Radiosynthesis of 1-[2-[18F]Fluoro-1-(hydroxymethyl)-Ethoxy]methyl-2-Nitroimidazole([18F]FENI)

II. 1. Radiosynthesis of 1-[2-[^{18}F]Fluoro-1-(hydroxymethyl)-Ethoxy]methyl-2-Nitroimidazole ([^{18}F]FENI)

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The 2-nitroimidazole nucleoside analog, RP-170[1-3], was developed as a potential radiosensitizer for hypoxic tumor cells and is reported to have similar reduction potential and radiosensitizing activity to those of misonidazole and etanidazole, which are metabolically trapped by hypoxic cells. Based on their selective binding and retention in hypoxic regions, it was expected that the radiolabeled derivative of RP-170 would serve as a useful probe for hypoxic tissues as does [^{18}F]fluoromisonidazole (FMISO)[4-8].

In this report, we describe a radiosynthesis of a fluorinated analog of RP-170, 1-[2-fluoro-1-(hydroxymethyl)-ethoxy]methyl-2-nitroimidazole (FENI) from no-carrier-added [^{18}F]fluoride.

The precursor **4** for the preparation of [^{18}F]FENI ([^{18}F]**2**) was synthesized from RP-170 (**1**), which was supplied by POLA Chemical Industries, Inc., according to the synthetic scheme shown in Figure 1. It was prepared in the overall yield of 44% based on **1**.

Nca [^{18}F]fluoride was produced via the ^{18}O(p,n)^{18}F reaction with a Cypris HM12 cyclotron (Sumitomo Heavy Ind.) and added to a glass vial containing K.2.2.2. (30 mg) in MeCN (1 mL). The solution was heated at 110℃ and evaporated to dryness with the aid of a He flow. To the residue was added a solution of **4** (5-6 mg) in dry DMF (1 mL), and the reaction mixture was heated at 110℃ for 5 min (see Fig. 2a). The reaction was quenched by adding H_2O (10 mL), and the resulting mixture was passed through a Sep-Pak Plus C18 cartridge, which was then washed with 0.05 N HCl (10 mL) and H_2O (10 mL). The ^{18}F-fluorinated product, [^{18}F]**5**, retained by the C18 was eluted with MeCN (4 mL). The eluate was evaporated to dryness. To the residue was added a 0.05 N NaOH solution of 50% ethanol-in-water and the mixture was heated for 1 min at 40℃ (see Fig. 2b). The reaction mixture was passed through an IC-H Plus cartridge for neutralization, and the eluate was evaporated to dryness. The residue was dissolved in an HPLC solvent (MeCN-H_2O: 15/85) and injected onto a semi-preparative HPLC C18 column (A-324, 10 mm×300 mm, YMC). The effluent at a flow rate of 6.0 mL/min was monitored with both radioactivity and UV detectors, and the fraction containing the desired product was collected (see Fig. 3).

Chemical and radiochemical purity was assayed by analytical HPLC on a reverse phase C18 column (Inertsil ODS 80A, 4.6 mm×250 mm, GL Sciences) with a solvent system of MeCN-H_2O (30/70). No other radioactive peak than [^{18}F]FENI or no UV peak corresponding to FENI was found.

The radiosynthesis consists of commonly used procedures, two reaction steps of ^{18}F-substitution and deprotection and two purification steps of solid phase extraction and final HPLC separation. Among them the first step mainly determined the radiochemical yield of the present preparation. As shown in Fig. 2a, it was observed that the radiochemical yield of [^{18}F]**5** gradually increased up to only 14% during the first 4 min and then decreased and more hydrophilic degradation products were found to increase in the reaction solution. It is suggested that the ether bond of **3** is likely to be cleaved by prolonged heating under the basic conditions.

The radioactive peak eluting at 6.5-7.0 min, corresponding to [^{18}F]FENI ([^{18}F]**2**), was collected and evaporated to dryness under reduced pressure. The residue was dissolved in saline. The overall synthesis time including HPLC purification and formulation was less than 90 min. The specific activity was estimated to be higher than 26 GBq/mmol (0.7 Ci/mmol) at the end of the synthesis. The average decay-corrected overall radiochemical yield was 6.2% (3-11%, 12 runs).

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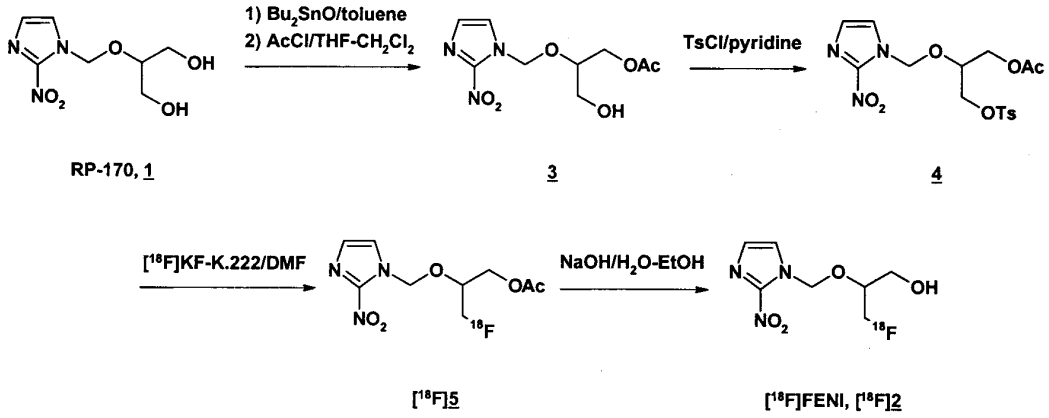

Figure 1. Synthetic method for [^{18}F]FENI.

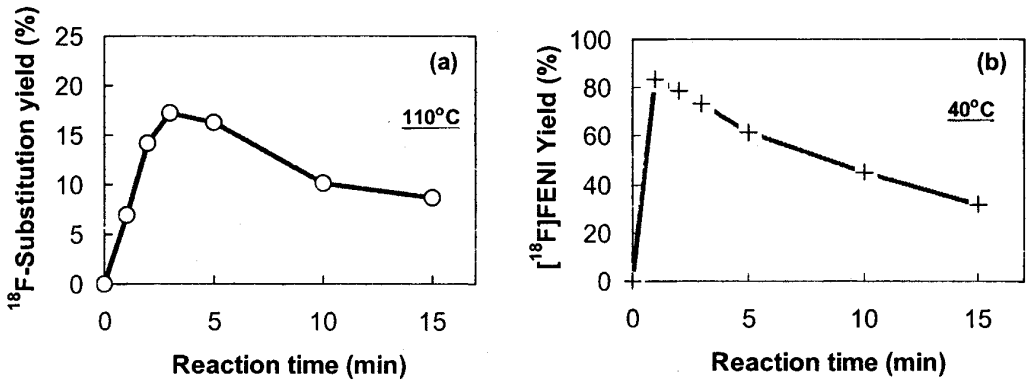

Figure 2. Optimization of ^{18}F-substitution (a) and deprotection (b).

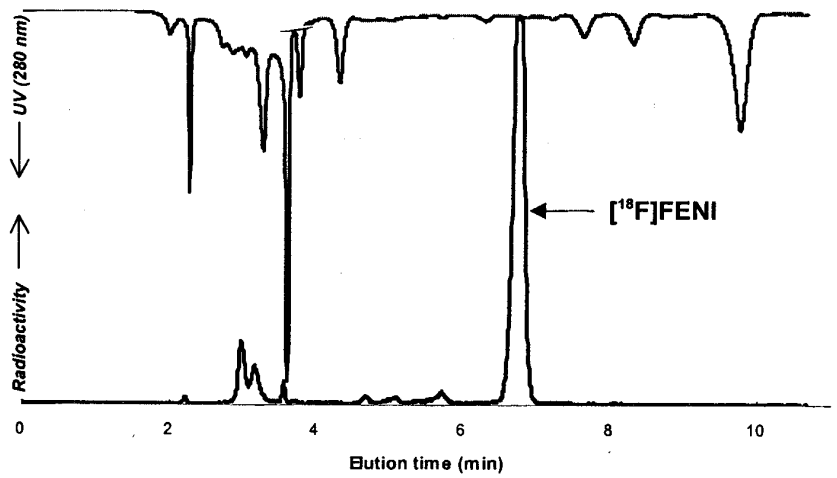

Figure 3. Semi-preparative HPLC separation.