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

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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; ($r^2_{cv}$).
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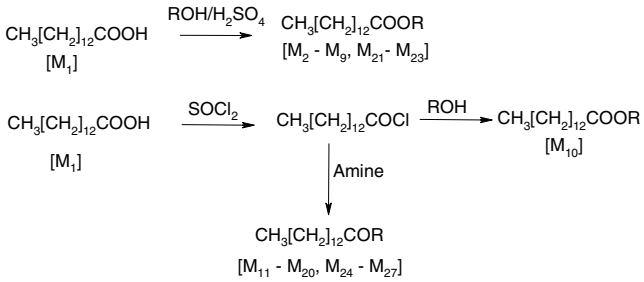


**Scheme 1.** Scheme for synthesis of myristic acid derivatives (**M-2**–**M-27**).

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 ($\kappa_1$,$\kappa\alpha_1$) 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.