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Research Article

Simple and High radiochemical yield synthesis of 2′-Deoxy-2′-[^{18}F]fluorouridine via a new nosylate precursor

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Summary

We synthesized 2'-deoxy-2'-[^{18}F]fluorouridine (**7**) as a radiotracer for positron emission tomography from a new nosylate precursor (**6**). This new precursor was synthesized from uridine in four steps. The overall synthetic yield was 9.4% and we have high stability of >98% purity up to 6 months at 4°C. The optimal manual [^{18}F]fluorination conditions were 30 mg of the precursor **6** in 500 µl of acetonitrile at 145°C for 15 min with 370 MBq of [^{18}F]fluoride. The [^{18}F]fluorination yield was 76.5 ± 2.7% ($n = 3$). After hydrolysis of protecting groups with 1 N HCl and purification by HPLC, the overall radiochemical yield and purity were 26.5 ± 1.4% and 98.2 ± 2.5%, respectively. The preparation time was 70.0 ± 10.5 min ($n = 3$ for each result). We also developed an automated method with a radiochemical yield and purity of 24.0 ± 2.8 and 98.0 ± 1.5% ($n = 10$) using a GE TracerLab MX chemistry module. This new nosylate precursor for 2'-deoxy-2'-[^{18}F]fluorouridine synthesis showed higher radiochemical yields and reproducibility than previous methods.

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Key Words: 2'-[^{18}F]fluorouridine; tumor cell proliferation; uridine; positron emission tomography; [^{18}F]fluoride; gene imaging

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Introduction

A variety of nucleoside analogs, including [^{11}C]thymidine,[1] [^{76}Br]bromodeoxyuridine,[2–4] [^{131}I]iododeoxyuridine,[5–6] and [^{18}F]fluorothymidine ([^{18}F]FLT)[7,8] have been developed for tumor imaging by single photon emission and positron emission tomography. Another nucleoside analog developed as an antitumor agent, 2'-deoxy-2'-fluorouridine (2'-FU) (**5**), has shown a high ratio of DNA incorporation in rat and woodchucks.[9,10] In the previous report, 2'-[^{18}F]FU was prepared from an anhydro-ring type precursor and labeled with $^{18}F^-$ so that it can be used to follow tumor cell proliferation.[10] Although the method for synthesizing 2-[^{18}F]FU is rapid and simple, the radiochemical yield is very low ($<1\%$), and the [^{18}F]fluorination step is slow and requires dioxane as a solvent.

In the previous study, we developed a more efficient method for producing 2'-[^{18}F]FU. We first examined the use of a triflate precursor (Figure 1).[11] We obtained an $82.4 \pm 3.6\%$ yield ($n=3$) of [^{18}F]fluorination as determined by thin-layer chromatography (TLC). This triflate precursor, however, was stable for only 1 day even below 0°C due to sensitivity to moisture. In addition, it was difficult to purify the precursor and final product due to the presence of breakdown products.

Recently, better results have been achieved using a new nosylate precursor in place of an anhydrothymidine precursor for [^{18}F]FLT synthesis.[12–15] This new nosylate precursor showed 5- to 10-fold higher radiochemical yields than the previous anhydrothymidine precursor, and it was stable at 4°C for several months. Therefore, we used the nosylate leaving group to synthesize 3',5'-di-*O*-tetrahydropyranyl-2'-*O*-nosyl-1-β-D-*arabino*pentofuranosyluracil (**6**) as a new precursor for [^{18}F]2'-FU and 2'-FU. In this study, we optimized [^{18}F]fluorination conditions with this precursor and applied them to an automatic production with disposable cassette type synthesis module.

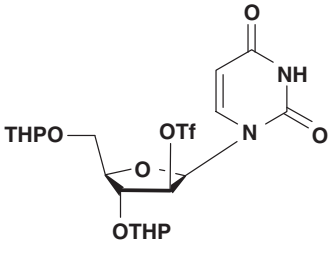

Figure 1. Chemical structure of the triflate precursor, 3',5'-di-*O*-tetrahydropyranyl-2'-*O*-triflate-1-β-D-*arabino*pentofuranosyluracil. In the previous report, this triflate leaving group procedure showed high [^{18}F]fluorination yields but very low chemical stability even below 0°C[11]

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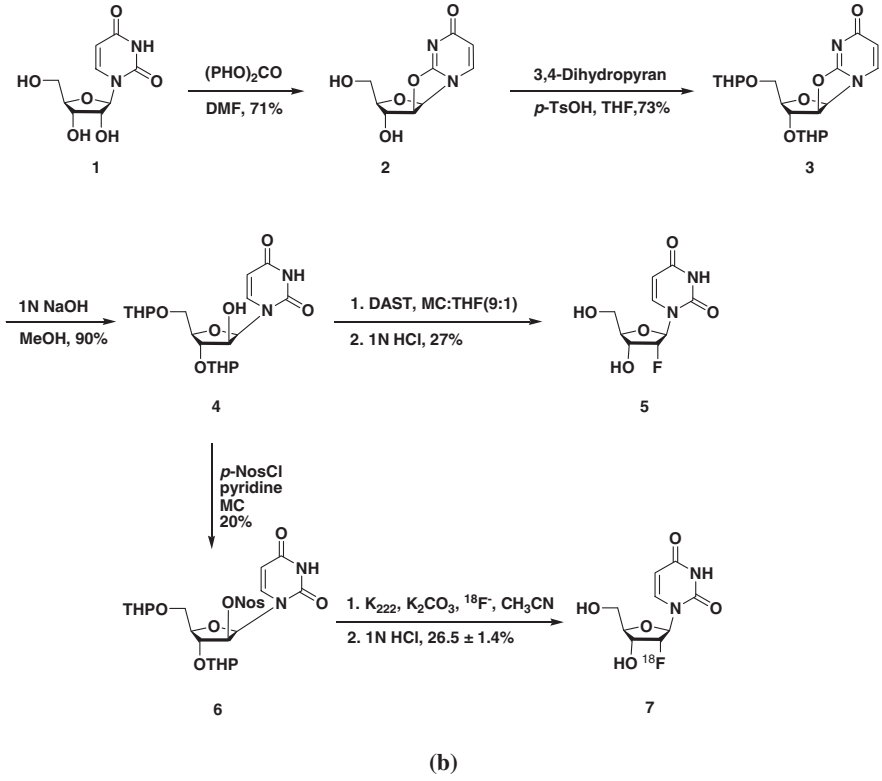
Results and discussion

*Synthesis of 2'-FU (**5**) and a nosylate precursor (**6**)*

We synthesized 3',5'-di-*O*-tetrahydropyranyl-2'-*O*-nosyl-1-β-D-*arabino*pentofuranosyluracil (**6**) as a new precursor for the synthesis of 2'-[^{18}F]FU from uridine via four steps (Scheme 1), with an overall yield of 9.4%. Starting from uridine (**1**), 2,2'-anhydro-1-β-D-*arabino*furanosyluracil (**2**) was obtained to protect the hydroxyl group at the 2'-position.[16] The remaining hydroxyl groups at the 3'- and 5'-positions were protected with tetrahydropyranyl (THP) groups, which we previously showed to give higher [^{18}F]fluorination yields than acetyl-, benzyl-, and dimethoxytrityl-protected precursors.[11]

The anhydro-ring opening reaction of compound **3** was carried out in 1 N NaOH. Unlabeled 2'-FU (**5**) was obtained using DAST ((diethylamino)sulfur trifluoride) as a fluorinating agent in 9:1 (v/v) CH_2Cl_2/THF, followed by



(b)

Scheme 1. Chemical and radiochemical synthesis of the precursor and 2'-[^{18}F]FU. The precursor, 3',5'-di-*O*-tetrahydropyranyl-2'-*O*-nosyl-1-β-D-*arabino*-pentofuranosyluracil, was synthesized from uridine in four steps, and [^{18}F]2'-FU was obtained from the precursor in two steps ([^{18}F]fluorination and hydrolysis of protecting groups)

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hydrolysis of THP-protecting groups of the ring-opened 3',5'-di-*O*-tetrahydropyranyl-1-β-D-arabinofuranosyluracil (**4**) with 1N HCl. Nosylation of **4** was performed using *p*-nitrophenylsulfonyl chloride and pyridine in CH_2Cl_2. This nosylated precursor **6** was isolated as a white solid after column chromatography purification on silica gel. Compared with the previous triflate precursor, this new nosylate precursor showed good stability (>95% after 6 months at 4°C). ^{1}H and ^{13}C NMR and elemental analyses confirmed the production of 2'-FU (**5**) and the nosylate precursor (**6**).

Radiochemistry

[^{18}F]fluorination yields of the nosylate precursor (**6**) were examined by TLC and autoradiography. As shown in Table 1, the yields depended on the reaction temperature and the precursor concentrations. The optimal [^{18}F]fluorination conditions were 30 mg of precursor (**6**) at 145°C for 15 min with 370 MBq of [^{18}F]fluoride. After purification by HPLC, we obtained a decay-corrected radiochemical yield of 26.5 ± 1.4% and a radiochemical purity of 98.2 ± 2.5%. The total synthetic time including HPLC purification was 70.0 ± 10.5 min ($n = 3$). The synthesis of 2'-[^{18}F]FU (**7**) was confirmed by co-injection of unlabeled 2'-FU standard (**5**) and [^{18}F]FU. They showed same retention time (14.4 min) on UV (254 nm) and radioactive spectrum because two compounds of same chemical structure have same *k*-factor. The crude, purified samples and co-injection HPLC spectrum was in Figure 2.

We selected 15 min as the reaction time for the [^{18}F]fluorination because it gave the maximum yield. Hydrolysis of the THP-protecting group was performed in 0.5 ml of 1 N HCl at 85°C for 10 min. This hydrolysis temperature was lower than in previous reports to prevent decomposition of the compound. Despite a lower temperature, hydrolysis was complete.

We found only two radioactive peaks on the radioTLC. We assumed that the major peak corresponded to the target product after [^{18}F]fluorination, but the yield was low. In contrast to radioTLC, HPLC purification procedures

Table 1. Effect of reaction temperature and precursor concentration on radiochemical synthesis of 2'-[^{18}F]FU

	Radiochemical yields (%) (decay-corrected, $n = 3$ for each condition)		
	mg precursor per 500 µl of CH3CN		
Temperature (°C)	10	20	30
105	1.9 ± 3.1	2.1 ± 0.9	2.3 ± 0.1
125	8.5 ± 4.7	13.0 ± 1.1	17.4 ± 1.2
145	10.3 ± 1.4	17.2 ± 2.1	26.5 ± 1.4

Reactions were carried out for 15 min.
Decay-corrected radiochemical yields from 370 MGBq/0.5 ml of [^{18}F]fluoride.

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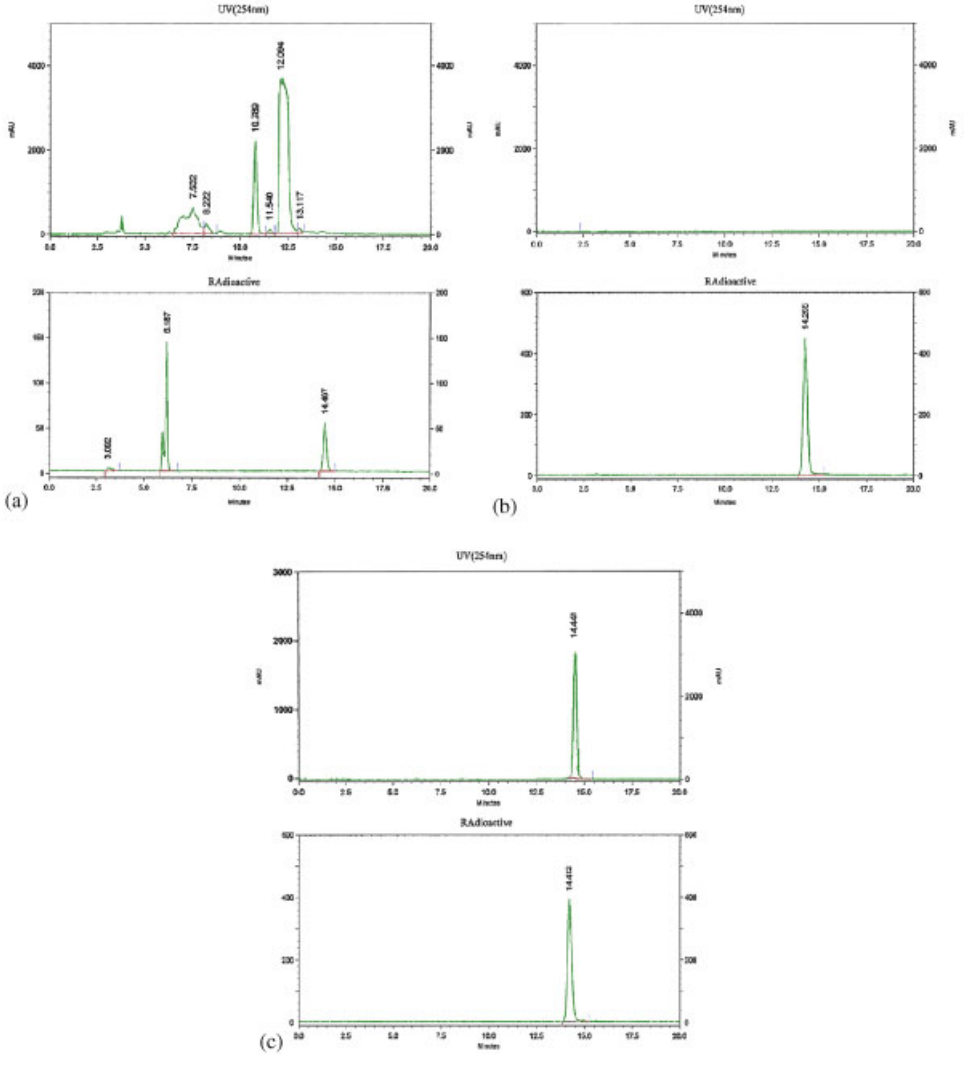

Figure 2. Purification of 2'-[^{18}F]FU: (a) HPLC profile of 2'-[^{18}F]FU (14.4 min) after crude HPLC purification; and (b) HPLC chromatogram of HPLC-purified 2'-[^{18}F]FU; and (c) HPLC chromatogram of coinjected purified 2'-FU and 2'-[^{18}F]FU. Unlike the TLC results, there were three radioactive peaks in the HPLC profile of the crude sample (a). Upper chromatogram shows UV detection, and lower chromatogram shows radioactivity. In (c) the retention times of 2'-FU and 2'-[^{18}F]FU were the same

separated the product into three distinct radioactive peaks, corresponding to $^{18}F^{-}$, an unknown polar [^{18}F]-labeled impurity product, and 2'-[^{18}F]FU. The unknown polar impurity was the major [^{18}F]-labeled compound. Although we tried to separate these three compounds on the radioTLC analysis with

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various radioTLC developing conditions, we could not effectively separated them. Unlike radioTLC analysis, HPLC analysis showed same results from two different columns of ODS C_{18} (Beckman) and Luna C_{18} (Phenomenex).

We also developed an automated method for preparing 2'-[^{18}F]FU using a cassette-type chemistry module. After HPLC purification, we obtained a radiochemical yield and purity of $24.0 \pm 2.8\%$ and $98.0 \pm 1.5\%$ ($n = 10$), respectively. The total preparation time including HPLC purification was 65.0 ± 2.7 min ($n = 10$). We used the same sequence program which was used for [^{18}F]FLT[14] synthesis in a previous report with minor modification of temperature and time. Because the reaction procedures such as [^{18}F]fluorination and followed hydrolysis steps are the same between [^{18}F]FU and [^{18}F]FLT but only the difference is [^{18}F]fluorination temperature and time. Although we had a slightly higher [^{18}F]fluorination temperature (145°C), the reaction vessel did not rupture and the disposable cassette system did not leak.

Conclusion

We developed a new nosylate precursor (**6**) for the synthesis of 2'-[^{18}F]FU. This new precursor shows higher stability and [^{18}F]fluorination yields than other precursors. We also developed a simple automated method for synthesizing this tracer with high radiochemical yields using a single disposable cassette.

Experimental

General

TLC was performed using Merck Silica Gel 60 F254, and chemical spots were checked by UV light or 5% H_2SO_4 charring. Flash column chromatography was performed using silica gel Merck 60 (Art 9385; 230–400 mesh). ^{1}H NMR spectra were obtained on 300 MHz spectrometers. NMR spectra were recorded in ppm (δ) in relation to tetramethylsilane as an internal standard unless stated otherwise and are reported as follows: chemical shift, multiplicity (br = broad, s = singlet, t = triplet, q = quartet, m = multiplet), coupling constant, and integration. Elemental analyses were performed using a Carlo Erba EA 1108 analyzer. All reagents were purchased from Sigma-Aldrich Korea (Seoul, Korea) and were of reagent grade.

*2,2'-Anhydro-1-β-*D*-arabinofuranosyluracil (***2***)*

To a stirred suspension of diphenyl carbonate (9.65 g; 45 mmol) and *N,N*-dimethylformamide (11 ml) in a flask, uridine (10 g; 41 mmol) was added, and the slurry was heated to 80°C. Next, sodium bicarbonate was added (40 mg; 0.50 mmol), and the mixture was heated at 110°–120°C for 4 h. The reaction mixture was allowed to cool to room temperature and the precipitate was

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isolated by filtration through a Buchner funnel. The solid was washed with two bed volumes of methanol and then suspended as a slurry in 15 ml of methanol and stirred for 30 min. The product was isolated by filtration and dried under vacuum to afford 2,2'-anhydro-1-β-D-*arabino*furanosyluracil (**2**) as a white solid (6.62 g; 71%). ^{1}H NMR (400 MHz, D_2O): δ 7.85 (d, 1 H, $J = 7.2$ Hz), 6.47 (d, 1 H, $J = 5.6$ Hz), 6.13 (d, 1 H, $J = 7.2$ Hz), 5.40 (d, 1 H, $J = 5.2$ Hz), 4.60 (s, 1 H), 4.33 (s, 1 H), 3.50 (m, 2 H).

*3',5'-Di-O-tetrahydropyranyl-2,2'-anhydro-1-β-D-arabinofuranosyluracil (**3**)*

To a suspension of (**2**) (4 g, 17.70 mmol) in THF (160 ml), *p*-toluenesulfonic acid (6.70 g; 35.40 mmol) was added at 0°C, after which 2,3-dihydropyran (16 ml; 177 mmol) was added dropwise at 0°C, and the reaction mixture was stirred at room temperature for 2 h, resulting in a clear solution. The reaction mixture was neutralized with triethylamine. The solvent was removed by evaporation and the residue was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ and water, and then dried with $MgSO_4$. The solvent was evaporated, and the crude product was purified by recrystallization in CH_2Cl_2-hexane to give 3'-5'-di-*O*-tetrahydropyranyl-2,2'-anhydro-1-β-D-*arabino*furanosyluracil (**3**) as a white solid (four diastereomers; 3.80 g; 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (s, 1 H), 6.25 (s, 1 H), 5.93 (s, 1 H), 5.49 & 5.27 (s, 1 H), 4.76–4.38 (m, 4 H), 3.86–3.82 (m, 6 H), 1.73–1.20 (m, 12 H).

*3',5'-Di-O-tetrahydropyranyl-1-β-D-arabinofuranosyluracil (**4**)*

3'-5'-di-*O*-tetrahydropyranyl-2,2'-anhydro-1-β-D-*arabino*furanosyluracil (**3**) (3.80 g; 9.60 mmol) was dissolved in methanol (60 ml) and mixed with 20 ml of 1 N NaOH. After stirring for 2 h at room temperature, the reaction was neutralized with acetic acid and evaporated. The residue was concentrated to give 3'-5'-di-*O*-tetrahydropyranyl-1-β-D-*arabino*furanosyluracil (**4**) as a foamy solid (four diastereomers; 3.60 g; 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (ddd, 1 H, $J = 8.0$, 2.0 Hz), 6.24 & 6.14 (dd & dd, 1 H, $J = 5.2$, 4.0 Hz), 5.59 (m, 1 H), 4.90 & 4.73 (m & s, 2 H), 4.51 (s, 1 H), 4.25 (m, 1 H), 4.13 (m, 1 H), 4.09–3.55 (m, 6 H), 1.88–1.54 (m, 12 H).

*2'-Deoxy-2'-fluorouridine (**5**)*

3',5'-di-*O*-tetrahydropyranyl-1-β-D-*arabino*furanosyluracil (**4**) (0.50 g, 1.21 mmol) was dissolved in 50 ml of 9:1 (v/v) CH_2Cl_2/THF. After the solution was cooled to 0°C, (diethylamino)sulfur trifluoride (0.4 ml; 3 mmol) was added, and the mixture was stirred for 7 h at room temperature. Next, 21 ml of 1 N HCl was added, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was neutralized with 1 M NaOH and the solvent was removed by evaporation. The residue was purified by column chromatography

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on silica gel with 9:1 (v/v) CH_2Cl_2/methanol as a solvent to give **5** as a foamy solid (80 mg; 27%). ^{1}H NMR (400 MHz, methanol-d_4): δ 8.00 (d, 1 H, J = 8.0 Hz), 5.98 (dd, 1 H, J = 1.6, 17.6 Hz), 5.69 (d, 1 H, J = 7.6 Hz), 5.02 (dd & dd, 1 H, J = 53.1, 4.4 Hz), 4.32 (dd & dd, 1 H, J = 20.3, 7.6 Hz), 4.01 (d, 1 H, J = 7.6 Hz), 3.94 (dd, 1 H, J = 12.4, 2.4 Hz), 3.76 (dd, 1 H, J = 12.6, 2.8 Hz). ^{13}C NMR (100 MHz, methanol-d_4): δ 168.0, 155.4, 142.8, 103.1, 95.5 ($J_{2',F}$ = 185.3 Hz), 90.4 ($J_{1',F}$ = 34.7 Hz), 85.0, 69.8 ($J_{3',F}$ = 16.4 Hz), 61.5. Calculated for $C_9H_{11}FN_2O_5$: C, 43.91; H, 4.50; N, 11.38. Found: C, 43.84; H, 4.72; N, 11.40.

*3',5'-Di-O-tetrahydropyranyl-2-O-p-nitrophenylsulfonyl-1-β-*D*-arabinofuranosyluracil (**6**)*

To a solution of (**4**) (1.80 g; 4.36 mmol) in CH_2Cl_2 (20 ml) and pyridine (2.3 ml), *p*-nitrophenylsulfonyl chloride (3.3 g; 14.8 mmol) was added dropwise at −20°C. The brown solution was stirred for 48 h at room temperature and washed with water, 1 N HCl, and water. The organic layer was dried by Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by column chromatography on silica gel with 1:1 (v/v) *n*-hexane/ethyl acetate to give 3'-5'-di-*O*-tetrahydropyranyl-2-*O*-*p*-nitrophenylsulfonyl-1-β-D-*arabino*-furanosyluracil (**6**) as a white solid (four diastereomers; 0.52 g; 20%). m.p.: 147°–148°C. ^{1}H-NMR (500 MHz, $CDCl_3$): 9.28 (d, 1 H, J = 14.4 Hz, NH), 8.40 (dd, 2 H, J = 2.2, 8.9 Hz, *p*-NO_2-benzene H), 8.04 (dd, 2 H, J = 2.5, 9.0 Hz, *p*-NO_2-benzene H), 7.61 (dd & dd, 1 H, J = 8.2, 12.8 Hz & J = 7.1, 8.2 Hz, H-6), 6.10 (d, 1 H, J = 4.0 Hz, H-5), 5.71 (m, 1 H, H-2'), 5.34–5.11 (m, 1 H, H-1'), 4.81-4.27 (m, 3 H, THP H-1, H-3' & THP H-1), 4.24 (m, 1 H, H-4'), 4.07–3.56 (m, 6 H, H-5' & THP H-5), 1.80–1.59 (m, 12 H, THP H-2,3,4). ^{13}C-NMR (125 MHz, $CDCl_3$): 163.0 & 162.9 (C-4), 151.3, 149.7 & 149.6 (C-2), 141.2, 141.0 & 140.8 (C-6), 129.5, 129.3, 124.83 & 124.76 (*p*-NO_2-benzene ring), 101.8 (C-5), 99.8, 99.5, 99.38, 99.35, 99.2, 98.5 & 98.3 (THP C-1), 84.7, 84.5, 84.0 & 83.9 (C-2'), 83.1, 82.9, 82.6 & 82.5 (C-1'), 82.1, 81.9, 81.6 & 81.5 (C-4'), 79.3 & 79.2 (C-3'), 66.7 & 66.2 (C-5'), 63.0, 62.9, 62.8, 62.7, 62.6 & 62.5 (THP C-5), 30.7, 30.6, 30.5 & 30.3 (THP C-2), 25.49, 25.46, 25.3 & 25.2 (THP C-4), 19.6, 19.4, 19.3 & 19.2 (THP C-3). Calculated for $C_{25}H_{31}N_3O_{12}S$: C, 50.25; H, 5.23; N, 7.03. Found: C, 50.46; H, 5.39; N, 6.97.

*Radiosynthesis of 2'-[^{18}F]FU (**7**)*

[^{18}F]Fluoride 370 MBq/0.5 ml was trapped on a QMA cartridge and eluted with a mixture of 22 mg of Kryptofix$_{222}$ in 300 µl of acetonitrile and 7 mg of K_2CO_3 in 300 µl of water. The solution was dried completely by azeotropic distillation with CH_3CN (3 × 500 µl) under a gentle N_2 gas stream at 100°C. The final dried residue was dissolved in 500 µl CH_3CN, and 10, 20, or 30 mg

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(25.3, 50.6, or 75.9 μmol) of nosylate precursor (**6**) were added to a closed-cap vial. The reaction mixture was stirred at 105, 125, or 145°C for 15 min and developed as dark brown color. After [^{18}F]fluorination, acetonitrile was removed, and the THP group was deprotected by adding 500 μl of 1 N HCl for 10 min at 85°C. After neutralization with 2 N NaOH, the reaction mixture was diluted with 2 ml of distilled water and then purified by HPLC. The synthesis of 2'-[^{18}F]FU (**7**) was confirmed by its coelution with unlabeled 2'-FU (**5**) at 14.4 min (Figure 1).

HPLC system and purification conditions

Compounds were purified and analyzed with a TSP P4000/UV 3000 system (Thermo Separation Product, USA) with an Econosil C_{18} column (Alltech; 10 μm; 10 × 250 mm) and a flow-type radioactive detector. Reaction mixtures were manually injected into the HPLC loop, and filterable impurities were removed with a 0.22-μm vented filter prior to injection into the HPLC. Compounds were eluted with water for 10 min, followed by 5% ethanol in water for 10 min.

Automated synthesis

We used a GE TracerLab MX [^{18}F]FDG module and the same sequence program[14] for [^{18}F]FLT synthesis with minor changes in the reaction temperature and time based on the results of manual synthesis. All Sep-Pak cartridges in the disposable cassette were removed, and manifolds 2 and 3 were connected with silicone tubing as described previously.[14] This cassette had four reagent supply vials. Acetonitrile (7 ml) was placed in vial 1 (blue), the precursor (30 mg) and 2 ml of CH_3CN in vial 2 (red), 1.75 ml of 2 N NaOH and 1.7 ml of citrate buffer in vial 3 (yellow), and 3 ml of 1 N HCl in vial 4 (green). Two 30-ml disposable syringes were installed.

2'-[^{18}F]FU was prepared by fluorination and hydrolysis (Scheme 1). [^{18}F]fluoride (3.7 GBq) delivered from a cyclotron was trapped on a QMA cartridge and eluted into the reactor with a mixture of 7 mg of K_2CO_3 in 300 μl of H_2O and 22 mg of K_{222} in 300 μl of CH_3CN. Following complete drying under vacuum and purging with nitrogen at 95°C, 30 mg of the precursor in 2 ml of CH_3CN was added. [^{18}F]fluorination was allowed to proceed for 150 s at 145°C, followed by 300 s at 85°C. The solvent was removed at 85°C for 2 min under vacuum pressure and nitrogen purging. Hydrolysis was performed with 1 N HCl at 85°C for 5 min. After hydrolysis, the reaction mixture was diluted with 2 N NaOH and buffer solution from the yellow vial, and the mixture was injected automatically by vacuum into the HPLC. Following HPLC, the purified 2'-[^{18}F]FU was passed through a 0.22-μm sterile filter and collected into a sterile vial.

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