SYNTHESIS AND IN SILICO TESTING OF NOVEL ANDROSTANE 1,3,4-THIADIAZOLINES

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INTRODUCTION:
It is widely known that N-, O- and S-heterocycles are important structural units present in many drugs, natural and synthetic products with broad spectrum of pharmacological activities. Among them, the 1,3,4-thiadiazoline nucleus is one of the most studied, and its potency is demonstrated by drugs that are currently in clinical use, such as cefazolin, megazol or acetazolamide [1].

OBJECTIVES:
Bearing this in mind, we have synthesized androstan-3-thiosemicarbazone derivatives in 17α-homo lactone and 17α-picolyl (1A and 1B, Figure 1) series, which were further subjected to ring closure reactions, affording 1,3,4-thiadiazolines (2A, 2B and 3A, 3B, Scheme 1) in good yields. In addition, the physicochemical properties of the obtained compounds were predicted using the web tool SwissADME (Table 1) and compared with Lipinski, Veber, Egan, Ghose and Muegge criteria [2].

RESULTS:

![Scheme 1](image)

**Scheme 1.** a) Acetic anhydride, Py, CHCl₃, reflux, 7 h (for A) or 80-85 °C, 3.5 h (for B); b) Propionic anhydride, Py, CHCl₃, reflux, 7 h (for A) or 80-85 °C, 3 h (for B).

**Table 1.** In silico physicochemical properties of compounds 1A/B, 2A/B and 3A/B.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formula</th>
<th>MW</th>
<th>HBD</th>
<th>HBA</th>
<th>LogP</th>
<th>rotb</th>
<th>TPSA</th>
<th>MR</th>
<th>No rings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>C₁₀H₁₀N₂O₅S</td>
<td>375.53</td>
<td>2</td>
<td>3</td>
<td>3.09</td>
<td>2</td>
<td>108.80</td>
<td>107.07</td>
<td>4</td>
</tr>
<tr>
<td>1B</td>
<td>C₁₀H₁₀N₂O₅S</td>
<td>452.66</td>
<td>3</td>
<td>3</td>
<td>4.09</td>
<td>4</td>
<td>115.62</td>
<td>134.08</td>
<td>5</td>
</tr>
<tr>
<td>2A</td>
<td>C₁₀H₁₀N₂O₅S</td>
<td>459.60</td>
<td>1</td>
<td>5</td>
<td>3.23</td>
<td>3</td>
<td>113.37</td>
<td>131.86</td>
<td>5</td>
</tr>
<tr>
<td>2B</td>
<td>C₁₀H₁₀N₂O₅S</td>
<td>536.73</td>
<td>2</td>
<td>5</td>
<td>4.11</td>
<td>5</td>
<td>120.19</td>
<td>158.86</td>
<td>6</td>
</tr>
<tr>
<td>3A</td>
<td>C₁₀H₁₀N₂O₅S</td>
<td>487.65</td>
<td>1</td>
<td>5</td>
<td>3.91</td>
<td>5</td>
<td>113.37</td>
<td>141.47</td>
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</tr>
<tr>
<td>3B</td>
<td>C₁₀H₁₀N₂O₅S</td>
<td>564.78</td>
<td>2</td>
<td>5</td>
<td>4.82</td>
<td>7</td>
<td>120.19</td>
<td>168.47</td>
<td>6</td>
</tr>
</tbody>
</table>

M.W: molecular weight expressed in Gahons; HBD: number of hydrogen bond donors; HBA: number of hydrogen bond acceptors; LogP: partition coefficient, average of five predictions (LOGP, XLOGP, WLOGP, MLOGP and Silicos-IT LogP); rotb: number of rotatable bonds; TPSA: topological polar surface area in Å²; MR: molar refractivity.

**Figure 1.** Graphical distribution of compounds 1A/B-3A/B using the BOILED-Egg predictive model for intestine and brain penetration.

**Figure 2.** The Bioavailability Radars of synthesized compounds 1-3. The pink area represents the optimal range for lipophilicity, polarity, solubility, saturation and flexibility.

CONCLUSIONS:
A suitable synthesis of new thiosemicarbazone and thiadiazoline derivatives was performed, starting from the corresponding 4-en-3-one androstanes. According to in silico ADME physicochemical properties, all compounds possess drug-like qualities which are required for Lipinski, Veber, Egan, Ghose and Muegge criteria. The bioavailability radars indicated that all compounds are in the optimal range for lipophilicity, polarity, solubility, saturation and flexibility, with a slight deviation in compounds 2B and 3B due to higher molecular weight. The BOILED-Egg model indicated that these compounds could be absorbable by the intestines (with the exception of 3B), but couldn’t penetrate the brain. From the obtained results it can be concluded that all compounds are good candidates for further in vitro studies.

REFERENCES:

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