

## *Supporting Information*

### **$\beta$ -Fluorofentanyls are pH-Sensitive Mu Opioid Receptor Agonists**

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## **2. Assay protocols**

To determine mu opioid receptor (MOR) Gi-mediated cAMP production, Promega's split luciferase-based GloSensor™ cAMP biosensor was used. HEK 293T cells were transfected with MOR and GloSensor pGloSensor™-22F cAMP DNA plasmids overnight, using a calcium phosphate transfection method. HEK 293T cells were subcultured into either 10 cm dishes (3 million cells per dish) or 15 cm dishes (8 million cells per dish) and incubated overnight. Alternatively, HEK 293T cells were seeded at a density of 6 million per 10 cm dish 4 hours prior to transfection. For each 10 cm dish of HEK 293T cells, 10 µg receptor DNA construct in 440 µL distilled water is mixed with 60 µL of 2 M CaCl<sub>2</sub>; the DNA/CaCl<sub>2</sub> solution is then added dropwise into 500 µL 2x HBS solution (50 mM HEPES, 280 mM NaCl, 10 mM KCl, 1.5 mM Na<sub>2</sub>HPO<sub>4</sub>, pH 7.00) while shaking. The mixture was incubated at room temperature for 10 min, then added to cells dropwise, which were then incubated overnight. For transfections in 15 cm dishes, reagents and DNA amounts were increased by 2.5 fold per dish. To prepare plates for assays, cells were seeded into PLL-coated 384-well white clear bottom cell culture plates in DMEM supplemented with 1% dFBS at a density of 15-20K cells, in a volume of 40 µL per well. The plates were used for assays after 6 hours or overnight.

On the day of assay, cells were removed from culture medium and receive 20 µL/well of assay buffer (20 mM HEPES, 1x HBSS, pH 7.40 OR 6.50), followed by addition of 10 µL of 3x drug solutions for 15 min at room temperature. To measure agonist activity for Gi-coupled receptors (such as MOR), 10 µL of 4 mM luciferin supplemented with isoproterenol at a final concentration of 200 nM was added, and luminescence counting was done after 15 min. Eight-point concentration-response curves were performed in duplicate twice on two separate lots of cells. For each compound, the results from the four replicates were averaged and EC<sub>50</sub> values were calculated by non-linear regression using the 4-parameter logistic equation.

## **3. Synthetic procedures**

### **a) General information**

All reagents and solvents, including anhydrous solvents, were purchased from commercial vendors and used as received. Deionized water was purified by charcoal filtration to a minimum resistance of 15 MΩ and used for reaction workups and in reactions with water. NMR spectra were recorded on Varian 300 MHz or 400 MHz spectrometers as indicated. Proton and carbon chemical shifts are reported in parts per million (ppm; δ) relative to tetramethylsilane (<sup>1</sup>H δ 0), or CDCl<sub>3</sub> (<sup>13</sup>C δ 77.16), (CD<sub>3</sub>)<sub>2</sub>CO (<sup>1</sup>H δ 2.05, <sup>13</sup>C δ 29.84), d<sub>6</sub>-DMSO (<sup>1</sup>H δ 2.50, <sup>13</sup>C δ 39.5), or CD<sub>3</sub>OD (<sup>1</sup>H δ 3.31, <sup>13</sup>C δ 49.00). NMR data are reported as follows: chemical shifts, multiplicity (obs = obscured, app = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex overlapping signals); coupling constant(s) in Hz; integration. Unless otherwise indicated, NMR data were collected at 25 °C. Filtration was performed by vacuum using VWR Grade 413 filter paper, unless otherwise noted. Unless otherwise noted, solutions were concentrated under reduced pressure using a rotary evaporator with Heidolph Rotovac vacuum pump, and final products, if non-volatile, were dried under high vacuum (typically <1 torr) using a Welch Duoseal 1400 belt-drive vacuum pump. Flash

chromatography was performed using Biotage SNAP cartridges filled with 40-60  $\mu\text{m}$  silica gel on Biotage Isolera automated chromatography systems with photodiode array UV detectors. Analytical thin layer chromatography (TLC) was performed on Agela Technologies 0.25 mm glass plates with 0.25 mm silica gel. Visualization was accomplished with UV light (254 nm) and  $\text{KMnO}_4$  stain, unless otherwise noted. Chemical names were generated and select chemical properties were calculated using either ChemAxon Marvin suite (<https://www.chemaxon.com>) or ChemDraw Professional 15.1. NMR data were processed using either MestreNova or ACD/NMR Processor Academic Edition (<http://www.acdlabs.com>) using the JOC report format. High-resolution mass spectra (HRMS) were obtained from the University of Cincinnati Environmental Analysis Service Center (EASC) with an Agilent 6540 Accurate-Mass with Q-TOF.

### **b) LC-MS characterization methods**

Tandem liquid chromatography/mass spectrometry (LC-MS) was performed on a Shimadzu LCMS-2020 with autosampler, photodiode array detector, and single-quadrupole MS with ESI and APCI dual ionization using a Peak Scientific nitrogen generator.

#### ***Method A***

*Column:* Phenomenex Gemini  $\text{C}_{18}$  (100 x 4.6 mm, 3  $\mu\text{m}$  particle size, 110  $\text{\AA}$  pore size)

*Column temperature:* 40  $^\circ\text{C}$

*Sample Injection:* 1–5  $\mu\text{L}$  of sample in MeCN or MeOH

*Chromatographic monitoring:* UV absorbance at 210 or 254 nm

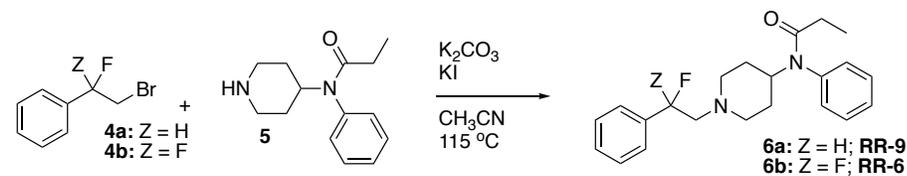
*Mobile Phase:* Solvent A:  $\text{H}_2\text{O}$  w/ 0.1% formic acid; Solvent B: MeOH w/ 0.1% formic acid

*Flow Rate:* 1.0 mL/min

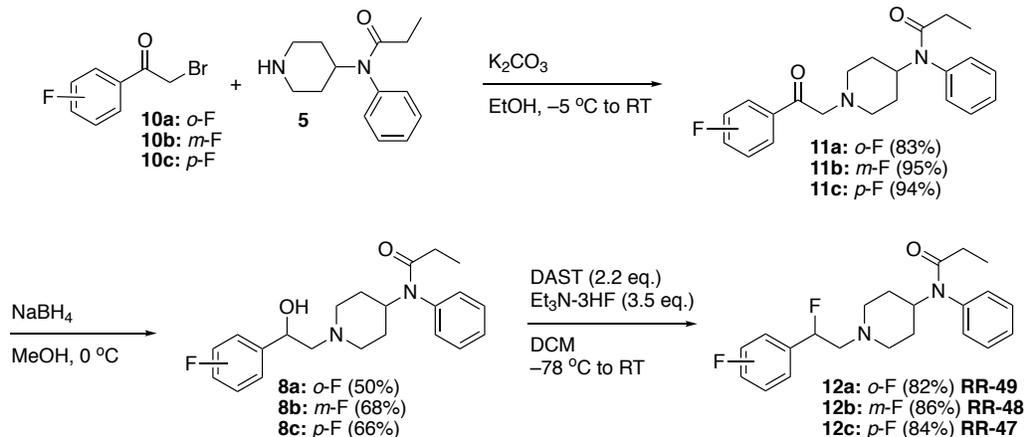
*Gradient:*  
 0 to 0.1 min: 25% MeOH (Isocratic)  
 0.1 min to 5 min: 25% to 95% MeOH (Gradient)  
 5 min to 7 min: 95% MeOH (Isocratic)

### **c) Synthetic schemes**

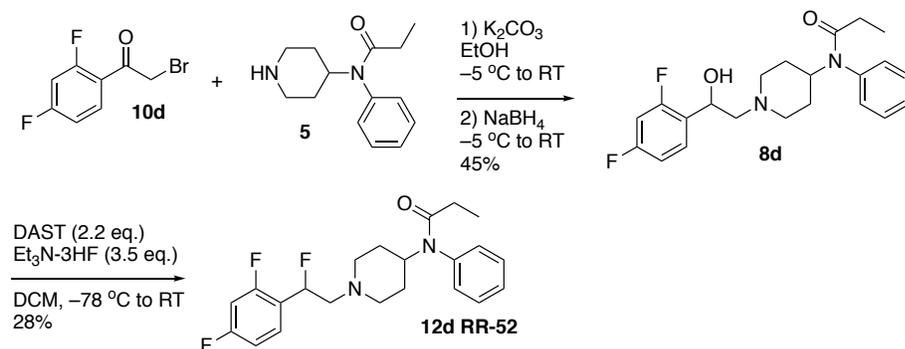
#### **Scheme 1. One-step synthesis of $\beta$ -fluorofentanyls**



### Scheme 3. 3-step synthesis of $\beta$ -fluorofentanyl

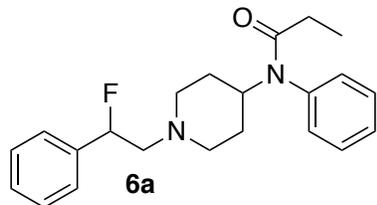


### Scheme 4. Synthesis of 12d



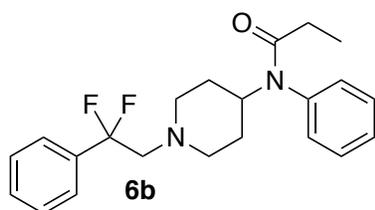
### d) Experimental procedures for fluorinated fentanyl analogs

It is assumed that all of the synthesized compounds described below may be highly potent  $\mu$  opioid receptor agonists, and could lead to dangerous respiratory depression in persons inadvertently exposed to them. Researchers should wear suitable protective gear (including gloves, glasses, and lab coats), especially to avoid exposed skin in the case of spills. As a precaution, we recommend disposing glassware, solid waste, and waste from chemical workups into separate suitably labeled waste containers. Secondary containers should be used whenever possible when transporting compounds and solutions.

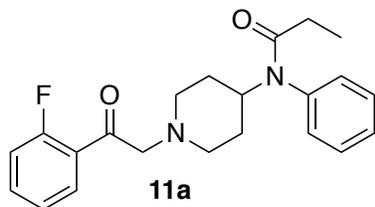


To a 4 mL vial, *N*-phenyl-*N*-(4-piperidyl)propanamide (25.6 mg, 0.11 mmol),  $K_2CO_3$  (30 mg, 0.22 mmol), and KI (9.4 mg, 0.06 mmol) were added with a magnetic stir bar. Acetonitrile (5

mL) was charged to the flask and then (2-bromo-1-fluoroethyl)benzene (37.1 mg, 0.18 mmol) was added. The reaction was stirred at 115 °C for 2 days. A sample aliquot was taken from the reaction, diluted with DCM in a microtube, and washed with half-saturated aq. Na<sub>2</sub>CO<sub>3</sub>. The organic layer was separated and analyzed by LC-MS to confirm reaction completion. The reaction was concentrated under reduced pressure, and the crude material was dissolved in a minimal amount of DCM and dry loaded on celite. The celite/crude material was loaded into an empty 10 g Biotage cartridge which was connected to a 12 g C18 column and purified by reverse phase chromatography (0–95% MeOH/water) to give **6a** as a yellow oil (10 mg, 25%). LC/MS t<sub>R</sub> = 1.42 min (Characterization Method A); m/z = 354.85 (M + H); <sup>1</sup>H NMR (300 MHz, CD<sub>2</sub>Cl<sub>3</sub>) δ = 7.46 - 7.27 (comp, 8 H), 7.12 - 7.04 (comp, 2 H), 5.69 - 5.44 (m, 1 H), 4.69 (tt, J = 4.0, 12.2 Hz, 1 H), 3.12 - 2.97 (m, 2 H), 2.87 (ddd, J = 9.3, 14.4, 17.2 Hz, 1 H), 2.64 - 2.43 (m, 1 H), 2.39 - 2.20 (m, 2 H), 1.93 (q, J = 7.4 Hz, 2 H), 1.86 - 1.74 (m, 2 H), 1.58 - 1.37 (m, 2 H), 1.02 (t, J = 7.5 Hz, 3 H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 173.8, 139.1, 139.0, 138.9, 130.7, 129.5, 128.7, 128.6, 128.5, 125.7, 125.6, 93.9, 91.6, 65.1, 64.7, 54.2, 53.5, 52.2, 30.8, 28.8, 9.9. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ = -176.18–176.42 (ddd, 17.7 Hz, 49 Hz, 1 F). HR-MS (ESI+) calcd. for C<sub>22</sub>H<sub>28</sub>FN<sub>2</sub>O (M + H) 355.2180, found 355.2192.

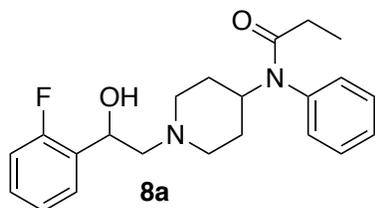


To a 4 mL vial, *N*-phenyl-*N*-(4-piperidyl)propanamide (24.7 mg, 0.106 mmol), K<sub>2</sub>CO<sub>3</sub> (30.4 mg, 0.220 mmol), and KI (5.70 mg, 0.0343 mmol) were added with a magnetic stir bar. Acetonitrile (5 mL) was charged to the vial and then (2-bromo-1,1-difluoro-ethyl)benzene (29.7 mg, 0.134 mmol) was added. The reaction was stirred at 90 °C for 2 days. A sample aliquot was taken from the reaction, diluted with DCM in a microtube, and washed with half-saturated aq. Na<sub>2</sub>CO<sub>3</sub>. The organic layer was separated and analyzed by LC-MS to confirm reaction completion. The reaction was concentrated under reduced pressure, and the crude material was dissolved in a minimal amount of DCM and dry loaded on celite. The celite/crude material was loaded onto an empty 10 g Biotage cartridge which was connected to a 12 g C18 column and purified by reverse phase chromatography (0–95% MeOH/water) to give **6b** as a yellow oil (12 mg, 31%); <sup>1</sup>H NMR (300 MHz, CD<sub>2</sub>Cl<sub>3</sub>) δ = 7.48 - 7.29 (m, 8 H), 7.11 - 6.98 (m, 2 H), 4.60 (tt, J = 3.8, 12.2 Hz, 1 H), 2.96 - 2.79 (m, 4 H), 2.48 - 2.33 (m, 2 H), 1.90 (q, J = 7.4 Hz, 2 H), 1.74 - 1.61 (m, 2 H), 1.35 (dq, J = 3.9, 12.2 Hz, 2 H), 1.00 (t, J = 7.4 Hz, 3 H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 173.7, 139.1, 137.0, 136.7, 136.3, 130.6, 129.9, 129.5, 128.5, 128.4, 125.6, 125.5, 125.4, 122.0, 64.2, 63.8, 63.5, 54.5, 52.2, 30.9, 28.7, 9.8. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ = -99.04. HR-MS (ESI+) calcd. for C<sub>22</sub>H<sub>27</sub>F<sub>2</sub>N<sub>2</sub>O (M + H) 373.2086, found 373.2093.



***N*-{1-[2-(2-fluorophenyl)-2-oxoethyl]piperidin-4-yl}-*N*-phenylpropanamide (11a)**

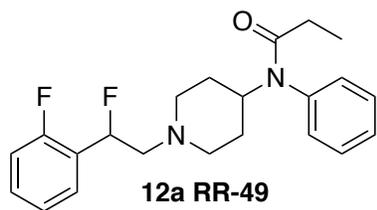
To a 20 mL scintillation vial with a stir bar was added *N*-phenyl-*N*-(4-piperidyl)propanamide (28.1 mg, 0.121 mmol), 2-bromo-1-(2-fluorophenyl)ethanone (33.7 mg, 0.155 mmol), and  $K_2CO_3$  (21.3 mg, 0.154 mmol). The vial was sealed, and flushed with nitrogen while in an ice bath at  $-5\text{ }^\circ\text{C}$ , then ethanol (10 mL) was added by syringe. The reaction was allowed to warm up to room temperature over 4 h, after which time a sample aliquot was taken from the reaction, diluted with DCM in a microtube, and washed with half-saturated aq.  $Na_2CO_3$ . The organic layer was separated and analyzed by TLC to confirm reaction completion. The reaction was concentrated under reduced pressure, and the crude material was dissolved in a minimal amount of DCM and loaded onto a 25 g silica column, and purified by flash chromatography (25 g  $SiO_2$ ; 0–5% MeOH/DCM) to give **11a** as a yellow oil (37 mg, 81%). TLC: mobile phase: MeOH:DCM (10:90),  $R_f = 0.68$ ; LC/MS  $t_R = 3.76$  min (Characterization Method A);  $m/z = 368.90$  (M + H);  $^1H$  NMR (400 MHz,  $CD_2Cl_3$ )  $\delta = 7.82$  (dt,  $J = 1.8, 7.5$  Hz, 1 H), 7.53 - 7.44 (m, 1 H), 7.41 - 7.31 (comp, 3 H), 7.22 - 7.14 (m, 1 H), 7.12 - 7.01 (comp, 3 H), 4.68 (tt,  $J = 4.0, 12.2$  Hz, 1 H), 3.73 (d,  $J = 3.3$  Hz, 2 H), 2.99 (d,  $J = 11.4$  Hz, 2 H), 2.27 (dt,  $J = 2.0, 11.8$  Hz, 2 H), 1.91 (q,  $J = 7.4$  Hz, 2 H), 1.81 - 1.70 (m, 2 H), 1.52 (dq,  $J = 3.9, 12.3$  Hz, 2 H), 0.99 (t,  $J = 7.5$  Hz, 3 H).  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta = 195.0, 173.5, 163.0, 160.5, 138.8, 134.6, 134.5, 130.6, 130.6, 130.4, 129.2, 128.2, 124.5, 124.5, 116.6, 116.4, 68.1, 68.0, 54.0, 51.9, 30.1, 28.6, 9.6$ .  $^{19}F$  NMR (376 MHz,  $CDCl_3$ )  $\delta = -107.73$ .



***N*-{1-[2-(2-fluorophenyl)-2-hydroxyethyl]piperidin-4-yl}-*N*-phenylpropanamide (8a)**

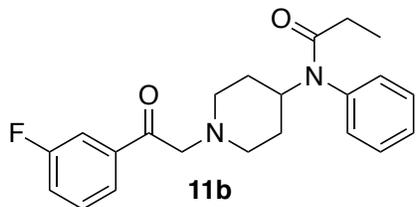
To an oven dried 20 mL scintillation vial with a stir bar was added **11a** (32.6 mg, 88.4  $\mu\text{mol}$ ), which was subsequently diluted in anhydrous MeOH (10 mL). The vial was cooled in an ice bath to  $0\text{ }^\circ\text{C}$ , and  $NaBH_4$  (9.2 mg, 243  $\mu\text{mol}$ ) was added. The vial was sealed and stirred while vented to an oil bubbler and allowed to gradually warm up to room temperature over 2 h. A sample aliquot was taken from the reaction, diluted with DCM in a microtube, and washed with half saturated  $Na_2CO_3$ . The organic layer was separated and analyzed by TLC to confirm reaction completion. The reaction was diluted with EtOAc (30 mL), washed with half-saturated aq.  $Na_2CO_3$  (2 x 15 mL), dried over with  $Na_2SO_4$ , filtered, and concentrated under reduced pressure. The crude product was dissolved in a minimal amount of DCM, loaded onto a 25 g  $SiO_2$  column,

and purified with flash chromatography (0–6% MeOH/DCM) to give **8a** as a yellow oil (16 mg, 50%). TLC: mobile phase: MeOH:DCM (10:90),  $R_f = 0.65$ ; LC/MS  $t_R = 3.65$  min (Characterization Method A);  $m/z = 370.90$  (M + H);  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta = 7.53 - 7.46$  (m, 1 H), 7.46 - 7.36 (comp, 3 H), 7.23 - 7.15 (m, 1 H), 7.15 - 7.04 (comp, 2 H), 6.96 (ddd,  $J = 1.2, 8.2, 10.6$  Hz, 1 H), 4.95 (dd,  $J = 2.9, 10.6$  Hz, 1 H), 4.67 (tt,  $J = 3.8, 12.1$  Hz, 1 H), 3.14 (d,  $J = 12.3$  Hz, 1 H), 2.77 (d,  $J = 11.7$  Hz, 1 H), 2.61 - 2.51 (m, 1 H), 2.45 (dt,  $J = 2.4, 11.9$  Hz, 1 H), 2.38 - 2.28 (m, 1 H), 2.25 - 2.14 (m, 1 H), 1.91 (q,  $J = 7.4$  Hz, 2 H), 1.85 - 1.72 (m, 2 H), 1.50 - 1.30 (m, 2 H), 1.00 (t,  $J = 7.5$  Hz, 3 H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta = 173.5, 138.9, 130.3, 129.4, 128.7, 128.6, 128.4, 127.2, 127.2, 124.2, 115.1, 114.8, 64.1, 63.1, 54.9, 52.0, 51.1, 30.9, 30.5, 28.5, 9.6$ .  $^{19}\text{F NMR}$  (376 MHz,  $\text{CDCl}_3$ )  $\delta = -120.33$ .



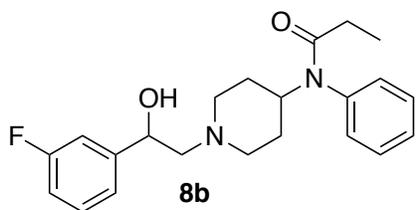
#### ***N*-{1-[2-fluoro-2-(2-fluorophenyl)ethyl]piperidin-4-yl}-*N*-phenylpropanamide (12a, RR-49)**

To an oven dried 20 mL scintillation vial with a stir bar was added **8a** (39.7 mg, 0.107 mmol). The vial was sealed and flushed with nitrogen for 5 min., then dry DCM (10 mL) was added by syringe. The solution was cooled to  $-78$  °C in an acetone/dry ice bath and to this were added triethylamine trihydrofluoride (20.0  $\mu\text{L}$ , 0.123 mmol) and DAST (10.0  $\mu\text{L}$ , 0.0757 mmol) by syringe, respectively. The reaction stirred at  $-78$  °C for 4 h, and then allowed to gradually warm up to room temperature overnight. A sample aliquot was taken from the reaction, diluted with EtOAc in a microtube, and washed with half-saturated  $\text{Na}_2\text{CO}_3$ . The organic layer was separated and analyzed by TLC to confirm reaction completion. The reaction was quenched with half-saturated aq.  $\text{Na}_2\text{CO}_3$  (6 mL) and allowed to vigorously stir for 10 min. The reaction mixture was then transferred to a separatory funnel and diluted with EtOAc (30 mL), washed with half-saturated aq.  $\text{Na}_2\text{CO}_3$  (2 x 15 mL), dried over with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The crude product was dissolved in a minimal amount of DCM, loaded onto a 10 g  $\text{SiO}_2$  column, and purified by flash chromatography (0–6% MeOH/DCM) to give **12a** as a yellow oil (13 mg, 82%). TLC: mobile phase MeOH:DCM (10:90),  $R_f = 0.67$ ; LC/MS;  $t_R = 4.10$  min (Characterization Method A);  $m/z = 373.25$  (M + H);  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta = 7.48 - 7.27$  (comp, 5 H), 7.21 - 6.95 (comp, 4 H), 5.99 - 5.75 (m, 1 H), 4.70 (tt,  $J = 3.8, 12.2$  Hz, 1 H), 3.13 - 3.00 (m, 1 H), 2.87 (ddd,  $J = 9.1, 14.4, 18.2$  Hz, 1 H), 2.71 - 2.49 (m, 1 H), 2.43 - 2.25 (comp, 2 H), 1.93 (q,  $J = 7.4$  Hz, 2 H), 1.80 (dd,  $J = 2.1, 12.4$  Hz, 2 H), 1.57 - 1.38 (comp, 2 H), 1.25 (s, 1 H), 1.02 (t,  $J = 7.4$  Hz, 3 H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta = 173.8, 139.0, 130.7, 130.2, 130.1, 129.5, 128.5, 127.3, 127.1, 124.5, 115.7, 115.4, 88.5, 86.1, 63.7, 63.4, 54.1, 53.4, 52.1, 30.7, 28.7, 9.8$ .  $^{19}\text{F NMR}$  (376 MHz,  $\text{CDCl}_3$ )  $\delta = -118.87, -184.19 - 184.46$  (ddd, 17.7 Hz, 49 Hz, 1 F). HR-MS (ESI+) calcd. for  $\text{C}_{22}\text{H}_{27}\text{F}_2\text{N}_2\text{O}$  (M + H) 373.2086, found 373.2099.



***N*-{1-[2-(3-fluorophenyl)-2-oxoethyl]piperidin-4-yl}-*N*-phenylpropanamide (11b)**

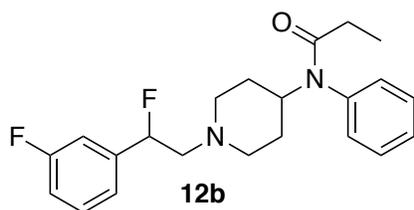
To a 20 mL scintillation vial with a stir bar was added *N*-phenyl-*N*-(4-piperidyl)propanamide (50.0 mg, 0.215 mmol), 2-bromo-1-(3-fluorophenyl)ethanone (60.0 mg, 0.276 mmol), and  $K_2CO_3$  (37.9 mg, 0.274 mmol). The vial was sealed, flushed with nitrogen, and chilled to  $-5\text{ }^\circ\text{C}$  in an ice bath, then ethanol (10 mL) was added. The reaction was allowed to warm up to room temperature over 4 h, after which time a sample aliquot was taken from the reaction, diluted with DCM in a microtube, and washed with half-saturated aq.  $Na_2CO_3$ . The organic layer was separated and analyzed by TLC to confirm reaction completion. The reaction was concentrated under reduced pressure, and the crude material was dissolved in a minimal amount of DCM and loaded onto a 25 g silica column, and purified by flash chromatography (0–5% MeOH/DCM) to give **11b** as an off-white solid (75 mg, 94%). TLC: mobile phase: MeOH:DCM (10:90); LC/MS  $t_R = 3.96$  min (Characterization Method A);  $m/z = 368.95$  (M + H);  $^1H$  NMR (400 MHz,  $CD_2Cl_2$ )  $\delta = 7.71 - 7.66$  (m, 1 H), 7.63 - 7.57 (m, 1 H), 7.42 - 7.31 (m, 4 H), 7.24 - 7.18 (m, 1 H), 7.09 - 7.02 (m, 2 H), 4.68 (tt,  $J = 3.9, 12.2$  Hz, 1 H), 3.72 (s, 2 H), 3.01 - 2.94 (m, 2 H), 2.25 (dt,  $J = 2.0, 11.8$  Hz, 2 H), 1.90 (q,  $J = 7.5$  Hz, 2 H), 1.81 - 1.71 (m, 2 H), 1.51 (dq,  $J = 3.8, 12.3$  Hz, 2 H), 0.99 (t,  $J = 7.4$  Hz, 3 H).  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta = 195.1, 173.5, 163.9, 161.5, 138.7, 138.0, 137.9, 130.4, 130.2, 130.2, 129.3, 128.3, 123.7, 123.6, 120.3, 120.1, 114.9, 114.7, 64.4, 53.7, 51.8, 30.4, 28.5, 9.6$ .  $^{19}F$  NMR (376 MHz,  $CDCl_3$ )  $\delta = -111.75$ .



***N*-{1-[2-(3-fluorophenyl)-2-hydroxyethyl]piperidin-4-yl}-*N*-phenylpropanamide (8b)**

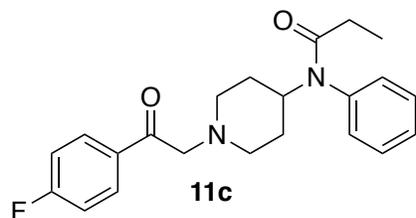
To an oven dried 20 mL scintillation vial with a stir bar was added **11b** (66.6 mg, 0.181 mmol), which was subsequently diluted in anhydrous MeOH (10 mL). The vial was cooled in an ice bath to  $0\text{ }^\circ\text{C}$ , then  $NaBH_4$  (19.8 mg, 0.523 mmol) was added. The vial was sealed and stirred while vented to an oil bubbler and allowed to gradually warm up to room temperature over 2 h. A sample aliquot was taken from the reaction, diluted with DCM in a microtube, and washed with half saturated  $Na_2CO_3$ . The organic layer was separated and analyzed by TLC to confirm reaction completion. The reaction was diluted with EtOAc (30 mL), washed with half-saturated aq.  $Na_2CO_3$  (2 x 15 mL), dried over with  $Na_2SO_4$ , filtered, and concentrated under reduced pressure. The crude product was dissolved in a minimal amount of DCM, loaded onto a 25 g  $SiO_2$  column, and purified with flash chromatography (0–6% MeOH/DCM) to give **8b** as a yellow oil (45 mg,

68%). TLC: mobile phase: MeOH:DCM (10:90),  $R_f = 0.65$ ; LC/MS  $t_R = 3.65$  min (Characterization Method A);  $m/z = 370.90$  (M + H);  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta = 7.46 - 7.36$  (comp, 3 H), 7.28 - 7.21 (m, 1 H), 7.10 - 7.01 (comp, 4 H), 6.94 - 6.87 (m, 1 H), 4.67 (tt,  $J = 3.9, 12.2$  Hz, 1 H), 4.60 (dd,  $J = 3.4, 10.6$  Hz, 1 H), 3.15 - 3.06 (m, 1 H), 2.81 - 2.72 (m, 1 H), 2.49 - 2.39 (m, 2 H), 2.31 (dd,  $J = 10.7, 12.5$  Hz, 1 H), 2.17 (dt,  $J = 2.3, 11.8$  Hz, 1 H), 1.91 (q,  $J = 7.4$  Hz, 2 H), 1.85 - 1.70 (m, 2 H), 1.48 - 1.27 (m, 2 H), 1.00 (t,  $J = 7.4$  Hz, 3 H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta = 173.5, 164.1, 161.7, 145.0, 144.9, 138.8, 130.3, 129.8, 129.7, 129.4, 128.4, 121.3, 121.2, 114.3, 114.1, 112.8, 112.5, 68.3, 65.7, 54.8, 52.0, 51.0, 30.8, 30.4, 9.6$ .  $^{19}\text{F NMR}$  (376 MHz,  $\text{CDCl}_3$ )  $\delta = -113.22$ .



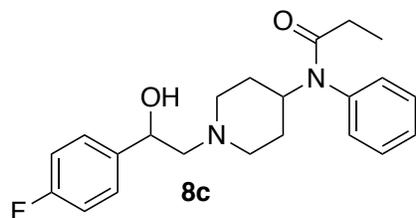
### *N*-{1-[2-fluoro-2-(3-fluorophenyl)ethyl]piperidin-4-yl}-*N*-phenylpropanamide (**12b**)

To an oven dried 20 mL scintillation vial with a stir bar was added **8b** (39.7 mg, 0.107 mmol). The vial was sealed and flushed with nitrogen gas for 5 min. and to this was added anhydrous DCM (10 mL) by syringe. The solution was cooled to  $-78$  °C in an acetone/dry ice bath, then triethylamine trihydrofluoride (40.0  $\mu\text{L}$ , 0.245 mmol) and DAST (20.0  $\mu\text{L}$ , 0.151 mmol) were added by syringe. The reaction stirred at  $-78$  °C for 4 h, and then allowed gradually to warm up to room temperature overnight. A sample aliquot was taken from the reaction, diluted with EtOAc in a microtube, and washed with half-saturated  $\text{Na}_2\text{CO}_3$ . The organic layer was separated and analyzed by TLC to confirm reaction completion. The reaction was quenched with half-saturated aq.  $\text{Na}_2\text{CO}_3$  (6 mL) and stirred vigorously for 10 min. The reaction mixture was then transferred to a separatory funnel and diluted with EtOAc (30 mL), washed with half-saturated aq.  $\text{NaHCO}_3$  (2 x 15 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The crude product was dissolved in a minimal amount of DCM, loaded onto a 10 g  $\text{SiO}_2$  column, and purified with flash chromatography (0–6% MeOH/DCM) to give **12b** as a yellow oil (35 mg, 86%). TLC: mobile phase MeOH:DCM (10:90),  $R_f = 0.67$ ; LC/MS  $t_R = 3.98$  min (Characterization Method A);  $m/z = 373.25$  (M + H);  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta = 7.45 - 7.27$  (comp, 4 H), 7.12 - 6.94 (comp, 5 H), 5.64 - 5.46 (m, 1 H), 4.69 (tt,  $J = 3.9, 12.2$  Hz, 1 H), 3.09 - 2.95 (m, 2 H), 2.83 (ddd,  $J = 9.0, 14.4, 17.5$  Hz, 1 H), 2.63 - 2.44 (m, 1 H), 2.38 - 2.23 (m, 2 H), 1.93 (q,  $J = 7.5$  Hz, 2 H), 1.85 - 1.73 (m, 2 H), 1.46 (t,  $J = 4.1, 8.2, 12.3$  Hz, 2 H), 1.02 (t,  $J = 7.5$  Hz, 3 H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta = 173.5, 161.5, 138.8, 130.4, 130.0, 129.3, 128.3, 120.9, 115.3, 115.1, 112.6, 112.5, 112.4, 112.3, 94.5, 92.6, 90.9, 64.6, 64.3, 53.9, 53.4, 51.9, 30.5, 28.5, 9.6$ .  $^{19}\text{F NMR}$  (376 MHz,  $\text{CDCl}_3$ )  $\delta = -112.48, -178.15 - 178.42$  (ddd, 17.7 Hz, 49 Hz, 1 F). HR-MS (ESI+) calcd. for  $\text{C}_{22}\text{H}_{27}\text{F}_2\text{N}_2\text{O}$  (M + H) 373.2086, found 373.2094.



### *N*-{1-[2-(4-fluorophenyl)-2-oxoethyl]piperidin-4-yl}-*N*-phenylpropanamide (**11c**)

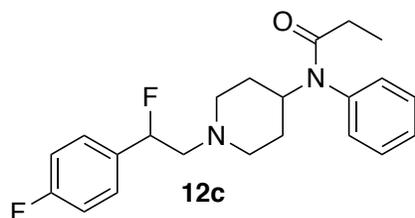
To a 20 mL scintillation vial with a stir bar was added *N*-phenyl-*N*-(4-piperidyl)propanamide (50.0 mg, 0.215 mmol), 2-bromo-1-(4-fluorophenyl)ethanone (60.0 mg, 0.276 mmol), and  $K_2CO_3$  (37.9 mg, 0.274 mmol). The vial was sealed, flushed with nitrogen, and chilled to  $-5\text{ }^\circ\text{C}$  in an ice bath. Ethanol (10 mL) was added by syringe, then the reaction was allowed to warm up to room temperature over 4 h, after which time a sample aliquot was taken from the reaction, diluted with DCM in a microtube, and washed with half-saturated aq.  $Na_2CO_3$ . The organic layer was separated and analyzed by TLC to confirm reaction completion. The reaction was concentrated under reduced pressure, and the crude material was dissolved in a minimal amount of DCM and loaded onto a 25 g  $SiO_2$  column, and purified by flash chromatography (0–5% MeOH/DCM) to give **11c** as an off-white solid (75 mg, 95%). TLC: mobile phase: MeOH:DCM (10:90),  $R_f = 0.68$ ; LC/MS  $t_R = 3.94$  min (Characterization Method A);  $m/z = 368.90$  (M + H);  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta = 7.99 - 7.90$  (m, 2 H), 7.43 - 7.31 (comp, 3 H), 7.12 - 7.01 (comp, 4 H), 4.68 (tt,  $J = 3.9, 12.2$  Hz, 1 H), 3.70 (s, 2 H), 3.02 - 2.90 (m, 2 H), 2.24 (dt,  $J = 2.0, 11.8$  Hz, 2 H), 1.90 (q,  $J = 7.5$  Hz, 2 H), 1.80 - 1.70 (m, 2 H), 1.50 (dq,  $J = 3.8, 12.3$  Hz, 2 H), 0.99 (t,  $J = 7.4$  Hz, 3 H).  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta = 194.8, 173.5, 167.0, 164.4, 138.8, 132.4, 132.3, 130.7, 130.6, 130.4, 129.3, 128.3, 115.7, 115.5, 64.3, 53.7, 51.8, 30.4, 28.5, 9.6$ .  $^{19}F$  NMR (376 MHz,  $CDCl_3$ )  $\delta = -104.86$ .



### *N*-{1-[2-(4-fluorophenyl)-2-hydroxyethyl]piperidin-4-yl}-*N*-phenylpropanamide (**8c**)

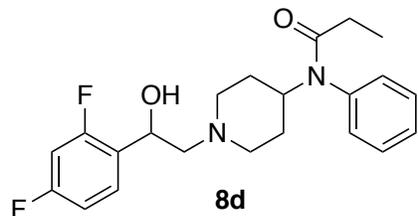
To an oven dried 20 mL scintillation vial with a stir bar was added **11c** (67.5 mg, 0.183 mmol) and anhydrous MeOH (10 mL). The vial was cooled in an ice bath to  $0\text{ }^\circ\text{C}$ , and  $NaBH_4$  (20.0 mg, 0.529 mmol) was added. The vial was sealed and stirred while vented to an oil bubbler and allowed to gradually warm up to room temperature over 2 h. A sample aliquot was taken from the reaction, diluted with DCM in a microtube, and washed with half saturated  $Na_2CO_3$ . The organic layer was separated and analyzed by TLC to confirm reaction completion. The reaction was diluted with EtOAc (30 mL), washed with half-saturated aq.  $Na_2CO_3$  (2 x 15 mL), dried over with  $Na_2SO_4$ , filtered, and concentrated under reduced pressure to give crude product. The crude product was dissolved in a minimal amount of DCM, loaded onto a 25 g silica column, and

purified with flash chromatography (25 g SiO<sub>2</sub>; 0–6% MeOH/DCM) to give **8c** as a yellow oil (66 mg, 50%). TLC: mobile phase: MeOH:DCM (10:90), R<sub>f</sub> = 0.65; LC/MS t<sub>R</sub> = 3.68 min (Characterization Method A); m/z = 370.95 (M + H); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.46 - 7.36 (comp, 3 H), 7.30 - 7.23 (m, 2 H), 7.11 - 7.04 (m, 2 H), 7.02 - 6.93 (m, 2 H), 4.66 (tt, J = 3.9, 12.2 Hz, 1 H), 4.58 (dd, J = 3.4, 10.6 Hz, 1 H), 3.16 - 3.07 (m, 1 H), 2.82 - 2.72 (m, 1 H), 2.50 - 2.38 (m, 2 H), 2.35 - 2.26 (m, 1 H), 2.15 (dt, J = 2.3, 11.8 Hz, 1 H), 1.91 (q, J = 7.4 Hz, 2 H), 1.86 - 1.70 (m, 2 H), 1.48 - 1.29 (m, 2 H), 1.00 (t, J = 7.4 Hz, 3 H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ = 173.5, 163.3, 160.9, 138.8, 137.7, 130.3, 129.4, 128.4, 127.4, 127.3, 115.2, 115.0, 68.3, 65.9, 54.9, 52.0, 51.0, 30.9, 30.5, 28.5, 9.6. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ = -115.38.



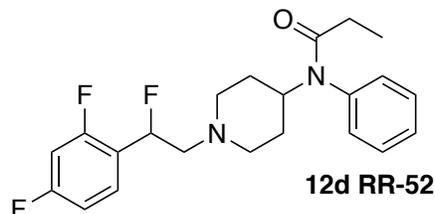
### *N*-{1-[2-fluoro-2-(4-fluorophenyl)ethyl]piperidin-4-yl}-*N*-phenylpropanamide (**12c**)

To an oven dried 20 mL scintillation vial with a stir bar was added **8c** (39.0 mg, 0.105 mmol). The vial was sealed and flushed with nitrogen gas for 5 min and to this was syringed anhydrous DCM (10 mL). The solution was cooled to -78 °C in an acetone/dry ice bath and to this was syringed Triethylamine trihydrofluoride (40.0 μL, 0.245 mmol) and DAST (20.0 μL, 0.151 mmol), respectively. The reaction stirred at -78 °C for 4 h, and then allowed gradually warm up to room temperature overnight. A sample aliquot was taken from the reaction, diluted with EtOAc in a microtube, and washed with half-saturated Na<sub>2</sub>CO<sub>3</sub>. The organic layer was separated and analyzed by TLC to confirm reaction completion. The reaction was quenched with half-saturated aq. Na<sub>2</sub>CO<sub>3</sub> (6 mL) and allowed to vigorously stir for 10 min. The reaction mixture was then transferred to a separatory funnel and diluted with EtOAc (30 mL), washed with half-saturated aq. Na<sub>2</sub>CO<sub>3</sub> (2 x 15 mL), dried over with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give crude product. The crude product was dissolved in a minimal amount of DCM, loaded onto a 10 g silica column, and purified with flash chromatography (10 g SiO<sub>2</sub>; 0–6% MeOH/DCM) to give **12c** as an off-white solid (33 mg, 84%). TLC: mobile phase MeOH:DCM (10:90), R<sub>f</sub> = 0.67; LC/MS t<sub>R</sub> = 3.93 min (Characterization Method A); m/z = 373.30 (M + H); <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ = 7.44 - 7.34 (m, 3 H), 7.28 (s, 2 H), 7.12 - 6.99 (m, 4 H), 5.62 - 5.45 (m, 1 H), 4.69 (tt, J = 3.9, 12.2 Hz, 1 H), 3.09 - 2.96 (m, 2 H), 2.84 (ddd, J = 9.0, 14.3, 17.0 Hz, 1 H), 2.60 - 2.43 (m, 1 H), 2.35 - 2.22 (m, 2 H), 1.93 (q, J = 7.5 Hz, 2 H), 1.84 - 1.74 (m, 2 H), 1.55 - 1.38 (m, 2 H), 1.02 (t, J = 7.5 Hz, 3 H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ = 173.5, 163.8, 161.4, 138.8, 130.4, 129.3, 128.3, 127.4, 127.3, 127.2, 115.5, 115.3, 92.8, 91.1, 64.6, 64.4, 53.9, 53.4, 51.9, 30.5, 28.5, 9.6. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ = -113.50, -175.40–175.30 (ddd, 17.7 Hz, 49 Hz, 1 F). HR-MS (ESI+) calcd. for C<sub>22</sub>H<sub>27</sub>F<sub>2</sub>N<sub>2</sub>O (M + H) 373.2086, found 373.2099.



***N*-{1-[2-(2,4-difluorophenyl)-2-hydroxyethyl]piperidin-4-yl}-*N*-phenylpropanamide (8d)**

To a 20 mL scintillation vial with a stir bar were added *N*-phenyl-*N*-(4-piperidyl)propanamide (52.8 mg, 0.227 mmol), 2-bromo-1-(2,4-difluorophenyl)ethanone (65.7 mg, 0.280 mmol), and  $K_2CO_3$  (45.3 mg, 0.328 mmol). The vial was sealed, flushed with nitrogen, and ethanol (10 mL) was added. The reaction was chilled to  $-5\text{ }^\circ\text{C}$  and stirred for 4 h, after which time, a sample aliquot was taken from the reaction, diluted with DCM in a microtube, and washed with half-saturated aq.  $Na_2CO_3$ . The organic layer was separated and analyzed by TLC to confirm reaction completion. The vial was kept in the ice bath at  $0\text{ }^\circ\text{C}$ , and  $NaBH_4$  (29.0 mg, 0.767 mmol) was added. The vial was sealed and stirred while vented to an oil bubbler and allowed to gradually warm up to room temperature over 2 h. A sample aliquot was taken from the reaction, diluted with DCM in a microtube, and washed with half-saturated  $Na_2CO_3$ . The organic layer was separated and analyzed by TLC to confirm reaction completion. The reaction was diluted with EtOAc (30 mL), washed with half-saturated aq.  $Na_2CO_3$  (2 x 15 mL), dried over with  $Na_2SO_4$ , filtered, and concentrated under reduced pressure. The crude product was dissolved in a minimal amount of DCM, loaded onto a 10 g  $SiO_2$  column, and purified with flash chromatography (0–6% MeOH/DCM) to give **8d** as a yellow oil (39 mg, 45%). TLC: mobile phase: MeOH:DCM (10:90),  $R_f = 0.57$ ; LC/MS  $t_R = 3.46$  min (Characterization Method A);  $m/z = 389.35.25$  (M + H);  $^1H$  NMR (400 MHz,  $CD_2Cl_2$ )  $\delta = 7.52 - 7.37$  (m, 4 H), 7.13 - 7.05 (m, 2 H), 6.89 - 6.80 (m, 1 H), 6.73 (ddd,  $J = 2.5, 8.7, 10.7$  Hz, 1 H), 4.90 (dd,  $J = 3.1, 10.5$  Hz, 1 H), 4.68 (tt,  $J = 3.9, 12.2$  Hz, 1 H), 3.17 - 3.08 (m, 1 H), 2.82 - 2.72 (m, 1 H), 2.59 - 2.41 (m, 2 H), 2.31 (dd,  $J = 10.5, 12.5$  Hz, 1 H), 2.20 (dt,  $J = 2.6, 11.7$  Hz, 1 H), 1.93 (q,  $J = 7.5$  Hz, 2 H), 1.87 - 1.75 (m, 2 H), 1.51 - 1.30 (m, 2 H), 1.01 (t,  $J = 7.5$  Hz, 3 H).  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta = 173.5, 138.9, 130.3, 129.4, 128.4, 128.3, 128.2, 128.2, 128.1, 111.4, 111.2, 103.7, 103.4, 103.1, 64.2, 62.8, 54.9, 52.0, 51.1, 30.9, 30.4, 28.5, 9.6$ .  $^{19}F$  NMR (376 MHz,  $CDCl_3$ )  $\delta = -112.15, -116.46$ .

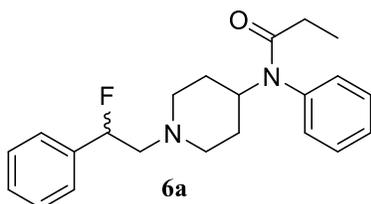


***N*-{1-[2-(2,4-difluorophenyl)-2-fluoroethyl]piperidin-4-yl}-*N*-phenylpropanamide (12d)**

To an oven dried 20 mL scintillation vial with a stir bar was added **8d** (39 mg, 0.100 mmol). The vial was sealed and flushed with nitrogen gas for 5 min and to this was syringed anhydrous DCM (10 mL). The solution was cooled to  $-78\text{ }^\circ\text{C}$  in an acetone/dry ice bath and to this was syringed

Triethylamine trihydrofluoride (60.0  $\mu\text{L}$ , 0.368 mmol) and DAST (30.0  $\mu\text{L}$ , 0.227 mmol), respectively. The reaction stirred at  $-78\text{ }^\circ\text{C}$  for 4 h, and then allowed gradually warm up to room temperature overnight. A sample aliquot was taken from the reaction, diluted with EtOAc in a microtube, and washed with half-saturated  $\text{Na}_2\text{CO}_3$ . The organic layer was separated and analyzed by TLC to confirm reaction completion. The reaction was quenched with half-saturated aq.  $\text{Na}_2\text{CO}_3$  (6 mL) and allowed to vigorously stir for 10 min. The reaction mixture was then transferred to a separatory funnel and diluted with EtOAc (30 mL), washed with half-saturated aq.  $\text{Na}_2\text{CO}_3$  (2 x 15 mL), dried over with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure to give crude product. The crude product was dissolved in a minimal amount of DCM, loaded onto a 10 g silica column, and purified with flash chromatography (10 g  $\text{SiO}_2$ ; 0–6% MeOH/DCM) to give **12d** as a clear yellow oil (11 mg, 28%). TLC: mobile phase EtOAc:hexanes (50:50),  $R_f = 0.38$ ; LC/MS  $t_R = 3.96$  min (Characterization Method A);  $m/z = 391.35$  (M + H);  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta = 7.44 - 7.32$  (m, 4 H), 7.12 - 7.03 (m, 2 H), 6.93 - 6.72 (m, 2 H), 5.90 - 5.71 (m, 1 H), 4.68 (tt,  $J = 3.9, 12.2$  Hz, 1 H), 3.01 (t,  $J = 9.7$  Hz, 2 H), 2.84 (ddd,  $J = 8.9, 14.4, 18.1$  Hz, 1 H), 2.65 - 2.46 (m, 1 H), 2.40 - 2.24 (m, 2 H), 1.92 (q,  $J = 7.4$  Hz, 2 H), 1.84 - 1.73 (m, 2 H), 1.45 (dp,  $J = 3.8, 12.1$  Hz, 2 H), 1.01 (t,  $J = 7.4$  Hz, 3 H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta = 173.8, 139.0, 130.7, 129.5, 128.5, 112.0, 111.9, 111.7, 111.6, 104.4, 104.1, 103.7, 88.1, 85.8, 63.7, 63.4, 54.2, 53.5, 52.1, 30.7, 28.8, 9.9$ .  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta = -109.82, -114.74, -182.83 - 183.10$  (ddd, 17.7 Hz, 49 Hz, 1 F). HR-MS (ESI+) calcd. for  $\text{C}_{22}\text{H}_{26}\text{F}_3\text{N}_2\text{O}$  (M + H) 391.1992, found 391.1997.

### 3. Compound characterization data

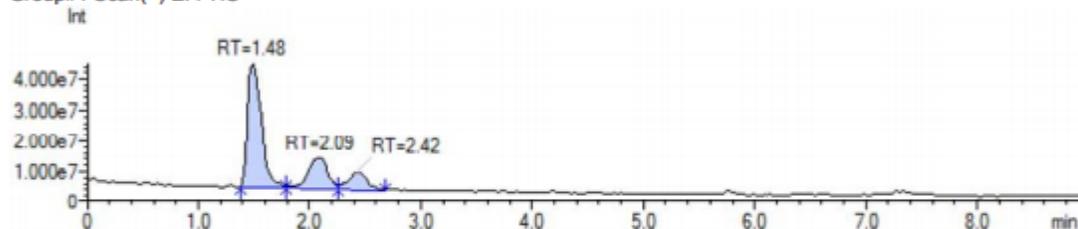


#### Shimadzu Open Solution

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**Experiment:** ricardo\_20170908\_02  
**Experiment Description:** Wizard-generated sample plate  
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**Sample Description:** RR-SAL-009-3  
**Data File Name:** C:\Data\docken\RICARDO\RR-SAL-009-3.lcd  
**Sample Location:** Plate Number: 1 - Position: 50  
**Run By:** ricardo  
**Run Started:** Friday, September 08, 2017 4:30:43 PM  
**Run Finished:** Friday, September 08, 2017 4:50:14 PM  
**Method:** 051817 Std Gemini 25 MeCN

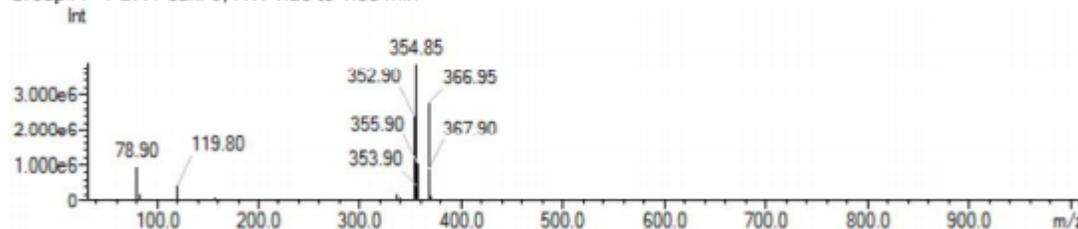
#### MS Chromatogram

Group#1 Scan(+) EI : TIC



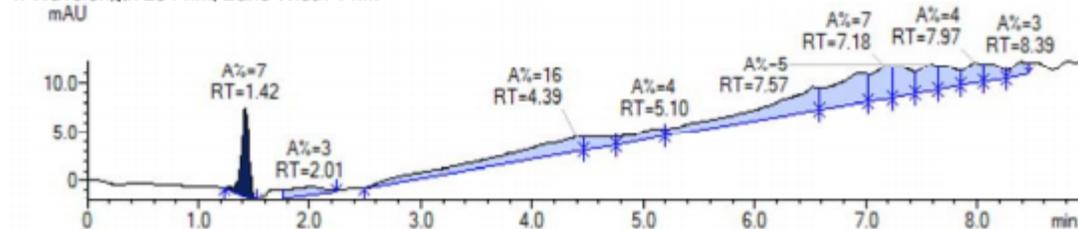
#### MS Spectrum

Group#1 - PDA Peak: 9, RT: 1.23 to 1.53 min

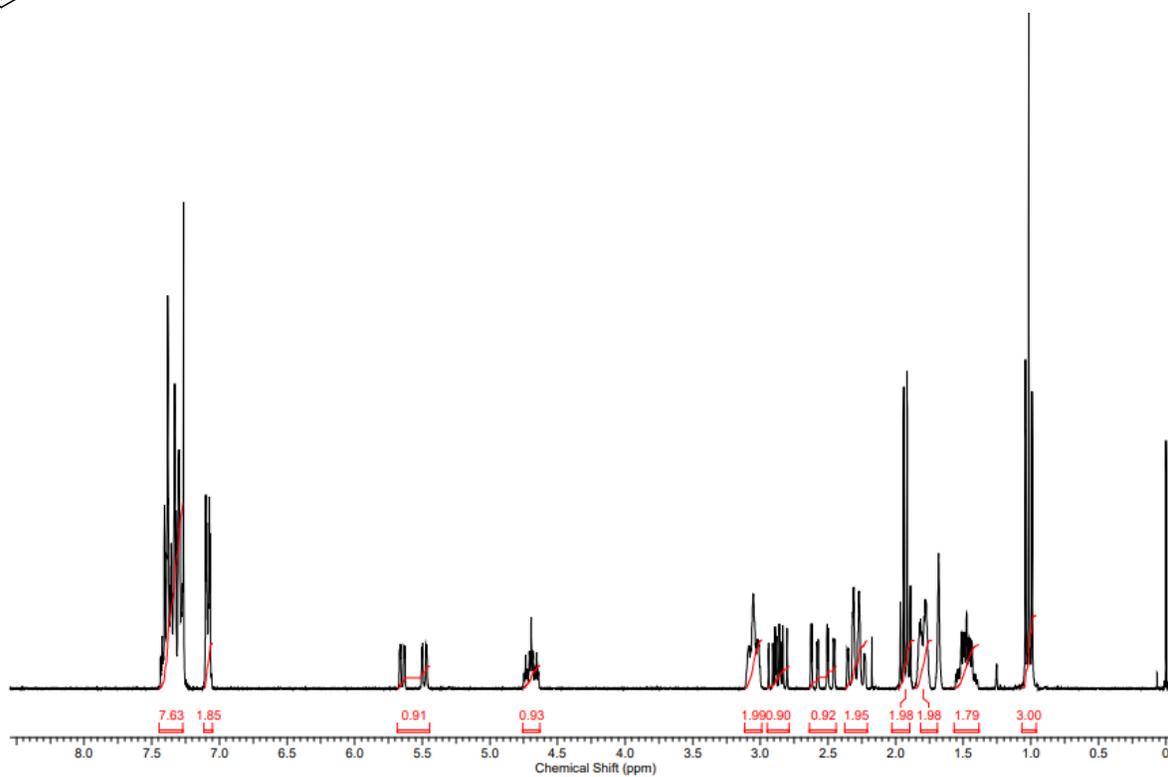
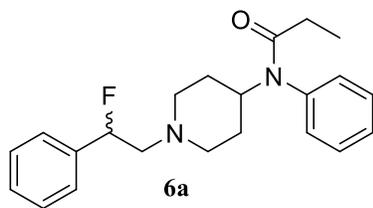


#### PDA Chromatogram

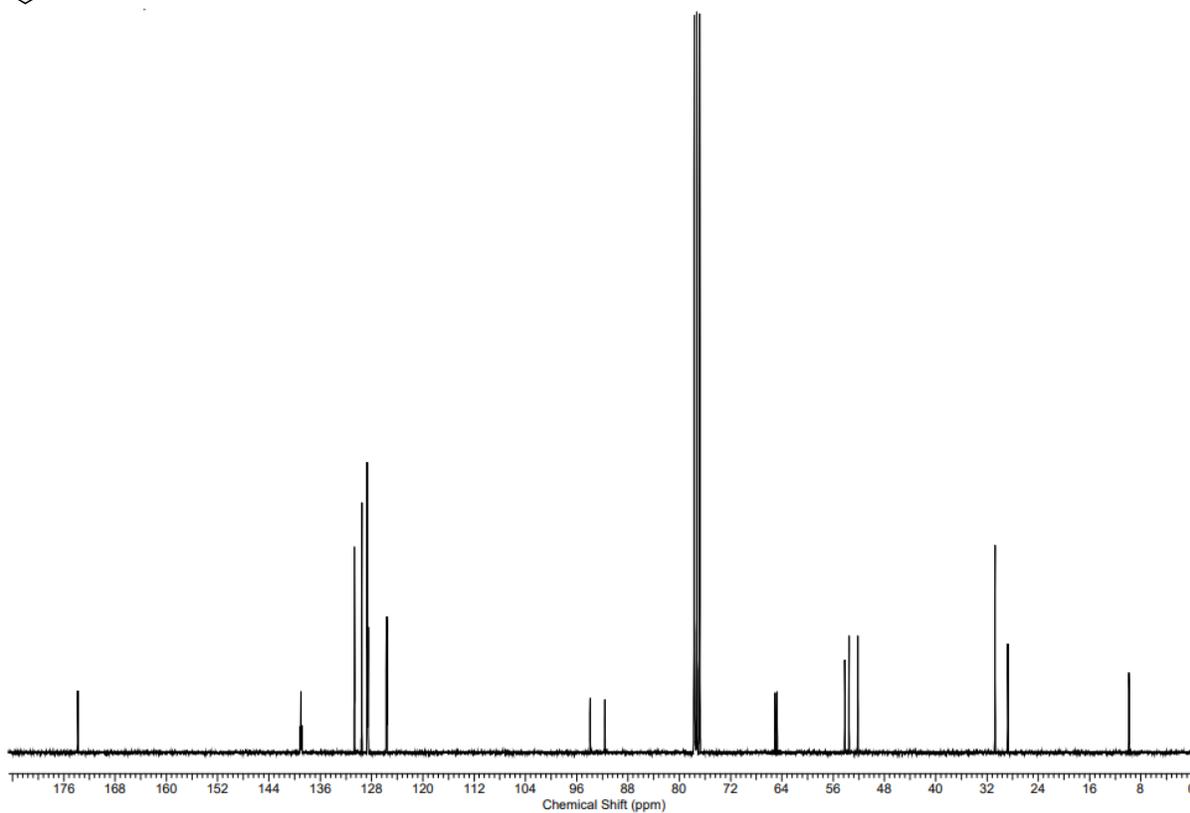
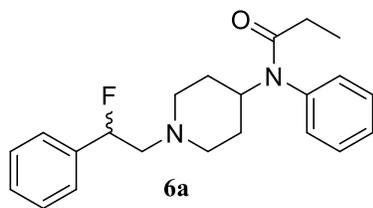
1: Wavelength 254 nm, Band Width 4 nm



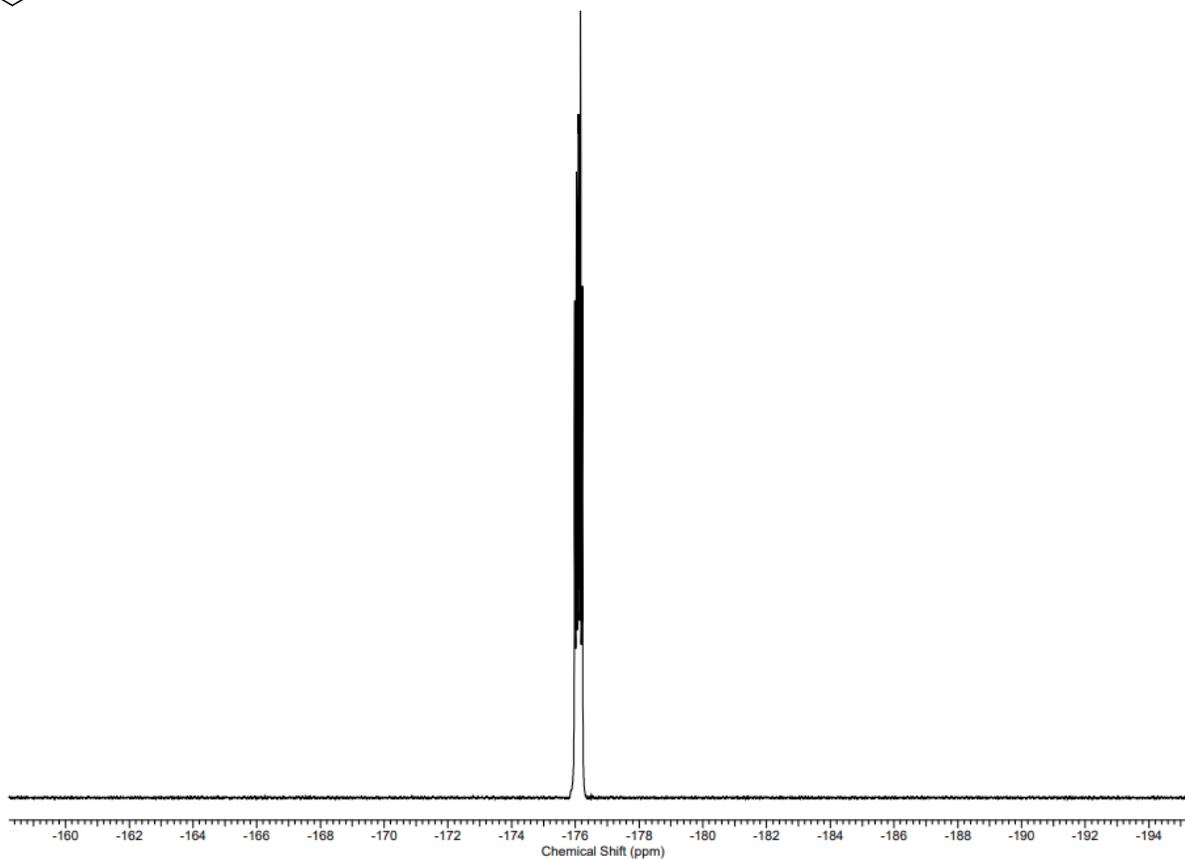
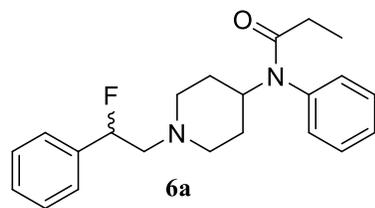
LC/MS (+ mode) for compound 6a



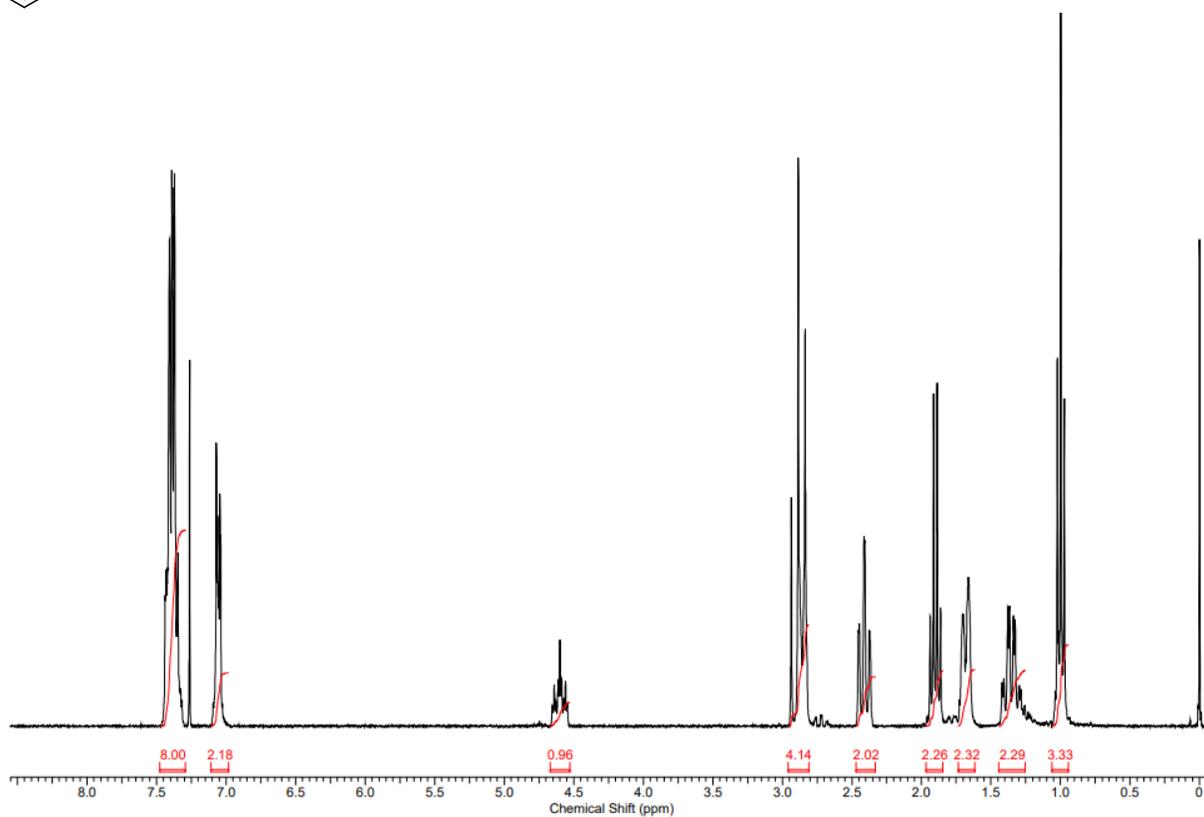
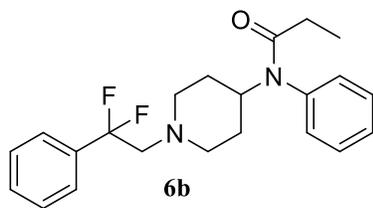
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) of compound **6a**



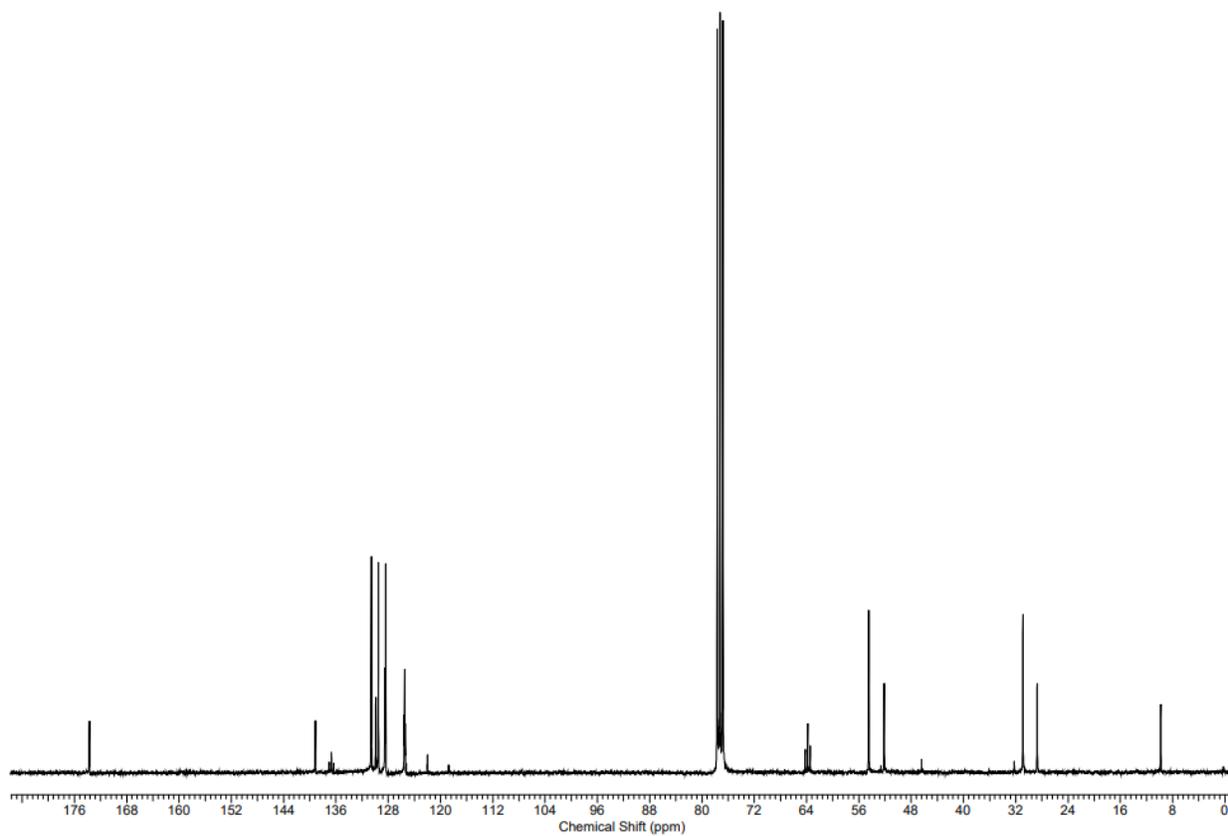
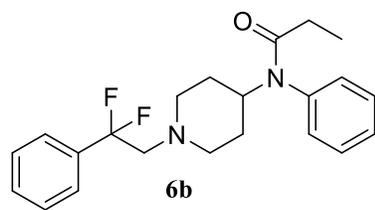
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of compound **6a**



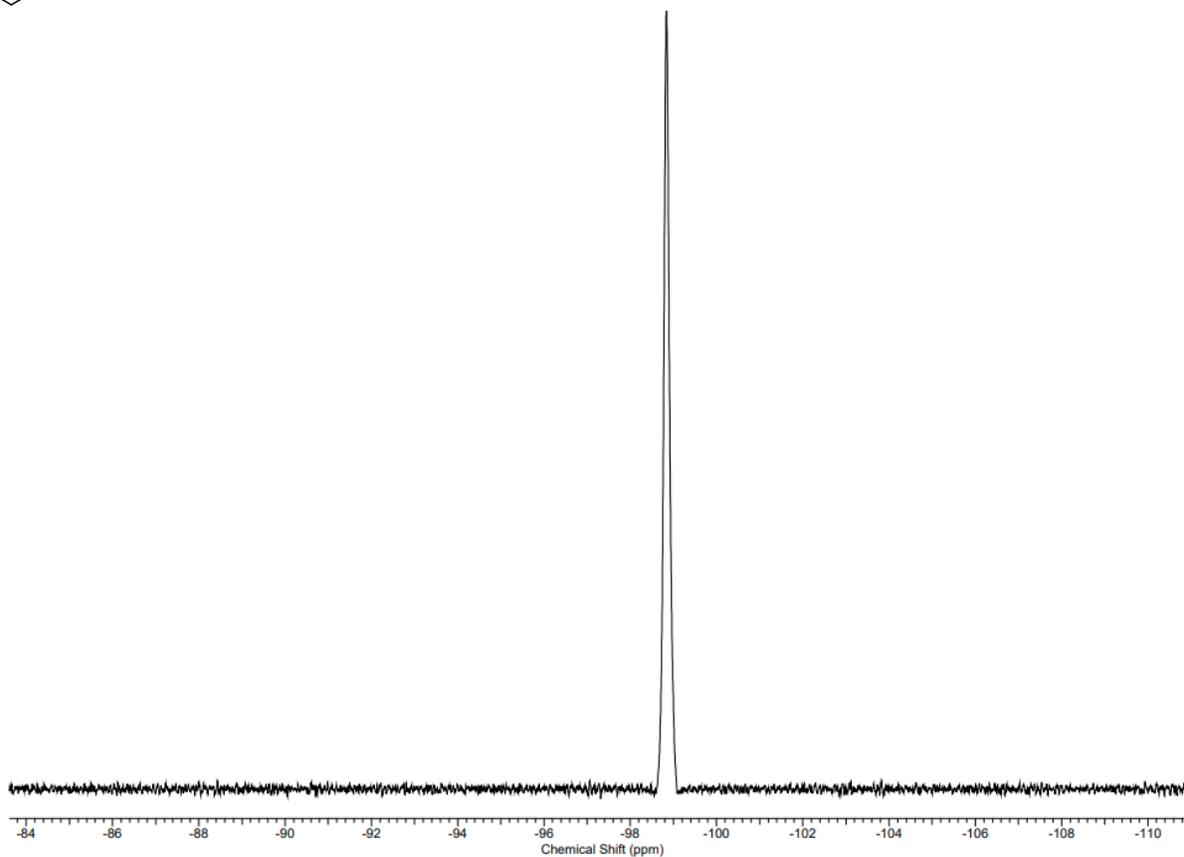
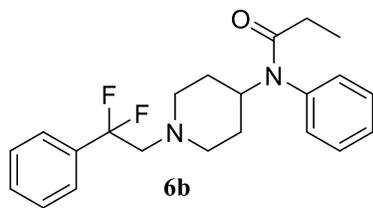
$^{19}\text{F}$  NMR (376 MHz,  $\text{CD}_3\text{OD}$ ) of compound **6a** as HCl salt



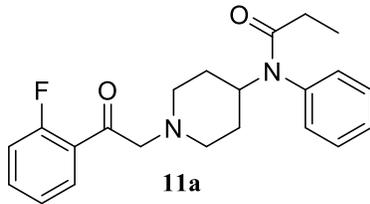
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) of compound **6b**



$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of compound **6b**



$^{19}\text{F}$  NMR (376 MHz,  $\text{CD}_3\text{OD}$ ) of compound **6b** as HCl salt

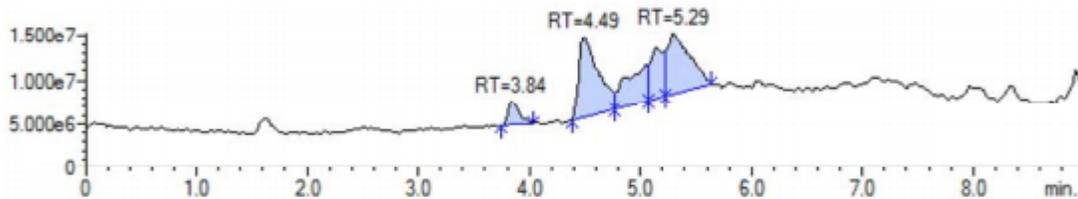


**Shimadzu Open Solution**

<b>Project:</b>	Dockendorff Lab
<b>Experiment:</b>	ricardo_20190525_04
<b>Experiment Description:</b>	Wizard-generated sample plate
<b>Sample:</b>	RR-SAL-041-3
<b>Sample Description:</b>	RR-SAL-041-3
<b>Data File Name:</b>	C:\Data\docken\RICARDO\RR-SAL-041-3.lcd
<b>Sample Location:</b>	Plate Number: 1 - Position: 41
<b>Run By:</b>	ricardo
<b>Run Started:</b>	Saturday, May 25, 2019 4:03:03 PM
<b>Run Finished:</b>	Saturday, May 25, 2019 4:33:32 PM
<b>Method:</b>	051817 Std Gemini 25 MeCN

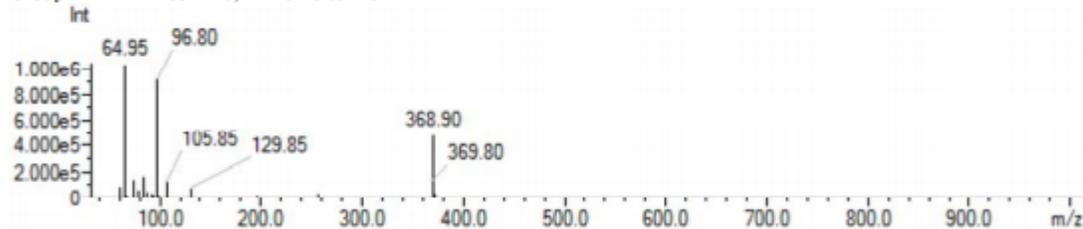
**MS Chromatogram**

Group#1 Scan(+) EI : TIC  
Int



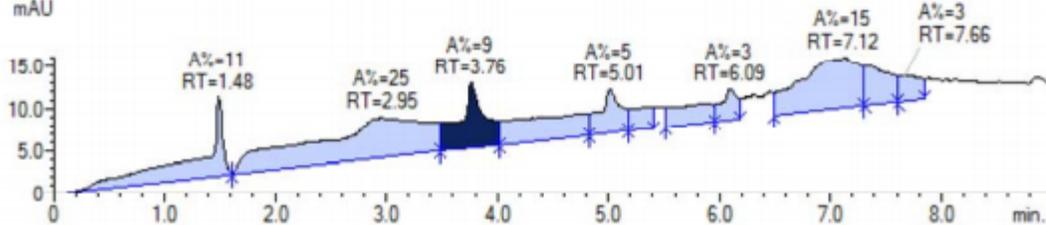
**MS Spectrum**

Group#1 - PDA Peak: 13, RT: 3.48 to 4.01 min

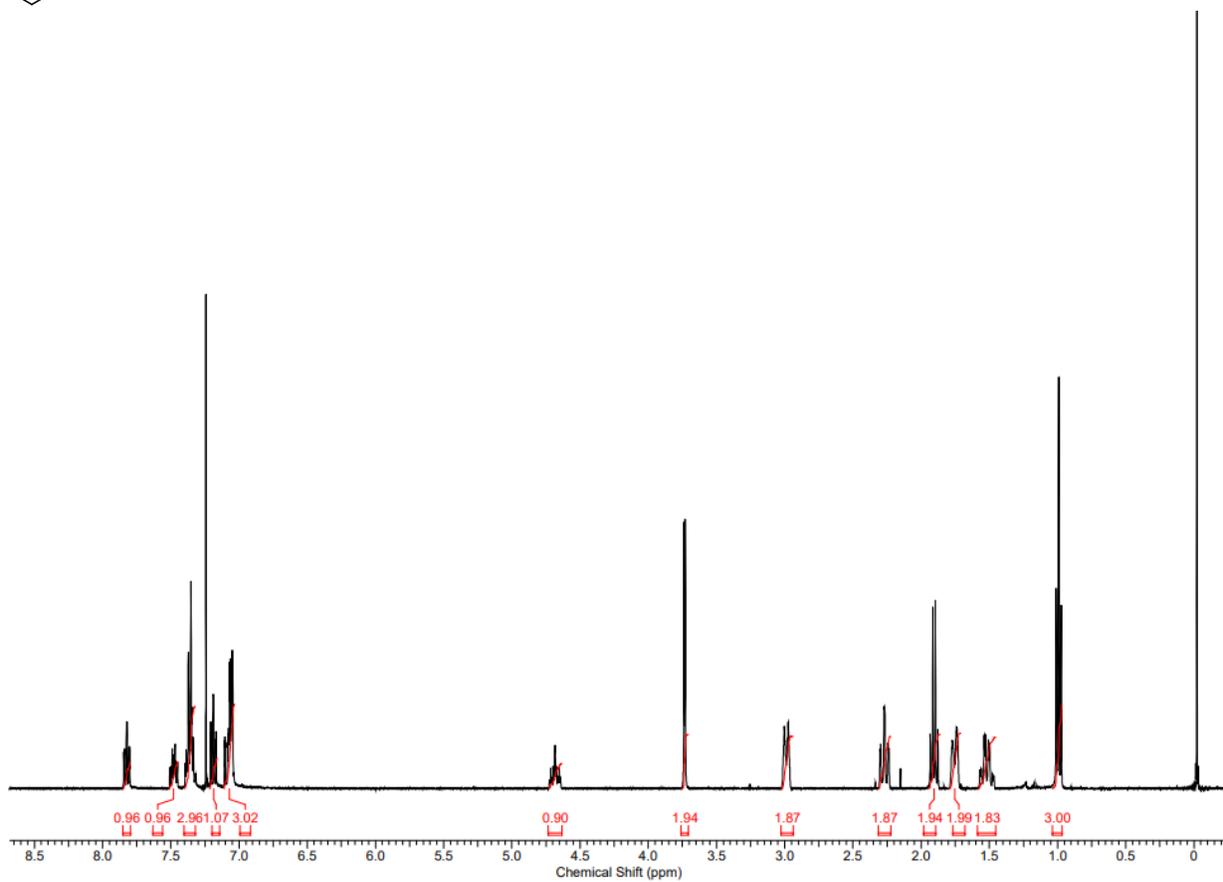
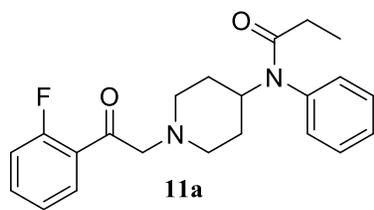


**PDA Chromatogram**

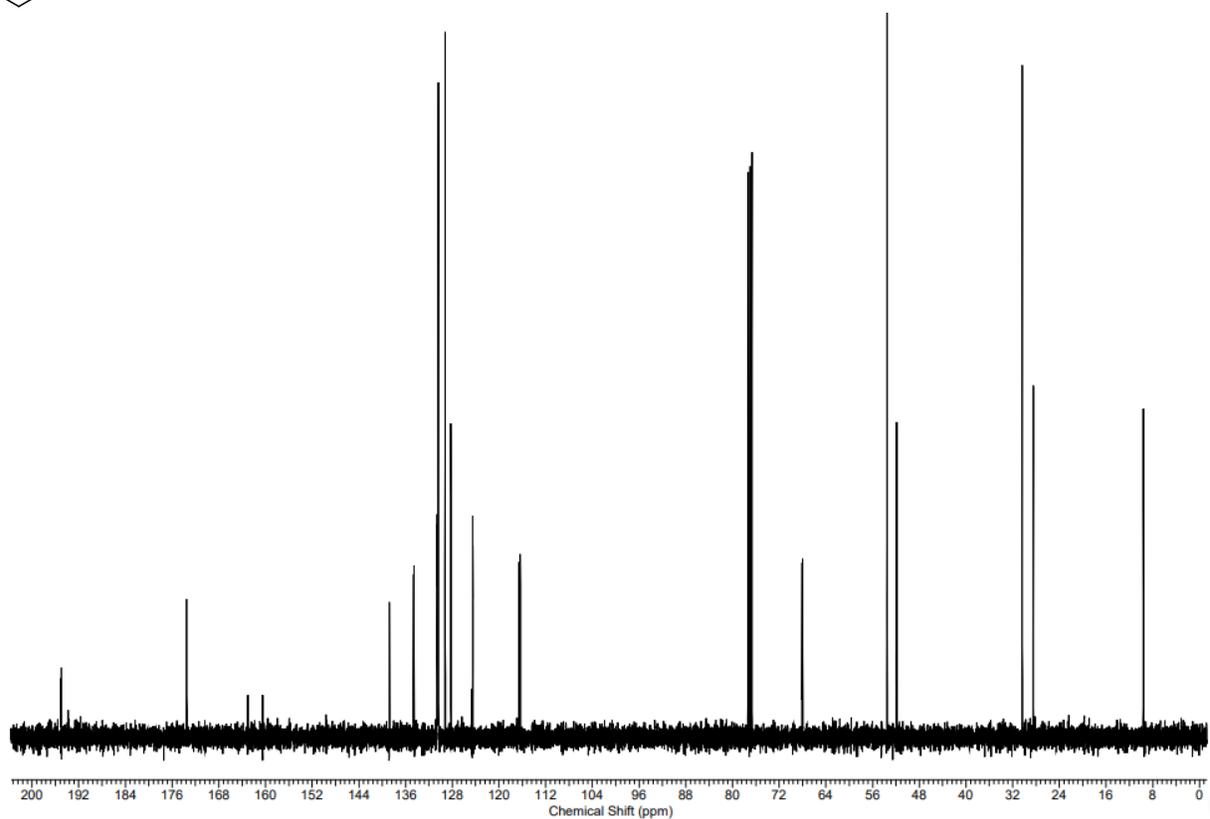
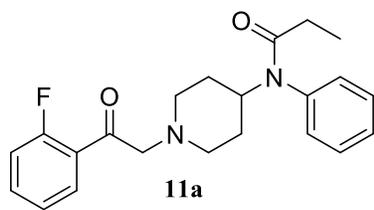
1: Wavelength 254 nm, Band Width 4 nm  
mAU



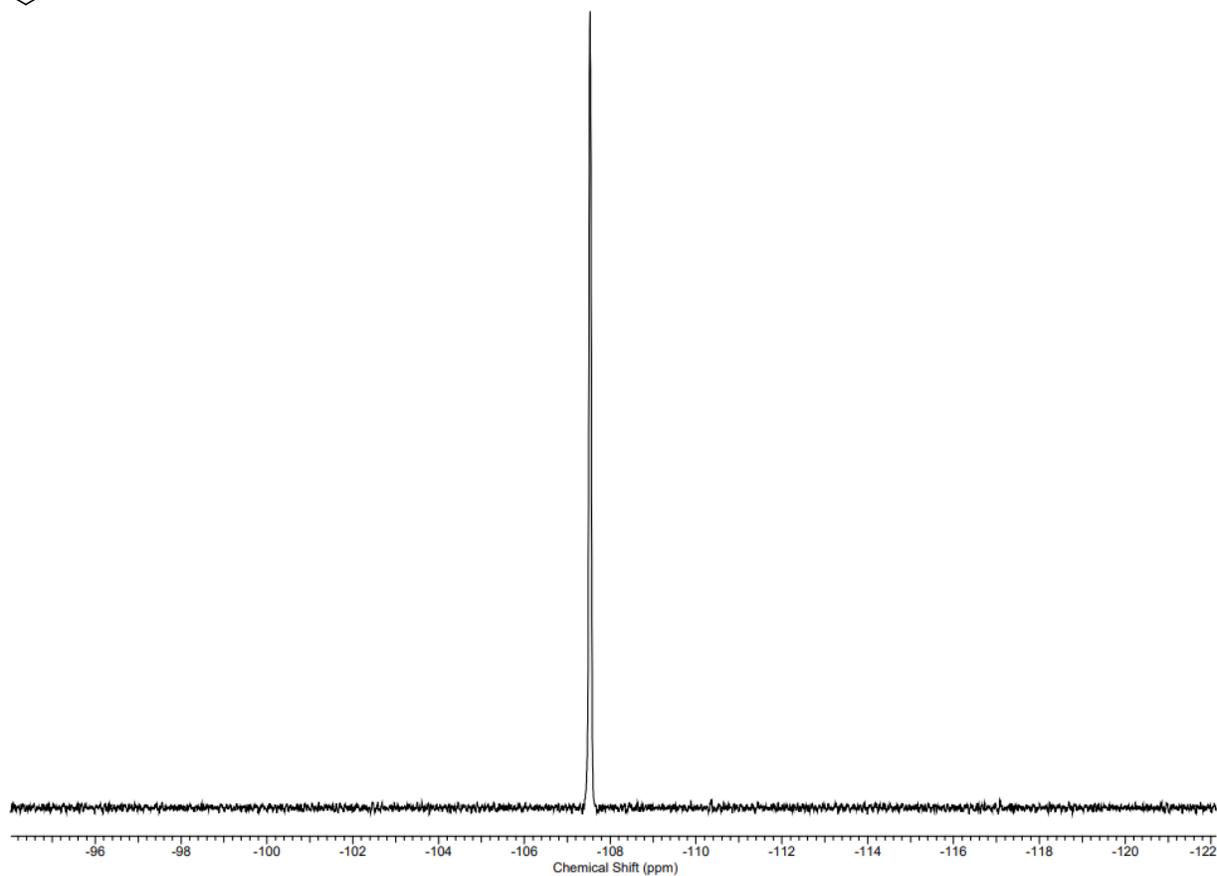
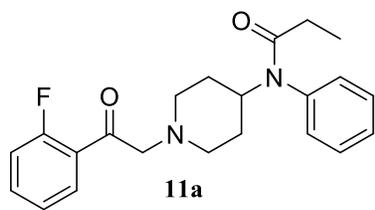
LC/MS (+ mode) for compound **11a**



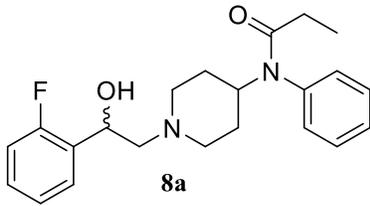
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of compound **11a**



$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of compound **11a**



$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of compound **11a**

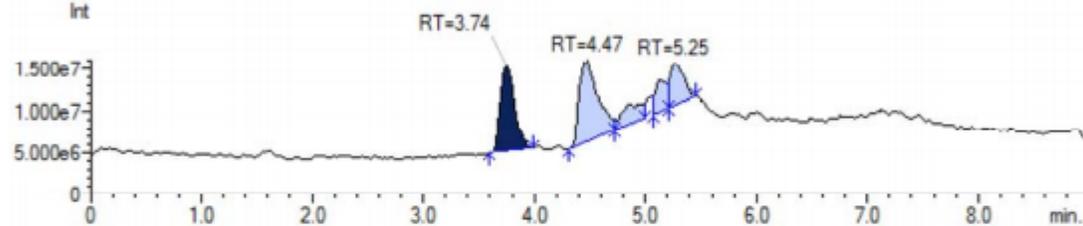


**Shimadzu Open Solution**

**Project:** Dockendorff Lab  
**Experiment:** ricardo\_20190525\_06  
**Experiment Description:** Wizard-generated sample plate  
**Sample:** RR-SAL-044-2  
**Sample Description:** RR-SAL-044-2  
**Data File Name:** C:\Data\docken\RICARDO\RR-SAL-044-2.lcd  
**Sample Location:** Plate Number: 1 - Position: 44  
**Run By:** ricardo  
**Run Started:** Saturday, May 25, 2019 4:54:04 PM  
**Run Finished:** Saturday, May 25, 2019 5:25:22 PM  
**Method:** 051817 Std. Gemini 25 MeCN

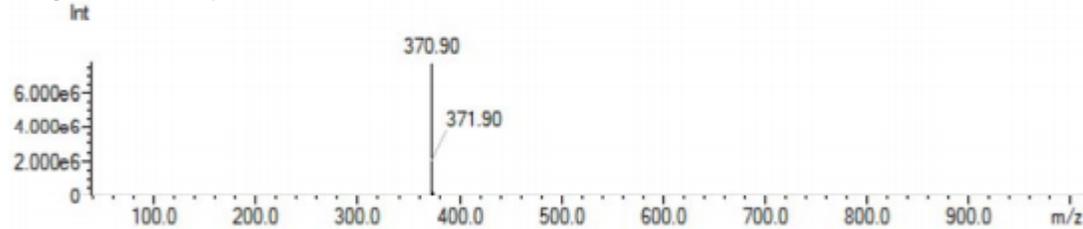
**MS Chromatogram**

Group#1 Scan(+) EI : TIC



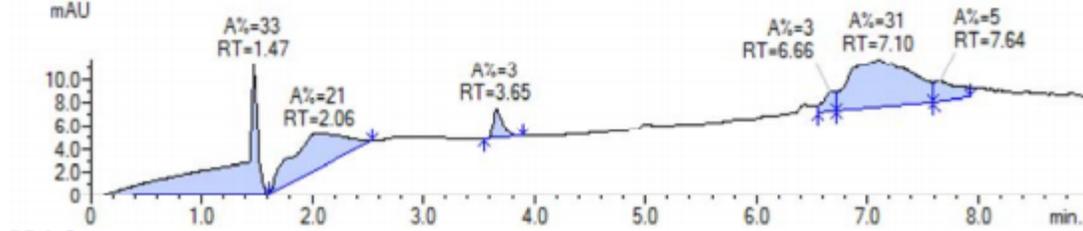
**MS Spectrum**

Group#1 - MS Peak: 1, RT: 3.59 to 3.98 min

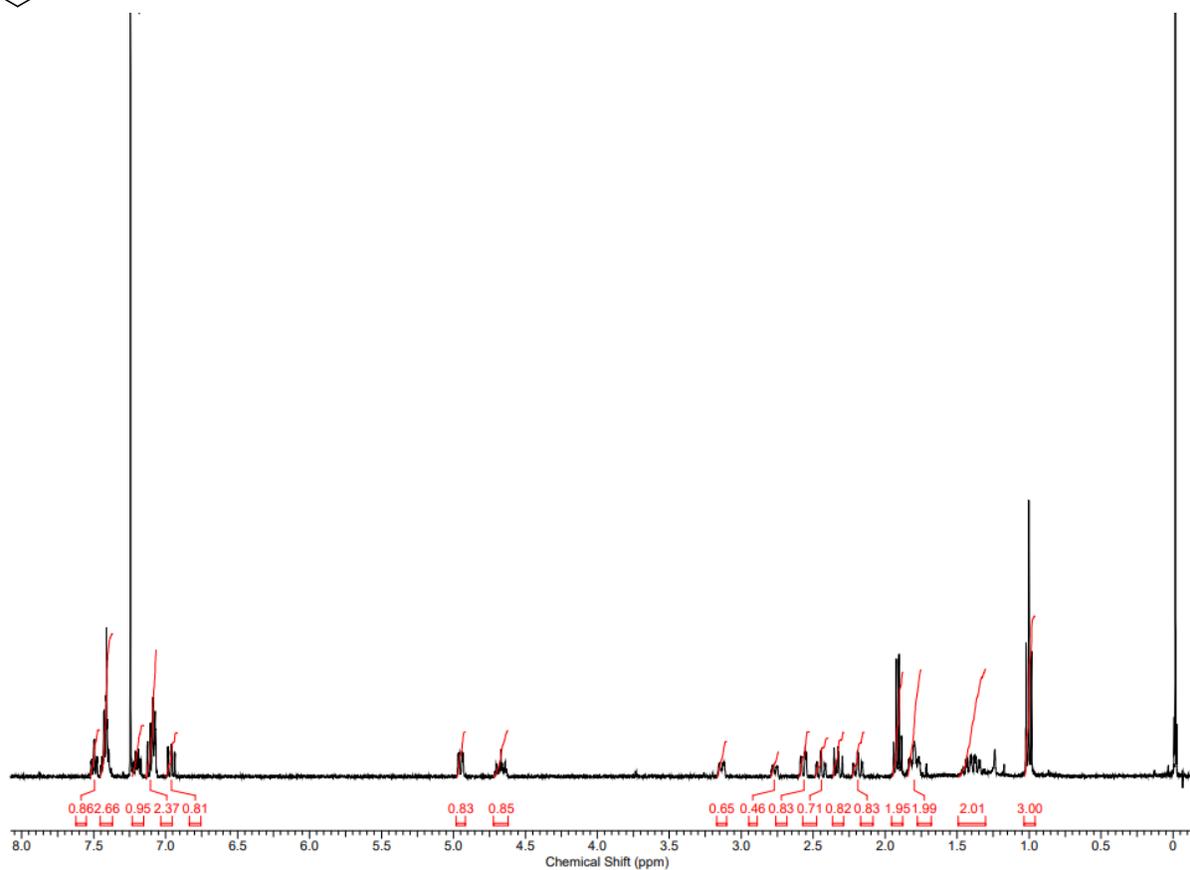
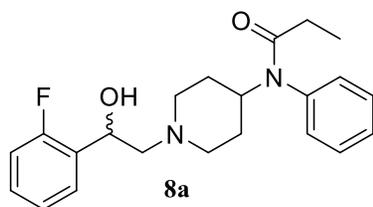


**PDA Chromatogram**

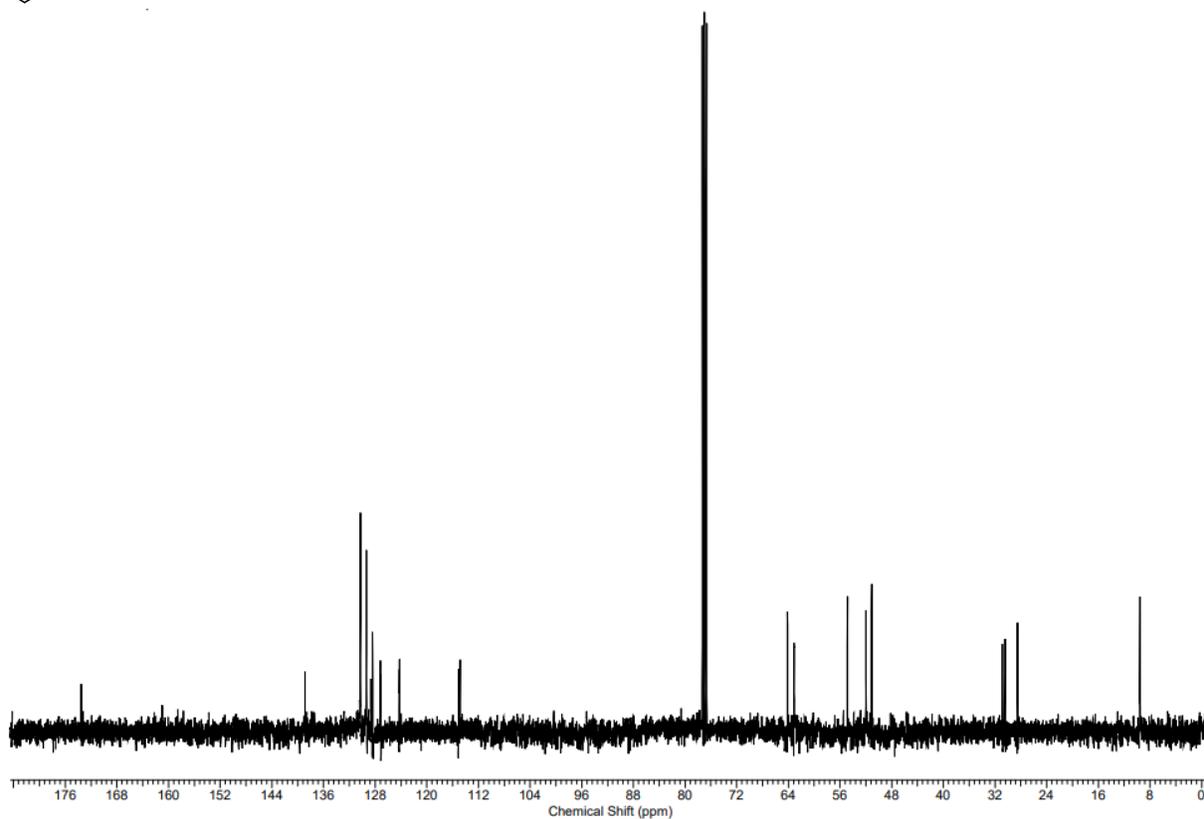
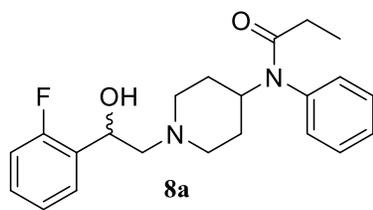
1: Wavelength 254 nm, Band Width 4 nm



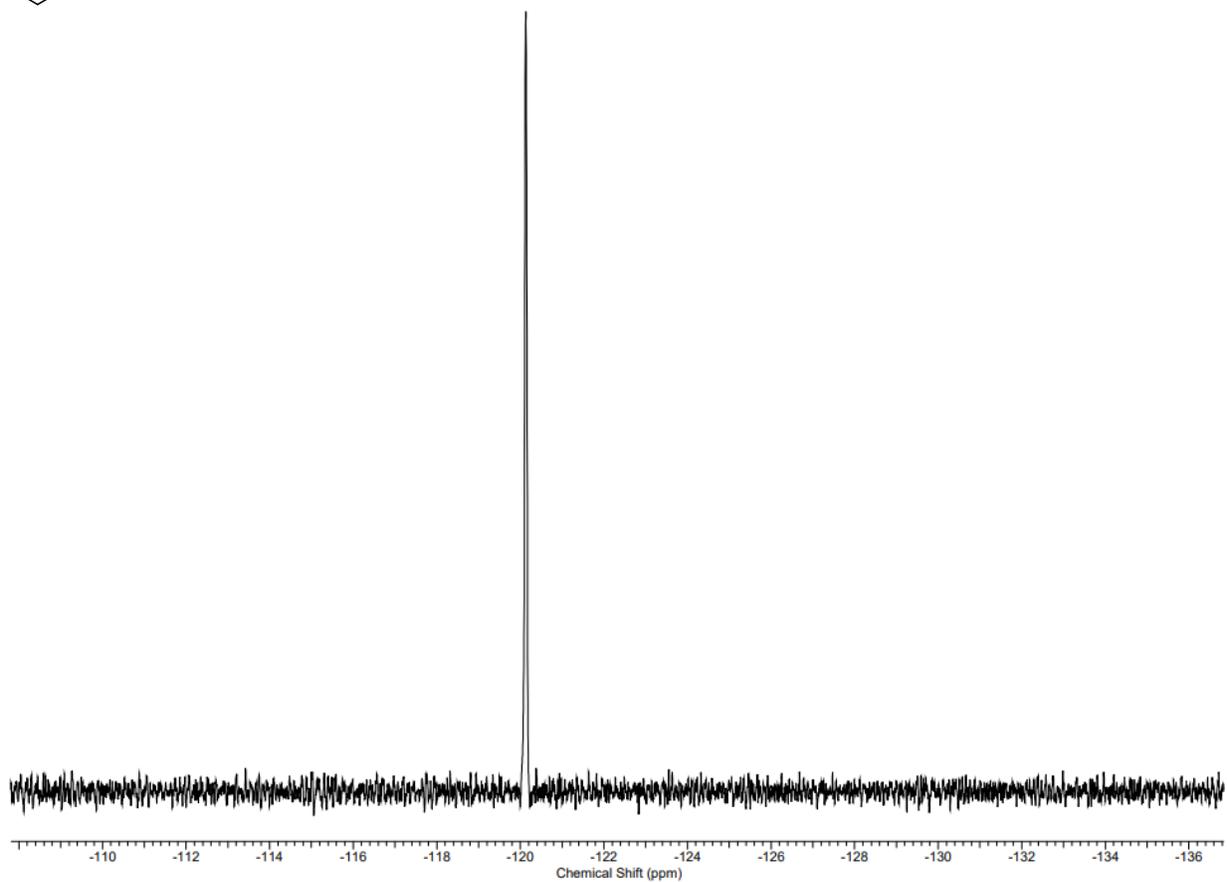
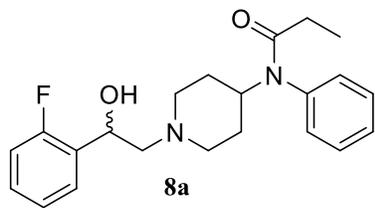
LC/MS (+ mode) for compound **8a**



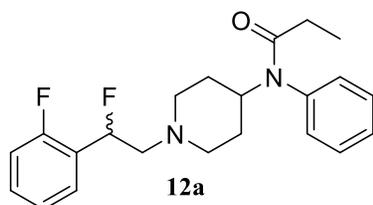
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of compound **8a**



$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of compound **8a**



$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of compound **8a**

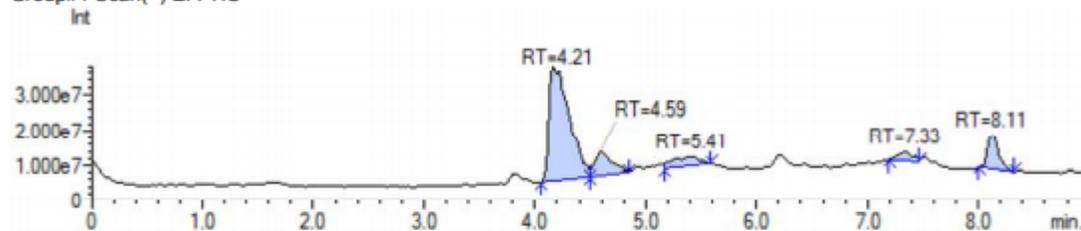


### Shimadzu Open Solution

<b>Project:</b>	Dockendorff Lab
<b>Experiment:</b>	ricardo_20190525_07
<b>Experiment Description:</b>	Wizard-generated sample plate
<b>Sample:</b>	RR-SAL-049-2
<b>Sample Description:</b>	RR-SAL-049-2
<b>Data File Name:</b>	C:\Data\docken\RICARDO\RR-SAL-049-2.lcd
<b>Sample Location:</b>	Plate Number: 1 - Position: 49
<b>Run By:</b>	ricardo
<b>Run Started:</b>	Saturday, May 25, 2019 5:25:27 PM
<b>Run Finished:</b>	Saturday, May 25, 2019 5:54:44 PM
<b>Method:</b>	051817 Std Gemini 25 MeCN

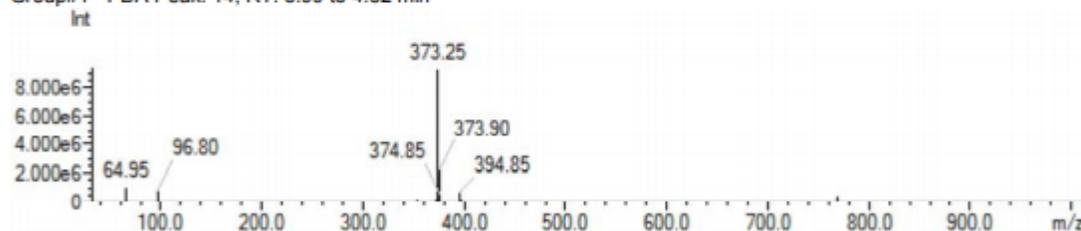
### MS Chromatogram

Group#1 Scan(+) EI : TIC



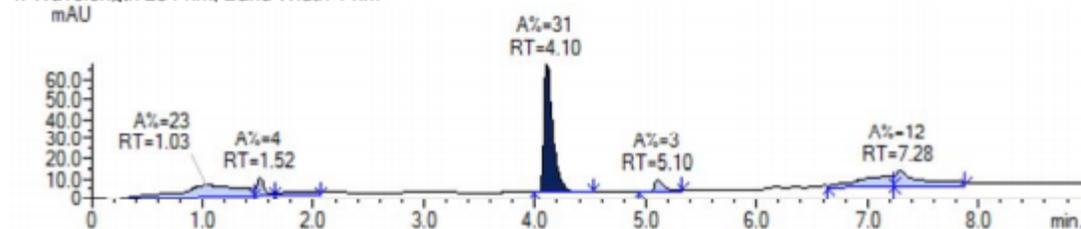
### MS Spectrum

Group#1 - PDA Peak: 14, RT: 3.99 to 4.52 min

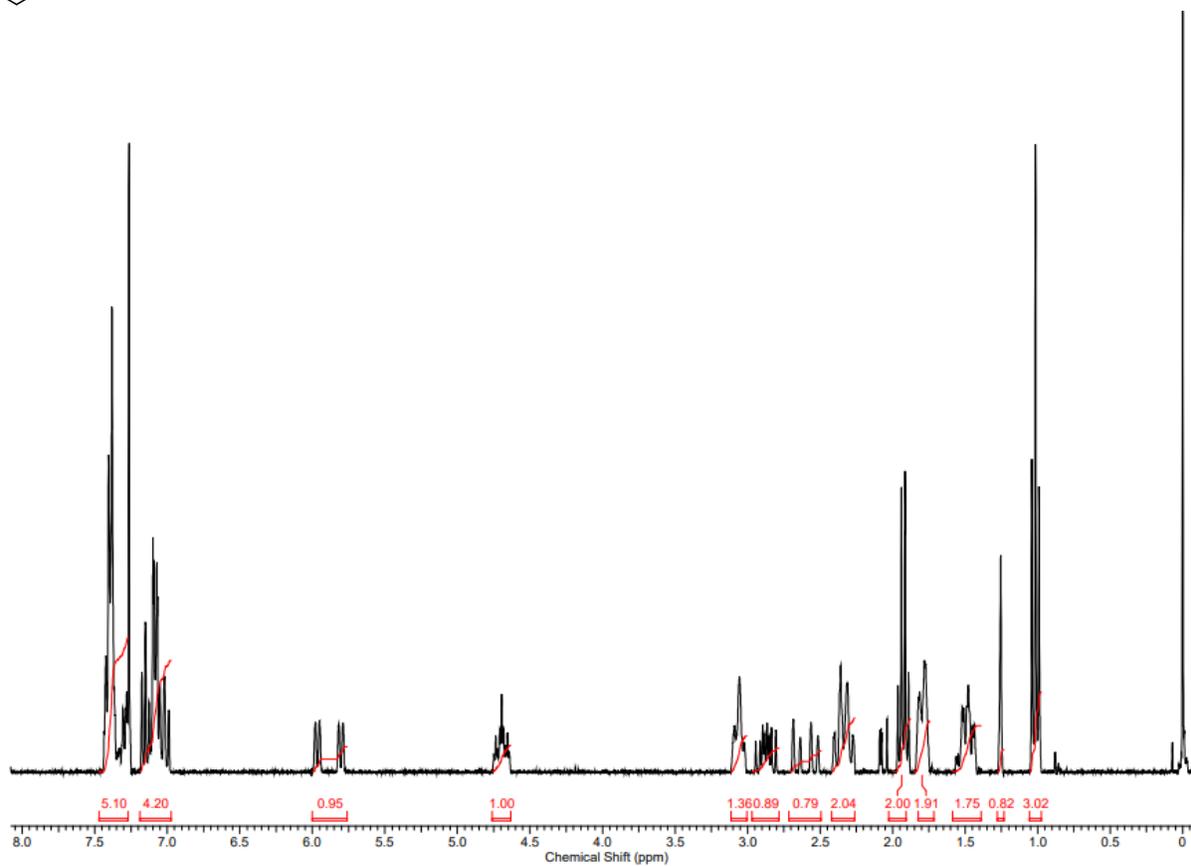
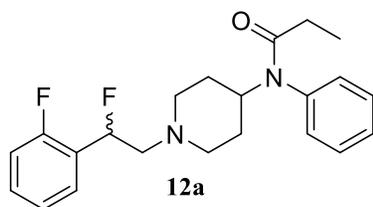


### PDA Chromatogram

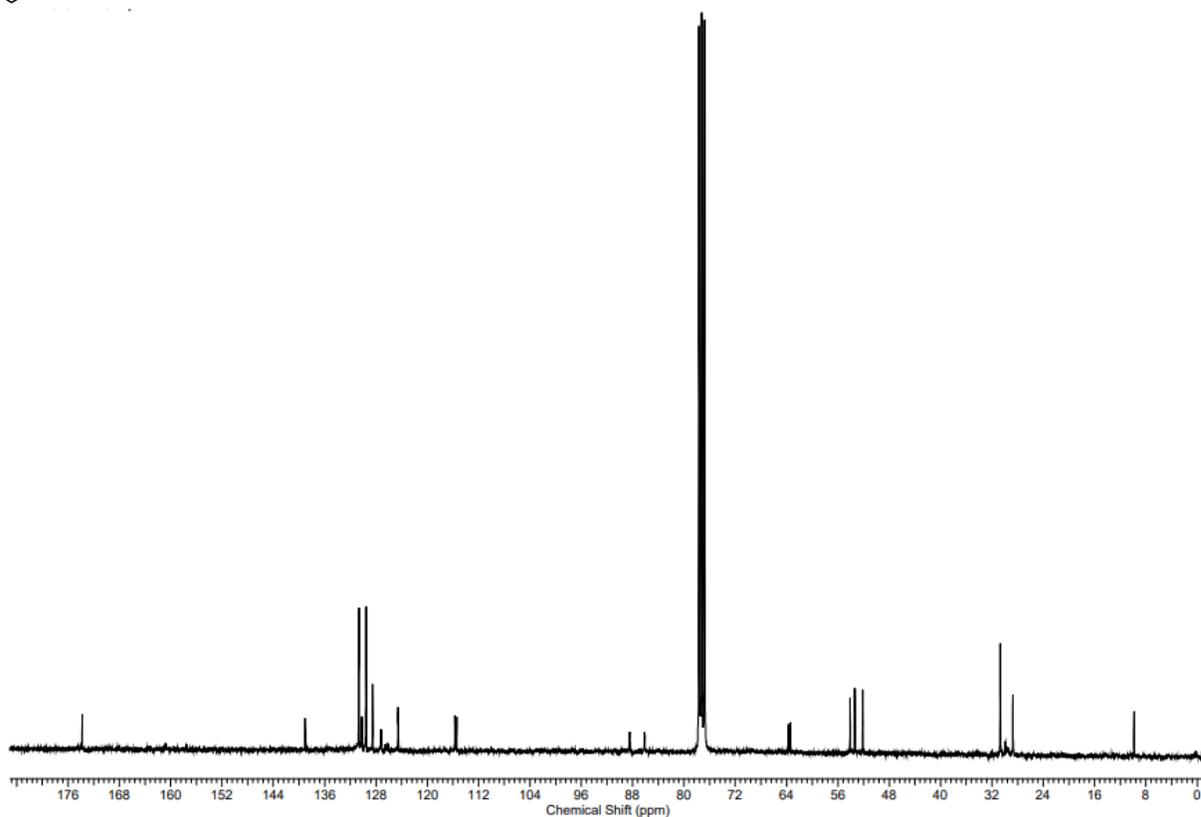
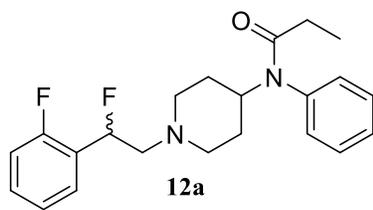
1: Wavelength 254 nm, Band Width 4 nm



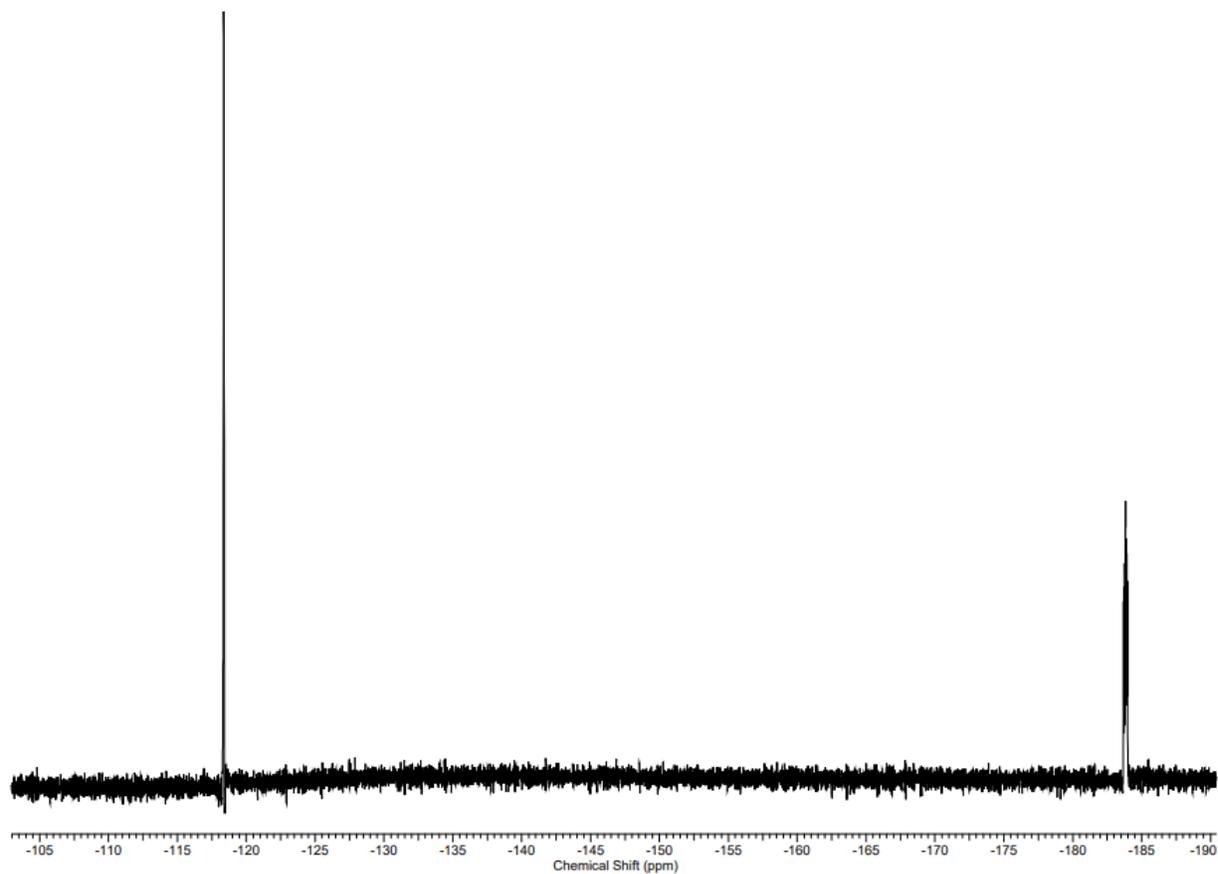
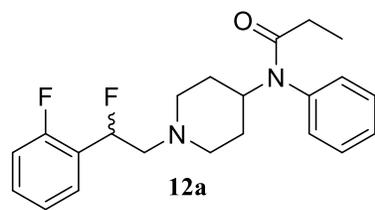
LC/MS (+ mode) for compound **12a**



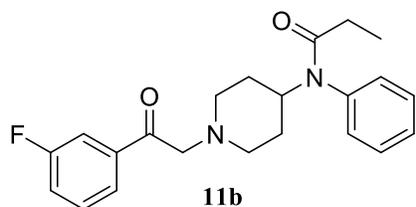
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) of compound **12a**



$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) of compound **12a**



$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of compound **12a**

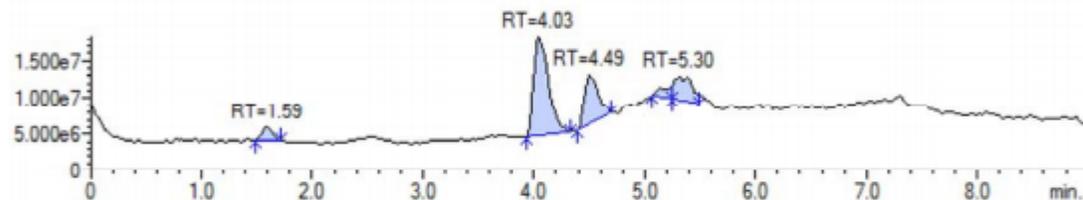


### Shimadzu Open Solution

<b>Project:</b>	Dockendorff Lab
<b>Experiment:</b>	ricardo_20190525_04
<b>Experiment Description:</b>	Wizard-generated sample plate
<b>Sample:</b>	RR-SAL-043-2
<b>Sample Description:</b>	RR-SAL-043-2
<b>Data File Name:</b>	C:\Data\docken\RICARDO\RR-SAL-043-2.lcd
<b>Sample Location:</b>	Plate Number: 1 - Position: 43
<b>Run By:</b>	ricardo
<b>Run Started:</b>	Saturday, May 25, 2019 4:03:03 PM
<b>Run Finished:</b>	Saturday, May 25, 2019 4:33:32 PM
<b>Method:</b>	051817 Std Gemini 25 MeCN

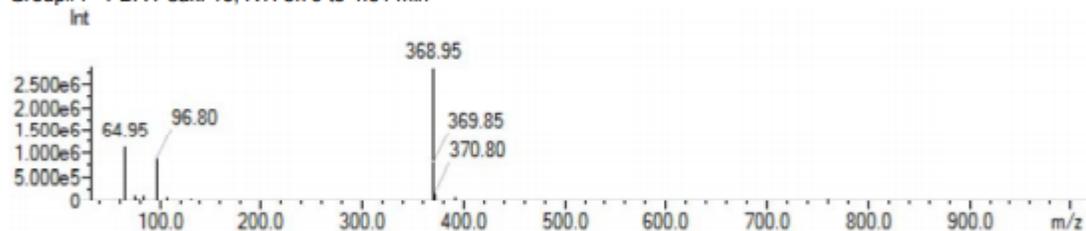
### MS Chromatogram

Group#1 Scan(+) EI : TIC  
Int



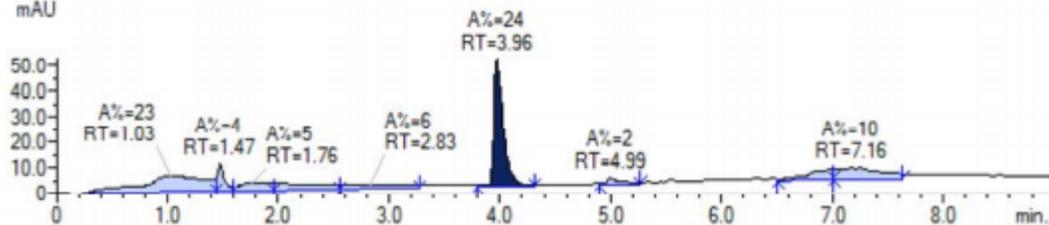
### MS Spectrum

Group#1 - PDA Peak: 16, RT: 3.79 to 4.31 min

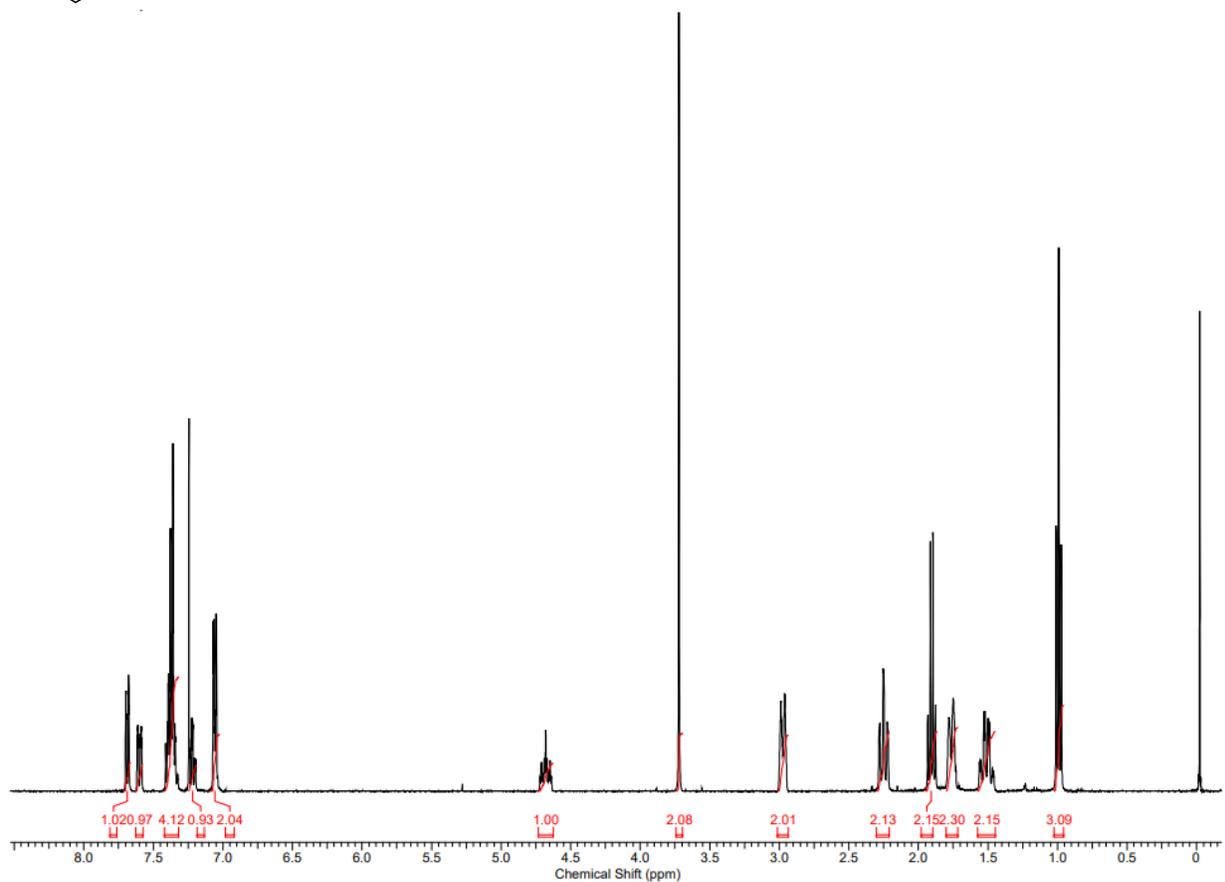
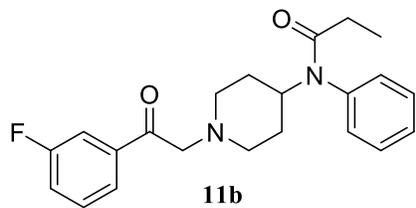


### PDA Chromatogram

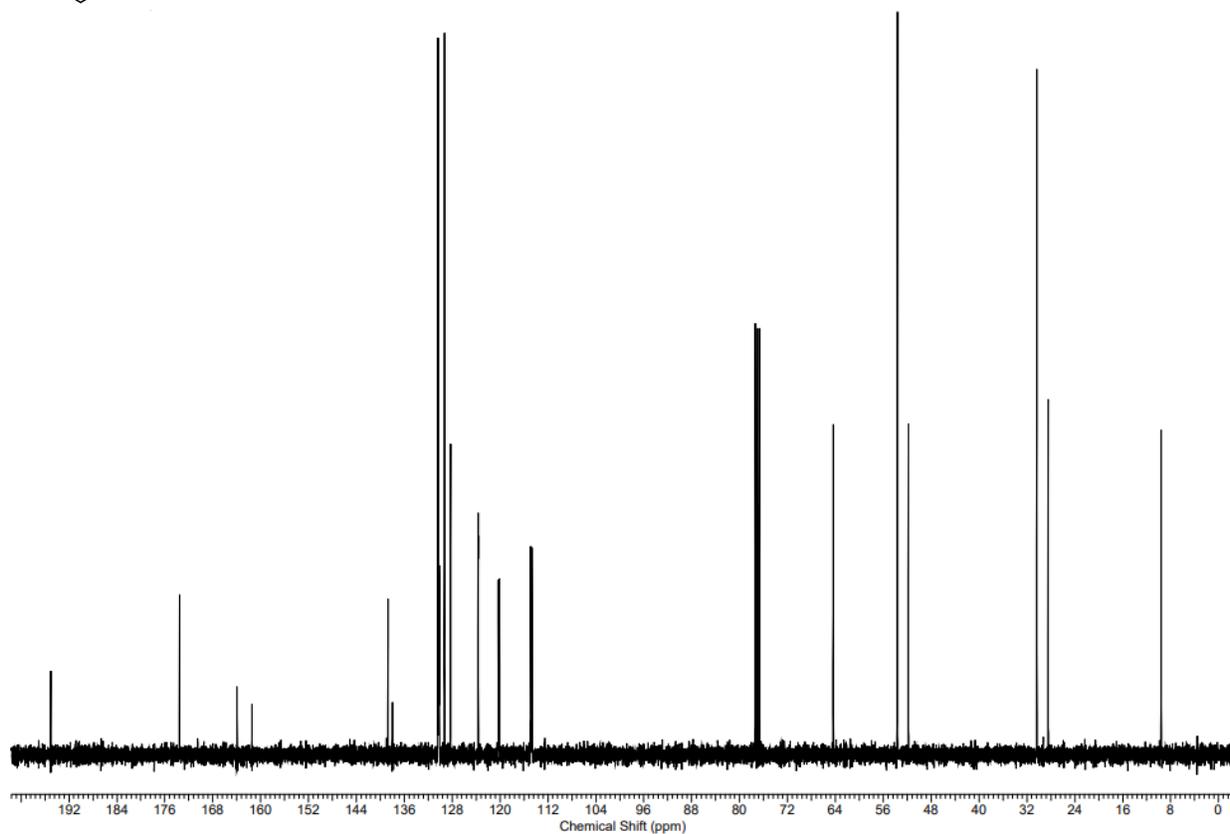
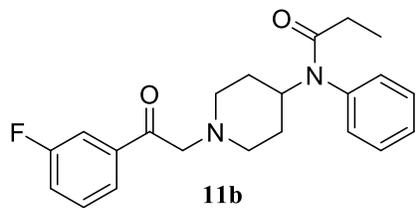
1: Wavelength 254 nm, Band Width 4 nm  
mAU



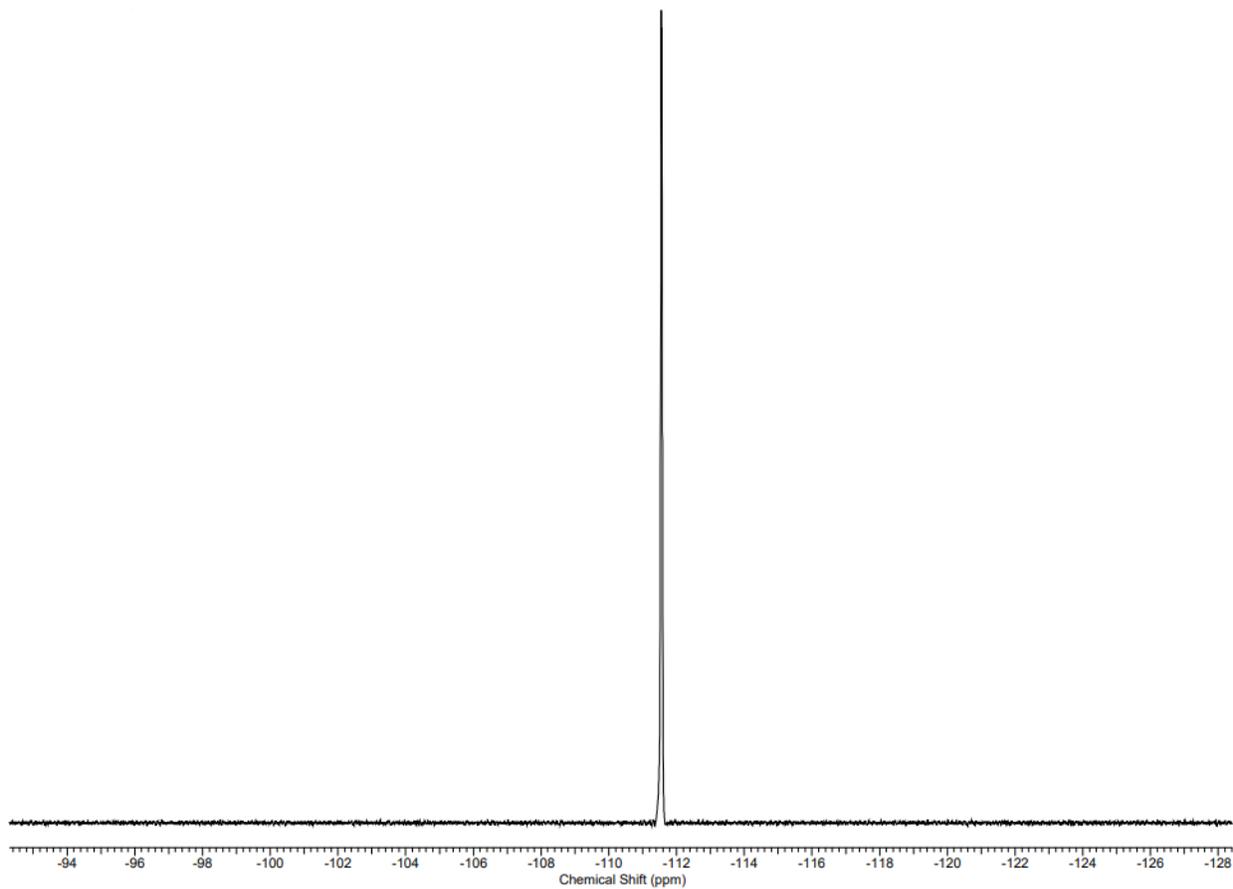
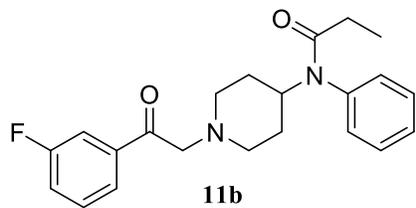
LC/MS (+ mode) for compound **11b**



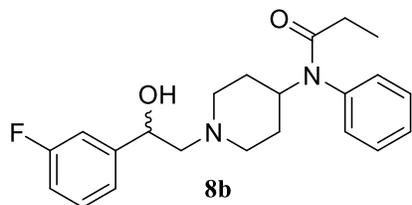
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of compound **11b**



$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of compound **11b**



$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of compound **11b**

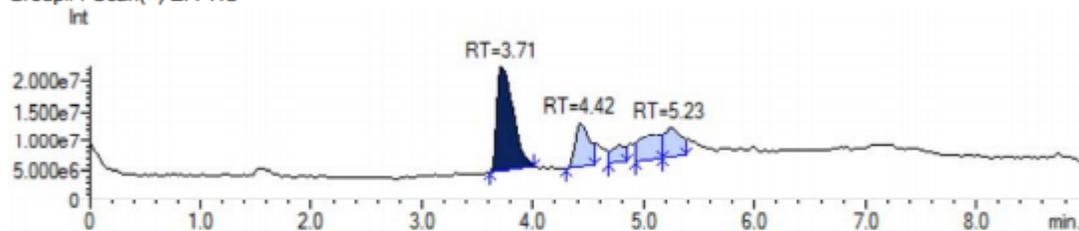


### Shimadzu Open Solution

**Project:** Dockendorff Lab  
**Experiment:** ricardo\_20190525\_06  
**Experiment Description:** Wizard-generated sample plate  
**Sample:** RR-SAL-046-2  
**Sample Description:** RR-SAL-046-2  
**Data File Name:** C:\Data\docken\RICARDO\RR-SAL-046-2.lcd  
**Sample Location:** Plate Number: 1 - Position: 46  
**Run By:** ricardo  
**Run Started:** Saturday, May 25, 2019 4:54:04 PM  
**Run Finished:** Saturday, May 25, 2019 5:25:22 PM  
**Method:** 051817 Std. Gemini 25 MeCN

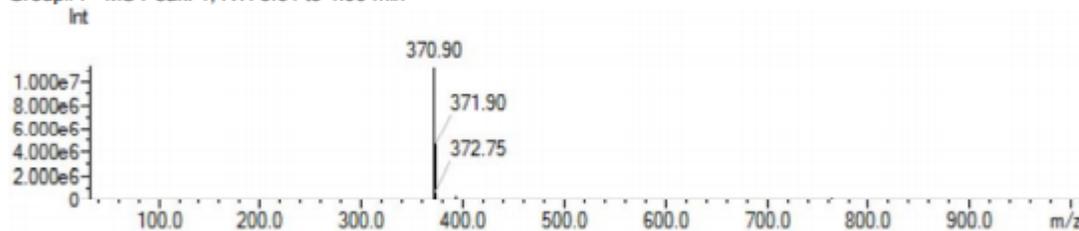
### MS Chromatogram

Group#1 Scan(+) EI : TIC



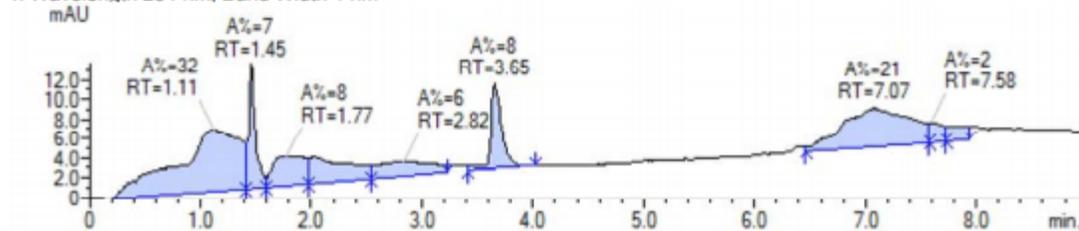
### MS Spectrum

Group#1 - MS Peak: 1, RT: 3.61 to 4.00 min

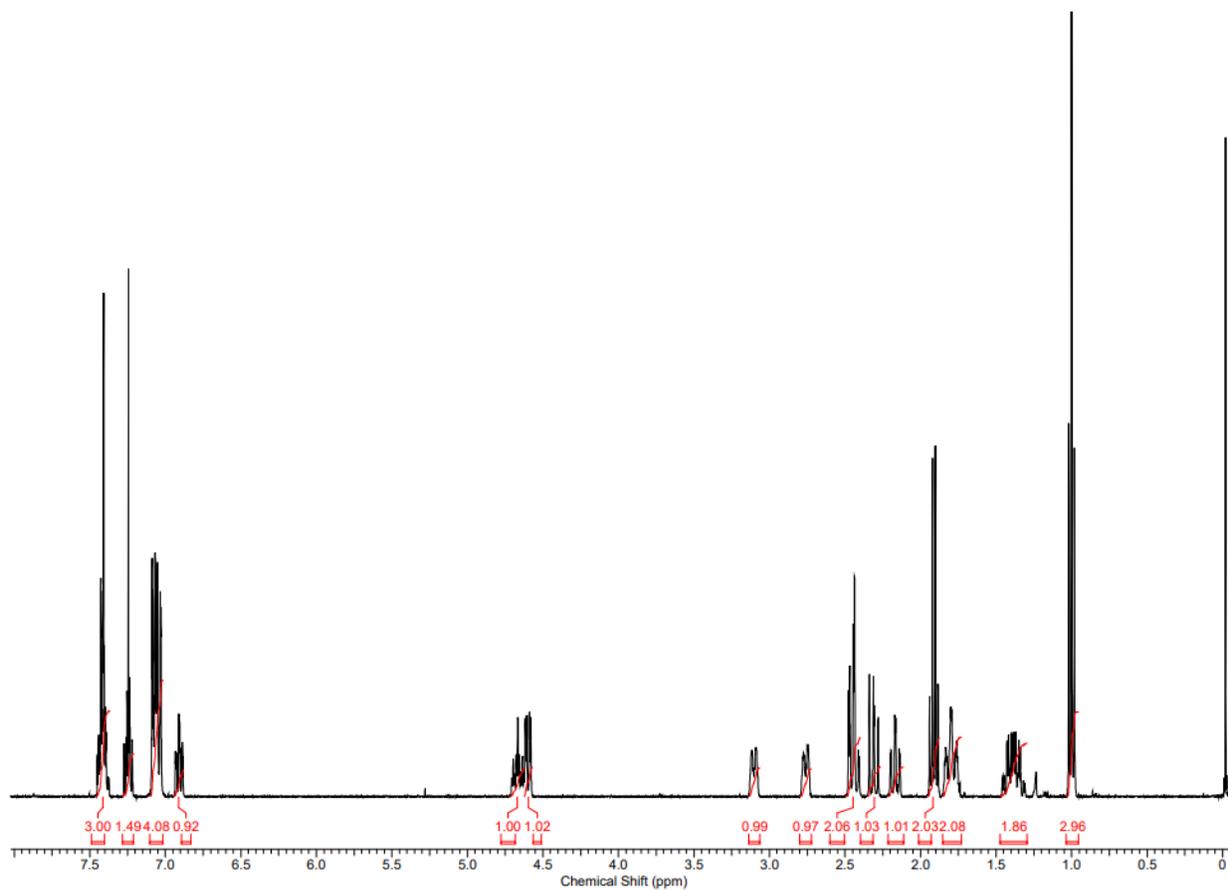
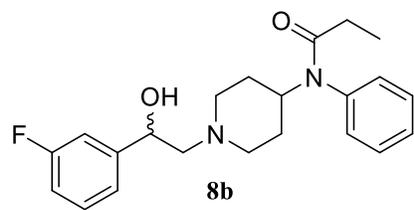


### PDA Chromatogram

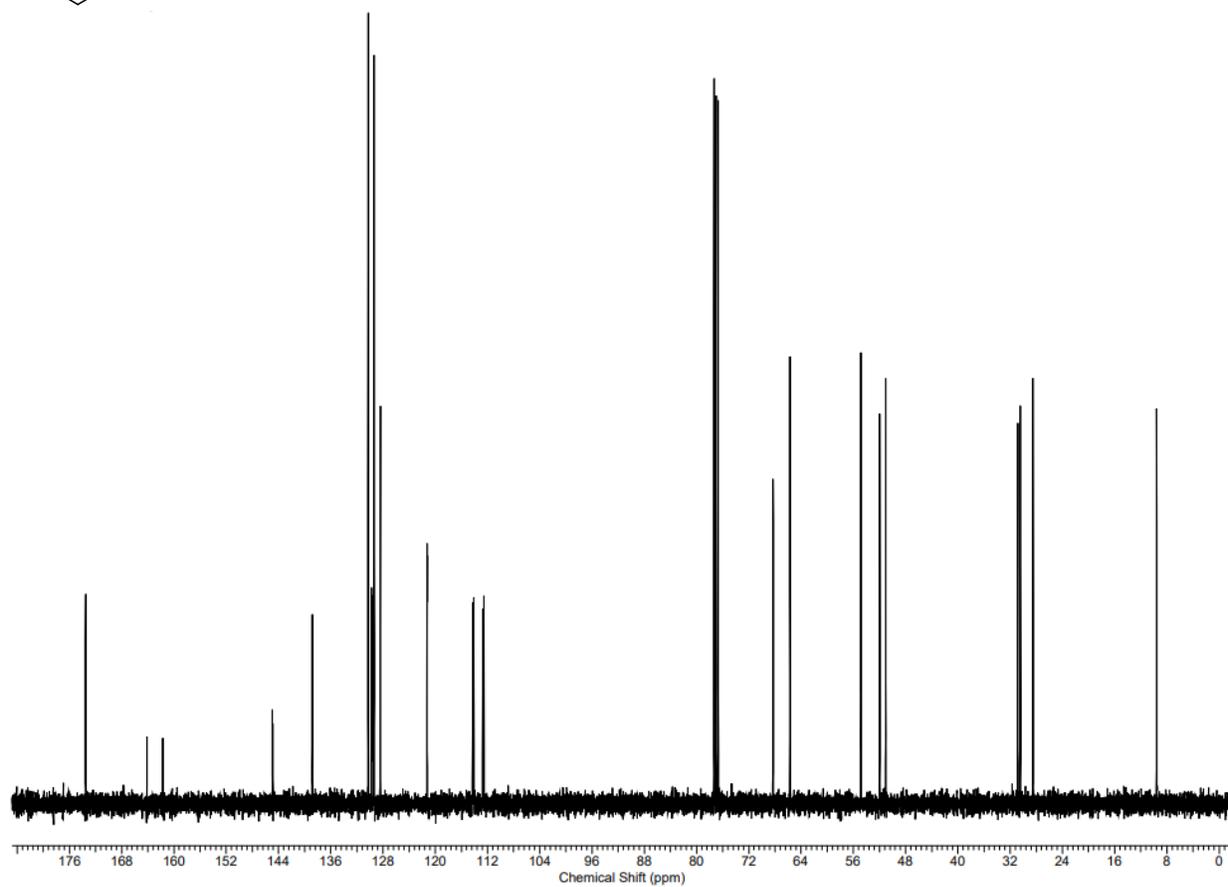
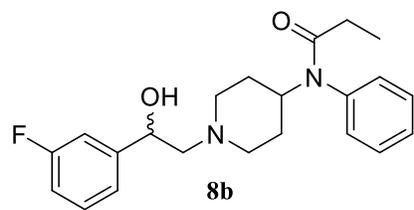
1: Wavelength 254 nm, Band Width 4 nm



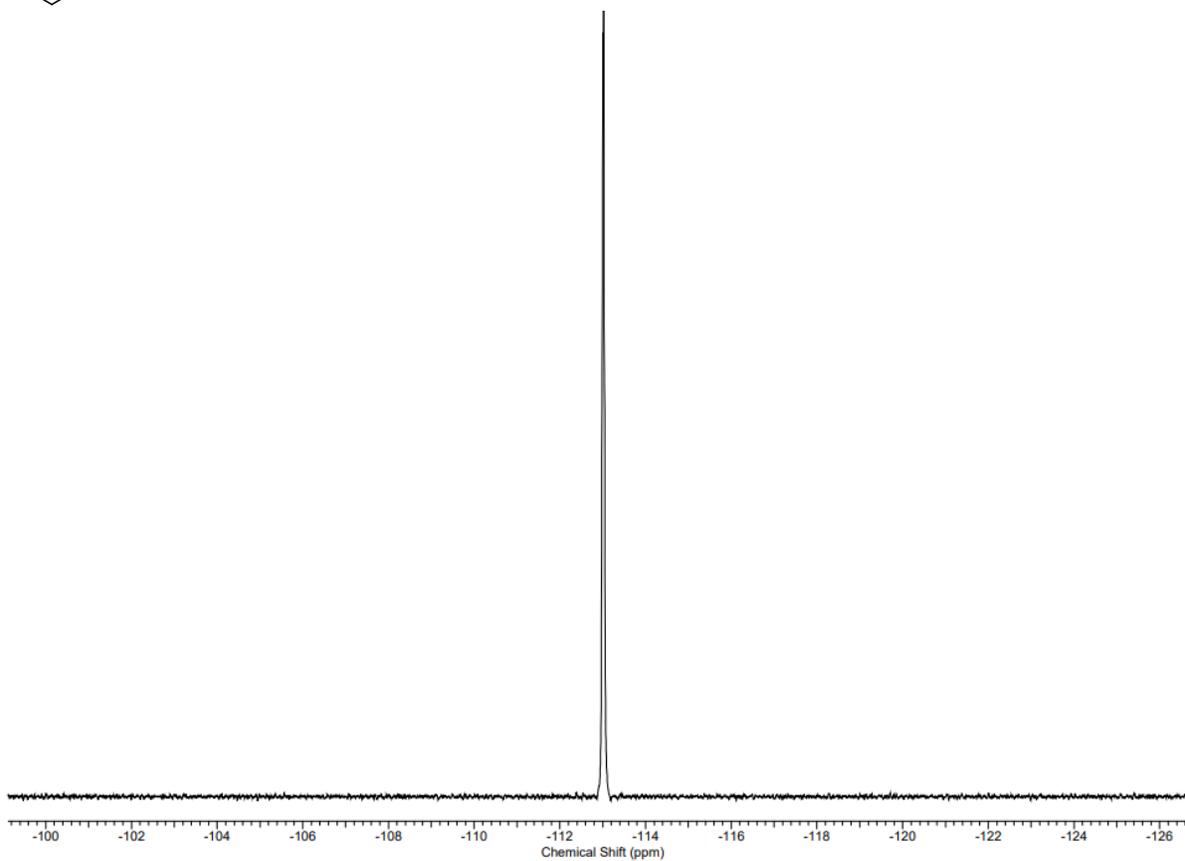
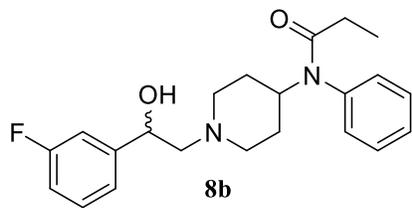
LC/MS (+ mode) for compound **8b**



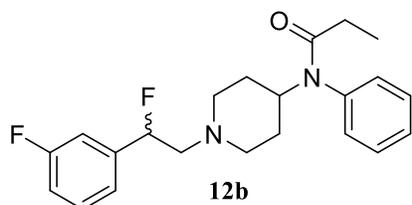
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of compound **8b**



$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of compound **8b**



$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of compound **8b**

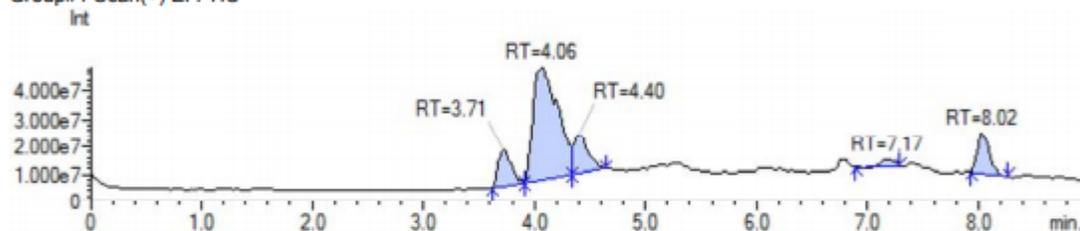


### Shimadzu Open Solution

<b>Project:</b>	Dockendorff Lab
<b>Experiment:</b>	ricardo_20190525_07
<b>Experiment Description:</b>	Wizard-generated sample plate
<b>Sample:</b>	RR-SAL-048-2
<b>Sample Description:</b>	RR-SAL-048-2
<b>Data File Name:</b>	C:\Data\docken\RICARDO\RR-SAL-048-2.lcd
<b>Sample Location:</b>	Plate Number: 1 - Position: 48
<b>Run By:</b>	ricardo
<b>Run Started:</b>	Saturday, May 25, 2019 5:25:27 PM
<b>Run Finished:</b>	Saturday, May 25, 2019 5:54:44 PM
<b>Method:</b>	051817 Std Gemini 25 MeCN

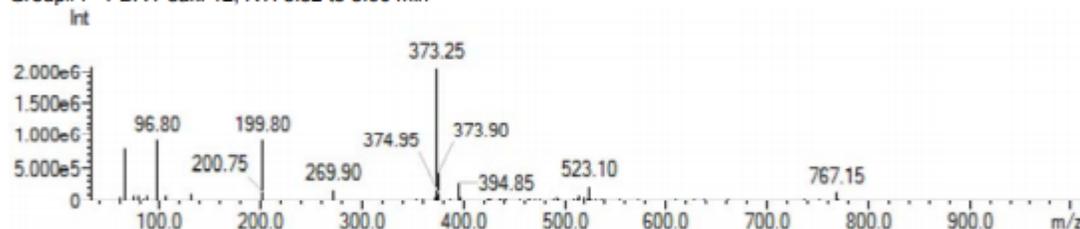
### MS Chromatogram

Group#1 Scan(+) El : TIC



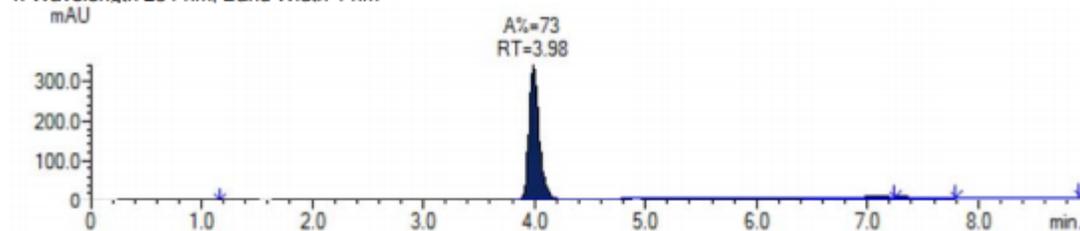
### MS Spectrum

Group#1 - PDA Peak: 12, RT: 3.82 to 8.90 min

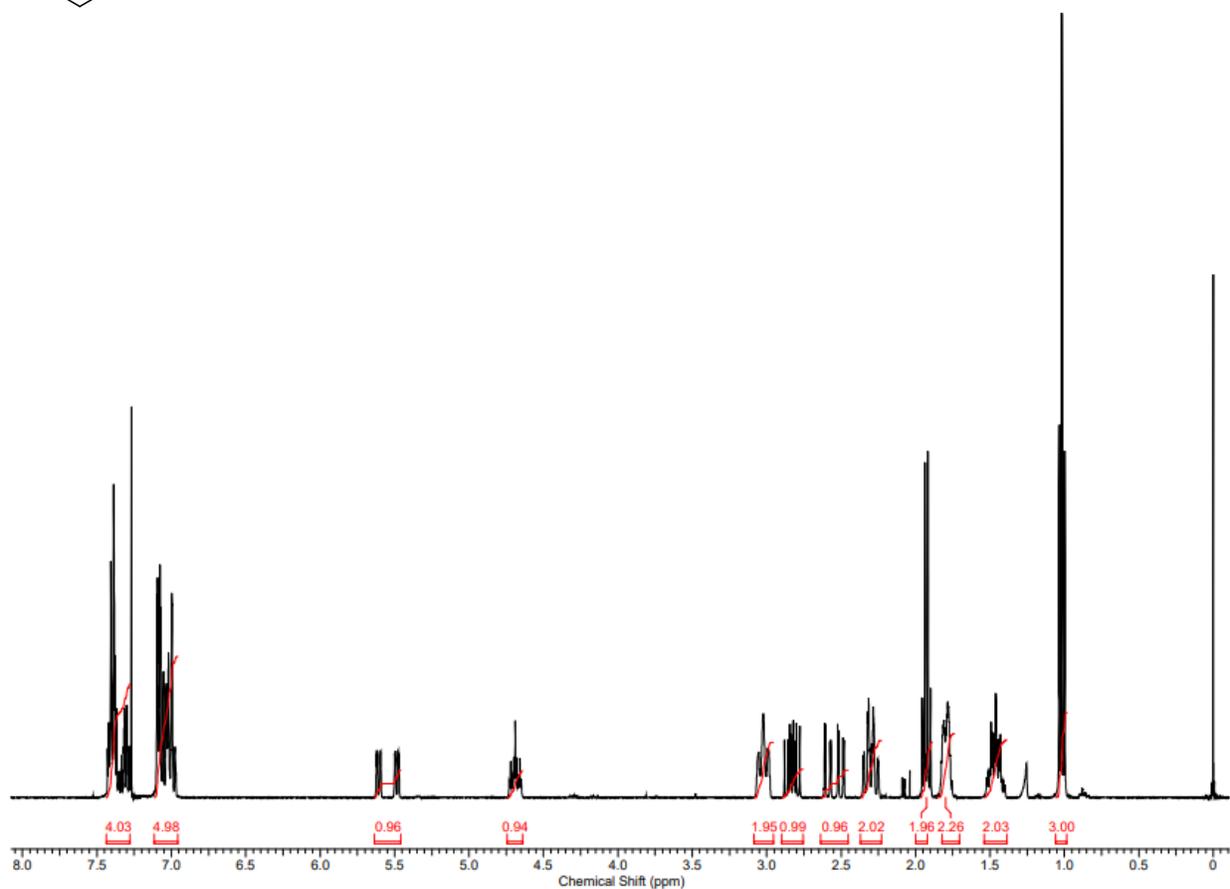
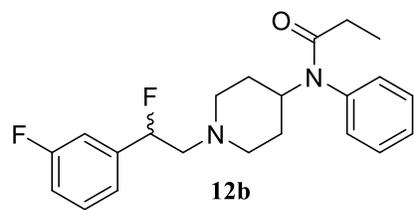


### PDA Chromatogram

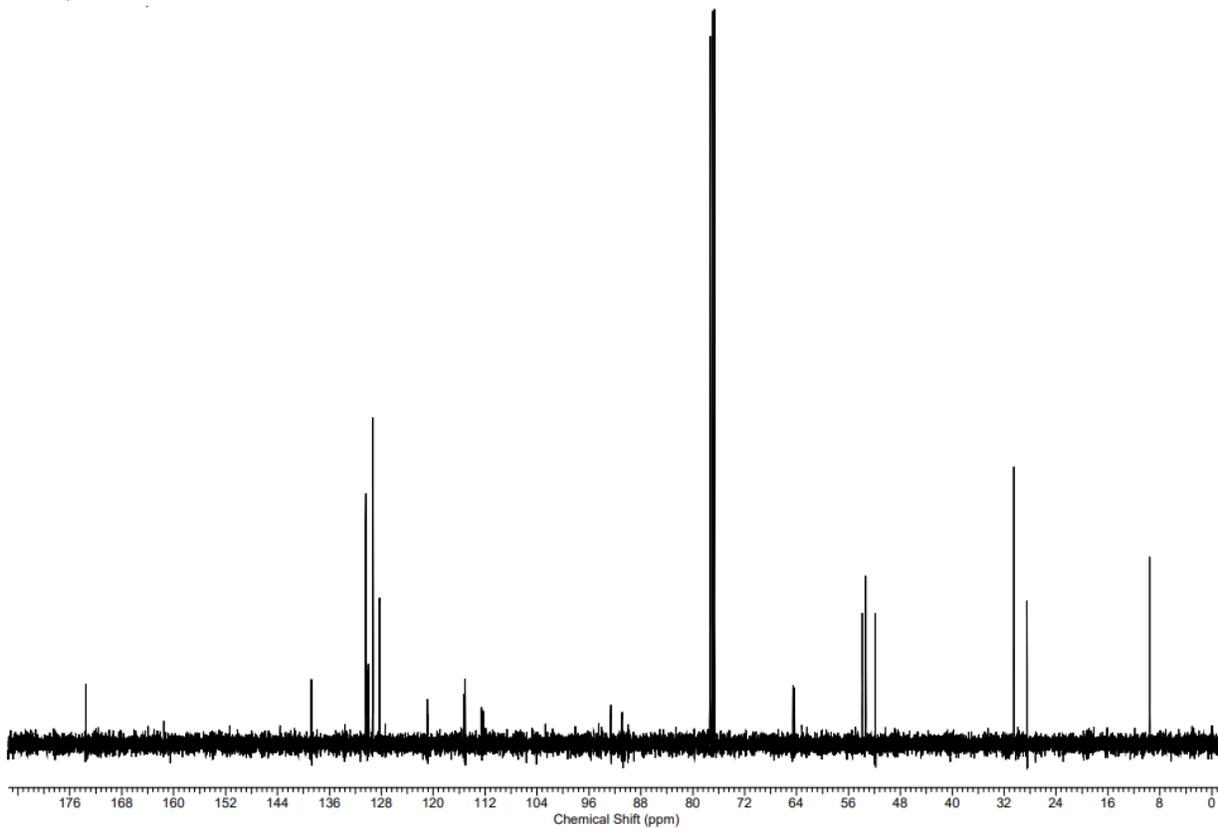
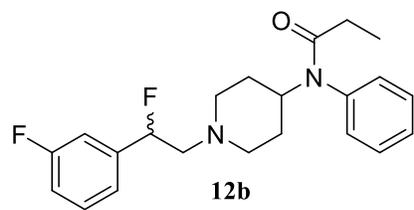
1: Wavelength 254 nm, Band Width 4 nm



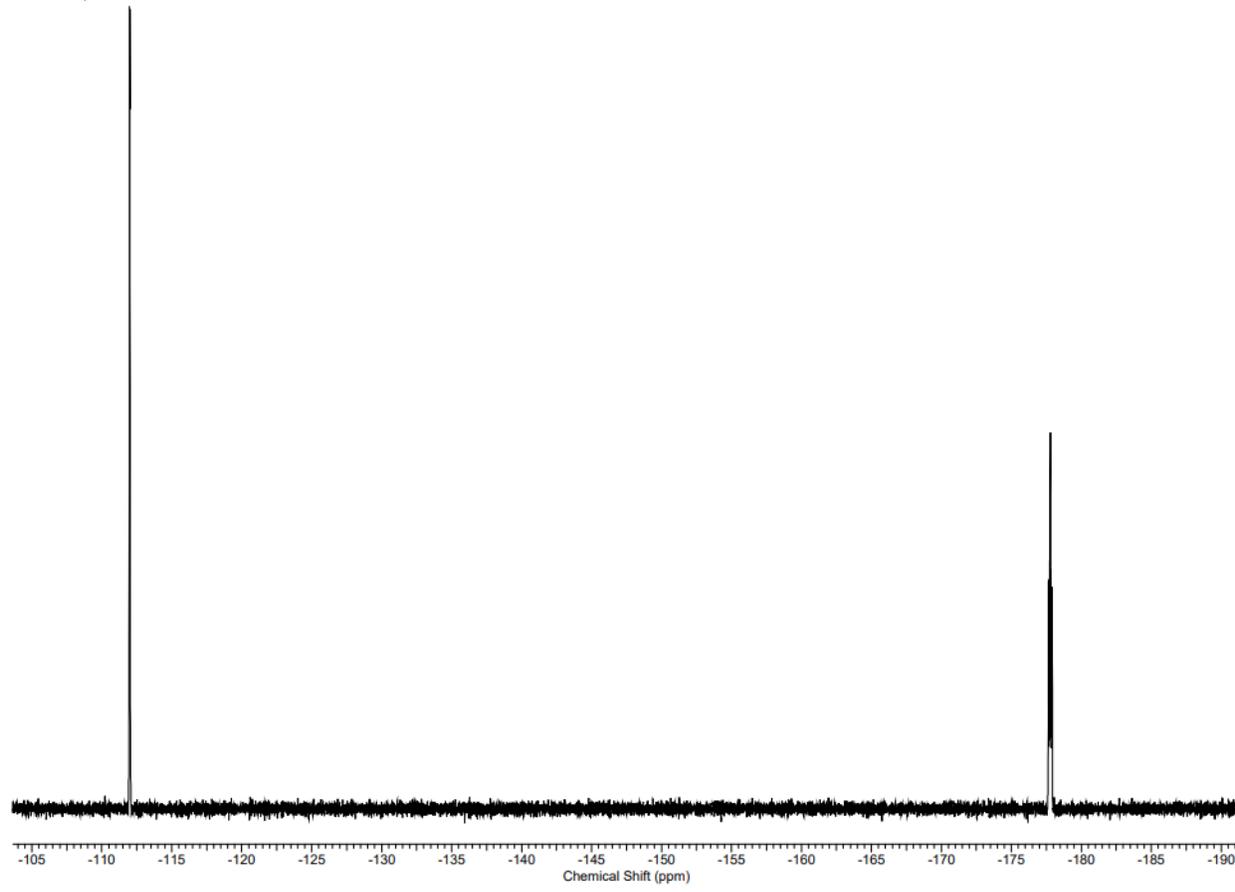
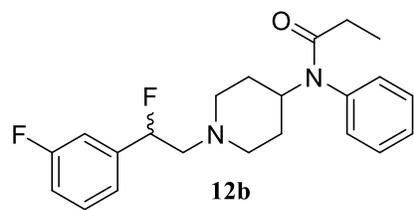
LC/MS (+ mode) for compound **12b**



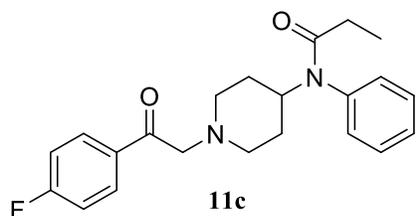
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of compound **12b**



$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of compound **12b**



$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of compound **12b**

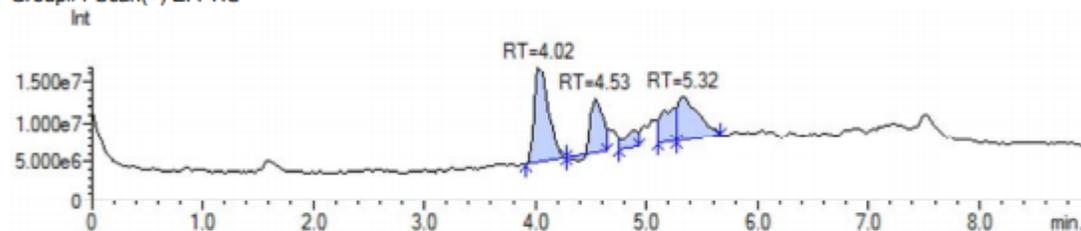


### Shimadzu Open Solution

<b>Project:</b>	Dockendorff Lab
<b>Experiment:</b>	ricardo_20190525_04
<b>Experiment Description:</b>	Wizard-generated sample plate
<b>Sample:</b>	RR-SAL-042-2
<b>Sample Description:</b>	RR-SAL-042-2
<b>Data File Name:</b>	C:\Data\docken\RICARDO\RR-SAL-042-2.lcd
<b>Sample Location:</b>	Plate Number: 1 - Position: 42
<b>Run By:</b>	ricardo
<b>Run Started:</b>	Saturday, May 25, 2019 4:03:03 PM
<b>Run Finished:</b>	Saturday, May 25, 2019 4:33:32 PM
<b>Method:</b>	051817 Std Gemini 25 MeCN

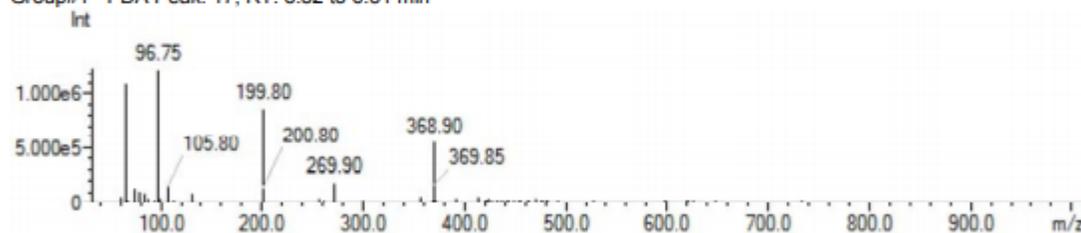
### MS Chromatogram

Group#1 Scan(+) EI : TIC



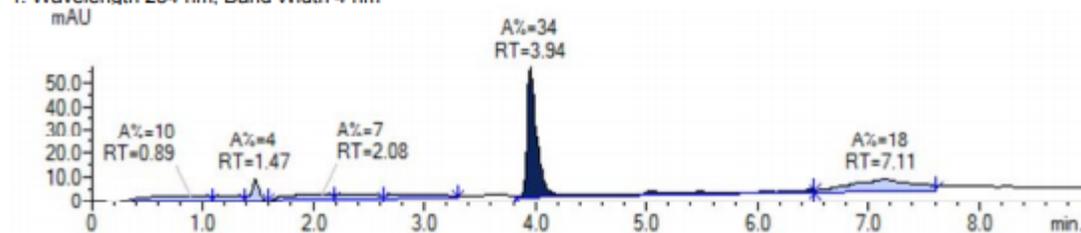
### MS Spectrum

Group#1 - PDA Peak: 17, RT: 3.82 to 6.51 min

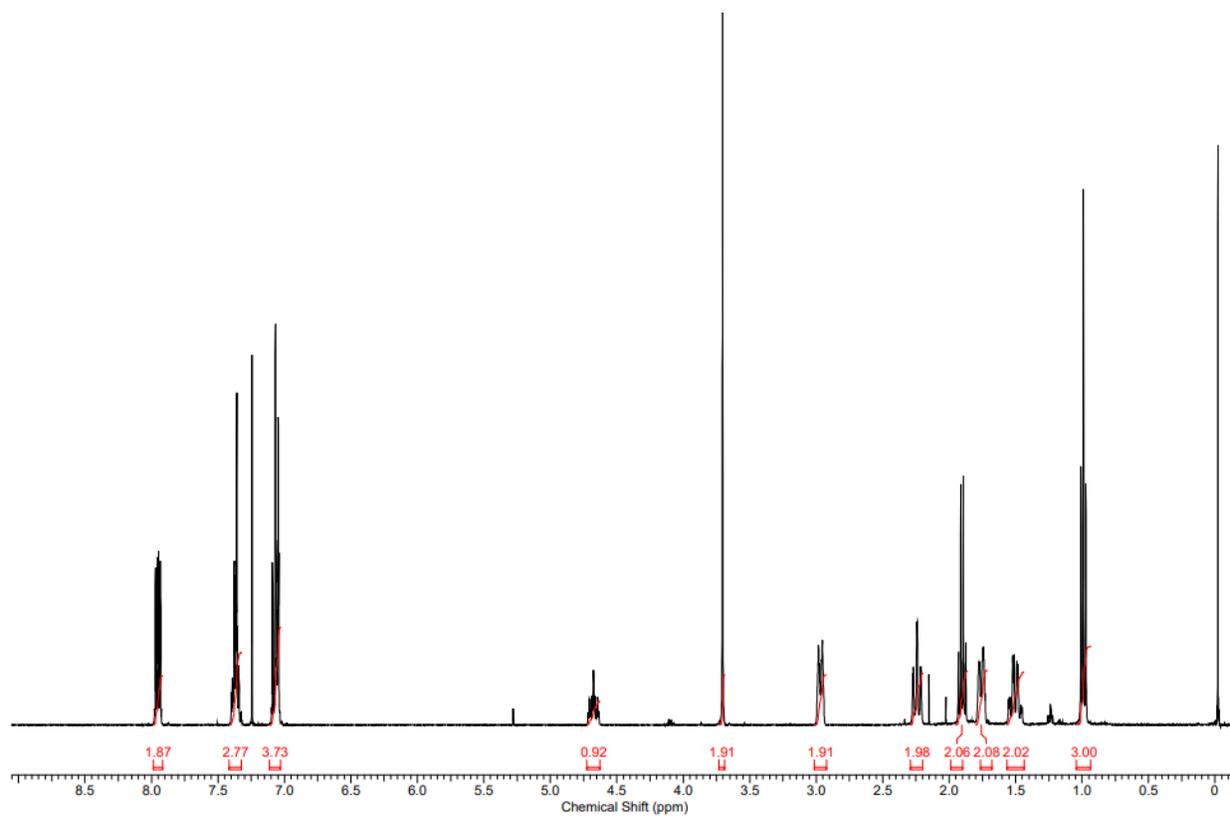
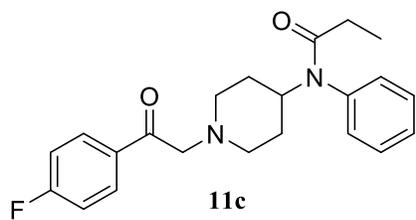


### PDA Chromatogram

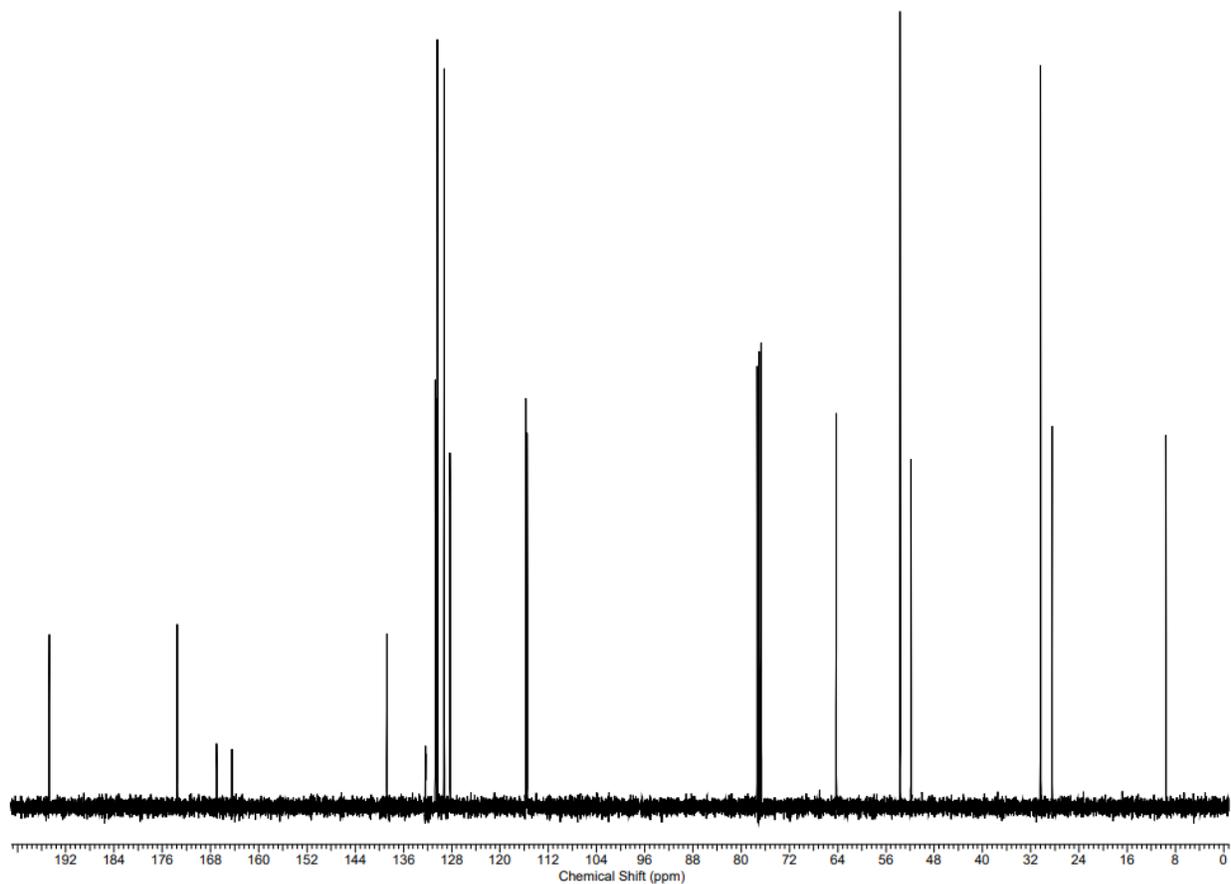
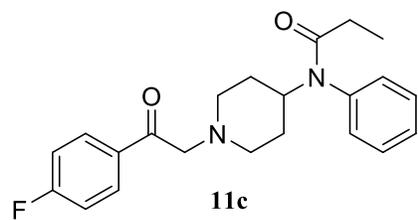
1: Wavelength 254 nm, Band Width 4 nm



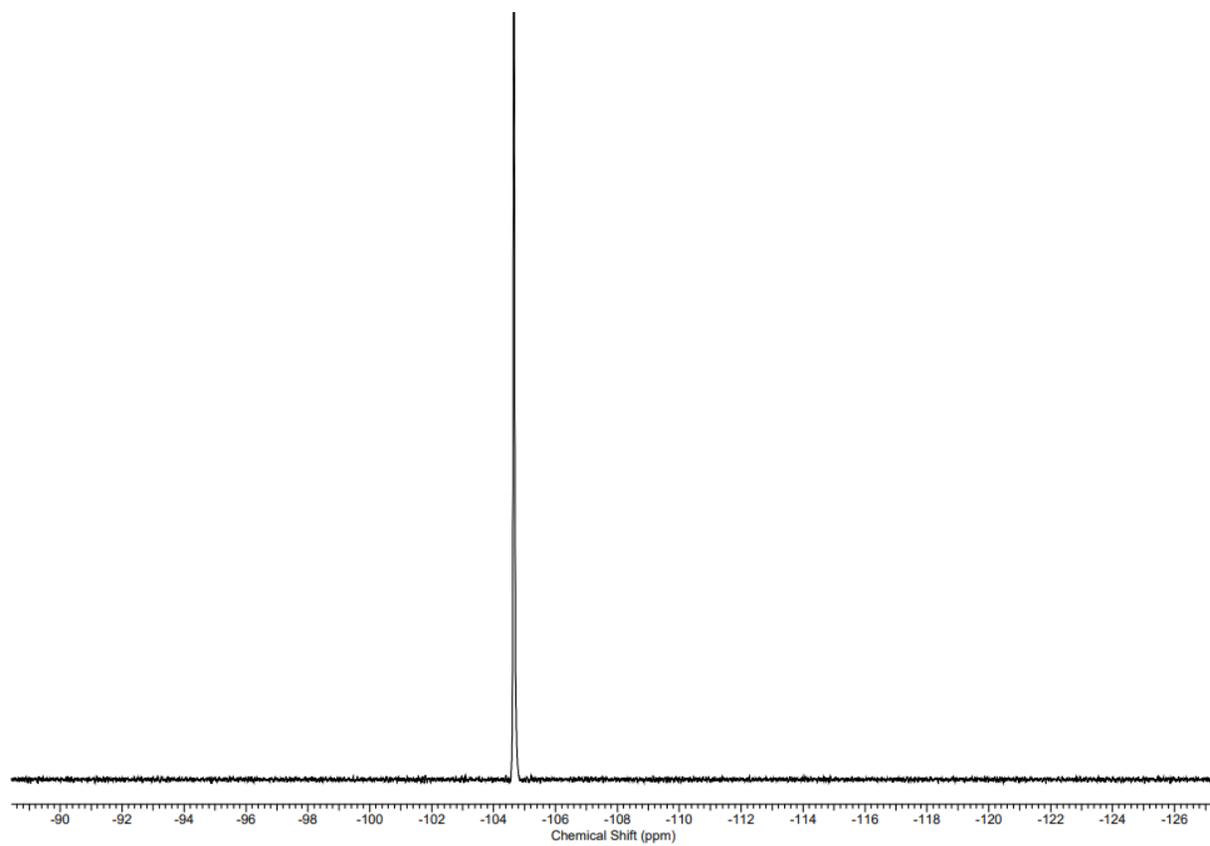
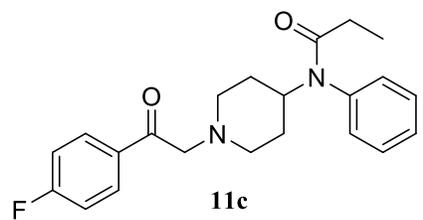
LC/MS (+ mode) for compound **11c**



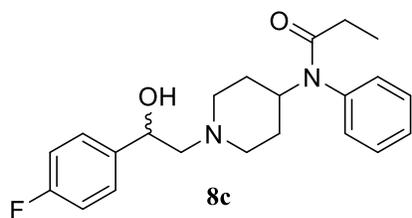
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) of compound **11c**



$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of compound **11c**



$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of compound **11c**

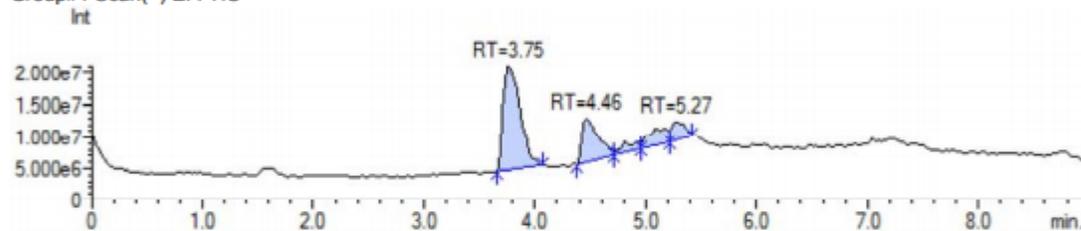


### Shimadzu Open Solution

**Project:** Dockendorff Lab  
**Experiment:** ricardo\_20190525\_06  
**Experiment Description:** Wizard-generated sample plate  
**Sample:** RR-SAL-045-2  
**Sample Description:** RR-SAL-045-2  
**Data File Name:** C:\Data\docken\RICARDO\RR-SAL-045-2.lcd  
**Sample Location:** Plate Number: 1 - Position: 45  
**Run By:** ricardo  
**Run Started:** Saturday, May 25, 2019 4:54:04 PM  
**Run Finished:** Saturday, May 25, 2019 5:25:22 PM  
**Method:** 051817 Std Gemini 25 MeCN

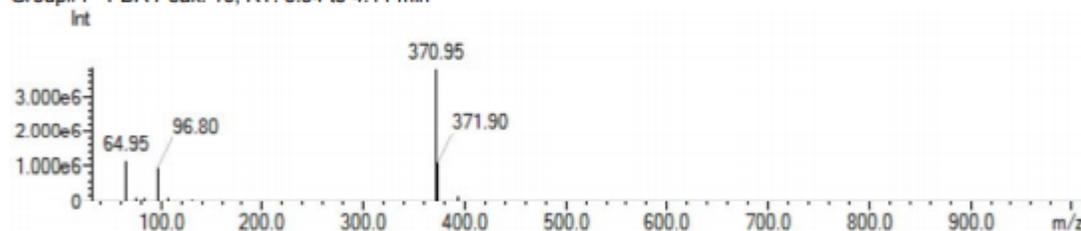
### MS Chromatogram

Group#1 Scan(+) EI : TIC



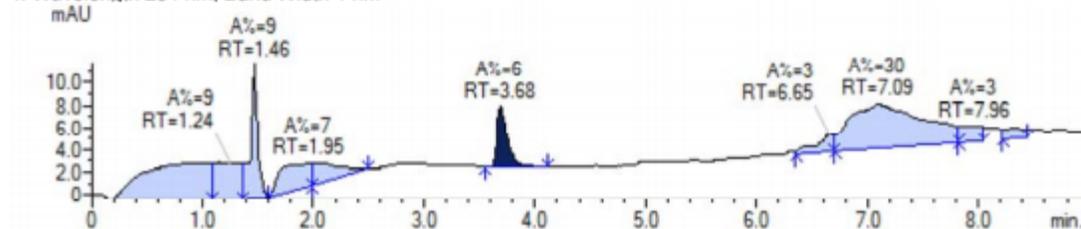
### MS Spectrum

Group#1 - PDA Peak: 16, RT: 3.54 to 4.11 min

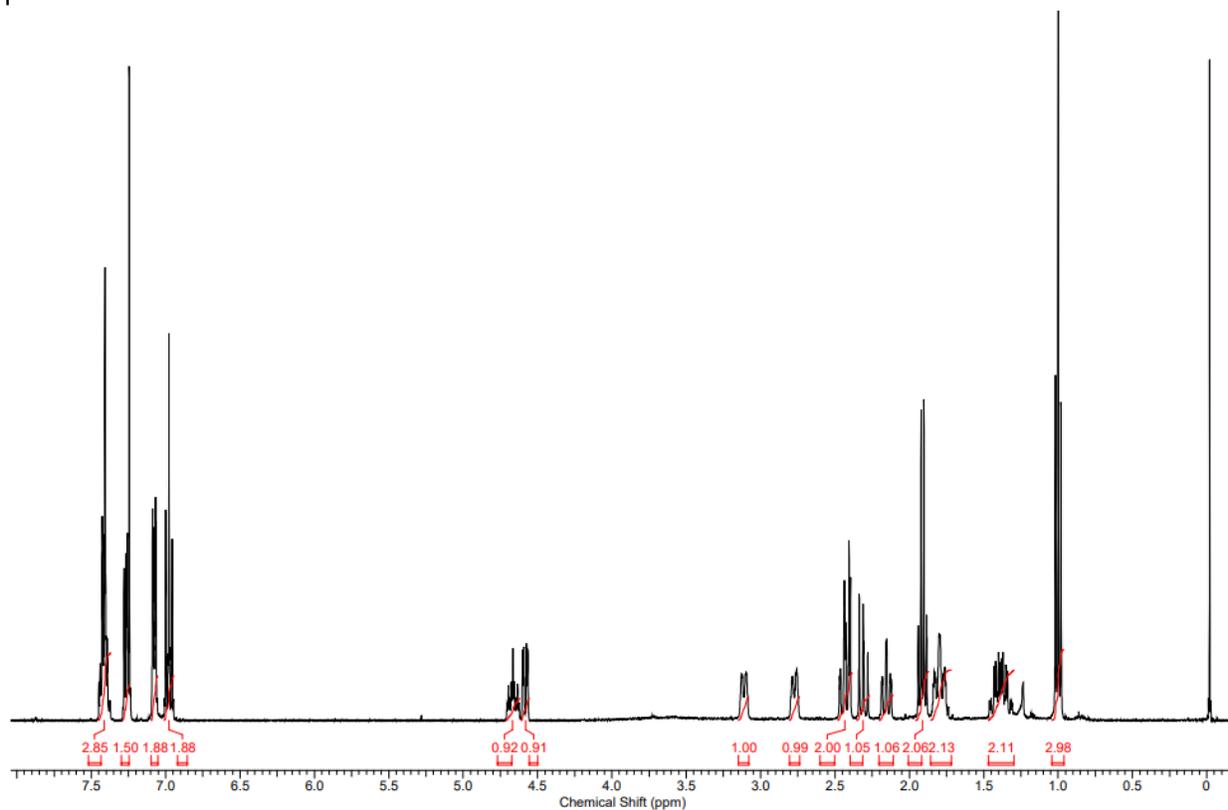
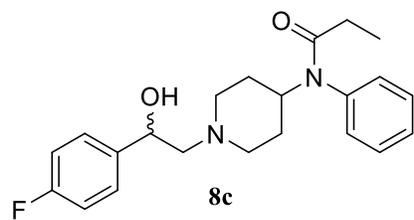


### PDA Chromatogram

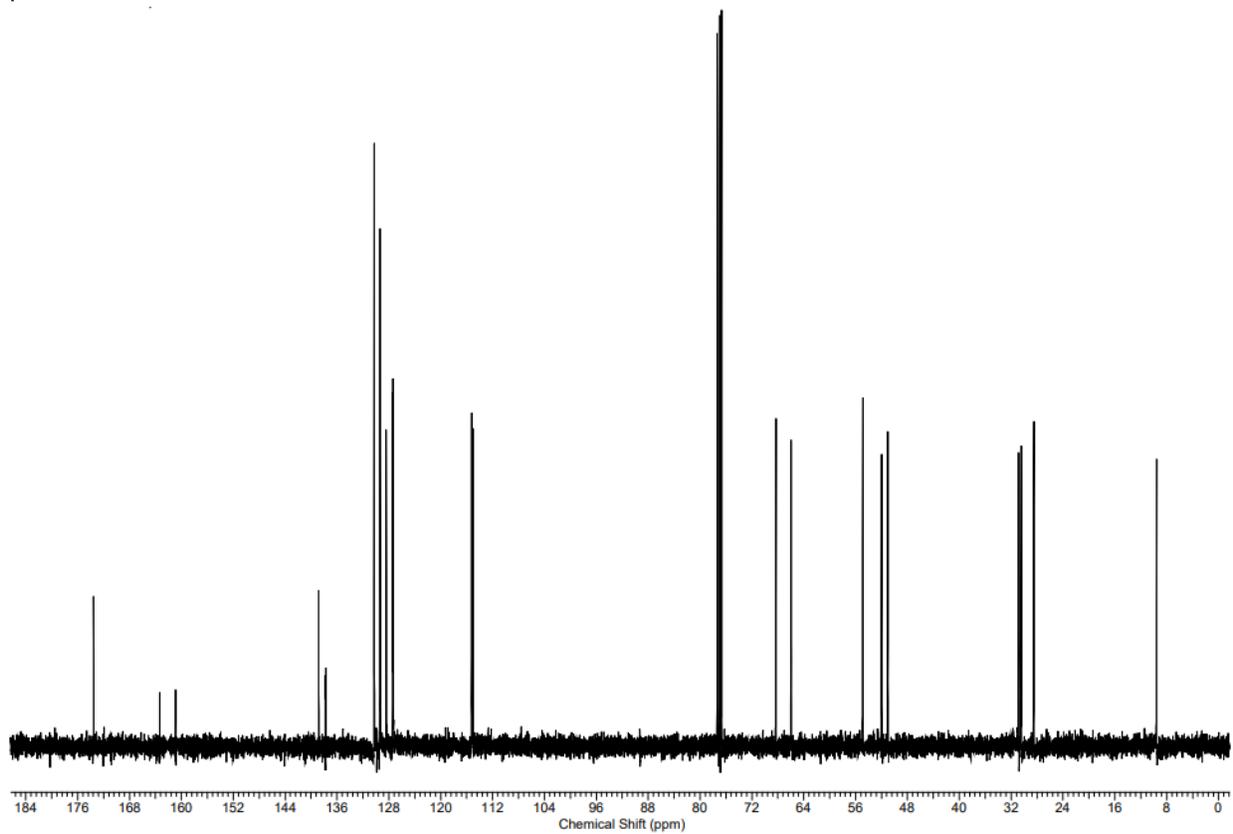
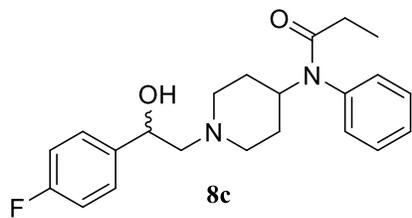
1: Wavelength 254 nm, Band Width 4 nm



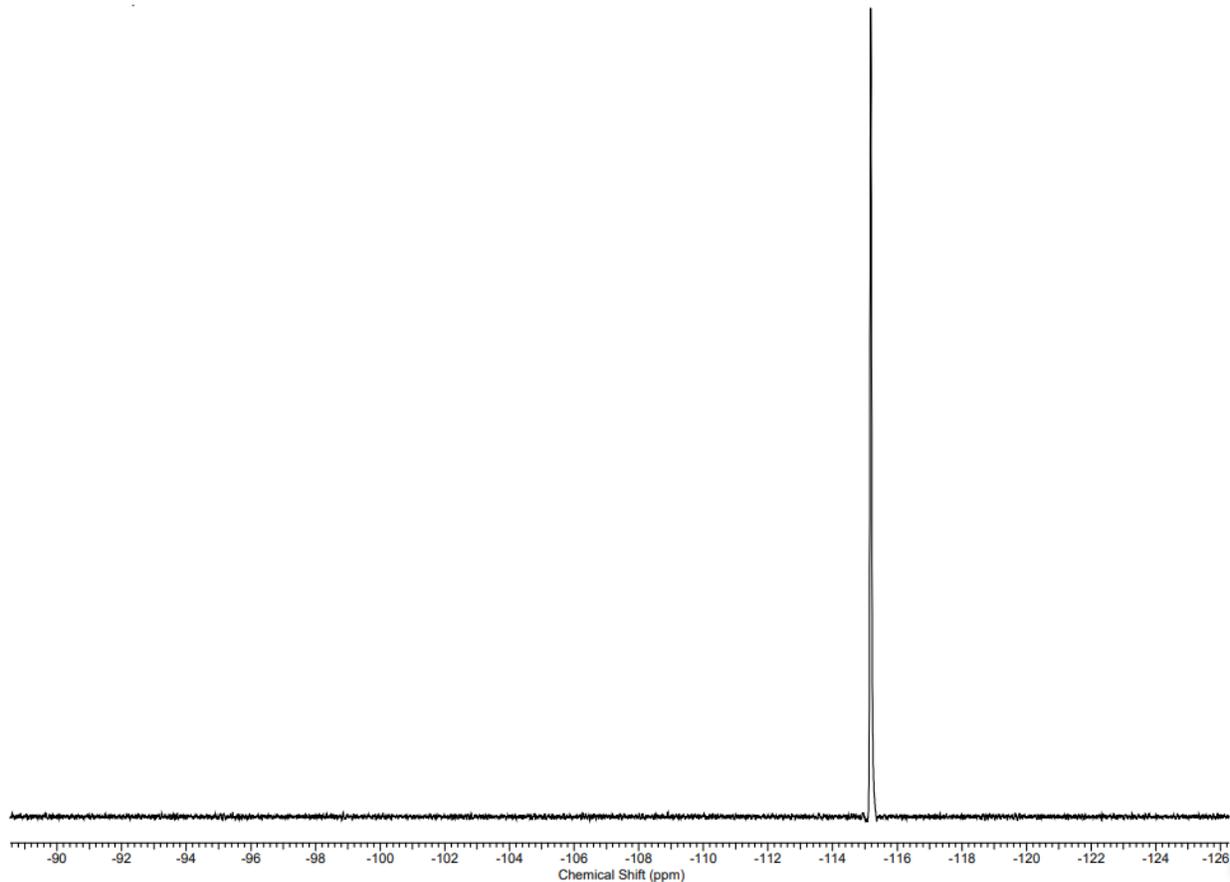
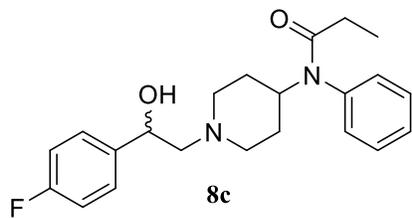
LC/MS (+ mode) for compound 8c



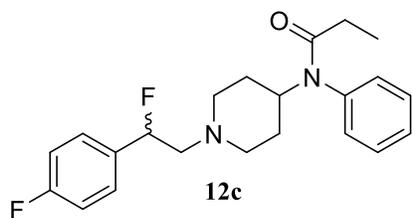
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of compound **8c**



$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of compound **8c**



$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of compound **8c**

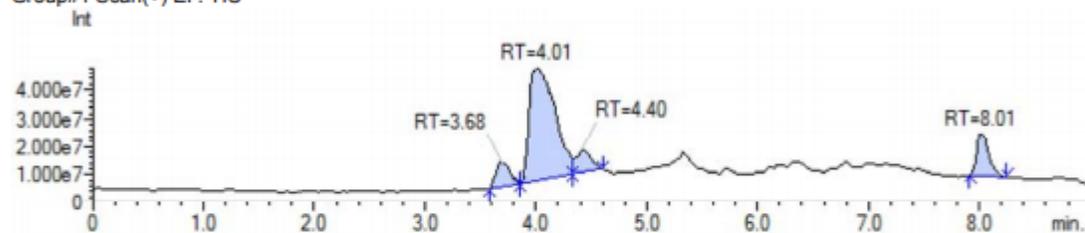


### Shimadzu Open Solution

**Project:** Dockendorff Lab  
**Experiment:** ricardo\_20190525\_07  
**Experiment Description:** Wizard-generated sample plate  
**Sample:** RR-SAL-047-2  
**Sample Description:** RR-SAL-047-2  
**Data File Name:** C:\Data\docken\RICARDO\RR-SAL-047-2.lcd  
**Sample Location:** Plate Number: 1 - Position: 47  
**Run By:** ricardo  
**Run Started:** Saturday, May 25, 2019 5:25:27 PM  
**Run Finished:** Saturday, May 25, 2019 5:54:44 PM  
**Method:** 051817\_Std\_Gemini\_25\_MeCN

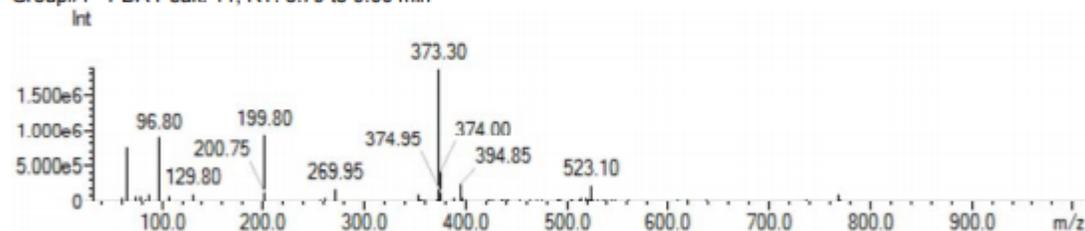
### MS Chromatogram

Group#1 Scan(+) EI: TIC



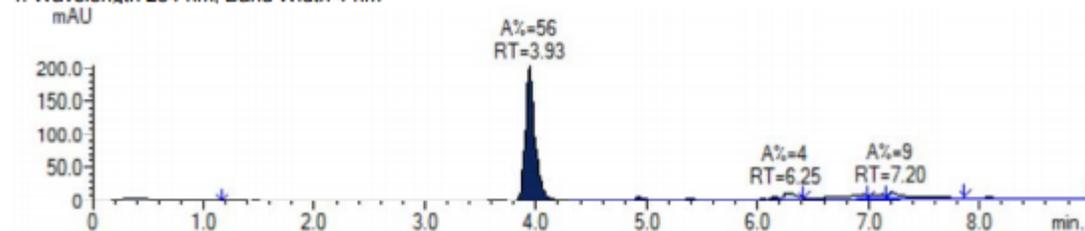
### MS Spectrum

Group#1 - PDA Peak: 11, RT: 3.79 to 9.00 min

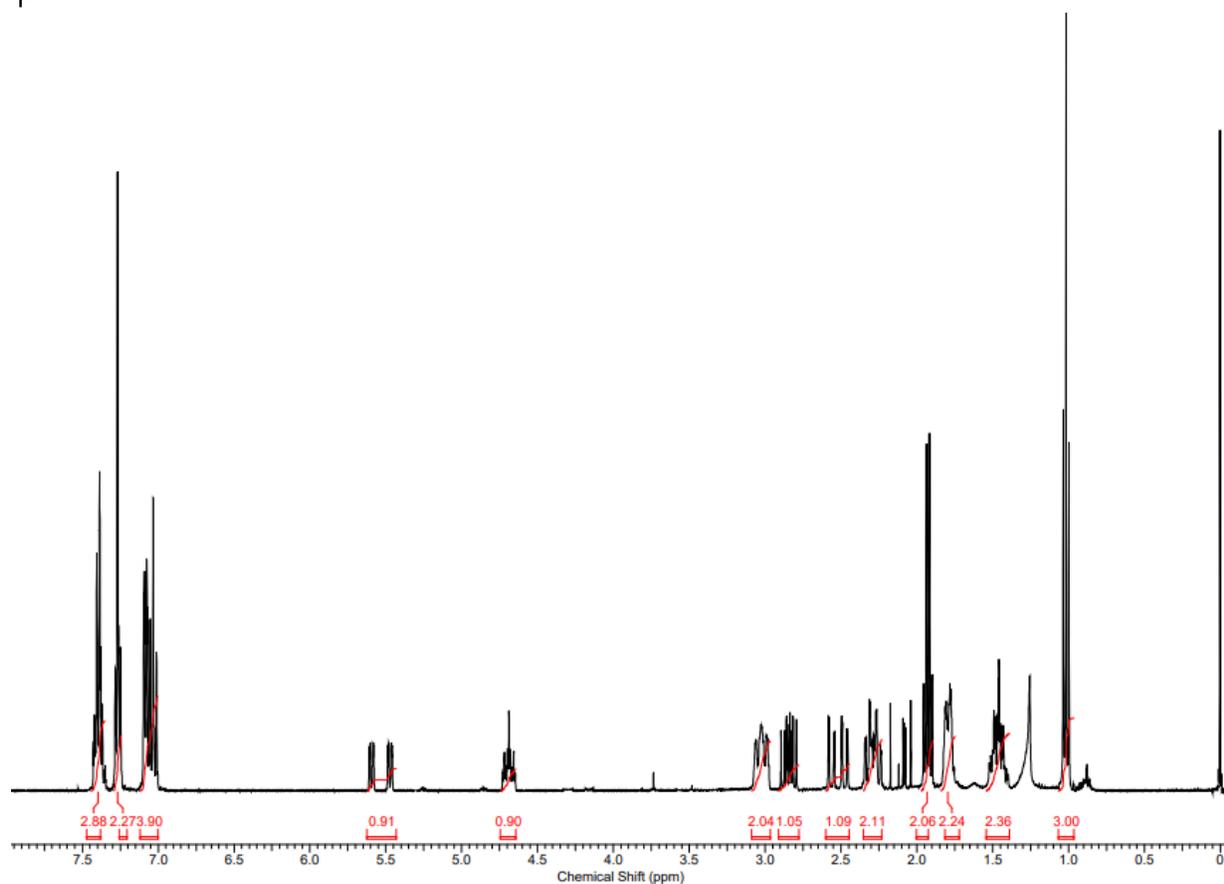
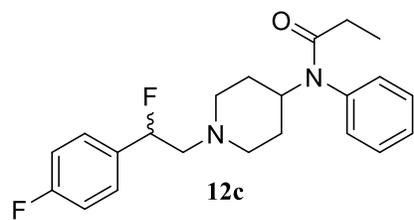


### PDA Chromatogram

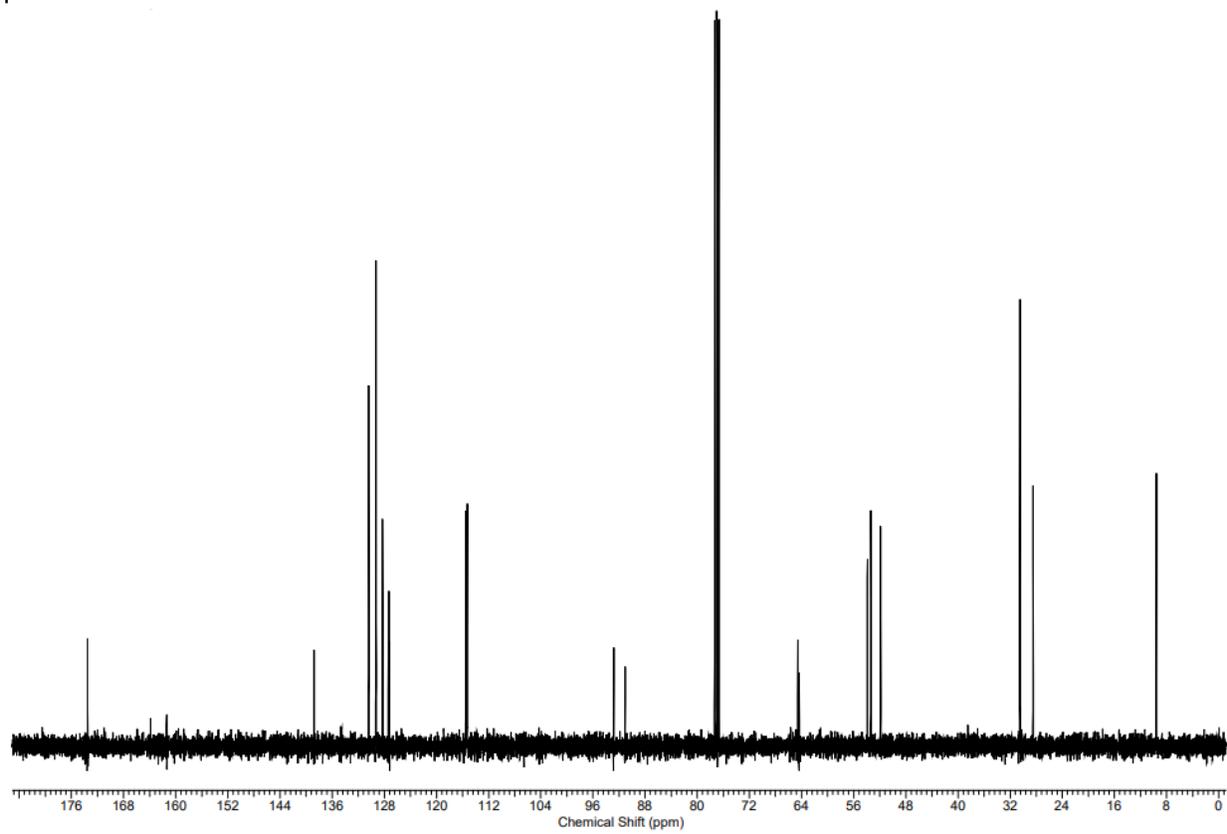
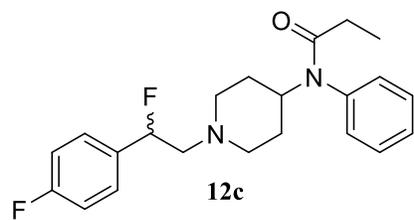
1: Wavelength 254 nm, Band Width 4 nm



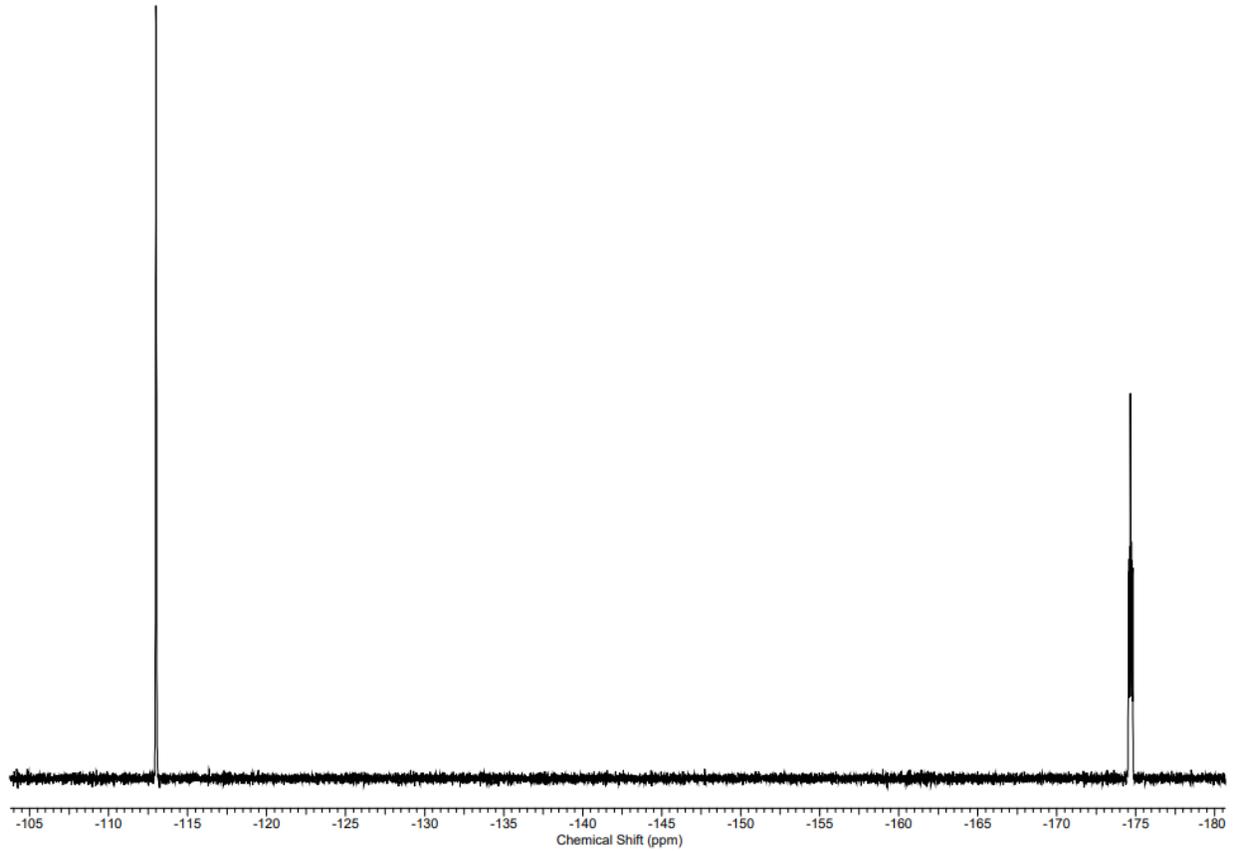
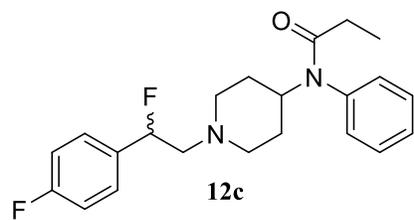
LC/MS (+ mode) for compound 12c



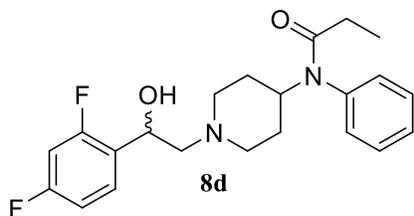
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of compound **12c**



$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of compound **12c**



$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of compound **12c**

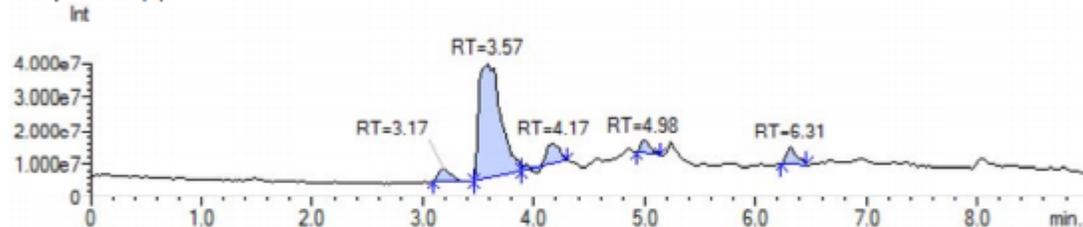


### Shimadzu Open Solution

**Project:** Dockendorff Lab  
**Experiment:** ricardo\_20190616\_03  
**Experiment Description:** Wizard-generated sample plate  
**Sample:** RR-SAL-051-2  
**Sample Description:** RR-SAL-051-2  
**Data File Name:** C:\Data\docken\RICARDO\RR-SAL-051-2.lcd  
**Sample Location:** Plate Number: 1 - Position: 90  
**Run By:** ricardo  
**Run Started:** Sunday, June 16, 2019 9:11:53 AM  
**Run Finished:** Sunday, June 16, 2019 9:24:29 AM  
**Method:** 051817\_Std\_Gemini\_25\_MeCN

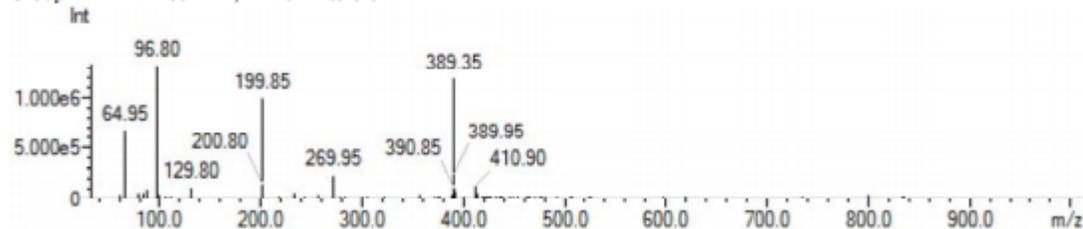
### MS Chromatogram

Group#1 Scan(+) EI : TIC



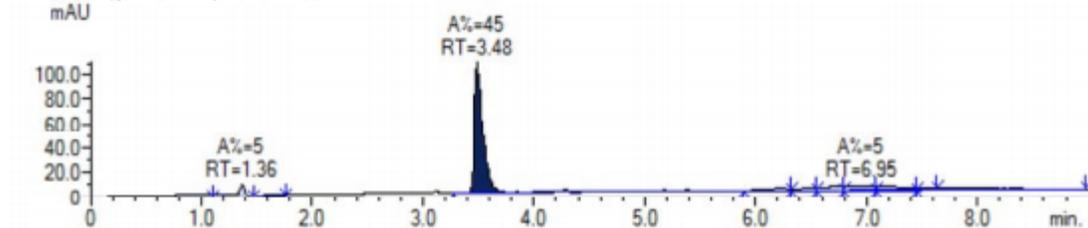
### MS Spectrum

Group#1 - PDA Peak: 14, RT: 3.27 to 8.97 min

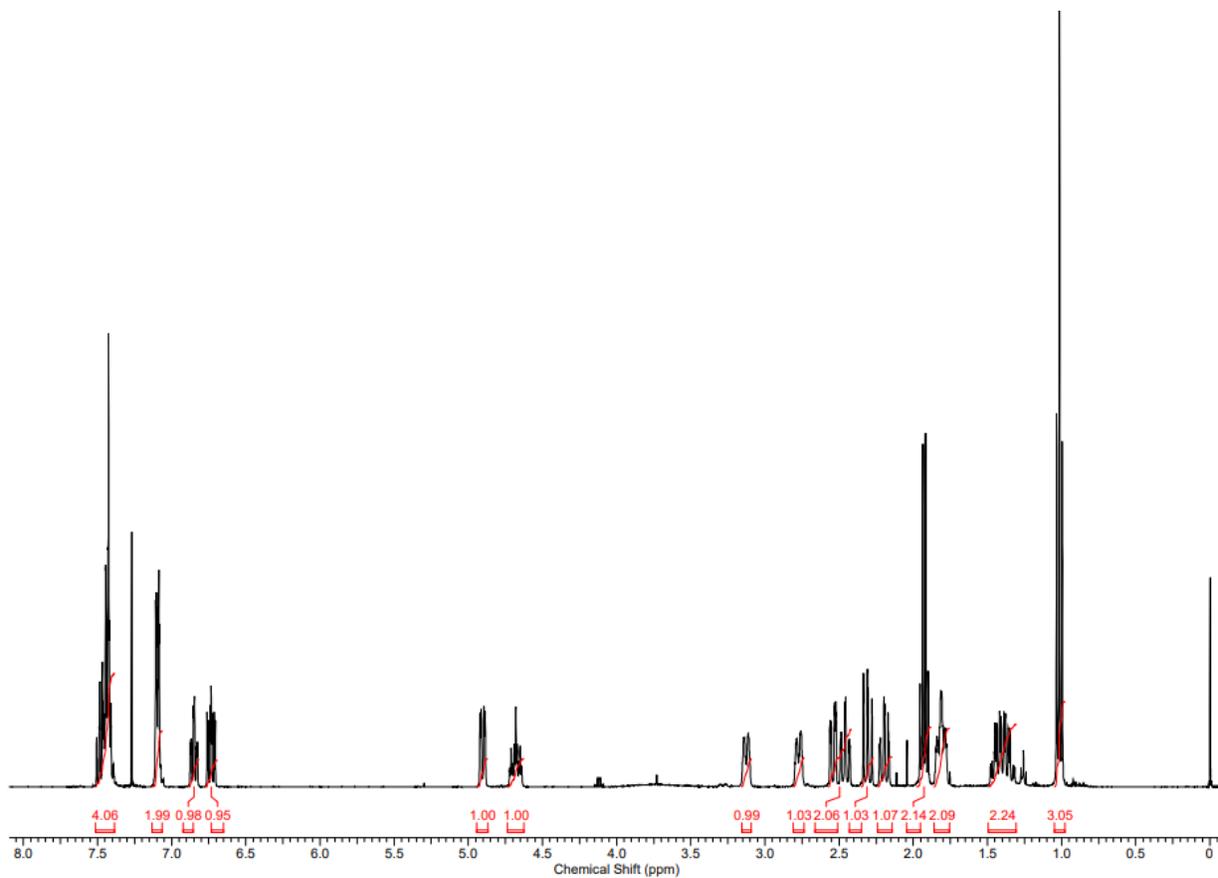
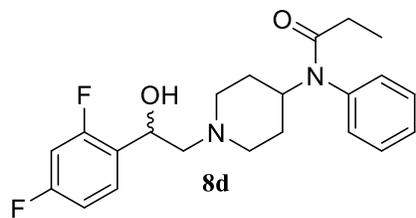


### PDA Chromatogram

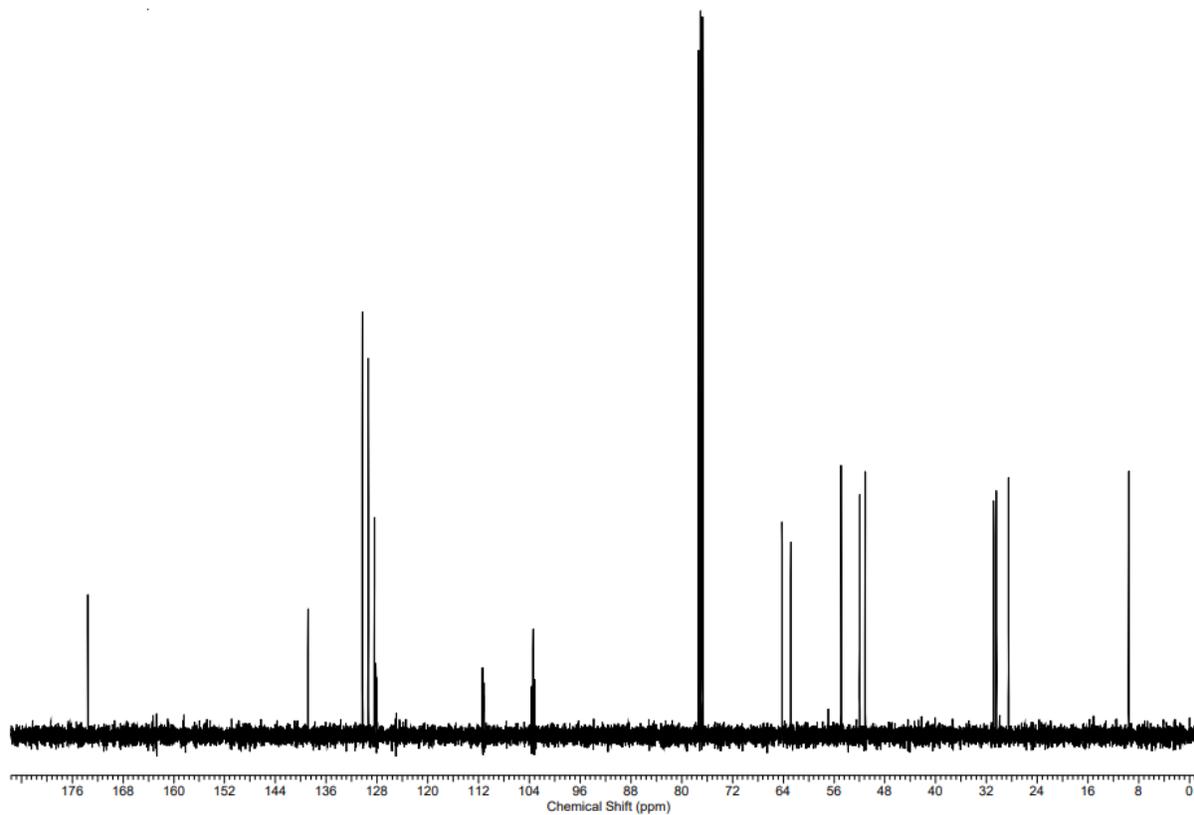
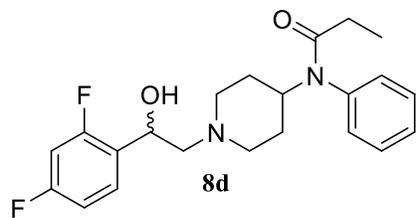
1: Wavelength 254 nm, Band Width 4 nm



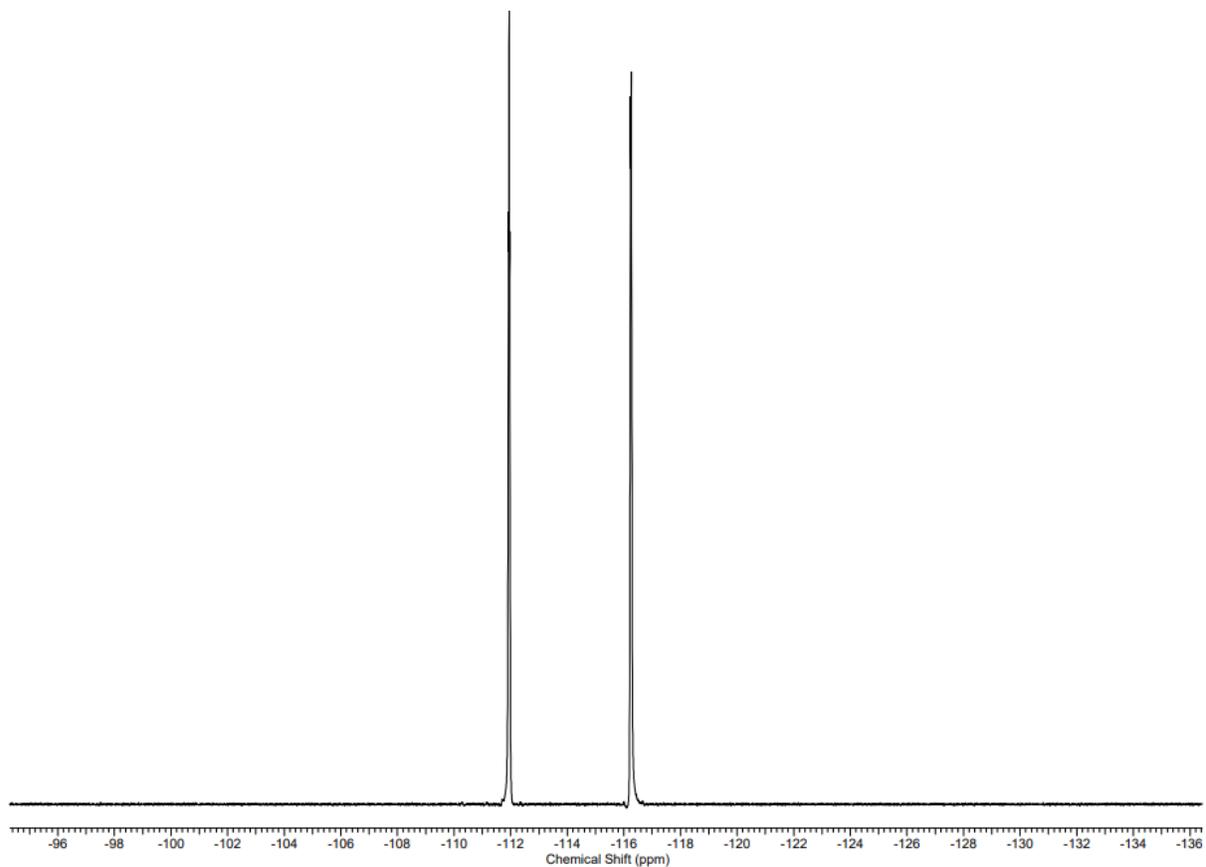
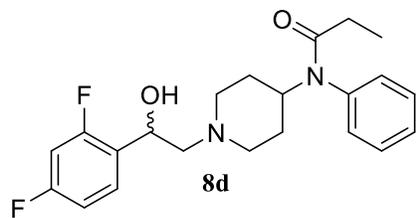
LC/MS (+ mode) for compound **8d**



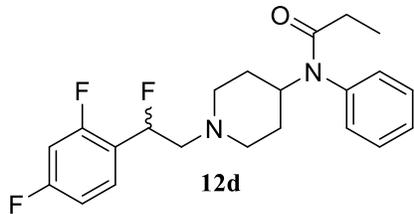
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of compound **8d**



$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ) of compound **8d**



$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of compound **8d**

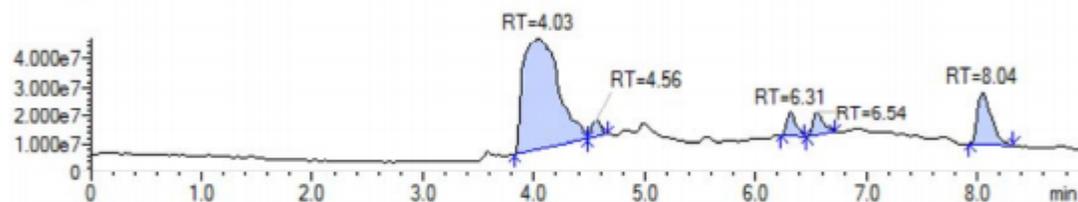


**Shimadzu Open Solution**

**Project:** Dockendorff Lab  
**Experiment:** ricardo\_20190616\_01  
**Experiment Description:** Wizard-generated sample plate  
**Sample:** RR-SAL-052-2  
**Sample Description:** RR-SAL-052-2  
**Data File Name:** C:\Data\docken\RICARDO\RR-SAL-052-3.lcd  
**Sample Location:** Plate Number: 1 - Position: 89  
**Run By:** ricardo  
**Run Started:** Sunday, June 16, 2019 8:32:10 AM  
**Run Finished:** Sunday, June 16, 2019 8:47:01 AM  
**Method:** 051817 Std Gemini 25 MeCN

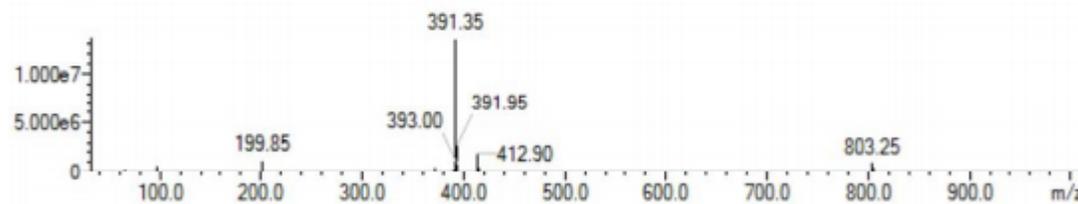
**MS Chromatogram**

Group#1 Scan(+) EI : TIC  
Int



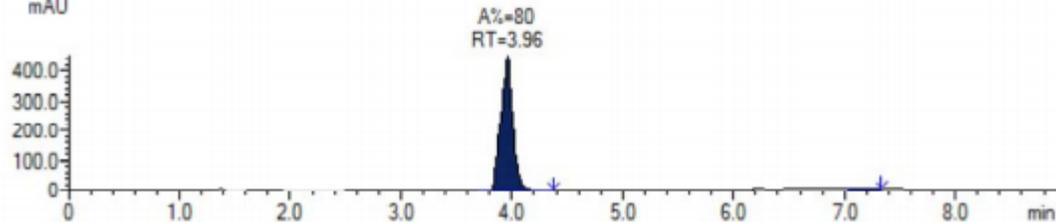
**MS Spectrum**

Group#1 - PDA Peak: 11, RT: 3.69 to 4.36 min  
Int

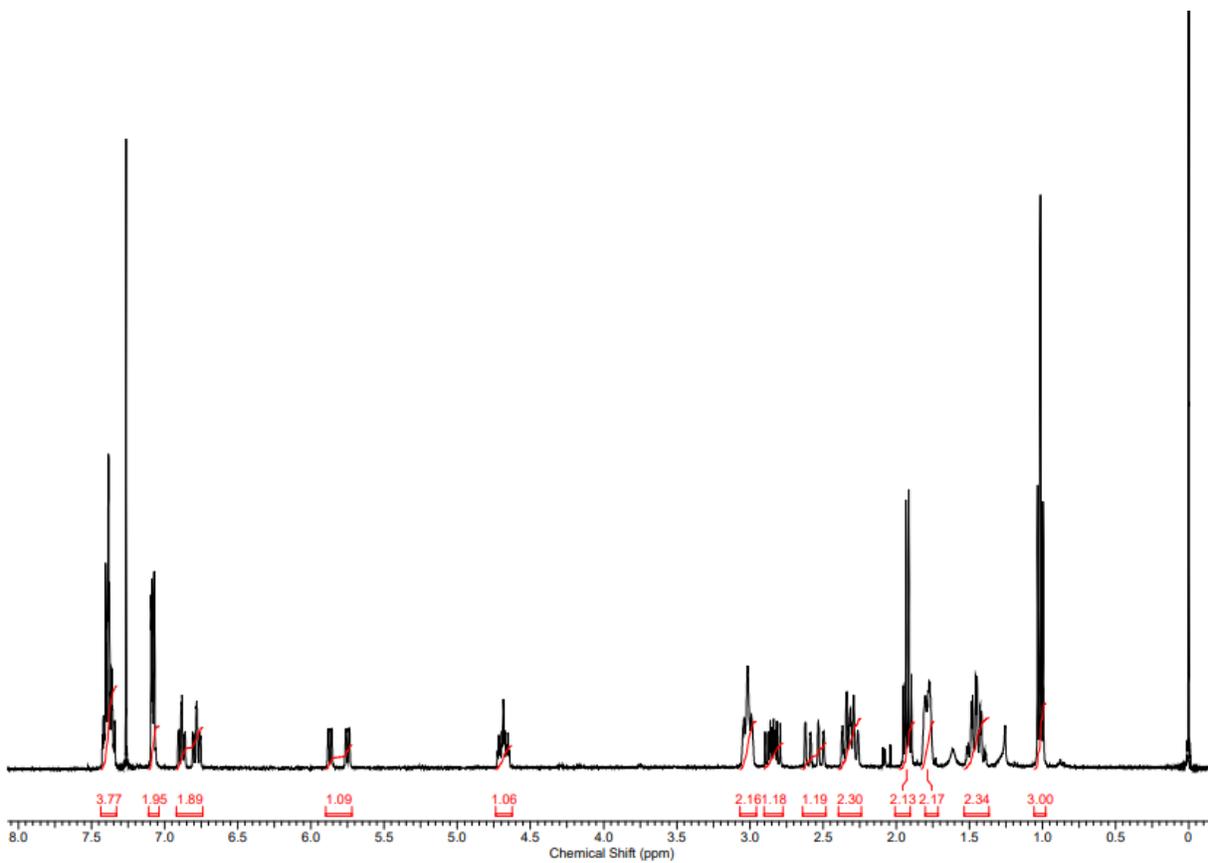
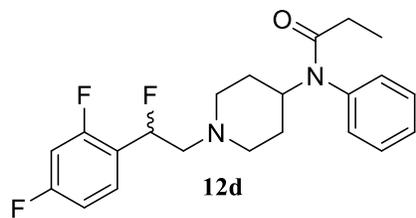


**PDA Chromatogram**

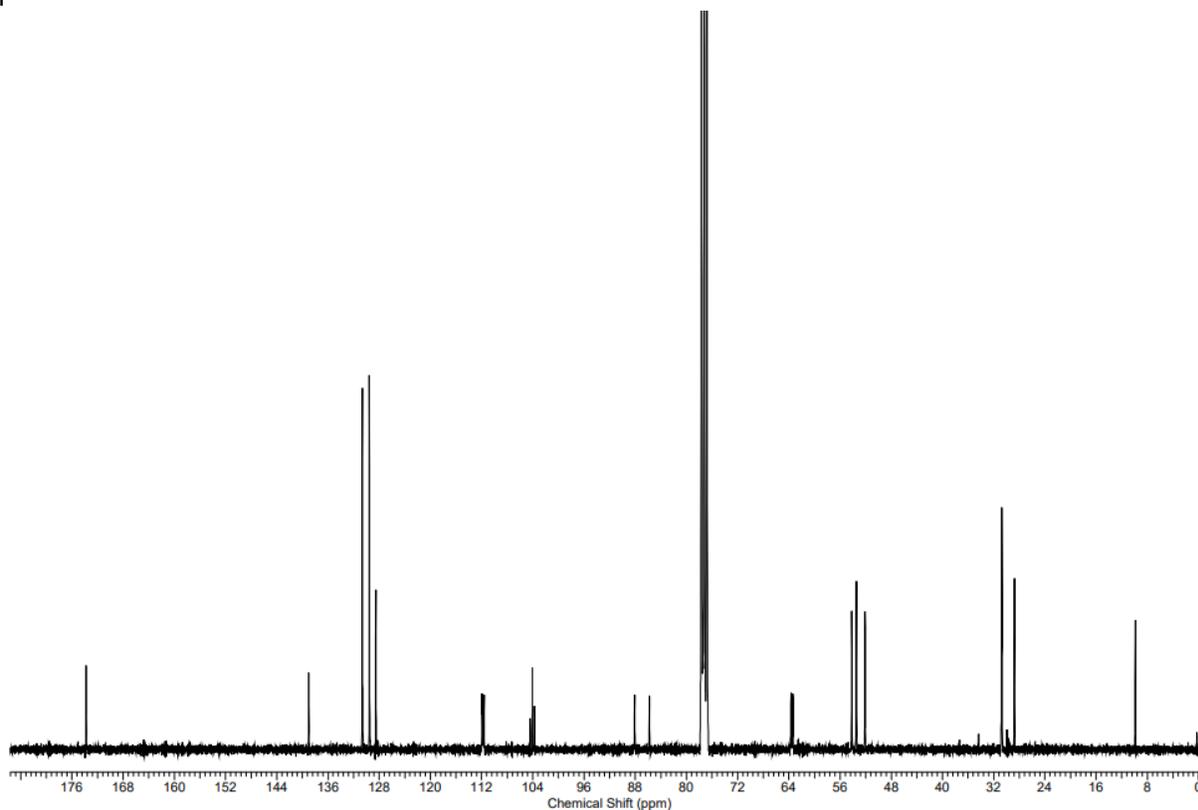
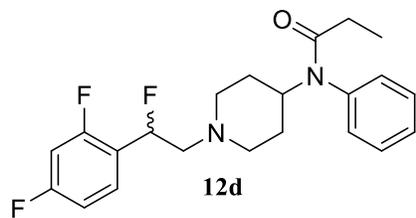
1: Wavelength 254 nm, Band Width 4 nm  
mAU



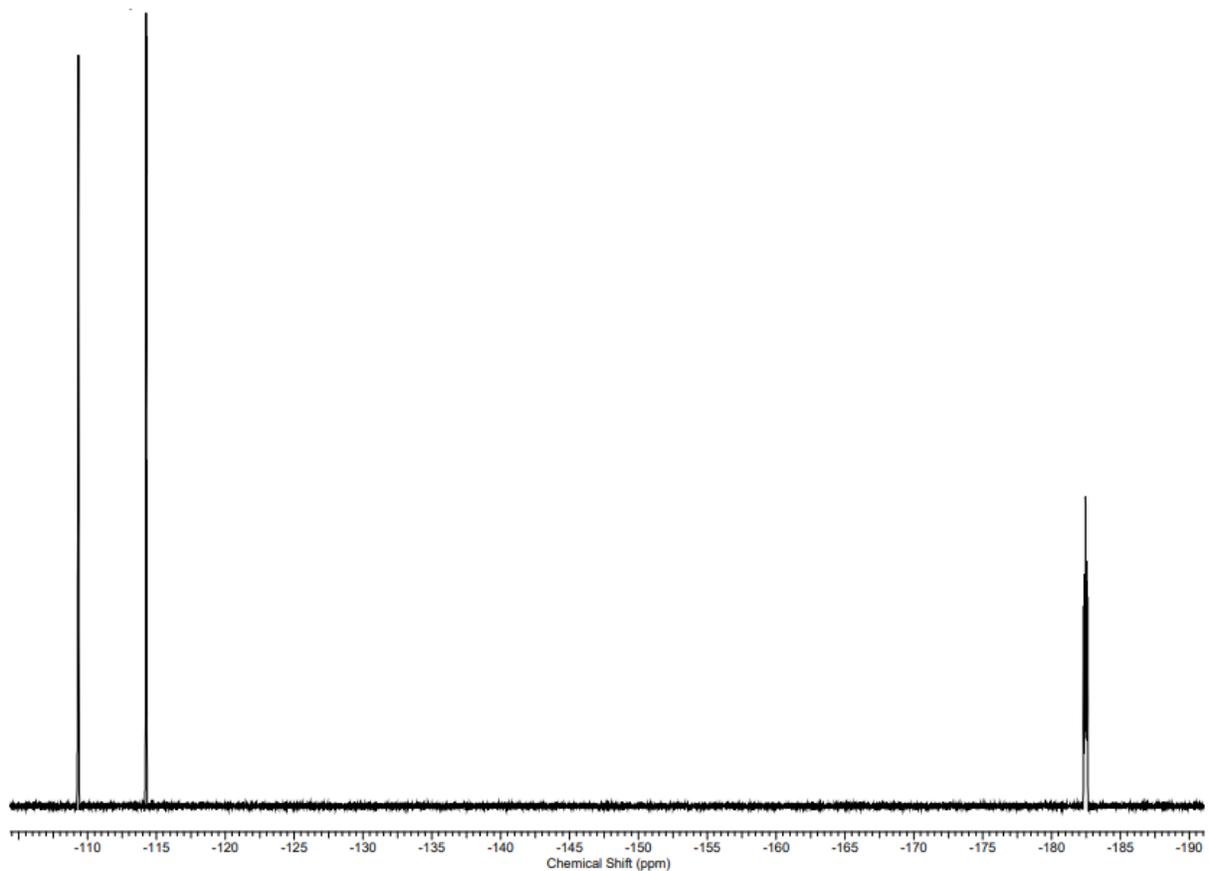
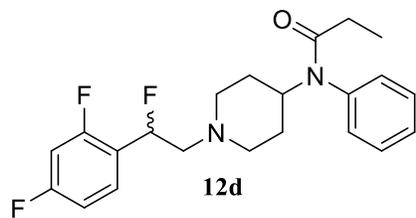
LC/MS (+ mode) for compound **12d**



$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) of compound **12d**



$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) of compound **12d**



$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ) of compound **12d**