Radiosynthesis and biological evaluation of [^{18}F]R91150, a selective 5-HT$_{2A}$ receptor antagonist for PET imaging

Objectives:

Serotonergic 5-HT$_{2A}$ receptors (5-HT$_{2A}$Rs) in cortical and forebrain regions are an important substrate for the neuromodulatory actions of serotonin in the brain. They have been implicated in the etiology of many neuropsychiatric disorders and serve as a target for (novel) antipsychotic, antidepressant and anxiolytic drugs. Positron emission tomography (PET) imaging using suitable radioligands can be applied for *in vivo* quantification of (alterations in) receptor densities and receptor occupancy for therapy evaluation[1]. Recently the radiosynthesis of the selective 5-HT$_{2A}$R antagonist [^{18}F]**R91150** was reported. However, the six-step radiosynthesis is cumbersome and time-consuming with low RCYs of <5%, obviating widespread use of this radioligand [2]. In this work, [^{18}F]**R91150** was prepared using late-stage Cu-mediated radiofluorination to simplify and accelerate synthesis of the radioligand.

Methods:

4-Amino-N-(1-(3-(4-[^{18}F]fluorophenoxy)propyl)-4-methylpiperidin-4-yl)-2-methoxy-benzamide ([^{18}F]**R91150**) was obtained by copper-mediated radiofluorination of the Boc-protected precursor **1** followed by deprotection of the radiolabeled intermediate [^{18}F]**2** with TFA. Subsequently, the desired 5-HT$_{2A}$-radioligand [^{18}F]**R91150** was isolated by analytical HPLC for *in vitro* autoradiography, performed on horizontal and sagittal rat brain slices to evaluate the binding profile. Therefore, brain slices were incubated for 1 h with [^{18}F]**R91150** (to display the total binding) and in a blocking experiment with a mixture of [$^{18/19}$F]**R91150** (to determine nonspecific binding) and exposed against phosphor-imaging plates for 90 min. In addition, the specific binding pattern of [^{18}F]**R91150** was verified in competition assays with the 5-HT$_{2A}$ targeting drugs altanserin, (+)-lisuride and (-)-lisuride.

Results:

Boc-protected [^{18}F]**R91150** ([^{18}F]**2)** was prepared in a yield of 10-15% (n.d.c, determined by radio-HPLC, n=3) within 10 min and isolated by SPE (C18 cartridge). Deprotection by TFA at 80 °C for 5 min succeeded quantitatively. Isolation by analytical radio-HPLC afforded the desired 5-HT$_{2A}$-radioligand [^{18}F]**R91150** in a yield of 10% (n.d.c.) after 60 min.

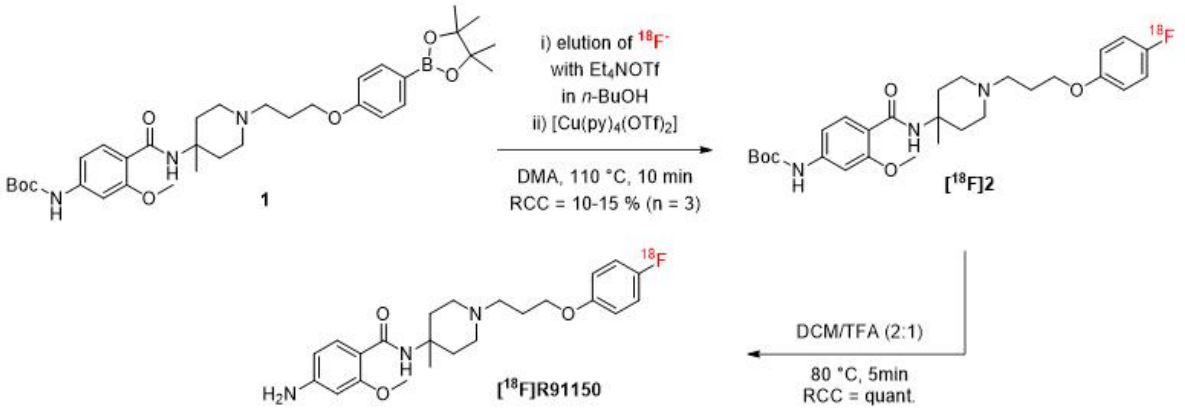
Autoradiographic examination of [^{18}F]**R91150** revealed discrete accumulation in specific brain areas (Fig.) that was entirely replaceable by non-radioactive R91150, altanserin and (+)-lisuride. As expected, the less 5-HT$_{2A}$ specific (-)-lisuride could not completely compete with the binding of [^{18}F]**R91150**.

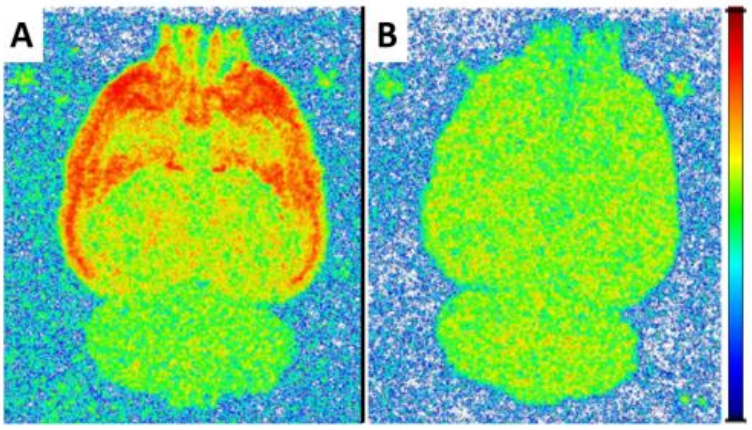
Conclusion:

The radiosynthesis of [^{18}F]**R91150** was simplified by using late stage Cu-mediated radiofluorination, facilitating the production in fair yields of 10% (n.d.c.) within 60 min. The *in vitro* evaluation of [^{18}F]**R91150** revealed the potential of this tracer for PET imaging of 5-HT$_{2A}$R status in the human brain. Future studies will focus on the in vivo behavior of [^{18}F]**R91150** and the transfer of its synthesis to an automated module for clinical applications.

References:

1. L'Estrade ET, Hansen HD, Erlandsson M, Ohlsson TG, Knudsen GM, Herth MM. . ACS Chem Neurosci 2018;9:1226-9.
2. Mühlhausen U, Ermert J, Coenen HH.. J Labelled Compd Radiopharm 2009;52:13-22.


i) elution of $^{18}F^-$
with Et_4NOTf
in *n*-BuOH
ii) $[Cu(py)_4(OTf)_2]$
DMA, 110 °C, 10 min
RCC = 10-15 % (n = 3)
1
$[^{18}F]$2
DCM/TFA (2:1)
80 °C, 5min
RCC = quant.
$[^{18}F]$R91150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