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In silico analysis of azadirachtin and its analogs on dihydrofolate reductase of *Plasmodium* species

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Abstract: The occurrence of mutations in dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS) genes has led to the emergence of resistance to antifolate antimalarials worldwide. Azadirachtin, a secondary metabolite is an antimalarial constituent of *Azadirachta indica* (Neem tree) that similarly acts on dihydrofolate reductase. The study aimed to conduct *in silico* analysis of the inhibitory potential of azadirachtin-derived compound analogs against DHFR in *Plasmodium* species using techniques such as molecular docking, and drug-likeness using Lipinski rule of 5, prediction of adsorption, distribution, metabolism, and excretion (ADME). The docking analysis was conducted using azadirachtin as a template and twenty-nine ligands of zinc drug-like analogs as well as two clinical drugs, proguanil, and pyrimethamine as positive control ligands. Molecular docking results predicted that the ligands inhibit dihydrofolate reductase enzyme (2BL9) out of which ten ligands were focused based on their binding energy scores. It was observed that azadirachtin yielded seven analogs that showed binding energies higher than azadirachtin at values -10.1, -9.7, -9.5, -9.5, -9.2, and -9.1 kcal/mol except for zinc72320527 which had the same binding energy as azadirachtin whereas the reference ligands, azadirachtin, proguanil, and pyrimethamine showed high affinity to 2BL9 with binding energies of -8.8, -7.7 and -7.3 kcal/mol respectively. They obeyed the Lipinski rule of five and from ADME data, gastrointestinal absorption of the molecules was high except for zinc72320527. The results of the study show that the analogs have potential use as antimalarial agents and could be synthesized for oral formulation with further modifications.

Keywords: azadirachtin; molecular docking; dihydrofolate reductase; *Plasmodium* spp.

1. Introduction

The agents that cause human malaria belong to one of five *Plasmodium* species: *Plasmodium vivax*, *P. ovale*, *P. malariae*, *P. falciparum*, and *P. knowlesi*. In severe cases, malaria can lead to anemia, renal failure, and the impairment of the respiratory and central nervous systems, leading to seizures and loss of consciousness [1]. In the past years, an improved commitment to combat malaria has arisen from governments of endemic countries and international organizations to eradicate the disease, including the application of insecticide-treated mosquito nets and artemisinin-based combination therapy (ACT) [2].

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Resistance to standard antimalarial is increasing at a faster rate than new drugs coming into use. Information regarding the development of resistance to the most effective medicines like artemisinin, mefloquine, and piperaquine has been noticed in East Thailand, Cambodia, and Vietnam, which calls for the development of drug-sensitive agents [3].

Azadirachta indica is an evergreen tree found in India, Africa, and North and South America and has been used in traditional medicine for more than 4000 years [4]. The importance of the neem tree, as it is commonly called, has been recognized by the US National Academy of Sciences, which published a report on its value in 1992 and shown from studies to inhibit *Plasmodium* species [5, 6].

Virtual studies on the chemical structures of antimalarial drugs derived from plant sources have not been investigated significantly in the literature. Virtual screening can predict the activity of analogs and offers a shortcut to synthesizing relevant or potential compounds devoid of a trial-and-error approach.

Molecular docking as a tool is one of such powerful approaches to understanding drug interactions, design, and discovery. It also offers a mechanical study of the effect of

placing a molecule (ligand) into a receptor-binding site of the target or specific region of the DNA/protein such that the interaction is non-covalent [7, 8]. Molecular docking provides a more economical way to find hits by screening large virtual compound libraries through *in silico* methods rather than actual wet lab experiments [9 -11].

DHFR is an ever-present enzyme found in all organisms with few exceptions, such as *Helicobacter pylori*; however, it is an essential enzyme that plays a significant role in the formation of DNA by managing folate agents [12]. Medically, DHFR inhibitors have a long history of use as anticancer agents and as anti-infective drugs against bacterial and protozoal pathogens, and the *Plasmodium* species DHFR enzyme is reliable and the best target for antimalarial drugs [13]. In *Plasmodium* species, DHFR and thymidylate synthase (TS) exists as single-chain bifunctional enzyme. In bifunctional DHFR-TS, individual DHFR and TS domains have polypeptide folds closely related structurally to their respective monofunctional counterparts [14]. It has been reported that the cytochrome P450 (CYP) system is associated with hepatic metabolism and is responsible for detoxifying foreign substances such as drugs, cellular metabolism, and homeostasis. Based on the classification of the enzyme system, CYP1, CYP2, and CYP3 families account for 70% of the total hepatic P450 content, while based on their expression in the liver, it appears that CYP3A accounts for about 30% of the total hepatic P450; CYP2, about 20%; CYP1A2, 13%; CYP2E1, 7%; CYP2A6, 4%; and CYP2D6, 2%. *In silico* predictions provides information on possible metabolic pathways for the drug-protein complex [15]. Therefore, the study aimed to explore the *in silico* (virtual) antimalarial evaluation of azadirachtin and its analogs against dihydrofolate reductase of *Plasmodium falciparum*.

2. Experimental

2.1 Literature search

Azadirachtin has been shown through studies to inhibit *Plasmodium* species. Lucantoni *et al.*, in a study, showed that azadirachtin inhibits *in vitro P. falciparum* and *P. berghei* microgamete exflagellation [7]. Azadirachtin was compared using the following databases and software: PubChem [16], Swiss similarity [17], azadirachtin-analogs viz: - Discovery Studio Visualizer; Protein Data Bank (PDB) [12]; Open Babel GUI software; Supercomputing Facility for Bioinformatics & Computational Biology [18] and AutoDock Vina as shown in table 1.

2.2 Ligand preparation and optimization

The 3D chemical structure of azadirachtin and its analogs were downloaded from the PubChem database [16] in .sdf format. The energy of the compounds was minimized and converted to .pdbq format using Open Babel software. In contrast, discovery studio was used to view the amino acids that bind to the protein. Table1 shows a summary of all the compounds used in this study. Parameters of Lipinski's rule of 5, such as molecular weight, Log P, the number of hydrogen bond donors, and the number of hydrogen bond acceptors, were selected from the Pro Tox-II database for all the compounds [19].

2.3 Protein retrieval and preparation

The crystal structure of the target proteins of Plasmodium was searched and downloaded in .pdb format via the protein data bank site. X-ray crystal structure of *P. vivax* dihydrofolate reductase in complex with pyrimethamine and its derivatives. The unwanted molecules, such as water and ligands in the complex with the protein structures (2BL9) retrieved [12], were removed using Discovery Studio visualizer software (Version 17.2.0), and Open Babel software was used to convert the proteins from .pdb to .pdbq format.

2.4 Docking studies with PyRx

Molecular docking studies were performed on azadirachtin and azadirachtin- analogs with the selected target protein of *P. vivax* dihydrofolate reductase (2BL9) in complex with pyrimethamine and its derivative by an automated docking tool, AutoDock Vina, which employed empirical free energy and a Lamarckian Genetic Algorithm. The docking simulation was repeated three times. The virtual screening with AutoDock Vina complex formation was achieved by allowing all rotatable bonds of the chemical ligands free choice of torsional degrees of freedom and Rapid Grid-Based (RGB) energy evaluation [20].

2.5 Adsorption, distribution, metabolism, excretion (ADME) analyses of lead compounds

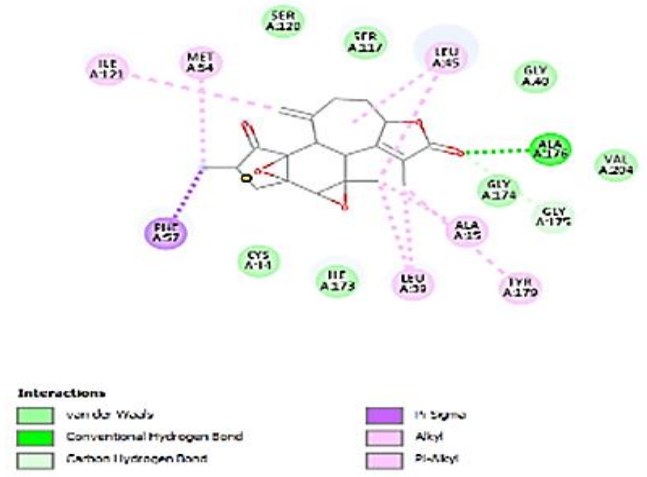
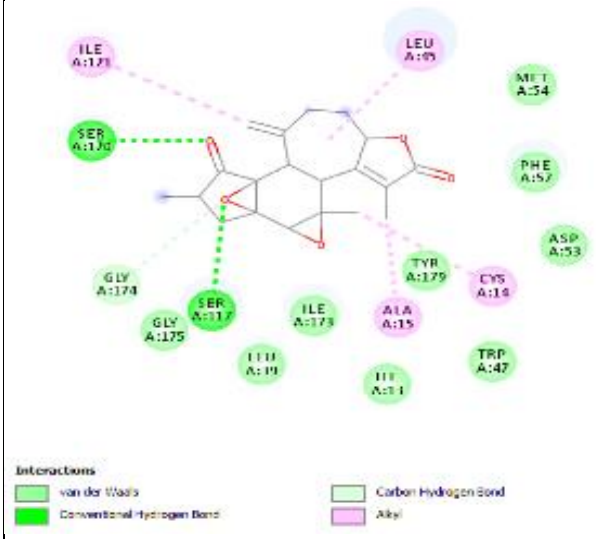
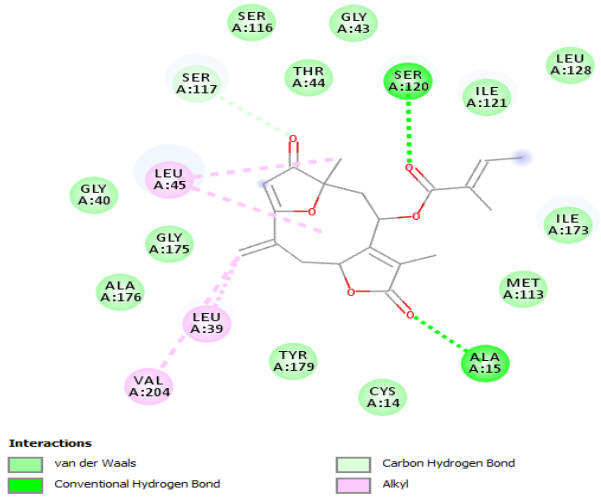
SwissADME [21] was used to study the adsorption and distribution of lead compounds. In the ADME studies, parameters assessed were: molecular weight, bioavailability score, drug-likeness values, blood-brain barrier permeability (BBB permeability), and gastrointestinal tract absorption (GI absorption) to provide information on the potential pharmacokinetic properties of the molecules.

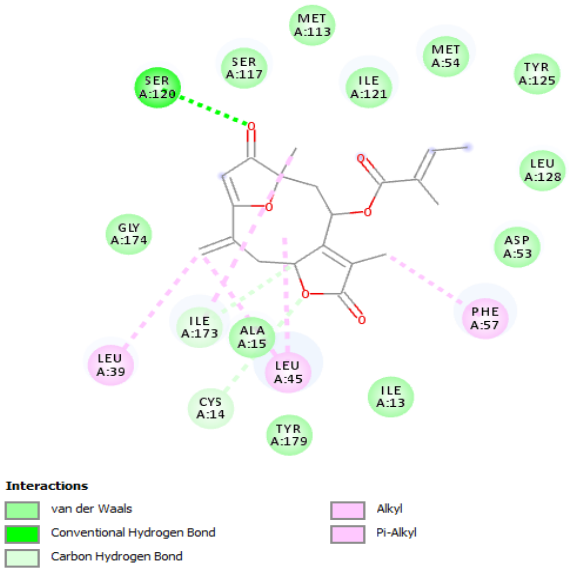
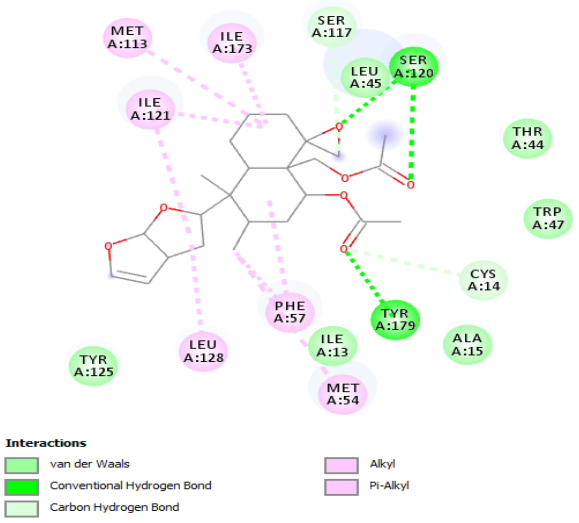
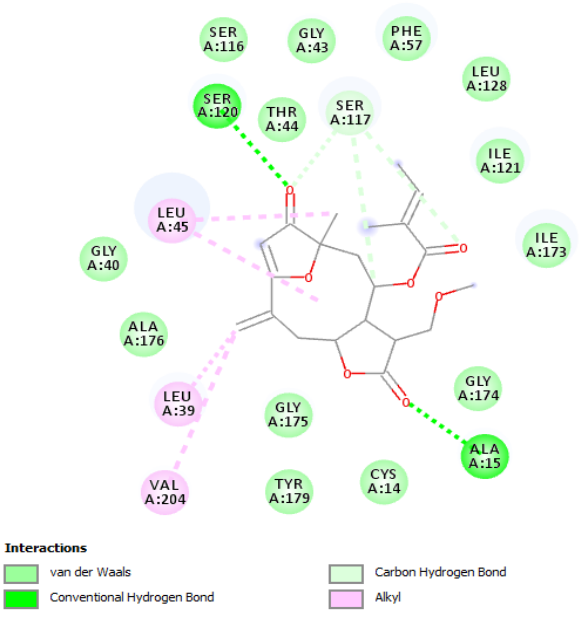
3. Results and discussion

3.1 Literature search

The results from the literature search show that the best-known active compounds in neem (*A. indica*) are azadirachtin, salanin, and nimbin; azadirachtin is stored in the leaves and seeds, and as the most abundant compound in the plant [22]. The first seven azadirachtin-analogs with the best docking scores compared to azadirachtin, the reference compound, and two clinical drugs, *i.e.*, pyrimethamine, are synthetic molecules obtained from zinc-drug-like compounds with 2D structures available in different proguanil were selected for further analysis (table 1). The docking of azadirachtin and azadirachtin-analogs with the target protein of *P. vivax* dihydrofolate reductase (2BL9) using AutoDock Vina in addition to two clinical drugs showed the following results in table 1.

Table 1. Molecular details of seven azadirachtin analogs, reference compounds, and clinical drugs produced by molecular docking.

Sl. No.	Zinc ID/ Compound Name	2D Structure	H-bond residues	Docking score (kcal/mol)
1	Zinc35465209 [**A**]		ALA: A176	-10.1
2	Zinc35465207 [**B**]		SER: A120, SER: A117	-9.7
3	Zinc72320071 [**C**]		SER: A120, ALA: A15	-9.5

4	Zinc72320523 [**D**]		SER: A120	-9.5
5	Zinc49022523 [**E**]		SER: A120, TYR: A179	-9.2
6	Zinc72320522 [**F**]		SER: A120, ALA: A15	-9.1

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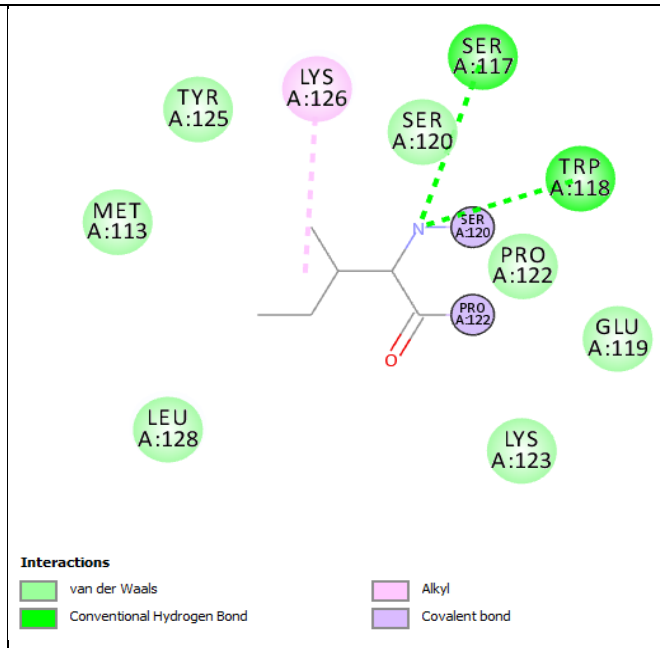
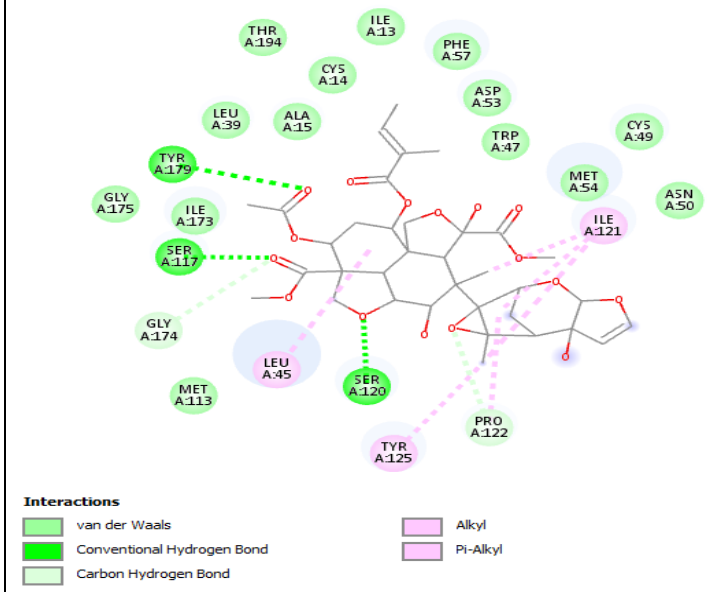
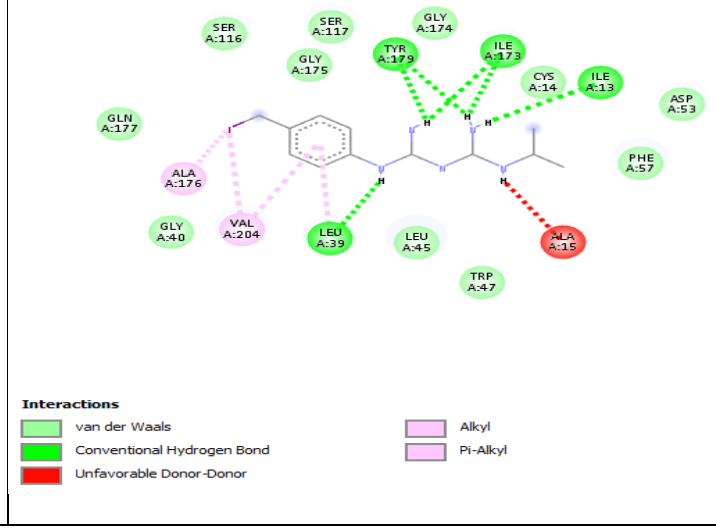
7	Zinc72320527 [**G**]		SER: A117, TRP: A118	-8.8
8	Azadirachtin (reference ligand) [**H**]		TYR: A179, SER: A117, SER: A120	-8.8
9	Proguanil (Clinical drug) [**I**]		LEU: A39, ILE: A13, ILE: A173, TYR: A179	-7.7

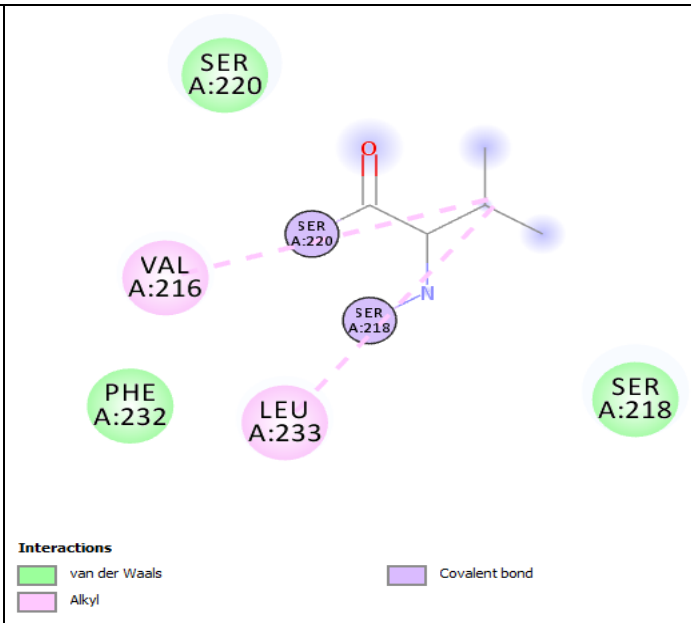
10	Pyrimethamine (Clinical drug) [**J**]		-	-7.3

Table 2. Drug-likeness prediction by SwissADME.

Compounds Name/ Zinc ID	Lipinski's	Ghose	Veber	BA
A-35465209	Yes: 0V	Yes	Yes	0.55
B-35465207	Yes: 0V	Yes	Yes	0.55
C-72320071	Yes: 0V	Yes	Yes	0.56
D-72320523	Yes: 0V	Yes	Yes	0.56
E-49022523	Yes: 0V	Yes	Yes	0.56
F-72320522	Yes: 0V	Yes	Yes	0.56
G-72320527	No: 2V	No: 3V	No: 1V	0.17
H-Azadirachtin (Reference ligand)	Yes: 0V	Yes	Yes	0.55
I-Proguanil (Clinical drug)	Yes: 0V	Yes	Yes	0.55
J-Pyrimethamine (Clinical drug)	Yes: 0V	Yes	Yes	0.56

Lipinski (Pfizer) Ghose (Amgen) Veber (GSK) BA (Bioavailability) V (violations)

3.2 Docking studies with PyRx

The compounds that passed the Lipinski rule of 5 drug-likeness and reference compounds were docked with (2BL9) to form a complex (table 1). Compound A (Zinc35465209) showed the highest docking score, as shown in table 1. The negative value of Gibb's free energy implies a strong bond and spontaneous interaction between 2BL9 and A (Zinc35465209) in the most favorable conformations. It was observed that six of the seven azadirachtin analogs had higher docking scores ranging from -10.1- 9.1 kcal/mol compared to azadirachtin, with a value of -8.8 kcal/mol. In contrast, the clinical drugs, proguanil, and pyrimethamine, had docking scores of -7.7 and -7.3 kcal/mol, respectively, using the PyRx software (table 1). According to Kuntz et al., small molecule docking is a fast way of approximating the docking pose of a ligand within a target protein, which can be used to predict the binding affinity [23]. Although molecular docking allows the prediction of the preferred pose of a ligand inside a receptor binding site by computation of the best energy scores. Some investigators postulate that critical factors such as the role of the solvent (water), the effect of H-bonding, and the system's dynamic nature must be considered to make realistic predictions of binding affinity through docking [24, 25]. A similar docking study on DHFR (receptor) and azadirachtin (ligand) binding affinity showed similar binding energy scores of -8.77 kcal/mol with H-bond interaction at amino acid residues, TYR 170 as against -8.8 kcal/mol and H-bond interaction at TYR A179, SER A117, A120 in our study [26].

3.3 Drug-likeness Prediction by SwissADME

Nine compounds satisfied Lipinski's pioneer rule of five for drug-likeness and Ghose and Veber filters (table 2) while

Table 3. SwissADME predictions of the stuctures.

Compound name /Zinc ID	GI Absorption	BBB permeant	P-gp	CYP 1A2	CYP 2A6	Log K_p (Skin permeation) cm/s
A-35465209	High	Yes	No	No	No	-7.88
B-35465207	High	Yes	No	No	No	-7.88
C-72320071	High	No	No	No	No	-6.63
D-72320523	High	No	No	No	No	-6.63
E-49022523	High	No	No	No	No	-6.63
F-72320522	High	No	No	No	No	-7.23
G-72320527	Low	No	Yes	No	No	-9.92
H-Azadirachtin (Reference ligand)	High	Yes	No	Yes	No	-5.91
I-Proguanil (Clinical drug)	High	No	Yes	No	No	-7.06
J-Pyrimethamine (Clinical drug)	High	Yes	No	Yes	No	-5.91

the compound labeled as G (zinc72320527) violated the rule. The Lipinski (Pfizer) rule of 5 and other filters are used to distinguish between drug-likeness and to predict the probability of success or failure as drug molecules. Different filters for drug-likeness, such as Ghose (Amgen), and Veber (GSK), originated from analyses by major pharmaceutical companies aiming to improve the quality of their proprietary chemical collections [27].

Molecules that follow two or more of the rules, *i.e.*, molecular mass less than 500 Dalton; high lipophilicity (expressed as Log P < 5); < 5 hydrogen bond donors; <10 hydrogen bond acceptors and molar refractivity between 40-130 are likely to be promising drug leads [28]. These filters assess parameters in early preclinical development to reduce cost and prevent late-stage preclinical and clinical trial failures. The bioavailability values ranged between 0.55-0.56 for all the azadirachtin derivatives, and the values were comparable to the reference compound azadirachtin and two clinical drugs (I and J) (table 2). This implies that they are likely readily released from dosage form formulation for absorption into the systemic circulation and drug effectiveness.

3.4 ADME analyses of lead compounds

The threshold values showing effectiveness for the bioavailability score, drug-like values, blood-brain permeability, and gastrointestinal absorption indices should fall within the ranges >30%, > 0.4, and > 0.18, respectively [20]. From table 3, the gastrointestinal absorption of all the molecules appeared to be high except for structure G (azadirachtin derivative). It could be concluded that these molecules, when synthesized, could be suitable for oral formulation as antimalarials. It was observed that analogs A and B could cross the blood-brain barrier suggesting that these molecules can be helpful in the treatment of cerebral malaria (table 3).

SwissADME is reported to estimate the ability of a structure to be a substrate of P-gp or inhibitor of the most important CYP isoenzymes. Major isoforms of CYP reported as substrates for most drug molecules are CYP1A2, CYPC19, CYP2C9, CYP2D6, and CYP3A4). From the literature, CYP and P-gp are believed to cooperate to improve the protection of tissues and organisms [27]. From table 3, the prediction model returned 'No' for analogs A-F implying that the compounds have a high probability of being non-substrates for P-gp except for analog G or non-inhibitors for CYP1A2 and CYP2A6. The inhibition of these isoenzymes could lead to pharmacokinetics-related drug-drug interaction [27]. The predictions for azadirachtin and pyrimethamine returned 'Yes' to cytochrome 1A2, and this could be due to the presence of hydroxyl and ester functional groups in azadirachtin.

In contrast, pyrimethamine has some amino groups responsible for the susceptibility to cytochrome 1A2. From the prediction data on skin permeability coefficient (log K_p), the values ranged between -9.92 to - 6.63 cm/s for analogs compared to -7.06 (proguanil) and -5.91 for azadirachtin and pyrimethamine. The more negative the log K_p, the less skin permeant the molecule is, which can be correlated with molecular size and lipophilicity [27].

4. Conclusion

Azadirachta indica plant was chosen because it is a source of malaria treatment in resource-poor communities worldwide. Azadirachtin, which acts on dihydrofolate reductase in *Plasmodium falciparum* by *in silico* evaluation in this study, has shown that six structural analogs generated

and scored virtually using standard protocols could serve as leads for designing antimalarial drugs. Some of these derivatives can be synthesized and evaluated, thus reducing the cost of the trial-and-error approach.

Declarations

Author Contribution: ORM performed the literature search, did molecular docking, and wrote the original draft of the manuscript; OCP performed the methodology and reviewed the manuscript; POO analyzed the data and interpreted, reviewed the manuscript, and supervised the project; FMA performed the method and collected the data; JOO contributed to the conceptualization and design of the experiments, interpretation of the data, reviewed the manuscript and supervised the project.

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Conflict of Interest: Authors declare no conflict of interest.

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