Synthesis and *in vitro* Affinities of Various MDL 100907 Derivatives as Potential ^{18}F-Radioligands for 5-HT$_{2A}$ Receptor Imaging with PET

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Objectives:

Radiolabelled piperidine derivatives such as [^{11}C]MDL 100907 and [^{18}F]altanserin have played an important role in diagnosing malfunction in the serotonergic neurotransmission. Concerning molecular imaging, the advantage of [^{18}F]altanserin (**b**) over [^{11}C]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 ^{18}F-fluorine. A drawback of [^{18}F]altanserin is its rapid and extensive metabolism. Four metabolites are formed in humans that cross the blood-brain-barrier, whereas metabolites of [^{11}C]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 ^{18}F-label as compared to an ^{11}C-label.[1,2]

Methods:

A variety of novel piperidine MDL 100907 derivatives, possible to label with ^{18}F-fluorine, were synthesized to improve molecular imaging properties of [^{11}C]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 K_i-values in the nanomolar range towards the 5-HT$_{2A}$ 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 ^{18}F-tracers for visualisation of the 5-HT$_{2A}$ receptor status. Medium affine compounds (e.g. VK-1) were synthesized and have K_i values between 30 and 120 nM (table 1).

All promising compounds show logP values between 2 and 3, i.e. within range of those for the established radiotracers altanserin and MDL 100907. The novel compounds MA-1 and (R)-MH.MZ thus appear to be promising high affine and selective tracers of ^{18}F-labelled analogues for 5-HT$_{2A}$ imaging with PET.[3]

Table 1. Receptor Binding Affinities of promising 5-HT$_{2A}$ ligands

Verbindung	K_i [nM]
MH.MZ	9.00 ± 0.10
MDL 100907	2.10 ± 0.13
(R)-MH.MZ	0.72 ± 0.12
MA-1	3.24±1.23

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-HT$_{2A}$ receptor in the nanomolar range.

References:

[1] Herth, M.M. et al. (2008); Total synthesis and evaluation of [^{18}F]MHMZ, Bioorg. Med. Chem. Lett. 1515-1519

[2] Huang et al. (1999), An Efficient Synthesis of the Precursors of [^{11}C]MDL 100907 Labeled in Two Specific Positions, J. Labelled Cpd. 42: 949 – 957

[3] Herth et al. (2009), Synthesis and in vitro afffinites of various MDL 100907 derivatives as potential 18F-radioligands for 5-HT$_{2A}$ imaging with PET, Bioorg. Med. Chem. (submitted)