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Design, synthesis, antibacterial, and QSAR studies of myristic acid derivatives

Balasubramanian Narasimhan,[a] Vishnukant Mourya[b] and Avinash Dhake[c,*]

[a]*Department of Pharmaceutical Sciences, Guru Jambheshwar University, Hisar-125001, India*
[b]*Government College of Pharmacy, Aurangabad-431005, India*
[c]*L.B. Rao Institute of Pharmaceutical Education and Research, B.D. Rao College Campus, Khambhat- 388620, India*

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Abstract—A series of esters and amides of myristic acid was synthesized and tested in vitro for antibacterial activity against Gram-positive and Gram-negative bacteria. All the compounds showed activity comparable to that of the standard drug, ciprofloxacin. The structural characteristics governing antibacterial activity of myristic acid derivatives was studied using QSAR methodology. The results showed that the antibacterial activity could be modeled using the topological descriptor, valence molecular connectivity index. The predictive ability of the models was cross-validated by construction of a test set. The low residual activity and high cross-validated r^2 values (r^2_{cv}) observed indicated the predictive ability of the developed QSAR models.

In recent years, the number of life-threatening infections caused by multidrug-resistant Gram-positive and Gram-negative bacteria has reached an alarming level in many countries around the world.[1,2] The contribution of simple organic acids in prevention of bacterial infections[3] directed us to search for new antimicrobial acid compounds.

In previous papers,[4–6] we described the preparation and antibacterial properties of derivatives of simple organic acids viz. sorbic acid, cinnamic acid, ricinoleic acid, and anacardic acid. The antibacterial potential of myristic acid was studied by us[7] and others[8,9]. Literature reports show that myristoylation leads to anti-HIV[10] activity and modification of G-protein-mediated signal transduction.[11]

Quantitative structure–activity relationships (QSAR) have been employed, and continue to be developed and employed, both to correlate information in data sets and as a tool to facilitate the discovery of new molecules with increased biological potency.[12] A large number of such QSAR models have been developed for different biological properties.[13–17] Recently, we have reported the development of useful QSAR models for antibacterial[4,5] and anti-inflammatory activities.[18]

In view of the above, in the present paper we describe a QSAR analysis for the series of myristic acid derivatives for the first time. Hansch analysis correlates biological activity values with electronic, steric, and hydrophobic, influences of structural variance through linear regression analysis. Therefore, the structural homogeneity of the present series has allowed a classical Hansch approach. The changes in electronic, steric, hydrophobic, and other characteristics induced by the substituents were correlated with the antibacterial activity using appropriate descriptors.

Myristic acid separated from our previous study[7] was utilized for preparation of derivatives. The esters of myristic acid were prepared by the reaction of myristic acid with corresponding alcohols in the presence of sulfuric acid and the amides were prepared by the reaction of acid chloride of myristic acid with corresponding amines (Scheme 1) as described in our previous study.[4,5] The synthesized compounds were characterized by spectroanalytical studies and the data were found to be in agreement with those of the assigned molecular structures. The physicochemical parameters and molecular structures of the myristic acid derivatives used in the present study are given in Table 1.

Keywords: Myristic acid; Antibacterial activity; QSAR; MLR; (r^2_{cv}).
* Corresponding author. Tel.: +91 2698 223455; fax: +91 2698 226637; e-mail: asdhake@yahoo.co.in

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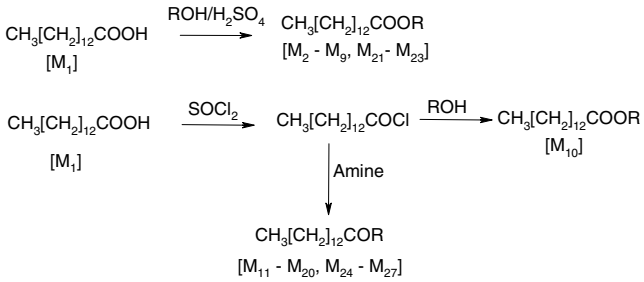

Scheme 1. Scheme for synthesis of myristic acid derivatives (**M-2**–**M-27**).

The newly obtained derivatives were evaluated for in vitro antibacterial activity against Gram-positive *Staphylococcus aureus*, *Micrococcus luteus*, and Gram-negative *Escherichia coli*. Double strength nutrient broth-I.P.[19] was employed for bacterial growth. Minimal inhibitory concentrations were determined by means of standard serial dilution method[20] and the −log MIC values are presented in Table 2. All of the reported compounds exhibited comparable in vitro activity against the tested bacterial strains compared to reference ciprofloxacin (S). In general, antimicrobial activity of the tested compounds follows the pattern:

$$S.\ aureus > M.\ luteus > E.\ coli.$$

The synthesized compounds showed a remarkable increase in antibacterial activity than the parent myristic acid. Further, a close inspection of screening results reveals that the anilides (**M-12**–**M-20**) of myristic acid exhibited strong antibacterial activity. It is worthwhile to note that the presence of a nitro group in the meta position of the aromatic ring of the anilides does not improve the antibacterial activity. The formation of esters also showed an improvement in the antibacterial activity of myristic acid derivatives. Further it is important to note that the absence of fluorine in the structure of anilides of myristic acid may be responsible for their lower activity in comparison to the standard drug, ciprofloxacin, even though they contain the aromatic ring with chlorine.

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.[21] Biological activity data determined as MIC values were first transformed to −log MIC on a molar basis, which was used as a dependent variable in the QSAR study. These were correlated with different molecular descriptors like log of octanol–water partition coefficient ($\log P$),[21] molar refractivity (MR),[22] Kiers molecular connectivity ($^2\chi^v$), and shape (κ_1,$\kappa\alpha_1$) topological indices,[23] Randic topological index (R),[24] Balban

Table 1. Physicochemical characteristics of myristic acid derivatives

$CH_3[CH_2]_{12}COOR$ $[M_1 - M_{10}, M_{21} - M_{23}]$	$CH_3[CH_2]_{12}COR$ $[M_{11} - M_{20}, M_{24} - M_{27}]$

Compound	R	Molecular formula	Mol wt	Mp/bp* (°C)	R_f value (benzene)	Yield (%)
Training set						
M-1	H	$C_{14}H_{28}O_2$	228.42	52–54	0.14	40
M-2	Me	$C_{15}H_{30}O_2$	242.45	121–124*	0.62	76
M-3	*i*-Pr	$C_{17}H_{34}O_2$	270.51	207–211*	0.58	88
M-4	*i*-Bu	$C_{18}H_{36}O_2$	284.54	227–229*	0.65	79
M-5	*n*-Pen	$C_{19}H_{38}O_2$	298.57	156–158*	0.79	62
M-6	*i*-Amyl	$C_{19}H_{38}O_2$	298.57	281–283*	0.66	89
M-7	*n*-Hex	$C_{20}H_{40}O_2$	312.60	185–187*	0.76	91
M-8	*n*-Hep	$C_{21}H_{42}O_2$	326.63	243–245*	0.56	68
M-9	*n*-Oct	$C_{22}H_{44}O_2$	340.66	235–237*	0.76	42
M-10	CH_2–Ph	$C_{21}H_{34}O_2$	318.55	288–290*	0.69	35
M-11	NH–NH_2	$C_{14}H_{30}ON_2$	242.46	116–119	0.10	83
M-12	$CH_3CH_2CH_2$–NH	$C_{17}H_{35}ON$	269.53	135–137	0.56	47
M-13	$CH_3(CH_2)_3$–NH	$C_{18}H_{37}ON$	283.56	166–168	0.45	62
M-14	Ph–NH	$C_{20}H_{33}ON$	303.54	71–74	0.38	68
M-15	(4-NO_2) Ph–NH	$C_{20}H_{32}O_3N_2$	348.54	130–132	0.49	22
M-16	(2-Cl) Ph–NH	$C_{20}H_{32}ONCl$	337.98	95–97	0.61	59
M-17	(3-Cl) Ph–NH	$C_{20}H_{32}ONCl$	337.98	136–138	0.42	69
M-18	(4-Cl) Ph–NH	$C_{20}H_{32}ONCl$	337.98	115–117	0.54	72
M-19	(2-CH_3O) Ph–NH	$C_{21}H_{35}O_2N$	333.57	156–158	0.67	86
M-20	(4-CH_3O) Ph–NH	$C_{21}H_{35}O_2N$	333.57	165–167	0.58	46
Test set						
M-21	Et	$C_{16}H_{32}O_2$	256.48	180–182*	0.60	82
M-22	*n*-Pr	$C_{17}H_{34}O_2$	270.51	217–219*	0.61	66
M-23	*n*-Bu	$C_{18}H_{36}O_2$	284.54	271–273*	0.58	74
M-24	NH_2	$C_{14}H_{29}ON$	227.44	80–82	0.10	87
M-25	(2-NO_2) Ph–NH	$C_{20}H_{32}O_3N_2$	348.54	146–148	0.45	18
M-26	(3-NO_2) Ph–NH	$C_{20}H_{32}O_3N_2$	348.54	211–213	0.22	84
M-27	$NH(Et)_2$	$C_{18}H_{37}ON$	283.56	68–70	0.13	24

* Boiling point.

Table 2. The in vitro activity of synthesized myristic acid derivatives

Compound	−log MIC		
	S. aureus	*M. luteus*	*E. coli*
Training set			
M-1	2.48	2.48	2.26
M-2	2.38	2.29	2.38
M-3	2.65	2.65	2.43
M-4	2.76	2.76	2.50
M-5	2.70	2.70	2.52
M-6	2.78	2.70	2.52
M-7	2.80	2.89	2.59
M-8	2.91	2.82	2.61
M-9	2.93	2.93	2.63
M-10	2.80	2.73	2.60
M-11	2.38	2.29	2.38
M-12	2.59	2.59	2.43
M-13	2.67	2.61	2.45
M-14	2.71	2.71	2.50
M-15	2.86	2.76	2.56
M-16	2.83	2.75	2.57
M-17	2.83	2.93	2.57
M-18	2.83	2.83	2.57
M-19	2.82	2.75	2.62
M-20	2.82	2.75	2.62
Test set			
M-21	2.41	2.61	2.61
M-22	2.63	2.63	2.34
M-23	2.58	2.36	2.45
M-24	2.59	2.29	2.51
M-25	2.86	2.76	2.46
M-26	2.56	2.46	2.56
M-27	2.58	2.67	2.65
S[a]	3.33	3.33	3.33

[a] Standard drug—ciprofloxacin.

topological index (J),[25] Wiener topological index (W),[26] Total energy (Te),[4] energies of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO),[27] dipole moment (μ), electronic energy (ElcE), nuclear energy (NuE), and molecular surface area (SA).[28] The values of these descriptors are presented in Table 3.

In the present work, a training set consisting of 20 molecules (**M-1**–**M-20**) was used for linear regression model generation and a prediction set consisting of 7 molecules (**M-21**–**M-27**) was used for the evaluation of generated linear regression model. The reference drug ciprofloxacin was not included in model generation as it belongs to a different structural series.

First, correlation analysis of various descriptors with biological activity was performed. The data are presented in Table 4, which shows that most of the parameters are highly correlated with antibacterial activity. A correlation matrix (Table 5) was constructed to find the interrelationship among the parameters, which shows that each parameter selected in the study is highly correlated with the other ($r > 0.8$) except the descriptors ionization potential, LUMO, and $^{3}\chi^{v}$. Any combination of these descriptors in multiple regression analysis may result with a model suffering from multicolinearity.

The topological parameter, valence molecular connectivity indices ($^{0}\chi^{v}$ and $^{2}\chi^{v}$) for the esters and amides of myristic acid, has been found to exhibit best correlation and high statistical significance ($p < 0.01$). The resulting best-fit models applying the principle of Parsimony are reported in Eqs. 1–3 together with statistical parameters of regression. It is important to note that all these models were developed by using the entire training set ($n = 20$), since no outliers were identified.

The quality of the models is indicated by the following parameters: r, correlation coefficient; F, Fisher's statistics; and s, standard error of estimation; r^2_{cv}, cross validated r^2 obtained by 'leave one out' (LOO) method.

QSAR model for antibacterial activity against E. coli

$$-\log\ \mathrm{MIC} = 0.061\ {}^{0}\chi^{v} + 1.635 \quad n = 20$$
$$r = 0.963\ F = 232.661\ s = 0.027\ r^2_{cv} = 0.902. \quad (1)$$

QSAR model for antibacterial activity against S. aureus

$$-\log\ \mathrm{MIC} = 0.217\ {}^{2}\chi^{v} + 1.375 \quad n = 20$$
$$r = 0.978\ F = 407.85\ s = 0.030\ r^2_{cv} = 0.931. \quad (2)$$

QSAR model for antibacterial activity against M. luteus

$$-\log\ \mathrm{MIC} = 0.229\ {}^{2}\chi^{v} + 1.268 \quad n = 20$$
$$r = 0.934\ F = 123.968\ s = 0.064\ r^2_{cv} = 0.810. \quad (3)$$

The coefficient of $^{0}\chi^{v}$ in the mono-parametric model in Eq. 1 is positive, indicating thereby that antibacterial activity of myristic acid derivatives against *E. coli* is directly proportional to the magnitude of $^{0}\chi^{v}$. The antibacterial activity increases with an increase in magnitude of $^{0}\chi^{v}$. This is evidenced by the values of $^{0}\chi^{v}$ in Table 3. The values of $^{0}\chi^{v}$ for compounds **M-8**, **M-9** are 16.04 and 16.75, respectively, which are higher than the $^{0}\chi^{v}$ values of other compounds in the training set which make them the most active compounds against *E. coli*. Similarly the compounds **M-1**, **M-2**, and **M-11** have the minimum $^{0}\chi^{v}$ values of 10.84, 11.80, and 11.47, respectively, and have minimum activity. Similar trend was observed in case of *S. aureus* and *M. luteus* with valence second order molecular connectivity index, $^{2}\chi^{v}$.

In order to confirm our results we have synthesized a prediction set consisting of 7 myristic acid derivatives viz. **M-21**–**M-27**, predicted their activities using the model expressed by Eqs. 1–3, and compared them with the observed values. We have also applied the same model to predict the activity of training set. The data presented in Table 6 show that the observed and the estimated activities are very close to each other evidenced by low values of residual activity.

The cross-validation of the models was also done by LOO technique.[29] The high cross-validated correlation coefficient (r^2_{cv} or q^2) values obtained for the best QSAR models indicated their reliability in predicting the antibacterial activity of myristic acid derivatives. But one should not forget the recommendations of Golbraikh et al.,[30] who have recently reported that

Table 3. Values of selected descriptors used in the linear regression analysis

Compound	log *P*	MR	$^{0}\chi^{v}$	$^{2}\chi^{v}$	κ_1	$\kappa\alpha_1$	*R*	*W*	Te	NuE	SA	IP
Training set												
M-1	4.82	67.88	10.84	4.68	16.00	15.63	7.77	667.00	−2822.89	14014.40	346.14	11.11
M-2	4.85	72.65	11.80	4.86	17.00	16.63	8.31	790.00	−2978.14	15413.50	368.85	11.10
M-3	5.61	81.82	13.38	5.82	19.00	18.63	9.16	1072.00	−3289.64	18420.30	409.43	11.03
M-4	6.07	86.39	14.09	6.36	20.00	19.63	9.66	1248.00	−3445.45	19944.70	429.84	11.06
M-5	6.46	91.12	14.63	6.21	21.00	20.63	10.31	1462.00	−3601.42	20933.20	455.99	11.06
M-6	6.46	91.00	14.79	6.48	21.00	20.63	10.20	1428.00	−3601.25	21519.40	458.92	11.06
M-7	6.85	95.73	15.34	6.57	22.00	21.63	10.81	1680.00	−3757.26	22335.40	477.03	11.06
M-8	7.25	100.33	16.04	6.92	23.00	22.63	11.31	1920.00	−3913.09	23749.30	498.96	11.05
M-9	7.64	104.93	16.75	7.27	24.00	23.63	11.81	2183.00	−4068.93	25178.70	521.52	11.05
M-10	6.63	97.26	14.90	6.43	21.04	19.90	11.33	1810.00	−3800.85	22399.10	450.42	9.69
M-11	3.94	74.19	11.47	4.85	17.00	16.59	8.31	790.00	−2942.72	15417.90	367.10	10.28
M-12	5.01	83.87	13.31	5.64	19.00	18.63	9.31	1088.00	−3189.91	18095.40	417.97	9.79
M-13	5.41	88.47	14.01	5.99	20.00	19.63	9.81	1265.00	−3345.74	19462.80	439.50	9.79
M-14	5.88	94.38	14.28	6.20	20.05	18.90	10.83	1576.00	−3545.33	20868.50	432.18	8.75
M-15	5.84	101.70	15.47	6.64	23.04	21.45	12.13	2230.00	−4376.26	25273.70	458.99	9.57
M-16	6.40	99.18	15.40	6.75	21.04	20.19	11.24	1746.00	−3905.39	22987.40	445.47	9.21
M-17	6.40	99.18	15.40	6.82	21.04	20.19	11.22	1762.00	−3905.40	22933.60	446.00	9.29
M-18	6.40	99.18	15.40	6.81	21.04	20.19	11.22	1778.00	−3905.45	22274.50	447.84	8.79
M-19	5.63	100.84	15.61	6.53	22.04	20.85	11.77	1939.00	−4021.19	24501.00	460.59	8.49
M-20	5.63	100.84	15.61	6.56	22.04	20.85	11.76	2003.00	−4021.17	24126.30	465.21	8.37
Test set												
M-21	5.19	77.40	12.51	5.09	18.00	17.63	8.81	930.00	−3133.93	16792.00	389.69	11.08
M-22	5.66	81.92	13.22	5.51	19.00	18.63	9.31	1088.00	−3289.76	18164.50	411.77	11.07
M-23	6.06	86.52	13.92	5.86	20.00	19.63	9.81	1265.00	−3445.59	19545.00	434.10	11.07
M-24	3.95	69.70	10.97	4.75	16.00	15.63	7.77	667.00	−2722.89	14022.90	354.22	10.52
M-25	5.84	101.70	15.47	6.61	23.04	21.45	12.15	2134.00	−4376.14	26473.70	454.39	9.72
M-26	5.84	101.70	15.47	6.64	23.04	21.45	12.13	2182.00	−4376.19	25385.70	458.38	9.48
M-27	5.13	88.99	14.26	5.85	20.00	19.63	9.76	1205.00	−3345.13	20257.10	433.32	9.56

Table 4. Correlation of −log MIC with molecular descriptors of myristic acid derivatives

Molecular descriptor	*S. aureus*	*M. luteus*	*E. coli*
log *P*	0.860	0.864	0.773
MR	0.942	0.866	0.961
$^{0}\chi^{v}$	0.963	0.899	0.963
$^{1}\chi^{v}$	0.948	0.898	0.937
$^{2}\chi^{v}$	0.979	0.934	0.932
$^{3}\chi^{v}$	0.382	0.370	0.262
κ_1	0.941	0.857	0.938
$\kappa\alpha_1$	0.917	0.851	0.901
R	0.918	0.824	0.947
W	0.921	0.823	0.935
Te	−0.919	−0.821	−0.922
NuE	0.948	0.854	0.958
SA	0.914	0.852	0.912
IP	−0.282	−0.217	−0.382
LUMO	−0.412	−0.332	−0.414

the only way to estimate the true predictive power of a model is to test their ability to predict accurately the biological activities of compounds from an external test set, that is, those compounds, which were not used for the model development. The low residual activity values observed in case of test set (**M-21**–**M-27**) justify the selection of the linear regression models expressed by Eqs. 1–3. Further the plot of linear regression predicted −log MIC values against the observed −log MIC values also favors the model expressed by Eq. 2 (Fig. 1).

Even though the sample size and the 'Rule of Thumb' allowed us to go for development of multi-parametric model in multiple linear regression analysis, the high interrelationship among the parameters restricted us for mono-parametric model. The multicolinearity occurs when two independent variables are correlated with each other that become a problem for a theoretical statistician. One should note that the change in signs of the coefficients, a change in the values of previous coefficient, change of significant variable into insignificant one or an increase in standard error of the estimate on addition of an additional parameter to the model are indications of high interrelationship among descriptors.

Nonlinear regression was applied to find out the relationship of log *P* with antibacterial activity. The models obtained by NLR do not show any appreciable improvement in correlation coefficient.

From the results and discussion made above we conclude that the myristic acid derivatives are more effective against Gram-positive rather than Gram-negative bacteria, *S. aureus* being the most sensitive organism among the bacterial species tested. The results of in vitro antibacterial activity studies indicate that the anilides of myristic acid are the most effective compounds. The QSAR studies indicated that the topological parameters, the valence second order molecular connectivity index, $^{2}\chi^{v}$, and valence zero order molecular connectivity index, $^{0}\chi^{v}$, can be used successfully for modeling antibacterial activity of myristic acid derivatives against

Table 5. Correlation matrix for myristic acid derivatives against *Staphylococcus aureus*

	−log MIC	log *P*	MR	$^{0}\chi^{v}$	$^{1}\chi^{v}$	$^{2}\chi^{v}$	$^{3}\chi^{v}$	κ_1	$\kappa\alpha_1$	*R*	*W*	Te	NuE	SA	IP	LUMO
−log MIC	1.000															
log *P*	0.860	1.000														
MR	0.942	0.766	1.000													
$^{0}\chi^{v}$	0.963	0.842	0.980	1.000												
$^{1}\chi^{v}$	0.948	0.881	0.958	0.987	1.000											
$^{2}\chi^{v}$	0.979	0.872	0.958	0.984	0.970	1.000										
$^{3}\chi^{v}$	0.382	0.166	0.273	0.275	0.156	0.387	1.000									
κ_1	0.941	0.819	0.955	0.977	0.975	0.947	0.176	1.000								
$\kappa\alpha_1$	0.917	0.859	0.902	0.957	0.973	0.933	0.121	0.983	1.000							
R	0.918	0.710	0.988	0.950	0.918	0.918	0.271	0.937	0.863	1.000						
W	0.921	0.732	0.977	0.947	0.923	0.913	0.223	0.954	0.889	0.991	1.000					
Te	−0.919	−0.705	−0.963	−0.937	−0.894	−0.912	−0.334	−0.940	−0.869	−0.981	−0.985	1.000				
NuE	0.948	0.758	0.985	0.976	0.946	0.949	0.297	0.974	0.922	0.985	0.985	−0.983	1.000			
SA	0.914	0.870	0.912	0.962	0.984	0.935	0.090	0.974	0.991	0.868	0.884	−0.849	0.915	1.000		
IP	−0.282	0.113	−0.473	−0.323	−0.240	−0.287	−0.282	−0.235	−0.090	−0.519	−0.441	0.440	−0.407	−0.130	1.000	
LUMO	−0.412	−0.126	−0.513	−0.376	−0.282	−0.385	−0.472	−0.345	−0.188	−0.598	−0.576	0.636	−0.516	−0.155	0.655	1.000

the bacterial species included in the present study. Contribution of topological descriptors in describing the antibacterial activity of acid derivatives was further evidenced by the results of our previous study.[4] The QSAR models are validated by the low residual antibacterial activities observed in case of prediction set.

All the melting and boiling points reported in the present study are uncorrected. The IR spectra were recorded with a Shimadzu FTIR 8000 spectrophotometer in KBr disks in case of solid and applied as thin film in case of liquid samples. The ^{1}H NMR spectra in $CDCl_3$ were recorded on an AC 300F NMR spectrophotometer using TMS as an internal standard. Purity of all the synthesized compounds was ascertained by TLC.

General procedure for synthesis of esters. The appropriate alcohol (0.74 mol) was poured into a round-bottomed flask containing myristic acid (**M-1**, 0.06 mol) and sulfuric acid (2 mL). The solution was refluxed until the completion of reaction. The reaction mixture was added to 200 mL of ice-cold water and the oily layer was separated, followed by extraction of the product with ether. The evaporation of ether resulted in pure product. The esters (**M-2**–**M-9**, **M-21**, and **M-23**) included in the present study were prepared by the above procedure.

General procedure for synthesis of amides. The acid chloride of myristic acid was prepared by the reaction of myristic acid with thionyl chloride. The solution of the corresponding amine (0.1 mol) in ether (50 mL) was added dropwise to a solution of acid chloride (0.06 mol) in ether (50 mL). The solution was stirred for 30 min and the precipitated amide was separated by filtration. The crude amides were recrystallized from alcohol. The amides (**M-11**–**M-20**, **M-24**, and **M-27**) included in the present study were prepared by the above procedure.

Structures of the synthesized compounds were confirmed on the basis of spectroanalytical data.

Analytical data for compound **M-2**. Bp (°C) 121–123, yield 76%; IR (cm^{-1}) 1743 (C=O), 2854 (CH_3); 1170 (C–O–C) ^{1}H NMR (δ ppm) 0.91 (t, 3H, CH_3), 2.30 (t, 2H, CH_2), 3.70 (s, 3H, OCH_3), 1.65 (m, 2H, CO–CH_2–CH_2–CH_2), 1.26 (m, 2H, $CH_2CH_2CH_2$).

Analytical data for compound **M-14**. Mp (°C) 71–73, yield 68%; IR (cm^{-1}) 1652 (C=O), 3280 (NH), 1600 (CH=CH, Ar); ^{1}H NMR (δ ppm) 7.21 (M, 5H, C_6H_5), 7.2 (s, 1H, NH), 2.30 (t, 3H, $COCH_2$), 1.67 (m, 2H, CO–CH_2–CH_2), 1.25 (m, 2H, $CH_2CH_2CH_2$), 0.90 (t, 3H, CH_3).

Analytical data for compound **M-21**. Bp (°C) 180–182, yield 82%; IR (cm^{-1}) 1739 (C=O), 2854 (CH_3); 1178 (C–O–C) ^{1}H NMR (δ ppm) 0.90 (t, 3H, CH_3), 2.25 (m, 2H, $CH_2CH_2CH_2$), 4.15 (q, 2H, OCH_2CH_3), 1.63 (m, 2H, CO–CH_2–CH_2–CH_2), 1.27 (t, 3H, $COCH_2CH_3$).

Table 6. Observed and predicted antibacterial activity of myristic acid derivatives against *Escherichia coli*, *Staphylococcus aureus,* and *Micrococcus luteus* using the best QSAR model viz. Eqs. 1–3, respectively

Compound	−log MIC for *S. aureus*			−log MIC for *M. luteus*			−log MIC for *E. coli*		
	Obsd	Pre. (Eq. 2)	Resi.	Obsd	Pre. (Eq. 3)	Resi.	Obsd	Pre. (Eq. 1)	Resi.
Training set									
M-1	2.48	2.39	0.09	2.48	2.34	0.14	2.26	2.30	−0.04
M-2	2.38	2.43	−0.05	2.29	2.38	−0.09	2.38	2.35	0.03
M-3	2.65	2.64	0.01	2.65	2.60	0.05	2.43	2.45	−0.02
M-4	2.76	2.76	0.00	2.76	2.72	0.04	2.50	2.49	0.01
M-5	2.70	2.72	−0.02	2.70	2.69	0.01	2.52	2.53	−0.01
M-6	2.78	2.78	0.00	2.70	2.75	−0.05	2.52	2.54	−0.02
M-7	2.80	2.80	0.00	2.89	2.77	0.12	2.59	2.57	0.02
M-8	2.91	2.88	0.03	2.82	2.85	−0.03	2.61	2.61	0.00
M-9	2.93	2.95	−0.02	2.93	2.93	0.00	2.63	2.66	−0.03
M-10	2.80	2.77	0.03	2.73	2.74	−0.01	2.60	2.54	0.06
M-11	2.38	2.43	−0.05	2.29	2.38	−0.09	2.38	2.33	0.05
M-12	2.59	2.60	−0.01	2.59	2.56	0.03	2.43	2.45	−0.02
M-13	2.67	2.67	0.00	2.61	2.64	−0.03	2.45	2.49	−0.04
M-14	2.71	2.72	−0.01	2.71	2.69	0.02	2.50	2.51	−0.01
M-15	2.86	2.82	0.04	2.76	2.79	−0.03	2.56	2.58	−0.02
M-16	2.83	2.84	−0.01	2.75	2.81	−0.06	2.57	2.57	0.00
M-17	2.83	2.85	−0.02	2.93	2.83	0.10	2.57	2.57	0.00
M-18	2.83	2.85	−0.02	2.83	2.83	0.00	2.57	2.57	0.00
M-19	2.82	2.79	0.03	2.75	2.76	−0.01	2.62	2.59	0.03
M-20	2.82	2.80	0.02	2.75	2.77	−0.02	2.62	2.59	0.03
Test set									
M-21	2.41	2.48	−0.07	2.61	2.43	0.18	2.61	2.40	0.21
M-22	2.63	2.57	0.06	2.63	2.53	0.10	2.34	2.44	−0.10
M-23	2.58	2.65	−0.07	2.36	2.61	−0.25	2.45	2.48	−0.03
M-24	2.59	2.41	0.18	2.29	2.36	−0.07	2.51	2.30	0.21
M-25	2.86	2.81	0.05	2.76	2.78	−0.02	2.46	2.58	−0.12
M-26	2.56	2.82	−0.26	2.46	2.79	−0.33	2.56	2.58	−0.02
M-27	2.58	2.64	−0.06	2.67	2.61	0.06	2.65	2.50	0.15

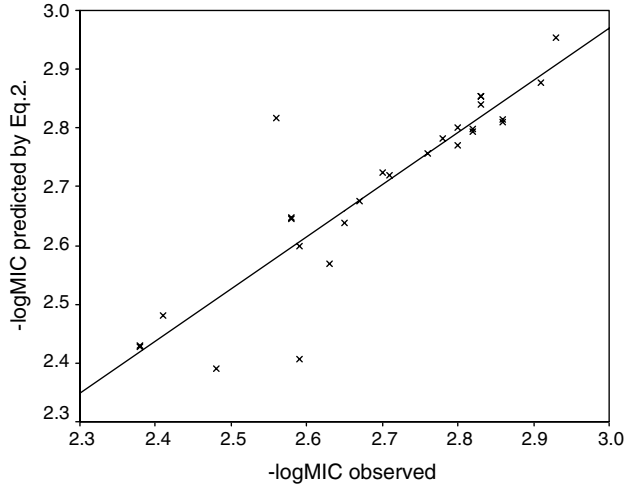

Figure 1. Plot of predicted −log MIC activity values against the experimental −log MIC values for the QSAR model by Eq. 2 for *Staphylococcus aureus*.

Analytical data for compound **M-24**. Mp (°C) 81–83, yield 87%; IR (cm^{-1}) 1635 (C=O), 3360 (NH), 3200 (NH), 1417 (C–N); ^1H NMR (δ ppm) 5.8 (s, 1H, NH), 2.19 (t, 2H, $COCH_2$), 1.58 (m, 2H, $CO–CH_2–CH_2$), 1.29 (m, 2H, $CH_2CH_2CH_2$), 0.90 (t, 3H, CH_3).

Biological studies. The in vitro antibacterial activity of the synthesized compounds against *S. aureus*, *M. luteus*, and *E. coli* was carried out by using serial dilution method in double strength nutrient broth-IP as a medium. The myristic acid derivatives were dissolved in DMSO to give a concentration of 10 μg/mL (stock solution).

QSAR analysis. The calculation of molecular descriptors of myristic acid derivatives as well as the regression analysis were carried out by using the molecular package TSAR 3D version 3.3.[31] The details of calculation of these descriptors are available in the literature [5,21–28] and therefore, they are not mentioned here.

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References and notes

1. Berber, I.; Cokmus, C.; Atalan, E. *Microbiology* **2003**, *72*, 54.
2. Mitscher, L. A.; Pillai, S. P.; Gentry, E. J.; Shankel, D. M. *Med. Res. Rev.* **1999**, *19*, 477.
3. Delgado, D. N.; Remers, W. A. In *Wilson and Gisvold's Textbook of Medicinal and Pharmaceutical Chemistry*, 10th ed.; Lippincott-Ravon: New York, 1998; p 173.

4. Narasimhan, B.; Kothawade, U. R.; Pharande, D. S.; Mourya, V. K.; Dhake, A. S. *Indian J. Chem. B* **2003**, *42*, 2828.
5. Narasimhan, B.; Belsare, D.; Pharande, D.; Mourya, V.; Dhake, A. *Eur. J. Med. Chem.* **2004**, *39*, 827.
6. Narasimhan, B.; Dhake, A. S. *Abstract of papers-CP-31*, 56th Indian Pharmaceutical Congress, Kolkota, India, December 03-05, 2004.
7. Narasimhan, B.; Dhake, A. *J. Med. Food* (Fall 2006, in press).
8. Carballeira, N. M. *Prog. Lipid Res.* **2002**, *41*, 437.
9. Ouattara, B.; Simard, R. E.; Holley, R. A.; Piette, G. J. P.; Begin, A. *Int. J. Food Microbiol.* **1997**, *7*, 155.
10. Parang, K.; Wiebe, L. I.; Knaus, E. E. *Antiviral Chem. Chemother.* **1998**, *9*, 311.
11. Hashimoto, Y.; Matsuda, T.; Matsuura, Y.; Haga, T.; Fukada, Y. *J. Biochem.* **2004**, *135*, 319.
12. Krogh, R.; Yunes, R. A.; Aandricopulo, A. D. *Farmaco* **2000**, *55*, 730.
13. Nieto, M. J.; Alovero, F. L.; Manzo, R. H.; Mazzieri, M. R. *Eur. J. Med. Chem.* **2005**, *40*, 361.
14. Ghafourian, T.; Barzegar-Jalali, M. *Farmaco* **2002**, *57*, 565.
15. Stanczak, A.; Borowiecka, J. *Farmaco* **2001**, *56*, 257.
16. Free, S. M.; Wilson, J. W. *J. Med. Chem.* **1964**, *7*, 395.
17. Hansch, C. *Farmaco* **2003**, *58*, 625.
18. Gangawal, N. A.; Narasimhan, B.; Mourya, V. K.; Dhake, A. S. *Indian J. Heterocycl. Chem.* **2003**, *12*, 201.
19. Pharmacopoeia of India; Ministry of Health Department: Govt. of India: New Delhi, 1996, Vol. II, p A-88.
20. Cappucino, J. G.; Sherman, N. In *Microbiology–A Laboratory Manual*; Addison Wesley: California, 1999; pp 263–265.
21. Hansch, C.; Fujita, T. *J. Am. Chem. Soc.* **1964**, *86*, 1616.
22. Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207.
23. Kier, L. B.; Hall, L. H. In *Molecular Connectivity in Chemistry and Drug Research*; Academic Press: New York, 1976; pp 129–145.
24. Randic, M. *J. Am. Chem. Soc.* **1975**, *97*, 6609.
25. Balban, A. T. *Chem. Phys. Lett.* **1982**, *89*, 399.
26. Wiener, H. *J. Am. Chem. Soc.* **1947**, *69*, 17.
27. Sharma, P.; Rane, N.; Gurram, V. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4185.
28. Randic, M. *Croat. Chem. Acta* **1993**, *66*, 289.
29. Wold, S.; Erikkson, L. Statistical Validation of QSAR Results. In *Chemometrics Methods in Molecular Design*; Water, H. V., Ed.; VCH Press: Weinheim, 1995; pp 309–318.
30. Golbraikh, A.; Tropsha, A. J. *Mol. Graph. Model.* **2002**, *20*, 209.
31. TSAR 3D Version 3.3, Oxford Molecular Limited, 2000.