QSAR ANALYSIS USING SEMI-EMPIRICAL AM1 METHOD, MOLECULAR DOCKING, AND ADMET STUDIES OF CHALCONE DERIVATIVES AS ANTIMALARIAL COMPOUNDS

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Received 21 September 2023
Accepted 02 December 2023

Abstract

Malaria is a serious caused by protozoan parasites such as *Plasmodium* groups and has fatal consequences for human health. The increase in the resistance of the *Plasmodium* parasites toward existing antimalarial drugs prompts the exploration of novel compounds. In this study, quantitative structure-activity relationship (QSAR) analysis using the semi-empirical AM1 method was conducted to identify the optimal model that relates physicochemical properties and biological activity of chalcone derivatives. In addition, ADMET prediction and molecular docking were also carried out. Multilinear regression calculations for statistical parameters of QSAR models revealed that Model 4, with 11 independent variables, provided the best predictions and exhibited a robust correlation with antimalarial activity represented by inhibitory concentration (IC_{50}). ADMET predictions indicated favorable absorption, distribution, metabolism, excretion, and toxicity properties, particularly for B_2D, showing promising antimalarial attributes. Molecular docking studies targeting 5 mutated PfDHODH proteins revealed B_2D's potential to reach therapeutic targets efficiently. It has low docking scores for mutations I (-10.5 kcal/mol), II (-8.6 kcal/mol), and V (-10.5 kcal/mol) with RMSD < 2Å, in carrying out its role for antimalarial activity. This research successfully identifies B_2D as an efficient inhibitor of PfDHODH receptors. Thus, it is a highly promising novel antimalarial drug.

Keywords*: ADMET prediction, antimalarial agents, chalcone derivative, molecular docking, QSAR*

Introduction

Malaria continues to be a major global health concern for many countries across the world, especially in sub-Saharan Africa, Asia, and South America. Malaria is caused by parasites of the genus *Plasmodium*. It has become a major public health concern due to the emergence of several drug-resistant such as chloroquine, quinoline, antifolate, and artemisinin. The resistance of *Plasmodium falciparum* toward antimalarial drugs also contributed to over 3 billion malarial cases, with an estimated annual mortality rate of around 500,000 people (WHO, 2021). Hence, it is crucial to find new antimalarial drugs with better pharmacological activity than currently available medication (Ibrahim *et al*., 2020). A recent development in the search for better antimalarial drugs is the successful synthesis of 55 chalcone derivatives, which have shown superior antimalarial activity when compared to chloroquine. This discovery has led researchers to consider these derivatives as a promising alternative to current anti-malarial agents. (Wilhelm *et al*., 2015).

Various organic compounds can be used as antimalarial agents. Chalcone is an unsaturated α, β-carbonyl compound, and crucial flavonoid from the synthetic products of natural materials with biological and pharmacological properties. It exhibits diverse biological activities, such as antibacterial (Xu *et al*., 2019), anticancer (Fang *et al*., 2019), antileishmanial (Silva *et al*., 2022), antifungal (Permana *et al*., 2022), antiviral, antimalarial (Wilhelm *et al*., 2015), antimicrobial (Nasir and Marwati, 2022), anti-inflammatory (Liu *et al*., 2014), antiprotozoal (Carvalho *et al*., 2012). It is interesting to note that chalcone derivatives have the potential to act on the trophozoite stage by inhibiting hemozoin formation, which makes them a promising candidate for non-resistant *Plasmodium falciparum* parasites (Qin *et al*., 2020).

QSAR, molecular docking, and ADMET analysis are important tools that aid in the design of new antimalarial drugs by minimizing trial and error as well as reducing the waste of time and costs that would otherwise be incurred (Fan *et al*., 2019; Pinzi and Rastelli, 2019). Numerous investigations encompassing Quantitative Structure-Activity Relationship (QSAR), ADMET prediction, and molecular docking have been conducted (Anggraeni *et al*., 2022; Arba *et al*., 2016; Waskitha *et al.*, 2016)

Waskitha *et al.* (2021) employed a stepwise multiple linear regression analysis for QSAR and molecular docking on chalcone derivative compounds that serve as antimalarial agents against the *Plasmodium falciparum* 3D7 strain. The results of the QSAR analysis revealed a robust correlation between the antimalarial activity of chalcone derivatives and electronic and molecular descriptors. Then, molecular docking results demonstrated the effective interaction of this compound at the active site of PfDHODH. In a previous study, Syahri *et al.* (2020) conducted QSAR and molecular docking analyses on 28 aminoalkylation chalcone derivatives as potential antimalarial agents. The QSAR analysis identified the best model as log IC50 = 705.132 (qC7)-65.573 (qC3)-24.845 (qC4)-4.634 (qC13)-220.479, and statistical analysis yielded an R^2 of 0.937, indicating that the QSAR model accurately predicted actual antimalarial activities with 93.7% precision. Molecular docking investigations explored the interactions of the synthesized compounds with the binding site of *Plasmodium falciparum dihydrofolate reductase-thymidylate synthase* (Pf-DHFR-TS) in both wild-type and quadruple mutant forms. Another study informs ADME analysis on compounds derived from Traditional Chinese Medicine, focusing on inhibitors of both wild-type and mutant *Plasmodium falciparum Dihydrofolate Reductase* (DHFR). The results presented promising docking scores for the eight analyzed compounds. Importantly, these compounds exhibited potential as drug candidates, demonstrating antiprotozoal activity and compliance with Lipinski's Rule of five criteria (Iwaloye et al., 2021).

Several chalcone derivatives have been synthesized by Wilhelm *et al*. (2015). However, It seems that no analysis has been conducted yet on QSAR, drug likeness, ADMET prediction, and simulation in the body in the form of molecular docking toward those compounds. Hence, this research aims to analyze the QSAR of several chalcone derivatives for determining the affecting parameters of chalcone derivatives as antimalarial drugs. Then, the performance of the new chalcone derivatives in the human body is predicted through molecular docking, drug likeness, and ADMET analysis to evaluate their properties as antimalarial drugs.

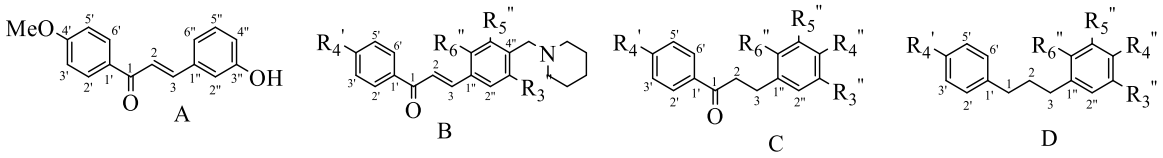
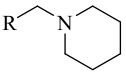
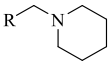
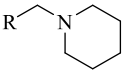
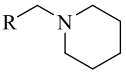
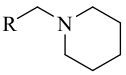
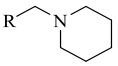
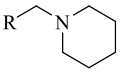
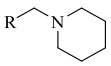
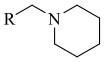
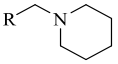
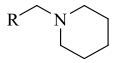
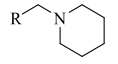
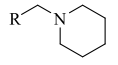
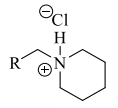
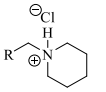
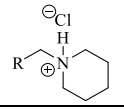


Figure 1. Molecular structures of chalcone derivatives that have been synthesized by obtained from Wilhelm *et al*. (2015).

Table 1. Chalcone derivatives and IC50 values as antimalarial compounds obtained from Wilhelm *et al*. (2015).

Compounds	R_4'	R_3''	R_4''	R_5''	R_6''	IC_{50} µg/mL
A_1	MeO	OH	H	H	H	11.30
B_1	MeO	OH		H	H	0.83
B_2	CF_3	H	OH		H	0.17
B_3	Br	OH		H	H	0.15
B_4	C_2H_5	OH		H	H	0.14
B_5	F	OH		H	H	0.10
D_1	MeO	OH		H	H	0.21
D_2*	MeO	OH		H		0.06
D_3*	CF_3	H	OH		H	0.01
D_4*	F	OH		H	H	0.07
D_5*	CH_3	OH		H	H	0.09
D_6	C_2H_5	OH		H	H	0.18
D_7		OH		H	H	0.18
D_8	MeO	OH		H	H	0.07
D_9*	F	OH		H	H	0.03
D_{10}*	H	OH		H	H	0.02

Research Methods

Materials

This research was conducted computationally, utilizing chalcone derivatives obtained from Wilhelm *et al*. (2015). The molecular structures of chalcone derivatives and their half maximal inhibitory concentrations (IC_{50}) are displayed in Table 1. IC_{50} values from Table 1 were used as the dependent variables

Instrumentation

The instruments used in this study were a set of computers equipped with an Intel® Core i5 Gen 8th 1.60 GHz

processor, 4 GB RAM, and 500 GB ROM. All descriptors (independent variables) were calculated using the HyperChem® software package version 8.0.7 with the semi-empirical AM1 method. Statistical analysis was conducted using IBM® SPSS® version 26. SwissADME was used to predict pharmacokinetic and drug-likeness parameters. Then, ADMET properties ere predicted by AdmetSAR. Meanwhile, Molecular docking was carried out by Discovery Studio Visualizer version 4.5, Open Babel, PyRx version 0.8, and PyMol version 2.5.7 software.

Procedure

1) QSAR analysis
   All chemical structures were geometrically optimized by HyperChem® software version 8.0.7 to obtain stable conformations using the Polak Ribiere algorithm, RMS gradient 0.001 kcal/$Å^{-1}$.mol^{-1} or 25.000 maximum cycles. The sets of several variables were determined to choose the influential descriptors. Multilinear Regression (MLR) analysis was employed to build QSAR models that determined the relationship between a set of predictors and their bioactivity potential (IC50). Statistical parameters like R, R^2, standard error (SE), F_{calc}/F_{tab}, and PRESS were used to validate resulted models. (Pingaew *et al*., 2022).
2) Drug-likeness and ADMET prediction
   The drug-likeness was conducted via the SwissADME program on the SwissADME website server (http://www.swisadme.ch/index.php) (Hadni *et al*., 2020). It was assessed through filters based on Lipinski, Ghose, Veber, Egan, and Muegge's rules using molecular weight, log P, partition coefficient value, number of hydrogen bond donors, and number of hydrogen bond acceptor parameters, etc. Besides that, synthetic accessibility difficulty testing at a range of 1 to 10 and bioavailability score testing. After that, the ADME test (Adsorption, Distribution, Metabolism, and Excretion) was predicted by admetSAR.
3) Molecular docking modeling
   Molecular docking analysis was conducted to identify interactions between the test compound and the target protein. The purpose of molecular docking is to analyze the complex binding affinities that form. The method employed in conducting molecular docking involves the use of PyRx software. The PfDHODH protein, which has undergone mutations and was identified through the PDB codes 6i55, 4b3z, 4cqa, 8wbv, and 6i4b from the RCSB Protein Data Bank, was prepared by removing the original ligand and water molecules. This process also included adding polar hydrogen atoms using Discovery Studio Visualizer software. Subsequently, molecular docking proceeded with the automatic configuration of Grid 3D and set the exhaustiveness value above 128. Compounds with an RMSD value less than 2 Å were considered successful and valid in their interactions. These results were then visualized in 2D and 3D to determine the position and type of interactions formed. Visualization was carried out using PyMOL and Discovery Studio Visualizer software.

Results and Discussion

QSAR Analysis

QSAR analysis was employed to design and optimize 16 chalcone derivative compounds using the semi-empirical AM1 method. This analysis finds regression functions that can predict the theoretical relationship between the biological activity and the descriptors of the molecular structure of each compound. Besides that, QSAR analysis prevents the waste of time as well as costs (Shou, 2020). Descriptors as independent

variables in this study encompassed eight parameters representing three main aspects: hydrophobic, electronic, and steric parameters. The descriptors included total atomic charge, dipole moment, E_{HOMO}, E_{LUMO}, polarizability, reactivity, molecular weight, and Log P, as outlined in Table 2.

Table 2. Descriptors of independent variables used in QSAR analysis for antimalarial activity of chalcone derivatives using the semi-empirical AM1 method.

Compound	Parameters						
	qC1	**qC2**	**qC3**	**qC1'**	**qC2'**	**qC3'**	**qC4'**
A_1	0.300442	-0.233087	-0.043491	-0.181684	-0.040062	-0.218366	0.104595
B_1	-0.093513	-0.140293	-0.136261	-0.104771	-0.094476	-0.201245	0.076915
B_2	0.294674	-0.263834	-0.009670	-0.109148	-0.088346	-0.091260	-0.143398
B_3	0.294886	-0.240854	-0.032562	-0.129474	-0.080732	-0.114843	-0.147105
B_4	0.296503	-0.236303	-0.040053	-0.148298	-0.075889	-0.141658	-0.044056
B_5	0.297982	-0.241355	-0.034024	-0.159371	-0.054488	-0.178086	0.114161
D_1	-0.117977	-0.152846	-0.125847	-0.105114	-0.096342	-0.152976	0.075379
D_2*	-0.118176	-0.152888	-0.128451	-0.105610	-0.096838	-0.154861	0.075499
D_3*	-0.131684	-0.152829	-0.117069	-0.036305	-0.134698	-0.078595	-0.166816
D_4*	-0.122646	-0.152867	-0.125327	-0.083763	-0.103209	-0.162469	0.085598
D_5*	-0.122529	-0.152331	-0.125869	-0.075196	-0.123486	-0.128278	-0.072383
D_6	-0.122685	-0.152324	-0.125866	-0.074009	-0.125158	-0.125092	-0.072199
D_7	-0.114929	-0.152705	-0.126204	-0.114779	-0.090326	-0.193105	0.067429
D_8	-0.118015	-0.152099	-0.126950	-0.106271	-0.093171	-0.202210	0.076122
D_9*	-0.122672	-0.152075	-0.126780	-0.084925	-0.103807	-0.163866	0.086499
D_{10}*	-0.123418	-0.152194	-0.126713	-0.071329	-0.126336	-0.127618	-0.131819

Table 2. Descriptors of independent variables used in QSAR analysis for antimalarial activity against chalcone derivatives using the semi-empirical AM1 method (cont'd).

Parameters							
qC5'	**qC6'**	**qC1''**	**qC2''**	**qC3''**	**qC4''**	**qC5''**	**qC6''**
-0.171408	-0.061951	-0.032966	-0.135364	0.075754	-0.200773	-0.095520	-0.144644
-0.154152	-0.092310	-0.004607	-0.158811	0.109294	-0.162156	-0.090873	-0.160877
-0.093359	-0.103436	-0.121021	-0.065508	-0.172900	0.133325	-0.171676	-0.058613
-0.116272	-0.096057	-0.037719	-0.135528	0.081159	-0.135567	-0.080066	-0.143730
-0.142053	-0.091225	-0.034168	-0.143458	0.106324	-0.148977	-0.095496	-0.148605
-0.179952	-0.069710	-0.033474	-0.194334	0.094088	-0.079545	-0.101020	-0.141142
-0.202064	-0.092778	-0.033811	-0.164778	0.112244	-0.166130	-0.088248	-0.167663
-0.200185	-0.092315	-0.026005	-0.171829	0.112912	-0.168269	-0.067041	-0.112420
-0.078175	-0.134053	-0.112246	-0.089333	-0.212105	0.077258	-0.097602	-0.075953
-0.163915	-0.103453	-0.035193	-0.165069	0.112548	-0.165073	-0.087916	-0.167269
-0.129067	-0.123739	-0.033795	-0.164827	0.112043	-0.166090	-0.088242	-0.167458
-0.126826	-0.124832	-0.033842	-0.164772	0.112020	-0.166057	-0.088238	-0.167435
-0.182203	-0.092218	-0.032951	-0.164675	0.111756	-0.166679	-0.088272	-0.167455
-0.152800	-0.096272	-0.029703	-0.213581	0.083021	-0.108463	-0.080157	-0.161917
-0.162310	-0.103187	-0.030366	-0.212465	0.083043	-0.104855	-0.082621	-0.159900
-0.127618	-0.127823	-0.028826	-0.212206	0.082539	-0.108035	-0.081785	-0.161073

Table 2. Descriptors of independent variables used in QSAR analysis for antimalarial activity against chalcone derivative compounds using the semi-empirical AM1 method (cont'd).

μ	**E_{LUMO}**	**E_{HOMO}**	**α(Å^3)**	**RE**	**MW**	**Log P**
3.129	-0.718975	-9.200168	28.60	83.04	254.29	1.07
3.075	-0.054692	-8.717509	40.10	112.30	337.46	1.41
4.202	-1.034838	-8.975642	39.28	111.81	389.42	2.93
4.535	-0.913759	-9.157406	40.34	114.13	400.32	2.41
4.789	-0.705091	-9.019870	41.39	115.47	349.47	2.91
2.504	-0.901074	-8.897831	37.63	106.72	339.41	1.76
2.863	0.3330184	-8.788849	40.30	111.18	339.48	1.67
1.069	0.351638	-8.714210	51.88	141.10	436.64	1.97
4.038	-0.313089	-8.956395	39.39	110.02	377.45	3.23
3.444	0.1442311	-8.925491	37.73	104.93	327.44	2.06
1.982	0.3295989	-8.865480	39.66	109.09	323.48	2.82
1.957	0.3299744	-8.866086	41.49	113.69	337.51	3.21
1.085	0.3795768	-8.224360	44.68	122.30	366.55	2.11
3.804	0.263980	-8.866085	42.03	115.22	375.94	1.58
2.539	0.05678504	-9.073904	39.47	108.97	363.90	1.98
2.983	0.2179514	-9.021310	39.56	108.84	345.91	2.58

Antimalarial activities of chalcone derivatives were examined by multilinear regression analysis using IBM® SPSS® software. This analysis aimed to assess the extent to which regression coefficients influence antimalarial activity (Utomo *et al*., 2017). The regression analysis generated seven QSAR equation models involving regression variables and antimalarial activity, as illustrated in Tables 3 and 4.

Table 3. Coefficients of selected independent variables for the 7 QSAR models obtained from the multilinear regression analysis of chalcone derivatives.

QSAR Models	Coefficient of independent variables														
	qC2	qC1'	qC3'	qC4'	qC5'	qC1''	qC2''	qC4''	qC5''	qC6''	μ	E_{LUMO}	E_{HOMO}	α	Const
1	-1.073	15.851	-30.581	-14.452	-24.347	-397.836	-143.143	-96.959	-23.249	19.646	-0.092	-4.292	-1.864	0.170	-81.906
2		15.444	-30.593	-14.546	-24.410	-399.000	-143.615	-97.328	-24.045	19.595	-0.092	-4.365	-1.881	0.172	-82.258
3		14.993	-27.129	-13.763	-22.307	-398.618	-147.643	-99.698	-26.125	26.384		-4.301	-1.294	0.152	-75.792
4			-15.977	-10.627	-13.582	-385.727	-143.829	-94.574	-18.860	26.423		-3.360	-1.107	0.123	-69.021
5			-10.230	-9.234	-8.695	-384.751	-149.410	-97.526	-19.436	34.736		-3.530		0.085	-56.098
6			-8.440	-6.684		-388.508	-152.017	-100.459	-22.336	36.882		-3.584		0.099	-55.969
7				-4.459		-380.830	-150.773	-99.688	-23.048	37.578		-3.545		0.083	-53.410

Table 4. Seven models and their statistical parameters for the correlation between molecular properties and antimalarial activity.

QSAR Models	Variables	R	R^2	SE	F_{Cal}/F_{Tab}	Press
1	qC2, qC1', qC3', qC4', qC5', qC1", qC2", qC4", qC5", qC6", μ, E_{LUMO}, E_{HOMO}, α	0.999	0.998	0.442	0.192	0.011
2	qC1', qC3', qC4', qC5', qC1", qC2", qC4", qC5", qC6", μ, E_{LUMO}, E_{HOMO}, α	0.999	0.998	0.312	5.207	0.013
3	qC1', qC3', qC4', qC5', qC1", qC2", qC4", qC5", qC6", E_{LUMO}, E_{HOMO}, α	0.999	0.998	0.265	17.340	0.079
4	qC3', qC4', qC5', qC1", qC2", qC4", qC5", qC6", E_{LUMO}, E_{HOMO}, α	0.999	0.998	0.257	29.633	0.038
5	qC3', qC4', qC5', qC1", qC2", qC4", qC5", qC6", E_{LUMO}, α	0.998	0.997	0.291	31.866	0.020
6	qC3', qC4', qC1", qC2", qC4", qC5", qC6", E_{LUMO}, α	0.998	0.996	0.301	38.357	0.177
7	qC4', qC1", qC2", qC4", qC5", qC6", E_{LUMO}, α	0.997	0.994	0.332	38.765	50.445

The best regression equation is based on several factors. These include high R and R^2 values, which should exceed 0.8 (80%) and approach 1 (100%) to demonstrate a strong relationship between independent and dependent variables (Evita *et al*., 2022). A small standard error (SE) indicates the accuracy of the regression equation in predicting actual or true values (Utomo *et al*., 2017). A large F_{cal}/F_{Tab} value indicates a significant confidence level at the 95% level between physicochemical properties and antimalarial activity (Zain *et al*., 2020). This suggests that the seven models utilized in the regression analysis have a strong relationship with the antimalarial activity of the 16 chalcone derivative compounds.

Based on the data in Table 4, 7 QSAR analysis models are using the backward method. Model/Equation 4 was selected as the best QSAR analysis model, involving 11 independent variables, including total atomic charge (qC3', qC4', qC5', qC1'', qC2'', qC4'', qC5'', qC6''), E_{LUMO}, E_{HOMO}, and polarizability (α) (Evita *et al*., 2022). The selected QSAR model has values of R = 0.999; R^2 = 0.998; SE = 0.257; F_{cal}/F_{Tab} = 29.633; Press = 0.038 (Muliadi *et al*., 2023).

$$\text{Log } IC_{50} = -69.021-(15.977\times qC3')-(10.627\times qC4')-(13.582\times qC5')-(385.727\times qC1'')-(143.829\times qC2'')-(94.574\times qC4'')-(18.860\times qC5'')+(26.423\times qC6'')-(3.360\times E_{LUMO})-(1.107\times E_{HOMO})+(0.123\times \alpha)$$

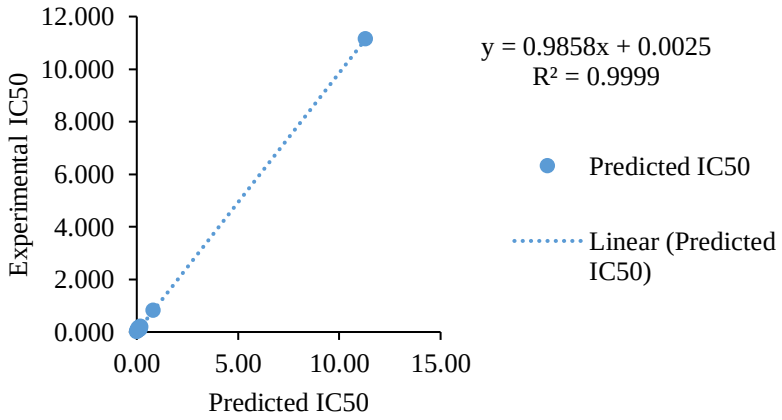


Figure 2. Linear regression of experimentally observed antimalarial activity (IC_{50}) versus the calculated values based on QSAR Model 4.

The descriptors resulting from the calculations for each compound were obtained using HyperChem software version 8.0.7 employing the semi-empirical AM1 method. These values were utilized to construct the Quantitative Structure-Activity Relationship (QSAR) equation through Multilinear Regression (MLR) analysis. The MLR analysis results indicate that Model 4 exhibits optimal regression quality. This model is considered a valid candidate for predicting IC_{50} values as it satisfies the predetermined statistical criteria and possesses descriptors specific to hydrophobic, electronic, and steric parameters (Arba *et al*., 2016; Hadanu 2015).

Several statistical criteria considered in Table 4 include values such as R > 0.8 (80%), R^2 approaching 1 (100%), F_{cal}/F_{tab} > 1, and a small standard error (SE). Among the 7 models presented in Table 4, Model 4 consistently stands out as the best model with values R = 0.999; R^2 = 0.998; SE = 0.257; F_{cal}/F_{tab} = 29.633; Press = 0.038. This model demonstrates excellent capability in predicting the antimalarial activity of chalcone derivatives. The conclusion is reinforced by the low Press value, indicating the QSAR model's proficiency in predicting antimalarial activities (Arba *et al*., 2016; Hadanu 2015).

A QSAR model is considered ideal when it approaches an R^2 value of 1, signifying a perfect correlation between independent and dependent variables. Other statistical parameters such as SE and F_{cal}/F_{tab} values also need consideration to evaluate the significance of the QSAR model. In this study, Model 4 is deemed the most reliable due to its smallest SE value, reflecting a thorough evaluation of antimalarial activities using the semi-empirical AM1 method (Hadanu 2015).

The research findings also reveal a structure-activity relationship in antimalarial compounds, where changes in substituent groups at specific positions can impact their bioactivity. Figure 2 reflects the predicted antimalarial activity (predicted IC_{50}) and correlation with experimental antimalarial activity (experimental IC_{50}) in Model 4, demonstrating linearity (R^2 = 0.9999) and a slope approaching 1. This indicates that Model 4 is valid both internally and externally.

Based on the parameters from the multilinear regression analysis in Table 4, these parameters appear to have a significant impact on pharmacological and bioactive activities. Among the 16 substituents in chalcone derivative compounds, compound B_2 is considered the best as its most significant parameters suggest the potential of compound B_2 as a new antimalarial drug candidate.

Drug-likeness and ADMET prediction

This analysis is carried out to predict drug-likeness, pharmacokinetics and related pharmacodynamics in the absorption, distribution, metabolism, and excretion of drugs in the human body to easily predict the distribution of clinically relevant drugs. The existence of ADMET assays is critical in supporting significant processes of discovery, development, and design of new drugs (Mahanthesh MT *et al*., 2020).

Table 5. Drug-likeness, Pharmacokinetic profile, and ADMET predictions of the chalcone derivative compound (B_2).

Compounds	GI *absorption*	BBB *permeant*	P-gp Subs	Inhibitors					Druglikness		
				CYP 1A2	CYP 2C19	CYP 2C9	CYP 2D6	CYP 3A4	Lipinski	Ghose	Veber
B_2	High	Positive	Negative	Yes	Yes	-	Yes	-	Yes	-	Yes
B_2A	High	Negative	Negative	Yes	-	-	-	-	Yes	Yes	Yes
B_2B	High	Negative	Negative	-	-	-	-	-	Yes	-	Yes
B_2C	Low	Negative	Positive	-	-	-	-	-	Yes	-	Yes
B_2D	Low	Negative	Negative	Yes	-	-	Yes	-	Yes	Yes	Yes
B_2E	High	Negative	Negative	-	Yes	-	Yes	-	Yes	-	Yes
B_2F	High	Negative	Negative	-	Yes	-	-	-	Yes	-	Yes
B_2G	Low	Negative	Negative	-	Yes	-	-	-	Yes	-	Yes
B_2H	High	Negative	Positive	Yes	Yes	Yes	-	-	Yes	Yes	Yes
B_2I	High	Negative	Positive	-	-	-	-	-	Yes	-	Yes
B_2J	Low	Negative	Negative	-	-	-	-	-	Yes	-	Yes
B_2K	Low	Negative	Positive	-	Yes	-	-	-	Yes	-	Yes
B_2L	High	Negative	Negative	-	Yes	-	-	-	Yes	-	Yes
B_2M	High	Negative	Negative	-	Yes	-	Yes	-	Yes	-	Yes
B_2N	High	Negative	Positive	-	Yes	-	-	-	Yes	-	Yes
B_2O	High	Negative	Positive	-	Yes	-	-	Yes	Yes	Yes	Yes
B_2P	Low	Negative	Negative	-	-	Yes	-	Yes	Yes	-	-
B_2Q	Low	Negative	Positive	-	Yes	-	-	-	-	-	Yes
B_2R	Low	Negative	Positive	-	-	Yes	-	-	-	-	-
B_2S	Low	Negative	Negative	-	Yes	-	-	-	-	-	-
B_2T	Low	Negative	Positive	-	-	-	-	-	Yes	-	Yes

Table 5. Drug-likeness, Pharmacokinetic profile, and ADMET predictions of the chalcone derivative compound (B_2) (cont'd).

Druglikness		Bioavailability Score	Synthetic accessibility	Carcinogens	Acute Oral Toxicity (kg/mol)	Class Toxicity
Egan	Muegge					
Yes	Yes	0.55	2.93	Non-carcinogens	3.21	III
Yes	Yes	0.55	3.53	Non-carcinogens	2.853	III
-	-	0.55	3.66	Non-carcinogens	2.658	III
-	-	0.55	3.89	Non-carcinogens	3.049	III
Yes	Yes	0.55	3.40	Non-carcinogens	2.949	III
Yes	-	0.55	4.11	Non-carcinogens	2.884	III
Yes	Yes	0.55	3.72	Non-carcinogens	2.878	III
-	-	0.55	4.15	Non-carcinogens	2.568	III
Yes	Yes	0.55	3.80	Non-carcinogens	2.995	III
Yes	Yes	0.55	3.68	Non-carcinogens	2.899	III
-	-	0.55	3.84	Non-carcinogens	2.504	III
-	-	0.55	4.26	Non-carcinogens	2.867	III
Yes	Yes	0.55	3.82	Non-carcinogens	2.899	III
Yes	Yes	0.55	3.82	Non-carcinogens	2.993	III
Yes	-	0.55	3.97	Non-carcinogens	2.75	III
Yes	Yes	0.55	3.42	Non-carcinogens	3.528	III
-	-	0.55	3.88	Non-carcinogens	2.415	III
-	-	0.55	4.39	Non-carcinogens	3.108	III
-	-	0.17	6.72	Non-carcinogens	4.41	III
-	-	0.17	4.85	Non-carcinogens	2.821	III
Yes	Yes	0.55	3.74	Non-carcinogens	2.89	III

Drug-likeness and ADMET prediction were conducted to understand how the B_2 derivatives would behave in the human body or relevant target organisms regarding absorption, distribution, metabolism, and excretion. This is crucial in developing medicinal chemistry, as displayed in Table 5.

Table 5 presents the predicted pharmacokinetic profile of the B_2 derivative compound that was analyzed using SwissADME. The pharmacokinetics of the B_2 derivative indicate a high absorption rate and low gastrointestinal distribution, with molecular plots falling within the BOILED-Egg area. These findings are supported by a bioavailability value of 0.55, indicating good quality as the drug efficiently reaches the systemic circulation, consistent with Lipinski, Ghose, Verber, Egan, and Muegge rules, except for compounds B_2R and B_2S. In addition, the Synthetic Accessibility scores of the B_2 derivative compounds are low (Komari *et al*., 2022).

The next pharmacological properties prediction was conducted for B_2 derivative compounds using the admetSAR website. This prediction encompassed absorption, distribution, metabolism, excretion, and toxicity. The obtained results, presented in Table 5, indicate that the B_2 derivative compounds exhibit both high and low gastrointestinal absorption values (GI absorption or HIA). These findings suggest efficient absorption in the human body and optimal absorption rates in the human intestines. Furthermore, the distribution prediction results for the B_2 derivative compounds indicate that, except for compound B_2, the other compounds show a lack of ability to traverse the blood-brain barrier (non-BBB permeant). The BBB parameter is crucial as it determines the compound's ability to pass through the blood-brain barrier, which tightly regulates the movement of ions, molecules, and cells between the blood and the brain. The analysis of distribution with inhibition and P-glycoprotein substrate parameters is significant, as P-glycoprotein is one of the drug transporters that influences the absorption and excretion of various drugs. Prediction results indicate that several B_2 derivative compounds, such as B_2, B_2A, B_2B, B_2D, B_2E, B_2F, B_2G, B_2J, B_2L, B2M, B_2P, and B_2S, are non-substrates and non-inhibitors of P-glycoprotein. Conversely, other compounds act as substrates and inhibitors of P-glycoprotein. Furthermore, the carcinogenic profile of B_2 derivative compounds indicates non-carcinogenic properties, accompanied by an acute oral toxicity level that is considered safe, with values ranging between 2.5 and 3.5 kg/mol. Therefore, these compounds can be categorized as acute oral toxicity category III (Nusantoro and Fadlan, 2020).

Figure 3 illustrates the visualization of the BOILED-Egg to analyze pharmacokinetic properties. It becomes intuitive to estimate passive gastrointestinal absorption (HIA) and brain penetration (BBB) concerning molecular orientation. The yellow-shaded area indicates a higher likelihood of brain invasion, while the white-shaded area suggests the potential for passive absorption through the digestive tract. Based on this visualization, B_2 derivative compounds tend to undergo passive absorption through the digestive tract, brain invasion, and face challenges in absorption due to their random distribution on the BOILED-Egg (Al Azzam *et al*., 2022).

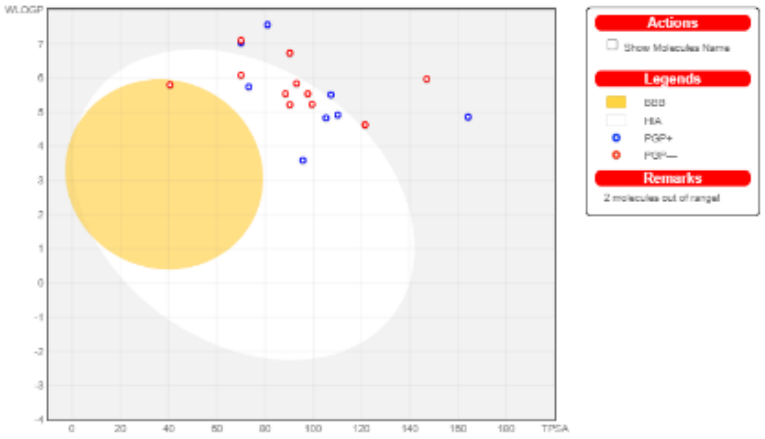


Figure 3. Pharmacokinetic BOILED-Egg parameters for 21 derivatives of B_2 chalcones, including predictions for human gastrointestinal absorption (HIA), blood-brain barrier (BBB), and P-glycoprotein (P-gp) (Deviana *et al*., 2021).

Molecular docking modeling

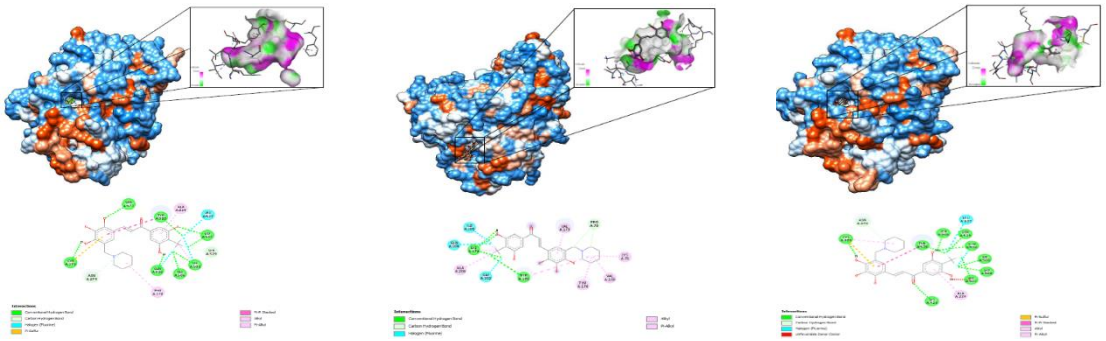
Molecular docking is a method used in drug discovery to predict interactions between test compounds and protein targets at the molecular level. This is achieved through in-silico modeling, which can predict binding affinity and favorable interactions between the compounds and the target proteins based on the lock-and-key model. Molecular docking modeling was conducted on selected B_2 derivative compounds in the QSAR analysis with the PfDHODH protein receptor in *Plasmodium falciparum* parasite cells that underwent mutations, with PDB codes (6i55, 4b3z, 4cqa, 8wbv, and 6i4b). This assay aimed to illustrate computationally simulated interactions, as indicated by low molecular docking values and the bonds formed between the selected B_2 derivative compounds and the 5 mutations of the PfDHODH protein. The interactions involve hydrogen bonds and hydrophobic interactions, as depicted in Table 6 and Figure 4.

Table 6. Antimalarial Activity in QSAR Analysis and the Best Molecular Docking Results of Chalcone Derivative Compounds.

Compounds	QSAR Analysis		Molecular Docking of PfDHODH Protein (kcal/mol)				
	Log IC50	IC50 (µM)	Mutations I	Mutations II	Mutations III	Mutations IV	Mutations V
B_2	-0.74	0.18	-10.4	-8.2	-10.6	-8.9	-10.3
B_2A	-0.04	0.92	-8.7	-8.3	-9.6	-8.5	-8.3
B_2B	-0.04	0.90	-8.6	-8.2	-7.6	-9.3	-7.9
B_2D	-0.03	0.93	-10.5	-8.6	-9.2	-8.5	-10.5
B_2F	-0.03	0.92	-8.1	-8.5	-8.6	-8.4	-7.5
B_2L	-0.03	0.93	-8.8	-8.4	-9.0	-8.2	-7.7
B_2M	-0.03	0.92	-8.5	-8.4	-9.3	-8.4	-7.2

Table 6 presents the results of QSAR analysis and molecular docking for the selected compound. B_2D is a promising antimalarial candidate after exhibiting low docking scores against three PfDHODH protein mutations (Mutation I: -10.5 kcal/mol, Mutation II: -8.6 kcal/mol, and Mutation V: -10.5 kcal/mol) with an RMSD value < 2Å. The low docking scores indicate strong interactions between an active compound and the targeted protein (Pratama *et al*., 2021). The robust interactions of B_2D with the three PfDHODH protein mutations involve residues such as ser A:477, tyr A:528, gly A:507, ile A:508, gly A:506, gln A:526, cys A:276 (Mutation I), lys A:171, tyr A:170 (Mutation II), dan cys A:276, tyr A:528, ser A:505, ser A:529, gln A:526, ile

A:508, gly A:506, gly A:507, lys A:429 (Mutation V) and participating in hydrogen bond conversions, as illustrated in Figure 4. These findings suggest that the chalcone derivative B_2D has the potency to inhibit PfDHODH protein receptors. Besides that, it can inhibit PfDHODH protein metabolism either mutated or not, (Waskitha *et al*., 2021).



Compound B_2D Mutation I | Compound B_2D Mutation II | Compound B_2D Mutation V

Figure 4. Visualization of 2D and 3D docking results of B_2D compound in mode 1 using Discovery Studio Visualizer version 4.5 on the active site of PfDHODH protein in *Plasmodium falciparum* parasite cells with mutations.

Conclusions

This study provides crucial insights concerning the relationship molecular structure of chalcone derivatives with their antimalarial activity by QSAR analysis, pharmacokinetic properties by ADMET analysis, and their interaction with the targeted molecules by molecular docking. QSAR analysis showed that model 4 emerged as the best QSAR equation, incorporating 11 performance parameters. This QSAR model can be used to design antimalarial compounds from chalcone derivatives with higher activity that will be synthesized and tested in the laboratory. ADMET analysis exhibits that B_2D has efficient absorption and distribution within the human body. In addition, it also satisfies all tested drug-likeness parameters such as Lipinski, Ghose, Veber, Egan, and Muegge. Besides that, B_2D demonstrates the potency for reaching therapeutic targets and displays adaptive molecular docking against three mutated PfDHODH protein receptors, augmenting its contribution to antimalarial activity.

Acknowledgment

The Authors appreciate the Ministry of Education, Republic of Indonesia, through SIMBELMAWA and Universitas Sembilanbelas November Kolaka for funding this research.

Conflicts of Interest

The authors declare no conflicts of interest.

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