Computer Aided Drug Designing of 1, 3, 4 - Thiadiazole and 1,2,4 -Triazole Derivatives as Ca (Ii) Carbonic Anhydrase Inhibitors

Dr. Manish Rao Ambedkar[1] , Dr. Ishwar Singh[2] Dr.Madhu Gupta[3]
[1]Department of Chemistry, Greater Noida Group of Institutions Greater Noida
[2]Department of Applied Science,M I E T,Greater Noida
[3]Department of Chemistry, M.M.H. College Ghaziabad (India)

Abstract:- **The IC_{50} is a drug concentration dose which concerns with inhibitory concentration that is required to inhibit the 50% growth of a test population of animal. The half maximal inhibitory concentration (IC_{50}) is a measure of the potency of a substance in inhibiting a specific biological or biochemical function. IC_{50} is a quantitative measure that indicates how much of a particular inhibitory substance (e.g. drug) is needed to inhibit, in vitro, a given biological process or biological component by 50%. Quantitative structure–activity relationship (QSAR) model for log IC_{50} for 22 compounds of 1,3,4-Thiadiazole and 1,2,4-triazole derivatives as carbonic anhydrase inhibitors is analysed 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 IC_{50} 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 IC_{50} values. The square of correlation coefficient (R^2) for the best model with , four molecular descriptors is 0.604.The residual value of the two compound is much higher than other compound is taken as outlier. After deleting these compound no 10 and 22 the value of R^2 is much improved, it comes out to be 0.751 .**

Keywords:- Quantitative structure–activity relationship (QSAR) model for log IC_{50}, 1,3,4-Thiadiazole and 1,2,4-triazole derivatives.

1. INTRODUCTION

The half maximal inhibitory concentration (IC_{50}) is a measure of the potency of a substance in inhibiting a specific biological or biochemical function. IC_{50} is a quantitative measure that indicates how much of a particular inhibitory substance (e.g. drug) is needed to inhibit, in vitro, a given biological process or biological component by 50%. The biological component could be an enzyme, cell, cell receptor or microorganism. IC_{50} values are typically expressed as molar concentration. IC_{50} is commonly used as a measure of antagonist drug potency in pharmacological research. IC_{50} is comparable to other measures of potency, such as EC_{50} for excitatory drugs. EC_{50} represents the dose or plasma concentration required for obtaining 50% of a maximum effect in

vivo. IC_{50} can be determined with functional assays or with competition binding assays. Sometimes, IC_{50} values are converted to the pIC_{50} scale.

$$pIC_{50} = -\log_{10}(IC_{50})$$

Due to the minus sign, higher values of pIC_{50} indicate exponentially more potent inhibitors. pIC_{50} is usually given in terms of molar concentration (mol/L, or M), thus requiring IC_{50} in units of M. The IC_{50} terminology is also used for some behavioral measures in vivo, such as a two bottle fluid consumption test. When animals decrease consumption from the drug-laced water bottle, the concentration of the drug that results in a 50% decrease in consumption is considered the IC_{50} for fluid consumption of that drug.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 CA-IX 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 j 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 1,2,4-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.

2. MATERIALS AND METHODS:-

2.1. Data Set:-

All data of the present investigation were obtained from the reference *(* Supuran CT *et al)*. The data set for this investigation consisted 22 compounds of 1,3,4-Thiadiazole and 1,2,4-triazole derivatives as carbonic anhydrase inhibitors is analysed using multiple linear regression analysis (MLRA) followed by statistical evaluation by NCSS software (IBM).The structure of parent compound is given in (Fig. 1).

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 1,2,4-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.

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 1,2,4-triazole derivatives . To select the sets of descriptors that are most relevant to log IC_{50} values and effectively show the relation between descriptors and log IC_{50} values of these compounds, four subsets with the descriptors from one tofour 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) R^2 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 (R^2) and The stability of the correlations was tested against the cross-validated coefficient (R^2CV). 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 22 was taken as an outlier and the entire exercise was repeated to obtain the new models.. We have observed that in our case R^2 for models with one, two, three and four molecular descriptors after deletion of compound no 10 and 22 is 0.587, 0.692, 0.732 and 0.751 respectively. Our results are much more superior then the result reported by Supuran CT et al.

4. CONCLUSION

A quantitative structure–activity relationship model was derived to study the log IC_{50} values of a diverse set of 22 compounds of 1,3,4-Thiadiazole and 1,2,4-triazole *derivatives.F*our QSAR models were developed with the squared correlation coefficient (R^2) of one, two, three and four molecular descriptors are 0.587,0.692,0.732 and 0.751. These models showed strong predictive ability. Among all the descriptors, topological descriptors were found to have high coding capabilities for the log IC_{50} values and were selected to represent the chemical structures. The present work provides an effective method for the prediction of the log IC_{50} values for the of 1,3,4-Thiadiazole and 1,2,4-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 IC_{50} values for unknown structures.

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

(1.) Topological parameters are the best parameters for modeling Log IC_{50} activity of 1,3,4-Thiadiazole and 1,2,4-triazole *derivatives.*

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

(3.) The best model suggests that for synthesizing new potent carbonic anhydrase inhibitor drugs.

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 ther 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) intd 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) bio org Med Chem let 14, 2357-2361

[21] Abbate F, Caetzee A Casini A , ciattini S Scozzafava A & Supuran CT (2004) bio org 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), bio org Med Chem let 14, 231-234.

[23] Abbate F. Casini A owa T. Scozzafava A & Supuran CT (2004) bio org 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

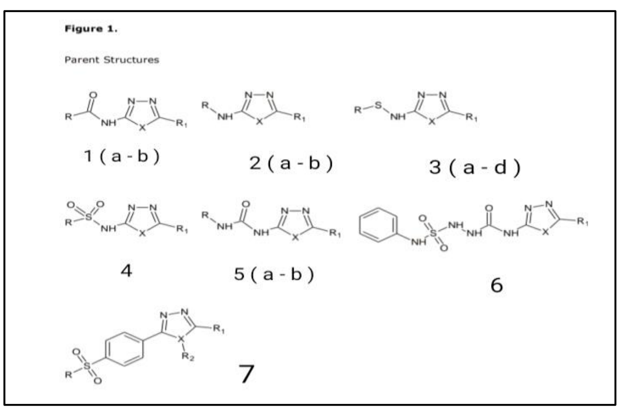


Table No. 1 Structures of 1, 3, 4-thiadiazole and 1,3,4-triazole and their derivatives along with their hCA-II and HCA-IX inhibitory activities

Comd .no	R	R1	R2	X	Log Ki hCA-II
1a	Ac	SO2NH2	-	S	7.9208
1b	H	SO2NH2	-	S	7.2219
2a	H	SH	-	S	5.0362
2b	Ac	SH	-	S	5.0555
3a	C6F5	SH	-	S	3.8894
3b	2-Pyridyl	SH	-	S	4.9914
3c	3-COOH-pyridine-2yl	SH	-	S	5.041
3d	Ph2N	SH	-	S	5.0315
4	4-NO2-C6H4	SH	-	S	5.0809
5a	2-NO2-C6H4	SH	-	S	3.6382
5b	Dansyl	SH	-	S	5.1024
6	3,4-Cl2-C6H3	SH	-	S	5.0401
7	-	SH	-	S	5.0862
8	Ph	SH	n-Pr	N	3.5591
9	4-Cl-C6H4	SH	n-Pr	N	3.209
10	4-Br- C6H4	SH	n-Pr	N	3.4179
11	Ph	SH	n-Bu	N	3.219
12	4-Cl-C6H4	SH	n-Bu	N	3.644
13	4-Br- C6H4	SH	n-Bu	N	5.0088
14	4-Br- C6H4	SH	4-Me-C6H4	N	3.6003
15	4-Br- C6H4	SH	3-Me-C6H4	N	3.5214
16	4-Br- C6H4	SH	4-MeO-C6H4	N	5.0044

Table No. 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
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

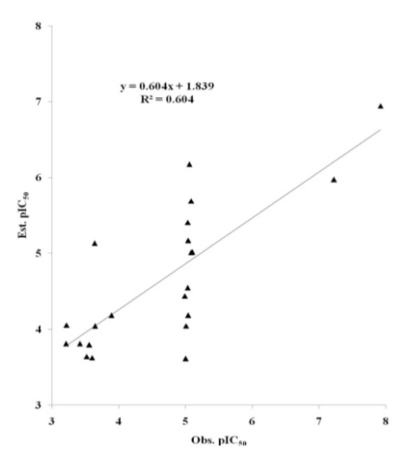
Table No. 3 Regression parameters and quality of correlation with hCA-II activity

Model No	Parameters used	A i =(1-4)	B	Se	R^2	R^2A	F	Q=R/Se
1	W	0.0008(±0.0003)	5.540	1.057	0.276	-	7.609	0.497
2	J	2.507(±0.640)	0.282	0.934	0.434	-	15.347	0.705
3	JhetZ	0.950(±0.264)	1.888	0.967	0.394	-	12.984	0.649
4	Jhetm	0.948(±0.264)	1.891	0.968	0.393	-	12.930	0.648
5	Jhetv	2.255(±1.177)	0.678	1.142	0.155	-	3.671	0.345
6	Jhete	1.956(±0.564)	0.159	0.981	0.376	-	12.027	0.625
7	Jhetp	1.582(±0.867)	1.755	1.150	0.143	-	3.331	0.329
8	$^0\chi$	-0.141(±0.050)	6.739	1.051	0.283	-	7.903	0.506
9	$^1\chi$	-0.217(±0.071)	6.759	1.023	0.321	-	9.447	0.554
10	$^2\chi$	-0.210(±0.079)	6.561	1.066	0.263	-	7.121	0.481
11	$^3\chi$	-0.244(±0.076)	6.420	1.011	0.337	-	10.153	0.574
12	$^0\chi^v$	-0.154(±0.053)	6.645	1.041	0.297	-	8.466	0.524
13	$^1\chi^v$	-0.214(±0.083)	6.359	1.076	0.249	-	6.628	0.464
14	$^2\chi^v$	-0.207(±0.097)	6.602	1.122	0.184	-	4.515	0.382
15	$^3\chi^v$	-0.252(±0.116)	5.843	1.116	0.192	-	4.750	0.393
16	Jhetp JhetZ	-1.680(±1.235) 1.446(±0.447)	3.520	0.947	0.447	0.389	7.693	0.706
17	$^1\chi$ $^2\chi$	-1.241(±0.483) 1.103(±0.516)	6.652	0.942	0.452	0.395	7.851	0.714
18	$^2\chi$ $^3\chi$	0.813(±0.402) -1.066(±0412)	4.978	0.941	0.454	0.397	7.908	0.716
19	J Jhete	14.473(±5.005) -10.109(±4.200)	2.634	0.839	0.566	0.521	12.408	0.897
20	J Jhete JhetZ	15.057(±4.936) -12.248(±4.440) 0..837(±0.643)	4.093	0.824	0.604	0.538	9.140	0.943

Table No. 4 Observed and estimated log Ki0 values using model 21.

Compd. no	Obs.log Ki (hCA-II)	Est. log Ki (hCA-II)	Residual
1	7.921	6.947	0.974
2	7.222	5.972	1.250
3	5.036	5.410	-0.374
4	5.056	6.174	-1.119
5	3.889	4.184	-0.294
6	4.991	4.440	0.551
7	5.041	4.185	0.856
8	5.032	4.547	0.484
9	5.081	5.013	0.068
10	3.638	5.133	-1.495
11	5.102	5.017	0.085
12	5.040	5.170	-0.130
13	5.086	5.693	-0.607
14	3.559	3.795	-0.236
15	3.209	3.810	-0.601
16	3.418	3.811	-0.393
17	3.219	4.055	-0.836
18	3.644	4.042	-0.398
19	5.009	4.045	0.964
20	3.600	3.625	-0.025
21	3.521	3.641	-0.119
22	5.004	3.612	1.393

Fig.2



Correlation between observed And estimated pIC_{50} using model 21.

BEFORE DELETION OF COMPOUND NO 10 AND 22 :-

One-variable model

Log Ki(hCA-II) = 2.507(±0.640)J+0.282
N= 22, R^2 = 0.434, Se= 0.934, F= 15.347, Q = 0.705

Two-variable model

Log Ki (hCA-II) = 14.473(±5.005)J-10.109(±4.200)Jhete+2.634
N= 22, R^2 = 0.566, R^2A = 0.521, Se= 0.839, F= 12.408, Q = 0.897

Three-varable model

Log Ki (hCA-II) = 15.057(±4.936)J-12.248(±4.440)Jhete +0.837(±0.643)JhetZ+4.093
N= 22, R^2 = 0.604, R^2A = 0.538,Se= 0.824, F= 9.140, Q = 0.943

Four-variable model

Log Ki (hCA-II) = 13.620(±5.243)J-8.794(±4.645)Jhete+3.176(±2.510)Jhetp- 5.136 (±4.109) Jhetv+4.338
N= 22, R^2 = 0.604, R^2A = 0. 511, Se= 0.847, F= 6.494, Q = 0.918

Table No. 5 After deletion of compouns no 10 and 22 best obtained models

Model No	Parameters used	Ai=(1-4)	B	Se	R^2	R^2A	F	Q=R/Se
22	J	3.033(±0.600)	-0.628	0.826	0.587	-	25.538	0.928
23	J Jhete	13.716(±4.467) - 9.050(±3.757)	1.509	0.733	0.692	0.656	19.078	1.135
24	J Jhete JhetZ	14.123(±4.305) - 11.084(±3.848) 0.857(±0.556)	2.989	0.705	0.732	0.681	14.535	1.214
25	J Jhete Jhetp Jhetv	12.344(±4.480) - 7.910(±3.997) 4.064(±2.152) - 6.396(±3.535)	3.481	0.702	0.751	0.685	11.318	1.234

Table No. 6 Observed and estimated pIC_{50} values using model 25

Compd. no	Obs. Log Ki (hCA-II)	Est. Log Ki (hCA-II)	Residual
1	7.921	7.120	0.801
2	7.222	6.453	0.769
3	5.036	5.781	-0.745
4	5.056	6.244	-1.189
5	3.889	4.311	-0.421
6	4.991	4.411	0.580
7	5.041	4.199	0.842
8	5.032	4.420	0.612
9	5.081	4.990	0.091
10	-	-	-
11	5.102	5.223	-0.120
12	5.040	5.008	0.032
13	5.086	5.691	-0.605
14	3.559	3.717	-0.158
15	3.209	3.733	-0.524
16	3.418	3.727	-0.309
17	3.219	3.924	-0.705
18	3.644	3.916	-0.272
19	5.009	3.912	1.096
20	3.600	3.439	0.161
21	3.521	3.458	0.064
22	-	-	-

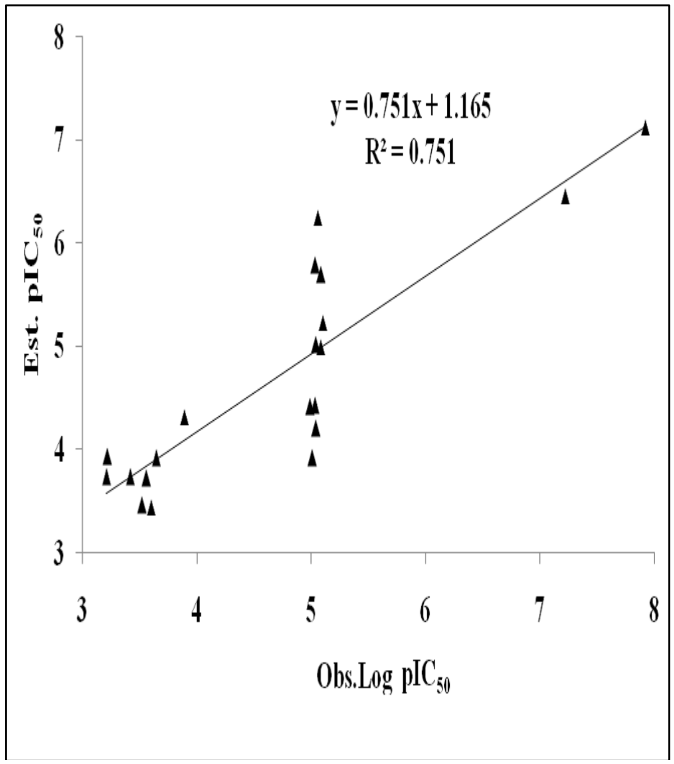


Fig.3 Correlation between observed vs estimated Log pIC_{50} values using model 25 (Table 4)

Table No. 7 cross validated parameters for the best models (after deletion of Com. 10 and 22)

Model No	Parameters used	PRESS/SSY	R^2cv	SPRESS	PSE
22	J	0.705	0.295	0.826	0.783
23	J Jhete	0.446	0.554	0.734	0.676
24	J Jhete JhetZ	0.367	0.633	0.706	0.631
25	J Jhete Jhetp Jhetv	0.331	0.669	0.702	0.608

MODELS AFTER DELETION OF COMPOUND NO 10 AND 22 :-

One-variable model

Log Ki (hCA-II) = 3.033(±0.600) J-0.628
N= 20, R^2 = 0.587, Se= 0.826, F= 25.538, Q = 0.928

Two-variable model

Log Ki (hCA-II) = 13.716(±4.467) J-9.050(±3.757) Jhete+1.509
N= 20, R^2 = 0.692, R^2A = 0.656, Se= 0.733, F= 19.078, Q = 1.135

Three-varable model

Log Ki (hCA-II) = 14.123(±4.305) J-11.084(±3.848) Jhete +0.857(±0.556) JhetZ+2.989 N= 20, R^2 = 0.732, R^2A = 0.681, Se= 0.705, F= 14.535, Q = 1.214

Four-variable model

Log Ki (hCA-II) = 12.344(±4.480) J-7.910(±3.997) Jhete+4.064(±2.152) Jhetp- 6.396(±3.535) Jhetv+3.481
N= 20, R^2 = 0.751, R^2A = 0.685, Se= 0.702, F= 11.318, Q = 1.234