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Exploration of QSAR: Oxadiazole derivatives as antimicrobial agents

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ABSTRACT

A quantitative structure activity relationship study on a series of 2, 5-(substituted) 1, 3, 4-oxadiazole analogues was made using combination of various thermodynamic, steric, electronic and spatial descriptors. Several statistical expressions were developed using stepwise multiple liner regression analysis. The best quantitative structure activity relationship models were further validated by leave-one-out method of cross-validation. The study revealed that the Thermodynamic property, i.e., Steric property like Ovality and pMIZ, contributed positively and Electronic property like Dipole Moment contributed positively and E_{HOMO} energy contributed negatively. The study suggested that substitution of group at R_1 & R_2 on oxadiazole ring by those groups which increase the electronic charge enhances the antimicrobial activity. The quantitative structure activity relationship study provides important structural insights in designing of potent antibacterial agents.

Keywords: Oxadiazole, antimicrobial activity, quantitative structure activity relationship.

INTRODUCTION

The dramatically rising prevalence of multidrug-resistant microbial infection in the past few decades has become a serious health care problem. In particular, the emergence of multidrug-resistant strains of gram-positive bacterial pathogens such as methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermis* and vancomycin-resistant *Enterococcus* is a problem of ever increasing significance [1-3]. In order to prevent this serious medical problem, the elaboration of the new types of drugs is a very actual task. The Oxadiazole analogues have been the aim of many researchers for many years because they constitute an important class of heterocyclic compounds exhibiting substantial chemotherapeutic properties [4-6]. Oxadiazoles are useful targets in the search for antibacterial and antifungal activity as they have been

associated with a wide variety of interesting properties. Members of this class of compound are known to possess diverse biological activities, such as antimicrobial [7], antimycobacterial [8], anti-inflammatory [9-11], anticonvulsant [12-13], anticancer [14], antihepatitis-B [15], psychotropic [16], antiaflatoxigenic [17] and insecticidal properties. Polyhalogen substituted oxadiazoles showed various activities [18]. Earlier research has shown that oxadiazoles possess antibacterial activities against *S. aureus, C. albicans, C. krusei, C. parapsilosis, T. paradoxa, E. Coli, B. subtilis* and *P. aeruginosa*able , and is able to inhibit bacterial and fungal growth. With the continuing development of clinical drug resistance among bacteria and the advent of resistance to the recently released agents quinupristin, dalfopristin and linezolid, the need for new, effective agents to treat multidrug- resistant Gram-positive infections remains important. Since the early 1990s, the epidemiology of pathogenic bacteria isolated from hospital infections has shifted from gram-negative organisms to gram-positive organisms, with the majority of nosocomial infections now caused by Gram-positive isolates. Increasingly, nosocomial pathogens are resistant to first-line antimicrobial agents, with 34% of *staphylococcus aureus* clinical isolates in the US, 26% of *S. aureus* isolates in Europe and 45% of *S. aureus* isolates in the western pacific, resistant to methicillin. Similarly, the incidence of vancomycin-resistancy among US enterococcal bloodstream isolates has now reached ~ 20%, with the frequency of penicillin-non-susceptibility[1] in US pneumococci at 34%.

Secondary metabolite formation (i.e., natural products), by microbes, is believed to be a Darwinian type response mechanism to environmental pressures. Some of these secondary metabolites are the basis for the widely used antibacterials (e.g., carbapenems, cephalosporins, macrolides, monobactams and penicillins) and antifungal agents(e.g., amphotericin B, nystatin). The introduction of these therapeutic agents has contributed significantly to reduce morbidity and deaths due to microbial infections. Ironically, as the pharmaceutical industry has created newer antibacterial and antifungal agents, the biological targets of these drugs have evolved mechanisms to overcome the effects of these potent drugs [2].

In the present work, we describe the QSAR studies from multivariable regression analysis (MRA) in order to investigate the quantitative effect between the various physicochemical parameters of oxadiazole derivative (Fig. 1) on their antibacterial activity against Gram-negative bacteria *E.Coli* ATCC-25922.

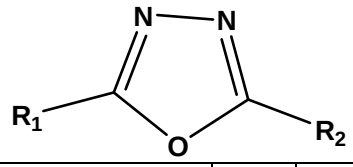
MATERIALS AND METHODS

The **Table I** shows the structural features of oxadiazole derivatives along with their biological activities (MIC µg/ml) reported by S.L.Gaonkar et al [4], Mari Sithambaram Karthikeyan et al [5], Erhan Palaska et al [6] and descriptors included in final QSAR model:

The biological activity data MIC (minimum inhibitory concentration in µg/ml) were converted to negative logarithmic dose in moles (pMIC) for QSAR analysis. The correlations were sought between inhibitory activity and various substituent constants at position R_1 & R_2 of the molecule. The series was subjected to molecular modelling via QSAR studies using CS Chem-Office 8.0 running on a Pentium core-2-duo processor [19]. Structures of all the compounds were sketched using builder module of the programme. These structures were then subjected to energy

minimization using force field molecular mechanics-2 (MM2) until the root mean square (RMS) gradient value became smaller than 0.1 kcal/mol. Å.

Table I: Structure, Antimicrobial Activities of Compounds and descriptors used in QSAR model:



Comp. No.	Substitution		IC_{50}	pIC_{50}	Structural descriptors			
	R1	R2			pMIZ	D_1	E_{HOMO}	Ovality
1	5-ethyl-2-(2-phenoxyethyl)pyridine	Phenyl	28	7.122	12266.6	-1.886	-8.961	1.668
2	5-ethyl-2-(2-phenoxyethyl)pyridine	4-ChloroPhenyl	14	7.462	15724.8	-1.029	-9.040	1.685
3	5-ethyl-2-(2-phenoxyethyl)pyridine	2,4-Di ChloroPhenyl	12	7.427	17583.3	-0.720	-8.960	1.692
4	5-ethyl-2-(2-phenoxyethyl)pyridine	4-Methoxyphenyl	15	7.427	15046.6	-0.891	-8.952	1.707
5	5-ethyl-2-(2-phenoxyethyl)pyridine	4-Nitrophenyl	14	7.473	17002.7	1.345	-9.125	1.695
6	5-ethyl-2-(2-phenoxyethyl)pyridine	2-Nitrophenyl	18	7.364	14775.6	-2.951	-9.256	1.688
7	5-ethyl-2-(2-phenoxyethyl)pyridine	p-tolyl	24	7.205	14138	-1.625	-8.710	1.695
8	5-ethyl-2-(2-phenoxyethyl)pyridine	o-tolyl	24	7.205	13377.8	-1.853	-8.927	1.676
9	5-ethyl-2-(2-phenoxyethyl)pyridine	pyridine-3-yl	19	7.292	13382.9	3.193	-9.083	1.665
10	5-ethyl-2-(2-phenoxyethyl)pyridine	pyridine-4-yl	14	7.424	13382.9	3.193	-9.083	1.665
11	2,4-dichloro-5-fluorobenzene	p-tolyloxymethyl	6.25	7.752	8104.49	-4.428	-9.109	1.564
12	2,4-dichloro-5-fluorobenzene	o-tolyloxymethyl	6.25	7.752	7570.45	-4.701	-9.577	1.552
13	2,4-dichloro-5-fluorobenzene	(2-chlorophenoxy)methyl)	6.25	7.776	8067.09	-3.768	-9.492	1.542
14	2,4-dichloro-5-fluorobenzene	(4-chloro-2-methylphenoxy)methyl	6.25	7.792	9478.17	-3.280	-9.317	1.569
15	2,4-dichloro-5-fluorobenzene	(4-chloro-3-methylphenoxy)methyl	12.5	7.491	10478.6	-3.664	-9.203	1.574
16	7-(2,4-dichloro-5-fluorophenyl)quinoline	p-tolyloxymethyl	25	7.283	10909.1	-4.824	-9.070	1.663
17	7-(2,4-dichloro-5-fluorophenyl)quinoline	o-tolyloxymethyl	12.5	7.584	10256.1	-5.173	-9.338	1.648
18	7-(2,4-dichloro-5-	(4-chlorophenoxy)methyl)	6.25	7.872	11341.1	-2.743	-9.263	1.639

	fluorophenyl)quinoline							
19	7-(2,4-dichloro-5-fluorophenyl)quinoline	(2-chlorophenoxy)methyl)	6.25	7.903	11148	-3.979	-9.325	1.643
20	7-(2,4-dichloro-5-fluorophenyl)quinoline	(4-chloro-2-methylphenoxy)methyl	6.25	7.915	13221.1	-4.091	-9.163	1.665
21	7-(2,4-dichloro-5-fluorophenyl)quinoline	(4-chloro-3-methylphenoxy)methyl	12.5	7.614	13536.5	-4.254	-9.196	1.672
22	7-(2,4-dichloro-5-fluorophenyl)quinoline	(2,4-dichlorophenoxy)methyl	6.25	7.932	11000.1	-2.282	-9.545	1.647
23	(naphthalen-1-yloxy)methyl	S	128	6.304	2283.28	3.280	-8.994	1.418
24	(naphthalen-2-yloxy)methyl	S	256	6.003	3256.71	2.973	-8.662	1.441
25	(naphthalen-1-yloxy)methyl	NH2	128	6.304	2173.76	-5.148	-8.454	1.391
26	(naphthalen-2-yloxy)methyl	NH2	256	6.003	2503.94	-1.589	-8.815	1.430
27	(naphthalen-1-yloxy)methyl	O	256	6.003	2270.1	0.612	-8.648	1.385
28	(naphthalen-1-yloxy)methyl	O	128	6.304	2586.21	3.795	-9.023	1.423

Minimized molecules were subjected to re-optimization via MOPAC method until the RMS gradient attained a value smaller than 0.0001 kcal/mol. Å. The descriptor values for all the molecules were calculated using "compute properties" module of program.

Stepwise multiple linear regression analysis method was used to perform QSAR analysis employing in-house VALSTAT programme [20]. The ± data within the parentheses are the error of regression coefficients associated with corresponding regression coefficients in regression equation. The best model was selected on the basis of various statistical parameters such as correlation coefficient (r), standard error of estimation (std), sequential Fischer test (F). Quality of the each model was estimated from the cross-validated squared correlation coefficient (Q^2). Calculated root mean square error (S_{DEP}), chance statistics evaluated as the ratio of the equivalent regression equations to the total number of randomized sets; a chance value of 0.001 corresponds to 0.1% chance of fortuitous correlation and boot-strapping square correlation coefficient (r^2_{bs}), which confirm the robustness and applicability of QSAR equation.

RESULT AND DISCUSSION

When data set was subjected to sequential multiple linear regression analysis, in order to develop QSAR between antimicrobial activity as dependent variables and substituent constants as independent variables, several equations were obtained. The statistically significant equations were considered as best model.

Model: 1

pMIC = pMIZ [5.707e-005(± 2.05221)] -D_1 [0.069 (± 0.033)] -E_{HOMO} [1.179 (± 0.359)] -[4.166(± 3.188)]

n=20, r=0.964, r^2=0.929, std=0.188, F=70.096, Q2 =0.904, r^2_{bs} = 0.935, $S_{PRESS=}$ 0.219, S_{DEP} =0.196

The model 1 shows that steric parameter (pMIZ) shows positive contribution and electronic parameters (Dipole moment and E_{HOMO} energy) show negative contribution towards the activity. The model has correlation coefficient (r) of 0. 964. It shows significance level more than 99.0% against tabulated value F=26.1, with a low standard deviation of estimation 0.087, demonstrate accuracy of the model. The robustness of model was shown by magnitude of the bootstrapping r^2, which was near to conventional r^2. The internal predictivity of model (q^2=0.904) was also good. The model once again favored by the least S_{PRESS} and S_{DEP} values. The observed, calculated and predicted activities (pMIC) for training set of model 1 is presented in **Table II.**

Table: II Training set activity (pMIC) (model: 1)

Comp. No.	Observed Activity(pMIC)	Calculated Activity(pMIC)	Predicted Activity(pMIC)
1	7.123	7.232	7.244
2	7.462	7.462	7.462
4	7.428	7.311	7.2877
5	7.473	7.472	7.472
6	7.364	7.792	7.847
8	7.206	7.253	7.260
9	7.292	7.089	7.024
11	7.752	7.345	7.292
12	7.752	7.884	7.932
13	7.776	7.749	7.742
14	7.792	7.588	7.569
15	7.491	7.538	7.542
17	7.585	7.789	7.821
19	7.904	7.742	7.724
22	7.933	7.875	7.863
23	6.305	6.344	6.360
24	6.004	6.030	6.038
25	6.305	6.283	6.251
27	6.004	6.120	6.153
28	6.305	6.36	6.385

The **figure I** shows plot of observed versus calculated pMIC values for training set molecules and **figure II** is plot of observed versus predicted pMIC values for same set (model 1)

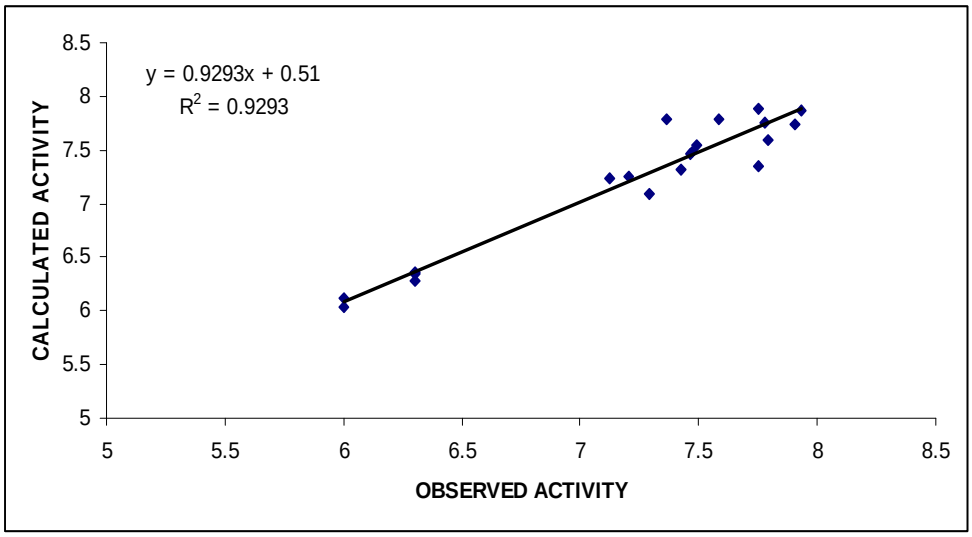


Fig. I: Discrete Plot of training set between observed vs. calculated by leave-one-out cross-validation pMIC values. (model: 1) $y=0.929x+0.51$, $r^2=0.9293$

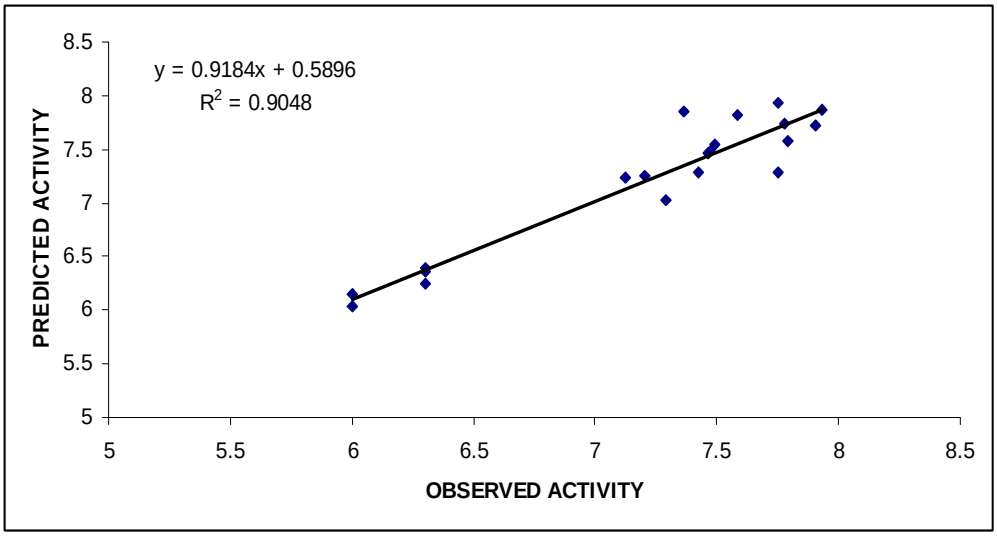


Fig. II: Discrete Plot of training set between observed vs. predicted by leave-one-out cross-validation pMIC values. (model: 1)
$y = 0.9184x + 0.5896$, $r^2 = 0.9048$

The **Table III** includes prediction of test set molecules and its usefulness in predicting activities of external molecules is indicated by **Figure III**, a plot of observed versus predicted pMIC for test set molecules:

Table: III Test set activity (model: 1)

Comp. No.	Observed Activity(pMIC)	Predicted Activity(pMIC)
3	7.428	7.298
7	7.206	7.173
10	7.425	7.106
16	7.283	7.612
18	7.873	7.627
20	7.916	7.672
21	7.615	7.736
26	6.004	6.521

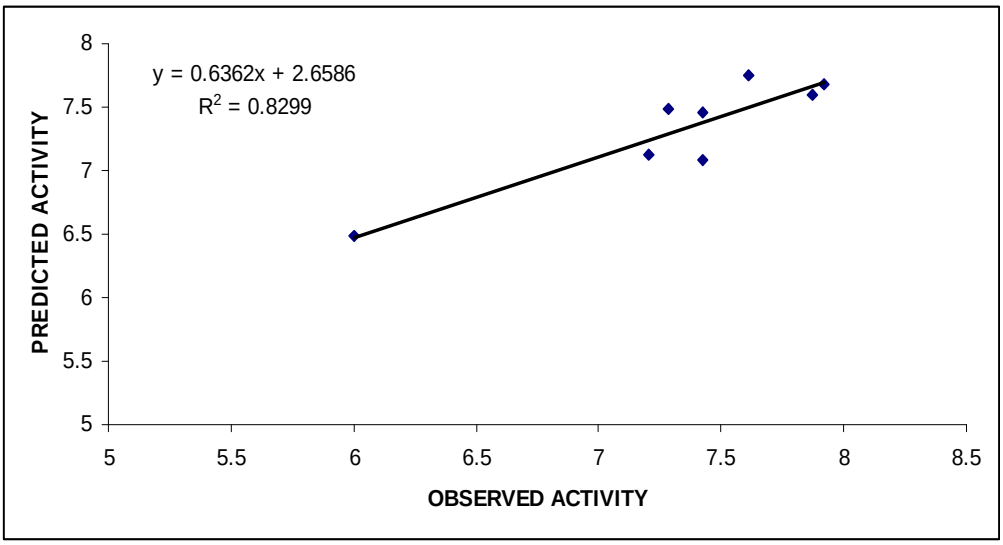


Fig. III: Discrete Plot of test set between observed vs. predicted by leave-one-out cross-validation pMIC values. (model: 1) y = 0.6362x + 2.658, r^2 = 0.8299

Model: II

$pMIC_{50}$= Ovality [2.558(± 0.980)] -D_1 [0.0653 (± 0.0345)] - E_{HOMO} [1.104 (± 0.386)] - [6.979(± 3.178)]

n=20, r=0.960, r^2=0.923, std=0.196, F=63.938, Q^2=0.894, r^2_{bs} = 0.925, S_{PRESS}=0.230, S_{DEP}=0.206

The model 2 shows that steric parameter (Ovality) shows positive contribution and electronic parameters (E_{HOMO} energy and dipole moment) show negative contribution towards the activity. The model has correlation coefficient (r) of 0.960. It shows significance level more than 99.0% against tabulated value F=26.1, with a low standard deviation of estimation 0.088, demonstrate accuracy of the model. The robustness of model was shown by magnitude of the bootstrapping r^2, which was near to conventional r^2. The internal predictivity of model (q^2=0.894) was also good. The model once again favored by the least S_{PRESS} and S_{DEP} values. The **table IV** involves the observed, calculated and predicted pMIC values for training set of model 2. The **figures IV**

& V are plot of observed versus calculated and observed versus predicted pMIC values for training set respectively.

Table: IV Training set activity (model: 2)

Comp. No.	Observed Activity(pMIC)	Model 2	
		Calculated Activity(pMIC)	Predicted Activity(pMIC)
1	7.123	7.312	7.342
2	7.462	7.384	7.373
4	7.427	7.336	7.314
5	7.473	7.350	7.322
6	7.364	7.752	7.797
8	7.206	7.291	7.307
9	7.292	7.106	7.044
11	7.752	7.375	7.328
12	7.752	7.880	7.927
13	7.776	7.700	7.679
14	7.792	7.542	7.514
15	7.491	7.453	7.450
17	7.585	7.892	7.941
19	7.904	7.787	7.774
22	7.933	7.927	7.926
23	6.305	6.371	6.396
24	6.004	6.084	6.108
25	6.305	6.255	6.178
27	6.004	6.079	6.103
28	6.305	6.381	6.416

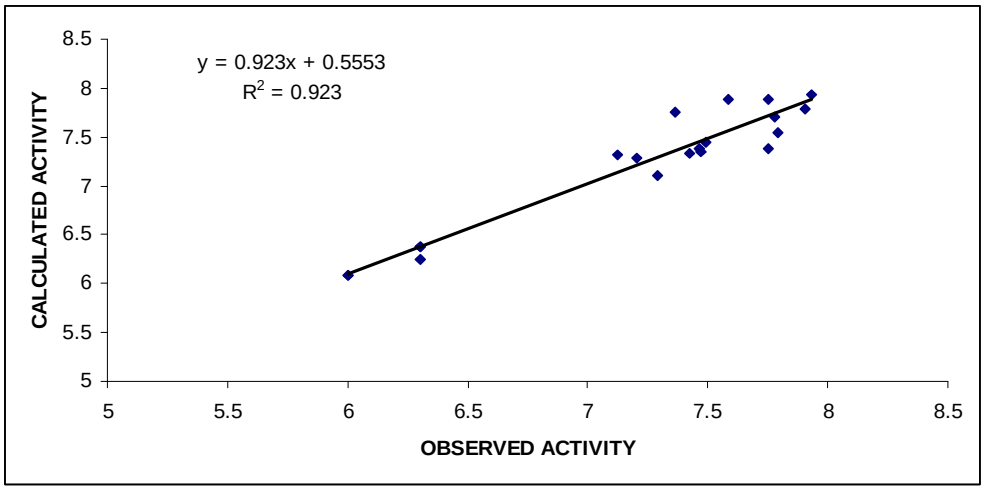


Fig. IV: Discrete Plot of training set between observed vs. calculated by leave-one-out cross-validation pMIC values. (model: 2)
$y = 0.923x + 0.5553$, $r^2 = 0.923$

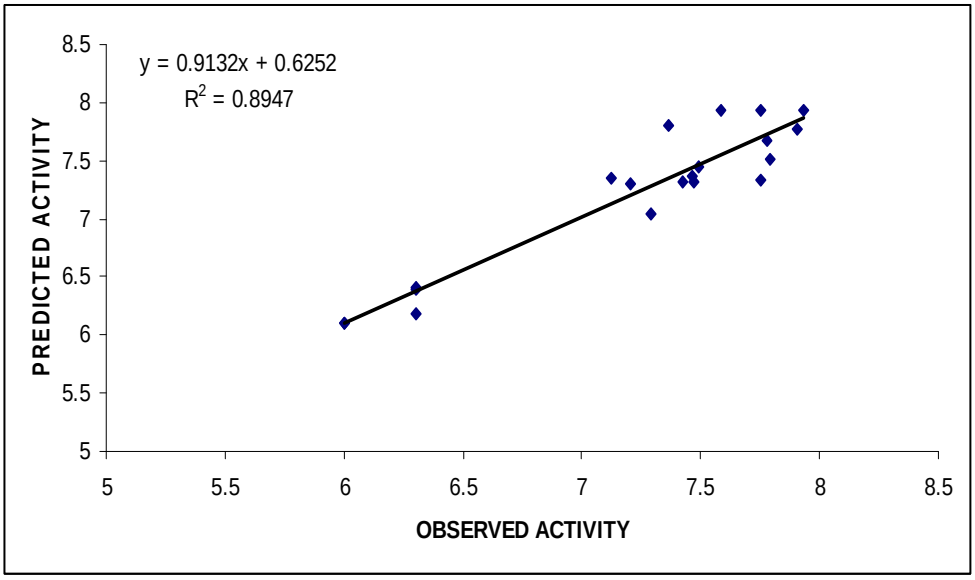


Fig. V: Discrete Plot of training set between observed vs. predicted by leave-one-out cross-validation pMIC values. (model: 2)

$y = 0.9132x + 0.6252$, $r^2 = 0.8947$

The predicted activities for test set molecules are presented in **Table V**.

Table: V Test set activity (model: 2)

Comp. No.	Observed Activity(pMIC)	Predicted Activity(pMIC)
3	7.428	7.298
7	7.206	7.173
10	7.425	7.106
16	7.284	7.612
18	7.873	7.627
20	7.916	7.672
21	7.615	7.736
26	6.004	6.521

The applicability of model 2 in predicting activities of external molecules is shown by a plot of observed versus predicted pMIC values for test set in **Figure VI.**

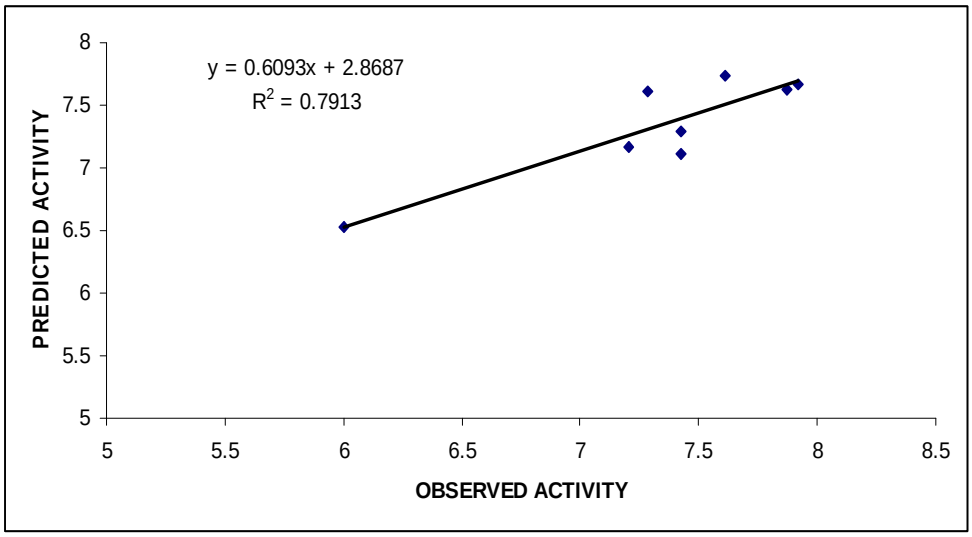


Fig. VI: Discrete Plot of test set between observed vs. predicted by leave-one-out cross-validation pMIC values. (model: 2) $y = 0.6093x + 2.8687$, $r^2 = 0.7913$

CONCLUSION

TABLE VI: Statistics of Significant Equations

Model No.	n	r^2	F	r^2_{bs}	Chance	S_{DEP}	S_{PRESS}	Q^2
1.	20	0.929	70.096	0.935	<0.001	0.196	0.219	0.904
2.	20	0.923	63.938	0.925	<0.001	0.206	0.230	0.894

E_{HOMO} and Dipole moment are electronic descriptors. E_{HOMO} is the highest occupied molecular orbital called frontier orbital and determines the way it interacts with other species. E_{HOMO} is the orbital that could act as an e- donor. Since it is outermost (highest energy), the negative contribution of E_{HOMO} energy suggested that substitution of group at oxadiazole ring with electron withdrawing group favourable for the antibacterial activity in the concerned microbes.

Dipole moment is the electrical dipole for a pair of opposite charges of electrons. Polar molecule creates dipole due to separation of charge. Electron donating group decreases the dipole moment hence increases the activity.

Ovality & pMIZ are steric descriptors. Ovality is the ratio of molecular surface area to the minimum surface area. The minimum surface area is the surface area of a sphere having a volume equal to the solvent excluded volume of the molecule .Computed from the Connolly molecular surface area & solvent excluded volume properties, bulkiness of the molecule increases the ovality hence increases the antimicrobial activity.

pMIZ descriptor contributes positively suggest that polar electronic interaction along with Z-axis are favourable for activity. Groups which can increases conformational flexibility of the molecule are detrimental.

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REFERENCES

[1] Abbanat D, Macielag M, Bush K, *Expert Opin. Investig. Drugs* **2003**, 12(3), 379- 399.
[2] Lee V, Hacker S, *J. Med. Chem.*,**1999**, 19, 521-542.
[3] Poole K, *Curr. Opin. Microbiol*, **2001**, 4, 500- 508.
[4] Gaonkar SL,Rai KML, Prabhuswamy B, *Eur. J. Med. Chem*, **2006**, *41*, 841–846.
[5] Karthikeyan S,Prasad DJ, Mahalinga M, Holla BS, Kumari NS, *Eur. J. Med. Chem*, **2008**, *43*, 25-31.
[6] Lay S, Ahin S, Palaska E, Ekizoglu M, Zalp OM, *ILFarmaco* **, 2002**, *57*, 539–542.
[7] Gulay S, Erhan P, Melika E, Meral O, *ILFarmaco*, **2001**, 57, 539-42.
[8] Ali MA, Shaharyar M, *Bioorg. Med. Chem. Lett.*, **2007**, 17, 3314-3316.
[9] Kadi Adnan A, El-broslly N R, Al-deeb OA, *Eur. J. Med. Chem* , **1997**, 42, 235-242.
[10] Omar FA,Mahfouz NM, and Rahman MA, *Eur. J. Med. Chem*.,**1996**, 31,819.
[11] Gswami BN, Kataky JCS, Baruah JN, *J. Heterocycl.Chem*., **1984**, 21,1225.
[12] Chaudhary SK, Chaudhary M, Chaudhary A, Parmar SS, *J. Pharm. Sciences*, **1978**, 67, 1507-1509.
[13] Ladva K, Patel P, Upadhyay P, Parekh H, *Ind.J.Chem.Sec.*,**1996**, 35,1062
[14] Aboraia AS, Abdel-Rahman HM, Mahfouz NM, El-Gendy MA, *Bioorg. Med. Chem.*,**2006**, 14, 1236–1246.
[15] Chin Tan TM, Chena Y, Hoe Kong K, Bai J, Li Y, Limc SG, Hong AT, Lama Y, *Antiviral Research*, **2006**, 71, 7–14.
[16] Liszkiewicz H, Glowiak T, Kowalska MW, Rutkowska M, Szelag A, *Pol.J.Chem.*, **1999**, 73,321.
[17] Mandour AH, Fawzi NM, El-Shihi TH, El-Bazza ZE, *Pak. J. Sci.Ind.Res.* ,**1995**, 38,402.
[18] Shi W, Quian X, Zhang R, Song G, *J. Agric. Food Chem.*, **2001**, 49, 124-130.
[19] CS Chem Office, Version 6.0. Cambridge Soft Corporation, Software Publishers Association, street, NW, Suite 700, Washington, D.C. 20036.
[20] Gupta AK, Arockia Babu M, Kaskhedikar SG, *Indian. J. Pharm. Sci.*, **2004**, 66: 396-402.