Supplementary Information

Synthesis and in vivo characterization of $^{18}$F-labeled difluoroboron-curcumin derivative for β-amyloid plaque imaging

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$^1$H and $^{19}$F NMR spectra of ligands

Fig. S1. $^1$H NMR spectrum of ligand 1

Fig. S2. $^{19}$F NMR spectrum of ligand 1
Fig. S3. $^1$H NMR spectrum of ligand 2

Fig. S4. $^{19}$F NMR spectrum of ligand 2
Fig. S5. $^1$H NMR spectrum of ligand 3

Fig. S6. $^{19}$F NMR spectrum of ligand 3
Fig. S7. $^1$H NMR spectrum of ligand 4

Fig. S8. $^{19}$F NMR spectrum of ligand 4
HPLC chromatograms of non-radioactive ligands

HPLC column: YMC-Pack C18, 4.6 x 250 mm, 5 µm
HPLC solvents: 30:70 TFA (0.1%, aq)-CH₃CN; flow rate: 1 mL/min
Detection: UV (254 nm) detector

**Fig. S9.** HPLC chromatogram of ligand 1
Retention time: 7.474 min
Area % of product: 99.974%

**Fig. S10.** HPLC chromatogram of ligand 2
Retention time: 10.208 min
Area % of product: 99.923%
**Fig. S11.** HPLC chromatogram of ligand 3  
Retention time: 8.958 min  
Area % of product: 99.729%

**Fig. S12.** HPLC chromatogram of ligand 4  
Retention time: 7.037 min  
Area % of product: 99.968%
HPLC chromatograms of radioligand

HPLC column: YMC-Pack C18, 4.6 x 250 mm, 5 µm
HPLC solvents: 25:75 TFA (0.1%, aq)-CH₃CN; flow rate: 1 mL/min
Detection: radioactivity detector (red) and UV (254 nm) detector (blue)

**Fig. S13.** HPLC chromatogram of ligand [¹⁸F]2
Retention time: 7.648 min
Area % of product: 100% (radiochemical purity)

**Fig. S14.** HPLC chromatogram of a mixture of [¹⁸F]2 and 2
Retention time: 7.605 min
Area % of product: 100% (radiochemical purity)
**Fig. S15.** Excitation and emission spectra of 2 (2.5 µM) in methanol

**Fig. S16.** Saturation binding curve of ligand 2 to Aβ aggregates
Table S1. Proposed polar product standards

<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
<th>TLC Rf*</th>
<th>TLC Rf**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polar radioactive products (brain)</td>
<td>–</td>
<td>0</td>
<td>0.59 (major), 0.80, 0.95</td>
</tr>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td>2-Fluoroethanol (Merck)</td>
<td>0.49</td>
<td>0.97</td>
</tr>
<tr>
<td><img src="image2.png" alt="Image" /></td>
<td>2-(2-Fluoroethoxy)ethanol</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><img src="image3.png" alt="Image" /></td>
<td>4-(2-(2-Fluoroethoxy)ethoxy) benzoic acid (S1)</td>
<td>0.25</td>
<td>0.79</td>
</tr>
<tr>
<td><img src="image4.png" alt="Image" /></td>
<td>4-(2-(2-Fluoroethoxy)ethoxy) cinnamic acid (S2)</td>
<td>0.23</td>
<td>0.76</td>
</tr>
</tbody>
</table>

* TLC plates were developed in a 4:1 mixture of ethyl acetate–hexane and visualized using KMnO₄ staining solution.
** TLC plates were developed in a 1:1:0.01 dichloromethane–methanol–triethylamine and visualized using KMnO₄ staining solution.

Synthesis of S1 and S2

4-(2-(2-Fluoroethoxy)ethoxy)benzoic acid (S1). 4-(2-(2-Fluoroethoxy)ethoxy)benzaldehyde (15 mg, 0.07 mmol) was dissolved in 0.3 mL of acetone, and to this solution was added dropwise a solution of KMnO₄ (16.8 mg, 0.11 mmol) in 0.3 mL of water. The reaction mixture was stirred at rt for 20 min. After the mixture was acidified with 0.1 N HCl to pH 2-3, it was extracted with ethyl acetate, washed with water, and then dried over Na₂SO₄. Flash column chromatography (9.5:0.5 dichloromethane-methanol) gave S1 (12 mg, 75%) as a white solid. ¹H NMR ((CD₃)₂CO) δ 10.93 (s,1H), 8.00 (d, J = 9 Hz, 2H), 7.07 (d, J =9 Hz, 2H), 4.62 (dt, J = 48 and 2.5 Hz, 2H), 4.27 (t, J = 4.5 Hz, 2H), 3.90 (t, J = 4.5 Hz, 2H), 3.84 (dt, J = 30 and 2.5 Hz, 2H); ¹⁹F NMR ((CD₃)₂CO) δ -223.50; MS (FAB) m/z 229 (M+H)⁺: HRMS calcd for C₁₁H₁₄FO₄, 229.0876; found, 229.0871.

![Diagram](image5.png)

Figure S1. Synthesis of S1. Reagents and conditions: (a) KMnO₄, acetone-water, rt, 20 min
4-(2-(2-Fluoroethoxy)ethoxy)cinnamic acid (S2). (E)-Methyl 3-(4-(2-(2-
hydroxyethoxy)ethoxy)phenyl)acrylate (1). Methyl 4-hydroxycinnamate (500 mg, 2.81 mmol) and K$_2$CO$_3$ (582 mg, 4.21 mmol) were dissolved in 10 mL of DMF, and the solution was stirred at rt for 15 min. After addition of 2-(2-chloroethoxy)ethanol (0.59 mL, 5.61 mmol), the reaction mixture was stirred at 100 °C overnight. The mixture was extracted with ethyl acetate, washed with water, saturated NH$_4$Cl solution, and then dried over Na$_2$SO$_4$. Flash column chromatography (1:1 hexane-ethyl acetate) gave 1 (600 mg, 80.2%) as a white solid. $^1$H NMR (CDCl$_3$) δ 7.67 (d, J = 16 Hz, 1H), 7.48 (d, J = 9 Hz, 2H), 7.34 (d, J = 16 Hz, 1H), 4.18 (s, 3H), 3.70 (s, t, J = 4 Hz, 2H), 3.69 (t, J = 3.5 Hz, 2H); MS (EI) m/z 266 (M$^+$): HRMS calcd for C$_{14}$H$_{18}$O$_5$, 266.1154; found, 266.1154.

(E)-Methyl 3-(4-(2-(tosyloxy)ethoxy)ethoxy)phenyl)acrylate (2). Compound 1 (300 mg, 1.13 mmol) was dissolved in 2 mL dichloromethane, and to this solution was added p-toluenesulfonyl chloride (333 mg, 1.35 mmol). After addition of triethylamine (0.94 mL, 6.76 mmol) at 0 °C (ice bath), the reaction mixture was stirred at rt overnight. After the reaction was quenched with saturated NH$_4$Cl solution, the reaction mixture was extracted with dichloromethane, washed with water, and then dried over Na$_2$SO$_4$. Flash column chromatography (1:1 hexane-ethyl acetate) gave 2 (430 mg, 90.8%) as a white solid. $^1$H NMR (CDCl$_3$) δ 7.80 (d, J = 8 Hz, 2H), 7.66 (d, J = 16 Hz, 1H), 7.47 (d, J = 9 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 9 Hz, 2H), 6.33 (d, J = 16 Hz, 1H), 4.20 (t, J = 5 Hz, 2H), 4.09 (t, J = 5 Hz, 2H), 3.81 (t, J = 3 Hz, 2H), 3.80 (s, 3H), 3.77 (t, J = 5 Hz, 2H), 2.41 (s, 3H); MS (EI) m/z 420 (M$^+$): HRMS calcd for C$_{21}$H$_{25}$O$_7$S, 420.1243; found, 420.1241.

(E)-Methyl 3-(4-(2-(fluoroethoxy)ethoxy)phenyl)acrylate (3). Compound 2 (98 mg, 0.23 mmol) was dissolved in 5 mL $t$-BuOH, and to this solution was added CsF (106 mg, 0.70 mmol). After the reaction mixture was stirred at 100 °C overnight, it was extracted with ethyl acetate, washed with water, and then dried over Na$_2$SO$_4$. Flash column chromatography (2:1 hexane-ethyl acetate) gave 3 (48 mg, 77.8%) as a white solid. $^1$H NMR (CDCl$_3$) δ 7.66 (d, J = 16 Hz, 1H), 7.48 (d, J = 9 Hz, 2H), 6.93 (d, J = 9 Hz, 2H), 6.33 (d, J = 16 Hz, 1H), 4.65 (dt, J = 47.5 and 4 Hz, 2H), 4.19 (t, J = 5 Hz, 2H), 3.92 (t, J = 5 Hz, 2H), 3.86 (dt, J = 29.5 and 4 Hz, 2H), 3.80 (s, 3H); MS (EI) m/z 268 (M$^+$): HRMS calcd for C$_{13}$H$_{15}$FO$_4$, 268.1111; found, 268.1106.

(E)-3-(4-(2-(Fluoroethoxy)ethoxy)phenyl)acrylic acid (S2). Compound 3 (30 mg, 0.11 mmol) was dissolved in 1 mL MeOH, and to this solution was added dropwise a solution of NaOH (13.4 mg, 0.34 mmol) in 0.5 mL water. The reaction mixture was stirred at rt overnight. After the mixture was acidified with 0.1 N HCl to pH 2-3, it was extracted with ethyl acetate, washed with water, and then dried over Na$_2$SO$_4$. Flash column chromatography (9.5:0.5 dichloromethane-methanol) gave S2 (15 mg, 53.7%) as a white solid. $^1$H NMR ((CD$_3$)$_2$CO) δ 10.60 (s, 1H), 7.65 (d, J = 9 Hz, 3H), 7.03 (d, J = 9 Hz, 2H), 6.41 (d, J = 16 Hz, 1H), 4.62 (dt, J = 47.5 and 3 Hz, 2H), 4.23 (t, J = 5 Hz, 2H), 3.89 (t, J = 3.5 Hz, 2H), 3.83 (dt, J = 30.5 and 3 Hz, 2H); $^{19}$F NMR ((CD$_3$)$_2$CO) δ -223.49; MS (EI) m/z 254 (M$^+$): HRMS calcd for C$_{13}$H$_{15}$FO$_4$, 254.0954; found, 254.0950.
Figure S2. Synthesis of S2. Reagents and conditions: (a) 2-(2-chloroethoxy)ethanol, K$_2$CO$_3$, DMF, 100 °C, overnight; (b) TsCl, Et$_3$N, CH$_2$Cl$_2$, rt, overnight; (c) CsF, t-BuOH, 100 °C, overnight; (d) NaOH, MeOH-water, rt, overnight