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Research Article

In Silico 3D QSAR Analysis of New Furanones Derivatives as Antibacterial agent

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Abstract
Three-dimensional quantitative structure activity relationship studies were carried out on a series of 21 Furanones derivative to find out the structural requirements for anti-bacterial activity by using Molecular Design Suite (MDS) 3.0.The best predictions were obtained from the model where seventeen compounds were considered in the training set and remaining five compounds in the test set. 3D QSAR approach was developed based on principles of the k-nearest neighbor method combined with various variable selection procedures was used. The kNN-MFA approach was used to generate models for given data set and these models were used to predict the activity of test molecules.
Keywords: 3D QSAR; V-Life; Furanones derivative; Anti-bacterial activity

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. 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, [1-4].

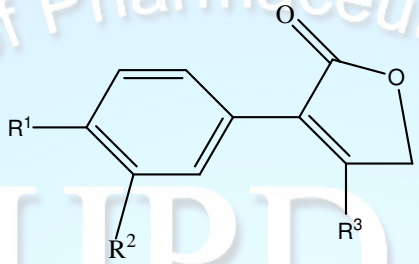
Furanone derivatives are a large family of heterocycles that include synthetically useful compounds, several natural products and drugs with diverse biological activities. Gram-positive bacteria cause a wide spectrum of infectious diseases, including nosocomial infections. While in the biofilm, bacteria exhibit increased resistance to antibiotics and the human immune system, causing difficulties in treatment. The mechanisms of resistance spreading in pathogenic bacterial populations call for the inhibition of new bacterial targets. [5-7].

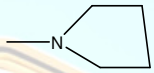
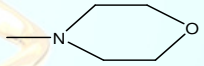
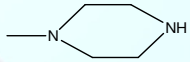
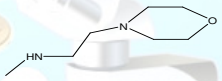
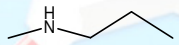
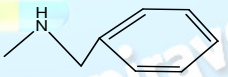
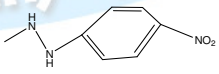
The inhibition of virulence targets could bring new antibacterial molecules with radically new mechanisms of action and represent an innovative therapeutic concept .Virulence is defined as the relative capacity of a microbe to cause damage in a host. Although this definition is simple, it does encompass a wide variety of bacterial functions such as the direct effectors of pathogenicity (e.g. toxins), and many of the functions that are not essential for basic metabolism (in vitro essential genes) that contribute to the establishment of an infection in the host and are validated by deletion mutants (essential in vivo). [7-10].

3D QSAR models are often sensitive to the particular alignment technique. Compounds having highest pIC_{50} values were selected as the template molecule and each molecule has to be superimposed onto template molecule (template based alignment).These aligned molecules were placed into a three dimensional cubic lattice of 2Å grid. The electrostatic and steric fields were generated at each grid point using methyl probe (sp^3 hybridized) of charge +1 by kNN method with default energy of 30 kcal/mol and 10 kcal/mol respectively and partial atomic charges were generated using Gasteiger-Marsii method. Electrostatic and steric fields were than generated around the aligned molecules in the grid. Negative value in electrostatic field descriptors (blue points in the dialog box) indicates that negative electronic potential is favorable for activity and more electronegative substituents group is preferred at that position, and posi-

tive electronic potential range indicates the vice-versa. Negative range in steric field (green points in the dialog box) signifies that negative steric potential is required for activity and less bulky substituents group is preferred in that region, positive value of steric descriptors reveals that positive steric potential is favorable for increase in activity and more bulky group is preferred in that region.

Table 1: Biological Activity Data of furanone derivatives as antibacterial



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

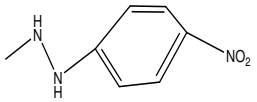
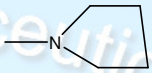
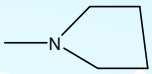
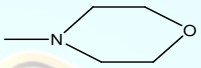
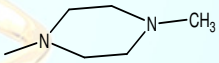
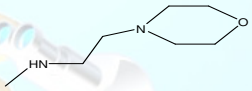
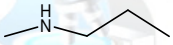
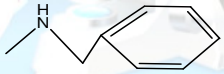
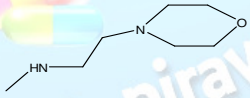
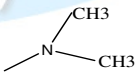
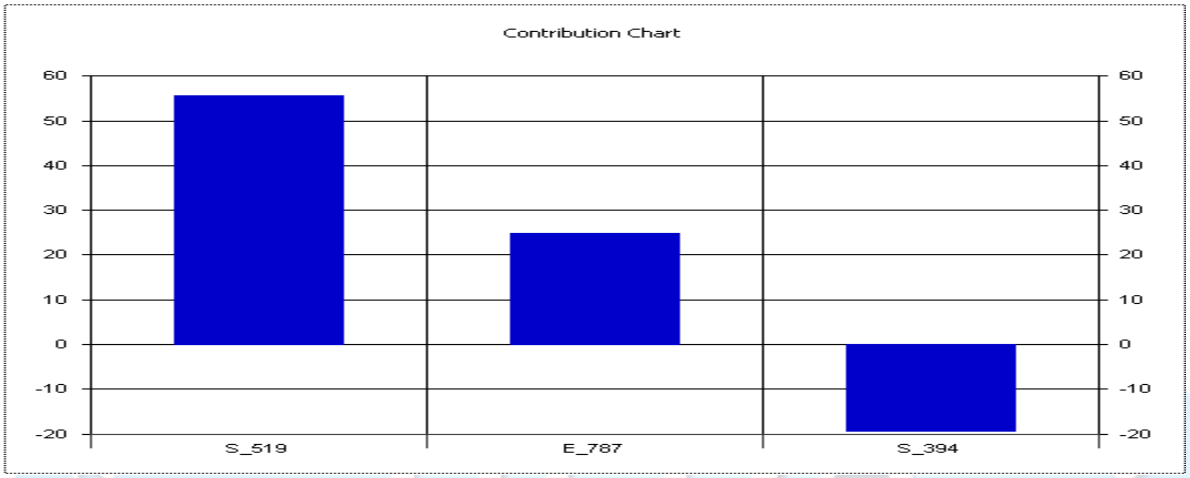
10.	H	H		0.85
11.	Cl	H		88.4
12.	H	Cl		12.6
13.	H	Cl		7.5
14.	H	Cl		25.7
15.	H	Cl		37.4
16.	H	Cl		65.2
17.	H	Cl		3.2
18.	H	Cl		52.4
19.	H	Cl		25.3
20.	MeO	MeO		68.3
21.	H	Br		61.4

Fig. 1. Contribution Chart of Descriptor For Biological Activity For 3D QSAR Model



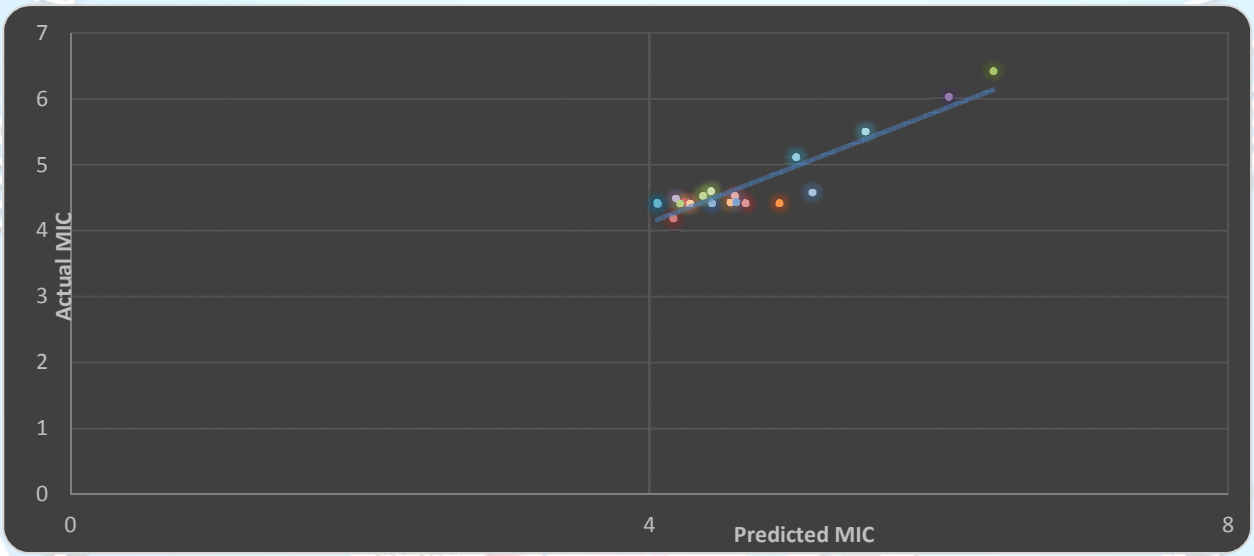


Fig. 2. Plot of cross-validated calculated activity of 3D QSAR mode

As generated by kNN-MFA in conjunction with stepwise (SW) forward-backward variable selection method. In the kNN-MFA method, several models were generated for the selected members of training and test sets, and the corresponding best models are reported here in. VLife Molecular Design Suite (V-Life MDS) allows user to choose probe, grid size, and grid interval for the generation of descriptors. The variable selection methods along with the corresponding parameters are allowed to be chosen, and optimum model is generated. [10-20].

MATERIALS AND METHODS

A dataset of twenty one furanone derivatives for their antibacterial activity have been taken for present QSAR work reported in Table 1. All molecular modeling techniques including 3D QSAR studies described here and performed on molecular modeling software V-Life MDS. We hereby report the models, as generated by kNN-MFA utilizing SA and SW forward variable selection methods for this

data set. In the kNN-MFA method, several models were generated for the given or selected members of training and test sets and the corresponding best models are reported here. The QSAR models developed by kNN-MFA include both the electronic and steric descriptors along with their range to indicate their importance for interaction in molecular field. Analysis of model suggested that both steric and electrostatic descriptors are important for interaction. All the QSAR models were evaluated on the basis of k i.e. no. of nearest neighbors; q2, i.e. cross validated r2 (by leave one out method) and pred_r2 for the external test set. In the dialog box, green points indicates steric region and blue indicates electronic.

The Negative coefficient indicates that more electronegative substitutions (CF_3, Cl, F, Br) are favorable for activity, while positive coefficient ((0.0545)) at S_519 and) E_787 (0.0659). Indicates substitution of a bulky group are favorable for activity. On the basis of 3D results show that higher steric and electronic group attached at specify position to increase the biological activity. Contribution chart is given in Fig. 1. The following statistical parameters were considered for comparison of the generated QSAR models: correlation coefficient (r), squared correlation coefficient (r^2), internal cross validation (q^2), predictive r^2 for external test set (pred r^2) for external validation, and Fischer's (F). Internal validation was carried out using leave-one-out (LOO) method. For calculating q^2, each molecule in the training set was eliminated once and the activity of the eliminated molecule was predicted by using the model developed by the remaining molecules. Plot of cross-validated calculated activity is given Fig.2

RESULT AND DISCUSSION

QSAR studies on furanones series resulted in several QSAR equation using partial least square (PLS) technique. Selection of test and training sets was based on uni-column statistics. Sixteen compounds were placed in the training set and five ((1, 3, 8, 15, 16) compounds in the test set. Test and training set was chosen randomly such that low, moderate and high-activity compounds were present in approximately the same proportions in both sets, which were confirmed by the results of uni-column statistics. .Selection of test and training set was based on uni-columns statistics. The best equation obtained by PLS in summarized here. The uni-column statistical analysis is summarized in Table 2. & Table 3.

Table 2: Uni-Column statistics for the 3D QSAR model

DATA SET	AVERAGE	MAX.	MIN.	STD. DEV	SUM
TRAINING	4.7682	6.3768	4.0535	0.6986	76.2917

TABLE 3: ACTUAL AND PREDICATED ACTIVITY WITH RESIDUAL ACTIVITY OF 3D QSAR MODEL FOR SERIES OF FURANONE 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

PARTIAL LEAST SQARE ANANALYSIS RESULT OF 3D QSAR MODELS

Log (1/MIC) = 0.0545(S_519) +0.0659(E_787)--0.0250(S_394) +5.1207

Statistical Data

n = 16, F= 93.63, r^2= 0.8699, q^2= 0.8224, r^2Se = 0.2608, q2se=0.3047pred r^2=0.7905 pred_r^2se= 0.2289

Above model was chosen as the best model as it showed a good correlation coefficient (r^2 = 0.8699) which explain 86% of the variance. The model showed an internal predication (q^2= 0.822) of 82% and predicivity for the external test (pred r^2=0.3047) of 30%. The overall statistical significance level was found to be exceed 99.9% with fitness (F=93.637). Fitness plot is give in Fig. 3.

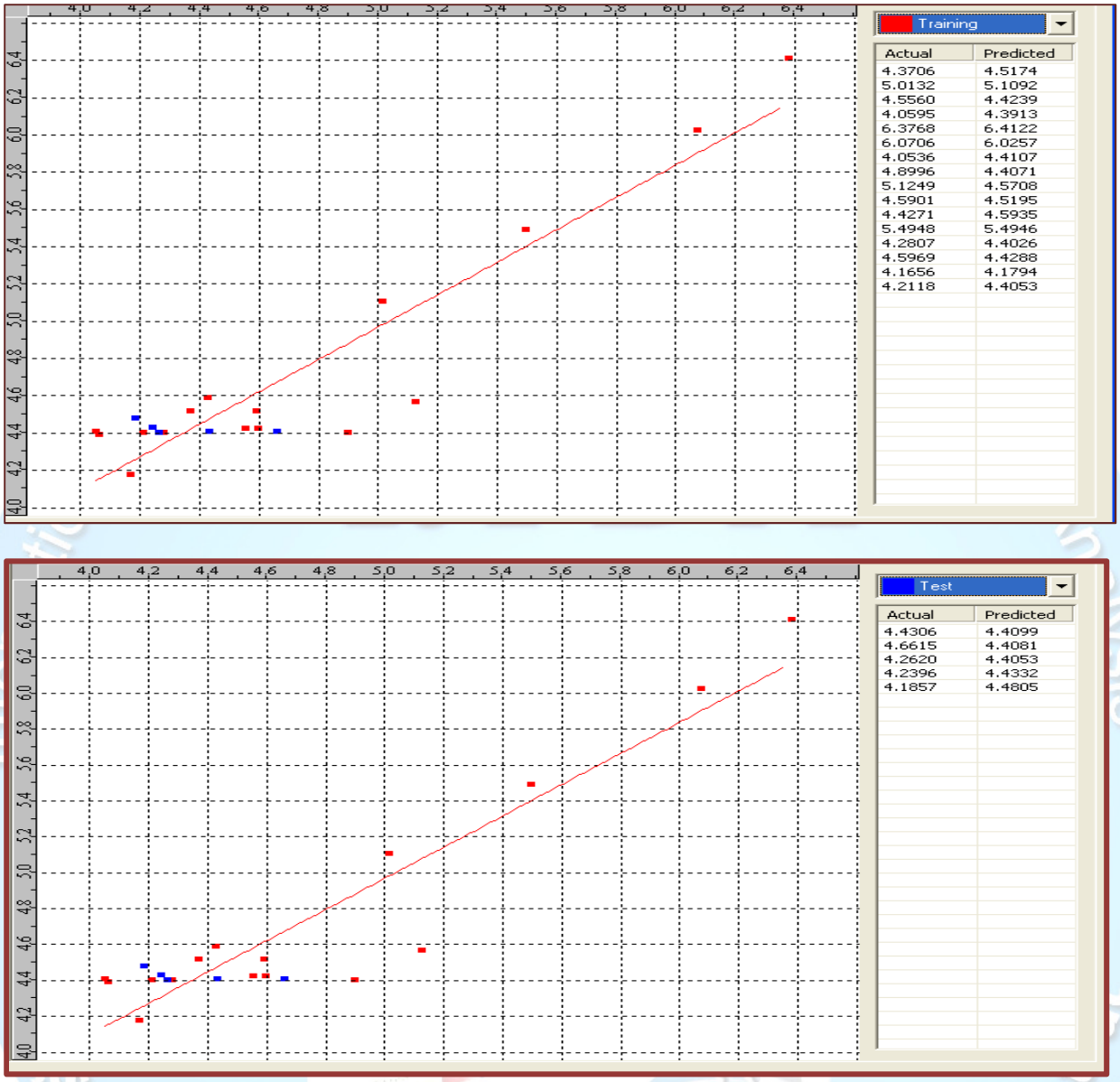


Figure 3- Fitness plot for SW kNN-MFA model

The kNN-MFA models provide direction for the design of new molecules in a rather convenient way.. The range of property values for the chosen points may aid in the design of new potent molecules. The range is based on the variation of the field values at the chosen points using the most active molecule and its nearest neighbor set. Negative range indicates that negative electrostatic potential and steric potential are favorable for increase in the activity and hence more electronegative substituent group is preferred in that region. Positive electro potential and steric potential are favorable for increase in activity and hence a less electronegative group is preferred in this region. Hence, this method is expected to provide a good alternative for the drug design.

The points which contribute to the SW kNN-MFA and SA kNN-MFA models in data sets are displayed in Fig.4. And Fig.5

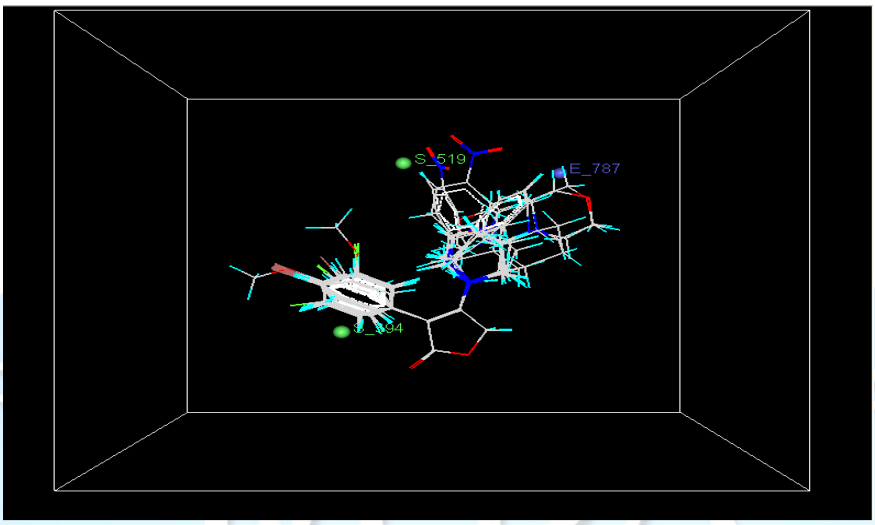


Figure.4. Distribution of chosen points in the SW kNN-MFA model

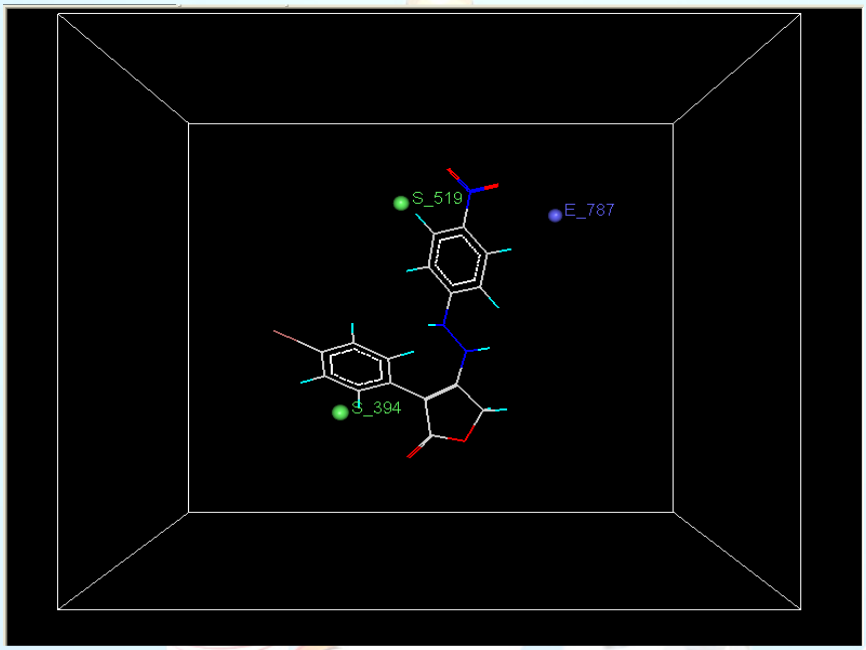


Fig. 5. Distribution of chosen points in the SA kNN-MFA model

In the dialog box, green points indicates steric region and blue indicates electronic. The Negative coefficient indicates that more electronegative substitutions (CF_3, Cl, F, Br) are favorable for activity, while positive coefficient ((0.0545)) at S_519 and) E_787 (0.0659). Indicates substitution of a bulky group are favorable for activity. Statistical data for SW kNN-MFA and SA kNN-MFA model was given in Table 4

Table 4. Statistical Result Of 3D QSAR Model For furanone Derivatives

kNN-MFA Method	Descriptors	Statistical Parameter
Stepwise (SW) Variable Selection	S_519(0.0545) E_787(0.0659) S_394(-0.0250) Constant:= 5.1207	Optimum Components = 1 n = 16 Degree of freedom = 14 r2 = 0.8699 q2 = 0.8224 F test = 93.6379 r2 se = 0.2608 q2 se = 0.3047 pred_r2 = 0.7905 pred_r2se = 0.2289 , pred_r^2se=0.371, test size= 5 n=17

CONCLUSION

The compounds were designed by using 3D QSAR study. The descriptors E_787, and S_519, S_394 were found to be responsible for the activity. New compounds have been designed on the basis of above facts and the prediction of activities for designed compounds was found to be more than the previous reported compounds

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