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QSAR study of thiobenzamides using quantum mechanical descriptors

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ABSTRACT

MLR analysis of four sets of thiobenzamides for the prediction of activity against MIC with M. *Avium*, M. *Tuberculosis*, *M. fortuitum* and M. *kansasii* have been done using the descriptors heat of formation, molecular weight, total energy, HOMO energy, LUMO energy, absolute hardness and electronegativity. Maximum number of descriptors used in MLR analysis is 4 and total number of MLR analysis done for each set is 90. Best QSAR models developed for the four sets have the value of regression coefficient greater than 0.9 indicating the reliability of the model. Single descriptor HOMO energy has the value of regression coefficient greater than 0.5 in the first, second and fourth set of derivatives of thiobenzamides. In the third set of thiobenzamides, no single descriptor has the value of regression coefficient greater than 0.5. In this case the combination of total and LUMO energy provide the value of regression coefficient greater than 0.5.

KEYWORDS

Avium;
Tuberculosis;
Fortuitum;
Kansasii;
Absolute hardness;
Electronegativity;
HOMO energies;
LUMO energies.

INTRODUCTION

Search for novel drugs against dangerous fungal and bacterial infections including tuberculosis and other mycobacterioses is one of the goals of the present-day pharmaceutical chemistry. New discoveries in the area of microbial regulatory mechanisms playing an important role in the process of infection have offered the opportunity for a totally new class of antimicrobial agents. The enhanced prevalence of infectious diseases threatens world population. Although tuberculosis appeared as a curable disease for years, it is regaining importance due to the multidrug resistance.[1,2] Worldwide statistics on tuberculosis surprisingly reveals that, nearly one–third of the world's population is infected with tuberculosis, with approximately eight million new patients every year.[3] A major issue is the increase of multi-drug resistant tuberculosis (MDRTB) giving rise to the disease expensive and incurable especially in immunodeficient subjects such as AIDS patients.[4] Hence, there is an increased demand to develop new antituberculosis agents effective against pathogens resistant to current treatment.

Amide compounds are very common in biological systems, but thioamides are rare. Correspondingly, reports of amide metabolism are very common, whereas comparatively little has been reported on bacterial thioamide metabolism. Thioamides are found naturally in the copper-chelating compound methanobactin described in *Methylosinus trichosporium* OB3b[5]. The antibiotic sulfinemycin, produced by *Streptomyces albus* NRRL 3384, has a primary thioamide S-oxide

moiety[6]. Thioacetamide has applications in leather, textile, paper, rubber, and petroleum industries[7], and 2,6-dichlorothiobenzamide (chlorthiamid) is used as a herbicide[8] . Thioamide compounds such as 2-ethyl-4-pyridinecarbothioamide (ethionamide) are important second-line drugs in the treatment of multidrug-resistant *Mycobacterium tuberculosis* and *M. leprae*[9,10]. In *M. tuberculosis,* oxidation of the thioamide sulfur is a necessary step in converting the prodrug ethionamide to its active form[11,12].

Waisser and his associates investigated[13-15] thiobenzmides (Figure 1) on various mycobacteria and related the activity of the thioamides with various physico chemical techniques. Several derivatives of thiomides were studied against M. avium, M. tuberculosis, M. fortuitum, M. kansasii. The QSAR derivatives of thiobenzamide were developed using electronic parameters and the results obtained indicated the correlation coefficient above 0.88. QSAR models with quantum chemical parameters are fast developing and in recent years valuable papers have been published.[16-21]

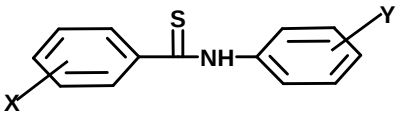

Figure 1 : Derivative of thiobenzmide

QSAR is a process whereby the structures of a set of compounds are quantified and then compared to the numerical values of a biological activity or a physical property. The challenge here has been to find some numerical code for a molecule or a fragment that is information-rich. This structure information and the measured property or activity is then processed into a mathematical model of relationship. From a quality model it is possible to predict and to design compounds for synthesis and testing that have a good possibility for activity.

A QSAR generally takes the form of a linear equation

Biological Activity = Const + $(C_1 P_1)$ + $(C_2 P_2)$ + $(C_3 P_3)$ +...

where the parameters P_1 through P_n are computed for each molecule in the series and the coefficients C_1 through C_n are calculated by fitting variations in the parameters and the biological activity.[22-27] In view of the importance of thiobenzamides as a potent inhibitor of mycobacteria, we have chosen to make QSAR study of the derivatives of thioamides.

We have studied the QSAR with the help of following quantum chemical parameters.

1. Heat of Formation (kcal/mole)
2. Molecular Weight
3. Total Energy (Hartree)
4. HOMO Energy (eV)
5. LUMO Energy (eV)
6. Absolute Hardness (eV)
7. Electronegativity (eV)

METHODOLOGY

Multi linear regression analysis

Multi linear Regression attempts to model the relationship between two are more explanatory variables and a response variable by fitting a linear equation to observed data. Every value of the independent variables and a response variable by fitting a linear to observed data. Every value of the independent variable χ is associated with a value of the dependent variable y. The population regression line for p explanatory variables $\chi_1, \chi_2 \ldots., \chi_p$ is defined to be $\mu_y = \beta_1 + \beta_1\chi_1 + \beta_2\chi_2 + \ldots\ldots + \beta_p\chi_p$.

This line described how the mean response μ_y changes with the explanatory variables. The observed values for y vary about their means μ_y changes with the explanatory variables. The observed values for y vary about their means μ_y and are assumed to have the same standard division σ. The fitted values $b_0, b_1,\ldots,b_p$ estimate the parameters $\beta_1 + \beta_1\chi_1 + \ldots\ldots \beta_p\chi_p$ of the population regression line.[56-61]

Since the observed values for y vary about their means μ_y, the multiple regression model included a term for this variation. I words, the model is expressed as DATA = FIT + RESIDUAL, where the "FIT" term represents the expression $\beta_0 + \beta_1\chi_1 + \beta_2\chi_2 + \ldots\ldots \beta_p\chi_p$. The "RESIDUAL" term represents the deviations of the observed values y from their means μ_y, which are normally distributed with mean 0 and variance σ. The notation for model deviation is ε. Formally, the model for multiple linear regressions, given *n* observations, is

$$y_i = \beta_0 + \beta_1\chi_{i1} + \beta_2\chi_{i2} + \ldots\ldots \beta_p\chi_{ip} + \varepsilon_I$$

for I = 1,2 …..*n*.

In the least squares model, the best-fitting line for the observed data is calculated by minimizing the sum of the squares of the vertical deviations from each data point to the line (if a point lies on the fitted line exactly, then its vertical division is 0). Because the deviations are first squared, then summed, there are no cancellations between positive and negative values. The least-squares estimates b_0, b_1,…..b_p are usually computed by statistical software.

The values fit by the equation b_0, $b_1\chi_{i1}$,…..$b_p\chi_{i\,p}$ are denoted $\hat{Y}_i$, and the residuals e_i are equal to y_i - $\hat{Y}_i$, the difference between the observed and fitted values. The sum of the residuals is equal to zero.

Descriptors used in QSAR study

The 3D modeling and geometry optimization[41,42] of all the derivatives of thiobenzamides described in TABLES 1-4 have been done by Cache software using PM3[43] method. The values of various descriptors for QSAR have also been evaluated with the same software using the same method. The principles on which the evaluation of various descriptors are described below:

Heat of formation

Heat of formation[44] is the heat released or absorbed (enthalpy change) during the formation of a pure substance from its elements, at constant pressure and usually denoted by ΔH_f. It is defined as

$$\Delta \mathbf{H_f} - \mathbf{H_f} - \sum_{\mathbf{a}} \mathbf{H_f^a}$$

H_f - quantum-chemically calculated total energy of the molecule

H_f^a - quantum-chemically calculated energies of isolated atoms, *a*

Molecular weight

Molecular weight is defined as Mass of a molecule of a substance, based on 12 as the atomic weight of carbon-12. It is calculated in practice by summing the atomic weights of the atoms making up the substance's molecular formula. The molecular weight of a hydrogen molecule (chemical formula H_2) is 2 (after rounding off); for many complex organic molecules (e.g., proteins, polymers) it may be in the millions.

Total energy[45,46]

It is defined as

$$\mathbf{E_{tot} = E_{el} + \sum_{A \neq B} Z_A Z_B \,/\, R_{AB}}$$

E_{el} - total electronic energy of the molecule
Z_A, Z_B - nuclear charges of atoms *A* and *B*
R_{AB} - distance between nuclei *A* and *B*

HOMO energy[47,48]

It is represented by the symbol εHOMO and is the energy of highest occupied molecular orbital.

$$\boldsymbol{\varepsilon_{HOMO} = \langle \varphi_{HOMO} | \hat{F} | \varphi_{HOMO} \rangle}$$

ϕ_{HOMO} - highest occupied molecular orbital

$\hat{F}$ - Fock operator

LUMO energy[47,48]

It is represented by the symbol εLUMO and is the energy of lowest unoccupied molecular orbital.

$$\boldsymbol{\varepsilon_{LUMO} = \langle \phi_{LUMO} | \hat{F} | \phi_{LUMO} \rangle}$$

ϕ_{LUMO} - lowest unoccupied molecular orbital

$\hat{F}$ - Fock operator

Absolute hardness[49-51]

It is defined as

$$\boldsymbol{\eta = (\varepsilon LUMO - \varepsilon HOMO)/2}$$

where

εLUMO - lowest unoccupied molecular orbital energy
εHOMO - highest occupied molecular orbital energy

Electronegativity

Parr etal.[42,49,55] have shown that the Electronega-

TABLE 1 : MIC of thiobenzamides with *M. avium*

Compound	Substituents		Log 1/C obsd
	X	Y	
T1C1	H	3-F	3.3
T1C2	3-Cl	3-F	3.9
T1C3	4-Cl	3-F	3.6
T1C4	4-NO2	3-F	3.9
T1C5	4-Me	3-F	3.3
T1C6	4-OMe	3-F	3.3
T1C7	3-Br	3-F	4.22
T1C8	H	4-F	3.6
T1C9	3-Cl	4-F	3.6
T1C10	4-Cl	4-F	3.3
T1C11	4-NO2	4-F	3.9
T1C12	4-Me	4-F	2.7
T1C13	4-OMe	4-F	2.7
T1C14	3-Br	4-F	3.6

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TABLE 2 : MIC of thiobenzamides with *M. tuberculosis*

Compound	Substituents		Log 1/C Obsd.
	X	Y	
T2C1	H	3-F	4.22
T2C2	3-Cl	3-F	4.22
T2C3	4-Cl	3-F	4.22
T2C4	4-NO2	3-F	4.52
T2C5	4-Me	3-F	3.6
T2C6	4-OMe	3-F	3.3
T2C7	3-Br	3-F	4.52
T2C8	H	4-F	3.6
T2C9	3-Cl	4-F	3.9
T2C10	4-Cl	4-F	3.9
T2C11	4-NO2	4-F	4.22
T2C12	4-Me	4-F	2.7
T2C13	4-OMe	4-F	2.7
T2C14	3-Br	4-F	3.9

TABLE 3 : MIC of thiobenzamides with *M. fortuitum*

Compound	Substituents		Log 1/C Obsd.
	X	Y	
T3C1	H	3-F	3.6
T3C2	3-Cl	3-F	3.9
T3C3	4-Cl	3-F	3.3
T3C4	4-NO2	3-F	3.9
T3C5	4-Me	3-F	3.3
T3C6	4-OMe	3-F	3.3
T3C7	3-Br	3-F	4.22
T3C8	H	4-F	3.6
T3C9	3-Cl	4-F	3.6
T3C10	4-Cl	4-F	3.3
T3C11	4-NO2	4-F	3.9
T3C12	4-Me	4-F	2.7
T3C13	4-OMe	4-F	2.7
T3C14	3-Br	4-F	3

tivity (χ) of any chemical species is equal to the negative value of chemical potential μ. Indeed it follows rigorously that

$$\chi = -\mu = 1/2.\ (I + A)$$
$$= -(\varepsilon HOMO + \varepsilon LUMO)/2$$

where I and A are ionization potential and electron affinity[52-54] of molecule.

RESULT AND DISCUSSION

We have considered eight quantum chemical descriptors viz. heat of formation, molecular weight, total energy, HOMO energy, LUMO energy, absolute hardness and electronegativity. We have performed MLR analysis for the prediction of activity by taking one, two, three and four descriptors in all the combinations. Total numbers of combinations of descriptors for each set of thiobenzamides are 90. The best QSAR models thus obtained are discussed below-

TABLE 4 : MIC of thiobenzamides with *M. kansasii*

Compound.	Substituents		Log 1/C Obsd.
	X	Y	
T4C1	H	3-F	3.9
T4C2	3-Cl	3-F	4.22
T4C3	4-Cl	3-F	4.22
T4C4	4-NO2	3-Fa	4.22
T4C5	4-Me	3-F	3.3
T4C6	4-OMe	3-F	3.3
T4C7	3-Br	3-F	4.22
T4C8	H	4-F	3.6
T4C9	3-Cl	4-F	3.6
T4C10	4-Cl	4-F	3.6
T4C11	4-NO2	4-F	4.22
T4C12	4-Me	4-F	2.7
T4C13	4-OMe	4-F	2.7
T4C14	3-Br	4-F	3.9

QSAR of MIC of thiobenzamides with *M. avium*

Best QSAR model for the prediction of activity in terms of log 1/C of the derivatives of thiobenzamides given in TABLE 1 contains heat of formation, total energy, HOMO energy and Electronegativity as descriptors. Values of all the descriptors used in MLR analysis are shown in TABLE 5 alongwith observed and predicted activity using this model. Regression equation of this QSAR model is given below and it possesses the high value of regression coefficient (rCV^2 = 0.52566) which indicates that the QSAR model is reliable.

APA = -0.0109025*ΔH_f + 0.0336171 * TE-2.42771 * $\in$HOMO + 2.5895 * χ-26.2701

rCV^2 = 0.52566

r^2 = 0.816574

TABLE 5 contains the values of descriptors, observed activities and predicted activities by best QSAR model APA of thiobenzamides against MIC with *M. Avium.* TABLES 5(a) to 5(g) shows the residual and regression analysis of this QSAR model indicating the reliability. Residual plot of normal probability is shown in

TABLE 5 : Values of descriptors (Heat of formation, molecular weight, total energy, HOMO energy, LUMO energy and Electronegativity), observed activities and predicted activities by best QSAR model APA of thiobenzamides against MIC with *M. avium*

Compound	Heat of Formation (kcal/mole)	Molecular Weight	Total Energy (Hartree)	HOMO Energy (eV)	LUMO Energy (eV)	Absolute Hardness (eV)	Electro-negativity (eV)	Obsd. Activity in terms of log (1/C)	Predicted activity by Best QSAR model APA
T1C1	43.674	231.287	-113.753	-8.703	-1.304	3.699	5.004	3.300	3.517
T1C2	37.402	265.732	-125.495	-8.763	-1.689	3.537	5.226	3.900	3.911
T1C3	37.278	265.732	-125.498	-8.770	-1.387	3.691	5.079	3.600	3.548
T1C4	122.446	276.285	-145.434	-9.027	-2.194	3.417	5.611	3.900	3.951
T1C5	32.231	245.314	-120.940	-8.667	-1.287	3.690	4.977	3.300	3.243
T1C6	3.482	261.313	-133.129	-8.644	-1.282	3.681	4.963	3.300	3.054
T1C8	43.627	231.287	-113.753	-8.684	-1.288	3.698	4.986	3.600	3.423
T1C9	35.464	265.732	-125.519	-8.762	-1.379	3.692	5.070	3.600	3.525
T1C10	35.351	265.732	-125.521	-8.750	-1.354	3.698	5.052	3.300	3.448
T1C11	124.698	276.285	-145.408	-9.007	-2.196	3.406	5.601	3.900	3.854
T1C13	3.455	261.313	-133.129	-8.625	-1.259	3.683	4.942	2.700	2.954
T1C14	51.553	310.183	-123.640	-8.787	-1.430	3.679	5.108	3.600	3.572

TABLE 5(a) : Regression summary for dependent variable for QSAR model APA

R = .90343691 R^2 = .81619825 Adjusted R^2 = .71116867 F(4,7) = 7.7711 p

	b*	Std.Err. - of b*	b	Std.Err. - of b	t(7)	p-value
Intercept			-26.3811	16.89488	-1.56148	0.162380
ΔH_f	-1.21103	0.691104	-0.0109	0.00623	-1.75231	0.123178
TE	0.99462	0.317126	0.0336	0.01071	3.13636	0.016463
∈HOMO	-0.90795	0.860303	-2.4439	2.31562	-1.05538	0.326308
χ	1.73888	0.899718	2.5832	1.33656	1.93269	0.094547

TABLE 5(b) : Variables currently in the equation for QSAR model APA

	b* in	Partial - Cor.	Semipart - Cor.	Tolerance	R-square	t(7)	p-value
ΔH_f	-1.21103	-0.552183	-0.283946	0.054975	0.945025	-1.75231	0.123178
TE	0.99462	0.764358	0.508220	0.261088	0.738912	3.13636	0.016463
∈HOMO	-0.90795	-0.370508	-0.171016	0.035477	0.964523	-1.05538	0.326308
χ	1.73888	0.589869	0.313176	0.032437	0.967563	1.93269	0.094547

TABLE 5(c) : Analysis of variance for QSAR model APA

	Sums of - Squares	df	Mean - Squares	F	p-value
Regress.	1.077382	4	0.269345	7.771128	0.010267
Residual	0.242618	7	0.034660		
Total	1.320000				

TABLE 5(d) : Redundancy of independent variables for QSAR model APA

	Toleran.	R-square	Partial - Cor.	Semipart - Cor.
ΔH_f	0.054975	0.945025	-0.552183	-0.283946
TE	0.261088	0.738912	0.764358	0.508220
∈HOMO	0.035477	0.964523	-0.370508	-0.171016
χ	0.032437	0.967563	0.589869	0.313176

TABLE 5(e) : Covariances of regression coefficients for QSAR model APA

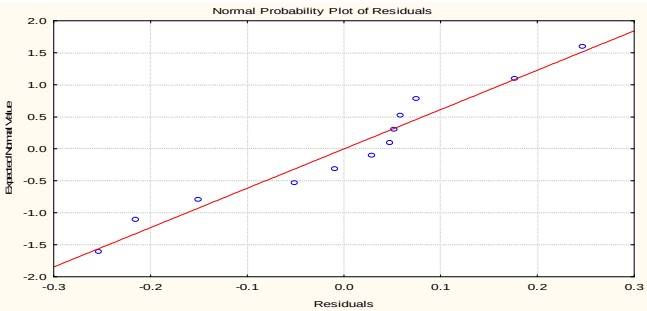
	ΔH_f	TE	∈HOMO	χ
ΔH_f	0.000039	-0.000037	0.007263	-0.003363
TE	-0.000037	0.000115	-0.001644	0.008760
∈HOMO	0.007263	-0.001644	5.362075	1.702199
χ	-0.003363	0.008760	1.702199	1.786391

TABLE 5(f) : Current status of sweep matrix for QSAR model APA

	ΔH_f	TE	∈HOMO	χ	Log 1/C Obsd.
ΔH_f	-18.1901	4.68834	-11.3952	9.5621	-1.21103
TE	4.6883	-3.83012	0.6888	-6.6500	0.99462
∈HOMO	-11.3952	0.68883	-28.1872	-16.2130	-0.90795
χ	9.5621	-6.65001	-16.2130	-30.8292	1.73888
Log 1/C Obsd.	-1.2110	0.99462	-0.9079	1.7389	0.18380

TABLE 5(g) : Predicted & residual values for QSAR model APA

Compound	Observed - Value	Predicted - Value	Residual	Standard - Pred. v.	Standard - Residual	Std.Err. - Pred.Val	Mahalanobis - Distance	Deleted - Residual	Cook's - Distance
T1C1	3.300000	3.516033	-0.21603	0.05123	-1.16040	0.108111	2.792742	-0.32594	0.206736
T1C2	3.900000	3.910203	-0.01020	1.31072	-0.05480	0.184056	9.834736	-0.45144	1.149462
T1C3	3.600000	3.548839	0.05116	0.15605	0.27481	0.101724	2.367440	0.07293	0.009165
T1C4	3.900000	3.951394	-0.0513	1.44234	-0.27605	0.129187	4.380013	-0.09912	0.027300
T1C5	3.300000	3.241861	0.05813	-0.82483	0.31229	0.098228	2.145569	0.08056	0.010427
T1C6	3.300000	3.054015	0.24598	-1.42505	1.32128	0.120611	3.700145	0.42389	0.435191
T1C8	3.600000	3.423616	0.17638	-0.24407	0.94743	0.122949	3.880830	0.31281	0.246260
T1C9	3.600000	3.525144	0.07485	0.08034	0.40208	0.096923	2.064729	0.10268	0.016492
T1C10	3.300000	3.450488	-0.1504	-0.15821	-0.80833	0.086662	1.466889	-0.19211	0.046150
T1C11	3.900000	3.852964	0.04703	1.12783	0.25265	0.137923	5.120607	0.10425	0.034423
T1C13	2.700000	2.953630	-0.25363	-1.74581	-1.36235	0.133323	4.724605	-0.52063	0.802145
T1C14	3.600000	3.571813	0.02818	0.22946	0.15140	0.087653	1.521696	0.03621	0.001678
Min.	2.700000	2.953630	-0.25363	-1.74581	-1.36235	0.086662	1.466889	-0.52063	0.001678
Max.	3.900000	3.951394	0.245985	1.44234	1.32128	0.184056	9.834736	0.42389	1.149462
Mean	3.500000	3.500000	-0.00000	0.00000	-0.00000	0.117279	3.666667	-0.03799	0.248786
Median	3.600000	3.520588	0.03761	0.06579	0.20203	0.114361	3.246444	0.054576	0.040287



Graph 1 : Normal probability plot of residuals for QSAR Model APA

Graph 1. Observed and predicted activities of MIC of thiobenzamides with M. *Avium* are shown in Graph 5.

QSAR of MIC of thiobenzamides with *M. tuberculosis*

Best QSAR model for the prediction of activity in terms of log 1/C of the derivatives of thiobenzamides given in TABLE 1 contains heat of formation, total energy, HOMO energy and Electronegativity as descriptors. Values of all the descriptors used in MLR analysis are shown in TABLE 6 alongwith observed and predicted activity using this model. Regression equation of this QSAR model is given below and it possesses the very high value of regression coefficient (r^2 = 0.918194) which indicates that the QSAR model is most reliable.

$BPA = -0.0168719 * \Delta H_f + 0.0543903 * TE - 8.93962 * \in HOMO + 1.01642 * \chi - 71.9487$

rCV^2 = 0.554923

r^2 = 0.918194

TABLE 6 contains the values of descriptors, observed activities and predicted activities by best QSAR model BPA of thiobenzamides against MIC with *M. Tuberculosis.* TABLES 6(a) to 6(g) shows the residual and regression analysis of this QSAR model indicating the reliability. Residual plot of normal probability is shown in Graph 2. Observed and predicted activities of MIC of thiobenzamides with M. *Tuberculosis* are shown in Graph 6.

QSAR of MIC of thiobenzamides with *M. fortuitum*

Best QSAR model for the prediction of activity in terms of log 1/C of the derivatives of thiobenzamides given in TABLE 1 contains molecular weight, total energy, HOMO energy and LUMO energy as descriptors. Values of all the descriptors used in MLR analysis are shown in TABLE 7 alongwith observed and pre-

TABLE 6 : Values of descriptors (Heat of formation, molecular weight, total energy, HOMO energy, LUMO energy and Electronegativity), observed activities and predicted activities by best QSAR model APA of thiobenzamides against MIC with *M. tuberculosis*

Compound	Heat of Formation (kcal/mole)	Molecular Weight	Total Energy (Hartree)	HOMO Energy (eV)	LUMO Energy (eV)	Absolute Hardness (eV)	Electronegativity (eV)	Obsd. Activity in terms of log (1/C)	Predicted activity by Best QSAR model BPA
T2C1	43.674	231.287	-113.75	-8.703	-1.304	3.699	5.004	4.22	4.019
T2C2	37.402	265.732	-125.5	-8.763	-1.689	3.537	5.226	4.22	4.247
T2C3	37.278	265.732	-125.5	-8.77	-1.387	3.691	5.079	4.22	4.162
T2C4	122.446	276.285	-145.43	-9.027	-2.194	3.417	5.611	4.52	4.48
T2C5	32.231	245.314	-120.94	-8.667	-1.287	3.69	4.977	3.6	3.47
T2C6	3.482	261.313	-133.13	-8.644	-1.282	3.681	4.963	3.3	3.073
T2C7	49.942	310.183	-123.64	-8.807	-1.444	3.681	5.126	4.52	4.423
T2C8	43.627	231.287	-113.75	-8.684	-1.288	3.698	4.986	3.6	3.824
T2C9	35.464	265.732	-125.52	-8.762	-1.379	3.692	5.07	3.9	4.109
T2C10	35.351	265.732	-125.52	-8.75	-1.354	3.698	5.052	3.9	3.981
T2C11	124.698	276.285	-145.41	-9.007	-2.196	3.406	5.601	4.22	4.253
T2C13	3.455	261.313	-133.13	-8.625	-1.259	3.683	4.942	2.7	2.881

TABLE 6(a) : Regression summary for dependent variable for BPA QSAR model

R = .95748527 R² = .91677804 Adjusted R² = .86922264 F(4,7) = 19.278 p						
	b*	Std.Err. - of b*	b	Std.Err. - of b	t(7)	p-value
Intercept			-71.5404	16.18699	-4.41962	0.003083
ΔH_f	-1.20882	0.451579	-0.0169	0.00630	-2.67687	0.031683
TE	1.04147	0.211009	0.0544	0.01102	4.93565	0.001683
∈HOMO	-2.13792	0.538179	-8.8700	2.23285	-3.97251	0.005375
χ	0.45934	0.608193	1.0559	1.39808	0.75525	0.474738

TABLE 6(c) : Analysis of variance for BPA QSAR model

	Sums of - Squares	df	Mean - Squares	F	p-value
Regress.	2.894452	4	0.723613	19.27810	0.000700
Residual	0.262748	7	0.037535		
Total	3.157200				

TABLE 6(e) : Covariances of regression coefficients for BPA QSAR model

	ΔH_f	TE	∈HOMO	χ
ΔH_f	0.000040	-0.000038	0.006187	-0.004095
TE	-0.000038	0.000121	-0.000097	0.009901
∈HOMO	0.006187	-0.000097	4.985638	1.720732
χ	-0.004095	0.009901	1.720732	1.954621

TABLE 6(b) : Variables currently in the equation for BPA QSAR model

	b* in	Partial – Cor.	Semipart – Cor.	Tolerance	R-square	t(7)	p-value
ΔH_f	-1.20882	-0.711229	-0.291875	0.058300	0.941700	-2.67687	0.031683
TE	1.04147	0.881357	0.538163	0.267016	0.732984	4.93565	0.001683
∈HOMO	-2.13792	-0.832301	-0.433147	0.041047	0.958953	-3.97251	0.005375
χ	0.45934	0.274493	0.082350	0.032141	0.967859	0.75525	0.474738

TABLE 6(d) : Redundancy of independent variables for BPA QSAR model

	Toleran.	R-square	Partial - Cor.	Semipart - Cor.
ΔH_f	0.058300	0.941700	-0.711229	-0.291875
TE	0.267016	0.732984	0.881357	0.538163
∈HOMO	0.041047	0.958953	-0.832301	-0.433147
χ	0.032141	0.967859	0.274493	0.082350

TABLE 6(f) : Current status of sweep matrix for BPA QSAR model

	ΔH_f	TE	∈HOMO	χ	Log 1/C Obsd.
ΔH_f	-17.1525	4.38843	-8.9904	10.7393	-1.20882
TE	4.3884	-3.74510	0.0375	-6.9366	1.04147
∈HOMO	-8.9904	0.03754	-24.3620	-15.1757	-2.13792
χ	10.7393	-6.93662	-15.1757	-31.1131	0.45934
Log 1/C Obsd.	-1.2088	1.04147	-2.1379	0.4593	0.08322

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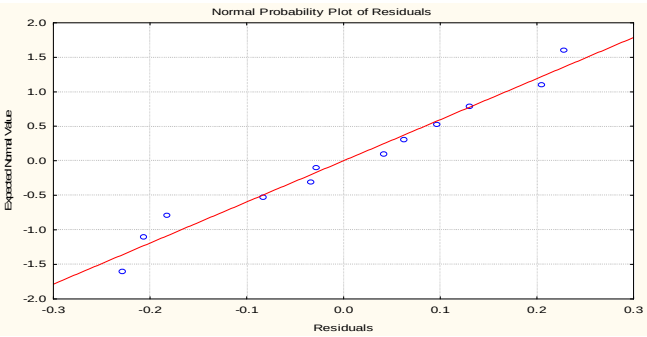
TABLE 6(g) : Predicted & residual values for BPA QSAR model

Compound	Observed-Value	Predicted-Value	Residual	Standard-Pred. Value	Standard-Residual	Std.Err.-Pred.Value	Mahalanobis- Distance	Deleted - Residual	Cook's - Distance
T2C1	4.220000	4.015438	0.20456	0.20555	1.05586	0.114004	2.892170	0.31291	0.18064
T2C2	4.220000	4.248693	-0.02869	0.66027	-0.14810	0.192154	9.903903	-1.75904	16.21799
T2C3	4.220000	4.157657	0.06234	0.48280	0.32178	0.097583	1.873934	0.08353	0.00943
T2C4	4.520000	4.478632	0.04136	1.10852	0.21352	0.134377	4.375091	0.07972	0.01629
T2C5	3.600000	3.469491	0.13050	-0.85875	0.67363	0.101796	2.120075	0.18028	0.04781
T2C6	3.300000	3.072464	0.22753	-1.63274	1.17443	0.125228	3.679087	0.39082	0.34002
T2C7	4.520000	4.423080	0.09692	1.00023	0.50026	0.110287	2.647845	0.14338	0.03550
T2C8	3.600000	3.828693	-0.22869	-0.15850	-1.18041	0.129080	3.966172	-0.41124	0.40000
T2C9	3.900000	4.106698	-0.20669	0.38345	-1.06688	0.093310	1.634877	-0.26912	0.08952
T2C10	3.900000	3.983156	-0.08315	0.14261	-0.42921	0.085418	1.221559	-0.10322	0.01104
T2C11	4.220000	4.253782	-0.03378	0.67019	-0.17437	0.143350	5.105414	-0.07465	0.01626
T2C13	2.700000	2.882215	-0.18221	-2.00362	-0.94051	0.136952	4.579872	-0.36420	0.35316
Min.	2.700000	2.882215	-0.22869	-2.00362	-1.18041	0.085418	1.221559	-1.75904	0.00943
Max.	4.520000	4.478632	0.22753	1.10852	1.17443	0.192154	9.903903	0.39082	16.21799
Mean	3.910000	3.910000	-0.00000	0.00000	-0.00000	0.121962	3.666667	-0.14924	1.47647
Median	4.060000	4.061068	0.006337	0.29450	0.03271	0.119616	3.285629	0.00253	0.06866



Graph 2 : Normal probability plot of residuals for QSAR Model BPA

dicted activity using this model. Regression equation of this QSAR model is given below and it possesses the very high value of regression coefficient (r^2 = 0. 960224) which indicates that the QSAR model is most reliable.

CPA67 = 0.0110484 * MW + 0.0583359 * TE-0.564052 * ∈HOMO - 1.64533 * ∈LUMO + 0.619554

rCV^2 = 0.910628

r^2 = 0.96041314

TABLE 7 contains the values of descriptors, observed activities and predicted activities by best QSAR model CPA of thiobenzamides against MIC with *M. fortuitum*. TABLES 7(a) to 7(g) shows the residual and regression analysis of this QSAR model indicating the reliability. Residual plot of normal probability is shown in Graph 3. Observed and predicted activities of MIC of thiobenzamides with M. *fortuitum* are shown in Graph 7.

QSAR of MIC of thiobenzamides with *M. kansasii*

Best QSAR model for the prediction of activity in terms of log 1/C of the derivatives of thiobenzamides given in TABLE 1 contains heat of formation, total energy, HOMO energy and Electronegativity as descriptors. Values of all the descriptors used in MLR analysis are shown in TABLE 8 alongwith observed and predicted activity using this model. Regression equation of this QSAR model is given below and it possesses the very high value of regression coefficient (r^2 = 0.875461) which indicates that the QSAR model is most reliable.

DPA = -0.0236675 * ΔH_f + 0.0556064 * TE-8.06317 * ∈HOMO + 2.67261 * χ-72.4748

rCV^2 = 0.683172

r^2 = 0.875461

TABLE 8 contains the values of descriptors, observed activities and predicted activities by best

TABLE 7 : Values of descriptors (Heat of formation, molecular weight, total energy, HOMO energy, LUMO energy and Electronegativity), observed activities and predicted activities by best QSAR model APA of thiobenzamides against MIC with *M. fortuitum*

Compound	Heat of Formation (kcal/mole)	Molecular Weight	Total Energy (Hartree)	HOMO Energy (eV)	LUMO Energy (eV)	Absolute Hardness (eV)	Electronegativity (eV)	Obsd. Activity in terms of log (1/C)	Predicted activity by Best QSAR model CPA
T3C1	43.674	231.287	-113.753	-8.703	-1.304	3.699	5.004	3.600	3.600
T3C2	37.402	265.732	-125.495	-8.763	-1.689	3.537	5.226	3.900	3.908
T3C3	37.278	265.732	-125.498	-8.770	-1.387	3.691	5.079	3.300	3.448
T3C4	122.446	276.285	-145.434	-9.027	-2.194	3.417	5.611	3.900	3.892
T3C5	32.231	245.314	-120.940	-8.667	-1.287	3.690	4.977	3.300	3.300
T3C7	49.942	310.183	-123.640	-8.807	-1.444	3.681	5.126	4.220	4.200
T3C8	43.627	231.287	-113.753	-8.684	-1.288	3.698	4.986	3.600	3.576
T3C9	35.464	265.732	-125.519	-8.762	-1.379	3.692	5.070	3.600	3.429
T3C10	35.351	265.732	-125.521	-8.750	-1.354	3.698	5.052	3.300	3.390
T3C11	124.698	276.285	-145.408	-9.007	-2.196	3.406	5.601	3.900	3.902
T3C13	3.455	261.313	-133.129	-8.625	-1.259	3.683	4.942	2.700	2.675

TABLE 7(a) : Regression summary for QSAR model CPA

R = .98000670 R^2 = .96041314 Adjusted R^2 = .93402190 F(4,6) = 36.391 p

	b*	Std.Err. - of b*	b	Std.Err. - of b	t(6)	p-value
Intercept			0.63020	7.777587	0.08103	0.938055
MW	0.59083	0.111963	0.01105	0.002094	5.27707	0.001870
TE	1.48989	0.166869	0.05841	0.006541	8.92854	0.000110
∈HOMO	-0.17511	0.295582	-0.56350	0.951178	-0.59242	0.575198
∈LUMO	-1.39142	0.329036	-1.64669	0.389399	-4.22879	0.005507

TABLE 7(b) : Variables currently in the equation for QSAR model CPA

	b* in	Partial - Cor.	Semipart - Cor.	Tolerance	R-square	t(6)	p-value
MW	0.59083	0.907047	0.428640	0.526326	0.473674	5.27707	0.001870
TE	1.48989	0.964367	0.725238	0.236946	0.763054	8.92854	0.000110
∈HOMO	-0.17511	-0.235078	-0.048121	0.075517	0.924483	-0.59242	0.575198
∈LUMO	-1.39142	-0.865316	-0.343492	0.060942	0.939058	-4.22879	0.005507

TABLE 7(c) : Analysis of variance for QSAR model CPA

	Sums of - Squares	df	Mean - Squares	F	p-value
Regress.	1.658895	4	0.414724	36.39136	0.000241
Residual	0.068377	6	0.011396		
Total	1.727273				

TABLE 7(d) : Redundancy of independent variables for QSAR model CPA

	Toleran.	R-square	Partial - Cor.	Semipart - Cor.
MW	0.526326	0.473674	0.907047	0.428640
TE	0.236946	0.763054	0.964367	0.725238
∈HOMO	0.075517	0.924483	-0.235078	-0.048121
∈LUMO	0.060942	0.939058	-0.865316	-0.343492

TABLE 7(e) : Covariances of regression coefficients for QSAR model CPA

	MW	TE	∈HOMO	∈LUMO
MW	0.000004	0.000006	0.001022	-0.000394
TE	0.000006	0.000043	0.001631	-0.001494
∈HOMO	0.001022	0.001631	0.904740	-0.329699
∈LUMO	-0.000394	-0.001494	-0.329699	0.151632

TABLE 7(f) : Current status of sweep matrix for QSAR model CPA

	MW	TE	∈HOMO	∈LUMO	Log (1/C) Obsd.
MW	-1.89996	-1.24942	-2.5735	2.6987	0.59083
TE	-1.24942	-4.22036	-1.9596	4.8819	1.48989
∈HOMO	-2.57350	-1.95963	-13.2421	13.1215	-0.17511
∈LUMO	2.69872	4.88188	13.1215	-16.4092	-1.39142
Log (1/C) Obsd.	0.59083	1.48989	-0.1751	-1.3914	0.03959

TABLE 7(g) : Predicted & residual values for QSAR model CPA

Compound	Observed - Value	Predicted - Value	Residual	Standard - Pred. Value	Standard - Residual	Std.Err. - Pred.Value	Mahalanobis - Distance	Deleted - Residual	Cook's - Distance
T3C1	3.600000	3.594186	0.00581	0.04822	0.05446	0.068094	3.159563	0.00980	0.000686
T3C2	3.900000	3.956885	-0.05688	0.93873	-0.53287	0.091976	6.514043	-0.22075	0.634846
T3C3	3.300000	3.463355	-0.16335	-0.27300	-1.53021	0.050604	1.337928	-0.21069	0.175066
T3C4	3.900000	3.889323	0.01067	0.77285	0.10002	0.076393	4.211870	0.02188	0.004304
T3C5	3.300000	3.281183	0.01881	-0.72027	0.17626	0.046982	1.027779	0.02333	0.001851
T3C7	4.220000	4.177884	0.04211	1.48133	0.39452	0.097772	7.479174	0.26130	1.005175
T3C8	3.600000	3.557132	0.04286	-0.04275	0.40156	0.065240	2.825654	0.06842	0.030684
T3C9	3.600000	3.444447	0.15555	-0.31942	1.45713	0.048007	1.113222	0.19498	0.134934
T3C10	3.300000	3.396401	-0.09640	-0.43738	-0.90303	0.048239	1.132820	-0.12113	0.052583
T3C11	3.900000	3.882865	0.01713	0.75699	0.16051	0.073330	3.809388	0.03244	0.008716
T3C13	2.700000	2.676339	0.02366	-2.20529	0.22164	0.097243	7.388560	0.13898	0.281307
Min.	2.700000	2.676339	-0.16335	-2.20529	-1.53021	0.046982	1.027779	-0.22075	0.000686
Max.	4.220000	4.177884	0.15555	1.48133	1.45713	0.097772	7.479174	0.26130	1.005175
Mean	3.574545	3.574545	-0.00000	0.00000	-0.00000	0.069444	3.636364	0.01805	0.211832
Median	3.600000	3.557132	0.01713	-0.04275	0.16051	0.068094	3.159563	0.02333	0.052583

TABLE 8 : Values of descriptors (Heat of formation, molecular weight, total energy, HOMO energy, LUMO energy and Electronegativity), observed activities and predicted activities by best QSAR model APA of thiobenzamides against MIC with *M. kansasii*

Compound	Heat of Formation (kcal/mole)	Molecular Weight	Total Energy (Hartree)	HOMO Energy (eV)	LUMO Energy (eV)	Absolute Hardness	Electronegativity	Obsd. Activity in terms of log (1/C)	Predicted activity by Best QSAR model DPA
T4C1	43.674	231.287	-113.753	-8.703	-1.304	3.699	5.004	3.900	3.717
T4C2	37.402	265.732	-125.495	-8.763	-1.689	3.537	5.226	4.220	4.289
T4C3	37.278	265.732	-125.498	-8.770	-1.387	3.691	5.079	4.220	3.955
T4C4	122.446	276.285	-145.434	-9.027	-2.194	3.417	5.611	4.220	4.325
T4C5	32.231	245.314	-120.940	-8.667	-1.287	3.690	4.977	3.300	3.225
T4C6	3.482	261.313	-133.129	-8.644	-1.282	3.681	4.963	3.300	3.005
T4C7	49.942	310.183	-123.640	-8.807	-1.444	3.681	5.126	4.220	4.177
T4C8	43.627	231.287	-113.753	-8.684	-1.288	3.698	4.986	3.600	3.510
T4C9	35.464	265.732	-125.519	-8.762	-1.379	3.692	5.070	3.600	3.907
T4C10	35.351	265.732	-125.521	-8.750	-1.354	3.698	5.052	3.600	3.760
T4C11	124.698	276.285	-145.408	-9.007	-2.196	3.406	5.601	4.220	4.085
T4C12	32.196	245.314	-120.940	-8.648	-1.269	3.690	4.958	2.700	3.017
T4C13	3.455	261.313	-133.129	-8.625	-1.259	3.683	4.942	2.700	2.795
T4C14	51.553	310.183	-123.640	-8.787	-1.430	3.679	5.108	3.900	3.934

TABLE 8(a) : Regression summary for dependent variable QSAR model DPA

R = .93498007 R² = 0.875461Adjusted R² = .81827118 F(4,9) = 15.634 p						
	b*	Std.Err. - of b*	b	Std.Err. - of b	t(9)	p-value
Intercept			-72.2004	16.66377	-4.33277	0.001897
ΔH_f	-1.56332	0.448529	-0.0237	0.00680	-3.48544	0.006879
TE	0.99500	0.231105	0.0556	0.01292	4.30539	0.001975
∈HOMO	-1.83013	0.539366	-8.0110	2.36096	-3.39311	0.007960
χ	1.10335	0.657532	2.7094	1.61466	1.67801	0.127655

TABLE 8(c) : Analysis of variance QSAR model DPA

	Sums of - Squares	df	Mean - Squares	F	p-value
Regress.	3.305554	4	0.826388	15.63379	0.000438
Residual	0.475732	9	0.052859		
Total	3.781286				

TABLE 8(e) : Covariances of regression coefficients QSAR model DPA

	ΔH_f	TE	∈HOMO	χ
ΔH_f	0.000046	-0.000047	0.005656	-0.005526
TE	-0.000047	0.000167	0.002007	0.013890
∈HOMO	0.005656	0.002007	5.574112	2.239742
χ	-0.005526	0.013890	2.239742	2.607126

TABLE 8(b) : Variables currently in the equation QSAR model DPA

	b* in	Partial - Cor.	Semipart - Cor.	Tolerance	R-square	t(9)	p-value
ΔH_f	-1.56332	-0.757914	-0.412095	0.069486	0.930514	-3.48544	0.006879
TE	0.99500	0.820463	0.509040	0.261736	0.738264	4.30539	0.001975
∈HOMO	-1.83013	-0.749172	-0.401179	0.048052	0.951948	-3.39311	0.007960
χ	1.10335	0.488163	0.198397	0.032333	0.967667	1.67801	0.127655

TABLE 8(d) : Redundancy of independent variables QSAR model DPA

	Toleran.	R-square	Partial - Cor.	Semipart - Cor.
ΔH_f	0.069486	0.930514	-0.757914	-0.412095
TE	0.261736	0.738264	0.820463	0.509040
∈HOMO	0.048052	0.951948	-0.749172	-0.401179
χ	0.032333	0.967667	0.488163	0.198397

TABLE 8(f) : Current status of sweep matrix QSAR model DPA

	ΔH_f	TE	∈HOMO	χ	Log 1/C Obsd.
ΔH_f	-14.3913	3.99595	-6.0986	10.6213	-1.56332
TE	3.9960	-3.82065	-0.5864	-7.2365	0.99500
∈HOMO	-6.0986	-0.58643	-20.8107	-14.9056	-1.83013
χ	10.6213	-7.23650	-14.9056	-30.9281	1.10335
Log 1/C Obsd.	-1.5633	0.99500	-1.8301	1.1033	0.12581

TABLE 8(g) : Predicted & residual values for QSAR model DPA

Compound	Observed - Value	Predicted - Value	Residual	Standard - Pred. v.	Standard - Residual	Std.Err. - Pred.Val	Mahalanobis - Distance	Deleted - Residual	Cook's - Distance
T4C1	3.900000	3.713481	0.186519	0.04090	0.81127	0.122936	2.78833	0.26120	0.07381
T4C2	4.220000	4.290944	-0.070944	1.18608	-0.30857	0.226213	11.65663	-2.22341	18.10786
T4C3	4.220000	3.951508	0.268492	0.51294	1.16781	0.106800	1.87663	0.34237	0.09570
T4C4	4.220000	4.324623	-0.104623	1.25287	-0.45506	0.158595	5.25735	-0.19960	0.07173
T4C5	3.300000	3.223192	0.076808	-0.93140	0.33408	0.100561	1.55844	0.09498	0.00653
T4C6	3.300000	3.004011	0.295989	-1.36607	1.28741	0.146438	4.34530	0.49803	0.38072
T4C7	4.220000	4.178576	0.041424	0.96324	0.18018	0.119037	2.55629	0.05660	0.00325
T4C8	3.600000	3.513616	0.086384	-0.35546	0.37573	0.134804	3.54061	0.13164	0.02254
T4C9	3.600000	3.904847	-0.304847	0.42040	-1.32593	0.102615	1.66109	-0.38068	0.10923
T4C10	3.600000	3.762512	-0.162512	0.13813	-0.70685	0.094270	1.25702	-0.19536	0.02428
T4C11	4.220000	4.085397	0.134603	0.77846	0.58545	0.168778	6.07722	0.29192	0.17376
T4C12	2.700000	3.020333	-0.320333	-1.33370	-1.39329	0.128309	3.12031	-0.46523	0.25506
T4C13	2.700000	2.795544	-0.095544	-1.77948	-0.41557	0.155814	5.04229	-0.17670	0.05426
T4C14	3.900000	3.931416	-0.031416	0.47309	-0.13664	0.094388	1.26248	-0.03778	0.00091
Min.	2.700000	2.795544	-0.320333	-1.77948	-1.39329	0.094270	1.25702	-2.22341	0.00091
Max.	4.220000	4.324623	0.295989	1.25287	1.28741	0.226213	11.65663	0.49803	18.10786
Mean	3.692857	3.692857	-0.000000	0.00000	-0.00000	0.132826	3.71429	-0.14300	1.38426
Median	3.750000	3.833679	0.005004	0.27927	0.02177	0.125622	2.95432	0.00941	0.07277

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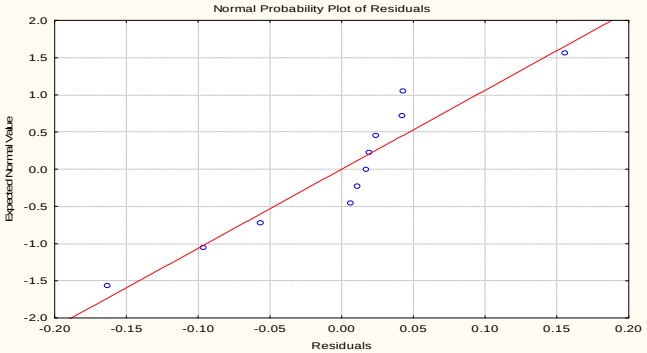
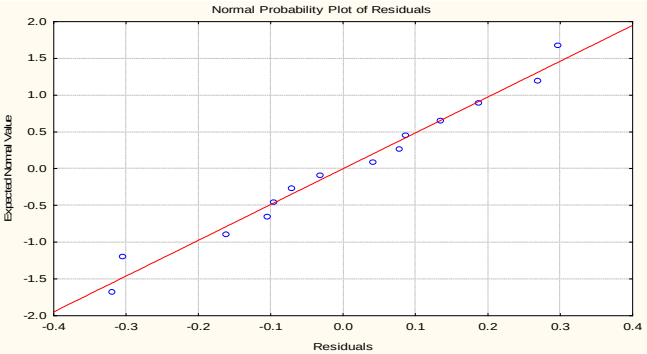
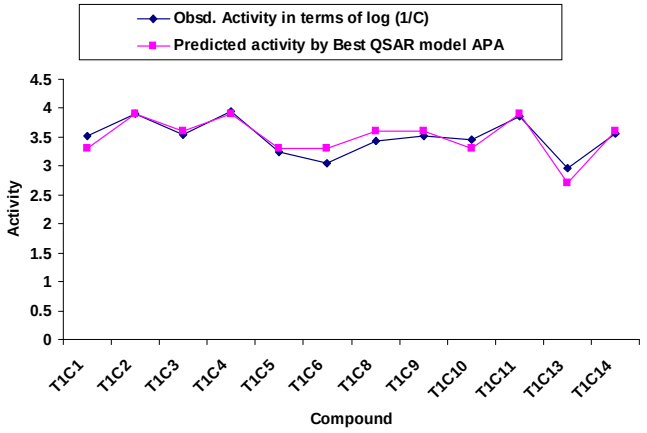


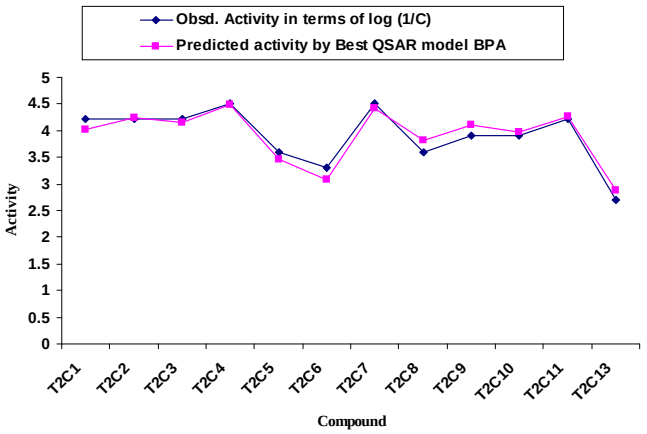
Graph 3 : Normal probability plot of residuals for QSAR Model CPA



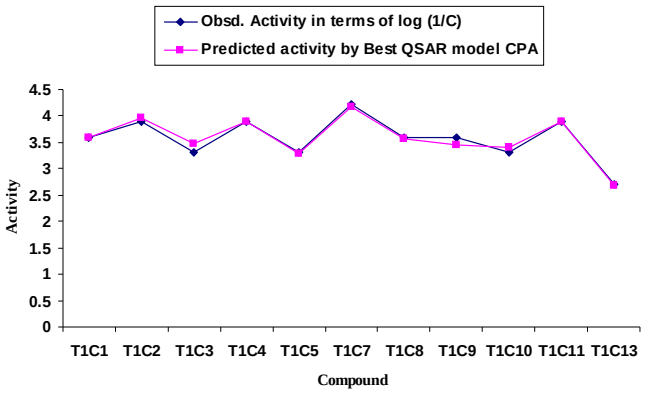
Graph 4 : Normal probability plot of residuals for QSAR Model DPA



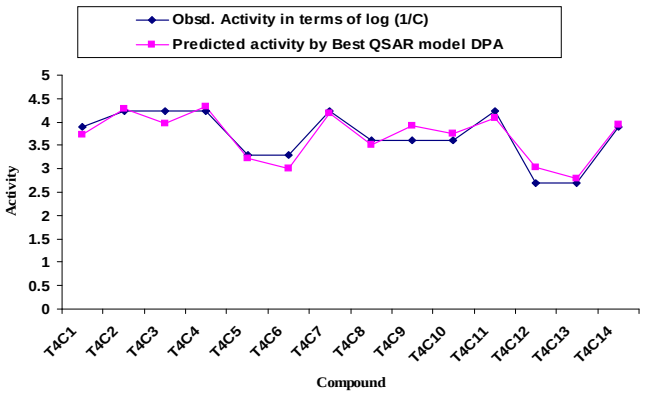
Graph 5 : Observed and predicted activity of thiobenzamides for QSAR model APA



Graph 6 : Observed and predicted activity of thiobenzamides for QSAR model BPA



Graph 7 : Observed and predicted activity of thiobenzamides for QSAR model CPA



Graph 8 : Observed and predicted activity of thiobenzamides for QSAR model DPA

QSAR model DPA of thiobenzamides against MIC with M. *kansasii*. TABLES 8(a) to 8(g) shows the residual and regression analysis of this QSAR model indicating the reliability. Residual plot of normal probability is shown in Graph 4. Observed and predicted activities of MIC of thiobenzamides with M. *kansasii* are shown in Graph 8.

CONCLUSION

All MLR analysis of the four sets of thiobenzamides indicates that HOMO energy is the best descriptor of activity of the derivatives of thiobenzamides against MIC with M. *Avium*, M. *Tuberculosis* and M. *kansasii*.

For the MIC of thiobenzamides with M. *fortuitum*, the combination of total energy and LUMO energy is the best descriptor of activity. MLR equations of the four sets of the derivatives of thiobenzamides having best descriptor are given below-

1. PA1 = -2.00902 * ∈HOMO - 14.1108
   rCV^2 = 0.487611
   r^2 = 0.557609
2. PA2 = -2.94849 * ∈HOMO - 21.9409
   rCV^2 = 0.38012
   r^2 = 0.505438
3. PA3 = 0.0441638 * TE - 1.77286 * ∈LUMO + 6.483
   rCV^2 = 0.552458
   r^2 = 0.679317
4. PA4 = -3.19928 * ∈HOMO - 24.3339
   rCV^2 = 0.439175
   r^2 = 0.534828

In the analysis of variance which is shown in the TABLES 5(c), 6(c), 7(c) and 8(c), the p-values are shown. The p-values in the second, third and fourth sets are approaching to zero (about 0.0001) indicating that the QSAR models developed for these sets are more reliable.

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