NOVEL SYNTHESIS OF [^{18}F]FE1-MDL 100907, A POTENTIAL 5-HT$_{2A}$ ANTAGONIST

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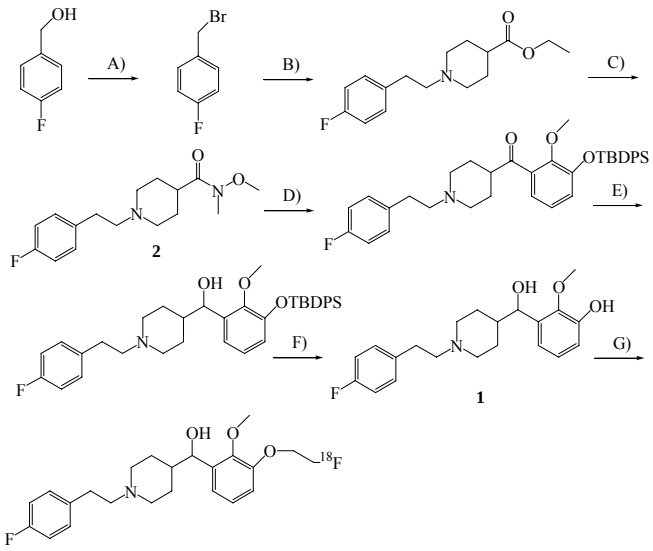
Introduction: Serotonergic 5-HT$_{2A}$ receptors are of central interest in the pathophysiology of schizophrenia and other diseases[1]. The serotonergic receptor antagonist [^{11}C]MDL 100907 shows high affinity and selectivity for 5-HT$_{2A}$ receptors *in vitro* and *in vivo*[2]. The K_i values are more than 100 fold higher for other receptors such as 5-HT$_{2C}$, α_1, D_1, D_2. It has also been proposed that the selectivity of [^{11}C]MDL 100907 is better than the selectivity of [^{18}F]altanserin[3]. Nevertheless, up to now any ^{18}F-derivatives of MDL 100907 exist. The aim of this study was to develop ^{18}F-analogs of MDL 100907.

Experimental: The synthetic route for the ^{18}F-labelling precursor MDL 105725 (**1**) via a key transformation of an ester to a keton via a Weinreb-amide intermediate (**2**) was carried out as published by Huang et al. (1999)[2] with some modifications. The fluoroalkylation of the precursor was conducted in dry DMF by addition of sodium hydride and 1-bromo-2-fluoroethane (Fig. 1).
The [^{18}F]fluoroalkylation of MDL 105725 was carried out with [^{18}F]FETos, produced in a self-made module, in try DMF at 100°C and in less than 15 minutes (Fig. 2). The final compound **4** [^{18}F]FE1-MDL 100907 ([3-(2-[^{18}F]fluoro-ethoxy)-2-methoxy-phenyl]-{1-[2-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}-methanol) was purified by HPLC (ET 250/8/4 Nucleosil ® 5 $C_{18;}$ MeCN / H_2O 40:60, R_f = 8.68 min).

Results and Discussion: Synthesis of the precursor MDL 105725 was carried out in yields of > 15%, whereas the final product FE1-MDL 100907 (**3**) was obtained in 40% yield. The labelled compound [^{18}F]FE1-MDL 100907 (**4**) could be obtained in > 80% yield. Separation of the compounds, i.e. MDL 105725 (R_f = 4.6 min), [^{18}F]FETos (R_f = 19.2 min) and [^{18}F]FE1-MDL100907 (R_f = 8.7 min) via HPLC was very efficient.

Conclusion: The new labelled compound [^{18}F]FE1-MDL 100907 was synthesized in high radiochemical yields of about 80% and high purity. In addition, an enantioselective synthesis is underway as in the case of MDL 100907 the R-enantiomer shows a 100-fold higher affinity to the 5-HT$_{2A}$ receptor subtype[4].
Autoradiograhic experiments and evaluation of FE1-MDL 100907 and [^{18}F]FE1-MDL 100907 are planed.

Figure 1: Syntheses of FE1-MDL 100907 and MDL 105725



A) PBr_3, Toluene B) K_2CO_3, DMF C) Me(MeO)NH HCl, EtMgBr, THF D) n-BuLi, THF, TBDPS-guajacol E) $NaBH_4$, MeOH F) K_2CO_3, MeOH, H_2O G) [^{18}F]FETos, DMF, 100°C

Figure 2: Radiosynthesis of [^{18}F]FE1-MDL 100907

[1] Kristiansen et al. (2005), Binding Characteristics of the 5-HT$_{2A}$ Receptor Antagonists Altanserin and MDL 100907, Synapse 58: 249 - 257
[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] Meltzer et al. (1998), Serotonin in Aging, Late-Life Depression, and Alzheimer`s Disease, Neuro-psychopharmacology 18: 407 - 430
[4] Heinrich et al. (2006), 1-(1-Phenethylpiperidin-4-yl)-1-phenylethanols as Potent and Highly Selective 5HT$_{2A}$ Antagonists, Chem. Med. Chem. 1: 245-255