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Multivariate Analysis for the Inhibition of Human Carbonic Anhydrase I

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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 multi parametric regression models. The proposed prediction set includes 25 molecules of benzene sulfonamides. Statistically significant model was derived by regression 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, diuretics, and anti-diabetic (insulin-releasers) and more recently also as endothelia antagonists[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 pKa of the sulfonamides[6-13].

The complexing ability to form supramolecular complex is dependent of this pKa parameter. It was observed that bacteriostatic activity of the sulfonamides was due to the presence of a larger proportion of sulfonamide in an active (ionized) form. The maximal activity was observed in sulfonamides whose pKa approximated the physiological pH. the functional relationship between acid dissociation constant (pKa) and the biological activity of sulfonamides is well established and could not be questioned

. 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..Recent report has indicated that Balaban index (J) is a very useful index for this purpose. Since pKa is also an important physicochemical parameter we thought worthy to investigate the usefulness of distance-based topological indices in general and Balaban index in particular for modeling pKa of sulfonamides The present paper will be useful to medicinal chemists interested in designing drugs, with benzene sulfonamides multi parametric models.

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. Carbonic Anhydrase –I is located in cytosol The

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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. The carbonic anhydrases form a family of enzymes that catalyze the rapid interconversion of carbon dioxide and water to bicarbonate and protons (or vice versa), a reversible reaction that occurs relatively slowly in the absence of a catalyst. The active site of most carbonic anhydrases contains a zinc ion; they are therefore classified as metalloenzymes. 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 multiple variables.

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.

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:

- Total Structure Connectivity Index
- Polarity Number
- Schultz Molecular Topological Index
- Xu Index
- Superpendentic Index
- Wiener index
- Harary H Index
- Balaban index

The topological indices have been calculated using software available in the literature. The software's that have been used are: DRAGON for calculation of indices and ACD labs 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.

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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.

$Y = \beta_0 + \beta_1 X + \beta_2 Y + \beta_3 Z + \ldots$

Where, β_0, 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 Total Structure Connectivity Index (Xt), Polarity Number (POL) , Schultz Molecular Topological Index (SMTI), Xu Index (Xu), Superpendentic Index (SPI) , Wiener index (W), Harary H Index , Balaban index (J) 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 model is

Log Ki (hCA-I) = -58.5932+ 91.8066 (Xt) + 0.3022 (POL) – 0.0052 (SMTI) +2.5978 (Xu) – 1.8983 (SPI) + 0.0125 (W) +0.0021 (HAR) + 3.3015 (J)

N=25, Multiple R= 0.9826, r^2 = 0.9656, Adjusted R= 0.9484, Standard Error= 0.2903 F= 56.1526

A perusal of table shows which models are statistically significant. Based on the information in Table2 and 3, we conclude that one model having multiple R=0.9826 is found to be most statistically signified. This model is, therefore, most appropriate for modeling CA-I inhibition. Thus, we have examined this model in more detail. It is a eight –parametric model consisting of correlating parameters: Xt, POL, SMTI, Xu, SPI, W, HAR, and J .From the rule thumb this model is justified.

CONCLUSION:

In CA I inhibition by benzene sulfonamides, most significant is the eight parametric model. After keen observation of the abovementioned model we can conclude that the biological activity is highly positively correlated with six topological descriptors and with remaining two, correlation is just opposite.

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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)

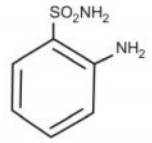
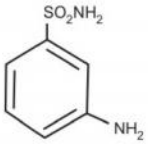
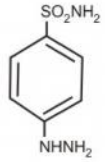
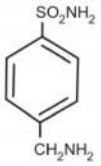
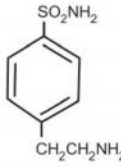
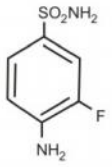
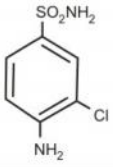
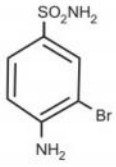
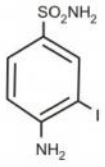
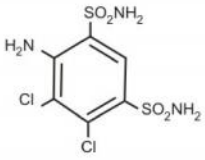
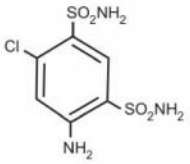
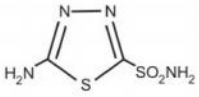
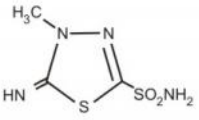
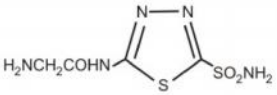
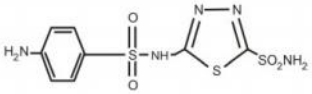
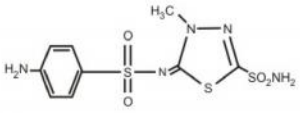
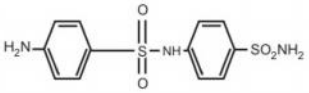
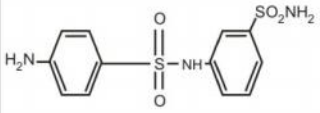
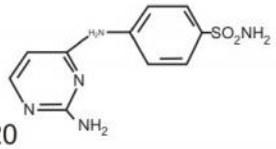
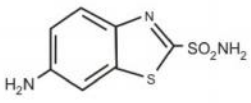
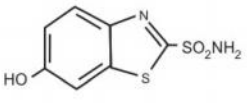
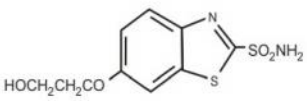
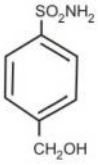
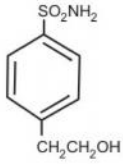
1 	2 	3 
4 	5 	6 
7 	8 	9 
10 	11 	12 
13 	14 	15 
16 	17 	18 
19 	20 	21 
22 	23 	24 
25 		

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Table 2 : TOPOLOGICAL DESCRIPTORS

	Log Ki CA I	Xt-9	POL-12	SMTI-16	Xu-20	SPI-21	W-22	HAR-24	J-42
1	4.6571	0.397	14	591	10.709	6.353	144	17.363	2.545
2	4.399	0.397	13	607	10.79	6.48	148	17.247	2.461
3	4.4472	0.397	13	623	10.89	6.581	152	17.188	2.394
4	4.8949	0.377	15	810	12.055	7.217	201	18.914	2.359
5	4.398	0.377	15	810	12.055	7.217	201	18.914	2.359
6	4.3223	0.359	16	1045	13.243	7.822	262	20.575	2.305
7	3.919	0.385	16	762	11.792	7.843	189	19.266	2.512
8	3.9912	0.385	16	762	11.792	7.843	189	19.266	2.512
9	3.813	0.385	16	762	11.792	7.843	189	19.266	2.512
10	3.7782	0.385	16	762	11.792	7.843	189	19.266	2.512
11	3.7854	0.334	29	1769	16.2	13.475	458	13.126	2.991
12	3.9243	0.342	25	1552	15.42	12.253	399	27.754	2.853
13	3.9345	0.42	10	468	9.715	5.981	113	15.419	2.449
14	3.9685	0.406	13	592	10.694	7.252	146	17.434	2.538
15	2.658	0.35	16	1274	14.216	9.259	323	22.437	2.343
16	0.7782	0.28	28	3530	19.84	13.073	853	35.704	1.861
17	0.9543	0.269	35	4386	21.413	14.954	1069	40.124	1.96
18	1.6233	0.273	31	4148	20.877	13.682	1004	37.529	1.816
19	1.6435	0.273	31	3964	20.654	13.477	960	37.75	1.9
20	2.8389	0.288	24	2810	18.249	10.163	669	31.133	1.731
21	1.845	0.329	19	1235	13.782	8.037	287	24.392	1.987
22	1.7403	0.329	19	1235	13.782	8.037	287	24.392	1.987
23	1.699	0.292	26	2565	17.875	11.212	622	31.804	1.909
24	4.3802	0.377	15	810	12.055	7.217	201	18.914	2.359
25	4.2553	0.359	16	1045	13.243	7.822	262	20.575	2.305

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Table 3: CA-I INHIBITION

Regression Parameters and Quality of Co-relation for Modeling CA I inhibitor with multiple variables

Model	Parameters Used	Multiple R	R Square	Adjusted R Square	Standard Error	F
1	Xt	0.8595	0.7387	0.7273	0.6676	65.0134
2	Xt,POL	0.8646	0.7477	0.7247	0.6707	32.5951
3	Xt,POL,SMTI	0.8708	0.7583	0.7237	0.6718	21.9626
4	Xt,POL,SMTI,Xu	0.8972	0.8049	0.7659	0.6184	20.6371
5	Xt,POL,SMTI,Xu,SPI	0.9761	0.9528	0.9404	0.3119	76.8135
6	Xt,POL,SMTI,Xu,SPI,W	0.9781	0.9568	0.9424	0.3065	66.5468
7	Xt,POL,SMTI,Xu,SPI,W,HAR	0.9781	0.9568	0.9391	0.3154	53.8810
8	Xt,POL,SMTI,Xu,SPI,W,HAR,J	0.9826	0.9656	0.9484	0.2903	56.1526

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