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Quantitave structure-activity relationship (QSAR) modeling of 1, 10-phenanthroline derivatives antimalarial compounds

David Ebuka Arthur*[1], Adamu A. Uzairu[1] and Aliyu M. JA'O[2]

[1]Department of Chemistry, Ahmadu Bello University Zaria, Nigeria
[2]Department of Chemical Sciences, Gombe, Nigeria
Corresponding author E-mail: hanslibs@myway.com

ABSTRACT

Quantitative Electronic Structure-Activity Relationship (QSAR) modeling of a series of 1,10-phenanthroline derivatives as antimalaria compounds was conducted using a set of molecular descriptors primarily atomic net charges (q), dipole moment (μ) E_{LUMO}, E_{HOMO}, polarizability (α) and log P. The descriptors were calculated after optimizing all the data sets using a semi-empirical method PM3. Antiplasmodial activities were taken as the activity of the drugs against chloroquine-resistant Plasmodium falciparum FCR3 strain and are presented as 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 the QSAR equation is given as:

$$\boldsymbol{M_4IC_{50}} = -qC_2(122.766) + qC_5(74.458) - qC_7(19.714) - qC_8(24.990) + qC_9(137.061) - qC_{10}(54.174) + qC_{11}(336.751) - qC_{12}(453.418) - Ehomo(0.086) + \alpha(0.705) - \mu(0.040) - LogP(2.582) - 6.67$$

The equation was significant on the 95% level with statistical parameters: n=16; r= 0.9985; r^2 = 0.9971; SE=0.5912; F_{calc}/F_{table} = 85.48. From the statistical analysis accompanying the revolution of this model, we concluded that the model generated was found to be better than the one proposed by hadanu et al., 2007.

Keywords: 1,10- phenanthroline derivatives, QSAR, descriptors, Antimalarial, E_{HOMO}

INTRODUCTION

Malaria is a significant problem in Nigeria, with potential for severe complications and mortality. Global estimates suggest that almost a million children die of malaria annually, second only to pneumonia and diarrhea [3], hence malaria remains a devastating global health problem. In addition, drug-resistant *Plasmodium falciparum* malaria continues to spread and at present involves almost all areas of the world. An increasing number of travelers are exposed to drug-resistant plasmodia.

The accounts of an increasing number of Clinical cases in the US averages to 1,300 per year, the majority of these deaths were found to be children, pregnant women, refugees, migrant workers, and non-immune travelers all over the world [13].

Although four species of the genus *Plasmodium* cause human malaria, *Plasmodium falciparum* is the deadliest and was the subject of this review. In this research, QSAR tool was incorporated with semi empirical methods which were used to calculate a number of properties/descriptors. In current practice, semi-empirical methods serve as efficient computational tools which can yield fast quantitative estimates for a number of properties [10].

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, but they are also less accurate, with errors that are less systematic and thus harder to correct.

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 [1].

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 available drugs for malaria [9]. QSAR studies of antimalarial activity represent an emerging and exceptionally important topic in the area of computer-aided drug design [2]. 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.

Due to the steady drop in the potency of traditional remedies and the rise in malarial by *P. falciparum* which is the most dangerous specie of the 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 [12]. Therefore, it is essential to find new drugs of antimalarial having a pharmacological activity higher than that of currently available drugs of antimalarial

MATERIALS AND METHODS

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 (IC_{50}) where IC_{50} is an effective concentration inhibiting 50% growth of the parasite [11].

All the compounds (Table 1) were calculated using package Spartan® Program Version 14.0 and complete geometry optimization with the semi-empirical Parameterized Model 3 (PM3) method was performed. Quantum-chemical descriptors were calculated for example: atomic net charges, dipole moment, E_{HOMO}, E_{LUMO}, Polarizability, log P [7].

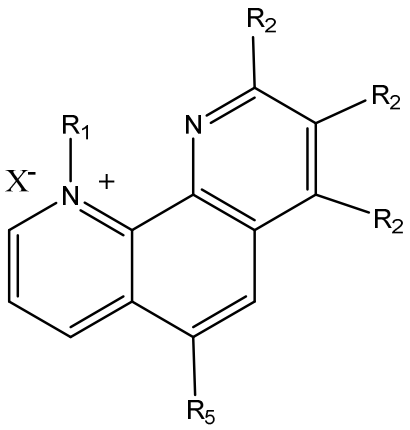
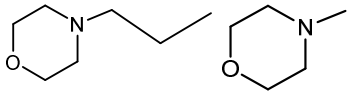


Table 1 Chemical structure and activity data of antimalarial 1,10-phenanthroline derivatives against FCR3 strain

Compounds	R1	R2	R3	R4	R5	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

RESULTS AND DISCUSSION

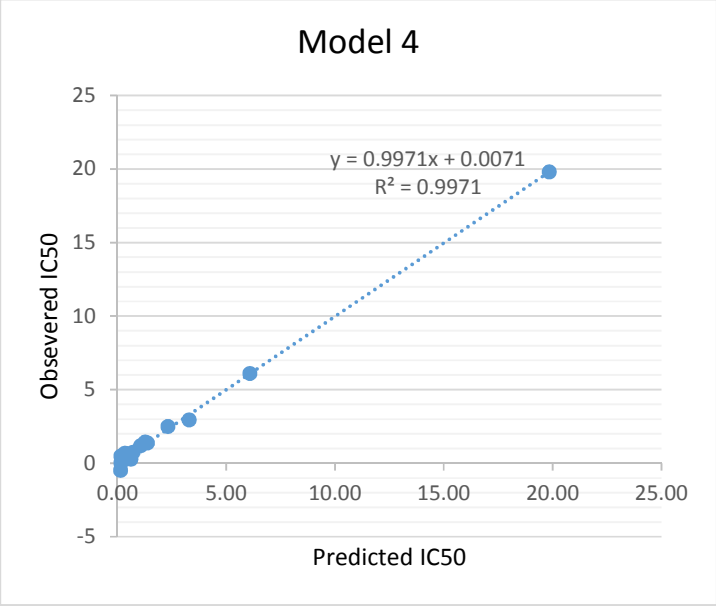
The molecular Descriptors or structural properties were determined from the repository menu and QSAR parameters section of the Spartan 14 software after the optimization of all the structures using parametric method (PM3), this includes calculations for the atomic net charges, dipole moment, log P and Polarizability. Table 2 outlines the values of the computed molecular descriptors and that of the IC50 values for all compounds.

Table 2.0 Descriptors variables used for QSAR analysis of antimalarial 1,10-phenantroline derivatives calculated with semi-empirical PM3 method

IC50	qN1	qC2	qC3	qC4	qC5	qC6	qC7	qC8	qC9	qN10	qC11	qC12	qC13	qC14	μ	α	log p
1.28	-0.020	-0.066	-0.144	-0.062	-0.080	-0.080	-0.062	-0.144	-0.066	-0.020	0.000	0.000	-0.078	-0.078	2.994	23.560	3.160
1.37	-0.021	-0.060	-0.123	-0.100	-0.386	0.053	-0.037	-0.150	-0.036	-0.027	-0.017	-0.030	0.044	-0.130	3.201	25.400	-0.760
2.32	-0.020	-0.065	-0.141	-0.061	-0.074	-0.086	-0.088	-0.117	-0.025	-0.017	-0.004	0.013	-0.076	-0.079	2.680	32.920	4.720
0.16	0.542	-0.176	-0.091	0.013	-0.100	-0.015	-0.096	-0.084	0.043	-0.118	-0.120	-0.006	-0.015	-0.059	13.166	35.200	4.530
0.16	0.538	-0.166	-0.093	0.012	-0.095	-0.020	-0.094	-0.086	0.039	-0.096	-0.117	-0.010	-0.018	-0.057	11.968	37.030	4.870
1.06	0.558	-0.171	-0.091	0.012	-0.094	-0.020	-0.093	-0.086	0.039	-0.101	-0.124	-0.010	-0.016	-0.056	10.178	37.670	4.080
0.15	0.547	-0.169	-0.093	0.011	-0.096	-0.019	-0.095	-0.089	0.039	-0.096	-0.120	-0.009	-0.017	-0.057	11.492	38.870	5.340
0.37	0.547	-0.169	-0.093	0.011	-0.096	-0.019	-0.095	-0.089	0.039	-0.096	-0.120	-0.009	-0.017	-0.057	10.946	46.210	6.920
0.71	-0.020	-0.063	-0.141	-0.060	-0.072	-0.087	0.048	-0.111	-0.030	-0.016	-0.003	0.009	-0.079	-0.082	2.819	33.620	5.050
3.29	-0.020	-0.067	-0.143	-0.062	-0.077	-0.084	-0.089	-0.085	-0.016	-0.021	-0.003	0.012	-0.076	-0.079	1.992	30.800	4.510
0.35	0.542	-0.177	-0.092	0.013	-0.103	-0.013	-0.099	-0.046	0.049	-0.122	-0.119	-0.008	-0.016	-0.060	8.310	33.080	4.310
6.08	-0.015	-0.177	-0.140	-0.067	-0.102	-0.052	0.162	-0.205	0.016	-0.056	-0.013	0.035	-0.065	-0.115	2.472	29.510	3.700
19.84	-0.020	-0.065	-0.144	-0.060	-0.074	-0.105	-0.031	-0.085	-0.035	-0.020	0.001	0.001	-0.082	-0.079	2.508	46.170	3.060
0.61	0.539	-0.174	-0.091	0.014	-0.101	-0.009	-0.033	-0.105	-0.001	-0.107	-0.115	-0.025	-0.017	-0.054	3.600	25.840	2.960
0.41	0.534	-0.165	-0.093	0.013	-0.096	-0.014	-0.029	-0.107	-0.005	-0.084	-0.113	-0.029	-0.020	-0.052	2.650	27.670	3.300
0.54	0.534	-0.165	-0.093	0.008	-0.096	-0.017	-0.029	-0.109	-0.007	-0.085	-0.117	-0.028	-0.020	-0.053	4.079	35.500	4.740

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

MODEL	VARIABLE	R2	ADJUSTED R2	^{F}calc/^{F}table	SE
1	qC5 qC7, qC9, qC11, qC12, μ, α, log P	0.9527	0.8987	17.63	1.558
2	qC7, qC9, qC11, qC12, μ, α, log P	0.9068	0.8254	11.13	2.045
3	qC5, qC7, qC8, qC9, qC11, qC12, μ, E_{homo} α, log P	0.9571	0.871	11.41	1.757
4	qC2, qC5, qC7, qC8, qC9, qC10, qC11, qC12, μ, E_{homo} α, logP	0.9971	0.985	85.48	0.591
5	qC2 + qC5 + qC7 + qN10 + qC11 + qC12 + α	0.8868	0.788	8.96	2.255



Observed IC50	Predicted IC50
1.28	1.43
1.37	1.37
2.32	2.49
0.16	0.01
0.16	0.49
1.06	1.19
0.15	-0.489
0.37	0.55
0.71	0.75
3.29	2.94
0.35	0.67
6.08	6.092
19.84	19.803
0.61	0.27
0.41	0.65
0.54	0.47

Fig. 2 A graphical representation of the model 4 validation

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

The models are as follows

1. $\mathbf{M_1IC_{50}} = qC_5(45.173) + qC_7(1.772) + qC_9(11.079) + qC_{11}(10.560) + qC_{12}(57.432) + \mu(0.335) + \alpha(0.758) - LogP(3.796) + 0.223$
2. $\mathbf{M_2IC_{50}} = qC_7(-13.236) - qC_9(132.632) - qC_{11}(131.032) + qC_{12}(387.50) - \mu(0.692) + \alpha(0.893) - LogP(3.520) - 16.429$
3. $\mathbf{M_3IC_{50}} = qC_5(79.356) - qC_7(3.728) - qC_8(43.484) + qC_9(141.379) + qC_{11}(79.436) - qC_{12}(237.372) + Ehomo(1.4229) + \alpha(0.707) - \mu(0.296) - LogP(3.750) + 18.872$
4. $\mathbf{M_4IC_{50}} = -qC_2(122.766) + qC_5(74.458) - qC_7(19.714) - qC_8(24.990) + qC_9(137.061) - qC_{10}(54.174) + qC_{11}(336.751) - qC_{12}(453.418) - Ehomo(0.086) + \alpha(0.705) - \mu(0.040) - LogP(2.582) - 6.673$
5. $\mathbf{M_4IC_{50}} = -qC_2(186.558) + qC_5(28.119) - qC_7(26.272) - qC_{10}(158.751) + qC_{11}(419.378) - qC_{12}(444.902) + \alpha(0.695) - 28.094$

Selection of the Best Model

According to result of calculation statistic of multilinear regression by using Microsoft excel 2013 (Table 3), 5 QSAR models as listed above were obtained, 1 of the QSAR model was found to best represent the relationship of chemical structure with their activity. Model 4 is the best model and is selected on the bases of:

- The value of r and r^2 for analysis data linearity shows that the model 4 have r equal to 0.9985 and r^2 is 0.9971.
- The smallest value of SE (Standard Error of Estimation) was found in model 4 having value equal to 0.5911.

- 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 4 which was selected as the best model because its have the biggest value (85.479) from 5 QSAR models.
- The 5 model QSAR have smaller value of PRESS (Predictive Residual Sum of Square) than any another QSAR models used on the course of this research.

Analysis of the relationship between molecular structure and antimalarial activity of 1, 10-phenanthroline derivatives against the FCR3 strain.

Log P is a measure of the drug's hydrophobicity, which was selected as a measure of its ability to pass through cell membranes, its value reflects the relative solubility of the drug in octanol (representing the lipid bilayer of a cell membrane) and water (the fluid within the cell and in blood) hence its correlation to the activities of data set, so its presence in the model strengthens the ability of the model to predict the possibility of the derivatives to penetrate the cell membrane of the microbes. Energy of the highest occupied molecular orbital was also found to be significant in the model, it suggest the fact that the ability of the analogues to inhibit this strain is highly influenced by the low value of their Ehomo, other quantum descriptors such as polarizability and some specific atomic charges were found to influence the model owing to their significance in the selected model.

CONCLUSION

In lieu of the computational study with 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 correlation study was done using 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*. The model 4 is significant on the 95% level with statistical parameters ($\mathbf{M_4 IC_{50}} = -\mathrm{qC}_2(122.766) + \mathrm{qC}_5(74.458) - \mathrm{qC}_7(19.714) - \mathrm{qC}_8(24.990) + \mathrm{qC}_9(137.061) - \mathrm{qC}_{10}(54.174) + \mathrm{qC}_{11}(336.751) - \mathrm{qC}_{12}(453.418) - \mathrm{Ehomo}(0.086) + \alpha(0.705) - \mu(0.040) - \mathrm{LogP}(2.582) - 6.673$). Although the descriptors polarizability (α), atomic net charges: qC^5, qC^9 and qC^{11} seems to be the most responsible for the pharmacological activity of the model.

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