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11. QSAR Analysis Of 1, 3, 4, - Thiadiazole And 1,3,4 - Triazole Dericatives as CA (IX) Carbonic Anhydrase Inhibitors

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Abstract:

The IC50 is a drug concentration dose which concerns with inhibitory concentration that is required to inhibit the 50% growth of a test population of animal. Quantitative structure–activity relationship (QSAR) model for log IC50 for 22 compounds of 1,3,4, -Thiadiazole and 1,3,4, -triazole derivatives as carbonic anhydrase inhibitors 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 log IC50 values and well understand the important structural factors affecting the experimental values, a set of physiochemical and topological parameters were taken into consideration. Four multivariable linear models derived from four 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 log IC50 values. The square of correlation coefficientc, R2, for the best model with, three molecular descriptors are 0.604. The residual value of the two compound is much higher than another compound is taken as outlier. After deleting this compound no10 and 11 the value of , R2,is much improved, it comes out to be 0.822. Our results are much more superior than 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.

11.1 Introduction:

Sixteen isoenzymes of - carbonic anhydrase are discovered till now; the main difference is in their subcellular location and catalytic activity 1. Among these four CAs are cytosolic

(CA-I, III, VII and XIII), two are mitochondrial CA- VA and CA-, one is secreted (CA-VI, and others are membrane bound (CA-IV, IX, XII and XIV). Three non- catalytic forms (CA-VIII, X and XI) are also reported and defined as carbonic anhydrase related proteins 2,3. A novel application of the CA inhibitors is their potential use in the treatment of hypoxic tumors 4-11. In tumor condition CA-IX and CA-XII are highly expressed in tumor cells, but not in normal cells 12-15. CA-IX is explicit in only a few normal tissues but it is found in high concentration in many tumor types, due to its transcriptional activation by hypoxia via transcription factor hypoxia- inducible factor. These properties make CAIX a useful maker and prognostic indicator for many types of tumors. In addition, it is also involved in regulation of pH and cell adhesion processes caused by tumor metabolism. Therefore CA-IX and CA-XII inhibitors are interesting and potential targets for design of anticancer drugs 16. Most CA inhibitors directly bind by deprotonated sulfonamide/sulfamate moiety to the catalytically critical Zn 2+ ion of the active site of the enzyme, taking part in a large number of polar and hydrophobic interactions with amino acid residues of the active site cavatity 17-23. Supuran et-al 24 studied the interactions of a small series of mercaptens with isozymes CA-I, II and IV. They suggested that – SH moiety of such derivatives may act as a zinc binding function in the design of CA inhibitors even though the potency of such compounds was lower than that of the sifonamides derivatives

In the present study quantitative structure activity relationship studies were performed on 1,3,4- thiadiazole and 1,3,4-triazole analogues in order to correlate the structural requirements for enzyme inhibition which may be useful in designing new molecules against hCA-II and hCA-IX enzyme.

11.2 Materials and Methods:

11.2.1 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 1,3,4, -Thiadiazole and 1,3,4, -triazole derivatives The structure of parent compound is given in (Figure 11.1).

11.2.2 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 for 22 compounds of 1,3,4, Thiadiazole and 1,3,4, -triazole 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.

11.3 Results and Discussion:

By using the multiple linear regression analysis (MLRA) method of 2D-QSAR, regression models were developed for 22 compounds of 1,3,4, -Thiadiazole and 1,3,4, -triazole derivatives. To select the sets of descriptors that are most relevant to log IC50 values and effectively show the relation between descriptors and log IC50 values of these compounds, four 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 reselection 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 observed that the residual value of twu compounds was much higher as compared to other compounds so this compound no 10 and 11 was taken as an outlier and the entire exercise was repeated to obtain the new models. We have observed that in our case R2 for models with one, two, three, four and five molecular descriptors after deletion of compound no 10 and 11 was.0.654,0.777 and 0.822 respectively. Our results are much more superior than 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.

11.4 Conclusion:

A quantitative structure–activity relationship model was derived to study the log IC50 values of a diverse set of 21 compounds of 1,3,4, -Thiadiazole and 1,3,4, triazole derivatives. Four QSAR models were developed with the squared correlation coefficient (R2) of one, two, and three molecular descriptors are 0.654,0.777 and 0.822. These models showed strong predictive ability. Among all the descriptors, topological descriptors were found to have high coding capabilities for the log IC50 values and were selected to represent the chemical structures. The present work provides an effective method for the prediction of the log IC50w values for the of 1,3,4, -Thiadiazole and 1,3,4, -triazole derivatives.

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 log IC50 values for unknown structures.

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

- Topological parameters are the best parameters for modeling Log IC50 activity of 1,3,4, -Thiadiazole and 1,3,4, -triazole derivatives.
- 2D QSAR modeling using MLRA analysis has been found to be better than 3D QSAR modeling (HM method as reported by Liu et al.)
- The best model suggests that for synthesizing new potent carbonic anhydrase inhibitor drugs.

11.5 References:

1. Sly WS & Hu P Y (1995) Annu Rev Biochem 64,375-401
2. Scozzafava A. mastrolorenzo A & supuran C.T. (2006) Expert Open their pat 16, 1627-1664.
3. Hilvo M. Tolvanen M. Clark A. shen B. shah G.N. Waheed A, Halvo P. hanninen M, hamalainen J.M, Vihinen M. sly W.S. & Parkkila S (2005) Biochem J 392, 83-92
4. Svastova E. Hulikova A. Rofajova M. zatovicova M. Gibadulinova A. Casini A. Cecchi A. Scozzafava A. Supuran Ct pasorek J & Pastorekova S (2004) FEBS Lett 577, 439-445
5. Supuran CT (2003) Expert opin invest drugs 12, 283-287
6. Supuran CT, Scozzafava A & Casini A (2003) Med res rev 23, 146-189
7. Scozzafava A, Owa T, Mostrolorenzo A & Supuran CT (2003) curr Med Chem 10, 925-953
8. Vullo D. Franchi M, Gallori E, pastorek J Scozzafava A Pastorekova S & Supuran CT (2003) J. Enz inhib Med Chem 18, 403-406.
9. Vullo D. Franchi M, Gallori E, pastorek J Scozzafava A Pastorekova S & Supuran CT (2003) J. Enz inhib Med Chem 13, 1005-1009.
10. Winum j Y, Vullo D Casini A, Montero J L, Scozzafava A & Supuran CT (2003) J Med Chem 46, 5471-5477.
11. Winum j Y, Vullo D Casini A, Montero J L, Scozzafava A & Supuran CT (2003) J Med Chem 46, 2197-2204.
12. Poter C & Harris A.L. (2004) cell Cyclic 3, 164-167.
13. Pastorekova S, Casim A Scozzafava A. Vullo D. Pastorek J 7 Supuran CT (2004) bioorg Med Chem Lett 14, 869-873
14. Rafajova m. Zatovicova m Kettmann r. Pastorek J & pastorekova S (2004) into oncol 24,995-1004.
15. Robertson N Potter C & Harns A L (2004) Cancer res 64, 6160-6165.
16. Pastrorekova S parkkila S Pastorek j & Supuran CT (2004) J Enz inhib Med Chem 19, 199-229.
17. Casini A Antel J. Abbate F. Scozzafava A david S Waldeck H. Schafer S 7 Supuran C.T. (2003) bio-org Med chem. Lett 13 841-845.
18. Abbte F. casini A Scozzafava A & Supuran CT (2003) Bioorg Med Chem Lett 14, 2357-2763.
19. Casini A, Abbate f, Scozzafava A & Supuran CT (2003) bioorg Med Chem 2759-2763.

20. Abbate F. Casini A Scozzafava A & Supuran CT (2004) bioorg Med Chem let 14, 2357-2361
21. Abbate F, Caetzee A Casini A, ciattini S Scozzafava A & Supuran CT (2004) bioorg Med Chem let 14, 337-341.
22. Abbate F. Winum J.Y., Potter B.V. casini A. Ciattini S. Scozzafava A & Supuran C.T. (2004), bioorg Med Chem let 14, 231-234.
23. Abbate F. Casini A owa T. Scozzafava A & Supuran CT (2004) bioorg Med Chem let 14, 217-223.
24. Almajan G.A. innocent A, Puccetti L. Manole G, Stelania B. Loana S Scozzafova A & Supuran CT (2005) bioorg med Chem Ltt 15, 2347-2352.

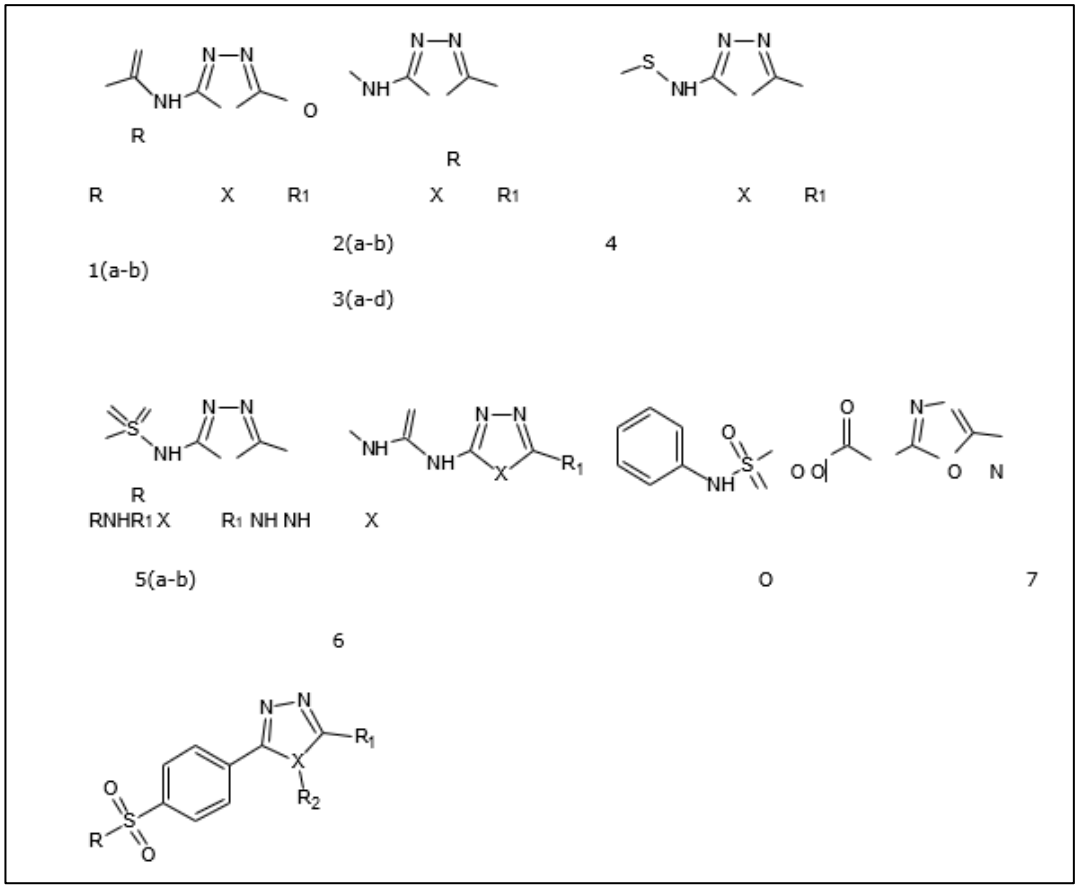


Figure 11.1: Parent Structures

Table 11.1: Structures of 1, 3, 4-thiadiazole and 1,3,4-triazole and their derivatives along with their hCA-II and HCA-IX inhibitory activities

Comd.no	R	R_1	R_2	X	Log Ki hCA-IX
1a	Ac	SO_2NH_2	-	S	7.602
1b	H	SO_2NH_2	-	S	7.3872
2a	H	SH	-	S	5.0315

Comd.no	**R**	**R_1**	**R_2**	**X**	**Log Ki hCA-IX**
2b	Ac	SH	-	S	5.0223
3a	C6F5	SH	-	S	3.5059
3b	2-Pyridyl	SH	-	S	3.5143
3c	3-COOH-pyridine-2yl	SH	-	S	3.6162
3d	Ph_2N	SH	-	S	3.567
4	4-NO_2-C_6H_4	SH	-	S	3.5918
5a	2-NO_2-C_6H_4	SH	-	S	3.5017
5b	Dansyl	SH	-	S	3.5287
6	3,4-Cl_2-C_6H_3	SH	-	S	3.567
7	-	SH	-	S	3.4921
8	Ph	SH	n-Pr	N	3.9245
9	4-Cl-C_6H_4	SH	n-Pr	N	5.0088
10	4-Br- C_6H_4	SH	n-Pr	N	3.1124
11	Ph	SH	n-Bu	N	3.5086
12	4-Cl-C_6H_4	SH	n-Bu	N	4.0141
13	4-Br- C_6H_4	SH	n-Bu	N	4.9393
14	4-Br- C_6H_4	SH	4-Me-C_6H_4	N	4.219
15	4-Br- C_6H_4	SH	3-Me-C_6H_4	N	3.4949
16	4-Br- C_6H_4	SH	4-MeO-C_6H_4	N	3.7167

Table 11.2: Calculated Topological and Connectivity Indices

Compd. no.	**W**	**J**	**JhetZ**	**Jhetm**	**Jhetv**	**Jhete**	**Jhetp**
1	391	2.371	4.082	4.083	2.139	2.948	2.275
2	204	2.352	4.918	4.920	2.187	3.065	2.451
3	41	2.257	4.565	4.567	2.156	2.959	2.338
4	125	2.181	3.511	3.512	1.887	2.749	1.888
5	584	2.013	3.004	3.022	1.765	2.695	1.635
6	263	1.706	2.659	2.660	1.599	2.262	1.565
7	467	1.765	2.655	2.655	1.647	2.362	1.586
8	665	1.693	2.447	2.447	1.651	2.212	1.600
9	605	1.615	2.852	2.853	1.584	2.111	1.693
10	689	1.994	3.733	3.734	1.905	2.633	2.070
11	1569	1.759	3.446	3.448	1.907	2.333	2.214
12	681	1.690	2.413	2.415	1.513	2.163	1.450
13	911	1.715	2.825	2.825	1.434	2.201	1.485
14	1405	1.549	2.467	2.467	1.808	2.089	1.894
15	1590	1.541	2.476	2.477	1.812	2.078	1.909
16	1590	1.541	2.483	2.485	1.819	2.076	1.915
17	1595	1.538	2.383	2.383	1.766	2.046	1.836

Compd. no.	W	J	JhetZ	Jhetm	Jhetv	Jhete	Jhetp
18	1795	1.531	2.396	2.397	1.773	2.039	1.854
19	1795	1.531	2.403	2.404	1.779	2.037	1.859
20	2380	1.335	2.094	2.095	1.560	1.817	1.604
21	2358	1.346	2.112	2.112	1.570	1.830	1.614
22	2645	1.325	2.068	2.068	1.504	1.809	1.530

Table 11.2: (contd….)

Compd. No.	0 x	1 x	2 x	3 x	0 v x	1 v x	2 v x	3 v x
1	11.638	6.804	7.199	4.609	9.054	5.850	5.141	3.339
2	9.190	5.537	5.531	3.463	7.223	4.966	4.393	2.997
3	5.276	3.288	3.023	1.957	5.038	2.831	2.658	1.348
4	7.560	4.682	4.414	2.608	6.869	3.747	3.275	1.702
5	13.447	8.414	7.979	7.077	9.851	5.488	4.663	2.861
6	9.096	6.343	5.524	4.195	8.217	4.813	3.933	2.319
7	11.544	7.648	7.057	5.236	9.496	5.412	4.432	2.622
8	13.079	9.343	8.052	6.668	11.682	7.035	5.556	3.698
9	12.251	8.148	7.386	5.621	10.759	6.428	5.428	3.655
10	14.044	8.899	8.776	6.298	11.575	7.434	6.575	4.508
11	19.113	12.132	12.298	9.874	16.955	11.874	12.220	9.097
12	13.121	8.542	7.994	5.982	11.869	6.619	5.616	3.556
13	14.588	9.444	9.202	6.006	12.297	7.882	6.536	3.851
14	17.156	11.536	10.439	8.945	14.835	9.495	7.666	5.771
15	18.027	11.930	11.061	9.356	15.891	9.973	8.243	6.094
16	18.027	11.930	11.061	9.356	16.722	10.388	8.722	6.370
17	17.864	12.036	10.793	9.214	15.542	9.995	8.019	6.059
18	18.734	12.430	11.414	9.625	16.599	10.473	8.597	6.382
19	18.734	12.430	11.414	9.625	17.429	10.888	9.076	6.658
20	20.596	13.858	13.206	11.209	18.617	11.410	9.742	7.089
21	20.596	13.858	13.218	11.126	18.617	11.410	9.745	7.056
22	21.303	14.396	13.375	11.617	19.025	11.522	9.604	7.127

Table 11.3: Regression parameters and quality of correlation with hCA-IX activity

Model No	Parameters used	Ai= (1-4)	B	Se	R^2	R^2A	F	Q=R/Se
1	W	0.000(±0.000)	4.767	1.172	0.104	-	2.327	0.275
2	J	2.475(±0.643)	-0.092	0.939	0.425	-	14.800	0.694
3	JhetZ	1.007(±0.2	1.291	0.922	0.445	-	16.03	0.724

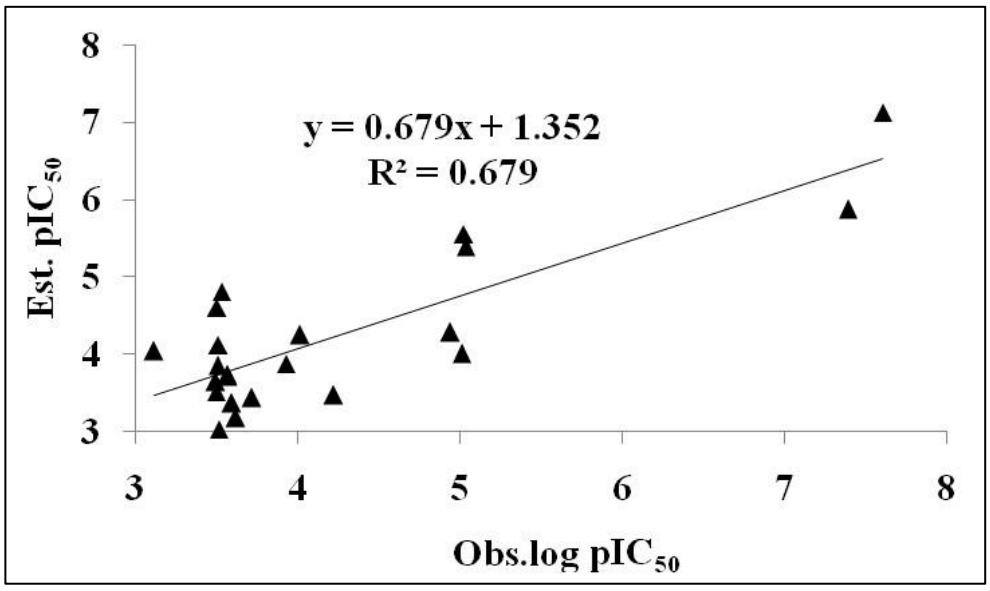
Model No	**Parameters used**	**Ai= (1-4)**	**B**	**Se**	**R^2**	**R^2A**	**F**	**Q=R/Se**
		52)					2	
4	Jhetm	1.006(±0.252)	1.294	0.924	0.444	-	15.968	0.721
5	Jhetv	4.086(±0.892)	-2.979	0.963	0.395	-	20.973	0.653
6	Jhete	2.002(±0.554)	-0.377	0.963	0.395	-	13.081	0.653
7	Jhetp	2.825(±0.688)	-0.948	0.912	0.457	-	16.858	0.741
8	0 X	-0.098(±0.055)	5.670	1.151	0.137	-	3.173	0.322
9	1 X	-0.160(±0.078)	5.772	1.125	0.174	-	4.227	0.371
10	2 X	-0.150(±0.085)	5.587	1.152	0.135	-	3.118	0.319
11	3 X	-0.170(±0.086)	5.458	1.132	0.165	-	3.966	0.359
12	0 v X	-0.110(±0.058)	5.641	1.141	0.152	-	3.574	0.342
13	1 v X	-0.144(±0.090)	5.369	1.166	0.113	-	2.551	0.288
14	2 v X	-0.149(±0.102)	5.329	0.096	1.177	-	2.131	11.301
15	3 v X	-0.161(±0.091)	4.982	1.189	0.079	-	1.705	0.236
16	Jhetp 3 v X	2.772(±0.6 66) -0.141(±0.091)	-0.183	0.882	0.518	0.467	10.211	0.816
17	Jhetp 2 v X	2.727(±0.6 68) -0.120(±0.077)	0.047	0.881	0.519	0.468	10.240	0.818
18	J 0 v X	4.383(±1.1 40) 0.167(±0.085)	-5.578	0.878	0.523	0.473	10.407	0.824
19	Jhetp J	1.823(±0.8 64) 1.392(±0.785)	-1.541	0.867	0.534	0.485	10.902	0.843
20	Jhetv J	2.971(±1.3 66) 0.976(±0.9	-2.715	0.862	0.540	0.491	11.148	0.852

Model No	Parameters used	Ai= (1-4)	B	Se	R^2	R^2A	F	Q=R/Se
		07)						
21	J W	4.648(±1.0 12) 0.001(±0.0 00)	-5.050	0.828	0.576	0.531	12.881	0.917
22	W Jhetp 3 v X	0.001(±0.0 01) 3.573(±0.7 72) - 0.541(±0.2 39)	-1.075	0.835	0.591	0.523	8.671	0.921
23	Jhetp 2 X 2 v X	3.769(±0.8 52) 0.493(±0.2 71) - 0.661(±0.3 06)	-2.660	0.832	0.594	0.526	8.762	0.926
24	W J 2 v X	0.002(±0.0 01) 4.842(±1.0 21) - 0.186(±0.1 69)	-4.780	0.823	0.602	0.536	9.093	0.943
25	J Jhete Jhetp	10.644(±4. 961) - 8.076(±4.2 73) 2.307(±0.8 50)	-0.046	0.814	0.611	0.547	9.443	0.960
26	W J 3 X	0.002(±0.0 01) 4.305(±1.0 19) - 0.332(±0.2 40)	-3.209	0.809	0.616	0.552	9.532	0.970
27	W J Jhete	0.001(±0.0 00) 11.870(±4. 994) - 5.977(±4.0 52)	-3.993	0.803	0.621	0.558	9.844	0.981
28	J Jhetv Jhete	11.618(±4. 829) 4.100(±1.3	-1.508	0.783	0.640	0.580	10.665	1.022
		40) - 9.471(±4.2 34)						
29	W J Jhetp 2 v X	0.002(±0.0 01) 2.963(±1.5 69) 1.680(±1.0 93) - 0.309(±0.1 81)	-3.636	0.794	0.651	0.569	7.928	1.016

Model No	**Parameters used**	**Ai= (1-4)**	**B**	**Se**	**R^2**	**R^2A**	**F**	**Q=R/Se**
30	W J 2 v χ Jhete	0.002(±0.0 01) 12.386(±4. 943) - 0.200(±0.1 63) - 6.233(±4.0 02)	-3.658	0.793	0.652	0.570	7.966	1.018
31	W J Jhete 2 X	0.002(±0.0 01) 12.346(±4. 931) - 6.436(±4.0 06) - 0.258(±0.2 06)	-2.416	0.791	0.653	0.572	8.009	1.022
32	Jhetv 2 χ 3 χ 2 v X	4.914(±1.0 46) 1.175(±0.4 65) - 0.783(±0.3	-5.094	0.789	0.655	0.574	8.077	1.026
		58) - 0.523(±0.2 67)						
33	W J Jhete Jhetp	0.0007(±0. 0005) 12.174(±4. 879) - 7.605(±4.1 28) 1.392(±1.0 11)	-2.905	0.784	0.659	0.579	8.223	1.035
34	W J Jhete Jhetv	0.0007(±0. 0005) 12.766(±4. 756) - 8.725(±4.1 44) 2.786(±1.5 87)	-3.642	0.761	0.679	0.604	9.005	1.083

Table 11.4: Observed and Estimated Ki Values Using Model 34

Compd. no	Obs. Log Ki (hCA-IX)	Est. Log Ki (hCA-IX)	Residual
1	7.602	7.124	0.478
2	7.387	5.870	1.518
3	5.032	5.387	-0.355
4	5.022	5.555	-0.533
5	3.506	3.847	-0.341
6	3.514	3.030	0.484
7	3.616	3.180	0.436
8	3.567	3.712	-0.145
9	3.592	3.371	0.220
10	3.502	4.605	-1.104
11	3.529	4.813	-1.285
12	3.567	3.728	-0.161
13	3.492	3.648	-0.156
14	3.925	3.877	0.048
15	5.009	4.004	1.004
16	3.112	4.041	-0.929
17	3.509	4.121	-0.612
18	4.014	4.245	-0.231
19	4.939	4.279	0.660
20	4.219	3.475	0.744
21	3.495	3.515	-0.020
22	3.717	3.437	0.279



Models before deletion One-variable:

Log Ki (hCA-IX) = 2.475(±0.643) J-0.092

N= 22, R2 = 0.425, R2A = 0.750, Se = 0.939, F= 14.800, Q = 0.694

Two-variable model: Log Ki (hCA-IX) = 4.648(±1.012) J+0.001(±0.000) W-5.050

N= 22, R2 = 0.576, R2A = 0.531, Se = 0.828, F= 12.881, Q = 0.917

Three-variable model:

Log Ki (hCA-IX) = 11.618(±4.829) J+4.100(±1.340) Jhetv-9.471(±4.234) Jhete- 1.508

N= 22, R2 = 0.640, R2A = 0.580, Se = 0.783, F= 10.665, Q = 1.022

Four-variable model:

Log Ki hCA-IX) = 0.0007(±0.0005) W+12.766(±4.756) J-8.725(±4.144) Jhete+2.786(±1.587) Jhetv-3.642

N= 22, R2 = 0.679, R2A = 0.604, Se = 0.679, F= 9.005, Q = 1.083

Table 11.5: After Deletion of Two Compounds (Compds. 10 and 11)

Model No	Parameters used	Ai = (1-4)	B	Se	R^2	R^2A	F	Q=R/Se
35	Jhetp	3.551(±0.609)	-2.097	0.754	0.654	-	34.051	1.073
36	J 3 v χ	5.434(±0.738) 0.576(±0.124)	-7.716	0.623	0.777	0.750	29.538	1.415
37	J 3 v χ 3 χ	4.634(±0.788) 1.037(±0.256) -0.392(±0.195)	-5.608	0.574	0.822	0.788	24.571	1.580

Table 11.6: observed and estimated Log Ki using model 37 (Table 4-2.11)

Compd. no	Obs. Log Ki (hCA-IX)	Est. Log Ki (hCA-IX)	Residual
1	7.602	7.036	0.566
2	7.387	7.042	0.345
3	5.032	5.482	-0.450

Compd. no	Obs. Log Ki (hCA-IX)	Est. Log Ki (hCA-IX)	Residual
4	5.022	5.242	-0.219
5	3.506	3.913	-0.408
6	3.514	3.058	0.456
7	3.616	3.238	0.378
8	3.567	3.459	0.108
9	3.592	3.464	0.128
10		-	-
11		-	-
12	3.567	3.567	0.000
13	3.492	3.980	-0.487
14	3.925	4.050	-0.126
15	5.009	4.187	0.822
16	3.112	4.473	-1.361
17	3.509	4.192	-0.684
18	4.014	4.334	-0.320
19	4.939	4.620	0.319
20	4.219	3.538	0.681
21	3.495	3.588	-0.093
22	3.717	3.371	0.345

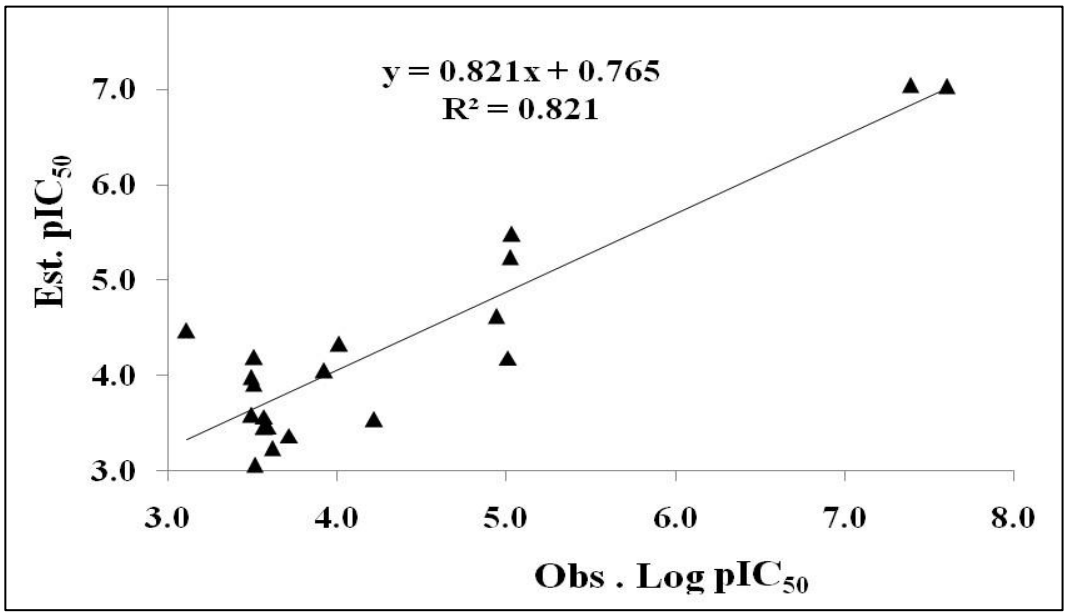


Figure 11.2: correlation between observed vs estimated log Ki values using model 37 (Table 4.1)

Table 11.7: Cross Validated Parameters

Moel No	Parameters used	PRESS/SSY	R2cv	SPRESS	PSE
35	Jhetp	0.529	0.471	0.754	0.715
36	J 3 v χ	0.288	0.712	0.624	0.575
37	J 3 v χ 3 χ	0.217	0.783	0.574	0.514

Models After Deletion:

One-variable model

Log Ki (hCA-IX) = 3.551(±0.609) Jhetp-2.097

N= 20, R2 = 0.654, Se = 0.754, F= 34.051, Q = 1.073

Two-variable model

Log Ki (hCA-IX) = 5.434(±0.738) J+0.576(±0.124) 3χ v -7.716

N= 20, R2 = 0.777, R2A = 0.750, Se = 0.623, F= 29.538, Q = 1.415

Three-variable model

Log Ki (hCA-IX) = 4.634(±0.788) J+1.037(±0.256) 3χ v-0.392(±0.195) 3χ -5.608

N= 20, R2 = 0.822, R2A = 0.788, Se = 0.574, F= 24.571, Q = 1.580.