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QSAR Study on Aromatic / Heteraromatic Sulphonamide Derivatives as Carbonic Anhydrase VII Inhibitaors Using Topological Indices

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ABSTRACT

The logarithmic n-octanol/water partition coefficient (log P) is a very important property which concerns water-solubility, carbonic anhydrase inhibitory activity of organic compounds. Quantitative structure–activity relationship (QSAR) model for logP of 24 Aromatic/heteraromatic sulphonamide derivatives is analyzed using multiple linear regression analysis (MLRA) followed by statistical evaluation by NCSS software (IBM). In order to indicate the influence of different molecular descriptors on logP values and well understand the important structural factors affecting the experimental values, a set of topological parameters were taken into consideration. Three multivariable linear models derived from three groups of different molecular descriptors were built. Moreover, each molecular descriptor in these models was discussed to well understand the relationship between molecular structures and their logP values. The square of correlation coefficientc, , R2, for the best model with , four molecular descriptors is0.826.The residual value of one of the compound is much higher than other compound is taken as outlier.After deleting this compound no 16 the value of , R2,is much improved, it comes out to be 0.8954. Our results are much more superior then the result reported by Meena tiwari et al. Therefore simple 2D QSAR reported by us is much betters then the 3D QSAR modeling of Meena tiwari et al.

I. INTRODUCATION

Carbonic Anhydrase VII isozymes are less studied and understood among the cytosolic CA's. Montgomery et al.10, isolated it from a human genomic library in 1991; showing 50, 56, and 49% identity with hCA-I, hCA-II and hCA-III isozyme respectively. Later Tashinan's group carried out purification, characterization and kinetic studies on the mouse isozyme, mCA VII, and concluded that this enzyme is also inhibited by sulfonamides with high Activity level in low nanomolar range11. Further Kinetic studies carried out by D. Vullo et al.12,suggested that CA-VII is similar

physiologically to the isozyme CA-II. Carbonic anhydrase VII has been shown to be highly expressed in the brain and promoting epileptogenesis13,14. Although X-ray crystal structure of hCA-VII is not known, however, the homology of the active-site amino acid sequence in hCA-VII is high with that of the well investigated (by X-ray crystallography) isoforms hCA-I and II. Thus, in addition to zinc ligands, some important amino acid residues for the catalytic/inhibition mechanisms are also identical to CA-I, II, and VII. These are His64 involved in proton transfer processes between the active site and the environment, Thr199, Glu106 involved in a network of hydrogen bonds with the zinc ligand, and Thr200, participating in the stabilization of inhibitors bound to the zinc ion, by formation of a hydrogen bond with its -OH moiety1,15,17. However, there are several amino acid residues in the active site of hCA-VII which are characteristic only of this isozyme and which may explain the inhibition. These amino acids are Asp67 (which is histidine in CA-I and Asn in CA-II) and Asp69 (which is Asn is CA-I and Gln in CA-II) (refs. 17-20). Many carbonic anhydrases isolated from other organisms open a new therapeutic target, such as α-CAsfromPlasmodiumfalciparumand Helicobacter pylori, and β-CAs from Mycobacterium tuberculosis, Candida albicans etc. Research is being carried out for developing specific inhibitors targeting these enzymes that would lead to conceptually novel therapies21,22. In the present study, quantitative structure activity relationshipstudieswereperformedon aromatic/heteroaromatic sulfonamide derivatives in order to correlate the structural requirements for enzyme inhibition which may be useful in designing new molecules against hCA-II and hCA-VII enzyme.

II. MATERIALS AND METHODS

2.1. Data Set

All data of the present investigation were obtained from the reference *(Meena tiwari et al., 2010).* The data set for this investigation consisted *of 24 Aromatic/heteraromatic sulphonamide derivatives*).

2.2. Molecular Descriptor Generation

To obtain a QSAR model, compounds are often represented by the molecular descriptors. The calculation process of the molecular descriptors was described as below: The two-dimensional molecular structures of *of 24 Aromatic/heteraromatic sulphonamide derivatives*). were drawn by Chem Sketch 12.0 then calculated some parameters. Then this optimize structure files were exported into software Dragon 6.0 to calculate all kinds of descriptors. The software Dragon 6.0 can calculate Physicochemical parameters, constitutional, topological, geometrical, descriptors and has been successfully used in various QSAR researches.Then value of all parameters put into NCSS statistical and data analysis software or SPSS (We can also use MSTAT instead of SPSS & NCSS) statistical

and data analysis software to get data regression and correlation. Constitutional descriptors are related to the number of atoms and bonds in each molecule. Topological descriptors include valence and non-valence molecular connectivity indices calculated from the hydrogen-suppressed formula of the molecule, encoding information about the size, composition, and the degree of branching of a molecule. The topological descriptors describe the atomic connectivity in the molecule. The geometrical descriptors describe the size of the molecule and require 3D-coordinates of the atoms in the given molecule. The electrostatic descriptors reflect characteristics of the charge distribution of the molecule. The quantum chemical descriptors offer information about binding and formation energies, partial atom charge, dipole moment, and molecular orbital energy levels.

III. RESULTS AND DISCUSSION

By using the multiple linear regression analysis (MLRA) method of 2D-QSAR, regression models were developed for 24 *Aromatic/heteraromatic sulphonamide derivatives*. To select the sets of descriptors that are most relevant to logP values and effectively show the relation between descriptors and logP values of these compounds, foure subsets with the descriptors from one to four were determined to establish the QSAR models. Multi-linear regression method for descriptor selection proceeds with a reselections of descriptors by sequentially eliminating descriptors which do not match any of the following criteria: (i) the F-test greater than one unit; (ii) R2 value less than a value defined at the start (default 0.01); (iii) the student's t-test less than that defined (default 0.1); and (iv) duplicate descriptors having a higher squared inter-correlation coefficient than a predetermined level (usually 0.8). The next step involves correlation of the given property with (i) the top descriptor in the above list with each of the remaining descriptors, and (ii) the next one with each of the remaining descriptors, etc. The goodness of the correlation is tested by the correlation coefficient (R2) and The stability of the correlations was tested against the cross-validated coefficient (R2CV). Besides, it will demonstrate which descriptors have bad or missing values, which descriptors are insignificant, and which descriptors are highly intercorelated .This information will be helpful in reducing the number of descriptors involved in the search for the best QSAR/QSPR model.. We have observed that in our case R2 for models with one, two, three, molecular descriptors are 0.7669, 0.8817 and0.8954 respectively.. Our results are much more superior then the result reported byMeena tiwari et al. Therefore simple 2D QSAR reported by us is much betters then the 3D QSAR modeling ofMeena tiwari et al.

IV. CONCLUSION

quantitative structure–activity relationship model was derived to study the logP values of a diverse set of for 24 *Aromatic/heteraromatic sulphonamide derivatives* . To select the sets of descriptors that are most relevant to for 24 *Aromatic/heteraromatic sulphonamide derivatives*. three QSAR models were developed with the squared correlation coefficient (R2) of one, two,and three, molecular descriptors are are 0.7669, 0.8817 and0.8954 respectively . These models showed strong predictive ability. Among all the descriptors, topological descriptors were found to have high coding capabilities for the logP values and were selected to represent the chemical structures. The present work provides an effective method for the prediction of the logP values for the carbonic anhydrase inhibitorss. This study also showed that the utility of the QSAR treatment involving descriptors derived solely from chemical structure and the correlation equation and descriptors can be used for the prediction of the logPw values for unknown structures.

Following conclusion may be drawn on the basis of above discussion.

(1.) Topological parameters are the best parameters for modeling LogP activity of carbonic anhydrase inhibitor.

(2.) 2D QSAR modeling using MLRA analysis has been found to be better than 3D QSAR modeling (HM method as reported byMeena tiwariiu et al.)

(3.) The best model suggests that for synthesizing new potent carbonic anhydrase inhibitors. The structure having higher value of Jhetm, Jhetp and J should be preferred.

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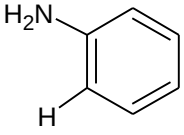
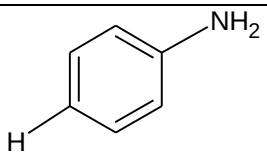
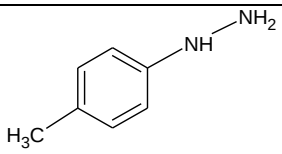
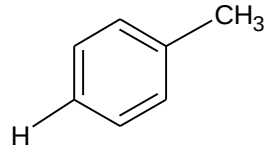
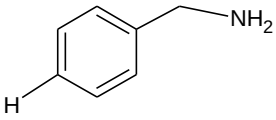
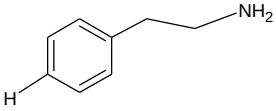
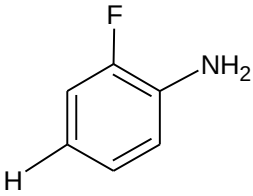
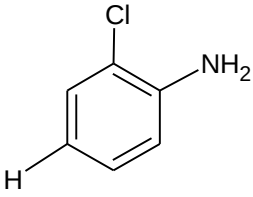
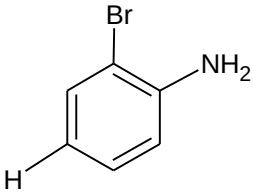
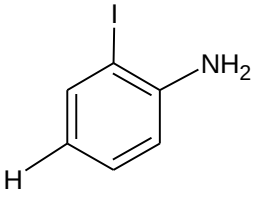
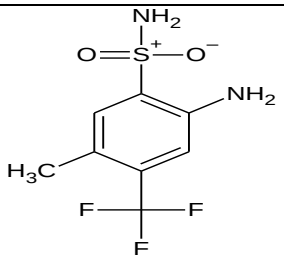
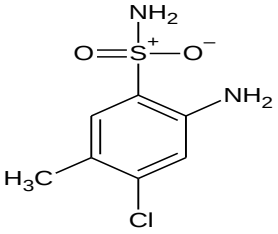
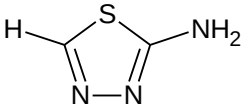
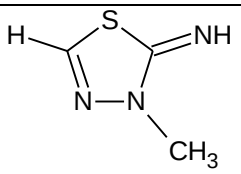
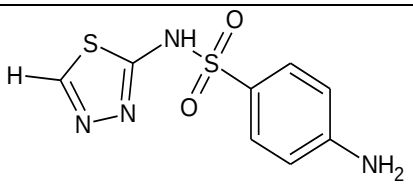
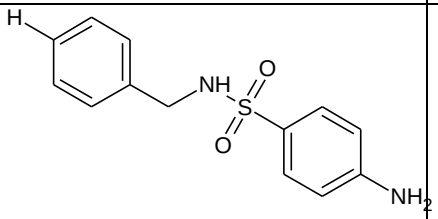
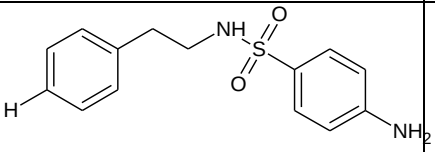
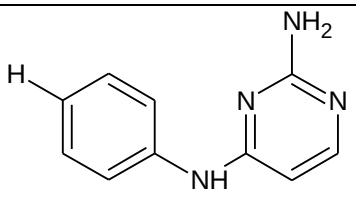
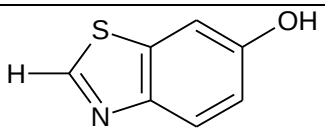
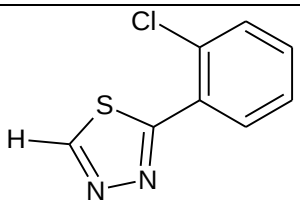
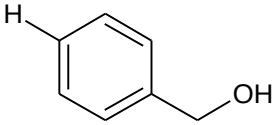
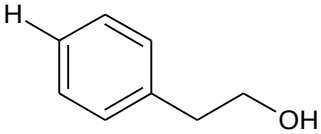
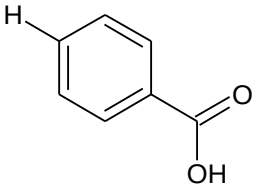
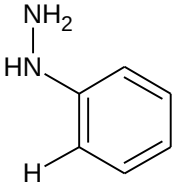
MODELING WITH HCA-II ACTIVITY

Table-1.1. Structure and activity data of sulfonamide derivatives as xarbonic anhydrase inhibitors

Compound No	R	hCA-II(pKi)	hCA-IV(pKi)
1		6.5302	7.3468

2		6.6198	7.1549
3		6.5279	7.0506
4		6.4948	7.0555
5		6.7696	7.1249
6		6.7959	7.0969
7		7.2218	7.1249
8		6.9586	6.9208
9		7.3979	7.2147
10		7.1549	6.8239

11		7.2007	7.0000
12		7.1249	6.6778
13		7.2218	8.284
14		7.7212	8.3653
15		8.699	8.1549
16		7.3372	7.2518
17		7.301	8.1871
18		7.4815	8.1675

19		7.5229	8.3979
20		7.9208	8.2676
21		8.0969	7.2218
22		6.9031	7.1805
23		6.8761	7.284
24		6.903	7.1675

Modeling With Pki (Hca-Ii) Activity

Table-1.4. statistical parameters and quality of correlation

Model No.	Parameters used	Ai = (1-4)	B	Se	R2	R2A	F	Q= R/Se
1	3Xv	0.298(±0.081)	6.256	0.455	0.382	-	13.597	1.360
2	3Xv 1Xv	0.846(±0.258) -0.401(±0.181)	6.848	0.395	0.499	0.451	10.461	1.791

3	W Jhetp 2Xv	-0.002(±0.001) -0.642(±0.181) 0.551(±0.122)	7.228	0.352	0.621	0.564	10.925	2.241
4	W Jhetp 3X 3Xv	-0.002(±0.001) -0.412(±0.176) 0.318(±0.272) 0.441(±0.173)	6.492	0.358	0.628	0.549	8.009	2.216

Table-1.5. Observed and Estimated values using model no 36.

Compound No	Obs. pKi	Est. pKi	Residual
1	6.530	6.704	-0.173
2	6.620	6.734	-0.114
3	6.528	7.004	-0.476
4	6.495	6.740	-0.245
5	6.770	6.928	-0.159
6	6.796	6.982	-0.186
7	7.222	6.975	0.246
8	6.959	6.944	0.014
9	7.398	7.081	0.317
10	7.155	7.165	-0.010
11	7.201	7.144	0.057
12	7.125	7.207	-0.082
13	7.222	7.162	0.060
14	7.721	7.580	0.141
15	8.699	8.275	0.424
16	7.337	7.554	-0.217
17	7.301	7.320	-0.019
18	7.482	7.398	0.083
19	7.523	8.026	-0.503
20	7.921	8.046	-0.125
21	8.097	6.945	1.152
22	6.903	6.998	-0.095

23	6.876	6.927	-0.051
24	6.903	6.942	-0.039

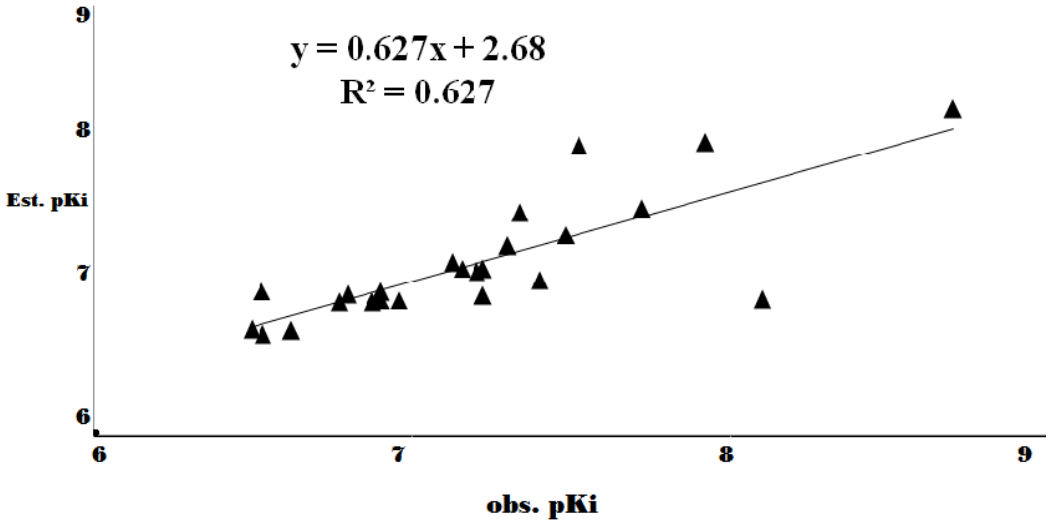


Fig.1. observed and estimated pKi values using model 36 (Table 1.5)

BEFORE DELETION MODELS

ONE-VARIABLE MODEL

pKi = 0.298(±0.081)3χv+6.256

n= 24, R2 = 0.382, Se= 0.455, F= 13.597, Q= 1.360

TWO VARIABLE MODEL

pKi = 0.846(±0.258) 3χv -0.401(±0.181) 1χv+6.848

n= 24, R2 = 0.499, R2A =0.451, Se= 0.395, F= 10.461, Q= 1.791

THREE VARIABLE MODEL

pKi = -0.002(±0.001) W-0.642(±0.181) Jhetp +0.551(±0.122) 2χv+7.228

n= 24, R2 = 0.621, R2A =0.564, Se= 0.395, F= 10.925, Q= 2.241

FOUR-VARIABLE MODEL

pKi = -0.002(±0.001) W-0.412(±0.176) Jhetp+0.318(±0.272) 3χ+0.441(±0.173) 3χv+6.492

n= 24, R2 = 0.628, R2A =0.549, Se= 0.358, F= 8.009, Q= 2.216

Table-1.6. Statistical parameters and quality of correlation after deletion of compound No 21.

Model No	Parameters used	Ai = (1-4)	B	Se	R2	R2A	F	Q
37	3Xv	0.332(±0.062)	6.095	0.355	0.534	-	24.060	2.058
38	3Xv 1Xv	0.920(±0.196) -0.429(±0.137)	6.722	0.298	0.688	0.656	22.010	2.784
39	W Jhetp 2Xv	-0.002(±0.000) -0.648(±0.118) 0.606(±0.080)	6.972	0.229	0.824	0.796	29.692	3.958
40	W Jhetp 3X 2Xv	-0.003(±0.001) -0.593(±0.124) 0.229(±0.179) 0.512(±0.108)	6.432	0.226	0.839	0.803	23.409	4.053

Table-1.7. Observed and Estimated pKi values using model no 40 (Table 5)

Compound No	Obs. pKi	Est. pKi	Residual
1	6.530	6.516	0.014
2	6.620	6.638	-0.018
3	6.528	6.918	-0.390
4	6.495	6.681	-0.186
5	6.770	6.814	-0.044
6	6.796	6.940	-0.144
7	7.222	6.882	0.340
8	6.959	6.838	0.121
9	7.398	7.035	0.363
10	7.155	7.157	-0.002
11	7.201	7.222	-0.021
12	7.125	7.258	-0.133
13	7.222	7.199	0.023
14	7.721	7.578	0.144
15	8.699	8.354	0.345
16	7.337	7.566	-0.229

17	7.301	7.254	0.047
18	7.482	7.385	0.097
19	7.523	7.970	-0.447
20	7.921	7.946	-0.025
21	8.097	-	-
22	6.903	6.950	-0.047
23	6.876	6.797	0.079
24	6.903	6.789	0.114

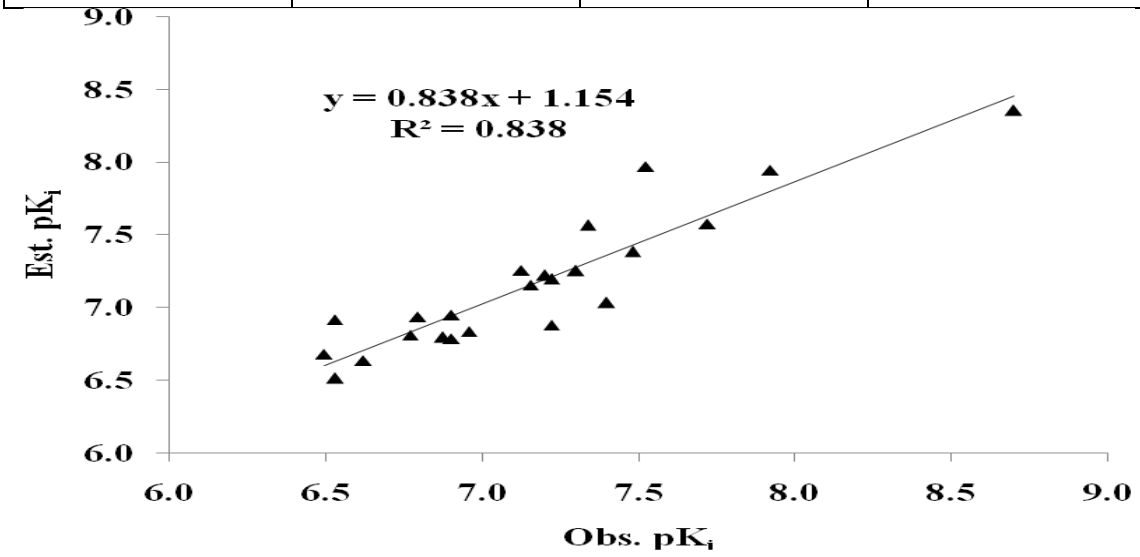


Fig.1. correlation between observed and estimated pKi values using model 40 (Table 5)

Table-1.8.: cross validated parameters for the obtained best models (Table 5)

Model. No.	Parameters used	PRESS/ SSY	R2CV	SPRESS	PSE
37	3Xv	0.873	0.127	0.355	0.339
38	3Xv 1Xv	0.454	0.546	0.298	0.278
39	W Jhetp 2Xv	0.213	0.787	0.229	0.208
40	W Jhetp 3X 2Xv	0.192	0.808	0.226	0.200

MODELS

ONE –VARIABLE MODEL

pKi = 0.332(±0.062)3χv +6.095

N= 23, R2 = 0.534, Se = 0.355, F= 24.060, Q = 2.058

TWO-VARIABLE MODEL

pKi = 0.920(±0.196) 3Xv-0.429(±0.137) 1Xv+6.722

N= 23, R2 = 0.688, R2A = 0.656, Se = 0.298, F= 22.010, Q = 2.784

THREE-VARIABLE MODEL

pKi = -0.002(±0.000) W-0.648(±0.118) Jhetp+0.606(±0.080) 2Xv+6.972

N= 23, R2 = 0.824, R2A = 0.796, Se = 0.229, F= 29.692, Q = 3.958

FOUR-VARIABLE MODEL

pKi = -0.003(±0.001) W-0.593(±0.124) Jhetp+0.512(±0.108) 2Xv+ 0.229(±0.179) 3X+6.432

N= 23, R2 = 0.839, R2A = 0.803, Se = 0.226, F= 23.409, Q = 4.053