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# MOLECULAR DOCKING, DRUG-LIKENESS AND SWISSADME EVALUATIONS OF THE INTERACTIONS OF 2'-SUBSTITUTED TRICLOSAN DERIVATIVES WITH *Plasmodium falciparum* ENOYL-ACYL CARRIER PROTEIN REDUCTASE

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## ABSTRACT

*The orthodox process of investigating lead molecules is a lengthy and laborious one that in most cases leads to minimal success. Molecular docking analysis provides an alternative path to drug discovery through the interactions of two or more complexes. Molecular docking studies were performed on 12 theoretically designed derivatives of 2'-substituted triclosan against a Plasmodium falciparum (P. falciparum) enoyl-acyl carrier protein reductase (PfENR) protein target as well as predicting their drug-likeness and SwissADME properties. The docking studies were carried out using the Molegro Virtual Docker (MVD) where the molecular interactions between the ligands and the target protein were studied. The docking analysis revealed 5-(((5-chloro-2-(4-chloro-2-hydroxyphenoxy)benzyl)amino)methyl) benzofuran-6-ol (re-rank docking score = -145.497 kcal/mol) as the most stable derivative. The compounds were all found to completely concord with the Lipinski rule regulations, in addition to the molar refractivity as well as the number of rotatable bonds appearing within acceptable limits. All compounds except 2–5 and 7 show high gastrointestinal absorption, and are non-inhibitors of cytochrome P450; CYP1A2 and CYP2C19 except CYP2C9, lack BBB penetration, and only compounds 2–7 and 12 were found to inhibit permeability-glycoprotein (P-gp) substrate. The findings suggest that some of the derivatives tend to increase the oral bioavailability of the substrate and most of them cannot be used in the treatment of cerebral malaria. These results may lead to future optimisation of the designed derivatives for improved antimalarial agents.*

***Keywords*:** Molecular docking, Drug-likeness, ADME, 2'-substituted triclosan, *Pf-ENR* protein.

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## INTRODUCTION

Millions of the world's population are infected with the deadly malaria disease yearly (Durojaye *et al.* 2019). Despite the enormous effort committed to the control and eradication of the disease, almost half of the world's population is in danger of the killer disease. Malaria was reported to cause sickness of more than 200 million and is responsible for the death of approximately 400,000 people annually (World Health Organization 2020). Malaria is caused by the parasite, *Plasmodium falciparum* (*P. falciparum*) the deadliest of the five human malaria causative parasites; *P. ovale, P. falciparum, P. vivax, P. knowlesi* and *P. malariae* (Rudrapal, Chetia and Singh 2017). The spread of the *P. falciparum* parasite is caused by the 'night-biting' mosquitoes.

The development of the *P. falciparum* in the infected red blood cells (RBCs) is a function of its ability to attach to the linings of small blood vessels. In addition to causing an impediment to the passage of fluid through the blood vessels, the parasite may also cause reductions in the deformability of uninfected RBCs in certain malaria (Weatherall 2002). Although the pathogenesis of this anomaly is unclear, its staunch relationship with acidosis may be responsible for compromising tissue blood flow. Malaria patients are usually drained and have a relatively reduced volume of circulating blood in the body (English *et al.* 1996) potentially exacerbating microvascular obstruction by reducing perfusion pressure.

The insufficient progress made in perfecting the malaria vaccine has led to the adoption of chemotherapy in the treatment of malaria (Narasimhan and Attaran 2003). Chloroquine has become a mainstay in the treatment of malaria ever since its first application (Ridley 2002). The emergence of drug-resistant strains of *P. falciparum* has become an incessant problem in the global efforts in the prevention and control of malaria. Therefore, chloroquine analogues have been found to have biological significance through the structural alterations of the analogues. These structural alterations have attracted huge attention in recent time (Sparatore *et al.* 2005; Iwaniuk *et al.* 2009).

Fatty acid synthase (FAS) is an integral component of membrane and energy development. Fatty acid synthesis in *Plasmodium* is a function of the dissociative process of enzymes composed of a FAS-II pathway (Schweizer and Hofmann 2004). This pathway was reported to be confined alongside an apicoplast, an organelle related to cyanobacteria (Ralph *et al.* 2004). The *P. falciparum* enoyl-acyl carrier protein reductase (*PfENR*) plays a decisive role in the fatty acid synthesis cycle through the reduction of trans-2-Enoyl-ACP to acyl ACP. Most of the FAS protein is observed to be of a single genetic design that was lacking within the enoyl-acyl carrier protein reductase (*ENR*) and the bacterial *ENR* sequence with a distinct structural observation from those of mammalian counterparts (Ling *et al.* 2004). These differences ensure that *ENR* becomes an important target for the development of unique antimalarial (Kapoor *et al.* 2004). The antibiotics, triclosan reported to be non-orally bioavailable, are a strong inhibitor of *Pf-ENR* enzyme activity (Nicola *et al.* 2007).

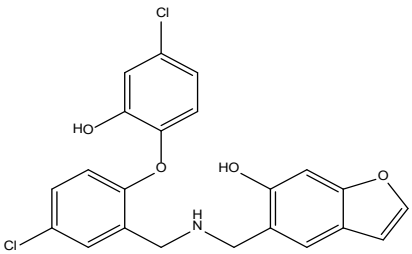
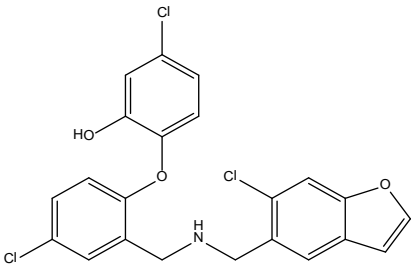
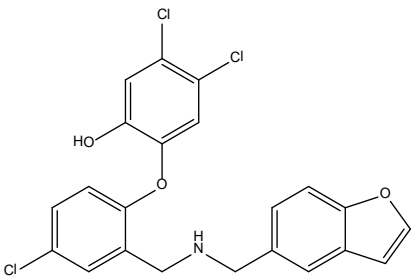
In this study, some derivatives of 2'-substituted triclosan, we previously designed and reported to have theoretically improved antimalarial activity, were screened for their antimalarial effectiveness and drug-likeness screening, and SwissADME prediction studies through the use of *in silico* tools. The molecular docking studies of the design compounds were performed against *P. falciparum* targeting *PfENR*. The research objectives are to predict the drug properties of our previously designed compounds as well as to understand the reason for the activity from their molecular interactions.

## METHODS

### Ligand Preparation

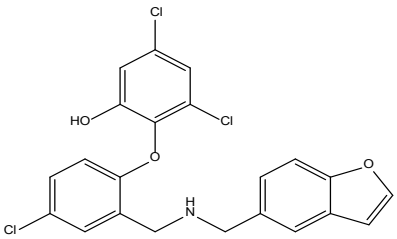
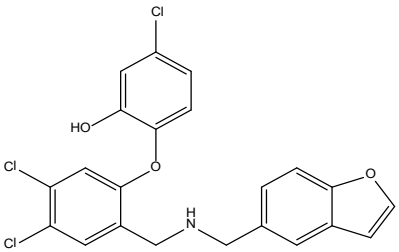
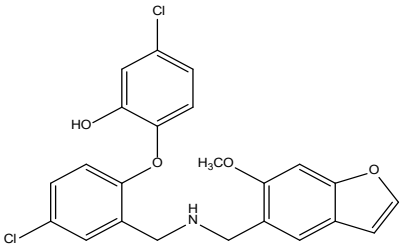
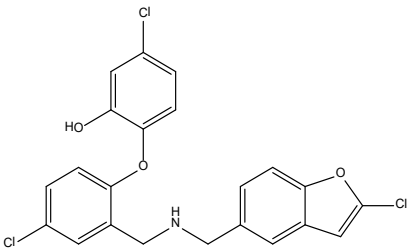
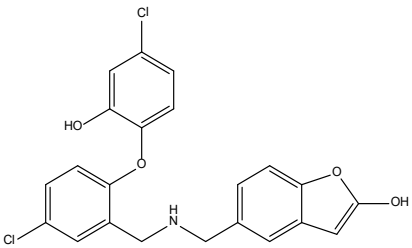
The 12 designed derivatives of 2'-substituted triclosan, shown in Table 1, were obtained from our previous research (Ibrahim *et al.* 2020). The derivatives were sketched with ChemDraw Ultra 12 and transferred to Spartan'14 version 1.1.2 software where they were fully optimised using a density functional theory (DFT/B3LYP/6-31G*) to achieve the optimal structures of the molecules. The optimised ligands were saved in a protein data bank (PDB) file format, after which the ligands were opened in the Molegro Virtual Docker (MVD) to be prepared by the preparation wizard.

**Table 1:** Chemical structures, IUPAC names and the theoretical activity of the designed derivatives of 2'-substituted triclosan.

| S/N | Name | Structures | $EC_{50}$ (μM) | -log $EC_{50}$ | Activity scale |
|---|---|---|---|---|---|
| 1 | 5-(((5-chloro-2-(4-chloro-2-hydroxyphenoxy) benzyl)amino)methyl) benzofuran-6-ol |  | 0.246 | 6.609 | + |
| 2 | 5-chloro-2-(4-chloro-2-((((6-chlorobenzofuran-5-yl)methyl)amino) methyl)phenoxy) phenol |  | 0.070 | 7.153 | ++ |
| 3 | 2-(2-(((benzofuran-5-ylmethyl) amino)methyl)-4-chlorophenoxy)-4,5-dichlorophenol |  | 0.106 | 6.976 | ++ |

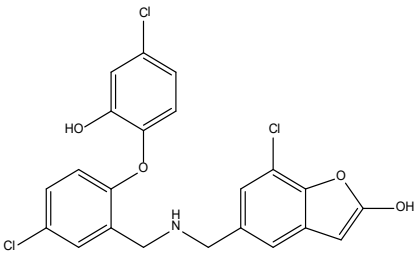
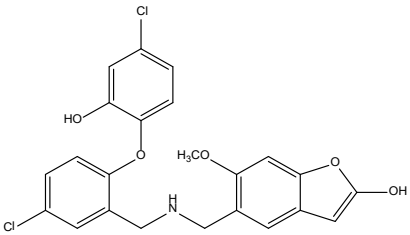
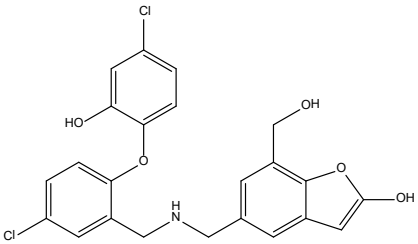
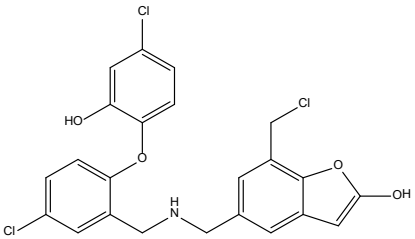
*(continued on next page)*

**Table 1:** (*continued*)

| S/N | Name | Structures | $EC_{50}$ (μM) | -log $EC_{50}$ | Activity scale |
|---|---|---|---|---|---|
| 4 | 2-(2-(((benzofuran-5-ylmethyl) amino)methyl)-4-chlorophenoxy)-3,5-dichlorophenol |  | 0.104 | 6.982 | ++ |
| 5 | 2-(2-(((benzofuran-5-ylmethyl)amino) methyl)-4,5-dichlorophenoxy)-5-chlorophenol |  | 0.124 | 6.905 | ++ |
| 6 | 5-chloro-2-(4-chloro-2-((((6-methoxybenzofuran-5-yl)methyl)amino) methyl)phenoxy) phenol |  | 0.249 | 6.603 | + |
| 7 | 5-chloro-2-(4-chloro-2-((((2-chlorobenzofuran-5-yl)methyl)amino) methyl)phenoxy) phenol |  | 0.112 | 6.951 | ++ |
| 8 | 5-(((5-chloro-2-(4-chloro-2-hydroxyphenoxy) benzyl)amino)methyl) benzofuran-2-ol |  | 0.239 | 6.622 | + |

*(continued on next page)*

**Table 1:** (*continued*)

| S/N | Name | Structures | $EC_{50}$ (μM) | -log $EC_{50}$ | Activity scale |
|---|---|---|---|---|---|
| 9 | 7-chloro-5-(((5-chloro-2-(4-chloro-2-hydroxyphenoxy) benzyl)amino)methyl) benzofuran-2-ol |  | 0.046 | 7.339 | ++ |
| 10 | 5-(((5-chloro-2-(4-chloro-2-hydroxyphenoxy) benzyl)amino) methyl)-6-methoxybenzofuran-2-ol |  | 0.061 | 7.217 | ++ |
| 11 | 5-(((5-chloro-2-(4-chloro-2-hydroxyphenoxy) benzyl)amino)methyl)-7-(hydroxymethyl) benzofuran-2-ol |  | 0.141 | 6.850 | ++ |
| 12 | 5-(((5-chloro-2-(4-chloro-2-hydroxyphenoxy) benzyl)amino)methyl)-7-(chloromethyl) benzofuran-2-ol |  | 0.012 | 7.930 | ++ |

*Notes:* ǂ Activity scale: ++ (moderately active) = 0.002 μM ≤ $EC_{50}$ ≤ 0.2 μM; + (low active) = $EC_{50}$ > 0.2 μM (Sakkiah *et al.* 2014).

## Protein Preparation

The high resolution (1.96 Å) 3-dimensional structure of the *PfENR* (PDB ID: 3LT0) containing its co-crystallised ligand (a molecule formed with the protein) used for the docking studies was gotten from the Research Collaboratory for Structural Bioinformatics (RCSB) PDB.

The protein was saved in PDB format after expelling the co-crystallised ligand. The protein preparation wizard of the MVD was employed for the preparation where charges, as well as hydrogen that may be missing from the protein, are fixed in the process. The binding pockets of the protein were searched within the in-built cavity algorithm performed by the MVD software.

**Molegro Virtual Docker**

The molecular interactions between the ligands and the target protein were carried out in MVD. The MVD software is known for its speed, accuracy and flexibility in conducting the docking procedures to predict how the ligand molecule will interact with the protein receptor (Pagadala, Syed and Tuszynski 2017). The docking begins with the ligand and target preparations which precede locating the binding cavity and then predicting the ligand-protein binding mode. The conformations produced are ranked using a scoring function, representing favourable protein-ligand complexes and differentiating between valid and invalid binding pose predictions. The re-ranking scoring function introduced to improve the docking results of the MolDock scoring is utilised as the preferred scoring function for the docking procedures. Using MVD software, flexible ligands were docked to 77 protein targets to test MolDock's docking accuracy. The binding modes of 87% of the complexes were determined by the MolDock. Glide and Surflex, on the other hand, have accuracy rates of 82% and 75%, respectively. On subgroups with 76 and 55 cases, FlexX got 58% and GOLD got 78%, respectively (Thomsen and Christensen 2006). Although, the software effort to restrict a ligand into a given region or improve the total energy of the system with 100 units of energy is regarded as its drawback. The MolDock Simplex Evolution docking algorithm was used by checking the boxes for the constrain poses to the cavity, energy minimisation and optimising H-bonds while setting the maximum iterations at 1,500, maximum population size at 50 and the energy threshold set at 100.00 with the values for *Tries* equals to 10, 10 and 30 for a min, quick and max tries, respectively. In addition to this, Max step = 300 and neighbour distance factor = 1.00 within the simplex evolution. The pose clustering was engaged to provide for numerous binding modes.

**Molecular Docking**

Molecular docking studies are used to determine the orientation and molecular interactions between the derivatives of 2'-substituted triclosan and the *PfENR* protein targets. The designed derivatives were imported into the binding sites of the specific protein targets for molecular interactions and analysis using the MVD tool. Where the MVD locates the binding pockets using its cavity detection algorithm. And the simulation was conducted by measuring the interaction between the ligands and the protein through the MolDock and re-rank scoring functions. Figure 1 shows the structure of the *PfENR* protein.

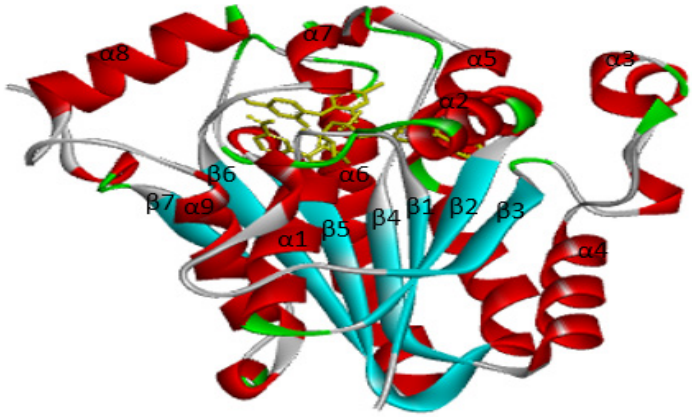



**Figure 1:** Structure of *PfENR* representing the subunit B of the *PfENR* tetramer with the co-factor NADH and inhibitor triclosan (in gold) bound to their active sites. Helices are shown in red, the strands in blue, NADH and triclosan are coloured by atom type.

### Drug Likeness and *in-silico* ADME Prediction

The trials and errors that are normally associated with drug developments were taken care of by computational techniques with a high success rate. Hence, *in silico* procedure has become a very important tool in drug identification and screening. Therefore, ligands absorption, distribution, metabolism and excretion (ADME) pharmacokinetic properties of the designed derivatives of 2'-substituted triclosan, are evaluated to determine their activity within the human body. The parameters evaluation covers the entire 12 designed derivatives. These pharmacokinetic properties were evaluated with an online ADME prediction tool (http://www.swissadme.ch). The drug-likeness of the designed derivatives was predicted based on Lipinski's Rule of 5 (Ro5). The Ro5 was to set drug-likeness basic rules for unique molecules (Lipinski, 2000). Molecules with H-bond donors (HBDs) ≤ 5, H-bond acceptors (HBAs) ≤ 10, molecular weight ≤ 500 Da and the implicit log of the partition coefficient between octanol and water (iLog P) ≤ 5 are likely to have good absorption or permeation. Hence, the molecules outside this range will unlikely to become orally bioavailable as a drug (Tareq 2010).

## RESULTS AND DISCUSSION

### Docking Simulation

The extracted *PfENR* protein was docked with the designed ligands, with the ligands choosing the best binding pockets within which the docking score was determined. In every docking run, the best poses were selected based on their scoring functions.

The results of the MolDock and re-rank scores of the best poses between the ligands and their target *PfENR* protein are summarised in Table 2. All designed derivatives show a higher docking score (binding affinity) than those of triclosan and chloroquine standard except for derivative 9 which has a lower binding affinity (-90.2504 kcal/mol) than the chloroquine standard. Compounds 1, 2, 3, 8 and 11 with re-rank scores -145.497

kcal/mol, -128.055 kcal/mol, -123.504 kcal/mol, -126.423 kcal/mol and -143.687 kcal/mol, respectively, are the most potent of the designed derivatives. In natural products, adding chlorine, methoxyl and hydroxymethyl groups to different places on the benzofuran part of the ligand is a crucial step. The antimalarial activity of the 2' substituted triclosan derivative was improved by chlorination, methoxylation and hydroxymethylation of the benzofuran part of the derivative, as reported in our previous research (Ibrahim *et al.* 2020). The structure-activity relationship was supported by docking studies, which revealed that compounds with the lowest docking scores (compounds 1 and 11) bind to the receptor better and form more stable poses. The observed interactions may be due to the substitution of hydrogen atoms with chlorine, methoxyl and hydroxymethyl groups at various places on the benzofuran component of the derivative.

**Table 2:** MolDock score, re-rank score, no. of H-bond(s), and H-bond energies of the ligands.

| S/N | MolDock score (kcal/mol) | Re-rank score (kcal/mol) | No. of H-bond(s) | H-bond energy (kcal/mol) |
|---|---|---|---|---|
| 1 | -175.439 | -145.497 | 5 | -6.8484 |
| 2 | -157.895 | -128.055 | 3 | -5.2087 |
| 3 | -153.051 | -123.504 | 1 | -8.1973 |
| 4 | -137.029 | -113.713 | 2 | -4.9434 |
| 5 | -149.095 | -118.861 | 1 | -0.8171 |
| 6 | -146.745 | -102.187 | 2 | -4.6791 |
| 7 | -123.011 | -96.3036 | 0 | 0.0000 |
| 8 | -156.577 | -126.423 | 2 | -3.8390 |
| 9 | -121.889 | -90.2504 | 1 | -1.9364 |
| 10 | -152.063 | -121.727 | 3 | -1.2843 |
| 11 | -173.638 | -143.687 | 8 | -12.0508 |
| 12 | -145.918 | -116.533 | 2 | -4.8552 |
| Triclosan | -107.765 | -87.4037 | 1 | -1.2204 |
| Chloroquine | -112.122 | -93.784 | 0 | -2.0032 |

The docking scores are the results of the interacting energy expressed in numeric values. Hence, the binding energy sums off the contributions from all the non-bonded interactions (such as hydrophobic, hydrogen bonding and van der Waals) between the protein residues and the ligands (Kitchen *et al.* 2004). The numbers of hydrogen bonds and the hydrogen bond energies for all the docked compounds were also reflected in Table 2. The hydrogen-bonding interactions of five most potent designed compounds mentioned earlier against the active site residues such as Trp113, Ala169, Gly129, Gly104, Ser215, Gly106, Trp131, Tyr111, Asp168, Ser170, and Gly112, are revealed in Table 3. The 3D binding modes and the 2D interactions images of the two most active compounds 1 and 11 are shown in Figure 2.

**Table 3:** Hydrogen bonding details between the protein receptor and five of the most active ligands.

| | | H-binding ligand | | | H-binding receptor | | |
|---|---|---|---|---|---|---|---|
| **S/N** | **H-bond** | **Element** | **Type** | **Residue** | **Element** | **Type** | **H-bond distance (Å)** |
| 1 | 5 | Cl | A | Trp113 | H | D | 1.7236 |
| | | O | A | Ala169 | H | D | 1.8850 |
| | | H | D | Gly129 | O | A | 2.4454 |
| | | H | D | Gly104 | O | A | 2.2481 |
| | | H | D | Ser215 | O | A | 2.2737 |
| 2 | 3 | N | A | Gly106 | H | D | 2.2505 |
| | | O | A | Trp131 | H | D | 2.0780 |
| | | H | D | Gly129 | O | A | 1.8018 |
| 3 | 1 | O | A | Tyr111 | H | D | 2.5211 |
| 8 | 2 | H | D | Asp168 | O | A | 2.0502 |
| | | H | D | Ser170 | O | A | 2.5969 |
| 11 | 8 | O | A | Gly112 | H | D | 2.2585 |
| | | O | A | Ala169 | H | D | 2.1565 |
| | | H | D | Asp168 | O | A | 1.7156 |
| | | H | D | Ser170 | O | A | 2.4649 |
| | | H | D | Gly129 | O | A | 2.7273 |
| | | H | D | Gly104 | O | A | 2.6541 |
| | | H | D | Ser215 | O | A | 2.1150 |
| | | H | D | Ser215 | O | A | 2.2065 |

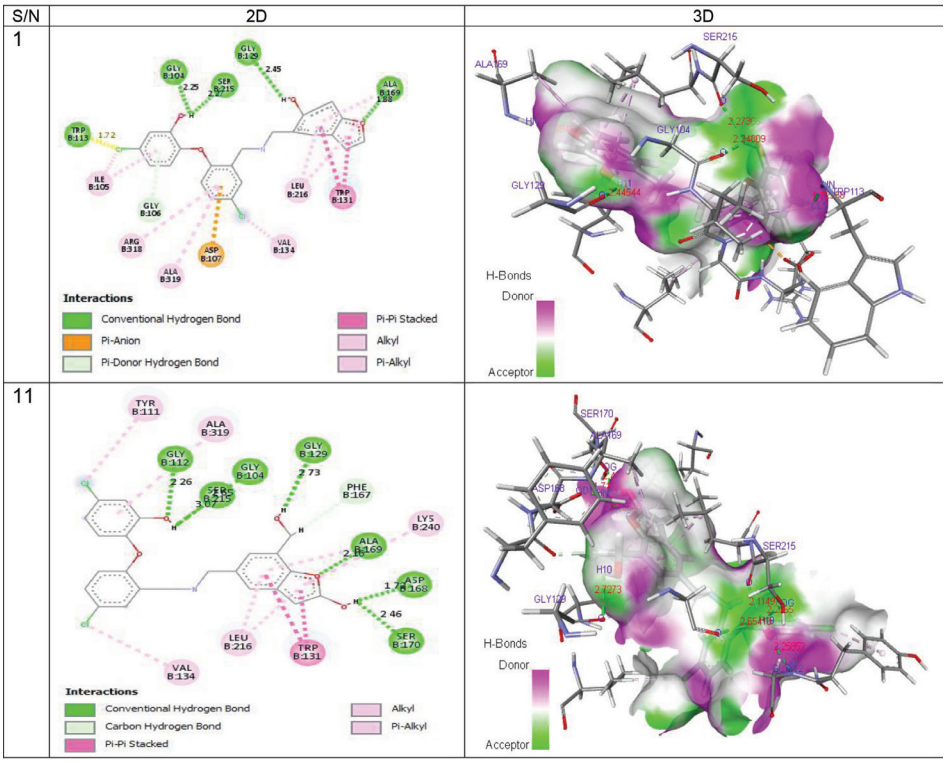



**Figure 2:** 2D and 3D docking pose showing interactions of the two most active compounds: 1 and 11 in the binding sites of *PfENR* protein.

Five hydrogen bonds were formed between compound 1 and the amino residues Trp113 (Cl··H··N), Ala169 (O··H··N), Gly129 (H··H··O), Gly104 (H··H··O) and Ser215 (H··H··O) with bond distances of 1.7236 Å, 1.8850 Å, 2.4454 Å, 2.2481 Å and 2.2737 Å, respectively. Compound 11 formed eight hydrogen bonds with amino residues Gly112 (O··H··N), Ala169 (O··H··N), Asp168 (H··H··O), Ser170 (H··H··O), Gly129 (H··H··O), Gly104 (H··H··O) and two Ser215 (H··H··O) with bond distances 2.2585 Å, 2.1565 Å, 1.7156 Å, 2.4649 Å, 2.7273 Å, 2.6541 Å, 2.1150 Å and 2.2065 Å, respectively. The hydrogen bonds along with other hydrophobic interactions are responsible for the observed high docking score of the active compounds. These hydrogen bonds interactions are responsible for the excellent stability between the protein receptor and ligand.

**Molecular Properties and Drug-Likeness**

The Lipinski's rule-of-five (Ro5) is a method for determining whether chemical compounds and potential medicines are drug-like. The Lipinski's Ro5 states that chemical compounds with a molecular weight (MW) of less than 500 g/mol, a logarithm of the partition coefficient (log P) of less than 5, HBDs of less than 5 and a HBA of less than 10 should be used as pharmaceuticals (Athar *et al*. 2019). The results of drug-likeness predictions for the designed compounds as displayed in Table 4, shows that all the designed compounds were found to pass the Ro5 test, hence they possess good permeability or absorption properties.

**Table 4:** Lipinski's parameters of the designed derivatives of 2'-substituted triclosan.

| Lipinski's parameters | | | | | | |
|---|---|---|---|---|---|---|
| **S/N** | **MW (≤ 500 Da)** | **iLogP (< 5)** | **#HBA (≤ 10)** | **#HBD (≤ 5)** | **TPSA (< 140 Å²)** | **#Lipinski violations** |
| 1 | 430.28 | 3.33 | 5 | 3 | 74.86 | 0 |
| 2 | 448.73 | 3.71 | 4 | 2 | 54.63 | 0 |
| 3 | 448.73 | 3.78 | 4 | 2 | 54.63 | 0 |
| 4 | 448.73 | 3.67 | 4 | 2 | 54.63 | 0 |
| 5 | 448.73 | 3.57 | 4 | 2 | 54.63 | 0 |
| 6 | 444.31 | 4.06 | 5 | 2 | 63.86 | 0 |
| 7 | 448.73 | 4.05 | 4 | 2 | 54.63 | 0 |
| 8 | 430.28 | 3.21 | 5 | 3 | 74.86 | 0 |
| 9 | 464.73 | 3.38 | 5 | 3 | 74.86 | 0 |
| 10 | 460.31 | 4.06 | 6 | 3 | 84.09 | 0 |
| 11 | 460.31 | 3.67 | 6 | 4 | 95.09 | 0 |
| 12 | 478.75 | 4.30 | 5 | 3 | 74.86 | 0 |

The violations of more than one Ro5 parameter ensure that the derivative will likely to have poor permeability or absorption. The values of MW, topological polar surface area (TPSA) and the iLogP coefficient displayed in Table 4 are indications of good membrane permeability and oral bioavailability of the compounds, while those of number of rotatable bonds (nRotb) account for the good intestinal availability. The iLogP values determined for the derivatives were found to be between 3.21 and 4.06, thus are lower than the recommended value by the Lipinski's Ro5 (Lipinski 2004). The values of TPSA in Å$^2$ within the range 140 > TPSA < 60 are indications of excellent intestinal absorption and good blood-brain barrier penetration, respectively (Maximo *et al*. 2015). The TPSA value for the designed derivatives lies between 54.63 Å$^2$ and 95.09 Å$^2$. This indicates that the designed derivatives could be used in the treatment of cerebral malaria in addition to its intestinal absorption.

### *In-silico* ADME Prediction

The values of the ADME properties of the designed derivatives of 2'-substituted triclosan presented in Table 5 were all within the permissible ranges. All of the compounds except 2–5 and 7 show high gastrointestinal absorption, non-inhibitors of cytochromeP450 (CYP450), enzymes (CYP1A2 and CYP2C19) except CYP2C9 and lacks BBB penetration indicating their non-usage in the treatment of cerebral malaria. Based on the ADME property, compound 12 has the highest molar refractivity (MR), ability to inhibit CYP1A2, CYP2C19 and behave as a permeability-glycoprotein (P-gp) substrate, hence it has the best drug-ability potential. The MR of all the compounds is within the ranges of 40–130, their nRotb were found to be within the limit of ≤ 10 (Zerroug *et al.* 2018), their log Kp values fall within the acceptable range of -8.0 < log Kp < -1.0 (Gaur *et al.* 2015) while compounds 2–7 and 12 inhibit P-gp substrate thereby increasing the oral bioavailability of its substrates.

**Table 5:** Calculated molecular properties of the designed derivatives of 2'-substituted triclosan.

| S/N | MR | log Kp (cm/s) | nRotb | BBB penetration | CYP1A2 inhibitor | P-gp substrate | GI absorption | CYP2C19 inhibitor | CYP2C9 inhibitor |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 113.86 | -4.8 | 6 | No | Yes | No | High | Yes | No |
| 2 | 116.84 | -4.61 | 6 | No | Yes | Yes | Low | Yes | No |
| 3 | 116.84 | -4.61 | 6 | No | Yes | Yes | Low | Yes | No |
| 4 | 116.84 | -4.61 | 6 | No | Yes | Yes | Low | Yes | No |
| 5 | 116.84 | -4.61 | 6 | No | Yes | Yes | Low | Yes | No |
| 6 | 118.33 | -5.04 | 7 | No | Yes | Yes | High | Yes | No |
| 7 | 116.84 | -4.37 | 6 | No | Yes | Yes | Low | Yes | No |
| 8 | 113.86 | -4.95 | 6 | No | Yes | No | High | Yes | No |
| 9 | 118.87 | -4.72 | 6 | No | Yes | No | High | Yes | No |
| 10 | 120.35 | -5.15 | 7 | No | Yes | No | High | Yes | No |
| 11 | 119.99 | -5.76 | 7 | No | Yes | No | High | Yes | No |
| 12 | 123.62 | -4.97 | 7 | No | Yes | Yes | High | Yes | No |

*Notes*: MR = molar refractivity; nRotb = number of rotatable bonds; log Kp = log of skin permeability; BBB = blood-brain barrier penetration; P-gp = permeability glycoprotein substrate; GI = gastrointestinal absorption; CYP450 = cytochrome P450 enzymes; CYP1A2, CYP2C9 and CYP2C19 inhibitors.

## CONCLUSION

The research on the docking, drug-likeness and SwissADME predictions of the theoretically derivatives of 2'-substituted triclosan revealed the several molecular interactions of the derivatives with their *PfENR* protein target. Among the interactions are several hydrogen bonds and other hydrophobic interactions. Compound 1, 5-(((5-chloro-2-(4-chloro-2-hydroxyphenoxy)benzyl)amino)methyl)benzofuran-6-ol with the lowest docking score -145.497 kcal/mol is regarded as the most active compound. The designed compounds were found to be in concordance with Lipinski's RO5. Their SwissADME studies revealed compounds 1, 6 and 8–12 having low gastrointestinal absorption, the compounds are found to be inhibitors of CYP1A2 and CYP2C19 but CYP2C9 in addition to lacking blood-brain barrier (BBB) penetration. The molar refractivity, the log of skin permeability, number of rotatable bonds were all within standard ranges plus most of the compounds showing inhibition of P-gp substrate. These properties may be taken into cognizance in synthesising the theoretical derivatives and general drug optimisations.

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