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QSAR Modeling of Bisbenzofuran Compounds using 2D-Descriptors as Antimalarial Agents

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ABSTRACT

In the present study we have performed Quantitative structure activity relationship (QSAR) analysis for 43bisbenzofuran derivatives to estimate the antimalarial activity using some 2D descriptors. Several significant QSAR models has been calculated for predicting the antimalarial activity ($-\log IC_{50}$) of these molecules by using the multiple linear regression (MLR) technique. Among the obtained QSAR models, a four parametric model was most significant having R^2=0.9502. An external set was used for confirming the predictive power of the models. High correlation between experimental and predicted antimalarial activity values, was obtained in the validation approach that displayed the good modality of the derived QSAR models.

Keywords; *bisbenzofuran derivatives, antimalarial activity, 2D descriptors, QSAR, MLR*

Introduction

According to the World Health Organization (WHO), malaria is globally recognized as serious problem of public health, mainly in the tropical and subtropical regions of the world. Thus Malaria is an infectious disease which is caused by the protozoa of the genus *Plasmodium*. Commonly four species of the parasite cause infection, *i.e*., *Plasmodium ovale*, *P. vivax*, *P. malariae*and *P. Falciparum.* Among them P. *Falciparum* being the most virulent to humans. The introduction of parasites in human organism can be through the bite of a female *Anopheles* mosquito, and it can also be injection or transfusion of infected blood and through the hypodermic syringes. It effects 40% population of more than a hundred countries and considered as one of the diseases that caused already great damage to millions of people [1-5]. Due to this about 300 million cases and at least one million consequent deaths are estimated annually. About 40% of malaria cases are registered in the world and about 90% deaths are mainly caused due to*P. falciparum.* For the treatment of malaria drugs such as chloroquine, mefloquine, pyrimethamine, dapsone, and cycloguanil are being used for years. But the resistance against malaria parasite strain is increasing continuously producing a big obstacle to chemotherapy of malaria disease[6-15].The massive use of classical antimalarials promoted fast selection of drug–resistant strains of *P. falciparum*, which requires an urgent development of new antimalarial drugs. Soidentification and design of novel drug molecules specifically affecting these targets could lead to better treatment of malaria. Recently the antimalarial activity of bisbenzofuran has generated interest among the drug researchers which has displayed activityagainst several strains of malaria. It has limited role to treat the diseases because of

protonation of its amidine group at physiological pH, pentamidineand also shows low oral availability. Drugrequiresparentral administration which makes the treatment less practical in rural areas. Pentamidine is tolerated by most patients in spite of some reported serious adverse effects [16, 17, 18].In this context it is very appropriate to search for options to find a potent antimalarial compound with improved potency and oral availability. Computational chemistry is an important tool to rational drug design. The quantitative structure-activity relationship (QSAR) approach by Hansch et al. helps to correlate the specific biological activities of compounds with the molecular properties of the compounds. The authors have successfully reported use of topological parameters for modeling antimalarial activity of 4-pyridones against *P. falciparum* T9-96 strains[19].

Materials and Methods

In the present work an attempt was made to find out a mathematical model which correlates the possible structural requirements and biological activity of in order to design of new and more potent compounds with strengthened biological activities. An analysis using the MLR method is applied to a series of 43bisbenzofurans derivatives with known biological activity[20].The biological activity has been given in terms of negative log of IC_{50} in order to convert the data into free energy change related values.

Structural details of the compound having antimalarial activity (bisbenzofurancation) used in present studyare given in Table-1.The parameters used for modeling the activity are VE1_D, VE1_B(e), GATS7p, GATS8p , CATS2D_04_DA, CATS2D_06_PL, B10[N-N], F08[C-C], DLS_07 , Psychotic-80 and cRo5. Here DLS_07 , Psychotic-80 , cRo5 are Drug-like indices descriptors, CATS2D_04_DA, CATS2D_06_PL, B10[N-N], F08[C-C] are 2D Atom Pairs parameters, GATS7p, GATS8p are 2D- autocorrelation parameters [21]and VE1_D, VE1_B(e) are 2D matrix-based descriptors. All these have been calculated using DRAGON software[22] and for regression purpose NCSS was used [23]. The calculated values along with biological activity –log $IC_{50}$are given inTable-2.The entire data set given in table 1 has been divided into training and test set and efforts have been made for obtaining the best suitable model for modeling the -log IC_{50} value. We have taken 31 compounds for training set and 12 compounds as test set. The generation of training and test sets is done on random basis. For statistical validation, variety of statistical parameters was calculated. All these statistically significant correlation models for the training set have been reported below along with their statistical parameters.

RESULT AND DISCUSSION:

The correlation matrixes of these parameters arereportedin Table-3 which clearly reveals that F08[C-C] is highly correlated with VE1_D and similarly B10[N-N] is highly correlated with CATS2D_06_PL and Psychotic-80 is highly correlated F08[C-C]. Hence while dealing with these parameters the collinearity defect should be checked.

Now, we will discuss the results obtained in successive regression analysis. It is pertinent to mention that the parameter which are auto-correlated should not be used in multiparametric analysis because they may result in to some defect in the model.

Through variable selection four parameters were selected and the data presented in Table-2 was subjected to regression analysis which yields significant models. These models along with their quality are reported in Table-5.

ONE-PARAMETRIC MODEL:

Among all the models, the best one parametric model contains B10 [N-N], having R^2 value equal to 0.8459. The model is as below:

$$\textbf{-logIC}_{50}=2.0051(\pm0.1589)\ B10[N\text{-}N]+0.1149 \quad (4.1.1)$$

N=31, Se = 0.1563, R^2 = 0.8459, R^2_{Adj}= 0.8406, F-ratio = 159.185, Q =5.8830

Here and here after N is total number of compounds ; Se is the standard error of estimation;R^2 is the square of correlation coefficient;R^2_{Adj} is the adjusted R^2;F is the Fisher's ratio and Q is the Pogliani's quality factor[24] which is the ration of R/Se (Pogliani, 1994,1996)

TWO-PARAMETRIC MODEL:

When cRo5 is added to the mono-parametric model, two parametric models are resulted with improved R^2 value. For this model R^2 comes out to be 0.9211and R^2_{Adj} also enhances from0.8406 to 0.9154. The model is reported as under

$$\textbf{IC}_{50}=2.0531(\pm0.1161)\ B10[N\text{-}N]-0.2881(\pm0.0558)\ cRo5+0.3550 \quad (2)$$

N=31 , Se = 0.1138, R^2 = 0.9211, R^2_{Adj}=0.9154, F-ratio = 163.392 , Q =8.4292

THREE-PARAMETRIC MODEL:

F08[C-C] has also been found to be an effective parameter in modeling log IC_{50}. When higher parametric models were tried with B10_N_N_, F08[C-C]as correlating parameters along with VE1_D in modeling the antimalarial activity, a improvement in the quality of the model is observed. For this model, R^2 comes out to be 0.9318.The value of R^2_{Adj} changes from 0.9154 to 0.9242 suggesting that the added parameter is favorable .The model is given below:

$\mathbf{IC_{50}}$=2.1541(±0.1176) B10_N_N_+0.0241(±0.0044) F08[C-C]-0.5575(±0.1052) VE1_D+2.2910 (3)

N= 31, Se = 0.1078, R^2= 0.9318, R^2_{Adj}= 0.9242, F-ratio = 122.890, Q =8.9532

FOUR -PARAMETRIC MODEL:

Finally, by adding 2D- autocorrelation parametersGATS7p atetra - parametric model having R^2=0.9502 is found to be the best model for modeling IC_{50} activity. The model contains B10 [N-N], F08[C-C], GATS7p and VE1_D as correlating parameter. The lowest values of SE and also highest value of F-ratio and Q-value further confirm our results. Addition of GATS7p is justified as R^2_{Adj} changes from 0.9242 to 0.9425. The model is found as under:

$\mathbf{IC_{50}}$= 1.9399 (±0.1235) B10[N-N]+0.0197 (±0.0041) F08[C-C]-0.9062(±0.2920) GATS7p -0.5498(±0.0916) VE1_D+3.3488 (4)

N=31, Se =0.0939, R^2 =0.9502, R^2_{Adj}= 0.9425, F-ratio =124.031, Q =10.3859

A close look at this model revels that out of four parameters contained, two (GATS7p, VE1_D) are having negative coefficients, while two of them are positive (B10 [N-N], F08[C-C]). The predictive potential of the model has been obtained by plotting a graph between observed and estimated activity values and such graph is demonstrated in Fig. 1.

PREDICTIVE POWER BASED ON CROSS VALIDATION:

Leave –one –out cross (leave –one –out) validation procedure"(Chaterjee*et al* .,2000) is being widely used to examine the suitability of predictive power of the model[25]. The obtained results are reported in Table-6 .As stated earlier the predicted residual sum of square (PRESS) is the most important cross-validation parameter accounting for good estimate of the real predictive error of the model. Its value less than SSY (sum of squares of response value) indicates that the model predicts better than the chance and can be considered statically significant. In our study, the value of PRESS is much lower than SSY indicating that all the models obtained are statically significant. The ration of PRESS/SSY can be used to calculate approximate confidence intervals of prediction of new compounds. To be a reasonable and significant QSAR model, the ratio PRESS/SSY should be less than 0.4 (PRESS/SSY < 0.4) and the value of this ratio 0.1 indicates an excellent model. A close observation of Table-6 shows that except the one parametric model (model1, Table4)all other models have the PRESS/SSY ratio more or less or nearer to 0.1 indicating thereby all the proposed models are having best predicting capacity.

R^2_{cv} is the cross validation squared correlation coefficient. The highest R^2_{cv} values 0.948 for four parametric model [(Model-30 and Table-4);Fig.1] confirms our findings. The two important cross-validation parameters uncertainty in prediction (S_{PRESS}) and predictive squared error (PSE) were also calculated. For this model, the value of SSY is highest, whereas, the values of PRESS, PRESS/SSY, S_{PRESS}, and PSE have been lowest, conforming our findings.

Final confirmation is obtained by calculating the estimated values of -log IC_{50} for the entire set of compounds using tetra parametric model and the same has been reported in Table-5.These values are in good agreement with the estimated value. Further confirmation is obtained by plotting a graph between observed and estimated -log IC_{50} values using four parametric model, the predictive power for the model comes out to be 0.9502, suggesting that 95 % variance in the data could be explained using this model. Therefore, this is the best model for modeling -iogIC_{50} values of the compound used in this study. The external predictive power of the model is assessed by predicting pIC50 value of the 9 test set molecules, which are not included in the QSAR model development.

Further, VIF (variance inflation factor), Eigen values (λi), condition number (k), tolerance (T) for all the independent parameters have been calculated or all the independent parameters used in the proposed models and they are reported in Table-7.The collinearity is observed if the value of VIF is greater than 10. In the table all the combination have VIF less

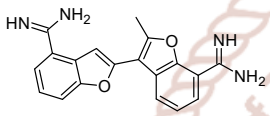
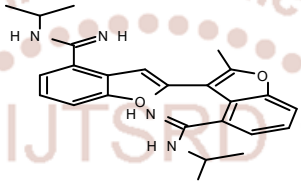
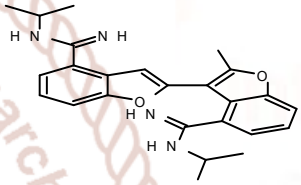
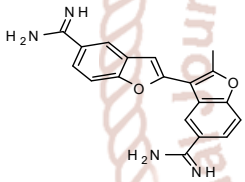
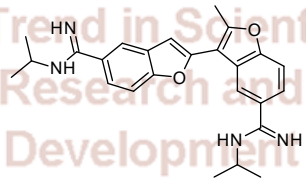
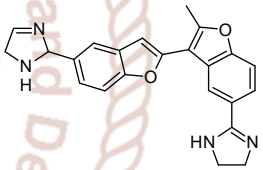
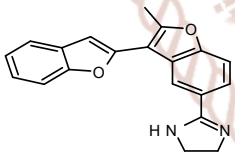
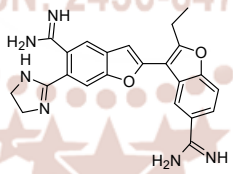
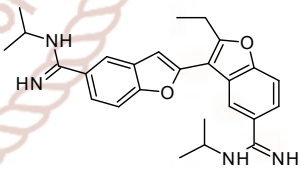
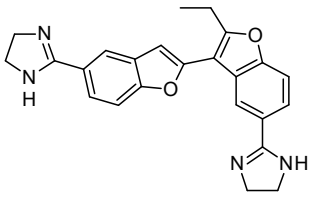
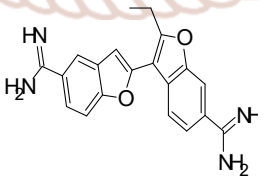
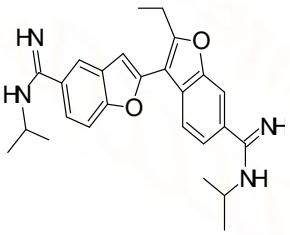
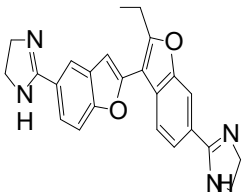
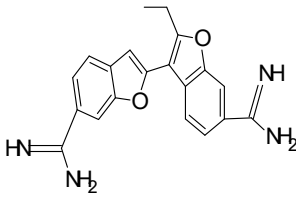
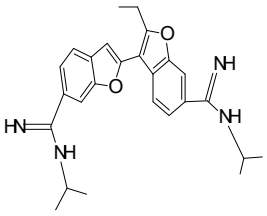
than 10 means all the proposed models are free from collinearity. And if λi, (Eigen value) is found to be greater than 5 then the model will suffer from collinearity. Here all the models have λi value less than 5 so all the models are free from the defect of collinearity. Condition number is another test forcollinearity if its value is found to be >100 then the collinearity exists but results indicate that values always <100 likewise. . Tolerance value equal to 1 or less indicates absence of collinearity Table-7 indicates that all the above mentioned parameters or models discussed in the study are free from multi-collinearity. The ridge traces are recorded in fig.-2 and fig.-3 respectively.

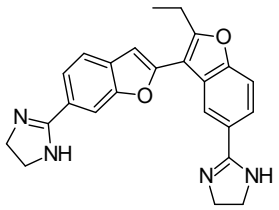
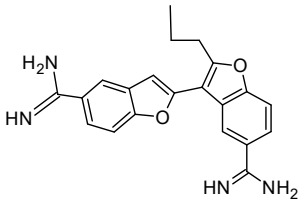
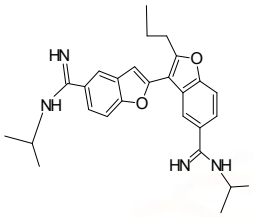
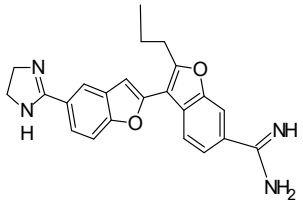
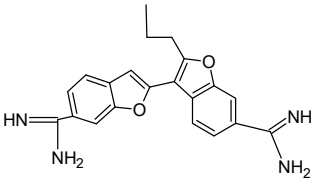
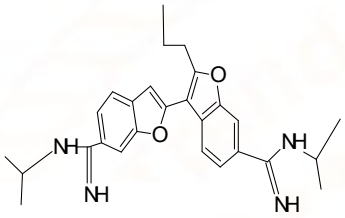
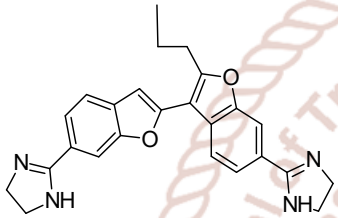
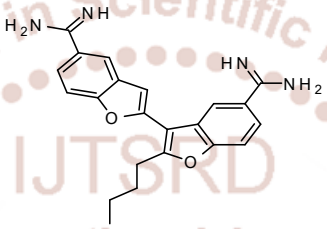
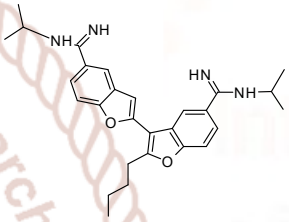
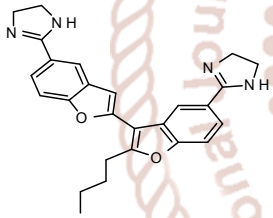
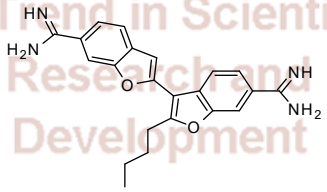
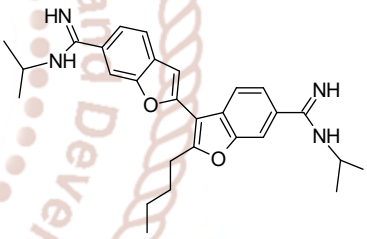
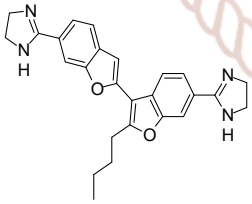
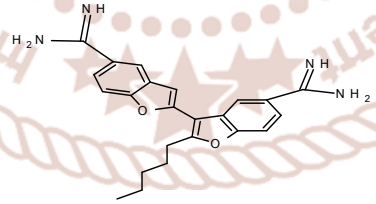
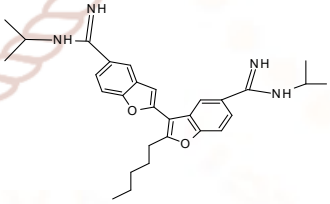
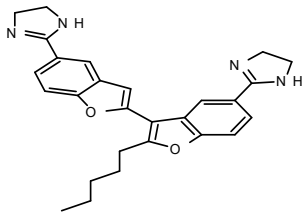
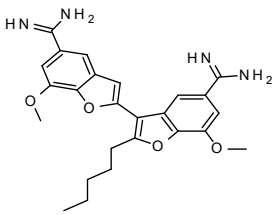
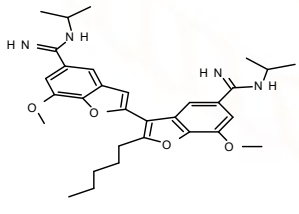
CONCLUSION:

1. Positive coefficient of B10[N-N] suggests that presence/absence of N - N at topological distance 10 plays a dominant role in deciding the antimalarial activity of present set of compounds.

2. The coefficient of both the GATS7p and VE1_D parameters are negative. Therefore molecules having higher value of polarizability and topological distance matrix should be avoided in designing synthesizing new compounds for better activity. Compounds with low value of these parameters will certainly give better activity.

Table 1 Structures of bisbenzofurancation used in the present study

1 	2 	3 
4 	5 	6 
7 	8 	9 
10 	11 	12 
13 	14 	15 

16 	17 	18 
19 	20 	21 
22 	23 	24 
25 	26 	27 
28 	29 	30 
31 	32 	33 
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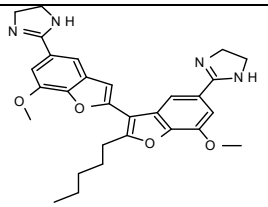
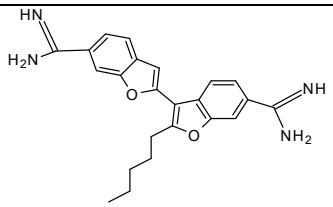
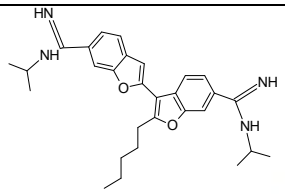
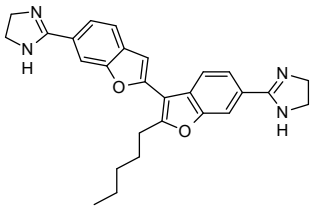
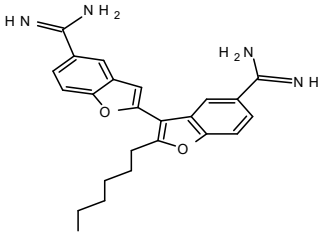
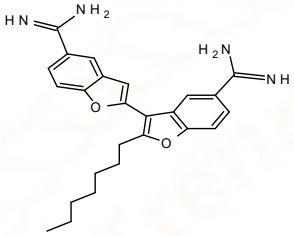
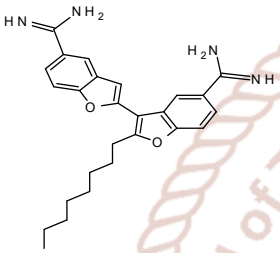
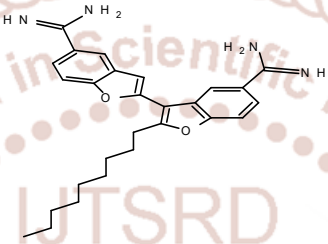
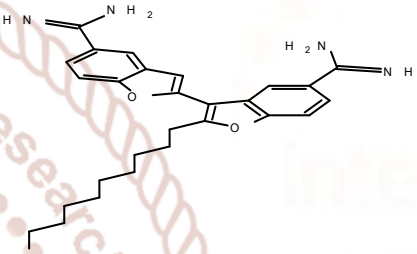
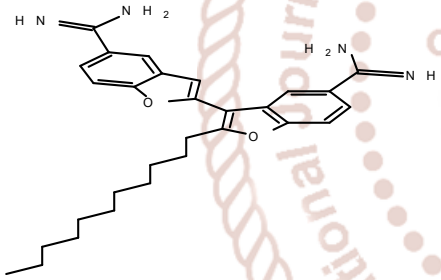
		
37 	38 	39 
40 	41 	42 
43 		

Table -2 values of the calculated descriptors along with their activity values

S. No.	IC_{50}	VE1_D	VE1_B (e)	GATS7p	GATS8p	CATS2D _04_DA	CATS2D _06_PL	B10 [N-N]	F08 [C-C]	DLS_07	Psychotic-80	cRo5
1*	0.068	4.617	4.07	0.978	1.078	2	2	0	10	1	1	1
2*	0.918	5.084	4.05	1.13	1.092	0	0	1	21	1	1	1
3	2.12	4.647	3.939	0.917	1.14	0	3	1	11	1	1	1
4*	0.028	4.541	3.844	1.087	1.054	0	0	0	11	1	1	1
5	0.102	4.987	3.941	1.047	1.102	0	0	0	20	1	1	1
6	0.034	4.843	3.789	1.14	0.98	0	0	0	17	1	1	1
7	0.022	4.294	3.641	1.127	1.032	0	0	0	12	1	1	1
8*	0.003	5.131	3.844	0.987	1.064	0	0	0	18	0.5	1	1
9	0.003	5.045	3.962	1.044	1.153	0	0	0	22	1	0	1
10	0.011	4.908	3.909	1.115	1.028	0	0	0	19	1	1	1
11	0.002	4.599	3.892	1.144	1.223	0	1	0	13	1	1	1
12	0.006	5.038	3.99	1.082	1.087	0	0	0	22	1	0	1
13	0.046	4.894	3.935	1.071	1.09	0	0	0	19	1	1	1
14	0.004	4.599	3.728	1.236	1.176	0	2	0	13	1	1	1
15	0.005	5.038	3.817	1.104	0.96	0	0	0	24	1	0	1
16	0.034	4.908	3.761	1.012	1.161	0	0	0	19	1	1	1
17*	0.041	4.714	3.873	1.109	1.118	0	0	0	16	1	1	1
18*	0.009	5.109	3.97	1.071	1.135	0	0	0	25	1	0	1
19*	0.004	4.866	3.873	1.224	1.081	0	1	0	18	1	1	1
20	0.037	4.683	3.736	1.256	1.142	0	2	0	16	1	1	1
21*	0.036	5.095	3.825	1.127	0.969	0	0	0	27	1	0	1
22	0.353	4.958	3.784	1.006	1.194	0	0	0	22	1	1	1
23*	0.032	4.817	3.877	1.145	1.15	0	0	0	20	1	1	1
24	0.01	5.182	3.974	1.097	1.157	0	0	0	29	1	0	1
25	0.026	5.062	3.922	1.168	1.057	0	0	0	26	1	1	1
26*	0.058	4.779	3.74	1.282	1.171	0	2	0	20	1	1	1
27	0.076	5.159	3.829	1.152	1.004	0	0	0	31	1	0	1
28*	0.164	5.031	3.788	1.043	1.213	0	0	0	26	1	1	1
29	0.067	4.926	3.878	1.087	1.181	0	0	0	23	1	1	1
30	0.02	5.266	3.976	1.063	1.18	0	0	0	32	0.5	0	1
31	0.067	5.156	3.923	1.118	1.088	0	0	0	29	1	0	1
32	0.066	5.329	3.861	1.06	1.043	0	0	0	29	0.5	1	1
33*	0.133	5.661	3.945	1.025	1.129	0	0	0	42	0.5	0	1
34	0.11	5.56	3.9	1.041	1.161	0	0	0	35	1	0	1

35	0.057	4.888	3.741	1.214	1.202	0	2	0	23	1	1	1
36	0.018	5.233	3.83	1.115	1.037	0	0	0	34	0.5	0	1
37	0.133	5.116	3.789	0.998	1.237	0	0	0	29	1	0	1
38	0.364	4.989	3.879	1.056	1.125	0	0	0	26	1	1	1
39	0.279	4.822	3.879	1.049	1.093	0	0	0	27	1	0	0
40	0.694	4.419	3.879	1.042	1.084	0	0	0	28	1	0	0
41	0.296	4.674	3.879	1.037	1.076	0	0	0	29	0.5	0	0
42	0.287	4.952	3.879	1.032	1.069	0	0	0	30	0.5	0	0
43	0.219	5.146	3.879	1.028	1.063	0	0	0	31	0.5	0	0

VE1_D =coefficient sum of the last eigenvector from topological distance matrix (2D matrix-based descriptors)
VE1_B(e)= coefficient sum of the last eigenvector from Burden matrix weighted by Sanderson electronegativity(2D matrix-based descriptors)
GATS7p =Geary autocorrelation of lag 7 weighted by polarizability (2D autocorrelations)
GATS8p =Geary autocorrelation of lag 8 weighted by polarizability (2D autocorrelations)
CATS2D_04_DA= CATS2D Donor-Acceptor at lag 04 (CATS 2D)
CATS2D_06_PL= CATS2D Positive-Lipophilic at lag 06 CATS (2D Atom Pairs)
B10[N-N] =Presence/absence of N - N at topological distance 10 (2D Atom Pairs)
F08[C-C] =Frequency of C - C at topological distance 8 (2D Atom Pairs)
DLS_07= modified drug-like score from Veber et al. (2 rules)(Drug-like indices)
Psychotic-80= Ghose-Viswanadhan-Wendoloski antipsychotic-like index at 80% (Drug-like indices)
cRo5 =Complementary Lipinski Alert index (Drug-like indices)

Table 4.1.3 Correlation matrix

	IC_{50}	VE1_D	VE1_B(e)	GATS7p	GATS8p	CATS2D_06_PL	B10 [N-N]
IC_{50}	1						
VE1_D	-0.290	1					
VE1_B(e)	0.166	0.424	1				
GATS7p	-0.561	-0.170	-0.402	1			
GATS8p	0.084	-0.014	0.026	-0.111	1		
CATS2D_06_PL	0.512	-0.403	-0.251	0.261	0.360	1	
B10[N-N]	0.920	-0.206	0.170	-0.432	0.085	0.628	1
F08[C-C]	-0.214	0.718	0.329	-0.218	-0.123	-0.557	-0.356
DLS_07	0.036	-0.285	-0.131	0.205	0.204	0.203	0.089
Psychotic-80	0.079	-0.394	-0.356	0.257	0.147	0.401	0.177
cRo5	-0.200	0.237	-0.090	0.296	0.189	0.182	0.080

	F08[C-C]	DLS_07	Psychotic-80	cRo5
F08[C-C]	1			
DLS_07	-0.517	1		
Psychotic-80	-0.723	0.343	1	
cRo5	-0.341	0.451	0.453	1

Table 4 Regression Parameters and Quality of Correlation

Model no	Parameters Used	A_i = (1-----4)	B	SE	R^2	R^2_{Adj}	F-ratio	Q=R/SE
01	DLS_07	0.0710 (±0.3618)	0.1155	0.3980	0.0013	0.0000	0.038	0.0906
02	Psychotic_80	0.0609 (±0.1427)	0.1482	0.3970	0.0062	0.0000	0.182	0.1983
03	GATS8p	0.4605 (±1.0130)	-0.3303	0.3968	0.0071	0.0000	0.207	0.2123
04	VE1_B_e_	0.7731 (±0.8536)	-2.8061	0.3927	0.0275	0.000	0.820	0.4223
05	cRo5	-0.2091(±0.1906)	0.3550	0.3902	0.0399	0.0068	1.204	0.5119
06	F08[C-C]	-0.0125(±0.0106)	0.4773	0.3891	0.0456	0.0127	1.386	0.5489
07	VE1_D	-0.4217(±0.2582)	2.2654	0.3811	0.0842	0.0526	2.667	0.7614
08	CATS2D_06_PL	0.2536 (±0.0789)	0.0978	0.3420	0.2626	0.2372	10.327	1.4985
09	GATS7p	-3.0310(±0.8296)	3.4705	0.3296	0.3152	0.2916	13.348	1.7036
10	B10[N-N]	2.0051 (±0.1589)	0.1149	0.1563	0.8459	0.8406	159.185	5.8830
11	B10[N-N] CATS2D_06_PL	2.1527 (±0.2031) -0.0534(±0.0461)	0.1274	0.1554	0.8529	0.8424	81.195	5.9418
12	B10[N-N] Psychotic_80	2.0383 (±0.1604) -0.0665(±0.0567)	0.1482	0.1553	0.8531	0.8426	81.313	5.9462
13	B10[N-N] VE1_D	1.9578 (±0.1595) -0.1531(±0.1063)	0.8738	0.1535	0.8565	0.8463	83.582	6.0286
14	B10[N-N] F08[C-C]_	2.1064 (±0.1645) 0.0076 (±0.0044)	-0.0703	0.1512	0.8608	0.8508	86.559	6.1352
15	B10[N-N] GATS7p	1.8150 (±0.1588) -1.0902(±0.3934)	1.3047	0.1409	0.8791	0.8704	101.768	6.6524
16	B10[N-N] cRo5	2.0531 (±0.1161) -0.2881(±0.0558)	0.3550	0.1139	0.9211	0.9154	163.392	8.4292
17	B10[N-N] cRo5 GATS8p	2.0441 (±0.1161) -0.2993(±0.0566) 0.3194 (±0.2959)	0.0110	0.1135	0.9243	0.9159	109.961	8.4688

18	B10[N-N] GATS7p VE1_D	1.6839 (±0.1503) -1.3914(±0.3696) -0.2545(±0.0917)	2.8947	0.1266	0.9059	0.8955	86.651	7.5179
19	B10[N-N] cRo5 GATS8p	2.0441 (±0.1161) -0.2993(±0.0566) 0.3194 (±0.2959)	0.0110	0.1135	0.9243	0.9159	109.961	8.4688
20	B10[N-N] cRo5 DLS_07	2.0418 (±0.1128) -0.3331(±0.0605) 0.1874 (±0.1127)	0.2238	0.1104	0.9284	0.9205	116.710	8.7250
21	GATS7p cRo5 B10[N-N]	-0.5630(±0.330) -0.2518(±0.0580) 1.9489 (±0.1280)	0.3466	0.1102	0.9287	0.9208	117.279	8.7461
22	B10_N_N F08[C-C] VE1_D	2.1541 (±0.1176) 0.0241 (±0.0044) -0.5575(±0.1052)	2.2910	0.1078	0.9318	0.9242	122.890	8.9532
23	B10[N-N] cRo5 GATS7p Psychotic_80	1.9040 (±0.1308) -0.2806(±0.0614) -0.6753(±0.3374) 0.0602 (±0.0459)	1.0557	0.1087	0.9332	0.9229	90.733	8.8833
24	B10[N-N] cRo5 DLS_07 F08[C-C]	2.1076 (±0.1180) -0.3207(±0.0595) 0.2707 (±0.1225) 0.0057(±0.0037)	-0.0005	0.1077	0.9344	0.9243	92.610	8.9744
25	B10[N-N] cRo5 GATS7p VE1_D	1.8582 (±0.1373) -0.2114(±0.0621) -0.8065(±0.3573) -0.1343(±0.0854)	1.8367	0.1073	0.9349	0.9249	93.381	9.0117
26	B10[N-N] DLS_07 F08[C-C] VE1_D	2.1734 (±0.1174) 0.1452 (±0.1155) 0.0272 (±0.0050) -0.5780(±0.1054)	2.1885	0.1067	0.9357	0.9258	94.543	9.0678
27	B10[N-N] cRo5 F08[C-C]	2.1271 (±0.1163) -0.1239(±0.0817) 0.0166(±0.0066)	1.7237	0.1053	0.9373	0.9277	97.182	9.1933

	VE1_D	-0.3850(±0.1533)						
28	B10[N-N] F08[C-C] Psychotic_80 VE1_D	2.1824 (±0.1155) 0.0308 (±0.0060) 0.0926 (±0.0571) -0.6044(±0.1062)	2.3142	0.1047	0.9380	0.9285	98.405	9.2508
29	B10[N-N] cRo5 DLS_07 GATS7p	1.9208 (±0.1222) -0.2982(±0.0597) 0.2156 (±0.1075) -0.6447(±0.3162)	0.8730	0.1045	0.9383	0.9288	98.803	9.2698
30	B10[N-N] F08[C-C] GATS7p VE1_D	1.9399 (±0.1235) 0.0197 (±0.0041) -0.9062(±0.2920) -0.5498(±0.0916)	3.3488	0.0939	0.9502	0.9425	124.031	10.3859

Table 5 observed and estimated IC_{50} values Using model 30 (Table 4)

Model No.	Obs. pIC_{50}	Est. pIC_{50}	Residual
1*	0.068	0.12111	-0.0531
2*	0.918	1.88321	-0.9652
3	2.12	2.12	0
4*	0.028	0.08382	-0.0558
5	0.102	0.053	0.049
6	0.034	-0.011	0.045
7	0.022	0.204	-0.182
8*	0.003	-0.012	0.01504
9	0.003	0.063	-0.06
10	0.011	0.015	-0.004
11	0.002	0.04	-0.038
12	0.006	0.033	-0.027
13	0.046	0.063	-0.017
14	0.004	-0.043	0.047
15	0.005	0.052	-0.047
16	0.034	0.108	-0.074
17*	0.041	0.06727	-0.0263
18*	0.009	0.06183	-0.0528

19*	0.004	-0.0811	0.08512
20	0.037	-0.048	0.085
21*	0.036	0.05818	-0.0222
22	0.353	0.146	0.207
23*	0.032	0.05681	-0.0248
24	0.01	0.078	-0.068
25	0.026	0.021	0.005
26*	0.058	-0.0464	0.10444
27	0.076	0.081	-0.005
28*	0.164	0.14979	0.01421
29	0.067	0.11	-0.043
30	0.02	0.122	-0.102
31	0.067	0.074	-0.007
32	0.066	0.031	0.035
33*	0.133	0.13493	-0.0019
34	0.11	0.04	0.07
35	0.057	0.015	0.042
36	0.018	0.133	-0.115
37	0.133	0.204	-0.071
38	0.364	0.162	0.202
39	0.279	0.28	-0.001
40	0.694	0.528	0.166
41	0.296	0.412	-0.116
42	0.287	0.283	0.004
43	0.219	0.2	0.019

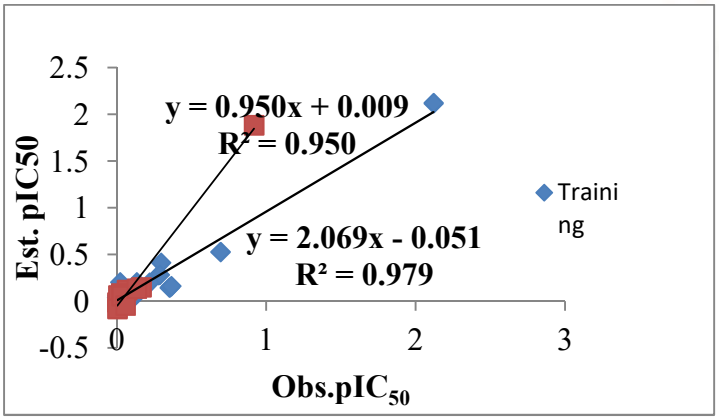


Fig.1 Correlation between observed and estimated pIC_{50}

Table 6 Cross validated parameters for the best obtained models

Model no	Parameters used	PRESS	SSY	PRESS/SSY	R^2_{cv}	S_{PRESS}	PSE
10	B10[N-N]	0.709	3.891	0.182	0.818	0.156	0.071
16	B10[N-N] cRo5	0.363	4.236	0.086	0.914	0.114	0.061
22	B10[N-N] VE1_D F08_C_C_	0.314	4.286	0.073	0.927	0.108	0.059
30	B10_N_N_ F08_C_C_ VE1_D GATS7p	0.229	4.37	0.052	0.948	0.094	0.055

Table 7 Ridge regression parameters for the best obtained models.

Model no	Parameters used	VIF	T	λ_i	K
10	B10[N-N]	1.0000	1.0000	1.0000	1.0000
16	B10[N-N]	1.0065	0.9936	1.080064	1.00
	cRo5	1.0065	0.9936	0.919936	1.17
22	B10[N-N]	1.1520	0.8680	1.895320	1.00
	VE1_D	2.0735	0.4823	0.840262	2.26
	F08_C_C_	2.2741	0.4397	0.264419	7.17
30	B10[N-N]	1.6753	0.5969	1.903822	1.00
	F08_C_C_	2.5824	0.3872	1.420041	1.34
	VE1_D	2.0750	0.4819	0.449074	4.24
	GATS7p	1.5276	0.6546	0.227063	8.38

VIF = Variance Inflation Factor

T = Tolerance

λ_i = Eigen values

k = Condition number

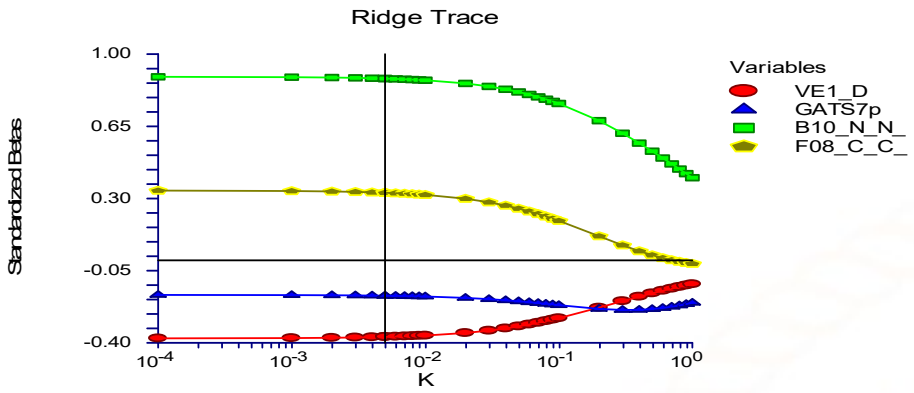


Fig.2 Ridge trace for four variable model

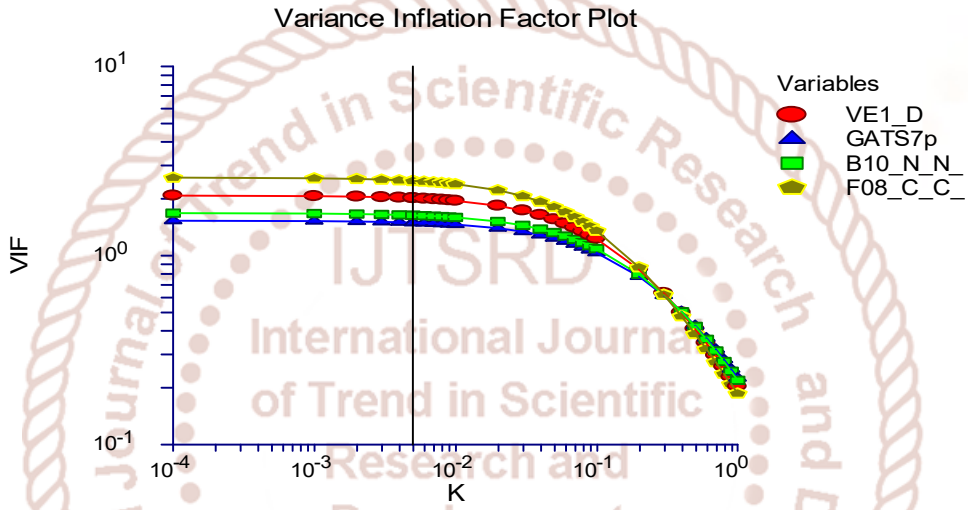


Fig. 3 VIF plot for four-variable model

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