Synthesis and in vitro Affinities of Various MDL 100907 Derivatives as Potential ¹⁸F-Radioligands for 5-HT₂A Receptor Imaging with PET

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Objectives:
Radiolabelled piperidine derivatives such as [¹¹C]MDL 100907 and [¹⁸F]altanserin have played an important role in diagnosing malfunction in the serotonergic neurotransmission. Concerning molecular imaging, the advantage of [¹⁸F]altanserin (b) over [¹¹C]MDL 100907 (a) is the possibility to perform equilibrium scans lasting several hours and to transport the tracer to other facilities based on the 110 minute half-life of ¹⁸F-fluorine. A drawback of [¹⁸F]altanserin is its rapid and extensive metabolism. Four metabolites are formed in humans that cross the blood-brain-barrier, whereas metabolites of [¹¹C]MDL 100907 do not enter the brain to any larger extent. The aim of this study was to synthesize a ligand combining the reported better selectivity and in vivo stability of MDL 100907 as compared to altanserin and the superior isotopic properties of an ¹⁸F-label as compared to an ¹¹C-label.¹²

Methods:
A variety of novel piperidine MDL 100907 derivatives, possible to label with ¹⁸F-fluorine, were synthesized to improve molecular imaging properties of [¹¹C]MDL 100907. Their in vitro affinities to a broad spectrum of neuroreceptors and their lipophilicities were determined and compared to the clinically used reference compounds MDL 100907 and altanserin.

Results:
The novel compounds MA-1 and (R)-MH.MZ show Kᵢ-values in the nanomolar range towards the 5-HT₂A receptor and insignificant binding to other 5-HT receptor subtypes or receptors. Interestingly, compounds MA-1, MH.MZ and (R)-MH.MZ provide a receptor selectivity profile similar to MDL 100907. These compounds could possibly be preferable antagonistic ¹⁸F-tracers for visualisation of the 5-HT₂A receptor status. Medium affine compounds (e.g. VK-1) were synthesized and have Kᵢ values between 30 and 120 nM (table 1).

Table 1. Receptor Binding Affinities of promising 5-HT₂A ligands

<table>
<thead>
<tr>
<th>Verbindung</th>
<th>Kᵢ [nM]</th>
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<tbody>
<tr>
<td>MH.MZ</td>
<td>9.00 ± 0.10</td>
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<tr>
<td>MDL 100907</td>
<td>2.10 ± 0.13</td>
</tr>
<tr>
<td>(R)-MH.MZ</td>
<td>0.72 ± 0.12</td>
</tr>
<tr>
<td>MA-1</td>
<td>3.24 ± 1.23</td>
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Conclusion:
A series of novel MDL 100907 derivatives containing a fluorine atom were synthesized and evaluated for their in vitro behaviour. Structure-Activity Relationships (SAR) studies suggested that the tested compounds had affinities to the 5-HT₂A receptor in the nanomolar range.

References:
² Huang et al. (1999), An Efficient Synthesis of the Precursors of [¹¹C]MDL 100907 Labeled in Two Specific Positions, J. Labelled Cpd. 42: 949 – 957
³ Herth et al. (2009), Synthesis and in vitro affinities of various MDL 100907 derivatives as potential ¹⁸F-radioligands for 5-HT₂A imaging with PET, Bioorg. Med. Chem. (submitted)