Novel efficient synthesis of D-[^{18}F]FMT using direct [18F]fluorination of triazolium salt leaving group-tethered precursor

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Objectives

O-([^{18}F]Fluoromethyl)-D-tyrosine (D-[^{18}F]FMT) was reported to have fast clearance property and high tumor-to-background ratio in the comparison study with the well-known [^{18}F]FET and [^{18}F]FPT [1]. Previously it was synthesized by the *O*-alkylation of tyrosine with in situ prepared [^{18}F]CH_2FBr or [^{18}F]CH_2OTs [2]. For more efficient synthesis, a direct [^{18}F]fluorination using a triazolium salt-tethered precursor was investigated.

Methods

The triazolium salt precursors in this study were prepared using a click chemistry (CuAAC reaction) [3]. [^{18}F]Fluorination of the triazolium salt precursors was optimized in various conditions. Chiral HPLC analysis was performed to confirm the possible epimerization during [^{18}F]fluorination.

Results

N-BOC, *O*-DMB protected triazolium salt precursor was prepared in 4-step synthesis in enantiomeric pure form. However, the nucleophilic [^{18}F]fluorination of the D-configured precursor gave 7-15% epimerized mixture. We promptly changed BOC protection group on amine with an epimerization-tolerable trityl (Tr) group. The *N*-Tr, *O*-DMB protected precursor was synthesized in 5 steps, and proved to give only pure D-[^{18}F]FMT with no empimerization. The direct [^{18}F]fluorination was performed in *t*-amyl alcohol solvent for 5 min at 110 ^{o}C, affording 85.7±2.2% (n=4) of radiochemical yield*. After evaporation of *t*-amyl alcohol solvent, subsequent deprotection was carried out in 4 N HCl in dioxane for 5 min at room temperature, giving 73.5±1.5% (n=4) of radiochemical yield*. During the deprotection reaction, [^{18}F]defluorination was observed to some extent (about 10%). The crude mixture was purified with HPLC. Total synthesis time was 50 min and radiochemical yield was 40% after HPLC purification. (*determined by radio-TLC analysis of the crude product)

Conclusion

The direct [^{18}F]fluorination of the triazolium salt precursor gave highly enantiomeric pure D-[^{18}F]FMT in high yield. This two-step synthesis is likely to be suited to the automated manufacturing of D-[^{18}F]FMT.

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