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3D QSAR analysis of new N-linked 5-triazolylmethyl oxazolidinones derivative as antibacterial agents

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Abstract

Three-dimensional quantitative structure activity relationship studies were carried out on a series of 21 N-linked 5-triazolylmethyl oxazolidinones compounds to find out the structural requirements for antibacterial activity by using Molecular Design Suite (MDS) 3.0.The best predictions were obtained from the model where thirteen compounds were considered in the training set and remaining eight 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; N-linked 5-triazolylmethyl oxazolidinones; Antibacterial activity.

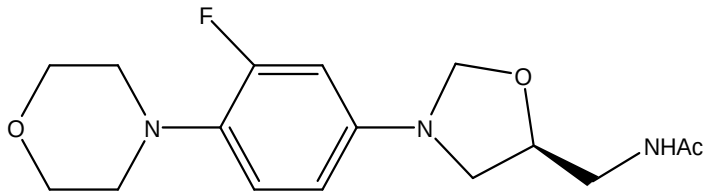
INTRODUCTION

Infections due to gram-positive bacteria such as methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *enterococcus faecium* (VREF) and penicillin resistant *Streptococcus pneumoniae* (PRSP) are the leading cause of morbidity and mortality in community today [1-5]. The successful control of disease caused by resistant strains of bacteria will require not only the development of new and improved antibacterial but also the rational use of available agents.

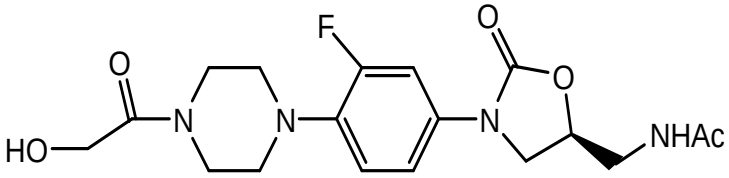
The oxazolidinones represent a novel chemical class of synthetic antibacterial agents. Linezolide [3-(fluorophenyl)-2- oxazolidinones] (Fig.1), is the first totally synthetic antibacterial agents in this new class. Oxazolidinones represent a new class of synthetic antibacterial agents with potent activity against clinically important susceptible and resistant Gram-positive pathogens [6]. Oxazolidinones inhibit the bacterial protein synthesis prior to the chain initiation step by binding

to the 23S rRNA of 50S ribosomal subunit and interfering with initiator fMET-tRNA binding to the P-site of the ribosomal peptidyltransferase center [7-8].

The rapid increase in three-dimensional structural information (3D) of bioorganic molecules coupled with the development of fast methods for 3D structure alignment (e.g. active analogue approach), has led to the development of 3D structural descriptors and associated 3D QSAR methods. We report here the development of a new method (kNN-MFA) that adopts a k-nearest neighbor principle for generating relationships of molecular fields with the experimentally reported activity.



linezolid



eperezolide

Figure 1- Structure of linezolid and eperezolid

The present communication is an attempt to explore the 3D QSAR of a series of oxazolidinones compounds. It is aimed at explaining the observed variation in biological activity as a function of various electrostatic and steric parameters thereby predicting the best lead compounds. These lead compounds can provide insight into substitution and configurationally requirements for optimum receptor, leading to the development of the compound with best pharmacological activity.

RESULTS AND DISCUSSION

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; q^2, i.e. cross validated r^2 (by leave one out method) and pred_r^2 for the external test set.

Values of different parameters,

Model 1 (SW kNN-MFA model)
E_743 (0.789 to 0.809), S_355 (-0.140 to 0.046)
(q^2 = 0.86, q^2_se = 0.34, Pred_r^2 = 0.51)

Model 2 (SA kNN-MFA model)
E_714 (-0.016 to 0.016), S_764 (-1.378 to 1.325) and E_296 (-0.4926 to 0.402)
(q^2 = 0.80, q^2_se = 0.23, Pred_r^2 = 0.44)

Most significant models were generated by SW variable selection method and simulated annealing method. The value of obtained cross validated correlation coefficient was found the q^2= 0.86 for SW and 0.80 for SA which are explain the goodness of internal predictivity of the model.

The external predictive power i.e. the value of pred_r^2 for a model is valuable in the evaluation of a QSAR model. SW model give 51% external predictive power whereas 44% was obtained with SA model.

A closer view to the selected descriptors suggested that descriptor E_743 and S_355 were included in SW kNN-MFA model and E_714, E_296 and S_764 were included in SA kNN-MFA model which play a significant role in the structure activity relationship (Table 1 and 2). Both the method used with electrostatic and steric field descriptor along with its k nearest neighbours (k=2) to evaluate the activity of new molecules. Developed kNN-MFA models showing the relative position and ranges of the corresponding important electrostatic and steric fields provide guidelines for designing new molecules.

Negative range indicates that negative electrostatic potential and steric potential are favorable for increase in the activity and hence more electronegative substituent groups are 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.

The kNN-MFA models provide direction for the design of new molecules in a rather convenient way. The points which contribute to the SW kNN-MFA and SA kNN-MFA models in data sets are displayed in (Fig. 2&3). 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.

In conclusion, a novel three-dimensional QSAR approach has been developed based on the principles of the k-nearest neighbor method. The method employs different variable selection procedures with stepwise forward and simulated annealing, for the data sets reported in this study. The location and range of function values at the field points selected by the models provide clues for the design of new molecules. 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.

Table 1- Value of descriptors for SW and SA-kNNMFA Model

S. No.	SW-kNN MFA		SA-kNN MFA		
	E_743	S_355	E_714	S_764	E_296
1.	1.078	-0.445	-1.378	0.402	-3.270
2.	0.425	-0.462	0.012	8.919	-2.435
3.	0.646	30.00	-9.042	-0.526	-0.414
4.	0.257	-0.181	1.249	-0.382	0.192
5.	-0.040	-0.161	1.250	-0.401	6.143
6.	0.241	-0.111	-5.361	-0.393	0.142
7.	0.789	-0.140	2.858	-0.454	0.225
8.	-0.084	-0.099	1.706	-0.376	0.017
9.	-0.025	-0.181	-2.43	-0.460	1.551
10.	1.039	-0.397	-1.32	-0.492	-0.838
11.	0.809	-0.046	0.220	-0.412	-1.856
12.	0.389	-0.169	-5.45	-0.469	0.715
13.	0.452	-0.348	0.097	6.620	-0.512
14.	0.007	-0.058	10.00	-0.368	0.427
15.	-7.890	-0.062	1.954	-0.454	0.587
16.	-0.102	-0.134	-10.0	-0.270	0.418
17.	0.655	-0.501	-2.53	-0.447	-0.334
18.	0.383	-0.106	-1.14	-0.449	-0.053
19.	0.416	-0.228	-3.22	-0.478	-0.070
20.	0.738	-0.168	-3.55	-0.401	0.226
21.	0.366	-0.220	-0.215	-0.430	0.090

Table 2- Statistical data for SW kNN-MFA and SA kNN-MFA model

Parameters	**SW kNN-MFA**	**SA kNN-MFA**
N (Train/ Test)	15/6	13/8
k NN	2	2
q2	0.86	0.80
q2_se	0.34	0.23
Predr2	0.51	0.4376
pred_r2se	0.4194	0.5618
Descriptors	E_743, S_355	E_714, S_764 E_296
Descriptor Range:	E_743 0.7894 to 0.8099	E_714 -0.0160 to 0.0169
	S_355 -0.1404 to 0.0468	S_764 -1.3787 to 1.3257
		E_296 -0.4926 to 0.4029

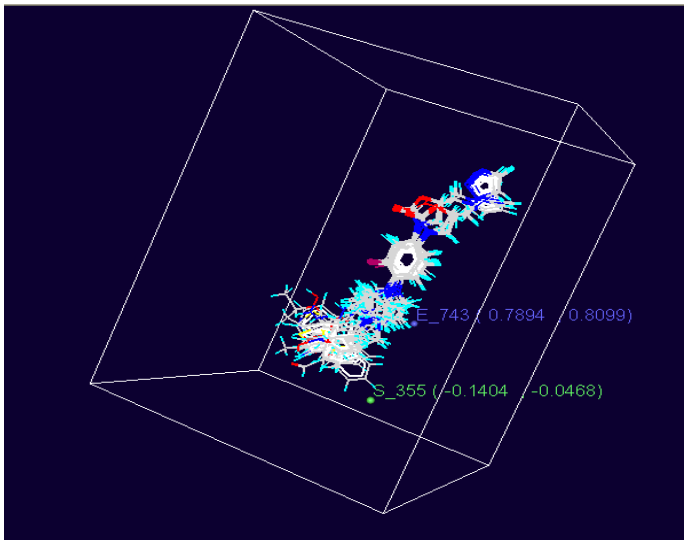


Figure 2- Distribution of chosen points in the SW kNN-MFA model

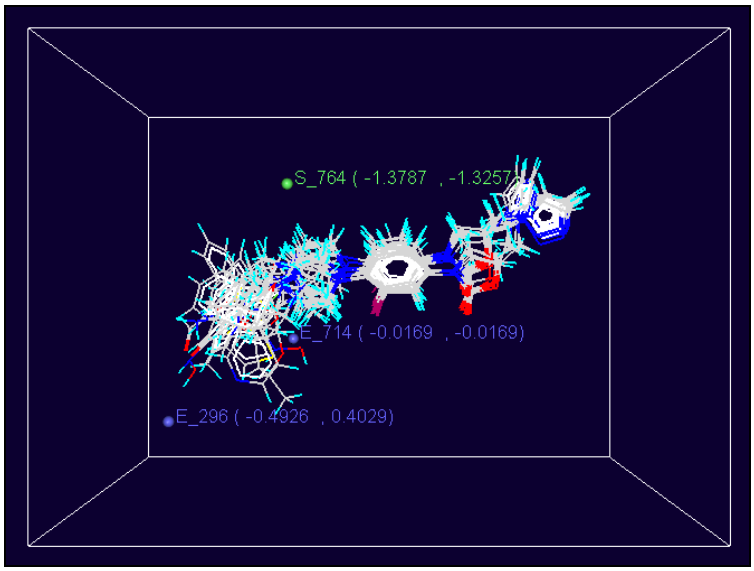


Figure 3- Distribution of chosen points in the SA kNN-MFA mo

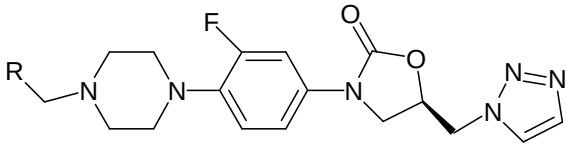
MATERIALS AND METHODS

The biological activity data used in present study is the inhibition of *Staphylococcus aureus* ATCC 29213 Gram-positive bacteria (MIC) by a series of N-linked 5-triazolylmethyl oxazolidinones derivatives. The synthesis and determination of the activity of these compounds have already been reported in literature [9]. Their study indicated the activity against bacterial cells of a range of arylsulfonyl Oxazolidinones bearing N-linked 5-triazolylmethyl groups. Table 1; list the structural features and anti-bacterial activity of the compounds under study. The biological data were converted to logarithmic scale (pIC_{50}) in mathematical operation mode of

software to reduce skewness of data set and then used for subsequent QSAR analysis as dependent variable.

The optimal training and test sets were generated using the sphere exclusion algorithm [10]. This algorithm allows the construction of training sets covering descriptor space occupied by representative points. The dissimilarity level was set to 5, higher the dissimilarity level, lesser is the predictive ability of QSAR model. The set data was observed for activity distribution as activity distribution plot (Fig. 4 a & b) which revealed that almost all the compounds in test set are within the minimum maximum limit of the training set.

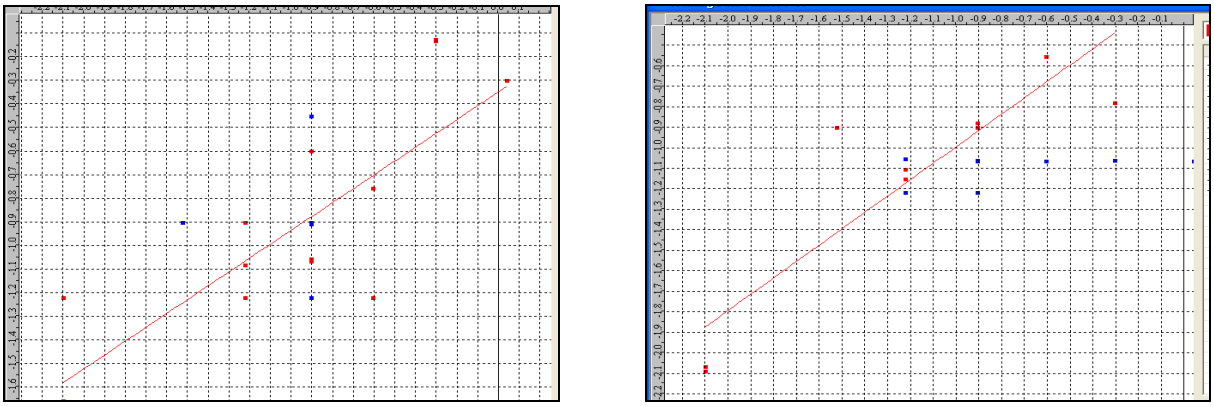
Table 1- Biological activity of N-linked 5-triazolylmethyl oxazolidinones derivatives as antibacterial



S.No.	R	MIC (µg/ml)*	pIC_{50}
1.	3-CHO-Ph	0.250	-0.6021
2.	4-CHO-Ph	0.008	-2.0969
3.	2-NO_2-Ph	0.125	-0.9031
4.	2-NH_2-Ph	0.125	-0.9031
5.	3-NO_2-Ph	0.030	-1.5230
6.	3-NH_2-Ph	0.250	-0.6021
7.	4-NO_2-Ph	0.500	-0.3011
8.	4-NH_2-Ph	0.125	-0.9031
9.	2-Pyridyl	0.125	-0.9031
10	3-Pyridyl	0.125	-0.9031
11.	4-Pyridyl	0.500	-0.3011
12.	2-Furyl	0.060	-1.2210
13.	3-Furyl	0.008	-2.0969
14.	5-Me-furan-2-yl	0.125	-0.9031
15.	5-Cl-furan-2-yl	0.125	-0.9031
16.	5-NO_2-furan-2-yl	0.060	-1.2210
17.	2-Thioenyl	0.060	-1.2210
18.	3-Thioenyl	0.060	-1.2210
19.	5-Br-thiophen-2-yl	0.060	-1.2210
20.	3-Me-thiophen-2-yl	0.100	-1.0000
21.	5-Me-thiophen-2-yl	0.125	-0.9031

* *Minimum inhibitory concentration against S. aureus ATCC9213 Gram-positive bacteria*

The selection of test and training set was further justified by unicolumn statistics calculated for each case of study. Once the training and test sets were generated, kNN methodology was applied to the descriptors generated over the grid.



(a) **(b)**

Figure 4- Fitness plot for (a) SW and (b) SA kNN-MFA model

The molecular modeling studies were performed using MDS 3.0, supplied by Vlife [11]. The structure of each compound was drawn in 2DAppL mode of software and exported in MDS to generate 3D structure. Energy minimization was performed using Merk Molecular Force Field (MMFF) until a convergence criterion of 0.001kcal/mol was attained. Complete geometry optimization was performed taking the most extended conformations as starting geometries. The most significant requisite for any 3D-QSAR study is to align the data set on a suitable conformational template, either by taking a reported crystal structure of a bioactive compound or by considering the most active compound.

In the present study, since we don't have any reported crystal structure, the most active compound was considered as a template for the alignment. The N-linked piperazine moiety of the bioactive molecule was used as a substructure and the rest of the molecules were aligned on it using database alignment method. For calculation of field descriptor values, both electro static and steric field type with cutoff values of 10.0 and 30.0 Kcal/mole respectively were selected and charge type was selected as Gasteiger-Marsili. Dielectric constant was set to 1.0 considering the distance dependent dielectric function.

The kNN-MFA models were generated using the variable selection methods, viz. stepwise (SW) forward- backward method and simulated annealing (SA) method [12-13].

Stepwise (SW) Method

The kNN-MFA model for all the antibacterial activities was developed using stepwise forward backward method with cross correlation limit set to 0.5 and term selection criteria as q^2. The method resulted in selection of compounds no. 5, 6, 8, 13, 16, and 21 as test set and remaining 15 compounds as a training set. F-test 'in' was set to 4.0 and F-test 'out' to 3.99. As some additional parameters, variance cutoff was set as 2 Kcal/mol Å and scaling & auto scaling, additionally the K-nearest Neighbor parameter setting was done within the range of 2-5 and prediction method was selected as distance base weighted average.

Simulated annealing (SA) method

The method resulted in selection of compounds no. 1, 2, 4, 5, 8, 10, 11, 13, 14, 15, 16, 17 and 19 as training set and remaining 8 compounds as a test set. The cross correlation limit was set as 0.5,

maximum temperature as 100, minimum temperature as 0.01, iteration at given temperature as 5, decrease temperature by 10, seed as 0, perturbation limit as 1 and term selection criteria as q^2. As some additional parameters, variance cutoff was set as 2 Kcal/mol Å and scaling & auto scaling, additionally the K-nearest Neighbor parameter setting was done within the range of 2-5 and prediction method was selected as distance base weighted average.

CONCLUSION

A novel three-dimensional QSAR approach has been developed based on the principles of the k-nearest neighbor method. The method employs different variable selection procedures with stepwise forward and simulated annealing, for the three data sets reported in this study. It can be seen that SW kNN-MFA methods generate better models with higher prediction accuracy as compared to the SA kNN-MFA procedure. The location and range of function values at the field points selected by the models provide clues for the design of new molecules. This method is expected to provide a good alternative for the generation of 3D QSAR models.

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