

4-Hydroxyphenyl-3-nitrobenzoate against Plasmeptsin II Malaria Parasite protease: Swiss Similarity, Molecular docking, ADMET, DFT and Dynamic Simulation

Elizabeth Funke OLARINOYE

`elizabeth_olarinoye@unilesa.edu.ng`

University Of Ilesa

Dayo Felix LATONA

Osun State University

Oluwaseun Adenike ADEFILA

University Of Ilesa

Taiwo Abiodun ADEKUNLE

Osun State University

Banjo SEMIRE

Ladoke Akintola University of Technology

Research Article

Keywords: Swiss Similarity, Molecular docking, Dynamic Simulation, ADMET, Antimalarial

Posted Date: May 21st, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9485908/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations:

No competing interests reported.

Table 8 is not available with this version

4-Hydroxyphenyl-3-nitrobenzoate against Plasmepsin II Malaria Parasite protease: Swiss Similarity, Molecular docking, ADMET, DFT and Dynamic Simulation.

Elizabeth Funke OLARINOYE ^{1*}, Dayo Felix LATONA ², Oluwaseun Adenike ADEFILA ³, Taiwo Abiodun ADEKUNLE ² and Banjo SEMIRE ⁴

¹Department of Industrial Chemistry, University of Ilesha, Ilesha, Osun State

²Department of Pure and Applied Chemistry, Osun State University, Osogbo, Osun State

³Department of Biochemistry, University of Ilesha, Ilesha, Osun State

⁴Computational Chemistry Research Group, Department of Pure and Applied Chemistry, Ladoke Akintola University of Technology, Ogbomosho, Nigeria

Corresponding elizabeth_olarinoye@unilesa.edu.ng, bsemire@lautech.edu.ng

Abstract

Malaria remains a significant global health burden, with more than 249 million cases reported annually worldwide. The disease disproportionately affects sub-Saharan Africa, where pregnant women and young children constitute the most vulnerable populations. Although several effective antimalarial therapies exist, prolonged treatment regimens often impede patient adherence and reduce therapeutic success. Moreover, the rapid emergence and spread of drug-resistant Plasmodium strains continue to undermine current control efforts, highlighting the urgent need for novel, more potent, and better-tolerated antimalarial agents. The current study used SWISS similarities investigations on 4-hydroxyl phenyl-3-nitro benzoate with Plasmepsin II (PDB ID: 1LEE) and the two standards chloroquine and lumefantrine were used, nine derivatives similar to 4-hydroxyl phenyl 3-nitro benzoate were obtained, molecular docking, density functional theory (DFT), and ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties were done, using Pyrex and

Discovery studio soft wares. Physiochemical and Pharmacokinetic analyses were carried out using SwissADMET and PKCSM online servers, five derivatives had better binding affinities, with good ADMET properties B3- Benorilate (-6.8 kcal/mol), B4- Salsalate (-6.9 kcal/mol), B6- 2-Oxo-2H-naphtho[1,8-bc]furan-6-yl 4-nitrobenzoate (-8.2 kcal/mol), B7- Phenylsalicylate (-6.6 kcal/mol), and B9- Phenyl aminosaliclylate (-6.6 kcal/mol) compare to Chloroquine (-6.1 kcal/mol) and Lumefantrine (-7.7 kcal/mol) used as standard drugs. From the ADMET and molecular dynamic simulation, compound B6 is a promising and potent hit compound for treating malaria disease compared to lumefantrine.

Keywords: Swiss Similarity, Molecular docking, Dynamic Simulation, ADMET, Antimalarial

1.0 Introduction

Malaria is a major global health threat caused by protozoan parasites of the *Plasmodium* genus, with an estimated 247 million cases reported across 84 malaria-endemic countries. Transmission occurs through the bite of an infected female *Anopheles* mosquito, which injects *Plasmodium* sporozoites into the human bloodstream (WHO 2020). These sporozoites rapidly migrate to the liver, where they invade hepatocytes and initiate an asymptomatic asexual replication phase. After maturation, they are released as merozoites into the bloodstream, where they invade red blood cells (RBCs), multiply, and rupture the host cells. The repeated invasion-and-lysis cycle leads to the clinical manifestations of malaria (Zekar and Sharman 2021).

During infection, *Plasmodium* progresses through several developmental stages, with the blood stage responsible for symptomatic disease in humans. Five *Plasmodium* species—*P. falciparum*, *P. vivax*, *P. malariae*, *P. knowlesi*, and *P. ovale*—cause malaria in humans, among which *P. falciparum* is the most prevalent and the most lethal (Sato 2021). Malaria symptoms are often non-specific and may include fever, chills, headache, nausea, vomiting, diarrhea, fatigue, and muscle aches. If untreated, the disease can progress to severe complications such as anemia, jaundice, organ failure, cerebral malaria, coma, and death. Although several antimalarial drugs, including Artemisinin-based Combination Therapies (ACTs) such as Artemether-lumefantrine (Coartem), Artesunate, Mefloquine,

Proguanil, and Atovaquone, have been widely used, malaria persists as a major public health challenge (Long and Hoffman 2002).

Plasmeprin II (Plm II) is an aspartic protease that plays a crucial role in the malaria parasite's lifecycle. It is primarily involved in the degradation of host hemoglobin within the parasite's acidic food vacuole, providing essential amino acids required for *Plasmodium* growth and survival. Because hemoglobin digestion is vital to parasite metabolism, Plm II is considered an important molecular target for the development of new antimalarial drugs. Beyond its function in hemoglobin catabolism, Plm II also contributes to the breakdown of the host red blood cell cytoskeleton, a process necessary for parasite egress and subsequent invasion of new erythrocytes (See et al. 2017). During the merozoite stage, Plm II localizes to the parasite periphery, where it supports cytoskeletal remodeling and facilitates efficient merozoite release. Given its central role in nutrient acquisition and parasite propagation, Plm II has been implicated in mechanisms associated with parasite survival and emerging resistance to existing antimalarial therapies. As resistance to current drugs continues to rise, identifying novel targets such as Plm II and designing potent inhibitors against them has become increasingly essential for advancing next-generation antimalarial strategies (Saini et al. 2021). Phytochemicals are naturally occurring bioactive compounds found in plants that contribute to their defense mechanisms and offer numerous health-promoting benefits in humans. Extensive research has linked phytochemicals to a reduced risk of various chronic diseases, including cardiovascular disorders, cancer, and neurodegenerative conditions, highlighting their therapeutic and preventive potential (Melini and Ruzzi 2025).

Swiss Similarity is an online ligand-based virtual screening platform designed to identify compounds with structural similarity and predicted bioactivity relative to a query molecule. It plays an important role in drug discovery by enabling the identification of new therapeutic candidates, facilitating scaffold hopping, and supporting structure–activity relationship (SAR) studies. Using a wide range of 2D and 3D molecular fingerprints, Swiss Similarity screens diverse chemical libraries containing commercially available molecules, bioactive compounds, and approved drugs. This allows

rapid and efficient exploration of small to very large molecular collections (Bragina et al. 2021). In the present study, molecular docking, DFT calculations, ADMET profiling, and molecular dynamics simulations were employed on Swiss Similarity of 4-hydroxyphenyl 3-nitrobenzoate to evaluate structural analog compounds. The goal was to identify novel drug-like candidates with potential inhibitory activity against plasmeprin II (PDB ID: 1LEE), a hemoglobin-degrading enzyme from *Plasmodium falciparum* for the development of new antimalarial therapeutics (Gheidari and Karimelahi 2024).

2.0 Materials and Methods

2.1 Swiss Similarity and ADMET Studies

Structure-similar compounds to 4-hydroxyphenyl-3-nitrobenzoate were identified using the Swiss Similarity platform (<http://www.swiss similarity.ch>). Approximately 100 bioactive compounds previously collected from *Morinda lucida* in our earlier study were screened, among which 4-hydroxyphenyl-3-nitrobenzoate demonstrated the best binding affinity (−8.3 kcal/mol). Based on this lead compound, nine structural derivatives were identified: B1, (5-methanoyl-2-nitro-phenyl) 2-(3-methoxyphenyl)ethanoate, B2, [(1S)-2-[(2,3-dimethoxyphenyl)methylamino]-1-(4-nitrophenyl)-2-oxidanylidene-ethyl] prop-2-enoate, B3 Benorilate, B4 Salsalate, B5 3-methylbut-2-en-1-yl (2E)-3-(3,4-dihydroxyphenyl)prop-2-enoate, B6, 2-oxo-2H-naphtho[1,8-bc]furan-6-yl 4-nitrobenzoate, B7 Phenyl salicylate, B8 1,4-dihydroxy-3-methylnaphthalen-2-yl) 4-aminobenzoate, and B9 Phenyl aminosalicylate.

Following procedures from our previous study, conformational searches were performed using Molecular Mechanics Force Field (MMFF 94) as implemented in Spartan 14 quantum chemical software package (Ekincioglu et al. 2021) to obtain the most stable conformer for each compound. Equilibrium geometry optimization was performed on the most stable conformers using Density Functional Theory (DFT) at the B3LYP/6-31+G(d,p) level (Athar et al. 2018), which were used for molecular docking. The molecular docking simulation was carried out using PyRx 0.8 operating on Auto Dock grid and Auto Dock Vina (Zulfat et al. 2024). The grid parameters used were: size (Å) -X = 66.2301, Y = 104.9300, Z = 9.2953 and coordinates (Å) -X = 84.4322, Y = 58.3046, Z = 57.4419.

The 3D structure of the protein target Plasmepsin II (PDB ID: 1LEE) was retrieved from the RCSB PDB database (<https://www.rcsb.org/>). Prior to docking, native ligand and non-essential molecules were removed using Discovery Studio. Plasmepsin II is an aspartic protease of *Plasmodium falciparum* that facilitates the breakdown of hemoglobin in the acidic food vacuole, supplying vital amino acids needed for parasite development and survival." It also contributes to the host erythrocyte cytoskeleton's cleavage, which facilitates parasite egress and subsequent invasion (Thakur 2024). Therefore, plasmepsin II is a desirable and promising target for the development of antimalarial drugs because of these crucial functions. Protein preparation included the addition of missing hydrogen atoms, completion of side chains, and assignment of secondary structural features. Validation using the Volume, Area, Dihedral Angle Reporter (VADAR) webserver confirmed the structural quality of the receptor, as supported by its Ramachandran plot (Nnyigide et al. 2022) as shown in Figure 1.

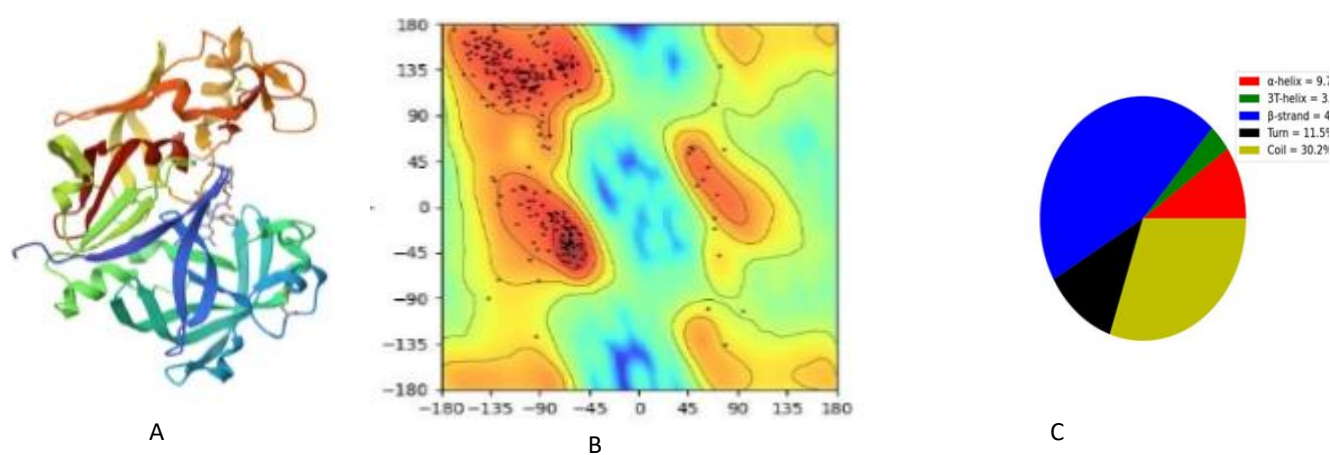


Figure 1: *P. falciparum* Plasmepsin II (1LEE): (a) clean protein (b) Ramachandran plot and (c) Secondary chain structure

3.0 Results and Discussion

Pharmacokinetic parameters were assessed using two in silico ADMET prediction platforms: SwissADME and pkCSM. SwissADME computed key physicochemical descriptors and predicted pharmacokinetic properties (Mvondo et al. 2021), as shown in Table 1. In contrast, pkCSM predicted the absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles of small molecules

relevant to drug discovery. SwissADME is an online prediction tool that can be accessed at <http://www.swissadme.ch>.

The drug likeness of the compounds were predicted by using the Lipinski's rule of 5, the rule was established to set drug likeness ground rules for new molecular entities, Lipinski's rule predicts hydrogen bond donor < 5, hydrogen bond acceptors < 10, molecular weight not more than 500, and calculated $\log P < 5$ and $TPSA < 140$ (Lipinski 2004). The molecular weight (MW) values of all derivatives listed in Table 5 are below 500 Da, indicating that they are relatively lightweight and can readily permeate cell membranes, thereby favoring oral absorption within the body. Notably, none of the compounds violated Lipinski's Rule of Five. Aqueous solubility (Log S) values are expected to fall within the range of -0.7 to $+0.5$; all derivatives met this criterion except B5 (4.05) and lumefantrine (8.33), suggesting that these two compounds may exhibit poor solubility when administered orally (Musa 2021).

All derivatives, together with the two standard drugs, displayed identical bioavailability scores of 0.55, which are considerably higher than the threshold value of 0.17. This indicates that the selected compounds possess excellent oral bioavailability. Polarity was evaluated using the total polar surface area (TPSA), for which the recommended range is 20–140 Å². All derivatives and standard compounds fell within this acceptable TPSA range, suggesting favorable intestinal absorption (Aldarhami et al. 2023). Molecular flexibility was assessed based on the number of rotatable bonds, which should not exceed nine for optimal oral bioavailability. All compounds, including chloroquine, satisfied this criterion except B2 and lumefantrine, which exceeded the recommended limit. Nevertheless, the overall results indicate good oral activity for most of the compounds (Kucharski et al. 2022). Skin permeability, assessed using Log K_p values, showed that all derivatives and standards were within the acceptable range of -8.0 to 1.0 , indicating favorable transdermal permeability profiles (Soriano-Meseguer et al. 2018).

Molar refractivity (MR), which should ideally range between 40 and 130 to support good absorption and oral bioavailability, further supported the suitability of the compounds. All derivatives

exhibited MR values within the range of 64.27–105.55 (Table 1), indicating adequate intestinal absorption, except lumefantrine, which showed a higher MR value of 152.61, suggesting reduced intestinal absorption (Caminero et al. 2023). The estimated Log P values (Table 5) were below the recommended threshold of 5 for all compounds except lumefantrine (Log P = 7.86), indicating that most derivatives possess favorable lipophilicity and good oral absorption characteristics without posing significant systemic toxicity concerns (Lipinski 2001). In line with Lipinski's criteria, all compounds complied with the hydrogen bond donor (HBD $\leq$ 5) requirement (Veber et al. 2008). Similarly, the hydrogen bond acceptor (HBA $\leq$ 10) values for all compounds were within the acceptable range, reflecting optimal membrane permeability (Kenny 2022).

Blood–brain barrier (BBB) permeability predictions revealed that B1, B2, B3, B4, B6, B8, and lumefantrine are unlikely to penetrate the BBB, making them less suitable for treating cerebral malaria but potentially advantageous due to reduced central nervous system (CNS) side effects (Yetunde et al. 2018). In contrast, B5, B7, B9, and chloroquine were predicted to cross the BBB, which may increase the risk of CNS-related side effects. Finally, gastrointestinal (GI) tract absorption analysis indicated that all derivatives exhibited high GI absorption, supporting their potential as orally active drug candidates, with the exception of lumefantrine, which showed low GI absorption despite being a standard drug (Nakanishi et al. 2022).

Table 1: The Lipinski properties with Swiss admet of the derivatives and the standard drug

S/N	Mw	Log P	GL absorption	BB B	nH D	nHBA	MR	LogKP (cm/s)	Log S	BS	TPSA (Å ²)	NRB	Class
B1	315.28	2.06	High	No	0	6	83.13	-6.43	-4.24	0.55	98.42	0	M.S
B2	400.38	2.10	High	No	1	7	105.55	-6.61	-3.80	0.55	119.68	0	Soluble
B3	313.30	2.51	High	No	1	5	83.65	-6.68	-3.50	0.55	81.70	7	Soluble
B4	258.23	2.26	High	No	2	5	66.82	-5.72	-3.56	0.55	83.83	4	Soluble
B5	248.27	2.52	High	Yes	2	4	70.23	-5.70	4.05	0.55	98.42	5	M.S
B6	3335.27	2.83	High	No	0	6	89.13	-5.58	-5.67	0.55	98.42	4	M.S
B7	229..23	2.27	High	Yes	2	3	64.27	-5.46	-3.57	0.55	72.55	3	Soluble
B8	309.32	2.94	High	No	3	4	88.76	5.66	-4.32	0.55	92.78	3	M.S
B9	229.23	2.27	High	Yes	2	3	4.27	5.46	-3.68	0.55	72.55	3	Soluble
Chloro	319.87	4.15	High	Yes	1	2	97.41	-4.96	-4.55	0.55	28.16	8	M.S
Lume	528.94	7.86	Low	No	1	2	152.61	-3.34	8.33	0.55	23.47	10	Soluble

Mw = Molecular Weight, HBD = Hydrogen Bond Donor, HBA = Hydrogen Bond Acceptor, BS = Bioavailability Score, MR = Molar Refractivity, TPSA = Topological Polar Surface Area, NRB = Number of rotatable bond, MS = Moderate Soluble, lume = lumefantrine, chloro = Chloroquine

Table 2 presents the PKSCM-predicted ADMET properties of the synthesized derivatives. For an orally administered drug to be effective, it should exhibit good human intestinal absorption (HIA), as the intestine is the primary site of drug absorption. Compounds with HIA values below 30% are considered poorly absorbed (Murakami 2017). As shown in Table 2, all derivatives demonstrated high intestinal absorption, except compound B2, which exhibited low absorption and is therefore predicted to be poorly absorbed. Caco-2 permeability, derived from human colorectal adenocarcinoma epithelial cells, is widely employed as an in vitro model of the human intestinal mucosa to predict drug absorption (Lozoya-Agullo et al. 2017). All derivatives exhibited high Caco-2 permeability, with the exception of B2, which showed comparatively low permeability. Water solubility (LogS) values, which range from -1 to 7 and are measured at 25 °C, indicate the aqueous solubility of compounds

(Lamoree et al. 2007). All derivatives fell within the acceptable solubility range, suggesting favorable aqueous solubility profiles.

P-glycoprotein (P-gp) is a major efflux transporter involved in the distribution and elimination of many xenobiotics across biological membranes (Elmeliegy et al. 2020). P-gp substrate activity was detected only for compounds B1, B3, B6, and lumefantrine, whereas the remaining compounds were not identified as P-gp substrates. This parameter is critical for evaluating drug permeability and bioavailability. Skin permeability is an important consideration in drug delivery and consumer product efficacy; compounds with $\log K_p > -2.5$ are considered to have low skin permeability. All derivatives exhibited low skin permeability values, indicating limited transdermal penetration (Abdallah et al. 2024). Regarding distribution, the volume of distribution at steady state (VD_{ss}) represents the theoretical extent to which a drug is distributed between plasma and tissues (Talevi & Bellera 2024). Higher VD_{ss} values indicate greater tissue distribution relative to plasma. Compounds with VD_{ss} values < -0.15 are considered to have low distribution, while values > 0.45 indicate high distribution. The VD_{ss} values of the derivatives ranged from -2.172 to 1.332 , reflecting varied tissue distribution tendencies.

The blood–brain barrier (BBB) protects the brain from exogenous compounds, and the ability of a drug to cross the BBB is an important factor in minimizing central nervous system–related side effects (Wu et al. 2023). Compounds with $\log \text{BBB} > 0.3$ are considered BBB permeable, whereas those with $\log \text{BBB} < -1$ are poorly distributed to the brain. Among the derivatives, compound B7 exhibited the highest BBB permeability, while compound B8 showed the lowest BBB permeability, as presented in Table 2 (Radchenko et al. 2020). In terms of metabolism, cytochrome P450 (CYP450) enzymes play a key role in drug detoxification, primarily in the liver, by oxidizing xenobiotics to facilitate excretion. None of the derivatives interacted as substrates of CYP2D6, except chloroquine. All ligands were predicted to inhibit CYP1A2, except compounds B2, B4, and chloroquine. Notably, compound B2 was identified as both a non-substrate and an inhibitor of CYP3A4, which may result in increased drug concentration and potential drug–drug interactions (Carvajal-Moreno et al. 2015). The remaining compounds showed no inhibitory effect on CYP3A4.

Assessment of excretion revealed that the total clearance values for most derivatives were relatively low, with the exception of chloroquine and lumefantrine. This suggests that the derivatives are not rapidly eliminated and may persist in the body long enough to reach their intended therapeutic targets (Musa 2021). Toxicity was evaluated *in silico* using the Ames test. The results presented in Table 8 indicate that compounds B5, B6, B7, and lumefantrine were predicted to be non-toxic, whereas compounds B1, B3, B4, B8, and chloroquine showed higher toxicity risk. Nevertheless, their relatively low total clearance values suggest acceptable systemic exposure within a stipulated time frame. Inhibition of the hERG potassium channel, which has led to the withdrawal of several drugs from the market due to cardiotoxicity, was not observed for most derivatives. However, compound B8 was predicted to exhibit hERG inhibition, indicating a potential risk of cardiotoxicity (El Sherbini et al. 2024).

Table 2: The PKSCM ADMET properties of the Derivatives

		B1	B2	B3	B4	B5	B6	B7	B8	B9	CHLO	LUM E
AB SO RP TI O N	Water solubility	-6.194	-5.295	-4.488	-2.71	-2.373	-5.309	-3.111	-3.715	-2.805	-4.249	3.927
	Caco2 permeability	0.439	-0.048	1.126	1.083	0.957	1.117	1.259	0.143	0.96	1.624	1.311
	Intestinal absorption (Human)	94.354	77.444	94.133	99.273	92.066	100	94.309	85.988	93.423	89.95	96.855
	Skin Permeability	-2.727	2.738	-3.015	-2.733	-2.914	-2.721	-2.797	-2.735	-2.817	-2.679	-2.929
	P-glycoprotein substrate	NO	YES	NO	YES	NO	NO	YES	YES	YES	YES	NO
	P-glycoprotein I inhibitor	YES	YES	NO	NO	NO	YES	NO	NO	NO	NO	YES
	P-glycoprotein II inhibitor	YES	YES	NO	NO	YES	YES	NO	YES	NO	NO	NO
DI ST RI BU TI O	VDss (human)	0.252	0.555	NO	-2.172	0.35	-0.537	0.068	-0.347	0.225	1.332	0.611
	Fraction unbound (human)	0.031	0.675	-0.486	0.141	0.384	0.038	0.153	0.164	0.182	0.191	0.384
	BBB permeability	-0.618	0.756	0.483	-0.101	-0.151	-0.773	0.057	-0.794	-0.032	0.349	0.861

N	CNS permeability	-1.935	0.2829	-2.343	-2.433	-2.369	-2.05	-1.688	-2.029	-2.233	-2.191	-3.239
METABOLISMS	CYP2D6 Substrate	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	NO
	CYP3A4 Substrate	YES	YES	YES	NO	NO	YES	NO	YES	NO	YES	YES
	CYP1A2 Inhibitor	YES	NO	YES	NO	YES	YES	YES	YES	YES	NO	YES
	CYP2C19 Inhibitor	YES	YES	YES	NO	YES	YES	YES	YES	NO	NO	NO
	CYP2C9 Inhibitor	YES	YES	NO	NO	NO	YES	NO	YES	NO	NO	NO
	CYP2D6 inhibitor	NO	NO	NO	NO	NO	NO	NO	YES	NO	YES	NO
	CYP3A4 Inhibitor	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO
EXCRETION	Total Clearance	0.247	0.707	0.498	0.52	0.562	0.626	0.563	0.356	0.466	1.092	1.031
	Renal OCT2 substrate	NO	NO	NO	NO	NO	NO	NO	YES	NO	YES	NO
TOXICITY	AMES toxicity	YES	YES	YES	NO	NO	YES	NO	NO	YES	YES	NO
	Max. tolerated dose (human)	0.342	0.081	0.55	1.012	-0.172	0.194	0.624	0.295	0.14	-0.167	0.074
	HERG I inhibitor	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
	HERG II inhibitor	YES	NO	YES	NO	NO	NO	NO	YES	NO	YES	NO
	Oral Rat Acute	2.691	2.648	2.184	2.848	2.074	2.325	1.954	2.585	2.411	2.85	2.429
	Oral Rat	1.114	2.003	1.488	2.926	1.591	1.31	1.923	2.167	1.089	1.026	1.043
	Hepatotoxicity	YES	YES	NO	NO	NO	YES	NO	YES	NO	YES	NO
	Skin Sensitisation	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO

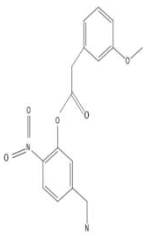
4.0 Molecular docking results and analysis

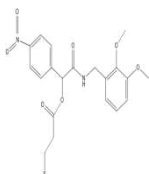
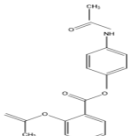
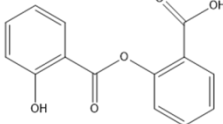
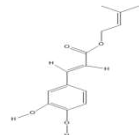
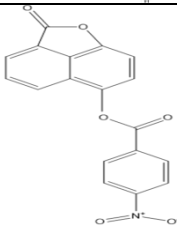
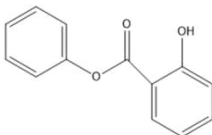
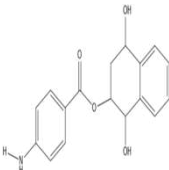
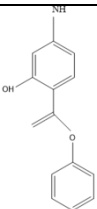
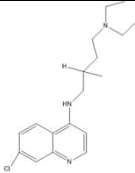
The binding affinities of the nine derivatives and the two reference standards (chloroquine and lumefantrine) that exhibited predicted activity against the Plasmeprin II (1LEE) receptor are presented

in Table 3. The binding energies ranged from -8.2 kcal/mol (B6) to -6.4 kcal/mol (B1 and B5). Specifically, B1 and B5 showed binding energies of -6.4 kcal/mol, B2 and B4 -6.9 kcal/mol, B3 -6.8 kcal/mol, B6 -8.2 kcal/mol, B7 and B9 -6.6 kcal/mol, and B8 -7.7 kcal/mol. The reference drugs chloroquine and lumefantrine exhibited binding energies of -6.1 and -7.7 kcal/mol, respectively. The molecular interactions of ligands B3, B4, B6, B7, B9, and the reference compounds with the active site of Plasmeprin II (1LEE) are summarized in Table 4. Ligand B3 formed a π -donor hydrogen bond with TYR192, a π - σ interaction with VAL178, and π -alkyl interactions with ILE212 and ILE300. B4 exhibited hydrogen bond interactions with THR217 and GLY216; GLY216 also showed an unfavorable acceptor-acceptor interaction. In addition, π -alkyl interactions were observed with VAL78 and ILE32, while a π - σ interaction occurred with ILE123.

Ligand B6 interacted with VAL140 via a π - π T-shaped interaction, TYR272 through a carbon-hydrogen bond, and LYS167 through both π -donor hydrogen bonding and π -carbon hydrogen bonding. LYS306 further contributed a carbon-hydrogen bond. Ligand B7 formed a conventional hydrogen bond with GLY36, π - π stacking and π - π T-shaped interactions with TYR77, and a π -donor hydrogen bond with TYR192. Ligand B9 showed conventional hydrogen bonding with GLY216 and ASP34, a π - π T-shaped interaction with TYR77, and a π - σ interaction with VAL78. Chloroquine interacted with GLU271 and GLN275 via conventional hydrogen bonds. Lumefantrine formed conventional hydrogen bonds with GLY136 and ASP134, a π donor hydrogen bond with SER79, alkyl interactions with PHE120, MET15, ILE290, VAL178, and LEU292, and π -alkyl interactions with TYR77, ILE212, ILE300, and TYR192, as detailed in Table 4.

Table 3: Binding affinity (BA), inhibition constant (K_i) and 2D structures of the nine derivatives.

COD E	STRUCTURE	DA (kcal/mol)	K_i (μ M)
B1		-6.4	20.44

B2		-6.9	8.80
B3		-6.8	10.41
B4		-6.9	8.80
B5		-6.4	20.44
B6		-8.2	0.98
B7		-6.6	14.59
B8		-7.7	2.28
B9		-6.6	14.59
Chloroquine		-6.1	33.92

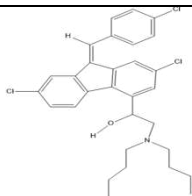
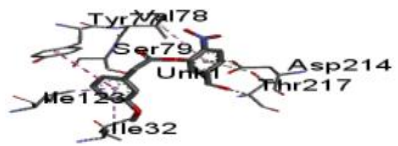
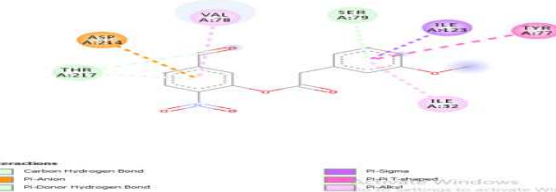
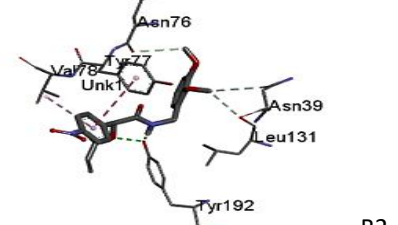
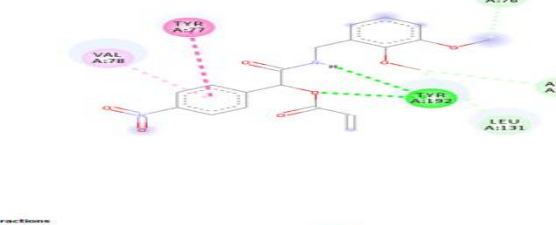
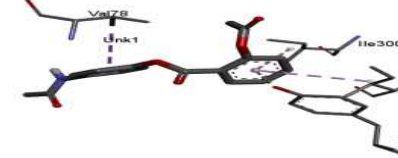
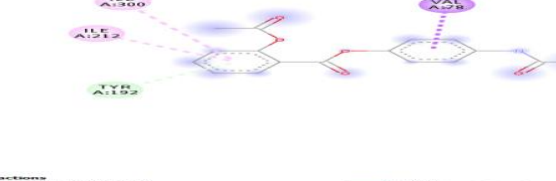
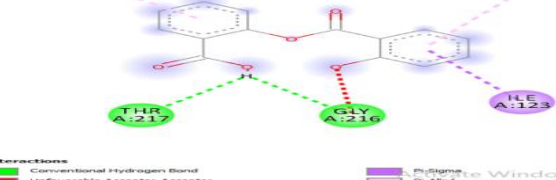
Lume fantrine		-7.7	2.28
------------------	---	------	------

Table 4: 3D interactions of the ligands with the receptors

 B1	 Interactions: Conventional Hydrogen Bond Pi-Anion Carbon Hydrogen Bond Pi-Sigma Pi-Pi T-shaped Pi-Pi Go to Settings to activate Windows.
 B2	 Interactions: Conventional Hydrogen Bond Carbon Hydrogen Bond Pi-Pi T-shaped Pi-Pi Go to Settings to activate Windows.
 B3	 Interactions: Pi-Donor Hydrogen Bond Pi-Sigma Pi-Pi Go to Settings to activate Windows.
 B4	 Interactions: Conventional Hydrogen Bond Unfavorable Acceptor-Acceptor Pi-Sigma Pi-Pi T-shaped Pi-Pi Go to Settings to activate Windows.
 B5	 Interactions: Conventional Hydrogen Bond Pi-Cation Pi-Donor Hydrogen Bond Pi-Pi T-shaped Pi-Pi Go to Settings to activate Windows.

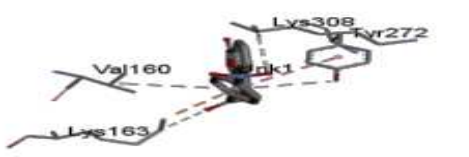
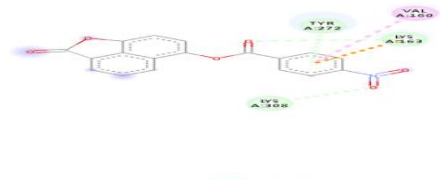
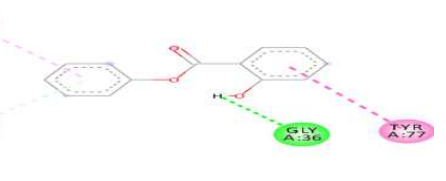
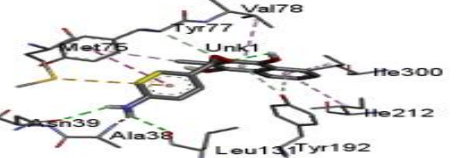
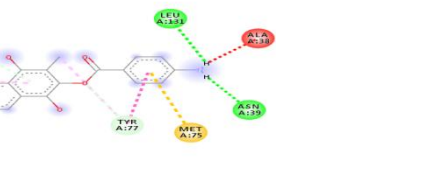
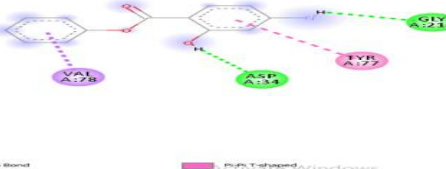
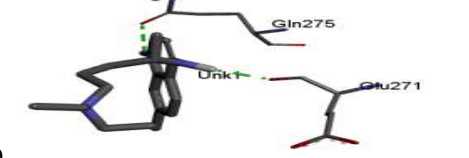
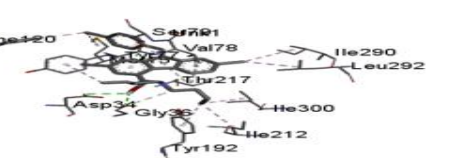
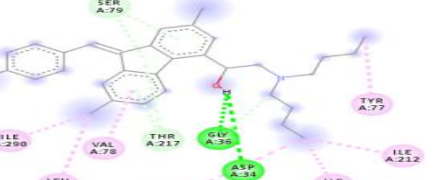
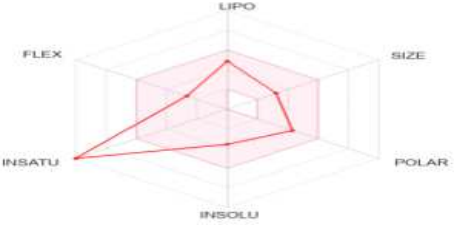
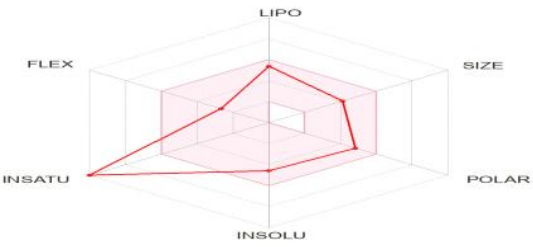
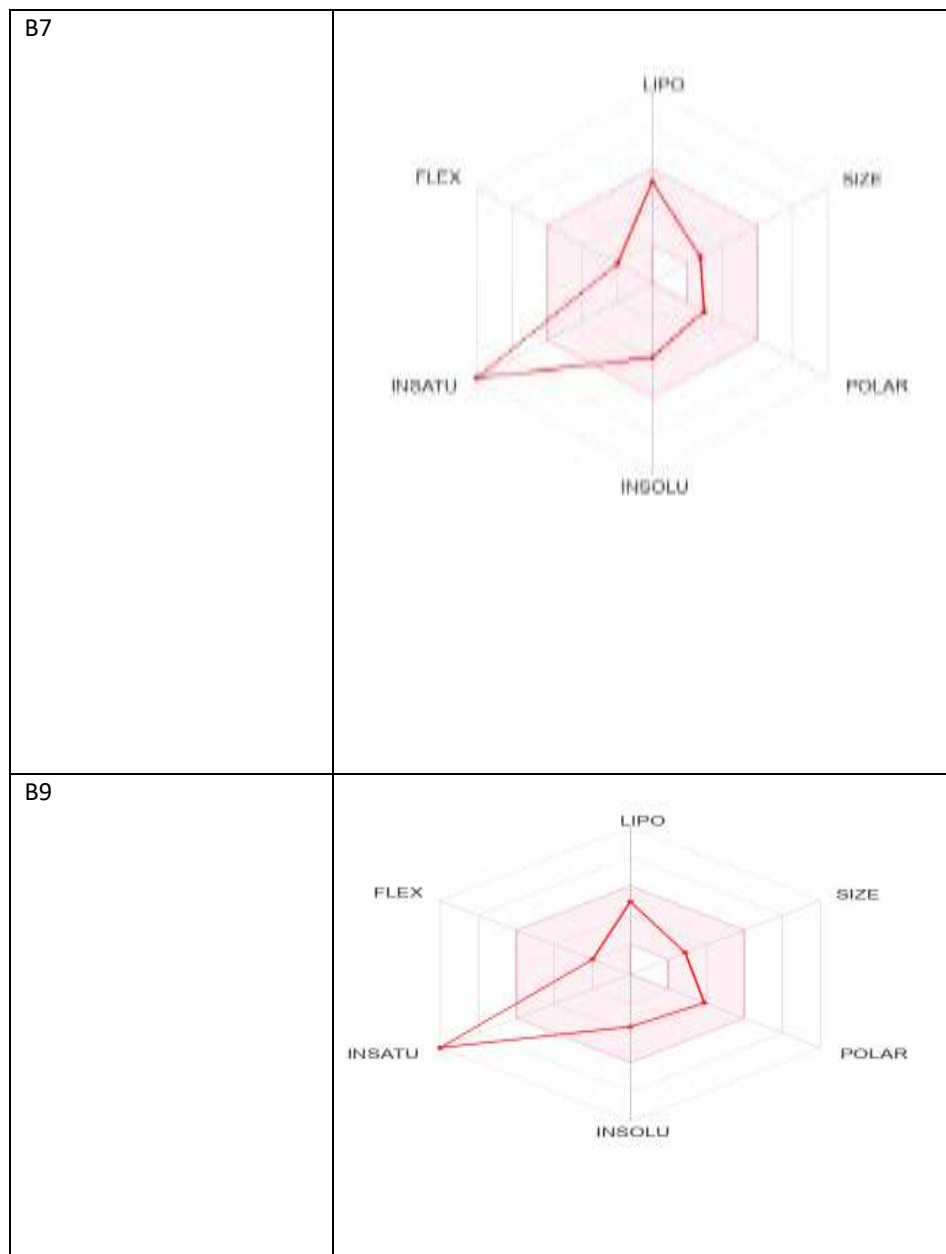
B6 	 Interactions - Conventional Hydrogen Bond - Carbon Hydrogen Bond - Unfavorable Donor-Donor - Pi-Donor Hydrogen Bond - Pi-Cation - Pi-Donor Hydrogen Bond - Pi-Pi T-shaped - Pi-Allyl Activate Windows Go to Settings to activate Windows.
B7 	 Interactions - Conventional Hydrogen Bond - Carbon Hydrogen Bond - Unfavorable Donor-Donor - Pi-Donor Hydrogen Bond - Pi-Cation - Pi-Donor Hydrogen Bond - Pi-Pi T-shaped - Pi-Allyl Activate Windows Go to Settings to activate Windows.
B8 	 Interactions - Conventional Hydrogen Bond - Carbon Hydrogen Bond - Unfavorable Donor-Donor - Pi-Donor Hydrogen Bond - Pi-Cation - Pi-Donor Hydrogen Bond - Pi-Pi T-shaped - Pi-Allyl - Pi-Sulfur - Pi-Stacked Activate Windows Go to Settings to activate Windows.
B9 	 Interactions - Conventional Hydrogen Bond - Carbon Hydrogen Bond - Unfavorable Donor-Donor - Pi-Donor Hydrogen Bond - Pi-Cation - Pi-Donor Hydrogen Bond - Pi-Pi T-shaped - Pi-Allyl Activate Windows Go to Settings to activate Windows.
CHLO 	 Interactions - Conventional Hydrogen Bond - Carbon Hydrogen Bond - Unfavorable Donor-Donor - Pi-Donor Hydrogen Bond - Pi-Cation - Pi-Donor Hydrogen Bond - Pi-Pi T-shaped - Pi-Allyl Activate Windows Go to Settings to activate Windows.
LUME 	 Interactions - Conventional Hydrogen Bond - Carbon Hydrogen Bond - Unfavorable Donor-Donor - Pi-Donor Hydrogen Bond - Pi-Cation - Pi-Donor Hydrogen Bond - Pi-Pi T-shaped - Pi-Allyl - Allyl Activate Windows Go to Settings to activate Windows.

Table 5 Show the Qualified Compounds of Oral bioavailability Radar of the best ligand using Swiss ADME prediction.

CODE	Compound Charts
------	-----------------

B3	 A radar chart with six axes labeled LIPO, SIZE, POLAR, INSOLU, INSATU, and FLEX. The chart features concentric grid lines representing five levels of magnitude. A red line connects the data points for each axis. The values are approximately: LIPO (1.5), SIZE (2.5), POLAR (2.0), INSOLU (2.0), INSATU (4.5), and FLEX (2.5).
B4	 A radar chart with six axes labeled LIPO, SIZE, POLAR, INSOLU, INSATU, and FLEX. The chart features concentric grid lines representing five levels of magnitude. A red line connects the data points for each axis. The values are approximately: LIPO (1.5), SIZE (2.0), POLAR (1.5), INSOLU (1.5), INSATU (4.5), and FLEX (2.0).
B6	 A radar chart with six axes labeled LIPO, SIZE, POLAR, INSOLU, INSATU, and FLEX. The chart features concentric grid lines representing five levels of magnitude. A red line connects the data points for each axis. The values are approximately: LIPO (1.5), SIZE (2.0), POLAR (1.5), INSOLU (1.5), INSATU (4.5), and FLEX (2.0).



Density functional theory (DFT) calculations were performed using the B3LYP exchange–correlation functional in combination with the 6-311G basis set (Salman et al. 2019). The energies of the highest occupied molecular orbital (E_{HOMO}) and the lowest unoccupied molecular orbital (E_{LUMO}), the HOMO–LUMO energy gap ($\Delta E_{\text{gap}} = E_{\text{HOMO}} - E_{\text{LUMO}}$), global hardness (η), electrophilicity index (ω), dipole moment (μ), and other relevant chemical descriptors were computed (Sidor & Sidor 2023). The calculated HOMO–LUMO energy gap followed the order: $B6 < B1 < B2 < \text{Lume} < \text{Chlo} < B5 < B4 < B7 < B3 < B9$. A lower energy gap indicates a greater ability of a ligand to donate electrons to interacting species. Consequently, ligands B6 and B1, which exhibit the lowest band gaps, are expected to possess higher chemical reactivity (Semire et al. 2016).

Ionization potential (IP), defined as the energy required to remove an electron from a molecule, is another important parameter influencing reactivity. Lower IP values favor electron donation and enhanced biological activity. The calculated IP values (Table 6) followed the order: B9 < B5 $\approx$ Chlo < Lume < B8 $\approx$ B3 $\approx$ B1 < B4 $\approx$ B7 < B2 < B6. Ligands with lower IP values, such as B9 (5.51 eV) and B5 (5.94 eV), are therefore more likely to readily lose electrons to the surrounding protein environment (Toma et al. 2020). Chemical hardness (η), which reflects molecular stability and resistance to charge transfer, was found to decrease in the order: B6 $\approx$ B7 < B1 < B2 < Lume < Chlo < B5 < B4 < B8 < B3 < B9. In contrast, chemical softness (S), an inverse measure of hardness and an indicator of molecular reactivity, followed the order: B6 $\approx$ B7 > B1 > B2 > Lume > Chlo $\approx$ B4 $\approx$ B5 > B8 > B3 > B9 (Semire et al. 2012). Higher softness values suggest increased reactivity and a greater tendency for intermolecular interactions. Since chemical hardness and softness are inversely related, molecules with lower hardness and higher softness are generally more reactive, whereas higher hardness corresponds to increased stability (Xu et al. 2017). Based on these descriptors, ligands B9, B5, and B4 exhibit a higher propensity to donate electrons and are therefore expected to interact more strongly with the target protein. Such interactions are likely mediated through cationic or anionic interactions involving electron transfer between the ligand HOMO and the receptor LUMO orbitals (Semire et al. 2016).

Table 6. Quantum Chemical Characteristics of the molecule in water

S/N	HOMO	LUMO	ΔE gap	LOGP	DM	BA	EA	σ	η
B1	-6.18	2.72	3.46	4.94	3.42	6.18	2.72	0.29	0.73
B2	-6.48	2.78	3.70	4.88	9.62	6.48	2.78	0.27	0.85
B3	-6.18	1.38	4.80	1.01	3.95	6.18	1.38	0.21	2.40
B4	-6.29	1.88	4.41	-0.30	3.20	6.29	1.88	0.23	2.21
B5	-5.94	1.61	4.33	0.64	1.61	5.94	1.61	0.23	2.17
B6	-6.66	4.13	2.53	-2.40	1.30	6.66	4.13	0.39	1.27
B7	-6.29	1.79	4.50	0.45	2.39	6.29	4.13	0.39	1.27
B8	-6.18	1.21	4.97	-1.16	4.41	6.29	1.79	0.32	2.25
B9	-5.51	0.37	5.14	-1.43	3.74	5.51	0.37	0.19	2.57
CHLO	-5.94	1.63	4.31	2.39	6.39	5.94	1.63	0.23	2.16
LUME	-6.10	2.08	4.20	3.38	3.92	6.10	2.08	0.25	2.01

DM = Dipole Moment, η = Chemical hardness, σ = Chemical softness, IP = Ionization potential, EA = Electron affinity, Chlo= Chloroquine, Lume = lumefantrine

4.0 Molecular Dynamic Simulation Analysis

Molecular dynamics (MD) simulations were conducted for 100 ns to evaluate the dynamic behavior of the docked complexes of Plasmeprin II (PDB ID: 1LEE) with 2-Oxo-2H-naphtho[1,8-bc]furan-6-yl 4-nitrobenzoate (B6) and the reference ligand, lumefantrine. The simulations were performed to monitor structural stability and conformational changes over time. The root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg), solvent-accessible surface area (SASA), and hydrogen-bond (H-bond) profiles were calculated across the 100 ns trajectories. Average values of these parameters are summarized in Table 7.

The RMSD trajectories of the protein backbone for the B6-bound complex increased from approximately 0.22 nm to 0.40 nm during the early stages of the simulation and subsequently stabilized within the range of ~0.30–0.35 nm for the remainder of the trajectory (Figure 2a). The lumefantrine-bound complex showed RMSD values increasing from ~0.15 nm to ~0.30 nm, with fluctuations reaching ~0.35–0.38 nm at later time points. No abrupt deviations were observed in either system during the simulation period (Lotfi-Sousefi et al. 2020).

RMSF analysis indicated residue-level fluctuations across the protein structure (Figure 2b). The B6-bound complex showed lower fluctuation amplitudes within residues approximately 50–90, while the lumefantrine-bound complex displayed a peak fluctuation of ~0.52 nm within the same region. The mean RMSF values for the B6 and lumefantrine complexes were 0.1056 nm and 0.1024 nm, respectively (Table 7) (Brown et al. 2020). The radius of gyration (Rg) was monitored to assess the overall compactness of the protein structure during the simulation. Both complexes exhibited Rg values ranging between ~2.30 and 2.40 nm throughout the 100 ns trajectory (Figure 3a), with no major changes observed over time (Pavan et al. 2022).

Solvent-accessible surface area (SASA) analysis showed that the B6-bound complex maintained SASA values in the range of approximately 230–238 nm² over the simulation period, whereas the lumefantrine-bound complex exhibited SASA values between ~240 and 245 nm² (Figure 3b). These values remained relatively stable throughout the trajectory (Mafethe et al. 2023; Musa et al. 2021). Hydrogen-bond analysis revealed that the B6-bound complex formed between 1 and 2 hydrogen bonds for most of the simulation, with occasional increases to 3 bonds. In contrast, the lumefantrine-bound complex predominantly formed 0–1 hydrogen bonds, with sporadic occurrences of 2 bonds over the 100 ns simulation period (Figure 3c) (Bulusu & Desiraju 2020; Shukla & Tripathi 2020; Pace et al. 2014; Oladunjoye 2021).

Table 7: Average mean values for RMSD, RMSF, ROG, SASA and H-Bonds of ligand-complexes.

COMPOUND	Average RMSD (nm)	Average RMSF (nm)	Average ROG (nm)	Average SASA Values (nm)	Average H-Bond (nm)
71768362 (B6)	0.2374	0.1056	2.0702	162.305	1.0883
LUMEFANTRINE (STANDARD)	0.2116	0.1024	2.0427	158.874	0.1061

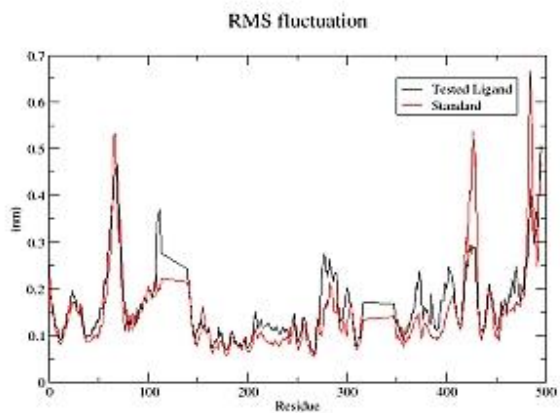
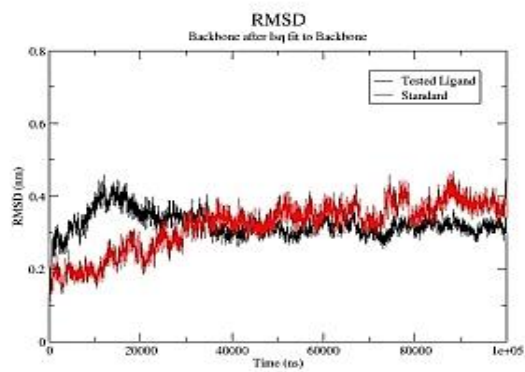


Fig 2. RMSD and RMSF Plot showing the Stability of the Tested ligand and the standard



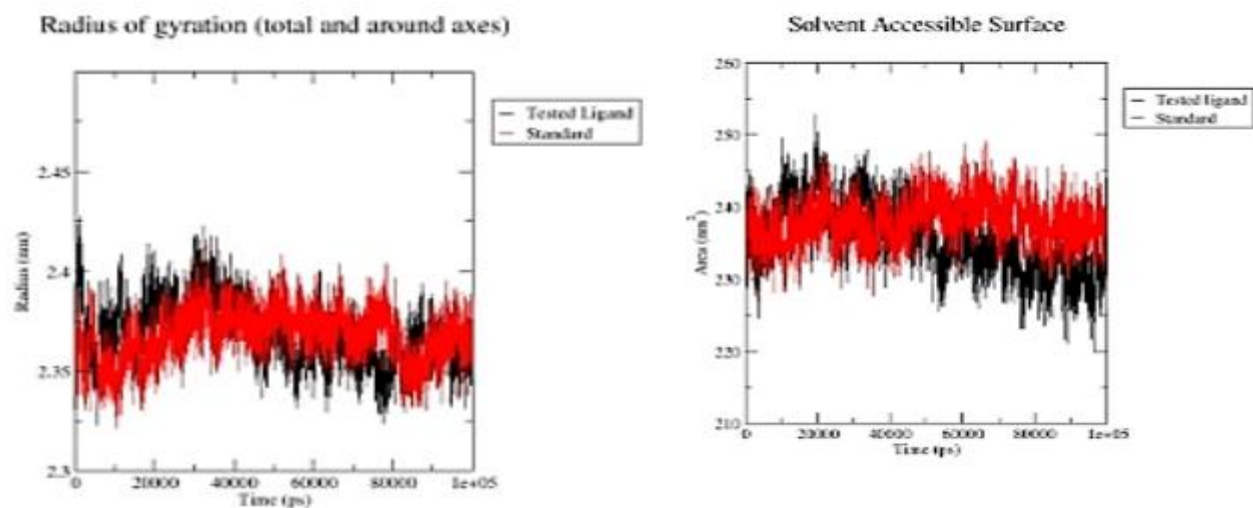


Fig 3: ROG and SASA plots showing the compactness and rigidity, solvent-exposed area of the tested ligand and the standard; Tested ligand = 2-Oxo-2H-naphtho[1,8-bc]furan-6-yl 4-nitrobenzoate (B6) and Standard = Lumefantrine

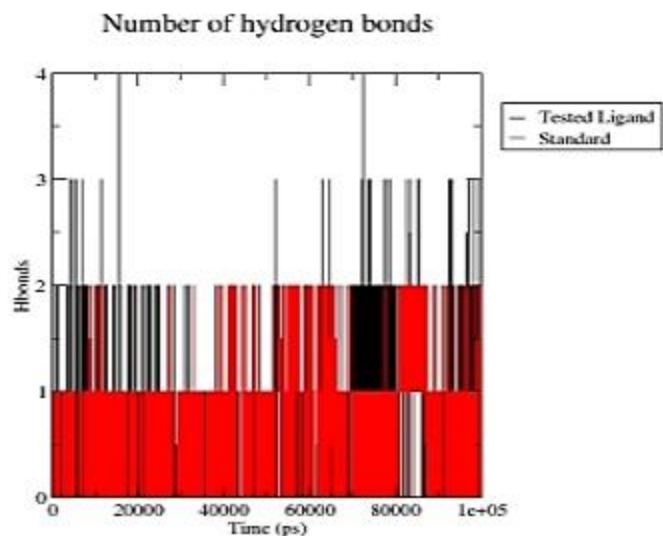


Fig 3c: Number of H-Bonds at each frame over trajectory of the tested ligand and the standard

Conclusion

In this study, computational approaches were employed to gain insights into the binding affinities of nine derivatives obtained from Swiss Similarity screening of 4-hydroxyl phenyl 3-nitrobenzoate, previously identified as potential antimalarial scaffolds. Molecular docking analyses were performed alongside ADMET and drug-likeness evaluations. Pharmacokinetic results indicated that only four of the nine derivatives were non-toxic and complied with Lipinski's rule of five. The reference antimalarial drugs, chloroquine and lumefantrine, exhibited promising binding affinities, demonstrating strong interactions with the target protein (1LEE) as reflected by their low docking scores. Overall, the results revealed that 2-oxo-2H-naphtho[1,8-bc]furan-6-yl 4-nitrobenzoate (B6) showed superior drug-like properties and antimalarial potential compared to the FDA-approved drug lumefantrine. Further studies are ongoing to elucidate its mechanism of action and to design additional derivatives aimed at enhancing antimalarial inhibitory activity.

Acknowledgement: The authors would like to thank the Department of Chemistry, Osun State University Osogbo, and Osun State Nigeria for providing the computational facility to carry out this study successfully.

- **Competing interest:** The authors have no competing interests to declare that are relevant to the content of this article.
- **Funding:** No funding was received to assist with the preparation of this manuscript.

CRediT taxonomy: Conceptualization: [Elizabeth Funke Olarinoye], Dayo Felix Latona; Methodology: [Banjo Semire] Elizabeth Funke Olarinoye; Formal analysis and investigation: [Elizabeth Funke Olarinoye], Dayo Felix Latona; Writing - original draft preparation: [Elizabeth Funke Olarinoye, Banjo Semire]; Writing - review and editing: [Elizabeth Funke Olarinoye], Banjo Semire; Funding acquisition: [Elizabeth Funke Olarinoye], Oluwaseun Adenike Adefila ; Resources: [Oluwaseun Adenike Adefila], Taiwo Abiodun Adekunle; Supervision: [Dayo Felix Latona], Banjo Semire.

References

1. Abdallah, R. M., Hasan, H. E., &Hammad, A. Predictive modeling of skin permeability for molecules: Investigating FDA-approved drug permeability with various AI algorithms. *PLOS Digital Health*, (2024) 3(4), e0000483.

2. Aldarhami, A., Bazaid, A. S., Alhamed, A. S., Alghaith, A. F., Ahamad, S. R., Alasmrri, Y. A. & Alreshidi, M. Antimicrobial potential of *Pithecellobium dulce* seed extract against pathogenic bacteria: in silico and in vitro evaluation. *BioMed Research International*, 2023(1), 2848198.
3. Athar, M., Das, S., Jha, P. C., & Jha, A. M. Conformational equilibrium study of calix [4] tetrolarenes using Density Functional Theory (DFT) and Molecular Dynamics simulations. *Supramolecular Chemistry*, (2018). 30(12), 982-993.
4. Bragina ME, Daina A, Perez MAS, Michielin O, Zoete V. The SwissSimilarity 2021 Web Tool: Novel Chemical Libraries and Additional Methods for an Enhanced Ligand-Based Virtual Screening Experience. *Int J Mol Sci*. 2022 Jan 12;23(2):811. doi: 10.3390/ijms23020811. PMID: 35054998; PMCID: PMC8776004.
5. Brown, R. P. *Synthesis, Stability and Dynamic Surface Chemistry of InP-Based Core/Shell Quantum Dots* (Doctoral dissertation, University of Maryland, Baltimore County).(2020).
6. Bulusu, G., & Desiraju, G. R. Strong and weak hydrogen bonds in protein–ligand recognition. *Journal of the Indian Institute of Science*, (2020). 100(1), 31-41.
7. Caminero Gomes Soares, A., Marques Sousa, G. H., Calil, R. L., & Goulart Trossini, G. H. Absorption matters: A closer look at popular oral bioavailability rules for drug approvals. *Molecular informatics*, (2023). 42(11), e202300115.
8. Carvajal-Moreno, M. Metabolic changes of aflatoxin B1 to become an active carcinogen and the control of this toxin. *Immunome Research*, (2015). 11(2), 1.
9. Ekinçioğlu, Y., Kılıç, H. Ş., & Dereli, Ö. DFT study of conformational analysis, molecular structure and properties of para-, meta- and ortho 4-methoxyphenyl piperazine isomers. *Brazilian Journal of Physics*, (2021). 51(4), 958-968.
10. El Sherbini, A., Liblik, K., Lee, J., Baranchuk, A., Zhang, S., & El-Diasty, M. . Opioids-induced inhibition of HERG ion channels and sudden cardiac death, a systematic review of current literature. *Trends in Cardiovascular Medicine*, (2024) 34(5), 279-285.
11. Elmeliegy, M., Vourvahis, M., Guo, C., & Wang, D. D. Effect of P-glycoprotein (P-gp) inducers on exposure of P-gp substrates: review of clinical drug–drug interaction studies. *Clinical pharmacokinetics*, (2020). 59(6), 699-714.

12. Gheidari, D., Mehrdad, M., & Karimelahi, Z. Virtual screening, ADMET prediction, molecular docking, and dynamic simulation studies of natural products as BACE1 inhibitors for the management of Alzheimer's disease. *Scientific Reports*, (2024). 14(1), 26431.
13. Kenny, P. W. Hydrogen-bond donors in drug design. *Journal of medicinal chemistry*, (2022) 65(21), 14261-14275.
14. Kucharski, D. J., Jaszczak, M. K., & Boratyński, P. J. A review of modifications of quinoline antimalarials: mefloquine and (hydroxy) chloroquine. *Molecules*, (2022). 27(3), 1003.
15. Lamoree, H., Legler, J., & Brouwer, A. Biomonitoring of Estrogenic Exposure and Identification of Responsible Compounds in Bream from Dutch Surface Waters. *tracing endocrine*, (2007) 26, 93.
16. Lipinski, C. A. Lead-and drug-like compounds: the rule-of-five revolution. *Drug discovery today: Technologies*, (2004). 1(4), 337-341.
17. Lipinski, C. A., *et al.* Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews*, (2001). 46(1-3), 3-26.
18. Long, C. A., & Hoffman, S. L. Malaria--from Infants to Genomics to Vaccines. *Science*, (2002). 297(5580), 345-347.
19. Lotfi-Sousefi, Z., Mehrnejad, F., Khanmohammadi, S., & Kaboli, S. F. Insight into the microcosm of the human growth hormone and its interactions with polymers and copolymers: a molecular dynamics perspective. *Langmuir*, (2020). 37(1), 90-104.
20. Lozoya-Agullo, I., Araujo, F., Gonzalez-Alvarez, I., Merino-Sanjuan, M., Gonzalez-Alvarez, M., Bermejo, M., & Sarmiento, B. . Usefulness of Caco-2/HT29-MTX and Caco-2/HT29-MTX/Raji B coculture models to predict intestinal and colonic permeability compared to Caco-2 monoculture. *Molecular pharmaceutics*, (2017) 14(4), 1264-1270.
21. Mafethe, O., Ntseane, T., Dongola, T. H., Shonhai, A., Gumede, N. J., & Mokoena, F. Pharmacophore model-based virtual screening workflow for discovery of inhibitors targeting Plasmodium falciparum Hsp90. *ACS omega*, (2023). 8(41), 38220-38232.

22. Melini V, Ruzzi M. Innovative Perspectives on Phytochemicals in Human Nutrition. *Nutrients*. 2025 Feb 17;17(4):711. doi: 10.3390/nu17040711. PMID: 40005040; PMCID: PMC11857875.
23. Murakami, T. Absorption sites of orally administered drugs in the small intestine. *Expert opinion on drug discovery*, (2017). 12(12), 1219-1232.
24. Musa, K. A. *Investigation of the Binding Characteristics of Anti-Malarial Drugs, Mefloquine, Lumefantrine and Pyrimethamine to Human Serum Albumin Using Spectroscopic and Molecular Docking Methods* (Doctoral dissertation, University of Malaya (Malaysia)).(2021).
25. Musa, K. A. *Investigation of the Binding Characteristics of Anti-Malarial Drugs, Mefloquine, Lumefantrine and Pyrimethamine to Human Serum Albumin Using Spectroscopic and Molecular Docking Methods* (Doctoral dissertation, University of Malaya (Malaysia)), (2021).
26. Musa, K. A. *Investigation of the Binding Characteristics of Anti-Malarial Drugs, Mefloquine, Lumefantrine and Pyrimethamine to Human Serum Albumin Using Spectroscopic and Molecular Docking Methods* (Doctoral dissertation, University of Malaya (Malaysia)). (2021).
27. Mvondo, J. G. M., Matondo, A., Mawete, D. T., Bambi, S. M. N., Mbala, B. M., & Lohohola, P. O. In silico ADME/T properties of quinine derivatives using SwissADME and pkCSM web servers. *Int. J. Trop. Dis. Health*, (2021) 42(11), 1-12.
28. Nakanishi *et al.* estimated gastrointestinal tract absorption using whole-body imaging following oral (2022) [¹²³I]MIBG administration.
29. Nnyigide O.S., Nnyigide T.O., Lee S.G., & Hyun K.. Protein Repair and Analysis Server: A Web Server to Repair PDB Structures, Add Missing Heavy Atoms and Hydrogen Atoms, and Assign Secondary Structures by Amide Interactions. *J. Chem. Inf. Model.*, 2022, 62, 4232–4246.
30. Oladunjoye, B. B. Structure-Based Virtual Screening of Selected Malaria Box Compounds Against a Multi-Staged Protein (Falstatin) in *Plasmodium falciparum*. (2021)

31. Pace, C. N., Fu, H., Lee Fryar, K., Landua, J., Trevino, S. R., Schell, D., ... & Grimsley, G. R. Contribution of hydrogen bonds to protein stability. *Protein Science*, (2014), 23(5), 652-661.
32. Pavan, M., Menin, S., Bassani, D., Sturlese, M., & Moro, S. Qualitative estimation of protein–ligand complex stability through thermal titration molecular dynamics simulations. *Journal of Chemical Information and Modeling*, (2022). 62(22), 5715-5728.
33. Radchenko, E. V., Dyabina, A. S., & Palyulin, V. A. Towards deep neural network models for the prediction of the blood–brain barrier permeability for diverse organic compounds. *Molecules*, (2020) 23(24), 5901.
34. Saini, E. K., Keiley, M. K., Fuller-Rowell, T. E., Duke, A. M., & El-Sheikh, M. Socioeconomic status and sleep among couples. *Behavioral sleep medicine*, (2021). 19(2), 159-177.
35. Salman, R. A. S., Dennis, M. S., Sandercock, P. A. G., Sudlow, C. L. M., Wardlaw, J. M., Whiteley, W. N., ... & Barber, M. Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART): a randomised, open-label trial. *The Lancet*, (2019). 393(10191), 2613-2623.
36. Sato, S. Plasmodium—a brief introduction to the parasites causing human malaria and their basic biology. *Journal of physiological anthropology*, (2021). 40(1), 1.
37. See, A., Liu, P. J., & Manning, C. D. Get to the point: Summarization with pointer-generator networks. *arXiv preprint arXiv*: (2017). 1704.04368.
38. Semire B.; Oyebamiji, A.; Ahmad, M. Theoretical Study on structure and Electronic Properties of 2,5- Bis [4-N, N-Diethylaminostyl] Thiophene and its furan and pyrrole Derivatives Using Density Functional Theory. *Pakistan Journal of Chemistry*, (2012), 2(4), 166-173
39. Semire, B., Oyebamiji, A., & Odunola, O. A. Design of (2Z)-2-cyano-2-[2-[(E)-2-[5-[(E)-2-(4-dimethylaminophenyl) vinyl]-2-thienyl] vinyl] pyran-4-ylidene] acetic acid derivatives as D-π-A dye sensitizers in molecular photovoltaics: a density functional theory approach. *Research on Chemical Intermediates*, (2016). 42(5), 4605-4619.

40. Semire, B., Oyebamiji, A., & Odunola, O. A. Design of (2Z)-2-cyano-2-[2-[(E)-2-[5-[(E)-2-(4-dimethylaminophenyl) vinyl]-2-thienyl] vinyl] pyran-4-ylidene] acetic acid derivatives as D- π -A dye sensitizers in molecular photovoltaics: a density functional theory approach. *Research on Chemical Intermediates*, (2016) 42(5), 4605-4619.
41. Shukla, R., & Tripathi, T. Molecular dynamics simulation of protein and protein–ligand complexes. In *Computer-aided drug design* (2020). (pp. 133-161). Singapore: Springer Singapore.
42. SIDIR, Y. G., & SIDIR, I. The study on QSAR and relations between molecular descriptors of 5, 8-quinolinequinone derivatives. *Gazi University Journal of Science*, (2023). 36(4).
43. Soriano-Meseguer, S., Fuguet, E., Port, A., & Rosés, M. Estimation of skin permeation by liquid chromatography. *ADMET and DMPK*, (2018) 6(2), 140-152.
44. Talevi, A., & Bellera, C. L. Drug distribution. In *ADME Processes in Pharmaceutical Sciences: Dosage, Design, and Pharmacotherapy* (2024). (pp. 55-79). Cham: Springer Nature Switzerland.
45. Thakur, V. Food Vacuole as a Drug Target. In *Drug Targets for Plasmodium Falciparum: Historic to Future Perspectives* (2024). (pp. 183-199). Singapore: Springer Nature Singapore.
46. Toma, M., Kuvek, T., & Vrcek, V. Ionization energy and reduction potential in ferrocene derivatives: comparison of hybrid and pure DFT functionals. *The Journal of Physical Chemistry A*, (2020) 124(39), 8029-8039.
47. Veber, D. F., *et al.* Molecular properties that influence the oral bioavailability of drug candidates. *Journal of Medicinal Chemistry*, (2002). 45(12), 2615-2623. Hughes, J. D., *et al.* (2008). Physiochemical drug properties associated with in vivo toxicological outcomes. *Bioorganic & Medicinal Chemistry Letters*, 18(17), 4872-4875.
48. WHO, D World malaria report 2020: 20 years of global progress and challenges. *World malaria report 2020*: p 299.
49. Wu, D., Chen, Q., Chen, X., Han, F., Chen, Z., & Wang, Y. The blood–brain barrier: Structure, regulation and drug delivery. *Signal transduction and targeted therapy*, (2023). 8(1), 217.

50. Xu, H., Xu, D. C., & Wang, Y. Natural indices for the chemical *hardness/softness of metal cations and ligands*. *ACS omega*, (2017). 2(10), 7185-7193.
51. Yetunde, O. A., James, O. O., & Adegboyega, A. O. Malaria, Antimalaria Drugs, Drug/Parasite Interactions, and the Brain: A Review of Impacts on Behaviour, Neurochemistry and Structure. *Central Nervous System Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Central Nervous System Agents)*, (2018). 18(3), 173-192.
52. Zekar, L., & Sharman, T. Plasmodium falciparum malaria. In *StatPearls [Internet]*. StatPearls Publishing.(2023).
53. Zulfat, M., Hakami, M. A., Hazazi, A., Mahmood, A., Khalid, A., Alqurashi, R. S., ... & Huang, X. Identification of novel NLRP3 inhibitors as therapeutic options for epilepsy by machine learning-based virtual screening, molecular docking and biomolecular simulation studies. *Heliyon*, (2024).10(15).