Novel High Affinity Histone Deacetylase Inhibitors as Potential Radiotracers for PET

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Introduction

• Histone deacetylases (HDACs) deacetylate histone side chains
• Class I HDACs 1, 2 and 3 are overexpressed in several types of cancer, neurodegenerative diseases and inflammation
• Deacetylation causes transcriptional silencing
  > Inhibition of HDACs leads to anticancer effects
• Structure of a HDAC inhibitor (HDACi) contains a cap group, a linker and a zinc-binding group (ZBG)
• Hydroxamic acids and ortho-aminoanilides emerged as valuable ZBGs (Figure 1)
• Advantages of o-aminoanilides: Class I selective HDACi, non mutagenic

Strategy

Figure 1: Schematic pharmacophore model and published hydroxamic acid and benzanilide HDACi [3]

Aim

• Development of novel, highly affine and selective fluorine-containing class I HDACi (Scheme 1)
• Synthesis of 18-fluorine labelled o-aminoanilide inhibitors for diagnostic imaging of tumors by positron emission tomography (PET)

Results

• The inhibitory activities (IC50) of HDACi were determined based on a modified in-house in vitro fluorogenic binding assay
• Highly potent HDACi were synthesized (Table 1)

Table 1: Inhibitory activity (IC50) of reference compounds and corresponding fluorinated derivatives towards HDACs

<table>
<thead>
<tr>
<th>Compound</th>
<th>HDAC1*</th>
<th>HDAC2*</th>
<th>HDAC3*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vorinostat</td>
<td>124.5 ± 16.6</td>
<td>200.57 ± 16.68</td>
<td>129.25 ± 5.85</td>
</tr>
<tr>
<td>Tacedinaline</td>
<td>636.33 ± 114.32</td>
<td>696.30 ± 10.50</td>
<td>262.55 ± 30.65</td>
</tr>
<tr>
<td>LSH-A30</td>
<td>4.40 ± 0.10</td>
<td>44.67 ± 6.89</td>
<td>&gt; 1110</td>
</tr>
<tr>
<td>OC59</td>
<td>4.78 ± 0.39</td>
<td>64.29 ± 4.46</td>
<td>&gt; 1110</td>
</tr>
<tr>
<td>OC70</td>
<td>4.83 ± 0.56</td>
<td>39.85 ± 3.18</td>
<td>&gt; 1110</td>
</tr>
</tbody>
</table>

* 1 hour preincubation of the test compound and the respective enzyme
** commercially available HDACi

Table 1: Inhibitory activity (IC50) of reference compounds and corresponding fluorinated derivatives towards HDACs

Outlook and Future Perspectives

• Three novel, highly potent fluorinated class I HDACi were developed: LSH-A30, OC59 and OC70
• Synthesis of the corresponding precursor for direct or indirect radiofluorination
• A fully automated radiosynthesis procedure will be established
• In vitro and in vivo evaluation of the selected 18F-labelled compounds

References