INTERNATIONAL JOURNAL OF PHARMACEUTICS & DRUG ANALYSIS

VOL.6, ISSUE 7, 2018; 548 – 556; http://ijpda.com; ISSN: 2348-8948

Research Article

Modeling of solubility by topological indices and physicochemical parameters of thia and aza crown ethers

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Date Received: 23rd June 2018; Date accepted: 11th July 2018; Date Published: 29th July 2018

Abstract

This paper deals with a Quantitative Structure Property relationship (QSPR) study on a large set of thia and aza crown ethers using a combination of topological indices and physicochemical parameters. The regression analysis has been carried out assuming linear relationship between ClogS and topological indices, physicochemical parameters. The analysis of the data has indicated that an excellent model is obtained when these topological indices are combined with some classical descriptor. The obtained model is further supported through cross validation.

Keywords: QSPR / Topological Indices / solubility thia and aza crown ethers

INTRODUCTION

Quantitative Structure Property Relationships i.e. QSPR is a relationship between structure and property. The aqueous solubility of compounds is an important molecular property, playing a major role in the behavior of compound in many area of interest. As many compounds exist for which the solubility data not available therefore prediction of solubility, based solely on molecular structure, should prove a useful tool. The solubility of drugs and chemicals in water phase has an essential influence on the extent of their absorption and transportation in the body. That is way solubility is considered to be very important parameter in current ADMET (Absorption, Distribution, Metabolism, Excretion and toxicity) research.[1-5]

The aqueous solubility is very important property for studied thia and aza crown ethers. The value of lipophilicity also depends on aqueous solubility and it plays key role in various applications such as transportation, ion selective electrode, switchable devises etc. hence the calculation of that type of compounds by using theoretical method is very much precious.[6] The basic assumption in the present work is that the solubility of the compound may be related to their structural descriptor as a multilinear function. In the present study, we have used 48 thia and aza crown ethers compounds for modeling of solubility using topological indices and physicochemical parameters.

Experimental

Molecular graphs:

The molecular graphs used for the calculation of topological indices were carbon-hydrogen as well as hetero atom hydrogen suppressed graphs.

ClogS:

The value of aqueous solubility ClogS is a unit stripped logarithm of the solubility measured in mol/liter at 25°C and pH 7.5. In our work the logS is calculated by ORISIS.

Topological Indices[5-7]

The topological indices: Connectivity indices (0χ, $0\chi Av$ and $3\chi A$), information indices (IDDM, TIC'0', IAC, BIC'0' and SIC'0'), Eccentricity indices (AECC and ECC), Xu index and centralization index (CENT) used in the present investigation were calculated by topological graphs of compounds.

Physicochemical parameters

We have calculated physicochemical parameters such as index of refraction (IOR), Nominal mass (NM), Parachor (Pa), Molar refractivity (MR) etc using chemsketch software version 11.5 for selected compound. The object is calculation of physicochemical parameters as structural invariants for the modeling of solubility of thia and aza crown ethers.

Indicator parameters8

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

no. of sulphur atoms, O-atom accounting for the oxygen atom and N-atom accounting for number of nitrogen atoms in compound. They assume only numerical value of the number of atoms present in the structure.

Statistical Parameters:

The regression analysis is a statistical method which has been found to be a versatile technique for QSAR/QSPR studies. The regression analysis was performed using maximum-R^2 method by the SPSS software. The cross-validation method evaluates the validity of a model by how well it fits data. (Table 2)

Results & Discussion

The chemical names of the thia and aza crown ethers are given in table 1 along with the estimated topological indices, physicochemical parameters and structural descriptor used in modeling. To obtain statistically significant model for modeling of lipophilicity we have used maximum R^2 method.

Quantitative structure activity / property relationships (QSAR/QSPR) are mathematical models obtain via statistical regression analysis aiming at predicting properties of molecules from their structure. Molecular activity and properties obtained experimentally are digital values but structures are in graphical form. Thus molecular topology involves the translation of molecular structure in to characteristic numerical descriptors which are known as topological indices. In chemical graph theory and topology, atoms are treated as vertices and the bonds edges. When certain condition are imposed on vertices, edges, or both a number is obtain which is called the topological index used in the modeling of physicochemical parameters, biological activities and toxicity of organic compounds.[9-15]

Initial statistical analysis has indicated that no statistically significant single linear regressions are possible for modeling solubility of the compounds. This indicates that the ClogS i.e. solubility is a function of more than one property and we have to choose more than one Ties, physicochemical parameters and structural descriptor, that have been tried for good result. Initially we tried to prepare multilinear regression model with using only physicochemical parameters, the one which is the best is given below:

ClogS = -0.533 - 0.069 * NM + 0.046 * PA - 0.154 * MR (1)

k= 3, SE = 0.917, R = 0.784, R^2adj = 0.588, F = 23.330

In above model, the value of initial statistical parameters shows that only physicochemical parameter is not capable to mimic solubility of unknown compounds. However with a hope of obtaining still better results we have carried out 9-parametric regression analysis by ion of physicochemical parameter and topological indices.

ClogS = 9.312-9.602 *IOR - 3.072 * IDDM + 0.241 * TIC'0' - 0.022 * MIM- 0.198 * IAC + 4.143 * IDE + 19.804 * BIC'0'+ 0.054 * Xu+0.817 * $^3\chi^{AV}$ (2)

k= 9, SE = 0.379, R = 0.971, R^2adj = 0.929, F = 69.852

For the aforementioned model, the value of statistical parameter is good but not significant for the correlation. Looking to such an excellent model, we have started stepwise regression analysis with topological indices and structural indicators and got below 9-parametric model with comparatively improved statistic.

ClogS =4.085 –0.599 *S-atom+0.288 *TIC'0'-3.636*IDDM+0.001*WAP-0.225*IAC +0.057*Xu +12.282*BIC'0'-0.003* CENT + 0.018*ECC (3)

k=9, SE = 0.362, R = 0.974, R2adj = 0.936, F = 76.97

Addition of the parameter J during the stepwise regression analysis and replace ECC with AECC yielded a 10-parametric regression expression with improved statistics, the resulted 10-parametric model is given below:

ClogS = 5.0004 –0.596 *S-atom+0.267 *TIC'0'-4.024*IDDM+0.001*WAP-1.023*J-0.200*IAC +0.054*Xu+13.673*BIC'0'+ 0.558* AECC-0.0024*CENT (4)

k= 10, SE = 0.355, R = 0.975, R2adj = 0.938, F = 71.810

When SIC'0' is added to eq.4, improvement observed in the statistics and the obtained 11-paramertic model is given below:

ClogS = 5.825 –0.604 *S-atom+0.251 *TIC'0'-4.066*IDDM+0.000*WAP-1.066*J - 0.197 *IAC + 0.059*Xu +28.684*BIC'0' +0.611*AECC - 16.483*SIC'0'- 0.002*CENT (5)

k= 11, SE = 0.338, R = 0.978, R2adj = 0.944, F = 72.832

The significant improvement in the statistics indicates its favorable role in the modeling of solubility. 12-parameric model having the best statistics than those described above. This model was containing S-atom, TIC'0', IDDM, WAP, J, IAC, Xu, BIC'0', 0χAV , CENT, 2χA and ECC as correlating parameters and is given below:

ClogS = 5.971 –0.667 *S-atom+0.304 *TIC'0'-3.859*IDDM+0.001*WAP-1.395*J-0.261* IAC + 0.111 * Xu + 19.040 * BIC'0' + 3.623*0χAV - 0.004*CENT-9.738*2χA + 0.026*ECC (6)

k= 12, SE = 0.316, R = 0.981, R2adj = 0.950314, F = 75.912

In the regression equation 6 some Ties have positive coefficient and some have negative coefficient. This means in some cases ClogS increase with magnitude of Ties with positive coefficient and vice versa. The initial statistics SE, R, R2adj and F statistics that the model 6 is found to be far superior than the other proposed model based on eq.1,2,3,4 and 5.

The multilinear regression model which is good for the modeling of solubility is discussed one by one. Firstly we have used quality factor (Q) for establishing the quality of the proposed models. This quality factor is defined as the ratio of correlation coefficient R and the standard error estimation SEE i.e. Q=R/SEE. Thus higher the value of R, lower the SEE and the larger will be quality of the model. The value of Q for model 6 is suggested that the model 6 is better than other 5 models. (Table 2)

We calculated several cross-validation parameters, the meanings of these parameters are given in experimental section and their values are presented in table-2. PRESS is a good estimate of the real prediction error of the model. If PRESS is smaller than the model predicts can be considered statistically significant. On the basis of this all 6 models proposed by us are good and model-6 is the best one. All cross-validation parameters PSE, R2cv, Q, Sprees, and PRESS are in favors of model-6.

Finally the predictive potential of the model is confirmed by calculating predictive correlation coefficient of the model (R2press), (fig-1) 0.899, for the expressed model-6 (equation 6). Thus R2 pred indicates that our improved model as expressed by equation-6 is the best.

Conclusion

From above mention result and discussion it is conclude that models which obtained by the combination of topological indices, physicochemical parameters and structural descriptor have better predictivity and quality.

Acknowledgements

Authors are thankful to late. Professor V.W. Bhagwat and late. Professor P. V. Khadikar for their valuable guidance and inspiration.

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Tabel 1- Compounds name and values of topological indices, structural descriptor and physicochemical parameters

No	Compound Name	LogS	Xu	ECC	AECC	X0AV	IAC	BIC'0'	IDDM	TIC'0'	Wap	2XA	J	IDE	3XAV	SIC'0'	CENT	IOR	MIM	MR	Pa	NM
1	1,4,7-Dioxathionane	-0.98	8.90	36	4	0.698	31.71	0.344	3.17	31.71	324	0.35	2	2	0.23	0.34	0	1.46	148.06	39.04	345	148
2	1,4,7-Trithionane	-2.35	8.90	36	4	0.88	28.95	0.314	3.17	28.95	324	0.35	2	2	0.54	0.31	0	1.57	180.01	52.15	407	180
3	1,4,8,11-Tetrathioacyclotetradecane	-3.50	14.56	98	7	0.855	45.32	0.262	3.81	45.32	1274	0.35	2	2.78	0.48	0.26	0	1.55	268.05	78.76	623	268
4	1,4,8,11-Tetrathioacyclotetradecan-6-ol	-3.10	15.44	107	7.1	0.819	51.87	0.289	3.9	51.87	1483	0.35	2.1	2.84	0.43	0.29	62	1.57	284.04	80.35	629	284
5	1,9-Dioxa-5,13-dithiacyclohexadecane	-2.67	16.64	128	8	0.734	55.82	0.262	4	55.82	1920	0.35	2	2.97	0.29	0.26	0	1.48	264.12	74.87	641	264
6	1,5,9,13-Tetrathiacyclohexadecane	-4.04	16.64	128	8	0.837	51.82	0.243	4	51.82	1920	0.35	2	2.97	0.43	0.24	0	1.54	296.08	87.98	703	296
7	1,4,7,10,13-Pentaoxa-16-thiacycloocta -decane	-0.74	18.64	162	9	0.653	61.81	0.273	4.17	61.81	2754	0.35	2	3.15	0.18	0.27	0	1.44	280.13	71.52	659	280
8	1,4,7,10-Tetraoxa-13,16-dithiacycloocta -decane	-1.43	18.64	162	9	0.698	63.42	0.28	4.17	63.42	2754	0.35	2	3.15	0.24	0.28	0	1.47	296.12	78.08	690	296
9	1,4,7,13-Tetraoxa-10,16-dithiacycloocta -decane	-1.43	18.64	162	9	0.698	63.42	0.28	4.17	63.42	2754	0.35	2	3.15	0.24	0.28	0	1.47	296.12	78.08	690	296
10	1,4-Dioxa-10,13-dithia-7,16-diazacyclooctadecane	-1.16	18.64	162	9	0.708	68.98	0.287	4.17	68.98	2754	0.35	2	3.15	0.26	0.29	0	1.47	294.14	81.57	706	294
11	1,4,10,13-Tetraoxa-7,16-dithiacyclooctadecane	-1.43	18.64	162	9	0.698	63.42	0.28	4.17	63.42	2754	0.35	2	3.15	0.23	0.28	0	1.47	296.11	78.08	690	296
12	1,4,7-Trioxa-10,13,16-trithiacyclooctadecane	-2.11	18.64	162	9	0.744	63.91	0.28	4.17	63.91	2754	0.35	2	3.15	0.31	0.28	0	1.49	312.09	84.64	721	312
13	1,10-Dioxa-4,7,13,16-tetrathiacyclooctadecane	-2.80	18.64	162	9	0.789	63.42	0.28	4.17	63.42	2754	0.35	2	3.15	0.36	0.28	0	1.52	328.07	91.19	752	328
14	1,4,10,13-tetrathia-7,16-diazacyclooctadecane	-2.53	18.64	162	9	0.799	64.98	0.271	4.17	64.98	2754	0.35	2	3.15	0.38	0.27	0	1.52	326.10	94.68	768	326
15	1,4,7,10,13,16-Hexathiacyclooctadecane	-4.17	18.64	162	9	0.88	57.91	0.256	4.17	57.91	2754	0.35	1.8	3.15	0.54	0.26	0	1.57	360.02	104.31	814	360
16	2,3,5,6,8,9-Hexahydro-1,10,4,7-benzodioxadithiacyclododecine	-3.01	16.07	108	6.7	0.676	48.98	0.296	3.99	48.98	3200	0.31	2	2.81	0.18	0.31	180	1.55	256.06	71.79	574	256
17	1,4-Dithia-7,10,13-triazacyclopentadecane	-1.10	26.08	105	7	0.626	55.4	0.28	3.91	55.41	1575	0.35	2	2.8	0.15	0.28	0	1.48	249.13	72.48	610	249
18	1,4,10-Trithia-7,13-diazacyclopentadecane	-1.92	26.08	105	7	0.62	54.67	0.28	3.91	54.67	1575	0.35	2	2.8	0.14	0.28	0	1.51	266.09	77.29	633	266
19	1-Oxa-4,13-dithia-7,10-diazacyclopentadecane	-1.24	26.08	105	7	0.62	57.4	0.3	3.91	57.42	1575	0.35	2	2.8	0.14	0.30	0	1.48	250.12	70.74	602	250
20	1-Oxa-7,10-dithia-4,13-diazacyclopentadecane	-1.24	26.08	105	7	0.62	57.42	0.3	3.91	57.42	1575	0.35	2	2.8	0.14	0.30	0	1.48	250.12	70.74	602	250

Tabel 1- continue……..

No	Compound Name	LogS	Xu	ECC	AECC	X0AV	IAC	BIC'0'	IDDM	TIC'0'	Wap	2XA	J	IDE	3XAV	SIC'0'	CENT	IOR	MIM	MR	Pa	NM
21	6-Oxa-3,9-dithia-15-azabicyclo[9.3.1] pentadeca-1(15),11,13-triene	-2.98	15.06	96	6.4	0.622	48.55	0.314	3.9	48.55	2656	0.35	1.8	2.68	0.14	0.33	102	1.57	241.06	68.24	543	241
22	3,6,9-Trithia-15-azabicyclo[9.3.1] pentadeca-1(15),11,13-triene	-3.67	15.96	96	6.4	0.55	45.8	0.3	3.9	45.80	2656	0.32	1.8	2.68	0.10	0.30	102	1.61	257.04	74.83	574	257
23	6-Methyl-3,9-dithia-6,15-diazabicyclo [9.3.1]pentadeca-1(15),11,13-triene	-2.49	16.98	106	6.6	0.6	50.89	0.29	3.99	50.90	3061	0.31	1.8	2.78	0.10	0.29	104	1.57	254.09	74.95	580	254
24	3,6,9,12-Tetrathia-18-azabicyclo[12.3.1] octadeca-1(18),14,16-triene	-4.28	18.09	133	7.4	0.58	55.93	0.28	4.16	55.93	4626	0.28	1.7	2.93	0.11	0.29	162	1.60	317.04	92.22	710	317
25	6,9-Dioxa-3,12-dithia-18-azabicyclo[12.3.1]octadeca-1(18),14,16-triene	-2.91	18.09	133	7.4	0.58	59.93	0.3	4.16	59.93	4626	0.28	1.7	2.93	0.10	0.30	162	1.54	285.09	79.11	648	285
26	6,9,12-Trioxa-3,15-dithia-21-azabicyclo [15.3.1]henicosa-1(21)17,19-triene	-2.86	21.03	195	9.2	0.59	70.8	0.29	4.39	70.82	7388	0.30	1.7	3.22	0.10	0.29	237	1.52	329.11	89.94	753	329
27	3,6,9,12,15-Pentaoxa-21-azabicyclo [15.3.1]-henicosal(21)17,19-triene	-0.80	21.03	195	9.2	0.59	65.96	0.27	4.39	65.96	7388	0.30	1.7	3.22	0.10	0.27	237	1.46	297.16	76.82	691	297
28	7-Methyl-3,11,17-triazabicyclo[11.3.1] heptadeca-1(17),1315-triene-2,12-dione	-2.53	19.51	154	7.7	0.584	63.14	0.3	4.31	62.06	5471	0.31	1.9	2.96	0.10	0.30	232	1.50	275.16	75.85	633	275
29	5-Oxa-2,8-dithia-13-azabicyclo[7.3.1] trideca-1(13),9,11-triene	-1.97	12.95	71	5.5	0.55	41.95	0.37	3.69	41.46	1716	0.30	2	2.45	0.10	0.37	69	1.60	213.03	59.05	463	213
30	5,8-Dioxa-2,11-dithia-16-azabicyclo [10.3.1]hexadeca-1(16),12,14-triene	-1.90	16.07	103	6.4	0.59	52.92	0.34	3.99	52.92	3233	0.32	1.8	2.7	0.10	0.30	120	1.56	257.05	69.88	568	257
31	2,5,8,11-Tetraoxa-16-azabicyclo[10.3.1] hexadeca-1(16),12,14-triene	-1.90	16.07	103	6.4	0.59	48.92	0.311	3.99	48.92	3233	0.32	1.8	2.7	0.10	0.32	120	1.48	225.10	56.77	506	225
32	(3S)-3-Methyl-2,8,5,11-tetraoxa-16-azabicyco[10.3.1]hexadeca-1(16),12,14-triene	-2.27	16.89	110	6.5	0.58	52.46	0.29	4.08	52.47	3679	0.31	1.7	2.75	0.08	0.29	161	1.47	239.12	61.48	546	239

Tabel 1- continue……..

No	Compound Name	LogS	Xu	ECC	AECC	X0AV	IAC	BIC'0'	IDDM	TIC'0'	Wap	2XA	J	IDE	3XAV	SIC'0'	CENT	IOR	MIM	MR	Pa	NM
33	2,5,8,11,14-Pentaoxa-19-azabicyclo [13.3.1]nonadeca-1(19),15,17-triene	-1.82	19.09	158	8.3	0.57	59	0.288	4.24	59.00	5452	0.30	1.6	3.06	0.10	0.29	186	1.47	269.13	67.6	611	269
34	5,8,11-Trioxa-2,14-dithia-19-azabicyclo[13.3.1]-nonadeca-1(19),15,17-triene-16-carbonitrile	-1.82	19.09	158	8.3	0.57	63.85	0.32	4.24	63.85	5452	0.30	1.6	3.06	0.10	0.32	186	1.53	301.08	80.71	673	301
35	2,5,8,11,14-Pentaoxa-19-azabicyclo[13.3.1]-nonadeca-1(19),15,17-triene-16-carbonitrile	-2.59	20.79	185	8.8	0.56	64.16	0.3	4.38	64.16	6958	0.31	2	3.19	0.09	0.30	389	1.53	294.12	72.82	638	294
36	2,5,8,11,14,17-Hexaaoxa-22-azabicyclo [16.3.1]-docosa-1(22),18,20-triene	-1.74	21.96	205	9.3	0.57	68.97	0.27	4.46	68.98	8508	0.32	1.6	3.26	0.10	0.27	264	1.46	313.15	78.43	716	313
37	2,5,8,11,14,17-Hexaaoxa-22-azabicyclo [16.3.1]-docosa-1(22),18,20-triene-19-carbonitrile	-2.39	23.58	236	9.8	0.56	70.46	0.27	4.58	74.47	10518	0.32	1.7	3.38	0.09	0.28	534	1.52	338.15	83.82	738	338
38	3,6,7,10-Tetrathia-16-azabicyclo [10.3.1]hexadeca-1(16),12,14-triene	-4.37	16.07	103	6.4	0.57	48.92	0.32	3.99	48.92	3233	0.32	1.8	2.74	0.10	0.32	120	1.63	289.01	83	630	289
39	3,11-Dithia-17,18-diazatricyclo[11.3.1.15.9]octadeca-1(17),5(18),6,8,13,15-hexaene	-4.33	17.68	126	7	0.5	49.39	0.29	4.16	49.39	7704	0.29	1.5	2.8	0.85	0.30	80	1.64	274.06	80.13	606	274
40	3,11-Dithia-17-azatricyclo[11.3.1.15.9]octadeca-1(17),5(18),6,8,13,15-hexaene	-5.13	17.68	126	7	0.5	47.25	0.27	4.24	47.26	7704	0.29	1.5	2.84	0.09	0.28	80	1.63	273.07	82.04	612	273
41	18-Fluoro-3,11-dithia-17-azatricyclo[11.3.1.15.9]-octadeca-1(17)5(18),6,8,13,15-hexaene	-5.44	18.47	134	7	0.55	52.55	0.31	4.58	52.56	8833	0.30	1.6	2.86	0.08	0.31	142	1.62	291.06	82.03	619	291
42	3,6,14,17-Tetrathia-23,24-diazatricyclo[17.3.1.18.12] tetracosa-1(23),8(24),9,11,19,21-hexaene	-5.60	23.41	234	9.7	0.57	70.91	0.27	4.58	70.92	18420	0.30	1.4	3.32	0.09	0.28	116	1.62	394.07	114.9	877	394

Tabel 1- continue……..

No	Compound Name	LogS	Xu	ECC	AECC	X0AV	IAC	BIC'0'	IDDM	TIC'0'	Wap	2XA	J	IDE	3XAV	SIC'0'	CENT	IOR	MIM	MR	Pa	NM
43	3,6,14,17-Tetraoxa-23,24-diazatricyclo[17.3.1.18.12]tetracosa-1(23),8(24),9,11,19,21-hexaene	-1.55	23.41	234	9.7	0.57	70.91	0.27	4.16	70.92	18420	0.30	1.4	3.32	0.09	0.28	116	1.52	330.16	88.68	754	330
44	3,11-Dioxa-17,18-diaztricyclo[11.3.1.15.9]octadeca-1(17),5(18),6,8,13,15-hexaene	-1.71	17.68	126	7	0.5	49.39	0.29	3.99	49.39	7704	0.29	1.5	2.84	0.85	0.30	80	1.57	242.11	67.02	544	242
45	2,5,11,14-Tetraoxa-19,20-diazatricyclo[13.3.1.16.10]icosa-1(19),6(20),7,9,15,17-hexaene	-7.08	18.81	158	7.9	0.54	56.36	0.307	4.39	39.38	5392	0.30	1.9	3.02	0.08	0.33	68	1.54	274.10	70.23	594	274
46	2,5,1114,17-Pentaoxa-22,23-diazatricyclo[16.3.1.16.10]tricosa-1(22),6(23),7,9999,18,20-hexaene	-5.25	22.44	202	8.9	0.55	66.99	0.29	4.7	59.31	12282	0.30	1.5	3.2	0.08	0.30	225	1.52	318.12	81.06	698	318
47	2,5,8,14,17,20-Hexaoxa-25,26-diazatricyclo[19999.3.1.19.13]hexacosa-1(25),9(26),10,12,21,23-hexaene	-3.42	19.07	278	10.7	0.556	77.4	0.277	4.58	77.40	23472	0.31	1.4	3.46	0.08	0.29	128	1.50	362.15	91.89	803	362
48	3,11,14,17-Tetraoxa-23,24-diazatricyclo[17.3.1.15.9]tetracosa-1(23),5(24),6,8,19,21-hexaene	-1.55	23.18	228	9.5	0.57	70.9	0.27	3.92	70.92	18420	0.31	1.5	3.2	0.09	0.28	294	1.52	330.16	88.68	754	330

Table 2- Cross-validation parameters for the proposed models

Model	*No. of Parameters*	*PRESS*	*PSE*	*R^2cv*	*Spress*	*Q*
1	3	37.02	0.878	0.370	0.917	0.854
2	9	5.454	0.337	0.939	0.379	2.563
3	9	4.983	0.323	0.945	0.362	2.689
4	10	4.653	0.311	0.954	0.355	2.751
5	11	4.116	0.293	0.955	0.338	2.893
6	12	3.505	0.270	0.962	0.316	3.100

Table 3- Comparison between ClogS and Predicted logS values for Model-6

Compound No	ClogS	Predicted logS	Residuals	Compound No	ClogS	Predicted logS	Residuals
1	-0.98	-0.893	-0.09	25	-2.91	-2.581	-0.33
2	-2.35	-2.258	-0.09	26	-2.86	-2.344	-0.52
3	-3.50	-3.72	0.22	27	-0.80	-1.603	0.80
4	-3.10	-3.502	0.40	28	-2.53	-2.342	-0.19
5	-2.67	-2.267	-0.40	29	-1.97	-2.051	0.08
6	-4.04	-3.761	-0.28	30	-1.90	-2.292	0.40
7	-0.74	-1.183	0.44	31	-1.90	-1.664	-0.23
8	-1.43	-1.485	0.06	32	-2.27	-2.198	-0.08
9	-1.43	-1.485	0.06	33	-1.82	-1.445	-0.37
10	-1.16	-1.076	-0.08	34	-1.82	-1.959	0.14
11	-1.43	-1.485	0.06	35	-2.59	-2.592	0.00
12	-2.11	-1.964	-0.15	36	-1.74	-2.033	0.30
13	-2.80	-2.49	-0.31	37	-2.39	-2.075	-0.31
14	-2.53	-2.558	0.03	38	-4.37	-4.314	-0.05
15	-4.17	-4.188	0.02	39	-4.33	-3.995	-0.33
16	-3.01	-3.091	0.08	40	-5.13	-4.764	-0.36
17	-1.10	-1.399	0.30	41	-5.44	-5.431	-0.01
18	-1.92	-2.121	0.20	42	-5.60	-5.705	0.11
19	-1.24	-0.949	-0.29	43	-1.55	-1.422	-0.13
20	-1.24	-0.954	-0.28	44	-1.71	-2.001	0.30
21	-2.98	-2.918	-0.07	45	-7.08	-6.891	-0.19
22	-3.67	-3.799	0.13	46	-5.25	-5.531	0.28
23	-2.49	-2.997	0.51	47	-3.42	-3.43	0.01
24	-4.28	-4.468	0.19	48	-1.55	-1.57	0.02