

Research Article

Radiosyntheses and Reactivities of Novel [^{18}F]2-fluoroethyl arylsulfonates

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Summary

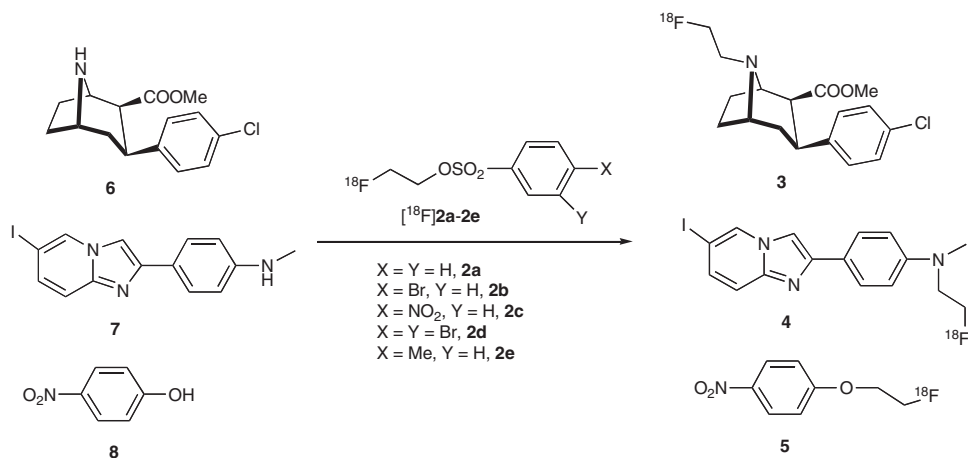
[^{18}F]2-Fluoroethyl tosylate ([^{18}F]FEOX, X = Ts) is widely used for labeling radiotracers for positron emission tomography (PET). Little work has been reported on syntheses of other [^{18}F]2-fluoroethyl arylsulfonates ([^{18}F]FEOX) that bear a less electron-rich aryl group, even though these might offer enhanced reactivities. Thus, a series of novel [^{18}F]FEOX (X = benzenesulfonyl, brosyl, nosyl, 3,4-dibromobenzenesulfonyl) were synthesized and reactivities compared to [^{18}F]FEOTs. Precursors for radiolabeling (*bis*-ethylene glycol arylsulfonates) and reference FEOX were synthesized (alcohol + arylsulfonyl chloride + KOSiMe_3 in THF). Regardless of substitution pattern, [^{18}F]FEOX (110°C, 5 min, acetonitrile) were obtained in similar decay-corrected isolated radiochemical yields (RCY; 47–53%). All [^{18}F]FEOX gave excellent RCYs (64–87%) of the dopamine uptake radioligand, [^{18}F]FECNT (130°C, 10 min, acetonitrile). The 3,4-dibromobenzenesulfonate gave the highest RCY of [^{18}F]FECNT (87%) and this HPLC-purified labeling agent was used directly for efficient [^{18}F]FECNT production. When the secondary aniline of an amyloid probe (HM-IMPY) or *p*-nitrophenol was reacted with [^{18}F]FEOX, RCYs were appreciably higher for brosylate and nosylate than for tosylate, while 3,4-dibromobenzenesulfonate again gave the highest RCY. Owing to the high reactivity of the new [^{18}F]FEOX and their ease of syntheses via stable precursors, such agents (particularly 3,4-dibromobenzenesulfonate) should be considered as alternatives to [^{18}F]FEOTs. Copyright © 2005 John Wiley & Sons, Ltd.

Key Words: fluorine-18; sulfonate ester; labeling agent

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Introduction

Fluorine-18 ($t_{1/2} = 109.8$ min) is a radionuclide used extensively with positron emission tomography (PET). The utility of ^{18}F can be ascribed, in part, to the numerous methods that allow for its efficient incorporation into a variety of radiotracers. Of recent interest to our group are radiotracers that possess an ^{18}F -2-fluoroethyl group such as the dopamine uptake radioligand, ^{18}F FECNT (**3**),¹ and the β -amyloid probe, ^{18}F FEM-IMPY² (**4**, Scheme 1). ^{18}F -2-Fluoroethyl tosylate (**2e**, Scheme 1) has featured as a labeling agent in this work. This arylsulfonate ester has been used extensively owing to its ease of radiosynthesis via a stable, commercially available precursor (ethylene glycol *di-p*-tosylate), stability towards intermediate purification, and acceptable reactivity with a variety of nucleophiles.^{3–6} Little work has been reported on the synthesis of other ^{18}F -2-fluoroethyl arylsulfonates that bear a less electron-rich aryl group, even though these might offer enhanced reactivities towards weak nucleophiles. Here we report a series of such labeling agents. Specifically, we provide details of the syntheses of the *bis*-ethylene glycol arylsulfonate ester precursors used for radiolabeling as well as the syntheses of the 2-fluoroethyl esters of benzenesulfonate (**2a**), brosylate (**2b**), nosylate (**2c**), and 3,4-dibromobenzenesulfonate ester (**2d**) and their ^{18}F -labeled counterparts (Scheme 1). Of note, **2a**, **2c**, and **2d**, are novel compounds that have not been prepared with an ^{18}F label.⁷ In this report we examine the reactivities of these new ^{18}F -fluoroethylating agents towards assorted nucleophiles (secondary amine, aniline nitrogen, and phenol) in comparison to the widely used arylsulfonate, ^{18}F -2-fluoroethyl tosylate (Scheme 1). Finally, we detail a highly efficient method for the radiosynthesis of ^{18}F FECNT where the

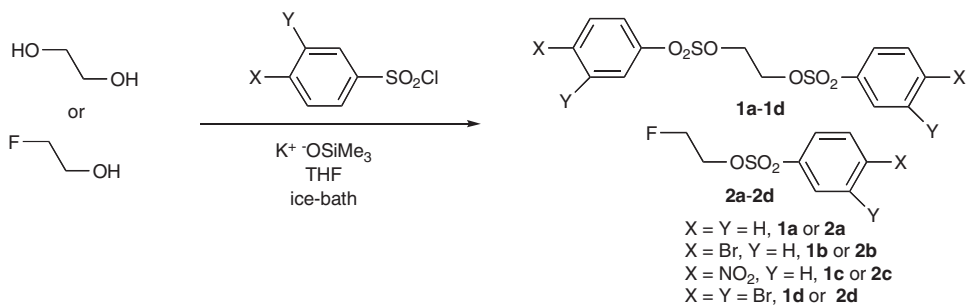


Scheme 1. Reaction of novel ^{18}F fluoroethyl arylsulfonates **2a–2d** and widely used **2e** with assorted nucleophiles

reactive and lipophilic alkylating agent [¹⁸F]**2d** is quickly purified by reverse phase HPLC and used directly to prepare [¹⁸F]FECNT in high radiochemical yield and chemical purity.

Results and discussion

bis-Ethylene glycol arylsulfonates (**1a–1d**) and 2-fluoroethyl arylsulfonates (**2a–2d**) were prepared by treatment of the appropriate alcohol with commercially available arylsulfonyl chloride using potassium trimethylsilanolate as base in tetrahydrofuran at ice-bath temperature (Scheme 2). Unoptimized isolated yields for **1a–1d** and **2a–2d** ranged from 32 to 64%. We found the use of potassium trimethylsilanolate to be superior, in terms of ease of work-up and yield, to the use of pyridine as previously reported in the synthesis of **1c**.⁸ *bis*-Sulfonate esters were stored at room temperature and showed minimal decomposition over the course of this work (6 months) as monitored by HPLC. To explore the reactivity of the *bis*-sulfonate esters (**1a–1e**) in a uniform manner, a Synthia radiochemistry apparatus⁹ possessing an x,y,z robotic arm, computer-controlled heaters, fraction collector, solid phase extraction (SPE) module, HPLC injector/column switcher, and gas flow controllers (He and N₂) was employed. [¹⁸F]Fluoride ion contained in [¹⁸O]water and potassium carbonate-Kryptofix[®] 222 was dried by cycles of acetonitrile addition and evaporation at 110°C under a nitrogen stream (200 ml/min). The dried, activated [¹⁸F]fluoride ion complex was subsequently treated with 8.1 μmol of one of the precursors **1a–1e** in acetonitrile (110°C, 5 min) and the labeled product isolated by reverse-phase HPLC. Average decay-corrected isolated radiochemical yields of [¹⁸F]**2a–2e** ranged from 47 to 53% (range of individual yields: 45–55%), regardless of the substitution pattern on the aryl ring of the sulfonate ester (Table 1). After HPLC purification of each product [¹⁸F]**2a–2e**, the radioalkylating agents were recovered (>85%) in a 1 ml volume of acetonitrile by SPE. The radiochemical



Scheme 2. Syntheses of *bis*-ethylene glycol arylsulfonates (**1a–1d**) and authentic 2-fluoroethyl arylsulfonates (**2a–2d**)

Table 1. Average isolated, decay-corrected radiochemical yields ($n \geq 3$) of [^{18}F]2-fluoroethyl arylsulfonates^a

| Precursor | [^{18}F]Product | HPLC isolated radiochemical yield (RCY; %) |
|-----------|----------------------------|--|
| 1a | 2a | 53 |
| 1b | 2b | 51 |
| 1c | 2c | 47 |
| 1d | 2d | 53 |
| 1e | 2e | 53 |

^a8.1 μmol precursor + $^{18}\text{F}^-/\text{K}_{222}/\text{K}_2\text{CO}_3$ in 1 ml MeCN, 5 min, 110°C.

yields of [^{18}F]2a–2e were not further optimized since the principal objective of this work was to compare the reactivities of [^{18}F]2a–2e under a standard set of conditions.

The secondary amine, 2 β -carbomethoxy-3 β -(4-chlorophenyl)nortropine (CNT, **6**) (2.7 μmol), was reacted with each of the purified [^{18}F]2-fluoroethyl arylsulfonates under the standard conditions (acetonitrile, 130°C, 10 min in open vessel). Resulting average isolated radiochemical yields for [^{18}F]FECNT **3** are presented in Table 2 and range from 64 to 87%. Use of the novel 3,4-dibromobenzenesulfonate ester, [^{18}F]2d, afforded **3** in highest radiochemical yield (87%). It was found that evaporation of the acetonitrile reaction solvent to dryness in the 10 min reaction time span, thereby effectively increasing the concentration of nucleophile, had a favorable effect on radiochemical yield. When ^{18}F -fluoroethylation of **6** was conducted in a septum-sealed V-vial using a 9-fold greater amount of nucleophile (23.4 μmol) in about 1 ml of acetonitrile, the radiochemical yields of **3** from [^{18}F]2d and [^{18}F]2e were only 54 and 18%, respectively (Table 2, entries 6 and 7). The feasibility of using an 'open vessel' radiolabeling procedure, which in the current case offers the advantages of minimizing the amount of costly precursor and increasing radiochemical yields, is dependent, in part, on the volatility of the ^{18}F -fluoroethylating species. To assess volatility in a practical manner, [^{18}F]2a–2e of known starting radioactivities were each heated in an open vessel, with helium sweep gas (10 ml/min) to minimize bumping, under conditions identical to those used to produce **3**, but with nucleophile (e.g. **6**) absent from the acetonitrile solution. After the 10 min concentration procedure, residual radioactivity was measured. The results (Table 3) revealed [^{18}F]2c and [^{18}F]2d to be less volatile than the widely employed [^{18}F]2e and in this regard to be well-suited for open vessel radiolabeling procedures. Volatility differences alone cannot account for increased radiochemical yields when using [^{18}F]2d compared to [^{18}F]2e to produce **3**; this is shown by the sealed reaction radiolabelings that minimize volatility differences in the agents [^{18}F]2d and [^{18}F]2e.

Table 2. Decay-corrected radiochemical yields of **3–6** upon reaction with novel fluoroethylating agents ([¹⁸F]**2a–2d**) and fluoroethyl tosylate ([¹⁸F]**2e**)

| Entry | Precursor | ¹⁸ F-labeling agent | [¹⁸ F]Product | HPLC isolated RCY (%) ^a |
|-----------------|-----------|--------------------------------|---------------------------|------------------------------------|
| 1 | 6 | 2a | 3 | 64 |
| 2 | 6 | 2b | 3 | 73 |
| 3 | 6 | 2c | 3 | 81 |
| 4 | 6 | 2d | 3 | 87 |
| 5 | 6 | 2e | 3 | 75 |
| 6 ^b | 6 | 2d | 3 | 54 |
| 7 ^b | 6 | 2e | 3 | 18 |
| 8 ^c | 6 | 2d | 3 | 84 |
| 9 ^d | 6 | 2e | 3 | 37 |
| 10 | 7 | 2b | 4 | 17 |
| 11 | 7 | 2c | 4 | 29 |
| 12 | 7 | 2d | 4 | 38 |
| 13 | 7 | 2e | 4 | 3 |
| 14 ^e | 7 | 2d | 4 | 5 |
| 15 | 8 | 2a | 5 | 23 |
| 16 | 8 | 2b | 5 | 34 |
| 17 | 8 | 2c | 5 | 50 |
| 18 | 8 | 2d | 5 | 63 |
| 19 | 8 | 2e | 5 | 19 |

^aAverage ($n \geq 2$).^b23.4 μmol of **6** in 1 ml total volume in sealed V-vial.^cNo SPE of [¹⁸F]**2d** (Method B, see experimental).^dNo SPE of [¹⁸F]**2e**-isolated in 7:3 v/v acetonitrile–water.^eNo SPE of [¹⁸F]**2d**-isolated in 95:5 v/v acetonitrile–water.**Table 3.** Percentage of starting [¹⁸F]2-fluoroethyl arylsulfonate radioactivity remaining in an open test tube upon heating 1 ml acetonitrile solution^a

| ¹⁸ F-labeling agent | Decay-corrected radioactivity remaining (%) |
|--------------------------------|---|
| 2a | 11 |
| 2b | 23 |
| 2c | 68 |
| 2d | 67 |
| 2e | 12 |

^a10 min, 130°C with He sweep gas (10 ml/min).

Differences in the reactivities of [¹⁸F]**2a–2e** became more pronounced as the aniline nitrogen of HM-IMPY **7** was employed as a weaker nucleophile, using the same radiolabeling conditions described above for **3** (Table 2, entries 10–13). Again, use of [¹⁸F]**2d** resulted in the highest radiochemical yield of **4** (38%) while use of the tosylate [¹⁸F]**2e** gave the lowest yield (3%). Intermediate radiochemical yields of 17 and 29% were noted for the brosylate and nosylate ¹⁸F-labeling agents, respectively. In the isolation of **4**, the only

other radioactive compound noted in the chromatogram was unreacted [^{18}F]2-fluoroethyl arylsulfonate ester. Increasing the precursor concentration and/or prolonged heating, as reported previously,² might result in even higher yields of **4**. Such experiments were not undertaken as it was our main focus to demonstrate the enhanced reactivities of the novel ^{18}F -alkylating agents versus the widely used [^{18}F]**2e** under a standard (but not fully optimized) set of conditions.

A similar reactivity profile of [^{18}F]**2d** > [^{18}F]**2c** > [^{18}F]**2b** > [^{18}F]**2a** \approx [^{18}F]**2e** was observed when the agents were reacted with the deactivated phenol **8** to give the radiolabeled ether **5**¹⁰ (Table 2, entries 15–19). An initial solvent composition of acetonitrile (1 ml) containing the ^{18}F -labeling agent and DMF (0.2 ml) containing **8** and 1 equivalent of methanolic tetrabutylammonium hydroxide was used for production of **5**.

Alternative methods of labeling by fluoroethylation using novel arylsulfonate leaving groups and/or [^{18}F]**2a–d** have yet to be explored. Such methods include direct [^{18}F]fluoride displacement of the mono arylsulfonate ester^{11,12} or a one-pot procedure where the intermediate [^{18}F]2-fluoroethyl arylsulfonate is used without purification.^{2,12} In general, however, both of these alternative methods may suffer from erratic yields and difficult HPLC purifications owing to the copious amounts of byproducts formed.

For production of [^{18}F]FECNT, the two-step radiolabeling sequence involving synthesis and purification of a labeling agent [^{18}F]**2a–2e** followed by alkylation of CNT proved most reliable. In addition to the high reactivity of [^{18}F]**2d**, a distinct advantage of this labeling agent is that it may be used directly for alkylation without intermediate SPE isolation. Owing to the high lipophilicity of [^{18}F]**2d**, this alkylating agent can be isolated within 6 min in a high organic content HPLC mobile phase (9:1 v/v, acetonitrile–water) from a semi-preparative C-18 column that is able to remove >99.9% of starting bis-sulfonate ester **1d**. It was found that the HPLC fraction containing [^{18}F]**2d** (ca 1.1 ml) could be combined directly with secondary amine **6** to give **3** in radiochemical yield (84%, Table 2, entry 8), similar to the yield from the method where HPLC-purified [^{18}F]**2d** is first isolated in neat acetonitrile via SPE (87%). For the purpose of comparison, direct reaction of the tosylate, [^{18}F]**2e**, in acetonitrile–water (7:3 v/v) with **6** gave **3** in only 37% radiochemical yield (Table 2, entry 9). Solid phase extraction of radiolabeling agents often requires manual manipulation of the radioactive solution, development of a custom-made SPE module,¹³ or use of a commercial apparatus often possessing a lone SPE module that is primarily intended for isolation of the final radiopharmaceutical rather than a radiolabeled intermediate. In the production of **3** via [^{18}F]**2d**, the need for intermediary SPE can be avoided and thus the radiochemistry sequence is simplified. Direct use of the HPLC collected fraction of [^{18}F]**2d** versus an intermediary SPE is not always

comparable. For example, it was found that reaction of the HPLC fraction containing [¹⁸F]2d in 1 ml of acetonitrile–water (95:5 v/v) with 7 resulted in lower radiochemical yield of 4 (5%, Table 2, entry 14) as compared to when [¹⁸F]2d was isolated in neat acetonitrile via SPE (38%). Thus, the use of the HPLC fraction of [¹⁸F]2d containing 5–10% water for direct reaction with nucleophiles needs to be assessed on a case by case basis.

Conclusions

Novel 2-fluoroethyl arylsulfonates possessing non-electron-donating substituents about the aryl ring were synthesized and also labeled with fluorine-18 (2a–2d). The reactivities of the novel labeling agents were compared to the widely used [¹⁸F]2-fluoroethyl tosylate (2e). Substituent pattern on the phenyl ring had minimal effect on radiochemical yield of the radiolabeled intermediates. The radiolabeled alkylating agents, prepared from stable, easily synthesized *bis*-ethylene glycol arylsulfonates, showed enhanced reactivity toward weak nucleophiles in comparison to 2e. In particular, [¹⁸F]2-fluoroethyl 3,4-dibromobenzenesulfonate demonstrated high reactivity, low volatility, and ease of purification making it an attractive alternative to [¹⁸F]2-fluoroethyl tosylate.

Experimental

Materials

All chemicals were obtained from commercial sources and used as received unless otherwise stated. Of note, 3,4-dibromobenzenesulfonyl chloride was obtained from Oakwood Products Inc. (West Columbia, SC). Standard samples of FECNT, 3, and CNT, 6, were obtained from Dr Mark Goodman (Emory University). Authentic standards of FEM-IMPY, 4, HM-IMPY, 7, 2-fluoroethyl 4-nitro-phenyl ether, 5, and 2-fluoroethyl tosylate, 2e, were available based on published methods from our laboratory.^{2,10}

General methods

HPLC analysis was performed on a Beckman Coulter (Fullerton, CA) Gold HPLC module (System Gold 126 gradient solvent module coupled with a variable wavelength 166 UV absorbance detector). In-line HPLC detection of radioactivity used a Bioscan (Washington, DC) flow count radioactivity detector (Pin diode). Radioactivity was measured using a Biodex Medical Systems (Shirley, NY) AtomlabTM 300 dose calibrator. Isolated radiochemical yields reported in Tables 2 and 3 are decay-corrected and an average from 2 or more reactions. Uncorrected melting points were determined with a capillary apparatus (Mel-Temp; Barnstead Thermolyne, Dubuque, IA). Analytical TLC was conducted on Macherey-Nagel silica gel 60 G-254 plates (250 μm; Alltech

Associates, Deerfield, IL). Normal phase column chromatography, using disposable silica gel cartridges (12–40 mm ID \times 150 mm length), was performed with a Horizon high-performance flash chromatography (HPFC) system (Biotage, Inc, Charlottesville, VA) equipped with UV detector (254 nm) and fraction collector. Elemental analyses were determined by Midwest Microlab (Indianapolis, IN). High-resolution mass spectrometry (HRMS) was performed at the University of Minnesota Mass Spectrometry facility. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained with a Bruker instrument. Chemical shifts are reported in ppm (δ) downfield relative to the signal from internal tetramethylsilane.

No-carrier-added [^{18}F]fluoride ion was prepared by the $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ nuclear reaction on a PETtrace cyclotron (GE Medical Systems, Milwaukee, WI). ^{18}O -enriched water (1.8 ml, >95% isotopic enrichment) was added to a titanium target equipped with titanium foils. The [^{18}O]water was bombarded (typically 20 $\mu\text{A} \times$ 120 min) with 18 MeV protons. Portions of the irradiated water (0.02–0.5 ml) were used for individual experiments. All radiolabeling reactions were conducted with the use of Synthia, a computer program driven synthesis module, developed at Uppsala PET Center, that enabled fine control of reaction parameters (e.g. oven temperature, reaction times, liquid transfers, HPLC injections, SPE).

General method: syntheses of ethyleneglycol-1,2 diarylsulfonates (1a – 1d) and 2-fluoroethyl arylsulfonates (2a – 2d)

To a round-bottomed flask cooled in an ice bath and kept under argon was added either 0.125–0.25 ml ethylene glycol (2.23–4.46 mmol) for **1a–1d** or 0.1 ml (1.7 mmol) 2-fluoroethanol dissolved in 2 ml anhydrous THF. Arylsulfonyl chloride (2.5 equiv. for **1a–1d**, 1.25 equiv. for **2a–2d**) dissolved in 3 ml THF was added. To this cooled solution was added potassium trimethylsilylanolate (5 equiv.) in portions over 30 min. The resulting slurry was stirred for 2 h at ice-bath temperature. The slurry was poured into 100 ml ice-cold water and the aqueous phase extracted with dichloromethane. The organic layer was dried over sodium sulfate, filtered, and dichloromethane removed by rotary evaporation. Final purification of the crude product was performed by silica HPFC.

Ethyleneglycol-1,2-benzenesulfonate (1a). Gradient HPFC (100% hexane to 50:50 v/v hexane–dichloromethane) gave a colorless oil that solidified (mp 40–42°C) upon standing (63% yield). TLC 70:30 v/v hexane–ethyl acetate ($R_f = 0.21$). ^1H NMR (400 MHz, CDCl_3 , δ): 4.23 (s, 4H), 7.53–7.58 (m, 4H), 7.66–7.68 (m, 2H), 7.84–7.88 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3 , δ): 67.03, 128.13, 129.58, 134.36, 135.58. HRMS-ESI: $m/z + \text{Na}$ calculated, 365.0124;

found, 365.0136. Analytically calculated for C₁₄H₁₄S₂O₆: C, 49.11; H, 4.12. Found: C, 49.27; H, 4.26.

Ethyleneglycol-1,2-4-bromobenzene sulfonate (1b). Gradient HPFC (50:50 hexane–dichloromethane to 100% dichloromethane) gave a white solid (mp 145°C) in 32% yield. TLC 20:80 v/v hexane–ethyl acetate (*R*_f=0.22). ¹H NMR (400 MHz, CDCl₃, δ): 4.26 (s, 4H), 7.71 (apparent s, 8H). ¹³C NMR (100 MHz, CDCl₃, δ): 67.17, 129.58, 129.79, 132.96, 134.58. HRMS-ESI: *m/z*+Na calculated, 520.8334; found, 520.8346. Analytically calculated for C₁₄H₁₂Br₂S₂O₆: C, 33.62; H, 2.42; Br, 31.95. Found: C, 33.78; H, 2.50; Br, 32.08.

Ethyleneglycol-1,2-4-nitrobenzene sulfonate (1c). Multiple extractions with dichloromethane (6 × 50 ml) gave solid material that was purified by HPFC (30:70 hexane–dichloromethane to 100% dichloromethane). A white solid (mp 194°C; literature⁸ mp 186°C) was isolated in 55% yield. TLC dichloromethane (*R*_f=0.36). ¹H NMR (400 MHz, CD₃CN, δ): 4.31 (s, 4H), 8.06 (dm, 4H, *J*=9.3 Hz), 8.37 (dm, 4H, *J*=9.3 Hz). HRMS-ESI: *m/z*+Na calculated, 454.9826; found, 454.9828. Analytically calculated for C₁₄H₁₂N₂S₂O₁₀: C, 38.89; H, 2.80; N, 6.48. Found: C, 39.25; H, 2.92; N, 6.50.

Ethyleneglycol-1,2-3,4-dibromobenzene sulfonate (1d). Gradient HPFC (100% hexane to 100% dichloromethane) gave white solid (mp 168°C) in 43% yield. TLC 20:80 v/v hexane–dichloromethane (*R*_f=0.37). ¹H NMR (400 MHz, CDCl₃, δ): 4.31 (s, 4H), 7.64 (dd, 2H, *J*=8.5, 2.0 Hz), 7.83 (d, 2H, *J*=8.5 Hz), 8.10 (s, 2H). ¹³C NMR (100 MHz, CDCl₃, δ) 67.22, 126.27, 127.34, 132.34, 132.66, 134.71, 135.59. HRMS-ESI: *m/z*+Na calculated, 676.6545; found 676.6513. Analytically calculated for C₁₄H₁₀Br₄S₂O₆: C, 25.56; H, 1.53; Br, 48.58. Found: C, 25.64; H, 1.51; Br, 48.20.

2-fluoroethyl-benzene sulfonate (2a). Gradient HPFC (100% hexane to 50:50 hexane–ethyl acetate) gave a colorless oil in 64% yield. TLC 70:30 v/v hexane–ethyl acetate (*R*_f=0.38). ¹H NMR (400 MHz, CDCl₃, δ): 4.30 (m, 2H, *J*_{HF}=27.2 Hz), 4.59 (m, 2H, *J*_{HF}=47.1 Hz), 7.58 (m, 2H), 7.68 (m, 1H), 7.95 (m, 2H). ¹³C NMR (100 MHz, CDCl₃, δ) 68.66 (*J*_{CF}=21.2 Hz), 80.52 (*J*_{CF}=174.1 Hz), 127.96, 129.36, 134.08, 135.64. HRMS-ESI: *m/z*+Na calculated, 227.0149; found 227.0151. Analytically calculated for C₈H₉FO₃S: C, 47.05; H, 4.44. Found: C, 47.09; H, 4.26

2-Fluoroethyl-4-bromobenzene sulfonate (2b). Gradient HPFC (100% hexane to 75:25 hexane–ethyl acetate) gave a colorless oil that solidified upon standing solid (mp 49°C) in 47% yield. TLC 70:30 v/v hexane–ethyl acetate (*R*_f=0.38). ¹H NMR (400 MHz, CDCl₃, δ): 4.31 (m, 2H, *J*_{HF}=27.2 Hz), 4.59 (m, 2H,

$J_{\text{HF}} = 47.0$ Hz), 7.72 (m, 2H), 7.80 (m, 12H). ^{13}C NMR (100 MHz, CDCl_3 , δ) 68.92 ($J_{\text{CF}} = 21.2$ Hz), 80.44 ($J_{\text{CF}} = 174.1$ Hz), 129.38, 129.43, 132.71, 134.68. HRMS-ESI: $m/z + \text{Na}$ calculated, 304.9254; found 304.9259. Analytically calculated for $\text{C}_8\text{H}_8\text{BrFO}_3\text{S}$: C, 33.94; H, 2.85; Br, 28.22. Found: C, 34.19; H, 2.87; Br, 28.27.

2-Fluoroethyl-4-nitrobenzenesulfonate (2c). Gradient HPFC (100% hexane to 80:20 hexane–ethyl acetate) gave a white solid (mp 118°C) in 50% yield. TLC 80:20 v/v hexane–ethyl acetate ($R_f = 0.21$). ^1H NMR (400 MHz, CDCl_3 , δ): 4.41 (m, 2H, $J_{\text{HF}} = 30.0$ Hz), 4.60 (m, 2H, $J_{\text{HF}} = 45.0$ Hz), 8.14 (d, 2H, $J = 6.0$ Hz), 8.41 (d, 2H, $J = 6.0$ Hz). ^{13}C NMR (100 MHz, CDCl_3 , δ): 69.58 ($J_{\text{CF}} = 20.5$ Hz), 80.30 ($J_{\text{CF}} = 174.1$ Hz), 124.52, 129.32, 141.54, 150.90. HRMS-ESI: $m/z + \text{NH}_4$ calculated, 267.0445; found 267.0460. Analytically calculated for $\text{C}_8\text{H}_8\text{FNO}_5\text{S}$: C, 38.56; H, 3.24; N, 5.62. Found: C, 38.46; H, 3.25; N, 5.49.

Synthesis of 2-fluoroethyl-3,4-dibromobenzenesulfonate (2d). Gradient HPFC (100% hexane to 50:50 hexane–dichloromethane) gave a white solid (mp 68–70°C) in 57% yield. TLC 20:80 v/v hexane–dichloromethane ($R_f = 0.63$). ^1H NMR (400 MHz, CDCl_3 , δ): 4.35 (dt, 2H, $^3J_{\text{FH}} = 26.0$ Hz, $J_{\text{HH}} = 4.0$ Hz), 4.61 (dt, 2H, $^3J_{\text{FH}} = 48.0$ Hz, $J_{\text{HH}} = 4.0$ Hz), 7.71 (dd, 1H, $J = 8.4$ Hz, 2.1 Hz), 7.83 (d, 1H, $J = 8.4$ Hz), 8.16 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3 , δ): 69.28 ($J_{\text{C-F}} = 21.1$ Hz), 80.35 ($J_{\text{C-F}} = 174.1$ Hz), 126.10, 127.39, 132.02, 132.73, 134.61, 135.99. HRMS-ESI: $m/z + \text{Na}$ calculated, 382.8359; found 382.8352. Analytically calculated for $\text{C}_8\text{H}_7\text{Br}_2\text{FSO}_3$: C, 26.54; H, 1.95; Br, 44.14. Found: C, 26.62; H, 1.94; Br, 44.17.

General method: syntheses of [^{18}F]2-fluoroethyl arylsulfonates ([^{18}F]2a–2e)

To a septum-sealed 5 ml V-vial containing 5 mg of Kryptofix[®] 222 and 0.5 mg of K_2CO_3 dissolved in 0.5 ml of acetonitrile–water (98:2 v/v) was added remotely [^{18}F]fluoride ion (ca 740–7400 MBq) in 0.02–0.5 ml [^{18}O]water. The [^{18}F]fluoride ion was dried by heating at 110°C with nitrogen sweep gas (200 ml/min) and addition of three 1 ml aliquots of acetonitrile over about 15 min. To the activated [^{18}F]fluoride ion complex, was added 8.1 μmol of a precursor (one of **1a–1e**) dissolved in 1 ml acetonitrile and the reaction heated for 5 min at 110°C before addition of 1 ml of water. The quenched reaction was injected onto a C-18 semi-preparative column (10 mm \times 250 mm) using either 10 μm Luna[®] (Phenomenex, Torrance, CA) or custom-packed 5 μm Adsorbosphere UHS (Alltech Associates, Deerfield, IL, Part No. C-6000F). Columns were eluted with isocratic mixtures of 70–95% acetonitrile/water (4–6 ml/min flow). Labeled product (one of [^{18}F]2a–2e from **1a–1e**, respectively) was collected in 1–2 ml of mobile phase and radioactivity measured. Dilution

of product with 20 ml of water was followed by SPE using 200 mg of C-18 packing in a 3 cm³ vacuum column assembly (Waters, Milford, MA). The SPE column containing the labeled product was dried with nitrogen gas (10 ml/min × 0.5 min) before elution of the product in 1 ml acetonitrile.

Syntheses of [¹⁸F]2β-carbomethoxy-3β-(4-chlorophenyl)-8-(2-fluoroethyl)nor-tropine ([¹⁸F]FECNT, [¹⁸F]3) via SPE isolated [¹⁸F]2a–2e (Method A)

To a 12 mm × 50 mm test tube containing 0.75 mg (2.7 μmol) of **6** dissolved in 0.2 ml acetonitrile was added labeling agent (one of [¹⁸F]2a–2e) in 1 ml acetonitrile and the radioactivity in the tube measured. To minimize bumping of the solution in the open tube, a helium sweep gas (10 ml/min) was introduced via disposable 3.5 in spinal needle. The reaction was heated for 10 min at 130°C at which time the oven was turned off and the reaction cooled for 5 min. Three ml of 40:60 acetonitrile/10 mM aqueous ammonium hydroxide pH 10.0 (initial mobile phase) was added to the tube and the crude [¹⁸F]3 injected onto an XTerra[®] Prep RP18 column (10 μ; 7.8 mm × 300 mm). A gradient HPLC method starting with initial mobile phase and ramping up to 70% acetonitrile over 30 min at 6 ml/min (UV = 229 nm) was employed. Pure [¹⁸F]3 (*t_R* = 19.2 min), well-resolved from **6** (*t_R* = 8.2 min), and labeling agent (*t_{RS}* = 6.5, 10.9, 8.2, 14.8, 8.4 min for [¹⁸F]2a–2e, respectively) was collected in about 4 ml of HPLC buffer, and the radioactivity assayed to determine isolated radiochemical yield based on initial labeling agent contained in the open tube.

Syntheses and formulation of [¹⁸F]FECNT ([¹⁸F]3) via direct collection of [¹⁸F]2d (Method B)

Typical example: Starting with 4.44 GBq (120 mCi) of [¹⁸F]fluoride ion 1.97 GBq (53 mCi) of pure [¹⁸F]2d was prepared from **1d** in 40 min, as described above. Purified [¹⁸F]2d (90:10 v/v MeCN–water, 4 ml/min; *t_R* = 5.3 min, *k'* = 1.1; **1d** *t_R* = 7.7 min, *k'* = 2.1 on UHS Adsorbosphere) was collected (ca 1.1 ml) directly into a 12 mm × 50 mm test tube containing 0.73 mg (2.6 μmol) of **6** dissolved in 0.1 ml acetonitrile. The ¹⁸F-fluoroethylation and HPLC purification were conducted as described in Method A to give 1.21 GBq (32.8 mCi) of [¹⁸F]3 that was isolated on a Waters 200 mg C-18 SPE column and eluted in 1 ml of USP grade ethanol. Addition of 9 ml of normal saline followed by sterile filtration through a Millipore Millex MP filter gave 1.10 GBq (29.7 mCi) of [¹⁸F]3 in a synthesis time of 97 min (46% decay-corrected yield). Specific radioactivity, chemical purity, and radiochemical purity of [¹⁸F]3 were assessed by analytical HPLC using a 4.6 mm × 250 mm 10 μ C-18 Luna[®] column. Mobile phase consisted of 50:50 v/v acetonitrile–10 mM ammonium formate at 2 ml/min (absorbance detector λ = 229 nm). Analytical HPLC analysis of a 0.1 ml aliquot of [¹⁸F]3 confirmed the

radioligand ($t_R = 7.7$ min) to be of high radiochemical and chemical purity ($> 90\%$). Comparison of the UV carrier peak associated with [^{18}F]3 to that of a calibration curve generated with authentic 3 enabled calculation of specific radioactivity that was 252 GBq/ μmol (6810 mCi/ μmol) at end of synthesis.

Syntheses of [^{18}F]6-iodo-2-[4'-N-(2-fluoroethyl)methylamino]phenyl-imidazo[1,2-a]pyridine, ([^{18}F]FEM-IMPY, [^{18}F]4), via SPE isolated [^{18}F] 2b–2e

Radiolabeled fluoroethylating agents [^{18}F]2b–2e were prepared and isolated as described above. Method A was followed for the radioalkylation reaction using 0.97 mg (2.8 μmol) of HM-IMPY. Semi-preparative HPLC employed a C-18 Luna[®] column using gradient conditions (40:60 v/v acetonitrile–10 mM ammonium hydroxide pH 9.5 to 90% acetonitrile over 30 min) at 6 ml/min (absorbance detector $\lambda = 254$). Pure [^{18}F]4 ($t_R = 15.6$ min), resolved from 7 ($t_R = 11.8$ min) and labeling agent ($t_{R_s} = 11.8, 9.4, 14.8$ and 10.2 min for [^{18}F]2b–2e, respectively), was collected in about 4 ml of HPLC buffer. The radioactivity was measured to determine isolated radiochemical yield of [^{18}F]4, based on starting labeling agent contained in the open tube.

Syntheses of [^{18}F]2-fluoroethyl-4-nitrophenyl ether ([^{18}F]5) via SPE isolated [^{18}F]2b–2e

[^{18}F]5 was prepared from [^{18}F]2a–2e in a similar manner to [^{18}F]4. Specifically, 1.2 mg (8.6 μmol) of 4-nitrophenol, 8, was dissolved in 0.2 ml DMF and then 8 μl of 1 M tetrabutylammonium hydroxide in methanol was added 30 s before the addition of the ^{18}F -fluoroethylating agent. Heating in an open vessel for 10 min at 130°C, as described above, was followed by HPLC purification. When [^{18}F]2d was used for production of [^{18}F]5, an UHS Adsorbosphere column running a gradient of 40% acetonitrile–water to 80% acetonitrile–water over 30 min (4.5 ml/min; UV 254 nm) was employed ([^{18}F]5 $t_R = 17.3$ min; [^{18}F]2d $t_R = 24.7$ min; 8 $t_R = 6.4$ min). When [^{18}F]2a–2c and [^{18}F]2e were used for production of [^{18}F]5, a methanol gradient was employed on the UHS Adsorbosphere column (35:65 v/v methanol–water to 80:20 methanol–water over 30 min, 3.5 ml/min; [^{18}F]5 $t_R = 27.5$ min; 8 $t_R = 15.3$ min; [^{18}F]2a–2c, [^{18}F]2e $t_{R_s} = 20.8, 29.0, 23.1$ and 25.6 min, respectively).

Assessment of volatility of [^{18}F]2a–2e

Radiolabeling agents were synthesized as described above and isolated via SPE in 1 ml of acetonitrile. The acetonitrile solution containing [^{18}F]2a–2e was transferred to a 12 mm \times 50 mm test tube containing 0.2 ml acetonitrile (precursor solvent blank) and the radioactivity assayed in a dose calibrator. This open tube was heated at 130°C for 10 min with helium sweep gas (10 ml/

min) during which time the acetonitrile was evaporated. Residual radioactivity left in the tube was measured to gauge the volatility of the [¹⁸F]2a–2e.

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