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QSAR Studies on Microbicidal Activity of Disubstituted 1,2,3-Triazoles having Ester Linkages

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A series of 1,4-disubstituted 1,2,3-triazoles (**1a**-**1t**) with two ester linkages was examined for *in vitro* antimicrobial potential against *Staphylococcus aureus*, *Escherichia coli*, *Klebsiellae pneumoniae*, *Enterobacter aerogenes*, *Candida albicans* and *Aspergillus niger*. Antimicrobial screening data indicated that synthesized triazoles displayed considerable microbicidal potency. QSAR studies of synthesized compounds were performed by multiple linear regression (MLR) analysis, statistically significant models were developed to explore biological activity trend on structural basis.

Keywords: Antibacterial activity, Antifungal activity, 1,2,3-Triazoles, QSAR.

INTRODUCTION

Over the past few years, continuous emergence of resistance in microorganisms along with side effects towards existing antimicrobials has become major health concern for the community. Various types of infections are increasing day by day due to these multidrug resistant bacteria and fungi. Owing to this, design and development of new structural leads has become major challenge for medicinal researchers. This justifies the attempt for synthesis of new, effective and safer antibacterial and antifungal agents with novel mode of action to combat newer microbial infections [1,2].

Triazoles correspond to class of bioactive heterocycles and have been recognized as key structural entity in several molecules of pharmaceutical importance [3]. These scaffolds reflected their role as antibacterial [4,5], antifungal [6], anti-HIV [7], anticancer [8,9], antitubercular [10,11], anticonvulsant [12], antiallergic [13], antioxidant [14], antiviral [15], antimalarial [16] agents *etc.*, in the field of medicinal chemistry. Inspite of the pharmaceutical applications, these triazole derivatives also found to possess industrial importance as optical brighteners, dyestuffs, photostabilizers, agrochemicals and corrosion inhibitors [17,18]. In the past, various synthetic approaches have been developed for the synthesis of 1,2,3-triazoles, however, Cu(I) catalyzed cycloaddition between terminal alkynes and azides invented by Sharpless *et al.* [19] and Meldal *et al.* [20] grown as a well established approach over classical [3+2] Huisgen cycloaddition [21] for the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles.

Despite the advances in technology to understand the mechanism of drug action, drug discovery is still complicated, expensive and time consuming task. Now a days, quantitative structure activity relationship (QSAR) has become an integral part of drug design due to its effective, statistically validated computational tool, mostly adopted for establishing correlation between structure of molecules and their biological activities [22]. It helps to envisage the biological spectrum of newly designed compounds from structural and electronic parameters, contributing for the drug discovery processes. Encouraged from above considerations, for the development of effective microbicidal substituted 1,2,3-triazoles [23-25], herein, we describe the QSAR studies of 20 ester linked 1,4-disubstituted 1,2,3-triazoles (**1a**–**1t**) possessing antimicrobial activities reported earlier [26].

EXPERIMENTAL

Dataset: All the synthesized triazoles (**1a**–**1t**) with antimicrobial activities reported previously [26] were considered for present QSAR study. The dataset was split into training

(20 compounds) and test (05 compounds) sets in a random manner. The QSAR models were created using training set compounds.

Structure preparation: The structures of the molecules under study were drawn and optimized with Marvin Sketch [27]. One base conformation was used for making all structures.

Parameters calculation: In order to quantify the molecules, various molecular descriptors (863 parameters containing one-, two-, three-dimensional parameters) were calculated by PaDEL Descriptor tool [28]. A molecule can be described differently by different descriptors. However some parameters can show similar meanings with similar values. Therefore, parameters with zero or constant or near-constant values were left out to reduce the recurrence and errors. Further, redundant descriptors were deleted and the remaining parameters were used in selection process of variables.

QSAR modeling and validation: The QSAR models were developed using multiple linear regression procedure in QSARINS. The resulted QSAR models were evaluated using different parameters suggested in literature [29].

RESULTS AND DISCUSSION

QSAR studies: Synthesized 1,4-disubstituted 1,2,3-triazole derivatives (**1a**–**1t**) with ester linkages were examined *in vitro* for antimicrobial activity against *Staphylococcus aureus* (MTCC 3160) and *Escherichia coli* (MTCC 443), *Klebsiellae pneumoniae* (NCDC 138), *Enterobacter aerogenes* (NCDC 106) and two fungi [*Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 282)] employing serial dilution technique [26]. Norfloxacin and fluconazole were used as reference drugs for antibacterial and antifungal strains, respectively. Results expressed in terms of minimum inhibitory concentrations (MIC, μmol/mL) were converted into pMIC (-log MIC) values and are presented in Table-1.

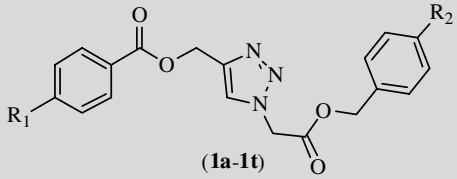
QSAR modeling of synthesized triazole derivatives (**1a**-**1t**) having ester linkages was worked out for explanation of observed antimicrobial activity trend on structural basis. The optimized 3D structures of the compounds were made with Marvin Sketch 5.10 [27] and alligned. PaDEL Descriptor tool [28] was used for calculating molecular descriptors (Total 1875 one-, two- and three-dimensional parameters). Selected descriptors are shown in Table-2. The whole dataset was divided into training and test sets (20 % of whole dataset) and linear models were developed by MLR (multiple linear regression) technique using MLR Plus Validation tool [30]. Statistically significant models were developed for activity against *S. aureus*, *E. coli* and *E. aerogenes*. For activity against other microbes, no significant model could be developed.

QSAR model for antibacterial activity against *S. aureus*: The best QSAR model for activity against *S. aureus* was a biparametric model described by the following equation:

$$\text{pMICsa} = -60.1132\ (\pm\ 5.0744)\ \text{WTPT-2} - 0.6782\ (\pm\ 0.1602)\ \text{L3e} + 123.7295\ (\pm\ 10.3664) \quad (1)$$

The contribution of both descriptors WTPT-2 and L3e towards activity is negative as shown by negative sign of their coefficients. Standardized coefficients of these parameters are -1.0544 and -0.3767 indicating more contribution of WTPT-2 than L3e to activity. For example, activity trend of compounds **1a**, **1b**, **1c**; **1e**, **1f**, **1g** and **1p**, **1q**, **1r** is **1a < 1b < 1c**; **1e < 1f < 1g** and **1p < 1q < 1r** while the reverse trend is followed by

TABLE-1
pMIC VALUES OF TARGET COMPOUNDS (**1a**–**1t**)



(**1a-1t**)

Compound	R_1	R_2	pMICsa	pMICec	pMICkp	pMICea	pMICca	pMICan
1a	H	H	0.5458	0.5458	0.5458	0.5458	0.8468	0.8468
1b	H	OCH_3	0.8824	0.8824	1.1831	0.8824	0.8824	1.1831
1c	H	NO_2	1.2000	0.8989	1.2000	1.2000	0.8989	1.2000
1d	H	Cl	0.8874	0.5864	0.8874	0.5864	0.8874	1.1884
1e	H	CH_3	0.5627	0.5627	0.5627	0.5627	0.8639	0.8639
1f	OCH_3	H	0.8824	0.8824	1.1831	0.8824	1.1831	1.1831
1g	OCH_3	OCH_3	1.2161	1.5171	1.2161	0.9154	1.2161	1.2161
1h	OCH_3	NO_2	1.2321	1.2321	1.5331	1.2321	1.5331	1.8416
1i	OCH_3	Cl	1.2211	1.2211	1.5214	0.9201	1.2211	1.5214
1j	OCH_3	CH_3	1.1993	1.1993	0.8979	0.8979	1.1993	1.5003
1k	NO_2	H	1.5017	1.2000	1.2000	0.8989	1.2000	1.5017
1l	NO_2	OCH_3	1.2321	1.2321	1.2321	0.9307	1.2321	1.2321
1m	NO_2	NO_2	1.8477	1.5482	1.5482	1.5482	1.8477	0.9144
1n	NO_2	Cl	1.5376	1.5376	1.2366	1.2366	1.2366	1.2366
1o	NO_2	CH_3	1.5157	1.2154	0.9144	0.9144	1.2154	0.9144
1p	CH_3	H	0.8639	0.8639	0.8639	0.8639	0.8639	1.4660
1q	CH_3	OCH_3	1.1993	1.1993	1.1993	0.8979	1.1993	1.1993
1r	CH_3	NO_2	1.5157	1.2154	1.5157	1.2154	1.2154	1.5157
1s	CH_3	Cl	1.2041	1.5045	1.2041	0.9027	1.2041	1.5045
1t	CH_3	CH_3	0.8801	0.8801	1.1811	0.8801	1.1811	1.1811

TABLE-2
CALCULATED DESCRIPTORS OF
TARGET COMPOUNDS (**1a–1t**)

Compd.	WTPT-2	L3e	ATS6m	RDF135v	piPC9
1a	2.035068	1.301889	4775.597	4.864069	5.857219
1b	2.028254	1.421883	5232.341	4.497687	5.931582
1c	2.021657	1.618824	5394.101	4.763690	6.033686
1d	2.028504	1.390776	5396.069	4.185389	5.876334
1e	2.028504	1.616271	5010.137	4.888152	5.876334
1f	2.028242	1.216993	5441.96	4.962116	5.931582
1g	2.022336	1.539906	5898.705	4.964133	6.000796
1h	2.016356	1.720267	6060.465	4.476971	6.096387
1i	2.022366	1.419320	6062.433	4.089443	5.949340
1j	2.022366	1.682614	5676.501	4.890646	5.949340
1k	2.021644	1.229298	5575.866	4.856389	5.966788
1l	2.016355	1.980989	6032.611	3.953865	6.033686
1m	2.010749	1.547128	6194.371	4.799765	6.126323
1n	2.016184	1.309783	6196.339	4.529647	5.983936
1o	2.016184	1.559795	5810.407	5.078799	5.983936
1p	2.028501	1.258420	5163.992	5.443979	5.913503
1q	2.022374	1.543196	5620.736	5.603666	5.983936
1r	2.016193	1.529523	5782.497	5.258523	6.081077
1s	2.022406	1.338402	5784.464	4.804259	5.931582
1t	2.022406	1.581626	5398.532	5.219110	5.931582

values of WTPT-2 parameter. WTPT-2 is a 2D descriptor defined by Molecular ID/number of atoms [31] while L3e is a 3D WHIM descriptor described as 3rd component size directional WHIM index/weighted by Sanderson electronegativity [32].

QSAR model for antibacterial activity against *E. coli*: The following equation shows the QSAR model for activity against *E. coli*:

$$\text{pMICec} = 0.0008\ (\pm\ 0.0001)\ \text{ATS6m} + 0.2573\ (\pm\ 0.0928)\ \text{RDF135v} - 4.5902\ (\pm\ 0.7822) \quad (2)$$

Sign of coefficients of both parameters, ATS6m and RDF135v, is positive signifying positive contribution of both variables in determination of the activity. The values of standardized coefficients of ATS6m and RDF135v are 1.001 and 0.31, respectively. This proves the higher involvement of ATS6m towards activity. For example, compound **1m** is most active followed by **1h**, **1r** and **1c**. The value of ATS6m also decreases in the same order. ATS6m is a 2D autocorrelation descriptor expressed as Broto-Moreau autocorrelation of lag 6 (log function) weighted by mass [33] while RDF135v is a RDF descriptors termed as Radial Distribution Function - 135/weighted by van der Waals volume [34].

QSAR model for antibacterial activity against *E. aerogenes*: The activity against *E. aerogenes* was explained by following monoparametric QSAR equation:

$$\text{pMICea} = 2.99873\ (\pm\ 0.37567)\ \text{piPC9} - 16.96108\ (\pm\ 2.2426) \quad (3)$$

The positive sign of coefficient of piPC9 illustrates direct correlation of this parameter with the activity. For example, the order of activities as well as piPC9 values of compounds **1c**, **1h**, **1m** and **1r** is same *i.e.* **1m > 1h > 1r > 1c**. piPC9 is a path count descriptor stated as conventional bond order ID number of order 9 (ln(1+x)) [35].

The values of different statistical parameters calculated for these QSAR models are exhibited in Table-3. It can be observed that the developed models have good fitting ability with high values of coefficient of determination R^2 and adjusted R^2. To test the chance correlation, y-randomization process was applied and the results show that the developed models are free from chance correlation. The internal predictive power of the models was assessed by LOO technique and high values of Q^2 for all the models confirmed good internal prediction ability of the described QSAR models. The true predictive ability of a model can be judged only by external evaluation and this task was achieved by predicting the activity of a test set. Different approaches were used for accomplishing this task as proposed by Gramatica and Sangion [36]. Values of all the external validation parameters like R^2_{ext}, RMSEP, Q^2_{f1}, Q^2_{f2}, Q^2_{f3}, are in good range showing good external predictive capability of the models. Further, the external predictive ability was also checked according to R^2_m criteria (after scaling) suggested by Roy *et al.* [37] and other criteria proposed by Golbraikh and Tropsha [38,39]. The above discussed QSAR

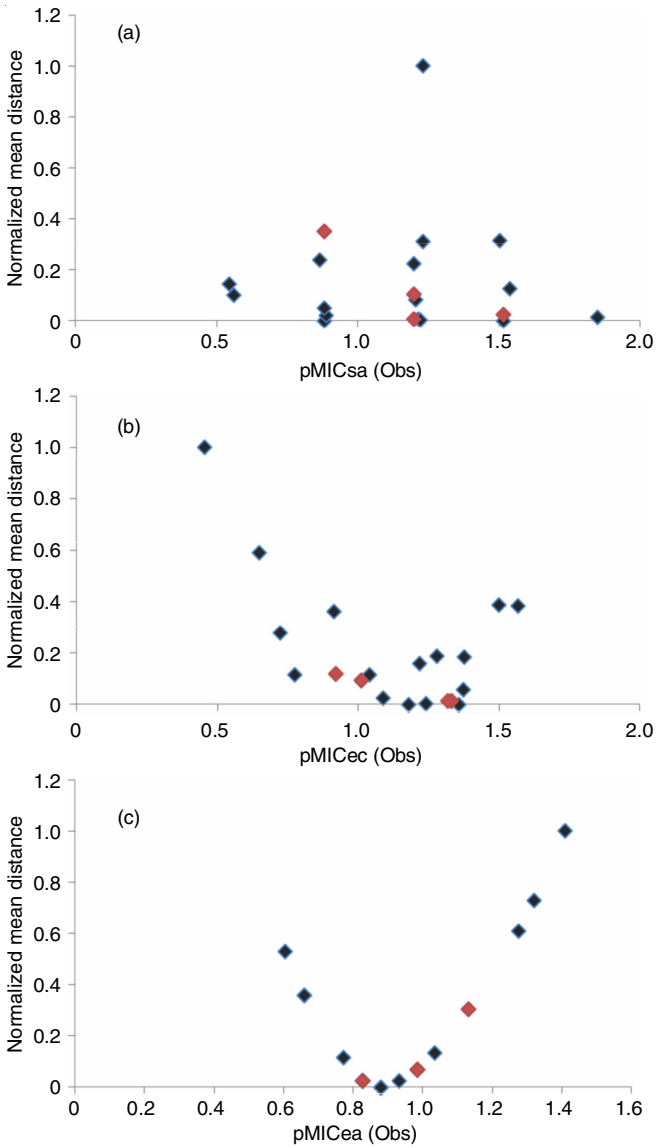


Fig. 1(a–c). Euclidean based applicability domain of QSAR models plot (black dots: training compounds, red dots: test compounds)

TABLE-3
STATISTICAL CHARACTERISTICS OF THE DEVELOPED QSAR MODELS

Statistical parameter	Eqn. 1	Eqn. 2	Eqn. 3	Statistical parameter	Eqn. 1	Eqn. 2	Eqn. 3
R^2	0.9157	0.8613	0.8199	Q^2_{f3}	0.9410	0.9030	0.9256
Adj-R^2	0.9027	0.8399	0.8070	RMSEP(test)	0.0843	0.1051	0.0703
PRESS	0.1626	0.2529	0.1910	CCC	0.9164	0.8367	0.8297
SEE	0.1118	0.1395	0.1168	Av. R^2_m(LOO)	0.8297	0.7282	0.6748
F	70.5667	40.3575	63.7182	ΔR^2_m(LOO)	0.0572	0.0951	0.1536
cR^2p	0.8664	0.8076	0.7958	Av. R^2_m(test)	0.8298	0.7241	0.6014
Q^2_{loo}	0.8776	0.7998	0.7607	ΔR^2_m(test)	0.0841	0.0764	0.1496
R^2_{ext}	0.8947	0.9564	0.7169	$\lvert R^2_0 - R'^2_0 \rvert$	0.0448	0.0049	0.1367
R^2_0	0.8847	0.9506	0.7161	K	1.0309	0.9146	0.9927
R'^2_0	0.8398	0.9555	0.5795	$(R^2-R^2_0)/R^2$	0.0112	0.0061	0.0010
Q^2_{f1}	0.8659	0.6139	0.7321	K'	0.9663	1.0922	1.0023
Q^2_{f2}	0.8581	0.5604	0.7131	$(R^2-R'^2_0)/R^2$	0.0614	0.0009	0.1917

models pass all these recommended tests. The Euclidean based applicability domain [40] was also calculated for all the compounds and is shown in Fig. 1(a-c). It can be clearly seen that all the training and test compounds fall in the applicability domain. The plots between observed *vs*. predicted activity and residuals *vs*. predicted activity are shown in Fig. 2(a-f). Observed and predicted activities along with residuals are shown in Table-4.

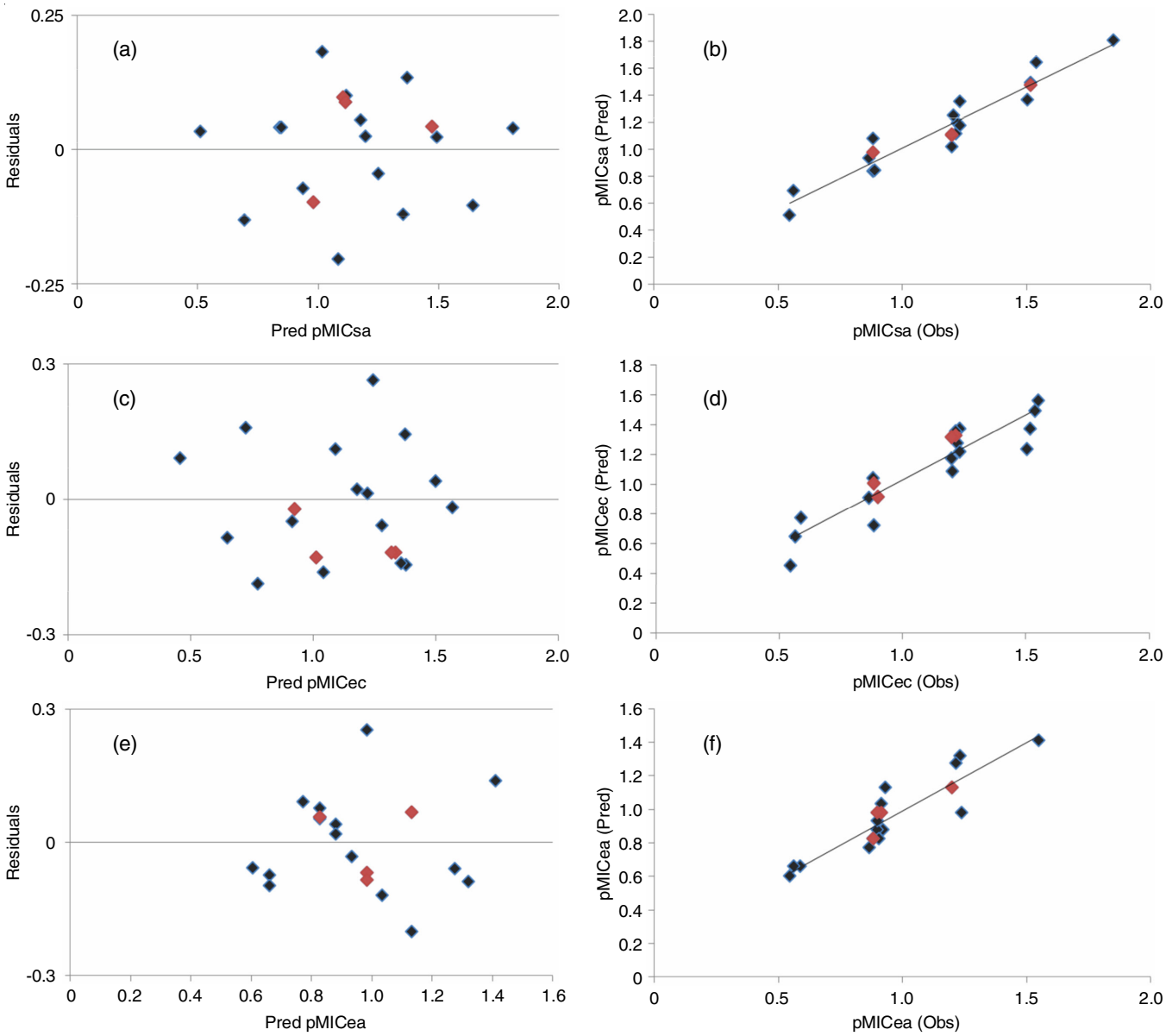


Fig. 2(a–f). Plot between residuals *vs*. predicted activity and observed *vs*. predicted activity and for the described QSAR models (black dots: training compounds, red dots: test compounds)

TABLE-4
OBSERVED AND PREDICTED ACTIVITIES OF THE COMPOUNDS (**1a–1t**) ALONG WITH RESIDUALS

Compound	pMICsa			pMICec			pMICea		
	Observed	Predicted	Residual	Observed	Predicted	Residual	Observed	Predicted	Residual
1a	0.5458	0.5121	0.0337	0.5458	0.4551	0.0906	0.5458	0.6032	-0.0574
1b	0.8824	0.8403	0.0420	0.8824	0.7237	0.1587	0.8824	0.8262	0.0562
1d	0.8874	0.8464	0.0410	0.5864	0.7734	-0.1870	0.5864	0.6605	-0.0741
1e	0.5627	0.6934	-0.1307	0.5627	0.6476	-0.0849	0.5627	0.6605	-0.0978
1g	1.2161	1.1160	0.1001	1.5171	1.3731	0.1440	0.9154	1.0337	-0.1183
1h	1.2321	1.3532	-0.1211	1.2321	1.3762	-0.1441	1.2321	1.3204	-0.0883
1i	1.2211	1.1960	0.0251	1.2211	1.2781	-0.0569	0.9201	0.8794	0.0407
1j	1.1993	1.0175	0.1818	1.1993	1.1777	0.0216	0.8979	0.8794	0.0185
1k	1.5017	1.3683	0.1334	1.2000	1.0889	0.1111	0.8989	0.9317	-0.0328
1l	1.2321	1.1764	0.0557	1.2321	1.2195	0.0126	0.9307	1.1323	-0.2016
1m	1.8477	1.8077	0.0400	1.5482	1.5657	-0.0174	1.5482	1.4101	0.1381
1n	1.5376	1.6419	-0.1043	1.5376	1.4977	0.0399	1.2366	0.9832	0.2534
1p	0.8639	0.9363	-0.0724	0.8639	0.9129	-0.0490	0.8639	0.7719	0.0920
1r	1.5157	1.4923	0.0234	1.2154	1.3565	-0.1411	1.2154	1.2745	-0.0591
1s	1.2041	1.2485	-0.0444	1.5045	1.2412	0.2633	0.9027	0.8262	0.0766
1t	0.8801	1.0835	-0.2035	0.8801	1.0414	-0.1613	0.8801	0.8262	0.0539
1c*	1.2000	1.1033	0.0966	0.8989	0.9206	-0.0217	1.2000	1.1323	0.0676
1f*	0.8824	0.9800	-0.0976	0.8824	1.0097	-0.1273	0.8824	0.8262	0.0562
1o*	1.5157	1.4724	0.0433	1.2154	1.3324	-0.1171	0.9144	0.9832	-0.0688
1q*	1.1993	1.1115	0.0878	1.1993	1.3168	-0.1175	0.8979	0.9832	-0.0853

*Test compounds

Conclusion

QSAR study was performed on 20 triazole derivatives with ester linkage for their antimicrobial activity. Different statistically significant multi-parametric QSAR models free from chance correlation, good fitting ability with high values of coefficient were developed for *S. aureus*, *E. coli* and *E. aerogenes*. Results of QSAR studies revealed that antimicrobial activity against Gram positive bacteria *i.e. S. aureus* were governed by WHIM descriptor weighted by Sanderson electronegativity while, antimicrobial activity against Gram negative bacteria *i.e. E. coli* and *E. aerogenes* were governed by RDF descriptor weighted by van der Waals volume and piPC9 descriptor, respectively.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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