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QSPR modeling of the lipophilicity of aziridine derivatives

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ABSTRACT

The paper describes QSPR studies on lipophilicity using a combination of topological indices as well as indicator parameters for a set of 51 derivatives of aziridine. Regression analysis of the data using maximum R^2 method reveals that $^1\chi^v$, $SIC'0'$, $^0\chi$ and ZM2V topological indices along with Cl-atom and N-atom indicator parameters are the best descriptors to be used, for modeling the lipophilicity. The low residual lipophilicity and high cross-validated R^2_{cv} values observed indicated the predictive ability of the developed QSPR models.

Keywords: QSPR, Topological Indices, Lipophilicity, Aziridine derivatives, Regression analysis

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INTRODUCTION

Quantitative Structure-activity relationship and Quantitative Structure-property relationship (QSAR/QSPR) studies are useful tools in the rational search for bioactive molecules. The main success of the QSAR/QSPR method is the possibility to estimate the characteristics of new chemical compounds without the need to synthesize and test them. QSPR models are mathematical equations relating chemical structure to a wide variety of physical, chemical and biological properties [1]. (QSPR/QSAR) represents an attempt to relate structural descriptors of molecules with their physicochemical properties and biological activities [2]. The lipophilicity expressed by the logarithmic partition coefficient (logP) is a very important physicochemical parameter which describes a partitioning equilibrium of solute molecules between water and an immiscible organic solvent [3-5]. Lipophilicity is an important endpoint used extensively in medicinal chemistry, drug design, pharmacy and enviroenmental toxicity in predicting biological and hazardous effect of organic compounds [6]. Lipophilicity can be determined either from the costly and time consuming experiments or from the approximate empirical formula with limited reliability [7]. However, the objective of the present study is not to introduce another method for the determination of logP, but to use topological indices for predicting lipophilicity (logP) of a series of Spiro-2-[3'-(2-phenyl)-3H-indolyl]-1-aryl-3-phenyl aziridines. It is interesting to record that the partitioning of organic compounds acting as drugs between aqueous and lipophilic phase is important for drug potency. No other physicochemical property has attracted as much interest in QSPR studies as lipophilicity. The use of topological indices in the modeling of lipophilicity is an important stage in QSPR studies. In the present work a large set of topological indices has been used. The basic assumption in the present work is that the lipophilicity (logP) value of the compounds can be related to their topological indices as a multilinear function. QSPR analysis was conducted to investigate the quantitative effect of structural properties of the compounds on their lipophilicity. In the present QSPR study, the topological indices and structural indicators are used as structural descriptors for 51derivatives of Spiro-2-[3'-(2-phenyl)-3H-indolyl]-1-aryl-3-phenyl aziridines [8] for modeling of lipophilicity.

MATERIALS AND METHODS

ClogP: The value of ClogP is calculated using Chem-Office Software version 8 for the set of 51 derivatives of aziridine

Topological Indices:
For modeling the lipophilicity following topological indices are used. The topological indices SIC$^{'}0^{'}$ (Structural Information Content of '0' Order),[9] $^{1}\chi^{v}$ (Valence Connectivity Index Chi-1)[10,11], $^{0}\chi$ (Connectivity Index Chi-0)[12] and ZM2V (Second Zagreb Index By Valence Vertex Degrees)[13] employed in the present study were calculated using hydrogen suppressed graph [14-16] of the compounds used. Such molecular graphs are obtained by deleting all the hydrogen atoms present in the structure.

Indicator Parameters:
Two different indicator parameters have been used to understand the impact of electronegative atom on the lipophilicity of the compounds. Indicator parameter Cl-atom accounts for the number of chlorine atom and N-atom accounts for the number of nitrogen atoms in the molecule.

Statistical Analysis:
The maximum R^2 improvement method [17] was used to propose statistically significant model and to identify prediction models. The regression analysis was performed by SPSS software.

Cross validation:
Cross-validation parameters which have been estimated are given in **Table-3** and are described below. Indication of the performance of the model is obtained from the cross-validation correlation coefficient R^2_{cv}, which is defined as:

$$R^2_{cv} = 1 - \frac{PRESS}{SSY}$$

PRESS (predicted residual errors sum of squares) is the sum of squared difference between actual and the predicted when the compound is omitted from the fitting process.

$$PRESS = \sum(Y_{cal} - Y_{pre.})^2$$

Uncertainty of Prediction

$$S_{PRESS} = \sqrt{\frac{PRESS}{(N-k-1)}}$$

The lower value of S_{press} indicates better model.

Predictive Square Error

$$PSE = \sqrt{\frac{PRESS}{N}}$$

The lower value of PSE indicates better model.

Quality factor

$$Q = \frac{R}{SEE}$$

Higher value of quality factor (Q) indicates better predictivity of model.

Sum of square of response values (SSY)

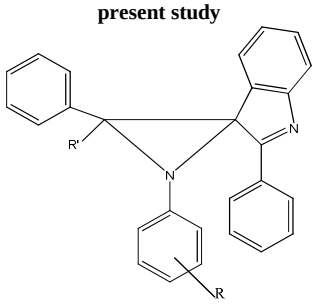
$$SSY = \sum(Y_{cal} - Y_{mean})^2$$

'SSY' suggests the overall predictive performance.

RESULTS AND DISCUSSION

The topological indices $^{1}\chi^{v}$, SIC $^{'}0^{'}$, $^{0}\chi$ and ZM2V along with structural indicators (Cl-atom and N-atom) used for Spiro-2-[3'-(2-phenyl)-3H-indolyl]-1-aryl-3-phenyl aziridines derivatives are given in **Table-1**. The table also records the log P and the position of substituents (R)and (R') on the compound.

Table-1: Structural variations, calculated lipophilicity value, structural indicator and topological indices for the compounds used in the present study



Compound	ClogP	R	R'	$^{1}\chi^{v}$	Cl-atom	SIC '0'	N-atom	$^{0}\chi$	ZM2V
1	6.3648	H	H	10.02	0	2.21	2	19.26	414.0
2	7.2482	2-Cl	H	10.11	1	3.23	2	20.13	449.0
3	7.2482	3-Cl	H	10.11	1	3.23	2	20.13	448.0
4	7.2482	4-Cl	H	10.11	1	3.23	2	20.13	448.0
5	5.697	2-OH	H	10.15	0	3.23	2	20.13	441.0
6	5.6974	3-OH	H	10.19	0	3.23	2	20.13	440.0
7	5.6974	4-OH	H	10.19	0	3.23	2	20.13	440.0
8	6.3871	2-OCH_3	H	10.47	0	3.21	2	20.84	451.0
9	6.3871	3-OCH_3	H	10.53	0	3.21	2	20.84	450.0
10	6.4734	2-NO_2	H	10.45	0	3.25	3	21.7	501.0
11	6.4734	3-NO_2	H	10.51	0	3.25	3	21.7	500.0
12	6.4734	4-NO_2	H	10.51	0	3.25	3	21.7	500.0
13	6.3026	2-COOH	H	10.54	0	3.24	2	21.7	481.0
14	6.3026	3-COOH	H	10.6	0	3.24	2	21.7	480.0
15	6.8634	2-CH_3	H	10.43	0	2.2	2	20.13	425.0
16	6.8634	3-CH_3	H	10.47	0	2.2	2	20.13	424.0
17	6.8634	4-CH_3	H	10.47	0	2.2	2	20.13	424.0
18	6.8834	H	CH_3	10.41	0	2.2	2	20.18	431.0
19	7.7672	2-Cl	CH_3	10.5	1	3.22	2	21.04	466.0
20	7.7672	3-Cl	CH_3	10.54	1	3.22	2	21.04	465.0
21	7.7672	4-Cl	CH_3	10.54	1	3.22	2	21.04	465.0
22	6.2164	2-OH	CH_3	10.55	0	3.22	2	21.04	458.0
23	6.2164	3-OH	CH_3	10.55	0	3.22	2	21.04	457.0
24	6.2164	4-OH	CH_3	10.55	0	3.22	2	21.04	457.0
25	6.9061	2-OCH_3	CH_3	10.92	0	2.22	2	21.75	468.0
26	6.9061	3-OCH_3	CH_3	10.92	0	2.22	2	21.75	467.0
27	6.9924	2-NO_2	CH_3	10.91	0	3.25	3	22.62	518.0
28	6.9924	3-NO_2	CH_3	10.9	0	3.25	3	22.62	517.0
29	6.9924	4-NO_2	CH_3	10.9	0	3.25	3	22.62	517.0
30	6.8216	2-COOH	CH_3	11	0	3.24	2	22.62	498.0
31	6.8216	3-COOH	CH_3	10.9	0	3.24	2	22.62	497.0
32	7.3824	2-CH_3	CH_3	10.82	0	2.2	2	21.04	442.0
33	7.3824	3-CH_3	CH_3	10.86	0	2.2	2	21.04	441.0
34	7.3824	4-CH_3	CH_3	10.86	0	2.2	2	21.04	441.0
35	7.3824	H	C_6H_5	12.07	0	2.19	2	23.28	503.0
36	8.8062	2-Cl	C_6H_5	12.17	1	3.21	2	24.16	538.0
37	8.8062	3-Cl	C_6H_5	12.21	1	3.21	2	24.16	537.0
38	8.8062	4-Cl	C_6H_5	12.21	1	3.21	2	24.16	537.0
39	7.2554	2-OH	C_6H_5	12.22	0	3.21	2	24.16	530.0
40	7.2554	3-OH	C_6H_5	12.21	0	3.21	2	24.16	529.0
41	7.2554	4-OH	C_6H_5	12.21	0	3.21	2	24.16	529.0
42	7.9451	2-OCH_3	C_6H_5	12.59	0	3.21	2	24.86	540.0
43	7.9451	3-OCH_3	C_6H_5	12.58	0	3.21	2	24.86	539.0
44	8.0314	2-NO_2	C_6H_5	12.58	0	3.23	3	25.74	590.0
45	8.0314	3-NO_2	C_6H_5	12.57	0	3.23	3	25.74	589.0
46	8.0314	4-NO_2	C_6H_5	12.57	0	3.23	3	25.74	589.0
47	7.8606	2-COOH	C_6H_5	12.67	0	3.22	2	25.74	570.0
48	7.8606	3-COOH	C_6H_5	12.66	0	3.22	2	25.74	569.0
49	8.4214	2-CH_3	C_6H_5	12.49	0	2.19	2	24.16	514.0
50	8.4214	3-CH_3	C_6H_5	12.53	0	2.19	2	24.16	513.0
51	8.4214	4-CH_3	C_6H_5	12.53	0	2.19	2	24.16	513.0

The topological indices are numerical representation of molecular structure. They are obtained by transforming molecular structure into its molecular graph *via* mathematical expression. Such transformation is carried out by deleting all the carbon-hydrogen as well as heteroatom hydrogen bonds in the molecular structure. In chemical graph theory and topology, atoms are treated as vertices and the bonds as edges, when certain conditions are imposed on vertices, edges or both, a number is obtained which is called the topological index. Such topological indices are used in the modeling of physico-chemical properties, biological activity and toxicity of organic compounds [18-20]. The examination of inter-correlations among molecular descriptors used and their correlation with lipophilicity to be modeled by regression analysis is the basic requirement to use the maximum-R^2 method. The correlation matrix obtained in the present study is given in **Table-2**.

Table-2: Intercorrelation matrix of structural descriptors for proposed model 5

	ClogP	$^1\chi^v$	Cl-atom	SIC '0'	N-atom	$^0\chi$	ZM2V
ClogP	1						
$^1\chi^v$	0.760	1					
Cl-atom	0.432	-0.113	1				
SIC '0'	-0.112	0.013	0.278	1			
N-atom	-0.012	0.078	-0.214	0.301	1		
$^0\chi$	0.688	0.960	-0.121	0.215	0.265	1	
ZM2V	0.611	0.861	-0.054	0.394	0.454	0.964	1

A perusal of **Table-2** shows that none of the topological indices correlate with ClogP singly to yield one variable model, i.e. no statistically significant mono-parametric model is possible for modeling the lipophilicity (ClogP). Thus, it can be concluded that stepwise multivariate regression analysis is required to obtain the statistically significant model. The aforementioned results show that out of the set of topological indices used by us, the indices $^1\chi^v$, SIC'0', $^0\chi$, ZM2V and the indicator parameters, are the better parameters for modeling lipophilicity. In order to justify the occurrence of highly correlated parameters in the proposed models we have used the recommendations made by Randic [21] wherein, highly intercorrelated descriptors can be used in multi-parametric correlations. The simple reason is that molecular descriptors carry different structural information. By discarding one of the descriptors, which commonly duplicates another, we may be discarding a descriptor that nevertheless may carry useful structural information in the parts in which it does not parallel with the other descriptors. Thus, as suggested by Randic we may safely say that $^1\chi^v$ and any other descriptor in combination with this is allowed statistically. For the modeling of lipophilicity, we have used maximum R^2 method in forward direction and finally obtained statistically significant models. The results show that a bi-parametric regression model containing $^1\chi^v$, Cl-atom, gave the best results. This model is found as:

$$\text{ClogP} = -1.054(\pm 0.562) + 0.720(\pm 0.050)*{}^1\chi^V + 1.11(\pm 0.120)*\text{Cl-atom} \quad (1)$$

$R = 0.921$, $R^2 = 0.848$, $R^2_{adj} = 0.841$, SE= 0.3249, F= 133.677, K= 2

Here, K is the number of topological invariants used in the regression, SE is the standard error of estimation, R is the correlation coefficient, R^2 is the squared correlation coefficient, R^2_{adj} is the adjustable R^2, F is the F-statics and the figures within the parenthesis are the standard error values of the coefficient.

Addition of parameter SIC'0' during the stepwise regression analysis yielded a tri parametric regression expression with improved statistics. No other tri-parametric model was found better than this model. This model is given as below:

$$\text{ClogP} = 0.301(\pm 0.440) + 0.732(\pm 0.035)*{}^1\chi^V + 1.285(\pm 0.088)*\text{Cl-atom} - 0.51(\pm 0.073)*\text{SIC'0'} \quad (2)$$

$R = 0.962$, $R^2 = 0.926$, $R^2_{adj} = 0.921$, SE= 0.2290, F= 195.967, K= 3

The significant improvement in the statistics indicates its favorable role in the modeling of lipophilicity. When N-atom indicator parameter is added to eqn. **3**, great improvement was observed in the statistics, no other topological index yields such an improvement in the statistics. Resulted tetra-parametric model is given below:

$$\text{ClogP} = -0.106(\pm 0.374) + 0.726(\pm 0.029)*{}^1\chi^V + 1.402(\pm 0.077)*\text{Cl-atom} - 0.633(\pm 0.065)*\text{SIC '0'} + 0.368(\pm 0.077)*\text{N-atom} \quad (3)$$

$R = 0.975$, $R^2 = 0.950$, $R^2_{adj} = 0.946$, SE= 0.1895, F= 220.291, K= 4

Looking into such an excellent result further regression analysis was not needed. But, with a hope of obtaining still better results, we have carried out several penta-parametric regression analyses. When $^{0}\chi$ is added to equation **3**, great improvement was observed in the statistics, the resulted penta-parametric model is given below:

ClogP = 0.442(± .464) + 0.357(± 0.196)*$^{1}\chi^{V}$ + 1.435(± 0.077)*Cl-atom – 0.769(± 0.096)*SIC $^{'}0^{'}$ + 0.243(± 0.100)*N-atom + 0.190(± 0.100)*$^{0}\chi$ (4)

R = 0.977, R^2 = 0.954, R^2_{adj} = 0.949, SE= 0.1843, F= 186.960, K= 5

Successive regression analysis resulted into a hexa-parametric model having the best statistics than those described above. This model contained $1\chi^{V}$, Cl-atom, SIC $^{'}0^{'}$, N-atom, $^{0}\chi$, and ZM2V as correlating parameters. The model, thus obtained, was excellent and is given below:

ClogP = – 3.474(± 0.509) – 0.264(± 0.135)*$^{1}\chi^{V}$ + 1.850(± 0.064)*Cl-atom – 0.343(± 0.073)*SIC $^{'}0^{'}$ + 1.209(± 0.121)*N-atom + 1.601(± 0.165)*$^{0}\chi$ – 0.049(± 0.005)*ZM2V (5)

R = 0.992, R^2 = 0.984, R^2_{adj} = 0.982, SE= 0.1094, F= 456.173, K= 6

The parameters contributing to model **5** have both, positive as well as negative contribution in the modeling of lipophilicity. For this model the R^2 value comes out to be 0.984 indicating that this model explains 98.4% variance of the lipophilicity. The initial statistics SE, R, R^2_{adj} and F indicate that the model described by eqn.5 is superior than the other proposed models (eqns.**1**, **2**, **3**, & **4**)

It is interesting to record that in all the models discussed above, the positive sign associated with structural descriptors indicate their positive role towards lipophilicity and negative sign associated with structural descriptors indicate their negative role towards lipophilicity. The predictive potency of the models is the establishment from cross validation analysis using the various cross validation parameters like PRESS (predicted residual sum of squares) S_{PRESS} (uncertainty of prediction) and PSE (Predictive square error)[17]

The predictive power, as determined by the pogliani Q parameter [22,23] for the model expressed by equation **5** (Q = 9.0676) confirms that this model has excellent statistics as well as excellent predictive power. Final support in favor of our findings is obtained by using the cross-validation method. The calculated cross-validation parameters for each of the models are discussed below.

For the model **5**, the value of Q is 9.0676, which is greater than other proposed model expressed by equations **1**, **2**, **3** & **4**.

PRESS is a good estimate of the real prediction error of the model. If PRESS is smaller than the model predicts better and can be considered statistically significant [24]. In this regard, the model **5** is the best one. S_{press} is another cross-validation parameter and is a measure of uncertainty of prediction. The lowest value of S_{PRESS} for the model **5** supports its highest predictive potential. PSE (predicted square error) is more directly related to uncertainty of prediction. The lowest value of PSE for the model **5** supports its highest predictive potential. For a model, PRESS/SSY should be smaller than 0.4 [25]. In our case the ratio PRESS/SSY ranges between 0.0167-0.1522 indicating all the proposed models are reliable QSPR models.

Table-3: Cross-validation parameters for the proposed models

Model	Parameter Used	PRESS	S_{PRESS}	PSE	Q	R^2_{CV}	PRESS/SSY	SSY
1	$^{1}\chi^{V}$, Cl-atom	5.0691	0.3249	0.3152	2.8347	0.8478	0.1522	33.297
2	$^{1}\chi^{V}$, Cl-atom, SIC $^{'}0^{'}$	2.4650	0.2290	0.2198	4.2008	0.9260	0.0740	33.297
3	$^{1}\chi^{V}$, Cl-atom, SIC $^{'}0^{'}$,N-atom	1.6520	0.1895	0.1799	5.1451	0.9504	0.0496	33.297
4	$^{1}\chi^{V}$, Cl-atom, SIC $^{'}0^{'}$,N-atom, $^{0}\chi$	1.5335	0.1843	0.1734	6.3011	0.9540	0.0460	33.297
5	$^{1}\chi^{V}$, Cl-atom, SIC $^{'}0^{'}$, N-atom,$^{0}\chi$, ZM2V	0.5582	0.1126	0.1046	9.0676	0.9833	0.0167	33.297

In order to confirm our findings, we have predicted the lipophilicity from models expressed by eqns. **4** & 5 which are discussed above. The predicted lipophilicities are then compared with their calculated values. Such a comparison is shown in **Table-4**. The difference between calculated and predicted lipophilicity (residue) is the least for the model expressed by eq. **5**, showing it to be the most appropriate model for modeling the lipophilicity of the present set of compounds.

Table-4: ClogP and Predicted logP values of Spiro-2-[3'-(2-phenyl)-3H-indolyl]-1-aryl-3-phenyl aziridine analogues derived from the regression eqns. 4 & 5.

Compound	ClogP	Predicted logP		Residual	
		Eq.4	Eq.5	Eq.4	Eq.5
1	6.3648	6.46505	6.08995	-0.10025	0.27485
2	7.2482	7.3131	7.2442	-0.0649	0.004
3	7.2482	7.3131	7.2932	-0.0649	-0.045
4	7.2482	7.3131	7.2932	-0.0649	-0.045
5	5.697	5.89238	5.77564	-0.19538	-0.07864
6	5.6974	5.90666	5.81408	-0.20926	-0.11668
7	5.6974	5.90666	5.81408	-0.20926	-0.11668
8	6.3871	6.1569	6.34473	0.2302	0.04237
9	6.3871	6.17832	6.37789	0.20878	0.00921
10	6.4734	6.5254	6.47215	-0.052	0.00125
11	6.4734	6.54682	6.50531	-0.07342	-0.03191
12	6.4734	6.54682	6.50531	-0.07342	-0.03191
13	6.3026	6.32222	6.22282	-0.01962	0.07978
14	6.3026	6.34364	6.25598	-0.04104	0.04662
15	6.8634	6.78441	6.83901	0.07899	0.02439
16	6.8634	6.79869	6.87745	0.06471	-0.01405
17	6.8634	6.79869	6.87745	0.06471	-0.01405
18	6.8834	6.78677	6.63034	0.09663	0.25306
19	7.7672	7.63292	7.76858	0.13428	-0.00138
20	7.7672	7.6472	7.80702	0.12	-0.03982
21	7.7672	7.6472	7.80702	0.12	-0.03982
22	6.2164	6.21577	6.29738	0.00063	-0.08098
23	6.2164	6.21577	6.34638	0.00063	-0.12998
24	6.2164	6.21577	6.34638	0.00063	-0.12998
25	6.9061	7.25176	7.18941	-0.34566	-0.28331
26	6.9061	7.25176	7.23841	-0.34566	-0.33231
27	6.9924	6.86442	6.99063	0.12798	0.00177
28	6.9924	6.86085	7.04227	0.13155	-0.04987
29	6.9924	6.86085	7.04227	0.13155	-0.04987
30	6.8216	6.66124	6.7413	0.16036	0.0803
31	6.8216	6.62554	6.8167	0.19606	0.0049
32	7.3824	7.09654	7.35996	0.28586	0.02244
33	7.3824	7.11082	7.3984	0.27158	-0.016
34	7.3824	7.11082	7.3984	0.27158	-0.016
35	7.3824	7.97608	7.63063	-0.59368	-0.24823
36	8.8062	8.8296	8.79825	-0.0234	0.00795
37	8.8062	8.84388	8.83669	-0.03768	-0.03049
38	8.8062	8.84388	8.83669	-0.03768	-0.03049
39	7.2554	7.41245	7.32705	-0.15705	-0.07165
40	7.2554	7.40888	7.37869	-0.15348	-0.12329
41	7.2554	7.40888	7.37869	-0.15348	-0.12329
42	7.9451	7.67754	7.86007	0.26756	0.08503
43	7.9451	7.67397	7.91171	0.27113	0.03339
44	8.0314	8.06879	8.02373	-0.03739	0.00767
45	8.0314	8.06522	8.07537	-0.03382	-0.04397
46	8.0314	8.06522	8.07537	-0.03382	-0.04397
47	7.8606	7.86561	7.7744	-0.00501	0.0862
48	7.8606	7.86204	7.82604	-0.00144	0.03456
49	8.4214	8.29322	8.38963	0.12818	0.03177
50	8.4214	8.3075	8.42807	0.1139	-0.00667
51	8.4214	6.46505	8.42807	0.1139	-0.00667

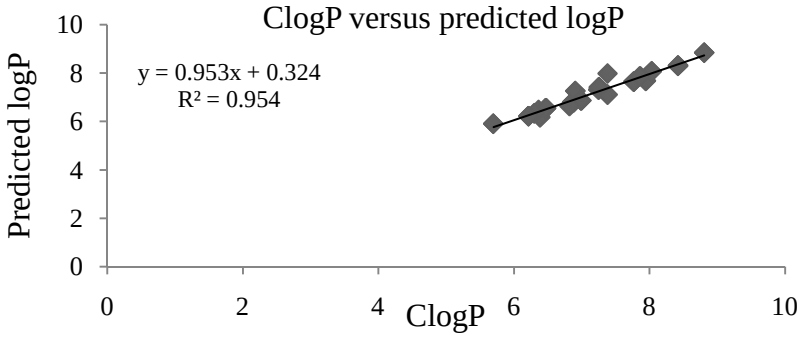


Figure-1:Correlation between calculated and predicted lipophilicity of 51 derivatives of Spiro-2-[3'-(2-phenyl)-3H-indolyl]-1-aryl-3-phenyl aziridine using equation 4.

In order to examine the relative potential of the proposed models we have further estimated their predictive correlation coefficients ($R^2_{pred.}$) by plotting graphs between calculated and predicted lipophilicity values using equations **4** and **5**. Such correlations are shown in Fig. **1** and **2** respectively. From figures **1** and **2** the $R^2_{pred.}$ values are found as 0.954 and 0.984, respectively, for the models expressed by eqns. **4** and **5**. This finally confirms that the model expressed by eq. **5** has the best predictive potential.

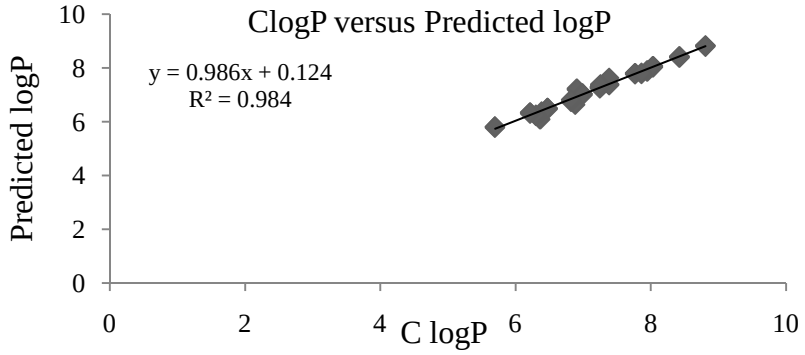


Figure-2: Correlation between calculated and predicted lipophilicity of 51 derivatives of Spiro- 2-[3'-(2-phenyl)-3H-indolyl]-1-aryl-3-phenyl aziridine using equation 5.

CONCLUSION

The lipophilicity of aziridine derivatives can be modeled using topological indices along with indicator parameter. The model constituted by the $^1\chi^v$, SIC $^{'}0^{'}$, $^0\chi$, ZM2V as molecular descriptors and Cl-atom, N-atom as Indicator parameter is the best model having best ability to predict the lipophilicity expressed as ClogP of the aziridine. The use of structural indicators, based on the number of electronegative atoms, gave better results with topological indices and thus elaborated the role of electronegative atoms in the modeling of lipophilicity. From the results, as discussed above, it is concluded that the model obtained by combination of topological indices and structural indicators have better quality and predictivity. The predictive power of the model is 98.4% meaning thereby, that it could explain 98% variance of the data.

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