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

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Objectives:

- ^{18}F-Labeled aromatic amino acids exhibit high potential for diagnostic applications using PET.
- Lack of convenient preparation methods.

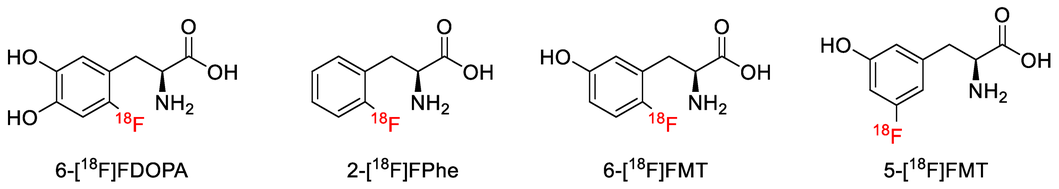

Fig. 1: Structures of studied ^{18}F-labeled aromatic amino acids prepared within this study

Aim: Development of a practical procedure for the preparation of ^{18}F-labeled aromatic amino acids on a preparative scale.

Methods:

- Synthesis of pinacol boronate ester (Bpin) precursors synthesized by Miyaura borylation.

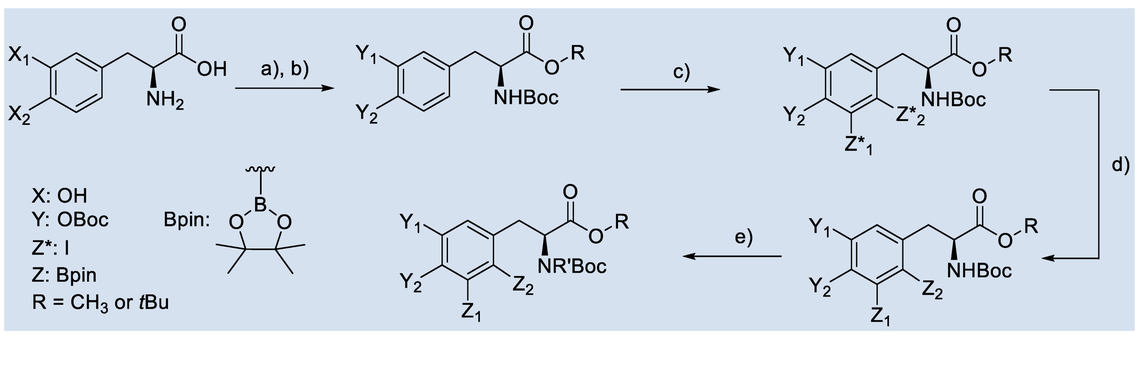

Fig. 2: Synthesis of Bpin precursors for 6-[^{18}F]FDOPA 1, 2-[^{18}F]FPhe, 5- and 6-[^{18}F]FMT; conditions: a) (for R= tBu) AcOtBu, $HClO_4$. b) Boc_2O, c) BTI, I_2 in DCM d) B_2pin_2, $Pd(dppf)Cl_2$, KOAc in DMF, e) 4-DMAP, Boc_2O in MeCN.
Bpin precursor for 6-[^{18}F]FDOPA: $X_{1,2}$ = OH, $Y_{1,2}$ = OBoc, Z_1 =H, Z_2 = Bpin, R = tBu, R' = Boc;
Bpin precursor for 2-[^{18}F]FPhe: $X_{1,2}$ = H, $Y_{1,2}$ = H, Z_1 =H, Z_2 = Bpin, R = tBu, R' = Boc;
Bpin precursor for 6-[^{18}F]FMT: X_1 = OH, X_2 = H, Y_1 = OBoc, Y_2 = H, Z_1 =H, Z_2 = Bpin, R = tBu, R' = Boc;
Bpin precursor for 5-[^{18}F]FMT: X_1 = OH, X_2 = H, Y_1 = OBoc, Y_2 = H, Z_1 = Bpin, Z_2 =H, R = CH_3, R' = H.

- Alcohol-enhanced Cu-mediated radiofluorination with $Cu(Py)_4(OTf)_2$:[1,2]
  - $[^{18}F]F^-$ fixed on a QMA-cartridge and eluted with Et_4NHCO_3 (1 mg) in MeOH with subsequent MeOH evaporation.
  - Addition of precursor (10 µmol) and $Cu(Py)_4(OTf)_2$ (20 µmol) in a mixture of DMA (500 µL) and *n*-BuOH (250 µL).
  - Heating to 110 °C for 20 min.
  - Hydrolysis with HCl (10.8 mol, 0.8 mL) 80 °C for 10 min.
  - HPLC-separation: Phenomenex Hydro-RP 4 µm 80 Å (4.6x250mm) column with 2 % EtOH 2-[^{18}F]FPhe and 5-[^{18}F]FMT) or 1 % EtOH: 6-[^{18}F]FMT (1 mL/min); Hamilton PRP-C18 (10x250 mm); 6-[^{18}F]FDOPA: 0.05 M $HCl_{(aq)}$ (3 mL/min).

Results and Discussion:

- Labeling precursors prepared in total yields of 5–17 % in 3–5 steps.
- *N,N*-Boc precursors of 6-[^{18}F]FDOPA, 2-[^{18}F]FPhe and 6-[^{18}F]FMT enabled more efficient radiosynthesis of the corresponding ^{18}F-labeled tracers in contrast to mono-Boc protected ones.
- During the copper-mediated ^{18}F-for-Bpin radiofluorination partial deprotection (loss of one Boc-group) (see Fig. 3).
- The corresponding ^{18}F-labeled aromatic amino acids were obtained in 40–66 % RCY within 110 to 120 min (cf. Table 1).
- Enantiomeric excess (ee) of 2-[^{18}F]FPhe, 6-[^{18}F]FDOPA and 6-[^{18}F]FMT > 94 %.

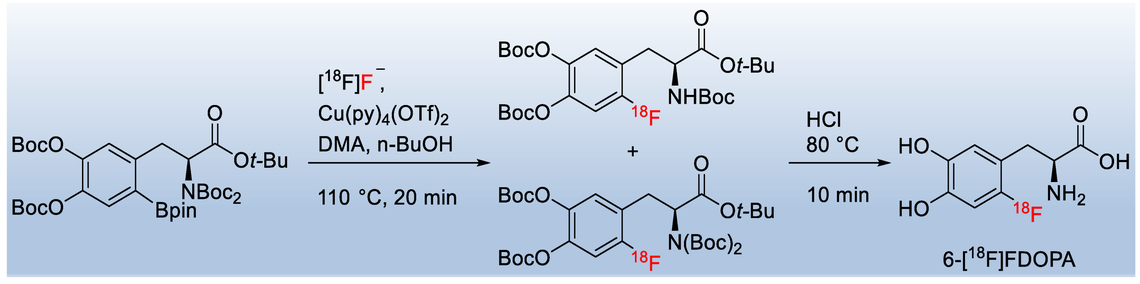

Fig. 3: Preparation of 6-[^{18}F]FDOPA.

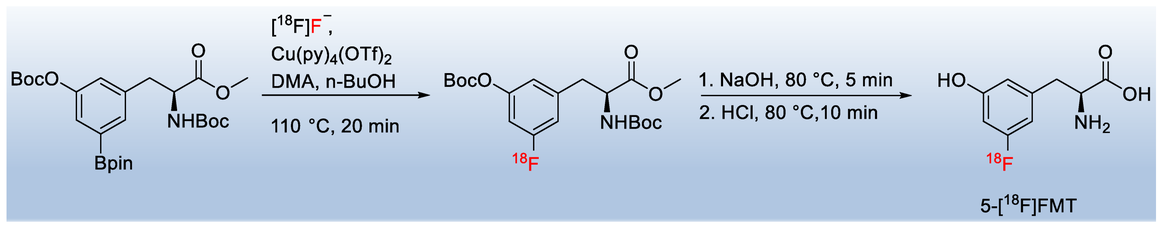

Fig. 4: Preparation of 5-[^{18}F]FMT.

- Successful transfer of the novel method into an automated synthesis module for the production of 2-[^{18}F]FPhe, 5- and 6-[^{18}F]FMT in 31–50 % RCY (see Tab. 1).

Tab. 1: Summary of results

Precursor →Tracer	RCY (manually)	RCY (automated)	Molar activity	*ee*
→ 6-[^{18}F]FDOPA	40 ± 4 % 110 min (n = 3)	n. d.	37 GBq/µmol	> 99 %
→ 2-[^{18}F]Fphe	57 ± 6 % 110 min (n = 3)	31 ± 6 % 110 min (n = 3)	185 GBq/µmol	> 99 %
→ 6-[^{18}F]FMT	48 ± 5 % 110 min (n = 3)	41 ± 8 % 110 min (n = 4)	251 GBq/µmol	> 99 %
→ 5-[^{18}F]FMT	66 ± 1 % 120 min (n = 3)	50 ± 2 % 120 min (n = 3)	121 GBq/µmol	94 %

Summary:
Convenient production of ^{18}F-labeld aromatic amino acids using alcohol enhanced Cu-mediated radiofluorination enabling the production of 6-[^{18}F]FDOPA, 2-[^{18}F]FPhe, 6-[^{18}F]FMT and 5-[^{18}F]FMT, in high amounts, sufficient for preclinical and clinical applications.

References:

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

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