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Molecular Modeling of Human Carbonic Anhydrase I Inhibitors with Sulfonamides

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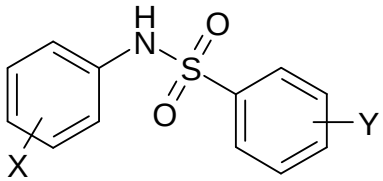
ABSTRACT – *The paper deals with QSAR study on the inhibitors of human carbonic anhydrase-I (CA-I) using topological indices with simple regression models. The proposed prediction set includes 25 molecules of benzene sulfonamides. Statistically significant model was derived by correlation analysis.*

Keywords- QSAR, CA-I, Regression analysis, topological indices

INTRODUCTION

Although the story of sulfonamides started with the discovery of their anti-microbial action, subsequent studies established their usefulness as a carbonic anhydrase inhibitors[1-5]. Studies to find out correlation between physicochemical properties and biological activities of sulfonamides indicated the dominating role played by their proton-ligand formation constant, more commonly known as acid dissociation constant pKa of the sulfonamides[6-13]. The pKa is related to solubility, distribution and partition coefficients, and permeability across membranes, protein binding and re-absorption in the kidneys. Earlier reports[14-20] have indicated that distance-based topological indices can be used very successfully for modeling, monitoring, and estimating various physicochemical parameters as well as physiological activities of the organic compounds acting as drugs. The maximal activity of sulfonamides was found on the physiological pH[7,8]. The present paper will be useful to medicinal chemists interested in modeling physiological activities of benzene sulfonamides.



General structure of sulfonamides

Carbonic anhydrase inhibitors were studied by many authors [21-30] through quantitative structure activity relationships (QSARs). Carbonic anhydrase are widespread enzymes present in different isoforms. The 12 catalytically active isoforms play important physiological and pathophysiological functions and are strongly inhibited by aromatic/heterocyclic sulfonamides. The field of quantitative structure–activity relationship (QSAR), formalized by Hansch and others in the early 1960s, is the discovery of empirical relationships between the chemical structure of drugs and their biological activity[31-36].

Carbonic anhydrase catalyses hydration of CO_2 in our body organs and this reaction is responsible for various diseases like glaucoma, hypertension and neuromuscular disorder in our body. Benzene sulfonamides inhibit these Carbonic anhydrases. Oxygen from SO2NH2 get attached with the metal from the enzyme, one hydrogen with the hydroxyl group, another with imidazole ring and the hydrophobic part gets attached with the amino acid from the enzyme, thus stabilizing the interaction. The aim of this paper is to predict the model of better biological activity with one variable.

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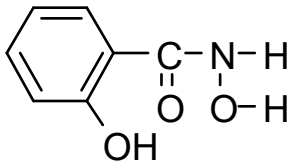
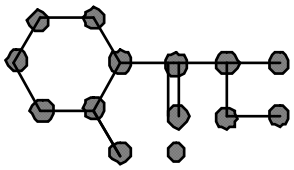
METHODOLOGY USED - Chemical graph theory is applied for modeling of drugs. We must here at the beginning emphasize the distinction between graphs and molecules. When one interprets vertices as atoms and edges as bonds, graphs show only the connectivities within a molecule. In obtaining graphs (molecular) from structure (molecular) all the carbon-hydrogen bonds are suppressed. For example Salicylic hydroxamic acid (SHA) is:



Then its molecular graph will be



The graph so obtained is called carbon-hydrogen suppressed molecular graph or simply molecular graph. The connectivities in the molecular graph are exceedingly important and it is of considerable interest to find all the results of a particular connectivity.The purpose of defining a topological index is to represent each chemical structure with a numerical value, keeping it at the same time as discriminatory as possible. Such indices may be used to classify structures and to predict chemical and biological properties. Owing to the loss of information resulting from the condensation of molecular topological features into a single number, none of the known topological indices can uniquely characterize molecular graphs. However, various indices have been used for correlating diverse physicochemical and biological properties. During last two decades many graph invariants have been developed and used for predicting properties or activities of molecules.

The Main topological indices that have been used in the study are mentioned below:

(i) Wiener index

(ii) Balaban index

(iii) Total Structure Connectivity Index

(iv) Polarity Number

(v) Schultz Molecular Topological Index

The topological indices have been calculated using software available in the literature. The software's that have been used are: DRAGON , LUKO-1 and ACD labs can be used for structure optimization. QSAR analysis is done using REGRESS-1, MARTHA, ORIGION software. Different combinations of topological indices have been used to identify descriptor (topological indices) sets with highest predictive folder.

Regression analysis is a simple method for investigating functional relationship among variables. Such relationship is expressed in the form of an equation or a model connecting the response or dependent variable and one or more explanatory or predictor (independent) variables.

$Y = \beta_o + \beta_1 X + \beta_2 Y + \beta_3 Z + \ldots$

Where, β_o, β_1, β_2,….., β_p are constant referred to as the model partition regression coefficients. The magnitude of β_1, β_2, … β_p play dominant role in deciding whether the proposed regression equation or regression expression or model is statistically significant.

RESULTS AND DISCUSSION

The results obtained in the present study for modeling of CA-I inhibition of a set of 25 benzene sulfonamides. The structural details of this set of compounds are shown in Table 1. With ACD Labs software, structures have been drawn and after that topological descriptors Wiener index(W), Total Structure Connectivity Index

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(Xt), Balaban Index (J), Polarity Number (POL) and Schultz Molecular Topological Index (SMTI) are calculated by Dragon software. The values of these descriptors are given in Table 2. The correlation and regression parameters are summarized in Table 3. The best QSAR formula is

Log CA-I = -4.8427+ 23.2420 (Xt)

N=25, Multiple R= 0.8594, r^2 = 0.7386, Adjusted R= 0.7273, Standard Error= 0.6675 F= 65.0134

CONCLUSION:

In CA I inhibition by benzene sulfonamides, the total structure connectivity has been found to be a dominant factor. Biological activity is highly positively correlated with structure connectivity index. On the other hand remaining factors does not hold so good.

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This article is dedicated to late Prof. Padmakar V. Khadikar (1936-2012)

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Table - I - 1, MOLECULAR STRUCTURE
(Figure 1 to 25)

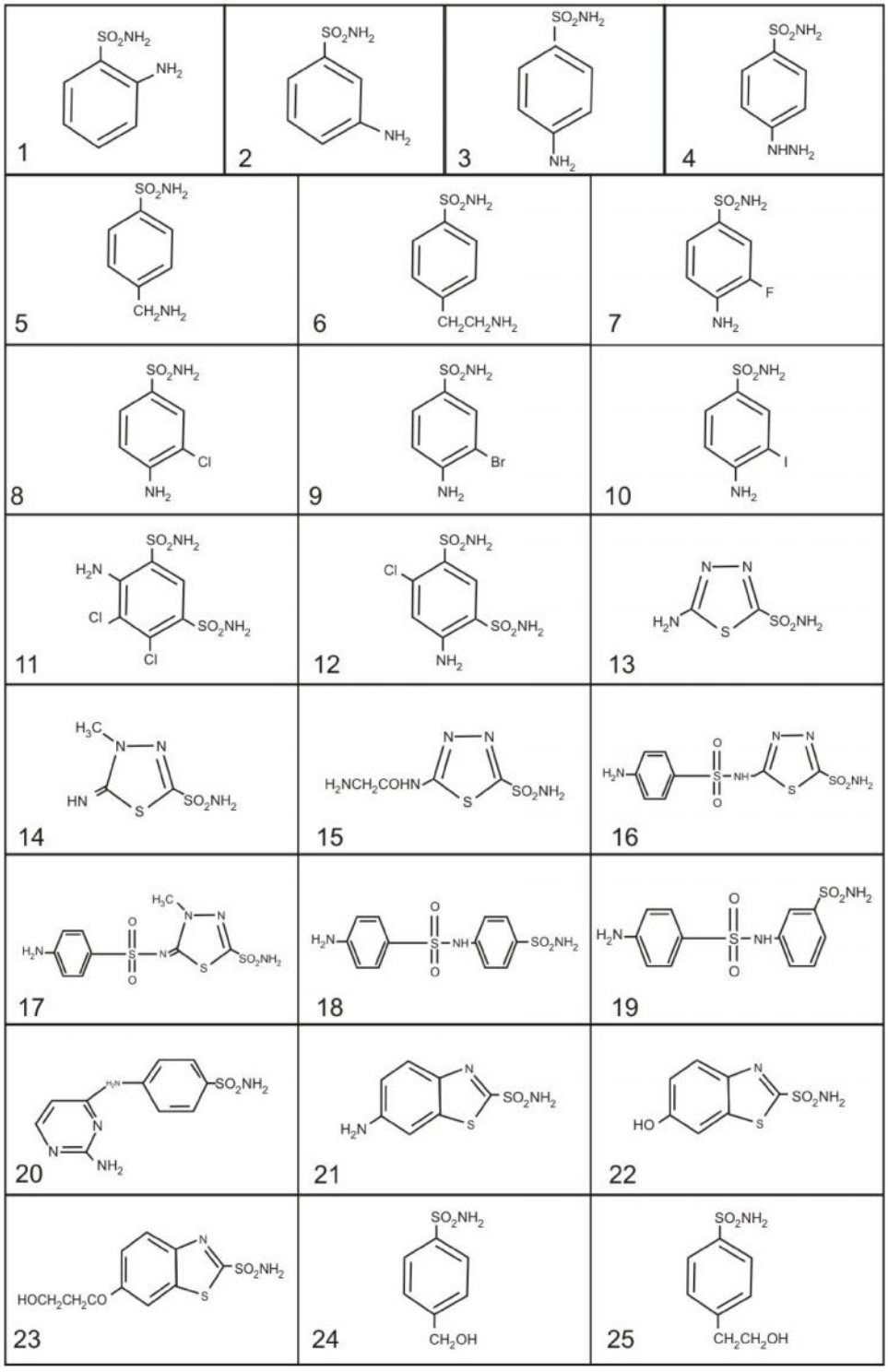

Table 2 : TOPOLOGICAL DESCRIPTORS						
S. No.	Log ki	Xt-9	POL-12	SMTI-	W-22	J-42

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	CA I			16		
1	4.6571	0.397	14	591	144	2.545
2	4.399	0.397	13	607	148	2.461
3	4.4472	0.397	13	623	152	2.394
4	4.8949	0.377	15	810	201	2.359
5	4.398	0.377	15	810	201	2.359
6	4.3223	0.359	16	1045	262	2.305
7	3.919	0.385	16	762	189	2.512
8	3.9912	0.385	16	762	189	2.512
9	3.813	0.385	16	762	189	2.512
10	3.7782	0.385	16	762	189	2.512
11	3.7854	0.334	29	1769	458	2.991
12	3.9243	0.342	25	1552	399	2.853
13	3.9345	0.42	10	468	113	2.449
14	3.9685	0.406	13	592	146	2.538
15	2.658	0.35	16	1274	323	2.343
16	0.7782	0.28	28	3530	853	1.861
17	0.9543	0.269	35	4386	1069	1.96
18	1.6233	0.273	31	4148	1004	1.816
19	1.6435	0.273	31	3964	960	1.9
20	2.8389	0.288	24	2810	669	1.731
21	1.845	0.329	19	1235	287	1.987
22	1.7403	0.329	19	1235	287	1.987
23	1.699	0.292	26	2565	622	1.909
24	4.3802	0.377	15	810	201	2.359
25	4.2553	0.359	16	1045	262	2.305

Table 3: CA-I INHIBITION

Regression Parameters and Quality of Co-relation for Modeling CA I inhibitor with one variable

Model	Parameters Used	Correlation R	R Square	Adjusted R Square	Standard Error	F
1	Xt	0.8595	0.7387	0.7273	0.6676	65.0134
2	POL	-0.7576	0.5740	0.5555	0.8523	30.9890
3	SMTI	-0.8232	0.6777	0.6637	0.7414	48.3550
4	W	-0.8145	0.6635	0.6488	0.7575	45.3461
5	J	0.7493	0.5614	0.5424	0.8648	29.4436

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