STRUCTURE-TOXICITY STUDY OF SOME PYRETHROIDAL ESTER INSECTICIDES

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INTRODUCTION

Pyrethroids constitute one of the most widely used classes of insecticides worldwide, having the following characteristics [1]: quick knock-down effect against insects, efficacy against insects with organophosphorus and/or carbamate-resistant strains, easy decomposition in the environment and low mammalian toxicity.

Although the specific mechanism of activity is uncertain, pyrethroids act primarily on the nervous system [2], on a variety of putative biochemical and physiological target sites, four of which merit consideration as sites of toxic action: voltage-sensitive sodium, calcium and chloride channels, and peripheral-type benzodiazepine receptors [3].

Toxicity of 37 pyrethroidal esters (Table 1), expressed by the logarithm of LD$_{50}$ values, measured against a susceptible strain of housefly (*Musca domestica*) was studied by multiple linear regression (MLR).

Stereoisomers selected according to the literature [4] were modeled by conformational analysis performed by molecular mechanics calculations. Structural descriptors of the title compounds calculated for these isomers were correlated to the logarithm of LD$_{50}$ values.

Table 1. Pyrethroidal ester structure

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</thead>
<tbody>
<tr>
<td>A1</td>
<td><img src="image1" alt="Structure A1" /></td>
<td>E1</td>
<td><img src="image2" alt="Structure E1" /></td>
<td>G1</td>
<td><img src="image3" alt="Structure G1" /></td>
<td>H2</td>
<td><img src="image4" alt="Structure H2" /></td>
<td>L3</td>
<td><img src="image5" alt="Structure L3" /></td>
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<td>A2</td>
<td><img src="image6" alt="Structure A2" /></td>
<td>E2</td>
<td><img src="image7" alt="Structure E2" /></td>
<td>G2</td>
<td><img src="image8" alt="Structure G2" /></td>
<td>H3</td>
<td><img src="image9" alt="Structure H3" /></td>
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<td>A3</td>
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<td>E3</td>
<td><img src="image11" alt="Structure E3" /></td>
<td>G3</td>
<td><img src="image12" alt="Structure G3" /></td>
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<td>E4</td>
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<td>G4</td>
<td><img src="image16" alt="Structure G4" /></td>
<td>I1</td>
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<td>B1</td>
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<td>G5</td>
<td><img src="image20" alt="Structure G5" /></td>
<td>J1</td>
<td><img src="image21" alt="Structure J1" /></td>
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<tr>
<td>B3</td>
<td><img src="image22" alt="Structure B3" /></td>
<td>E10</td>
<td><img src="image23" alt="Structure E10" /></td>
<td>G6</td>
<td><img src="image24" alt="Structure G6" /></td>
<td>J2</td>
<td><img src="image25" alt="Structure J2" /></td>
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<td>C1</td>
<td><img src="image26" alt="Structure C1" /></td>
<td>F5</td>
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<td>G7</td>
<td><img src="image28" alt="Structure G7" /></td>
<td>K2</td>
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<td>D1</td>
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<td>G8</td>
<td><img src="image32" alt="Structure G8" /></td>
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<tr>
<td>D2</td>
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<td>F13</td>
<td><img src="image35" alt="Structure F13" /></td>
<td>G9</td>
<td><img src="image36" alt="Structure G9" /></td>
<td>K4</td>
<td><img src="image37" alt="Structure K4" /></td>
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</tbody>
</table>
Definition of target property and molecular structures

Experimental LD$_{50}$ values of 37 pyrethroidal ester derivatives have been previously [4] measured against a susceptible strain of housefly (Musca domestica). Their logarithm was considered as dependent variable.

Starting structures were first built by the Marwin Sketch [5] software and then conformational analysis was performed by the OMEGA [6] program.


Compound descriptors were calculated by several programs: Dragon (Dragon Professional 5.5/2007, Talete S.R.L., Milano, Italy), Instant JChem (Instant JChem v. 6.0, Chemaxon Ltd., Budapest, Hungary) and EPI Suite™ (US EPA. [2012]. Estimation Programs Interface Suite™ for Microsoft® Windows, v. 4.11. United States Environmental Protection Agency, Washington, DC, USA.)

Multiple linear regression (MLR) analysis [7] has been applied after variable selection carried out by the genetic algorithm included in the QSARINS v. 1.2 program [8].

METHODS

Model validation

- The leave-one-out cross-validation procedure was employed for internal validation, the over fitting of data and model applicability was controlled by comparing the root-mean-square errors (RMSE) of training and validation sets and the predictive power of the model by the concordance correlation coefficient (CCC) [9].

- Y-scrambling was used to check the model robustness and predictive power.

- The Multi-Criteria Decision Making (MCDM) [16] was employed to summarize the performances of a certain number of criteria simultaneously

RESULTS AND DISCUSSION

Table 2. MLR statistical results for the training, cross-validated and test sets

<table>
<thead>
<tr>
<th>Model</th>
<th>Equation</th>
<th>R²</th>
<th>Q²</th>
<th>R²(adj)</th>
<th>SEE</th>
<th>RMSE(tr)</th>
<th>RMSE(ex)</th>
<th>KXX</th>
<th>ΔK</th>
<th>CCC(tr)</th>
<th>CCC(ex)</th>
<th>MCDM</th>
<th>R² LMO</th>
<th>Q² LMO</th>
<th>R² Yscr</th>
<th>Q² Yscr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>log LD₉₀ = −0.35(±0.22) − 0.99(±0.47)EEig02d − 0.55(±0.31)BEH₃m + 0.62(±0.32)BEL₈m − 1.92(±0.76)KOAWIN log Kaw</td>
<td>0.857</td>
<td>0.789</td>
<td>0.828</td>
<td>0.252</td>
<td>0.225</td>
<td>0.231</td>
<td>0.209</td>
<td>0.151</td>
<td>0.923</td>
<td>0.812</td>
<td>0.794</td>
<td>0.860</td>
<td>0.860</td>
<td>0.17</td>
<td>-0.32</td>
</tr>
<tr>
<td>2</td>
<td>log LD₉₀ = −0.54(±0.24) − 0.97(±0.44)EEig04d + 0.44(±0.30)nC₉p − 2.06(±0.82)KOAWIN log Kaw</td>
<td>0.759</td>
<td>0.668</td>
<td>0.724</td>
<td>0.319</td>
<td>0.292</td>
<td>0.222</td>
<td>0.377</td>
<td>0.101</td>
<td>0.863</td>
<td>0.808</td>
<td>0.742</td>
<td>0.761</td>
<td>0.761</td>
<td>0.13</td>
<td>-0.25</td>
</tr>
<tr>
<td>3</td>
<td>log LD₉₀ = −0.41(±0.25) − 0.79(±0.37)EEig02d − 0.74(±0.30)MW + 0.52(±0.27)BEL₈m − 1.83(±0.72)KOAWIN log Kaw</td>
<td>0.834</td>
<td>0.756</td>
<td>0.800</td>
<td>0.271</td>
<td>0.243</td>
<td>0.258</td>
<td>0.261</td>
<td>0.148</td>
<td>0.909</td>
<td>0.769</td>
<td>0.754</td>
<td>0.840</td>
<td>0.840</td>
<td>0.17</td>
<td>-0.33</td>
</tr>
</tbody>
</table>

* R² – correlation coefficient, Q² – leave-one-out ‘crossvalidated r²’, R²(adj) – adjusted R², SEE – standard error of estimates, RMSE - root mean squared error, MAE - mean absolute error, CCC - concordance correlation coefficient, for the training (tr), and test (ex) sets; MCDM all - Multi-Criteria Decision Making calculated for fitting cross-validation and external validation; R² LMO and Q² LMO – leave many-out correlation coefficient and cross-validation coefficients; R² Yscr and Q² Yscr-Y scramble correlation and cross-validation coefficients; EEig02d-Eigenvalue 02 from edge adj. matrix weighted by dipole moments; BEH₃m-highest eigenvalue n. 3 of Burden matrix / weighted by atomic masses; BEL₈m-lowest eigenvalue n. 8 of Burden matrix / weighted by atomic masses; KOAWIN Log Kaw–air-water partition coefficients; nC₉p-number of terminal primary C(sp3); MW-molecular weight
The dataset was divided in training and a randomly selected (25% of the total number of compounds) test set. Compounds: C1, D1, G1, H3 and L3 were included in the test set.

Seven outliers (compounds A1, B1, B3, F12, F13, G2 and H5) were found and removed from the final MLR models.

The MLR models are completely satisfactory in the fitting, but have modest predictive power.

Model 1 (considered best) is stable and internally predictive, not obtained by chance.
RESULTS AND DISCUSSION

Figure 1. Williams plot – predicted by fitting for model 1

Figure 2. Williams plot – predicted by leave-one-out (LOO) for model 1
RESULTS AND DISCUSSION

Figure 3. Experimental versus logLD_{50} values predicted by fitting for model 1

Figure 4. Experimental versus logLD_{50} values predicted by LOO for model
CONCLUSIONS

- The obtained MLR models are satisfactory in the fitting, but have modest predictive power.

- The presence number of terminal primary C(sp3) group is favorable for low toxicity.

- High values of air-water partition coefficients and of molecular weight can be associated with high toxicity of the title compounds.
ACKNOWLEDGEMENTS

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