QUANTITAVE STRUCTURE-ACTIVITY RELATIONSHIP ANALYSIS (QSAR) OF ANTIMALARIAL 1,10-PHENANTHROLINE DERIVATIVES COMPOUNDS

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ABSTRACT

Quantitative Electronic Structure-Activity Relationship (QSAR) analysis of a series of 1,10-phenanthroline derivatives as antiplasmodial compounds have been conducted using atomic net charges (q), dipole moment (μ) E_{LUMO}, E_{HOMO}, polarizability (α) and log P as the descriptors. The descriptors were obtained from computational chemistry method using semi-empirical PM3. Antiplasmodial activities were taken as the activity of the drugs against chloroquine-resistant Plasmodium falciparum FCR3 strain and are presented as the value of ln $(1/IC_{50})$ where IC_{50} is an effective concentration inhibiting 50% of the parasite growth. The best model of QSAR model was determine by multiple linear regression method and giving equation of QSAR:

$$\ln 1/IC_{50} = 3.732 + (5.098)\, qC_5 + (7.051)\, qC_7 + (36.696)\, qC_9 + (41.467)\, qC_{11} - (135.497)\, qC_{12} + (0.332)\, \mu - (0.170)\, \alpha + (0.757) \log P.$$

The equation was significant on the 95% level with statistical parameters: n=16; r=0.987; r^2= 0.975; SE=0.317; F_{calc}/F_{table} = 15.337 and gave the PRESS=0.707. Its means that there were only a relatively few deviations between the experimental and theoretical data of antimalarial activity.

Keywords: *QSAR, antimalarial, semi-empirical method, 1,10-phenanthroline*.

INTRODUCTION

Malaria remains one of the most devastating diseases, causing as many as 2.7 million deaths annually with an estimated 400 to 900 million new cases each year [1]. Malaria endemic areas include Africa, South East Asia, India and South America; however, the disease is spreading to new areas, such as Central Asia, and Eastern Europe. Local transmission of malaria in the United States, unheard of in the era between World War II and 1980, now accounts for an increasing number of cases [2]. Clinical cases in the US are now in average of 1,300 per year [3]. Worldwide, the majority of deaths occur in children; other high risk groups include pregnant women, refugees, migrant workers, and non immune travelers-over 20 million Western tourists at risk annually (fact sheets from Malaria Foundation International). Although four species of the genus *Plasmodium* cause human malaria, *Plasmodium falciparum* is the deadliest and will be the subject of this review.

During the past two decades an increasing number of quantitative structure-activity/property relationship (QSAR/QSPR) models have been studied using theoretical molecular descriptors for predicting biomedical, activity, toxicological, and technological properties of chemicals. QSAR/QSPR are mathematical models that seek to predict complicated physicochemical/biological properties of chemicals from their simpler experimental or calculated properties. The main problem with the use of experimental data as independent variables in QSAR is that they are not available for the majority of chemical structures, real or hypothetical.

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 [4]. Therefore, it is essential to find new drugs of antimalarial having a pharmacological activity higher than that of currently

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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.

QSAR studies of antimalarial activity represent an emerging and exceptionally important topic in the area of computed-aided drug design. Although the demand for '*in silico*' discovery is clear in all areas of human therapeutics, the field of anti-infective drugs has a particular need for computational solutions enabling rapid identification of novel therapeutic leads.

In this research semi empirical methods were used to calculate a number of properties/descriptors. In current practice, semiempirical methods serve as efficient computational tools which can yield fast quantitative estimates for a number of properties. 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. Compared with *ab initio* or density functional methods, semi empirical calculations are much faster, typically by several orders of magnitude [5], but they are also less accurate, with errors that are less systematic and thus harder to correct.

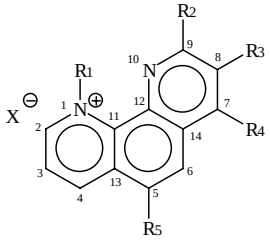
Among the classes of drugs that are effective in the treatment of the *P. falciparum* malarial, there is the 1,10-phenanthroline and its derivatives. The 1,10-phenanthroline derivatives was synthesized from 8-aminoquinoline and 1,10-phenanthroline as a starting material. The five models of diaza-analogs of the phenanthrene skeleton were synthesized, described and evaluated for their antiplasmodial activity. From that evaluation, the 1,10-phenanthroline ring system appeared as a new class of potential antimalarial compounds [6]. Previous QSAR analysis have been reported using electronic descriptor producing by AM1 calculation [7,8] using 13

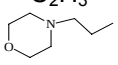
EXPERIMENTAL SECTION

Geometry Optimization and Calculation of Molecular Descriptors

QSAR models are evaluated using sets of 1,10-phenanthroline 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 ln ($1/IC_{50}$) where IC_{50} is an effective concentration inhibiting 50% growth of the parasite [8-10]. As the activities were measured under two different conditions, the activities for 1-13 [8] were rescaled with respect to activities for 14-16 [9,10] by using ln ($1/IC_{50}$) obtained from two experiments.

Table 1. Chemical structure and activity data of antimalarial 1,10-phenanthroline derivatives againts FCR3 strain



Compounds	R_1	R_2	R_3	R_4	R_5	X^-	IC_{50} (μM)
1	-	H	H	H	H	-	1.28
2	-	H	H	H	NO_2	-	1.37
3	H	CH_3	C_2H_5Cl	Cl	H	Cl	2.32
4	CH_3	CH_3	C_2H_5Cl	Cl	H	I	0.16
5	C_2H_5	CH_3	C_2H_5Cl	Cl	H	I	0.16
6	C_2H_4OH	CH_3	C_2H_5Cl	Cl	H	I	1.06
7	C_3H_7	CH_3	C_2H_5Cl	Cl	H	I	0.15
8	C_7H_{15}	CH_3	C_2H_5Cl	Cl	H	I	0.37
9	-	CH_3	C_2H_5Cl	N_3	H	-	0.71
10	-	CH_3	C_2H_3	Cl	H	-	3.29
11	CH_3	CH_3	C_2H_3	Cl	H	I	0.35
12	-	CH_3	C_2H_3	OH	H	-	6.08
13	-	CH_3			H	-	19.84
14	CH_3	H	H	H	H	SO_4^{2-}	0.61
15	C_2H_5	H	H	H	H	SO_4^{2-}	0.41
16	$PhCH_2$	H	H	H	H	Cl	0.54

All the compounds (Table 1) were calculated using package HyperChem® Program Version 7.0 and complete geometry optimization with the semi-empirical Parameterized Model 3 (PM3) method was performed. Quantum-chemical descriptors were calculated, as for example: atomic net charges, dipole moment, E_{HOMO}, E_{LUMO}, polarizability and log P.

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 Evaluation

The steps of quantitative structure-activity relationship analyses were conducted at this research: to determinate a series 1,10-phenanthroline derivatives compound to be analyzed along with value of IC_{50} yielded through laboratory experiment; to look for elementary ring structure of 1,10-phenanthroline derivatives compound, which is the most stable using optimization process; to calculate descriptor through optimized structure; statistical analysis process to get equation of QSAR; selected of the best equation model of QSAR; to design the new compound of 1,10-fenantrolin derivatives according to the best model of QSAR and consider of eligibility of synthesis; and making of 1,10-phenanthroline derivatives resulted from molecular design which has the highest predicted value of IC_{50} to be synthesized in laboratory.

The net charge atoms for three dimension of molecule structure which have experienced of converged at process of optimization can be recorded through menu file; start log; compute; single point and then stop log. The net charge of atoms on its structural compound can be seem through display menu, labels and charge.

RESULT AND DISCUSSION

Descriptor is a parameter or property of molecule used as independent variables in calculation of predicted activity (theoretical IC_{50}). The descriptors used in this research are atomic net charges, dipole moment, log P, $E_{HOMO-LUMO}$ and polarizability. To obtain the structural properties of each test compound and modeling compound after process of geometry optimization, the calculation proses is continued with single point at sub menu. Descriptors or structural properties produced from calculation with single point were atomic net charges and dipole moment, whereas descriptors of log P and 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 $E_{HOMO-LUMO}$ descriptors would not be obtained if calculation was performed using molecular mechanic method. All of the descriptors was given in Table 2.

To calculate of structural electronic and other descriptors of a series 1,10-phenanthroline derivatives was conducted with the semi empiric PM3 method. PM3 method which is better method than the others semi empiric method. Method of PM3 is repair method of before all like MNDO method [11], which can predicts compounds having valence many with the best accuracies [12]. The PM3 method can be used for the analysis of a series 1,10-phenanthroline derivatives, because 1,10-phenanthroline derivatives is organic compound considering atoms as C, H, Cl, Br, O, and N.

Selection of the Best Model

According to result of calculation statistic of multilinear regression by using SPSS version 13.0 for windows were obtained 6 QSAR models as listed in Table 4. From 6 QSAR models were determined 1 of the best QSAR model. Model 5 is the best model. Model 5 is selected as the best model among 6 QSAR models, based on:

1. The value of r and r^2 to look for analysis data linearity that the model 5 having r equal to 1 is 0.987 and r^2 is 0.975.
2. The smallest value of SE (Standard Error of Estimation) is model 5 having value equal to 0.317.
3. If the value of F exceed value of F_{table} or comparison of F_{calc}/F_{table} more than 1. All models have value of F_{calc}/F_{table} more than 1, but model 5 selected as the best model because its have the biggest value (15.377) from 6 QSAR models.
4. The 5 model QSAR have smaller value of PRESS (Predictive Residual Sum of Square) than another QSAR models.

The value of r = 0.987 and r^2 = 0.975 to indicate that correlation between electronic structure (independent variables) with antimalarial activity very firm. Its mean that change of activity of antimalarial ln $(1/IC_{50})$ a series 1,10-phenanthroline derivatives compound resulted 98.7% from the existence of change of descriptor: electronic structure, dipole moment, E_{LUMO}, E_{HOMO}, log P and polarizability, that all are independent variables. Comparing parameters F and SE of the six models, it is easily revealed that model 5 is the best model because it has 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 indicate that H_1 accepted and its showing correlates electronic structure (dependent variables) a series 1,10-phenanthroline derivatives between activity of anti-

Table 2. Descriptors/independent variables used for QSAR analysis of antimalarial 1,10-phenanthroline derivatives calculated by semi-empirical PM3 method

C N	*Atomic net charges (Coulomb)*									
	qN1	qC2	qC3	qC4	qC5	qC6	qC7	qC8	qC9	qN10
1.	-0.0202	-0.0659	-0.1440	-0.0617	-0.0804	-.08045	-0.0617	-0.1440	-0.0659	-0.0202
2.	-0.0206	-0.0599	-0.1225	-0.0998	-0.3857	0.0526	-0.0368	-0.1503	-0.0356	-0.0274
3.	-0.0196	-0.0652	-0.1411	-0.0612	-0.0739	-0.0864	-0.0884	-0.1173	-0.0245	-0.0172
4.	0.5424	-0.1758	-.09056	0.0134	-0.1000	-0.0148	-0.0964	-0.0836	0.0427	-0.1184
5.	0.5379	-0.1664	-0.0933	0.0124	-0.0948	-0.0202	-0.0938	-0.0855	0.0386	-0.0964
6.	0.5582	-0.1709	-0.0911	0.0122	-0.0940	-0.0197	-0.0933	-0.0856	0.0385	-0.1013
7.	0.5470	-0.1693	-0.0926	0.0109	-0.0955	-0.0191	-0.0952	-0.0885	0.0394	-0.0961
8.	0.5470	-0.1692	-0.0926	0.0106	-0.0956	-0.0191	-0.0952	-0.0886	0.0394	-0.0958
9.	-0.0196	-0.0632	-0.1405	-0.0596	-0.0723	-0.0868	0.0476	-0.1110	-0.0301	-0.0162
10.	-0.0195	-0.0665	-0.1425	-0.0619	-0.0770	-0.0840	-0.0886	-0.0849	-0.0157	-0.0214
11.	0.5422	-0.1774	-0.0916	0.0125	-0.1027	-0.0128	-0.0987	-0.0457	0.0488	-0.1221
12.	-0.0152	-0.1774	-0.1402	-0.0668	-0.1022	-0.0524	0.1624	-0.2053	0.0158	-0.0558
13.	-0.0196	-0.0652	-0.1438	-0.0601	-0.0741	-0.1051	-0.0308	-0.0852	-0.0352	-0.0198
14.	0.5394	-0.1742	-0.0906	0.0137	-0.1014	-0.0092	-0.0332	-0.1048	-0.0012	-0.1066
15.	0.5341	-0.1648	-0.0933	0.0126	-0.0964	-0.0143	-0.0288	-0.1067	-0.0054	-0.0840
16.	0.5344	-0.1652	-0.0926	0.0080	-0.0958	-0.0171	-0.0293	-0.1087	-0.0066	-0.0850

Comp. Number	Atomic net charges (Coulomb)				μ (Debyes)	E_{LUMO} (eV)	E_{HOMO} (eV)	α ($Å^3$)	*Log P*
	qC11	qC12	qC13	qC14					
1.	-0.0001	-0.0001	-0.0781	-0.0781	2.994	-0.8424	-9.1490	23.56	3.16
2.	-0.0170	-0.0297	0.0441	-0.1299	3.201	-1.8023	-9.8023	25.40	-0.76
3.	-0.0037	0.0133	-0.0757	-0.0785	2.680	-1.0354	-9.1276	32.92	4.72
4.	-0.1196	-0.0064	-0.0154	-0.0593	13.166	-5.5444	-12.4635	35.20	4.53
5.	-0.1173	-0.0103	-0.0180	-0.0568	11.968	-5.4590	-12.4885	37.03	4.87
6.	-0.1243	-0.0095	-0.0162	-0.0563	10.178	-5.5364	-12.5304	37.67	4.08
7.	-0.1201	-0.0089	-0.0167	-0.0571	11.492	-5.4470	-12.4678	38.87	5.34
8.	-0.1201	-0.0088	-0.0166	-0.0572	10.946	-5.4318	-12.4608	46.21	6.92
9.	-0.0028	0.0087	-0.0785	-0.0818	2.819	-1.1732	-9.2587	33.62	5.05
10.	-0.0030	0.0120	-0.0759	-0.0794	1.992	-0.9261	-9.0156	30.80	4.51
11.	-0.1185	-0.0084	-0.0158	-0.0595	8.310	-5.4604	-12.4248	33.08	4.31
12.	-0.0134	0.0351	-0.0653	-0.1154	2.472	-0.7732	-8.8104	29.51	3.70
13.	0.0008	0.0013	-0.0816	-0.0788	2.508	-0.9541	-9.1034	46.17	3.06
14.	-0.1148	-0.0250	-0.0174	-0.0538	3.600	-5.5515	-13.0506	25.84	2.96
15.	-0.1125	-0.0289	-0.0198	-0.0515	2.650	-5.4698	-13.0854	27.67	3.30
16.	-0.1166	-0.0277	-0.0200	-0.0529	4.079	-5.3122	-12.6540	35.50	4.74

Table 3. Six selected models and their statistical parameters for the correlation between molecular properties and antimalarial activity of antimalarial 1,10-phenanthroline derivatives

Model	Variables	R	F_{calc}/F_{table}	SE	PRESS
1.	qC2, qC5, qC7, qC8, qC9, qN10, qC11, qC12, μ, E_{HOMO}, α, log P	0.988	4.701	0.468	0.658
2.	qC2, qC5, qC7, qC8, qC9, qC11, qC12, μ, E_{HOMO}, α, log P.	0.988	6.831	0.405	0.661
3.	qC5, qC7, qC8, qC9, qC11, qC12, μ, E_{HOMO}, α, log P	0.988	9.350	0.363	0.664
4.	qC5,qC7, qC9, qC11, qC12, μ, E_{HOMO}, α, log P	0.988	12.431	0.332	0.665
5.	qC5, qC7, qC9, qC11, qC12, μ, α, log P	0.987	15.337	0.317	0.707
6.	qC7, qC9, qC11, qC12, μ, α, log P	0.984	15.317	0.338	1.319

Table 4. Coefficient of selected independent variables for 6 QSAR models as obtained from multilinear regression analysis

Model	Coefficient of independent variables												
	qC2	qC5	qC7	qC8	qC9	qN10	qC11	qC12	μ	E_{HOMO}	α	Log P	*Const*
1.	6.740	7.056	6.481	-6.570	46.507	-4.97	51.942	-141.178	0.319	-0.297	-0.164	0.739	1.063
2.	2.457	4.697	6.530	-2.393	37.897		50.044	-123.847	0.328	-0.426	-0.163	0.735	-0.470
3.		4.266	6.303	-1.484	36.537		53.521	-124.365	0.333	-0.468	-0.163	0.752	-1.078
4.		3.116	6.497		32.114		51.069	-114.488	0.332	-0.512	-0.162	0.750	-1.667
5.		5.098	7.051		36.696		41.467	-135.497	0.332		-0.170	0.757	3.732
6.			5.365		20.430		25.447	-98.252	0.292		-0.155	0.788	1.848

malarial (ln $1/IC_{50}$) 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 5 indicating that models 1, 2, 3, 4 and 5 have relative same value of PRESS, while model 6 having highest PRESS value (1.319). The small value of PRESS to indicate that antimalarial activity of experiment between activity of predict have very small difference value. The mentioned can be make guide that the model 5 have more good ability activity of antimalarial 1,10-phenanthroline derivatives to design. The model 5 is presented at Table 5 and 6, completely can be write at following.

ln 1/I

$$C_{50} = 3.732 + (5.098)\, qC_5 + (7.051)\, qC_7 + (36.696)\, qC_9 + (41.467)\, qC_{11} - (135.497)\, qC_{12} + (0.332)\, \mu - (0.170)\, \alpha + (0.757) \log P. \quad (1)$$

n=16; r=0.987; r^2= 0.975; SE=0.31741;
F_{calc}/F_{table} = 15.337; PRESS=0.707.

The QSAR model obtained is ideal if its has r^2 value equal to 1 and its indicating that correlation independent variable between dependent variables is very perfect and significance [10] if its has r^2 value equal to 0 indicating structural electronic and properties of molecular (dependent variables) between antimalarial activity ln ($1/IC_{50}$) have no correlation or no significance. The statistical parameters commonly using r^2 value because its have more correctness level than r value. The r^2 value have larger interval than r value so that small difference which no perceived at r value but its can perceived clearly at r^2 value. The r and r^2 value as statistical parameter 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 other statistical parameters, beside r and r^2 which need to be paid attention in this research is SE and F value. The smallest values of SE to express the model obtained is progressively and more significance. At Table 5 showing the model 5 was selected the most significance at trust level 95%. Ones statistical

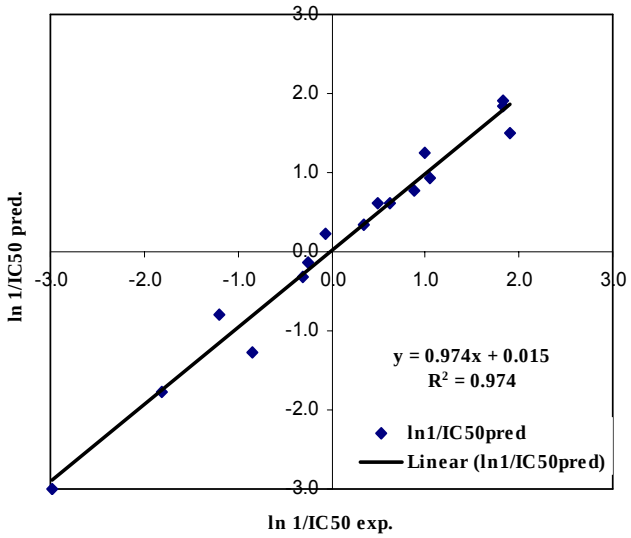


Fig 1. Linear regression of experimentally observed antimalarial activity ln ($1/IC_{50}$) versus calculated one based on QSAR model 5

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 six QSAR models was listed in Table 3. The model 5 is the most reliable model because its has the smallest value.

The result of evaluation antimalarial activity [predicted ln ($1/IC_{50}$)] and correlation with antimalarial activity [experiment ln ($1/IC_{50}$)] for the model 5 by using semi empiric PM3 method have linearity (r^2 = 0.9748) and slope value (0.974) can be seen at Table 7 and Fig. 1.According to the value of variable dipole moment, polarizability, and log P were obtained by the variation of atoms included in multilinear analysis (Table 4), atoms C_5, C_7, C_9, C_{11} and C_{12} seems the most responsible for the pharmacological activity.

CONCLUSION

We have used a semi-empirical molecular calculation PM3 to study the correlation of antimalarial activity of a series of 1,10-phenanthroline derivatives drugs against chloroquine-resistant FCR3 strain. The

best overall correlation is given by the computed molecular properties of atomic net charges of heterocyclic ring, dipole moment, LUMO-HOMO energies, polarizability and log P.

Significant regression model was obtained by multiple linear regression method for structural properties of 1,10-phenanthroline derivatives versus antimalarial activity against Plasmodium falciparum. We were reported the descriptors dipole moment (μ), polarizability (α), atomic net charges: qC_5, qC_7, qC_9, qC_{11} and qC_{12} seems to be the most responsible for the pharmacological activity. The model 5 is significant on the 95% level with statistical parameters (eq 1).

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