Research Article
CODEN (USA): IJPLCP

[Pandey & Pandey, 3(11 Suppl.): Nov., 2012]
ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES

Modelling of Ca inhibitory activity of sulfonamides

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Abstract

In the present investigation the applicability of various physicochemical parameters are tested for the QSAR study on sulfonamides. For the modeling of Inhibitory activities of sulfonamides the regression analysis shows that even in the multi parametric correlation of physicochemical parameters give significant regression coefficients. Furthermore using combinations of physicochemical parameters along with the indicator parameters, a tremendous improvement in the statistics has been observed. The results are critically discussed on the basis of regression data.

Key-Words: QSAR, Inhibitory activity, Modeling, Sulfonamides

Introduction

Quantatative Structure Activity Relationship (QSAR) has been established as a well known research tool and is being widely used in the field of pharmaceutical chemistry, industry and environmental studies[1]. The basic assumption underlying in QSAR studies is that the structure of a molecule determines its behavior. The compound used for the treatment of diseases having sulfur in its structure are known as sulfa drugs. More than 20 sulfonamides are now used in clinical practice[2]. Sulfamethoxypyridazine, Sulfachlor-pyridazine, Sulfadimethoxine, Sulfomethoxine, Sulfamethyldiazine and Sulfamoxol are used for clinical practice. [3-5] Carbonic anhydrase (CA) is a zinc enzyme commonly found in the plant and animal kingdoms, acting as a highly efficient catalyst for the reversible hydration of CO_2 to bicarbonate.[1, 4]

Agrawal and Khatikar[6] have undertaken topological indices to model the CA I, CA II and CA IV inhibitory activities. They have used Wiener index, Szeged index, Balabon index, first order, Valence connectivity indices and Branching index (B) for modelling of bilogical activity of carbon anhydrase inhibitors. They gave exellent results.

In the present investigation a QSAR study is performed over a set of 40 sulfonamides. This is the extension of previous studies based on the application of topological and physicochemical parameters in QSAR.

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Material and Methods

The study was carried on the compounds prepaired by Supuram[7] et al 1966 (Table 1). They have used activities of sulfonamides inhibitory activity logKi (hCAI). The series of sulfonamides used in present study.

Parameters used-

We have used chemsketch program of ACD Lab for calculation of various physiochemical parameters like Molecular weight (MW), Molar refraction (MR), Molar volume (MV), Parachor (Pr), Surface tension (γ), Density (d), Polarizability (α), and Index of refraction (n) and adapted step wise regration analysis for obtaining a model with best statistics. The calculated parameters for all the 40 compounds are reported in table 2.

Correlation Matrix

We have studied the inter correlation of the parameters along with the one biological activity and indicator parameters. Such a correlation matrix is reported in table 3. Parameters showing very good correlation with logKi(hCA I) MR, MV, Pr, n, IP2, IP3 and IP4 are the parameters witch shows good correlation.

Results and Discussion

Sulfonamides used in the present study are reported in table 1. Table 1 also shows the logKi (hCA I) activity and four indicator parameters IP1, IP2, IP3 and IP4. Various physicochemical parameters calculted using ACD lab software are reported in table 2. Table 3 shows the correlation of these parameters as well as their correlation with logKi (hCA I). On the basis of correlation matrix, we may infer that MW and MV are the parameters which can be used for modeling the log

logKi (hCAI) activity. Similiarly MR has also get some potential for this purpose. The multiparametric model is-

Log Ki(hCAI) = 0.0203 (±0.0065) MR – 0.0231 (±0.0053) MV + 0.0028 (±0.0013)Pr + 1.3846 (±0.6484) n + 0.1843 (±0.1535)IP_1- 0.1061 (±0.1018) IP_2 – 0.9586 (±0.0907) IP_4 + 3.2977

n = 37 SE= 0.2422 R= 0.9564 R^2 = 0.9038 F= 44.4780 Q=3.9488

Conclusion

On the basis of above bindins we conclude that logKi (hCA I) activity can be modelled using the physicochemical parameters MR, MV, Pr, n, IP1, IP2 and IP4. Our results are better than the earlier reported results.

References

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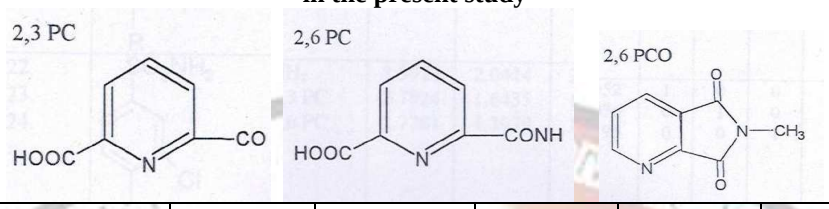
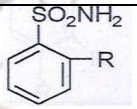
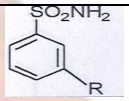
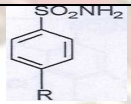
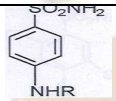
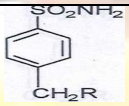
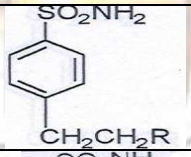
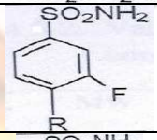
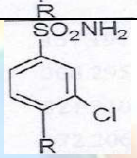
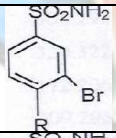
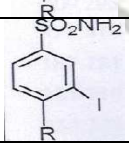
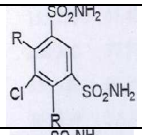
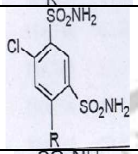
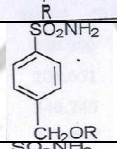
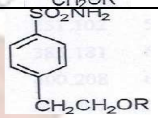
Table 1: The structure, inhibiton activity log Ki (hCA I) for a series of sulfonamides used in the present study



Compd. No.	Structure	R	Log Ki(hCAI)	IP1	IP2	IP3	IP4
1.		NH_2	4.6571	1	0	0	0
2.		2,3 PC	4.3222	0	1	0	0
3.		2,6 PC	4.3010	0	0	1	0
4.		NH_2	4.3979	1	0	0	0
5.		2,3 PC	4.3010	0	1	0	0
6.		2,6 PC	4.2672	0	0	1	0
7.		NH_2	4.4472	1	0	0	0
8.		2,3 PC	4.1903	0	1	0	0
9.		2,6 PC	4.1761	0	0	1	0
10.		NH_2	4.8949	1	0	0	0
11.		2,3 PC	4.3324	0	1	0	0
12.		2,6 PC	4.3139	0	0	1	0
13.		NH_2	4.3979	1	0	0	0
14.		2,3 PC	3.0170	0	1	0	0
15.		2,6 PC	2.9345	0	0	1	0
16.		NH_2	4.3222	1	0	0	0
17.		2,3 PC	2.9569	0	1	0	0
18.		2,6 PC	2.7404	0	0	1	0
19.		NH_2	3.9192	1	0	0	1
20.		2,3 PC	2.7324	0	1	0	1
21.		2,6 PC	2.7076	0	0	1	1
22.		NH_2	3.9912	1	0	0	1
23.		2,3 PC	2.7924	0	1	0	1
24.		2,6 PC	2.7781	0	0	1	1
25.		NH_2	3.8129	1	0	0	1
26.		2,3 PC	2.7818	0	1	0	1
27.		2,6 PC	2.7600	0	0	1	1
28.		NH_2	3.7781	1	0	0	1
29.		2,3 PC	2.7853	0	1	0	1
30.		2,6 PC	2.7782	0	0	1	1

31. 32. 33.		NH_2 2,3 PC 2,6 PC	3.7853 2.6990 2.6532	1 0 0	0 1 0	0 0 1	1 1 1
34. 35. 36.		NH_2 2,3 PC 2,6 PC	3.9243 2.7782 2.5682	1 0 0	0 1 0	0 0 1	1 1 1
37. 38.		H 2,6 PCO	4.3802 3.3118	0 0	0 0	0 1	0 0
39. 40.		H 2,6 PCO	4.2553 3.3010	0 0	0 0	0 0	0 0

IP_1 = 1, if NH_2 group is present at R position, otherwise 0
IP_2 = 1, if 2,3 PC group is present at R position, otherwise 0
IP_3 = 1, if 2,6 PC group is present at R position, otherwise 0
IP_4 = 1, if halogen group is present in basic structure, otherwise 0

Table 2: Values of physicochemical parameters calculated for compounds used in the Present study

Compd. No.	MW	MR	MV	Pr	n	γ	d	α
1	157.191	39.19	118.3	313	1.576	48.8	1.327	15.53
2	306.295	72.94	201	588.2	1.645	73.2	1.523	28.91
3	321.31	76.33	208.1	614.2	1.654	76.8	1.543	30.28
4	172.206	42.8	120.6	340.9	1.627	83.7	16.97	16.98
5	308.295	72.94	201	588.2	1.846	73.2	1.523	28.91
6	320.322	78.53	214.8	618.7	1.851	68.7	1.49	31.13
7	172.206	42.5	126.6	340.9	1.627	63.7	1.427	76.87
8	309.296	72.94	201	588.2	1.646	73.2	1.523	28.91
9	321.31	76.33	208.1	514.2	1.654	75.5	1.543	30.26
10	187.221	46.46	125	369.2	1.665	76	1.497	18.41
11	321.31	76.62	201.8	616.5	1.883	87	1.691	30.36
12	338.324	70.98	208.8	642.5	1.601	89.5	1.61	31.17
13	155.233	47.43	138.3	301	1.601	57.4	1.346	16.86
14	320.3	77.57	216.2	628.3	1.64	72.5	1.488	30.75
15	335.336	80.96	222.2	654.3	1.648	75.1	1.508	32
16	200.259	52.7	154.8	421.1	1.487	54.6	1.283	20.64
17	334.348	62.2	229.3	668.3	1.635	72.1	1.457	32.58
18	349.363	85.59	236.5	394.4	1.664	74.5	1.478	33.93
19	190.196	42.92	124.3	348.3	1.609	60.5	1.523	17.01
20	324.285	73.05	205.2	595.5	1.63	70.8	1.579	28.96
21	339.3	76.44	212.3	621.6	1.63	73.4	1.597	30.3
22	206.651	47.63	132.6	378	1.637	66	1.558	18.88

23	340.74	77.76	231	625.3	1.65	74.2	1.599	30.62
24	355.754	61.18	220	651.3	1.659	76.7	1.616	32.17
25	251.102	50.52	136.8	392	1.66	67.3	1.834	20.03
26	385.181	60.66	217.2	639.3	1.664	74.9	1.772	31.97
27	400.208	64.05	224.3	666.3	1.672	77.4	1.784	33.32
28	398.103	55.73	142.7	414.9	1.709	71.3	2.088	22.09
29	432.192	85.88	223.1	662.1	1.595	77.5	1.936	34.03
30	447.206	89.25	230.1	566.2	1.702	79.6	1.942	35.36
31	300.745	63.69	163.8	513.6	1.705	96.6	1.835	26.24
32	568.923	123.95	324.6	1006.2	1.699	92.9	1.752	49.13
33	599.952	130.74	338.7	1060.2	1.698	95.9	1.766	51.83
34	320.175	64.9	173.5	522.8	1.671	82.4	1.845	25.72
35	419.819	90.2	241.9	733	1.668	84.1	1.734	35.76
36	434.834	93.6	249	759	1.675	86.3	1.746	37.1
37	221.662	50.17	144.1	405.4	1.613	62.5	1.537	19.89
38	367.808	86.73	244.9	696.7	1.644	85.5	1.501	35.17
39	201.244	49.98	148.7	408.3	1.587	56.3	1.353	19.81
40	347.39	88.53	249.4	699.7	1.628	61.9	1.392	35.05

Table 4: Comparison of estimated biological activity log Ki (hCAI) with their observed values using model

Comp. No.	Obser.	Model	residue
1	4.6571	4.577	0.0801
2	4.3222	4.093	0.2292
3	4.301	4.074	0.227
4	4.3979	4.742	-0.3441
5	4.301	4.331	-0.03
6	4.2672	4.198	0.0692
7	4.4472	4.58	-0.1328
8	4.1903	4.095	0.0953
9	4.1761	3.791	0.3851
10	4.8949	4.839	0.0559
11	4.3324	4.521	-0.1886
12	4.3139	3.947	0.3669
13	4.3979	4.249	0.1489
14	3.017	-	-
15	2.9345	-	-
16	4.3222	4.27	0.0522
17	2.9569	3.324	-0.3671
18	2.7404	-	-
19	3.9192	3.728	0.1912
20	2.7324	3.07	-0.3376
21	2.7976	3.05	-0.3424
22	3.9912	3.741	0.2502
23	2.7924	3.087	-0.2946
24	2.7781	2.6	0.1781
25	3.8129	3.768	0.0449

26	2.7818	2.632	0.1498
27	2.76	2.614	0.146
28	3.7781	3.86	-0.0819
29	2.7853	3.056	-0.2707
30	2.7782	2.809	-0.0308
31	3.7853	3.777	0.0083
32	2.699	2.425	0.274
33	2.6532	2.31	0.2822
34	3.9243	3.54	0.3843
35	2.7782	2.959	-0.1808
36	2.5682	2.937	-0.3688
37	4.3802	4.474	-0.0938
38	3.3118	3.589	-0.2772
39	4.2553	4.328	-0.0727
40	3.301	3.504	-0.203

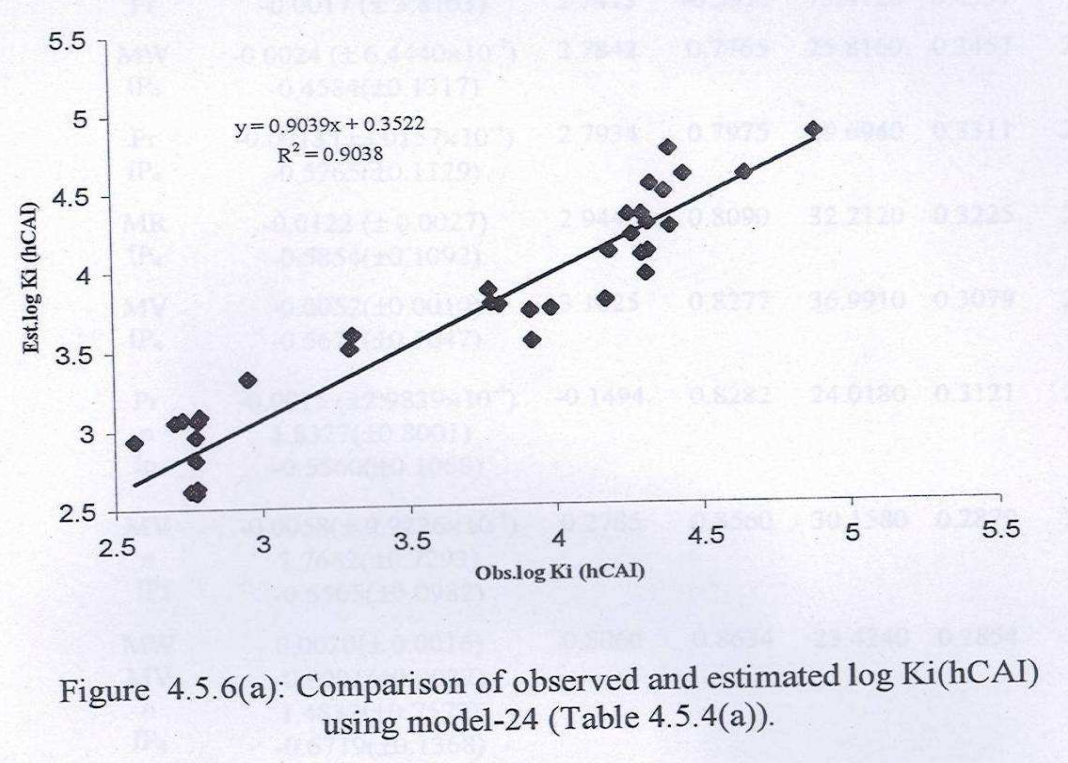


Figure 4.5.6(a): Comparison of observed and estimated log Ki(hCAI) using model-24 (Table 4.5.4(a)).

Fig.: Comparison of observed and estimated log Ki (hCAI) using model