Fast and convenient access to [^{18}F]flumazenil via diaryliodonium salts

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Objectives: Flumazenil is a high affinity antagonist for the benzodiazepine binding site of the $GABA_A$ receptor ($GABA_A$-Bz) and the corresponding PET-tracer [^{18}F]flumazenil ([^{18}F]FMZ) is already an established and important radiotracer. Unfortunately, the common direct nucleophilic labelling of the nitromazenil precursor results only in low radiochemical yields and revealed to be sensitive and unreliable. First studies by B. S. Moon *et al.* [1] towards the development of a diaryliodonium salt precursor offer a promising approach for an easy single step access to [^{18}F]FMZ with higher radiochemical yields in a robust and convenient procedure. The aim of this work is the development and comparison of differently substituted diaryliodonium salt precursors for the direct radiosynthesis of [^{18}F]FMZ.

Methods: Starting from nitromazenil which was produced according to a recently reported procedure [2], we synthesized aminomazenil using $TiCl_3$ as reducing reagent. This was converted to iodomazenil by a uncatalysed *Sandmeyer*-reaction in a paste reaction in an agate-mortar using *p*-TsOH, KI and $NaNO_2$ [3].

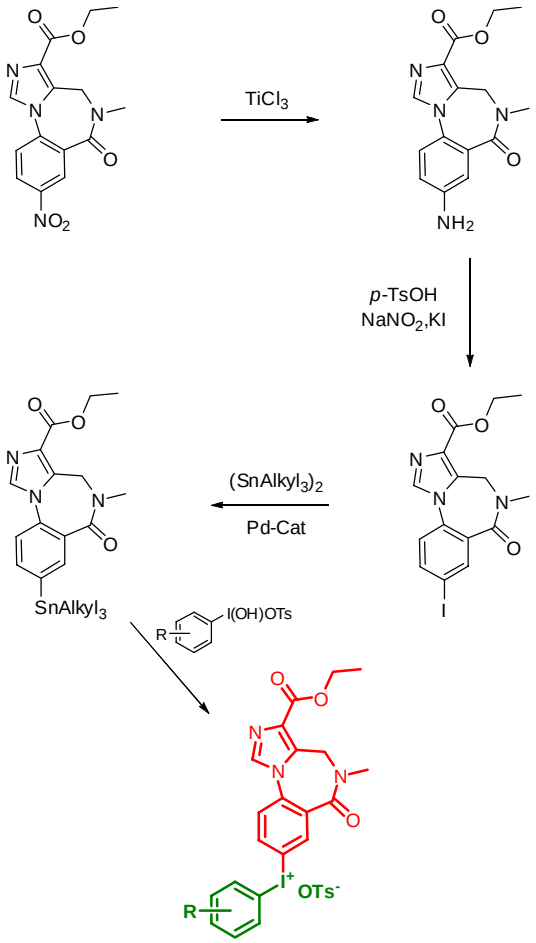

Figure 1: Synthesis of diaryliodonium salt precursers starting from nitromazenil.

Afterwards, the corresponding tributylstannyl compound was formed by a palladium catalysed reaction using bis(trialkyl)tin [4]. To get the differently substituted diaryliodonium salts as ^{18}F-labelling precursors, the stannylated compound was treated with the corres-ponding [hydroxyl(tosyloxy)iodo]arenes.

Results: After gram-scale production of nitromazenil, the amino derivative could be synthesized in high yields (67-70%). The following replacement of the amino group in an uncatalysed *Sandmeyer*-reaction using potassium iodide was successful with moderate yields of ~45%. In the following step, the trialkylstannyl compound could be isolated in satisfying yields and further treatment with [hydroxyl(tosyloxy)iodo]arenes led to the desired diaryliodonium salt precursors (Figure 2).

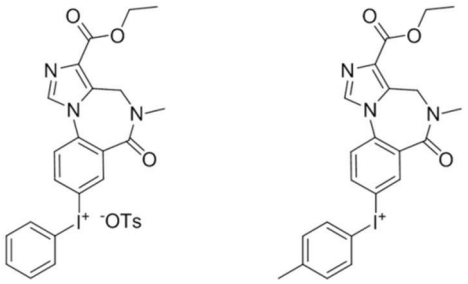

Figure 2: Two of the new diaryliodonium salt precursors for [^{18}F]flumazenil.

Conclusions: First diaryliodonium salt precursors for the direct labelling of [^{18}F]FMZ were successfully synthesized and preliminary labelling studies using [^{18}F]fluoride showed very promising results. Further highly activated diaryliodonium salt precursors for [^{18}F]FMZ are currently under development.

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References:

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