Fluorine for Hydroxy Substitution in Biogenic Amines: Asymmetric Synthesis and Biological Evaluation of Fluorine-18-Labeled β-Fluorophenylalkylamines as Model Systems

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This work explores the biomimetic potential of [^{18}F]fluorine for hydroxy substitution in β-phenethanolamines as a possible strategy for developing radiotracers for *in vivo* imaging. Stereospecific syntheses of the two model compounds (1*R*,2*S*)-1-[^{18}F]fluoro-1-deoxyephedrine ([^{18}F]FDE) and (1*S*,2*S*)-1-[^{18}F]fluoro-1-deoxypseudoephedrine ([^{18}F]FDP) were achieved in high radiochemical yield (62%, decay corrected) and high specific activity (>2500 Ci/mmol) by reaction of [^{18}F]fluoride ion with the appropriate chiral cyclic sulfamidate precursor. Both tracers exhibited good stability toward metabolic defluorination *in vivo*. High, homogeneous brain uptake (~8% of injected dose) was observed after intravenous injection in mice similar to that reported for the structurally related analog [^{11}C]methamphetamine. The 1*R*,2*S* isomer (FDE) showed a 3-fold higher concentration of radioactivity in whole brain as compared to the 1*S*,2*S* isomer (FDP). These results suggest possible employment of this strategy for chiral radiolabeling of biologically important phenethanolamines and catecholamines.

Introduction

The selective introduction of fluorine into biologically active molecules for modification of their pharmacological behavior is an important endeavor in drug design.[1] Numerous compounds incorporating fluorine as either a bioisosteric replacement for hydrogen[2] or an isoelectronic replacement for the hydroxy group[3] have been reported. Moreover, interest in fluorine chemistry has intensified in recent years with the use of ^{18}F-labeled radiotracers for the study of biochemical processes in living animals and humans by positron emission tomography (PET). Fluorine-18, due to its relatively long half-life ($t_{1/2}$ = 110 min) and low positron energy (0.635 MeV), has excellent properties for tomographic imaging.[4] Consequently, methods for the stereoselective and efficient ^{18}F labeling of biologically important compounds need to be developed.

As part of an overall effort to develop radiotracers for mapping the sympathetic nervous system of the heart by PET, we wished to evaluate side-chain ^{18}F-labeled analogs of biogenic amines. In particular, we were interested in examining the effect of a stereospecific replacement of the β-hydroxy group of biogenic β-phenethanolamines with fluorine. The stereoselective incorporation of fluorine into organic molecules has often been a challenging task.[5] Recent reports, however, have demonstrated that cyclic sulfamidates undergo facile nucleophilic substitution with a variety of nucleophiles at the oxygen-bearing carbon atom to afford enantiomerically pure products in good to excellent yields.[6] Synthesis of a ^{18}F-labeled analog of the noncompetitive *N*-methyl-D-aspartate antagonist MK-801 via a cyclic sulfamidate intermediate has been previously reported by us.[7] Lyle and co-workers have also reported the synthesis of enantiomerically pure (1*R*,2*S*)- and (1*R*,2*R*)-β-fluoromethamphetamine diastereomers from chiral acyclic sulfamidate precursors.[8] However, extension of this approach to the synthesis of ^{18}F-labeled biogenic amines has, to our knowledge, never been reported.

Our goals in this preliminary study were 2-fold: (a) to determine the feasibility of a stereospecific replacement of the β-hydroxy group in biogenic amines with ^{18}F and (b) to determine if such benzylic fluoro derivatives would remain stable *in vivo* toward metabolic defluorination. For convenience, the commercially available biogenic amines (1*R*,2*S*)-(−)-ephedrine and (1*S*,2*S*)-(+)-pseudoephedrine were used as model compounds. We report here a novel route to the synthesis of side-chain radiofluorinated biogenic amine analogs from chiral cyclic sulfamidate precursors that achieves the stereospecific introduction of ^{18}F at the β-carbon atom in high radiochemical yields. Preliminary biodistribution studies in mice were also conducted in order to evaluate the *in vivo* stability of the ^{18}F label at this site.

Results and Discussion

Chemistry. The retrosynthetic pathway for the synthesis of (1*R*,2*S*)-1-[^{18}F]fluoro-1-deoxyephedrine ([^{18}F]-FDE) and (1*S*,2*S*)-1-[^{18}F]fluoro-1-deoxypseudoephedrine ([^{18}F]FDP) from (1*S*,2*S*)-(+)-pseudoephedrine and (1*R*,2*S*)-(−)-ephedrine, respectively, is shown in Scheme 1. Treatment of (1*S*,2*S*)-(+)-pseudoephedrine with $SOCl_2$ in the presence of Et_3N provided the cyclic sulfamidites **1a,b** in 72% yield as a 3:1 diastereoisomeric mixture which were separated by flash chromatography (Scheme 2). Each diastereomer provided the cyclic sulfamidate **2** upon oxidation with sodium periodate in the presence of $RuCl_3$ as catalyst. Fluorination was achieved by refluxing **2** with a KF/CaF_2 mixture in CH_3CN in the presence of Kryptofix [2.2.2.] followed by acid hydrolysis of the *N*-sulfonic acid intermediate to provide the pure 1*R*,2*S* stereoisomer **3** (FDE) in 54% yield. A similar approach starting with (1*R*,2*S*)-(−)-ephedrine afforded the corresponding 1*S*,2*S* stereoisomer **6** (FDP).

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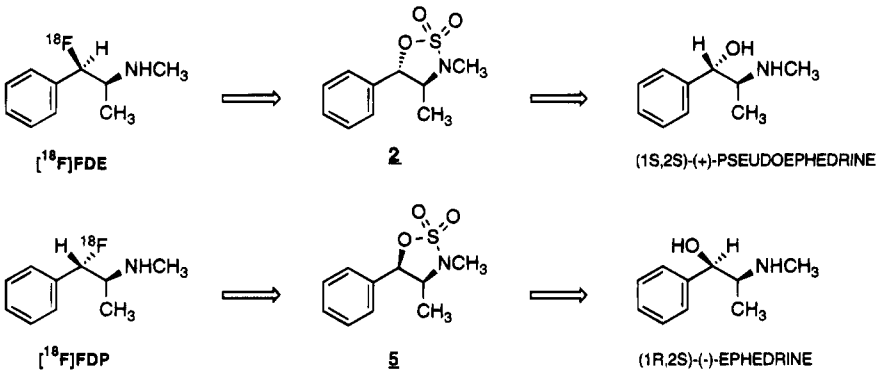
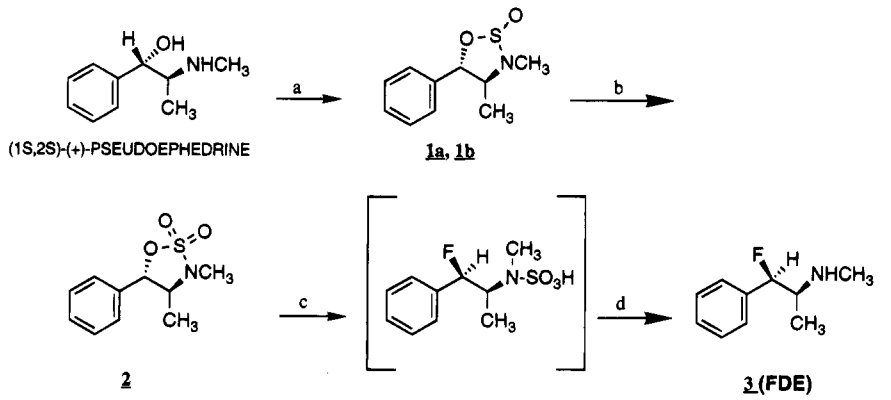
Scheme 1. Retrosyntheses of [^{18}F]FDE and [^{18}F]FDP

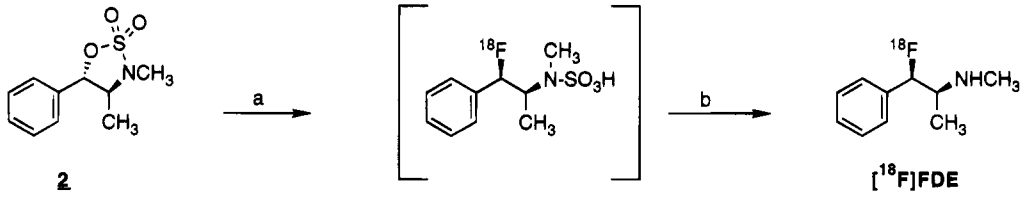


Scheme 2. Synthesis of (1*R*,2*S*)-1-Fluoro-1-deoxyephedrine (FDE) and Cyclic Sulfamidate Precursor[a]



[a] Reagents: (a) $SOCl_2/Et_3N$, CH_2Cl_2, −78 °C; (b) $NaIO_4$, $RuCl_3$, CH_3CN:H_2O (1:1); (c) KF/CaF_2, Kryptofix [2.2.2], CH_3CN, 80 °C; (d) 20% aq H_2SO_4:Et_2O (1:1).

Scheme 3. Radiosynthesis of (1*R*,2*S*)-1-[^{18}F]Fluoro-1-deoxyephedrine ([^{18}F]FDE)[a]



[a] Reagents: (a) K^{18}F/Kryptofix [2.2.2]; CH_3CN, 90 °C; (b) 20% aq H_2SO_4:Et_2O (1:1).

The stereochemical homogeneity of FDE and FDP was confirmed by ^{1}H NMR analysis of the crude product which displayed a doublet of doublets ($J_{F\text{-}H}$ and $J_{H\text{-}H}$) for the C-1 proton. No other resonance for the C-1 proton that would result from partial racemization at this carbon was observed. Examination of the proton-decoupled ^{19}F NMR showed a single fluorine resonance at −191.2 and −174.7 Hz for FDE and FDP, respectively. The proton-coupled fluorine spectrum of FDE showed H−F coupling of 47.9 Hz (geminal H) and 26.9 Hz (vicinal H) confirming the *trans* stereochemical relationship between fluorine and the vicinal hydrogen. Likewise, the proton-coupled fluorine resonance of FDP showed an H−F coupling of 48.5 Hz (geminal H) and 9.2 Hz (vicinal H), as expected of a fluorine−vicinal hydrogen *cis* stereochemical relationship.[9]

Synthesis of the fluorine-18-labeled derivatives was conducted using procedures similar to that described for the unlabeled analogs (Scheme 3). Nucleophilic attack by [^{18}F]fluoride ion at the C-1 carbon of the cyclic sulfamidate precursor provided the corresponding ^{18}F-labeled *N*-sulfonic acid derivatives which were not isolated. Initial attempts at base-catalyzed hydrolysis of this intermediate to give the corresponding ^{18}F-labeled amine according to the method of Alker[6a] were unsuccessful. A single radioactive product was obtained utilizing this procedure which, upon TLC analysis, did not match authentic FDE or FDP. This product was not further characterized. Acid-catalyzed hydrolysis using a two-phase solvent system according to the procedure of White *et al.*,[6c] however, proceeded smoothly to afford the fluoro derivatives [^{18}F]FDE and [^{18}F]FDP in high radiochemical yield (62%) and radiochemical purity (>98%). HPLC analysis of the crude labeled reaction mixture using a chiral column (Crownpak) showed the presence of a single optical isomer in each case. Further purification by reverse-phase HPLC was conducted to remove chemical impurities. Elution with NaH_2PO_4:EtOH provided the radiotracers in a readily injectable formulation requiring only dilution with physiological saline. The synthesis and the HPLC purification of the radiotracers were accomplished in a 65 min period.

The distributions of [^{18}F]FDE and [^{18}F]FDP in selected mouse tissues are reported in Tables 1 and 2, respectively. Both fluorinated tracers showed an increased concentration of radioactivity in cerebral cortex at 1 min compared to other brain regions; however, this

Table 1. Biodistribution of (1*R*,2*S*)-1-[^{18}F]Fluoro-1-deoxyephedrine ([^{18}F]FDE) in CD-1 Mice

	time (min)			
tissue[a,b]	1[c]	5	30	120
striatum	20.60 ± 1.36	11.32 ± 0.96	5.80 ± 0.56	0.28 ± 0.04
cortex	24.92 ± 1.12	12.64 ± 1.00	6.92 ± 0.72	0.36 ± 0.04
cerebellum	20.36 ± 1.16	9.44 ± 0.76	4.96 ± 0.40	0.32 ± 0.04
femur	2.16 ± 0.60	3.04 ± 0.16	3.60 ± 0.16	6.40 ± 1.40
lung	28.36 ± 4.72	11.60 ± 1.12	7.36 ± 0.80	0.48 ± 0.08
liver	17.36 ± 0.44	15.00 ± 1.76	7.92 ± 1.04	1.28 ± 0.24
blood	2.68 ± 0.20	1.48 ± 0.12	1.72 ± 0.08	0.16 ± 0.04

[a] Data reported as percent injected dose per gram (mean ± SEM) normalized to a 25 g mouse. [b] Female mice ($N = 6$ per data point). [c] $N = 3$ per data point.

Table 2. Biodistribution of (1*S*,2*S*)-1-[^{18}F]Fluoro-1-deoxypseudoephedrine ([^{18}F]FDP) in CD-1 Mice

	time (min)			
tissue[a,b]	1[c]	5	30	120
striatum	15.44 ± 1.68	9.52 ± 0.80	3.56 ± 0.36	0.12 ± 0.00
cortex	19.76 ± 1.96	10.08 ± 0.80	3.92 ± 0.32	0.12 ± 0.00
cerebellum	15.84 ± 1.88	7.76 ± 0.64	2.76 ± 0.28	0.12 ± 0.00
femur	1.92 ± 0.20	3.12 ± 0.52	3.64 ± 0.28	6.68 ± 0.40
lung	11.88 ± 1.48	9.72 ± 0.84	5.44 ± 0.32	0.56 ± 0.04
liver	12.76 ± 1.24	12.52 ± 1.48	9.44 ± 0.56	4.52 ± 0.48
blood	2.40 ± 0.20	1.92 ± 0.20	2.24 ± 0.24	0.16 ± 0.00

[a] Data reported as percent injected dose per gram (mean ± SEM) normalized to a 25 g mouse. [b] Female mice ($N = 6$ per data point). [c] $N = 3$ per data point.

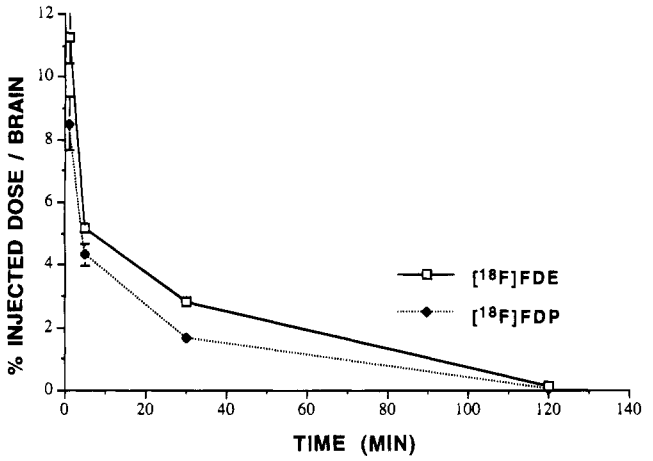


Figure 1. Time course of uptake and clearance of radioactivity in mouse brain for [^{18}F]FDE and [^{18}F]FDP.

selectivity diminished at later time intervals (i.e., 120 min). [^{18}F]FDE showed a higher concentration of radioactivity in whole brain as compared to [^{18}F]FDP (percent injected dose in brain values were approximately 30%, 20%, and 70% greater at 1, 5, and 30 min, respectively; Figure 1). High initial brain uptake (>8% ID at 1 min after injection) followed by a rapid washout phase (<3% ID at 30 min postinjection) was demonstrated by both radiotracers (Figure 1). By comparison, carbon-14-labeled racemic ephedrine shows a much lower brain extraction followed by a very slow washout from rat brain.[10] Thus, replacement of the β-hydroxy group in ephedrine with fluorine significantly improves brain extraction and suggests that, in this series of compounds, fluorine mimics a hydrogen rather than a hydroxyl group (*vide infra*).

The fluorinated compounds described herein show similar, albeit moderately higher, brain extraction to that reported for the structurally similar analog [^{11}C]-methamphetamine.[11] Introduction of a fluorine atom

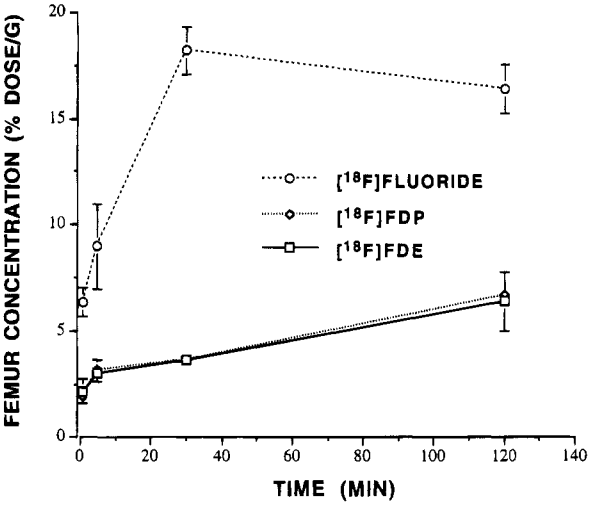


Figure 2. Time course of uptake of radioactivity in mouse bone (femur) for [^{18}F]FDE, [^{18}F]FDP, and [^{18}F]fluoride.

at the β-carbon in amphetamines is known to significantly reduce the basicity of the amino group presumably by a combination of hydrogen bonding and inductive effects.[12] Indeed, the apparent partition coefficients[13a] of 3.3 and 3.8 obtained for [^{18}F]FDE and [^{18}F]-FDP, respectively, indicate that less than 25% of these molecules will exist in the ionized form in blood at physiological pH.[13b] Methamphetamine ($pK_a = 10.11$), by contrast, would be expected to have greater than 99% of its molecules in the ionized form in blood.[14] The relatively higher proportion of free-base form in blood would be expected to result in higher brain extraction of the fluoro derivatives described in this study. High uptake of radioactivity was also observed in the lung and liver after injection of both radiotracers. Accumulation of lipophilic amines in lung tissue is well documented.[15] Although [^{18}F]FDE had a 2.5-fold higher lung concentration at 1 min as compared to [^{18}F]FDP, it showed faster clearance from this tissue resulting in similar lung concentrations for the two tracers by 120 min. [^{18}F]FDE showed similar behavior in the liver, with higher initial liver accumulation than [^{18}F]FDP at early time intervals followed by a faster clearance of radioactivity resulting in a 3-fold lower liver concentration than [^{18}F]FDP at 120 min.

Fluoride ion has high affinity for bone, and accumulation of [^{18}F]fluoride ion in this tissue is often used as an index of the stability of a radiofluorinated tracer toward metabolic defluorination.[16] The time-dependent uptake of radioactivity in bone (femur) for the two radiotracers was therefore determined and compared to that of controls administered [^{18}F]fluoride ion alone (Figure 2). Neither tracer at 2 h postinjection exhibits bone radioactivity as high as that observed for [^{18}F]-fluoride ion, indicating that these benzylic fluorides are relatively stable toward *in vivo* metabolic defluorination. The relative metabolic stability of fluoroalkyl systems bearing β-heteroatom substituents such as nitrogen and oxygen has been attributed to a combination of inductive and resonance effects.[17] Although levels of radioactivity in bone could likely show a steeper increase beyond 2 h postinjection, imaging studies, especially in a clinical setting, should be complete in less than 2 h. In addition, use of modern PET scanners will allow good delineation between bone and soft tissue activity. The observed initial low level of defluorination, therefore, suggests

that this class of compounds could be potentially useful as *in vivo* PET radiotracers.

Since the primary focus of this work was to ascertain the stability of the ^{18}F label at the β-carbon of biogenic amines toward *in vivo* radiodefluorination and not the development of a ^{18}F-labeled ephedrine analog for *in vivo* imaging, the identity of metabolites, if any, in the brain was not determined. However, it is likely that initial brain uptake observed at 1 min postinjection, which is close to the time required for a single pass,[18] represents mostly unchanged tracer. Numerous studies on the *in vivo* metabolism of *N*-alkylamphetamines in rat suggest that metabolites in brain generally appear hours rather than minutes after injection. Most relevant is the study of the ^{123}I-labeled radiopharmaceutical *N*-isopropyl-*p*-iodoamphetamine in rats by Baldwin and Wu[19] which indicates that the N-dealkylated product is the only brain metabolite and that this metabolite forms slowly in the brain.

In summary, we describe procedures for the stereospecific incorporation of [^{18}F]fluorine at the β-carbon of biogenic amines. This transformation can be achieved rapidly and in high radiochemical yield and specific activity using chiral cyclic sulfamidate precursors accessible from commercially available biogenic amines. These β-fluorinated compounds were highly extracted into brain and demonstrated good *in vivo* stability in mice biodistribution studies. The latter observation has prompted the application of this radiolabeling strategy to compounds of greater interest, such as *m*-hydroxyephedrine[20] and epinephrine,[21] which are known to selectively localize in adrenergic nerve endings.

Experimental Section

Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR spectra were obtained on a Bruker WM-360 (360 MHz) instrument with tetramethylsilane (TMS) as internal standard. ^{19}F NMR spectra were recorded on a Bruker instrument at 235 MHz with $CFCl_3$ as external standard. Infrared spectra were recorded on a Perkin-Elmer 727B spectrometer. Mass spectra were obtained on a Finnigan 4021 GCMS/DS (low-resolution) or a UG70-250-S (high-resolution) instrument. Optical rotations were obtained with a Perkin-Elmer 241 polarimeter. Chemical reagents were obtained from Aldrich Chemical Co., Milwaukee, WI. Flash chromatography was performed by the method of Still *et al.*[22] using Merck silica gel 60 (230–400 mesh). Elemental analyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI.

Thin-layer chromatography of the radiolabeled compounds was performed on either Analtech (10 cm, 250 μm) or Whatman K6F (20 cm, 250 μm) silica gel glass-backed plates. TLC chromatograms were scanned for radioactivity using a Berthold Model LB 2832 TLC-linear analyzer equipped with a Model LB 500 data acquisition system. Plates were analyzed by UV absorbance and by spraying with ethanolic phosphomolybdic acid reagent followed by charring.

Preparative HPLC purification of the radiofluorinated compounds was carried out on a Perkin-Elmer Series 410 liquid chromatograph using a Waters μBondapak C-18, 10 μm (4.6 × 300 mm) column with 0.2 M NaH_2PO_4 (pH = 4): 95% ethanol (95:5, v/v) at a flow rate of 3 mL/min. UV absorbance was monitored at 268 nm using an Applied Biosystems 757 UV detector, and radioactivity was monitored with an ORTEC radioisotope ratemeter. The retention times of [^{18}F]FDE and [^{18}F]FDP were 4.7 and 6.1 min, respectively, under these conditions.

Specific activity determinations for the radiofluorinated compounds were estimated from a standard curve relating mass to UV absorbance peak area as previously described.[23] The average specific activities (N = 2) of [^{18}F]FDE and [^{18}F]-FDP were 2530 and 2986 Ci/mmol, respectively.

A Crownpak CR(+), 5 μm (4 × 150 mm) chiral column was used with 113 mM aqueous $HClO_4$, pH = 1, at a flow rate of 1.2 mL/min with radioactivity and UV detection (254 nm) for analysis of the chiral purity of the radiofluorinated derivatives. Under these assay conditions the retention times of [^{18}F]FDE and [^{18}F]FDP were 14.1 and 12.2 min, respectively.

Determination of Apparent Partition Coefficients (P'). This was determined by a modification of the shake-flask method using the radiofluorinated tracers as previously reported.[24] In a typical procedure 400 μCi of [^{18}F]FDE was partitioned between *n*-octanol (3.5 mL) and pH 7.4 phosphate buffer (3.5 mL) in a Pyrex glass centrifuge tube (10 mL). The tube was capped and gently inverted by hand (80 inversions in 2 min) followed by centrifugation at 2500 rpm for 5 min to facilitate separation of the two layers. Aliquots of each layer (2 mL) were removed by syringe and assayed in a Capintec dose calibrator for activity. The procedure was repeated thrice by removal of 2 mL of the octanol layer each time and addition of 1.5 mL of fresh octanol followed by 3.5 mL of fresh phosphate buffer, inversion, and centrifugation. The values reported represent an average of four such consecutive readings. [^{18}F]-FDE and [^{18}F]FDP gave P' values of 3.3 and 3.8, respectively, under these conditions.

Animal Biodistribution Studies. CD-1 mice (20–25 g; Charles River, Wilmington, MA) were injected via the tail vein under light ether anesthesia with 7–10 μCi of the ^{18}F-labeled radiotracer. The animals were sacrificed by decapitation at designated time intervals, and selected peripheral tissues (lung, liver, and femur) were removed. The brain was rapidly removed and dissected into regions of interest[25] (striatum, cerebral cortex, cerebellum, and remainder of brain tissue, etc). Blood samples were also obtained. All samples were assayed for radioactivity in an automatic γ counter and then weighed. Data were calculated as percent injected dose per gram (% ID/g) for all tissues.

Cyclic Sulfamidites 1 and 4. General Procedure. These were prepared using methods reported by Alker[6a] and Baldwin.[6b] A stirred solution of $SOCl_2$ (1.83 g, 15.4 mmol) in dry CH_2Cl_2 (40 mL) was treated dropwise at −78 °C under an argon atmosphere with a solution of (1*S*,2*S*)-(+)-pseudoephedrine (2.47 g, 15 mmol) and Et_3N (3.04 g, 30 mmol) in dry CH_2Cl_2 (40 mL). Stirring was continued at −78 °C for a further 2 h after the addition was complete. The resulting solution was then warmed slowly to room temperature and stirred for an additional 16 h at which point TLC analysis (silica; hexane:EtOAc, 2:1) indicated completion of the reaction. The reaction mixture was concentrated under reduced pressure, and the crude products were partitioned between EtOAc (50 mL) and saturated brine (50 mL). The aqueous layer was further extracted with EtOAc (50 mL), and the combined organic layers were washed with H_2O (50 mL) and dried over anhydrous Na_2SO_4. Concentration under reduced pressure afforded the crude product as a colorless oil (mixture of diastereomers) which was purified by flash chromatography.

***N*-Methyl-(4*S*)-methyl-(5*S*)-phenyl-1,2,3-oxathiazolidine *S*-Oxide (1a and 1b).** The title compound was isolated in 72% yield as a mixture of diastereomers. ^1H NMR (360 MHz) analysis indicated a 3:1 ratio of diastereomers which were separated by flash chromatography on silica gel (hexane:EtOAc, 5:2). The more polar isomer **1a** (major product) was isolated as a colorless oil: $[\alpha]_D$ = +34.5° (c = 5.4, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 7.42–7.37 (m, 5H, aromatic H), 5.55 (d, 1H, J = 8.90 Hz, H_5), 3.27–3.23 (m, 1H, H_4), 2.89 (s, 3H, NCH_3), 1.29 (d, 3H, J = 6.2 Hz, CH_3).

The less polar isomer **1b** (minor product) was isolated as white needles: mp 80–81 °C; $[\alpha]_D$ = +72.3° (c = 2.5, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 7.47–7.37 (m, 5H, aromatic H), 4.95 (d, 1H, J = 9.84 Hz, H_5), 3.45–3.41 (m, 1H, H_4), 2.63 (s, 3H, NCH_3), 1.22 (d, 3H, J = 6.1 Hz, CH_3); HRMS (CI with CH_4, diastereoisomeric mixture) calcd for $C_{10}H_{13}NSO_2H$ (MH^+) 212.0745, found 212.0732.

***N*-Methyl-(4*S*)-methyl-(5*R*)-phenyl-1,2,3-oxathiazolidine *S*-Oxide (4a and 4b).** A similar procedure using (1*R*,2*S*)-(−)-ephedrine gave the title compound in 86% yield

as a mixture of diastereomers. ^{1}H NMR (360 MHz) analysis indicated a 2:1 ratio of diastereomers which were separated by flash chromatography on silica gel (hexane:EtOAc, 5:2). The more polar isomer **4a** (major product) was isolated as white needles: mp 120−122 °C; $[\alpha]_D$ = +192.3° (c = 2.6, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.41−7.18 (m, 5H, aromatic H), 5.90 (d, 1H, J = 7.24 Hz, H_5), 3.99−3.91 (m, 1H, H_4), 2.66 (s, 3H, NCH_3), 0.80 (d, 3H, J = 6.49 Hz, CH_3).

Less polar isomer **4b** (minor product) was isolated as a pale yellow oil that solidified on standing: $[\alpha]_D$ = −71.5° (c = 2.1, DMF); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.45−7.31 (m, 5H, aromatic H), 5.64 (d, 1H, J = 6.49 Hz, H_5), 3.81−3.73 (m, 1H, H_4), 2.84 (s, 3H, NCH_3), 0.99 (d, 3H, J = 6.85 Hz, CH_3); HRMS (CI with CH_4, diastereoisomeric mixture) calcd for $C_{10}H_{13}NSO_2H$ (MH^+) 212.0745, found 212.0734.

Cyclic Sulfamidates 2 and 5. General Procedure. Following the procedure of Baldwin *et al.*[6b] a solution of **1b** (0.40 g, 1.89 mmol) in CH_3CN (12 mL) was cooled to 0 °C and treated successively with a catalytic portion of $RuCl_3{\cdot}H_2O$ (4 mg) and $NaIO_4$ (0.44 g, 2.08 mmol). The reaction mixture was then treated with H_2O (12 mL), allowed to warm to room temperature, and stirred for a further 2 h at which point TLC analysis (hexane:EtOAc, 2:1) indicated completion of the reaction. Following dilution of the reaction mixture with Et_2O (50 mL), the organic layer was removed and the aqueous layer extracted further with Et_2O (2 × 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ (50 mL) and saturated brine (50 mL) and dried over anhydrous Na_2SO_4. Concentration under reduced pressure gave an oil which crystallized on trituration with hexane.

***N*-Methyl-(4*S*)-methyl-(5*S*)-phenyl-1,2,3-oxathiazolidine *S*,*S*-dioxide (2):** yield, 45% from **1a** and 81% from **1b**; mp 63−65 °C (Et_2O:hexane); $[\alpha]_D$ = −11.2° (c = 2.14, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.44 (s, 5H, aromatic H), 5.18 (d, 1H, J = 9.38 Hz, H_5), 3.47−3.43 (m, 1H, H_4), 2.79 (s, 3H, NCH_3), 1.26 (d, 3H, J = 6.09 Hz, CH_3). Anal. ($C_{10}H_{13}NO_3S$) C, H, N.

***N*-Methyl-(4*S*)-methyl-(5*R*)-phenyl-1,2,3-oxathiazolidine *S*,*S*-dioxide (5):** yield, 93% from **4a** and 95% from **4b**; mp 142−144 °C ($CHCl_3$:hexane); $[\alpha]_D$ = +28.4° (c = 2.04, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.41−7.37 (m, 5H, aromatic H), 5.69 (d, 1H, J = 6.60 Hz, H_5), 3.91−3.88 (m, 1H, H_4), 2.78 (s, 3H, NCH_3), 0.89 (d, 3H, J = 6.54 Hz, CH_3). Anal. ($C_{10}H_{13}NO_3S$) C, H, N.

General Procedure for Synthesis of Fluorinated Analogs 3 and 6. A solution of **2** (227 mg, 1 mmol) in dry CH_3CN (10 mL) was treated with KF (320 mg of a mixture of KF:CaF_2, 1:4, 1.1 mmol) followed by 376 mg (1 mmol) of 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (Kryptofix [2.2.2]) and heated with stirring at 80 °C for 1 h. The reaction mixture was filtered hot and the residue rinsed with boiling CH_3CN (10 mL). The filtrate was concentrated, and the residue was treated with Et_2O (5 mL) and aqueous 20% H_2SO_4 (3 mL) and stirred at room temperature for 18 h. The reaction mixture was basified (pH = 8) with solid $NaHCO_3$, the Et_2O layer removed, and the aqueous layer extracted further with EtOAc (2 × 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated, and the residue was flash chromatographed on silica gel (EtOAc:CH_3OH, 7:3) to give **3** as a pale yellow oil. A portion was converted to the hydrochloride salt of **3** by treatment with ethereal HCl and recrystallization from CH_3OH:Et_2O.

(1*R*,2*S*)-(−)-1-Fluoro-1-deoxyephedrine hydrochloride (3): yield, 90 mg (54%); mp 180−182 °C dec (CH_3OH:Et_2O); $[\alpha]_D$ = −21.7° (c = 1.1, CH_3OH); ^{1}H NMR (HCl salt; CD_3OD) δ 7.49−7.38 (m, 5H, aromatic H), 6.05 (dd, 1H, J = 48.0, 2.1 Hz, CHF), 3.74−3.64 (m, 1H, C*H*CH_3), 2.84 (s, 3H, NCH_3), 1.17 (d, 3H, J = 6.95 Hz, CH_3); ^{19}F NMR (HCl salt; CD_3OD, $CFCl_3$ as external standard) δ −191.2 (dd, J = 47.9, 26.9 Hz, FCH); ^{13}C NMR (HCl salt; CD_3OD) δ 130.07, 129.93, 126.04, 125.95, 93.75, 91.78, 60.42, 60.18, 31.68, 9.57; MS (free base; CI with NH_3) m/z (rel intensity) 169 (19.5, MH_2^+), 168 (100, MH^+), 149 (12), 148 (60.6), 147 (7.3), 146 (17.6), 132 (8.9), 106 (4.9), 105 (4.0), 91 (3.4); HRMS (free base; CI with NH_3) calcd for $C_{10}H_{14}NFH$ (MH^+) 168.1188, found 168.1185. Anal. ($C_{10}H_{14}NF{\cdot}HCl$) C, H, N.

(1*S*,2*S*)-(+)-1-Fluoro-1-deoxypseudoephedrine hydrochloride (6): yield, 106 mg (63%) starting from **5**; mp 218−221 °C dec (CH_3OH:Et_2O); $[\alpha]_D$ = +40.5° (c = 1.8, CH_3OH) (lit.[8] $[\alpha]_D$ = +51.2° (c = 3, 1.0 M HCl)); ^{1}H NMR (HCl salt; CD_3OD) δ 7.48 (s, 5H, aromatic H), 5.53 (dd, 1H, J = 48.1, 9.3 Hz, CHF), 3.87−3.76 (m, 1H, C*H*CH_3), 2.80 (s, 3H, NCH_3), 1.12 (dd, 3H, J = 6.9, 0.57 Hz, CH_3); ^{19}F NMR (HCl salt; CD_3OD, $CFCl_3$ as external standard) δ −174.7 (dd, J = 48.5, 9.2 Hz, FCH); ^{13}C NMR (HCl salt; CD_3OD) δ 132.77, 131.32, 130.20, 128.30, 96.48, 94.55, 59.85, 59.61, 30.76, 12.20; MS (free base; CI with NH_3) m/z (rel intensity) 169 (11.75, MH_2^+), 168 (100, MH^+), 148 (3.75), 136 (32.8); HRMS (free base; CI with NH_3) calcd for $C_{10}H_{14}NFH$ (MH^+) 168.1188, found 168.1176. Anal. ($C_{10}H_{14}NF{\cdot}HCl$) C, H, N.

Radiochemistry. High specific activity, no-carrier-added [^{18}F]fluoride ion was prepared by irradiation of a [^{18}O]H_2O target as previously described.[26] In a typical procedure to an aqueous solution (0.5 mL) of [^{18}F]fluoride (22 mCi) and aqueous 1.8 M K_2CO_3 (10 μL) was added Kryptofix [2.2.2] (10 mg), and the mixture was evaporated to dryness at 90 °C by azeotropic removal of H_2O with anhydrous CH_3CN (3 × 0.5 mL) under a gentle stream of argon. Anhydrous CH_3CN (0.3 mL) was added to the residue, and the resolubilized [^{18}F]fluoride ion (19.2 mCi) was transferred to a V-vial (Pierce) containing **5** (3 mg, 13.2 μmol). The vial was tightly capped and heated at 85−90 °C for 20 min. The warm solution was evaporated to dryness under a gentle stream of argon and the residue treated with 0.8 mL of a 1:1 mixture of Et_2O and 20% aqueous H_2SO_4 and stirred at room temperature for a further 25 min. The Et_2O layer was removed, the acidic solution was extracted once with Et_2O (1 mL), and the combined Et_2O layers were discarded. The aqueous layer was then treated with Et_2O (1 mL) and made basic (pH = 9) with 30% NH_4OH, and the organic layer was removed. The basic solution was extracted further with Et_2O (2 × 1 mL), and the combined Et_2O layers were dried over anhydrous Na_2SO_4. Radio-TLC analysis (silica; EtOAc:CH_3OH:Et_3N, 5:5:0.1) indicated the product to be greater than 98% radiochemically pure (R_f of **6** = 0.5). The average radiochemical yield was 62% (decay corrected; N = 4) prior to HPLC purification. Chiral HPLC analysis showed a single radiofluorinated peak (retention time = 12.19 min) coincident with authentic **6**.

A portion of the Et_2O solution was evaporated to dryness under argon flow, resolubilized with aqueous 0.2 M NaH_2PO_4 (pH = 4), and subjected to reverse-phase HPLC purification as described to remove chemical impurities. The radiochemical and chemical purities of the tracers after HPLC purification were greater than 98%. The retention time for [^{18}F]FDP was 6.1 min. Radio-TLC and radio-HPLC analysis 2 h after formulation indicated <5% decomposition.

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