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QSAR STUDIES OF ANTIBACTERIAL RICINOLEIC ACID DERIVATIVES

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A series of ricinoleic acid derivatives have been synthesized and tested for antibacterial activity with respect to four standard strains. Dibromoricinoleic acid (DBRA) showed high activity comparable with that of the reference drug ciprofloxacin. QSARs between various physicochemical indices and the antibacterial activity of a training set including 12 compounds were analyzed. The topological parameter, the valence second-order molecular connectivity index ($^2\chi^v$), and the electronic parameter of total energy (TE) proved to be important for the antibacterial activity of compounds studied. The proposed QSAR models were validated using the leave-one-out procedure. The validity of these models was confirmed by predicting the activity of a set of three compounds (not present in the training set).

The importance of acids as antimicrobial drugs is well established in pharmaceutical chemistry. Previously, we reported on the antimicrobial activity of simple organic acids such as sorbic, cinnamic, ricinoleic, and myristic [1 – 3]. Ricinoleic acid [*R* (*Z*)-12-hydroxy-9-octadecanoic acid] is a major component of castor oil [4]. Previous reports delineate the laxative [5 – 6], analgesic, and antiinflammatory [7] activity of this compound. The antibacterial potential of ricinoleic acid was reported by Lin et al. [8].

In continuation of our previous studies on the quantitative structure – activity relationships (QSARs) of antimicrobial acid derivatives [2], the present paper reports on the

Scheme 1. Synthesis of ricinoleic acid derivatives (**R-1** to **R-15**).

relationship between structure and antibacterial activity of ricinoleic acid derivatives. The esters and amides of ricinoleic acid were prepared using a method described previously [2], followed by their *in vitro* antibacterial screening. The proposed structures of newly synthesized compounds were confirmed by spectroscopic measurements. In the present study, we have used linear regression analysis for modeling antibacterial activity of ricinoleic acid derivatives.

EXPERIMENTAL CHEMICAL PART

The melting and boiling points reported in the present study are uncorrected. The IR spectra were recorded with a Shimadzu FTIR 8000 spectrophotometer as KBr discs in case of solid substances and as thin film in case of liquid samples. The ^{1}H NMR spectra in $CDCl_3$ were recorded on a Bruker AC 300F NMR spectrometer using TMS as the internal standard. Elemental analyses for C and H were performed using a Vario-EL instrument. Ricinoleic acid derivatives were synthesized according to Scheme 1. The purity of the synthesized compounds was confirmed by single spot TLC patterns, where the mobile phase was benzene and the stationary phase was silica gel G (chromatography grade).

General procedure for the synthesis of esters. Esters were derived from ricinoleic acid, which was prepared by alkaline hydrolysis of castor oil [9]. The appropriate alcohol (0.74 mole) was charged into a round bottom flask containing ricinoleic acid (17.4 g, 0.06 mole) and sulfuric acid (2 ml). The solution was refluxed until the completion of reaction. The reaction mixture was poured into 200 ml of ice-cold water, the oily layer was separated and extracted with ether, and then ether was evaporated to yield a pure target product. Esters **R-2** to **R-7** and **R-9** (Table 1) included in the present study were prepared using this method.

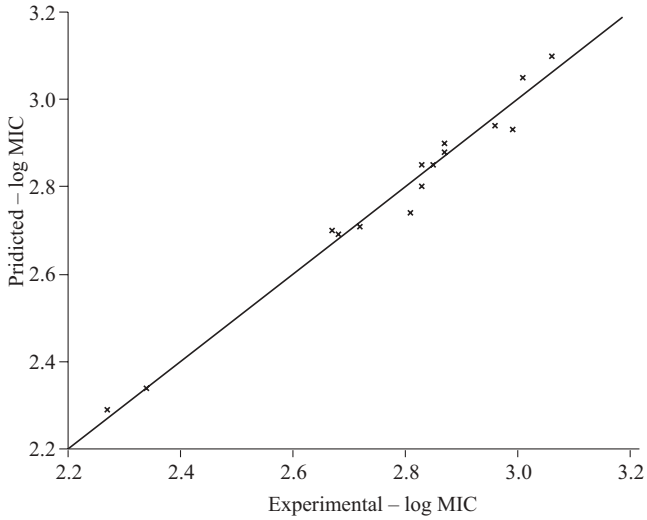

Fig. 1. Plot of the predicted –logMIC values against experimental — logMIC values for the QSAR model described by Eq. (1) for *S. aureus*.

General procedure for the synthesis of amides. Ricinoleic acid chloride was prepared via the reaction of ricinoleic acid with thionyl chloride. A solution of the corresponding amine (0.1 mole) in ether (50 ml) was added dropwise to the solution of acid chloride (0.06 mole) in ether (50 ml) and the mixture was stirred for 30 min. Then, the solvent was evaporated to yield the target amide. All

Table 1

Physicochemical Characteristics of Ricinoleic Acid Derivatives

CH_3-$(CH_2)_5$-CH(OH)-CH_2-CH=CH-$(CH_2)_7$-COOR (**R-1** – **R-7**, **R-11**, **R-13**, **R-14**)
CH_3-$(CH_2)_5$-CH(OH)-CH_2-CH(Br)-CH(Br)-$(CH)_7$-COOR (**R-10**)
CH_3-$(CH_2)_5$-CH(OH)-CH_2-CH=CH-$(CH_2)_7$-COR (**R-12**, **R-15**)

Compound	R	Empirical formula	MW	B.p., °C	R_f (benzene)	Yield, %
		Training set				
R-1	H	$C_{18}H_{34}O_3$	298.52	243 – 245	0.41	95
R-2	Me	$C_{19}H_{36}O_3$	312.55	97 – 99	0.58	66
R-3	Et	$C_{20}H_{38}O_3$	326.58	217 – 219	0.64	69
R-4	*n*-Pr	$C_{21}H_{40}O_3$	340.61	282 – 284	0.67	82
R-5	*i*-Pr	$C_{21}H_{40}O_3$	340.61	262 – 264	0.61	69
R-6	*n*-Bu	$C_{22}H_{42}O_3$	354.64	151 – 153	0.59	70
R-7	Isoamyl	$C_{23}H_{44}O_3$	368.67	217 – 219	0.69	77
R-8	$HOOC(CH_2)_7COOH$	$C_9H_{16}O_4$	188.25	103 – 105*	0.15	20
R-9	$H_3COOC(CH_2)_7COOCH_3$	$C_{11}H_{20}O_4$	216.31	138 – 140	0.38	62
R-10	DBRA***	$C_{18}H_{34}O_3Br_2$	458.32	117 – 119	0.56	75
R-11	Ph	$C_{24}H_{38}O_3$	374.62	93 – 95	0.29**	58
R-12	NH_2	$C_{18}H_{35}O_2N$	297.54	65 – 67	0.15**	46
		Prediction set				
R-13	*n*-octyl	$C_{26}H_{50}O_3$	410.76	186 – 188	0.71	76
R-14	CH_2Ph	$C_{25}H_{40}O_3$	388.65	105 – 107	0.35**	58
R-15	NH–Ph	$C_{24}H_{39}O_2N$	373.64	72 – 74	0.32**	22

* m.p. ** TLC mobile phase: benzene – petroleum ether (1 : 1); *** DBRA = dibromoricinolenic acid.

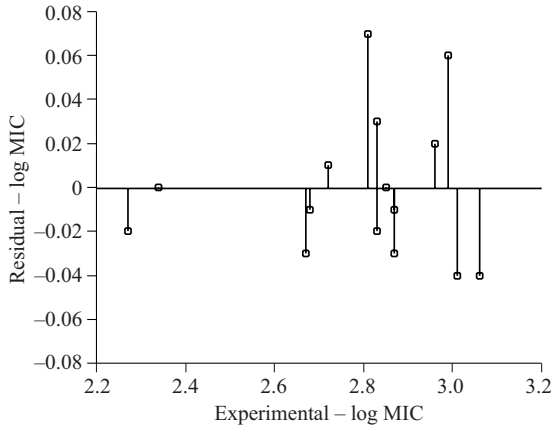

Fig. 2. Plot of the residual –logMIC values against experimental –logMIC values for the QSAR model described by Eq. (1) for *S. aureus*.

amides presented in Table 1 were prepared using this method.

Analytical data for compound **R-3**: b.p., 217 – 219°C; Yield, 69%; IR spectrum (ν_{max}, cm^{-1}): 3422 (OH), 1736 (C=O), 1655 (CH=CH); ^1H NMR spectrum in $CDCl_3$ (δ, ppm): 0.83 (m, 2H, $CH_3CH_2CH_2$), 5.40 – 5.50 (dd, 1H, CH=CH, J_{cis} 7.19 Hz), 3.53 (q, 1H, CH-OH), 1.93 (m, 2H, CH_2-CH=CH), 1.19 (m, 2H, $CH_2CH_2CH_2$), 4.03 (q, 2H, $COOCH_2CH_3$); Found (%): C, 73.53; H, 11.68; for $C_{20}H_{38}O_3$ anal. calcd. (%): C, 73.57; H, 11.72.

Analytical data for compound **R-4**: b.p., 282 – 284°C; Yield, 82%; IR (ν_{max}, cm^{-1}): 3367 (OH), 1736 (C=O), 1654 (CH=CH); ^1H NMR spectrum in $CDCl_3$ (δ, ppm): 0.96 (t, 3H, CH_3), 1.68 (m, 2H, $OCH_2CH_2CH_3$), 5.27 – 5.32 (dd, 1H, CH=CH, J_{cis} 6.47 Hz), 2.01 (s, H, OH), 1.9 – 2.2 (m, 2H, $CH_2CH_2CH_2$), 4.04 (t, 2H, $OCH_2CH_2CH_3$); Found (%): C, 74.01, H, 11.78; for $C_{21}H_{40}O_3$ anal. calcd. (%): C, 74.07; H, 11.84.

Table 2

***In vitro* Antibacterial Activity of Synthesized Ricinoleic Acid Derivatives**

Compound	–logMIC**			
	S. aureus	*B. Subtilis*	*M. luteus*	*P. aeruginosa*
	Training set			
R-1	2.68	2.68	2.98	2.60
R-2	2.72	2.70	2.80	2.70
R-3	2.81	2.81	2.91	2.71
R-4	2.83	2.83	3.04	2.75
R-5	2.83	2.93	3.04	2.83
R-6	2.85	2.95	3.06	2.85
R-7	2.96	2.87	3.08	2.79
R-8	2.27	2.10	2.27	2.18
R-9	2.34	2.16	2.34	2.34
R-10	3.06	3.06	3.06	3.06
R-11	2.87	2.97	3.08	2.87
R-12	2.67	2.60	2.77	2.60
	Prediction set			
R-13	3.01	3.12	3.01	2.91
R-14	2.99	2.99	2.99	2.89
R-15	2.87	2.97	3.08	2.79
S*	3.33	3.33	3.33	3.33

* Reference drug (ciprofloxacin).
** MIC values in μM.

EXPERIMENTAL BIOLOGICAL PART

The *in vitro* antibacterial activity of the synthesized compounds was tested against *S. aureus*, *B. subtilis*, *M. luteus* and *P. aeruginosa* using the conventional serial dilution technique [10] in double strength nutrient broth-I.P. as a medium [11]. Initially, ricinoleic acid derivatives were dissolved in DMSO to a concentration of 10 μg/ml (stock solution).

EXPERIMENTAL QSAR PART

In an attempt to determine the role of structural features, QSAR studies were undertaken using the linear free energy relationship (LFER) model of Hansch and Fujita [12]. Biological activity data expressed in terms of the minimum inhibiting concentration (MIC) values were first converted into –logMIC on molar basis, which was used as a dependent variable in the QSAR study. These values were correlated with various molecular descriptors [12 – 13] representing logarithms of octanol – water partition coefficient (log*P*), molar refractivity (MR), Kiers' molecular connectivity ($^2\chi^v$) and shape topological indices (κ_1, $\kappa\alpha_1$), Randić's topological index (R), Balban's topological index (J), Wiener's topological index (W), total energy (TE), energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), dipole moment (μ), electronic energy (ElE), nuclear energy (NuE) and molecular surface area (SA). The values of these descriptors are presented in Table 3.

In the present work, a training set comprising 12 molecules (**R-1** to **R-12**) was used for linear regression model generation, and a prediction set consisting of 3 molecules (**R-13** to **R-15**) was used for the evaluation of the generated linear regression model. The molecular descriptors of ricinoleic acid derivatives were calculated and the regression analysis was carried out using the TSAR 3D (version 3.3) molecular package [14].

RESULTS AND DISCUSSION

The structures of the synthesized compounds were characterized using spectroscopic and analytical measurements, and these data were found to agree with the assigned molecular structures. Physicochemical parameters and molecular structures of the ricinoleic acid derivatives used in the present study are given in Table 1. All the reported compounds exhibited comparable *in vitro* activity against the bacterial strains tested in comparison to the reference drug ciprofloxacin (S) (Table 2). In general, the antimicrobial properties of the tested compounds follow the pattern (in the order of decreasing activity)

M. luteus > *B. subtilis* > *S. aureus* > *P. aeruginosa*

A thorough analysis of screening results revealed that dibromoricinoleic acid (DBRA) exhibited strong antibacterial activity. It should be noted that the removal of a do-

Table 3

Values of Selected Descriptors Used in the Linear Regression Analysis

Compound	log*P*	MR	$^2\chi^v$	κ_1	$\kappa\alpha_1$	R	TE	μ	ElE	NuE	SA
R-1	5.09	89.07	5.91	21.00	20.33	10.16	–3738.27	2.18	–24378.30	20640.00	433.52
R-2	5.12	93.84	6.09	22.00	21.33	10.70	–3893.52	1.84	–26057.60	22164.10	456.40
R-3	5.46	98.59	6.32	23.00	22.33	11.20	–4049.31	1.63	–27698.70	23649.40	476.05
R-4	5.93	103.11	6.74	24.00	23.33	11.70	–4205.14	1.79	–29349.00	25143.80	501.32
R-5	5.87	103.01	7.06	24.00	23.33	11.56	–4205.02	2.13	–29619.80	25414.70	499.62
R-6	6.33	107.71	7.09	25.00	24.33	12.20	–4360.97	1.61	–30960.60	26599.60	520.10
R-7	6.73	112.19	7.71	26.00	25.33	12.60	–4516.63	1.81	–33224.40	28707.80	538.24
R-8	1.61	46.54	3.06	13.00	12.26	6.13	–2657.44	3.35	–12812.00	10154.60	249.18
R-9	1.67	56.08	3.42	15.00	14.26	7.20	–2967.94	3.33	–15767.20	12799.30	294.34
R-10	5.89	103.01	8.88	23.00	23.55	10.97	–4445.74	1.54	–29590.70	25145.00	479.39
R-11	6.80	113.62	7.30	25.04	23.59	13.22	–4560.12	2.39	–32790.10	28230.00	517.83
R-12	4.22	90.89	5.98	21.00	20.33	10.16	–3638.27	2.01	–24187.10	20548.90	434.71
R-13	7.91	126.12	8.50	29.00	28.33	14.20	–4984.31	0.41	–37469.00	32484.60	612.24
R-14	6.89	118.45	7.66	26.04	24.59	13.72	–4716.25	0.88	–34272.90	29556.60	536.40
R-15	6.15	115.57	7.43	25.04	23.59	13.22	–4460.71	2.69	–32480.70	28020.00	517.91
S*	1.32	86.49	6.37	17.42	15.59	11.56	–4489.90	7.81	–31141.00	26635.00	341.75

* Reference drug (ciprofloxacin).

uble bond in the structure of ricinoleic acid by addition of bromine caused remarkable increase in the antibacterial activity, which is similar to the case of dibromocinnamic acid used in our previous study [2]. The synthesized compounds showed remarkable increase in the antibacterial activity as compared to that of the parent ricinoleic acid. However, the low antibacterial activity observed in case of azelaic acid (**R-8**, a saturated acid derived from ricinoleic acid and its dimethyl ester **R-9**), indicates that the removal of unsaturation leads to a decrease in the antibacterial activity.

It is also important to note that the presence of halogen in the structure may improve the antimicrobial activity. This fact was supported by the presence of a halogen atom (fluorine) in the structure of ciprofloxacin. The most active compound DBRA (**R-10**) is lacking in the aromatic ring when compared to the structure of ciprofloxacin, which may account for its lower activity in comparison to the standard drug. Similarly, the absence of halogen in the structure of phenyl and benzyl esters (**R-11**, **R-14**) and anilide (**R-15**) of ricinoleic acid may be responsible for their low activity in comparison to that of ciprofloxacin, even though these compounds contain the aromatic ring.

The reference drug ciprofloxacin was not included in QSAR model generation because it belongs to a different structural series. A correlation matrix (Table 4) was constructed to find the interrelationship among the parameters, which shows that each parameter selected in the study is highly correlated with the other ($r > 0.8$). Any combination of these descriptors in multiple regression analysis may result in a model suffering form the high interrelationship between the parameters. Even though the sample size and the 'Rule of Thumb' allowed us to go up to a maximum of biparametric model in multiple linear regression analysis, the high interrelationship between the parameters restricted the consideration to a monoparametric model.

Table 4

Correlation Matrix for Ricinoleic Acid Derivatives against *S. aureus*

	–logMIC	log*P*	MR	$^2\chi^v$	κ_1	$\kappa\alpha_1$	R	J	W	TE	LUMO	HOMO	μ	ElE	NuE	SA
–logMIC	1.000															
Log*P*	0.942	1.000														
MR	0.947	0.987	1.000													
$^2\chi^v$	0.993	0.922	0.929	1.000												
κ_1	0.934	0.985	0.995	0.908	1.000											
$\kappa\alpha_1$	0.962	0.981	0.991	0.941	0.994	1.000										
R	0.905	0.982	0.991	0.880	0.989	0.972	1.000									
J	0.120	–0.082	–0.071	0.114	–0.032	0.054	–0.176	1.000								
W	0.851	0.957	0.955	0.825	0.959	0.930	0.982	–0.274	1.000							
TE	–0.971	–0.982	–0.983	–0.956	–0.976	–0.981	–0.972	0.059	–0.945	1.000						
LUMO	–0.289	–0.201	–0.172	–0.347	–0.090	–0.106	–0.167	0.477	–0.181	0.279	1.000					
HOMO	0.691	0.833	0.856	0.654	0.865	0.832	0.863	–0.103	0.808	–0.753	0.180	1.000				
μ	–0.883	–0.832	–0.850	–0.855	–0.850	–0.886	–0.790	–0.356	–0.692	0.821	–0.036	–0.761	1.000			
ElE	–0.950	–0.989	–0.994	–0.931	–0.993	–0.989	–0.989	0.077	–0.968	0.993	0.192	–0.812	0.820	1.000		
NuE	0.947	0.989	0.994	0.927	0.994	0.989	0.990	–0.079	0.969	–0.991	–0.183	0.817	–0.819	–1.000	1.000	
SA	0.937	0.984	0.995	0.912	0.999	0.995	0.986	–0.015	0.950	–0.974	–0.085	0.870	–0.862	–0.991	0.992	1.000

Table 5

Observed and Predicted Antibacterial Activity of Ricinoleic Acid Derivatives against bacterial species using the best model

Compound	For *S. aureus* using Eq. 1			*P. aeruginosa* using Eq. 2			*M. luteus* using Eq. 4			*B. subtilis* using Eq. 5		
	Obs.	Calc.	Res.	Obs.	Calc.	Res.	Obs.	Calc.	Res.	Obs.	Calc.	Res.
						Training set						
R-1	2.68	2.69	–0.01	2.60	2.63	–0.03	2.98	2.83	0.15	2.68	2.65	0.03
R-2	2.72	2.71	0.01	2.70	2.66	0.04	2.80	2.86	–0.06	2.70	2.72	–0.02
R-3	2.81	2.74	0.07	2.71	2.69	0.02	2.91	2.91	0.00	2.81	2.80	0.01
R-4	2.83	2.80	0.03	2.75	2.75	0.00	3.04	2.99	0.05	2.83	2.88	–0.05
R-5	2.83	2.85	–0.02	2.83	2.80	0.03	3.04	3.05	–0.01	2.93	2.88	0.05
R-6	2.85	2.85	0.00	2.85	2.80	0.05	3.06	3.06	0.00	2.95	2.96	–0.01
R-7	2.96	2.94	0.02	2.79	2.89	–0.10	3.08	3.18	–0.1	2.87	3.03	–0.16
R-8	2.27	2.29	–0.02	2.18	2.23	–0.05	2.27	2.27	0.00	2.10	2.10	0.00
R-9	2.34	2.34	0.00	2.34	2.28	0.06	2.34	2.34	0.00	2.16	2.26	–0.10
R-10	3.06	3.10	–0.04	3.06	3.05	0.01	3.06	3.10	0.04	3.06	3.00	0.06
R-11	2.87	2.88	–0.01	2.87	2.83	0.04	3.08	3.10	–0.02	2.97	3.06	–0.09
						Prediction set						
R-12	2.67	2.70	–0.03	2.60	2.64	–0.04	2.77	2.84	–0.07	2.60	2.60	0.00
R-13	3.01	3.05	–0.04	2.91	3.00	–0.09	3.01	2.93	0.08	3.12	3.27	–0.15
R-14	2.99	2.93	0.06	2.89	2.88	0.01	2.99	3.17	–0.18	2.99	3.13	–0.14
R-15	2.87	2.90	–0.03	2.79	2.85	–0.06	3.08	3.12	–0.04	2.97	3.01	–0.04

We can conclude that, among all monoparametric models, the model based on the valence second-order molecular connectivity index ($^2\chi^v$) gives the best results for the antibacterial activity against *S. aureus*:

$$-\log MIC = 0.139\ ^2\chi^v + 1.866 \qquad (1)$$

with $n = 12$, $r = 0.992$, $r_{cv}^2 = 0.985$, $F = 661.72$, and $s = 0.029$. Here and below, n is the total number of compounds, r is the correlation coefficient, r_{cv}^2 is the cross-validated correlation coefficient obtained using the leave-one-out technique, F is Fisher's statistics, and s is the standard error of estimation. The coefficient at $^2\chi^v$ in the mono-parametric model described by Eq. (1) is positive, which indicates that the antibacterial activity of ricinoleic acid derivatives against *S. aureus* is directly proportional to the magnitude of $^2\chi^v$ (the antibacterial activity increases with the $^2\chi^v$ value). This is evidenced by the data on $^2\chi^v$ in Table 3, where the values of $^2\chi^v$ for DBRA (**R-10**, $^2\chi^v = 8.88$) and isoamyl ricinoleate (**R-7**, $^2\chi^v = 7.71$) are higher than those for other compounds in the training set. Thus, **R-10** and **R-7** are the most active compounds against *S. aureus*. Similarly, compounds **R-8** and **R-9** are characterized by the minimum $^2\chi^v$ values (3.06 and 3.42, respectively) and, accordingly, have minimum activity.

It is noteworthy that compound **R-3** (ethyl ricinoleate) having $^2\chi^v = 6.32$, which is close to the index of ciprofloxacin, (the reference drug with $^2\chi^v = 6.37$) is more potent than the parent ricinoleic acid and less potent than DBRA (**R-10**). It is probably due to the fact compound **R-3** is lacking in halogen groups.

Apart from $^2\chi^v$, the electronic parameter of total energy (TE) also showed good correlation with the activity against *S. aureus* ($r = 0.970$). The value of TE for DBRA (TE = –4445.79) is closer to the value of ciprofloxacin (TE = –4489.90) than the TE values of other compounds in the training set, which also makes DBRA the most active compound in the training set.

In order to confirm our results, we have synthesized a prediction set consisting of three ricinoleic acid derivatives (**R-13** to **R-15**), predicted their antibacterial activity using the model described by Eq. (1), and compared the results with the observed values. We have also applied the same model to predict the activity of compounds in the training set. The data presented in Table 5 show that the observed and the estimated activities are very close to each other, as evidenced by low values of residues. A linear regression plot of the predicted –logMIC values against observed –logMIC values (Fig. 1) also favors the model described by Eq. (1). To investigate the existence of a systematic error in developing the linear regression model, the residuals of linear regression predicted values of –logMIC were plotted against the experimental –logMIC values (Fig. 2). The spreading of residues on both sides from zero indicates that no systematic error exists in the proposed linear regression model.

In comparison to *S. aureus*, the ricinoleic acid derivatives are less effective against *P. aeruginosa*. The QSAR study indicated that the $^2\chi^v$ was also the parameter providing highly significant statistical equation among the monoparametric models describing the antibacterial activity against *P. aeruginosa*:

$$-\log MIC = 0.141\ ^2\chi^v + 1.801, \qquad (2)$$

with $n = 12$, $r = 0.979$, $r_{cv}^2 = 0.932$, $F = 232.66$, and $s = 0.051$. This result shows that the antibacterial activity against *P. aeruginosa* is similar to the case of *S. aureus*. By the same token, the electronic parameter of total energy is another parameter that gives a good (next to $^2\chi^v$) monoparametric model for the antibacterial activity against *P. aeruginosa*:

$$-\log MIC = 0.0004\ Te + 1.206, \quad (3)$$

with $n = 12$, $r = 0.955$, $r^2_{cv} = 0.875$, $F = 104.16$, and $s = 0.074$.

The ricinoleic acid derivatives under consideration are also highly effective against *M. luteus*. The QSAR study indicates that the $^2\chi^v$ descriptor provides a statistically significant monoparametric model. This model is expressed by the following equation describing the antibacterial activity against *M. luteus*:

$$-\log MIC = 0.195\ ^2\chi^v + 1.674, \quad (4)$$

with $n = 12$, $r = 0.979$, $r^2_{cv} = 0.946$, $F = 232.54$, and $s = 0.070$. Here, the positive coefficient at $^2\chi^v$ indicates that the antibacterial activity of ricinoleic acid derivatives against *M. luteus* is directly proportional to the magnitude of $^2\chi^v$. The best fit of the model expressed by Eq. 4 is confirmed by low values of the residue (Table 5).

In the case of *B. subtilis*, the maximum correlation ($r = 0.976$) among various monoparametric models was observed for the model based on TE:

$$-\log MIC = -0.0005\ TE + 0.776, \quad (5)$$

with $n = 12$, $r = 0.976$, $r^2_{cv} = 0.980$, $F = 201.54$, and $s = 0.070$. Here, the best fit of the above linear regression model is also evidenced by the lowest value of residues (Table 5). The monoparametric model employing $^2\chi^v$ gives equally good results:

$$-\log MIC = 0.179\ ^2\chi^v + 1.591, \quad (6)$$

with $n = 12$, $r = 0.970$, $r^2_{cv} = 0.908$, $F = 160.01$, and $s = 0.078$.

Nonlinear regression (NLR) was used to find out a relationship between log*P* and the antibacterial activity. The NLR with log*P* did not show any appreciable improvement in the correlation coefficient even though a marginal increase in the *r* value was observed.

From the results and discussion made above, we conclude that the ricinoleic acid derivatives are effective against Gram-positive rather than Gram-negative bacteria, *M. luteus* being the most sensitive microorganism among the bacterial species tested. The results of our *in vitro* antibacterial activity investigation showed that the DBRA (**R-10**) was the most effective antibacterial agent. The QSAR studies indicated that the topological parameter, the valence second-order molecular connectivity index ($^2\chi^v$), and the electronic parameter of total energy (TE) can be successfully used for modeling the antibacterial activity of ricinoleic acid derivatives against the bacterial species included in the present study. The contribution of topological and electronic descriptors in describing the antibacterial activity of acid derivatives was also evidenced by the results of our previous study [2]. The QSAR models were cross-validated by the high $^2\chi^v$ values obtained for the developed linear regression models using the leave-one-out technique, as well as by the low values of residues observed for compounds of the prediction set.

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ВЗАИМОСВЯЗЬ СТРУКТУРЫ И АНТИБАКТЕРИАЛЬНОЙ АКТИВНОСТИ ПРОИЗВОДНЫХ РИЦИНОЛЕИНОВОЙ КИСЛОТЫ

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Синтезирован ряд производных (эфиров и амидов) рицинолеиновой кислоты и исследована их антибактериальная активность в отношении четырех стандартных штаммов. Наибольшую активность (сравнимую с действием ципрофлоксацина) проявила дибромрицинолеиновая кислота. Анализ взаимосвязи структуры соединений и их антибактериальной активности (для обучающей выборки из 12 соединений) показал, что корреляция структуры и антибактериальных свойств лучше всего описывается однопараметрическими моделями на основе топологического параметра связности ($^2\chi^v$) и электронного параметра полной энергии (TE).