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Prediction of physiochemical parameters for anti-tubercular potentials of Mannich and Schiff bases

Umaa. K[1], Sudha Rani. S[2], Sangeetha. G[2] and Maida Engels. S. E[3]

[1]*Department of Pharmaceutical Chemistry, PSG College of Pharmacy, Coimbatore*
[2]*Department of Chemistry, PSGRKC for Women, Coimbatore*
[3]*Department of Pharmaceutical Chemistry, PSG College of Pharmacy, Coimbatore*

ABSTRACT

A quantitative structure activity relationship study was performed on series of substituted Mannich bases of 5-hydroxy-2-methyl-4H-pyran-4-ones and Schiff"s bases of Benzothiazole obtained from an elaborate literature survey as anti-tuberculosis compounds for establishing quantitative relationship between biological activity and their physiochemical/structural properties. In recent years, a large number of newer drugs are promoted in treatment of tuberculosis especially due to the emergence of MDR (multi drug resistant) and XDR (extensive drug resistant) tuberculosis. Theoretical results are in accord with the invitro experimental data with reported growth inhibitory activity towards Mycobacterium tuberculosis. Various physico chemical descriptors and the reported minimum inhibitory concentration values of different derivatives on mycobacterium tuberculosis were used as independent variables and dependent variables respectively. Antituberculosis activity was predicted through QSAR model, developed by forward feed multiple linear regression method with leave-one-out approach. Relationship correlating measure of QSAR model was 85% (R^2 =0.85).QSAR studies indicate that Principal moment of inertia and log p value correlate with anti-tubercular activity in the case of mannich bases and refractivity and ovality correlate with the anti-tubercular activity of schiff's bases. These results could offer useful references for understanding mechanisms and directing the molecular design of new lead compounds with improved anti-tubercular activity. The generated QSAR model revealed the importance of structural, thermodynamic and electro topological parameters. The quantitative structure activity relationship provides an important structural insight in designing of potent antitubercular agents.

Keywords: Antimycobacterial property, Hansch analysis, Mannich base, Physiochemical parameters , QSAR, Schiff 's base.

INTRODUCTION

Tuberculosis (TB) remains the world's greatest public health challenge. It was declared since 1993 by the World Health Organization (WHO), as global health emergency. Worldwide resurgence of TB is due the acquired immunodeficiency syndrome (AIDS) epidemic, which started in the mid-1980s and the outbreak of multidrug resistant and extremely drug resistant tuberculosis [1]. Multidrug- resistant TB(MDR-TB) is resistant to front-line drugs (isoniazid and rifampicin, the most powerful anti-TB drugs) and extensively drug- resistant TB (XRD-TB) is resistant to front-line as well as second-line drugs [2,3]. Thus, there is an urgent need for anti-TB drugs with improved properties such as: Enhanced activity against MDR strains, reduced toxicity, shortened duration of therapy, rapid mycobactericidal mechanism of action and the ability to penetrate host cells and exert antimycobacterial effect in the intracellular environment.

The Quantitative Structure Activity Relationship (QSAR) has remained as an important tool in drug design. Many scientists have worked on it and improved the strength, utility and efficiency of this vital technique in molecular

modeling. The original formulation of the method was in two dimensions, the molecular descriptors i.e., the physico-chemical constants were correlated with the biological activity but with the vast advances in technology many descriptors/dimensions have been added leading to the 3D, 4D, 5D and 6DQSAR techniques. The different forms of QSAR have not only contributed to understanding the pharmacophoric features required for improvement in the activity but has also helped to improve the pharmacokinetic and pharmacodynamics of drug candidates. In the QSAR technique, it does not require information about the receptor and hence is helpful in the design and improvement of drug molecules against vital disorders as well as against the neglected diseases. Under these circumstances, QSAR is a good weapon for predicting and classifying biological activities of untested chemicals. Many QSAR studies have been reported in the literature both on the synthesized molecules tested against the organism and also on molecules directed against specific targets of the microorganisms. Thus it has become inexorably essential in lead discovery, optimization to lead development and computer aided drug designing. Needless to state that a statistically validated QSAR model is capable of predicting the biological activity of a new chemical within the same series in lieu of the time-consuming and intensive process of chemical synthesis and biological evaluation. Applied judicially, QSAR can save substantial amount of time, money and human resource [4,5]. The objective of present work was designed to study the quantitative structure activity relationship on series of substituted Mannich bases of 5-hydroxy-2-methyl-4H-pyran-4-ones and Schiff"s bases of Benzothiazole for establishing quantitative relationship between biological activity and their physiochemical Parameters for anti-tubercular potentials.

EXPERIMENTAL SECTION

The antimycobacterial data of 22 Mannich bases of 5-hydroxy-2-methyl-4H-pyran-4-ones were taken from the reported work of Barkin Berket et al., [6] and is furnished in **Figure 1** and **Table 1**. A set of 17 Benzo [d] isothiazole, benzothiazole and thiazole Schiff's bases were taken from the reported work in a published article from reported work by Vicini et al., [7] and is given in the **Figure 2** and **Table 2**. Various descriptors studied are shown in **Table 3**. The values of log MIC have been considered for computational work.

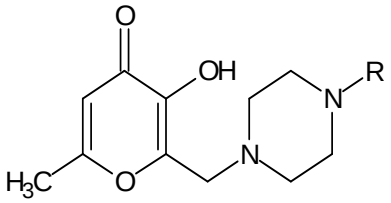

Figure 1: Mannich bases of 5-hydroxy-2-methyl-4H-pyran-4-ones

Table 1: MIC of Various Compounds

COMPOUND NO	R-GROUP	MIC
1.	2-cyanophenyl	32
2.	2-cyanoethyl	32
3.	3,4-dichlorophenyl	32
4.	4-chlorobenzyl	16
5.	4-hydroxyphenyl	32
6.	2-phenylethyl	64
7.	2-ethoxyethyl	128
8.	2-methylphenyl	32
9.	2-methoxyethyl	128
10.	Propan-2-yl	128
11.	2-chlorophenyl	4
12.	Phenyl	8
13.	2-methoxyphenyl	16
14.	3-chlorophenyl	8
15.	3-methylphenyl	16
16.	3-cynophenyl	16
17.	Cyclohexyl	16
18.	Pyridine-2-phenyl	16
19.	Pyridine-4-phenyl	16
20.	Cyclohexyl methyl	8
21.	2-hydroxyethyl	16
22.	2-fluorophenyl	16

All the structures of these derivatives were constructed using Chem Draw and transferred to Chem 3D for converting them into 3D structures.[8] The energy minimization of the molecules was done using MM2 force field followed by semi empirical AMI (Austin model) [9] and Hamiltonian method available in MOPAC module by fixing root mean square gradient as 0.1 and 0.0001kcal/mol. Most stable structure for all the compounds was

generated and used for calculating various thermodynamic, steric and electronic descriptors. Values of descriptors with their equation are shown and the values of observed and predicted activity are shown. All the calculated descriptor values were considered as independent variables and biological activity taken into account as the dependent variable. VALSTAT [10] software was used to generate QSAR models by multiple linear regression analysis. Cross validation was performed using leave-one out method. Statistical measures [11] used were: n-number of molecules in regression, r2-correlation coefficient, F-test (Fischer's value) for statistical significance and S-standard deviation.

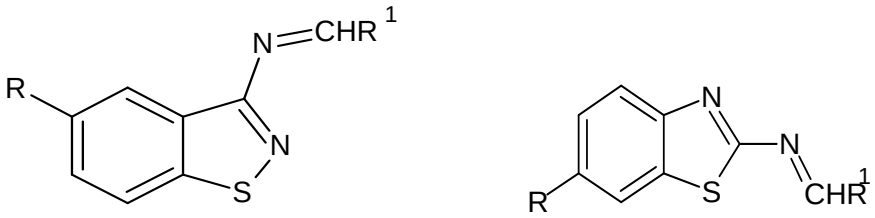

Figure 2: Benzo[d]isothiazole, benzothiazole and thiazole Schiff's bases

Table 2: MIC of Various Compounds

COMPOUND NO	R GROUP	R1 GROUP	IC_{50} VALUE
1.	H	3-Cl C_6H_4	100
2.	H	4-OCH_3 C_6H_4	100
3.	H	2-OH ,3-$OCH_3C_6H_4$	78
4.	H	4-OH,3-$OCH_3C_6H_5$	42
5.	CH_3	2-OH C_6H_4	100
6.	CH_3	2-Cl C_6H_4	100
7.	CH_3	3-Cl C_6H_4	83
8.	CH_3	4-OCH_3 C_6H_4	100
9.	H	C_6H_5	73
10.	H	2-Cl C_6H_4	73
11.	F	3-Cl C_6H_4	100
12.	O C_2H_5	4-OH C_6H_4	100
13.	H	C_6H_5	100
14.	H	3-Cl C_6H_4	100
15.	H	4-OCH_3 C_6H_4	100
16.	4-OCH_3 C_6H_4	C_6H_5	100
17.	4-OCH_3 C_6H_4	3-OCH_3,4-OH C_6H_3	100

To denote the correlation between physicochemical parameters as independent variable and anti-mycobacterial activity as dependent variable, the data were transferred to statistical program VALSTAT. Sequential multiple linear regression analysis method (in sequential multiple regression, the program searches for all permutations and combinations sequentially for the dataset) was applied for the same. The best model was selected on the basis of statistical parameters like observed squared correlation coefficient (r^2), standard error of estimate(s), and sequential Fischer test (F). Z score (absolute difference between values of model and activity field, divided by the square root of mean square error of data set) was taken as a measure of outlier detection. To interpret the self-consistency of derived models, they were validated using leave one out analysis (LOO) and the predictive ability was assessed using cross-validated squared correlation coefficient (r^2), bootstrapping squared correlation coefficient (r^2_{bs}), 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),and outliers (on the basis of Z-score value). The ± data with in parentheses are the standard deviation, associated with the coefficient of descriptors in regression equations. Each of the statistical parameters mentioned above were used for assessing the statistical significance of QSAR. The best models obtained are given below along with their statistical measures.

Table 3: Descriptors Considered for the QSAR Study

S.No	Descriptor	Type
1	Heat of formation (HF)	Thermodynamic
2	Boiling Point (BP)	Thermodynamic
3	Critical Pressure (CP)	Thermodynamic
4	Critical Temperature (CT)	Thermodynamic
5	Critical Volume (CV)	Thermodynamic
6	Henry's Law constant (H)	Thermodynamic
7	Ideal Gas Thermal Capacity (IGTC)	Thermodynamic
8	LogP	Thermodynamic
9	Melting Point (MP)	Thermodynamic
10	Molar Refractivity (MR)	Thermodynamic
11	Standard Gibbs Free Energy (SGFE)	Thermodynamic
12	Connolly Accessible Area (CAA)	Steric
13	Connolly Molecular Area (CMA)	Steric
14	Connolly Solvent-Excluded Volume (SEV)	Steric
15	Ovality (OVA)	Steric
16	Principal Moment of Inertia – X (PMI-X)	Steric
17	Principal Moment of Inertia – Y (PMI-Y)	Steric
18	Principal Moment of Inertia – Z (PMI-Z)	Steric
19	Dipole Moment (D)	Electronic
20	Dipole Moment – X Axis (DX)	Electronic
21	Dipole Moment – Y Axis (DY)	Electronic
22	Dipole Moment – Z Axis (DZ)	Electronic
23	Electronic Energy (EE)	Electronic
24	HOMO Energy (HOMO)	Electronic
25	LUMO Energy (LUMO)	Electronic
26	Repulsion Energy (RE)	Electronic
27	Bend Energy (Eb)	Thermodynamic
28	Charge - Charge Energy (CCE)	Thermodynamic
29	Dipole - Dipole Energy (DDE)	Thermodynamic
30	Non-1,4 VDW Energy (Ev)	Thermodynamic
31	Stretch Energy (SE)	Thermodynamic
32	Stretch-Bend Energy (SEE)	Thermodynamic
33	Torsion Energy (Et)	Thermodynamic
34	Total Energy (E)	Thermodynamic
35	Vander Waals 1,4 Energy (VDWE)	Thermodynamic

RESULTS AND DISCUSSION

In the present study, an attempt has been made to find structural requirement for inhibition of mycobacterium tuberculosis using QSAR. The QSAR models have been obtained after removal of few compounds as outliners. The statistical quality of regression equations were justified by parameters like correlation coefficient (r), Percentage of explained variance (%EV), probability factor related to F-ratio, standard error of estimate (s).

1.QSAR analysis of Mannich bases

Initially twenty two chemical entities were used for QSAR modeling against 35 chemical and physical descriptors. Only three descriptors were found to be significant and seem to be responsible for the *invitro* anti tubercular activity. A multiple linear regression QSAR model was developed using leave one out approach for prediction of biological activity of antituberculosis drug molecules.

TABLE 4: Comparison of Observed Activity with Predicted Activity

S.NO	OBSERVED ACTIVITY (pIC_{50})	PREDICTED AVTIVITY									
		Model.1	Model.2	Model.3	Model.4	Model.5	Model.6	Model.7	Model.8	Model.9	Model.10
1	0.66439	0.682932	0.683062	0.682279	0.682409	0.65558	0.655413	0.649649	0.649478	0.643765	0.643582
2	0.66439	0.723604	0.724957	0.723108	0.724463	0.694414	0.692915	0.694924	0.693429	0.694337	0.692832
3	0.66439	0.805283	0.81544	0.804984	0.81553	0.786272	0.775188	0.689169	0.775747	0.784441	0.773338
4	0.83048	0.800733	0.800643	0.800407	0.800318	0.767569	0.767637	0.768212	0.768281	0.774168	0.774238
5	0.66439	0.684405	0.684531	0.684045	0.684172	0.647894	0.647724	0.648804	0.648635	0.671488	0.671334
6	0.55365	0.697757	0.69789	0.697315	0.697448	0.657587	0.657405	0.658347	0.658167	0.683239	0.683076
7	0.47456	0.706547	0.706637	0.706076	0.706166	0.66605	0.665917	0.666845	0.666714	0.664484	0.664345
8	0.66439	0.686818	0.686898	0.686412	0.686493	0.647513	0.647388	0.647928	0.647804	0.644285	0.644152
9	0.47456	0.68743	0.687539	0.689278	0.689386	0.66676	0.666629	0.66717	0.66704	0.663446	0.663307
10	0.47456	-1.07229	-1.07541	-1.35693	-1.36056	0.668491	0.668806	0.668891	0.669206	0.665038	0.665347
11	1.66096	1.30898	1.31039	1.31016	1.31157	1.43433	1.43291	1.43146	1.43004	1.44228	1.44087
12	1.10731	11.4987	11.4811	11.5035	11.4859	11.9807	12.0002	11.9683	11.9878	12.0097	12.0294
13	0.83048	0.667632	0.667742	0.667913	0.668022	0.632733	0.632582	0.633924	0.633775	0.412838	0.413709
14	1.10731	0.722717	0.72274	0.722425	0.722448	0.688312	0.688257	0.689169	0.689115	2.91513	2.91702
15	0.83048	0.983174	0.982738	0.98293	0.982493	0.95728	0.957739	0.957864	0.958323	0.956841	0.957298
16	0.83048	0.705396	0.705447	0.705068	0.705119	0.669989	0.669902	0.67087	0.670785	0.676662	0.676577
17	0.83048	0.695504	0.695575	0.695148	0.695219	0.677871	0.677775	0.669331	0.669229	0.720796	0.720736
18	0.83048	0.681063	0.681146	0.680738	0.680822	1.40184	1.40595	2.32345	2.33023	0.644223	0.64409
19	0.83048	0.704823	0.704256	0.7045	0.703932	0.667301	0.667877	0.668333	0.668908	0.667483	0.668057
20	1.10731	2.88332	2.94628	2.88733	2.95035	3.38811	3.29434	3.37369	3.27978	3.38002	3.28884
21	0.83048	0.666516	0.666624	0.666538	0.666647	0.635119	0.634969	0.634969	0.63482	0.626026	0.625863
22	0.83048	0.715894	0.71602	0.716073	0.716199	0.681899	0.681729	0.682656	0.682487	0.682279	0.682104

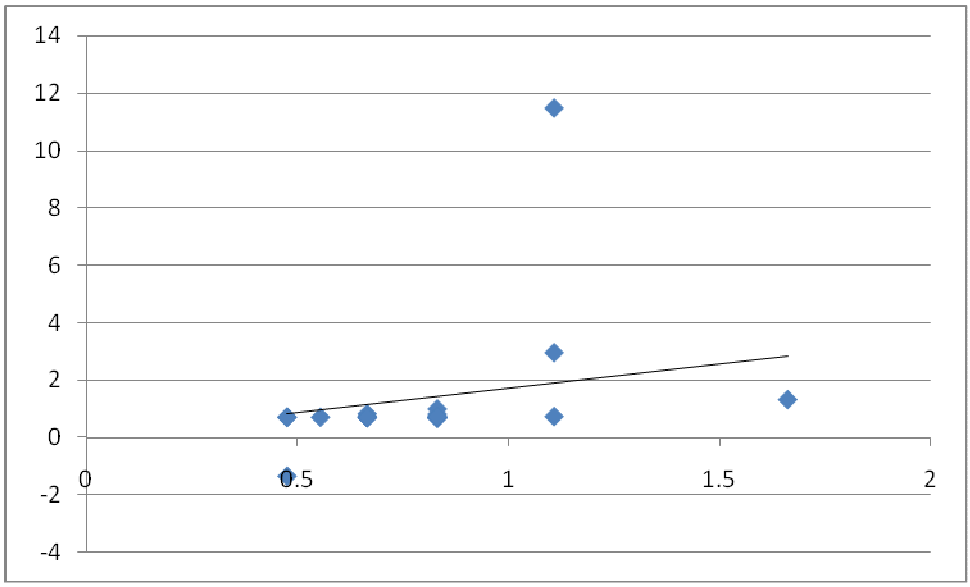

Figure 3: Most significant modelobserved for Mannich Bases (Plot between observed activity and predicted activity. BA= [0.683781(± 0.093801)] + Log P [4.42032e-005(± 1.4828e-005)] +MW [-4.6971e-007(± 7.00922e-007)] +PMI-X [1.12747e-006(± 8.65817e-007)]. Correlation coefficient (r) =0.913918, r squared=0.835247, std=0.137187, F=18.5888. The p value is < 0.001, considered extremely significant.

The above QSAR mathematical model equation derived through multiple linear regression method, shows relationship between *invitro* experimental activity (MIC) and two dependent descriptors. (**Figure 3** and **Table 4**). Pertaining to the data observed for mannich bases of 5-hydroxy-2-methyl-4H-pyran-4-one derivatives, Principal moment of Inertia, log P value and molecular weight have been found to be more significant. The spatial parameter PMIY plays an important role in explaining the antituberculosis activity of the above discussed pyranone derivatives. It contributed positively to the expression, which suggested that bulky groups around Y axis in molecules are favorable for activity. Moreover log P contributes positively and this hydrophobic parameter is mainly considered in QSAR equation for the lipophilic nature of drugs. It is also reported that log P not only considers the penetration and distribution and also deals with interaction of drugs with receptors.

2.QSAR analysis of Benzo[d]isothiazole, benzothiazole and thiazole Schiff's bases

In order to develop QSAR between anti tuberculosis activity and physico chemical parameters, a set of 17 Benzo[d]isothiazole, benzothiazole and thiazole Schiff's bases were subjected to multiple linear regression analysis (MLR). Out of various models obtained, two models were considered to be best as they show good correlation coefficient(r=0.974, 0.966) and other statistical parameters. (**Figure 4 and Figure 5**). A good correlation between experimental and predicted biological activity for compounds in the test further highlights the reliability of the constructed QSAR model as in **Table 5**.

TABLE 5: Comparison of Observed Activity with Predicted Activity

S.NO	OBSERVED ACTIVITY(pIC_{50})	PREDICTED AVTIVITY									
		Model.1	Model.2	Model.3	Model.4	Model.5	Model.6	Model.7	Model.8	Model.9	Model.10
1	0.5	0.504896	0.506431	0.508114	0.461755	0.504659	0.508338	0.506888	0.506785	0.50691	0.506857
2	0.5	0.503817	0.507451	0.509277	0.503144	0.505206	0.50796	0.507692	0.507276	0.507292	0.507669
3	0.528	0.513437	0.51631	0.515408	0.51856	0.512255	0.517104	0.516763	0.516425	0.516521	0.516707
4	0.616	0.740395	0.684216	0.690406	0.639669	0.725019	0.709726	0.685668	0.668549	0.688674	0.668388
5	0.5	0.501615	0.508045	0.510599	0.511978	0.509903	0.201825	0.512252	0.512178	0.512002	0.511875
6	0.5	0.504445	0.508071	0.469387	0.5096	0.507242	0.508067	0.508147	0.508221	0.50802	0.507896
7	0.521	0.501467	0.505256	0.503765	0.506486	0.418803	0.505474	0.50516	0.505771	0.505104	0.505191
8	0.5	0.508697	0.506799	0.50547	0.508014	0.505208	0.50719	0.506955	0.50689	0.506631	0.506932
9	0.528	0.541696	0.511842	0.504576	0.504924	0.501493	0.504117	0.503862	0.503822	0.50384	0.503751
10	0.528	0.505166	0.506943	0.650443	0.508099	0.504851	0.507287	0.507077	0.505991	0.50841	0.508001
11	0.5	0.504215	0.507622	0.512048	0.497781	0.505382	0.508108	0.508238	0.413346	0.510213	0.507855
12	0.5	0.504047	0.479476	0.506927	0.495892	0.50547	0.508167	0.507915	0.507367	0.50751	0.50791
13	0.5	0.503477	0.336879	0.505417	0.509073	0.504687	0.507119	0.506898	0.506828	0.506573	0.506108
14	0.5	0.504536	0.500723	0.506462	0.511018	0.505648	0.508378	0.507803	0.508027	0.507705	0.13838
15	0.5	0.506852	0.509344	0.506927	0.513341	0.50808	0.510741	0.568414	0.510376	0.517141	0.510069
16	0.5	0.506385	0.509567	0.508377	0.571864	0.50747	0.509703	0.509462	0.509532	0.509312	0.50957
17	0.5	0.503976	0.507347	0.50615	0.510679	0.505259	0.507696	0.507688	0.507592	0.507291	0.507692

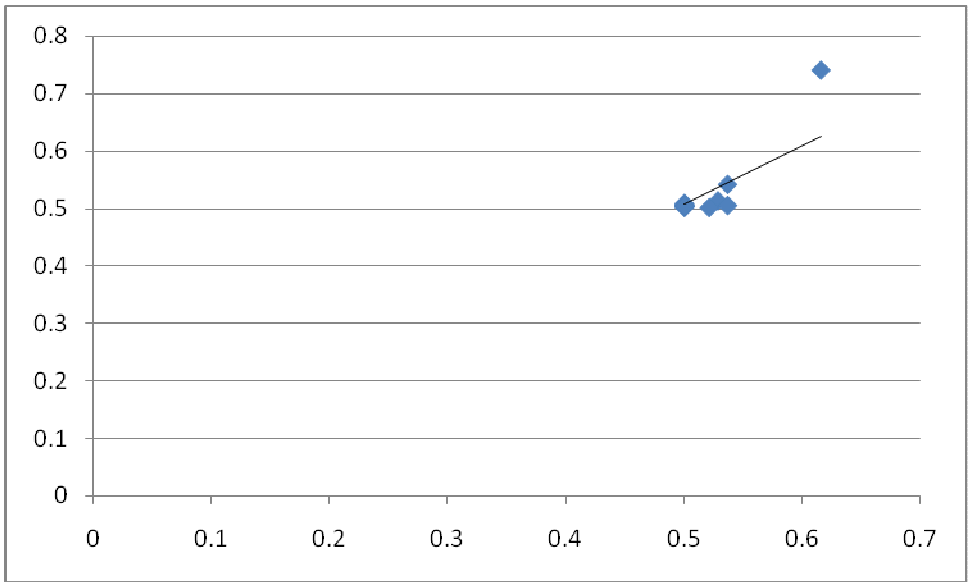

Figure 4 Significant Model of Benzo[D]Isothiazole, Benzothiazole and Thiazole Schiff's Bases (Plot Between Obsereved Activity and Predicted Activity. BA= [0.503433(± 0.00609771)] +MR [7.29383e-007(± 1.30887e-007)] +Oval [4.90803e-007(± 2.89863e-007)]

Correlation coefficient (r) = 0.974917, r squared = 0.950464, std = 0.00834708, F = 86.3429. The p value is < 0.002, considered significant.

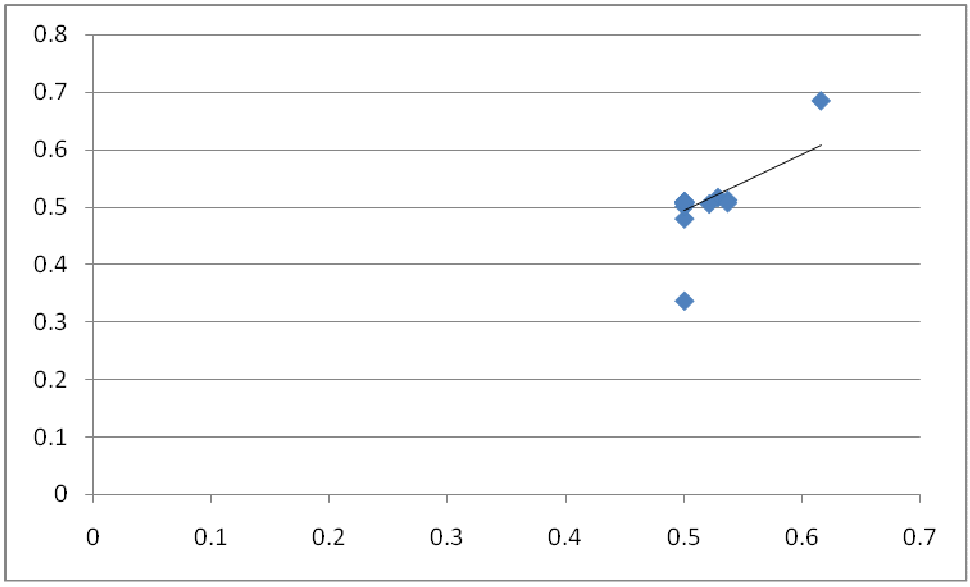

Figure 5 Significant Model of Benzo[D]Isothiazole, Benzothiazole and Thiazole Schiff's Bases (Plot Between Obsereved Activity and Predicted Activity). BA=[0.50674(0.00683765)] +MR [7.26285e-007(± 1.51058e-007)] +CAA [-1.15684e-006(± 8.80154e-007)]

Correlation coefficient (r) = 0.966416, r squared=0.93396,std=0.00963781, F=63.6402. The p value is < 0.002, considered significant.

CONCLUSION

Among the various models obtained, the models 1 and 2 (fig 4,5) proved to possess significant QSAR equation showing that Molar Refractivity, Ovality and Connolly accessible surface area which have contributed positively, showing the importance of these descriptors in the designing of novel Benzo[d]isothiazole, benzothiazole and thiazole Schiff's bases for the antituberculosis activity. Molar refractivity represents the real volume of molecules are related, not only to the volume but also to the London dispersion forces that act in the drug-receptor interaction. Connolly Accessible surface area is computation of surface properties which could be of fundamental importance to surface based protein science and engineering.

On the basis of the results discussed above, it can be concluded that 22 mannich bases (5-hydroxy-2-methyl-4H-pyran-4-ones) have been subjected to hansch analysis and the principal moment of inertia, Molecular weight and log P show a promising contribution to the biological activity and 17 schiff bases showed a correlating equation with ovality, connoly accessible surface area and molar refractivity as the physio chemical parameters towards anti tuberculosis activity. The good correlation between experimental and predicted biological activity for compounds in the further highlights the reliability of the constructed QSAR model. The finding of the study will be helpful in the design of the potent anti-tuberculosis drugs.

REFERENCES

[1] World Health Organisation (WHO) Facts Sheets on Tuberculosis **2011** http://www.who.int /mediacentre /factsheets /fs104/en/
[2] Scior T, Morales IM, Solon M, Eisel SG, Domeyer D, Laufer S. Arch. Pharm. Pharm. Med. Chem., **2002**, 11, 511-525.
[3] Farmer P, Bayona J, Becerra M. Int. J. Tuberc. Lung Dis., **1998**, 2, 869-876.
[4] Hansc C, Leo A. Exploring QSAR fundamental and applications in chemistry and Biology, American Chemical Society, Washington D.C.**1995**.
[5] Karalson M, Molecular descriptors in QSAR/QSPR, Wiley-Interscience (**2000**)
[6] BarkinBerk, Demet U.S, Sinem. Turk J Chem., **2011**, 35,317-330.
[7] Vicini P, Geronikaki A, Incerti M. Bioorg. Med. Chem., **2003**, 11, 4785-4789.
[8] Chemdraw 3D Ultra software for calculating physicochemical parameters, www.cambridgesoft.com
[9] Keir L B. **1971**. Molecular Orbital Theory in Drug Research, Newyork: Academic press.
[10] Gupta AK, Babu MA, Kaskhedikar SG. Indian J. Pharm. Sci., **2004**, 66, 396-402.
[11] Kubinyi H. **1993**. Hanch Analysis and related approaches, New York: Weinheim.
[12] Rajasekaran S, Gopalakrishna Rao, Sanjay Pai PN. J Comput Method.Mol.Des., **2011**, 1(3), 69-82.

[13] Vasanthanathan P, Lakshmi M, Arockiababu M, Gupta AK, Kaskhedikar SG. Chem Pharm Bull., **2006**, 54(4), 583-587.
[14] Sivakumar PM, Sethukailasam, GeethaBabu, Mukesh Doble. Chem Biol Drug Des., **2008**, 29, 283-292.