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**Research Article**

# How to increase the reactivity of [$^{18}$F]fluoroethyl bromide: [$^{18}$F]fluoroethylation of amine, phenol and amide functional groups with [$^{18}$F]FEtBr, [$^{18}$F]FEtBr/NaI and [$^{18}$F]FEtOTf

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## Summary

[$^{18}$F]Fluoroethyl bromide ([$^{18}$F]FEtBr) is a useful synthetic precursor to synthesize $^{18}$F-labeled compounds. However, the lower reactivity of [$^{18}$F]FEtBr with amine, phenol and amide functional groups than that of [$^{11}$C]$CH_3$I partly limits its wide application in the synthesis of [$^{18}$F]fluoroethylated compounds. The aim of this study was to increase the reactivity of [$^{18}$F]FEtBr with various nucleophilic substrates for PET tracers containing amine, phenol and amide moieties. The present strategies included (1) adding NaI into the reaction mixture of [$^{18}$F]FEtBr and substrate, where [$^{18}$F]FEtI is reversibly formed and becomes more reactive; (2) converting [$^{18}$F]FEtBr into much more reactive [$^{18}$F]FEtOTf, similar to conversion of [$^{11}$C]$CH_3$I into [$^{11}$C]$CH_3$OTf. By these efforts, the [$^{18}$F]fluoroethylation efficiency of various substrates containing amine, phenol and amide groups with [$^{18}$F]FEtBr/NaI and [$^{18}$F]FEtOTf was significantly improved, compared with the corresponding reaction efficiency with [$^{18}$F]FEtBr. Copyright © 2003 John Wiley & Sons, Ltd.

**Key Words:** [$^{18}$F]FEtBr; [$^{18}$F]FEtBr/NaI; [$^{18}$F]FEtOTf; [$^{18}$F]fluoroethylation; PET tracer

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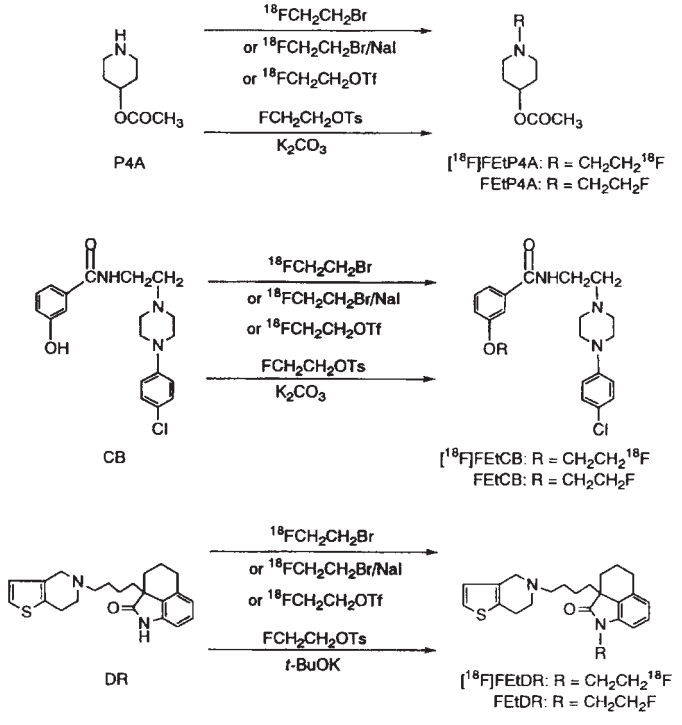
## Introduction

Fluorine-18 ($^{18}F$, $\beta^+$; 96.7%, $T_{1/2} = 109.8$ min) is of considerable importance in radiochemistry for positron emission tomography (PET) due to its optimal decay characteristics. [$^{18}F$]fluoroethyl bromide ([$^{18}F$]FEtBr) is a useful alkylating reagent for introducing $^{18}F$ into substrates containing amine, phenol and amide functional groups.[1,2] However, compared with [$^{11}C$]methyl iodide ([$^{11}C$]$CH_3I$), [$^{18}F$]FEtBr has been used to a much more limited extent, and for the most part only in research areas. One of the explanations might be that the characteristics such as affinity and lipophilicity of the [$^{18}F$]fluoroethyl homolog could be different from those of the [$^{11}C$]methyl tracer. In fact, the [$^{18}F$]fluoroethyl analog of McN5652, a PET ligand for imaging 5-HT serotonin uptake sites, has been found to display inferior tracer properties relative to the methyl prototype [$^{11}C$]McN5652.[3] However, there are certainly several examples of dopamine radioligands where the fluoroethyl substitution led to significant improvement in tracer behavior over the methyl analog.[4–6]

Recently, we developed an automated system for synthesizing $^{18}F$-labeled compounds using [$^{18}F$]FEtBr as a precursor.[7,8] Using this system, we prepared [$^{18}F$]FEtBr in a reproducible radiochemical yield of 60–75% (corrected for the decay, based on total [$^{18}F$]$F^-$) and synthesized several [$^{18}F$]fluoroethylated ligands.[7,8] However, in our experiments, we faced a major difficulty, that is, the lower reactivity of [$^{18}F$]FEtBr with substrates containing amine, phenol and amid functional groups than that of [$^{11}C$]$CH_3I$. For example, in the preparation of [$^{18}F$]FEtP4A (Scheme 1),[8] a PET tracer for imaging brain acetylcholinesterase, 4-piperidyl acetate (P4A) reacted with [$^{18}F$]FEtBr at 130°C for 30 min to afford [$^{18}F$]FEtP4A with a radiochemical yield of 35–44% ($n = 3$, after HPLC purification, based on [$^{18}F$]FEtBr), whereas, the $^{11}C$-methyl homolog [$^{11}C$]MP4A can be easily obtained by reacting P4A with [$^{11}C$]$CH_3I$ at 70°C for 3 min with a high radiochemical yield of 60–85% (based on [$^{11}C$]$CH_3I$).

In the present work, the aim was to increase the reactivity of [$^{18}F$]FEtBr with various substrates containing amine, phenol, and amide functional groups (Scheme 1). In this study, the strategies included (1) adding NaI into the reaction mixture of [$^{18}F$]FEtBr and nucleophilic substrates, where [$^{18}F$]fluoroethyl iodide ([$^{18}F$]FEtI) is reversibly formed and becomes more reactive with the substrates than [$^{18}F$]FEtBr; (2) converting [$^{18}F$]FEtBr into [$^{18}F$]fluoroethyl triflate ([$^{18}F$]FEtOTf),[9] a




**Scheme 1. [18F]Fluoroethylation of amine, phenol and amide groups: Radiosyntheses of [18F]FEtP4A, [18F]FEtCB and [18F]FEtDR**

highly reactive intermediate by analogy with [11C]methyl triflate ([11C]$CH_3OTf$).[10]

As model substrates, 4-piperidyl acetate (P4A, amine type), *N*-[2-[4-(4-chlorophenyl)piperazin-1-yl]ethyl]-3-hydroxybenzamide (CB, phenol type) and 2a-[4-(4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-5-yl)butyl]-2*a*,3,4,5-tetrahydro-1H-benz[*cd*]-indole-2-one (DR, amide type) were selected to react with [18F]FEtBr, respectively (Scheme 1). The reason for this selection was that the 11C-methyl analogs of these substrates have been developed as putative tracers for brain acetylcholinesterase,[8] dopamine $D_4$ receptor[11] or 5-$HT_7$ serotonin receptor.[12] The [18F]fluoroethylated analogs of these substrates may be useful to image the receptors such as the $D_4$ and 5-$HT_7$ with possibly low densities in the primate brain.

## Results and Discussion

In organic synthesis, the most common and simple method for increasing the reactivity of alkyl chloride or bromide with nucleophilic

substrate is utilization of metal iodide (NaI, KI, etc.) as a catalyst. The mechanism involves reversible formation of alkyl iodide intermediate that is more reactive towards a nucleophile. Thus, this approach was used to raise the reactivity of [$^{18}$F]FEtBr with nucleophilic substrate by forming [$^{18}$F]FEtI as an intermediate.

The application of [$^{11}$C]$CH_3$OTf in place of [$^{11}$C]$CH_3$I into the synthesis of $^{11}$C-radiopharmaceuticals for PET has recently become a trend.[13,14] Similarly, with [$^{11}$C]$CH_3$OTf, [$^{18}$F]fluoroethyl triflate ([$^{18}$F]FEtOTf) was employed to augment the efficiency of [$^{18}$F]fluoroethylation. [$^{18}$F]FEtOTf was synthesized by flowing [$^{18}$F]FEtBr into a graphite carbon column containing silver triflate (AgOTf), and was trapped directly into the reaction mixture containing substrates.[9] To optimize the condition for synthesizing [$^{18}$F]FEtOTf from [$^{18}$F]FEtBr, two treatments were modified based on the general procedure of changing [$^{11}$C]$CH_3$I into [$^{11}$C]$CH_3$OTf: (1) raising the oven temperature to 280–300°C for heating the column containing AgOTf; (2) decreasing the flow rate of helium gas carrying [$^{18}$F]FEtBr to 30–50 ml/min through the AgOTf column.

To confirm the identity of the radioactive product, the non-radioactive fluoroethylated derivatives (FEtP4A, FEtCB and FEtDR) were synthesized by the reaction of P4A, CB, and DR with 1-fluoro-2-tosyloxyethane with a chemical yield of 57–72%, respectively (Scheme 1).

### *2.1. [$^{18}$F]Fluoroethylation of P4A with [$^{18}$F]FEtBr, [$^{18}$F]FEtBr/NaI and [$^{18}$F]FEtOTf*

[$^{18}$F]FEtP4A, was previously prepared by reacting P4A, an amine substrate, with [$^{18}$F]FEtBr using a newly developed automated system.[8] However, the reaction efficiency of P4A with [$^{18}$F]FEtBr was markedly lower than with [$^{11}$C]$CH_3$I. Only under rather vigorous conditions (30 min and 130°C), could adequate amounts of [$^{18}$F]FEtP4A be obtained and used for animal experiments.

[$^{18}$F]FEtBr/NaI was used to raise the reactivity of [$^{18}$F]FEtBr with P4A via [$^{18}$F]FEtI as an intermediate. As shown in Table 1, when NaI (1 mg) was added to the reaction mixture in advance, P4A reacted with [$^{18}$F]FEtBr at 130°C for 10 min to give [$^{18}$F]FEtP4A in a good radiochemical yield of 74%, whereas, without the added NaI, the reaction of P4A with [$^{18}$F]FEtBr afforded [$^{18}$F]FEtP4A only in 18% yield under the same conditions (130°C, 10 min). Moreover, the efficiency of generating [$^{18}$F]FEtP4A increased with the reaction time,

and at 30 min, the fluoroethylated yield of P4A even reached 90%. In addition, the amount of NaI (1, 5 or 10 mg) did not affect the efficiency of [$^{18}$F]fluoroethylation (data not shown).

After trapping [$^{18}$F]FEtOTf into the DMF solution containing P4A for 10 min by helium gas at 25°C, the radiochemical yield of [$^{18}$F]FEtP4A was determined using HPLC at once. In the reaction mixture, 71% of the total radioactivity was found to represent [$^{18}$F]FEtP4A, and 29% was [$^{18}$F]FEtBr (Table 1). This finding reflected that the conversion efficiency of [$^{18}$F]FEtBr into [$^{18}$F]FEtOTf was at least 71%, since P4A did not react with [$^{18}$F]FEtBr at 25°C. As was expected, [$^{18}$F]FEtOTf displayed a higher reactivity with amine substrate than [$^{18}$F]FEtBr as well as [$^{18}$F]FEtBr/NaI.

### *2.2. [$^{18}$F]Fluoroethylation of CB with [$^{18}$F]FEtBr, [$^{18}$F]FEtBr/NaI and [$^{18}$F]FEtOTf*

There are many *O*-[$^{11}$C]methylated PET tracers prepared from phenol substrates, for example, [$^{11}$C]raclopride,[15] [$^{11}$C]FLB-457,[16] etc. The [$^{18}$F]fluoroethylation of a phenol substrate is a natural evolution and may be encouraged for developing PET tracers because of the relatively high reactivity and convenient treatment of phenoxide obtained from phenol and base. CB was selected as a model substance for comparing the reactivity of [$^{18}$F]FEtBr with those of [$^{18}$F]FEtBr/NaI and [$^{18}$F]FEtOTf, and establishing a general labeling condition for

**Table 1. Yields of $^{18}$F-fluoroethylation of P4A under various conditions**

| Reagent | Temperature (°C) | Time (min) | Radiochemical yield[a] (%) |
|---|---|---|---|
| [$^{18}$F]$FCH_2CH_2Br$ | 25 | 10 | No reaction |
| | 130 | 5 | $7 \pm 1.3$ |
| | 130 | 10 | $18 \pm 3.1$ |
| | 130 | 20 | $32 \pm 2.5$ |
| | 130 | 30 | $56 \pm 5.3$ (45)[b] |
| [$^{18}$F]$FCH_2CH_2Br$/NaI | 130 | 5 | $46 \pm 5.1$ |
| | 130 | 10 | $74 \pm 1.9$ |
| | 130 | 20 | $86 \pm 5.0$ |
| | 130 | 30 | $90 \pm 1.3$ (62)[b] |
| [$^{18}$F]$FCH_2CH_2OTf$ | 25 | 10 | $71 \pm 2.0$ (50)[b] |

[a] Radiochemical yield (mean $\pm$ SE, $n = 3$) as determined by analytic HPLC from a sample withdrawn from the reaction mixture.
[b] Decay corrected radiochemical yield (%) after HPUC purification for one of the reaction mixtures based on the total [$^{18}$F]FEtBr.

[$^{18}$F]fluoroethylation of phenol substrate (Table 2). In the presence of NaI, the yield of [$^{18}$F]FEtCB was gradually increased by prolonging the reaction from 5 to 30 min and the most consistent high yield (62%) was obtained at 30 min. Raising the reaction temperature from 70°C to 120°C and keeping the mixture for 10 min could further heighten the [$^{18}$F]fluoroethylation yield from 37 to 68% (Table 2).

The corresponding reaction of CB/NaH with [$^{18}$F]FEtOTf to give [$^{18}$F]FEtCB was conducted (Table 2). The [$^{18}$F]fluoroethylation proceeded rapidly with [$^{18}$F]FEtOTf trapping for 10 min at 25°C, and the radiochemical yield of [$^{18}$F]FEtCB reached 68% at the end of trapping. Even without NaH, the reaction of [$^{18}$F]FEtOTf with CB in DMF could give [$^{18}$F]FEtCB with a radiochemical yield of 12% (Table 2). A synergistic effect may explain this observation. Firstly, the phenolic hydroxy group may itself act as a weak nucleophile for the reaction with [$^{18}$F]FEtOTf. Secondly, the piperazine moiety may act as a weak base to form a more reactive phenoxide ion.

### *2.3. [$^{18}$F]Fluoroethylation of DR with [$^{18}$F]FEtBr, [$^{18}$F]FEtBr/NaI and [$^{18}$F]FEtOTf*

[$^{18}$F]FEtSP, a successful PET tracer for imaging dopamine $D_2$ receptor, was synthesized by the [$^{18}$F]fluoroethylation of an amide substrate

**Table 2. Yields of $^{18}$F-flouroethylation of CB under various conditions**

| Reagent | Base | Temperature (°C) | Time (min) | Radiochemical yield[a] (%) |
|---|---|---|---|---|
| [$^{18}$F]$FCH_2CH_2Br$ | NaH | 25 | 10 | 6 ± 1.7 |
| | | 70 | 5 | 5 ± 2.6 |
| | | 70 | 10 | 25 ± 3.7 |
| | | 70 | 20 | 40 ± 3.1 |
| | | 70 | 30 | 48 ± 0.9 (32)[b] |
| | | 120 | 10 | 39 ± 5.6 |
| [$^{18}$F]$FCH_2CH_2Br$/NaI | NaH | 70 | 5 | 18 ± 2.0 |
| | | 70 | 10 | 37 ± 5.0 |
| | | 70 | 20 | 57 ± 4.8 |
| | | 70 | 30 | 62 ± 1.5 (51)[b] |
| | | 110 | 10 | 68 ± 7.3 |
| [$^{18}$F]$FCH_2CH_2OTf$ | None | 25 | 10 | 12 ± 2.1 |
| | NaH | 25 | 10 | 68 ± 1.9 (50)[b] |

[a] Radiochemical yield (mean ± SE, $n = 3$) as determined by analytic HPLC from a sample withdrawn from the reaction mixture.
[b] Decay corrected radiochemical yield (%) after HPLC purification for one of the reaction mixtures based on the total [$^{18}$F]FEtBr.

spiperone.[4,5] Although amide itself is a very weak nucleophile, the sodium salt of amide becomes very reactive after treatment of amide with a base such as NaH. DR is a second amide substrate and was readily transformed to its sodium salt using NaH. Even without NaI, heating the mixture of DR/NaH with [$^{18}$F]FEtBr at 70°C for 10 min could afford [$^{18}$F]FEtDR in a radiochemical yield of 71% (Table 3). This finding reflected that the sodium salt of amide had adequate reactivity with [$^{18}$F]FEtBr. However, the presence of NaI conversely decreased the efficiency (26%) of producing [$^{18}$F]FEtDR under the similar conditions. On analyzing the reaction mixture, most of DR was found to disappear in the mixture. A possible reason for this phenomenon was that the sodium salt of amide DR might be unstable on exposure to NaI. A similar result was observed when the amide substrate spiperone was treated with NaH, followed by NaI. Spiperone also appeared to undergo ring fission in the presence of NaH and NaI.

On the other hand, DR/NaH reacted readily with [$^{18}$F]FEtOTf at 25°C to afford [$^{18}$F]FEtDR in a high radiochemical yield of 82% (Table 3). Moreover, in place of NaH, utilization of NaOH or *n*-$Bu_4NOH$ as the base could also give the product with a moderate yield of 37–46%. However, using NaOH or *n*-$Bu_4NOH$, DR reacted with [$^{18}$F]FEtBr at

**Table 3. Yields of [$^{18}$F]fluoroethylation of DR under various conditions**

| Reagent | Base | Temperature (°C) | Time (min) | Radiochemical yield[a] (%) |
|---|---|---|---|---|
| [$^{18}$F]$FCH_2CH_2Br$ | NaH | 25 | 10 | 5 ± 0.4 |
| | | 70 | 5 | 54 ± 5.1 |
| | | 70 | 10 | 71 ± 6.2 |
| | | 70 | 20 | 93 ± 2.5 |
| | | 70 | 30 | 94 ± 0.9 (80)[b] |
| | NaOH | 25 | 10 | 3 ± 0.6 |
| | *n*-$Bu_4NOH$ | 25 | 10 | 4 ± 1.7 |
| [$^{18}$F]$FCH_2CH_2Br$/NaI | NaH | 70 | 5 | 19 ± 2.0 |
| | | 70 | 10 | 26 ± 6.1 |
| | | 70 | 20 | 37 ± 3.5 |
| | | 70 | 30 | 38 ± 1.9(25)[b] |
| [$^{18}$F]$FCH_2CH_2OTf$ | NaH | 25 | 10 | 82 ± 1.3 (67)[b] |
| | NaOH | 25 | 10 | 37 ± 6.1 |
| | *n*-$Bu_4NOH$ | 25 | 10 | 46 ± 0.7 |

[a] Radiochemical yield (mean ± SE, $n = 3$) as determined by analytic HPLC from a sample withdrawn from the reaction mixture.
[b] Decay corrected radiochemical yield (%) after HPLC purification for one of the reaction mixtures based on the total [$^{18}$F]FEtBr.

25°C for 10 min to give the product only in a poor radiochemical yield of $<5\%$ (Table 3).

## Conclusions

The reactivity of [$^{18}$F]FEtBr was increased by using NaI to generate [$^{18}$F]FEtI or converting [$^{18}$F]FEtBr to [$^{18}$F]FEtOTf. By these efforts, the radiochemical yields of [$^{18}$F]fluoroethylated compounds were augmented. Therefore, these approaches can be applied in the synthesis of $^{18}$F-fluoroethylated compounds starting from [$^{18}$F]FEtBr as the synthetic precursor.

## Experimental

### *Materials & general methods*

Melting points (mp) were uncorrected. Nuclear magnetic resonance ($^1$H-NMR) spectra were recorded on a JNM-GX-270 spectrometer (JEOL, Tokyo) with tetramethylsilane as an internal standard. All chemical shifts (δ) were reported in parts per million (ppm) downfield from the standard. Fast atom bombardment mass spectra (FAB-MS) were obtained on a JEOL NMS-SX102 spectrometer (JEOL, Tokyo). Column chromatography was performed on Merck Kieselgel gel 60 $F_{254}$ (70–230 mesh). Fluorine-18 ($^{18}$F) was produced by the $^{18}$O(p, n)$^{18}$F nuclear reaction using a CYPRIS HM-18 cyclotron (Sumitomo Heavy Industry, Tokyo). Radioactivity was determined with a dose calibrator (IGC-3R Curiemeter, Aloka, Tokyo). HPLC was performed using a JASCO HPLC system (JASCO, Tokyo): effluent radioactivity was monitored using an NaI (Tl) scintillation detector system. If not otherwise stated, chemicals were purchased from Aldrich Chemical (Milwaukee, WI) and Wako Pure Industries (Osaka) with the highest grade commercially available.

### *N-Fluoroethyl-4-piperidyl acetate (FEtP4A)*

FEtP4A was synthesized by reacting 4-piperidyl acetate (P4A) with 1-fluoro-2-tosyloxyethane and anhydrous $K_2CO_3$ according to the method described previously.[8]

*N-[2-[4-(4-Chlorophenyl)piperazin-1-yl]ethyl]-3-fluoroethylbenzamide (FEtCB)*

A mixture of N-[2-[4-(4-chlorophenyl)piperazin-1-yl]ethyl]-3-hydroxybenzamide (CB, 140 mg, 0.65 mmol),[17] 1-fluoro-2-tosyloxyethane (300 mg, 1.3 mmol) and anhydrous $K_2CO_3$ (200 mg, 1.4 mmol) in DMF (3 ml) was heated at 70°C for 10 h. The reaction mixture was quenched with $CHCl_3$, and washed with water and saturated NaCl solution. After the organic layer was dried over $Na_2SO_4$, the solvent was removed to give a residue. The residue was chromatographed on silica gel with $CHCl_3$/hexane (3/1) to give FEtCB (181 mg, 72%) as a colorless crystal. mp: 137–138°C (recrystallized from $CHCl_3/CH_3OH = 20/1$). $^1$H-NMR (DMSO-$d_6$ + $CDCl_3$) δ: 7.15–7.41 (5H, m), 7.01–7.08 (1H, m), 6.83–6.90 (3H, m), 4.49 (2H, dt, $J_{H,F} = 42$ Hz, $J_{H,H} = 6$ Hz), 3.85 (3H, s), 3.61 (2H, dt, $J_{H,F} = 28$ Hz, $J_{H,H} = 6$ Hz), 3.10–3.21 (4H, m), 2.55–2.94 (8H, m). FAB–MS (m/e) calculated for $C_{21}H_{26}ClFN_3O_2$ ($M^+ + 1$): 406.18. Found: 406.19.

*1-Fluoroethyl-2a-[4-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl)butyl]-2a,3,4,5-tetrahydro-1H-benz[cd]-indole-2-one (FEtDr)*

A mixture of 2a-[4-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl)butyl]-2a,3,4,5-tetrahydro-1H-benz[cd]-indole-2-one (DR, 180 mg, 0.5 mmol),[18] 1-fluoro-2-tosyloxyethane (220 mg, 1 mmol) and potassium t-butoxide (220 mg, 2 mmol) in DMF (10 ml) was stirred at 25°C for 24 h. The reaction mixture was quenched with AcOEt, and washed with water and saturated NaCl solution. After the organic layer was dried over $Na_2SO_4$, the solvent was removed to give a residue. The residue was chromatographed on silica gel with $CHCl_3$/hexane (1/5) to give FEtDR (123 mg, 61%) as a colorless crystal. mp: 82–83°C (recrystallized from AcOEt/hexane = 1/1). $^1$H-NMR($CDCl_3$ + DMSO-$d_6$)δ: 7.19–7.38 (2H, m), 6.70–7.11 (3H, m), 5.09 (2H, dt, $J_{H,F} = 40$ Hz, $J_{H,H} = 5$ Hz), 3.88 (2H, dt, $J_{H,F} = 32$ Hz, $J_{H,H} = 5$ Hz), 3.08–3.51 (6H, m), 2.40–2.64 (6H, m). 1.18–1.66 (5H, m), 2.07–2.42 (4H, m), 1.18–1.66 (5H, m). FAB-MS (m/e) calculated for $C_{24}H_{29}FN_2OS$ ($M^+ + 1$): 413.08. Found: 413.21.

*Radionuclide production*

Aqueous [$^{18}$F]$F^-$ solution was produced by $^{18}$O(p,n)$^{18}$F reaction on 10–20 atom% enriched [$^{18}$O]$H_2O$ using 18 MeV protons (15.8 MeV on target) from the cyclotron. After bombardment, the irradiated water was passed through a Dowex 1-X8 anion exchange column (carbonate

form; 3 mm ϕ × 25 mm), for trapping [$^{18}$F]$F^-$ and enabling collection of the enriched [$^{18}$O]$H_2O$ for recycling use. Then, the [$^{18}$F]$F^-$ was removed from the resin by elution with aqueous potassium carbonate solution into a glass vial containing $CH_3CN$/Kryptofix 2.2.2.

### *Radiosynthesis of [$^{18}$F]FEtBr and [$^{18}$F]FEtOTf*

The preparation procedure of [$^{18}$F]FEtBr has been described in detail elsewhere.[9] Briefly, the [$^{18}$F]$F^-$ from the irradiating room was transported to a Pyrex glass vessel in a hot cell. After the [$^{18}$F]$F^-$ was dried to remove $H_2O$ and $CH_3CN$, 2-trifluoromethanesulfonyloxy ethylbromide (1) in o-DCB was added into the radioactive vessel. The [$^{18}$F]FEtBr resulted in this vessel was then distilled under a helium flow, passed through a small column filled with Ascarite and phosphorus pentoxide, and cooled into another vessel containing anhydrous DMF (300–500 µl) for trapping at −15––20°C.

[$^{18}$F]FEtOTf was prepared by passing [$^{18}$F]FEtBr through a steel column (3 mm ϕ × 40 mm, oven temperature: 280–300°C) containing AgOTf (100 mg) impregnated graphite carbon (300 mg) with the helium gas flow (30–50 ml/min) and trapped into a reaction vessel containing anhydrous DMF (300 µl).

### *General analysis procedure for identification and radiochemical yield*

After the reaction was finished, [$^{18}$F]FEtP4A, [$^{18}$F]FEtCB or [$^{18}$F]FEtDR was purified from the typical reaction mixture using a semi-preparative HPLC system. The HPLC purification conditions are as follows:

*For [$^{18}$F]FEtP4A, column*: Megapak SIL C18-10 (JASCO, 10 mm ϕ × 150 mm); mobile phase: 5 mM $CH_3COONH_4$ (pH = 4.8)/$CH_3CN$ (9/1); flow rate: 4 ml/min; retention time: 11.7 min.

*For [$^{18}$F]FEtCB*: Capcell Pak $C_{18}$ (SHISEIDO, 10 mm ϕ × 150 mm); $CH_3OH/H_2O/Et_3N$ (7/3/0.05); 6.0 ml/min; 8.7 min.

*For [$^{18}$F]FEtDR, column*: Capcell Pak $C_{18}$ (SHISEIDO, 10 mm ϕ × 150 mm); $CH_3CN/H_2O/Et_3N$ (7/3/0.05); 6.0 ml/min; 7.9 min.

The fraction corresponding to each radioactive product was collected in a rotary evaporator and evaporated to dryness at about 90°C under reduced pressure. After the residue was re-dissolved in 3 ml of distilled water, the product ([$^{18}$F]FEtP4A, [$^{18}$F]FEtCB or [$^{18}$F]FEtDR) was obtained with a radiochemical purity of >95%. The confirmation of identity for each product was achieved by co-injection with the non-

radioactive standard using an analytic HPLC column. Since FEtP4A displayed no special absorption on UV spectrum (200–400 nm), [$^{18}$F]FEtP4A was further characterized with the unlabeled FEtP4A using radio-TLC as described above.[10]

The analytic HPLC conditions are as follows:

*For [$^{18}$F]FEtP4A*: Megapak SIL C18 (JASCO, 4.6 mm $\phi \times$ 150 mm); 50 mM $CH_3COONH_4$ (pH = 3.3)/$CH_3CN$ (3/7); 2 ml/min; 3.8 min.

*For [$^{18}$F]FEtCB*: Capcell Pak $C_{18}$ (SHISEIDO, 4.6 mm $\phi \times$ 150 mm); $CH_3OH/H_2O/Et_3N$ (7/3/0.05); 2.0 ml/min; 5.2 min.

*For [$^{18}$F]FEtDR, column*: Capcell Pak $C_{18}$ (SHISEIDO, 4.6 mm $\phi \times$ 150 mm); $CH_3CN/H_2O/Et_3N$ (7/3/0.05); 2.0 ml/min; 5.6 min.

The radiochemical yield shown in Tables 1–3 was determined by analytic HPLC from a sample withdrawn from the reaction mixture under the analytical conditions described above.

### *Reactions of substrates with [$^{18}$F]FEtBr, [$^{18}$F]FEtBr/NaI or [$^{18}$F]FEtOTf*

The [$^{18}$F]FEtBr (80–370 MBq) was trapped into a solution of anhydrous DMF (300 µl) containing substrate (0.8–1.1 mg) and base (if required, NaH: 10 µl, 1.5 g/20 ml DMF or 0.5 N NaOH: 3 µl or 10% *n*-$Bu_4NOH/H_2O$: 10 µl) at −15––20°C. The reaction mixture was heated to 25, 70, 110 or 130°C and kept for 5–30 min. After the reaction was finished, the [$^{18}$F]fluoroethylation yield for each mixture at 5, 10, 20 or 30 min was determined and the reaction mixture at 30 min was purified.

The [$^{18}$F]FEtBr (80–370 MBq) was trapped to a solution of anhydrous DMF (300 µl) containing NaI (1.0 mg), substrate (0.8–1.1 mg) and base (if required, NaH: 10 µl, 1.5 g/20 ml DMF) at −15–−20°C. After the reaction was finished, the [$^{18}$F]fluoroethylation yield for each mixture at 5, 10, 20 or 30 min was determined and the reaction mixture at 30 min was purified.

The [$^{18}$F]FEtBr (80–370 MBq) was passed through a steel column (3 mm $\phi \times$ 40 mm, oven temperature: 280–300°C) containing AgOTf (100 mg) impregnated graphite carbon (300 mg) with a helium gas flow (30–50 ml/min). [$^{18}$F]FEtOTf was trapped into a reaction vessel containing anhydrous DMF (300 µl), substrate (0.8–1.1 mg) and base (if required, NaH: 10 µl, 1.5 g/20 ml DMF; or 0.5 N NaOH: 3 µl; or 10% *n*-$Bu_4NOH/H_2O$: 10 µl) at 25°C. This procedure always required about 10 min. After the [$^{18}$F]FEtOTf was trapped, the reaction was terminated at −15––20°C. The [$^{18}$F]fluoroethylation yield for each reaction mixture was determined and the mixture was purified.

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