

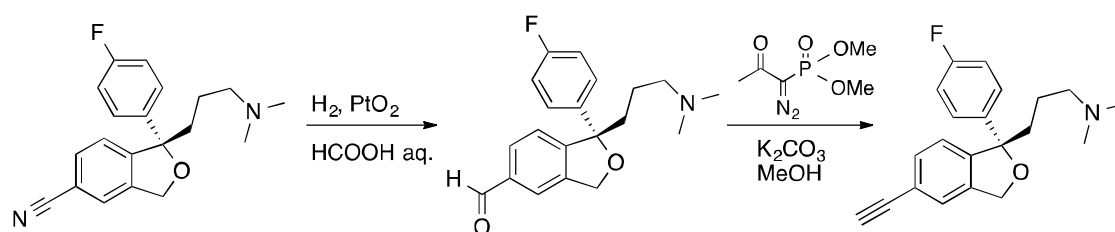
## SUPPLEMENTARY MATERIALS

### **Direct visualization of an antidepressant analog using surface-enhanced Raman scattering in the brain**

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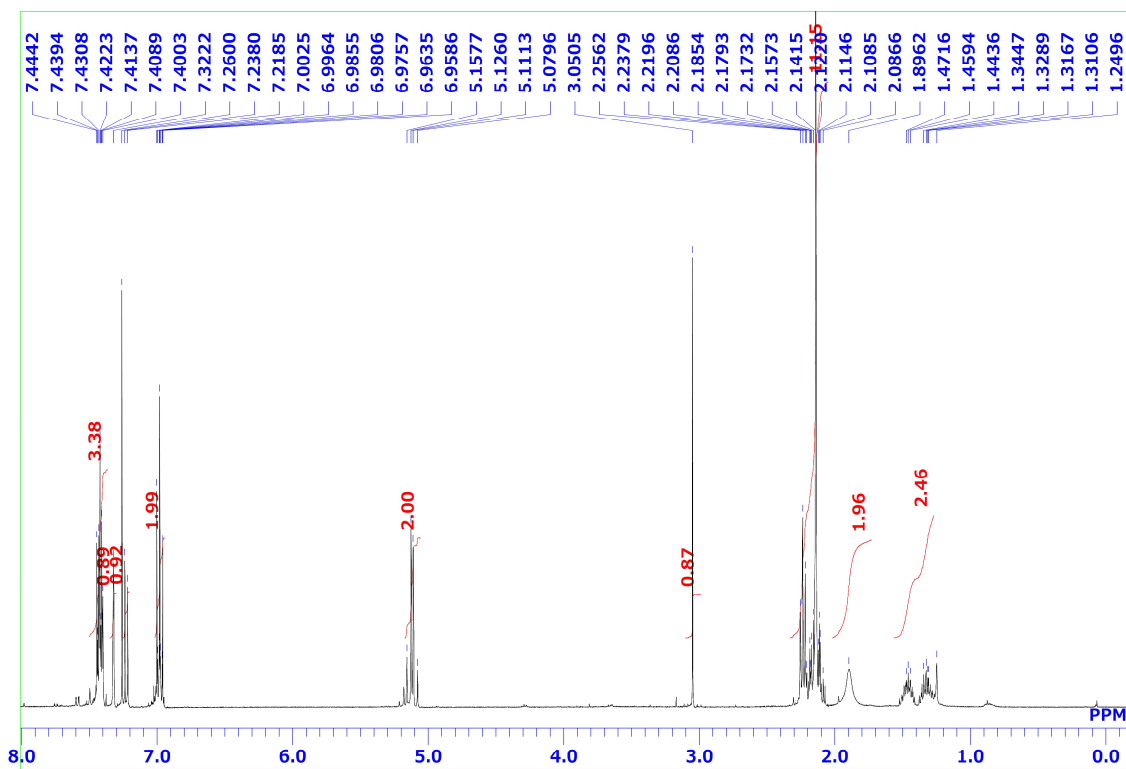
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## Supplemental Figure 1



Supplemental Figure 1. Synthesis of Alk-S-Cit from S-Cit.

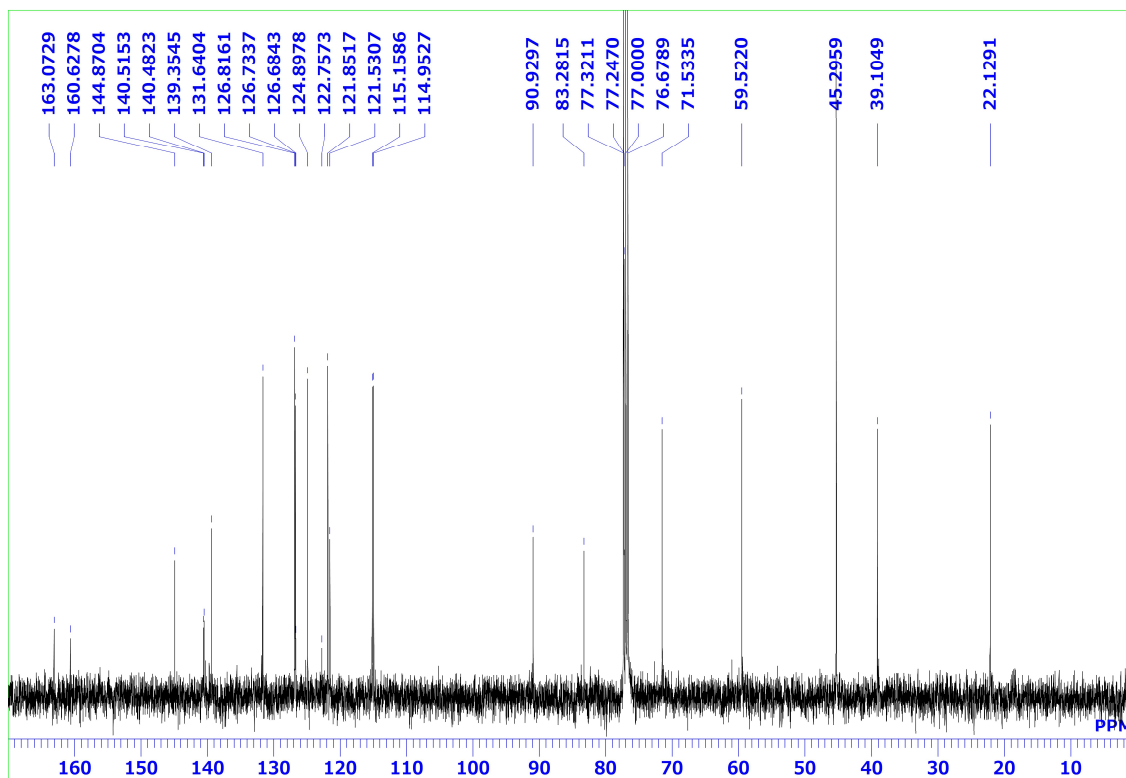
## Supplemental Figure 2



### Supplemental Figure 2. <sup>1</sup>H-NMR spectrum of Alk-S-Cit.

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.45-7.40 (3H, m), 7.32 (1H, s), 7.23 (1H, d, *J* = 7.8 Hz), 6.98 (2H, t, *J* = 8.8 Hz), 5.12 (2H, AB-q, *J* = 12.7 Hz), 3.05 (1H, s), 2.24 (2H, t, *J* = 7.3 Hz), 2.21-2.05 (2H, m), 2.14 (6H, s), 1.51-1.25 (2H, m).

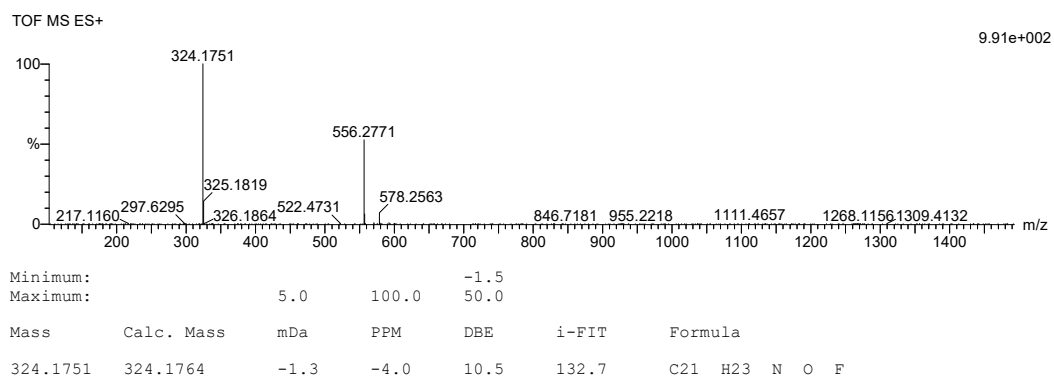
### Supplemental Figure 3



**Supplemental Figure 3.  $^{13}\text{C}$  NMR spectrum of Alk-S-Cit.**

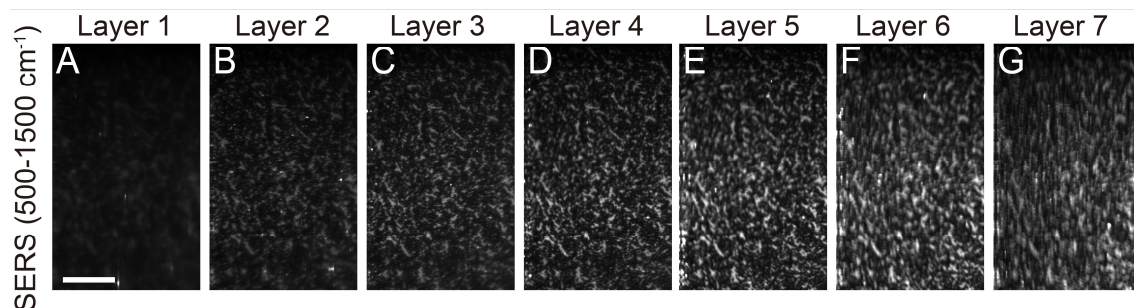
$^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 161.9 (d,  $^1J_{\text{C-F}} = 245$  Hz), 144.9, 140.5 (d,  $^4J_{\text{C-F}} = 3.3$  Hz), 139.4, 131.6, 126.8 (2C) (d,  $^3J_{\text{C-F}} = 8.2$  Hz), 124.9, 121.9, 121.5, 115.1 (2C) (d,  $^2J_{\text{C-F}} = 20.6$  Hz), 90.9, 83.3, 77.2, 71.5, 59.5, 45.3 (2C), 39.1, 22.1.

## Supplemental Figure 4



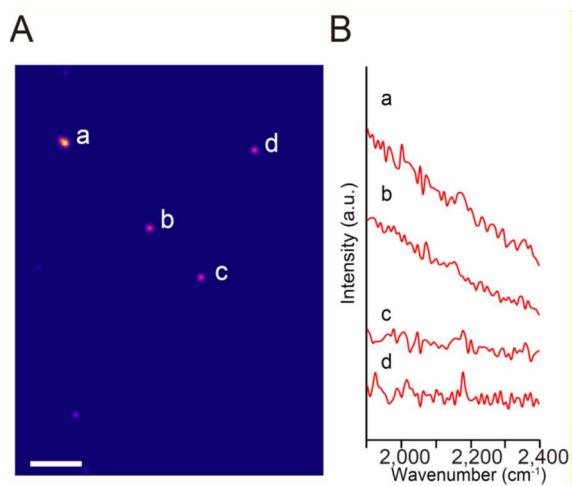
**Supplemental Figure 4. HR-ESI-TOF-MS spectrum of Alk-S-Cit measured in positive mode.**

### Supplemental Figure 5



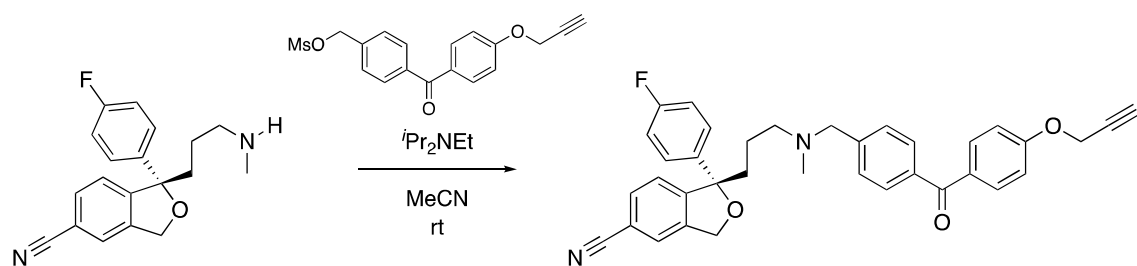
**Supplemental Figure 5. Permeation of silver nanoparticles in the brain tissue. (A-G) Serial images of SERS signals from the fingerprint region (500-1500 cm<sup>-1</sup>) at 2  $\mu$ m intervals of the same field of view. Layers 1 and 2; outside the brain tissue, Layers 3 and 4; brain tissue surface, Layers 5-7; brain tissue. Scale bar is 50  $\mu$ m.**

## Supplemental Figure 6



**Supplemental Figure 6. Alk-S-Cit SERS signals in a brain region with low expression of the SERT. (A) Representative image of SERS signal of Alk-S-Cit on the dorsomedial periaqueductal gray. (B) (a–d) SERS spectra at positions shown in (A). Scale bar is 10  $\mu\text{m}$ .**

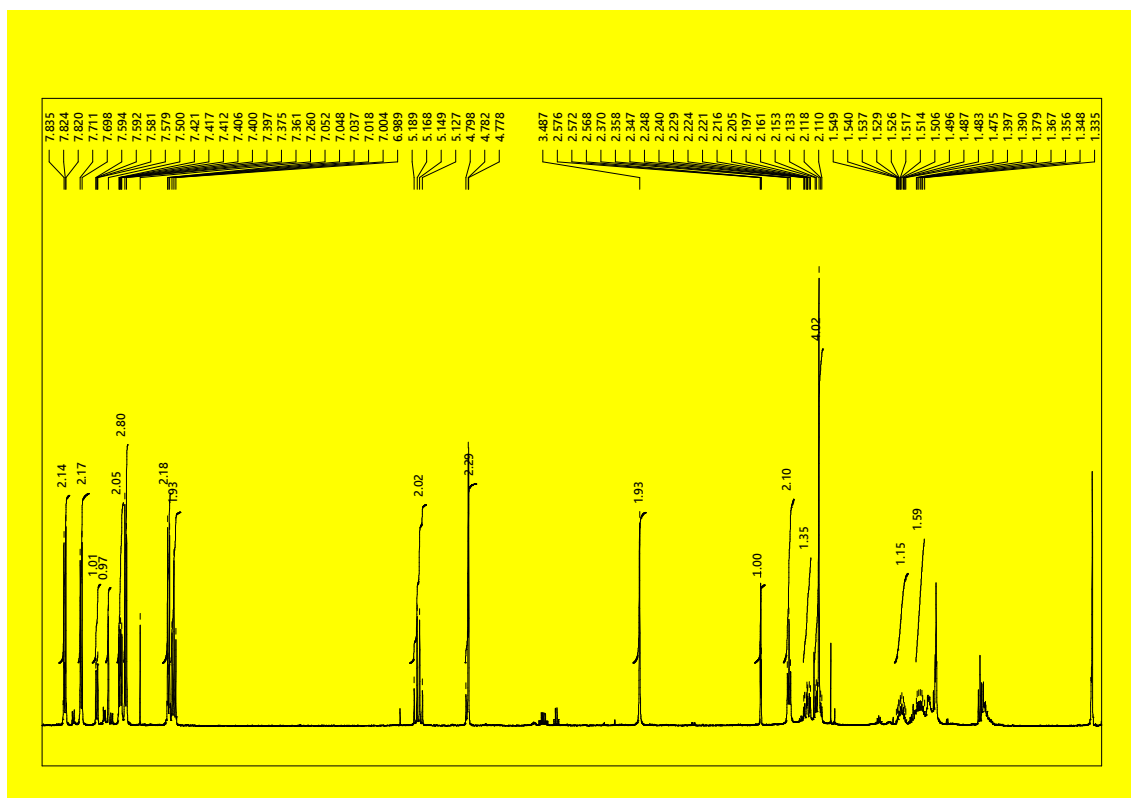
**Supplemental Figure 7**



**Supplemental Figure 7. Synthesis of Benz-Alk-S-Cit.**



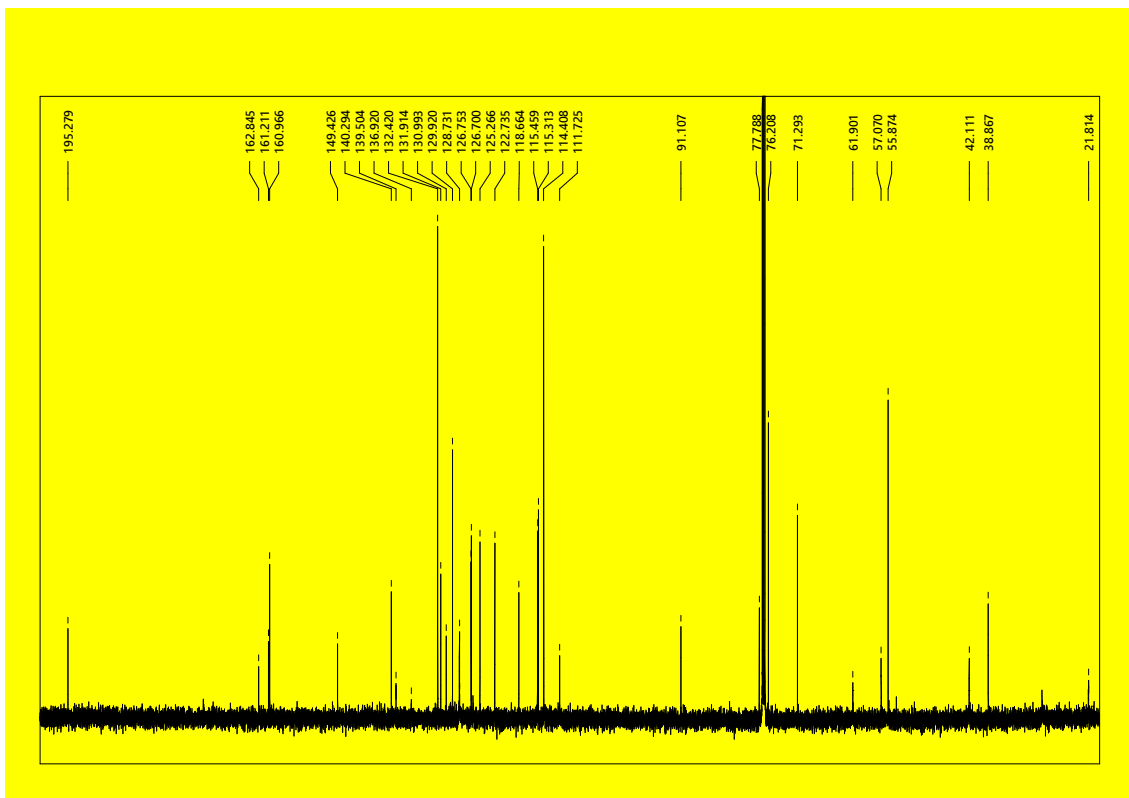
## Supplemental Figure 8



**Supplemental Figure 8.  $^1\text{H}$  NMR spectrum of Benz-Alk-S-Cit.**

$^1\text{H}$ -NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.83 (2H, d,  $J = 9.0$  Hz), 7.71 (2H, d,  $J = 8.4$  Hz), 7.59 (1H, d,  $J = 7.8$  Hz), 7.50 (1H, s), 7.41 (2H, dd,  $J = 9.0, 5.4$  Hz), 7.37 (3H, d,  $J = 7.8$  Hz), 7.05 (2H, d,  $J = 9.0$  Hz), 7.01 (2H, t,  $J = 9.0$  Hz), 5.18 (1H, d,  $J = 13.2$  Hz), 5.14 (1H, d,  $J = 12.6$  Hz), 4.78 (2H, s), 3.50 (2H, br s), 2.57 (1H, t,  $J = 2.4$  Hz), 2.36 (2H, t,  $J = 6.6$  Hz), 2.22 (1H, ddd,  $J = 14.4, 11.4, 4.8$  Hz), 2.16-2.11 (4H, m), 1.55-1.48 (1H, m), 1.40-1.34 (1H, m).

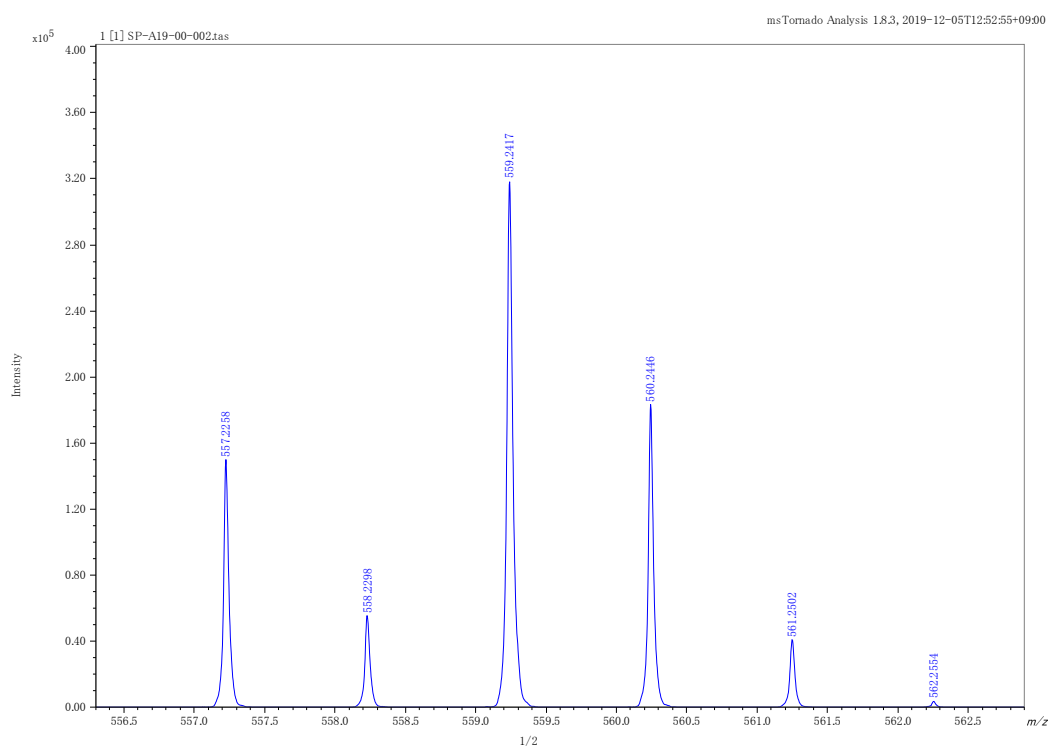
## Supplemental Figure 9



### Supplemental Figure 9. <sup>13</sup>C NMR spectrum of Benz-Alk-S-Cit.

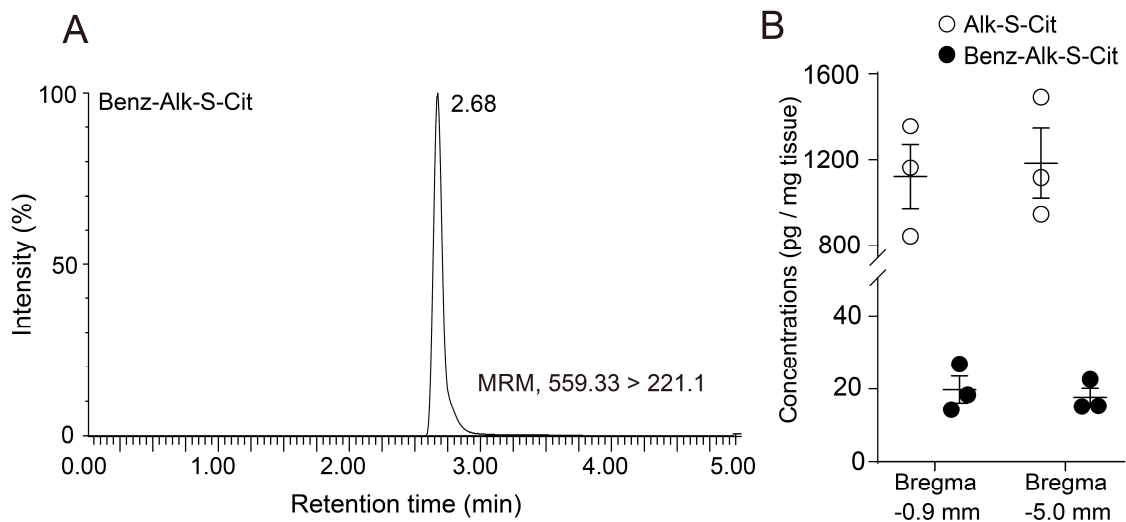
<sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>) δ: 195.3, 162.0 (d, <sup>1</sup>J<sub>C-F</sub> = 245.1118.7 Hz), 161.0, 149.4, 140.3, 139.5, 136.9, 132.4 (2C), 131.9, 131.0, 129.9 (2C), 128.7, 126.7 (d, <sup>3</sup>J<sub>C-F</sub> = 7.95 Hz) (2C), 125.3, 122.7 (2C), 118.7, 115.4 (d, <sup>2</sup>J<sub>C-F</sub> = 21.9 Hz) (2C), 114.4 (2C), 111.7, 91.1, 77.8, 76.2, 71.3, 61.9, 57.1, 55.9 (2C), 42.1, 38.9, 21.8

## Supplemental Figure 10



Supplemental Figure 10. MALDI-TOF-MS spectrum of Benz-Alk-S-Cit.

**Supplemental Figure 11**



**Supplemental Figure 11. In vivo brain transitivity of Benz-Alk-S-Cit.** (A) Mass chromatogram of Benz-Alk-S-Cit in tissue homogenate as determined by LC-MS/MS multiple reaction monitoring (MRM). (B) Brain concentrations of Alk-S-Cit (open circles) and Benz-Alk-S-Cit (filled circles). Samples were prepared according to those in Figure 2.

**Supplementary table 1. MRM transition and parameters for S-citalopram, Alk-S-Cit and**

**Benz-Alk-S-Cit**

	<i>m/z</i> of precursor ion	<i>m/z</i> of product ion	Cone voltage (V)	Collision energy (eV)
S-Citalopram	325.2	262.3	40	20
		108.8	40	24
Alk-S-Cit	324.3	261.0	32	18
		108.7	32	28
Benz-Alk-S-Cit	559.33	221.1	58	34
		181.9	58	50