QSAR ANALYSIS OF BENZOTHIAZOLE DERIVATIVES OF ANTIMALARIAL COMPOUNDS BASED ON AM1 SEMI-EMPIRICAL METHOD

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ABSTRACT

Quantitative Structure and Activity Relationship (QSAR) analysis of 13 benzothiazoles derivatives compound as antimalarial compounds have been performed using electronic descriptor of the atomic net charges (q), dipole moment (μ), E_{LUMO}, E_{HOMO} and polarizability (α). The electronic structures as descriptors were calculated through HyperChem for Windows 7.0 using AM1 semi-empirical method. The descriptors were obtained through molecules modeling to get the most stable structure after geometry optimization step. The antimalarial activity (IC_{50}) were taken from literature. The best model of QSAR model was determined by multiple linear regression approach and giving equation of QSAR: Log IC_{50} = 23.527 + 4.024 (qC_4) + 273.416 (qC_5) + 141.663 (qC_6) – 0.567 (E_{LUMO}) – 3.878 (E_{HOMO}) – 2.096 (α). The equation was significant on the 95% level with statistical parameters: n = 13, r = 0.994, r^2 = 0.987, SE = 0.094, F_{calc}/F_{table} = 11.212, and gave the PRESS = 0.348. Its means that there were only a relatively few deviations between the experimental and theoretical data of antimalarial activity.

Keywords: *benzothiazoles; QSAR analysis; antimalarial activity; semi-empirical method; multiple linear regression*

ABSTRAK

Analisis Hubungan Kuantitatif Struktur dan Aktivitas (HKSA) terhadap 13 senyawa turunan aminobenzotiazol sebagai senyawa antimalaria yang dilakukan menggunakan deskriptor elektronik muatan atom bersih (q), momen dipol (μ), E_{LUMO}, E_{HOMO} dan polarisabilitas (α). Struktur elektronik sebagai deskriptor telah dilakukan perhitungan melalui perangkat lunak HyperChem untuk Windows 7.0 menggunakan metode semi-empirik AM1. Dekskriptor-deskriptor telah diperoleh melalui pemodelan molekul untuk memperoleh struktur yang paling stabil setelah proses optimasi geometri. Nilai aktivitas antimalaria (IC_{50}) diperoleh melalui literatur. Persamaan model QSAR terbaik telah ditentukan melalui pendekan regresi multilinear dan diperoleh persamaan QSAR: Log IC_{50} = 23,527 + 4,024 (qC_4) + 273,416 (qC_5) + 141,663 (qC_6) – 0,567 (E_{LUMO}) – 3,878 (E_{HOMO}) – 2,096 (α). Persamaan tersebut signifikan pada taraf 95% dengan parameter statistik: n = 13, r = 0,994, r^2 = 0,987, SE = 0,094, F_{hitung}/F_{tabel} = 11,212 dan nilai PRESS = 0,348. Hal tersebut menunjukkan nilai deviasi yang kecil antara data aktivitas antimalaria secara eksperimen dan teoritis.

Kata Kunci: *benzotiazol; analisis QSAR; aktivitas antimalaria; metode semi-empirik; regresi multilinear*

INTRODUCTION

The development of resistance of *Plasmodium falciparum* to conventional antimalarial drugs caused a serious global problem to combat malaria. Despite increased attention to malaria eradication, the disease causes more than a million deaths each year [1-2]. *P. falciparum*, the protozoan agent responsible for cerebral malaria, is the most worrying parasite, in particular with chloroquine and multi-resistant strains. Besides the worldwide development of chloroquine-resistant *P. falciparum*, resistance has also developed to a variety of quinoline analogues, antifolates, inhibitors of electron transport and perhaps now to artemisinin [3-4]. Ninety percent of malaria-related deaths occur in Sub-Saharan Africa. The advent of long-lasting insecticidal nets and artemisinin based combination therapy, plus a revival of support for indoor residual spraying of insecticide, presents a new opportunity for large-scale malaria control. Malaria is commonly associated with poverty, but is also a cause of poverty and a major hindrance to economic development [5].

Several antimalarial drugs have been formulated for the treatment and prevention of the disease, but

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these have led to develop of resistance by the parasites to most of the drugs in use. Specifically, there is reportedly, rapid spread of *P. falciparum* resistance to available antimalarial drugs [6]. Thus, there is a constant need for developing new antimalarial compounds. Ethnic medicine has provided two of the most efficacious drugs, Quinine and Artemisinin (and its analogs) and the ongoing screening of medicinal plants yields new lead compounds [7]. Work has been done on malaria vaccines with limited success and more exotic controls, such as genetic manipulation of mosquitoes to make them resistant to the parasite, have also been considered [8].

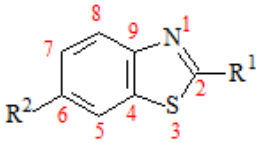
The traditional remedies are no longer effective and the incidence of malarial by *P. falciparum,* the most dangerous species of parasite, continues to grow, while some traditional drugs such as chloroquine and its congeners are losing their activity due to the increasing multi drug resistance [9]. Therefore, it is essential to find new drugs of antimalarial having a pharmacological activity higher than that of currently available drugs of antimalarial. In this connection, Quantitative Structure-Activity Relationship (QSAR) analysis plays an important role to minimize trial and error in designing new antimalarial drugs.

In a QSAR analysis, the central task is to find a regression function that predicts the activity of the molecule in high accuracy. Hence, the present study is aimed at to establish the QSAR between experimental antiplasmodial activity and structure electronic descriptors which may focus on the molecular structures of the compounds. In last decades, QSAR have been applied in many areas enabling to prevent time consuming and cost during the analysis of biological activities of interest [10]. The main hypothesis involved in any QSAR is the assumption hat the variation of the behavior of chemical compounds, as expressed by any experimentally measured biological property, can be correlated with numerical entities related to some aspect of the chemical structure termed molecular descriptors [11-12]. Descriptors are generally used to describe different characteristics/attributes of the chemical structure in order to yield information about the activity/property being studied. In general, QSAR studies are effected by various factors from which the most relevant are: (a) the selection of the best molecular descriptors that should include maximum information of molecular structures and a minimum overlap between them; (b) the optimal number of descriptors to be included in the model; (c) the use of suitable modeling methods; (d) the composition of the training and test sets; and (e) the employment of validation techniques to verify the predictive performance of the developed models.

We consider that the linear methodology is the statistical technique for analyzing present dataset of benzothiazoles derivatives series, as few experimental observations are available on it and thus it is necessary to employ the lowest number of optimized parameters during the model development. In this way, we resort to the Replacement Method (RM) as variable subset selection approach applied on a pool containing more than a thousand of descriptors, as this technique has been successful for selecting relevant structural descriptors [13-17]. Finally, another main interest of present research is to apply the so derived QSAR models for estimating the antiplasmodial potency on some new structures, for which there still are no experimental activities.

In this research AM1 semi-empirical methods were used to calculate a number of descriptors, because the samples in this research have large number molecular compounds and bulky structures [18-24]. The AM1 semi-empirical method was used to calculate a number of descriptors, because the structure of benzothiazole derivatives having bulky structures, N atoms and S atom. The AM1 semi-empirical method more easy to calculate a number of descriptors than using PM3 semi-empirical method. In current practice, AM1 semi-empirical methods serve as efficient computational tools which can yield fast quantitative estimates for a number of descriptors. This may be particularly useful for correlating large sets of experimental and theoretical data, for establishing trends in classes of related molecules, and for scanning a computational problem before proceeding with higher level treatments. Among the classes of drugs that are effective in the treatment of the *P. falciparum* malarial, there is the benzothiazoles and its derivatives. The benzothiazoles derivatives was synthesized from benzothiazoles as a starting material. The best models of QSAR were modeled, described and evaluated for their antiplasmodial activity. From that evaluation, the benzothiazoles appeared as a new class of potential antiplasmodial compounds [25]. Benzoathiazoles cyclic ring system with multiple applications which have been the subject of great interest because of their biological activities. The 2-substituents benzothiazole has emerged in its usage as a core structure in the diversified therapeutically applications [26]. Previous QSAR analysis has been reported using electronic descriptor producing by AM1 calculation using 13 benzothiazoles series compound.

Table 1. Chemical structure and activity data of antimalarial compounds of benzothiazoles derivatives against FCR3 strain, obtained from [25]



No	R^1	R^2	Log IC_{50}
1.	Cl	NH_2	2.132
2.	$NHCOCH_3$	NH_2	2.081
3.	NH_2	NH_2	1.656
4.	$N(CH_3)_2$	NH_2	0.579
5.	$N(C_2H_5)_2$	NH_2	0.528
6.	$NCH_3(C_3H_7)$	NH_2	1.029
7.	$NHCH_2CH_2N(C_2H_5)_2$	NH_2	0.949
8.	NHC_3H_7	NH_2	1.683
9.	NHPh	NH_2	1.318
10.	NHPh-*p*-$N(CH_3)_2$	NH_2	0.564
11.	$NHCH_2CH_2OH$	NH_2	1.376
12.	NHPh(*o*-OCH_3)*p*-$NHSO_2CH_3$	NH_2	1.437
13.	NHPh-*m*-OH	NH_2	1.463

Table 2. Descriptors/independent variables used for QSAR analysis of antimalarial compounds of benzothiazoles derivatives calculated by semi-empirical AM1 method

Comp. Number	Atomic net charges (Coulomb)									μ (Debyes)	E_{LUMO} (ev)	E_{HOMO} (ev)	α (Å^3)
	qN1	qC2	qS3	qC4	qC5	qC6	qC7	qC8	qC9				
1	-0.068	-0.253	0.430	-0.255	-0.200	0.142	-0.210	-0.018	-0.177	4.233	-0.431	-8.362	18.71
2	-0.153	-0.120	0.514	-0.321	-0.157	0.060	-0.179	-0.050	-0.072	1.738	-0.287	-8.157	21.89
3	-0.182	-0.039	0.310	-0.258	-0.182	0.119	-0.201	-0.047	-0.069	1.878	0.169	-7.769	18.17
4	-0.175	-0.048	0.326	-0.266	-0.182	0.118	-0.201	-0.047	-0.070	1.785	0.205	-7.659	21.80
5	-0.165	-0.073	0.353	-0.282	-0.154	0.053	-0.178	-0.055	-0.061	1.488	-0.082	-8.014	25.47
6	-0.145	-0.108	0.371	-0.278	-0.160	0.062	-0.182	-0.049	-0.074	0.926	-0.178	-8.153	26.53
7	-0.155	-0.097	0.355	-0.275	-0.156	0.058	-0.179	-0.052	-0.066	0.360	-0.157	-8.128	32.33
8	-0.154	-0.097	0.352	-0.275	-0.156	0.058	-0.179	-0.052	-0.066	0.985	-0.151	-8.122	23.64
9	-0.158	-0.042	0.313	-0.251	-0.186	0.126	-0.203	-0.040	-0.079	2.690	-0.178	-7.809	27.79
10	-0.140	-0.097	0.355	-0.237	-0.158	0.061	-0.181	-0.049	-0.070	0.709	-0.245	-7.861	32.81
11	-0.144	-0.105	0.360	-0.274	-0.159	0.062	-0.181	-0.049	-0.070	2.371	-0.214	-8.189	22.44
12	-0.145	-0.102	0.370	-0.275	-0.159	0.064	-0.181	-0.049	-0.071	4.324	-0.769	-8.151	34.59
13	-0.159	-0.045	0.320	-0.250	-0.186	0.127	-0.203	-0.039	-0.080	4.158	-0.264	-7.894	24.43

EXPERIMENTAL SECTION

Materials

Benzothiazoles derivatives compounds were taken from literature [25]. Logarithmic of inhibition concentration 50% (log IC_{50}) was used as dependent variable in Table 1.

Instrumentation

For this study, a Laptop equipped with Intel® Dual Core Processor 2.20 GHz; RAM 1 GB and HDD 250 GB was used. All the compounds (Table 1) were calculated using package HyperChem® Program Version 8.0 for Windows and complete geometry optimization with the semi-empirical AM1 method, statistical program IBM® SPSS® version 16 for Windows.

Procedure

Computational methods

QSAR descriptors were calculated for each of the compounds in Table 1 using the QSAR module of semi-empirical AM1 method. A full list of descriptors considered is reported in Table 2. The QSAR models are evaluated using sets of benzothiazoles derivatives compounds whose molecular structure and antiplasmodial activity are known (Table 1). Antiplasmodial activity of these compound were taken as the activity against chloroquine resistant *P. falciparum* (FCR3) strain and is presented as the value of log IC_{50} where IC_{50} is an effective concentration inhibiting 50% growth of the parasite [25]. All the compounds (Table 1) were calculated using HyperChem® and complete geometry optimization with the semi-empirical AM1 method was performed. The geometry was optimized to an RMS Root Mean Square (RMS), gradient of

Table 3. The six selected models and their statistical parameters for the correlation between molecular properties and antimalarial activity of benzothiazoles derivatives

QSAR Models	*Variables*	R	R^2	SE	F_{calc}/F_{table}	*PRESS*
1	qN1, qC2, qS3, qC4, qC5, qC6, qC9, μ , E_{LUMO}, E_{HOMO}, α	0.997	0.994	0.148	0.058	0.317
2	qC2, qS3, qC4, qC5,qC6, qC9, μ, E_{LUMO}, E_{HOMO}, α	0.997	0.993	0.107	1.553	0.461
3	qC2, qS3, qC4, qC5, qC6, μ , E_{LUMO}, E_{HOMO}, α	0.997	0.993	0.089	5.480	0.414
4	QS3, qC4,qC5,qC6, E_{LUMO}, E_{HOMO}, α	0.995	0.989	0.095	7.734	0.410
5	qC4,qC5,qC6, E_{LUMO}, $E_{HOMO,}$ α	0.994	0.987	0.094	11.212	0.348
6	qC5,qC6, E_{LUMO}, E_{HOMO}, α	0.989	0.979	0.110	10.876	0.365

Table 4. Coefficient of selected independent variables for six QSAR models as obtained from multilinear regression analysis

QSAR Models	*Coefficient of independent variables* (Coulomb)											
	qN1	qC2	qS3	qC4	qC5	qC6	qC9	μ	E_{LUMO}	E_{HOMO}	A	Constants
1.	3.821	2.623	1.709	6.254	243.903	130.281	3.956	-0.577	-3.827	-2.325	-0.139	18.842
2.		1.878	2.109	7.854	229.237	123.807	3.772	-0.567	-3.817	-2.414	-0.136	15.751
3.		3.227	2.067	7.582	236.896	125.621		-0.576	-3.858	-2.385	-0.138	16.948
4.			1.102	6.151	287.668	147.490		-0.537	-3.668	-2.195	-0.133	24.666
5.				4.024	273.416	141.663		-0.567	-3.878	-2.096	-0.138	23.527
6.					246.564	130.268		-0.537	-3.660	-1.912	-0.125	20.006

0.001 kcal/(Å mol) in vacuo (Polak-Ribière method). Quantum chemical descriptors were calculated, as for example: atomic net charges, dipole moment, E_{HOMO}, E_{LUMO}, and polarizability. From all the descriptors above mentioned, it can be considered that some of them give valuable information about the influence of electronic and coefficient partition features upon the biological activity of drug molecules. In this work, the molecular descriptors were selected so that they represent the features necessary to quantify the activity.

QSAR models evaluation

Evaluation of QSAR model has five steps. The first step is to determine a benzothiazoles series compound to be analyzed along with value of IC_{50} yielded through laboratory experiment. The second step is to select a set of descriptors, which is likely to be related to the biological activity of interest and to look for elementary ring structure of benzothiazoles series compound, which is the most stable using optimization process. The third step is to calculate descriptor through optimized structure. The fourth step is to formulate a mathematical equation that reflects the relationship between the biological activity and the chosen descriptors through statistic analysis using SPSS 16 for Windows to get equation of QSAR, and the finally step is to validate the QSAR models.

RESULT AND DISCUSSION

The QSAR analysis included the 13 compounds presented in Table 1, which let us to investigate models with up to five variables. Descriptor is a parameter or property of molecule used as independent variables in calculation of predicted activity (theoretical log IC_{50}). The descriptors used in this research are atomic net charges, dipole moment, log P, E_{HOMO}, E_{LUMO}, and polarizability. To obtain the structural properties of each test compound and modeling compound after process of geometry optimization, the calculation process is continued with single point at sub menu. Descriptors or structural properties yielded from calculation with single point were atomic net charges and dipole moment, whereas descriptors of polarizability were obtained from "menu compute" of QSAR properties. E_{HOMO}, E_{LUMO} descriptors can be obtained from the menu compute, vibrations then click orbital sub menu. The E_{HOMO} and E_{LUMO} descriptors would not be obtained if calculation was performed using molecular mechanic method. All of the descriptors were given in Table 2. To calculate of atomic net charges and other descriptors of a benzothiazoles series derivatives was conducted with the semi-empiric AM1 method. Method of AM1 is repair method of before all like MNDO method [11], which can predicts compounds having valence many with the best accuracies [26]. The AM1 method can be used for the analysis of a series benzothiazoles derivatives, because benzothiazoles derivatives is organic compound considering atoms as C, H, N, and S.

Selection of the Best Model

According to result of calculation statistic of multilinear regression by using SPSS version 16.0 for windows were obtained six QSAR model as listed in Table 3 and Table 4. From six equation models were determined model 5 of the best QSAR model. Model 5 is selected as the best model among 6 models, based

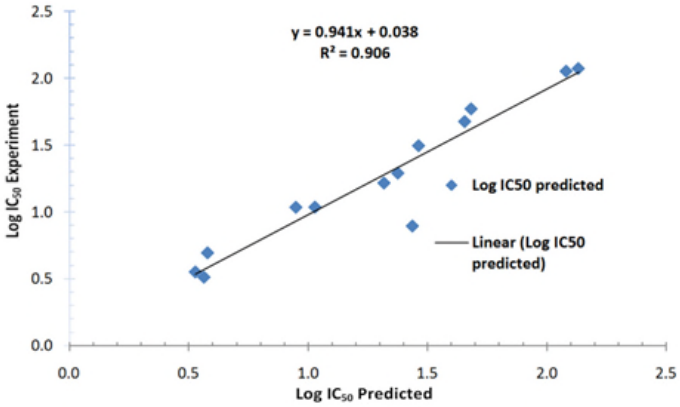


Fig 1. Linear regression of experimentally observed antimalarial activity Log IC_{50} versus calculated one based on QSAR Model 5

on the value of r and r^2 to look for analysis data linearity that the model 5 having r equal to 1 is 0.994 and r^2 is 0.987. The smallest value of SE (Standard Error of Estimation) is model 5 having value of SE equal to 0.094. If the value of F exceed value of F_{table} or comparison of F_{calc}/F_{table} more than 1. The model 5 have value of F_{calc}/F_{table} is 11.212. The 5 model QSAR have smaller value of PRESS (0.348) than another QSAR model.

The value of r = 0.994 and r^2 = 0.987 to indicate that correlation between electronic structure (independent variables) with antimalarial activity very firm. Its mean that change of activity of antimalarial Log IC_{50} a series benzothiazoles derivatives compound resulted 99.4% from the existence of change of descriptor: electronic structure, dipole moment, E_{LUMO}, E_{HOMO}, and polarizability, that all are independent variables. Comparing parameters F and SE of the six models, it is easy revealed that model 5 is the best model because it highest F and lowest SE value. According to F value indicated that model 5 is significance at trust level 95% as shown by ratio of F_{calc}/F_{table} which the value more than 1. The value of F_{calc} larger than F_{table} to indicated that H_1 accepted and its showing correlates electronic structure (dependent variables) a series benzothiazoles derivatives between activity of antimalarial (Log IC_{50}) having significance relation at trust level 95%. Meanwhile, the smallest value of SE to indicate that the QSAR model have very small deviation of data or have highest significance data. At Table 3 indicating that model 5 have smallest value of PRESS than another models. The small value of PRESS to indicate antimalarial activity of experiment between activity of predict have very small difference value. The mentioned can be made guide that the model 5 have more good ability activity of antimalarial benzothiazoles derivatives to design. The descriptors selected for modeling antimalarial activity of chalcone derivatives are summarized in Tables 3 and 5. The best model generated for FCR3 strain is model 5. The model 5 is presented at Table 3 and 4, completely can be write at following.

Log IC_{50} = 23.527 + 4.024 (qC_4) + 273.416 (qC_5) + 141.663 (qC_6) – 0.567 (E_{LUMO}) – 3.878 (E_{HOMO}) – 2.096 (α); n = 13, r = 0.994, r^2 = 0.987, SE = 0.094, F_{calc}/F_{table} = 11.212, and PRESS = 0.348.

The QSAR model obtained is ideal if its has r^2 value equal to and its indicating that correlation independent variable between dependent variables is perfect and significance [27-28] if its has r^2 value equal to 0 indicating structural electronic and properties of molecular (dependent variables) between antimalarial activity Log IC_{50} have no correlation or no significance. The statistical parameters commonly using r^2 value because have more correctness level than r value. The value of r^2 have larger interval than r value so that small difference which no perceived at r value but its can perceived clearly at r^2. The r and r^2 value as statistical parameters only showing linearity measures of relevant model, but cannot depict measure of predicts of equation model, so that require to be paid attention by other statistical parameters.

The others statistical parameters, beside r and r^2 which need to be paid attention in this research is SE and F value. The smallest value of SE to express the model obtained is progressively and more significance. At Table 3 showing the model 5 was selected the most significance at trust level 95%. Ones statistical parameters to look for ability of QSAR model is to be analyze of PRESS parameter. The smallest value of PRESS to indicate the QSAR model have good ability to predict antimalarial activity. The PRESS value of QSAR models was listed in Table 3. The model 5 is the most reliable model because it has the smallest value.

The result of evaluation antimalarial activity [predicted Log IC_{50}] and correlation with antimalarial activity [experiment Log IC_{50}] for the model 5 by using semi-empiric AM1 method have linearity (r^2 = 0.906) and slope value (0.962) can be seen at Fig. 1. According to the value of variable dipole moment, polarizability, E_{LUMO}, E_{HOMO}, were obtained by the variation of atoms included in multilinear analysis (Table 4), atomic net charges: C_4, C_5, C_6, dipole moment, E_{LUMO}, E_{HOMO} and polarizability seems the most responsible for the pharmacological activity. In this study of structure-antimalarial activity relationship interestingly reveal that change of the structure of substituent group at C_4, C_5, C_6, dipole moment, E_{LUMO}, E_{HOMO} and polarizability position commonly results the change of its bioactivity. Among those 2-substituent benzothiazole derivatives another substituted molecules have already received considerable attention due to their potential activity.

Table 5. New designed benzothiazoles antimalarial compounds and predicted log IC_{50} calculated using the best QSAR model

Compounds	Substituents		Predicted Log IC_{50}	IC_{50}
	R^1	R^2		
14	Cl	$NH(PhCH_2)$	-1.858	0.013
15	Cl	$NCOCH_3(PhCH_2)$	-1.653	0.022
16	Cl	$NC_5H_{11}(PhCH_2)$	-0.919	0.120
17	Cl	$N(C_5H_{11})_2$	0.236	1.723
18	$N(CH_3)_2$	$NH(PhCH_2)$	-2.332	0.005
19	$N(CH_3)_2$	$NCOCH_3(PhCH_2)$	-1.991	0.010
20	$NH(COCH_3)$	$N(PhCH_2)_2$	-2.372	0.004
21	$NH(COCH_3)$	$NH(PhCH_2)$	-2.157	0.006
22	$N(COCH_3)_2$	$N(PhCH_2)_2$	-1.976	0.011
23	$N(COCH_3)_2$	$NH(PhCH_2)$	-1.568	0.027
24	$NH(PhCH_2)$	$N(PhCH_2)_2$	-1.853	0.014
25	$NH(PhCH_2)$	$NH(PhCH_2)$	-2.987	0.001
26	$N(PhCH_2)_2$	$N(PhCH_2)_2$	-1.889	0.013
27	$N(PhCH_2)_2$	$NH(PhCH_2)$	-1.289	0.051

Design of New Antimalarial Benzothiazole Derivatives

In this research, the design molecule of new antimalarial of benzothiazole derivatives has been done on the basis of the selected QSAR model obtained and this equation model was then used to predict their activity. In designing the structure of the new antimalarial compounds, -Cl, -NHR and $-NR_2$ substituents attached to the main structure of benzothiazole were modified so that the higher antimalarial activity of the new designed molecule compared to that of the previously synthesized compounds was achieved. Table 5 lists the detailed substituent of new antimalarial compounds that have been designed on the basis of the above assumption along with their predicted activity values calculated using the best QSAR model. In this study, the alkyl (R) as substitutions has been replaced using more and less bulkier substituent to evaluate the effect antimalarial activity. The evaluation was done by comparing the predicted log IC_{50} values of the corresponding compounds. Results of the study show that there is a significant difference in the value of predicted log IC_{50} when R is varied substituent to keep the different and it has been highest antimalarial activity.

There are 3 factors that are used in the selection of the new benzothiazole derivative candidates, i.e. theoretical activity obtained from QSAR equation calculation, the possibility in synthesizing the new compound and the ease to get the reactant for synthesis. Based on the prediction calculation of their activity, some new compounds which may have better antimalarial activity are proposed e.g. compounds 18, 20, 21, and 25 (Table 5). These four candidates could guide the synthesis procedures of new candidates of benzothiazole derivatives become more focus.

CONCLUSION

We have used a semi-empirical molecular calculation AM1 to study the correlation of antimalarial activity of a series of benzothiazoles derivatives drugs against chloroquine-resistant FCR3 strain. The model 5 is the best model on the 95% level with statistical parameters. The overall correlation is given by the computed molecular properties of atomic net charges, dipole moment, E_{LUMO}, E_{HOMO}, and polarizability (α). Significant regression model was obtained by multiple linear regression method for structural properties of benzothiazoles derivatives versus antimalarial activity against *P. falciparum*. In this research, it has been found that the descriptors polarizability, E_{LUMO}, E_{HOMO}, atomic net charges: C_4, C_5, and C_6 as hypothetical active of molecular region of benzothiazoles derivatives, seems to be the most responsible for the pharmacological activity. Based on the best QSAR model obtained, it has been designed some new antimalarial compounds which have predicted antimalarial activities higher than those of the existing compounds. This new designed compounds are suggested to be further synthesized and then tested for their antimalarial activity in the laboratory.

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