Preparation of ^{18}F-labeled aromatic amino acids by copper-mediated radiofluorination

Daniel Modemann[1], Boris D. Zlatopolskiy[2], Bernd Neumaier[1,2], Johannes Ermert[1]

1 *Forschungszentrum Jülich GmbH, Institute of Neuroscience and Medicine, INM-5, Nuclear Chemistry, Jülich, Germany*
2 *Uniklinik Köln, Institute of Radiochemistry and Experimental Molecular Imaging, Cologne, Germany*

Objectives: [^{18}F]Fluorophenylamino acids exhibit great potential for diagnostic applications using PET. Nevertheless, their clinical application is still strongly restricted owing to cumbersome production methods. Recently novel transition metal-mediated ^{18}F-fluorination methods have been introduced into radiochemistry enabling to achieve radiofluorination of arenes regardless of their electronic properties [1]. The aim of this work was to develop a method for the efficient production of ^{18}F-labeled aromatic amino acids in high doses by means of alcohol-enhanced Cu(II)-mediated radiofluorination of arylboronic acid pinacol esters (PBE) [2].

Methods: The PBE precursors were synthesized by Miyaura borylation of the corresponding N-BOC protected iodoaromatic amino acid esters. The synthesis of 6-[^{18}F]FDOPA, L-2-[^{18}F]fluorophenylalanine (2-[^{18}F]FPhe), 6-[^{18}F]fluoro-L-*meta*-tyrosine (6-[^{18}F]FMT) and 5-[^{18}F]fluoro-L-*meta*-tyrosine (5-[^{18}F]FMT) were performed with $(py)_4Cu(II)(OTf)_2$ as catalyst. The labeling conditions were optimized with respect to temperature, solvent and amount of $(py)_4Cu(II)(OTf)_2$. The intermediates were purified by SPE and hydrolyzed with HCl affording after HPLC-purification the desired product.

Results: The precursors for radiolabeling were synthesized in overall yields of 3 to 17 %. The ^{18}F-labelling reactions were performed using *n*-butanol as a co-solvent improving the RCYs significantly. In the case of 6-[^{18}F]fluoro-L-3,4-dihydroxyphenylalanine (6-[^{18}F]FDOPA), RCY increased from 8 % (without the use of n-butanol for alcohol enhancement) to 40 % using alcohol-enhanced Cu(II)-mediated radiofluorination. Furthermore, the radiosynthesis of 2-[^{18}F]FPhe, 6-[^{18}F]FMT and 5-[^{18}F]FMT using boronic acid pinacol esters was transferred to a remote-controlled synthesis device. High RCYs lead to product activities of 2.4–18.8 GBq enabling preclinical studies.

Conclusions: The combination of alcohol–enhanced and copper-mediated radiofluorination of BPE as labelling precursors was studied with regard to the automated synthesis of several aromatic amino acids. 6-[^{18}F]FDOPA, 2-[^{18}F]FPhe, 6-[^{18}F]fluoro-L-*meta*-tyrosine (6-[^{18}F]FMT) and 5-[^{18}F]fluoro-L-*meta*-tyrosine (5-[^{18}F]FMT) were obtained in high RCY of 40–66% and up to > 99% *ee*. This enables their synthesis in large amount of radioactivity and high radiochemical and enantiomeric purity, which is necessary for their use in preclinical studies.

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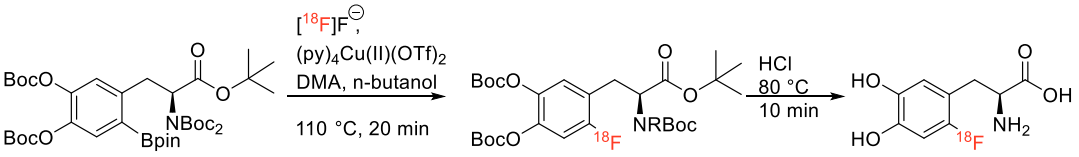
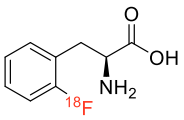
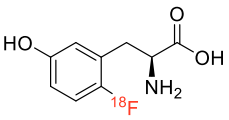
References: [1] S. Preshlock, M. Tredwell, V. Gouverneur, *Chem. Rev.* **2016**, *116*, 719-766. [2] J. Zischler, N. Kolks, D. Modemann, B. Neumaier, B. D. Zlatopolskiy, *Chem. - Eur. J.* **2017**, *23*, 3251-3256.



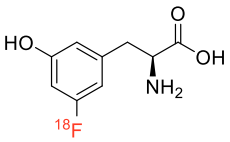
6-[^{18}F]FDOPA



2-[^{18}F]FPh



6-[^{18}F]FMT



5-[^{18}F]FMT