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Modelling of Carbonic Anhydrase Inhibitory Activity of Sulfonamides Using Molecular Negentropy

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Abstract—The present paper deals with the modelling of carbonic anhydrase inhibitory activity of sulfonamides using molecular negentropy (*N*). Excellent results are obtained in multiple regression analysis upon introduction of indicator parameters. The results are critically discussed on the basis of statistical data obtained from regression analysis.

Introduction

Kier[1] has stated that a drug molecule may be regarded as a message containing information in the form of electron probability field distributed in the space around a framework of atomic nuclii and that drug receptor interaction may be viewed as a presentation of the message, with its information content, to a receiver. He further stated that some information in the message may be interpretable by the receiver or receptor, leading to the beginning of events culminating in the biological response. Thus, efficiency of a drug depends on the information content and its quality as judged by the receptor. The quality content in the drug molecule depends on the ability of the receptor to interpret the fields and to translate the information into a significant change in the receptor and its adjacent structures.

Consequent to the above, Kier[1] has introduced a new type of information theoretic index, namely molecular negentropy, *N*, which is defined as:

$$N = n, i = n\left(-K\sum_j P_j \log P_j\right) \quad (1)$$

where *i* is the Negentropy per atom which is computed from Shannon's formula:

$$i = -K\sum_j P_i \log P_j \quad (2)$$

Here, P_j is in the complete array of probability and *K* is a constant depending upon the logarithmic base and *j* is the set, and *n* is the number of atoms in the molecule. Further details for calculating molecular negentropy (N) are given in the experimental section.

Kier[1] observed that, molecular negentropy *N*, can be structurally used for modelling tadpole narcosis, vapour toxicity, heat of vaporization etc. However, in-spite of the fact that the molecular negentropy (*N*) can be used in drug designing, very little work is done in this respect. However, recently we have used molecular negentropy[2–14] for modelling drug activity.

At this stage it is worthy to record that Supuran[15] has carried out an extensive research work in developing quantitative structure–activity relationships (QSARs) for a large series of carbonic anhydrase and has published several research papers related to this aspect. However, the molecular descriptors used by Supuran[15] were other than topological indices. In view of this we have undertaken topological studies on carbonic anhydrase inhibitors. In our earlier studies we have used the Wiener (W),[16] Szeged (Sz)[17–20] zero ($^0\chi^v$) and first-order ($^1\chi^v$) valence-connectivity indices,[21] Balaban (J),[22,23] and Branching (B)[24] indices for modelling biological activity of carbonic anhydrase inhibitors. We observed that such types of distance-based topological indices are very useful for this purpose.[25–28]

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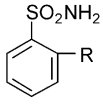
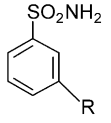
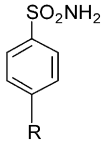
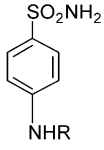
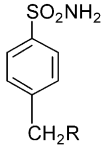
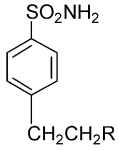
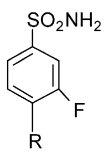
In continuation to our earlier work,[25–28] we now extend our stdy in that we have used molecular negentropy, *N*, (information theoretical index) for modelling carbonic anhydrase inhibitory activity of sulfonamides as reported by Supuran et al.[29] (Table 1). The results as discussed below indicate that molecular negentropy (*N*) can be used successfully for modelling inhibitory activity of isozymes CAI, CAII (cytosolic forms) and CAIV (membrane bound form) involved in important physiological processes. The carbonic anhydrase inhibitory data against the esterase activity of 3-CA isozymes, viz. hCAI, hCAII, bCAIV (h = human, b = bovine isozymes) as reported by Supuran et al.[29] were adopted for this purpose.

Results and Discussion

A perusal of Table 2 shows that the molecular negentropy (*N*) does equally well for modelling all the three inhibitory activities: log K_i(hCAI), log K_i(hCAII) and log K_i(bCAIV); but is slightly worse for modelling log K_i(hCAII) activity. The data also show that these activities are influenced to a greater extent by the indicator parameters I_1 and I_4 i.e., presence of $-NH_2$ and 2,6-PCO respectively at the position $-R$ (Table 2).

There are several X-ray crystal structures of sulfonamide-CA complexes. By exploiting the crystal structures of such complexes, many sulfonamides were successfully optimized and modified. It is obvious that one could differentiate interaction modes of CA inhibition with three different isoenzymes of CA by the regression equations and the X-ray structures. In the absence of detailed X-ray results one has to depend only on regression equations. This is found to be the case in the present study also. We have, therefore, interpreted the physico-chemical meaning of the QSAR equations, especially the correlations of the indicators with the

Table 1. The structure, inhibition activities: log K_i(hCAI), log K_i(hCAII) and log K_i(bCAIV) for a series of sulfonamides used in the present study

Compd	Structure	*R*	log K_i (hCAI)	log K_i (hCAII)	log K_i (bCAIV)
1		NH_2	4.6571	2.4698	3.1173
2		2,3 PC	4.3222	2.4472	2.4914
3		2,6 PC	4.301	2.415	2.4771
4		NH_2	4.3979	2.3802	3.3424
5		2,3 PC	4.301	2.3979	2.4843
6		2,6 PC	4.2672	2.3838	2.4548
7		NH_2	4.4472	2.4771	3.4771
8		2,3 PC	4.1903	2.1206	2.2304
9		2,6 PC	4.1761	2.0828	2.1761
10		NH_2	4.8949	2.5052	3.5072
11		2,3 PC	4.3324	2.4393	2.4771
12		2,6 PC	4.3139	2.4314	2.4829
13		NH_2	4.3979	2.2304	3.4472
14		2,3 PC	3.017	1.6232	1.8976
15		2,6 PC	2.9345	1.5563	1.8451
16		NH_2	4.3222	2.2041	3.3892
17		2,3 PC	2.9569	0.9542	1.7324
18		2,6 PC	2.7404	0.8451	1.6021
19		NH_2	3.9192	1.7782	2.2553
20		2,3 PC	2.7324	1	1.6628
21		2,6 PC	2.7076	0.9031	1.6435

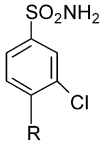
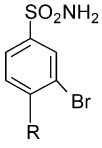
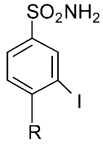
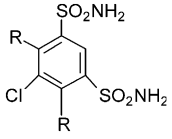
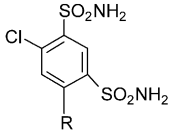
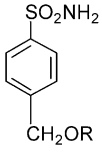
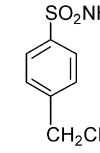
Compd	Structure	*R*	log K_i (hCAI)	log K_i (hCAII)	log K_i (bCAIV)
22		NH_2	3.9912	2.0414	2.5052
23		2,3 PC	2.7924	1.6435	1.8976
24		2,6 PC	2.7781	1.3979	1.8195
25		NH_2	3.8129	1.6021	1.8195
26		2,3 PC	2.7818	1.4917	1.8751
27		2,6 PC	2.76	1.4771	1.8388
28		NH_2	3.7781	1.8451	2.0969
29		2,3 PC	2.7853	1.5185	1.8451
30		2,6 PC	2.7782	1.4914	1.7924
31		NH_2	3.7853	1.4472	2.243
32		2,3 PC	2.699	1.0792	1.8388
33		2,6 PC	2.6532	1	1.7404
34		NH_2	3.9243	1.8751	2.2041
35		2,3 PC	2.7782	0.9542	1.7782
36		2,6 PC	2.5682	0.9542	1.6812
37		H	4.3802	2.0969	2.7482
38		2,6 PCO	3.3118	1.301	2.0792
39		H	4.2553	2.0414	2.6532
40		2,6 PCO	3.301	1.1761	2.0212

Table 2. Molecular negentropy (N) and indicator parameters (I_1, I_2, I_3, and I_4) for the set of sulfonamides used in the present study (see Table 1)

Compd	N	I_1	I_2	I_3	I_4
1	17.6719	1	0	0	0
2	35.2770	0	1	0	0
3	41.2203	0	0	1	0
4	17.6719	1	0	0	0
5	35.2770	0	1	0	0
6	41.2203	0	0	1	0
7	17.6719	1	0	0	0
8	35.2770	0	1	0	0
9	41.2203	0	0	1	0
10	21.1407	1	0	0	0
11	39.1296	0	1	0	0
12	45.1535	0	0	1	0
13	19.7890	1	0	0	0
14	40.4712	0	1	0	0
15	46.5372	0	0	1	0
16	27.1175	1	0	0	0
17	45.7920	0	1	0	0
18	51.9558	0	0	1	0
19	19.6251	1	0	0	1
20	37.2330	0	1	0	1
21	43.1739	0	0	1	1
22	19.6251	1	0	0	1
23	37.2330	0	1	0	1
24	43.1739	0	0	1	1
25	19.6251	1	0	0	1
26	37.2330	0	1	0	1
27	43.1904	0	0	1	1
28	19.6251	1	0	0	1
29	37.2330	0	1	0	1
30	43.1739	0	0	1	1
31	24.6912	1	0	0	1
32	43.2040	0	1	0	1
33	49.3392	0	0	1	1
34	24.6912	1	0	0	1
35	43.2040	0	1	0	1
36	49.3392	0	0	1	1
37	21.1407	0	0	0	0
38	43.3510	0	0	0	0
39	24.8960	0	0	0	0
40	48.7350	0	0	0	0

interaction between inhibitors and CAs. The results are discussed below.

In view of the above, we now discuss the regression models (QSAR equations) obtained for modelling the aforementioned activities in a step-wise fashion.

Modelling of log K_i(hCAI) activity

The data presented in Table 4 show that statistically significant models start coming with bi-variant regressions. The bi-variate regression containing molecular negentropy (N) and an indicator parameter I_4 as the correlating parameters though gave a good value for the correlation coefficient R is discarded on the ground that the coefficient of molecular negentropy (N) is smaller than its standard deviation. Such models are not allowed statistically.[4–6]

In view of our failure in obtaining statistically significant bi-variate correlations, we attempted tri-variate correlations.

Three tri-variate models are obtained for modelling log K_i(hCAI) out of which two are rejected on the same basis as above. In the triparametric model containing N, I_1 and I_4. N has the coefficient much smaller than its standard deviation. Similarly, in the other tri-parametric model containing N, I_2 and I_4:.$_2$ has the coefficient much smaller than its standard deviation. Thus, only a tri-parametric model containing N, I_3 and I_4 gave statistically significant model. This model is found as:

$$\log K_i(\text{hCAI}) = -0.0516(\pm 0.0061)N + 0.2946 \times (\pm 0.1452)I_3 - 0.8732 \times (\pm 0.1064)I_4 + 5.7072 \quad (3)$$

$$n = 40,\ \text{Se} = 0.3339,\ R = 0.9025,\ F = 52.674,\ Q = 2.7029.$$

Here, and hereafter n is the number of compounds used, Se is the standard error of estimation, R is the correlation coefficient, F is Fischer's ratio and Q is the quality factor.

The aforementioned model suggests that decrease in molecular negentropy favors the exhibition of log K_i(hCAI) activity. By definition the numerical value of the negentropy (N) decreases with greater multiplicity within each set or for a smaller number of sets. This observation translates into awareness that molecular negentropy ranks molecules according to symmetry. Similarly, to the molecular negentropy (N), the indicator parameter I_4 has a negative effect on the exhibition of activity; while I_3 favours the activity. This means that the presence of 2,6-PCO group retards the inhibition activity, while the presence of 2,6-PC favours the same.

Further regression analyses containing more than three correlation parameters gave models with worsted statistics than the models discussed above.

Modelling of log K_i(hCAII) activity

The data presented in Table 5 also show that like log K_i(hCAI) activity the log K_i(hCAII) activity is also modelled by a triparametric model. Here also, the only statistically significant tri-variate model is the one containing N, I_1 and I_4 and is found as:

$$\log K_i(\text{hCAII}) = -0.0361(\pm 0.0096)N - 0.2288 \times (\pm 0.2276)I_1 - 0.5661 \times (\pm 0.1122)\ I_4 + 3.3311 \quad (4)$$

$$n = 40,\ \text{Se} = 0.3469,\ R = 0.7956, F = 20.696,\ Q = 2.2934.$$

The regression parameters and quality of correlation for the above model (eq 4) show that compared to log

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

	Log K_i(hCAI)	Log K_i(hCAII)	Log K_i(bCAIV)	N	I_1	I_2	I_3	I_4
log K_i(hCAI)	1.0000							
log K_i(hCAII)	0.9118	1.0000						
log K_i(bCAIV)	0.8587	0.8162	1.0000					
N	−0.6739	−0.5784	−0.6966	1.0000				
I_1	0.5233	0.3844	0.6055	−0.8460	1.0000			
I_2	−0.2659	−0.1358	−0.2919	0.2451	−0.4286	1.0000		
I_3	−0.3186	−0.2092	−0.3500	0.6069	−0.4286	−0.4286	1.0000	
I_4	−0.6070	−0.5580	−0.5633	0.0373	0.0658	0.0658	0.0658	1.0000

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

S. N.	Parameters used	A_i where $i=1,2,3,..$	Constant	Se	R	R^2	F-ratio	Q value $Q=R/Se$
1	N	$A_1=-0.0456$ (±0.0081)	5.1923	0.5575	−0.6739	0.4542	31.617	1.2088
2	N I_4	$A_1=-0.0041$ (±0.0051) $A_2=-0.8615$ (±0.1106)	5.5288	0.3477	0.8906	0.7932	70.976	2.5614
3	N I_2 I_4	$A_1=-0.0429$ (±0.0052) $A_2=-0.1160$ (±0.1242) $A_3=-0.8554$ (±0.1110)	5.5196	0.3483	0.8934	0.7981	47.444	2.565
4	N I_1 I_4	$A_1=-0.0421$ (±0.0098) $A_2=0.0563$ (±0.2321) $A_3=-0.8665$ (±0.1139)	5.444	0.3522	0.8908	0.7936	46.134	2.5292
5	N I_3 I_4	$A_1=-0.0516$ (±0.0061) $A_2=0.2946$ (±0.1452) $A_3=-0.8732$ (±0.1064)	5.7072	0.3339	0.9025	0.8145	52.674	2.7029

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

S. N.	Parameters used	A_i where $i=1,2,3,..$	Constant	Se	R	R^2	F-ratio	Q value $Q=R/Se$
1	N	$A_1=-0.0289(\pm0.0066)$	2.7573	0.4546	−0.5784	0.3345	19.104	1.2723
2	N I_1 I_4	$A_1=-0.0361(\pm0.0096)$ $A_2=-0.2288(\pm0.2276)$ $A_3=-0.5661(\pm0.1122)$	3.3311	0.3469	0.7956	0.633	20.696	2.2935

K_i(hCAI); the combination of molecular negentropy (N) with I_1 and I_4 is less effective for modelling log K_i(hCAII), and that decrease in the value of molecular negentropy (N) favours exhibition of the activity. The indicator parameters I_1 and I_4 have also retarding effect. Hence, presence of $-NH_2$ group as well as of 2,6-PCO have a negative role in the exhibition of log K_I(hCAII) activity.

Modelling of log K_i(bCAIV) activity

Unlike the earlier two cases discussed above, in this case of modelling log K_i(bCAIV) activity a bi-paramtric model is found statistically significant for modelling. This model is found as:

$$\log K_i(\text{bCAIV}) = -0.0458(\pm0.0040)N - 0.6045 \times (\pm0.0878)I_4 + 3.7488 \quad (5)$$

$$n = 40,\ \text{Se} = 0.2760,\ R = 0.8800,\ F = 63.493,$$

$$Q = 5.1884.$$

From the regression eq [5] we concluded that the molecular negentropy (N) and substitution of 2,6-PCO have negative role in the exhibition of log K_i(bCAIV) activity.

The data presented in Table 6 also show that two trivariate models having slightly better statistics are also possible. Out of these two models, the one containing N, I_1, I_4 gave better results. This model is found as:

$$\log K_i(\text{bCAIV}) = -0.0239(\pm0.0075)N + 0.3037 \times (\pm0.1773)I_1 - 0.6317 \times (\pm0.0870)I_4 + 3.2914 \quad (6)$$

$$n = 40,\ \text{Se} = 0.2691,\quad R = 0.8896,$$

$$F = 45.518,\ Q = 5.3182.$$

Once again decrease in molecular negentropy and substitution of 2,6-PCO favours the exhibition of log K_i(bCAIV), while the presence of $-NH_2$ group is favourable in this direction.

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

S. N.	Parameter(s) used	A_i where $i=1,2,3,..$	Constant	Se	R	R^2	F-ratio	Q value
1	N	$A_1=-0.0358$ (±0.0060)	3.5127	0.4114	−0.6966	0.4853	35.825	0.01693
2	N I_4	$A_1=-0.0348$ (±0.0040) $A_2=-0.6045$ (±0.0878)	3.7488	0.276	0.88	0.7744	63.493	3.1884
3	N I_3 I_4	$A_1=-0.0392$ (±0.0050) $A_2=0.1742(\pm0.0.1181)$ $A_3=-0.6114$ (±0.0866)	3.8543	0.2717	0.8873	0.7872	44.397	3.2657
4	N I_1 I_4	$A_1=-0.0239$ (±0.0075) $A_2=0.3037$ (±0.1773) $A_3=-0.6317$ (±0.0870)	3.2914	0.2691	0.8896	0.7914	45.518	3.3058

Higher parametric models failed to give better statistics than the models discussed above.

In order to confirm our results we have estimated log K_i(hCAI), log K_i(hCAII) and log K_i(bCAIV) activities from the models expressed by eqs 3, 4 and 6 respectively and compared them with the observed activities. Such comparisons are shown in Tables 7, 8, and 9 respectively for log K_i(hCAI), log K_i(hCAII) and log K_i(bCAIV). The data show that the observed and calculated activities are very close to each other. The residue, that is, the difference between observed and calculated activities in each case confirms our results.

Table 7. Estimated values of log K_i(hCAI) from eq 3 and their comparison with observed values

Compd	Observed log K_i(hCAI)	Estimated log K_i(hCAI)	
		eq 3	
		Estimated	Residual
1	4.657	4.795	−0.1380
2	4.322	3.886	0.4357
3	4.301	3.874	0.4267
4	4.398	4.795	−0.3972
5	4.301	3.886	0.4145
6	4.267	3.874	0.3929
7	4.447	4.795	−0.3479
8	4.190	3.886	0.3038
9	4.176	3.874	0.3018
10	4.895	4.616	0.2788
11	4.332	3.688	0.6448
12	4.314	3.671	0.6426
13	4.398	4.686	−0.2880
14	4.017	3.618	−0.6014
15	4.935	3.600	−0.6654
16	4.322	4.308	0.0146
17	4.957	3.344	−0.3869
18	4.740	3.320	−0.5798
19	4.919	3.821	0.0981
20	4.732	2.912	−0.1799
21	4.708	2.900	−0.1926
22	4.991	3.821	0.1701
23	4.792	2.912	−0.1199
24	4.778	2.900	−0.1221
25	3.813	3.821	−0.0082
26	2.782	2.912	−0.1305
27	2.760	2.899	−0.1394
28	3.778	3.821	−0.0430
29	2.785	2.812	−0.1270
30	2.778	2.900	−0.1220
31	3.785	3.560	0.2257
32	2.699	2.604	0.0949
33	2.653	2.582	0.0712
34	3.924	3.560	0.3647
35	2.778	2.604	0.1741
36	2.568	2.582	−0.0138
37	4.380	4.616	−0.2359
38	3.312	3.470	−0.1580
39	4.255	4.422	−0.1670
40	3.301	3.192	0.1091

Table 8. Estimated values of log K_i(hCAII) from eq 4 and their comparison with observed values

Compd	Observed log K_i(hCAII)	Estimated log K_i(hCAII)	
		eq 4	
		Estimated	Residual
1	2.470	2.515	−0.0450
2	2.447	2.143	0.3047
3	2.415	1.868	0.5474
4	2.380	2.515	−0.1346
5	2.398	2.143	0.2554
6	2.384	1.868	0.5162
7	2.477	2.515	−0.0377
8	2.121	2.143	−0.0219
9	2.083	1.868	0.2152
10	2.505	2.358	0.1475
11	2.439	1.952	0.4869
12	2.431	1.671	0.7608
13	2.223	2.515	−0.2920
14	1.623	1.878	−0.2551
15	1.556	1.593	−0.0365
16	2.204	2.067	0.1367
17	0.954	1.603	−0.6490
18	0.845	1.309	−0.4642
19	1.778	1.560	0.2186
20	1.000	1.288	−0.2882
21	0.903	1.013	−0.1103
22	2.041	1.708	0.3333
23	1.644	1.437	0.2068
24	1.398	1.162	0.2359
25	1.602	1.759	−0.1572
26	1.492	1.488	0.0038
27	1.477	1.212	0.2653
28	1.845	1.880	−0.0353
29	1.519	1.609	−0.0905
30	1.491	1.334	0.1571
31	1.447	1.871	−0.4234
32	1.079	1.420	−0.3411
33	1.000	1.129	−0.1289
34	1.875	1.660	0.2155
35	0.954	1.131	−0.1765
36	0.954	0.839	0.1149
37	2.097	2.416	−0.3195
38	1.301	1.819	−0.5183
39	2.041	2.276	−0.2344
40	1.176	1.539	−0.3626

Table 9. Estimated values of log K_i(bCAIV) from eq 6 and their comparison with observed values

Compd	Observed log K_i(bCAIV)	Estimated log K_i(bCAIV)	
		eq 6	
		Estimated	Residue
1	3.117	3.202	−0.0846
2	2.491	2.507	−0.0152
3	2.477	2.322	0.1548
4	3.342	3.202	0.1405
5	2.484	2.507	−0.0223
6	2.455	2.322	0.1325
7	Outlier		
8	2.230	2.507	−0.2762
9	2.176	2.322	−0.1462
10	3.507	3.097	0.4107
11	2.477	2.380	0.0974
12	2.483	2.191	0.2920
13	3.447	3.198	0.2492
14	1.898	2.330	−0.4329
15	1.845	2.139	−0.2943
16	3.389	2.903	0.4866
17	1.732	2.147	−0.4149
18	1.602	1.951	−0.3487
19	2.255	2.324	−0.0684
20	1.663	1.692	−0.0289
21	1.644	1.508	0.1359
22	2.505	2.417	0.0881
23	1.898	1.785	0.1126
24	1.820	1.601	0.2186
25	1.820	2.449	−0.6297
26	1.875	1.817	0.0579
27	1.839	1.632	0.2066
28	2.097	2.525	−0.4284
29	1.845	1.893	−0.0482
30	1.792	1.709	0.0832
31	2.243	2.509	−0.2663
32	1.839	1.763	0.0756
33	1.740	1.568	0.1722
34	2.204	2.377	−0.1727
35	1.778	1.591	0.1970
36	1.681	1.386	0.2950
37	2.748	2.706	0.0422
38	2.079	2.288	−0.2086
39	2.653	2.610	0.0428
40	2.021	2.101	−0.0799

The statistically significant models based on molecular negentropy (N) as discussed above indicate that correlations of molecular negentropy (N) with CA-activities suggest that molecular negentropy encodes an appreciable description of the structure influencing the activity. In such studies, the receptor may be viewed as responding to sulfonamide group in a specific way. The response of the receptor to the remainder of sulfonamide moiety probably is nonspecific, that is, there is no particular need for a specific atom or group to enhance the interaction. The receptor responds to all bonds and atoms in a roughly cumulative way, which is characteristic of dispersion forces among non-polar moieties. Negentropy, which encodes the information content in the molecule, quantitates the variety of structural features and the associated probabilities of interaction with the receptor.

Kier[1] has stated that a molecule of biological interest alone may be regarded as a message made up of atoms and bonds containing information transmitted to a receptor or receptive tissue. The information content or negentropy is a meaningful parameter in some structure–activity analysis such as in some non-specific interactions. Kier[1] further added that drug molecules that are active at highly structured, specific receptors certainly contain information. The probability of atom information are altered in a complex way from purely random choice due to marked differences in interaction forces between certain atoms in an agonist molecule and complementary positions of a receptors. We believe that such important observations of Kier[1] are applicable to the present cases also.

Conclusions

From the aforementioned results and discussions we conclude that molecular negentropy (N) can be used successfully for modelling carbonic anhydrase inhibitory activity of sulfonamides. Improved results are obtained upon introduction of indicator parameters along with molecular negentropy. Furthermore, the results can be used for the development of more efficient and inexpensive anti-glaucoma drugs using the proposed model.

Experimental

Carbonic anhydrase activity

As stated earlier, the carbonic anhydrase inhibitory activity as reported by Supuran et al.[29] (Table 1) were adopted for the present study. The inhibition constant, K_i, were determined as described by Pocker and Stone[30] and were converted into their log units. Enzyme concentrations were 3.5 nM for hCAII, 12 nM for hCAI, and 36 nM for bCAIV.

Molecular negentropy

An approach to the calculation of the molecular negentropy (N) of a molecule can be derived from a consideration of molecular graphs as shown by Rashevsky,[31] who pointed out the biological implications of such a parameter.

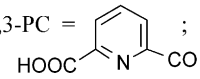
Based on the above, and as mentioned in the introductory section the molecular negentropy[1] (N) for the set of 40 sulfonamides (Table 1) were calculated using eqs 1 and 2 as described in the introduction section. These values are recorded in Table 2.

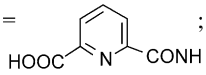
Indicator parameters

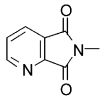
The preliminary regression analysis indicated a need of indicator parameters for obtaining better result. On the basis of substituents present in the sulfonamide moiety we have used four such indicator parameters I_1, I_2, I_3 and I_4. These indicator parameters were taken as unity when the following groups are present at R respectively:

$$-\mathrm{NH_2}(I_1);\ \ 2{,}3-\mathrm{PC}(I_2);\ \ 2{,}6-\mathrm{PC}(I_3)$$

$$\text{and } 2{,}6-\mathrm{PCO}(I_4)$$

where, 2,3-PC = 

; 2,6-PC = 

; 2,6-PCO = 

In the absence of these substituents the respective indicator parameters were taken as zero. The values I_1, I_2, I_3 and I_4 are also presented in Table 2.

Regression analysis

The regression analyses of the data were carried out using the maximum R^2 method[32] and the resulting regression data are presented in Table 4. Before carrying out the R^2 method a correlation matrix is obtained as shows in Table 3. In addition, we have also calculated quality factor Q for deciding the quality of correlation. This quality factor is defined[33] as the ratio of the correlation coefficient (R) to standard error of estimation (Se) i.e., $Q = R/\mathrm{Se}$.

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References and Notes

1. Kier, L. B. *J. Pharm. Sci.* **1980**, *69*, 807.
2. Agrawal, V. K.; Khadikar, P. V. *Bioorg. Med. Chem.* **2001**, *9*, 2787.
3. Agrawal, V. K.; Khadikar, P. V. *Bioorg. Med. Chem.* **2001**, *9*, 3035.
4. Agrawal, V. K.; Karmarkar, S.; Khadikar, P. V. *SAR QSAR Environ. Res.* **2001**, *12*, 529.
5. Agrawal, V. K.; Srivastava, R.; Khadikar, P. V. *Acta Pharm.* **2001**, *51*, 117.
6. Agrawal, V. K.; Sachan, S.; Khadikar, P. V.; Karmarkar, S. *Acta Pharm.* **2001**, *51*, 189.
7. Agrawal, V. K.; Sachan, S.; Khadikar, P. V. *Nat. Acad. Sci. Letters* **2001**, *24*, 16.
8. Agrawal, V. K.; Sachan, S.; Khadikar, P. V. *Acta Pharm* **2000**, *50*, 281.
9. Agrawal, V. K.; Joseph, S.; Khadikar, P. V.; Karmarkar, S. *Acta Pharm.* **2000**, *50*, 329.
10. Agrawal, V. K.; Sachan, S.; Khadikar, P. V. *Pol. J. Pharmacol.* **2000**, *52*, 39.
11. Agrawal, V. K.; Joseph, S.; Khadikar, P. V. *Nat. Acad. Sci. Letters* **2000**, *23*, 57.
12. Soni, S. K.; Agrawal, V. K.; Khadikar, P. V.; Srivastava, A. K. *J. Indian Chem. Soc.* **2000**, *77*, 133.
13. Agrawal, V. K.; Sachan, S.; Karmarkar, S.; Khadikar, P. V. *Nat. Acad. Sci. Letters* **2000**, *23*, 129.
14. Sachan, S.; Bano, S.; Agrawal, V. K.; Khadikar, P. V.; Srivastava, A. K. *Nat. Acad. Sci. Letters* **1999**, *22*, 199.
15. (a) Supuran, C. T.; Clare, B. W. *Eur. J. Med. Chem.* **1995**, *30*, 687. (b) Maren, T. H.; Clare, B. W.; Supuran, C. T. *Roum. Chem. Quart. Rev.* **1994**, *2*, 259. (c) Clare, B. W.; Supuran, C. T. *Eur. J. Med. Chem.* **1997**, *32*, 311. (d) Supuran, C. T.; Clare, B. W. *Eur. J. Med. Chem.* **1998**, *33*, 489. (e) Supuran, C. T.; Clare, B. W. *Eur. J. Med. Chem.* **1999**, *34*, 41. (f) Clare, B. W.; Supuran, C. T. *Eur. J. Med. Chem.* **1999**, *34*, 463. (g) Clare, B. W.; Supuran, C. T. *Eur. J. Med. Chem.* **2000**, *35*, 859.
16. Wiener, H. *J. Am. Chem. Soc.* **1947**, *69*, 17.
17. Gutman, I. *Graph Theory Notes New York* **1994**, *27*, 9.
18. Khadikar, P. V.; Deshpande, N. V.; Kale, P. P.; Dobrynin, A.; Gutman, I.; Domotor, G. *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 547.
19. Khadikar, P. V.; Kale, P. P.; Deshpande, N. V.; Karmarkar, S.; Agrawal, V. K. *Commun. Math. Comput. Chem. (MATCH)* **2001**, *43*, 7.
20. Khadikar, P. V.; Karmarkar, S.; Agrawal, V. K. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 934.
21. Randic, M. *J. Am. Chem. Soc.* **1975**, *97*, 6609.
22. Balaban, A. T. *Chem. Phys. Lett.* **1982**, *89*, 399.
23. Khadikar, P. V.; Sharma, S.; Sharma, V.; Joshi, S.; Lukovits, I.; Kaveeshwar, M. *Bull. Soc. Chim. Belg.* **1997**, *106*, 767.
24. Todeschini, R.; Consonni, V. *Handbook of Molecular Descriptors*; Wiley-VCH: Weinheim, 2000.
25. Saxena, A.; Khadikar, P. V. *Acta Pharm.* **1999**, *49*, 171.
26. Agrawal, V. K.; Khadikar, P. V. *Bioorg. Med. Chem.* **2001**, *9*, 3287.
27. Agrawal, V. K.; Sharma, R.; Khadikar, P. V. *Bioorg. Med. Chem.* **2002**, *10*, 2993.
28. Saxena, A. *Quantitative Structure–Activity Relationships for a Group of Sulfonamide Schiff's Base Inhibitors of Carbonic Anhydrase*. PhD thesis, Devi Ahilya University, Indore, India, 2000.
29. Scozzafava, A.; Menabuoni, L.; Mincione, F.; Briganti, F.; Mincione, G.; Supuran, C. T. *J. Med. Chem.*, **1999**, *42*, 2641.
30. Pocker, Y.; Stone, J. T. *Biochemistry* **1967**, *6*, 678.
31. Rashevsky, N. *Bull. Math. Biophys.* **1955**, *17*, 229.
32. Chaterjee, S.; Hadi, A. S.; Price, B. *Regression Analysis by Examples*, 3rd ed.; Wiley: New York, 2000.
33. Pogliani, L. *Amino Acids* **1994**, *6*, 141.