Automated radiosynthesis of [^{18}F]DOPA and [^{18}F]FMT via copper-mediated nucleophilic F-18 Fluorination of arylstannanes on a new synthesizer

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Introduction

Over the last decades, 6-[^{18}F]fluoro-L-3,4-dihydroxyphenylalanine ([^{18}F]DOPA) has gained an increasing interest for imaging neuroendocrine tumors, brain tumors, and Parkinson's disease. This contributed to the demand to simplify the synthetic procedure of its production. Various nucleophilic synthesis methods[1] have been reported to avoid the issues of electrophilic synthesis such as low availability of [^{18}F]F_2 and low molar activity. Recently, transition metal-mediated ^{18}F-fluorination methods have been applied to radiochemistry enabling radiofluorination of arenes[2,3].

Objective

This study aimed to develop an efficient production of [^{18}F]DOPA including its analog (6-[^{18}F]fluoro-L-m-tyrosine ([^{18}F]FMT)) by means of Cu(II)-mediated radiofluorination of tin-precursors on a new Neptis® synthesizer (Modular).

Methods

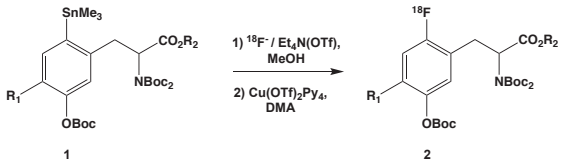

Figure 1 Synthesis of Protected [^{18}F]DOPA (R_1 = OBoc, R_2 = Me) and [^{18}F]FMT (R_1 = H, R_2 = Et)

The stannylated precursors (compound 1) were obtained by BOC protection of the *N*- position of the commercial precursors from ABX. Protected [^{18}F]DOPA and [^{18}F]FMT (compound 2) were synthesized via nucleophilic radiofluorination using the Neptis® synthesis module.

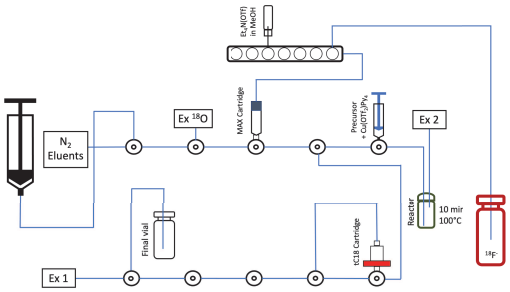

Figure 2 Layout of the radiosynthesizer

To hydrolyze protected-[^{18}F]DOPA, different approaches have been explored as shown in the scheme below.

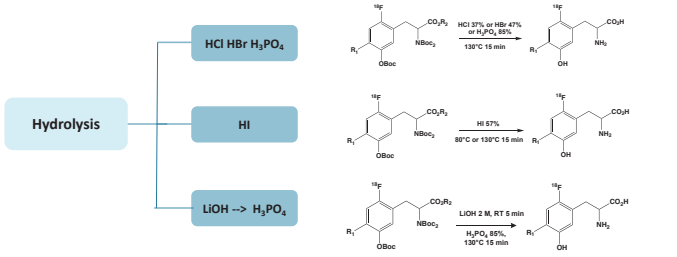

Figure 3 Hydrolysis methods

Results

The radiosynthesis afforded protected [^{18}F]DOPA 52 ± 7% (n=6) and protected [^{18}F]FMT 63 ± 8% (n=6) (TLC yield). After trapping and washing steps on a Waters SepPak tC18 cartridge, radiochemical yields (RCY) of 42 ± 6% ([^{18}F]DOPA, n=5) and 53 ± 7% ([^{18}F]FMT, n=3), respectively, were obtained after 40 minutes of radiosynthesis. Cu- and Sn-content after purification were determined by ICP-MS. Total metal residue was below the limit according to the ICH Guidelines[4] (340 and 640 µg/day, respectively for Cu and Sn).

	Cu (ppb)	Sn (ppb)	Cu (µg)	Sn (µg)
Protected [^{18}F]DOPA	95.7 ± 24.1	226.7 ± 19.2	0.19 ± 0.05	0.45 ± 0.04
Protected [^{18}F]FMT	17.8 ± 5.7	381.3 ± 63.9	0.04 ± 0.01	0.76 ± 0.13

Table 1 Concentrations (ppb) and amounts (µg) of Cu and Sn in the solution of protected [^{18}F]DOPA (n=4) and [^{18}F]FMT (n=3)

- **Hydrolysis with HCl 37%, HBr 47%, and H_3PO_4 85%**

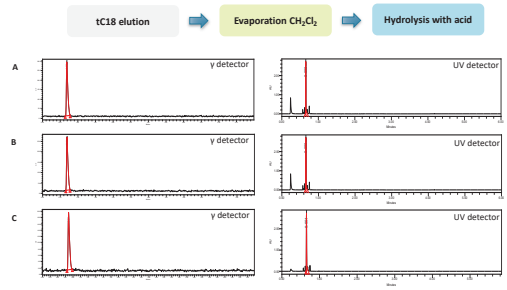

Figure 4 [^{18}F]DOPA hydrolyzed by HCl 37%, HBr 47%, and H_3PO_4 85% at 130°C 15min in γ detector (A, B and C) (left) and the co-injection of [^{19}F]DOPA reference and [^{18}F]DOPA (UV detector, 280 nm) (right)

- **Hydrolysis with HI 57%**

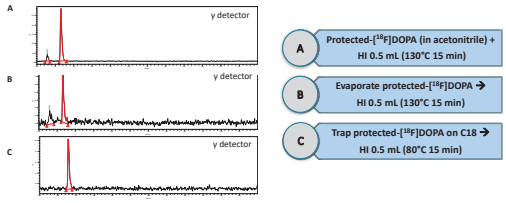

Figure 5 [^{18}F]DOPA with different hydrolysis conditions with HI 57%

- **Hydrolysis with LiOH and H_3PO_4 85%**

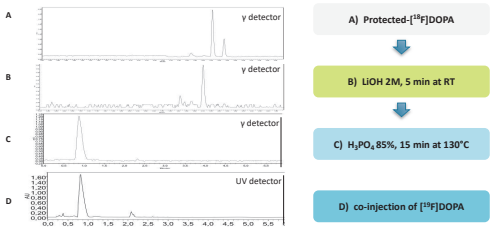

Figure 6 Protected-[^{18}F]DOPA (A), protected-[^{18}F]DOPA after incubation with LiOH 2M for 5 min at RT (B), [^{18}F]DOPA after incubation H_3PO_4 85% for 15 min at 130°C (C), and coinjection of [^{19}F]DOPA in UV detector (D)

Conclusions and Perspectives

We have demonstrated the feasibility of the synthesis of [^{18}F]FDOPA and [^{18}F]FMT in a standard one-reactor synthesis module. The Cu-mediated radiofluoro-destannylation offered protected [^{18}F]DOPA and [^{18}F]FMT within 40 min. At this moment, the hydrolysis was achieved by adding acid or a solution of LiOH to protected [^{18}F]DOPA followed by acid. The purity of [^{18}F]DOPA is now being determined with chiral HPLC. This synthesis would simplify and shorten the time for the procedure of [^{18}F]DOPA .

References

1. Krasikova, Raisa N. "Nucleophilic Synthesis of 6-L-[18F]FDOPA. Is Copper-Mediated Radiofluorination the Answer?." *Molecules* 25.19 (2020): 4365.
2. Makaravage, Katarina J., et al. "Copper-mediated radiofluorination of arylstannanes with [18F]KF." *Organic letters* 18.20 (2016):5440-5443.
3. Zarrad, Fadi et al. "A practical method for the preparation of 18F-labeled aromatic amino acids from nucleophilic [18F] fluoride and stannyl precursors for electrophilic radiohalogenation." *Molecules* 22.12 (2017): 2231.
4. Guideline for Elemental Impurities. In Q3D; ICH: Geneva, Switzlerand, (2013):39-40.

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