DUAL TARGETING OF ADENOSINE A₂A RECEPTORS AND MONOAMINE OXIDASE B BY 4H-3,1-BENZOTHIAZIN-4-ONES

Anne Stößel[1], Sonja Hinz[1], Petra Küppers[1], Jag Heer[2], Michael Gütschow[1], and Christa E. Müller[1]

1. Introduction

Blockade of A₂A adenosine receptors (A₂A-ARs)² and inhibition of monoamine oxidase B (MAO-B)² in the brain are both considered as attractive strategies for the treatment of neurodegenerative diseases such as Parkinson’s disease (PD). A dual-acting drug, addressing two pharmacological targets may display an enhanced therapeutic potential and a reduced risk of side effects as compared to drug combinations.⁴

2. Synthesis

Scheme 1. (a) PCl₃/NC, acetonitrile, RT, 20 min; (b) 1. concd H₂SO₄, 100 °C, 4 h, 2. NaN₃CO₂; (iii) 1. RCOOH, N,N,N',N'-tetramethylurea, 2,4,6-trichlorobenzoyl chloride, THF, RT, 1 h, 2. pyridine, toluene, reflux, 2 h.

In Scheme 1, the general synthetic route is outlined. An anthranilic acid derivative 1 was reacted with benzoyl isothiocyanate, followed by an acid-promoted cyclization to generate the thiazine skeleton 2. Acylation with different carboxylic acids implemented structural diversity at the exocyclic 2-amino group (R). Different substituents (R', R'') were introduced and the benzene ring was bioisotopically replaced by thiophene moieties.

3. Results

Figure 1. The newly synthesized compounds 3a–3c were investigated in adenosine receptor radioligand binding studies and in enzyme inhibition studies at MAO-B. Structural optimization and SAR analyses led to the development of potent and selective A₂A-AR antagonists and MAO-B inhibitors. With regard to the dual approach four derivatives can be highlighted (6–9, purple circle, Table 1).

Table 1. Selected dual-acting derivatives 6–9.

<table>
<thead>
<tr>
<th>compd</th>
<th>A₂A IC₅₀ (nM)</th>
<th>MAO-B IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>80.9 ± 21.3 (h)</td>
<td>17.6 ± 3.7 (h)</td>
</tr>
<tr>
<td>9</td>
<td>101 ± 10 (r)</td>
<td>42.7 ± 19.8 (r)</td>
</tr>
<tr>
<td>7</td>
<td>64.9 ± 12.4 (h)</td>
<td>95.3 ± 8.8 (h)</td>
</tr>
<tr>
<td>6</td>
<td>294 ± 137 (r)</td>
<td>621 ± 39 (r)</td>
</tr>
<tr>
<td>29</td>
<td>82.5 ± 29.5 (h)</td>
<td>69.7 ± 6.1 (h)</td>
</tr>
<tr>
<td>28</td>
<td>693 ± 141 (r)</td>
<td>291 ± 107 (r)</td>
</tr>
<tr>
<td>25</td>
<td>39.5 ± 5.8 (h)</td>
<td>34.9 ± 2.5 (h)</td>
</tr>
<tr>
<td>24</td>
<td>423 ± 76 (r)</td>
<td>186 ± 37 (r)</td>
</tr>
</tbody>
</table>

*IC₅₀: 50% inhibitory concentration; h: human enzyme; r: rat enzyme.

5. Mechanism of MAO-B Inhibition

Human MAO-B was treated with 6–9 or with the irreversible inhibitor selegiline, or the reversible inhibitor safinamide as reference compounds (Fig. 3). In contrast to selegiline, the measurements clearly indicated a reversible mode of inhibition for 6–9 as evidenced by an elevated fluorescence.

6. Conclusion

4H-3,1-Benzothiazin-4-ones and thienothiazine analogues represent a structurally novel class of compounds with a dual mechanism of action: as

(i) Adenosine A₂A Antagonist

(ii) Monoamine Oxidase B Inhibitor

hA₂A Kᵢ 39.5 nM
hA₂A Kᵢ 2500 nM
hA₂A Kᵢ >1000 nM
hA₂A Kᵢ >1000 nM

The new compounds may serve as pharmacological tools for proof-of-concept in vivo studies to validate the proposed dual target approach as a novel strategy for the treatment of PD and other neurodegenerative diseases.

7. References and Acknowledgements


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