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QSAR analysis on some 8-methoxy quinoline derivatives as H37R$_V$ (MTB) inhibitors

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Abstract: A quantitative structure–activity relationship (QSAR) study has been performed on 8-methoxy quinoline based on inhibitors of $H_{37}R_V$ (MTB). The compounds in the selected series were characterized by physicochemical and topological descriptors calculated using 2D-QSAR module of VLife MDS software. Correlations between different inhibitory activities and calculated predicted variables were established through employing the multiple linear regressions, Stepwise forward-backward method. The results of the study indicate that $H_{37}R_V$ (MTB) inhibitory activities of 8-methoxy quinoline can be successfully explained in terms of physicochemical parameters of the molecule. The generated QSAR model revealed the importance of structural, thermodynamic and electrotopological parameters. The quantitative structure activity relationship provides important structural insight in designing of potent antitubercular agent.

Keywords: Antimycobacterial activity; Antitubercular activity; 8-Methoxyquinolone Carboxylic acids.

Introduction

Mycobacterium tuberculosis, a human pathogen causing tuberculosis (TB), claims more human lives than any other bacterial pathogens.[1-3] About one-third of the world population is infected with *M. tuberculosis*, 10% of which will develop the disease at some point in their lives.[4] The current treatment of active TB is basically a four drug regimen comprising isoniazid (INH), rifampin, pyrazinamide, and ethambutol for a period of at least 6 months. The failure of patients to complete the therapy has led to the emergence of multidrug resistant TB (MDRTB). Moreover, the pandemic of human immunodeficiency virus (HIV), which dramatically increases susceptibility to develop active TB, has exacerbated the situation. World Heath Organization (WHO) has declared TB a global public health emergency.[5] There is an urgent need for new chemotherapeutic agents to combat the emergence of the resistance and strategies, which can effectively shorten the duration of chemotherapy. INH, a well-known antitubercular drug, is believed to kill mycobacteria by inhibiting the biosynthesis of mycolic acid critical components of the mycobacterial cell wall. The catalase and peroxidase activities are thought to participate in the drug sensitivity mechanism by converting INH in vivo into its biologically active form, which then acts on its intracellular target.[6-7] quinoline exhibit potent in vitro and in vivo antitubercular activity. Quinolones inhibit both bacterial type II topoisomerase, DNA gyrase and topoisomerase IV, which are essential enzymes catalyzing DNA supercoiling and decatenation reactions.[8-10]

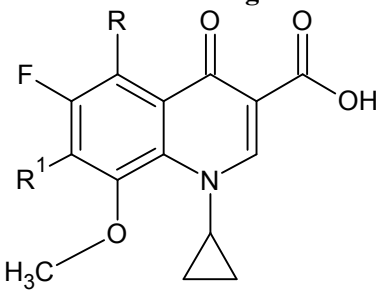
Material and Method

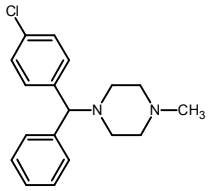
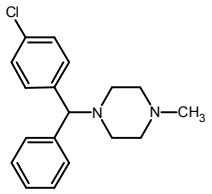
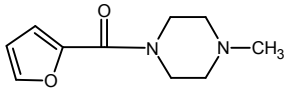
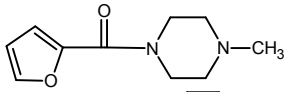
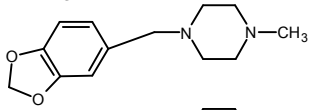
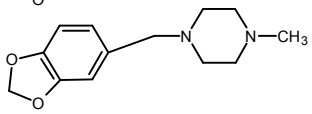
8-methoxyquinoline carboxylic acids exhibiting the potent antimycobacterial Activity was taken from the reported work by Palaniappan Senthilkumar *et al*[11].The literature values and general structure of the molecule are given in table 1. The activity data given as MIC values. The biological activity value [MIC (μM)] reported in literature are converted to -log scale and

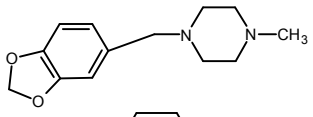
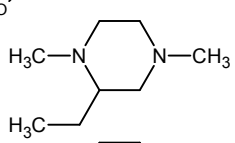
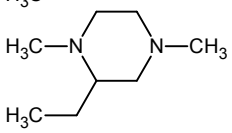
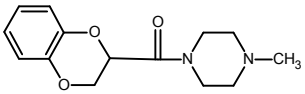
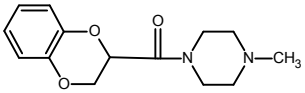
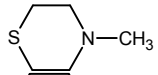
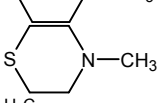
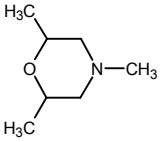
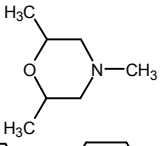
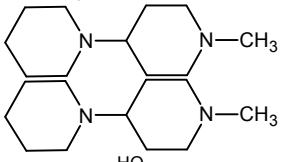
subsequently used as the dependent variable for the QSAR analysis. The -log values of MIC along with the structure of the 34 compounds in the series is presented in table 1.

All the computational studies were performed on HP5502 computer using the software VLife MDS. All 34 Molecules were sketched using the VLife MDS software. Optimizations of the sketched compounds were done by batch minimization process using merck molecular force field (MMFF) computations of the VLife MDS. Then optimized molecules were selected for calculation of the physiochemical descriptors by inserting biological activity as a dependable variable. Various 2D descriptors were calculated for optimized structures of the molecules using QSAR module of VLifeMDS. A large number of descriptors were generated by the VLife MDS like structural, topological, electrotopological and thermodynamic descriptor. The descriptor pool was reduced by removing invariable column in VLife MDS. The remaining physicochemical descriptors were taken into account for the reported analysis. The manual data selection method was used for data selection and variable selection was performed by Stepwise forward-backward method. The QSAR model was generated by using multiple linear regression method. The program search for all permutation and combition sequentially for the given data set which provides best models based on "squared correlation coefficient $r^{2"}$. The program also computes the crossed validated q^2, F-test and pred_r^2. Additionally developed QSAR model also computes r^2_se, q^2_se, and pred_r^2se.[12]

Table-1: Biological Activity Data and Calculated –Log value for 8- Methoxy Quinoline derivatives



C.No.	R	R_1	MIC (µM)	-LogMIC(µM)
01.	H		11.12	-1.046
02.	NO_2		1.28	-0.1072
03.	H		13.72	-1.1373
04.	NO_2		6.25	-0.7958
05.	H		1.57	-0.1958
06.	NO_2		0.35	0.4559

07.	NH_2		3.06	-0.4857
08.	H		13.84	-1.1411
09.	NO_2		3.14	-0.4969
10.	H		1.49	-0.1731
11.	NO_2		1.37	-0.1367
12.	H		2.06	-0.3138
13.	NO_2		1.84	-0.2648
14	H		3.99	-0.6009
15	NO_2		0.89	0.0506
16.	H		7.06	-0.8488
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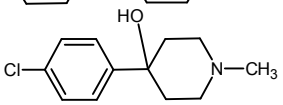
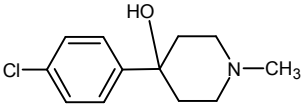
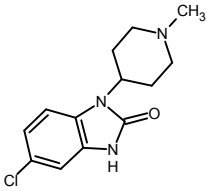
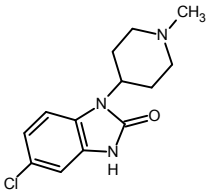
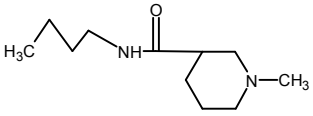
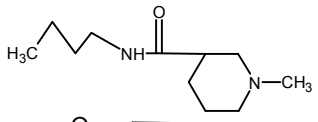
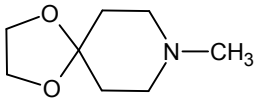
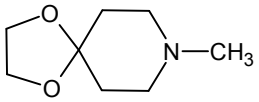
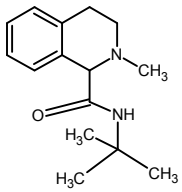
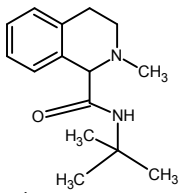
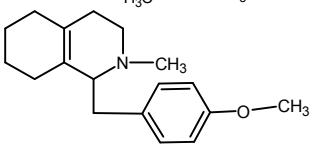
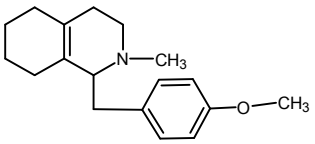
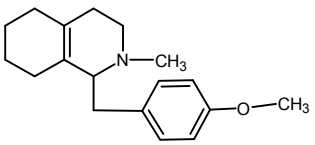
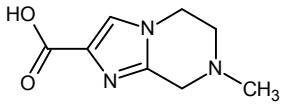
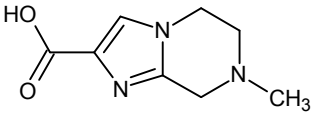
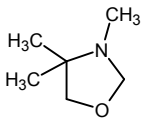
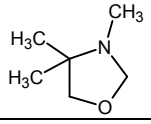
18.	H		6.43	-0.8082
19.	NO_2		5.88	-0.7693
20.	H		5.94	-0.7737
21.	NO_2		5.47	-0.7379
22.	H		1.69	-0.2278

23.	NO_2		1.55	-0.1903
24.	H		0.93	0.03151
25	NO_2		0.84	0.0757
26.	H		12.31	-1.0902
27.	NO_2		1.14	-0.1492
28.	H		1.46	-0.1643
29.	NO_2		0.16	0.7958
30.	NH_2		2.85	-0.4548
31.	H		3.53	-0.5477
32	NO_2		3.120	-0.4941
33	H		4.14	-0.6170
34	NO_2		1.85	-0.2671

Molecules and their structures considered for 2D-QSAR study along with calculated and residual activities

Result and Discussion

In search of new and potent $H_{37}R_V$ (MTB) inhibitors, QSAR analysis on a series of 8-methoxy quinoline was performed by using VLife MDS software. Various physiochemical parameters were calculated for datasheet and after removing the invariable descriptors, 82 descriptors were used in model building. The physiochemical descriptors and inhibitory activity was taken as independent and dependent variables respectively. Correlations were established between the biological activity and calculated molecular physiochemical descriptors through multiple linear regression (Stepwise forward-backward).

Among the generated QSAR models; five models were selected on the basis of various statistical parameters such as squared correlation co-efficient (r2) which is relative measure of quality of fit. Fischer's value (F test) which represents F-ratio between the variance of calculated and observed activity, standard error (r2_se) representing absolute measure of quality of fit, and cross-validated square correlation co-efficient (q2), standard error of cross-validated square correlation co-efficient (q2_se), predicted squared regression (pred_r2) and standard error of predicted squared regression (pred_r2se) to estimate the predictive potential of the models respectively.

QSAR model generated for different inhibitory activity data were as follows:

Model 1:

log1_MIC= + 0.2905(± 0.0643) SssOcount + 0.0228(± 0.0008) T_T_O_7 + 0.5814(± 0.1552) SssssCE-index-0.4343(±0.1037)SsssNcount - 0.2028(± 0.0765) T_N_O_3 + 0.2338 ……

n = 28, Degree of freedom = 22, r2 = 0.7683, q2 = 0.6259, F test = 14.5902, r2 se = 0.2461, q2 se = 0.3127, pred_r2 = 0.5977, pred_r2se = 0.2379 …….

Uni-Column Statistics: Training set

Column Name	Average	Max	Min	StdDev	Sum
log1_MIC	-0.4126	0.7960	-1.1370	0.4615	-11.5520

Uni-Column Statistics: Test set

Column Name	Average	Max	Min	StdDev	Sum
log1_MIC	-0.4800	-0.1730	-1.1410	0.3677	-2.8800

The unicolumn statistics shows that the test set is interpolative i.e. derived within the max-min range of training set.

The mean and standard deviation of the training and test set provides insight to the relative difference of mean and point density distribution.

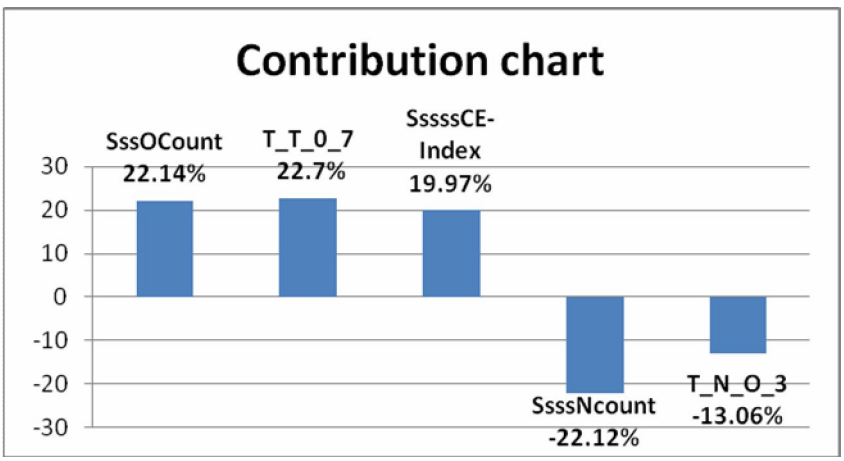


Fig.1: Contribution chart for model-1

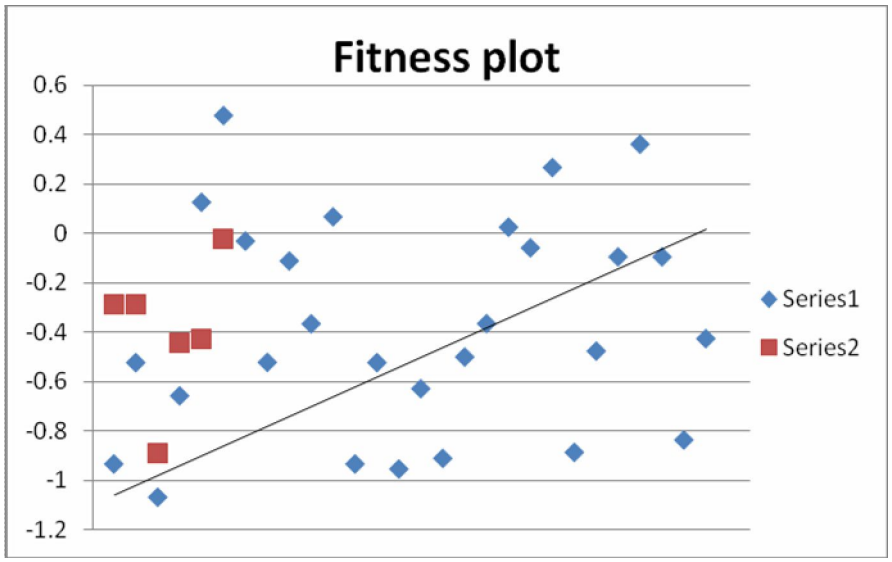


Fig.2: Fitness Plot between the experimental [-Log MIC (µM)] and Predicted Activities Log MIC (µM)] for model-1 [Training Set (blue spots) and test set (red spots)]

Table-2: Correlation Matrix of different Parameters in Model-1

	SssOcount	**SsssNcount**	**SssssCEindex**	**T_T_O_7**	**T_N_O_3**	**Score**
SssOcount	**1**	0.05411	-0.03134	0.065038	-0.08769	5
SsssNcount	0.05411	**1**	0.466075	-0.1353	-0.13032	5
SssssCE-index	-0.03134	0.466075	**1**	-0.2426	0.136413	5
T_T_O_7	0.065038	-0.1353	-0.2426	**1**	0.055282	5
T_N_O_3	-0.08769	-0.13032	0.136413	0.055282	**1**	5

Model-1 has good correlation between biological activity and parameters as r^2=0.76 and 76% variance in inhibitory activity. The low standard error of r2_se=0.24 demonstrates accuracy of the model. F value shows the 99.9% statistical significance of the regression model. Validation parameters high Pred_r^2=0.59, cross validated q^2=0.62 and low Pred_r^2se=0.23 and q^2_se=0.31 reflects the very good predictive power of the model. In this model five descriptors SssOcount, T_T_O_7, SssssCE-index, SsssNcount, and T_N_O_3 were highly correlated to biological activity. The good agreement between experimental and predicted value of the test set compounds. Contribution chart, fitness plot and correlation matrix of different parameters are given in figure1, figure 2 and table 2 respectively.

1. The descriptor **SssOcount** in the model represents the electro topological state. This can define the total number of oxygen connected with two single bonds. It shows positive correlation with biological activity.
2. **T_T_O_7** is alignment independent descriptor. It is signify the any atom which is separated from Oxygen atom by 7 bonds in a molecule. It is positively correlated with biological activity.
3. **SssssCE-index** is electrotopological state indices for the total no of carbon connected with four single bonds. It is positively correlated with biological activity.
4. **SsssNcount** represents the electro topological state which can define the total number of nitrogen connected with three single bonds. It shows negative correlation with biological activity.
5. **T_N_O_3** This is the count of number of Nitrogen atoms (single double or triple bonded) separated from any oxygen atom (single double or triple bonded)by 3 bonds in a molecule. It shows negative correlation with biological activity.

Model 2:

log1_MIC= + 0.3822(± 0.0628) SssOcount + 0.0221(± 0.0008) T_T_O_7 - 0.4956(± 0.1024) SsssNcount+0.7190(±0.1643)SssssCE-index+ 0.1552(± 0.0471) T_C_Cl_6 -0.2802……

n = 29, Degree of freedom = 23, r2 = 0.7700, q2 = 0.6547, F test = 15.3974, r2 se = 0.2455, q2 se = 0.3008, pred_r2 = 0.5651, pred_r2se = 0.2144……

Uni-Column Statistics: Training set

Column Name	Average	Max	Min	StdDev	Sum
log1_MIC	-0.4264	0.7960	-1.1410	0.4639	-12.3650

Uni-Column Statistics: Test set

Column Name	Average	Max	Min	StdDev	Sum
log1_MIC	-0.4134	0.0320	-0.8490	0.3247	-2.0670

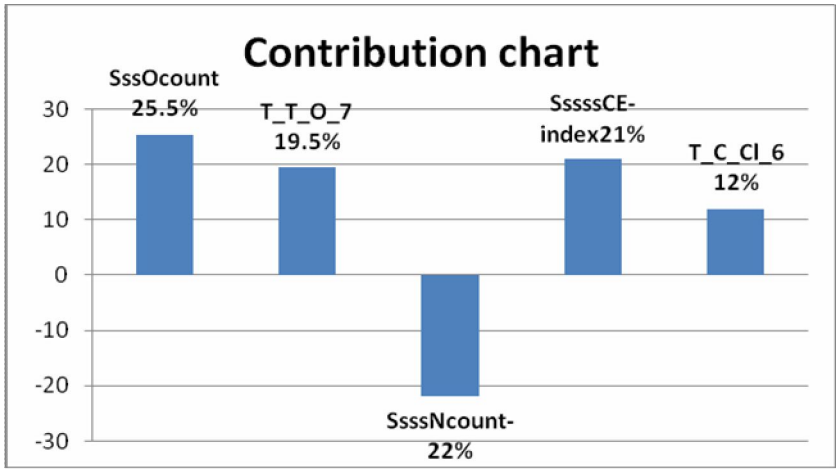


Fig.3: Contribution chart for model-2

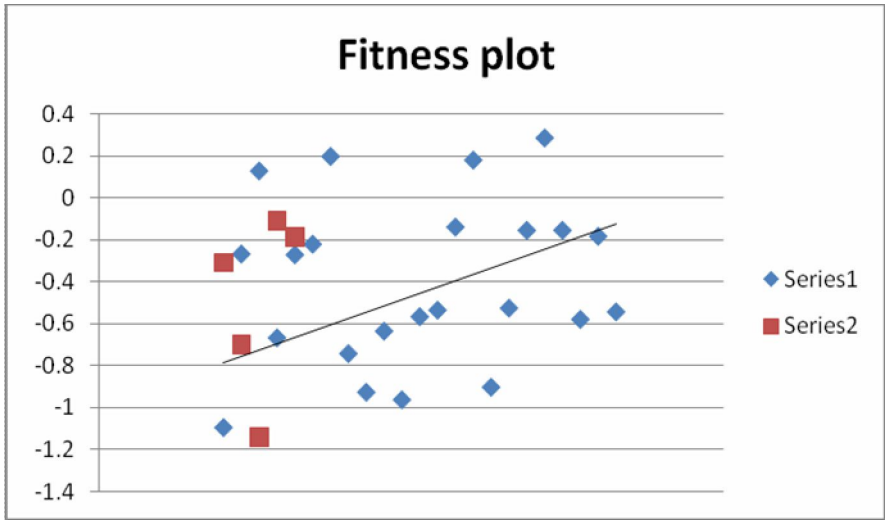


Fig.4:Fitness Plot between the experimental [-Log MIC (µM)] and Predicted Activities [-Log MIC (µM)] for model-2 [Training Set (blue spots) and test set (red spots)]

Table-3: Correlation Matrix of different Parameters in Model-2

	SssOcount	SsssNcount	SssssCEindex	T_T_O_7	T_C_Cl_6	Score
SssOcount	**1**	0.05411	-0.03134	0.065038	-0.29898	5
SsssNcount	0.05411	**1**	0.466075	-0.1353	0.153169	5
SssssCE-index	-0.03134	0.466075	**1**	-0.2426	-0.25967	5
T_T_O_7	0.065038	-0.1353	-0.2426	**1**	0.060897	5
T_C_Cl_6	-0.29898	0.153169	-0.25967	0.060897	**1**	5

Model-2 has good correlation between biological activity and parameters as r^2=0.77 and 77% variance in inhibitory activity. The low standard error of r2_se=0.24 demonstrates accuracy of the model. F value shows the 99.9% statistical significance of the regression model. Validation parameters high Pred_r^2=0.56, cross validated q^2=0.65 and low Pred_r^2se=0.21 and q^2_se=0.30 refelects the very good predictive power of the model. In this model five descriptors SssOcount, T_T_O_7, SsssNcount, SssssCE-index, and T_C_Cl_6 were highly correlated to biological activity. The good agreement between experimental and predicted value of the test set compounds. Contribution chart, fitness plot and correlation matrix of different parameters are given in figure 3, figure 4 and table 3 respectively

1. The descriptor **SssOcount** in the model represents the electro topological state. which can define the total number of oxygen connected with two single bonds. It shows positive correlation with biological activity.
2. **T_T_O_7** is alignment independent descriptor. It is signify the any atom which is separated from Oxygen atom by 7 bonds in a molecule. It is positively correlated with biological activity.
3. **SsssNcount** represents the electro topological state which can define the total number of nitrogen connected with three single bonds. It shows negative correlation with biological activity.
4. **SssssCE-index** is electrotopological state indices for the total no of carbon connected with four single bonds. It is positively correlated with biological activity.
5. **T_C_Cl_6** is alignment independent descriptor this is the count of number of Carbon atoms (single double or triple bonded) separated from any clorine atom (single or double bonded) by 6 bond distance in a molecule. Is shows the positive correlation with biological activity.

Model 3:

log1_MIC= + 0.2026(± 0.0151) T_T_O_1 - 0.1260(± 0.0344) SaaOE-index + 0.1779(± 0.0460)SdssCE-index+0.7328(±0.1939)SulfursCount+0.0926(± 0.0104) RotatableBondCount -0.0794(±0.0315) SsNH2E-index-2.3520……

n = 28, Degree of freedom = 21, r2 = 0.7615, q2 = 0.5906, F test = 11.1766, r2 se = 0.2561, q2_se=0.3355, pred_r2=0.5164, pred_r2se=0.2612……

Uni-Column Statistics: Training set

Column Name	Average	Max	Min	StdDev	Sum
log1_MIC	-0.4546	0.7960	-1.1410	0.4624	-12.7300

Uni-Column Statistics: Test set

Column Name	Average	Max	Min	StdDev	Sum
log1_MIC	-0.2837	0.0510	-0.7740	0.3255	-1.7020

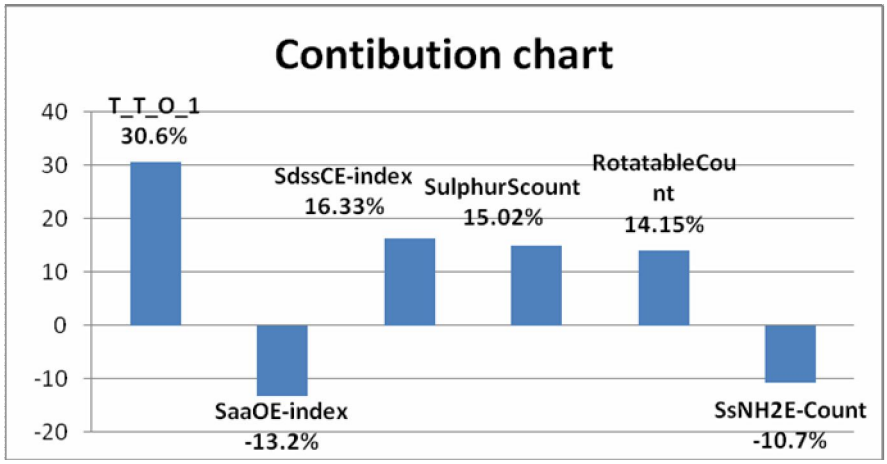


Fig.5: Contribution chart for model-3

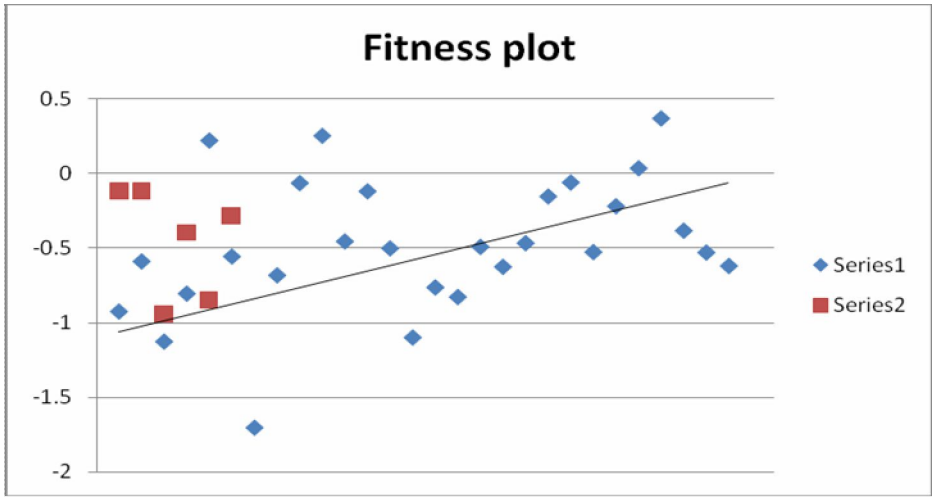


Fig.6: Fitness Plot between the experimental [-Log MIC (µM)] and Predicted Activities [-Log MIC (µM)] for model-3 [Training Set (blue spots) and test set (red spots)]

Table-4: Correlation Matrix of different Parameters in Model-3

	T_T_O_1	SaaOE-index	SdssCE-index	Sulfurs Count	Rotatabl BondCount	SsNH2E-index	Score
T_T_O_1	**1**	0.172735	-0.2979	-0.2474	0.082273	0.030895	6
SaaOE-index	0.172735	**1**	-0.12322	-0.0625	-0.06718	-0.06249	6
SdssCE-index	-0.2979	-0.12322	**1**	-0.00848	0.057625	0.363818	6
Sulfurs Count	-0.2474	-0.0625	-0.00848	**1**	-0.35152	-0.06249	6
Rotatable BondCount	0.082273	-0.06718	0.057625	-0.35152	**1**	0.21864	6
SsNH2E-index	0.030895	-0.06249	0.363818	-0.06249	0.21864	**1**	6

Model-3 was fulfilled the many rules of selection criteria's like correlation coefficient r =0.76 for *in-vivo* activity with low standard error of squared correlation coefficient r2_se=0.25 show the relative good fitness of the model. F value shows the 99.9% statistical significance of the regression model. Validation parameters high Pred_r^2 =0.51, cross validated q^2= 0.59 and low Pred_r^2se=0.26 and q^2_se=0.33. In this model six descriptors T_T_O_1, SaaOE-index, SdssCE-index, SulfursCount, RotatableBondCount, and SsNH2E-index were highly correlated to biological activity. Contribution chart, fitness plot and correlation matrix of different parameters are given in figure 5, figure 6 and table 4 respectively

1. **T_T_O_1** is Count of non hydrogen atoms separated from oxygen atom by a distance of 1 bond. Is shows the positive correlation with biological activity.
2. **SaaOE-index** is Electrotopological state indices for number of oxygen atom connected with two aromatic bonds. It shows negative correlation with biological activity.
3. **SdssCE-index** is Electrotopological state indices for number of carbon atom connected with one double and two single bonds. Is shows the positive correlation with biological activity.
4. **SulfursCount** This descriptor signifies number of sulphur atoms in a compound. Is shows the positive correlation with biological activity
5. **RotatableBondCount** It counts the Number of rotatable bonds. It shows the positive correlation with biological activity.
6. **SsNH2E-index** is Electrotopological state indices for number of –NH2 group connected with one single bond. It shows negative correlation with biological activity.

Model 4:

log1_MIC= + 0.4194(± 0.0582) SssOcount + 0.0369(± 0.0055) T_2_2_4 - 0.2004(± 0.0779) T_O_O_3 - 0.4259 (±0.2083) T_N_Cl_6- 1.7409…….

n = 24, Degree of freedom =19, r2 = 0.7882, q2 = 0.6479, F test = 17.6812, r2 se = 0.2030, q2se=0.2617, pred_r2=0.5472, pred_r2se=0.2698……..

Uni-Column Statistics: Training set

Column Name	Average	Max	Min	StdDev	Sum
log1_MIC	-0.4569	0.7960	-1.1410	0.4627	-12.7920

Uni-Column Statistics: Test set

Column Name	Average	Max	Min	StdDev	Sum
log1_MIC	-0.2733	0.0510	-0.7740	0.3163	-1.6400

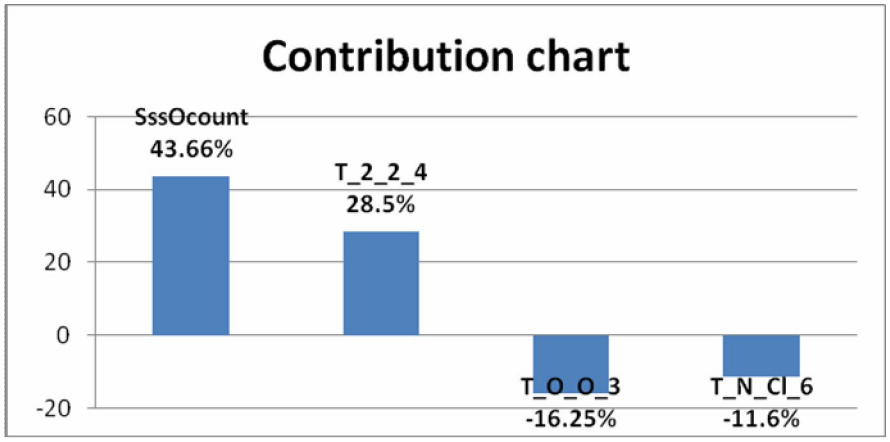


Fig.7: Contribution chart for model-4

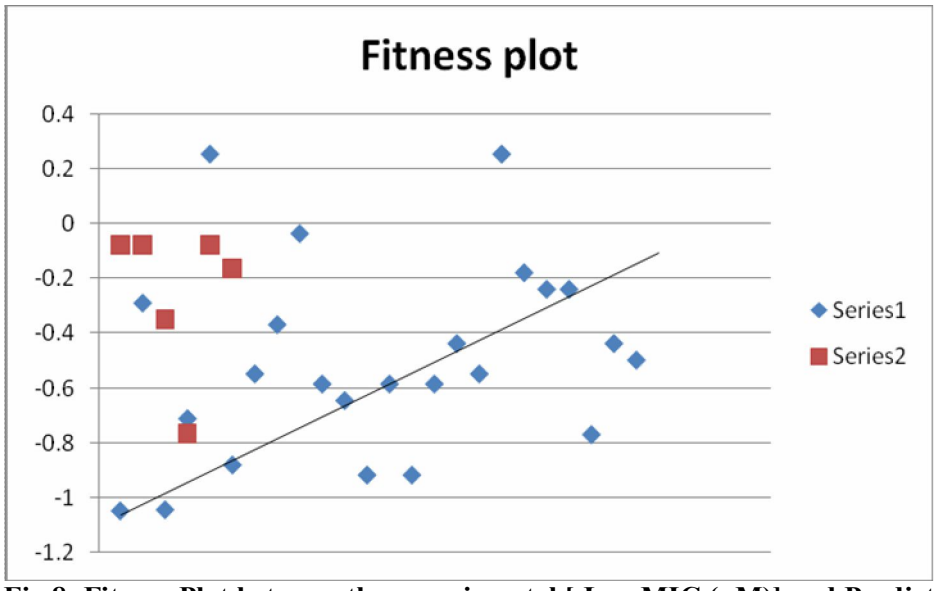


Fig.8: Fitness Plot between the experimental [-Log MIC (µM)] and Predicted Activities [-Log MIC (µM)] for model-4 [Training Set (blue spots) and test set (red spots)]

Table-5: Correlation Matrix of different Parameters in Model-4

	SssOcount	**SsssNcount**	**SssssCE-index**	**SaasCE-index**	**T_T_O_7**	**Score**
SssOcount	**1**	0.05411	-0.03134	0.067296	0.065038	5
SsssNcount	0.05411	**1**	0.466075	0.257126	-0.1353	5
SssssCE-index	-0.03134	0.466075	**1**	0.122446	-0.2426	5
SaasCE-index	0.067296	0.257126	0.122446	**1**	-0.83751	5
T_T_O_7	0.065038	-0.1353	-0.2426	-0.83751	**1**	5

Model-4 was fulfill the many rules of selection criteria's like correlation coefficient r = 0.69 for *in-vivo* activity with low standard error of squared correlation coefficient r2_se=0.23 show the relative good fitness of the model. F value shows the 99.9% statistical significance of the regression model. Validation parameters high Pred_r^2 =0.71, cross validated q^2= 0.55 and low Pred_r^2se=0.38 and q^2_se=0.28. In this model four descriptors SssOcount, T_2_2_4, T_O_O_3, T_N_Cl_6 were highly correlated to biological activity. Contribution chart, fitness plot and correlation matrix of different parameters are given in figure 7, figure 8 and table 5 respectively

1. The descriptor **SssOcount** in the model represents the electro topological state. This can define the total number of oxygen connected with two single bonds. It shows positive correlation with biological activity.
2. **T_2_2_4** This is the count of number of double bounded atoms (i.e. any double bonded atom, T_2) separated from any other double bonded atom by 4 bonds in a molecule. It shows positive correlation with biological activity.
3. **T_O_O_3** This is the count of number of Oxygen atoms (single double or triple bonded) separated from any other oxygen atom by 3 bond distance in a molecule. It shows negative correlation with biological activity.
4. **T_N_Cl_6** This is the count of number of Nitrogen atoms (single double or triple bonded) separated from any chlorine atom (single double or triple bonded)by 6 bonds in a molecule. It shows negative correlation with biological activity.

Model 5:

log1_MIC= + 0.2863(± 0.0537) SssOcount + 0.1748(± 0.0124) T_O_O_7 - 0.4620(± 0.0881) SsssNcount+0.6318(±0.1638)SssssCE-index+0.0860(±0.0160)SaasCE-index-0.3950……

n = 28, Degree of freedom = 22, r2 = 0.7449, q2 = 0.5810, F test = 12.8487, r2 se = 0.2235, q2se=0.2865,pred_r2=0.7546,pred_r2se=0.1980……

Uni-Column Statistics: Training set

Column Name	Average	Max	Min	StdDev	Sum
log1_MIC	-0.4496	0.7960	-1.1410	0.4597	-13.0390

Uni-Column Statistics: Test set

Column Name	Average	Max	Min	StdDev	Sum
log1_MIC	-0.2786	0.0510	-0.8080	0.3190	-1.3930

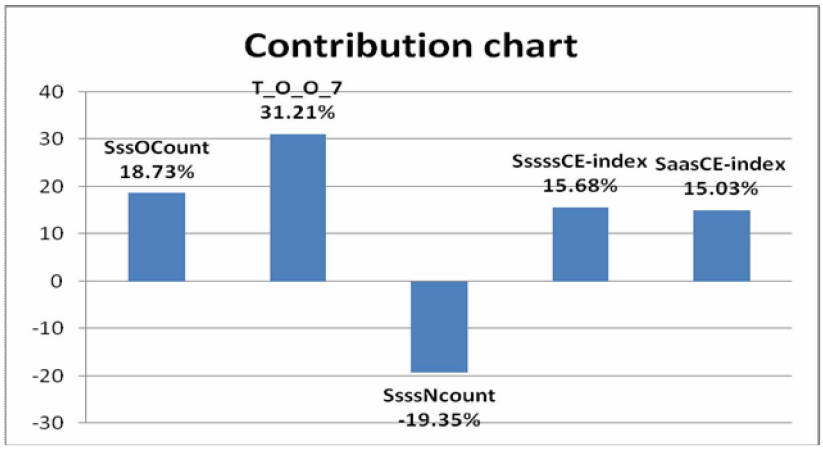


Fig.9: Contribution chart for model-5

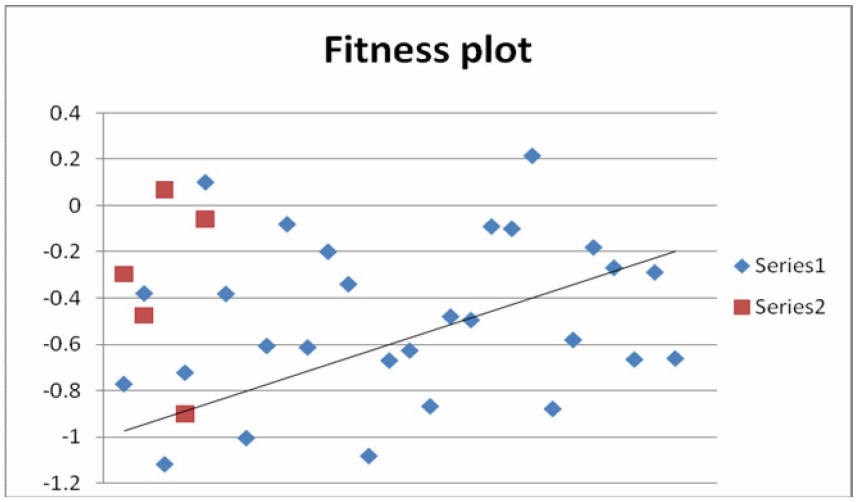


Fig.10: Fitness Plot between the experimental [-Log MIC (µM)] and Predicted Activities [-Log MIC (µM)] for model-5 [Training Set (blue spots) and test set (red spots)]

Table-6: Correlation Matrix of different Parameters in Model-5

	SssOcount	SsssNcount	SssssCE-index	SaasCE-index	T_T_O_7	Score
SssOcount	**1**	0.05411	-0.03134	0.067296	0.065038	5
SsssNcount	0.05411	**1**	0.466075	0.257126	-0.1353	5
SssssCE-index	-0.03134	0.466075	**1**	0.122446	-0.2426	5
SaasCE-index	0.067296	0.257126	0.122446	**1**	-0.83751	5
T_T_O_7	0.065038	-0.1353	-0.2426	-0.83751	**1**	5

Model-5 was fulfill the many rules of selection criteria's like correlation coefficient r = 0.74 for *in-vivo* activity with low standard error of squared correlation coefficient r2_se=0.22 show the relative good fitness of the model. F value shows the 99.9% statistical significance of the regression model. Validation parameters high Pred_r^2 =0.75, cross validated q^2= 0.58 and low Pred_r^2se=0.19 and q^2_se=0.28. In this model five descriptors SssOcount, T_O_O_7, SsssNcount, SssssCE-index, and SaasCE-index were highly correlated to biological activity. Contribution chart, fitness plot and correlation matrix of different parameters are given in figure 9, figure 10 and table 6 respectively

1. The descriptor **SssOcount** in the model represents the electro topological state. This can define the total number of oxygen connected with two single bonds. It shows positive correlation with biological activity.
2. **T_T_O_7** is alignment independent descriptor. It is signify the any atom which is separated from Oxygen atom by 7 bonds in a molecule. It is positively correlated with biological activity.
3. **SsssNcount** represents the electro topological state which can define the total number of nitrogen connected with three single bonds. It shows negative correlation with biological activity.
4. **SssssCE-index** is electro topological state indices for the total no of carbon connected with four single bonds. It is positively correlated with biological activity.
5. **SaasCE-index** is Electro topological state indices for number of carbon atom connected with one single bond along with two aromatic bonds. It is positively correlated with biological activity.

Comparison of different models:

The developed models were analyzed to find common properties of the $H_{37}R_V$ (MTB) inhibitors, their positive or negative contribution in activity and check the predictivity of the model for new compounds of the same series before synthesis. Different parameters selected for different models are given in Table-7.

Table-7: Different Parameters Selected for Regression Equation for different Models

Model	Parameter-1	Parameter-2	Parameter-3	Parameter-4	Parameter-5	Parameter-6
Model1	SssOcount (+0.2905)	T_T_O_7 (+0.0228)	SssssCE-index (+0.5814)	SsssNcount (-0.4343)	T_N_O_3 (-0.2028)	
Model2	SssOcount (+0.3822)	T_T_O_7 (+0.0221)	SssssCE-index (+0.7190)	SsssNcount (-0.4956)	T_C_CL_6 (+0.1552)	
Model3	T_T_O_1 (+0.2026)	SaaOE-index (-0.1260)	SdssCE-index (+0.1779)	Sulfurcount (+0.7328)	Rotatable bond count (+0.0926)	SsNH2E-index (-0.0794)
Model4	SssOcount (+0.4194)	T_2_2_4 (+ 0.0369)	T_O_O_3 (-0.2004)	T_N_CL_6 (-0.4259)		
Model5	SssOcount (+0.2863)	T_T_O_7 (+0.1748)	SssssCE-index (+0.6318)	SsssNcount (-0.4620)	SaaSCE-index (+0.0860)	

Table-8: Statistical and Validation Parameters of five different Models

Model no.	n	Degree of freedom	r^2	q^2	F- test	r^2_se	q^2_se	pred_r^2	pred_r^2se
Model1	28	22	0.7683	0.6259	14.5902	0.2461	0.3127	0.5977	0.2379
Model2	29	23	0.7700	0.6547	15.3974	0.2455	0.3008	0.5651	0.2144
Model3	28	21	0.7615	0.5906	11.1766	0.2561	0.3355	0.5164	0.2612
Model4	24	19	0.7882	0.6479	17.6812	0.2030	0.2617	0.5472	0.2698
Model5	28	22	0.7449	0.5810	12.8487	0.2235	0.2865	0.7546	0.1980

n- number of molecules, r^2- correlation co-efficient, q^2- cross-validated square correlation co-efficient, F- test-Fischer's value, r^2_se- standard error of correlation co-efficient, q^2_se- standard error of cross-validated square correlation co-efficient, pred_r^2- predicted squared regression, pred_r^2se- standard error of predicted squared regression

Table-9: Descriptor used in the significant QSAR Model-1 with value.

Compound No	SssOcount	T_T_O_7	SssssCE-index	SsssNcount	T_N_O_3
01	1	11	0	3	2
02	1	29	0	3	2
03	1	14	0	3	3
04	1	32	0	3	3
05	3	14	0	3	2
06	3	32	0	3	2
07	3	14	0	3	2
08	1	13	0	3	2
09	1	31	0	3	2
10	3	16	0	3	3
11	3	34	0	3	3
12	1	10	0	2	2
13	1	28	0	2	2
14	2	13	0	2	3
15	2	32	0	2	3
16	1	11	0	3	2
17	1	29	0	3	2
18	1	16	-0.97821	2	2
19	1	34	-1.1251	2	2
20	1	12	0	3	2
21	1	30	0	3	2
22	1	16	0	2	2
23	1	34	0	2	2
24	3	20	-0.59369	2	2
25	3	38	-0.74058	2	2
26	1	16	-0.51305	2	3
27	1	37	-0.6321	2	3
28	2	16	0	2	2
29	2	36	0	2	2
30	2	16	0	2	2
31	1	14	0	2	4
32	1	32	0	2	4
33	2	13	-0.45089	2	2
34	2	37	-0.69308	2	2

In this sequence, **SssOcount** a physico-chemical parameter is common in four models out of five models. This parameter show positive contribution in four models. It is desirable properties of $H_{37}R_V$ (MTB) inhibitors. One another interesting feature of $H_{37}R_V$ (MTB) inhibitors is number of the **SssssCE-index** present in compound which is common parameter in three models and it is positively contributing to $H_{37}R_V$ (MTB) inhibitory activity so it is desirable properties of $H_{37}R_V$ (MTB) inhibitors. And **SsssNcount** present in compound which is common parameter in three models out of five models. This parameter show negative contribution so decreasing the no of nitrogen connected with three single bond of the compound is desirable properties of $H_{37}R_V$ (MTB) inhibitors. The result obtained from the significant models is given in Table-8.

From comparison of different statistical parameters and validation parameters of the model-1, model-2, model-3 and model-4 mention in table-7, 8, find a result that model-1 is the significant model. It has good correlation between biological activity and parameters as r^2=0.76 and 76% variance in inhibitory activity. The low standard error of r2_se=0.24 demonstrates accuracy of the model. F value shows the 99.9% statistical significance of the regression model. Validation parameters high Pred_r^2=0.59, cross validated q^2=0.62 and low Pred_r^2se=0.23 and q^2_se=0.31. Model -2, Model-3, Model-4 and model-5 also have good predictivity. Descriptors used in the Significant QSAR Model-1 with value given in Table-9.

QSAR model with reliable predictive power for $H_{37}R_V$ (MTB) inhibitory activity has been successfully generated. The good correlation between experimental and predicted biological activity for compounds in the test set further highlights the reliability of the constructed QSAR model. The result of the study suggests the involvement of number of carbon atoms connected to four single bonds and number of nitrogen connected with three single bonds will augment inhibitory activity of these molecules against $H_{37}R_V$. One of the prime electrotopological requirements for better inhibition of $H_{37}R_V$ is that the compounds should have less number of carbon atoms connected with four single bonds. $H37R_V$ inhibition may be achieved by reducing number of oxygen connected with two single bonds. The finding of the study will be helpful in the design of the potent $H_{37}R_V$ (MTB) inhibitors which are useful for anti-tubercular activity.

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