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QSAR STUDIES OF SULPHONAMIDES AS CARBONIC ANHYDRASE II INHIBITORS USING TOPOLOGICAL INDICES

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ABSTRACT In this paper topological indices have been used in modeling log KI activity of 47 organic compounds acts as carbonic anhydrase II inhibitors. The 7-parametric model gave excellent results which contains mixed parameters. The results are discussed using different statistical parameters.

KEYWORDS : Qsar Modeling, Log Ki, Topological Indices

1. INTRODUCTION

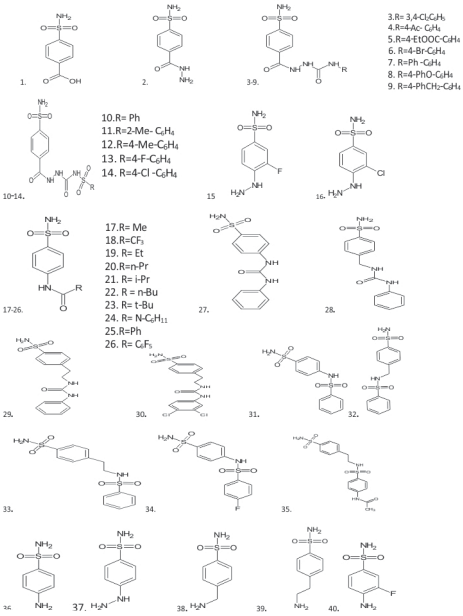
Sulphonamide inhibitors of Carbonic anhydrase are extensively used in clinical medicine and as diagnostic species, their main applications being in the treatment of glaucoma, macular edema, epilepsy, bronchitis, pneumonia and other neurological disorders. Carbonic anhydrase inhibition of sulfanilamide discovered by Mann and Keilin has led to important drugs such as the sulfamides with CA inhibitory properties. Several such drugs are presently available, such as the recently introduced topical sulfonamides dorzolamide and brinzolamide, in addition to the classical, systemically acting inhibitors acetazolamide, methazolamide, ethoxzolamide, and dichlorophenamide which have been adopted clinically for more than 45 years[1-3].

Sulfonamide CAIs derivatives of simple aromatic or heterocyclic aromatic sulfonamides have already shown with excellent CA inhibitory properties against many CA isozymes isolated so far in diverse organisms. Many drug derivatives of heterocyclic and aromatic classes of sulfonamides have been modelled, synthesized and investigated for their biological activity[4].

The aromatic/heterocyclic sulfonamides act as carbonic anhydrase inhibitors and other types of derivatives show diuretic activity, hypoglycaemic activity, anticancer properties or may act as inhibitors of the aspartic HIV protease being used for the treatment of AIDS and HIV infection among other During the last few years, Supuran and his co-workers has deeply studied different aromatic sulfonamides as most effective carbonic anhydrase II inhibitors[5]. Since weaker CAIs as compared to heterocyclicones many aromatic substituted sulfonamides were used to be strong inhibitors with low KI values within the nanomolar range. Special attention was paid to aromatic sulphonamides substituted at the para position as they exhibit higher affinity with the zinc enzyme compared to an orthosubstituted aromatic sulfonamide. This may be due to the steric impairment of the ortho -substituent for the binding of such compounds to the Zn (II) ion within the enzyme active site.

Due to the biological importance of sulfonamides as potent CAIs, quantitative structure–activity/property relationship (QSAR/QSPR) models have been proposed for the modelling and prediction of CA inhibitory activity of different aromatic and heterocyclic aromatic sulfonamides using different molecular, topological descriptors. QSARs are mathematical relationships between a set of descriptors and the biological activity of the system being studied. QSAR models can be used as a useful tool in drug design, as they have the potential to shorting out the time and effort required to develop new compounds by reducing expensive and time-consuming trial-and-error experiments[6-8]. Our objective is to model a fast and reliable method to predict the CA inhibition activity of sulfonamides. The sulfonamides used in associate hydrazine moieties, ureas, sulfureas or simple aliphatic derivatives. The proposed model can be used as a first step for the formulation of an optimization problem from which the best para-substituent will be derived.

For this QSAR analysis we have selected a list of 47 para-substituted sulfonamides from the work of Melagraki and co-workers[6]. The aromatic sulfonamides are presented in Scheme 1. The inhibition data are expressed in erms of nanomolar affinity (KI) for the investigated isozyme. First, the chemical structures were designed using Chemsketch19 and were saved as .mol files. We have used Dragon software to calculate the topological indices data of 11 descriptors shown in Table 1, which are related to the arrangements of atoms in compounds as no. & types, of atoms, branching and no of multiple bonds etc[9-14]. Topological indices are a common useful tool for QSAR/QSPR taking into account their simplicity and rapidity of computation. This is particularly valuable now as one can analyze structures used for QSAR studies prior to any high throughput synthesis and testing.



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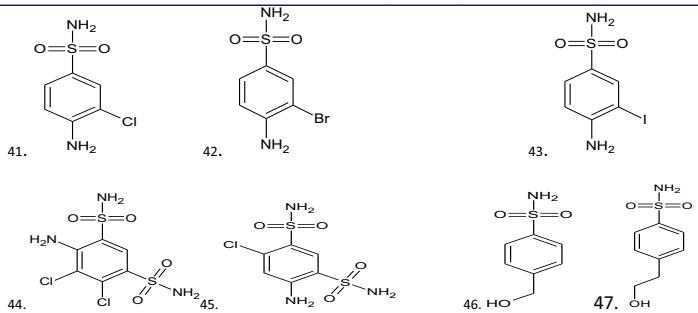

Scheme No.1: Structure of Sulphonamide Derivatives

Table 1 : Calculated Descriptors and Carbonic Anhydrase II Inhibitors (log K_i)

Comp. No.	log KI	FW	Xt	X3	X0v	XMOD	ZM1Mad	ZM1Per	ZM2Mad	Pol	piPC03	piPC05
1	2.4116	201.19	0.366	3.939	6.805	46.806	106.969	445.73	118.265	17	3.932	4.673
2	2.0934	215.22	0.35	4.445	7.291	50.368	110.837	468.72	124.046	19	3.989	4.71
3	1.1139	403.24	0.25	8.359	13.914	88.998	205.67	846.47	222.378	36	4.564	5.361
4	1.1761	394.4	0.24	8.423	13.463	89.94	189.163	866.57	206.799	37	4.477	5.247
5	0.9542	408.4	0.235	9.051	13.963	93.168	193.163	889.61	212.464	39	4.511	5.257
6	0.8633	413.24	0.253	7.787	13.611	88.554	234.502	784.5	215.412	33	4.5	5.313
7	1.0414	412.46	0.223	9.86	14.647	95.618	196.631	868.77	221.148	42	4.71	5.553
8	1.2553	428.46	0.219	10.01	15.055	99.333	204.838	919.25	228.135	42	4.7	5.513
9	1.1761	426.48	0.219	10.01	15.147	98.517	200.631	891.81	224.148	42	4.7	5.513
10	1.8261	336.36	0.257	7.377	11.647	77.82	162.631	722.53	180.148	31	4.369	5.112
11	1.7324	412.4	0.243	8.906	14.188	96.872	227.486	902.05	261.715	41	4.682	5.416
12	0.9912	412.4	0.243	8.912	14.188	96.77	227.486	902.05	259.045	40	4.673	5.438
13	0.9777	416.4	0.243	8.912	14.066	97.637	231.316	940.66	261.955	40	4.673	5.438
14	0.959	432.8	0.243	8.912	14.822	99.946	243.005	940.66	268.804	40	4.673	5.438
15	1.7076	205.2	0.366	4.096	6.761	47.657	108.453	460.53	121.752	18	3.932	4.727
16	1.8808	221.66	0.366	4.096	7.517	49.966	120.142	460.53	130.199	18	3.932	4.727
17	2.3909	268.21	0.324	5.237	8.478	59.054	145.826	644.88	154.781	23	4.043	4.754
18	2.1239	268.21	0.324	5.237	8.478	59.054	145.826	644.88	154.781	23	4.043	4.754
19	2.3655	228.26	0.336	4.504	7.844	52.764	114.809	480.75	126.436	19	3.932	4.7
20	2.356	226.25	0.317	5.1	7.844	52.971	122.809	488.43	139.603	22	4.111	5.075
21	2.4116	242.29	0.329	4.915	8.344	55	120.809	504.11	133.935	21	3.989	4.727
22	2.3304	256.32	0.313	4.858	8.844	58.764	122.809	526.83	134.436	21	3.97	4.736
23	2.3617	256.3	0.324	5.237	8.844	56.804	128.809	527.79	143.434	23	4.043	4.754
24	1.7993	270.3	0.303	5.108	9.344	61.764	126.809	549.87	138.436	22	3.989	4.745
25	1.5682	276.29	0.28	6.231	9.844	64.971	138.809	580.59	155.935	26	4.369	5.204
26	1.2304	366.2	0.26	8.965	11.734	81.723	187.963	890.44	218.66	42	4.73	5.648
27	2.3802	291.32	0.273	6.268	10.291	68.278	145.029	616.39	160.268	26	4.331	5.165
28	2.0212	305.35	0.266	6.6	10.791	71.324	148.696	639.35	164.101	27	4.344	5.159
29	1.8751	319.37	0.26	6.841	11.291	74.324	152.696	662.39	167.935	28	4.357	5.142
30	1.1139	388.26	0.253	7.823	13.559	85.502	195.735	786.33	210.164	33	4.466	5.273
31	1.6902	312.36	0.277	6.597	10.977	75.517	185.449	666.59	213.005	29	4.466	5.308
32	1.6021	326.39	0.27	6.979	11.477	78.563	189.116	689.55	215.169	30	4.477	5.273
33	1.4472	340.41	0.264	7.215	11.977	81.563	193.116	712.59	219.002	31	4.489	5.236
34	0.9542	330.35	0.273	7.007	11.355	78.746	195.28	728.56	222.916	31	4.511	5.375
35	1.8751	397.46	0.246	8.262	13.832	93.275	217.384	841.85	243.996	37	4.595	5.394
36	2.4771	172.2	0.397	3.241	5.936	40.476	93.568	362.66	103.776	13	3.738	4.489
37	2.5051	187.21	0.377	3.649	6.383	44.327	98.622	398.56	109.997	15	3.807	4.554
38	2.2304	186.23	0.377	3.649	6.436	43.769	97.235	385.62	108.609	15	3.807	4.554
39	2.2041	200.25	0.359	3.768	6.936	46.769	101.235	408.66	112.443	16	3.829	4.595
40	1.7782	190.19	0.385	3.823	6.314	43.806	103.399	424.63	115.531	16	3.871	4.673
41	2.0414	206.64	0.385	3.823	7.07	46.116	115.087	424.63	123.978	16	3.871	4.673
42	1.6021	251.1	0.385	3.823	7.9	51.312	165.439	424.63	146.8	16	3.871	4.673
43	1.8451	298.1	0.385	3.823	8.471	56.508	248.477	424.63	170.933	16	3.871	4.673
44	1.4472	320.17	0.334	5.661	10.692	71.782	199.147	676.81	232.389	29	4.317	5.242
45	1.8751	305.15	0.342	4.85	10.245	68.928	192.121	642.6	217.167	25	4.22	5.081
46	2.0969	187.21	0.377	3.649	6.397	44.123	97.98	398.41	109.272	15	3.807	4.554
47	2.0414	201.24	0.359	3.768	6.897	47.123	101.98	421.45	112.94	16	3.829	4.595

The descriptors have been used to compute, for highest correlation coefficient value it is necessary to decide which ones will be used. Among the 11 indices the selection of the best combinations was made with the use of an Elimination Selection Stepwise Regression (ES-SWR) algorithm that was developed inhouse. The aim of variable subset selection is to reach optimal model complexity in predicting a response variable by a reduced set of descriptors that are not highly intercorrelated having multicollinearity. The descriptors that after shorting out giving the attachment, position, multiplicity of attaching groups and mean information content based on the vertex degree equality and the edge equality both, taken for the correlation analysis to model the potent sulfonamide drug. The DRAGON software for testing of best product has been used for the collection of the data of compounds study for the nature of attaching groups. This software offers several hundreds of descriptors from different perspectives relating to empirical, constitutional and topological indices characteristic to the molecules under multi-descriptor class environment[15-16]. We have been drawn the structure of the studied

compounds in ACD/Chemsketch using the standard procedure. The CP-MLR is a 'filter' based variable selection procedure for model development in QSAR studies by using NCSS software.

Table 2: Results of Regression Analysis

S. No.	Parameters Used	Ai(1…3)	Intercept	SE	R2	AR2	R2CV	F-Ratio
1	FW	-0.005	3.2386	0.2985	0.6651	0.6577	0.637	89.385
2	FW,	-0.007						
	XT	-3.3756	4.8853	0.2915	0.6879	0.6737	0.6422	48.49
3	FW	-0.0087						
	Xt	-4.5557						
	Zmimad	0.0019	5.4483	0.2937	0.6903	0.6687	0.621	31.95
4	FW	-0.0094						
	Xt	-8.6849						
	ZM1Mad	0.0045						
	piPC05	-0.8474	10.7398	0.2788	0.7274	0.7014	0.6631	28.018
5	FW	-0.0139						
	Xt	-9.6682						
	ZM1Mad	0.0078						
	piPC05	-1.328						
	Pol	0.0372	13.2771	0.2769	0.7375	0.7055	0.6577	23.041
6	FW	-0.0115						
	Xt	-11.2816						
	ZM1Mad	0.0057						
	piPC05	-1.2988						
	Pol	0.074						
	X3	-0.2653	13.8923	0.2746	0.7482	0.7104	0.6354	19.805
After deleting Com. No.24 and 27								
7	FW	-0.011						
	Xt	-11.6539						
	Zmimad	0.0055						
	piPC05	-1.6171						
	Pol	0.0966						
	X3	-0.3461	15.3604	0.2571	0.7828	0.7485	0.6775	22.82

Model No.1

Log K_i = 3.2386 (±0.1634) - 0.0049(±0.0005)*FW

n= 47 r^2 = 0.8155 Se =0.2985 F –Ratio = 89.39

Here and thereafter, n = number of data point, R^2= regression coefficient, Se= Standard Error of estimation, F= Fischer statistics. As the coefficient of FW in Model No.1 is negative, the CA inhibition increases with a decrease in the value of FW. The value of correlation coefficient r = 0.9030, which means that it can predict 81.55% variance of CA inhibition.

Model No.2

Log K_i = 4.8853(±0.9331) - 0.0070 (±0.0012)*FW - 3.3756(±1.8847)*Xt

n= 47 r = 0.8293 Se =0.2951 F –Ratio = 48.49

Topological indices are numerical quantifier of molecular topology and are sensitive to bonding pattern, symmetry, content of heteroatom as well as degree of complexity of atomic neighborhoods. Since structure of a compound depends derived from information based upon connectivity can reveal the role of structural or sub-structural information of a molecules in estimating biological activity. Further we have obtained various multiple regression model by increasing no. of descriptors in which model no. 7 is significant.

Model No.7

Log K_i =15.3604 (±3.1193) - 0.011(±0.0047)*FW - 11.6539 (±3.3579)*Xt
+0.0055 (±0.0042)*ZM1Mad - 1.6171(± 0.4967)*piPC05
+ 0.0966(±0.0390)*Pol - 0.3461 (±0.1999)*X3

n= 45 r^2 = 0.8847 Se =0.2571 F –Ratio = 22.82

In this study we have calculate correlation by cross validation method of 7 models, out of which model no 7 (hexa parametric) with correlation coefficient r = 0.9058, and low press error leads to the development of statistically significant QSAR model, which allows understanding of the molecular properties/features that play an important role in governing the variation in the activities. In addition, this QSAR study allowed investigating influence of very simple and easy to compute descriptors in determine biological activities which could shed light on the key factors that may aid in design of novel potent molecules..

The randomization test suggests that the developed model have a probability of less than 1% that the model is generated by chance. The plot of observed vs predicted activity is shown in Fig. From the plot it can be sheen that MLR model is able to predict the activity of training set quit well (all Points are close to regression line) as well as external.

CONCLUSION

In view of result and discussions, we conclude that topological descriptor FW,Xt, ZM1Mad, piPC05, Pol and X3 can be successfully used for the QSAR study of sulphonamides as carbonic anhydrase II inhibitors using topological indices as potent antimicrobial drugs. These results will help medical as well as agriculture scientists in the design and prediction of new sulfonamide drugs exhibiting better activities than these reported in this result.

Table 3: Predicted log K_i and Observed log K_i with Residual

Comp. No.	Observed log K_i	Predicted log K_i	Residual
1	2.41	2.20	0.20
2	2.09	2.21	-0.12
3	1.11	1.08	0.02
4	1.17	1.46	-0.28
5	0.95	1.35	-0.39
6	0.86	1.08	-0.22
7	1.04	0.99	0.04
8	1.25	0.92	0.32
9	1.17	0.92	0.25
10	1.82	1.75	0.06
11	1.73	1.39	0.34
12	0.99	1.25	-0.26
13	0.97	1.23	-0.25
14	0.95	1.11	-0.15
15	1.70	2.12	-0.41
16	1.88	2.00	-0.12

17	2.39	2.17	0.21
18	2.12	2.17	-0.05
19	2.36	2.25	0.10
20	2.35	2.02	0.33
21	2.41	2.22	0.18
22	2.33	2.27	0.05
23	2.36	2.21	0.14
24	1.56	1.77	-0.21
25	1.23	1.18	0.04
26	2.02	1.72	0.30
27	1.87	1.69	0.17
28	1.11	1.19	-0.08
29	1.69	1.67	0.01
30	1.60	1.64	-0.03
31	1.44	1.65	-0.20
32	0.95	1.51	-0.56
33	1.87	1.33	0.53
34	2.47	2.24	0.23
35	2.50	2.28	0.22
36	2.23	2.28	-0.05
37	2.20	2.35	-0.15
38	1.77	2.02	-0.25
39	2.04	1.91	0.12
40	1.60	1.70	-0.10
41	1.84	1.64	0.19
42	1.44	1.42	0.01
43	1.87	1.61	0.25
44	2.09	2.28	-0.18
45	2.04	2.34	-0.30

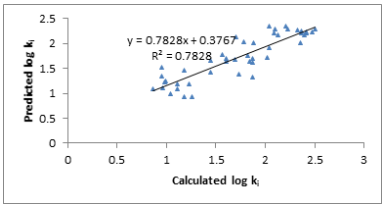

Fig 1: Graph plotted between predicted log KI and calculated log Ki

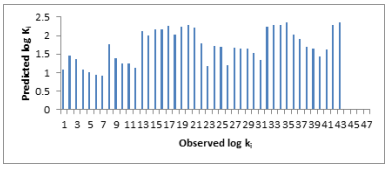

Fig 2: Graph plotted between predicted Residual and obrseved log KI

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