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Role of Equalized Electronegativity in Modeling HIV-RT Inhibitory Activity

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ABSTRACT

The present paper deals with the investigation of HIV-RT inhibitory activity of 45 compounds. Different topological parameters, including distance based topological and connectivity indices have been chosen for modeling pIC50 activity of these compounds. The MLR shows that the best model is obtained using a five parametric model containing Jhete, Jhetp, 4χ, logP, χeq. The QSAR model derived from the above mentioned descriptors were found to be statistically significant and exhibited superior predictive power. The correlation between calculated and experimental activity was 0.79 and the reliability of the model was validated with leave-one-out cross-validation method. Its predictive capability was further validated using a test set of 11 inhibitors similar to the training set of inhibitors.

Keywords: *HIV-RT, connectivity indices, log P, QSAR, MLR*

Introduction

When Human Immunodeficiency virus attacks the living system, the result is very serious as it breaks down the body's immune system and results into a deadly disease known as AIDS [1,2] This virus is a type of retrovirus which has a reverse transcriptase (RT). Scientists who have worked for many years took interest in this field and ultimate solution to this problem is obtained in the form of HIV-RT, an enzyme which converts viral RNA into a double stranded viral DNA which allows HIV to integrate into human

Computational Details

The structural details of the 45 compounds are given in Table 1.It is divided into training (34 compounds) and test set (11). The topological indices used for modeling HIV-RT inhibitors were calculated using DRAGON [13] software and are presented in Table 2. This table also includes observed activity value of the compounds used in the present study (pIC_{50}).The correlation among the topological indices is calculated by using correlation matrix which is reported in Table 3.While performing variable selection for multiple regression using all the DRAGON descriptors together with equalized electronegativity we observed that out of all the descriptors used equalized electronegativity (χ_{eq}) is the descriptor to start one-variable modeling of HIV-RT inhibition. Also, that all the models obtained during variable selection invariably contain χ_{eq} as one of the correlating descriptor indicating that χ_{eq} plays a dominating role in modeling HIV-RT inhibition. The results obtained herein indicated that more reliable models can be obtained when χ_{eq} is combined with other topological indices.

At this stage it is worthy to mention that when two or more atoms initially of different electronegativities combine chemically, they adjust to same intermediate electronegativity with in the compound. That is, the electron will flow from the more electronegative atom creating a partial positive charge on the former and partial negative charge on the later. As the positive charge on the electropositive atom increases, its effective nuclear charge increases. Hence, its electronegativity increases. The same trends happening in the opposite direction for the more electronegative atom until two have the same electronegativity. This principle has gained wide acceptance [12-16]. In the

frame of the Sanderson's principle [17], it is generally believed that partial charge acquired by an atom through chemical combination is proportional to the difference between the final equalized electronegativity and the initial pre-bonded electronegativity charge conservation equation leads to a general expression for equalized electronegativity (χ_{eq})

$$\chi_{eq} = N/\Sigma\ V/X \quad [1]$$

Where N is the total number of atoms in the species formula, V is the number of atoms of a particular element in the species formula and χis the electronegativity of particular atom. Earlier Agrawal and Khadikar[18] have successfully used equalized electronegativity for modeling toxicity of nitrobenzene derivatives in which they have obtained reasonably good results by combining χ_{eq} with other topological indices. There also they observed that out of several descriptors used it was χ_{eq}alone which gave statistically significant one-variable model. In the present study therefore, we have used χ_{eq} along with few other topological indices for modeling HIV-RT inhibitors.

Balaban Heteroatom Index (J_{het})

This is an extension of Balaban index (J) [19-21] to molecules containing heteroatoms. In the case of hetero atoms differentiation is made between the atoms of different kinds by modifying the corresponding elements of the distance matrix **D**. For instance, the following modification was suggested for the diagonal elements:

$$(\mathbf{D})_{ii} = 1 - (Z_c / Z_i) \quad [2]$$

Where $Z_c = 6$ and Z_i is determined by the number of all electrons of atom i or namely Z_i is the atomic number of given elements.

The off-diagonal elements of the modified distance matrix for heteroatom systems are given by the following equation:

$$(\mathbf{D})_{ij} = \Sigma\ k_r\ r \quad [3]$$

Where, the summation is over r bonds.

The bond parameter k_r is given by the following expression:

$$k_r = 1/ w_r\ X\ (Z_c)^2 / (Z_i + Z_j) \quad [4]$$

Where w_r is the bond weight with values of 1, 1.5,2, and 3 for single, an aromatic, double and triple bond respectively.

Randic Molecular Connectivity Index

The branching or connectivity index originally defined by Randic [22] is referred to as the path-1 molecular connectivity $^1\chi$. The value of $^1\chi$ reflects both the size and the branching of the structure. It is related to the size of the molecule because when extra atoms and bonds are added, more terms are added to the summation, and the value grows.$^1\chi$is also related to the degree of branching of the molecule because, when more branching occurs, the denominators for those terms become larger and the terms themselves become smaller, thus decreasing the overall value for the index.Randic molecular connectivity index is defined as

$$\chi = \sum_{edges\ ij} \left(D_i D_j\right)^{-1/2} \quad [5]$$

D_i and D_j - the edge degrees (atom connectivity) of the molecular graph.

Randicindices of different orders

$$^m\chi = \sum_{path} \left(D_i D_j ... D_k\right)^{-1/2} \quad [6]$$

logP- Partition Coefficient [23-24] (Lipophilicity)

$$\log\ P_{oct/wat} = \log\left(\frac{[solute]_{octanol}}{[solute]^{un-ionized}_{water}}\right) \quad [7]$$

Different mod els were obtained using one to five correlating parameters. The quality and the regression parameters of these models were also calculated. The comparison of the calculated activity using the most appropriate model (model 18) is made with the experimental activity. Fig. 1 records correlation between experimental and estimated activities of training sets.

Results and Discussion:

The compounds used in the present study have been listed in Table 1. Those with * denotes the compounds used for test set and remaining are in the training set. The topological parameters along with biological activity in the form of pIC50have been summarized in Table 2. Table 3 demonstrates the correlation matrix

showing inter correlation among all the parameters. A close observation of this table clearly indicates that:

1. No mono-parametric correlation is capable ofmodeling the pIC50 value of present set of compounds;however logP, J_{hetp} and $^{\chi}_{eq}$ are the most suitable parameters to be used in multiparametric modeling.

2. $^{4}\chi$ and J_{hete} are moderately correlated whereas J_{hete} and J_{hetp} also show good correlation.However, this correlation has a lower magnitude than the previous one.

The entire data setis divided into training and test sets. The training set was subjected to regression analysis using NCSS software. All thestatistically significant models along with their quality have been summarized in Table 4. This Table also includes the values of Pogliani's quality factor Q [25-27], which is the ratio of R and Se.

The best three, four and five-parametric models, which are most significant, are given below:

(i) Three-variable model(Model 14, Table-4)

$pIC_{50=}$-2.4300±(0.7833) J_{hetp}+0.4901±(0.1521) logP-6.1642±(1.2395) χ_{eq}+23.6746

N=34, R^2=0.6156, R^2_A=0.5771, Se=0.0677, F=16.012, Q=11.5847

(ii) Four-variable model(Model 17, Table-4)

$pIC_{50=}$-11.4322±(2.3692) J_{hete}-4.5078±(0.8445) J_{hetp}+2.3568±(0.4961) $^{4}\chi$-5.3358±(1.0854) χ_{eq}+33.1638

N=34, R^2=0.7332, R^2_A=0.6964, Se=0.0574, F=19.924, Q=14.9176

(iii) Five-variable model(Model 18, Table-4)

$pIC_{50=}$-9.6436±(2.2178) J_{hete}-4.0804±(0.7726) J_{hetp}+0.3416±(0.1207) logP+2.1044±(0.4540) $^{4}\chi$-5.2982±(0.9741) χ_{eq} + 28.6878

N=34, R^2=0.7926, R^2_A=0.7555, Se=0.0515, F=21.399, Q=17.2870

1. When 4χ is added to three-variable model, then the value of R^2 shows significant improvement. Also the adjusted R^2 value changes from 0.5771 to 0.6964, suggesting that the addition of $4\chi$is favourable.

2. Further improvement is observed when J_{hete}, J_{hetp}, logP, 4χ and $^{\chi}$eq have been taken together resulting into a five-parametric model (model 18, Table 4). Here R^2 is 0.7926 and Pogliani's quality factor has a value 17.2870. This value is the highest among all the models.

Therefore the five parametric model is the best model for modeling the pIC_{50} activity of compounds used in the present study.

From the calculations, it is observed that statistically significant models start pouring from three-variable model (model-14, Table 4). Also, that the proposed models invariably contain equalized electronegativity (χ_{eq}) as one of the correlating parameters. This demonstrates the dominating role of χ_{eq} in modeling HIV-RT inhibitors. Further it is also observed that the proposed models contain logP as correlating parameter. This shows that hydrophobicity is another important parameter for the exhibition of the activity. It is interesting to mention that in all the proposed models the coefficient of χ_{eq} is negative, while that of logP is positive. This means that increase in the hydrophobicity and decrease in the equalized electronegativity is favourable for the exhibition of the activity. The proposed modelsshow that Balaban type indices also support the exhibition of the activity. Their negativecoefficients all over indicate that decrease in their magnitude favours exhibition of the activity.

It is interesting to mention that in all the above cases, both R^2 and R^2_A goes on increasing with each addition of the correlating parameters. Naturally R^2 will always increase with each addition of correlating parameters. However, R^2_A will increase if the added parameter is favourable for the exhibition of activity otherwise it will decrease in our case. Since R^2_A goes on increasing indicating that the added parameter is favorable for the exhibition of the activity.

The best five-parametric model was used for estimating the pIC_{50} value of training set. Such values are reported in Table 5. The predictive potential of this model has been obtained by plotting a graph between observed pIC_{50} and estimated pIC_{50} values. Such correlation is depicted in Fig. 1.

To validate the model cross validation parameters have been calculated and they are reported in Table 6. It is an established fact that PRESS is a good estimate of the real predictive power of the model. If PRESS is smaller than SSY, the model predicts better than chance and can be considered statistically significant. Table 6

shows that in this regard, all the models proposed by us are better than chance and are statistically significant. The ratio PRESS / SSY can be used to calculate the approximate confidence interval of the prediction of new compounds. To be a reasonably good QSAR model, this ratio should be smaller than 0.4. The models proposed by us are having this ratio smaller than 0.4 and therefore, the model-18 has excellent predictive power. The developed models are cross-validated by leave-one-out method. Another cross-validated parameter related to uncertainty of prediction, the PSE, has also been calculated. The lowest value of PSE for model 18 supports its highest predictive potential (power).The low value of PSE and S_{PRESS} and high value of R^2_{CV} suggest that the five-parametric model is most appropriate in predicting pIC_{50} value of present set of compounds.

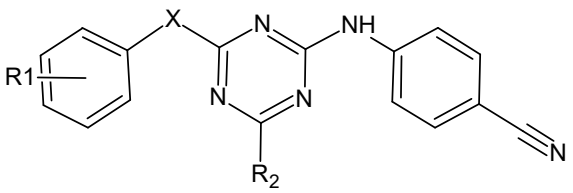
This model was further validated by estimation of pIC_{50} value for the test set. The results are reportedin Table 7. A close look at this table reveals that estimated activities are in good agreement with the observed activities. Hence, model 18 can be used for modeling the pIC_{50} activity of present set of compounds. The correlation potential for the test set is 0.835, which is better than the correlation potential of the training set.

Conclusions:

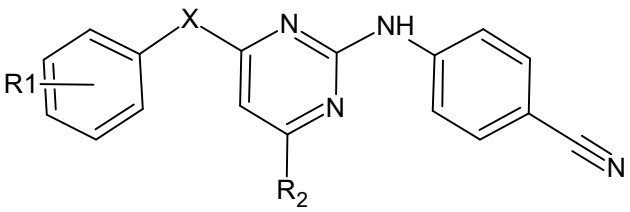
Following conclusions may be drawn.

1. The topological indices in combination with equalized electronegativity are best suitable for modeling the anti HIV activity of present set of compounds.
2. Topological indices alone are not able to model the biological activity in present set of compounds.
3. Negative coefficients of Balaban type indices suggest that they have retarding effect towards the pIC_{50} values, hence in future designing of potent compounds their lower values will give results.
4. Higher value of logP will favour the activity as its coefficient is positive in the model.
5. Due to negative coefficient of χ_{eq}, lowelectronegativity value will enhance the biological activity.

Table 1: Structural details of compounds used in the present study.



Compd.	R1	X	R2
1	2,4-diCl	CH_2	NH_2
2	2,4,6-triCl	CH_2	NH_2
3	2,4,6-triMe	CH_2	NH_2
*4	2,6diCl	CH_2	Cl
5	2,6diCl	CH_2	NHMe
6	2,6diCl	CH_2	NMe_2
7	2,6diCl	CH_2	NHOMe
*8	2,6diCl	CH_2	NHOEt
9	2,6diCl	CH_2	SMe
10	2,6diCl	CH_2	SH
11	2,6diCl	CH_2	OMe
*12	2,6diCl	CH_2	OH
13	2,6diCl	CH_2	F
14	2,4,6-triMe	NH	H
15	2,6-diMe-4-Me	NH	H
*16	2,6-diMe-4-Br	NH	H
17	2,6-diMe-4-CN	NH	H
18	2,4,6-triMe	O	H
19	2,4,6-triMe	S	H
*20	2,4,6-triMe	S	NH_2
21	2,6-diMe	O	NH_2
22	2,6-diMeO	O	NH_2
23	2,4,6-triCl	O	NH_2
*24	2,4,6-triBr	O	NH_2
25	2,6-diCl-4-F	O	NH_2
26	2,6-diBr-4-Me	O	NH_2
27	2,6-diMe-4-Br	O	NH_2
*28	2,6-diMe-4-Cl	O	NH_2



29	2,4,6-triMe	NH	H
30	2,6-diMe-4-CN	O	H
31	2,6-diMe-4-Br	O	H
*32	2,6-diMe-4-Br	**S**	H
33	2,4,6-triMe	O	H
34	2,4-diBr-6-F	NH	H
35	2,4,6-triCl	NH	H
*36	2,6-diCl-6-Me	NH	H
37	2,6-diBr-4-Me	NH	H
38	2,6-diMe-4-Br	NH	H
		*40	

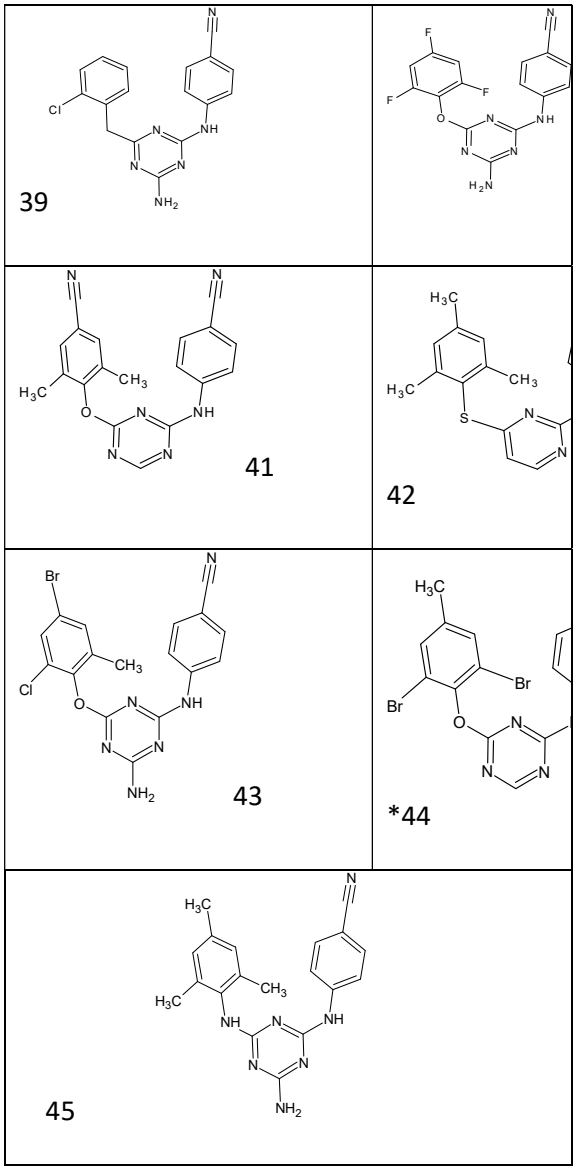


Table 2.Calculated values of the topological parameters for the compounds used in the present study with equalizedelectronegativity values and their experimental pIC_{50} values

Compd. No.	pIC_{50}	J_{hetp}	J_{hete}	$^4\chi$	logP	χ_{eq}
1	7.85	1.443	1.966	7.136	5.03	2.437
2	8.85	1.487	2.008	7.755	5.55	2.460
3	9.10	1.478	1.991	7.755	5.40	2.356
4*	5.97	1.476	2.003	7.230	6.00	2.460
5	8.15	1.474	2.044	7.368	5.39	2.419
6	6.78	1.491	2.093	7.493	6.08	2.404

7	8.21	1.412	2.081	7.679	5.02	2.438
8*	7.61	1.373	2.088	7.763	5.36	2.421
9	7.74	1.523	2.038	7.368	6.47	2.419
10	7.03	1.479	1.999	7.230	5.90	2.437
11	7.92	1.448	2.055	7.368	5.56	2.419
12*	6.80	1.453	2.004	7.230	5.53	2.456
13	5.28	1.439	2.006	7.230	5.71	2.805
14	9.52	1.296	1.989	7.303	6.39	2.366
15	9.30	1.307	1.998	7.303	6.94	2.430
16*	9.22	1.301	1.993	7.303	6.66	2.395
17	9.00	1.311	1.993	7.418	5.70	2.401
18	9.22	1.178	2.046	7.303	6.28	2.380
19	8.70	1.557	1.955	7.303	6.84	2.365
20*	8.54	1.594	2.026	7.755	6.63	2.369
21	8.51	1.203	2.114	7.230	5.56	2.397
22	7.51	1.166	2.180	7.869	4.27	2.433
23	8.62	1.220	2.137	7.755	6.45	2.505
24*	8.27	1.227	2.131	7.755	6.89	2.492
25	8.14	1.198	2.140	7.755	5.94	2.520
26	8.70	1.223	2.127	7.755	6.62	2.449
27	8.82	1.218	2.122	7.755	6.34	2.414
28*	8.46	1.216	2.124	7.755	6.20	2.417
29	9.00	1.319	1.981	7.303	6.21	2.351
30	8.96	1.209	2.043	7.418	5.41	2.398

31	8.54	1.201	2.042	7.303	6.37	2.393
32*	8.24	1.598	1.952	7.303	6.94	2.376
33	8.54	1.197	2.038	7.303	6.10	2.364
34	9.22	1.303	1.999	7.303	6.38	2.466
35	9.15	1.326	1.999	7.303	6.60	2.460
36*	9.00	1.323	1.993	7.303	6.47	2.417
37	8.68	1.330	1.990	7.303	6.76	2.409
38	8.64	1.324	1.985	7.303	6.48	2.378
39	6.89	1.424	1.968	6.801	4.51	2.415
40*	7.29	1.155	2.147	7.755	4.92	2.551
41	8.40	1.191	2.051	7.418	5.59	2.417
42	8.44	1.590	1.948	7.303	6.66	2.349
43	8.68	1.220	2.129	7.755	6.47	2.518
44*	8.89	1.187	2.056	7.303	6.83	2.517
45	9.00	1.332	2.060	7.755	6.18	2.371

*** Test set**

Table 3: Correlation matrix

	pIC_{50}	J_{hetp}	J_{hete}	$^4\chi$	logP	χ_{eq}
pIC_{50}	1.0000					
J_{hetp}	-0.3238	1.0000				
J_{hete}	-0.0783	-0.6138	1.0000			
$^4\chi$	0.1741	-0.2610	0.7188	1.0000		
logP	0.4431	0.0404	-0.2120	-0.0456	1.0000	
χ_{eq}	-0.5348	-0.1544	0.2816	0.0888	-0.1304	1.0000

Table 4.Regression parameters and quality of correlation of training set

Model No.	Parameters Used	Ai=(1……5)	B	Se	R^2	R^2_A	F-ratio	Q=R/Se
1	J_{hete}	-1.0896±(2.5160)	10.6063	0.1055	0.0058	0.0000	0.188	0.7219
2	$^4\chi$	0.8480±(0.6237)	2.0823	0.0251	0.0546	0.0251	1.848	9.3094
3	J_{hetp}	-2.4445±(1.1434)	11.6545	0.0989	0.1250	0.0976	4.571	3.5749
4	logP	0.5715±(0.2138)	4.9694	0.0956	0.1825	0.1570	7.140	4.4686
5	χ_{eq}	-6.4581±(1.5531)	24.0632	0.0852	0.3508	0.3305	17.290	6.9517
7	$^4\chi$ χ_{eq}	1.0213±(0.4938) -6.6968±(1.4837)	17.0517	0.0812	0.4295	0.3927	11.670	8.0710
8	J_{hetp} χ_{eq}	-2.5104±(0.8935) -6.5212±(1.4089)	27.5771	0.0773	0.4826	0.4492	14.550	8.9870
9	logP χ_{eq}	0.5051±(0.1719) -6.0923±(1.4011)	20.1569	0.0766	0.4922	0.4599	15.025	9.1589
10	χ_{eq} J_{hete} logP	-6.3164±(1.4361) 1.5333±(1.8988) 0.5263±(0.1749)	17.4473	0.0770	0.5030	0.4533	10.122	9.2107
11	J_{hete} J_{hetp} $^4\chi$	-14.4222±(3.0483) -5.1418±(1.1110) 2.6533±(0.6555)	24.9501	0.0764	0.5109	0.4620	10.445	9.3557
12	J_{hetp} $^4\chi$ χ_{eq}	-2.1460±(0.9084) 0.7208±(0.4781) -6.6805±(1.3849)	22.1189	0.0758	0.5190	0.4709	10.790	9.5042
13	J_{hete} J_{hetp}	-3.7404±(2.2677) -3.5538±(1.0754)	35.2443	0.0752	0.5256	0.4781	11.078	9.6407

	χ_{eq}	-5.9629±(1.4125)						
14	logP $^4\chi$ χ_{eq}	0.5033±(0.1608) 1.0148±(0.4358) -6.3307±(1.3147)	13.2045	0.0716	0.5699	0.5269	13.253	10.5434
14	J_{hetp} logP χ_{eq}	-2.4300±(0.7833) 0.4901±(0.1521) -6.1642±(1.2395)	23.6746	0.0677	0.6156	0.5771	16.012	11.5847
15	J_{hete} J_{hetp} logP χ_{eq}	-2.4651±(2.0739) -3.1240±(0.9727) 0.4514±(0.1545) -5.8245±(1.2638)	29.0356	0.0673	0.6334	0.5829	12.527	11.8256
16	J_{hetp} logP $^4\chi$ χ_{eq}	-2.0627±(0.7857) 0.4911±(0.1471) 0.7260±(0.4133) -6.3240±(1.2020)	18.1689	0.0655	0.6525	0.6046	13.615	12.3324
17	J_{hete} J_{hetp} $^4\chi$ χ_{eq}	-11.4322±(2.3692) -4.5078±(0.8445) 2.3568±(0.4961) -5.3358±(1.0854)	33.1638	0.0574	0.7332	0.6964	19.924	14.9176
18	J_{hete} J_{hetp} logP $^4\chi$ χ_{eq}	-9.6436±(2.2178) -4.0804±(0.7726) 0.3416±(0.1207) 2.1044±(0.4540) -5.2982±(0.9741)	28.6878	0.0515	0.7926	0.7555	21.399	17.2870

Table 5: Observed and estimated values of pIC_{50} (training set) using model no 18

Compd. no	Actual pIC_{50}	Predicted pIC_{50}	Residual
1	7.85	7.66	0.19
2	8.85	8.44	0.41
3	9.10	9.14	-0.04
5	8.15	7.49	0.66
6	6.78	7.53	-0.75
7	8.21	7.82	0.39
9	7.74	7.72	0.02
10	7.03	7.69	-0.66
11	7.92	7.55	0.37
13	5.28	5.78	-0.50
14	9.52	9.23	0.29
15	9.30	8.95	0.35
17	9.00	8.96	0.04
18	9.22	9.06	0.17
19	8.70	8.66	0.04
21	8.51	7.81	0.70
22	7.51	8.04	-0.53
23	8.62	8.35	0.27
25	8.14	8.16	-0.02
26	8.70	8.79	-0.09
27	8.82	8.95	-0.13
29	9.00	9.24	-0.24
30	8.96	8.81	0.16
31	8.54	8.96	-0.42
33	8.54	9.08	-0.54
34	9.22	8.58	0.64
35	9.15	8.59	0.56
37	8.68	8.98	-0.30
38	8.64	9.13	-0.49
39	6.89	6.96	-0.07
41	8.40	8.77	-0.37
42	8.44	8.61	-0.17
43	8.68	8.37	0.31

Table 6: Cross validation parameters for the proposed models

Model No.	Parameters used	PRESS	SSY	PRESS /SSY	R^2_{CV}	S_{PRESS}	PSE
14	J_{hetp}logpχ_{eq}	9.6744	15.4904	0.6245	0.3755	0.5679	0.2845
17	J_{hete} J_{hetp}, $\chi_{eq}{}^4\chi$	6.714	18.4508	0.3639	0.6361	0.4812	0.1975
18	J_{hetp}, $J_{hete}\chi_{eq}$ logp $^4\chi$	5.2195	19.9452	0.2617	0.7383	0.4318	0.1535

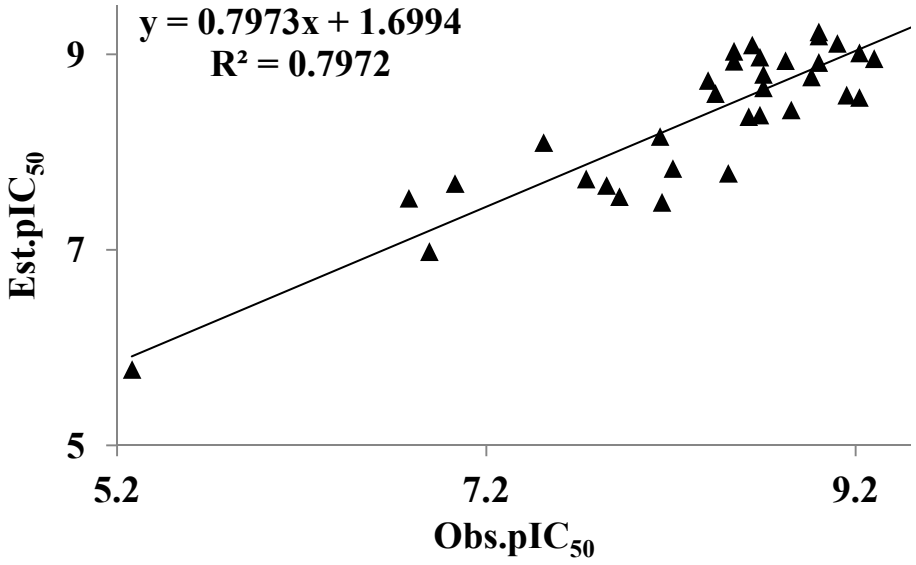
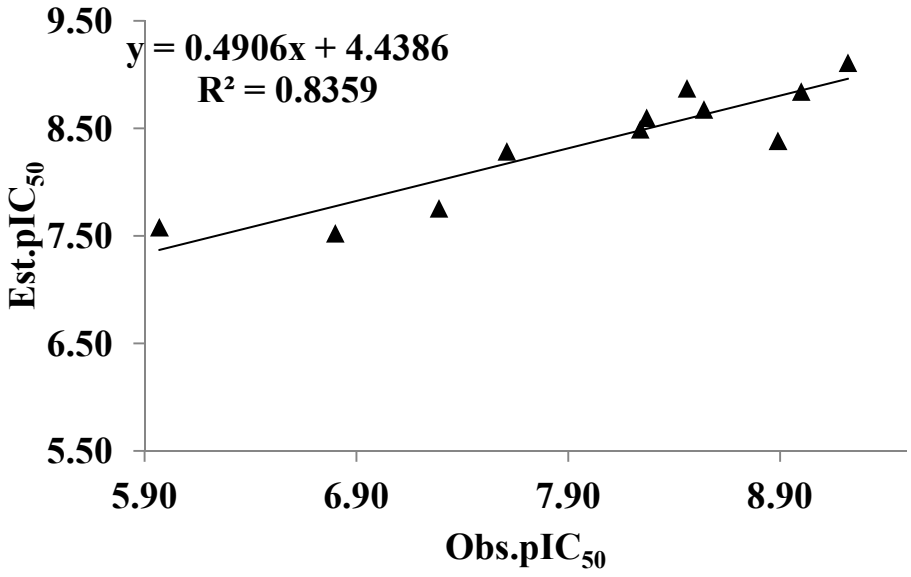


Figure 1: Correlation between observed and estimated pIC_{50} using training set (model 18)

Table 7: Observed and estimated values of pIC_{50} of test set molecules using model 18

Compd. No.	Obs.pIC_{50}	Est.pIC_{50}	Residual
4	5.97	7.58	-1.61
8	7.61	8.29	-0.68
12	6.80	7.52	-0.72
16	9.22	9.11	0.11
20	8.54	8.68	-0.14
24	8.27	8.60	-0.33
28	8.46	8.87	-0.41
32	8.24	8.49	-0.25
36	9.00	8.84	0.16
40	7.29	7.76	-0.47
44	8.89	8.39	0.50

Figure 3.Correlation between observed and estimated pIC_{50} of test set by external cross validation using model 18



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