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Abstract

Motivation. Quantitative structure–activity relationships (QSAR) analysis has been carried out on a series of 1,2,4–triazole analogs as antibacterial using set of spatial, thermodynamic, and electronic descriptors.

Method. The dataset was subjected to molecular modeling and QSAR studies using Chem–Office Software version 8.0 (Cambridge Soft). All the structures were minimized through molecular mechanics followed by MOPAC, and models were developed through regression.

Results. The QSAR model suggests that an electronic parameter (D_4) and a steric parameter (PMI_X) play a significant role in explaining the variance in activity. PMI_X describes the mass distribution over the molecule on the X coordinate in spatial arrangement, and suggests that the increase in bulkiness on the X coordinate of molecule increases the inhibitory activity. The dipole moment has also a positive correlation with the inhibitory activity.

Conclusions. The QSAR analysis revealed a wide range of variation for the cross–validated squared correlation coefficient, namely R^2_{cv} = 0.741 for *P. aeruginosa*, R^2_{cv} = 0.646 for *C. albicans*, R^2_{cv} = 0.515 for *T. viride*, R^2_{cv} = 0.432 for *A. niger*, R^2_{cv} = 0.306 for *P. mirabilis*, R^2_{cv} = 0.353 for *B. subtilis*, and R^2_{cv} = 0.143 for *S. aureus*, respectively. The study showed that for antimicrobial activities of 1,2,4–triazole analogs, the dipole moment plays a key role.

Keywords. Quantitative structure–activity relationships; antimicrobial activity; 1,2,4–triazole analogs.

1 INTRODUCTION

The number of life–threatening infections caused by multi–drug–resistance gram–positive pathogens has reached an alarming level in community and the hospitals [1]. Infections caused by these organisms pose a serious challenge to the scientific community and the need for an effective therapy has led to a search for novel antibacterial agents. Substituted 1,2,4–triazole derivatives have been the aim of many researchers for many years because they constitute an important class of

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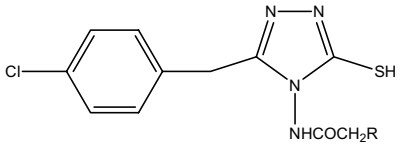
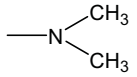
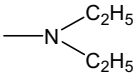
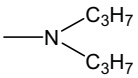
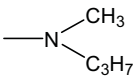
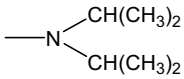
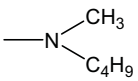
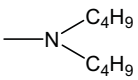
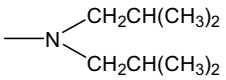
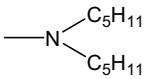
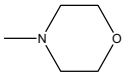
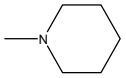
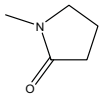
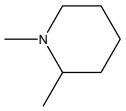
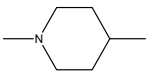
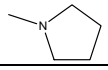
heterocyclic compounds with antibacterial and antifungal activity [2–9].

Table 1. Analogs of 1,2,4–Triazoles and their Various Antimicrobial Activities



Comp.	R	MIC (μg/mL)						
		**PM*	**PA*	**BS*	**SA*	*AN	*CA	*TV
NU–1		68	88	92	126	68	62	76
NU–2		76	98	94	148	76	72	82
NU–3		112	94	76	148	114	136	114
NU–4		122	86	82	152	92	112	98
NU–5		146	56	116	154	72	36	54
NU–6		134	74	112	136	98	112	104
NU–7		118	98	114	118	134	98	112
NU–8		114	86	112	124	136	96	114
NU–9		142	96	128	138	128	102	124
NU–10		74	86	92	36	72	36	54
NU–11		132	146	98	150	110	74	96
NU–12		142	92	72	118	92	94	78
NU–13		78	128	94	142	134	116	148
NU–14		118	96	106	72	152	112	136
NU–15		134	158	138	116	112	132	94

** PM – P. mirabilis* (*MTCC–425*), *PA – P. aeruginosa* (*MTCC–424*), *BS – B. subtilis* (*MTCC–619*), *SA – S. aureus* (*MTCC–96*), *AN – A. niger* (*MTCC–1344*), *CA – C. albicans* (*MTCC–227*), *TV – T. viride* (*MTCC–167*). #pMIC values are negative logarithm of MIC.

Moreover, structure–activity relationship for 1,2,4–triazole derivatives have revealed that the substitution of the 4th position is decisive for the biological activity and position 5 is important for

the intensity of the activity [7–9]. Ever since scientists began to measure or quantify, the physical and biological properties of the natural world, they also sought patterns or relationships between the measurements they made. It was not until 1930's that knowledge of the extent and the rates of chemical processes, together with the properties of the reacting molecules (shape, size and electronic properties) allowed correlations to be made between the nature of molecules and their tendency to react. These arouse our interest for establishing correlation between physicochemical properties of molecules with their biological activity. Further exploration of responsible properties may be help in development of more potent anti–microbial agents.

2 MATERIALS AND METHODS

The antimicrobial data of 1,2,4–triazole derivatives containing 15 compounds with activity on *P. mirabilis*, *P. aeruginosa*, *B. subtilis*, *S. aureus*, *A. niger*, *C. albicans*, and *T. viride* were taken from the research work of Upmanyu *et al*. [10] (Table 1). The biological activity data MIC (minimum inhibitory concentration in μg/ml) were initially converted to μM/l followed by acquired negative logarithm (pMIC) for QSAR analysis (Table 2).The series was subjected to molecular modeling and QSAR studies using CS Chem–Office Software version 8.0 (Cambridge soft) [11] running on a P–III processor. Structures of all the compounds (Table 1) were sketched using builder module of the program. These structures were then subjected to energy minimization using molecular mechanics (MM2) until the root mean square (RMS) gradient value became smaller than 0.1 kcal/mol Å. Minimized molecules were subjected to re–optimization via Austin model–1 (AM1) method until the root mean square (RMS) gradient attained a value smaller than 0.01 kcal/mol Å using MOPAC.

Table 2. pMIC of 1,2,4–Triazoles Analogs Against Various Microorganisms

Comp.	*PM		*PA		*BS		*SA	
	[f]MIC (μM/l)	[#]pMIC	[f]MIC (μM/l)	[#]pMIC	[f]MIC (μM/l)	[#]pMIC	[f]MIC (μM/l)	[#]pMIC
NU–1	208.7	3.680	270.1	3.568	282.4	3.549	386.7	3.413
NU–2	214.8	3.668	276.9	3.558	265.6	3.576	418.2	3.379
NU–3	293.3	3.533	246.1	3.609	199.0	3.701	387.5	3.412
NU–4	344.8	3.462	243.0	3.614	231.7	3.635	429.5	3.367
NU–5	382.4	3.418	146.7	3.834	303.8	3.517	403.3	3.394
NU–6	364.2	3.439	201.1	3.696	304.4	3.517	369.7	3.432
NU–7	287.8	3.541	239.0	3.622	278.1	3.556	287.8	3.541
NU–8	278.1	3.556	209.8	3.678	273.2	3.564	302.5	3.519
NU–9	324.2	3.489	219.2	3.659	292.2	3.534	315.0	3.502
NU–10	201.2	3.696	233.8	3.631	250.1	3.602	97.9	4.009
NU–11	360.8	3.443	399.0	3.399	267.8	3.572	410.0	3.387
NU–12	388.1	3.411	251.5	3.600	196.8	3.706	322.5	3.491
NU–13	205.3	3.688	336.9	3.472	247.4	3.607	373.8	3.427
NU–14	310.6	3.508	252.7	3.597	279.0	3.554	189.5	3.722
NU–15	380.8	3.419	449.1	3.348	392.2	3.406	329.7	3.482

* *PM – P. mirabilis* (*MTCC–425*), *PA – P. aeruginosa* (*MTCC–424*), *BS – B. subtilis* (*MTCC–619*), *SA – S. aureus* (*MTCC–96*), *AN – A. niger* (*MTCC–1344*), *CA – C. albicans* (*MTCC–227*), *TV – T. viride* (*MTCC–167*). [f] minimum inhibitory concentration in micromole per liter, [#]pMIC values are negative logarithm of MIC.

Table 2. (Continued)

Comp.	*AN		*CA		*TV	
	[f]MIC (μM/l)	[#]pMIC	[f]MIC (μM/l)	[#]pMIC	[f]MIC (μM/l)	[#]pMIC
NU–1	208.7	3.680	190.3	3.721	233.3	3.632
NU–2	214.8	3.668	203.5	3.692	231.7	3.635
NU–3	298.5	3.525	356.1	3.448	298.5	3.525
NU–4	260.0	3.585	316.5	3.500	276.9	3.558
NU–5	188.6	3.725	94.3	4.026	141.4	3.849
NU–6	266.4	3.575	304.4	3.517	282.7	3.549
NU–7	326.8	3.486	239.0	3.622	273.2	3.564
NU–8	331.7	3.479	234.2	3.630	278.1	3.556
NU–9	292.2	3.534	232.9	3.633	283.1	3.548
NU–10	195.7	3.708	97.9	4.009	146.8	3.833
NU–11	300.6	3.522	202.3	3.694	262.4	3.581
NU–12	251.5	3.600	256.9	3.590	213.2	3.671
NU–13	352.7	3.453	305.3	3.515	389.6	3.409
NU–14	400.1	3.398	294.8	3.530	358.0	3.446
NU–15	318.3	3.497	375.2	3.426	267.2	3.573

The group of calculated thermodynamic descriptors included bend energy (E_b), heat of formation (H_f), total energy (E_T), stretch energy (E_S), stretch bend energy (E_{SB}) and torsion energy (E_{tor}). Steric descriptors derived were Connolly accessible area (*CAA*), Connolly molecular area (*CMA*), Connolly solvent excluded volume (*CSEV*), exact mass (*EM*), molecular weight (*MW*), principal moment of inertia–X component (PMI_X), principal moment of inertia–Y component (PMI_Y), principal moment of inertia–Z component (PMI_Z), molar refractivity (*MR*) and ovality (*OVAL*) apart from this Partition coefficient calculated as *LOGP*. Electronic descriptors such as dipole moment–X component (D_1), dipole moment–Y component (D_2), dipole moment–Z component (D_3), dipole moment (D_4), electronic energy (E_E), highest occupied molecular orbital energy (E_{HOMO}), lowest unoccupied molecular orbital energy (E_{LUMO}), repulsion energy (E_{REP}), VDW–1,4–energy (E_{14}) and Non–1, 4–VDW energy (E_{nvd}) were calculated. Stepwise multiple linear regression analysis method was used to perform QSAR analysis employing in–house VALSTAT [12] program. The best model was selected on the basis of various statistical parameters such as correlation coefficient (*r*), standard error of estimation (*SEE*) and sequential Fischer test (*F*). The model was further validated on various statistical parameters like leave–one–out cross–validated square correlation coefficient (R^2_{cv}), randomize biological activity data test (*Chance*) and test for outliers using Z–score value (Z_{val}). These confirm the robustness and applicability of QSAR equation on the structural analogs.

3 RESULTS AND DISCUSSION

When data set was subjected to stepwise multiple linear regression analysis, in order to develop QSAR between antibacterial activity in various microbes as dependent variables and physicochemical properties as independent variables, several equations were obtained.

The statistically significant equation Eq. (1) with the coefficient of correlation R = 0.921 was

considered as model for antibacterial activity against *P. aeruginosa*, which explains 84.7% variance in inhibitory activity (Table 3) with low value of standard error of estimation (0.052). The model shown internal statistical significance level more than 99.9% as F–value ($F_{(3,11)}$ =20.371 against tabulated $F_{(3,11\ \alpha\ 0.001)}$ =13.7.

$$\text{pMIC}_{(P.aeruginosa)} = 3.252 + 8.099\text{e}{-5}(\pm 2.422\text{e}{-5})PMI_X + 0.078(\pm 0.012)\ D_4 - 0.011(\pm 0.004)\ E_{tor}$$
$$n = 15 \quad R = 0.921 \quad \%EV = 84.842 \quad F_{(2,11)} = 20.37 \quad p<0.001 \quad SEE = 0.052 \quad R^2_{cv} = 0.741 \qquad (1)$$
$$S_{PRESS} = 0.068 \quad PSE = 0.058$$

Table 3. Calculated value (Cal) with residual (R_{cal}) and Z–score data (Z_{val}) of 1,2,4–triazoles analogs for various antimicrobial activities obtained by QSAR study

Comp.	pMIC$_{(A.niger)}$			pMIC$_{(P.aeruginosa)}$			pMIC$_{(B.subtilis)}$			pMIC$_{(S.aureus)}$		
	Cal	R_{cal}	Z_{Val}	Cal	R_{cal}	Z_{Val}	Cal	R_{cal}	Z_{Val}	Cal	R_{cal}	Z_{Val}
NU–1	3.68	0.00	0.10	3.58	–0.01	–0.31	3.58	–0.04	–0.78	3.31	0.11	1.11
NU–2	3.64	0.03	0.72	3.56	0.00	0.00	3.58	–0.01	–0.17	3.41	–0.04	–0.37
NU–3	3.56	–0.04	–0.87	3.57	0.04	0.76	3.60	0.10	2.24	3.46	–0.05	–0.54
NU–4	3.62	–0.03	–0.71	3.65	–0.04	–0.78	3.56	0.07	1.59	3.44	–0.07	–0.73
NU–5	3.74	–0.01	–0.29	3.81	0.02	0.49	3.49	0.02	0.55	3.37	0.03	0.29
NU–6	3.59	–0.01	–0.28	3.68	0.02	0.34	3.57	–0.05	–1.13	3.46	–0.02	–0.24
NU–7	3.52	–0.03	–0.78	3.62	0.00	–0.01	3.58	–0.02	–0.55	3.43	0.11	1.17
NU–8	3.49	–0.02	–0.35	3.70	–0.02	–0.42	3.59	–0.02	–0.48	3.54	–0.02	–0.25
NU–9	3.44	0.10	2.19	3.65	0.01	0.23	3.61	–0.07	–1.63	3.52	–0.02	–0.18
NU–10	3.63	0.08	1.78	3.55	0.08	1.82	3.59	0.02	0.37	3.92	0.09	0.93
NU–11	3.48	0.04	0.84	3.50	–0.10	–2.07	3.56	0.01	0.23	3.49	–0.10	–1.07
NU–12	3.59	0.00	0.11	3.65	–0.05	–1.06	3.71	–0.01	–0.17	3.52	–0.02	–0.25
NU–13	3.47	–0.01	–0.30	3.51	–0.04	–0.86	3.58	0.03	0.67	3.54	–0.11	–1.16
NU–14	3.46	–0.06	–1.41	3.52	0.07	1.61	3.56	–0.01	–0.11	3.49	0.23	2.37
NU–15	3.53	–0.03	–0.75	3.34	0.01	0.25	3.44	–0.03	–0.64	3.59	–0.10	–1.07

Table 4. Inter–correlation matrix of substituent constants used in QSAR analysis

	LOGP	PMI_X	D_1	D_2	D_4	E_{HOMO}	E_T	E_b	*DDE*	E_{nvd}	E_S	E_{SB}	E_{tor}
LOGP	1.000												
PMI_X	0.253	1.000											
D_1	0.070	0.035	1.000										
D_2	0.463	0.031	0.203	1.000									
D_4	0.206	0.307	0.862	0.071	1.000								
E_{HOMO}	0.441	0.710	0.197	0.315	0.589	1.000							
E_T	0.769	0.508	0.123	0.094	0.155	0.124	1.000						
E_b	0.468	0.362	0.219	0.368	0.089	0.574	0.020	1.000					
DDE	0.387	0.076	0.312	0.781	0.236	0.141	0.012	0.066	1.000				
E_{nvd}	0.386	0.298	0.627	0.475	0.189	0.446	0.251	0.661	0.176	1.000			
E_S	0.314	0.397	0.271	0.141	0.344	0.051	0.719	0.225	0.198	0.147	1.000		
E_{SB}	0.321	0.228	0.048	0.456	0.085	0.469	0.135	0.072	0.735	0.106	0.051	1.000	
E_{tor}	0.141	0.154	0.029	0.609	0.060	0.063	0.034	0.327	0.400	0.192	0.062	0.186	1.000

The intercorrelations of the descriptor in the model are insignificant (Table 4) indicating that all the descriptors in the model were contributing independently to the biological activity. The model was further analyzed for the outlier by the Z–score method (Z_{val}), which is helpful in identification of unexplainable structurally diverse analogs. If the model should not have any outlier considered as a best one. The Z_{value} for individual compounds lies within the specific range (<|2.5|), indicated absence of outliers. Test revealed that the model is able to explain the structurally diverse analogs

and also helpful in designing more potent compounds using contributed physiochemical descriptors.

The model was subjected to leave–one–out (*LOO*) cross–validation method, the value of R^2_{cv} ≥0.3 in cross–validation method corresponds to a confidence limit greater than 95%, which minimized the risk of finding significant explanatory equation for the biological activity just by mere opportunity. The value of cross–validated squared correlation coefficient (R^2_{cv} = 0.741), predictive residual sum of square (S_{PRESS} = 0.068) and standard error of predictivity (*PSE* = 0.058) suggested good predictivity of the biological activity (Table 5). Randomize biological activity data test (*Chance* < 0.001) revealed that the results were not based on chance correlation.

Table 5. QSAR statistics of significant equations

Eq.	r^2	*SEE*	*F*	*ICAP* [a]	Chance	R^2_{cv}	S_{PRESS}	*PSE*
1	0.847	0.052	20.371	0.308	0.001	0.741	0.068	0.058
2	0.794	0.050	14.136	0.387	0.001	0.453	0.082	0.070
3	0.671	0.109	7.445	0.359	0.011	0.143	0.175	0.150
4	0.789	0.092	13.717	0.574	0.003	0.646	0.120	0.103
5	0.787	0.062	13.546	0.363	0.001	0.515	0.094	0.080
6	0.627	0.051	6.176	0.359	0.011	0.353	0.067	0.058
7	0.567	0.079	4.806	0.387	0.008	0.306	0.099	0.085

[a] The maximum limit of inter–correlation among the descriptors used in generation of equations.

The above model suggested that electronic parameter (D_4) and steric parameter (PMI_X) play a significant role in explaining the variance in activity. PMI_X that describes mass distribution over the molecule on X–component in spatial arrangement, contributed positively to the activity suggesting that the increase in bulkiness on X–component of molecule is favourable for the inhibitory activity. Dipole moment is also contributed positively to the activity. Study revealed that R–group play crucial role in the activity. The polar nature of R–group favors inhibitory activity against *P. aeruginosa*.

The QSAR antimicrobial activity against *A. niger*, correlation coefficient (0.891) was established in Eq. (2). The equation showed overall internal statistical significance level better than 99.9% as it exceeded the tabulated $F_{(3,11\ \alpha\ 0.001)}$ = 13.7 (Table 3).

$$\begin{gathered} \mathrm{pMIC}_{(A.niger)} = 3.713 + 0.063(\pm 0.011)\, D_4 + 0.045(\pm 0.015)\, DDE - 0.072(\pm 0.014)\, LOGP \\ n = 15 \quad R = 0.891 \quad \%EV = 79.388 \quad F_{(2,11)} = 14.136 \quad p<0.001 \quad SEE = 0.050 \\ R^2_{cv} = 0.434 \quad S_{PRESS} = 0.082 \quad PSE = 0.070 \end{gathered} \tag{2}$$

The model was further subjected to statistical validation, the values of leave–one–out cross–validation (R^2_{cv} = 0.452, S_{PRESS} = 0.081, *PSE* = 0.070), chance statistics (*Chance*<0.001) and Z–score data (absence of outlier) suggested the robustness of the model (Tables 3 and 5).

The above model suggested that electronic parameter (D_4 and *DDE*) play a significant role in explaining the variance in activity. Dipole moment is related to the resultant vectors of molecular charge distribution in three dimensions and can be altered through the incorporation of electronegative group. This study revealed that D_4 and *DDE* contributed positively to the activity

and modification at R position in such a fashion that resultant dipole of the overall molecule would be enhanced might be result in more potent inhibitors against *A*. *niger*.

Similarly QSAR models were obtained for *S*. *aureus*, *C*. *albicans*, *T*. *viride*, *B*. *subtilis* and *P*. *mirabilis*, with the following correlation coefficients: R = 0.819 in Eq. (3), R = 0.888 in Eq. (4), R = 0.887 in Eq. (5), R = 0.792 in Eq. (6), and R = 0.753 in Eq. (7) respectively (Table 3 and 6).

$$\mathrm{pMIC}_{(S.aureus)} = -0.018 + 0.085(\pm 0.027)\, D_1 + 0.055(\pm 0.017)\, E_b + 0.162(\pm 0.077)\, E_S$$
$$n = 15 \quad R = 0.819 \quad \%EV = 67.067 \quad F_{(2,11)} = 7.445 \quad p<0.01 \quad SEE=0.109 \qquad (3)$$
$$R^2_{\mathrm{cv}} = 0.143 \quad S_{PRESS} = 0.175 \quad PSE = 0.150$$

$$\mathrm{pMIC}_{(C.albicans)} = 10.179 + 1.002(\pm 0.248)\, E_{HOMO} + 0.107(\pm 0.018)\, E_b - 0.030(\pm 0.007)\, E_{tor}$$
$$n = 15 \quad R = 0.888 \quad \%EV = 78.854 \quad F_{(2,11)} = 13.717 \quad p<0.001 \quad SEE=0.092 \qquad (4)$$
$$R^2_{\mathrm{cv}} = 0.646 \quad S_{PRESS} = 0.120 \quad PSE = 0.103$$

$$\mathrm{pMIC}_{(T.viride)} = 2.243 + 0.044(\pm 0.014)\, D_4 + 0.052(\pm 0.010)\, E_b - 5.894\mathrm{e}{-5}(\pm 3.034\mathrm{e}{-5})\, PMI_X$$
$$n = 15 \quad R = 0.887 \quad \%EV = 78.677 \quad F_{(2,11)} = 13.546 \quad p<0.002 \quad SEE = 0.062 \qquad (5)$$
$$R^2_{\mathrm{cv}} = 0.515 \quad S_{PRESS} = 0.094 \quad PSE= 0.080$$

$$\mathrm{pMIC}_{(B.subtilis)} = 2.378 + 0.114(\pm 0.035)\, \mathrm{E_S} - 0.030(\pm 0.014)\, D_2 - 0.009(\pm 0.003)\, E_T$$
$$n = 15 \quad R = 0.792 \quad \%EV = 62.726 \quad F_{(2,11)}=6.176 \quad p<0.05 \quad SEE=0.051 \qquad (6)$$
$$R^2_{\mathrm{cv}} = 0.353 \quad S_{PRESS} = 0.067 \quad PSE= 0.058$$

$$\mathrm{pMIC}_{(P.mirabilis)} = 4.620 + 0.353(\pm 0.148)\, E_{SB} - 0.053(\pm 0.022)\, LOGP - 0.029(\pm 0.010)\, E_{nvd}$$
$$n = 15 \quad R = 0.753 \quad \%EV = 56.701 \quad F_{(2,11)} = 4.806 \quad p<0.05 \quad SEE = 0.079 \qquad (7)$$
$$R^2_{\mathrm{cv}} = 0.306 \quad S_{PRESS} = 0.099 \quad PSE = 0.085$$

Table 6. Calculated value (Cal) with residual (R_{cal}) and Z–score data (Z_{val}) of 1,2,4–triazoles analogs for various antimicrobial activities obtained by QSAR study

Comp.	$\mathrm{pMIC}_{(P.\ mirabilis)}$			$\mathrm{pMIC}_{(C.\ albicans)}$			$\mathrm{pMIC}_{(T.\ viride)}$		
	Cal	R_{cal}	Z_{Val}	Cal	R_{cal}	Z_{Val}	Cal	R_{cal}	Z_{Val}
NU–1	3.62	0.06	0.80	3.67	0.05	0.64	3.57	0.06	1.06
NU–2	3.65	0.01	0.20	3.59	0.10	1.19	3.60	0.04	0.72
NU–3	3.62	–0.09	–1.31	3.60	–0.15	–1.83	3.58	–0.06	–1.05
NU–4	3.48	–0.01	–0.19	3.61	–0.11	–1.33	3.58	–0.02	–0.33
NU–5	3.44	–0.02	–0.35	4.01	0.01	0.14	3.85	0.00	–0.03
NU–6	3.45	–0.02	–0.22	3.61	–0.09	–1.16	3.56	–0.01	–0.15
NU–7	3.53	0.01	0.15	3.66	–0.03	–0.41	3.58	–0.01	–0.24
NU–8	3.45	0.11	1.51	3.57	0.06	0.75	3.53	0.02	0.44
NU–9	3.53	–0.04	–0.56	3.58	0.05	0.64	3.52	0.03	0.49
NU–10	3.66	0.03	0.46	4.00	0.01	0.10	3.75	0.08	1.52
NU–11	3.53	–0.09	–1.26	3.54	0.15	1.83	3.49	0.10	1.74
NU–12	3.41	0.00	0.03	3.53	0.06	0.75	3.71	–0.04	–0.74
NU–13	3.53	0.16	2.27	3.56	–0.04	–0.53	3.49	–0.08	–1.52
NU–14	3.52	–0.01	–0.18	3.55	–0.02	–0.25	3.47	–0.02	–0.39
NU–15	3.51	–0.09	–1.35	3.47	–0.04	–0.53	3.66	–0.08	–1.52

The models were further subjected to statistical validation; the values of leave–one–out cross–validation are significant (R^2_{cv} = 0.306 to 0.645) except Eq. (3) (R^2_{cv} = 0.143) which shown moderate value (Table 5).

Antimicrobial activity of 1,2,4–triazole analogs against *S*. *aureus* contributed positively by dipole moment of X component, stretch energy and bend energy. Similarly E_{HOMO} and bend energy

contributed positively to antimicrobial activity against *C. albicans*. Bend energy is indicative of deformation of the structure. E_{HOMO} is an electronic descriptor, indicating that the highest energy level of the molecule that contains electrons it governs the molecular properties and reactivities thus measures the electrophilicity of the molecule. Positive contribution of the E_{HOMO} energy in the model suggested that the molecule may interact on electron deficient areas of the receptor and the substitution of electron releasing group in the molecule will impart the positive influence to the activity.

In case of *T. viride* microbe's resultant dipole and bend energy contributed positively while PMI_X contributed negatively. *B. subtilis* and *P. mirabilis* showed moderate correlation coefficient value. The inhibitory activity against *B. subtilis* contributed by stretch energy positively while against *P. mirabilis* stretch bend energy play significant role.

The study showed that for antimicrobial activities of 1,2,4–triazole analogs diploe moment play key role against varies microbes, which might be imparted for electronic interaction of the 1,2,4–triazole analogs with nucleic acid of the microbes. Also QSAR analysis gave insight to some common important structural features, exploration of these features may help in development of improved antimicrobial agents against specific microbes.

4 CONCLUSIONS

The QSAR analysis revealed a wide range of variation for the cross–validated squared correlation coefficient, namely $R^2_{cv} = 0.741$ for *P. aeruginosa*, $R^2_{cv} = 0.646$ for *C. albicans*, $R^2_{cv} = 0.515$ for *T. viride*, $R^2_{cv} = 0.432$ for *A. niger*, $R^2_{cv} = 0.306$ for *P. mirabilis*, $R^2_{cv} = 0.353$ for *B. subtilis*, and $R^2_{cv} = 0.143$ for *S. aureus*, respectively. The study showed that for antimicrobial activities of 1,2,4–triazole analogs, the dipole moment plays a key role.

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