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QSPR Evidences for Topological Indices to Mimic Lipophilicity of Thia and Aza-Crown Ethers

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QSPR study on a large set of thia and aza crown ethers has been carried out for the modelling of lipophilicity, using topological indces. The stepwise multilinear regression analysis of the data has indicated that an excellent model is obtained when these topological indices are combined with some structural indcators. The obtained models are critically discussed and examined by various types of cross validation parameters.

Key Words: QSPR, Topological indices, Lipophilicity, Crown ether.

INTRODUCTION

Lipophilicity is livingston point used extensively in medicinal chemistry, pharmaceutical, agriculture chemistry and environment toxicity to predict biological and hazardous effects of chemicals[1]. No other physico-chemical property has attracted as much interest in quantitative strucutre property relationship studies (QSPR) as lipophilicity.

The lipophilicity of crown ether has very much importance in transportation, extraction and separation studies. Drug action, pharmacology and phase catalysis studies also deals with the partitioning attitude of crown ether compounds in lipophilic and aqueous phase[2]. The use of topological indices and structural indicators in the modelling of lipophilicity is an important stage in QSPR studies. We have used a large set of topological indices Zm^2V^3, ($^2\chi^V$, $^0\chi$ and $^1\chi^V$)[4,5], SPI[6], (BIC'0', AAC and IVDM)[7], HyWt[8] and sulphur, nitrogen, oxygen atoms as structural indicators. The basic assumption in the present work is that the lipophilicity (log P) value of the compounds can be related to their structural descriptors as a multilinear function. In the present QSPR study, the topological indices and structural indicators are used as structural descriptors for 48 thia- and aza-crown ethers for the modelling of lipophilicity study.

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EXPERIMENTAL

C log P: The value of C log P is calculated using ORISIS computer software for the set of 48 thia- and aza-crown ethers.

Topological indices: Zagreb valence vertex degree index (Zm^2V)[3], connectivity indices ($^2\chi^V$, $^0\chi$ and $^1\chi^V$)[4,5], suprependentic index (SPI)[6], bond information content index of '0' order (BIC'0')[7], mean information index of atomic composition (AAC)[7], mean information content on the vertex degree magnitude (IVDM)[17] and Hyper-Detour index (HyWt)[8] used in the present investigation were calculated by using all hydrogen suppressed topological graphs of thia- and aza-crown ethers.

Indicator parameters: In present study three different indicator parameters are used to understand the impact of number of electronegative atoms on their property. Indicator parameter S-atom accounting for number of sulphur atoms, O-atom accounting for number of oxygen atoms and N-atom accounting for number of nitrogen atoms in the compound. They assume only numerical value of the number of atoms present in the structure.

Statistical analysis: The regression analysis was performed using maximum-R^2 method in forward direction by the SPSS software.

Cross validation: The models having the best correlation potential need not to have the best predictive value too. As opposed to traditional regression method, the cross-validation method evaluates the validity of a model by how well it predicts data rather than how well it fits data. We have estimated cross-validation parameters, which are presented in Table-3 and meanings of some are given below. Indication of the performance of the model is obtained from the cross-validated 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 the actual and the predicted when the compound is omitted from the fitting process.

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

In addition to PRESS and R^2_{cv}, some parameters are also needed to evaluated the quality factor (Q). Uncertainty of prediction (S_{PRESS}) Root mean square errors (RMS) and predictive square error (PSE) are needed to decide predictive potential of the proposed models. The calculation of these parameters are available in the literature, therefore the details are not given here.

RESULTS AND DISCUSSION

Present results, as discussed below, establish that out objective is highly fulfilled. For a set of 48 thia and aza crown ethers we obtained good predictve models[10].

The value of calculated lipophilicity (C log P) and topological indices along with structural indicators used are also summarized in Table-1.

TABLE-1
STRUCTURAL DETAILS, CALCULATED LIPOPHILICITY VALUE, TOPOLOGICAL INDICES AND STRUCTURAL INDICATORS FOR COMPOUNDS

Compd. No.	Compounds structure	C log P	S-atom	Zm^2V	$^2\chi^V$	$^0\chi$	BIC'0'	SPI	N-atom	AAC	O-atom	$^1\chi^V$	IVDM	HyWt
1	1,4,7-Dioxathionane	1.057	1	62	3.062	6.364	0.344	3.0	0	1.51	2	4.387	3.17	900
2	1,4,7-Trithionane	2.555	3	20	5.511	6.364	0.314	3.0	0	1.38	0	6.696	3.17	900
3	1,4,8,11-Tetrathioacyclotetradecane	4.168	4	34	8.056	9.899	0.262	3.7	0	1.33	0	9.928	3.81	5390
4	1,4,8,11-Tetrathioacyclotetradecan-6-ol	3.154	4	53	8.131	10.770	0.289	8.0	0	1.48	1	10.003	3.88	6307
5	1,9-Dioxa-5,13-dithiacyclohexadecane	3.598	2	85	6.313	11.314	0.262	4.0	0	1.39	2	8.619	4.00	9248
6	1,5,9,13-Tetrathiacyclohexadecane	5.096	4	42	8.763	11.314	0.243	4.0	0	1.29	0	10.928	4.00	9248
7	1,4,7,10,13-Pentaoxa-16-thiacyclooctadecane	0.865	1	146	4.899	12.728	0.273	4.2	0	1.47	5	7.619	4.17	14877
8	1,4,7,10-Tetraoxa-13,16-dithiacyclooctadecane	1.614	2	125	6.124	12.728	0.280	4.2	0	1.51	4	8.774	4.17	14877
9	1,4,7,13-Tetraoxa-10,16-dithiacyclooctadecane	1.613	2	125	6.124	12.728	0.280	4.2	0	1.51	4	8.774	4.17	14877
10	1,4-Dioxa-10,13-dithia-7,16-diazacyclooctadecane	0.673	2	109	6.399	12.728	0.287	4.2	2	1.57	2	9.033	4.17	14877
11	1,4,10,13-Tetraoxa-7,16-dithiacyclooctadecane	1.614	2	125	6.124	12.728	0.280	4.2	0	1.51	4	8.774	4.17	14877
12	1,4,7-Trioxa-10,13,16-trithiacyclooctadecane	2.363	3	104	7.348	12.728	0.280	4.2	0	1.52	3	9.928	4.17	14877
13	1,10-Dioxa-4,7,13,16-tetrathiacyclooctadecane	3.122	4	82	8.730	12.728	0.280	4.2	0	1.51	2	11.083	4.17	14877
14	1,4,10,13-Tetrathia-7,16-diazacyclooctadecane	2.172	4	66	8.848	12.728	0.271	4.2	2	1.48	0	11.342	4.17	14877
15	1,4,7,10,13,16-Hexathiacyclooctadecane	4.610	6	40	11.03	12.728	0.256	4.2	0	1.38	0	13.392	4.17	14877
16	2,3,5,6,8,9-Hexahydro-1,10,4,7-benzodioxadithiacyclododecine	3.136	2	156	5.818	11.054	0.296	4.0	0	1.53	2	7.777	4.37	9909
17	1,4-Dithia-7,10,13-triazacyclopentadecane	0.268	2	116	3.470	10.600	0.280	3.9	3	1.46	0	5.780	3.90	7140
18	1,4,10-Trithia-7,13-diazacyclopentadecane	1.487	3	124	3.340	10.600	0.280	3.9	2	1.48	0	5.650	3.90	7140
19	1-Oxa-4,13-dithia-7,10-diazacyclopentadecane	0.738	2	124	3.340	10.600	0.300	3.9	2	1.55	1	5.650	3.90	7140
20	1-Oxa-7,10-dithia-4,13-diazacyclopentadecane	0.737	2	124	3.340	10.600	0.300	3.9	2	1.55	1	5.650	3.90	7140
21	6-Oxa-3,9-dithia-15-azabicyclo[9.3.1]pentadeca-1(15),11,13-triene	2.311	2	178	2.720	10.347	0.314	3.9	1	1.62	1	4.570	3.89	7141
22	3,6,9-Trithia-15-azabicyclo[9.3.1]pentadeca-1(15),11,13-triene	3.060	3	178	3.220	10.347	0.300	3.9	1	1.52	0	5.130	3.89	7141
23	6-Methyl-3,9-dithia-6,15-diazabicyclo[9.3.1]-pentadeca-1(15),11,13-triene	2.061	2	179	3.980	11.220	0.290	8.4	2	1.50	0	5.630	3.96	8185
24	3,6,9,12-Tetrathia-18-azabicyclo[12.3.1]octadeca-1(18),14,16-triene	3.745	4	206	3.950	12.500	0.280	4.2	1	1.51	0	6.210	4.16	14790
25	6,9-Dioxa-3,12-dithia-18-azabicyclo[12.3.1]-octadeca-1(18),14,16-triene	2.247	2	206	3.950	12.500	0.300	4.2	1	1.62	2	6.210	4.16	14790
26	6,9,12-Trioxa-3,15-dithia-21-azabicyclo[15.3.1]-henicosa-1(21)17,19-triene	2.183	2	234	4.560	14.590	0.290	4.6	1	1.61	3	7.290	4.38	27302

27	3,6,9,12,15-Pentaoxa-21-azabicyclo[15.3.1]-henicosa-1(21)17,19-triene	0.572	0	234	4.560	14.590	0.270	4.6	1	1.50	5	7.290	4.38	27302
28	7-Methyl-3,11,17-triazabicyclo[11.3.1]heptadeca-1(17),13,15-triene-2,12-dione	2.773	0	251	4.930	14.370	0.300	37.6	3	1.51	2	6.890	4.20	16700
29	5-Oxa-2,8-dithia-13-azabicyclo[7.3.1]trideca-1(13),9,11-triene	2.157	2	186	2.600	8.900	0.370	3.6	1	1.73	1	4.200	3.68	4032
30	5,8-Dioxa-2,11-dithia-16-azabicyclo[10.3.1]-hexadeca-1(16),12,14-triene	2.093	2	196	3.630	11.050	0.340	4.0	1	1.71	2	5.790	3.98	9255
31	2,5,8,11-Tetraoxa-16-azabicyclo[10.3.1]-hexadeca-1(16),12,14-triene	1.516	0	196	3.630	11.050	0.311	4.0	1	1.58	4	5.790	3.98	9255
32	(3S)-3-Methyl-2,5,8,11-tetraoxa-16-azabicyclo-[10.3.1]hexadeca-1(16),12,14-triene	1.919	0	225	3.790	11.900	0.290	8.4	1	1.54	4	5.760	4.05	10577
34	5,8,11-Trioxa-2,14-dithia-19-azabicyclo[13.3.1]-nonadeca-1(19),15,17-triene	2.029	2	242	3.800	13.180	0.320	4.3	1	1.68	3	6.400	4.23	18317
35	2,5,8,11,14-Pentaoxa-19-azabicyclo[13.3.1]-nonadeca-1(19),15,17-triene-16-carbonitrile	1.265	0	285	4.150	14.750	0.300	11.1	2	1.64	5	6.800	4.36	23567
36	2,5,8,11,14,17-Hexaoxa-22-azabicyclo[16.3.1]-docosa-1(22),18,20-triene	1.388	0	270	4.460	15.200	0.270	4.7	1	1.53	6	7.490	4.45	32906
37	2,5,8,11,14,17-Hexaoxa-22-azabicyclo[16.3.1]-docosa-1(22),18,20-triene-19-carbonitrile	1.610	0	313	4.780	16.870	0.270	12.6	2	1.62	6	7.880	4.56	40854
38	3,6,7,10-Tetrathia-16-azabicyclo[10.3.1]hexadeca-1(16),12,14-triene	1.251	4	214	3.370	11.100	0.320	4.0	1	1.58	0	5.297	3.98	9255
39	3,11-Dithia-17-azatricyclo[11.3.1.15,9]octadeca-1(17),5(18),6,8,13,15-hexaene	2.880	2	244	4.230	12.200	0.290	4.2	2	1.54	0	5.900	4.15	14569
40	3,11-Dithia-17-azatricyclo[11.3.1.15,9]octadeca-1(17),5(18),6,8,13,15-hexaene	3.749	2	228	4.410	12.200	0.270	4.2	1	1.43	0	6.080	4.15	14569
41	18-Fluoro-3,11-dithia-17-azatricyclo[11.3.1.15,9]-octadeca-1(17)5(18),6,8,13,15-hexaene	3.808	2	264	4.500	13.080	0.310	9.0	1	1.59	0	6.190	4.20	16715
42	3,6,14,17-Tetrathia-23,24-diazatricyclo[17.3.1.18,12]tetracosa-1(23),8(24),9,11,19,21-hexaene	4.250	4	300	5.450	16.400	0.270	4.9	2	1.54	0	8.100	4.56	45501
43	3,6,14,17-Tetraoxa-23,24-diazatricyclo[17.3.1.18,12]tetracosa-1(23),8(24),9,11,19,21-hexaene	10.029	0	300	5.450	16.400	0.270	4.9	2	1.54	4	8.100	4.56	45501
45	2,5,11,14-Tetraoxa-19,20-diazatricyclo-[13.3.1.1^{6,11}]icosa-1(19),6(20),7,9,15,17-hexaene	2.749	0	316	4.022	13.623	0.307	4.0	2	1.79	4	6.354	4.30	9165
47	2,5,8,14,17,20-Hexaoxa-25,26-diazatricyclo-[19.3.1.1^{10,14}]hexacosa-1(25),9(26),10,12,21,23-hexaene	2.662	0	372	5.247	17.865	0.277	5.1	2	1.61	6	8.508	4.68	62575
48	3,11,14,17-Tetraoxa-23,24-diazatricyclo-[17.3.1.1^{5,10}]tetracosa-1(23),5(24),6,8,19,21-hexaene	1.029	0	300	5.400	16.450	0.270	4.9	2	1.54	4	8.100	4.56	45586

For the modelling of lipophilicity, we have used maximum-R^2 method in forward direction and finally obtained statistically significant models. In the proposed model, k is the number of structural invariants used in the regression, SE is the standard error of estimation, R is the correlation coefficient, R^2adj is the adjustable R^2, F is the F-statics and Q is the quality factor. Additionally, 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), R^2_{cv} (cross validation correlation coefficient) and PSE (predictive square error)[11].

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 used in the modelling of physico-chemical properties, biological activity and toxicity of organic compounds[9,12-17].

The preliminary requirement to use the maximum-R^2 method is to 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
INTERCORRELATIONS MATRIX OF STRUCTURAL DESCRIPTOR FOR PROPOSED MODEL

	C log P	S-atom	HyWt	N-tom	SPI	$^1\chi^V$	O-atom	AAC	$^2\chi^V$	BIC'0'	$^0\chi$	Zm^2v	IVDM
C log P	1.00												
S-atom	0.55	1.00											
HyWt	-0.06	-0.38	1.00										
N-atom	-0.34	-0.41	0.35	1.00									
SPI	0.06	-0.27	0.12	0.38	1.00								
$^1\chi^V$	0.40	0.43	0.23	-0.35	-0.03	1.00							
O-atom	-0.44	-0.75	0.55	0.02	0.09	0.06	1.00						
AAC	-0.31	-0.47	0.21	0.39	0.04	-0.47	0.39	1.00					
$^2\chi^V$	0.49	0.53	0.07	-0.42	-0.03	0.97	-0.11	-0.56	1.00				
BIC'0'	-0.25	-0.15	-0.39	0.04	0.02	-0.68	-0.11	0.62	-0.61	1.00			
$^0\chi$	-0.02	-0.39	0.90	0.40	0.26	0.31	0.59	0.30	0.13	-0.48	1.00		
Zm^2v	-0.15	-0.66	0.69	0.57	0.24	-0.37	0.51	0.66	-0.49	0.08	0.73	1.00	
IVDM	0.02	-0.34	0.81	0.34	0.16	0.31	0.54	0.30	0.15	-0.49	0.96	0.70	1.00

The correlation matrix shows that the topological indices IVDM, $^0\chi$, HyWt, $^2\chi^V$, $^1\chi^V$, IVDM and $^0\chi$ are highly correlated. Thus, a model containing any combination

of these indices may suffer from the defect due to collinearity. To overcome this difficulty we have used the recommendations of Randic[18]. The correlation matrix (Table-2) also shows that none of the molecular descriptors used are capable of modelling lipophilicity independently. Thus, it can be concluded that step-wise multivariate regression analysis is required to obtain the statistically significant models.

Initial multivariate regression analysis indicates that meaningful regression models are obtained when multi parametric regression with eight or more correlating parameters are used. One such eight-parameter model is given below:

$$\text{C log P} = 9.278 + 0.541*\text{S-atom} + 0.025*\text{Zm}^2\text{V} + 0.530*{}^2\chi^V - 0.830*{}^0\chi - 39.700*\text{BIC'0'} + 0.085*\text{SPI} - 0.465*\text{N-atom} + 4.300*\text{AAC} \quad (1)$$

k = 8, SE = 0.555, R = 0.898, R^2adj = 0.767, F = 20.384.

For the aforementioned model, the value of initial statistical parameter is good but not significant for the correlation. Looking to such an excellent result there was no need to attempt for further regression analysis. However, with a hope of obtaining still better results we have carried out several 9-parametric regression analysis and the one yielded significantly improved statistics with addition of O-atom is:

$$\text{C log P} = 6.285 + 0.176*\text{S-atom} + 0.004*\text{Zm}^2\text{V} + 0.098*{}^2\chi^V + 0.169*{}^0\chi - 39.700*\text{BIC'0'} + 0.085*\text{SPI} - 0.465*\text{N-atom} + 4.300*\text{AAC} - 1.226*\text{O-atom} \quad (2)$$

k = 9, SE = 0.527, R = 0.911, R^2adj = 0.790, F = 20.614.

Addition of the parameter ${}^1\chi^V$ druing the stepwise regression analysis yielded a 10-parametric regression expression with improved statistics. No other 10-parametric model was found better than this model. This model is given as below:

$$\text{C log P} = 5.671 - 0.450*\text{S-atom} + 0.035*\text{Zm}^2\text{V} - 2.635*{}^2\chi^V - 1.338*{}^0\chi - 34.459*\text{BIC'0'} + 0.122*\text{SPI} - 1.296*\text{N-atom} + 5.073*\text{AAC} - 1.015*\text{O-atom} + 3.561*{}^1\chi^V \quad (3)$$

k = 10, SE = 0.411, R = 0.948, R^2adj = 0.872, F = 32.934.

The significant improvement in the statistics indicates its favourable role in the modelling of lipophilicity. When IVDM is added to eqn. 4, great improvement was observed in the statistics. No other topological index yields such an improvement in the statistics; the resulted 11-parametric model is given below:

$$\text{C log P} = 5.671 - 0.450*\text{S-atom} + 0.035*\text{Zm}^2\text{V} - 2.635*{}^2\chi^V - 1.338*{}^0\chi - 34.459*\text{BIC'0'} + 0.122*\text{SPI} - 1.296*\text{N-atom} + 5.073*\text{AAC} - 1.015*\text{O-atom} + 3.561*{}^1\chi^V - 2.751*\text{IVDM} \quad (4)$$

k = 11, SE = 0.360, R = 0.962, R^2adj = 0.902, F = 40.364.

Successive regression analysis resulted into a 12-parametric model having the best statistics than those describe above. This model contained S-atom, Zm^2V, ${}^2\chi^V$, ${}^0\chi$, BIC'0', SPI, N-atom, AAC, O-atom, ${}^1\chi^V$, IVDM and HyWt as correlating parameters. The model, thus obtained, was excellent and is given below:

$$C \log P = 11.930 - 0.626*S\text{-atom} + 0.035*Zm^2V - 2.907*{}^2\chi^V - 1.434*{}^0\chi - 61.672*BIC'0' + 0.153*SPI - 1.593*N\text{-atom} + 12.222*AAC - 1.226*O\text{-atom} + 3.856*{}^1\chi^V - 2.081*IVDM + 0.00003656*HyWt \quad (5)$$

k = 12, SE = 0.339, R = 0.967, R^2adj = 0.913, F = 41.955.

The parameters contributing to model-5 have both, positive as well as negative contribution in the modelling of lipophilicity. The initial statistics SE, R, R^2adj and F indicate that the model as described by eqn. 5 is found to be far superior than the other proposed models (eqns. 1-4).

The aforementioned results can be further established by estimating and comparng quality factor. This quality factor Q is defined by the ratio of the correlation coefficient (R) to the standard error of estimation (SE). That is Q = R/SEE. For the model-5, the value of Q is 2.855, which is greater than other proposed model expressed by eqns. 1-4, respectively.

We have estimated cross validation parameters to explain present results. The meaning of these parameters is given in experimental section and their values are recorded in Table-3. PRESS is a good estimate of the real prediction error of the model. If PRESS is smaller then the model predicts better and can be considered statistically significant. In this regard, all the five models proposed by us (Table-3) are good and model 5 is the best one.

TABLE-3
CROSS-VALIDATION PARAMETERS FOR THE PROPOSED MODELS

Model	No. of parameters	PRESS	PSE	R^2_{CV}	S_{PRESS}	Q
1	8	12.001	0.522	0.761	0.555	1.619
2	9	10.560	0.469	0.795	0.527	1.728
3	10	6.244	0.361	0.889	0.411	2.308
4	11	4.678	0.312	0.918	0.360	2.668
5	12	4.013	0.289	0.931	0.339	2.855

S_{PRESS} is another cross-validation parameter and is a measure of uncertainty of prediction. However, in present case S_{PRESS} is found to be the same as that of SE, thus both these parameters carry same meaning and use of S_{PRESS} is useless. In such case we have still another cross validation parameter named as predicted square error (PSE). This parameter is more directly related to uncertainty of prediction. The lowest value of PSE (Table-3) for the model 5 expressed by eqn. 5, supports its highest predictive potential.

Finally, the predictive potential of the model is confirmed by calculating predictive correlation coefficient of model-5 (R^2_{pred}) (Fig.1, Table-4). Thus R^2_{pred} (0.935) indicates that our improved model as expressed by eqn. 5 is the best.

Conclusion

From the results, as discussed above, it is conclude that models obtained by combination of topological indices and structural indicators have better quality and

TABLE-4
COMPARISON BETWEEN C log P AND PREDICTED log P VALUES FOR MODEL-5

Compd. No.	C log P	Predicted log P	Residual	Compd. No.	C log P	Predicted log P	Residual
1	1.057	1.095	-0.038	25	2.247	2.292	-0.045
2	2.555	2.818	-0.263	26	2.183	1.985	0.198
3	4.168	4.303	-0.135	27	0.572	0.676	-0.104
4	3.154	3.258	-0.104	28	2.773	2.853	-0.080
5	3.598	3.424	0.174	29	2.157	1.644	0.513
6	5.096	4.844	0.252	30	2.093	2.059	0.034
7	0.865	0.922	-0.057	31	1.516	1.017	0.499
8	1.614	1.692	-0.078	32	1.919	1.747	0.172
9	1.613	1.692	-0.079	33	1.453	1.263	0.190
10	0.373	0.868	-0.195	34	2.029	2.034	-0.005
11	1.614	1.692	-0.078	35	1.265	0.796	0.469
12	2.363	2.575	-0.212	36	1.388	1.407	-0.019
13	3.112	2.709	0.403	37	1.610	1.829	-0.219
14	2.172	2.216	-0.044	38	1.251	2.334	-1.083
15	4.610	4.489	0.121	39	2.880	2.615	0.265
16	3.136	3.325	-0.189	40	3.749	3.677	0.072
17	0.268	0.294	-0.026	41	3.808	4.056	-0.248
18	1.487	1.665	-0.178	42	4.250	3.845	0.405
19	0.738	0.737	0.001	43	1.029	1.448	-0.419
20	0.737	0.737	0.000	44	1.157	1.147	0.010
21	2.311	2.173	0.138	45	2.749	3.236	-0.487
22	3.060	3.248	-0.188	46	2.705	2.548	0.157
23	2.061	1.636	0.425	47	2.662	2.430	0.232
24	3.745	3.404	0.341	48	1.029	1.525	-0.496

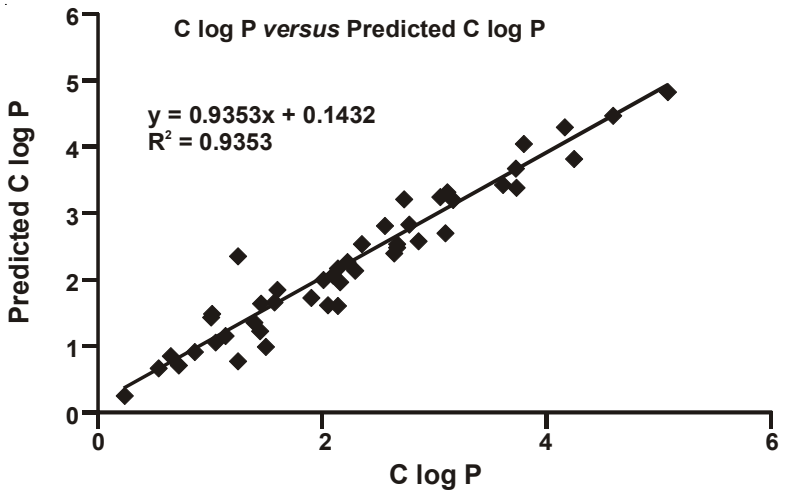

Fig. 1. Correlation of calculated and predicted liphophilicity of 48 thia and aza crown ethers using model-5

predictivity. The use of structural indicators, based on the number of electronegative atoms, gave found better results with topological indices and thus elaborated the role of electronegative atoms in the modelling of lipophilicity.

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