Synthesis of [^{3}H]Fallypride Using [^{3}H]Methyl Nosylate

T. Heß[1], C. Meisterhans[2], F. Roesch[1]
[1]Institute of Nuclear Chemistry, Johannes-Gutenberg-University Mainz, Germany; [2]RC Tritec AG, Teufen, Switzerland

Introduction:
Dopamine is the predominant catecholamine-neurotransmitter in the human brain. Malfunctions in the dopaminergic neurotransmission are associated to several neuropsychiatric diseases, such as Parkinson's, Alzheimer's and Huntington's disease as well as schizophrenia. Various radiolabelled benzamides which are highly selective towards the D_2/D_3-receptors have been developed and are used to visualise these receptors *in vivo* via PET/SPECT. One of the most promising structures is the ^{18}F-labelled benzamide [^{18}F]fallypride. Due to its excellent affinities and selectivity it is an ideal tracer for visualizing receptor availabilities in brain regions with high and low receptor density. However, long-term experiments as e.g. autoradiographies and replacement studies are limited to the short half-life of [^{18}F]fluorine. The introduction of tritium into a molecule, with its half-life of 12.3 a and a maximum β-energy of 18.6 keV, provides a way to accomplish the desired experiments, also providing higher precision in autoradiography. Consequently, it was the aim to introduce a tritium label into the original fallypride structure.

Methods:
Tritium can be introduced via many different routes into organic molecules. One of the most favoured synthetic pathways is the halogen/tritium-exchange using tritium gas and catalysts like palladium. Due to the allyl-group and the obliged reduction of the double bond this pathway cannot be implemented. Another possibility of introducing the desired tritium label is the methylation via a tritium methylating agent such as [^{3}H]methyl iodide. The 2-methoxy group in the benzamide structure offers a good approach for the introduction of the tritiated methyl-group.

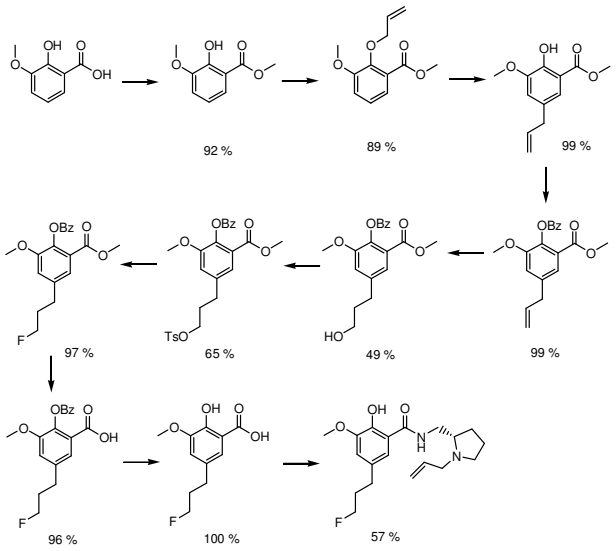

Figure 1. Synthesis of norfallypride

Based on the published procedure [1] for [^{11}C]fallypride, the 2-hydroxy-precursor was synthesized with slight modifications. After optimisation of the labelling reaction using ^{1}H-analogues of the tritium methylating agents, the final tritium labelling of 3.5 mg desmethyl-precursor with 40 mCi [^{3}H]methyl nosylate was carried out by RC Tritec AG (Teufen, Switzerland).

Results:
The desired labelling precursor was synthesised starting from 2-hydroxy-3-methoxy-benzoic acid using a benzyl-protecting group in 10 steps with an over all yield of 14%. First labelling for optimisation of the labelling with methyl iodide resulted in yields below 50% (determined via HPLC). The use of methyl nosylate, Cs_2CO_3 and DMF at room temperature resulted in 98% yield. These conditions were chosen for the [^{3}H]-labelling. The [^{3}H]methyl nosylate was synthesized starting from tritium gas over 5 steps, purification via semi-preparative HPLC resulted in 15 mCi of [^{3}H]fallypride with a radiochemical purity of >99 % (HPLC). Starting from [^{3}H]methyl nosylate the radiochemical yield was 38%.

Figure 2. Labelling with [^{3}H]methyl nosylate

Conclusions:
A multi-step synthesis starting from 2-hydroxy-3-methoxy-benzoic acid provided the 2-hydroxy-labelling precursor. After optimisation of the labelling reaction, the precursor was reacted with [^{3}H]methyl nosylate to give [^{3}H]fallypride. HPLC purification afforded 15 mCi [^{3}H]fallypride with a radiochemical purity of >99 % (HPLC).
Further experiments will focus on *in vitro* and *ex vivo* autoradiographic tests analysing local high-resolution D2-like receptor distributions and densities

References
[1] Mukherjee J., Shi B., Christian B.T.; Chattopadhyay S., Narayanan T.K., Bioorganic and Medicinal Chemistry, Volume 12 (1), 2004, pp. 95-102