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Predictive Comparative QSAR Modeling of 4–Pyridones as Potent Antimalarials

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Abstract

Motivation. Malaria is one of the most life threatening diseases in tropical developing world. Chloroquine resistance occurs due to mutation in protozoal genes. It has got significance to synthesize new drugs for targeting specific enzyme or bind with receptor or to disrupt the life cycle of *P. falciparum*. Principal component regression analysis (PCRA), stepwise regression, factor analysis multiple linear regression (FA–MLR), partial least squares (PLS) and factor analysis partial least squares (FA–PLS) techniques were applied on some 4–pyridones to find structurally significant quantitative structure–activity relationship (QSAR) models developed using different descriptors for further improved antimalarial activity.

Method. Comparative QSAR study was performed on some 4–pyridones by using PCRA, stepwise regression, FA–MLR, PLS and FA–PLS techniques to find structural requirements for further improved antimalarial activity.

Results. The QSAR study shows significances of electrotopological state atom index (ETSA) indices as well as frontier electron density at atom numbers 1 and 9, grid surface area and molecular volume. These may be beneficial for the potent antimalarial activity. It also reveals that at atom numbers 1 and 9 electrophilic attack may be favorable for higher antimalarial activity. Electrostatic potential at the atom number 1 may also play pivotal role in the antimalarial activity of 4–pyridones.

Conclusions. Electrophilic substitution as well as electronic interactions at atom 1 and 9 and increasing molecular volume and grid surface area of 4–pyridones may be beneficial for higher antimalarial activity.

Keywords. 4–Pyridones; potent antimalarials; k–MCA; PCRA; FA–MLR; FA–PLS.

Abbreviations and notations

ETSA, electrotopological state atom index	MLR, multiple linear regression
EP, electrostatic potential charges	PCRA, principal component regression analysis
FA, factor analysis	PLS, partial least squares
k–MCA, k–means cluster analysis	QSAR, quantitative structure–activity relationship

1 INTRODUCTION

Malaria is one of the oldest and widespread diseases having major health hazards in tropical developing world. It is causing death about 1.5 to 2.7 million per year [1]. *Plasmodium falciparum* resistant to chloroquine is the main reason for death in malaria. The *pfcrt* gene in the protozoa

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encodes the transporter protein resulting pores through which protonated chloroquine exits the lysosome. Chloroquine resistance is also due to a number of mutations in the *pfcrt* gene [2]. For chloroquine resistant strains of *P. falciparum*, sulfadoxine and pyrimethamine fixed combinations are used. For the resistance to other antimalarial drugs, atovaquone and proguanil fixed combinations are prescribed for prophylaxis and treatment of malaria. Gene mutation for cytochrome–b causes resistance to atovaquone. Hence, proguanil is used in combinations with atovaquone for less or no resistance as well as for synergistic activity. Proguanil is having greater affinity for plasmodial enzyme than the human counterpart. It blocks folate uptake by inhibiting the bacterial dihydrofolate reductase and by blocking the conversion of tetrahydrofolate from dihydrofolate [3]. Thus, it has got significance to synthesize new drugs for targeting specific enzyme or bind with receptor or to disrupt the life cycle of *P. falciparum*. 4–Pyridones showed improved activity against chloroquine–resistant strains as well as atovaquone–resistant *Plasmodium* sp. Hence, we tried to find the structural requirements of 4–pyridones having potent antimalarial activity by predictive comparative QSAR modelling as a part of our composite program of rational drug design, discovery and development [4–38]. For the development of QSAR models of 4–pyridones, in vitro antimalarial activity against *P. falciparum* T9–96 strains was collected [39]. To obtain linear relationship with independent variables, the inhibitory activity of 4–pyridones (IC_{50}) against *P. falciparum* T9–96 strain was converted to the negative logarithmic scale (pIC_{50}) for the development of QSAR equations. The general structure of 4–pyridones with arbitrary numbering is shown in Figure 1.

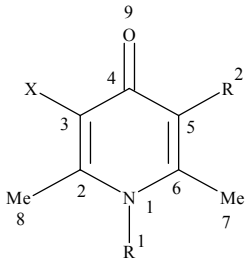


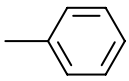
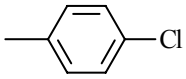
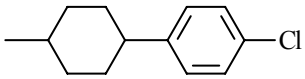
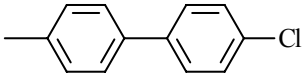
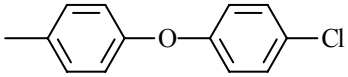
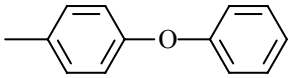
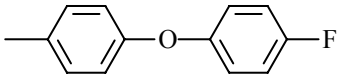
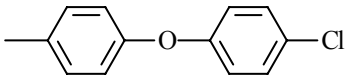
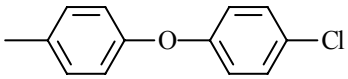
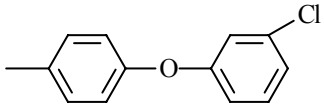
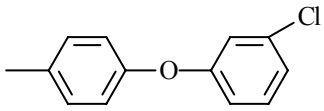
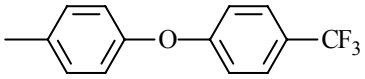
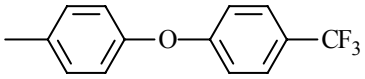
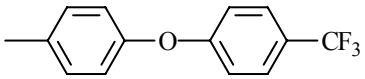
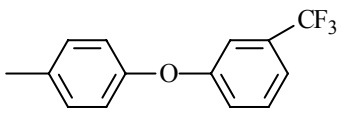
Figure 1. The general structure of 4–pyridones with arbitrary numbering.

2 MATERIALS AND METHODS

2.1 Biological activity data

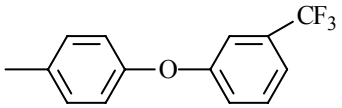
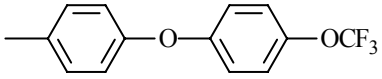
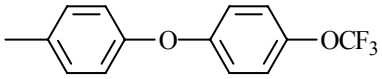
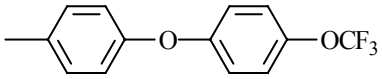
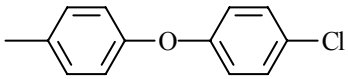
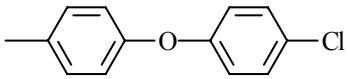
For the development of QSAR models of 4–pyridones, in vitro antimalarial activity in terms of IC_{50} (μM) against *P. falciparum* T9–96 strains were taken from the published work of Yeates *et al*. [39]. To obtain linear relationship with independent variables, the inhibitory activity of 4–pyridones against *P. falciparum* T9–96 strain (IC_{50}) was converted to the negative logarithmic scale (pIC_{50}). Structures and the biological activity data of 4–pyridones are shown in Table 1.

Table 1. Structures and Biological Activity Data of 4–Pyridone Derivatives [39]

Cpd[a]	R^1	R^2	X	IC_{50}(μM)	pIC_{50}
1	H	n-C_8H_{17}	Cl	4.00	5.40
2	H		Cl	11.00	4.96
3	H		Cl	2.50	5.60
4	H		Cl	0.05	7.30
5	H		Cl	0.40	6.40
6[b]	H		Cl	0.06	7.22
7	H		Br	0.15	6.82
8	H		Br	0.04	7.40
9	H		H	0.25	6.60
10[b]	H		Br	0.04	7.40
11	H		Cl	0.03	7.52
12[b]	H		Br	0.03	7.52
13	H		H	0.50	6.30
14	H		Cl	0.06	7.22
15	H		Br	0.03	7.52
16	H		Cl	0.03	7.52

[a] Compound number; [b] Compounds are designed for the test set

Table 1. (Continued)

Cpd[a]	R^1	R^2	X	IC_{50}(μM)	pIC_{50}
17	H		Br	0.03	7.52
18	H		H	0.16	6.80
19[b]	H		Cl	0.03	7.52
20[b]	H		Br	0.03	7.52
21	OH		Br	0.45	6.35
22	OH		H	2.20	5.66

2.2 Parameters and Dataset used

The negative logarithm of the inhibitory activity (pIC_{50}) of 4–pyridones against *P. falciparum* T9–96 strains was used as the dependent parameter to develop QSAR models. QSAR study was performed using topological descriptors like electrotopological state atom (ETSA) indices (*S*) [40–42] as well as quantum chemical descriptors like partition coefficient (*LogP*), molar refractivity (*MR*), grid surface area (*GSA*), polarizability (*Pol*), molar volume (*Vol*), atomic mass (*Mass*) and electronic descriptors like electronegative potential charges (*EP*) as well as frontier electron density related to highest occupied molecular orbital (*FEH*) and indicator parameters to consider quantitatively the effect of the structural variation on antimalarial activity of 4–pyridones.

2.2.1 Electrotopological state atom index (ETSA)

The electrotopological state atom index (ETSA) [40–42] is an atom based topological descriptor encoding electronic as well as topological environment of each skeletal atom on a molecule. ETSA comprises two components: (1) the intrinsic topological and electronic state (I_i) of an atom; (2) the effect of the environment (perturbation factor, ΔI_j) influencing the atom considering differences in the intrinsic topological states of different atoms and topological distance among these which determine the magnitude of interactions.

Electronic factors include the concept of polarity, charge and energy levels. Topological factors attribute the arrangement of atoms across the skeleton, concepts of steric relations and bulk as well as the relationships between various non–bonded parts of a molecule. The intrinsic value includes

both electronic and topological information. The count of π and lone pair of electrons give important electronic information. The important topological attribute is the relative location of the atoms within the molecule or the relative degree of mantle–atom or buried–atom nature. The intrinsic state value of an atom is expressed as:

$$I_i = [(2/N)^2\delta^v + 1] / \delta \quad (1)$$

where N stands for the principle quantum number of valence electrons, δ^v and δ indicate the count of valence electrons and sigma electrons associated with the atom i in the hydrogen–suppressed graph.

The perturbation effect (ΔI_j) stands for the influence of information field on the intrinsic atom value (I_i). It is the function of the difference in intrinsic values I_i (of an atom i) and I_j (of atom j) and expressed as:

$$\Delta I_j = f(I_i - I_j) \quad (2)$$

The influence of the atom j on the atom i decrease with the increase in the topological distance in the shortest path (graph separation) between atom i and j. To account for this, Eq. (2) is modified with a function r_{ij}^2 which is the square of graph separation, i.e., the count of skeletal atoms in the shortest path connecting the atoms i and j including both atoms. The general expression for the perturbation effect is as follows:

$$\Delta I_j = \sum(I_i - I_j) / r_{ij}^2 \quad (3)$$

Summation of the intrinsic state of an atom and the field is called electrotopological state (E–state) of the atom and expressed as:

$$S_i = I_i + \Delta Ij \quad (4)$$

In E–state, the bonded interactions depend on difference in electronegativity among the adjacent atoms and the non–bonded component may act through the inductive effect across the skeleton. The non–bonded component may act through the inductive effect across the skeleton. The non–bonded interaction is a function of the graph separation factor and the difference of electronegativity. Thus, E–state represents electronic distribution information modified by both local and global topology. The information encoded in the E–state value for an atom is the electronic accessibility at that atom. This index is used to determine the pharmacophore moieties of biologically active congeneric compounds.

2.2.2 Frontier electron density

Frontier electron theory [43] assumes that the least tightly bound electron would be the most reactive with an electrophilic reagent. The π–electrons in HOMO, thus, would be important in a reaction. The electrophilic reactivity is predicted to occur at a position in the molecule that has the highest electron density in HOMO.

2.3 Statistical Analysis

The statistical methods used to develop QSAR models are cluster analysis (CA) [44], correlation analysis [45], principle component regression analysis (PCRA) [46], factor analysis (FA) [47–50], multiple linear regression analysis (MLR) [45] as well as partial least square (PLS) [47] method. Leave–one–out (LOO) cross validation method [51] was applied to validate the QSAR models.

2.3.1 Validation of QSAR models

Leave–one–out (LOO) cross validation method [51] was applied to validate the QSAR models developed. The predictive powers of these equations were justified by this method. Predicted residual sum of square (*PRESS*), total sum of squares (*SSY*), cross–validated R^2 (R^2_{CV}), standard deviation error of prediction (*SDEP*) and standard error of *PRESS* (S_{PRESS}) were considered for validation of these models.

2.4 Computer Software used

Different quantum chemical as well as statistical software are used for QSAR analyses.

2.4.1 Software for calculating topological descriptors

Atom type E–state indices (ETSA) were calculated using the computer program ‘mouse’ [52] developed in our laboratory. In this program, molecular connection table in specified format as well as intrinsic values of different atoms are given as inputs and ETSA indices of atoms are obtained as outputs.

2.4.2 Quantum chemistry software

Different quantum chemical descriptors like molar refractivity (*MR*), partition coefficient (*LogP*), grid surface area (*GSA*), polarizability (*Pol*), molar volume (*Vol*), atomic mass (*Mass*) and electronic descriptors like free electron density related to the highest occupied molecular orbitals (*FEH*) were calculated by using Hyperchem release 7.0 Pro. Package [53]. With Hyperchem, the energy minimization of 3–D structures was done with the molecular mechanical (MM+) force field without cut off for non–bonded interactions, solvation and constrains. The energy minimized structures were subjected to geometrical optimization by semiempirical Austin Model 1 (AM1) method [54] using Polak–Rebiere algorithm with a RMS gradient of 0.1 kcal / Å mol

2.4.3 Software for calculating electronic descriptors

Electronic descriptor like electrostatic potential charge (EP) at each atom was calculated using the software Chem 3D Pro package [55]. Electrostatic potential charges were calculated with the AM1 method [54] whereas energy minimization of the compounds was done by RHF (Restricted Hartree–Fock: closed shell) wave function. 2D structures were drawn with Chem 3D Ultra and

converted to 3D structure with Chem 3D Pro. After energy minimizations of all compounds, electrostatic potential charges of common atoms (Figure 1) were calculated.

2.4.4 Software for statistical analyses

All the statistical analyses were done with developed in our laboratory software, 'Multi Regress' [56] and 'Least Square' [57].

3 RESULTS AND DISCUSSION

3.1 Cluster Analysis

For designing the test set and the training set, k–means cluster analysis (k–MCA) [44] was performed. k–MCA splits these compounds into 2 clusters containing 13 and 9 members each. From each cluster, 25% members are selected randomly for the test set. The test set is formed with five compounds (compound no. **6**, **10**, **12**, **19** and **20**) and the remaining seventeen compounds were treated as the training set. QSAR models were developed depending on the training set.

Table 2. Descriptors used to develop QSAR models

Cpd [a]	S_1 [b]	S_9 [b]	EP_1 [b]	GSA [b]	Vol [b]	FEH_1 [b]	FEH_9 [b]
1	3.177	12.025	–0.671	543.810	892.470	–1.219	–1.053
2	3.114	12.059	–0.664	415.360	673.320	–0.361	–0.129
3	3.096	12.111	–0.664	439.560	716.750	–0.109	–0.082
4	3.248	12.532	–0.638	614.790	1042.560	–0.528	–0.405
5	3.152	12.436	–0.655	548.220	923.80	–0.147	–0.083
6 [c]	3.130	12.423	–0.657	570.360	958.130	–0.131	–0.167
7	3.222	12.488	–0.697	554.000	932.40	–0.024	–0.055
8	3.192	12.485	–0.698	560.530	941.950	0.112	0.140
9	3.194	12.205	–0.587	550.540	922.550	–0.054	–0.134
10 [c]	3.215	12.508	–0.682	578.800	975.540	0.130	0.157
11	3.129	12.426	–0.671	568.330	958.260	0.038	0.054
12 [c]	3.214	12.511	–0.698	577.570	975.490	0.032	0.043
13	3.127	12.207	–0.594	567.080	958.650	0.028	0.019
14	3.063	12.424	–0.663	586.930	995.430	–0.183	–0.065
15	3.148	12.510	–0.691	594.740	1012.200	0.193	0.070
16	3.051	12.428	–0.659	585.510	994.550	–0.121	–0.048
17	3.136	12.513	–0.700	594.910	1011.480	–0.112	–0.046
18	3.131	12.225	–0.595	581.660	981.720	–0.104	–0.047
19 [c]	3.067	12.442	–0.660	600.650	1017.740	–0.186	–0.054
20 [c]	3.152	12.528	–0.689	607.370	1034.390	–0.243	–0.073
21	1.013	12.556	–0.475	597.000	1011.470	–0.052	–0.125
22	1.022	12.253	–0.422	572.200	958.320	0.139	–0.048

[a] Compound number; [b] As per text and subscripts are atom numbers as per Figure 1; [c] Compounds are designed for the test set.

3.2 Correlation Analysis

Correlation analysis [45] was carried out with the response variable and independent parameters of the training set. Intercorrelated independent parameters were not considered for multiple linear regression analysis and eliminated stepwise depending on their individual correlation with the

biological activity. The calculated values of selected independent parameters to develop QSAR models are listed in Table 2. The correlation matrix among the response variable and those selected descriptors are shown in Table 3.

Table 3. Correlation matrix of descriptors and the response variable

	pIC50	S_1	S_9	EP_1	*GSA*	*Vol*	FEH_1	FEH_9
pIC50	1.00	0.29	0.80	–0.36	0.72	0.75	0.40	0.43
S_1		1.00	–0.11	–0.88	–0.18	–0.17	–0.23	–0.07
S_9			1.00	–0.11	0.69	0.72	0.44	0.43
EP_1				1.00	0.18	0.17	0.20	0.03
GSA					1.00	1.00	0.16	0.06
Vol						1.00	0.20	0.10
FEH_1							1.00	0.96
FEH_9								1.00

3.3 Principal Component Regression Analysis (PCRA)

In PCRA [46], five factor scores with factor loading more than 0.70 were extracted by the principle component method and rotated by *VARIMAX* rotation. These factor scores were used as independent parameters for developing QSAR equations. As factor scores contain information for the different descriptors, the chance for loss of information is less. Using forward selection method the following equation was developed:

$$pIC_{50} = 6.806(\pm0.097) + 0.670(\pm0.091)\,f2 + 0.216(\pm0.089)\,f4 - 0.246(\pm0.090)\,f3$$
$$n = 17 \quad R = 0.909 \quad R^2 = 0.826 \quad R^2_A = 0.786 \quad F_{(3,13)} = 20.559 \quad p<0.00003 \quad SEE = 0.387 \quad (5)$$
$$PRESS = 2.782 \quad SSY = 11.199 \quad R^2_{cv} = 0.752 \quad SDEP = 0.405 \quad S_{PRESS} = 0.463$$

where '*n*' is the number of compounds in the training set. Eq. (5) explains 78.60% and predicts 75.20% variances of antimalarial activity. The 95% confidence intervals of regression coefficients are mentioned in the parentheses. Eq. (5) shows the importance of factors 2, 3 and 4. Factor 2 was highly loaded with S_9, *GSA*, *logP*, *Mass*, *Vol*, *MR* and *Pol*. It shows importance of these descriptors.

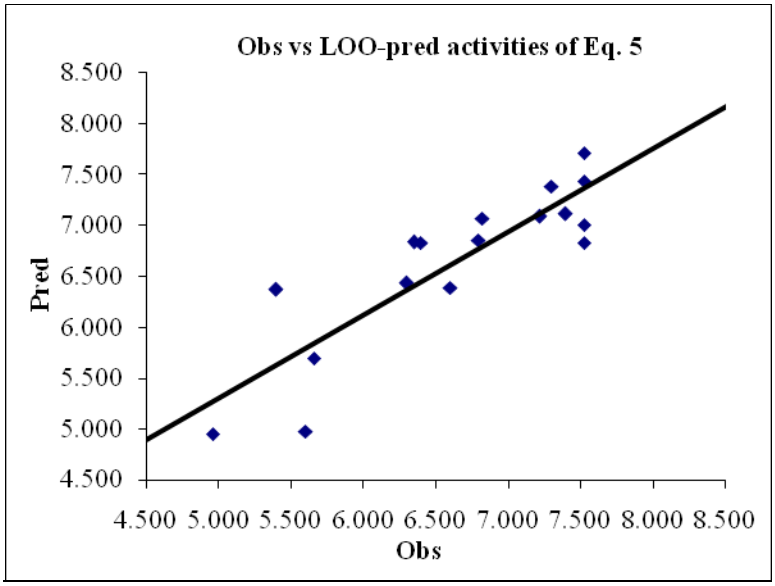


Figure 2. The Observed vs. Predicted values for Equation 5

Factor 3 shows importance of parameters like S_3, EP_2, EP_3, EP_4 and EP_9. Factor 4 was highly loaded with S_1, S_2, S_6, S_7, S_8 and EP_1. It shows importance of these descriptors. '*S*' terms along with numbers in the subscript denote the ETSA indices at that specified position (as per Figure 1). '*EP*' terms along with the subscript numbers similarly stand for the electrostatic potential charges of those corresponding atoms (Figure 1). The Observed (Obs) vs. LOO–predicted activities (Pred) of Eq. (5) are represented in Figure 2.

3.4 Stepwise Regression

In stepwise method, Eq. (6) was obtained with one quantum chemical descriptor and two electronic parameters. The statistical qualities of the MLR equations were justified by parameters like correlation coefficient (*R*), adjusted R^2 (R^2_A), variance ratio (*F*) at specified degrees of freedom, probability factor related to F–ratio (*p*) and standard error of estimate (*SEE*).

$$pIC_{50} = -2.912(\pm0.844) + 0.007(\pm0.000)\ Vol - 5.403(\pm0.800)\ EP_1 + 1.127(\pm0.232)\ FEH_9$$
$$n = 17 \quad R = 0.964 \quad R^2 = 0.930 \quad R^2_A = 0.913 \quad F_{(3,13)} = 57.216 \quad p<0.00000 \quad SEE = 0.246 \qquad (6)$$
$$PRESS = 1.490 \quad SSY = 11.199 \quad R^2_{cv} = 0.867 \quad SDEP = 0.296 \quad S_{PRESS} = 0.339$$

Eq. (6) explains 91.30% and predicts 86.70% of variances of biological activity. Eq. 6 shows the significance of molar volume (*Vol*) of these molecules, electrostatic potential charge at the atom number 1 (EP_1) and frontier electron density related to highest occupied molecular orbital at the atom number 9 (FEH_9).

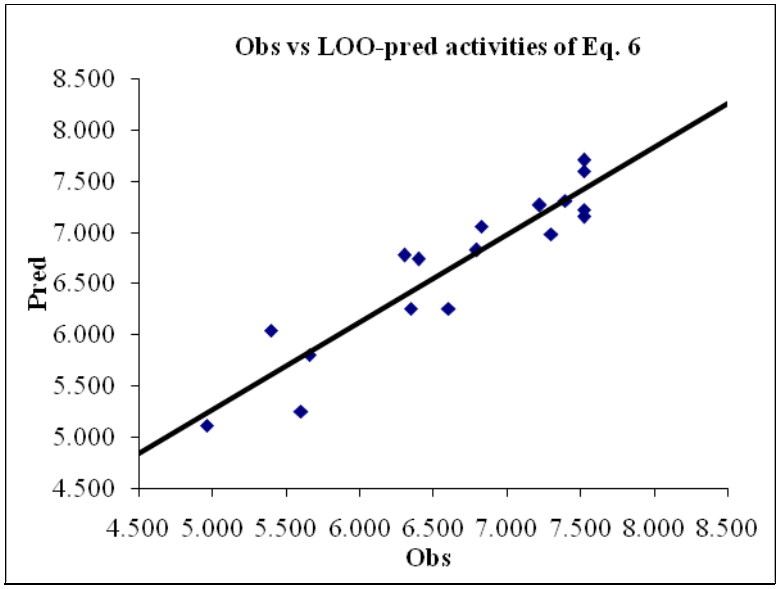


Figure 3. The Observed vs. LOO–predicted activities for Equation 6

The increase in the molar volume (*Vol*) suggests that with the increase of the value of this parameter antimalarial activity may be increased. The negative coefficient of EP_1 indicates that with the decrease in the electrostatic potential charge of the atom number 1 may be conductive to higher antimalarial activity of these compounds. Electrophilic attacks may likely to occur in those atoms

where the electrostatic potential charges are negative. Eq. (6) suggests that electrophilic substitutions may be favorable at N_1 (as shown in Figure 1) as well as the higher negative electrostatic potential at N_1 may be beneficial as far as the potent antimalarial activity is concerned. *EP* charge of N_1 may depend on the halogen substitution at position X (Figure 1). The positive coefficient of the frontier electron density related to highest occupied molecular orbital at the atom number 9 (FEH_9) may be indicative of the higher antimalarial activity with the increase of this parameter. Again, it may also explain that in O_9 (as shown in Figure 1) electrophilic substitution may be favorable regarding higher antimalarial activity. The Observed (Obs) vs. LOO–predicted activities (Pred) of Eq. 6 is graphically represented in Figure 3.

Table 4. Factor loadings of variables after *VARIMAX* rotation

Descriptors	Factor 1[a]	Factor 2[a]	Factor 3[a]	Factor 4[a]	Factor 5[a]	Communality[b]
pIC_{50}	–0.173	**0.851**	–0.229	–0.302	–0.174	0.929
S_1	0.105	–0.044	–0.032	**–0.915**	–0.247	0.912
S_2	0.038	–0.036	0.203	**–0.910**	0.254	0.936
S_3	–0.232	0.109	**0.859**	0.005	0.358	0.932
S_4	0.304	–0.118	0.256	–0.493	0.646	0.832
S_5	0.647	–0.245	0.076	–0.596	0.304	0.933
S_6	0.444	–0.257	0.023	**–0.851**	0.050	0.991
S_7	0.465	–0.250	0.002	**–0.810**	0.133	0.952
S_8	0.127	–0.071	0.124	**–0.906**	0.307	0.952
S_9	–0.234	**0.759**	–0.492	–0.013	0.005	0.872
EP_1	–0.059	0.034	0.483	**0.775**	0.240	0.896
EP_2	–0.029	0.054	**–0.987**	0.078	0.016	0.985
EP_3	0.012	–0.083	**0.986**	–0.079	–0.023	0.986
EP_4	–0.182	0.079	**–0.939**	0.229	0.019	0.974
EP_5	**0.787**	0.083	0.102	–0.570	–0.033	0.962
EP_6	**–0.701**	–0.043	–0.466	0.489	–0.005	0.951
EP_7	0.516	0.187	0.339	–0.240	0.122	0.489
EP_8	0.095	0.152	0.278	0.306	0.268	0.274
EP_9	–0.203	–0.106	**0.761**	0.325	0.141	0.757
SAA	0.103	0.663	–0.055	0.228	0.081	0.512
GSA	0.154	**0.965**	0.056	0.116	0.117	0.985
LogP	–0.005	**0.923**	0.280	0.045	0.055	0.935
Mass	–0.313	**0.900**	–0.228	0.107	0.047	0.973
Vol	0.109	**0.974**	0.046	0.104	0.096	0.983
MR	–0.182	**0.962**	–0.033	0.088	0.048	0.970
Pol	–0.135	**0.950**	–0.021	0.117	0.067	0.939
R3_Cl	0.477	–0.380	–0.227	–0.072	–0.572	0.756
R3_Br	–0.337	0.359	–0.622	–0.036	0.436	0.820
FEH_1	**–0.916**	0.287	0.046	0.106	0.075	0.939
FEH_2	0.442	0.152	–0.040	–0.113	**0.767**	0.822
FEH_3	**0.934**	–0.118	–0.054	–0.133	0.251	0.970
FEH_4	0.159	0.093	–0.076	0.137	**0.928**	0.919
FEH_5	**0.921**	0.051	–0.056	–0.289	0.036	0.940
FEH_6	0.552	0.438	–0.188	0.291	0.445	0.814
FEH_7	–0.452	–0.397	0.146	–0.228	0.358	0.564
FEH_8	0.047	0.013	–0.139	0.180	**–0.838**	0.756
FEH_9	**–0.936**	0.224	–0.014	–0.013	–0.118	0.940
Prp.Total	0.196	0.223	0.159	0.175	0.113	0.866

[a]F1–5 represents the factor loading of the variables, factor loading more than 0.700 are shown in bold face; [b] Communality of a variable is the sum squares of its loading in different factors

3.5 Factor Analysis –Multiple Linear Regression (FA–MLR)

Factor analysis [47–50] was performed as the data preprocessing step for variable selection to develop QSAR equations on the training set containing the response variable and all independent variables. Principal component method was employed to extract these factors and then rotated by *VARIMAX* (Variance maximizing) rotation. From the factor analysis performed on data matrix comprising the response variable and all the independent variables, it is observed that five factors with factor loading more than 0.70 can explain data matrix to the extent of 86.63%. Antimalarial activity (pIC_{50}) was highly loaded in factor 2 (highly loaded with S_9, *GSA*, *LogP*, *Mass*, *Vol*, *MR* and *Pol*) and factor 4 (highly loaded with S_1, S_2, S_6, S_7, S_8 and EP_1). It was moderately loaded with factor 1 (highly loaded with EP_5, EP_6, FEH_1, FEH_3, FEH_5 and FEH_9) and factor 3 (highly loaded with S_3, EP_2, EP_3, EP_4 and EP_9). It was poorly loaded with factor 5 (highly loaded with FEH_2, FEH_4 and FEH_8). *FEH* terms with the subscript numbers indicate the frontier electron density related to the highest occupied molecular orbital of that corresponding atom numbers (as shown in Figure 1). Factor loading of these variables after *VARIMAX* rotation are shown in Table 4.

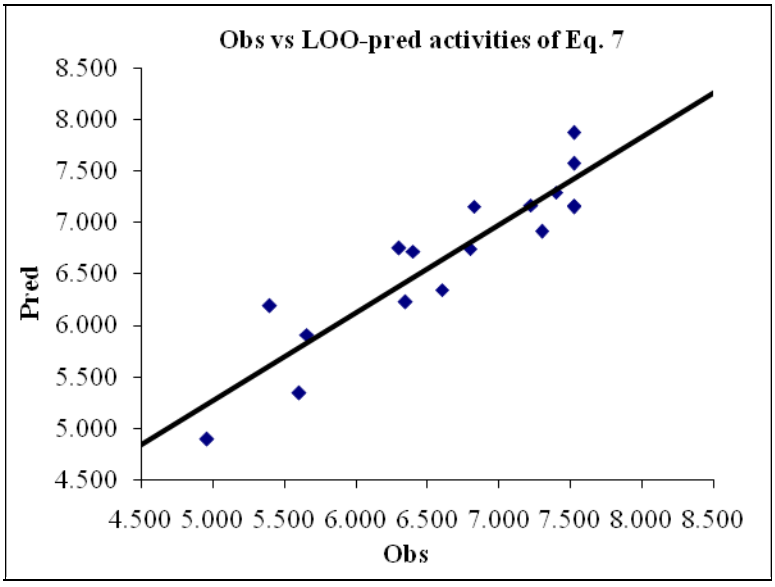


Figure 4. The Observed vs. Predicted values for Eq. (7).

Multiple linear regression (MLR) analysis was carried out to develop QSAR models. After excluding the intercorrelated parameters, different combinations of parameters having factor loading more than 0.70 were subjected to MLR technique. By FA–MLR technique, another equation was obtained:

$$pIC_{50} = -3.104\ (\pm 0.889) + 0.006\ (\pm 0.001)\ Vol - 6.021\ (\pm 0.858)\ EP_1 + 0.918\ (\pm 0.207)\ FEH_1$$
$$n = 17 \quad R = 0.956 \quad R^2 = 0.921 \quad R^2_A = 0.903 \quad F_{(3,13)} = 50.826 \quad p<0.00000 \quad SEE = 0.260 \qquad (7)$$
$$PRESS = 1.814 \quad SSY = 11.199 \quad R^2_{cv} = 0.838 \quad SDEP = 0.327 \quad S_{PRESS} = 0.374$$

Eq. (7) explains 90.30% and predicts 83.80% of variances of biological activity. From Eq. (7), it is evident that molar volume of the whole molecule, electrostatic potential charge at the atom

number 1 and the frontier electron density related to the highest occupied molecular orbital at the atom number 1 play important roles in antimalarial activity. The positive coefficient of the molar volume implies that higher values of this descriptor may correspond to higher antimalarial activity. The negative coefficient of EP_1 suggests that with decreasing the electrostatic potential of the atom number 1 electrophilic attack may be favorable for higher antimalarial activity of these compounds. *EP* charge of N_1 may depend on the halogen substitution at position X (Figure 1) that is evidenced by the higher negative electrostatic potential at N_1. Eq. (7) also reveals that the increasing value of the frontier electron density related to the highest occupied molecular orbital at N_1 (Figure 1) may be beneficial for higher biological activity. At N_1 (Figure 1), electrophilic attack may be favorable as far as the higher antimalarial activity is concerned. The Observed (Obs) vs. LOO–predicted activities (Pred) of Eq. (7) is graphically represented in Figure 4.

Another equally significant model was obtained and is shown in Eq. (8):

$$\begin{aligned} pIC_{50} &= -3.889\ (\pm 0.968) + 0.012\ (\pm 0.001)\ GSA - 6.201\ (\pm 0.871)\ EP_1 + 1.009\ (\pm 0.208)\ FEH_1 \\ n &= 17 \quad R = 0.959 \quad R^2 = 0.919 \quad R^2_A = 0.901 \quad F_{(3,13)} = 49.461 \quad p<0.00000 \quad SEE = 0.263 \\ PRESS &= 2.090 \quad SSY = 11.199 \quad R^2_{cv} = 0.813 \quad SDEP = 0.351 \quad S_{PRESS} = 0.401 \end{aligned} \tag{8}$$

Eq. (8)explains 91.90% and predicts 81.30% of variances of biological activity. Eq. (8) reveals the significance of grid surface area, electrostatic potential charge at the atom number 1 as well as the frontier electron density related to the highest occupied molecular orbital at the atom number 1. It is evidenced from the decreasing value of EP_1 as well as the increasing value of FEH_1 that electrophilic attack may be favorable at N_1 (as shown in Figure 1) for higher antimalarial activity. *EP* charge and the frontier electron density of N_1 may depend on the halogen substitution at position X (Figure 1). Increasing value of the grid surface area may be required for antimalarial activity. The Observed (Obs) vs. LOO–predicted activities (Pred) of Eq. (8) is presented in Figure 5.

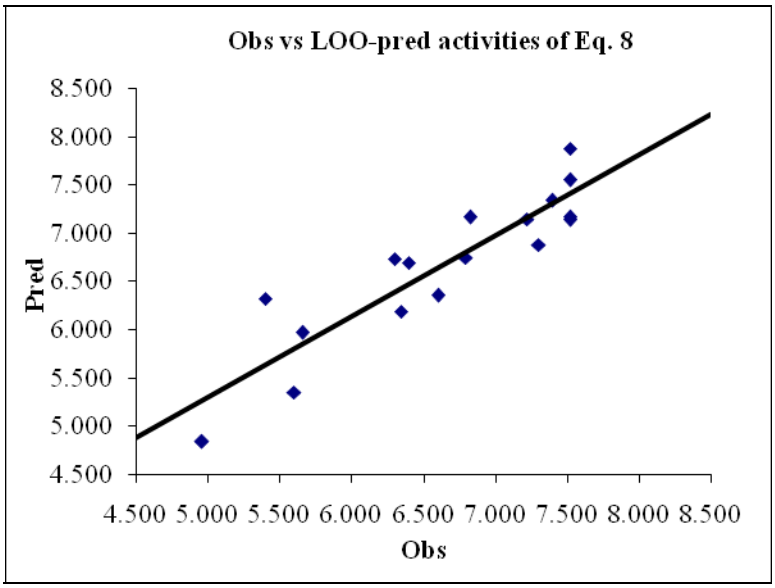


Figure 5. The Observed vs. Predicted values for Equation 8.

Another trivariate significant model was developed and that is shown in Eq. (9):

$$pIC_{50} = -3.726\ (\pm 0.899) + 0.013\ (\pm 0.001)\ GSA - 5.532\ (\pm 0.795)\ EP_1 + 1.248\ (\pm 0.229)\ FEH_9$$
$$n = 17 \quad R = 0.965 \quad R^2 = 0.931 \quad R^2_A = 0.915 \quad F_{(3,13)} = 58.247 \quad p<0.00000 \quad SEE = 0.244 \qquad (9)$$
$$PRESS = 1.648 \quad SSY = 11.199 \quad R^2_{cv} = 0.853 \quad SDEP = 0.311 \quad S_{PRESS} = 0.356$$

Eq. (9) explains 91.50% and predicts 85.30% of variances of biological activity. Here, the positive coefficient of the grid surface area implies that higher values of this descriptor may correspond to higher antimalarial activity. In Eq. (9), N_1 may be favorable for the electrophilic attack. *EP* charge of N_1 may depend on the halogen substitution at position X (Figure 1). Eq. (9) also reveals that the increasing value of the frontier electron density related to the highest occupied molecular orbital at O_9 (Figure 1) may be beneficial for higher antimalarial activity. At O_9 (Figure 1), electrophilic attack may be favorable as far as the higher antimalarial activity is concerned. The Observed (Obs) vs. LOO–predicted activities (Pred) of Eq. (9) is presented in Figure 6.

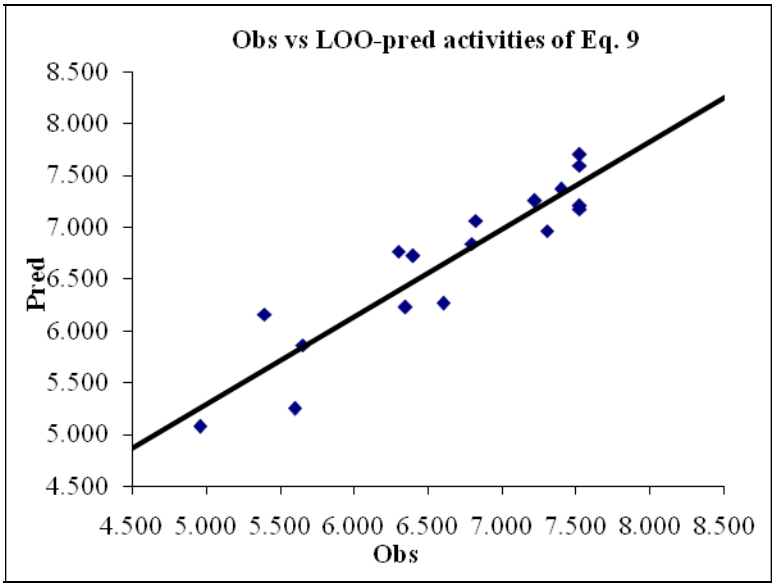


Figure 6. The Observed vs. Predicted values for Eq. (9).

Table 5. *t* and *p* Values of QSAR Models 5–9

Eq.	Intercept/Parameter	*t*–value	*p*–value	Eq.	Intercept/Parameter	*t*–value	*p*–value
5	Intercept	70.410	0.000000	**6**	Intercept	–3.449	0.004315
	*f*2	7.361	0.000005		*Vol*	10.609	0.000000
	*f*4	–2.737	0.016961		EP_1	–6.758	0.000013
	*f*3	2.436	0.030012		FEH_9	4.855	0.000314
7	Intercept	–3.492	0.003971	**8**	Intercept	–4.016	0.001468
	Vol	9.628	0.000000		*GSA*	9.492	0.000000
	EP_1	–7.019	0.000009		EP_1	–7.116	0.000008
	FEH_1	4.447	0.000659		FEH_1	4.858	0.000313
9	Intercept	–4.144	0.001154				
	GSA	10.708	0.000000				
	EP_1	–6.958	0.000010				
	FEH_9	5.438	0.000113				

All the coefficients of parameters and intercepts in all equations are of 95% confidence intervals as supported by their *t*– and *p*–values shown Table 5. In Eqs. (5)–(9), the recommended ratio of

number of data point to number of predicted parameters of 1:5 were maintained [58–59]. The observed (Obs), calculated (Calc), residual (Res), predicted residual (Pres), LOO–predicted activities (Pred) of Eqs. (5)–(9) are shown in Table 6a and 6b.

Table 6a. Observed (obs), calculated (Calc), residual (Res), predicted residual (Pres) and LOO–predicted (Pred) activities of Eqs. (5)–(6)

Cpd[a]	Obs	Eq. 5				Eq. 6			
		Calc	Res	Pres	Pred	Calc	Res	Pres	Pred
1	5.398	6.279	–0.881	–0.970	6.368	5.504	–0.106	–0.644	6.042
2	4.959	4.954	0.004	0.008	4.950	5.037	–0.078	–0.156	5.115
3	5.602	5.204	0.399	0.629	4.973	5.383	0.220	0.351	5.252
4	7.301	7.372	–0.071	–0.084	7.385	7.057	0.244	0.314	6.988
5	6.398	6.797	–0.399	–0.429	6.827	6.720	–0.322	–0.345	6.743
7	6.824	7.024	–0.200	–0.243	7.066	7.036	–0.212	–0.238	7.062
8	7.398	7.155	0.243	0.286	7.112	7.324	0.073	0.088	7.310
9	6.602	6.450	0.152	0.218	6.384	6.288	0.314	0.343	6.259
11	7.523	6.879	0.644	0.695	6.828	7.194	0.329	0.368	7.155
13	6.301	6.394	–0.093	–0.129	6.430	6.737	–0.436	–0.479	6.780
14	7.222	7.101	0.121	0.135	7.087	7.261	–0.040	–0.044	7.266
15	7.523	7.449	0.074	0.087	7.436	7.675	–0.153	–0.184	7.707
16	7.523	7.071	0.452	0.515	7.008	7.252	0.271	0.299	7.224
17	7.523	7.674	–0.151	–0.188	7.711	7.590	–0.067	–0.080	7.603
18	6.796	6.836	–0.039	–0.055	6.851	6.823	–0.028	–0.030	6.826
21	6.347	6.581	–0.235	–0.487	6.833	6.284	0.062	0.092	6.255
22	5.658	5.678	–0.021	–0.040	5.697	5.730	–0.073	–0.150	5.808

[a]Compound number

Table 6b. Observed (obs), calculated (Calc), residual (Res), predicted residual (Pres) and LOO–predicted (Pred) activities of Eqs. (7)–(9)

Cpd[a]	Obs	Eq. 7				Eq. 8				Eq. 9			
		Calc	Res	Pres	Pred	Calc	Res	Pres	Pred	Calc	Res	Pres	Pred
1	5.398	5.607	–0.209	–0.789	6.187	5.641	–0.243	–0.923	6.321	5.524	–0.126	–0.764	6.162
2	4.959	4.926	0.033	0.065	4.893	4.900	0.059	0.121	4.837	5.016	–0.057	–0.117	5.076
3	5.602	5.442	0.161	0.262	5.340	5.450	0.152	0.247	5.355	5.382	0.220	0.352	5.250
4	7.301	7.010	0.291	0.389	6.912	6.988	0.313	0.416	6.885	7.039	0.262	0.334	6.967
5	6.398	6.695	–0.297	–0.318	6.716	6.674	–0.276	–0.295	6.693	6.700	–0.302	–0.324	6.721
7	6.824	7.117	–0.293	–0.334	7.158	7.129	–0.305	–0.347	7.171	7.040	–0.216	–0.242	7.066
8	7.398	7.309	0.088	0.106	7.292	7.351	0.047	0.057	7.341	7.371	0.027	0.033	7.365
9	6.602	6.365	0.237	0.259	6.343	6.376	0.226	0.247	6.355	6.291	0.311	0.339	6.263
11	7.523	7.188	0.335	0.375	7.148	7.206	0.317	0.355	7.168	7.215	0.308	0.345	7.178
13	6.301	6.712	–0.411	–0.450	6.751	6.698	–0.397	–0.435	6.736	6.725	–0.424	–0.466	6.767
14	7.222	7.174	0.048	0.053	7.169	7.155	0.067	0.074	7.148	7.253	–0.031	–0.034	7.256
15	7.523	7.794	–0.271	–0.346	7.869	7.801	–0.278	–0.355	7.878	7.673	–0.150	–0.180	7.703
16	7.523	7.200	0.323	0.356	7.167	7.175	0.348	0.382	7.141	7.233	0.290	0.319	7.203
17	7.523	7.564	–0.042	–0.049	7.572	7.552	–0.029	–0.034	7.557	7.581	–0.058	–0.069	7.592
18	6.796	6.749	0.047	0.051	6.745	6.750	0.045	0.049	6.746	6.834	–0.038	–0.041	6.837
21	6.347	6.266	0.081	0.120	6.227	6.243	0.103	0.153	6.194	6.264	0.083	0.122	6.224
22	5.658	5.778	–0.120	–0.252	5.909	5.807	–0.149	–0.312	5.970	5.756	–0.098	–0.202	5.860

[a]Compound number

3.6 Partial Least Square (PLS)

Partial least square method [47] was also carried out for developing QSAR models as a part of QSAR study. The number of optimum components or latent variables was found to be three by cross–validation method. Based on standardized regression coefficient, the following equation was

obtained which is shown below:

$$pIC_{50} = -18.854 - 2.777\ EP_1 + 0.291\ S_1 + 1.499\ S_9 + 0.004\ GSA + 0.002\ Vol + 0.704\ FEH_1$$
$$n = 17 \quad R = 0.962 \quad R^2 = 0.926 \quad R^2_A = 0.909 \quad F_{(3,13)} = 54.32 \quad p<0.00000 \quad SEE = 0.827 \qquad (10)$$
$$PRESS = 1.177 \quad SSY = 11.199 \quad R^2_{cv} = 0.895 \quad SDEP = 0.263 \quad S_{PRESS} = 0.301$$

Eq. (10) explains 90.90% and predicts 89.50% variances of biological activity. Here, one can observe that along with electrostatic potential charge at the atom number 1 (EP_1) (as per Figure 1), grid surface area (*GSA*), molecular volume (*Vol*) as well as frontier electron density related to highest occupied molecular orbital at the atom number 1 (FEH_1), there is significance of ETSA indices at the atom numbers 1 and 9 (S_1 and S_9) (as per Figure 1). Increasing values of S_1 and S_9 may be helpful for higher antimalarial activity due to the electronic interactions at these positions of those atoms with transporter proteins of plasmodial genes to prevent gene mutations. Similarly, increasing value of *GSA* and *Vol* may be necessary for antimalarial activity. Increasing values of FEH_1 as well as decreasing value of EP_1 may be beneficial for higher antimalarial activity. It also emphasizes that N_1 position may be favorable for electrophilic attack as far as the higher antimalarial activity is concerned.

3.7 Factor Analysis–Partial Least Square (FA–PLS)

After factor analysis was performed on data matrix comprising the response variable and all the independent variables having factor loading more than 0.70, these were subjected to PLS technique. The number of optimum components or latent variables was found to be three by cross–validation method to obtain Eq. (11). Based on standardized regression coefficient, the following variables were selected for equation Eq. (11):

$$pIC_{50} = -18.418 + 0.670\ FEH_9 + 0.005\ Vol + 0.312\ S_1 + 1.485\ S_9 - 2.033\ EP_1$$
$$n = 17 \quad R = 0.973 \quad R^2 = 0.946 \quad R^2_A = 0.934 \quad F_{(3,13)} = 25.17 \quad p<0.00000 \quad SEE = 2.112 \qquad (11)$$
$$PRESS = 1.224 \quad R^2_{cv} = 0.891 \quad SDEP = 0.268 \quad S_{PRESS} = 0.307$$

Eq. (11) explains 93.40% and predicts 89.10% variances of biological activity. Here also, as like Eq. (10), increasing the value of *Vol*, ETSA indices, i.e., S_1 and S_9 as well as FEH_9 and decreasing value of EP_1 (as shown in Figure 1) may be beneficial for the higher antimalarial activity. Eq. (11) also emphasizes that the higher probability of electrophilic attack may be favorable at O_9 for higher antimalarial activity. S_1 and S_9 signify that these positions may be beneficial for antimalarial activity due to the electronic interactions of these positions with transporter proteins of plasmodial gene to prevent gene mutations. Decreasing value of EP_1 also suggests that electrophilic interaction may be favorable at N_1 for higher antimalarial activity.

3.8 Prediction of Test Set Compounds

On the basis of developed QSAR models on the training set, the activity of the test set compounds were predicted and R^2_{pred} values for the test set compounds were calculated. Predicted

values of the test set compounds were calculated on the basis of Eqs. (5)–(11). The observed and the predicted values of the test set compounds of Eqs. (5)–(11) are listed in Table 7. Significant R^2_{pred} values for the test set were obtained and shown as follows: R^2_{pred} = 0.930 for Eq. (5), R^2_{pred} = 0.948 for Eq. (6), R^2_{pred} = 0.959 for Eq. (7), R^2_{pred} = 0.963 for Eq. (8), R^2_{pred} = 0.951 for Eq. (9), R^2_{pred} = 0.937 for Eq. (10), R^2_{pred} = 0.953 for Eq. (11).

Table 7. Observed and predicted values of the test set compounds

Cpd [a]	Obs	Predicted Value						
		Eq. (5)	Eq. (6)	Eq. (7)	Eq. (8)	Eq. (9)	Eq. (10)	Eq. (11)
6	7.222	6.936	6.867	6.947	6.973	6.887	6.949	6.931
10	7.398	7.424	7.482	7.447	7.491	7.533	7.427	7.436
12	7.523	7.403	7.44	7.454	7.477	7.464	7.403	7.397
19	7.523	7.282	7.410	7.302	7.304	7.426	7.191	7.314
20	7.523	7.792	7.654	7.527	7.504	7.644	7.447	7.594

[a] Compound number

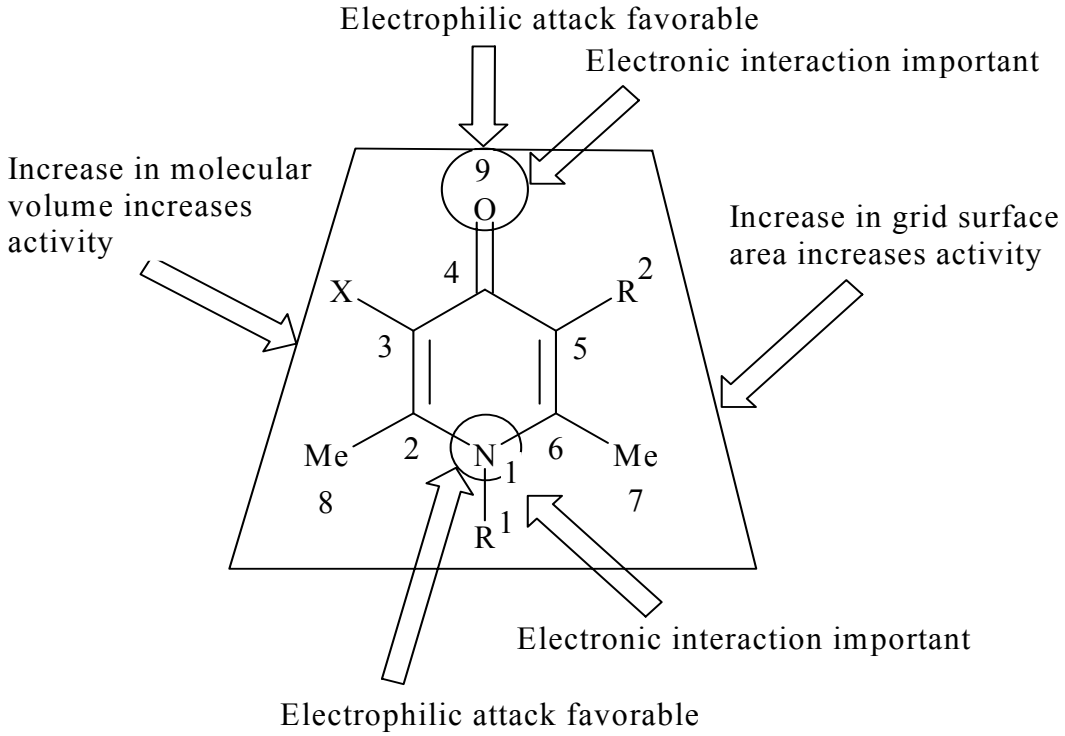


Figure 7. Important atoms and substituents of 4–pyridones for potent antimalarial activity.

4 CONCLUSIONS

QSAR models reveal structural requirements of 4–pyridones for their potent antimalarial activity. It is found that the increasing values of the ETSA indices at atom numbers 1 and 9 (Figure 1) are important for antimalarial activity. These may be due to the electronic interactions with the transporter proteins of protozoal gene by these positions. At N_1, the decreasing value of electrostatic potential charge implies that at this position electrophilic attack may be favorable for antimalarial activity. It also emphasizes that the increasing values of the frontier electronic density related to the

highest occupied molecular orbital at atom numbers 1 and 9 (Figure 1) may be beneficial for antimalarial activity. At those positions electrophilic attack may be favorable as far as the potent antimalarial activity is concerned. The increasing values of molecular volume as well as grid surface area may be beneficial for potent antimalarial activity of 4–pyridones. Important atoms and substituents of 4–pyridones for potent antimalarial activity are shown in Figure 7.

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5 REFERENCES

[1] K. Park (Ed. 15), *Preventive & social medicine*, Banarsidas Bhanot, India, 1997.
[2] Wilson and Gisvold's *Textbook of Organic medicinal and Pharmaceutical Chemistry*, (Ed. 11), Lipincott Williams & Wilkins, Philadelphia, 2004, pp.288.
[3] H. P. Rang, M. M. Dale, J. M. Ritter and P. K. Moore, *Pharmacology*, Churchill Livingstone, Edinburgh, 2003.
[4] K. Srikanth, C.A. Kumar, D. Goswami, A. U. De, and T. Jha, Quantitative structure activity relationship (QSAR) studies of some substituted benzenesulphonyl glutamines as tumor suppressors, *Ind. J. Biochem. Biophys*. **2001**, *38*, 120–123.
[5] K. Srikanth, B. Debnath. and T. Jha., Synthesis, biological evaluation and QSAR study on antitumor activity of 1,5–*N*,*N*′–Disubstituted–2–(substituted benzenesulphonyl) glutamamides, *Bioorg. Med. Chem*. **2002**, *10*, 1841–1854.
[6] K. Srikanth, C.A. Kumar, B. Ghosh, and T. Jha, Synthesis, screening and quantitative structure–activity relationship (QSAR) study on some glutamine analogues for possible anticancer activity, *Bioorg. Med. Chem*. **2002**, *10*, 2119–2131.
[7] B. Debnath, K. Srikanth, S. Banarjee, T. Jha, 1,5–*N*,*N*′–Disubstituted–2–(substituted benzenesulphonyl) glutamamides as antitumor agents. Part 2. Synthesis, biological activity and QSAR study, *Internet Electron. J. Mol. Des*. **2002**, *1*, 488–502, www.biochempress.com
[8] K. Srikanth, B. Debnath and T. Jha, QSAR study on adenosine kinase inhibition of pyrrolo[2,3–d] pyrimidine nucleoside analogs using Hansch approach, *Bioorg. Med. Chem. Lett*. **2002**, *12*, 899–902.
[9] B. Debnath, S. P. Vishnoi, B. Sa, and T. Jha, QSAR study on some dihydrofolate reductase inhibitors, *Internet Electron. J. Mol. Des*. **2003**, *2*, 128–136, www.biochempress.com
[10] B. Debnath, S. Samanta, K. Roy and T. Jha, QSAR study on some p–arylthio cinnamides as antagonists of biochemical ICAM–1/LFA–1 interaction and ICAM–1/JY–8 cell adhesion in relation to anti–inflammatory activity, *Bioorg. Med. Chem*. **2003**, *11*, 1615–1619.
[11] B. Debnath, S. Samanta, S. K. Naskar, K. Roy and T. Jha, QSAR study on the affinity of some arylpiperazines towards the 5–HT1A/α1–adrenergic receptor Using E–state index, *Bioorg. Med. Chem. Lett*. **2003**, *13*, 2837–2842.
[12] T. Jha, B. Debnath, S. Samanta and A.U. De, QSAR studies on some substituted glutamine analogs as possible anticancer agents, *Internet Electron. J. Mol. Des*. **2003**, *2*, 539–545, www.biochempress.com
[13] B. Debnath, S. Gayen, S. K. Naskar, K. Roy and T. Jha, QSAR study on some azidopyridinyl neonicotinoids insecticides for their selective affinity towards the *Drosophila* nicotinic receptor over mammalian α4β2 receptor using electrotopological state atom index, *Drug Des. Discov*. **2003**, *18*, 81–89.
[14] B. Debnath, S. Gayen, S. Bhattacharya, S. Samanta, and T. Jha, QSAR study on some pyridoacridine ascididemin analogs as anti–tumor agents, *Bioorg. Med. Chem*. **2003**, *11*, 5493–5499.
[15] S. Samanta, K. Srikanth, S. Banerjee, B. Debnath, S. Gayen and T. Jha, 5–*N*–Substituted–2–(Substituted Benzenesulphonyl) Glutamines as Antitumor Agents II: Synthesis, Biological Activity and QSAR Study, *Bioorg. Med. Chem*. **2004**, *12*, 1413–1423.
[16] S. Gayen, B. Debnath, S. Samanta and T. Jha, QSAR Study on Some Anti–HIV HEPT Analogues Using Physicochemical And Topological Parameters, *Bioorg. Med. Chem*. **2004**, *12*, 1493–1503.
[17] B. Debnath, S. Gayen, A. Basu, B. Ghosh, K. Srikanth and T. Jha, Quantitative Structure–Activity Relationship Study Using Refractotopological State Atom Index on Some Neonicotinoid Insecticides, *Bioorg. Med. Chem*.

2004, *12*, 6137–45.
[18] B. Debnath, S. Gayen, A. Basu, K. Srikanth and T. Jha, Quantitative structure–activity relationship study on some benzodiazepine derivatives as anti–alzheimer agents, *J. Mol. Mod*. **2004**, *10*, 328–334.
[19] B. Debnath, S. Samanta, S. Gayen, A. Basu, B. Ghosh and T. Jha, QSAR Study on 5–*N*–Substituted–2–(Substituted Benzenesulphonyl) Glutamines as Antitumor Agents through Synthesis and Biological Evaluation: Part III, *Internet Electron. J. Mol. Des*. **2005**, *4*, 393–412. www.biochempress.com
[20] S. Samanta, B. Debnath, S. Gayen, B. Ghosh, A. Basu and T. Jha, QSAR Modeling of Dopamine D2 receptor binding affinity of 6–methoxy benzamides using atom type electrotopological state index, *IL Farmaco* **2005**, *10*, 818–825.
[21] S. Gayen, B. Debnath, S. Samanta, B. Ghosh, A. Basu and T. Jha, 1,5–*N*,*N*′–Disubstituted–2–(Substituted Benzenesulphonyl)–Glutamamide Analogues as Anticancer Agents. Part 3. Synthesis, Biological Screening and QSAR Study, *Internet Electron. J. Mol. Des*. **2005** , *4*, 393, www.biochempress.com
[22] S. Samanta, Sk. M. A., P. Panda and T. Jha, Pharmacophore Mapping of Tricyclic Isoxazoles for Their Affinity Towards Alpha–2 Adrenoreceptors, *Internet Electron. J. Mol. Des*. **2006**, *5*, 503–514. www.biochempress.com
[23] S. Samanta, S. Gayen, B. Ghosh, P Panda, K. Srikanth and T. Jha, QSAR Analysis of Some Indirubin Derivatives as Potent and Selective Inhibitors of Cyclin–Dependent Kinases and Glycogen Synthase Kinase–3, *Int. J. Appl. Chem*. **2006**, *2*, 169–180.
[24] S. Samanta, B. Debnath, A. Basu, S. Gayen, K, Srikanth and T. Jha, Exploring QSAR on 3–aminopyrazoles as antitumor agents for their inhibitory activity of CDK2/cyclin A. *Eur. J. Med. Chem*. **2006**, *41*, 1190 – 1195.
[25] B. Debnath, S. Gayen, S. Samanta, A. Basu, B. Ghosh and T. Jha, QSAR Study on Some Synthesized and Biologically Evaluated Glutamine Analogs as Possible Anticancer Agents, *Ind. J. Chem*. **2006**, *45*, 93–99.
[26] A. Basu, S. Gayen, S. Samanta, P. Panda, K. Srikanth and T. Jha, QSAR modeling of neonicotinoid insecticides for their selective affinity towards Drosophila nicotinic receptors over mammalian $\alpha_4\beta_2$ receptors. *Can. J. Chem*. **2006**, *84*, 458–463.
[27] S. Samanta, P. Panda, Sk. M. Alam, and T. Jha, Structural Requirements of 2–Phenylimidazo[1,2–α] pyridineacetamide Analogs to Improve Affinity and Selectivity towards Central and/or Peripheral Benzodiazepine Receptors, *Internet Electron. J. Mol. Des*. **2007**, *5*, 503–518. www.biochempress.com
[28] P. Panda, S. Samanta, Sk. M. Alam, S. Basu and T. Jha, QSAR for Analogs of 1,5–*N*,*N*–Disubstituted–2–(substituted benzenesulphonyl)–glutamamide as possible Antitumor Agents. *Internet Electron. J. Mol. Des*. **2007**, *5*, 280–301. www.biochempress.com
[29] Sk. M. Alam, S. Samanta, A. K. Halder, S. Basu and T. Jha, Structural finding of R/S–3,4–dihydro–2,2–dimethyl–6—halo–4–(substituted phenylaminocarbonylamino)–2H–1–benzopyrans as selective pancreatic β–cells $K_{ATP-p\beta}$ channel openers. *Can. J. Chem*. **2007**, *85*, 1053–1063.
[30] Samanta, S.; Panda, P.; Alam, Sk. M.; Jha, T. Search for Structural Requirements of 2–Phenylimidazo [1,2–α]pyridineacetamide Analogs to Improve Affinity and Selectivity towards Central and/or Peripheral Benzodiazepine Receptors, *Internet Electron J. Mol. Des*. **2007**, *6*, 183–199. www.biochempress.com
[31] T. Jha, S. Samanta, S. Basu, A. K. Halder, N. Adhikari, M. K. Maiti, QSAR Study On Some Orally Active Uracil Derivatives as Human Gonadotropin–Releasing–Hormone Receptor Antagonists, *Internet Electron. J. Mol. Des*. **2008**, *7*, 234–250. www.biochempress.com
[32] S. Samanta, Sk. M. Alam, P. Panda, and T. Jha, Possible anticancer agents: QSAR analogs of glutamamide: synthesis and pharmacological activity of 1,5–*N*,*N*′–disubstituted–2–(substituted benzenesulphonyl) glutamamides, *Eur. J. Med. Chem*. **2009**, *44*, 70–82.
[33] Sk. M. Alam, S. Samanta, A. K. Halder and T. Jha, QSAR modelling of pancreatic beta–cell KATP channel openers R/S–3,4–dihydro–2,2–dimethyl–6–halo–4–(substituted phenylaminocarbonylamino)–2H–1–benzopyrans using MLR–FA techniques, *Eur. J. Med. Chem*. **2009**, *44*, 359–364.
[34] A. K. Halder, N. Adhikari and T. Jha, Comparative QSAR modeling of 2–phenylindole–3–carbaldehyde derivatives as potential antimitotic agents, *Bioorg. Med. Chem. Lett*. **2009**, *19*, 1737–1739.
[35] T. Jha, P. Chakrabortty, N. Adhikari, A. K. Halder, M. K. Maiti, QSAR Study on Coumarins as Antimeningoencephalitic Agents, *Internet Electron. J. Mol. Des*. **2009**, *8*, 1–13. www.biochempress.com
[36] A. K. Halder, N. Adhikari, T. Jha, Structural Findings of 2–Phenylindole–3–Carbaldehyde Derivatives for Antimitotic Activity by FA–sMLR QSAR Analysis, *Chem. Biol. Drug Des*. **2010**, *75*, 204–213.
[37] N. Adhikari, M. K. Maiti, T. Jha, Predictive comparative QSAR modelling of (phenylpiperazinyl–alkyl) oxindoles as selective 5–HT_{1A} antagonists by stepwise regression, PCRA, FA–MLR and PLS techniques, *Eur. J. Med. Chem*. **2010**, *45*, 1119–1127.
[38] A. K. Halder, N. Adhikari, M. K. Maiti, T. Jha, Synthesis, pharmacological activity and comparative QSAR modeling of 1,5–*N*,*N*′–substituted–2–(substituted naphthalenesulphonyl) glutamamides as possible anticancer agents, *Eur. J. Med. Chem*. **2010**, *45*, 1760–1771.
[39] C. L. Yeates, J. F. Batchelor, E. C. Capon, N. J. Cheesman, M. Fry, A. T. Hudson, M. Pudney, H. Trimming, J. Woolven, J. M. Bueno, J. Chicharro, E. Fernández, J. M. Fiandor, D. Gargallo–Viola, F. G. de las. Heras, E.

Herreros and M. L. León, *J. Med. Chem.* **2008**, *51*, 2845–2852.
[40] C de Gregorio, L. B. Kier and L. H. Hall, QSAR modeling with the electrotopological state indices: Corticosteroids, *J. Comput. Aid. Mol. Des.* **1998**, *12*, 557–561.
[41] K. Rose, L. H. Hall and L. B. Kier, Modeling Blood–Brain Barrier Penetration Using the Electrotopological State, *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 651–666.
[42] L. B. Kier and L. H. Hall, *Molecular Structure Description: The Electrotopological State*, Academic Press, San Francisco, **1999**.
[43] S. P. Gupta, *Quantum Biology*, New Age International Publishers, New Delhi, **1996**, 45.
[44] A. Tropsha, *In Burger's Medicinal Chemistry and Drug Discovery*, D. J. Abraham, (Eds.); John Wiley and sons, Inc., New Jersey, 2003, Vol. 1, pp. 49–75.
[45] G. W. Sendecor, W. G. Cochran, *Multiple Regression in Statistical Methods*, Oxford & IBH: New Delhi, **1967**.
[46] R. Franke, Theoretical drug design methods; Elsevier: Amsterdam, 1984; pp184–195.
[47] J. T. Leonard, K. Roy, Comparative QSAR modeling of CCR5 receptor binding affinity of substituted 1–(3,3–diphenylpropyl)–piperidinyl amides and ureas. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4467–4474.
[48] J. T. Leonard, K. Roy, QSAR by LFER model of HIV protease inhibitor mannitol derivatives using FA–MLR, PCRA and PLS techniques. *Bioorg. Med. Chem.* **2006**, *14*, 1039–1046.
[49] P. Bhattacharya, K. Roy, QSAR of adenosine A_3 receptor antagonist 1,2,4–triazolo[4,3–a]quinoxalin–1–one derivatives using chemometric tools. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3737.
[50] P. Bhattacharya, J. T. Leonard, K. Roy, Exploring QSAR of thiazole and thiadiazole derivatives as potent and selective human adenosine A_3 receptor antagonists using FA and GFA techniques. *Bioorg. Med. Chem.* **2005**, *13*, 1159–1165.
[51] I. V. Tetko, V. Y. Tanchuk and A. E. Villa, *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 1407–1421.
[52] Mouse, a computer program written in C++language developed by Jadavpur University.
[53] Hypercube, Inc. Hyperchem Professional Release 7.0 is a computer program developed by Hypercube Inc., Gainesville, Florida. www.hyper.com
[54] A. R. Leach, *Molecular modeling principles and applications*, 2nd Ed., Prentice Hall, **2001**, 97–98.
[55] Chem 3D Pro Version 5.0 and Chem Draw Ultra Version 5.0 are software programs developed by Cambridge Soft Corporation, U. S. A.
[56] Multiregress is a statistical software developed by Jadavpur University.
[57] Least Square is a statistical software developed by Jadavpur University.
[58] H. Kubinyi, QSAR: Hansch Analysis and Related Approaches, VCH, New York, 1993.
[59] L. Eriksson, J. Jaworska, A. P. Worth, M. T. Cronin, R. M. McDowell and P. Gramatica, *Environ. Health Perspect.* **2003**, *111*, 1361–1375.