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Structural Model Design of Xanthone Compounds as Antimalarial Activity

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Abstract- *Xanthones* and their derivatives have been reported to exhibit inhibitory activities towards *Plasmodium falciparum*. In order 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 *xanthones* derivatives with different structure. The accuracy and predictive power of the proposed QSAR model were verified, optimized, and validated by semi empiric PM3 method. The result of this research showed that the best QSAR model was model 3.

Index Terms- Anti-plasmodialagents, Structural Models Design, xanthone.

I. INTRODUCTION

Malaria is the main health problems in subtropical and tropical countries. There are 105 countries in the world in malaria endemic and more than 500 million cases or more than 2.7 million people deaths by malaria each year. In Indonesia, malaria is still become a health problem, particularly in eastern Indonesia. In the year 2003 the *Annual ParactemiaIncidence* (API) reported that there were 175 - 558 cases. Further, annual malaria incidents are more than 2.48 million and 211 deaths among 227.5 million is people of Indonesian.

The spread of malaria is so quickly and wide because of its parasites resistant, especially *Plasmodium falciparum* toward *chloroquine*.Because of that, researchers want to find new malarial drugs which more potential. Several approaches had been conducted to find new antimalarial drugs, for examples through modification of chemical structure of antimalarial compounds so that they have higher anti-plasmodium activity. Exploration of natural product as drugs traditionally has been applied for malaria treatment (Mustofa, 2000). For instance, derivatives of *xanthone* (Figure. 1) compounds have been known as potential antimalarial activity against *Plasmodium falciparum*. Based on description above and considering some factors as mentioned by previous researchers, therefore the writer conducted the QSAR analysis toward 16 compounds of *xanthone* derivatives (1-16) as shown at table (1). The 16 of *xanthone* derivatives series have been tested the *anti-plasmodial* activity by Likhitwitayawuid*et al* (1998).

The QSAR analysis in this research is different from that which has been conducted by Mustofa and Tahir (2001). Mustofa and Tahir (2001) used atomic net-charge as a descriptor with semi empiric AM1 method, this research used not only atomic net-charge as descriptors but also dipole moment, Log P and polarizability with semi empiric PM3 method. Then, by performing QSAR analysis towards 16 *xanthone* derivatives, model equations were determined to predict and to get information about antimalarial activity of *xanthone* compounds. The use of the electronic structure of the molecule based on semi empirical calculation have also been reported. This can lead to useful model equations for the prediction of anti-malarial activity from the calculated atomic net charges (Mudasir, *et al*, 2003 and Tahir, *et al*, 2005). Furthermore, this approach has also been proven to be very helpful in obtaining an indication concerning the active center of molecules (Polman, *et al*, 1998).

II. METHODE

Model Set-up

The atomic electron net charges, dipole moment, Log P, polarizability have been evaluated by Mulliken population analysis based on standard semi empiricaly PM3 method using chemical software Hyper-Chem version 7,0. PM3 calculation is known to give quite satisfactory results for the chemistry of *xanthone* compounds derivatives containing hydroxyl groups. Geometries for stationary points were identified by medium of energy with respect to geometric parameters using Polak-Ribiere algorithm included in HyperChem package with convergence limit of 0.01 kcal $mol^{-1}A^{-1}$. Many possible linearrelationships between calculated atomic charges and anti-malarial activity were evaluated by using SPSS statistical software. The main objective is to obtain a model with a few variables descriptors as possible but still describing the anti-malarial activity satisfactorily.

Hanschequation of these relations are:

$$\text{Log } IC_{50} = A(\text{LogP}) - B(\text{LogP})^2 + C(E) + D(\rho\sigma) + E + \ldots \quad (1)$$

III. RESULT AND DISCUSSION

The calculated PM3 descriptors, such as atomic net charges, dipole moment, Log P and polarizability, of *xanthone* derivatives used in models are determined based on eq. 1 aqnd listed in table (2). This allows the exclusion of less relevant atoms and provides opportunity for a gradual evaluation of the atoms influencing significantly of the anti-malarial activity of molecules.

Selection for the Best Design Model

In order to obtain the best design model that correlates with independent variables (descriptors) and dependent variable (antimalarial activity), regression analysis using SPSS software package have been performed. Twelve independent variables consisting of 15 atomic net charges qC_1, qC_2, qC_3, qC_4, qC_5, qC_6, qC_8, qC_9, qC_{10}, qC_{11}, qC_{12}, qC_{13}, qC_{14}, qC_{15} and qO_7. As well as net charge of *xanthone* and dipole moment, Log P and polarizability were included in the model set- up. At the first step, all variables are included in the model and the less relevant variables were then eliminated gradual from the model. This procedure finally gave 12 QSAR models andValue R, F, F-hit/F-tab are as listed in table (3). *The statistical parameters obtained Standard Deviation (SD) model 1 and model 3 from linear according to Eq. (1). collected in table (4).* From table 3 it is evaluated that some models can immediately be eliminated because their $F_{elevated}/F_{table}$ value are lower than unity, which means that the models are statistically not exist or rejected. In Table 5, content Model 1, qC1,qC12,qC13, moment dipole,Log P, Log IC_{50eval} and Log $IC_{50exp.}$In Table. 6, content Model 3, qCO7,qC12,qC13, moment dipole, Log IC50eval and Log IC50 exp. In table. 7. Content,Log IC_{50}eval and Log IC_{50}exp Model 1 In table 8.content Log IC_{50}eval and Log IC_{50}exp Model 3 and in t able9.conten Value PRESS or Value Y

On the other hand, it is clearly shown that there are 2 selected models which show a relatively good correlation between anti-malarial activity of the best model among 12 models selected as listed in table 3 and 4 is not adequate only by comparing the R size, especially for model 1, and 3 because their R values are 0,970. and 0,843. Therefore we should also consider other statistical parameter of F (model significance) and SD (Standard Deviation), it seems that model 1 it the best model from the viewpoint of statistical parameters, Standard Deviation (SD) and F value (model significance). However, this model consisted of almost all descriptors avoilable and thus it is not the simplest model and therefore this model is excluded from selection.

Now, the remaining possible models are model 1 and 3. By comparing the parameters F and SD of two models, it is easily observed that model 3 is the best model because it has highest f and relatively lower SD and contains only 4 variables which means that the model is the quite sample, thus model 3 is selected as the best QSAR model. This model could therefore retionalize the search for new *xanthone*derivatives which have been antimalarial activity of these series *xanthone* derivatives, necessary due to the rapid resistance development of *Plasmodium falciparum.*

Model Validation

It has been conducted that model 3 is the best model from the point of view of statistical parameters of the linear analysis. To see how good the model predict the activity of the *xanthone* series, calculation of the antimalarial activity for each *xanthone*analogs has been performed using model 12 and results (predicted Log (IC_{50}) was plotted against those obtained by experiments (observed Log IC_{50}) by regression method to see how well they correlate each other (Fig 2). It is obvious from this figure that model 3 predicts very well the activity of the series of *xanthone* as indicated by the values of the slope and correlation coefficient (R) of the plot which is approaching unity, is 0.970 and 0.843, respectively.

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 (9) again confirms that model 3 is the most reliable model because in induces the smallest PRESS value.

Evaluation Model and Prediction of Most Influencing Atoms.

According to the fitting coefficient values obtained by the variation of descriptors included as summarized in table 3, we may concluded that atom C_1, C_{12}, C_{13} and q-ring seem to be the most responsible atoms for the anti-plasmodium inhibition activity of the molecules. Although some models listed in table (5 and 6) also include dipole moment and Carbon atoms of *xanthone*, the values of their coefficient are relatively small indicating that these atoms are of rather less importance and therefore can be eliminated from the model. By we immediately observed that C_1, C_{12} and C_{13} assume prominent role in most as compared with the others, and that either O_7, C_{12} and C_{13} has a significant influence, respectively.

IV. 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 anti-plasmodium against wild type of the *xanthone* derivatives. The best overall correlation is given by the computed molecular properties of atomic net charges of *xanthone* derivatives and moment dipole, Log P, polarity. It is gratifying to observe that the most influencing atoms of the *xanthone*, in term of possible mode of docking of the molecule well to the targeted *xanthone* derivatives. It has also been demonstrated from this result that semi-empirical PM3, although induces possible error sources, still seem to be a necessary and acceptable compromise for quantum calculations on series of *xanthone* derivatives of this size, including the search for most influencing atoms.

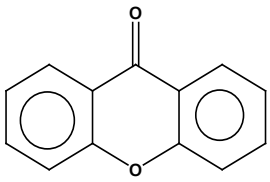

Figure 1. The molecular *xanthone* compounds

Table 1. The 16 of *xanthone* derivatives series and the anti-plasmodial activity

No	Compounds	Log IC_{50}
1	1	1.70
2	2	2.00
3	3	1.88
4	4	2.00
5	5	1.20
6	6	-.60
7	7	.70
8	8	-.40
9	9	.00
10	10	-1.00
11	11	2.00
12	12	-1.10
13	13	.40
14	14	.48
15	15	.18
16	16	.48

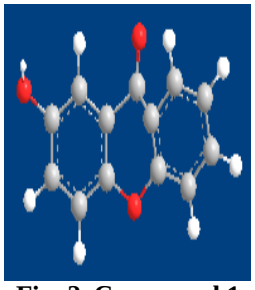

Fig 2. Compound 1

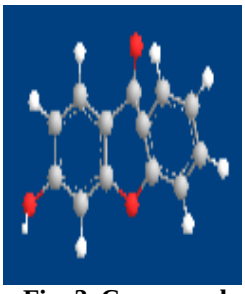

Fig 3. Compound

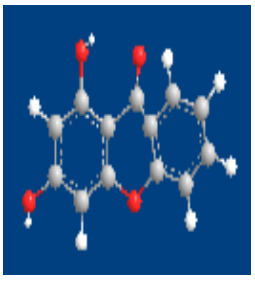

Fig 4 Compound 3

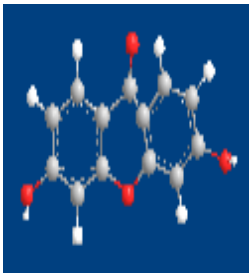

Fig 5 Compound 4

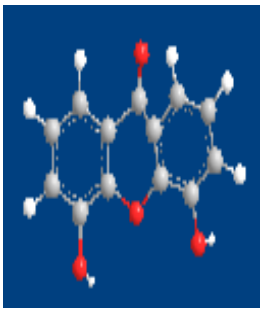

Fig 6 Compound 5

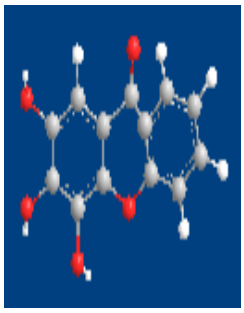

Fig 7. Compound 6

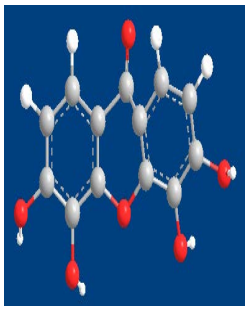

Fig 8.Compound 7

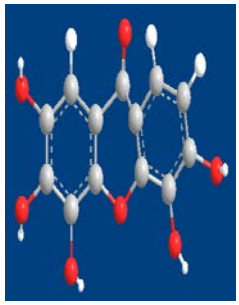

Fig 9.Compound 8

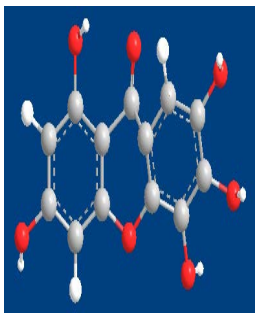

Fig10Compound 9

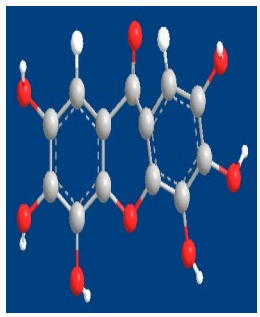

Fig11Compound 10

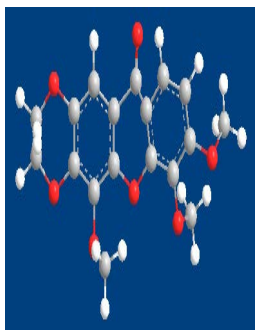

Fig12 Compound 11

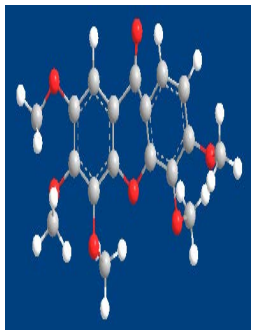

Fig 13 Compound 12

Fig14 Compound 13

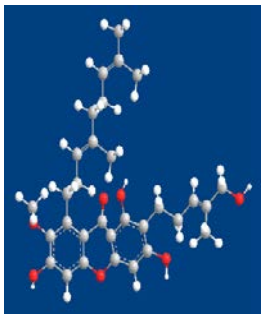

Fig 15Compound 14

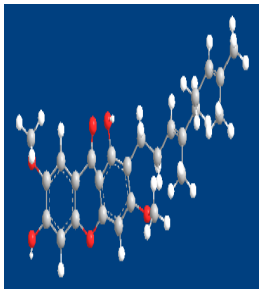

Fig 16. Compound 15

Fig 17Compound 16

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

qC1	qC2	qC3	qC4	qC5	qC6	qO7
0.06	-0.08	-0.11	0.08	-0.18	-0.11	-0.10
-0.19	0.16	-0.26	0.16	-0.26	0.03	-0.10
-0.26	0.21	-0.31	0.21	-0.37	0.26	-0.10
-0.19	0.16	-0.25	0.16	-0.26	0.03	-0.10
-0.11	-0.10	0.07	0.03	-0.18	-0.05	-0.09
0.05	0.10	-0.03	0.06	-0.19	-0.11	-0.11
-0.17	0.13	-0.05	0.09	-0.23	0.00	-0.09
0.05	0.10	-0.02	0.05	-0.19	-0.11	-0.09
-0.26	0.21	-0.30	0.21	-0.38	0.26	-0.07
0.05	0.10	-0.02	0.06	-0.19	-0.11	-0.08
0.01	0.09	0.00	0.10	-0.21	-0.04	-0.07
0.04	0.12	0.04	0.12	-0.20	-0.01	-0.08
-0.03	0.15	-0.21	0.15	-0.24	0.04	-0.11
-0.03	0.14	-0.25	0.14	-0.24	0.06	-0.11
-0.03	0.15	-0.25	0.14	-0.24	0.05	-0.11
-0.03	0.15	-0.25	0.15	-0.24	0.05	-0.11

qC8	qC9	qC10	qC11	qC12	qC13	qC14	qO15
0.12	-0.22	0.39	-0.15	-0.04	-0.15	-0.01	-0.33
0.11	-0.22	0.40	-0.15	-0.04	-0.15	-0.01	-0.33
0.12	-0.22	0.43	-0.15	-0.04	-0.15	0.00	-0.38
0.15	-0.26	0.40	-0.20	0.16	-0.24	0.04	-0.34
0.09	-0.19	0.39	0.06	-0.14	-0.10	-0.05	-0.32
0.12	-0.22	0.40	-0.15	-0.04	-0.15	-0.01	-0.33
0.11	-0.22	0.40	0.02	0.06	-0.19	0.00	-0.33
0.12	-0.22	0.40	0.02	0.06	-0.20	0.00	-0.33
0.08	-0.18	0.43	0.06	0.03	0.02	-0.10	-0.38
0.08	-0.18	0.40	0.05	0.03	0.02	-0.10	-0.33
0.13	-0.25	0.40	-0.03	0.13	-0.22	0.03	-0.33
0.12	-0.21	0.39	0.03	0.13	-0.14	0.01	-0.32
0.18	-0.30	0.42	-0.24	0.20	-0.31	0.24	-0.03
0.18	-0.30	0.42	-0.24	0.20	-0.31	0.24	-0.03
0.18	-0.30	0.42	-0.24	0.20	-0.32	0.24	-0.03
0.16	-0.27	0.41	-0.21	0.16	-0.23	0.21	-0.03

moment	LogP	polarz	massa	volume	$LogIC_{50}$
1.54	-0.45	22.51	212.20	601.56	1.70
3.24	-0.45	22.51	212.51	602.82	2.00
3.96	-1.47	23.15	228.20	614.29	1.88
2.53	-1.47	23.15	228.20	622.66	2.00
2.99	-1.47	23.15	229.20	619.81	1.20
3.03	-2.50	23.79	244.20	640.11	-0.60
3.75	-3.52	2.52	260.20	659.74	0.70
4.08	-4.53	25.06	276.20	679.77	-0.40
3.46	-4.55	25.06	276.20	672.94	0.00
3.37	-3.57	25.70	292.20	699.08	-1.00
2.80	-4.39	34.24	346.34	946.99	2.00
5.22	-5.63	43.84	486.39	1,238.20	-1.10
5.45	1.41	58.72	520.67	1,329.36	0.40
5.49	1.25	56.88	506.64	1,489.98	0.48
2.90	0.25	57.52	522.69	1,326.67	0.18
3.68	-0.19	49.73	452.55	1,313.75	0.48

Table 3. Value R, F, Feval/Ftable

Model	R	Feval	Feval/Ftable
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	0.4
V	0.786	1.346	0.381
VI	0.757	1.122	0.46
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 4. Standard Deviation (SD) model 1 and model 3

No	Model	Standard Deviation (SD)
1	Model 1	SD= 24.490
2	Model 3	SD=0.12878

Table 5. Model 1

No	Compound	qC_1	qC_{12}	qC_{13}	Mom dipol	Log P	Log IC_{50eval}	Log IC_{50exp}
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. 6 Model 3

No	Compound	qO7	qC12	qC13	Mom dipol	Log IC_{50eval}	Log IC_{50exp}
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	-	0.16	-	3.68	0.80398	0.48
		0.11		0.23			

Table. 7. Log IC_{50}eval and Log IC_{50}exp Model 1

No	Log IC_{50eval}	Log $IC_{50\ exp}$	Δ	Δ^2
1	8.71508	0.40	8.31506	69.1402228036
2	8.55082	0.48	8.07082	65.1381354724
3	4.6459	0.15	4.4959	20.21311681
4	5.18288	0.48	5.04488	25.4508142144

Table 8. Log IC_{50}eval and Log IC_{50}exp Model 3

No	Log IC_{50eval}	Log $IC_{50\ exp}$	Δ	Δ^2
1	3.07318	1.7	1.37318	1.88562
2	1.98008	2.0	-0.01992	0.00039
3	1.9078	0.18	1.7278	2.98528
4	0.80398	0.48	0.32398	0.10496

Table9. Value Y

No.	Model	Value (Y)
1	Model $_1$	Y_1 = 4.72408
2	Model $_3$	Y_3 = 0.965178

V. ACKNOWLEDGE

1. Research and Technology Ministry, **KNRT-RI**, Focus Field of **Health and Medicine Techniques** Jakarta, Indonesia.
2. Doctor Grant, Gadjah Mada University, Indonesia.

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