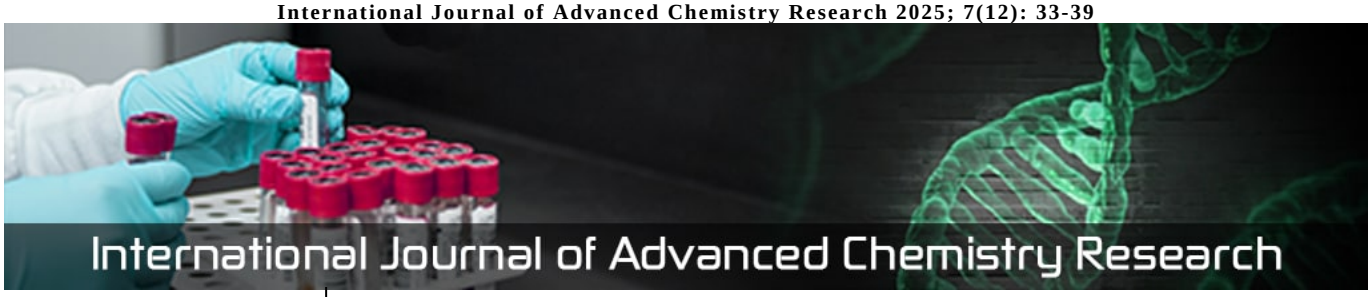

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Ram Prakash Rajwade
Department of Chemistry, Faculty of Science, Shri Rawatpura Sarkar University, Raipur, Chhattisgarh, India

Leena Jaisawal
Department of Chemistry, Faculty of Science, Shri Rawatpura Sarkar University, Raipur, Chhattisgarh, India

Nidhi Saju
Department of Chemistry, Faculty of Science, Shri Rawatpura Sarkar University, Raipur, Chhattisgarh, India

Ritu Sao
Department of Chemistry, Faculty of Science, Shri Rawatpura Sarkar University, Raipur, Chhattisgarh, India

Corresponding Author:
Ram Prakash Rajwade
Department of Chemistry, Faculty of Science, Shri Rawatpura Sarkar University, Raipur, Chhattisgarh, India

2DQSPR approach towards the lipophilicity of n-arylhydroxamic acids: A key role of steric and hydrogen bond factors using PLS method

Ram Prakash Rajwade, Leena Jaisawal, Nidhi Saju and Ritu Sao

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Abstract
Hydroxamic acids are a group of weak organic acids having the general formula RC(=O)N(R')OH, shows a wide spectrum of activities in analytical, agricultural, biological and medicinal fields. The logarithmic n-octanol/water partition coefficient ($logP_{O/W}$) is an important property for pharmacology, toxicology and medicinal chemistry. Some commonly available software including XLOGP, KowWin, CLOGP, ALOGPS and miLOGP were used to estimate the log $P_{O/W}$ values of the hydroxamic acids. Moderate correlation were obtained between the shake flask derived $logP_{O/W}$ and the software computed $logP_{O/W}$, with squared correlation coefficients (R^2) ranging from 0.4022 to 0.5688.
Quantitative structure-property relationship (QSPR) for the lipophilic behaviour, $logP_{(O/W)}$, of N-arylhydroxamic acid (HAs) is analysed using the molecular descriptors by partial least square (PLS) regression. The cross-validation Q^2 cum values for the optimal QSPR model of HAs is above 0.860 (remarkably higher than 0.500), indicating good predictive-abilities for $logP_{O/W}$ values of HAs. The resulting QSPR model shows that $logP_{O/W}$ values of HAs are mainly governed by molar volume (Vx), excess molar refraction (XRM), energy GAP (E_{HOMO}- E_{LUMO}), hydrogen bond parameters (α, β) and chlorine atoms attached in upper or/and lower phenyl rings (I_{Cl}).

Keywords: $logP_{O/W}$, PM6, QSPR, Hydroxamic acid, PLS

Introduction
The logarithmic n-octanol/water partition coefficient ($logP_{O/W}$) is widely used to represent molecular lipophilicity. A lipophilicity parameter is a useful tool in the field of quantitative structure- activity relationships (QSARs) for several biological effects, because lipophilicity affects absorption, transmembrane transport, bioavilability hydrophobic drug receptor interaction, metabolism, pharmacological activity as well as toxicity of molecule [1,2] Lipophilicity of chemicals is important both for predicting pharmacokinetics and pharmcodynamics of drugs and toxicants [3]. $LogP_{O/W}$ is also an important parameter in studying their environmental fate, e.g. bioaccumulation in fish or absorption on soil and sediments. Therefore, accurate $logP_{O/W}$ values are important for the prediction of biological or environmental properties of compound.
The hydroxamic acid functional group, –C(=O) N·ROH, is a key structural constitutent of many biomolecules, some of which are naturally occurring [4] and others, such as the peroxidose, matrix metalloproteinase and urease inhibitors [5,6] are of synthetic origin. Hydroxamic acids represent a wide spectrum of bioactive compounds that have hypotensive [7], anticancer [8-12], antitumor [13-15], antimalarial [16-20], antituberculosis and antifungal as key functional of potential chemotherapeutics targeting cardiovascular, HIV and Alzheimer's diseases [21,22]. Quantitative structure-property relationship (QSPR) has been demonstrated to be an effective computational tool in understanding the interrelation between the structure of molecule and their properties [23-26]. Therefore, the objective of the present investigation to develop QSPR model for $logP_{O/W}$ of the hydroxamic acidsbased on molecular descriptors by partial least square (PLS) regression. The commonly available compute programmes: XLOGP, KowWin, CLOGP, ALOGPS and MilogP were used to estimate the logP data for

hydroxamic acids. The results obtained are computed with experimental $logP_{O/W}$ of hydroxamic acids.

Materials and Methods

Materials

The experimental results of the logarithmic n-octanol/water partition coefficient ($logP_{O/W}$) of hydroxamic acids are taken from literature [27, 28] and are summarized in (Table 1).

Lipophilicity calculations

A number of different computer programmes have been recently developed for the estimation of lipophilocity of compounds based on their structure. In the study, five commonly available computer programmes based on different calculation methods for computing logP have been compared.

The validity of these programmes was evaluated by how well the calculated log P values agreed with this experimentally determined $logP_{O/W}$ values for hydroxamic acids.

The SMILES (Simplified Molecular Input Line Entry System) notation created by the structure drawing programs Cambridge softs chemdraw pro was used as chemical structure for all programs commonly available computer programs were used to estimate $logP_{O/W}$ of Hydroxamic Acids are as XLOGP (based on atom contribution) [29], KowWin (based on atom/fragment contribution) [30] and CLOGP (based on fragmental contributions) [31], ALOGPS2.2 (based on atom type electrotopological state, indices and neutral networking modeling [32-35], and MilogP (based on group contribution) [36]. LogP data obtained with five software packages will listed in Table 1.

Molecular modeling

The PM6 Hamiltonian method of MOPAC 2009 contained in the Ampac software version 9 [37] was used to compute semiemperical quantum chemical descriptors. Bio-Loom program of Biobyte co-operation [38] was used to compute excess molar refraction, XRM. The data are listed on Table 2.

Table 1: Lipophilicity Parameters of Hydroxamic Acids with the logP values obtained by different computer programs

Serial No.	Hydroxamic acid	logP Exp	XLOGP	KowWin	CLOGP	ALOGPS	MilogP
1	N-phenylbenzo-	2.50	1.87	1.94	2.32	1.78	2.76
2	N-phenyl-4-chlorobenzo-	2.52	3.08	2.58	3.23	2.70	3.43
3	N-phenyl-4-methoxybenzo-	2.54	2.42	2.02	2.52	1.89	2.81
4	N-phenyl-4-nitrobenzo-	2.52	2.28	1.75	2.48	1.82	2.71
5	N-phenylcinnamo-	2.54	2.88	2.32	3.29	2.36	3.39
6	N-phenylcinnamo-	2.46	2.81	2.48	2.82	2.58	3.16
7	N-p-tolylbenzo-	2.47	2.81	2.48	2.82	2.58	3.20
8	N-p-tolyl-2-furo-	2.41	2.21	1.61	2.00	1.90	2.46
9	N-m-chlorophenylbenzo-	2.73	3.08	2.58	3.29	2.73	3.39
10	N-p-chlorophenylbenzo-	2.47	3.08	2.58	3.29	2.71	3.43
11	N-p-chlorophenyl-2-chlorobenzo-	2.71	3.08	2.58	3.23	2.69	3.39
12	N-o-tolyl-4-chlorobenzo-	2.79	3.44	3.13	3.73	3.01	3.83
13	N-phenyl-4-ethoxybenzo-	2.69	2.79	2.51	3.05	2.41	3.19
14	N-o-tolyl-4-ethoxybenzo-	2.76	3.15	3.06	3.55	2.89	3.59
15	N-p-tolyl-4-ethoxybenzo-	2.74	3.15	3.06	3.55	2.93	3.64

Table 2: Molecular Descriptors of Hydroxamic Acids

Serial No.	Ehomo (eV)	Elumo (eV)	Elumo-Ehomo (eV)	Dm (Debye)	αa	βa	Vxa ($cm^3 \cdot mol^{-1}$)	XRM ($cm^3 \cdot mol^{-1}$)	ICl
1	-8.7084	-0.6558	8.0526	2.645	0.56	1.35	172.20	1.010	0
2	-8.8430	-0.9426	7.9004	3.020	0.67	1.70	200.65	1.090	1
3	-8.5895	-0.5119	8.0776	4.481	0.76	1.99	225.00	0.960	0
4	-9.1433	-1.8483	7.2950	6.413	0.85	2.36	255.32	1.040	0
5	-8.6581	-0.9158	7.7423	3.533	0.78	2.03	228.88	1.430	0
6	-8.4938	-0.6125	7.8813	3.887	0.66	1.69	198.64	1.010	0
7	-8.4922	-0.5932	7.8990	2.697	0.72	1.85	211.73	1.010	0
8	-8.5061	-0.6591	7.8470	2.793	0.64	1.24	160.46	0.810	0
9	-8.9460	-0.8331	8.1129	4.270	0.64	1.94	225.99	1.090	1
10	-8.7915	-0.8552	7.9363	3.740	0.54	1.38	174.02	1.090	1
11	-8.7044	-0.8843	7.8201	3.500	1.56	2.40	263.18	1.090	1
12	-8.6501	-0.8554	7.7947	4.148	1.67	2.53	278.11	1.090	1
13	-8.5552	-0.4680	8.0872	4.696	1.72	2.55	273.37	0.960	0
14	-8.3674	-0.3810	7.9864	5.409	1.71	2.69	288.45	0.960	0
15	-8.3317	-0.4824	7.8493	4.751	1.77	2.70	288.57	0.960	0

Statistical methods

QSPR models were developed using PLS regression as implemented in Simca (SIMCA-Version 11.0, Umetric AB and Ersoft AB) software, the condition for the computation were based on the default option of the software. The criterion used to determine the model dimensional-the number of significant PLS component is cross validation (Cv). The obtained QSPR model is considered to have good prediction ability when the cumulative cross validated regression coefficient (Q^2) for the extracted component Q^2cum, is large than 0.5. Model adequacy was mainly measured as the number of PLS principal component (A), Q^2cum, their correlation coefficient between observed values and filled values (R).

Results and Discussion

Correlation between experimental $log_{o/w}$ and computated log P values

$\log P_{O/W} = a+b\ (logP)$ (1)

The correlation between the log Po/w and obtained by computation were summaries in Table 2. The experimentally determined log $P_{O/W}$ values correlate with the lipophilicity data (logP) computed using software XLOGP (r^2=0.4190), KowWin (r^2=0.5563), CLOGP (r^2=0.5688), ALOGPS (r^2=0.4022) and MilogP (r^2=0.5202).

The cross-validation (q^2) value of experimental logP versus computational logP are shown in figure show that the programs used in present study did not give reasonable data for this set of compound ($q^2 \leq 0.5$)

Table 3: Linear relationships between experimental logP and calculated logP of hydroxamic acids

	a	b	R^2	sd	F	n
XLOGP	2.0485	0.1933	0.4190	0.1018	9.373	15
KowWin	2.0788	0.2096	0.5563	0.0890	16.296	15
ClogP	2.0087	0.1935	0.5688	0.0877	17.151	15
ALOGPS	2.1154	0.1930	0.4022	0.1032	8.745	15
MilogP	1.8096	0.2429	0.5202	0.0925	14.094	15

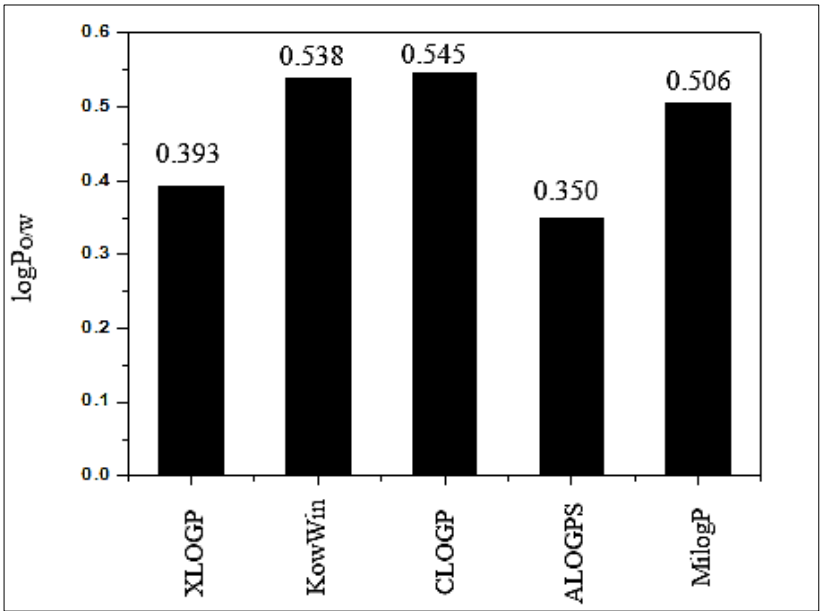

Fig 1: The cross-validation (q^2) $logP_{O/W}$ versus computed logP values of 15 Hydroxamic Acids

2DQSPR analysis

To develop the 2DQSPR, several descriptors of steric, electronic and hydrogen bond parameters were used to characterize the compounds. Molar volume and excess molar refraction are chosen to characterize the steric component. Electronic was represented by energy of highest occupied molecular orbital (E_{HOMO}), energy of lowest unoccupied molecular orbital (E_{LUMO}), energy GAP (E_{LUMO} - E_{HOMO}) and dipole moment (Dm). Hydrogen bond donor acidity, α and acceptor basicity, β as hydrogen bond parameter and variable indicator $I_{Cl,}$ when chlorine atom in hydroxamic acid moiety I_{Cl}=1 and absent I_{Cl}=0.

PLS analysis

In a PLS model, variable importance in the projection (VIP) is a parameter that shows that the importance of variable. According to the manual of simca-p (version 11), VIP is the sum and all model dimensions of the contribution of variable influences (VIN) for given PLS dimension (a) and a given x term (k), VIN^2 is computed form the squared PLS weight of that x term multiplied by the parent explained the sum of squares (SS) by that PLS dimension. VIP value is calculated from the accumulated value and all PLS dimension, divide by the total percent explained SS by the PLS,

$$VIP_k = \sum (VIP)^2_k \quad (2)$$

Model and multiplied by the number of terms in the model. The terms with values of VIP are the most relvant for explaining depended variable.

To obtain an optimal model the following PLS analysis procedure are adopted. At first, a PLS model with all the predictor variables was calculated. Then the variable with the lowest VIP value was eliminated and a new PLS regression was performed, leading to a new PLS model. This procedure was repeated till only main predictor variables were recommended the optimal PLS model was selected with respected to the statistics Q^2_{cum}, the root mean square error of calibration (RMSEC) and the root mean square of prediction (RMSEP).

PLS analysis was initially applied to the complete data set of 15 compounds and 9 descriptors. The preliminary analysis yielded a model which accounts for 93.6% of the variation in $logP_{O/W}$ (r^2 =0.936) at a predictability level of 73.0% (q^2 =0.730). It was improved by removing that parameters which did not make significant contributions to $logP_{O/W}$ (E_{HOMO}, E_{LUMO} and $Dm_{)}$.

Analytical QSPR equation thus obtained is as follow,

$$logP_{O/W} = 3.160x10^{-1}\ (Vx) + 3.140 \times 10^{-1}\ (\alpha) + 2.890x10^{-1}\ (\beta) + 3.132\ x10^{-1}\ (I_{Cl}) + 2.531 \times 10^{-1}\ (E_{HOMO}\text{-}E_{LUMO}) + 5.354\ x10^{-1}\ (XRM) + 20.131 \quad (3)$$

To establish the predictive power of a model, one needs to divide the available data set into the training and test sets. In general, training set should contain 60-80% of the full data. For assigning compounds to training and test sets, compounds were ordered by $logP_{O/W}$ values, and every third was selected for the test set, the remaining compounds were used as a training set. The test and training sets comprised 5 and 10 compounds, respectively and indicated in Table 4 (Model II). The model fitting for model I and model II are listed in Table 5.

Table 4: Calculated $logP_{O/W}$ of N-aryhydroxamic acids by models I and II

S. No.	$logP_{O/W}$				
	Model I	Residue	Model II		Residue
			Training set	Test set	
1.	2.449	0.051	2.464		0.036
2.	2.571	-0.051	–	2.545	-0.025
3.	2.563	-0.023	2.557		-0.017
4.	2.503	0.017	2.528		-0.008
5.	2.541	-0.001	–	2.589	-0.049
6.	2.478	-0.018	2.491		-0.031
7.	2.510	-0.040	–	2.519	-0.049
8.	2.391	0.019	2.398		0.012
9.	2.646	0.084	–	2.604	0.126
10.	2.518	-0.028	2.496		-0.006
11.	2.742	-0.031	2.713		-0.003
12.	2.770	0.020	–	2.740	0.050
13.	2.730	-0.040	2.723		-0.033
14.	2.737	0.022	2.730		0.030
15.	2.721	0.019	2.720		0.020

Table 5: Model fitting for models I and II

Models	N^{tr}	A	$R^2_{X(adj)(cum)}$	$R^2_{y(adj)(cum)}$	Q^2_{cum}	RSMEE	N^{ts}	RSMEP
I	15	1	0.466	0.829	0.791			
		2	0.664	0.913	0.867	0.041		
II	10	1	0.476	0.921	0.854			
		2	0.667	0.965	0.884	0.027	5	0.069
N^{tr} = No. of compounds in training set and N^{ts}= No. of compounds in test set.								

In model I, six predictor variables involved which are condensed into two PLS components. The VIP values of Vx, α and β are larger than 1, indicating that these three descriptors are more significant than I_{Cl}, E_{HOMO}-E_{LUMO} and XMR.

Table 6: The VIPs and PLS weight (W* [1] and (W* [2]) for the molecular descriptors including in model I

Model I			
Variables	**VIP**	**W* [1]**	**W* [2]**
Vx	1.333	0.556	0.016
α	1.301	0.552	-0.068
β	1.295	0.570	-0.004
I_{Cl}	0.713	0.040	0.117
E_{LUMO}-E_{HOMO}	0.575	0.115	0.710
XRM	0.124	0.216	0.723

Table 7: The VIPs and PLS weight (W* [1] and (W* [2]) for the molecular descriptors including in model II

Model II			
Variables	**VIP**	**W* [1]**	**W* [2]**
α	1.430	0.597	0.244
Vx	1.350	0.563	-0.094
β	1.333	0.555	-0.134
I_{Cl}	0.480	0.100	0.806
E_{LUMO}-E_{HOMO}	0.276	0.046	0.490
XRM	0.225	0.084	0.208

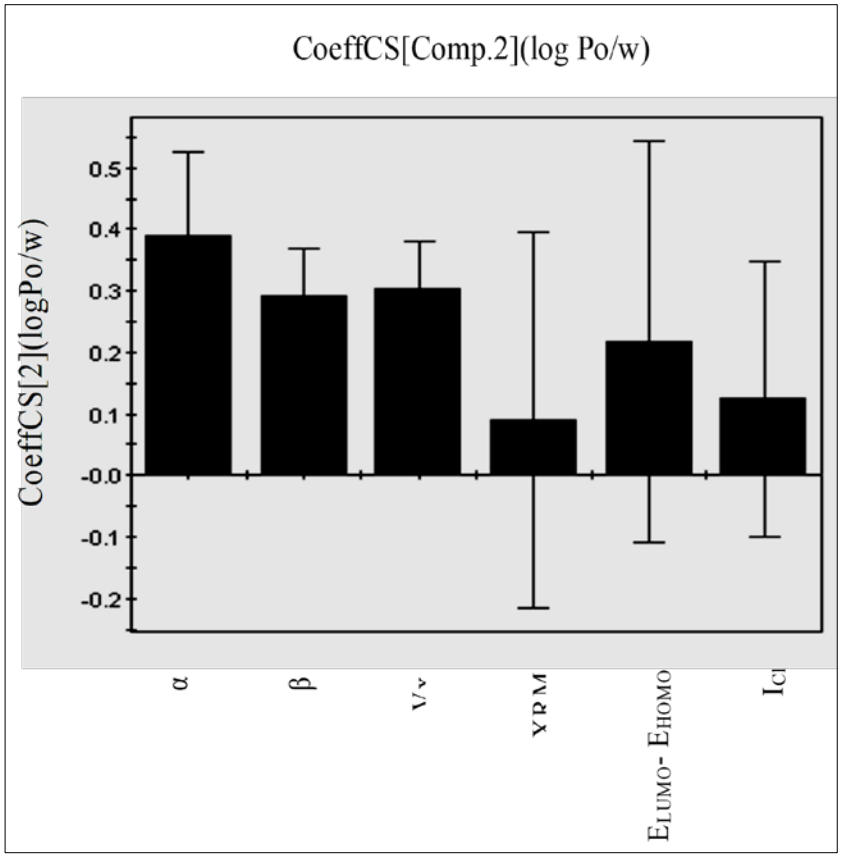

Fig 2: Coefficent plot for PLS model II derives from 10 hydroxamic acids and 6 descriptors based on the 2th component.

The first PLS component is mainly related to Vx, α and β. Increasing Vx, α and β values of hydroxamic acids leads to increase in $logP_{O/W}$ values.

The second PLS component is loaded primarily on I_{Cl}, E_{HOMO}-E_{LUMO} and XMR. As indicated by pseudo-regression coefficient, increasing value of I_{Cl}, E_{HOMO}-E_{LUMO} and XMR lead to increase in $logP_{O/W}$ values of hydroxamic acids. The VIPs and PLS weight of model I and model II are presented in Table 6 and Table 7, respectively.

Figure 2 is the coefficient plot of the PLS model II. This plot identifies the parameters that contributed most to activity (as reflected by the length of the bar), and the nature of the correlation (direct = positive coefficient or inverse = negative coefficient). Two PLS components were selected in model II. The first PLS component is mainly related to the descriptors Vx, α and β for which the W* [1] value in larger 0.550. The second component is loaded primarily on I_{Cl}, E_{HOMO}-E_{LUMO} and XMR. Figure 3 and 4 shows the plot of prediced $logP_{O/W}$ and obseved $logP_{O/W}$ of model I and Model II, respectively.

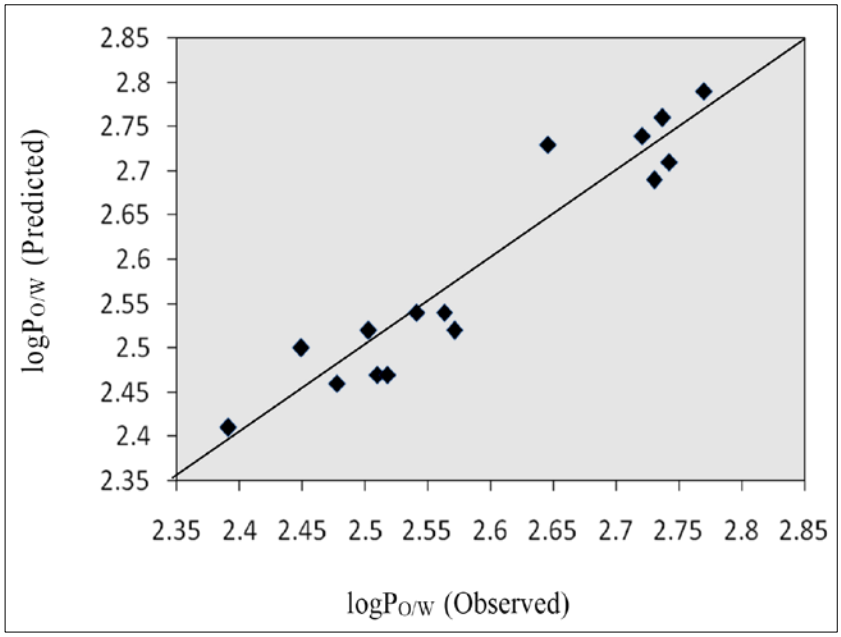

Fig 3: Plot of predicted $logP_{O/W}$ versus $logP_{O/W}$ observed values of hydroxamic acids by model I.

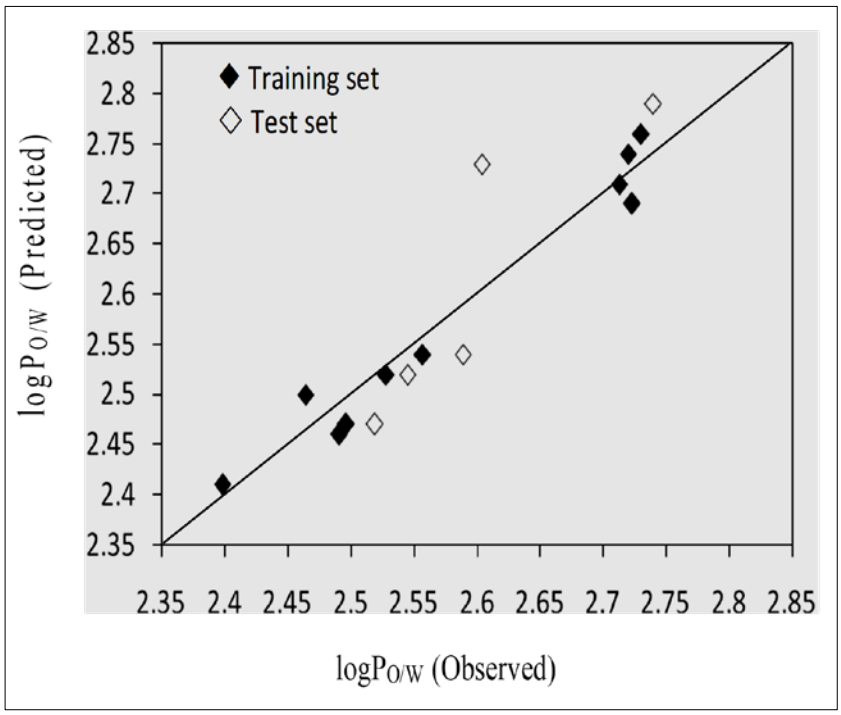

Fig 4: Plot of predicted $logP_{O/W}$ versus $logP_{O/W}$ observed values of hydroxamic Acids by model II.

Conclusion

By partial least squares (PLS) regression, QSPR model reported herein provide interesting insight in understanding the steric, electronic, hydrogen bond parameters and structural requirements of lipophilicity among these set of compounds.

The cross validated Q^2_{cum} values of QSPR model of hydroxamic acids is 0.861 (remarkably higher than 0.500), indicating good predictive-abilities for $logP_{O/W}$ values.

The current studies indicates that increasing values of Vx, α, β, I_{Cl}, E_{HOMO}-E_{LUMO} and XMR leads to increase the lipophilic characters of hydroxamic acids.

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Conflicts of Interest

The authors declare no conflict of interest.

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