# Radiolabeling and evaluation of MDL 100,907 derivates as potential $^{18}$F-radioligands to determine changes in endogenous serotonin

**Kramer V[1], Herth M[1], Palner M[2], Knudsen G[2], Lüddens H[3], F Rösch**
[1]Institute of Nuclear Chemistry, Johannes Gutenberg-University, Mainz, Germany
[2]Center for Integrated Molecular Brain Imaging, Rigshospitalet, Copenhagen, Denmark
[3]Department of Psychiatry, Clinical Research Group, Mainz, Germany

**Objectives:** PET ligands that are able to detect changes in the concentration of endogenous serotonin are a valuable tool to study the pathophysiology of depressions and the effects of its pharmacotherapies[1]. The purpose of this study was to explore the effect of paroxetine-induced increased serotonin levels on the binding of the 5-HT$_{2A}$ antagonist (R)-[$^{18}$F]MH.MZ and its nitroderivate (R)-[$^{18}$F]VK1.MZ.

**Methods:** The *in vitro*-affinity for the inactive fluoro-compound (R)-VK1.MZ was determined in a [$^{3}$H]MDL 100,907 binding assay (Tab 1).

Table 1: In vitro affinities of the synthesized ligand to the 5HT$_{2A}$-receptor

| compound | K$_i$ [nM] |
|---|---|
| (R)-MH.MZ | 0.7 |
| (R)-VK1.MZ | 12 |

Both radioligands were labeled with $^{18}$F by fluoroethylation of the corresponding phenolic precursors using 2-[$^{18}$F]fluorethyltosylate[2] (Fig 1).

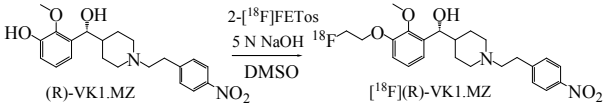


Figure 1: Radiosynthesis of (R)-[$^{18}$F]VK1.MZ

The radiolabeling procedure for (R)-[$^{18}$F]VK1.MZ was optimized due to time, temperature and solvent (Fig 2).

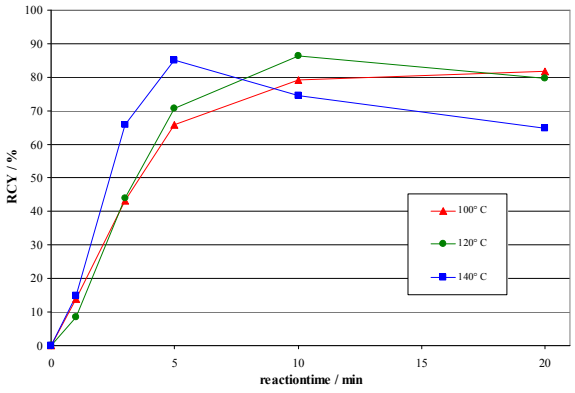


Figure 2: Radiosynthesis of [$^{18}$F](R)-VK1.MZ

Purification was carried out by HPLC and cartridge separation. Competition studies with serotonin were performed by autoradiography[3] and a first µPET-study was carried out.

**Results:** Both ligands demonstrate good affinities in the nanomolar range and a high selectivity for the 5-HT$_{2A}$ receptor. Optimization of the radiochemical reaction conditions for (R)-VK1.MZ gave radiochemical yields of about 85 % for the fluoroethylation after 5 minutes. The final formulation took no longer than 80 minutes and provided the labeled compound in a radiochemical yield of 50 % with a purity > 96 % and a typical specific activity of about 10 GBq/µmol. Autoradiographic studies of (R)-[$^{18}$F]MH.MZ showed excellent binding properties (BP = 8.3), whereas (R)-[$^{18}$F]VK1.MZ showed a lower specific binding (BP = 2.4) (Fig 2). This is probably due to the decreased affinity. For both ligands the specific binding could be reduced significantly by the addition of 100 nM serotonin.

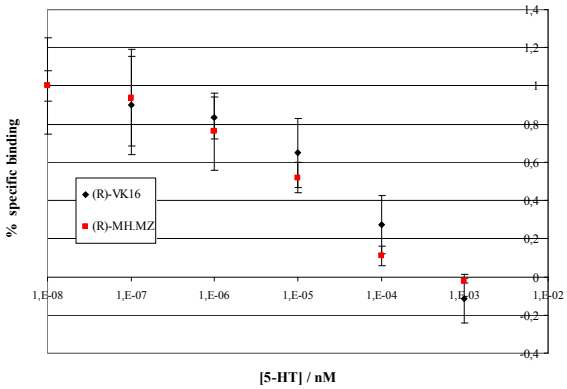


Figure 2: Competition study with serotonin

**Conclusion:** The reaction parameters for the radiolabeling of (R)-[$^{18}$F]VK1.MZ were optimized. (R)-[$^{18}$F]MH.MZ and (R)-[$^{18}$F]VK1.MZ could be obtained as an injectable solution in good radiochemical yields. Both tracers showed good binding properties *in vitro* and their specific binding could be reduced by the addition of physiological amounts of serotonin.

**Outlook**: µPET-studies with male rats under the influence of paroxetine are being performed in the close future using (R)-[$^{18}$F]MH.MZ due to its higher BP.

**Literatur:**

[1] Giovacchini G, Lang L, Ma Y, Herscovitch P, Eckelman WC, Carson RE; (**2005**); Neuroimage 28, 238
[2] Bauman A, Piel M, Schirrmacher R, Rösch F; (**2003**); Tetrahedron Letters 44/51, 9165
[3] Herth MM, Debus F, Piel M, Palner M, Knudsen GM, Lüddens H, Rösch F; (**2008**); Bioorg. Med. Chem. Lett. 18, 1515