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2D-QSAR analysis on some 8-methoxy quinoline derivatives as $H37R_V$ (MTB) inhibitors with comparison of different model

*Kalpana Prajapati[1], Satkar Prasad[2], Sailesh Kumar Ghatuary[3], Anil Sarathe[4], Gaurab Duby[5], Reena Sheride[6].

[1](Dept. of Pharmachemistry, RKDF School of Pharmaceutical Science. Bhopal, India)
[2](Dept. of Pharmaceutics , RKDF School of Pharmaceutical Science. Bhopal, India)
[3](Dept. of Pharmacology, RKDF School of Pharmaceutical Science. Bhopal, India)
Corresponding Author: kalpana Prajapati

***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 regression, 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.*

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I. 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]

II. 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]

III. 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

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

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.

In this sequence, **SssOcount** a physico-chemical parameter is common in both 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 both 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 both 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, 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. 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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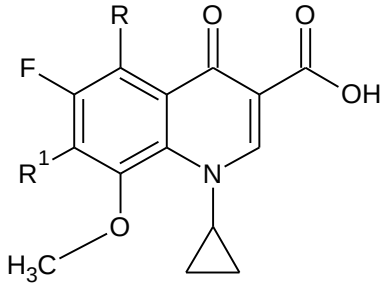
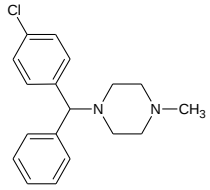
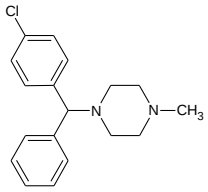
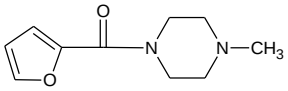
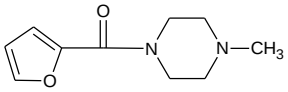
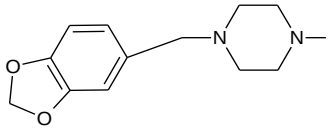
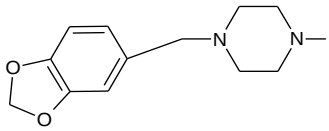
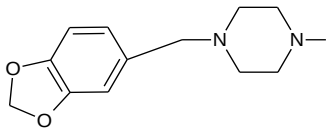
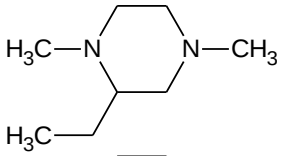
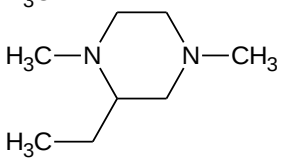
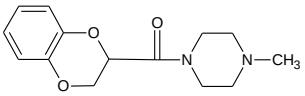
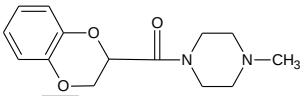
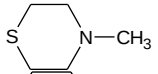
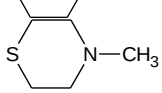
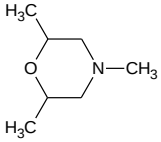
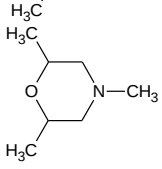
[12] Molecular design suite 3.5, V-life Sciences Technologies Pvt. Ltd. Pune: India.

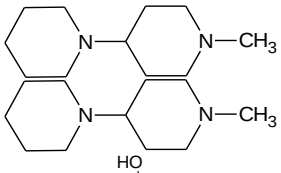
Illustrations:

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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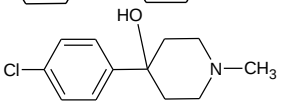
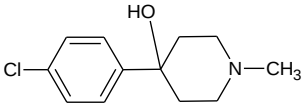
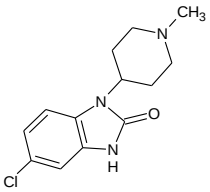
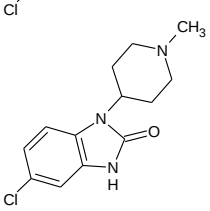
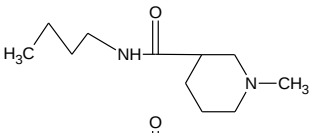
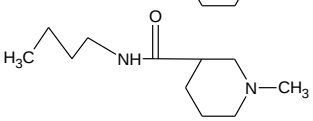
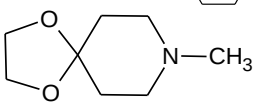
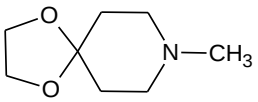
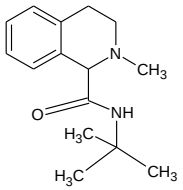
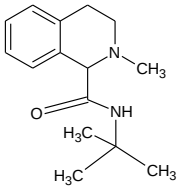
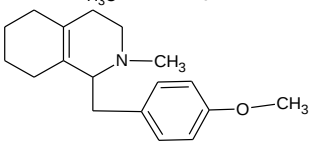
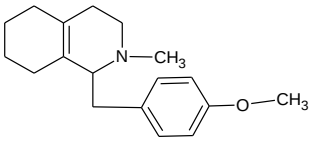
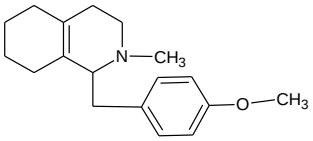
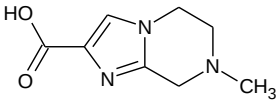
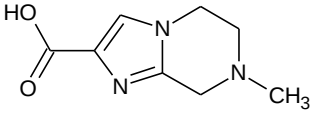
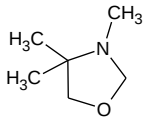
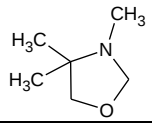
18.	H		6.43	-0.8082
19.	NO_2		5.88	-0.7693
20.	H		5.94	-0.7737
21.	NO_2		5.47	-0.7379
22.	H		1.69	-0.2278
23.	NO_2		1.55	-0.1903
24.	H		0.93	0.03151
25	NO_2		0.84	0.0757
26.	H		12.31	-1.0902
27.	NO_2		1.14	-0.1492
28.	H		1.46	-0.1643

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

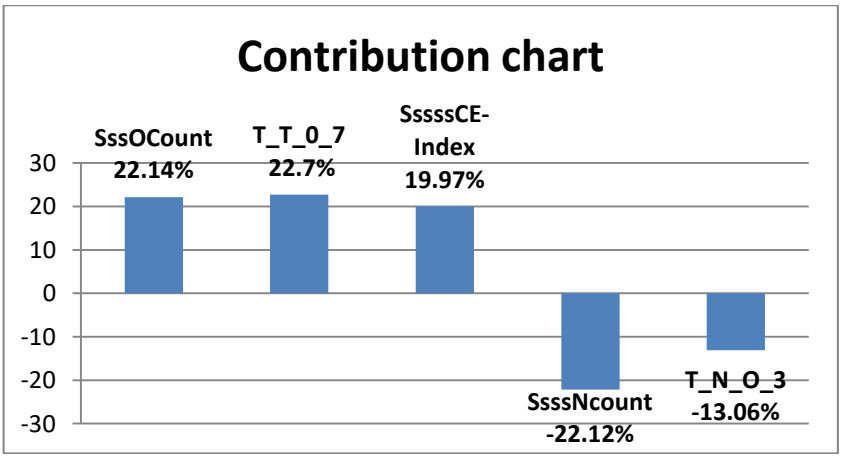


Fig.1: Contribution chart for model-1

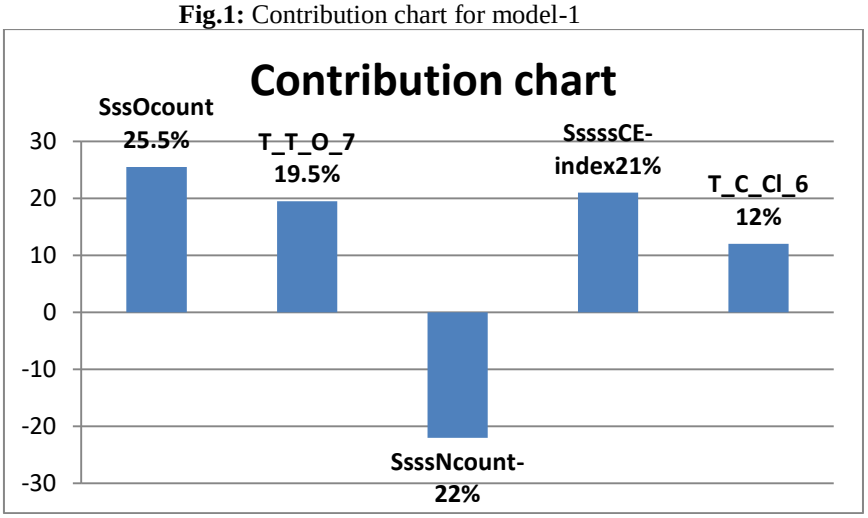


Fig.3: Contribution chart for model-2

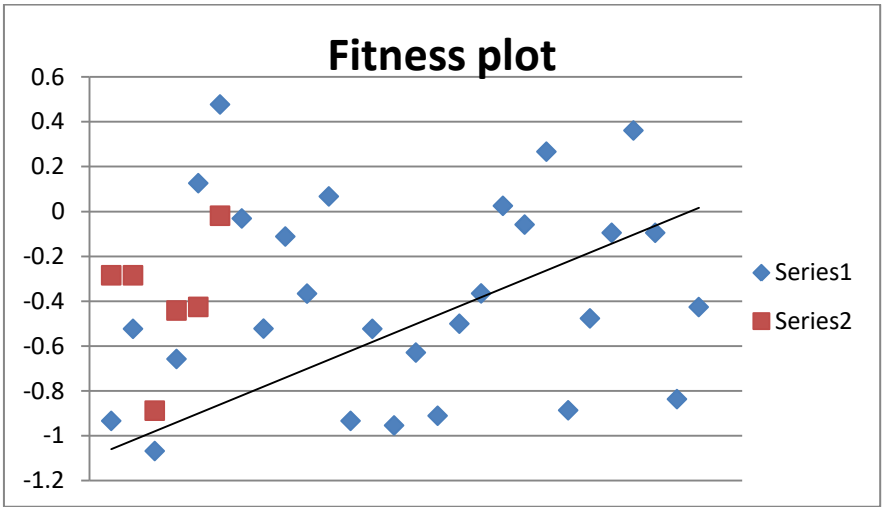


Fig.2: Fitness Plot between the experimental [-Log MIC (µM)] and Predicted Activities Log MIC (µM)] for model-1 [Training Set (blue spots) and test set (red spots)]

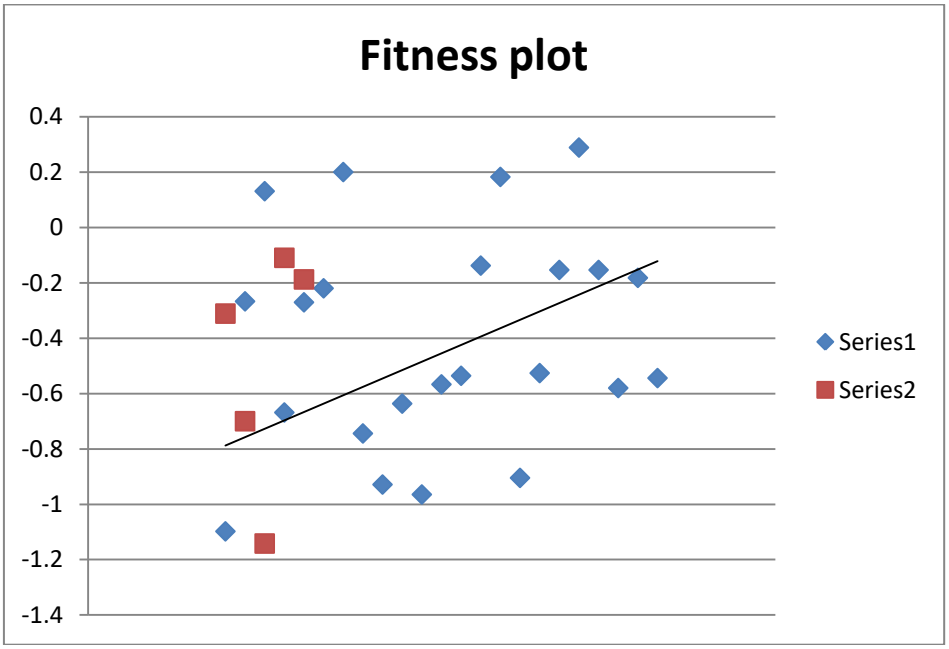


Fig.4: Fitness Plot between the experimental [-Log MIC (µM)] and Predicted Activities [-Log MIC (µM)] for model-2 [Training Set (blue spots) and test set (red spots)]

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-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

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

TABLE-7: DIFFERENT PARAMETERS SELECTED FOR REGRESSION EQUATION FOR DIFFERENT MODELS

Model	**Parameter-1**	**Parameter-2**	**Parameter-3**	**Parameter-4**	**Parameter-5**
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	SsssNcount (-0.4956)	T_C_CL_6 (+0.1552)

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

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: Z score value of two different models

Dep Variable ➡	**ZScore R^2**	**ZScore Q^2**	**Best Rand R^2**	**Best Rand Q^2**	**Alpha Rand R^2**	**Alpha Rand Q^2**	**Z Score Pred R^2**	**best Rand Pred R^2**	**alpha Rand Pred R^2**
Model-1	6.45373	5.79275	0.37075	0.01205	0.0000	0.00000	1.85882	0.37483	0.05000
Model-2	8.24004	6.50567	0.27897	-0.08241	0.0000	0.00000	1.19232	0.53049	0.00000

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 10

Table 10 Different parameters selected for regression equation for different models

Model	Parameter-1	Parameter-2	Parameter-3	Parameter-4	Parameter-5
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)

In this sequence, **SssOcount** a physico-chemical parameter is common in both. 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 both 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 both 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 11.

Table 11 Statistical and validation parameters of two 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

From comparison of different statistical parameters and validation parameters of the model-1, model-2, mention in table no-5.7, 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, also have good predictivity

12: Actual and predicted activity with residual of best model-1

Table 12: Actual and predicted activities [MIC (µM)] with residual values for the 28 training set compounds of model-1

Compound No.	Actual (-Log MIC)	Predicted (-Log MIC)	Residual(-Log MIC)
01	-1.0460	-0.9336	-0.1124
02	-0.1070	-0.5231	0.4161
03	-1.1370	-1.0680	-0.069
04	-0.7960	-0.6575	-0.1385
06	0.4560	0.1260	0.33
09	-0.4970	-0.4774	-0.0196
11	-0.1370	-0.0309	-0.1061
12	-0.3140	-0.5221	0.2081
13	-0.2650	-0.1115	-0.1535
14	-0.6010	-0.3660	-0.235
15	0.0510	0.0673	-0.0163
16	-0.8490	-0.9336	0.0846
17	-0.8070	-0.5231	-0.2839
18	-0.8080	-0.9540	0.146
19	-0.7690	-0.6289	-0.1401
20	-0.7740	-0.9108	0.1368
21	-0.7380	-0.5003	-0.2377
22	-0.2280	-0.3852	0.1572
23	-0.1900	0.0523	-0.2423
24	0.0320	-0.0583	0.0903
25	0.0760	0.2669	-0.1909
26	-1.0900	-0.8864	-0.2036
27	-0.1490	-0.4766	0.3276
28	-0.1640	-0.0948	-0.0692
29	0.7960	0.3614	0.4346
30	-0.4550	-0.0948	-0.3602
31	-0.5480	-0.8365	0.2885
32	-0.4940	-0.4260	-0.068

Table 13: Actual and predicted activities [MIC (µM)] with residual values for the 06 test set compounds of model-1

Compound No.	Actual (-Log MIC)	Predicted (-Log MIC)	Residual(-Log MIC)
05	-0.1960	-0.2843	0.0883
07	-0.4860	-0.2843	-0.2017
08	-1.1410	-0.8880	-0.253
10	-0.1730	-0.4415	0.2685
33	-0.6170	-0.4254	-0.1916
34	-0.2670	-0.0188	-0.2482

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Kalpana Prajapati. "2D-QSAR analysis on some 8-methoxy quinoline derivatives as H37RV (MTB) inhibitors with comparison of different model." IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) 12.4 (2017): 11-19.