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3D QSAR analysis of quinolone based s-triazines as antimicrobial agent

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Abstract: A series of structurally similar 1,3,5-triazine derivatives as antimicrobials have been subjected for QSAR analysis using VLife MDS 3.5 software. The compounds were divided into training and test set. Best QSAR model was selected on the basis of various statistical parameters like square correlation coefficient (r^2), cross validated square correlation coefficient (q^2) and sequential Fischer test (F). 3D QSAR study reveals that less electronegative substitution at C-6 position, slightly less bulky group on the quinolone ring and more bulky substitutions on phenyl ring of template improve the antimicrobial activity.
Keywords: 3D QSAR, 1,3,5-triazine, antimicrobial activity, 3D Descriptors.

INTRODUCTION

Due to the increasing number of multidrug resistant strains developed by the microbes, currently used antimicrobial agents are ineffective. Bacterial and fungal diseases are very common, therefore, the design and synthesis of novel antimicrobial molecules has been of enormous interest in recent years. The 1,3,5-triazine exhibited biological importance such as antimicrobial (1), anticancer (2) and antiviral (3) agents. The 1,3,5-triazine is an inexpensive, commercially available reagent and the different reactivities of the substituent chlorine atoms, which are controlled by temperature makes its use more attractive (4).

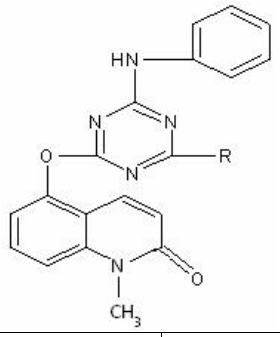
The quinolones such as ciprofloxacin, ofloxacin, enoxacin, are established synthetic antibacterial agent. They corrupt the activities of prokaryotic type II topoisomerase, DNA gyrase, topoisomerase IV and induce them to kill the cells by generating high level of double stranded DNA breaks (5). So there is a need to correlate antimicrobial activity and the physicochemical parameters of the compound by QSAR methods for increasing the potency of the molecules.

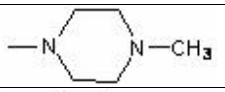
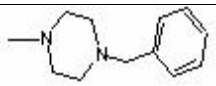
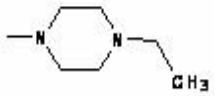
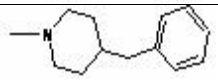
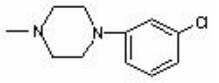
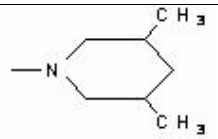
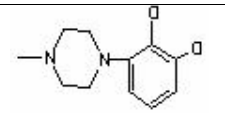
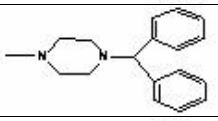
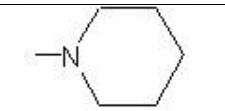
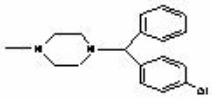
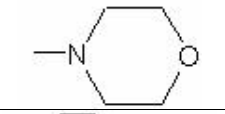
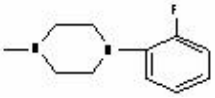
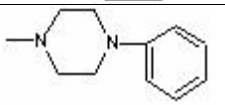
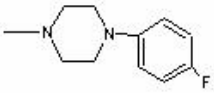
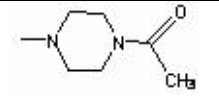
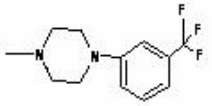
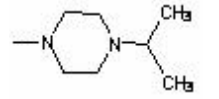
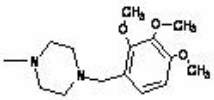
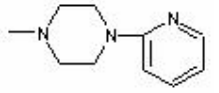
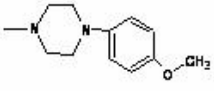
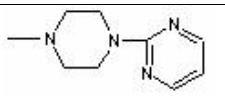
MATERIALS AND METHODS

BIOLOGICAL ACTIVITY DATA

The 21 compounds containing 1,3,5-triazine nucleus and their antimicrobial activity against *Staphylococcus aureus* were selected from literature (6). The logarithm to the base 10 of antimicrobial activity as zone of inhibition was used as dependent variable to develop the 3D QSAR model. The structure of compounds along with antimicrobial activity in terms of zone of inhibition against S*taphylococcus aureus* are shown in Table 1.

Table 1. Structure and antmicrobial activity of compounds used in QSAR study (Training set and Test set)



Compound	R	Zone of inhibition (mm)	Compound	R	Zone of inhibition (mm)
1		19	**12**		21
2		20	**13**		23
3		23	**14**		28
4		28	**15**		22
5		22	**16**		25
6		21	**17**		24
7		19	**18**		25
8		24	**19**		28
9		23	**20**		26
10		21	**21**		27
11		20			

GEOMETRY OPTIMIZATION

3D QSAR studies of 1,3,5-triazine were carried out by using Molecular Design Suit software version 3.5 (7). The 3D structures of all compounds have been constructed using MDS 3.5 and their geometries were subsequently optimized to make the conformation having least potential energy. Energy minimization was performed using Merck Molecular Force Field (MMFF) and MMFF charge for an atom followed by distance dependent dielectric constant of 1.0 and convergence criteria (rms gradient) of 0.01kcal/mol (8).

ALIGNMENT OF MOLECULES

All molecules were aligned by template-based methods where template is built by considering the common structure in the series. The structure of 1,3,5-triazine template is shown in Figure 1. Highly bioactive energetically stable conformation in this series of compound is chosen as reference molecule (Figure 2) on which other molecules in the series are aligned, considering the template as a basis for alignment (Figure 3). The 3D descriptors for each optimized molecule were calculated by "compute descriptors" module of the software and selected descriptors are shown in Table 2.

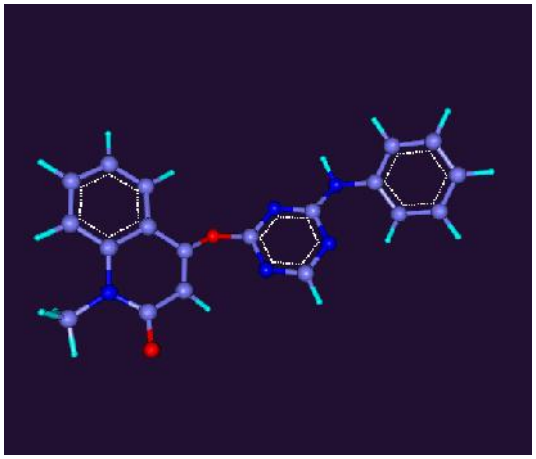


Figure 1: Template

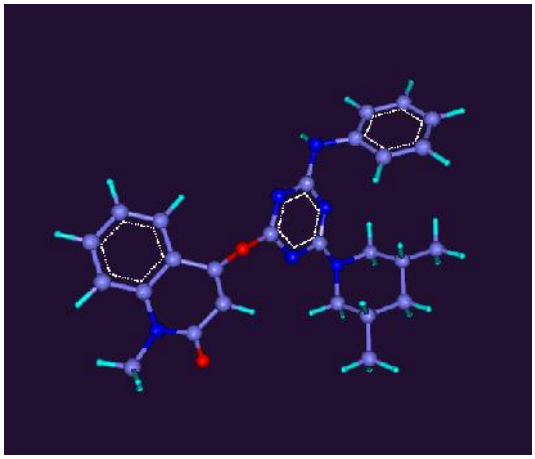


Figure 2: Reference molecule

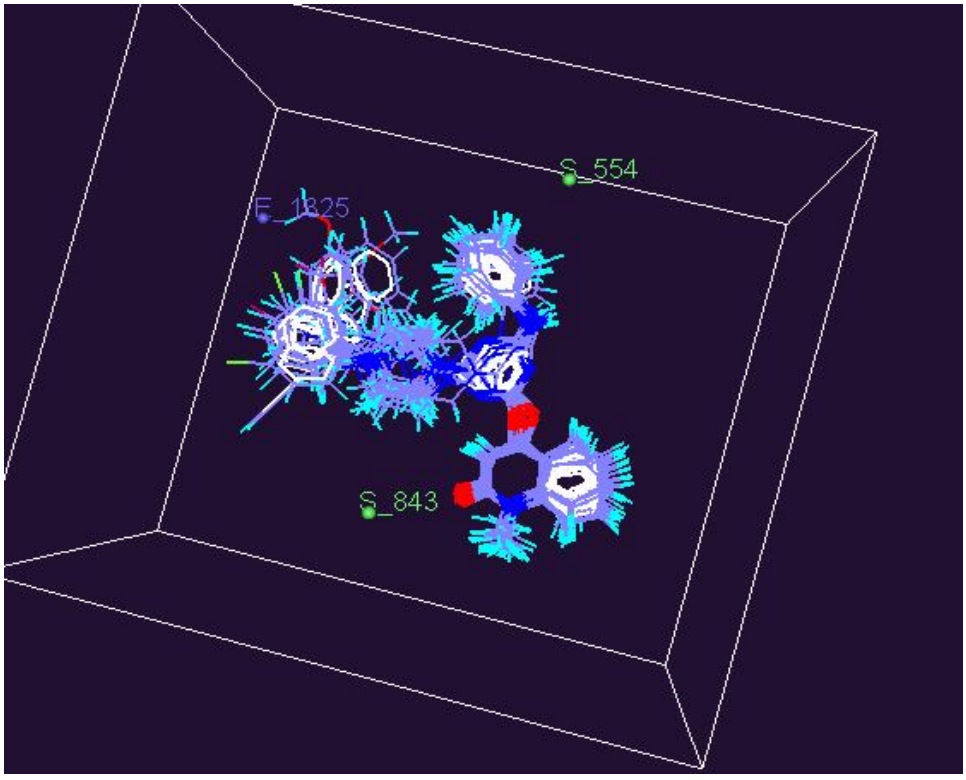


Figure 3: Distribution of chosen points in template based alignment (Model 1)

Table 2. Selected Molecular 3D Descriptor

COMP	E_1325	S_554	S_843	COMP	E_1325	S_554	S_843
1	0.139594	-0.29554	-0.38593	**12**	0.458079	-0.29737	-0.34079
2	-0.36744	-0.37579	-0.32753	**13**	-0.04118	-0.21074	-0.51193
3	-0.13431	-0.27345	-0.37206	**14**	0.298386	-0.022	-0.39995
4	-0.25416	-0.03073	-0.34384	**15**	0.344484	-0.31597	-0.44708
5	0.134819	-0.31201	-0.39322	**16**	0.458079	-0.29741	-0.43831
6	0.564963	-0.14528	-0.37248	**17**	-0.04118	-0.33905	-0.40332
7	0.052602	-0.32606	-0.39207	**18**	0.13968	-0.27163	-0.35823
8	-0.32793	-0.24855	-0.33696	**19**	0.245529	-0.22411	-0.4192
9	-0.06733	-0.1487	-0.32862	**20**	0.027471	0.109397	-0.32862
10	0.298386	-0.29921	-0.32039	**21**	-0.22252	-0.24667	-0.39009
11	0.344484	-0.23843	-0.32197				

Table 3. The actual, predicted and residual biological activity for 3D QSAR model

Compound	Actual	Predicted	Residue	Compound	Actual	Predicted	Residue
1	1.2788	1.3447	-0.0659	**12**	1.3424	1.3722	-0.0298
2	1.3010	1.3125	-0.0115	**13**	1.3617	1.4604	-0.0987
3	1.3617	1.3872	-0.0255	**14**	1.3010	1.3131	-0.0121
4	1.3222	1.2972	0.025	**15**	1.4314	1.4262	0.0052
5	1.3424	1.3586	-0.0432	**16**	1.4150	1.4313	-0.0163
6	1.3222	1.3051	0.0171	**17**	1.3802	1.3790	0.0012
7	1.2788	1.3647	-0.0859	**18**	1.4472	1.4485	-0.0013
8	1.4472	1.4369	0.0103	**19**	1.4472	1.4213	0.0259
9	1.3617	1.3830	-0.0213	**20**	1.3222	1.3323	-0.0101
10	1.3802	1.3707	0.0095	**21**	1.3979	1.3840	0.0139
11	1.3939	1.3908	0.0061				

ACTIVITY PREDICTION

The predictability of the QSAR model would be good if the biological activity predicted by QSAR model do not appreciably differ from the observed. The model selected on the basis of r^2, q^2 and F-test. QSAR model was evaluated using statistical measures such as n represents number of observations, df is degree of freedom, r is square root of multiple R-square for regression, q is cross validated r^2 and F is F - statistic for the regression model.

COMPUTATIONAL DETAILS

3D QSAR

Several 3D QSAR techniques such as comparative molecular field analysis (COMFA), comparative molecular similarity analysis (COMSIA) and *k*-nearest neighbor (*k*NN) are being used in modern QSAR research (9). In the present study, molecular field analysis coupled with partial least squares (PLS) was applied to obtain a 3D QSAR model, PLS is frequently used as the regression method in 3D QSAR. The calculated steric and electrostatic field descriptors were used as independent variables and zone of inhibition values were used as dependent variables in PLS regression analysis to derive the 3D QSAR model.

RESULTS AND DISCUSSION

Log BA = 1.2387 + 0.2065 S_554 – 0.5086 S_843 – 0.1166 E_1325

n = 16, Degree of freedom = 13, r = 0.9506, r^2 = 0.9037, q^2 = 0.8074, F test = 60.9692

The model 1 describes the optimum structural features for antimicrobial activity. The training set of 16 molecules and test set of 5 molecules was used. S_554, S_843 and E_1325 are the steric and electrostatic field energy interaction between methyl probe and compounds at there corresponding spatial grid points of 554, 843 and 1325. The model 1 is

validated by predicting the biological activities of the molecules as indicated in the Table 3. The model 1 suggests that, the steric descriptors S_554 with positive coefficient represents more bulky substitutions and the steric descriptors S_843 with negative coefficient represents less bulky substitutions is favorable in this region. Electrostatic field descriptor E_1325 with negative coefficient indicates that the less electronegative groups are favorable in this region. 3D QSAR study reveals that less electronegative substitution at C-6 position, slightly less bulky group on the quinolone ring and more bulky substitutions on phenyl ring of template improves the antimicrobial activity.

CONCLUSION

QSAR analysis of novel series of 1,3,5-triazine reveals that with less electronegative substitution at C-6 position, slightly less bulky group on the quinolone ring and more bulky substitutions on phenyl ring of template improves antimicrobial activity.

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