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QSAR study on topically acting sulfonamides incorporating GABA moieties: A molecular connectivity approach

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Dedicated to Professor P. V. Khadikar and his wife Kusum Khadikar on the eve of their 70th birthday.

Abstract—A quantitative Structure–activity relationship study (QSAR) on a set of carbonic anhydrase (CA, EC 4.2.1.1) inhibitors is reported using first-order valence connectivity index ($^1\chi^v$). The inhibitory activity against three isozymes CAI, CAII (cystolic forms), and CAIV (membrane bound form), some of which are involved in important physiological processes, were considered for this purpose. All the three activities were excellently modeled by $^1\chi^v$ in multi-parametric regression containing indicator parameters. The results are critically discussed on the basis of various regression parameters.

Several thousand different aromatic/heterocyclic sulfonamides carbonic anhydrase (CA, EC 4.2.1.1) inhibitors were synthesized in the last 50 years in the search of diverse pharmacological agents[1,2] but the number of amino acid/oligopeptide derivatives among them is unexpectedly small. Consequently, a large series of 53 compounds were synthesized by Supuran and co-workers[3] and investigated for their inhibitory activity against physiologically relevant CA isozymes, such as CAI, II, and IV. The syntheses involved the reaction of 26 aromatic/heterocyclic sulfonamides containing amino, imino, hydrazine or hydroxyl groups with *N-tert*-butoxycarbonyl-γ-aminobutyric acid (Boc-GABA) in the presence of carbodimide derivatives. The resulting water-soluble compounds were assayed as inhibitors of the cytosolic isozymes hCAI, and II and the membrane bound form bCAIV, which were involved in important physiological processes. Some of these new derivatives effectively inhibited hCAII and bCAIV, the two isozymes considered to play a critical role in aqueous humor secretion within the ciliary processes of the eye. Some compounds were then investigated in an animal model of glaucoma (hypertensive rabbits), when strong and long-lasting intraocular pressure (IOP) lowering has been evidenced. Recent QSAR studies[4–15] made by us on this class of compounds revealed that the CA inhibitory activities of such compounds could be modeled successfully using topological and information theoretic indices. In majority of the investigated cases, it was observed that the use of indicator parameters resulted in statistically excellent models. Prompted by the success in using topological indices in modeling CA inhibitory activity, in this paper we report the use of first-order valence connectivity index[16,17] ($^1\chi^v$) in developing quantitative Structure–activity relationship (QSAR) on topically acting sulfonamides incorporating GABA moieties (Table 1). The results as discussed below show that $^1\chi^v$ in combination with indicator parameters can be used successfully for modeling inhibitory activities against all the three isozymes, that is, hCAI, hCAII, and bCAIV. Such a modeling is performed using maximum R^2 method following step wise regression analysis.[18]

The large set of 53 sulfonamides, chosen for the present study, is presented in Table 1. Surprisingly, only a single topological index viz., first-order valence connectivity ($^1\chi^v$) is found useful in modeling the activities. The

Keywords: QSAR; Sulfonamide; Carbonic anhydrase; Molecular connectivity; Regression analysis.
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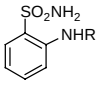
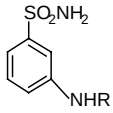
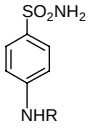
Table 1. Structural details of sulfonamides used in present investigation



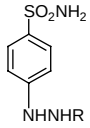
1.R=H
28. R= GABA



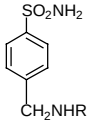
2. R=H
29. R=GABA



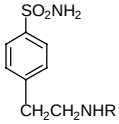
3. R=H
30. R=GABA



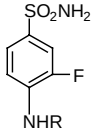
4. R=H
31. R=GABA



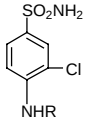
5. R=H
32. R=GABA



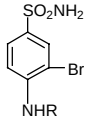
6. R=H
33. R=GABA



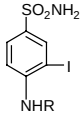
7. R=H
34. R=GABA



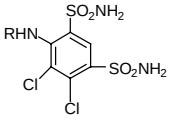
8. R=H
35. R=GABA



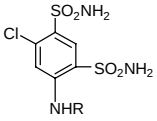
9. R=H
36. R= GABA



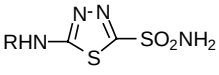
10. R=H
37. R= GABA



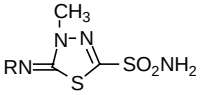
11. R=H
38. R= GABA



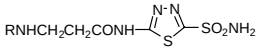
12. R=H
39. R=GABA



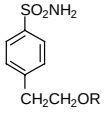
13. R=H
40. R=GABA



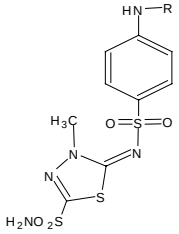
14. R=H
41. R=GABA



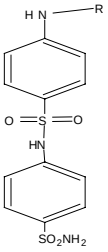
15. R=H
42. R=GABA



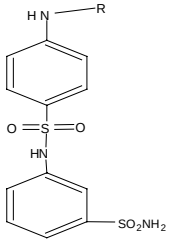
16. R=H
43. R=GABA



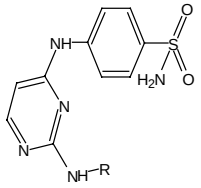
17. R=H



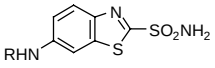
18. R=H
45. R=GABA



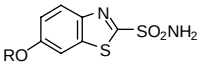
19. R=H
46. R=GABA



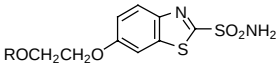
20. R=H
47. R=GABA



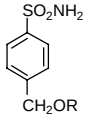
21. R=H
48. R=GABA



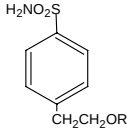
22. R=H
49. R=GABA



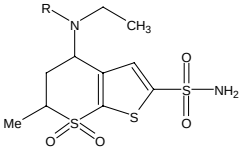
23. R=H
50. R=GABA



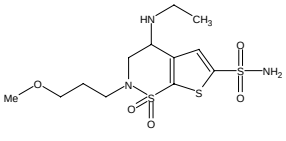
24. R=H
51. R=GABA



25. R=H
52. R=GABA



26.R=H
(Dorzolamide)
53. R=GABA



27. (brinzolamide)

GABA=
$H_2NCH_2CH_2\ CH_2CO$-

calculated values of $^{1}\chi^{v}$ using the software of Lukovits are recorded in Table 2. This also contains information regarding the indicator parameters (Ip_1, Ip_2, and Ip_3) used. They are considered unity if GABA is present at R (Ip_1), halogen is present in the sulfonamide moieties (Ip_2) and a five-membered ring is present in the molecule (Ip_3). In the absence of such structural information the indicator parameters Ip_1, Ip_2, and Ip_3 are considered zero. The intercorrelatedness among the activities, $^{1}\chi^{v}$, and the indicator parameters presented in Table 3 demonstrated that no mono-parametric model is possible for modeling any of the activity and that in multi-parametric regressions $^{1}\chi^{v}$ and Ip_3 are the most useful parameters to be used there in.

Table 2. The inhibition activities: $\log K_i$(hCAI), $\log K_i$(hCAII), and $\log K_i$(bCAIV), first-order valence connectivity index ($^{1}\chi^{v}$), and values of indicator parameters (Ip_1, Ip_2, and Ip_3) for a series of sulfonamides used in the present study

Compound	$\log K_i$(hCAI)	$\log K_i$(hCAII)	$\log K_i$(bCAIV)	$^{1}\chi^{v}$	Ip_1	Ip_2	Ip_3
1	4.6571	2.4699	3.1173	4.436	0	0	0
2	4.3980	2.3802	3.3425	4.430	0	0	0
3	4.4472	2.4771	3.4771	4.430	0	0	0
4	4.8949	2.5051	3.5071	4.680	0	0	0
5	4.3980	2.2304	3.4471	4.903	0	0	0
6	4.3223	2.2041	3.3891	5.403	0	0	0
7	3.9190	1.7781	2.2553	4.535	0	1	0
8	3.9912	2.0414	2.5051	4.913	0	1	0
9	3.8130	1.6020	1.8196	5.328	0	1	0
10	3.7782	1.8450	2.0970	5.614	0	1	0
11	3.7854	1.4471	2.2430	7.639	0	1	0
12	3.9243	1.8750	2.2041	7.149	0	1	0
13	3.9345	1.7781	2.7324	4.480	0	0	1
14	3.9685	1.2788	2.5502	4.889	0	0	1
15	2.6580	0.4771	2.0970	6.157	0	0	1
16	0.7782	0.3010	0.6990	8.776	0	0	1
17	0.9543	0.7781	0.9030	9.132	0	0	1
18	1.6233	0.7781	1.6990	8.726	0	0	0
19	1.6435	0.9543	1.7243	8.726	0	0	0
20	2.8389	1.0792	2.1876	6.481	0	0	0
21	1.8450	0.9543	1.2788	6.018	0	0	1
22	1.7403	0.9030	1.2304	5.953	0	0	1
23	1.6990	0.8450	1.1760	7.038	0	0	1
24	4.3802	2.0970	2.7481	4.811	0	0	0
25	4.2553	2.0414	2.6533	5.311	0	0	0
26	4.6990	0.9543	1.6533	9.723	0	0	1
27	—	0.5051	1.6560	10.907	0	0	1
28	4.3010	2.2945	2.3857	6.613	1	0	0
29	4.2356	2.2600	2.3325	6.607	1	0	0
30	4.1819	2.0493	2.2149	6.607	1	0	0
31	4.3521	2.3264	2.4843	6.857	1	0	0
32	3.1903	1.5051	1.8389	7.064	1	0	0
33	2.9165	1.4771	1.7924	7.564	1	0	0
34	2.7243	1.0000	1.5798	6.712	1	1	0
35	2.7481	1.4914	1.7994	7.090	1	1	0
36	2.7160	1.4771	1.7781	7.505	1	1	0
37	2.6990	1.4314	1.7481	7.791	1	1	0
38	2.6533	1.0000	1.6990	9.816	1	1	0
39	2.5440	0.9543	1.6990	9.327	1	1	0
40	2.4771	0.9030	1.6335	6.657	1	0	1
41	2.4914	1.0000	1.6233	7.052	1	0	1
42	1.3802	0.6990	1.1760	8.319	1	0	1
43	1.0791	0.4771	0.9543	10.953	1	0	1
44	1.1760	0.6020	1.1461	11.310	1	0	1
45	1.7994	1.1461	1.8750	10.903	1	0	0
46	1.7854	1.1140	1.8260	10.903	1	0	0
47	1.7076	1.0414	1.6990	8.658	1	0	0
48	1.1461	0.6990	1.0791	8.195	1	0	1
49	1.1760	1.7324	1.0791	8.104	1	0	1
50	1.0000	0.6020	1.0414	9.181	1	0	1
51	3.2430	1.8634	2.2553	6.953	1	0	0
52	3.2304	1.8196	2.1903	7.453	1	0	0
53	1.7481	0.7781	1.5051	11.845	1	0	1

Ip_1 = 1 if GABA present at R position, otherwise 0; Ip_2 = 1 if halogen is present in the compound, otherwise 0; Ip_3 = 1 if a five-membered ring is present, otherwise 0.

Table 3. Correlation matrix for the intercorrelation of various molecular descriptors and $\log K_i$(hCAI), $\log K_i$(hCAII), and $\log K_i$(bCAIV)

	$\log K_i$(hCAI)	$\log K_i$(hCAII)	$\log K_i$(bCAIV)	$^1\chi^v$	Ip_1	Ip_2	Ip_3
$\log K_i$(hCAI)	1.0000						
$\log K_i$(hCAII)	0.8513	1.0000					
$\log K_i$(hCAIV)	0.8459	0.8431	1.0000				
$^1\chi^v$	−0.7264	−0.6949	−0.6880	1.0000			
Ip_1	−0.2915	−0.1636	−0.3773	0.4927	1.0000		
Ip_2	0.1714	0.0801	−0.0198	−0.0919	0.0102	1.0000	
Ip_3	−0.5703	−0.6511	−0.5831	0.3133	−0.0253	−0.4045	1.0000

We have attempted multiple regression analysis separately for modeling each of the CAI, CAII, and CAIV inhibitory activities using stepwise regression analysis adopting maximum R^2 method. In doing so the activities reported earlier by Supuran and co-workers[3] are converted into their logarithms (Table 2). The results obtained for modeling $\log K_i$(hCAI), $\log K_i$(hCAII), and $\log K_i$(bCAIV) are presented in Tables 4, 5, and 6, respectively. The general observation of the data presented in these tables indicates that $^1\chi^v$ is the most appropriate topological index for modeling the activities. Also, that out of the three-indicator parameters used, Ip_3 in combination with $^1\chi^v$ gave better results. At this stage it is interesting to record that $^1\chi^v$ accounts for the number of atoms, first-order branching, and effect due to heteroatom, while Ip_3 is responsible for the presence of a five-membered ring in the sulfonamide moiety. These information taken together indicate that number of atoms, first-order branching, heteroatom, and the five-membered ring are responsible for the exhibition of all the three inhibitory activities. We now discuss the modeling of $\log K_i$(hCAI).

Modeling of $\log K_i$(hCAI). A perusal of Table 3 shows that none of the parameters ($^1\chi^v$, Ip_1, Ip_2, and Ip_3) independently correlates significantly with the activity. It means that statistically good mono-parametric regression expressions are not possible for modeling

Table 4. Regression parameters and quality of correlation for modeling $\log K_i$(hCAI) activity

Model No.	Parameters used	A_i, i = 1,2,3	B (intercept)	Se	Correlation coefficient (R)	F ratio	$Q = R/Se$
1	$^1\chi^v$	−0.5049(±0.0593)	6.4882	0.7833	−0.7757	72.510	−0.9902
2	$^1\chi^v$	−0.5770(±0.0713)	6.7670	0.7672	0.7911	39.305	1.0311
	Ip_1	0.4640(±0.2665)					
3	$^1\chi^v$	−0.4434(±0.0425)	6.4391	0.5500	0.8987	98.708	1.6340
	Ip_3	−1.2086(±0.1703)					
4	$^1\chi^v$	−0.4869(±0.0523)	6.6019	0.5444	0.9031	67.824	1.6589
	Ip_1	0.2686(±0.1912)					
	Ip_3	−1.1730(±0.1705)					

Table 5. Regression parameters and quality of correlation for modeling $\log K_i$(hCAII) activity

Model No.	Parameters used	A_i, i = 1,2,3	B (intercept)	Se	Correlation coefficient (R)	F ratio	$Q = R/Se$
1	$^1\chi^v$	−0.2224(±0.0301)	3.0586	0.4354	−0.7371	54.721	−1.6930
2	$^1\chi^v$	−0.2488(±0.0350)	3.1410	0.4306	0.7503	28.985	1.7425
	Ip_1	0.2086(±0.1465)					
3	$^1\chi^v$	−0.1657(±0.0221)	2.8942	0.2997	0.8879	83.772	2.9627
	Ip_3	−0.6981(±0.0967)					
4	$^1\chi^v$	0.1593(±0.0188)	3.0080	0.2542	0.9226	83.853	3.6295
	Ip_2	−0.4052(±0.0940)					
	Ip_3	−0.8649(±0.0907)					

Table 6. Regression parameters and quality of correlation for modeling $\log K_i$(bCAIV) activity

Model No.	Parameters used	A_i, i = 1,2,3	B (intercept)	Se	Correlation coefficient (R)	F ratio	$Q = R/Se$
1	$^1\chi^v$	−0.2704(±0.0389)	3.9158	0.5144	−0.7080	48.230	−1.3764
2	$^1\chi^v$	−0.2353(±0.0.0314)	3.8877	0.4055	0.8346	53.935	2.0581
	Ip_3	−0.6907(±0.1256)					
3	$^1\chi^v$	−0.2309(±0.0281)	4.0221	0.3629	0.8730	49.134	2.4057
	Ip_2	−0.4644(±0.1303)					
	Ip_3	−0.8581(±0.1218)					

$\log K_i$(hCAI). However, when $^1\chi^v$ is combined with Ip_3 considerably better statistics is obtained (Table 4). Here, regression analysis indicated that compounds 26 and 53 are outliers (compound no. **27** is not reported to be active). Therefore, they are deleted from the regression procedure. The model so obtained is reported as under

$$\begin{aligned}\log K_i(\text{hCAI}) = &-0.4434(\pm0.0425)^1\chi^v \\ &-1.2086(\pm0.1703)Ip_3 + 6.4391, \\ n = 50,\ Se = 0.5500,\ R = 0.8987,& \\ F = 98.708,\ Q = 1.6340.& \end{aligned} \quad (1)$$

Here and thereafter, n is the number of data points, Se is the standard error of estimation, R is the multiple correlation coefficient, F is the Fisher statistics, and Q is the quality factor[19–21] ($Q = R/Se$). All other two-variable modeling resulted in inferior statistics than the above model Eq. 1. Improved results are obtained by adding the Ip_1 term to the above Eq. 1. Finally, this tri-parametric regression containing $^1\chi^v$, Ip_1, and Ip_3 gave the excellent model

$$\begin{aligned}\log K_i(\text{hCAI}) = &-0.4869(\pm0.0523)^1\chi^v \\ &+0.2686(\pm0.1912)Ip_1 \\ &-1.1730(\pm0.1705)Ip_3, \\ n = 50, Se = 0.5444,\ R = 0.9031,\ F = 67.824,& \\ Q = 1.6589.& \end{aligned} \quad (2)$$

No higher parametric regressions resulted in having better statistics than the tetra-parametric expression given above.

It is interesting to mention that in all the equations discussed above the coefficients of $^1\chi^v$ and Ip_3 terms are negative. Since $^1\chi^v$ accounts for the first-order branching and presence of heteroatoms, its negative coefficient indicates that the presence of heteroatoms and first-order branching are not favorable for the exhibition of $\log K_i$(hCAI) activity. Also, Ip_3 accounts for the presence/absence of a five-membered ring. So, its negative coefficient indicates that the presence of a five-membered ring is not favorable for the exhibition of activity. In Eq. 2, the coefficient of Ip_1 is positive. This indicator parameter accounts for the presence/absence of GABA moiety at R. Hence, the positive coefficient of Ip_1 indicates that the presence of GABA moiety at R is favorable for the exhibition of the activity.

Modeling of $\log K_i$(hCAII) activity. We now discuss the potential of $^1\chi^v$ for modeling $\log K_i$(hCAII) activity. The preliminary regression analysis has shown that the compounds **15**, **18**, **20**, **21**, and **49** are outliers. These compounds, therefore, are deleted from the further regression analysis. The data presented in Tables 3 and 5 indicate that $^1\chi^v$ alone is incapable of modeling the activity. However, as in earlier cases, here also its combinations with the indicator parameters resulted in regression expressions with better statistics. The data presented in Table 5 show that the statistics goes on improving as we pass from two to higher variable regressions and that the tri-parametric models gave the best results

$$\begin{aligned}\log K_i(\text{hCAII}) = &-0.1593(\pm0.0188)^1\chi^v \\ &-0.4052(\pm0.0940)Ip_2 \\ &-0.8649(\pm0.0907)Ip_3 + 3.0080, \\ n = 48,\ Se = 0.2542,\ R = 0.9226,& \\ F = 83853,\ Q = 3.6295.& \end{aligned} \quad (3)$$

Like the earlier case, here also the coefficient of $^1\chi^v$ and Ip_3 terms are negative. Hence, the earlier physical significances can also be attached to them in Eq. 3.

Modeling $\log K_i$(bCAIV) activity. We now discuss the use of $^1\chi^v$ for modeling $\log K_i$(bCAIV) activity. Here, the preliminary regression analysis indicated that compounds **26**, **27**, and **53** are outliers. Therefore, they are deleted from the regression procedure. The data presented in Tables 3 and 6 indicate that $^1\chi^v$ alone is incapable of modeling $\log K_i$(bCAIV) activity and that the combinations of $^1\chi^v$ with indicator parameters gave statistically significant results of Table 6. The only difference between this and earlier two cases is that here the tri-parametric expression was found to yield best results. The tri-parametric model, which gave the best results for modeling $\log K_i$(bCAIV) activity (Table 6), was found as below

$$\begin{aligned}\log K_i(\text{bCAIV}) = &-0.2309(\pm0.0281)^1\chi^v \\ &-0.4644(\pm0.1303)Ip_2 \\ &-0.8581(\pm0.1218)Ip_3, \\ n = 50,\ Se = 0.3629,\ R = 0.8730,\ F = 49.134,& \\ Q = 2.4.& \end{aligned} \quad (4)$$

Like the earlier two cases, here also the coefficient of $^1\chi^v$, Ip_2, and Ip_3 are negative. They, therefore, carry the same physical significance as before. Also, the coefficient Ip_2 is negative as it was observed before, it is evident that the presence of halogen is not favorable for the exhibition of $\log K_i$(bCAIV) activity.

In order to confirm our results, we have estimated $\log K_i$(hCAI), $\log K_i$(hCAII), and $\log K_i$(bCAIV) activity using the corresponding best regression expressions: that is Eqs. 2–4, respectively, and compared them with their observed values. Such a comparison is shown in Table 7. In this Table 7 shows that the observed and estimated activities are very close to each other. In obtaining further support in favor of our results we have calculated predictive correlation coefficients from the plots of observed versus calculated activity using three best models, which gave a predictive correlation coefficient (R^2_{pred}.) 0.8156, 0.8510, and 0.7622, respectively, for CAI, CAII, and CAIV. These plots are reported as in Figures. 1–3.

The use of distance-based topological indices is quite useful in modeling carbonic anhydrase inhibitory activity. The most interesting observation was that a single topological index, $^1\chi^v$, afforded satisfactory results. Furthermore, the use of $^1\chi^v$ is most suited for modeling $\log K_i$(hCAI) and $\log K_i$(hCAII).

Topological indices. All distance based topological indices were computed using hydrogen-suppressed graphs in

Table 7. Estimated value of $\log K_i$(hCAI), $\log K_i$(hCAII), and $\log K_i$(bCAIV) from Eqs. 2–4 and their comparison with observed value

Compound	$\log K_i$(hCAI), Eq. 2			$\log K_i$(hCAII), Eq. 3			$\log K_i$(bCAIV), Eq. 4		
	Obs.	Est.	Res.	Obs.	Est.	Res.	Obs.	Est.	Res.
1	4.657	4.442	0.215	2.470	2.301	0.169	3.117	2.998	0.119
2	4.398	4.445	−0.047	2.380	2.302	0.078	3.343	2.999	0.344
3	4.448	4.445	0.003	2.477	2.302	0.175	3.477	2.999	0.478
4	4.895	4.323	0.572	2.505	2.262	0.243	3.507	2.941	0.566
5	4.398	4.215	0.183	2.230	2.227	0.003	3.447	2.890	0.557
6	4.322	3.971	0.351	2.204	2.147	0.057	3.389	2.774	0.615
7	3.919	4.394	−0.475	1.778	1.880	−0.102	2.255	2.510	−0.255
8	3.991	4.210	−0.219	2.041	1.820	0.221	2.505	2.423	0.082
9	3.813	4.008	−0.195	1.602	1.754	-0.152	1.820	2.327	−0.507
10	3.779	3.868	−0.089	1.845	1.708	0.137	2.097	2.261	−0.164
11	3.786	2.882	0.904	1.447	1.386	0.061	2.243	1.794	0.449
12	3.925	3.121	0.804	1.875	1.464	0.411	2.204	1.907	0.297
13	3.935	3.248	0.687	1.778	1.429	0.349	2.732	2.129	0.603
14	3.969	3.048	0.921	1.279	1.364	−0.085	2.550	2.035	0.515
15	2.658	2.431	0.227	0.477	—	—	2.097	1.742	0.355
16	0.779	1.156	−0.377	0.301	0.745	−0.444	0.699	1.137	−0.438
17	0.955	0.982	−0.027	0.778	0.688	0.090	0.903	1.055	−0.152
18	1.624	2.353	−0.729	0.778	—	—	1.699	2.007	−0.308
19	1.644	2.353	−0.709	0.954	1.184	−0.230	1.724	2.007	−0.283
20	2.839	3.446	−0.607	1.079	—	—	2.188	2.525	−0.337
21	1.845	2.499	−0.654	0.954	—	—	1.279	1.774	−0.495
22	1.740	2.530	−0.790	0.903	1.195	−0.292	1.230	1.789	−0.559
23	1.699	2.002	−0.303	0.845	1.022	−0.177	1.176	1.539	−0.363
24	4.380	4.259	0.121	2.097	2.241	−0.144	2.748	2.911	−0.163
25	4.256	4.016	0.240	2.041	2.162	−0.121	2.653	2.796	−0.143
26	4.699	—	—	0.954	0.594	0.360	2.386	—	—
27	—	—	—	0.505	0.405	0.100	1.656	—	—
28	4.301	3.651	0.650	2.295	1.954	0.341	2.386	2.495	−0.109
29	4.237	3.653	0.584	2.260	1.955	0.305	2.333	2.496	−0.163
30	4.181	3.653	0.528	2.049	1.955	0.094	2.215	2.496	−0.281
31	4.352	3.532	0.820	2.326	1.915	0.411	2.484	2.439	0.045
32	3.190	3.431	−0.241	1.505	1.883	−0.378	1.839	2.391	−0.552
33	2.917	3.187	−0.270	1.477	1.803	−0.326	1.792	2.275	−0.483
34	2.725	3.602	−0.877	1.000	1.533	−0.533	1.580	2.008	−0.428
35	2.748	3.418	−0.670	1.491	1.473	0.018	1.799	1.920	−0.121
36	2.716	3.216	−0.500	1.477	1.407	0.070	1.778	1.824	−0.046
37	2.699	3.077	−0.378	1.431	1.361	0.070	1.748	1.758	−0.010
38	2.654	2.091	0.563	1.000	1.039	−0.039	1.699	1.291	0.408
39	2.544	2.329	0.215	0.954	1.117	−0.163	1.699	1.404	0.295
40	2.477	2.456	0.021	0.903	1.082	−0.179	1.634	1.627	0.007
41	2.491	2.264	0.227	1.000	1.019	−0.019	1.623	1.535	0.088
42	1.380	1.647	−0.267	0.699	0.818	−0.119	1.176	1.243	−0.067
43	1.079	0.364	0.715	0.477	0.398	0.079	0.954	0.634	0.320
44	1.176	0.191	0.985	0.602	0.341	0.261	1.146	0.552	0.594
45	1.799	1.562	0.237	1.146	1.271	−0.125	1.875	1.504	0.371
46	1.786	1.562	0.224	1.114	1.271	−0.157	1.826	1.504	0.322
47	1.708	2.655	−0.947	1.041	1.629	−0.588	1.699	2.023	−0.324
48	1.146	1.707	−0.561	0.699	0.837	−0.138	1.079	1.271	−0.192
49	1.176	1.752	−0.576	1.732	—	—	1.079	1.292	−0.213
50	1.000	1.227	−0.227	0.602	0.680	−0.078	1.041	1.044	−0.003
51	3.243	3.485	−0.242	1.863	1.900	−0.037	2.255	2.416	−0.161
52	3.230	3.242	−0.012	1.820	1.821	−0.001	2.190	2.301	−0.111
53	1.748	—	—	0.778	0.256	0.522	1.5051	—	—

which all the carbon–hydrogen as well as heteroatom-hydrogen bonds are deleted.

First-order valence connectivity index ($^1\chi^v$). The connectivity index $\chi = \chi(G)$ of a graph G is defined as under

$$^1\chi = {}^1\chi(G) = \sum_{ij} [\delta_i \delta_j]^{-0.5}, \qquad (5)$$

where δ_i and δ_j are valencies of vertices i and j, equal to the number of bonds connected to the atoms i and j in G.

In the case of heterosystems, 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 $^1\chi^v$. This version of the connectivity index is called the valence connectivity index and is defined[16,17] as under

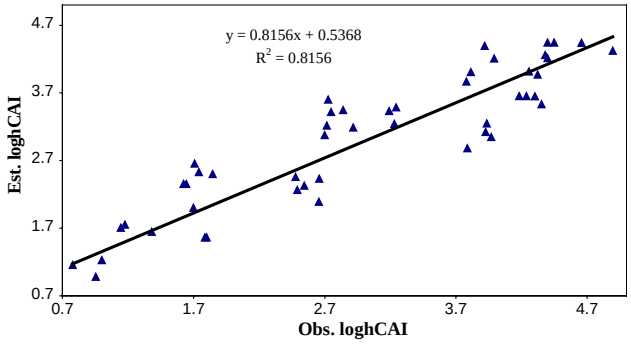


Figure 1. Correlation of observed and estimated $\log K_i$ (hCAI) using Eq. 2.

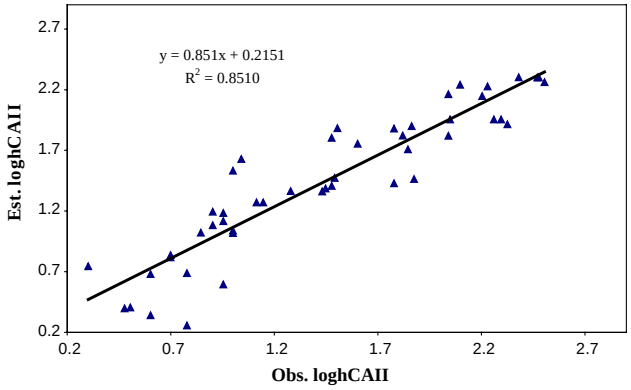


Figure 2. Correlation of observed and estimated $\log K_i$ (hCAII) using Eq. 3.

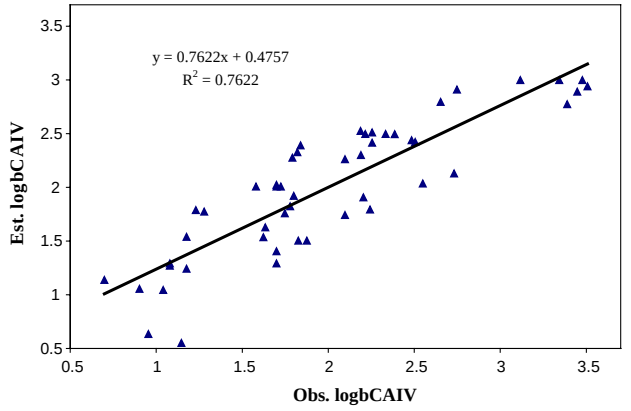


Figure 3. Correlation of observed and estimated $\log K_i$ (hCAIV) using Eq. 4.

$$ {}^{1}\chi^{v} = {}^{1}\chi^{v}(G) = \sum_{ij} [\delta_i^v \delta_j^v]^{-0.5}, \tag{6} $$

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

$$ \delta_i^v = \frac{Z_i^v - H_i}{Z_i - Z_i^v - 1}, \tag{7} $$

where Z_i is the atomic number of atom *i*, Z_i^v is the number of valence electrons of the atom *i*, and H_i is the number of hydrogen atoms attached to atom *i*. The DRAGON software is used which takes account of halogen ${}^{1}\chi^{v}$ values (δ^v values for Cl = 0.78, Br = 0.26, and I = 0.16).

Indicator parameters. Three-indicator parameters, viz., Ip_1, Ip_2, and Ip_3 have been used in the present study. The indicator parameter Ip_1 has been taken as 1 when GABA is present at R position. When halogen is present in the compound, the indicator parameter Ip_2 is assigned a value of unity. Similarly, when a five-membered ring is present, indicator parameter Ip_3 has been taken as unity. In the absence of such situations, the corresponding values of indicator parameters are taken as zero.

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