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Original article

QSAR study on carbonic anhydrase inhibitors: aromatic/heterocyclic sulfonamides containing 8-quinoline-sulfonyl moieties, with topical activity as antiglaucoma agents

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Abstract

Quantitative structure–activity-relationship (QSAR) study on aromatic/heterocyclic sulfonamides containing 8-quinoline-sulfonyl carbonic anhydrase (CA) inhibitors has been carried out topologically using first-order valence connectivity index ($^1\chi^v$). Excellent results are obtained against all the three isozymes; CA I, II and IV of the zinc enzyme CA by using indicator parameters along with $^1\chi^v$.

Keywords: QSAR; Carbonic anhydrase inhibitors; Valence connectivity; Regression analysis; Aromatic; Hetrocyclic sulfonamides

1. Introduction

A series of water-soluble carbonic anhydrase (CA, EC 4.2.1.1) inhibitors were obtained by reaction of aromatic/hetrocyclic sulfonamides containing a free amino, amino hydrazine or hydroxy group with 8-quinoline-sulfonyl chloride, in the search of more effective topically acting antiglaucoma drugs [1]. Efficient inhibition of these newly synthesized compounds was observed against the three physiologically relevant isozymes; CA I, II and IV, these compounds being most active against CA II (in nanomolar range), the enzyme playing a major role in aqueous humor secretion within the eye [2].

The sulfonamides represent an important class of biologically active compounds. The antibacterial sulfonamides continue to play an important role in chemotherapy, alone or in combination with other drugs. The sulfonamides that inhibit the zinc enzyme carbonic anhydrase (CA, EC 4.2.1.1) possess many applications as diuretic, antiglaucoma, anticancer or antiepileptic drugs [2–5].

Quantitative structure–activity-relationship studies (QSARs) using molecular descriptors other than topological indices have been reported earlier, by Clare and Supuran [3–5]. Later on, it has been observed that use of topological indices is quite successful for such QSAR analyses [6–8]. It is worth mentioning that topological indices are the graph-theoretical descriptors obtained by transforming molecular structures into the corresponding molecular graphs [9–11]. Such transformation is performed by deleting all the carbon–hydrogen and heteroatom-hydrogen bonds in the molecular structures.

In continuation to our earlier work on QSAR studies on CA inhibitors using topological indices [6–8], in the present study we report QSAR study on aromatic and heterocyclic sulfonamides containing 8-quinoline-sulfonyl moieties, previously reported by Borras et al. [1] (Table 1). The results, as discussed below, show that all the three inhibitory activities namely hCAI, hCAII and hCAIV of the referred sulfonamides were successfully modeled by a single topological index, viz. Kier and Hall first-order valence connectivity index ($^1\chi^v$) [12,13]. The results discussed below show that excellent results are obtained when $^1\chi^v$ is combined with indicator parameters. The statistics of the fitting are impressive and indicate that the equations (models) derived are

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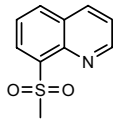
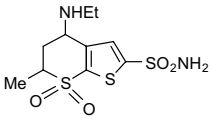
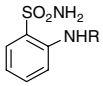
Table 1
Structures of sulfonamides used in the present investigation



8QS



1. Dorzolamide



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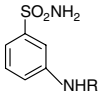
22. R= 8QS



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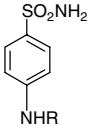

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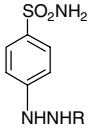

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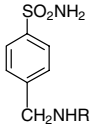

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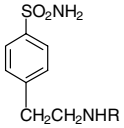

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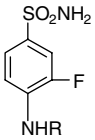

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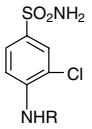

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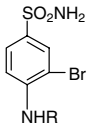

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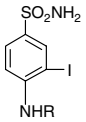

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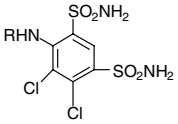

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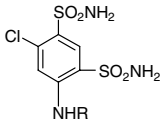

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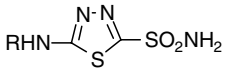

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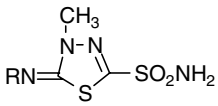
34. R= 8QS



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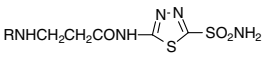
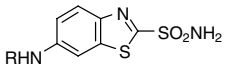


16. R=H
36. R= 8QS



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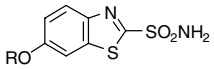

18. R=H
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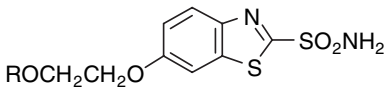

19. R=H
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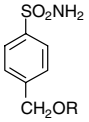

20. R=H
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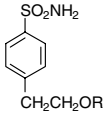
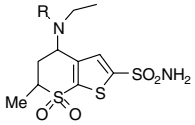


21. R=H
41. R= 8QS



42. R=8QS

Table 2
Inhibition activities: log K_I(hCAI), log K_I(hCAII), log K_I(hCAIV) first-order valence connectivity and values of indicator parameters for sulfonamides used in the present study

Compound number	log K_I(hCAI)	log K_I(hCAII)	log K_I(hCAIV)	$^1\chi^v$	Ip_1	Ip_2	Ip_3
1	4.699	0.9542	1.6532	5.852	0	0	1
2	4.6571	2.4698	3.1173	2.889	0	0	0
3	4.3979	2.3802	3.3424	2.883	0	0	0
4	4.4472	2.4771	3.4771	2.883	0	0	0
5	4.8949	2.5051	3.5072	3.133	0	0	0
6	4.3979	2.2304	3.4472	3.357	0	0	0
7	4.322	2.2041	3.3892	3.857	0	0	0
8	3.9191	1.7782	2.2553	2.988	0	1	0
9	3.9912	2.0414	2.5052	2.988	0	1	0
10	3.8129	1.6021	1.8195	2.988	0	1	0
11	3.7782	1.8451	2.0969	2.988	0	1	0
12	3.7953	1.4472	2.243	3.79	0	1	0
13	3.9243	1.8751	2.2041	3.678	0	1	0
14	3.3945	1.8751	2.2041	2.117	0	0	1
15	3.9685	1.2788	2.5502	2.525	0	0	1
16	2.658	0.4771	2.0969	3.741	0	0	1
17	1.8451	0.9542	1.2788	3.654	0	0	1
18	1.7404	0.9031	1.2304	3.59	0	0	1
19	1.699	0.8451	1.1761	4.675	0	0	1
20	4.3802	2.0969	2.7482	3.265	0	0	0
21	4.2553	2.0414	2.6532	3.765	0	0	0
22	4.3263	2.4683	2.4425	6.773	1	0	0
23	4.301	2.4314	2.525	6.768	1	0	0
24	4.1903	2.1271	2.2455	6.768	1	0	0
25	4.3424	2.4771	2.5798	7.018	1	0	0
26	3.0934	1.8751	2.0934	8.191	1	0	0
27	3.0414	1.7782	2.0128	7.725	1	0	0
28	2.7364	1.5051	1.9868	6.874	1	1	0
29	2.7924	1.6435	1.8976	6.874	1	1	0
30	2.7818	1.6532	1.9191	6.874	1	1	0
31	2.7853	1.6021	1.8751	6.874	1	1	0
32	2.699	1.5052	1.8388	7.673	1	1	0
33	2.7782	1.5911	1.7624	7.832	1	1	0
34	1.5185	0.301	0.9542	6.002	1	0	1
35	1.4624	0.4771	1.0792	6.4	1	0	1
36	1.2553	0.4771	1.0792	7.663	1	0	1
37	1.0792	0.6021	1	7.492	1	0	1
38	1	0.301	1	7.457	1	0	1
39	1.1761	0.4771	0.9542	8.532	1	0	1
40	3.3324	1.8451	2.0969	7.123	1	0	0
41	3.301	1.8195	2.0607	7.612	1	0	0
42	2.2304	0.699	1	9.646	1	0	1

Ip_1 = 1 when 8QS is present at R position, otherwise 0; Ip_2 = 1 when halogen is present in the compound, otherwise 0; Ip_3 =1 if five-membered ring is present, otherwise 0.

good predictors of the activities. There is no problem of intercorelations with any of the variables in the equations proposed. Furthermore, the study is impressive that no mixture of topological descriptors has been necessary to obtain statistically satisfactory results.

2. Results and discussion

The structural details of a large series (42 compounds) of aromatic/heterocyclic sulfonamides containing 8-quinoline-sulfonyl moieties used in the present investigation are given in Table 1. The inhibitory activities in log units [log K_I-(hCAI), log K_I(hCAII), log K_I(hCAIV)] of this set of sulfonamides are recorded in Table 2. This Table 2 also contains the values of the indicator parameters Ip_1, Ip_2 and Ip_3.The details concerning these indicator parameters are given in Section 4.

A perusal of Table 2 shows that no degeneracy is present in the activity, however, small degeneracy is observed in $^1\chi^v$. This is due to the fact that this index belong to second-order

Table 3
Correlation matrix for the intercorrelation of various molecular descriptors

	log K_I(hCAI)	log K_I(hCAII)	log K_I(hCAIV)	$^1\chi^v$	Ip_1	Ip_2	Ip_3
log K_I(hCAI)	1.0000						
log K_I(hCAII)	0.8658	1.0000					
log K_I(hCAIV)	0.8817	0.8734	1.0000				
$^1\chi^v$	–0.5024	–0.3379	–0.5533	1.0000			
Ip_1	–0.4722	–0.2313	–0.4710	0.9303	1.0000		
Ip_2	0.0535	0.0966	–0.0405	–0.0520	0.0000	1.0000	
Ip_3	–0.6754	–0.8412	–0.6762	0.0977	0.0000	–0.4472	1.0000

topological indices [14]. Balaban [14] has shown that such indices inspite of their degeneracies can be used successfully in modeling physicochemical properties as well as physiological activities of organic compounds acting as drugs. This is found to be the case in the present study also.

The correlatedness shown in Table 3 indicates that all the three inhibitory activity (hCAI, hCAII, hCAIV) are mutually inter-correlated, while $^1\chi^v$ is not that correlated with activity. This shows that it is not possible to obtain mono-parametric model using $^1\chi^v$ for modeling the activity. This Table 3 also shows that out of the three indicator parameters (Ip_1, Ip_2 and Ip_3), the parameter Ip_3 is significantly correlated with all the three activities and the correlation of Ip_3 with log K_I(hCAII) is the highest. This parameter Ip_3 is responsible for the presence/absence of a five-membered ring in the sulfonamide moiety. Thus, the presence of five-membered ring is the major factor for the exhibition of inhibitory activities and that the effect due to five-membered ring is most prominent for the exhibition of hCAII. The correlation matrix shows that multi-parametric regressions [15] involving combination of $^1\chi^v$ with the indicator parameters (Ip_1, Ip_2 and Ip_3) will result into statistically significant regression expressions for modeling all the three activities.

In view of the above, we have carried out step-wise regression analysis using maximum R^2-method [15]. The results obtained are presented in Tables 4–6, respectively, for modeling hCAI, hCAII and hCAIV activities.

A persual of Table 4 shows that $^1\chi^v$ alone does not give good results. However, the bi-parametic regression expression involving $^1\chi^v$ and Ip_3 is statistically significant. However, when $^1\chi^v$ is coupled with the indicator parameters Ip_2 and Ip_3, an excellent regression expression is obtained. No other tri-parametric regression is found more superior than this model. In obtaining this regression expression we have to delete compound **1** as an outlier. At present we can not provide convincing reasons for such a deviation and thus assume it to be due to the regression procedure adopted by us. The model is found as below:

$$K_I(\text{hCAI}) = -0.2435(\pm 0.0334)\,{}^1\chi^v - 0.8008(\pm 0.1736)Ip_2 - 2.0818(\pm 0.1703)Ip_3 + 5.3835 \quad (1)$$

$n = 41$, $S.E. = 0.4546$, $R = 0.9251$, $F = 73.224$ and $Q = 2.0350$.

Here and hereafter, n is the number of compounds used, S.E. is the standard error of estimation, R is multiple correlation coefficient, F is F-statistics and Q is the Pogliani's quality factor [17,18]. The above Eq. (1) shows that the

Table 4
Regression parameters and quality of correlation for modeling log K_I(hCAI) activity

Model number	Parameter used	A_i, i = 1, 2, 3	B (intercept)	S.E.	Correlation coefficient (R)	R^2	F-ratio	$Q = R$/S.E.
1	$^1\chi^v$	A_1 = –0.2770(±0.0728)	4.6686	0.9957	–0.5205	0.2709	14.493	–0.5227
2	$^1\chi^v$	A_1 = –0.2420(±0.0413)	5.0327	0.5629	0.8792	0.7730	64.683	1.5619
	Ip_3	A_2 = –1.7392(±0.1897)						
3	$^1\chi^v$	A_1 = –0.2435(±0.0334)	5.3835	0.4546	0.9251	0.8558	73.224	2.0350
	Ip_2	A_2 = –0.8008(±0.1736)						
	Ip_3	A_3 = –2.0818(±0.1703)						

Table 5
Regression parameters and quality of correlation for modeling log K_I(hCAII) activity

Model number	Parameter used	A_i, i = 1, 2, 3	B (intercept)	S.E.	Correlation coefficient (R)	R^2	F-ratio	$Q = R$/S.E.
1	$^1\chi^v$	A_1 = –0.1100(±0.0501)	2.1625	0.6660	–0.3316	0.1100	4.819	–0.4979
2	$^1\chi^v$	A_1 = –0.0651(±0.0236)	2.3160	0.3094	0.9015	0.8128	82.485	2.9137
	Ip_3	A_2 = –1.2565(±0.1052)						
3	$^1\chi^v$	A_1 = –0.0661(±0.0164)	2.5489	0.2148	0.9551	0.9122	128.097	4.4465
	Ip_2	A_2 = –0.5308(±0.0820)						
	Ip_3	A_3 = –1.4832(±0.0810)						

Table 6
Regression parameters and quality of correlation for modeling log K_I(hCAIV)activity

Model number	Parameter used	A_i, i = 1, 2, 3	B (intercept)	S.E.	Correlation coefficient (R)	R^2	F-ratio	$Q = R$/S.E.
1	$^1\chi^v$	A_1 = –0.1945(±0.0476)	3.1285	0.6375	–0.5473	0.2996	16.679	–0.8585
2	$^1\chi^v$	A_1 = –0.1595(±0.0312)	3.2676	0.4125	0.8452	0.7143	47.505	2.0490
	Ip_3	A_2 = –1.0402(±0.1400)						
3	$^1\chi^v$	A_1 = –0.1608(±0.0216)	3.5781	0.2862	0.9307	0.8661	79.787	3.2519
	Ip_2	A_2 = –0.7079(±0.1093)						
	Ip_3	A_3 = –1.3426(±0.1078)						

coefficients of all the three correlating parameters are negative. That is, K_I(hCAI) is negatively linearly correlated with $^1\chi^v$, Ip_2 and Ip_3. Furthermore, the magnitude of the parameter Ip_3 is the largest. That is out of the three parameters involved in the regression Eq. (1), Ip_3 plays a dominating role. Now, $^1\chi^v$ distinguishes the degree of unsaturation and the presence of heteroatoms. Thus, the negative coefficient of $^1\chi^v$ indicates negative effect due to these parameters on the exhibition of log K_I(hCAI) activity. The indicator parameters Ip_2 and Ip_3, respectively, indicate the presence of halogen and five-membered ring in sulfonamide moieties. Thus, their negative coefficient in Eq. (1) indicates negative role of halogen and five-membered ring on the exhibition of log K_I(hCAI) activity. It is interesting to record that no statistically better regression expressions could be obtainable involving the indicator parameter Ip_1. That is, the presence of 8-quinoline-sulfonyl moieties is not that important in the exhibition of log K_I-(hCAI) activity.

The regression parameters and quality of correlations for modeling K_I(hCAII) are given in Table 5. Here also, similar results as discussed above are obtained. Once again a tri-parametric regression contains $^1\chi^v$, Ip_2 and Ip_3 is found statistically most significant:

$$K_I(\text{hCAII}) = -0.0661(\pm 0.0164)^1\chi^v - 0.5308(\pm 0.0820)\text{Ip}_2 - 1.4832(\pm 0.0810)\text{IP}_3 + 2.5489 \quad (2)$$

$n = 41$, S.E. = 0.2148, $R = 0.9551$, $F = 128.057$ and $Q = 4.4405$.

In obtaining above regression Eq. (2) compound **14** is deleted as an outlier. That is, now the outlier is changed from compound **1** to compound **14**. This probably is due to different mechanism of action involved in the exhibition of K_I-(hCAII) activity. The physical significance of the model expressed by Eq. (2) is the same as described above. The non-occurrence of a model containing Ip_1 indicator once again show that 8-quinoline-sulfonyl moieties have no significant role in the exhibition of this activity [K_I(hCAII)] also. The parameters involved in the regressions (Table 5) indicate that the tri-parametric regression expression containing $^1\chi^v$, Ip_2 and Ip_3 is better for modeling K_I(hCAII) than for modeling K_I(hCAI) activity. Also, same is the case for bi-parametric regressions containing $^1\chi^v$ and Ip_3.

Finally, the results obtained for modeling K_I(hCAIV) activity are given in Table 6. Once again similar results are obtained and the tri-parametric regression expression containing $^1\chi^v$, Ip_2 and Ip_3 is found to be the most appropriate for modeling K_I(hCAIV) activity. This expression is found as below:

$$\log K_I(\text{hCAIV}) = -0.1608(\pm 0.0216)^1\chi^v - 0.7079(\pm 0.1093)\text{Ip}_2 - 1.3426(\pm 0.1070)\text{Ip}_3 + 3.5781 \quad (3)$$

$n = 41$, S.E. = 0.2862, $R = 0.9307$, $F = 79.787$ and $Q = 3.2519$.

In obtaining above results the compound **15** was to be deleted from the regression procedure. It is interesting to record that in all the three modeling discussed here the outliers are different. Though the deletion of one compound out of 42 will not effect the result greatly, the deletion of different compounds indicates different type of mechanism of action in the exhibition of referred activities. Once again, the physical significance of the parameters involved in Eq. (3) is the same as discussed above.

In order to confirm our results we have estimated K_I-(hCAI), K_I(hCAII) and K_I(hCAIV) activity from Eqs. (1)–(3), respectively, and compared them with the corresponding observed activities. Such a comparison is shown in Table 7. The predictive correlation coefficient obtained from the Figs. 1–3, i.e. $R^2_{\text{pred}} = 0.8558$, 0.9122 and 0.8661, respectively, indicates that the tri-parametric model that contain $^1\chi^v$, Ip_2 and Ip_3 is more appropriate for modeling K_I(hCAII) activity.

3. Conclusion

The results and discussion made above indicates that the CA inhibitory activities of the sulfonamide under present study can be modeled successfully by a single topological index, i.e. $^1\chi^v$ and that its combinations with indicator parameters (Ip_2 and Ip_3) gave excellent models. The results also show that presence of 8-quinoline is not that important in the

Table 7
Estimated values of log K_I(hCA I), log K_I(hCAII) and log K_I(hCAIV) from equations, respectively, and their comparison with observed value

Compound number	log K_I(hCAI) Eq. (1)			log K_I(hCAII) Eq. (2)			log K_I(hCAIV) Eq. (3)		
	Observed	Estimated	Result	Observed	Estimated	Result	Observed	Estimated	Result
1	4.699	–	–	0.954	0.679	0.275	1.653	1.294	0.359
2	4.657	4.68	–0.023	2.47	2.358	0.112	3.117	3.113	0.004
3	4.398	4.682	–0.284	2.38	2.358	0.022	3.342	3.114	0.228
4	4.447	4.682	–0.235	2.477	2.358	0.119	3.477	3.114	0.363
5	4.895	4.621	0.274	2.505	2.342	0.163	3.507	3.074	0.433
6	4.398	4.566	–0.168	2.23	2.327	–0.097	3.447	3.038	0.409
7	4.322	4.444	–0.122	2.204	2.294	–0.09	3.389	2.958	0.431
8	3.919	3.855	0.064	1.778	1.821	–0.043	2.255	2.39	–0.135
9	3.991	3.855	0.136	2.041	1.821	0.22	2.505	2.39	0.115
10	3.813	3.855	–0.042	1.602	1.821	–0.219	1.82	2.39	–0.57
11	3.778	3.855	–0.077	1.845	1.821	0.024	2.097	2.39	–0.293
12	3.795	3.66	0.135	1.447	1.767	–0.32	2.243	2.261	–0.018
13	3.924	3.687	0.237	1.875	1.775	0.1	2.204	2.279	–0.075
14	3.395	2.786	0.609	1.875	–	–	2.204	1.895	0.309
15	3.969	2.687	1.282	1.279	0.899	0.38	2.55	–	–
16	2.658	2.391	0.267	0.477	0.818	–0.341	2.097	1.634	0.463
17	1.845	2.412	–0.567	0.954	0.824	0.13	1.279	1.648	–0.369
18	1.74	2.428	–0.688	0.903	0.828	0.075	1.23	1.658	–0.428
19	1.699	2.163	–0.464	0.845	0.757	0.088	1.176	1.484	–0.308
20	4.38	4.589	–0.209	2.097	2.333	–0.236	2.748	3.053	–0.305
21	4.255	4.467	–0.212	2.041	2.3	–0.259	2.653	2.973	–0.32
22	4.326	3.734	0.592	2.468	2.101	0.367	2.443	2.489	–0.046
23	4.301	3.736	0.565	2.431	2.101	0.33	2.525	2.49	0.035
24	4.19	3.736	0.454	2.127	2.101	0.026	2.246	2.49	–0.244
25	4.342	3.675	0.667	2.477	2.085	0.392	2.58	2.449	0.131
26	3.093	3.389	–0.296	1.875	2.007	–0.132	2.093	2.261	–0.168
27	3.041	3.503	–0.462	1.778	2.038	–0.26	2.013	2.336	–0.323
28	2.736	2.909	–0.173	1.505	1.564	–0.059	1.987	1.765	0.222
29	2.792	2.909	–0.117	1.643	1.564	0.079	1.898	1.765	0.133
30	2.782	2.909	–0.127	1.653	1.564	0.089	1.919	1.765	0.154
31	2.785	2.909	–0.124	1.602	1.564	0.038	1.875	1.765	0.11
32	2.699	2.714	–0.015	1.505	1.511	–0.006	1.839	1.636	0.203
33	2.778	2.676	0.102	1.591	1.5	0.091	1.762	1.611	0.151
34	1.519	1.84	–0.321	0.301	0.669	–0.368	0.954	1.27	–0.316
35	1.462	1.743	–0.281	0.477	0.642	–0.165	1.079	1.206	–0.127
36	1.255	1.436	–0.181	0.477	0.559	–0.082	1.079	1.003	0.076
37	1.079	1.478	–0.399	0.602	0.57	0.032	1	1.031	–0.031
38	1	1.486	–0.486	0.301	0.573	–0.272	1	1.036	–0.036
39	1.176	1.224	–0.048	0.477	0.501	–0.024	0.954	0.863	0.091
40	3.332	3.649	–0.317	1.845	2.078	–0.233	2.097	2.433	–0.336
41	3.301	3.53	–0.229	1.82	2.046	–0.226	2.061	2.354	–0.293
42	2.23	0.953	1.277	0.699	0.428	0.271	1	0.684	0.316

exhibition of the refereed activities viz. (hCAI), (hCAII) and (hCAIV).

4. Experimental

4.1. The inhibition values

K_I(hCAI), K_I(hCAII) and K_I(hCAIV) were adopted from the work of Borras et al. [1].We have converted these values to their log form and used in the present investigations.

4.2. First-order connectivity index ($^1\chi^v$)

The connectivity index $\chi = \chi(G)$ of a graph G is defined by Randic [16] as under:

$$\chi = \chi(G) = \sum_{ij} [\delta_i \ \delta_j]^{-0.5} \quad (4)$$

where δ_i and δ_j are the valencies of the vertices i and j, respectively, 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

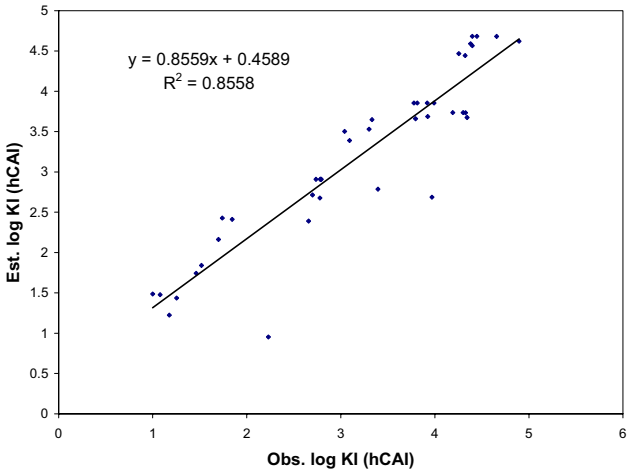


Fig. 1. Correlation of observed and estimated log K_I(hCAI) using Eq. (1).

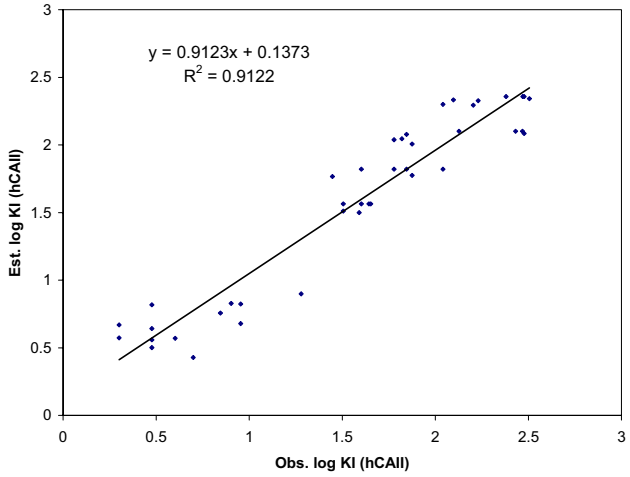


Fig. 2. Correlation of observed and estimated log K_I(hCAII) using Eq. (2).

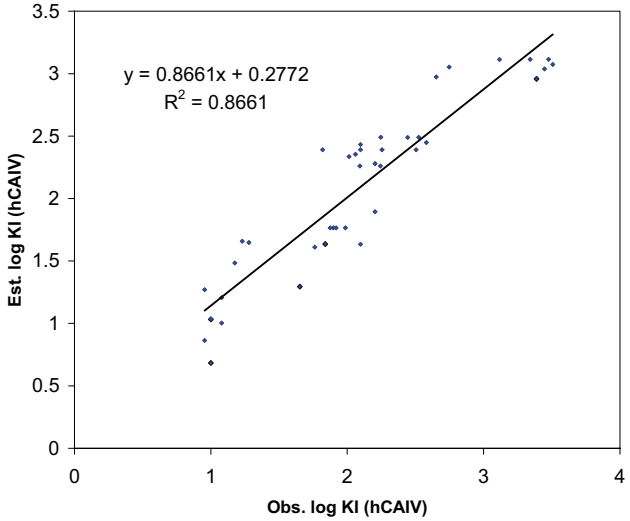


Fig. 3. Correlation of observed and estimated log K_I(hCAIV) using Eq. (3).

denoted by ${}^1\chi^v$. This version of the connectivity index is called the valence connectivity index and is defined [12,13] as under:

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

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

$$ \delta_i^v = \frac{Z_i^v - H_i}{Z_i - Z_j - 1} \tag{6} $$

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.

Now-a-days the connectivity and the valence connectivity indices expressed by Eqs. (5) and (6) are termed as first-order connectivity and first-order valence connectivity indices, respectively.

4.3. Indicator parameters

Three indicator parameters Ip_1, Ip_2 and Ip_3 have been used in the present study. The indicator parameter Ip_1 has been taken 1 when 8QS 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 five-membered ring is present, indicator parameter Ip_3 has been taken as unity. In absence of such situations the corresponding values of indicator parameters are taken as zero.

5. Computations

All the computations were carried out in Power Macintosh 9600/233. The computation of ${}^1\chi^v$ from the hydrogen-suppressed molecular graphs have been carried out using Luko-1 program supplied by Professor Lukovits, Hungarian Academy of Sciences, Budapest, Hungary. Similarly, his Regress-1 was used for making statistical analysis.

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