1,2,4–Oxadiazole Esters as *Aedes aegypti* Larvicides

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INTRODUCTION

Compounds containing the 1,2,4- oxadiazole ring have been extensively studied because of their biological properties.[1] Recently, our group have successfully introduced a new application for methyl 3-(3-aryl-1,2,4-oxadiazol-5-yl) propanoates as larvicidal agents against the larvae of *Aedes aegypti*, the vector of the Dengue fever disease. The intensity of this activity, in turn, depends not only on the nature of the substituent attached to the phenyl ring, as well as their position. Larvicidal bioassays performed on DQF/UFPE[2] showed that the compound with a chlorine substituent at the *para* position of the phenyl ring has a LC_{50} = 23.6 μ mol L^{-1}, whereas the compound substituted with a bromine in the same position has a LC_{50} = 16.3 μ mol L^{-1}. Therefore, the aim of the current study is to investigate the Quantitative Structure-Activity Relationships (QSAR) between the larvicidal activity and molecular descriptors for the series of methyl 3-(3-aryl-1,2,4-oxadiazol-5-yl) propanoates.

METHODS

B3LYP/6-311G(d,p) calculations, using the standard internal criteria of the Gaussian 03 program, were performed to obtain the electronic properties: i) atomic charge or sum of atomic charges, ii) the electric dipole moment, iii) HOMO and LUMO energies. To evaluate the lipophilicity the parameter LogP was calculated using the program Kowwin 1.67[3]. Multiple Linear Regression (MLR) was used to obtain the QSAR model using STATISTICA 6.0 software. Only low correlated descriptors were employed.

RESULTS AND DISCUSSION

The QSAR model between the experimental LC_{50} values (8.4 – 132.0 μ mol L^{-1}) and the molecular descriptors is given in the equation below:

$$log\left(\frac{1}{LC_{50}}\right) = -15.22 + 67.60qC_3 - 0.94\Sigma q_{benzene} + 0.62logP$$

with, n = 11, R^2 = 0.98 and F = 63.39. The quality of this model can also be appreciated in Figure 1 by the comparison between predicted and experimental activities.

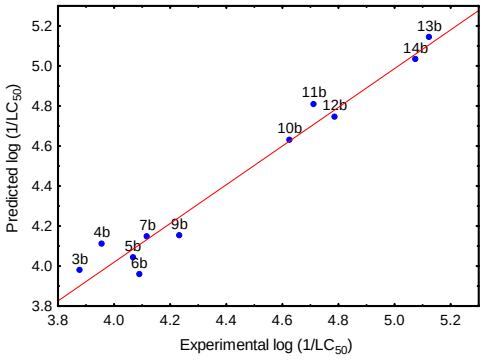

Figure 1. Predicted versus experimental activities.

Using the QSAR model, it was possible to predict a new compound that showed a best larvicidal activity (6.07 μ mol L^{-1}).

CONCLUSIONS

From our QSAR studies it was possible to understand the dependence of the larvicidal activity with the molecular structure for a set of compounds. We were also able to predict one new compound that exhibited better activity in the series. This way, we can point out which molecular modifications must be done towards the next generation of methyl 3-(3-aryl-1,2,4-oxadiazol-5-yl) propanoates with improved larvicidal activity against the larvae of *Aedes aegypti* mosquito.

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