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Research Article

In-Silico Design and Evaluation of the Anti-Wolbachia Potential of Boron-Pleuromutilins

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Abstract

Filariasis (Lymphatic filariasis and Onchocerciasis) is a common neglected tropical disease caused by parasitic nematodes called filarial worms, which often host the *Wolbachia* bacteria. A good treatment approach seeks *Wolbachia* as a drug target. Here, a computer-aided design of some boron-pleuromutilin analogs was conducted using the ligand-based drug design approach while performing molecular docking investigation and pharmacokinetics analyses to evaluate their drug-likeness properties. The newly designed compounds (**49a**, **49b**, and **49c**) showed improved inhibitory activities (pEC_{50}) over those of the template and the clinically relevant pleuromutilins (retapamulin and lefamulin) in the order; **49b** (pEC_{50} = 9.0409) > **49c** (8.8175) > **49a** (8.5930) > template (**49**) (8.4222) > retapamulin (6.7403) > lefamulin (6.1369). Standard docking performed with OTU deubiquitinase (6W9O) revealed the order of binding energies; **49c** (-88.07 kcal/mol) > **49b** (-84.26 kcal/mol) > doxycycline (-83.70 kcal/mol) > template (-82.57 kcal/mol) > **49a** (-78.43 kcal/mol) > lefamulin (-76.83 kcal/mol) > retapamulin (-76.78 kcal/mol), with the new compounds all showing good pharmacological interactions with the receptor's amino acids. The new analogs were also predicted to be orally bioavailable with better pharmacokinetic profiles than the template, retapamulin, lefamulin, and doxycycline having no more than one violation of Lipinski's ROF. Therefore, the newly designed compounds could be considered potential anti-filarial drug candidates.

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INTRODUCTION

Lymphatic Filariasis (LF), also known as elephantiasis and onchocerciasis (river blindness), are common Neglected Tropical Diseases (NTD) caused by some parasitic nematode worms[1]. Filarial worms such as *Wuchereria bancrofti*, *Brugia timori*, and *Brugia malayi* are the causative organisms for LF and are usually transmitted by the *Culex* mosquitoes. Onchocerciasis, on the hand, is caused by *Onchocerca volvulus* being transmitted from one person to another by blood-feeding blackflies[2]. Elephantiasis alone is responsible for not less than 2.8 million disabilities globally, while River blindness is the world's second leading infectious cause of blindness[3].

The global program intended to eliminate these filarial diseases started far back through the Mass Drug Administration (MDA) of the combination therapy; ivermectin, albendazole, and diethylcarbamazine, either as a dual (annual to bi-annual) or triple-drug (once every three years) treatment[3,4]. However, it became unlikely that the MDA regimen would be enough to eliminate filariasis in all endemic areas, majorly due to their inability to kill the macro-filarial[5]. Given the current scenario, a macro-filaricidal agent is required to kill adult worms and drastically reduce both diseases' elimination periods[6]. Fortunately, one unique characteristic of these filarial worms is their symbiotic co-existence with a known bacterium called

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Wolbachia[7]. In the search for new anti-filarial drugs, some researchers have chosen *Wolbachia* as an anti-filarial drug target. Previous research has shown that eliminating *Wolbachia* from the host filarial nematodes leads to anti-filarial effects by reducing adult worm's lifespan[8,9]. Although the anti-bacteria drug doxycycline has been used clinically for the treatment of filarial diseases over the years, the treatment method is not efficient enough for use through MDA owing to its requirement for extended treatment periods (4-6 weeks) as well as contraindications in pregnancy and children[9]. Therefore, advances in developing new anti-*Wolbachia* agents with short treatment periods and reduced complications are necessary.

Ubiquitination is a biological process that significantly regulates several cellular processes in living cells, especially eukaryotes[10]. Manipulation of the host ubiquitin signaling is often observed amongst bacterial and viral pathogens, including *Wolbachia*. This manipulation is possible because most pathogens possess deubiquitinases that enable them to subvert host signaling[11]. As a result, the viability of bacteria within the host may be seriously affected by deubiquitinase inactivation. A common deubiquitinase is Ovarian Tumor (OTU) deubiquitinase[11,12]. Pleuromutilin was first reported in 1951 from the basidiomycetes *Pleurotus mutilis* (FR.) Sacc and *Pleurotus passeckerianus* Pilat[13]. Pleuromutilin and its analogs are antibacterial drugs that are inhibitors of protein synthesis in bacteria. Examples of antibiotics in this class include retapamulin, valnemulin, and tiamulin[14]. In the mid-1970s, much work was reported on using pleuromutilins as antibiotics for veterinary purposes only[13]. Since then, several works have been undertaken to develop derivatives of the base structure for human use. Retapamulin became the first approved pleuromutilin antibiotic for human use, approved by the FDA in 2007[15]. Pleuromutilins have generally been reported to show potency against Gram-positive and some fastidious Gram-negative organisms[15]. In 2021, Ugbe *et al*.[16] carried out the activity modeling, molecular docking, and pharmacokinetic studies of some boron-pleuromutilin derivatives as anti-*Wolbachia* agents with the potential for the treatment of LF and onchocerciasis.

Computer-aided modeling approaches such as QSAR modeling, molecular docking, drug-likeness properties prediction, molecular dynamics (MD) simulation, homology modeling, and others play a crucial role in drug discovery owing to their advantages over the conventional methods in terms of timeliness, cost-effectiveness, and reliability[17,18]. In the present study, therefore, OTU deubiquitinase from *Wolbachia pipientis* wMel with PDB ID 6W9O was adopted as the therapeutic protein target for the newly designed boron-pleuromutilin analogs. The crystal structure of OTU deubiquitinase determined by X-ray diffraction and expressed in *Escherichia coli* was obtained from the RCSB protein data bank and used in this study[11]. This work focuses on the ligand-based design of some boron-pleuromutilin analogs as novel *Wolbachia* inhibitors while subjecting them to molecular docking investigation, oral bioavailability test, and ADMET properties prediction to evaluate their pharmacological and drug-likeness properties.

MATERIALS AND METHODS

Materials

The hardware used was an HP laptop computer with the following specifications: Processor (Intel® Core™ i5-4210U CPU @1.70GHz 2.40 GHz), Installed RAM (8.00 GB), System Type (64-bit operating system, x64-based processor), Edition (Windows 10 Home Single Language), Version 21H2. Software used includes ChemDraw Ultra v. 12.0.2, Spartan '14 v. 1.1.4, Biovia Discovery Studio Visualizer v. 16.1.0.15350, and Generic Evolutionary Method for molecular docking (iGEMDOCK). The online web servers; http://www.swissadme.ch/index.php and http://biosig.unimelb.edu.au/pkcsm were used for the pharmacokinetics properties prediction[19,20].

Methods

Design template

From the results of our previous work on the anti-*Wolbachia* activity modeling of 52 boron-pleuromutilin derivatives[16], compound **49** (**Figure 1**) with a predicted activity (pEC_{50}) value of 8.4220 and a relatively better pharmacokinetic profile was identified as the template for designing improved derivatives. The QSAR model equation and its associated molecular descriptors, as obtained from our previous study[16], were presented in **Equation 1** and **Table I**, respectively.

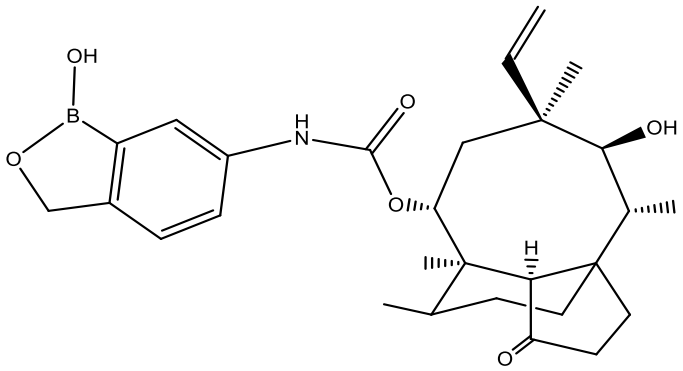


Figure 1. Two-dimensional structure of the template molecule (**49**).

$$pEC_{50} = 18.608123445 \times SpMax3\_Bhm + 38.931870819 \times SpMin3\_Bhs + 1.297730563 \times minHBint5 - 1.288520115 \times mindO - 2.058961109 \times MLFER\_BO + 0.199866243 \times RDF75v - 0.664720197 \times L3i - 107.380579189 \quad \textbf{[1]}$$

Table I. The QSAR model equation and the associated molecular descriptors

S/No	Symbol	Descriptor	Class	Mean Effect
1	SpMax3_Bhm	Largest absolute eigenvalue of Burden modified matrix - n 3 / weighted by relative mass	2D	0.5865
2	SpMin3_Bhs	Smallest absolute eigen value of Burden-modified matrix—n 3/weighted by the relative I-state	2D	0.5920
3	minHBint5	Minimum E-State descriptors of strength for potential Hydrogen Bonds of path length 5	2D	-0.0011
4	mindO	Minimum atom-type E-State: = O	2D	-0.1479
5	MLFER_BO	Overall or summation solute hydrogen bond basicity	2D	-0.0444
6	RDF75v	Radial distribution function - 075 / weighted by relative van der Waals volumes	3D	0.0279
7	L3i	2nd component size directional WHIM index/ weighted by relative Sanderson electronegativities	3D	-0.0130

Drug design

Three boron-pleuromutilin analogs were designed using the ligand-based design approach by substituting, adding, and inserting substituent(s) into the template (**49**). The various modifications were made at positions 3, 4, and 12 of the structural template (**Figure 2**). Compound **49a** was designed by modifying the 12-position of the pleuromutilin core by introducing methyl group (CH_3-) as R_1. Also, substituting hydrogen at position 4 of the benzoxaborole group with a methyl group (R_2) and introducing a methylene group (-CH_2) as R_1 resulted in **49b**. Inserting a methyl group (R_3) at position 3 of the benzoxaborole group while also keeping R_1 as methyl group produced compound **49c**.

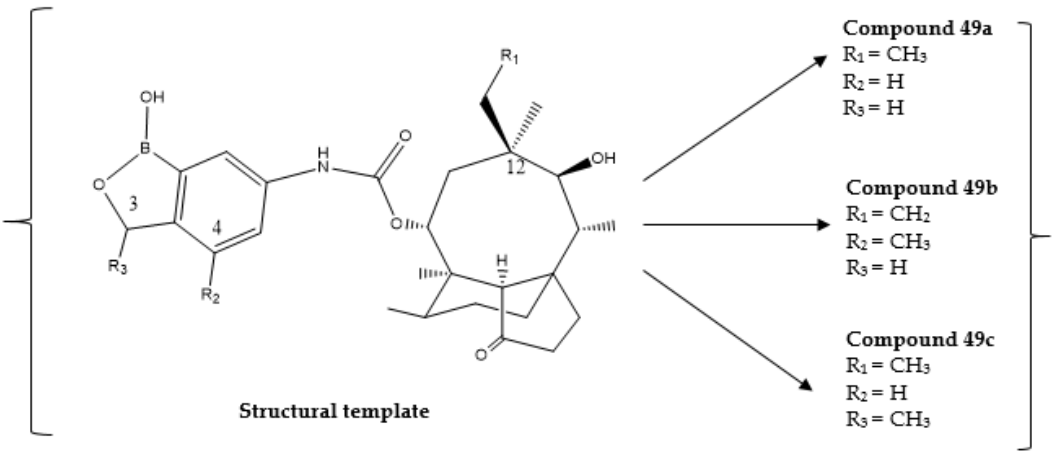


Figure 2. The design schemes.

Preparation of the ligands and descriptors calculation

The molecular structures of the template (**49**), newly designed, and the reference compounds (lefamulin, retapamulin, and doxycycline) were first drawn using ChemDraw Ultra, saved as MDL mol file format, and after that, fed separately into the Spartan software for energy minimization and geometry optimization. The structures were then pre-optimized using Molecular Mechanics Force Field (MMFF) before the optimization using Density Functional Theory (DFT) with a B3LYP/6-31G basis set[21-23]. The resulting stable conformations of the various analogs were saved in MDL SD and PDB file formats for subsequent analyses involving descriptor calculation and molecular docking study, respectively. The resulting data in SD file format were then fed into the Pharmaceutical Data Exploration Laboratory (PaDEL)-descriptor software to generate the descriptor pool from where the values of the seven descriptors were extracted16.

Preparation of the protein receptor and molecular docking investigation

The crystal structure of OTU deubiquitinase (PDB ID 6W9O) was obtained from the RCSB Protein Data Bank in PDB file format and then prepared separately using the Biovia Discovery Studio Visualizer by excluding water molecules and co-crystallized ligands found within the protein structures[20]. The receptor's Chain A was utilized. A Molecular docking investigation was performed between the receptor and the prepared ligands using the iGEMDOCK tool. iGEMDOCK is a program for computing a ligand conformation and orientation relative to the target protein's active sites. Here, the blind docking approach was used with the docking accuracy parameter settings for standard docking. This setting specified a population size of 200, a number of generations equal to 70, and a number of solutions equal to 2. GEMDOCK is an automatic system that generates all related docking variables, such as atom formal charge, atom type, and the ligand-binding site of a protein[24]. The resulting protein-ligand interaction profiles and docked poses were analyzed using the iGEMDOCK's post-screening analysis tool and the Biovia Discovery Studio Visualizer[25,26].

Prediction of pharmacokinetic properties

Drug-likeness and ADMET properties prediction are necessary for the initial stage of drug discovery because only molecules with good pharmacokinetic profiles make the pre-clinical phase of drug research[21]. The present study predicted the pharmacokinetic properties of the lead molecule, the newly designed, and the reference compounds by employing http://www.swissadme.ch/index.php and http://biosig.unimelb.edu.au/pkcsm for drug-likeness and ADMET profiling respectively. Lipinski's 'rule of five' (ROF), a widely used criterion for oral bioavailability, was used to assess the newly designed compounds for oral bioavailability[16,18].

RESULTS AND DISCUSSION

Drug design and activity/affinity prediction

Three new analogs of boron-pleuromutilin (**49a**, **49b**, and **49c**) were designed by the Ligand-based drug design method. The QSAR model (**Equation 1**) was used to predict the binding activities of the various compounds, while the binding energy of interactions was obtained from the docking simulation. The molecular structures, predicted bioactivities (pEC_{50}), and binding energies of the template, newly designed compounds, and the two clinically relevant pleuromutilins, as well as the standard drug (doxycycline), were presented in **Table II**, while the calculated values of the various descriptors were shown in **Table III**.

The binding activities of the various compounds were predicted adequately by the QSAR model equation (**Equation 1**). The predicted pEC_{50} of all the newly designed compounds were greater than those of the Template and the reference compounds in the order; **49b** (pEC50 = 9.0409) > **49c** (8.8175) > **49a** (8.5930) > template (**49**) (8.4222) > retapamulin (6.7403) > lefamulin (6.1369). The contribution of each descriptor to the inhibitory activities of the various compounds is expressed by the value of its Mean Effect (ME). From **Table I**, SpMin3_Bhs was reported as having the largest positive ME value of 0.592016. SpMin3_Bhs is the smallest absolute eigenvalue of Burden modified matrix – n 3/ weighted by relative I-state. As such, introducing an electronegative atom or electron withdrawing group is said to decrease the value of its coefficient, which in turn decreases the molecules' anti-proliferative activities[27]. This implies that an electron-donating group will increase the molecule's inhibitory activity. The newly designed compounds' relatively higher predicted pEC_{50} values may

be attributed to introducing of the methyl moiety, an electron-donating group that releases electrons to the ring system through a positive inductive effect. Therefore, this provides a reasonable explanation for their high anti-*Wolbachia* activity.

Table II. Molecular structures, predicted pEC_{50}, and binding energies of the template, newly designed, and reference compounds

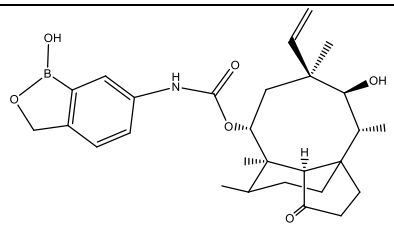
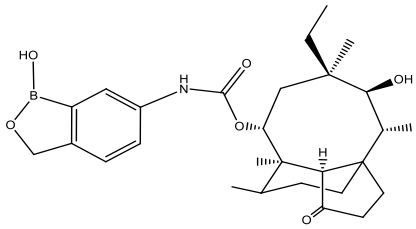
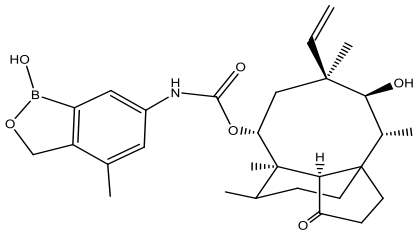
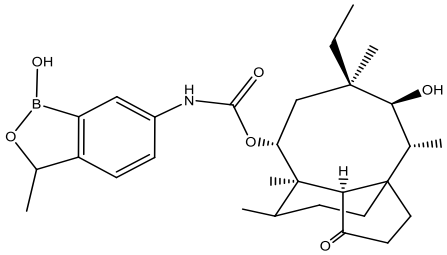
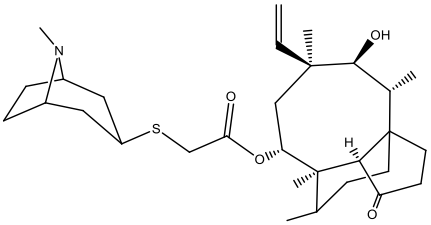
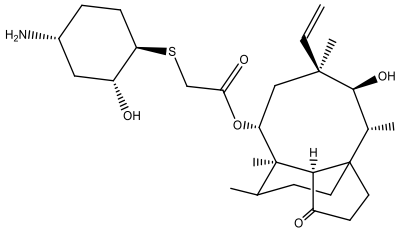
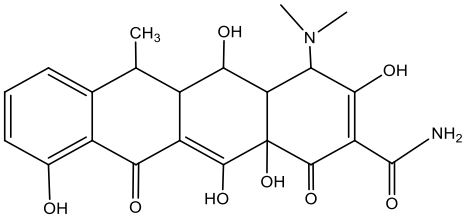
Compound ID	Molecular structure	Predicted pEC_{50}	Binding energy
Template (**49**)		8.422169	-82.57
49a		8.592983	-78.43
49b		9.040934	-84.26
49c		8.817465	-88.07
Retapamulin		6.740265	-76.78
Lefamulin		6.136877	-76.83
Doxycycline		-	-83.70

Table III. Calculated descriptors for the template, newly designed, and reference compounds

Comp ID	SpMax3_Bhm	SpMin3_Bhs	minHBint5	mindO	MLFER_BO	RDF75v	L3i
Template (**49**)	3.615	1.7597	0.0712	13.287	1.893	12.627	2.365
49a	3.6018	1.7625	-0.0887	13.313	1.857	14.524	2.2208
49b	3.6152	1.7597	0.02824	13.399	1.881	16.619	2.3738
49c	3.6023	1.7833	-0.1211	13.378	1.877	13.364	2.5185
Retapamulin	3.6543	1.7172	-0.1047	13.47	2.223	14.381	2.3145
Lefamulin	3.6147	1.7107	-0.5427	13.302	2.365	19.119	2.1869

Molecular docking study

A molecular docking simulation was conducted between the receptor, OTU deubiquitinase (6W9O), and the various compounds using the iGEMDOCK molecular docking tool to provide insight into the mode of binding interactions at the ligand-receptor interface and the associated binding energies. The results (binding energies) of the docking investigation were included in **Table II**, while **Table IV** and **Figures 3** to **9** showed the predicted pharmacological interaction profiles of the various compounds with the target protein (6W9O). Binding energies of the receptor-ligand interactions are necessary to describe how well ligands fit into active sites of the target protein to form the most energetically stable drug-receptor complex[28]. The receptor-ligand binding process is spontaneous, indicated by the negative values of the binding energy change[28]. Hence, the potential drug candidate's chances to initiate protein biochemical action/reaction increase as the binding energy becomes more negative[26].

Table IV. Predicted pharmacological interaction profiles of the various compounds with the protein target (6W9O)

Comp ID	Hydrogen bond interactions			Hydrophobic interactions
	Amino acid	Type	Distance (Å)	
Template	ARG-122	Conventional	2.19, 2.67, 2.69	TRP-123 (π-π stacked), π-alkyl (TYR-113, ARG-122), ARG-122 (steric bump), ASN-112 (Acceptor-acceptor clash)
	TRP-123	Conventional	3.28	
	TRP-123	π-donor	2.33	
49a	TYR-171	π-donor	3.88	TYR-171 (π-π T shaped), Alkyl (ARG-83, LYS-140, LEU-159)
	ASN-172	Carbon-hydrogen	2.91	
	LYS-187	Conventional	2.81	
49b	SER-163	Conventional	3.90	LYS-166 (Alkyl)
	TYR-171	Conventional	3.72	
49c	SER-155	Carbon-hydrogen	3.36	HIS-157 (π-π T shaped), HIS-157 (π-Sigma), π-alkyl (ALA-168, TYR-176), Alkyl (PRO-39, LYS-173, VAL-174)
	HIS-157	Conventional	4.89	
	VAL-174	Conventional	3.34, 4.99	
Retapamulin	HIS-157	Carbon-hydrogen	4.17	HIS-157 (π-sigma), π-alkyl (TYR-176, HIS-157), Alkyl (LEU-156, VAL-174, TYR-176, LYS-173, ALA-168), HIS-157 (Miscellaneous)
	ALA-168	Carbon-hydrogen	5.68	
	VAL-174	Conventional	3.93	
Lefamulin	LYS-140	Conventional	5.78, 5.84	Alkyl (LEU-159, LYS-166, LYS-140)
	ASP-175	Carbon-hydrogen	5.07	
	ASP-178	Conventional	4.23	
Doxycycline	CYS-134	Conventional	3.81	LYS-138 (Alkyl), LYS-140 (π-alkyl)
	GLU-135	Carbon-hydrogen	3.95	
	LYS-138	Conventional	3.97	
	VAL-139	Conventional	5.56	
	ASN-162	Conventional	3.53, 5.26, 5.39	

Analyses of the docking results in **Table II** revealed that compounds **49b** and **49c** showed relatively higher binding energies than the template, reference pleuromutilins, and reference drug doxycycline in the order; **49c** (-88.07 kcal/mol) > **49b** (-84.26 kcal/mol) > doxycycline (-83.70 kcal/mol) > template (-82.57 kcal/mol) > **49a** (-78.43 kcal/mol) > lefamulin (-76.83 kcal/mol) > retapamulin (-76.78 kcal/mol). **Table IV** and **Figures 3** to **9** showed the predicted pharmacological interaction profiles of the various compounds with the target protein. In general, as seen in **Table IV**, the interactions between these molecules (ligands) and the protein's amino acid residues were characterized by hydrogen bonding (H-bonding), hydrophobic interactions, and Van der Waals interactions, which are highly desirable for the reversibility of drug-receptor binding. H-bonds, alongside hydrophobic interactions, play a vital role in docked complex stabilization and enhancing the binding affinity of the ligand at the ligand-receptor interface[29]. In addition, H-bond plays a crucial role in determining the specificity of ligand binding[30]. The binding profile of the lead molecule (**Figure 3**) contained some unfavorable interactions, steric bump with ARG-22 at an interaction distance of 4.82Å, and acceptor-acceptor clash with ASN-112 at 4.67Å. All the interactions observed in the binding profiles of the newly designed and the reference compounds were favorable. The new

analogs could not compete favorably with the reference drug doxycycline regarding hydrogen bonding interactions but clearly showed more hydrophobic interactions than doxycycline. Therefore, the newly designed analogs have demonstrated adequate binding interactions with the target protein (OTU deubiquitinase), indicating their potential to arrest the protein receptor, an important factor that governs several activities essential for the viability of the bacteria (*Wolbachia*).

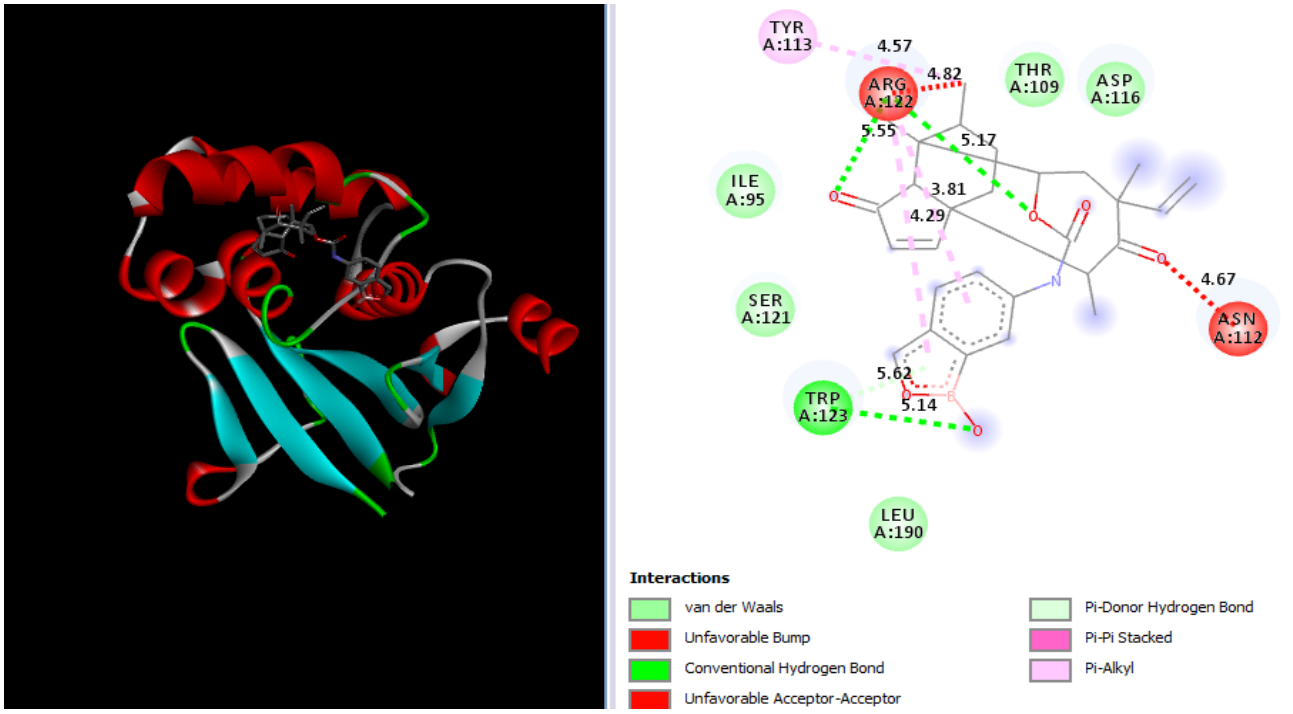


Figure 3. Binding interactions between 6W9O and the template (**49**).

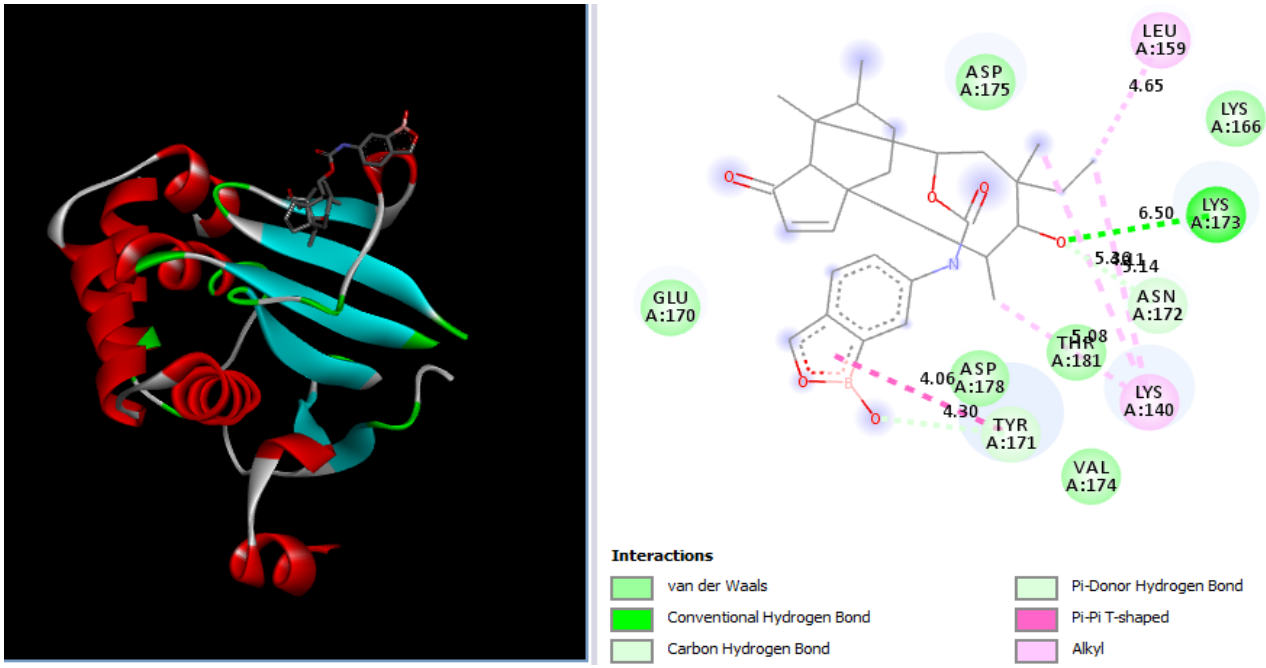


Figure 4. Binding interactions between 6W9O and compound **49a**.

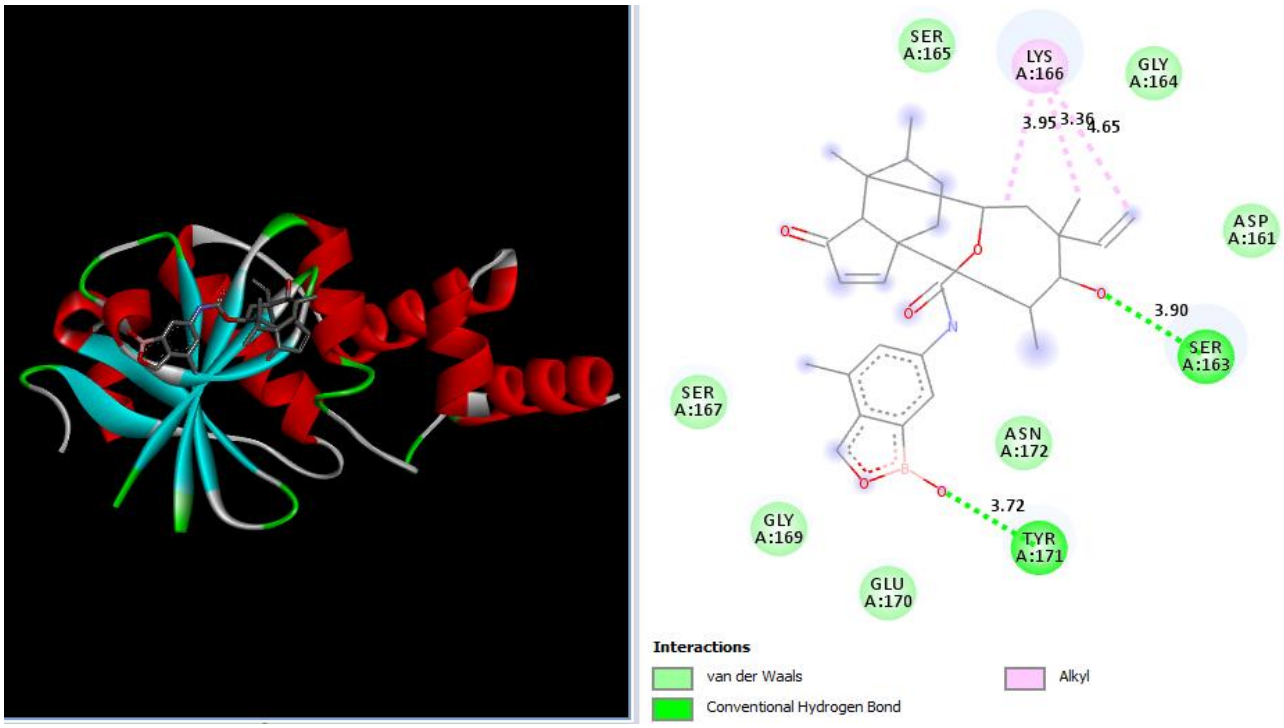


Figure 5. Binding interactions between 6W9O and compound **49b**.

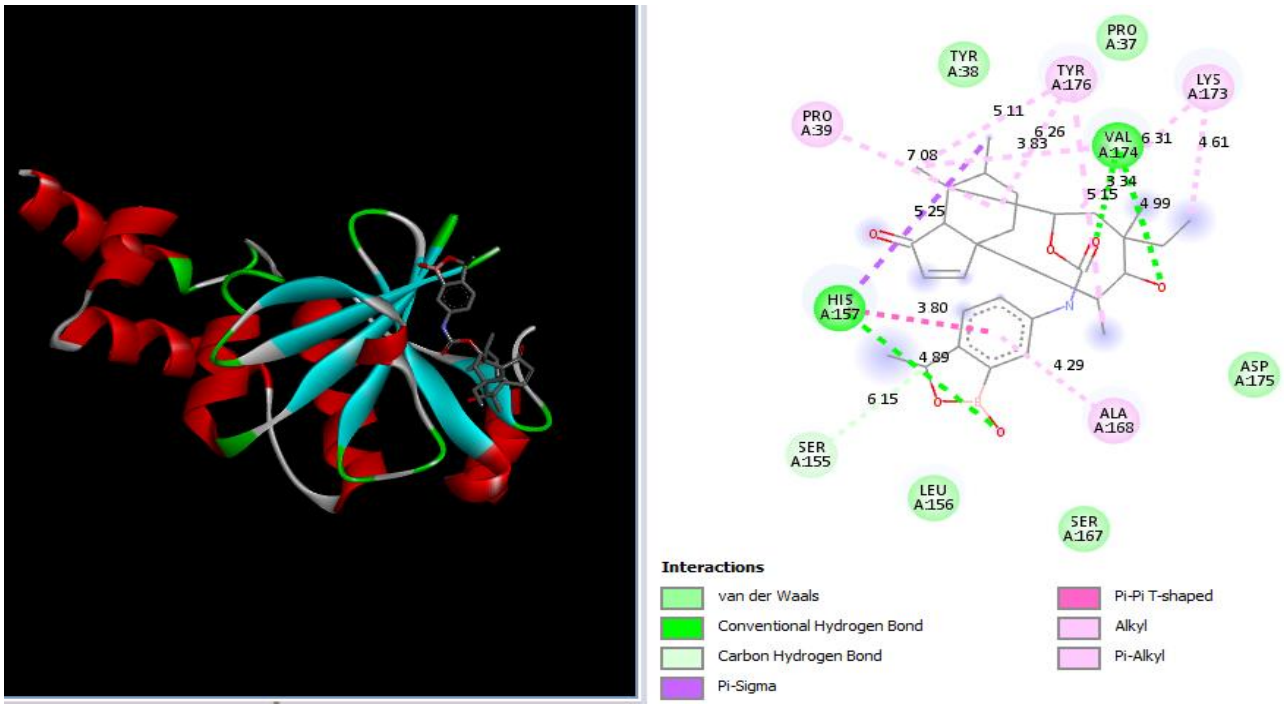


Figure 6. Binding interactions between 6W9O and compound **49c**.

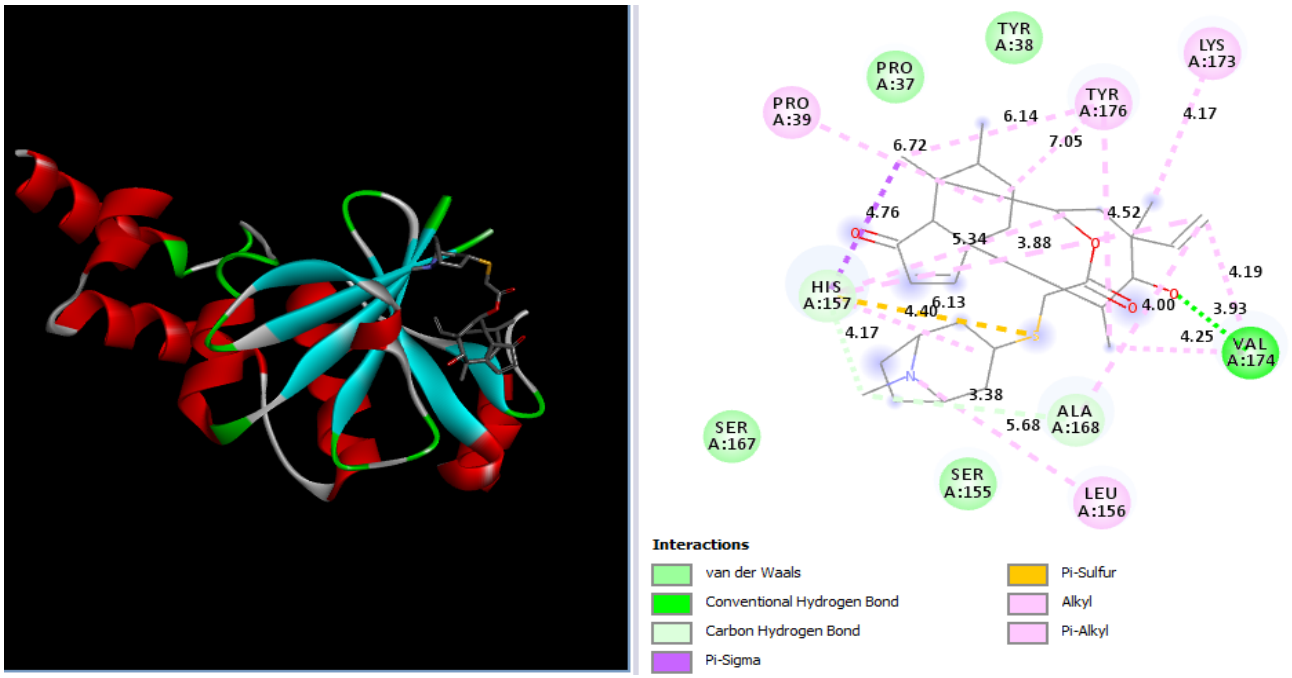


Figure 7. Binding interactions between 6W9O and retapamulin.

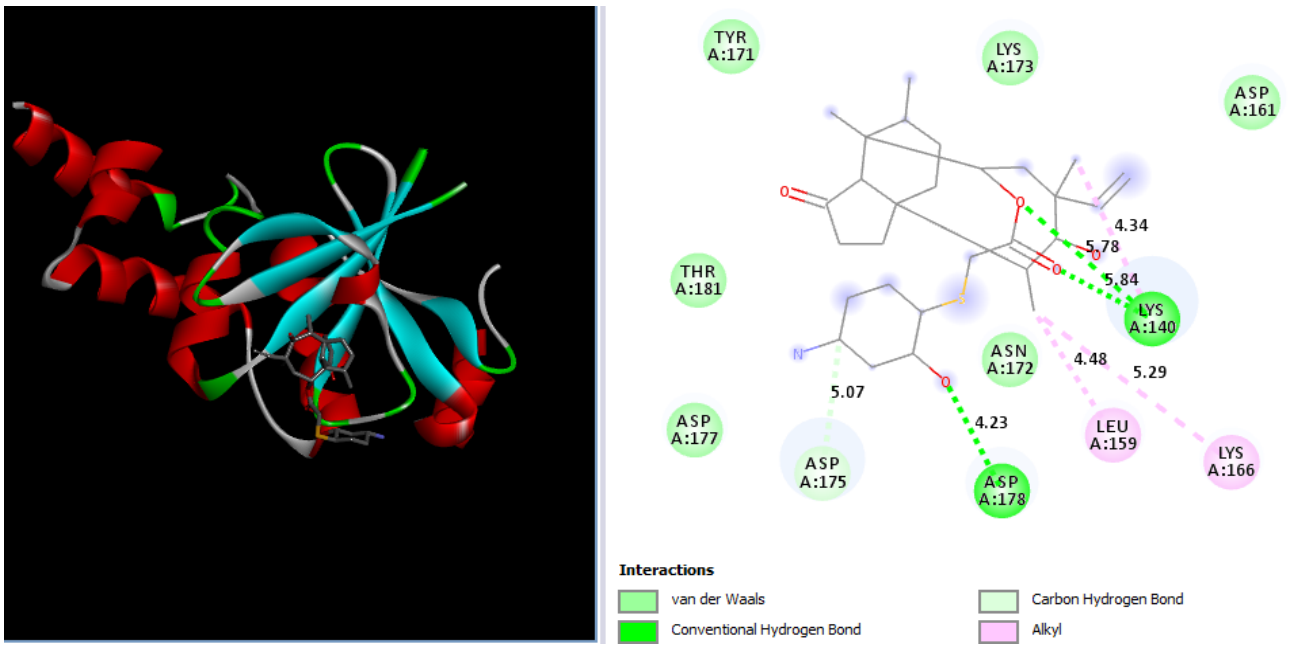


Figure 8. Binding interactions between 6W9O and lefamulin.

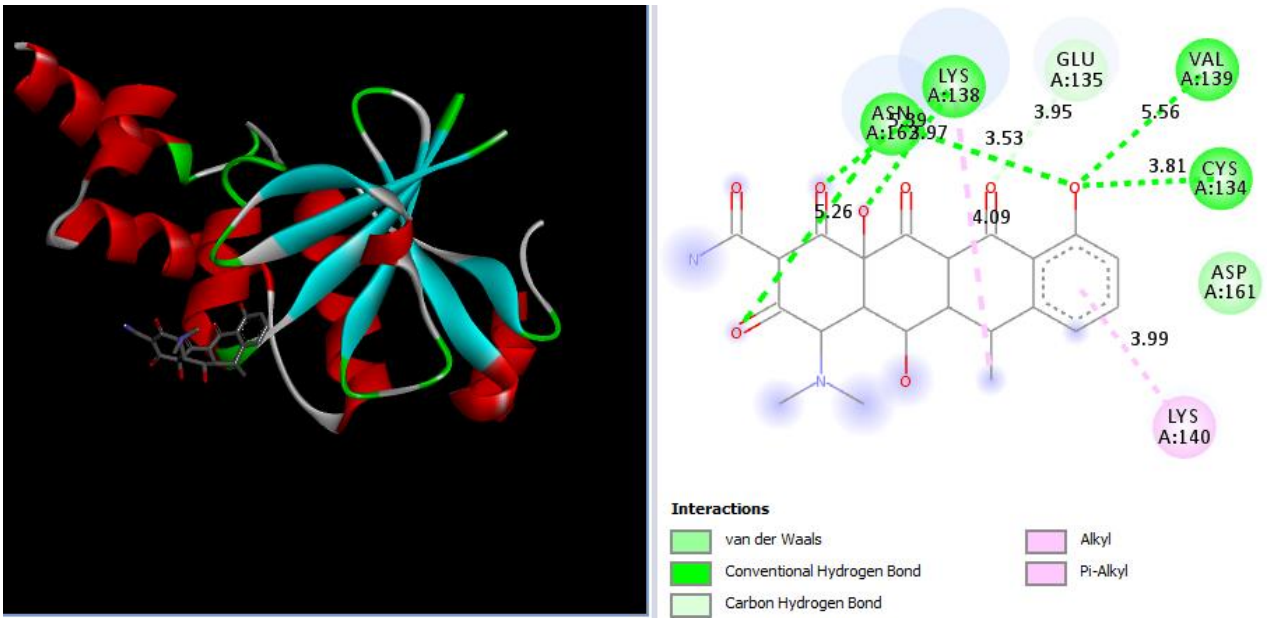


Figure 9. Binding interactions between 6W9O and doxycycline.

Evaluation of pharmacokinetic properties

Drug-likeness analysis and ADMET study were conducted on the three compounds (**49a**, **49b**, and **49c**) to evaluate their oral-bioavailability and compared identical with those of the lead compound and the reference drugs (retapamulin, lefamulin, and doxycycline). The results of both investigations are presented in **Tables V** and **VI**. Furthermore, **Figure 10** shows the oral bioavailability radar of the newly designed molecules, the template, the two clinically relevant pleuromutilins, and doxycycline.

Lipinski's rule for oral-bioavailability states that a drug molecule is more likely to have poor absorption or permeation when it has Hydrogen Bond Donors (HBD) of greater than 5, Hydrogen Bond Acceptors (HBA) > 10, Molecular Weight (MW) > 500, and lipophilicity (MLOGP > 4.15 or WLOGP > 5)[31]. Usually, molecules that obey at least three of the four requirements are said to be orally bioavailable[21]. **Table V** shows that all the molecules obeyed Lipinski's ROF since they satisfied at least three of the four requirements with **49a**, and the template showed no violation. Also, the reported Topological Polar Surface Area (TPSA) values for all molecules are less than 140 $Å^2$ except for doxycycline with a TPSA of 181.62 $Å^2$, indicating the likelihood of doxycycline being poorly absorbed. The synthetic accessibility scores of the newly designed molecules range from 6.66 to 6.83, indicating fewer rigors in their laboratory synthesis compared to retapamulin and lefamulin, with 7.51 and 6.95, respectively. However, the reference drug doxycycline with 5.15 is predicted to have a relatively more accessible synthetic pathway. The predicted ADMET properties in **Table VI** showed good intestinal absorption of more than 90% for all newly designed compounds, which are well clear of the 30% threshold value, and compare well with those of the template (93.385%), retapamulin (94.196%), lefamulin (81.211%), and doxycycline (31.193%, very poor).

All the molecules presented are substrates of P-glycoprotein, which act as a biological barrier by extruding toxins and xenobiotics, including drugs, out of cells. Interestingly, they are also inhibitors of both P-glycoprotein I and II except doxycycline, a shred of evidence that the molecules may mediate well to reach their target sites without being isolated by the P-glycoprotein. Additionally, the newly designed compounds and the template are substrates and inhibitors of Cytochrome P450 (CYP-3A4), an essential enzyme for drug metabolism in the body, which means a well-regulated (optimal) metabolic process for the molecules in the body. Retapamulin and lefamulin, on the other hand, are substrates of this enzyme only, while doxycycline is neither substrate nor inhibitor. Furthermore, all the molecules presented showed Blood Brain Barrier (BBB) permeability (Log BB) of less than 0.3, indicating they do not readily permeate through the blood-brain barrier. Also, the molecules all showed poor Central Nervous System (CNS) permeability since Log PS < -2. The total clearance for a drug molecule in the body for these molecules is within the accepted range, while they showed no AMES toxicity, indicating that the molecules are non-mutagenic and, as such, are non-carcinogenic[32,33]. From **Figure 10**, the colored zone represents the suitable physicochemical space for oral bioavailability, in which the template and the new analogs fit slightly better than the reference compounds. Based on the predicted parameters, the newly designed molecules are said to

relatively possess better pharmacokinetic profile than the reference compounds being that they showed high intestinal absorption, no more than 1 ROF violation, lower synthetic accessibility score, substrates and inhibitors of CYP-3A4, and no AMES toxicity.

Table V. Predicted drug-likeness properties of the newly designed compounds and reference drugs

Comp ID	MW (g/mol)	TPSA (Å²)	MLOGP	HBD	HBA	RO5 Violation	SA
Template	495.42	105.09	2.46	3	6	0	6.59
49a	497.43	105.09	2.54	3	6	0	6.66
49b	509.44	105.09	2.65	3	6	1	6.77
49c	511.46	105.09	2.74	3	6	1	6.83
Retapamulin	517.76	92.14	4.04	1	5	1	7.51
Lefamulin	507.73	135.15	2.84	3	6	1	6.95
Doxycycline	444.43	181.62	2.08	6	9	1	5.15

Note: SA – Synthetic accessibility

Table VI. Predicted ADMET properties of the newly designed compounds and reference drugs

ID	Absorption				Distribution		Metabolism		Excretion	Toxicity
	Intestinal absorption (%)	P-glycoprotein Substrate	P-glycoprotein Inhibitor I	P-glycoprotein Inhibitor II	BBB Permeability Log BB	CNS Permeability Log PS	CYP-3A4 Substrate	CYP-3A4 Inhibitor	Total clearance	AMES toxicity
Tem	93.385	Yes	Yes	Yes	-0.785	-2.849	Yes	Yes	0.163	No
49a	94.238	Yes	Yes	Yes	-0.817	-2.82	Yes	Yes	0.134	No
49b	93.859	Yes	Yes	Yes	-0.78	-2.803	Yes	Yes	0.111	No
49c	92.621	Yes	Yes	Yes	-0.846	-2.71	Yes	Yes	0.064	No
Ret	94.196	Yes	Yes	Yes	-0.736	-2.844	Yes	No	0.491	No
Lef	81.211	Yes	Yes	Yes	-0.986	-3.331	Yes	No	0.433	No
Dox	31.193	Yes	No	No	-1.763	-3.829	No	No	0.241	No

Note: Tem – template; Ret – retapamulin; Lef – lefamulin; Dox - doxycycline

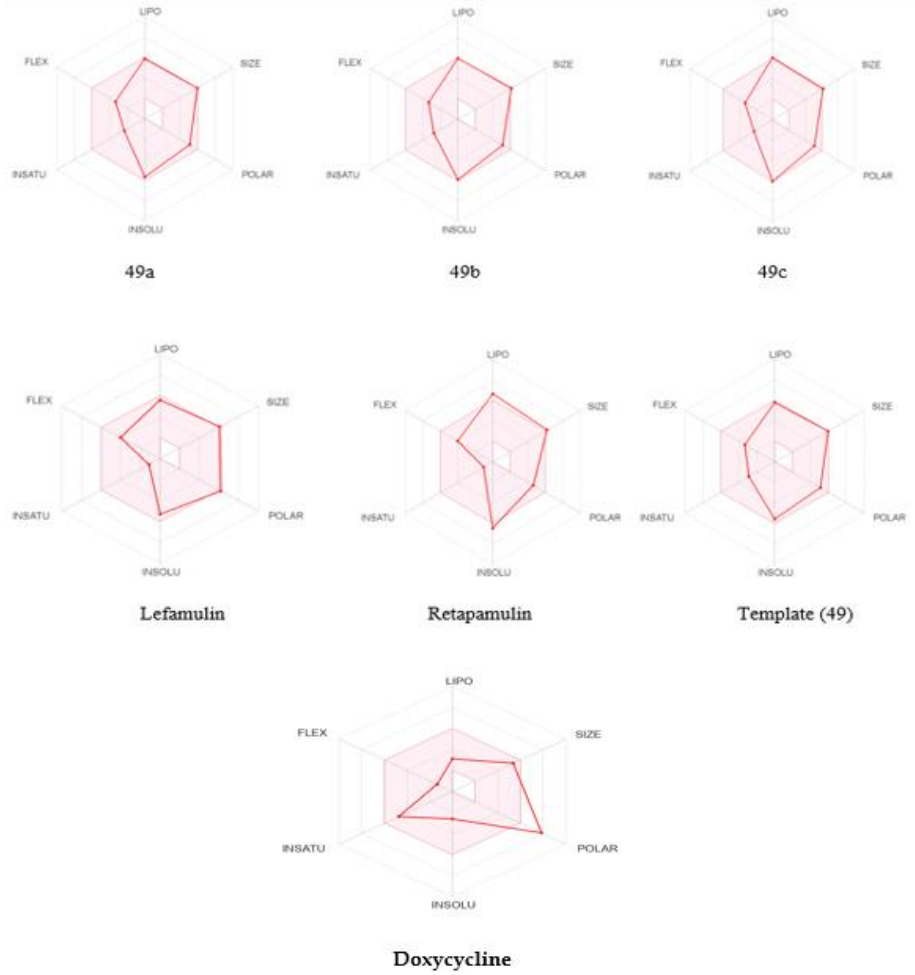


Figure 10. Oral bioavailability radar of the newly designed compounds, template, lefamulin, retapamulin, and doxycycline.

CONCLUSION

Computer-aided design of three boron-pleuromutilin analogs (**49a**, **49b**, and **49c**) as *Wolbachia* inhibitors were carried out using compound **49** as the template while also performing molecular docking study and pharmacokinetic analysis to evaluate their pharmacological and drug-likeness properties. The newly designed compounds had improved inhibitory activities (pEC_{50}) than those of the template and the two clinically relevant pleuromutilin compounds (lefamulin and retapamulin). The binding energies of interactions of the newly designed compounds were relatively higher while showing better pharmacokinetic profiles than the reference compounds because they showed higher human intestinal absorption, lower synthetic accessibility scores, substrates and inhibitors of CYP-3A4, and no AMES toxicity. As a result, this study has provided medicinal chemists with helpful information on the new derivatives as anti-filarial agents. More so, laboratory tests (*in vitro* and *in vivo*) could be carried out to validate the computational results.

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AUTHORS' CONTRIBUTION

All authors conceived and designed the study. **Fabian A. Ugbe** carried out the study and drafted the manuscript. **Gideon A. Shallangwa** conducted the technical editing. All authors read and approved the final manuscript.

DATA AVAILABILITY

All data related to this study are included herein.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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