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QSAR Modelling of New Triazolothiadiazole Derivatives as Antimicrobials

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ABSTRACT

In this research, twenty nine analogues having variable inhibition of Escherichia coli were subjected to quantitative structure activity relationship analysis. Various thermodynamic, electronic and steric parameters were calculated using Chem 3D package of molecular modeling software Chem office 8.0. QSAR models were generated employing sequential multiple regression method using in-house statistical program VALSTAT. Statistically significant models with R-values 0.90 were obtained. Models were validated using leave one out and bootstrapping methods. Results obtained shows that stretch energy, dipole-dipole energy, HOMO energy and Non-1, 4 VDW Energy are contributing to biological activity. Findings of present study reveal that substituent those decrease the flexibility of molecule results in increase in antimicrobial potency, aryl substituent would enhance the antimicrobial activity of compounds and presence of electron withdrawing group in structure is favorable for antibacterial activity of triazolothiadiazoles.

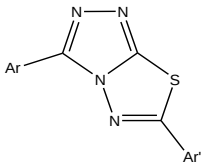
Keywords: Triazolothiadiazoles, Antimicrobials, QSAR, Quantitative structure, property relationships

INTRODUCTION

Triazolothiadiazole system may be viewed as a cyclic analogue of two very important compounds [1]. Thiosemicarbazide and biguanide/thioguanide which often display diverse biological activity [2]. More over the triazolothiadiazole substituted in the 3 and 6 positions by aryl, alkyl or heterocyclic moiety possess pharmacological activities [3-6] such as antibacterial, antifungal activity, antiviral activity, anti-inflammatory, and analgesic, herbicidal and anti-HIV-1 effects. 1,2,4-triazole and 1,3,4-triazoles represent one of the most biologically active classes of compounds, possessing a wide spectrum of activities. A literature, survey indicated that 1,2,4-triazole and 1,3,4-triazole thiadiazloes derivatives play vital role as synthetic drugs. These observations led to the conception that triazolothiadiazole derivatives would possess potential antimicrobial properties. This Quantitative Structure-Activity Relationship (QSAR) study enables the investigators to establish a reliable quantitative structure activity and structure-property relationships to derive a QSAR model to predict the activity of novel molecules prior to their synthesis [7]. A data set of 29 molecules exhibiting potent antibacterial activity against *Escherichia coli* has been taken from published article of T. Karabasanagouda et al., [8] and S.N. Swamy et al. [9]. The overall process of QSAR model development can be divided into three stages namely, the data preparation, data analysis and model validation, representing a standard practice of any QSAR modeling [10-16]. In this research, an attempt has been made to describe the QSAR analysis of triazolothiadiazole derivatives to study and deduce a correlation between structure and antimicrobial activity of these derivatives.

MATERIALS AND METHODS

A data set of 29 molecules exhibiting potent antibacterial activity against *E. coli* has been taken from published article of T. Karabasanagouda et al. and S.N. Swamy et al. All the values of biological data were shown in Minimum Inhibitory Concentration (MIC) (µg/ml), which was converted into –log MIC (µg/ml) for convenience of computational work. Structures of reported compounds and PMIC values are shown in Table 1. QSAR study was done on these 29 compounds (Tables 1-6 and Figures 1-8).



General structure of triazolothiadiazole

Table 1: Structure of triazolothiadiazole derivatives along with their MIC and $_{P}$MIC values

Compound No.	Ar	Ar'	MIC	$_{P}$MIC
1	$CH_2OC_6H_4SCH_3$	C_6H_5	6.25	7.75
2	$CH_2OC_6H_4SCH_3$	2-ClC_6H_4	25	7.17
3	$CH_2OC_6H_4SCH_3$	4-$CH_3C_6H_4$	6.25	7.77
4	$CH_2OC_6H_4SCH_3$	4-$OCH_3C_6H_4$	6.25	7.79
5	$CH_2OC_6H_4SCH_3$	4-$NH_2C_6H_4$	6.25	7.77
6	$CH_2OC_6H_4SCH_3$	2,3-$(Cl)_2C_6H_4$	6.25	7.83
7	$CH_2OC_6H_4SCH_3$	$C_6H_5CH_2$	6.25	7.77
8	$CH_2OC_6H_4SC_2H_5$	C_6H_5	6.25	7.77
9	$CH_2OC_6H_4SC_2H_5$	2-ClC_6H_4	25	7.21
10	$CH_2OC_6H_4SC_2H_5$	4-$CH_3C_6H_4$	6.25	7.79
11	$CH_2OC_6H_4SC_2H_5$	4-$OCH_3C_6H_4$	25	7.2
12	$CH_2OC_6H_4SC_2H_5$	4-$NH_2C_6H_4$	25	7.19
13	$CH_2OC_6H_4SC_2H_5$	2,3-$(Cl)_2C_6H_4$	25	7.24
14	$CH_2OC_6H_4SC_2H_5$	2-OHC_6H_4	25	7.19
15	$CH_2OC_6H_4SO_2CH_3$	C_6H_5	12.5	7.49
16	$CH_2OC_6H_4SO_2CH_3$	2-ClC_6H_4	12.5	7.53
17	$CH_2OC_6H_4SO_2CH_3$	3-ClC_6H_4	12.5	7.53
18	$CH_2OC_6H_4SO_2CH_3$	C6H_5CH_2	12.5	7.51
19	$CH_2OC_6H_4SO_2CH_3$	2,3-$(Cl)_2C_6H_4$	6.25	7.86
20	CH_3	C_6H_4Cl	41	6.79
21	C_2H_5	C_6H_4Cl	13	7.31
22	C_6H_5	C_6H_4Cl	15	7.32
23	4-$CH_3C_6H_5$	C_6H_4Cl	17	7.28
24	4-Cl-C_6H_5	C_6H_4Cl	40	6.94
25	CH_3	C_3H_7	39	6.79
26	C_2H_5	C_3H_7	12	7.32
27	C_6H_5	C_3H_7	14	7.33
28	4-$CH_3C_6H_5$	C_3H_7	15	7.32
29	4-Cl-C_6H_5	C_3H_7	38	6.95

Methodology and software used for QSAR analysis

The molecular modeling study was performed using CS ChemOffice 2004 and regression analysis was carried out on VALSTAT. The compounds in the series were sketched using ChemDraw module of ChemOffice. The sketched structures were subjected to energy minimization using Allinger's MM2 force field followed by semi empirical AM1 (Austin Model) Hamiltonian method available in MOPAC module by fixing root mean square gradient as 0.1 and 0.0001 kcal/Mol A° respectively. The values of descriptor (like thermodynamic, steric and electronic,) for all the molecules were calculated using "compute properties" module of Chemultra. The calculated values were then tabulated along with biological activity. The QSAR models were generated using biological activity as dependent variable and descriptors as independent variables. In the present study, sequential multiple linear regression analysis was performed to generate various equations which were further validated by most popular Leave One Out (LOO) cross-validation method to ensure their robustness. The generated QSAR models were validated for predictive ability inside the model (Leave one out method) using VALSTAT. The statistical program which is tailored specifically for QSAR statistics estimates the predictive potential of model by calculating the validation parameters squared cross–correlation coefficient (q2), standard deviation of sum of square of difference between predicted and observed values (SPRESS) and Standard Deviation of Error of Prediction (SDEP).

Table 2: Calculated substituent constants used in 3D-QSAR analysis of triazolothiadiazoles

Compound No.	Stretch energy (Q)	Dipole-dipole energy (R)	HOMO energy(AE)	Non-1,4 VDW energy (AF)
1	16.14	-4.17	-8.01	-1.18
2	8.39	-2.26	-8.1	2.33
3	15.99	-4.18	-8.05	-0.68
4	16.56	-4.19	-8.05	0.25
5	19.18	-4.12	-7.91	-0.43
6	16.45	-4.18	-8.08	11.05
7	15.89	-4.14	-7.97	-2.8
8	15.47	-4.27	-7.96	-0.17
9	12.74	-3.06	-8.35	1.24
10	15.66	-4.26	-7.95	-3.51
11	15.11	-3.57	-8.35	-2.73
12	13.86	-2.85	-8.41	-2.8
13	12.48	-2.95	-8.49	-3.85
14	2	-6.73	-8.4	-4.45
15	21.64	-1.94	-9.35	-3.23
16	22.61	-1.92	-9.31	10.91
17	22.59	-1.94	-9.43	-1.67
18	22.62	-1.91	-9.36	-3.85
19	22.97	-1.92	-9.36	11.25
20	6.02	-1.87	-9.11	1.74
21	9.88	-2.6	-8.87	11.03
22	9.92	-2.56	-8.61	7.71

23	9.93	-2.57	-8.53	10.72
24	9.89	-2.57	-8.73	10.21
25	10.2	-2.7	-8.98	-2.99
26	10.22	-2.69	-8.96	-3.3
27	10.26	-2.69	-8.73	-2.19
28	10.58	-2.81	-8.65	-1.56
29	10.43	-2.67	-8.77	-5.6

RESULTS AND DISCUSSION

FTIR spectroscopy of drug

Biological activity data and various physicochemical parameters were taken as dependent and independent variables respectively and correlations were established using sequential multiple regression analysis. The descriptors selected for modeling antibacterial activity of triazolothiadiazoles are summarized in Table 2. Among the many correlations generated, two best models were selected on the basis of statistical significance. The best models obtained are given below along with their statistical measures.

Model 1: Parent equation

BA=[6.24186 (± 0.261315)]+Q [0.0654959 (± 0.01742)]+R [-0.202829 (± 0.0644588)]+AE [-3.30672e-005 (± 2.35304e-005)]

Contribution of parameters to model is: Q:R:AE: 2.49915:1.72252:1 n=28, r=0.898438, r^2=0.80719, variance=0.0199388, std=0.141205, F=33.4917, FIT=275.425.

Training-test set equation

BA=[6.3109 (± 0.262132)]+Q [0.0627601 (± 0.0172347)]+R [-0.202202 (± 0.0677932)]+AE [-3.57432e-005 (± 2.33371e-005)]

Contribution of parameters to model is Q:R:AF: n=23, r=0.906716, r^2=0.822135, variance=0.0177467, std=0.133217, F=29.2741, FIT=280.135

Model 2: Parent equation

BA=[6.24618 (± 0.26407)]+Q [0.0641464 (±0.0172144)]+R [-0.197591 (± 0.0637312)]+AF [-0.000219438 (± 0.000163466)]

Contribution of parameters to model is Q:R:AF:: 2.67013:1.83056:1, n=28, r=0.895931, r^2=0.802693, variance=0.0204039, std=0.142842, F=32.546, FIT=267.648.

Training-test set equation

BA=[6.3126 (± 0.263128)]+Q [0.0617991 (± 0.0169394)]+R [-0.198354 (± 0.0667528)]+AF [-0.000244006 (± 0.000161255)]

Contribution of parameters to model is Q:R:AF::2.26356:1.81684:1, n=23, r=0.905881, r^2=0.820621, variance=0.0178978, std=0.133783, F=28.9736, FIT=277.259.

Table 3: Observed, calculated and predicted pMIC values of training set compounds using 3D-QSAR Equation for model 1

Compounds	Observed pMIC	Calculated pMIC	Predicted pMIC
1	7.53	7.58	7.60
2	6.79	6.96	7.02
3	7.75	7.77	7.77
4	7.77	7.90	7.94
5	7.77	7.69	7.68
6	7.32	7.35	7.36
7	7.2	7.41	7.45
8	7.28	7.17	7.16
9	7.33	7.24	7.23
10	7.49	7.56	7.58
11	7.83	7.73	7.72
12	7.17	6.94	6.89
13	7.19	7.30	7.56
14	7.77	7.71	7.70
15	7.32	7.24	7.24
16	7.21	7.24	7.24
17	7.77	7.68	7.67
18	7.32	7.21	7.20
19	6.95	7.22	7.24
20	7.79	7.64	7.62
21	7.31	7.33	7.33
22	7.24	7.17	7.15
23	7.19	7.26	7.27

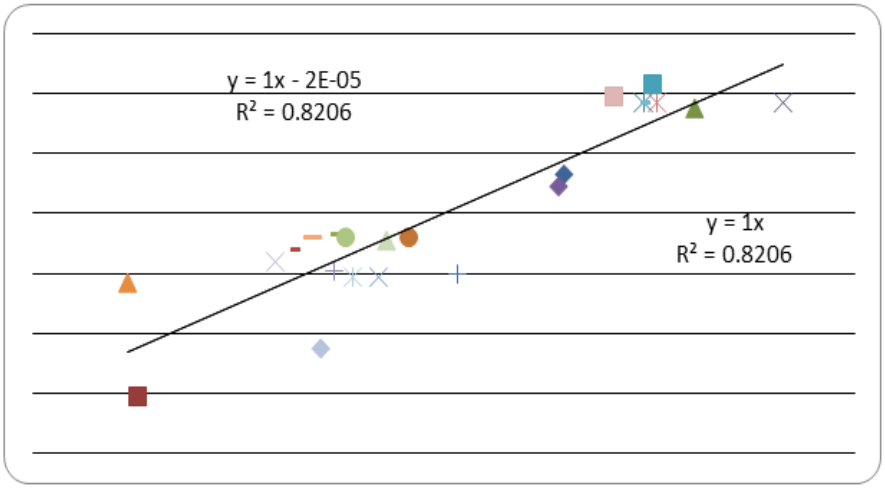


Figure 1: Discrete plot of observed *vs.* calculated pMIC values by leave-one-out cross-validation for model 1

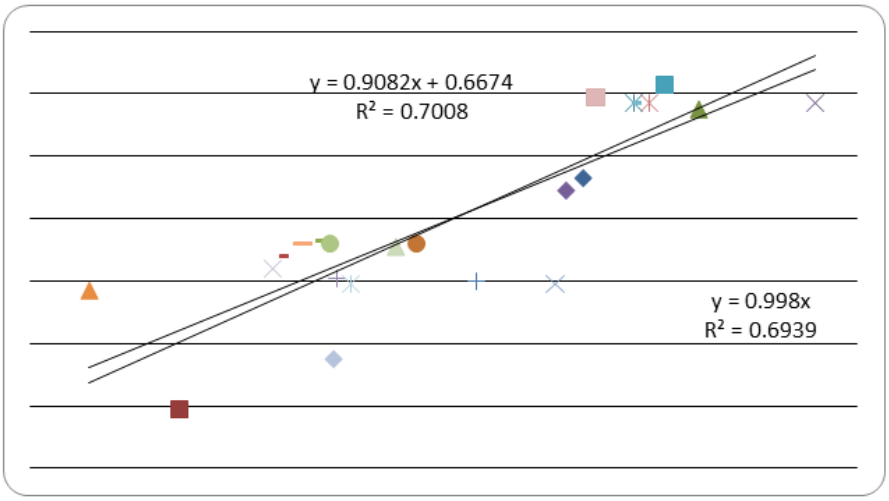


Figure 2: Discrete plot of observed *vs.* predicted pMIC values by leave-one-out cross-validation for model 1

Table 4: Observed and predicted pMIC values of test set compounds using 3D-QSAR Equation for model 1

Compounds	Observed pMIC	Predicted pMIC
1	7.51	7.53
2	6.94	7.18
3	7.79	7.69
4	7.86	7.57
5	7.53	7.58

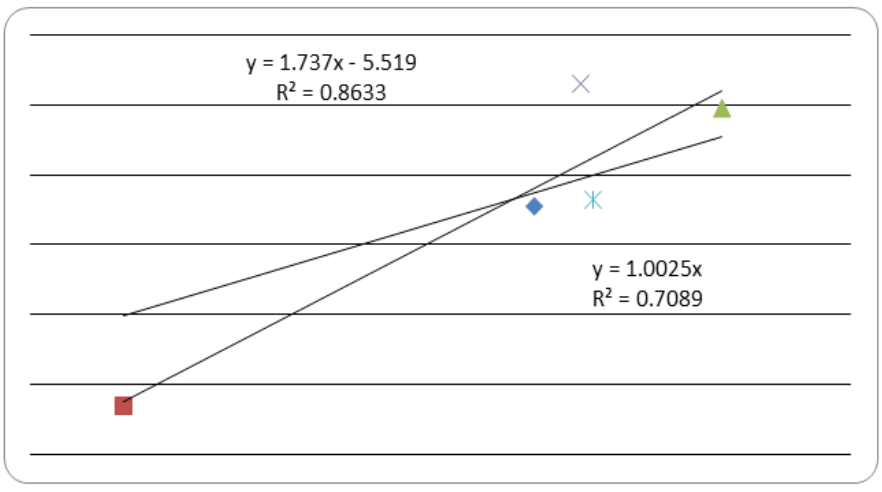


Figure 3: Discrete plot of observed *vs.* predicted pMIC values by leave-one-out cross-validation for model 1

Table 5: Observed, calculated and predicted pMIC values of training set compounds using 3D-QSAR Equation for model 2

Compounds	Observed pMIC	Calculated pMIC	Predicted pMIC
1	7.53	7.57	7.59
2	6.79	6.95	7.01
3	7.75	7.77	7.77
4	7.77	7.90	7.93
5	7.77	7.69	7.68
6	7.32	7.35	7.36
7	7.2	7.42	7.45
8	7.28	7.18	7.17
9	7.33	7.25	7.24
10	7.49	7.57	7.59
11	7.83	7.70	7.69
12	7.17	6.94	6.88
13	7.19	7.30	7.57
14	7.77	7.71	7.70
15	7.32	7.26	7.25
16	7.21	7.24	7.24
17	7.77	7.69	7.68
18	7.32	7.21	7.20
19	6.95	7.22	7.24
20	7.79	7.65	7.63
21	7.31	7.32	7.32
22	7.24	7.15	7.13
23	7.19	7.27	7.28

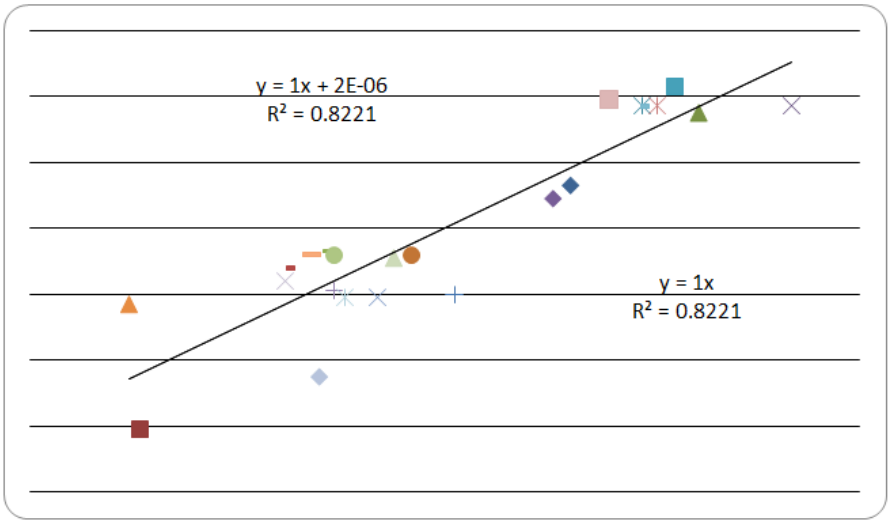


Figure 4: Discrete plot of observed *vs.* calculated pMIC values by leave-one-out cross-validation for model 2

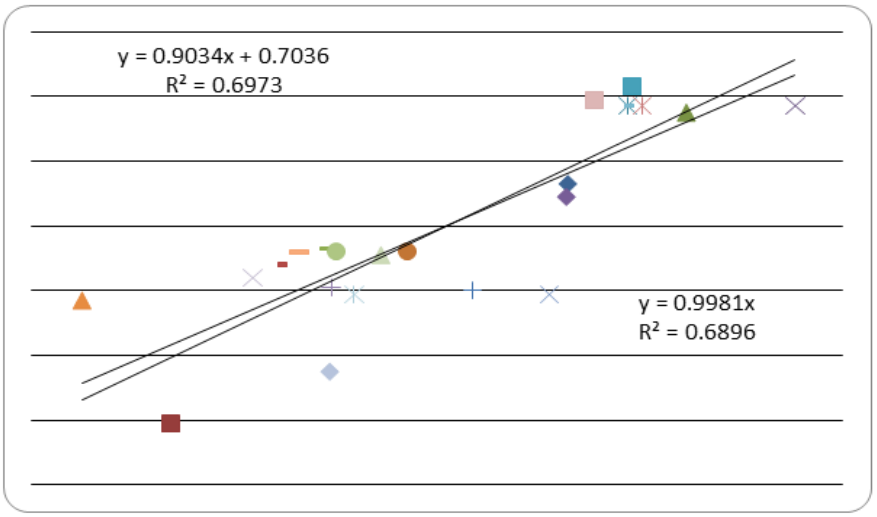


Figure 5: Discrete plot of observed *vs.* predicted pMIC values by leave-one-out cross-validation for model 1

Table 6: Observed and predicted pMIC values of test set compounds using 3D-QSAR Equation for model 2

Compounds	Observed pMIC	Predicted pMIC
1	7.51	7.55
2	6.94	7.17
3	7.79	7.69
4	7.86	7.54
5	7.53	7.57

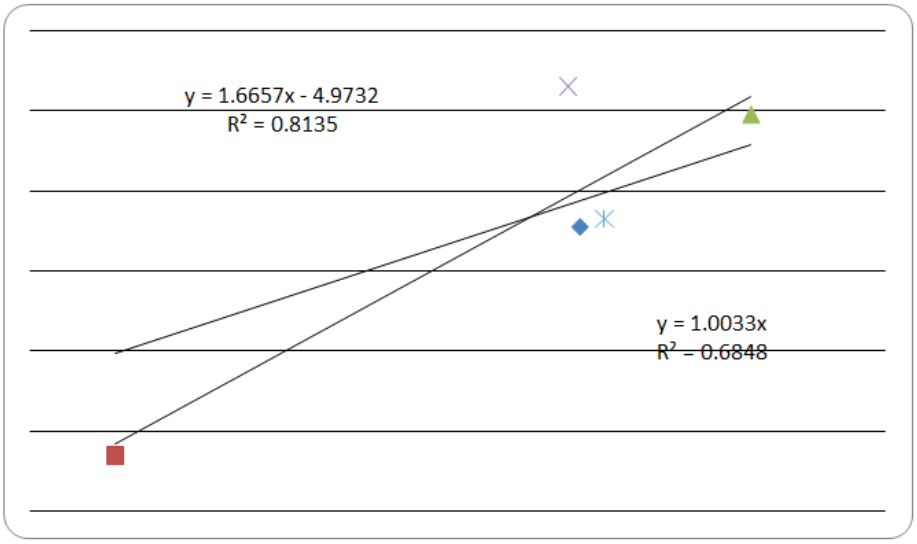


Figure 6: Discrete plot of observed *vs.* predicted pMIC values by leave-one-out cross-validation for model 2

Validation of models

Once the equation is obtained, it is important to determine its reliability and significance. The validation of the equation is done by cross-validation/leave-one out method. The results are shown below (Table 7).

Table 7: Validation of models

Model no.	I	II
N	23	23
R	0.906	0.905
r^2	0.822	0.820
Variance	0.017	0.017
Std	0.133	0.133
F	29.274	28.973
FIT	280.135	277.259
Q^2	0.691	0.687
SDep	0.159	0.160
Spress	0.175	0.176
r^2 prediction	0.702	0.684
Chance	<0.001	<0.001

In the above QSAR models n is the number of data points, r is correlation coefficient, r^2 is squared correlation coefficient, std is standard deviation or standard error of estimate. Accuracy in the analysis is shown by low values of standard error of estimate. F represents Fischer ratio between the variances of calculated and observed activities. The correlation coefficient value (r=0.906 for model I and r=0.905, for model II) represents the better fit of the regression and good predictive ability and robustness of the model. Both of the models have significance level better than the 99.95% as it exceeded the tabulated F=29.27 and F=28.97 for model I and II respectively. Very low S_{PRESS} and S_{DEP} of the models indicate predictively of the models. Low standard error of estimation (std=0.133 for model I and std=0.133, for model II) suggests a high degree of confidence in model. Chance is the ratio of the equivalent regression equations to the total number of randomized sets; (chance value of 0.001 corresponds to 0.1% chance of fortuitous correlation) (Figures 7 and 8).

In model I and II stretch energy contributed positively to the biological activity whereas dipole- dipole energy contributed negatively to the biological activity. HOMO energy and Non-1, 4 VDW Energy contributed negatively to the biological activity in model I and II respectively. Stretch energy is the thermodynamic parameter that deals with conformational flexibility of molecule. Negative contribution of stretch energy suggests that substituent that decrease the flexibility of nucleus will enhance the activity. The dipole- dipole energy descriptor in the models represents the sum of electrostatic terms resulting from the interaction of two dipoles. The descriptor bears a positive coefficient, which suggests significance of dipole-dipole interactions for the antibacterial activity which means increase in magnitude of dipole-dipole interaction will increase the activity of compounds. HOMO is an electronic descriptor and represents the highest energy level in the molecule that contains electron pairs. HOMO represents ability to donate electrons. It is important in governing molecular reactivity and properties and measures the nucleophilicity of the molecule. Negative contribution suggested that molecule will interact on electron rich areas on receptor and the substitution of electron withdrawing groups in the molecule will impart the positive influence on activity. Non-1, 4 VDW Energy is the energy for the through space interaction between pairs of atoms that are separated by more than three atoms. Negative contribution of Non-1, 4 VDW

Energy (attractive force between active substituent and enzyme binding sites) in biological activity indicates that minimizing parameters with suitable substituent enhance the activity. Thus aryl substituent may increase activity while alkyl or bulky groups may decrease activity.

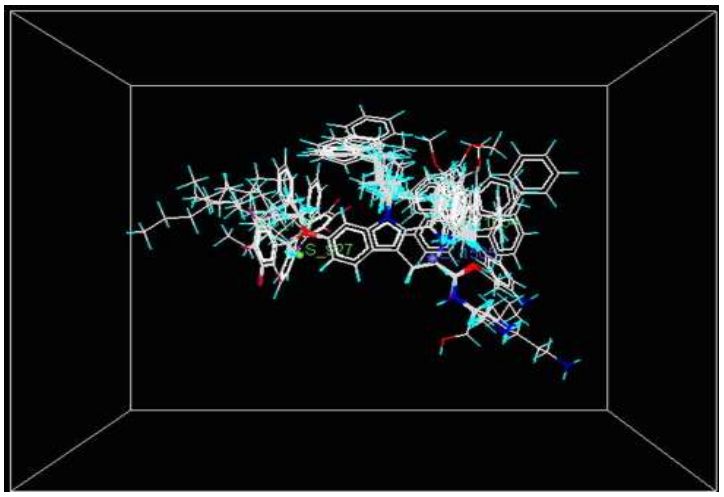


Figure 7: Stereo view of the molecular rectangular field grid around the superposed molecular units of triazolothiadiazole derivative series of compounds using SW kNN MFA method (Alignment of the molecules)

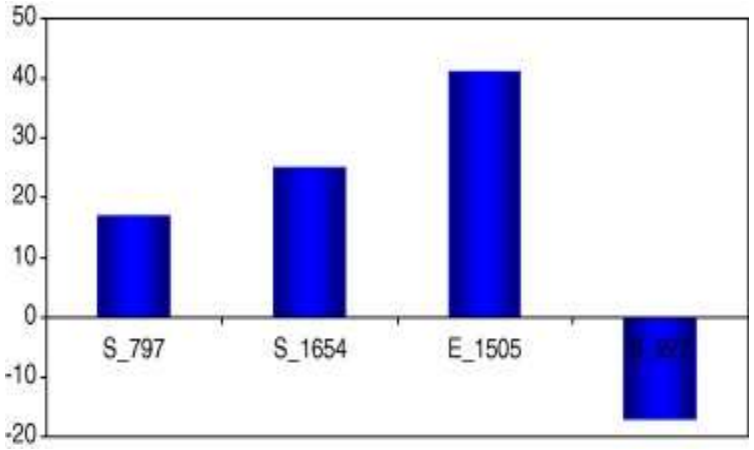


Figure 8: Contributions of descriptors for biological activity developed using SW-kNN-MFA equation for 3D-QSAR

CONCLUSIONS

QSAR analysis was performed on a series of triazolothiadiazoles using molecular modeling program ChemOffice 2001. QSAR models were proposed for antimicrobial activity of the thiadiazinoacridines using Chem SAR descriptors employing sequential multiple regression analysis method. The predictive power of each model was estimated with boot strapping *r*2 method and leave–one–out cross validation method. It was observed from the selected models that biological activity of triazolothiadiazoles is governed by thermodynamic and electronic properties of the molecules.

Findings of present study reveal that substituent those decrease the flexibility of molecule results in increase in antimicrobial potency, aryl substituent would enhance the antimicrobial activity of compounds and presence of electron withdrawing group in structure is favorable for antibacterial activity of triazolothiadiazoles. The finding of the study will be helpful in the design of potent analogues of triazolothiadiazoles. Finally, it is hoped that the work presented here will play an important role in understanding the relationship of physiochemical parameters with structure and biological activity. By studying the QSAR model one can select the suitable parameter for designing active compound for antimicrobial activity with maximum potency.

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