of *Pf*DHODH.

The stability of the tested compounds was also assessed by analyzing the *RMSD* of the ligand relative to the protein, with the results presented in Fig. 5b. All three compounds exhibited an initial increase in *RMSD* at 8 ns, reflecting the ligand adaptation process within the complex at the beginning of the simulation. Following this phase, the *RMSD* patterns for compounds **C1** and **C8** remained stable up to 25 ns, while compound **C5** maintained stability only during the first 10 ns. Throughout the remainder of the simulation, the *RMSD* values of all three compounds fluctuated but generally remained within a normal range, likely due to receptor flexibility. The mean *RMSD* values for the ligand within protein were 0.19, 0.27 and 0.28 nm for compounds **C1**, **C5** and **C8**, respectively. The lower *RMSD* value of compound **C1** indicates that it remained more stable within the binding pocket throughout the simulation.

The flexibility of amino acid residues due to interactions with the ligand was analyzed using the *RMSF* plot (Fig. 5c). Although the *RMSF* plot exhibited a fluc-

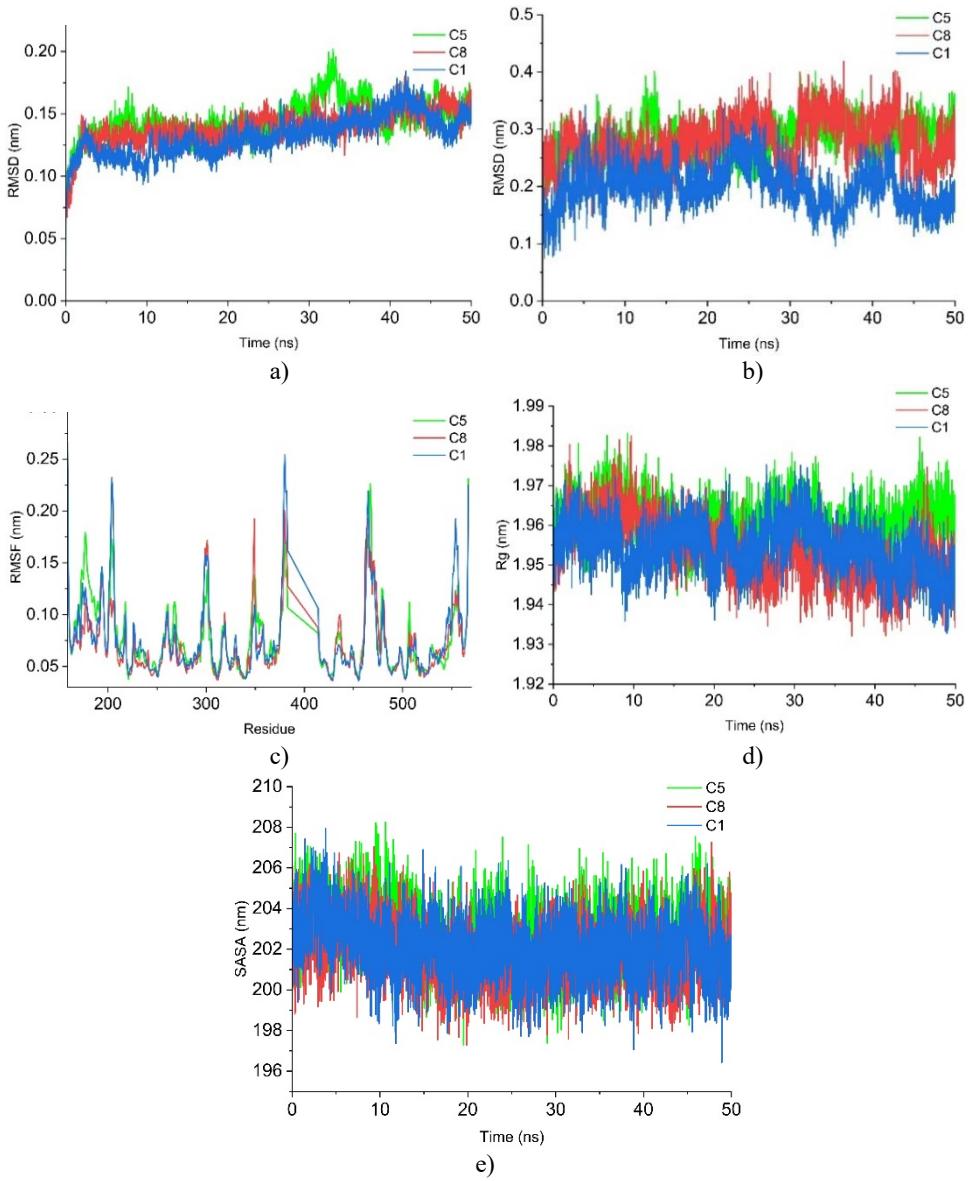


Fig. 5. Molecular dynamic results represented by: a) R*MSD* of the protein backbone, b) *RMSD* of the ligand fit to protein, c) *RMSF*, d) radius of gyration and e) *SASA* plots.

tuating pattern, key residues such as His185, Phe188, Arg265 and Val532 had low *RMSF* values. This indicates that their rigidity plays a significant role in maintaining stable interactions with the tested compounds.[24,25] To further evaluate the stability of the complex, we analyzed the compactness of the receptor, as shown

in Fig. 5d. Complex **C1** exhibited a stable trend up to 30 ns, followed by a decrease in the radius of gyration (*Rg*) value until the end of the simulation. This decline in *Rg* suggests a protein folding phenomenon,[25] which aids in the retention of the stability of the complex. The mean *Rg* values for complexes **C1** and **C8** were 1.95 nm, while complex **C5** exhibited a slightly higher *Rg* value of 1.96 nm.

The interaction between the receptor and surrounding water molecules plays a crucial role in stabilizing the complex. This analysis is presented in the *SASA* plot (Fig. 5e). Generally, the *SASA* values for the three complexes show an initial increase during the first 5 ns, which indicates the initial interaction between the solvent and the receptor surface. Afterward, the *SASA* values decrease up to 15 ns, at which point they stabilize for the remainder of the simulation. These stable *SASA* values suggest that the tested compounds have improved access to the receptor's binding site.[26] Additionally, a high number of hydrogen bond interactions between the tested compounds and the binding site during the simulation contributes to maintaining the stability of the complex.[27] However, the mean number of hydrogen bonds for compound **C5** is only one throughout the simulation (Fig. 6). Analysis of hydrogen bond occupancy revealed that compound **C5** formed hydrogen bonds with Arg265 (0.22 %) and Cys175 (0.32 %), Table II, which are the lowest percentages among the tested compounds.

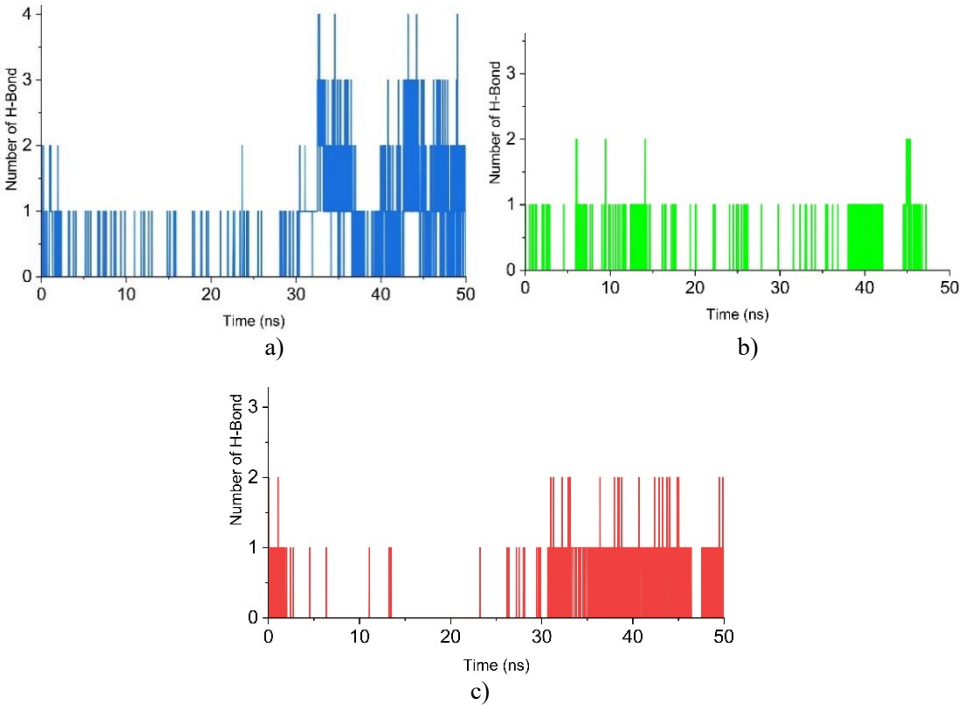


Fig. 6. Number of hydrogen bonds detected in the receptor with: a) **C1**, b) **C5** and c) **C8**.

TABLE II. Hydrogen bond occupancy of prenylated flavonoid compounds

Compound	Donor	Acceptor	Occupancy, %
C1	C1 568-Side	CYS184-Main	0.12
	C1 568-Side	VAL532-Main	0.14
	C1 568-Side	CYS175-Main	1.14
	C1 568-Side	HIS185-Side	5.14
	C1 568-Side	GLY181-Main	0.06
	ARG265-Side	C1 568-Side	4.28
	C1 568-Side	LEU187-Main	0.44
C5	ARG265-Side	C5 568-Side	0.22
	C5 568-Side	GLY181-Main	0.16
	C5 568-Side	CYS175-Main	0.32
C8	C8 568-Side	HIS185-Side	0.12
	C8 568-Side	GLY181-Main	0.30
	ARG265-Side	C8 568-Side	3.12

Compound **C8** temporarily lost its hydrogen bond from 5 ns to 30 ns during the simulation, but it re-established a hydrogen bond, averaging one bond during the final 20 ns. Hydrogen bond occupancy analysis revealed that compound **C8** acted as a hydrogen donor to Arg265 with an occupancy of 3.12 % and as a hydrogen acceptor to Cys185 with an occupancy of 0.12 %. In contrast, compound **C1** consistently maintained hydrogen bond interactions throughout the simulation. Notably, it exhibited an increase in the mean number of hydrogen bonds, rising to three from 35 ns until the end of the simulation. Compound **C1** demonstrated strong interactions both within the binding site and the hydrophobic region through hydrogen bonding. The interactions with Arg265 and His185 had hydrogen bond occupancies of 4.28 and 5.14 %, respectively, which were the highest values among the tested compounds. These findings indicate that compound **C1** exhibits optimal interaction stability with the *Pf*DHODH receptor compared to compounds **C5** and **C8**.

CONCLUSION

The evaluation of nine active compounds from *Artocarpus champeden* as potential *Pf*DHODH inhibitors identified compound **C1** as the most promising candidate. Compound **C1** demonstrated the highest binding energy of –37.8 kJ/mol, indicating a stable interaction with the receptor's binding site. This finding is consistent with molecular dynamics simulations over 50 ns, where the **C1** complex remained stable based on *RMSD* ligand fit protein analysis and sustained hydrogen bond interactions throughout the simulation. Therefore, compound **C1** is recommended for isolation and further validation of its antimalarial activity through *in vitro* assays in a wet laboratory.

ИЗВОД

КОМПЈУТЕРСКО ПРОУЧАВАЊЕ ИНХИБИТОРНОГ ПОТЕНЦИЈАЛА ДИХИДРООРОТАТ-ДЕХИДРОГЕНАЗЕ ПРИРОДНИМ ЈЕДИЊЕЊИМА ИЗ *Artocarpus champeden* У СВОЈСТВУ АНТИМАЛАРИЈСКИХ АГЕНАСА

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Диходрооротат-дехидрогеназа из *Plasmodium falciparum* (*Pf*DHODH) је кључна мета у развоју антималаријских лекова, јер има важну улогу у инхибирању раста паразита, ометајући стварање пиримидина у циркулацији. *Artocarpus champeden* садржи прениловане флавоноиде са потенцијалном антималаријском активношћу. У овој студији су испитане хемијске интеракције активних једињења *A. champeden* применом *in silico* методе. Интеракција девет једињења са *Pf*DHODH (PDB ID: 6I55) је проучавана и њихова стабилност испитана применом молекулских динамичких симулација. Молекулско моделовање је указало да су једињења **C1**, **C5** и C6 обећавајући кандидати, са афинитетом везивања од –37,80, –35,28, односно –34,44 kJ/mol. His185 и Arg265 су кључни везујући остаци који интерагују са испитаним једињењима на сличан начин као контролни лиганд DZB. 50-ns молекулска динамичка симулација је потврдила стабилност ових једињења. Такође, испитивање интеракције водоника кроз симулације је показало да су у једињењу **C1** присутне водоничне везе са His185 и Arg265.

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