Cancer is among the leading causes of death worldwide [1]. Multidrug resistance (MDR) is one of the main challenges in cancer treatment, in which overexpression of P-glycoprotein (P-gp) plays an important role [2, 3].

*Plectranthus* genus (Lamiaceae) is a great source of cytotoxic compounds that could be used as lead molecules for drug development [4,5].

**Results**

**Graphic 1.** P-gp inhibition in an MDR cancer cell line

- 4 displayed inhibition potential similar to Dex-Ver (pos. control)
- Benzoyloxy substituent in position 12 is important for P-gp inhibition

**Figure A.** Top-ranked docking pose at M site for compounds 3 (orange), 4a (yellow), 4b (cyan), 5 (blue) and 5a (green)

- 3 and 4 may act as non-competitive inhibitors
- One Benzoyloxy substituent seems important for P-gp inhibition

**Table 1.** Docking results, protein-ligand contacts for the tested compounds obtained by LigPlot

<table>
<thead>
<tr>
<th>Compounds</th>
<th>H-site</th>
<th>R-site</th>
<th>M-site</th>
<th>Clc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-8.8</td>
<td>-8.6</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-8.7</td>
<td>-9.2</td>
<td>W</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-10.5</td>
<td>-11.6</td>
<td>-10.4</td>
<td>S</td>
</tr>
<tr>
<td>3a</td>
<td>-9.2</td>
<td>-10.2</td>
<td>-10.3</td>
<td>S</td>
</tr>
<tr>
<td>3b</td>
<td>-9.3</td>
<td>-9.2</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-9.3</td>
<td>-9.9</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td>-9.2</td>
<td>-10.4</td>
<td>-10.7</td>
<td>S</td>
</tr>
</tbody>
</table>

**Molecular dynamics (MD):**

MD of theoretical derivatives 3a, 3b and 4a (data not presented [3]) suggest:

- The presence of a second benzoyloxy moiety does not significantly contribute to the binding affinity towards P-gp
- The presence of a para substitution decreases the calculated ΔG<sub>bind</sub>

**Conclusions**

- Compounds 3 and 4 (and its theoretical derivatives 3a, 3b and 4a) may act as a non-competitive efflux modulators when bound to the M-site.
- *In vitro* results are in agree with MD and docking predictions in which only one benzoyloxy moiety is needed to promote stronger interactions with P-gp.
- Future generation of novel royleanone derivatives will involve i) a selective modification of position C-12 with chemical moieties smaller than unsubstituted benzoyl rings and ii) the modification of the substitution pattern of the benzoyloxy moiety at position C-6.

**References**


**Acknowledgments**

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