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Brief Article

Synthesis, Radiosynthesis, and Biological Evaluation of Carbon-11 and Fluorine-18 (*N*-Fluoroalkyl) Labeled 2β-Carbomethoxy-3β-(4'-(3-furyl)phenyl)tropanes and -nortropanes: Candidate Radioligands for in Vivo Imaging of the Serotonin Transporter with Positron Emission Tomography

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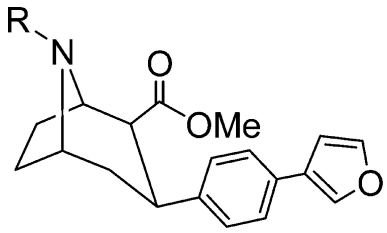

R = H, Me, $(CH_2)_2F$, $(CH_2)_3F$, $(CH_2)_4F$

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Synthesis, Radiosynthesis, and Biological Evaluation of Carbon-11 and Fluorine-18 (*N*-Fluoroalkyl) Labeled 2*β*-Carbomethoxy-3*β*-(4'-(3-furyl)phenyl)-tropanes and -nortropanes: Candidate Radioligands for in Vivo Imaging of the Serotonin Transporter with Positron Emission Tomography

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2*β*-Carbomethoxy-3*β*-(4′-(3-furyl)phenyl)nortropane (**1**) was synthesized along with the *N*-methyl (**2**), *N*-fluoroethyl (**3**), *N*-fluoropropyl (**4**), and *N*-fluorobutyl (**5**) derivatives. The binding affinity for each compound to the human serotonin, dopamine, and norepinephrine transporters was determined using transfected HEK-293 cells. Radiolabeling and microPET brain imaging studies were performed with [^{11}C]**1**, [^{11}C]**2**, and [^{18}F]**3** to determine their utility as in vivo imaging agents.

Introduction

Investigations into the neurochemical mechanism of cocaine addiction revealed that cocaine binds to the serotonin transporter (SERT), the dopamine transporter (DAT), and the norepinephrine transporter (NET).[1] Efforts to develop cocaine antagonists resulted in the synthesis of numerous tropane derivatives with varying affinities for these monoamine transporters.[2,3] These efforts revealed that SERT affinity and selectivity could be enhanced by N-demethylation to give a nortropane analogue and by alkylation of the 4′-position of the 3*β*-phenyl ring.[4−6] Further exploration indicated that unsaturated substituents in the 3*β*-phenyl ring (4′-position) increased SERT potency of the ligand.[7,8]

As part of ongoing research in our laboratories to develop SERT-specific tropane and nortropane positron emission tomography (PET) and single photon emission computerized tomography (SPECT) imaging agents,[9] we have been exploring the incorporation of unsaturated groups or heterocycles in the 4′-position of the 3*β*-phenyl ring. We report here the synthesis and biological evaluation of 2*β*-carbomethoxy-3*β*-(4′-(3-furyl)phenyl)nortropane (3FPNT, **1**)[10] and 2*β*-carbomethoxy-3*β*-(4′-(3-furyl)-phenyl)tropane (3FPT, **2**) and the radiolabeling and evaluation of [^{11}C]**1** and [^{11}C]**2** as in vivo microPET imaging agents for the SERT. Additionally, we have explored whether the selectivity of SERT vs DAT binding can be enhanced by incorporation of *N*-(*ω*-fluoroalkyl) groups.[5,11] To this end we synthesized the *N*-fluoroethyl (**3**), *N*-fluoropropyl (**4**), and *N*-fluorobutyl (**5**) derivatives of **1** and explored the microPET imaging properties of [^{18}F]**3**. Recently, the synthesis and monoamine transporter affinity have been reported for 2*β*-carbomethoxy-3*β*-(3′-(2-furyl)phenyl)tropane[12] and 2*β*-carbomethoxy-3*β*-[4′-(substituted thiophenyl)]phenyltropanes.[13]

Chemistry

p-Bromophenylnortropane **6**[9] (Scheme 1) was coupled to 3-(tri-*n*-butylstannyl)furan (**7**)[14] to give **1**. Hydrolysis of **1** in refluxing 1,4-dioxane/H_2O[15] afforded nortropane acid **8** (the X-ray crystal structure of zwitterionic **8** is reported in the Supporting Information), which was *N*-Boc protected to give the radiolabeling precursor **9**. Reaction of **1** with the appropriate bromofluoroalkane afforded the *N*-(*ω*-fluoroalkyl)nortropanes **3**−**5**. *p*-Bromophenyltropane **10**[9] was coupled to **7** to give **2**, which was hydrolyzed in refluxing 1,4-dioxane/H_2O to afford the radiolabeling precursor **11**.

Radiochemistry

The radiosynthesis of [^{11}C]**1** is shown in Scheme S1 in the Supporting Information. 3FPNT *N*-Boc acid **9** was deprotonated with 0.1 M $Bu_4NOH_{(aq)}$ and O-methylated with $^{11}CH_3I$. The Boc group was cleaved under acidic conditions, the reaction mixture was neutralized, and [^{11}C]**1** was purified by HPLC. The HPLC fractions containing [^{11}C]**1** were combined, and the product was isolated by solid-phase extraction according to a previously reported procedure.[16] The octanol/water partition coefficient of [^{11}C]**1** was measured according to a known procedure[17] and found to be log $P_{7.4} = 1.25$. The radiosynthesis of [^{11}C]**2a** was accomplished through O-methylation of **11** as shown in Scheme S2. The radiosynthesis of [^{11}C]**2b** was accomplished through N-methylation of **1** as shown in Scheme S3. The radiosynthesis of [^{18}F]**3** was achieved by N-alkylation of **1** with [^{18}F]-fluoroethyl brosylate (Scheme S4). The octanol/water partition coefficient of [^{18}F]**3** was determined to be log $P_{7.4} = 2.27$.

In Vitro Competition Assays

Tropanes **1** and **2** and **3**−**5** were screened for binding to human monoamine transporters using in vitro competition binding assays in HEK-293 cells stably expressing the transfected human SERT, DAT, or NET accord-

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Scheme 1

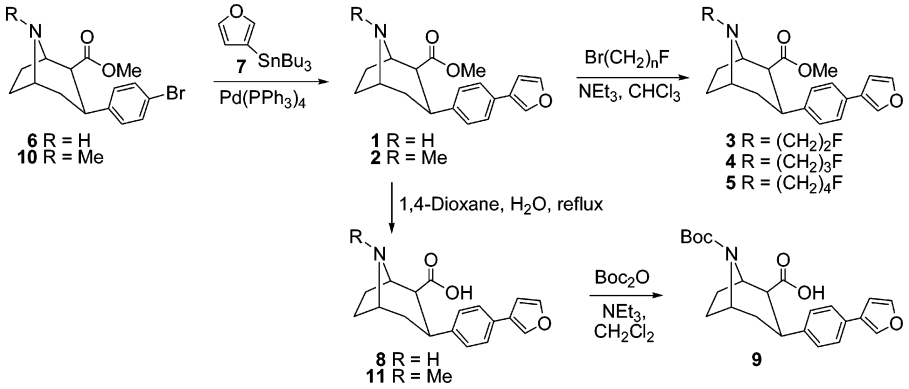

Table 1. Results of in Vitro Competition Binding Assays with Human Monoamine Transporters

	K_i (nM)[a]			SERT selectivity	
compd	SERT	DAT	NET	DAT/SERT	NET/SERT
1	0.11 ± 0.01	4.30 ± 0.95	4.52[b]	39.1	41.1
2	0.25 ± 0.03	2.18 ± 0.39	88.28[b]	8.7	353.1
3	0.49 ± 0.06	5.99 ± 0.11	551.60[b]	11.7	1081.6
4	0.46 ± 0.00	3.12 ± 0.11	1465.50 ± 82.73	6.8	3185.9
5	0.31 ± 0.05	2.12 ± 0.07	667.20 ± 151.60	7.6	2382.9

[a] $n = 2$. [b] $n = 1$.

ing to a previously reported procedure.[9] The binding affinities for each transporter were determined using [^{3}H]citalopram (SERT), [^{125}I]RTI-55 (DAT), or [^{3}H]-nisoxetine (NET). The data in Table 1 indicate that **1** has a higher affinity for the SERT as expected for a nortropane compared to it's tropane analogue **2**.[4] Furthermore, **1** is ~40 times more selective for the SERT than the DAT or NET, whereas **2** is less than 9 times as selective for the SERT over the DAT. The data in Table 1 also indicate that incorporation of an *N*-(ω-fluoroalkyl) group does not result in an increased affinity of the ligand for the SERT compared to **2** nor does this improve selectivity for the SERT over the DAT.

In Vivo Nonhuman Primate Imaging

The in vivo regional brain uptake of [^{11}C]**1**, [^{11}C]**2**, and [^{18}F]**3** was determined in anesthetized rhesus and cynomolgus monkeys using a Concorde microPET P4 instrument according to a previously reported procedure.[9] Baseline studies were initially performed to determine the extent of uptake of [^{11}C]**1**, [^{11}C]**2**, and [^{18}F]**3** in the SERT-rich regions of the brain. Figures S1 and S2 (Supporting Information) show the time−activity curves for the brain regions of cynomolgus monkeys after injection of [^{11}C]**2a** and [^{11}C]**2b**, respectively. The data in Figure S1 indicate that the uptake of [^{11}C]**2a** in the putamen and caudate increases continuously throughout the course of the study without reaching equilibrium. A similar result is observed after the injection of [^{11}C]**2b** (Figure S2). This is attributed to the binding of [^{11}C]**2** primarily to the DAT rather than the SERT as a result of the significantly greater concentration of DAT than SERT in these brain regions. Therefore, no further imaging studies were performed with [^{11}C]**2**.

Figure S3 shows the time−activity curves obtained after injection of [^{11}C]**1** into a cynomolgus monkey. The data indicate a high uptake in the caudate (C), putamen (P), thalamus (T), midbrain (MB), and medulla (Med) with peak uptake achieved after 85−95 min. Comparison of the uptake in these regions to cerebellum[18] (Cer) uptake after 95 min afforded the following ratios: P/Cer = 2.68, MB/Cer = 2.64, C/Cer = 2.47, Med/Cer = 2.20, T/Cer = 2.01. These ratios reflect the known distribution of SERT in the brain. Figure S4 shows the time−activity curves for a study where the SERT binding sites were preblocked by injection with the SERT selective ligand (*R,S*)-citalopram·HBr (1.5 mg/kg) 30 min prior to the injection of [^{11}C]**1**. As shown by these results, significant uptake of [^{11}C]**1** is only observed in the caudate and putamen, indicating that when the SERT sites are blocked, [^{11}C]**1** will bind to another site, presumably the DAT. This would be expected on the basis of the binding affinities reported in Table 1. Figure S5 shows the time−activity curves for a chase study where the DAT selective ligand RTI-177 (0.3 mg/kg) was administered 60 min after injection of [^{11}C]**1**. There is a similar uptake of [^{11}C]**1** in the caudate and putamen in this study, as was observed in the baseline study in Figure S3, and this uptake is not displaced by RTI-177, suggesting that [^{11}C]**1** is primarily bound to the SERT in these studies. Figure S6 shows the time−activity curves for a chase study using the NET selective ligand reboxetine (1.5 mg/kg) at 60 min after injection of [^{11}C]**1**. Injection of reboxetine failed to displace [^{11}C]**1**, further indicating that uptake in the brain is a result of preferential binding to the SERT.

Imaging studies were also performed with [^{18}F]**3** to take advantage of the longer half-life of ^{18}F (109.8 min). Although the data in Table 1 indicate that **3** has a lower affinity for the SERT than **4** or **5**, **3** has a higher selectivity for the SERT over the DAT than **4** or **5**. Figure S7 shows the time−activity curves for a baseline study with [^{18}F]**3** in a cynomolgus monkey. This study shows that [^{18}F]**3** has good kinetics, but the high uptake observed suggests that [^{18}F]**3** is binding to the DAT and the SERT in the putamen and caudate. This was verified by performing a chase study with the DAT selective ligand RTI-113 (Figure S8), which resulted in a nearly complete displacement of [^{18}F]**3** from the putamen and caudate. Therefore, no further imaging studies were performed with [^{18}F]**3**.

Conclusions

A 3-furyl ring was incorporated into the 4-position of the phenyl ring of a 3β-tropane to give the nortropane **1**, the tropane **2**, and the *N*-(ω-fluoroalkyl) derivatives **3**−**5**. In vitro competition binding assays with human

monoamine transporters indicated that **1** had the highest affinity for the SERT of all the compounds tested, but **1** also showed a modest affinity for the DAT and NET. N-Alkylation reduced the SERT affinity of **2**−**5** relative to **1** and increased the DAT affinity of **2**, **4**, and **5** relative to **1**. In vivo microPET brain imaging studies in anesthetized monkeys with [^{11}C]**1** showed a high uptake of [^{11}C]**1** in the SERT-rich regions of the brain, but blocking and chase studies revealed that some binding to the DAT may also be involved. MicroPET studies with [^{11}C]**2** and [^{18}F]**3** demonstrated that N-alkylation results in a preferential shift to DAT binding of these compounds in the caudate and putamen. Taken together, these results indicate that incorporation of a 3-furyl ring into the 4-position of the phenyl ring of a 3β-tropane or nortropane does not significantly enhance the selectivity for the SERT over the DAT or NET, and therefore, any further PET imaging studies to translate a candidate from this series to human use are not warranted.

Experimental Section

2β-Carbomethoxy-3β-(4′-(3-furyl)phenyl)nortropane (3FPNT, 1). 3β-(4′-Bromophenyl)nortropane (**6**) (100 mg, 3.08 × 10^{-4} mol), 3-(tri-*n*-butylstannyl)furan (**7**) (456 mg, 1.28 mmol, 4.2 equiv), palladium(tetrakis(triphenylphosphine)) (36 mg, 3.12 × 10^{-5} mol, 0.1 equiv), and Ar-purged toluene (15 mL) were stirred at reflux under Ar for 16.5 h, cooled, and poured onto a dry silica plug (43 mm height × 43 mm i.d.). The product was eluted under vacuum with $CHCl_3$ (75 mL), hexane/EtOAc/NEt_3 75:20:5 (200 mL), 50:45:5 (200 mL), 30:70:5 (400 mL) v/v/v, and then 5% NEt_3/EtOAc. The solvent was removed to give a yellow oil that was further purified by radial chromatography (1 mm silica, hexane/EtOAc/NEt_3 75:20:5 (300 mL) and then 50:45:5 v/v/v). The solvent was removed to give a colorless oil that was dried under vacuum to afford 62 mg (65%) of a white solid. Samples for binding assays and elemental analysis were further purified by preparative thin-layer chromatography (TLC). TLC R_f = 0.08 (50:45:5 v/v/v hexane/EtOAc/NEt_3), R_f = 0.33 (85:10:5 v/v/v $CHCl_3$/EtOAc/NEt_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, 1 H, J = 1.2 Hz), 7.47 (dd, 1 H, J = 2.0 and 1.6 Hz), 7.41 (d, 2 H, J = 8.4 Hz), 7.20 (d, 2 H, J = 8.4 Hz), 6.68 (dd, 1 H, J = 1.2 and 0.8 Hz), 3.76 (m, 1 H), 3.72 (m, 1 H), 3.39 (s, 3 H), 3.26 (dt, 1 H, J = 5.9 Hz, J = 12.8 Hz), 2.76 (m, 1 H), 2.44 (td, 1 H, J = 2.9 Hz, J = 12.9 Hz), 2.19−1.97 (m, 3 H), 1.82−1.63 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.02, 143.74, 141.19, 138.46, 130.70, 127.90, 126.26, 125.82, 108.88, 56.43, 53.76, 51.31, 51.22, 35.55, 33.80, 29.18, 27.76. HRMS (EI) Calcd for $C_{19}H_{21}NO_3$: 311.1521. Found: 311.1524. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50; O, 15.41. Found: C, 70.07; H, 6.70; N, 4.34; O, 15.57. HPLC: t_R = 4.8 min (Waters Nova-Pak C_{18} 3.9 mm × 150 mm, 75:25:0.1 v/v/v MeOH/H_2O/NEt_3, 1 mL/min), 96% purity by HPLC for sample used for binding assay and elemental analysis.

2β-Carbomethoxy-3β-(4′-(3-furyl)phenyl)tropane (3FPT, 2). 3β-(4′-Bromophenyl)tropane (**10**) (102 mg, 3.02 × 10^{-4} mol), 3-(tri-*n*-butylstannyl)furan (**7**) (856 mg, 2.40 mmol, 7.9 equiv), palladium(tetrakis(triphenylphosphine)) (36 mg, 3.12 × 10^{-5} mol, 0.1 equiv), and Ar-purged toluene (15 mL) were stirred at reflux under Ar for 17 h, cooled, and poured onto a dry silica plug (43 mm height × 43 mm i.d.). The product was eluted under vacuum with $CHCl_3$ (75 mL) and then 75:20:5 v/v/v hexane/EtOAc/NEt_3 to give an off-white solid that was further purified by radial chromatography (2 mm silica, 90:8:2 v/v/v hexane/EtOAc/NEt_3) to afford 40 mg (41%) of a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (s, 1 H), 7.45 (dd, 1 H, J = 1.2 Hz, J = 1.8 Hz), 7.39 (d, 2 H, J = 8.1 Hz), 7.26 (d, 2 H, J = 8.1 Hz), 6.67 (m, 1 H), 3.57 (m, 1 H), 3.50 (s, 3 H), 3.38 (m, 1 H), 3.01 (dt, 1 H, J = 5.4 Hz, J = 13.2 Hz), 2.92 (br dd, 1 H, J = 3.6 Hz, J = 4.2 Hz), 2.61 (td, 1 H, J = 2.4 Hz, J = 12.6 Hz), 2.23, (s, 3 H), 2.21 (m, 1 H), 2.11 (m, 1 H), 1.72 (m, 2 H), 1.62 (m, 1 H). HRMS (EI) Calcd for $C_{20}H_{23}NO_3$: 325.1678. Found: 325.1682. Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30; O, 14.75. Found: C, 72.65; H, 7.13; N, 4.26; O, 14.29.

***N*-(2-Fluoroethyl)-2β-carbomethoxy-3β-(4′-(3-furyl)phenyl)nortropane (3).** 3FPNT **1** (24 mg, 7.71 × 10^{-5} mol), 1-bromo-2-fluoroethane (70 μL, 0.94 mmol, 12.2 equiv), NEt_3 (13 μL, 9.3 × 10^{-5} mol, 1.2 equiv), and $CHCl_3$ (5 mL) were stirred at reflux under Ar for 23 h. The solvent was removed to give a brown residue that was purified by preparative TLC (75:20:5 v/v/v hexane/EtOAc/NEt_3 × 2) to afford 8 mg (29%) of a white solid: TLC R_f = 0.28 (75:20:5 v/v/v hexane/EtOAc/NEt_3); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (br d, 1 H, J = 0.6 Hz), 7.45 (br dd, 1 H, J = 1.8 Hz), 7.40 (d, 2 H, J = 7.8 Hz), 7.27 (d, 2 H, J = 7.8 Hz), 6.67 (br d, 1 H, J = 0.6 Hz), 4.51 + 4.43 and 4.47 + 4.39 (4 m, 2 H, $^2J_{HF}$ = 47.4 and 48.0 Hz), 3.79 (m, 1 H), 3.52 (s, 3 H), 3.45 (m, 1 H), 3.03 (m, 1 H), 2.95 (t, 1 H, J = 4.2 Hz), 2.62 (m, 3 H), 2.14 (m, 1 H), 2.02 (m, 1 H), 1.79 (m, 1 H), 1.70 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.16, 143.70, 142.11, 138.44, 130.09, 127.96, 126.54, 125.65, 109.07, 84.14 (d, $^1J_{CF}$ = 165.0 Hz), 63.81, 62.59, 53.90 (d, J_{CF} = 20.7 Hz), 52.90, 51.26, 34.18, 34.00, 26.43, 25.94. HRMS (EI) Calcd for $C_{21}H_{24}O_3NF$: 357.1740. Found: 357.1750. Anal. Calcd for $C_{21}H_{24}O_3NF$: C, 70.57; H, 6.77; N, 3.92; O, 13.43. Found: C, 67.84; H, 6.70; N, 3.94; O, 15.16.

***N*-(3-Fluoropropyl)-2β-carbomethoxy-3β-(4′-(3-furyl)phenyl)nortropane (4).** 3FPNT **1** (29 mg, 9.31 × 10^{-5} mol), 1-bromo-3-fluoropropane (0.1 mL, 1.1 mmol, 11.7 equiv), NEt_3 (16 μL, 0.11 mmol, 1.2 equiv), and $CHCl_3$ (5 mL) were stirred at reflux under Ar for 16 h. The solvent was removed to give a brown residue that was purified by preparative TLC (75:20:5 v/v/v hexane/EtOAc/NEt_3) to give 22 mg (64%) of a white solid: TLC R_f = 0.31 (75:20:5 v/v/v hexane/EtOAc/NEt_3); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (s, 1 H), 7.45 (dd, 1 H, J = 1.8 Hz), 7.39 (d, 2 H, J = 7.8 Hz), 7.26 (d, 2 H, J = 7.8 Hz), 6.67 (dd, 1 H, J = 0.6 and 1.2 Hz), 4.53 (dt, 2 H, $^3J_{HH}$ = 6.0 Hz, $^2J_{HF}$ = 47.4 Hz), 3.69 (m, 1 H), 3.49 (s, 3 H), 3.41 (m, 1 H), 3.03 (dt, 1 H, J = 5.4 Hz, J = 12.6 Hz), 2.94 (t, 1 H, J = 3.9 Hz), 2.60 (td, 1 H, J = 3.0 Hz, J = 12.0 Hz), 2.39 (m, 2 H), 2.10 (m, 1 H), 2.02 (m, 1 H), 1.82−1.62 (3 m, 5 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.16, 143.68, 142.21, 138.43, 130.05, 127.95, 126.53, 125.62, 109.06, 82.49 (d, $^1J_{CF}$ = 163.1 Hz), 63.38, 61.73, 52.99, 51.14, 49.47, 34.20, 34.15, 30.24 (d, J_{CF} = 18.6 Hz), 26.23, 26.14. HRMS (EI) Calcd for $C_{22}H_{26}O_3NF$: 371.1897. Found: 371.1882. Anal. Calcd for $C_{22}H_{26}O_3NF$: C, 71.14; H, 7.06; N, 3.77, O, 12.92. Found: C, 69.42; H, 7.11; N, 3.63; O, 12.22.

***N*-(4-Fluorobutyl)-2β-carbomethoxy-3β-(4′-(3-furyl)phenyl)nortropane (5).** 3FPNT **1** (27 mg, 8.67 × 10^{-5} mol), 1-bromo-4-fluorobutane (0.1 mL, 0.93 mmol, 10.7 equiv), NEt_3 (15 mL, 0.11 mmol, 1.2 equiv), and $CHCl_3$ (5 mL) were stirred at reflux under Ar for 16 h. The solvent was removed to give a brown residue that was purified by preparative TLC (75:20:5 v/v/v hexane/EtOAc/NEt_3) to afford 23 mg (69%) of a white solid: TLC R_f = 0.32 (75:20:5 v/v/v hexane/EtOAc/NEt_3); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (s, 1 H), 7.45 (s, 1 H), 7.39 (d, 2 H, J = 8.4 Hz), 7.27 (d, 2 H, J = 8.4 Hz), 6.67 (s, 1 H), 4.45 (dt, 2 H, $^3J_{HH}$ = 6.0 Hz, $^2J_{HF}$ = 47.4 Hz), 3.69 (m, 1 H), 3.48 (s, 3 H), 3.40 (m, 1 H), 3.03 (dt, 1 H, J = 5.4 Hz, J = 13.2 Hz), 2.94 (m, 1 H), 2.60 (td, 1 H, J = 1.8 Hz, J = 12.3 Hz), 2.29 (m, 2 H), 2.10 (m, 1 H), 2.00 (m, 1 H), 1.80−1.68 (m, 4 H), 1.63 (m, 1 H), 1.47 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.25, 143.68, 142.31, 138.43, 130.04, 127.97, 126.54, 125.62, 109.07, 84.39 (d, $^1J_{CF}$ = 163.9 Hz), 63.12, 61.67, 53.19, 53.06, 51.16, 34.24, 28.34, 28.22, 26.21, 26.16, 24.85. HRMS (EI) Calcd for $C_{23}H_{28}O_3NF$: 385.2053 Found: 385.2052. Anal. Calcd for $C_{23}H_{28}O_3NF$: C, 71.66; H, 7.32; N, 3.63; O, 12.45. Found: C, 69.96; H, 7.26; N, 3.53; O, 12.80.

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Supporting Information Available: MicroPET imaging time−activity curves, radiolabeling schemes, experimental details, X-ray crystal structure of zwitterionic **8**, crystal packing analysis, and X-ray crystallographic experimental and data tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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