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Research Article

STRUCTURAL INSIGHT FOR BENZIMIDAZOLE AS ANGIOTENSIN II AT_1 RECEPTOR ANTAGONIST BY USING MOLECULAR PROPERTY AND BIOLOGICAL ACTIVITY CORRELATION": QSAR APPROACH

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ABSTRACT

A quantitative structure activity relationship (QSAR) analysis of a set 90 benzimidazole analogues as angiotensin II(AII) AT1 receptor antagonists was performed to explore substitutional requirements for a favorable receptor drug interaction. The QSAR models were generated using Hansch analysis. Stepwise Regression was carried out to derive a predictive model on 62 analogues. The predictive ability of the model developed was assessed using a test set of 28 compounds. The internal (correlation coefficient r^2) and external consistency (predictive r^2) of the final Hansch QSAR model was 0.83 and 0.33 respectively. nDB, RDF080u and R6u were the parameter shown the positive contribution for the biological activity and hence reveal that geometrical, structural, and shape descriptors govern the A II AT1 antagonistic activity. These studies will be useful to design new A II antagonist with improved potency.

Keyword: Benzimidazole, AII antagonist, AT1 receptor, Hypertension, RAS

INTRODUCTION

Angiotensin II (A II) AT1receptor antagonist are widely used in treatment of hypertension and maintenance of homeostatis[1, 2] because of their lesser side effect and better therapeutic profile [3].They act by blocking the Renin Angiotensin System (Fig.2)

Losartan is the Prototype AII antagonist served as a lead and various chemical modifications have made for the development of newer compounds of this category. In general all the Sartan like Candesartan, Zolasartan, Irbesartan, and Telmisartan, Olmesartan are composed of an appropriately substituted heterocyclic nucleus coupled to an acidic group bearing biphenyl system through a methylene linker as per SAR described by D.J. Carini *etal*[4].Varied substitutions in benzimidazole nucleus have been extensively studied for this purpose.Candesartan and Telmisartan are clinically used AII antagonist having substituted benzimidazole nucleus at with carboxyl function at 7-position and benzimidazole at 6-position respectively[5,6]. The 5 position of benzimidazole has been exploited with the synthesis of nitro, amino, carboxaamido and sulfonyl groups and found more and equally active than candesartan. [7, 8,9] Kohara *et al*[10] reported the 5-oxo-1, 2, 4-oxadiazole and its thio analog are lipophillic bioisosteric replacement for the tetrazole unit, their derivative exhibit enhanced activity and oral bioavailability.Kubo *et al*[11,12] studied 2-substitution and the substitution on benzene ring of the bezimidazoles with the various substituent.2- Alkyl benzimidazole based AT1 receptor antagonist bearing N-Phenylpyrrole moiety was also studied by the Jin Yi xu *et al*[13]. An important step in drug action is the interaction of the drug with a biological receptor. The QSAR approach is deals with the situation indirectly[14]. It correlates the biological activity of the ligand with their structural or physicochemical property and extends the correlated property for the prediction of new ligand. The aim of present study is to gain insight into the structural and molecular requirement for substituted benzimidazole nucleus influencing the A II AT1 receptor antagonistic activity, herein we depict QSAR analysis of 90 compound to explore the diversity at all the substitution on to the benzimidazoles nucleus for AII antagonistic activity. The relevance of the model used for the design of novel derivatives should be assessed not only in terms of predictivity, either internal or external, but also in terms of their ability to provide a chemical and structural explanation of their binding interaction. These results should provide guidelines for design of more potent and selective AII antagonist.

MATERIALS AND METHODS

The A-II receptor antagonistic activity data of substituted benzimidazole derivatives were taken from the reported work [10, 11, 12] (Fig.1, Table 1).

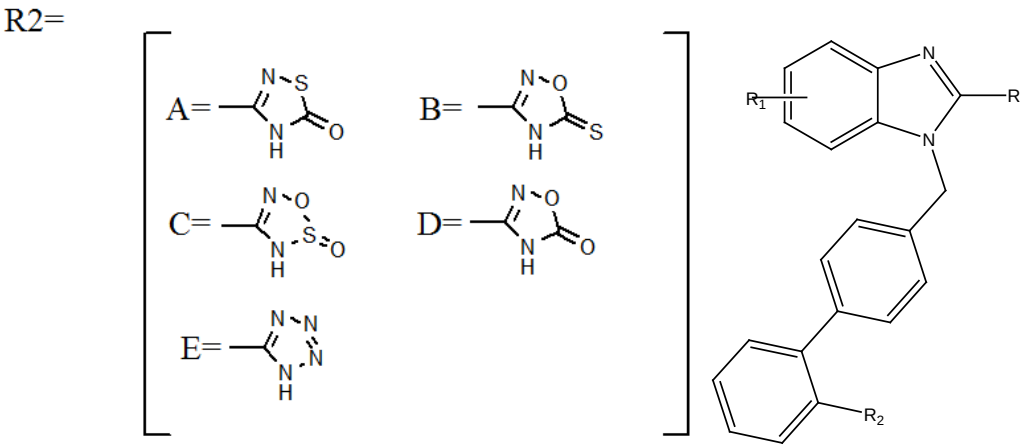

Fig. 1: Lead compound for Substituted Benzimidazole analogs

Table 1: Structure, activities and Descriptors of set of substituted Benzimidazole used in training and test set

S. No.	R_1	R	R_2	IC_{50}	pIC_{50}	nDB	RDF080u	E3s	R6u+	RTe
1	COOMe	MeO	Tet	4.9	6.309	3	29.25	0.326	0.124	24.301
2	COOMe	EtO	Tet	0.66	7.180	3	30.64	0.274	0.12	23.571
3	COOEt	PrO	Tet	10	6	3	34.18	0.298	0.121	24.304
4	COOMe	CH_2=$CHCH_2O$	Tet	8.5	6.070	4	28.95	0.256	.129	23.954
5	COOMe	Ets	Tet	4.4	6.356	3	24.78	0.275	0.119	22.879
6	COOH	Me	Tet	1.9	6.721	3	16.80	0.15	0.128	22.977
7	COOH	Et	Tet	0.46	7.337	3	18.20	0.215	0.147	23.6
8	COOH	Pr	Tet	1.7	6.769	3	24.60	0.235	0.131	24.234
9	COOH	i-Pr	Tet	0.82	7.086	3	21.95	0.295	0.178	24.666
10	COOH	c-Pr	Tet	0.84	7.075	3	19.11	0.253	0.182	24.312
11	COOH	i-Bu	Tet	32	5.494	3	27.1	0.286	0.131	24.756
12	COOH	Pen	Tet	5.6	6.251	3	30.41	0.332	0.119	23.787
13	COOH	$MeOCH_2$	Tet	2.5	6.602	3	20.09	0.274	0.124	23.302
14	COOH	$EtOCH_2$	Tet	4.4	6.356	3	21.64	0.294	0.119	23.271
15	COOH	$MeSCH_2$	Tet	1.5	6.823	3	21.38	0.277	0.122	22.567
16	COOH	$EtSCH_2$	Tet	3	6.522	3	25.10	0.297	0.117	22.609
17	COOH	$MeOCH_2CH_2$	Tet	5.8	6.236	3	27.56	0.336	0.129	23.858
18	COOH	$MeSCH_2CH_2$	Tet	6.2	6.207	3	24.35	0.265	0.127	23.167
19	COOH	$MeNHCH_2$	Tet	8	6.096	3	21.35	0.284	0.127	23.56
20	COOH	MeO	Tet	0.32	7.494	3	23.11	0.296	0.156	23.515
21	COOH	EtO	Tet	1.1	6.958	3	24.73	0.313	0.139	23.089
22	COOH	PrO	Tet	1.9	6.721	3	26.33	0.326	0.124	23.112
23	COOH	CF_3CH_2O	Tet	5.8	6.236	3	20.46	0.257	0.141	24.427
24	COOH	MeNH	Tet	1.7	6.769	3	18.86	0.231	0.15	23.36
25	COOH	EtNH	Tet	0.62	7.207	3	22.52	0.3	0.137	23.326
26	COOH	PrNH	Tet	0.39	7.408	3	25.24	0.326	0.125	23.428
27	COOH	BuNH	Tet	6.5	6.187	3	29.29	0.343	0.122	23.532
28	COOH	MeS	Tet	1.2	6.920	3	14.57	0.285	0.15	22.608
29	COOH	EtS	Tet	1.7	6.769	3	18.39	0.319	0.134	22.421
30	COOH	PrS	Tet	1.2	6.920	3	22.11	0.33	0.12	22.552
31	COOH	Bu	Tet	5.5	6.259	3	31.02	0.312	0.12	23.716
32	Dup-753	Bu	Tet	1.5	6.823	2	23.87	0.248	0.141	24.747
33	COOMe	EtO	A	7.5	6.124	3	29.10	0.316	0.142	24.191
34	COOH	EtS	A	4.7	6.327	3	18.69	1	0.105	23.089
35	COOH	Et	B	3.4	6.468	3	21.22	0.303	0.138	24.291
36	COOH	Pr	B	3.9	6.408	3	22.96	0.197	0.113	23.763
37	COOH	Bu	B	7.6	6.119	3	28.97	0.202	0.087	22.671
38	COOH	MeS	B	10	6	3	14.91	0.249	0.129	23.169
39	COOH	Bu	D	9	6.045	3	20.18	0.327	0.111	23.057
40	COOMe	EtO	D	4.4	6.356	3	25.12	0.281	0.099	22.942
41	COOH	EtO	D	4.2	6.376	3	16.02	0.295	0.122	22.419
42	COOMe	Bu	Tet	3.2	6.494	3	19.10	0.283	0.117	22.851
43	COOMe	EtO	Tet	0.66	7.180	3	23.73	0.208	0.134	23.45
44	COOH	Bu	Tet	5.5	6.259	3	25.46	0.342	0.108	24.104
45	COOH	EtO	Tet	1.1	6.958	3	34.34	0.156	0.104	23.099
46	COOH	Et	A	0.69	7.161	3	42.56	0.159	0.093	23.767
47	COOH	Pr	A	3.6	6.443	3	40.10	0.183	0.08	22.94
48	COOH	MeO	A	3.6	6.443	3	18.56	0.168	0.095	22.34
49	COOH	EtO	A	2.5	6.602	3	29.53	0.185	0.126	23.826
50	COOH	PrO	A	9.2	6.036	3	35.40	0.236	0.098	23.779
51	COOH	MeS	A	5	6.301	3	37.12	0.191	0.082	23.132
52	COOH	MeNH	A	5.4	6.267	3	36.241	0.214	0.11	24.287
53	COOH	EtNH	A	1.3	6.886	3	46.638	0.184	0.1	23.756
54	COOH	EtS	B	6.9	6.161	3	19.53	0.157	0.137	24.337
55	COOMe	EtO	C	4.6	6.337	3	29.90	0.215	0.076	22.568
56	COOH	Me	A	9.7	6.013	3	21.39	0.119	0.089	22.741
57	COOH	Bu	D	6.2	6.207	3	33.78	0.273	0.096	23.365
58	COOH	Bu	A	7.2	6.142	3	16.36	0.167	0.128	23.436
59	H	Butane	Tet	9	6.045	1	28.99	0.264	0.077	22.227
60	5-OMe	Butane	Tet	9.1	6.040	1	33.1	0.371	0.071	22.648
61	6- OMe	Butane	Tet	11	5.958	1	30.17	0.332	0.102	22.644
62	5-Cl	Butane	Tet	15	5.823	1	27.92	0.357	0.076	22.714
63	6-Cl	Butane	Tet	31	5.508	1	26.41	0.349	0.075	22.684
64	7- OMe	Butane	Tet	28	5.552	1	28.96	0.262	0.081	22.853
65	4-CO_2Me	Butane	Tet	72	5.142	2	33.22	0.348	0.066	23.044
66	5-CO_2Me	Butane	Tet	7.4	6.130	2	37.41	0.317	0.093	22.452
67	6-CO_2Me	Butane	Tet	4.4	6.356	2	30.62	0.311	0.068	22.368
68	7-CO_2Me	Butane	Tet	3.2	6.494	2	37.14	0.199	0.079	22.76
69	5-Me,7-CO_2Me	Butane	Tet	8.7	6.060	2	43.3	0.166	0.072	22.776
70	5-Cl,7-CO_2Me	Butane	Tet	4.4	6.060	2	34.05	0.302	0.08	22.815

71	6-Me,7-CO_2Et	Butane	Tet	9.1	6.356	2	43.06	0.191	0.089	23.253
72	4-$CONH_2$	Butane	Tet	130	6.040	2	29.00	0.376	0.07	23.307
73	7-CO_2Et	Butane	Tet	14	4.886	2	37.57	0.236	0.071	23.369
74	7-COOBU	Butane	Tet	12	5.853	2	52.24	0.585	0.08	23.914
75	5-COOH	Butane	Tet	55	5.920	2	31.17	0.335	0.068	22.94
76	6-COOH	Butane	Tet	90	5.259	2	35.12	0.167	0.067	22.87
77	7-COOH	Butane	Tet	5.5	5.045	2	33.04	0.593	0.098	23.268
78	5-Me,7-COOH	Butane	Tet	13	6.259	2	39.82	0.302	0.092	23.06
79	5-Cl, 7-COOH	Butane	Tet	11	5.886	2	31.23	0.334	0.094	23.165
80	6-Me ,7-COOH	Butane	Tet	3.4	5.958	2	38.79	0.17	0.118	23.801
81	H	Butane	COOH	11	6.468	2	22.79	0.319	0.087	22.858
82	7-COOH	Butane	COOH.	6.6	5.958	3	20.81	0.146	0.112	24.169
83	7-COOH	Butane	1-Me-Tet.	34	6.180	3	26.12	0.244	0.084	22.779
84	7-CONHiPr	Butane	Tet	5.4	5.468	2	52	0.221	0.085	25.051
85	7-CH_2OH	Butane	Tet	4.5	6.267	1	37.94	0.224	0.106	23.263
86	7-CH_2OMe	Butane	Tet	6	6.346	1	34.01	0.167	0.084	23.001
87	7-CH_2NMe_2	Butane	Tet	24	6.221	1	35.124	0.131	0.116	24.912
88	7-Me	Butane	Tet	3.3	5.619	1	32.156	0.317	0.119	22.943
89	7-OH	Butane	Tet	11	5.958	1	30.794	0.311	0.092	23.074
90	7-CH_2COOH	Butane	Tet	26	5.585	2	31.237	0.185	0.105	24.681

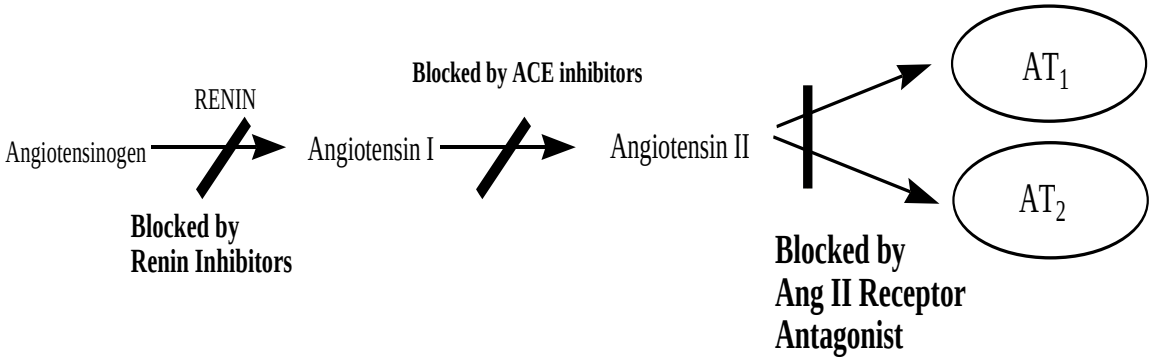

Fig. 2: Blocking of RAS by A II receptor antagonist

The biological activity data (IC_{50} in 10^{-7} M) was converted to negative logarithmic mole dose (pIC_{50}) for quantitative structure activity relationship (QSAR) analysis. The molecular modeling study was performed using CS ChemOffice[15] version 10 and Dragon[16] program while the regression analysis was carried on the VALSTAT[17] Series was divided into training set of 62 compounds and test set of 28 compounds on the basis of structural diversity and cover the complete range of variation in antagonist activity. The molecular structures of compounds were sketched by using Chem Draw and then ChemUltra used to convert them into 3D structures. The energy minimization of the molecule was done using molecular mechanics (MM2) until the RMS gradient value became smaller than 0.1 kcal/mol Å. The energy minimized molecules were subjected to the re-optimization via Austin model-1 (AM1) Hamiltonian method until the RMS gradient attained a value smaller than 0.0001 kcal/mol Å using MOPAC. The molecule was saved as MOL file format. Pursuly, the MOL file was used for the calculation of various Descriptors using DRAGON program. The data were used in order to establish a correlation between physicochemical parameters as independent variables and pIC_{50} as dependent variable employing sequential multiple linear regression analysis method by statistical programe Valstat. In this regression analysis, the program searches all the permutation and combination sequentially for the data set. The ± data within the parentheses are the standard deviation, associated with coefficient of descriptors in regression equations. The best model was selected from the various statistically significant equations on the basis of observed squared correlation coefficient (r^2), standard error of estimate (Std), sequential Fischer test (F), bootstrapping squared correlation coefficient (r^2_{bs}), bootstrapping standard deviation (S_{bs}), cross validated squared correlation coefficient using leave one out procedure (Q^2), chance statistics (evaluated as the ratio of the equivalent regression equations to the total number of randomized sets; a chance value of 0.001 corresponds to 0.1% chance of fortuitous correlation), outliers (on the basis of Z-score value) and predictive squared correlation coefficient of test set (r^2_{pred}).

RESULTS AND DISCUSSIONS

In this study, an attempt has been made to explorer structural requirement for the Ang II antagonistic activity at all the substitution site on substituted benzimidazole analogs as an AT_1 receptor antagonist. Hence QSAR study was done by using series of set of compound having Total of 90 compounds with the biological activity determined by same biological model. The multivariant expressions were developed on the basis of adjustable correlation coefficient (r^2adj). Adjustable correlation coefficient is a measure of the % explained variation in the dependent variable that takes into account the relationship between the number of cases and the number of independent variable in the regression model. Whereas r^2 will always increase when an independent variable is added, r^2adj will decrease if the added variable does reduce the unexplained variation enough to offset the loss of degrees of freedom.

It is necessary that the proposed models should have both the statistical quality as well as better predictive power therefore all the expressions were tested for internal and external validation. Both the validation put forward decision making input for selection of QSAR models. Internal validation was carried out using leave one out cross validation method, bootstrapping technique and randomized biological activity test while external validation confirmed with test set data. Tri-variant expressions (Eqn 1)(Table 2)which fulfill all the validation up to significant level were considered as QSAR eqn.1 respectively.

pIC_{50} = [14.5281(± 1.725)] +nDB [0.200(± 0.0635)] +RDF080u [0.038(± 0.0070)]+E3s [-1.800(± 0.510)] +R6u+ [22.603(± 2.433)] +RTe

[-0.506(± 0.083)] ----------Eqn 1

Table 2: QSAR statistics of significant equation 1

Eqn. no.n	N	r	r^2	r^2 adj	Std	F	r2bs	Sbs	chance	q2	S_{PRESS}	S_{DEP}	r^2pred	Out-lier
1	62	0.831	0.691	0.664	0.306	25.12	0.699	0.094	0.001	0.62	0.337	0.321	0.33	Nil

n = No. of compounds, r = Coeff.of Correlation, r^2= Coefficient of Determination, std = Standard Deviation, F = Sequential Fischer test value, r^2bs = Bootstrapping r^2 ,q^2 = Cross Validated r^2 ,S_{PRESS} = Predicted residual sum of squares, S_{DEP} = Standard error of prediction, r^2pred = Coefficient of Determination of Prediction

Table 3: Correlation matrix of descriptors used in eqn.1

Descriptor	nDB	RDF080u	E3s	R6u+	Rte
nDB	1.00				
RDF080u	0.404	1.00			
E3s	0.067	0.470	1.00		
R6u+	0.453	0.500	0.270	1.00	
RTe	0.178	0.184	0.205	0.471	1.00

The selected models has correlation coefficient more than (r=0.800), which accounts for more than 69% of the variance in the activity, also the inter-correlation among the parameters is less than 0.500 (Table 3).

The equation shows, that in multi-variant model, dependent variable can be predicted from a linear combination of the independent variables. The P value is less than 0.01 for each physiochemical parameters involved in model generation. The data showed overall internal statistical significance level better than 99.9% as it exceeded from the tabulated F (5,62 α 0.001) = 5.25 Models were further tested for outlier by Z-score method and no compound was found to be an outlier, which suggested that the models are able to explain the structurally diverse analogs that are helpful in designing of more potent compounds using physiochemical parameters.

A model selected based on various statistical approaches were used to confirm the robustness and practical applicability of equations. Equation showed probability of chance correlation is less than 0.1% in randomize biological activity test. Bootstrapping technique were employed to confirmed the contribution of descriptors of the molecules to the activity were equi-intense or of different rank. The value of bootstrapping squared correlation coefficient and bootstrapping standard deviation implies that the equations are proper representative of the group of analogs The internal consistency of the training set was confirmed by using leave one out (loo) cross validation method to ensure the robustness of the equations. Equation showed good internal consistency (q^2 = <0.62), which reduces the probability of coincidental correlation of the expression. Although equation showed good internal consistency; they may not be applicable for the analogs which were never used in the generation of the correlation. Therefore, the external extrapolation power of the equations was further authenticated by a test set of twenty nine compounds. A value of predictive squared correlation coefficient (r^2pred) is 0.33 for eqn.1.Test set supported significantly robustness, productiveness and wide applicability of the eqn. 1 (Figure 3, 4 & 5). In general the model fulfills the statistical validation criteria to the significant extent.

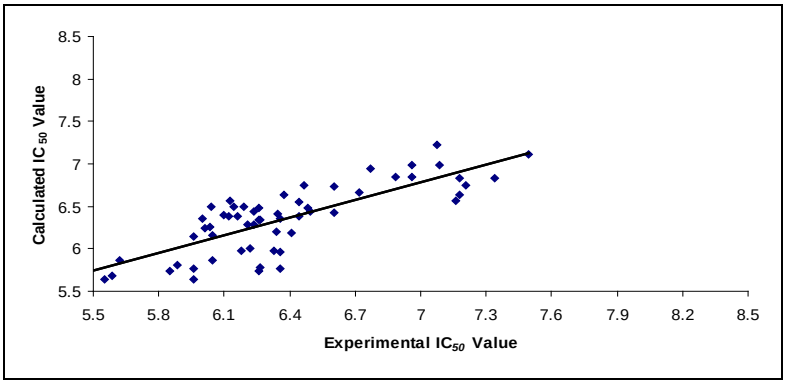

Fig. 3: A Plot between Experimental pIC_{50} and calculated pIC_{50} of training set using eqn.1

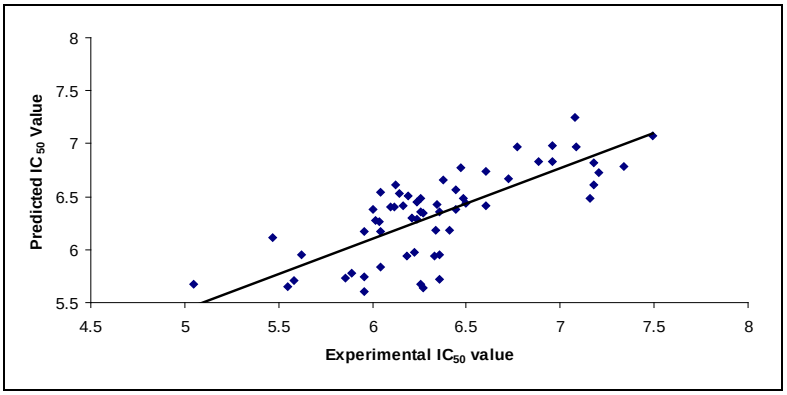

Fig. 4: A Plot between observed pIC_{50} and predicted (LOO) pIC_{50} of Training set using eqn. 1

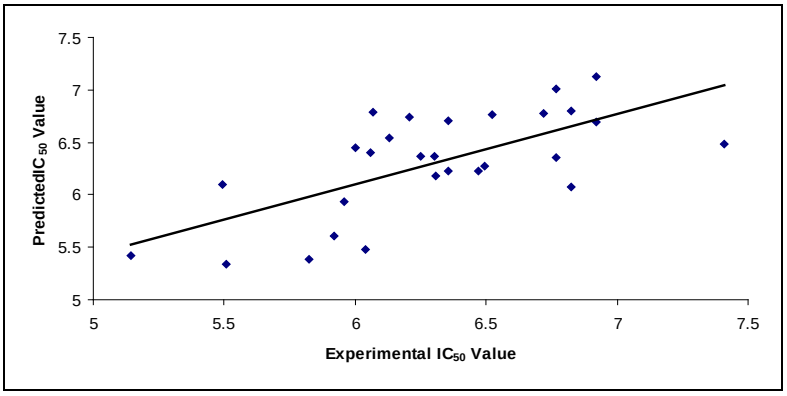

Fig. 5: A Plot between observed pIC_{50} and predicted pIC_{50} of Test set with eqn.1

The positive contribution of nDB[323] belongs to the constitutional descriptor related to no. of double bond independent on molecular connectivity and conformation atom suggested that the double bonds is decisive in the interaction with receptor. RDF080u[324] is contributing positively to the biological activity and belongs to the radial distribution function (RDF) 8.0 /unweighted is a molecular descriptor obtained by the radial basis functions centered on different interatomic distances (from 0.4A to 15.5 A). The RDF of an ensemble of N atoms can be interpreted as the probability distribution to find an atom in a spherical volume of radius r. The RDF used in this work is as follows:

$$g(r) = f\sum_{1}^{N-1}\sum_{j>i}^{N} A_i A_j e^{-B(r-r_{ij})^2}$$

$$1\Big/\sqrt{\sum_{r}[g(r)]^2}$$

Where f is a scaling factor, N is the number of atoms, A are atomic properties of atoms i and j, B is smoothing parameter which defines the probability distribution of the individual distances, rij is distance between the atoms i and j, g(r) was calculated at a number of discrete points with defined intervals. Each molecule was represented by a vector of length 32. The parameter B was set to 25 Å-2 corresponding to a total resolution of 0.2 Å in the defined distance r. The RDF for the structure derivations was calculated with the atomic properties. The RDF code has been proven to be a good representation for the 3D structure which has several merits like independence from the number of atoms; unambiguity regarding the three-dimensional arrangement of the atoms and invariance against translation and rotation of the entire molecule. RDF080u is radial distribution function at 8.0 interatomic distance unweighted by Van der Waals volume suggested enthalpic contribution to the activity and it might be responsible for the interaction with hydrophobic pocket of the macromolecule. R6u+[325] is the GETAWAY descriptors, the GETAWAY class of descriptors represents [Geometry, Topology and Atom-Weights Assembly] group of descriptors, which are based on a leverage matrix. These molecular descriptors match the three dimensional molecular geometry provided by the molecular influence matrix and atom relatedness by molecular topology, with chemical information by using various atomic weight schemes like atomic mass, polarizability, Van der Waals volume, and electronegativity. Therefore, this class of descriptors is highly sensitive to the 3-dimensional molecular structure. GETAWAY descriptors are used to compare molecules or even conformers taking into account their molecular shape, size symmetry and atom distributions.

Positive contribution of R6u$^+$ descriptor encoding both geometrical information given by the influence molecular matrix and the topological information given by the molecular graph is significant for the activity.

E3s is the symbol corresponds to 3rd component accessibility directional whim index/weighted` by atomic elecrotopological states. It is molecular among the WHIM descriptor to the obtained on statistical indices of the atom projected on to 3 principal component obtained from weighed covariance matrices of the atomic coordinates.E3s contributing negatively to the biological activity was suggesting that topological of the molecule is important for drug receptor interactions.

RTe contribute negatively to the biological activity and indicating that the geometry of the molecule is decisive parameter in ligand receptor interaction. RTe is among the GETAWAY descriptor considers the leverage-weighted total index/ weighted by atomic Sanderson electro negativities. The negative contributions suggest that non-polar substitution is favorable.

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