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Quantitative Structure Activity Relationship Analysis of N-Substituted Phenazine-1-carboxamides Analogs as Anti-mycobacterial Agents

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Abstract

Mycobacterium tuberculosis (MTB) claims lives that are more human each year than any other Bacterial Pathogen. 1/3rd of the world's population is already infected with TB. Every year, more than eight million new people develop active tuberculosis, and 2 million people die from TB. In view of above and as a part of our effort to develop newer anti-tubercular agents, molecular modeling analysis was performed to develop QSAR models that show substantial predictive promise for N-substituted phenazine-1-carboxamides. The QSAR model explains 76.4 percent variance in activity with low standard error of estimation (0.222). Model showed statistical significant internal predictivity (q^2=0.600) and external predictivity (r^2_{pred}=0.447) values. The detailed structural investigation revealed that the anti-tubercular activity is predominantly explained by the radial distribution functions (RDF080m & RDF085m), topological descriptor (IC3) and empirical descriptor (Hy). The structural insights gleaned from the study are helpful in design of inhibitors with enhanced potency.

Key-Words: QSAR, N-substituted phenazine-1-carboxamides analogs, Anti-tubercular activity, Molecular descriptors

Introduction

Infection by *Mycobacterium tuberculosis* is a major public health problem and remains a leading cause of death worldwide. According to the World Health Organization (WHO), about one third of the global population is infected with *Mycobacterium tuberculosis* (Mtb). Annually, nearly 8 million of the infected people develop active TB and 2 million die.[1,2] Today, drug-resistant strains of *M. tuberculosis* as well as multidrug-resistant (MDR) strains have been documented in most countries. MDR-TB defined as disease caused by *M. tuberculosis* resistant to at least rifampicin and isoniazid. Although MDR-TB is curable, it requires protracted chemotherapy (up to 2 years), which is more expensive and often more toxic to patients.[3] More recently, the spread of extensively drug-resistant (XDR) TB, characterized by resistance to at least isoniazid and rifampicin plus any fluoroquinolone and any one of the second-line injectable antituberculous drugs, has become common in many countries.[4,5] Therefore, development of new drugs is one of the essential problems for the treatment of drug-resistant, MDR- and XDR-TB.

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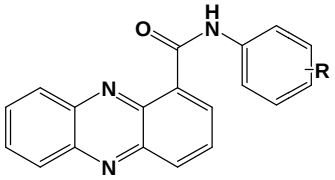
Within the last 50 years, several phenazine derivatives showing antimicrobial activity against fungi, yeasts and bacteria have been discovered.[6] At present, approximately 50 natural and synthetic phenazine compounds differing only in modifications of the parent heterocycle have been described. Generation of structural modifications mainly leads to phenazines with different physical properties and changes in the spectrum of their activity.[7] Tubermycin B (phenazine-1-carboxylic acid (PCA)) as well as several derivatives of phenazine show moderate antitubercular activity,[8] whilst clofazimine, which belongs to the riminophenazine class, is effective against *M. tuberculosis*, *Mycobacterium avium* and *Mycobacterium leprae*.[9,10]

The QSAR analysis of the anti-mycobacterial inhibitors is the recent interested area of research. The QSAR was performed on a series of novel phenazine-1-carboxamides. The emphasis was focused on the quantification of structure activity relationship with a view to delineate the influence of key physicochemical properties on mycobacterial inhibitory activity, which will aid in the designing of potent and safer inhibitors. The quantification of physicochemical properties was done with the help of regression technique.

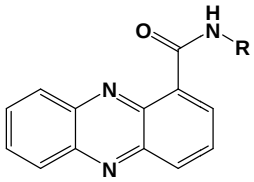
Material and Methods

The *M. tuberculosis* minimum inhibitory concentration data of phenazine-1-carboxamides analogs was taken from the reported work of Logu e*t al.*[11] (Table I). The inhibitory activity data (MIC in mM) was converted to negative logarithmic dose in mole (pMIC) because a QSAR is a linear free energy relationship, and from the Van't Hoff isotherm, free energy change during a process is proportional to the logarithm of the rate or equilibrium constant of the process (ΔG= -2.303 RTlogK). Initially the series was subjected to Fujita-Ban analysis using regression technique in order to estimate the de novo contribution of substituent to the activity of the scaffold.

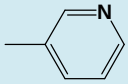
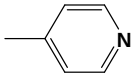
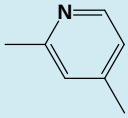
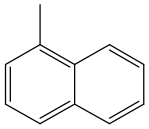
Table I: Compounds and their activity against *Mycobacterium tuberculosis* (H37Rv) used in training and test sets



Comp. No. 1-16, 21-27



Comp. No. 17-20

Comp. No.	R	MIC data against *M. tuberculosis* H37Rv (mg/L)
1	2-CH_3	0.39
2	4-CH_3	0.78
3	2-CF_3	0.39
4	3-CF_3	0.78
5	4-CF_3	0.39
6	3-OCH_3	0.39
7	4-OCH_3	0.78
8	4-$COOCH_3$	25
9	3-Cl	0.39
10	2-F	1.56
11	3-F	0.78
12	4-F	0.19
13	3-Br	0.19
14	2,3-$(CH_3)_2$	0.39
15	3,4-$(CH_3)_2$	0.39
16	3,4-$(OCH_3)_2$	0.39
17		0.78
18		1.56
19		0.78
20		1.56
21	H	3.12
22	2-OCH_3	0.78
23	4-OCF_3	0.39
24	2-Cl	0.39
25	2,6-$(CH_3)_2$	3.12
26	2,5-$(CH_3)_2$	0.78
27	3,5-$(CH_3)_2$	0.39

The molecular modeling study was performing by using *CS ChemOffice*[12] and *Dragon*[13] program while the regression analysis was carried out on *VALSTAT*[14]. Structure of all the compounds was sketched out by builder module of the program. The sketched structures were subjected to energy minimization using molecular mechanics (MM2) until the root mean square (RMS) gradient value became smaller than 0.1 kcal/molA°. The energy-minimized molecules were subjected to re-optimization via Austinmodel-1 (AM1) method until the RMS gradient attained a value smaller than 0.01 kcal/molA° using MOPAC. The geometry optimization of the lowest energy structure carried out using EF routine. The minimized molecule was saving as MOL file format. The MOL file was use for calculation of various physicochemical properties with the help of *Dragon* program. Series was divided into a training set of 20 compounds and a test set of 7 compounds on the basis of structural diversity and cover the complete range of variations in inhibitory activity.

The data was transfer to the statistical program in order to establish a correlation between physicochemical parameters as independent variable and pMIC as dependent variable employing sequential multiple linear regression analysis method. In sequential

multiple linear regression, the program searches for all the permutation and combination sequentially for the given data set. The data within the parentheses is the standard deviation associated with the coefficient of descriptor in regression equation. The various statistically significant equations were taken in consideration on the basis of observed squared correlation coefficient (r^2), the standard error of estimate (SEE) and the sequential Fischer test (F). The internal predictive powers of the equations were validated by leaveone- out (loo) cross-validation method[15,16] considering predicted residual sum of square (PRESS), total sum of squares (SSY), cross-validated squared correlation coefficient (q^2), and standard deviation error of prediction (SDEP). The q^2 is defined as

$$q^2 = 1 - \sum (Y_{pred} - Y_{act})^2 / \sum (Y_{act} - Y_{mean})^2$$

Where Y_{pred}, Y_{act}, and Y_{mean} are predicted actual and mean values of the pMIC, respectively.

$\sum (Y_{pred} - Y_{act})^2$ is the predictive residual error sum of squares (PRESS). PRESS is an important cross-validation parameter as it is a good approximation of the real predictive error of the models. Bootstrapping analysis was performing to ascertained robustness and statistical confidence against the model. Bootstrapping squared correlation coefficient (r^2_{bs}) is the average squared correlation coefficient of subset of compounds used in regression. Chances of fortuitous correlation were tested with the help of Chance statistics (evaluated as the ratio of the equivalent regression equations to the total number of randomized sets; a chance value of 0.001 corresponds to 0.1% chance of fortuitous correlation). Test for outliers, which confirm the applicability of QSAR equation on the structural analogs were performed with the help of Z-score value. The external predictive power of the equation has been analyzed with the help of test set using predictive correlation coefficient (r^2_{pred}).

Results and Discussion

Fujita-Ban analysis was carried out in order to find out de novo contribution of the substituent to the activity of the scaffold (**Table II**). The multi-variant regression expression (Eq.(1)) indicated that many groups have poor contribution to the inhibitory activity, which is further supported by high standard error of the substituent coefficient.

pMIC = 0.374[2-CH_3] + 0.354[4-CH_3] + 0.653[2-CF_3] +0.352[3-CF_3] +0.631[4-CF_3] + 0.330[2-OCH_3] + 0.517[3-OCH_3] + 0.292[4-OCH_3] -1.162[4-$COOCH_3$] + 0.645[4-OCF_3] +0.625[2-Cl] + 0.644[3-Cl] + 0.042[2-F] + 0.343[3-F] + 0.997[4-F] + 0.919[3-Br] - 0.670[6-CH_3] + 0.377[3-CH_3] + 0.134[5-CH_3] + 8.280

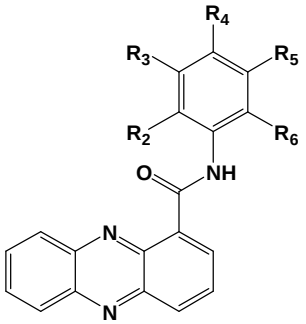
n=23, r^2=0.936, SE=0.323, F=2.3174 Eq.(1)

pMIC = 0.472 [4-F] -0.822[6-CH3] -1.688[4-$COOCH_3$] -0.483[2-F] +8.805

n=23, r=0.869, SE=0.257, F=13.986 Eq.(2)

Fujita–Ban analysis of antimycobacterial activity of phenazine-1-carboxamides analogs inferred that the substitutions of small electron withdrawing group at R_4 position (Table II) are favorable. Substitutions on ortho position of ring (R_2 & R_6) are unfavorable. Fujita–Ban expression gave insight to some important structural features, i.e., smaller electron withdrawing moiety at 4nd position of ''Ring '' is optimal for the activity and ortho substitutions might be produce hindrance in hydrogen bond formation with macromolecules.

Table II: Fujita-Ban matrix of phenazine-1-carboxamides analogs with their pMIC



The multivariant expressions were developed on the basis of adjustable correlation coefficient (r^2_{adj}). This parameter explains statistical significance of incorporated physicochemical descriptors in SEQ-MLR. r^2_{adj} takes into account of adjustment of conventional correlation coefficient(r^2). If r^2_{adj} value decline by the addition of a physicochemical descriptor to the equation it is indicated that descriptor was not contributed fairly. Adjustable correlation coefficient is a measure of % explained variation of regression expression. Correlation co-efficient (r^2) is always increases when an independent variable was added to the equations. Study has furnished uni and bi-variant expression with moderate correlation coefficient [Eq. (3) and (4)] but the r^2_{adj} value is increasing significantly from uni to bi-variant expression (**Table III**).

pMIC = -1.585(±0.280) ***Hy***+ 7.533

n=20, r=0.800, SE=0.282, F=31.963 Eq.(3)

pMIC = 0.959(±0.466) ***Lop*** -1.928(±0.307)***Hy*** + 6.732(±0.437)

n=20, r=0.844, SE=0.260, F=20.985 Eq.(4)

pMIC = 1.130(±0.336) ***E1m*** -1.949(±0.901) ***R2v*** - 1.746(±0.235) ***Hy*** + 8.519

n=20, r=0.889, SE=0.227, F=20.223 Eq.(5)

Significant improvement in r^2_{adj} value emphasizes to explore the higher variant expressions. Proposed models should have to satisfy both statistical quality and predictive power. Therefore, all the expressions were tested for internal and external corroboration. Both the validations put forward decision- making input for selection of QSAR models. Internal corroboration was carried out using leave-one-out cross-validation method, bootstrapping technique and randomized biological activity test while external corroboration confirmed with the help of test set data. Tetra-variant expressions eqn. (6) which fulfill all the corroboration criteria up to significant level were considered as QSAR model.

pMIC = 0.908(±0.779)***IC3***+0.052(±0.020)***RDF080m***+0.115(±0.040)***RDF085m*** -1.741(±0.232) ***Hy*** + 2.529

n=20, r=0.902, SE=0.222, F=16.378 Eq.(6)

Different statistical parameters of QSAR model are shown in table III. Equation shows significant correlation coefficient (r^2=0.813), which account for 76.4% of the explained variance in the activity calculated as $r^2_{adj} = r^2 (1 - 1/F)$ that depict in percentage when multiplied by 100. The data showed overall internal statistical significance level better than 99.9% as the calculated variance ratio i.e., Fischer value (F) exceeded the tabulated $F_{(4,15\alpha0.001)}$ =12.7. Fischer value suggested that the equations are applicable for more than 999 out of 1000 times. The orthogonality of the descriptors in the model was established through variance inflation factor (VIF)[17,18] values and inter-correlation among the descriptors (ICAP) (**Table IV**). The VIF is defined as $1/1-r^2_i$, where r_i is the multiple correlation coefficient for the *i*th variable regressed on the p-1 others, p is being the number of variables contributed to the model. VIF value larger than 10 indicates that the information of the descriptors may be hidden by the correlation of the other descriptors[19]. VIF is less than 2.0184 for all the contributing descriptors revealed that the descriptors are fairly independent to each others. The low value of ICAP (0.300) also supported fairly independent contribution. We have also made attempts to investigate predictive power of the proposed model by using quality factor (QF). This is calculated by Pogliani's method[20,21] which defines QF as the ratio of correlation coefficient to standard error of estimation (SEE). Larger value of QF (4.061) will be supporting for better predictive power of the model. For reliability of the model, we have calculated regression associated statistical parameter called probable error of correlation (PE).[22] Goodness of fit calculated as PE= $2(1- r 2)/3 \sqrt{n}$, if the value of correlation coefficient (r) is more than six time of PE than the expression is good and reliable. In this model, value of coefficient of correlation is significantly higher than 6PE, supporting reliability and goodness.

The model was further analyzed for the outlier by the Z-score method (Z-value), the outlier test helps in the identification of unexplainable structurally diverse analogs. The persuasive QSAR model should not have any outlier. The Z-value for individual compounds lies within the specific range (<I2.5I), which indicated the absence of outliers. Test revealed that the model is able to explain the structurally diverse analogs and is helpful in the designing of more potent compounds using physiochemical descriptors shown in **Table V**.

The chance of fortuitous correlation is checked with the help of randomized biological activity test (Chance), which is evaluated as ratio of the equivalent regression equations to the total number of randomized sets. Chance value of 0.003 corresponds to 0.3% chance of fortuitous correlation.

To further access the robustness and statistical confidence of the model, bootstrapping analysis was performed. The bootstrapping analysis gives an overview about contribution of individual molecules to the QSAR model. The r^2_{bs} is average squared correlation coefficient calculated during the validation procedure which is computed from a subset of compounds used one at a time for the validation procedure while S_{bs} is the standard deviation in multiple run of a given data set. If the value of r^2_{bs} is at par to conventional r^2 and S_{bs} is low, than the model is robust and promising. In our study both values (r^2_{bs} = 0.746 & S_{bs} = 0.356) fall within the agreement.

The quality of the final equation obtained via SEQMLR was confirmed by means of the Kubinyi Function (FIT).[23,24] It is closely relates to the Fisher ratio (F), although the main disadvantage of F is its sensitivity to changes in d. If d is small sensitivity is high and vice- versa. The FIT has a low sensitivity towards changes in d values, as long as they are small numbers, and a substantially increasing sensitivity for large d values. FIT defined as; FIT ={$r^2 \cdot$(n-d- 1)}/{(n+ d^2)(1 - r^2)}, where n is number of compounds, d is optimal descriptors and r^2 is squared correlation coefficient. The model showed value of FIT (1.820) revealed quality of fitness.

Predictivity of the model was assured with the help of cross-validated constraints like q^2, S_{PRESS} and S_{DEP} obtained by 'leave one out (loo)' method. In this, model was built with N - 1 compounds and the Nth compound is predicted (**Table V & Figure 1 & 2**).

Each compound is left out from the model derivation and predicted in turn. The value of q^2 is the basic requirement for declaring a model to be a valid one is $q^2 > 0.5$[25]. Internal corroboration was carried out using leave-n-out cross-validation method and Y-scrambling test. *Chance* value (less than 0.001) of model revealed that the result was not based on prospective correlation. Similarly mean randomized squared correlation coefficient (R^2_{mean} = 0.208) and randomized standard deviation (SE_{rand} = 0.161) are also supporting that the results are not based on chance correlation. Although equations showed good internal consistency ($_1q^2$ = 0.600; S_{DEP}=0.282 & $_5q^2$ = 0.558; S_{DEP}=0.296), they may not be applicable for the analogs, which were never used in the generation of the correlation. Therefore, predictive power of Eqn. (6) was further confirmed by a test set of seven compounds.

The selected mathematical expression (model) are able to predict the activity of test set compound, which supported by r^2_{pred} (0.447) and low standard error of prediction (0.198) values. The predicted activity of test set compounds are very close to their actual activity, which indicate the robustness of model (**Table V, Figure 1 & 3**).

The QSAR model contributed positively by radial distribution functions (RDF080m & RDF085m) and topological descriptor (information content index neighborhood symmetry of order 3 IC3) while negatively through empirical descriptor (hydrophilic factor Hy). The percentage contributions of each descriptor are shown in **Figure 4**.

The RDF[26-28] of an ensemble of N atoms can be interpreted as the probability distribution to find an atom in a spherical volume of radius r. The RDFs used in this study are as follows:

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

$$f = 1/\sqrt{\sum_{r}\left[g(r)\right]^2},$$

where f is a scaling factor, N is the number of atoms, A is the atomic properties of atoms i and j, B is smoothing parameter which defines the probability distribution of the individual distances, rij is distance between the atoms i and j, g(r) was calculated at a number of discrete points with defined intervals. Each molecule was represented by a vector of length 32. The parameter B was set to 25 $A^{\circ-2}$ corresponding to a total resolution of 0.2 A° in the defined distance r. The RDF for the structure was calculated with the atomic properties. The RDF code has been proven to be a good representation for the 3D structure which has several merits like independence from the number of atoms; unambiguity regarding the three-dimensional arrangement of the atoms and invariance against translation and rotation of the entire molecule. RDF080m & RDF085m descriptors were contributed positively to the activity, revealed that increase in atomic masses are favorable for the activity. The atomic masses might be helpful for the activity through enthalpy gain by the non-bonded interactions with macromolecule.

IC3 is topological information indices of a graph based on neighbor degrees and edge multiplicity. The index based on first neighbor degrees and edge multiplicity. From the obtained equivalence classes in the hydrogen-filled multigraph, for each rth order (usually r = 0 - 6), the rth order neighborhood Information Content IC_r, is calculated as defined

$$IC_r = -\sum_{g=1}^{G}\frac{A_g}{A}.\log_2\frac{A_g}{A}$$

where g runs over the $\boldsymbol{G}$ equivalence classes, $\boldsymbol{A}$, is the cardinality of the gth equivalence class and $\boldsymbol{A}$ is the total number of atoms. It represents a measure of structural complexity per vertex.

Hy is an empirical descriptor related to the hydrophilicity of compounds. A simple empirical index related to hydrophilicity of compounds based on count descriptors. It is defined as:

$$Hy = \frac{\left(1+N_{Hy}\right).\log_2\left(1+N_{Hy}\right)+N_C.\left(\frac{1}{A}.log_2\frac{1}{A}\right)+\sqrt{N_{Hy}/A^2}}{\log_2\left(1+A\right)}$$

Where NHy is the number of hydrophilic groups (-OH, -SH, -NH), N_C the number of carbon atoms and A the number of atoms (hydrogen excluded). The negative contribution of hydrophilic factor suggested that lipophilic character of compound essential for the activity. Lipophilicity of the N-substituted phenazine-1-carboxamides analogs might be play crucial role in the cell permeability of the compounds.

Conclusion

In this study, molecular feature based quantification of inhibitory activity and binding key interaction with macromolecule have been explored. QSAR results elucidate that the hydrophobic, non-bonded interactions (van der Waals interaction) and atom connectivity affects activities of N-substituted

phenazine-1-carboxamides analogs as anti-tubarcular. The results show that the QSAR model is robust and has good predictive ability. These models are not only able to predict the activity of test compounds but also explained the important structural features of the molecules in a quantitative manner. The study provided useful clues about the structural requirement for effective anti-tubercular target interaction chemistry and hence for the improvement of the biological activity. In conclusion, the results derived in present study can provide a preliminary valuable guidance for continuing search for potential anti-tubercular prior to synthesis.

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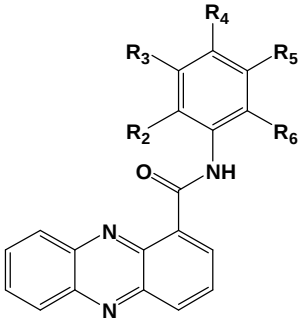
Table II: Fujita-Ban matrix of phenazine-1-carboxamides analogs with their pMIC



Compno.	R_2					R_3						R_4						R_5	R_6	pMIC
	CH_3	CF_3	OCH_3	Cl	F	Cl	F	Br	CH_3	CF_3	OCH_3	OCH_3	$COOCH_3$	OCF_3	CH_3	CF_3	F	CH_3	CH_3	
1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8.962
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	8.691
3	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8.932
4	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	8.631
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	8.910
6	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	8.910
7	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	8.686
8	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	7.117
9	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	8.924
10	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8.322
11	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	8.623
12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	9.277
13	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	9.199
14	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	8.906
15	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	8.952
16	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	8.974
21	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7.982
22	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8.609
23	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	8.924
24	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8.905
25	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	7.983
26	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	8.604
27	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	8.974

Table III: Regression and Quality Parameters of Equations

Eq.	*n*	r^2	r^2_{adj}	*Var*	*SE*	*QF*	*PE*	*FIT*	*AIC*	*Outlier*
6	20	0.814	0.764	0.049	0.222	4.061	0.028	1.820	0.082	Nil
5	20	0.791	0.752	0.052	0.228	3.908	0.031	2.092	0.078	One
4	20	0.712	0.678	0.067	0.260	3.251	0.043	1.749	0.091	Nil
3	20	0.640	0.620	0.079	0.282	2.837	0.054	1.522	0.097	Nil

Table IV: Pair Wise Correlation and VIF Values of the Descriptors used in QSAR Model

Descriptors	*VIF*	*Pair wise correlation coefficient of descriptors*			
		Hy	***IC3***	***RDF080m***	***RDF085m***
Hy	1.099	1.000			
IC3	1.135	0.195	1.000		
RDF080m	1.154	0.051	0.256	1.000	
RDF085m	1.145	0.196	0.131	0.288	1.000

TableV: Observed, calculated and predicted (loo) and predicted pMIC values with Z-score and residual of phenazine-1-carboxamides analogs used in QSAR analysis

Comp. no.	[a]Exp.	[b]Cal	[c]Calres	[d]Z-score	[e]pred(loo)	[f]pred(loo)res
1	8.962	8.656	0.306	1.552	8.619	0.343
2	8.691	8.751	-0.060	-0.302	8.756	-0.065
3	8.932	8.822	0.111	0.561	8.789	0.143
4	8.631	8.648	-0.016	-0.082	8.650	-0.019
5	8.910	8.848	0.062	0.317	8.830	0.080
6	8.910	8.922	-0.011	-0.056	8.925	-0.015
7	8.686	8.966	-0.280	-1.421	9.015	-0.329
8	7.117	7.127	-0.010	-0.048	7.734	-0.617
9	8.924	8.777	0.147	0.745	8.766	0.158
10	8.322	8.498	-0.176	-0.891	8.538	-0.216
11	8.623	8.679	-0.056	-0.281	8.686	-0.063
12	9.277	8.957	0.320	1.619	8.799	0.478
13	9.199	9.225	-0.027	-0.135	9.284	-0.085
14	8.906	8.717	0.189	0.960	8.698	0.208
15	8.952	8.765	0.187	0.948	8.750	0.202
16	8.974	8.870	0.104	0.529	8.825	0.149
17	8.673	8.630	0.043	0.216	8.621	0.052
18	8.325	8.391	-0.066	-0.336	8.421	-0.096
19	8.626	8.955	-0.330	-1.672	9.071	-0.446
20	8.325	8.763	-0.438	-2.221	8.895	-0.570
[g]21	7.982	-	-	-	8.365	-0.383

[g]22	8.609	-	-	-	8.735	-0.126
[g]23	8.924	-	-	-	9.026	-0.102
[g]24	8.905	-	-	-	9.402	-0.497
[g]25	7.983	-	-	-	8.329	-0.346
[g]26	8.604	-	-	-	8.844	-0.240
[g]27	8.974	-	-	-	8.889	0.085

[a]Experimental pMIC value of compound, [b]Calculated pMIC value of compound using model [c]Residual pMIC value of calculated data, [d]Z-score value obtained from model,[e]Predicted (loo) data of the compounds, [f]Residual value of predicted(loo) data of the compounds. [g]Test set compounds.

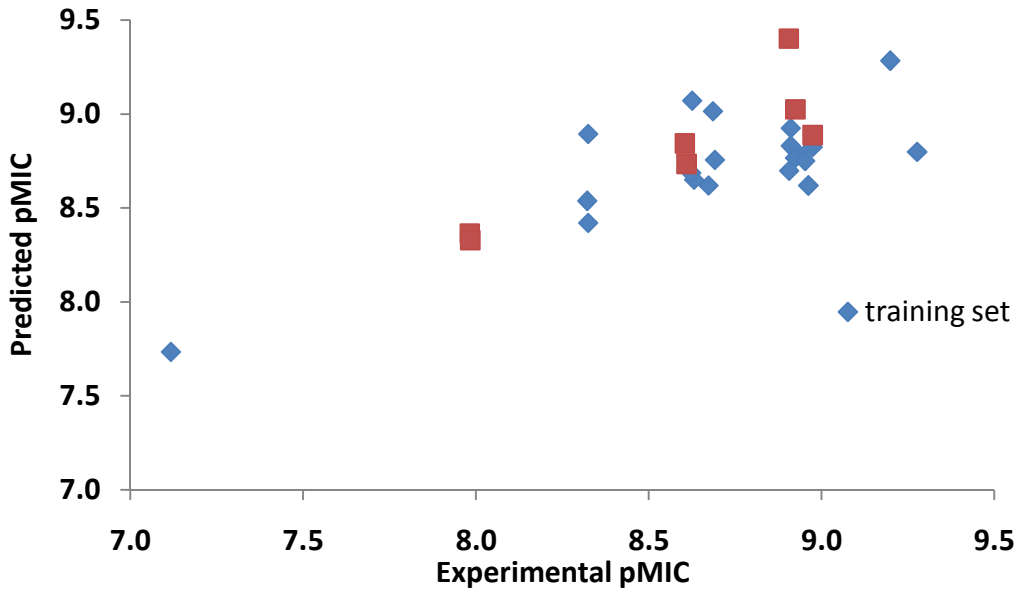


Fig. 1: Graphical representation of experimental versus predicted pMIC of training and test set

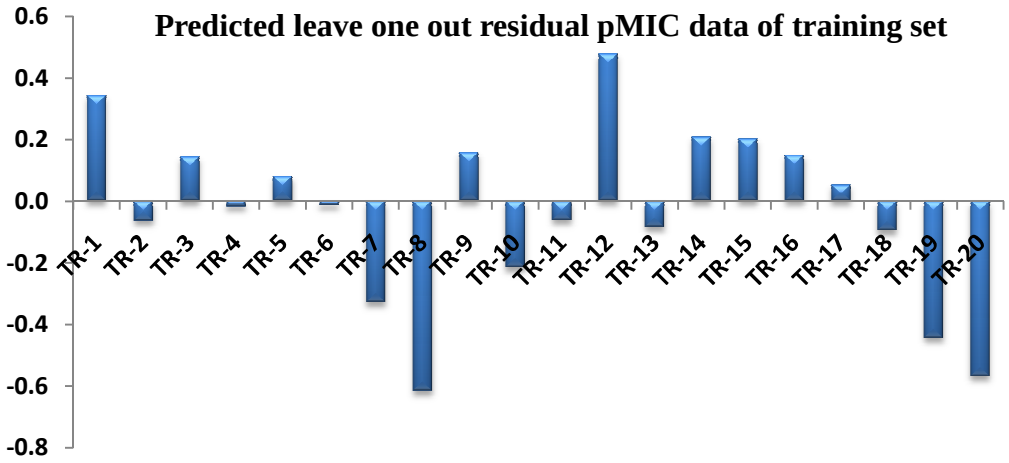


Fig. 2: Graphical representation of predicted leave one out residual data of training set

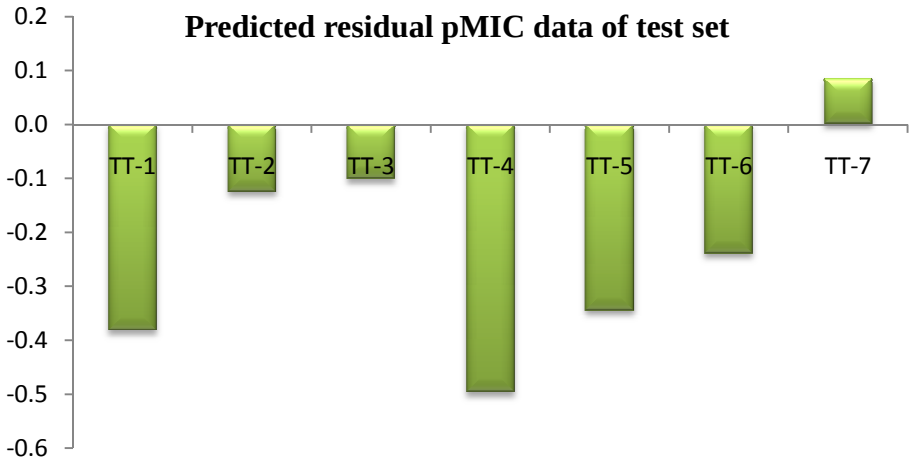


Fig. 3: Graphical representation of predicted residual data of test set

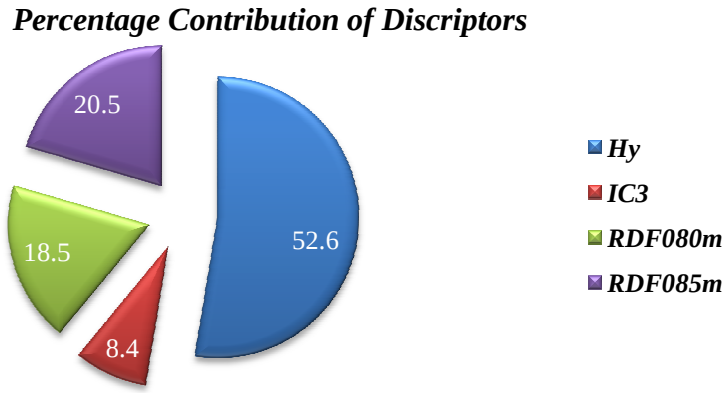


Fig. 4: Graphical representation of percentage contribution of descriptors

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