Synthesis of [^{18}F]Fluorocholine Analogues as a Potential Imaging Agent for PET Studies

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There have been intensive studies concerning [^{11}C]choline ([^{11}C]methyldimethyl(β-hydroxyethyl) ammonium) (**1**) which is known as a very effective tracer in imaging various human tumors localized in brain, lung, esophagus, rectum, prostate and urinary bladder using Positron Emission Tomography (PET) and there is increasing interest in ^{18}F labelled choline (**2**) and proved to be useful to visualize prostate cancer. We have prepared six ^{18}F labelled alkyl choline derivatives (**3a-3c**, **4a-4c**) from ditosylated and dibrominated alkanes in moderate yields. The six alkyl tosylate or bromate ammonium salts have been synthesized as precursors. Radiofluorination was achieved by the treatment of precursors with $^{18}F^-$ in the presence of Kryptofix-2.2.2.. The labeling yields varied ranging from 7 to 25%.

Key Words : Positron Emission Tomography (PET), [^{18}F]Fluorocholine derivatives

Introduction

Choline is a natural ammonium salt and a constituent of biologically important molecules such as acetylcholine and lecithin. Choline is incorporated into cells across cell membranes via two different types of routes.[1] One route is related to phosphorylcholine synthesis. Phosphorylcholine is utilized for the generation of phosphatidylcholine, a major membrane phospholipid (lecithin). The other route is involved in acetylcholine synthesis. Previous studies showed that tumors contain large amounts of membrane phospholipids, especially phosphatidylcholine, so the visualization of membrane phospholipids could give direct information on tumor growth.[2] Because of high rate of phospholipid synthesis in tumors **1** has been known to be used as a radiopharmaceutical for PET. Hara T. *et al.* showed that **1** is a very effective tracer in imaging various human tumors localized in the brain, lung, esophagus, rectum, prostate and urinary bladder.[3,4] But, frequent synthesis is required and difficult to use in a routine imaging procedure due to short half-life of ^{11}C (20 min). To settle cumbersome synthesis of **1**,[5] ^{18}F labeled choline (**2**) has been developed.[6]

Fluorine-18 has been regarded as an ideal positron-emitting-nuclide. Its moderate physical half-life (110 minutes) allows more flexible syntheses and scanning than its ^{11}C analogues. There was a similar study on [^{18}F]fluoroalkylating agent for ^{18}F-radiolabeling of amine.[7] **2** is known to be a potentially useful PET tracer for detection of metastatic prostate cancer and recurrent brain tumor.[8,9] We previously reported the synthesis and biological evaluation of **1** and **2**.[10] Hara T. *et al.* reported the preparation and biological evaluation of **3a**[11] and Iwata R. *et al.* developed the simple purification method of **2**.[12] We have prepared three ^{18}F labelled alkyl choline derivatives (**3a-3c**, **4a-4c**) from ditosylated and dibrominated alkanes. Di-substituted alkanes were labelled with ^{18}F for 5 min at 95 °C, followed by coupling reaction (85 °C, 30 min) with dimethylethanolamine. The [^{18}F]fluorination yield of dibrominated alkanes was significantly low. The fluorinated derivatives also have been synthesized as standard compounds. In this study, we'd like to report the synthesis and purification of the [^{18}F]fluoroalkyl substituted choline derivatives. This study can be used for the preparation of other [^{18}F]fluoroalkyl substituted compounds.

Results and Discussion

The standard compounds N,N-dimethyl-*N*-fluoroalkyl-*N*-2-hydroxyethylammonium *p*-toluenesulfonate **3a-3c** and *N,N*-dimethyl-*N*-fluoroalkyl-*N*-2-hydroxyethylammonium

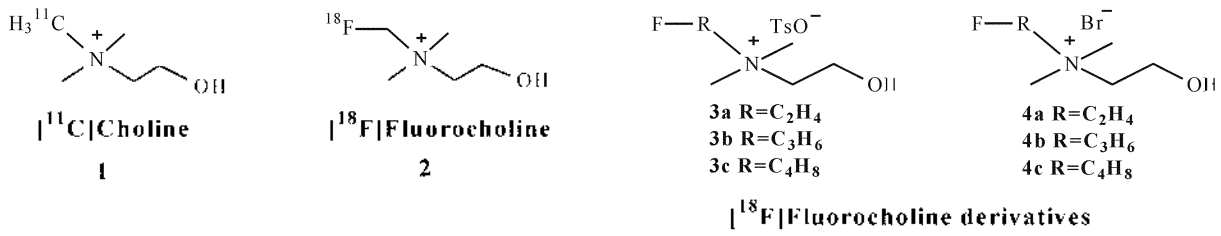
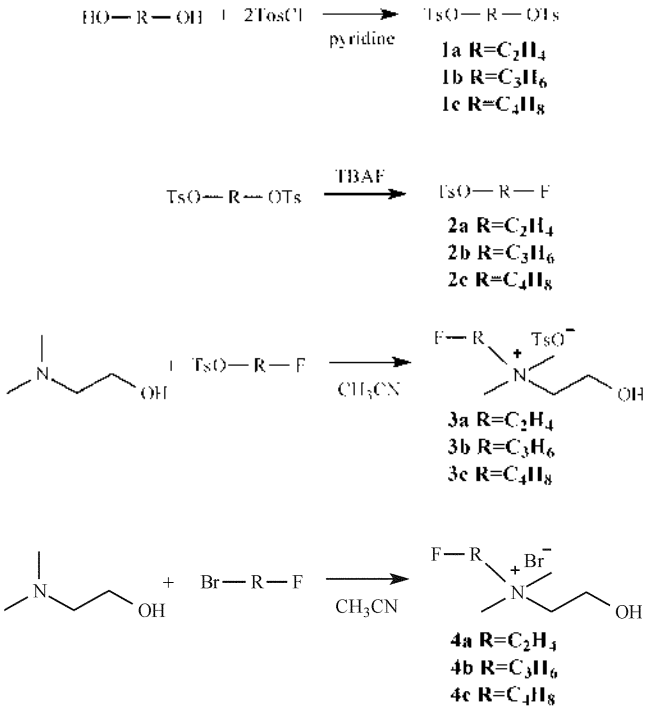


Figure 1. Structure of |^{11}C|choline, |^{18}F|fluorocholine and |^{18}F|fluorocholine derivatives.



Scheme 1. The synthesis of fluorocholine derivatives.

bromide **4a-4c** were synthesized in 3 steps from alkanediols as shown in Scheme 1.

Ditosylated alkanediols were used in order to introduce alkyl groups of different chain lengths. Tosyl group is known to be a good leaving group for both nucleophillic substitution reaction with ^{18}F and coupling reaction with nitrogen of amine group. Fluorine substitution reaction is very susceptible to reaction conditions because both substitution and elimination can take place simultaneously during reaction. Tetrabutylammoniumfluoride trihydrate, which was dried with acetonitrile by the method of azeotropic distillation was treated with ditosylated alkane in acetonitrile to give fluoro-*p*-toluenesulfonyloxyalkane. And then the reaction with *N,N*-dimethylethanolamine gave tosylated reference compounds **3a-3c**. Brominated reference compounds **4a-4c** was prepared from the reaction of fluorobromoalkane with *N,N*-dimethylethanolamine. The structure of reference compounds was confirmed by ^{1}H-nuclear magnetic resonance, ^{19}F-nuclear magnetic resonance and mass spectrometry. The ^{1}H-NMR signals of the methylene group in ω-position of the fluoroalkyl compounds at 3.80-4.59 ppm can be analyzed as a doublet of triplet (dt; $^{2}J_{HF}$ = 48-51 Hz, $^{3}J_{HH}$ = 45.6 Hz). The ^{19}F-NMR signals at -220~-223 ppm can be analyzed as a triplet of triplet (tt; $^{2}J_{HF}$ = 48-51 Hz, $^{3}J_{HF}$ = 27-30 Hz).

The reference compounds were recrystallized from acetonitrile and diethylether. Ammonium salt shows particular behavior in mass spectrum where ammonium cation peak (C^+) and molecular ion + ammonium cation $(M-C)^+$ peak which is shown in Figure 2 caused by electrostatic interaction were observed.

Radioactive **[^{18}F]3a-[^{18}F]3c** were synthesized as shown in Scheme 2.

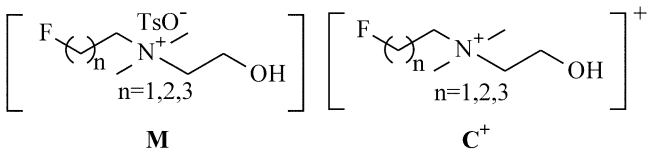
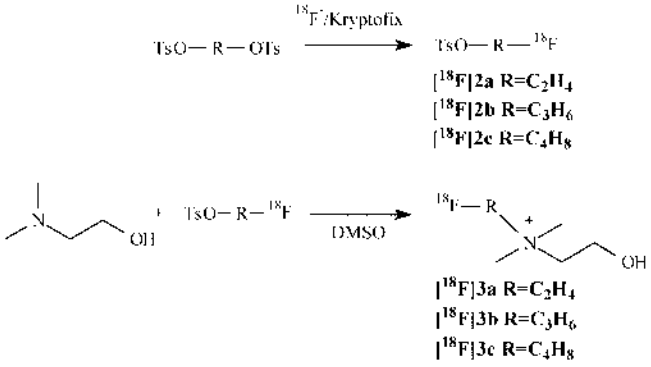


Figure 2. Structural description of M and C^+



Scheme 2. The labeling of [^{18}F]fluorocholine derivatives.

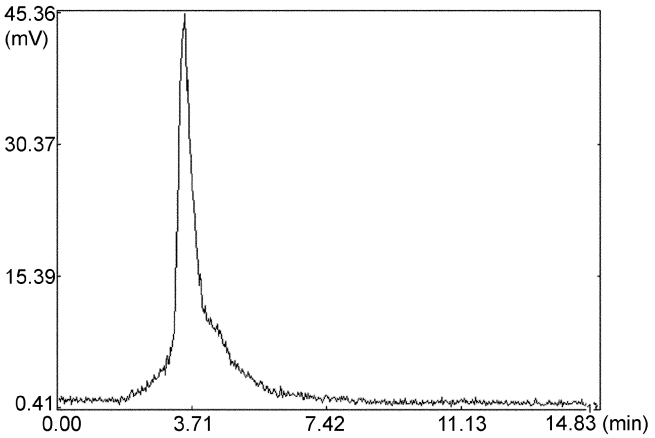
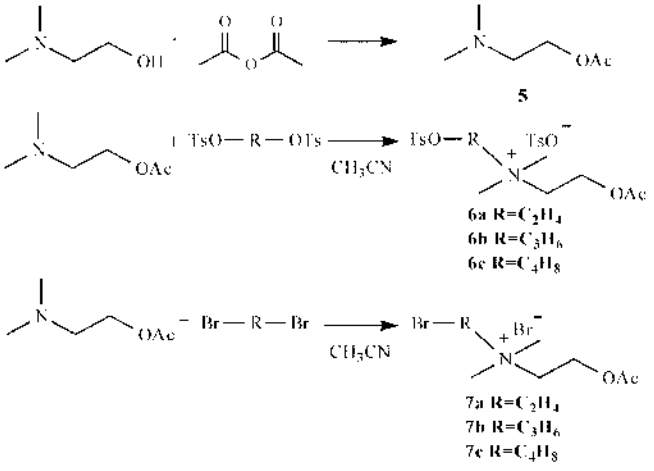


Figure 3. HPLC chromatogram of 4-[^{18}F]fluoro-1-p-toluenesulfonyloxybutane.

Labeling reaction was carried out in acetonitrile with kryptofix 2.2.2. as a phase transfer catalyst. Reaction time was found to be an important factor in labeling reaction. Over 30 minutes reaction gave mostly by-product which was not fully elucidated and optimal reaction conditions observed was 5 minutes reaction and 95 °C. Radio-TLC chromatogram is shown in Figure 3.

By-product was obtained as shown in Figure 3 in case of longer than 30 minute's reaction time. We also tried to carry out [^{18}F]fluoride substitution reaction with two other precursors, **6a-6c** and **7a-7c**, but labeling yield was unsatisfactory. The synthesis of **6a-6c** and **7a-7c** are shown in Scheme 3.

Trace amount of silver nitrate was used as a catalyst for brominated precursor. By the combination of two Sep-Pak cartridges, a purified final product was obtained. Alumina Sep-Pak cartridge was useful to remove ^{18}F anion, and weak ion-exchange Sep-Pak cartridge, which is used to purify **1** was effective to isolate the quaternary amine products.



Scheme 3. The synthesis of the precursors.

In our previous study we performed comparison study for both **1** and **2** with glioma and colon adenocarcinoma. Both compounds were found to be more promising on colon cancer daignosis than glioma.[10] From this point of view, we will carry out further studies with **[^{18}F]3a-[^{18}F]3c** to validate its biological properties depending on cancer cell lines and especially for colon adenocarcinoma.

Conclusion

Three ^{18}F labelled choline derivatives (**[^{18}F]3a-[^{18}F]3c**) and standard compounds (**3a-3c**) were synthesized in radiochemical yields ranging from 18-24% to be investigated as potential PET tracers. Although standard compounds (**4a-4c**) were prepared, we couldn't obtain its radioactive analogues (**[^{18}F]4a-[^{18}F]4c**) due to low [^{18}F]fluorination yield of dibromoalkane compared to ditosylated alkane. We have found the optimal conditions for radioactive [^{18}F]fluorination of ditosylalkane as followes: i) At 95 °C and 5 minute's reaction, [^{18}F]fluorination of ditosylalkane was achieved in high yields up to 92%. ii) After 15 minute's reaction, the [^{18}F]fluoroalklyated by-product was increased. Six other precursors (**6a-6c, 7a-7c**) have shown low reactivity of [^{18}F]fluorination due to electrostatic interaction of ammonium cation against [^{18}F]fluorine substitution. The synthetic method of **[^{18}F]3a-[^{18}F]3c** preparation was established via labelling and coupling reaction.

Experimental Section

N,N-dimethylaminoethanol, acetic anhydride, p-toluenesulfonyl chloride, anhydrous pyridine and Kryptofix® 2.2.2. were purchased from Aldrich Co.. Acetonitrile was obtained from MERCK. All sep-pak cartridge used were purchased from Waters. All solvents were of analytical grade and used without further purification. Thin layer chromatography was performed using silica gel 60 F_{254}. Melting points were measured on a MEL-TEMP device. ^{1}H-NMR spectra were measured on a Varian Gemini-200 spectrometer and referenced to tetramethylsilane. ^{19}F-NMR spectra were measured on a Bruker, Avance DPX-300 spectrometer and referenced with trichlorofluoromethane. Mass spectrometer was obtained with JMS-AX505WA, JEOL. All reactions were carried out under a positive pressure of nitrogen gas. [^{18}F]Fluorine was produced on a MC-50 cyclotron by irradiation of $H_2{}^{18}O$ water target at Korea Cancer Center hospital. The radiochemical purity was performed by HPLC (μ-Bondapak C18 column, 300 × 3.9 mm, 10 μm, Waters; Eluent : NaH_2PO_4 (3 mM); Flow rate : 1 mL/min) with a Young-Lin M930 pump and a M720 to detect UV absorbance and a Raytest GABI series to measure radioactivity.

1,2-Di-*p*-toluene sulfonyloxyetane (1a)[13]. To 40.0 mL of anhydrous pyridine, 1.5 mL (31.5 mmol) of ethanediol was added dropwise and the mixture was stirred until ethanediol was dissolved completely. 5.0 g (26.2 mmol) of *p*-toluenesulfonyl chloride in 10 mL of anhydrous pyridine was added slowly and the reaction mixture stirred for 30 min in ice bath. The reaction mixture was stirred for additional 1 h at room temperature and the resulting compound was taken up in 30 mL of dichloromethane and 50 mL of 0.1 N HCl. Dichlomethane layer bearing the compound was separated and washed three times with 200 mL of water and dried over anhydrous sodium sulfate. After concentration *in vacuo*, the residue was purified by column chromatography. Yield of **1a**: 8.5 g (87.6%); Rf = 0.53 (Hexane : Methylene Chloride : Methanol = 10 : 9 : 1, v/v), m.p. 126-129 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) 7.58 (d, 4H), 7.40 (d, 4H), 4.23 (s, 4H), 2.46 (s, 6H).

1,3-Di-*p*-toluene sulfonyloxypropane (1b)[13]. 2.3 mL (31.5 mmol) of propanediol and 5.0 g (26.2 mmol) of *p*-toluenesulfonyl chloride were converted into **1b** as described for the homologue **1a**. Yield of **1b**: 8.7 g (86.4%); Rf = 0.55 (Hexane : Methylene Chloride : Methanol = 10 : 9 : 1, v/v), m.p. 124-126 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) 7.57 (d, 4H), 7.39 (d, 4H), 4.12 (t, 4H), 2.45 (s, 6H), 2.04 (q, 2H).

1,4-Di-*p*-toluene sulfonyloxybutane (1c)[13]. 2.8 mL (31.5 mmol) of butanediol and 5.0 g (26.2 mmol) of *p*-toluenesulfonyl chloride in 10 mL of anhydrous pyridine were converted into **1c** as described for the homologue **1a**. Yield of **1c**: 9.2 g (88.1%); Rf = 0.56 (Hexane : Methylene Chloride : Methanol = 10 : 9 : 1, v/v), m.p. 82-84 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) 7.78 (d, 4H), 7.36 (d, 4H), 4.06 (s, 4H), 2.43 (br, 6H), 1.78 (br, 4H).

2-Fluoro-1-*p*-toluenesulfonyloxyethane (2a)[14]. 2.12 g (8.1 mmol) of tetrabutylammonium fluoride trihydrate (TBAF) was dried with anhydrous acetonitrile (3 × 5 mL) under the stream of the nitrogen gas at 87 °C. 2.0 g (5.40 mmol) of **1a** and 25 mL of anhydrous acetonitrile were added to the reaction mixture. The reaction mixture was stirred for 4 hrs at 87 °C. After concentration in vacuo, the residue was purified by column chromatography. Yield of **2a**: 0.37 g (32.5%); Rf = 0.70 (Hexane : Methylene Chloride : Methanol = 10 : 9 : 1, v/v), ^{1}H-NMR (200 MHz, $CDCl_3$) 7.82 (d, 2H), 7.38 (d, 2H), 4.74 (t, 1H), 4.48 (t, 1H), 4.37 (t, 1H), 4.21 (t, 1H), 2.36 (s, 3H).

3-Fluoro-1-*p*-toluenesulfonyloxypropane (2b)[14]. 2.0 g (5.2 mmol) of **1b** and 2.04 g (7.8 mmol) of TBAF were

converted into **2b** as described for the homologue **2a**. Yield of **2b**: 0.37 g (32.5%); Rf = 0.72 (Hexane : Methylene Chloride : Methanol = 10 : 9 : 1, v/v). ^{1}H-NMR (200 MHz, $CDCl_3$) 7.85 (d, 2H), 7.40 (d, 2H), 4.64 (t, 1H), 4.39 (t, 1H), 4.20 (t, 2H), 2.48 (s, 3H), 2.15 (quintet, 1H), 2.01 (quintet, 1H).

4-Fluoro-1-*p*-toluenesulfonyloxybutane (2c)[14]. 2.0 g (31.5 mmol) of **1c** and 1.97 g (7.5 mmol) of TBAF were converted into **2c** as described for the homologue **2a**. Yield of **2c**: 0.33 g (30.4%); Rf = 0.73 (Hexane : Methylene Chloride : Methanol = 10 : 9 : 1, v/v). ^{1}H-NMR (200 MHz, $CDCl_3$) 7.82 (d, 2H), 7.39 (d, 2H), 4.56 (t, 1H), 4.34 (t, 1H), 4.13 (t, 2H), 2.46 (s, 3H), 1.92-1.62 (m, 4H).

***N,N*-Dimethyl-*N*-2-fluoroethyl-*N*-2-hydroxyethylammonium *p*-toluenesulfonate(standard compound) (3a).** 0.27 mL (2.74 mmol) of *N,N*-dimethyl-2-ethylamine was dissolved in 10 mL of anhydrous acetonitrile. 0.3 g (1.37 mmol) of **2a** was added and refluxed for 1hr. Acetonitrile was removed *in vacuo* to obtain a solid product that was recrystallized from diethyl ether. Yield of **3a**: 0.38 g (89.5%); Rf = 0.23 (Chloroform : Methanol = 5 : 1, v/v). m.p. 85-87 °C. ^{1}H-NMR (200 MHz, CD_3CN) 7.64 (d, 2H), 7.23 (d, 2H), 5.03 (t, 1H), 4.80 (t, 1H), 3.93 (m, 2H), 3.85 (t, 1H), 3.72 (t, 1H), 3.54 (t, 2H), 3.18 (s, 6H), 2.34 (s, 3H), ^{19}F-NMR (300 MHz, CD_3CN) -220.39 (tt, $^2J_{HF}$ = 51 Hz, $^3J_{HF}$ = 30 Hz); MS (FAB+, C^-: ammonium cation, M: ammonium salt) calcd C^+ 136, $(C+M)^-$ 443, obsd C^- 136, $(C+M)^+$ 443.

***N,N*-Dimethyl-*N*-3-fluoropropyl-*N*-2-hydroxyethylammonium *p*-toluenesulfonate(standard compound) (3b).** 0.25 mL (2.58 mmol) of *N,N*-dimethyl-2-ethylamine and 0.3 g (1.29 mmol) of **2b** were converted into **3b** as described for the homologue **3a**. Yield of **3b**: 0.30 g (72.0%); Rf = 0.25 (Chloroform : Methanol = 5 : 1, v/v). m.p. 128-130 °C. ^{1}H-NMR (200 MHz, CD_3CN) 7.71 (d, 2H), 7.23 (d, 2H), 4.68 (t, 1H), 4.42 (t, 1H), 3.93 (m, 2H), 3.58-3.42 (m, 4H), 3.16 (s, 6H), 2.46-2.32 (m, 2H), 2.24 (s, 3H), ^{19}F-NMR (300 MHz, CD_3CN) -232.44 (tt, $^2J_{HF}$ = 48 Hz, $^3J_{HF}$ = 28 Hz); MS (FAB+, C^-: ammonium cation, M: ammonium salt) calcd C^+ 150 $(C+M)^+$ 471, obsd C^+ 150 $(C+M)^+$ 471.

***N,N*-Dimethyl-*N*-4-fluorobutyl-*N*-2-hydroxyethylammonium *p*-toluenesulfonate(standard compound) (3c).** 0.24 mL (2.44 mmol) of *N,N*-dimethyl-2-ethylamine and 0.3 g (1.22 mmol) of **2c** were converted into **3c** as described for the homologue **3a**. Yield of **3c**: 0.28 g (68.2%); Rf = 0.24 (Chloroform : Methanol = 5 : 1, v/v). m.p. 96-98 °C. ^{1}H-NMR (200 MHz, CD_3CN) 7.63 (d, 2H), 7.23 (d, 2H), 4.62 (t, 1H), 4.39 (t, 1H), 3.93 (m, 2H), 3.52 (t, 2H), 3.42 (t, 2H), 3.16 (s, 6H), 2.46-2.32 (m, 2H), 2.24 (s, 3H), 1.821.62 (m, 2H), ^{19}F-NMR (300 MHz, CD_3CN) 221.17 (tt, $^2J_{HF}$ = 48 Hz, $^3J_{HF}$ = 27 Hz); MS (FAB+, C^+: ammonium cation, M: ammonium salt) calcd C^+ 164 $(C+M)^-$ 499, obsd C^+ 164, $(C+M)^+$ 499.

***N,N*-Dimethyl-*N*-2-fluoroethyl-*N*-2-hydroxyethylammonium bromide(standard compound) (4a).** 0.5 mL (6.71 mmol) 2-fluoro-1-bromoethane was dissolved in 25 mL of anhydrous acetoniirile. 1.0 mL (10.07 mmol) of *N,N*-dimethyl-2-ethylamine was added and heated at 85 °C for 2 hrs. Acetonitrile was removed in vacuo to produce a solid product that could be recrystallized from diethyl ether and acetonitrile. Yield of **4a**: 0.91 g (64.2); R_f = 0.23 (Chloroform : Methanol = 5 : 1); m.p.: 122-124 °C. ^{1}H-NMR (200 MHz, CD_3CN) 5.09 (t, 1H), 4.84 (t, 1H), 3.99 (t, 2H), 3.85 (t, 2H), 3.64 (t, 2H), 3.27 (s, 6H), ^{19}F-NMR (300 MHz, CD_3CN) -220.39 (tt, $^2J_{HF}$ = 51 Hz, $^3J_{HF}$ = 30 Hz); MS (FAB+, C^-: ammonium cation, M: ammonium salt) calcd C^- 136, $(C+M)^+$ 351, obsd C^- 136, $(C+M)^+$ 351.

***N,N*-Dimethyl-*N*-3-fluoropropyl-*N*-2-hydroxyethylammonium bromide(standard compound) (4b).** 0.5 mL (5.45 mmol) of 3-fluoro-1-bromoethane and 0.8 mL (8.18 mmol) of *N,N*-dimethyl-2-ethylamine and were converted into **4b** as described for the homologue **4a**. Yield of **4b**: 0.86 g (68.4); R_f = 0.23 (Chloroform : Methanol = 5 : 1); m.p.: 140-143 °C. ^{1}H-NMR (200 MHz, CD_3CN) 4.71 (t, 1H), 4.49 (t, 1H), 4.01-3.97 (m, 2H), 3.61-3.47 (m, 4H), 3.16 (s, 6H), 2.34 (m, 2H). ^{19}F-NMR (300 MHz, CD_3CN) -223.55 (tt, $^2J_{HF}$ = 51 Hz, $^3J_{HF}$ = 27 Hz); MS (FAB+, C^+: ammonium cation, M: ammonium salt) calcd C^+ 150 $(C+M)^-$ 379, obsd C^- 150 $(C+M)^+$ 379.

***N,N*-Dimethyl-*N*-4-fluorobutyl-*N*-2-hydroxyethylammonium bromide(standard compound) (4c).** 0.5 mL (4.66 mmol) of 4-fluoro-1-bromoethane and 0.7 mL (6.99 mmol) of *N,N*-dimethyl-2-ethylamine and were converted into **4c** as described for the homologue **4a**. Yield of **4c**: 0.83 g (72.5); R_f = 0.23 (Chloroform : Methanol = 5 : 1); m.p.: 104-106 °C; R_f = 0.23 (Chloroform : Methanol = 5 : 1); ^{1}H-NMR (200 MHz, CD_3CN) 4.63 (t, 1H), 4.42 (t, 1H), 3.99-3.95 (m, 2H), 3.49-3.47 (m, 4H), 3.14 (s, 6H), 1.82 (m, 4H), ^{19}F-NMR (300 MHz, CD_3CN) -221.00 (tt, $^2J_{HF}$ = 48 Hz , $^3J_{HF}$ = 27 Hz); MS (FAB+, C^+: ammonium cation, M: ammonium salt) butyl calcd C^+ 164 $(C+M)^+$ 407, obsd C^- 164, $(C+M)^+$ 407.

***N,N*-Dimethyl-2-aminoethylacetate (5).** A mixture of *N,N*-dimethylaminoethanol (20.0 mL, 0.2 mmol) and acetic anhyride (22.6 mL, 0.24 mmol) was stirred for 1 h under ice bath. **5** was isolated by fractional distillation. Yield of **5**: 10.0 mL (40%). b.p 142 °C, ^{1}H-NMR (200 MHz, $CDCl_3$) 4.16 (t, J = 5.4 Hz, 2H), 2.57 (t, J = 5.4 Hz, 2H), 2.29 (s, 6H), 2.08 (s, 3H).

***N*-2-Acetoxyethyl-*N,N*-dimethyl-*N*-2-*p*-toluenesulfonyloxyethylammonium *p*-toluenesulfonate (6a).** 1.55 mL (9.7 mmol) of *N,N*-Dimethyl-2-aminoethylacetate was dissolved in 30 mL of acetonitrile. 3.0 g (8.09 mmol) of 1,2-toluenesulfonyloxyethane was added and refluxed for 1 hr. Acetonitrile was removed in vacuo to give a solid product that could be recrystallized from diethyl ether. Yield of **6a**: 3.28 g (83.3%); Rf = 0.56 (Chloroform : Methanol = 5 : 1, v/v). m.p 118-120 °C, ^{1}H-NMR (200 MHz, CD_3CN) 7.79 (d, J = 8 Hz, 2H), 7.71 (d, J = 8 Hz, 2H), 7.38 (d, J = 8 Hz, 2H), 7.17 (d, J = 8 Hz, 2H), 4.58-4.42 (m, 4H), 4.22-4.12 (m, 2H), 4.02-3.92 (m, 2H), 3.41 (s, 6H), 2.46 (s, 3H), 2.38 (s, 3H), 2.17 (s, 3H).

***N*-2-Acetoxyethyl-*N,N*-dimethyl-*N*-3-*p*-toluenesulfonyloxypropylammonium *p*-toluenesulfonate (6b).** 1.49 mL (9.36 mmol) of *N,N*-Dimethyl-2-aminoethylacetate and 3.0 g (7.8 mmol) of 1,3-toluenesulfonyloxypropane were converted into **6b** as described for the homologue **6a**. Yield of

6b: 3.51 g (81.6%); Rf = 0.58 (Chloroform : Methanol = 5 : 1, v/v), m.p 122-124 °C. ^{1}H-NMR (200 MHz, CD_3CN) 7.78 (d, J = 8 Hz, 2H), 7.72 (d, J = 8 Hz, 2H), 7.36 (d, J = 8 Hz, 2H), 7.16 (d, J = 8 Hz, 2H), 4.56-4.42 (m, 4H), 4.24-4.14 (m, 2H), 4.02-3.92 (m, 2H), 3.40 (s, 6H), 2.47 (s, 3H), 2.39 (s, 3H), 2.19 (s, 3H), 1.82 (s, 2H).

***N*-2-Acetoxyethyl-*N,N*-dimethyl-*N*-4-*p*-toluenesulfonyloxybutylammonium *p*-toluenesulfonate (6c).** 1.2 mL (6.27 mmol) of *N,N*-Dimethyl-2-aminoethylacetate and 3.0 g (7.53 mmol) of 1,4-toluenesulfonyloxybutane were converted into **6c** as described for the homologue **6a**. Yield of **6c**: 3.85 g (87.2%); Rf = 0.62 (Chloroform : Methanol = 5 : 1, v/v), m.p 142-144 °C. ^{1}H-NMR (200 MHz, CD_3CN) 7.79 (d, J = 8 Hz, 2H), 7.74 (d, J = 8 Hz, 2H), 7.34 (d, J = 8 Hz, 2H), 7.15 (d, J = 8 Hz, 2H), 4.54-4.42 (m, 4H), 4.22-4.12 (m, 2H), 4.02-3.92 (t, 2H), 3.41 (s, 6H), 2.47 (s, 3H), 2.39 (s, 3H), 2.17 (s, 3H), 1.92-1.68 (m, 4H).

***N*-2-Acetoxyethyl-*N*-2-bromoethyl-*N,N*-dimethylammonium bromide (7a).** 0.5 mL (5.8 mmol) of 1,2-Dibromoethane and 1.1 mL (7.0 mmol) of *N,N*-Dimethyl-2-aminoethylacetate were dissolved in 10 mL of anhydrous acetonitrile. The mixture was refluxed with stirring for about 1 hr. After removal of solvent by rotary evaporation, recrystallization with acetonitrile and diethyl ether gave **7a** as a colorless solid. Yield of **7a**: 1.60 g (82.3%); Rf = 0.46 (Chloroform : Methanol = 5 : 1, v/v), m.p 142-144 °C, ^{1}H-NMR (200 MHz, CD_3CN) 4.64-4.42 (m, 2H), 3.92-3.80 (m, 2H), 3.65-3.52 (m, 4H), 3.28 (s, 6H), 2.12 (s, 3H).

***N*-2-Acetoxyethyl-*N*-2-bromopropyl-*N,N*-dimethylammonium bromide (7b).** 0.5 mL (4.93 mmol) of 1,3-Dibromopropane and 0.9 mL (5.91 mmol) of *N,N*-Dimethyl-2-aminoethylacetate were converted into **7b** as described for the homologue **7a**. Yield of **7b**: 1.34 g (78.1%); Rf = 0.46 (Chloroform : Methanol = 5 : 1, v/v), m.p 142-146 °C, ^{1}H-NMR (200 MHz, CD_3CN) 4.54-4.42 (m, 2H), 3.92-3.71 (m, 2H), 3.27 (s, 6H), 2.26 (s, 3H), 2.15-2.07 (m, 2H).

***N*-2-Acetoxyethyl-*N*-2-bromobutyl-*N,N*-dimethylammonium bromide (7C).** 0.5 mL (4.19 mmol) of 1,4-Dibromobutane and 0.9 mL (5.02 mmol) of *N,N*-Dimethyl-2-aminoethylacetate were dissolved in 10 mL of anhydrous acetonitrile. The mixture was refluxed with stirring for about 1 hr. After removal of solvent by rotary evaporation, recrystallization with acetonitrile and diethyl ether gave **7c** as a colorless solid. Yield of **7c**: 1.18 g (77.5%); Rf = 0.46 (Chloroform : Methanol = 5 : 1, v/v), m.p 136-138 °C, ^{1}H-NMR (200 MHz, CD_3CN) 4.56-4.44 (m, 2H), 3.72-3.60 (m, 2H), 3.48-3.37 (m, 4H), 3.12 (s, 6H), 2.06 (s, 3H), 1.82-1.78 (m, 4H).

***N,N*-Dimethyl-*N*-2-[^{18}F]fluoroethyl-*N*-2-hydroxyethylammonium *p*-toluenesulfonate ([^{18}F]3a).** The aqueous [^{18}F]-fluoride (50mCi) was added to a reaction vial containing a solution of 13 μmol of Kryptofix 2.2.2® and 17 μmol of K_2CO_3 and the water was removed with anhydrous acetonitrile (1 mL × 3) under the stream of the nitrogen gas at 93 °C. Compounds produced transferred to a vial containing 5 mg of **1a** and was dissolved in 1 mL of dimethylsulfoxide. The reaction vial was sealed and heated on the heating block. Radiolabeling was carried out at 95 °C for 5 min. After [^{18}F]fluoroethyl *p*-toluenesulfonate (**2a**) was confirmed by radio-TLC, *N,N*-dimethyl-2-ethylamine was added with trimethyl amine into the vial. The reaction mixture was stirred for 30 min at 85 °C. The reaction progress was measured by radio-TLC. After the mixture was cooled to room temperature, it was passed through a cation exchange Sep-Pak cartridge to remove $^{18}F^-$ and a alumina Sep-Pak cartridge to remove the residue. [^{18}F]**3a** was eluted with 2 mL of saline. The radiochemical yield was about 23.2% and the radiochemical purity was 96% after purification.

***N,N*-Dimethyl-*N*-3-[^{18}F]fluoropropyl-*N*-2-hydroxyethylammonium *p*-toluenesulfonate ([^{18}F]3b).** [^{18}F]**3b** was obtained as described for the homologue. [^{18}F]**3a.** The radiochemical yield was about 18.2% and the radiochemical purity was over 96% after purification.

***N,N*-Dimethyl-*N*-4-[^{18}F]fluorobutyl-*N*-2-hydroxyethyl)ammonium *p*-toluenesulfonate ([^{18}F]3c).** [^{18}F]**3c** was obtained as described for the homologue [^{18}F]**3a.** The radiochemical yield was about 24.6% and the radiochemical purity was over 96% after purification.

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