

*Supporting Information*

**Aryl *N*-[ $\omega$ -(6-Fluoroindol-1-yl)alkyl]carbamates as Inhibitors of Fatty Acid Amide  
Hydrolase, Monoacylglycerol Lipase, and Butyrylcholinesterase:  
Structure-Activity Relationships and Hydrolytic Stability**

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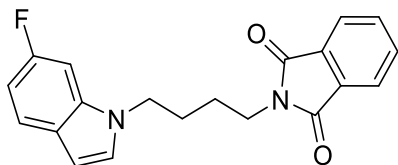
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**Synthesis of target compounds**                      **S2 – S17**

**<sup>1</sup>H NMR spectra of the target compounds**      **S18 – S30**

## Synthesis of target compounds

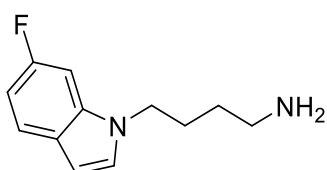
### 2-[4-(6-Fluoroindol-1-yl)butyl]isoindoline-1,3-dione (**9**)



**Figure S1.** Structure of **9**

A solution of 6-fluoroindole (502 mg, 3.72 mmol) in dry DMF (30 mL) was treated with sodium hydride (60 % dispersion in mineral oil) (298 mg, 7.45 mmol) and stirred at room temperature for 30 min until no further formation of hydrogen could be observed. The suspension was added dropwise to a solution of *N*-(4-bromobutyl)phthalimide (3.38 g, 12.0 mmol) and potassium iodide (868 mg, 5.23 mmol) in dry DMF (30 mL) and the resulting mixture was heated at 90 °C for 3.5 h. The reaction mixture was concentrated, diluted with saturated aqueous NaCl solution and exhaustively extracted with ethyl acetate. The combined organic layers were dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated. The crude product was purified by chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 8:2) to give **9** as a solid (239 mg, 19 %). C<sub>20</sub>H<sub>17</sub>FN<sub>2</sub>O<sub>2</sub> (336.4); mp 116 – 117°C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 1.66 – 1.75 (m, 2H), 1.82 – 1.92 (m, 2H), 3.71 (t, *J* = 7.0 Hz, 2H), 4.11 (t, *J* = 7.0 Hz, 2H), 6.45 (dd, *J* = 3.2 Hz und 0.8 Hz, 1H), 6.84 (ddd, *J* = 9.1 Hz, 8.6 Hz and 2.3 Hz, 1H), 7.00 (dd, *J* = 10.0 Hz and 2.6 Hz), 7.07 (d, *J* = 3.1 Hz, 1H), 7.50 (dd, *J* = 8.6 Hz and 5.4 Hz, 1H), 7.69 – 7.74 (m, 2H), 7.81 – 7.87 (m, 2H); HRMS (APCI, direct probe) *m/z* [M+H]<sup>+</sup> calculated: 337.1347, found: 337.1318.

### 4-(6-Fluoroindol-1-yl)butan-1-amine (**10**)

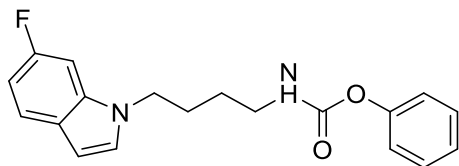


**Figure S2.** Structure of **10**

A solution of compound **9** (231 mg, 0.69 mmol) in ethanol (15 mL) was reacted with hydrazine hydrate (24 % in H<sub>2</sub>O) (1.26 mL) in the same manner as described for the preparation of **13**. Additionally, the reaction product was purified by chromatography on silica gel (ethyl acetate/methanol/triethylamine, 9:1:0.1) to give **10** as an oil (97 mg, 68 %). C<sub>12</sub>H<sub>15</sub>FN<sub>2</sub> (206.3); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 1.41 – 1.51 (m, 2H), 1.79 – 1.91 (m, 2H), 2.71 (t, *J* = 7.1 Hz, 2H), 4.08 (t, *J* = 7.0 Hz, 2H), 6.46 (dd, *J* = 3.1 Hz and 0.7 Hz,

1H), 6.86 (ddd,  $J = 9.5$  Hz, 8.6 Hz and 2.2 Hz, 1H), 7.00 (dd,  $J = 10.0$  Hz and 2.3 Hz, 1H), 7.07 (d,  $J = 3.2$  Hz, 1H), 7.52 (dd,  $J = 8.6$  Hz and 5.5 Hz, 1H); HRMS (APCI, direct probe)  $m/z$   $[M+H]^+$  calculated: 207.1292, found: 207.1284.

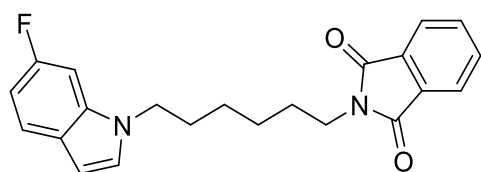
**Phenyl *N*-[4-(6-fluoroindol-1-yl)butyl]carbamate (11)**



**Figure S3.** Structure of **11**

A solution of compound **10** (97 mg, 0.47 mmol) and *N,N*-diisopropylethylamine (DIPEA) (96  $\mu$ L, 72 mg, 0.56 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (10 mL) was treated dropwise at 0 °C with phenyl chloroformate (71  $\mu$ L, 89 mg, 0.57 mmol). After stirring at room temperature for 15 min, the solvent was distilled off and the crude product was purified by chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 8:2) to yield **11** as a solid (83 mg, 54 %).  $\text{C}_{19}\text{H}_{19}\text{FN}_2\text{O}_2$  (326.4); mp 89 – 90 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 1.54 – 1.59 (m, 2H), 1.87 – 1.94 (m, 2H), 3.27 (q,  $J = 6.8$  Hz, 2H), 4.11 (t,  $J = 6.9$  Hz, 2H), 4.98 (t,  $J = 5.1$  Hz, 1H), 6.47 (dd,  $J = 3.1$  Hz and 0.9 Hz, 1H), 6.87 (ddd,  $J = 9.6$  Hz, 8.6 Hz and 2.2 Hz), 7.02 (dd,  $J = 10.0$  Hz and 2.3 Hz, 1H), 7.07 (d,  $J = 3.1$  Hz, 1H), 7.09 – 7.12 (m, 2H), 7.19 (tt,  $J = 7.2$  Hz and 1.2 Hz, 1H), 7.32 – 7.38 (m, 2H), 7.53 (dd,  $J = 8.6$  Hz and 5.4 Hz, 1H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 27.3, 27.6, 40.7, 46.2, 95.8 (d,  $J_{\text{C-F}} = 26.1$  Hz), 101.6, 108.3 (d,  $J_{\text{C-F}} = 24.7$  Hz), 121.7, 121.9 (d,  $J_{\text{C-F}} = 10.2$  Hz), 125.2, 125.5, 128.3 (d,  $J_{\text{C-F}} = 3.7$  Hz), 129.4, 136.1 (d,  $J_{\text{C-F}} = 11.7$  Hz), 151.1, 154.9, 159.9 (d,  $J_{\text{C-F}} = 237.5$  Hz); HRMS (APCI, direct probe)  $m/z$   $[M+H]^+$  calculated: 327.1503, found: 327.1474.

**2-[6-(6-Fluoroindol-1-yl)hexyl]isoindoline-1,3-dione (15)**

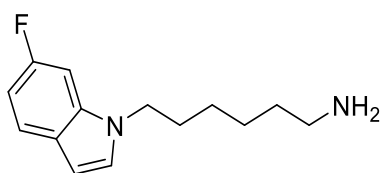


**Figure S4.** Structure of **15**

Sodium hydride (60 % dispersion in mineral oil) (296 mg, 7.40 mmol) was carefully added to a solution of 6-fluoroindole (500 mg, 3.70 mmol) in dry DMF (30 mL). The suspension was stirred at room temperature for 30 min until no further formation of hydrogen could be observed. Subsequently, the mixture was added dropwise to a solution of *N*-(6-bromohexyl)phthalimide (1.49 g, 4.80 mmol) in dry DMF (30 mL) and stirred at 90 °C. After 1.5 h, the mixture was cooled down to ambient temperature and stirred overnight. The

reaction mixture was concentrated, diluted with brine and exhaustively extracted with ethyl acetate. The combined organic layers were dried with anhydrous  $\text{Na}_2\text{SO}_4$ , concentrated, and chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate, 8:2) to yield **15** as an oil (691 mg, 51 %).  $\text{C}_{22}\text{H}_{21}\text{FN}_2\text{O}_2$  (364.4);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 1.32 – 1.41 (m, 4H), 1.61 – 1.71 (m, 2H), 1.78 – 1.86 (m, 2H), 3.66 (t,  $J = 7.1$  Hz, 2H), 4.04 (t,  $J = 7.1$  Hz, 2H), 6.44 (dd,  $J = 3.2$  Hz and 0.8 Hz, 1H), 6.84 (ddd,  $J = 9.6$  Hz, 8.7 Hz and 2.3 Hz, 1H), 6.98 (dd,  $J = 10.0$  Hz and 2.3 Hz, 1H), 7.05 (d,  $J = 3.1$  Hz, 1H), 7.50 (dd,  $J = 8.6$  Hz and 5.4 Hz, 1H), 7.68 – 7.73 (m, 2H), 7.81 – 7.86 (m, 2H); HRMS (APCI, direct probe)  $m/z$   $[\text{M}+\text{H}]^+$  calculated: 365.1660, found: 365.1651.

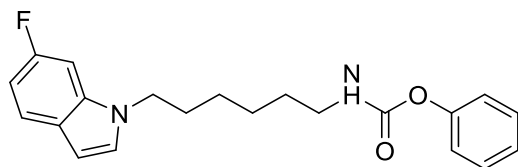
### 6-(6-Fluoroindol-1-yl)hexan-1-amine (16)



**Figure S5.** Structure of **16**

A solution of compound **15** (652 mg, 1.79 mmol) in ethanol (15 mL) was treated with hydrazine hydrate (24 % in  $\text{H}_2\text{O}$ ) (3.3 mL) in the same manner as described for the preparation of **13** to yield **16** as an oil (419 mg, 100%).  $\text{C}_{14}\text{H}_{19}\text{FN}_2$  (234.3).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 1.28 – 1.40 (m, 4H), 1.40 – 1.49 (m, 2H), 1.77 – 1.86 (m, 2H), 2.68 (t,  $J = 6.9$  Hz, 2H), 4.04 (t,  $J = 7.1$  Hz, 2H), 6.45 (dd,  $J = 3.2$  Hz and 0.9 Hz, 1H), 6.86 (ddd,  $J = 9.6$  Hz, 8.7 Hz and 2.3 Hz, 1H), 7.00 (dd,  $J = 10.1$  Hz and 2.3 Hz, 1H), 7.06 (d,  $J = 3.2$  Hz, 1H), 7.51 (dd,  $J = 8.6$  Hz and 5.4 Hz, 1H); HRMS (APCI, direct probe)  $m/z$   $[\text{M}+\text{H}]^+$  calculated: 235.1605, found: 235.1628.

### Phenyl *N*-[6-(6-fluoroindol-1-yl)hexyl]carbamate (17)

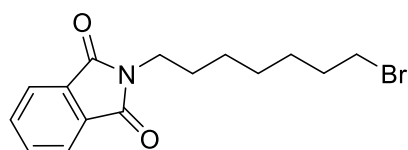


**Figure S6.** Structure of **17**

A solution of compound **16** (121 mg, 0.52 mmol) and DIPEA (104  $\mu\text{L}$ , 79 mg, 0.61 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (10 mL) was treated dropwise at 0 °C with phenyl chloroformate (77  $\mu\text{L}$ , 96 mg, 0.61 mmol). After stirring at room temperature for 2 h, the solvent was distilled off and the crude product was purified by chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 8:2) to yield **17** as a solid (173 mg, 94 %).  $\text{C}_{21}\text{H}_{23}\text{FN}_2\text{O}_2$  (354.4); mp 93 – 94 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 1.33 – 1.41 (m, 4H), 1.51 – 1.58 (m, 2H), 1.81

– 1.87 (m, 2H), 3.23 (q,  $J = 6.8$  Hz, 2H), 4.06 (t,  $J = 7.0$  Hz, 2H), 4.96 (t,  $J = 5.1$  Hz, 1H), 6.46 (dd,  $J = 3.2$  Hz and 0.6 Hz, 1H), 6.87 (ddd,  $J = 9.5$  Hz, 8.7 Hz and 2.3 Hz, 1H), 7.00 (dd,  $J = 10.0$  Hz and 2.3 Hz, 1H), 7.06 (d,  $J = 3.2$  Hz, 1H), 7.10 – 7.13 (m, 2H), 7.19 (tt,  $J = 7.3$  Hz and 1.1 Hz, 1H), 7.32 – 7.38 (m, 2H), 7.52 (dd,  $J = 8.6$  Hz and 5.4 Hz, 1H);  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 26.5, 26.8, 29.9, 30.1, 41.2, 46.6, 95.8 (d,  $J_{\text{C-F}} = 26.4$  Hz), 101.4, 108.1 (d,  $J_{\text{C-F}} = 24.7$  Hz), 121.7, 121.8 (d,  $J_{\text{C-F}} = 10.1$  Hz), 125.1, 125.4, 128.3 (d,  $J_{\text{C-F}} = 3.6$  Hz), 129.4, 136.1 (d,  $J_{\text{C-F}} = 12.0$  Hz), 151.2, 154.7, 159.9 (d,  $J_{\text{C-F}} = 237.0$  Hz); HRMS (APCI, direct probe)  $m/z$   $[\text{M}+\text{H}]^+$  calculated: 355.1816, found: 355.1807.

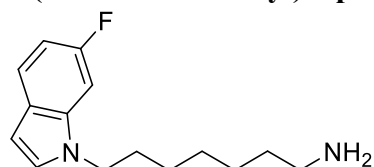
### 2-(7-Bromoheptyl)isoindoline-1,3-dione (**18**)



**Figure S7.** Structure of **18**

A mixture of potassium phthalimide (2.25 g, 12.1 mmol), 1,7-dibromoheptane (5.00 g, 19.4 mmol), and dry DMF (50 mL) was stirred at 100°C for 8 h. After cooling and dilution with water and brine, the reaction mixture was exhaustively extracted with diethyl ether. The combined organic phases were dried with anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated. The residue was chromatographed on silica gel (cyclohexane/ethyl acetate, 9:1) to give **18** as an oil (1.75 g, 45%).  $\text{C}_{15}\text{H}_{18}\text{BrNO}_2$  (324.2);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 1.32 – 1.39 (m, 4H), 1.39 – 1.46 (m, 2H), 1.63 – 1.72 (m, 2H), 1.80 – 1.88 (m, 2H), 3.39 (t,  $J = 6.8$  Hz, 2H), 3.65 – 3.70 (m, 2H), 7.70 (dd,  $J = 3.0$  Hz and 5.5 Hz, 2H), 7.84 (dd,  $J = 3.1$  Hz and 5.4 Hz, 2H); HRMS (APCI, direct probe)  $m/z$   $[\text{M}+\text{H}]^+$  calculated: 324.0594, found: 324.0603.

### 7-(6-Fluoroindol-1-yl)heptan-1-amine (**20**)

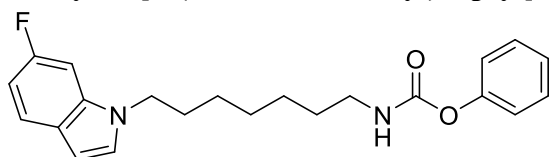


**Figure S8.** Structure of **20**

6-Fluoroindol (0.73 g, 5.40 mmol) was reacted with *N*-(7-bromoheptyl)phthalimide (1.74 g, 5.37 mmol) in a manner similar to that described for the synthesis of **15**. To a solution of obtained 2-[7-(6-fluoroindol-1-yl)heptyl]isoindoline-1,3-dione (**19**) (1.9 g) in ethanol (50 mL) was added hydrazine hydrate (24% in  $\text{H}_2\text{O}$ ) (8.9 mL). The mixture was heated under reflux for 3 h. After cooling to room temperature, the pH was adjusted to 10-12 with dilute aqueous NaOH. Then, the mixture was diluted with brine and extracted exhaustively with dichloromethane. The combined organic layers were dried with anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate, then

methanol) to yield **20** as an oil (0.64 g, 48%). C<sub>15</sub>H<sub>21</sub>FN<sub>2</sub> (248.4); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 1.22 – 1.34 (m, 4H), 1.34 – 1.43 (m, 2H), 1.74 – 1.87 (m, 2H), 1.90 – 2.07 (m, 2H), 2.64 (t, *J* = 7.1 Hz, 2H), 4.00 – 4.06 (m, 2H), 6.43 – 6.47 (m, 1H), 6.82 – 6.90 (m, 1H), 6.99 (dd, *J* = 2.5 Hz and 10.2 Hz, 1H), 7.05 (dd, *J* = 0.9 Hz and 3.2 Hz, 1H), 7.45 – 7.56 (m, 1H); HRMS (APCI, direct probe) *m/z* [M+H]<sup>+</sup> calculated: 249.1762, found: 249.1787.

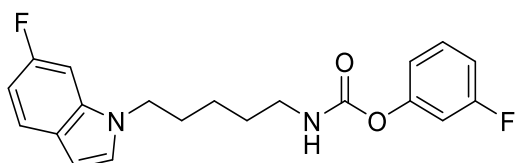
### Phenyl *N*-[7-(6-fluoroindol-1-yl)heptyl]carbamate (**21**)



**Figure S9.** Structure of **21**

To a solution of **20** (0.64 g, 2.58 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added DIPEA (170 μL, 0.99 mmol) followed by phenyl chloroformate (125 μL, 0.99 mmol). After stirring at room temperature for 4 h, silica gel was added to the mixture and the solvent was distilled off. The residue was placed on a silica gel column and eluted with cyclohexane/ethyl acetate (9:1) to give **21** as a solid (234 mg, 64%). C<sub>22</sub>H<sub>25</sub>FN<sub>2</sub>O<sub>2</sub> (368.5); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 1.31 – 1.38 (m, 6H), 1.51 – 1.57 (m, 2H), 1.78 – 1.87 (m, 2H), 3.19 – 3.28 (m, 2H), 4.05 (t, *J* = 7.1 Hz, 2H), 4.98 (s, 1H), 6.46 (dd, *J* = 0.9 Hz and 3.2 Hz, 1H), 6.82 – 6.90 (m, 1H), 6.97 – 7.03 (m, 1H), 7.07 (d, *J* = 3.2 Hz, 1H), 7.09 – 7.14 (m, 2H), 7.16 – 7.22 (m, 1H), 7.31 – 7.39 (m, 2H), 7.50 – 7.55 (m, 1H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ (ppm) 26.5, 26.8, 28.8, 29.7, 30.0, 41.1, 46.5, 95.7 (d, *J*<sub>C-F</sub> = 26.1 Hz), 101.1, 107.9 (d, *J*<sub>C-F</sub> = 24.7 Hz), 121.5, 121.6, 121.6, 124.9, 125.2, 128.2 (d, *J*<sub>C-F</sub> = 3.6 Hz), 129.2, 136.0 (d, *J*<sub>C-F</sub> = 12.1 Hz), 151.0, 154.6, 159.7 (d, *J*<sub>C-F</sub> = 236.9 Hz); HRMS (APCI, direct probe) *m/z* [M+H]<sup>+</sup> calculated: 369.1973, found: 369.1990.

### 3-Fluorophenyl *N*-[5-(6-fluoroindol-1-yl)pentyl]carbamate (**27**)

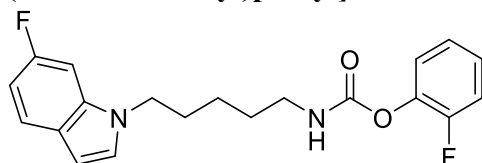


**Figure S10.** Structure of **27**

A solution of **13** (120 mg, 0.54 mmol) in dry THF (10 mL) was treated with DIPEA (93 μL, 70 mg, 0.54 mmol) followed by a solution of 3-fluorophenyl chloroformate (95 mg, 119 mg, 0.54 mmol) in dry THF (20 mL). After stirring the mixture at room temperature for 3 h, silica gel was added and the solvent distilled off. The residue was loaded on the top of a silica gel column. Elution with cyclohexane/ethyl acetate (19:1 to 9:1) gave **27**, which was further purified by preparative RP18 chromatography using acetonitrile/water (80:20) as eluent to give **27** as an oil (9 mg, 5%). C<sub>20</sub>H<sub>20</sub>F<sub>2</sub>N<sub>2</sub>O<sub>2</sub> (358.4); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.33 –

1.42 (m, 2H), 1.55 – 1.64 (m, 2H), 1.84 – 1.92 (m, 2H), 3.20 – 3.27 (m, 2H), 4.08 (t,  $J = 6.9$  Hz, 2H), 4.98 (s, 1H), 6.47 (d,  $J = 3.2$  Hz, 1H), 6.84 – 6.93 (m, 4H), 6.98 – 7.02 (m, 1H), 7.07 (d,  $J = 3.2$  Hz, 1H), 7.26 – 7.33 (m, 1H), 7.50 – 7.55 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  24.0, 29.5, 29.6, 41.0, 46.3, 95.7 (d,  $J_{\text{C-F}} = 26.3$  Hz) 101.3, 108.0 (d,  $J_{\text{C-F}} = 24.5$  Hz), 109.6 (d,  $J_{\text{C-F}} = 24.4$  Hz), 112.2 (d,  $J_{\text{C-F}} = 21.0$  Hz), 117.2 (d,  $J_{\text{C-F}} = 3.5$  Hz), 121.7 (d,  $J_{\text{C-F}} = 10.1$  Hz), 125.0, 128.11 (d,  $J_{\text{C-F}} = 3.7$  Hz), 130.0 (d,  $J_{\text{C-F}} = 9.4$  Hz), 135.9 (d,  $J_{\text{C-F}} = 12.0$  Hz), 154.0, 159.7 (d,  $J_{\text{C-F}} = 237.2$  Hz), 162.8 (d,  $J_{\text{C-F}} = 246.9$  Hz); HRMS (APCI, direct probe)  $m/z$   $[\text{M}+\text{H}]^+$  calculated: 359.1566, found: 359.1580.

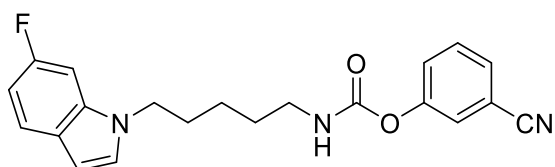
### 2-Fluorophenyl *N*-[5-(6-fluorindol-1-yl)pentyl]carbamate (**28**)



**Figure S11.** Structure of **28**

A solution of **13** (120 mg, 0.54 mmol) in dry THF (10 mL) was treated with DIPEA (93  $\mu\text{L}$ , 70 mg, 0.54 mmol) followed by a solution of 2-fluorophenyl chloroformate (95 mg, 0.54 mmol) in dry THF (15 mL). After stirring the mixture at room temperature for 1 h, silica gel was added and the solvent distilled off. The residue was loaded on the top of a silica gel column. Elution with cyclohexane/ethyl acetate (19:1 to 9:1) gave **28**, which was further purified by preparative RP18 chromatography using acetonitrile/water (80:20) as eluent to give **28** as an oil (45 mg, 23%).  $\text{C}_{20}\text{H}_{20}\text{F}_2\text{N}_2\text{O}_2$  (358.4);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.33 – 1.42 (m, 2H), 1.53 – 1.63 (m, 2H), 1.82 – 1.91 (m, 2H), 3.20 – 3.27 (m, 2H), 4.06 (t,  $J = 7.0$  Hz, 2H), 5.13 (s, 1H), 6.47 (d,  $J = 3.1$  Hz, 1H), 6.84 – 6.91 (m, 1H), 6.99 – 7.03 (m, 1H), 7.07 (d,  $J = 3.1$  Hz, 1H), 7.08 – 7.21 (m, 4H), 7.50 – 7.56 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  24.0, 29.4, 29.6, 41.1, 46.3, 95.7 (d,  $J_{\text{C-F}} = 26.2$  Hz), 101.3, 108.0 (d,  $J_{\text{C-F}} = 24.7$  Hz), 116.6 (d,  $J_{\text{C-F}} = 18.6$  Hz), 121.6 (d,  $J_{\text{C-F}} = 10.1$  Hz), 124.1, 124.3 (d,  $J_{\text{C-F}} = 3.8$  Hz), 125.0, 126.6 (d,  $J_{\text{C-F}} = 7.2$  Hz), 128.2, 135.9 (d,  $J_{\text{C-F}} = 12.0$  Hz), 138.5 (d,  $J_{\text{C-F}} = 12.2$  Hz), 155.9 (d,  $J_{\text{C-F}} = 248.6$  Hz), 153.7, 159.7 (d,  $J_{\text{C-F}} = 239.9$  Hz); HRMS (APCI, direct probe)  $m/z$   $[\text{M}+\text{H}]^+$  calculated: 359.1566, found: 359.1571.

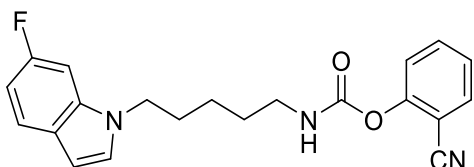
### 3-Cyanophenyl *N*-[5-(6-fluorindol-1-yl)pentyl]carbamate (**30**)



**Figure S12.** Structure of **30**

A solution of triphosgene (148 mg, 0.50 mmol) in dry THF (5 mL) was added at 0 °C to a solution of 3-hydroxybenzonitrile (167 mg, 1.40 mmol) and DIPEA (255  $\mu$ L, 193 mg, 1.49 mmol) in dry THF (10 mL). The mixture was stirred for 2 h at the same temperature. After warming up to ambient temperature, a solution of compound **13** (112 mg, 0.51 mmol) and DIPEA (85  $\mu$ L, 64mg, 0.50 mmol) in dry THF (5 mL) was slowly added and stirring was continued at room temperature for 2.5 h. The reaction mixture was concentrated and directly purified by chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 7:3). Further purification was carried out by preparative RP-HPLC (acetonitrile/H<sub>2</sub>O/formic acid, 70:30:0.1) to yield compound **30** as a solid (112 mg, 61 %). C<sub>21</sub>H<sub>20</sub>FN<sub>3</sub>O<sub>2</sub> (365.4); mp 79 – 80 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) 1.23 – 1.31 (m, 2H), 1.44 – 1.51 (m, 2H), 1.70 – 1.78 (m, 2H), 3.03 (q, *J* = 6.6 Hz, 2H), 4.12 (t, *J* = 7.1 Hz, 2H), 6.42 (dd, *J* = 3.2 Hz and 0.9 Hz, 1H), 6.84 (ddd, *J* = 9.8 Hz, 8.6 Hz and 2.3 Hz, 1H), 7.33 – 7.37 (m, 2H), 7.43 (ddd, *J* = 8.3 Hz, 2.4 Hz and 1.1 Hz, 1H), 7.51 (dd, *J* = 8.6 Hz and 5.5 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.60 – 7.62 (m, 1H), 7.67 (dt, *J* = 7.8 Hz and 1.2 Hz, 1H), 7.88 (t, *J* = 5.7 Hz, 1H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) 23.4, 28.7, 29.3, 40.3, 45.5, 96.1 (d, *J*<sub>C-F</sub> = 26.3 Hz), 100.7, 107.2 (d, *J*<sub>C-F</sub> = 24.4 Hz), 112.0, 118.2, 121.3 (d, *J*<sub>C-F</sub> = 10.3 Hz), 124.7, 125.4, 127.2, 128.9, 129.2 (d, *J*<sub>C-F</sub> = 3.5 Hz), 130.9, 135.7 (d, *J*<sub>C-F</sub> = 12.3 Hz), 151.2, 153.6, 158.8 (d, *J*<sub>C-F</sub> = 234.0 Hz); IR (neat):  $\tilde{\nu}$  [cm<sup>-1</sup>] 2234 (cyano group); HRMS (ESI) *m/z* [M+H]<sup>+</sup> calculated: 366.1612, found: 366.1612.

### 2-Cyanophenyl *N*-[5-(6-fluoroindol-1-yl)pentyl]carbamate (**31**)

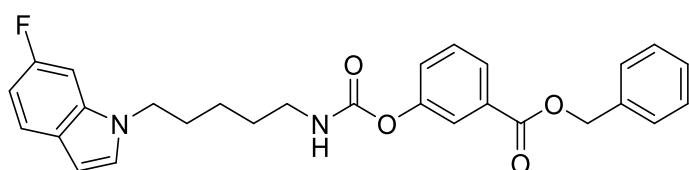


**Figure S13.** Structure of **31**

A solution of triphosgene (145 mg, 0.49 mmol) in dry THF (5 mL) was added at 0 °C to a solution of 2-hydroxybenzonitrile (169 mg, 1.42 mmol) and DIPEA (255  $\mu$ L, 193 mg, 1.49 mmol) in dry THF (10 mL). The mixture was stirred for 2 h at the same temperature. After warming up to ambient temperature, a solution of compound **13** (109 mg, 0.49 mmol) and DIPEA (85  $\mu$ L, 64 mg, 0.50 mmol) in dry THF (5 mL) was slowly added and stirring was continued at room temperature for 2.5 h. The reaction mixture was concentrated and directly purified by chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 8:2). Further purification was carried out by preparative RP-HPLC (acetonitrile/H<sub>2</sub>O/formic acid, 70:30:0.1) to yield compound **31** as a solid (87 mg, 49 %). C<sub>21</sub>H<sub>20</sub>FN<sub>3</sub>O<sub>2</sub> (365.4); mp 107 – 108 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) 1.27 – 1.35 (m, 2H), 1.48 – 1.56 (m, 2H), 1.71 – 1.80 (m, 2H), 3.07 (td, *J* = 6.9 Hz and 5.7 Hz, 2H), 4.13 (t, *J* = 7.2 Hz, 2H), 6.43 (dd,

$J = 3.1$  Hz and  $0.9$  Hz, 1H), 6.85 (ddd,  $J = 9.8$  Hz,  $8.6$  Hz and  $2.4$  Hz, 1H), 7.31 – 7.38 (m, 3H), 7.41 (td,  $J = 7.6$  Hz and  $1.1$  Hz, 1H), 7.52 (dd,  $J = 8.6$  Hz and  $5.6$  Hz, 1H), 7.73 (ddd,  $J = 8.3$  Hz,  $7.5$  Hz and  $1.7$  Hz, 1H), 7.87 (dd,  $J = 7.7$  Hz and  $1.7$  Hz, 1H), 8.10 (t,  $J = 5.7$  Hz, 1H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) 23.3, 28.6, 29.3, 40.4, 45.5, 96.1 (d,  $J_{\text{C-F}} = 26.2$  Hz), 100.7, 106.36, 107.3 (d,  $J_{\text{C-F}} = 24.7$  Hz), 115.5, 121.3 (d,  $J_{\text{C-F}} = 10.2$  Hz), 123.6, 124.7, 126.0, 129.2 (d,  $J_{\text{C-F}} = 3.5$  Hz), 133.3, 134.7, 135.6 (d,  $J_{\text{C-F}} = 12.5$  Hz), 152.6, 153.1, 158.8 (d,  $J_{\text{C-F}} = 234.3$  Hz); IR (neat):  $\tilde{\nu}$  [ $\text{cm}^{-1}$ ] 2232 (cyano group); HRMS (ESI)  $m/z$   $[\text{M}+\text{H}]^+$  calculated: 366.1612, found: 366.1599.

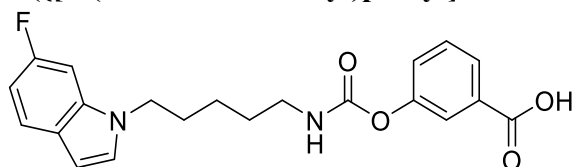
### Benzyl 3-({[5-(6-fluoroindol-1-yl)pentyl]carbamoyl}oxy)benzoate (34)



**Figure S14.** Structure of **34**

A solution of triphosgene (388 mg, 1.31 mmol) in dry THF (10 mL) was added at  $0\text{ }^{\circ}\text{C}$  to a solution of benzyl 3-hydroxybenzoate (589 mg, 2.58 mmol) and DIPEA (442  $\mu\text{L}$ , 334 mg, 2.58 mmol) in dry THF (10 mL). The mixture was stirred for 3 h at the same temperature. After warming up to ambient temperature, a solution of compound **13** (286 mg, 1.30 mmol) and DIPEA (221  $\mu\text{L}$ , 171 mg, 1.32 mmol) in dry THF (5 mL) was slowly added and stirring was continued at room temperature overnight. After work-up and purification as described for compound **32**, the product **34** was yielded as an oil (347 mg, 56 %).  $\text{C}_{28}\text{H}_{27}\text{FN}_2\text{O}_4$  (474.5);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 1.33 – 1.43 (m, 2H), 1.55 – 1.64 (m, 2H), 1.83 – 1.92 (m, 2H), 3.24 (q,  $J = 6.8$  Hz, 2H), 4.07 (t,  $J = 7.0$  Hz, 2H), 4.99 (t,  $J = 6.1$  Hz, 1H), 5.36 (s, 2H), 6.46 (dd,  $J = 3.1$  Hz and  $0.9$  Hz, 1H), 6.86 (ddd,  $J = 9.6$  Hz,  $8.6$  Hz and  $2.3$  Hz, 1H), 7.00 (dd,  $J = 10.0$  Hz and  $2.3$  Hz, 1H), 7.06 (d,  $J = 3.2$  Hz, 1H), 7.31 – 7.46 (m, 7H), 7.52 (dd,  $J = 8.6$  Hz and  $5.4$  Hz, 1H), 7.80 (dd,  $J = 2.4$  Hz and  $1.6$  Hz, 1H), 7.92 (dt,  $J = 7.7$  Hz and  $1.4$  Hz, 1H); HRMS (APCI, direct probe)  $m/z$   $[\text{M}+\text{H}]^+$  calculated: 475.2028, found: 475.2041.

### 3-({[5-(6-Fluoroindol-1-yl)pentyl]carbamoyl}oxy)benzoic acid (35)

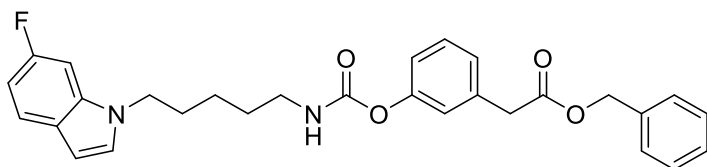


**Figure S15.** Structure of **35**

A catalytic amount of palladium (10 %) on activated charcoal (28 mg) was added to a solution of compound **34** (284 mg, 0.60 mmol) in THF/methanol (1:1) (8 mL). The

suspension was stirred vigorously under a balloon filled with hydrogen at room temperature for 4 h. After addition of Celite 545, the catalyst was filtered off and the filtrate was evaporated. The crude product was purified by silica gel chromatography (cyclohexane to cyclohexane/ethyl acetate/formic acid, 8:2:0.1) to yield **35** (189 mg, 82 %) as a solid.  $C_{21}H_{21}FN_2O_4$  (384.4); mp 133 – 134 °C.  $^1H$  NMR (600 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) 1.24 – 1.32 (m, 2H), 1.47 – 1.53 (m, 2H), 1.73 – 1.79 (m, 2H), 3.04 (td,  $J = 7.0$  Hz and 5.8 Hz, 2H), 4.14 (t,  $J = 7.1$  Hz, 2H), 6.44 (dd,  $J = 3.1$  Hz and 0.9 Hz, 1H), 6.86 (ddd,  $J = 9.7$  Hz, 8.6 Hz and 2.3 Hz, 1H), 7.32 – 7.37 (m, 3H), 7.48 – 7.53 (m, 2H), 7.59 (dd,  $J = 2.5$  Hz and 1.6 Hz, 1H), 7.77 (dt,  $J = 7.7$  Hz and 1.3 Hz, 1H), 7.82 (t,  $J = 5.8$  Hz, 1H), 13.15 (s, 1H);  $^{13}C$  NMR (151 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) 23.4, 28.7, 29.3, 40.3, 45.5, 96.2 (d,  $J_{C-F} = 26.3$  Hz), 100.7, 107.3 (d,  $J_{C-F} = 24.6$  Hz), 121.3 (d,  $J_{C-F} = 10.3$  Hz), 122.3, 124.7, 125.7, 126.2, 129.3 (d,  $J_{C-F} = 3.6$  Hz), 129.6, 132.1, 135.66 (d,  $J_{C-F} = 12.6$  Hz), 151.1, 154.0, 158.8 (d,  $J_{C-F} = 234.1$  Hz), 166.6; HRMS (APCI, direct probe)  $m/z$   $[M+H]^+$  calculated: 385.1558, found: 385.1579.

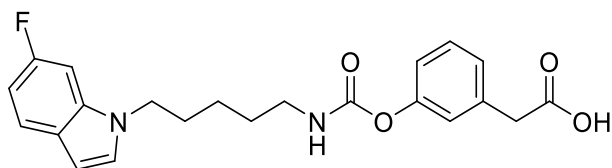
#### Benzyl 2-[3-({5-(6-fluoroindol-1-yl)pentyl}carbamoyl)oxy)phenyl]acetate (**40**)



**Figure S16.** Structure of **40**

A solution of triphosgene (269 mg, 0.91 mmol) in dry THF (10 mL) was added at 0 °C to a solution of benzyl (3-hydroxyphenyl)acetate (438 mg, 1.81 mmol) and DIPEA (306  $\mu$ L, 231 mg, 1.79 mmol) in dry THF (10 mL). The mixture was stirred for 3 h at the same temperature. After warming up to ambient temperature, a solution of compound **13** (202 mg, 0.92 mmol) and DIPEA (153  $\mu$ L, 116 mg, 0.90 mmol) in dry THF (5 mL) was slowly added and stirring was continued at room temperature overnight. After work-up and purification as described for compound **32**, the product **40** was yielded as an oil (289 mg, 65 %).  $C_{29}H_{29}FN_2O_4$  (488.6);  $^1H$  NMR (600 MHz,  $CDCl_3$ ):  $\delta$  (ppm) 1.35 – 1.40 (m, 2H), 1.56 – 1.62 (m, 2H), 1.84 – 1.90 (m, 2H), 3.23 (q,  $J = 6.7$  Hz, 2H), 3.67 (s, 2H), 4.07 (t,  $J = 7.0$  Hz, 2H), 4.98 (t,  $J = 6.0$  Hz, 1H), 5.13 (s, 2H), 6.47 (dd,  $J = 3.1$  Hz and 0.8 Hz, 1H), 6.87 (ddd,  $J = 9.6$  Hz, 8.6 Hz and 2.3 Hz, 1H), 7.01 (dd,  $J = 10.0$  Hz and 2.4 Hz, 1H), 7.04 (ddd,  $J = 8.1$  Hz, 2.4 Hz and 1.0 Hz, 1H), 7.06 – 7.08 (m, 2H), 7.12 (dt,  $J = 7.6$  Hz and 1.3 Hz, 1H), 7.29 – 7.37 (m, 6H), 7.52 (dd,  $J = 8.6$  Hz and 5.4 Hz, 1H); HRMS (APCI, direct probe)  $m/z$   $[M+H]^+$  calculated: 489.2184, found: 489.2210.

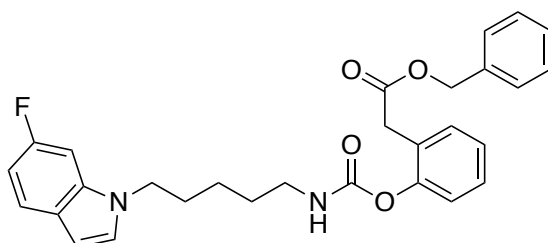
**2-[3-({[5-(6-Fluoroindol-1-yl)pentyl]carbamoyl}oxy)phenyl]acetic acid (41)**



**Figure S17.** Structure of **41**

A catalytic amount of palladium (10 %) on activated charcoal (28 mg) was added to a solution of compound **40** (251 mg, 0.51 mmol) in THF/methanol (1:1) (5 mL). The suspension was stirred vigorously under a balloon filled with hydrogen at room temperature for 3 h. After addition of Celite 545, the catalyst was filtered off and the filtrate was evaporated. The crude product was first purified by silica gel chromatography (cyclohexane/ethyl acetate/formic acid, 9:1:0.1 to 7:3:0.1). Further purification was carried out by preparative RP-HPLC (acetonitrile/H<sub>2</sub>O/formic acid, 55:45:0.1) to yield **41** as an oil (160 mg, 78 %). C<sub>22</sub>H<sub>23</sub>FN<sub>2</sub>O<sub>4</sub> (398.4); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 1.33 – 1.40 (m, 2H), 1.53 – 1.61 (m, 2H), 1.82 – 1.90 (m, 2H), 3.22 (q, *J* = 6.7 Hz, 2H), 3.63 (s, 2H), 4.06 (t, *J* = 7.0 Hz, 2H), 4.99 (t, *J* = 5.9 Hz, 1H), 6.46 (dd, *J* = 3.2 Hz and 0.9 Hz, 1H), 6.86 (ddd, *J* = 9.7 Hz, 8.6 Hz and 2.3 Hz, 1H), 6.98 – 7.05 (m, 2H), 7.05 – 7.08 (m, 2H), 7.11 (dt, *J* = 7.7 Hz and 1.2 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.52 (dd, *J* = 8.6 Hz and 5.4 Hz, 1H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ (ppm) 24.2, 29.6, 29.8, 40.7, 41.1, 46.5, 95.8 (d, *J*<sub>C-F</sub> = 26.3 Hz), 101.4, 108.2 (d, *J*<sub>C-F</sub> = 24.7 Hz), 120.7, 121.8 (d, *J*<sub>C-F</sub> = 10.2 Hz), 122.8, 125.1, 126.5, 128.3 (d, *J*<sub>C-F</sub> = 3.6 Hz), 129.6, 134.8, 136.1 (d, *J*<sub>C-F</sub> = 11.7 Hz), 151.2, 154.7, 159.9 (d, *J*<sub>C-F</sub> = 237.2 Hz), 176.0; HRMS (ESI) *m/z* [M+H]<sup>+</sup> calculated: 399.1715, found: 399.1726.

**Benzyl 2-[2-({[5-(6-fluoroindol-1-yl)pentyl]carbamoyl}oxy)phenyl]acetate (42)**

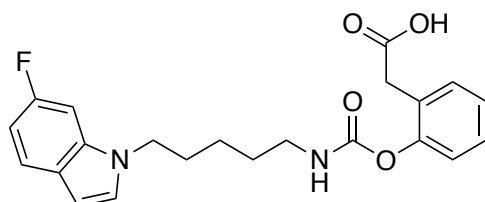


**Figure S18.** Structure of **42**

A solution of triphosgene (269 mg, 0.91 mmol) in dry THF (5 mL) was added at 0 °C to a solution of benzyl (2-hydroxyphenyl)acetate (438 mg, 1.81 mmol) and DIPEA (306 μL, 231 mg, 1.79 mmol) in dry THF (10 mL). The mixture was stirred for 2.5 h at the same temperature. After warming up to ambient temperature, a solution of **13** (202 mg, 0.92 mmol) and DIPEA (153 μL, 116 mg, 0.90 mmol) in dry THF (5 mL) was slowly added and stirring was continued at room temperature overnight. After work-up as described for compound **32** and chromatography on silica gel (hexane/ethyl acetate, 8:2), **42** was yielded as an oil (54 mg,

12%).  $C_{29}H_{29}FN_2O_4$  (488.6);  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  1.28 – 1.38 (m, 2H), 1.45 – 1.54 (m, 2H), 1.79 – 1.88 (m, 2H), 3.13 (q,  $J = 6.7$  Hz, 2H), 3.61 (s, 2H), 4.06 (t,  $J = 7.0$  Hz, 2H), 5.12 (s, 2H), 6.46 (dd,  $J = 3.2$  Hz and 0.9 Hz, 1H), 6.87 (ddd,  $J = 9.6$  Hz, 8.6 Hz and 2.3 Hz, 1H), 7.00 (dd,  $J = 9.8$  Hz and 2.3 Hz, 1H), 7.06 (d,  $J = 3.1$  Hz, 1H), 7.13 – 7.20 (m, 2H), 7.26 – 7.35 (m, 7H), 7.52 (dd,  $J = 8.4$  Hz and 5.4 Hz, 1H); HRMS (APCI, direct probe)  $m/z$   $[M+H]^+$  calculated: 489.2184, found: 489.2212.

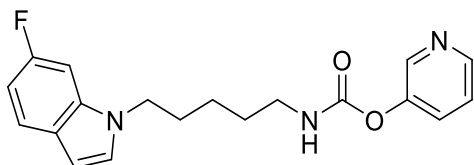
### 2-[2-({[5-(6-Fluoroindol-1-yl)pentyl]carbamoyl}oxy)phenyl]acetic acid (43)



**Figure S19.** Structure of **43**

To a solution of **42** (52 mg, 0.11 mmol) in 5 mL methanol/THF (1:1) was added palladium (10 %) on charcoal in catalytic amounts (10 mg). The mixture was stirred under a balloon filled with hydrogen at room temperature for 2 h. After filtration over Celite 545, the filter cake was washed with ethyl acetate and the filtrate was evaporated to dryness. Purification by chromatography on silica gel (1. cyclohexane/ethyl acetate, 8:2; 2. ethyl acetate/formic acid 100:0.7) yielded **43** (39 mg, 92 %) as an oil.  $C_{22}H_{23}FN_2O_4$  (398.4);  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  1.22 – 1.32 (m, 2H), 1.44 – 1.53 (m, 2H), 1.70 – 1.79 (m, 2H), 3.02 (q,  $J = 6.7$  Hz, 2H), 3.48 (s, 2H), 4.13 (t,  $J = 7.1$  Hz, 2H), 6.43 (dd,  $J = 3.1$  Hz and 0.9 Hz, 1H), 6.86 (ddd,  $J = 9.8$  Hz, 8.6 Hz and 2.3 Hz, 1H), 7.03 (dd,  $J = 8.1$  Hz and 1.3 Hz, 1H), 7.13 – 7.18 (m, 1H), 7.23 – 7.37 (m, 3H), 7.52 (dd,  $J = 8.6$  Hz and 5.5 Hz, 1H), 7.70 (t,  $J = 5.7$  Hz, 1H), 12.27 (s, 1H).

### Pyridin-3-yl *N*-[5-(6-fluoroindol-1-yl)pentyl]carbamate (44)

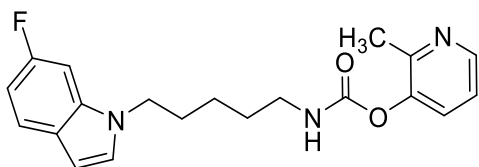


**Figure S20.** Structure of **44**

A solution of triphosgene (146 mg, 0.49 mmol) in dry THF (5 mL) was added at 0 °C to a solution of 3-hydroxypyridine (133 mg, 1.40 mmol) and DIPEA (255  $\mu$ L, 193 mg, 1.49 mmol) in dry THF (10 mL). The mixture was stirred for 4.5 h at the same temperature. After warming up to ambient temperature, a solution of compound **13** (108 mg, 0.49 mmol) and DIPEA (85  $\mu$ L, 64 mg, 0.50 mmol) in dry THF (5 mL) was slowly added and stirring was

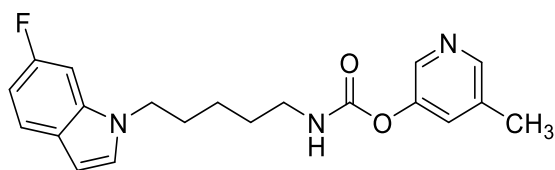
continued at room temperature for 5.5 h. The reaction mixture was concentrated and directly purified by chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 8:2 to 6:4). Further purification was carried out by preparative RP-HPLC (acetonitrile/H<sub>2</sub>O/formic acid, 50:50:0.1) to yield compound **44** as an oil (98 mg, 59 %). C<sub>19</sub>H<sub>20</sub>FN<sub>3</sub>O<sub>2</sub> (341.4); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ (ppm) 1.34 – 1.40 (m, 2H), 1.56 – 1.63 (m, 2H), 1.84 – 1.90 (m, 2H), 3.24 (q, *J* = 6.9 Hz, 2H), 4.08 (t, *J* = 7.0 Hz, 2H), 5.31 (t, *J* = 6.0 Hz, 1H), 6.46 (dd, *J* = 3.2 Hz and 0.9 Hz, 1H), 6.86 (ddd, *J* = 9.5 Hz, 8.6 Hz and 2.3 Hz, 1H), 7.00 (dd, *J* = 9.8 Hz and 2.3 Hz, 1H), 7.06 (d, *J* = 3.1 Hz, 1H), 7.41 (dd, *J* = 8.4 Hz and 4.8 Hz, 1H), 7.52 (dd, *J* = 8.6 Hz and 5.4 Hz, 1H), 7.64 – 7.67 (m, 1H), 8.44 – 8.49 (m, 2H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>): δ (ppm) 24.2, 29.5, 29.8, 41.2, 46.4, 95.8 (d, *J*<sub>C-F</sub> = 26.2 Hz), 101.5, 108.2 (d, *J*<sub>C-F</sub> = 24.4 Hz), 121.8 (d, *J*<sub>C-F</sub> = 10.3 Hz), 124.5, 125.1, 128.3 (d, *J*<sub>C-F</sub> = 3.7 Hz), 131.0, 136.1 (d, *J*<sub>C-F</sub> = 11.8 Hz), 141.9, 144.6, 148.3, 153.5, 159.8 (d, *J*<sub>C-F</sub> = 237.1 Hz); HRMS (ESI) *m/z* [M+H]<sup>+</sup> calculated: 342.1612, found: 342.1616.

## 2-Methylpyridin-3-yl *N*-[5-(6-fluoroindol-1-yl)pentyl]carbamate (**45**)

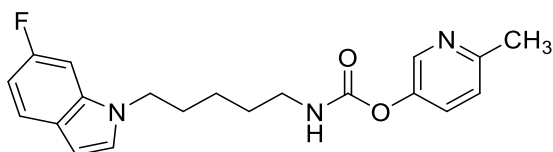


**Figure S21.** Structure of **45**

A solution of triphosgene (152 mg, 0.51 mmol) in dry THF (5 mL) was added at 0 °C to a solution of 3-hydroxy-2-methylpyridine (153 mg, 1.40 mmol) and DIPEA (255 μL, 193 mg, 1.49 mmol) in dry THF (10 mL). The mixture was stirred for 3 h at the same temperature. After warming up to ambient temperature, a solution of compound **13** (115 mg, 0.52 mmol) and DIPEA (85 μL, 64 mg, 0.50 mmol) in dry THF (5 mL) was slowly added and stirring was continued at room temperature for 2 h. The reaction mixture was concentrated and directly purified by chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 6:4). Further purification was carried out by preparative RP-HPLC (acetonitrile/H<sub>2</sub>O, 45:55) to yield **45** as an oil (49 mg, 27 %). C<sub>20</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>2</sub> (355.4); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ (ppm) 1.35 – 1.40 (m, 2H), 1.58 – 1.63 (m, 2H), 1.85 – 1.91 (m, 2H), 2.45 (s, 3H), 3.25 (q, *J* = 6.7 Hz, 2H), 4.08 (t, *J* = 6.9 Hz, 2H), 5.09 (t, *J* = 6.2 Hz, 1H), 6.47 (dd, *J* = 3.2 Hz and 0.9 Hz, 1H), 6.87 (ddd, *J* = 9.5 Hz, 8.6 Hz and 2.3 Hz, 1H), 7.00 (dd, *J* = 10.0 Hz and 2.3 Hz, 1H), 7.06 (d, *J* = 3.2 Hz, 1H), 7.17 (dd, *J* = 8.0 Hz and 4.9 Hz, 1H), 7.40 – 7.43 (m, 1H), 7.52 (dd, *J* = 8.6 Hz and 5.4 Hz, 1H), 8.35 (dd, *J* = 4.7 Hz and 1.4 Hz, 1H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>): δ (ppm) 19.3, 24.2, 29.6, 29.8, 41.2, 46.5, 95.8 (d, *J*<sub>C-F</sub> = 26.1 Hz), 101.5, 108.2 (d, *J*<sub>C-F</sub> = 24.7 Hz), 121.8 (d, *J*<sub>C-F</sub> = 10.3 Hz), 122.0, 125.1, 128.3 (d, *J*<sub>C-F</sub> = 3.8 Hz), 130.1, 136.1 (d, *J*<sub>C-F</sub> = 12.1 Hz), 145.8, 146.1, 151.7, 153.9, 159.9 (d, *J*<sub>C-F</sub> = 237.5 Hz); HRMS (ESI) *m/z* [M+H]<sup>+</sup> calculated: 356.1769, found: 356.1783.

**5-Methylpyridin-3-yl *N*-[5-(6-fluoroindol-1-yl)pentyl]carbamate (47)****Figure S22.** Structure of **47**

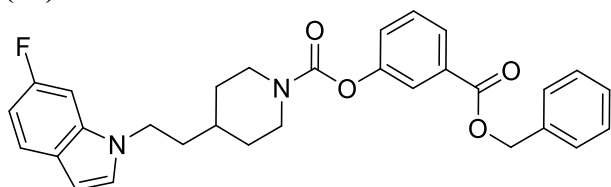
A solution of triphosgene (163 mg, 0.55 mmol) in dry THF (5 mL) was added at 0 °C to a solution of 3-hydroxy-5-methylpyridine (168 mg, 1.54 mmol) and DIPEA (281  $\mu$ L, 212 mg, 1.64 mmol) in dry THF (10 mL). The mixture was stirred for 3 h at the same temperature. After warming up to ambient temperature, a solution of compound **13** (121 mg, 0.55 mmol) and DIPEA (94  $\mu$ L, 71 mg, 0.55 mmol) in dry THF (5 mL) was slowly added and stirring was continued at room temperature for 3 h. The reaction mixture was concentrated and directly purified by chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 1:1). Further purification was carried out by preparative RP-HPLC (acetonitrile/H<sub>2</sub>O, 50:50) to yield **47** as an oil (37 mg, 19 %). C<sub>20</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>2</sub> (355.4); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 1.35 – 1.40 (m, 2H), 1.57 – 1.63 (m, 2H), 1.85 – 1.91 (m, 2H), 2.37 (s, 3H), 3.24 (q,  $J$  = 6.9 Hz, 2H), 4.08 (t,  $J$  = 7.0 Hz, 2H), 5.12 (t,  $J$  = 6.2 Hz, 1H), 6.47 (dd,  $J$  = 3.2 Hz and 0.9 Hz, 1H), 6.86 (ddd,  $J$  = 9.6 Hz, 8.6 Hz and 2.3 Hz, 1H), 7.00 (dd,  $J$  = 9.9 Hz and 2.4 Hz, 1H), 7.06 (d,  $J$  = 3.2 Hz, 1H), 7.39 (t,  $J$  = 2.3 Hz, 1H), 7.52 (dd,  $J$  = 8.7 Hz and 5.4 Hz, 1H), 8.24 – 8.31 (m, 2H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 18.4, 24.2, 29.6, 29.8, 41.2, 46.5, 95.8 (d,  $J_{C-F}$  = 26.1 Hz), 101.5, 108.2 (d,  $J_{C-F}$  = 24.3 Hz), 121.3 (d,  $J_{C-F}$  = 10.2 Hz), 125.1, 128.3 (d,  $J_{C-F}$  = 3.8 Hz), 130.6, 134.5, 136.1 (d,  $J_{C-F}$  = 12.1 Hz), 139.8, 146.2, 147.8, 153.1, 159.9 (d,  $J_{C-F}$  = 237.1 Hz); HRMS (APCI, direct probe)  $m/z$  [M+H]<sup>+</sup> calculated: 356.1769, found: 356.1800.

**6-Methylpyridin-3-yl *N*-[5-(6-fluoroindol-1-yl)pentyl]carbamate (48)****Figure S23.** Structure of **48**

To a solution of 6-methylpyridin-3-ol (61 mg, 0.56 mmol) and DIPEA (95  $\mu$ L, 72 mg, 0.56 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> was carefully added under nitrogen and at -30 °C trichloromethyl chloroformate (94  $\mu$ L, 154 mg, 0.78 mmol). After stirring at room temperature for 4 h, the solvent was removed. A solution of the residue and DIPEA (95  $\mu$ L, 72 mg, 0.56 mmol) in dry THF (5 mL) was treated with a solution of **13** (123 mg, 0.56 mmol) in dry THF (5 mL) and stirred at room temperature overnight. After addition of some silica gel, the solvent was distilled off and the residue was loaded on the top of a silica gel column. Elution with

cyclohexane/ethyl acetate (7:3) gave **48** as an oil (60 mg, 30%).  $C_{20}H_{22}FN_3O_2$  (355.4);  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  1.32 – 1.40 (m, 2H), 1.55 – 1.61 (m, 2H), 1.83 – 1.91 (m, 2H), 2.55 (s, 3H), 3.23 (q,  $J = 6.7$  Hz, 2H), 4.07 (t,  $J = 7.1$  Hz, 2H), 5.09 – 5.15 (m, 1H), 6.46 (d,  $J = 3.1$  Hz, 1H), 6.83 – 6.89 (m, 1H), 6.97 – 7.02 (m, 1H), 7.06 (d,  $J = 3.2$  Hz, 1H), 7.15 (d,  $J = 8.4$  Hz, 1H), 7.39 (dd,  $J = 8.5$  Hz and 2.8 Hz, 1H), 7.50 – 7.55 (m, 1H), 8.30 (d,  $J = 2.7$  Hz, 1H);  $^{13}C$  NMR (151 MHz,  $CDCl_3$ )  $\delta$  23.6, 24.0, H, 29.4, 29.6, 41.0, 46.3, 95.7 (d,  $J_{C-F} = 26.1$  Hz), 101.3, 108.0 (d,  $J_{C-F} = 24.4$  Hz), 121.7 (d,  $J_{C-F} = 10.1$  Hz), 123.4, 125.0, 128.1, 129.7, 135.9 (d,  $J_{C-F} = 11.7$  Hz), 142.1, 145.6, 154.0, 155.0, 159.7 (d,  $J_{C-F} = 237.2$  Hz). HRMS (APCI, direct probe)  $m/z$   $[M+H]^+$  calculated: 356.1769, found: 356.1809.

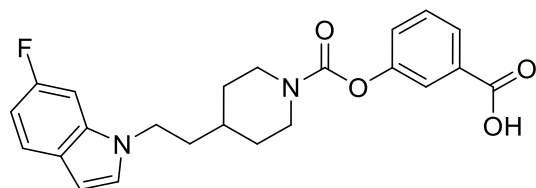
**3-[(Benzyloxy)carbonyl]phenyl 4-[2-(6-fluoroindol-1-yl)ethyl]piperidine-1-carboxylate (55)**



**Figure S24.** Structure of **55**

A solution of triphosgene (243 mg, 0.82 mmol) in dry THF (10 mL) was added to a solution of benzyl 3-hydroxybenzoate (382 mg, 1.67 mmol) and DIPEA (282  $\mu$ L, 213 mg, 1.65 mmol) in dry THF (10 mL) at 0 °C. After stirring at this temperature for 2 h, the mixture was allowed to warm up to room temperature. Then, a solution of compound **52** (209 mg, 0.85 mmol) and DIPEA (141  $\mu$ L, 106 mg, 0.82 mmol) in dry THF (5 mL) was slowly added and stirring was continued overnight. After work-up as described for compound **32** and chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 17:3), the product **55** was yielded as an oil (133 mg, 32 %).  $C_{30}H_{29}FN_2O_4$  (500.6);  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.27 – 1.38 (m, 2H), 1.45 – 1.57 (m, 1H), 1.75 – 1.87 (m, 4H), 2.81 (t,  $J = 12.8$  Hz and 12.8 Hz, 2x 0.5H), 2.94 (t,  $J = 12.3$  Hz and 12.3 Hz, 2x 0.5H), 4.13 (t,  $J = 7.1$  Hz, 2H), 4.20 – 4.33 (m, 2H), 5.36 (s, 2H), 6.49 (dd,  $J = 3.1$  Hz and 0.9 Hz, 1H), 6.88 (ddd,  $J = 9.6$  Hz, 8.6 Hz and 2.2 Hz, 1H), 7.00 (dd,  $J = 9.9$  Hz and 2.3 Hz, 1H), 7.07 (d,  $J = 3.2$  Hz, 1H), 7.32 (ddd,  $J = 8.1$  Hz, 2.4 Hz and 1.1 Hz, 1H), 7.34 – 7.38 (m, 1H), 7.38 – 7.42 (m, 2H), 7.42 – 7.46 (m, 3H), 7.54 (dd,  $J = 8.6$  Hz and 5.4 Hz, 1H), 7.77 – 7.79 (m, 1H), 7.92 (dt,  $J = 7.7$  Hz and 1.3 Hz, 1H); HRMS (ESI)  $m/z$   $[M+H]^+$  calculated: 501.2184, found: 501.2200.

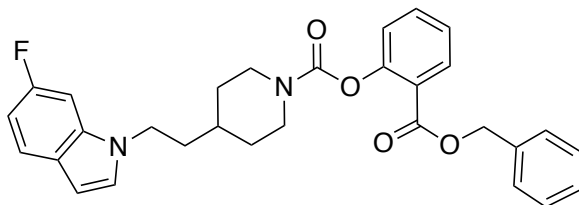
**3-({4-[2-(6-Fluoroindol-1-yl)ethyl]piperidine-1-carbonyl}oxy)benzoic acid (**56**)**



**Figure S25.** Structure of **56**

A solution of compound **55** (113 mg, 0.23 mmol) in THF/methanol (1:1) (5 mL) was treated with a catalytic amount of palladium (10 %) on activated charcoal (11 mg). The obtained suspension was stirred vigorously under a balloon filled with hydrogen at room temperature for 3 h. The catalyst was filtered off over Celite 545 and the solvent was removed. The resulting residue was purified by chromatography on silica gel (cyclohexane/formic acid, 100:1 to cyclohexane/ethyl acetate/formic acid, 7:3:0.1) followed by preparative RP-HPLC (acetonitrile/H<sub>2</sub>O/formic acid, 50:50:0.1) to yield **56** as an oil (64 mg, 69 %). C<sub>23</sub>H<sub>23</sub>FN<sub>2</sub>O<sub>4</sub> (410.4); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 1.29 – 1.37 (m, 2H), 1.48 – 1.56 (m, 1H), 1.77 – 1.87 (m, 4H), 2.82 (t, *J* = 12.9 Hz and 12.9 Hz, 2x 0.5H), 2.96 (t, *J* = 12.7 Hz and 12.7 Hz, 2x 0.5H), 4.14 (t, *J* = 7.3 Hz, 2H), 4.23 – 4.34 (m, 2H), 6.49 (dd, *J* = 3.0 Hz and 0.8 Hz, 1H), 6.88 (ddd, *J* = 9.5 Hz, 8.6 Hz and 2.3 Hz, 1H), 7.00 (dd, *J* = 9.9 Hz and 2.4 Hz, 1H), 7.08 (d, *J* = 3.1 Hz, 1H), 7.38 (ddd, *J* = 8.0 Hz, 2.4 Hz and 1.1 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.54 (dd, *J* = 8.6 Hz and 5.4 Hz, 1H), 7.83 (dd, *J* = 2.4 Hz and 1.6 Hz, 1H), 7.94 (dt, *J* = 7.7 Hz and 1.3 Hz, 1H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 31.8, 32.2, 33.5, 36.5, 44.0, 44.5, 44.8, 95.7 (d, *J*<sub>C-F</sub> = 26.4 Hz), 101.7, 108.3 (d, *J*<sub>C-F</sub> = 24.4 Hz), 121.9 (d, *J*<sub>C-F</sub> = 10.3 Hz), 123.7, 125.2, 127.2, 127.5, 128.0 (d, *J*<sub>C-F</sub> = 3.5 Hz), 129.1, 130.7, 136.0 (d, *J*<sub>C-F</sub> = 12.1 Hz), 151.6, 153.4, 159.9 (d, *J*<sub>C-F</sub> = 237.7 Hz), 170.4, HRMS (ESI) *m/z* [M+H]<sup>+</sup> calculated: 411.1715, found: 411.1710.

**2-[(Benzyloxy)carbonyl]phenyl 4-[2-(6-fluoroindol-1-yl)ethyl]piperidine-1-carboxylate (**57**)**

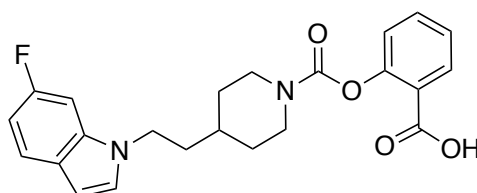


**Figure S26.** Structure of **57**

To a stirring solution of triphosgen (60 mg, 0.20 mmol) in dry THF (5 mL) was added at 0 °C benzyl salicylate (59 μL, 69 mg, 0.30 mmol) and DIPEA (69 μL, 52 mg, 0.40 mmol). After stirring at 0 °C for 2 h, a solution of **52** (50 mg, 0.20 mmol) and DIPEA (35 μL, 26 mg, 0.20 mmol) in dry THF (5 mL) was added and the mixture was further stirred at room temperature for 6 h. The solvent was evaporated and the residue was purified by chromatography on silica

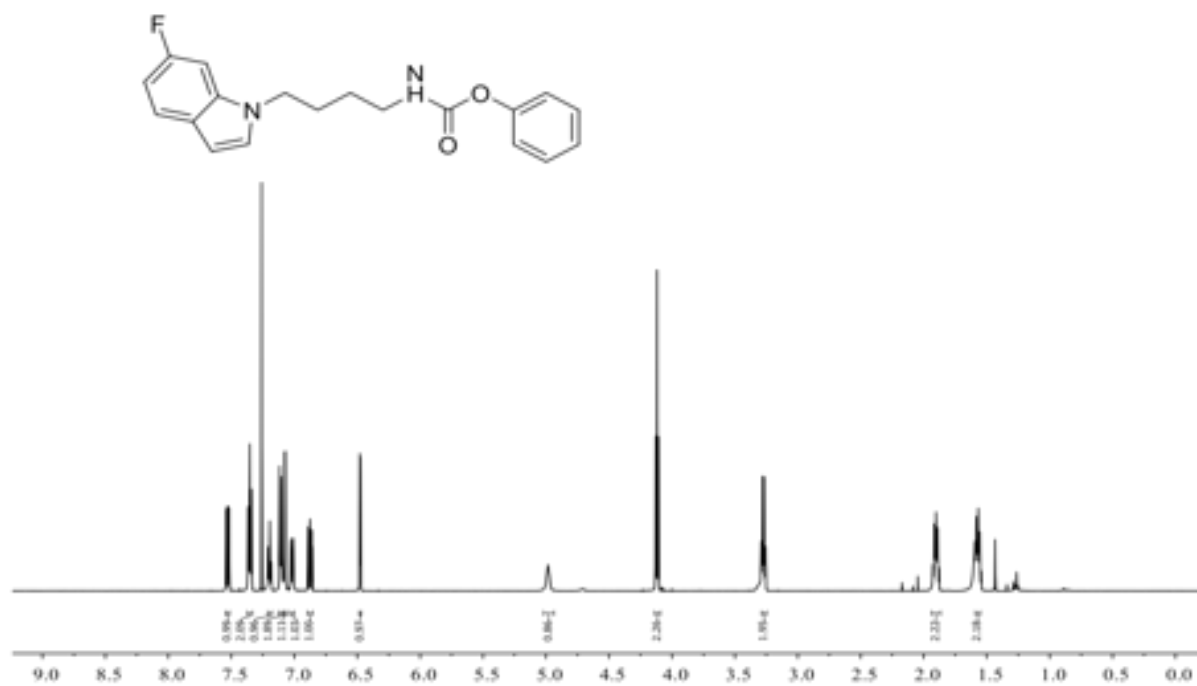
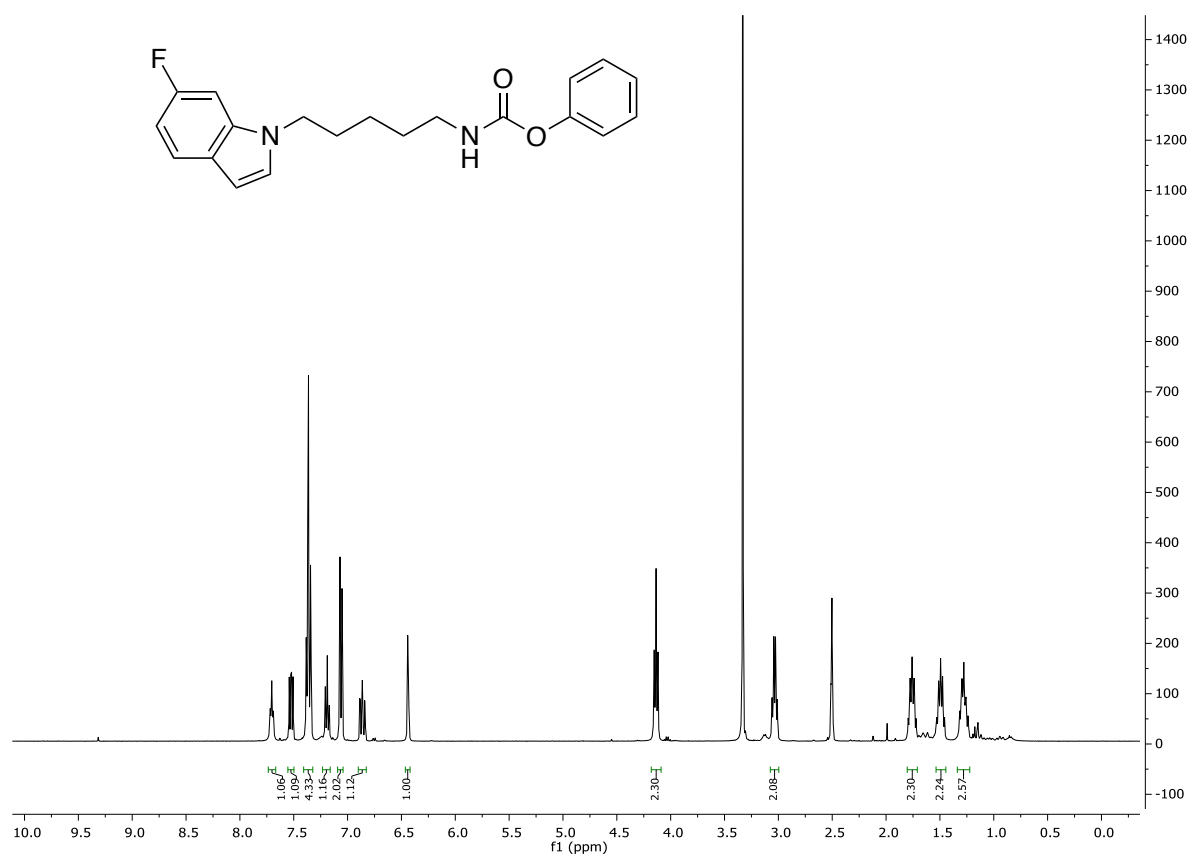
gel (cyclohexane/ethyl acetate, 8:2) to yield **57** as an oil (72 mg, 71 %).  $C_{30}H_{29}FN_2O_4$  (500.6);  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  1.24 – 1.30 (m, 2H), 1.37 – 1.45 (m, 1H), 1.64 – 1.72 (m, 2H), 1.76 – 1.82 (m, 2H), 2.61 – 2.80 (m, 2H), 4.08 – 4.23 (m, 4H), 5.30 (s, 2H), 6.49 (dd,  $J = 3.2$  Hz and 0.9 Hz, 1H), 6.89 (ddd,  $J = 9.6$  Hz, 8.7 Hz and 2.3 Hz, 1H), 6.97 – 7.02 (m, 1H), 7.07 (d,  $J = 3.2$  Hz, 1H), 7.14 (dd,  $J = 8.0$  Hz and 1.2 Hz, 1H), 7.27 – 7.41 (m, 6H), 7.50 – 7.57 (m, 2H), 8.01 (dd,  $J = 7.8$  Hz and 1.7 Hz, 1H); HRMS (APCI, direct probe)  $m/z$   $[M+H]^+$  calculated: 501.2184, found: 501.2205.

**2-({4-[2-(6-Fluoroindol-1-yl)ethyl]piperidine-1-carbonyl}oxy)benzoic acid (**58**)**



**Figure S27.** Structure of **58**

To a solution of **57** (71 mg, 0.14 mmol) in 5 mL methanol/THF (1:1) was added palladium (10 %) on charcoal in catalytic amounts (10 mg). The mixture was stirred under a balloon filled with hydrogen at room temperature for 4 h. After filtration over Celite 545, the filtrate was evaporated to dryness. Purification by preparative RP-HPLC (acetonitrile/ $H_2O$ /formic acid, 8:2:0.1) yielded **58** (36 mg, 62 %) as an oil.  $C_{23}H_{23}FN_2O_4$  (410.4);  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.30 – 1.45 (m, 2H), 1.48 – 1.55 (m, 1H), 1.72 – 1.79 (m, 2H), 1.81 – 1.88 (m, 2H), 2.75 – 3.01 (m, 2H), 4.11 (t,  $J = 8.1$  Hz, 2H), 4.18 – 4.39 (m, 2H), 6.47 (dd,  $J = 3.2$  Hz and 0.9 Hz, 1H), 6.87 (ddd,  $J = 9.5$  Hz, 8.8 Hz and 2.4 Hz, 1H), 6.97 – 7.02 (m, 1H), 7.06 (d,  $J = 3.2$  Hz, 1H), 7.16 (dd,  $J = 8.1$  Hz and 1.2 Hz, 1H), 7.21 (ddd,  $J = 8.1$  Hz, 7.7 Hz and 1.2 Hz, 1H), 7.50 – 7.58 (m, 2H), 7.96 (dd,  $J = 7.8$  Hz and 1.8 Hz, 1H); HRMS (APCI, direct probe)  $m/z$   $[M+H]^+$  calculated: 411.1715, found: 411.1725.

**<sup>1</sup>H NMR spectra of the target compounds****Figure S28.** Compound 11**Figure S29.** Compound 14

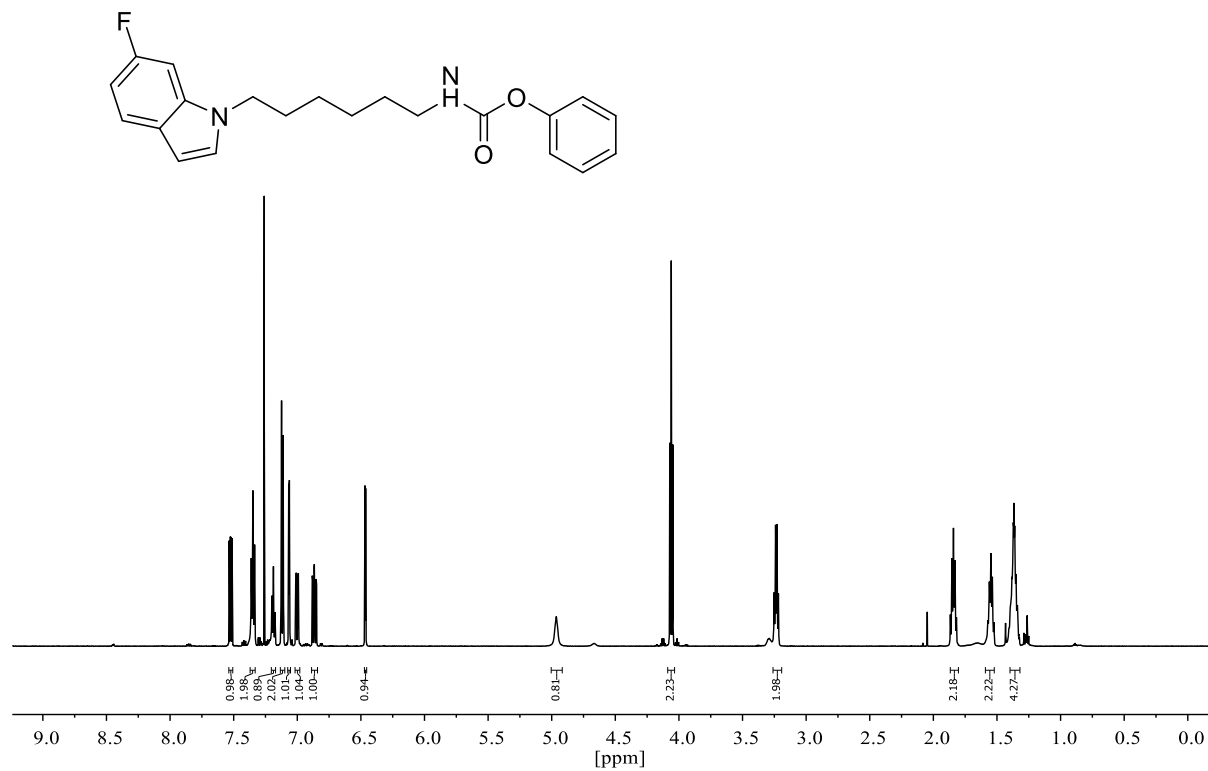


Figure S30. Compound 17

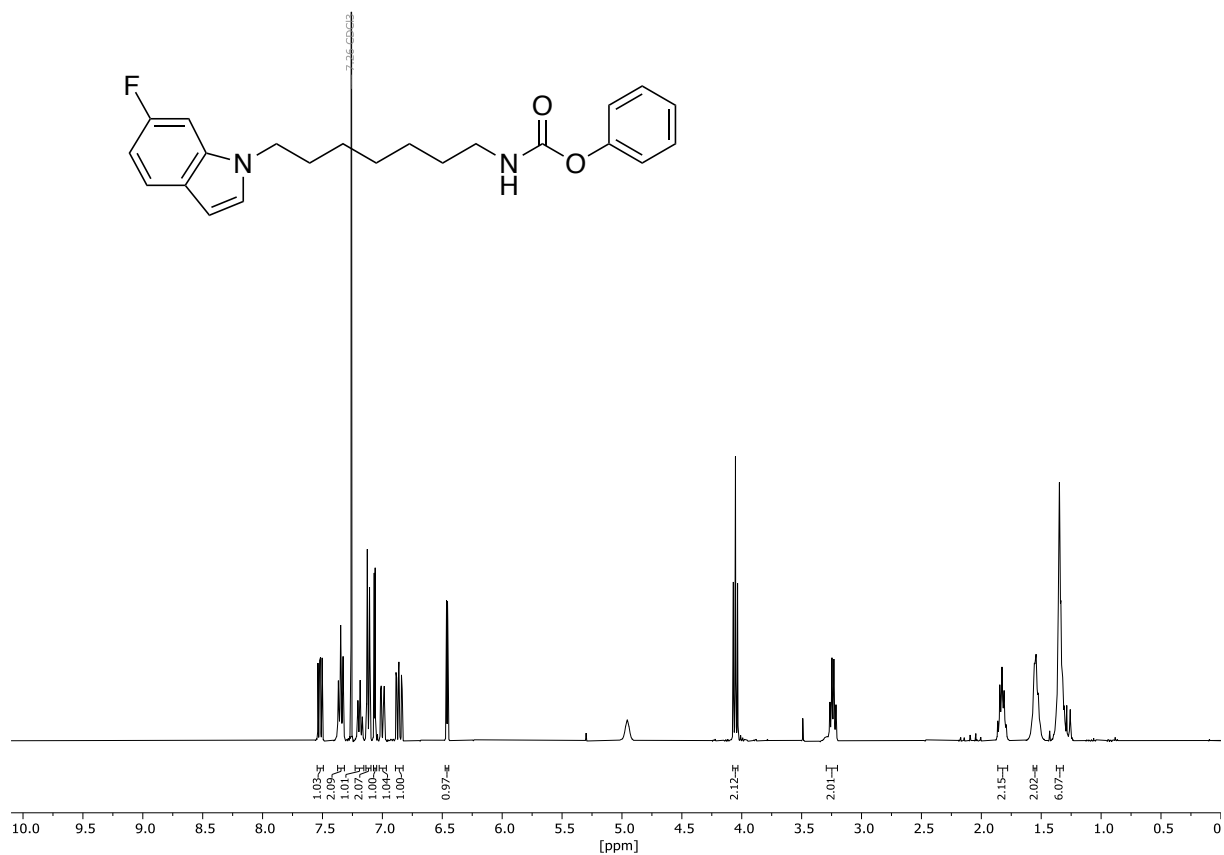


Figure S31. Compound 21

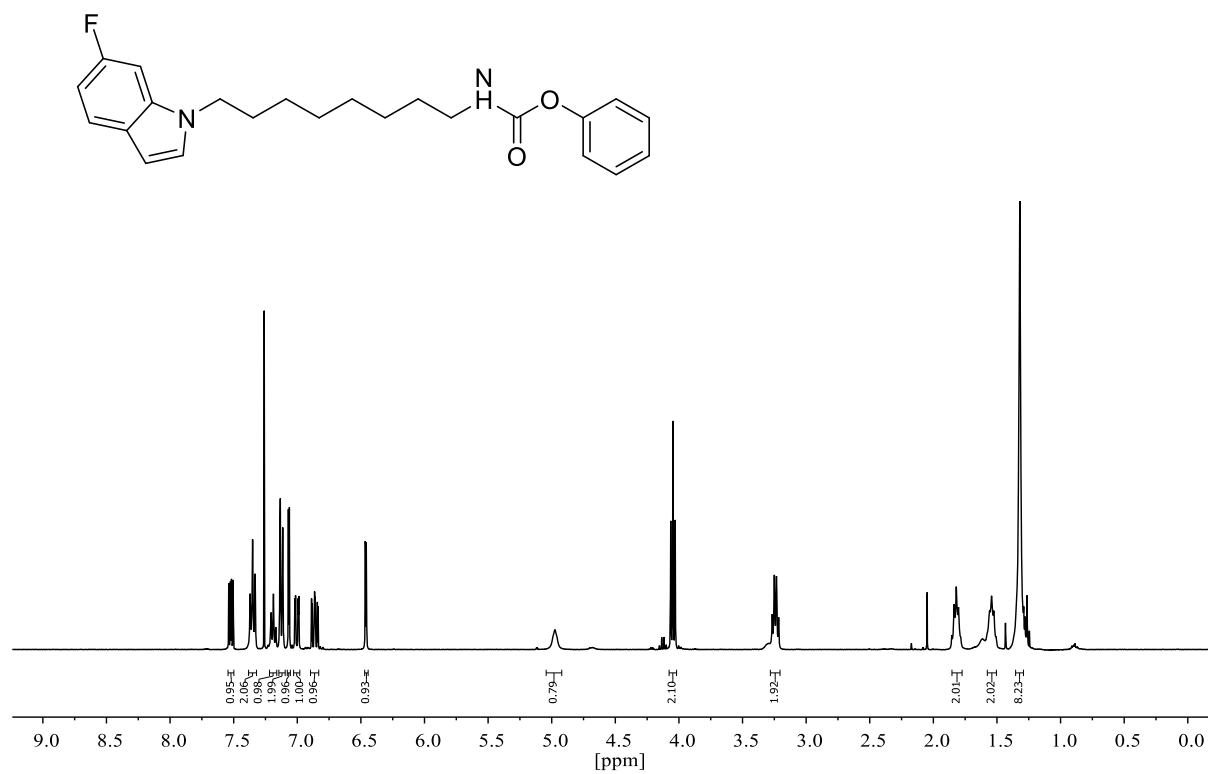


Figure S32. Compound 25

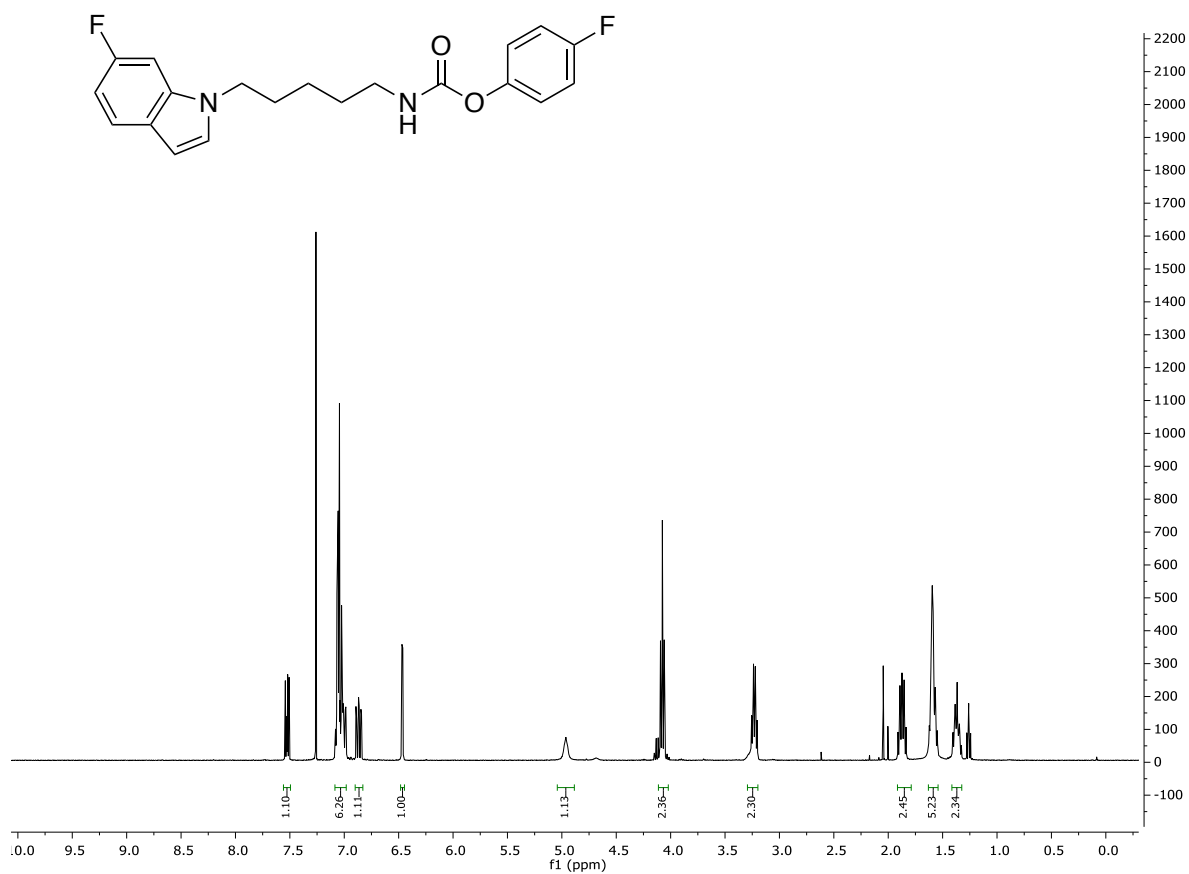


Figure S33. Compound 26

S21

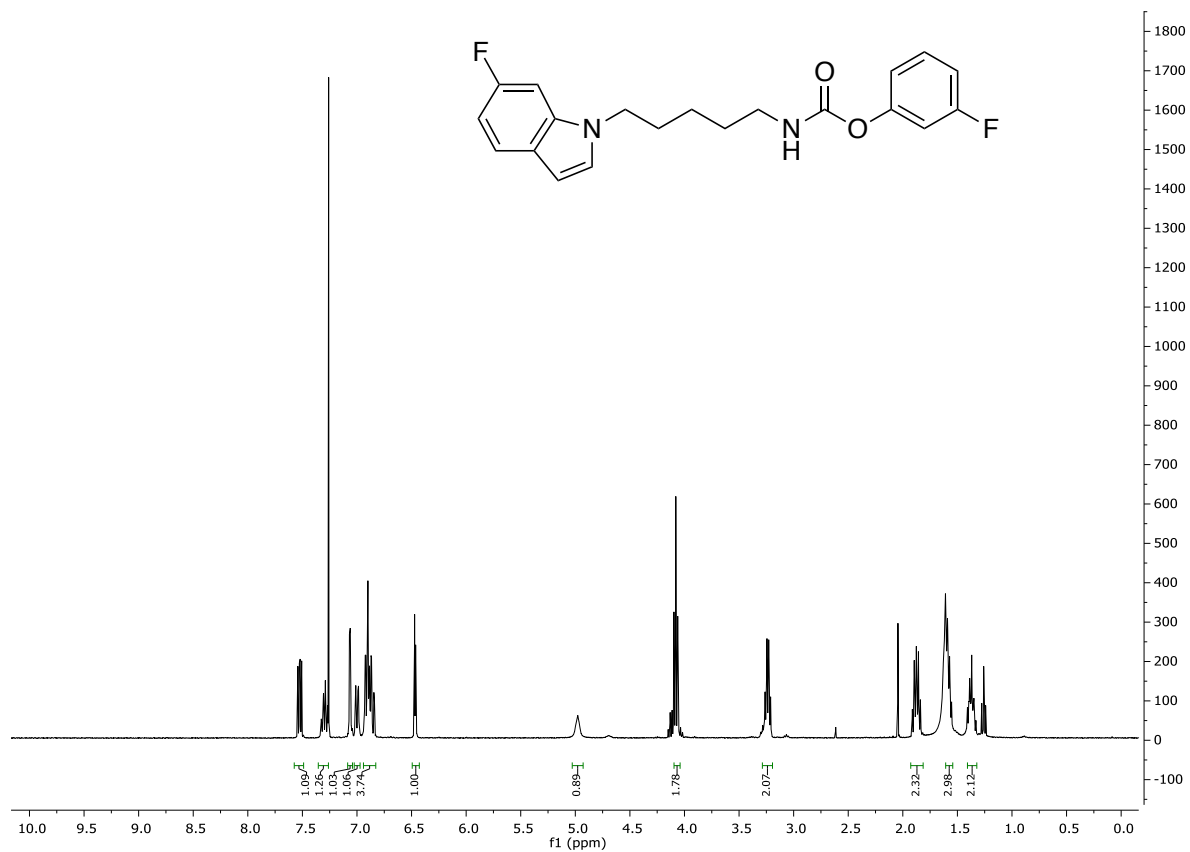


Figure S34. Compound 27

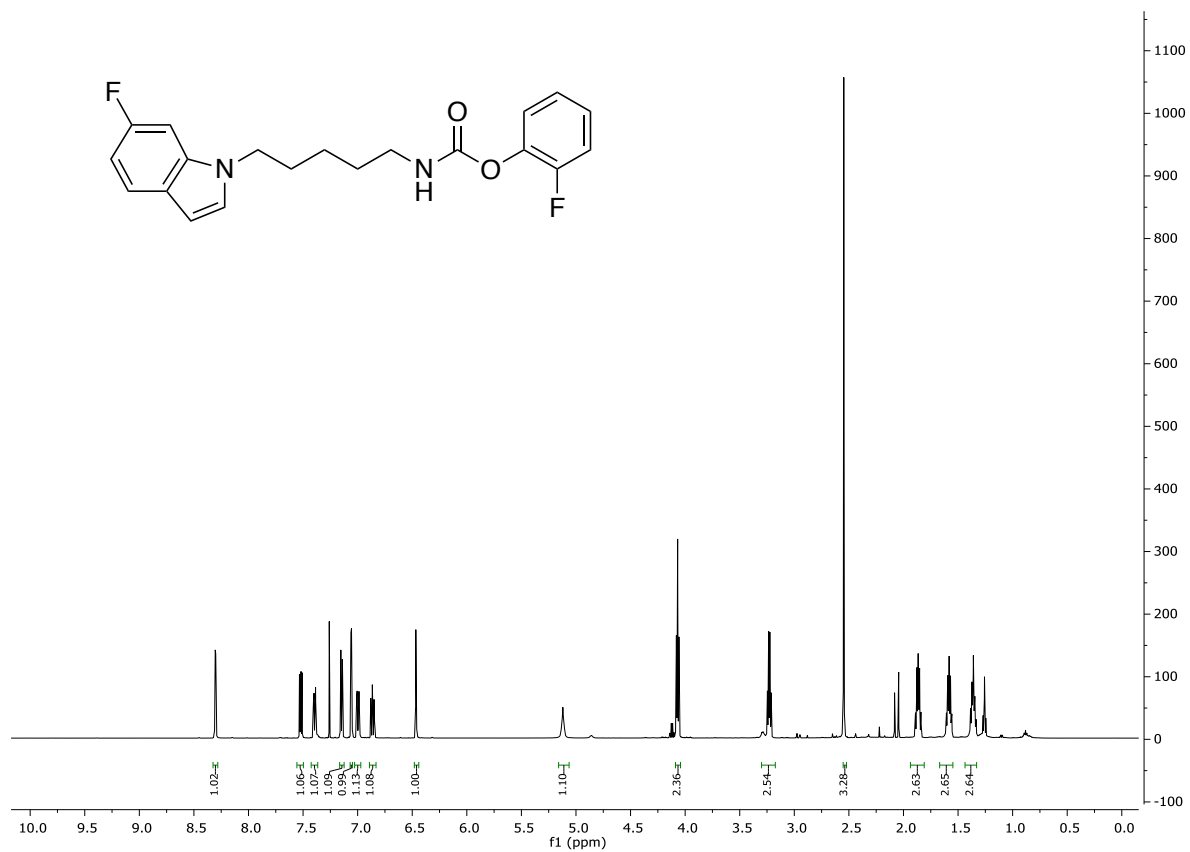


Figure S35. Compound 28

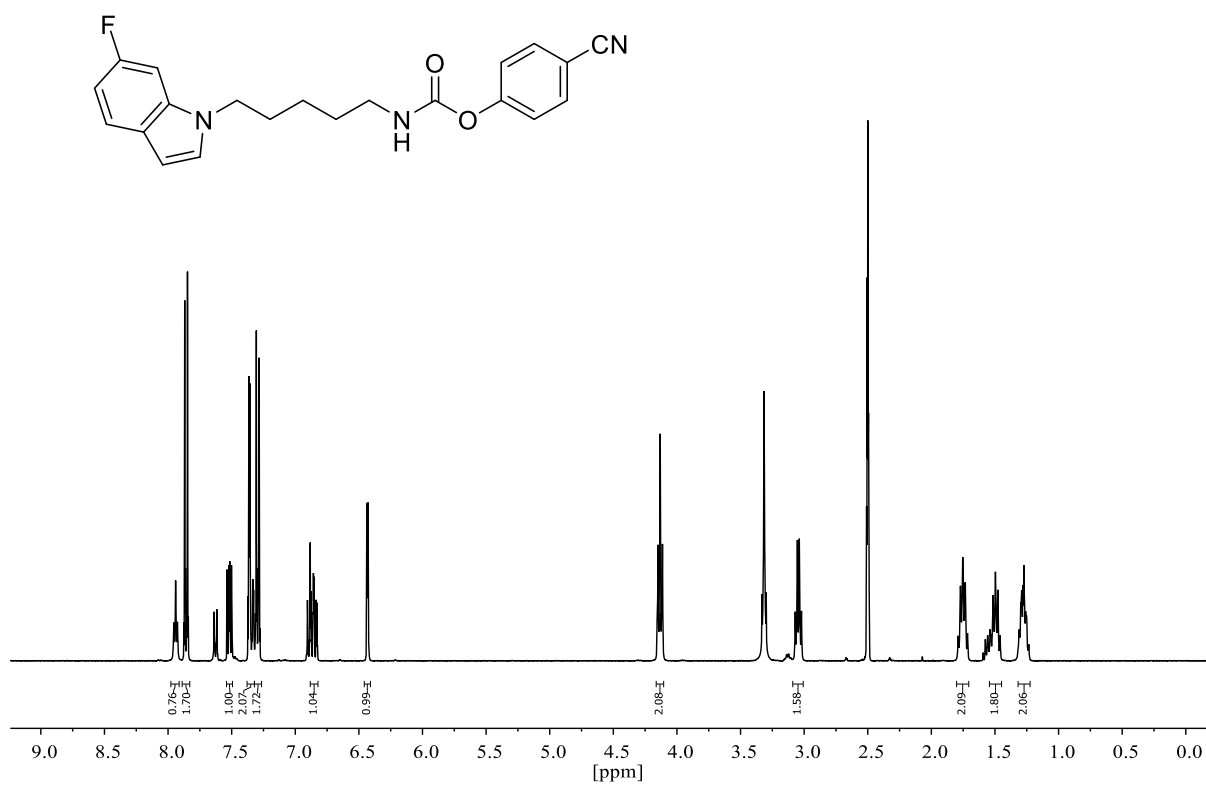


Figure S36. Compound 29

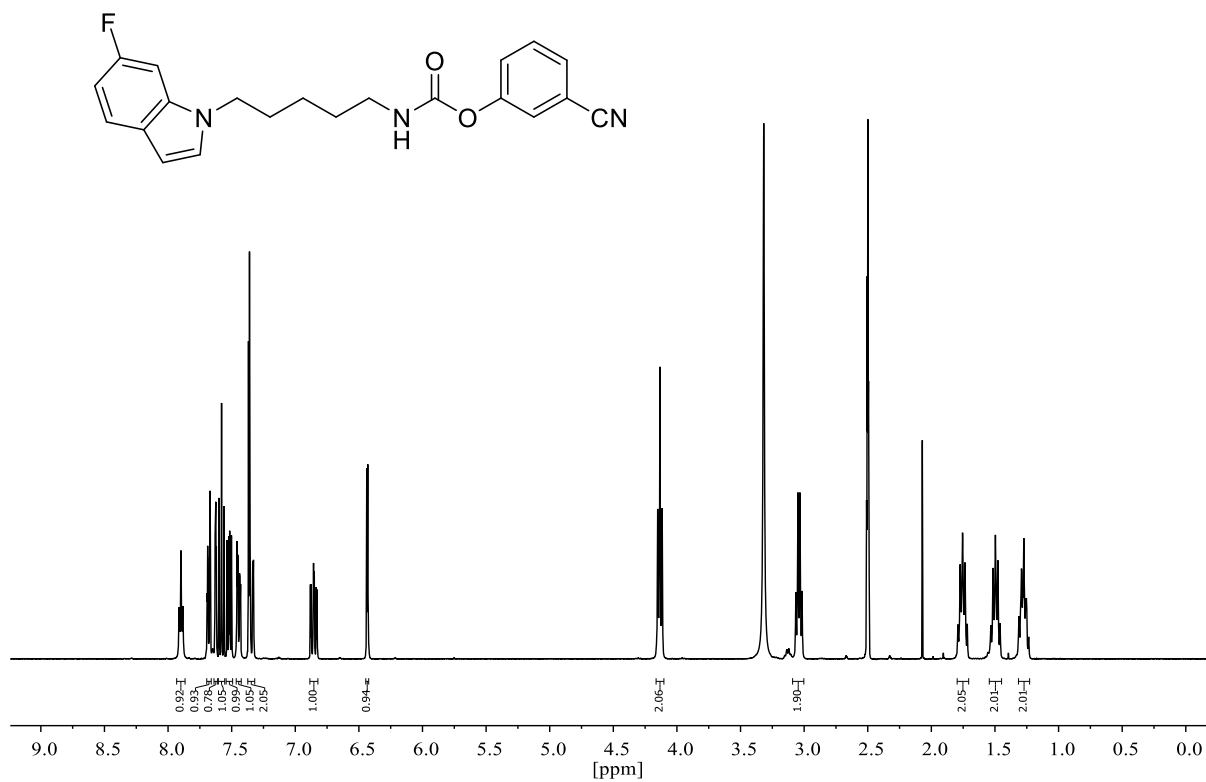


Figure S37. Compound 30

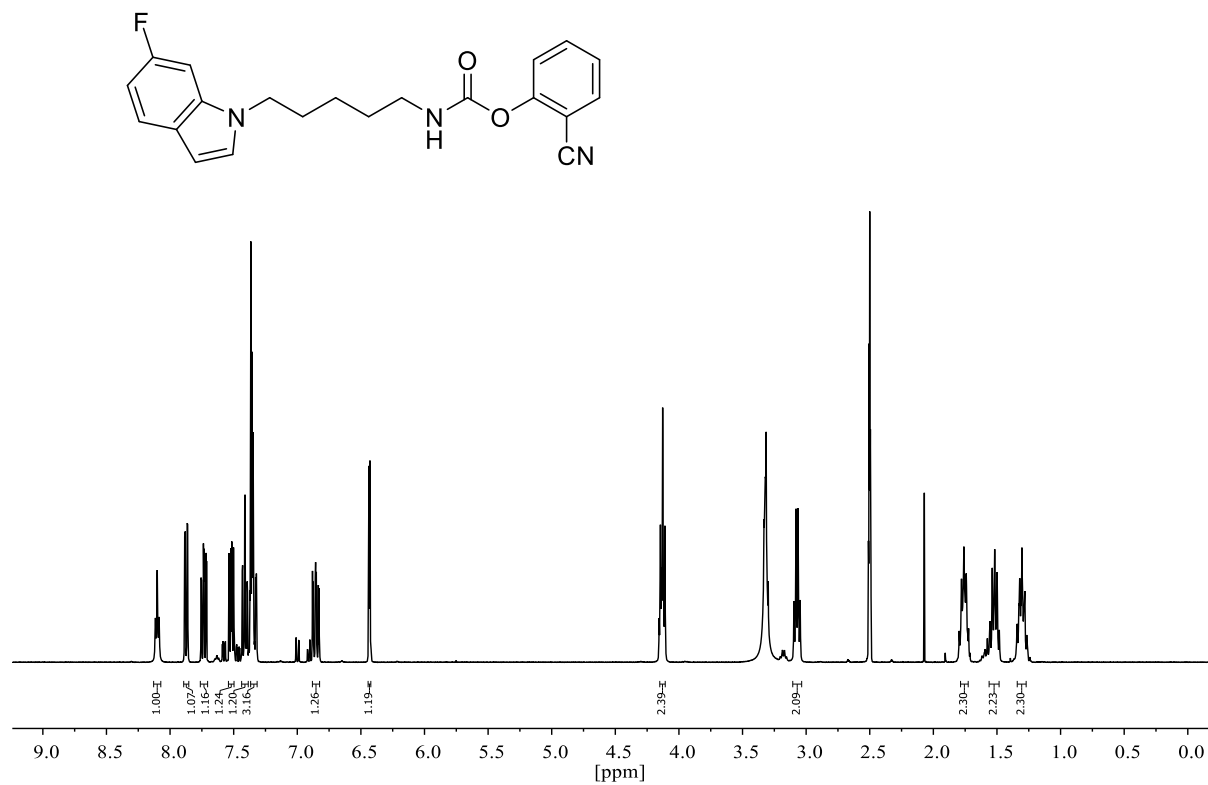


Figure S38. Compound 31

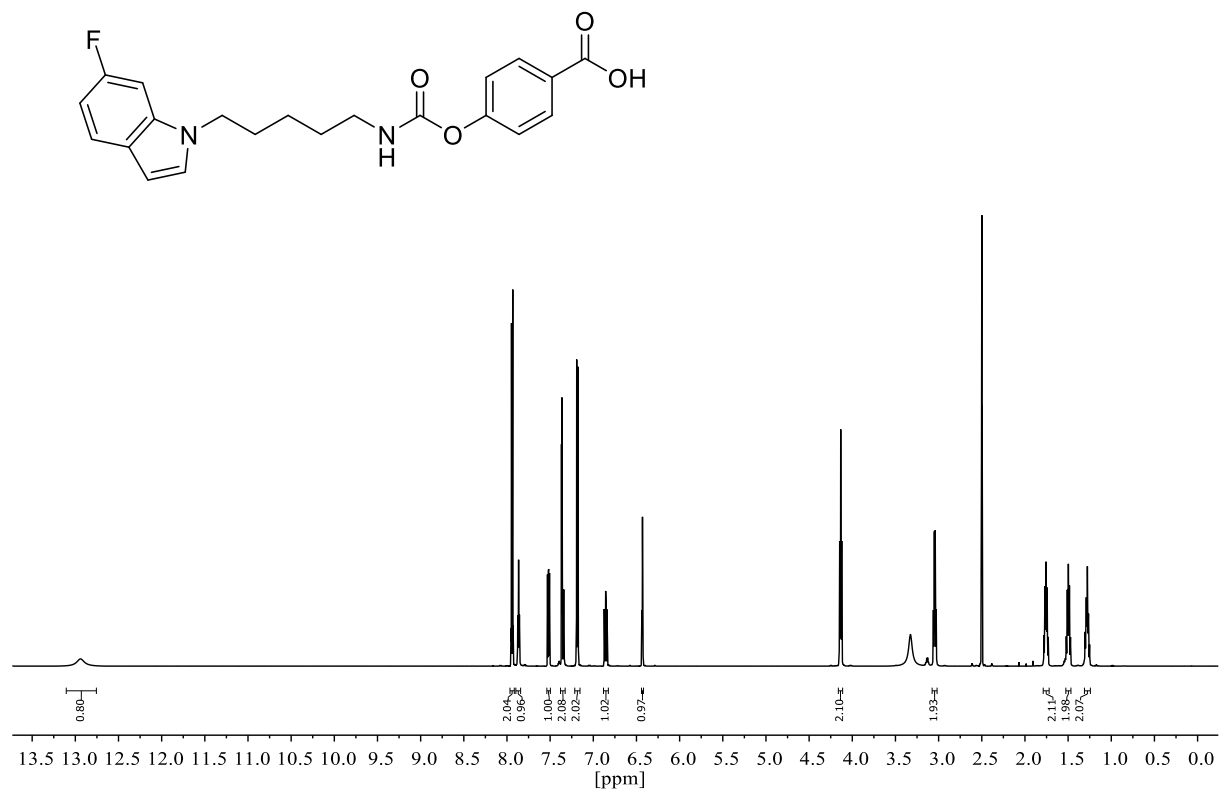


Figure S39. Compound 33

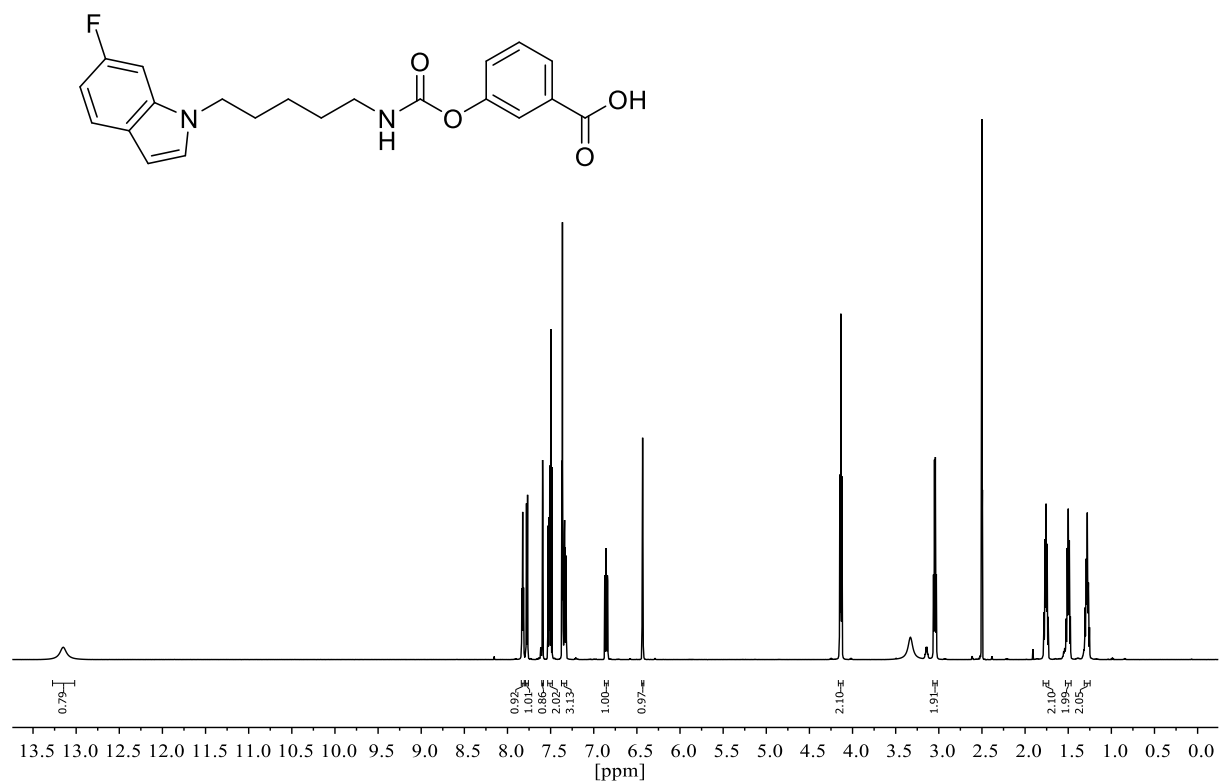


Figure S40. Compound 35

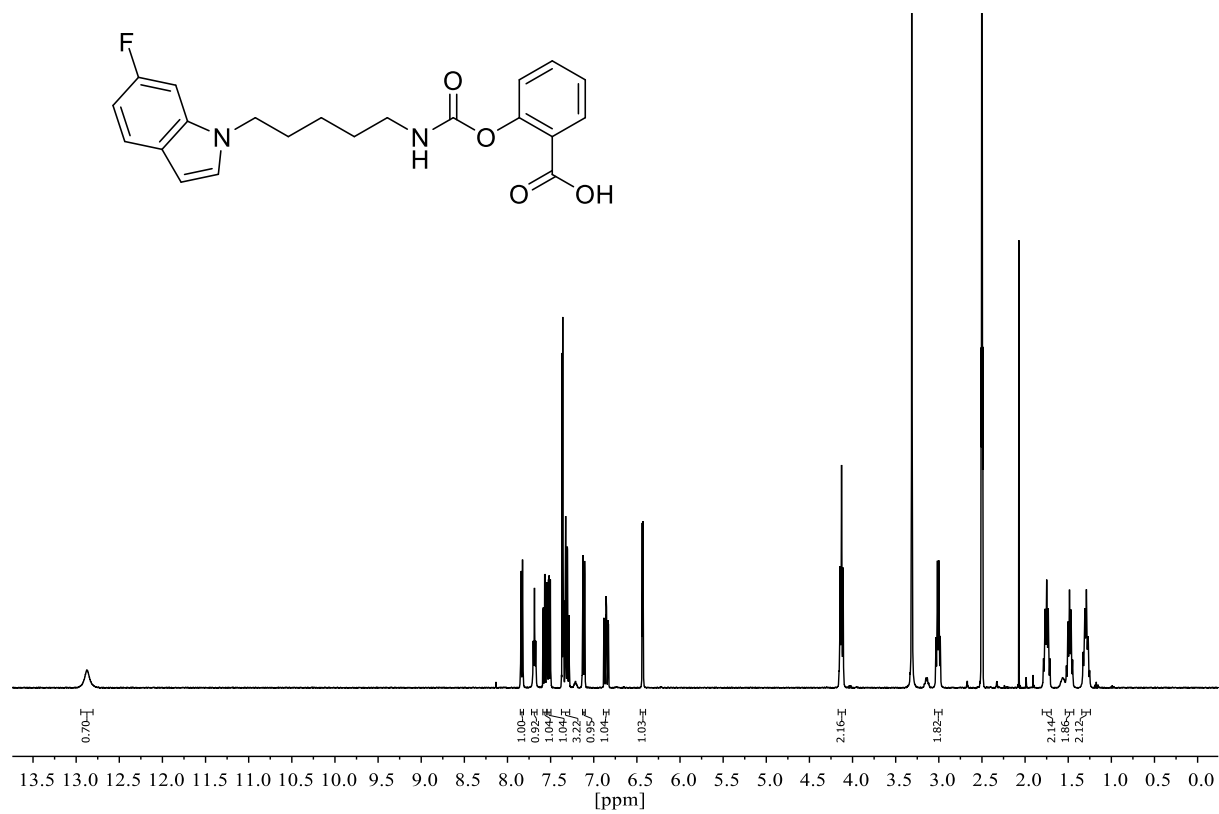


Figure S41. Compound 37

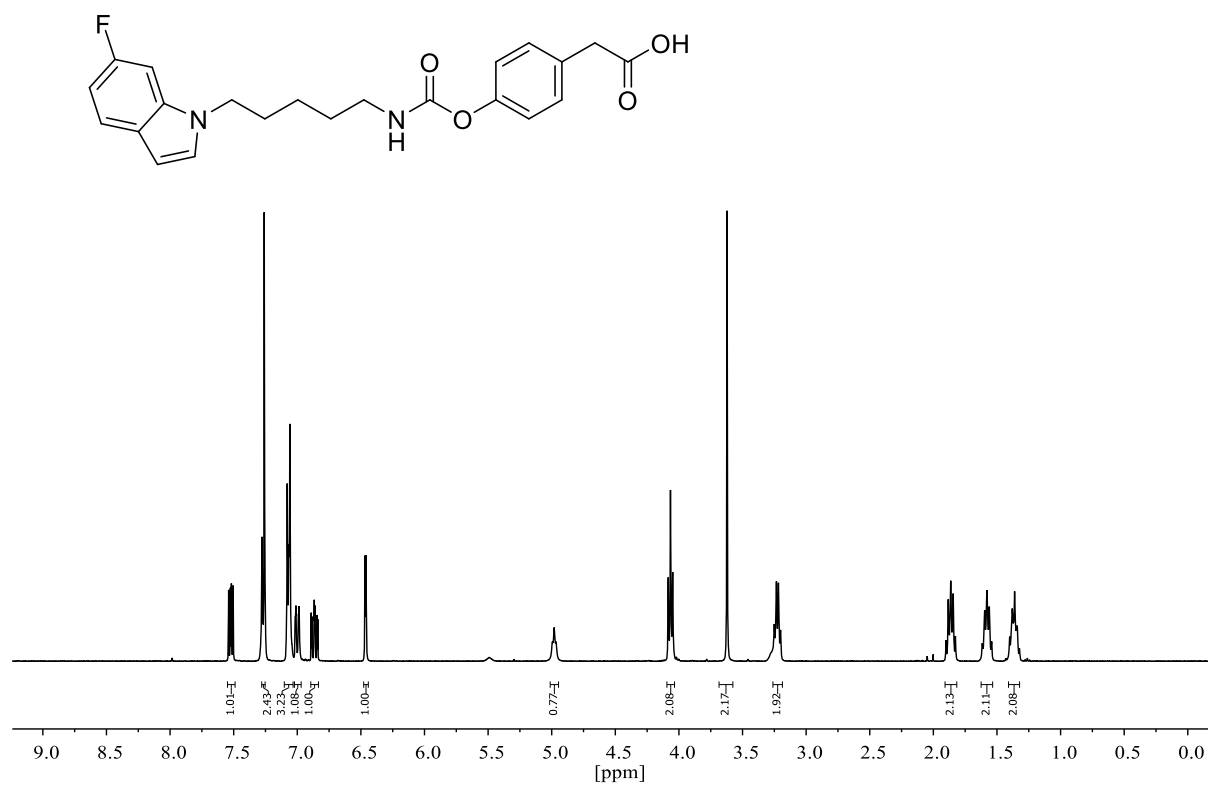


Figure S42. Compound 39

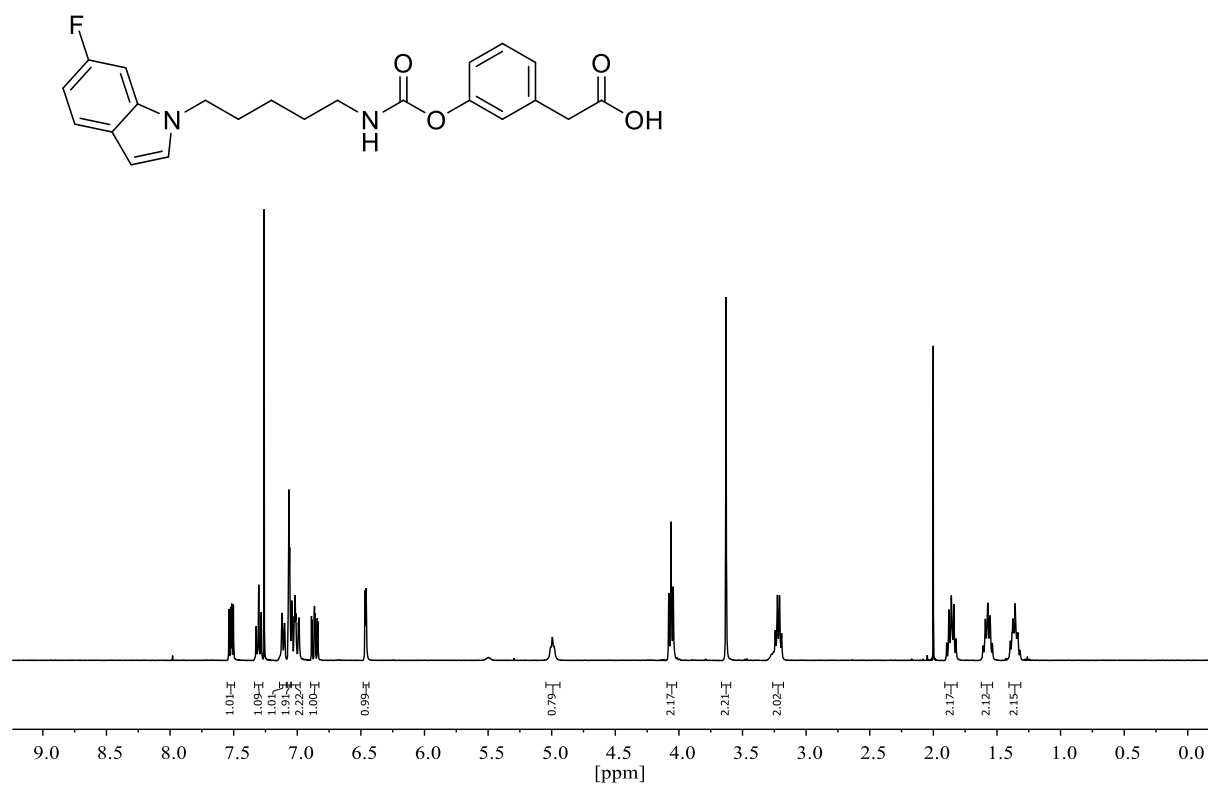


Figure S43. Compound 41

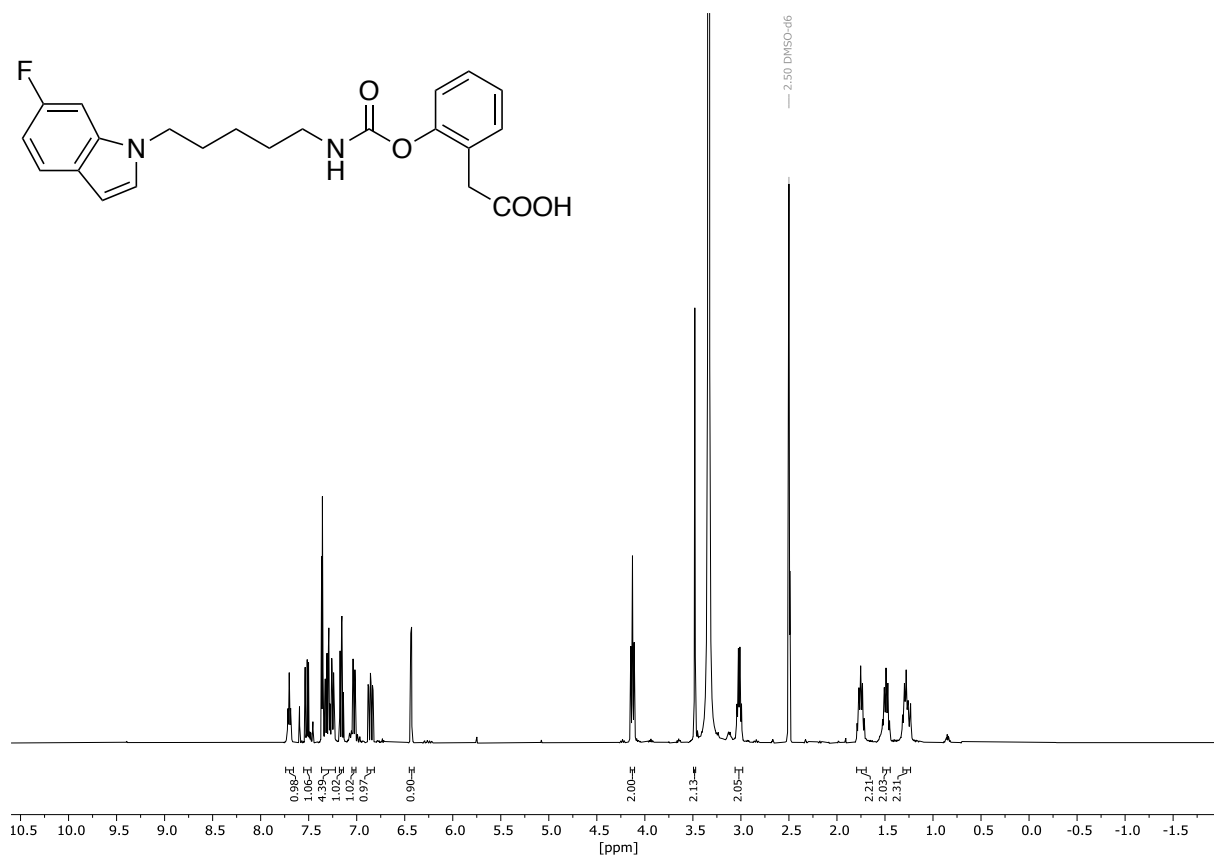


Figure S44. Compound 43

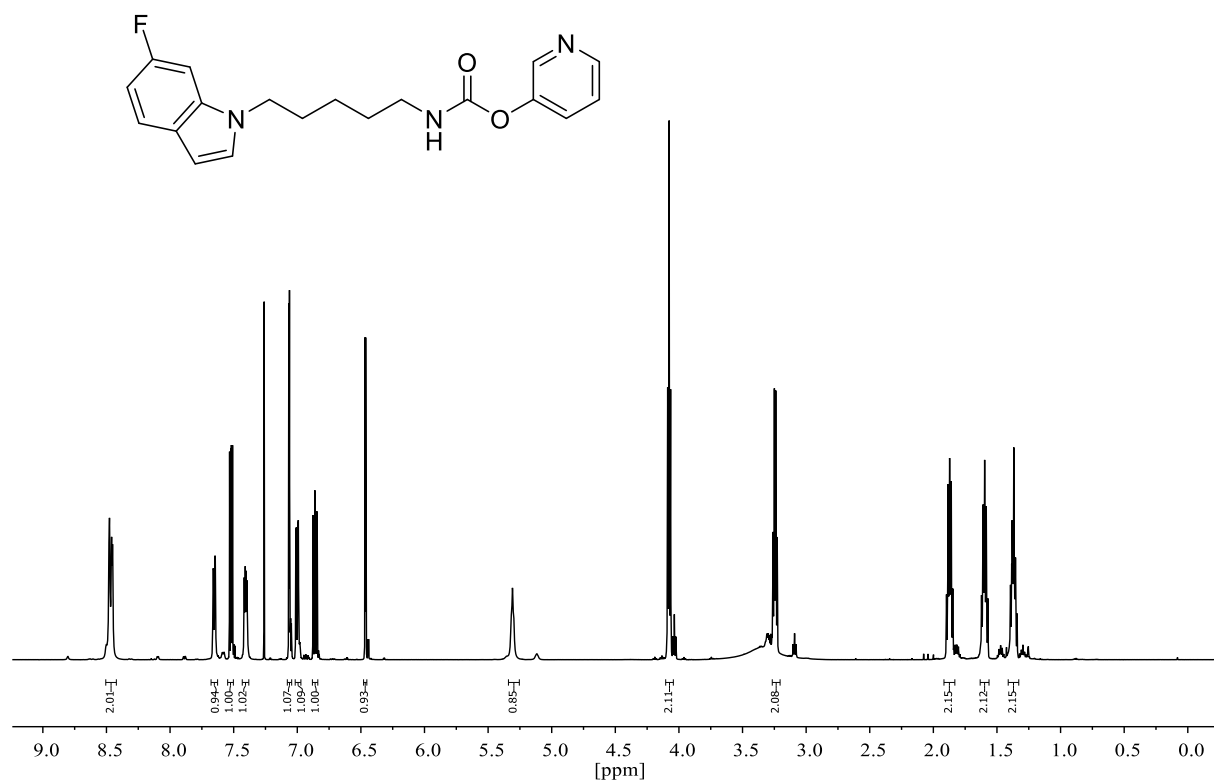


Figure S45. Compound 44

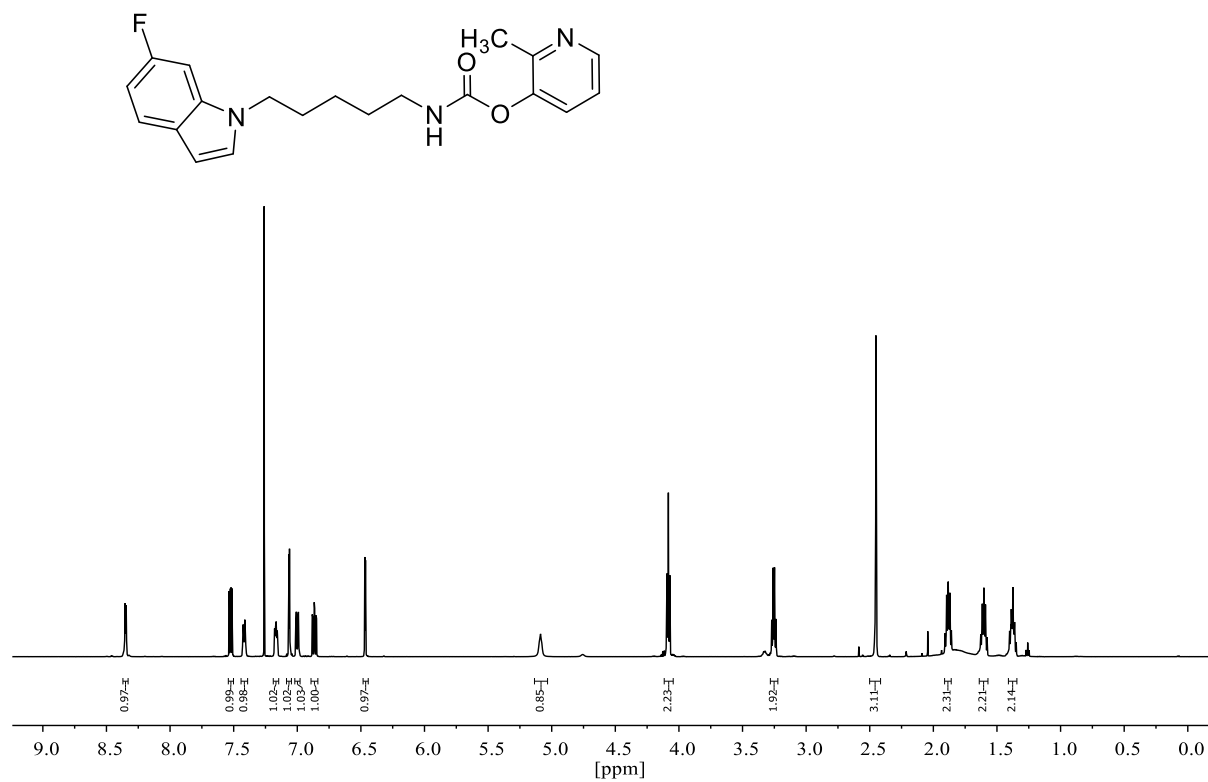


Figure S46. Compound 45

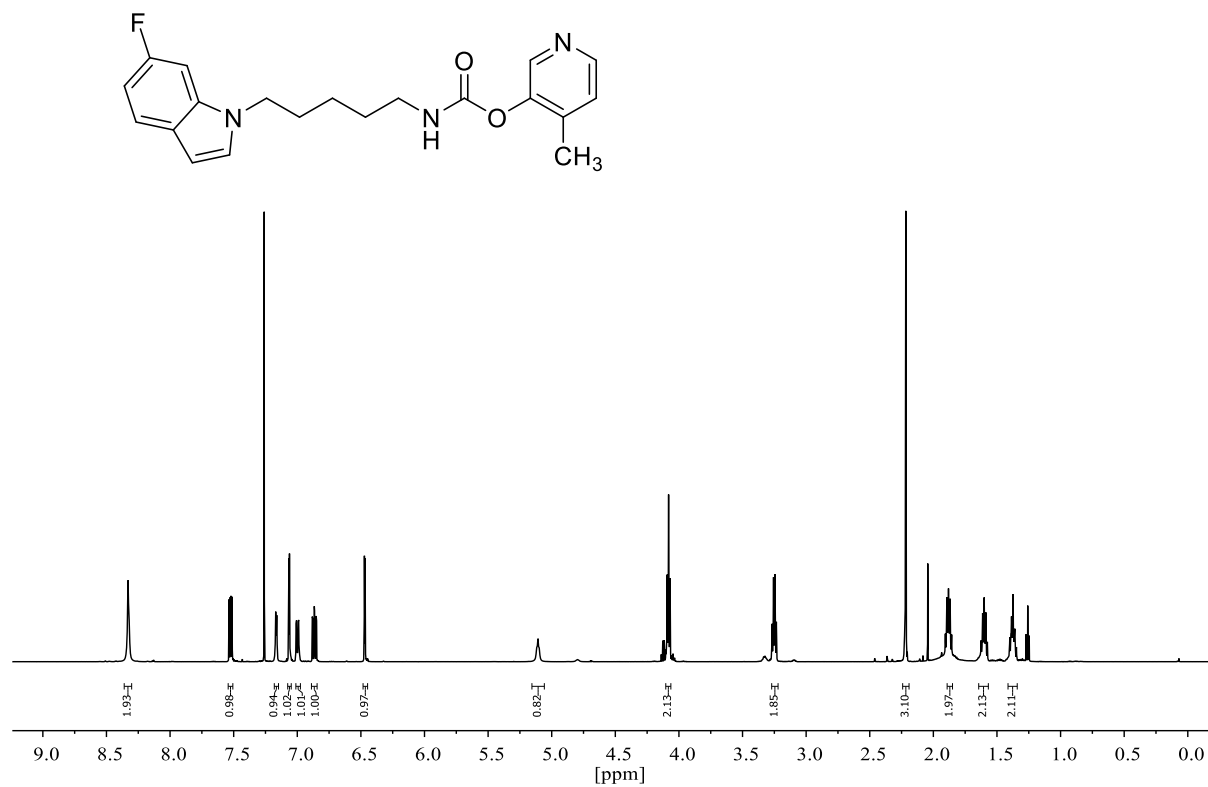


Figure S47. Compound 46

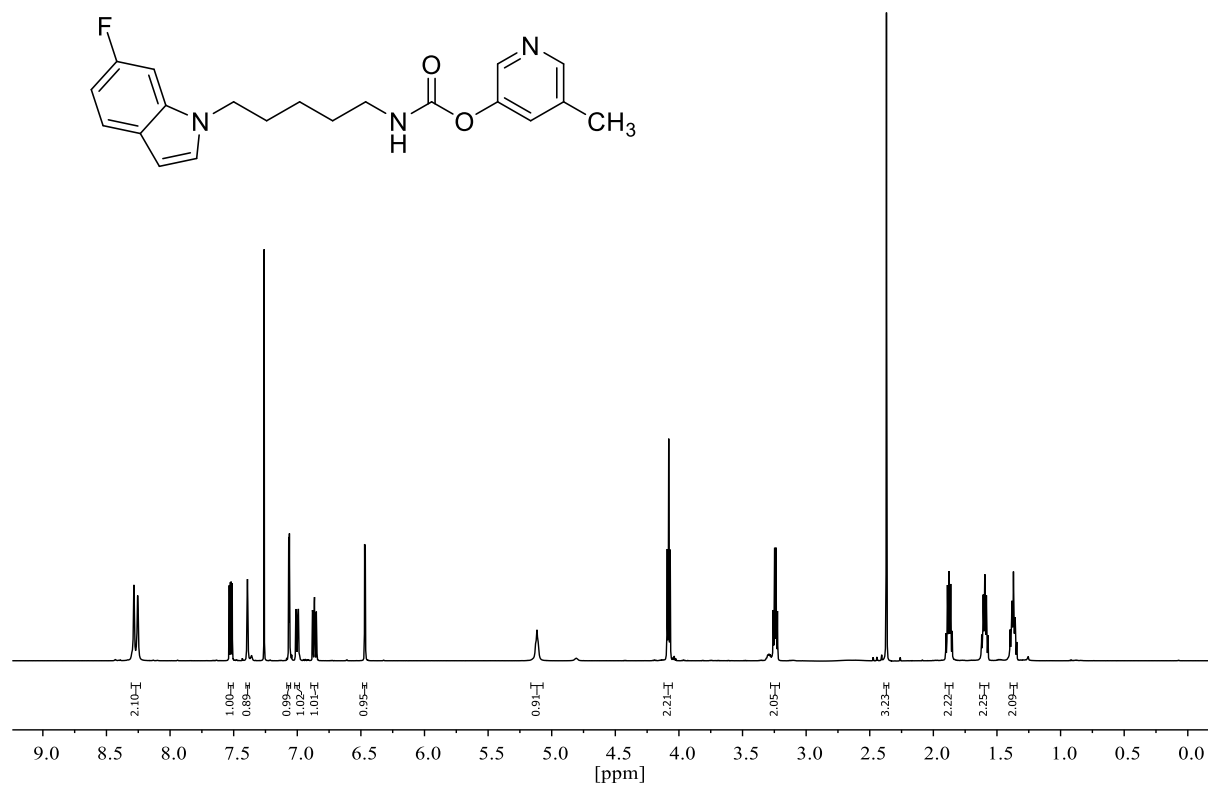


Figure S48. Compound 47

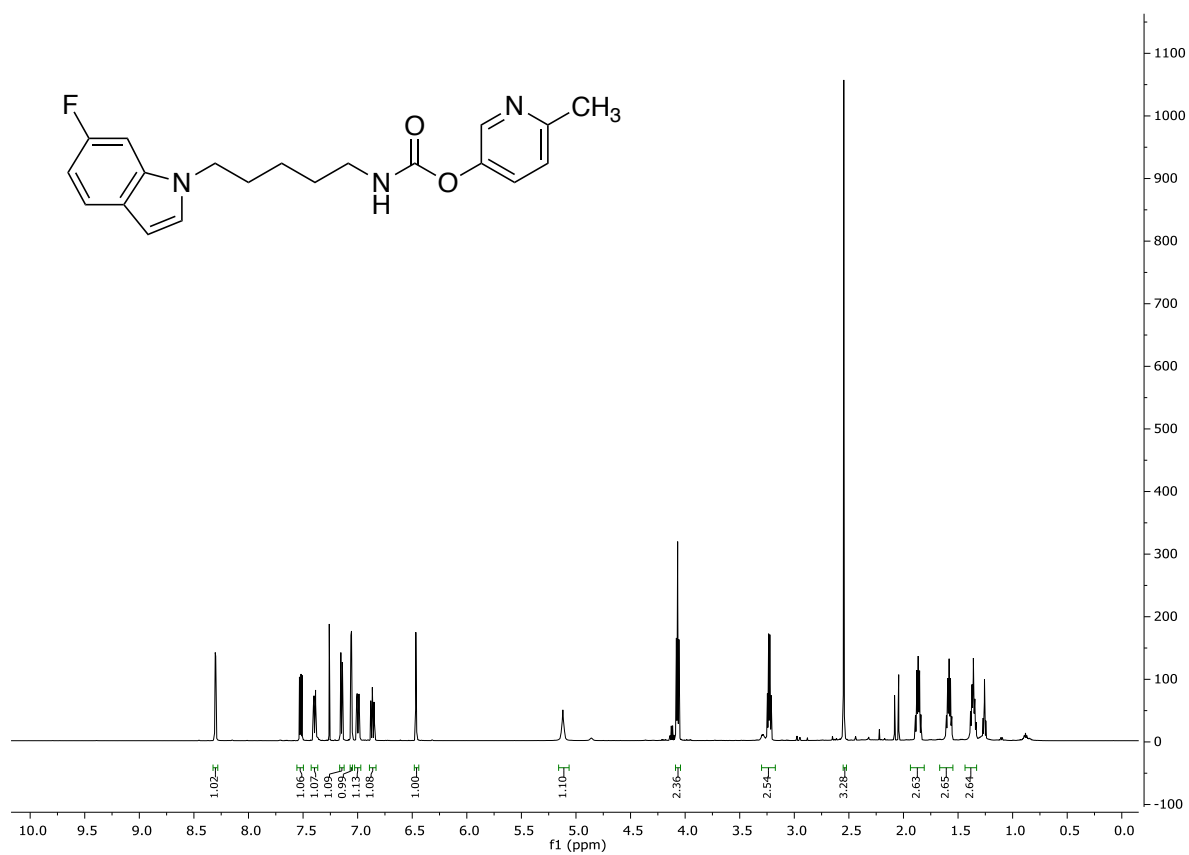


Figure S49. Compound 48

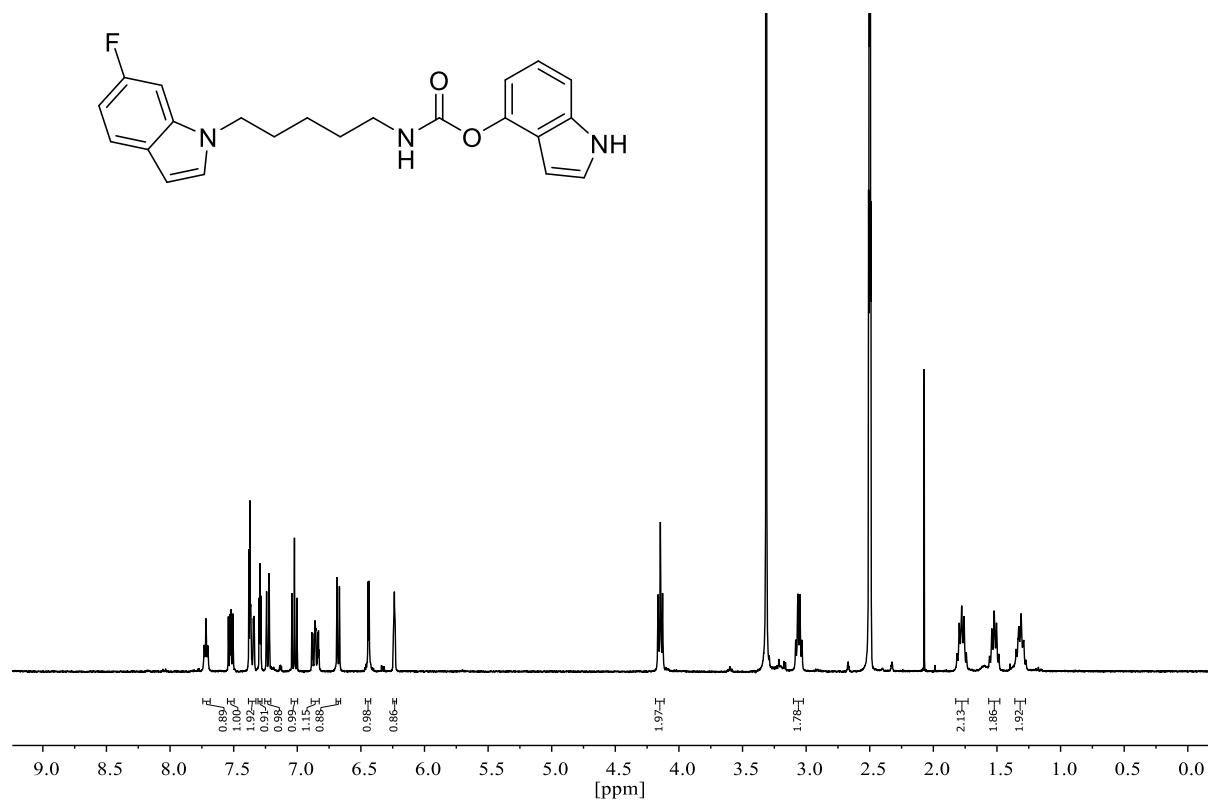


Figure S50. Compound 49

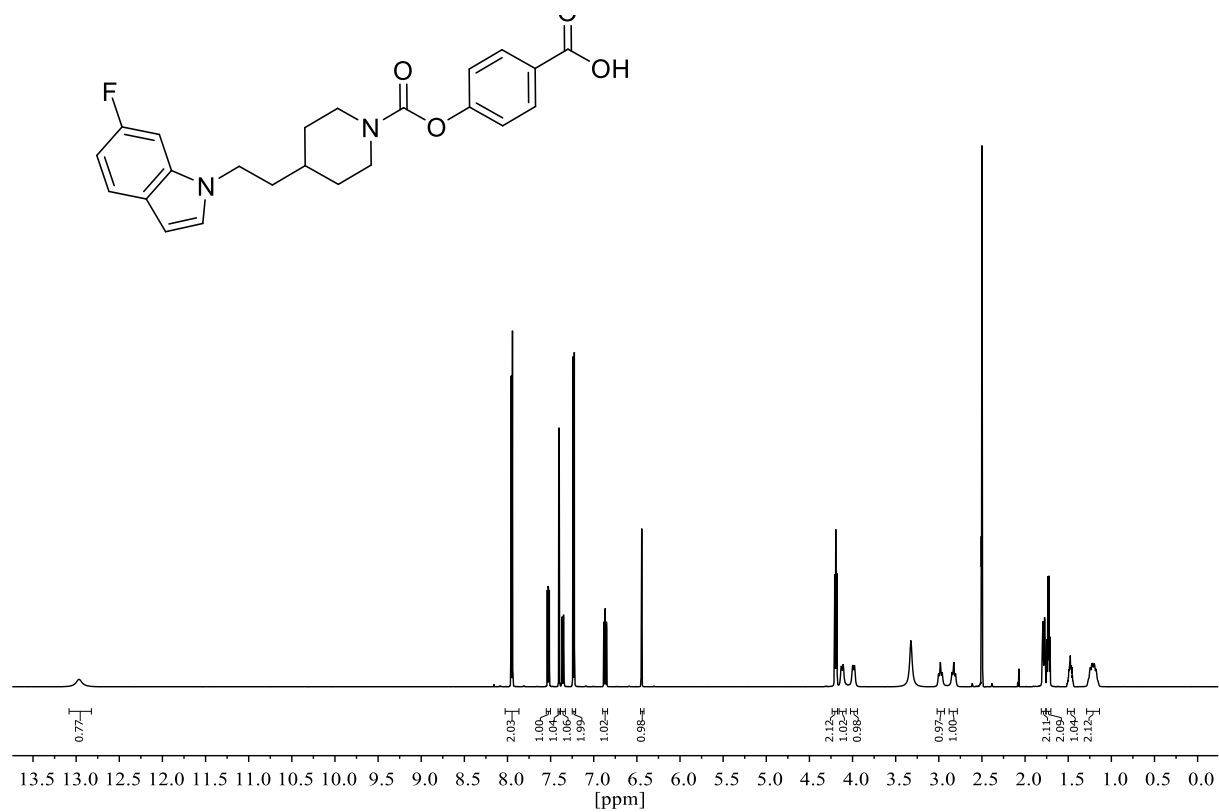


Figure S51. Compound 54

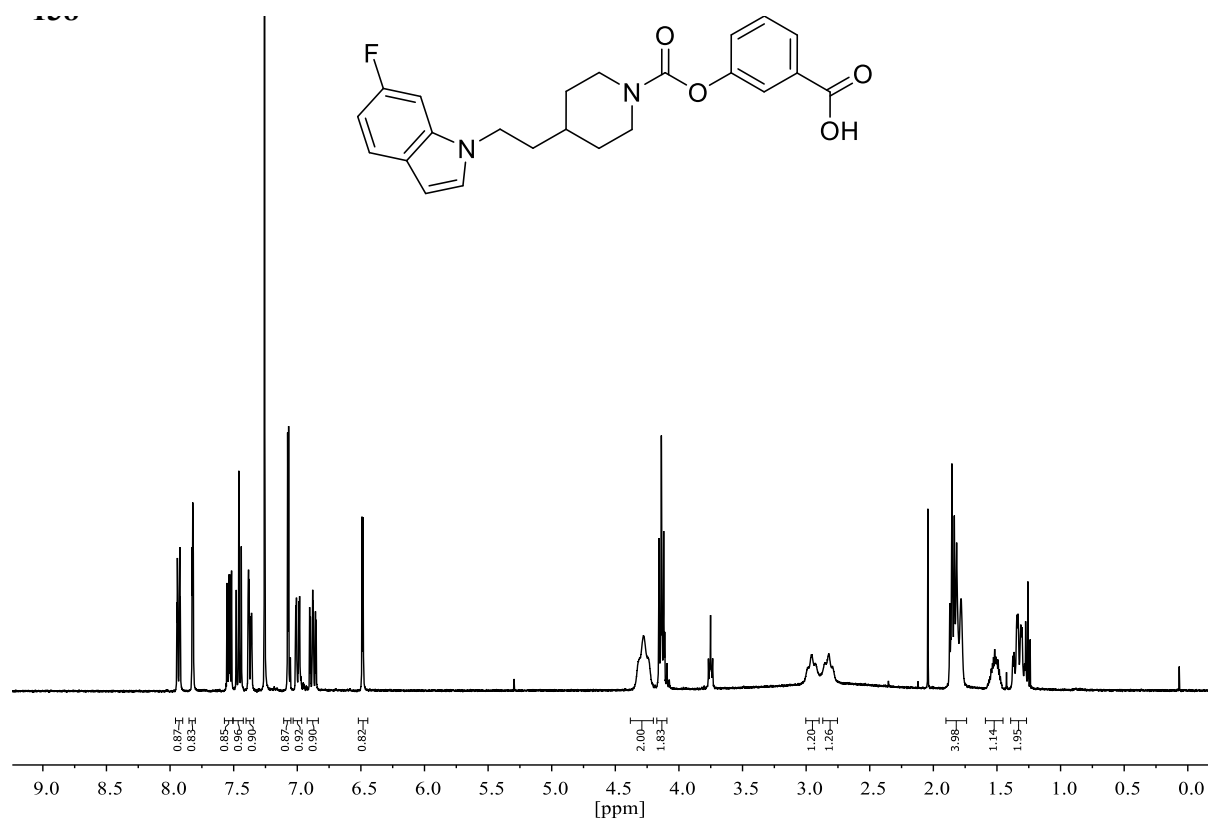


Figure S52. Compound 56

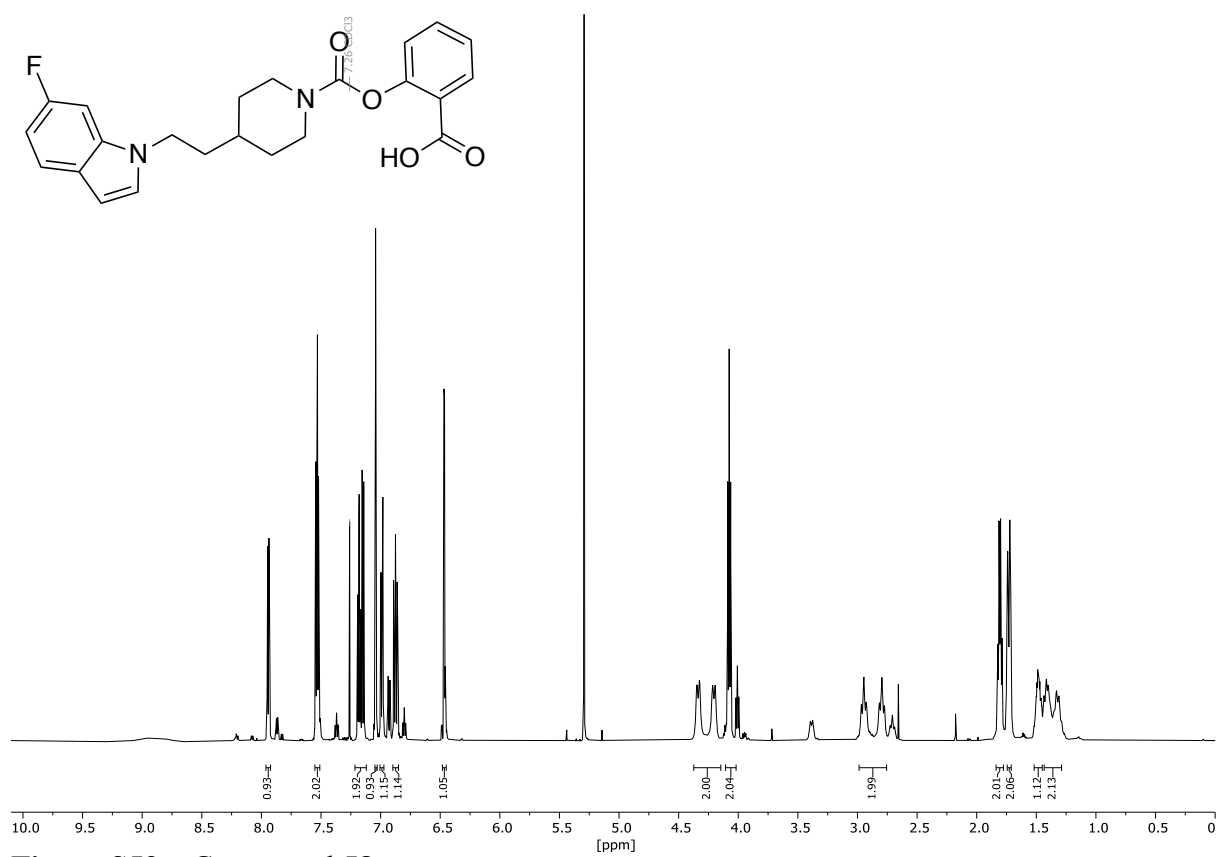


Figure S53. Compound 58