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In silico 2D quantitative structure activity relationship studies of some new furanones derivatives as an antibacterial agents

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Abstract
A set of twenty-one compounds Furanones derivatives with anti-bacterial activity was subjected to the two dimensional quantitative structure activity relationships studies using V life molecular drug design suit. Drug Designing module describe with various combinations of molecular connectivity indices, electro topological indices, alignment independent descriptors and other 2D descriptors. Furanones derivatives was taken as the lead molecule and QSAR model developed using multiple regression approach. For each set of descriptors, the best multi-linear QSAR equations were obtained by the stepwise variable selection method using leave-one-out cross-validation as selection criterion. Logarithmic inverse value of IC_{50} was taken as dependent variable and electro topological descriptor (SdOE-index and SsCH3E-index) was taken as independent variable. The best QSAR model ($r^2 = 0.7614$, F = 20.73, r^2 se = 0.36, q^2 se = 0.4248, Pred_r^2 = 0.5038, pred_r^2se = 0.3595) has acceptable statistical quality and predictive potential as indicated by the value of cross validated squared correlation coefficient ($q^2 = 0.679$. Thus this validated model brings important structural insight to aid the design of novel anti-bacterial activity.

Keywords: Anti-bacterial, 2D-QSAR, $IC_{50,}$ Descriptor etc

1. Introduction
The development of antimicrobial agents to treat infections has been one of the most noteworthy medical achievements of the past century. Antimicrobial resistance is a threat to mankind because most of the infection causing bacteria has become multidrug resistant [1, 4]. Antibiotic resistant bacteria may keep people sick longer, and sometimes people are unable to recover at all. The increasing antibiotic resistance of most clinically relevant bacteria creates an urgent need for new antibacterial classes that are not affected by resistance mechanisms already present in the bacterial population [5, 7]. QSAR models are mathematical equations constructing a relationship between chemical structures and biological activities. These models have another ability, which is providing a deeper knowledge about the mechanism of biological activity. In the first step of a typical QSAR study one needs to find a set of molecular descriptors with the higher impact on the biological activity of interest [8, 9].
The objective of present work is to determine the physicochemical parameters, which governs the anti-bacterial activity with a view to provide a better rational design of some more potent drugs in the present series. QSAR studies were performed to identify associated molecular properties and also to optimize their activity.

2. Materials and methods
Selection of series
The series of twenty-one compounds of Furanones derivatives were reported to have anti-bacterial activity. All the values of biological data's were expressed as IC_{50} values. For present biological activity data's were converted to –Log unit in mathematical operation mode to reduce skewness of data set. The structure of each compound was drawn in 2dappl mode of software and export in 3D mode for create 3D model. Energy minimization was performed of each model using MMFF. The basis of energy minimization is that the drug binds to effectors/receptor in the most stable form i.e. minimum energy state form. The general structure of these analogues is reported in, Fig. 1, and compounds with their biological activity data are shown in (Table 1). The molecular modeling studies were performed using MDS 3.0, supplied by V Life science [16].

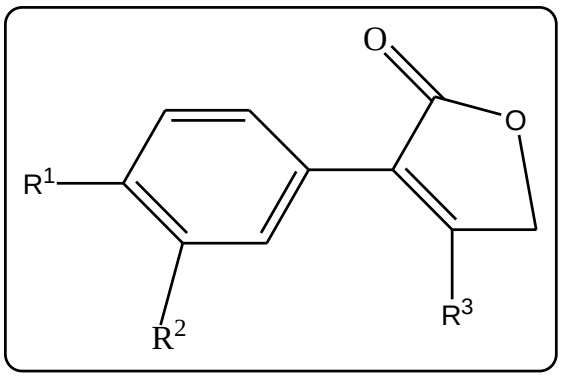
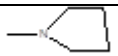
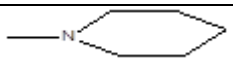
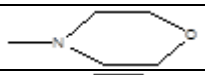
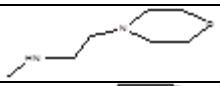
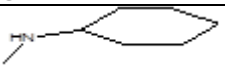
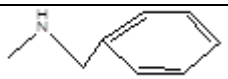
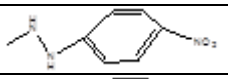
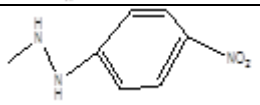
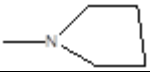
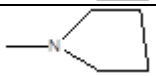
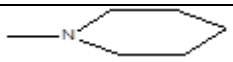
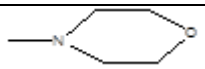
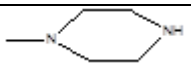
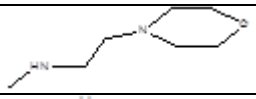
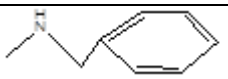
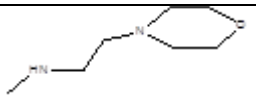
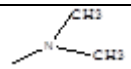


Fig 1: General structure of Furanones derivatives

Table 1: Biological Activity of Data of Furanones derivatives as Anti-bacterial Agents

S. No.	R^1	R^2	R^3	MIC µM
1.	Br	H		37.1
2.	Br	H		21.8
3.	Br	H		42.6
4.	Br	H		54.7
5.	Br	H		9.7
6.	Br	H		27.8
7.	Br	H		87.2
8.	Br	H		57.6
9.	Br	H		0.42
10.	H	H		0.85
11.	Cl	H		88.4
12.	H	Cl		12.6
13.	H	Cl		7.5
14.	H	Cl		25.7
15.	H	Cl		37.4
16.	H	Cl		65.2
17.	H	Cl		3.2
18.	H	Cl		52.4
19.	H	Cl		25.3
20.	MeO	MeO		68.3
21.	H	Br		61.4

Generation of QSAR equation

The relationship between biological activities and various descriptors is established by sequential multiple regression analysis (MLR) using MDS 3.0, in order to obtain QSAR models. Anti-bacterial activity data and various physiochemical parameters were taken as independent and dependent variables respectively and correlation were established between them by employing multiple sequential regression (MLR) method [10, 12]. For the generation of the QSAR model we have selected the five test set and sixteen training set. Selection of training and test set was based on uni-column statistics, Table 2. 16 compounds were placed in the training set and 5 compounds (1, 3, 8, 15, and 16) in the test set,

Table 2: Uni-column statistics

Data set	Average	Max.	Min.	Std. Dev	Sum
Training	4.7761	6.3768	4.0535	0.6982	76.4175
Test	4.3307	4.4306	4.1858	0.1120	21.6537

All chemical structures and their descriptors [13, 15] i.e. molecular connectivity indices (MCI), electro topological indices (EI), alignment independent (AI) descriptors and other 2D descriptors such as logP (partition coefficient) etc. were calculated by using V Life MDS software [16].

3. Result and discussion

A quantitative structure activity relationship (QSAR) study on a series of analogs of Furanones derivatives for their anti-bacterial activity has been made using combination of various descriptors. Different physicochemical parameters were taken for each substituent in order to obtain QSAR models. Selection of best QSAR equation the following statistical parameters were considered to generate QSAR models: correlation coefficient (r), squared correlation coefficient (r^2), standard error of estimate (s) and Fisher's value (F), which represent F-ratio between the variance of calculated and observed activity.

In order to validate the generated QSAR models leave one out (LOO) method was used. Cross validated squared correlation coefficient (q^2), standard deviation of sum of square of difference between predicted and observed value and standard deviation of error of prediction were also used for each model to estimate the predictive potential of models. Actual & predicted biological activity with residuals for Furanones series was reported in Table 4 and Fig. 4.

All models were screened on the basis of intercorrelation with in the descriptors (<0.9) leave one out cross-validated squared correlation coefficient (q^2>0.6), Table 3 and Fig 2.

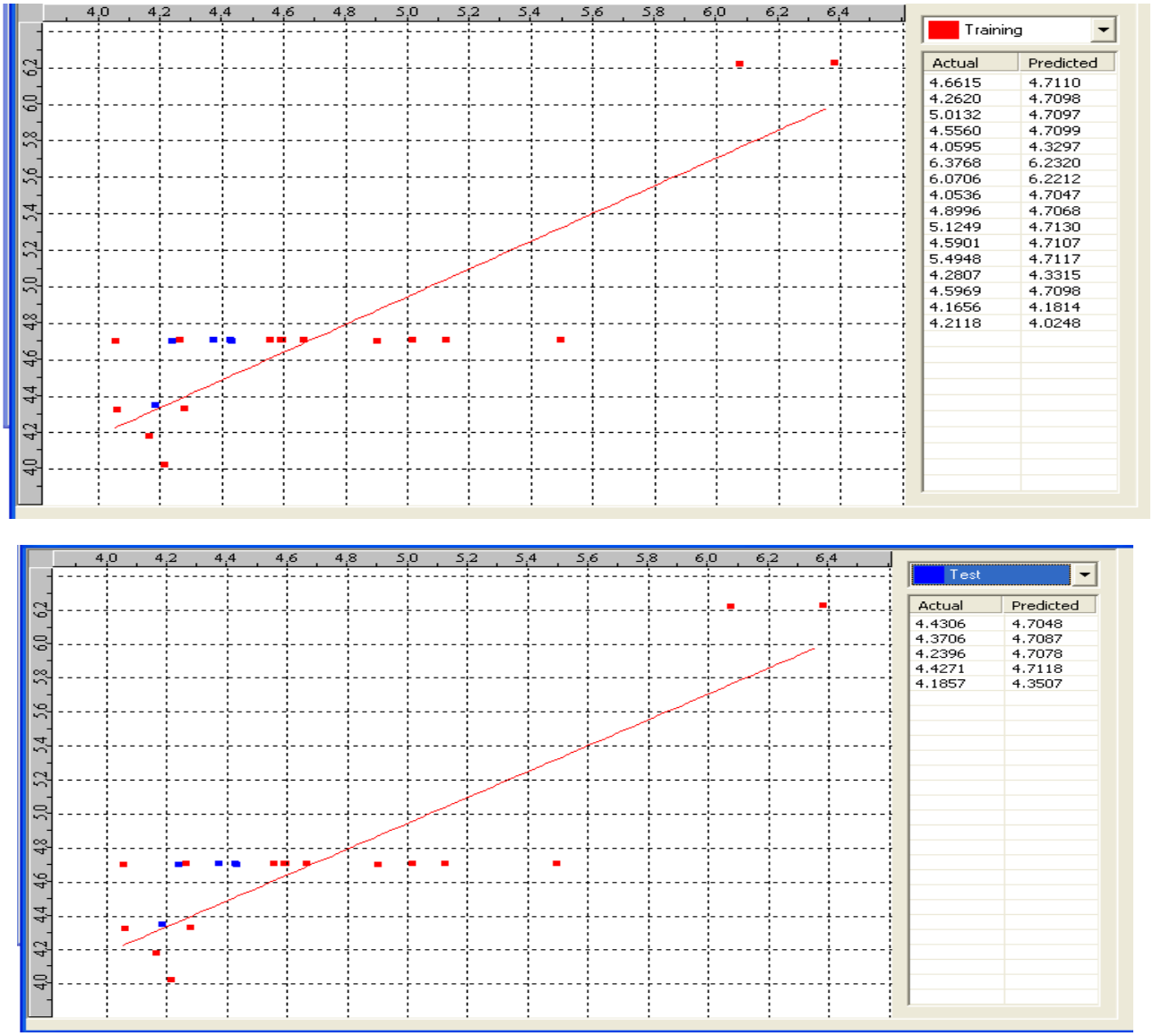


Fig 2: Plot of cross-validated calculated activity obtained (model 1)

Table 3: Statistical Data for Best model

N	r^2	q^2	F-test	r^2 se	q^2 se q	pred_r^2	pred_r^2se
16	0.7614	0.6793	20.7394	0.3664	0.4248	0.5038	0.3595

The stepwise regression analysis generated a large number of QSAR equation, out of which the best equation was found to be as given below-

Model-1: Multiple linear regression analysis (MLR)

Log (1/MIC) = 0.0715 (±0.0094) SdOE-index - 0.1716 (±0.0726) SsCH3E-index + 3.8517

From the results (Model 1) it was found that electro topological descriptor SdOE-index contributes positively towards biological activity, whereas SsCH3E-index contributes negatively towards biological activity. Low standard error of estimate of this model (se<0.4) demonstrates the accuracy of the model. Higher Q^2 value reflects good predictive potential of the model. To ascertain the predictivity of the model, internal validation using leave one out cross validation process, bootstrapping technique test was performed. The model's Q^2>0.6 supported the predictive ability and significance model. The r^2 supported the robustness of the model, as well as indicated that, no single compound of the series contributed much more to the model. The parameters SdOE-index (70%) were contributed positively and SsCH3E-index (30%), were negatively contributed in anti-bacterial activity, Fig. 3.

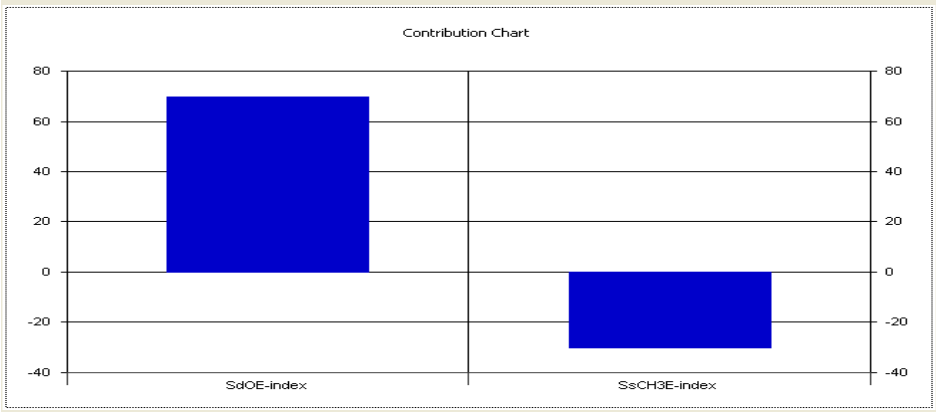


Fig 3: Contribution chart of descripter for model 1(MLR method)

Table 4: Actual & predicted biological activity with residuals for Furanones derivatives

Compound No.	Actual *pMIC*	Predicted *pMIC*	Residual *pMIC*
1	4.430626	4.704812	-0.27419
2	4.661544	4.710957	-0.04941
3	4.37059	4.708722	-0.33813
4	4.262013	4.70984	-0.44783
5	5.013228	4.709662	0.303566
6	4.555955	4.709934	-0.15398
7	4.059484	4.329685	-0.2702
8	4.239578	4.707764	-0.46819
9	6.376751	6.232037	0.144714
10	6.070581	6.221229	-0.15065
11	4.430626	4.704812	-0.27419
12	4.899629	4.706815	0.192814
13	5.124939	4.712959	0.41198
14	4.590067	4.710725	-0.12066
15	4.427128	4.711842	-0.28471
16	4.185752	4.350702	-0.16495
17	5.49485	4.711665	0.783185
18	4.280669	4.331495	-0.05083
19	4.596879	4.709767	-0.11289
20	4.165579	4.181355	-0.01578
21	4.211832	4.024789	0.187043

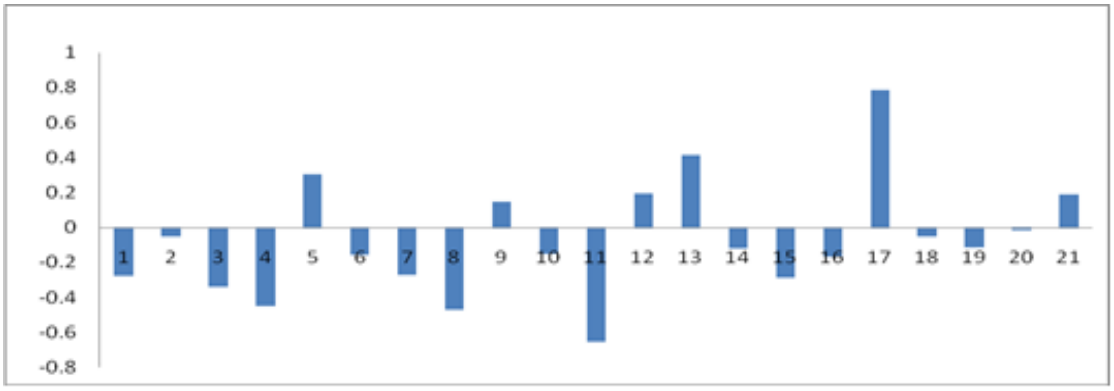


Fig 4: Residual MIC chart of 2D QSAR

4. Conclusion

From the results (Model 1) obtained, it was concluded that electro topological descriptor SdOE-index (70%) contributes positively towards biological activity, whereas SsCH3E-index (30%) contributes negatively towards biological activity. This suggests that by Modification in electro topological indices will be helpful for designing of more potent anti-bacterial agents. Results of the QSAR studies may be utilized for the rational designing of the compounds with expectation to obtain the potent anti-bacterial agents, which would be patented in the near future.

5. References

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antibacterial activity of Schiff's and Mannich bases of Isatin and its derivatives. Acta. Pharm. Turc. 1998; 40:33-38.
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