Supporting Information

2'-(2-((dimethylamino)methyl)-4'- (2-fluoroalkoxy)-phenylthio)benzenamine Derivatives as Serotonin Transporter Imaging Agents

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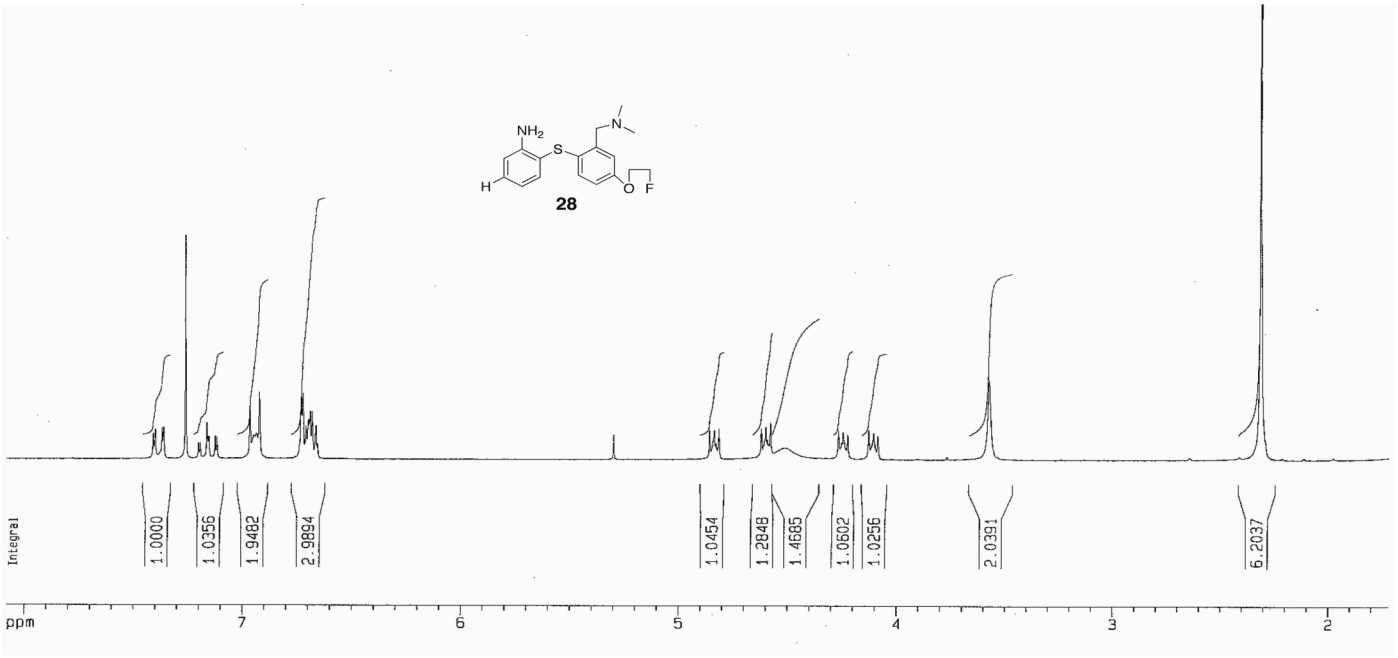
General information. All reagents used were commercial products and were used without further purification unless otherwise indicated. Flash chromatography (FC) was performed using silica gel 60 (230-400 mesh, Sigma-Aldrich). Preparative thin layer chromatography (PTLC) was performed on silica gel plates with a fluorescent indicator that was visualized with light at 254 nm (Analtech). For each procedure, "standard workup" refers to the following steps: addition of the indicated organic solvent, washing the organic layer with water then brine, separation of the organic layer from the aqueous layer, drying off the combined organic layers with sodium sulfate or magnesium sulfate, filtering off the solid and concentrating the filtrate under reduced pressure. Microwave reactions were performed at the InitiatorTM microwave reactor (Biotage). 1H NMR spectra were obtained at 200 MHz (Bruker DPX spectrometer). Chemical shifts were reported as δ values (parts per million) relative to internal TMS. Coupling constants were reported in hertz. The multiplicity is defined by s (singlet), d (doublet), t (triplet), br (broad) or m (multiplet). High-resolution MS experiments were performed at University of Pennsylvania. Analytical HPLC analysis was carried out using an Agilent 1100 series LC. Two systems were used to confirm the purity of some compounds listed in this section, system A conditions: phenomenex Gemini 5μ C18 110A reverse-phased analytical column (250 × 4.6 mm, 5 μm), 80/20 CH_3CN/10mM ammonium formate (pH = 7) water buffer, 1.0 mL/min, UV 254 nm; system B conditions: Phenomenex Silica column (4.6 × 250 mm, 5 μm), EtOAc/ MeOH (80/20), 1.0 mL/min, UV 254 nm. All compounds reported in this paper showed greater than 95% purity in both systems.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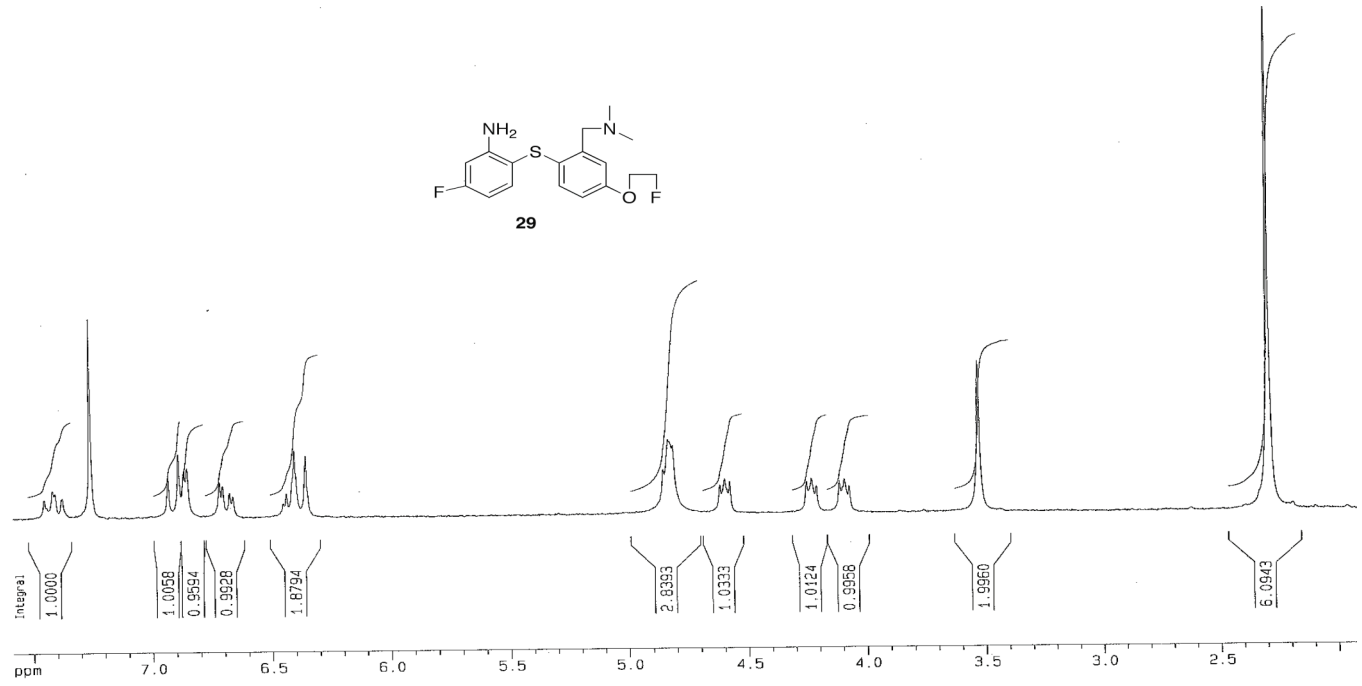
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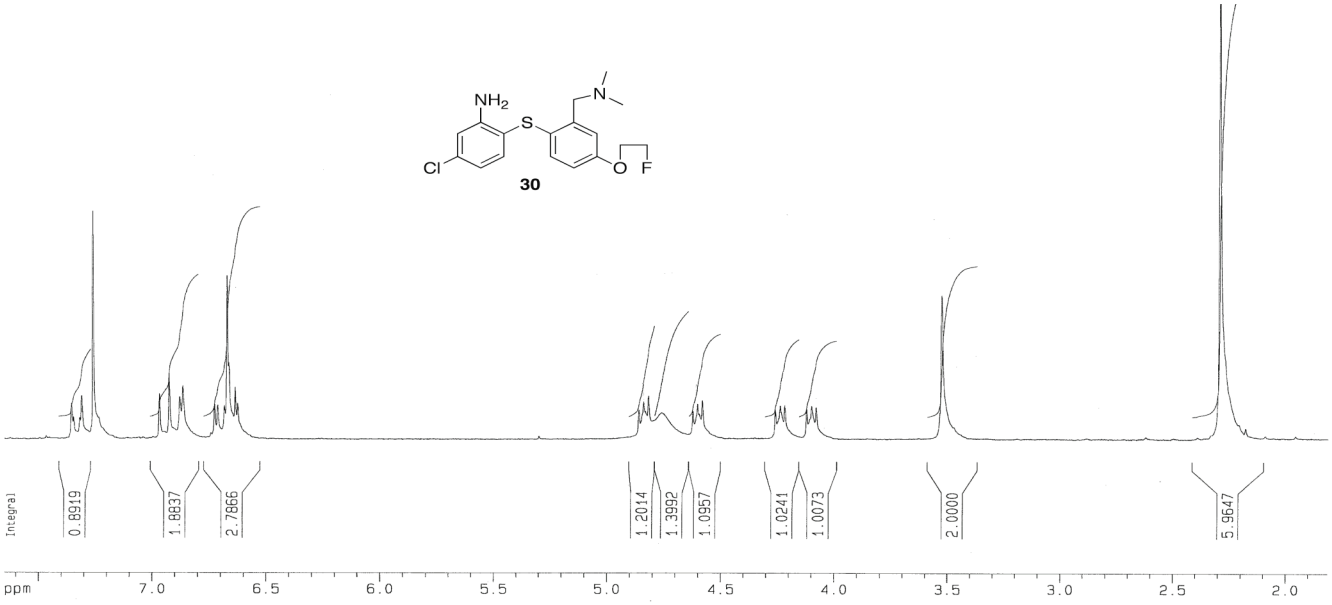
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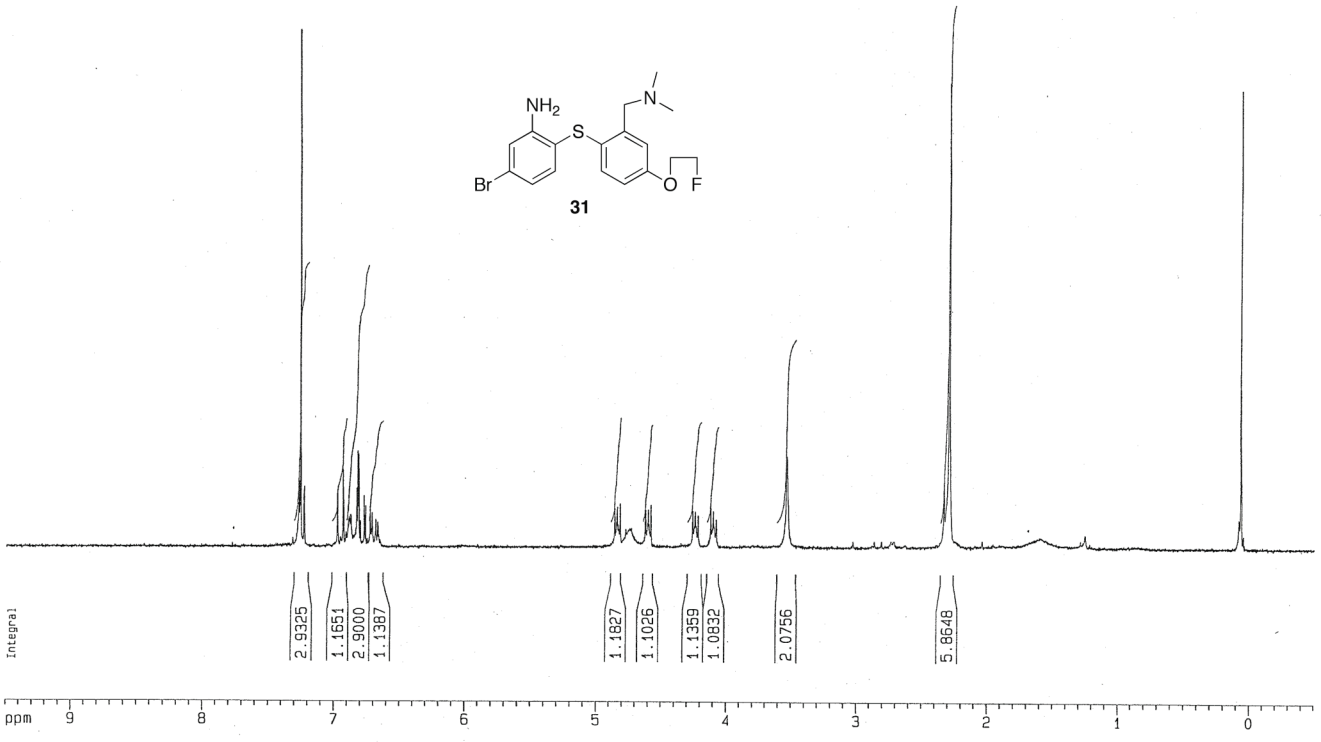
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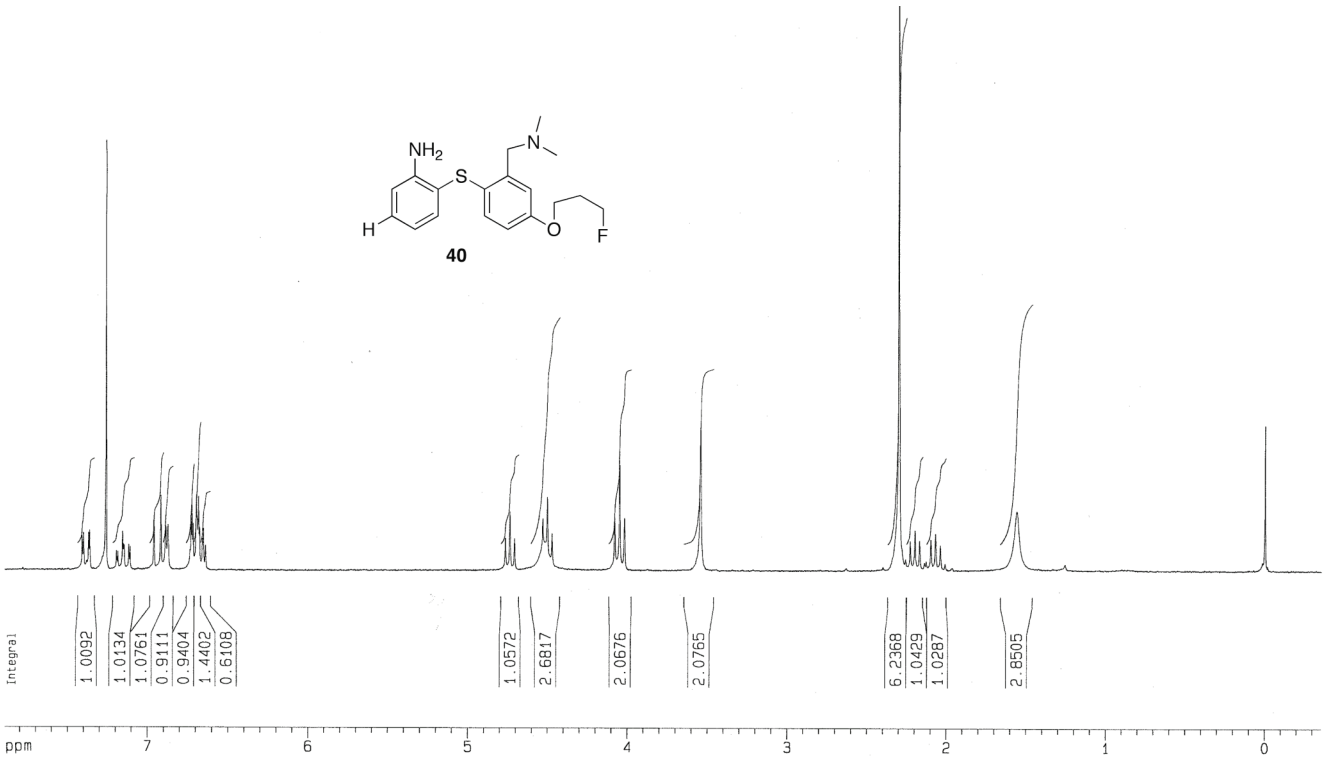
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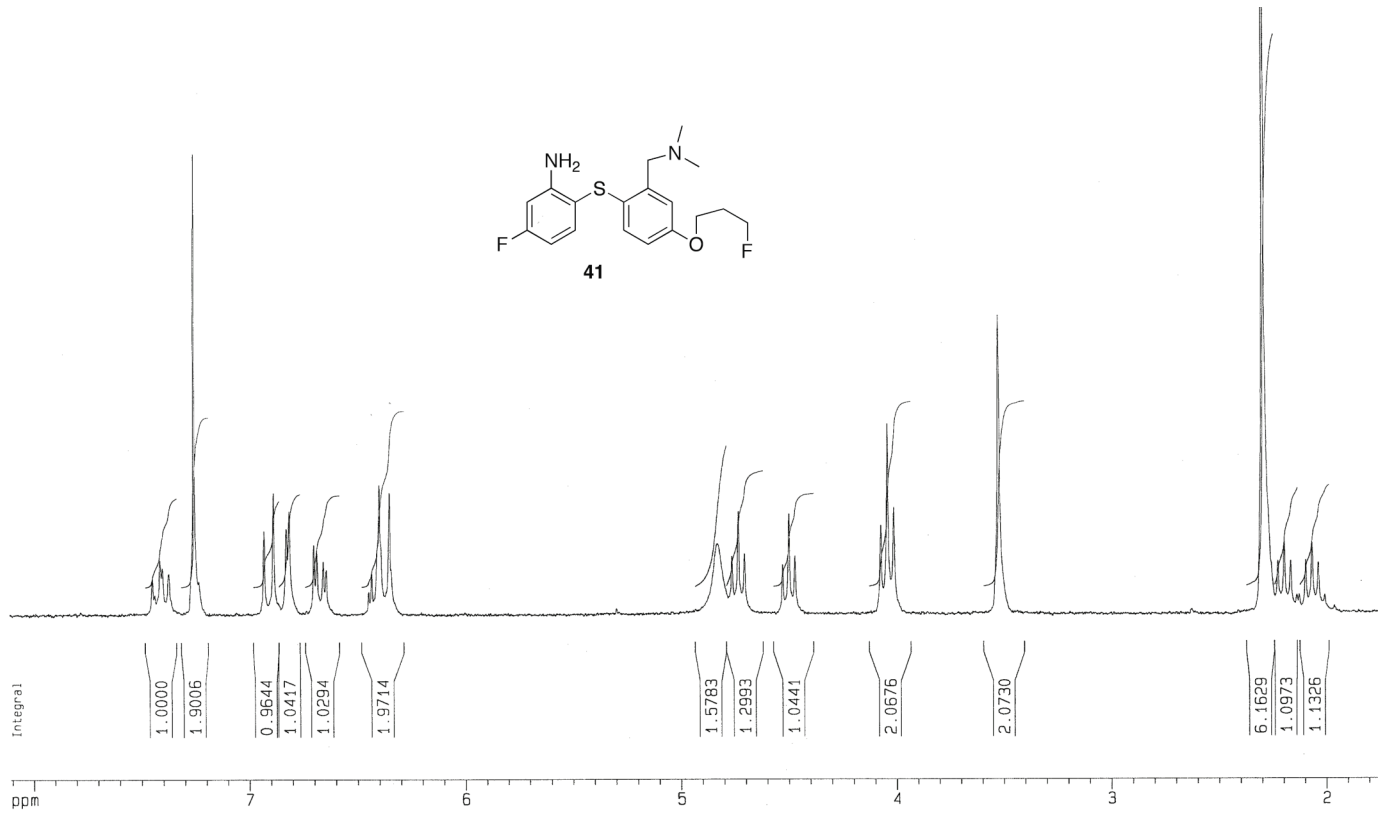
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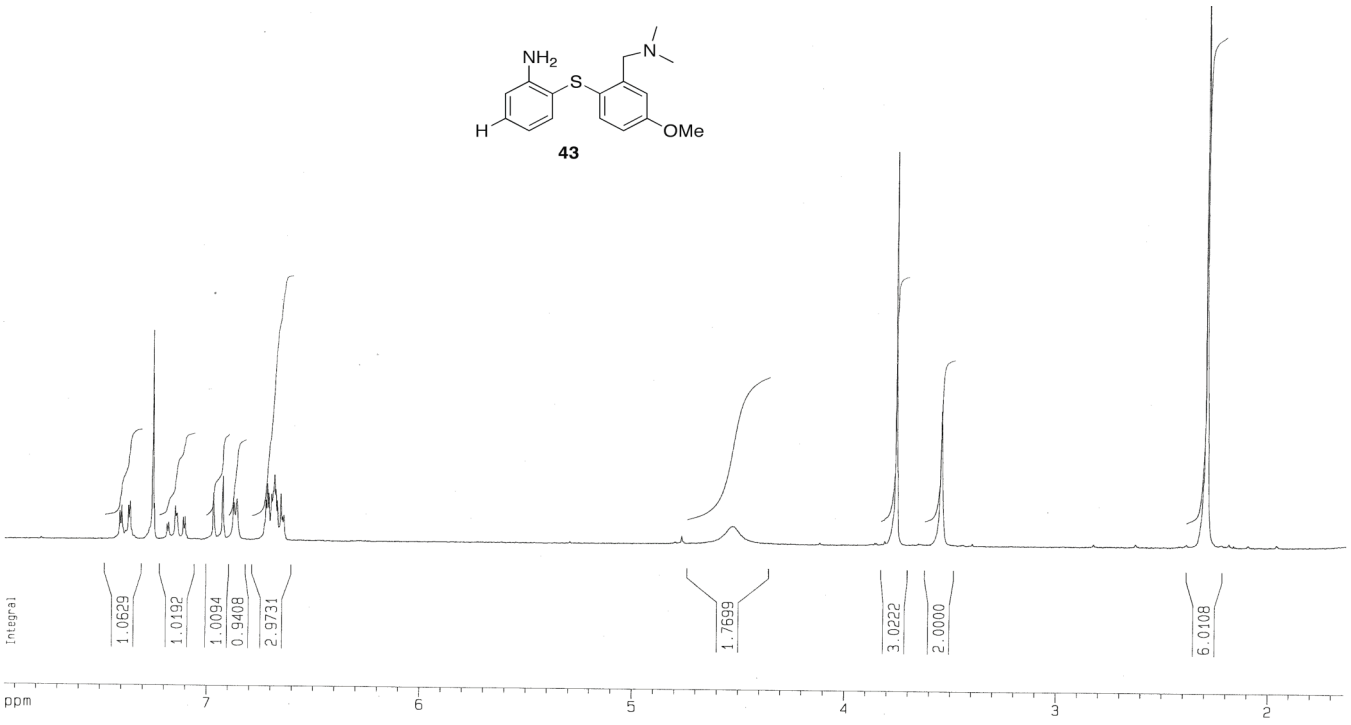
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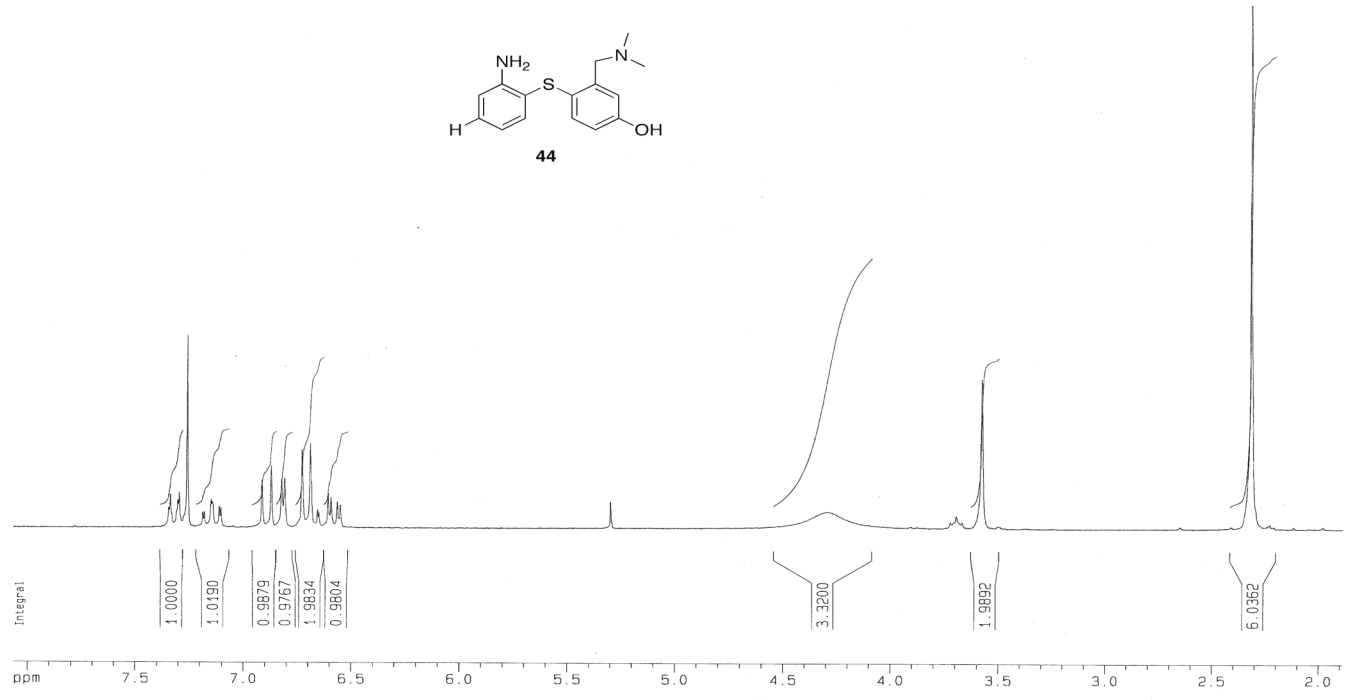
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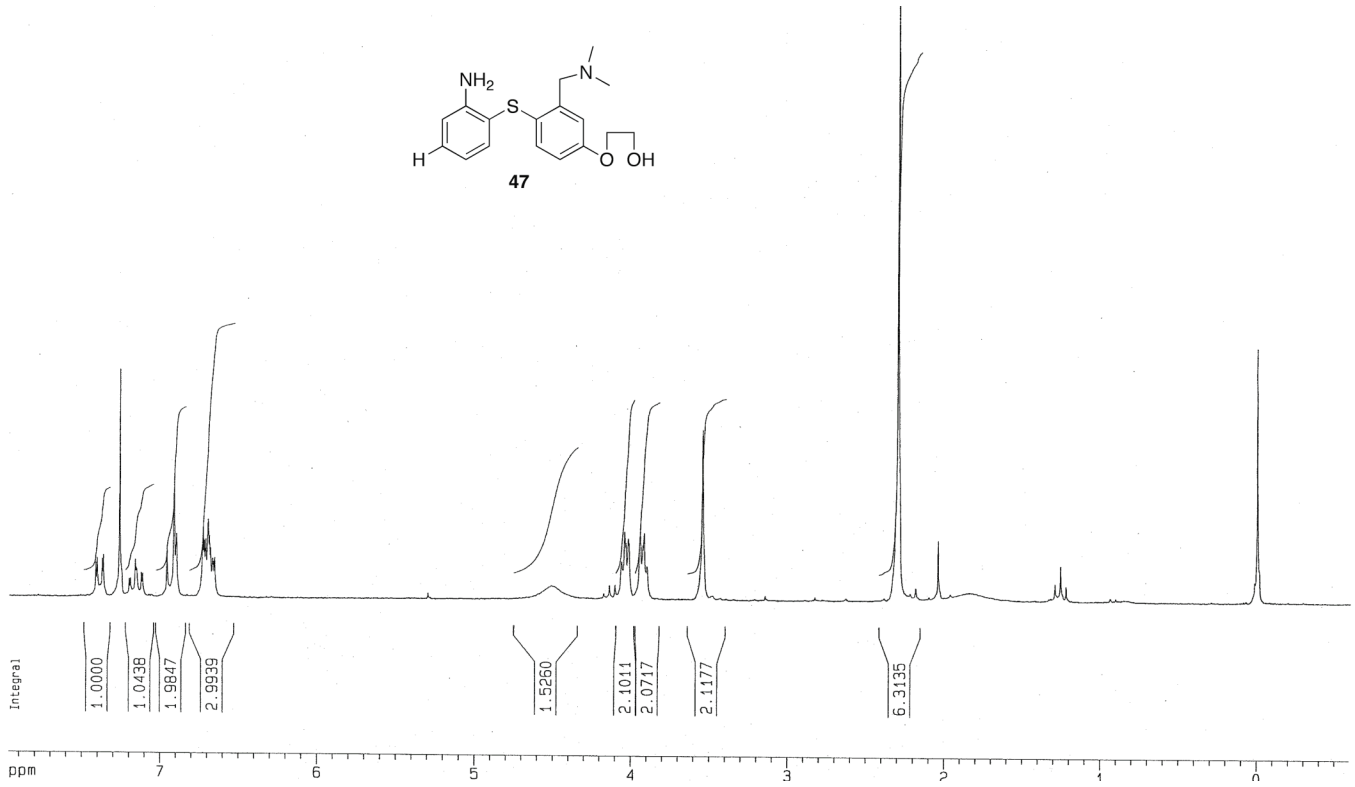
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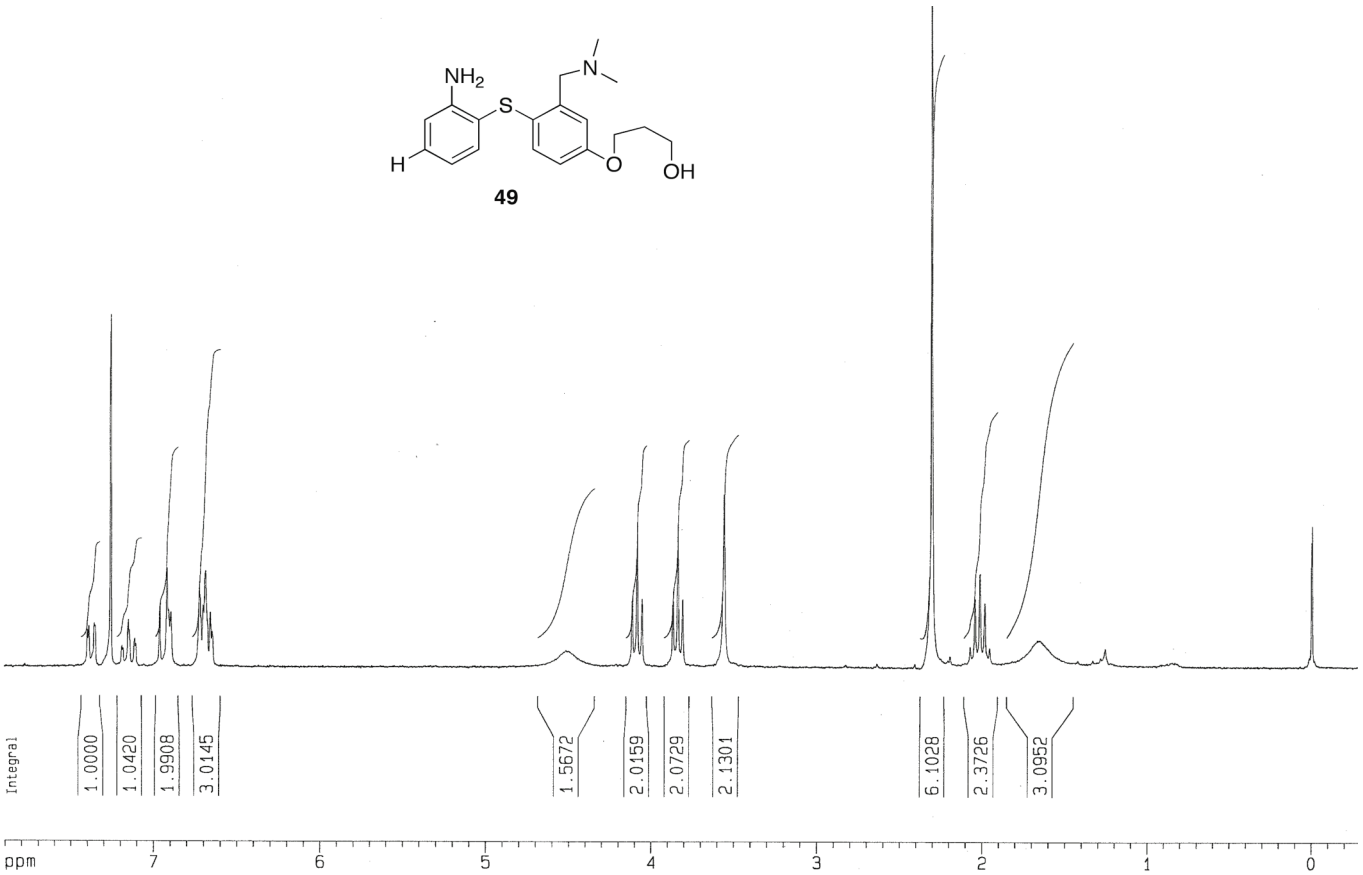
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Table 1. Purity of the synthesized compounds checked by two different HPLC systems

Compound	**HPLC System A**[a]		**HPLC System B**[b]	
	Retention Time (min)	Purity (%)	Retention Time (min)	Purity (%)
28	3.6	98.7	5.1	98.4
29	3.9	99.0	5.7	98.1
30	4.7	96.1	5.3	97.9
31	5.7	98.0	5.3[c,d]	98.9
40	4.0	99.4	4.4	99.0
41	4.6	98.5	6.0	98.2
42	6.4	95.0	6.8[c]	98.3
43	3.7	99.3	5.3	98.5
44	2.9	97.9	6.0	98.7
47	2.9	98.0	9.7	98.1
48	3.1	96.4	7.6	95.0
49	3.0	96.9	8.5	97.8

[a]System A conditions: phenomenex Gemini 5μ C18 110A reverse-phased analytical column (250 × 4.6 mm, 5 μm), 80/20 CH_3CN/10mM ammonium formate (pH = 7) water buffer, 1.0 mL/min, UV 254 nm; [b]system B conditions: Phenomenex Silica column (4.6 × 250 mm, 5 μm), EtOAc/ MeOH (80/20), 1.0 mL/min; [c]EtOAc/i-PrOH (80/20) UV 265 nm; [d]2.0 mL/min.

Table 2. F-18 labeling and partition coefficients[a] of compounds

Compound	RCY (%)	RCP (%)	SA (Ci/μmol)	LogP	n
[^{18}F]**28**	8-32	>98	0.52-1.66	2.15	3
[^{18}F]**29**	25	>99	1.67	2.47	1
[^{18}F]**30**	23	>99	3.0	2.71	1
[^{18}F]**31**	11-18	>99	0.42-0.73	2.52	5
[^{18}F]**40**	9-27	>98	0.44-7.5	2.54	7
[^{18}F]**41**	13-25	>99	0.95-2.6	2.65	2
[^{18}F]**42**	16	>99	5.7	3.30	1

RCY: Radiochemic

al yield (decay corrected), RCP: Radopchemical purity, SA: Specific activity (EOS). n: number of times the experiment were performed

[a]Partition (P) measured between 1-octanol and buffer (pH 7.4).

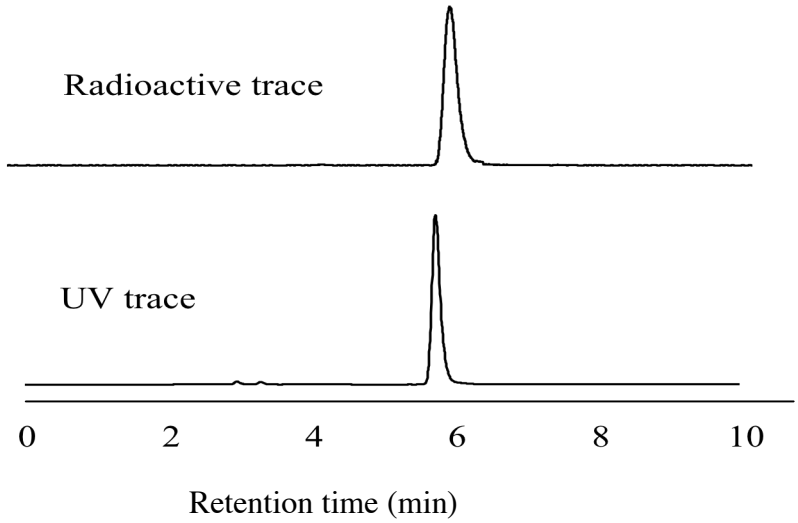
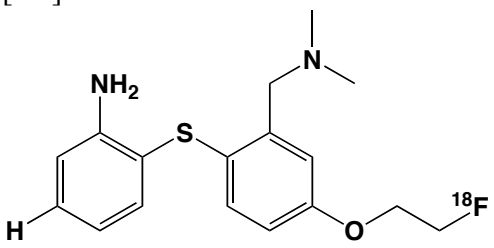


Fig. 1. HPLC profiles of [^{18}F]**42** (top) and **42** (bottom). HPLC condition: Agilent 1100 series; Gemini C-18 column CH_3CN/ammonium formate (10 mM) 8/2 1mL/min 254 nm t_R = (UV) 5.74 min, (ϒ) 5.93 min. The slight difference in retention time between the radioactive peak and the UV peak is due to the sequential configuration of detector systems.

Table 3. Biodistribution (% dose/organ) and regional brain uptake (% dose/g) of [^{18}F]**28** in rats (*iv* injection)

[^{18}F]**28**



Organ distribution (% dose/organ ± SD)

Organ	2 min	30 min	60 min	120 min	240 min
Skin	8.78 ± 1.76	8.66 ± 1.09	8.44 ± 1.10	4.32 ± 0.18	3.77 ± 0.64
Blood	11.86 ± 1.43	4.74 ± 1.18	3.10 ± 0.59	4.06 ± 0.40	1.74 ± 0.15
Heart	0.95 ± 0.05	0.17 ± 0.01	0.12 ± 0.01	0.09 ± 0.00	0.04 ± 0.01
Lung	13.21 ± 1.15	2.25 ± 0.36	1.40 ± 0.30	0.53 ± 0.04	0.33 ± 0.05
Liver	9.90 ± 1.85	4.24 ± 0.39	3.74 ± 0.12	7.68 ± 0.19	2.26 ± 0.19
Pancreas	0.92 ± 0.03	0.24 ± 0.04	0.19 ± 0.03	0.08 ± 0.00	0.04 ± 0.01
Spleen	1.22 ± 0.03	0.65 ± 0.18	0.35 ± 0.18	0.26 ± 0.03	0.09 ± 0.02
Kidney	7.93 ± 0.35	4.56 ± 1.54	4.04 ± 1.44	2.66 ± 0.29	1.94 ± 0.05
Muscle	16.55 ± 5.48	9.46 ± 0.93	8.24 ± 2.11	4.24 ± 0.77	2.28 ± 0.32
Bone	8.67 ± 0.35	7.11 ± 0.05	4.87 ± 0.95	2.92 ± 0.36	3.30 ± 0.38
Brain	1.84 ± 0.32	1.41 ± 0.06	1.21 ± 0.37	0.42 ± 0.06	0.18 ± 0.05

Regional brain distribution (% dose/g ± SD)

Region	2 min	30 min	60 min	120 min	240 min
CB	0.83 ± 0.10	0.30 ± 0.05	0.18 ± 0.06	0.09 ± 0.03	0.03 ± 0.00
HY	1.06 ± 0.23	1.07 ± 0.05	1.00 ± 0.26	0.74 ± 0.18	0.20 ± 0.06
HP	0.99 ± 0.16	0.77 ± 0.09	0.68 ± 0.16	0.35 ± 0.10	0.06 ± 0.06
CX	1.26 ± 0.19	0.97 ± 0.05	0.86 ± 0.32	0.43 ± 0.11	0.07 ± 0.03
ST	1.01 ± 0.12	0.80 ± 0.08	0.70 ± 0.24	0.36 ± 0.05	0.08 ± 0.02

Cortex (CX), striatum (ST), hippocampus (HP), cerebellum (CB) and hypothalamus (HY)

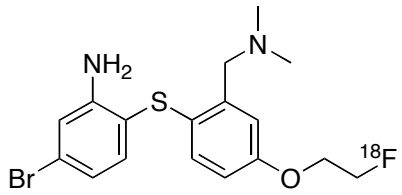
Ratio to cerebellum

Region	2 min	30 min	60 min	120 min	240 min
HY/CB	1.28 ± 0.32	3.59 ± 0.62	5.52 ± 2.22	7.83 ± 2.96	6.58 ± 2.25
HP/CB	1.19 ± 0.25	2.59 ± 0.53	3.75 ± 1.45	3.71 ± 1.52	2.14 ± 1.91
CX/CB	1.53 ± 0.30	3.26 ± 0.57	4.78 ± 2.29	4.60 ± 1.77	2.44 ± 0.99
ST/CB	1.22 ± 0.21	2.69 ± 0.53	3.87 ± 1.78	3.85 ± 1.25	2.72 ± 0.85

***** Organ and regional brain distribution for the 120 min timepoint were done on separate days.

Table 4. Biodistribution (% dose/organ) and regional brain uptake (% dose/g) of [^{18}F]**31** in rats (*iv* injection)

[^{18}F]**31**



Organ distribution (% dose/organ ± SD)

Organ	2 min	30 min	60 min	120 min	240 min	360 min
Skin	5.30 ± 2.07	7.06 ± 0.83	7.86 ± 0.58	7.07 ± 1.10	6.79 ± 0.40	6.52 ± 0.78
Blood	4.67 ± 0.99	5.70 ± 0.32	7.05 ± 1.25	6.19 ± 1.49	5.21 ± 0.56	4.75 ± 0.41
Heart	1.38 ± 0.36	0.23 ± 0.04	0.21 ± 0.01	0.19 ± 0.05	0.12 ± 0.00	0.13 ± 0.03
Lung	10.3 ± 1.77	4.63 ± 0.52	3.44 ± 0.72	2.98 ± 0.41	2.10 ± 0.05	1.89 ± 0.26
Liver	11.1 ± 2.65	4.58 ± 0.21	3.45 ± 0.39	2.85 ± 0.37	2.13 ± 0.20	1.86 ± 0.18
Spleen	1.05 ± 0.13	0.70 ± 0.06	0.68 ± 0.27	0.54 ± 0.16	0.39 ± 0.06	0.29 ± 0.05
Kidney	5.33 ± 1.06	2.85 ± 0.49	2.44 ± 0.21	2.00 ± 0.42	1.53 ± 0.27	1.13 ± 0.09
Muscle	18.2 ± 5.56	15.9 ± 0.85	15.5 ± 0.67	10.2 ± 1.26	8.37 ± 1.14	8.98 ± 1.18
Bone	9.88 ± 0.95	8.17 ± 0.29	8.53 ± 0.55	9.30 ± 1.95	12.5 ± 0.83	15.3 ± 3.21
Brain	2.05 ± 0.24	1.88 ± 0.18	1.92 ± 0.29	2.16 ± 0.14	1.57 ± 0.12	1.36 ± 0.16

Regional brain distribution (% dose/g ± SD)

Region	2 min	30 min	60 min	120 min	240 min	360 min
CB	1.07 ± 0.15	0.59 ± 0.06	0.46 ± 0.05	0.48 ± 0.01	0.26 ± 0.03	0.23 ± 0.02
HY	1.01 ± 0.15	1.19 ± 0.10	1.37 ± 0.22	1.78 ± 0.24	1.10 ± 0.13	0.98 ± 0.15
HP	0.94 ± 0.14	0.96 ± 0.07	1.01 ± 0.11	1.08 ± 0.08	0.77 ± 0.10	0.70 ± 0.10
CX	1.54 ± 0.12	1.14 ± 0.12	1.11 ± 0.15	1.39 ± 0.18	0.82 ± 0.06	0.72 ± 0.05
ST	1.02 ± 0.17	1.09 ± 0.10	1.27 ± 0.16	1.37 ± 0.11	0.98 ± 0.06	0.86 ± 0.13

Ratio to Cerebellum

Region	2 min	30 min	60 min	120 min	240 min	360 min
HY/CB	0.95 ± 0.19	2.04 ± 0.27	2.97 ± 0.58	3.70 ± 0.51	4.26 ± 0.70	4.32 ± 0.75
HP/CB	0.88 ± 0.18	1.63 ± 0.20	2.21 ± 0.34	2.23 ± 0.17	2.99 ± 0.51	3.08 ± 0.51
CX/CB	1.45 ± 0.23	1.95 ± 0.28	2.41 ± 0.42	2.90 ± 0.38	3.21 ± 0.43	3.20 ± 0.35
ST/CB	0.96 ± 0.21	1.86 ± 0.25	2.76 ± 0.46	2.84 ± 0.24	3.84 ± 0.49	3.80 ± 0.65

Cortex (CX), striatum (ST), hippocampus (HP), cerebellum (CB) and hypothalamus (HY)