QSAR STUDY OF XANTHONE DERIVATIVES AS ANTI PLASMODIAL AGENTS

Amanatie[1,*], Jumina[2], Mustofa[3], M. Hanafi[4], and Ria Armunanto[2]

[1]*Student of Doctoral Program, Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Gadjah Mada, Yogyakarta, Indonesia*

[2]*Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Gadjah Mada, Yogyakarta, Indonesia*

[3]*Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia*

[4]*Center for Chemical Research, Indonesian Institute of Science (LIPI), Serpong Tangerang, Indonesia*

ABSTRACT

Xanthones and their derivatives have been reported to exhibit inhibitory activities towards Plasmodium falciparum. To provide deep insight into the correlation between inhibitory activities and structures of xanthones, linear regression method was employed to establish QSAR models for 16 xanthone derivatives that have diverse structures. The accuracy and predictive power of the proposed QSAR model were verified by semi empirical PM3 method, optimation, and validation. The result showed that the best model is model 3 i.e. Log $1/IC_{50}$ = Σ (-1.446)$qO_{(7)}$+ (-8.775)$q.C_{(12)}$ + (-10.592)$qC_{(13)}$ + 1,979; Y = PRESS = 1.124192.

INTRODUCTION

The spreading of malaria is so quickly and very widespread expanding, because of its resistant parasites, especially *Plasmodium falciparum* to chloroquine. Such a thing has pushed the researchers to find new malarial drugs which are more potential. Several approaches had been conducted to find new antimalarial drugs, for examples through modification of chemical structure toward antimalarial compounds having higher antiplasmodium activity and exploration of natural products, especially to traditional drugs that have been applied for malaria treatment [1]

Based on that description and considering some factors which have been mentioned by some researchers, hence we have conducted a QSAR analysis toward 16 compounds of xanthone derivatives as listed in table (1) (compounds 1-16), which have been reported by Likhitwitayawuid [2]. The QSAR analysis in this research is different from QSAR analysis which has been conducted by Tahir and Mustofa [3] which only used atomic net-charge as descriptor and semi empiric AM1 method. This research used atomic net-charge, dipole moment, log P as well as polarizability as descriptors in semi empiric PM3 method. The calculation using those descriptors was carried out to obtain the best new model equation. The equation was then used to predict and get information about antimalarial activity of xanthone derivatives. The xanthone derivatives have been well known as potential antimalarial activity against *Plasmodium falciparum*.

This research, besides using atomic net-charge, this is also uses other descriptors i.e. dipole moment, log P and polarizability procedure by semi empiric PM3 method. Those considerations were carried out to obtain the best new equation model. In this study, the QSAR analysis of 16 xanthone derivates is conducted using atomic net charge calculated by semi empiric PM3 method as main descriptors to obtain model equation for predicting antimalarial activity and to get information about activity antimalarial of xanthone compounds. Derivatives of xanthone compounds have been known as potential antimalarial activity against *Plasmodium falciparum*.

The xanthone structure compounds were illustrated in Fig. 1, while chemical structure derivatives of xanthone as well as their xanthone activities are presented in Table 1.

The use of the electronic structure of the molecule based on semi empirical calculation, such as PM3 as descriptors in QSAR study, has been shown in some
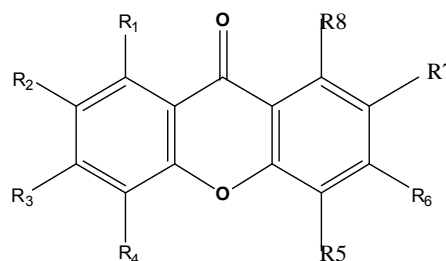

Fig 1. The structure xanthone compound

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* Corresponding author. Tel/Fax : +62-8179444737
Email address : amanatie_ama@yahoo.com

Table 1. Series 16 xanthone derivatives and antiplasmodial activity

No	Group atom C								Log IC_{50}
	R1	R2	R3	R4	R5	R6	R7	R8	
1	H	OH	H	H	H	H	H	H	1.70
2	H	H	OH	H	H	H	H	H	2.00
3	OH	H	OH	H	H	H	H	H	1.88
4	H	H	OH	H	H	OH	H	H	2.00
5	H	H	H	OH	OH	H	H	H	1.20
6	H	OH	OH	OH	H	H	H	H	-.60
7	H	H	OH	OH	OH	OH	H	H	.70
8	H	OH	OH	OH	OH	OH	H	H	-.40
9	OH	H	OH	H	OH	OH	OH	H	.00
10	H	OH	OH	OH	OH	OH	OH	H	-1.00
11	H	OMe	OMe	OMe	OMe	OMe	H	H	2.00
12	H	OAc	OAc	OAc	OAc	OAc	H	H	-1.10
13	C_5H_{10}	OMe	OH	C_5H_{10}	H	OH	C_5H_{10}	OH	.40
14	$C_{11}H_{19}$	OMe	OH	H	H	OH	C_6H_{12}	OH	.48
15	$C_{11}H_{19}$	OMe	OH	H	H	OH	C_7H_{13}	OH	.18
16	H	OMe	OH	H	H	OH	$C_{11}H_{19}$	OH	.48

reports. This can lead to useful model equations for the prediction of antimalarial activity from the calculated atomic net charges [4].

EXPERIMENTAL SECTION

Materials

This research is a theoretical study that uses PM3 semi empirical method in QSAR models of xanthone derivatives. The structure of xanthone compound is illustrated in Fig. 1, while the structures of xanthone derivatives as well as their xanthone activities are presented in Table 1. All xanthone derivatives are used in computational chemistry calculation to produce predictors. 16 xanthone derivatives as antimalarial agents are applied to statistical calculation as dependent variable for antiplasmodial activities. Data are obtained from the journal have been reported to show antimalarial activities by Likhitwitayawuid [2].

Instrumentation

Computational chemistry calculations are conducted at Yogyakarta State University, Yogyakarta, Indonesia and Organic Chemistry Laboratory of Mathematics and Natural Science, Yogyakarta State University, Yogyakarta, Indonesia, and Organic Chemistry Laboratory, Faculty of Mathematics and Natural Science Universitas Gadjah Mada, Yogyakarta, Indonesia. Calculations were performed on, Intel (R) Pentium IV with 2.66 GHz processor, 2.77GB of RAM, and 40 GB Harddisk Drive, The software's used are Hyperchem ver. 7.0 (for electronic calculation and predictor) and SPSS ver. 15.0 (for statistical analysis).

Procedure

Semi-Empirical PM3 Method Selection

Each compound is drawn into a three dimensional (3D) model of compound. Then calculations of parameters are set up for each model. The semi-empirical PM3 method was chosen in this study. This method was successively to develop and to refine of the previous methods such as AM1 semi-empirical. The 16 series consists of xanthone derivatives, group atom C and the value of antiplasmodial activity (Log IC_{50}).

Electronic Parameters Calculation Results

The Computational chemistry calculations were performed using semi-empirical method PM3. This method was improved from the previous methods such as MNDO [5] which can predict the compounds with an oxidation number of lots. One result of the calculation by using computational chemistry programs can provide output data in the form of the atomic net charge. In Table 2 presents data on the atomic net charge for the carbon atoms of the 16 compounds, which used for QSAR analysis.

Data in Table 2 contains the IC_{50} values for 16 xanthone derivatives having antimalarial activity [6], so we get the results of the relationship between log IC_{50} with atomic net charge of 16 compounds that were analyzed as presented in Table 2.

The value of the atomic net charge, dipole moment, log P, and polarisability from xanthone derivatives. Table 2 shows that there is influence of group substituent. Substitution of an atom on C_2 instance will result in the reduction of the C_2 negative charge relative to the load from the C_2 atom cluster compounds without substituent. The existence of this cluster resulted in partial reduction of the charge induction.

Table 2. Value atomic net charges, dipole moment, log P and polarizability of xanthone derivatives used in the models

qC1	qC2	qC3	qC4	qC5	qC6	qO7	qC8	qC9	qC10	qC11	qC12	qC13	qC14	qO15	moment	logP	polarz	massa	volume	logIC50
0.06	-0.08	-0.11	0.08	-0.18	-0.11	-0.10	0.12	-0.22	0.39	-0.15	-0.04	-0.15	-0.01	-0.33	1.54	-0.45	22.51	212.20	601.56	1.70
-0.19	0.16	-0.26	0.16	-0.26	0.03	-0.10	0.11	-0.22	0.40	-0.15	-0.04	-0.15	-0.01	-0.33	3.24	-0.45	22.51	212.51	602.82	2.00
-0.26	0.21	-0.31	0.21	-0.37	0.26	-0.10	0.12	-0.22	0.43	-0.15	-0.04	-0.15	0.00	-0.38	3.96	-1.47	23.15	228.20	614.29	1.88
-0.19	0.16	-0.25	0.16	-0.26	0.03	-0.10	0.15	-0.26	0.40	-0.20	0.16	-0.24	0.04	-0.34	2.53	-1.47	23.15	228.20	622.66	2.00
-0.11	-0.10	0.07	0.03	-0.18	-0.05	-0.09	0.09	-0.19	0.39	0.06	-0.14	-0.10	-0.05	-0.32	2.99	-1.47	23.15	229.20	619.81	1.20
0.05	0.10	-0.03	0.06	-0.19	-0.11	-0.11	0.12	-0.22	0.40	-0.15	-0.04	-0.15	-0.01	-0.33	3.03	-2.50	23.79	244.20	640.11	-0.60
-0.17	0.13	-0.05	0.09	-0.23	0.00	-0.09	0.11	-0.22	0.40	0.02	0.06	-0.19	0.00	-0.33	3.75	-3.52	2.52	260.20	659.74	0.70
0.05	0.10	-0.02	0.05	-0.19	-0.11	-0.09	0.12	-0.22	0.40	0.02	0.06	-0.20	0.00	-0.33	4.08	-4.53	25.06	276.20	679.77	-0.40
-0.26	0.21	-0.30	0.21	-0.38	0.26	-0.07	0.08	-0.18	0.43	0.06	0.03	0.02	-0.10	-0.38	3.46	-4.55	25.06	276.20	672.94	0.00
0.05	0.10	-0.02	0.06	-0.19	-0.11	-0.08	0.08	-0.18	0.40	0.05	0.03	0.02	-0.10	-0.33	3.37	-3.57	25.70	292.20	699.08	-1.00
0.01	0.09	0.00	0.10	-0.21	-0.04	-0.07	0.13	-0.25	0.40	-0.03	0.13	-0.22	0.03	-0.33	2.80	-4.39	34.24	346.34	946.99	2.00
0.04	0.12	0.04	0.12	-0.20	-0.01	-0.08	0.12	-0.21	0.39	0.03	0.13	-0.14	0.01	-0.32	5.22	-5.63	43.84	486.39	1,238.20	-1.10
-0.03	0.15	-0.21	0.15	-0.24	0.04	-0.11	0.18	-0.30	0.42	-0.24	0.20	-0.31	0.24	-0.03	5.45	1.41	58.72	520.67	1,329.36	0.40
-0.03	0.14	-0.25	0.14	-0.24	0.06	-0.11	0.18	-0.30	0.42	-0.24	0.20	-0.31	0.24	-0.03	5.49	1.25	56.88	506.64	1,489.98	0.48
-0.03	0.15	-0.25	0.14	-0.24	0.05	-0.11	0.18	-0.30	0.42	-0.24	0.20	-0.32	0.24	-0.03	2.90	0.25	57.52	522.69	1,326.67	0.18
-0.03	0.15	-0.25	0.15	-0.24	0.05	-0.11	0.16	-0.27	0.41	-0.21	0.16	-0.23	0.21	-0.03	3.68	-0.19	49.73	452.55	1,313.75	0.48

Table 3. Corelation variable of log IC_{50} vs net charge atoms

Variable	qC1	qC2	qC3	qC4	qC5	qC6	qO7	qC8	qC9	qC10	qC11	qC12	qC13	qC14	qO15	logIC50
qC1	1	0.06	-0.08	-0.11	0.08	-0.18	-0.11	-0.10	0.12	-0.22	0.39	-0.15	-0.04	-0.15	-0.01	-0.33
qC2	0.06	1	0.016	0.16	-0.26	0.16	-0.26	0.03	-0.10	0.11	-0.22	0.40	-0.15	-0.04	-0.15	-0.01	-0.33
qC3	-0.08	0.016	1	-0.31	0.21	-0.37	0.26	-0.10	0.12	-0.22	0.43	-0.15	-0.04	-0.15	0.00	-0.38
qC4	-0.11	-0.26	-0.31	1	0.16	-0.26	0.03	-0.10	0.15	-0.26	0.40	-0.20	0.16	-0.24	0.04	-0.34
qC5	0.08	0.16	0.21	0.16	1	-0.18	-0.05	-0.09	0.09	-0.19	0.39	0.06	-0.14	-0.10	-0.05	-0.32
qC6	-0.18	-0.26	-0.37	-0.26	-0.18	1	-0.11	-0.11	0.12	-0.22	0.40	-0.15	-0.04	-0.15	-0.01	-0.33
qO7	-0.11	0.03	0.26	0.03	-0.05	-0.11	1	-0.09	0.11	-0.22	0.40	0.02	0.06	-0.19	0.00	-0.33
qC8	-0.10	-0.10	-0.10	-0.10	-0.09	-0.11	-0.09	1	0.12	-0.22	0.40	0.02	0.06	-0.20	0.00	-0.33
qC9	0.12	0.11	0.12	0.15	0.09	0.12	0.11	0.12	1	-0.18	0.43	0.06	0.03	0.02	-0.10	-0.38
qC10	-0.22	-0.22	-0.22	-0.26	-0.19	-0.22	-0.22	-0.22	-0.18	1	0.40	-0.03	0.13	-0.22	0.03	-0.33
qC11	0.39	0.40	0.43	0.40	0.39	0.40	0.40	0.40	0.43	0.40	1	0.03	0.13	-0.14	0.01	-0.32
qC12	-0.15	-0.15	-0.15	0.20	0.06	-0.15	0.02	0.02	0.06	-0.03	0.03	1	0.20	-0.31	0.24	-0.03
qC13	-0.04	-0.04	-0.04	0.16	-0.14	-0.04	0/06	0.06	0.03	0.13	0.13	0.20	1	-0.31	0.24	-0.03
qC14	-0.15	-0.15	-0.15	-0.24	-0.10	-0.15	-0.19	-0.20	-0.02	0.22	-0.14	-0.31	-0.31	1	0.24	-0.03
qO15	-0.01	-0.01	0.00	0.04	-0.05	-0.01	-0.00	0.00	-0.10	0.03	0.01	0.24	0.24	0.24	1	0.24
Log IC50	-0.33	-0.33	-0.38	-0.34	-0.32	-0.33	-0.33	-0.38	-0.33	-0.33	-0.32	-0.03	-0.03	-0.03	0.24	1

The C originally bounded by H atoms. The atomic charge on C was quite negative, but after the H atom is replaced with a cluster, the atomic charge at C will decrease to the negative value. This indicated that the position of H in more distant groups resulted in large differences in atomic charge on an atom with clusters substituent different. The groups substituent -CH_3 and -OCH_3, a reduction of the negative value will be greater with substituent -OCH_3-CH_3 compared with, this is because the position of the atoms H-OCH_3 on farther than the-CH_3. Substitution at an atom effect also on the increase or decrease the negative value of the atomic charge on the atoms in the next position. It will induce the atoms on the next position.

The induction process can be explained as follows. The existence of substitutions in a single atom, would lead to the induction pattern of the partial charge of each atom, from C_1 to C_{15} reduction which will occur or negative value addition in alternating intervals. E.g. to substitutions at the C_2 atom charge will decrease the negative values, as well as for the C_3 and C_5 are the atoms C_1, C_3 and C_5 would increase the negative value. For substitution in the sequence e.g. C atoms C_3 and C_4 will induce the atoms in other positions of C_1, C_2, C_{12} and C_{13} that is becoming increasingly negative values. This can be presented in Table 3.

Results Analysis of QSAR

Regression analysis was used to determine the variable-free variables selected in model building QSAR equation. The statistical parameters used in the regression analysis as a factor in decision-making is R determination, SD and F. Independent variables can be reduced and supplemented. For a good analysis, then for n independent variables at least 2n +1 data sample used for analysis. In this study, 16 samples derivatives compounds xanthone means for good statistical analysis, used at least nine independent variable. They can be obtained from the main structure of the atomic net charge that is on the ring in xanthone compounds that includes C_1, C_2, C_3, C_4, C_5, C_6, O_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, and C_{15}.

The study was based on the position of substitution, which occur relatively influence on the antimalarial activity of xanthone derivatives. Based on relatively small sample size, get a good equation, so in

Table 4. QSAR Model, R value, Fcount, F_{count}/F_{table}

Model	R	F_{count}	F_{count}/F_{tab}
I	0.97	18.871	0.001
II	0.635	1.183	0.396
III	0.843	4.315	0.045
IV	0.711	1.224	0.400
V	0.786	1.346	0.381
VI	0.757	1.122	0.460
VII	0.854	2.248	0.196
VIII	0.911	2.627	0.136
IX	0.635	1.8	0.225
X	0.812	2.318	0.168
XI	0.921	4.689	0.056
XII	0.834	2.746	0.126

Table 5. Standard Deviation (SD) model 1 and model 3

No	Model	Standard Deviation (SD)
1	Model 1	SD = 1.15600
2	Model 3	SD = 1.13768

this study used 15 independent variables that qC_1, qC_2, qC_3, qC_4, qC_5, qC_6, qO_7, qC_8, qC_9, qC_{10}, qC_{11}, qC_{12}, qC_{13}, qC_{14}, qO_{15} to be involved in statistical analysis. The data are presented in Table 2.The moment dipole, log P and polarizabilities of the ring are not involved in the QSAR test. Without a factor that should be used in the design of new antimalarial drugs.

Log IC_{50} correlation with the atomic net charge
To see the distant relationship between the variables and performed correlations among variables involved. It is done mainly by looking at the level of influence of each of the atomic net charge against the log IC_{50} value. The value of the correlation between variables was calculated by statistical analysis. The values of the correlation between variables are presented in Table 3. Correlation is stronger for the data which approximates the value of R = 1 or R = -1. Table 4 shows that the independent variable is relatively strong influence on the value of antimalarial activity. log IC_{50} is the value of activities of *plasmodium falciparum*. This figure is quite close to one. Therefore, if there is a substitution group allegedly positioned anywhere on the ring in xanthone due to the changes in the value of the net charge of atoms C_1 and C_2 would result in a change in the activity of xanthone derivatives. Furthermore, if observed further shows that there are significant differences or the influence of independent variables qC_1, qC_2, qC_3, qC_4, qC_5, qC_6, qO_7, qC_8, qC_9, qC_{10}, qC_{11}, qC_{12}, qC_{13}, qC_{14}, qO_{15}, and qC_{16} against not free variable log IC_{50} is different. The Table 6 shows that qC_{12}, qC_{13}, qC_{14} and qC_{15} for model 1 are dominant. Table 7 showed that qC_1, qC_2, qO_{15} and qC_{16} for model 3 are dominant. Therefore we need further analysis to determine the best equation model with the most significant data. Equation of these relations is [8]:

$$\text{Log } 1 / IC_{50} = \sum P_{(7)}q_{(7)} + P_{(12)}q_{(12)} + P_{(13)}q_{(13)} + D \qquad (1)$$

$$\text{PRESS} = \sum{}^{n}\left(\log IC_{50} \text{ experiment - log}IC_{50} \text{ prediction}\right)^2 \quad (2)$$

RESULT AND DISCUSSION

The calculated PM3 atomic net charges, dipole moment, log P and polarizability of xanthone derivatives used in models are listed in Table (2) in searching for appropriate models according to eq.(1). This allows the exclusion of less relevant atoms and provides opportunity for a gradual evaluation of y the atoms influencing significantly of the anti malarial activity of molecules.

Multilinear regression analysis

Statistical analysis is used to process data on the determination of the best QSAR equation model using multilinear regression analysis. From the data correlation is known that qC_1, qC_2, qC_3, qC_4, qC_5, qC_6, qO_7, qC_8, qC_9, qC_{10}, qC_{11}, qC_{12}, qC_{13}, qC_{14}, qO_{15} are dependent variable against log IC_{50} is relatively the same. It is difficult to determine exactly where the most dominant variable. Therefore it is performed a variety of independent variables to obtain the best QSAR equation model. Using variation of 12 combinations of four variables obtained QSAR equation model was chosen worthy to be studied, the R value, F value and F_{eval}/F_{table} presented in Table 5. This equation was chosen based on the value of R, F value, F_{eval}/F_{table}. The equation was chosen to have relatively high R value close to 1 or -1 which means the equation quite linier (linearity test). The more linear means the better expected evaluation. In statistical analysis, commonly used R for R is greater accuracy compared to r. Selected equations is presented in Table 5. The equations which have a relatively high R is firstly performed. The highest R value for 0.970 is a model 1 involving the independent variable, while the lowest R value for 0.635 is the model of 2 and 9 involving the free variable. The range of values for R is 0-1. For R values equal to zero means no relationship at all among the independent variables and the atomic net charge dependent variable log IC_{50}. If the value of R close to one means that the regression equation are ideal stated. This means that the correlation between independent variables and no free perfect [7]. If a relatively high R value close to 1 indicates that activity relationship of compounds that have antimalarial activity with electronic structure xanthone derivative compounds is an ideal linear relationship. However, only the parameter R represents the size of the model equations linearity concerned, the analysis was continued with advanced statistical parameters.

Table 6. Model 1

No	Compound	qC_1	qC_{12}	qC_{13}	Mom dipole	logP	Log $IC_{50\ eval}$	Log $IC_{50\ exp}$
1	13	-0.3	0.20	-0.31	5.45	1.41	8.71508	0.40
2	14	-0.3	0.20	-0.31	5.49	1.25	8.55082	0.48
3	15	-0.3	0.20	-0.32	2.90	0.25	4.6459	0.15
4	16	-0.3	0.16	-0.23	3.68	-0.19	5.18288	0.48

Table 7. Model 3

No	Compound	qO7	qC12	qC13	Mom dipole	Log $IC_{50\ eval}$	Log $IC_{50\ exp}$
1	1	-0.10	-0.04	-0.15	1.54	3.07318	1.7
2	2	-0.10	-0.04	-0.15	3.24	1.98008	2.0
3	15	-0.11	0.20	-0.32	2.90	1.9078	0.18
4	16	-0.11	0.16	-0.23	3.68	0.80398	0.48

Table 8. Log $IC_{50\ hit}$ and log $IC_{50\ exp}$ of Model 1

No	Log $IC_{50\ hit}$	Log $IC_{50\ exp}$	log $IC_{50\ exp}$ - log $IC_{50\ hit}$	Δ^2
1	0.7073	0.40	-0.3073	0.094433
2	-0.967921	0.48	-1.447921	0.209647
3	0.755808	0.15	-0.605808	0.367003
4	1.726755	0.48	-1.246755	0.0155439

Table 9. Log $IC_{50\ eval}$ and log $IC_{50\ exp}$ of Model 3

No	Log $IC_{50\ eval}$	Log $IC_{50\ exp}$	log $IC_{50\ exp}$ - log $IC_{50\ hit}$ (Δ)	Δ^2
1	-4.65515	1.7	6.35515	40.38793
2	-0.779654	2.0	2.779654	7.7266476
3	-1.68471	0.18	1.86471	3.477143
4	-1.85655	0.48	2.33655	5.459465

Significance of data is then performed by observing the standard Deviation (SD). The smaller the standard deviation (SD), are the more significant data. SD parameters in this study provide useful information because the value is spreading of on 1.13768, and then subsequently used to test the parameters of F. The greater F value, the more significant data. If the observed value of F, then the highest F value was to model one. Amounted to 18.871. Medium for the lowest F value is model 6 with a value of 1,122 and then by using the F table for comparison. F value is calculated relative to F_{table}. Calculate the F_{ratio}/F_{table} is presented. Data will be significantly calculate if the $F_{ratio}/F_{table} > 1$ or F calculated > F_{table} of Table 5 shows that F_{eval}/F_{table} is smaller than one is to model 3 with a value of 0.045. Table 6 and 7 shows model 1 and model 3.

The model 3 involved three independent variables qC_1, qC_2, qC_3, qC_4, qC_5, qC_6, qO_7, qC_8, qC_9, qC_{10}, qC_{11}, qC_{12}, qC_{13}, qC_{14}, qO_{15}, although very high R value of 0.970 shows that the ratio value of $F_{eval}/F_{table} = 0.045$ is less smaller than one F_{eval} of means that F is much smaller than the F_{table}. This regression equation was statistically acceptable. It means that the three models can be selected as the best QSAR equation models of the 12 selected QSAR equations. Having obtained the best equation model, conducted a review between the variables involved to see the relationship between variables.

Determination of the best QSAR equation model

Based on the calculation of regression statistics obtained a strong correlation between changes in molecular structure represented by the electronic parameters derivatives compounds and antimalarial activity xanthone substituted. Of the 12 equations obtained by a model equation was chosen the best three models presented in Table 5.

The selection model of equation 3 as the best of the 16 models are based on the selection equation: 1). A small price for the level of trust 0.001 means passing the borderline level of significance is p-0.05 or the data is quite significant. 2). Price R and SD (standard deviation, of R= 0.843 and SD = 1.1703. 3). Price F i.e. if the value of F exceeds the value of F table or a ratio value of F_{eval}/F_{table} is smaller than one. F_{eval}/F_{table} for model 3 = 0.045.

Thus the equation is significant enough to be the model best QSAR equations from a series of compounds derived antimalarial xanthone. SD value that represents the value of standard deviation which has a relatively small amount of 1.13708 R value of 0.843 means that about 84.3% variations of log IC_{50} values caused by the variation of the atomic net charge free variable. In other words we can say that changes in the antimalarial activity of compounds derived xanthone on a series of compounds derived xanthone around 84.3%. It is caused by changes in electron density in the selected atoms. R value is close to 1 means that the correlation between independent variables and no free near-perfect, the influence of independent variables in this case the atomic net charge against the log IC_{50} quite perfect (ideal). F value is a measure of the level of significance of differences in the regression equation model. F value is 4.815 with F value ratio/F table value of 0.045 is received so the regression model 3 can be accepted as the best QSAR equation model.

Table 10. Value Y

No.	Model	Value (Y) = PRESS
1	Model $_1$	Y_1 = 0.9927
2	Model $_3$	Y_3 = 1.124192

Parameter values and SD for three models are presented in the Table 10.

Further validation of the best model may be evaluated by comparing PRESS (predictive residual sum of square) value of the model 1 in Table 5 and the model 3 in Table 6. This parameter is defined as sum of square of difference between observed activity and predicted activity calculated by the corresponding model. The model with the smallest value of PRESS is the best model because it implies that the difference between the observed and the predict activities is minimal. Results of PRESS calculation for each model as listed in Table 5 again confirms that model 3 is the most reliable model because in induces the smallest PRESS value.

The best QSAR regression equation based on equation 1, and the parameters in the Table it is Hansch analysis:

$$\text{Log } 1/\text{IC}_{50} = \sum P_{(7)}q_{(7)} + P_{(12)}q_{(12)} + P_{(13)}q_{(13)} + D$$

$$\text{Log } 1/\text{IC}_{50} = \sum -1.446 \text{ q O}_{(7)} + -8.775 \text{ q C}_{(12)} + -10.592 \text{ q C}_{(13)} + 1,979$$

Y = PRESS = 1.124192
n = 16, R = 0,843, SD = 1.13768, F_{eval}/F_{table} = 0.045

CONCLUSION

We have used a semi empirical molecular orbital calculation PM-3 to study the correlation between atomic net charge and the antimalarial activity of a series antiplasmodium against wild type of the xanthone derivatives. The best QSAR regression equation is:

$$\text{Log } 1/\text{IC}_{50} = \sum -1.446 \text{ q O}_{(7)} + -8.775 \text{ q C}_{(12)} + -10.592 \text{ q C}_{(13)} + 1,979$$

Y = PRESS = 1.124192
n = 16, R = 0,843, SD = 1.13768, F_{eval}/F_{table} = 0.045

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