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QSAR Approach of Selective Carbonic Anhydrase Inhibitors

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ABSTRACT: Quantitative structure activity relationship studies have been conducted on a series (24 compounds) of sulfonamide derivatives with selective carbonic anhydrase inhibitory activity using NCSS software. The topological descriptor are used as independent variable while pKi is used as dependent variable. The best prediction have been obtained for hCA-VII enzyme inhibition activity (R^2= 0.9329 and R^2_{CV}=0.9281). Results are interpreted on the basis of multiple regression and cross validation.

Key words: QSAR, sulfonamide, carbonic anhydrase inhibitors.

I. INTRODUCTION

QSARs are increasingly used to predict a wide range of activities and toxicities of drugs, pesticides, food additives and environmental pollutants.

Some sulfonamide compounds like Acetazolamide, methazolamide, dichlorophenamide, ethoxolamide and dorzolamide, as carbonic anhydrase (CA-II) isozyme inhibitors, used for the treatment of glaucoma[1]. Glaucoma, the leading cause of blindness worldwide, is the general term for a group of ophthalmic disorders characterized by an increase in IOP. This gives rise to damage to the optic disc and visual field disturbances of the eye. IOP[2] increases through an imbalance between the production and drainage of aqueous humor. Agents such as mentioned above, used to treat glaucoma are designed to decrease IOP[3]. All the drugs used for the treatment of glaucoma have some systemic side effects[4]. To reduce side effects of the drugs, it is of interest to develop new agents for the topical use of CA-II inhibitors for the long-term management of glaucoma.

The aromatic/heteroaromatic part of the carbonic anhydrase viz; sulfonamide/sulfamate/sulfamide interacts with hydrophilic and hydrophobic residues of CA-I, CA-II, CA-IV and CA-VII while in case of CA-VII isozymes are less studied and understood among the cytosolic CA's. Montogomery et. al.[5] isolated it from a human geonomic library in 1991; showing 50,56, and 49% identity with hCA-I, hCA-II and hCA-III isozyme respectively.

Many carbonic anhydrase isolated from other organisms open a new therapeutic target, such as α-CAs from plasmodium falciparum and helicobacter pylori and β-CAs from mycobacterium tuberculosis, candida albicans etc.

For the researchers, the prospect of overcoming the systemic side effects of a drug, achieving an effect at a much lower dose, is very attractive. Modification of the structure of a known drug is one way to develop new drugs. For this purpose,Tadeschini et al[6] have synthesized and reported new five acetazolamide-like and eight sulfanilamide-like derivatives, which are the subject of the present study. These new derivatives have been obtained by modification of acetazolamide and sulfanilamide using the tail approach. The inhibition constants (*K*I) of these new molecules against the carbonic anhydrase enzyme CA-VII are shown in Table 1, are much lower than their mother molecule acetazolamide and sulfanilamide. Therefore, these derivatives can be the subject of further investigation to explore the possibilities of becoming candidate drugs. Quantitative structure activity relationships (QSAR) studies are tools of predicting endpoints of interest in organic molecules acting as drugs[7/]. Many physiological activities of molecules can be related to their composition and structures. Molecular descriptors, which are the numerical representation of the molecular structures, are used to perform QSAR analysis[8].

In present study, quantitative structure activity relationship studies were performed on aromatic/heteroaromatic sulfonamide derivatives in order to correlate the structural requirements for enzyme inhibition which may be useful in designing new molecule against hCA-II and hCA-VII enzyme.

QSAR analysis is one of the most effective approaches for optimizing lead compounds and designing new drugs. Excellent QSAR models can aid in understanding the mechanism of the action of drugs and may save the cost and time in the course of developing a new drug when compared with empirical procedure.[9-11.] QSAR study on carbonic anhydrase inhibitors were studied earlier by many authors.[12-21] The present study data set is made up of 24 compounds for hCA-VII (human carbonic anhydrase) inhibitory activity. The carbonic anhydrase inhibition activity data of these sulphonamide derivatives is taken from reported work of Pothen et. al. [22] and given in table 1.

Table 1: Structure and Activity data of sulfonamide derivatives as carbonic anhydrase inhibitor.

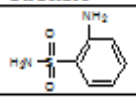
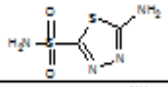
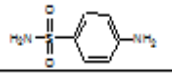
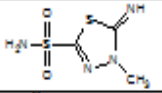
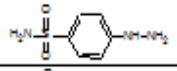
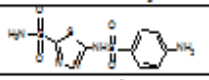
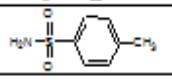
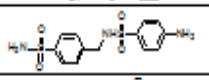
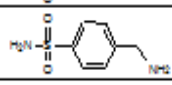
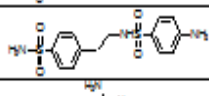
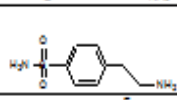
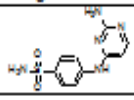
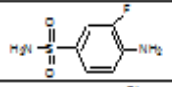
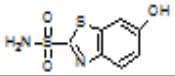
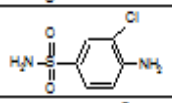
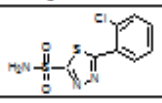
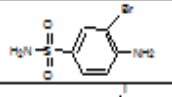
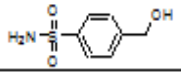
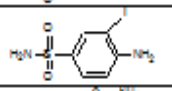
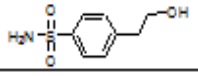
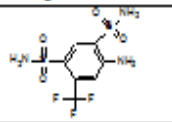
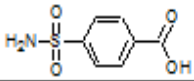
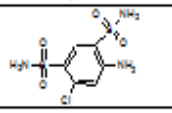
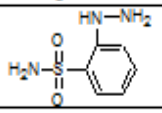
S. No.	Compd.	Structure	hCA-VII-pKi	S. No.	Compd.	Structure	hCA-VII-pKi
1	**Sulf-1**		7.3468	13	**Sulf-13**		8.284
2	**Sulf-2**		7.1549	14	**Sulf-14**		8.3653
3	**Sulf-3**		7.0506	15	**Sulf-15**		8.1549
4	**Sulf-4**		7.0555	16	**Sulf-16**		7.2518
5	**Sulf-5**		7.1249	17	**Sulf-17**		8.1871
6	**Sulf-6**		7.0969	18	**Sulf-18**		8.1675
7	**Sulf-7**		7.1249	19	**Sulf-19**		8.3979
8	**Sulf-8**		6.9208	20	**Sulf-20**		8.2676
9	**Sulf-9**		7.2147	21	**Sulf-21**		7.2218
10	**Sulf-10**		6.8239	22	**Sulf-22**		7.1805
11	**Sulf-11**		7	23	**Sulf-23**		7.284
12	**Sulf-12**		6.6778	24	**Sulf-24**		7.1675

Table 1 also contains structure of 24 sulphonamides used in preset study. While calculated molecular descriptors such as χ_{eq}, W, J, Randic etc are given in Table 2.

Table 3 contains the correlation between inhibition activity of sulfonamides with different parameters. Table 4 represents result of regression analysis as different models. Table 5 represents the result of cross-validation analysis, Table 4 and Table 7 represent the predicted values of inhibitory activity of sulfonamides from model no.14 and 17 respectively.

Statistical Analysis:

In present study we used the maximum R^2 improvement method with sequential fisher test to identify prediction models. This method finds the best one variable model, the best two variable models and so for the prediction of property activity. Several models (Combination of variables) were examined to identify combinations of variables with good prediction capabilities. In all regression models developed, we have examined a variety of statistics associated with residues e.g. the wilks Shapiro test

for normality and cooks D- statistics for outliers to obtain the most reliable results.

Multiple regression analysis for correlating activities of the sulphonamides with molecular descriptors was carried out by using NCSS software. Several multiple regression were attempted using the correlation matrix from this programme and the best results are considered and discussed in developing QSAR and hence, for modeling the carbonic anhydrase inhibitory activities of the sulphonamides in the present study.

In the first step of regression analysis inspection of correlation matrix (Table IV) indicates the colinearity exists between (i) J and $^0\chi^V$, (ii) J and Randic is slightly poor correlation exists between IR_1 and J with hCA-VII inhibitory activity. This indicates that J and IR_1 will be useful in developing multivariate correlations for modeling the carbonic anhydrase inhibitory activity of these sulphonamides .

Inspection of correlations presented in table-III indicates that J, IR_1 and W play an important role and gave better results. Significant correlations are expressed by the following equations.

1) pki =7.2133 + 1.0807(±0.1720)IR_1
n=24, R^2 = 0.6422, Se = 0.3422,
F ratio = 39.484, Q =2.3419 ..(i)

2) pki = 8.5950 -0.3719(±0.0985)J
+0.7266(±0.1651)IR_1
n=24, R^2 = 0.7868, Se = 0.2703,
F ratio = 38.758, Q = 3.2815 ...(ii)

3) pki =12.1573 -1.4314(±1.0726)χ_{eq}
-0.3612(±0.0971)J + 0.8511
(±0.1870)IR_1
n=24, R^2 = 0.8043, Se = 0.2654,
F ratio = 27.393, Q = 3.3791 ...(iii)

4) pki = 10.0386 +0.0012(±0.0007)W
- 0.4570(±0.1626)J- 0.4949
(±0.2682)Randic+0.6655
(±0.2006)IR_1
n=24, R^2 = 0.8202, Se = 0.2610,
F ratio = 21.662, Q = 3.4697 ...(iv)

Even in this analysis we found that two compounds are serious outliers. They are compound **17 and 18**. They were deleted from the data set and for remaining 22 compounds the resulted models are given below:

pki=9.6508-1.0502(±0.6279)χ_{eq}
+0.2574(±0.5563)$^0\chi^V$+1.2774 (±0.0919)IR_1
n=22, R^2 = 0.9294, Se = 0.1535, F ratio = 78.959, Q = 6.2808 (v)

However, the variance of 92% in the data is observed in the best tri parametric models shown above. Further investigation was attempted for still better model by combining topological descriptor together. Such models are reported in Table IV-6.4 by model no. 17 and 18.

pKi=10.0577-1.0149(± 0.6373)χ_{eq} + 0.0005 (± 0.0005)W-0.1842(±0.1754) Randic+1.2779(± 0.0922)IR_1
n=22, R^2=0.9329, Se=0.1540,
F-ratio=59.104, Q=6.2721 (vi)

pKi=9.7294-1.0017 (± 0.6328)χ_{eq}.- 0.1019 (± 0.1108)J+0.7847 (± 0.8006)$^0\chi^V$+1.1657 (± 0.1526)IR_1
n=22, R^2=0.9327, Se=0.1542, F-ratio=58.923, Q=6.2633 (vii)

A dramatic improvement in the quality of model is observed the R^2 changes from 0.80 to 0.92. The Q value also shows that the three parametric model containing χ_{eq}, zero-order valence connectivity and indicator descriptor is the best for modeling the pki values of the compounds present in the study. The pki values for the compounds used are calculated using the best model. Such values are reported in table. Also we have obtained the predictive power of the best model by plotting a graph between observed and estimated pki. Such a comparison is demonstrated in Fig-2. The predictive power of third model comes out to be 0.9327.

From the cross-validation method due to the small value of PRESS/SSY and very close value of R^2_{CV} to R^2 represents that model no.17 is best model for this study. Ridge regression is also applied for model no.17, variance inflation factor for each variable is found less then 10, so multi co linearity is not a problem for this model.(Fig. 3)

CONCLUSION

A perusal of above models reveals that:

1. Branching and cyclization favor the inhibitory activity as the coefficients
   Associated with $^0\chi^V$ and IR_1 are positive.
2. The equalized electro negativity has negative coefficients showing their negative role towards pki.
3. The indicator descriptor shows a positive role towards the inhibitory activity.

Table 2: Calculated Descriptor of 24 sulfonamides.

Comp. No	χ_{eq}	W	J	$^0\chi^V$	randic	IR_1
1	2.4947	144	4.123	0.434	2.5185	0
2	2.4947	152	3.9159	0.4122	2.5185	0
3	2.5001	201	3.9123	0.3726	2.7185	0
4	2.4588	152	4.122	0.4122	2.5449	0
5	2.4671	201	4.0986	0.3726	2.7685	0
6	2.4465	262	4.2175	0.3374	3.0185	0
7	2.5631	189	3.7402	0.3937	2.7075	0
8	2.5408	189	3.7402	0.3937	2.7075	0
9	2.5335	189	3.7402	0.3937	2.7075	0
10	2.5207	189	3.7402	0.3937	2.7075	0
11	2.6839	624	4.0514	0.3001	4.1304	0
12	2.6	399	3.9804	0.3317	3.5024	0
13	2.6541	113	3.2095	0.4585	2.0739	1
14	2.5851	146	3.655	0.43	2.2975	1
15	2.5896	853	2.3538	0.2435	4.5924	1
16	2.4931	1195	2.5888	0.2099	5.287	0
17	2.478	1408	2.5933	0.1945	5.537	0
18	2.514	669	2.3287	0.2409	4.3601	0
19	2.5715	287	2.3573	0.3536	3.4003	1
20	2.5808	434	2.2396	0.3054	3.7893	1
21	2.4927	201	3.9123	0.3726	2.7949	0
22	2.4676	262	4.0488	0.3374	2.8073	0
23	2.5621	252	3.487	0.3487	2.8073	0
24	2.5001	185	4.242	0.404	2.7185	0

χ_{eq} : Equalized Electronegativity
W : Wiener Index
IR1 : Indicator Parameter (1 if heterocyclic ring is present in R substitution otherwise 0).
J : Balaban Index
$^0\chi^V$: Zero Order Connectivity Index
Randic : Connectivity Index

Table 3: Correlation Matrix of 24 Sulfonamide

	hCA-VII	χ_{eq}	W	J	$^{0}\chi^{V}$	Randic	IR_1
hCA-VII	1.0000						
χ_{eq}	0.2944	1.0000					
W	0.3077	0.000028	1.0000				
J	-0.7682	-0.2487	-0.6276	1.0000			
$^{0}\chi^{V}$	-0.2479	0.0458	-0.9224	0.6393	1.0000		
Randic	0.2958	0.0397	0.9709	-0.6716	-0.9649	1.0000	
IR_1	0.8013	0.5387	-0.0062	-0.5680	0.0459	0.0121	1.0000

Table 4: Result of Regression analysis.

Model No.	Parameter used	Ai (i = 1, 2, 3…)	Intercept	Square root of MSE	R^2	AR^2	R	F- ratio	Q
1.	J	A_1= -0.6183	9.6127	0.3662	0.5902	0.5716	0.7682	31.684	2.0978
2.	IR_1	A_1=1.0807	7.2133	0.3422	0.6422	0.6259	0.8014	39.484	2.3419
3.	W IR_1	A_1=0.0005 A_2=1.0833	7.0237	0.2985	0.7400	0.7152	0.8602	29.882	2.8817
4.	J $^{0}\chi^{V}$	A_1=-0.8301 A_2=3.2258	9.2222	0.3258	0.6903	0.6608	0.8308	23.405	2.5500
5.	J IR_1	A_1=-0.3719 A_2=0.7266	8.5950	0.2703	0.7868	0.7665	0.8870	38.758	3.2815
6.	$^{0}\chi^{V}$ IR_1	A_1=-2.2366 A_2=1.0984	7.9967	0.3079	0.7234	0.6971	0.8505	27.465	2.7623
7.	Randic IR_1	A_1=0.1716 A_2=1.0760	6.6636	0.3076	0.7240	0.6978	0.8509	27.548	2.7663
8.	χ_{eq} W IR_1	A_1=-1.7752 A_2=0.0005 A_3=1.2250	11.4903	0.2896	0.7670	0.7320	0.8758	21.943	3.0242
9.	χ_{eq} J IR_1	A_1=-1.4314 A_2=-0.3612 A_3=0.8511	12.1573	0.2654	0.8043	0.7749	0.8968	27.393	3.3791
10.	χ_{eq} Randic IR_1	A_1=-1.8864 A_2=0.1757 A_3=1.2265	11.3973	0.2973	0.7545	0.7176	0.8686	20.485	2.9216
11.	W J IR_1	A_1=0.0001 A_2=-0.3336 A_3=0.7635	8.4217	0.2763	0.7879	0.7561	0.8876	24.767	3.2125
12.	J $^{0}\chi^{V}$ IR_1	A_1=-0.4244 A_2=0.5199 A_3=0.6726	8.6077	0.2760	0.7883	0.7566	0.8879	24.832	3.2170
13.	χ_{eq} W J IR_1	A_1=-1.4855 A_2=0.0001 A_3=-0.3056 A_4=O.9090	12.0420	0.2708	0.8065	0.7657	0.8981	19.794	3.3165

Model No.	Parameter used	Ai (i = 1, 2, 3…)	Intercept	Square root of MSE	R^2	AR^2	R	F- ratio	Q
14.	W J Randic IR_1	A_1=0.0012 A_2=-0.4570 A_3=-0.4949 A_4=0.6655	10.0386	0.2610	0.8202	0.7823	0.9056	21.662	3.4697
After deleting compd. No. 18 & 17									
15.	χ_{eq} W IR_1	A_1=-1.0625 A_2=0.0000 A_3=1.2771	9.7792	0.1544	0.9286	0.9167	0.9636	77.991	6.2409
16.	χ_{eq} $^0\chi^V$ IR_1	A_1=-1.0502 A_2=0.2574 A_3=1.2774	9.6508	0.1535	0.9294	0.9176	0.9641	78.959	6.2808
17.	χ_{eq} W Randic IR_1	A_1=-1.0149 A_2=0.0005 A_3=-0.1842 A_4=1.2779	10.0577	0.1540	0.9329	0.9171	0.9659	59.104	6.2721
18.	χ_{eq} J $^0\chi^V$ IR_1	A_1=-1.0017 A_2=-0.1019 A_3=0.7847 A_4=1.1657	9.7294	0.1542	0.9327	0.9169	0.9658	58.923	6.2633

Table 5*:* Cross-validation parameters.

Model no.	Parameter	PRESS	SSY	PRESS/SSY	R^2_{CV}	R^2A	S_{PRESS}
14.	W,J,Randic,IR_1	1.2946	5.9040	0.2193	0.7807	0.7823	0.2610
15.	χ_{eq},W,IR_1	0.4291	5.5781	0.0769	0.9231	0.9167	0.1544
16.	χ_{eq},$^0\chi^V$,IR_1	0.4242	5.5829	0.0760	0.924	0.9176	0.1535
17.	χ_{eq},W,Randic, IR_1	0.4030	5.6042	0.0719	0.9281	0.9171	0.1540
18.	χ_{eq},J,$^0\chi^V$,IR_1	0.4041	5.6031	0.0721	0.9279	0.9169	0.1542

PRESS-Predicted residual sum of squares, SSY-Sum of squares of regression value , R^2_{CV}-Cross- validation correlation coefficient, R^2_A=Adjusted R^2, S_{PRESS}= Uncertainty of prediction

Table 6: Actual and predicted carbonic anhydrase inhibitor's activity before deletion of outlier.

Comp. No.	Actual	Predicted	Residual
1	7.347	7.061	0.285
2	7.155	7.138	0.016
3	7.051	7.140	-0.089
4	7.056	7.062	-0.006
5	7.125	7.071	0.054
6	7.097	7.026	0.071
7	7.125	7.204	-0.079
8	6.921	7.204	-0.283
9	7.215	7.204	0.011
10	6.824	7.204	-0.380
11	7.000	7.088	-0.088
12	6.678	7.114	-0.437
13	8.284	8.128	0.156
14	8.365	7.962	0.403
15	8.155	8.446	-0.291
16	7.252	7.632	-0.380
17	8.187	7.630	0.557
18	8.168	7.729	0.439
19	8.398	8.445	-0.047
20	8.268	8.489	-0.221
21	7.222	7.140	0.082
22	7.181	7.089	0.091
23	7.284	7.298	-0.014
24	7.168	7.017	0.150

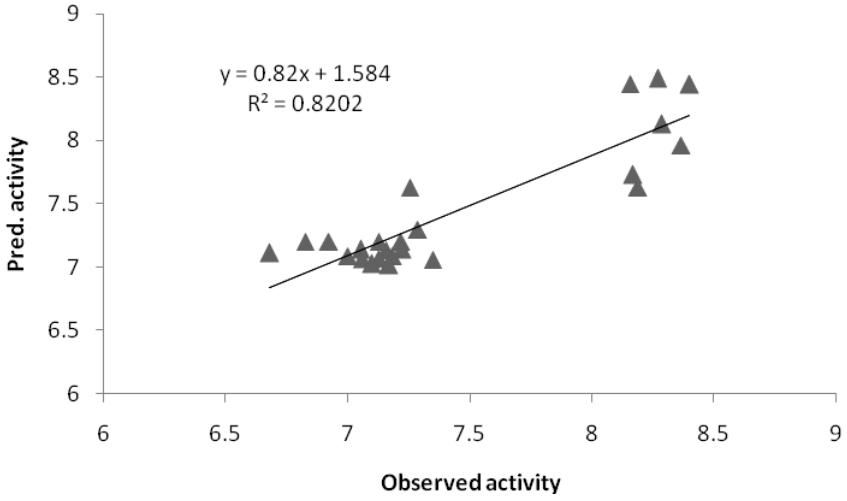


Fig 1: Graph between actual and predicted pKi of carbonic anhydrase of 24 sulfonamide

Table 7: Actual and predicted pKi values of carbonic anhydrase inhibitors after deleting outlier no.17 and 18.

Comp. No.	Actual	Predicted	Residual
1	7.347	7.143	0.204
2	7.155	7.137	0.018
3	7.051	7.121	-0.071
4	7.056	7.175	-0.119
5	7.125	7.156	-0.031
6	7.097	7.168	-0.072
7	7.125	7.060	0.064
8	6.921	7.084	-0.163
9	7.215	7.092	0.123
10	6.824	7.105	-0.281
11	7.000	6.910	0.090
12	6.678	7.006	-0.328
13	8.284	8.259	0.025
14	8.365	8.324	0.041
15	8.155	8.271	-0.116
16	7.252	7.087	0.165
19	8.398	8.319	0.079
20	8.268	8.297	-0.029
21	7.222	7.129	0.093
22	7.181	7.146	0.034
23	7.284	7.050	0.234
24	7.168	7.129	0.038

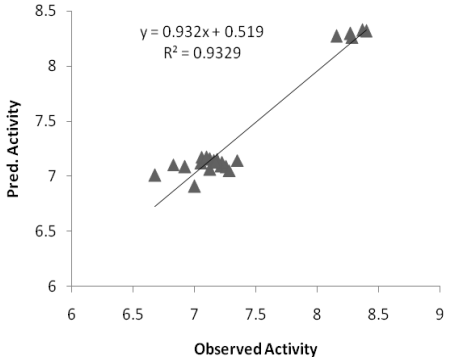


Fig. 2. Graph between actual and predicted carbonic deleting outlier .

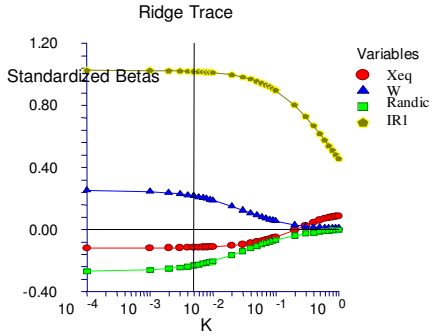


Fig. 3. Results of Ridge regression anhydrase inhibitor after for model no. 17.

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