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Novel use of chemical shift in NMR as molecular descriptor: a first report on modeling carbonic anhydrase inhibitory activity and related parameters

Padmakar V. Khadikar,[a,*] Vimukta Sharma,[b] Sneha Karmarkar[a] and Claudiu T. Supuran[c]

[a]*Research Division, Laxmi Fumigation and Pest Control (P) Ltd, 3, Khatipura, Indore 452 007, India*
[b]*Department of Pharmacy, Maharaja Ranjeet Singh College, Indore, India*
[c]*University of Florence, Dipartimento di Chimica, Laboratoria di Chemica Bioinorganica, Via della Lastruccia polo Scientifico 50019 Sest Fiorentino, Italy*

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Abstract—A novel use of NMR chemical shift of the SO_2NH_2 protons (in dioxane as solvent) as a molecular descriptor is described for modeling the inhibition constant for benzene sulfonamides against the zinc enzyme carbonic anhydrase (CA, EC 4.2.1.1). The methodology is extended to model diuretic activity and lipophilicity of benzene sulfonamide derivatives. The regression analysis of the data has shown that the NMR chemical shift is incapable of modeling lipophilicity. However, it is quite useful for modeling the diuretic activity of these derivatives. The results are compared with those obtained using distance-based topological indices: Wiener (W)-, Szeged (Sz)-, and PI (Padmakar-Ivan) indices.

1. Introduction

Carbonic anhydrases (CAs, EC 4.2.1.1) are wide spread zinc enzymes present in archaea and bacteria, algae, green plants, and animals. These enzymes are very efficient catalysts for the reversible hydration of CO_2 to bicarbonate and are inhibited by sulfonamides possessing the general formula RSO_2NH_2, where R = aryl; hetaryl; perhaloalkyl. These sulfonamide inhibitors of the zinc enzyme carbonic anhydrase are widely used as pharmacological agents in the treatment of a variety of disorders: treatment of glaucoma, gastro-duodenal ulcers, certain neurological disorders, motion and altitude sickness, and many others.[1] Consequently, a large number of aromatic, heterocyclic, and aliphatic sulfonamides have been synthesized and tested for their CA inhibitory properties and some of them are widely used clinical or investigational drugs. In this regard $-SO_2NH_2$ group plays a dominating role.[1]

In view of the above several quantitative structure–activity relationship (QSAR) studies were carried out[1–10] by others and by us. Such QSAR studies were reported for aromatic as well as heterocyclic sulfamides. The first CA inhibitory QSAR study[5] included substituted benzene sulfonamides of the type $R–C_6H_4–SONH_2$.

Accordingly, the electronic properties of the $-SO_2NH_2$ group are important for the inhibitory effects of a series of 2-, 3-, and 4-substituted benzene sulfonamides.

The parameters used in the earlier QSAR studies were some physicochemical parameters related to molecular structure and also Hansch parameters. In our recent studies we have successfully used distance-based topological indices for modeling inhibitory activity and thus for QSAR studies.[11–16]

One of the authors (PVK) in the recent studies proposed and established that chemical shift in NMR (δ) can be used as a molecular descriptor in developing QSAR and/or QSPR (quantitative structure–property relationship) models.[17,18] Thus, ^{13}C NMR chemical shifts (δ) were used in QSAR studies for modeling toxicity,

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* Corresponding author. Tel.: +91 0731 531906; e-mail: pvkhadikar@rediffmail.com

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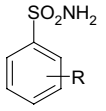
Table 1. Structural details of benzene sulfonamides, their inhibition constant (pK_i), diuretic activity (pC), lipophilicity (log P) and NMR chemical shifts (δ) of the SO_2NH_2 protons



S. No.	R	pK_i	pC	log P	δ (ppm)	IP_1	IP_2	IP_3	IP_4
1	*p*-MeNH	4.82	−0.036	0.31	5.78	0	0	1	0
2	*p*-NH_2	4.64	−0.301	0.025	5.85	0	0	1	0
3	*p*-MeO	5.35	0.188	1.72	6.01	0	0	1	0
4	*p*-Me	5.42	0.182	2.61	6.06	0	0	1	0
5	*m*-Me	5.30	0.176	2.55	6.07	0	1	0	0
6	H	5.22	0.130	0.70	6.12	0	0	0	0
7	*p*-Cl	5.72	0.286	1.69	6.26	0	0	1	0
8	*p*-Br	5.92	0.267	2.98	6.25	0	0	1	0
9	*m*-Cl	5.64	0.292	2.19	6.30	0	1	0	0
10	*p*-Ac	5.96	0.398	0.53	6.34	0	0	1	0
11	*p*-CN	5.96	1.000	0.30	6.42	0	0	1	0
12	*m*-NO_2	5.89	0.678	0.53	6.51	0	1	0	0
13	*p*-NO_2	6.05	0.824	0.31	6.48	0	0	1	0
14	3,4-Cl_2	6.40	0.243	4.07	6.37	0	0	0	1
15	3-NO_2, 4-Cl	6.77	0.322	1.30	6.50	0	0	0	1
16	3-CF_3, 4-NO_2	6.85	0.580	1.90	6.62	0	0	0	1
17	*o*-Me	4.80	0.301	3.53	6.30	1	0	0	0
18	*o*-Cl	5.52	0.301	3.83	6.39	1	0	0	0
19	*o*-NO_2	5.07	0.301	1.69	6.39	0	0	0	0

Me—methyl, Ac—acetyl, *o*—ortho, *m*—meta, *p*—para, IP_1—indicator parameter for *ortho*-substitution, IP_2—indicator parameter for *meta*-substitution, IP_3—indicator parameter for *para*-substitution, IP_4—indicator parameter for di-substitution.

organic reactivity, H-acidity, s-character, steric energy, ultrasonic sound velocity etc.[19–22] This has prompted us to use NMR chemical shift (δ) for modeling carbonic anhydrase inhibition constant and other related parameters of benzene sulfonamides. Since, –SO_2NH_2 group dominates the inhibition, we have used NMR chemical shift (δ) of the –SO_2NH_2 protons (in dioxan as solvent) for this purpose. Fortunately such chemical shifts for the series of sulfonamides used (Table 1) in the present study are available in the literature.[21] We have, therefore, used the reported NMR chemical shifts in the present study. The results, as discussed below, show that the NMR chemical shifts (δ) of the –SO_2NH_2 protons can be used very successfully for modeling, monitoring, and estimating inhibition activity (pK_i) as well as diuretic activity (pC) of the series of sulfonamides used in the present study. However, the methodology is not that useful for modeling lipophilicity (log P) of the sulfonamides used. In addition, we have also investigated and compared the relative power of the –SO_2NH_2 NMR shifts for modeling pK_i and pC and compared them with the important distance-based topological indices: Wiener (W)-,[23] Szeged (Sz)-,[24,25] and PI (Padmakar-Ivan) indices[26–28] used by us earlier.

2. Results and discussion

The set of 19 benzene sulfonamides used in the present investigation is given in Table 1. The corresponding values of the inhibition constant K; and diuretic activities ($1/c$) are expressed as pK_i and pC, along with pK_i (log P), are presented in Table 1. The NMR chemical shift (δ) of the –SO_2NH_2 protons in dioxane as solvent, are also summarized in Table 1. The calculated values of Wiener (W)-, Szeged (Sz)-, and PI (Padmakar-Ivan) indices are shown in Table 2.

(i) Modeling inhibition activity pK_i ($-\log K_i$): The simple regression analysis considering all the 19 sulfon-

Table 2. Calculated values of distance-based topological indices (W, Sz, PI), Hammett σ parameters and Hansch hydrophobic parameter (π) for the benzene sulfonamides used in the present study (Ref. Table 1)

S. No.	W	Sz	PI	σ	π
1	201	306	126	−0.840	−0.231
2	152	236	104	−0.660	−1.137
3	201	306	126	−0.268	0.163
4	162	236	104	−0.170	0.505
5	148	228	104	−0.069	0.540
6	114	177	84	0.000	0.000
7	152	236	104	0.227	0.531
8	152	236	104	0.232	1.053
9	148	228	104	0.373	0.981
10	325	472	176	0.502	−0.105
11	201	306	126	0.660	−0.083
12	240	354	150	0.710	0.242
13	252	378	126	0.778	0.328
14	189	291	126	0.600	1.134
15	289	427	176	0.937	1.603
16	484	694	266	1.208	1.420
17	144	220	104	—	0.526
18	144	220	104	—	0.427
19	228	330	150	—	0.033