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QUANTITATIVE STRUCTURE–ACTIVITY RELATIONSHIPS (QSAR) STUDY ON NOVEL 4-AMIDINOQUINOLINE AND 10-AMIDINOBENZONAPHTHYRIDINE DERIVATIVES AS POTENT ANTIMALARIA AGENT

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ABSTRACT

Quantitative structure–activity relationships (QSAR) has been a reliable study in the development of models that predict biological activities of chemical substances based on their structures for the development of novel chemical entities. This study was carried out on 44 compounds of 4-amidinoquinoline and 10-amidinobenzonaphthyridine derivatives to develop a model that relates their structures to their activities against Plasmodium falciparum. Density Functional Theory (DFT) with basis set B3LYP/6-31G was used to optimize the compounds. Genetic Function Algorithm (GFA) was employed in selecting descriptors and building the model. Four models were generated and the model with best internal and external validation has internal squared correlation coefficient (R^2) of 0.9288, adjusted squared correlation coefficient (R_{adj}) of 0.9103, leave-one-out (LOO) cross-validation coefficient (Q^2_{cv}) value of 0.8924 and external squared correlation coefficient (R^2) value of 0.8188. The model was found to be influence positively by GATS6e, TDB10s and RDF30v descriptors and negatively by AATSC1s, GATS6c and C2SP2 descriptors. The external validation and statistical test conducted confirm the stability, robustness and the predictive power of the generated model and can be used for designing novel 4-amidinoquinoline and 10-amidinobenzonaphthyridine derivatives with better antimalaria activities.*

1. INTRODUCTION

Malaria remains one of the most lives threatening infection worldwide with prevalent cases in African region (WHO 2018). The World Health Organization report (2018) on malaria revealed that in 2017 a projected two hundred and nineteen million malaria cases occurred worldwide where 5 countries took almost half of the instances: 25% from Nigeria, 11% from Democratic Republic of Congo, 5% from Mozambique and India and Uganda 4% each. And an estimate of 435 000 deaths from the disease worldwide was reported. Children below 5 years age are the most affected group responsible for 61% (266 000) of all the deaths globally in 2017 (WHO 2018). *Plasmodium*, a protozoan of the genus is the causative organism of malaria infection which has 5 species infecting humans namely, *P. knowlesi, P. malariae, P. vivax, P. ovale and P. falciparum* which is the most dangerous (Cohen et al., 2012). In an effort to find solution to this deadly illness, many researches are conducted by testing numerous molecular structures against *Plasmodium falciparum* strains to find out their most effective inhibitors. Quinoline moiety has been considered by medicinal chemists as one of the vital pharmacophores responsible for imparting antimalarial action (Mishra et al., 2014). Chloroquine, a 4-aminoquinoline has been used as the foremost antimalarial medicine since World War II (Krafts et al., 2012) but its therapeutic effect in fighting this fatal human illness is seriously hindered by the wide spread of chloroquine resistant *P. falciparum* (Uhlemann and Krishna, 2005); (Plowe, 2005). Mefloquine was usually used as a malaria prophylactic medicine (Palmer et al., 1993,) but its medicinal significance as an antimalarial drug is seriously compromised by toxicity and high cost. Hence, there remains a pressing need for new and affordable antimalarial drugs (Fidock, 2010).

Recently, 44 novel 4-amidinoquinoline (4-AMQ) and 10-amidinobenzonaphthyridine (10-AMB) derivatives were synthesized and tested to have antimalarial activities against D6, W2 and C235 strains of *P. falciparum* (Ai et al., 2015). The new 4-AMQ derivatives differ from chloroquine mainly by replacement of the 4-amino group of chloroquine with amidine (4-NHCR=NH) functional group. Addition of amino group to the new 4-AMQ series could supply to the drug's biological receptors a potential additional binding site, leading to a considerable change in pharmacological profiles from chloroquine and its congeners (Ai et al., 2015). Amidine being a stronger base than 4-aminoquinoline is an additional advantage to the novel 4-amidino analogs over chloroquine (Raczynska et al., 1998). Strong basicity of amidines may make the new amidines enhanced inhibitors of hemozoin formation and also results in more stable DNA intercalation, which are believed to account for chloroquine antimalarial action (Ai et al., 2015).

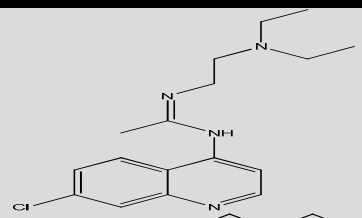
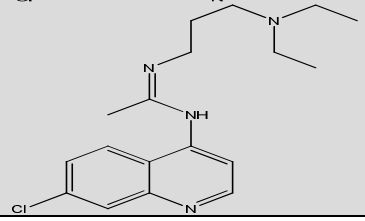
Effective and vigorous methods for screening chemical databases against molecules with known activities/properties are needed so as to discover novel drug candidates (Tropsha, 2010). Quantitative Structure-Activity Relationships (QSAR) modeling technique gives an efficient way for finding the model that connect structure of chemical compounds and their biological action in order to develop novel drug candidates. Generally, QSAR study can be defined as the method of generating empirical relationships (models) of the form $Y_i=k'(R_1, R_2,\ldots,R_n)$ by applying mathematical and statistical techniques, where Y_i are biological activities/properties of molecules, R_1, $R_2,\ldots,R_n$ are molecular descriptors (structural properties) of compounds calculated or experimentally measured, and k' is some empirically established mathematical transformation applied to descriptors to calculate the property values for all molecules (Tropsha, 2010). This research was aim at generating QSAR model predicting the activities of 4-AMQ and 10-AMB derivatives as potent antimalaria agents.

2. MATERIALS AND METHOD

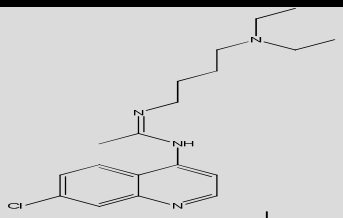
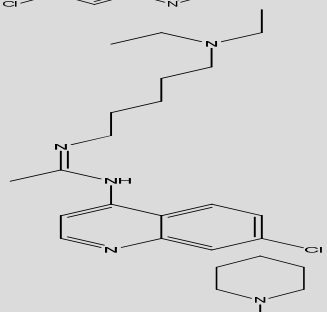
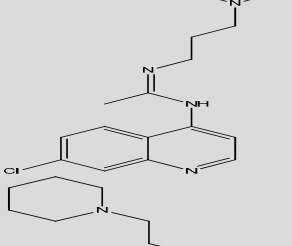
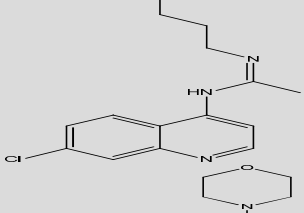
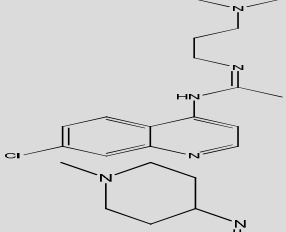
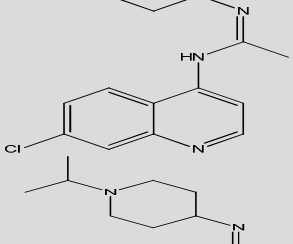
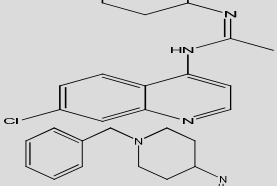
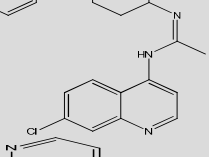
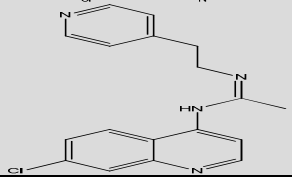
2.1 Data collection

Forty-four compounds of 4-amidinoquinoline and 10-amidinobenzonaphthyridine derivatives and their antimalarial activities against W2 strain of *Plasmodium falciparum* were obtained from the article (Ai et al., 2015) and used herein. The inhibitory antimalarial activities of the compounds reported as IC_{50} (nM) were transformed to pIC_{50} (pIC_{50} = -logIC_{50}) for use in this study. Structures of the molecules and their activities were shown in Table 1.

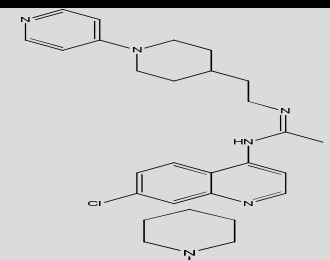
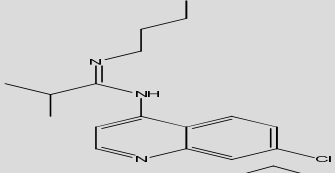
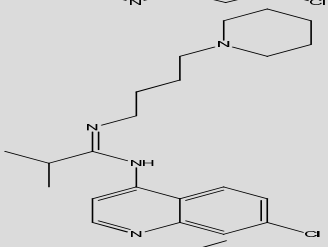
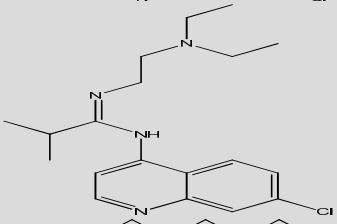
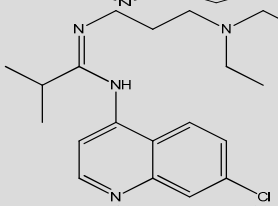
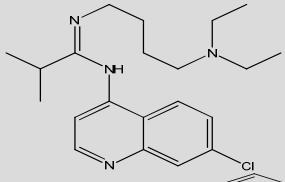
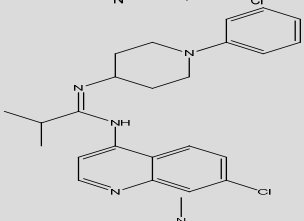
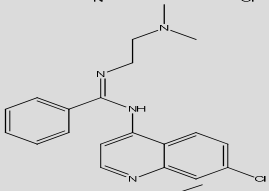
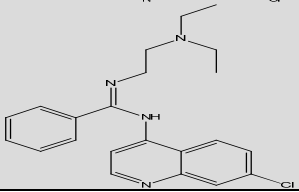
Table 1 - Molecular structures of 4-amidinoquinoline and 10-amidinobenzonaphthyridine derivatives and their antimalarial activities.

S/N	Compound	Structures	IC_{50} (nM)	pIC_{50}
1	A1		296	6.5287
2	A2		226	6.6459

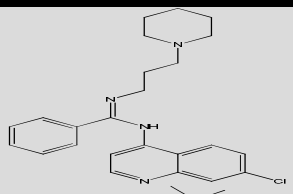
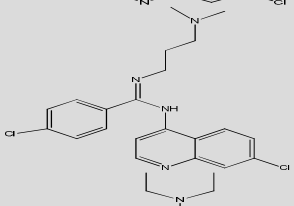
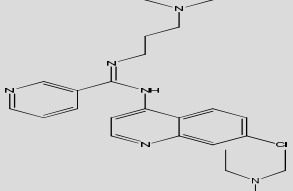
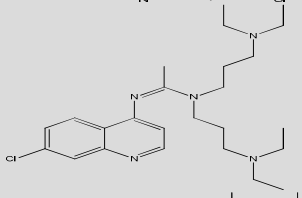
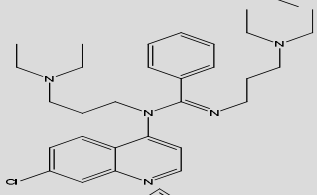
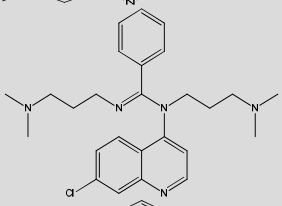
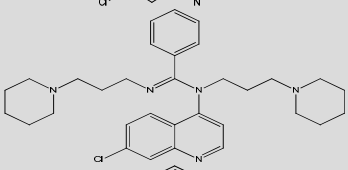
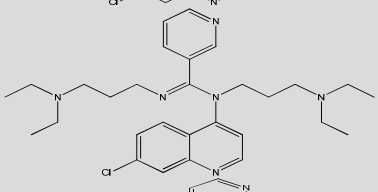
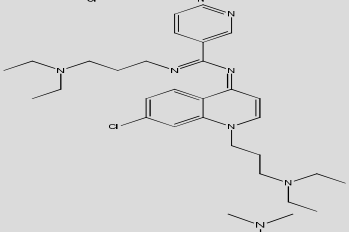
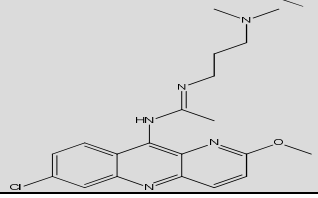
Continued Table 1

S/N	Compound	Structures	IC_{50} (nM)	pIC_{50}
3	A3		98.3	7.0074
4	A4		455	6.342
5	A5		36	7.4437
6	A6		126	6.8996
7	A7		295	6.5302
8	A8		275	6.5607
9	A9		166	6.7799
10	A10		199	6.7011
11	A11		617	6.2097

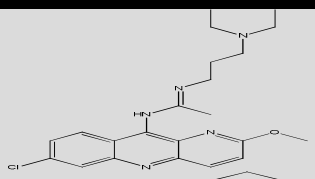
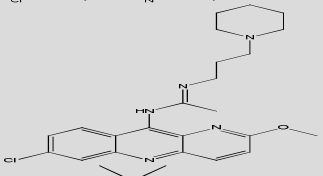
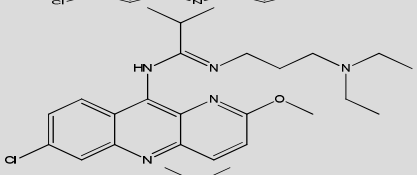
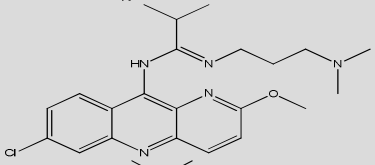
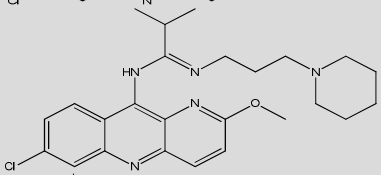
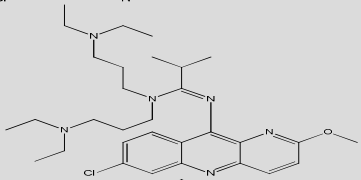
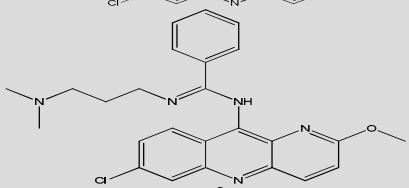
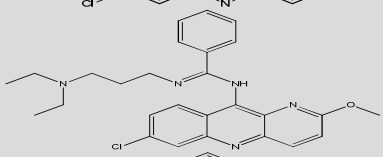
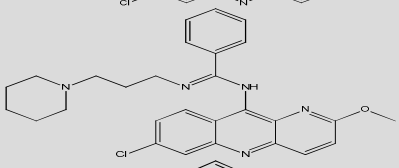
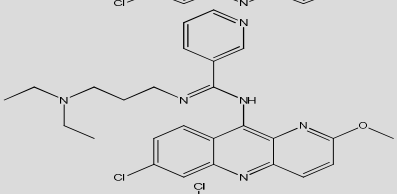
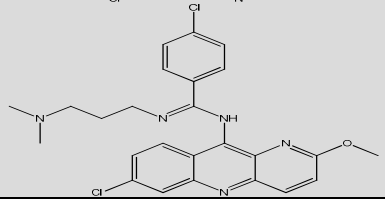
Continued Table 1

S/N	Compound	Structures	IC_{50} (nM)	pIC_{50}
12	A12		193	6.7144
13	A13		91	7.041
14	A14		18.6	7.7305
15	A15		97	7.0132
16	A16		42	7.3768
17	A17		254	6.5952
18	A18		58.7	7.2314
19	A19		9.2	8.0362
20	A20		7.2	8.1427

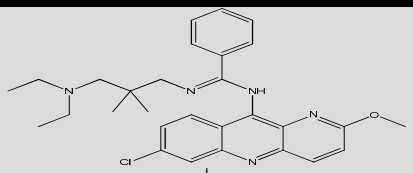
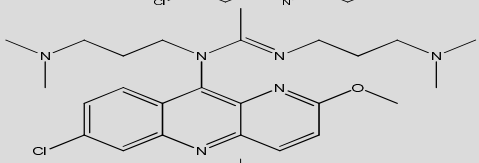
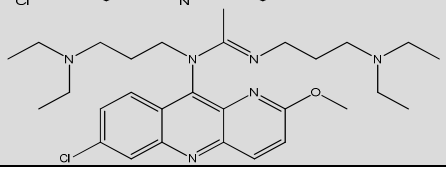
Continued Table 1

S/N	Compound	Structures	IC_{50} (nM)	pIC_{50}
21	A21		15.7	7.8041
22	A22		2.9	8.5376
23	A23		203	6.6925
24	B24		121	6.9172
25	A25		76.8	7.1146
26	A26		121	6.9172
27	A27		16	7.7959
28	A28		383	6.4168
29	C29		3917	5.407
30	D30		100	7

Continued Table 1

S/N	Compound	Structures	IC_{50} (nM)	pIC_{50}
31	D31		41	7.3872
32	D32		24.9	7.6038
33	D33		8.8	8.0555
34	D34		9.7	8.0132
35	D35		3.96	8.4023
36	E36		6.1	8.2147
37	D37		1.98	8.7033
38	D38		5.6	8.2518
39	D39		3.3	8.4815
40	D40		20.6	7.6861
41	D41		6.6	8.1805

Continued Table 1

S/N	Compound	Structures	IC_{50} (nM)	pIC_{50}
42	D42		61	7.2147
43	D43		80.8	7.0926
44	D44		9.5	8.0223

2.2 Geometric optimization

The compounds structures shown in Table 1 were drawn and optimized with chemdraw version 12.0.2 software (Li et al., 2004) and Spartan 14 Version 1.1.4 software (using B3LYP functional and 6-31G basis set) (Becke, 1993) respectively.

2.3 Molecular descriptors calculation

1875 molecular descriptors of the optimized molecules of 4-amidinoquinoline and 10-amidinobenzonaphthyridine derivatives were computed with PaDEL-Descriptor software version 2.20 (Yap, 2011).

2.4 Normalization and data pretreatment

Using Eq. 1, the descriptors obtained were normalized so that each variable will have equal opportunity in influencing construction of a good model (Singh, 2013).

$$X = \frac{X_i - X_{min}}{X_{max} - X_{min}} \quad (1)$$

where X is the normalized descriptors, X_i is the descriptor's value for each molecule, X_{min} and X_{max} are minimum and maximum value for each descriptor. In order to eliminate redundancy in the normalized data, it was then pretreated using Data Pretreatment software gotten from Drug Theoretical and Cheminformatics Laboratory (DTC Lab).

2.5 Data Division

Kennard and Stone's algorithm (Kennard and Stone, 1969) was employed to divide the pretreated data into training set (70%) with which the model was generated and test set (30%) with which the model externally validated. This was achieved using Data Division software gotten from DTC Lab.

2.6 Model Generation

Using Genetic Function Algorithm (GFA) technique in Material Studio software, regression analysis was carried out to build the model (using training set), where the dependent variable is the activities in pIC_{50} and the independent variable is the descriptors.

2.7 Internal validation of the model generated

The model generated was assessed using Friedman formula (Friedman, 1991) defined as;

$$LOF = \frac{SEE}{(1 - \frac{c+dp}{M})^2} \quad (2)$$

where LOF, SEE, c, d, p and M are the Friedman's Lack of fit (a measure of fitness of a model), standard error of estimation, the number of terms in the model, user-defined smoothing parameter, total number of descriptors in the model and the number of compound in the training set respectively.

SEE is defined as;

$$SEE = \sqrt{\frac{(Y_{exp} - Y_{prd})^2}{N-P-1}} \quad (3)$$

which is the same as the standard deviation of the model whose value if low a model is said to be good.

Correlation coefficient, R^2 of a built model is another parameter considered, and the model is good if its value is close to 1.0. It is defind as;

$$R^2 = 1 - \sqrt{\frac{\Sigma(Y_{exp} - Y_{prd})^2}{\Sigma(Y_{exp} - Y_{mtrn})^2}} \quad (4)$$

where Y_{prd}, Y_{exp} and Y_{mtrn} are the predicted, experimental and mean experimental activities in the training set, respectively. The value of R^2 is varies directly to the number of descriptors hence; the model stability is not reliable on it. Thus, to have a model that is reliable and stable, R^2 is adjusted according to the expression:

$$R^2_{adj} = \frac{(n-1)(R^2-p)}{n-p-1} \quad (5)$$

where p is the number of descriptors in the model and n number of compounds used in training set.

The cross-validation coefficient, Q^2_{cv} expressed as:

$$Q^2_{cv} = 1 - \frac{\Sigma(Y_{prd} - Y_{exp})^2}{\Sigma(Y_{exp} - Y_{mtrn})^2} \quad (6)$$

where Y_{prd}, Y_{exp} and Y_{mtrn} are respectively the predicted, experimental and average experimental activity in the training set.

2.8 External Validation of the model generated

The generated model was assessed (using test set) for external validation by the value of R^2_{test} expressed as;

$$R^2_{test} = 1 - \frac{\Sigma(Y_{prd} - Y_{exp})^2}{(Y_{exp} - Y_{mtrn})^2} \quad (7)$$

where Y_{prd} and Y_{exp} are respectively the predicted and experimental activities of the test set and Y_{mtrn} the mean training set experimental activity. The nearer the value is to 1, the better the model built (Tropsha et al., 2003).

2.9 Y-Randomization test

Random Multi-Linear regression models are generated (using training set) in Y-randomization test whose R^2 and Q^2 values have to be low for the QSAR model to be robust (Tropsha et al., 2003). Coefficient of determination cR^2_p, whose value has to be higher than 0.5 for the model to pass the test is also calculated in the Y-randomization test and is expressed as;

$$cR^2_p = R\ x\ (R^2 - R^2_r)^2 \quad (8)$$

where R is the correlation coefficient for Y-randomization and R^2_r is the average 'R' of the random models.

2.10 Applicability domain of the generated model

Leverage (h_i) method was used in describing the applicability domain of the built models (Veerasamy et al., 2011) and for a chemical compound is expressed as;

$$h_i = X_i(X^TX)^{-1}X_I^T \quad (9)$$

where X_i is matrix of training compounds i. X is the n x k descriptor matrix of the training set compound and X^T is the X transpose matrix used to generate the model. The warning leverage, h^* is the maximum value for X and is expressed as;

$$h^* = \frac{3(p+1)}{n} \quad (10)$$

2.11 Quality assurance of the generated model

Internal and external validations parameters presented in Table 2 give the minimum required values for a QSAR model to be predictable and reliable (Veerasamy et al., 2011).

Table 2 - The minimum required values for a QSAR model to be generally acceptable.

Symbol	Name	Value
R^2	Coefficient of determination	≥0.6
$P_{(95\%)}$	Confidence interval at 95% confidence level	<0.05
Q^2_{cv}	Cross validation coefficient	<0.5
R^2 - Q^2_{cv}	Difference between R^2 and Q^2_{cv}	≤0.3
$N_{ext.\ test\ set}$	Minimum number of external test set	≥5
cR^2_p	Coefficient of determination for Y-randomization	>0.5

3. RESULTS AND DISCUSSION

QSAR models ware built with genetic function algorithm (GFA) of material studio software to study how the chemical structure of 4-amidinoquinoline and 10-amidinobenzonaphthyridine correlate with their biological activities as potent antimalaria. Four QSAR models ware generated out of which one model was selected for its statistical significance and reported herein as follow:

pIC_{50} = 14.810925996 * **AATSC1s**
+ 6.681327289 * **GATS6c**
- 9.114874822 * **GATS6e**
+ 0.123280114 * **C2SP2**
- 0.143459063 * **TDB10s**
- 0.175971323 * **RDF30v**
+ 10.613625719

Validation parameters of the model are presented in Table 3 which is in agreement with the minimum required values presented in Table 2.

Table 3 - Validation parameters for the selected model

S/N	Parameter	Value
1	Friedman LOF	0.20237800
2	R^2_{train}	0.92883400
3	Adjusted *R*-squared	0.91026900
4	Cross-validated *R*-squared (Q^2_{cv})	0.89242000
5	Significant regression	Yes
6	Significance-of-regression *F*-value	50.03138900
7	Critical SOR *F*-value (95%)	2.53977400
8	Replicate points	1
9	Experimental error computed	0.38471400
10	Lack-of-fit points	22
11	Minimum experimental. error for nonsignificant LOF (95%)	0.00000000
12	R^2_{test}	0.818799

The model comprises of Autocorrelation (**AATSC1s, GATS6c** and **GATS6e**), Topological (**C2SP2 and TDB10s**) and Radial Distribution Function (**RDF30v**) descriptors. AATSC1s is a 2D Centered Moreau-Broto autocorrelation of lag 1/ weighted by intrinsic state descriptor based on spatial dependent autocorrelation function measuring the relationship strenght between atomic or molecular properties and space separating them (lag). GATS6c and GATS6e are 2D Geary autocorrelation of lag - 6/ weighted by gasteiger charge and by atomic Sanderson electronegativities respectively. In these descriptors, the Geary coefficients are any physico-chemical property calculated for each atom of the molecule, which in the case of GATS6c and GATS6e are gasteiger charge and atomic Sanderson electronegativities respectively. C2SP2 is 2D carbon type topological descriptors based on Sp^2 Carbon bound to 2 other Carbons. TDB10s is 3D topological distance-based autocorrelation – lag 10/ weighted by 1-state and RDF30v is 3D Radial distribution function – 030/ weighted by van der Waals volumes.

Table 4 shows the experimental and predicted activities and residual values of 4-amidinoquinoline and 10-amidinobenzonaphthyridine derivatives as potent *Plasmodium falciparum* inhibitors. The low residual values of experimental and predicted activity of the compounds indicate high predictability of the model built.

Table 4 - Experimental and Predicted activities for the compounds with residual.

Compounds	Experimental activity (pIC_{50})	Predicted activity (pIC_{50})	Residual
A1[a]	6.528708	6.779761	0.251053
A2	6.645892	6.730196	-0.0843
A3	7.007446	7.098008	-0.09056
A4	6.341989	6.496949	-0.15496
A5	7.443697	6.922351	0.521346
A6	6.899629	6.922351	-0.02272
A7	6.530178	6.53576	-0.00558
A8	6.560667	6.489362	0.071306
A9[a]	6.779892	6.642563	-0.13733
A10	6.701147	6.909541	-0.20839
A11	6.209715	6.134458	0.075257
A12	6.714443	6.438233	0.27621
A13	7.040959	7.211756	-0.1708
A14[a]	7.730487	7.219964	-0.51052
A15[a]	7.013228	7.420503	0.407275
A16	7.376751	7.21833	0.15842
A17	6.595166	6.692652	-0.09749
A18	7.231362	7.090104	0.141258
A19	8.036212	8.016864	0.019348
A20[a]	8.142668	7.944233	-0.19843
A21	7.8041	7.867564	-0.06346
A22	8.537602	8.483321	0.054281
A23	6.692504	6.992115	-0.29961
B24	6.917215	6.903046	0.014169
A25[a]	7.114639	6.981649	-0.13299
A26	6.917215	7.128248	-0.21103
A27[a]	7.79588	7.220324	-0.57556
A28	6.416801	6.692684	-0.27588
C29	5.407046	5.296375	0.110671
D30	7	6.936253	0.063747
D31	7.387216	7.455029	-0.06781
D32[a]	7.603801	7.731471	0.127671
D33[a]	8.055517	7.915156	-0.14036
D34	8.013228	7.870129	0.1431
D35[a]	8.402305	8.091832	-0.31047
E36[a]	8.21467	7.718828	-0.49584
D37[a]	8.703335	7.892822	-0.81051
D38[a]	8.251812	8.182895	-0.06892
D39	8.481486	8.445233	0.036254
D40	7.686133	7.755245	-0.06911

D41[a]	8.180456	8.591661	0.411205
D42	7.21467	7.138944	0.075726
D43	7.092589	7.379998	-0.28741
D44	8.022276	7.674236	0.34804

[a]Test set

Table 5 presents the Pearson's correlation matrix, Variance Inflation Factor and Mean Effect of the six descriptors in the model. The correlation matrix shows no important inter-correlation among the descriptors in the built model except for GATS6c and GATS6e. The correlation between GATS6c and GATS6e is indicated by the values of Variance Inflation Factor of the two descriptors which are greater than 4 but less than 10. Hence the descriptors in the built model were good enough. The positive sign of the mean effect values of the descriptors GATS6e, TDB10s and RDF30v indicates that increase in these descriptors increase the activities of the molecules while the magnitudes indicate the extent of their respective influences. The negative sign of the mean effect values of the descriptors AATSC1s, GATS6c and C2SP2 indicates that increase in these descriptors decrease the activities of the molecules while the magnitudes indicate the extent of their respective influences.

Table 5 - Pearson's correlation, Variance Inflation Factor (VIF) and Mean Effect (ME) of descriptors used in the model.

	Inter-correlation							
Descriptor	AATSC1s	GATS6c	GATS6e	C2SP2	TDB10s	RDF30v	VIF	ME
AATSC1s	1						1.3484	-0.0209
GATS6c	-0.01086	1					9.5210	-1.6362
GATS6e	0.221962	0.87143	1				7.6607	1.9844
C2SP2	-0.14295	0.498492	0.245009	1			2.5457	-0.3366
TDB10s	0.252823	-0.11211	-0.01111	0.152104	1		1.6508	0.7158
RDF30v	0.031	0.145263	0.152462	0.302408	-0.30734	1	1.5174	0.2935

Y- Randomization result shown in table 6 confirms that the QSAR model built is reliable, robust and stable for the low R^2 and several trials Q^2 values. The result also shows that the model is good and not gotten by chance for the value of cR^2p (>0.5).

Table 6 - *Y*- Randomization test result.

Model	R	R^2	Q^2
Original	0.96376	0.928834	0.89242
Random 1	0.303553	0.092144	-0.43608
Random 2	0.434119	0.18846	-0.65337
Random 3	0.42922	0.18423	-0.33598
Random 4	0.294643	0.086814	-0.66419
Random 5	0.462415	0.213827	-0.50357
Random 6	0.48295	0.233241	-0.47657
Random 7	0.487534	0.237689	-0.26116
Random 8	0.405283	0.164254	-0.51102
Random 9	0.412277	0.169972	-0.31391
Random 10	0.624219	0.389649	0.040793
Random Models Parameters			
Average r :	0.433621		
Average r^2 :	0.196028		
Average Q^2 :	-0.41151		
cRp^2 :	0.82951		

Fig. 1 present the Plot of predicted activity against experimental activity of both training and test set. Linearity of this plot indicates the high predictive power of the built model. Plot of standardized residual against experimental activity presented in Fig. 2 shows the dispersal of standardized residual values on both sides of zero, hence there was no systematic error in the generated model (Jalali et al., 2004).

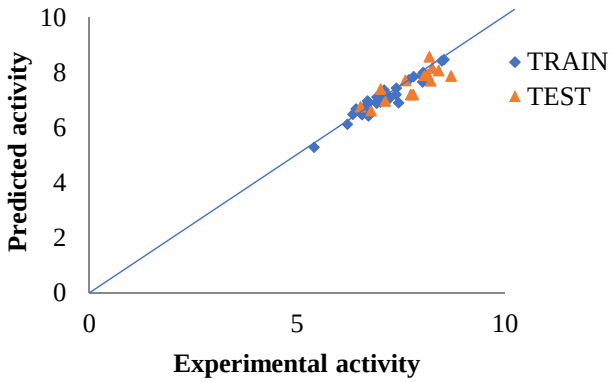


Fig. 1 - Plot of predicted activity against experimental activity of both training and test set.

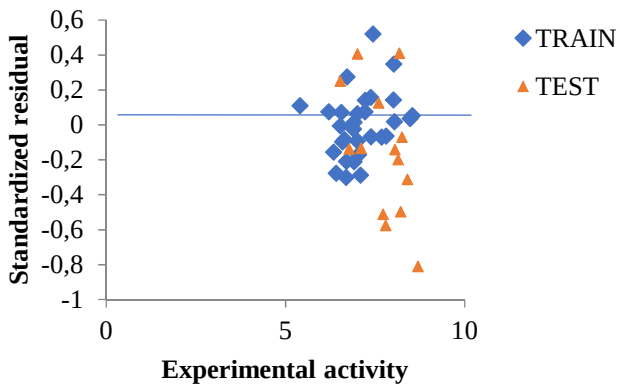


Fig. 2 - Plot of Standardized residual activity against experimental activity.

Fig. 3 shows the Williams plot of the standardized residuals against the leverages. It is clear that all compounds are within the applicability domain except for two influential compounds (i.e., compounds A1 and A14) whose leverage values are greater than the warning leverage ($h* = 0.70$). This may be due to their molecular structure as it differs from that of others.

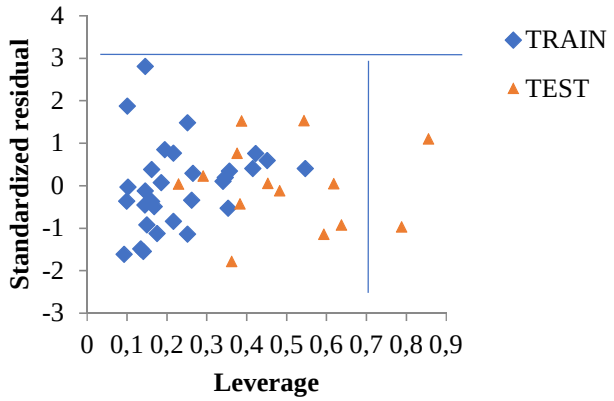


Fig. 5 - Plot of the standardized residuals against the leverages (Williams plot).

4. CONCLUSION

QSAR study of 44 compounds of 4-amidinoquinoline and 10-amidinobenzonaphthyridine derivatives as potent antimalaria was performed by employing Genetic Function Approximation (GFA) technique in Material Studio software to generate four models. The best model out the four models generated has internal and external R^2 values of 0.92883400 and 0.818799 respectively was found to be influence by AATSC1s, GATS6c, GATS6e, C2SP2, TDB10s and RDF30v descriptors. GATS6e, TDB10s and RDF30v were found to affect the model positively while AATSC1s, GATS6c and C2SP2 negatively. The model was validated to be stable, reliable and robust and can be employed in designing new 4-amidinoquinoline and 10-amidinobenzonaphthyridine derivatives with better potency to inhibit *Plasmodium falciparum.*

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