QSAR APPROACH AND SYNTHESIS OF CHALCONE DERIVATIVES AS ANTIMALARIAL COMPOUND AGAINST *Plasmodium Falciparum* 3D7 Strain

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ABSTRACT

A quantitative structure-activity relationship (QSAR) analysis of serial chalcone derivatives as antimalarial agents against *Plasmodium falciparum* strain 3D7 (Pf3D7) was conducted, it was then used to predict the activity of several synthesized chalcones. The QSAR analysis was performed using stepwise multiple linear regression, and the results showed that the antimalarial activity of chalcone derivatives had a strong correlation towards electronic and molecular descriptors. The best QSAR model was used for designing 3 chalcone derivatives which were further synthesized, characterized, and tested as an antimalarial agent. This study revealed that (E)-3-(4-methoxyphenyl)-1-(2,4-dimethoxyphenyl) prop-2-en-1-one had an excellent activity as an antimalarial agent with an IC₅₀ value of 1.29 μ M. Molecular docking results showed that it interacted nicely on the PfDHODH active site.

Keywords: Chalcone, QSAR Approach, Antimalarial Agent, Claisen-Schmidt Condensation, Molecular Docking

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INTRODUCTION

Malaria is an endemic disease caused by *Plasmodium* parasites. Among many *Plasmodium* parasites, *Plasmodium falciparum* is the deadliest malaria parasite.¹ The World Health Organization (WHO) in 2017 reported that there were 219 million cases and 435 deaths caused by malarial symptoms.² However, in other studies, the resistance of antimalarial agents has been an exclusive problem with *P. falciparum*, which is resistant to chloroquine.³ Therefore, it is necessary to find novel antimalarials that can overcome drug resistance. Chalcones are natural products that belong to the flavonoid family, which have a wide range of biological properties such as anticancer⁴ and antimalaria.⁵ Suma et al. synthesized some chalcone derivatives via Claisen Schmidt condensation⁶, and it has also been reported that functional groups modification and design of chalcone derivatives can affect its antimalarial activity.⁷ One method which could be used for designing new compounds with better biological activity than its lead compound is Quantitative Structure-Activity Relationship (QSAR). Several studies have been conducted to determine QSAR descriptors using the Density Functional Theory (DFT) by computational method.^{8,9} Another computational method, such as molecular docking, could give information about the interaction and stability of drugs and their target. Other studies have been carried out to improve the activity of novel antimalarial agents by targeting *Plasmodium falciparum* dihydroorotate dehydrogenase (PfDHODH) enzyme as its specific target.^{10,11} Recently, Ibrahim et al. designed some indolyl-3-ethanone- α -thioethers derivatives as antimalarial agents based on the QSAR approach and molecular docking targeting PfDHODH.¹² However, there is still no comprehensive study regarding the design of chalcone-based antimalarial agents based on QSAR approach and molecular docking study targeting PfDHODH. This research aimed to design some chalcone derivatives based on QSAR approaches and then evaluate them as antimalarial agents targeting *P. falciparum* 3D7 strain. Furthermore, all designed chalcone derivatives were docked against PfDHODH to evaluate their mechanism of action as antimalarial agents.

EXPERIMENTAL

QSAR Data Set

A total of 27 chalcone derivatives was taken from the literature⁷ (Table-1). The inhibition concentration (IC_{50}) values were converted to pIC_{50} ($\log \frac{1}{IC_{50}(M)}$) and the antimalarial activity could be categorized into five groups which are inactive ($IC_{50} > 200 \mu M$); low (IC_{50} 100-200 μM); moderate (IC_{50} 20-100 μM); good (IC_{50} 1-20 μM); and excellent ($IC_{50} < 1 \mu M$).¹³

Table-1: Chalcone Derivatives Data Set and Their Antimalarial Activity⁷

Comp.	R	R ₁	R ₂	R ₃	R ₄	IC ₅₀ (μM)	pIC ₅₀	Antimalarial Activity
1	4-OH	Allyl	OH	OCH ₃	H	38.5	4.414	Moderate
2	4-Cl	Allyl	OH	OCH ₃	H	28.0	4.552	Moderate
3 ^a	4-Cl	Allyl	OCH ₃	OCH ₃	H	3.9	5.408	Good
4	4-OCH ₃	Allyl	OCH ₃	OCH ₃	H	4.3	5.366	Good
5	3,4-OCH ₂ O-	Allyl	OCH ₃	OCH ₃	H	4.7	5.327	Good
6	4-Br	Allyl	OCH ₃	OCH ₃	H	5.3	5.275	Good
7	4-NO ₂	Allyl	OCH ₃	OCH ₃	H	12.5	4.903	Good
8	4-Cl	Allyl	O-Allyl	OCH ₃	H	7.8	5.107	Good
9 ^a	3,4-diCl	H	O-Allyl	OCH ₃	H	10.0	5.000	Good
10	4-Br	H	O-Allyl	OCH ₃	H	8.1	5.091	Good
11	4-F	H	O-Allyl	OCH ₃	H	23.0	4.638	Moderate
12	3-Cl	H	O-Allyl	OCH ₃	H	5.3	5.275	Good
13	4-OCH ₃	H	O-Allyl	OCH ₃	H	22.5	4.647	Moderate
14	3,4-OCH ₂ O-	H	O-Allyl	OCH ₃	H	38.5	4.414	Moderate
15	4-NH ₂	H	O-Allyl	OCH ₃	H	36.0	4.443	Moderate
16	H	H	O-Allyl	OCH ₃	H	38.0	4.420	Moderate
17	4-O-Allyl	H	O-Allyl	OCH ₃	H	7.4	5.130	Good
18	4-Cl	H	H	OCH ₃	O-Allyl	12.5	4.903	Good
19 ^a	4-Cl	H	OCH ₃	O-Allyl	H	18.0	4.744	Good
20	4-Cl	H	OH	OCH ₃	H	28.0	4.552	Moderate
21	4-Cl	H	O-Butyl	OCH ₃	H	14.8	4.829	Good
22	4-Cl	H	O-CH ₂ - Ph-4-Br	OCH ₃	H	8.0	5.096	Good
23	4-Cl	O-CH ₃	O-Allyl	OCH ₃	H	3.8	5.420	Good
24	4-Cl	H	O-Allyl	H	H	43.0	4.366	Moderate
25 ^a	4-Cl	H	H	H	O-Allyl	9.0	5.045	Good
26	4-Cl	H	O-Allyl	O-C ₂ H ₅	H	28.0	4.552	Moderate
27 ^a	3-O-Allyl 4-OCH ₃	H	Cl	H	H	8.6	5.065	Good

^a) compound test set

QSAR Analysis

The geometry optimization of 27 chalcone derivatives and quantum descriptors calculations were conducted using DFT/B3LYP with a 6-31G basis set using Gaussian 09¹⁴, whereas molecular descriptors were calculated using HyperChem.¹⁵ The quantum descriptors were net atomic charges on chalcone derivatives structure, HOMO energy (E_{HOMO}), and LUMO energy (E_{LUMO}). Whereas molecular descriptors were molecular volume (VOL), polarizability (POL), surface area (SA), molar refractivity (MR), log P, and molecular weight (MW).⁸ Correlation models of QSAR were evaluated using multiple linear regression analysis by employing BuildQSAR software with pIC_{50} as dependent variables and

descriptors as independent variables. In multiple linear regression analysis using BuildQSAR software, descriptors that are not significantly correlated to pIC_{50} were removed to get better equation.^{8,16} All of the descriptors were given in supplementary files. The best QSAR model was selected according to its statistical parameters of internal validation and external validation. Internal validation parameters were r^2 value, standard error of estimate (SEE), F_{cal}/F_{tab} , and predicted residual error sum of squares (PRESS), whereas external validation statistical parameters were also r^2 value, PRESS, and r^2_m .¹⁷ This QSAR equation was used to predict the antimalarial activity of several new hypothetical chalcone derivatives.

Materials

All materials used for chalcone synthesis were originated from E. Merck with pro analysis grade and used without further purification, i.e., *p*-anisaldehyde, acetophenone, 4-hydroxyacetophenone, 2,4-dimethoxyacetophenone, potassium hydroxide, sodium hydroxide, ethanol, methanol, hydrochloric acid 37%, dichloromethane, *n*-hexane, and ethyl acetate. Materials used for the antimalarial activity assay were *P. falciparum* 3D7 strain, Red Blood Cells (RBC), immersion oil, methanol, sorbitol, Roswell Park Memorial Institute (RPMI) medium, Hydroxyethylpiperazine (HEPES), gentamycin, serum 10%, and Giemsa 10%.

Instrumentations

Melting points were recorded by a digital melting point apparatus on Electrothermal 9100 and uncorrected. Thin-layer chromatography (TLC) was performed on pre-coated silica gel plates. Mass spectra were obtained from GC-MS spectrometer (Shimadzu QP2010S). Infrared spectra were recorded on Shimadzu Prestige-21 (KBr). 1H and ^{13}C -NMR characterizations were carried out on JEOL JNM-ECA (500 MHz (1H) and 125 MHz (^{13}C)) using tetramethylsilane (TMS) as an internal standard. The equipment used for the antimalarial test were microplate 96 well with Lid (Iwaki), centrifuge (SORVALL MC 12V), Ultrasonic Generator (42 kHz, Krisbow), Elisa Reader (BioRad Benchmark), CO_2 incubator, laminar airflow cabinet (Esco Class II BSC), autoclave, object-glass, and inverted microscope.

Synthesis of (E)-3-(4-methoxyphenyl)-1-phenyl prop-2-en-1-one (Chalcone A)

Acetophenone (0.61 g, 5 mmol) was diluted in methanol (5 mL), then 15% KOH (10 mL) and *p*-anisaldehyde (0.61 mL, 5 mmol) were added dropwise. The mixture was irradiated for 1.5 h by an ultrasonic generator. The mixture was neutralized using HCl 10%; the precipitates were washed with distilled water and dried inside a vacuum desiccator. The solid product was recrystallized with ethanol to give chalcone **A** (0.96 g, 80.67%) as yellow solid. m.p 67-69 °C. IR (KBr, cm^{-1}): 1658 (C=O), 1597 and 1512 (C=C Ar), 1265 (C-O-C), 987 (C=C trans). 1H -NMR (500 MHz, $CDCl_3$) δ (ppm): 3.86 (3H, s, OCH_3), 6.94 (2H, d, J 8.4 Hz, H_{Ar-B}), 7.42 (1H, d, J 15.6 Hz, $=CH_\alpha$), 7.50 (2H, t, H_{Ar-B}), 7.59 (3H, dd, J 7.8, 8.5 Hz, H_{Ar-A}), 7.79 (1H, d, J 15.6 Hz, $=CH_\beta$), 8.01 (2H, d, J 8.4 Hz, H_{Ar-A}). ^{13}C -NMR (125 MHz, $CDCl_3$) δ (ppm): 55.6 (OCH_3), 114.6, 120.0 ($=CH_\alpha$), 127.8, 128.6, 128.7, 130.4, 132.7, 138.7, 144.9 ($=CH_\beta$), 161.9, 190.8 (C=O). Mass spectrum (EI): m/z 238 (M^+), 207, 161, 133, 108, 77 (base peak), 51.

Synthesis of (E)-3-(4-methoxyphenyl)-1-(4-hydroxyphenyl) prop-2-en-1-one (Chalcone B)

This was prepared as described for chalcone **A** from 4-hydroxyacetophenone (0.68 g, 5 mmol) in methanol, 40% KOH (15 mL) and *p*-anisaldehyde (0.61 mL, 5 mmol) to give chalcone **B** (0.92 g, 72.38%) as yellow solid. m.p 188-190 °C. IR (KBr, cm^{-1}): 3132 (OH), 1643 (C=O), 1597 and 1512 (C=C Ar), 1219 (C-O-C), 995 (C=C trans). 1H -NMR (500 MHz, $CDCl_3$) δ (ppm): 3.80 (3H, s, OCH_3), 6.89 (2H, d, J 8.40 Hz, H_{Ar-A}), 6.99 (2H, d, J 9.10 Hz, H_{Ar-B}), 7.64 (1H, d, J 15.50 Hz, $=CH_\alpha$), 7.75 (1H, d, J 15.60 Hz, $=CH_\beta$), 7.80 (2H, d, J 8.45 Hz, H_{Ar-B}), 8.04 (2H, d, J 8.40 Hz, H_{Ar-A}). ^{13}C -NMR (125 MHz, $CDCl_3$) δ (ppm): 55.6 (OCH_3), 114.6, 115.6, 119.7 ($=CH_\alpha$), 127.7, 129.5, 130.8, 131.4, 143.0 ($=CH_\beta$), 161.4, 162.2, 187.4 (C=O). Mass spectrum (EI): m/z 254 (M^+), 239, 211, 161, 121, 108, 93, 77, 65 (base peak), 39.

Synthesis of (E)-3-(4-methoxyphenyl)-1-(2,4-dimethoxyphenyl) prop-2-en-1-one (Chalcone C)

This was prepared as described for chalcone **A** from 2,4-dimethoxyacetophenone (0.54 g, 3 mmol) in methanol, 20% NaOH (5 mL) and *p*-anisaldehyde (0.36 mL, 3 mmol) and the mixture was stirred at room temperature for 24 h. After working up, the product was recrystallized from ethanol to give chalcone **C**

(0.78 g, 86.70%) as a yellow solid. m.p 86-87 °C. IR (KBr, cm^{-1}): 1643 (C=O), 1605 (C=C alkene), 1582 (C=C Ar), 1250 (C-O-C), 980 (C-H trans). $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ (ppm): 3.84 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 6.50 (1H, d, J 2.0 Hz, $\text{H}_{\text{Ar-A}}$), 6.56 (1H, dd, J 2.0, 9.0 Hz, $\text{H}_{\text{Ar-A}}$), 6.91 (2H, d, J 8.6 Hz, $\text{H}_{\text{Ar-B}}$), 7.39 (1H, d, J 16 Hz, $=\text{CH}_\alpha$), 7.55 (2H, d, J 8.6 Hz, $\text{H}_{\text{Ar-B}}$), 7.65 (1H, d, J 16 Hz, $=\text{CH}_\beta$), 7.74 (1H, d, J 9.0 Hz, $\text{H}_{\text{Ar-A}}$). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ (ppm): 55.5 ($-\text{OCH}_3$), 55.6 ($-\text{OCH}_3$), 55.8 ($-\text{OCH}_3$), 98.8, 105.2, 114.4, 122.6 ($=\text{CH}_\alpha$), 125.1, 128.3, 130.1, 132.8, 142.2 ($=\text{CH}_\beta$), 160.3, 161.3, 164.1, 190.8 (C=O). Mass spectrum (EI): m/z 298 (M^+), 283, 165, 135, 121 (base peak), 107, 91, 77.

Antimalarial Assay against *P. falciparum* 3D7 strain

Antimalarial testing was carried out by dissolving 5 mg of sample in 50 μL DMSO (stock concentration solution of 5000 $\mu\text{g/mL}$). Hence, a series of diluted solution (5, 1, 0.5, 0.1, and 0.05 $\mu\text{g/mL}$) was prepared from stock solution. The parasite used here was ring-stage parasites adjusted to parasitemia $\pm 1\%$. A series of tested solutions (100 μL) in varying concentrations was taken and poured into a well (96 wells). Then 100 μL parasites were added until the concentration was adjusted to 2.5, 0.5, 0.25, 0.05, and 0.025 $\mu\text{g/mL}$. The assay wells were incubated for 48 h at 37 °C. Blood smears were made from the cultures, and then the blood smears were stained using Giemsa 10%. The percent inhibition was determined by counting infected erythrocytes for every group of 1000 cells of erythrocytes under a microscope. The IC_{50} values, the concentration required to inhibit parasite growth by 50%, were determined using linear interpolation from the growth inhibition curves generated for each sample-parasite combination.¹⁸

Molecular Docking Study

All designed chalcone derivatives were docked against the receptor, i.e., *Plasmodium falciparum* dihydroorotate dehydrogenase (PfDHODH) (PDB: 1TV5). The ligand-receptor preparation was performed using Discovery Studio¹⁹ and Autodock Tools 1.5.6. At the protein-ligand preparation step, all solvent molecules were omitted then hydrogen atoms and Kollman charges were added to the receptor. The grid box size was set to 15 x 15 x 15 Å with a grid spacing of 1.00 Å centered to the native ligand, while the exhaustiveness value was set to 100. Redocking against native ligand (inhibitor A26) was also conducted to validate the molecular docking procedure, and the root means square deviation (RMSD) of redocking should be < 2.00 Å.^{20,21} The calculation of RMSD value was performed by PyMOL software without any fitting.²² Molecular docking and redocking procedure were carried out using AutoDock Vina.²³ The docked pose with the lowest binding affinity was chosen as the most appropriate docked conformation.

RESULTS AND DISCUSSION

Four QSAR equations and their statistical parameters were obtained from multiple linear regression calculation (Table-2). The coefficient of determination (r^2) of the four QSAR equations obtained exceeded 0.6, so it could be said that all models have a good correlation towards experimental pIC_{50} .¹⁷ In addition, all of the resulted QSAR models also had the $F_{\text{cal}}/F_{\text{tab}}$ values of more than 1. This value showed that the descriptors on the QSAR equation simultaneously affect the antimalarial activity at a significance level of 95%¹⁷. The lower value of SEE indicated that the model has a lower deviation from experimental data. The complete equation of models 1 to 4, respectively, are:

$$\text{pIC}_{50} = 0.0125 \times (\text{VOL}) - 0.147 \times (\text{MR}) + 0.0115 \times (\text{MW}) + 1.5481 \times (\text{qC}_{12}) + 35.1286 \times (\text{qC}_{10}) - 0.6037$$

$$\text{pIC}_{50} = 0.0082 \times (\text{SA}) + 0.0122 \times (\text{MW}) - 0.0709 \times (\text{MR}) + 22.3351 \times (\text{E}_{\text{HOMO}}) + 50.389 \times (\text{qC}_{10}) + 1.4152 \times (\text{qC}_{12}) + 3.1403$$

$$\text{pIC}_{50} = 0.0129 \times (\text{VOL}) - 0.155 \times (\text{MR}) + 0.0123 \times (\text{MW}) + 1.8001 \times (\text{qC}_{12}) - 0.7814 \times (\text{qC}_2) + 44.7523 \times (\text{qC}_{10}) + 45.9206 \times (\text{qC}_8) + 4.3202$$

$$\text{pIC}_{50} = 0.0108 \times (\text{MW}) + 0.0089 \times (\text{SA}) - 0.0685 \times (\text{MR}) - 8.7472 \times (\text{qC}_6) + 41.4389 \times (\text{qC}_{10}) - 5.3773 \times (\text{qC}_4) + 27.317 \times (\text{qC}_8) + 2.0235 \times (\text{qC}_{12}) + 2.0865$$

To choose the best QSAR equation, all of the QSAR models have to be validated externally. External validation was carried out to test the ability of all QSAR models that satisfy the statistical criteria in

predicting antimalarial activity outside the training set compounds (Table-3). It showed that model 4 had the lowest r^2 and PRESS. All models are valid due to their r^2 values of more than 0.6.¹⁷ Another statistical parameter, such as $r_m^2 > 0.5$, indicates that the model is acceptable and has a good predictive ability.¹⁷ However, it showed that only model 2 satisfied these statistical parameters. Therefore, model 2 was selected as the best QSAR equation.

Table-2: Four QSAR Models and Their Statistical Properties

Model	Descriptors	r	r^2	SEE	F	F_{cal}/F_{tab}	PRESS
1	qC_{10} , qC_{12} , VOL, MR, MW	0.912	0.831	0.170	15.839	5.342	0.495
2	qC_{10} , qC_{12} , E_HOMO, SA, MR, MW	0.935	0.873	0.152	17.331	6.075	0.349
3	qC_2 , qC_8 , qC_{10} , qC_{12} , VOL, MR, MW	0.954	0.910	0.133	20.375	7.301	0.260
4	qC_4 , qC_6 , qC_8 , qC_{10} , qC_{12} , SA, MR, MW	0.959	0.920	0.130	18.798	6.800	0.249

Table-3: Experimental and Predicted pIC_{50} Value of the Test Set

Test Set Compound	Experimental pIC_{50}	Predicted pIC_{50}			
		Model 1	Model 2	Model 3	Model 4
3	5.408	5.062	5.114	5.035	5.036
9	5.000	4.760	4.761	4.764	4.733
19	4.744	4.515	4.430	4.461	4.427
25	5.045	4.712	4.878	4.692	4.729
27	5.065	4.776	4.642	4.743	5.145
PRESS		0.424	0.449	0.503	0.416
r^2		0.975	0.862	0.959	0.593
r_m^2		0.415	0.626	0.423	0.433

Based on the best QSAR equation (model 2), increasing molecular weight (MW), surface area (SA), HOMO energy (E_HOMO), and net atomic charge on C_{10} (qC_{10}) and C_{12} (qC_{12}) would also increase antimalarial activity. However, increasing molar refractivity (MR) would decrease antimalarial activity. The higher value of net atomic charge on C_{10} and C_{12} could be obtained by the presence of electron-donating groups that could also increase the HOMO energy (E_HOMO).²⁴ Electron-donating groups such as hydroxyl and methoxy could affect the HOMO energy of chalcone derivatives, and they play an important role in producing good antimalarial activity that would lead to the destruction and death of the parasite.²⁵⁻²⁷ Based on QSAR analysis, several chalcones derivatives with electron-donating groups were proposed, and then they were synthesized via Claisen Schmidt reactions; the synthetic scheme is outlined in Fig.-1.

A: $R_1 = R_2 = H$, $R_3 = OCH_3$
 B: $R_1 = H$, $R_2 = OH$, $R_3 = OCH_3$
 C: $R_1 = R_2 = R_3 = OCH_3$

Fig.-1: The Synthesis Scheme of the Present Work

All the chalcones were characterized using IR, 1H -NMR, ^{13}C -NMR, and MS spectroscopies. Chalcones IR spectra depicted the existence of C_{sp^2} -H bending band at $979-997\text{ cm}^{-1}$, indicating the presence of trans-disubstituted alkene and $1643-1658\text{ cm}^{-1}$ which is characteristic of $C=O$ of enone or α,β -unsaturated ketone functional group.⁷ GC-MS spectra showed the molecular ion (M^+), which is related to the molecular weight of each chalcone. The 1H -NMR spectra of chalcones displayed two doublets with a coupling constants value (J) of $15.0-15.55\text{ Hz}$, indicating the existence of trans coupling of alkene protons.²⁵ In addition, the ^{13}C -

NMR spectrum clearly showed the presence of an alkene carbon (C_α and C_β) resonating at 119-120 and 143-144 ppm and carbonyl at 187-190 ppm for chalcone A-C. From all the evidence above, it can be concluded that all chalcones were successfully synthesized.

The synthesized chalcones were then assayed as antimalarial agents against *P. falciparum* 3D7 using microtechnique methods, and the result was presented in Table-5. It was shown that chalcones A-C have an IC_{50} value between 1-20 μM , indicating that all of them were categorized as good antimalarial agents.¹³ From this table, the *in vitro* testing and QSAR analysis revealed that chalcone C had the highest antimalarial activity. This was due to chalcone C having three methoxy groups, which increased its surface area (SA), molecular weight (MW), and HOMO energy (E_{HOMO}). It showed that the lower value of IC_{50} from QSAR analysis would also give the lower IC_{50} from *in vitro* testing. The correlation (r) of IC_{50} based on QSAR analysis and *in vitro* testing was found to be 0.858. It indicated that the QSAR equation has a good trend in predicting antimalarial activity.

Table-5: Comparison of Antimalarial Activity based on QSAR Analysis and *In Vitro* Assays

Chalcone	QSAR Analysis		<i>In vitro</i> Testing
	pIC ₅₀	IC ₅₀ (μM)	IC ₅₀ (μM)
A	4.19	64.29	4.21
B	4.42	37.65	3.87
C	5.11	7.70	2.59
Correlation	0.858

Fig.-2: Interaction of Chalcone C on the Active Site of PfDHODH

Molecular docking results showed that all designed chalcones interacted nicely with the active site of PfDHODH. These results showed that the binding affinity of chalcone A, B, and C, was -9.2, -8.9, and -8.2 kcal/mol, respectively, whereas the native ligand (inhibitor A26) was found to be -9.0 kcal/mol. This indicated that all chalcones could potentially inhibit the receptor. As shown in Fig.-2, chalcone C bound stably on important amino acid residues of Leu172, Phe171, Cys175, Gly181, Cys184, Phe188, Phe227, Ile263, Arg265, Tyr528, Val532, Gly535, and Met536, which play an important role in inhibiting PfDHODH.¹¹

CONCLUSION

The QSAR analysis and synthesis of chalcone derivatives as an antimalarial compound towards *P. falciparum* 3D7 strain were carried out. The best and fitted QSAR equation is model 2, and it was used for designing some substituted chalcones to get a potential antimalarial agent. The synthesized chalcone derivatives with electron-donating groups were tested as an antimalarial agent against *P. falciparum* 3D7 strain, and the result showed that chalcone C with an IC_{50} value of 1.29 μM has excellent activity as an antimalarial agent. Molecular docking results showed that chalcone C could be an inhibitor of PfDHODH potentially.

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