Asian Journal of Chemistry; Vol. 32, No. 11 (2020), 2839-2845

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2020.22846

A QSAR Modeling on Aurone Derivatives as Antimalarial Agents

R. HADANU

Department of Chemistry Education, Faculty of Teacher Training and Education Science, Sembilanbelas November Kolaka University, Sulawesi Tenggara 93517, Indonesia

Corresponding author: E-mail: ruslinhadanu@gmail.com

Received: 3 June 2020; *Accepted*: 21 July 2020; *Published online*: 28 October 2020; AJC-20106

A quantitative structure activity relationship (QSAR) analysis was performed on several aurones and its derivatives (**1-16**) and **17-21** compounds were used as internal and external tests, respectively. For aurone compounds, QSAR analysis has not been conducted. The semi-empirical PM3 method of HyperChem for Windows 8.0 was used to optimise the aurone derivative structures to acquire descriptors. For 15 influential descriptors, the multilinear regression MLR analysis was conducted by employing the backward method, and four new QSAR models were obtained. According to statistical criteria, model 2 was the optimum QSAR model for predicting the inhibition concentration (IC_{50}) theoretical value against novel aurone derivatives. The modelling of 40 (**22-61**) aurone compounds was achieved. Six novel compounds (**54**, **55**, **58**, **59**, **60** and **61**) were synthesized in a laboratory because the IC_{50} of these compounds was lower than that of chloroquine (IC_{50} = 0.14 μM).

Keywords: QSAR, Modeling, Aurone, MLR, Antimalarial activity.

INTRODUCTION

Currently, in 91 countries, malaria is a global health problem, especially in the tropical and subtropical regions [1] with reported 219 million cases in 2017. In Southeast Asia and particularly in Indonesia 10,950,000 and 4,380,000, respectively, malaria cases were reported [2]. Parasites have become highly resistant to malaria drugs including *Plasmodium falciparum* has become resistant towards chloroquine [3,4]. Apart from this problem of resistant towards antimalarial drugs, as a malaria vector, mosquito resistance has emerged [5].

Antimalarial drugs have been attempted to be developed by using a variety of organic compound derivatives and by isolating natural products, such as artemisinin derivative compounds [6], phenanthroline compound derivatives [7], new aurone compounds [8], derivatives of quinoline compounds [1,9,10], triazine compounds [11], xanthone derivative compounds [12], benzothiazole derivatives [13], mangosteen compounds [14], flavone derivatives [15], chalcone derivatives [16], 1-(4-methylphenyl)-2,5-dimethylpyrrole derivatives [17], berberine-[1,2,3]-triazole derivative compounds [18], acyloxybenzyl and alkoxyalkyl derivatives [19], 2-pyrazoyl quinolone derivative compounds [20], *Periploca linearifolia* extract [21], compounds of marine sponge *Hyrtios erectus* [22] and *Croton macrostachyus* stem bark extracts [23]. The antimalarial activities of the compounds of polyoxygenated cyclohexene acquired from the roots of *Uvaria cherrevensis* plant [24] that have fucosterol compounds [25] been studied. The antimalarial activity acquired through *Streptomyces asterosporus* isolation was also tested [26]. The activity of the aforementioned natural products and organic compounds as an antimalarial drug is lower than that of chloroquine.

Currently, many drugs are developed through computer assistance by using the QSAR analysis. QSAR can be used to predict quantitative relationships between the biological activities and the descriptions of physical and chemical properties of compounds. The analysis of QSAR is based on the Hansch, the type of employed parameter, the comparative molecular field analysis (CoMFA) or QSAR-3D and the Free-Wilson [27]. The QSAR analysis was performed on the series of aurone compounds to acquire new compounds having antimalarial activity higher than the antimalarial activity of chloroquine drugs.

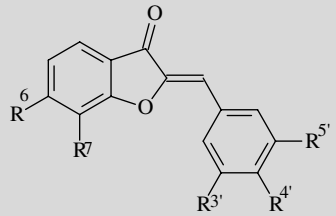
EXPERIMENTAL

In this study, 21 aurone derivative compounds were synthesized and tested for antimalarial activity in the laboratory as method reported by Carrasco *et al*. [8]. Table-1 presents the structure of derivatives of the aurone compound. Tables 2 and 3 present the IC_{50} of 16 internal test compounds as dependent variables and that of 5 external test compounds, which are aurone derivatives [8]. HyperChem 8.0 for Windows software and computer hardware tools (a Sony Vaio Laptop equipped with an Intel Dual Core Processor 2.20 GHz; 500 GB HDD, 1 GHz RAM) were employed in the QSAR analysis to obtain 3D structures and to optimize the geometry of external test compounds (compounds **17-21**) and fitting compounds (compounds **1-16**) and to model the structure of the derivatives of aurone compound (compounds **22-61**). By employing SPSS 19.0 for Windows software, the MLR analysis was conducted to acquire the equation model of QSAR.

Calculation of descriptors: The 3D structure of all the compounds of internal test (**1-16**), external test (**17-21**) and derivative model of aurone (**22-61**) were obtained using HyperChem 8.0 for Windows software and then optimized to acquire a highly stable structure conformation for aurone compounds. To optimize structure, the Polak-Ribiere algorithm or the peer gradient and semi-empirical parameterised model 3 (PM3) method were used with a ground-state root mean square value of 0.001 kcal/(Å mol). The descriptor data obtained using a single point menu provided the descriptors as dipole moment (μ), atomic net charge, Log P and polarisability (α). E_{HOMO} and E_{LUMO} descriptors were acquired from the orbital and compute menus. Table-2 presents the descriptor data; Table-4 presents the coefficients of independent variables and constants of 4 QSAR equation models. Rajkhowa *et al*. [28] selected the descriptors according to their type to perform the QSAR analysis on artemisinin compounds to use them as antimalarial drugs.

QSAR analysis using MLR method: The experimentally obtained IC_{50} value is the dependent variable (Table-2). By contrast, dipole moment (μ), atomic net charges, E_{HOMO}, E_{LUMO}, Log P and polarizability (α) (Table-2), which were analyzed through MLR to determine descriptors that influence the activity of the derivatives of aurone, are independent variables. The MLR analysis of antimalarial activity and numerous descriptors was conducted in 2 steps. First, the MLR analysis of 21 descriptors ((qO1, qC2, qC3, qC4, qC5, qC6, qC7, qC8, qC9, qC10, qC1′, qC2′, qC3′, qC4′, qC5′, qC6′, E_{HOMO}, E_{LUMO}, dipole moment (μ), Log P, and polarizability (α)) was conducted, which provided an equation of model QSAR. In the first stage of the analysis, the equation model of QSAR provided 15

TABLE-1
CHEMICAL STRUCTURE AND ACTIVITY DATA OF ANTIMALARIAL COMPOUNDS OF AURONE DERIVATIVES OBTAINED FROM CARRASCO *et al*. [8]



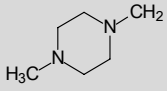
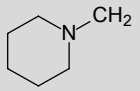
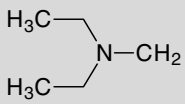
No	R^6	R^7	$R^{3'}$	$R^{4'}$	$R^{5'}$
1	H	H	H	Br	H
2	H	H	OCH_3	OCH_3	OCH_3
3	H	H	H	$PhCH_2$	H
4	H	H	H	4'-(3'-Quinoline)	H
5	H	H	H	4'-[5'-(Pyridin-2'-NH_2)	H
6	H	H	H	4-($NHCH_2Ph$)	H
7	H	H	Ph	H	H
8	H	H	3'-(C_6H_4-4'-F)	H	H
9	H	H	$PhCH_2$	H	H
10	H	H	3'-[5'-(Pyridin-2'-NH_2)]	H	H
11	H	OCH_3	H	H	H
12	OH	H	H	4'-(OC_6H_4-4'-CH_3)	H
13	6-(N-Pyridin-3'-NH_2) F^-	H	H	H	H
14	OH		H	H	H
15	OH		H	H	H
16	OH		H	H	H

TABLE-2
DESCRIPTORS/INDEPENDENT VARIABLES USED FOR QSAR ANALYSIS OF ANTIMALARIAL COMPOUNDS OF AURONE DERIVATIVES

Fitting comp.	Descriptor																				log IC_{50} (μM)
	qO1	qC2	qC3	qC4	qC5	qC6	qC7	qC8	qC9	qC10	qC1'	qC2'	qC3'	qC4'	qC5'	qC6'	μ	E_{Lumo}	E_{Homo}	α ($Å^3$)	log P	
1	-0102	-0.078	0.376	0.021	-0.153	-0.038	-0.134	0.098	-0.248	-0.045	-0.047	-0.071	-0.084	-0.105	-0.084	-0.070	2.066	-1.094	-9.280	27.98	1.16	0.51
2	-0.106	-0.106	0.380	0.019	-0.155	-0.040	-0.137	0.097	-0.245	-0.012	-0.103	-0.053	-0.160	-0.022	-0.164	-0.075	2.976	-0.983	-8.319	30.38	0.16	0.90
3	-0.100	-0.087	0.377	0.020	-0.155	-0.039	-0.136	0.100	-0.249	-0.033	-0.060	-0.072	-0.101	-0.063	-0.111	-0.079	2.104	-0.969	-9.066	36.85	2.12	0.87
4	-0.101	-0.082	0.376	0.020	-0.154	-0.038	-0.134	0.099	-0.248	-0.040	-0.051	-0.070	-0.102	-0.020	-0.105	-0.070	1.358	-1.193	-8.814	40.49	0.54	0.82
5	-0.104	-0.068	0.375	0.022	-0.151	-0.037	-0.133	0.096	-0.247	-0.059	-0.020	-0.081	-0.077	-0.073	-0.075	-0.070	7.478	-2.388	9.236	34.88	0.64	0.57
6	-0.101	-0.095	0.378	0.020	-0.156	-0.039	-0.137	0.100	-0.248	-0.022	-0.090	-0.044	-0.151	-0.049	-0.155	-0.064	2.986	-0.934	-8.510	38.20	0.82	0.70
7	-0.101	-0.086	0.377	0.020	-0.155	-0.039	-0.135	0.099	-0.249	-0.035	-0.051	-0.077	-0.029	-0.095	-0.100	-0.066	2.122	-0.997	8.941	35.02	1.72	0.72
8	-0.102	-0.084	0.377	0.020	-0.154	-0.038	-0.135	0.098	-0.248	-0.039	-0.049	-0.077	-0.031	-0.094	-0.099	-0.084	1.367	-1.062	-9.032	34.93	1.12	0.64
9	-0.100	-0.087	0.377	0.020	-0.155	-0.039	-0.136	0.099	-0.249	-0.034	-0.053	-0.072	-0.076	-0.088	-0.101	-0.058	2.075	-0.974	-9.135	36.85	2.12	0.36
10	-0.101	-0.084	0.377	0.020	-0.155	-0.038	-0.135	0.099	-0.249	-0.038	-0.052	-0.082	-0.022	-0.090	-0.101	-0.057	1.816	-0.992	-8.670	35.66	-0.03	0.41
11	-0.111	-0.069	0.372	-0.020	-0.114	-0.086	-0.133	0.023	-0.207	-0.052	-0.048	-0.076	-0.107	-0.108	-0.114	-0.119	2.137	-1.315	-8.951	31.68	-0.33	0.68
12	-0.103	-0.091	0.383	0.059	-0.201	0.164	-0.237	0.145	-0.292	-0.027	-0.090	-0.049	-0.173	0.093	-0.143	-0.054	2.487	-0.992	-8.876	38.13	-0.26	0.77
13	-0.121	-0.094	0.403	0.061	-0.213	0.030	-0.195	0.144	-0.289	-0.012	-0.066	-0.084	-0.114	-0.087	-0.103	-0.108	2.851	-1.275	-8.190	36.11	-1.29	0.48
14	-0.106	-0.088	0.383	0.061	-0.204	0.177	-0.239	0.156	-0.293	-0.031	-0.054	-0.091	-0.106	-0.091	-0.104	-0.085	2.924	-0.988	-9.128	38.93	-0.54	0.60
15	-0.108	-0.088	0.387	0.060	-0.205	0.182	-0.221	0.146	-0.293	-0.032	-0.055	-0.096	-0.115	-0.059	-0.104	-0.052	2.605	-0.980	-9.089	37.58	0.38	0.07
16	-0.109	-0.087	0.383	0.058	-0.203	0.177	-0.223	0.147	-0.291	-0.034	-0.050	-0.098	-0.107	-0.090	-0.103	-0.055	2.157	-1.275	-8.190	36.52	0.35	0.54

descriptors (qO1, qC2, qC6, qC2′, qC3′, qC4′, qC5′, qC6′, μ, E_{HOMO}, E_{LUMO}, Log P and α), which greatly affect the antimalarial activity. In the second stage, the descriptors that affected the first stage were analyzed and 4 equation models of QSAR were obtained. Table-5 presents the prediction residual Error number of square (PRESS) and the values of statistical parameters, such as r^2, r, SE, $F_{calculate}/F_{table}$ and $t_{calculate}/t_{table}$, for the four equation models of QSAR. Through the MLR analysis,

TABLE-3
log IC_{50} EXPERIMENTS AND log IC_{50} THEORETICAL FOR AURONE DERIVATIVE EXTERNAL TEST COMPOUNDS

Compd.	log IC_{50} experiment	log IC_{50} calculated
17	0.48	0.43
18	0.60	0.58
19	0.07	0.10
20	0.52	0.52
21	0.54	0.61

the value of a constant was obtained. To calculate the theoretical IC_{50} activity of the derivatives of aurone compounds, the coefficients of all independent variables that were involved in QSAR equations were employed. Furthermore, PRESS values were obtained by using the square of difference between the experimental and theoretical IC_{50} values. To determine the predictive ability and validity of all the equation models of QSAR, acquired PRESS value was employed.

Design of new aurone derivatives as antimalarials: To obtain new compounds having antimalarial drugs, the analysis was performed using a design of the aurone derivatives having a higher antimalarial activity than that activity of previously reported compounds. New aurone compounds were designed by changing the positions and types of functional groups/atoms present in the structural skeleton of aurone compounds. Mainly at the active central region the locations and types of functional groups/atoms were changed with the consideration of the synthesis feasibility in a laboratory. Functional group or atoms are the descriptors, which predominantly affected the antimalarial activity of the novel derivatives of aurone. To calculate descriptors for test compounds and for the modelled novel aurone derivatives (Table-6), the same method was used. The theoretical IC_{50} of designed compounds was calculated using the optimum QSAR equation.

RESULTS AND DISCUSSION

The QSAR analysis was performed in the following stages: (i) determination of the basic framework of all the derivatives of aurone with IC_{50} values [8], (ii) structure optimization of the derivatives of aurone, (iii) descriptor (independent variables) selection, (iv) calculations of descriptors, (v) bivariate analysis, (vi) MLR, (vii) determination of the optimal QSAR equation, and (viii) modelling of the novel derivatives of aurone.

As ingredients, aurone compounds had two criteria: (i) all aurone compounds, namely fitting, external test and modelled compounds, must exhibit a basic homologous structure, and (ii) these compounds must exhibit IC_{50} values higher than those obtained from laboratory experiments. The structures of external test, fitting and modelled compounds were optimized using the same method that was employed to acquire the conformational structure with the lowest energy. The 3D molecular structure was considered stable if it had the smallest energy profile. Descriptors were obtained under these conditions for the QSAR analysis. In QSAR analysis, a bivariate analysis was conducted to estimate the relationship among variables.

During the analysis of bivariate correlation, correlations between dipole moment (μ), atomic net charge variables, E_{HOMO}-E_{LUMO}, Log P, polarizability (α), and Log IC_{50} were obtained. An absolute value existed for the correlation that approached the number -1 or 1, which indicated that 1 exhibited a positive correlation and strong relationship. By contrast, -1

TABLE-4
CONSTANTS AND COEFFICIENTS OF SELECTED INDEPENDENT VARIABLES FOR FOUR QSAR MODEL

QSAR models	Coefficient of independent variables						
	O1	C2	C3	C6	C7	C10	C2'
1	-283.108	290.260	-303.352	-9.958	-21.199	220.476	-28.201
2	-294.829	294.933	-311.852	-9.843	-21.497	224.908	-26.997
3	-305.420	286.177	-317.629	-10.353	-22.172	216.926	-27.555
4	-297.632	232.205	-304.444	-9.881	-21.391	176.691	-20.746

QSAR models	Coefficient of independent variables							Constants
	C3'	C4'	C6'	M	E_{LUMO}	E_{HOMO}	log P	
1	-0.980	9.201	12.035	0.167	2.101	0.010	0.235	116.961
2	–	9.608	11.868	0.186	2.155	0.007	0.254	119.652
3	–	10.344	9.557	0.225	2.303	–	0.261	119.465
4	–	10.623	–	0.237	2.320	–	0.206	109.160

TABLE-5
FOUR SELECTED MODELS AND THEIR STATISTICAL PARAMETERS

QSAR models	Variables	r	r^2	Adjusted R square	SE	t_{calc}/t_{tab} (0.05)	F_{calc}/F_{table} (0.05)	PRESS
1	qO1, qC2, qC3, qC6, qC7, qC10, qC2', qC3', qC4', qC6', μ, E_{Lumo}, E_{Homo}, and Log P	0.998	0.995	0.932	0.055	2.046	0.806	230.253
2	qO1, qC2, qC6, qC7, qC10, qC2', qC3', qC4', qC6', μ, E_{Lumo}, E_{Homo}, and Log P	0.996	0.992	0.940	0.052	3.096	2.206	6.505
3	qO1, qC2, qC6, qC7, qC10, qC2', qC3', qC4', qC6', μ, E_{Lumo}, and Log P	0.988	0.976	0.881	0.077	2.519	1.726	19.859
4	qO1, qC2, qC6, qC7, qC10, qC2', qC3', qC4', μ, E_{Lumo}, and Log P	0.982	0.965	0.867	0.073	2.711	2.081	128.851

was considered to exhibit a powerful and negative correlation. The count value for the Pearson correlation r among descriptors confirmed a close correlation among the descriptors: qO1-qC3 (-0.768), qO1-Log P (0.731), qC2-qC10 (-0.960), qC2-qC11 (0.853), qC2-qC5' (0.728), qC2-E_{LUMO} (-0.635), qC3-qC4 (0.745), qC3-qC5 (-0.804), qC3-qC8 (0.677), qC3-qC9 (-0.724), qC4-qC5 (-0.804), qC3-qC8 (0.677), qC3-qC9 (-0.724), qC4-qC5 (-0.804), qC3-qC8 (0.677), qC3-qC9 (-0.724), qC4-qC5 (-0.993), qC4-qC6 (0.888), qC4-qC7 (-0.934), qC4-qC8 (0.983), qC4-qC9 (-0.998), qC5-qC6 (-0.884), qC5-qC7 (0.893), qC4-qC9 (-0.998), qC5-qC6 (-0.884), qC5-qC7 (0.893), qC5-qC8 (-0.962), qC5-qC9 (0.991), qC6-qC7 (-0.777), qC6-qC8 (0.842), qC6-qC9 (-0.909), qC7-qC8 (-0.980), qC7-qC9 (0.842), qC6-qC9 (-0.909), qC7-qC8 (-0.980), qC7-qC9 (0.830), qC6-qC9 (-0.909), qC7-qC8 (-0.980), qC7-qC9 (0.930), qC8-qC9 (-0.980), qC1′-qC2′ (-0.751), qC1′-qC3′ (0.704), qC1′-qC4′ (-0.617), qC1′-qC5′ (0.949), qC1′-qC6′ (-0.765), qC2′-qC4′ (0.664), qC2′-qC4′ (-0.731), qC2′-qC5′ (0.766), qC3′-qC4′ (-0.632), qC3′-qC5′ (0.715), qC4′-qC5′ (-0.600), qC4′-qC6′ (0.740), qC5′-qC6′ (-0.785), μ-E_{LUMO} (-0.839), μ-E_{HOMO} (0.627) and E_{LUMO}-E_{HOMO} (-0.611). The calculated values of bivariate correlation among the aforementioned descriptors were always higher than the r_{table} values (0.623) for the n of 16; thus, these descriptors exhibited a strong relationship at 0.01 (1%) significance level. The negative and positive values indicate the direction of the influence of descriptors on the activity and not whether the descriptors influence the activity. The coefficient of bivariate correlation among qC5-qC9 was 0.991, and it exhibited a sig value (2-tailed) of > 0.005, which indicated that the qC5-qC9 variables exhibited a stronger relationship than did other variables. The smallest relationship value of 0.001 was obtained for qC6 and μ variables, which indicated a weak relationship between qC6 and μ. According to the results of the bivariate analysis, several independent variables exist and dependent variables exhibit significant relationships. Thus, MLR can be conducted on a data group to acquire the relationship between the antimalarial activity and structure of aurone compounds. The MLR analysis of dependent and independent (descriptor) (Log IC_{50}) variables provided four equation models of QSAR. According to the statistical parameter criteria in Table-5, model 2 equation of QSAR was the best optimal QSAR equation.

$$\text{Log } IC_{50} = 119.652 - 294.829(qO1) + 294.933(qC2) - 311.852(qC3) - 9.843(qC6) - 21.497(qC7) + 224.908(qC10) - 26.997(qC2') + 9.608(qC4') + 11.868(qC6') + 0.186(\mu) + 2.155(E_{LUMO}) + 0.007(E_{HOMO}) + 0.254(\text{Log P})$$

The statistical criteria for the model 2 equation of QSAR are as follows: (r) = 0.996, n = 16, (r^2) = 0.992, SE = 0.052, $t_{calculate}/t_{table}$ = 3.096, PRESS = 6.505, and $F_{calculate}/F_{table}$ = 2.206. The relationship linearity obtained for the predictive and experimental log IC_{50} values (internal test compounds **1-16**) evidenced the accuracy of model 2 equation of QSAR (Fig. 1). The linearity (r^2 = 0.993) graph (Fig. 1) shows that the optimal QSAR equation, that is, the internal test model 2, exhibits a substantially high confidence level. The closer is the r^2 value to 1, the higher is the influence of independent variables on dependent variables. Smaller SE and PRESS values lead to a higher confidence

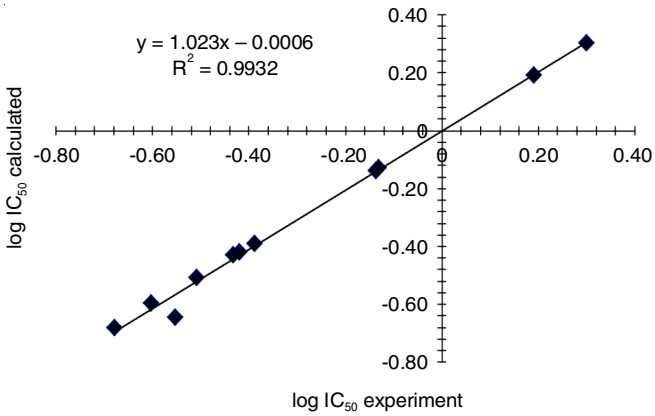


Fig. 1. Relationship of log IC_{50} predictions with log IC_{50} experiments

level of the equation model of QSAR [29]. By contrast, higher $t_{calculate}/t_{table}$ and $F_{calculate}/F_{table}$ values result in a higher validity of the equation model of QSAR. Table-5 indicates that the confidence level of model 2 of QSAR equation is the optimum.

The model 2 of QSAR equation was validated as optimum by employing external test compounds (**17-21**). These compounds were excluded from the MLR analysis for the determination of the optimal model QSAR equation. The model 2 of the QSAR equation was validated using external test compounds to determine it capacity in predicting the theoretical IC_{50} of the derivatives of aurone.

The r^2 value (0.970) obtained from a graph of relationship between the experimental and predicted Log IC_{50} (Fig. 2) was used to validate the model 2 of QSAR equation as optimal. The r^2 value (0.970) approached 1, indicating that the model 2 of the QSAR equation is optimal and valid. According to the r^2 of 0.970, the model 2 of QSAR equation accurately predicts theoretical IC_{50} because the relationship between theoretical and experimental log IC_{50} against the external test compound was highly significant.

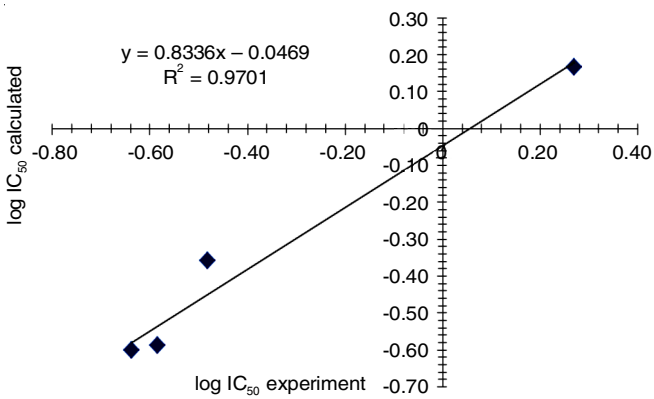


Fig. 2. Relationship log IC_{50} predictions with log IC_{50} external compound test experiments

Design of new aurone derivatives as an antimalarial agent: The reasons for designing the derivatives of aurone are as follows: (i) to ensure that termination and retrosynthesis studies can be used to prepare new derivatives of aurone in a laboratory, (ii) to study the active sides of the homologous frameworks of aurone compounds, and (iii) to determine that

functional groups or atoms are bound to the basic framework structure using the disconnection and retrosynthesis results. Different functional groups or atoms attached to a basic aurone framework can lead to variations in chemical, physical and atomic charge properties, which changes the antimalarial activity of the studied compounds [30]. This finding was supported by the results presented in Tables 1, 2 and 5. Compounds having different structures exhibit varied antimalarial activities. The structures of different compounds of aurone exhibit different net charge of atoms, molecular and electronic properties, and descriptors, thereby providing various IC_{50} values.

The model 2 of QSAR indicted that as a consequence of the design, independent variables that affect the theoretical IC_{50} of aurone compounds include qO1, qC2, qC3, qC6, qC7, qC10, qC2′, qC4′, qC6′, E_{HOMO}, E_{LUMO}, μ and Log P. Aurone derivatives were designed through the substitution of functional groups or atoms on C4, C5, C6, C7, C2′, C3′, C3′, C5′ and C6′ atoms. The substitution of various functional groups or atoms into C4, C5, C6, C7, C2′, C3′, C4′, C5′ and C6′ atoms caused theoretical IC_{50} of aurone derivatives to be different from the IC_{50} of the modelled compounds (Table-6). Theoretical IC_{50} was calculated by entering descriptors, such as atomic charge, into the model 2 of the QSAR equation. New aurone derivatives having smallest IC_{50} exhibited the highest antimalarial activity. Aurone derivatives with a promising antimalarial activity were synthesized in the laboratory.

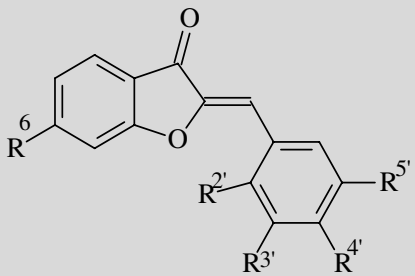
Several derivatives of aurone, which were acquired through modelling and exhibited smaller IC_{50} than IC_{50} of chloroquine (0.14 μM), were proposed to be prepared in the laboratory. Six aurone derivatives are recommended to be synthesized, which are compound 54, 55, 58, 59, 60 and 61 with an IC_{50} of 0.0002, 0.0001, 0.0527, 0.0527, 0.0054 and 0.0076 μM, respectively. By contrast, compounds **22-53**, **56** and **57** are not recommended for laboratory synthesis because they exhibit a high antimalarial activity. A compound recommended for synthesis is the derivative of aurone with the activity of hem polymerization inhibition if they have an IC_{50} lower than IC_{50} of chloroquine for antimalarial activity (0.14 μM) [8]. Two derivative of aurone, 54 and 55 (0.0002 and 0.0001 μM, respectively) exhibit a considerably higher antimalarial activity than chloroquine does, which is a priority for preparation. In the laboratory, the synthesis of the derivatives of aurone was given priority over the compounds that can be easily synthesized [30]. The IC_{50} of chloroquine (0.14 μM) was considered the standard for determining the derivative of aurone to be recommended for laboratory synthesis. This study only recommends the aurone derivative with IC50 of < 0.14 μM [8].

The active sites in the structural skeleton of aurone compounds that exhibit a promising theoretical antimalarial activity are as follows: -C_2H_5 bound to the C2′, C4′ and C5′ atoms, -OH attached to the C6 atoms, -Ph attached to the C3′ atoms, -Cl bound to the C6 atoms, -CH_3 linked to the C4′ and C5′ atoms, and -(*N*-pyridin-3′-NH_2) F^- attached to the C6 atom (Table-6).

Conclusion

From the optimal model of QSAR equation, the relationship between the independent variables and antimalarial activity of the 16 derivatives of aurone was acquired. Log IC_{50} = 119.652 – 294.829(qO1) + 294.933(qC2) – 311.852(qC3) – 9.843(qC6) – 21.497(qC7) + 224.908(qC10) – 26.997(qC2′) + 9.608(qC4′) + 11.868(qC6′) + 0.186(μ) + 2.155(E_{LUMO}) + 0.007(E_{HOMO}) + 0.254(Log P); (r^2) = 0.992, r = 0.996, $t_{calculate}$/t_{table} = 3.096, Fcalculate/Ftable = 2.206, SE = 0.052, and PRESS = 6,505. According to model 2 of the QSAR equation, qO1, qC2, qC3, qC6, qC7, qC10, qC2′, qC4′, qC6′, E_{HOMO}, E_{LUMO}, μ and Log P are the variables influencing the IC_{50} of aurone derivatives. A total of 40 new derivatives of aurone were modelled on the basis of the influential variables. The six designed derivatives of aurone that are recommended to be prepared and that exhibit a high antimalarial activity include **54**, **55**, **58**, **59**, **60** and **61**. Compounds **54** and **55** (0.0002 and 0.0001 μM, respectively) exhibit a higher antimalarial activity than chloroquine (0.14 μM) does, which is a priority for preparation.

TABLE-6
STRUCTURE OF AURONE COMPOUNDS DERIVED FROM MODELING RESULTS RECOMMENDED FOR SYNTHESIS IN THE LABORATORY



Comp.	Atom/functional group					log IC_{50} predicted (μM)
	R6	R2′	R3′	R4′	R5′	
54	OH	C_2H_5	Ph	CH_3	C_2H_5	0.0002
55	OH	C_2H_5	Ph	C_2H_5	C_2H_5	0.0001
58	Cl	C_2H_5	Ph	CH_3	C_2H_5	0.0527
59	Cl	C_2H_5	Ph	C_2H_5	C_2H_5	0.0586
60	-(N-Pyridin-3'-NH_2) F^-	C_2H_5	Ph	CH_3	CH_3	0.0054
61	-(N-Pyridin-3'-NH_2) F^-	C_2H_5	Ph	C_2H_5	CH_3	0.0076

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. L.C.S. Pinheiro, L.M. Feitosa, F.F.D. Silveira and N. Boechat, *An. Acad. Bras. Cienc.*, **90(1 suppl 2)**, 1251 (2018); https://doi.org/10.1590/0001-3765201820170830
2. World Health Organization, World Malaria Report 2018, Printed in Luxembourg, p. 36 (2018).
3. K. Sharma, A. Shrivastava, R.N. Mehra, G.S. Deora, M.M. Alam, M.S. Zaman and M. Akhter, *Arch. Pharm.*, **351**, 1700251 (2018); https://doi.org/10.1002/ardp.201700251
4. W.H. Wernsdorfer and D. Payne, *Pharmacol. Ther.*, **50**, 95 (1991); https://doi.org/10.1016/0163-7258(91)90074-V
5. World Health Organization, World Malaria Report 2016, Printed in France, p. 33 (2016).
6. C.B.R. Santos, J.B. Vieira, C.C. Lobato, L.I.S. Hage-melim, R.N.P. Souto, C.S. Lima, E.V.M. Costa, D.S.B. Brasil, W.J.C. Macêdo and J.C.T. Carvalho, *Molecules*, **19**, 367 (2014); https://doi.org/10.3390/molecules19010367
7. R. Hadanu, S. Mastjeh, M. Mustofa, E.N. Sholikhah, M.A. Wijayanti and I. Tahir, *Indones. J. Chem.*, **7**, 72 (2010); https://doi.org/10.22146/ijc.21716
8. M.P. Carrasco, A.S. Newton, L. Gonçalves, A. Góis, M. Machado, J. Gut, F. Nogueira, T. Hänscheid, R.C. Guedes, D.J.V.A. dos Santos, P.J. Rosenthal and R. Moreira, *Eur. J. Med. Chem.*, **80**, 523 (2014); https://doi.org/10.1016/j.ejmech.2014.04.076
9. A. Najafi, S. Sobhanardakani and M. Marjani, *J. Chem.*, **2013**, Article ID 560415 (2013); https://doi.org/10.1155/2013/560415
10. R.P. Pore and S.S. Mahajan, *Eur. J. Pharm. Med. Res.*, **5**, 304 (2018).
11. Amanatie, Jumina, Mustofa and Hanafi, *IOP Conf. Ser.: Mater. Sci. Eng*., **333**, 012061 (2018); https://doi.org/10.1088/1757-899X/333/1/012061
12. X. Nqoro, N. Tobeka and B.A. Aderibigbe, *Molecules*, **22**, 2268 (2017); https://doi.org/10.3390/molecules22122268
13. R. Hadanu, S. Idris and I.W. Sutapa, *Indones. J. Chem.*, **15**, 86 (2015); https://doi.org/10.22146/ijc.21228
14. R. Hadanu and Syamsudin, *Asian J. Chem.*, **25**, 6136 (2013); https://doi.org/10.14233/ajchem.2013.14289
15. R. Hadanu, *Asian J. Chem.*, **30**, 148 (2018); https://doi.org/10.14233/ajchem.2018.20988
16. L.F. Motta, A.C. Gaudio and Y. Takahata, *Internet Electron. J. Mol. Des.*, **5**, 555 (2006).
17. D.J. Hall, C.G. Martin, M. Welford and S.L. Debbert, *Biochem. Mol. Biol. Educ.*, **46**, 424 (2018); https://doi.org/10.1002/bmb.21138
18. N. Batra, V. Rajendran, D. Agarwal, I. Wadi, P.C. Ghosh, R.D. Gupta and M. Nath, *ChemistrySelect*, **3**, 9790 (2018); https://doi.org/10.1002/slct.201801905
19. C. Courtens, M. Risseeuw, G. Caljon, P. Cos and S. Van Calenbergh, *ACS Med. Chem. Lett.*, **9**, 986 (2018); https://doi.org/10.1021/acsmedchemlett.8b00223
20. W.D. Hong, S.C. Leung, K. Amporndanai, J. Davies, R.S. Priestley, G.L. Nixon, N.G. Berry, S.S. Hasnain, S. Antonyuk, S.A. Ward, G.A. Biagini and P.M. O'Neill, *ACS Med. Chem. Lett.*, **9**, 1205 (2018); https://doi.org/10.1021/acsmedchemlett.8b00371
21. W.Y. Belay, A.E. Gurmu and Z.B. Wubneh, *Evid. Based Complement. Altern. Med.*, **2018**, 4169397 (2018); https://doi.org/10.1155/2018/4169397
22. E. Ju, A. Latif, C. Kong, Y. Seo, Y. Lee, S.R. Dalal, M.B. Cassera and D.G.I. Kingston, *Z. Naturforsch. C J. Biosci.*, **73**, 397 (2018); https://doi.org/10.1515/znc-2018-0025
23. J.K. Obey, M.M. Ngeiywa, P. Kiprono, S. Omar, A. von Wright, J. Kauhanen and C. Tikkanen-Kaukanen, *J. Pathogens*, **2018**, 2393854 (2018); https://doi.org/10.1155/2018/2393854
24. R. Lekphrom, K. Kanokmedhakul, F. Schevenels and S. Kanokmedhakul, *Fitoterapia*, **127**, 420 (2018); https://doi.org/10.1016/j.fitote.2018.01.018
25. P. Perumal, R. Sowmiya, S.P. Kumar, S. Ravikumar, P. Deepak and G. Balasubramani, *Nat. Prod. Res.*, **32**, 1316 (2018); https://doi.org/10.1080/14786419.2017.1342081
26. S. Zhang, J. Zhu, D.L. Zechel, C. Jessen-Trefzer, R.T. Eastman, T. Paululat and A. Bechthold, *ChemBioChem*, **19**, 272 (2018); https://doi.org/10.1002/cbic.201700428
27. H.M. Patel, M.N. Noolvi, P. Sharma, V. Jaiswal, S. Bansal, S. Lohan, S.S. Kumar, V. Abbot, S. Dhiman and V. Bhardwaj, *Med. Chem. Res*., **23**, 4991 (2014); https://doi.org/10.1007/s00044-014-1072-3
28. S. Rajkhowa, I. Hussain, K.K. Hazarika, P. Sarmah and R.C. Deka, *Comb. Chem. High Throughput Screen.*, **16**, 590 (2013); https://doi.org/10.2174/1386207311316080002
29. L. Eriksson, J. Jaworska, A.P. Worth, M.T.D. Cronin, R.M. McDowell and P. Gramatica, *Environ. Health Persp*., **111**, 1361 (2003).
30. N. Adhikari, A.K. Halder, C. Mondal and T. Jha, *Med. Chem. Res*., **22**, 6029 (2013); https://doi.org/10.1007/s00044-013-0590-8