Prediction of Anti-mycobacterial Activity of 2-(4-(4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy)acetic acid Analogs: A QSAR Approach

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Abstract

Tuberculosis is one of the most prevalent infectious disease affecting approximately 8 million people every year. The emergence of multidrug resistant tuberculosis together with the spread of severe opportunistic disseminated infections is the tremendous problem. With this view in the present study, an attempt has been made to explore physicochemical requirements of 2-(4-(4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy)acetic acid analogs for binding with *Mycobacterium tuberculosis* $H_{37}Rv$ and isoniazid resistant strains. The quality of QSAR models obtained from regression within acceptable statistical range (explained variance ranging from 81.9 to 87.4%). The study shows that molecular geometry, atomic masses, hydrogen acceptor donor interactions are driving forces for describing the activity of 2-(4-(4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy)acetic acid as anti-mycobacterial agents.

Keywords: 2-(4-(4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy)acetic acid analogs; anti-mycobacterial activity; modified Free Wilson analysis; QSAR

1. Introduction

Tuberculosis (TB) is still recognized as a disease of worldwide incidence. It poses a global healthcare emergency with an estimated 8 million new cases and 1.8 million fatalities per annum worldwide.[1, 2] TB control has been made difficult in recent years by the apparent synergy between the causative agent, *Mycobacterium tuberculosis*, and HIV.[3, 4] The ability of *Mycobacterium tuberculosis* (MTB) to grow and persist in host and to establish and maintain a state of latent tuberculosis infection from which it can reactivate to cause disease is critical to its extraordinary success as a pathogen. Actively replicating tubercle bacilli die when abruptly deprived of oxygen. They shift into a state of dormancy, when allowed to adapt in gradually diminishing supply of oxygen. To keenly control TB, the development of drugs that are active against these "Dormant" organisms is necessary, prolonged deprivation of nutrients results in a marked slowing of bacterial growth and concomitant phenotypic resistance. Given this

backdrop, the effective control of TB requires the identification of new drug targets and the discovery of novel drugs.[5, 6]

With the current chemotherapy, drug resistance is the tremendous problem. In addition, the length and complexity of current TB treatment regimens results in poor patient compliance, a major contributing factor in the emergence of multi-drug-resistant tuberculosis[7] (MDRTB) and extensively drug-resistant tuberculosis (XDRTB)[8]. In spite of this, emergence of multiple drug resistant TB together with the spread of severe opportunistic disseminated infections that have focused the attention of scientific community throughout the world on urgent need for anti-mycobacterial agents. However, powerful new anti-tuberculosis drugs with new mechanism of action have not been developed in the last 40 years.
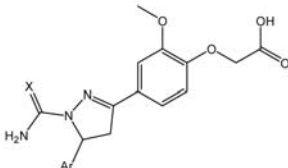
Quantitative structure activity relationships (QSAR) studies are tools of prediction endpoints of interest on organic compounds acting as drugs, which have not been experimentally determined. Many physiological activities
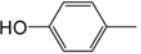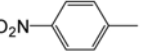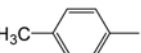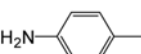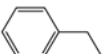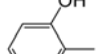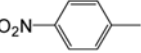
of compounds can be related to their composition and structure. The QSAR analysis of the anti-mycobacterial agents is the current highly concerned area of research. Several reports have been published regarding pyrazoline or phenoxyacetic acid derivatives are active against many mycobacteria. The QSAR analysis highlights the descriptors for important characteristic of antitubercular activity of these derivatives in relation to the confirmation of mo-

lecule, penetration into biological system and affinity towards receptor through electrostatic interaction.
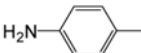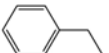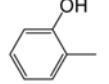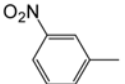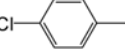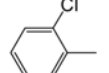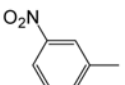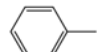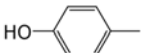
The purpose of this study was to develop some good, statistically significant QSAR models to correlate and predict antitubercular activity of 2-(4-(4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy)acetic acid derivatives. These QSAR model allow the prediction of antitubercular activity with an aim to reduce the number of compounds

Table 1. Structures and *in vitro* anti-mycobacterial activities against *Mycobacterium tuberculosis* ($H_{37}R_v$ and Isoniazid resistant strain)

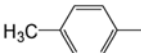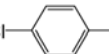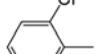| Comp.	Ar	X	MTB[a] MIC₁(in μ/ml)	MTB[a] pMIC₁[c]	INH Res MTB[b] MIC₂(in μ/ml)	INH Res MTB[b] pMIC₂[c]
T-1		S	6.25	4.790	6.25	4.790
T-2	HO—	S	0.20	6.303	0.20	6.303
T-3	O₂N—	S	6.32	4.833	6.25	4.838
T-4	F—	S	0.96	5.624	0.96	5.624
T-5	H₃C—	S	6.15	4.813	6.15	4.813
T-6	H₂N—	S	12.5	4.506	12.5	4.506
T-7		S	6.25	4.806	6.25	4.806
T-8	OH	S	0.58	5.840	0.58	5.840
T-9	O₂N—	O	6.25	4.822	6.25	4.822
T-10	F—	O	3.16	5.088	3.25	5.076
T-11	H₃C—	O	4.12	4.969	6.25	4.788
T-12	Cl—	O	0.13	6.492	0.13	6.492
T-13	Cl	O	1.26	5.506	1.26	5.506

Comp.	Ar	X	MTB[a] MIC$_1$ (in µ/ml)	MTB[a] pMIC$_1$[c]	INH Res MTB[b] MIC$_2$ (in µ/ml)	INH Res MTB[b] pMIC$_2$[c]
T-14	H$_2$N—	O	5.32	4.859	5.42	4.851
T-15		O	6.25	4.788	6.25	4.788
T-16	OH	O	0.58	5.822	0.58	5.822
T-17	O$_2$N	O	6.25	4.822	6.25	4.822
TT-1	Cl—	S	0.06	6.845	0.06	6.845
TT-2	Cl	S	0.12	6.544	0.12	6.544
TT-3	O$_2$N	S	6.25	4.838	3.12	5.140
TT-4		O	6.25	4.772	6.12	4.781
TT-5	HO—	O	1.23	5.496	1.23	5.496

[a] *Mycobacterium tuberculosis* $H_{37}R_v$, [b] Isoniazid-resistant *Mycobacterium tuberculosis*, [c] negative logarithm of MIC in mole

synthesis for antitubercular therapy with respect to cost, time. It's also aid in the designing of potent and safer inhibitors. The quantification of responsible physicochemical properties was done with the help of regression techniques.

2. Experimental

Biological activity: The set of 2-(4-(4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy)acetic acid analogs and their anti-mycobacterial minimum inhibitory concentration data (MIC$_1$ against H$_{37}$Rv and MIC$_2$ against isoniazid resistant strain) were taken from the reported work of Shaharyar et al[9]. These activity values were converted into negative logarithmic molar dose for quantification of structural features (Table 1).

Descriptors computation: In pursuit of potent antitubercular drugs, *de-novo* contribution was explored through Fujita Ban method, substituent contribution have been investigated through Hansch substituent constant[10–11] while molecular modeling study was performed using CS ChemOffice.[12] Structure of all the compounds was sketched using builder module of the program. Least energy conformers were generated through molecular mechanics (MM2) until the root mean square

(RMS) gradient value became smaller than 0.1 kcal/mol Å and subsequently subjected to re-optimization via MOPAC using Austin model-1 (AM1) method until the RMS gradient attained a value smaller than 0.001 kcal/mol Å. The basis of energy minimization is that the drug binds to the receptor in the most stable form i.e. minimum energy state form. The minimized molecule was saved as MOL file format. These files were used for calculation of various physicochemical descriptors with the help of DRAGON.[13]

Regression Analysis: In order to gain insight to the essential structural and physiochemical requirements for anti-mycobacteral activity in this class of molecules, 22 compounds were selected. These were divided into training set of 17 compounds and test set of 5 compounds. An effort to develop quantitative mathematical model, sequential multiple regression analysis was performed through VALSTAT[14]. Preliminary model were selected on the basis of following statistical parameters; *n*-number of compounds, *r*-multiple correlation coefficient, r^2_{adj} – adjustable squared correlation coefficient, *SEE*-standard error of estimation, *F*- Fisher's statistics. Selected models were further validated using various statistical parameter like predictive power by internal (leave N out cross validation, bootstrapping and randomization method) and external validation method.

3. Results and Discussion

In the present study, efforts have been made to find the structural requirements for the inhibitory activity of 2-(4-(4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy)acetic acid analogs against *M. tuberculosis*. Quantitative models were developed by means of *de-novo* contribution, substituent constant contribution and structural contribution considering regression methodology.

Contribution of basic scaffold i.e., 2-{4-(4,5-dihydro-1*H*-3-pyrazolyl)-2-methoxyphenoxy}acetic acid and substituent moieties were explored through modified Free Wilson analysis (Table 2). The multi-parametric mathematical expression against $H_{37}Rv$ indicated that many substituent's have poor contribution to the inhibitory activity. However, the multi-variant model was further evaluated by reducing the number of substituents to conquer the 95% confidence level. The successive regression analysis yielded tri-parametric models against $H_{37}Rv$ (Eqn-1), with imperative structural features.

$$pMIC_1 = 0.900(\pm0.321) \ 4\text{-}OHC_6H_4 + 1.669(\pm0.321)$$
$$4\text{-}ClC_6H_4 + 1.025(\pm0.321) \ 2\text{-}ClC_6H_4 + 4.999$$

$$n = 22, \quad r = 0.823, \quad r^2_{adj} = 0.624, \quad SEE = 0.428,$$
$$F = 12.620 \tag{1}$$

Modified Free Wilson analysis of inhibitory activity of pyrazol-3-yl analogs concluded that the substitutions at 2nd and 4th position of phenyl ring present on 5th position of pyrazolyl are crucial for the activity. Although literature reveals that substitution of thio moiety at N1 position of pyrazoline ring improves the antitubercular activity instead of carbonyl moiety.

It is interesting to mention that, further correlation between inhibitory activity and the substituent constant was extended by Hansch approach. Regression furnished several equations, but statistically significant tri-parametric model against $H_{37}Rv$ was considered (Eqn. 2).

$$pMIC_1 = 1.566(\pm0.223)\pi + 1.989(\pm0.300)HD + 1.202(\pm0.326)\mathcal{F} + 4.583$$

$$n = 22, \quad r = 0.873, \quad r^2_{adj} = 0.722, \quad SEE = 0.368,$$
$$F = 19.203 \tag{2}$$

Eqn-2 has a correlation coefficient (0.873), which accounted for 72.2% of variance in the activity. The data showed

Table 2. Modified Free Wilson matrix of 2-(4-(4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy)acetic acid analogs

Comp.	μ	4-OH C_6H_4	4-NO$_2$ C_6H_4	4-F C_6H_4	4-CH$_3$ C_6H_4	4-Cl C_6H_4	4-NH$_2$ C_6H_4	3-NO$_2$ C_6H_4	2-Cl C_6H_5	2-OH C_6H_4	$C_6H_5CH_2$	S
T-1	1	0	0	0	0	0	0	0	0	0	0	1
T-2	1	1	0	0	0	0	0	0	0	0	0	1
T-3	1	0	1	0	0	0	0	0	0	0	0	1
T-4	1	0	0	1	0	0	0	0	0	0	0	1
T-5	1	0	0	0	1	0	0	0	0	0	0	1
T-6	1	0	0	0	0	0	1	0	0	0	0	1
T-7	1	0	0	0	0	0	0	0	0	0	1	1
T-8	1	0	0	0	0	0	0	0	0	1	0	1
T-9	1	0	1	0	0	0	0	0	0	0	0	0
T-10	1	0	0	1	0	0	0	0	0	0	0	0
T-11	1	0	0	0	1	0	0	0	0	0	0	0
T-12	1	0	0	0	0	1	0	0	0	0	0	0
T-13	1	0	0	0	0	0	0	0	1	0	0	0
T-14	1	0	0	0	0	0	1	0	0	0	0	0
T-15	1	0	0	0	0	0	0	0	0	1	0	0
T-16	1	0	0	0	0	0	0	0	1	0	0	0
T-17	1	0	0	0	0	0	0	1	0	0	0	0
TT-1	1	0	0	0	0	1	0	0	0	0	0	1
TT-2	1	0	0	0	0	0	0	0	1	0	0	1
TT-3	1	0	0	0	0	0	0	1	0	0	0	1
TT-4	1	0	0	0	0	0	0	0	0	0	0	0
TT-5	1	1	0	0	0	0	0	0	0	0	0	0

that overall internal statistical significance level better than 99.9% as it exceeded the tabulated $F_{(3,18\ \alpha\ 0.001)} = 9.42$. The P value of each substituent constant is less than 0.001, suggests linear relationship between the descriptors and activity.

Swain Lupton field constant ($\mathcal{F}$) is an electronic parameter and it's contributed positively to the model. Hydrogen donor (*HD*) is pharmacophoric feature and its representative of hydrogen donor acceptor interaction, which is crucial for the activity. Hansch ð substituent constant describes the contribution of a substituent to the lipophilicity of a compound, which is decisive in mycobacterial cell wall infiltration.

In extend of our study; structural contributions were explored through DRAGON descriptors against H$_{37}$Rv and INH resistant strain of *Mycobacterium tuberculosis*. The series was divided into a training set of 17 compounds (T-1 to T-17) and test set of 5 compounds TT-1 to TT-5 (Table 1), on the basis of structural diversity and complete range of variation in inhibitory activity. Statistical significance expressions against H$_{37}$Rv (Eqn 3 & 4) and against INH resistant strain (Eqn 5 & 6) were selected respectively.

$$pMIC_1 = 14.779(\pm1.783)\ ATS8m + 5.064(\pm0.563)\ GATS1e - 1.021(\pm0.127)\ N\text{-}069 - 8.750$$

$$n = 17,\quad r = 0.938,\quad r^2_{adj} = 0.853,\quad SEE = 0.228,$$
$$F = 31.949 \tag{3}$$

$$pMIC_1 = 1.027(\pm0.166)\ nO + 91.436(\pm16.274)\ X1Av + 9.686(\pm1.118)\ GATS3e - 43.722$$

$$n = 17,\quad r = 0.924,\quad r^2_{adj} = 0.819,\quad SEE = 0.253,$$
$$F = 25.184 \tag{4}$$

$$pMIC_2 = 15.402(\pm1.666)\ ATS8m + 5.149(\pm0.526)\ GATS1e - 1.018(\pm0.119)\ N\text{-}069 - 9.163$$

$$n = 17,\quad r = 0.948,\quad r^2_{adj} = 0.874,\quad SEE = 0.213,$$
$$F = 38.134 \tag{5}$$

$$pMIC_2 = 1.051(\pm0.164)\ nO + 93.737(\pm16.043)\ X1Av + 9.827(\pm1.102)\ GATS3e - 44.770$$

$$n = 17,\quad r = 0.928,\quad r^2_{adj} = 0.828,\quad SEE = 0.250,$$
$$F = 26.709 \tag{6}$$

Selected set of mathematical expressions showed correlation coefficient better than 0.920, which accounted for more than 81.9% of the variance in the activity. The data showed overall internal statistical significance level better than 99.9% as it exceeded the tabulated $F_{(3,13\ \alpha\ 0.001)} = 11.9$. The P value of each substituent constant is less than 0.001, suggests linear relationship between the descriptors and activity. Predicted leave one out (LOO) and Predicted value of test set showed in Table 3.

Table 3. 2-(4-(4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy)acetic acid analogs predicted (LOO) pMIC$_1$ & pMIC$_2$ and Predicted pMIC$_1$ & pMIC$_2$ values with residual (Res) for training and test set respectively.

*Comp.	Eqn.3		Eqn.4		Eqn.5		Eqn.6	
	[a]pMIC$_1$	Res	[a]pMIC$_1$	Res	[b]pMIC$_2$	Res	[b]pMIC$_2$	Res
T-1	4.980	−0.190	4.502	0.288	4.962	−0.172	4.475	0.315
T-2	6.131	0.172	6.148	0.155	6.162	0.140	6.157	0.146
T-3	4.574	0.260	4.513	0.320	4.600	0.238	4.491	0.347
T-4	5.211	0.413	5.311	0.313	5.235	0.389	5.290	0.334
T-5	4.792	0.021	4.867	−0.054	4.768	0.045	4.850	−0.037
T-6	4.975	−0.470	4.825	−0.319	4.988	−0.482	4.799	−0.293
T-7	5.118	−0.313	5.150	−0.344	5.109	−0.303	5.139	−0.333
T-8	5.702	0.138	5.916	−0.076	5.705	0.135	5.919	−0.079
T-9	4.885	−0.064	4.936	−0.115	4.862	−0.041	4.915	−0.093
T-10	5.206	−0.117	5.564	−0.476	5.180	−0.104	5.539	−0.462
T-11	4.543	0.426	4.788	0.181	4.538	0.250	4.786	0.001
T-12	6.360	0.132	5.911	0.581	6.386	0.106	5.913	0.580
T-13	5.862	−0.357	5.954	−0.448	5.851	−0.345	5.954	−0.448
T-14	4.481	0.378	4.637	0.222	4.440	0.411	4.603	0.248
T-15	4.926	−0.138	4.942	−0.154	4.862	−0.075	4.926	−0.138
T-16	5.741	0.082	5.848	−0.026	5.700	0.122	5.844	−0.021
T-17	5.041	−0.220	4.936	−0.115	5.025	−0.204	4.915	−0.093
TT-1	6.957	−0.112	6.103	0.742	7.032	−0.187	6.110	0.735
TT-2	5.716	0.828	5.841	0.703	5.738	0.806	5.844	0.700
TT-3	5.157	−0.319	4.604	0.234	5.195	−0.055	4.589	0.551
TT-4	4.927	−0.155	4.546	0.226	4.877	−0.096	4.520	0.261
TT-5	5.968	−0.472	6.094	−0.598	5.946	−0.450	6.095	−0.599

* T-1 to T-17 are training set compounds while TT-1 to TT-5 are test set compounds, [a] predicted negative logarithm of MIC against *Mycobacterium tuberculosis* H$_{37}$R$_v$, [b] predicted negative logarithm of MIC against Isoniazid-resistant *Mycobacterium tuberculosis* strain.

Table 4. QSAR statistics of significant equations

Eqn.	n	r	r^2_{adj}	SEE	F	QF	VIF	r^2_{bs}	Chance	$_nQ^2$	S_{PRESS}	S_{DEP}	r^2_{pred}
1	22	0.823	0.624	0.428	12.620	1.922	–	–	<0.002	–	–	–	–
2	22	0.873	0.722	0.368	19.203	2.371	1.074 to 2.904	0.781	<0.001	0.606	0.438	0.428	–
3	17	0.938	0.853	0.228	31.949	4.108	1.788 to 2.537	0.896	<0.001	0.726	0.315	0.303	0.715
4	17	0.924	0.819	0.253	25.384	3.647	1.746 to 6.437	0.865	<0.001	0.754	0.298	0.287	0.589
5	17	0.948	0.874	0.213	38.134	4.439	1.788 to 2.537	0.906	<0.001	0.761	0.298	0.286	0.719
6	17	0.927	0.828	0.250	26.709	3.715	1.746 to 6.437	0.877	<0.001	0.764	0.296	0.284	0.451

Regression analysis revealed that identical physicochemical properties contributed towards the inhibitory activities of 2-(4-(4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy)acetic acid analogs against $H_{37}Rv$ and INH resistant strains of *Mycobacterium tuberculosis* with at par multiple regression coefficients (Eqn. 3 & 5 and Eqn. 4 & 6). Regression analysis depicted that this compounds might be act through enzymes, which is not affected through INH.

Effect of inter correlation of descriptors were checked through variance inflation factor (VIF)[15]. VIF value is calculated from $1/(1 – r^2)$, where r^2 is the multiple correlation coefficient of one descriptor's effect regressed on the remaining molecular descriptors. If VIF value is larger than 10, information of descriptor might be overlap with other descriptors. In models VIF values of these descriptors positioned in the range of 1.78 to 6.44 (Table 4). Therefore, from VIF analysis it is clear that the descriptors used in models are considerably self-governing.

This quality factor QF is defined as the ratio of correlation coefficient to the standard error of estimation that is QF = *r*/SEE and is used to account for the predictive power of the model. Obviously, the larger value of r, the smaller SEE, and higher will be QF, as well as better will be the predictive power of the model. QF value for Eqn. 3 to 6 falls in between 3.64–4.44.

Goodness of fit is calculated as probable error of correlation (PE), if the value of multiple correlation coefficients is more than six times of PE than the expression is good and reliable.

QSAR should be evaluated according to its ability to predict the activity of molecules, which contains the data, the dependent activity and the independent variables. Such an evaluation can be done by cross-validation method, which is based on 'leave-n-out' concept. In each step 'n' molecules are randomly or on turn excluded from the QSAR table. The QSAR equation is then calculated and used to predict the activity of these n molecules. The methodology yields cross-validated parameters, PRESS (predictive residual sum of squares), SSY (sum of the square of the response value), $_nQ^2$ (overall predictive ability), S_{PRESS} (uncertainty of predictive), and S_{DEP} (predictive square error). Parameters obtained for models discussed above are given in Table 4.

The predicted activity of test set compounds are very close to their actual activity, which indicate the robustness of model and also indicates that it can be used confidently for predicting the anti-mycobacterial activity of similar compounds (Table 3). The correlation of observed to predicted LOO activity are shown in Figure 1 & 2 for training set while predicted activity of test set are shown in Figure 3 & 4.

Inhibitory activity of 2-(4-(4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy)acetic acid analogs in eqn. 3 and 5 mainly govern through ATS8m and GATS1e positively while N-069 negatively. Similarly eqn. 4 and 6 are contributed through nO, X1Av, GATS3e positively. ATS8m is Broto-Moreau Autocorrelation Descriptor[16] weighted by atomic mass. It's calculated from the molecular graphs, by summing the product of atom weights of terminal atoms of
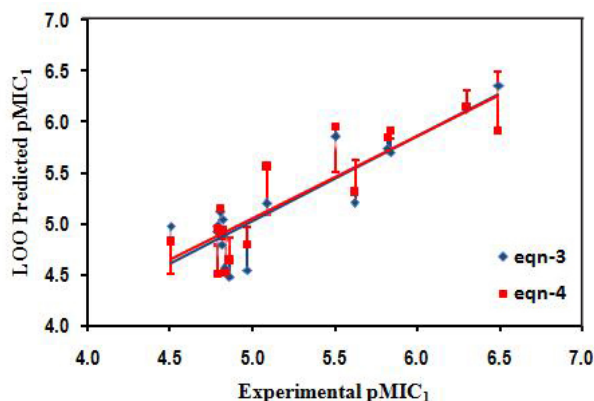

Figure 1. Graphical representation of experimental & LOO (leave one out) predicted $pMIC_1$ obtained from eqn-3 and 4 against *Mycobacterium tuberculosis* $H_{37}Rv$ strain
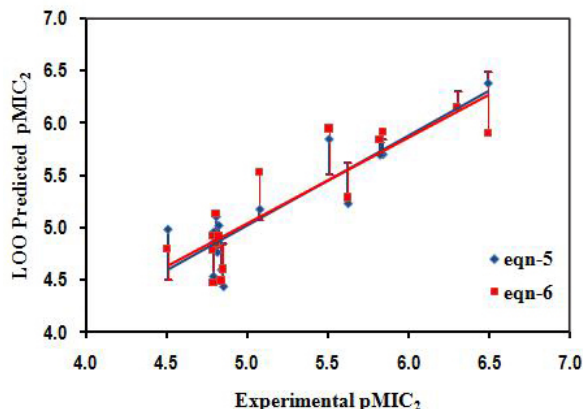

Figure 2. Graphical representation of experimental & LOO (leave one out) predicted $pMIC_2$ obtained from eqn-5 and 6 against *Mycobacterium tuberculosis* Isoniazid resistant strain
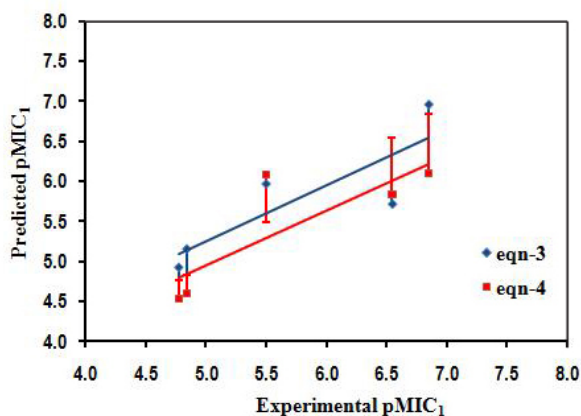
Figure 3. Graphical representation of experimental & predicted p-MIC$_1$ obtained from eqn-3 and 4 against *Mycobacterium tuberculosis* H$_{37}$Rv strain
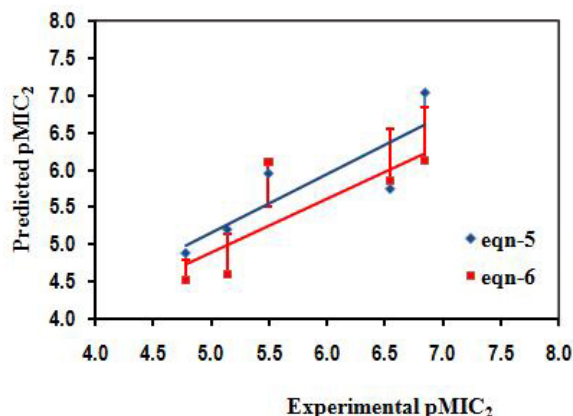

Figure 4. Graphical representation of experimental & predicted p-MIC$_2$ obtained from eqn-5 and 6 against *Mycobacterium tuberculosis* Isoniazid resistant strain

considering path length 8. Broto-Moreau Autocorrelation Descriptors can be calculated from following equation;

$$ATSdw = \sum_{i=1}^{n} \sum_{j=1}^{n} \delta_{ij}(w_i w_j) \tag{7}$$

where, w_i and w_j are the atomic masses weights of the atoms i and j, and δ_{ij} is Kronecker delta, that is, $\delta_{ij} =1$ if the ij^{th} entry in the Topological Level Matrix is $= d$, and $\delta_{ij} = 0$ otherwise.

GATS1e and GATS3e are Gray autocorrelation descriptors weighted by atomic Sanderson electronegativities and calculated from molecular graphs at path length 1 and 3 respectively. Sanderson electronegativities[17] allow the estimation of bond energies in a wide range of compounds. Sanderson electronegativities are representative of molecular geometry. X1Av is average valence connectivity index chi-1. X1Av mathematically expressed as

$$\chi^m v = \sum_{\kappa-1}^{\kappa} (\Pi\delta_i^v)_\kappa^{-1/2} \tag{8}$$

Where, $(\Pi\delta_i^v)$ is the product of the valence vertex degrees of the atoms that form a connected subgraph with $m = 1$ edges, and K is the total number of such distinct connected subgraphs (the H-depleted molecular graph) each having $m = 1$ edges. Its accounts for the presence of heteroatoms and double and triple bonds. N-069 is Ar-NH2/X-NH2 atom centered fragments defined by Ghose-Crippen.[18] nO is number of Oxygen which play crucial role in Hydrogen acceptor donor interaction.

4. Conclusion

The molecular modeling study of 2-(4-(4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy)acetic acid analogs brings im-

portant structural insight to aid the design of potent anti-mycobacterial agents. The QSAR models are statistically sound and explain more than 80% of the variance in the experimental activity with significant predictive power as is evidenced from the predicted activity of test set compounds. The study shows that molecular geometry, atomic masses, hydrogen acceptor donor interaction are driving forces for describing the activity of 2-(4-(4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy)acetic acid analogs as anti-mycobacterial agents. Modified Free Wilson analysis of inhibitory activity of pyrazol-3-yl analogs concluded that the substitutions at 2nd and 4th position of phenyl ring present on 5th position of pyrazolyl are crucial for the activity. Hansch substituent constant also explain the importance of associated substitution in the molecule, which should be taken in to account while designing new inhibitors. 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.

6. Reference

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Povzetek

Tuberkuloza je najpogostejša infektivna bolezen, ki vsako leto prizadene približno 8 milijonov ljudi. Pojav odpornosti na zdravila proti tuberkulozi, skupaj z razširjenjem hudih oportunističnih infekcij predstavlja vse večji problem. Predstavljena študija opisuje fizikalno kemijske zahteve analogov fenoksi ocetne kisline za vezavo z $H_{37}Rv$ in isoniazid odpornim sevom *Mycobacterium tuberculosis.* Kvaliteta pridobljenih QSAR modelov, pridobljenih z regresijo, je bila v okviru sprejemljivih statističnih območij (razložena varianca od 81.9 to 87.4 %). Študija kaže, da so geometrija molekul, atomske mase, ter interakcije med donorji in akceptorji vodilne gonilne sile za opis aktivnosti fenoski ocetne kisline kot anti-mikobakterijskega agensa.