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QSAR Study on Tadpole Narcosis

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Abstract—This paper deals with a Quantitative Structure–Activity Relationship (QSAR) study on a large set of 123 compounds using a combination of topological indices as well as Abraham's molecular descriptors. The results have shown that an excellent model ($R = 0.9542$) is obtained in hexa-parametric correlation containing W, logRB (topological indices) along with R_2, $\Sigma\pi_2^H$, $\Sigma\beta_2^O$ and V_x as the correlating parameters. The results are discussed critically.

Introduction

Abraham and Rafols[1] have reported factors that influence tadpole narcosis using LFER (linear free-energy relationship) approach. They observed that the narcotic concentration of solutes in mol dm^{-3} is given by the following relationship:

$$\log(1/C_{nar}) = 0.579 + 0.824R_2 - 0.334\Sigma\pi_2^H - 2.871\Sigma\beta_2^O + 3.097V_x \quad (1)$$

where the descriptors used are: R the solute excess molar refraction, $\Sigma\pi_2^H$ the solute dipolarity/polarizability, $\Sigma\beta_2^O$ the solute hydrogen-bond basicity and V_x is solute volume.

Applying aforementioned relationship to a set of 84 compounds Abraham and Rafols[1] obtained the correlation coefficient $r = 0.9730$ and the standard deviation (SD) = 0.246 log units. The above relationship (eq 1) shows that solute hydrogen-bond basicity and solute volume are the main parameters influencing the tadpole narcosis and that hydrogen-bond acidity has no effect at all.

For the same set of the compounds, Abraham and Rafols[1] further observed that tadpole narcosis is related to water–octanol partition coefficient ($\log P_{(oct)}$) according to the following equation:

$$\log(1/C_{nar}) = 1.129 + 0.8331\ \log P_{(oct)} \quad n = 84,\ r = 0.9212,\ SD = 0.407 \quad (2)$$

The statistics of (eq 2) is improved by the addition of Vx as the second correlating parameter:

$$\log(1/C_{nar}) = 0.621 + 0.7431\ \log P_{(oct)} + 0.668\ V_x \quad n = 84,\ r = 0.9400,\ SD = 0.359 \quad (3)$$

Finally, Abraham and Rafols[1] added additional compounds, thus, increasing the set of 84 compounds to 114 and arrived at a conclusion that the tadpole narcosis is a general phenomenon.

Considering tadpole narcosis as a general biological property (SP) Meyer and Hemmi[2] proposed the following relationship between logSP and the partition coefficient (logP):

$$\log SP = a \times \log P + C \quad (4)$$

Needless to state that here SP stands for tadpole narcosis. This relationship (eq 4), now-a-days, is referred as

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the Overton–Meyer relationship; or some times just as the Overton rule, and has been applied to numerous series of biological results.[3,4]

During recent years, our research is concerned mainly to investigate the use of topological and/or other molecular descriptors in place of logP.[5–11] Thus, our primary objective is to study the modeling tadpole narcosis using topological indices and/or their combinations with other molecular descriptors. We have, therefore, initially used a larger set of distance-based topological indices (W, Sz, $^1\chi$, B, J, and logRB) along with the aforementioned Abraham's molecular descriptors (R_2, $\Sigma\pi_2^H$, α_2^H, $\Sigma\beta_2^O$ and V_x), thus making a total of 11 molecular descriptors. Another objective of our present study is to investigate whether or not our methodology will be useful for more than 84 compounds. In doing so we have considered: (i) tadpole narcosis as a general phenomenon, and (ii) used only those compounds from the original set[1] for which logP values are reported by Abraham and Rafols.[1] We did this to support our primary objective, that is use of topological and/or their combinations with other molecular descriptors in place of logP. The results as discussed below show that both the objectives of our present study are fulfilled.

At this stage, it is worth reporting that the topological indices used are: Wiener index (W),[12] Szeged index (Sz),[13,14] first order connectivity index ($^1\chi$), branching index (B),[15] Balaban index (J),[16] and logRB.[17] Also, that the statistical analysis for obtaining the excellent model is done following maximum R^2 method.[18] The quality factor (Q),[19,20] though criticized recently,[21] has been found useful in obtaining predictive potential of the proposed models.

Results and Discussion

Table 1 records the set of 123 compounds used in the present study. The narcotic activity (log $1/C_{nar}$) and the Abraham's molecular descriptors (R_2, $\Sigma\pi_2^H$, α_2^H, $\Sigma\beta_2^O$ and V_x) for the set of 123 compounds are also recorded in Table 1. It is recorded that here C_{nar} is the narcotic concentration, that is the minimum concentration recorded for narcosis in mol dm^{-3}. As stated in the introduction section it is to be noted that the narcotic concentration is related to the partition coefficient of the solute between water and olive oil[2] and other related partition coefficients.[3]

The topological indices (W, Sz, $^1\chi$, B, J, logRB) as calculated from the Luko-1 program of Lukovits are presented in Table 2. The correlation matrix as given in Table 3 reflects the mutual correlatedness. In addition, this correlation matrix gives the correlations of molecular descriptors (topological indices and Abraham's molecular descriptors with tadpole narcosis (log $1/C_{nar}$).

The initial regression procedure, using maximum R^2 method,[18] has indicated that statistically useful regression models start coming with the model having six parameters. It resulted into five hexa-parametric regression expressions out of which the one containing R_2, $\Sigma\pi_2^H$ $\Sigma\beta_2^O$, V_x, W and logRB as the correlating parameters gave better result. This model is found as under:

$$\begin{aligned}\log(1/C_{nar}) &= 1.0079 + 1.2975(\pm 0.2059)R_2 \\ &\quad - 1.0016(\pm 0.2211)\Sigma\pi_2^H - 1.7924 \\ &\quad \times (\pm 0.2746)\Sigma\beta_2^O + 2.4560 \\ &\quad \times (\pm 0.2838)V_x + 0.0120(\pm 0.0054)W \\ &\quad - 0.0379(\pm 0.0187)\log RB \\ n &= 123,\ SE = 0.5807,\ \ r = 0.8644, \\ F &= 57.120,\ \ Q = 1.4885,\ \ p = 0.000\end{aligned} \quad (5)$$

Here and hereafter, n is the number of compounds used, SE is the standard error of estimation, r is the multiple correlation coefficient, F is the F-ratio, Q is the quality factor and p is the probability.

Eq. 5 shows that the solute-volume (V_x) plays a dominating role in the exhibition of the tadpole narcosis of the set of 123 compounds used. Also, among the distance-based topological indices used in the multi-parametric regression, W and logRB are more useful for modeling tadpole narcosis (log $1/C_{nar}$).

The successive regression analysis resulted into four statistically significant seven-parametric regression models. However, only one out of these seven regressions gave better results than the regression model discussed above. This model is found to contain R_2, $\Sigma\pi_2^H$ $\Sigma\beta_2^O$, V_x, W, $^1\chi$, B and logRB as the correlating parameters. This model is found as given below:

$$\begin{aligned}\log(1/C_{nar}) &= 0.7712 + 1.0463(\pm 0.1991)R_2 \\ &\quad - 1.2475(\pm 0.2124)\Sigma\pi_2^H - 1.9686 \\ &\quad \times (\pm 0.2578)\Sigma\beta_2^O + 1.2220 \\ &\quad \times (\pm 0.3824)V_x + 0.0144(\pm 0.0050)W \\ &\quad + 0.5087(\pm 0.1143)\,{}^1\chi(\text{or B}) \\ &\quad - 0.0528(\pm 0.0177)\log RB \\ n &= 123,\ \ SE = 0.5387,\ \ r = 0.8856, \\ F &= 59.720,\ \ Q = 1.6439,\ \ p = 0.000\end{aligned} \quad (6)$$

Our results, therefore, show that the combination of topological indices with the Abraham's molecular descriptors can be used to model tadpole narcosis of higher number of compounds (i.e., 123 compounds rather than 84 compounds).

In view of the above Abraham and Rafols[1] added additional compounds to the set of 84 compounds from the Overton's data[22,23] thus making a new set consisting

Table 1. Name of the compounds used, their tadpole narcosis ($\log 1/C_{nar}$) and Abraham's molecular descriptors

Compd no.	Compd name	$\log(1/C_{nar})$	R_2	Π_2^H	$\Sigma\alpha_2^H$	$\Sigma\beta_2^o$	V_x
1	Pentane	2.55	0.000	0.000	0.000	0.000	0.8131
2	2-Methylbut-2-ene	2.64	0.159	0.080	0.000	0.070	0.7710
3	Trichloromethane	2.85	0.425	0.490	0.150	0.020	0.6167
4	Tetrachloromethane	3.14	0.458	0.380	0.000	0.000	0.7391
5	Chloroethane	2.35	0.227	0.400	0.000	0.100	0.5128
6	1,2-Dichloromethane	2.63	0.416	0.640	0.100	0.110	0.6352
7	Bromoethane	2.57	0.366	0.400	0.000	0.120	0.5654
8	Iodoethane	2.96	0.640	0.400	0.000	0.150	0.6486
9	Diethylether	1.47	0.041	0.250	0.000	0.450	0.7309
10	Propanone	0.54	0.179	0.700	0.040	0.490	0.5470
11	Butanone	1.04	0.166	0.700	0.000	0.510	0.6879
12	Pentan-2-one	1.72	0.143	0.680	0.000	0.510	0.8288
13	Pentan-3-one	1.54	0.154	0.660	0.000	0.510	0.8288
14	Camphor	2.88	0.450	0.850	0.000	0.560	1.3161
15	Ethylformate	1.16	0.146	0.660	0.000	0.380	0.6057
16	Methylacetate	1.10	0.142	0.640	0.000	0.450	0.6057
17	Ethylacetate	1.52	0.106	0.620	0.000	0.450	0.7466
18	Propylacetate	1.96	0.092	0.600	0.000	0.450	0.8875
19	Butylacetate	2.30	0.071	0.600	0.000	0.450	1.0284
20	Isobutylacetate	2.24	0.052	0.570	0.000	0.470	1.0284
21	Pentylacetate	2.72	0.067	0.600	0.000	0.450	1.1693
22	Ethylpropanoate	1.96	0.087	0.580	0.000	0.450	0.8875
23	Ethylbutanoate	2.37	0.068	0.580	0.000	0.450	1.0284
24	Ethylpentanoate	2.72	0.049	0.580	0.000	0.450	1.1693
25	Butylpentanoate	3.60	0.033	0.560	0.000	0.450	1.4511
26	Ethylisobutanoate	2.24	0.034	0.550	0.000	0.470	1.0284
27	Triacetin	1.64	0.136	1.300	0.000	0.350	1.5999
28	Acetonitrile	0.44	0.237	0.900	0.070	0.320	0.4042
29	Nitrometane	1.09	0.313	0.950	0.060	0.310	0.4237
30	Pentanamide	1.30	0.400	1.300	0.500	0.620	0.9286
31	*N*-Ethylurethane	1.40	0.236	0.820	0.240	0.610	0.9873
32	Methanol	0.24	0.278	0.440	0.430	0.470	0.3082
33	Ethanol	0.54	0.246	0.420	0.370	0.480	0.4491
34	Propan-1-ol	0.96	0.236	0.420	0.370	0.480	0.5900
35	Propan-2-ol	0.89	0.212	0.360	0.330	0.560	0.5900
36	Butan-1-ol	1.42	0.224	0.420	0.370	0.480	0.7309
37	2-Methylprpan-1-ol	1.35	0.217	0.390	0.370	0.480	0.7309
38	2-Methylpropan-2-ol	0.89	0.180	0.300	0.310	0.600	0.7309
39	3-Methylbutan-1-ol	1.64	0.192	0.390	0.370	0.480	0.8718
40	2-Methylbutan-2-ol	1.20	0.194	0.300	0.310	0.600	0.8718
41	Octan-1-ol	3.40	0.199	0.420	0.370	0.480	1.2950
42	Menthol	3.97	0.400	0.480	0.320	0.610	1.4677
43	Ethane-1,2-diol	0.19	0.404	0.900	0.580	0.780	0.5078
44	Ethanethiol	2.09	0.392	0.350	0.000	0.240	0.5539
45	Carbondisulphide	3.28	0.876	0.260	0.000	0.030	0.4905
46	Triethylphosphate	1.96	0.000	1.000	0.000	1.060	1.3934
47	Benzene	2.68	0.610	0.520	0.000	0.140	0.7164
48	*m*-Xylene	3.42	0.623	0.520	0.000	0.160	0.9982
49	Naphthalene	4.19	1.340	0.920	0.000	0.200	1.0854
50	Phenanthrene	5.25	2.055	1.290	0.000	0.260	1.4540
51	Methylphenylether	2.82	0.708	0.750	0.000	0.290	0.9160
52	1,3-Dimetoxybenzene	3.35	0.816	1.010	0.000	0.450	1.1160
53	1,4-Dimetoxybenzene	3.05	0.806	1.000	0.000	0.500	1.116
54	Acetophenone	3.04	0.818	1.010	0.000	0.480	1.0139
55	Aniline	1.96	0.955	0.960	0.260	0.500	0.8162
56	*N*,*N*-Dimethylanilene	2.85	0.957	0.840	0.000	0.470	1.0980
57	Diphenylamine	4.43	0.700	0.880	0.600	0.380	1.4240
58	Azobenzene	4.74	0.680	1.200	0.000	0.440	1.4808
59	Acetanilide	2.31	0.870	1.400	0.500	0.670	1.1133
60	*p*-Metoxyacetanilide	2.09	0.970	1.630	0.480	0.860	1.3133
61	*p*-Etoxyacetanilide	2.55	0.940	1.600	0.480	0.840	1.4542
62	Phenol	2.28	0.805	0.890	0.600	0.300	0.7751
63	*o*-Cresol	2.92	0.840	0.860	0.520	0.300	0.9160
64	*m*-Cresol	2.75	0.822	0.880	0.570	0.340	0.9160
65	*p*-Cresol	2.75	0.820	0.870	0.570	0.310	0.9160
66	2-Isopropylphenol	4.26	0.822	0.790	0.520	0.440	1.3387
67	4-*tert*-Pentylphenol	4.52	0.810	0.890	0.560	0.410	1.4796
68	2-Methoxyphenol	2.57	0.837	0.910	0.220	0.520	0.9747
69	Catechol	2.12	0.970	1.070	0.850	0.520	0.8338
70	Resorcinol	1.64	0.980	1.000	1.100	0.580	0.8338
71	Hydroquinone	2.12	1.000	1.000	1.160	0.600	0.8338

(continued)

Table 1 (*continued*)

Compd no.	Compd name	$Log(1/C_{nar})$	R_2	II_2^H	$\Sigma\alpha_2^H$	$\Sigma\beta_2^o$	V_x
72	Vanilin	2.48	1.040	1.040	0.320	0.670	1.1313
73	Eugenol	3.91	0.946	0.990	0.220	0.510	1.3544
74	Phenylthiourea	2.18	1.250	1.720	0.490	0.780	1.1774
75	Coumarin	3.24	1.060	1.790	0.000	0.460	1.0619
76	Phthalide	2.37	0.950	1.900	0.000	0.460	0.9640
77	Piperonol	2.78	0.990	1.600	0.000	0.520	1.0227
78	Pyridine	1.60	0.631	0.840	0.000	0.470	0.6753
79	Quinoline	2.72	1.268	0.970	0.000	0.510	1.0443
80	Antipyrine	1.89	1.320	1.500	0.000	1.480	1.5502
81	Caffine	1.92	1.400	1.550	0.000	1.340	1.3632
82	Morphine	2.76	2.200	2.340	0.860	1.790	2.0648
83	Phenylurea	2.34	1.110	1.400	0.770	0.770	1.0726
84	Acetamide	0.77	0.460	1.300	0.540	0.680	0.5059
85	Methylurethane	0.57	0.263	0.820	0.240	0.610	0.8464
86	Nicotine	3.51	0.865	1.340	0.000	0.940	1.3710
87	2-Propylpiperidine	3.48	0.364	0.440	0.100	0.690	1.2270
88	Urea	0.60	0.500	1.000	0.500	0.900	0.4648
89	*N*-Ethylurethane	1.46	0.236	0.820	0.240	0.610	0.9873
90	*N*-Propylurethane	2.18	0.225	0.820	0.240	0.610	1.1282
91	*N*-Isobutylurethane	2.50	0.202	0.790	0.240	0.610	1.2691
92	*N*-Isopentylurethane	2.93	0.190	0.790	0.240	0.610	1.4100
93	Methanol	0.23	0.278	0.440	0.430	0.470	0.3082
94	Ethanol	0.72	0.246	0.420	0.370	0.480	0.4491
95	Propan-1-ol	1.14	0.236	0.420	0.370	0.480	0.5900
96	Butan-1-ol	1.97	0.224	0.420	0.370	0.480	0.7309
97	Pentan-1-ol	2.54	0.219	0.420	0.370	0.480	0.8718
98	Hexan-1-ol	3.24	0.210	0.420	0.370	0.480	0.0127
99	Heptan-1-ol	3.64	0.211	0.420	0.370	0.480	1.1536
100	Octan-1-ol	4.24	0.199	0.420	0.370	0.480	1.2950
101	Nonan-1-ol	4.43	0.193	0.420	0.370	0.480	1.4354
102	Decan-1-ol	1.90	0.191	0.420	0.370	0.480	1.5763
103	Undecan-1-ol	5.09	0.181	0.420	0.370	0.480	1.7170
104	Dodecan-1-ol	5.33	0.175	0.420	0.370	0.480	1.8580
105	Butan-2-ol	1.77	0.217	0.360	0.330	0.560	0.7309
106	Pentan-2-ol	2.32	0.195	0.360	0.330	0.560	0.8718
107	Hexan-2-ol	2.86	0.187	0.360	0.330	0.560	1.0127
108	Heptan-2-ol	3.48	0.188	0.360	0.330	0.560	1.1536
109	Octan-2-ol	4.21	0.158	0.360	0.330	0.560	1.2950
110	Cyclohexanol	2.30	0.460	0.540	0.320	0.570	0.9040
111	Cycloheptanol	2.89	0.513	0.540	0.320	0.580	1.0450
112	Cyclooctanol	3.41	0.578	0.540	0.320	0.580	1.1860
113	Cyclodecanol	4.08	0.621	0.540	0.320	0.580	1.4677
114	Pentan-1,5-diol	1.72	0.388	0.950	0.720	0.920	0.9305
115	Hexan-1,6-diol	1.60	0.385	0.950	0.750	0.920	1.0714
116	Heptan-1,7-diol	2.48	0.381	0.950	0.750	0.920	1.2123
117	Octan-1,8-diol	3.02	0.380	0.950	0.750	0.920	1.3532
118	Nonan-1,9-diol	3.19	0.370	0.950	0.750	0.920	1.4941
119	Decan-1,10-diol	3.60	0.370	0.950	0.750	0.920	1.6350
120	Dodecan-1,12-diol	4.41	0.360	0.950	0.750	0.920	1.9168
121	Acetal	1.92	0.000	0.670	0.000	0.076	1.0714
122	Benzamide	2.52	0.990	1.500	0.490	0.670	0.9728
123	Benzylalcohol	2.70	0.803	0.870	0.390	0.560	0.9160

of 114 compounds. They obtained the following regression model for modeling $\log(1/C_{nar})$:

$$\begin{aligned}\log(1/C_{nar}) &= 0.595 + 0.805(\pm 0.107)R_2 - 0.725 \\ &\times (\pm 0.135)\Sigma\pi_2^H - 2.489(\pm 0.166)\Sigma\beta_2^O \\ &+ 3.341(\pm 0.115)V_x \qquad (7)\\ n &= 114,\ \ SE = 0.341, r = 0.9520, \\ F &= 263.000\end{aligned}$$

When we attempted our methodology to the above referred set of 114 compounds we obtained slightly better model than the model given by eq 7. However, ours is the six parametric model containing R_2, $\Sigma\pi_2^H$ $\Sigma\beta_2^O$, V_x, W, and logRB and is found as below:

$$\begin{aligned}\log(1/C_{nar}) &= 0.4461 + 0.9574(\pm 0.1281)R_2 \\ &- 0.5530(\pm 0.1310)\Sigma\pi_2^H - 2.4493 \\ &\times (\pm 0.1729)\Sigma\beta_2^O + 3.3111 \\ &\times (\pm 0.1839)V_x + 0.0095(\pm 0.0031)W \qquad (8)\\ &- 0.0330(\pm 0.0109)\log RB \\ n &= 114,\ \ SE = 0.3217,\ \ r = 0.9592, \\ F &= 205.103,\ \ Q = 2.9816,\ \ p = 0.000\end{aligned}$$

Table 2. Value of various calculated topological indices for the compounds used in the present study

Compd	Sz	W	$^1\chi$ (= B)	J	Log(RB)
1	20	20	2.4142	2.1906	5.6630
2	20	20	2.4142	2.1906	5.6630
3	9	9	1.7321	2.3238	2.0794
4	16	16	2.0000	3.0237	4.1589
5	4	4	1.4142	1.6330	0.6931
6	10	10	1.9142	1.9747	2.4849
7	4	4	1.4142	1.6330	0.6931
8	4	4	1.4142	1.6330	0.6931
9	20	20	2.4142	2.1906	5.6630
10	9	9	1.7321	2.3238	2.0794
11	18	18	2.2701	2.5395	4.9698
12	32	32	2.7701	2.6272	9.5342
13	32	32	2.7701	2.6272	9.5342
14	174	123	4.9830	2.3963	39.5886
15	20	20	2.4142	2.1906	5.6630
16	18	18	2.2701	2.5395	4.9698
17	32	32	2.7701	2.6272	9.5342
18	52	52	3.2701	2.6783	15.9311
19	79	79	3.7701	2.7158	24.3021
20	71	71	3.6639	3.0988	22.2872
21	114	114	4.2701	2.7467	34.7732
22	50	50	3.3081	2.8318	15.4203
23	76	76	3.8081	2.8621	23.6090
24	110	110	4.3081	2.8766	33.9259
25	200	200	5.3081	3.0171	60.3280
26	71	71	3.6639	3.0988	22.2872
27	424	424	6.9136	3.8357	128.6710
28	4	4	1.4142	1.6330	0.6931
29	9	9	1.7321	2.3238	2.0794
30	143	143	4.6807	3.1296	44.2428
31	98	98	4.2187	3.3248	31.0637
32	4	4	1.4142	1.6330	0.6931
33	10	10	1.9142	1.9747	2.4849
34	20	20	2.4142	2.1906	5.6630
35	18	18	2.2701	2.5395	4.9698
36	35	35	2.9142	2.3391	10.4505
37	32	32	2.7701	2.6272	9.5342
38	28	28	2.5607	3.1685	8.1479
39	29	29	2.8425	2.0939	8.1479
40	44	44	3.1213	3.3604	13.5231
41	165	165	4.9142	2.6476	48.9613
42	291	191	5.6471	2.5012	61.5396
43	35	35	2.9142	2.3391	10.4505
44	10	10	1.9142	1.9747	2.4849
45	4	4	1.4142	1.6330	0.6931
46	166	166	5.1820	3.7902	53.1685
47	54	27	3.0000	2.0000	7.4547
48	110	62	3.7877	2.1924	19.0038
49	243	109	4.9663	1.9254	34.4240
50	677	271	6.9495	1.4792	86.8067
51	109	64	3.9319	2.1250	19.6969
52	192	121	4.8637	2.2465	38.3361
53	200	125	4.8637	2.1738	39.0780
54	142	88	4.3045	2.2284	27.6625
55	142	88	4.3045	2.2284	27.6625
56	142	88	4.3045	2.2284	27.6625
57	505	307	6.8770	1.8180	95.8633
58	498	399	6.9319	1.8247	113.7509
59	228	156	5.2152	2.3206	49.7028
60	360	250	6.1471	2.4103	79.2185
61	445	316	6.6471	2.3868	98.6359
62	109	64	3.9319	2.125	19.6969
63	142	86	4.3425	2.2973	27.1516
64	146	88	4.3257	2.2317	27.6625
65	150	90	4.3257	2.1804	28.0679
66	366	244	6.1851	2.4968	77.8967
67	372	252	6.0977	2.4021	78.9751
68	184	117	4.8805	2.3400	37.4198
69	184	117	4.8805	2.3400	37.4198
70	192	121	4.8637	2.2465	38.3361
71	200	125	4.8637	2.1738	39.0780

(continued)

Table 2 (*continued*)

Compd	Sz	W	$^1\chi$ (=B)	J	Log(RB)
72	303	198	5.8124	2.4127	63.1978
73	376	254	6.2956	2.3891	80.4242
74	340	250	6.1259	2.3975	79.2185
75	308	144	5.3602	1.9323	45.7908
76	185	106	4.8707	2.0146	33.5078
77	248	147	5.3982	1.9100	46.4839
78	54	27	3.0000	2.0000	7.4547
79	243	109	4.9663	1.9254	34.4240
80	414	284	6.6984	2.0049	90.7187
81	423	258	6.5366	2.2264	84.4145
82	2224	940	11.2019	1.6177	297.6837
83	340	250	6.1259	2.3975	79.2185
84	29	29	2.6427	2.9935	8.5533
85	70	70	3.6807	3.1708	21.9995
86	323	242	5.9319	1.9062	72.3677
87	187	121	4.8425	2.2513	38.3361
88	65	65	3.5534	3.4642	20.5724
89	98	98	4.2187	3.3248	31.0637
90	135	135	4.7187	3.3759	42.5846
91	168	168	5.1294	3.6998	53.4405
92	219	219	5.6294	3.7309	68.8326
93	4	4	1.4142	1.6330	0.6931
94	10	10	1.9142	1.9747	2.4849
95	20	20	2.4142	2.1906	5.6630
96	35	35	2.9142	2.3391	10.4505
97	56	56	3.4142	2.4475	17.0297
98	84	84	3.9142	2.5301	25.5549
99	120	120	4.4142	2.5951	36.1595
100	165	165	4.9142	2.6476	48.9613
101	220	220	5.4142	2.6909	64.0657
102	286	286	5.9142	0.7272	81.5680
103	364	364	6.4142	2.7582	101.5552
104	455	455	6.9142	2.7848	124.1073
105	31	31	2.8081	2.7542	9.2462
106	50	50	3.3081	2.8318	15.4203
107	76	76	3.8081	2.8621	23.6090
108	110	110	4.3081	2.8766	33.9259
109	153	153	4.8081	2.8862	46.4764
110	109	64	3.9319	2.1250	19.6969
111	121	88	4.4319	2.1827	27.7803
112	217	121	4.9319	2.1611	38.5184
113	381	206	5.9319	2.1690	65.6057
114	120	120	4.4142	2.5951	36.1595
115	165	165	4.9142	2.6476	48.9613
116	220	220	5.4142	2.6909	64.0657
117	286	286	5.9142	2.7272	81.5680
118	364	364	6.4142	2.7582	101.5552
119	455	455	6.9142	2.7848	124.1073
120	560	560	7.4142	2.8079	149.2986
121	75	75	3.8081	2.9196	23.3858
122	228	156	5.2152	2.3206	49.7028
123	148	94	4.4319	2.0779	29.2719

Table 3. Correlation matrix for the inter-correlation of various parameters

	$Log(1/C_{nar})$	R_2	II_2^H	$\Sigma\alpha_2^H$	$\Sigma\beta_2^o$	V_x	Sz	W	$^1\chi$ (=B)	J	LogRB
$Log(1/C_{nar})$	1.0000										
R_2	0.2792	1.0000									
II_2^H	0.0334	0.7176	1.0000								
$\Sigma\alpha_2^H$	−0.0069	0.1971	0.2062	1.0000							
$\Sigma\beta_2^o$	−0.1016	0.2964	0.5560	0.4269	1.0000						
V_x	0.6653	0.2710	0.3706	0.1545	0.4539	1.0000					
Sz	0.4088	0.6108	0.6037	0.3071	0.5716	0.7002	1.0000				
W	0.5055	0.4163	0.5414	0.3693	0.5935	0.8501	0.9077	1.0000			
$^1\chi$ (=B)	0.5826	0.5238	0.6231	0.3501	0.5943	0.8948	0.8242	0.9098	1.0000		
J	−0.0772	−0.4667	−0.0769	0.0435	0.1926	0.1800	−0.1372	0.0474	0.0950	1.0000	
logRB	0.4935	0.4577	0.5737	0.3616	0.6093	0.8468	0.9305	0.9962	0.9216	0.0402	1.0000

Thus, our model expressed by (eq 8) gave slightly better results than given by Abraham and Rafols[1] model (eq 7) but it suffers from the defect in that six parameters used in place of four parameters has been used by the Abraham and Rafols.[1] This better statistics is due to the presence of W and logRB indices. The other points raised in discussing the merits/demerits of Abraham and Rafols[1] model are applicable to our model (eq 8) also.

In order to confirm our results we have estimated $\log(1/C_{nar})$ from the above most appropriate models and compared them with the experimental $\log(1/C_{nar})$ values. Such a comparison is shown in Table 4. The comparison and the difference between observed and estimated tadpole narcosis (residue) shows that the model expressed by (eq 6) is the best model for modeling tadpole narcosis of 123 compounds and that (eq 8) is the best model for this purpose containing 114 compounds. The predicted correlation coefficients estimated from Figures 1–3 ($r^2 = 0.7843$) and ($r^2 = 0.9201$) also confirm our findings.

Finally, it is worth mentioning that the Abraham and Rafols[1] model based on logP for a set of 114 compounds is found as:

$$\log(1/C_{nar}) = 1.210 + 0.835(\pm 0.031)\log P_{oct}$$
$$n = 114,\quad r = 0.9301,\quad SD = 0.419,\quad F = 718 \tag{9}$$

However, for the small set of 114 compounds, we obtained a model (eq 8) which gave better statistics than the model expressed by (eq 9).

Conclusion

The aforementioned results show that we can combine topological and Abraham's molecular descriptors to obtain a model with better statistics. However, record that the model expressed by (eq 9) uses a single correlating parameter compared to six parametric model expressed by (eq 8).

Experimental

Tadpole narcosis

The tadpole narcosis data were adopted from the work of Abraham and Rafols.[1]

Abraham's molecular descriptors. Abraham's molecular descriptors (R_2, $\Sigma\pi_2^H$, $\Sigma\beta_2^O$, V_x) were adopted from the work of Abraham and Rafols.[1]

Molecular graphs. The carbon-hydrogen suppressed molecular graphs were used for the calculation of topological indices W, Sz, $^1\chi$, B, J, logRB (Table 2).

Topological indices

Wiener index (W). The Wiener index (W) is a widely used topological index.[12] It is based on the vertex distances of the respective molecular graph.

Molecular graph can be denoted by G and having v_1, v_2, $v_3,\ldots,v_n$ as its vertices. Let $d(v_i, v_j|G)$ stands for the shortest distance between the vertices v_i and v_j. Then the Wiener index is defined as:

$$W = W(G) = 1/2\sum_{i=1}^{n}\sum_{j=1}^{n} d(v_i, v_j|G) \tag{10}$$

Szeged index (Sz). Let e be an edge of the molecular graph G. Let $n_1(e|G)$ be the number of vertices of G lying closer to one end of e; let $n_2(e|G)$ be the number of vertices of G lying closer to the other end of e. Then the Szeged index (Sz) is defined[13,14] as:

$$Sz(G) = Sz = \sum_e n_1(e|G)n_2(e|G) \tag{11}$$

with the summation going over all the edges of G.

In cyclic graphs, there are edges equidistant from both the ends of edge e; by definition of Sz such edges are not taken into account.

First-order connectivity index ($^1\chi$,). The connectivity index $\chi = \chi(G)$ of a graph G is defined by Randic[24,25] as under (eq 12):

$$\chi = \chi(G) = \sum_{ij}[\delta_i\ \delta_j]^{-0.5} \tag{12}$$

where δ_i and δ_j are the valence of a vertex i and j, equal to the number of bonds connected to the atoms i and j, in G.

In the case of hetero-systems the connectivity is given in terms of valence delta values δ_i^v and δ_j^v of atoms i and j and is denoted by χ^v. This version of the connectivity index is called the valence connectivity index and is defined[24,25] as under (eq 13):

$$\chi^v = \chi^v(G) = \sum_{ij}\left[\delta_i^v\ \delta_j^v\right]^{-0.5} \tag{13}$$

where the sum is taken over all bonds i–j of the molecule. Valence delta values are given by the following expression:

$$\delta_i^v = \frac{Z_i^v - H_i}{Z_i - Z_j - 1} \tag{14}$$

where Z_i is the atomic number of atom i, Z_i^v is the number of valence electron of the atom i and H_i is the number of hydrogen atoms attached to atom i.

Table 4. Comparison of observed and estimated tadpole narcosis ($\log(1/C_{nar})$ from different models

Compd	Obs. $\log(1/C_{nar})$	Estimated $\log(1/C_{nar})$ using					
		Model-5		Model-6		Model-8	
		Est.	Res.	Est.	Res.	Est.	Res.
1	2.55	3.03	−0.48	2.982	−0.432	3.142	−0.592
2	2.64	2.928	−0.288	2.859	−0.219	2.939	−0.299
3	2.85	2.577	0.273	2.22	0.63	2.592	0.258
4	3.14	3.071	0.069	2.708	0.432	3.137	0.003
5	2.35	2.004	0.346	1.68	0.67	1.91	0.44
6	2.63	2.295	0.335	1.954	0.676	2.338	0.292
7	2.57	2.277	0.293	1.85	0.72	2.169	0.401
8	2.96	2.784	0.176	2.18	0.78	2.633	0.327
9	1.47	1.825	−0.355	1.727	−0.257	1.669	−0.199
10	0.54	1.033	−0.493	0.69	−0.15	0.859	−0.319
11	1.04	1.325	−0.285	1.06	−0.02	1.254	−0.214
12	1.72	1.657	0.063	1.448	0.272	1.693	0.027
13	1.54	1.691	−0.151	1.484	0.056	1.714	−0.174
14	2.88	2.946	−0.066	2.904	−0.024	3.26	−0.38
15	1.16	1.368	−0.208	1.31	−0.15	1.3	−0.14
16	1.1	1.26	−0.16	1.127	−0.027	1.139	−0.039
17	1.52	1.574	−0.054	1.502	0.018	1.565	−0.045
18	1.96	1.92	0.04	1.889	0.071	2.009	−0.049
19	2.3	2.246	0.054	2.24	0.06	2.437	−0.137
20	2.24	2.196	0.044	2.156	0.084	2.376	−0.136
21	2.72	2.61	0.11	2.614	0.106	2.888	−0.168
22	1.96	1.929	0.031	1.926	0.034	2.013	−0.053
23	2.37	2.252	0.118	2.275	0.095	2.439	−0.069
24	2.72	2.591	0.129	2.626	0.094	2.871	−0.151
25	3.6	3.363	0.237	3.39	0.21	3.787	−0.187
26	2.24	2.192	0.048	2.162	0.078	2.37	−0.13
27	1.64	3.4	−1.76	3.387	−1.747	—	—
28	0.44	0.855	−0.415	0.501	−0.061	0.745	−0.305
29	1.09	0.977	0.113	0.722	0.368	0.881	0.209
30	1.3	1.435	−0.135	1.587	−0.287	1.57	−0.27
31	1.4	1.824	−0.424	1.918	−0.518	1.903	−0.503
32	0.24	0.864	−0.624	0.705	−0.465	0.353	−0.113
33	0.54	1.175	−0.635	1.095	−0.555	0.774	−0.234
34	0.96	1.508	−0.548	1.487	−0.527	1.222	−0.262
35	0.89	1.396	−0.506	1.314	−0.424	1.04	−0.15
36	1.42	1.837	−0.417	1.865	−0.445	1.662	−0.242
37	1.35	1.857	−0.507	1.827	−0.477	1.673	−0.323
38	0.89	1.688	−0.798	1.573	−0.683	1.401	−0.511
39	1.64	2.187	−0.547	2.039	−0.399	2.133	−0.493
40	1.2	2.041	−0.841	1.992	−0.792	1.856	−0.656
41	3.4	3.292	0.108	3.384	0.016	3.474	−0.074
42	3.97	3.519	0.451	3.558	0.412	3.72	0.25
43	0.19	0.504	−0.314	0.591	−0.401	0.095	0.095
44	2.09	2.122	−0.032	1.936	0.154	1.887	0.203
45	3.28	3.057	0.223	2.644	0.636	2.707	0.573
46	1.96	1.507	0.453	1.359	0.601	1.739	0.221
47	2.68	2.829	−0.149	2.882	−0.202	2.783	−0.103
48	3.42	3.485	−0.065	3.496	−0.076	3.632	−0.212
49	4.19	4.137	0.053	4.237	−0.047	4.228	−0.038
50	5.25	5.452	−0.202	5.432	−0.182	5.598	−0.348
51	2.82	2.927	−0.107	3.007	−0.187	2.992	−0.172
52	3.35	2.99	0.36	3.036	0.314	3.151	0.199
53	3.05	2.917	0.133	2.958	0.092	3.038	0.012
54	3.04	2.696	0.344	2.658	0.382	2.779	0.261
55	1.96	2.402	−0.442	2.582	−0.622	2.234	−0.274
56	2.85	3.271	−0.421	3.138	−0.288	3.309	−0.459
57	4.43	3.905	0.525	4.256	0.174	4.178	0.252
58	4.74	4.018	0.722	4.195	0.545	4.311	0.429
59	2.31	2.258	0.052	2.252	0.058	2.398	−0.088
60	2.09	2.318	−0.228	2.209	−0.119	2.486	−0.396
61	2.55	2.748	−0.198	2.607	−0.057	2.978	−0.428
62	2.28	2.549	−0.269	2.742	−0.462	2.517	−0.237
63	2.92	2.952	−0.032	3.12	−0.2	2.997	−0.077
64	2.75	2.842	−0.092	2.991	−0.241	2.873	−0.123
65	2.75	2.912	−0.162	3.068	−0.318	2.956	−0.206
66	4.26	3.76	0.5	3.963	0.297	3.908	0.352
67	4.52	4.1	0.42	4.071	0.449	4.422	0.098

(continued)

Table 4 (*continued*)

Compd	Obs. Log(1/C_{nar})	Estimated log(1/C_{nar}) using					
		Model-5		Model-6		Model-8	
		Est.	Res.	Est.	Res.	Est.	Res.
68	2.57	2.631	−0.061	2.871	−0.301	2.579	−0.009
69	2.12	2.297	−0.177	2.639	−0.519	2.151	−0.031
70	1.64	2.286	−0.646	2.619	−0.979	2.06	−0.42
71	2.12	2.296	−0.176	2.619	−0.499	2.044	0.076
72	2.48	2.876	−0.396	3.097	−0.617	2.774	−0.294
73	3.91	3.658	0.252	3.791	0.119	3.808	0.102
74	2.18	2.401	−0.221	2.371	−0.191	2.45	−0.27
75	3.24	2.368	0.872	2.422	0.818	2.723	0.517
76	2.37	1.884	0.486	1.903	0.467	2.275	0.095
77	2.78	2.273	0.507	2.446	0.334	2.49	0.29
78	1.6	1.843	−0.243	1.805	−0.205	1.682	−0.082
79	2.72	3.337	−0.617	3.439	−0.719	3.236	−0.516
80	1.89	2.345	−0.455	1.97	−0.08	2.103	−0.213
81	1.92	2.117	−0.197	1.914	0.006	1.836	0.084
82	2.76	3.388	−0.628	2.672	0.088	2.852	−0.092
83	2.34	2.3	0.04	2.515	−0.175	2.17	0.17
84	0.77	0.35	0.42	0.221	0.549	0.171	0.599
85	0.57	1.52	−0.95	1.576	−1.006	—	—
86	3.51	2.634	0.876	2.511	0.999	—	—
87	3.48	2.816	0.664	2.926	0.554	2.813	0.667
88	0.6	0.184	0.416	0.501	0.099	—	—
89	1.46	1.824	−0.364	1.918	−0.458	1.903	−0.443
90	2.18	2.163	0.017	2.258	−0.078	2.332	−0.152
91	2.5	2.494	0.006	2.554	−0.054	2.749	−0.249
92	2.93	2.854	0.076	2.89	0.04	3.183	−0.253
93	0.23	0.864	−0.634	0.705	−0.475	0.353	−0.123
94	0.72	1.175	−0.455	1.095	−0.375	0.774	−0.054
95	1.14	1.508	−0.368	1.487	−0.347	1.222	−0.082
96	1.97	1.837	0.133	1.865	0.105	1.662	0.308
97	2.54	2.179	0.361	2.241	0.299	2.107	0.433
98	3.24	0.071	3.169	1.389	1.851	—	—
99	3.64	2.905	0.735	2.997	0.643	3.011	0.629
100	4.24	3.292	0.948	3.384	0.856	—	—
101	4.43	3.717	0.713	3.798	0.632	3.96	0.47
102	1.9	4.19	−2.29	4.249	−2.349	—	—
103	5.09	4.702	0.388	4.733	0.357	5.017	0.073
104	5.33	5.279	0.051	5.273	0.057	5.602	−0.272
105	1.77	1.742	0.028	1.727	0.043	1.494	0.276
106	2.32	2.054	0.266	2.078	0.242	1.917	0.403
107	2.86	2.391	0.469	2.438	0.422	2.353	0.507
108	3.48	2.756	0.724	2.811	0.669	2.805	0.675
109	4.21	3.105	1.105	3.163	1.047	—	—
110	2.3	2.285	0.015	2.443	−0.143	2.145	0.155
111	2.89	2.664	0.226	2.825	0.065	2.601	0.289
112	3.41	3.083	0.327	3.228	0.182	3.09	0.32
113	4.08	3.825	0.255	3.92	0.16	3.981	0.099
114	1.72	1.267	0.453	1.383	0.337	1.071	0.649
115	1.6	1.664	−0.064	1.778	−0.178	1.541	0.059
116	2.48	2.093	0.387	2.195	0.285	2.03	0.45
117	3.02	2.568	0.452	2.647	0.373	2.548	0.472
118	3.19	3.08	0.11	3.131	0.059	3.089	0.101
119	3.6	3.664	−0.064	3.677	−0.077	3.679	−0.079
120	4.41	4.65	−0.24	4.447	−0.037	4.773	−0.363
121	1.92	2.846	−0.926	2.878	−0.958	—	—
122	2.52	1.968	0.552	2.081	0.439	1.992	0.528
123	2.7	2.444	0.256	2.606	0.094	2.326	0.374

—Indicates deletion of nine compounds from the larger set of 123 making smaller set of 118 compounds; the model expressed by (eq 8) uses only 114 compounds.

Now-a-days, the connectivity and the valence connectivity indices expressed by eqs 12 and 13 are termed as first-order connectivity and first-order valence connectivity indices, respectively.

Branching index (B) and logRB. The branching index B and logRB have been calculated by the method as described in literature.[15,16]

Balaban index (J). The Balaban index, J (the average distance sum connectivity index) is defined[17] by:

$$J = J(G)\frac{M}{\mu + 1}\sum_{\text{bonds}}\left(d_i\ d_j\right)^{-1/2} \quad (15)$$

where M is the number of bonds in a graph G, μ is the cyclomatic number of G and d_i's ($i=1, 2, 3,\ldots,N$) are the distance sums (distance degrees) of atoms in G such that

$$d_i = \sum_{j=1}^{N} (D)_{ij} \tag{16}$$

The cyclomatic number μ of G indicates the number of independent cycles in G and is equal to the minimum number of cuts (removal of bonds) necessary to convert a polycylic structure into an acyclic structure:

$$\mu = M - N + 1 \tag{17}$$

One way to compute the Balaban index (J) for hetero-system is to modify the elements of the distance matrix for hetero-system as follows: (i) The diagonal elements:

$$(D)_{ij} = 1 - (Z_c/Z_i) \tag{18}$$

where $Z_c = 6$ and Z_i = atomic number of the given element.

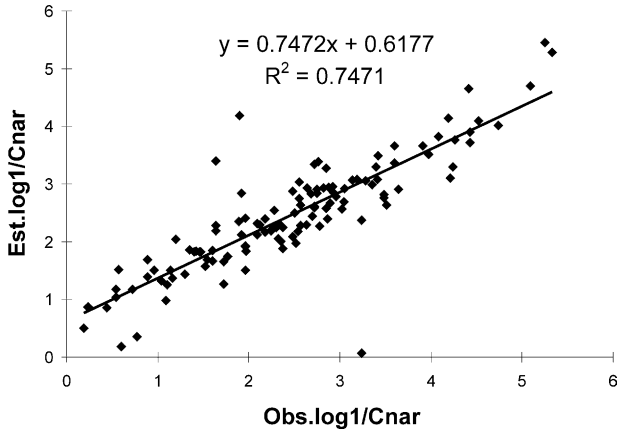

Figure 1. Correlation between observed and estimated $\log(1/C_{nar})$ using eq 5.

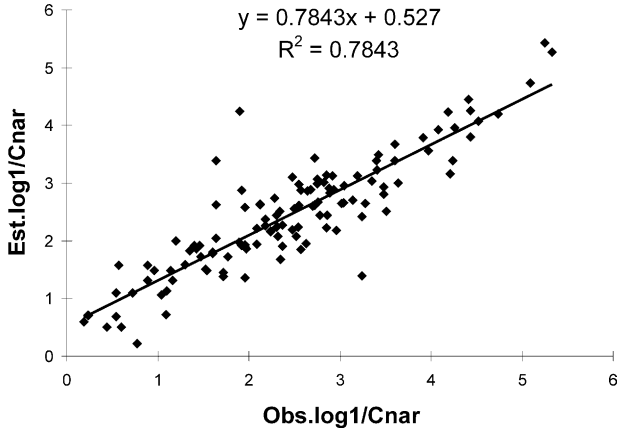

Figure 2. Correlation between observed and estimated $\log(1/C_{nar})$ using eq 6.

(ii) The off-diagonal elements:

$$(D)_{ij} d_i = \sum_r k_r \tag{19}$$

where the summation is over all bonds. The bond parameter k_r is given by:

$$k_r = 1/b_r\left(Z_c^2/Z_i Z_j\right)$$

where b_r is the bond weight with values: 1 for single bond, 2 for double bond, 1.5 for aromatic bond and 3 for triple bond.

Quality factor (Q). The quality factor (Q) is defined[19,20] as the ratio of correlation coefficient (R) to the standard error of estimation (SE), that is $Q = R/\mathrm{SE}$. Thus, higher the value of R, the lower the SE, the larger will be Q, and better will be the quality of the model.

Regression analysis. Maximum R^2 improvement method is to identify prediction models.[18] This method finds the 'best' one variable model, the 'best' two variable model and so forth for the prediction of property/activity. Several models (combinations of variables) were examined to identify combinations of variables with good prediction capabilities. In all regression models developed a variety of statistics associated with residues, that is the Wilks–Shapiro test for normality and Cooks D-statistics for outliers, to obtain the most reliable results were examined.[18]

Multiple regression analyses for correlating tadpole narcosis of the present set of compounds with the aforementioned molecular descriptors were carried out using *Regress-1* software as supplied by Professor I. Lukovits, Hungarian Academy of Sciences, Budapest, Hungary. Several multiple regressions were attempted using correlation matrix from this program and the best results were considered and discussed in developing QSAR and hence, for modeling the tadpole narcosis of the compounds.

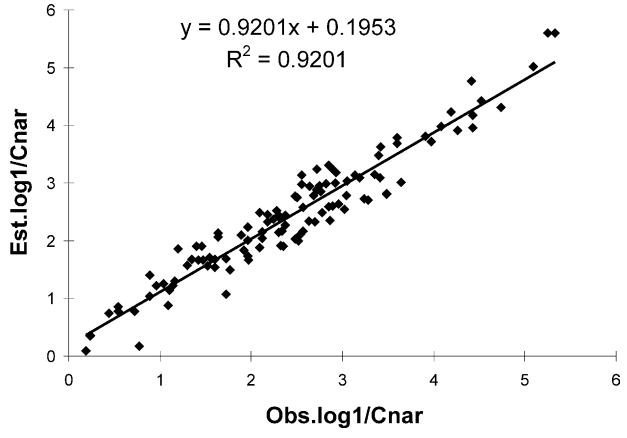

Figure 3. Correlation between observed and estimated $\log(1/C_{nar})$ using eq 8.

Computations. All the computations were carried out in Power Macintosh 9600/233.

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