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[^{18}F]Fluoromethyl iodide ([^{18}F]FCH_2I): preparation and reactions with phenol, thiophenol, amide and amine functional groups

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Abstract

In this study, we report the synthesis and reactivity of [^{18}F]fluoromethyl iodide ([^{18}F]FCH_2I) with various nucleophilic substrates and the stabilities of [^{18}F]fluoromethylated compounds. [^{18}F]FCH_2I was prepared by reacting diiodomethane (CH_2I_2) with [^{18}F]KF, and purified by distillation in radiochemical yields of 14–31% ($n = 25$). [^{18}F]FCH_2I was stable in organic solvents commonly used for labeling and aqueous solution with pH 1–7, but was unstable in basic solutions. [^{18}F]FCH_2I displayed a high reactivity with various nucleophilic substrates such as phenol, thiophenol, amide and amine. The [^{18}F]fluoromethylated compounds synthesized by the reactions of phenol, thiophenol and tertiary amine with [^{18}F]FCH_2I were stable for purification, formulation and storage. In contrast, the [^{18}F]fluoromethylated compounds synthesized by the reactions of primary or secondary amines, and amide with [^{18}F]FCH_2I were too unstable to be detected or purified from the reaction mixtures. Defluorination of these [^{18}F]fluoromethyl compounds was a main decomposition route.

Keywords: [^{18}F]Fluoromethyl iodide; [^{18}F]Fluoromethylation; PET ligand; Defluorination

1. Introduction

Reaction of perfluoroalkyl halides with nucleophilic substrates containing O, S, N and P atoms is a significant characteristic of perfluoroalkyl halides [1]. It was reported that many perfluoroalkyl halides such as CF_2Cl_2, CF_2Br_2, CF_2BrCl, $CHClF_2$, CF_3Br and CF_3I reacted easily with phenol, thiophenol and aniline in the presence of base to yield the corresponding fluorinated products in good chemical yields [1]. Fluoromethyl iodide (FCH_2I), as an analogue of the perfluoroalkyl halides which was previously prepared by reacting diiodomethane (CH_2I_2) with mercury iodide, is also expected to display high reactivity with nucleophiles [2]. However, unlike other perfluoroalkyl halides, the characteristics including reactivity and stability of FCH_2I have not been elucidated nor reviewed well. So far, only several reactions of FCH_2I with nucleophilic substrates were reported. FCH_2I reacted with triphenyl phosphine to form a stable ylide, which was an effective route for introducing fluoromethyl moiety to a substrate [2]. Further, FCH_2I reacted with phenol, benzoic acid, diphenylamine, and α-toluenethiol to give the corresponding fluoromethylated products [3]. However, the reactions of FCH_2I with these nucleophiles were not reproducible since some of the fluoromethylated products seemed unstable [4,5]. It was reported that fluoromethyldialkylamine derivatives, which were prepared by cleaving *N*,*N*-acetals (aminals) with acid fluoride but were not synthesized by reacting FCH_2I with dialkyl amines, were unstable [4].

On the other hand, in the flurine-18 (^{18}F) chemistry, [^{18}F]fluoromethylation of nucleophilic substrates has become an effective approach for developing a positron emission tomography (PET) ligand [6–11]. Since

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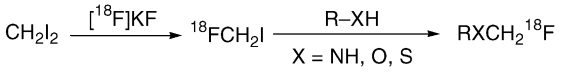


Scheme 1. Preparation of [^{18}F]FCH$_2$I and reaction of [^{18}F]FCH$_2$I with phenol, thiophenol, amide and amine.

[^{18}F]fluoromethyl group displays similar electronic and steric properties with [^{11}C]methyl group, the [^{18}F]fluoromethylated ligands [12,13] may have tracer properties such as binding affinity and pharmacokinetics, etc. similar to the corresponding [^{11}C]methyl ligands prepared from the same substrates. However, although the radiosyntheses of [^{18}F]FCH$_2$Br [6–9], [^{18}F]FCH$_2$I [3] and [^{18}F]FCH$_2$OTf [10,11] were previously carried out, the application of [^{18}F]fluoromethylation for labeling has been limited to a much narrower extent compared with [^{11}C]methylation, [^{18}F]fluoroethylation and [^{18}F]fluoropropylation. The inconvenient preparation and undetermined reactivity of [^{18}F]fluoromethyl regents and the putative instability of [^{18}F]fluoromethylated products may preclude the wide usefulness of [^{18}F]fluoromethylation.

In the present study, we tried to elucidate the stability and reactivity of [^{18}F]FCH$_2$I with various nucleophilic substrates, and to examine the stability of [^{18}F]fluoromethylated compounds. Since the isotopic effects of ^{18}F on ^{19}F are generally small [14], the characteristic of [^{18}F]FCH$_2$I may be extremely similar with that of the non-radioactive FCH$_2$I. Here, we report (1) efficient synthesis of [^{18}F]FCH$_2$I with a reproducible yield (Scheme 1); (2) stability of [^{18}F]FCH$_2$I in organic solvents and aqueous solutions; (3) reactivity of [^{18}F]FCH$_2$I with phenol, thiophenol, amide and amine functional groups (Scheme 1); (4) stabilities of [^{18}F]fluoromethylated products.

2. Results and discussion

2.1. Preparation of [^{18}F]FCH$_2$I from CH$_2$I$_2$

[^{18}F]FCH$_2$I was previously synthesized by a displacement reaction of CH$_2$I$_2$ with [^{18}F]KF [3]. To obtain this reagent in a more reproducible yield and with improved purity, we performed the fluorination reaction (Scheme 1) using an automated system previously developed in our laboratory for production of [^{18}F]FCH$_2$CH$_2$Br [15].

The reaction of [^{18}F]KF with CH$_2$I$_2$ was fast and it was typically allowed to proceed within 2 min at 110 °C in our experiment. After [^{18}F]F$^-$ produced from the irradiated target chamber was dried to remove CH$_3$CN and water, CH$_2$I$_2$ in *o*-dichlorobenzene was added into the heated mixture containing [^{18}F]KF and 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8,8,8]hexacosane (Kryptofix 222, phase transfer reagent). Using helium gas, [^{18}F]FCH$_2$I resulted in the mixture was distilled at once, passed through short columns filled with NaOH and P$_2$O$_5$, and then trapped into an organic solvent (DMF, CH$_3$CN or THF) on cooling. The purification of [^{18}F]FCH$_2$I (bp: 53–54 °C [16]) by distillation was effective, since this procedure can leave behind all non-volatile impurities such as metal ions from the irradiated target chamber, the unreacted [^{18}F]F$^-$ and the phase transfer reagent. However, long-time distillation caused increase in the amount of CH$_2$I$_2$ (bp: 180 °C) flushed to the trapped solution of [^{18}F]FCH$_2$I and decreased the efficiency of fluoromethylation significantly. The NaOH and P$_2$O$_5$ columns could delete any acidic and basic radiochemical impurity contained in the [^{18}F]FCH$_2$I vapor. In the final trapped solution (500 μL), the radiochemical purity of [^{18}F]FCH$_2$I was greater than 98%, and the concentration of CH$_2$I$_2$ was less than 10 ppm detected by HPLC analysis as shown in Section 4. The automated process took 21 ± 2 min from the end of bombardment with a reproducible radiochemical yield of 14–31% (n = 25).

2.2. Stability of [^{18}F]FCH$_2$I in organic solvents and aqueous solutions

The results on the stability of [^{18}F]FCH$_2$I in organic solvents and aqueous solutions are listed in Table 1. The radiochemical purity of the [^{18}F]FCH$_2$I solution was monitored by analytical HPLC in a radioactivity concentration of 37–130 MBq/mL. After maintaining the product for

Table 1
Stability of [^{18}F]FCH$_2$I in organic solvents and aqueous solutions at 25 °C

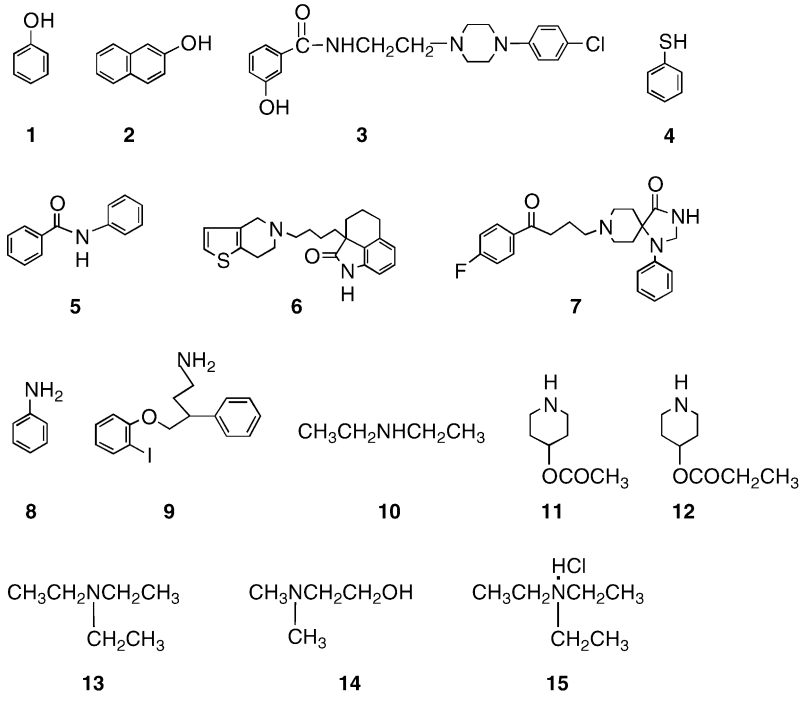
Solvent[a]	Maintenance time (min)	Radiochemical purity (%)[b]	Solvent	Maintenance time (min)	Radiochemical purity (%)
DMF	10	96	DMF/NaH[c]	10	74
	180	93	Acetone/NaOH[d]	10	53
THF	10	98	H$_2$O, pH 7	10	97
	180	89	H$_2$O, pH 3	10	95
CH$_3$CN	10	97	H$_2$O, pH 1	10	87
	180	95	H$_2$O, pH 9	10	71
Acetone	10	98	H$_2$O, pH 11	10	12
	180	89	H$_2$O, pH 14	10	3

[a] 500 μL.
[b] Radiochemical yield was determined by analytical HPLC on the reaction mixture. All results were presented as mean values (n = 3) with a maximum range of ±5%.
[c] 10 μL, 1.5 g/20 mL DMF.
[d] 5 μL, 0.2 N aqueous NaOH solution.

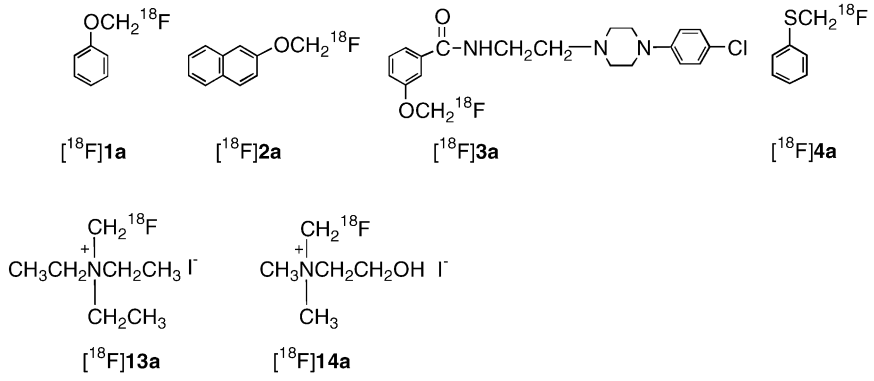
180 min at 25 °C, the radiochemical purity of [^{18}F]FCH_2I remained >90% in the organic solvents commonly used for labeling, e.g., DMF, THF, acetone and CH_3CN. Even in aqueous solutions of pH 1–7, [^{18}F]FCH_2I was also relatively stable with minor decomposition (<15%). The stability of [^{18}F]FCH_2I against base was also examined since a basic reaction condition was often necessary for labeling nucleophilic substrates. As shown in Table 1, in the basic conditions (NaH/DMF and NaOH/acetone), the radiochemical purities of [^{18}F]FCH_2I products were decomposed to 74 and 53% after maintaining them for 10 min at 25 °C. Moreover, [^{18}F]FCH_2I was unstable in the aqueous NaOH solution of pH 9–14, and [^{18}F]F^- was detected in these alkaline solutions. Defluorination of [^{18}F]FCH_2I may be a main decomposition route, which was often observed in the synthesis and in vivo evaluation of ^{18}F-labeled compounds [17].

2.3. Reactions of [^{18}F]FCH_2I with phenol, thiophenol, amide and amine functional groups

As model nucleophilic substrates, we first selected some simple organic structures with one functional group to determine their reactivities with [^{18}F]FCH_2I (Scheme 2). Then, we selected some substrates of PET ligands for imaging the distribution of neurotransmitters and enzymes in a brain (Scheme 2). These substrates with phenol, thiophenol, amide and amine functional groups had been reacted with [^{11}C]CH_3I and [^{18}F]FCH_2CH_2Br to form [^{11}C]methylated and [^{18}F]fluoroethylated ligands which were stable for purification, storage and in vivo evaluation [18]. Therefore, comparing the [^{18}F]fluoromethylated products (Scheme 3) with the corresponding [^{11}C]methyl and [^{18}F]fluoroethyl analogues is helpful to further elucidate the characteristics



Scheme 2. Structures of nucleophilic substrates used in this study.



Scheme 3. Structures of stable [^{18}F]fluoromethylated compounds identified in this study.

Table 2
Reactivity of [^{18}F]FCH_2I with phenol, thiophenol, amide and amine at 25 °C

Substrate No.	Base	Radiochemical yield (%)[a] for reaction mixture		Radiochemical purity (%)[b] for final product after purification	
		[^{18}F]fluoromethylated product	[^{18}F]F^-	[^{18}F]fluoromethylated product	[^{18}F]F^-
1	NaH	86	<1	96	n.d.[d]
2	NaH	76	3	99	<1
3	NaH	85	1	98	n.d.
4	NaH	91	2	96	n.d.
5	NaH	54	10	n.d.	81
6	NaH	80	7	<1.	90
7	NaH	45	20	n.d.	89
8	–[c]	n.d.[d]	33	—[e]	
9	–	n.d.	66	—	
10	–	n.d.	40	—	
11	–	n.d.	95	—	
12	–	n.d.	85	—	
13	–	46	7	97	<1
14	–	38	11	96	2
15	–	n.d.	n.d.	—	

[a] Radiochemical yield was determined by analytical HPLC from a sample withdrawn from the reaction mixture. All results were presented as mean values (n = 3) with a maximum range of ±5%.
[b] Radiochemical purity was determined by analytical HPLC from a sample withdrawn from the final product. All results were presented as mean values (n = 3) with a maximum range of ±5%.
[c] No base was used.
[d] No corresponding peak was detected.
[e] The reaction mixture was not purified.

of [^{18}F]FCH_2I. Moreover, since the isotopic effects of ^{18}F on ^{19}F are generally small [14], the reactivity of [^{18}F]FCH_2I with nucleophilic substrates may be extremely similar to that of the non-radioactive FCH_2I.

The results on the reactions of [^{18}F]FCH_2I with phenol, thiophenol, amide and amine are shown in Table 2.

Although phenol and thiophenol themselves are not strong nucleophiles, they form reactive alkoxide and thiolate for alkylation by treatment with a base such as NaH, NaOH or n-Bu_4NOH. As can be seen in Table 2, in the presence of NaH, phenol (**1**) and 2-naphthol (**2**) displayed high reactivities with [^{18}F]FCH_2I to form [^{18}F]**1a** and [^{18}F]**2a** with 86 and 75% radiochemical yields. Compound **3** [18a] reacted with [^{18}F]FCH_2I to give [^{18}F]**3a** in a high radiochemical yield (85%). Although **3** has amide and piperazine moieties in its molecule, these functional groups did not react with [^{18}F]FCH_2I. The [^{11}C]methylation of **3** also occurred only at the hydroxy group to form the O-[^{11}C]methylated product in a moderate radiochemical efficiency (41%) under the same condition [18a]. Because of the high electron-withdrawing effect of fluorine, [^{18}F]FCH_2I is more reactive than [^{11}C]CH_3I with nucleophile substrates. Similar to phenol, thiophenol (**4**) also displayed an excellent reactivity with [^{18}F]FCH_2I with a labeling efficiency of 91%.

To determine the stabilities of [^{18}F]fluoromethylated products, [^{18}F]**1a–4a** were purified from the reaction mixtures using semi-preparative HPLC, respectively, under the conditions shown in Section 4. The radioactive fractions corresponding to [^{18}F]**1a–4a** were concentrated to remove the eluting phases, and re-dissolved with saline to give radiochemically pure (>95%) products (Table 2). After leaving these products at 25 °C for 180 min, [^{18}F]**1a–4a** were found to retain >95% radiochemical purities in the saline solutions (data not shown). In addition to these compounds, [^{18}F]FMcN5652, a [^{18}F]fluoromethylated thiophenol derivative was also reported to be stable for purification, formulation and storage [12].

Reactivities of three amide substrates **5–7** with [^{18}F]FCH_2I were examined after they were treated with NaH in advance, respectively (Table 2). The sodium salt of N-phenyl benzamide (**5**) was highly reactive with [^{18}F]FCH_2I to give a main product observed in analytical HPLC chart for the reaction mixture. However, the product appeared unstable and purification was not successful. The sodium salt of amide **6** [18b] was reacted with [^{18}F]FCH_2I for 10 min at 25 °C. After the reaction was terminated, a main product peak was observed in the analytical HPLC chart for the reaction mixture (Fig. 1a). By comparing the retention time (t_R = 6.7 min) of this peak with those of the [^{11}C]methylated (t_R = 6.6 min) [18b] and [^{18}F]fluoroethylated (t_R = 6.9 min) [18c] of **6** under the same HPLC conditions, which were proportional to their lipophilicities, the product could be assumed to the [^{18}F]fluoromethylated product of **6**. To determine the identity and stability, the [^{18}F]fluoromethylated product was tried to purify from the reaction mixture using a semi-preparative HPLC system. However, HPLC analysis for the fraction corresponding to the [^{18}F]fluoromethylated product showed that a by-product was yielded during purification in addition to the desired peak (Fig. 1b). Using ion exchange chromatography, the by-product was assigned to [^{18}F]F^- by co-injection with the standard KF solution. After removing the HPLC solvents carefully under reduced pressure at 40 °C, the peak corresponding to the [^{18}F]fluoromethylated product disappeared,

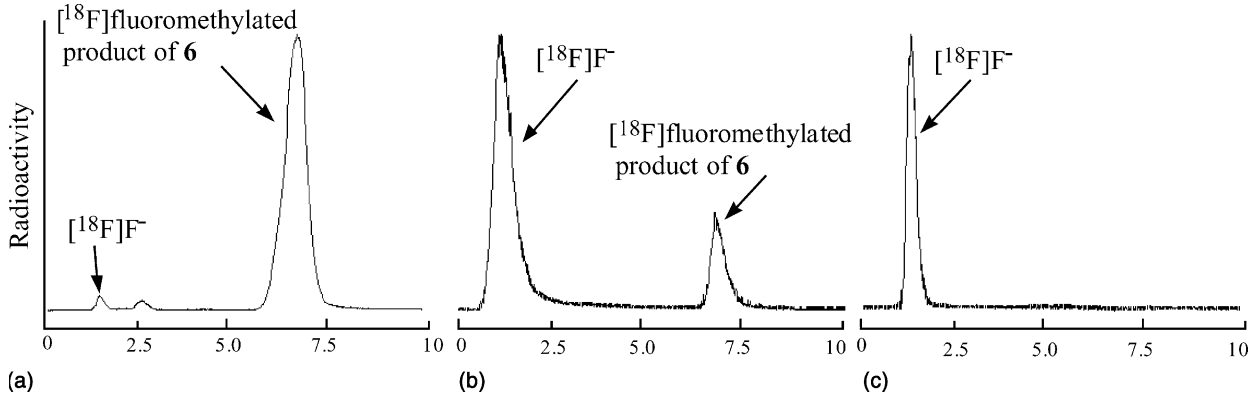


Fig. 1. Reaction of $[^{18}F]FCH_2I$ with amide **6**: (a) HPLC chart for the reaction mixture of **6** and $[^{18}F]FCH_2I$; (b) HPLC chart for the radioactive fraction corresponding the $[^{18}F]$fluoromethylated product of **6** after purification using semi-preparative HPLC; (c) HPLC chart for the final product re-dissolved in saline after removing the eluting phase under reduced pressure at 40 °C. HPLC conditions: Capcell Pak C_{18} (Ø 4.6 mm × 250 mm), CH_3CN/H_2O (7/3), 2 mL/min.

and only $[^{18}F]F^-$ was detected in the saline solution of the left residue (Fig. 1c). Another amide **7** [18c] also showed a similar reaction pattern to **6**.

Primary, secondary and tertiary amines displayed different reaction results when they were reacted with $[^{18}F]FCH_2I$ as shown in Table 2. In the case of primary and secondary amines (**8**–**12**), no desired fluoromethylated products were obtained. In addition to the unreacted $[^{18}F]FCH_2I$, only $[^{18}F]F^-$ as a main product was detected in the reaction mixtures, although these substrates could react with $[^{11}C]CH_3I$ and $[^{18}F]FCH_2CH_2Br$ to form corresponding stable $[^{11}C]$methylated and $[^{18}F]$fluoroethylated products [18c,d]. In contrast to the primary and secondary amines, tertiary amines **13** and **14** reacted with $[^{18}F]FCH_2I$ to form the desired tetraammonium products $[^{18}F]$**13a** and $[^{18}F]$**14a** with moderate radiochemical yields, respectively. Moreover, $[^{18}F]$**13a** and $[^{18}F]$**14a** could be purified from the reaction mixtures to give radiochemically pure (>95%) products which were stable for 180 min at 25 °C. In fact, $[^{18}F]$**14a** ($[^{18}F]$choline) which could be reproducibly synthesized by reacting **14** with $[^{18}F]FCH_2Br$ or $[^{18}F]FCH_2OTf$, is currently used as a PET marker for oncology [8–10]. On the other hand, the hydrochloride of tertiary amine **15** did not react with $[^{18}F]FCH_2I$ as expected.

In the present experiments, $[^{18}F]$**1a**–**4a** and $[^{18}F]$**13a**,**14a** prepared by the reactions of phenols **1**–**3**, thiophenol **4** and tertiary amines **13**,**14** with $[^{18}F]FCH_2I$ were stable, whereas the $[^{18}F]$fluoromethylated products prepared by the reactions of amides **5**–**7** with $[^{18}F]FCH_2I$ were unstable for purification and storage, although their presence in the reaction mixtures could be determined. However, the $[^{18}F]$fluoropromethylated products by the reactions of primary (**8**,**9**) and secondary (**11**,**12**) amines were not detected in the reaction mixtures. On consideration of the high reactivity of $[^{18}F]FCH_2I$, we believe that these amines **8**–**12** can react with $[^{18}F]FCH_2I$ to yield the $[^{18}F]$fluoromethylated products. Failure to detect their presence in the reaction mixtures may be that these products were too unstable. These findings are consistent with Bohme's results which fluoromethyldialkylamines were unstable (**4**). Defluorination was found to be a main decomposition route of the unstable $[^{18}F]$fluoromethylated products in these experiments.

3. Conclusions

In this study, we examined the preparation, stability and reactivity of $[^{18}F]FCH_2I$ and the stability of $[^{18}F]$fluoromethylated compounds. $[^{18}F]FCH_2I$ was prepared by reacting CH_2I_2 with $[^{18}F]F^-$ in a radiochemical yield of 14–31% ($n = 25$). This reagent was stable in various organic solvents and unstable in basic solutions. $[^{18}F]FCH_2I$ displayed high reactivity with phenol, thiophenol, amide and amine functional groups. The $[^{18}F]$fluoromethylated products from phenol, thiophenol and tertiary amine were stable for purification and storage, whereas those from amide and primary or secondary amines were unstable. Therefore, the application scope of $[^{18}F]$fluoromethylation for labeling was much narrower than that of $[^{11}C]$methylation. The substrates selected for $[^{18}F]$fluoromethylation may be limited to phenol, thiophenol and tertiary amine compounds.

Since the isotopic effects of ^{18}F on ^{19}F are very small, the characteristics of $[^{18}F]FCH_2I$ and $[^{18}F]$fluoromethylated compounds elucidated in the present study should be extremely similar to those of the non-radioactive FCH_2I and fluoromethylated compounds. These findings obtained by using $[^{18}F]FCH_2I$ may be applicable to the non-radioactive FCH_2I and fluoromethylated products.

4. Experimental

4.1. Materials and general methods

Nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JNM-GX-270 spectrometer 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. Column chromatography was done 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 a NaI (Tl) scintillation detector system. The following columns were used: Finepak Sil C18 for analysis or Megapak Sil C18 for purification (JASCO, Tokyo), Capcell Pak C_{18} (SHISEIDO, Tokyo) and J'sphore ODS H80 (YMC, Tokyo). In the analysis of ^{18}F-labeled compounds, unlabeled reference samples **1a**–**4a** and **13a**,**14a** were used for comparison in all HPLC runs. If not otherwise stated, chemicals were purchased from Aldrich Chemical (Milwaukee, WI) and Wako Pure Industries (Osaka) with the highest grade commercially available.

4.2. Fluoromethyl phenyl ether (*1a*)

A mixture of phenol (**1**, 18 mg, 0.2 mmol), FCH_2I (40 mg, 0.25 mmol) and anhydrous K_2CO_3 (30 mg, 0.21 mmol) in ether (2 mL) was stirred at 0 °C for 3 h. The reaction mixture was chromatographed on silica gel with pentane to give **1a** (8 mg, 31%) as a colorless liquid. ^1H-NMR ($CDCl_3$): δ 5.35 (2H, d, J = 46 Hz), 7.10–7.49 (5H, m). FAB-MS (*m/e*) calcd for C_7H_7FO (M^+ + 1): 127.05. Found: 127.13.

4.3. Fluoromethyl 2-naphthyl ether (*2a*)

A mixture of 2-naphthol (**2**, 14 mg, 0.1 mmol), FCH_2I (20 mg, 0.125 mmol) and anhydrous K_2CO_3 (15 mg, 0.11 mmol) in ether (2 mL) was stirred at 0 °C for 10 h. The reaction mixture was chromatographed on silica gel with pentane to give **2a** (12 mg, 68%) as a colorless liquid. ^1H-NMR ($CDCl_3$): δ 5.27 (2H, d, J = 46 Hz), 6.86–7.19 (2H, m), 7.29–7.84 (5H, m). FAB-MS (*m/e*) calcd for $C_{11}H_9FO$ (M^+ + 1): 177.06. Found: 177.20.

4.4. N-[2-[4-(4-Chlorophenyl)piperazin-1-yl]ethyl]-3-fluoromethylbenzamide (*3a*)

A mixture of *N*-[2-[4-(4-chlorophenyl)piperazin-1-yl]ethyl]-3-hydroxybenzamide (**3**, 14 mg, 0.039 mmol) [18a], FCH_2I (7 mg, 0.044 mmol) and anhydrous K_2CO_3 (12 mg, 0.086 mmol) in DMF (3 mL) was stirred at 25 °C for 3 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 (5/1) to give **3a** (10 mg, 65%) as a colorless crystal; m.p.: 107–109 °C (recrystallized from $CHCl_3/CH_3OH$ = 20/1). ^1H-NMR ($CDCl_3$) δ: 2.55–2.94 (8H, m), 3.15–3.24 (4H, m), 5.31 (2H, d, J = 46 Hz), 6.82–6.93 (3H, m), 7.10–7.51 (6H, m), 11.69 (1H, br). FAB-MS (*m/e*) calcd for $C_{20}H_{23}ClFN_3O_2$ (M^+ + 1): 392.18. Found: 392.27.

4.5. Fluoromethyl thiophenyl ether (*4a*)

A mixture of thiophenol (**4**, 11 mg, 0.1 mmol), FCH_2I (20 mg, 0.125 mmol) and anhydrous K_2CO_3 (15 mg, 0.105 mmol) in ether (2 mL) was stirred at 0 °C for 12 h. The reaction mixture was chromatographed on silica gel with pentane to give **4a** (7 mg, 49%) as a colorless liquid. ^1H-NMR ($CDCl_3$) δ: 5.65 (2H, d, J = 46 Hz), 7.04–7.57 (5H, m). FAB-MS (*m/e*) calcd for C_7H_7FO (M^+ + 1): 143.05. Found: 143.15.

4.6. Fluoro-N,N,N-triethylmethylammonium iodide (*13a*)

A mixture of triethylamine (**13**, 20 mg, 0.2 mmol), FCH_2I (32 mg, 0.2 mmol) in methanol/ether (1/2, 4 mL) was stood at 4 °C for 48 h. The precipitate resulting from the reaction mixture was filtered to give **13a** (4 mg, 7%) as a colorless crystal. FAB-MS (*m/e*) calcd for $C_7H_{17}FIN$ (M^+ + 1): 262.04. Found: 262.10.

4.7. N,N-Dimethyl-N-fluoromethyl-2-hydroxyethanaminium iodide (*14a*)

A mixture of *N*,*N*-dimethylethanolamine (**14**, 22 mg, 0.25 mmol), FCH_2I (40 mg, 0.25 mmol) in methanol/ether (1/2, 4 mL) was stood at 4 °C for 72 h. The precipitate resulting from the reaction mixture was filtered to give **14a** (5 mg, 8%) as a colorless crystal. FAB-MS (*m/e*) calcd for $C_5H_{13}FINO$ (M^+ + 1): 250.00. Found: 250.07.

4.8. Production of [^{18}F]fluoride

Aqueous [^{18}F]fluoride ([^{18}F]F^-) was produced in a target chamber by $^{18}O(p, n)^{18}F$ reaction on 10–20% enriched [^{18}O]H_2O using 18 MeV protons (15.8 MeV on target) from the cyclotron. After bombardment, the irradiated water was transferred by helium gas through a PEEK tube into a Dowex 1-X8 anion exchange column (carbonate form; Ø 3 mm × 25 mm), for trapping [^{18}F]F^- and enabling collection of the enriched [^{18}O]H_2O for recycling use. The [^{18}F]F^- was removed from the resin by elution with aqueous K_2CO_3 (3.3 mg/300 μL) solution into a glass vial containing Kryptofix 222 (30 mg) in CH_3CN (1.5 mL) and transported to a reaction vessel in a hot cell.

4.9. Radiosynthesis of [^{18}F]FCH_2I

After [^{18}F]F^- from the irradiating room was dried to remove H_2O and CH_3CN at 110 °C for 15 min, CH_2I_2 (50 μL) in *o*-dichlorobenzene (300 μL) was flowed into the radioactive mixture with a helium gas. Then, [^{18}F]FCH_2I resulted in this vessel was distilled under a helium flow (90–

100 mL/min) at 130 °C for 2 min and cooled into another vessel containing solvents (500 μL) for trapping at −15 to −20 °C. The radiochemical yield of [^{18}F]FCH_2I was 14–31% (n = 13) based on the total [^{18}F]F^- recovered from the target room. The radiochemical purity of [^{18}F]FCH_2I was assayed by analytical HPLC (FinePak Sil C18-T5, Ø 4.6 mm × 250 mm). The mobile phase was KH_2PO_4 (10 mM)/CH_3CN (1/1) with a flow rate of 2 mL/min and the retention time was 4.3 min for [^{18}F]FCH_2I. Confirmation for the identity of [^{18}F]FCH_2I was achieved by co-injection with the authentic non-radioactive FCH_2I prepared by the reaction of CH_2I_2 with HgF_2 [2].

4.10. Determination on stability of [^{18}F]FCH_2I in various solvents

The stability of [^{18}F]FCH_2I in various trapped solvents was evaluated by monitoring its radiochemical purity using the HPLC system described above. After leaving the solution for the designated time spans, the radiochemical purities of the [^{18}F]FCH_2I solutions were measured according to the analytical condition described above, respectively.

4.11. Reactions of [^{18}F]FCH_2I with phenol, thiophenol, amide and amine

[^{18}F]FCH_2I (80–370 MBq) was trapped into a solution of anhydrous DMF (500 μL) containing each substrate (0.8–1.1 mg) and base (if required, NaH: 10 μL, 1.5 g/20 mL DMF) at −15 to −20 °C. Then the reaction mixture was warmed to 25 °C and kept for 10 min. After the reaction was terminated by adding CH_3CN/H_2O (1/1, 200 μL), the radiochemical yields of [^{18}F]fluoromethylated products were determined by analytic HPLC.

The analytical conditions for the fluoromethylated products [^{18}F]**1a**–**4a** and [^{18}F]**13a**,**14a** were as follows. [^{18}F]**1a**: J'sphore ODS H80 (Ø 4 mm × 150 mm), CH_3CN/H_2O (1/1), 2 mL/min, 5.6 min. [^{18}F]**2a**: J'sphore ODS H80 (Ø 4 mm × 150 mm), CH_3CN/H_2O (6.5/3.5), 2 mL/min, 4.9 min. [^{18}F]**3a**: Capcell Pak C_{18} (Ø 4.6 mm × 250 mm), $CH_3OH/H_2O/Et_3N$ (7/3/0.05), 1.7 mL/min, 7.3 min. [^{18}F]**4a**: J'sphore ODS H80 (Ø 4 mm × 150 mm), CH_3CN/H_2O (7/3), 2 mL/min, 7.2 min. [^{18}F]**13a** and [^{18}F]**14a**: FinePak Sil C18-T5 (Ø 4.6 mm × 150 mm), KH_2PO_4 (10 mM)/CH_3CN (4/1), 2.0 mL/min, 5.1 and 3.2 min.

4.12. Determination for stability of [^{18}F]fluoromethylated compounds

After the reaction was finished, the [^{18}F]fluoromethylated compound was purified from the radioactive mixture using a reverse-phase HPLC system. The HPLC conditions for purifying the corresponding products were similar to the analytical conditions listed above, with the exception of semi-preparative column (Ø 10 mm × 250 mm) and flow rate (6 mL/min). The fraction corresponding to the desired radioactive product was collected in a rotary evaporator and evaporated to dryness at about 40 °C under reduced pressure. After the residue was re-dissolved in 3 mL of saline, the product was obtained with a radiochemical purity of >95%. Confirmation for the identity of each product was achieved by co-injection with the non-radioactive authentic sample using the analytical HPLC column.

The stability of the [^{18}F]fluoromethylated compound in its prepared form was evaluated by monitoring its radiochemical purity using the HPLC system described above. After these products were maintained for 180 min, their radiochemical purities were measured.

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