

# **Supporting Information**

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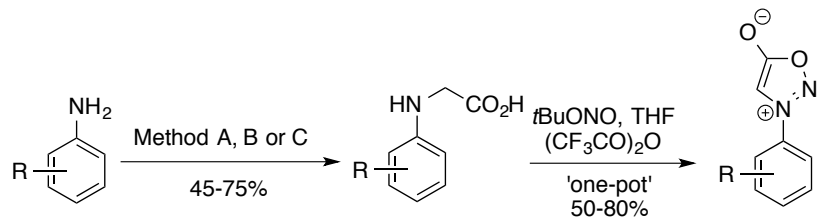
## 1. Materials and Methods

### *Chemistry-General procedures*

All chemicals and reagents were purchased from commercial sources and used without further purification. DBCO-amine (**DIBAC**) and DBCO-NHS (**22**) were purchased from Conju-Probe, San Diego, CA. All deuterated solvents were purchased from Cambridge Isotope Laboratories. Unless otherwise noted, reactions were carried out in oven-dried glassware under an atmosphere of argon using commercially available anhydrous solvents. Solvents used for extractions and chromatography were not anhydrous. Reactions and chromatography fractions were analyzed by thin-layer chromatography (TLC) using Merck precoated silica gel 60 F<sub>254</sub> glass plates (250 μm) and visualized by ultraviolet irradiation, potassium permanganate stain or ninhydrin stain. Flash column chromatography was performed using E. Merck silica gel 60 (230–400 mesh) with compressed air. NMR spectra were recorded on a Bruker ARX 400 (400 MHz for <sup>1</sup>H; 100 MHz for <sup>13</sup>C) or Bruker ARX 500 (500 MHz for <sup>1</sup>H; 125 MHz for <sup>13</sup>C) spectrometers. Chemical shifts are reported in parts per million (ppm, δ) using the residual solvent peak as the reference. The coupling constants, *J*, are reported in Hertz (Hz), and the multiplicity identified as the following: br (broad), s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). High-resolution electrospray mass spectrometry data was collected with a Waters LCT Premier XE time-of-flight instrument controlled by MassLynx 4.1 software. For some samples, high-resolution mass spectra were obtained on Thermo Scientific™ Exactive Mass Spectrometer with DART ID-CUBE. Samples were dissolved in methanol and infused using direct loop injection from a Waters Acquity UPLC into the Multi-Mode Ionization source. Fluorine-19 reference standards were purchased from Alfa Aesar, Fisher Scientific, Oakwood Chemical, Combi-Blocks and used as received, unless otherwise stated in Section 2.2. [D-Ala<sup>2</sup>, D-Leu<sup>5</sup>]-Enkephalin (cas [60284-47-1]) was purchased from Bachem Americas (product H-1276) and used as received.

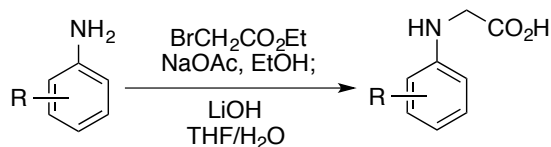
## 2. Experimental Data

### 2.1 Synthesis and characterization of N-arylsydnonones



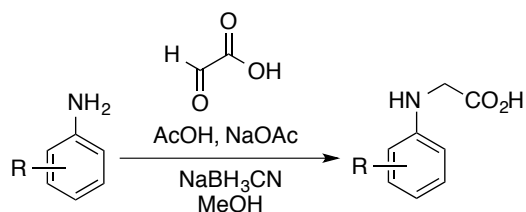
Sydnone derivatives were synthesized in two steps from commercially available anilines. First, *N*-substituted glycine derivatives were prepared following one of three protocols described herein (Method A, B or C). Second, *N*-nitrosation followed by cyclodehydration of the resulting nitrosamine in 'one-pot' furnished the mesoionic *N*-arylsydnonones in good yields.

#### *Synthesis of N-substituted glycine derivatives:*

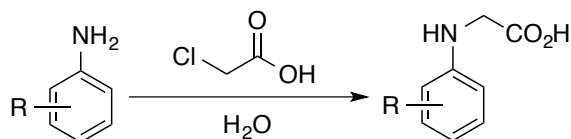


**Method A:** To a suspension of aniline (10 mmol) and sodium acetate (12 mmol) in ethanol (20 mL) was added ethyl bromoacetate (12 mmol). The mixture was stirred at reflux for 7 h and left overnight at room temperature. The reaction mixture was poured into crushed ice and the precipitate was filtered and dried. To the crude ester dissolved in water/tetrahydrofuran (1:1) (25 mL) was added lithium hydroxide (1.1 mmol). The mixture was stirred at 0 °C for 1 h and allowed to warm to room temperature for 4 h. The reaction mixture was acidified to pH 2 by dropwise addition of HCl (2.0 M solution). The resulting precipitate was filtered, washed with water, and purified by recrystallization from a mixture ethanol/water to afford *N*-arylglycine.

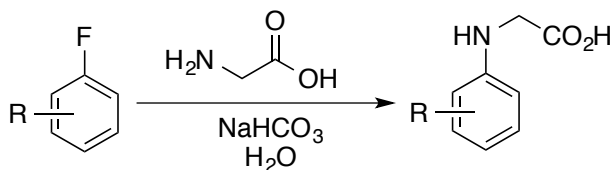




**Method B:** To a solution of aniline (5 mmol) in methanol (25 mL) at 0 °C were added sodium acetate (10 mmol), glacial acetic acid (20 mmol), glyoxylic acid monohydrate (7.5 mmol) and sodium cyanoborohydride (5.05 mmol). The solution was warmed slowly to ambient temperature over 3 h. The mixture was filtered through a plug of SiO<sub>2</sub> and washed with a solution of acetic acid (1% in ethyl acetate). The organic layer was washed with brine and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in *vacuo*. The glycine derivatives were purified by recrystallization from a mixture ethanol/water or by column chromatography on silica gel eluting with ethyl acetate/hexane 4:6 (v/v).



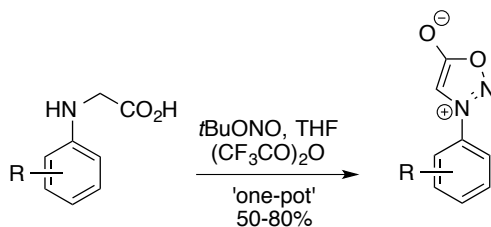
**Method C:** To a stirred solution of aniline (15 mmol) in water (30 mL) was added chloroacetic acid (2.84 g, 30 mmol) and the reaction mixture was stirred at reflux overnight. The resulting precipitate was filtered, dissolved in NaOH (6.0 M solution) and the aqueous solution was washed with ethyl acetate. The combined aqueous extracts were acidified at 0 °C to pH 2 with HCl (4.0 M solution). The resulting precipitate was filtered, washed with water and dried to afford the desired glycine derivative. The crude product was used without further purification.



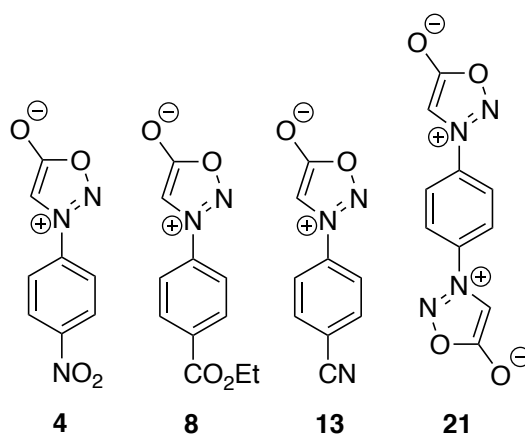
**Method D:** To a solution of aryl fluoride (1 mmol) in water (15 mL) was added glycine (1.1 mmol) and sodium bicarbonate (1.5 mmol) and reaction mixture was stirred at reflux

for 8 h. Reaction mixture was acidified to pH 2 with HCl (4.0 M solution). Solid obtained was filtered and washed with ice-cold water to obtain *N*-aryl glycine.

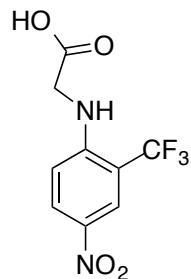
**Preparation of *N*-aryl sydnones:**



To a mixture of *N*-substituted glycine derivative (1 mmol) in anhydrous THF (10 mL) was added *t*Butyl or isoamyl nitrite (1.1 mmol). The mixture was stirred at room temperature for 30 min and trifluoroacetic anhydride (1.15 mmol) was added at 0 °C. The reaction was allowed to warm to room temperature and stirred for 1 h. Ethyl acetate was added and the reaction was quenched with a saturated solution of sodium bicarbonate. The aqueous layer was extracted with ethyl acetate and the organic layers were combined, dried over MgSO<sub>4</sub> and concentrated *in vacuo* to obtain *N*-aryl sydnones. The crude products were purified by recrystallization from ethanol: hexane (8:2) or from methanol: hexanes (6:4).

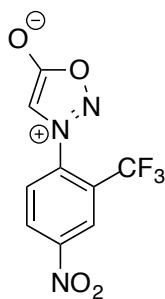


Sydnones **4**, **8**, **13**, and **21** were prepared following literature procedure.<sup>1,2</sup> The <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic data for these compounds were consistent with that previously reported.



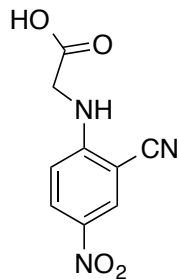
**Gly-5**

**(4-nitro-2-(trifluoromethyl)phenyl)glycine (Gly-5):** Synthesized via Method D. Yield = 62 %.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  12.94 (s, 1H), 8.20 (dd,  $J$  = 7.2, 2.5 Hz, 2H), 6.95 (t,  $J$  = 5.7 Hz, 1H), 6.84 – 6.77 (m, 1H), 4.09 (d,  $J$  = 5.9 Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  171.22, 150.44, 136.07, 129.55, 125.31, 123.50, 112.98, 111.23, 44.85; HRMS (ESI)  $m/z$  calcd for  $\text{C}_9\text{H}_7\text{F}_3\text{N}_2\text{O}_4$  [M+H] 263.028, found 263.030.



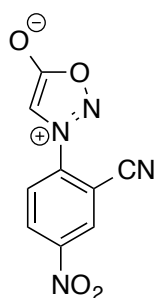
**5**

**3-(4-nitro-2-(trifluoromethyl)phenyl)-1,2,3-oxadiazol-3-ium-5-olate (5):** Yield = 90%.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.87 (dd,  $J$  = 8.7, 2.4 Hz, 1H), 8.79 (d,  $J$  = 2.4 Hz, 1H), 8.44 (d,  $J$  = 8.7 Hz, 1H), 7.79 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  168.15, 150.27, 135.66, 131.53, 130.04, 126.46, 124.04, 123.10, 100.81; HRMS (ESI)  $m/z$  calcd for  $\text{C}_9\text{H}_4\text{F}_3\text{N}_3\text{O}_4$  [M+H] 276.020, found 276.020.



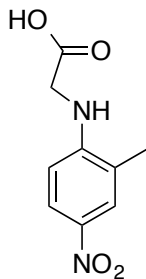
**Gly-6**

**(2-cyano-4-nitrophenyl)glycine (Gly-6):** Synthesized via Method D. Yield = 60 %.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.46 (d,  $J$  = 2.7 Hz, 1H), 8.21 (dd,  $J$  = 9.5, 2.6 Hz, 1H), 7.55 (t,  $J$  = 6.0 Hz, 1H), 6.82 (d,  $J$  = 9.5 Hz, 1H), 4.12 (d,  $J$  = 6.1 Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  171.08, 154.80, 136.72, 130.87, 130.09, 116.36, 112.11, 94.56, 44.66; HRMS (ESI)  $m/z$  calcd for  $\text{C}_9\text{H}_7\text{N}_3\text{O}_4$  [M+H] 222.0510, found 222.0503.



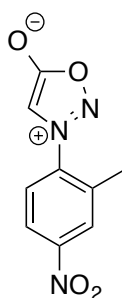
**6**

**3-(2-cyano-4-nitrophenyl)-1,2,3-oxadiazol-3-ium-5-olate (6):** Yield = 45%.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  9.16 (d,  $J$  = 2.5 Hz, 1H), 8.84 (dd,  $J$  = 8.9, 2.5 Hz, 1H), 8.37 (d,  $J$  = 8.9 Hz, 1H), 7.91 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  168.25, 149.89, 139.46, 130.82, 130.45, 126.69, 113.49, 109.81, 99.21; HRMS (ESI)  $m/z$  calcd for  $\text{C}_9\text{H}_4\text{N}_4\text{O}_4$  [M+H] 233.0301, found 233.0298.



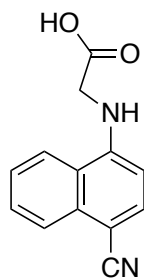
**Gly-7**

**2-((2-methyl-4-nitrophenyl)amino)acetic acid (Gly-7):** Synthesized via Method C (Yield = 13%).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.91-7.86 (m, 2H), 6.4 (d,  $J$  = 8.8 Hz, 1H), 6.24 (t,  $J$  = 4.8 Hz, 1H), 3.57 (d,  $J$  = 4.8 Hz, 2H), 2.13 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  172.1, 152.3, 135.8, 125.8, 125.0, 121.4, 108.6, 47.1, 17.4; HRMS (APCI)  $m/z$  calcd for  $\text{C}_9\text{H}_{10}\text{N}_2\text{O}_4$  [M+H] 211.0706, found 211.0713.



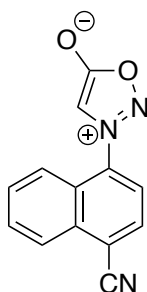
**7**

**3-(2-methyl-4-nitrophenyl)-1,2,3-oxadiazol-3-ium-5-olate (7):** Yield = 45%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.34 (d,  $J$  = 2.8 Hz, 1H), 8.3 (dd,  $J$  = 8.4, 2.8 Hz, 1H), 7.67 (d,  $J$  = 8.8 Hz, 1H), 6.54 (s, 1H), 2.49 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  168.2, 149.7, 136, 127.2, 126.8, 122.7, 96.9, 17.7; HRMS (APCI)  $m/z$  calcd for  $\text{C}_9\text{H}_8\text{N}_3\text{O}_4$  [M+H] 222.0509, found 222.0505.



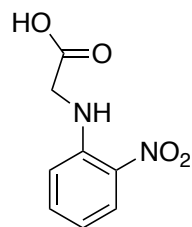
**Gly-9**

**2-((4-cyanonaphthalen-1-yl)amino)acetic acid (Gly-9):** Synthesized via Method B. (Yield = 22%)  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.14 (d,  $J$  = 8.4 Hz, 1H), 7.89 (dd,  $J$  = 8.4, 1.2 Hz, 1H), 7.77 (d,  $J$  = 8 Hz, 1H), 7.65 (ddd,  $J$  = 8.4, 6.8, 0.8 Hz, 1H), 7.52 (ddd,  $J$  = 10, 6.8, 1.6 Hz, 1H), 7.21 (t,  $J$  = 4.8 Hz, 1H), 6.36 (d,  $J$  = 8.4 Hz, 1H), 3.64 (d,  $J$  = 4.8 Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  148.4, 135.6, 133.5, 129, 125.9, 125, 122.4, 122.0, 120.1, 103, 93.2, 47.2; HRMS (APCI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_2$  [M+H] 227.0815, found 227.0807.



**9**

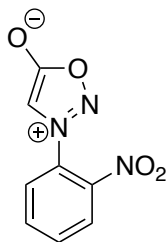
**3-(4-cyanonaphthalen-1-yl)-1,2,3-oxadiazol-3-ium-5-olate (9):** Yield = 39%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.45 (dt,  $J$  = 8.8, 0.8 Hz, 1H), 8.1 (d,  $J$  = 7.6 Hz, 1H), 7.95-7.83 (m, 3H), 7.81 (d,  $J$  = 7.6 Hz, 1H), 6.73 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  133.4, 131.3, 130.8, 130.7, 126.8, 126.2, 122.7, 122.0, 115.3; HRMS (APCI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_8\text{N}_3\text{O}_2$  [M+H] 238.0611, found 238.060.



**Gly-10**

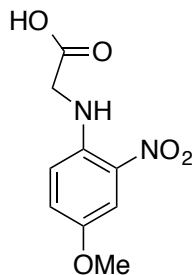
**2-((2-nitrophenyl)amino)acetic acid (Gly-10):** Synthesized via Method C (Yield = 8%).

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.32 (t,  $J$  = 5.2 Hz, 1H), 8.05 (dd,  $J$  = 8.4, 1.6 Hz, 1H), 7.5 (ddd,  $J$  = 8.8, 7.2, 1.6 Hz, 1H), 6.87 (dd,  $J$  = 8.8, 1.2 Hz, 1H), 6.69 (ddd,  $J$  = 8.4, 6.8, 1.2 Hz, 1H), 4.13 (d,  $J$  = 5.2 Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  171.5, 144.9, 137, 131.8, 126.6, 116.2, 115.4, 44.6; HRMS (APCI)  $m/z$  calcd for  $\text{C}_8\text{H}_8\text{N}_2\text{O}_4$  [M+H] 197.0557, found 197.0547.



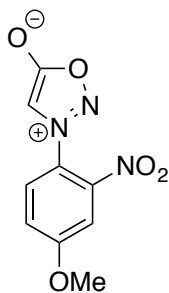
**10**

**3-(2-nitrophenyl)-1,2,3-oxadiazol-3-ium-5-olate (10)** Yield = 29%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.30-8.28 (m, 1H), 7.94-7.92 (m, 2H), 7.73-7.71 (m, 1H), 6.65 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  168.3, 134.7, 133.7, 127.8, 126.5, 97.6; HRMS (ESI)  $m/z$  calcd for  $\text{C}_8\text{H}_6\text{N}_3\text{O}_4$  [M+H] 208.0353, found 208.0344.



**Gly-11**

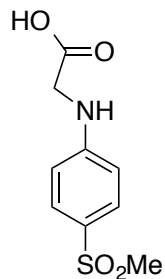
**(4-methoxy-2-nitrophenyl)glycine (Gly-11):** Synthesized via method A. Yield = 30 %.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  12.97 (s, 1H), 8.20 (d,  $J$  = 5.1 Hz, 1H), 7.46 (d,  $J$  = 3.0 Hz, 1H), 7.22 (dd,  $J$  = 9.3, 3.0 Hz, 1H), 6.86 (d,  $J$  = 9.4 Hz, 1H), 4.09 (d,  $J$  = 5.4 Hz, 2H), 3.70 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  171.69, 149.77, 140.79, 130.80, 127.49, 117.06, 107.02, 56.09, 44.84. HRMS (APCI)  $m/z$  calcd for  $\text{C}_9\text{H}_{10}\text{N}_3\text{O}_5$  [M-H] 225.0511, found 225.0511.



**11**

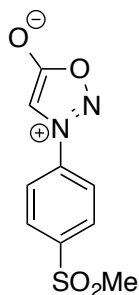
**3-(4-methoxy-2-nitrophenyl)-1,2,3-oxadiazol-3-ium-5-olate (11):** Yield = 35%.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.02 (d,  $J$  = 8.9 Hz, 1H), 7.89 (d,  $J$  = 2.8 Hz, 1H), 7.66 (s, 1H), 7.59 (dd,  $J$  = 8.9, 2.8 Hz, 1H), 3.95 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  168.58, 162.71, 144.57, 130.06, 120.43, 119.87, 112.24, 99.46, 57.40; HRMS (ESI)  $m/z$  calcd for  $\text{C}_9\text{H}_7\text{N}_3\text{O}_5$  [M+H] 238.0446, found 238.0447.





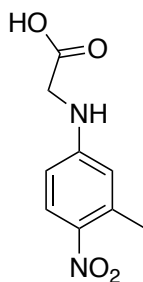
**Gly-12**

**2-((4-(methylsulfonyl)phenyl)amino)acetic acid (Gly-12):** Synthesized via Method C (Yield = 59%).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  12.65 (s, 1H), 7.53 (d,  $J$  = 9.2 Hz, 2H), 6.85 (t,  $J$  = 6 Hz, 1H), 6.64 (d,  $J$  = 8.8 Hz, 2H), 3.87 (d,  $J$  = 5.6 Hz, 2H), 3.0 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  172.3, 152.8, 129.1, 127.1, 111.8, 44.9, 44.4; HRMS (APCI)  $m/z$  calcd for  $\text{C}_9\text{H}_{11}\text{NO}_4\text{S}$  [M+H] 230.0482, found 230.0475.



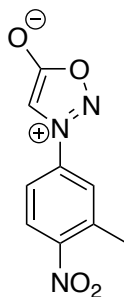
**12**

**3-(4-(methylsulfonyl)phenyl)-1,2,3-oxadiazol-3-ium-5-olate (12):** Yield = 56%  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.23-8.17 (m, 4H), 7.88 (s, 1H), 3.31 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  168.8, 144.4, 138.3, 129.5, 123.3, 96.1, 43.6; HRMS (APCI)  $m/z$  calcd for  $\text{C}_9\text{H}_9\text{N}_2\text{O}_4\text{S}$  [M+H] 241.0277, found 241.0266.



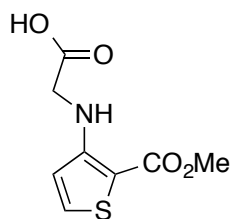
**Gly-14**

**(3-Methyl-4-nitro-)phenyl)glycine (Gly-14):** Synthesized via Method B. Yield = 68%.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  12.71 (s, 1H), 7.94 (d,  $J$  = 9.1 Hz, 1H), 7.20 (s, 1H), 6.54 (dd,  $J$  = 9.1, 2.5 Hz, 1H), 6.50 (d,  $J$  = 2.0 Hz, 1H), 3.96 (d,  $J$  = 6.1 Hz, 2H), 2.50 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  171.97, 153.48, 137.41, 137.31, 128.24, 114.41, 110.37, 44.41, 22.47; HRMS (APCI)  $m/z$  calcd for  $\text{C}_9\text{H}_{10}\text{N}_2\text{O}_4$  [M-H] 209.0562, found 209.0559.



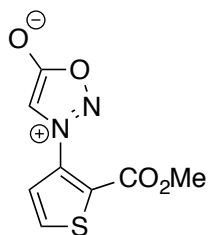
**14**

**3-(3-methyl-4-nitrophenyl)-1,2,3-oxadiazol-3-ium-5-olate (14):** Yield = 50%.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.25 (d,  $J$  = 8.8 Hz, 1H), 8.14 (d,  $J$  = 2.3 Hz, 1H), 8.03 – 7.98 (m, 1H), 7.87 (s, 1H), 2.58 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  168.76, 151.12, 137.24, 135.65, 126.79, 126.11, 120.97, 95.99, 19.69; HRMS (ESI)  $m/z$  calcd for  $\text{C}_9\text{H}_7\text{N}_3\text{O}_4$  [M+H] 222.050, found 222.0482.



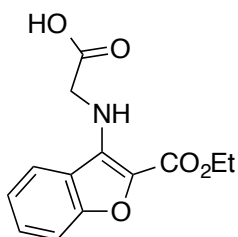
**Gly-15**

**2-((2-(methoxycarbonyl)thiophen-3-yl)amino)acetic acid (Gly-15):** Synthesis via Method B (Yield = 32%).  $^1\text{H}$  and  $^{13}\text{C}$  NMR were identical to reported spectroscopic data.<sup>1a</sup>



**15**

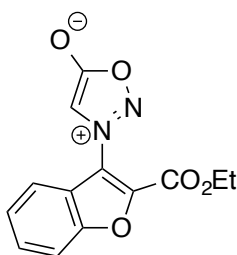
**3-(2-(methoxycarbonyl)thiophen-3-yl)-1,2,3-oxadiazol-3-ium-5-olate (15):** Yield = 77%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.74 (d,  $J = 5.6$  Hz, 1H), 7.37 (d,  $J = 5.6$  Hz, 1H), 6.78 (s, 1H), 3.89 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  168.6, 159.2, 131.9, 128.4, 125.7, 98.2, 53.2; HRMS (APCI)  $m/z$  calcd for  $\text{C}_8\text{H}_7\text{N}_2\text{O}_4\text{S}$  [M+H] 227.0121, found 227.0117.



**Gly-16**

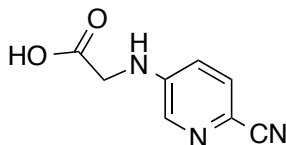
**2-((2-(ethoxycarbonyl)benzofuran-3-yl)amino)acetic acid (Gly-16):** Synthesized via Method B. Yield = 19%  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  7.93 (d,  $J = 8$  Hz, 1H), 7.48-

7.42 (m, 2H), 7.21-7.17 (m, 1H), 6.79-6.77 (m, 1H), 4.24 (q,  $J = 7.2$  Hz, 2H), 1.28 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  161.0, 154.4, 144.0, 141.2, 129.3, 126.7, 124, 122.5, 121.8, 112.7, 59.7, 53.5, 49.3; HRMS (APCI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{13}\text{NO}_5$  [M+H] 264.0866, found 264.086.



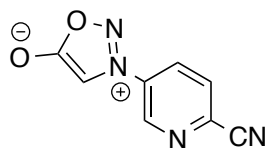
**16**

**3-(2-(ethoxycarbonyl)benzofuran-3-yl)-1,2,3-oxadiazol-3-ium-5-olate (16):** Yield = 31%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.79 (dt,  $J = 8, 0.8$  Hz, 1H), 7.72 (dt,  $J = 8.4, 0.8$  Hz, 1H), 7.68-7.64 (m, 1H), 7.53-7.49 (m, 1H), 6.05 (s, 1H), 4.48 (q,  $J = 7.2$  Hz, 2H), 1.41 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  168.5, 157.1, 153.4, 138.7, 130.1, 126.2, 121.3, 120.9, 115, 113.1, 98.2, 63.1, 14.1; HRMS (APCI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}_5$  [M+H] 275.0662, found 275.0652.



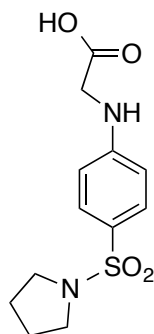
**Gly-17**

**2-((6-cyanopyridin-3-yl)amino)acetic acid (Gly-17):** Synthesized via Method B (Yield = 17%).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.04 (d,  $J = 2.8$  Hz, 1H), 7.54 (d,  $J = 8.8$  Hz, 1H), 6.86-6.83 (m, 2H), 3.56 (d,  $J = 4.8$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  171.8, 147.5, 137.7, 130, 119.7, 117.4, 116.4, 46.1; HRMS (APCI)  $m/z$  calcd for  $\text{C}_8\text{H}_7\text{N}_3\text{O}_2$  [M+H] 178.0611, found 178.0605.



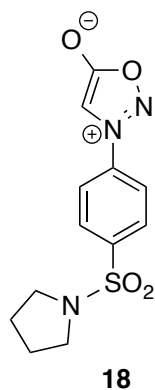
17

**3-(6-cyanopyridin-3-yl)-1,2,3-oxadiazol-3-ium-5-olate (17):** Yield = 18%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.16 (dd, *J* = 2.8, 0.8 Hz, 1H), 8.3 (dd, *J* = 8.4, 2.4 Hz, 1H), 8.02 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.91 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 168, 143.5, 137.2, 130.2, 129.4, 115.5, 93.9; HRMS (APCI) *m/z* calcd for C<sub>8</sub>H<sub>5</sub>N<sub>4</sub>O<sub>2</sub> [M+H] 189.0407, found 189.040.

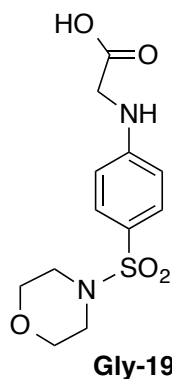


Gly-18

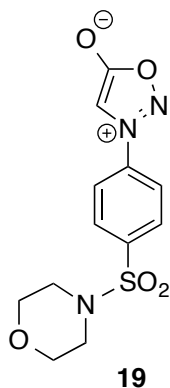
**2-((4-(pyrrolidin-1-ylsulfonyl)phenyl)amino)acetic acid (Gly-18):** Synthesized via Method B (Yield = 69%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.41 (d, *J* = 8.8 Hz, 2H), 6.61 (d, *J* = 8.8 Hz, 2H), 6.44 (s, 1H), 3.13 (s, 2H), 3.01-2.98 (m, 4H), 1.59-1.56 (m, 4H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 172.9, 152.3, 129.5, 121.3, 111.7, 48.1, 46.4, 25; HRMS (APCI) *m/z* calcd for C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>S [M+H] 285.0904, found 285.0889.



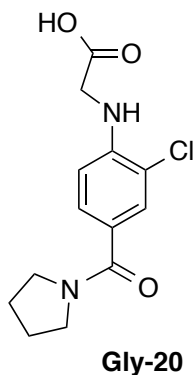
**3-(4-(pyrrolidin-1-ylsulfonyl)phenyl)-1,2,3-oxadiazol-3-ium-5-olate (18):** Yield = 45%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.09 (d,  $J = 8.8$  Hz, 2H), 7.9 (d,  $J = 8.8$  Hz, 2H), 6.83 (s, 1H), 3.3 (t,  $J = 6.8$  Hz, 4H), 1.83 (t,  $J = 6.8$  Hz, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  168.5, 141.6, 137.3, 129.4, 122.1, 93.8, 48.1, 25.4; HRMS (APCI)  $m/z$  calcd for  $\text{C}_{12}\text{H}_{14}\text{N}_3\text{O}_4\text{S}$  [ $\text{M}+\text{H}$ ] 296.070, found 296.0685.



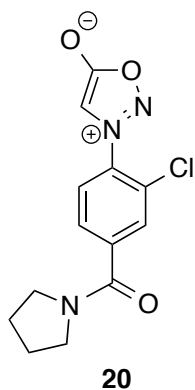
**2-((4-(morpholinosulfonyl)phenyl)amino)acetic acid (Gly-19):** Synthesized via Method B. (Yield = 41%)  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  7.36 (d,  $J = 8.8$  Hz, 2H), 6.67-6.64 (m, 3H), 3.57 (t,  $J = 4.8$  Hz, 4H), 2.73 (t,  $J = 4.8$  Hz, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-d}_6$ )  $\delta$  172.2, 152.7, 130, 119.9, 113.2, 65.7, 46.4, 44.8; HRMS (APCI)  $m/z$  calcd for  $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_5\text{S}$  [ $\text{M}+\text{H}$ ] 301.0853, found 301.084.



**3-(4-(morpholinylsulfonyl)phenyl)-1,2,3-oxadiazol-3-ium-5-olate (19):** Yield = 28%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.03 (d, *J* = 8.8 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H), 6.81 (s, 1H), 3.79-3.76 (m, 4H), 3.09-3.07 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 168.4, 149.4, 139.9, 129.9, 122.2, 93.7, 66.0, 45.9; HRMS (APCI) *m/z* calcd for C<sub>12</sub>H<sub>14</sub>N<sub>3</sub>O<sub>5</sub>S [M+H] 312.0649, found 312.0632.

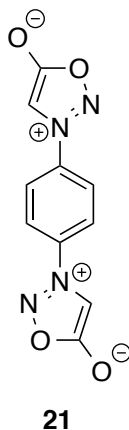


**2-((2-chloro-4-(pyrrolidine-1-carbonyl)phenyl)amino)acetic acid (Gly-20):** Synthesized via Method B. Yield = 34%. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 7.42 (d, *J* = 2 Hz, 1H), 7.32 (dd, *J* = 8.4, 2 Hz, 1H), 6.49 (d, *J* = 8.4 Hz, 1H), 5.82 (s, 1H), 3.58 (s, 2H), 3.4 (s, 4H), 1.77 (s, 4H); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>) δ 167.5, 145.3, 129, 128.4, 124.6, 117.04, 115, 110.5, 49.7, 49, 46.6; HRMS (APCI) *m/z* calcd for C<sub>13</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>3</sub> [M+H] 283.0844, found 283.0834.



**3-(2-chloro-4-(pyrrolidine-1-carbonyl)phenyl)-1,2,3-oxadiazol-3-ium-5-olate (20):**

Yield = 58%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.81-7.8 (m, 1H), 7.65-7.64 (m, 2H), 6.65 (s, 1H), 3.66 (t, *J* = 6.8 Hz, 2H), 3.43 (t, *J* = 6.4 Hz, 2H), 2.05-1.92 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 168.4, 165.8, 142.4, 133.1, 130.2, 129.5, 127.2, 126.9, 97.8, 49.6, 46.6, 26.4, 24.3; HRMS (APCI) *m/z* calcd for C<sub>13</sub>H<sub>13</sub>ClN<sub>3</sub>O<sub>3</sub> [M+H] 294.0625, found 294.0640.

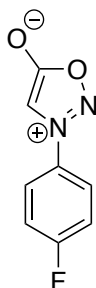


**3-(4-(5-oxido-1,2,3)4-oxadiazol-3-yl)phenyl)-1,2,3-oxadiazol-3-ium-5-olate (21):**

Synthesized following literature protocol.<sup>1c</sup> Yield = 72%. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 8.28 (s, 2H), 7.93 (s, 1H); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>) δ 168.83, 137.23, 124.03, 96.05; HRMS (ESI) *m/z* calcd for C<sub>10</sub>H<sub>6</sub>N<sub>4</sub>O<sub>4</sub> [M+H] 246.0389, found 246.039.

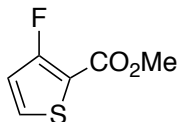


## 2.2 Synthesis and characterization of [<sup>19</sup>F]fluorinated reference standards



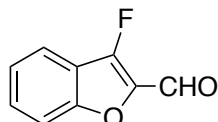
**Ref-4b**

Reference standard **Ref-4b** was prepared following literature procedure.<sup>1d</sup> The <sup>1</sup>H, <sup>13</sup>C and <sup>19</sup>F NMR spectroscopic data for this compound matched that previously reported.



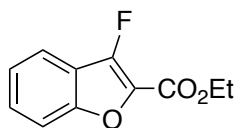
**Ref-15a**

**Methyl 3-fluorothiophene-2-carboxylate (Ref-15a)** was prepared from commercially available 3-fluoro-thiophene-2-carboxylic acid, following literature protocol.<sup>3</sup> 3-fluoro thiophene-2-carboxylic acid (1 mmol), MeI (1.2 mmol) and sodium carbonate (3.5 mmol) in DMF (5 ml) were stirred at room temperature. After 24 h, the residue was diluted with sat. NH<sub>4</sub>Cl solution and the product was extracted with ethyl acetate. The organic layer was washed with water, concentrated and purified by flash column silica gel chromatography to afford **Ref-15a** in 45% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.41 (dd, *J* = 5.6, 3.6 Hz, 2H), 6.85 (d, *J* = 5.6 Hz, 1H), 3.88 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 160.9, 160.1 (d, *J* = 274.6 Hz), 130.1 (d, *J* = 10.1 Hz), 118.5 (d, *J* = 25 Hz), 115.0, 52.1; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -114.9; HRMS (APCI) *m/z* calcd for C<sub>6</sub>H<sub>6</sub>FO<sub>2</sub>S [M+H] 161.0067, found 161.0065.



**24**

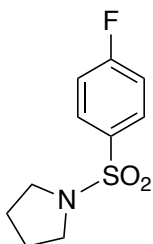
**3-Fluorobenzofuran-2-carbaldehyde (24):** n-BuLi (1.6 M in hexane, 1.1 mmol) was added dropwise into a solution of commercially available 3-fluorobenzofuran (1 mmol) in THF (3 ml) at -78 °C and stirred for 30 min. Ethyl formate (10 mmol) was added to the mixture and the mixture was stirred at -78 °C. After 2 h, the reaction was quenched with sat. NH<sub>4</sub>Cl solution and extracted with ethyl acetate. The organic layer was dried by sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash column silica gel chromatography to obtain the desired aldehyde in 70% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.0 (s, 1H), 7.8 (d, *J* = 8 Hz, 1H), 7.62-7.54 (m, 2H), 7.4 (ddd, *J* = 8, 6.8, 1.6 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 176.1, 153.8 (d, *J* = 9.2 Hz), 136.6 (d, *J* = 17.4 Hz), 130.8 (d, *J* = 1.4 Hz), 124.6, 120.3 (d, *J* = 3 Hz), 117.8 (d, *J* = 16.8 Hz), 115.0, 113.4 (d, *J* = 21.9 Hz); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -156.5; HRMS (APCI) *m/z* calcd for C<sub>9</sub>H<sub>6</sub>FO<sub>2</sub> [M+H] 165.0346, found 165.0340.



**Ref-16a**

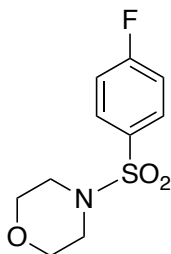
**Ethyl 3-fluorobenzofuran-2-carboxylate (Ref-16a)** was prepared from 3-fluorobenzofuran-2-carbaldehyde **24** following literature protocol.<sup>4</sup> To 3-fluorobenzofuran-2-carbaldehyde (0.5 mmol) in MeOH at 0 °C were added iodine (0.65 mmol) in methanol and KOH (1.5 mmol) successively. After stirring for 2 h at 0 °C, sat. NaHSO<sub>3</sub> was added and the methanol was evaporated under reduced pressure. Water was added and the solution was extracted with DCM. The organic layers were combined, dried with sodium sulfate and concentrated *in vacuo*. The crude mixture was purified by flash column silica gel chromatography to afford **Ref-16a** in 40%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.7 (d, *J* = 8 Hz, 1H), 7.55-7.48 (m, 2H), 7.4 (ddd, *J* = 8, 6.4, 1.6 Hz, 1H), 4.47 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 158.6, 152.6 (d, *J* = 39.5 Hz), 151.3 (d, *J* = 242.6 Hz), 129.4 (d, *J* = 18.7 Hz), 129, 124.1, 119.6 (d, *J* =

3 Hz), 118.6 (d,  $J = 18$  Hz), 113.0 (d,  $J = 1.7$  Hz), 61.5, 14.3;  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -153.1; HRMS (APCI)  $m/z$  calcd for  $\text{C}_{11}\text{H}_{10}\text{FO}_3$  [M+H] 209.0608, found 209.0602.



**Ref-18a**

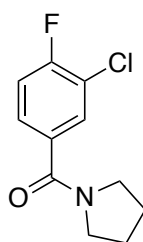
**1-((4-Fluorophenyl)sulfonyl)pyrrolidine (Ref-18a):** To a solution of pyrrolidine (2.2 mmol) and TEA (2.2 mmol) in THF at 0 °C was added dropwise 4-fluorobenzenesulfonyl chloride (2 mmol). The reaction mixture was warmed to room temperature and stirred. The reaction was washed with 5% HCl solution, extracted by ethyl acetate, dried by sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash column silica gel chromatography to afford **Ref-18a** in 87% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.87-7.82 (m, 2H), 7.23-7.18 (m, 2H), 3.24 (t,  $J = 6.8$  Hz, 4H), 1.79-1.76 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  165.1 (d,  $J = 252.7$  Hz), 133.2 (d,  $J = 3.3$  Hz), 130.1 (d,  $J = 9.1$  Hz), 116.2 (d,  $J = 22.2$  Hz), 47.9, 25.3;  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -105.6; HRMS (APCI)  $m/z$  calcd for  $\text{C}_{10}\text{H}_{13}\text{FNO}_2\text{S}$  [M+H] 230.0646, found 230.0644.



**Ref-19a**

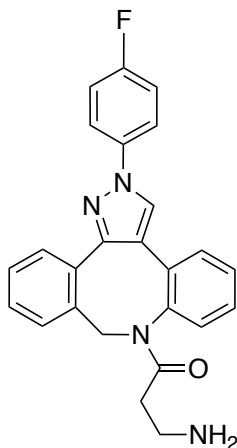
**4-((4-Fluorophenyl)sulfonyl)morpholine (Ref-19a):** To a solution of morpholine (2.2 mmol) and TEA (2.2 mmol) in THF at 0 °C was added dropwise 4-fluorobenzenesulfonyl chloride (2 mmol). The reaction mixture was warmed to room

temperature and stirred. The reaction was washed with 5% HCl solution, extracted by ethyl acetate, dried by sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash column silica gel chromatography to afford **Ref-19a** in 95% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.8-7.75 (m, 2H), 7.26-7.22 (m, 2H), 3.75 (t,  $J = 4.8$  Hz, 4H), 3.01-2.99 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  165.4 (d,  $J = 254$  Hz), 131.3 (d,  $J = 3.2$  Hz), 130.5 (d,  $J = 9.3$  Hz), 116.5 (d,  $J = 22.5$  Hz), 66.1, 46.0;  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -104.5; HRMS (APCI)  $m/z$  calcd for  $\text{C}_{10}\text{H}_{13}\text{FNO}_3\text{S}$  [M+H] 246.0595, found 246.0591.



**Ref-20a**

**(3-Chloro-4-fluorophenyl)(pyrrolidin-1-yl)methanone (Ref-20a)** was prepared from 3-chloro-4-fluorobenzoic acid following literature protocol.<sup>5</sup> A suspension of 3-chloro-4-fluorobenzoic acid (1 mmol) in dichloromethane (4 ml) was treated portionwise over 5 min with 1,1'-carbonyldiimidazole (1 mmol) at room temperature with stirring under argon. This mixture was stirred at room temperature for a further 30 mins. Pyrrolidine (1 mmol) was added to the reaction mixture slowly over 15 minutes and the mixture was stirred at room temperature under argon for 1 h. The reaction mixture was washed twice with sat. sodium bicarbonate solution. The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column silica gel chromatography to afford **Ref-20a** in 33% yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.56 (dd,  $J = 7.2, 2$  Hz, 1H), 7.38 (ddd,  $J = 8.4, 4.8, 2$  Hz, 1H), 7.12 (dd,  $J = 8.4$  Hz, 1H), 3.58 (t,  $J = 6.8$  Hz, 2H), 3.39 (t,  $J = 6.4$  Hz, 2H), 1.96-1.82 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  167.2, 158.8 (d,  $J = 250.6$  Hz), 134.2 (d,  $J = 4.2$  Hz), 130, 127.4 (d,  $J = 7.6$  Hz), 121.1 (d,  $J = 17.9$  Hz), 116.5 (d,  $J = 21.3$  Hz), 49.6, 46.4, 26.4, 24.4;  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -112.8; HRMS (APCI)  $m/z$  calcd for  $\text{C}_{11}\text{H}_{12}\text{ClFNO}$  [M+H] 228.0586, found 228.0576.



**3-amino-1-(2-(4-fluorophenyl)-2,9-dihydro-8H-dibenzo[*b,f*]pyrazolo[4,3-*d*]azocin-8-yl)propan-1-one:** To a solution of DIBAC-amine (3 mg, 10.8  $\mu\text{mol}$ ) in acetonitrile (1 mL) was added sydnone **4b** (1.96 mg, 10.8  $\mu\text{mol}$ ). The reaction mixture was stirred at room temperature for 8 hrs. The crude mixture was purified on semi-preparative HPLC to produce the [ $^{19}\text{F}$ ]-pyrazole in 98% yield. Mixture of two regioisomers were collected together. HRMS (APCI)  $m/z$  calcd for  $\text{C}_{25}\text{H}_{21}\text{FN}_4\text{O}$  [ $\text{M}+\text{H}$ ]413.1778, found 413.1765.

### 3. Computational Details

#### 3.1 Complete computational methods:

Density functional theory calculations were performed with Gaussian 09. Geometries were optimized and their vibrational frequencies obtained at the M06-2X/6-311+G(d,p) level of theory.<sup>6</sup> Unless specified otherwise, the SMD solvation model for DMSO was also included in the calculations.<sup>7</sup> Normal mode frequency analysis was used to confirm that stationary points were either minima (no imaginary frequency) or saddle-points (TS, one (1) imaginary frequency) on the potential energy surface. All saddle-points were further analyzed with the Intrinsic Reaction Coordinate (IRC) tools to verify that they connected the expected minima. ZPE, enthalpy and free energy corrections were also obtained at this level of theory, using a standard state of 1 atmosphere of pressure and 298 K. Structures were illustrated using CYLview.<sup>8</sup> To obtain atomic charges and orbital energies, natural bond order (NBO) analysis (pop=nbo keyword in Gaussian 09) was performed at the HF/6-311+G(d,p) level (gas phase) on the M06-2X-optimized structures.

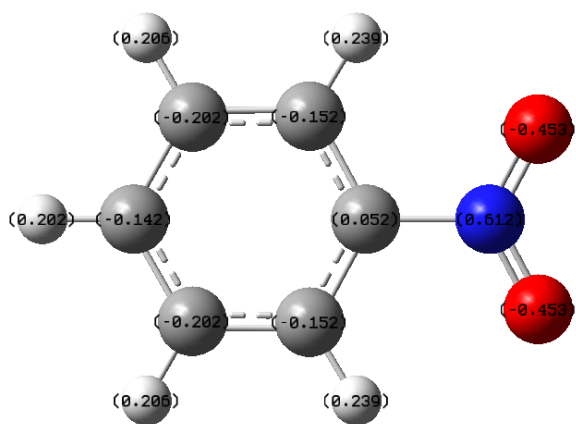
#### 3.2 Full list of authors for reference 19a (Gaussian 09):

Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O.

Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2013.

### 3.3 NBO analysis of reactants

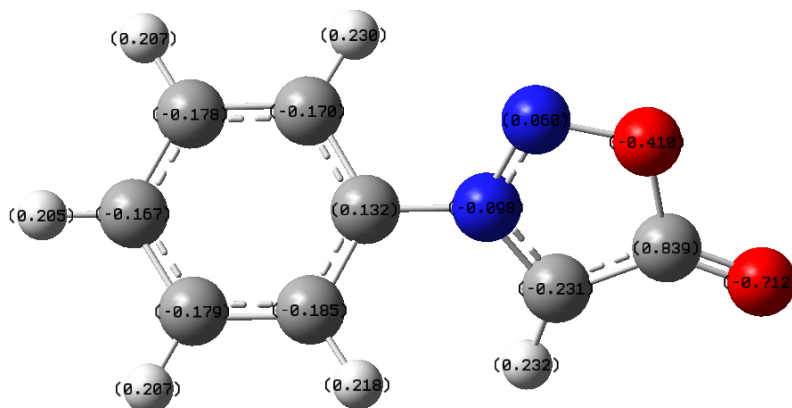
#### 1) Nitrobenzene



Important values:

- C(1): +0.05
- C(4): -0.14
- Phenyl ring (total): +0.29
- Nitro (total): -0.29
- Dipole moment: 5.41 D

#### 2) Phenylsydnone

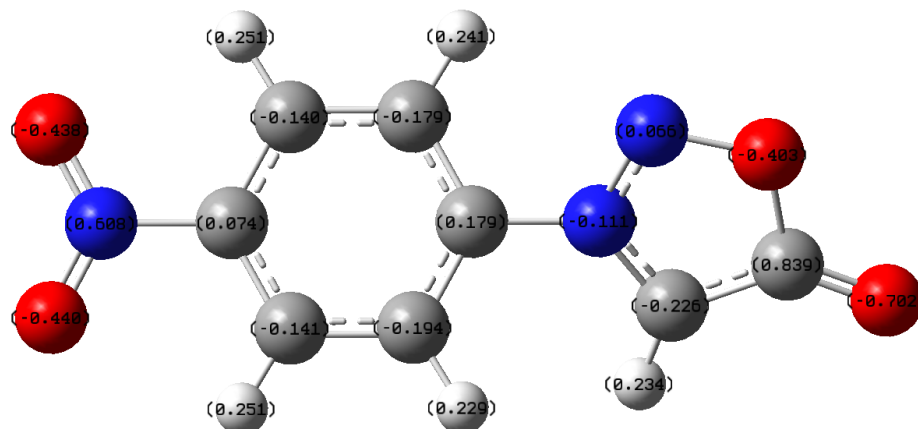


Important values:

- C(1): +0.13
- C(4): -0.17

- Phenyl ring (total): +0.32
- Sydnone (total): -0.32
- Dipole moment: 8.99 D

### 3) *p*-Nitrophenylsydnone (4)



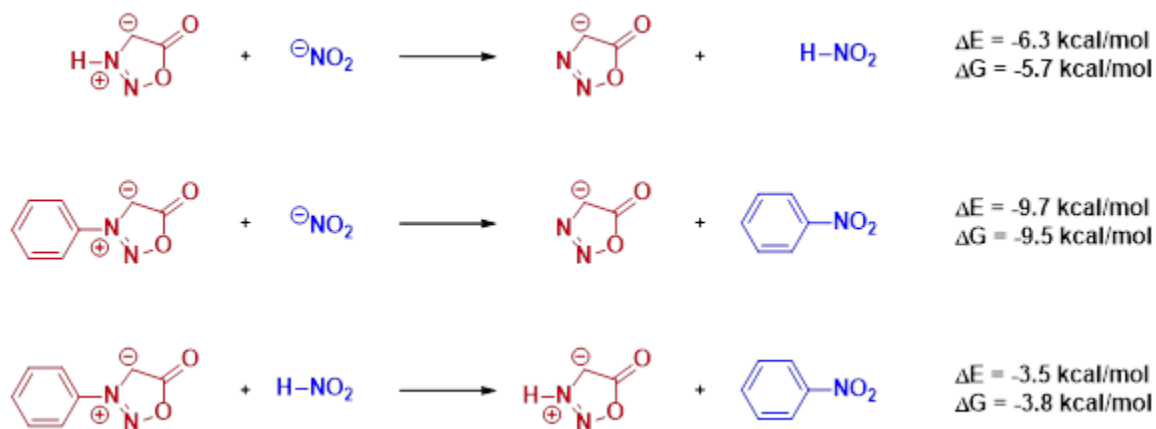
Important values:

- C(1) (sydnone-bearing): +0.18
- C(4) (nitro-bearing): +0.07
- Phenyl ring (total): +0.57
- Nitro (total): -0.27
- Sydnone (total): -0.30
- Dipole moment: 3.40 D

In compound 4, a bigger positive charge is found at C(1) than C(4). This trend of the sydnone being more electronegative than the nitro is also found in parent phenylsydnone vs nitrobenzene.



### 3.4 Isodesmic equations



Each component of these isodesmic equations was calculated at the M06-2X/6-311+G(d,p)/SMD(DMSO) level of theory.

The first equation indicates that in a simple proton transfer reaction, the sydnone anion is more stable than the nitrite anion by 5.7 kcal/mol. Therefore, the sydnone anion is more electronegative and polarizable, is better to stabilize a negative charge due to its conjugation over more atoms, and as such is a better leaving group.

The second equation indicates that when the sydnone and nitro are substituents on a phenyl ring, the energy difference becomes greater (-9.5 kcal/mol). Since the anionic components in equations 1 and 2 are identical, this increased energy difference can only be explained by nitrobenzene being more stable than phenylsydnone. This difference is almost identical to that of the products resulting from the formation of **4a** and those of **4b** (10.0 kcal/mol). Thus, the difference in exergonicity is related to both the better stability of the sydnone anion vs the nitrite, but also the preference for an aryl ring to be conjugated with a nitro.

The third equation confirms the above-mentioned fact, quantifying the energy difference between nitrobenzene and phenylsydnone at 3.8 kcal/mol. Therefore, we can conclude

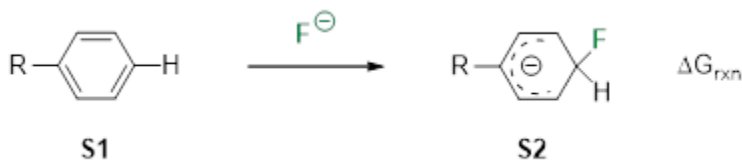
that a nitro substituent better enjoys better conjugation with a phenyl ring than a sydnone does. The absence of co-planarity in phenylsydnones (see below) explains this difference.

### 3.5 Prediction of the Hammett $\sigma_p^-$ constant for sydnone

To evaluate the  $\sigma_p^-$  constant of sydnone, we studied the hypothetical reaction shown in Table S1, where a fluoride anion attacks the *para* position of substituted benzenes **S1** to form Meisenheimer  $\sigma$ -complexes **S2**. We correlated our computed  $\Delta G_{\text{rxn}}$  with the known  $\sigma_p^-$  values of the substituents. These values are obtained by comparing the ionization of substituted phenols or aniliniums to those of the parent (R=H) compound.<sup>9</sup> The correlations were then used to extrapolate the  $\sigma_p^-$  constant of sydnone.

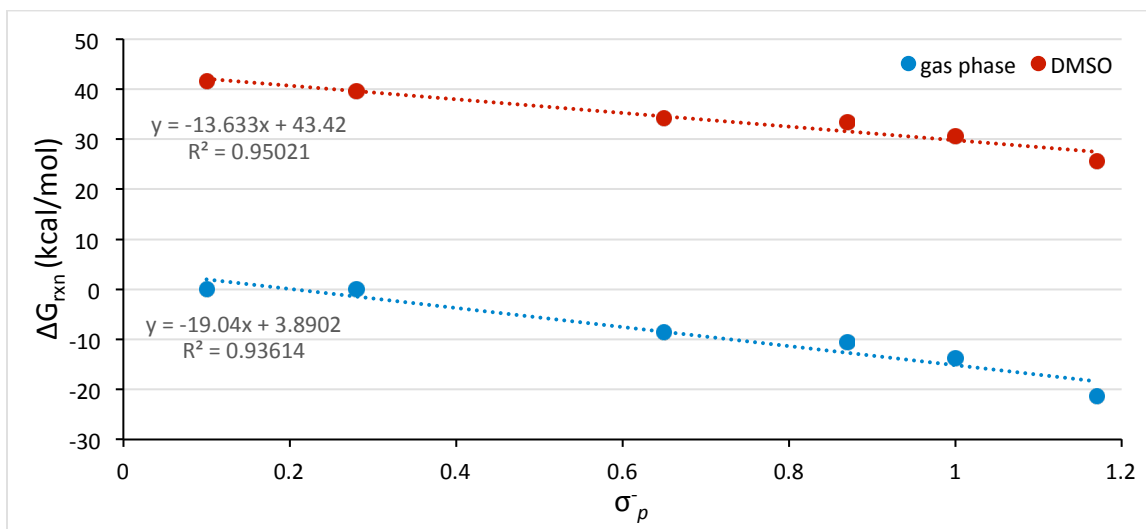
The geometries of all compounds were optimized at the M06-2X/6-311+G(d,p) level of theory, in the gas phase. Vibrational frequencies were calculated at that level and used to obtain the free energy correction using normal mode analysis. Single-point energy calculations were then realized at the same level, but adding the SMD solvation model for DMSO. To get the free energies in DMSO, the free energy correction was added to the refined energy. The obtained refined energies were compared to those in the gas-phase to compute the DMSO solvation energy of each structure ( $\Delta E_{\text{solv}} = E_{\text{DMSO}} - E_{\text{gas}}$ ). As such,  $\Delta\Delta E_{\text{solv}} = \Delta E_{\text{solv}}(\sigma\text{-complex}) - \Delta E_{\text{solv}}(\text{R-Ph}) - \Delta E_{\text{solv}}(\text{F}^-)$ , where  $\Delta E_{\text{solv}}(\text{F}^-) = -88.8$  kcal/mol.

**Table S1:** Free energies of reaction and solvation energies as a function of substituent.



R	cmpd	$\sigma_p^-$	$\Delta G_{\text{rxn}}$	$\Delta\Delta E_{\text{solv}}$ (DMSO)	$\Delta G_{\text{rxn}}$ (DMSO)
---	------	--------------	-------------------------	---------------------------------------	--------------------------------

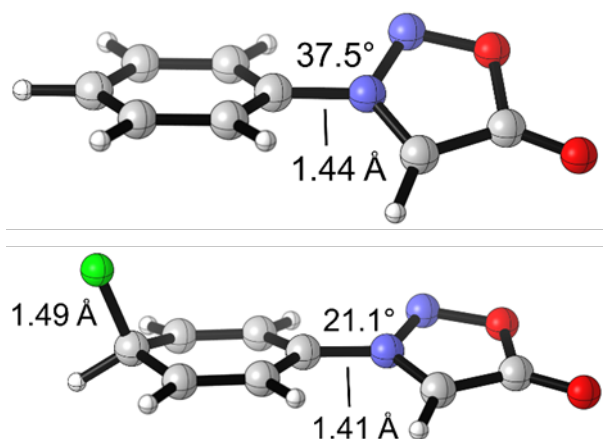
			(kcal/mol)	(kcal/mol)	(kcal/mol)
NO <sub>2</sub>	<b>S1a</b>	1.17	-21.3	46.8	25.5
CN	<b>S1b</b>	1.00	-13.7	44.4	30.7
COCH <sub>3</sub>	<b>S1c</b>	0.87	-10.5	43.9	33.5
CF <sub>3</sub>	<b>S1d</b>	0.65	-8.6	42.9	34.3
Br	<b>S1e</b>	0.28	0.0	39.5	39.5
Ph	<b>S1f</b>	0.10	0.0	41.6	41.6
Sydnone	<b>S1g</b>	?	-20.8	53.4	32.6



**Figure S1.** Calculated free energy of reaction  $\Delta G_{\text{rxn}}$  as a function of Hammett  $\sigma_p^-$  constant.

From the two correlations shown in Figure S1 above, we determine the  $\sigma_p^-$  constant of sydnone at 1.30 for the values in the gas phase, and 0.79 for values taken in implicit DMSO. As the  $\Delta G_{\text{rxn}}$  values in implicit DMSO have more relevance to the measured  $\sigma_p^-$  constants of the substituents and provide a better correlation, we estimate the  $\sigma_p^-$  constant of sydnone at **0.79**.

Therefore, despite a stronger electron-withdrawing capacity and greater dipolar moment (see NBO analysis section, above), a sydnone is between the COCH<sub>3</sub> and CF<sub>3</sub> groups in terms of mesomeric (–M) stabilization. Of note, phenylsydnone is not planar in its ground state, but rotates in plane significantly after fluoride addition (Figure S2), highlighting how the non-co-planarity of arylsydnones represents a barrier to the sydnone group acting as a good –M substituent.

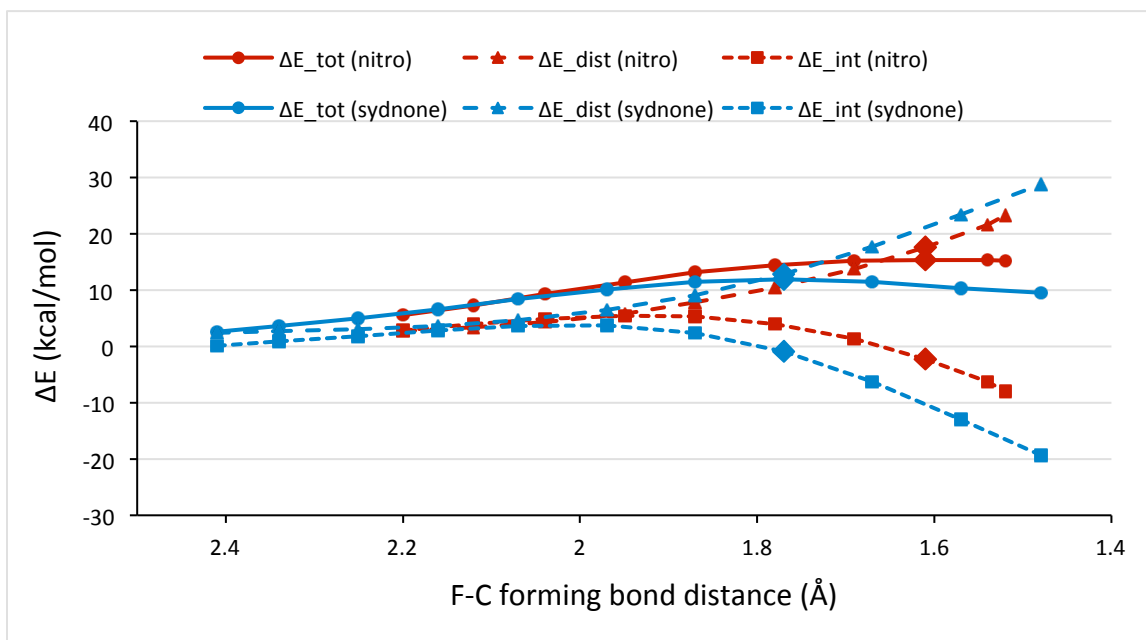


**Figure S2.** Calculated structures of compound **S1g** (above) and **S2g** (below), showing how the sydnone becomes more coplanar with the aryl ring when it has to stabilize a negative charge through resonance.

### 3.6 Distortion/interaction analysis along the reaction coordinate

The IRC analyses for both the C(1) and C(4) addition transition states were computed at the M06-2X/6-311+G(d,p)/SMD(DMSO) level (Gaussian 09 keyword: `irc=(calcfc,recalc=2,stepsize=5,maxpoints=30,direction)`, where *direction* is either “forward” or “reverse”). From these IRC plots, every 4 points were selected as data, with 7 points being taken before the TS and up to 3 points being taken after the TS, in addition to the TS geometry. From these structures, single-point energy calculations were performed at the M06-2X/6-311+G(d,p)/SMD(DMSO) level for the full geometry and when the fluorine atom was removed. These energies were used to obtain the distortion ( $\Delta E_{\text{dist}}$ ) energy of the substrate part and its interaction energy with fluoride ( $\Delta E_{\text{int}}$ ) at each point along the coordinate, following a typical distortion/interaction procedure such as  $\Delta E_{\text{tot}} = \Delta E_{\text{dist}} + \Delta E_{\text{int}}$ .<sup>10</sup>

These three energies are plotted below along the reaction coordinate, defined as the forming C–F bond distance (Figure S3). The position of the transition state, for both pathways, is highlighted by large diamonds as data points.



**Figure S3.** Total energy, distortion energy and interaction energy along the reaction coordinate, defined by the forming C–F bond distance, in Å. Addition to the sydnone-bearing C(1) in blue, addition to the nitro-bearing C(4) in red.

From this graph, two effects can be understood. First, the distortion of the substrate is greater for the reaction at the sydnone carbon. This indicates that attack at this carbon incurs more movement of the substituents, which is reasonable since the whole sydnone group has to rotate during this attack. Second, the main difference between the pathways is the interaction energy, which is greater along the reaction coordinate for the reaction at the sydnone carbon. This is consistent with the fact that the sydnone is a better  $-I$  substituent, which makes the fluoride-carbon interaction more favorable.

### 3.7 Cartesian coordinates, energies and vibrational frequencies

#### Points on the potential energy surface, isodesmic equations and NBO calculations

These geometries, energies and free energy corrections were obtained at the M06-2X/6-311+G(d,p)/SMD(DMSO) level of theory.

#### Fluoride (F<sup>-</sup>)

Charge: -1

F 0.00000 0.00000 0.00000

There are no imaginary frequencies.

SCF energy: -99.984027 hartree

zero-point correction: +0.000000 hartree

enthalpy correction: +0.002360 hartree

free energy correction: +0.014159 hartree

#### *p*-nitrophenylsydnone (4)

Charge: 0

N 1.75762 0.10136 0.05065  
N 2.32535 1.13450 0.58393  
O 3.64439 0.90023 0.45618  
C 3.89692 -0.33306 -0.17156  
C 2.59687 -0.82990 -0.42555  
H 2.26440 -1.72481 -0.91973  
O 5.02674 -0.70982 -0.36957  
C 0.32104 0.05498 0.02291  
C -0.30671 -1.15669 0.27507  
C -0.37415 1.22535 -0.25004  
C -1.69248 -1.20110 0.25273  
H 0.26938 -2.04511 0.50178  
C -1.75980 1.18284 -0.26336  
H 0.15536 2.14597 -0.45876  
C -2.38499 -0.02934 -0.01288  
H -2.21915 -2.12506 0.44899  
H -2.33750 2.07207 -0.47569  
N -3.86137 -0.07410 -0.03029  
O -4.39694 -1.15075 0.12843  
O -4.45717 0.96862 -0.20136

There are no imaginary frequencies.

SCF energy: -772.758916 hartree

zero-point correction: +0.135078 hartree

enthalpy correction: +0.147219 hartree

free energy correction: +0.096286 hartree

#### TS 1b

Charge: -1

N 1.99970 -0.11382 0.03932  
N 2.61103 -1.21822 0.32742  
O 3.92972 -0.93956 0.17050  
C 4.12799 0.39475 -0.19880  
C 2.81634 0.90752 -0.27946  
H 2.45830 1.87426 -0.58140  
O 5.24484 0.83092 -0.37883  
C 0.57459 -0.08283 0.07576  
C -0.08752 1.09685 0.42097  
C -0.15505 -1.22132 -0.27722  
C -1.46189 1.13841 0.45394  
H 0.47692 1.99013 0.66530  
C -1.52931 -1.19940 -0.25453  
H 0.36326 -2.11439 -0.60730  
C -2.22974 -0.04764 0.22677  
H -1.98081 2.05163 0.71037  
H -2.10061 -2.06510 -0.56035  
N -3.57704 0.21396 -0.49962  
O -4.05654 1.32340 -0.41862  
O -4.07735 -0.70125 -1.11558  
F -3.01230 -0.43732 1.58214

1 imaginary frequency: -218.75 cm<sup>-1</sup>.

SCF energy: -872.718403 hartree

zero-point correction: +0.134652 hartree

enthalpy correction: +0.147946 hartree

free energy correction: +0.094564 hartree

#### TS 1a

Charge: -1

N -1.71291 0.12097 0.06197  
N -2.05890 1.19425 -0.56375  
O -3.37394 1.03696 -0.81626  
C -3.84615 -0.19675 -0.33591  
C -2.69453 -0.77315 0.24184  
H -2.55496 -1.69708 0.77020  
O -5.00678 -0.51207 -0.47436  
C -0.28741 -0.04422 0.39973  
C 0.34111 -1.16240 -0.21726  
C 0.45620 1.15782 0.55716  
C 1.70009 -1.15934 -0.41065  
H -0.25836 -2.02275 -0.48783  
C 1.81446 1.14522 0.36365  
H -0.05075 2.05202 0.89482

C	2.44567	-0.01801	-0.09388
H	2.19126	-2.02611	-0.83362
H	2.39647	2.03918	0.54662
N	3.86570	-0.01602	-0.30961
O	4.39750	-1.03494	-0.73219
O	4.49709	1.00274	-0.05801
F	-0.67428	-0.56401	2.04533

1 imaginary frequency:  $-357.29 \text{ cm}^{-1}$ .

SCF energy: -872.723894 hartree  
 zero-point correction: +0.134405 hartree  
 enthalpy correction: +0.147799 hartree  
 free energy correction: +0.093881 hartree

**Int b**

Charge: -1

N	-1.97978	0.12713	-0.06467
N	-2.62185	1.23560	-0.26409
O	-3.93141	0.92455	-0.06528
C	-4.09035	-0.43023	0.23469
C	-2.77054	-0.92428	0.22929
H	-2.38819	-1.90007	0.46431
O	-5.19188	-0.89772	0.43795
C	-0.56241	0.11645	-0.15750
C	0.17358	1.26930	0.14922
C	0.10542	-1.04739	-0.55617
C	1.54140	1.27045	0.06951
H	-0.34159	2.16528	0.47711
C	1.47292	-1.07465	-0.65283
H	-0.45803	-1.93866	-0.81142
C	2.26758	0.10050	-0.37286
H	2.10996	2.15240	0.33365
H	1.98972	-1.97236	-0.96566
N	3.48884	-0.24732	0.61332
O	3.82982	0.58988	1.41948
O	3.99913	-1.34146	0.50765
F	3.15631	0.42251	-1.50538

There are no imaginary frequencies.

SCF energy: -872.718765 hartree  
 zero-point correction: +0.135164 hartree  
 enthalpy correction: +0.148927 hartree  
 free energy correction: +0.093461 hartree

**Int a**

Charge: -1

N	1.68315	0.09652	0.17448
N	1.71940	-1.18174	0.29899
O	2.99541	-1.52284	0.00554
C	3.76228	-0.39528	-0.32008
C	2.83756	0.66726	-0.19279
H	2.95916	1.72537	-0.32971

O	4.93216	-0.50228	-0.61336
C	0.32114	0.77770	0.32984
C	-0.34420	0.87166	-0.97557
C	-0.46636	0.14926	1.39542
C	-1.64164	0.50361	-1.13394
H	0.23982	1.26551	-1.79944
C	-1.76389	-0.19888	1.20162
H	0.02161	0.00611	2.35212
C	-2.38883	-0.02793	-0.05655
H	-2.11471	0.60984	-2.10246
H	-2.33223	-0.62576	2.01872
N	-3.72405	-0.40613	-0.24003
O	-4.24639	-0.26660	-1.35393
O	-4.36031	-0.87040	0.71524
F	0.77927	2.07454	0.74568

There are no imaginary frequencies.

SCF energy: -872.729779 hartree  
 zero-point correction: +0.135206 hartree  
 enthalpy correction: +0.148647 hartree  
 free energy correction: +0.094633 hartree

**TS 2b**

Charge: -1

N	1.93457	-0.16211	0.07049
N	2.60350	-1.27017	0.01505
O	3.89334	-0.89123	-0.18149
C	4.01491	0.50033	-0.21515
C	2.68767	0.94759	-0.04901
H	2.27458	1.93902	-0.06606
O	5.09587	1.02710	-0.37497
C	0.52040	-0.20819	0.23537
C	-0.12527	0.80542	0.95160
C	-0.20524	-1.30317	-0.24818
C	-1.48638	0.76547	1.13597
H	0.45151	1.60605	1.40200
C	-1.56642	-1.36216	-0.07404
H	0.30924	-2.11043	-0.75687
C	-2.26593	-0.27133	0.53305
H	-1.99630	1.53005	1.70775
H	-2.14224	-2.20111	-0.44307
N	-3.32635	0.47693	-0.72343
O	-3.59071	1.65988	-0.62527
O	-3.69970	-0.21612	-1.65061
F	-3.37908	-0.66188	1.29583

1 imaginary frequency:  $-186.56 \text{ cm}^{-1}$ .

SCF energy: -872.717655 hartree  
 zero-point correction: +0.133773 hartree  
 enthalpy correction: +0.147296 hartree  
 free energy correction: +0.092533 hartree

**TS 2a**

Charge: -1

N	1.67552	0.23859	-0.18019
N	1.50400	-0.91171	-0.69630
O	2.68349	-1.58552	-0.50575
C	3.59668	-0.77887	0.17389
C	2.88160	0.42524	0.37128
H	3.18047	1.34324	0.84400
O	4.71046	-1.18927	0.44352
C	0.20826	1.27050	-0.06451
C	-0.56485	1.05138	-1.25300
C	-0.40155	0.96406	1.19968
C	-1.76011	0.39168	-1.18399
H	-0.15600	1.38675	-2.19831
C	-1.59516	0.30067	1.24530
H	0.13494	1.23169	2.10207
C	-2.27537	-0.02156	0.05712
H	-2.32705	0.20135	-2.08663
H	-2.03439	0.04004	2.19986
N	-3.51834	-0.70647	0.11649
O	-4.10821	-0.96279	-0.93186
O	-3.96850	-1.02900	1.21472
F	0.94432	2.44091	-0.06451

1 imaginary frequency:  $-322.99 \text{ cm}^{-1}$ .

SCF energy: -872.725111 hartree  
zero-point correction: +0.133968 hartree  
enthalpy correction: +0.147254 hartree  
free energy correction: +0.093211 hartree

#### Nitrite (NO<sub>2</sub>)

Charge: -1

N	0.00000	0.45331	0.00000
O	1.05812	-0.19827	0.00000
O	-1.05812	-0.19838	0.00000

There are no imaginary frequencies.

SCF energy: -205.229993 hartree  
zero-point correction: +0.008350 hartree  
enthalpy correction: +0.012208 hartree  
free energy correction: +0.015274 hartree

#### *p*-fluoronitrobenzene (4a)

Charge: 0

C	0.00000	0.00000	2.04355
C	0.00046	1.21947	1.38709
C	-0.00046	-1.21947	1.38709
C	0.00000	1.21946	0.00088
H	0.00120	2.14164	1.95427
C	0.00000	-1.21946	0.00088
H	-0.00120	-2.14164	1.95427
C	0.00000	0.00000	-0.66440

H	0.00016	2.14881	-0.55221
H	-0.00016	-2.14881	-0.55221
N	0.00000	0.00000	-2.13387
O	-0.01800	1.07246	-2.70463
O	0.01800	-1.07246	-2.70463
F	0.00000	0.00000	3.38628

There are no imaginary frequencies.

SCF energy: -535.939838 hartree  
zero-point correction: +0.095570 hartree  
enthalpy correction: +0.104194 hartree  
free energy correction: +0.061935 hartree

#### *p*-fluorophenylsydnone (4b)

Charge: 0

N	1.05953	0.10338	0.05279
N	1.61857	1.15226	0.56120
O	2.94233	0.92733	0.43615
C	3.20341	-0.31768	-0.15907
C	1.90809	-0.83172	-0.39969
H	1.58259	-1.74080	-0.87202
O	4.33714	-0.69145	-0.34824
C	-0.37649	0.04046	0.02046
C	-0.99619	-1.16362	0.32543
C	-1.08806	1.18597	-0.31160
C	-2.38230	-1.22575	0.29630
H	-0.41097	-2.03441	0.59545
C	-2.47429	1.12515	-0.33506
H	-0.56820	2.10297	-0.55927
C	-3.08436	-0.07923	-0.03173
H	-2.91251	-2.14007	0.53127
H	-3.07300	1.98957	-0.59403
F	-4.42880	-0.13949	-0.05921

There are no imaginary frequencies.

SCF energy: -667.510780 hartree  
zero-point correction: +0.124145 hartree  
enthalpy correction: +0.134599 hartree  
free energy correction: +0.088129 hartree

#### Sydnone anion

Charge: -1

N	1.40938	0.58160	0.00013
N	1.36832	-0.68758	-0.00024
O	0.00992	-1.06526	0.00019
C	-0.76786	0.06776	-0.00026
C	0.17489	1.11869	0.00006
H	0.00005	2.18069	0.00035
O	-1.99568	-0.00443	0.00002

There are no imaginary frequencies.



SCF energy: -336.816843 hartree  
zero-point correction: +0.038254 hartree  
enthalpy correction: +0.043290 hartree  
free energy correction: +0.010814 hartree

### Nitrobenzene

Charge: 0

C	-2.50501	0.00000	0.00000
C	-1.81372	1.20847	0.04410
C	-1.81372	-1.20847	-0.04410
C	-0.42474	1.21894	0.04040
H	-2.35502	2.14587	0.08154
C	-0.42474	-1.21894	-0.04040
H	-2.35502	-2.14587	-0.08154
C	0.23827	0.00000	0.00000
H	0.13185	2.14594	0.07248
H	0.13186	-2.14594	-0.07248
N	1.71145	0.00000	0.00000
O	2.28232	1.06669	-0.11083
O	2.28231	-1.06669	0.11083
H	-3.58879	-0.00000	0.00000

There are no imaginary frequencies.

SCF energy: -436.699148 hartree  
zero-point correction: +0.103808 hartree  
enthalpy correction: +0.111531 hartree  
free energy correction: +0.071885 hartree

### Phenylsydnone

Charge: 0

N	-0.63621	-0.09876	0.04967
N	-1.17964	-1.15654	0.55642
O	-2.50717	-0.94792	0.43992
C	-2.78671	0.29556	-0.14993
C	-1.49934	0.82636	-0.39554
H	-1.18841	1.74154	-0.86568
O	-3.92615	0.65489	-0.33306
C	0.80077	-0.01691	0.01093
C	1.40455	1.19623	0.31026
C	1.52475	-1.15395	-0.32177
C	2.79208	1.26708	0.27222
H	0.80584	2.05789	0.58095
C	2.91140	-1.06486	-0.34885
H	1.01247	-2.07656	-0.56505
C	3.54281	0.14067	-0.05436

H	3.28520	2.20292	0.50535
H	3.49620	-1.93857	-0.61015
H	4.62438	0.20300	-0.08073

There are no imaginary frequencies.

SCF energy: -568.270462 hartree  
zero-point correction: +0.132334 hartree  
enthalpy correction: +0.141976 hartree  
free energy correction: +0.097550 hartree

### H-NO<sub>2</sub>

Charge: 0

N	-0.00002	0.31882	0.00002
O	-1.07973	-0.22455	-0.00001
O	1.07975	-0.22454	-0.00001
H	0.00001	1.36105	-0.00005

There are no imaginary frequencies.

SCF energy: -205.682239 hartree  
zero-point correction: +0.022767 hartree  
enthalpy correction: +0.026652 hartree  
free energy correction: +0.001014 hartree

### H-sydnone

Charge: 0

N	-1.32618	0.49221	0.00028
N	-1.28018	-0.79257	-0.00029
O	0.03852	-1.07537	0.00022
C	0.82053	0.09418	0.00001
C	-0.15105	1.12394	-0.00047
H	-0.05261	2.19379	0.00108
O	2.02785	0.03436	-0.00001
H	-2.25063	0.92810	0.00016

There are no imaginary frequencies.

SCF energy: -337.259111 hartree  
zero-point correction: +0.051717 hartree  
enthalpy correction: +0.056865 hartree  
free energy correction: +0.024186 hartree

## Structures for the $\sigma_p^-$ constant calculations

These geometries were optimized at the M06-2X/6-311+G(d,p) level of theory, in the gas phase. Free energy corrections were calculated by normal mode frequency analysis, also at this level. Single-point energy refinements were then performed at the M06-2X/6-311+G(d,p)/SMD(DMSO) level. Below, both the gas phase and DMSO energies are listed for each compound.

### Fluoride (F<sup>-</sup>)

Charge: -1

F	0.00000	0.00000	0.00000
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There are no imaginary frequencies.

SCF energy (gas phase): -99.842468 hartree

SCF energy (DMSO): -99.984027 hartree

zero-point correction: +0.000000 hartree

enthalpy correction: +0.002360 hartree

free energy correction: +0.014159 hartree

### Acetophenone (S1c)

Charge: 0

C	2.58027	0.11591	0.00012
C	1.96121	-1.13243	-0.00008
C	1.81189	1.27493	0.00004
C	0.57697	-1.21972	-0.00007
H	2.56101	-2.03482	-0.00023
C	0.42378	1.18754	0.00002
H	2.29252	2.24579	0.00006
C	-0.20170	-0.05988	0.00004
H	0.07185	-2.17824	-0.00019
H	-0.16505	2.09727	0.00018
O	-2.20605	-1.30231	0.00012
C	-1.69676	-0.20661	0.00009
C	-2.54347	1.04670	-0.00012
H	-2.32724	1.65371	0.88223
H	-2.32739	1.65329	-0.88284
H	-3.59224	0.75867	-0.00010
H	3.66186	0.18429	-0.00037

There are no imaginary frequencies.

SCF energy (gas phase): -384.828985 hartree

SCF energy (DMSO): -384.841683 hartree

zero-point correction: +0.138886 hartree

enthalpy correction: +0.147543 hartree

free energy correction: +0.106310 hartree

### Biphenyl (S1f)

Charge: 0

C	-0.74213	-0.00000	0.00000
C	-1.45573	1.12327	-0.42793
C	-1.45574	-1.12327	0.42793
C	-2.84550	1.12353	-0.42821
H	-0.91490	1.99296	-0.78458
C	-2.84551	-1.12353	0.42821
H	-0.91490	-1.99297	0.78457
C	-3.54539	0.00000	-0.00000
H	-3.38315	1.99994	-0.77085
H	-3.38316	-1.99993	0.77085
C	0.74212	-0.00000	0.00000
C	1.45572	-1.12325	-0.42798
C	1.45572	1.12325	0.42798
C	2.84552	-1.12355	-0.42813
H	0.91496	-1.99298	-0.78462
C	2.84552	1.12355	0.42813
H	0.91495	1.99297	0.78462
C	3.54541	0.00000	-0.00000
H	3.38311	-1.99994	-0.77090
H	3.38310	1.99995	0.77090
H	4.62875	0.00000	-0.00000
H	-4.62873	0.00001	-0.00000

There are no imaginary frequencies.

SCF energy (gas phase): -463.215648 hartree

SCF energy (DMSO): -463.227567 hartree

zero-point correction: +0.182185 hartree

enthalpy correction: +0.192013 hartree

free energy correction: +0.147520 hartree

### Bromobenzene (S1e)

Charge: 0

C	2.86689	0.00039	-0.00001
C	2.17047	-1.20329	0.00001
C	2.16965	1.20347	0.00003
C	0.77887	-1.21200	0.00002
H	2.70678	-2.14455	-0.00005
C	0.77854	1.21202	-0.00002
H	2.70647	2.14458	0.00004

C	0.10079	-0.00039	-0.00000
H	0.22864	-2.14390	0.00002
H	0.22669	2.14290	0.00000
H	3.94991	0.00074	-0.00016
Br	-1.80028	-0.00003	-0.00000

There are no imaginary frequencies.

SCF energy (gas phase): -2805.771189 hartree  
 SCF energy (DMSO): -2805.779698 hartree  
 zero-point correction: +0.091027 hartree  
 enthalpy correction: +0.097643 hartree  
 free energy correction: +0.060189 hartree

**Trifluorotoluene (S1d)**

Charge: 0

C	-2.82256	-0.00026	0.01278
C	-2.12962	1.20604	0.00200
C	-2.12903	-1.20631	0.00197
C	-0.73988	1.21015	-0.01842
H	-2.67090	2.14410	0.00658
C	-0.73937	-1.20971	-0.01846
H	-2.66987	-2.14463	0.00649
C	-0.05406	0.00042	-0.03067
H	-0.18978	2.14303	-0.03402
H	-0.18875	-2.14229	-0.03415
H	-3.90586	-0.00055	0.02599
C	1.44757	0.00015	-0.00278
F	1.96205	-1.07833	-0.61194
F	1.96260	1.08280	-0.60398
F	1.92277	-0.00476	1.25488

There are no imaginary frequencies.

SCF energy (gas phase): -569.251443 hartree  
 SCF energy (DMSO): -569.258176 hartree  
 zero-point correction: +0.106357 hartree  
 enthalpy correction: +0.115057 hartree  
 free energy correction: +0.072769 hartree

**Benzonitrile (S1b)**

Charge: 0

C	-0.00006	-2.17040	0.00000
C	-1.20707	-1.47758	0.00000
C	1.20698	-1.47763	0.00000
C	-1.21315	-0.08947	0.00000
H	-2.14492	-2.01907	0.00000
C	1.21313	-0.08953	0.00000
H	2.14480	-2.01918	0.00000
C	0.00000	0.60275	0.00000
H	-2.14416	0.46335	0.00000
H	2.14415	0.46326	0.00000
H	-0.00008	-3.25373	0.00000
C	0.00004	2.04043	0.00000

N	0.00014	3.19056	0.00000
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There are no imaginary frequencies.

SCF energy (gas phase): -324.437621 hartree  
 SCF energy (DMSO): -324.448429 hartree  
 zero-point correction: +0.099848 hartree  
 enthalpy correction: +0.106869 hartree  
 free energy correction: +0.069593 hartree

**Nitrobenzene (S1a)**

Charge: 0

C	2.50518	-0.00009	0.00001
C	1.81393	-1.20822	0.00001
C	1.81381	1.20823	0.00000
C	0.42472	-1.21750	0.00000
H	2.35535	-2.14580	0.00000
C	0.42490	1.21762	-0.00001
H	2.35578	2.14552	0.00000
C	-0.23823	-0.00006	-0.00001
H	-0.14332	-2.13766	0.00000
H	-0.14363	2.13747	-0.00001
N	-1.71855	-0.00001	-0.00002
O	-2.27813	-1.07457	0.00000
O	-2.27795	1.07464	0.00002
H	3.58847	0.00011	-0.00001

There are no imaginary frequencies.

SCF energy (gas phase): -436.688550 hartree  
 SCF energy (DMSO): -436.698970 hartree  
 zero-point correction: +0.104106 hartree  
 enthalpy correction: +0.111837 hartree  
 free energy correction: +0.072101 hartree

**Phenylsydnone (S1g)**

Charge: 0

N	-0.63612	-0.09970	0.04700
N	-1.17950	-1.17632	0.51217
O	-2.49904	-0.97172	0.40773
C	-2.79802	0.30562	-0.14147
C	-1.50216	0.84372	-0.36314
H	-1.19874	1.76508	-0.82049
O	-3.92646	0.66607	-0.30958
C	0.79765	-0.01750	0.01321
C	1.40535	1.19716	0.29740
C	1.52792	-1.15558	-0.30019
C	2.79206	1.27267	0.25567
H	0.80610	2.05827	0.56676
C	2.91354	-1.06488	-0.32941
H	1.01184	-2.08228	-0.51494
C	3.54466	0.14503	-0.05669
H	3.28313	2.21188	0.47713
H	3.49961	-1.94193	-0.57431

H	4.62546	0.20882	-0.08581
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There are no imaginary frequencies.

SCF energy (gas phase): -568.250203 hartree  
SCF energy (DMSO): -568.270010 hartree  
zero-point correction: +0.132624 hartree  
enthalpy correction: +0.142276 hartree  
free energy correction: +0.097935 hartree

#### $\sigma$ -complex\_acetophenone (S2e)

Charge: -1

C	2.24267	-0.05413	-0.32850
C	1.48716	1.21381	-0.37931
C	1.37063	-1.24176	-0.40843
C	0.14122	1.25638	-0.19456
H	2.05184	2.13182	-0.50840
C	0.02371	-1.15771	-0.22165
H	1.84336	-2.20731	-0.55752
C	-0.65915	0.08272	-0.07278
H	-0.37764	2.21017	-0.17361
H	-0.55013	-2.08118	-0.22814
O	-2.69592	1.26084	0.18269
F	3.00844	-0.10489	0.95223
C	-2.07987	0.19215	0.09380
C	-2.89990	-1.10201	0.16585
H	-2.82228	-1.66485	-0.76846
H	-2.55144	-1.75026	0.97361
H	-3.94101	-0.83181	0.33849
H	3.07987	-0.08590	-1.03404

There are no imaginary frequencies.

SCF energy (gas phase): -484.700864 hartree  
SCF energy (DMSO): -484.785126 hartree  
zero-point correction: +0.139383 hartree  
enthalpy correction: +0.149456 hartree  
free energy correction: +0.104892 hartree

#### $\sigma$ -complex\_biphenyl (S2f)

Charge: -1

C	0.29822	0.04775	-0.15191
C	1.04617	-1.09784	-0.52742
C	1.05291	1.23757	0.00745
C	2.40725	-1.09208	-0.66524
H	0.51010	-2.00319	-0.80244
C	2.41547	1.28072	-0.10586
H	0.53418	2.16694	0.22758
C	3.21825	0.06092	-0.25830
H	2.91860	-1.97636	-1.03128
H	2.93855	2.22451	0.00956
F	3.88607	-0.24751	1.07305
C	-1.15022	0.01756	-0.03888
C	-1.94954	1.17778	-0.17144

C	-1.85477	-1.18363	0.21269
C	-3.33166	1.13748	-0.06455
H	-1.47083	2.12477	-0.39062
C	-3.23846	-1.22281	0.30289
H	-1.29332	-2.09712	0.36948
C	-4.00163	-0.06352	0.16889
H	-3.89725	2.05728	-0.18057
H	-3.72897	-2.17149	0.49992
H	-5.08217	-0.09368	0.24717
H	4.12461	0.19672	-0.85609

There are no imaginary frequencies.

SCF energy (gas phase): -563.070157 hartree  
SCF energy (DMSO): -563.157350 hartree  
zero-point correction: +0.182140 hartree  
enthalpy correction: +0.193481 hartree  
free energy correction: +0.145396 hartree

#### $\sigma$ -complex\_bromobenzene (S2e)

Charge: -1

C	-2.55653	0.00000	-0.35144
C	-1.76399	-1.21359	-0.46069
C	-1.76399	1.21359	-0.46069
C	-0.40053	-1.20712	-0.25074
H	-2.27335	-2.15720	-0.62307
C	-0.40053	1.20712	-0.25074
H	-2.27335	2.15720	-0.62307
C	0.28138	0.00000	-0.09395
H	0.15317	-2.14046	-0.25049
H	0.15317	2.14046	-0.25049
F	-3.27853	0.00000	1.06940
H	-3.47993	0.00000	-0.93256
Br	2.19578	0.00000	0.12184

There are no imaginary frequencies.

SCF energy (gas phase): -2905.625330 hartree  
SCF energy (DMSO): -2905.712480 hartree  
zero-point correction: +0.090946 hartree  
enthalpy correction: +0.099327 hartree  
free energy correction: +0.057735 hartree

#### $\sigma$ -complex\_trifluorotoluene (S2d)

Charge: -1

C	-2.52239	-0.00134	-0.32818
C	-1.71518	-1.22191	-0.44675
C	-1.72057	1.22282	-0.44368
C	-0.35775	-1.20353	-0.27601
H	-2.22834	-2.16451	-0.60400
C	-0.36275	1.21050	-0.27215
H	-2.23786	2.16349	-0.59871
C	0.35840	0.00505	-0.14949
H	0.19421	-2.13934	-0.29251

H	0.18448	2.14886	-0.28546
F	-3.22039	-0.00540	1.02632
H	-3.41661	-0.00260	-0.95796
C	1.80162	0.00232	0.07555
F	2.42926	1.11306	-0.39417
F	2.19636	-0.06042	1.39254
F	2.44100	-1.05716	-0.49326

There are no imaginary frequencies.

SCF energy (gas phase): -669.118913 hartree  
 SCF energy (DMSO): -669.198787 hartree  
 zero-point correction: +0.106324 hartree  
 enthalpy correction: +0.116588 hartree  
 free energy correction: +0.069863 hartree

**$\sigma$ -complex\_benzonitrile (S2b)**

Charge: -1

C	0.03313	-1.85561	0.00000
C	0.24318	-1.06782	1.22598
C	0.24318	-1.06782	-1.22598
C	0.24318	0.29648	1.21079
H	0.32353	-1.59978	2.16783
C	0.24318	0.29648	-1.21079
H	0.32353	-1.59978	-2.16783
C	0.20153	1.03482	0.00000
H	0.32119	0.84306	2.14662
H	0.32119	0.84306	-2.14662
F	-1.37836	-2.38052	0.00000
H	0.56641	-2.81102	0.00000
C	0.23872	2.44637	0.00000
N	0.26754	3.60740	0.00000

There are no imaginary frequencies.

SCF energy (gas phase): -424.314966 hartree  
 SCF energy (DMSO): -424.396556 hartree  
 zero-point correction: +0.100610 hartree  
 enthalpy correction: +0.108966 hartree  
 free energy correction: +0.068403 hartree

**$\sigma$ -complex\_nitrobenzene (S2a)**

Charge: -1

C	-2.17363	0.00000	-0.33450
C	-1.35712	-1.23545	-0.38158
C	-1.35712	1.23545	-0.38158
C	-0.01423	-1.22210	-0.19149
H	-1.87763	-2.17690	-0.51934
C	-0.01423	1.22210	-0.19149
H	-1.87763	2.17690	-0.51934
C	0.69660	0.00000	-0.05389

H	0.55433	-2.14380	-0.17579
H	0.55433	2.14380	-0.17578
N	2.08021	0.00000	0.10155
O	2.68863	-1.08201	0.17281
O	2.68863	1.08201	0.17280
F	-2.95930	-0.00000	0.91073
H	-2.98092	0.00000	-1.07487

There are no imaginary frequencies.

SCF energy (gas phase): -536.578898 hartree  
 SCF energy (DMSO): -536.656232 hartree  
 zero-point correction: +0.105240 hartree  
 enthalpy correction: +0.114191 hartree  
 free energy correction: +0.071827 hartree

**$\sigma$ -complex\_phenylsydnone (S2g)**

Charge: -1

N	-1.04067	-0.12501	0.00451
N	-1.59522	-1.26935	0.27360
O	-2.94157	-1.02849	0.28170
C	-3.21616	0.32197	0.03930
C	-1.93988	0.88599	-0.13810
H	-1.66418	1.88003	-0.42340
O	-4.35865	0.73279	0.01032
C	0.35641	-0.02980	-0.12204
C	1.12709	-1.18019	-0.40221
C	1.00049	1.22501	-0.08040
C	2.47789	-1.09958	-0.55824
H	0.61514	-2.12446	-0.55006
C	2.35134	1.33070	-0.22985
H	0.41686	2.12861	0.06032
C	3.22430	0.14255	-0.28190
H	3.04133	-1.98260	-0.83740
H	2.81972	2.30798	-0.22054
F	3.91590	0.00693	1.02932
H	4.09212	0.27431	-0.93498

There are no imaginary frequencies.

SCF energy (gas phase): -668.138209 hartree  
 SCF energy (DMSO): -668.214404 hartree  
 zero-point correction: +0.133078 hartree  
 enthalpy correction: +0.144195 hartree  
 free energy correction: +0.096121 hartree

## 4. Radiochemistry

### 4.1 General Materials and Methods

No-carrier-added [ $^{18}\text{F}$ ]fluoride was produced by the  $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$  nuclear reaction in a Siemens RDS-112 cyclotron at 11 MeV using a 1 mL tantalum target with havar foil. Unless otherwise stated, reagents and solvents were commercially available and used without further purification. HPLC grade acetonitrile and trifluoroacetic acid were purchased from Fisher Scientific. Anhydrous acetonitrile, dimethyl sulfoxide and tetraethylammonium bicarbonate were purchased from Sigma-Aldrich. Sterile product vials were purchased from Hollister-Stier. QMA-light Sep-Paks and tC18 light cartridges were purchased from Waters Corporation. Radio-TLCs were analyzed using a miniGITA\* TLC scanner. HPLC purifications were performed on a Knauer Smartline HPLC system with inline Knauer UV (254 nm) detector and gamma-radiation coincidence detector and counter (Bioscan Inc.). Semi-preparative HPLC was performed using Phenomenex reverse-phase Luna column (10 × 250 mm, 5  $\mu\text{m}$ ) with a flow rate of 4 mL/min. Final purity and identity of compounds were determined by analytical HPLC analysis performed with a Phenomenex reverse-phase Luna column (4.6 × 250 mm, 5  $\mu\text{m}$ ) with a flow rate of 1 mL/min. All chromatograms were collected by a GinaStar (Raytest) analog to digital converter and GinaStar software.

#### Preparation of [ $^{18}\text{F}$ ]tetraethylammonium fluoride ([ $^{18}\text{F}$ ]TEAF)

Dry [ $^{18}\text{F}$ ]TEAF was prepared using an ELIXYS automated radiosynthesizer (Sofie Biosciences). [ $^{18}\text{F}$ ]Fluoride was delivered to the ELIXYS in [ $^{18}\text{O}$ ]H<sub>2</sub>O (1 mL) via nitrogen gas push and trapped on a QMA cartridge to remove the [ $^{18}\text{O}$ ]H<sub>2</sub>O. Trapped [ $^{18}\text{F}$ ]fluoride was subsequently eluted into the reaction vial using a solution containing Et<sub>4</sub>NHCO<sub>3</sub> (9-10 mg) in acetonitrile and water (1 mL, 8:2). Contents in the reaction vial were subjected to a nitrogen stream and evaporated by heating the vial to 110 °C while applying a vacuum for 3.5 min, with stirring. Acetonitrile (1.3 mL) was passed through the QMA cartridge to wash remaining activity into the reaction vial. The combined contents in the reaction vial were dried by azeotropic distillation (heating to 110 °C under vacuum) for 2 min. Anhydrous acetonitrile (1.3 mL) was directly added to the reaction vial and azeotropic distillation was repeated once more until dryness, approximately 3-4 min. The reaction vial was cooled to 30 °C under nitrogen pressure and

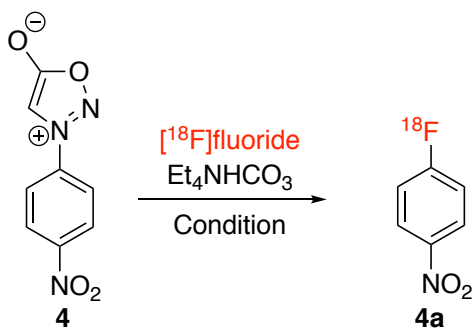
DMSO (1 mL) was added to provide anhydrous [ $^{18}\text{F}$ ]TEAF which was used for subsequent reactions.

## 4.2 Synthesis and characterization of $^{18}\text{F}$ -labeled compounds

**General experimental procedure:** Radiochemistry experiments were conducted in a 4 mL glass vial containing *N*-arylsydnone (4-5 mg) with 250-350  $\mu\text{Ci}$  of [ $^{18}\text{F}$ ]TEAF in 150-200  $\mu\text{L}$  of DMSO. The contents were heated to 150  $^{\circ}\text{C}$  for 5-20 min and progress of the reaction was observed by radio-TLC. An aliquot of the crude reaction mixture was spotted on a silica gel coated TLC plate, developed in a glass chamber with acetonitrile:water (95:5) as the eluent and analyzed using a miniGITA\* TLC scanner. The radiochemical conversion (RCC) was calculated by dividing the integrated area of the  $^{18}\text{F}$ -fluorinated product peak by the total integrated area of all peaks on the TLC and multiplying by 100 to convert to percentage units. Analytical HPLC was used to confirm product identity and purity via UV absorbance at 254 nm, by coinjection with the  $^{19}\text{F}$ -reference standard. An aliquot of the crude reaction mixture (10  $\mu\text{L}$ ) was added to the  $^{19}\text{F}$ -reference standard (1 mg/mL) in acetonitrile (10  $\mu\text{L}$ ) and the sample was injected into the analytical HPLC.

### 4.3 Optimization Screen

Table. S2 Optimization of radiofluorination using 4-nitro-phenyl sydnone 4.

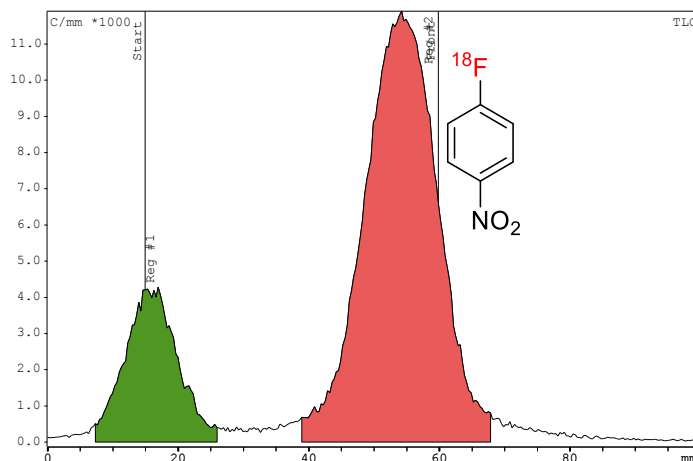


Entry	Condition	RCC (%)
1.	CH <sub>3</sub> CN/60 °C/ 20 min	10
2.	CH <sub>3</sub> CN/ 90 °C/20 min	22
3.	DMF/ 135 °C/10 min	5
4.	DMSO/ 110 °C/10 min	30
5.	DMSO/ 130 °C/10 min	44
<b>6.</b>	<b>DMSO/ 150 °C/5 min</b>	<b>80</b>
7.	DMSO/150 °C/10 min	78

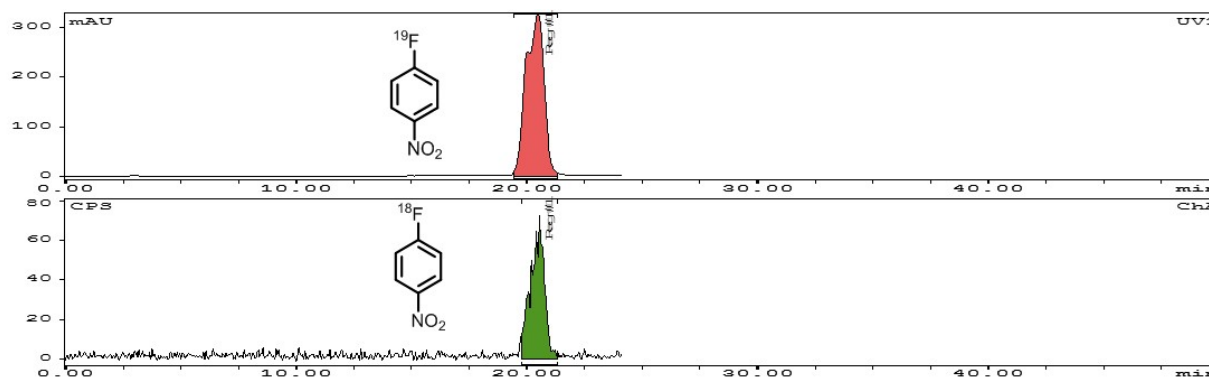


#### 4.4 Radio-TLC/Radio-HPLC analysis of $^{18}\text{F}$ -labeled compounds

(Note: the reaction mixture was spotted on the baseline of the TLC plate which corresponds to about 20 mm on the horizontal axis of the radio TLC scan)

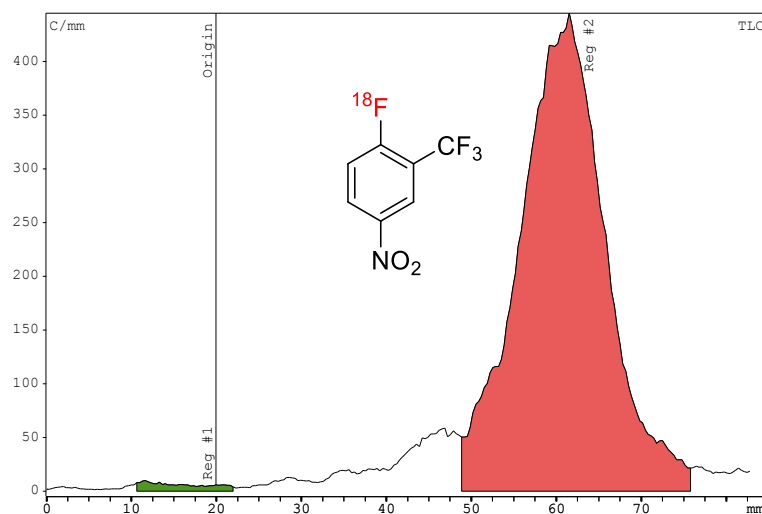


Run	1	2	3	4	mean	Standard deviation
Radio TLC yield (%)	76	74	82	80	78	3

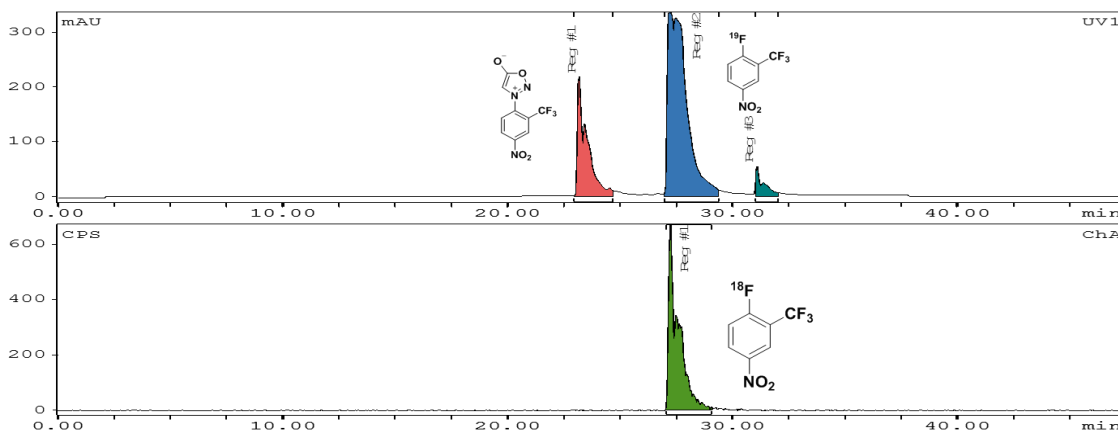


**Figure S4. Radiosynthesis and characterization of [ $^{18}\text{F}$ ]Fluoro-4-nitrobenzene 4a.**

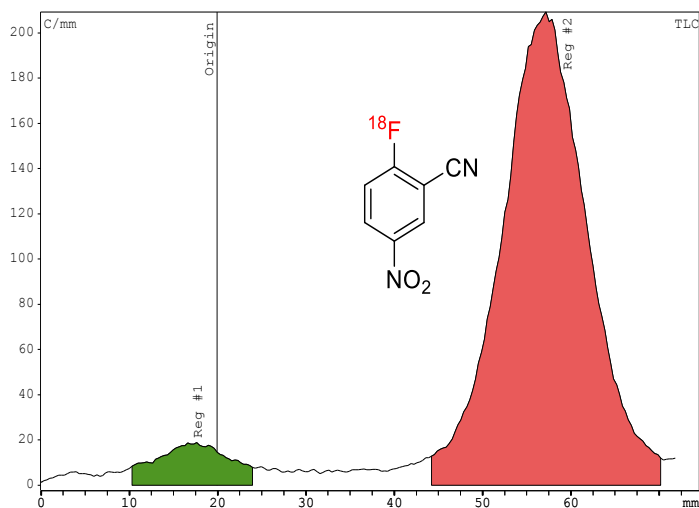
Example of integrated radio-TLC scan (upper). Radio-HPLC with 254 nm UV trace of  $^{19}\text{F}$  reference standard (middle) and radioactivity trace of reaction mixture (lower). HPLC mobile phase: 10% Acetonitrile in water (both 0.1% TFA) to 90% acetonitrile in water over 25 min.



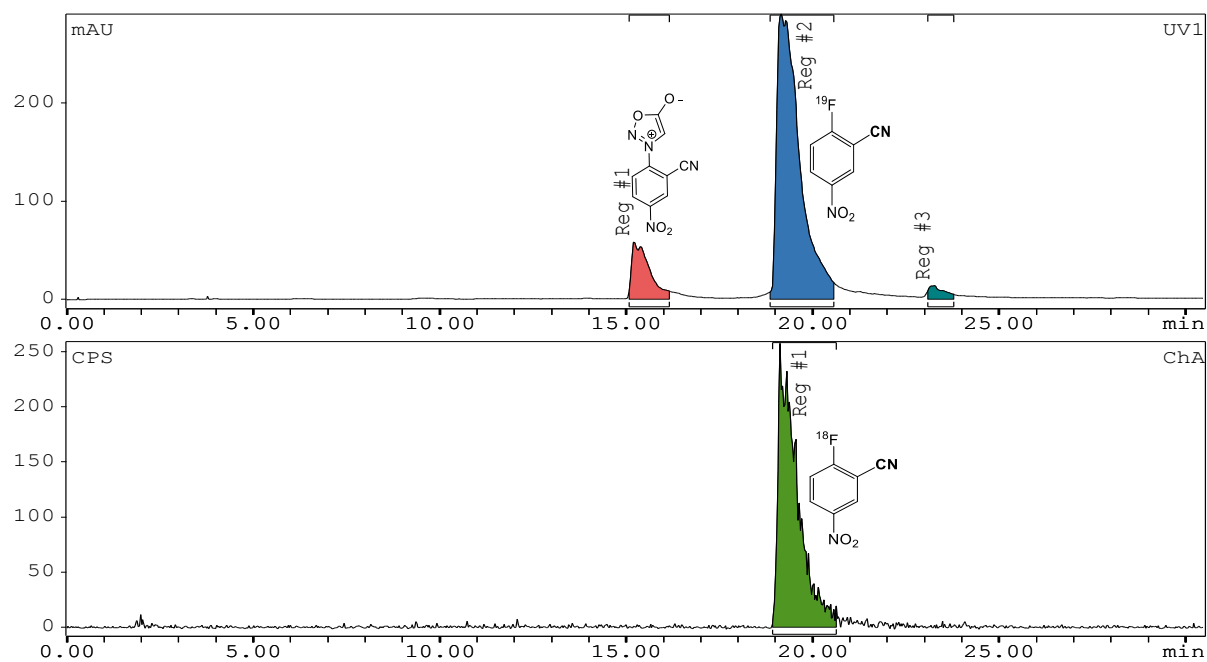
Run	1	2	3	4	mean	Standard deviation
Radio TLC yield (%)	96	98	92	96	96	2



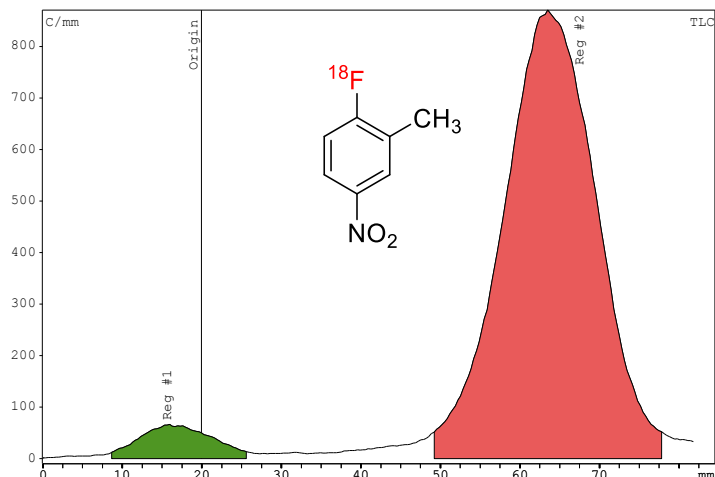
**Figure S5. Radiosynthesis and characterization of [ $^{18}\text{F}$ ]Fluoro-4-nitro-2-(trifluoromethyl)benzene 5a.** Example of integrated radio-TLC scan (upper). Radio-HPLC with 254 nm UV trace of  $^{19}\text{F}$  reference standard (middle) and radioactivity trace of reaction mixture (lower). HPLC mobile phase: 5% Acetonitrile in water (both 0.1% TFA) for 3 min then to 90% acetonitrile in water over 25 min



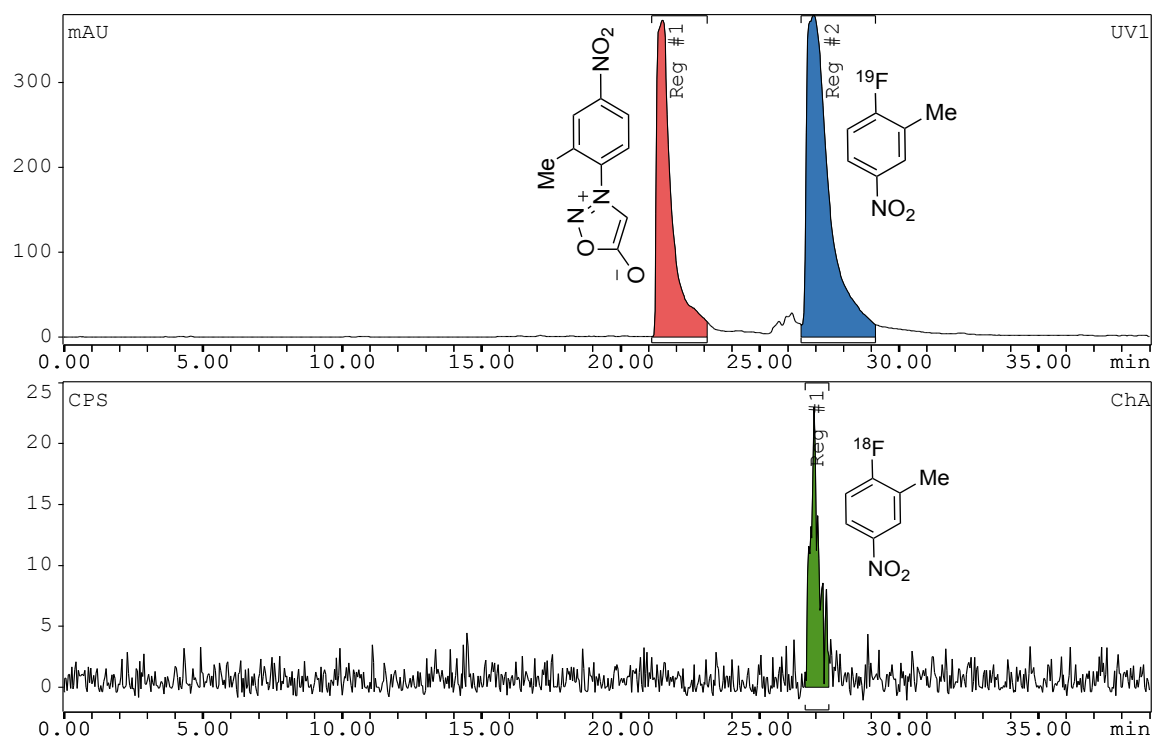
Run	1	2	3	4	mean	Standard deviation
Radio TLC yield (%)	92	94	90	92	92	1



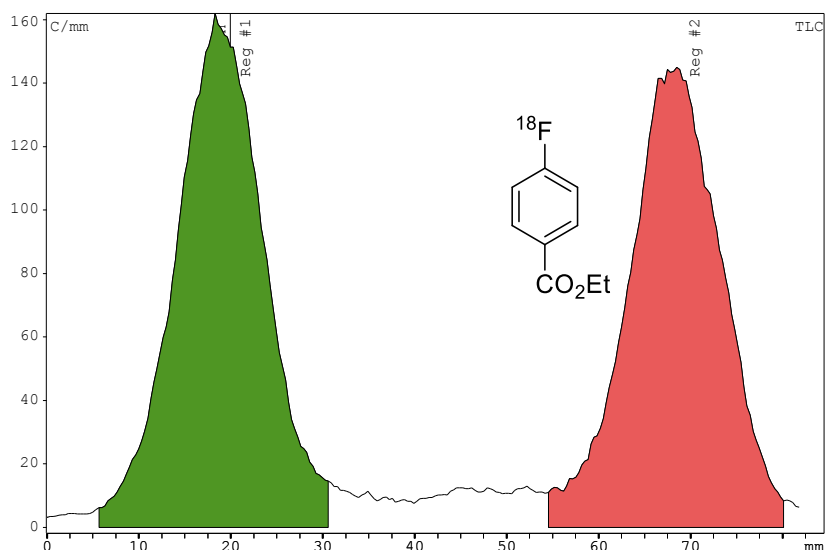
**Figure S6. Radiosynthesis and characterization of 2-[<sup>18</sup>F]-Fluoro-5-nitrobenzonitrile 6a.** Example of integrated radio-TLC scan (upper). Radio-HPLC with 254 nm UV trace of <sup>19</sup>F reference standard (middle) and radioactivity trace of reaction mixture (lower). HPLC mobile phase: 5% Acetonitrile in water (both 0.1% TFA) for 3 min then to 90% acetonitrile in water over 25 min.



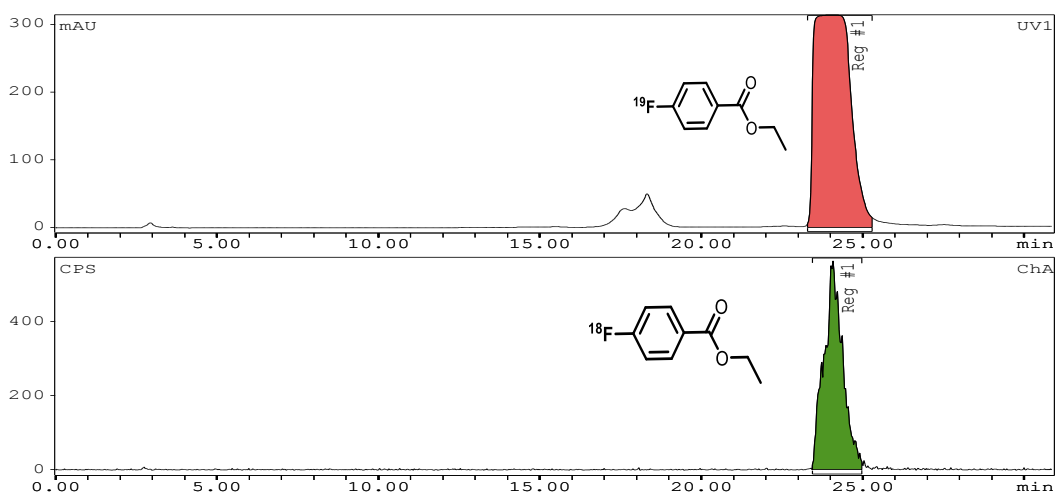
Run	1	2	3	4	mean	Standard deviation
Radio TLC yield (%)	94	92	91	95	93	2



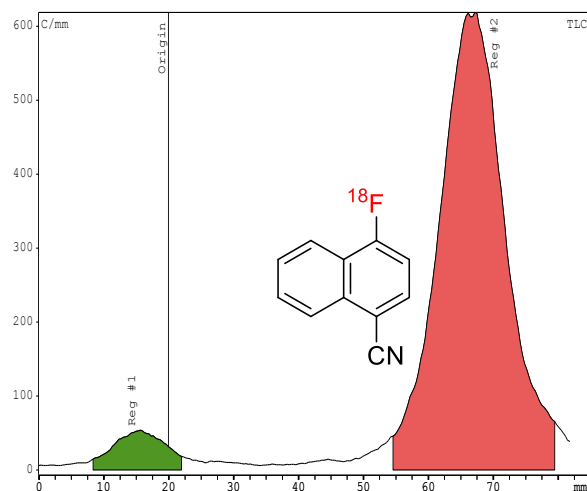
**Figure S7. Radiosynthesis and characterization of [ $^{18}\text{F}$ ]Fluoro-2-methyl-4-nitrobenzene 7a.** Example of integrated radio-TLC scan (upper). Radio-HPLC with 254 nm UV trace of  $^{19}\text{F}$  reference standard (middle) and radioactivity trace of reaction mixture (lower). HPLC mobile phase: 5% Acetonitrile in water (both 0.1% TFA) for 3 min then to 90% acetonitrile in water over 25 min.



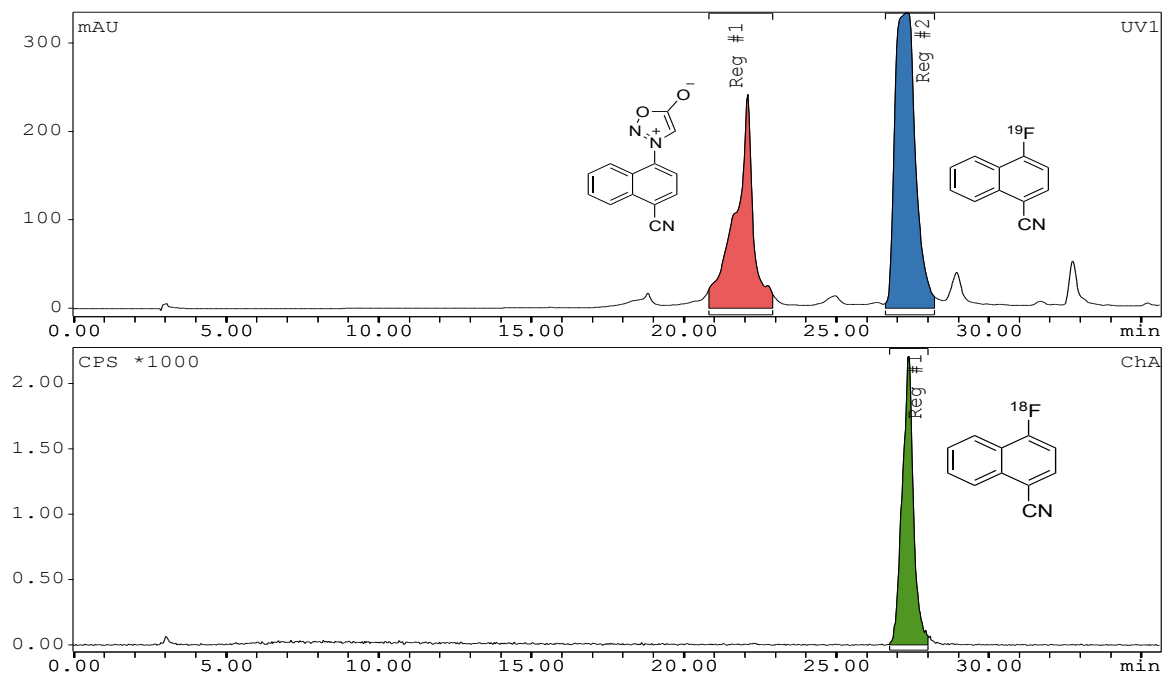
Run	1	2	3	mean	Standard deviation
Radio TLC yield (%)	49	51	54	51	2



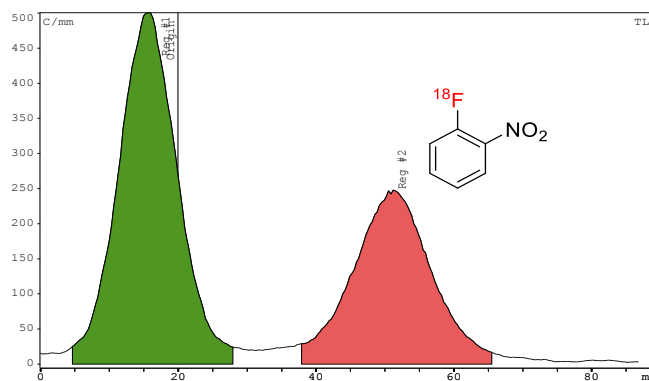
**Figure S8. Radiosynthesis and characterization of 4-[<sup>18</sup>F]-Fluoro-ethylbenzoate 8a.** Example of integrated radio-TLC scan (upper). Radio-HPLC with 254 nm UV trace of <sup>19</sup>F reference standard (middle) and radioactivity trace of reaction mixture (lower). HPLC mobile phase: 10% Acetonitrile in water (both 0.1% TFA) to 95% acetonitrile in water over 30 min.



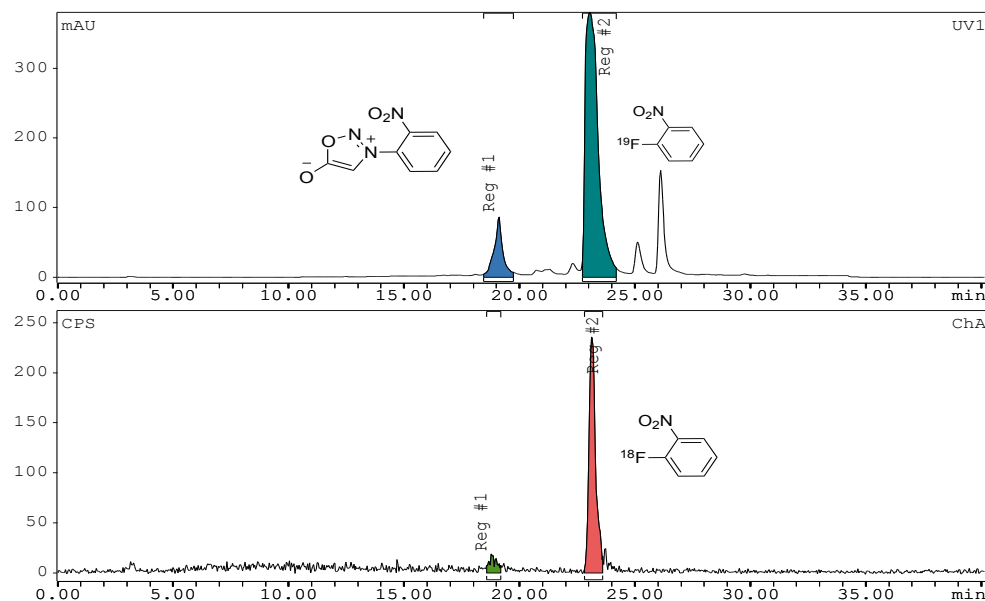
Run	1	2	3	mean	Standard deviation
Radio TLC yield (%)	92	92	93	92	1



**Figure S9. Radiosynthesis and characterization of 4-[<sup>18</sup>F]-Fluoro-1-naphthonitrile 9a.** Example of integrated radio-TLC scan (upper). Radio-HPLC with 254 nm UV trace of <sup>19</sup>F reference standard (middle) and radioactivity trace of reaction mixture (lower). HPLC mobile phase: 5% Acetonitrile in water (both 0.1% TFA) for 3 min then to 90% acetonitrile in water over 30 min.



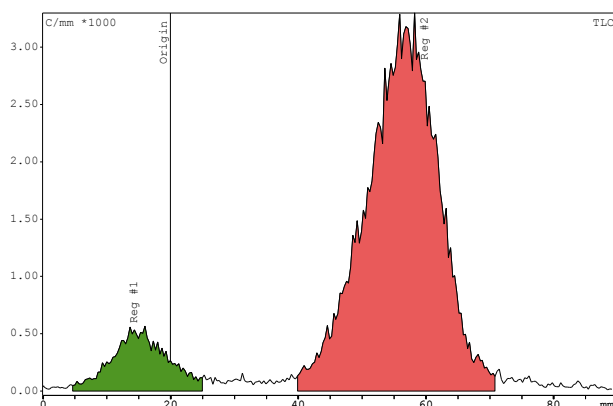
Run	1	2	3	mean	Standard deviation
Radio TLC yield (%)	39	31	23	31	7



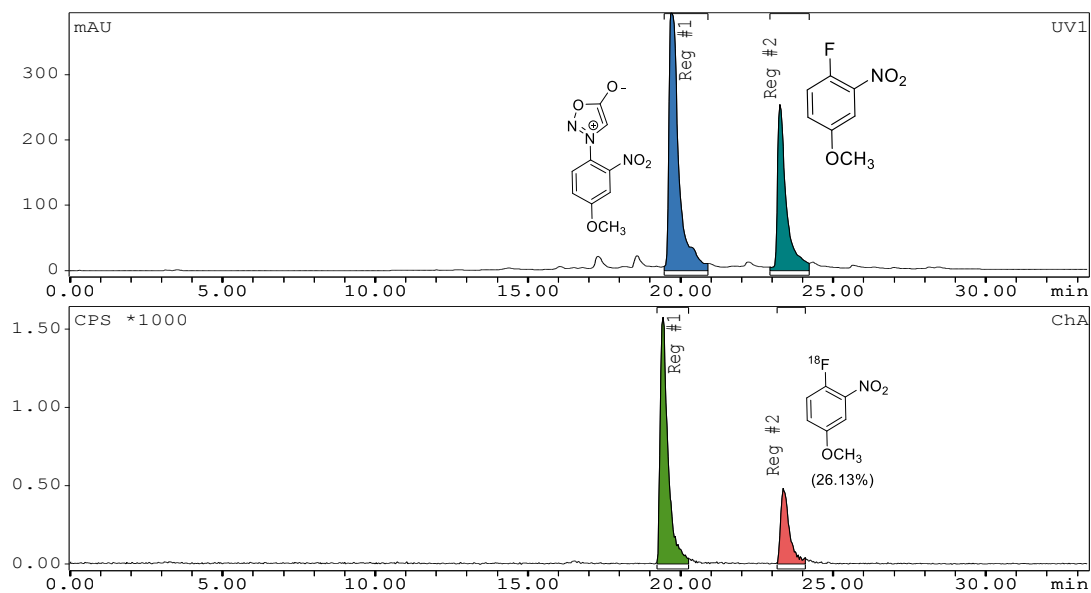
\*Note: RCC calculated by multiplying the mean relative peak integration from radio-TLC with the radio-HPLC peak integration corresponding to  $[^{18}\text{F}]\mathbf{10a} = (31) \cdot (91.9/100) = 28.5\%$

**Figure S10. Radiosynthesis and characterization of 4-[ $^{18}\text{F}$ ]-Fluoro-2-nitrobenzene  $\mathbf{10a}$ .**

Example of integrated radio-TLC scan (upper). Radio-HPLC with 254 nm UV trace of  $^{19}\text{F}$  reference standard (middle) and radioactivity trace of reaction mixture (lower). HPLC mobile phase: 5% Acetonitrile in water (both 0.1% TFA) for 3 min then to 90% acetonitrile in water over 35 min.



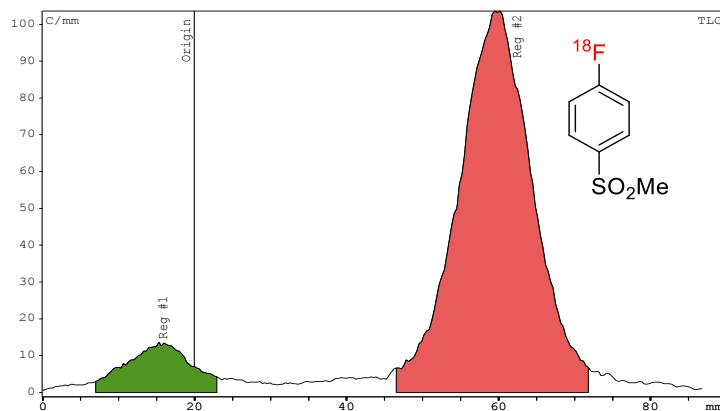
Run	1	2	3	4	mean	Standard deviation
Radio TLC yield (%)	88	87	88	92	89	2



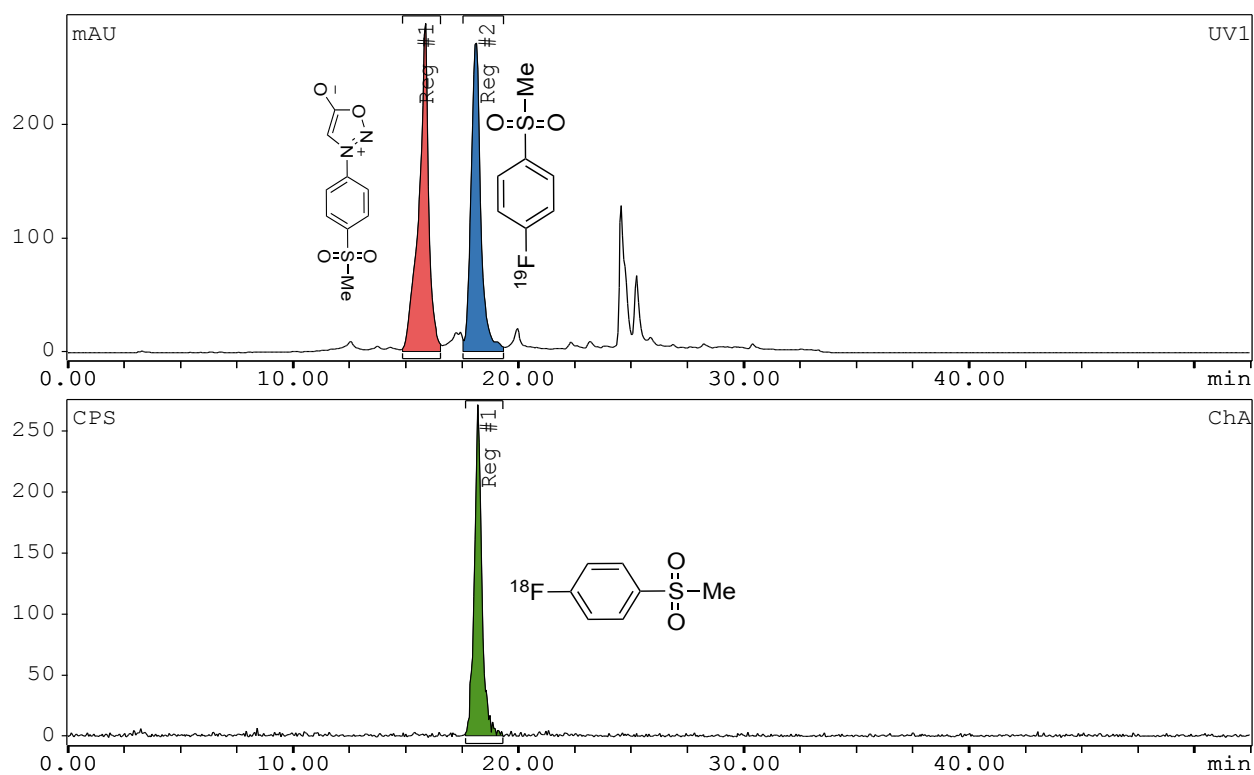
\*Note: RCC calculated by multiplying the mean relative peak integration from radio-TLC with the radio-HPLC peak integration corresponding to  $[^{18}\text{F}]\mathbf{11a} = (89) \cdot (26.13/100) = 23.2\%$

**Figure S11. Radiosynthesis and characterization of 1- $[^{18}\text{F}]$ -Fluoro-4-methoxy-2-nitrobenzene **11a**.** Example of integrated radio-TLC scan (upper). Radio-HPLC with 254 nm UV trace of  $^{19}\text{F}$  reference standard (middle) and radioactivity trace of reaction mixture (lower). HPLC mobile phase: 5% Acetonitrile in water (both 0.1% TFA) for 3 min then to 90% acetonitrile in water over 30 min.

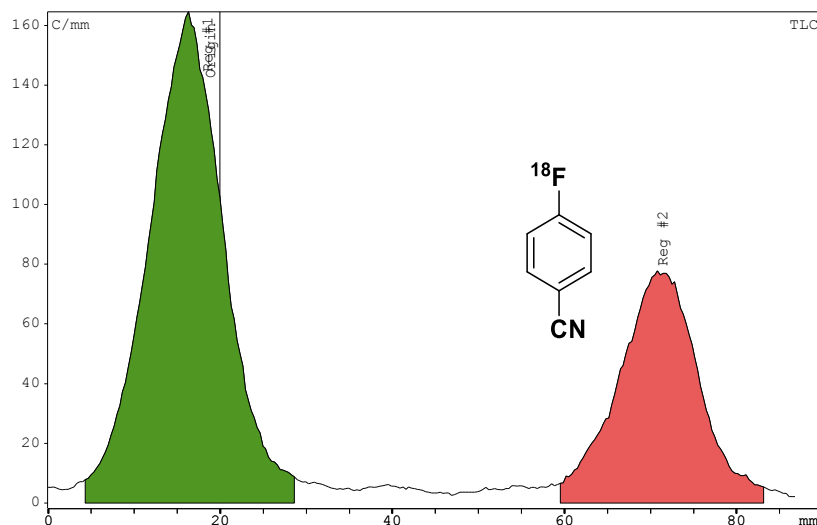




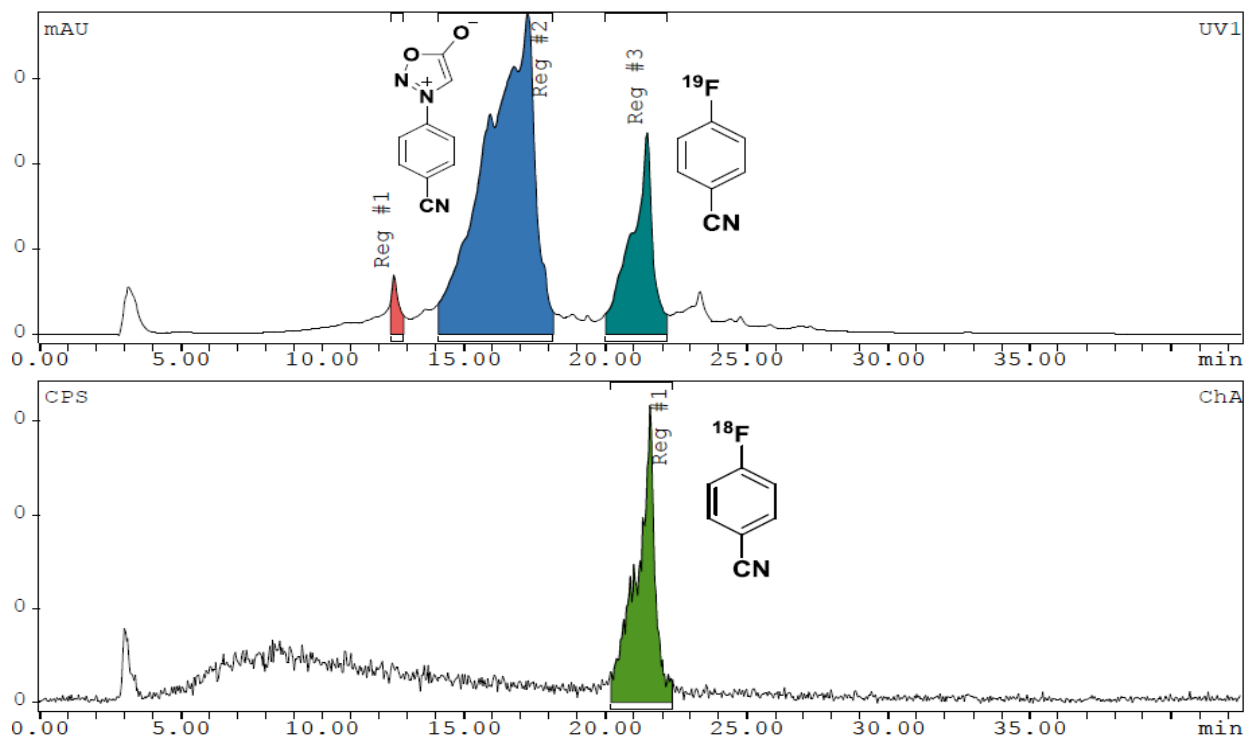
Run	1	2	3	4	mean	Standard deviation
Radio TLC yield (%)	72	72	76	87	77	7.8



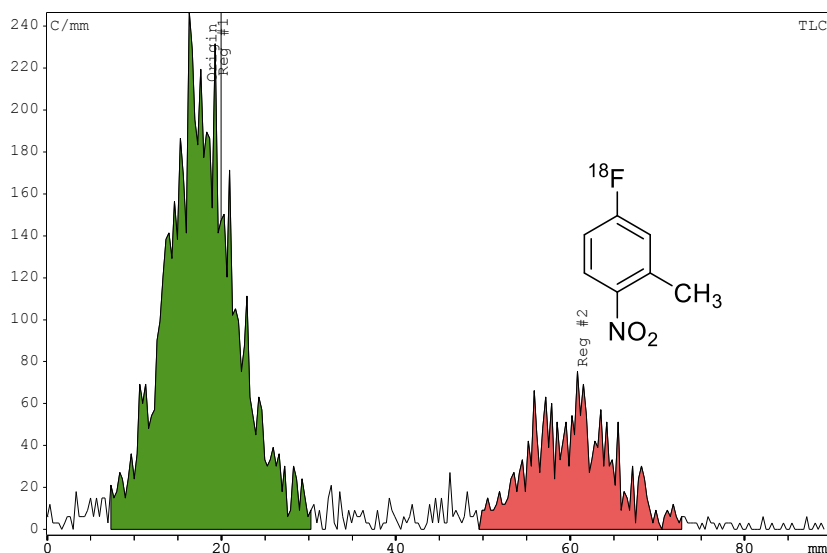
**Figure S12. Radiosynthesis and characterization of 1-[<sup>18</sup>F]-Fluoro-4-(methylsulfonyl)benzene 12a.** Example of integrated radio-TLC scan (upper). Radio-HPLC with 254 nm UV trace of <sup>19</sup>F reference standard (middle) and radioactivity trace of reaction mixture (lower). HPLC mobile phase: 5% Acetonitrile in water (both 0.1% TFA) for 3 min then to 90% acetonitrile in water over 30 min.



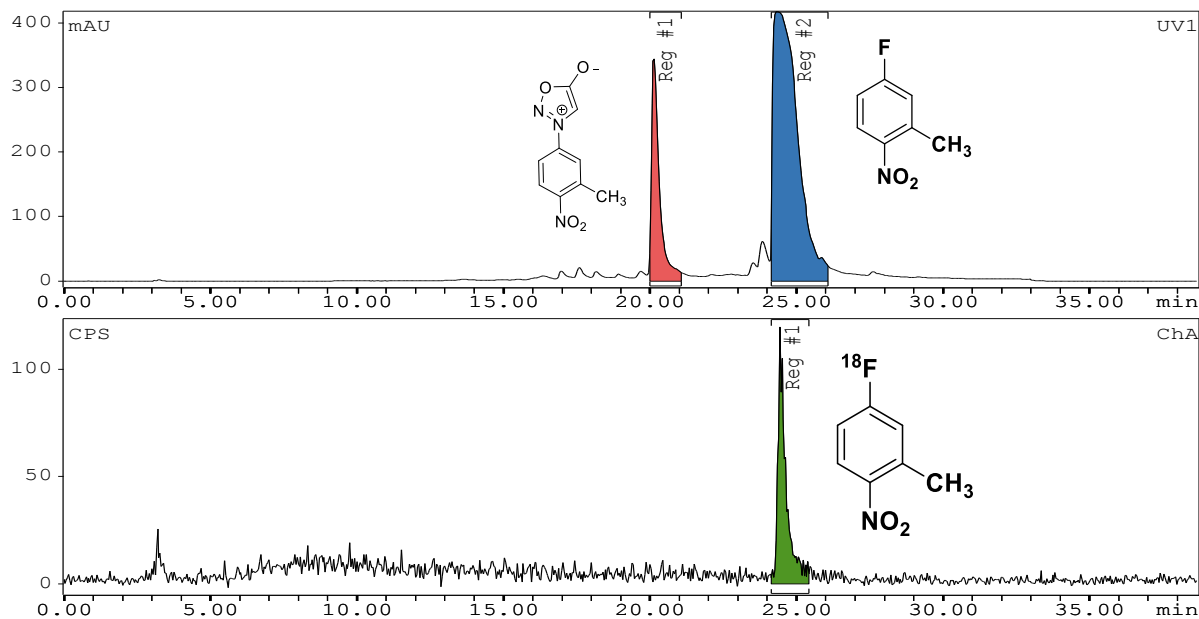
Run	1	2	3	4	5	mean	Standard deviation
Radio TLC yield (%)	25	33	28	26	33	29	4



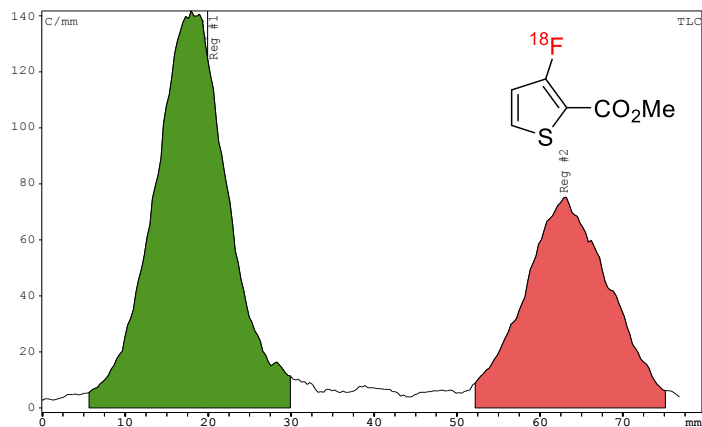
**Figure S13. Radiosynthesis and characterization of 4-[<sup>18</sup>F]-Fluorobenzonitrile 13a.** Example of integrated radio-TLC scan (upper). Radio-HPLC with 254 nm UV trace of <sup>19</sup>F reference standard (middle) and radioactivity trace of reaction mixture (lower). HPLC mobile phase: 10% Acetonitrile in water (both 0.1% TFA) to 95% acetonitrile in water over 30 min.



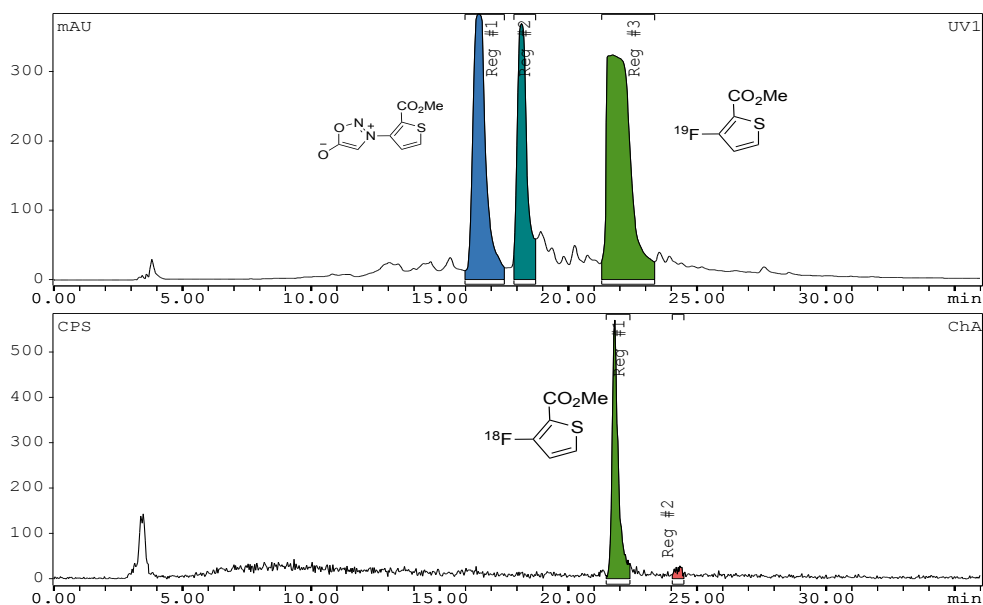
Run	1	2	3	mean	Standard deviation
Radio TLC yield (%)	23	24	22	23	1



**Figure S14. Radiosynthesis and characterization of 4-[<sup>18</sup>F]-Fluoro-2-methyl-1-nitrobenzene 14a.** Example of integrated radio-TLC scan (upper). Radio-HPLC with 254 nm UV trace of <sup>19</sup>F reference standard (middle) and radioactivity trace of reaction mixture (lower). HPLC mobile phase: 5% Acetonitrile in water (both 0.1% TFA) for 3 min then to 90% acetonitrile in water over 25 min.

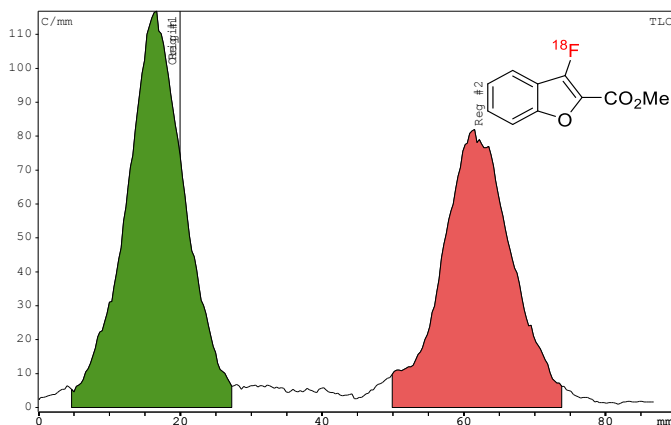


Run	1	2	3	4	mean	S. deviation
Radio TLC yield (%)	36	31	36	36	35	2

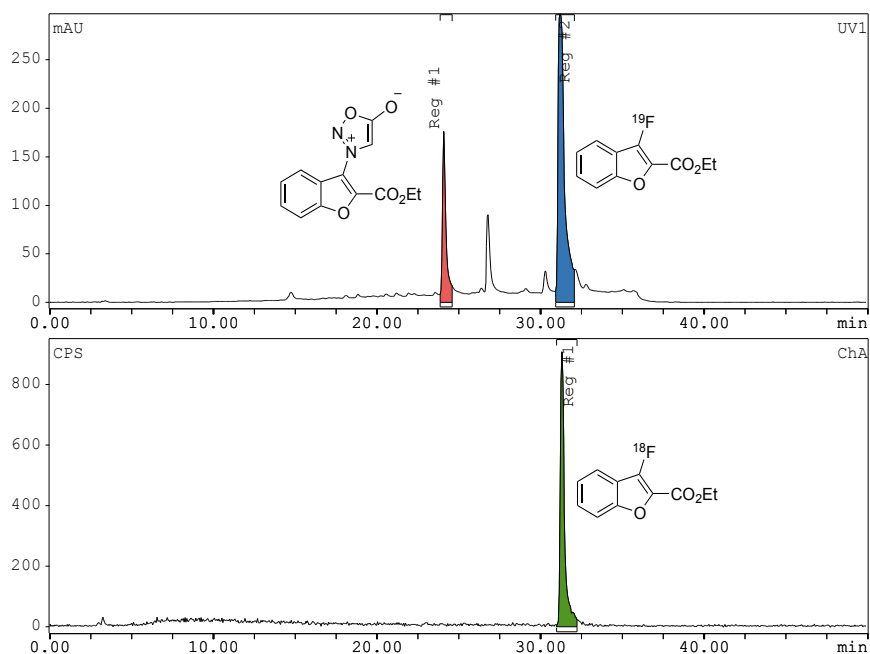


\*Note: RCC calculated by multiplying the mean relative peak integration from radio-TLC with the radio-HPLC peak integration corresponding to  $[^{18}\text{F}]\mathbf{15a} = (35) \cdot (95/100) = 33\%$

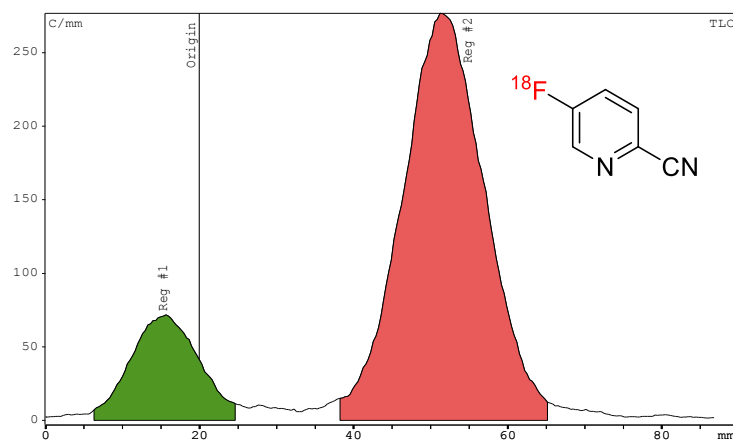
**Figure S15. Radiosynthesis and characterization of 4- $[^{18}\text{F}]$ -Fluoro-2-nitrobenzene  $\mathbf{15a}$ .** Example of integrated radio-TLC scan (upper). Radio-HPLC with 254 nm UV trace of  $^{19}\text{F}$  reference standard (middle) and radioactivity trace of reaction mixture (lower). HPLC mobile phase: 5% Acetonitrile in water (both 0.1% TFA) for 3 min then to 90% acetonitrile in water over 35 min.



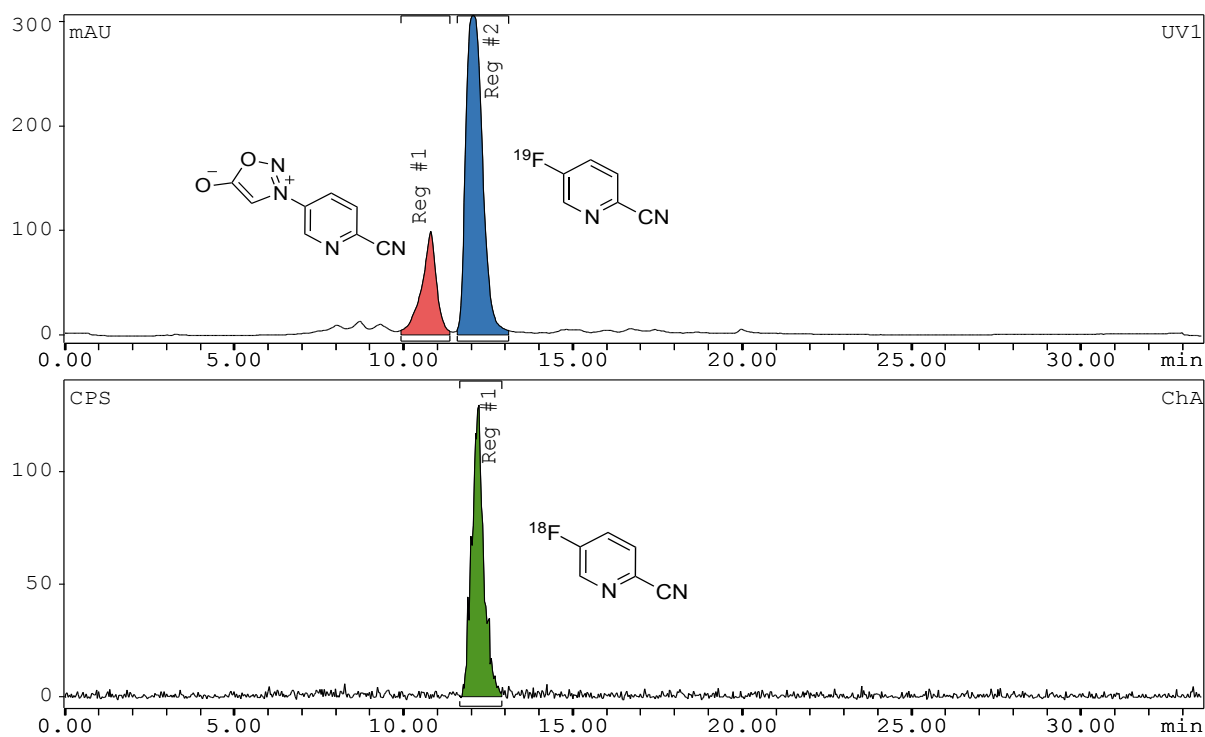
Run	1	2	3	mean	Standard deviation
Radio TLC yield (%)	46	45	45	45	1



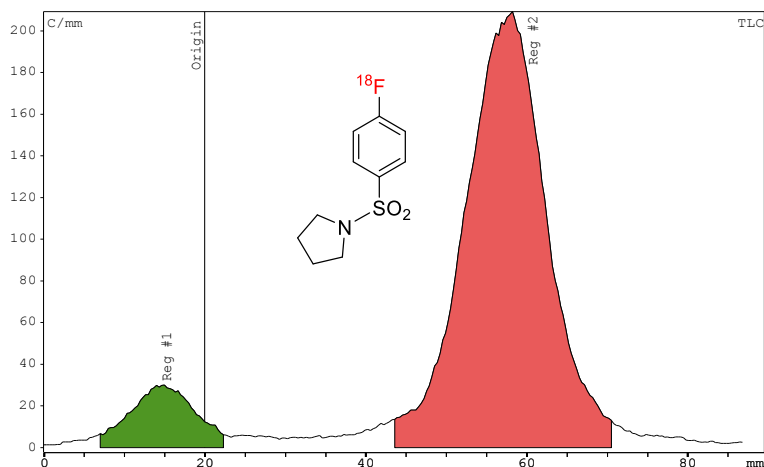
**Figure S16. Radiosynthesis and characterization of methyl-3-[<sup>18</sup>F]-fluorobenzofuran-2-carboxylate 16a.** Example of integrated radio-TLC scan (upper). Radio-HPLC with 254 nm UV trace of <sup>19</sup>F reference standard (middle) and radioactivity trace of reaction mixture (lower). HPLC mobile phase: 5% Acetonitrile in water (both 0.1% TFA) for 3 min then to 90% acetonitrile in water over 35 min.



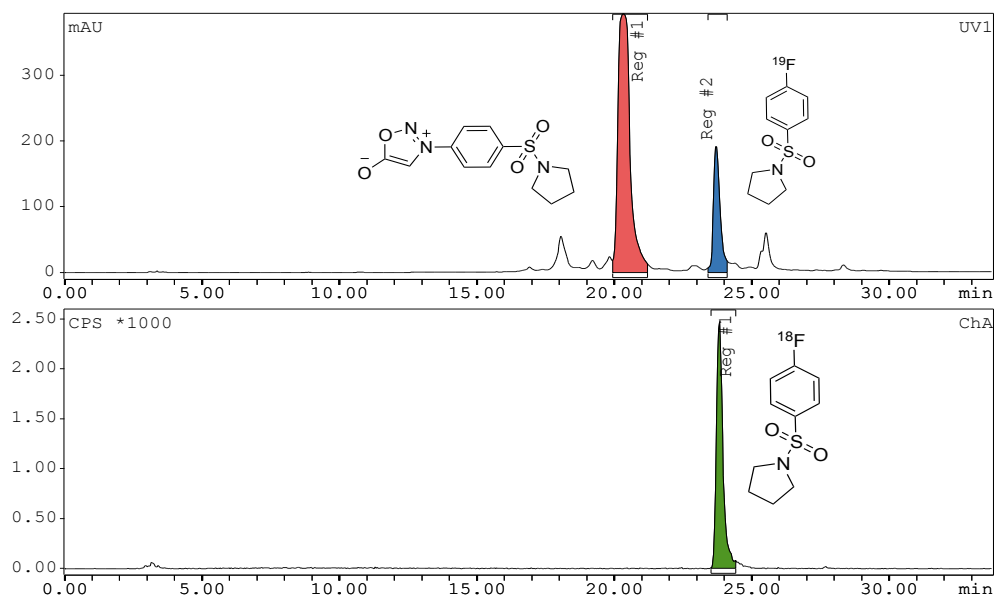
Run	1	2	3	mean	Standard deviation
Radio TLC yield (%)	80	82	80	80	1



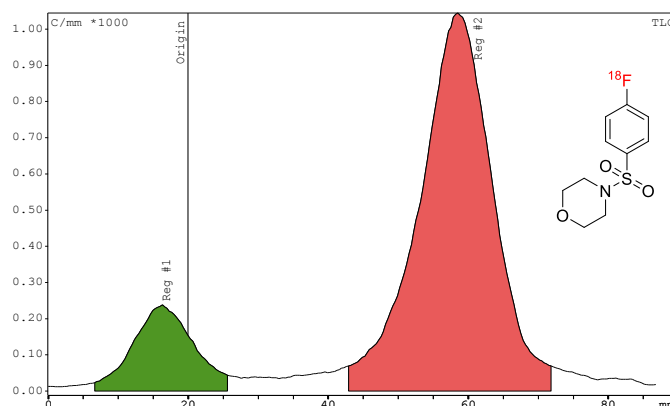
**Figure S17. Radiosynthesis and characterization of 5-[<sup>18</sup>F]fluoro-picolinonitrile 17a.** Example of integrated radio-TLC scan (upper). Radio-HPLC with 254 nm UV trace of <sup>19</sup>F reference standard (middle) and radioactivity trace of reaction mixture (lower). HPLC mobile phase: 5% Acetonitrile in water (both 0.1% TFA) for 3 min then to 90% acetonitrile in water over 35 min.



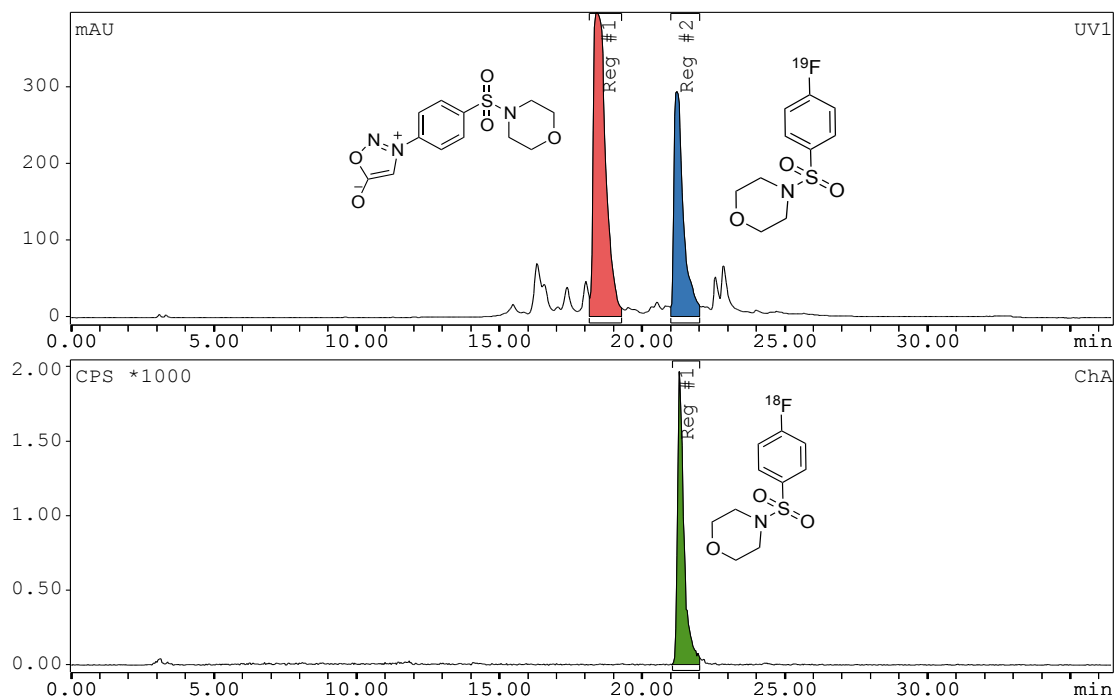
Run	1	2	3	mean	Standard deviation
Radio TLC yield (%)	85	80	89	85	4



**Figure S18. Radiosynthesis and characterization of 1-(4-[<sup>18</sup>F]fluorophenyl)sulfonylpyrrolidine 18a.** Example of integrated radio-TLC scan (upper). Radio-HPLC with 254 nm UV trace of <sup>19</sup>F reference standard (middle) and radioactivity trace of reaction mixture (lower). HPLC mobile phase: 5% Acetonitrile in water (both 0.1% TFA) for 3 min then to 90% acetonitrile in water over 30 min.

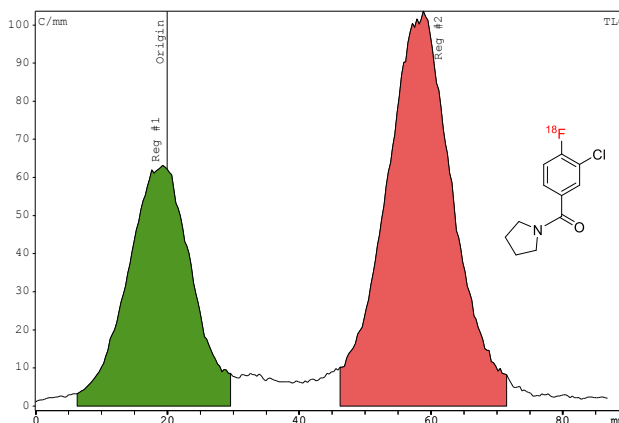


Run	1	2	3	mean	Standard deviation
Radio TLC yield (%)	64	82	84	77	9

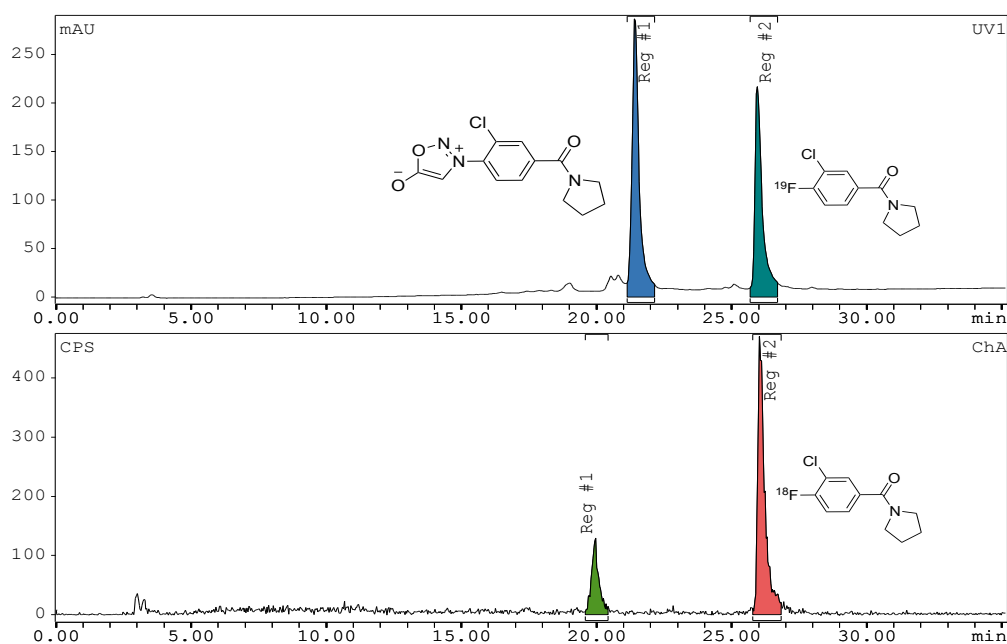


**Figure S19. Radiosynthesis and characterization of 4-(4-[<sup>18</sup>F]fluorophenyl) sulfonyl morpholine 19a.** Example of integrated radio-TLC scan (upper). Radio-HPLC with 254 nm UV trace of <sup>19</sup>F reference standard (middle) and radioactivity trace of reaction mixture (lower). HPLC mobile phase: 5% Acetonitrile in water (both 0.1% TFA) for 3 min then to 90% acetonitrile in water over 35 min.





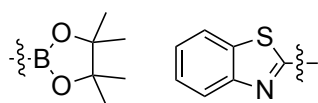
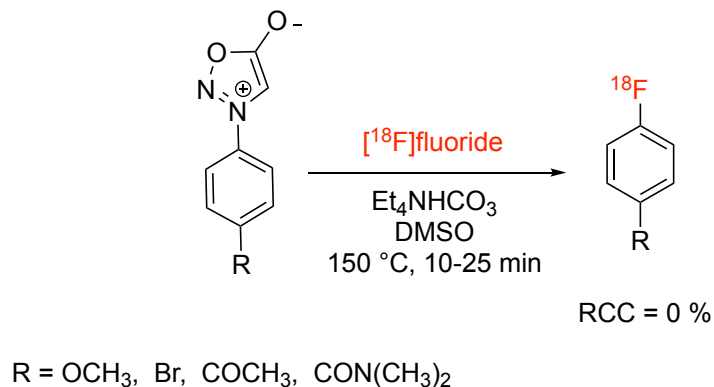
Run	1	2	3	mean	Standard deviation
Radio TLC yield (%)	63	60	59	61	2



\*Note: RCC calculated by multiplying the mean relative peak integration from radio-TLC with the radio-HPLC peak integration corresponding to  $[^{18}\text{F}]\mathbf{20a} = (61) \cdot (77/100) = 47\%$

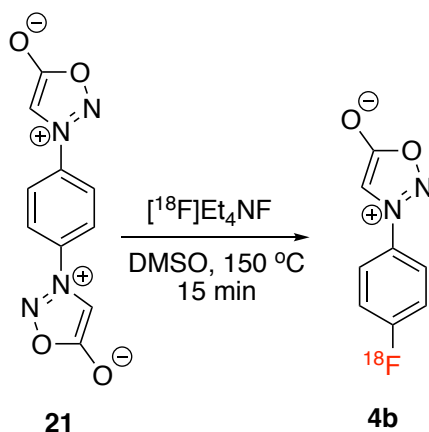
**Figure S20. Radiosynthesis and characterization of (3-chloro-4- $[^{18}\text{F}]$ fluorophenyl) (pyrrolidin-1-yl)methanone  $\mathbf{20a}$ .** Example of integrated radio-TLC scan (upper). Radio-HPLC with 254 nm UV trace of  $^{19}\text{F}$  reference standard (middle) and radioactivity trace of reaction mixture (lower). HPLC mobile phase: 5% Acetonitrile in water (both 0.1% TFA) for 3 min then to 90% acetonitrile in water over 30 min.

## 4.5 Unactivated aryl sydnones



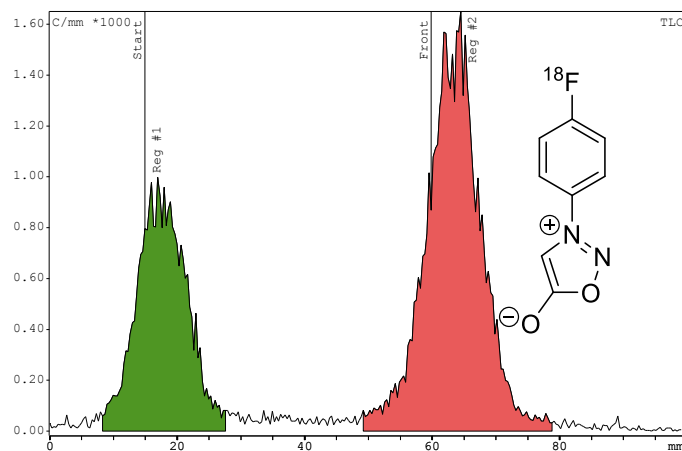
**Scheme S1. Unactivated aryl sydnones.** A series of electron rich aryl sydnones were subjected to the reaction conditions but failed to give detectable [<sup>18</sup>F]fluorinated products.

## 4.6 Optimization and Preparation of 4-[<sup>18</sup>F]fluorophenyl sydnone **4b**

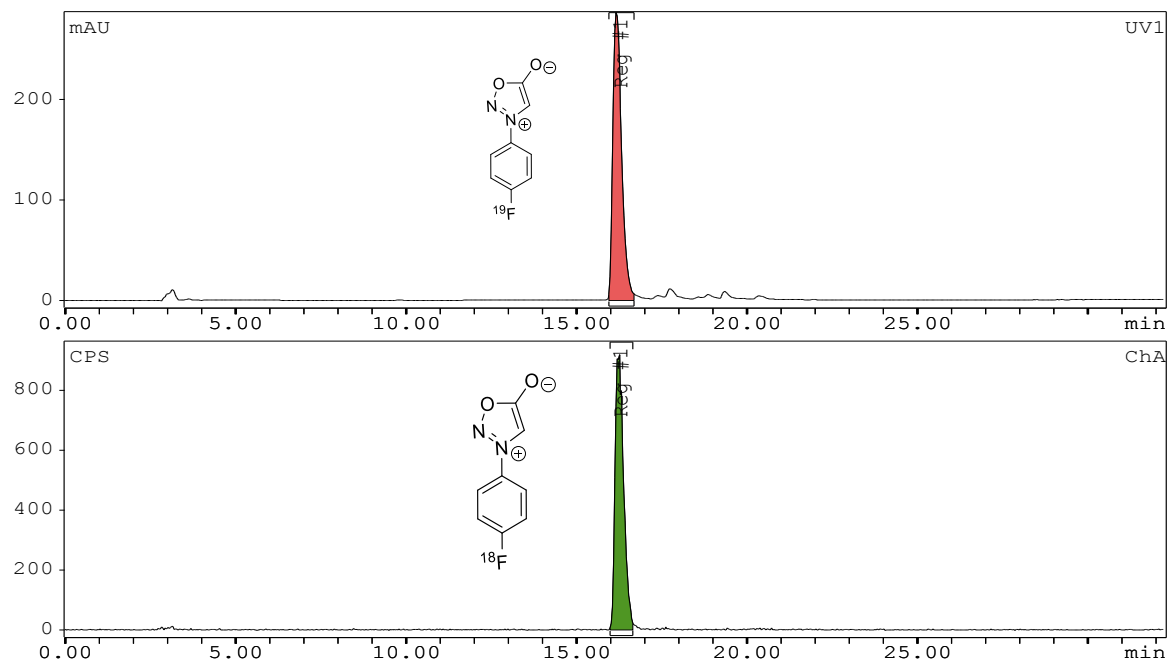


**4-[<sup>18</sup>F]fluorophenyl sydnone (**4b**):** To anhydrous [<sup>18</sup>F]Et<sub>4</sub>NF (15-45 mCi), prepared using an ELIXYS synthesis module, was added phenyl bis-sydnone **21** (4-5 mg) in 0.5 mL of DMSO. The contents were stirred at 150 °C for 15 min. The reaction mixture was cooled to room temperature and diluted with 4 mL water before purification via semi-preparative HPLC (5% Acetonitrile in

water (both 0.1% TFA) 0-5 min then to 50% acetonitrile in water over 40 min). The HPLC fraction was collected (retention time, 21 min) in 30 mL of water and passed through tC18 Sep-Pak, which was preactivated by sequential washing of ethanol (5 mL) and water (10 mL). The product was eluted with diethyl ether (2 mL) or acetonitrile (1.5 mL). The product identity and purity were determined by radio-HPLC as described previously. Non-decay-corrected radiochemical yields were calculated as the percentage of radioactive product (isolated after HPLC purification) from the amount of activity trapped on QMA cartridge at the start of synthesis.

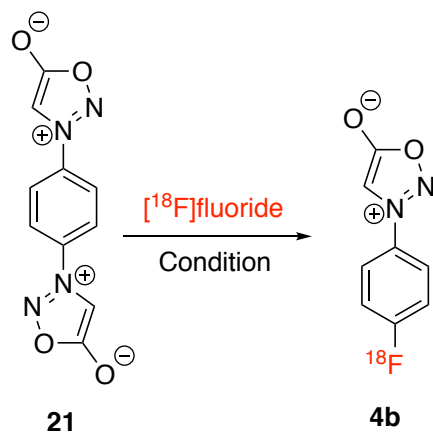


Run	1	2	3	4	5	6	mean	Standard Deviation
Radio TLC yield (%)	61	63	53	60	58	52	58	4



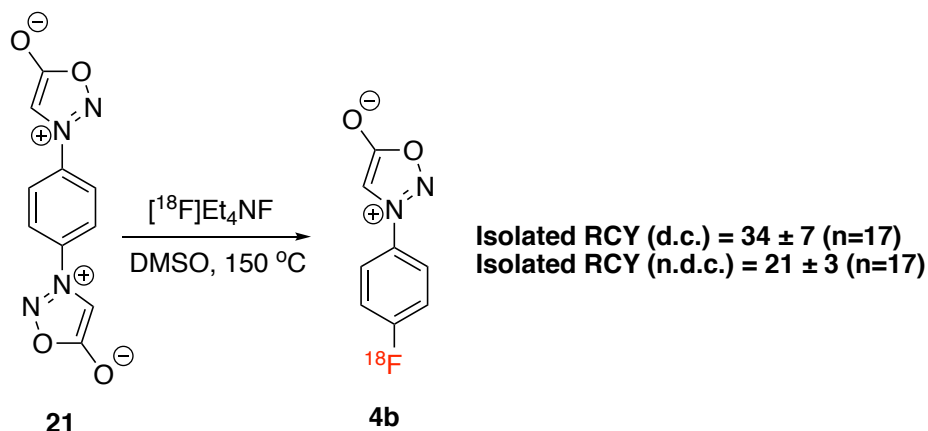
**Figure S21. Radiosynthesis and characterization of 4- $^{18}\text{F}$ fluorophenyl sydnone 4b.** Example of integrated radio-TLC scan (upper). Radio-HPLC with 254 nm UV trace of  $^{19}\text{F}$  reference standard (middle) and radioactivity trace of purified 4- $^{18}\text{F}$ fluorophenyl sydnone (lower). HPLC mobile phase: 10% Acetonitrile in water (both 0.1% TFA) to 90% acetonitrile in water over 30 min.

**Table. S3. Screen of different bases for optimized radiofluorination conditions.**



Entry	Qty. Bissyd/ DMSO (mL)	Base (Qty) (solvent system)	Temp(°C)/ Time(min)	n.d.c. RCY [%]
1.	<b>7.2 mg/0.8mL</b>	<b>NEt<sub>4</sub>HCO<sub>3</sub> (10 mg) (9:1 ACN:H<sub>2</sub>O)</b>	<b>150°C/15</b>	<b>17</b>
2.	7.2 mg/0.8 mL	NEt <sub>4</sub> HCO <sub>3</sub> (11 mg) (9:1 ACN:H <sub>2</sub> O)	130°C/15	9
3.	6.5 mg/0.8 mL	K <sub>2</sub> CO <sub>3</sub> /K222 (1.2 mg/11 mg) (7:3 ACN: H <sub>2</sub> O)	150°C/10	15
4.	4 mg/ 0.8 mL	K <sub>2</sub> CO <sub>3</sub> /K222 (1.8 mg/12 mg) (7:3 ACN: H <sub>2</sub> O)	150 °C/15	11.4
5.	5.2 mg/ 0.8mL	Aqu.NBu <sub>4</sub> HCO <sub>3</sub> (0.075M) 160 μL in 7:3 ACN:H <sub>2</sub> O)	150 °C/15	9.5
6.	8 mg/ 0.6 mL	NBu <sub>4</sub> OH (6.5 uL) (1:1 ACN:H <sub>2</sub> O) 1mL	150 °C/20	2.8

**Table. S4. Synthesis of 4-[<sup>18</sup>F]fluorophenyl sydnone 4b using optimized conditions.**



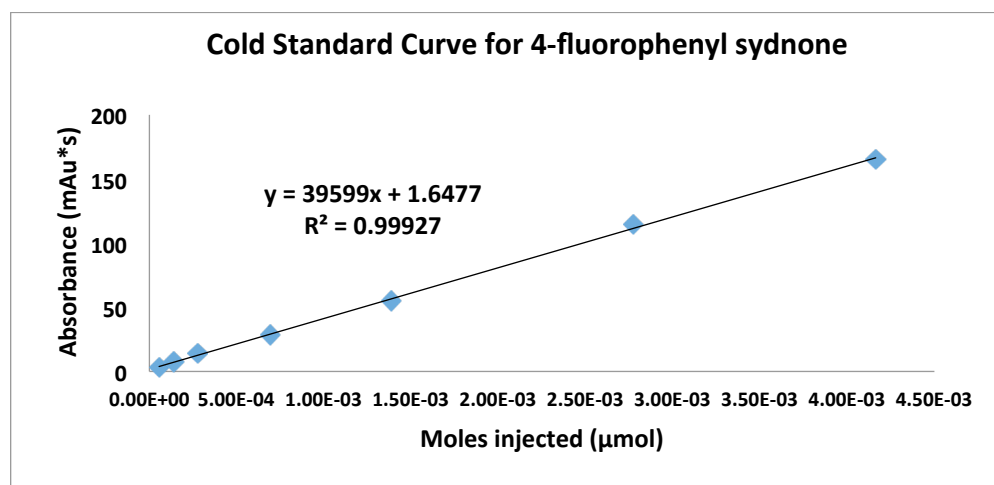
Entry	Qty. Bissyd/ DMSO (mL)	Base (Qty)	Temp(°C)/Time(min)	d.c. RCY [%]	n.d.c RCY [%]
1.	4.2 mg/0.8 mL	NEt <sub>4</sub> HCO <sub>3</sub> (10 mg) (9:1 ACN:H <sub>2</sub> O)	150°C/15	48	26.7
2.	7mg/0.6 mL	NEt <sub>4</sub> HCO <sub>3</sub> (12 mg) (8:2 ACN:H <sub>2</sub> O)	150 °C/10	32	17
3.	7 mg/0.6 mL	NEt <sub>4</sub> HCO <sub>3</sub> (11 mg) (8:2 ACN:H <sub>2</sub> O)	150 °C/15	37	20.1
4.	7 mg/0.45 mL	NEt <sub>4</sub> HCO <sub>3</sub> (11 mg) (8:2 ACN:H <sub>2</sub> O)	150°C/15	35	21.3
5.	6 mg/ 0.6mL	NEt <sub>4</sub> HCO <sub>3</sub> (10 mg) (8:2) (ACN:H <sub>2</sub> O)	150°C/15	22.0	18.5
6.	5 mg/0. 5mL	NEt <sub>4</sub> HCO <sub>3</sub> (11 mg) (8:2) (ACN:H <sub>2</sub> O)	150°C/15	32	22
7.	5 mg/ 0.45mL	NEt <sub>4</sub> HCO <sub>3</sub> (10 mg) (8:2 ACN:H <sub>2</sub> O)	150°C/15	38.4	19.7
8.	4.7 mg/ 0.45mL	NEt <sub>4</sub> HCO <sub>3</sub> (11 mg) (8:2 ACN:H <sub>2</sub> O)	150°C/15	29	16.4
9.	4.5 mg/ 0.45mL	NEt <sub>4</sub> HCO <sub>3</sub> (11 mg) (8:2) (ACN:H <sub>2</sub> O)	150°C/15	28	22.2
10.	4.5mg/0.45mL	NEt <sub>4</sub> HCO <sub>3</sub> (10.4 mg) (8:2) (ACN:H <sub>2</sub> O)	150°C/15	42	23.1
11.	4.0 mg/0.5mL	NEt <sub>4</sub> HCO <sub>3</sub> (10.5 mg) (8:2) (ACN:H <sub>2</sub> O)	150°C/8	38	21
12.	3.5 mg/ 0.5mL	NEt <sub>4</sub> HCO <sub>3</sub> (10.02 mg) (8:2) (ACN:H <sub>2</sub> O)	150°C/12	25	16
13.	3.6 mg/ 0.5mL	NEt <sub>4</sub> HCO <sub>3</sub> (10.5 mg) (8:2) (ACN:H <sub>2</sub> O)	150°C/12	37	26
14.	2 mg/ 0.45mL	NEt <sub>4</sub> HCO <sub>3</sub> (10.5 mg) (8:2) (ACN:H <sub>2</sub> O)	150°C/15	26	17.1

15.	1.0 mg/0.45mL	NEt <sub>4</sub> HCO <sub>3</sub> (10.4 mg) (8:2) (ACN:H <sub>2</sub> O)	150°C/15	44	21.1
16.	1.0 mg/0.5mL	NEt <sub>4</sub> HCO <sub>3</sub> (9.8 mg) (8:2) (ACN:H <sub>2</sub> O)	150°C/12	34	18.4
17.	1.0 mg/0.5 mL	NEt <sub>4</sub> HCO <sub>3</sub> (9.8 mg) (8:2) (ACN:H <sub>2</sub> O)	150 °C/15	32	22

#### 4.7 Molar radioactivity of 4-[<sup>18</sup>F]fluorophenyl sydnone **4b**

Molar radioactivity of 4-[<sup>18</sup>F]fluorophenyl sydnone **4b** was determined by the following method. A sample of known volume of purified **4b** was injected into the analytical HPLC. The absorbance (mAu\*s) of UV peak corresponding to the radiofluorinated product **4b** was identified and measured. The UV area was used to calculate the concentration of the product based on linear regression analysis of 4-fluorophenyl sydnone (**Ref-4b**). A calibration curve was generated from standard solutions (5 µg/mL), by measuring the UV absorbance at different concentrations (performed in duplicate). The activity injected (Ci/mL) divided by concentration of the product measured from linear regression (µmol/mL) afforded the molar specific activity in Ci/µmol or GBq/ µmol.

**Table. S5. Measurement of specific activity for isolated 4-[<sup>18</sup>F]fluorophenyl sydnone **4b**.**



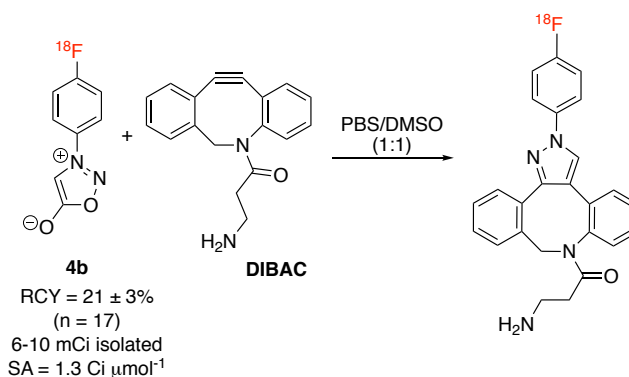
Volume Injected (µL)	Concentration (µg/mL)	Mass injected (µg)	Moles injected (µmol)	Absorbance (mAu*s)
2	5	0.01	5.55E-05	3
5	5	0.025	1.39E-04	7.5
10	5	0.05	2.78E-04	13.87
25	5	0.125	6.94E-04	28.54
50	5	0.25	1.39E-03	54.85

100	5	0.5	2.78E-03	114.56
150	5	0.75	4.16E-03	165.12

Value at time of injection					
Volume Injected (μL)	Activity Injected (μCi)	Absorbance (mAu*s)	Moles from Curve (μmol)	Molar radioactivity (Ci/μmol)	Molar radioactivity (GBq/μmol)
100	400	11.9	2.59E-04	1.54E+00	57.16
50	450	18.4	4.23E-04	1.06E+00	39.36
50	350	14	3.12E-04	1.12E+00	41.52

## 5. Cycloaddition reaction of DIBAC and 4-[<sup>18</sup>F]fluorophenyl sydnone **4b**

Table. S6. Optimization of cycloaddition reaction conditions.

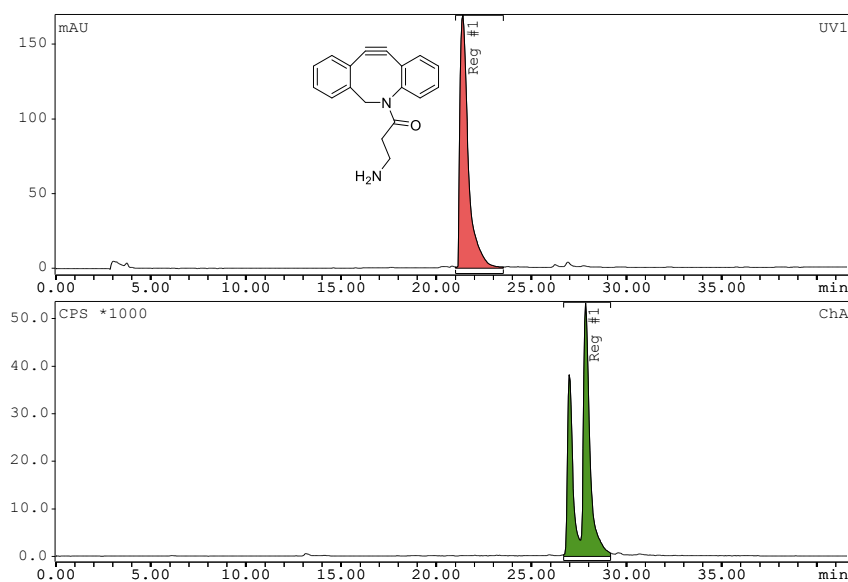


**DIBAC** in PBS:DMSO (1:1) (200 μL) was added to purified 4-[<sup>18</sup>F]fluorophenyl sydnone **4b** (2 mCi – 5 mCi) and stirred at various times/temperatures. The crude reaction mixture was injected into analytical HPLC to confirm RCC of pyrazole cycloadduct. The identity of the radiolabeled product was confirmed by coinjection with the <sup>19</sup>F-reference standard.



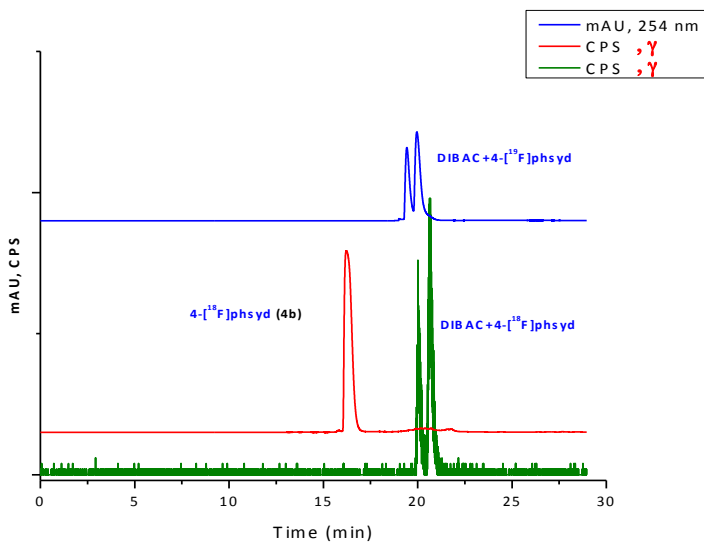
Entry	Solvent/ DIBAC (Conc.)	Temp (°C)	Time (min)	RCC (%) <sup>a</sup>
1	DMSO:PBS (1:1)/ 1mM	37	5	25
2	DMSO:PBS (1:1)/ 1mM	37	15	75
3	DMSO:PBS (1:1)/ 1mM	37	30	98
4	DMSO:PBS (1:1)/ 1mM	40	30	98.1
5	DMSO:PBS (1:1)/ 1mM	50	5	77
<b>6</b>	<b>DMSO:PBS (1:1)/ 1mM</b>	<b>50</b>	<b>8</b>	<b>99.5</b>
7	DMSO:PBS (1:9)/ 1mM	50	2	58
8	DMSO:PBS (1:9)/ 1mM	50	10	88
<b>9</b>	<b>DMSO:PBS (1:1)/ 2mM</b>	<b>37</b>	<b>15</b>	<b>98.5</b>
10	DMSO:PBS (1:1)/ 2mM	37	25	98.5

<sup>a</sup> Yield is based on HPLC analysis



**Figure S22. Crude cycloaddition of 4-[<sup>18</sup>F]fluorosydnone 4b with DIBAC. Radio-HPLC with 254 nm UV trace of unreacted DIBAC (top) and radioactivity trace of cycloadduct product**

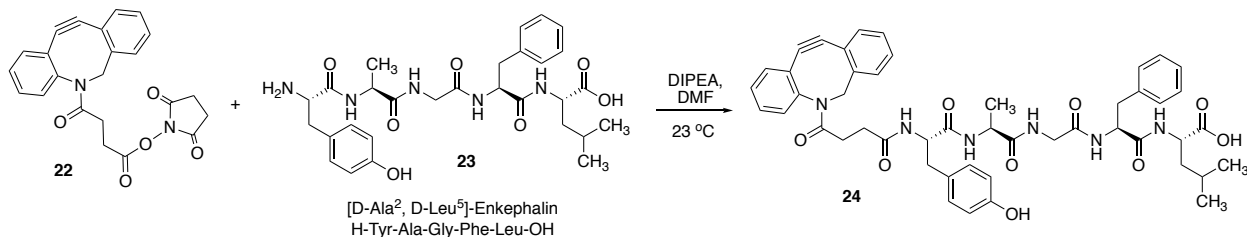
(lower). Complete conversion is confirmed as no residual peak for **4b** is detected in the radioactivity HPLC trace. HPLC mobile phase: 10% acetonitrile in water with 0.1% TFA to 70% over 40 min then to 95% acetonitrile at 45 min.



**Figure S23. HPLC traces for cycloaddition reaction between **4b** and DIBAC.** UV trace of purified pyrazole reference standard (blue). Radio-HPLC traces of starting material **4b** (red) overlaid with crude [3+2] cycloaddition product pyrazole (green). HPLC mobile phase: 10% acetonitrile in water with 0.1% TFA to 80% over 30 min.

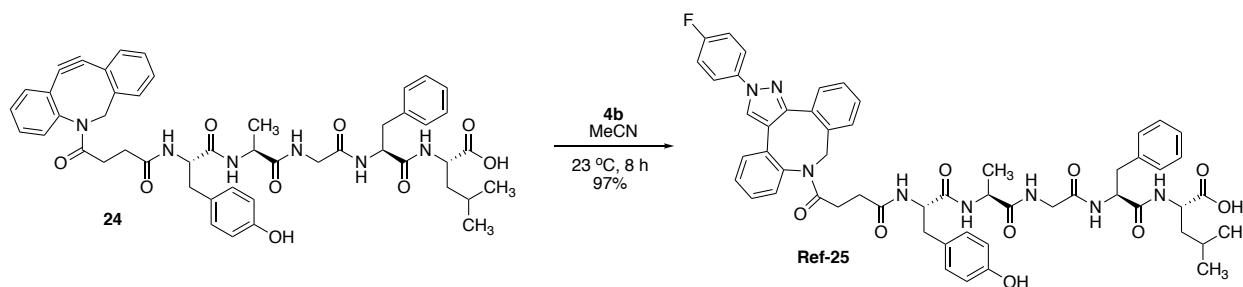
## 6. $^{18}\text{F}$ -labeling of neuropeptide [D-Ala<sup>2</sup>, D-Leu<sup>5</sup>]-Enkephalin **23**

### Synthesis of DIBAC-Peptide conjugate **24**:



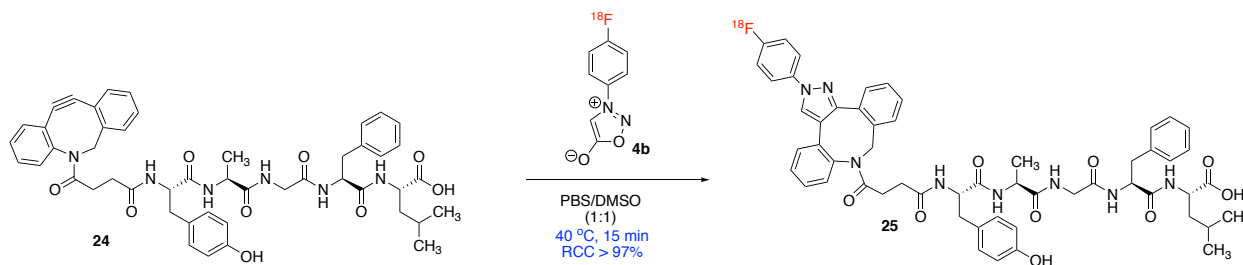
DIBAC-NHS ester **22** (5.3 mg, 13.16  $\mu\text{mol}$ ) was added to a solution of [D-Ala<sup>2</sup>, D-Leu<sup>5</sup>]-Enkephalin (H-Tyr-Ala-Gly-Phe-Leu-OH) **23** (5 mg, 8.77  $\mu\text{mol}$ ) and DIPEA (2.2  $\mu\text{L}$ , 13.16  $\mu\text{mol}$ ) in 0.4 mL of DMF. The reaction mixture was stirred at room temperature for 12 hrs. The crude mixture was purified on semi-preparative HPLC to produce DIBAC-peptide conjugate **24** in 61% yield as white solid. HRMS (ESI)  $m/z$  calcd for C<sub>48</sub>H<sub>53</sub>N<sub>6</sub>O<sub>9</sub> [M+H] 857.3874, found 857.3895.

### Synthesis of peptide reference standard Ref-25:



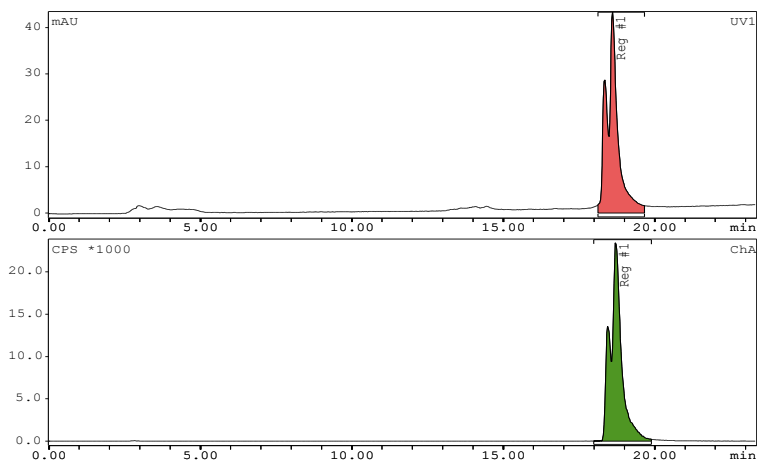
To a solution of DIBAC-peptide conjugate **24** (1.0 mg, 1.16  $\mu\text{mol}$ ) in acetonitrile (0.5 mL) was added sydnone **4b** (0.22 mg, 1.22  $\mu\text{mol}$ ). The reaction mixture was stirred at room temperature for 8 h. The crude mixture was purified on semi-preparative HPLC to produce **Ref-25** in 97 % yield. Mixture of two regioisomers were collected together. HRMS (ESI)  $m/z$  calcd for C<sub>55</sub>H<sub>56</sub>FN<sub>8</sub>O<sub>9</sub> [M-H] 991.4160, found 991.4124.

### Synthesis of [<sup>18</sup>F]-labeled [D-Ala<sup>2</sup>, D-Leu<sup>5</sup>]-Enkephalin **25**:

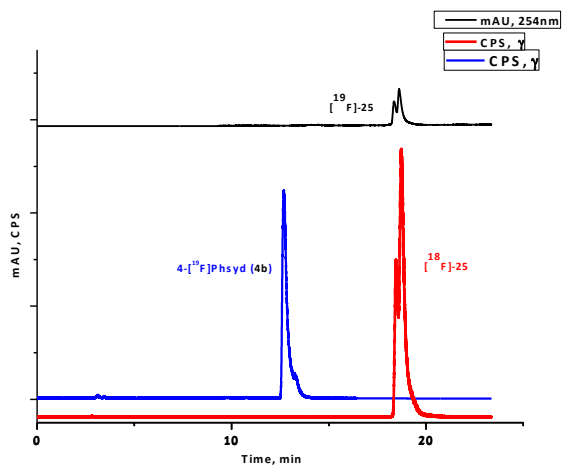


DIBAC-peptide conjugate **24** (1.5 mM) in PBS:DMSO (1:1) (300  $\mu\text{L}$ ) was added to purified 4-[<sup>18</sup>F]fluorophenyl sydnone **4b** (2 mCi – 5 mCi) and stirred at 40 °C for 15 min. The crude reaction mixture was injected into analytical HPLC to confirm >97% conversion to pyrazole **25**.

The identity of the radiolabeled product **25** was confirmed by co-injection with the  $^{19}\text{F}$ -reference standard.



**Figure S24. Purified  $^{18}\text{F}$ -labeled [D-Ala<sup>2</sup>, D-Leu<sup>5</sup>]-Enkephalin **25**.** Radio-HPLC with 254 nm UV trace of reference standard **Ref-25** (top) and radioactivity trace of cycloadduct product **25** (lower). Mixture of two regioisomers were collected together. HPLC mobile phase: 10% acetonitrile in water (both with 0.1% TFA) to 90% over 20 min then to 95% acetonitrile at 25 min.



**Figure S25. HPLC traces for cycloaddition reaction between **4b** and DIBAC-peptide conjugate **24**.** UV trace of purified **Ref-25** reference standard (black). Radio-HPLC trace of starting material **4b** (blue) overlaid with crude [3+2] cycloaddition product **25** (red). HPLC mobile phase: 10% acetonitrile in water (both with 0.1% TFA) to 90% over 20 min.

## 7. Full list of authors for references 7e, 8a and 29

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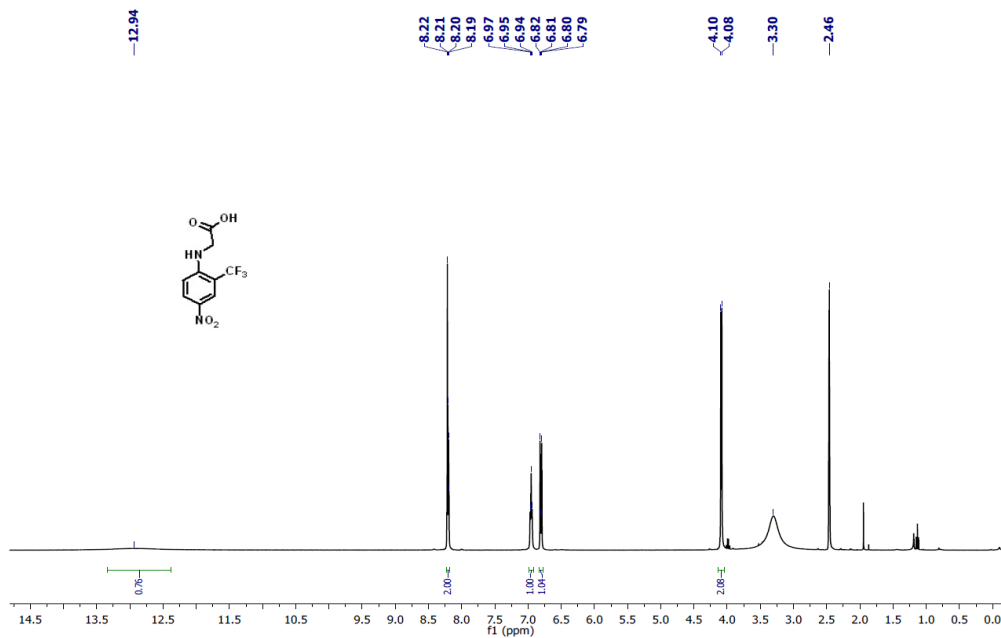
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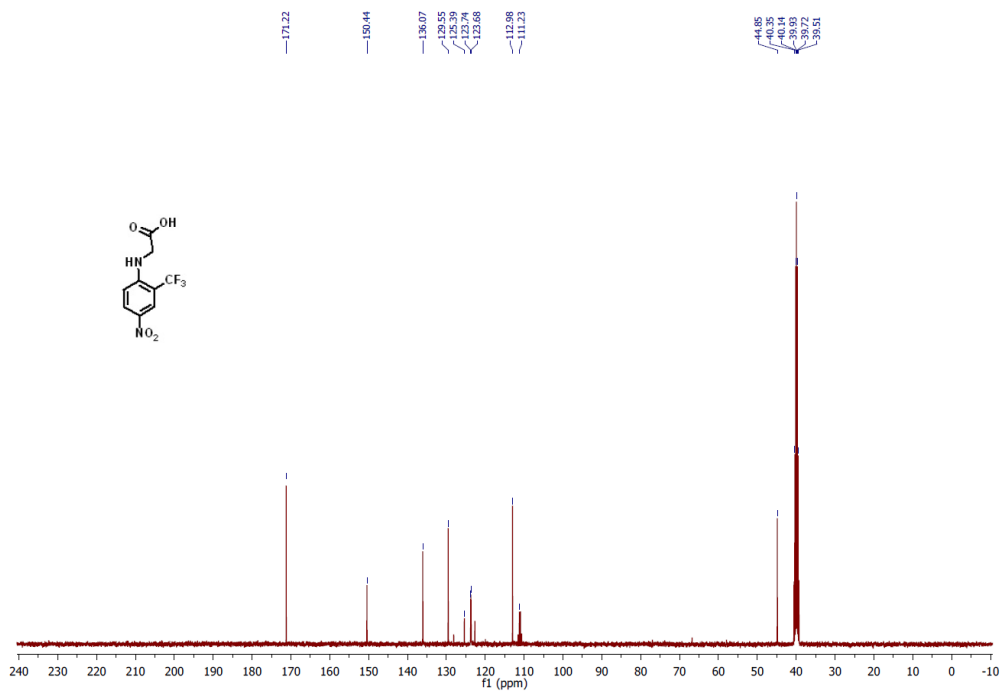
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## 9. NMR Spectra

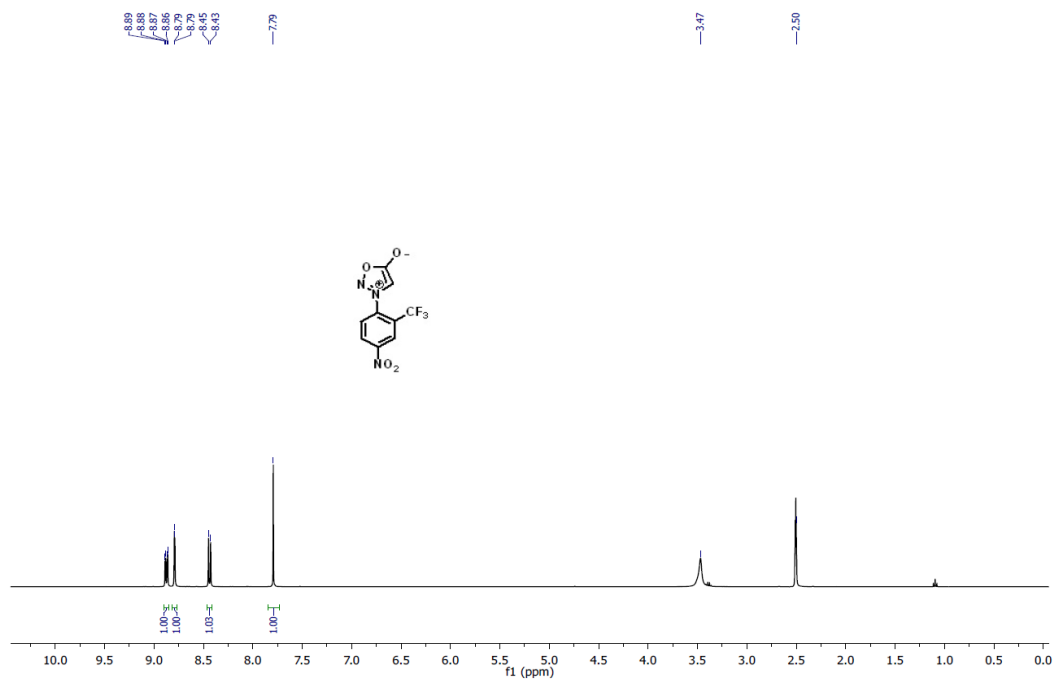
$^1\text{H}$  NMR for **Gly-5** (400 MHz,  $\text{DMSO-d}_6$ )



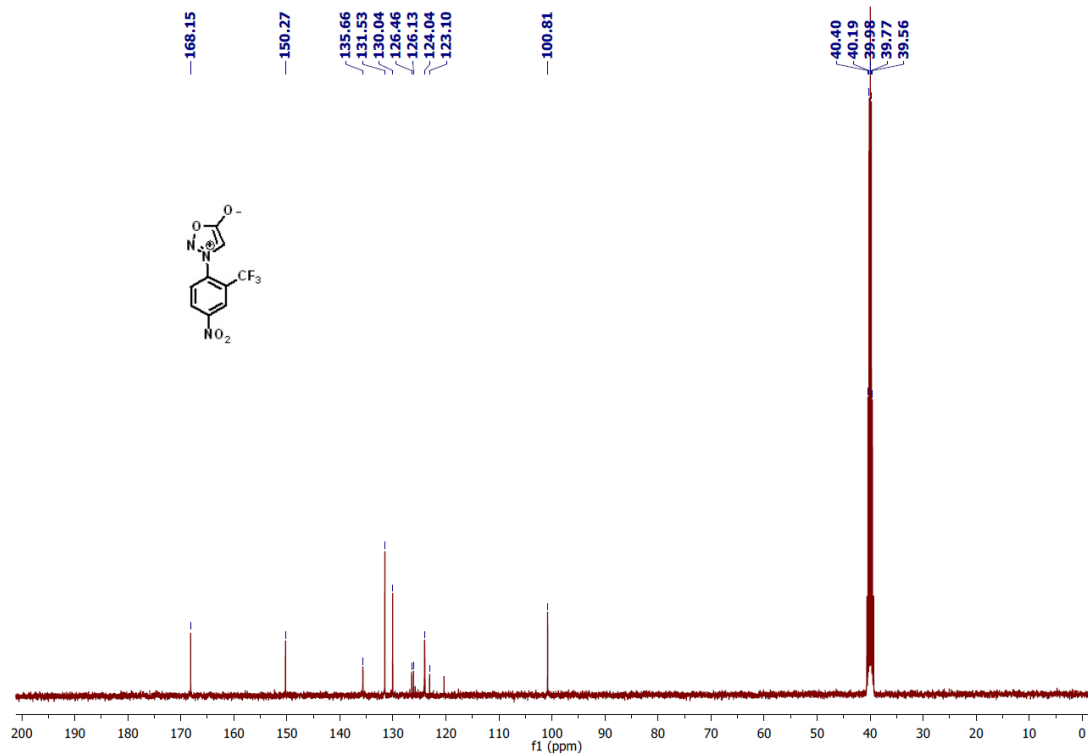
$^{13}\text{C}$  NMR for **Gly-5** (100 MHz,  $\text{DMSO-d}_6$ )



$^1\text{H}$  NMR for **5** (400 MHz, DMSO- $d_6$ )

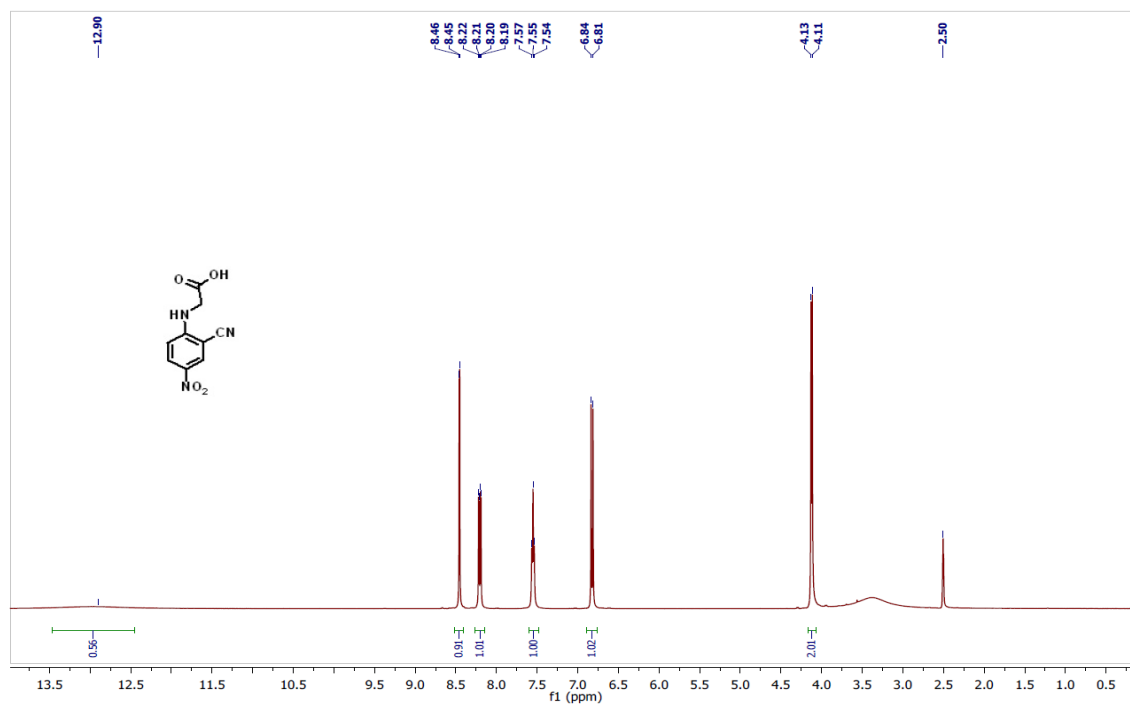


$^{13}\text{C}$  NMR for **5** (100 MHz, DMSO- $d_6$ )

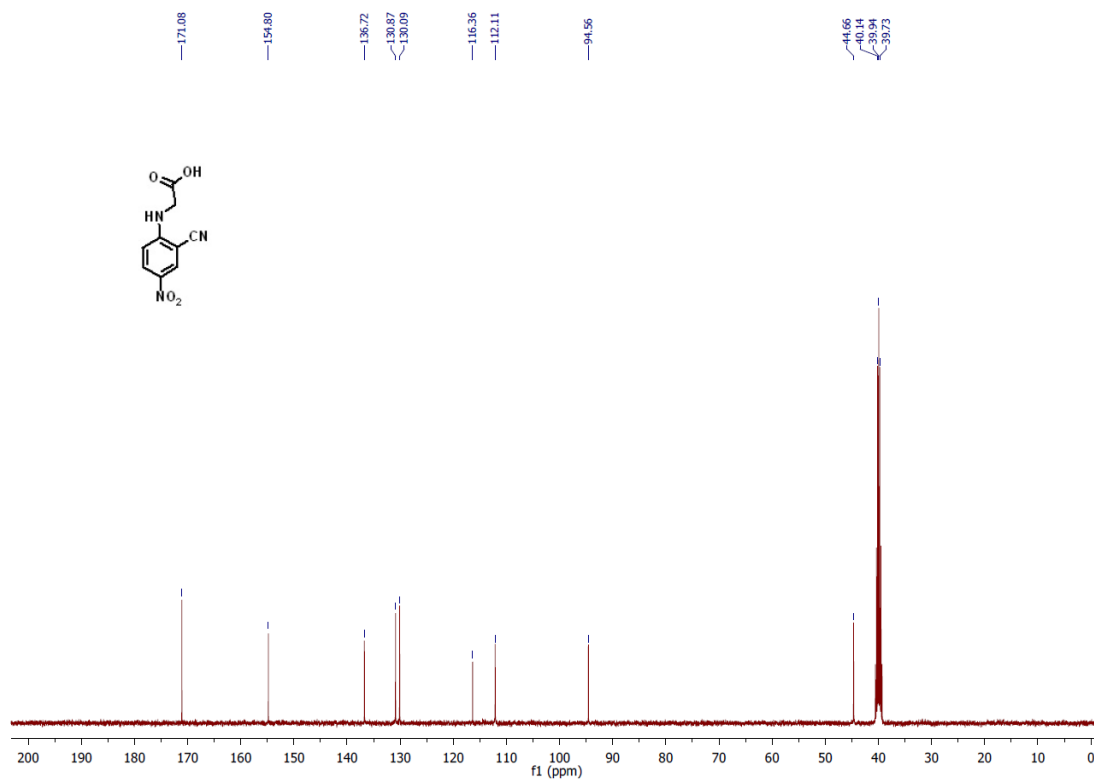




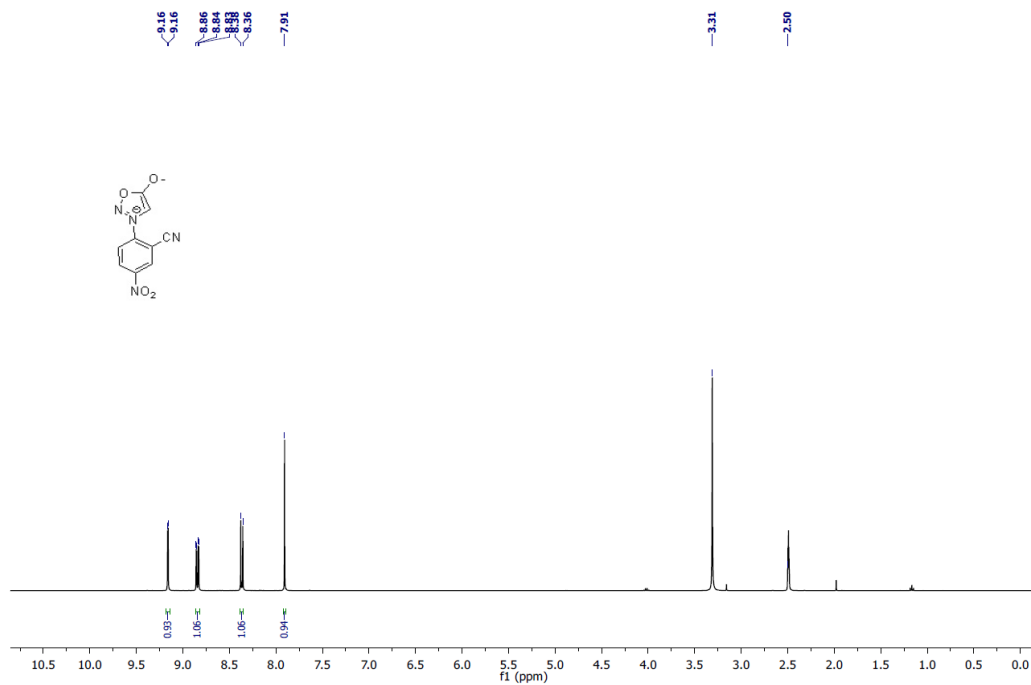
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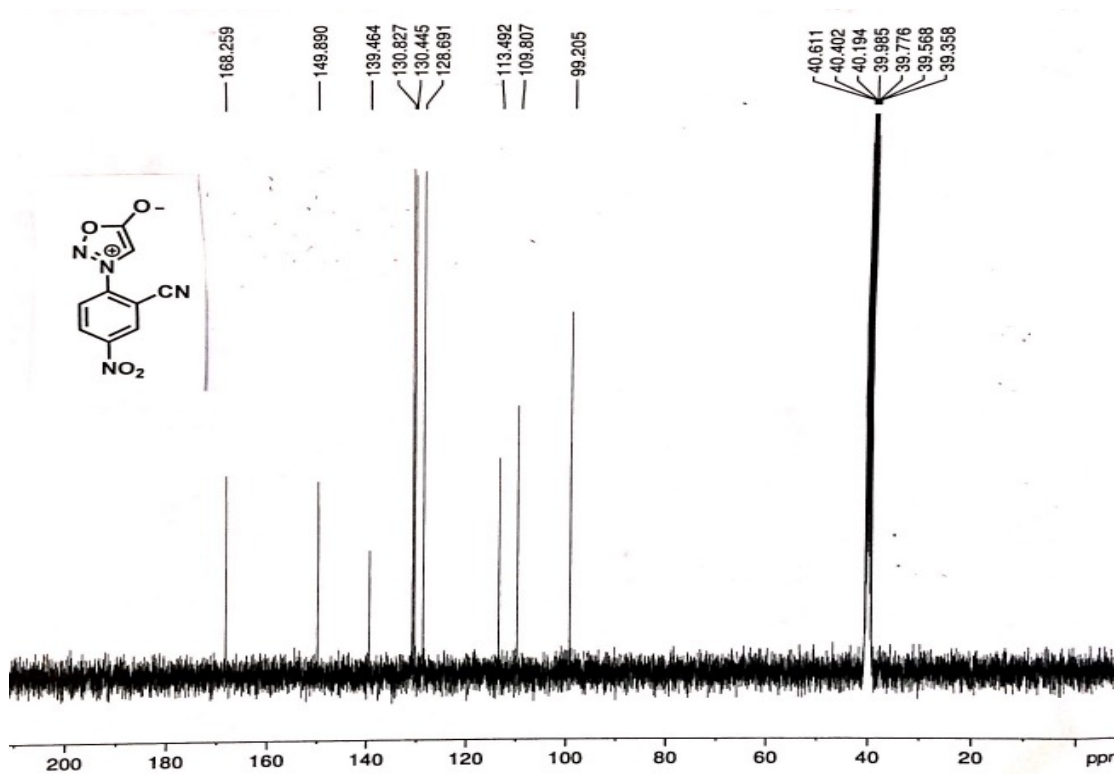
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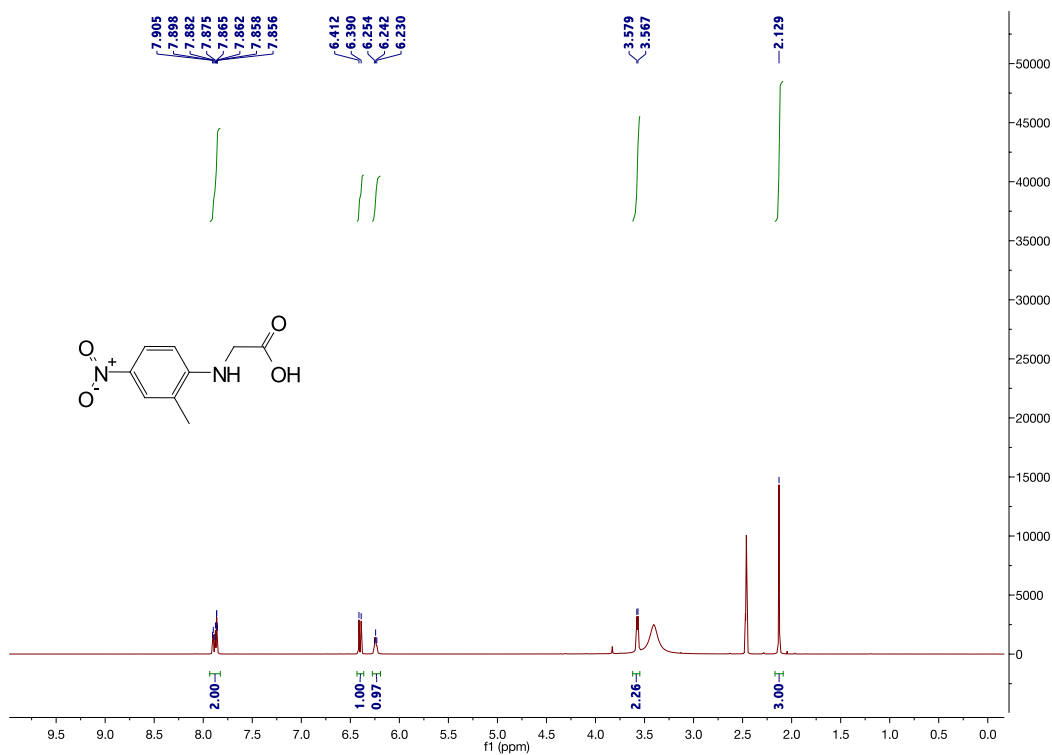
$^1\text{H}$  NMR for **6** (400 MHz, DMSO- $d_6$ )



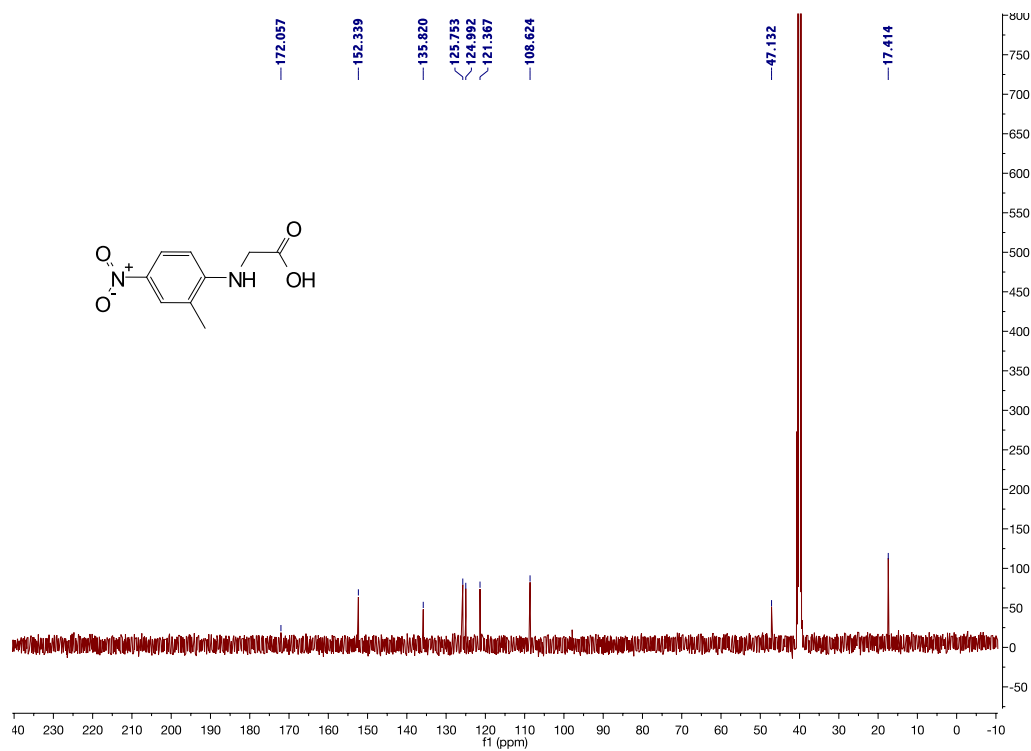
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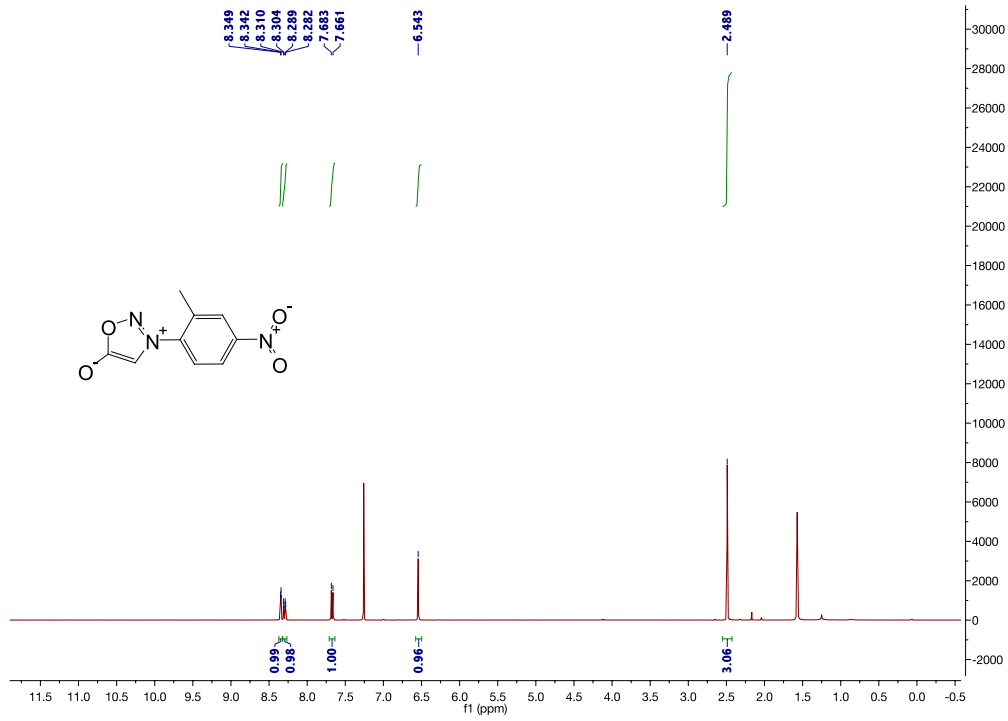
<sup>1</sup>H NMR for Gly-7 (400 MHz, DMSO-d<sub>6</sub>)



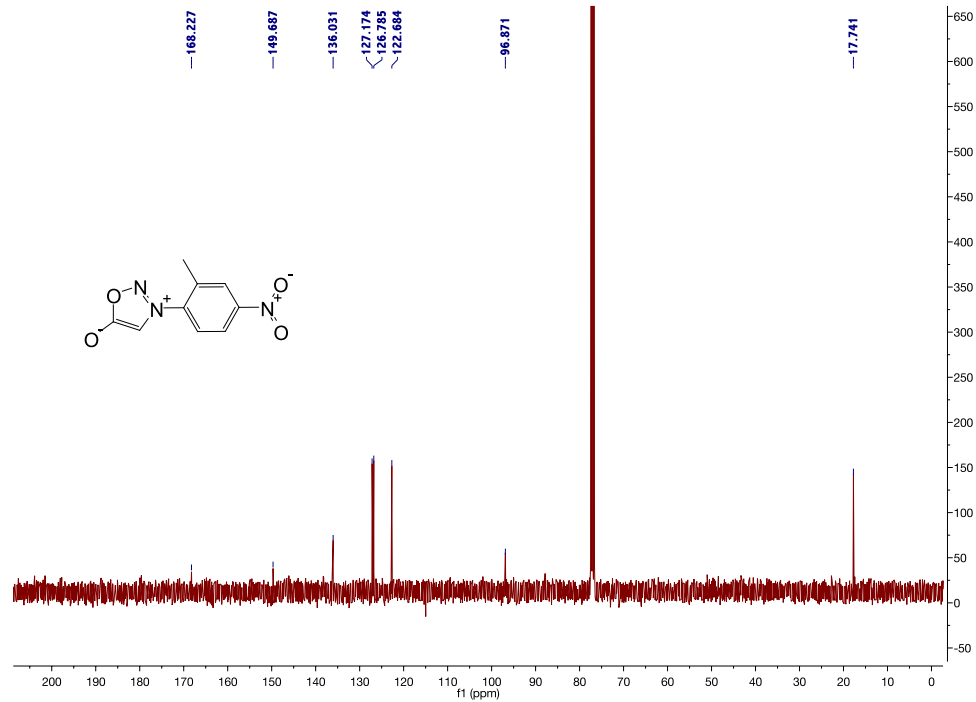
<sup>13</sup>C NMR for Gly-7 (100 MHz, DMSO-d<sub>6</sub>)



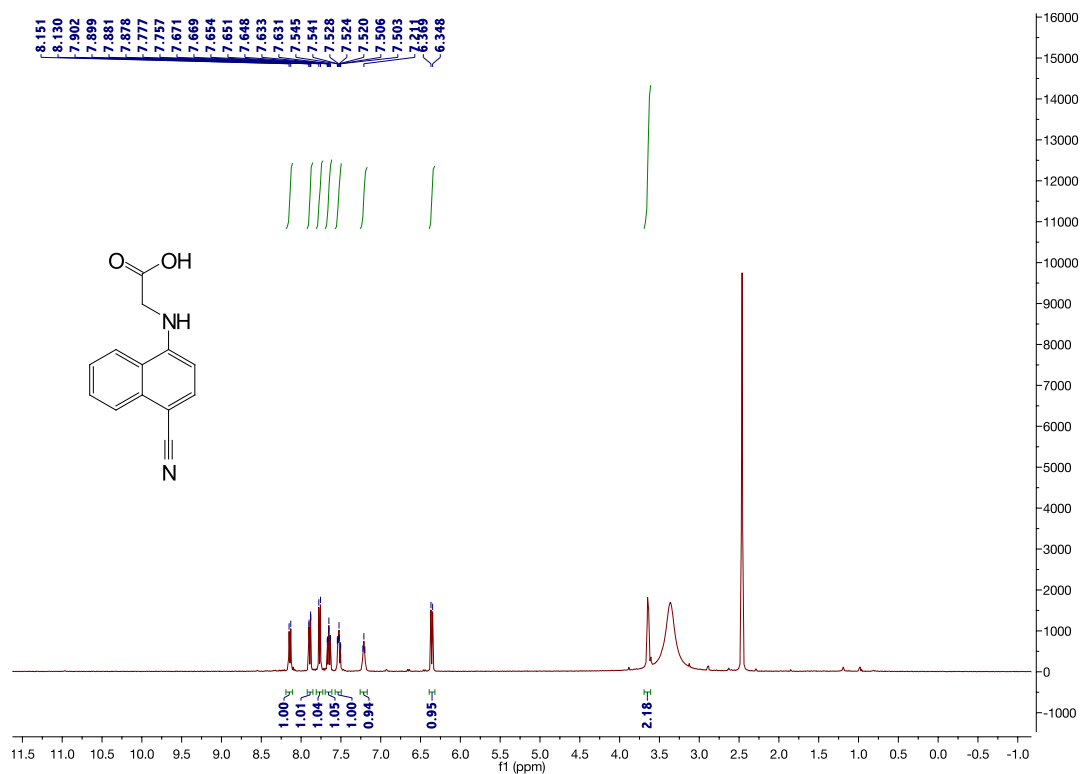
<sup>1</sup>H NMR for 7 (400 MHz, CDCl<sub>3</sub>)



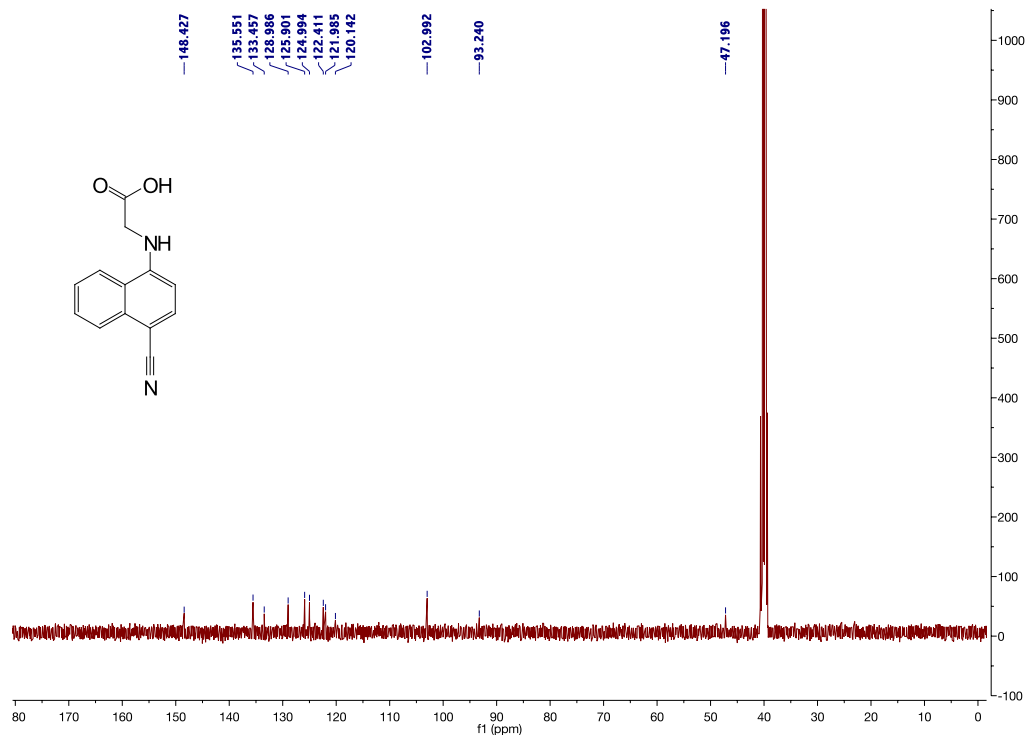
<sup>13</sup>C NMR for 7 (100 MHz, CDCl<sub>3</sub>)



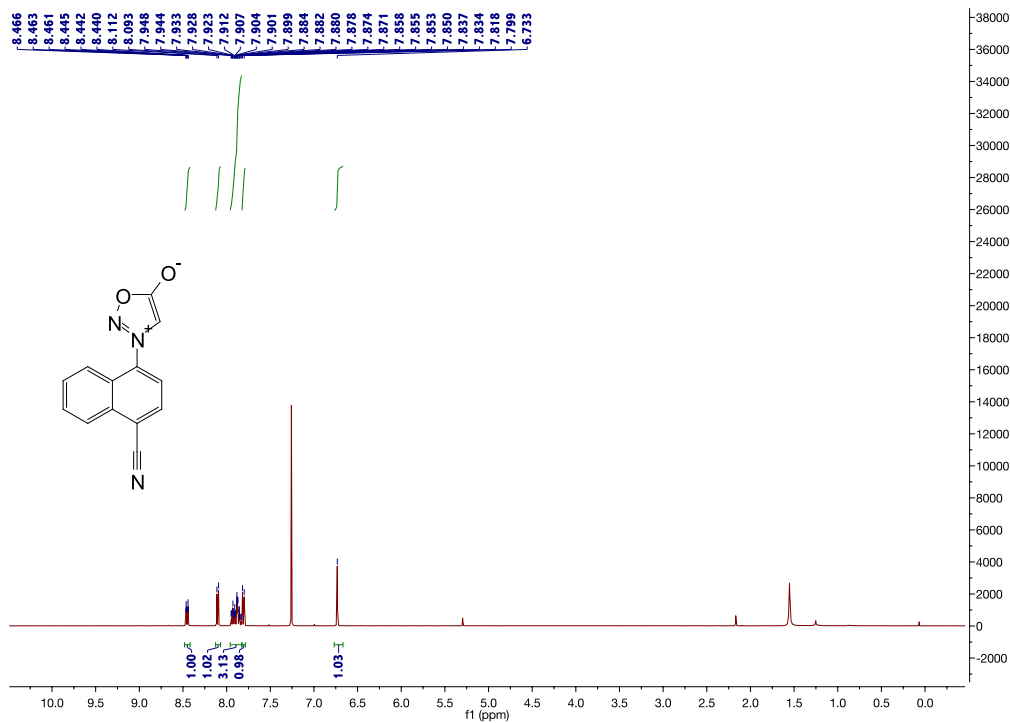
<sup>1</sup>H NMR for Gly-9 (400 MHz, DMSO-d<sub>6</sub>)



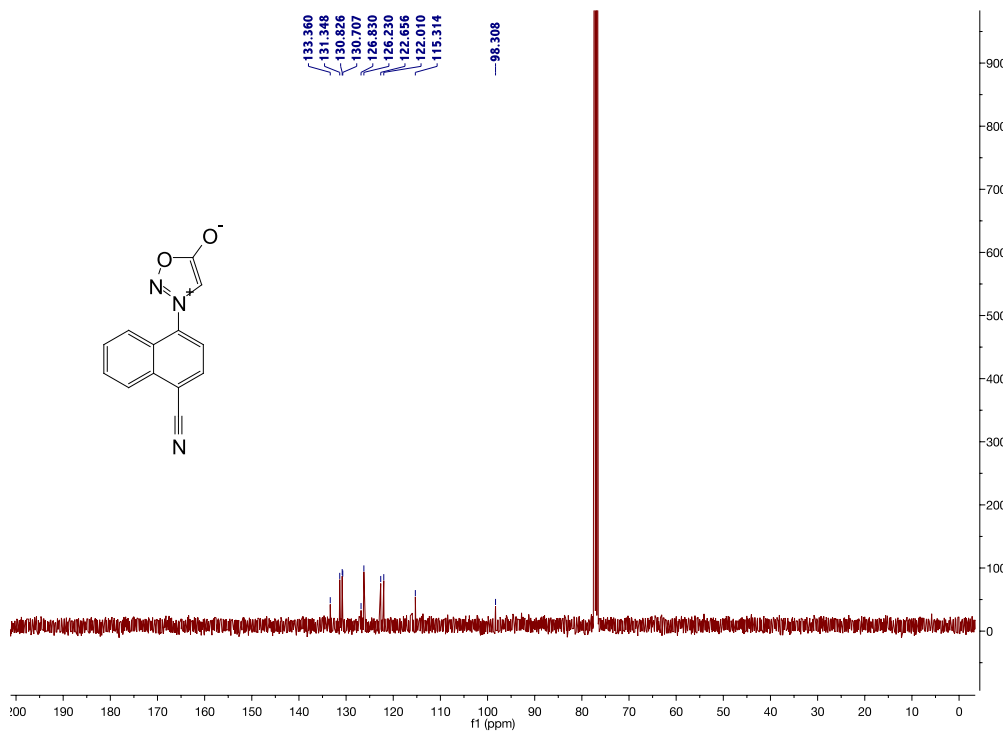
<sup>13</sup>C NMR for Gly-9 (100 MHz, DMSO-d<sub>6</sub>)



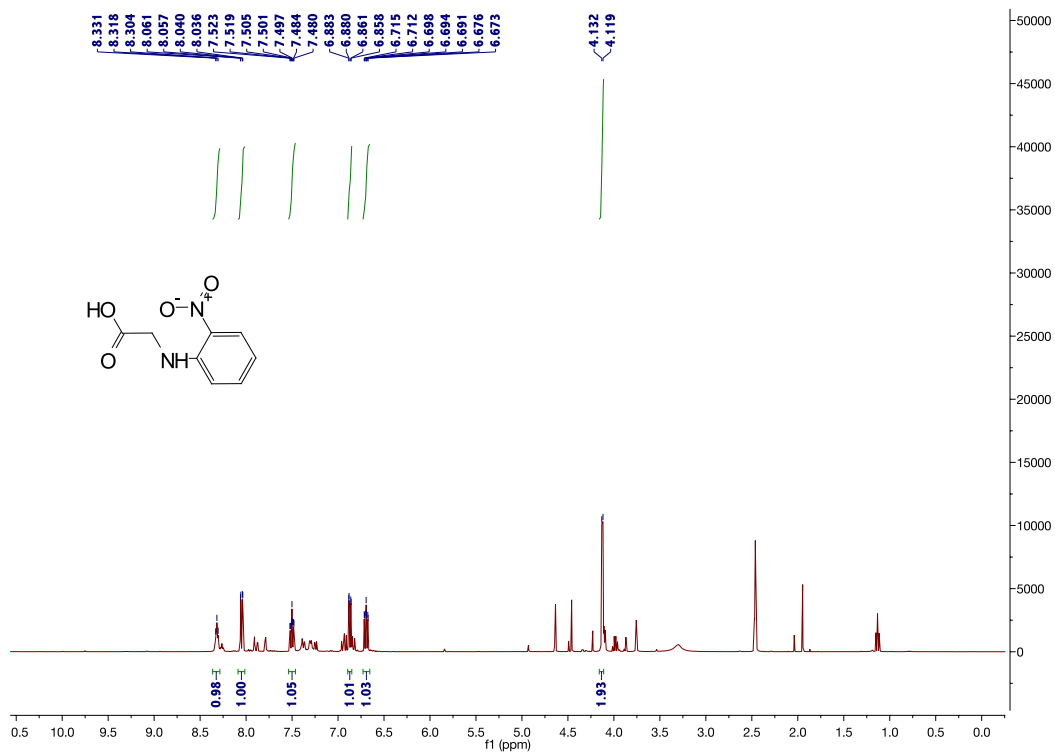
<sup>1</sup>H NMR for **9** (400 MHz, CDCl<sub>3</sub>)



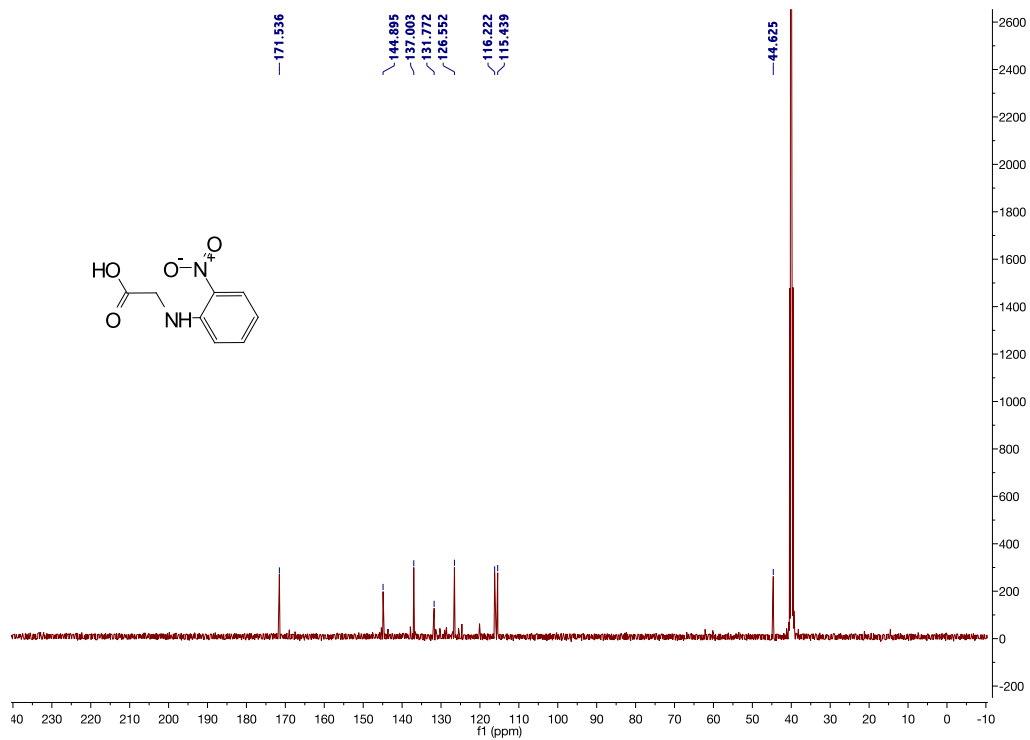
<sup>13</sup>C NMR for **9** (100 MHz, CDCl<sub>3</sub>)



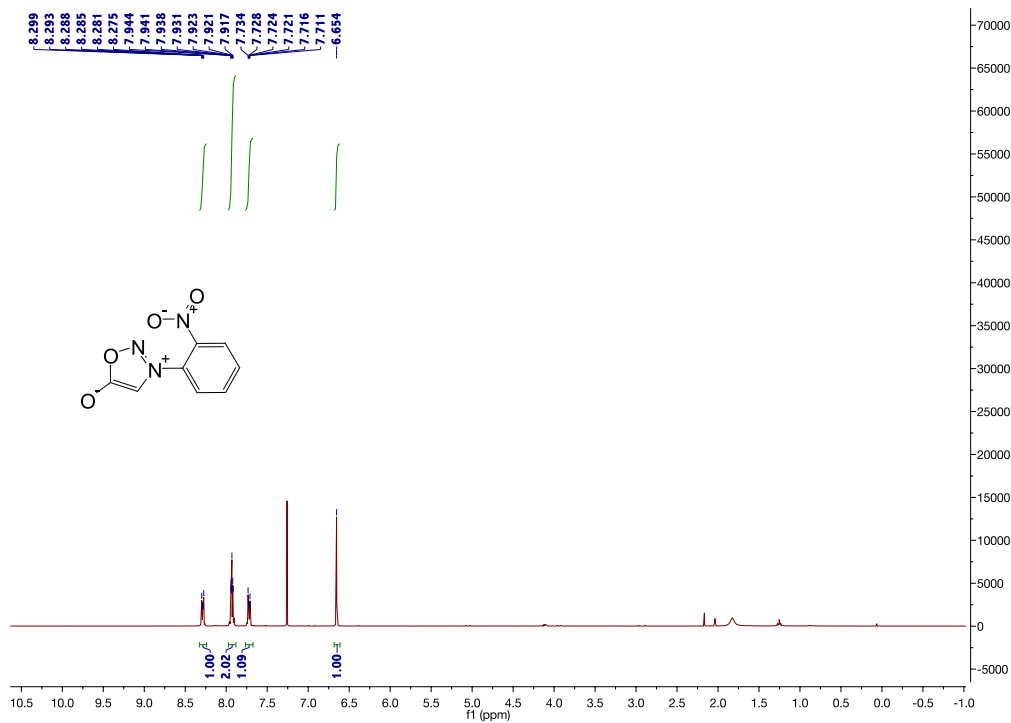
<sup>1</sup>H NMR for Gly-10 (400 MHz, DMSO-d<sub>6</sub>)



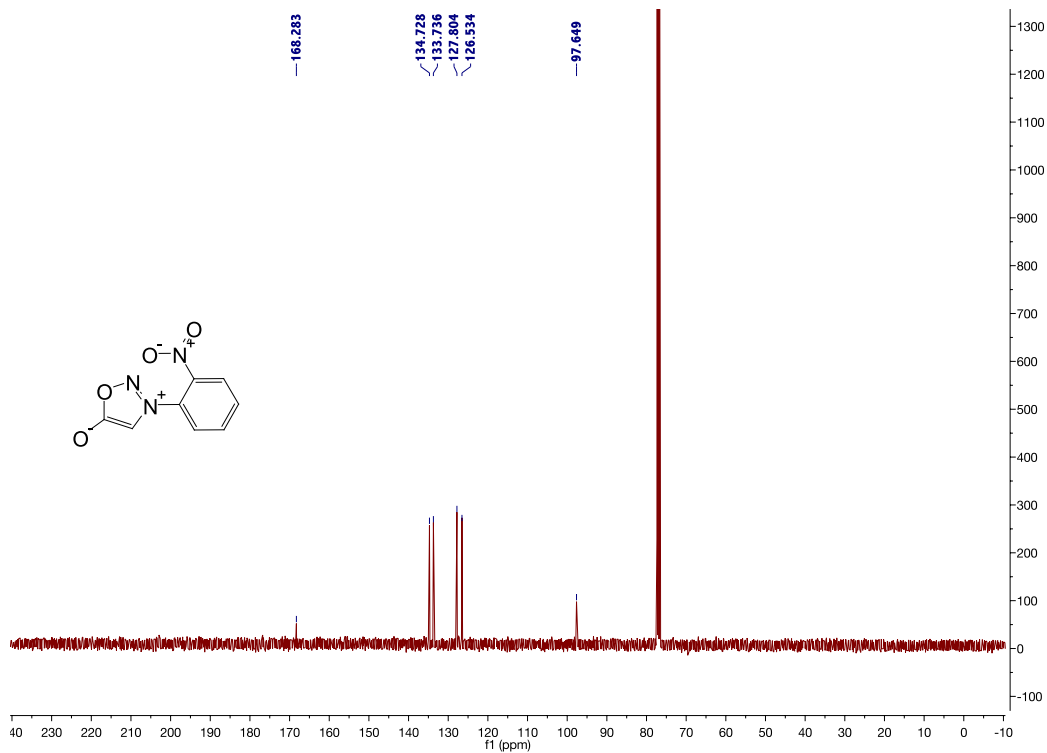
<sup>13</sup>C NMR for Gly-10 (100 MHz, DMSO-d<sub>6</sub>)



<sup>1</sup>H NMR for **10** (400 MHz, CDCl<sub>3</sub>)

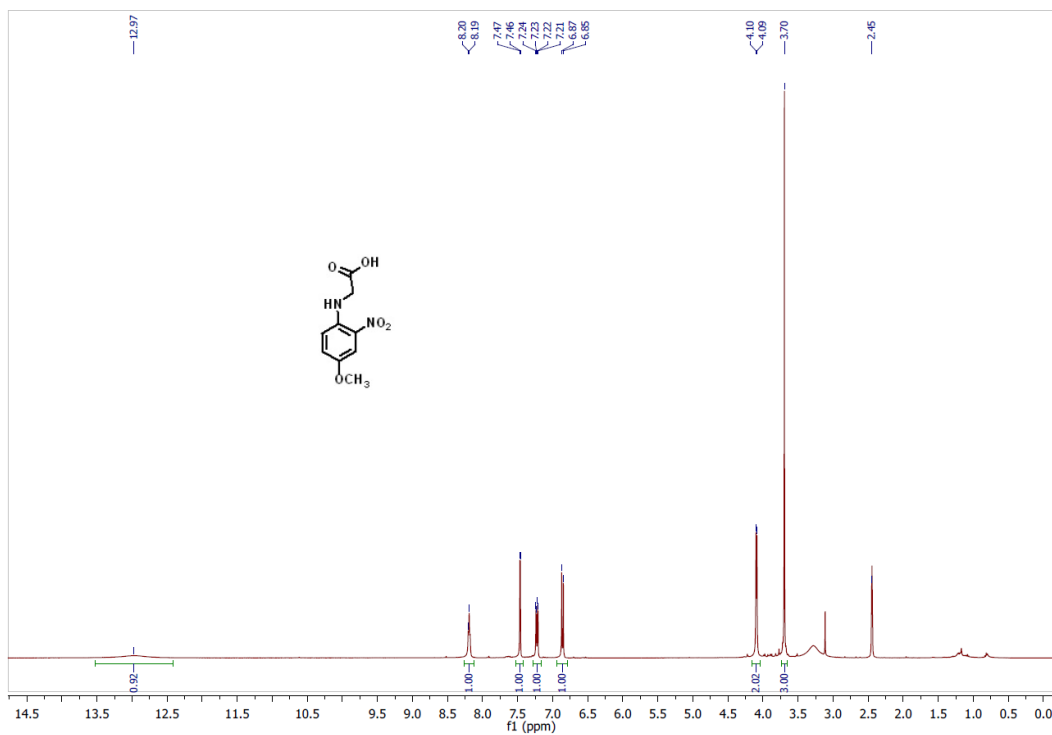


<sup>13</sup>C NMR for **10** (100 MHz, CDCl<sub>3</sub>)

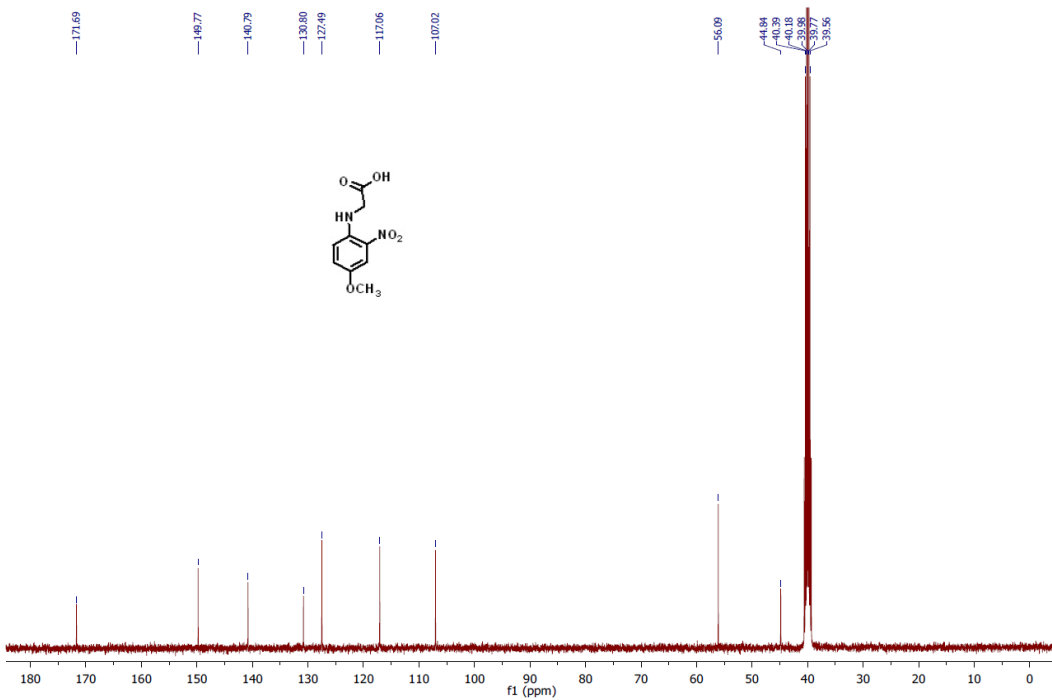




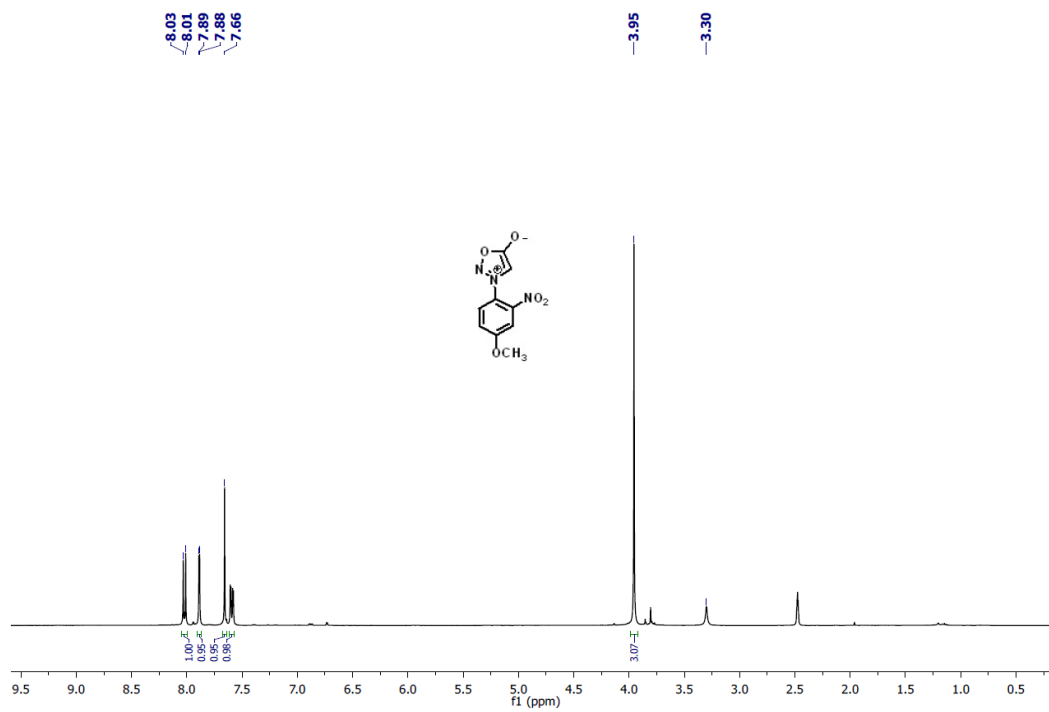
<sup>1</sup>H NMR for Gly-11 (400 MHz, DMSO-d<sub>6</sub>)



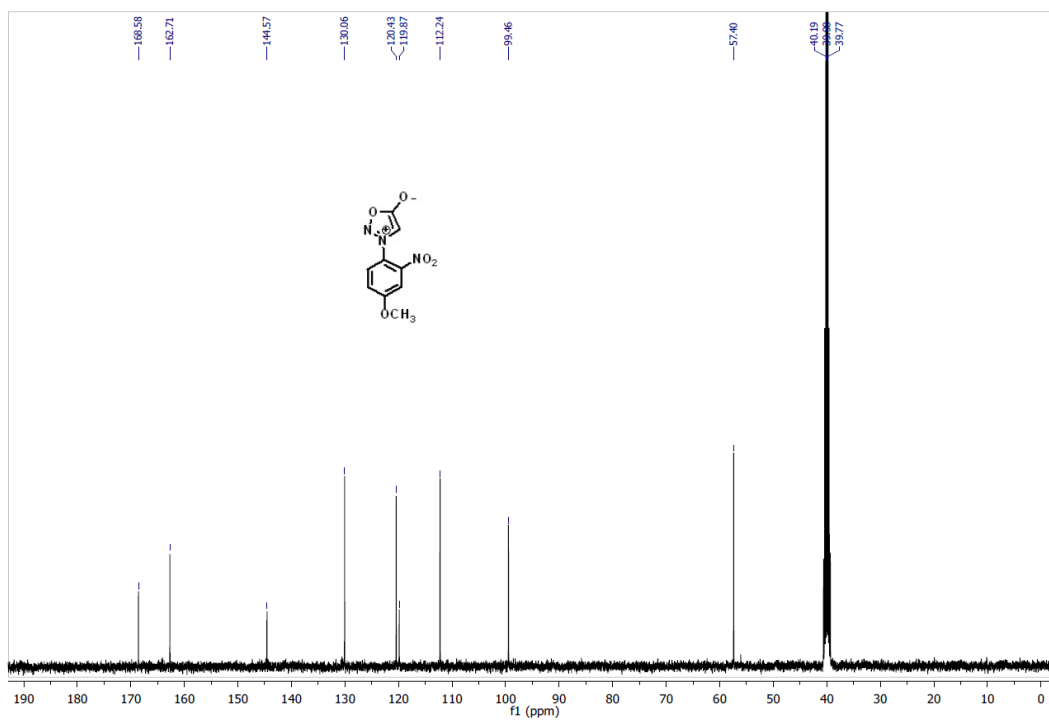
<sup>13</sup>C NMR for Gly-11 (100 MHz, DMSO-d<sub>6</sub>)



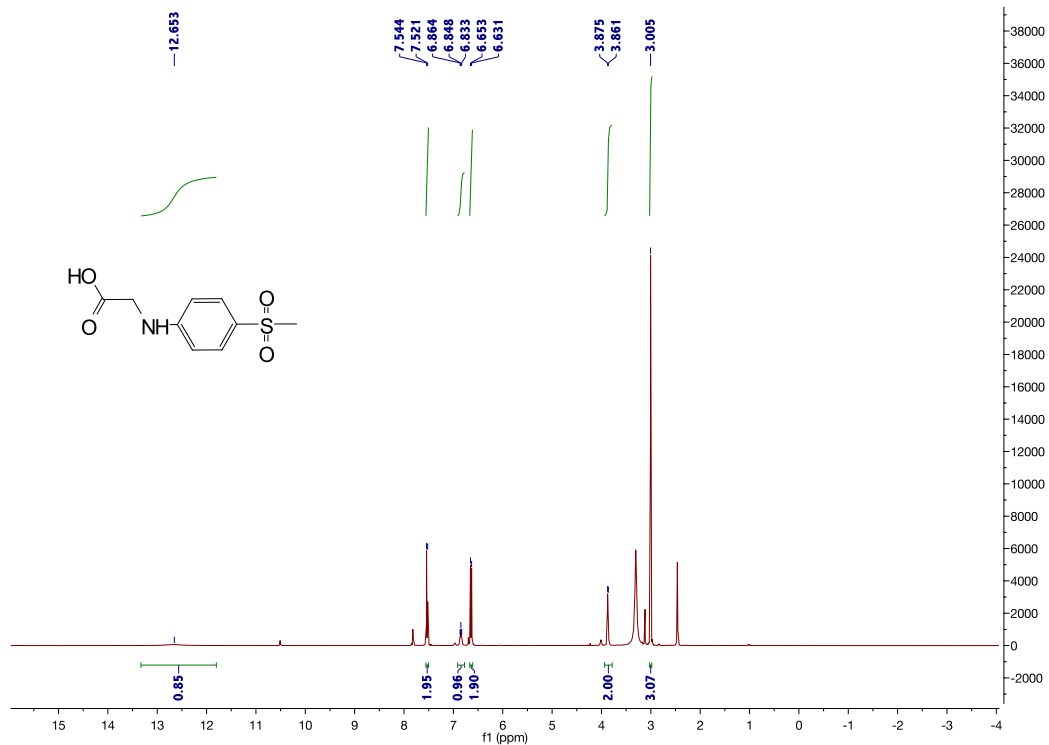
$^1\text{H}$  NMR for **11** (400 MHz, DMSO- $d_6$ )



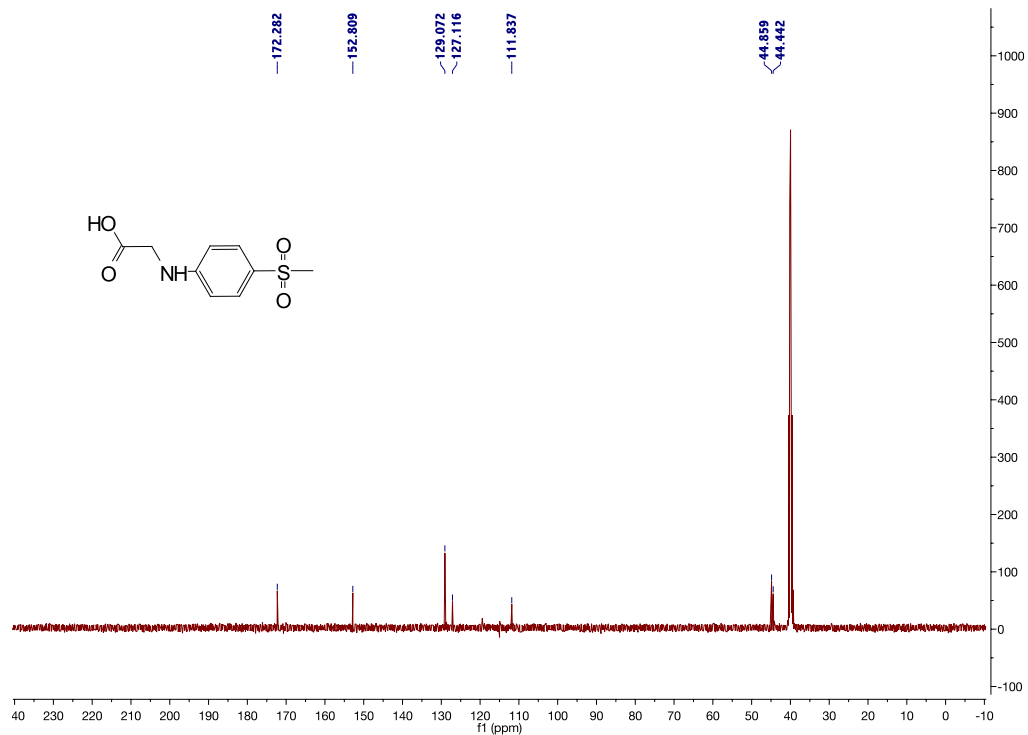
$^{13}\text{C}$  NMR for **11** (100 MHz, DMSO- $d_6$ )



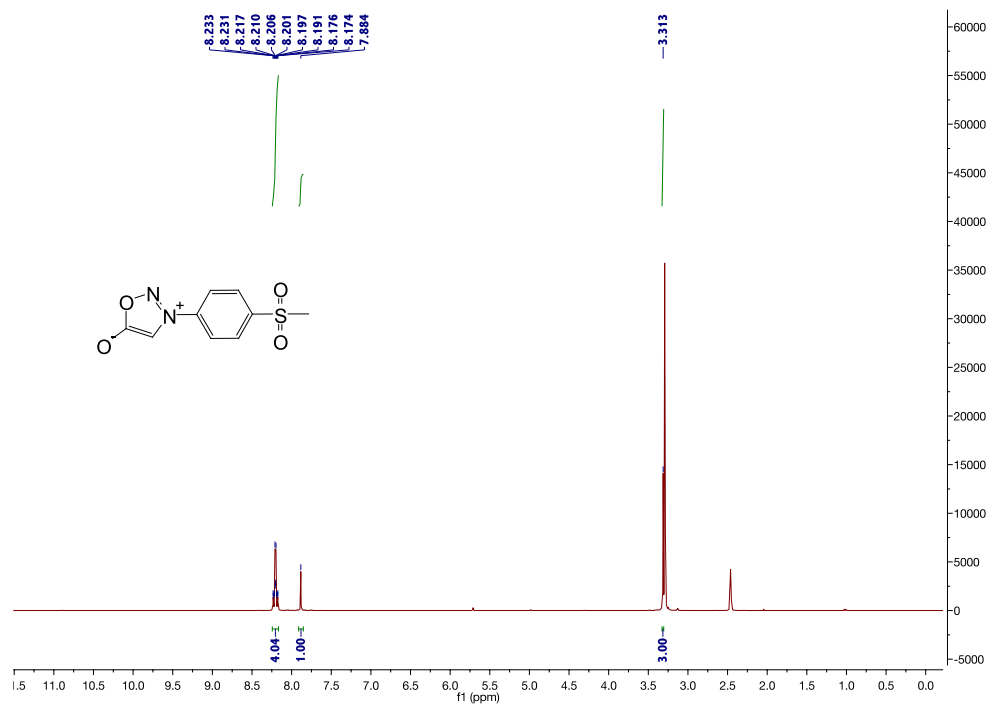
<sup>1</sup>H NMR for Gly-12 (400 MHz, DMSO-d<sub>6</sub>)



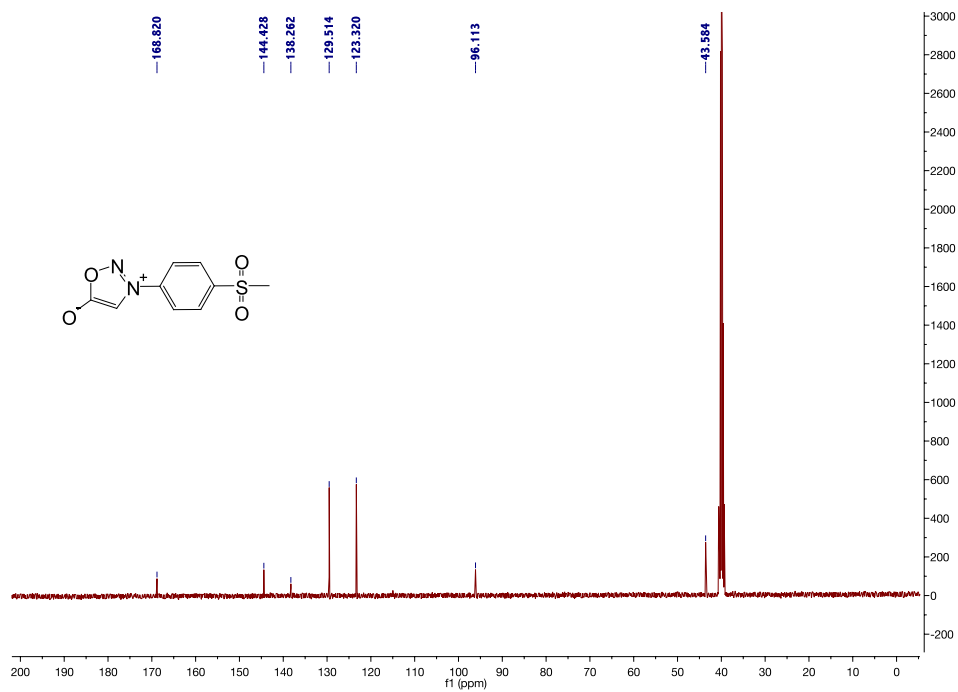
<sup>13</sup>C NMR for Gly-12 (100 MHz, DMSO-d<sub>6</sub>)



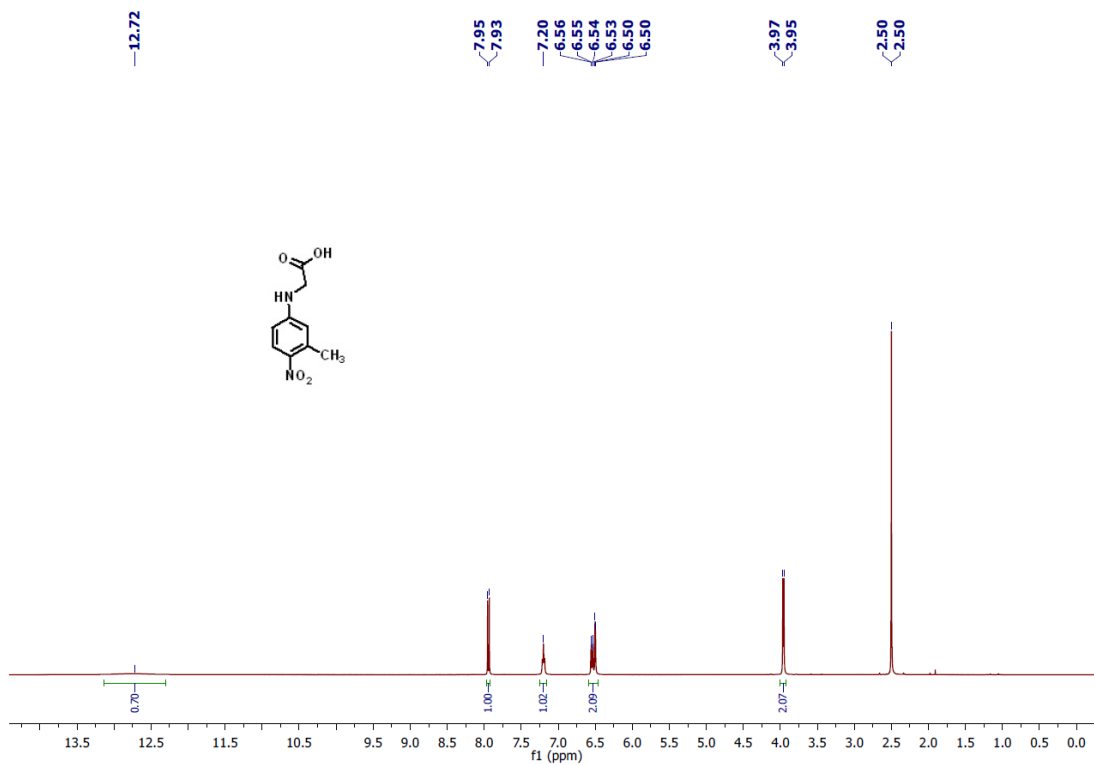
<sup>1</sup>H NMR for **12** (400 MHz, DMSO-d<sub>6</sub>)



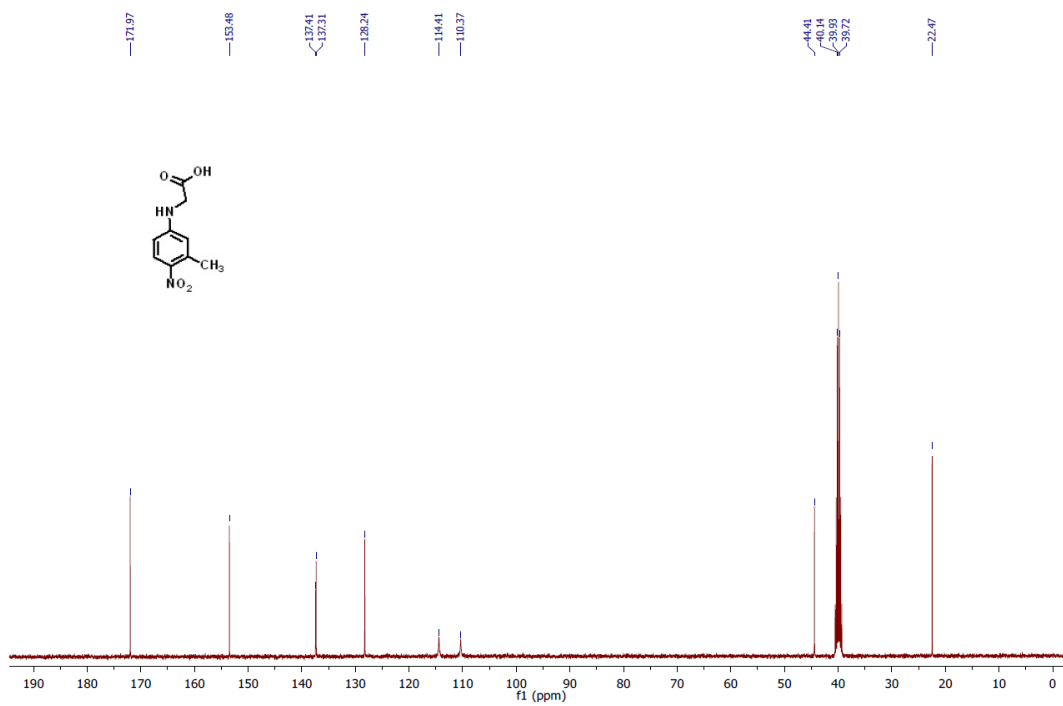
<sup>13</sup>C NMR for **12** (100 MHz, DMSO-d<sub>6</sub>)



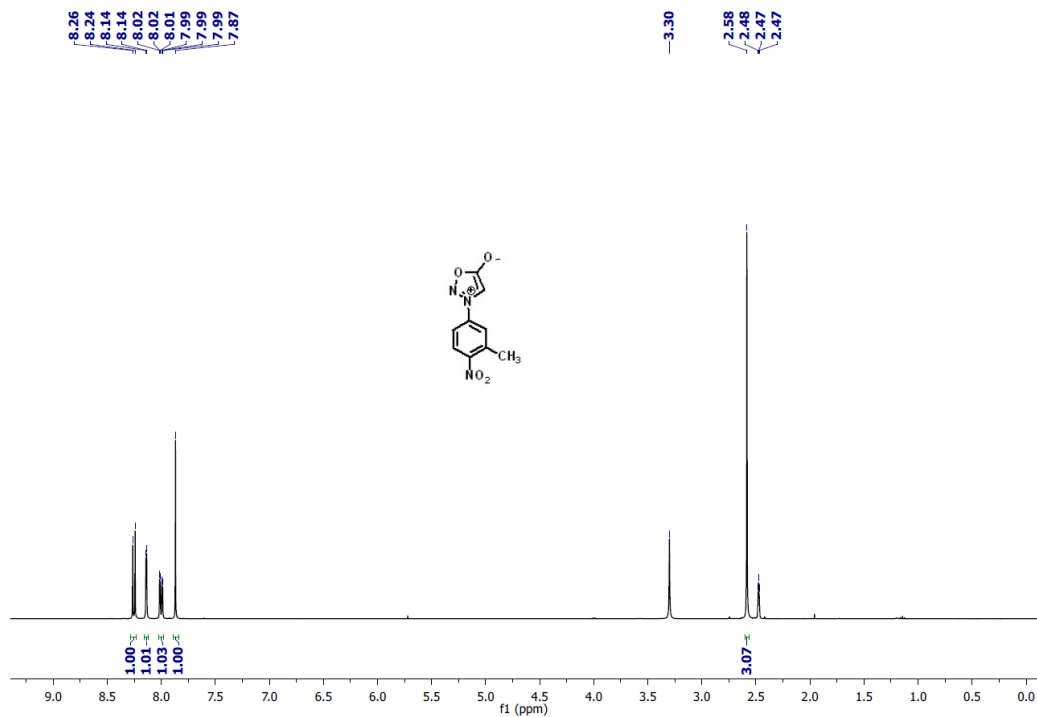
<sup>1</sup>H NMR for Gly-14 (400 MHz, DMSO-d<sub>6</sub>)



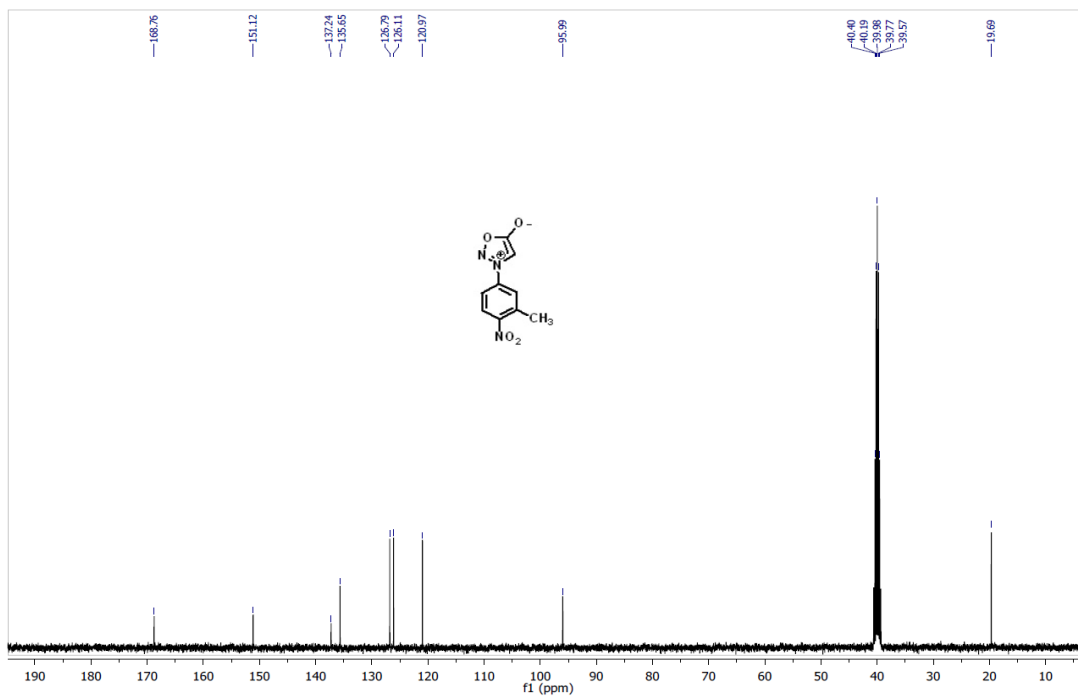
<sup>13</sup>C NMR for Gly-14 (100 MHz, DMSO-d<sub>6</sub>)



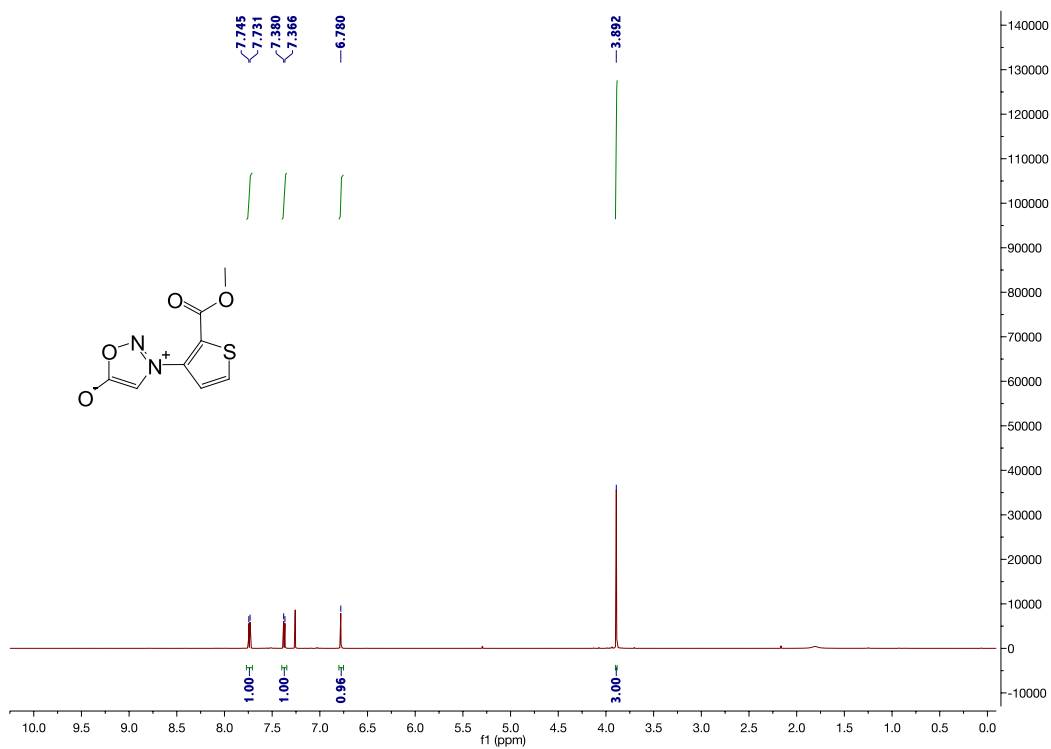
<sup>1</sup>H NMR for **14** (400 MHz, DMSO-d<sub>6</sub>)



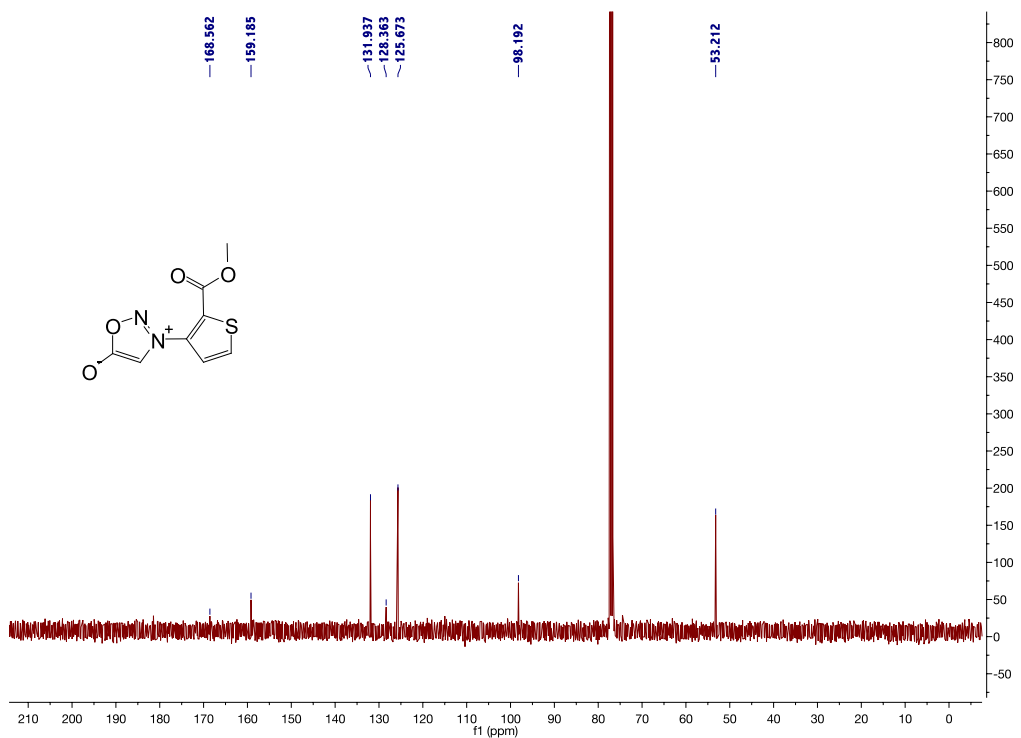
<sup>13</sup>C NMR for **14** (100 MHz, DMSO-d<sub>6</sub>)



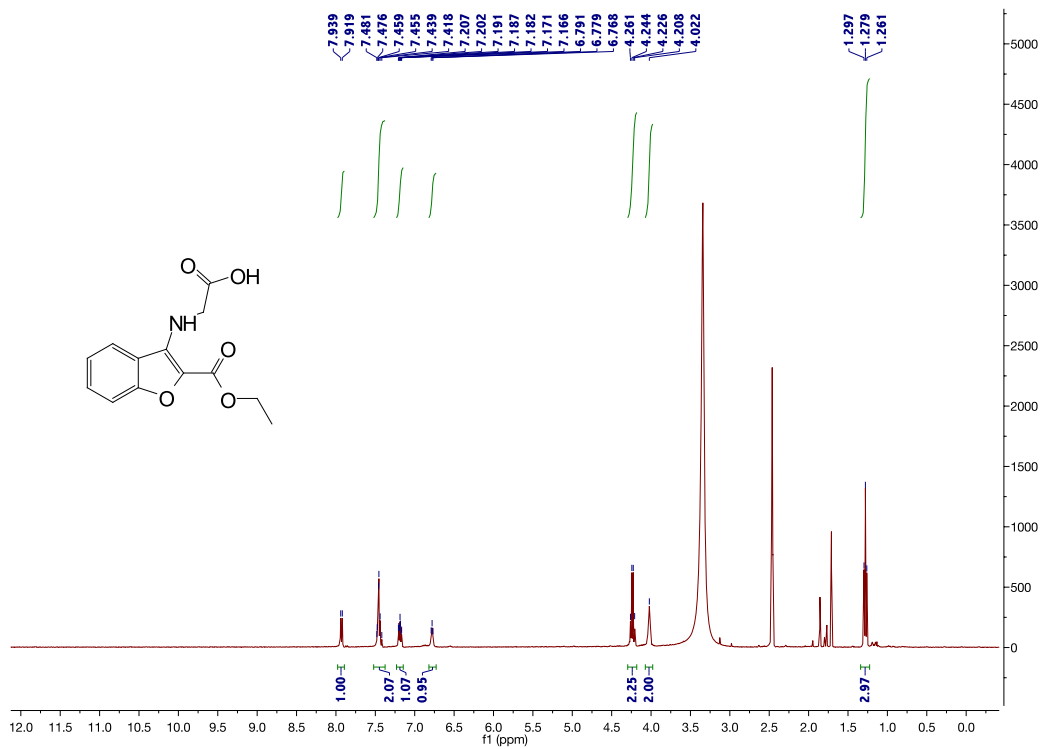
<sup>1</sup>H NMR for **15** (400 MHz, CDCl<sub>3</sub>)



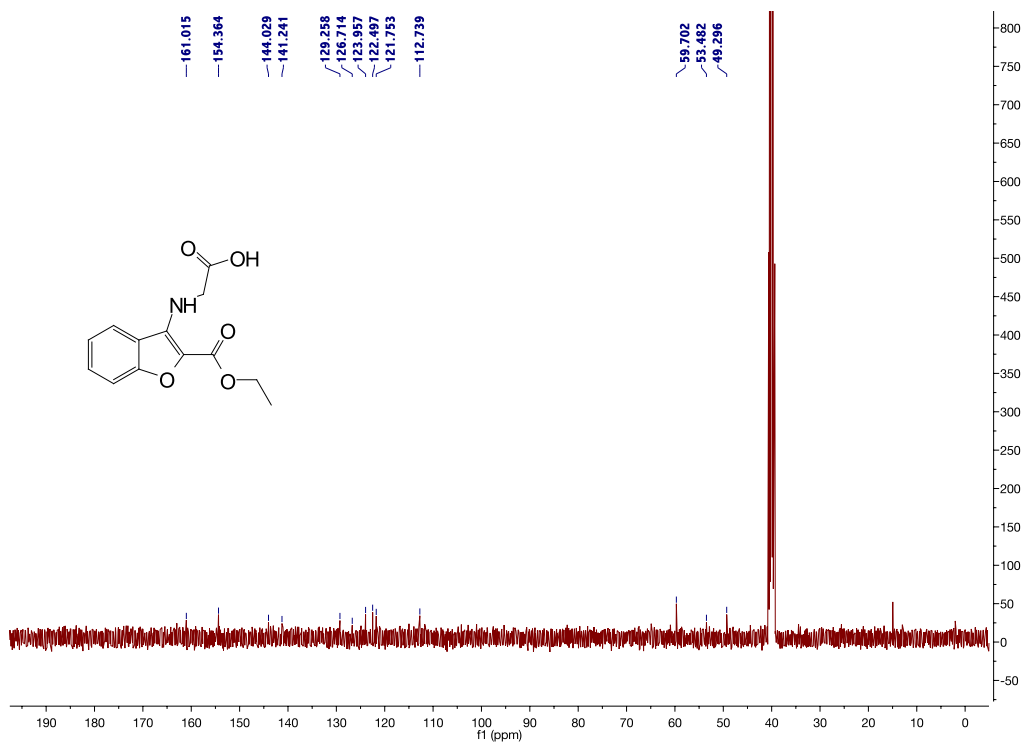
<sup>13</sup>C NMR for **15** (100 MHz, CDCl<sub>3</sub>)



<sup>1</sup>H NMR for Gly-16 (400 MHz, DMSO-d<sub>6</sub>)

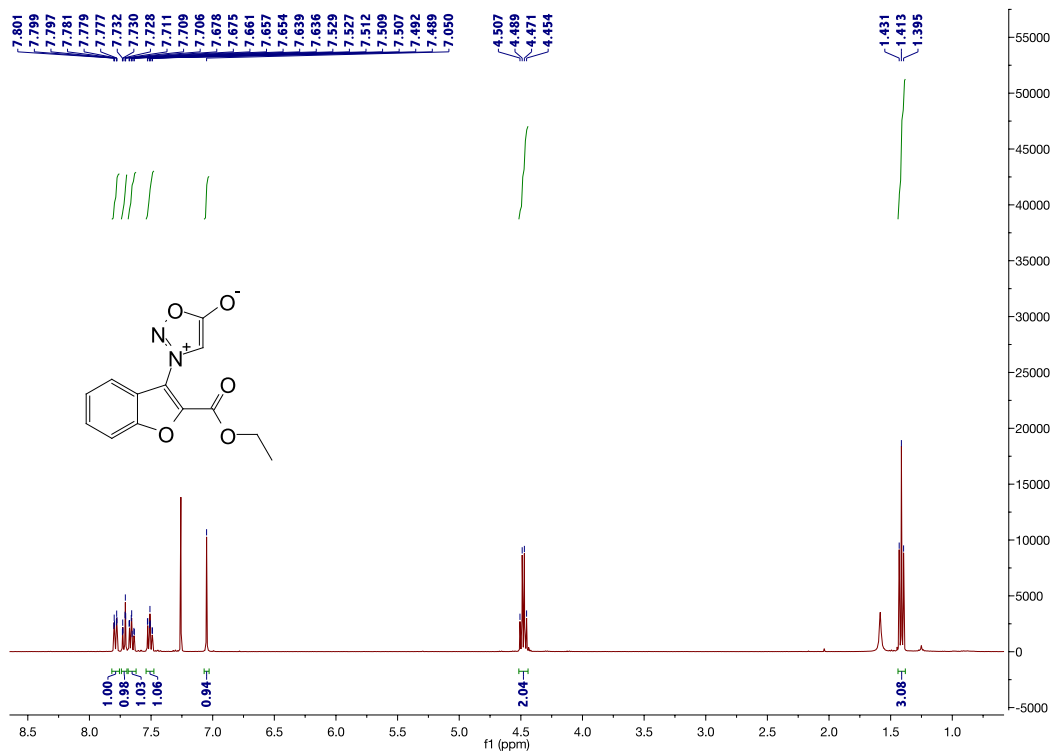


<sup>13</sup>C NMR for Gly-16 (100 MHz, DMSO-d<sub>6</sub>)

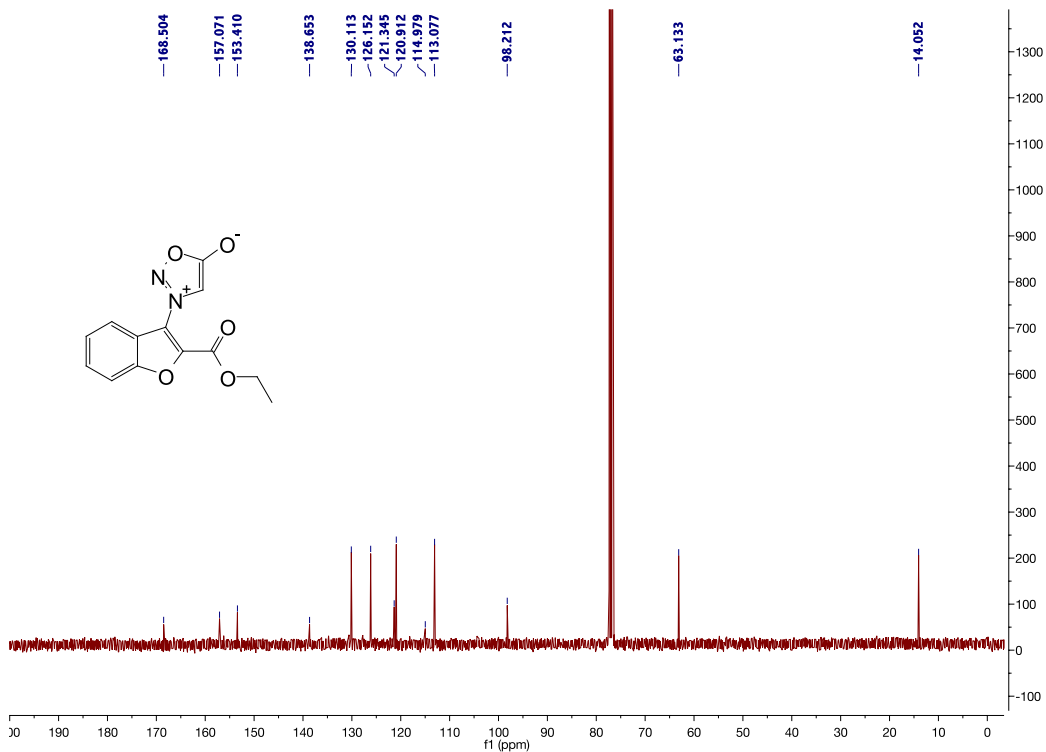




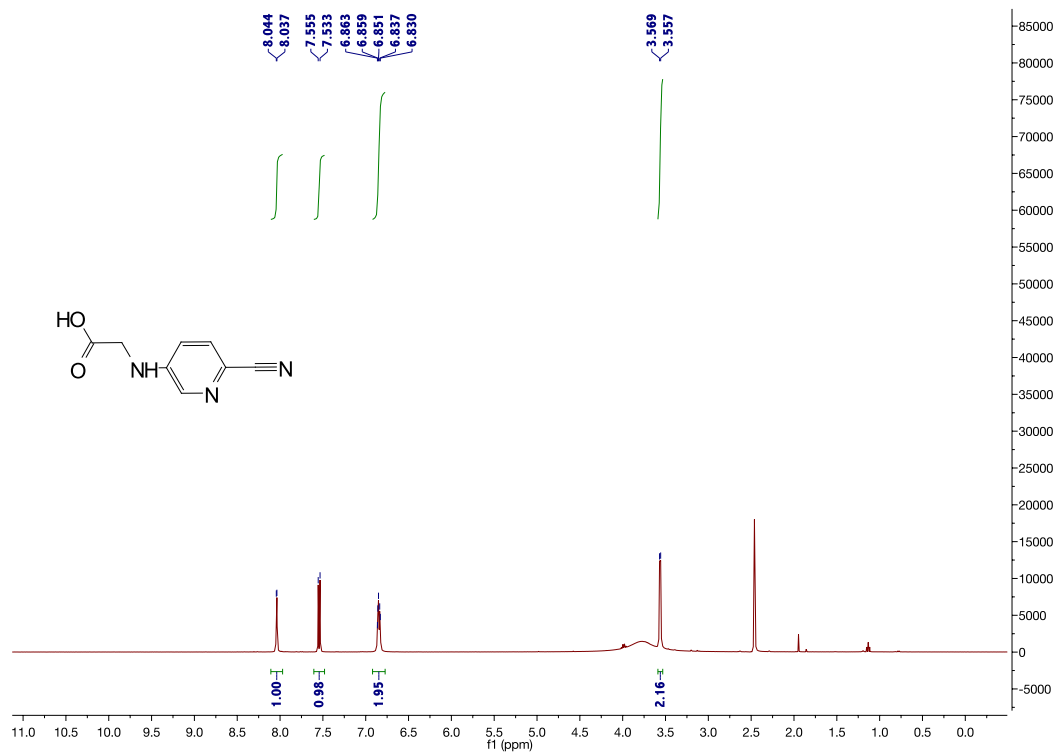
<sup>1</sup>H NMR for **16** (400 MHz, CDCl<sub>3</sub>)



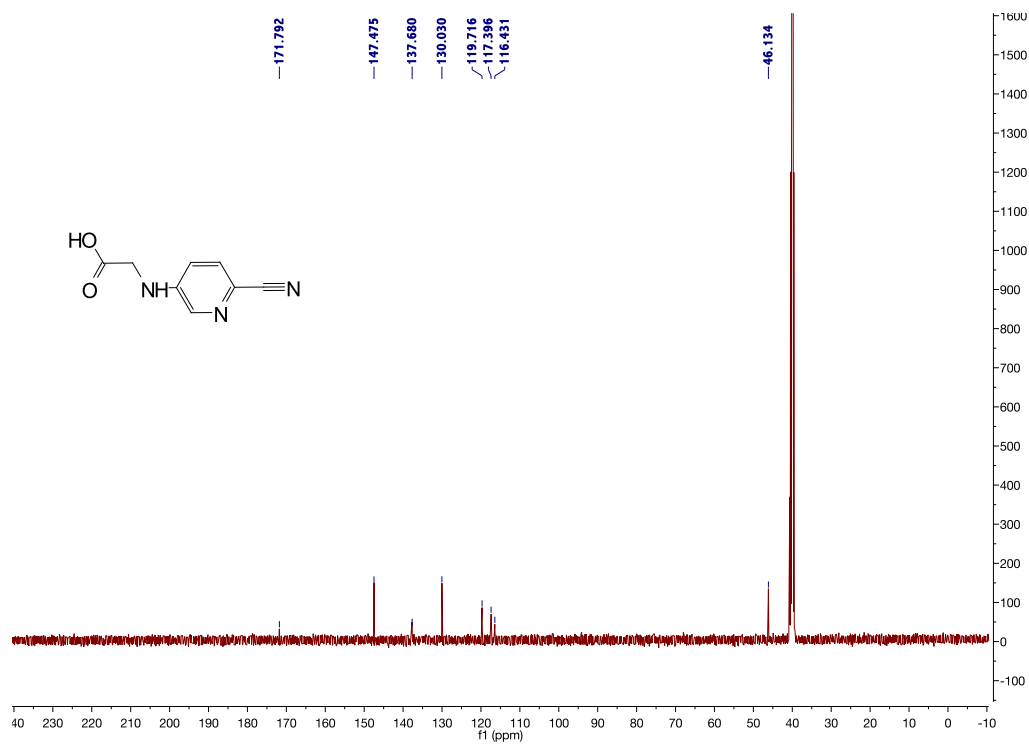
<sup>13</sup>C NMR for **16** (100 MHz, CDCl<sub>3</sub>)



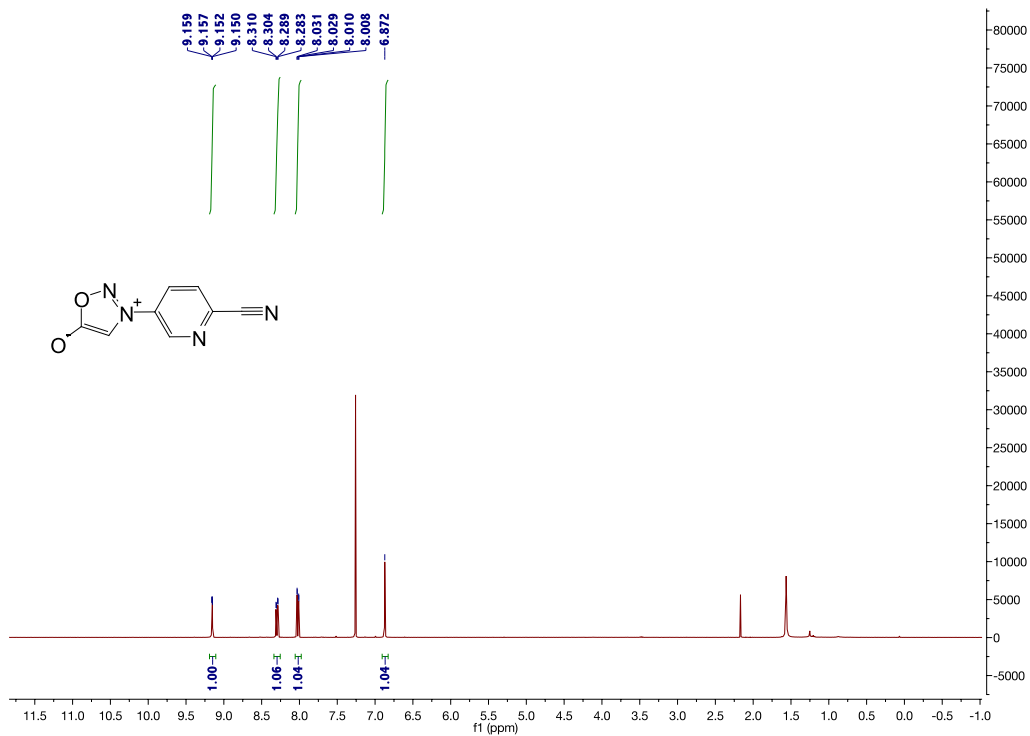
<sup>1</sup>H NMR for Gly-17 (400 MHz, DMSO-d<sub>6</sub>)



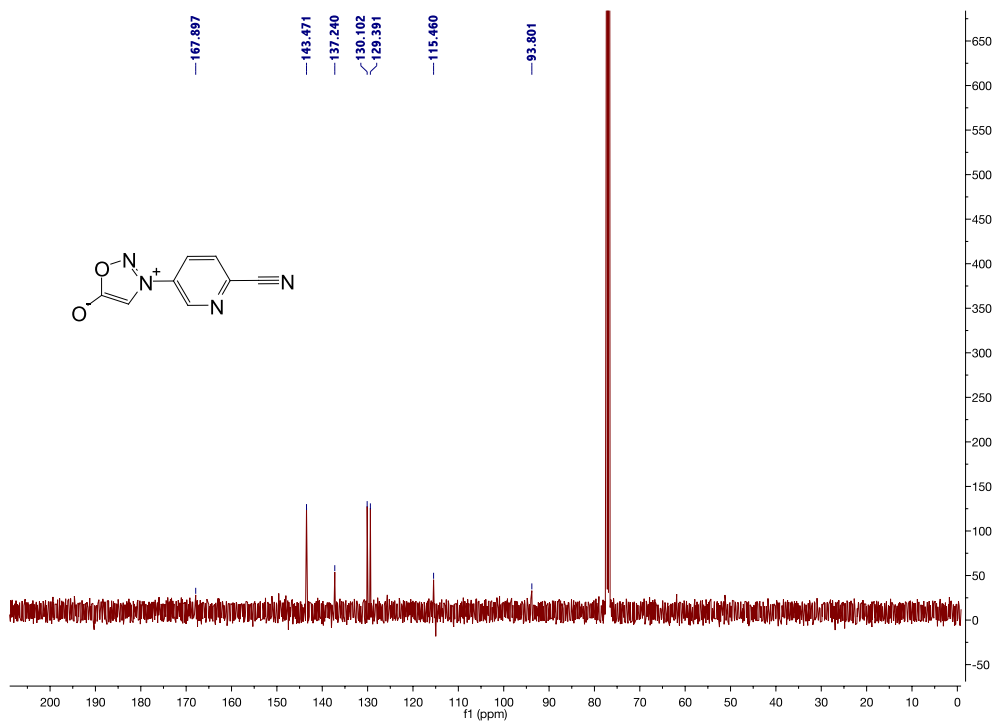
<sup>13</sup>C NMR for Gly-17 (100 MHz, DMSO-d<sub>6</sub>)



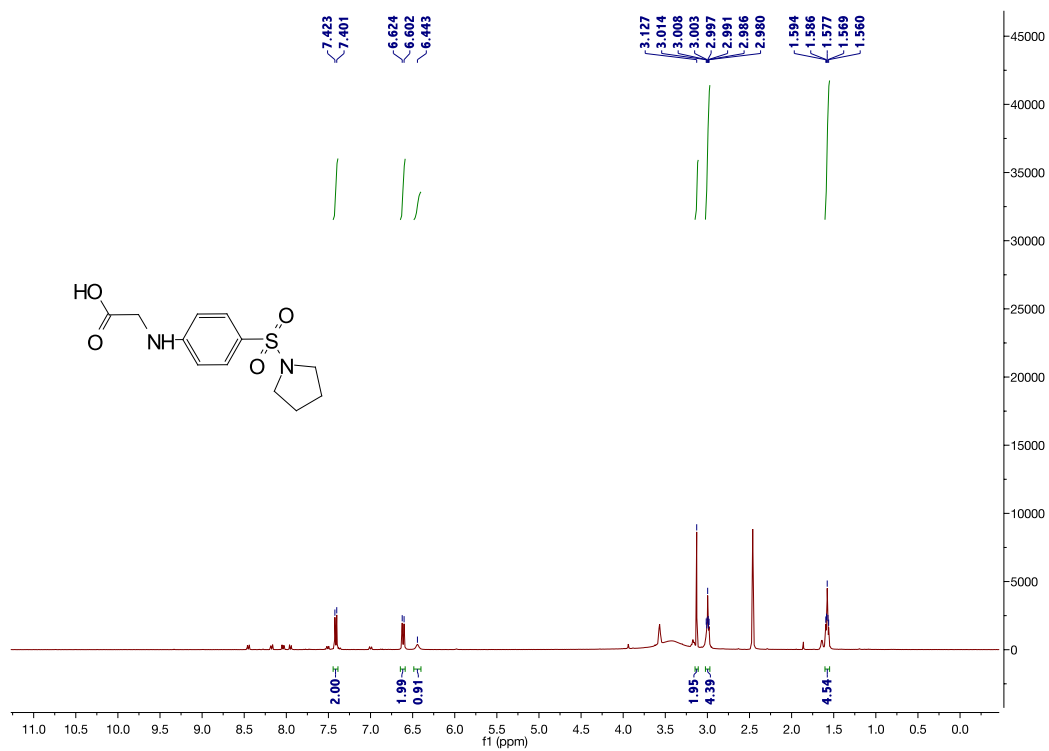
$^1\text{H}$  NMR for **17** (400 MHz,  $\text{CDCl}_3$ )



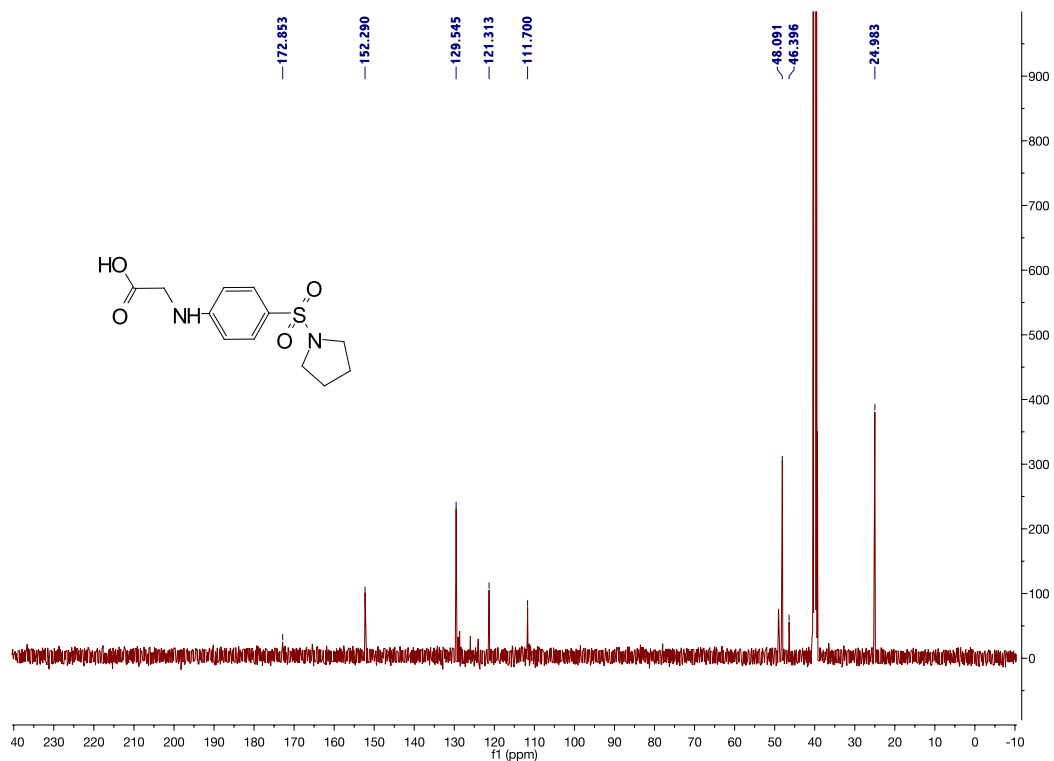
$^{13}\text{C}$  NMR for **17** (100 MHz,  $\text{CDCl}_3$ )



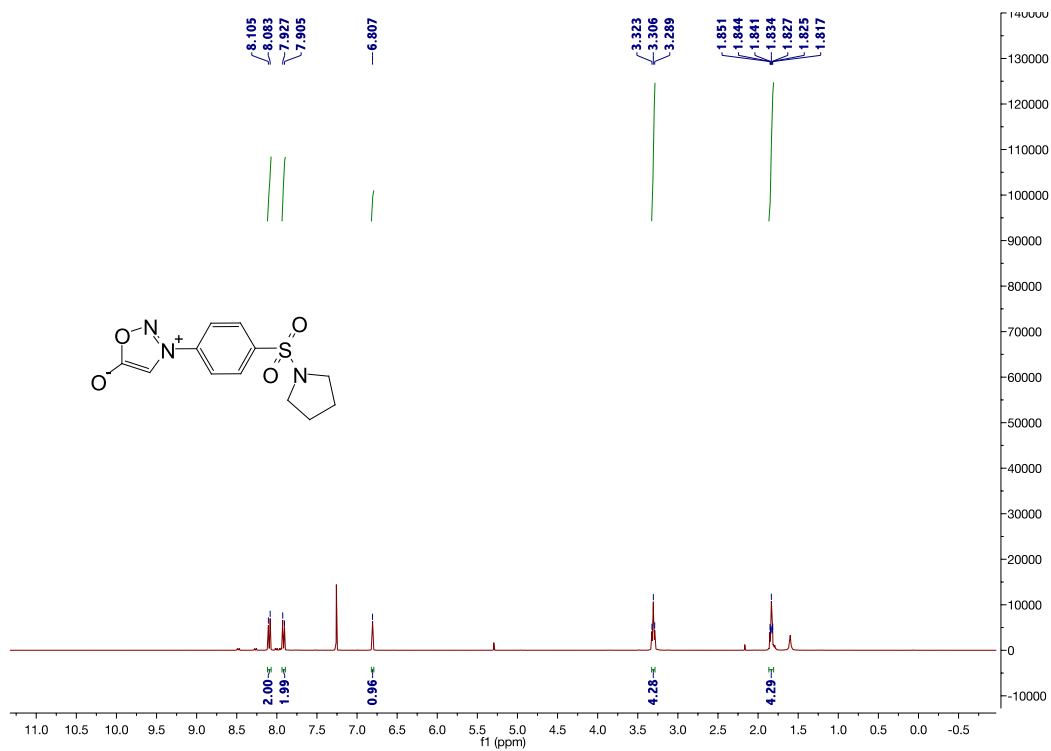
<sup>1</sup>H NMR for Gly-18 (400 MHz, DMSO-d<sub>6</sub>)



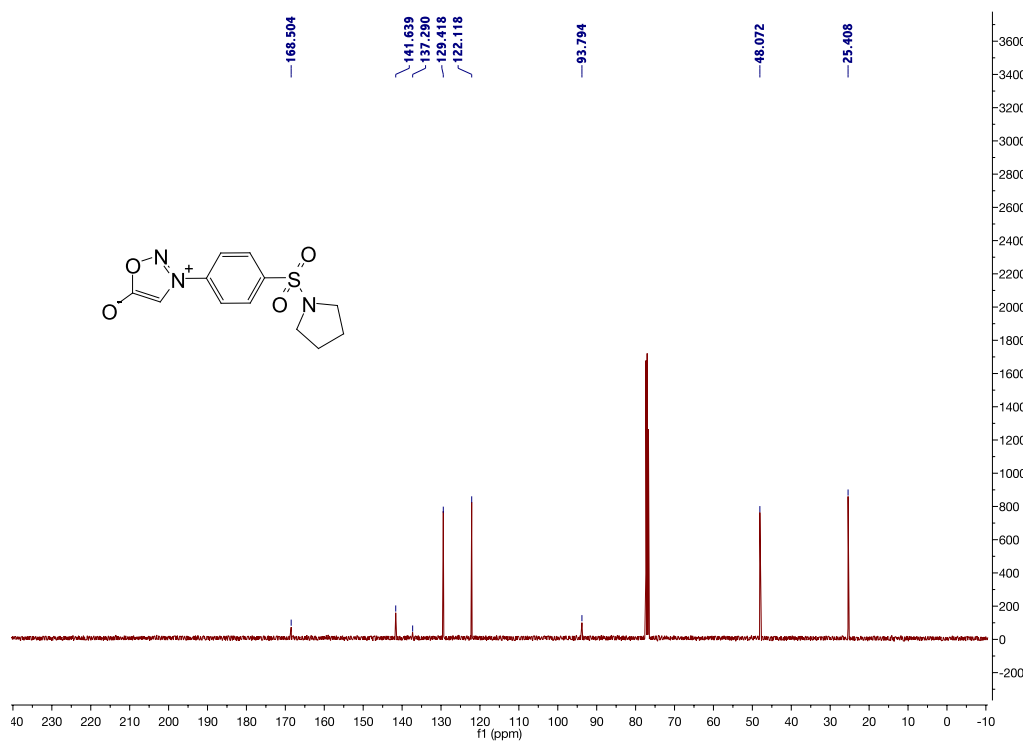
<sup>13</sup>C NMR for Gly-18 (100 MHz, DMSO-d<sub>6</sub>)



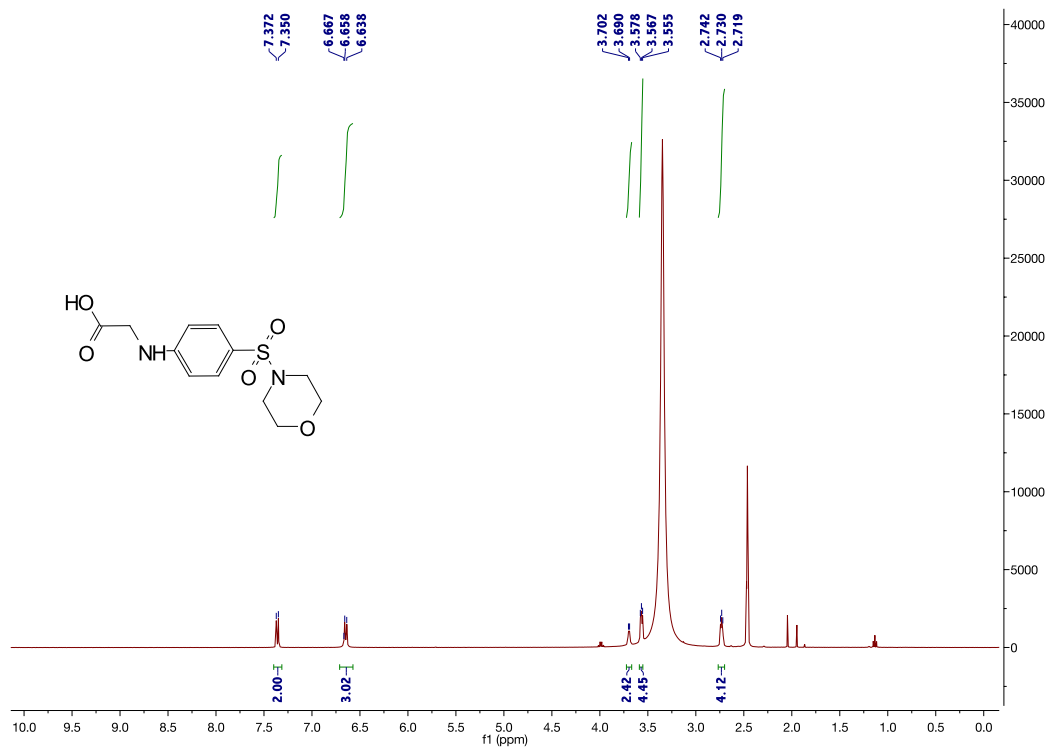
<sup>1</sup>H NMR for **18** (400 MHz, CDCl<sub>3</sub>)



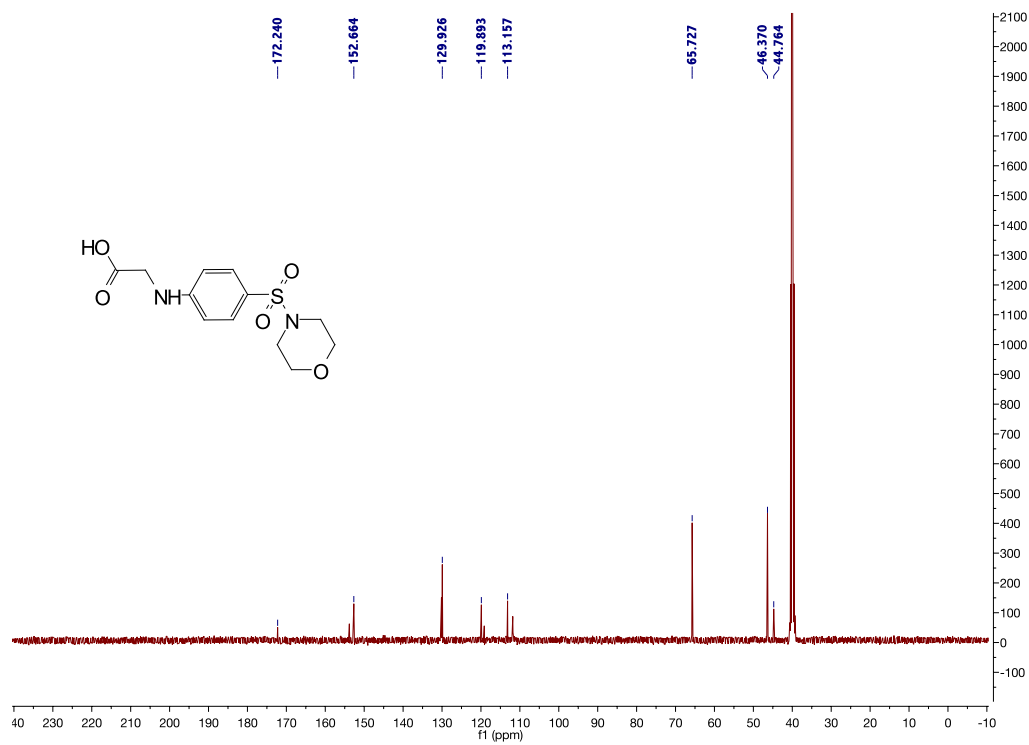
<sup>13</sup>C NMR for **18** (100 MHz, CDCl<sub>3</sub>)



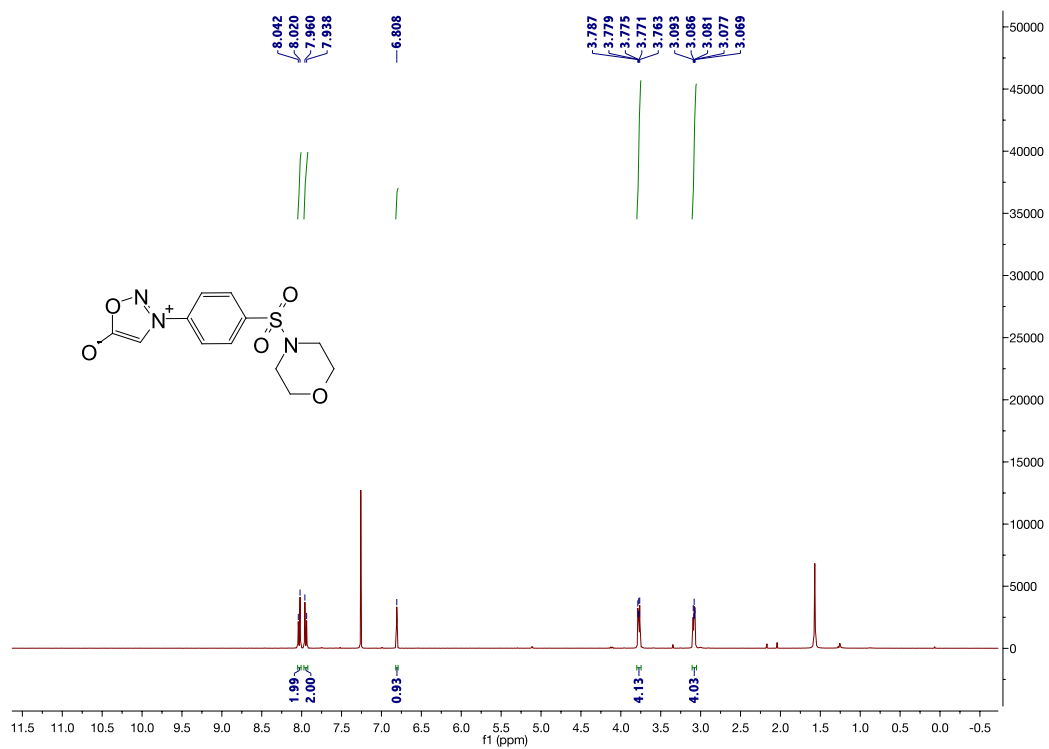
<sup>1</sup>H NMR for Gly-19 (400 MHz, DMSO-d<sub>6</sub>)



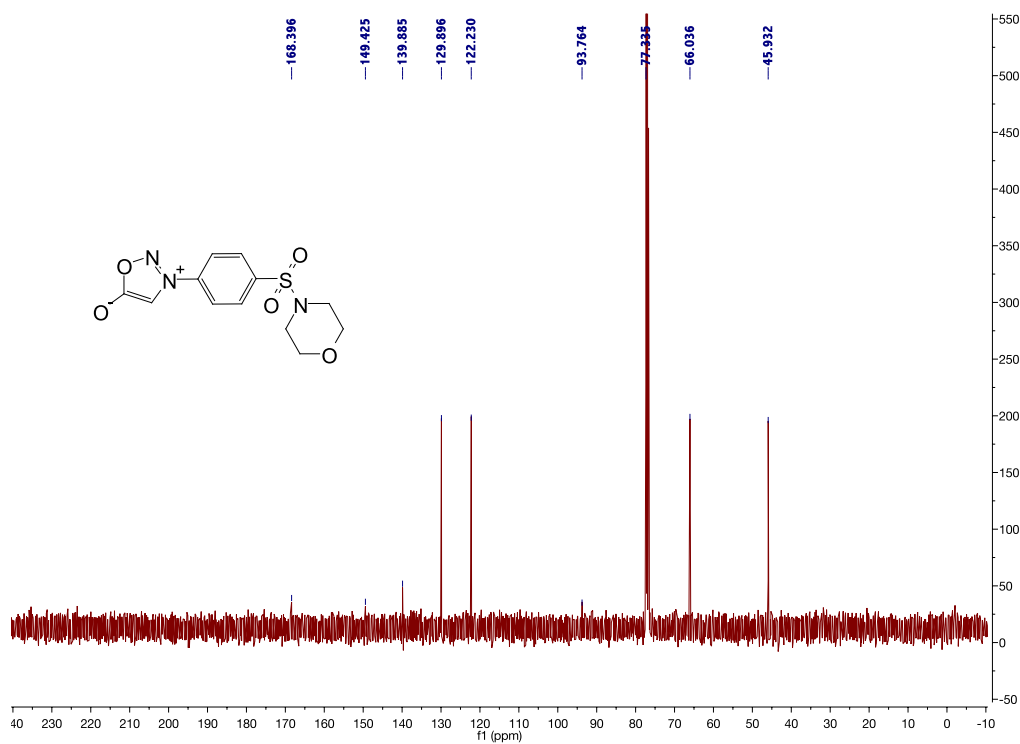
<sup>13</sup>C NMR for Gly-19 (100 MHz, DMSO-d<sub>6</sub>)



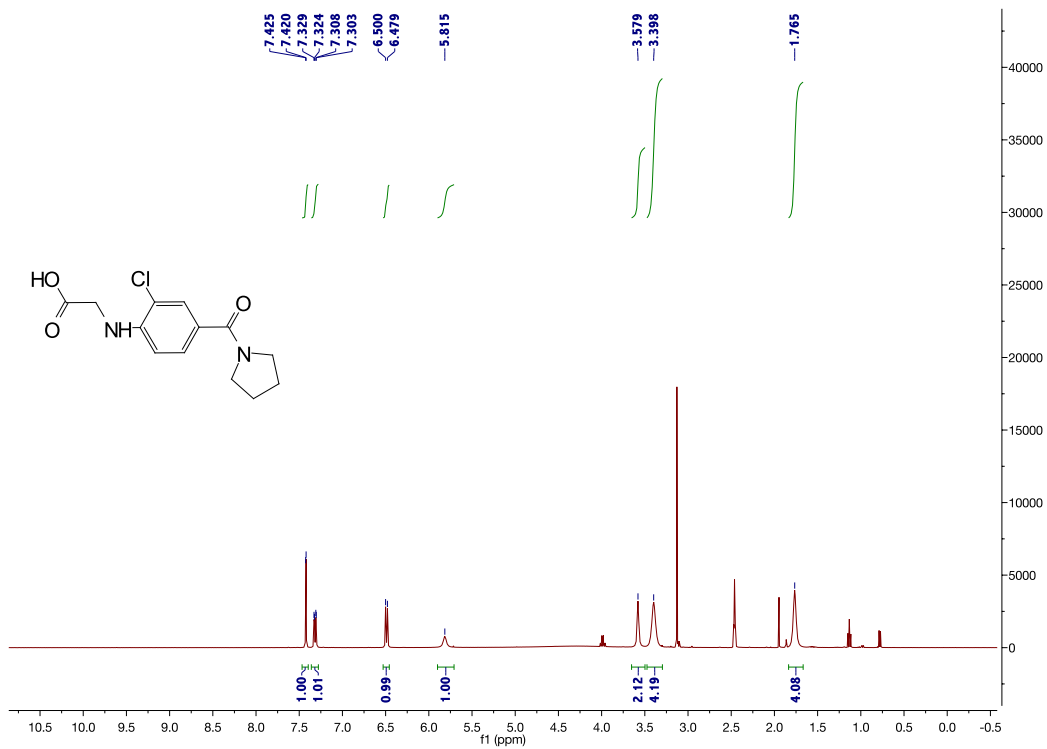
<sup>1</sup>H NMR for **19** (400 MHz, CDCl<sub>3</sub>)



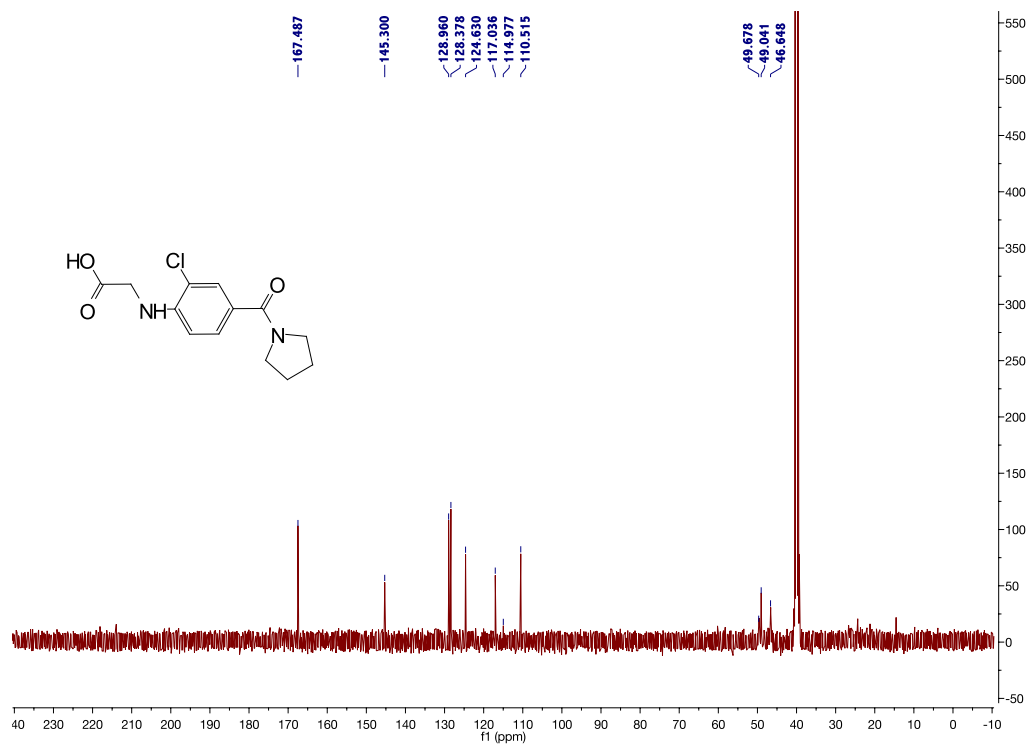
<sup>13</sup>C NMR for **19** (100 MHz, CDCl<sub>3</sub>)



<sup>1</sup>H NMR for Gly-20 (400 MHz, DMSO-d<sub>6</sub>)

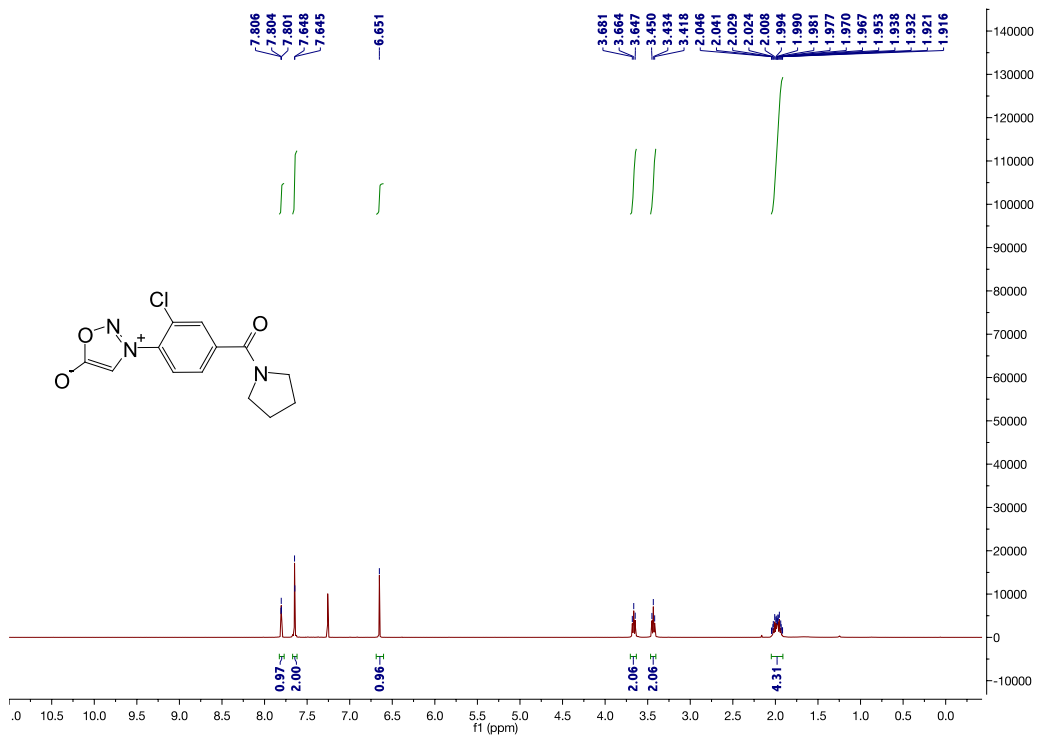


<sup>13</sup>C NMR for Gly-20 (100 MHz, DMSO-d<sub>6</sub>)

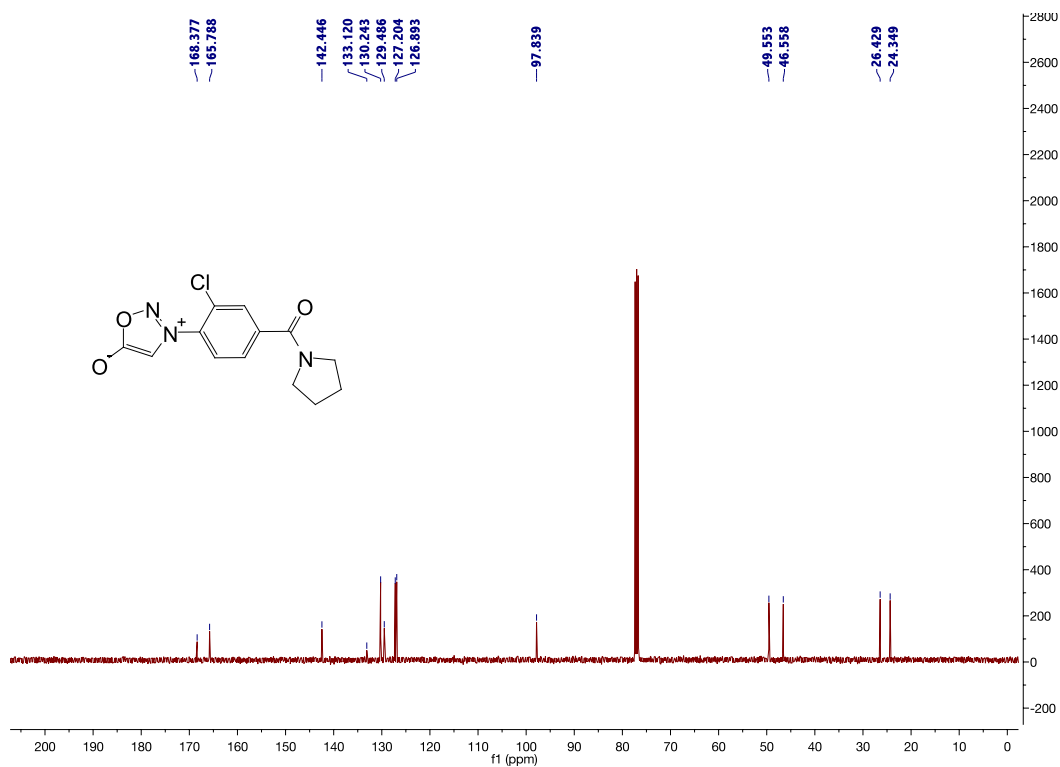




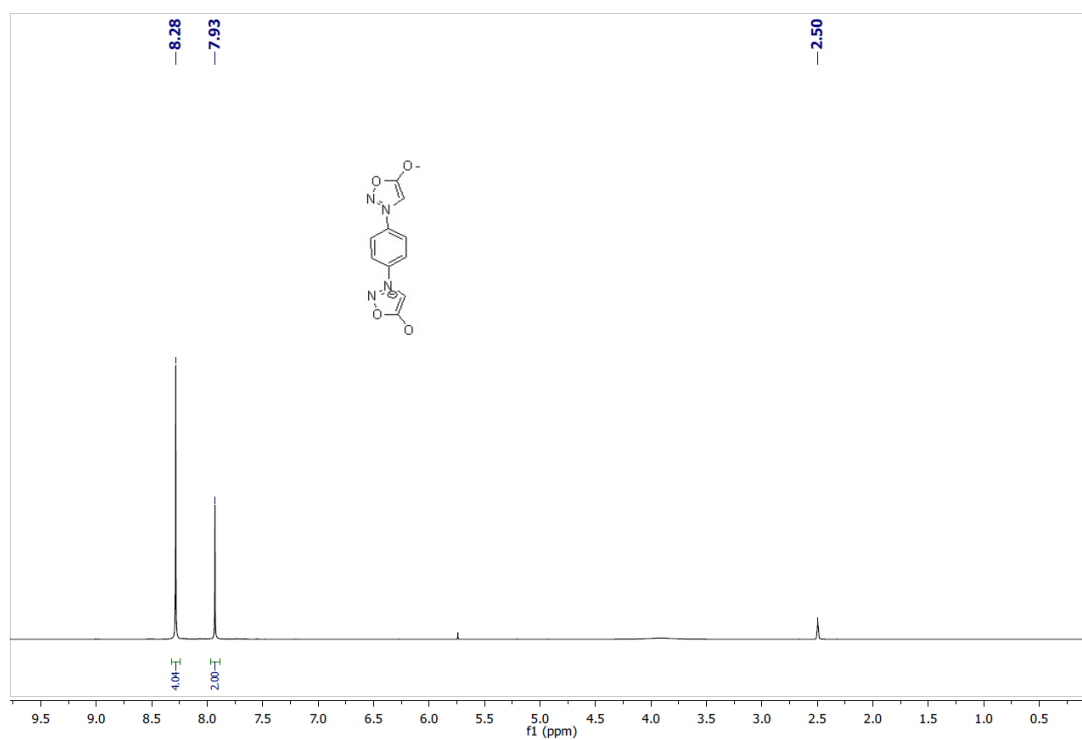
<sup>1</sup>H NMR for **20** (400 MHz, CDCl<sub>3</sub>)



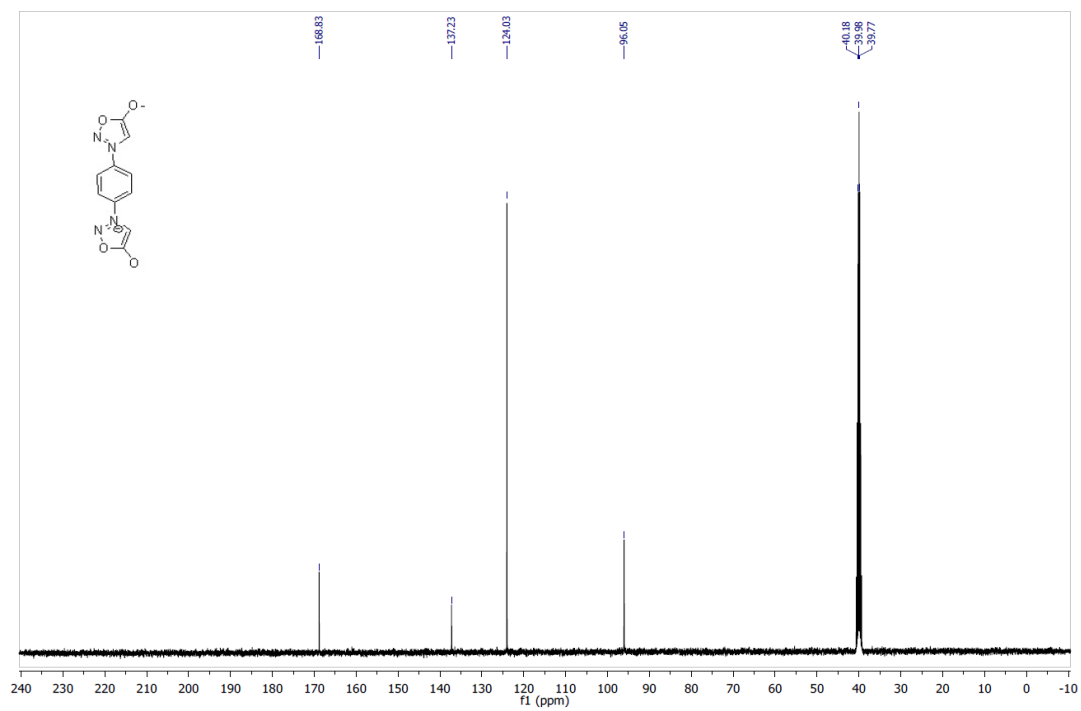
<sup>13</sup>C NMR for **20** (100 MHz, CDCl<sub>3</sub>)



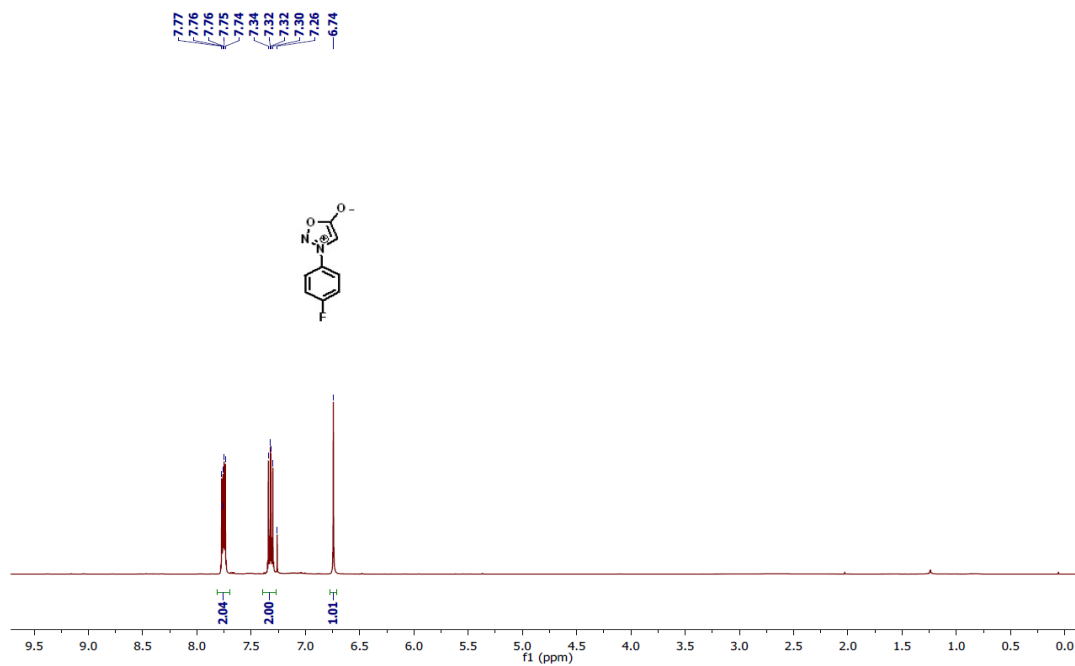
$^1\text{H}$  NMR for **21** (400 MHz, DMSO- $d_6$ )



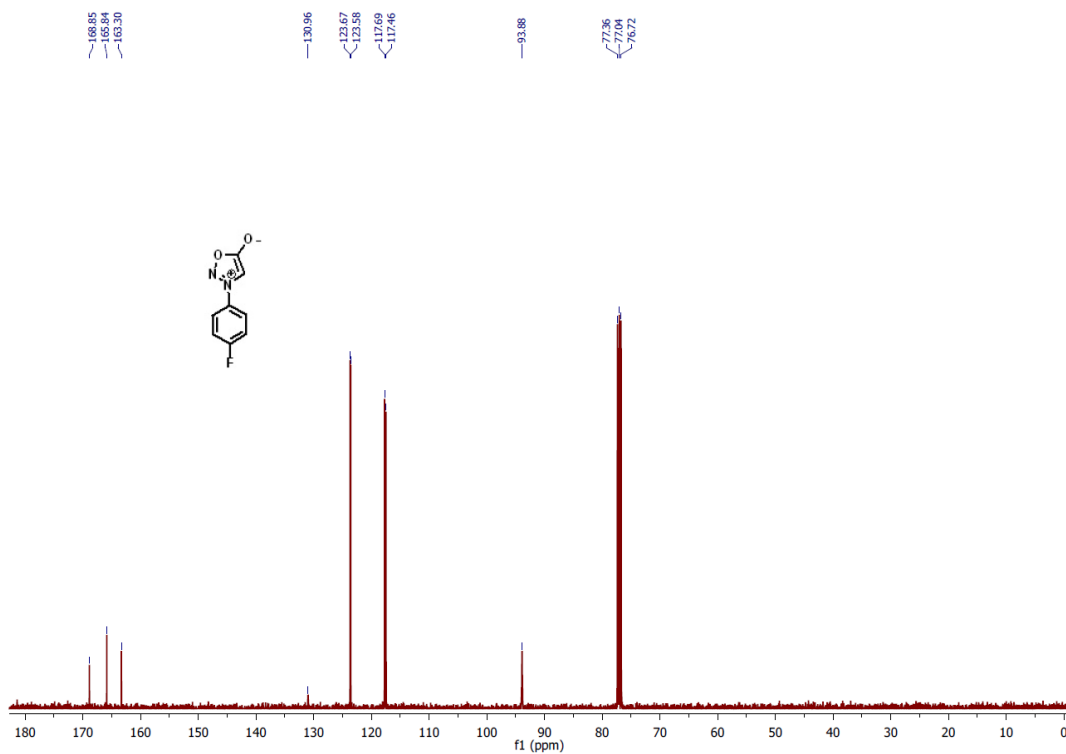
$^{13}\text{C}$  NMR for **21** (100 MHz, DMSO- $d_6$ )



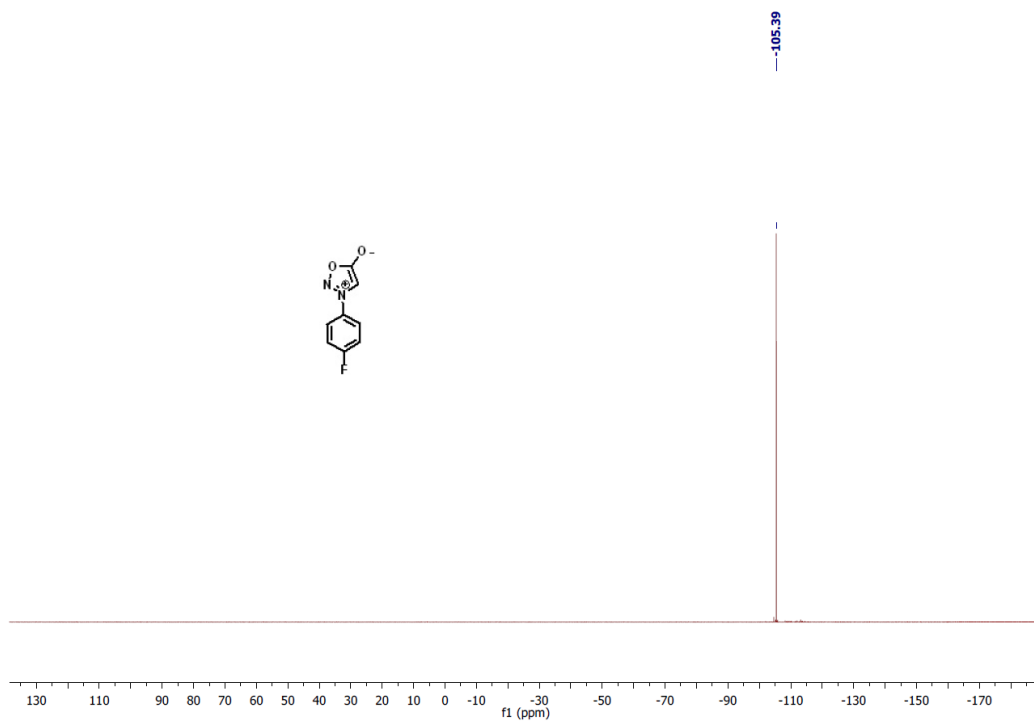
<sup>1</sup>H NMR for **Ref-4b** (400 MHz, CDCl<sub>3</sub>)



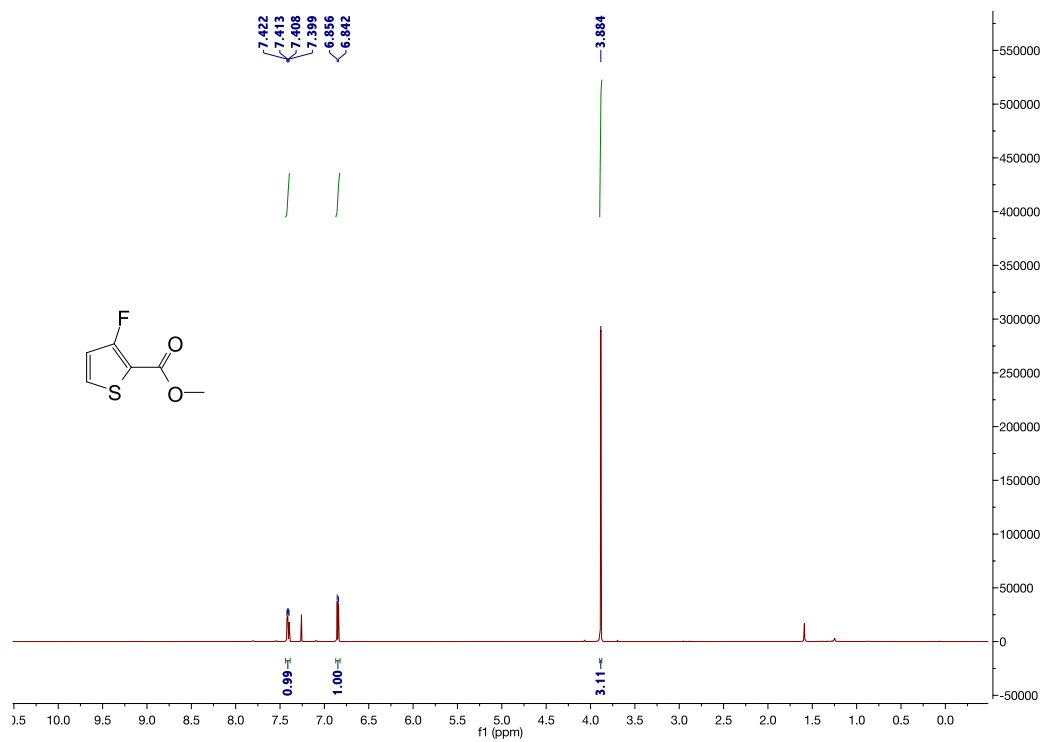
<sup>13</sup>C NMR for **Ref-4b** (100 MHz, CDCl<sub>3</sub>)



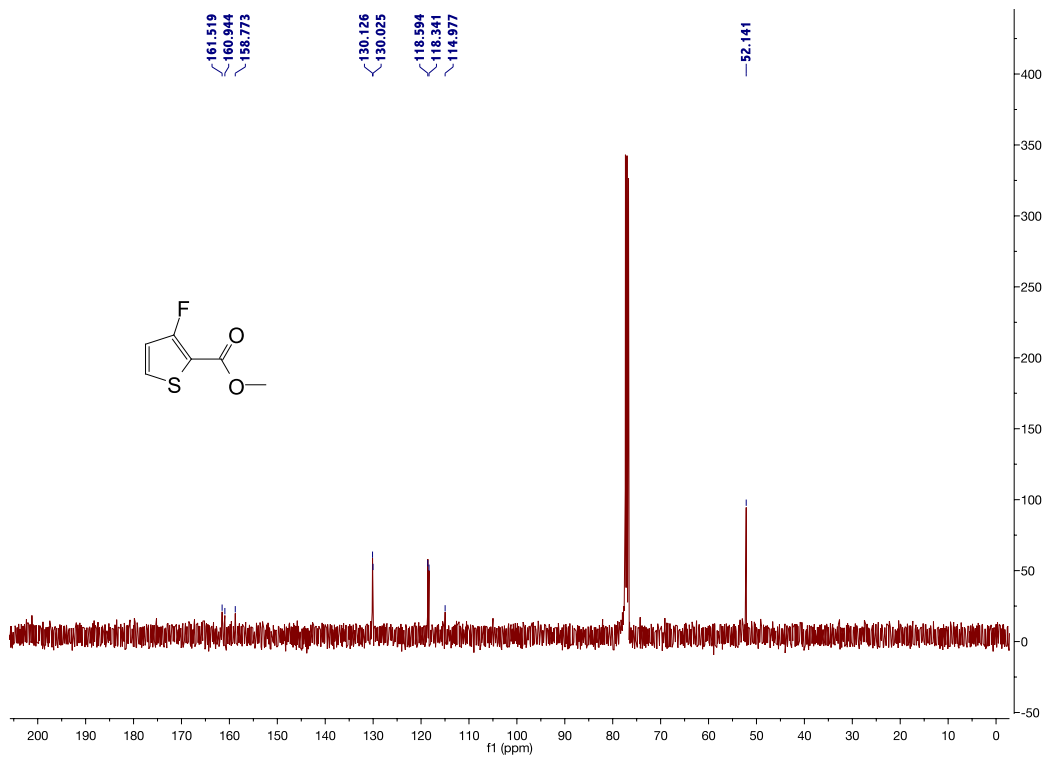
$^{19}\text{F}$  NMR for **Ref-4b** (376 MHz,  $\text{CDCl}_3$ )



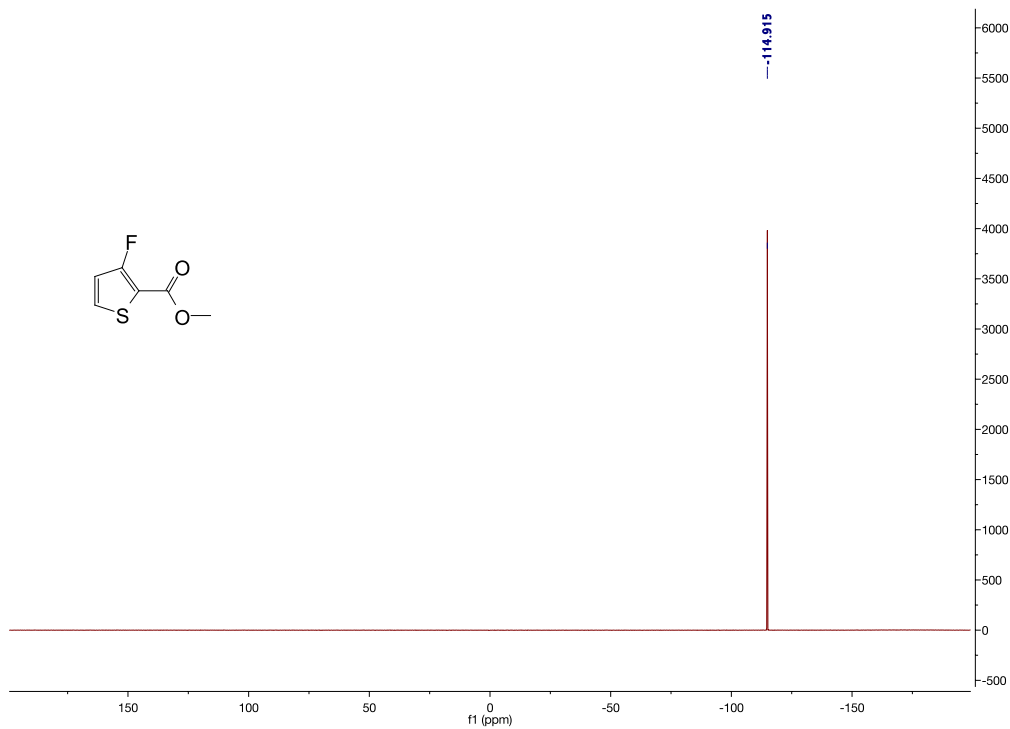
$^1\text{H}$  NMR for **Ref-15a** (400 MHz,  $\text{CDCl}_3$ )



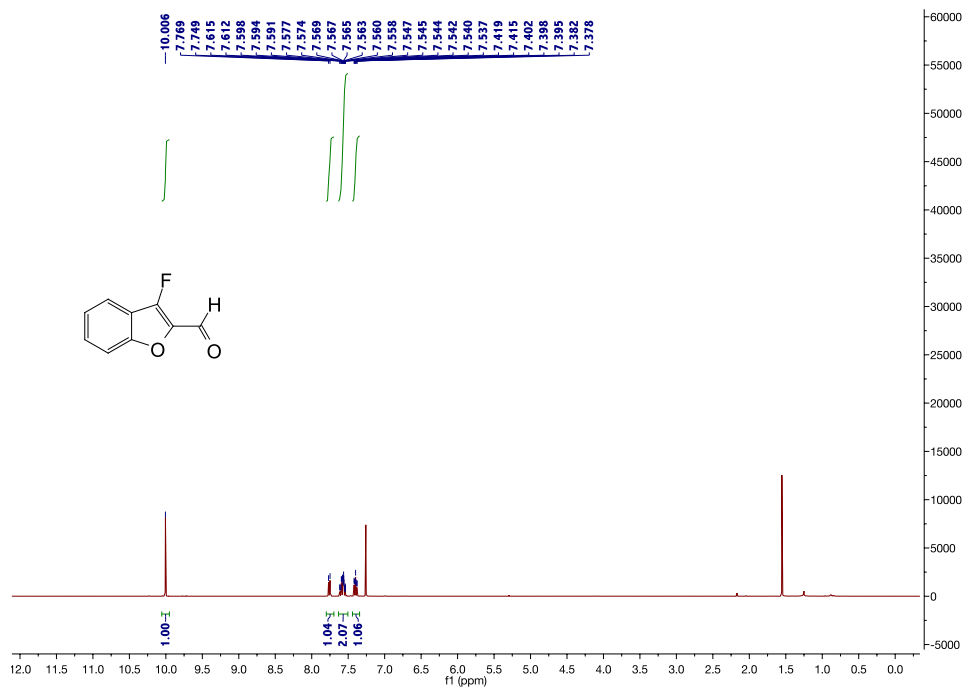
<sup>13</sup>C NMR for **Ref-15a** (100 MHz, CDCl<sub>3</sub>)



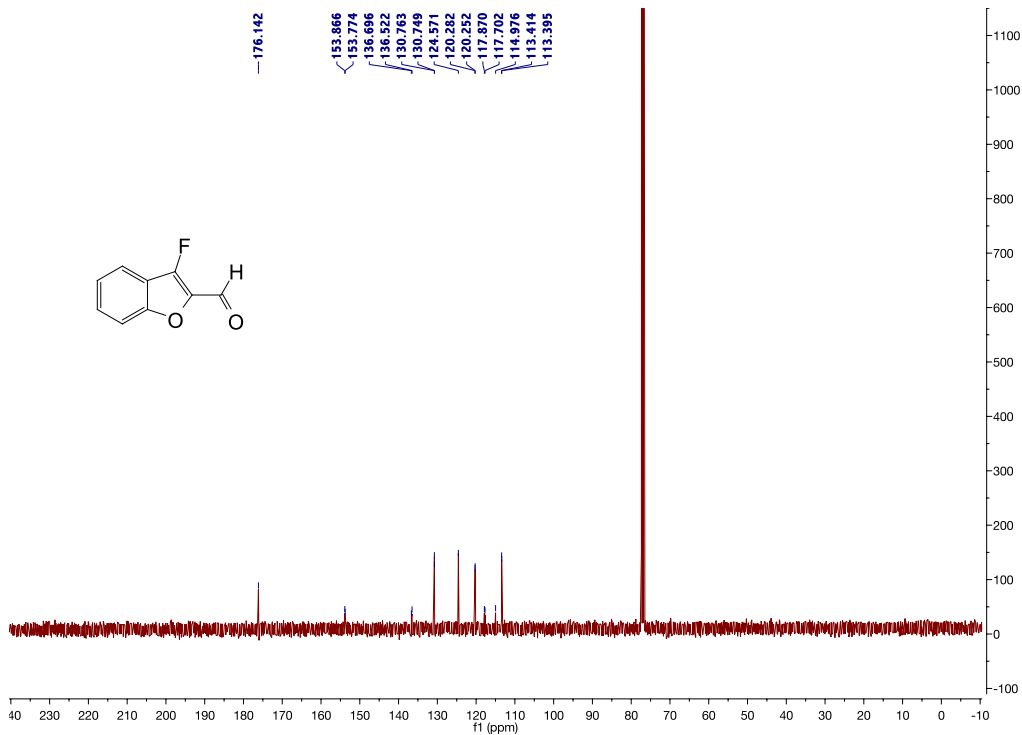
<sup>19</sup>F NMR for **Ref-15a** (376 MHz, CDCl<sub>3</sub>)



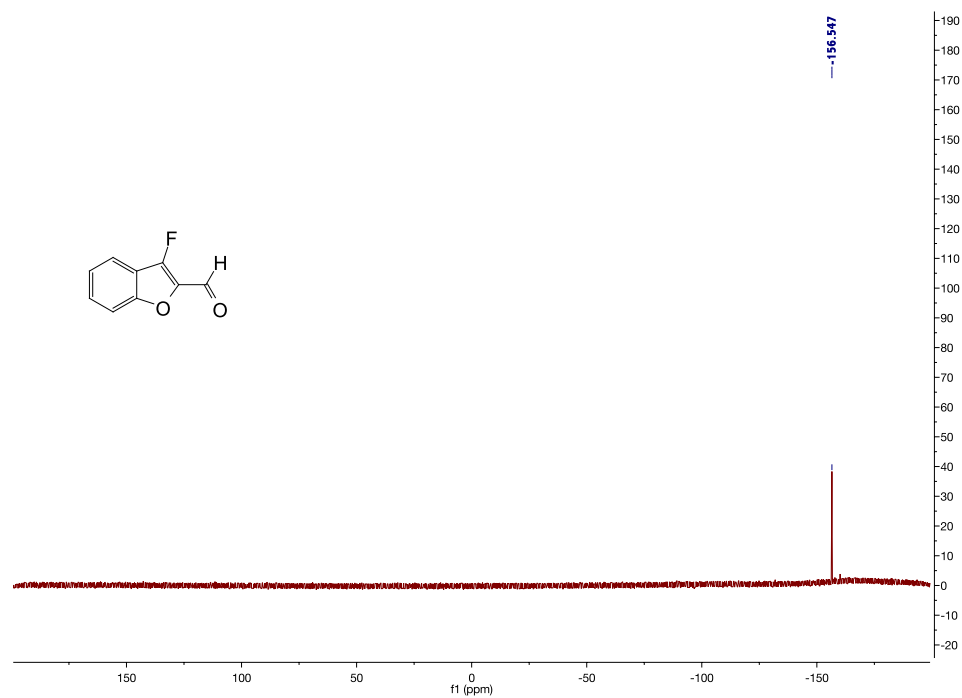
<sup>1</sup>H NMR for **24** (400 MHz, CDCl<sub>3</sub>)



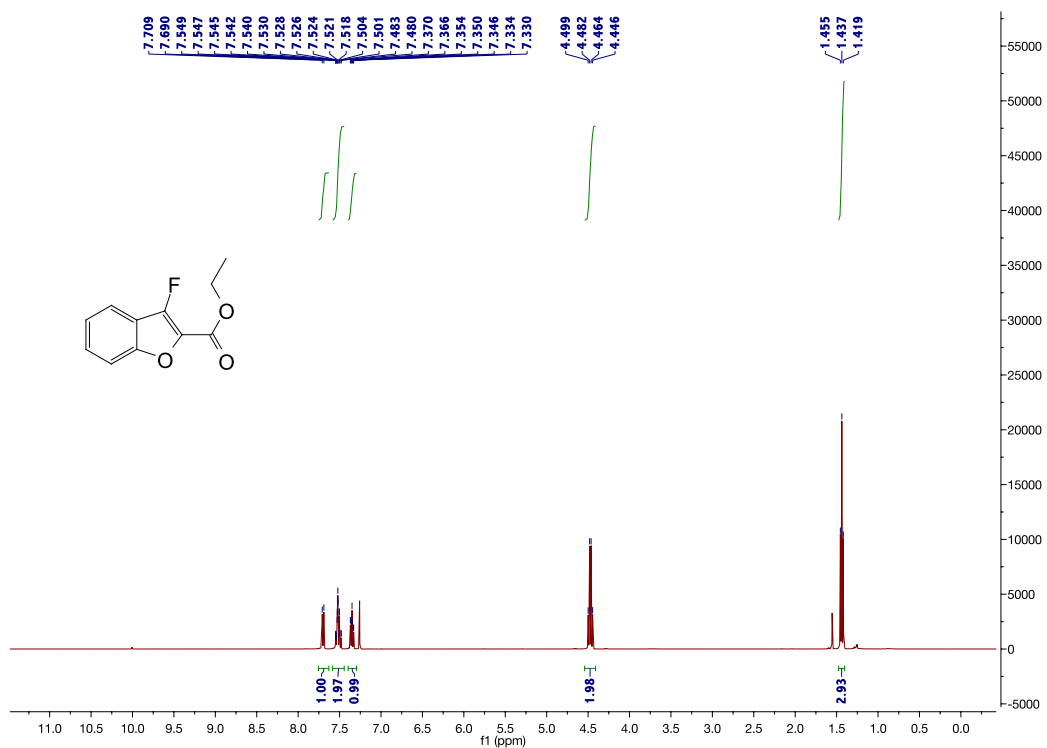
<sup>13</sup>C NMR for **24** (100 MHz, CDCl<sub>3</sub>)



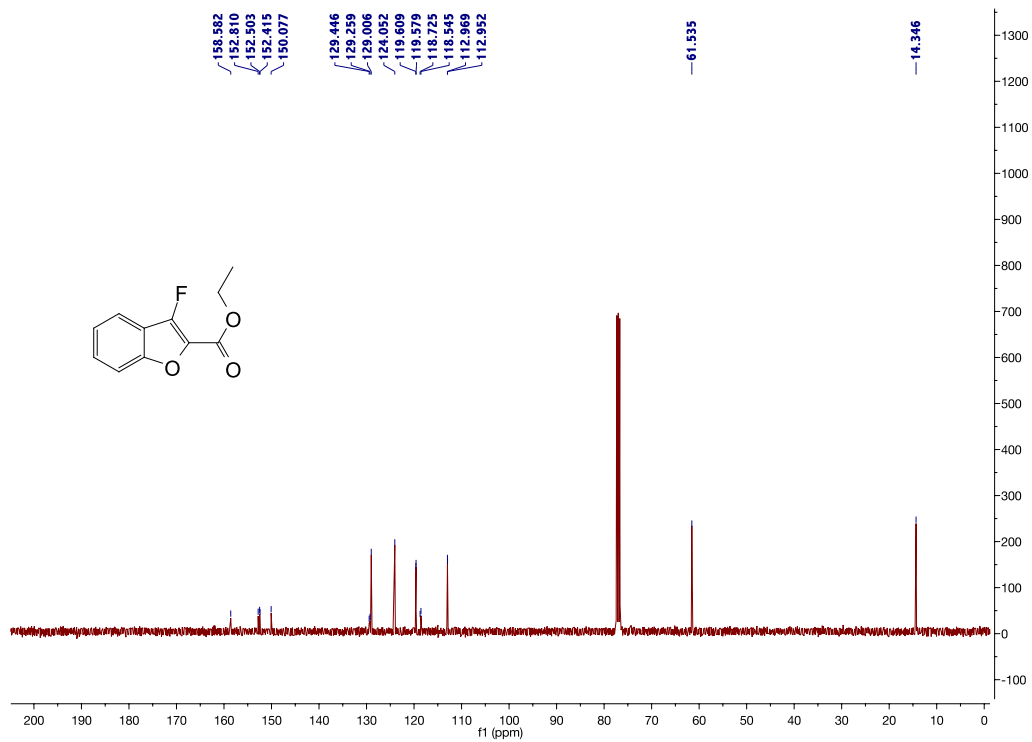
$^{19}\text{F}$  NMR for **24** (376 MHz,  $\text{CDCl}_3$ )



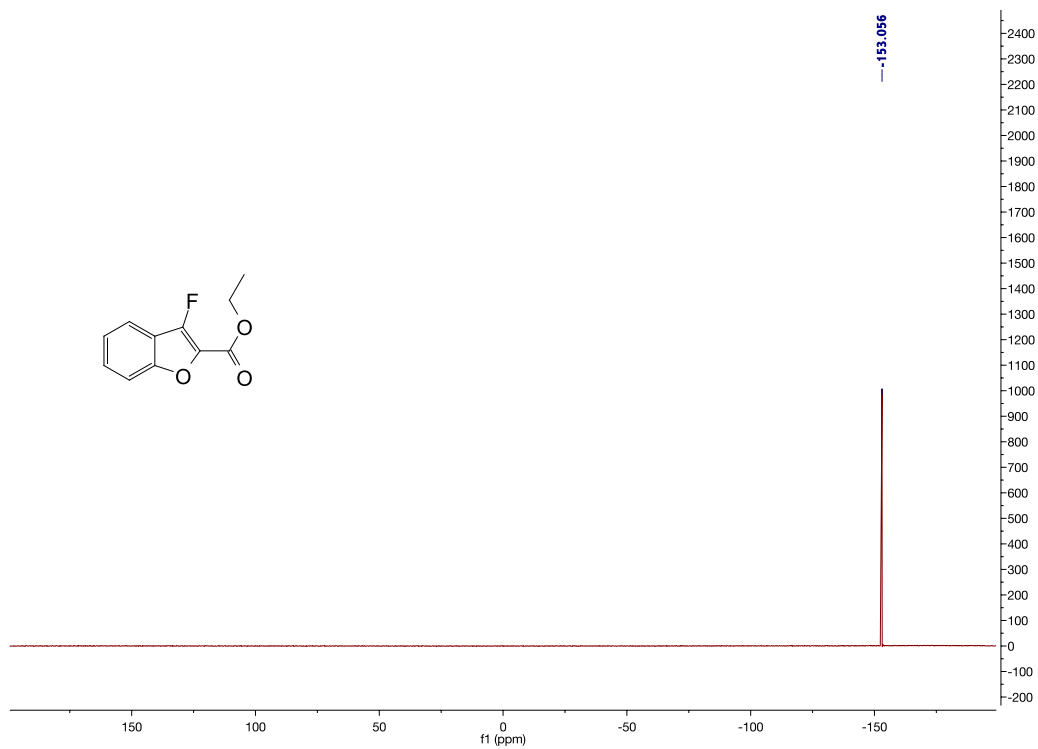
$^1\text{H}$  NMR Ref-16a (400 MHz,  $\text{CDCl}_3$ )



<sup>13</sup>C NMR Ref-16a (100 MHz, CDCl<sub>3</sub>)

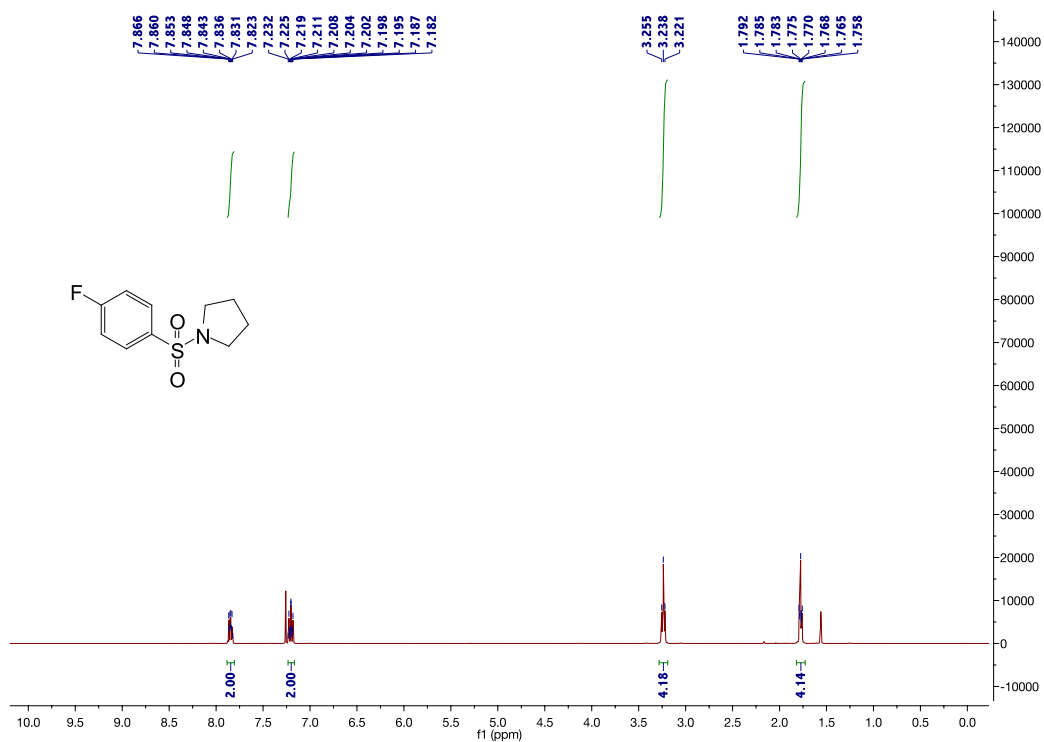


<sup>19</sup>F NMR Ref-16a (376 MHz, CDCl<sub>3</sub>)

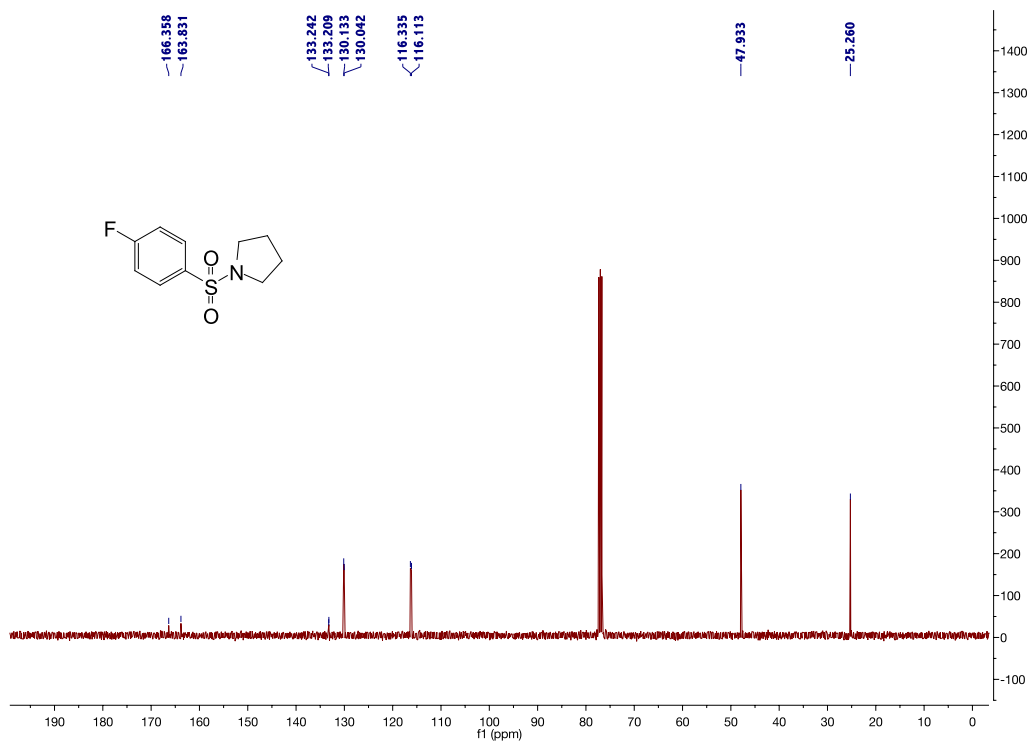




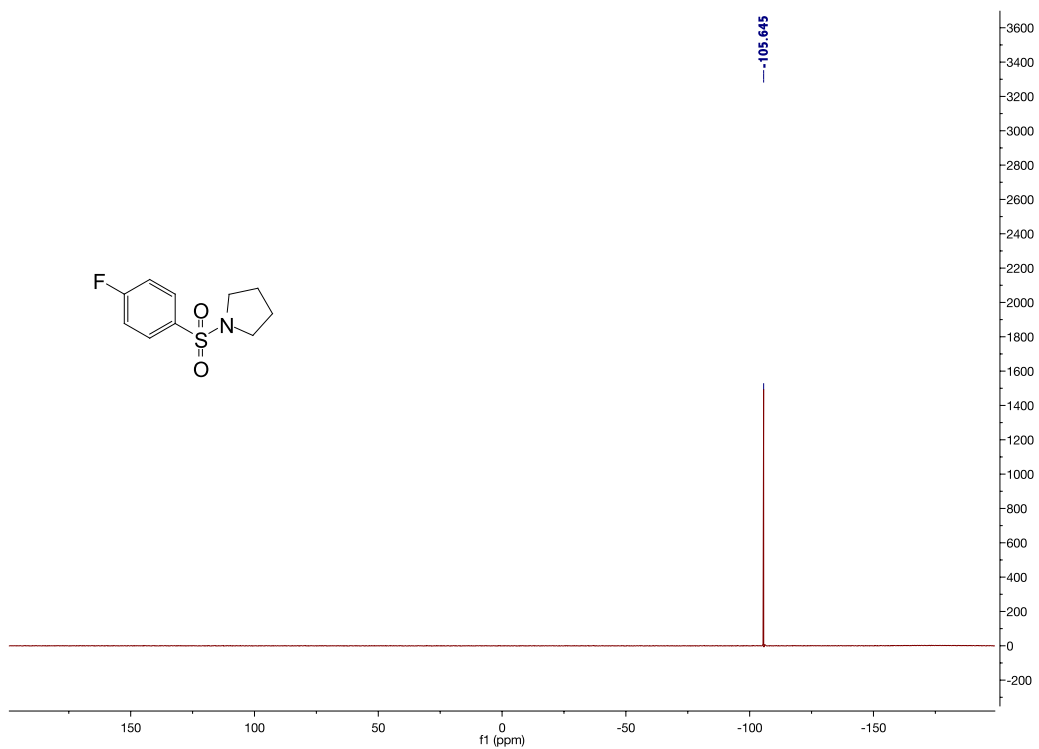
<sup>1</sup>H NMR Ref-18a (400 MHz, CDCl<sub>3</sub>)



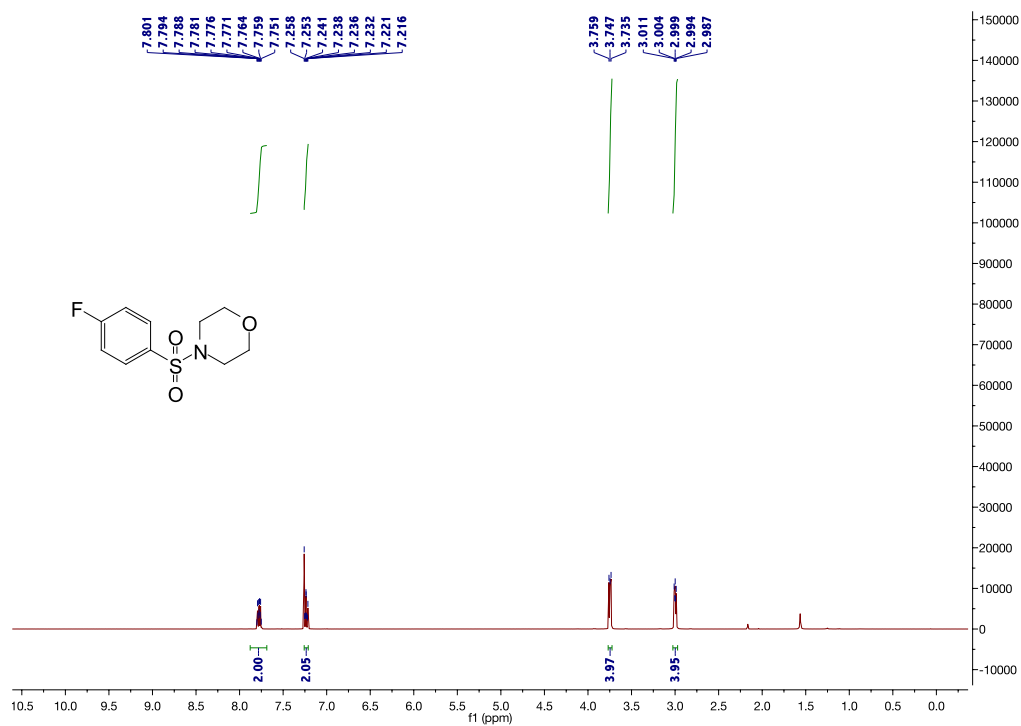
<sup>13</sup>C NMR Ref-18a (100 MHz, CDCl<sub>3</sub>)



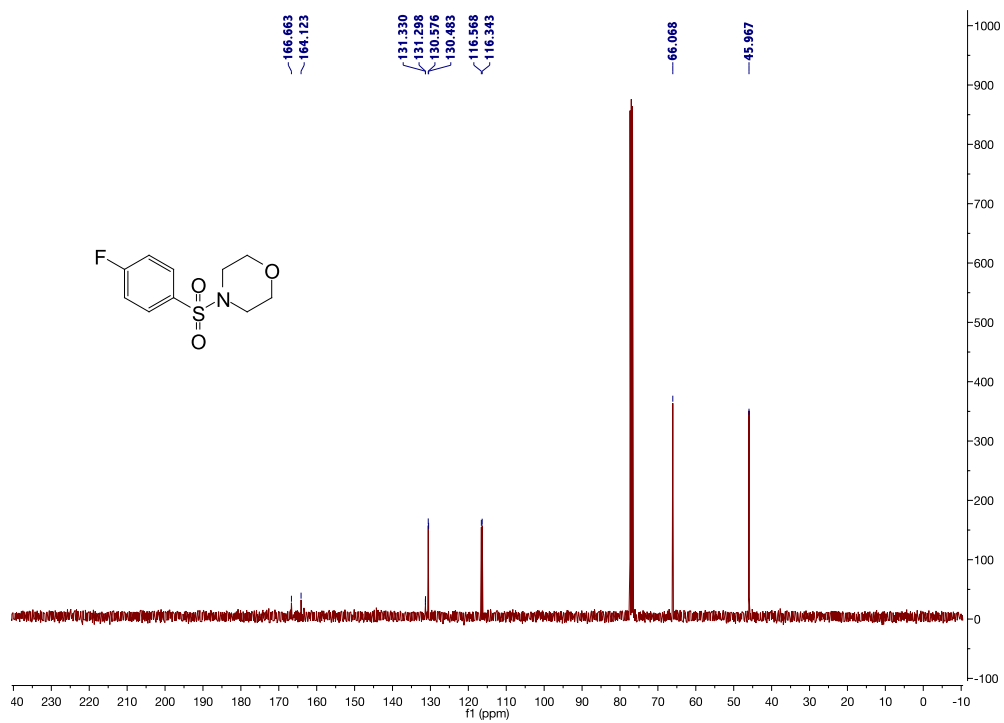
<sup>19</sup>F NMR Ref-18a (376 MHz, CDCl<sub>3</sub>)



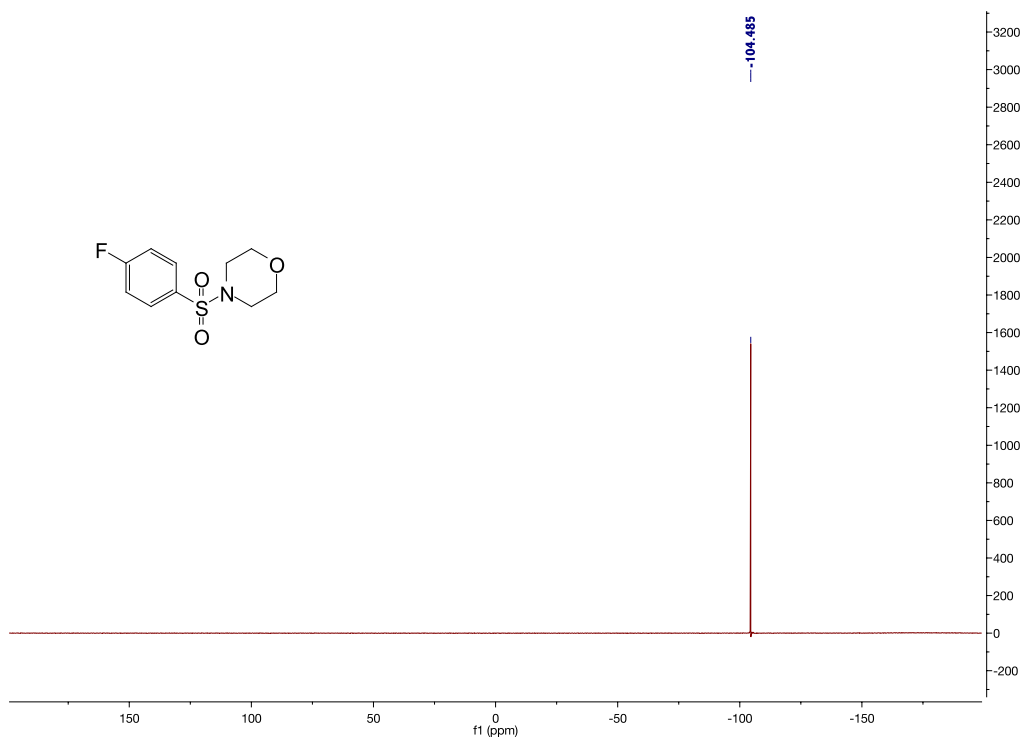
<sup>1</sup>H NMR Ref-19a (400 MHz, CDCl<sub>3</sub>)



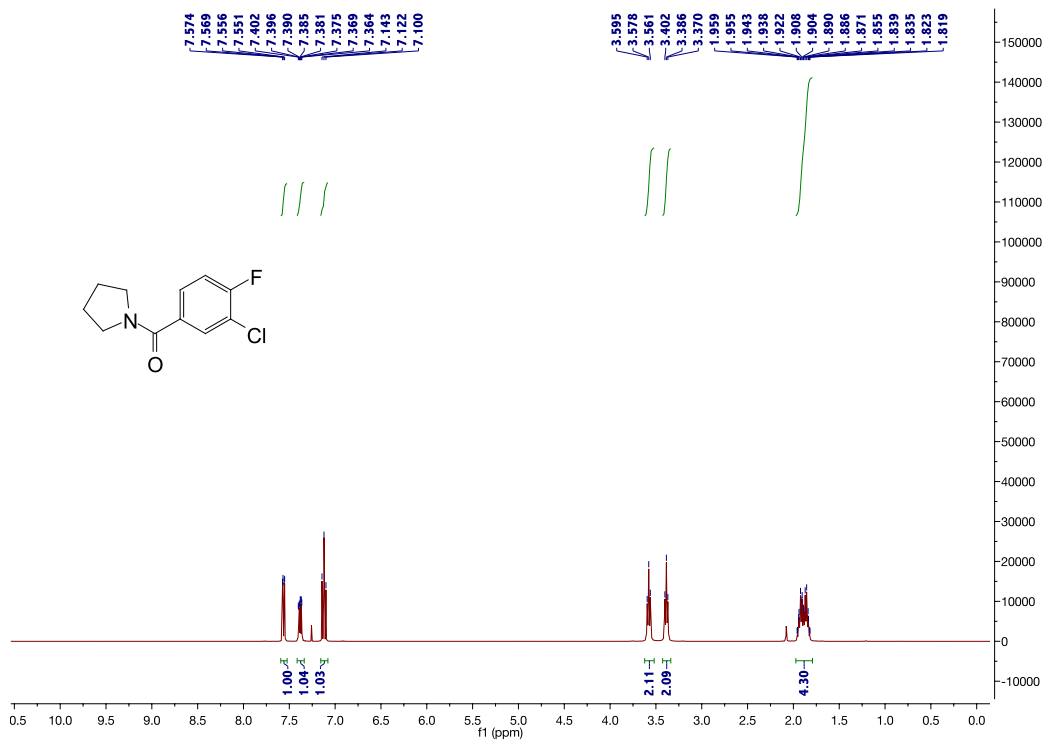
<sup>13</sup>C NMR Ref-19a (100 MHz, CDCl<sub>3</sub>)



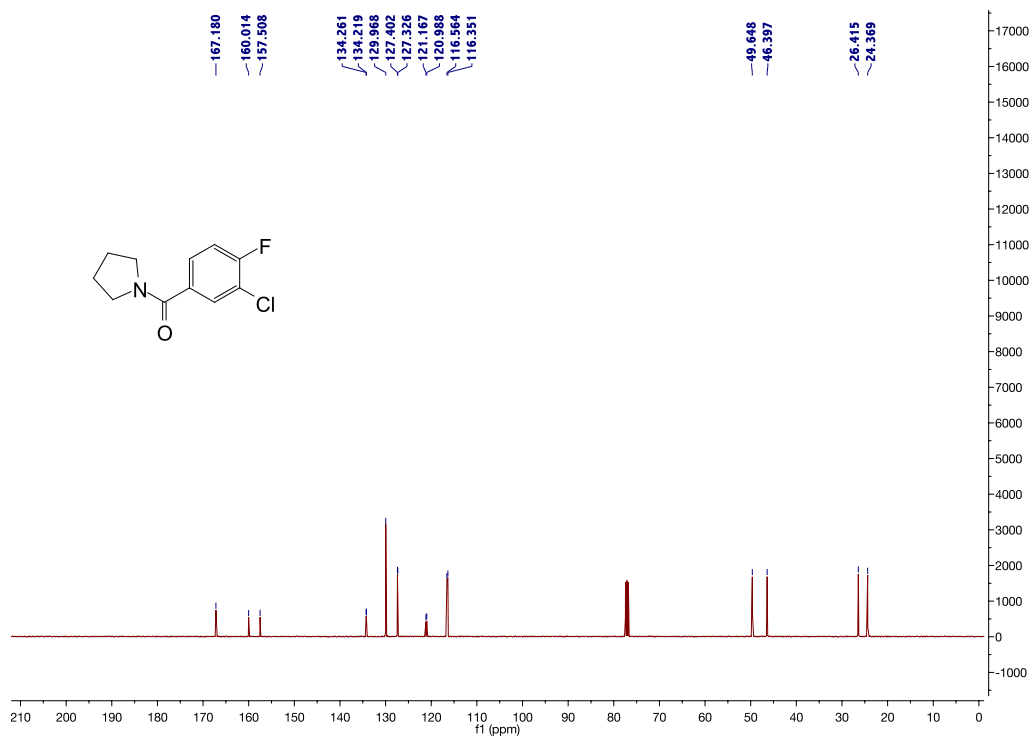
<sup>19</sup>F NMR Ref-19a (376 MHz, CDCl<sub>3</sub>)



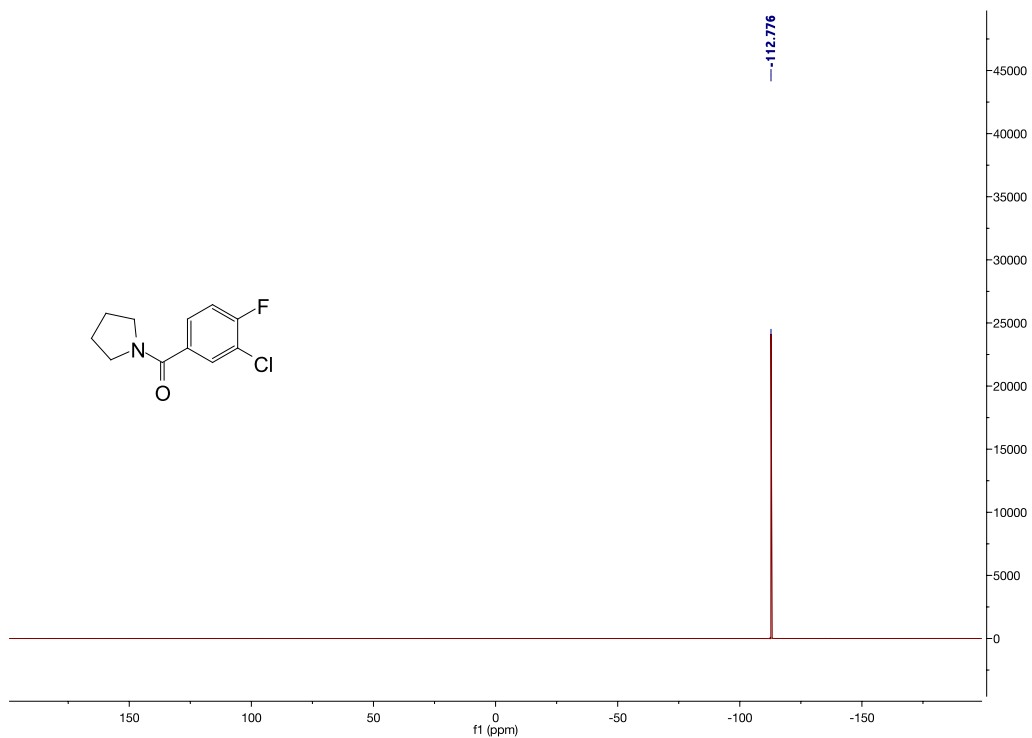
<sup>1</sup>H NMR Ref-20a (400 MHz, CDCl<sub>3</sub>)



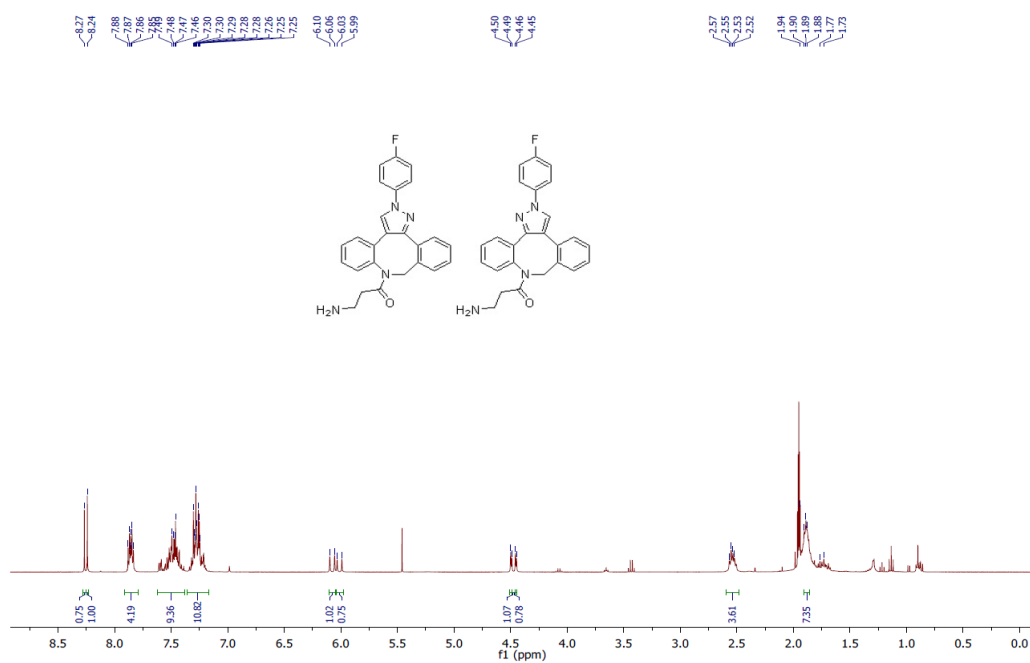
<sup>13</sup>C NMR Ref-20a (100 MHz, CDCl<sub>3</sub>)



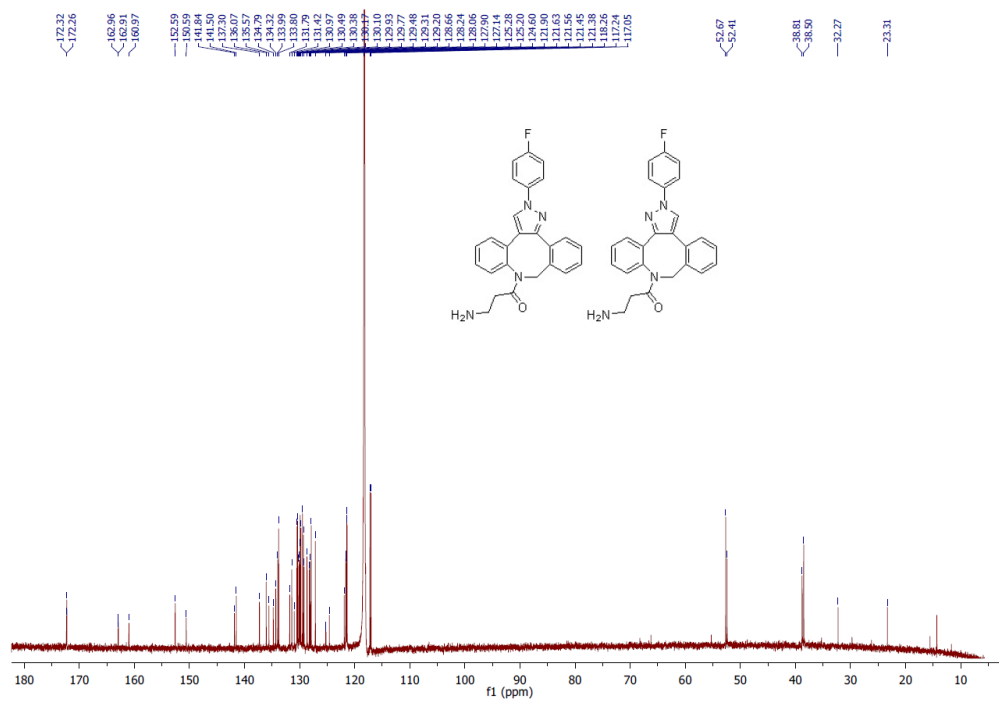
<sup>19</sup>F NMR Ref-20a (376 MHz, CDCl<sub>3</sub>)



<sup>1</sup>H NMR pyrazole (400 MHz, CD<sub>3</sub>CN, mixture of isomers)



<sup>13</sup>C NMR pyrazole (100 MHz, CD<sub>3</sub>CN, mixture of isomers)



<sup>19</sup>F NMR pyrazole (376 MHz, CD<sub>3</sub>CN, mixture of isomers)

