Original Research **https://doi.org/10.5281/zenodo.21002109**

Volume 8, Issue 1, pp 1-13, June 2026

ACHIEVERS JOURNAL OF SCIENTIFIC RESEARCH

Open Access Publications of Achievers University, Owo

Available Online at *www.achieversjournalofscience.org*

In Silico Investigation of 4-Hydroxyphenyl-3-nitrobenzoate Derivatives as Potential Inhibitors of Plasmodium falciparum Lactate Dehydrogenase Using Swiss Similarity, Molecular Docking, and ADMET Analysis

E.F. Olarinoye[1*], D.F. Latona[2], Sunday Adeoye[1], O.N. Oladoye[3], and Banjo Semire[3]

[1]Department of Industrial Chemistry, University of Ilesha, Ilesha, Osun State.
[2]Department of Pure and Applied Chemistry, Osun State University, Osogbo, Osun State.
[3]Computational Chemistry Research Group, Department of Pure and Applied Chemistry, Ladoke Akintola University of Technology, Ogbomoso, Nigeria.

[*]**Corresponding Author's Email Address:** elizabeth_olarinoye@unilesa.edu.ng, dayo.latona@uniosun.edu.ng

Submitted: March 5, 2025; **Revised:** May 18, 2026; **Accepted:** May 29, 2026; **Published:** June 28, 2026

Abstract

Malaria remains a major global health challenge due to the increasing resistance of *Plasmodium falciparum* to existing antimalarial drugs. This study investigated structurally related analogues of 4-hydroxyphenyl-3-nitrobenzoate as potential inhibitors of *Plasmodium falciparum* lactate dehydrogenase (PfLDH, PDB ID: 1CET) using SwissSimilarity screening, molecular docking, and ADMET analysis. Seven analogues were identified and evaluated alongside chloroquine and lumefantrine as reference compounds. Among the screened compounds, A3, A5, and A4 exhibited stronger binding affinities (−7.7, −7.5, and −7.4 kcal/mol, respectively) than chloroquine (−6.1 kcal/mol) and comparable affinity to lumefantrine (−7.1 kcal/mol). ADMET predictions revealed favorable pharmacokinetic properties for the lead compounds. Furthermore, A3 demonstrated stable binding interactions within the PfLDH active site through hydrogen bonding and hydrophobic interactions. These findings suggest that A3 may serve as a potential lead compound for further experimental evaluation as an antimalarial agent.

Keywords: Swiss Similarity, ADMET, Molecular docking, Antimalarial

1.0 Introduction

Malaria is an infectious disease transmitted by female Anopheles mosquitoes that affect the world population and kill over one million people every year (Talapko, *et al*., 2019). Plasmodium parasites are responsible for human malaria. *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium knowlesi, and Plasmodium malariae* are the five major Plasmodium species responsible for human malaria. It is a life-threatening disease caused by parasites belonging to five species of the genus Plasmodium falciparum which is transmitted through the bite of infected female Anopheles mosquitoes (Nosten *et al.,* 2022). In 2017 as per the WHO report, 219 million cases of malaria were reported in 87 countries and the estimated number of deaths was found to be 435,000 (Shibeshi *et al.,* 2020). Despite such large figures there is still no widely used efficacious vaccine available for malaria parasites. In the 21st century, the drug resistance has emerged to almost all classes of antimalarial drugs and therefore a sudden leap has been witnessed in malaria-related mortality, especially in Africa.

Plasmodium falciparum is transmitted to humans through the bite of infected female Anopheles mosquitoes. Immediately the Plasmodium parasites are transmitted, they quickly travel to the liver via the bloodstream to infect the liver cells and the parasites grow, multiply, and reproduce thousands of merozoite cells (Alemayehu *et al*., 2023). Several drugs such as Chloroquine, proguanil, artemisinin, Atovaquone, and quinine have been used to treat malaria. Major challenges associated with these antimalarial drugs include the lack of vaccine and the resistance of *Plasmodium falciparum* to these antimalarial drugs (Wicht *et al.,* 2020). The increasing resistance to existing antimalarial drugs has required the development of new chemical compounds with improved antimalarial activity and distinctive mechanisms of action. (Hosseinzadeh *et al*.,2023).

SwissADMET is a free online tool that can help in assessing the drug-likeness and chemistry of drug compounds. Swiss ADME provides an interactive interface that can help find information on ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) (Mvondo *et al*.,2021). Comparisons were conducted for the accuracy of results obtained from ADMET software. PubChem (https://pubchem.ncbi.nlm.nih.gov) refers to an online server providing information about chemical compounds, molecules, and biological activities. The database is managed by the National Center for Biotechnology Information (NCBI) involving the National Library of Medicine. It plays a major role in drug development in various fields including lead identification and compound target profiling. (Kim *et al.,* 2022).

The present study aimed to identify structurally related derivatives of 4-Hydroxylphenyl-3-nitrobenzoate as potential inhibitors of the PfLDH active site using SwissSimilarity screening, molecular docking, and ADMET analysis.

2.0 Materials and Methods

2.1 Swiss Similarity and ADMET Studies

The compounds examined in this study were obtained through a ligand-based virtual screening approach using the SwissSimilarity platform (http://www.swisssimilarity.ch). Originally, approximately 100 bioactive compounds previously identified from *Morinda lucida* in our earlier study (Olarinoye *et al.,* 2026) were screened against *Plasmodium falciparum* Glutathione

reductase (1ONF). Among these compounds, 4-hydroxyphenyl-3-nitrobenzoate exhibited the best docking affinity (–8.3 kcal/mol) and favorable ADMET properties and a total binding energy value of (-19.09 kcal/mol).Using the chemical structure of 4-hydroxyphenyl-3-nitrobenzoate as the query molecule, SwissSimilarity was employed to search for structurally related analogues from publicly available chemical databases integrated within the platform, including compounds with similar molecular structures and pharmacophore features. The screening generated several structurally correlated derivatives, from which seven compounds were selected : A1, (Phenyl salicylate), A2, (Benorilate), A3, (1,4-dihydroxy-3-methylnaphthalen-2-yl 4-aminobenzoate), A4, (2-oxo-2H-naphtho[1,8-bc]furan-6-yl4-nitrobenzoate), A5,[(1S)-2-[(2,3-dimethoxyphenyl)methylamino]-1-(4-nitrophenyl)-2-oxidanylidene-ethyl] prop-2-enoate], A6, (Phenyl aminosalicylate),A7, (5-methanoyl-2-nitro-phenyl) 2-(3-methoxyphenyl)ethanoate), Chloroquine and Lumefantrine. The chemical structures of the selected derivatives were subsequently retrieved in structure-data format from publicly accessible databases such as PubChem (https://pubchem.ncbi.nlm.nih.gov) and prepared for computational analysis. Prior to molecular docking and ADMET evaluation, the ligand structures were converted into appropriate three-dimensional conformations and subjected to geometry optimization to obtain stable conformations suitable for molecular docking studies.

The molecular docking simulation was carried out using Pyrex 0.8 operating on AutoDock grid and AutoDock Vina. The grid constraints used were: size (Å) X = 27.5183, Y = 26.3422, Z =9.3206 and coordinates (Å) X =57.2943, Y = 44.1083, Z = 25.0000 respectively. The 3D structure of the protein was retrieved from the RCSB database (https://www.rcsb.org/). Prior to docking, intrinsic ligand and non-essential molecules were detached using Discovery Studio (Javaid *et al*., 2026).

RSCB PDB database (https://www.rscb.org/), the Protein Target Retrieval 3D structure files of *Plasmodium falciparum* Lactate dehydrogenase (LDH) with PDB ID: 1CET was acquired and saved in pdb file format. Lactate dehydrogenase is an enzyme that is involved in generating energy in the body by facilitating the conversion of pyruvate into lactate in a reversible manner. PfLDH is an essential glycolytic enzyme involved in parasite energy metabolism and is considered a promising antimalarial drug target (Biro *et al*., 2022). Therefore, PfLDH plays a serious role in the glycolytic pathway of the malaria parasite by catalyzing the interconversion of pyruvate and lactate during energy metabolism. The protein was improved through repair, additional hydrogen and side chain atoms were included, secondary structure was assigned, and Ramachandran analysis revealed that the protein structure was good through VADAR server (Nnyigide *et al*., 2022) as shown in Figure 1.

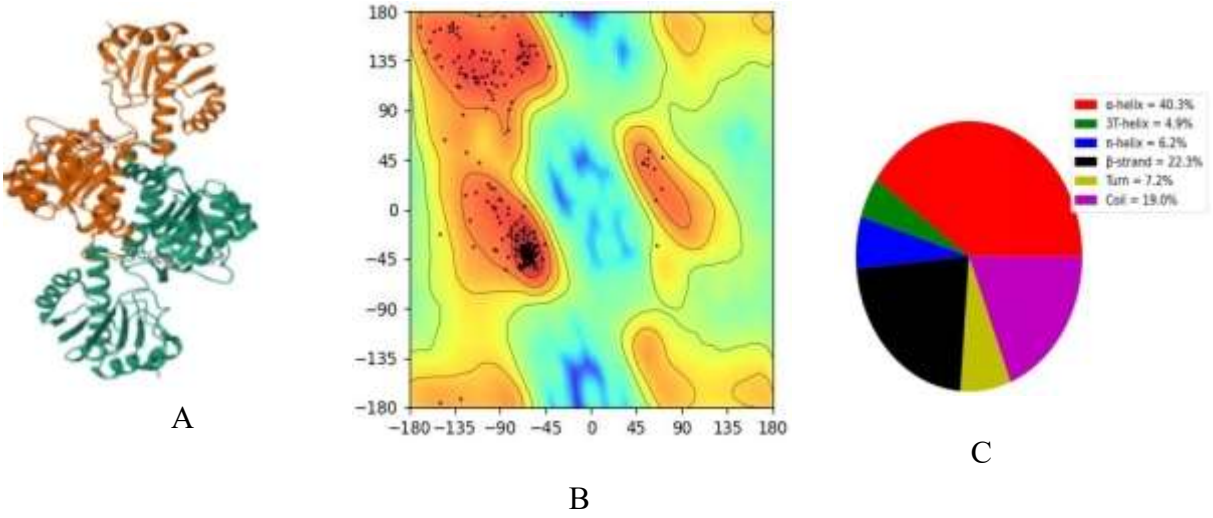


Figure 1: Structural preparation and validation of *Plasmodium falciparum* lactate dehydrogenase (PfLDH; PDB ID: 1CET): (A) clean protein (B) Ramachandran plot and (C) Secondary chain structure.

3.0 Results and Discussion

Following similarity screening, the pharmacokinetic properties of the identified compounds were evaluated using SwissADME and pkCSM. Lipinski's rule of five physicochemical parameters was used to analyze bioactive drug-like compounds with specific biological targets. Based on the rule of five, a drug molecule is expected to have a molecular weight below 500 g/mol (Theerawatanasiriku *et al.,* 2020), logP below 5, HBD below 5, HBA below 10, and TPSA below 140Å^2. As evident in Table 1, all the compounds had excellent molecular weights below 500 g/mol except Lumefantrine, whose molecular weight was 528.94 g/mol. Log p values of all the compounds were less than 5 except Lumefantrine with the value greater than 5, HBD values and HBA values were within the acceptable ranges suggesting favorable oral drug-likeness properties. Therefore, the TPSA of all the compounds is less than 140A^2, meaning most compounds demonstrated acceptable physicochemical and predicted pharmacokinetic properties. They also have good biological membranes crossing ability (Alhyari *et al.,* 2022). The solubility in water is shown by Log S, where the absorption rate is usually higher. Water solubility at 250 °C is efficient in all the compounds of oral drugs. Caco-2 permeability was an important factor, where Caco-2 permeability refers to the human epithelial colorectal adenocarcinoma cell line; it was important in assessing permeability (Kus, *et al*., 2023). High Caco-2 permeability exists in all the compounds except compounds A1 and A6. Human intestinal absorption is the main area for the absorption process. The small intestine percentage value is the absorption value. Percentage value of more than 30% in a compound is considered high, while that of less than 30% is considered low. In Table 1, all the compounds had high absorption values, ranging from 99.273 to 74.444 (Billat *et al*., 2017). The volume of distribution (VDss) refers to an imaginary volume that represents a uniform distribution of a substance at a particular concentration level within human plasma. A higher VDss indicates more extensive distribution of the drug in tissues compared to plasma. If the VDss value is above 0.15, it shows a high level, whereas if below 0.15, it indicates a low level. As illustrated in table one, the VDss range was between 1.332 and -

2.172, having minimum and maximum values respectively (Laborante *et al*.,2025). BBB permeability predicts the ability of compounds to penetrate the central nervous system indicating probable central nervous system penetration. The value above 0.3 shows easy crossing of the brain and the value below -1 shows poor distribution of the compound to the brain. Compounds A2 and A5 demonstrated a higher predicted ability to cross the blood- brain barrier. Conversely, the four compounds (A1, A3, A4, and A 6) poorly distribute to the brain. During metabolism, the substrates of Cytochromes P450 enzymes exist primarily in the liver. All compounds except Chloroquine were predicted not to be CYP2D6 substrates, whereas all compounds reacted with the CYP450 1A2 inhibitor except for compounds A4, A5, and Chloroquine. Drug compound excretion happens through the kidney and liver. The table below shows the total clearance rate values of the compounds, which range between 0.247 and 1.092.

The AMES test is crucial for predicting the potential mutagenicity of a drug candidate (Bhandare *et al*., 2025). All compounds are positive regarding the mutagenic potential except for A3 and A4. No compounds will cause skin sensitization. From the table below, compounds A3, A5, A7, and Chloroquine are positive for hepatotoxicity. Compared with standard antimalarial drugs, the identified derivatives also revealed favorable predicted pharmacokinetic properties. Most compounds satisfied Lipinski's rule of five, exhibited high gastrointestinal absorption, and displayed acceptable bioavailability profiles. In contrast, lumefantrine violated certain drug-likeness criteria due to its relatively high molecular weight (528.94) and LogP value (7.86). Furthermore, compounds A3 and A4 were predicted to be non-mutagenic in the AMES toxicity assessment, suggesting relatively safer pharmacological profiles than some of the reference compounds. These comparative observations suggest that the identified derivatives, particularly A3, possess pharmacokinetic, physiochemical and binding characteristics comparable to or better than several previously reported PfLDH inhibitors. Therefore, these compounds may represent promising scaffolds for further optimization and experimental validation in antimalarial drug development. To further investigate the inhibitory potential of the compounds, molecular docking studies were performed against PfLDH.

Table 1: Lipinski Drug-Likeness and Physicochemical Properties of the Selected Derivatives and Reference Antimalarial Drugs

S/N	Mw	Log P	Gl absorption	BBB	nHBD	nHBA	MR	LogKP (cm/s)	Log S	BS	TPSA (A^2)	NRB	Class
A1	229.23	2.27	High	YES	2	3	4.27	-5.46	-3.68	0.55	72.55	3	S
A2	313.30	2.51	High	No	1	5	83.65	-6.68	-3.50	0.55	81.70	0	S
A3	309.32	2.94	High	No	3	4	88.76	-5.66	-4.32	0.55	92.78	3	M.S
A4	335.27	2.83	High	No	0	6	89.13	-5.58	-5.67	0.55	98.42	4	M.S
A5	400.38	2.10	High	NO	1	7	105.55	-6.61	-3.80	0.55	119.68	0	S
A6	330.42	2.27	High	YES	2	3	5.36	-5.46	-3.78	0.55	84.55	3	M.S
A7	315.28	2.06	High	NO	0	6	83.13	-6.43	-4.24	0.55	98.42	0	M.S
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	0	S

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

Table 2: The PKSCM ADMET properties of the Derivatives

		A1	A2	A3	A4	A5	A6	A7	CHLO	LUME
ABSORPTION	Water solubility	-2.805	-4.488	-3.715	-2.71	-5.295	-2.805	-6.192	-4.249	3.927
	Caco-2 permeability	0.96	-1.126	0.143	1.083	-0.048	0.96	0.439	1.624	1.311
	Intestinal absorption (Human)	93.423	94.139	85.988	99.273	77.444	93.423	94.354	89.95	96.855
	Skin Permeability	-2.817	-3.015	-27.35	-2.733	2.738	-2.817	-2.727	-2.679	-2.929
	P-glycoprotein substrate	YES	NO	YES	YES	YES	YES	NO	YES	NO
	P-glycopro	NO	NO	NO	NO	YES	NO	YES	NO	YES

	tein I inhibitor									
	P-glycoprotein II inhibitor	NO	NO	YES	NO	YES	NO	YES	NO	NO
DISTRIBUTION	VDss (human)	0.225	0.555	-0.347	-2.172	0.555	0.225	0.252	1.332	0.611
	Fraction unbound (human)	0.182	-0.486	0.164	0.141	0.675	0.182	0.031	0.191	0.384
	BBB permeability	-0.032	0.483	-0.794	-0.101	0.756	-0.032	-0.618	0.349	0.861
	CNS permeability	-2.233	-2.343	-2.029	-2.433	0.2829	-2.233	-1.935	-2.191	-3.239
METABOLISM	CYP2D6 Substrate	NO	NO	NO	NO	NO	NO	NO	YES	NO
	CYP3A4 Substrate	NO	YES	YES	NO	YES	NO	YES	YES	YES
	CYP1A2 Inhibitor	YES	YES	YES	NO	NO	YES	YES	NO	YES
	CYP2C19 Inhibitor	NO	YES	YES	NO	YES	NO	YES	NO	NO
	CYP2C9 Inhibitor	NO	NO	YES	NO	YES	NO	YES	NO	NO
	CYP2D6 Inhibitor	NO	NO	YES	NO	NO	NO	NO	YES	NO
	CYP3A4 Inhibitor	NO	NO	NO	NO	YES	NO	NO	NO	NO
EXCR	Total Clearance	0.466	0.498	0.356	0.52	0.707	0.466	0.247	1.092	1.031

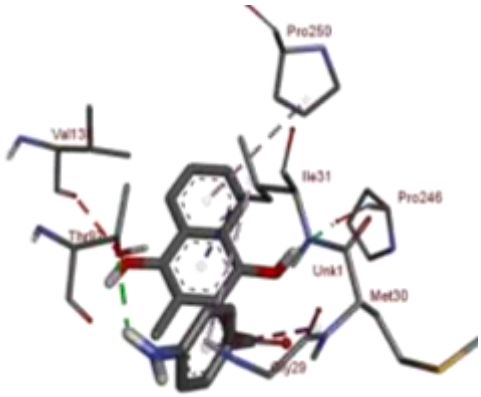
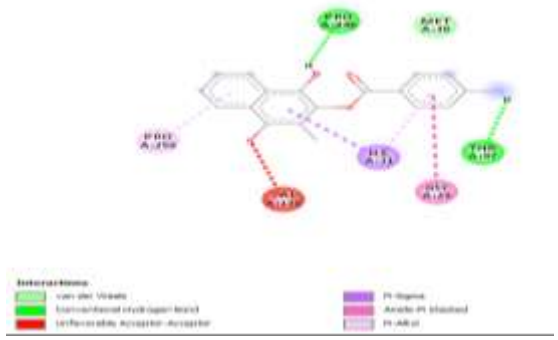
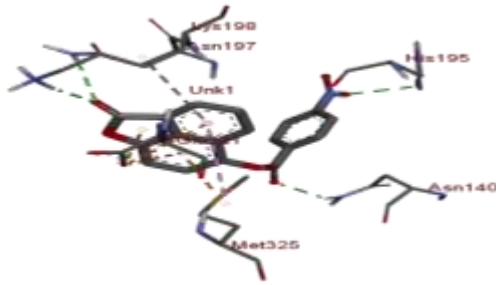
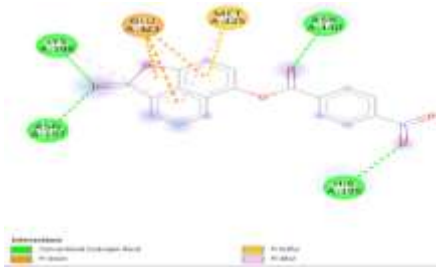
ETIONTOXICITY	Renal OCT2substrate	NO	NO	YES	NO	NO	NO	NO	YES	NO
	AMES toxicity	YES	YES	NO	NO	YES	YES	YES	YES	NO
	Max. tolerated dose (human)	0.14	0.55	0.295	1.012	0.081	0.14	0.342	-0.167	0.074
	HERG I inhibitor	NO	NO	NO	NO	NO	NO	NO	NO	NO
	HERG II inhibitor	NO	YES	YES	NO	NO	NO	YES	YES	NO
	Oral Rat Acute	2.411	2.184	2.585	2.848	2.648	2.411	2.691	2.85	2.429
	Oral Rat	1.089	1.488	2.167	2.926	2.003	1.089	1.114	1.026	1.043
	Hepatotoxicity	NO	NO	YES	NO	YES	NO	YES	YES	NO
	Skin Sensitization	NO	NO	NO	NO	NO	NO	NO	NO	NO

4.0 Molecular Docking Results and Analysis

Molecular docking of the ligands and the standard drugs Chloroquine and lumefantrine were performed against Plasmodium falciparum lactate dehydrogenase (PDB: 1CET). The results were displayed in Table 3. Docking validation was performed by re-docking the co-crystallized ligand into the active site of 1CET. The accuracy of the docking protocol was evaluated, the native ligand in the receptor (1CET) was viewed in the active centre using Discovery studio revealed the active-site grid coordinates of X =27.5183, Y = 26.3422, Y = 9.3206 before and after re-docking of the native ligand with the receptor. The RMSD obtained between the experimental and re-docked poses was less than 2.0 Å, indicating reliable reproduction of the native binding positioning and validating the docking protocol. The binding affinities ranged from 6.1 to 7.7kcal/mol and the inhibition constant (Ki) ranged from 1.83 and 28.46 µM. Among the chosen compounds, A3 had the best binding affinity, according to the molecular docking studies. The binding affinities of the seven derivatives and the two reference standards (Chloroquine and Lumefantrine) that exhibited predicted activity against Lactate dehydrogenase (1CET) receptor (Afolabi *et al*., 2024) are presented in Table 3. The binding energies ranged from −7.7 kcal/mol (A3) to −6.3kcal/mol (A1 to A7). Precisely, A1 showed binding energies of

−6.3 kcal/mol, A2 −7.0 kcal/mol, A3 −7.7 kcal/mol, A4 −7.4 kcal/mol, A5 −7.5 kcal/mol, A6 −6.4kcal/mol and A7 -6.5 kcal/mol. The reference drugs Chloroquine and Lumefantrine displayed binding energies of −6.1 and −7.1 kcal/mol, respectively. A3 interacted with PRO 250 through Pi-Alkyl bond, VAL 138 through unfavorable acceptor- acceptor, PRO246, THR 97 through hydrogen bond, MET 30 through Van der Waals, ILE 31 through Pi- sigma bond, GLY 29 through Amide Pi-stacked.

A4 interacted with LYS 198, ASN 197, ASN 140, HIS 195 through hydrogen bond, GLY 321 through Pi-Anion, MET 325 through Pi-sulfur. A5 interacted with MET 325, PRO 141 through Pi-Alkyl bond, ASN 140, LYS 198 through hydrogen bonding, ASN 197 through Van der Waals, ALA 236 through Pi-alkyl bond, GLY 196 through Pi-sigma bond, HIS 195-carbon hydrogen bond, HIS 195 through Amide Pi-stacked, HIS 195 through Pi-Pi T- shaped. Chloroquine interacted with MET 199, ASP 230 through hydrogen bonding and VAL 233 through Pi-sigma bond. Lumefantrine interacted with HIS 195 through Pi-carbon bond, VAL 138, LEU 163 through Alkyl bond, VAL 240 through Pi-Alkyl bond, TYR 247 through Alkyl bond, and GLY 99 through hydrogen bond. Therefore, A3 demonstrated stronger binding affinity than chloroquine and lumefantrine, suggesting improved stabilization within the PfLDH active site. The docking protocol was validated by re-docking the co-crystallized ligand into the active site of PfLDH and calculating the RMSD between docked and crystallographic poses.

<table>
<tr><td>A3
 
</td><td>  </td></tr>
<tr><td>A4
 
</td><td>  </td></tr>
</table>

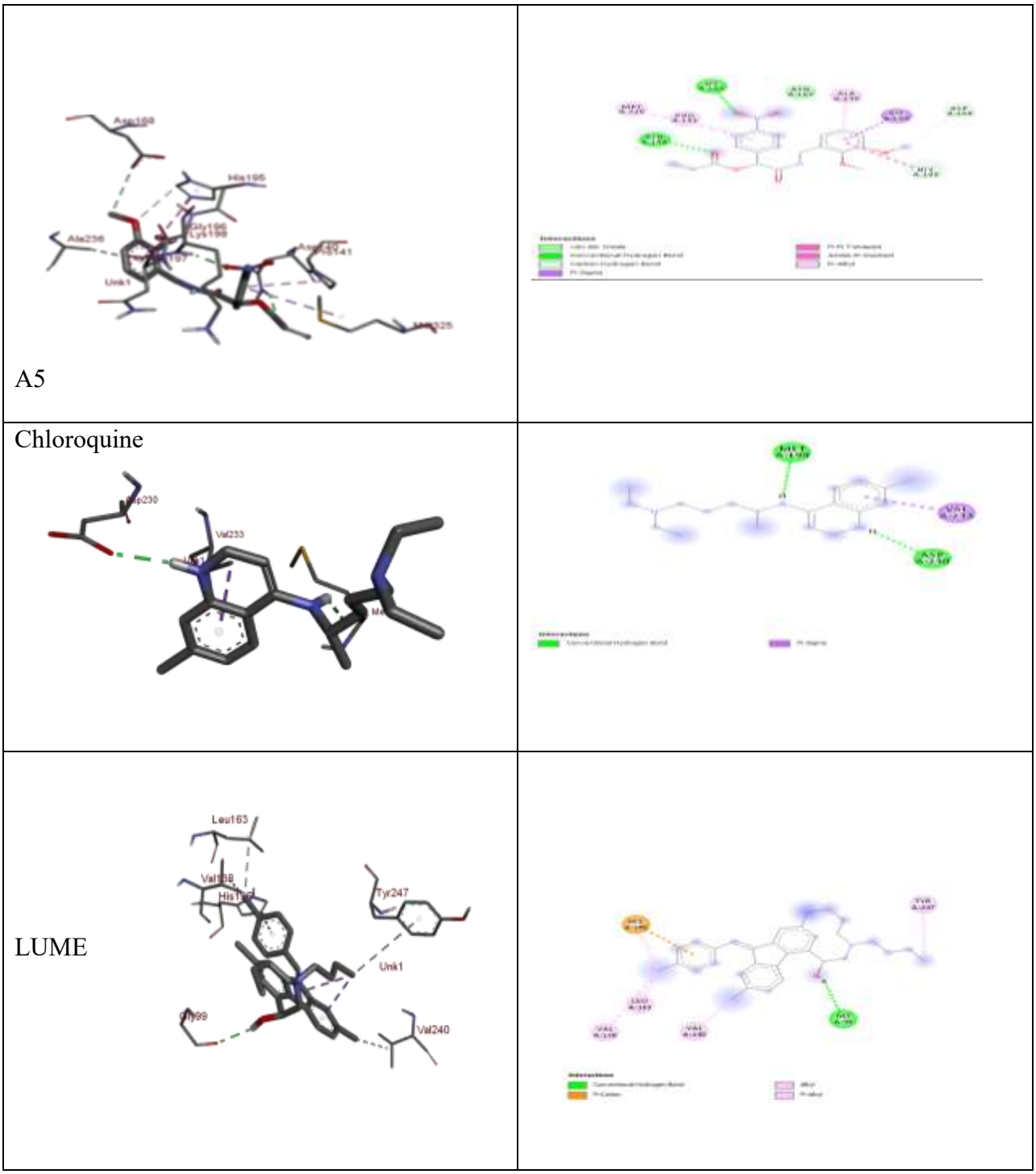


Figure 2: Molecular interaction profiles of compounds A3, A4, A5,Chloroquine and Lumefantrine compounds within the active site of PfLDH (PDB ID:1CET).

Table 3: Binding affinity and non-binding interaction of (1CET) receptor with the ligands

S/N	Binding Affinity ΔG (Kcal/mol)	Inhibition constant Ki(μM)	1CET receptor amino acids forming H-bond with ligand	Electrostatic /Hydrophobic interaction involved
A3	-7.7	1.83	THR 97	PRO 250, VAL 138, PRO 246, MET 30, ILE 31, THR 97, GLY 29
A4	-7.4	4.40	LYS 198, ASN 197, ASN 140	GLY 321, MET 325, LYS 198, ASN 197, ASN 140
A5	-7.5	2.58	ASN 140, LYS 198,	MET 325, PRO 141, LYS 198, ASN 197, ALA 236, GLY 196, HIS 195, ASP 168, HIS 195
Chloro	-6.1	28.46	MET 199, ASP 230	MET 199, ASP 230, VAL 233
Lume	-7.1	5.12	GLY 99	VAL 138, LEU 163, VAL 240, TYR 247, GLY 99

5.0 Conclusion

In this work, 4-hydroxy 3-nitrophenyl benzoate derivatives may serve as prospective inhibitors of lactate dehydrogenase enzymes, to develop novel antimalarial drugs. As predicted by ADMET studies and molecular docking procedure, the ligand 1,4-dihydroxy-3-methylnaphthalen-2-yl) 4-aminobenzoate (A3) showed promising affinity towards the target protein compared to other drugs. Based on ADMET properties, A3 1,4-dihydroxy-3-methylnaphthalen-2-yl) 4-aminobenzoate demonstrated favorable docking and ADMET profiles and may warrant further experimental evaluation. Additionally, the docking results provide preliminary computational insights that require further validation through molecular dynamics simulations and experimental studies.

6.0 References

1. Afolabi, H. A., Busari, A., Alabi, A. A. T., Maradesa, A. T., Adeleke, S., Bayo, A. S., ... & Adegoke, N. A. (2024). Modelling piperide-based derivatives as potential inhibitors of Plasmodium falciparum lactate dehydrogenase: QSAR and docking studies. *Scientific African*, *25*, e02320. https://doi.org/10.1016/j.sciaf.2024.e02320
2. Alemayehu, A. (2023). Biology and epidemiology of Plasmodium falciparum and Plasmodium vivax gametocyte carriage: implication for malaria control and

elimination. *Parasite Epidemiology and Control*, *21*, e00295. https://doi.org/10.1016/j.parepi.2023.e00295

3. Alhyari, D. H. (2022). *Physicochemical and biopharmaceutical characterization of novel derivatives of gallic acid* (Doctoral dissertation).
4. Bhandare, S. D. (2025). Advancements in toxicological risk assessment: integrating Ferguson's principle, computational models, and drug safety guidelines, a comprehensive framework for improving risk assessment and resource management in toxicology. *Toxicology Research*, *14*(3), tfaf065. https://doi.org/10.1093/toxres/tfaf065
5. Billat, P. A., Roger, E., Faure, S., & Lagarce, F. (2017). Models for drug absorption from the small intestine: where are we and where are we going? *Drug discovery today*, *22*(5), 761-775. https://doi.org/10.1016/j.drudis.2017.01.007
6. Biro, G. P. (2022). Oxygen and ATP: the Energy Economy of the Cell. In *Blood substitutes and oxygen biotherapeutics* (pp. 21-32). Cham: Springer International Publishing. https://doi.org/10.1007/978-3-030-94487-4_2
7. Hosseinzadeh, E., Foroumadi, A., & Firoozpour, L. (2023). What is the role of phytochemical compounds as capping agents for the inhibition of aggregation in the green synthesis of metal oxide nanoparticles? A DFT molecular level response. *Inorganic Chemistry Communications*, *147*, 110243. https://doi.org/10.1016/j.inoche.2022.110243
8. Javaid, S., Ali, N., Shahid, S., & Majeed, M. N. (2026). Identification of natural FGFR3 inhibitor for glioma using integrated computational and microRNA regulatory analysis. *Scientific Reports*. https://doi.org/10.1038/s41598-026-45845-y
9. Kim, S., Cheng, T., He, S., Thiessen, P. A., Li, Q., Gindulyte, A., & Bolton, E. E. (2022). PubChem protein, gene, pathway, and taxonomy data collections: bridging biology and chemistry through target-centric views of PubChem data. *Journal of molecular biology*, *434*(11), 167514. https://doi.org/10.1016/j.jmb.2022.167514
10. Kus, M., Ibragimow, I., & Piotrowska-Kempisty, H. (2023). Caco-2 cell line standardization with pharmaceutical requirements and in vitro model suitability for permeability assays. *Pharmaceutics*, *15*(11), 2523. https://doi.org/10.3390/pharmaceutics15112523
11. Laborante, M. (2025). A Review of Quantifying Drug Diffusion in Human Tissues for Assessing Drug Dispersion in the Body.
12. Mvondo, J. G. M., Matondo, A., Mawete, D. T., Bambi, S. M. N., Mbala, B. M., & Lohohola, P. O. (2021). In silico ADME/T properties of quinine derivatives using SwissADME and pkCSM webservers. *Int. J. Trop. Dis. Health*, *42*(11), 1-12. https://doi.org/10.9734/ijtdh/2021/v42i1130497
13. Nnyigide, O. S., Nnyigide, T. O., Lee, S. G., & Hyun, K. (2022). 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. *Journal of Chemical Information and Modeling*, *62*(17), 4232-4246. https://doi.org/10.1021/acs.jcim.2c00313
14. Nosten, F., Richard-Lenoble, D., & Danis, M. (2022). A brief history of malaria. *La presse médicale*, *51*(3), 104130. https://doi.org/10.1016/j.lpm.2022.104130
15. Shibeshi, M. A., Kifle, Z. D., & Atnafie, S. A. (2020). Antimalarial drug resistance and novel targets for antimalarial drug discovery. *Infection and drug resistance*, 4047-4060. https://doi.org/10.2147/IDR.S279605

16. Talapko, J., Škrlec, I., Alebić, T., Jukić, M., & Včev, A. (2019). Malaria: the past and the present. *Microorganisms*, *7*(6), 179. https://doi.org/10.3390/microorganisms7060179
17. Theerawatanasirikul, S., Kuo, C. J., Phetcharat, N., & Lekcharoensuk, P. (2020). In silico and in vitro analysis of small molecules and natural compounds targeting the 3CL protease of feline infectious peritonitis virus. *Antiviral research*, *174*, 104697. https://doi.org/10.1016/j.antiviral.2020.104927
18. Wicht, K. J., Mok, S., & Fidock, D. A. (2020). Molecular mechanisms of drug resistance in Plasmodium falciparum malaria. *Annual review of microbiology*, *74*(1), 431-454. https://doi.org/10.1146/annurev-micro-020518-115546