



QSAR STUDY FOR ANTIMALARIAL ACTIVITY OF 4-AMINOQUINOLINES DERIVATIVES

Balendra Singh^{*1}, Shailja Sachan² and Bhupendra Kumar Verma³

¹Department of Chemistry, A.P.S. University, Rewa (M.P.) INDIA PIN. 486003.

^{2,3}Department of Chemistry, Govt. M.S. Golwalkar, College, Rewa (M.P.) INDIA PIN. 486001.

***Corresponding Author: Balendra Singh**

Department of Chemistry, A.P.S. University, Rewa (M.P.) INDIA PIN. 486003.

Article Received on 14/08/2019

Article Revised on 03/09/2019

Article Accepted on 24/09/2019

ABSTRACT

This study describes QSAR analysis of quinolines derivatives as antimalarial activity. The models are generated by using NCSS and E-Dragon Software. Best model represents a significant value of correlation coefficient (r^2), Adjusted R^2 and F-ratio as 0.8722, 0.8382 and 25.604 respectively. The activity contribution of these compounds to analyze the predictive ability of QSAR model where described. Generated model from 20 molecules revealed an increased combinational 2d autocorrelation between topological descriptors and antimalarial activity.

KEYWORDS: QSAR, Hansch approach, antimalarial activity.

1. INTRODUCTION

Malaria is the one of the most widespread diseases in the world. With approximately 243 million cases and 863,000 attributed death reported globally in 2009.^[1] Its control is globally a high priority task. Primarily effecting the world most disadvantaged populations. Chloroquine (CO), a low cost drug is widely used for antimalarial agents. A part from artemisinin derivatives resistance to all antimalarial has been recorded.^[2-3]

Quinoline is a hetrocyclic aromatic organic compound. It is colourless hygroscopic liquid with astrong orders. In 1934 the drug chloroquine was synthesized for the first time (cook & zumla, 2009). Which become first in class of the quinine based drugs termed the 4-aminoquinoline is based on the natural crystalline alkaloid quinine found in cinchona bark.

The objective of this study was first to develop QSAR models and to explain the antimalarial activity of 4-aminoquinoline derivative structurally related to CQ against p. falciparum various clones (3D7,W2) in vitro using theoretical molecular descriptor. The second aim was to establish regression models to predict the blood to plasma concentration ratio (Rb) using mainly in silico molecular descriptors. Some recent QSAR models and reviews are reported an antimalarial compound.^[4-11]

The quantitative structure- activity relationship (QSAR) approach help to correlate the specific biological activities or physical properties of a series of compounds with measured or computed molecular properties of the compound in terms of descriptors (Hansch et al.2001). A

wide variety of descriptors such as steric, electronic and distance based topological descriptors have been reported for use in QSAR analysis.^[12-18]

The aim of present work is to derive some statically significant QSAR models for Antimalarial activity of 4-aminoquinolines Drugs using genetic – MLR. The result obtained may contribute to further designing novel antimalarial agents.

2. MATERIAL AND METHOD

The QSAR model for the estimation of the log IC_{50} of various antimalarial drugs is established in the following steps the molecular structure input and generated of the files containing the chemical structures is stored in the computer readable formate quantum machanics geometry is optimized with an ab initio method structural descriptors are computed structural descriptors are selected and the structure log IC_{50} model is generated by the MLR and statistical analysis. The antimalarial activity of 4-aminoquinolines derivatives.

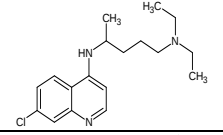
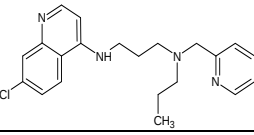
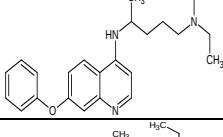
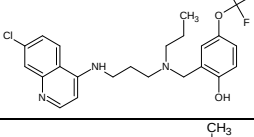
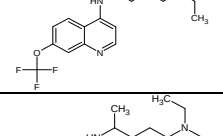
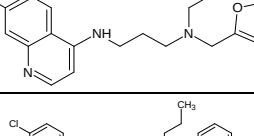
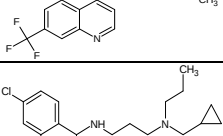
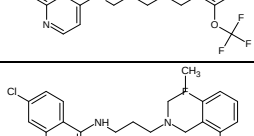
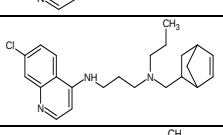
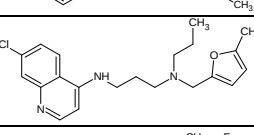
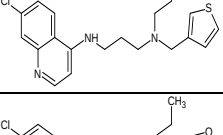
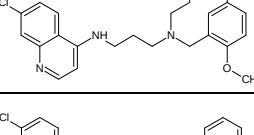
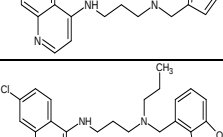
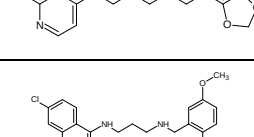
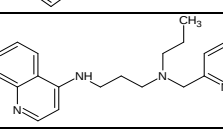
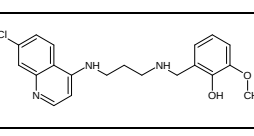
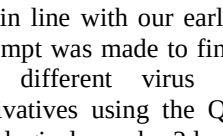
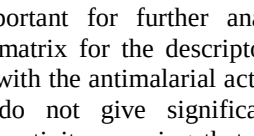
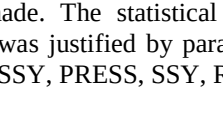
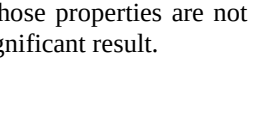
All of the molecules were drawn in to the E-Dragon software. The E-Dragon software package was used for calculating the molecular descriptors. Some of the descriptors are obtained directly from the chemical structure, e.g. constitutional, 2d autocorrelation, geometrical and topological descriptors. Other chemical and physical properties were determined by the chemical structure (lipophilicity, hydrophilicity, electronic descriptors). One way to avoid data redundancy is to exclude descriptors that are highly inter-correlated with each other before performing statistical analysis.

3. RESULT AND DISCUSSION

In the earlier times QSAR study of 4-aminoquinolines was mostly based on the Hansch approach. QSAR study for 4-aminoquinolines derivatives using 2d autocorrelation properties such as ATS4m, ATS5m, ATS6m, ATS4e, ATS4i, ATS5i and topological properties such as MAXDN, psi-i-1, psi-e-0, LOC have been reported on the literature. In view of this and in

line with our earlier work in the present study an attempt was made to find the structural for inhibition of different virus strain by 4-aminoquinolines derivatives using the QSAR approach with several topological and 2d autocorrelation descriptors, were made. The statistical quality of the regression equation was justified by parameters such as R^2 , F-Ratio, PRESS/SSY, PRESS, SSY, R^2_{cv} and S press.

Table 1: Structures 4- aminoquinolines derivatives with Antimalarial Activity.

Com.No.	Compound structure	log1/ IC ₅₀	Com.No.	Compound structure	log1/ IC ₅₀
1		-1.23	11		-1.70
2		-2.06	12		-0.78
3		-1.79	13		-0.87
4		-1.71	14		-1.85
5		-1.16	15		-0.91
6		-1.32	16		-1.11
7		-1.70	17		-0.70
8		-1.65	18		-0.40
9		-0.30	19		-1.11
10		-1.80	20		-0.67

In view of this and in line with our earlier work in the present study an attempt was made to find the structural for inhibition of different virus strain by 4-aminoquinolines derivatives using the QSAR approach with several topological and 2d autocorrelation descriptors, were made. The statistical quality of the regression equation was justified by parameters such as R^2 , F-Ratio, PRESS/SSY, PRESS, SSY, R^2_{cv} and S press.

It was important for further analysis to develop a correlation matrix for the descriptors utilized and their correlation with the antimalarial activities; but all chosen descriptor do not give significant correlation with antimalarial activity meaning that in mono – parametric regression those properties are not appropriate to obtain statically significant result.

Table 2: Calculated, Topological Descriptors of 4-Aminoquinolines Derivatives.

Com. No	ATS4m	ATS5m	ATS6m	ATS4e	MAX DN	ATS 4i	ATS 5i	Psi-i-1	Psi-e-0	LOC
1	3.514	3.359	3.304	3.397	1.956	3.426	3.252	10.082	7.855	2.181
2	3.674	3.603	3.585	3.672	1.982	3.691	3.618	13.108	10.027	1.819
3	3.727	3.616	3.584	3.707	6.16	3.742	3.625	11.541	10.051	2.217
4	3.66	3.559	3.481	3.638	5.892	3.681	3.588	11.341	9.537	2.161
5	3.573	3.392	3.267	3.463	1.39	3.492	3.287	11.15	8.235	0.896
6	3.692	3.608	3.533	3.594	1.397	3.63	3.528	13.71	9.708	0.806
7	3.686	3.613	3.514	3.536	1.395	3.564	3.421	12.085	8.964	0.849
8	3.646	3.538	3.43	3.544	1.404	3.575	3.44	11.827	8.934	0.849
9	3.861	3.696	3.678	3.778	1.414	3.798	3.619	14.255	10.406	0.769
10	3.671	3.562	3.483	3.571	1.405	3.611	3.485	12.273	9.295	0.827
11	3.868	3.717	3.656	3.786	2.37	3.803	3.638	13.696	10.418	0.995
12	4.025	3.959	3.903	3.941	6.266	3.968	3.887	14.864	12.418	1.109
13	3.727	3.633	3.605	3.588	1.645	3.611	3.486	12.361	9.309	0.902
14	3.995	3.988	3.854	3.908	6.217	3.941	3.926	14.391	11.947	1.095
15	3.919	3.795	3.69	3.832	2.572	3.863	3.723	13.677	10.436	0.995
16	3.679	3.571	3.493	3.58	1.867	3.607	3.48	12.325	9.31	0.902
17	3.871	3.777	3.729	3.784	2.533	3.813	3.704	13.657	10.42	0.995
18	3.701	3.427	3.322	3.604	1.392	3.627	3.326	12.96	9.341	0.362
19	3.676	3.508	3.375	3.576	2.218	3.6	3.401	12.382	9.337	0.721
20	3.709	3.454	3.328	3.613	2.308	3.633	3.351	12.402	9.346	0.721

It was important for further analysis to develop a correlation matrix for the descriptors utilized and their correlation with the antimalarial activities; but all chosen descriptor do not give significant correlation with antimalarial activity meaning that in mono – prametric regression those properties are not appropriate to obtain statically significant result.

All topological and 2d autocorrelation descriptor (table 2) are selected as independent variables MIC as independent values and the stepwise multiple linear regression (MLR) resulting in the following given below equation. Among the several modes generated best are selected for the discussion. The selection based on the previously mentioned statistical parameters.

We correlated the activity of 4-amioquinoline derivatives with various physiochemical, electronic and steric parameters. After many trial equation-1 was found to be promising.

$$\log 1/IC_{50} = -10.3326 + 6.9695 \cdot ATS4m - 4.7892 \cdot ATS5i - \text{-----}1$$

$$n = 20 \quad R^2 = 0.6856, \quad R^2A = 0.6487, \quad F\text{-Ratio} = 18.539$$

The development of QSAR model eq-1 show the importance of 2d autocorrelation ATS5i has negative coefficient. It represents that when the value of ATS5i increases the antimalarial activity decreases. The correlation coefficient between the 2d autocorrelation descriptors and antimalarial activity ($r = 0.8280$), which is low and indicates that the model is not significant and we need triparametric model.

$$\log 1/IC_{50} = -11.0227 + 4.1399 \cdot ATS6m + 8.8998 \cdot ATS4i - 10.6270 \cdot ATS5i - \text{-----}2$$

$$n = 20 \quad R^2 = 0.7728, \quad R^2A = 0.7302, \quad F\text{-Ratio} = 18.145$$

The QSAR model eq-2 stated with the addition of 2d autocorrelation parameters ATS5i negatives coefficient but ATS6M and ATS4i parameter are positive coefficient. The Positive value descriptors increase the antimalarial activity. The correlation coefficient between the 2d autocorrelation and antimalarial activity is ($r = 0.8791$), which is good but not best.

$$\log 1/IC_{50} = -11.2087 + 15.5584 \cdot ATS4 - 12.2784 \cdot ATS5m + 5.1444 \cdot ATS6m - 6.0211 \cdot MAXDN - \text{-----}3$$

$$n = 20 \quad R^2 = 0.8722, \quad R^2A = 0.8382, \quad F\text{-Ratio} = 25.604$$

The model eq-4 is statistically significant model and demonstrates the importance of different combination of 2d autocorrelation and topological descriptors. in mode eq-3topological descriptor MAXDN is negatively correlated while ATS4m and ATS6m are positive correlated with antimalarial activity. The correlation coefficient between the descriptors and antimalarial activity is ($r = 0.9339$). The correlation coefficient were found to be good in eq-3, with maximum F-Ratio value.

Table 3: Cross validation statistical parameters.

Modal	n	PRESS	SSY	PRESS/SSY	R^2_{CV}	R^2_{adj}	S_{press}
1	20	2.2781	5.2146	0.4368	0.5631	0.6487	0.3375
2	20	1.8032	5.2147	0.3458	0.6542	0.7302	0.3003
3	20	1.0876	5.2148	0.2085	0.7914	0.8382	0.2332

We have undertaken a cross –validation methodology for deciding the predictive power of proposed model (eq-1 to eq-3). This was needed because a model with good statistics may not have good predictive potential. The various cross –validation parameters calculate for the proposed models are present in Table-3 and are discussed below PRESS appears to be an important cross validation parameter accounting for good estimate of the real predictive error of the model . When its value is less than SSY, the model predicts better than by change alone and can be considered statically significant and are better than chance. For QSAR model to be considered reasonable, PRESS/SSY should be smaller than 0.4 and the data present in Table-4 indicate that model no.4 proposed are significant. Finally in order to conform our finding antimalarial activity was compared with the

corresponding values reported in table -2. These comparisons are shown in Table-4. The values agree well within experimental error. The residual is the difference between observed and calculated antimalarial activity.

The real usefulness of QSAR model s is not just their ability reproduce known data verified by their fitting power (R^2), but is mainly their potential for predictive applications. for this reason the model calculations were performed by maximizing the explained variance in prediction verified by the leaves-one out cross – the possibility of overestimating the model predictive by using R^2 procedure as is strongly recommended for QSAR modelling. This indicates that the obtained regression model has a good internal and external predictive power.

Table 4: Antimalarial screening summary.

Com.	Actual	Predicted	Residual	Com.	Actual	Predicted	Residual
1	-1.23	-1.236	0.006	11	-0.7	-0.655	-0.045
2	-2.06	-1.953	-0.107	12	-0.78	-0.847	0.067
3	-1.79	-1.504	-0.286	13	-0.87	-0.888	0.018
4	-1.71	-1.961	0.251	14	-1.85	-1.723	-0.127
5	-1.16	-1.311	0.151	15	-0.91	-0.922	0.012
6	-1.32	-1.532	0.212	16	-1.11	-1.402	0.292
7	-1.7	-1.435	-0.265	17	-0.7	-0.958	0.258
8	-1.65	-1.617	-0.033	18	-0.4	-0.315	-0.085
9	-0.3	-0.345	0.045	19	-1.11	-1.258	0.148
10	-1.8	-1.236	0.006	20	-0.67	-0.546	-0.124

To realize the effect of multicollinearity between the descriptors which affects the activity of model we proceed the ridge trace the graph which show that there is mild multicollinearity problem does not affect the variance of developed model.

4. CONCLUSION

This model was developed to predict the structural features of quinolines derivatives which Is required for the molecules. In view of the result and discussion above, we conclude that topological descriptor such as ATS4m, ATS5m, ATS6m and ATS4e can be successfully used for 4-aminoquinolines derivatives as antimalarial drugs. These results will help medical scientists in the designing and prediction of compounds which increased activity and thus the synthesis of new 4-aminoquinolines derivatives exhibiting belts activities than those reported in this result.

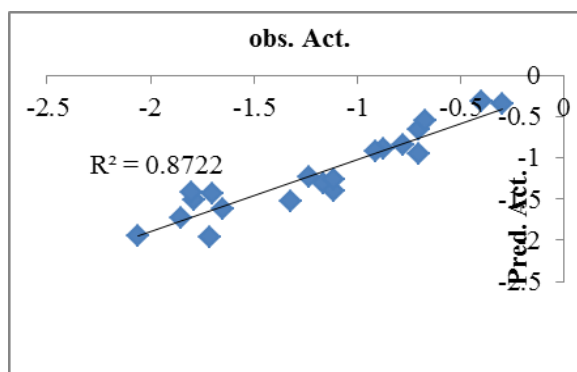


Fig -1 Plots of pred. v/s experimentally obs, activity of 4-aminoquinolines.

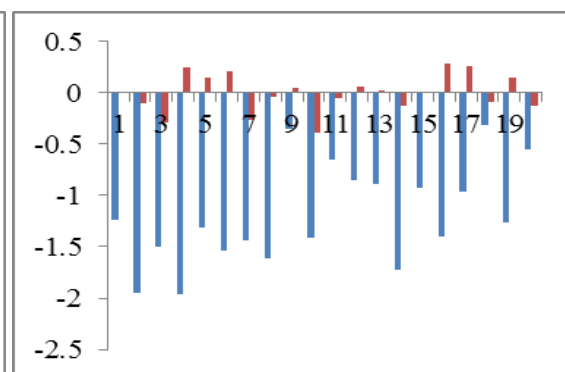


Fig-2 plots of residual value and Antimalarial Exp. observed activity of 4-aminoquinolines

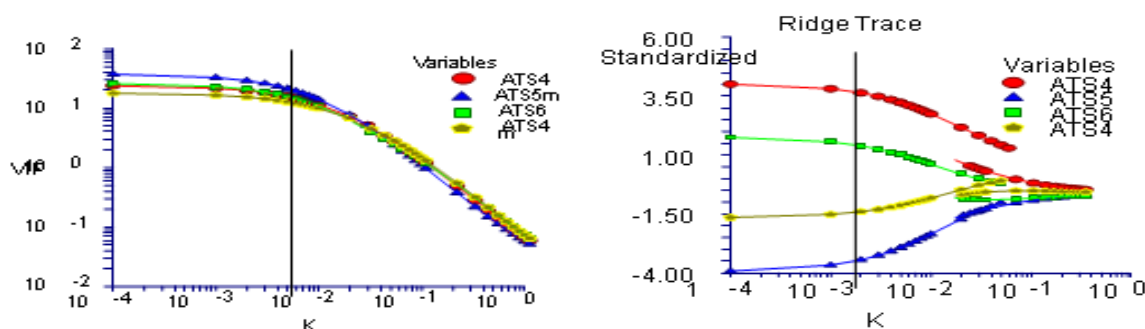


Fig. 3 plots between VIF and K.

5. REFERENCES

- World Health Organization, (world malaria report), 2009.
- White PJ, (Antimalarial drugs resistance). *jAntimicrob. Chemothe*, 1992; 30: S71-S78.
- White, N.J. and Olliro. (Rational for combination chemotherapy for malaria). *Parasitol*, 1996; 12: 399-401.
- Katritzky AR, Kulshyn OV, (Computational Design of Chemicals for the Control of Mosquitoes). *Bioorg. Med. Chem.*, 2006; 14: 2333-2357.
- Garcia-Domenech R, Lopez-Pina W, Sanchez-Perdomo, (Nuclear Receptors as Drug Targets) *Int.j of Pharma*, 2008; 363: 78-84.
- Ojha H, Gahlot P, Tiwari AK, Pathak M, (Piggyback' Approach for Antimalarial Drug Discovery). *Che Bio Drug Des.*, 2011; 77: 57-62.
- Ojha PK, Roy K, (Structural Bioinformatics: Applications in Preclinical Drug Discovery Process). *Eur J Med Chem*, 2010; 45: 4645-4656.
- Ojha PK, Roy K, (Chemometric modelling of antimalarial activity of aryltriazolylhydroxamates). *Mol. Simul*, 2010; 36: 939-952.
- Shah P, Siddiqi MI, (3D-QSAR studies on triclosan derivatives as Plasmodium falciparum enoyl acyl carrier reductase inhibitors). *Env Res*, 2010; 21: 527-545.
- Bask SC, Mills D, Hawkin DM, Bhattacharjee AK, (3D-QSAR studies on triclosan derivatives as Plasmodium falciparum enoyl acyl carrier reductase inhibitors) *Env. Res*, 2010; 21: 103-125.
- Roy K, Ojha P K, (Advances in quantitative structure-activity relationship models of antimalarials) *Expert Opinion on Drug Disc*, 2010; 5: 751-778.
- Consonni VJ, (Structure/Response Correlations and Similarity/Diversity Analysis by GETAWAY Descriptors). *Chem. Inf Comput Sci*, 2002; 42: 693.
- Krenkel GJ, (Theochem). *Mol Struct*, 2001; 542: 107.
- *Krenkel LB, (Molecular Connectivity in Structure-Activity Analysis, RSP-Wiley, Chetster UK, 1986.
- Ghasemi J, (Topological Modeling of Acetophenones as Antibacterial Agents: A QSAR/QSPR Approach). *Farahni Ann. Chim*, 2006; 96: 327.
- Ghasemi J, (Spectrophotometric Investigation of The Acidity Constants of Fluorescein in Various Water-Organic Solvent Media). *Ann Chim in press*, 2008; 1257-1268.
- Subramaniam R, (Topological Modeling of Acetophenones as Antibacterial Agents: A QSAR/QSPR Approach) *Der Pharmacia Sinica*, 2011; 2(3): 146-155.
- Sanmati, KJ, Sarthak R, (Topological Modeling of Acetophenones as Antibacterial Agents: A QSAR/QSPR Approach). *Der Pharmacia Sinica*, 2011; 2(3): 20-30.