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MODELING FOR THE INHIBITION OF HUMAN CARBONIC ANHYDRASE IV

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ABSTRACT

This paper deals with study of inhibition of human carbonic anhydrase IV by benzene sulfonamides. QSAR and molecular modeling studies have been performed on a series of CA IV with benzene sulfonamides. The proposed prediction set includes 25 molecules of benzene sulfonamides. Statistically significant models were derived by correlation analysis. Quality of regression increases with variables. The model obtained by deleting outliers allow us to confirm that the six parametric model is the most significant model for modeling biological activity. The efficiency of the proposed model is around 92%. The predictive power has been examined by leave one out procedure.

KEYWORDS

QSAR, CA-IV, Regression analysis and Topological indices.

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INTRODUCTON

Carbonic anhydrase is an zinc metallic enzyme which is found in red blood cells, gastric mucosa, pancreatic cells, and renal tubules. It has a property of catalyzation of the interconversion of carbon dioxide (CO_2) and carbonic acid (H_2CO_3). Carbonic anhydrase plays an important role in respiration. Although it is important yet the reaction is responsible for different types of disorders in human body such as hyper tension, neuromuscular disorder and glaucoma.

Benzene sulfonamides have anti-microbial action. Further studies illustrate their usefulness as carbonic anhydrase inhibitors[1-5]. There is a direct correlation between physicochemical properties and biological activities of sulfonamides. Here dominating role is played by their proton-ligand formation constant that is PKa. It is more commonly known as acid

dissociation constant pKa of the sulfonamides. Two things are very important in this regard that distance-based topological indices and connectivity 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 drug and The maximal activity of sulfonamides was found on the physiological pH[6-8].

General structure of sulfonamides

Carbonic anhydrase inhibitors were studied by many authors through quantitative structure activity relationships (QSARs)[9-16]. Carbonic anhydrace are widespread enzymes present in different is forms. Benzene sulfonamides inhibit Carbonic anhydrases. Sulfonamides have SO2NH2 group. From this Oxygen get attached with the metal from the enzyme, one hydrogen with the hydroxyl group, another hydrogen with imidazole ring and the hydrophobic part gets attached with the amino acid from the enzyme, thus stabilizes the interaction. The aim of this paper is to predict the model of better biological activity with one, two and multiple variables for inhibition of CA IV.

METHODOLOGY USED

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 connectivity within a molecule. In obtaining graphs (molecular) from structure, all the carbon-hydrogen bonds are suppressed. For example, Salicylic hydroxamic acid (SHA) is:

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. Topological indices may be used to classify structures and to predict chemical and biological properties. During last two decades many graph invariants have been developed and used for predicting properties or activities of molecules.

The topological indices have been calculated using software available in the literature. The software's that have been used are: ACD labs can be used for structure of molecules. Dragon evaluation is used for calculation of various indices. QSAR analysis is done by data analysis. Different combinations of topological indices have been used to identify descriptor (topological indices) sets with highest predictive folder.

Regression analysis is the multiple regression method which shows relation between biological activity and various indices.

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

Where, β_o, β_1, β_2… are referred 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 model is statistically significant[17-20].

RESULTS AND DISCUSSION

The results obtained in the present study for modeling of CA-IV inhibition of a set of 25 benzene sulfonamides. The structural details of this set of compounds are shown in Table No.1. With ACD Labs software, structures have been drawn and after that topological descriptors Detour Index (w), Xu Index (Xu), Total Structure Connectivity Index (Xt), Polarity Number (POL), Harary H Index (Har) are calculated by Dragon software. All these indices have two dimensional information. The values of these descriptors are given in

Log Ki (CA-IV) = 3.1663 -0.0013 (w) Eq. (1)

N=23, Multiple R= 0.7692, R^2 = 0.5917, Adjusted R square= 0.5722, SE = 0.5293 F= 30.4269

Table No.2: The correlation and regression parameters are summarized in Table No.3. The best QSAR formula for single variable is

Where N is the number of compounds, R is correlation, R^2 is squared correlation coefficient, SE is the standard error and F is the F ratio between the variances of observed and calculated activities. After the analysis of above mentioned descriptors only w that is Detour index is capable in providing better results for the inhibition of CA IV.

The detour index of a graph is a graph invariant which is related with half the sum of all

off-diagonal matrix elements. It shows the network density. As regression equation (1) suggests that coefficient with detour index is negative. It means decrease in detour index leads to increase in activity of the model. Compound number 11 is having least residual thus it will give the best inhibitory activity.

When we consider two variable systems than the most significant model is derived as under:

Log Ki (CA-IV) = -0.2864+ 9.043371 (Xt) -0.02564 (HAR) Eq. (2)

N=25, Multiple R= 0.7368, R^2 = 0.5429, Adjusted R square= 0.5013, SE = 0.5892F= 13.0634

We observe that in case of bi parametric models, magnitude of the correlation coefficient of various models are very close. In above model, structure connectivity index is having a positive coefficient which is showing that as connectivity increases, activity increases but for Harary Index it is just opposite. Of all bi parametric models, none has achieved the satisfactory target.

As the number of variables increases, we proceed towards better inhibition. Here co-relating descriptors are different. Xu and Wiener index have the same effect as that of structure connectivity index. Schulz molecular index and SPI has same effect as that of Harary index.

Log Ki (CA-IV) = 6.6566- 0.0203 (SMTI) + 0.0133 (Xu) - 0.702 (SPI) + 0.0882(W) Eq. (3)

N=25, Multiple R= 0.0.8636, R^2 = 0.7458, Adjusted R square= 0.6950, SE = 0.4607 F= 14.6739

Finally we observed this six parametric model (Eq.4) which is showing considerable improvement in regression statistics. Value of F is almost same as model shown in Eq. (3). Values of SMTI and Wiener are also almost same in eq. 3 and 4, showing the stability of the model. Correlation coefficient has been increases from 0.8636 to 0.8985, it's a sign of more efficient model. After a keen observation, unfortunately this model suffers from statistical defect due to larger variation than that of coefficient. A careful examination shows that compound number 3, 9 and 23 have highest absolute present error. By deleting these outliers, we obtained the following model as most significant for the inhibitory activity of human carbonic anhydrase IV.

Log Ki (CA-IV) = -28.0337+ 56.5382 (Xt) + 0.2199 (POL) – 0.0153 (SMTI) + 1.3300 (Xu)
– 1.2809 (SPI) + 0.0602 (W) Eq. (4)

N=25, Multiple R= 0.8985, R^2 = 0.8073, Adjusted R square= 0.7430, SE = 0.4228 F= 12.5697

Log Ki (CA-IV) = -34.8473+ 66.2927 (Xt) + 0.2534 (POL) – 0.0135 (SMTI) + 1.6293
(Xu) – 1.3457 (SPI) + 0.0504 (W) Eq. (5)

N=22, Multiple R= 0.9292, R^2 = 0.8634, Adjusted R square= 0.8087, SE = 0.3548 F= 15.8044

Table No.1: Molecular structure
(Figure 1 to 25)

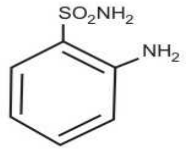
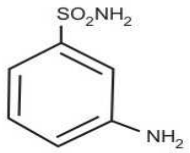
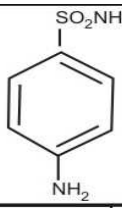
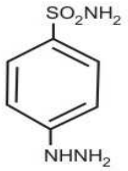
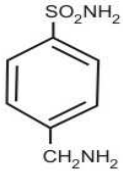
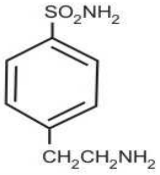
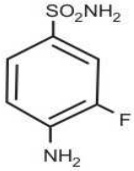
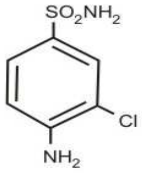
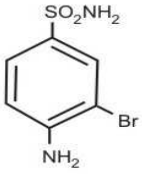
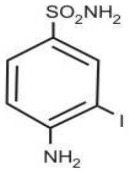
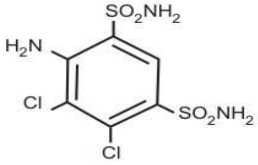
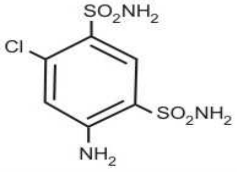
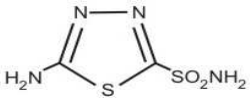
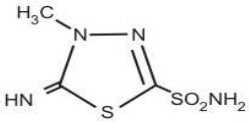
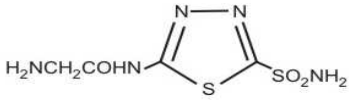
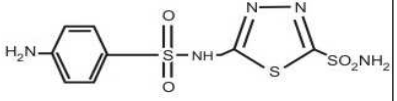
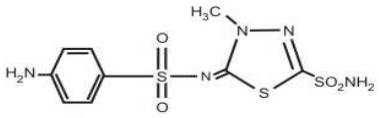
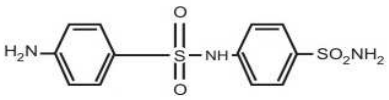
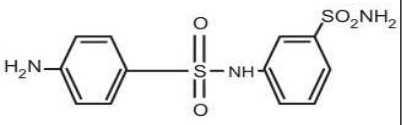
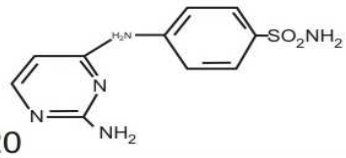
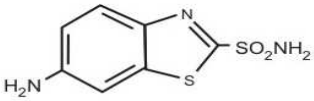
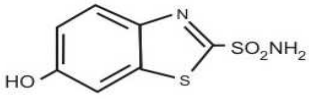
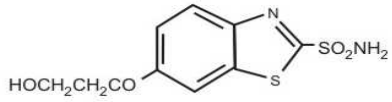
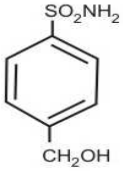
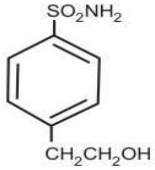
1 	2 	3 	4 
5 	6 	7 	
8 	9 	10 	
11 	12 	13 	
14 	15 	16 	
17 	18 	19 	
20 	21 	22 	
23 	24 	25 	

Table No.2: Values of Topological Descriptors

S.No	Logki CAIV	□t-9	POL-12	SMTI-16	Xu-20	SPI-21	W-22	HAR-24	w-32	J-42
1	3.1173	0.397	14	591	10.709	6.353	144	17.363	256	2.545
2	3.3425	0.397	13	607	10.79	6.48	148	17.247	252	2.461
3	3.4771	0.397	13	623	10.89	6.581	152	17.188	248	2.394
4	3.5071	0.377	15	810	12.055	7.217	201	18.914	309	2.359
5	3.4471	0.377	15	810	12.055	7.217	201	18.914	309	2.359
6	3.3891	0.359	16	1045	13.243	7.822	262	20.575	382	2.305
7	2.2553	0.385	16	762	11.792	7.843	189	19.266	309	2.512
8	2.5051	0.385	16	762	11.792	7.843	189	19.266	309	2.512
9	1.8196	0.385	16	762	11.792	7.843	189	19.266	309	2.512
10	2.097	0.385	16	762	11.792	7.843	189	19.266	309	2.512
11	2.243	0.334	29	1769	16.2	13.475	458	13.126	716	2.991
12	2.2041	0.342	25	1552	15.42	12.253	399	27.754	621	2.853
13	2.7324	0.42	10	468	9.715	5.981	113	15.419	177	2.449
14	2.5502	0.406	13	592	10.694	7.252	146	17.434	225	2.538
15	2.097	0.35	16	1274	14.216	9.259	323	22.437	435	2.343
16	0.699	0.28	28	3530	19.84	13.073	853	35.704	1242	1.861
17	0.903	0.269	35	4386	21.413	14.954	1069	40.124	1660	1.96
18	1.699	0.273	31	4148	20.877	13.682	1004	37.529	1436	1.816
19	1.7243	0.273	31	3964	20.654	13.477	960	37.75	1480	1.9
20	2.1876	0.288	24	2810	18.249	10.163	669	31.133	1051	1.731
21	1.2799	0.329	19	1235	13.782	8.037	287	24.392	643	1.987
22	1.2304	0.329	19	1235	13.782	8.037	287	24.392	643	1.987
23	1.176	0.292	26	2565	17.875	11.212	622	31.804	1150	1.909
24	2.7481	0.377	15	810	12.055	7.217	201	18.914	309	2.359
25	2.6533	0.359	16	1045	13.243	7.822	262	20.575	382	2.305

Table No.3: Observed and Estimated Log Ki Values for Eq. 5

S.No	Logki CAIV (Observed)	Logki CAIV (Estimated)	Residuals
1	3.1173	3.1976144	-0.0803144
2	3.3425	2.8908919	0.4516081
3	3.5071	3.071948	0.435152
4	3.4471	3.071948	0.375152
5	3.3891	3.1555581	0.2335419
6	2.2553	2.6279492	-0.3726492
7	2.5051	2.6279492	-0.1228492
8	2.097	2.6279492	-0.5309492
9	2.243	2.1077343	0.1352657
10	2.2041	1.9538893	0.2502107
11	2.7324	2.6878233	0.0445767
12	2.5502	2.3939234	0.1562766
13	2.097	2.1934591	-0.0964591
14	0.699	0.8810159	-0.1820159
15	0.903	1.2877807	-0.3847807

16	1.699	1.3147235	0.3842765
17	1.7243	1.4936358	0.2306642
18	2.1876	2.1677691	0.0198309
19	1.2799	1.2108982	0.0690018
20	1.2304	1.2108982	0.0195018
21	2.7481	3.071948	-0.323848
22	2.6533	3.1555581	-0.5022581

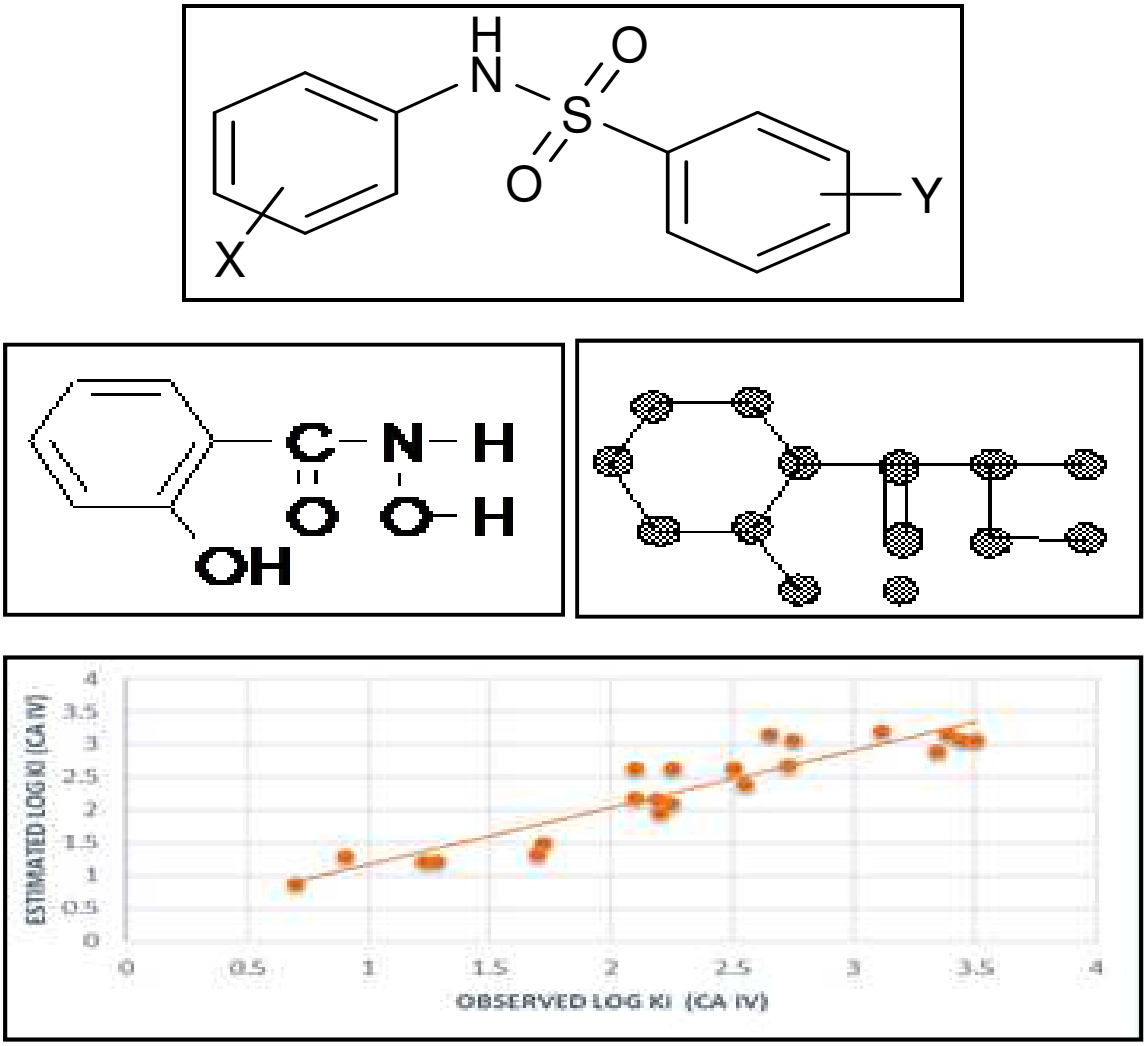


Figure No.1: Corelation between observed and estimated logki CAIV

CONCLUSION

The model obtained by deleting outliers allow us to confirm that the six parametric model is the most significant model for modeling biological activity. Using above model, estimation of binding constant has been done. These estimated values are compared with the observed values. Both the values are quite similar. Compound number 22 is the best compound from the series taken of various sulfonamides for binding activity towards CA IV. From mechanistic point of view, eq. 5 suggests that high polarity and high connectivity in the molecule is desirable for binding.

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

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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