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Topological modeling of lipophilicity, diuretic activity, and carbonic inhibition activity of benzene sulfonamides: a molecular connectivity approach

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Dedicated to Navin Jain on his 29th birthday

Abstract—A large series of distance-based topological indices has been used for modeling lipophilicity, diuretic activity, and carbonic anhydrase inhibition activity of a library of simple substituted benzene sulfonamides. The results have shown that the topological approach used is quite useful for modeling carbonic anhydrase inhibition and the use of molecular connectivity is the best for this purpose. Excellent results are obtained in multiparametric regressions. The results are critically discussed on the basis of statistical parameters.

1. Introduction

The enzyme carbonic anhydrase (CA, carbonate hydrolase, EC 4.2.1.1) is involved in a variety of physiological and physiopathological processes. Many different isoforms of CA are present in mammalians, each having specific function. Among its inhibitors, sulfonamides are important clinical agents. They are used in variety of diseases particularly in the treatment of glaucoma, gastro-duodenal ulcers, certain neurological disorders, motion, and altitude sickness. It is interesting to mention that the synthesis and testing of the wide variety of new drugs as CA inhibitors, and their SAR are widely investigated by the medicinal chemist community.[1–6]

Quantitative structure–activity relationship (QSAR) is a versatile methodology helpful in screening a large library of possible drugs for selectivity and potency in that mathematical models are formed that correlate molecular structure to an activity/property/toxicity of interest.[2–6] In this methodology the molecular structure is first encoded for yielding molecular descriptors, which are numerical values corresponding to topological, geometry, and/or electronic structural features. Among the CA inhibitors this methodology was first applied[7] to substituted benzene sulfonamide of the type mentioned in Figure 1.

In the report by Hansch and co-workers[8] the biological activity of benzene sulfonamides was modeled using Hansch parameters. Subsequently Kakeya et al.[9] reported correlations of 19 substituted benzene sulfonamides of which three were *ortho*-substituted and thus deleted from the final calculations. Such deletion was due to *ortho*-effects exhibited by them. In their attempt, Kakeya et al. used Hansch and Hammett's parameters.[7,8] Our recent investigations[10–20] have shown that

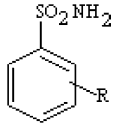

Figure 1. Substituted benzene sulfonamides (see Table 1 for details).

Keywords: Topological modeling; QSAR; Lipophilicity; Benzene sulfonamide; Carbonic anhydrase; Inhibition activity; Diuretic activity; Regression analysis.
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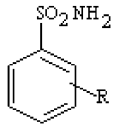
Table 1. Structural details, lipophilicity ($\log P$), diuretic activity ($\log 1/c$), carbonic anhydrase inhibition activity ($\log K_i$), σ, and π values for the benzene sulfonamides used in the present study



Compound no.	R	$\log P$	$\log 1/c$	$-\log K_i$	π	$\sum\sigma$
1	*p*-MeNH	−0.5086	−0.0362	4.8740	−0.231	−0.840
2	*p*-NH_2	−1.6020	−0.3010	4.6383	−1.137	−0.660
3	*p*-MeO	0.2355	0.1875	5.3468	0.163	−0.268
4	*p*-Me	0.4166	0.1818	5.4203	0.505	−0.170
5	*m*-Me	0.4065	0.1760	5.3011	0.540	−0.069
6	H	−0.1549	0.1303	5.2165	0.000	0.000
7	*p*-Cl	0.2278	0.2855	5.7213	0.531	0.227
8	*p*-Br	0.4742	0.2671	5.9209	1.053	0.232
9	*m*-Cl	0.3404	0.2922	5.6383	0.981	0.373
10	*p*-Ac	−0.2757	0.3979	5.9587	−0.105	0.502
11	*p*-CN	−0.5228	1.0000	5.9587	−0.083	0.660
12	*m*-NO_2	−0.2757	0.6776	5.8861	0.2424	0.710
13	*p*-NO_2	−0.5086	0.8241	6.0458	0.328	0.778
14	3,4-Cl_2	0.6095	0.2430	6.3980	1.134	0.600
15	3-NO_2, 4-Cl	0.1139	0.3222	6.7696	1.603	0.937
16	3-CF_3, 4-NO_2	0.2787	0.5797	6.8539	1.420	1.208
ortho-Substituted benzene sulfonamides (deleted for the final regression)						
17	*o*-Me	0.5477	−0.3010	4.7959	0.526	—
18	*o*-Cl	0.5477	−0.3010	5.5229	0.427	—
19	*o*-NO_2	0.2788	−0.3010	5.0706	0.033	—

distance-based topological indices can be used successfully in modeling property/activity related to CA inhibition in that in many cases the topological approach is found more effective. This has prompted us to undertake the present investigation in which we have used a series of distance-based topological indices for modeling lipophilicity, diuretic activity, and carbonic anhydrase inhibition activity of benzene sulfonamides used by Kakeya et al.[9] Of course, following them we have deleted the three *ortho*-substituted compounds in our study also. Like Kakeya et al.[9] our study is for 16 benzene sulfonamides (Table 1). The results as discussed below indicate that molecular connectivity indices are better suited for our study. Our attempt is, therefore, basically a molecular connectivity approach.

2. Results and discussion

The set of benzene sulfonamides used in the present study is shown in Table 1. This Table 1 also contains the lipophilicity (P), diuretic activity ($1/c$), and inhibition constant (K_i) converted into their log units, that is, as $\log P$, $\log(1/c)$ and $\log K_i$, respectively. The topological indices used being Wiener (W) (Ref. 21), Szeged (Sz) (Refs. 22–24), Padmakar–Ivan (PI) (Refs. 25–27); and Randic molecular connectivity indices ($^0\chi$, $^1\chi$, $^2\chi$) (Ref. 28). In addition, we have also used π and σ parameters reported Kakeya et al.[9] The methods for calculating distance-based topological indices, viz W, Sz, PI, $^0\chi$, $^1\chi$, and $^2\chi$ are well documented. For their calculations we have used the program prepared by Raj Singh Sisodia. The calculated values of these topological indices along with those of π and σ are recorded in Table 2.

We shall discuss the modeling of lipophilicity, diuretic activity, and carbonic anhydrase inhibition activity separately under three different headings. The modeling is attempted using maximum R^2-method.[34–36]

2.1. Modeling of lipophilicity

In a QSAR model, the hydrophobicity/lipophilicity of a compound is usually expressed as the logarithm of 1-octanol/water partition coefficient ($\log P$). The same is done in the present case also. Also, our earlier studies[29–33] have shown that distance-based topological indices can be used for modeling $\log P$, and that except for $^1\chi$, PI index is found most appropriate for this purpose. Data presented in Table 3 shows that none of the topological indices, including σ, are capable of modeling $\log P$ when used independently. However, the data did show that among W, Sz, PI, the PI index will be a better index to be used in modeling $\log P$. These results also indicate that no mono-parametric models, except for π, are possible for modeling $\log P$. Here, π yielded statistically significant model for modeling $\log P$. This is obvious as π is defined as: $\pi = \log P_x - \log P_H$ where $P_{x,H}$ represents partition coefficients for the x-substituted and unsubstituted (H) derivatives. The model based on π parameter is found as

$$\log P = -0.3310 + 0.65527(\pm 0.1253)\pi$$
$$n = 16, \quad \mathrm{Se} = 0.3388, \quad R = 0.8134, \quad F = 27.3712,$$
$$P = 1.2702 \times 10^{-4} \qquad (1)$$

Table 2. Distance-based topological indices (W, Sz, PI, $^0\chi$, $^1\chi$, $^2\chi$) calculated for the benzene sulfonamides used in the present study

Compound no.	W	Sz	PI	$^0\chi$	$^1\chi$	$^2\chi$
1	201	306	126	9.1902	5.5370	5.4919
2	152	236	104	8.4831	4.9990	5.3228
3	201	306	126	9.1902	5.5370	5.4959
4	152	236	104	8.4831	4.9990	5.3228
5	148	228	104	8.4831	4.9990	5.3347
6	114	177	84	7.6129	4.6052	4.7010
7	152	236	104	8.4831	4.9990	5.3228
8	152	236	104	8.4831	4.9990	5.3228
9	148	228	104	8.4831	4.9990	5.3347
10	325	472	176	10.7676	6.3929	6.7132
11		306	126	9.1902	5.5370	5.4919
12	240	354	150	10.0605	5.9097	6.2337
13	252	378	150	10.0605	5.9097	6.2217
14	189	291	126	9.3534	5.4097	5.8306
15	289	427	176	10.9307	6.3204	6.7612
16	404	694	266	13.4307	7.3317	8.7564
ortho-Substituted benzene sulfonamides (deleted for the final regression)						
17	144	220	104	8.4831	5.0159	5.2343
18	144	220	104	8.4831	5.0259	5.2343
19	228	330	150	10.0605	5.9265	6.1648

Table 3. Regression parameters and quality of correlations for modeling CA inhibitory activity ($\log K_i$) of benzene sulfonamides used in the present study

S.no.	TI(s) used	Se	R	R^2_A	F	P	Q
Mono-parametric regressions							
43	W	0.4724	0.6767	—	11.8255	0.00399	1.4324
44	Sz	0.4707	0.6797	—	12.0223	0.00377	1.4440
45	PI	0.4564	0.7029	—	13.6735	0.00239	1.5400
46	$^0\chi$	0.4440	0.7220	—	15.2459	0.00159	1.6261
47	$^1\chi$	0.4639	0.6908	—	12.7789	0.00305	1.4891
48	$^2\chi$	0.4401	0.7277	—	15.7619	0.0014	1.6534
49	σ	0.2530	0.9190	—	76.0900	<0.0001	3.6324
50	π	0.3933	0.7901	—	23.2638	2.7094×10^{-4}	2.0088
Bi-parametric regressions							
51	W, σ	0.2537	0.9246	0.8325	82.4852	<0.0001	3.6444
52	Sz, σ	0.2578	0.9251	0.8337	83.0387	<0.0001	3.5880
53	PI, σ	0.2513	0.9261	0.8337	84.3837	<0.0001	3.6852
54	$^0\chi$, σ	0.2490	0.9275	0.8387	86.2148	<0.0001	3.7248
55	$^1\chi$, σ	0.2529	0.9251	0.8336	83.0874	<0.0001	3.6579
56	$^2\chi$, σ	0.2485	0.9277	0.8393	86.4304	<0.0001	3.7331
57	W, π	0.2912	0.8989	0.7794	124.4768	<0.0001	3.0868
58	Sz, π	0.2899	0.9003	0.7813	89.8786	<0.0001	3.1055
59	PI, π	0.2936	0.8976	0.7757	87.1708	<0.0001	3.0572
60	$^0\chi$, π	0.2853	0.9036	0.7882	62.3282	<0.0001	3.1671
61	$^1\chi$, π	0.2815	0.9062	0.7937	64.2998	<0.0001	3.2191
62	$^2\chi$, π	0.2969	0.8951	0.7707	56.4225	<0.0001	3.0148
63	σ, π	0.1904	0.9582	0.9056	156.9408	<0.0001	5.0325
Tri-parametric regressions							
64	W, σ, π	0.1757	0.9673	0.9196	94.5886	<0.0001	5.5054
65	Sz, σ, π	0.1743	0.9679	0.9209	96.3481	<0.0001	5.5530
66	PI, σ, π	0.1770	0.9668	0.9185	93.0406	<0.0001	5.4621
67	$^0\chi$, σ, π	0.1737	0.9681	0.9252	97.0032	<0.0001	5.5734
68	$^1\chi$, σ, π	0.1725	0.9685	0.9226	98.3387	<0.0001	5.6144
69	$^2\chi$, σ, π	0.1788	0.9662	0.9168	91.2444	<0.0001	5.4038

The above results indicate that W, Sz, PI, $^0\chi$, $^1\chi$, $^2\chi$, and σ are not suitable parameters for modeling $\log P$ as no significant correlations were obtained with these descriptors and $\log P$. This failure to find a statistical significant correlation (except with π) indicates that other structural considerations are more important as determinants of lipophilicity ($\log P$).

Consequent to above, and following maximum R^2-method,[34] we have attempted several bi-parametric regressions. The results have shown that binary combinations of topological index with π yielded statistically significant models. The quality of the models, more or less, is found similar, combination of ${}^0\chi$ and π is found the best. This bi-parametric model is found as below:

$$\log P = 0.8905 - 1.1348(\pm 0.0599)\,{}^0\chi + 0.7658(\pm 0.1207)\pi$$
$$n = 16, \quad \mathrm{Se} = 0.2982, \quad R = 0.8697, \quad R^2_{\mathrm{A}} = 0.7190,$$
$$F = 43.4713, \quad P = 1.030 \times 10^{-4} \qquad (2)$$

Here and thereafter, n—the number of compounds, Se—standard error of estimation, R—multiple correlation coefficient, R^2_{A}—adjustable R^2, F—Fisher's statistics, and P—probability.

The negative coefficient of ${}^0\chi$ in the above Eq. 2 indicates that the number and type of atoms have negative effect on exhibition of $\log P$. However, the hydrophobic parameter π is favorable for this purpose as indicated by its positive coefficient.

Successive regression analysis yielded tri-parametric models containing (i) ${}^0\chi$, π, σ, and (ii) PI, π, σ, respectively, with slightly better R and S values.

Looking to the sample size (number of compounds used) and high collinearity between the topological indices we could not go far still higher parametric regressions. This is in accordance with the 'rule of thumb' and thus we can at the most go for tri-parametric regression analysis.

2.2. Modeling of diuretic activity ($\log 1/c$)

The results obtained for modeling diuretic activity ($\log 1/c$) indicated that only σ gives statistically significant results. Failure of obtaining statistically significant results using π indicates that diuretic activity is independent of this parameter. The statistically significant correlation with σ is found as below:

$$\log 1/c = -0.2279 - 0.4200(\pm 0.09427)\sigma$$
$$n = 16, \quad \mathrm{Se} = 0.2129, \quad R = 0.7657, \quad F = 19.8409,$$
$$P = 5.4436 \times 10^{-4} \qquad (3)$$

The above Eq. 3 indicates that the electronic effect of substitution has negative effect on the exhibition diuretic activity ($\log 1/c$).

The stepwise regression analysis yielded several bi-parametric regression models out of which two (i) containing ${}^2\chi$ and σ and (ii) containing σ and π gave better statistics. However, in these models ${}^2\chi$ and σ, respectively, have equal value for the coefficient and standard deviation. They are, therefore, not acceptable statistically. Finally, a tri-parametric model containing ${}^2\chi$, σ, π gave still better statistics. In this model ${}^2\chi$ and π have nearly equal values for their coefficients as well as standard deviations. In this regards it is worthy to mention that it is traditional in reporting statistics that the minimal acceptance criteria is significant at the 95% confidence level for reporting equations and for each variable in such equations. This is usually determined by Student's t test, which should be significant at the 0.5 level. Very approximately, this translates to the standard error of the parameter being no greater than half the value of the parameter, that is, the coefficient must be less than 2 standard deviations, and not 1. In view of this all the tri-parametric regressions and all other analyzed equations which violets this requirement or in which coefficient and standard deviation of one or more of the correlating parameters are similar are not acceptable. This, therefore, is considered as one of the important criteria for acceptability of statistics.

2.3. Modeling of carbonic inhibition activity ($\log K_{\mathrm{i}}$)

The results obtained for modeling carbonic anhydrases inhibition activity ($\log K_{\mathrm{i}}$) are presented in Table 3. The results obtained are very much encouraging. All the parameters/molecular descriptors yielded quite a good statistics for modeling inhibitory activity ($\log K_{\mathrm{i}}$). Among the topological indices used ${}^2\chi$ gives the best result (Table 3). This mono-parametric model containing ${}^2\chi$ is found as below:

$$\log K_{\mathrm{i}} = 2.9766 + 0.4727(\pm 0.1191)\,{}^2\chi$$
$$n = 16, \quad \mathrm{Se} = 0.4401, \quad R = 0.7277, \quad F = 15.7586,$$
$$P = 0.0014 \qquad (4)$$

This means that here also the second order branching is the favorable parameter for the exhibition of the inhibitory activity.

Between the non-topological parameters: σ and π, σ gives excellent result (Table 3). This mono-parametric model containing σ is found as below:

$$\log K_{\mathrm{i}} = 5.5137 + 0.9771(\pm 0.1120)\sigma$$
$$n = 16, \quad \mathrm{Se} = 0.2539, \quad R = 0.9190,$$
$$F = 76.0900, \quad P \leqslant 0.0001 \qquad (5)$$

This shows that electronic effect of the substituents play a dominating role in the exhibition of the inhibitory activity.

Unlike the earlier cases, here the bi-parametric regressions of each of the topological index with σ on one hand and π on the other hand yielded statistically excellent models (Table 3). However, the binary combinations of each of the topological index with π resulted into slightly lower statistics. Furthermore, the bi-parametric model containing σ and π was the most appropriate:

$$\log K_{\mathrm{i}} = 5.4341 + 0.7427(\pm 0.1086)\sigma + 0.3104(\pm 0.0907)\pi$$
$$n = 16, \quad \mathrm{Se} = 0.1904, \quad R = 0.9582, \quad R^2_{\mathrm{A}} = 0.9056,$$
$$F = 156.9573, \quad P \leqslant 0.0001 \qquad (6)$$

Finally, successive regression analysis yielded tri-parametric models, all having excellent statistics (Table 3).

However, the model containing $^1\chi$, σ, π gave slightly better results:

$$\log K_i = 4.5778 + 0.1593(\pm 0.0812)^1\chi + 0.5928(\pm 0.1246)\sigma + 0.3306(\pm 0.0828)\pi$$
$$n = 16, \quad \mathrm{Se} = 0.1725, \quad R = 0.9655, \quad R_A^2 = 0.9226,$$
$$F = 89.3702, \quad P \leqslant 0.0001 \qquad (7)$$

2.4. Modeling based on *ortho*-, *meta*-, *para*-, and di-substituted benzene sulfonamides

Finally, we have subdivided the data set (19 compounds) into *ortho*-, *meta*-, *para*-, and di-substituted benzene sulfonamides. In each of this categories we have included the parent (unsubstituted) sulfonamide for comparison and carried out regression analysis for modeling $\log P$, $\log 1/c$, and $\log K_i$. In the following table the number of compounds belonging to each of the category together with the parent compound are given in the brackets. The results, in terms of correlation coefficient are summarized below:

When the parent compound **6** is deleted further improvement in correlation coefficient is observed. However, when we did so the number of compounds belonging to *ortho*-, *meta*-, and di-substituted category reduces to three and those for the *para*-substituted compounds the number reduces to nine. Thus, the improvement in the correlation coefficient may also be attributed to decrease in the sampling (decrease in the number of compounds under a specified category).

TI	Correlation coefficient for modeling		
	$\log P$	$\log 1/c$	$\log K_i$
ortho-Substituted benzene sulfonamides (**6**, **17**–**19**)			
W	—	−0.5909	—
Sz	—	−0.6092	—
PI	—	−0.6316	—
$^0\chi$	—	−0.6844	—
$^1\chi$	—	−0.6396	—
$^2\chi$	—	−0.6931	—
meta-Substituted benzene sulfonamides (**5**, **6**, **9**, **12**)			
W	—	0.9768	−0.8865
Sz	—	0.9743	−0.8893
PI	—	0.9718	−0.8912
$^0\chi$	—	0.9596	−0.8953
$^1\chi$	—	0.9720	−0.8911
$^2\chi$	—	0.9403	−0.8947
para-Substituted benzene sulfonamides (**1**, **2**, **3**, **4**, **6**, **7**, **8**, **10**, **11**, **13**)			
W	—	0.4299	−0.4502
Sz	—	0.4376	−0.4505
PI	—	0.4477	−0.4541
$^0\chi$	—	0.4546	−0.4588
$^1\chi$	—	0.4591	−0.4296
$^2\chi$	—	0.4066	0.4952
Di-substituted benzene sulfonamides (**6**, **14**–**16**)			
W	—	0.9962	−0.7949
Sz	—	0.9965	−0.8060
PI	—	0.9949	−0.8183
$^0\chi$	—	0.9874	−0.8668
$^1\chi$	—	0.9841	−0.8618
$^2\chi$	—	0.9960	−0.8371

The results given above indicate that even when we subdivided 19 sulfonamides as *ortho*-, *meta*-, *para*-, and di-substituted benzene sulfonamides, none of the topological index when used singly are capable of modeling lipophilicity ($\log P$). Only for the sulfonamides belonging to *meta*- and di-substituted sulfonamides the topological indices gave statistically significant models for modeling $\log 1/c$ and $\log K_i$; while for *para*-substituted sulfonamides statistically poor results are obtained.

3. Conclusions

From the results and discussion made above we conclude that in the present set of benzene sulfonamides, statistically significant results are obtained after deleting *ortho*-substituted sulfonamides. Also, that no mono-parametric models based on topological index(s) are possible for modeling lipophilicity ($\log P$) and diuretic activity ($\log 1/c$). However, such modeling is possible for modeling carbonic inhibition activity. The hydrophobic parameter π is responsible for the exhibition of lipophilicity, while the electronic parameter σ is responsible for modeling diuretic activity of the sulfonamides used. In case of carbonic anhydrase inhibition both σ and π are responsible, and that σ is more in this respect.

4. Experimental

4.1. Lipophilicity, diuretic activity, and carbonic inhibition constant

These activities are taken from the literature and are used after converting to them to their log units.

4.2. Topological indices

All the topological indices were calculated using molecular graphs of the benzene sulfonamide obtained by deleting all the C–H and hetero-atom hydrogen bonds from their molecular structures. The calculations of these topological indices (W, Sz, $^0\chi$, $^1\chi$, $^2\chi$) are well mentioned in the literature and, therefore, their details of calculations are omitted in this paper. As stated earlier the computer programme developed by Raj Singh Sisodia is used for the calculations of the topological indices.

4.3. Regression analysis

The regression analysis was performed by stepwise using maximum R^2 method. Regress-1 program provided by Lukovits is used for this purpose.

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