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Research Article

A general synthesis of 2′-deoxy-2′-[^{18}F]fluoro-1-β-D-arabinofuranosyluracil and its 5-substituted nucleosides

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Summary

Several 2′-deoxy-2′-[^{18}F]fluoro-1-β-D-arabinofuranosyluracil derivatives have been synthesized. Coupling of 1-bromo-2-deoxy-2-[^{18}F]fluoro-3,5-di-O-benzoyl-α-D-arabinofuranose **2** with protected uracil derivatives **3a–e** followed by hydrolysis and high-performance liquid chromatography purification produced the radiolabeled nucleosides **4a–e** in 15–30% yield (d. c.), >99% radiochemical purity and 55.5–103.6 GBq/μmol specific activities. Copyright © 2003 John Wiley & Sons, Ltd.

Key Words: fluorine-18; nucleoside

Introduction

Radiolabeled pyrimidine nucleosides such as [^{11}C]-FMAU and [^{124}I]-FIAU are potential PET imaging agents for tumor proliferation and gene expression, respectively.[1–5] However, the short half-life of ^{11}C and potential for de-iodination of ^{124}I are less than optimal for imaging purposes. The [^{18}F]-labeled compounds should be more advantageous.

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In addition, other 2′-deoxy-2′-[^{18}F]fluoro-5-substituted-1-β-D-arabinofuranosyluracil nucleosides[6,7] may be potential imaging agents. Conventional syntheses of such 2′-deoxy-2′-fluoro-nucleosides are not suitable for the respective [^{18}F]-labeled products.[8–11] We reported earlier a method suitable for [^{18}F]-FMAU.[12–14] Now we report here syntheses of other 2′-deoxy-2′-[^{18}F]fluoro-arabinofuranosyluracil analogues by the same process thus providing a general synthetic method for such of [^{18}F]-nucleosides.

Results and discussion

The scheme for the synthesis of the [^{18}F]-labeled nucleosides **4a–e** is shown in Figure 1. Compound **2** was prepared in two steps as previously reported.[14] In the first step fluorination reaction, $\sim$10 μmol of the precursor **1**, and $\sim$7 μmol of *n*-Bu_4NHCO_3 produced a radiochemical yield of 58–68%. Any variation from this stoichiometry lowers the yields of the desired product. A lower amount of *n*-Bu_4NHCO_3 apparently does not extract the ^{18}F-fluoride efficiently from the reaction vial. Excess *n*-Bu_4NHCO_3 is presumably converted to *n*-Bu_4NOH, and hydroxide ion competes with fluoride ion reducing the yield.

Compound **2** was recovered by evaporation of the solvent and excess reagents azeotropically removed with toluene. The amount of toluene is important, and 1 ml appears to be ideal. A smaller volume reduces the yield of the coupled product in the subsequent step. A residual trace of acetic acid converts the compound **2** to the 1-acetoxy derivative.

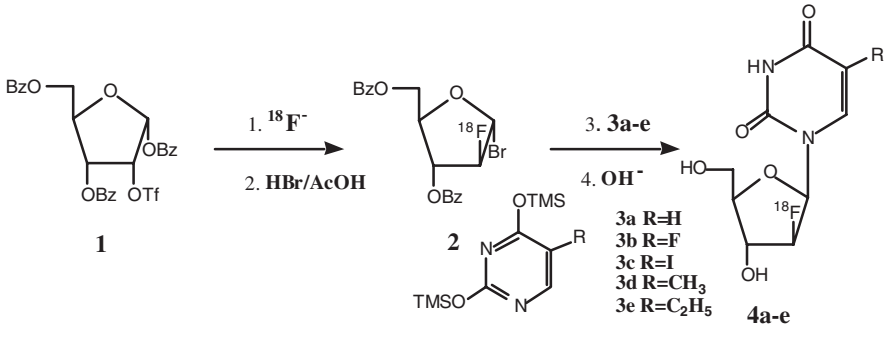

Figure 1. Synthetic scheme of 2′-deoxy-2′-[^{18}F]fluoro-1-β-D-arabinofuranosyluracil nucleosides

Coupling of the 1-bromo-2-[^{18}F]fluorosugar **2** with pyrimidine silyl ethers **3a–e** requires 1 h for optimum yield. The silyl derivative of thymine (**3d**) seems to be rather sensitive to the presence of moisture as indicated by the appearance of solvent turbidity during the addition of the thymine silyl ether solution to the reaction vessel. The crude reaction mixture was passed through a Sep-Pak cartridge (silica) and eluted with 10% methanol in dichloromethane to reduce the amount of unreacted pyrimidine present. After basic hydrolysis, the coupled products produced the desired nucleosides **4a–e**, which were isolated by high-performance liquid chromatography (HPLC) purification.

Analysis of the products, **4a–e** by HPLC showed a single radioactive peak co-eluting with an authentic standard of the respective nucleosides; The overall radiochemical yields of this synthesis was 15–30% (d.c.) from the EOB. The radiochemical purity was > 99% with specific activities 55.5–103.6 GBq/μmol. The synthesis time was 3.5–4.0 h from the EOB. In typical syntheses, 444–666 MBq of labeled products were obtained from 7400–9620 MBq of [^{18}F] fluoride.

Experimental

Reagents and instrumentation

2-O-(trifluoromethylsulfonyl)-1,3,5-tri-O-benzoyl-α-D-ribofuranose **1**, 1-bromo-2-deoxy-2-[^{18}F]fluoro-3,5-di-O-benzoyl-α-D-arabinofuranose **2** and pyrimidine-2,5-bis-trimethylsilyl ether **3a–e** were prepared following literature methods.[9,10,14] Intermediate radiolabeled products were not isolated but used directly in the subsequent steps. The corresponding unlabeled compounds were isolated and characterized by ^{1}H and ^{19}F NMR and mass spectrometry.

Proton and ^{19}F NMR spectra were recorded on a Brucker 500 MHz spectrometer using tetramethylsilane as an internal reference and hexafluorobenzene as an external reference, respectively. Mass spectra were obtained on a Finnigan 400 mass spectrometer at the University of Minnesota using ammonia chemical ionization technique. HPLC was performed as reported.[14] Acetonitrile/water solvent systems, 5.0% MeCN for FAU (**4a**), 7.5% for FFAU (**4b**) and FMAU (**4d**), and 10% for FIAU (**4c**) and FEAU (**4e**) were used for purification of the radiolabeled nucleoside and quality control analyses.

*2′-Deoxy-2′-[^{18}F]fluoro-5-substitued-1-β-*D*-arabinofuranosyluracil derivatives 4a–e*

The radiolabeled nucleosides **4a–e** were prepared following the reported method.[14] Briefly, compound **2** was heated with freshly prepared 2,4-bis-O-(trimethylsilyl)uracil derivatives **3a–e** (75–85 μmol, 8–9 equiv.) in 1,2-dichloroethane (0.5 ml) at ~100°C for 60 min. The reaction mixture was cooled, passed through a Sep-Pak cartridge (silica) and eluted with 10% methanol in dichloromethane (2.5 ml). After solvent evaporation the crude product was heated for 5 min at reflux with sodium methoxide (1 M solution in methanol, 0.03 ml). The crude product was cooled, neutralized, diluted with HPLC solvent and purified by HPLC at a flow of 4.05 ml/min. After solvent evaporation, the pure product was re-dissolved in saline and filtered through a 0.22 μm filter. An aliquot of the final product was analyzed by analytical HPLC, and found to be co-eluting with the authentic compound.

Unlabeled chemical syntheses were performed in the similar manner except in larger scale (40–50 mg of **1**). The ^{1}H NMR spectra were consistent with the literature.[6, 9–11] Additional data was obtained with ^{19}F NMR spectra as presented. Compounds **4a**: DMSO-D_6: ^{19}F NMR: $\delta = -196.6$ (dt). **4b**: D_2O: ^{19}F NMR: $\delta = -166.8$ (d), -199.6 (dt). **4c**: DMSO-D_6: ^{19}F NMR: $\delta = -196.3$ (dt). **4d**:[13]. **4e**: DMSO-D_6: ^{19}F NMR: $\delta = -197.2$ (m).

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