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Nucleophilic synthesis of 6-[18F]fluoro-L-DOPA via copper mediated radiofluorination

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Background and objectives Radiopharmaceuticals for positron emission tomography (PET) bearing electron rich [18F]fluorinated arenes are still in limited use as the direct introduction of [18F]fluoride via commonly used SNAr is not suitable. Recently, several transition metal-mediated labeling strategies were have been introduced, to address this problem. Among them radiofluorination of pinacol esters of arylboronic acids (ArylBPin) mediated by copper triflate complex with pyridine (Tredwell at al., 2014) is one of the more promising synthetic avenues under development. This new methodology allows facilitate access to clinically relevant radiotracers, 18F-ring fluorinated aromatic amino acids, drug-like molecules and others. However, implementation of the copper-mediated fluorination in automated synthesizers remains a challenging task. Several studies indicated that the choice of phase-transfer catalyst (PTC) and corresponding base used for the generation of reactive [18F]fluoride species has a profound impact on the 18F-fluorination fluorination of base-sensitive ArylBPin precursors. Here we introduce a new 18F-processing protocol using tetrabutylammonium triflate (TBAOTf) as a neutral PTC and its application in the preparation of 6-[18F]fluoro-L-DOPA via copper-mediated fluorination of commercially available ArylBPin precursor.

Methodology Radiolabeling precursor, 3,4-OMOM-6-(BPin)DOPA(Boc2)-OtBu (Fig.1), was kindly provided by ABX, Germany. Aqueous [18F]fluoride was loaded onto QMA carb SepPak cartidge (46 mg) from the male side, the cartridge was rinsed by 1.5 mL of i-PrOH and dried with helium. 18F was eluted in the opposite direction using a solution of 12.5 µmol of TBAOTf in 0.6 mL i-PrOH directly to a solution of 5 µmol of Cu(OTf)2Py4, 8 µmol of labeling precursor in 0.3 mL DMA. The mixture was heated in a sealed vial at 110℃ for 15 min under air. After intermediate purification (two C18 SepPak cartridges in a series) and acid hydrolysis the crude 6-[18F]fluoro-L-DOPA was purified by HPLC: RP-Amide, Supelco, 250 x 10 mm, NaOAc 10 mM + AcOH 50 mM + 0,1 g/l ascorbic acid; flow 4 ml/min; Rt 9 min.

Results and discussion First, developed 18F-processing protocol allowed eliminate conventional azeotropic drying step and facilitate automation. The use of TBAOTf as a PTC provides a high 18F-elution efficiency (up to 90%) and radiochemical conversion of 83±6 (n=7) as determined by radioTLC. The desired tracer was obtained in a RCY of 20% (non-optimized, corrected for decay), radiochemical purity > 97% and enantiomeric purity > 98% within 80 min synthesis time. Notably, the suggested procedure employed reduced amounts of expensive precursor (8 µmol) and Cu-catalyst (8 µmol). Work is now in progress to optimize hydrolysis and purification conditions to increase isolated radiochemical yield.

Conslusion The suggested novel 18F-processing protocol enables the simple and efficient production of 6-[18F]fluoro-LDOPA from commercially available ArylBPin precursor avoiding time consuming solvent evaporation steps. This method can be further extended for the preparation of other 18F-ring fluorinated amino acids.

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