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IJPBS |Volume 1| Issue 4 |OCT-DEC |2011|501-509

2D-QSAR Study of Novel Oxazoline Benzyl Ester Derivatives as Anti-Tuberculosis Agents

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Research Article

RECEIVED ON 28-10-2011 **ACCEPTED ON 12-11-2011**

ABSTRACT

The QSAR study brings important structural insight to aid the design of novel anti-TB agents. 2D-QSAR model for a set of 33 substituted oxazoline derivatives that have anti-TB activity was developed. The anti-TB activity data and various parameters (physicochemical and alignment independent) were taken as dependent and independent variables respectively. The correlation was established between them by employing multiple sequential regression method. Ycompdipole , XKaveragehydrophilicity and the count of number of Carbon atoms separated from any Fluorine atom by six bond in molecule were found to influence biological activity. The statistical data r^2 =0.8845, q^2=0.8371, Ftest =34.4543, Pred_r^2 = 0.7590 signified that the model developed was robust and good predictive ability. These findings can be helpful in the development and optimization of new anti-TB drug containing substituted oxazoline benzyl esters.

KEYWORDS: *2D QSAR, anti-TB drug, Benzyl Ester, oxazoline*

INTRODUCTION

The enhanced prevalence of infectious disease named Tuberculosis (TB) in tropical and subtropical countries is becoming a major health problem worldwide. This disease causes the death of two million people annually [1]. The World Health Organization (WHO) estimates that *Mycobacterium Tuberculosis* the causative bacillus of TB will infect 30 million people within the next 20 years[2]. The clinical management of TB has relied heavily on a limited number of drugs such as Isonicotinic acid, Hydrazide, Rifampicin, Ethambutal, Streptomycin, Ethionamide, Pyrazinamide, Fluroquinolones etc [3]. However with the advent of these chemotherapeutic agents the spread of TB has not been eradicated completely because of prolonged treatment schedules [4], development of multidrug resistance(MDR) and extremely drug resistance (XDR) strain of the mycobacterium [5], increasing incidence of disease in HIV infected patients. Thus new drugs divulgent from these of contemporary medication is urgently required. An alternative way for overcoming the absence of experimental measurements for biological systems is based on the activity to formulate quantitative structure activity relationship (QSAR) [6]. In QSAR study the structure is translated into the molecular descriptors, describing different relevant features of the compounds through mathematical formula obtained by the chemical graph theory, information theory, quantum mechanics etc [7]. The 2D-QSAR makes use of worksheet facility that allows evaluation of 1000+ molecular descriptors and calculation of QSAR equation using several regression methods. In present work we performed 2D-QSAR study for *(s)-Benzyl 2-(2-(benzyloxy)phenyl)-4,5-dihydrooxazole-4-carboxylate* derivatives for establishing predictive models on the data explored by Miller *et al.* [8] ,using modeling software Vlife MDS 3.5. The findings can be helpful for designing new active derivatives.

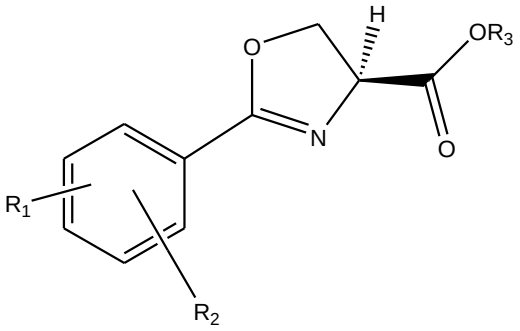
MATERIALS AND METHODS:

The molecular modeling studies were performed using MDS 3.5, supplied by VLife sciences. The software was installed on Pentium 4 personal computer with the window XP operating system.

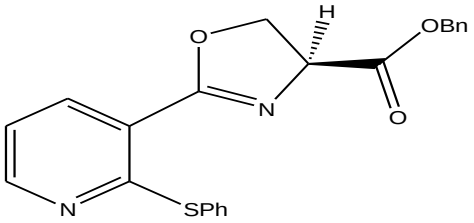
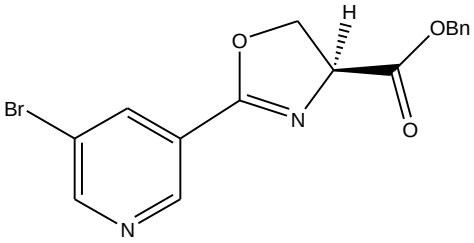
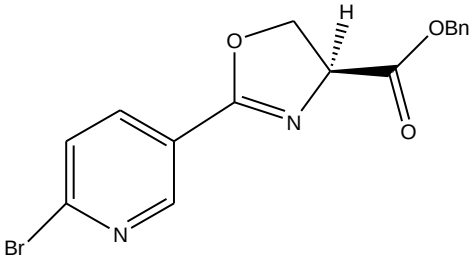
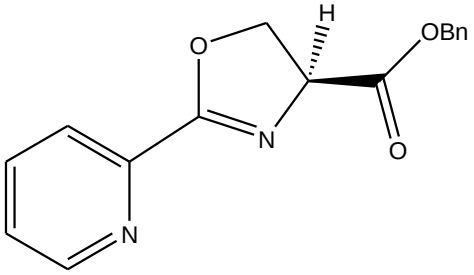
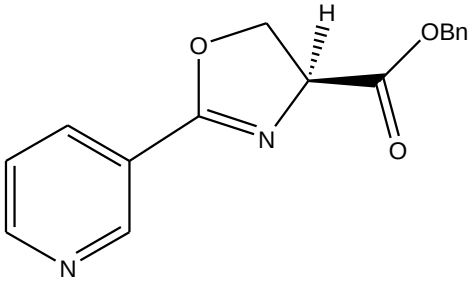
Dataset

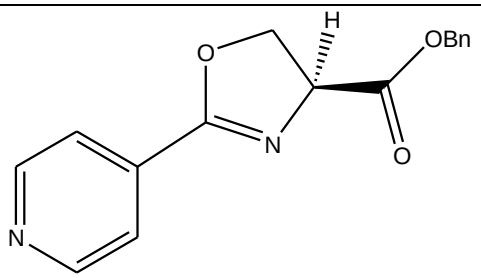
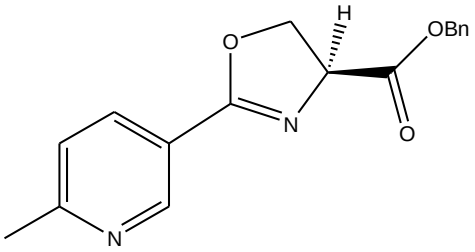
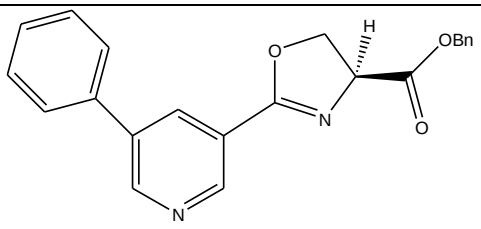
The biological and chemical experimental data of substituted oxazoline derivatives appearing in **Table-1** were used from the work of Miller *et al* [8]. The biological activity was taken as the logarithm of the inverse of GAST assay values. The GAST assay values were determined by Miller *et al* by incubating *M. tuberculosis* for one week with test compounds in glycerol-alanine-salts medium without added iron but with Tween-80 (GAST). Miller *et al.* tested in vitro the non iron binding dibenzyl protected oxazoline (which is a precursor in the synthesis of mycobactin S and T) and found that it displayed notable anti-TB activity and was non toxic for VERO cells. Further Miller *et al.* explored structure activity relationship of the lead compound in order to improve activity by synthesizing series of derivatives of lead compound.

Table 1 Structures of oxazoline derivatives with biological activity



Compound	R_1	R_2	R_3	GAST (microM)
1.	H	2-Cl	Bn	15.2
2.	4-Cl	H	Bn	14.9
3.	H	3-Cl	Me	68.7
4.	H	3-Cl	H	106
5.	4-OEt	H	Bn	2.29
6.	4-OMe	3-Cl	Bn	7.58
7.	4-OMe	3-F	Bn	3.91
8.	H	3-F	Bn	6.86
9.	4-Cl	3-F	Bn	6.49
10.	4-NO_2	H	Bn	7.59
11.	4-NO_2	3-F	Bn	3.68
12.	3-Cl	2-OBn	Bn	34.0

13.	4-F	2-NO_2	Bn	40.4
14.	4-NO_2	2-F	Bn	8.70
15.				13.4
16.				26.6
17.				21.1
18.				127
19.				92.9

20.				81.3
21.	4-OMe	3-OMe	Bn	21.6
22.	H	2-OMe	Bn	29.2
23.	4-OPr	H	Bn	22.4
24.	4-OiPr	H	Bn	14.9
25.	4-OBu	H	Bn	5.11
26.	4-CH_3	H	Bn	27.3
27.	4-NO_2	2-OBn	Bn	4.86
28.	H	3-OMe	Bn	42.5
29.	H	3-CN	Bn	75.1
30.	H	3-Br	Bn	52.5
31.				122
32.				29.8
33.	4-NH_2	H	Bn	26.8

Optimization of molecular structures [9]:

The structure of each compound was drawn in Chem-Draw software in mol format. These structures imported in MDS 3.5 software and converted to 3D model. Energy minimization was performed of each 3D model using Merk molecular Force Field (MMFF) until the root mean square gradient values becomes smaller than 0.001 kcal/mol A°. The energy minimization was

carried as the drug binds to receptor in the most stable minimum energy state form. These structures were further used for calculating various physicochemical descriptors.

Descriptor calculation [9, 10]:

The VLife MDS 3.5 program was employed for the calculation of different descriptors including topological index (J), connectivity index (x), radius of gyration (R_G), moment of inertia, Wiener index(W), balaban index(J), centric index , hosoya index (Z), information based indices, XlogP, hydrophobicity, elemental count, path count, chain count, pathcluster count, molecular connectivity index (chi), kappa values, electro topological state indices, electrostatic surface properties, dipole moment, polar surface area(PSA), alignment independent descriptor (AI). The selected physicochemical parameters in final model are given in **Table-2**. The predicted and experimental biological activities with residual values were presented in **Table-3**. **2D-QSAR model development [9, 10]:**

Table 2

MolecularDescriptor	Description
XKAverageHydrophilicity	Average hydrophilic value on the vdW surface.
T_C_F_6	This is the count of number of Carbon atoms (Single double or triple bonded) separated from any Fluorine atom (single or double bonded) by 6 bond distance.
YcompDipole	This descriptor signifies the y component of the dipole moment.
MomInertiaY	This descriptor signifies moment of interia at Y-axix.

Table 3

Molecule	observed	predicted	residual	molecule	observed	predicted	Residual
1.	-1.1818	-1.29157	-0.10977	18.	-2.1038	-2.04817	0.05563
2.	-1.1731	-1.21109	-0.03799	19.	-1.9680	-1.96142	0.006578
3.	-1.8369	-1.99072	-0.15382	20	-1.9100	-1.7985	0.111501
4.	-2.0253	-2.27246	-0.24716	21	-1.3344	-1.24111	0.093289
5.	-1.4842	-1.11407	0.370128	22	-1.4653	-1.49133	-0.02603
6.	-0.8796	-1.03043	-0.15083	23	-1.3502	-1.01484	0.335361
7.	-0.5921	-0.61773	-0.02563	24	-1.1731	-1.08177	0.091331
8.	-0.8363	-0.83975	-0.00344	25	-0.7084	-0.88946	-0.18106
9.	-0.8122	-0.68472	0.127482	26	-1.4361	-1.28126	0.154845
10.	-0.8802	-1.14523	-0.26503	27	-0.6866	-1.19291	-0.50631
11.	-0.5658	-0.55594	0.009863	28	-1.6283	-1.30179	0.326512
12.	-1.5314	-1.45933	0.072073	29	-1.8756	-1.53484	0.340762

13.	-1.6020	-1.6537	-0.0517	30	-1.7201	-1.29122	0.428881
14.	-0.9395	-1.05848	-0.11898	31	-2.0863	-1.82593	0.260372
15.	-1.1271	-1.36803	-0.24093	32	-1.4742	-1.12447	0.349728
16.	-1.4248	-1.44763	-0.02283	33	-1.4281	-1.47989	-0.05179
17.	-1.3242	-1.36328	-0.03908				

The calculated descriptors were gathered in a data matrix. The invariable descriptors were removed from the original data matrix. The descriptors were correlated with each other. The highly auto-correlated (r › 0.5) descriptors were not considered for final equation.(**Table-4**) The anti-TB activity data and various parameters (physicochemical and alignment independent) were taken as dependent and independent variables respectively. In the generation of QSAR model we had selected ten molecules in test and twenty three in training set. The total set of compounds was initially divided randomly into two groups as training and test sets (with 23 compounds in training set and 10 compounds in the test set). Test and training set compounds were chosen manually in such a manner that low, moderate and high activity compounds and compounds with different substituents were present in both sets. Training set compounds were used to develop the QSAR models and the test set compounds were used to validate the developed model. The test set finalized was having molecules numbered as 19, 20, 49, 50, 52, 53, 54, 55, 56, 57. The correlation was established between dependent and independent variables by employing multiple sequential regression (MLR), partial least square (PLS) and principal component regression (PCR) method using random selection. The multiple sequential regression method gave more convincing results then other methods. So the results discussed were obtained from MLR method only.

Table 4 Autocorrelation table

	YcompDipole	MomInertiaY	XKAverageHydrophilicity	T_C_F_6
YcompDipole	1.000000	-0.199666	-0.033239	0.219352
MomInertiaY	-0.199666	1.000000	0.395733	-0.068791
XKAvgHydrophilicity	-0.033239	0.395733	1.000000	0.235530
T_C_F_6	0.219352	-0.068791	0.235530	1.000000

RESULTS AND DISCUSSION

The best 2D-QSAR model found to be the stepwise multiple linear regression analysis.

$_{P}$GAST = 5.4075(± 0.8813) XK Average Hydrophiliicity + 0.3156 (± 0.0074) T_C_F_6 - 0.1055(±0.0312)Ycompdipole +0.0001MomInertiaY-1.5445 …**Eq.1**

The statistical parameters obtained were

N=23, Degree of freedom = 18, r^2 =0.8845, q^2=0.8371, Ftest =34.4543,

r^2_se =0.1600, q^2_se = 0.1900, Pred_r^2 = 0.7590, Pred_r^2se = 0.2815.

Here N is the number of molecules in the training set, r^2 is the squared correlation coefficient, r^2_se and q^2_se are standard error of estimate, q^2 is cross validated r^2 obtained by leave one out (LOO) technique, F is fisher's value which represent the ratio between the variance of actual and predicted activity which were employed to judge the validity of regression equation. The predicted r^2 for external test (Pred_r^2) and r^2 › 0.7 qualifies the model to be predictive[11]. There was no significant improvement in r^2 and q^2 for the models containing more than four variables so Eq.1 was selected as the best significant model on the basis of high r^2 and q^2 values. The squared correlation coefficient (r^2) obtained was 0.8845 explains 88.45% variance in anti-TB activity depends on the parameters selected in the equation. The standard error of estimate (r^2_se & q^2_se) was less. Fisher's value (F=34.45) which represents the ratio of the variance explained by the model and the variance due to the error in the model was sufficiently high. High values of the F-test indicated that the model is statistically significant. The q^2 = 0.83 (q^2 > 0.5) qualifies the equation to be valid model according to recommendations of Golbraikh and Trophsa [12]. The plot between experimental and predicted activity validates regression equation (**Fig.1**). To determine the existence of the systemic error in the model development we had plotted observed activity against residual values (**Fig.2**). The propagation of residuals on both side of zero indicated that there is no systemic error in the development of QSAR model. The interrelatedness among the different descriptors can lead to highly unstable regression coefficients which make it impossible to know the relative importance of an index and underestimate the utility of the regression coefficients of the model [13, 14]. So the auto correlation matrix allowed was (r < 0.5) signify the correlated values less than 0.5 only considered **Table 4**. Thus it can be considered from the statistical data and the plot that the predictive potential of model was good enough. The observance of low residual values (**Table-3**) indicates the validity and productivity of equation. The percent contribution of different descriptors in influencing the biological activity was shown in **Fig. 3**.

Fig. 1 Fitness plot (observed vs predicted biological activity)

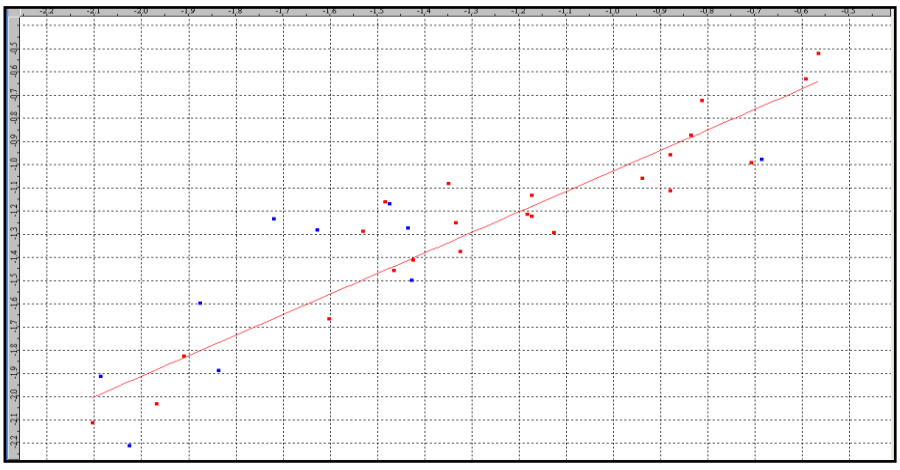


Fig.2 Observed values against residual values

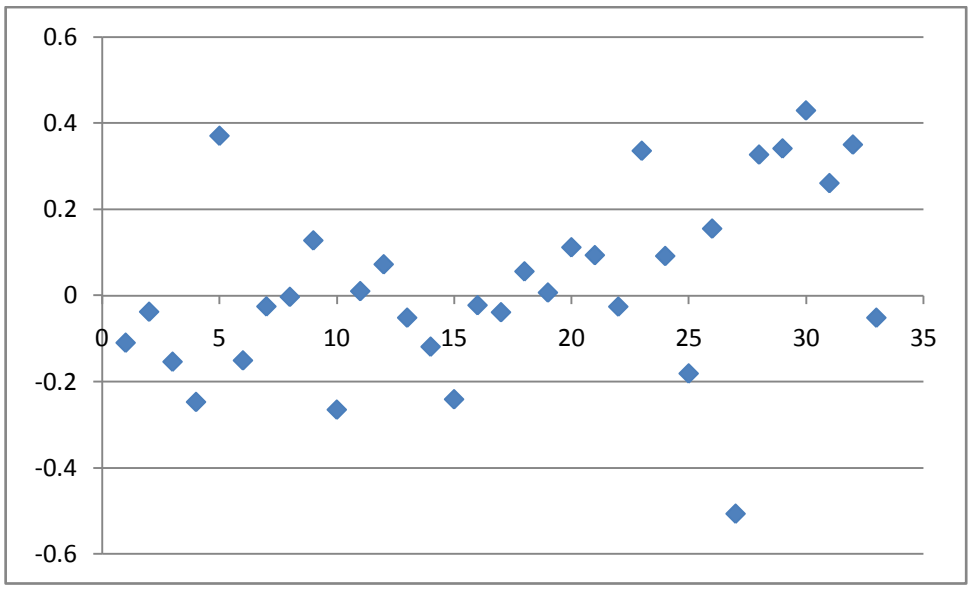
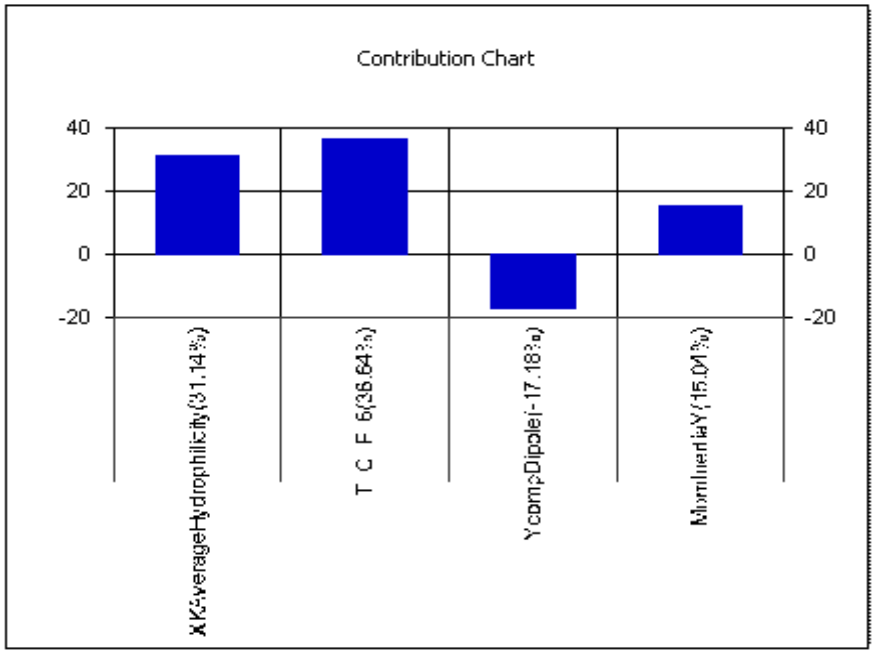


Fig.3 Contribution of each descriptor



CONCLUSION

In this study, it was possible to obtain a 2D-QSAR model for a set of 33 substituted oxazoline derivatives that have anti-TB activity. The model developed was significant and robust. The negative coefficient of Ycompdipole indicate that there was a inverse relationship between the anti-TB activity of substituted oxazoline and Ycompdipole. This means deceasing the value of Ycompdipole, the anti-TB activity can be increased. The importance of dipole moment in modulating anti-TB activity may be due to the presence of carbonyl group (C^{+}-O^{-}) whose

permanent polarization is seen due to elecrtonegativity difference between the atoms. The carbonyl oxygen of substituted oxazoline may involve in making fruitful binding interactions with amino acid present at the target site through hydrogen bonding. The molecular property dipole moment thus plays a critical role in modulating anti-TB profile of this class of compounds. The positive and significantly higher coefficient of XKaveragehydrophilicity indicate that even with small increment in XKaverage hydrophilicity, there is significant increase in anti-TB activity. If the count of number of Carbon atoms separated from any Fluorine atom by six bond increases in the molecule then anti-TB activity increases. These findings can be helpful in the development and optimization of new anti-TB drug containing substituted oxazolines.

Acknowledgements

Authors are grateful to Prof. Dasharath Sagare for providing infrastructure and facilities to reinforce research activity. We are also thankful to Dr. M. N. Deodhar, PDEA's SGRS College of Pharmacy, Saswad for technical support and guidence.

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