Development of small molecule inhibitors of ECM collagen secretion.

Electronic Supplementary Information (ESI)

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1.0 Chemistry

1.1 General methods and procedures.

All solvents and reagents were purchased from commercial sources and used as received. Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} coated aluminum-backed TLC sheets and visualized using a UV lamp (254 nm) or $KMnO_4$ staining. Flash column chromatography was carried out using RediSep gold® silica gel columns (400—632 mesh, pore size 60 Å, 20—40 µm) on a CombiFlash Nextgen 300+ (Teledyne Isco) automated purification system. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker 400 MHz spectrometer. ^{1}H NMR spectra chemical shifts (δ) are reported in parts per million (ppm) referenced to residual protonated solvent peak (chloroform-d δ = 7.26 ppm). Spectral data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, app t = apparent triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, br = broad), coupling constant (*J*) in Hertz (Hz), and integration. ^{13}C NMR spectra chemical shifts (δ) are reported in parts per million (ppm) and were referenced to carbon resonances in the NMR solvent (chloroform-d δ = 77.1 ppm). ^{19}F NMR spectra chemical shifts (*δ*) are reported in parts per million (ppm) and are uncorrected. High resolution mass spectra were obtained on a Waters Xevo G2-XS QToF high resolution mass spectrometer.

General procedure A: alkylation of phenols with benzyl halides. Phenol derivative (1.00 equiv.) was then dissolved in DMF and treated with 60% (*wt*) sodium hydride suspension in mineral oil (1.20 equiv.). The solution was stirred for ten minutes before addition of desired benzyl halide (1.20 equiv.). Once complete, the reaction was diluted with ethyl acetate and washed with a 1 M aqueous solution of hydrochloric acid, water, and brine. The organic phase was dried over anhydrous sodium sulfate, filtered and solvent was removed under reduced pressure. The crude isolate was purified by flash column chromatography on silica gel to afford the desired product.

General procedure B: Knoevenagel-Doebner reaction[1]. The benzaldehyde derivative (1.00 equiv.) was dissolved in pyridine, and malonic acid (3.00 equiv.) and piperidine (0.50 equiv.) were added. The solution was heated to 115 °C until the evolution of CO_2 had stopped and then cooled to room temperature. The solvent was removed under reduced pressure and the crude isolate was suspended in a 1.00% (*v*/*v*) aqueous solution of hydrochloric acid. The suspension was stored at 4 °C overnight and the precipitate was collected *via* filtration and washed with cyclohexane to yield the desired cinnamic acid derivative, which was used without further purification.

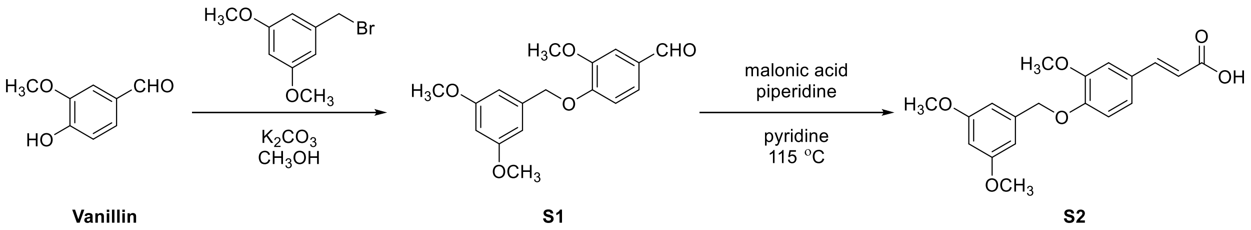
General procedure C: amidation reaction. *Method A*[2]: The carboxylic acid (1.10 equiv.) was dissolved in dichloromethane and *p*-toluenesulfonic anhydride (1.2 equiv.) and *N,N*-dimethylaminopyridine (2.4 equiv.) were added. The mixture was stirred for 10 minutes before addition of the amine (1.00 equiv.). The reaction mixture was stirred at room temperature until complete, then quenched with saturated aqueous sodium bicarbonate. The solution was extracted with ethyl acetate (x3) and the organic layers were combined and washed with saturated aqueous sodium bicarbonate, water, and brine. The organic phase was dried over anhydrous sodium sulfate, filtered and the solvent was removed under reduced pressure. The crude isolate was purified by flash column chromatography on silica gel to afford the desired amide. *Method B*: The carboxylic acid (1.00 equiv.) and HATU (1.20 equiv.) were dissolved in dichloromethane. *N,N*-diisopropylethylamine (3.00 equiv.) was added and the solution was stirred for five minutes before addition of the amine (1.20 equiv.). The solution was stirred at room temperature until complete, diluted with dichloromethane and washed with water (x2) and brine. The organic phase was dried over anhydrous sodium sulfate, filtered and solvent was removed under reduced pressure. The crude isolate was purified by flash column chromatography on silica gel to afford the desired amide.

General procedure D: S_NAr reaction of fluoro-substituted benzaldehydes. Amine (1.50 equiv.) was added to a stirred solution of 4-fluoro-3-methoxybenzaldehyde (1.00 equiv.) and potassium carbonate (1.50 equiv.) in DMSO:water (2.5:1 *v/v*). The solution was heated to 100 °C overnight and then cooled to room temperature. The solution was diluted with water and extracted three times with ethyl acetate. The organic extracts were combined and dried over anhydrous sodium sulfate, filtered and solvent was removed under reduced pressure. The crude isolate was purified by flash column chromatography on silica to afford the desired product.

General procedure E: ester hydrolysis. To a solution of ester (1.00 equiv.) in THF:water 2:1 (*v/v*) was added lithium hydroxide (5.00 equiv.). The reaction was heated to reflux and stirred until complete, then cooled to room temperature. Solution pH was adjusted to < 4 by addition of hydrochloric acid before extracting with ethyl acetate (x3). The organic extracts were combined and washed with brine, then dried over anhydrous sodium sulfate, filtered and solvent was removed under reduced pressure to afford the desired product, which was used without further purification.

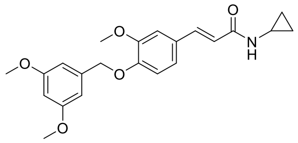
General procedure F: acylation or sulfonylation of anilines. *Method A*[3]: to a stirred solution of aniline (1.00 equiv.) and sodium carbonate (1.20 equiv.) in dichloromethane was added acyl chloride (1.20 equiv.). The solution was stirred at room temperature until complete, then diluted with water. The solution was extracted with dichloromethane (3x) and the organic extracts were combined and dried over anhydrous sodium sulfate, filtered and solvent was removed under reduced pressure. The crude isolate was purified by flash column chromatography on silica gel to afford the desired product. *Method B*[4]: to a solution of aniline (0.10 g, 0.36 mmol, 1.00 equiv.) in pyridine (5.00 mL) was added acyl- or sulfonyl chloride (1.20 equiv.). The solution was stirred at room temperature until complete, then diluted with dichloromethane. The solution was washed with a 1.00 M aqueous solution of hydrochloric acid, water, and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and solvent was removed under reduced pressure. The crude isolate was purified by flash column chromatography on silica gel to afford the desired product.

1.2 Synthesis and characterization: series 1 compounds.



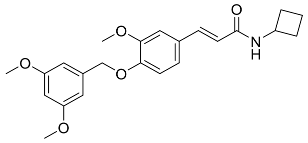
A round bottom flask equipped with Teflon-coated stir bar was charged with vanillin (9.89 g, 65.0 mmol, 1.00 equiv.), 3,5-dimethoxybenzyl bromide (18.0 g, 78.0 mmol, 1.20 equiv.), potassium carbonate (2.90 g, 21.0 mmol, 1.20 equiv.) and methanol (50 mL). The solution was stirred at room temperature overnight and then solvent was removed under reduced pressure. The crude material was dissolved in dichloromethane and washed with water (x3). The organic phase was dried over anhydrous sodium sulfate, filtered and solvent was removed under reduced pressure to yield **S1** as a white solid (18.3 g, 93%), which was used without further purification. **S1** was then used to generate **S2** according to **general procedure B**; **S2** was isolated as a white solid (15.0 g, 72%). ^{1}H NMR (400 MHz, CDCl$_3$): *δ* (ppm) 7.73 (d, *J* = 15.9 Hz, 1H), 7.12 (d, *J* = 2.0 Hz, 1H), 7.08 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.61 (d, *J* = 2.4 Hz, 2H), 6.43 (t, *J* = 2.3 Hz, 1H), 6.34 (d, *J* = 15.9 Hz, 1H), 5.18 (s, 2H), 3.96 (s, 3H), 3.82 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): *δ* (ppm) 171.8, 161.1, 150.6, 149.8, 146.8, 139.0, 127.5, 122.9, 115.0, 113.5, 110.4, 105.0, 99.9, 70.9, 56.0, 55.4.

_(E)-N_-cyclopropyl-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)acrylamide (3a).



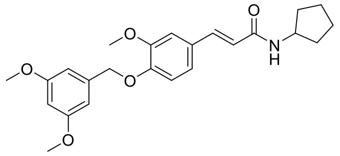
Prepared from **S2** (300 mg, 0.88 mmol, 1.10 equiv.) and cyclopropylamine (0.06 mL, 0.80 mmol, 1.00 equiv.) according to **general procedure C** (*method A*). White solid (250 mg, 82% yield). ^{1}H NMR (400 MHz, CDCl$_3$): *δ* (ppm) 7.57 (d, *J* = 15.5 Hz, 1H), 7.08–6.95 (m, 2H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.61 (d, *J* = 2.3 Hz, 2H), 6.42 (t, *J* = 2.3 Hz, 1H), 6.22 (d, *J* = 15.5 Hz, 1H), 5.72 (s, 1H), 5.15 (s, 2H), 3.93 (s, 3H), 3.81 (s, 6H), 2.85–2.78 (m, 1H), 0.88–0.80 (m, 2H), 0.61–0.49 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): *δ* (ppm) 167.4, 161.1, 149.7, 149.7 140.8, 139.2, 128.3, 121.7, 118.4, 113.7, 110.4, 105.0, 99.9, 70.9, 56.0, 55.4, 22.9, 6.7. HRMS (ESI, *m/z*): calcd for[$C_{22}H_{26}NO_5$] (M + H)$^+$ 384.1805, found 384.1807.

_(E)-N_-cyclobutyl-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)acrylamide (3b).



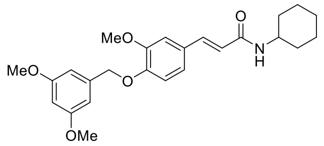
Prepared from **S2** (300 mg, 0.88 mmol, 1.10 equiv.) and cyclobutylamine (0.07 mL, 0.80 mmol, 1.00 equiv.) according to **general procedure C** (*method A*). White solid (310 mg, 96% yield). ^{1}H NMR (400 MHz, CDCl$_3$): *δ* (ppm) 7.51 (d, *J* = 15.5 Hz, 1H), 7.06–6.94 (m, 2H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 2H), 6.39 (t, *J* = 2.3 Hz, 1H), 6.22 (d, *J* = 15.5 Hz, 1H), 5.84–5.77 (m, 1H), 5.11 (s, 2H), 4.60–4.46 (m, 1H), 3.89 (s, 3H), 3.77 (s, 6H), 2.46–2.33 (m, 2H), 1.97–1.82 (m, 2H), 1.78–1.66 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): *δ* (ppm) 165.2, 161.2, 149.8, 149.8, 140.9, 139.4, 128.5, 121.7, 118.9, 113.8, 110.5, 105.1, 100.0, 71.0, 56.1, 55.5, 45.0, 31.6, 15.3. HRMS (ESI, *m/z*): calcd for[$C_{23}H_{28}NO_5$] (M + H)$^+$ 398.1967, found 398.1968.

_(E)-N_-cyclopentyl-3-(4-((3,5-dimethoxybenzyl) oxy)-3-methoxyphenyl) acrylamide (3c).



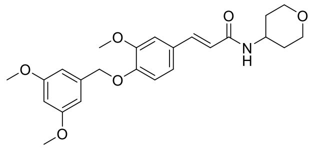
Prepared from **S2** (210 mg, 0.55 mmol, 1.10 equiv.) and cyclopentylamine (0.05 mL, 0.60 mmol, 1.00 equiv.) according to **general procedure C** (*method A*). White solid (180 mg, 88% yield). ^{1}H NMR (400 MHz, CDCl$_3$): *δ* (ppm) 7.55 (d, *J* = 15.5 Hz, 1H), 7.05 (d, *J* = 2.0 Hz, 1H), 7.04–6.98 (m, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.61 (d, *J* = 2.3 Hz, 2H), 6.42 (t, *J* = 2.3 Hz, 1H), 6.25 (d, *J* = 15.5 Hz, 1H), 5.58 (d, *J* = 7.4 Hz, 1H), 5.15 (s, 2H), 4.47–4.28 (m, 1H), 3.93 (s, 3H), 3.81 (s, 6H), 2.14–2.02 (m, 2H), 1.77–1.62 (m, 4H), 1.51–1.41 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): *δ* (ppm) 165.6, 161.1, 149.7, 149.6, 140.5, 139.3, 128.4, 121.6, 119.0, 113.7, 110.3, 105.0, 100.0, 70.9, 56.0, 55.4, 51.4, 33.3, 23.8. HRMS (ESI, *m/z*) calcd for [$C_{24}H_{30}NO_5$] (M + H)$^+$ 412.2124, found 412.2120.

***(E)*-*N*-cyclohexyl-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)acrylamide (3d).**



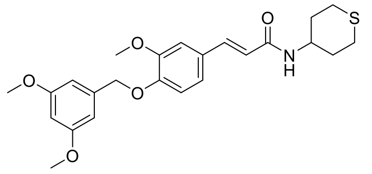
Prepared from **S2** (70.0 mg, 0.20 mmol, 1.00 equiv.) and cyclohexylamine (20.0 mg, 0.24 mmol, 1.20 equiv.) according to **general procedure C** (*method B*). White solid (60.0 mg, 64% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.52 (d, *J* = 15.5 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 6.99 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 2H), 6.39 (t, *J* = 2.3 Hz, 1H), 6.23 (d, *J* = 15.5 Hz, 1H), 5.46 (d, *J* = 8.0 Hz, 1H), 5.11 (s, 2H), 3.90 (s, 3H), 3.90 (1H), 3.79 (s, 6H), 2.00–1.96 (m, 2H), 1.75–1.70 (m, 2H), 1.68–1.62 (m, 1H), 1.46–1.35 (m, 2H), 1.25–1.12 (m, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 165.2, 161.2, 149.8, 149.7, 140.6, 139.4, 128.6, 121.7, 119.4, 113.8, 110.5, 105.1, 100.0, 71.1, 56.1, 55.5, 48.4, 33.4, 25.7, 25.0. HRMS (ESI, *m/z*) calcd for [C$_{25}$H$_{32}$NO$_5$] (M + H)$^+$ 426.2280, found 426.2281.

***(E)*-3-(4-((3,5-dimethoxy9benzyl)oxy)-3-methoxyphenyl)-*N*-(tetrahydro-2H-pyran-4-yl)acrylamide (3e).**



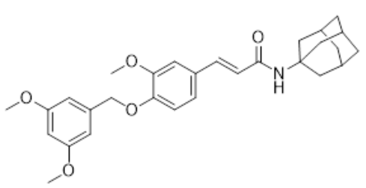
Prepared from **S2** (380 mg, 1.10 mmol, 1.10 equiv.) and 4-aminotetrahydropyran (0.10 mL, 1.00 mmol, 1.00 equiv.) according to **general procedure C** (*method A*). White solid (390 mg, 91% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.54 (d, *J* = 15.5 Hz, 1H), 7.05–6.96 (m, 2H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 2H), 6.39 (t, *J* = 2.3 Hz, 1H), 6.24 (d, *J* = 15.5 Hz, 1H), 5.53 (d, *J* = 8.0 Hz, 1H), 5.11 (s, 2H), 4.19–4.05 (m, 1H), 4.02–3.92 (m, 2H), 3.90 (s, 3H), 3.78 (s, 6H), 3.54–3.47 (m, 2H), 1.98–1.94 (m, 2H), 1.58–1.43 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 165.4, 161.2, 149.9, 149.8, 141.2, 139.3, 128.3, 121.8, 118.8, 113.8, 110.5, 105.1, 100.0, 71.0, 66.9, 56.1, 55.5, 45.9, 33.4. HRMS (ESI, *m/z*) calcd for [C$_{24}$H$_{30}$NO$_6$] (M + H)$^+$ 428.2073, found 428.2074.

***(E)*-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-*N*-(tetrahydro-2H-thiopyran-4-yl)acrylamide (3f).**



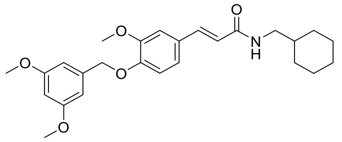
Prepared from **S2** (380 mg, 1.10 mmol, 1.10 equiv.) and 4-aminotetrahydrothiopyran (120 mg, 1.00 mmol, 1.00 equiv.) according to **general procedure C** (*method A*). White solid (430 ,g, 97% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.53 (d, *J* = 15.5 Hz, 1H), 7.06–6.96 (m, 2H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 2H), 6.39 (t, *J* = 2.3 Hz, 1H), 6.23 (d, *J* = 15.5 Hz, 1H), 5.52 (d, *J* = 8.3 Hz, 1H), 5.12 (s, 2H), 3.99–3.91 (m, 1H), 3.90 (s, 3H), 3.78 (s, 6H), 2.85–2.73 (m, 2H), 2.71–2.61 (m, 2H), 2.33–2.22 (m, 2H), 1.66–1.52 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 165.2, 161.2, 149.9, 149.8, 141.2, 139.3, 128.3, 121.9, 118.8, 113.8, 110.5, 105.1, 100.0, 71.0, 56.1, 55.5, 47.8, 34.4, 28.0. HRMS (ESI, *m/z*) calcd for [C$_{24}$H$_{30}$NO$_5$S] (M + H)$^+$ 444.1845, found 444.1848.

(E)-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-N-(adamantyl)acrylamide (3g).



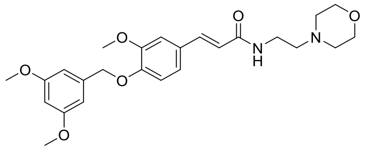
Prepared from **S2** (340 mg, 1.00 mmol, 1.00 equiv.) and 1-adamantylamine (180 mg, 1.20 mmol, 1.20 equiv.) according to **general procedure C** (*method B*). Brown solid (400 mg, 84% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.45 (d, *J* = 15.5 Hz, 1H), 7.01 (d, *J* = 2.0 Hz, 1H), 6.97 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 2H), 6.39 (t, *J* = 2.3 Hz, 1H), 6.19 (d, *J* = 15.5 Hz, 1H), 5.27 (s, 1H), 5.11 (s, 2H), 3.90 (s, 3H), 3.78 (s, 6H), 2.12–2.04 (m, 9H), 1.76–1.65 (m, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 165.1, 161.1, 149.7, 149.5, 140.0, 139.3, 128.5, 121.6, 120.3, 113.7, 110.2, 105.0, 99.9, 70.9, 56.0, 55.4, 52.2, 41.8, 36.4, 29.5. HRMS (ESI, *m/z*) calcd for [$C_{29}H_{36}NO_5$] (M + H)$^+$ 478.2593, found 478.2598.

(E)-N-(cyclohexylmethyl)-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)acrylamide (3h).



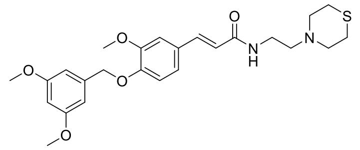
Prepared from **S2** (380 mg, 1.10 mmol, 1.10 equiv.) and cyclohexanemethylamine (0.13 mL, 1.00 mmol, 1.00 equiv.) according to **general procedure C** (*method A*). White solid (400 mg, 91% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.53 (d, *J* = 15.5 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 6.99 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 2H), 6.39 (t, *J* = 2.3 Hz, 1H), 6.26 (d, *J* = 15.5 Hz, 1H), 5.69 (t, *J* = 5.9 Hz, 1H), 5.11 (s, 2H), 3.90 (s, 3H), 3.77 (s, 6H), 3.22 (app t, *J* = 6.5 Hz, 2H), 1.80–1.70 (m, 4H), 1.69–1.62 (m, 1H), 1.57–1.46 (m, 1H), 1.29–1.13 (m, 3H), 1.01–0.91 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 166.2, 161.2, 149.8, 149.7, 140.7, 139.4, 128.5, 121.7, 119.1, 113.8, 110.5, 105.1, 100.0, 71.7, 56.1, 55.5, 40.1, 38.2, 31.0, 26.5, 26.0. HRMS (ESI, *m/z*) calcd for [$C_{26}H_{34}NO_5$] (M + H)$^+$ 440.2437, found 440.2440.

(E)-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-N-(2-morpholinoethyl)acrylamide (3i).



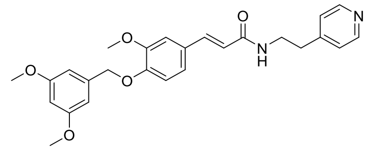
Prepared from **S2** (340 mg, 1.00 mmol, 1.00 equiv.) and 4-(2-aminoethyl)morpholine (0.16 mL, 1.20 mmol, 1.20 equiv.) according to **general procedure C** (*method B*). White solid (440 mg, 97% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.53 (d, *J* = 15.5 Hz, 1H), 7.06 (d, *J* = 2.0 Hz, 1H), 7.01 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.58 (d, *J* = 2.2 Hz, 2H), 6.39 (t, *J* = 2.2 Hz, 1H), 6.31 (d, *J* = 15.5 Hz, 1H), 6.29 (1H), 5.11 (s, 2H), 3.91 (s, 3H), 3.77 (s, 6H), 3.75 (app t, *J* = 4.5 Hz, 4H), 3.52–3.48 (m, 2H), 2.62 (t, *J* = 5.8 Hz, 2H), 2.56 (app t, *J* = 4.5 Hz, 4H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 166.7, 161.2, 149.9, 149.9 141.1, 139.3, 128.4, 122.0, 118.6, 113.8, 110.5, 105.1, 100.0, 71.0, 66.8, 57.5, 56.2, 55.5, 53.4, 36.0. HRMS (ESI, *m/z*) calcd for [$C_{25}H_{33}N_2O_6$] (M + H)$^+$ 457.2339, found 457.2239.

(E)-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-*N*-(2-thiomorpholinoethyl) acrylamide (3j).



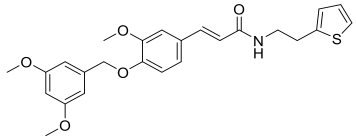
Prepared from **S2** (340 mg, 1.00 mmol, 1.00 equiv.) and 4-(2-aminoethyl)-thiomorpholine (0.19 mL, 1.30 mmol, 1.30 equiv.) according to **general procedure C** (*method A*). White solid (380 mg, 81% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.54 (d, J = 15.5 Hz, 1H), 7.07–6.98 (m, 2H), 6.84 (d, J = 8.3 Hz, 1H), 6.58 (d, J = 2.3 Hz, 2H), 6.39 (t, J = 2.3 Hz, 1H), 6.27 (d, J = 15.5 Hz, 1H), 6.15–6.06 (m, 1H), 5.12 (s, 2H), 3.92 (s, 3H), 3.78 (s, 6H), 3.51–3.42 (m, 2H), 2.79–2.73 (m, 4H), 2.72–2.66 (m, 4H), 2.56 (t, J = 6.0 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 166.1, 161.2, 149.8, 149.8, 140.9, 139.3, 128.4, 121.9, 118.8, 113.8, 110.5, 105.1, 100.0, 71.1, 57.4, 56.2, 55.5, 55.0, 36.0, 28.0. HRMS (ESI, *m/z*) calcd for [$C_{25}H_{33}N_2O_5S$] (M + H)$^+$ 473.2110, found 473.2112.

(E)-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-*N*-(2-(pyridin-4-yl)ethyl)acrylamide (3k).



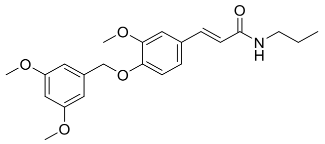
Prepared from **S2** (340 mg, 1.00 mmol, 1.00 equiv.) and 4-(2-aminoethyl)pyridine (0.14 mL, 1.20 mmol, 1.20 equiv.) according to **general procedure C** (*method B*). White solid (410 mg, 91% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 8.54–8.47 (m, 2H), 7.64–7.58 (m, 1H), 7.55 (d, J = 15.5 Hz, 1H), 7.33–7.25 (m, 1H), 7.06 (d, J = 2.0 Hz, 1H), 7.00 (dd, J = 8.4, 2.0 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.60 (d, J = 2.3 Hz, 2H), 6.42 (t, J = 2.3 Hz, 1H), 6.25 (d, J = 15.5 Hz, 1H), 5.84–5.77 (m, 1H), 5.14 (s, 2H), 3.93 (s, 3H), 3.81 (s, 6H), 3.78–3.63 (m, 2H), 2.93 (t, J = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 166.3, 161.1, 150.0, 149.7, 147.8, 141.1, 139.2, 136.6, 128.2, 123.7, 121.9, 118.4, 113.7, 110.2, 105.0, 99.9, 70.9, 56.0, 55.4, 40.5, 33.0. HRMS (ESI, *m/z*) calcd for [$C_{26}H_{29}N_2O_5$] (M + H)$^+$ 449.2076, found 449.2081.

(E)-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-*N*-(2-(thiophen-2-yl)ethyl)acrylamide (3l).



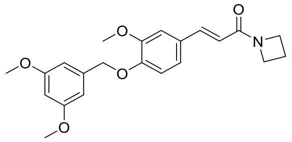
Prepared from **S2** (340 mg, 1.00 mmol, 1.00 equiv.) and 2-thiopheneethylamine (0.14 mL, 1.20 mmol, 1.20 equiv.) according to **general procedure C** (*method B*).White solid (360 mg, 80% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.53 (d, J = 15.5 Hz, 1H), 7.17 (dd, J = 5.1, 1.2 Hz, 1H), 7.07–6.89 (m, 3H), 6.88–6.85 (m, 1H), 6.83 (d, J = 8.3 Hz, 1H), 6.58 (d, J = 2.4 Hz, 2H), 6.39 (t, J = 2.3 Hz, 1H), 6.21 (d, J = 15.5 Hz, 1H), 5.80–5.70 (m, 1H), 5.12 (s, 2H), 3.90 (s, 3H), 3.78 (s, 6H), 3.69–3.64 (m, 2H), 3.10 (t, J = 6.5 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 166.1, 161.1, 149.7, 149.7, 141.4, 141.0, 139.2, 128.3, 127.1, 125.5, 124.0, 121.8, 118.6, 113.7, 110.3, 105.0, 99.9, 70.9, 56.0, 55.4, 41.0, 30.0. HRMS (ESI, *m/z*) calcd for [$C_{25}H_{28}NO_5S$] (M + H)$^+$ 454.1688, found 454.1691.

(E)-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-*N*-propylacrylamide (3m).



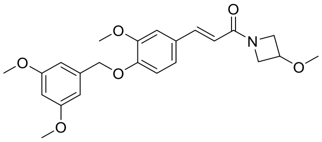
Prepared from **S2** (380 mg, 1.10 mmol, 1.10 equiv.) and propylamine (0.08 mL, 1.00 mmol, 1.00 equiv.) according to **general procedure C** (*method A*). White solid (380 mg, 97% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.53 (d, J = 15.5 Hz, 1H), 7.06–6.96 (m, 2H), 6.83 (d, J = 8.3 Hz, 1H), 6.61–6.55 (m, 2H), 6.39 (t, J = 2.3 Hz, 1H), 6.25 (d, J = 15.5 Hz, 1H), 5.62 (t, J = 5.4 Hz, 1H), 5.11 (s, 2H), 3.90 (s, 3H), 3.78 (s, 6H), 3.41–3.30 (m, 2H), 1.62–1.56 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 166.1, 161.1, 149.7, 149.6, 140.6, 139.3, 128.4, 121.6, 118.9, 113.7, 110.4, 105.0, 99.9, 70.9, 56.0, 55.4, 41.5, 23.0, 11.4. HRMS (ESI, *m/z*) calcd for [$C_{22}H_{28}NO_5$] (M + H)$^+$ 386.1967, found 386.1966.

(E)-1-(azetidin-1-yl)-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)prop-2-en-1-one (3n).



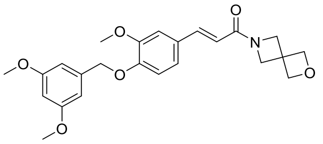
Prepared from **S2** (300 mg, 0.88 mmol, 1.10 equiv.) and azetidine (0.05 mL, 0.80 mmol, 1.00 equiv.) according to **general procedure C** (*method A*). White solid (240 mg, 78% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.59 (d, J = 15.6 Hz, 1H), 7.06–7.00 (m, 2H), 6.87 (d, J = 8.8 Hz, 1H), 6.61 (d, J = 2.3 Hz, 2H), 6.42 (t, J = 2.3 Hz, 1H), 6.33 (d, J = 15.6 Hz, 1H), 5.12 (s, 2H), 4.32 (app t, J = 7.6 Hz, 2H), 4.19–4.08 (m, 2H), 3.92 (s, 3H), 3.78 (s, 6H), 2.35–2.30 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 166.4, 161.2, 149.8, 149.8, 141.3, 139.4, 128.7, 121.8, 113.9, 113.8, 111.0, 105.1, 100.0, 71.1, 56.2, 55.5, 50.2, 48.2, 15.5. HRMS (ESI, *m/z*) calcd for [$C_{22}H_{26}NO_5$] (M + H)$^+$ 384.1811, found 384.1815.

(E)-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-1-(3-methoxyazetidin-1-yl)prop-2-en-1-one (3o).



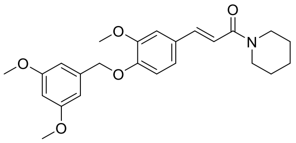
Prepared from **S2** (300 mg, 0.88 mmol, 1.10 equiv.) and 3-methoxyazetidine (0.08 mL, 0.80 mmol, 1.00 equiv.) according to **general procedure C** (*method A*). White solid (160 mg, 48% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.57 (d, J = 15.6 Hz, 1H), 7.07–7.00 (m, 2H), 6.84 (d, J = 8.9 Hz, 1H), 6.58 (t, J = 1.6 Hz, 2H), 6.39 (t, J = 2.3 Hz, 1H), 6.30 (d, J = 15.6 Hz, 1H), 5.12 (s, 2H), 4.46–4.36 (m, 1H), 4.30–4.21 (m, 2H), 4.16–4.09 (m, 1H), 4.02–3.95 (m, 1H), 3.92 (s, 3H), 3.78 (s, 6H), 3.33 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 166.7, 161.2, 150.0, 149.8, 141.8, 139.3, 128.5, 121.9, 113.9, 113.8, 111.0, 105.1, 100.0, 71.1, 69.1, 56.3, 56.2, 55.5, 55.0. HRMS (ESI, *m/z*) calcd for [$C_{23}H_{28}NO_6$] (M + H)$^+$ 414.1917, found 414.1920.

(E)-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-1-(2-oxa-6-azaspiro[3.3]heptan-6-yl)prop-2-en-1-one (3p).



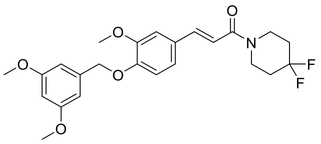
Prepared from **S2** (380 mg, 1.10 mmol, 1.10 equiv.) and 2-oxa-6-azaspiro[3.3]heptane (0.09 mL, 1.00 mmol, 1.00 equiv.) according to **general procedure C** (*method A*). White solid (260 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.56 (d, J = 15.6 Hz, 1H), 7.03 (d, J = 7.6 Hz, 2H), 6.88–6.81 (m, 1H), 6.58 (d, J = 2.3 Hz, 2H), 6.39 (t, J = 2.3 Hz, 1H), 6.26 (d, J = 15.6 Hz, 1H), 5.12 (s, 2H), 4.82 (s, 2H), 4.81 (s, 2H), 4.43 (br s, 2H), 4.25 (br s, 2H), 3.92 (s, 3H), 3.78 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 166.4, 161.1, 149.9, 149.7, 142.0, 139.2, 128.2, 121.8, 113.7, 113.2, 110.8, 105.0, 99.8, 80.9, 70.9, 59.8, 57.5, 56.1, 55.4, 37.9. HRMS (ESI, *m/z*) calcd for [$C_{24}H_{28}NO_6$] $(M + H)^+$ 426.1917, found 426.1913.

(E)-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-1-(piperidin-1-yl)prop-2-en-1-one (3q).



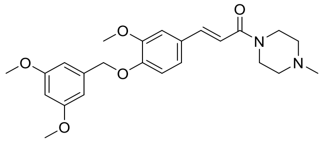
Prepared from **S2** (300 mg, 0.88 mmol, 1.10 equiv.) and piperidine (0.08 mL, 0.80 mmol, 1.00 equiv.) according to **general procedure C** (*method A*). White solid (300 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.57 (d, J = 15.4 Hz, 1H), 7.06–6.99 (m, 2H), 6.88–6.80 (m, 1H), 6.74 (d, J = 15.4 Hz, 1H), 6.58 (d, J = 2.3 Hz, 2H), 6.39 (t, J = 2.3 Hz, 1H), 5.12 (s, 2H), 3.93 (s, 3H), 3.78 (s, 6H), 3.73–3.45 (m, 4H), 1.73–1.55 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 165.6, 161.2, 149.8, 149.6, 142.2, 139.4, 129.1, 121.5, 115.8, 113.9, 110.7, 105.0, 99.9, 71.0, 56.2, 55.5, 24.8; *four piperidine carbon signals not observed due to quadrupolar effects of the nitrogen atom*. HRMS (ESI, *m/z*) calcd for [$C_{24}H_{30}NO_5$] $(M + H)^+$ 412.2124, found 412.2126.

(E)-1-(4,4-difluoropiperidin-1-yl)-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)prop-2-en-1-one (3r).



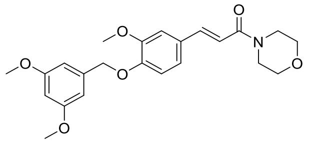
Prepared from **S2** (380 mg, 1.10 mmol, 1.10 equiv.) and 4,4-difluoropiperidine hydrochloride (0.16 g, 1.00 mmol, 1.00 equiv.) according to **general procedure C** (*method A*).White solid (330 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.62 (d, J = 15.3 Hz, 1H), 7.08–7.00 (m, 2H), 6.86 (d, J = 8.9 Hz, 1H), 6.72 (d, J = 15.3 Hz, 1H), 6.58 (d, J = 2.2 Hz, 2H), 6.39 (t, J = 2.3 Hz, 1H), 5.13 (s, 2H), 3.93 (s, 3H), 3.78 (s, 6H), 3.80–3.76 (m, 4H), 2.10–1.95 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 165.9, 161.2, 150.0, 149.9, 143.8, 139.2, 128.6, 121.8, 114.4, 113.9, 110.8, 105.1, 100.0, 77.1, 56.3, 55.5*; five piperidine carbon signals not observed due to quadrupolar effects of the nitrogen atom*. ^{19}F NMR (376 MHz, $CDCl_3$): δ (ppm) −97.74 (m). HRMS (ESI, *m/z*) calcd for [$C_{24}H_{28}F_2NO_5$] $(M + H)^+$ 448.1936, found 448.1938.

(E)-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-1-(4-methylpiperazin-1-yl)prop-2-en-1-one (3s).



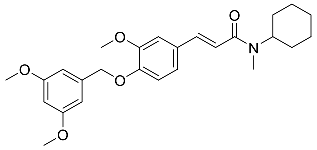
Prepared from **S2** (300 mg, 0.88 mmol, 1.10 equiv.) and 1-methylpiperazine (0.09 mL, 0.80 mmol, 1.00 equiv.) according to **general procedure C** (*method A*). White solid (290 mg, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* (ppm) 7.59 (d, *J* = 15.3 Hz, 1H), 7.07–6.99 (m, 2H), 6.85 (d, *J* = 8.9 Hz, 1H), 6.71 (d, *J* = 15.3 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 2H), 6.39 (t, *J* = 2.3 Hz, 1H), 5.12 (s, 2H), 3.92 (s, 3H), 3.78 (s, 6H), 3.76–3.59 (m, 4H), 2.44 (app t, *J* = 5.1 Hz, 4H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* (ppm) 165.4, 160.9, 149.5, 149.4, 142.5, 139.0, 128.6, 121.5, 114.9, 113.5, 110.4, 104.8, 99.6, 70.7, 55.9, 55.1, 55.1, 54.6, 45.8, 45.5, 41.9. HRMS (ESI, *m/z*) calcd for $[C_{24}H_{31}N_2O_5]$ (M + H)$^+$ 427.2233, found 427.2233.

(*E*)-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-1-morpholinoprop-2-en-1-one (3t).



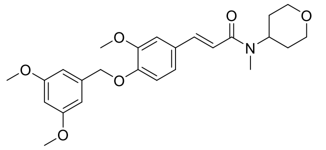
Prepared from **S2** (300 mg, 0.88 mmol, 1.10 equiv.) and morpholine (0.07 mL, 0.80 mmol, 1.00 equiv.) according to **general procedure C** (*method A*). White solid (300 mg, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* (ppm) 7.62 (d, *J* = 15.3 Hz, 1H), 7.07–6.99 (m, 2H), 6.85 (d, *J* = 8.8 Hz, 1H), 6.68 (d, *J* = 15.3 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 2H), 6.39 (t, *J* = 2.3 Hz, 1H), 5.12 (s, 2H), 3.92 (s, 3H), 3.78 (s, 6H), 3.75–3.69 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* (ppm) 165.9, 161.2, 149.9, 149.8, 143.3, 139.3, 128.7, 121.8, 114.5, 113.8, 110.7, 105.1, 99.9, 71.0, 67.0, 56.2, 55.5; *three morpholine carbon signals not observed due to quadrupolar effects of the nitrogen atom*. HRMS (ESI, *m/z*) calcd for $[C_{23}H_{28}NO_6]$ (M + H)$^+$ 414.1917, found 414.1921.

(E)-*N*-cyclohexyl-3-(4-((3,5-dimethoxybenzyl) oxy)-3-methoxyphenyl)-*N*-methylacrylamide (3u).



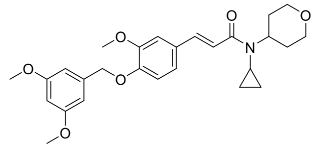
Prepared from **S2** (210 mg, 0.55 mmol, 1.10 equiv.) and *N*-methylcyclohexylamine (0.07 mL, 0.50 mmol, 1.00 equiv.) according to **general procedure C** (*method A*). White solid (180 mg, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* (ppm) 7.58 (d, *J* = 15.3 Hz, 1H), 7.04 (d, *J* = 7.0 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 15.3 Hz, 1H), 6.59 (d, *J* = 2.3 Hz, 2H), 6.39 (t, *J* = 2.3 Hz, 1H), 5.13 (s, 2H), 3.93 (s, 3H), 3.78 (s, 6H), 2.95 (d, *J* = 26.5 Hz, 3H), 1.92–1.64 (m, 5H), 1.64–1.51 (m, 2H), 1.51–1.28 (m, 3H), 1.24–1.01 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* (ppm) 166.3, 161.2, 149.7, 149.6, 142.2, 139.4, 129.2, 121.5, 116.8, 113.9, 110.9, 105.1, 100.0, 71.1, 56.2, 55.5, 31.3, 30.0, 25.8; *two carbon signals not observed due to quadrupolar effects of the nitrogen atom*. HRMS (ESI, *m/z*) calcd for $[C_{26}H_{34}NO_5]$ (M + H)$^+$ 440.2437, found 440.2437.

***(E)*-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-*N*-methyl-*N*-(tetrahydro-2H-pyran-4-yl)acrylamide (3v).**



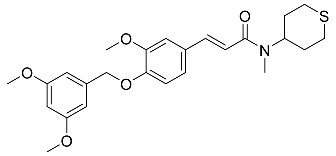
Prepared from **S2** (380 mg, 1.10 mmol, 1.10 equiv.) and *N*-methyloxane-4-amine (120 mg, 1.00 mmol, 1.00 equiv.) according to **general procedure C** (*method A*). White solid (290 mg, 66% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.60 (d, *J* = 15.3 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 15.3 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 2H), 6.39 (t, *J* = 2.3 Hz, 1H), 5.13 (s, 2H), 4.09–3.99 (m, 2H), 3.93 (s, 3H), 3.78 (s, 6H), 3.62–3.41 (m, 2H), 3.01 (s, 3H), 2.00–1.46 (m, 5H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 166.7, 161.1, 149.8, 149.7, 142.7, 139.3, 128.9, 121.6, 116.2, 113.8, 110.9, 105.2, 99.9, 71.0, 67.4, 56.2, 55.4, 55.4, 49.9, 29.8. HRMS (ESI, *m/z*) calcd for [C$_{25}$H$_{32}$NO$_6$] (M + H)$^+$ 442.2230, found 442.2229.

***(E)*-*N*-cyclopropyl-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-*N*-(tetrahydro-2H-pyran-4-yl)acrylamide (3w).**



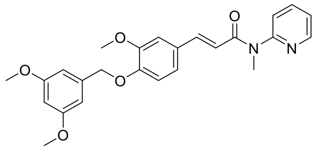
Prepared from **S2** (380 mg, 1.10 mmol, 1.10 equiv.) and *N*-cyclopropyloxan-4-amine (0.14 mL, 1.00 mmol, 1.00 equiv.) according to **general procedure C** (*method A*). White solid (440 mg, 94% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.54 (d, *J* = 15.5 Hz, 1H), 7.14–7.02 (m, 3H), 6.89–6.81 (m, 1H), 6.59 (d, *J* = 2.2 Hz, 2H), 6.39 (t, *J* = 2.3 Hz, 1H), 5.13 (s, 2H), 4.44–4.38 (m, 1H), 4.07–3.99 (m, 2H), 3.92 (s, 3H), 3.78 (s, 6H), 3.53–3.47 (m, 2H), 2.69–2.59 (m, 1H), 2.17–2.08 (m, 2H), 1.74 (ddd, *J* = 12.1, 4.1, 1.9 Hz, 2H), 1.01–0.93 (m, 2H), 0.93–0.85 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 168.8, 161.1, 149.7, 149.6, 141.4, 139.3, 129.1, 121.3, 118.2, 113.8, 111.1, 105.0, 99.8, 71.0, 67.9, 56.1, 55.4, 54.8, 31.6, 26.9, 9.4. HRMS (ESI, *m/z*) calcd for [C$_{27}$H$_{34}$NO$_6$] (M + H)$^+$ 468.2386, found 468.2386.

***(E)*-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-*N*-methyl-*N*-(tetrahydro-2H-thiopyran-4-yl)acrylamide (3x).**



Prepared from **S2** (380 mg, 1.10 mmol, 1.10 equiv.) and *N*-methylthian-4-amine hydrochloride (170 mg, 1.00 mmol, 1.00 equiv.) according to **general procedure C** (*method A*). White solid (440 mg, 96% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.59 (d, *J* = 15.3 Hz, 1H), 7.10–7.00 (m, 2H), 6.85 (d, *J* = 8.6 Hz, 1H), 6.69 (d, *J* = 15.3 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 2H), 6.39 (t, *J* = 2.3 Hz, 1H), 5.13 (s, 2H), 4.64–4.52 (m, 1H), 3.93 (s, 3H), 3.78 (s, 6H), 3.17–2.58 (m, 7H), 2.12–1.94 (m, 2H), 1.90–1.76 (m, 1H), 1.70–1.61 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 166.4, 161.2, 149.8, 149.8, 142.8, 139.3, 128.9, 121.6, 116.1, 113.9, 110.8, 105.1, 99.9, 71.0, 56.2, 55.5, 55.5, 52.1, 31.6, 28.9. HRMS (ESI, *m/z*) calcd for [C$_{25}$H$_{32}$NO$_5$S] (M + H)$^+$ 458.2001, found 458.2005.

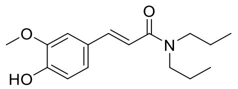
(E)-3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-N-methyl-N-(pyridin-2-yl)acrylamide (3y).



Prepared from **S2** (380 mg, 1.10 mmol, 1.10 equiv.) and 2-methylaminopyridine (0.10 mL, 1.00 mmol, 1.00 equiv.) according to **general procedure C** (*method A*). White solid (420 mg, 97% yield). *H-bonding between one N-CH$_3$ proton and the pyridine nitrogen is observed, causing a downfield shift for one N-CH$_3$ proton signal; assignment is supported by 2D COSY and HSQC NMR experiments*. ^{1}H NMR (400 MHz, CDCl$_3$): *δ* (ppm) 8.55 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.67 (td, *J* = 7.8, 1.8 Hz, 1H), 7.58 (d, *J* = 15.6 Hz, 1H), 7.30 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.24–7.18 (m, 1H), 7.05 (d, *J* = 2.0 Hz, 1H), 7.01 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.95 (t, *J* = 5.0 Hz, 1H, *one of N-CH$_3$ H-bonding to pyridine*), 6.84 (d, *J* = 8.3 Hz, 1H), 6.58 (d, *J* = 2.3 Hz, 2H), 6.44–6.36 (m, 2H), 5.12 (s, 2H), 4.70 (d, *J* = 4.9 Hz, 2H, *two of N-CH$_3$*), 3.91 (s, 3H), 3.78 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): *δ* (ppm) 166.1, 161.1, 156.4, 149.7, 149.7, 149.0, 140.9, 139.3, 136.8, 128.4, 122.4, 122.2, 121.8, 118.7, 113.7, 110.3, 105.0, 99.9, 70.9, 56.0, 55.4, 44.6. HRMS (ESI, *m/z*) calcd for [$C_{25}H_{27}N_2O_5$] (M + H)$^+$ 435.1920, found 345.1922.

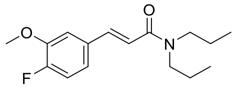
1.3 Synthesis and characterization: series 2 compounds.

(E)-3-(4-hydroxy-3-methoxyphenyl)-N,N-dipropylacrylamide (8).



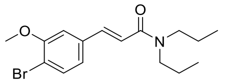
Prepared from ferulic acid (4.85 g, 25.00 mmol, 1.00 equiv.) and dipropylamine (4.11 mL, 30.00 mmol, 1.20 equiv.) according to **general procedure C** (*method B*). White solid (6.10 g, 88% yield). Spectral data are in agreement with previous reports[5]. ^{1}H NMR (400 MHz, CDCl3) δ (ppm) ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.59 (d, *J* = 15.3 Hz, 1H), 7.05–6.80 (m, 3H), 6.71 (d, *J* = 15.3 Hz, 1H), 3.89 (s, 3H), 3.40–3.32 (m, 4H), 1.96–1.34 (m, 4H), 1.01–0.89 (m, 6H).

(E)-3-(4-fluoro-3-methoxyphenyl)-N,N-dipropylacrylamide (9a).



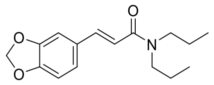
4-fluoro-3-methoxycinnamic acid was prepared from 4-bromo-3-methoxybenzaldehyde (500 mg, 3.24 mmol, 1.00 equiv.) using **general procedure B**. **9a** was prepared from 4-fluoro-3-methoxycinnamic acid (390 mg, 2.00 mmol, 1.00 equiv.) and dipropylamine (0.33 mL, 2.40 mmol, 1.20 equiv.) according to **general procedure C** (*method B*). White solid (460 mg, 83% yield). ^{1}H NMR (400 MHz, CDCl$_3$): *δ* (ppm) 7.65 (d, *J* = 15.3 Hz, 1H), 7.14–7.05 (m, 3H), 6.76 (dd, *J* = 15.3, 0.6 Hz, 1H), 3.95 (s, 3H), 3.47–3.33 (m, 4H), 1.80–1.56 (m, 4H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): *δ* (ppm) 166.1, 153.3 (d, *J* = 249.6 Hz), 148.0, 141.2 (d, *J* = 1.6 Hz), 132.4 (d, *J* = 4.0 Hz), 120.5 (d, *J* = 7.2 Hz), 118.0 (d, *J* = 2.5 Hz), 116.5 (d, *J* = 18.9 Hz), 113.2 (d, *J* = 2.2 Hz), 56.4, 49.9, 48.6, 23.1, 21.1, 11.5, 11.4. ^{19}F NMR (376 MHz, CDCl$_3$): *δ* (ppm) −132.81 (m). HRMS (ESI, *m/z*) calcd for [$C_{16}H_{23}FNO_2$] (M + H)$^+$ 280.1713, found 280.1711.

***(E)*-3-(4-bromo-3-methoxyphenyl)-*N,N*-dipropylacrylamide (9b).**



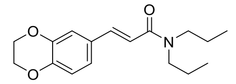
4-Bromo-3-methoxycinnamic acid was prepared from 4-bromo-3-methoxybenzaldehyde (4.95 g, 23.00 mmol, 1.00 equiv.) according to **general procedure B**. **9b** was prepared from 4-bromo-3-methoxycinnamic acid (1.54 g, 6.00 mmol, 1.00 equiv.) and dipropylamine (0.99 mL, 7.20 mmol, 1.20 equiv.) according to **general procedure C** (*method B*). White solid (1.91 g, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64 (d, *J* = 15.3 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.05 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.99 (d, *J* = 1.9 Hz, 1H), 6.84 (d, *J* = 15.3 Hz, 1H), 3.95 (s, 3H), 3.49–3.33 (m, 4H), 1.76–1.56 (m, 4H), 1.03–0.91 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 165.8, 156.1, 141.2, 136.3, 133.5, 120.5, 118.8, 112.9, 111.5, 56.3, 49.9, 48.6, 23.1, 21.1, 11.5, 11.4. HRMS (ESI, *m/z*) calcd for $[C_{16}H_{23}BrNO_2]$ (M + H)$^+$ 340.0912, found 340.0914.

***(E)*-3-(benzo[d][1,3]dioxol-5-yl)-*N,N*-dipropylacrylamide (10a).**



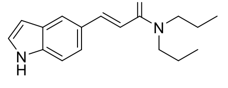
Prepared from 3,4-(methylenedioxy)cinnamic acid (380 mg, 2.00 mmol, 1.00 equiv.) and dipropylamine (0.33 mL, 2.40 mmol, 1.20 equiv.) according to **general procedure C** (*method B*). White solid (500 mg, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64 (d, *J* = 15.3 Hz, 1H), 7.05 (d, *J* = 1.7 Hz, 1H), 7.02 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 15.3 Hz, 1H), 6.01 (d, *J* = 2.6 Hz, 2H), 3.52–3.27 (m, 4H), 1.81–1.54 (m, 4H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 166.2, 148.8, 148.2, 141.9, 130.0, 123.7, 115.9, 108.5, 106.4, 101.4, 49.9, 48.6, 23.1, 21.2, 11.5, 11.4. HRMS (ESI, *m/z*) calcd for $[C_{16}H_{22}NO_3]$ (M + H)$^+$ 276.1600, found 276.1601.

***(E)*-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-*N,N*-dipropylacrylamide (10b).**



Prepared from 3-(2,3-dihydro-1,4-benzodioxin-6-yl)prop-2-enoic acid (410 mg, 2.00 mmol, 1.00 equiv.) and dipropylamine (0.33 mL, 2.40 mmol, 1.20 equiv.) according to **general procedure C** (*method B*). White solid (520 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.61 (d, *J* = 15.3 Hz, 1H), 7.08 (d, *J* = 2.1 Hz, 1H), 7.04 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 15.3 Hz, 1H), 4.39–4.23 (m, 4H), 3.53–3.29 (m, 4H), 1.77–1.58 (m, 4H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 166.3, 144.9, 143.6, 141.7, 129.3, 121.8, 117.6, 116.1, 64.5, 64.3, 49.9, 48.6, 23.1, 21.2, 11.5, 11.4. HRMS (ESI, *m/z*) calcd for $[C_{17}H_{24}NO_3]$ (M + H)$^+$ 290.1756, found 290.1757.

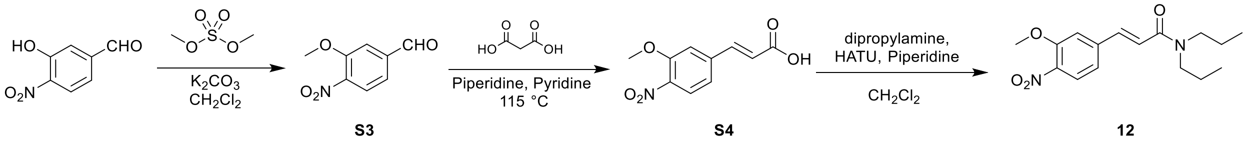
***(E)*-3-(1H-indol-5-yl)-*N,N*-dipropylacrylamide (11).**



3-(1*H*-indole-5-yl)prop-2-enoic acid was prepared from 1*H*-indole-5-carbaldehyde (2.90 g, 20 mmol, 1.00 equiv.) according to **general procedure B**. **11** was prepared from 3-(1*H*-indole-5-yl)prop-2-enoic acid (560 mg, 3.00 mmol, 1.00 equiv.) and dipropylamine (0.49 mL, 3.60 mmol, 1.20 equiv.) according to **general procedure C** (*method B*). White solid (470 mg, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.65

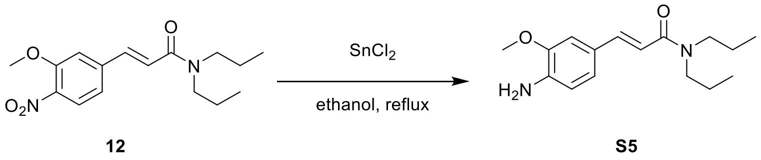
(brs, 1H), 7.89 (d, *J* = 15.2 Hz, 1H), 7.85–7.80 (m, 1H), 7.47–7.37 (m, 2H), 7.26 (dd, *J* = 3.1, 2.5 Hz, 1H), 6.85 (d, *J* = 15.2 Hz, 1H), 6.62–6.57 (m, 1H), 3.55–3.33 (m, 4H), 1.79–1.59 (m, 4H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 166.8, 144.0, 136.7, 128.2, 127.6, 125.2, 121.5, 121.5, 114.8, 111.5, 103.2, 50.0, 48.7, 23.1, 21.3, 11.5, 11.4. HRMS (ESI, *m/z*) calcd for [$C_{17}H_{23}N_2O$] (M + H)$^+$ 271.1805, found 271.1813.

(E)-3-(3-methoxy-4-nitrophenyl)-*N,N*-dipropylacrylamide (12).



3-hydroxy-4-nitrobenzaldehyde (12.0 g, 72.00 mmol, 1.00 equiv.) and anhydrous potassium carbonate (11.0 g, 79.20 mmol, 1.10 equiv.) were dissolved in anhydrous acetone (100 mL) with stirring. Dimethyl sulfate (7.51 mL, 79.20 mmol, 1.10 equiv.) was added slowly at room temperature and the solution was stirred overnight. The solvent removed under reduced pressure and the crude isolate was purified by flash column chromatography on silica gel to give 3-methoxy-4-nitrobenzaldehyde **S3** (12.8 g, 98% yield). **S4** was prepared from **S3** (12.7 g, 70.00 mmol, 1.00 equiv.) according to **general procedure B** (13.9 g, 89% yield).

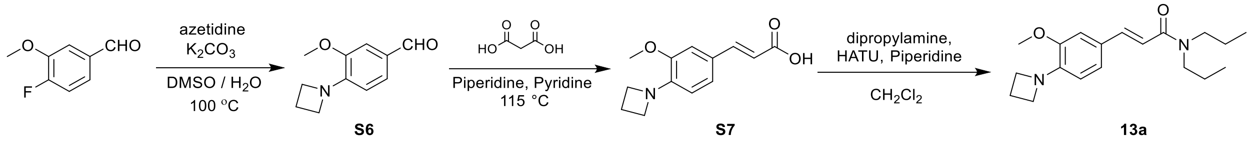
12 was prepared from **S4** (10.0 g, 45.0 mmol, 1.00 equiv.) and dipropylamine (7.40 mL, 54.0 mmol, 1.20 equiv.) according to **general procedure C** (*method B*). White solid (12.9 g, 96% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.90 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 15.4 Hz, 1H), 7.21 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.14 (d, *J* = 1.7 Hz, 1H), 6.93 (d, *J* = 15.4 Hz, 1H), 4.02 (s, 3H), 3.49–3.33 (m, 4H), 1.77–1.58 (m, 4H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 165.2, 153.4, 141.7, 139.8, 139.4, 126.3, 122.0, 118.5, 113.3, 56.6, 50.0, 48.7, 23.1, 21.1, 11.5, 11.3. HRMS (ESI, *m/z*) calcd for [$C_{16}H_{23}N_2O_4$] (M + H)$^+$ 307.1658, found 307.1658.



Prepared according to literature procedure[6]. SnCl$_2$·2H$_2$O (26.0 g, 0.14 mol, 3.00 equiv.) was added to a solution of **12** (14.0 g, 45.7 mmol, 1.00 equiv.) in ethanol (120 mL). The mixture was stirred at reflux for three hours, cooled to room temperature and solvent was removed under reduced pressure. The residue was taken up with a saturated aqueous solution of sodium bicarbonate and a saturated aqueous solution of Rochelle's salt (1:1 v/v). The aqueous phase was extracted with ethyl acetate (x3) and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and solvent was removed under reduced pressure. The crude isolate was purified by flash column chromatography on silica gel to afford **S5** (11.1 g, 88% yield). ^{1}H NMR (400 MHz, CHCl$_3$) δ 7.61 (d, *J* = 15.2 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 6.91 (s, 1H), 6.67 (d, *J* = 7.9

Hz, 1H), 6.62 (d, *J* = 15.2 Hz, 1H), 4.02 (br s, 2H), 3.88 (s, 3H), 3.36 (d, *J* = 5.6 Hz, 4H), 1.81–1.54 (m, 4H), 1.03–0.86 (m, 6H).

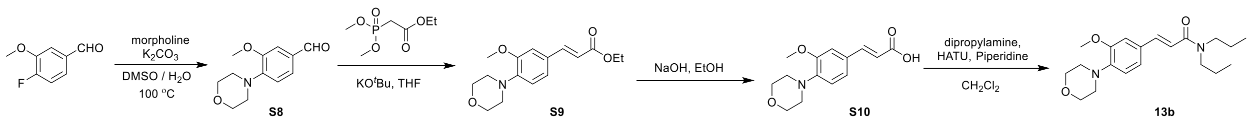
(E)-3-(16zetidinedin-1-yl)-3-methoxyphenyl)-*N,N*-dipropylacrylamide (13a).



S6 was prepared from 4-fluoro-3-methoxybenzaldehyde (2.66 g, 17.3 mmol, 1.00 equiv.) and azetidine (1.48 mL, 26.0 mmol, 1.50 equiv.) according to **general procedure D**. White solid (2.85 g, 86% yield). **S7** was prepared from **S6** (1.10 g, 5.75 mmol, 1.00 equiv.) according to **general procedure B**.

13a was prepared from **S7** (350 mg, 1.50 mmol, 1.00 equiv.) and dipropylamine (0.25 mL, 1.80 mmol, 1.20 equiv.) according to **general procedure C** (*method B*). White solid (450 mg, 95%). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.61 (d, *J* = 15.2 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.89 (s, 1H), 6.61 (d, *J* = 15.2 Hz, 1H), 6.37 (d, *J* = 7.8 Hz, 1H), 3.97 (t, *J* = 6.6 Hz, 4H), 3.80 (s, 3H), 3.44–3.28 (m, 4H), 2.32–2.25 (m, 2H), 1.68–1.49 (m, 4H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 166.7, 152.8, 149.0, 142.7, 126.3, 121.8, 113.6, 112.5, 110.5, 55.6, 54.1, 49.9, 48.6, 23.1, 21.2, 17.8, 11.5, 11.4. HRMS (ESI, *m/z*) calcd for [C$_{19}$H$_{29}$N$_2$O$_2$] (M + H)$^+$ 317.2229, found 317.2231.

(E)-3-(3-methoxy-4-morpholinophenyl)-*N,N*-dipropylacrylamide (13b).

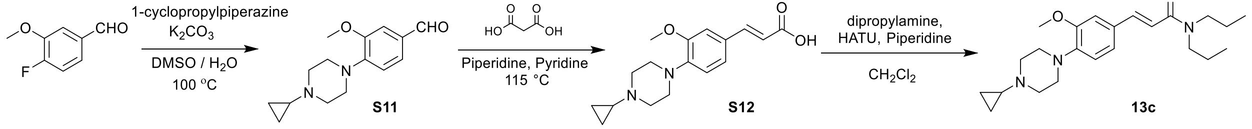


S8 was prepared from 4-fluoro-3-methoxybenzaldehyde (2.00 g, 13.0 mmol, 1.00 equiv.) and morpholine (1.68 mL, 19.5 mmol, 1.50 equiv.) according to **general procedure D**. White solid (2.60 g, 90% yield).

To a stirred solution of ethyl dimethylphosphonoacetate (0.81 mL, 4.92 mmol, 1.20 equiv.) in tetrahydrofuran (20.0 mL) at 0 °C was added potassium *tert*-butoxide (550 mg, 4.92 mmol, 1.20 equiv.). The mixture was stirred for 30 minutes before addition of **S8** (910 mg, 4.10 mmol, 1.00 equiv.) and the solution was allowed to warm to room temperature and stirred for an additional four hours. The reaction was quenched by addition of a saturated aqueous solution of ammonium chloride and extracted with ethyl acetate (3x). The organic extracts were combined and dried over anhydrous sodium sulfate, filtered and solvent was removed under reduced pressure. The crude isolate was purified by flash column chromatography on silica gel to yield **S9** as a white solid (810 mg, 68% yield). **S9** was then dissolved in a 10% solution of sodium hydroxide in ethanol to obtain **S10**, which was used without further purification.

13b was prepared from **S10** (320 mg, 1.20 mmol, 1.00 equiv.) and dipropylamine (0.20 mL, 1.44 mmol, 1.20 equiv.) according to **general procedure C** (*method B*). White solid (400 mg, 97% yield). ^{1}H NMR (400 MHz, CDCl$_3$): *δ* (ppm) 7.64 (d, *J* = 15.3 Hz, 1H), 7.13 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.98 (d, *J* = 1.9 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.71 (d, *J* = 15.3 Hz, 1H), 3.89 (s, 3H), 3.89–3.87 (m, 4H), 3.41–3.34 (m, 4H), 3.12–3.09 (m, 4H), 1.70–1.59 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): *δ* (ppm) 166.3, 152.1, 142.5, 142.1, 130.4, 121.0, 117.9, 116.1, 110.8, 67.1, 55.5, 50.9, 49.9, 48.6, 23.1, 21.2, 11.5, 11.4. HRMS (ESI, *m/z*) calcd for [$C_{20}H_{31}N_2O_3$] (M + H)$^+$ 347.2335, found 347.2334.

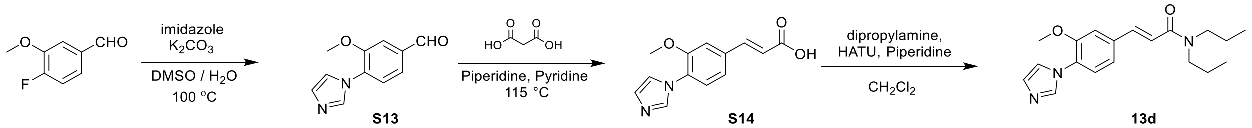
(E)-3-(3-methoxy-4-(4-cyclopropylpiperizin-1-yl)phenyl)-*N,N*-dipropylacrylamide (13c).



S11 was prepared from 4-fluoro-3-methoxybenzaldehyde (3.01 g, 20.0 mmol, 1.00 equiv.) and 1-cyclopropylpiperazine (4.01 mL, 30.0 mmol, 1.50 equiv.) according to **general procedure D**. White solid (4.53 g, 87% yield). **S12** was prepared from **S11** (2.60 g, 10.0 mmol, 1.00 equiv.) according to **general procedure B**.

13c was prepared from **S12** (420 mg, 1.40 mmol, 1.00 equiv.) and dipropylamine (0.23 mL, 1.68 mmol, 1.20 equiv.) according to **general procedure C** (*method B*). White solid (450 mg, 83%). ^{1}H NMR (400 MHz, CDCl$_3$): *δ* (ppm) 7.66 (d, *J* = 15.3 Hz, 1H), 7.14 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.99 (d, *J* = 1.9 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.73 (d, *J* = 15.3 Hz, 1H), 3.93 (s, 3H), 3.46–3.33 (m, 4H), 3.15–3.10 (m, 4H), 2.84 (app t, *J* = 4.9 Hz, 4H), 1.77–1.59 (m, 5H), 0.98 (t, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.2 Hz, 3H), 0.56–0.46 (m, 4H). ^{13}C NMR (100 MHz, CDCl$_3$): *δ* (ppm) 166.4, 152.1, 143.0, 142.2, 130.1, 121.0, 118.1, 115.8, 110.8, 55.5, 53.4, 50.4, 49.9, 48.6, 38.5, 23.1, 21.2, 11.5, 11.4, 5.8. HRMS (ESI, *m/z*) calcd for [$C_{23}H_{36}N_3O_2$] (M + H)$^+$ 386.2808, found 386.2808.

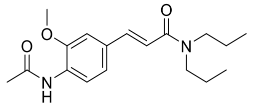
(E)-3-(4-(1H-imidazol-1-yl)-3-methoxyphenyl)-*N,N*-dipropylacrylamide (13d).



S13 was prepared from 4-fluoro-3-methoxybenzaldehyde (2.00 g, 13.0 mmol, 1.00 equiv.) and imidazole (1.33 g, 19.5 mmol, 1.50 equiv.) according to **general procedure D**. White solid (2.23 g, 85% yield). **S14** was prepared from **S13** (1.49 g, 7.40 mmol, 1.00 equiv.) according to **general procedure B**.

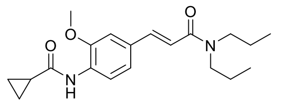
13d was prepared from **S14** (0.49 g, 2.00 mmol, 1.00 equiv.) and dipropylamine (0.33 mL, 2.40 mmol, 1.20 equiv.) according to **general procedure C** (*method B*). White solid (450 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* (ppm) 7.91 (t, *J* = 1.2 Hz, 1H), 7.70 (d, *J* = 15.4 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.28–7.23 (m, 2H), 7.21 (t, *J* = 1.2 Hz, 1H), 7.16 (d, *J* = 1.7 Hz, 1H), 6.88 (d, *J* = 15.4 Hz, 1H), 3.92 (s, 3H), 3.48 – 3.37 (m, 4H), 1.78 – 1.59 (m, 4H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* (ppm) 165.7, 152.5, 140.9, 137.7, 136.6, 128.5, 127.0, 125.5, 120.2, 120.0, 119.4, 112.0, 56.0, 50.0, 48.6, 23.1, 21.1, 11.5, 11.4. HRMS (ESI, *m/z*) calcd for [$C_{19}H_{26}N_3O_2$] (M + H)$^+$ 328.2025, found 328.2024.

***(E)*-3-(4-acetamido-3-methoxyphenyl)-*N,N*-dipropylacrylamide (14a).**



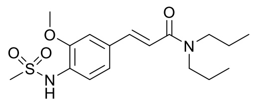
Prepared from **S5** (100 mg, 0.38 mmol, 1.00 equiv.) and acetyl chloride (0.03 mL, 0.46 mmol, 1.20 equiv.) according to **general procedure F** (m*ethod A*). White solid (110 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* (ppm) 8.38 (d, *J* = 8.4 Hz, 1H), 7.80 (br s, 1H), 7.62 (d, *J* = 15.3 Hz, 1H), 7.21 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.95 (d, *J* = 1.7 Hz, 1H), 6.75 (d, *J* = 15.3 Hz, 1H), 3.85 (s, 3H), 3.37–3.24 (m, 4H), 2.14 (s, 3H), 1.67–1.47 (m, 4H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* (ppm) 168. 3, 166.3, 147.7, 142.1, 131.2, 129.0, 120.5, 119.7, 117.0, 109.8, 55.9, 50.0, 48.7, 25.1, 23.2, 21.3, 11.6, 11.5. HRMS (ESI, *m/z*) calcd for [$C_{18}H_{27}N_2O_3$] (M + H)$^+$ 319.2022, found 319.2024.

***(E)*-3-(4-cyclopropanamido-3-methoxyphenyl)-*N,N*-dipropylacrylamide (14b).**



Prepared from **S5** (60.0 mg, 0.21 mmol, 1.00 equiv.) and cyclopropanecarbonyl chloride (0.02 mL, 0.25 mmol, 1.20 equiv.) according to **general procedure F** (m*ethod A*). White solid (70.0 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.37 (d, *J* = 8.5 Hz, 1H), 8.04 (s, 1H), 7.62 (d, *J* = 15.4 Hz, 1H), 7.17 (dd, *J* = 8.5, 1.9 Hz, 1H), 6.95 (d, *J* = 1.9 Hz, 1H), 6.74 (d, *J* = 15.4 Hz, 1H), 3.93 (s, 3H), 3.41–3.35 (m, 4H), 1.70–1.54 (m, 5H), 1.11–1.06 (m, 2H), 0.98–0.90 (m, 5H), 0.89–0.82 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* (ppm) 171.7, 166.2, 147.51, 142.0, 130.8, 129.2, 120.5, 119.5, 116.7, 109.7, 55.8, 49.9, 48.6, 23.1, 21.2, 16.1, 11.5, 11.4, 8.1. HRMS (ESI, *m/z*) calcd for [$C_{20}H_{29}N_2O_3$] (M + H)$^+$ 345.2178, found 345.2179.

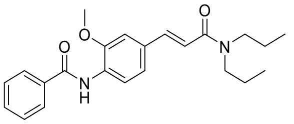
***(E)*-3-(3-methoxy-4-(methylsulfonamido)phenyl)-*N,N*-dipropylacrylamide (15a).**



Prepared from **S5** (100 mg 0.36 mmol, 1.00 equiv.) and methane sulfonyl chloride (0.03 mL, 0.46 mmol, 1.20 equiv.) according to **general procedure F** (m*ethod A*). White solid (110 mg, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* (ppm) 7.65 (d, *J* = 15.3 Hz, 1H), 7.28–7.26 (m, 2H), 7.18 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.07 (d, *J* = 1.9 Hz, 1H), 6.82 (d, *J* = 15.3 Hz, 1H), 3.95 (s, 3H), 3.44 (s, 3H), 3.44–3.34 (m, 4H), 1.69–1.58 (m, 4H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* (ppm) 165.5, 157.42, 140.7, 139.8, 132.5, 123.3, 120.6, 120.0, 112.1, 56.2, 50.0, 48.6, 43.6, 23.1, 21.1, 11.5, 11.3. HRMS (ESI, *m/z*) calcd for [$C_{17}H_{27}N_2O_4S$] (M + H)$^+$ 355.1692, found 355.1696.

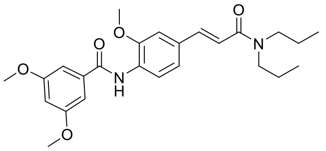
1.4 Synthesis and characterization: series 3 compounds.

_(E)-N_-(4-(3-(dipropylamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenyl)benzamide (14c).



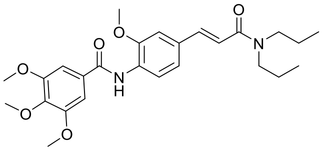
Prepared from **S5** (100 mg, 0.36 mmol, 1.00 equiv.) and benzoyl chloride (0.05 mL, 0.43 mmol, 1.20 equiv.) according to **general procedure F** (*method B*). White solid (130 mg, 93% yield). ^{1}H NMR (400 MHz, CDCl$_3$): *δ* (ppm) 8.64 (s, 1H), 8.59 (d, *J* = 8.4 Hz, 1H), 7.97–7.89 (m, 2H), 7.69 (d, *J* = 15.3 Hz, 1H), 7.61–7.50 (m, 3H), 7.32–7.25 (m, 1H), 7.03 (d, *J* = 1.8 Hz, 1H), 6.81 (d, *J* = 15.3 Hz, 1H), 4.00 (s, 3H), 3.51–3.37 (m, 4H), 1.77–1.59 (m, 4H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): *δ* (ppm) 166.2, 165.2, 148.1, 141.9, 135.1, 131.9, 131.4, 129.0, 128.8, 127.1, 120.5, 119.7, 117.0, 109.7, 56.0, 49.9, 48.6, 23.1, 21.2, 11.5, 11.4. HRMS (ESI, *m/z*) calcd for [$C_{23}H_{29}N_2O_3$] (M + H)$^+$ 381.2178, found 381.2177.

_(E)-N_-(4-(3-(dipropylamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenyl)-3,5-dimethoxybenzamide (14d).



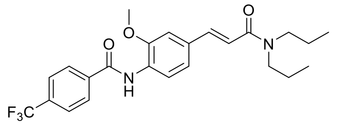
Prepared from **S5** (100 mg, 0.36 mmol, 1.00 equiv.) and 3,5-dimethoxybenzoyl chloride (90.0 mg, 0.43 mmol, 1.20 equiv.) according to **general procedure F** (*method B*). White solid (150 mg, 94% yield). ^{1}H NMR (400 MHz, CDCl$_3$): *δ* (ppm) 8.56 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 15.3 Hz, 1H), 7.27 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.04 (dd, *J* = 5.9, 2.2 Hz, 3H), 6.81 (d, *J* = 15.3 Hz, 1H), 6.66 (t, *J* = 2.2 Hz, 1H), 3.99 (s, 3H), 3.89 (s, 6H), 3.48–3.37 (m, 4H), 1.69 (m, 4H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): *δ* (ppm) 166.2, 165.0, 161.1, 148.2, 141.9, 137.3, 131.4, 128.9, 120.5, 119.7, 117.0, 109.7, 105.2, 103.7, 55.9, 55.7, 49.9, 48. 6, 23.1, 21.2, 11.5, 11.4. HRMS (ESI, *m/z*) calcd for [$C_{25}H_{33}N_2O_5$] (M + H)$^+$ 441.2389, found 441.2384.

_(E)-N_-(4-(3-(dipropylamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenyl)-3,4,5-trimethoxybenzamide (14e).



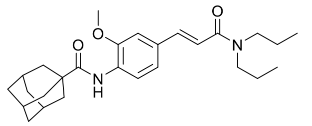
Prepared from **S5** (100 mg, 0.36 mmol, 1.00 equiv.) and 3,4,5-trimethoxybenzoyl chloride (100 mg, 0.43 mmol, 1.20 equiv.) according to **general procedure F** (*method B*). White solid (150 mg, 91% yield). ^{1}H NMR (400 MHz, CDCl$_3$): *δ* (ppm) 8.47–8.39 (m, 2H), 7.59 (d, *J* = 15.3 Hz, 1H), 7.22–7.15 (m, 1H), 7.04 (s, 2H), 6.94 (d, *J* = 1.8 Hz, 1H), 6.72 (d, *J* = 15.3 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 6H), 3.85 (s, 3H), 3.38–3.27 (m, 4H), 1.67–1.49 (m, 4H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): *δ* (ppm) 166.2, 165.0, 153.4, 148.1, 141.9, 141.5, 131.4, 130.6, 128.9, 120.5, 119.7, 117.0, 109.8, 104.7, 61.0, 56.5, 56.0, 49.9, 48.6, 23.1, 21.2, 11.5, 11.4. HRMS (ESI, *m/z*) calcd for [$C_{26}H_{35}N_2O_6$] (M + H)$^+$ 471.2495, found 471.2493.

***(E)-N*-(4-(3-(dipropylamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenyl)-4-(trifluoromethyl)benzamide (14f).**



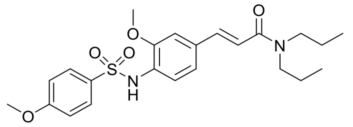
Prepared from **S5** (100 mg, 0.36 mmol, 1.00 equiv.) and 4-(trifluoromethyl)benzoyl chloride (0.07 mL, 0.43 mmol, 1.20 equiv.) according to **general procedure F** (*method B*). White solid (140 mg, 90% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 8.60 (brs, 1H), 8.53 (d, *J* = 8.3 Hz, 1H), 8.04–7.97 (m, 2H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 15.3 Hz, 1H), 7.29–7.22 (m, 1H), 7.01 (d, *J* = 1.8 Hz, 1H), 6.79 (d, *J* = 15.3 Hz, 1H), 3.97 (s, 3H), 3.45–3.34 (m, 4H), 1.76–1.56 (m, 4H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 166.2, 164.0, 148.3, 141.9, 138.5, 133.7 (q, *J* = 32.5 Hz), 132.0, 128.6, 127.7, 126.0 (q, *J* = 3.8 Hz), 123.8 (q, *J* = 273.1), 120.6, 119.9, 117.4, 109.9, 56.1, 50.0, 48.7, 23.2, 21.3, 11.6, 11.5. ^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) −62.98. HRMS (ESI, *m/z*) calcd for [C$_{24}$H$_{28}$F$_3$N$_2$O$_3$] (M + H)$^+$ 449.2052, found 449.2049.

(1s,3s)-*N*-(4-(*(E)*-3-(dipropylamino)-3-oxoprop-1-en-1-yl)-2-methoxyphenyl)adamantane-1-carboxamide (14g).



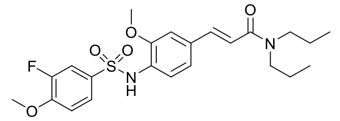
Prepared from **S5** (100 mg, 0.360 mmol, 1.00 equiv.) and 1-adamantanecarbonyl chloride (90.0 mg, 0.43 mmol, 1.20 equiv.) according to **general procedure F** (*method A*). White solid (150 mg, 92% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 8.45 (d, *J* = 8.4 Hz, 1H), 8.15 (s, 1H), 7.62 (d, *J* = 15.3 Hz, 1H), 7.18 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.95 (d, *J* = 1.9 Hz, 1H), 6.74 (d, *J* = 15.3 Hz, 1H), 3.94 (s, 3H), 3.44–3.32 (m, 4H), 2.13–2.06 (m, 3H), 1.97 (d, *J* = 3.0 Hz, 6H), 1.82–1.74 (m, 6H), 1.65 (m, 4H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 176.1, 166.3, 148.0, 142.0, 130.8, 129.2, 120.5, 119.5, 116.6, 109.6, 55.9, 49.9, 48.6, 42.0, 39.3, 36.5, 28.2, 23.1, 21.2, 11.5, 11.4. HRMS (ESI, *m/z*) calcd for [C$_{27}$H$_{39}$N$_2$O$_3$] (M + H)$^+$ 439.2961, found 439.2957.

***(E)*-3-(3-methoxy-4-((4-methoxyphenyl)sulfonamido)phenyl)-*N,N*-dipropylacrylamide (15b).**



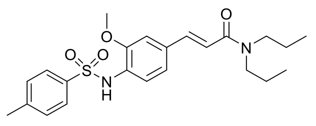
Prepared from **S5** (100 mg, 0.36 mmol, 1.00 equiv.) and 4-methoxybenzenesulfonyl chloride (90.0 mg, 0.43 mmol, 1.20 equiv.) according to **general procedure F** (*method B*). White solid (130 mg, 81% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.77–7.66 (m, 2H), 7.55 (d, *J* = 15.3 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.13–7.06 (m, 2H), 6.92–6.84 (m, 2H), 6.82 (d, *J* = 1.8 Hz, 1H), 6.70 (d, *J* = 15.3 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.42–3.30 (m, 4H), 1.70–1.54 (m, 4H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 166.0, 163.2, 149.1, 141.6, 132.4, 130.8, 129.4, 127.4, 120.4, 120.1, 117.4, 114.1, 110.2, 55.8, 55.6, 49.9, 48.6, 23.1, 21.1, 11.5, 11.4. HRMS (ESI, *m/z*) calcd for [C$_{23}$H$_{31}$N$_2$O$_5$S] (M + H)$^+$ 447.1954, found 447.1956.

(E)-3-(4-((3-fluoro-4-methoxyphenyl)sulfonamido)-3-methoxyphenyl)-***N,N***-dipropylacrylamide (15c).



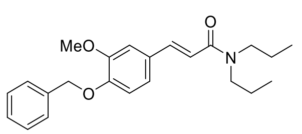
Prepared from **S5** (100 mg, 0.36 mmol, 1.00 equiv.) and 3-fluoro-4-methoxybenzenesulfonyl chloride (100 mg, 0.43 mmol, 1.20 equiv.) according to **general procedure F** (*method B*). White solid (150 mg, 92% yield). ^{1}H NMR (400 MHz, CDCl$_3$): *δ* (ppm) 7.60–7.45 (m, 4H), 7.14–7.07 (m, 2H), 6.97–6.88 (m, 1H), 6.83 (d, *J* = 1.8 Hz, 1H), 6.72 (d, *J* = 15.3 Hz, 1H), 3.90 (s, 3H), 3.75 (s, 3H), 3.46–3.30 (m, 4H), 1.71–1.54 (m, 4H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl131.2$_3$): *δ* (ppm) 166.1, 151.6 (d, *J* = 251.4 Hz), 151.8 (d, *J* = 10.6 Hz), 149.4, 141.4, 132.9, 131.2 (d, *J* = 5.8 Hz), 126.9, 124.8 (d, *J* = 3.8 Hz), 120.4, 120.4, 117.8, 115.4 (d, *J* = 20.3 Hz), 112.7 (d, *J* = 2.0 Hz), 110.3, 56.5, 55.9, 50.0, 48.7, 23.2, 21.2, 11.5, 11.4. ^{19}F NMR (376 MHz, CDCl$_3$): *δ* (ppm) −131.90 9 (m). HRMS (ESI, *m/z*) calcd for [$C_{23}H_{30}FN_2O_5S$] (M + H)$^+$ 465.1859, found 465.1860.

(E)-3-(3-methoxy-4-((4-methylphenyl)sulfonamido)phenyl)-***N,N***-dipropylacrylamide (15d).



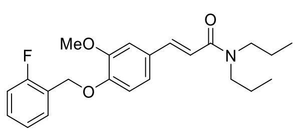
Prepared from **S5** (100 mg, 0.36 mmol, 1.00 equiv.) and 4-toluenesulfonyl chloride (80.0 mg, 0.43 mmol, 1.20 equiv.) according to **general procedure F** (*method B*). White solid (150 mg, 96% yield). ^{1}H NMR (400 MHz, CDCl$_3$): *δ* (ppm) 7.71–7.61 (m, 2H), 7.55 (d, *J* = 15.3 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.25–7.14 (m, 2H), 7.13–7.05 (m, 2H), 6.81 (d, *J* = 1.8 Hz, 1H), 6.70 (d, *J* = 15.3 Hz, 1H), 3.70 (s, 3H), 3.36 (dt, *J* = 15.8, 7.5 Hz, 4H), 2.35 (s, 3H), 1.62 (dq, *J* = 15.8, 7.5 Hz, 4H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): *δ* (ppm) 166.0, 149.1, 143.9, 141.5, 136.3, 132.5, 129.5, 127.3, 127.2, 120.3, 120.0, 117.5, 110.3, 55.8, 49.9, 48.6, 23.1, 21.5, 21.1, 11.5, 11.4. HRMS (ESI, *m/z*) calcd for [$C_{23}H_{31}N_2O_4S$] (M + H)$^+$ 431.2005, found 431.2003.

(E)-3-(4-(benzyloxy)-3-methoxyphenyl)-***N,N***-dipropylacrylamide (16a).



Prepared from **8** (80.0 mg, 0.27 mmol, 1.00 equiv.) and benzyl bromide (0.04 mL, 0.32 mmol, 1.20 equiv.) according to **general procedure A**. White solid (20.0 mg, 21%). Spectral data are in agreement with previous reports[5].^{1}H NMR (400 MHz, CDCl$_3$) *δ* (ppm) 7.64 (d, *J* = 15.3 Hz, 1H), 7.49–7.30 (m, 5H), 7.11–7.01 (m, 2H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.70 (d, *J* = 15.3 Hz, 1H), 5.21 (s, 2H), 3.94 (s, 3H), 3.49–3.28 (m, 4H), 1.74–1.53 (m, 4H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H).

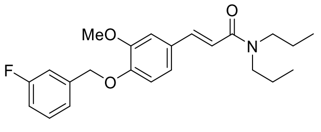
(E)-3-(4-((2-fluorobenzyl)oxy)-3-methoxyphenyl)-***N,N***-dipropylacrylamide (16b).



Prepared from **8** (80.0 mg, 0.27 mmol, 1.00 equiv.) and 2-fluorobenzyl bromide (0.04 mL, 0.32 mmol, 1.20 equiv.) according to **general procedure A**. White solid (60.0 mg, 54%). ^{1}H NMR (400 MHz, CDCl$_3$): *δ* (ppm) 7.65 (d, *J* = 15.3 Hz, 1H), 7.55 (td, *J* = 7.5, 1.8 Hz, 1H), 7.36–7.30 (m, 1H), 7.18 (td, *J* = 7.5, 1.2 Hz, 1H), 7.13–7.08 (m, 2H), 7.06 (d, *J* = 2.0 Hz, 1H), 6.93 (d, *J* = 8.3

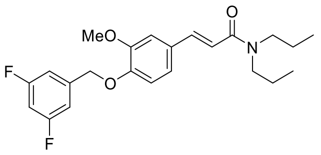
Hz, 1H), 6.72 (d, *J* = 15.3 Hz, 1H), 5.27 (s, 2H), 3.95 (s, 3H), 3.47–3.35 (m, 4H), 1.75–1.58 (m, 4H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): *δ* (ppm) 166.3, 160.5 (d, *J* = 246.4) 149.8, 149.3, 142.0, 129.7 (d, *J* = 8.3 Hz), 129.6, 129.6 (d, *J* = 8.5 Hz), 129.5 (d, *J* = 18.5 Hz), 124.4 (d, *J* = 3.7 Hz), 121.1, 116.2, 115.3 (d, *J* = 21.4 Hz), 113.8, 111.3, 64.7 (d, *J* = 4.5 Hz), 56.2, 49.9, 48.6, 23.1, 21.2, 11.5, 11.4. ^{19}F NMR (376 MHz, CDCl$_3$): *δ* (ppm) −118.67 (m). HRMS (ESI, *m/z*) calcd for [$C_{23}H_{29}FNO_3$] (M + H)$^+$ 386.2131, found 386.2136.

***(E)*-3-(4-((3-fluorobenzyl)oxy)-3-methoxyphenyl)-*N,N*-dipropylacrylamide (16c).**



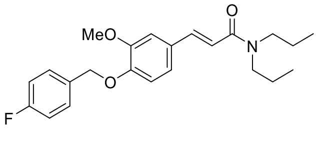
Prepared from **8** (100 mg, 0.36 mmol, 1.00 equiv.) and 3-fluorobenzyl bromide (0.05 mL, 0.43 mmol, 1.20 equiv.) according to **general procedure A**. Clear oil (60.0 mg, 40%). ^{1}H NMR (400 MHz, CDCl$_3$): *δ* (ppm) 7.65 (d, *J* = 15.3 Hz, 1H), 7.36 (td, *J* = 8.1, 5.8 Hz, 1H), 7.26–7.15 (m, 2H), 7.10–7.05 (m, 2H), 7.05–6.99 (m, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.72 (d, *J* = 15.3 Hz, 1H), 5.19 (s, 2H), 3.96 (s, 3H), 3.47–3.35 (m, 4H), 1.75–1.58 (m, 4H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): *δ* (ppm) 166.4, 163.2 (d, *J* = 246.4), 149.9, 149.3, 142.1, 139.6 (d, *J* = 7.3 Hz), 130.3 (d, *J* = 8.2 Hz), 129.5, 122.7 (d, *J* = 2.9 Hz), 121.2, 116.3, 115.0 (d, *J* = 21.0 Hz), 114.2 (d, *J* = 22.1 Hz), 114.0, 111.3, 70.3 (d, *J* = 2.0 Hz), 56.2, 50.1, 48.7, 23.2, 21.3, 11.6, 11.5. ^{19}F NMR (376 MHz, CDCl$_3$): *δ* (ppm) −112.72 (m). HRMS (ESI, *m/z*) calcd for [$C_{23}H_{29}FNO_3$] (M + H)$^+$ 386.2131, found 386.2130.

***(E)*-3-(4-((3,5-difluorobenzyl)oxy)-3-methoxyphenyl)-*N,N*-dipropylacrylamide (16d).**



Prepared from **8** (80.0 mg, 0.27 mmol, 1.00 equiv.) and 3,5-difluorobenzyl bromide (0.04 mL, 0.32 mmol, 1.20 equiv.) according to **general procedure A**. White solid (38.0 mg, 35%). Spectral data are in agreement with previous reports^5. ^{1}H NMR (400 MHz, CDCl$_3$): *δ* (ppm) 7.65 (d, *J* = 15.3 Hz, 1H), 7.12–7.05 (m, 2H), 7.04–6.97 (m, 2H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.81–6.76 (m, 1H), 6.73 (d, *J* = 15.3 Hz, 1H), 5.17 (s, 2H), 3.96 (s, 3H), 3.47–3.35 (m, 4H), 1.75–1.60 (m, 4H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H).

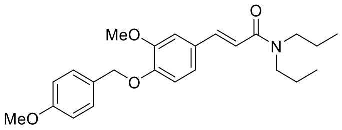
***(E)*-3-(4-((4-fluorobenzyl)oxy)-3-methoxyphenyl)-*N,N*-dipropylacrylamide (16e).**



Prepared from **8** (80.0 mg, 0.27 mmol, 1.00 equiv.) and 4-fluorobenzyl bromide (0.04 mL, 0.32 mmol, 1.20 equiv.) according to **general procedure A**. White solid (50.0 mg, 47%). ^{1}H NMR (400 MHz, CDCl$_3$): *δ* (ppm) 7.65 (d, *J* = 15.3 Hz, 1H), 7.49–7.39 (m, 2H), 7.14–7.03 (m, 4H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.72 (d, *J* = 15.3 Hz, 1H), 5.16 (s, 2H), 3.94 (s, 3H), 3.47–3.35 (m, 4H), 1.75–1.62 (m, 4H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): *δ* (ppm) 166.4, 162.6 (d, *J* = 246.6 Hz), 149.9, 149.4, 142.1, 132.6 (d, *J* = 3.1 Hz), 129.4, 129.3 (d, *J* = 8.1 Hz), 121.2, 116.3, 115.6 (d, *J* = 21.6 Hz), 114.0, 111.2, 70.5, 56.2, 50.0, 48.7, 23.2, 21.3, 11.6, 11.5.

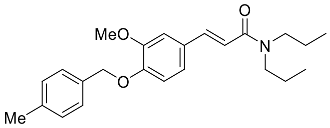
^{19}F NMR (376 MHz, CDCl$_3$): δ (ppm) −114.26 (m). HRMS (ESI, *m/z*) calcd for [C$_{23}$H$_{29}$FNO$_3$] (M + H)$^+$ 386.2131, found 386.2126.

(E)-3-(3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)-*N,N*-dipropylacrylamide (16f).



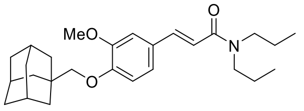
Prepared from **8** (80.0 mg, 0.27 mmol, 1.00 equiv.) and 4-methoxybenzyl chloride (0.04 mL, 0.32 mmol, 1.20 equiv.) according to **general procedure A**. White solid (30.0 mg, 28%). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.55 (d, *J* = 15.3 Hz, 1H), 7.33–7.24 (m, 2H), 6.98 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.95 (d, *J* = 2.0 Hz, 1H), 6.88–6.76 (m, 3H), 6.60 (d, *J* = 15.3 Hz, 1H), 5.04 (s, 2H), 3.83 (s, 3H), 3.73 (s, 3H), 3.37–3.25 (m, 4H), 1.65–1.49 (m, 4H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 166.6, 159.5, 149.8, 149.7, 142.4, 129.0, 128.9, 128.8, 121.2, 115.7, 114.0, 113.9, 111.2, 70.8, 56.1, 55.3, 50.0, 48.7, 23.0, 21.2, 11.4. HRMS (ESI, *m/z*) calcd for [C$_{24}$H$_{32}$NO$_4$] (M + H)$^+$ 386.2131, found 386.2136.

(E)-3-(3-methoxy-4-((4-methylbenzyl)oxy)phenyl)-*N,N*-dipropylacrylamide (16g).



Prepared from **8** (80.0 mg, 0.27 mmol, 1.00 equiv.) and 4-methylbenzyl bromide (0.04 mL, 0.32 mmol, 1.20 equiv.) according to **general procedure A**. White solid (30.0 mg, 28%). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.54 (d, *J* = 15.3 Hz, 1H), 7.28–7.21 (m, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 7.00–6.92 (m, 2H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.60 (d, *J* = 15.3 Hz, 1H), 5.07 (s, 2H), 3.84 (s, 3H), 3.36–3.24 (m, 4H), 2.27 (s, 3H), 1.64–1.48 (m, 4H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 166.4, 149.7, 149.6, 142.2, 137.7, 133.8, 129.3, 128.9, 127.3, 121.2, 115.9, 113.8, 111.2, 70.9, 56.1, 49.9, 48.6, 23.1, 21.2, 21.2, 11.5, 11.4. HRMS (ESI, *m/z*) calcd for [C$_{24}$H$_{32}$NO$_3$] (M + H)$^+$ 382.2382, found 382.2382.

(E)-3-(4-(adamantan-1-yl)methoxy)-3-methoxyphenyl)-*N,N*-dipropylacrylamide (16h).

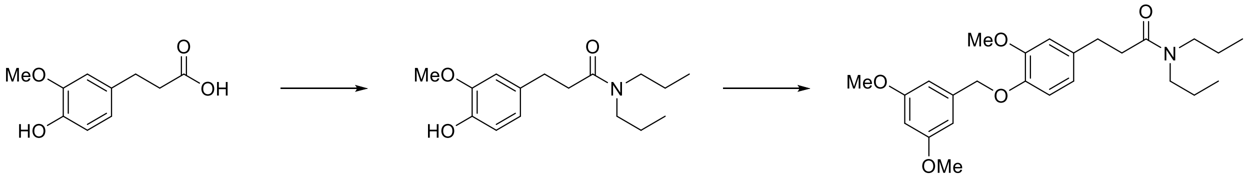


To a stirred solution of **8** (150 mg, 0.53 mmol, 1.00 equiv.) and bromomethyl adamantane (150 mg, 0.64 mmol, 1.20 equiv.) in DMF (5.00 mL) was added cesium carbonate (520 mg, 1.59 mmol, 3.00 equiv.) and potassium iodide (320 mg, 1.91 mmol, 3.60 equiv.). The solution was heated to 100 °C and stirred overnight before cooling to room temperature. The solution was diluted with water and extracted with ethyl acetate. The organic phase was then washed with water and brine. The organic phase was collected and dried over anhydrous sodium sulfate, filtered and solvent was removed under reduced pressure. The crude isolate was purified by flash column chromatography on silica gel to yield **16h** as a white solid (90.0 mg, 38% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.55 (d, *J* = 15.3 Hz, 1H), 7.01 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.95 (d, *J* = 2.1 Hz, 1H), 6.78 (d, *J* = 8.3 Hz, 1H), 6.60 (d, *J* = 15.3 Hz, 1H), 3.81 (s, 3H), 3.49 (s, 2H), 3.40–3.23 (m, 4H), 1.99–1.91 (m, 3H), 1.74–1.50 (m, 16H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H). ^{13}C

NMR (100 MHz, $CDCl_3$): δ (ppm) 166.4, 151.3, 149.8, 142.2, 128.4, 121.8, 115.5, 113.3, 112.2, 79.5, 56.8, 49.9, 48.6, 39.5, 37.1, 34.1, 28.2, 23.1, 21.2, 11.5, 11.4. HRMS (ESI, *m/z*) calcd for $[C_{27}H_{40}NO_3]$ $(M + H)^+$ 426.3008, found 426.3012.

1.5 Synthesis and characterization: series 4 compounds.

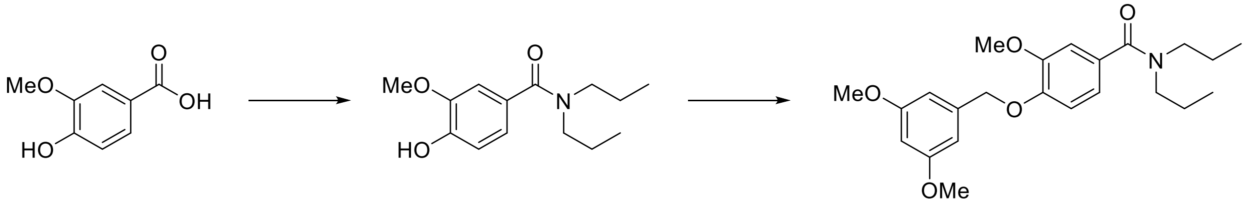
3-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-*N,N*-dipropylpropanamide (18).



S15 **18**

3-(4-hydroxy-3-methoxyphenyl)propanoic acid (200 mg, 1.00 mmol, 1.00 equiv.) and HATU (1.2 equiv.) were dissolved in dichloromethane. *N,N*-diisopropylethylamine (3.00 equiv.) was added and the solution was stirred for five minutes before addition of the dipropylamine (1.20 equiv.). The solution was stirred at room temperature until complete, diluted with dichloromethane and washed with water (x2) and brine. The organic phase was dried over anhydrous sodium sulfate and solvent was removed under reduced pressure. The crude isolate was purified by flash column chromatography on silica gel to afford **S15** (210 mg, 74 % yield), which was then dissolved in DMF and treated with 60% (*wt*) sodium hydride suspension in mineral oil (40.0 mg, 0.88 mmol, 1.20 equiv.). The solution was stirred for ten minutes before addition of 3,5-dimethoxybenzyl bromide (200 mg, 0.88 mmol, 1.20 equiv). Once complete, the reaction was diluted with ethyl acetate and washed with a 1.00 M aqueous solution of hydrochloric acid, water, and brine. The organic phase was dried over anhydrous sodium sulfate, filtered and solvent was removed under reduced pressure. The crude isolate was purified by flash column chromatography on silica gel to yield **18** as a white solid (290 mg, 92%). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.82–6.75 (m, 2H), 6.67 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.59 (d, *J* = 2.2 Hz, 2H), 6.38 (t, *J* = 2.3 Hz, 1H), 5.07 (s, 2H), 3.87 (s, 3H), 3.78 (s, 6H), 3.31–3.22 (m, 2H), 3.14–3.06 (m, 2H), 2.90 (dd, *J* = 8.8, 6.8 Hz, 2H), 2.60–2.52 (m, 2H), 1.63–1.43 (m, 4H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 171.9, 161.1, 149.7, 146.6, 140.1, 135.2, 120.4, 114.6, 112.6, 105.1, 99.9, 71.4, 56.1, 55.5, 49.8, 47.9, 35.4, 31.5, 22.4, 21.1, 11.6, 11.4. HRMS (ESI, *m/z*) calcd for $[C_{25}H_{36}NO_5]$ $(M + H)^+$ 430.2593, found 430.2593.

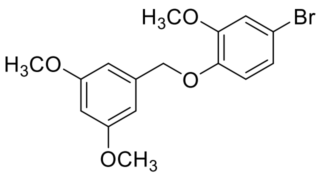
4-((3,5-dimethoxybenzyl)oxy)-3-methoxy-*N,N*-dipropylbenzamide (20).



S16 **20**

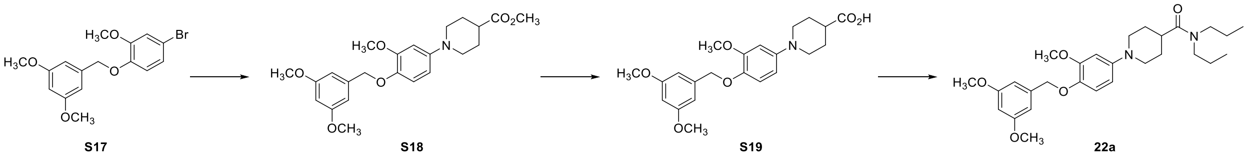
S16 was prepared from 4-hydroxy-3-methoxybenzoic acid (80.0 mg, 0.50 mmol, 1.00 equiv.) and dipropylamine (0.08 mL, 0.60 mmol, 1.20 equiv.) according to **general procedure C** (Method B). White solid (70.0 mg, 52% yield). To a stirred solution of **S16** (70.0 mg, 0.26 mmol, 1.00 equiv.) and 3,5-dimethoxybenzyl bromide (70.0 mg, 0.29 mmol, 1.10 equiv.) in acetone (10 mL) was added potassium carbonate (50.0 mg, 0.39 mmol, 1.50 equiv.) and the solution was stirred overnight at room temperature. The solution was then filtered, and solvent was removed under reduced pressure. The crude isolate was purified by flash column chromatography on silica gel to yield **20** as a white solid (30.0 mg, 25%). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 6.97 (t, *J* = 1.1 Hz, 1H), 6.87 (d, *J* = 1.1 Hz, 2H), 6.61 (d, *J* = 2.3 Hz, 2H), 6.42 (t, *J* = 2.3 Hz, 1H), 5.14 (s, 2H), 3.92 (s, 3H), 3.81 (s, 6H), 3.55–3.15 (m, 4H), 1.74–1.55 (m, 4H), 1.05–0.76 (m, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 171.5, 161.1, 149.5, 148.8, 139.3, 130.4, 119.3, 113.5, 110.9, 104.96, 100.0, 71.1, 56.1, 55.4, 51.0, 46.5, 21.8, 20.9 11.3, 11.3. HRMS (ESI, *m/z*) calcd for [$C_{23}H_{32}NO_5$] (M + H)+ 402.2280, found 402.2285.

4-Bromo-1-((3,5-dimethoxybenzyl)oxy)-2-methoxybenzene (S17).



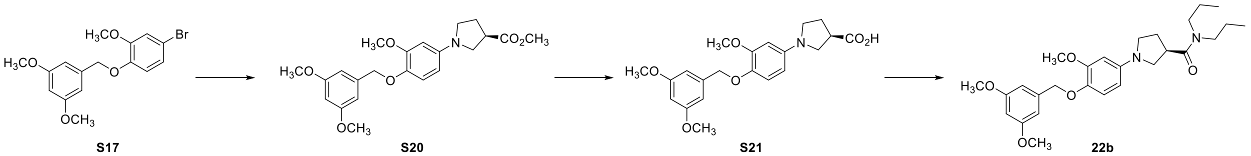
To a stirred solution of 4-bromo-2-methoxyphenol (10.0 g, 49.3 mmol, 1.00 equiv.) and 3,5-dimethoxybenzyl bromide (13.7 g, 59.1 mmol, 1.20 equiv.) in acetone (100 mL) was added potassium carbonate (10.3 g, 73.9 mmol, 1.50 equiv.) and the solution was stirred overnight at room temperature. The solution was then filtered, and solvent was removed under reduced pressure. The crude isolate was purified by flash column chromatography on silica gel to yield **S17** as a white solid (15.1 g, 87%). ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.03 (d, *J* = 2.3 Hz, 1H), 6.98 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 6.60 (d, *J* = 2.3 Hz, 2H), 6.42 (t, *J* = 2.3 Hz, 1H), 5.10 (s, 2H), 3.91 (s, 3H), 3.81 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 161.1, 150.5, 147.4, 139.3, 123.4, 115.5, 115.3, 113.5, 105.0, 99.9, 71.3, 56.2, 55.4.

1-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-*N,N*-dipropylpiperidine-4-carboxamide (22a).



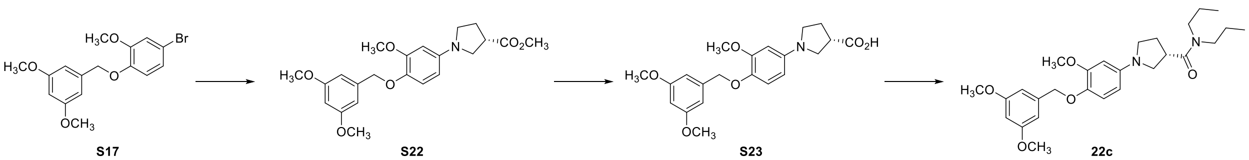
In a round bottom flask equipped with Teflon-coated stir bar is placed **S17** (430 mg, 1.20 mmol, 1.00 eq), methyl piperidine-4-carboxylate, hydrochloride (215 mg, 1.20 mmol, 1.00 equiv.), cesium carbonate (1.56 g, 4.80 mmol, 4.00 eq), $Pd_2(dba)_3$ (55.0 mg, 0.06 mmol, 0.05 equiv.), and XantPhos (104 mg, 0.18 mmol, 0.15 equiv.). The flask was evacuated and backfilled with argon gas (3x) before addition of anhydrous toluene. The solution was heated at 100 °C and stirred overnight. After cooling to room temperature, the solution was diluted with ethyl acetate and washed with water and then brine. The organic phase was dried over anhydrous sodium sulfate, filtered and solvent was removed under reduced pressure. The crude isolate was purified by flash column chromatography on silica gel to yield **S18** as a colorless oil (165 mg, 33% yield). **S18** was hydrolysed following **general procedure E** to generate **S19** (140 mg, 88% yield), which was then coupled with dipropylamine following **general procedure C** (*Method B*) to yield **22a** as a white solid (153 mg, 90% yield). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.03 (d, J = 2.3 Hz, 1H), 6.78 (d, J = 8.7 Hz, 1H), 6.60 (d, J = 2.3 Hz, 1H), 6.40–6.37 (m, 2H), 5.02 (s, 2H), 3.88 (s, 3H), 3.78 (s, 6H), 3.61–3.57 (m, 2H), 3.33–3.21 (m, 4H), 2.67–2.64 (m, 2H), 2.54–5.49 (m, 1H), 2.08–1.98 (m, 2H), 1.77 (d, J = 12.5 Hz, 2H), 1.66–1.50 (m, 4H), 0.94 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 171.6, 161.0, 150.4, 147.4, 142.4, 140.26, 115.7, 108.5, 105.0, 103.7, 99.8, 72.0, 56.0, 55.4, 50.9, 49.4, 47.6, 38.8, 29.2, 22.9, 21.0, 11.4, 11.3. HRMS (ESI, *m/z*) calcd for $[C_{28}H_{41}N_2O_5]$ $(M + H)^+$ 485.3010, found 485.3009.

(*R*)-1-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-*N,N*-dipropylpyrrolidine-3-carboxamide (22b).



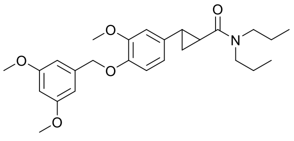
In a round bottom flask equipped with Teflon-coated stir bar is placed **S17** (180 mg, 0.50 mmol,1.00 eq), (*R*)-methyl pyrrolidine-3-carboxylate, hydrochloride (80.0 mg, 0.50 mmol, 1.00 equiv.), cesium carbonate (650 mg, 2.00 mmol, 4.00 eq), $Pd_2(dba)_3$ (30.0 mg, 0.03 mmol, 0.05 equiv.), and XantPhos (40.0 mg, 0.08 mmol, 0.15 equiv.). The flask was evacuated and backfilled with argon gas (3x) before addition of anhydrous toluene. The solution was heated at 100 °C and stirred overnight. After cooling to room temperature, the solution was diluted with ethyl acetate and washed with water and then brine. The organic phase was dried over anhydrous sodium sulfate, filtered and solvent was removed under reduced pressure. The crude isolate was purified by flash column chromatography on silica gel to yield **S20** as a colorless oil (90.0 mg, 47% yield). **S20** was hydrolysed following **general procedure E** to generate **S21** (90.0 mg, 96% yield), which was then coupled with dipropylamine following **general procedure C** (*Method B*) to yield **22b** as a white solid (20.0 mg, 20% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) = 6.84 (d, J = 8.6 Hz, 1H), 6.63 (d, J = 2.3 Hz, 2H), 6.40 (t, J = 2.3 Hz, 1H), 6.21 (d, J = 2.7 Hz, 1H), 6.04 (dd, J = 8.7, 2.7 Hz, 1H), 5.01 (s, 2H), 3.90 (s, 3H), 3.81 (s, 6H), 3.56–3.26 (m, 9H), 2.41–2.27 (m, 1H), 2.26–2.14 (m, 1H), 1.72–1.52 (m, 4H), 0.96 (t, J = 7.4 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 172.6, 160.9, 151.1, 144.1, 140.7, 139.6, 117.8, 105.2, 103.4, 99.9, 97.9, 72.9, 56.0, 55.4, 51.9, 49.7, 48.3, 48.0, 40.6, 29.8, 22.9, 22.1, 11.5, 11.3. HRMS (ESI, *m/z*) calcd for [$C_{27}H_{39}N_2O_5$] (M + H)$^+$ 471.2859, found 471.2859.

(*S*)-1-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-*N,N*-dipropylpyrrolidine-3-carboxamide (22c).



In a round bottom flask equipped with Teflon-coated stir bar is placed **S17** (180 mg, 0.50 mmol,1.00 eq), (*S*)-methyl pyrrolidine-3-carboxylate, hydrochloride (80.0 mg, 0.50 mmol, 1.00 equiv.), cesium carbonate (650 mg, 2.00 mmol, 4.00 eq), Pd$_2$(dba)$_3$ (30.0 mg, 0.03 mmol, 0.05 equiv.), and XantPhos (40.0 mg, 0.08 mmol, 0.15 equiv.). The flask was evacuated and backfilled with argon gas (3x) before addition of anhydrous toluene. The solution was heated at 100 °C and stirred overnight. After cooling to room temperature, the solution was diluted with ethyl acetate and washed with water and then brine. The organic phase was dried over anhydrous sodium sulfate, filtered and solvent was removed under reduced pressure. The crude isolate was purified by flash column chromatography on silica gel to yield **S22** as a colorless oil (80.0 mg, 39% yield). **S22** was hydrolysed following **general procedure E** to generate **S23** (60.0 mg, 83 % yield), which was then coupled with dipropylamine following **general procedure C** (*Method B*) to yield **22c** as a white solid (20.0 mg, 29% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ *(ppm)* = 6.84 (d, J = 8.7 Hz, 1H), 6.63 (d, J = 2.3 Hz, 2H), 6.40 (t, J = 2.3 Hz, 1H), 6.21 (d, J = 2.7 Hz, 1H), 6.04 (dd, J = 8.7, 2.7 Hz, 1H), 5.01 (s, 2H), 3.90 (s, 3H), 3.81 (s, 6H), 3.55–3.24 (m, 9H), 2.41–2.27 (m, 1H), 2.26–2.14 (m, 1H), 1.72–1.52 (m, 4H), 0.96 (t, J = 7.4 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 172.6, 161.0, 151.1, 144.1, 140.7, 139.6, 117.8, 105.2, 103.4, 99.9, 97.9, 72.9, 56.0, 55.4, 52.0, 49.7, 48.3, 48.0, 40.6, 29.8, 22.9, 22.1, 11.5, 11.3. HRMS (ESI, *m/z*) calcd for [$C_{27}H_{39}N_2O_5$] (M + H)$^+$ 471.2859, found 471.2859.

2-(4-((3,5-dimethoxybenzyl)oxy)-3-methoxyphenyl)-*N,N*-dipropylcyclopropane-1-carboxamide (23).



To a suspension of anhydrous chromium(II) chloride (230 mg, 1.88 mmol, 4.00 equiv.) and **1** (200 mg, 0.47 mmol, 1.00 equiv.) in tetrahydrofuran was added dropwise chloroiodomethane (0.13 mL, 1.76 mmol, 3.75 equiv.) at room temperature and under argon atmosphere. The solution was heated to reflux and stirred overnight, then cooled to room temperature and quenched by the addition of a 1 M aqueous solution of hydrochloric acid. The solution was extracted with diethyl ether (x3) and the combined organic extracts were washed with saturated aqueous ammonium chloride solution, dried over anhydrous sodium sulfate, and filtered. Solvent was removed under reduced pressure and the crude isolate was purified flash column chromatography on silica gel to yield **23** as a clear oil (100 mg, 49% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.78 (d, J = 8.3 Hz, 1H), 6.72 (d, J = 2.1 Hz, 1H), 6.59 (d, J = 2.3 Hz, 2H), 6.57–6.53 (m, 1H), 6.38 (t, J = 2.3 Hz, 1H), 5.07 (s, 2H), 3.88 (s, 3H), 3.78 (s, 6H), 3.41–3.22 (m, 4H), 2.43 (dd, J = 4.2, 2.7 Hz, 1H), 1.85 (ddd, J = 8.2, 5.3, 4.2 Hz, 1H), 1.68–1.49 (m, 5H), 1.18 (ddd, J = 8.2, 6.3, 4.2 Hz, 1H), 0.88 (t, J = 7.4 Hz, 3H), 0.86 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 171.6, 161.0, 149.6, 146.7, 139.9, 134.5, 117.7, 114.5, 111.0, 105.0, 99.8, 71.3, 56.1, 55.4, 49.8, 48.5, 25.4, 23.1, 22.8, 21.2, 16.0, 11.4, 11.3. HRMS (ESI, *m/z*) calcd for $[C_{26}H_{36}NO_5]$ $(M + H)^+$ 442.2593, found 442.2596.

2.0 Biology

2.1 General methods and procedures.

Cell Culture. Human primary dermal fibroblasts (PCS-201-012, ATCC), normal skin fibroblasts (CRL-2524, ATCC), human primary lung fibroblasts (PCS-201-013, ATCC) lot #70041445 (hPFLs #1) and lot #70046876 (hPLFs #2), normal lung fibroblasts IMR90 (CCL-186, ATCC) and WI38 (CCL75, ATCC), and human embryonic kidney 293T were used in this study. The cells were cultured in their respective media according to the suppliers.

Collagen-1 ELISA and Cell Viability Assay. Human primary dermal fibroblasts (hPDFs), normal skin and lung fibroblasts (IMR90, WI38) cells were seeded onto 96-well plates (2000 cells/well) for 24 hours, then starved in MEM 0.5% FBS and treated with the candidate compound (1.25-40 µM; 6 concentrations) alongside recombinant TGFβ1 (rTGFβ1; 10 ng/mL; used to mimic profibrotic conditions). After 72 hours of treatment, the supernatant is collected and processed for pro-collagen1α1 production using an ELISA assay (ab210966, Abcam). In parallel, toxicity of the compounds was tested using CyQuant NF Cell Proliferation Assay, (Thermo Fisher Scientific). This assay measures cell proliferation based on cellular DNA content and was performed according to the manufacture protocol. The IC_{50} for each compound was calculated using GraphPad Prism software nonlinear regression analysis. For ELISA IC_{50} values, the DMSO control was considered as IC_{100}, and rTGFβ1 as IC_{00}. The CyQuant IC_{50} values were normalized to rTGFβ1.

Western Blot. Human primary dermal or lung fibroblasts (hPDFs, hPLF #1, hPLF #2) were seeded onto 6-well plates (200,000 cells/well). Twenty-four hrs later, the cells were starved for 24 h with MEM 0.5% FBS, then treated with the candidate compounds (40 µM for hPDFs; 20 µM for hPLFs #1 and #2), in addition of recombinant TGFβ1 (10 ng/mL). The cells were harvested and lysed 24 h after treatment. Protein was extracted using Immunoprecipitation buffer (150 mM NaCl, 5 mM EDTA, 50 mM Hepes pH 7.6, 1.5% Nonidet P-40); with protease inhibitor cocktail (Roche). Electrophoresis was performed with Bolt 4-20% Gels (Life Technologies, Carlsbad, CA, USA). Detection of all proteins was undertaken with Pierce ECL (#32209). Antibodies used were anti-collagen-1 (ab260043, abcam, 1:2000), and anti-β-actin (A1978, Sigma, 1:5000).

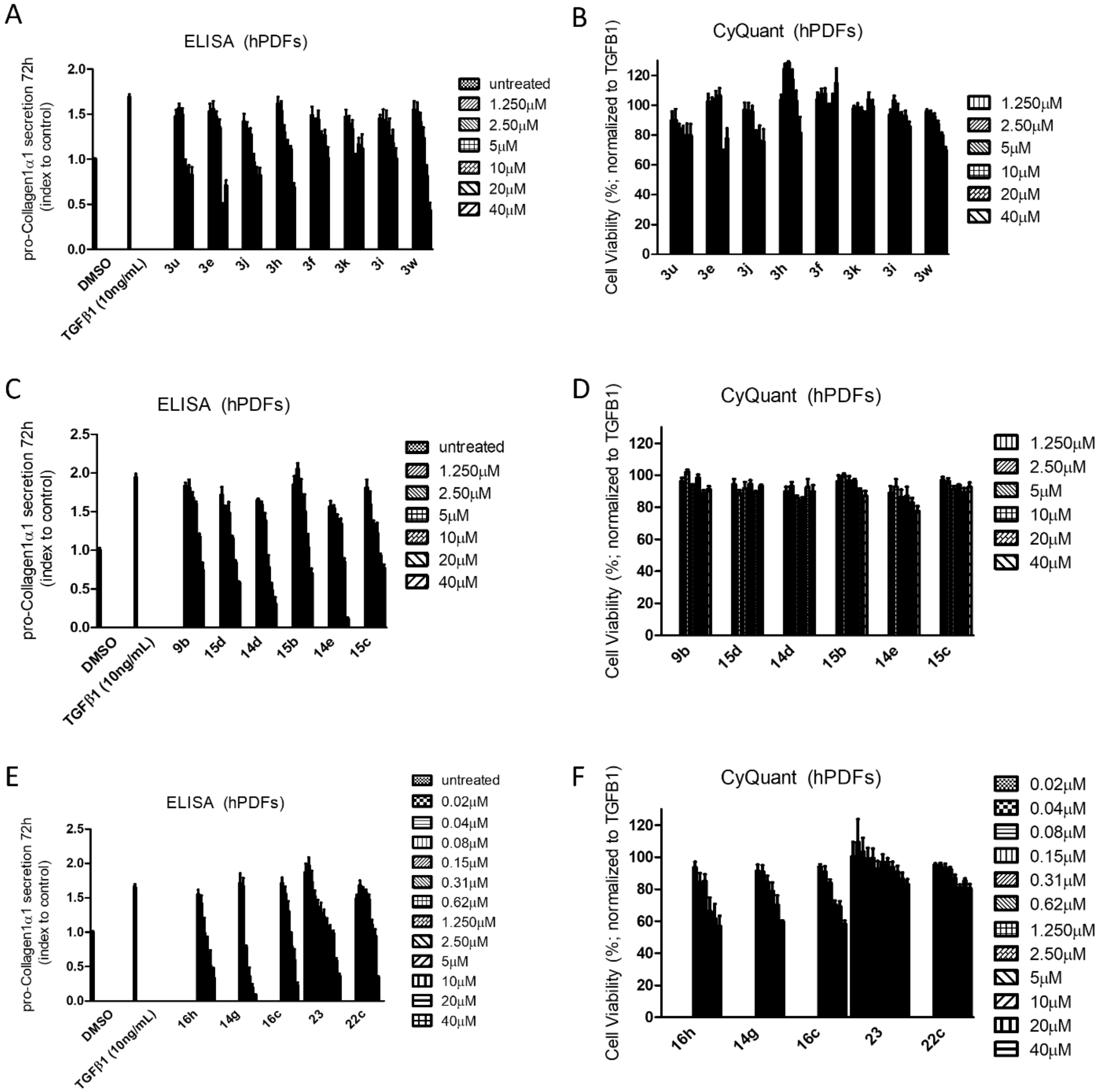
Quantitative Real-Time PCR (qRT–PCR). The hPDFs, the hPLFs #1 and #2 were subjected to similar treatment as for protein extraction, except that 5 ng/mL of rTGFβ1 was used. The Total RNA Purification Kit (Norgen Biotek, Thorold, ON, Canada) was used to isolate mRNA. The iScript cDNA Synthesis Kit (BioRad, Hercules, CA, USA) was used to perform the reverse-transcription of 1 µg or 500 ng of total RNA. qRT-PCR was performed using SYBR Green (Roche, Basel, Switzerland) using the following primers: Collagen (Forward: CAGCCGCTTCACCTACAGC, Reverse: TTTTGTATTCAATCACTGTCTTGCC); PPARG (Forward: GGCTTCATGACAAGGGAGTTTC, Reverse: AACTCAAACTTGGGCTCCATAAAG); CD36 (Forward: TCTTTCCTGCAGCCCAATG, Reverse: AGCCTCTGTTCCAACTGATAGTGA); GAPDH (Forward: AGGGCTGCTTTTAACTCTGGT, Reverse: CCCCACTTGATTTTGGAGGGA); 18s rRNA (Forward: GTAACCCGTTGAACCCCATT, Reverse: CCATCCAATCGGTAGTAGCG). mRNA expression was normalized to two housekeeping genes (GAPDH and 18s rRNA) and the relative expression was calculated using the $2^{-\Delta\Delta CT}$ method[7].

Luciferase Reporter Assay for PPAR activity. HEK293T cells were seeded onto 96-well plates, 24 hours later, the cells were co-transfected with PPRE-Luc and pRL-SV Renilla plasmids using JetPRIME and treated with the desired compounds. The next day, firefly and Renilla activities were measured using the Dual-Luciferase Reporter Assay (Promega).

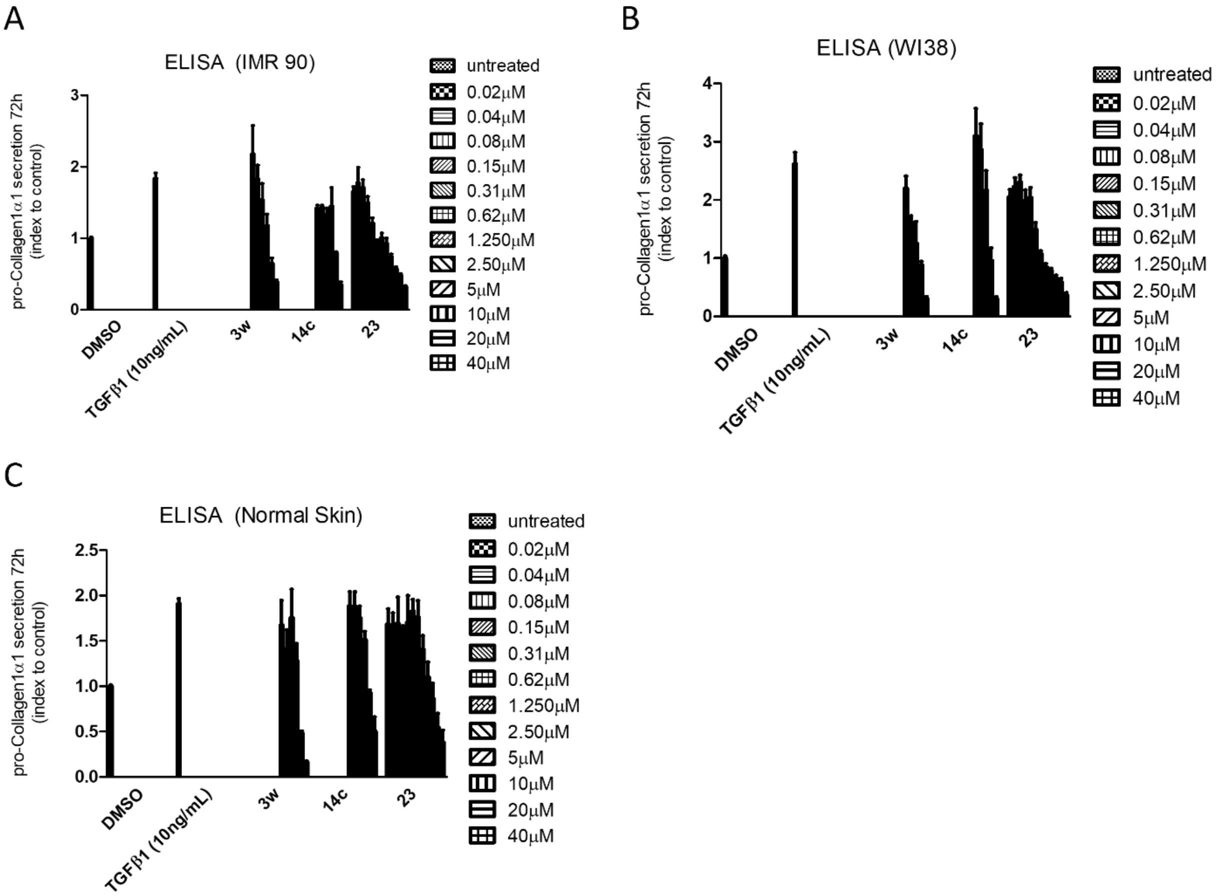
Mouse liver microsomal stability assay. Assay was performed by WuXi AppTec using CD-1 mouse liver microsomes (IPHASE; Cat No. 0121E1.01, Lot 23E005) following the vendor's standard protocol. $T_{1/2}$ was generated from sampling aliquots at T= 0, 5, 15, 30, 25, 60 min.

Statistical analysis. The statistical difference between groups was calculated by one-way ANOVA test, followed by the Dunnett's post-test. Data were represented as the mean ± standard error of the mean (SEM) of three independent experiments. Analysis and graphs were generated using GraphPad Prism software.

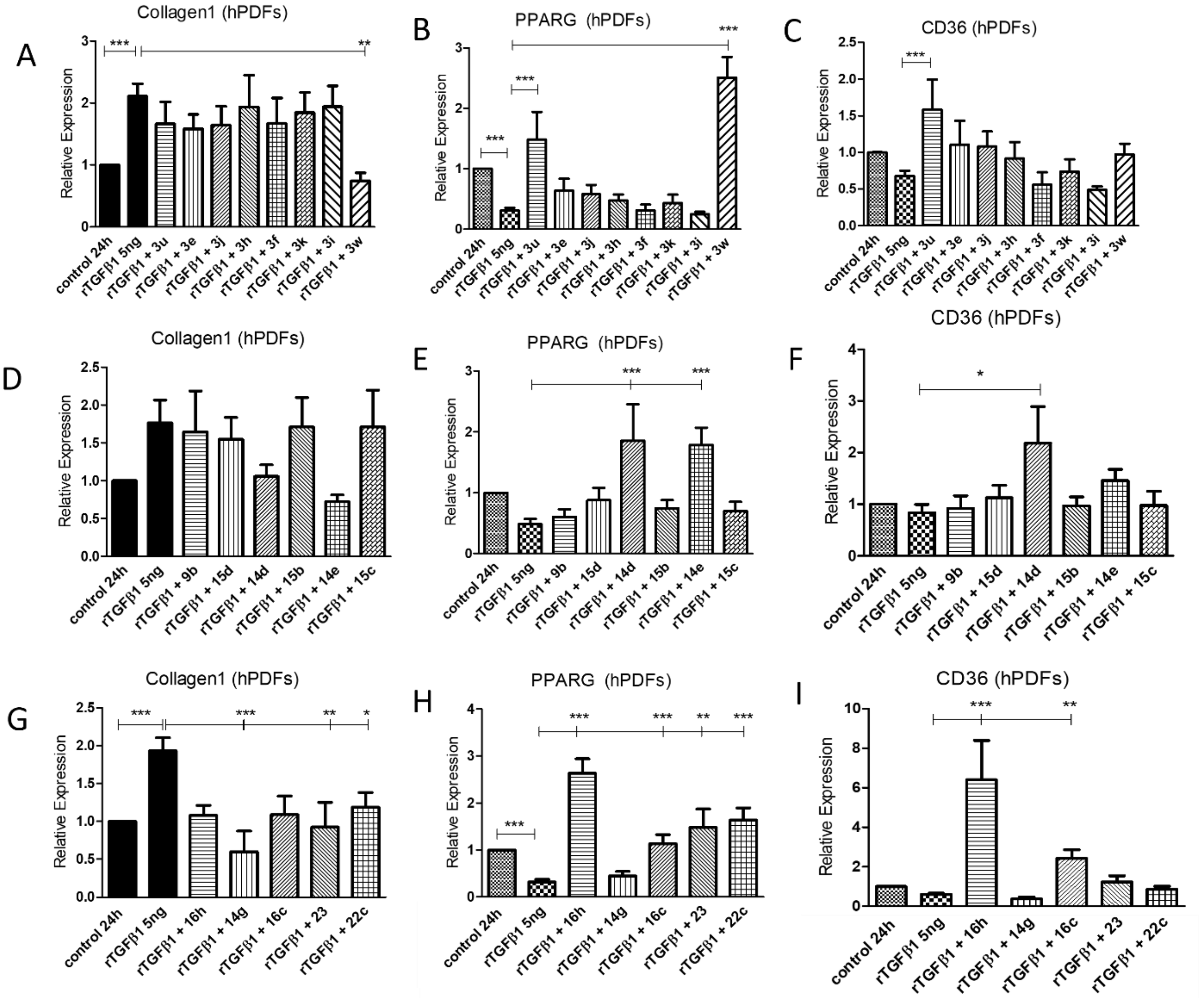
2.2 Supplementary *in vitro* data



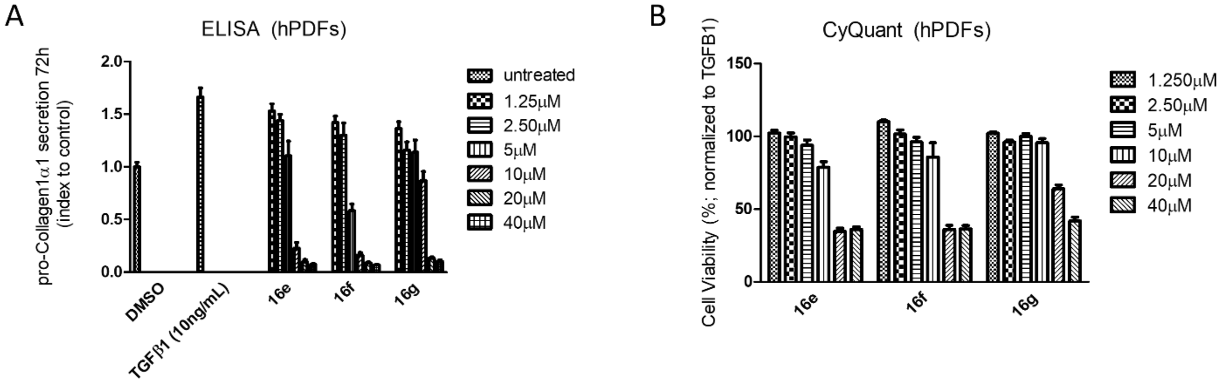
Supplementary Figure 1. Collagen-1 ELISA performed on hPDFs after 72h of rTGFβ1 (10 ng/mL) incubation in addition of a dose response treatment of (A) series 1 compounds, (C) series 2 and 3 compounds and (E) series 3 and 4 compounds. Cell viability assessed by CyQuant on hPDFs after 72 h of rTGFβ1 (10 ng/mL) incubation in addition of a dose response of (B) series 1 compounds, (D) series 2 and 3 compounds and (F) series 3 and 4 compounds.



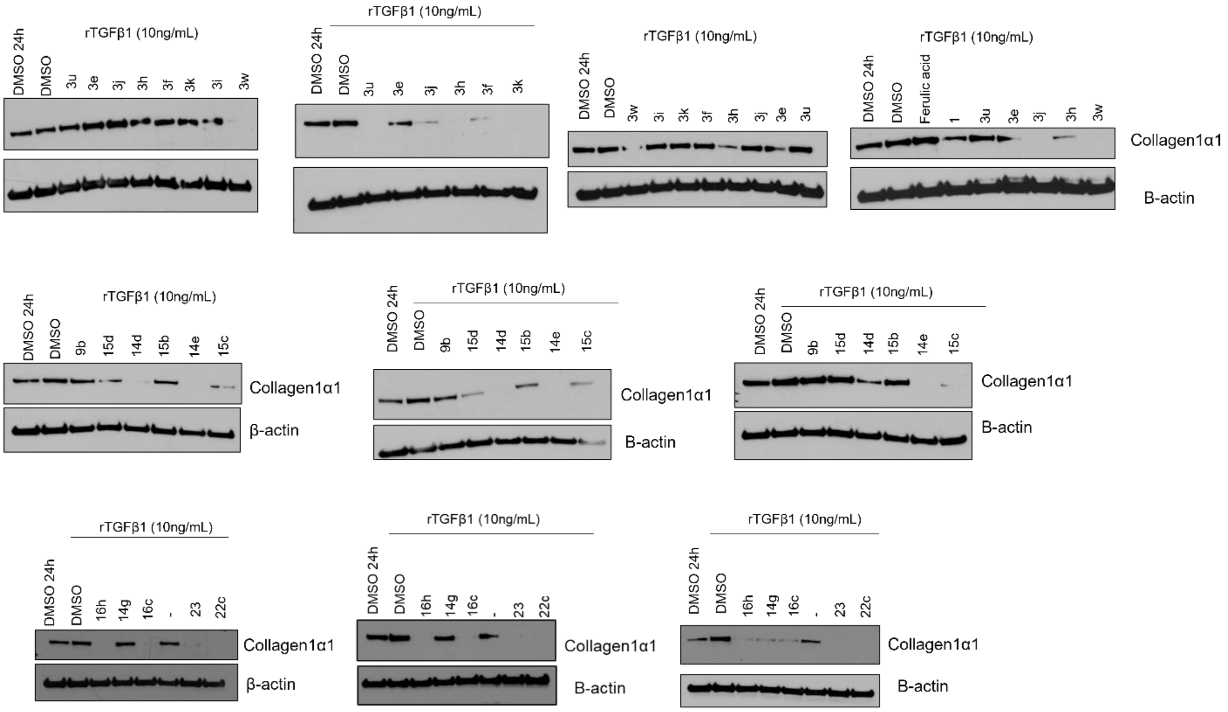
Supplementary Figure 2. Collagen-1 ELISA performed on (A) IMR 90 normal fibroblasts, (B) WI38 normal fibroblasts and (C) normal skin fibroblasts after 72 h of rTFGβ1 (1 0ng/mL) incubation in addition of a dose response of compounds **3w**, **14c** and **23**.



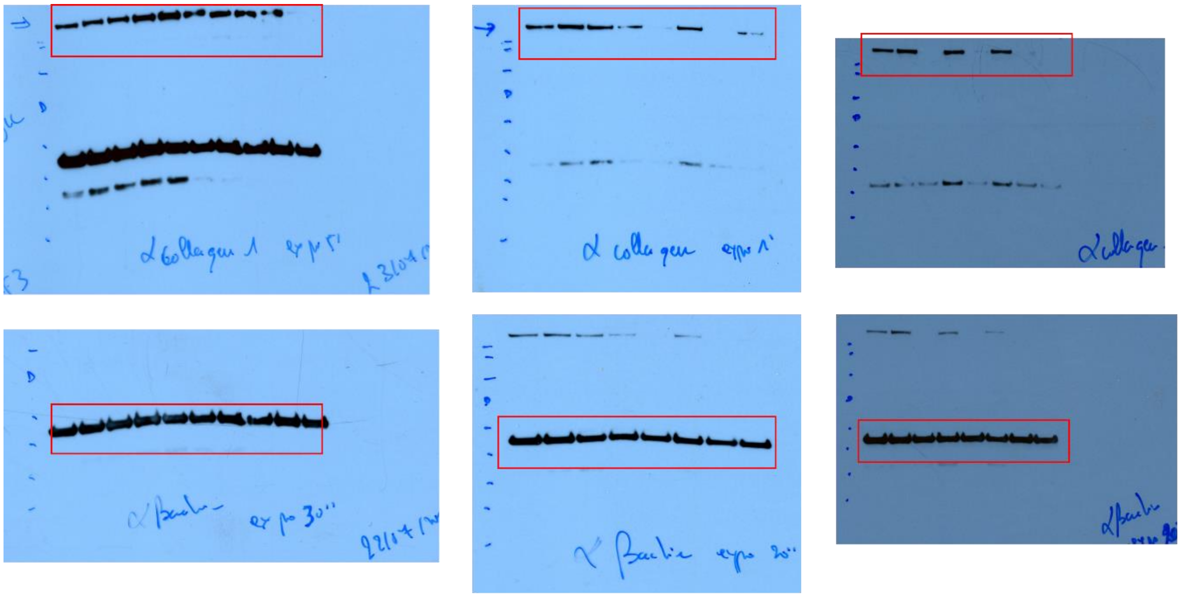
Supplementary Figure 3. Relative gene expression was assessed by qRT-PCR after hPDFs were treated for 72 h with rTGFβ1 (10 ng/mL) in addition to 40 µM of compounds. Collagen-1 expression: (A) series 1 compounds, (D) series 2 and 3 compounds and (G) series 3 and 4 compounds. PPARG expression: (B) series 1 compounds, (E) series 2 and 3 compounds and (H) series 3 and 4 compounds. CD36 expression: (C) series 1 compounds, (F) series 2 and 3 compounds and (I) series 3 and 4 compounds.



Supplementary Figure 4. (A) Collagen-1 ELISA on hPDFs after 72 h of rTGFβ1 (10 ng/mL) incubation in addition of a dose response treatment of compounds **16e**, **16f** and **16g**. (B) Associated cell viability assessed by CyQuant.

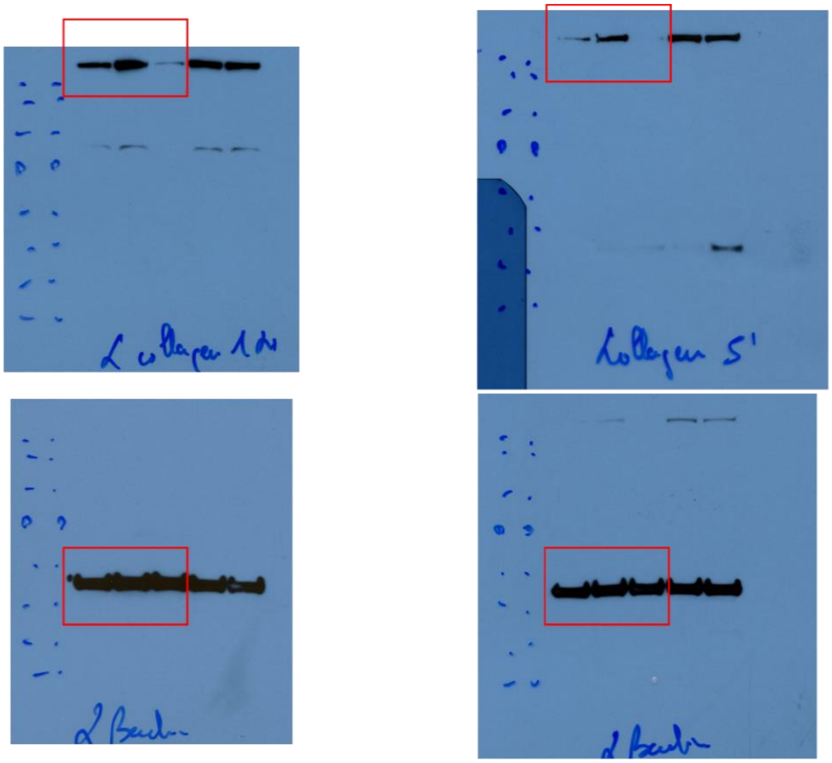


Supplementary Figure 5. Replicates of Western blots for series 1—4 compounds in hPDFs.



Uncropped WB Figure 2A. **Uncropped WB Figure 2B.** **Uncropped WB Figure 2C.**

Supplementary Figure 6. Uncropped Western blots for **Figure 2A—C**.



Uncropped WB Figure 4A. **Uncropped WB Figure 4B.**

Supplementary Figure 7. Uncropped Western blots for **Figure 4A and B**.

2.3 CAPE plasma stability and hydrolysis to caffeic acid.

A DMSO solution of CAPE (5 mg/mL) was prepared, and 10 µl was added to 990 µl of ice cold blank plasma (male CD-1 mouse K2 EDTA; BioIVT, lot337591); initial concentration of 50 µg/mL CAPE. A 50 µl aliquot was immediately transferred to a microcentrifuge tube containing 200 µl ice cold IS spiking solution (4 µg/mL in acetonitrile) for T = 0 sample. The plasma sample was incubated at 37 °C or 0 °C and 50 µl aliquots were transferred to ice cold spinking buffer (200 µl) at T = 5, 10, 20, and 30 minutes. All sample aliquots were briefly vortexed before centrifugation at 15000 rpm for 15 min at 4 °C. The supernatant was collected and sample aliquots were diluted with two volumes of 0.1% formic acid in water. The concentration of substrates (CAPE and caffeic acid) was determined by LCMS-MS (Waters G2-XS QTOF). The results are summarized in **Supplementary Table 1 and 2**.

Supplementary Table 1. Stability of CAPE in CD-1 mouse plasma.

Caffeic Acid Phenethyl Ester												
	AUC		**% Remaining**		**Ln Remaining**		**R^2**		**ke (min^{-1})**		**$T_{1/2}$ (min)**	
Time	**Ice**	**37°c**	**Ice**	**37°c**	**Ice**	**37°c**	**Ice**	**37c**	**Ice**	**37c**	**Ice Water**	**37°c**
0	33.2	33.2	100%	100%	4.6	4.6	0.99	0.74	0.0126	0.2021	**54.9**	**3.4**
5	31.0	2.3	93%	7%	4.5	1.9						
10	28.7	0.118	86%	0%	4.5	-1.0						
20	26.1	0.064	78%	0%	4.4	-1.6						
30	22.5	0.046	68%	0%	4.2	-2.0						

Supplementary Table 2. Increasing concentration of caffeic acid from CAPE hydrolysis during incubation in CD-1 mouse plasma at 0 °C (ice) and 37 °C.

Caffeic Acid				
	µg/mL		**µM**	
Time	**Ice**	**37°c**	**Ice**	**37°c**
0	1.2	1.2	6.66	6.66
5	10.7	38.2	59.39	212.03
10	13.9	37.1	77.15	205.93
20	18.3	34.7	101.58	192.61
30	22.6	32.6	125.44	180.95

3.0 References:

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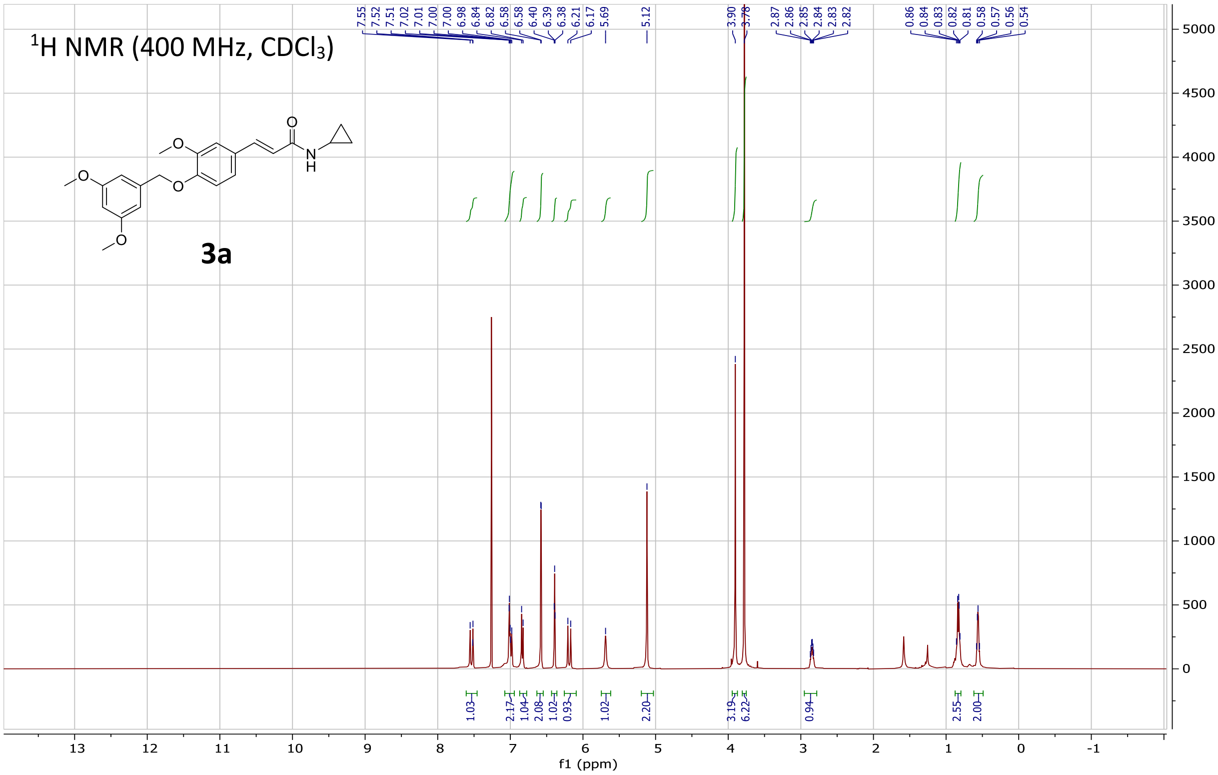
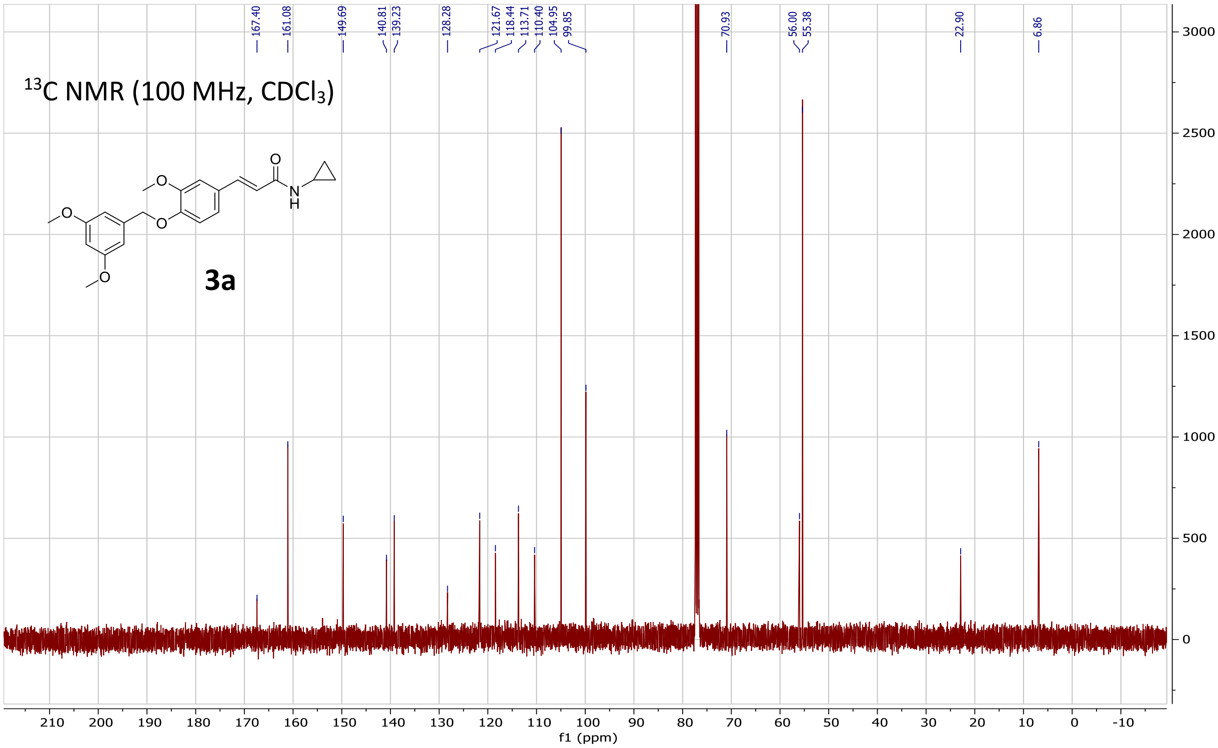
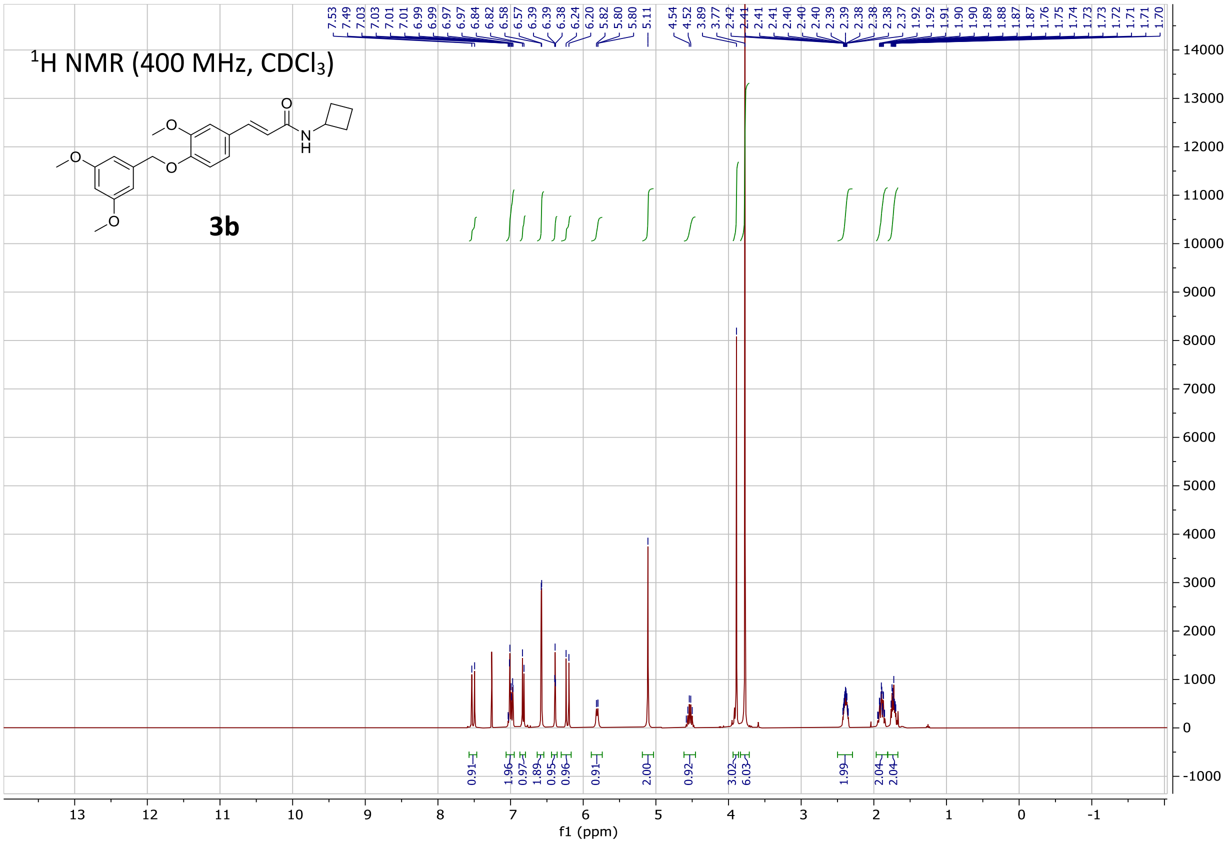
4.0 NMR spectra (^{1}H, ^{13}C, ^{19}F) for new compounds

4.1 Series 1 compounds.



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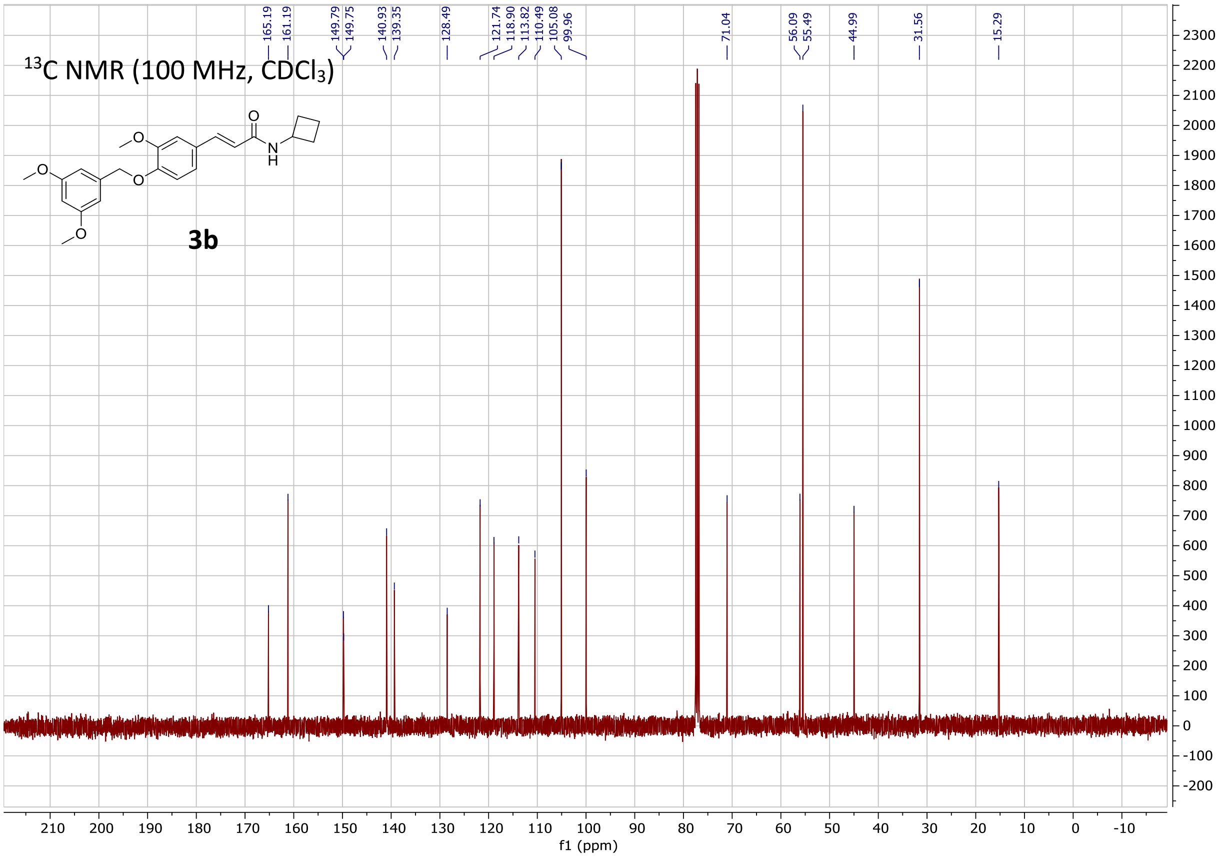
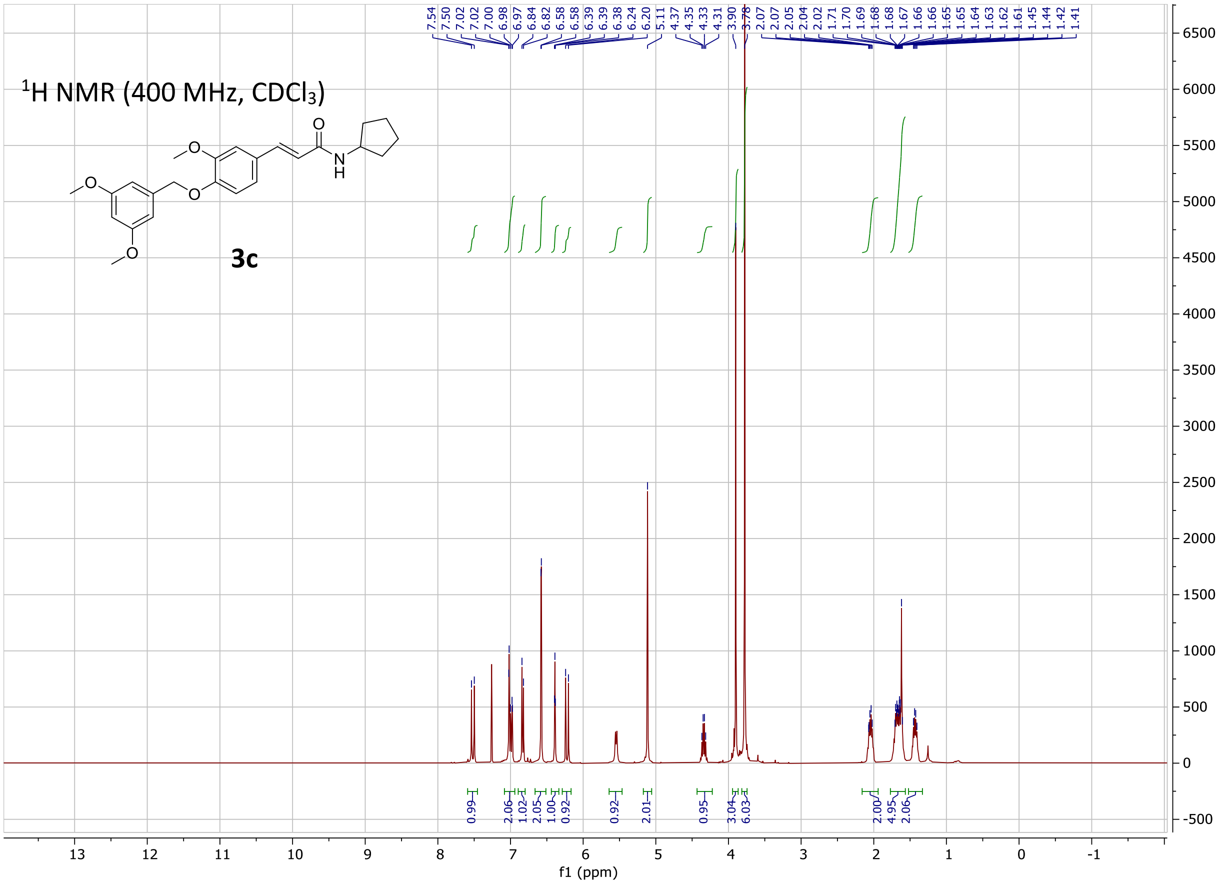
3b
O
N
H
7.53 7.49 7.03 7.03 7.01 7.01 6.99 6.99 6.97 6.97 6.84 6.82 6.58 6.57 6.39 6.39 6.38 6.24 6.20 5.82 5.80 5.80 5.11 4.54 4.52 3.89 3.77 2.42 2.41 2.41 2.41 2.40 2.40 2.40 2.39 2.39 2.38 2.38 2.38 2.37 1.92 1.92 1.91 1.90 1.90 1.89 1.88 1.87 1.87 1.76 1.75 1.74 1.73 1.73 1.72 1.71 1.71 1.70
0.91 1.96 0.97 1.89 0.95 0.96 0.91 2.00 0.92 3.02 6.03 1.99 2.04 2.04
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)
14000 13000 12000 11000 10000 9000 8000 7000 6000 5000 4000 3000 2000 1000 0 -1000


^{13}C NMR (100 MHz, CDCl$_3$)
3b
O
N
H
165.19 161.19 149.79 149.75 140.93 139.35 128.49 121.74 118.90 113.82 110.49 105.08 99.96 71.04 56.09 55.49 44.99 31.56 15.29
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
2300 2200 2100 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100 -200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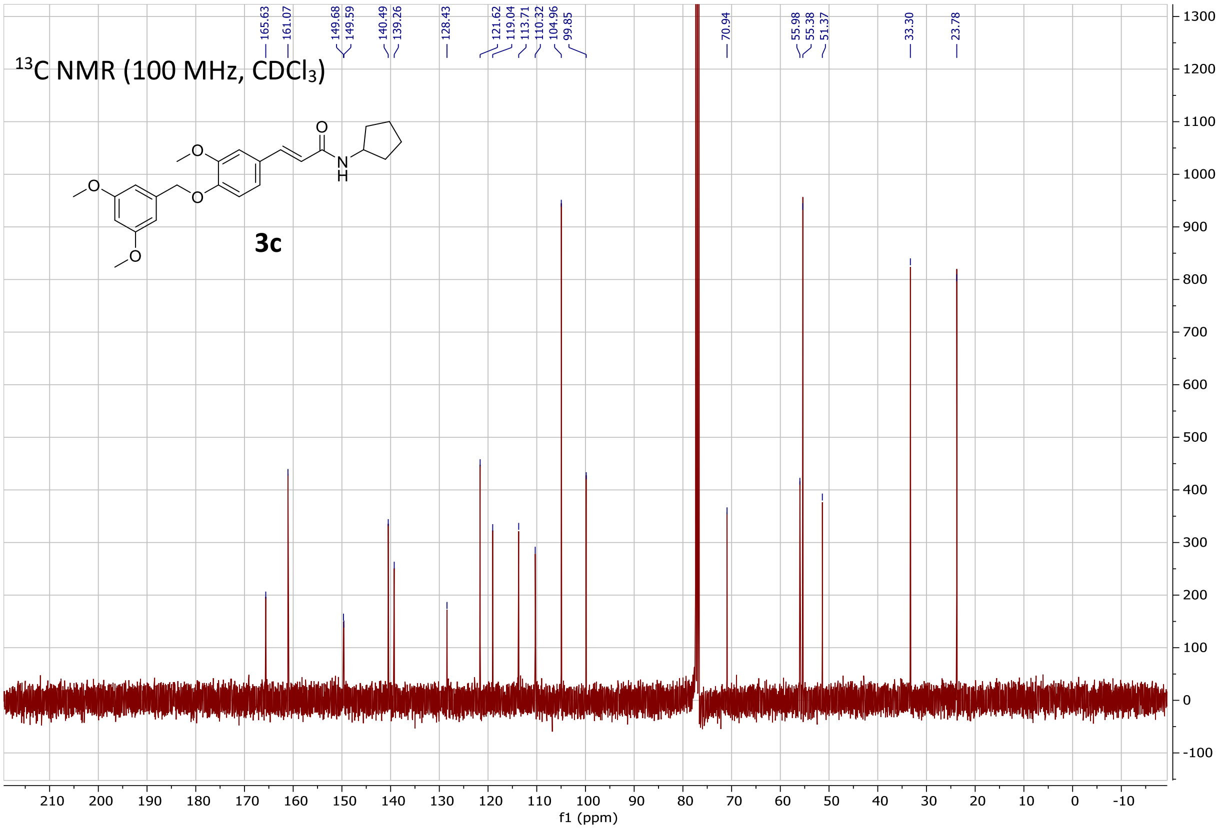
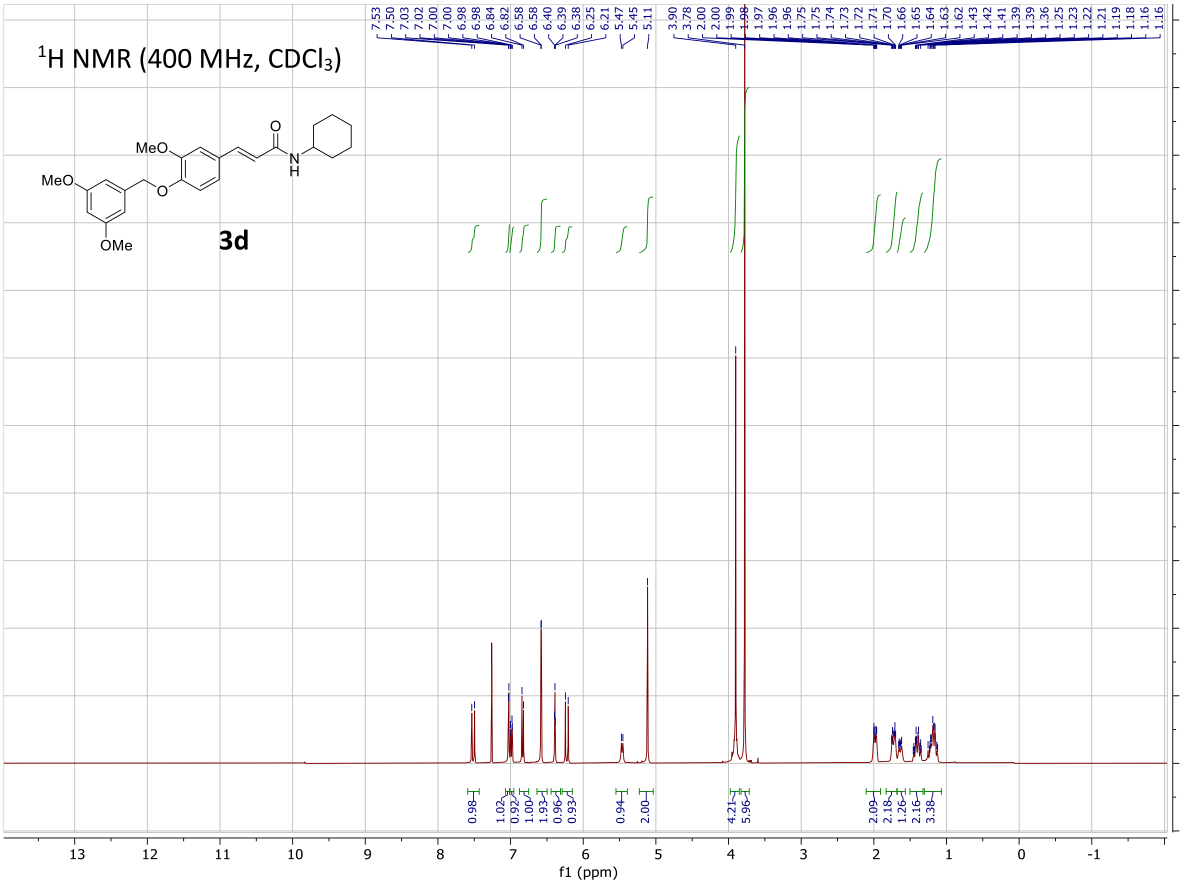
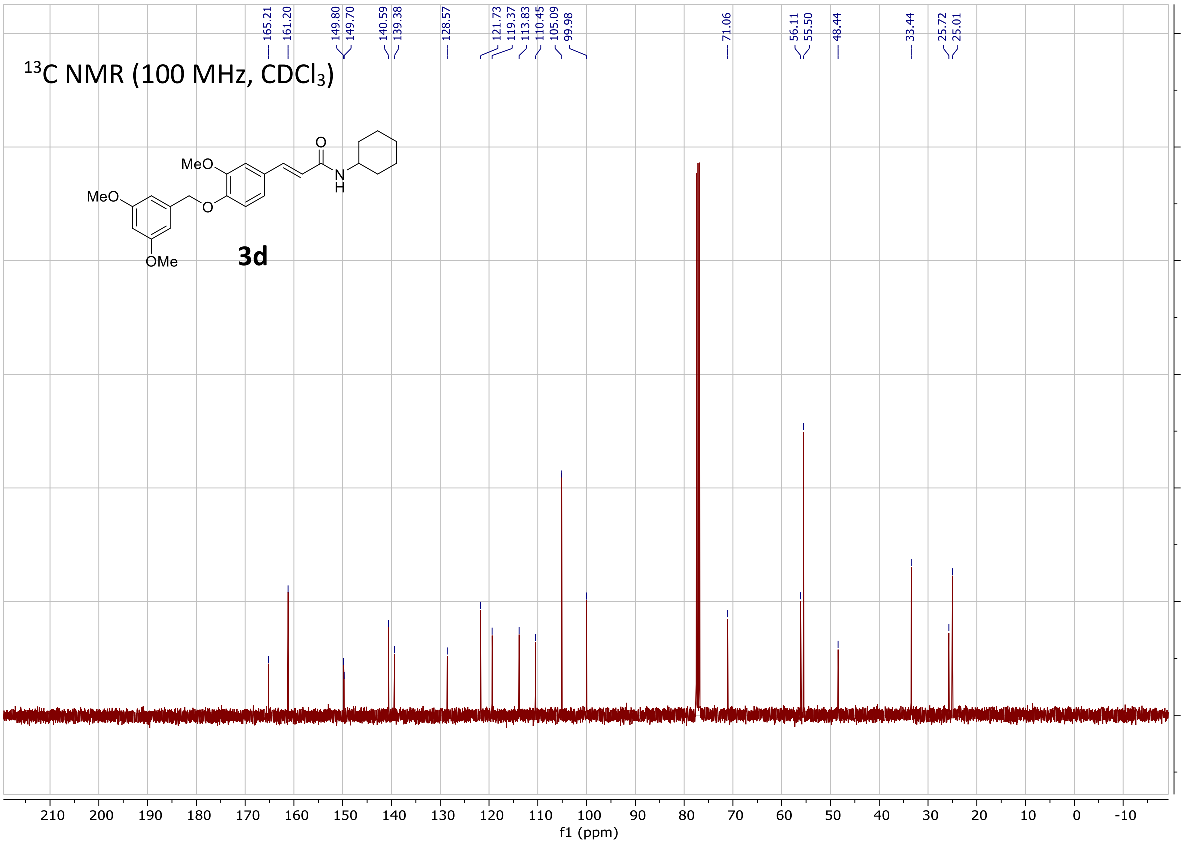
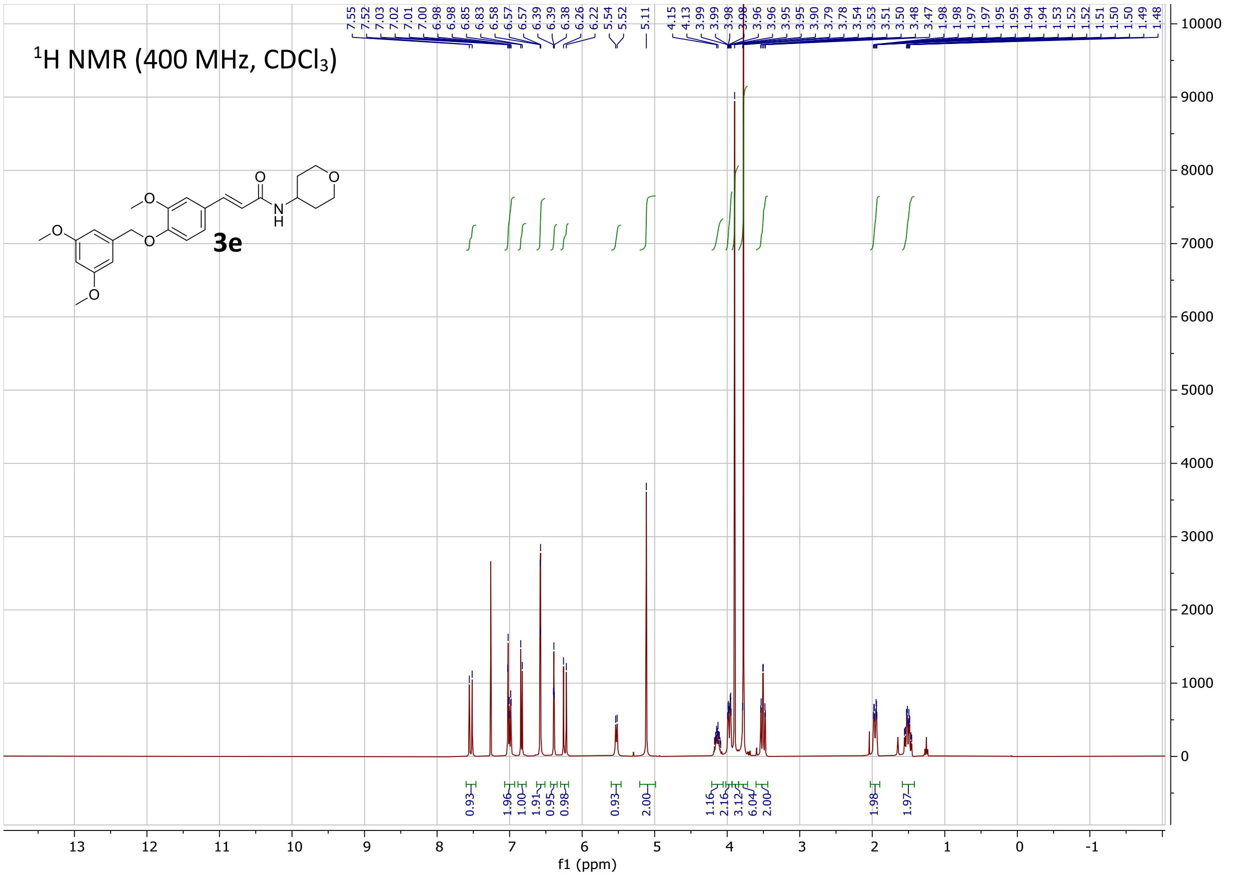
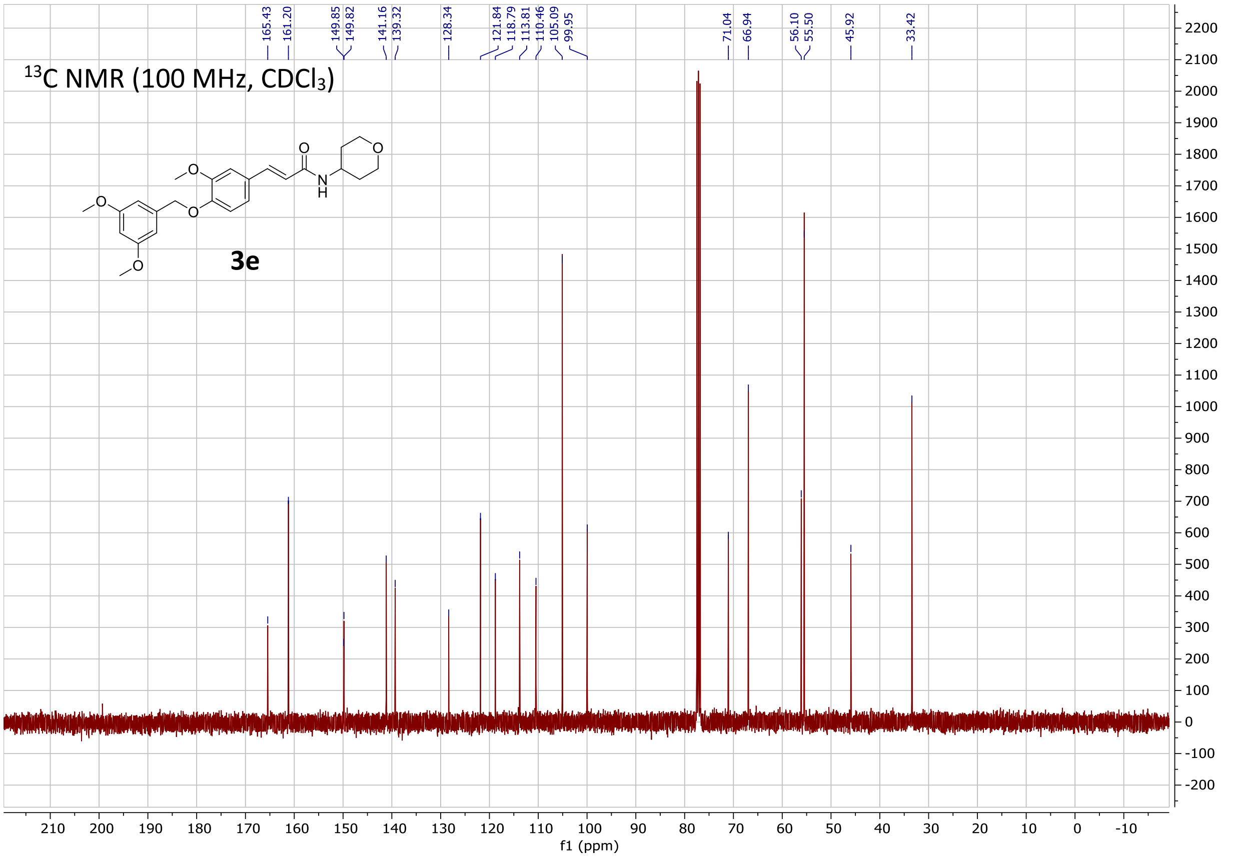

^{13}C NMR (100 MHz, $CDCl_3$)


^{1}H NMR (400 MHz, CDCl$_3$)
MeO
MeO
O
OMe
O
N
H
3d
7.53
7.50
7.03
7.02
7.00
7.00
6.98
6.98
6.84
6.82
6.58
6.58
6.40
6.39
6.38
6.25
6.21
5.47
5.45
5.11
3.90
3.78
2.00
2.00
1.99
1.98
1.97
1.96
1.96
1.75
1.75
1.74
1.73
1.72
1.71
1.70
1.66
1.65
1.64
1.63
1.62
1.43
1.42
1.41
1.39
1.39
1.36
1.25
1.23
1.22
1.21
1.19
1.18
1.16
1.16
0.98
1.02
0.92
1.00
1.93
0.96
0.93
0.94
2.00
4.21
5.96
2.09
2.18
1.26
2.16
3.38
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

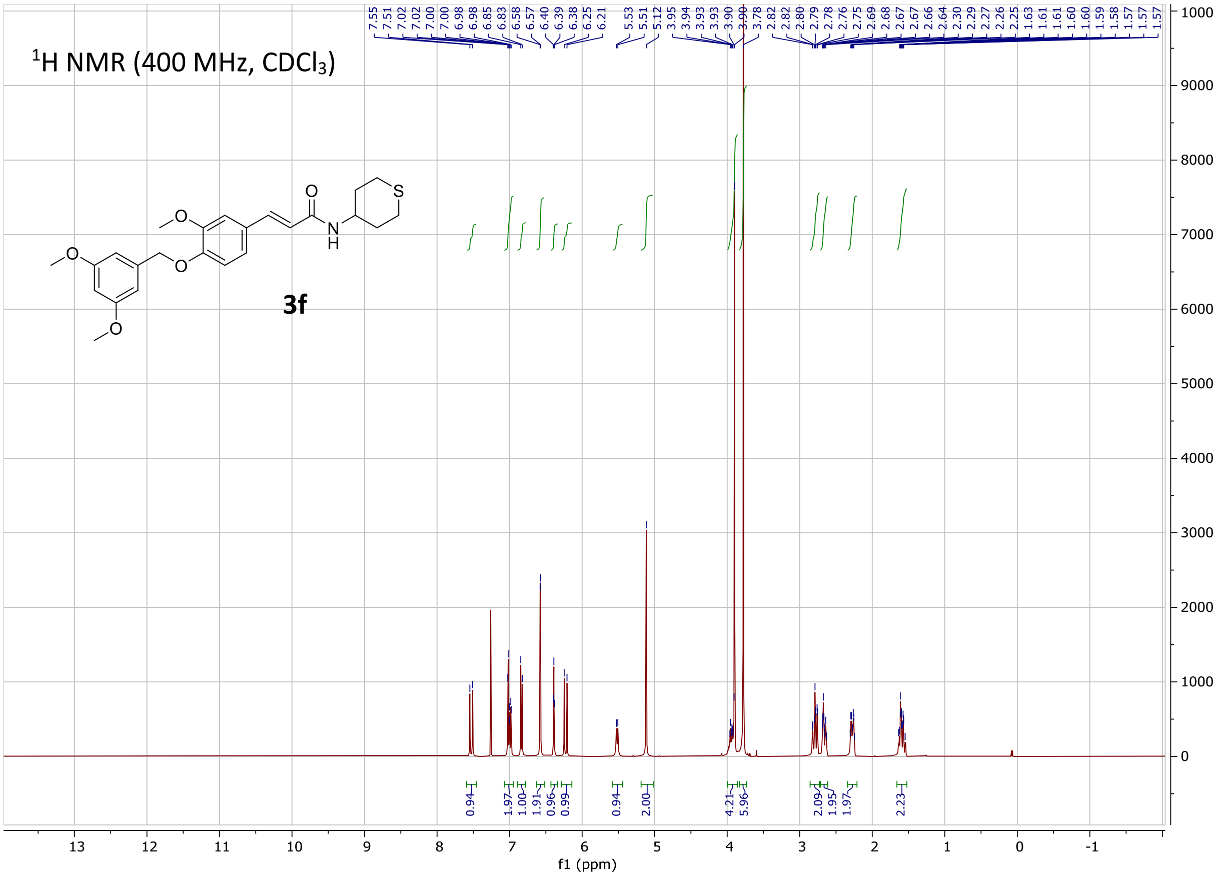

^{13}C NMR (100 MHz, CDCl$_3$)
MeO
MeO
O
OMe
O
N
H
3d
165.21
161.20
149.80
149.70
140.59
139.38
128.57
121.73
119.37
113.83
110.45
105.09
99.98
71.06
56.11
55.50
48.44
33.44
25.72
25.01
3000
2500
2000
1500
1000
500
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

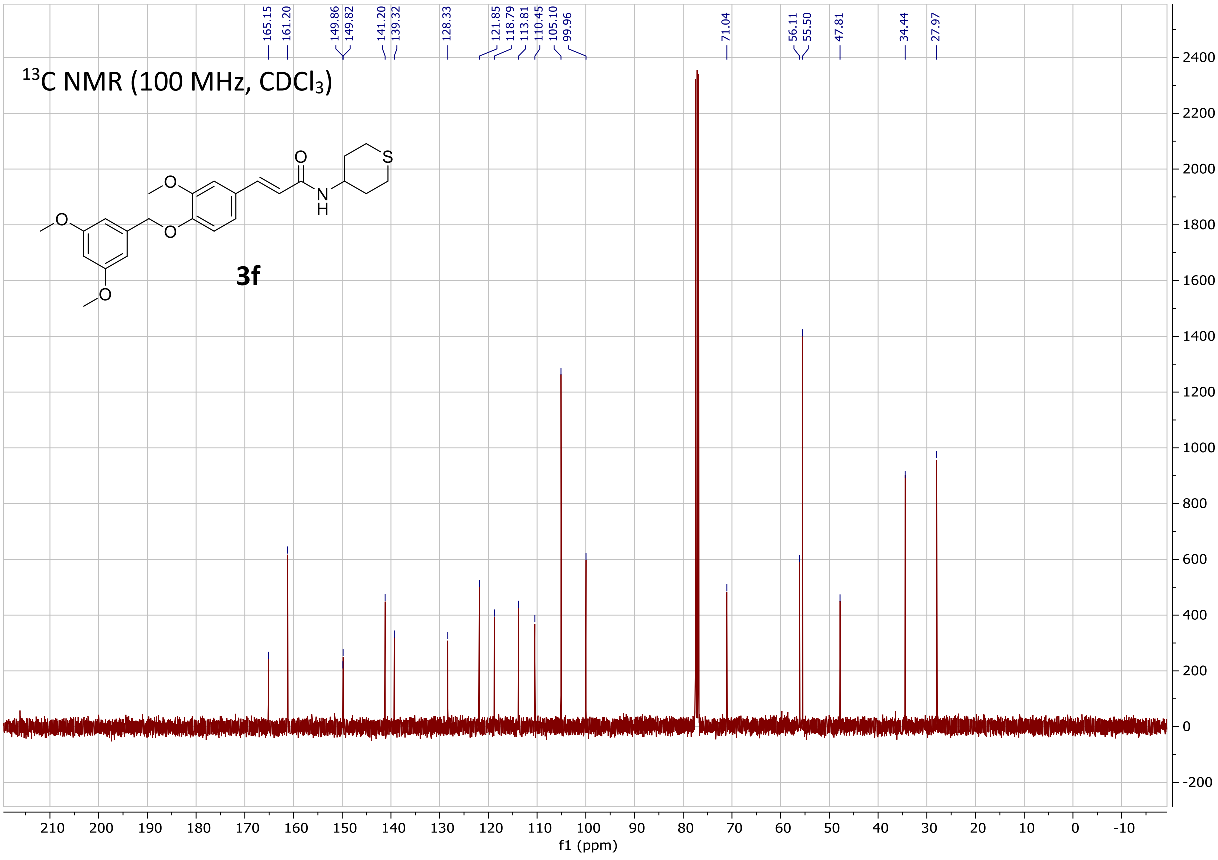

^{1}H NMR (400 MHz, CDCl$_3$)

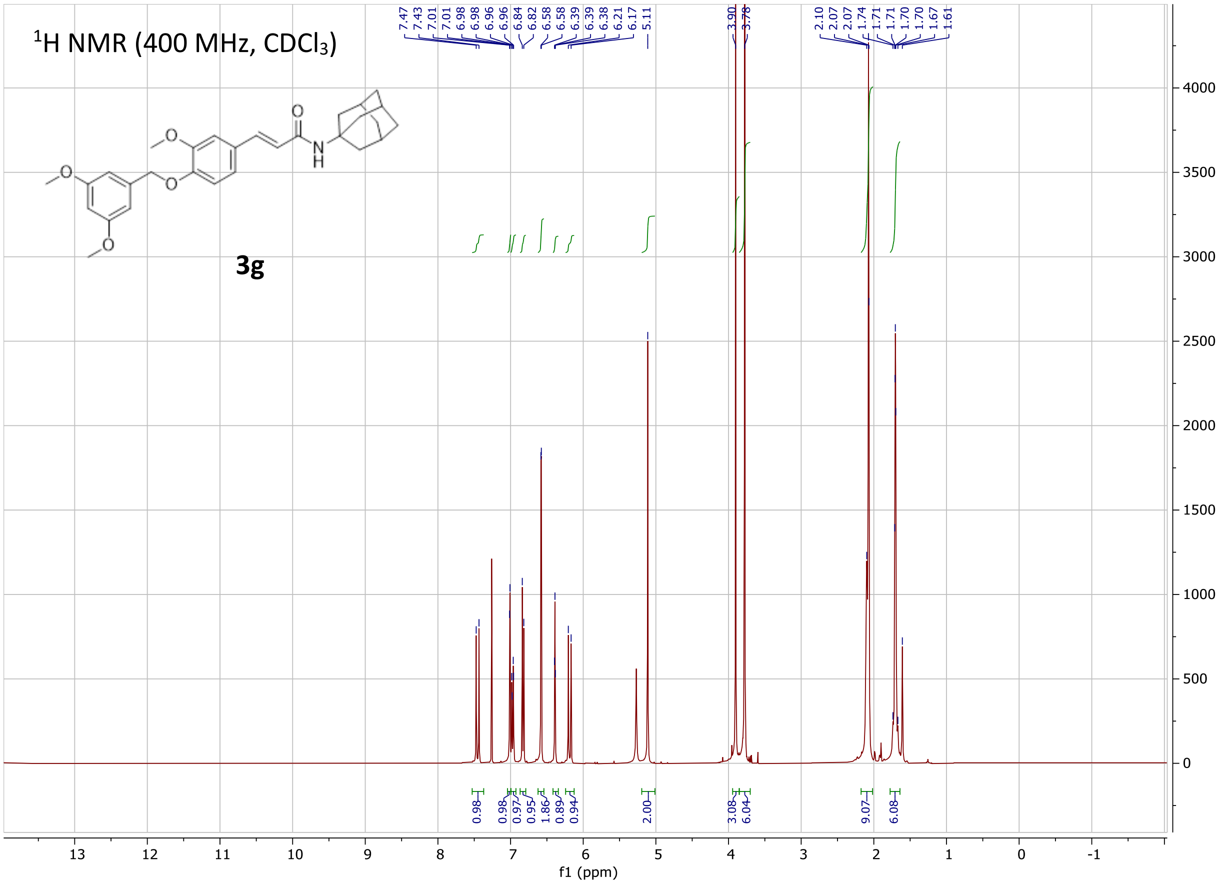
3e

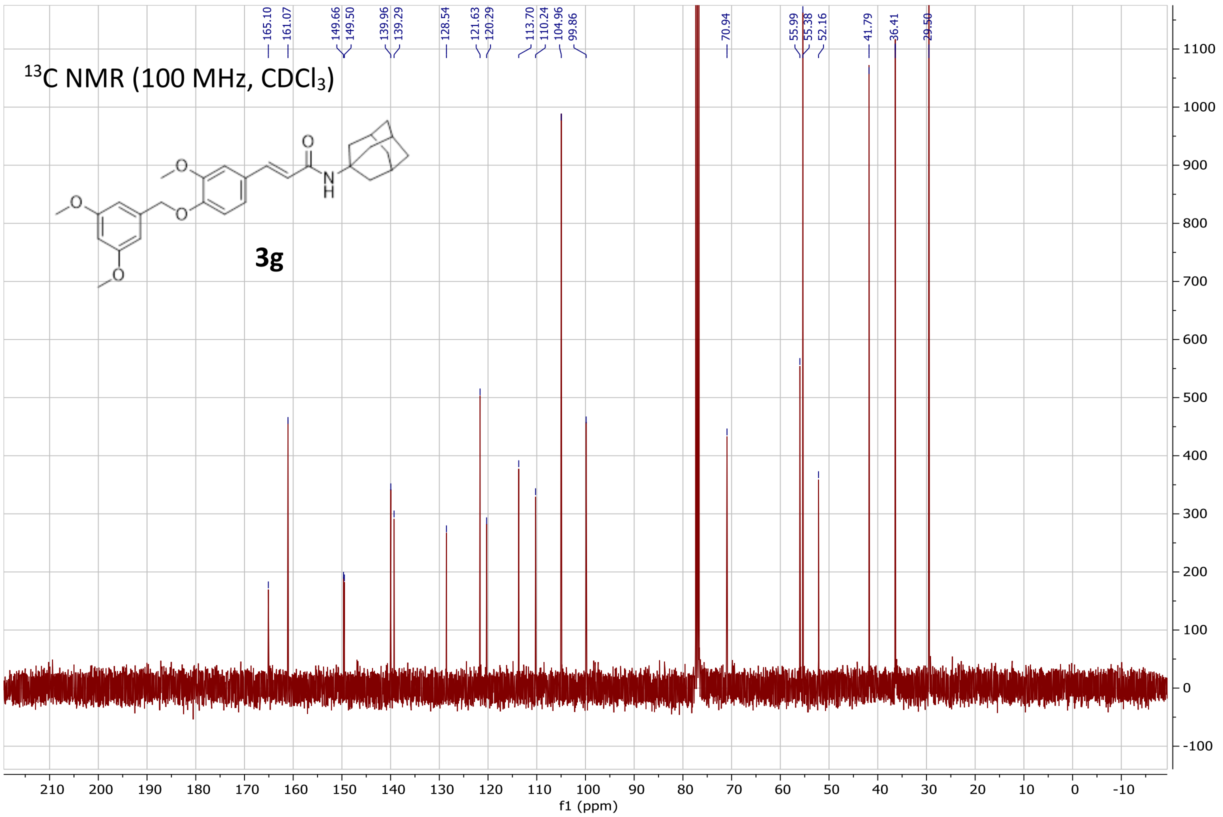

^{13}C NMR (100 MHz, CDCl$_3$)

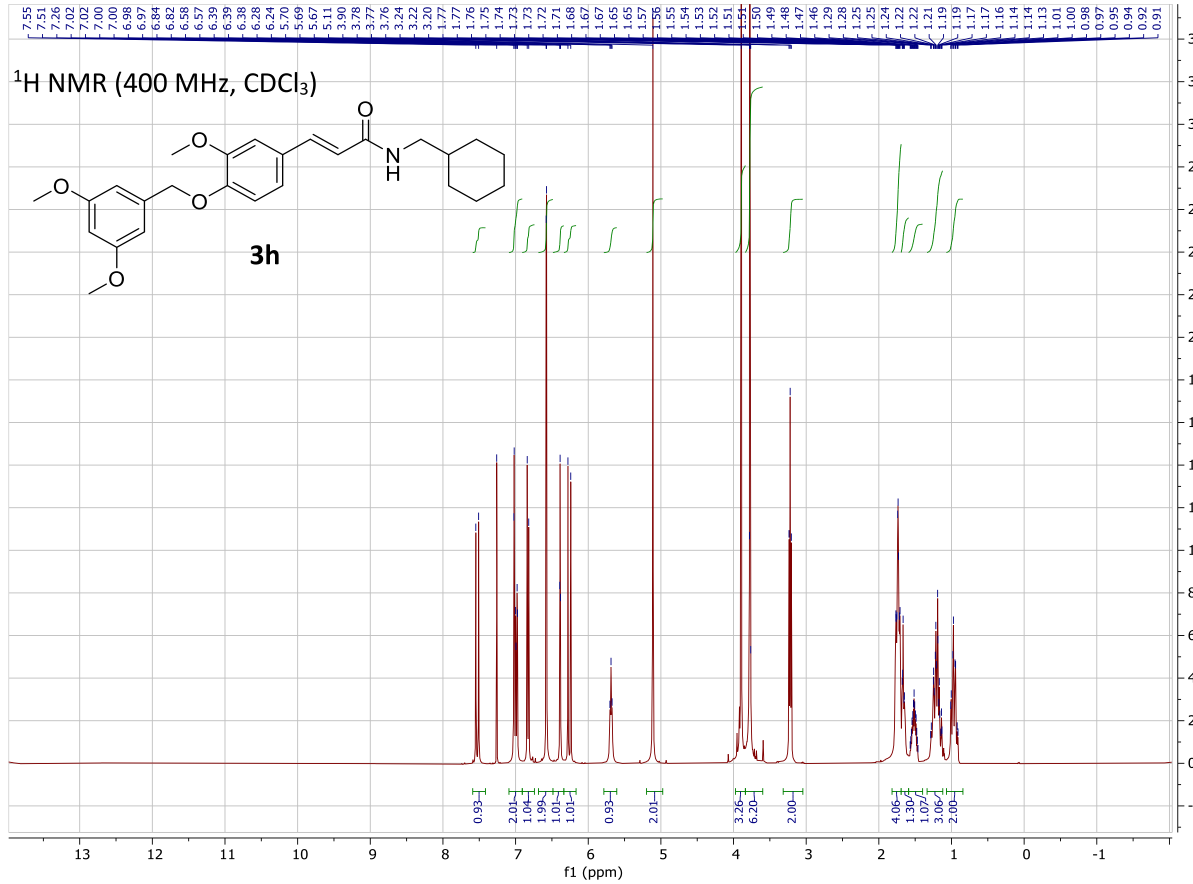
3e


1H NMR (400 MHz, CDCl3)
3f
O
S
N
H
O
O
O
O
7.55 7.51 7.02 7.02 7.00 7.00 6.98 6.98 6.85 6.83 6.58 6.57 6.40 6.39 6.38 6.25 6.21 5.53 5.51 5.12 3.95 3.94 3.93 3.93 3.90 3.90 3.78 2.82 2.82 2.80 2.79 2.78 2.76 2.75 2.69 2.68 2.67 2.67 2.66 2.64 2.30 2.29 2.27 2.26 2.25 1.63 1.61 1.61 1.60 1.60 1.59 1.58 1.57 1.57 1.57
0.94 1.97 1.00 1.91 0.96 0.99 0.94 2.00 4.21 5.96 2.09 1.95 1.97 2.23
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)
10000 9000 8000 7000 6000 5000 4000 3000 2000 1000 0

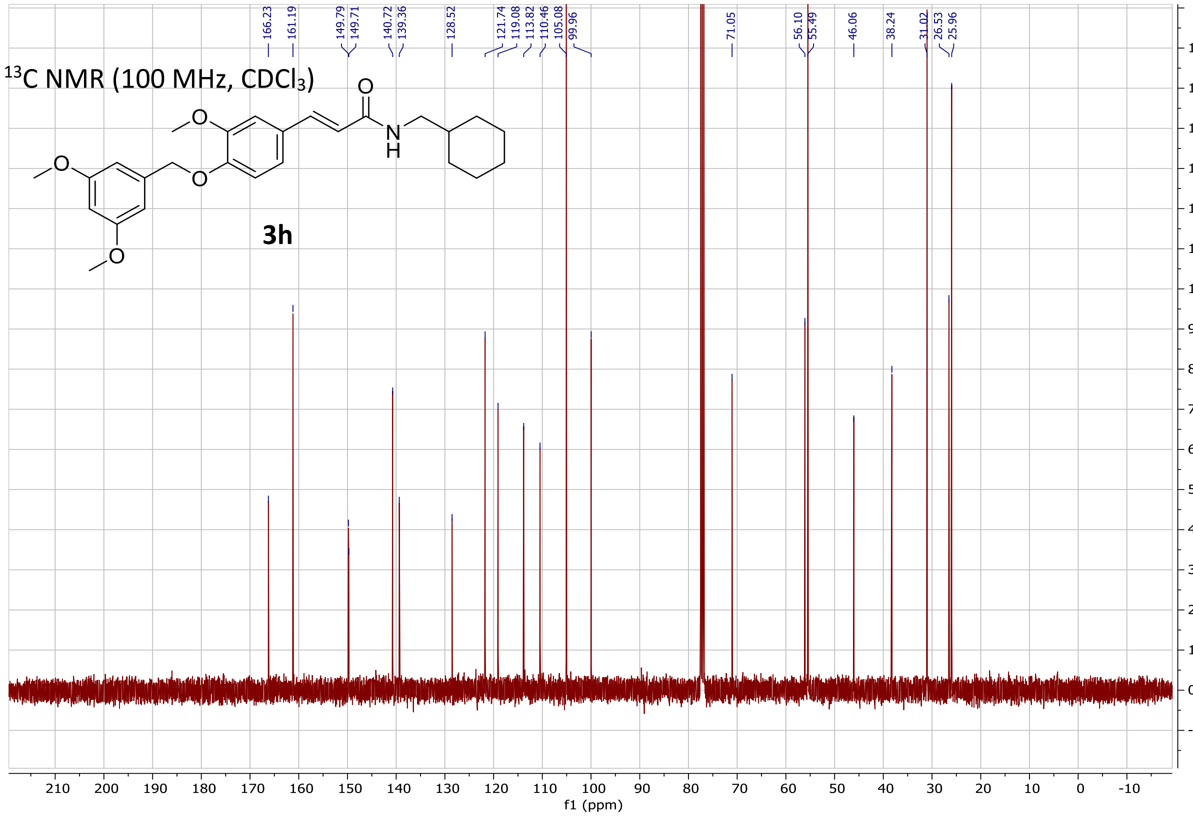

13C NMR (100 MHz, CDCl3)
3f
O
S
N
H
O
O
O
O
165.15 161.20 149.86 149.82 141.20 139.32 128.33 121.85 118.79 113.81 110.45 105.10 99.96 71.04 56.11 55.50 47.81 34.44 27.97
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
2400 2200 2000 1800 1600 1400 1200 1000 800 600 400 200 0 -200


^{1}H NMR (400 MHz, CDCl$_3$)
3g
7.47
7.43
7.01
7.01
6.98
6.98
6.96
6.96
6.84
6.82
6.58
6.58
6.39
6.39
6.38
6.21
6.17
5.11
3.90
3.78
2.10
2.07
2.07
1.74
1.71
1.71
1.70
1.67
1.61
0.98
0.98
0.97
0.95
1.86
0.89
0.94
2.00
3.08
6.04
9.07
6.08
4000
3500
3000
2500
2000
1500
1000
500
0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

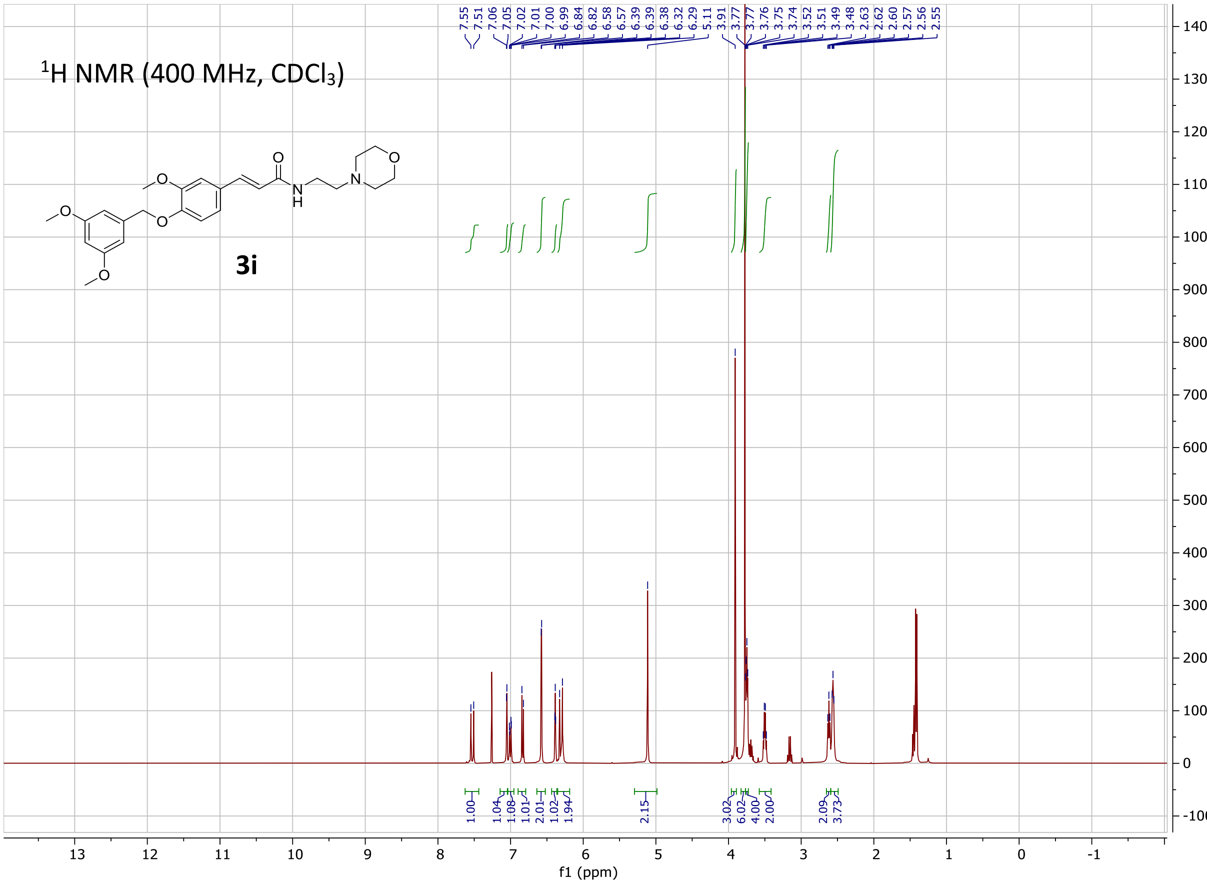

^{13}C NMR (100 MHz, CDCl$_3$)
3g
165.10
161.07
149.66
149.50
139.96
139.29
128.54
121.63
120.29
113.70
110.24
104.96
99.86
70.94
55.99
55.38
52.16
41.79
36.41
29.50
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



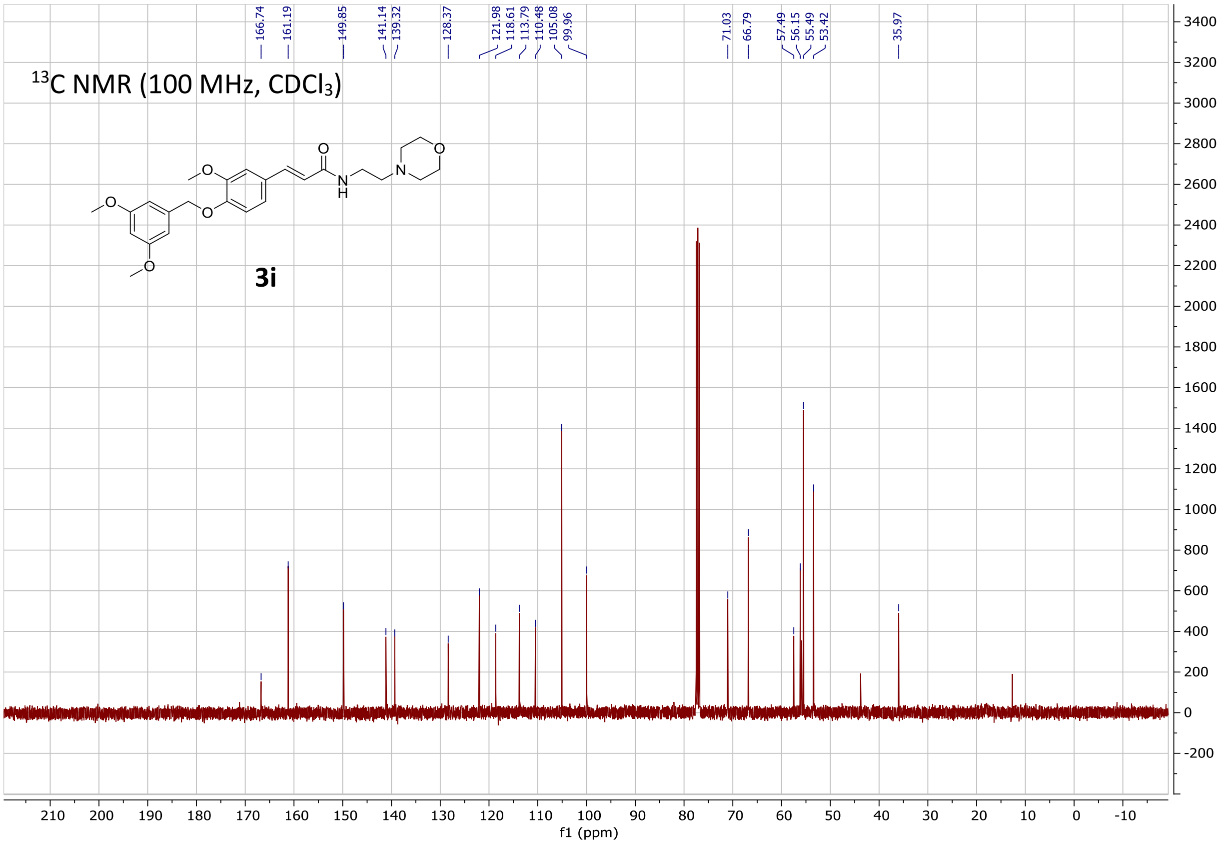
^{1}H NMR (400 MHz, CDCl$_3$)
3h
O
O
O
O
O
N
H
7.55 7.51 7.26 7.02 7.00 6.98 6.97 6.84 6.82 6.58 6.57 6.39 6.39 6.38 6.28 6.24 5.70 5.69 5.67 5.11 3.90 3.78 3.77 3.76 3.24 3.22 3.20 1.77 1.77 1.76 1.75 1.74 1.73 1.73 1.72 1.71 1.68 1.67 1.67 1.65 1.65 1.57 1.56 1.55 1.54 1.53 1.52 1.51 1.51 1.50 1.49 1.48 1.47 1.46 1.29 1.25 1.25 1.24 1.22 1.22 1.21 1.19 1.19 1.17 1.17 1.16 1.14 1.14 1.13 1.01 1.00 0.98 0.97 0.95 0.94 0.92 0.91
0.93 2.01 1.04 1.99 1.01 1.01 0.93 2.01 3.26 6.20 2.00 4.06 1.30 1.07 3.06 2.00
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)
3400 3200 3000 2800 2600 2400 2200 2000 1800 1600 1400 1200 1000 800 600 400 200 0 -200



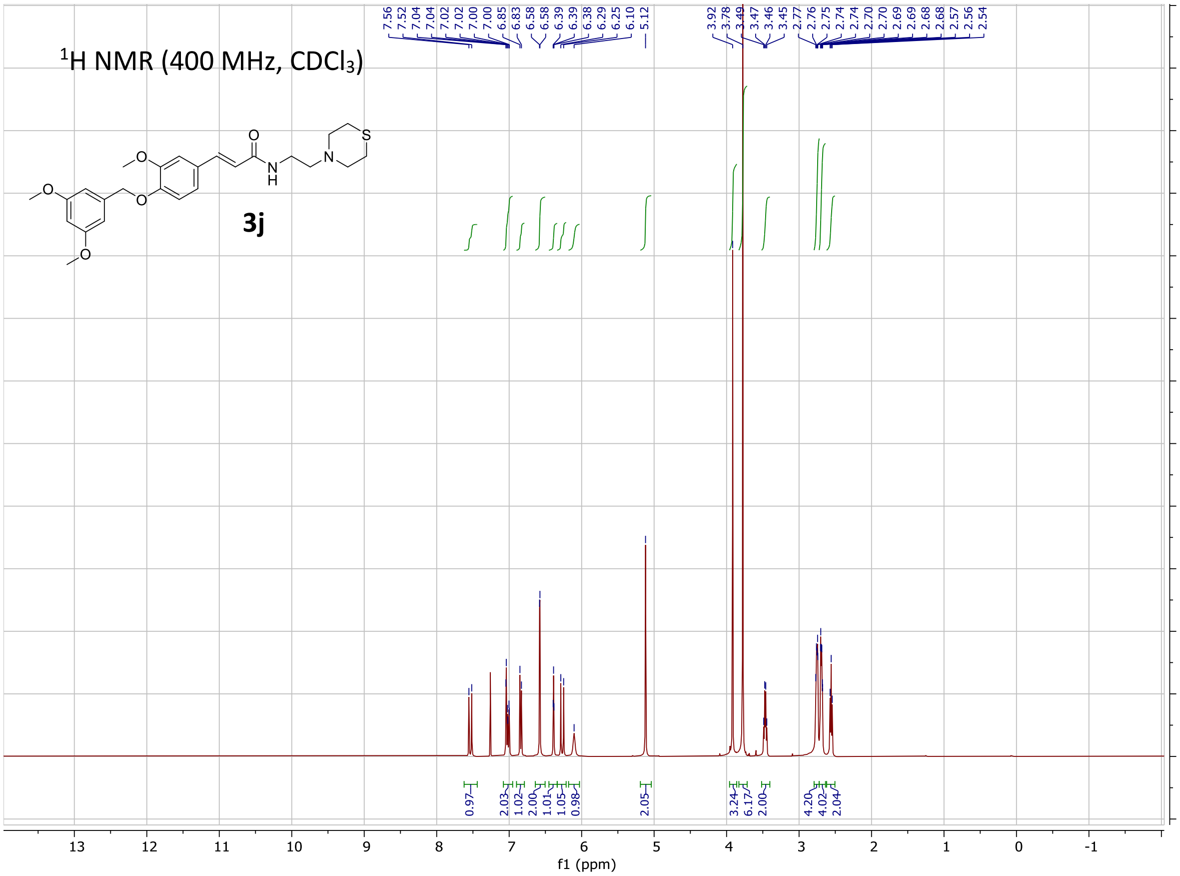
^{13}C NMR (100 MHz, CDCl$_3$)
3h
O
O
O
O
O
N
H
166.23 161.19 149.79 149.71 140.72 139.36 128.52 121.74 119.08 113.82 110.46 105.08 99.96 71.05 56.10 55.49 46.06 38.24 31.02 26.53 25.96
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100

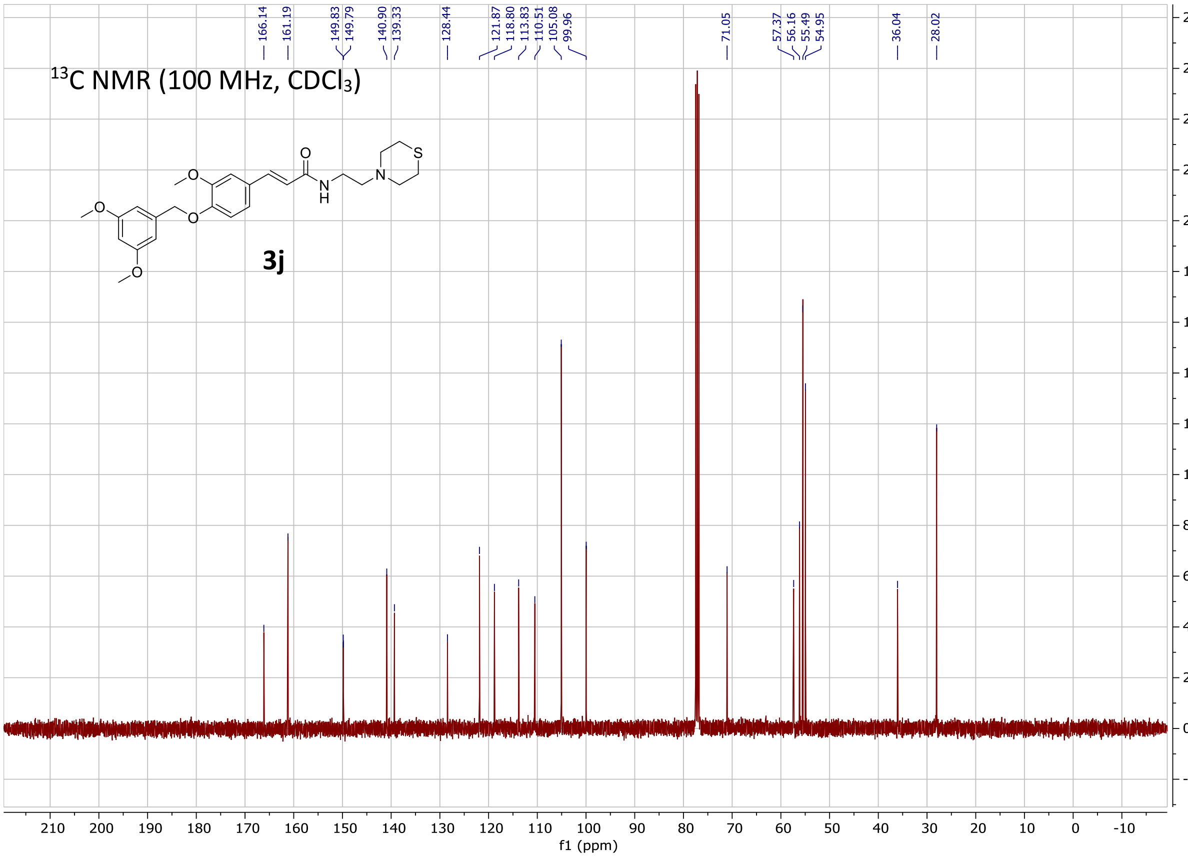


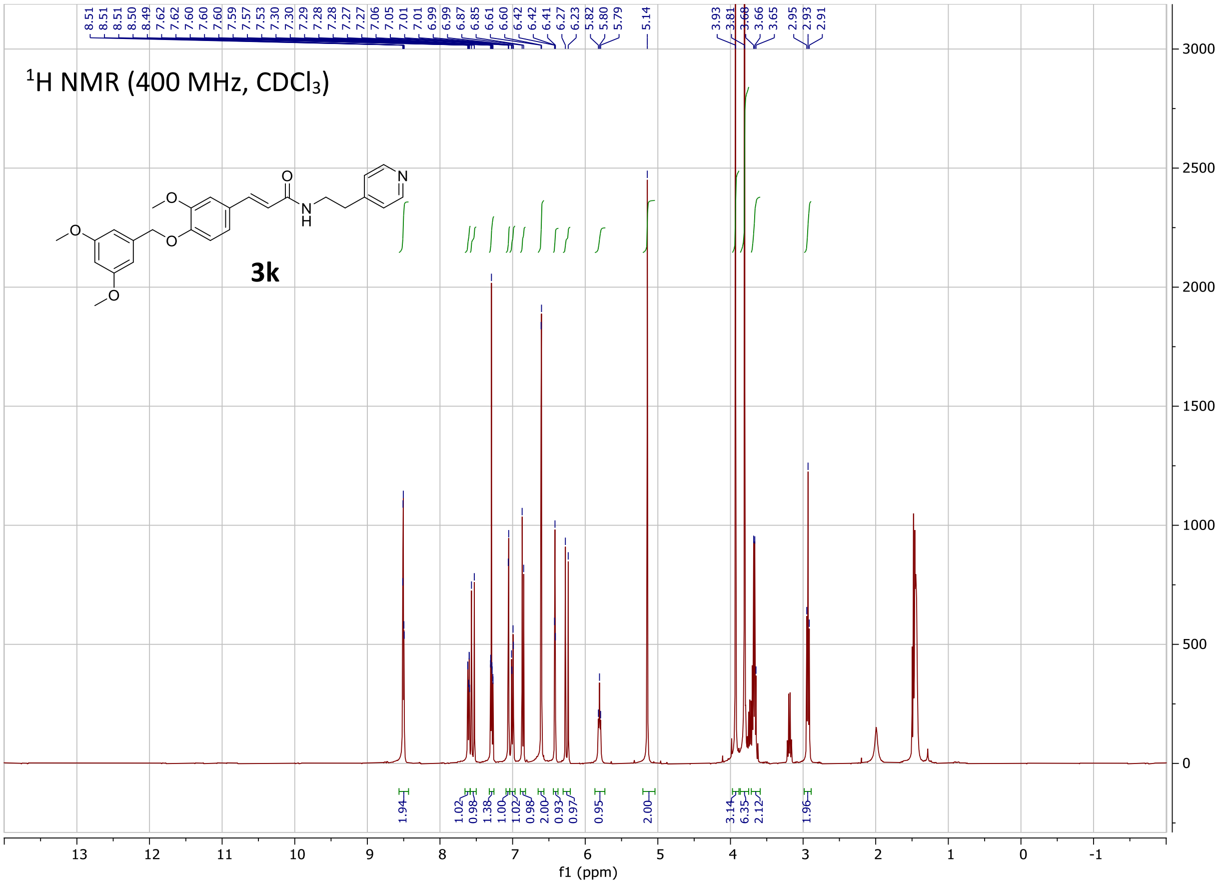
7.55
7.51
7.06
7.05
7.02
7.01
7.00
6.99
6.84
6.82
6.58
6.57
6.39
6.39
6.38
6.32
6.29
5.11
3.91
3.77
3.77
3.76
3.75
3.74
3.52
3.51
3.49
3.48
2.63
2.62
2.60
2.57
2.56
2.55
^{1}H NMR (400 MHz, CDCl$_3$)
O
O
O
O
O
N
H
N
O
3i
1.00
1.04
1.08
1.01
2.01
1.02
1.94
2.15
3.02
6.02
4.00
2.00
2.09
3.73
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

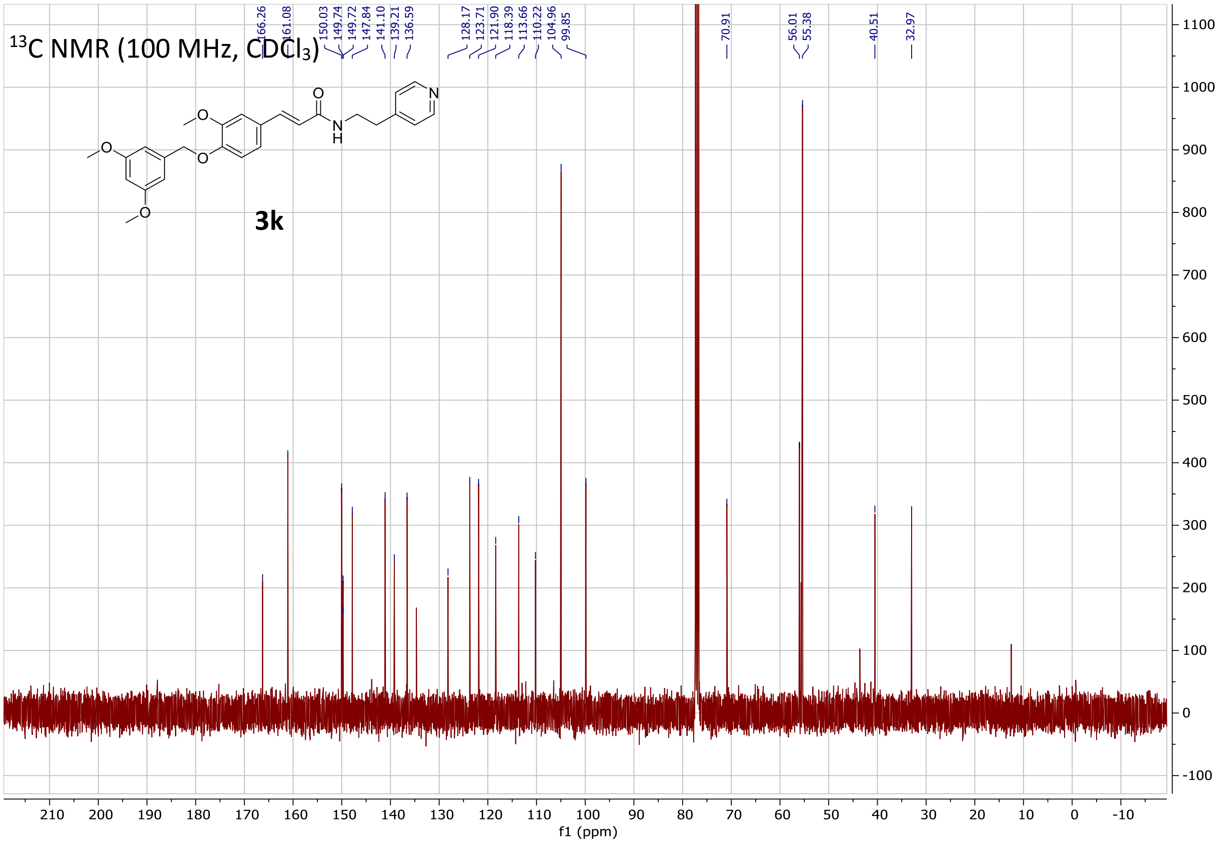


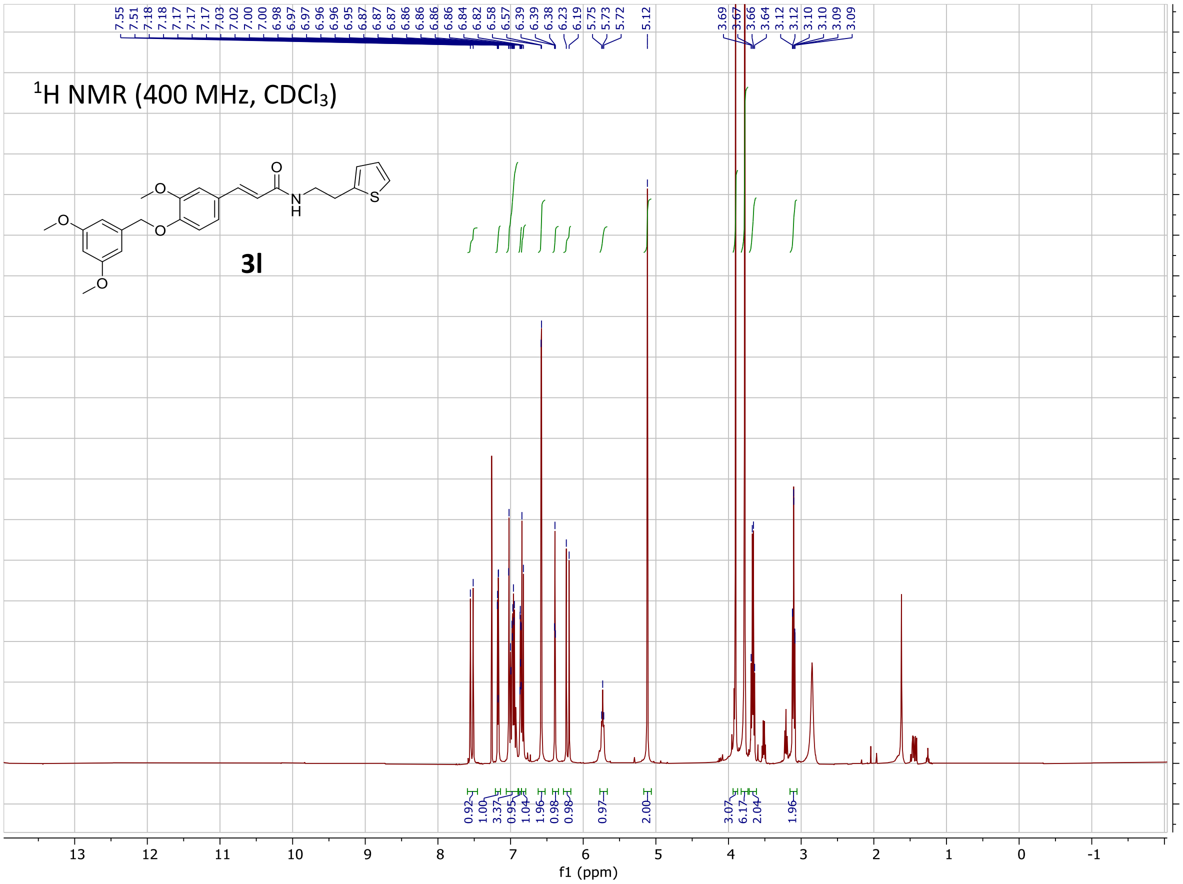
166.74
161.19
149.85
141.14
139.32
128.37
121.98
118.61
113.79
110.48
105.08
99.96
71.03
66.79
57.49
56.15
55.49
53.42
35.97
^{13}C NMR (100 MHz, CDCl$_3$)
O
O
O
O
O
N
H
N
O
3i
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


^{1}H NMR (400 MHz, CDCl$_3$)
3j
7.56 7.52 7.04 7.04 7.02 7.02 7.00 6.85 6.83 6.58 6.58 6.39 6.39 6.38 6.29 6.25 6.10 5.12
3.92 3.78 3.49 3.47 3.46 3.45 2.77 2.76 2.75 2.74 2.74 2.70 2.69 2.69 2.68 2.57 2.56 2.54
0.97 2.03 1.02 2.00 1.01 1.05 0.98 2.05 3.24 6.17 2.00 4.20 4.02 2.04
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)
11000 10000 9000 8000 7000 6000 5000 4000 3000 2000 1000 0 -1000

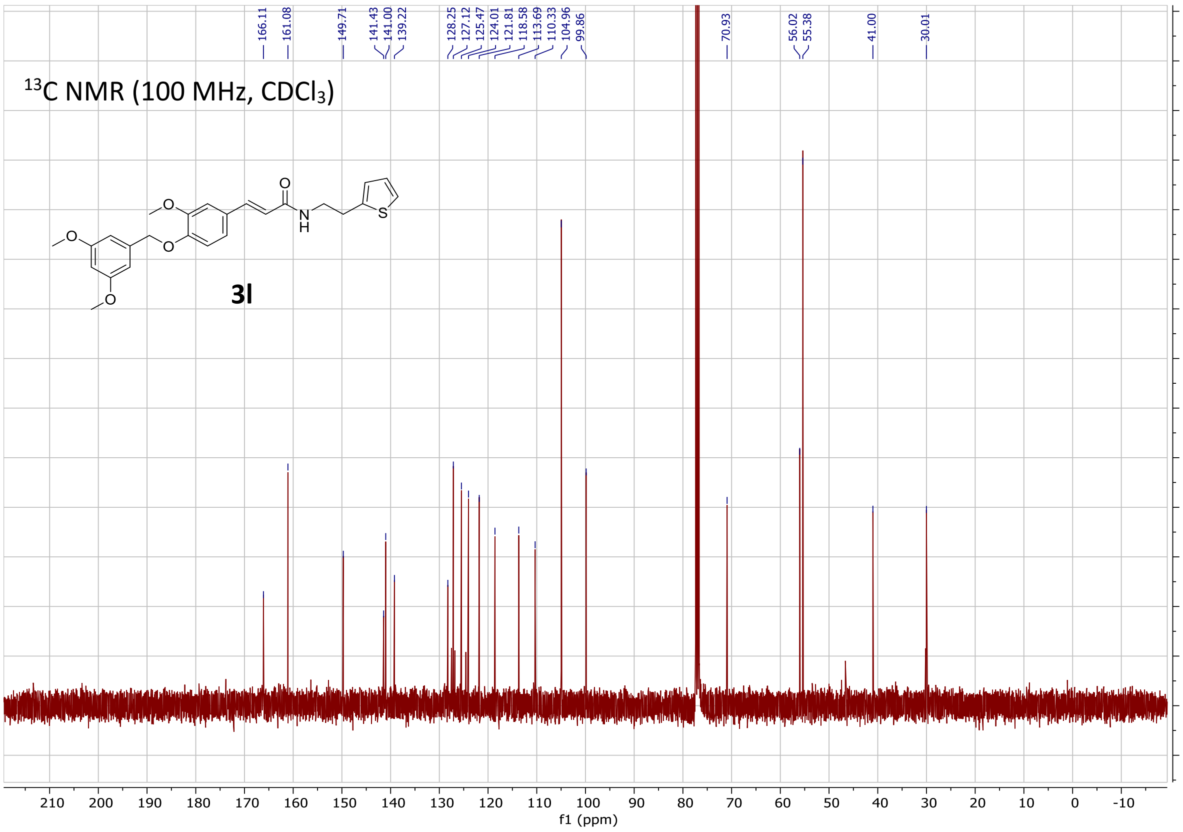

^{13}C NMR (100 MHz, CDCl$_3$)
3j
166.14 161.19 149.83 149.79 140.90 139.33 128.44 121.87 118.80 113.83 110.51 105.08 99.96 71.05 57.37 56.16 55.49 54.95 36.04 28.02
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
2800 2600 2400 2200 2000 1800 1600 1400 1200 1000 800 600 400 200 0 -200


^{1}H NMR (400 MHz, CDCl$_3$)
3k
O
N
H
8.51 8.51 8.51 8.50 8.49 7.62 7.62 7.60 7.60 7.60 7.59 7.57 7.53 7.30 7.30 7.29 7.28 7.28 7.27 7.27 7.06 7.05 7.01 7.01 6.99 6.99 6.87 6.85 6.61 6.60 6.42 6.42 6.41 6.27 6.23 5.82 5.80 5.79 5.14 3.93 3.81 3.68 3.66 3.65 2.95 2.93 2.91
1.94 1.02 0.98 1.38 1.00 1.02 0.98 2.00 0.93 0.97 0.95 2.00 3.14 6.35 2.12 1.96
3000 2500 2000 1500 1000 500 0
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)

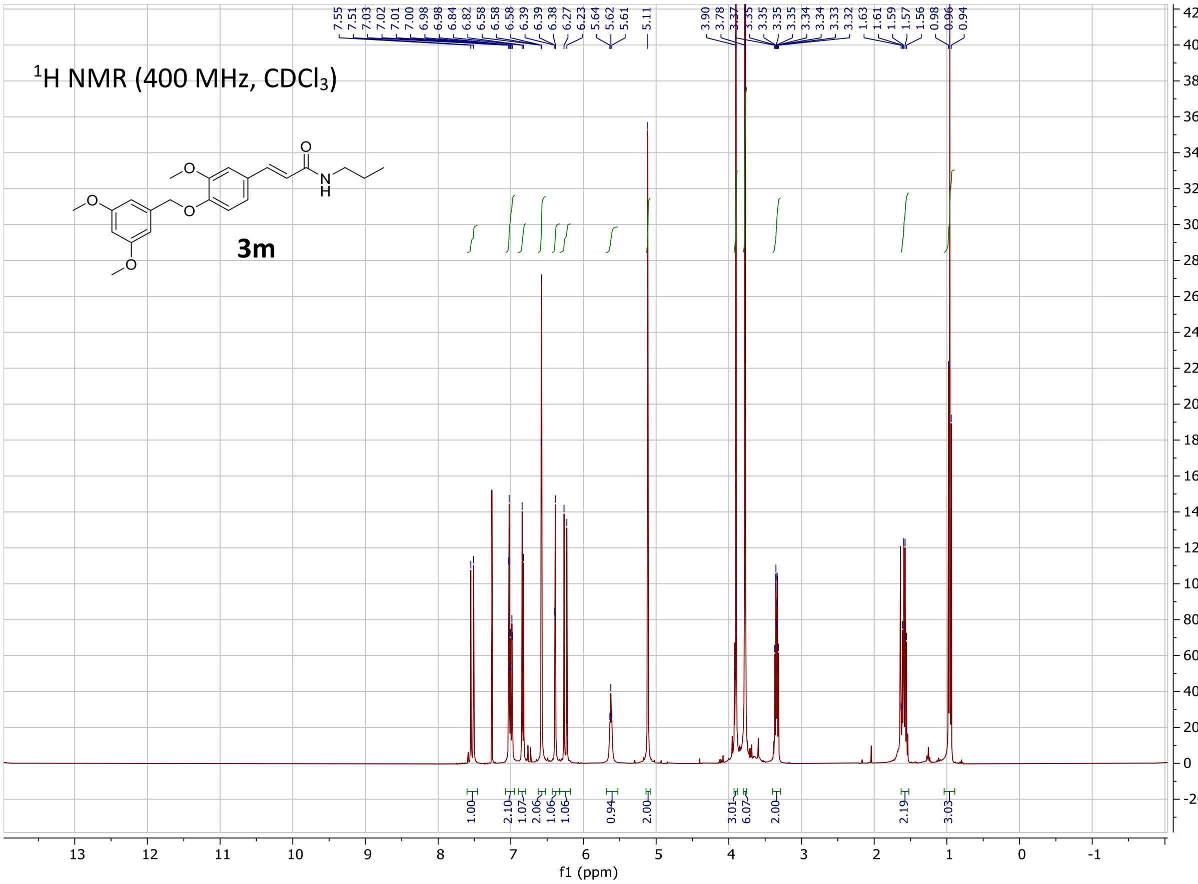

^{13}C NMR (100 MHz, CDCl$_3$)
3k
O
N
H
166.26 161.08 150.03 149.74 149.72 147.84 141.10 139.21 136.59 128.17 123.71 121.90 118.39 113.66 110.22 104.96 99.85 70.91 56.01 55.38 40.51 32.97
1100 1000 900 800 700 600 500 400 300 200 100 0 -100
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


^{1}H NMR (400 MHz, CDCl$_3$)

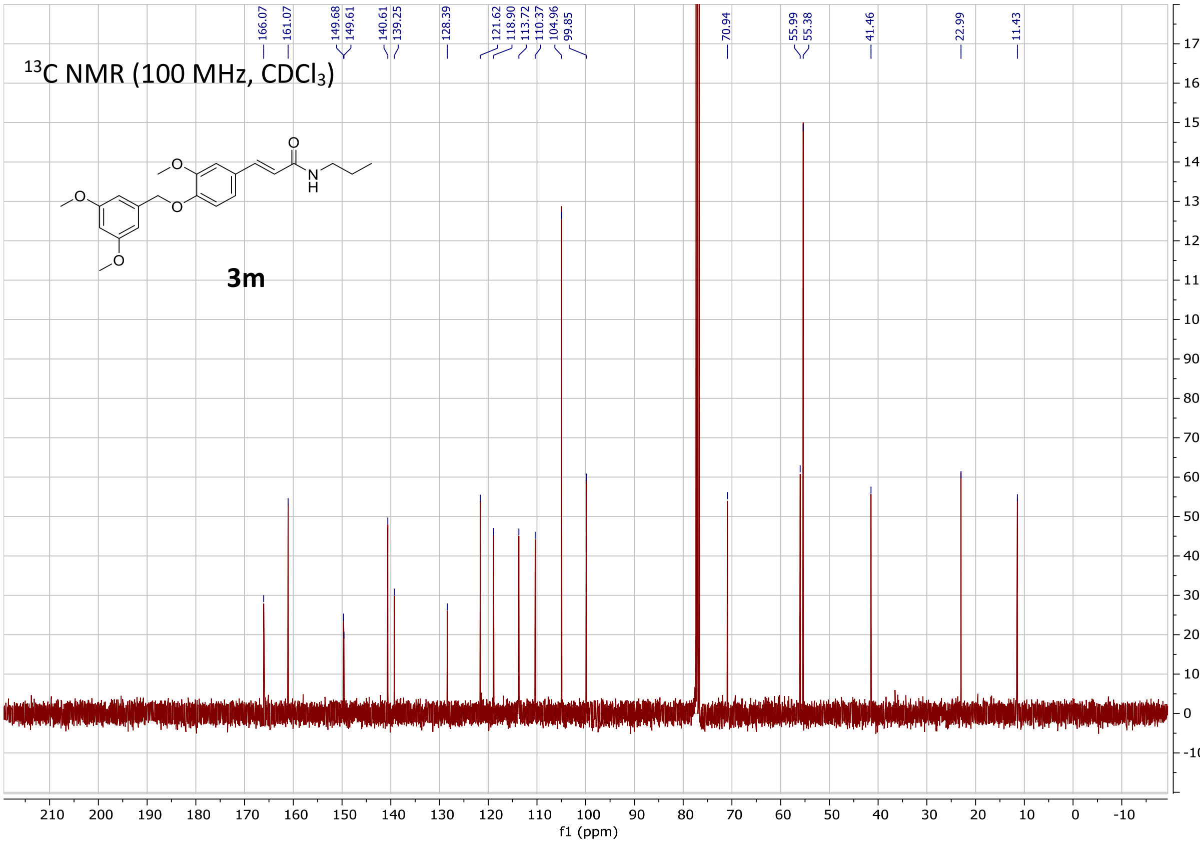
3l

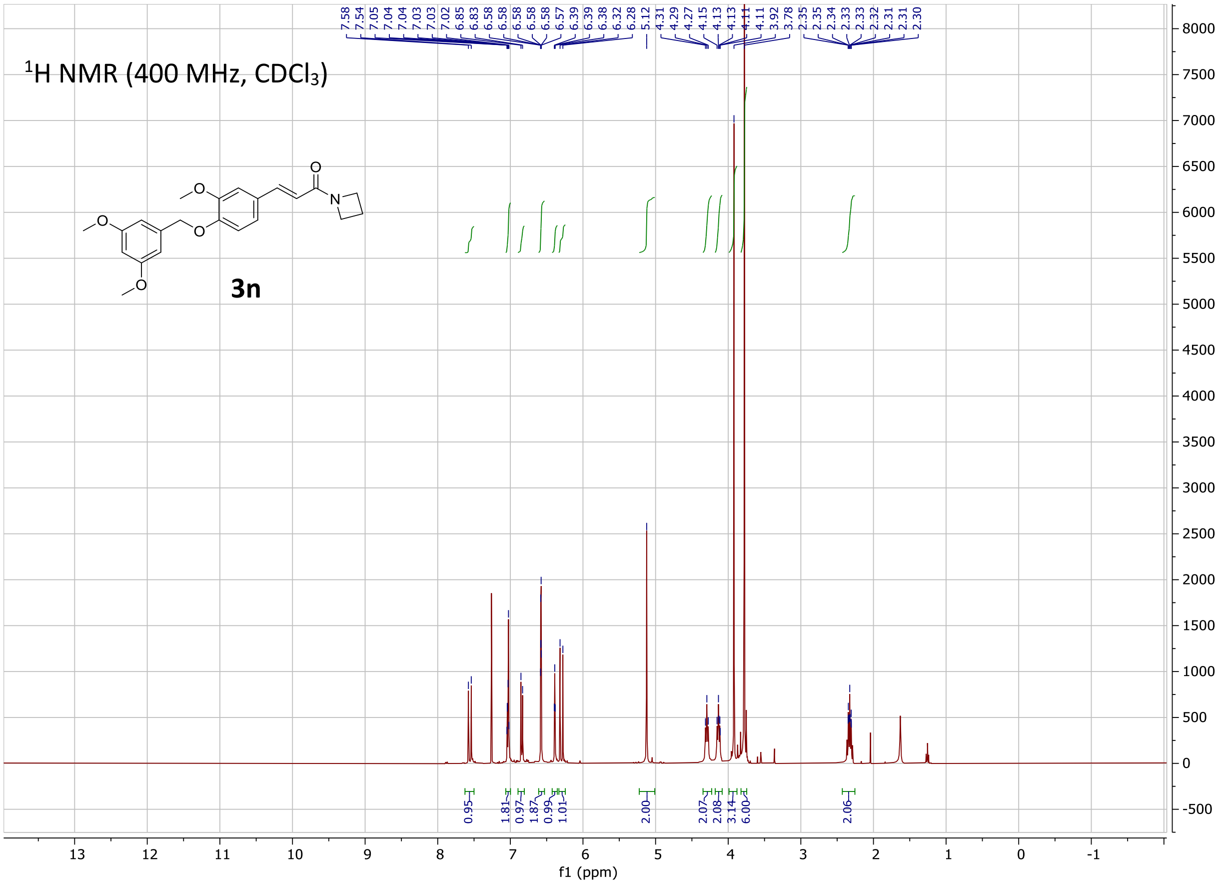

^{13}C NMR (100 MHz, CDCl$_3$)

3l

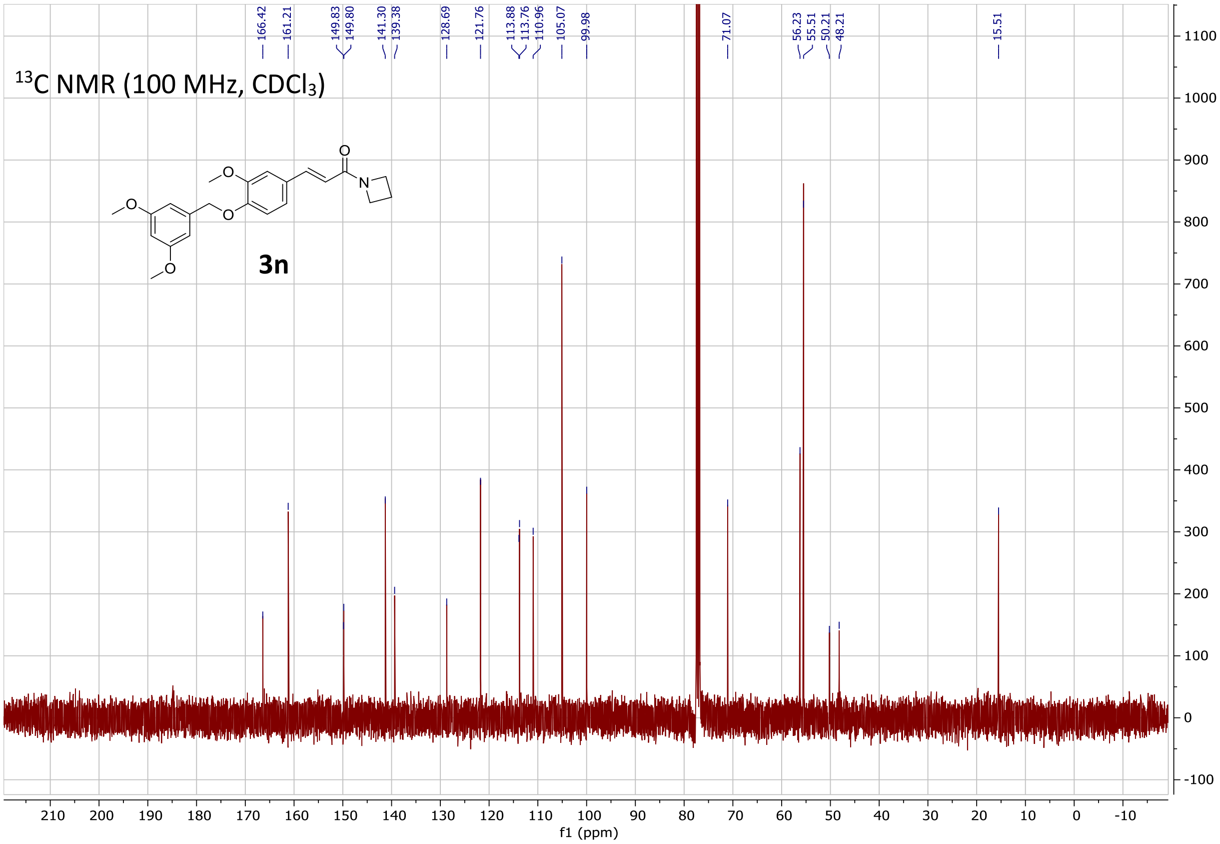
^{1}H NMR (400 MHz, CDCl$_3$)
O
O
O
O
O
N
H
7.55
7.51
7.03
7.02
7.01
7.00
6.98
6.98
6.84
6.82
6.58
6.58
6.58
6.39
6.39
6.38
6.27
6.23
5.64
5.62
5.61
5.11
3.90
3.78
3.37
3.35
3.35
3.35
3.35
3.34
3.34
3.33
3.32
1.63
1.61
1.59
1.57
1.56
0.98
0.96
0.94
1.00
2.10
1.07
2.06
1.06
1.06
0.94
2.00
3.01
6.07
2.00
2.19
3.03
4200
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

3m

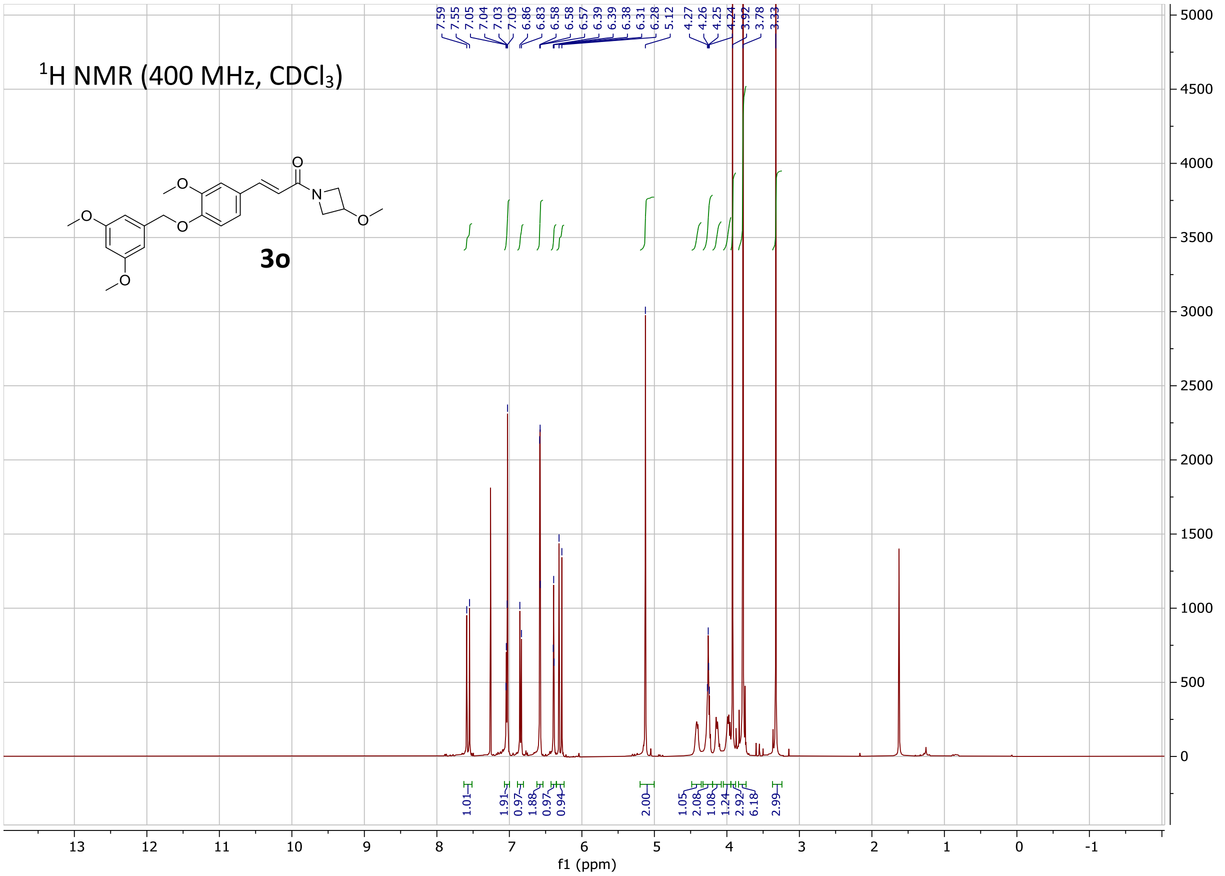

^{13}C NMR (100 MHz, CDCl$_3$)
3m
166.07
161.07
149.68
149.61
140.61
139.25
128.39
121.62
118.90
113.72
110.37
104.96
99.85
70.94
55.99
55.38
41.46
22.99
11.43
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



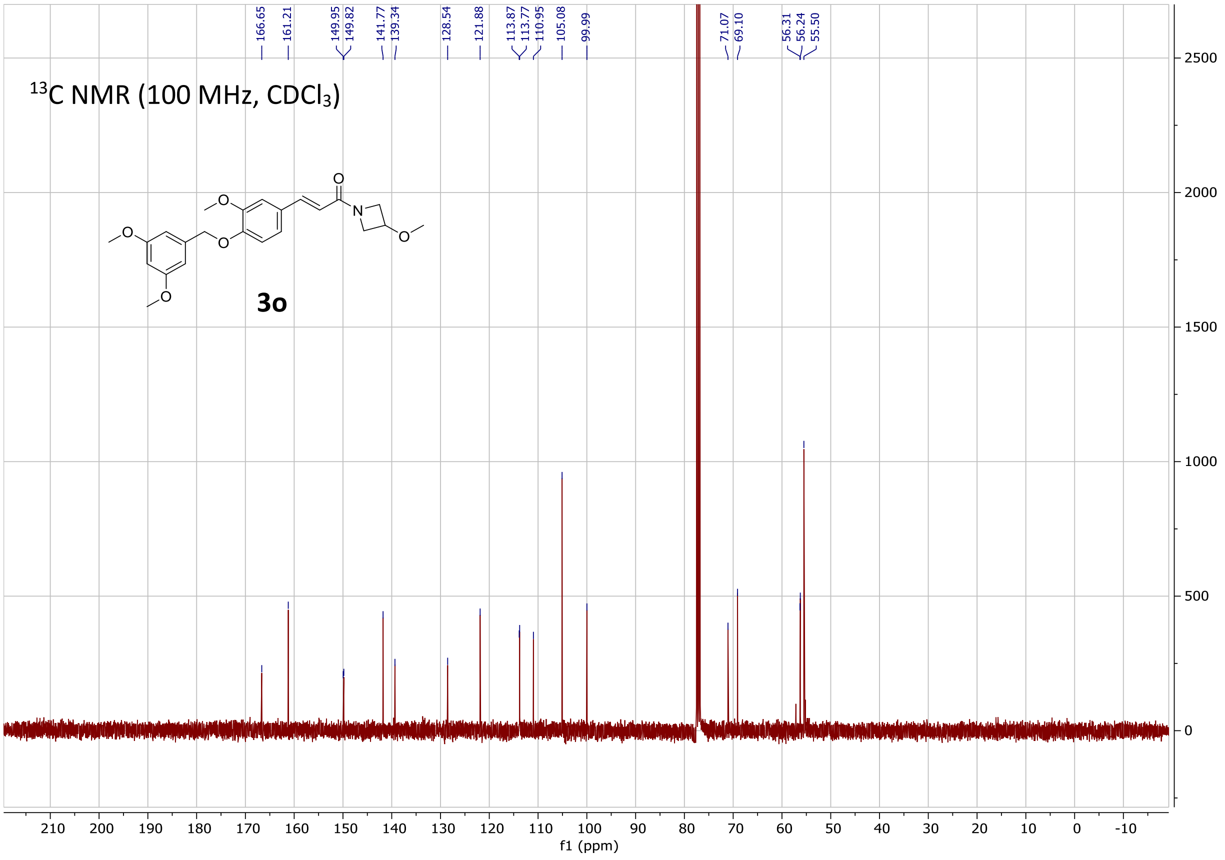
^{1}H NMR (400 MHz, CDCl$_3$)
3n
7.58 7.54 7.05 7.04 7.04 7.03 7.03 7.02 6.85 6.83 6.58 6.58 6.58 6.58 6.58 6.57 6.39 6.39 6.38 6.32 6.28 5.12 4.31 4.29 4.27 4.15 4.13 4.13 4.11 4.11 3.92 3.78 2.35 2.35 2.34 2.33 2.33 2.32 2.31 2.31 2.30
0.95 1.81 0.97 1.87 0.99 1.01 2.00 2.07 2.08 3.14 6.00 2.06
f1 (ppm)
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
8000 7500 7000 6500 6000 5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0 -500



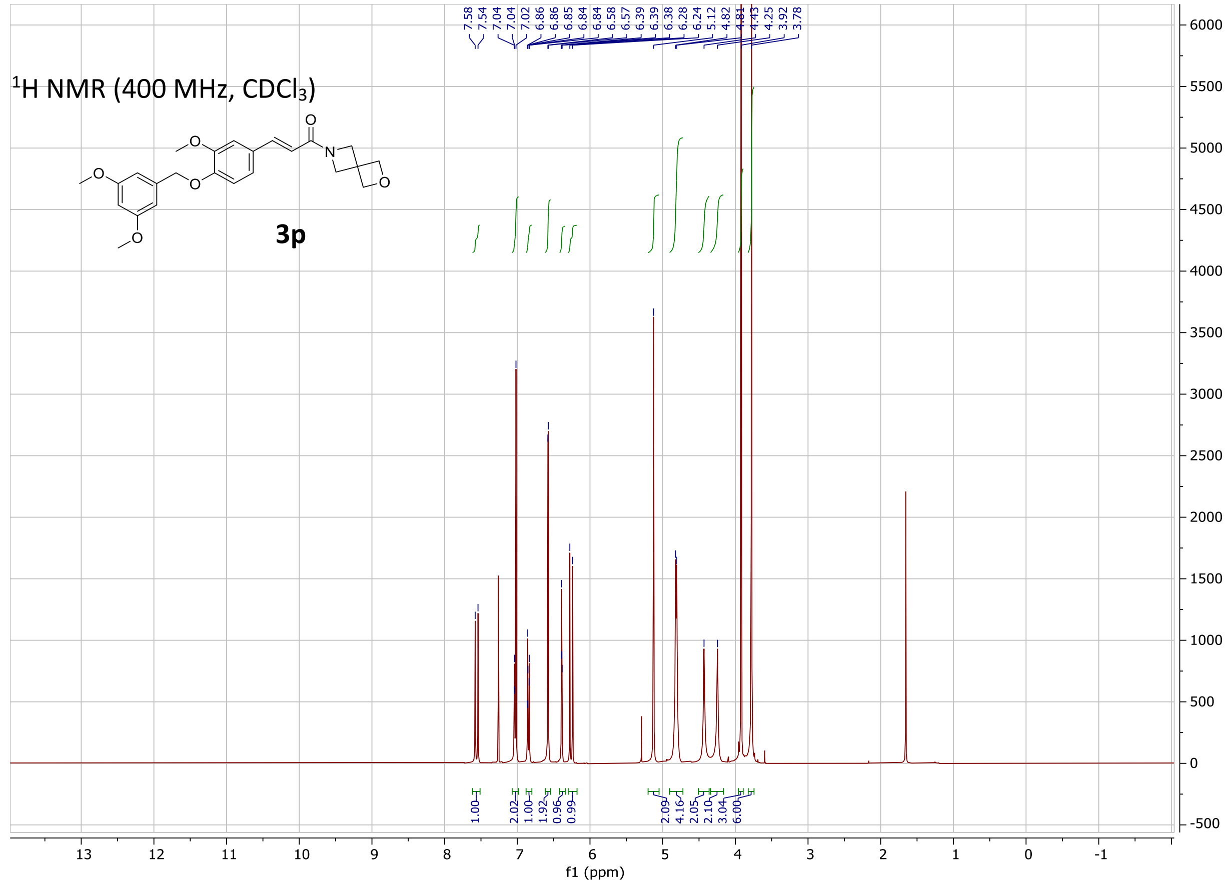
^{13}C NMR (100 MHz, CDCl$_3$)
3n
166.42 161.21 149.83 149.80 141.30 139.38 128.69 121.76 113.88 113.76 110.96 105.07 99.98 71.07 56.23 55.51 50.21 48.21 15.51
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
1100 1000 900 800 700 600 500 400 300 200 100 0 -100

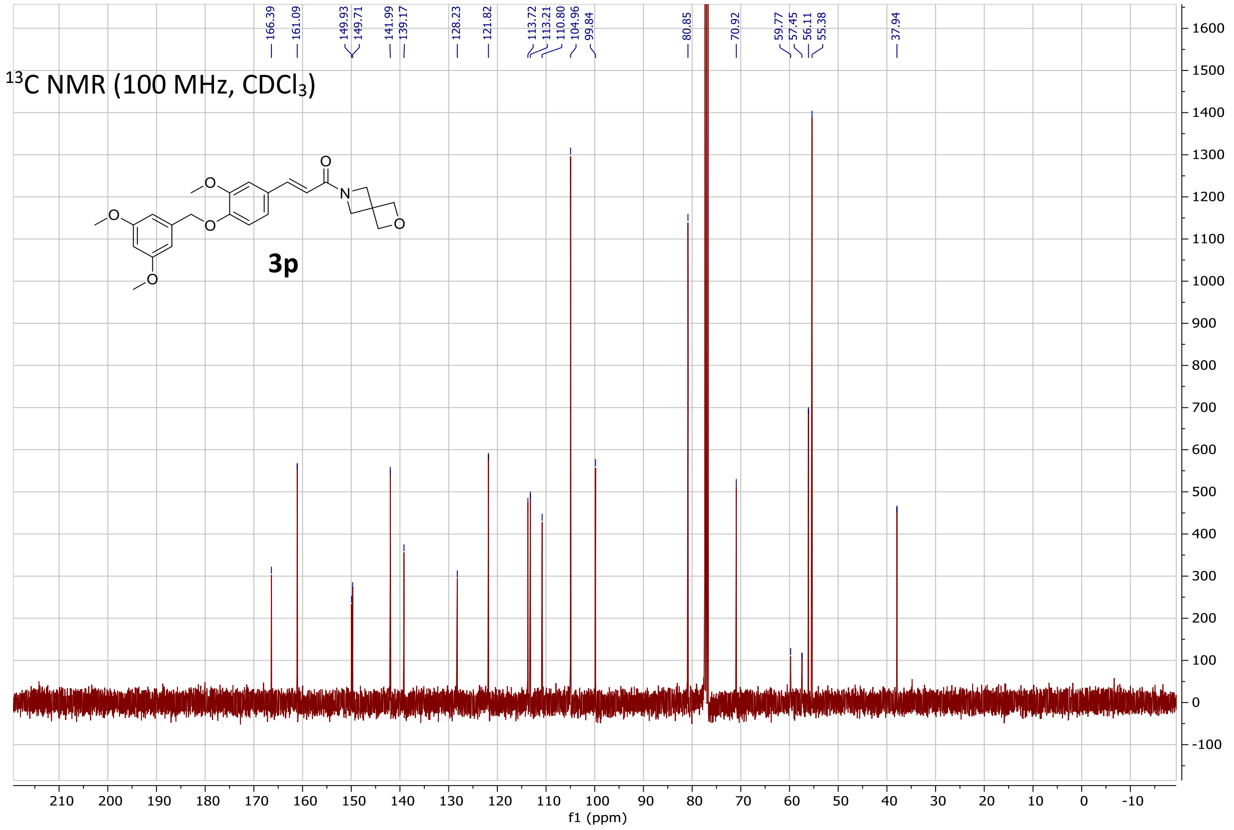


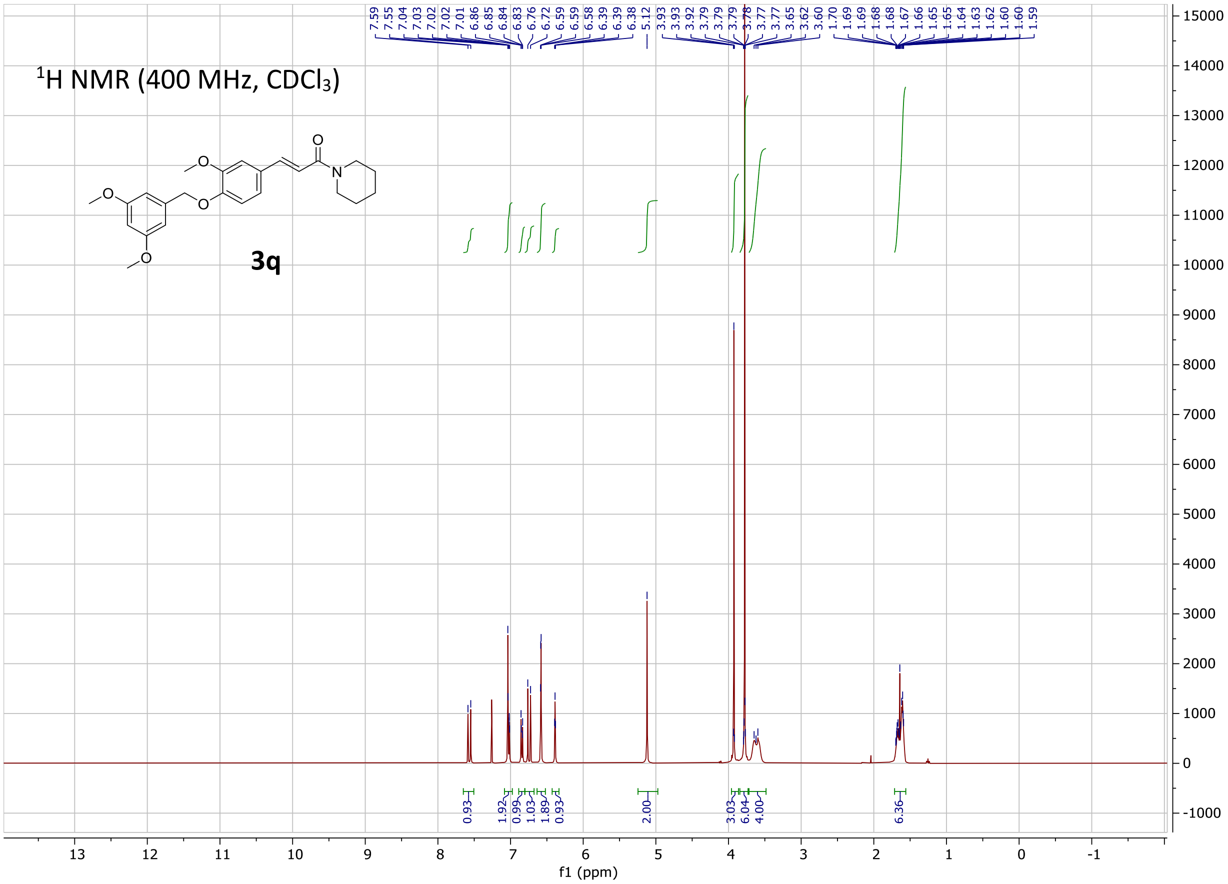
^{1}H NMR (400 MHz, CDCl$_3$)
3o
7.59
7.55
7.05
7.04
7.03
7.03
6.86
6.83
6.58
6.58
6.57
6.39
6.39
6.38
6.31
6.28
5.12
4.27
4.26
4.25
4.24
3.92
3.78
3.33
1.01
1.91
0.97
1.88
0.97
0.94
2.00
1.05
2.08
1.08
1.24
2.92
6.18
2.99
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0

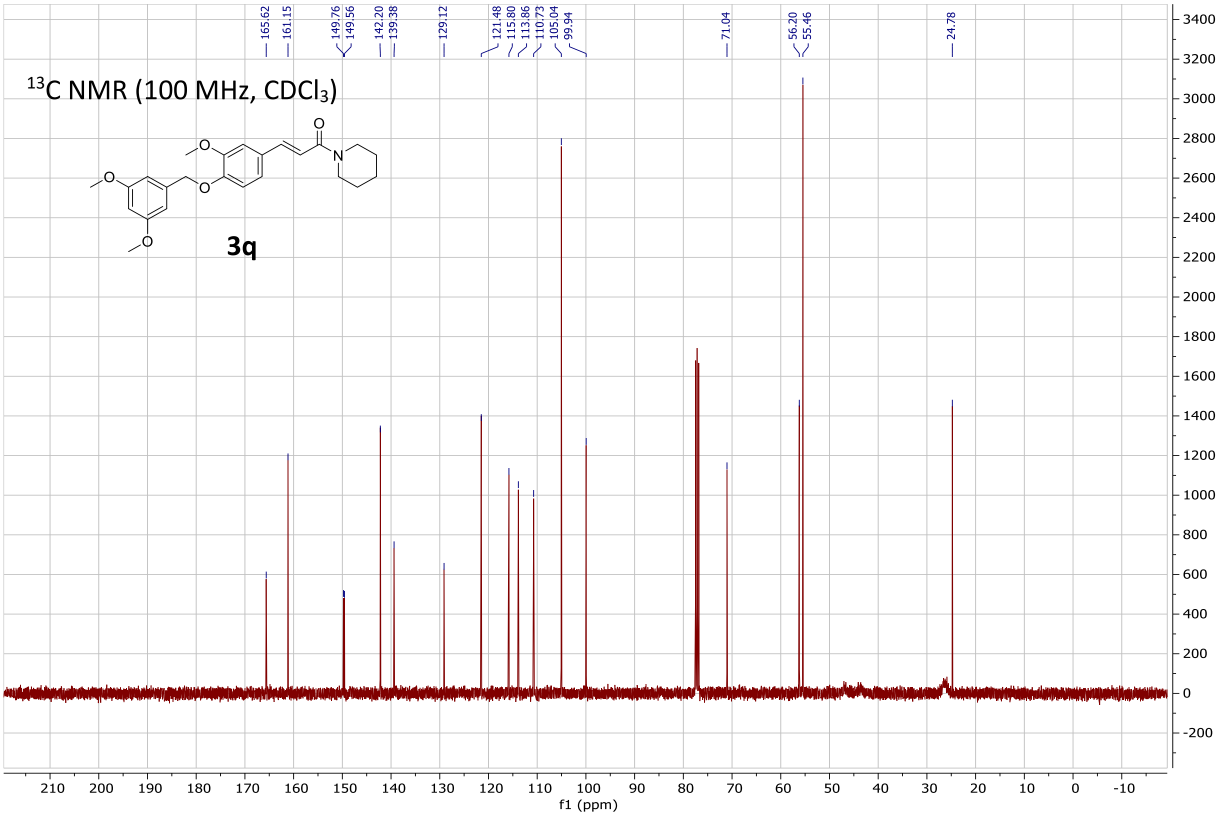


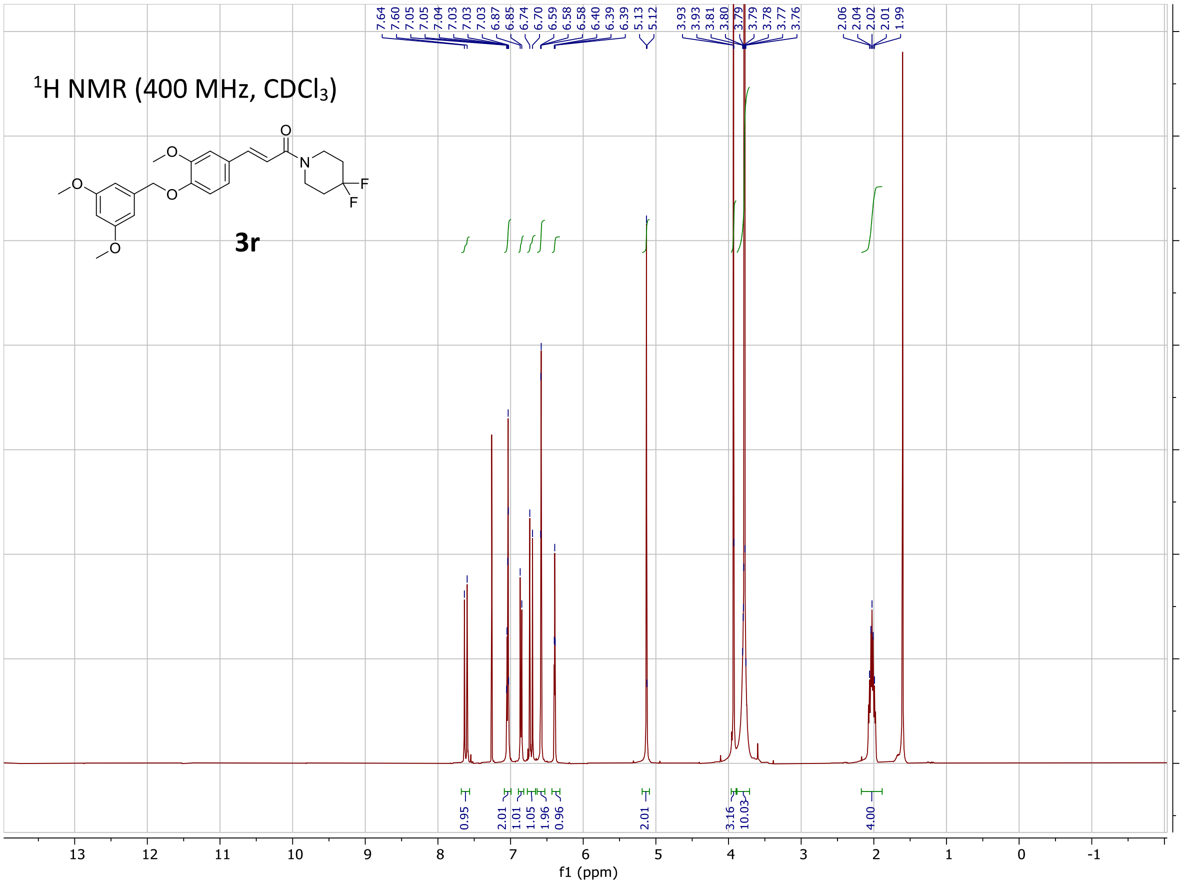
^{13}C NMR (100 MHz, CDCl$_3$)
3o
166.65
161.21
149.95
149.82
141.77
139.34
128.54
121.88
113.87
113.77
110.95
105.08
99.99
71.07
69.10
56.31
56.24
55.50
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
2500
2000
1500
1000
500
0


^{1}H NMR (400 MHz, CDCl$_3$)
3p
7.58
7.54
7.04
7.04
7.02
6.86
6.86
6.85
6.84
6.84
6.58
6.57
6.39
6.39
6.38
6.28
6.24
5.12
4.82
4.81
4.43
4.25
3.92
3.78
1.00
2.02
1.00
1.92
0.96
0.99
2.09
4.16
2.05
2.10
3.04
6.00
f1 (ppm)
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500

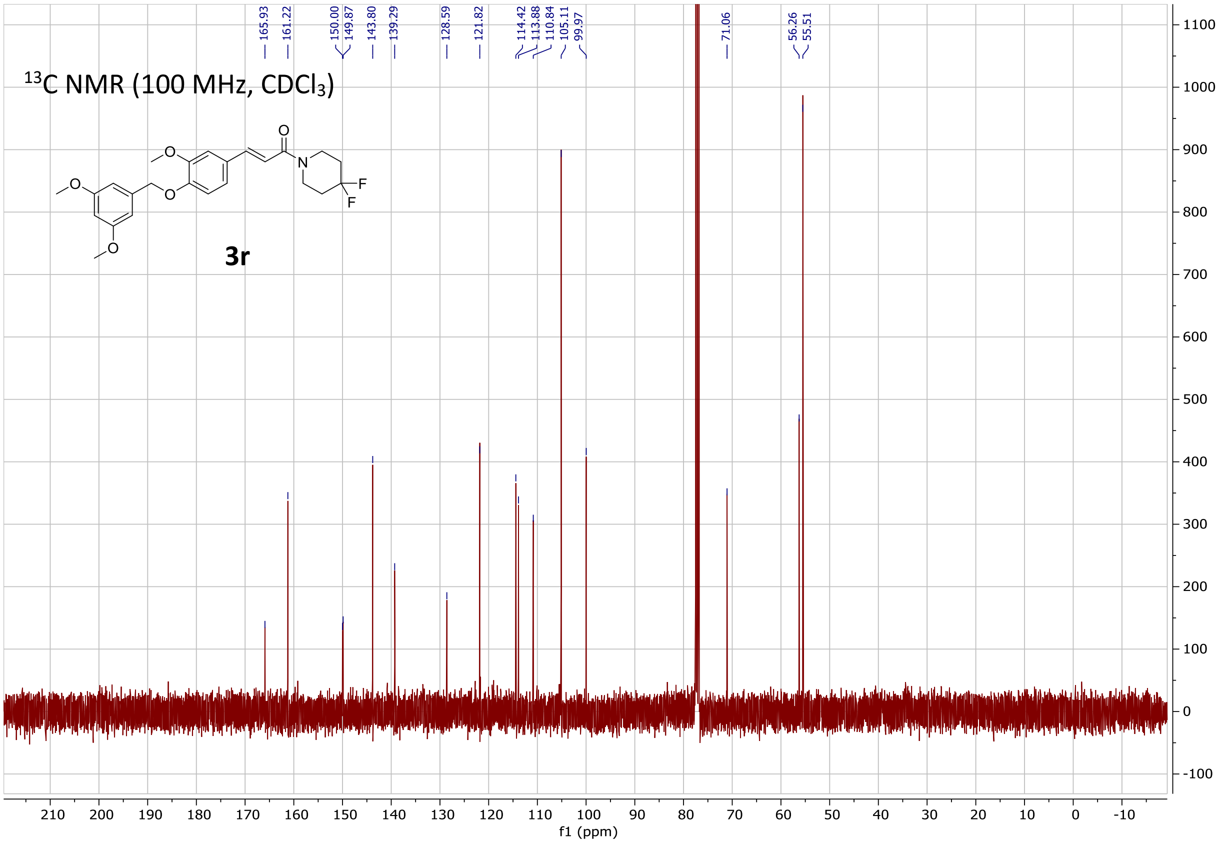

^{13}C NMR (100 MHz, CDCl$_3$)
3p
166.39
161.09
149.93
149.71
141.99
139.17
128.23
121.82
113.72
113.21
110.80
104.96
99.84
80.85
70.92
59.77
57.45
56.11
55.38
37.94
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100

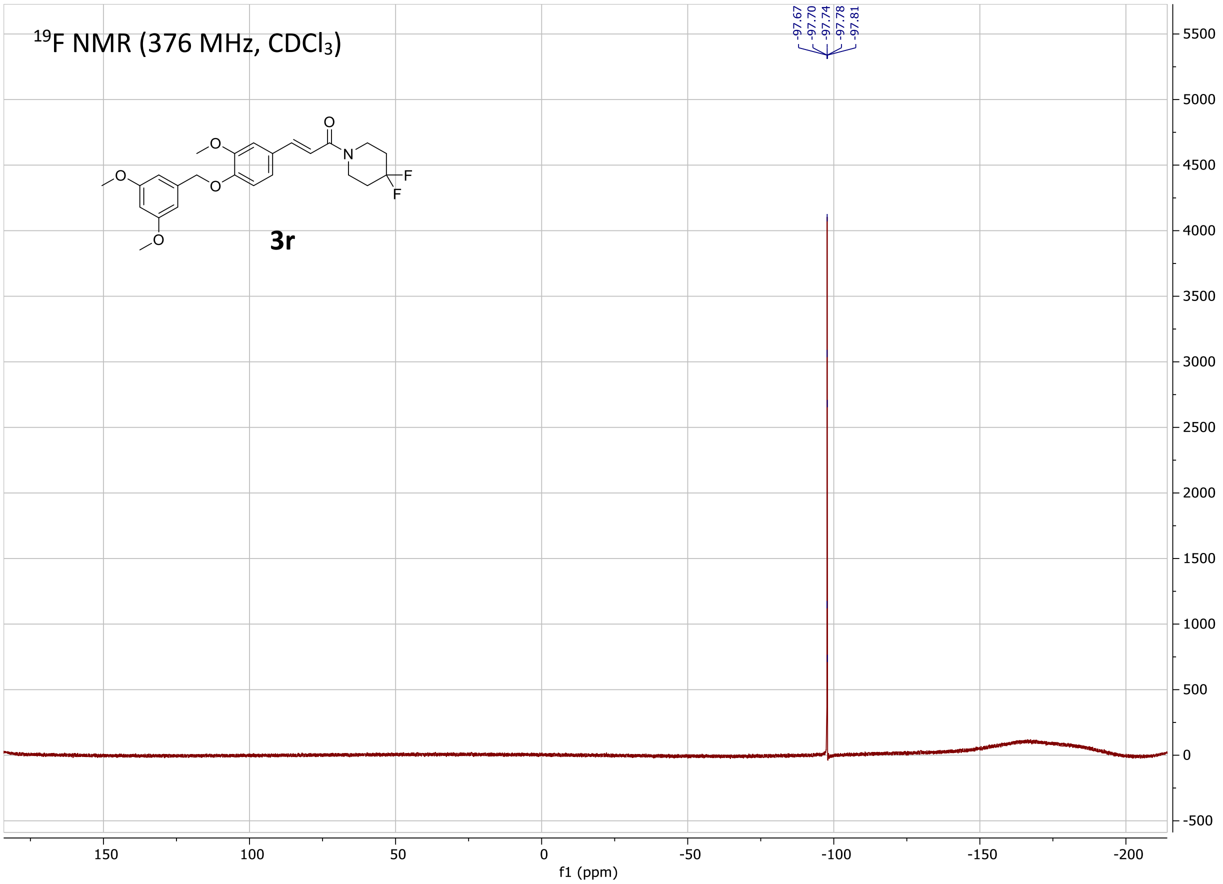

^{1}H NMR (400 MHz, CDCl$_3$)
3q
7.59 7.55 7.04 7.03 7.02 7.02 7.01 6.86 6.85 6.84 6.83 6.76 6.72 6.59 6.59 6.58 6.39 6.39 6.38
5.12
3.93 3.93 3.92 3.79 3.79 3.79 3.78 3.77 3.77 3.65 3.62 3.60
1.70 1.69 1.69 1.68 1.68 1.67 1.66 1.65 1.65 1.64 1.63 1.62 1.60 1.60 1.59
0.93 1.92 0.99 1.03 1.89 0.93 2.00 3.03 6.04 4.00 6.36
f1 (ppm)


^{13}C NMR (100 MHz, CDCl$_3$)
3q
165.62 161.15 149.76 149.56 142.20 139.38 129.12 121.48 115.80 113.86 110.73 105.04 99.94 71.04 56.20 55.46 24.78
f1 (ppm)

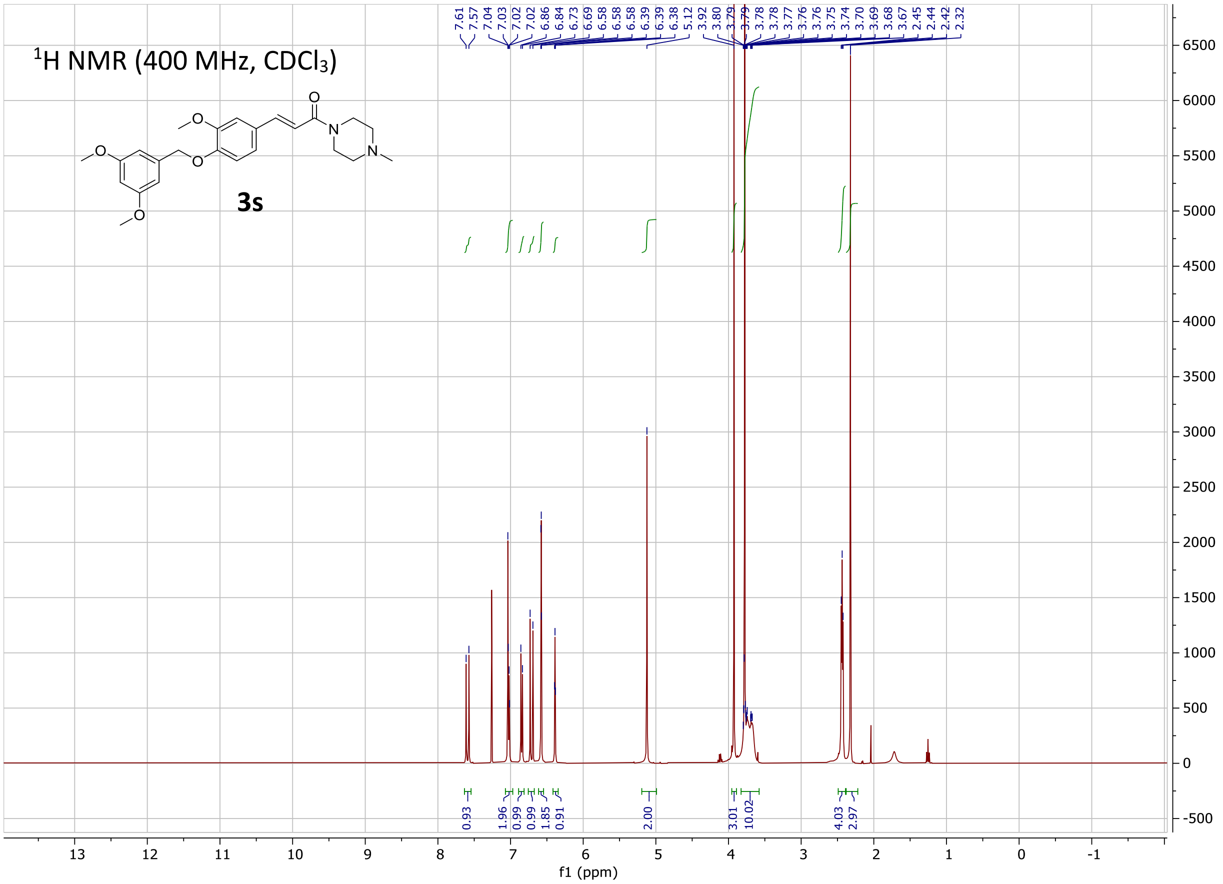

3r

^{1}H NMR (400 MHz, CDCl$_3$)
O
N
F
F
O
O
O
O
7.64
7.60
7.05
7.05
7.04
7.03
7.03
7.03
6.87
6.85
6.74
6.70
6.59
6.58
6.58
6.40
6.39
6.39
5.13
5.12
3.93
3.93
3.81
3.80
3.79
3.79
3.78
3.77
3.76
2.06
2.04
2.02
2.01
1.99
0.95
2.01
1.01
1.05
1.96
0.96
2.01
3.16
10.03
4.00
3500
3000
2500
2000
1500
1000
500
0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

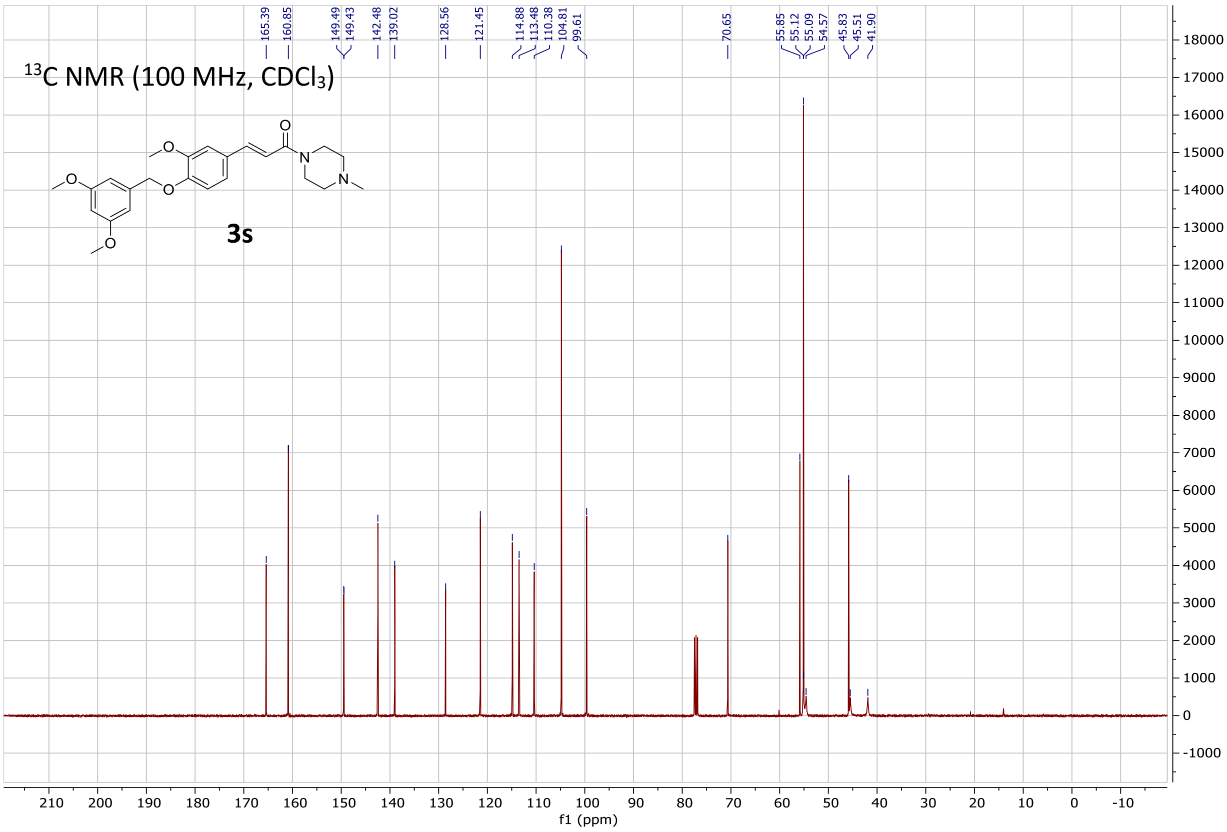

^{13}C NMR (100 MHz, CDCl$_3$)
3r
O
N
F
F
O
O
O
O
165.93
161.22
150.00
149.87
143.80
139.29
128.59
121.82
114.42
113.88
110.84
105.11
99.97
71.06
56.26
55.51
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


^{19}F NMR (376 MHz, $CDCl_3$)

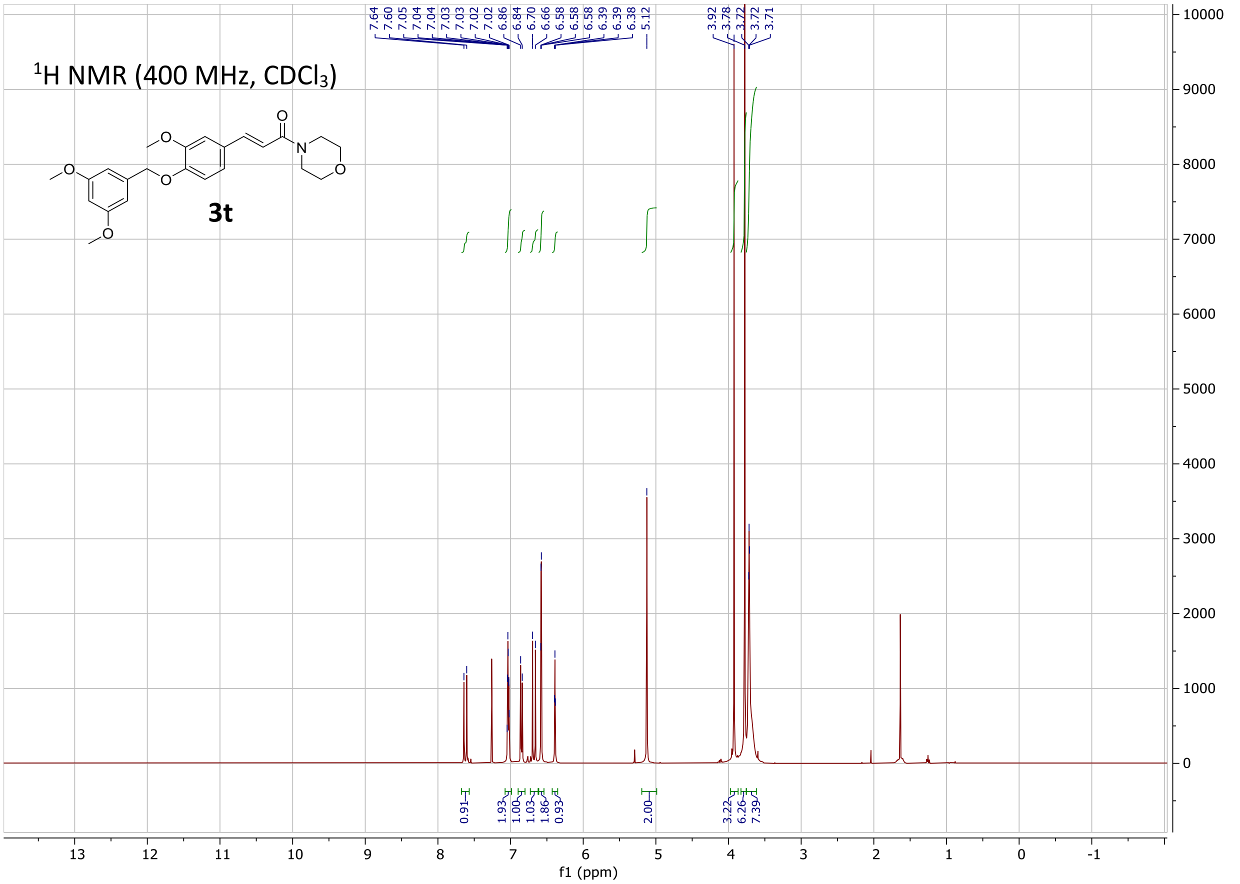
3r

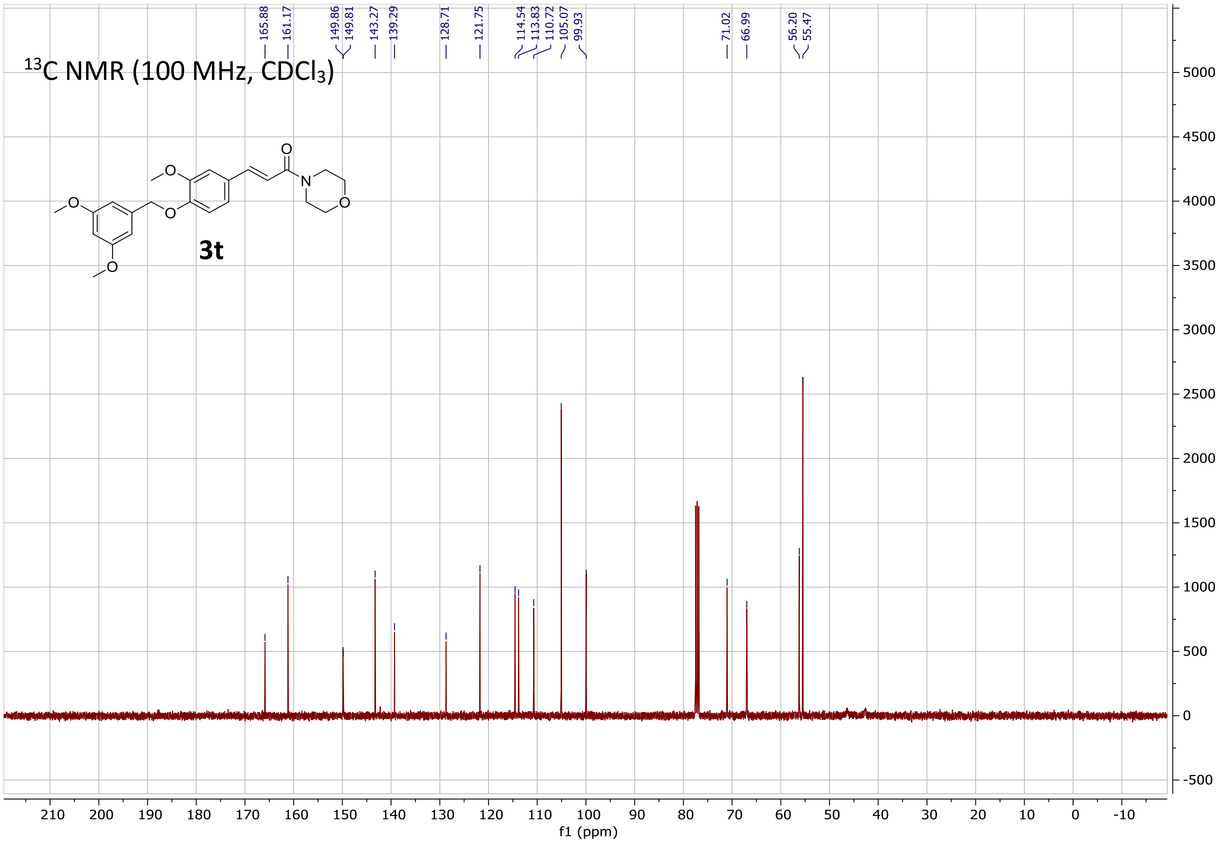


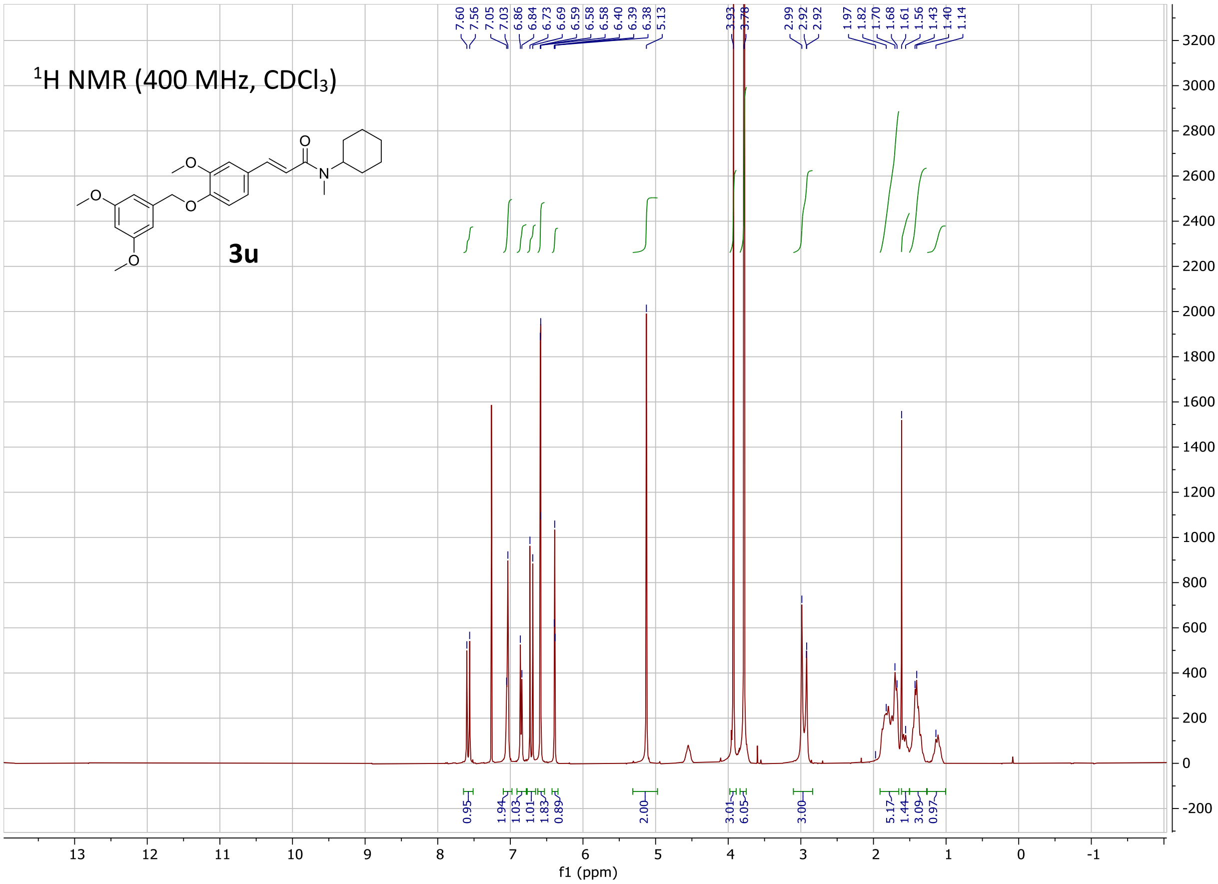
^{1}H NMR (400 MHz, CDCl$_3$)
3s
O
N
N
7.61 7.57 7.04 7.03 7.02 7.02 6.86 6.84 6.73 6.69 6.58 6.58 6.58 6.39 6.39 6.38 5.12 3.92 3.80 3.79 3.79 3.78 3.78 3.77 3.76 3.76 3.75 3.74 3.70 3.69 3.68 3.67 2.45 2.44 2.42 2.32
0.93 1.96 0.99 0.99 1.85 0.91 2.00 3.01 10.02 4.03 2.97
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)
6500 6000 5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0 -500



^{13}C NMR (100 MHz, CDCl$_3$)
3s
O
N
N
165.39 160.85 149.49 149.43 142.48 139.02 128.56 121.45 114.88 113.48 110.38 104.81 99.61 70.65 55.85 55.12 55.09 54.57 45.83 45.51 41.90
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
18000 17000 16000 15000 14000 13000 12000 11000 10000 9000 8000 7000 6000 5000 4000 3000 2000 1000 0 -1000

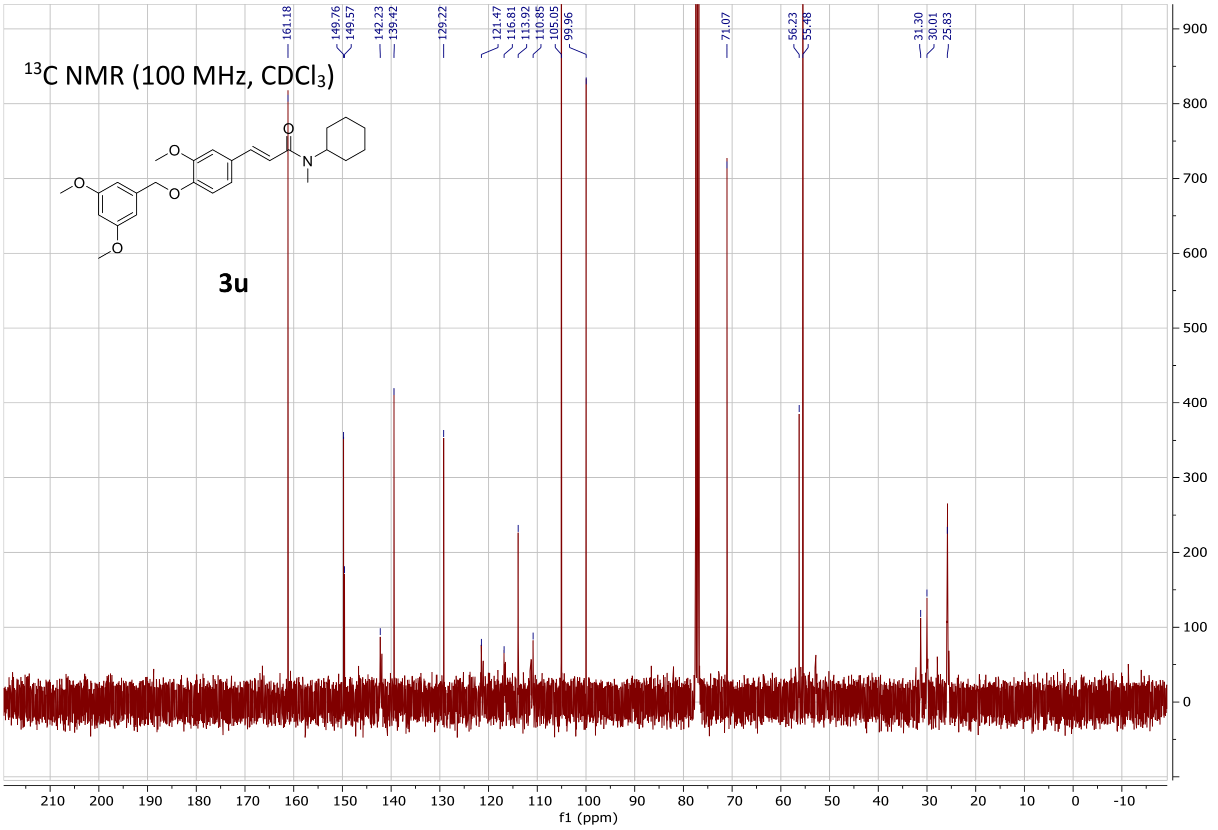

^{1}H NMR (400 MHz, CDCl$_3$)
3t
O
N
O
O
O
O
O
7.64
7.60
7.05
7.04
7.04
7.03
7.03
7.02
7.02
6.86
6.84
6.70
6.66
6.58
6.58
6.58
6.39
6.39
6.38
5.12
3.92
3.78
3.72
3.72
3.71
0.91
1.93
1.00
1.03
1.86
0.93
2.00
3.22
6.26
7.39
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


^{13}C NMR (100 MHz, $CDCl_3$)
3t
165.88
161.17
149.86
149.81
143.27
139.29
128.71
121.75
114.54
113.83
110.72
105.07
99.93
71.02
66.99
56.20
55.47
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



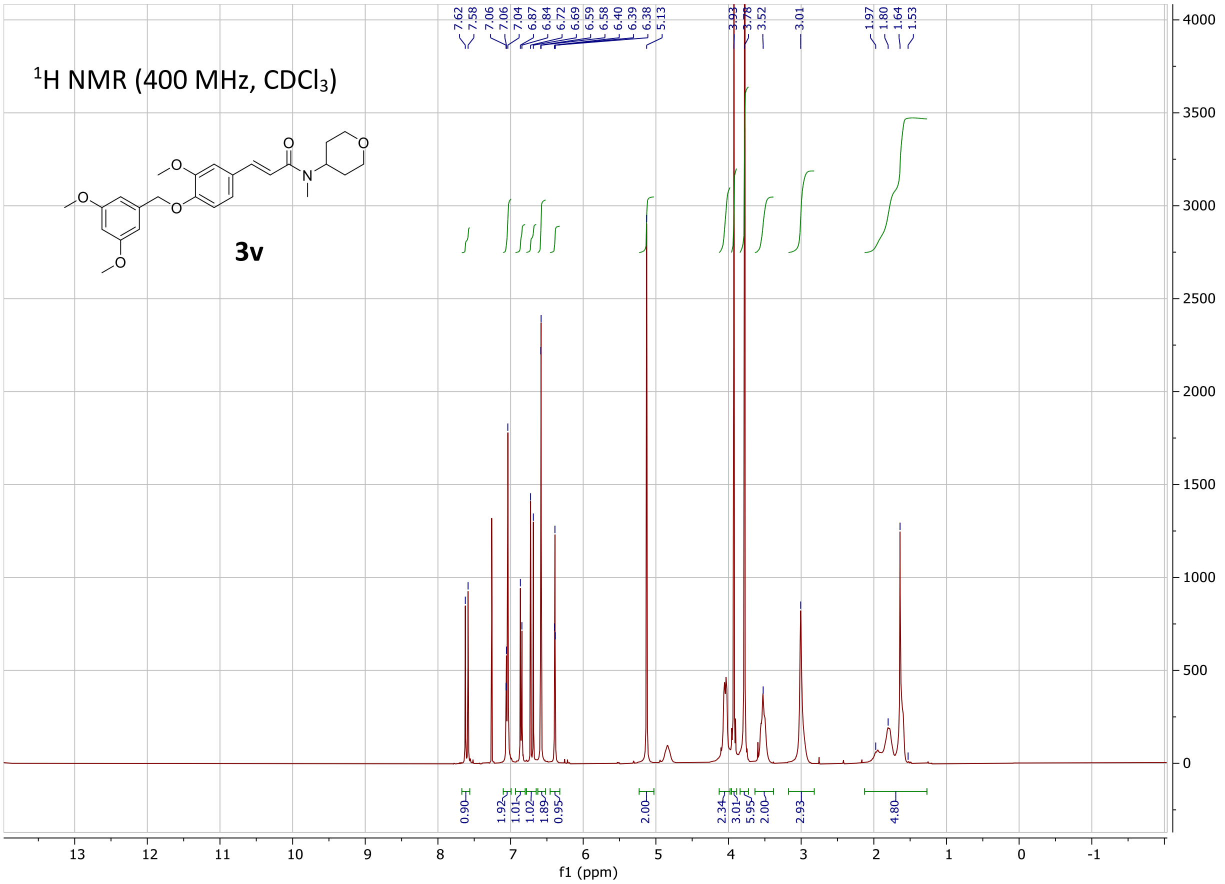
^{1}H NMR (400 MHz, CDCl$_3$)

3u

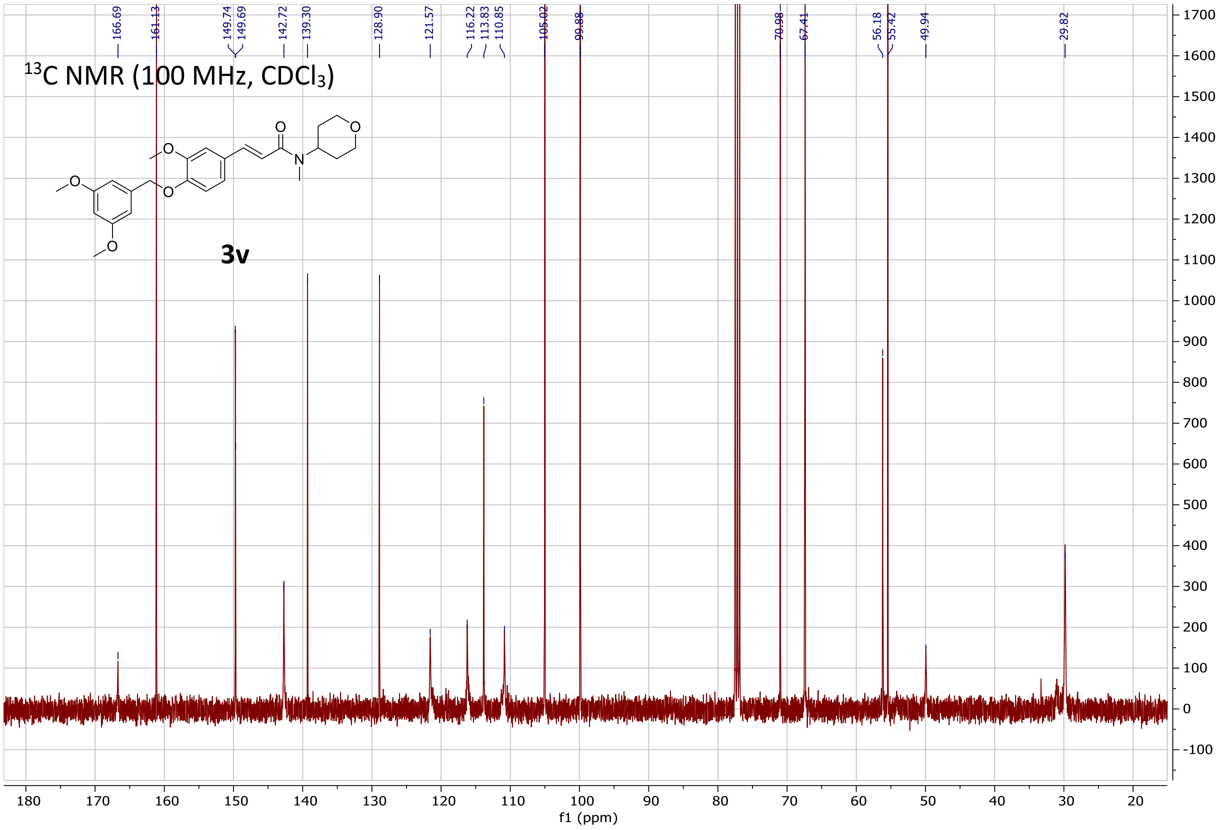


^{13}C NMR (100 MHz, CDCl$_3$)

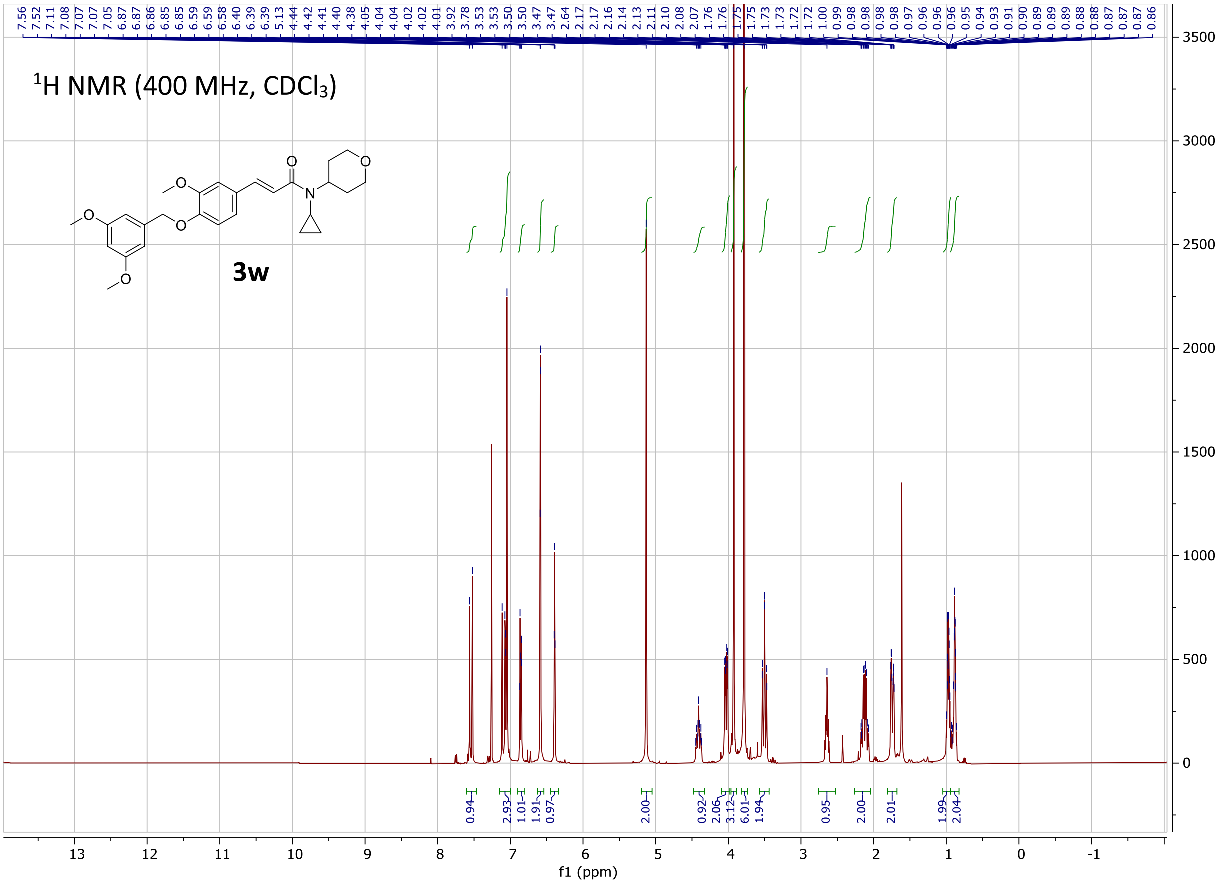
3u

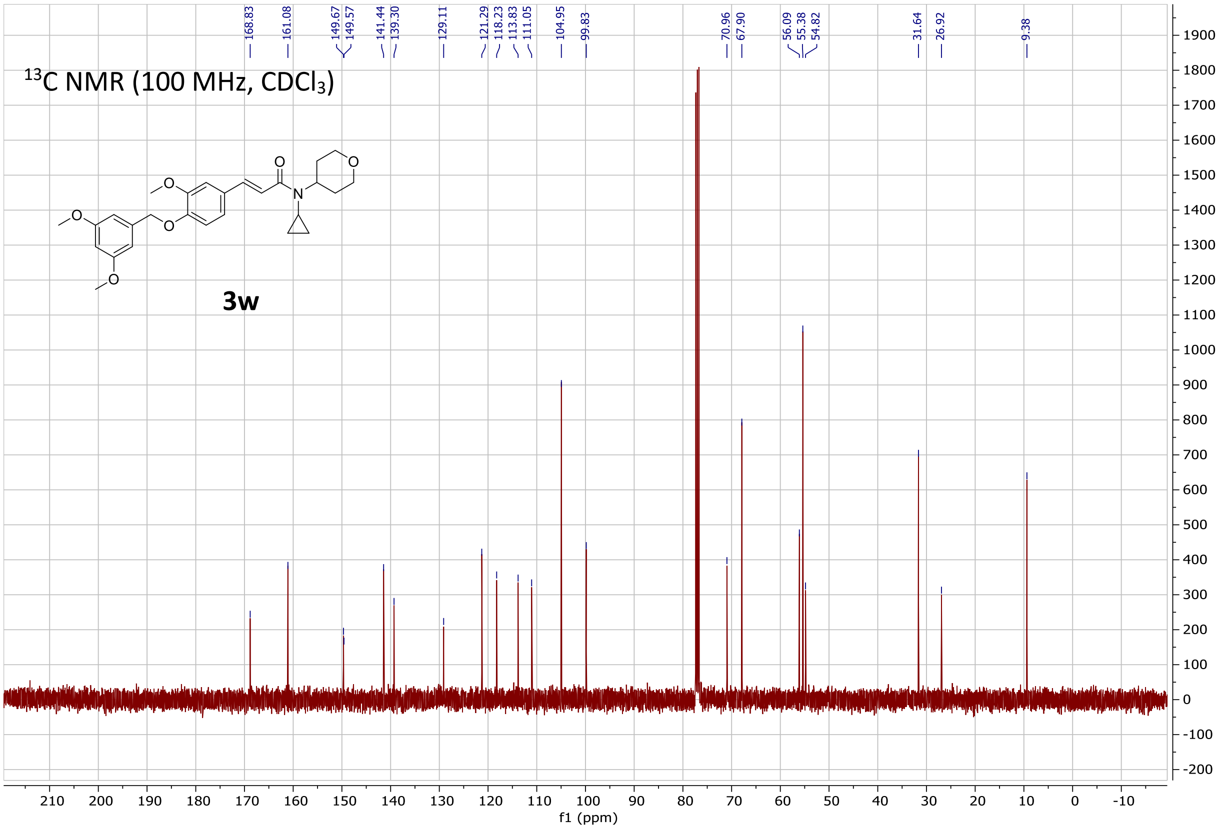

^{1}H NMR (400 MHz, $CDCl_3$)

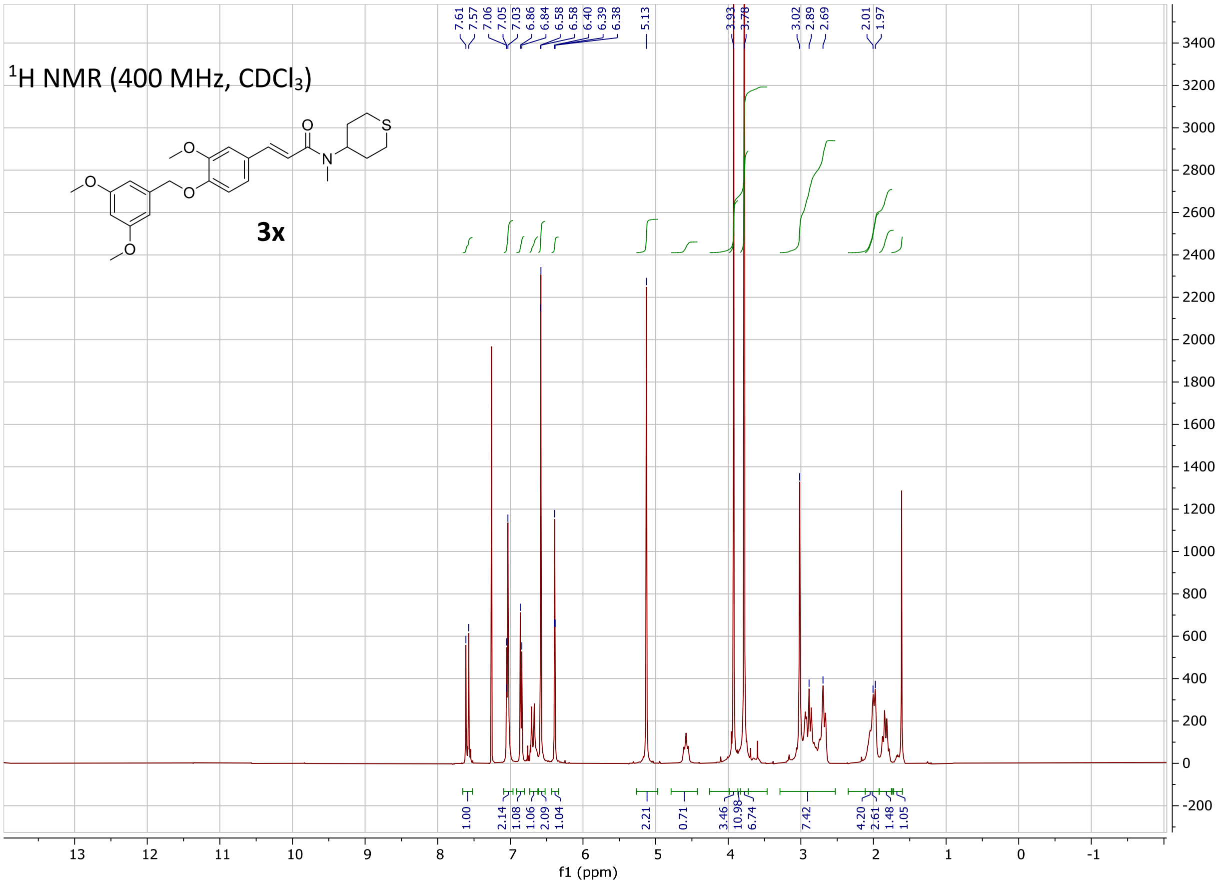
3v


^{13}C NMR (100 MHz, $CDCl_3$)

3v

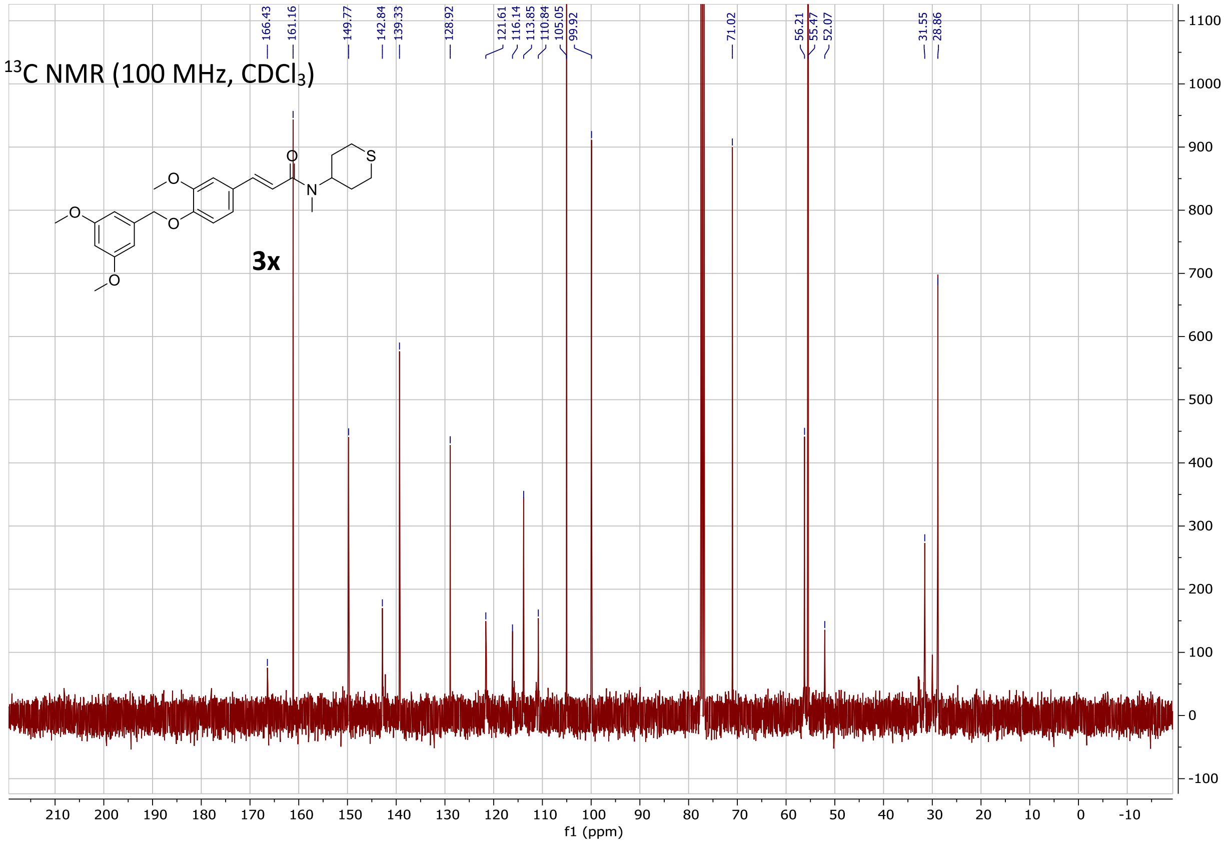

7.56
7.52
7.11
7.08
7.07
7.05
6.87
6.86
6.85
6.85
6.59
6.59
6.58
6.40
6.39
6.39
5.13
4.44
4.42
4.41
4.40
4.38
4.05
4.04
4.04
4.02
4.02
4.01
3.92
3.78
3.53
3.53
3.50
3.50
3.47
3.47
2.64
2.17
2.17
2.16
2.14
2.13
2.11
2.10
2.08
2.07
1.76
1.76
1.75
1.75
1.73
1.73
1.72
1.72
1.00
0.99
0.98
0.98
0.98
0.98
0.97
0.96
0.96
0.96
0.96
0.95
0.94
0.93
0.91
0.90
0.89
0.89
0.89
0.88
0.88
0.87
0.87
0.86
¹H NMR (400 MHz, CDCl₃)
O
O
O
O
N
O
O
3w
0.94
2.93
1.01
1.91
0.97
2.00
0.92
2.06
3.12
6.01
1.94
0.95
2.00
2.01
1.99
2.04
3500
3000
2500
2000
1500
1000
500
0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


168.83
161.08
149.67
149.57
141.44
139.30
129.11
121.29
118.23
113.83
111.05
104.95
99.83
70.96
67.90
56.09
55.38
54.82
31.64
26.92
9.38
¹³C NMR (100 MHz, CDCl₃)
O
O
O
O
N
O
O
3w
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



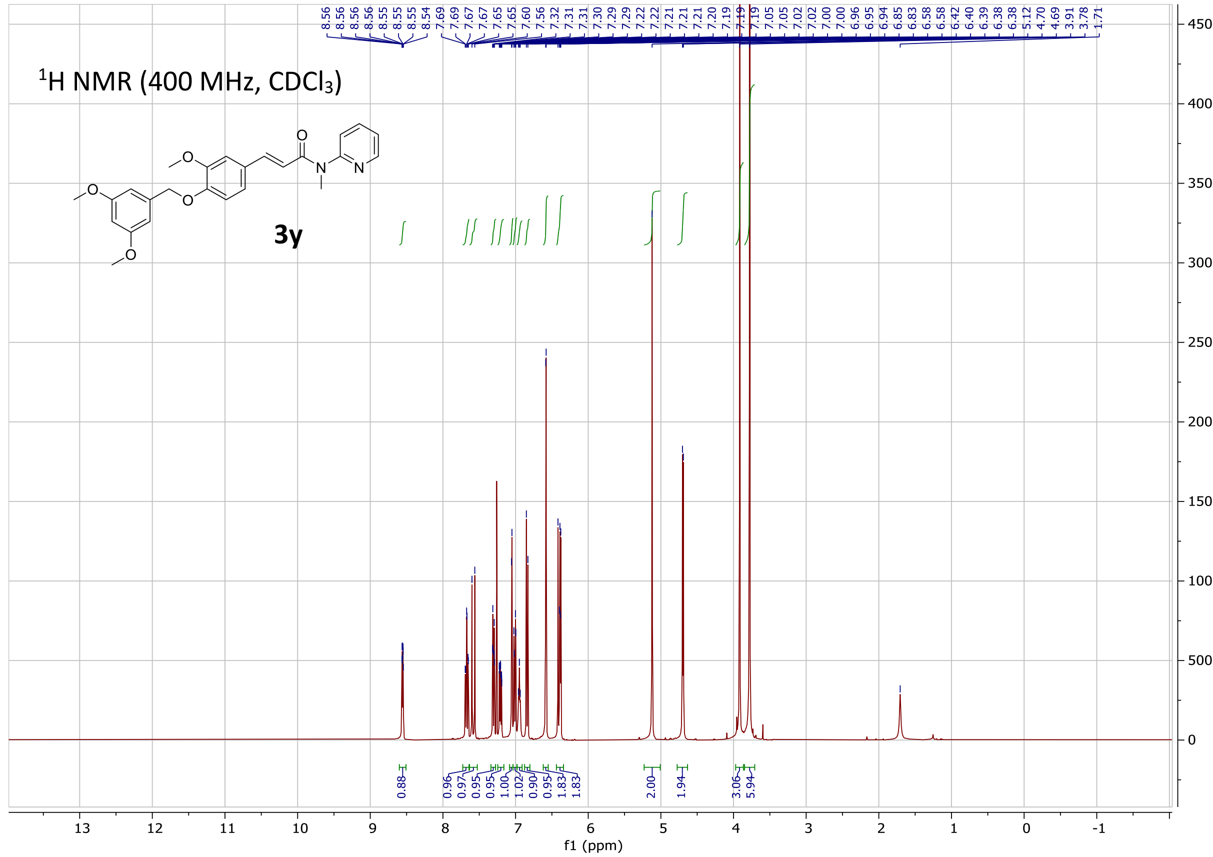
^{1}H NMR (400 MHz, $CDCl_3$)

3x



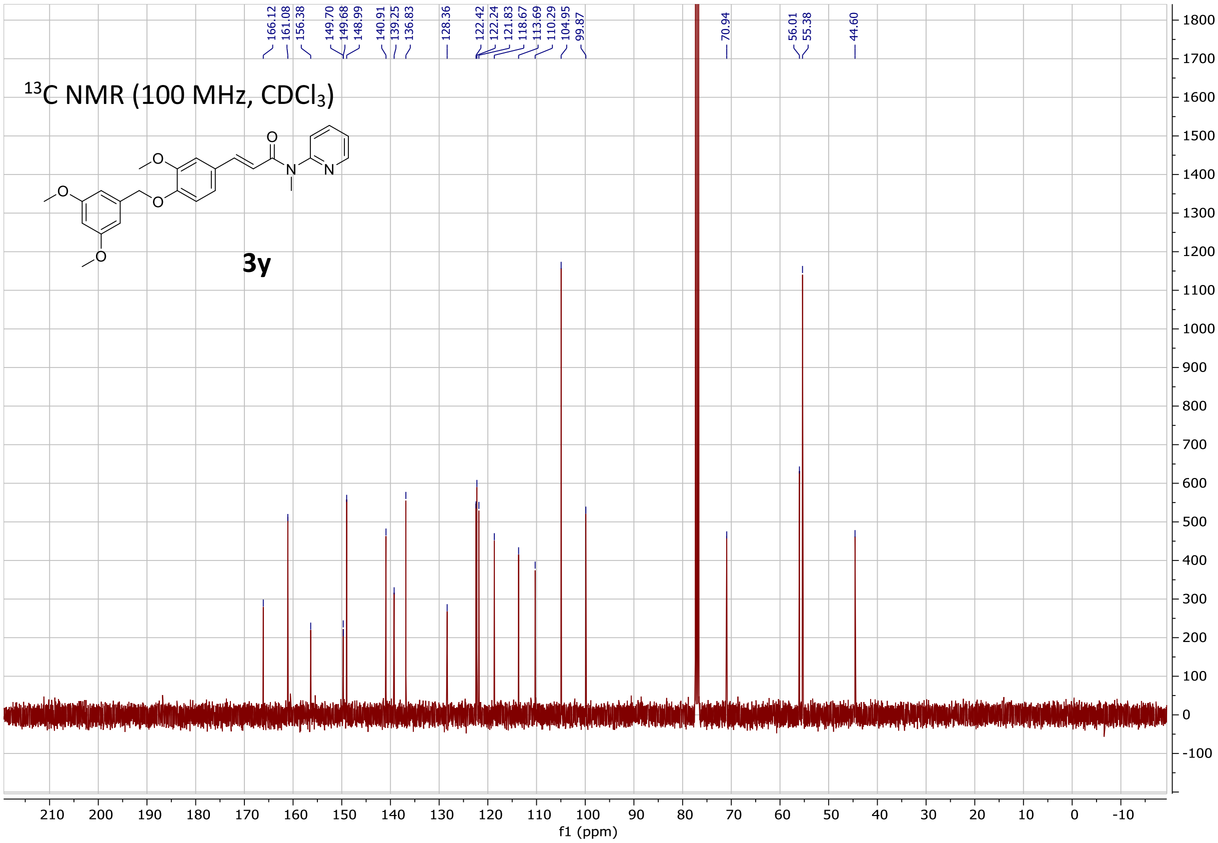
^{13}C NMR (100 MHz, $CDCl_3$)

3x



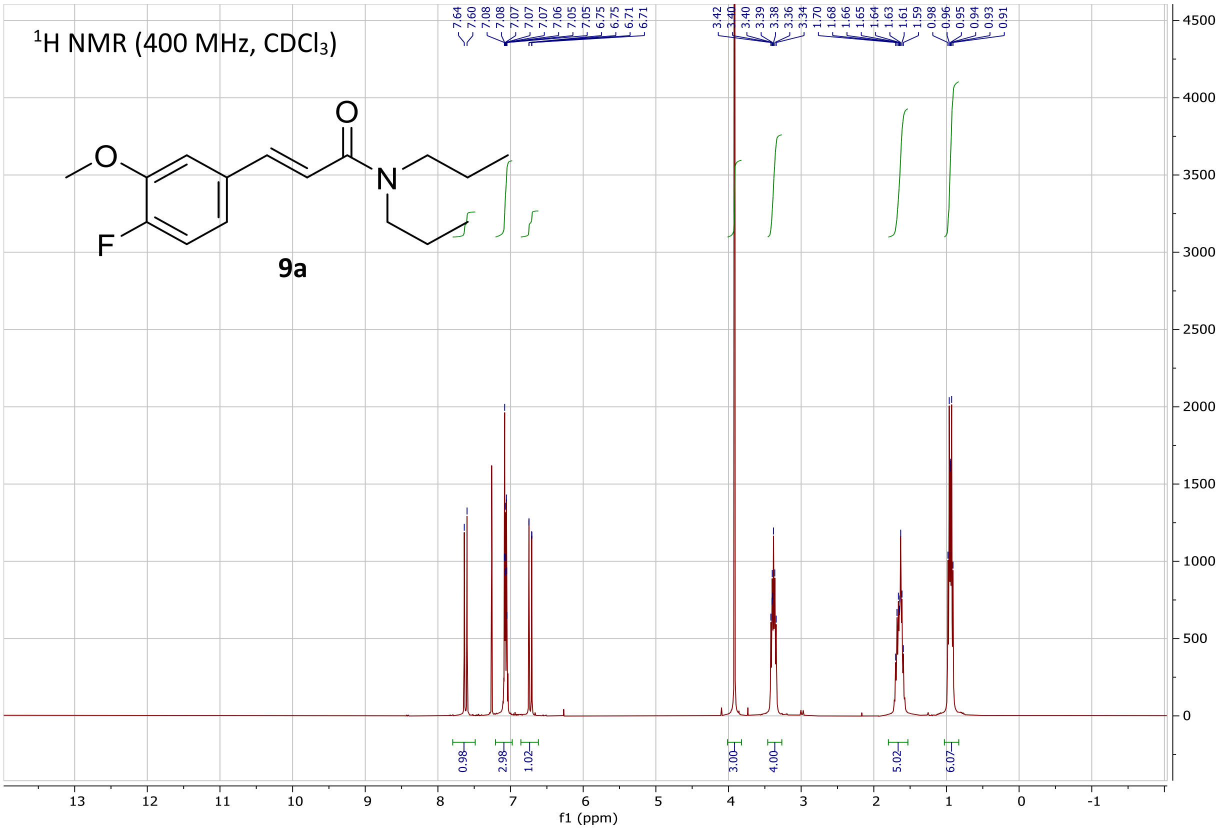
^{1}H NMR (400 MHz, $CDCl_3$)

3y



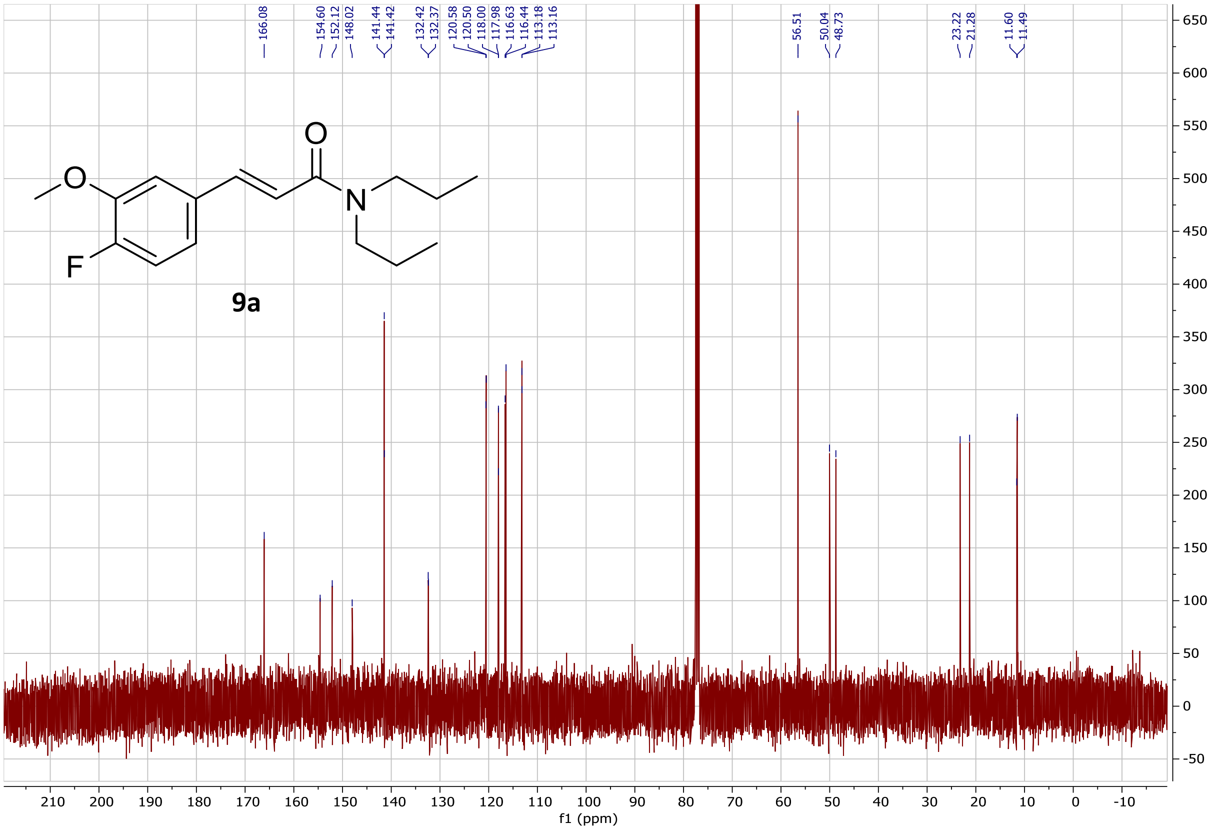
3y

4.2 Series 2 compounds.

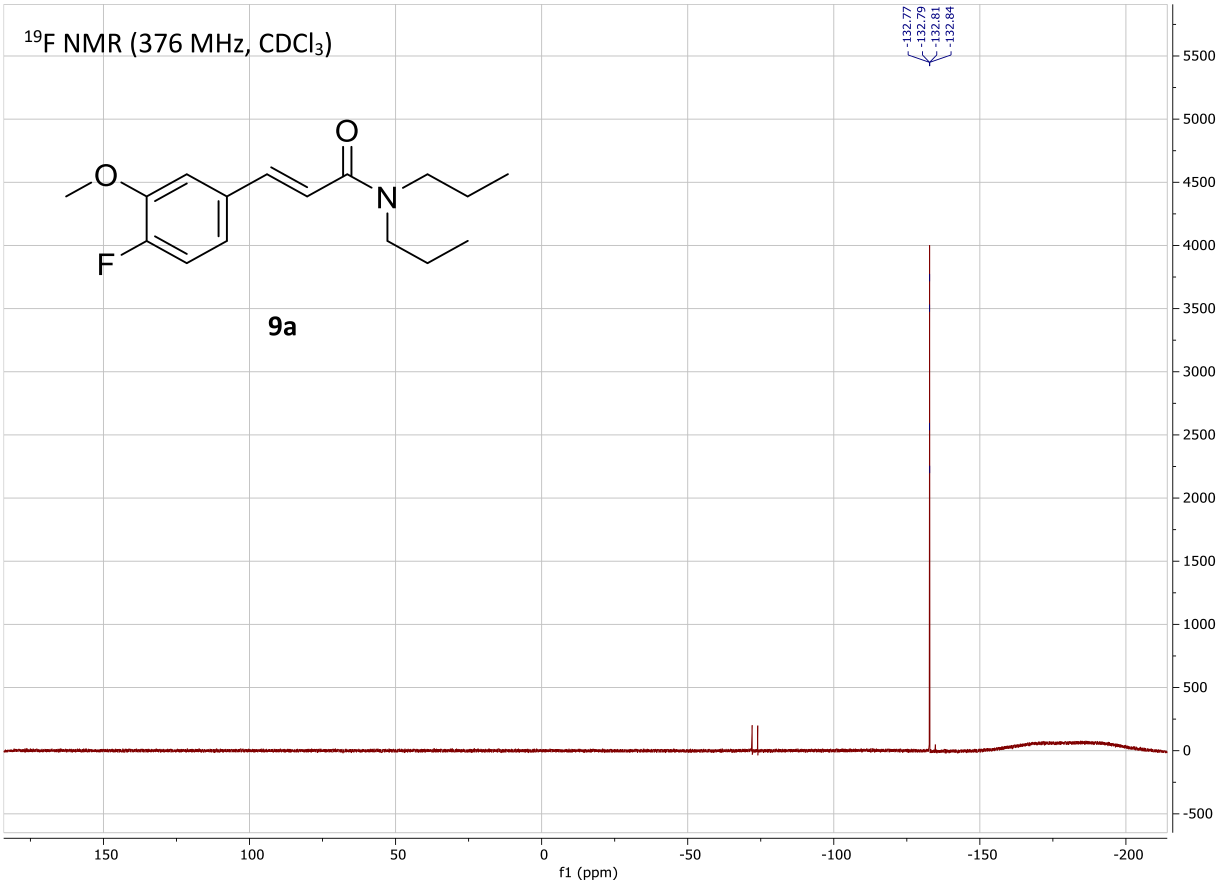


9a

^{13}C NMR (100 MHz, CDCl$_3$)

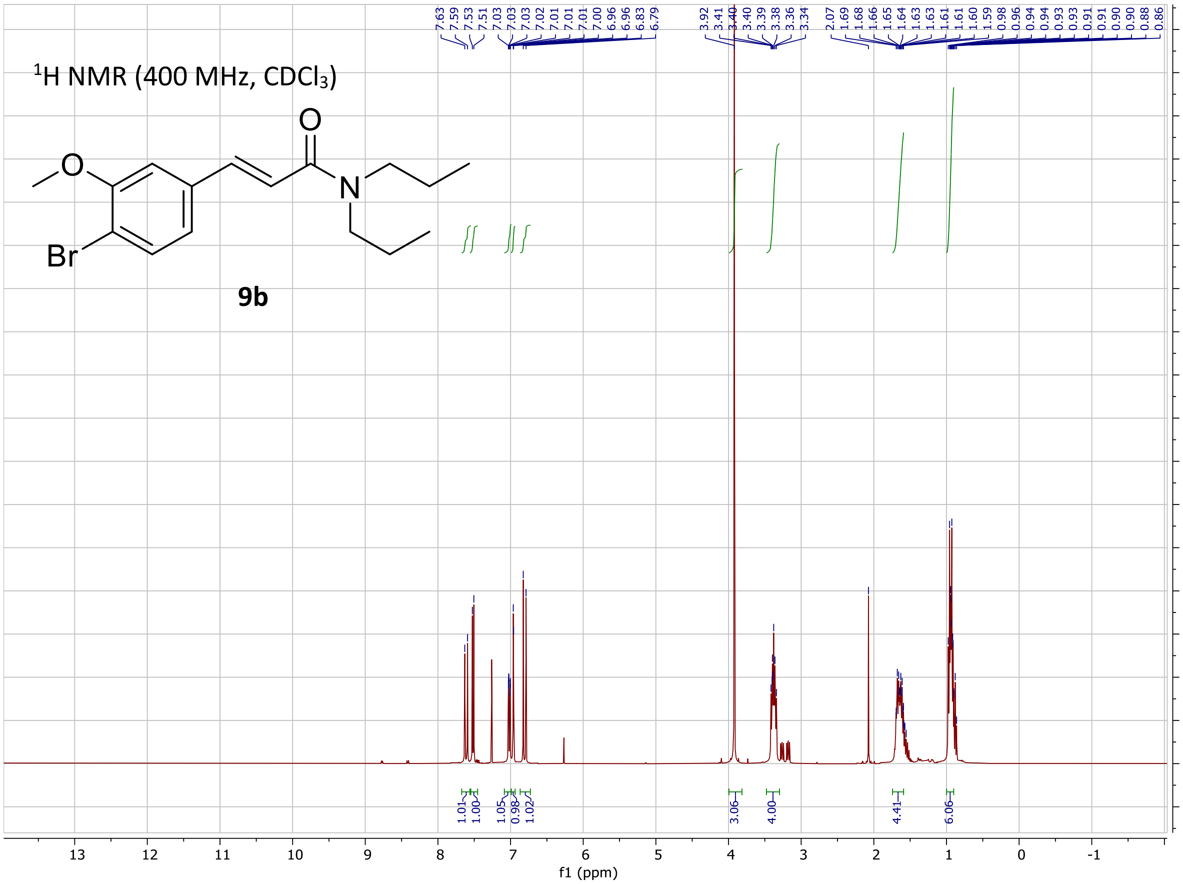


9a

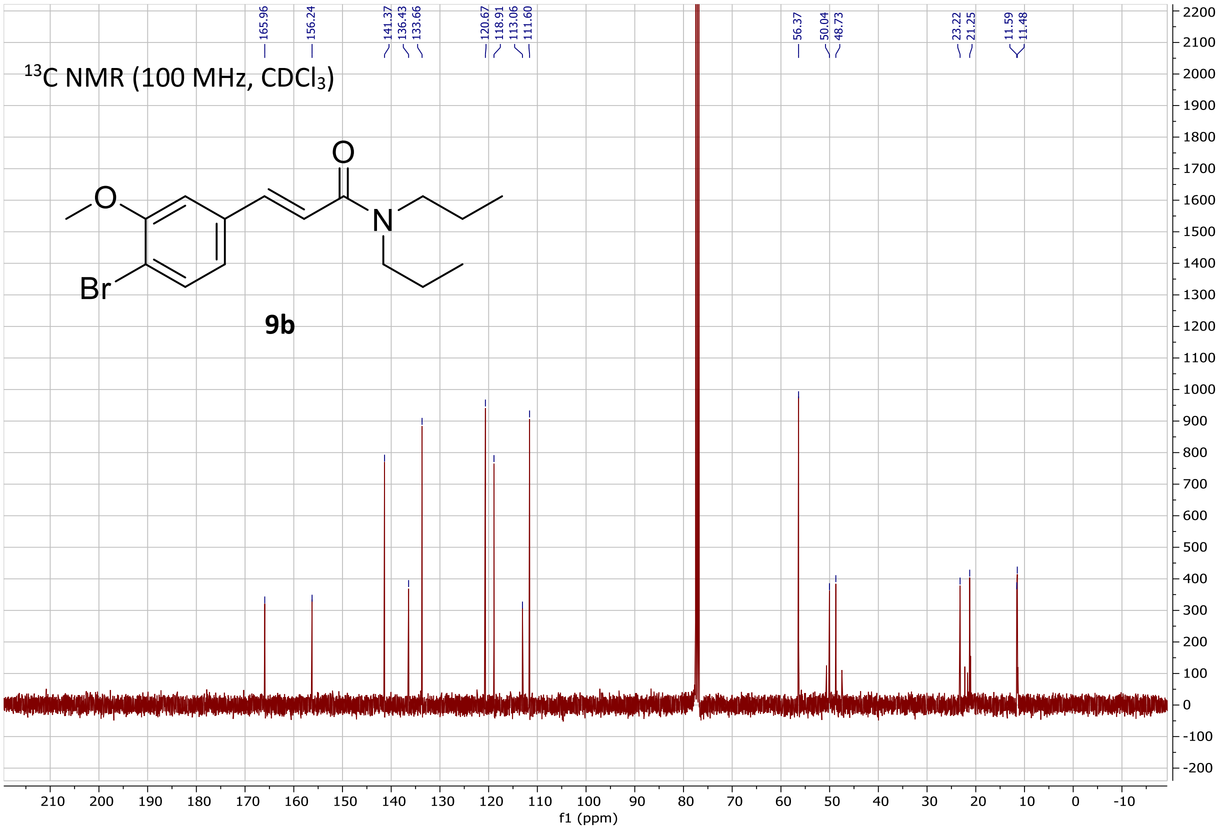


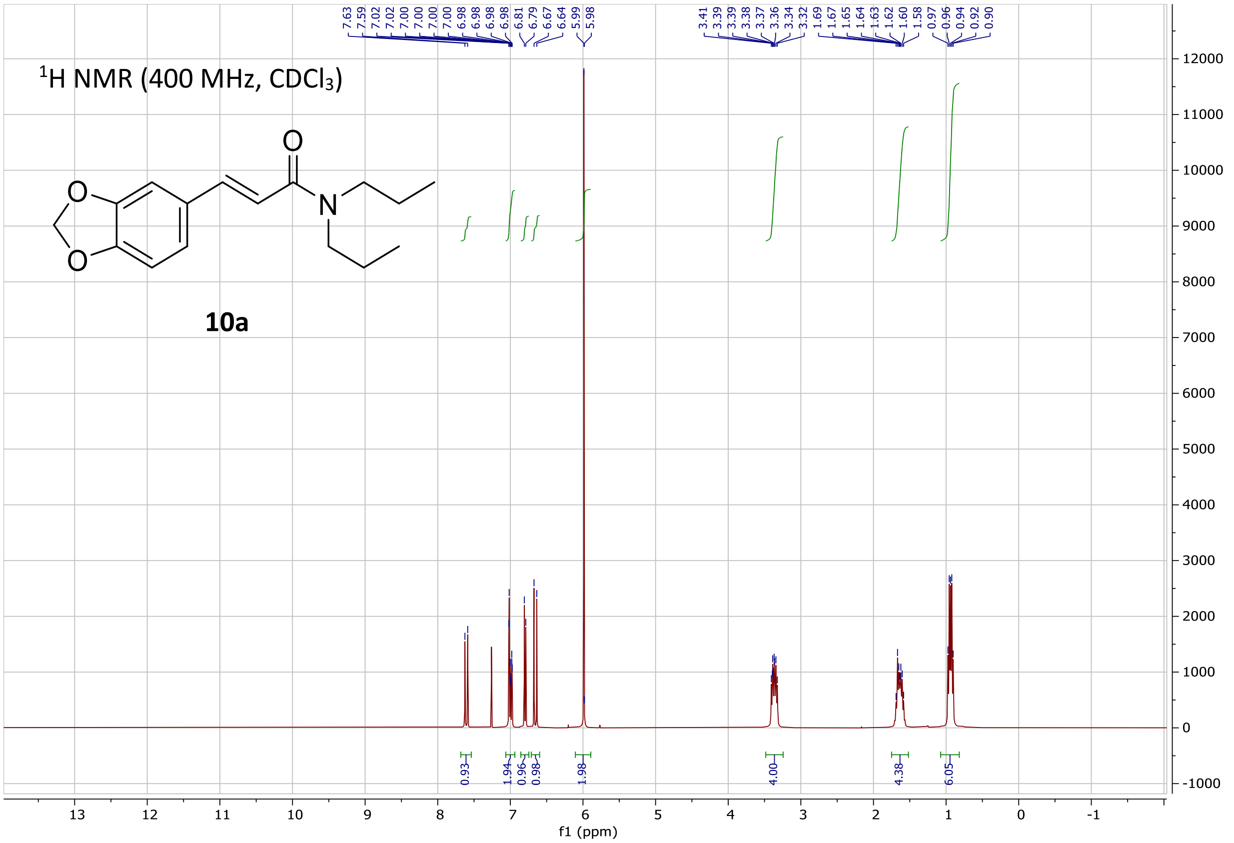
^{19}F NMR (376 MHz, $CDCl_3$)

9a



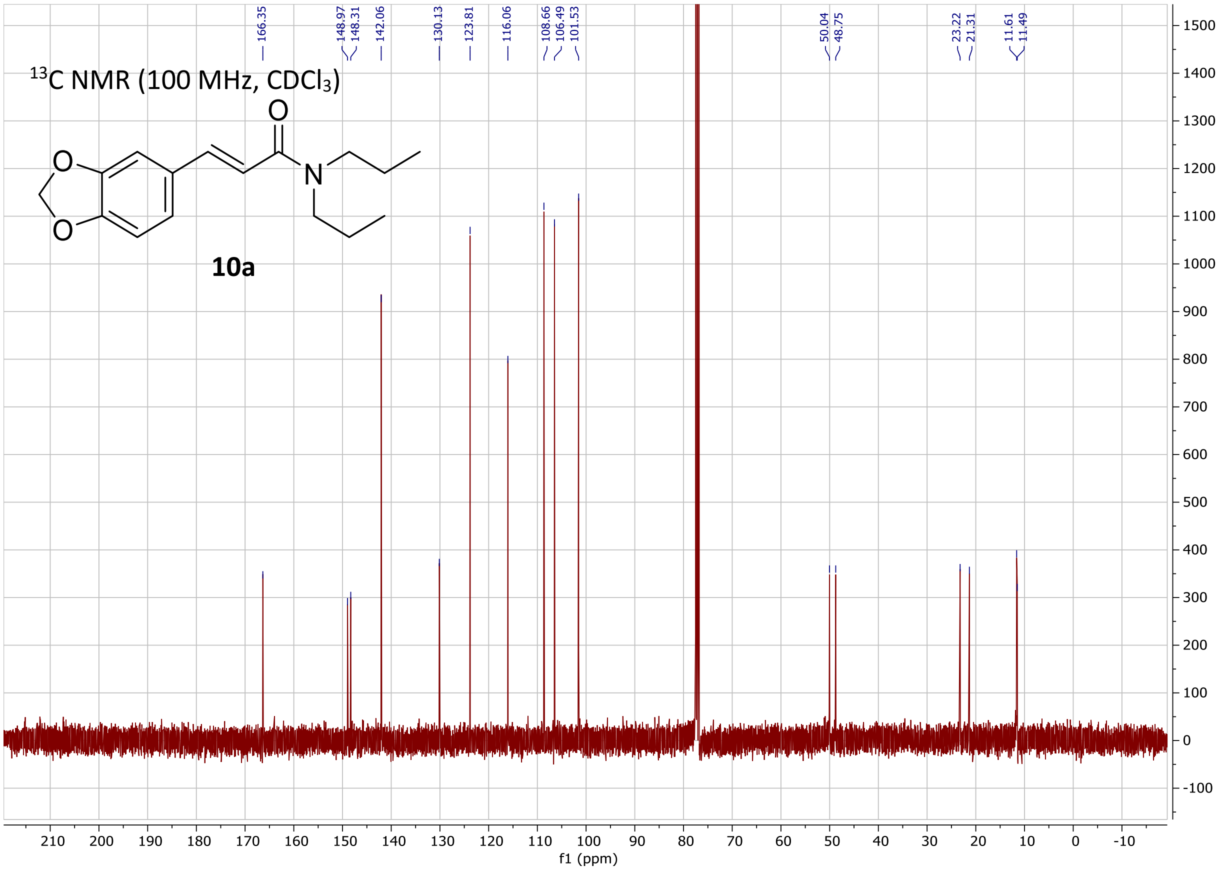
1H NMR (400 MHz, CDCl3)
O
O
N
Br
9b
7.63
7.59
7.53
7.51
7.03
7.03
7.03
7.02
7.01
7.01
7.01
7.00
6.96
6.96
6.83
6.79
3.92
3.41
3.40
3.40
3.39
3.38
3.36
3.34
2.07
1.69
1.68
1.66
1.65
1.64
1.63
1.63
1.61
1.61
1.60
1.59
0.98
0.96
0.94
0.94
0.93
0.93
0.91
0.91
0.90
0.88
0.86
1.01
1.00
1.05
0.98
1.02
3.06
4.00
4.41
6.06
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500


^{13}C NMR (100 MHz, CDCl$_3$)
O
N
O
Br
9b
165.96
156.24
141.37
136.43
133.66
120.67
118.91
113.06
111.60
56.37
50.04
48.73
23.22
21.25
11.59
11.48
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



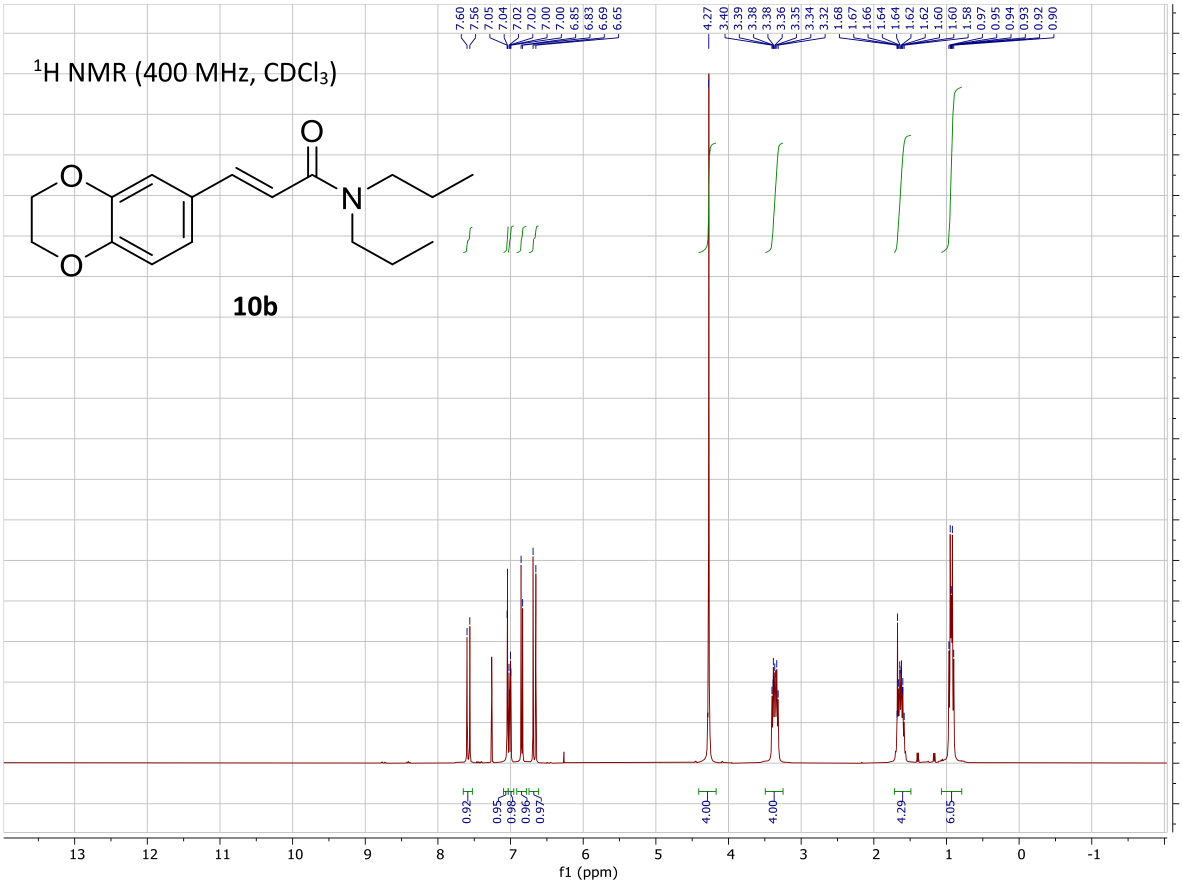
^{1}H NMR (400 MHz, CDCl$_3$)

10a

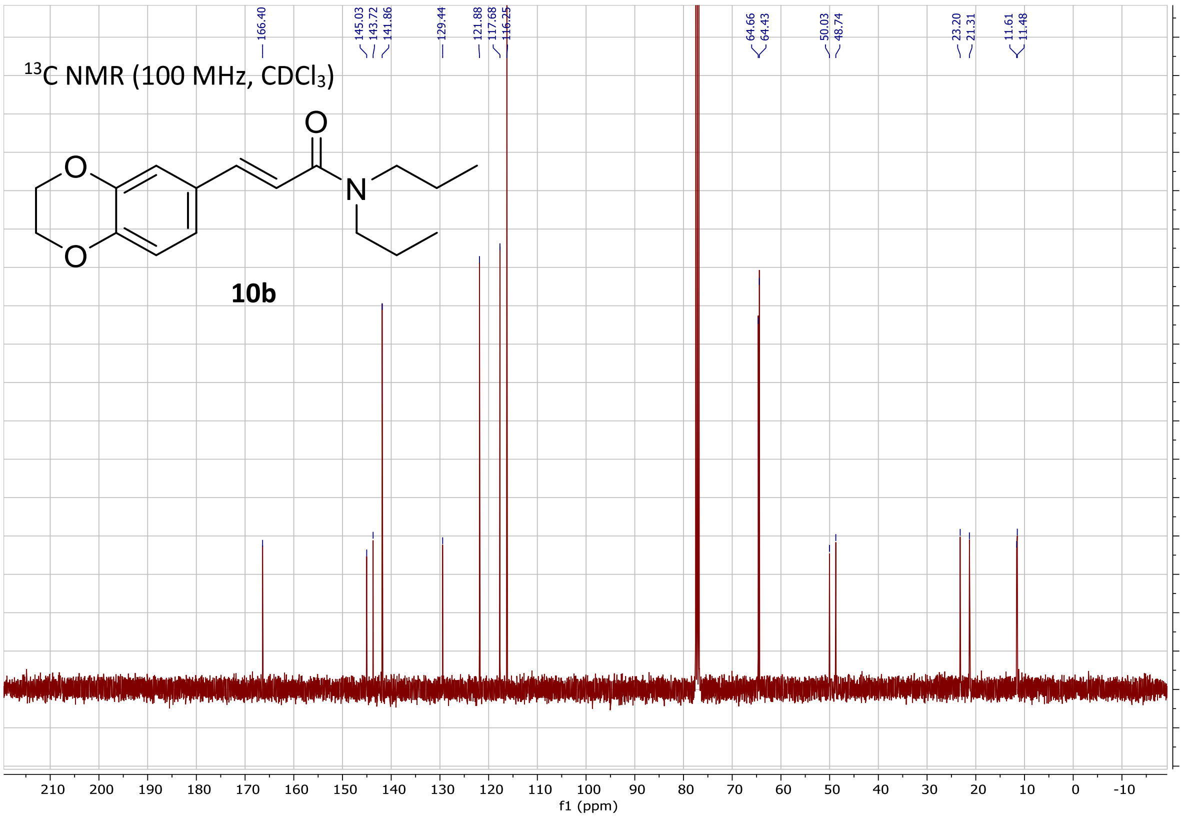


^{13}C NMR (100 MHz, CDCl$_3$)

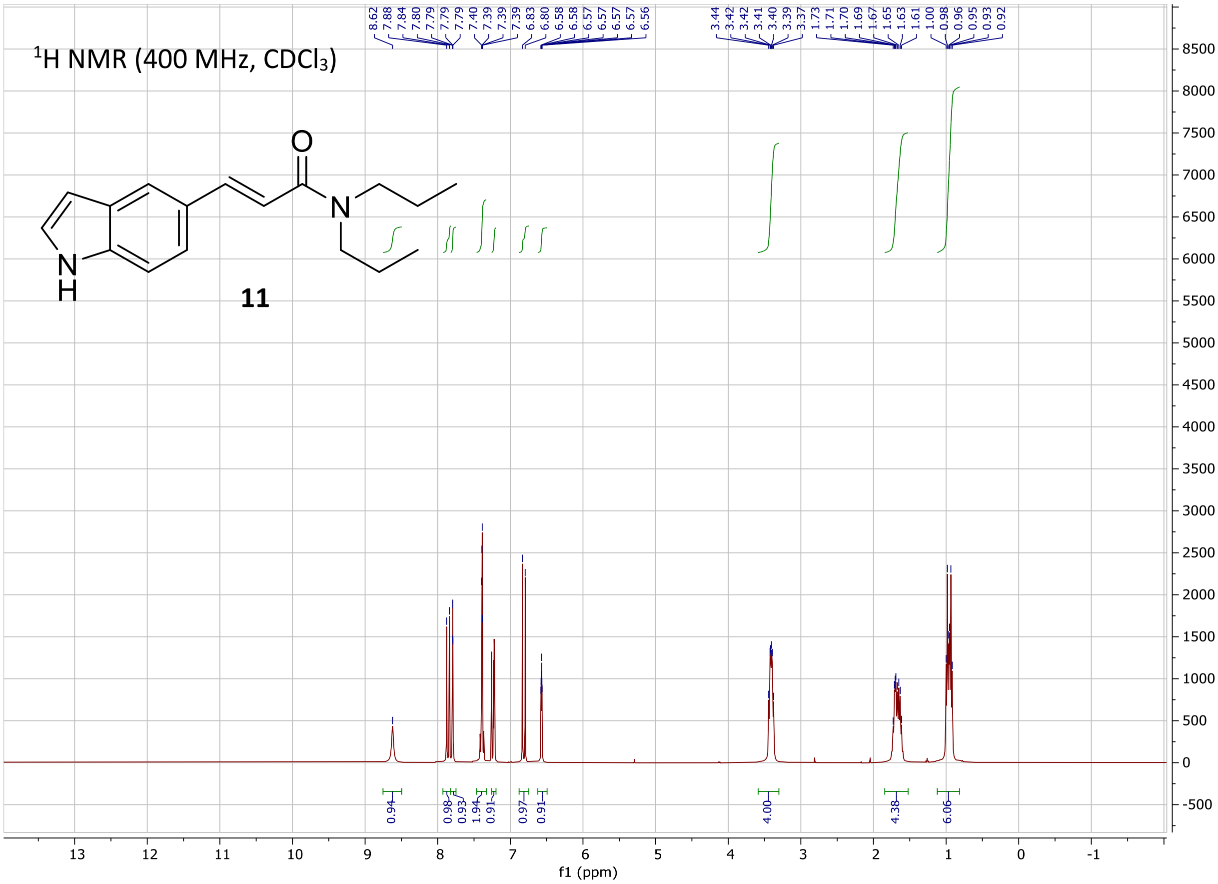
10a

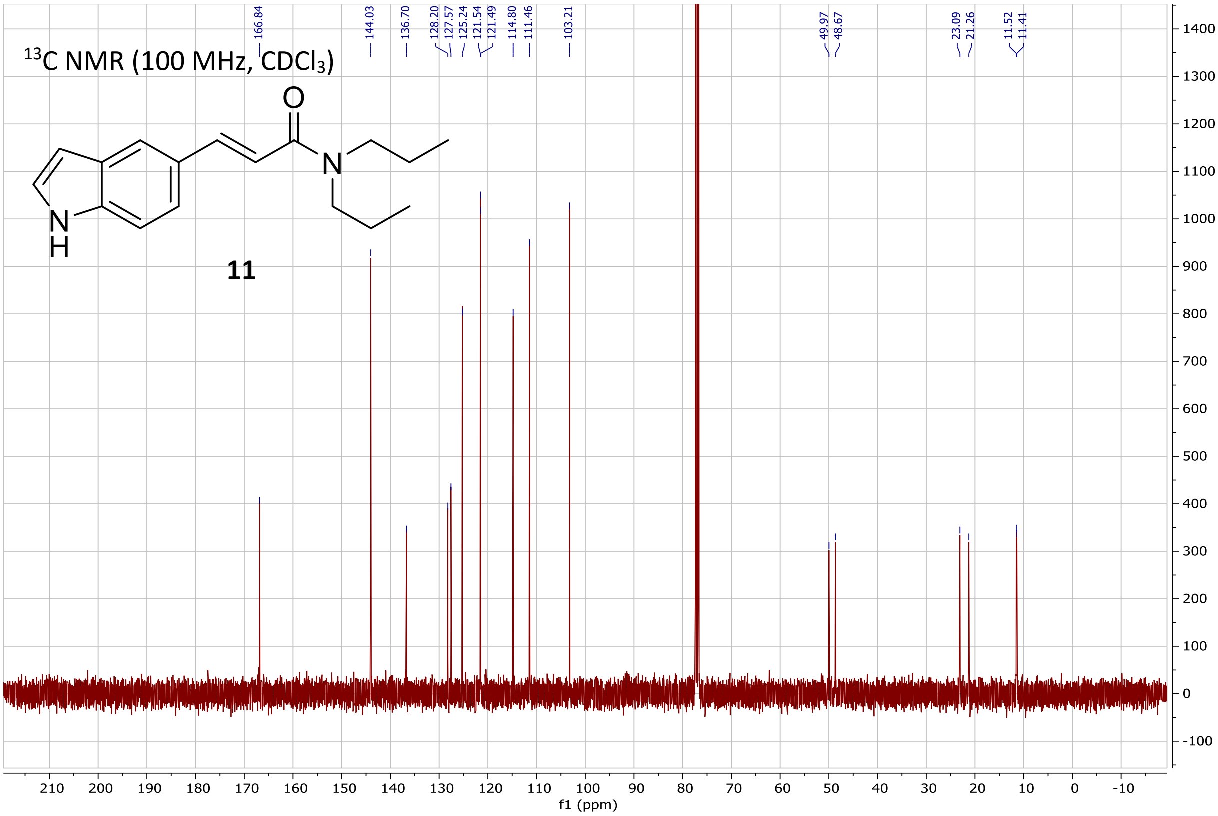


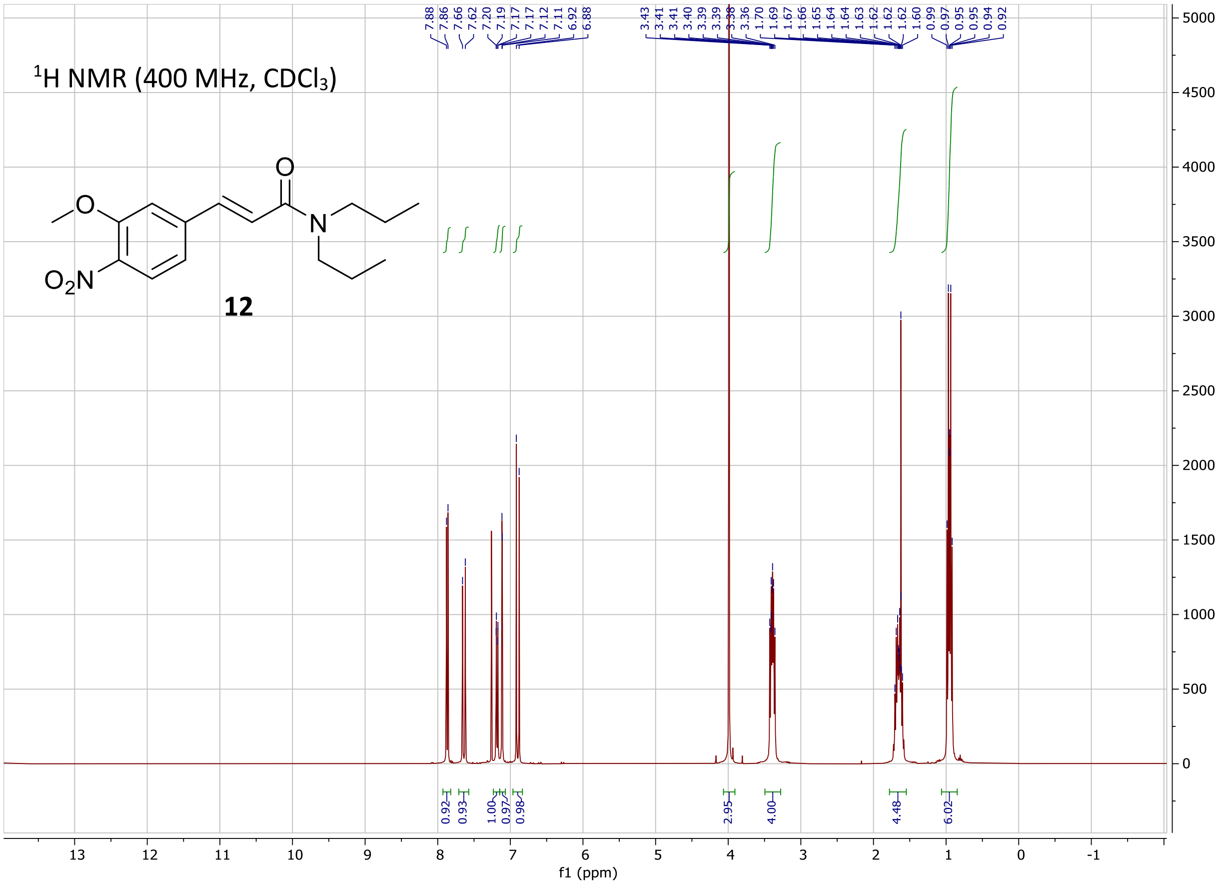
^{1}H NMR (400 MHz, CDCl$_3$)
O
O
O
N
10b
7.60
7.56
7.05
7.04
7.02
7.02
7.00
7.00
6.85
6.83
6.69
6.65
4.27
3.40
3.39
3.38
3.38
3.36
3.35
3.34
3.32
1.68
1.67
1.66
1.64
1.64
1.62
1.62
1.60
1.60
1.58
0.97
0.95
0.94
0.93
0.92
0.90
0.92
0.95
0.98
0.96
0.97
4.00
4.00
4.29
6.05
f1 (ppm)



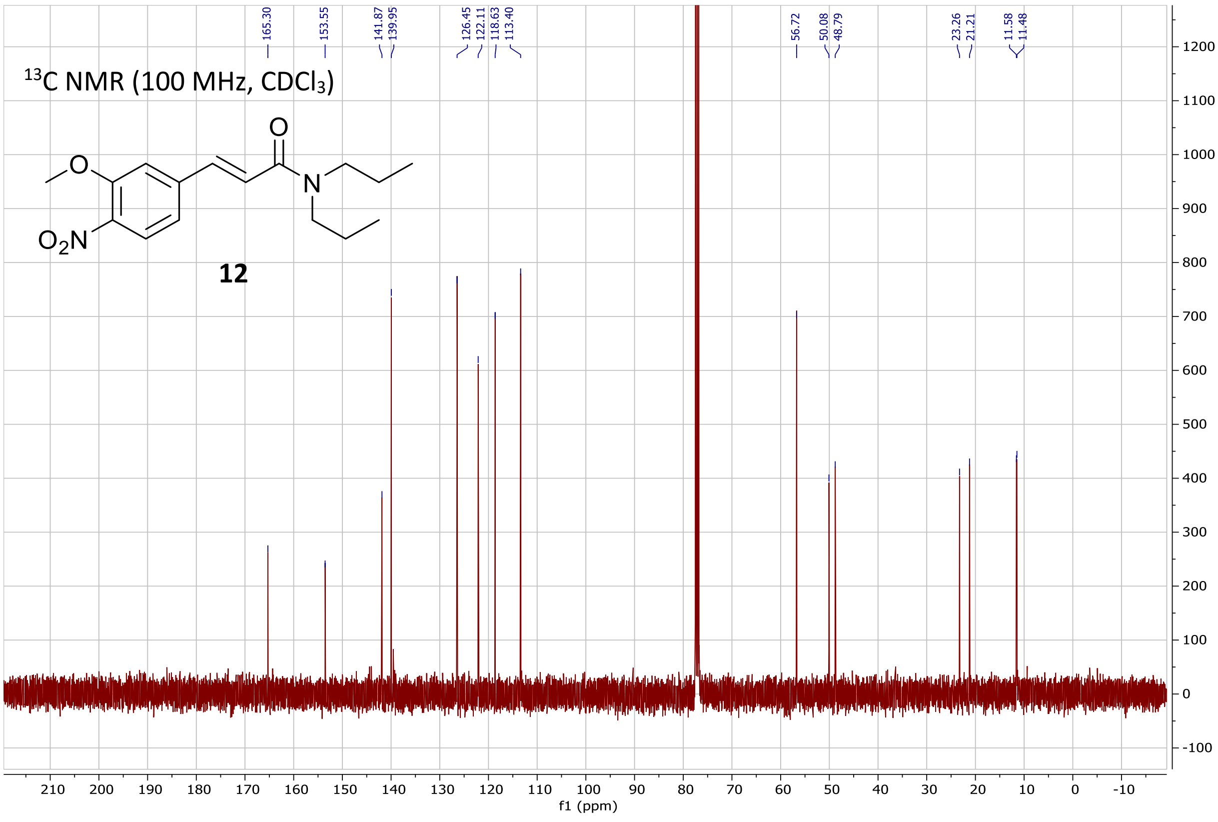
^{13}C NMR (100 MHz, CDCl$_3$)
O
O
O
N
10b
166.40
145.03
143.72
141.86
129.44
121.88
117.68
116.25
64.66
64.43
50.03
48.74
23.20
21.31
11.61
11.48
f1 (ppm)


1H NMR (400 MHz, CDCl3)
O
N
N
H
11
8.62
7.88
7.84
7.80
7.79
7.79
7.40
7.39
7.39
7.39
6.83
6.80
6.58
6.58
6.57
6.57
6.57
6.56
3.44
3.42
3.42
3.41
3.40
3.39
3.37
1.73
1.71
1.70
1.69
1.67
1.65
1.63
1.61
1.00
0.98
0.96
0.95
0.93
0.92
0.94
0.98
0.93
1.94
0.91
0.97
0.91
4.00
4.38
6.06
f1 (ppm)
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
8500 8000 7500 7000 6500 6000 5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0 -500


13C NMR (100 MHz, CDCl3)
O
N
N
H
11
166.84
144.03
136.70
128.20
127.57
125.24
121.54
121.49
114.80
111.46
103.21
49.97
48.67
23.09
21.26
11.52
11.41
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100

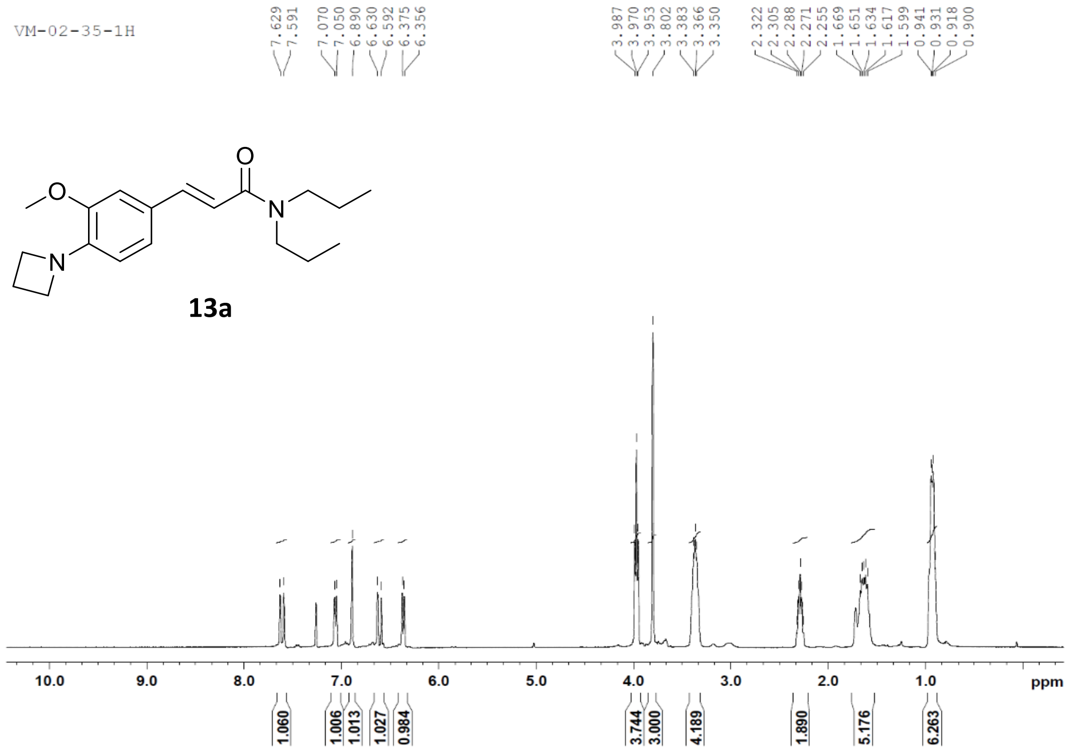


^1H NMR (400 MHz, $CDCl_3$)
12
7.88 7.86 7.66 7.62 7.20 7.19 7.17 7.17 7.12 7.11 6.92 6.88
3.43 3.41 3.41 3.40 3.39 3.39 3.38 3.36 1.70 1.69 1.67 1.66 1.65 1.64 1.64 1.63 1.62 1.62 1.62 1.60 0.99 0.97 0.95 0.95 0.94 0.92
0.92 0.93 1.00 0.97 0.98 2.95 4.00 4.48 6.02
f1 (ppm)



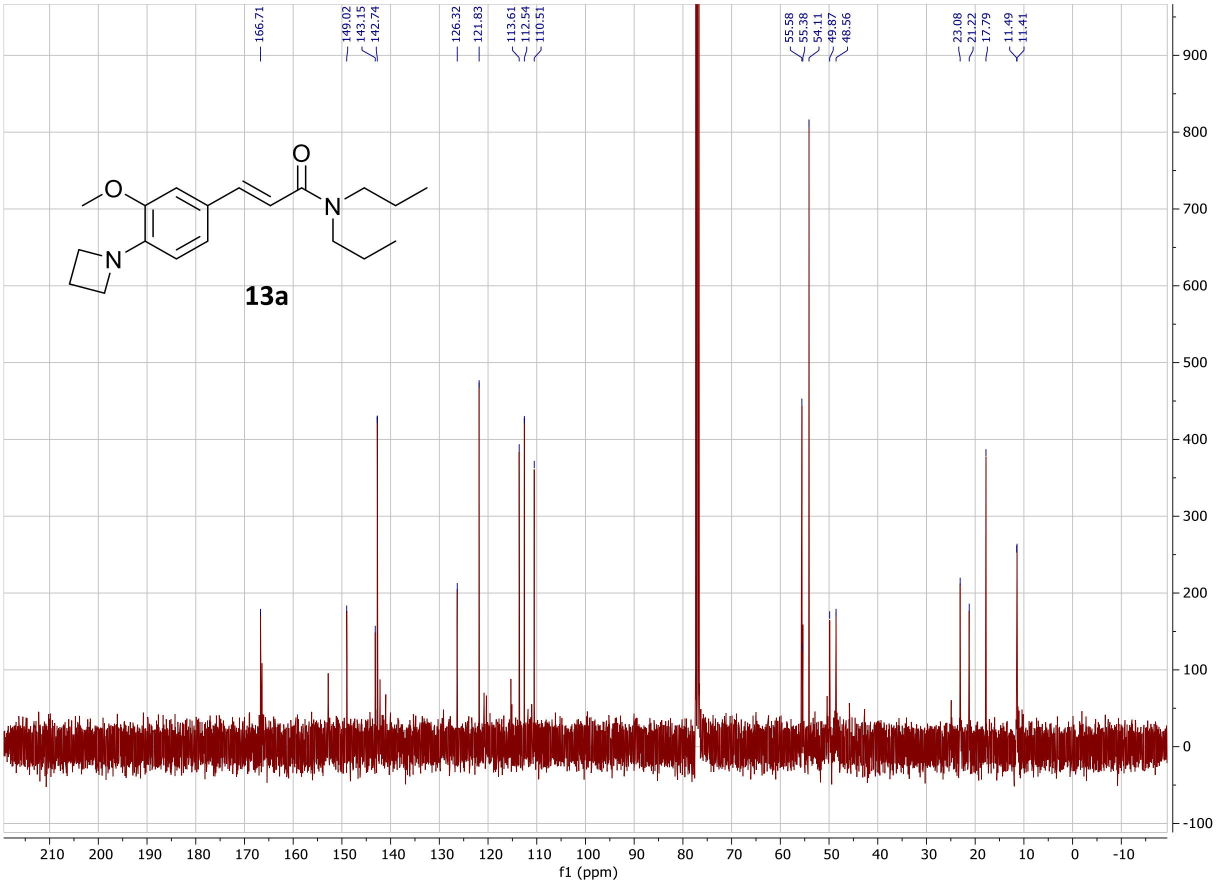
^{13}C NMR (100 MHz, $CDCl_3$)
12
165.30 153.55 141.87 139.95 126.45 122.11 118.63 113.40 56.72 50.08 48.79 23.26 21.21 11.58 11.48
f1 (ppm)

^{1}H NMR (400 MHz, CDCl$_3$)

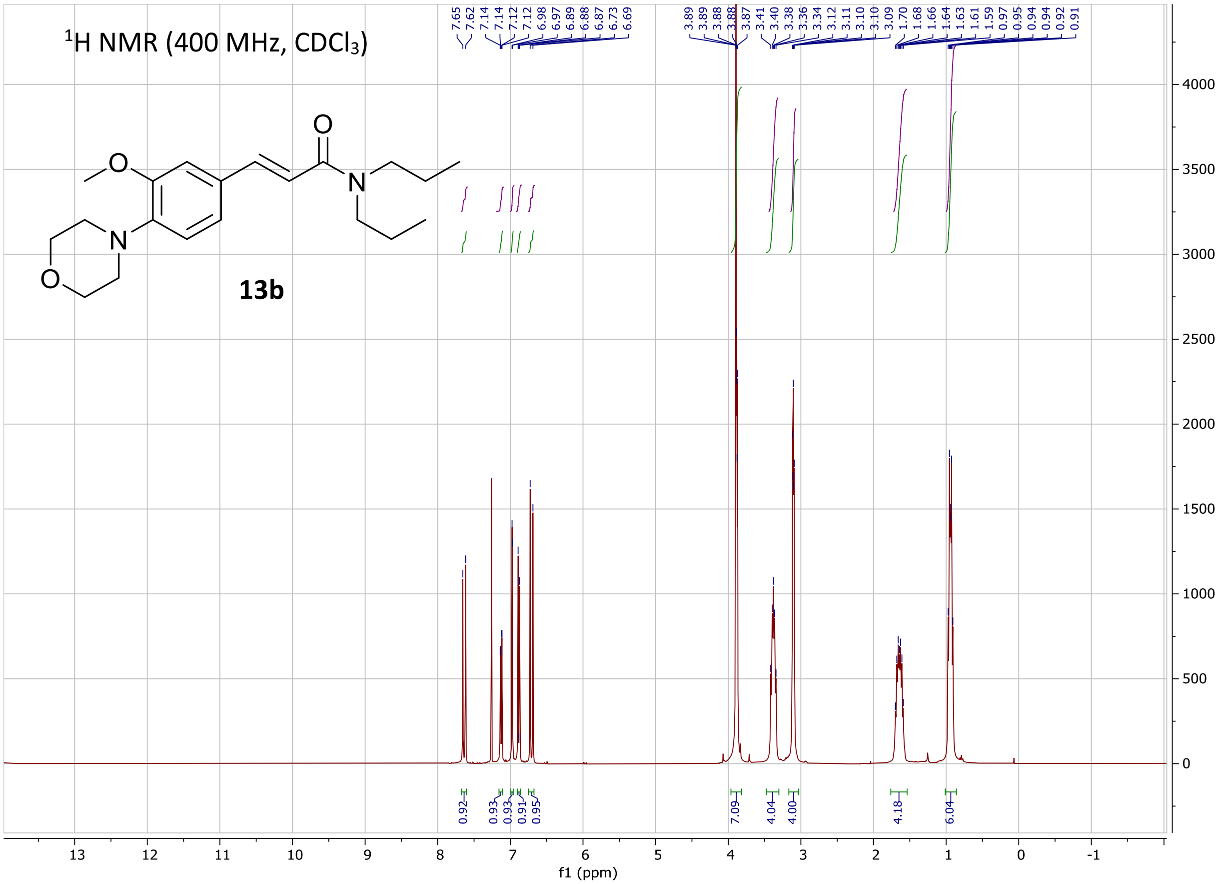


13a

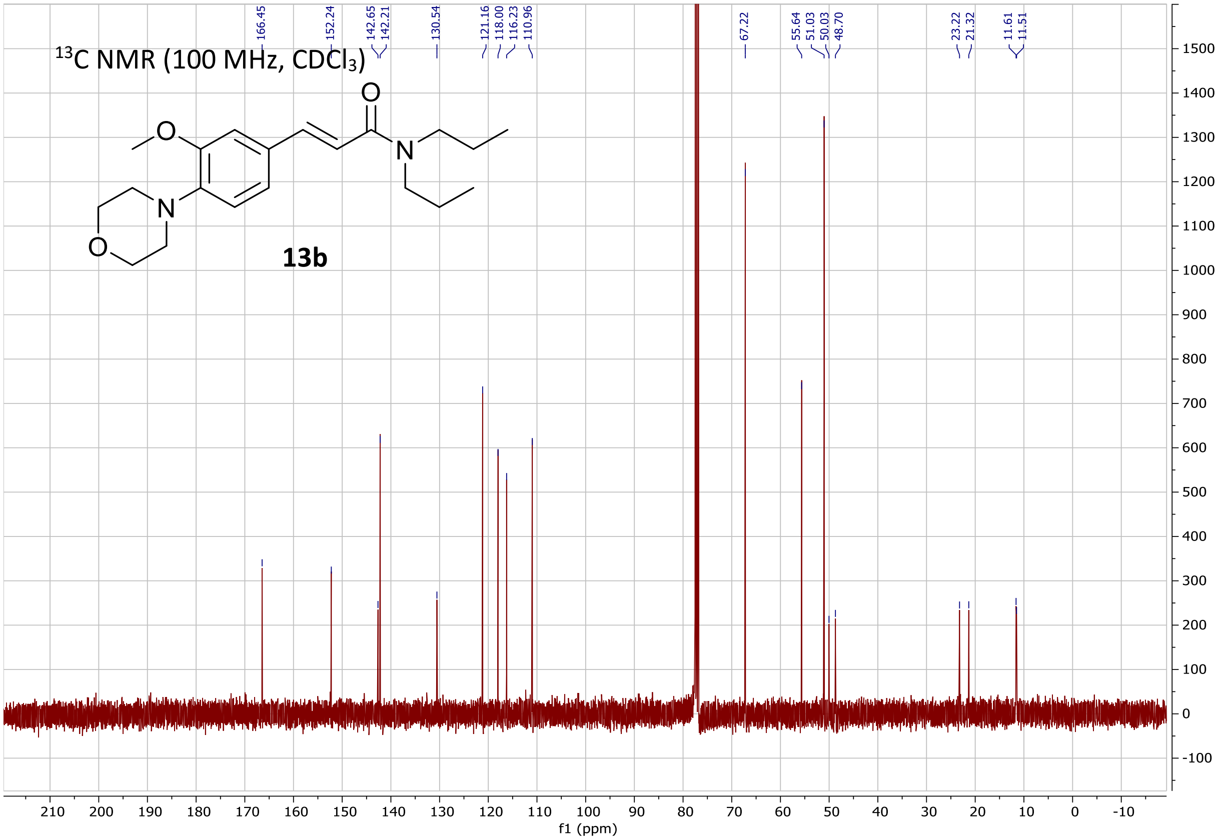
^{13}C NMR (100 MHz, CDCl$_3$)


166.71
149.02
143.15
142.74
126.32
121.83
113.61
112.54
110.51
55.58
55.38
54.11
49.87
48.56
23.08
21.22
17.79
11.49
11.41
O
O
N
N
900
800
700
600
500
400
300
200
100
0
-100
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

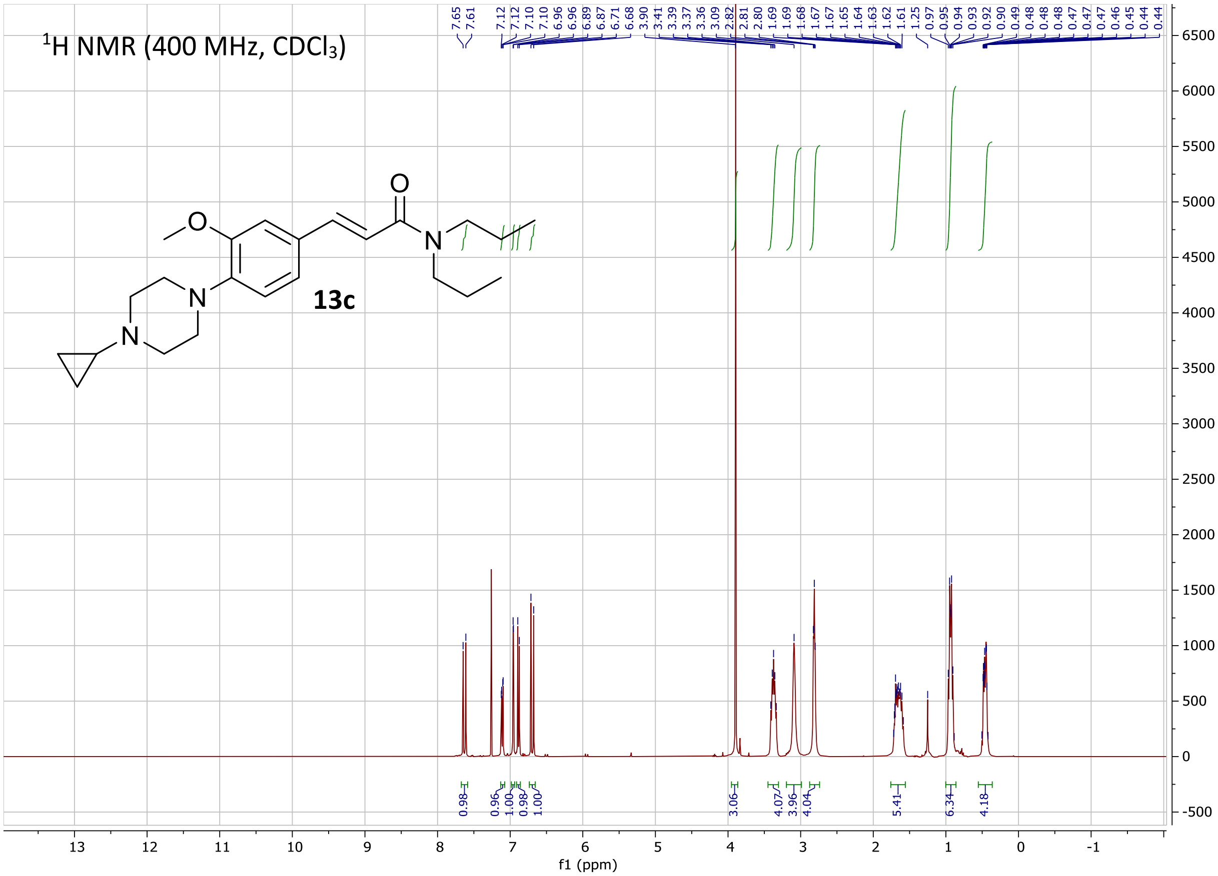
13a



^{1}H NMR (400 MHz, CDCl$_3$)
13b
O
N
O
N
O
7.65
7.62
7.14
7.12
7.12
6.98
6.97
6.89
6.88
6.87
6.73
6.69
3.89
3.89
3.88
3.88
3.87
3.41
3.40
3.38
3.36
3.34
3.12
3.11
3.10
3.09
1.70
1.68
1.66
1.64
1.63
1.61
1.59
0.97
0.95
0.94
0.94
0.92
0.91
0.92
0.93
0.93
0.91
0.95
7.09
4.04
4.00
4.18
6.04
4000
3500
3000
2500
2000
1500
1000
500
0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

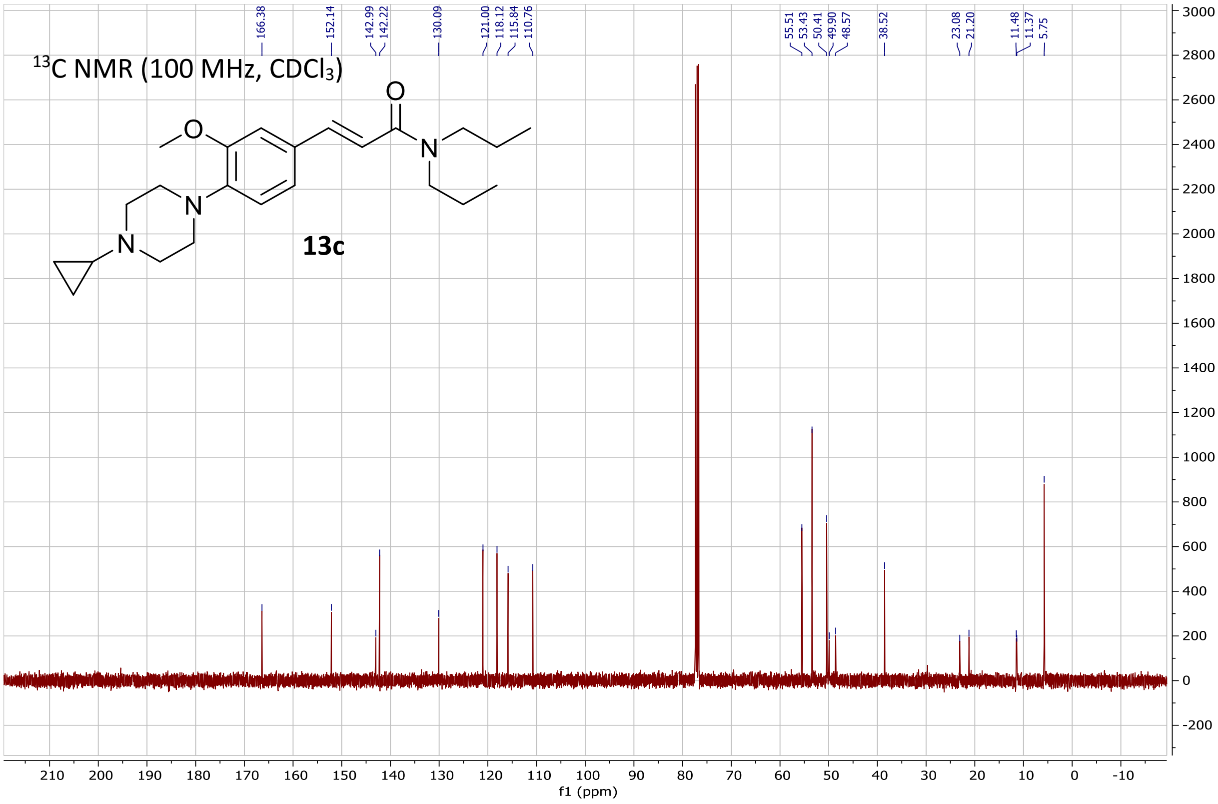


^{13}C NMR (100 MHz, CDCl$_3$)
13b
O
N
O
N
O
166.45
152.24
142.65
142.21
130.54
121.16
118.00
116.23
110.96
67.22
55.64
51.03
50.03
48.70
23.22
21.32
11.61
11.51
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



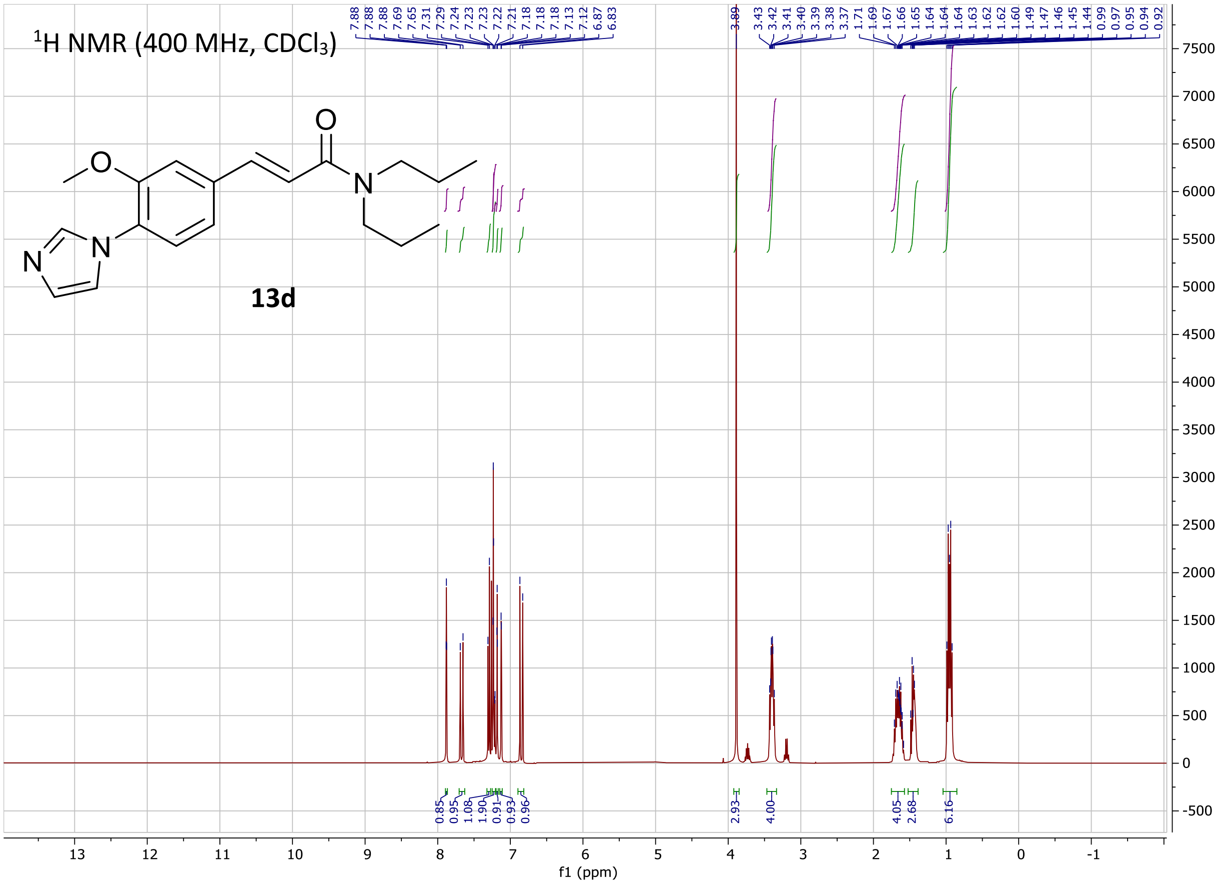
^{1}H NMR (400 MHz, $CDCl_3$)

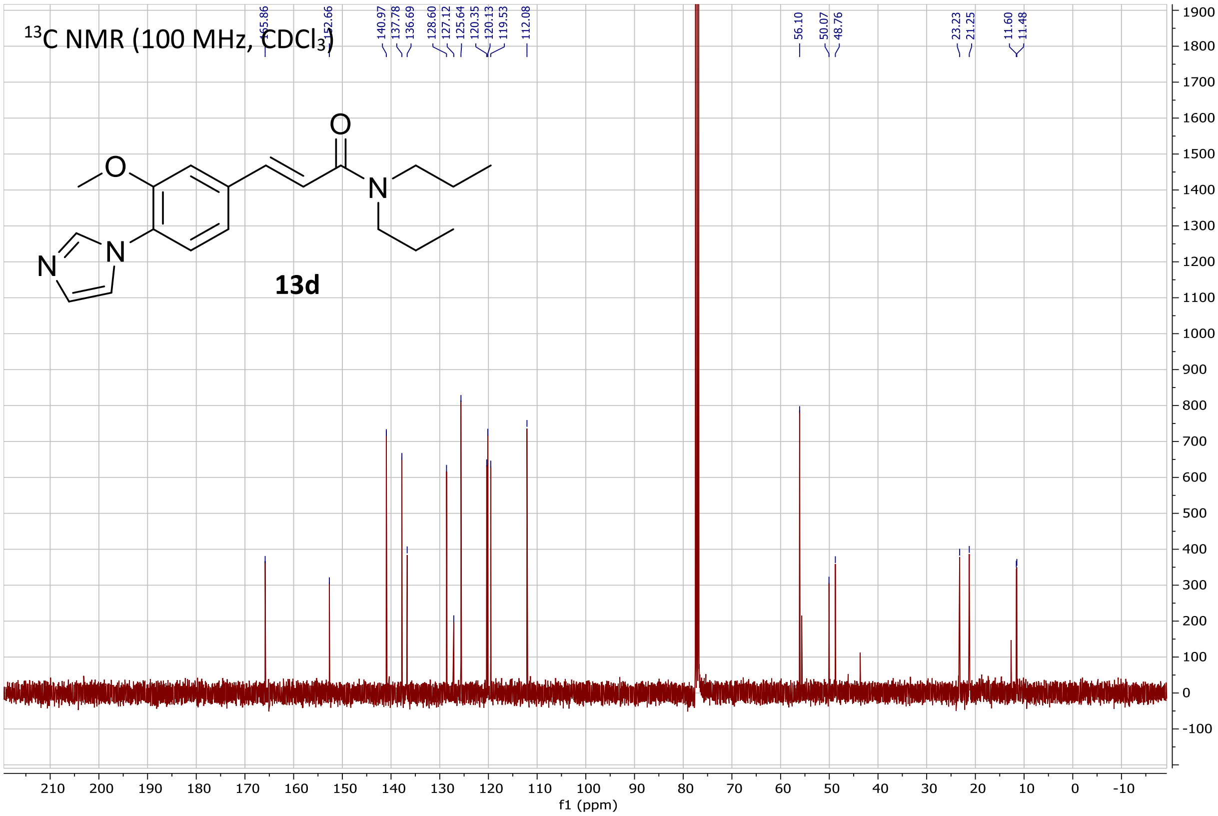
13c

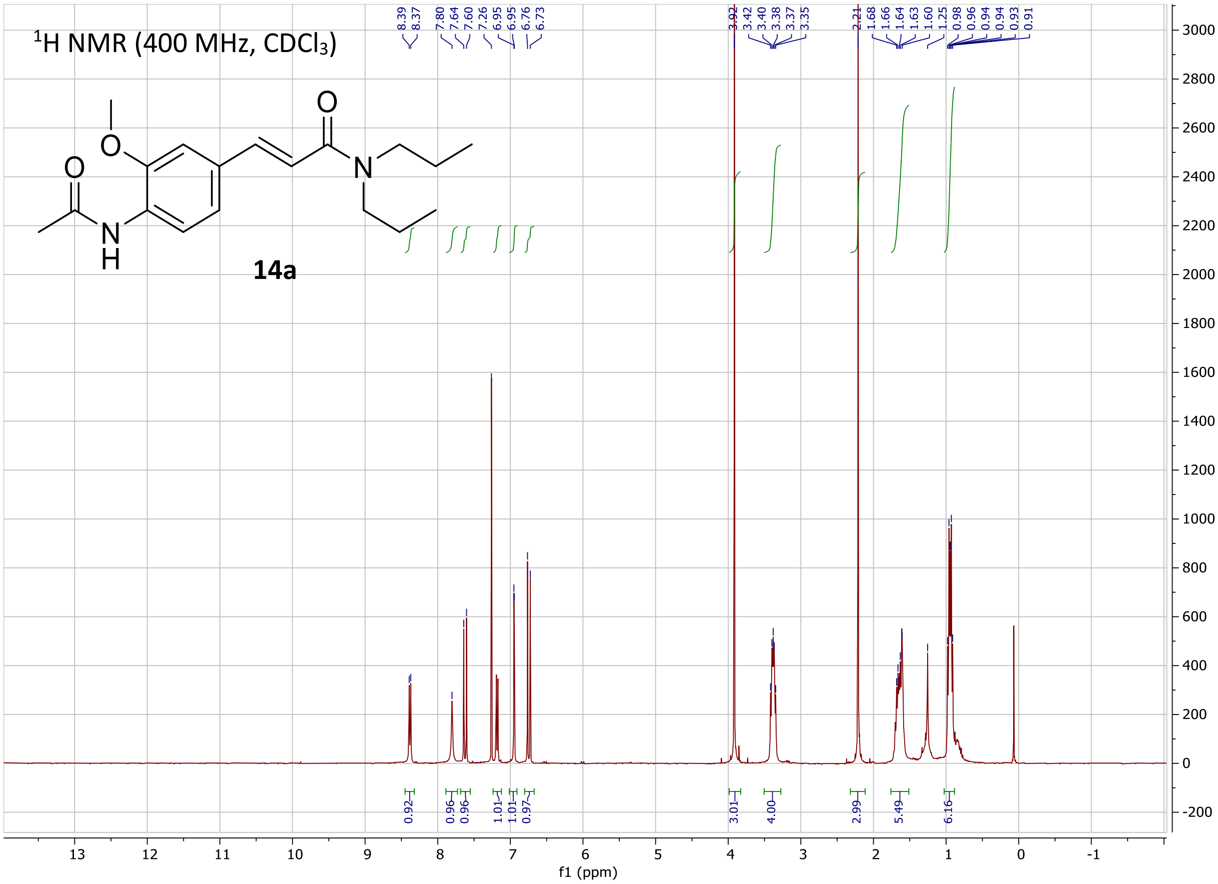


^{13}C NMR (100 MHz, $CDCl_3$)

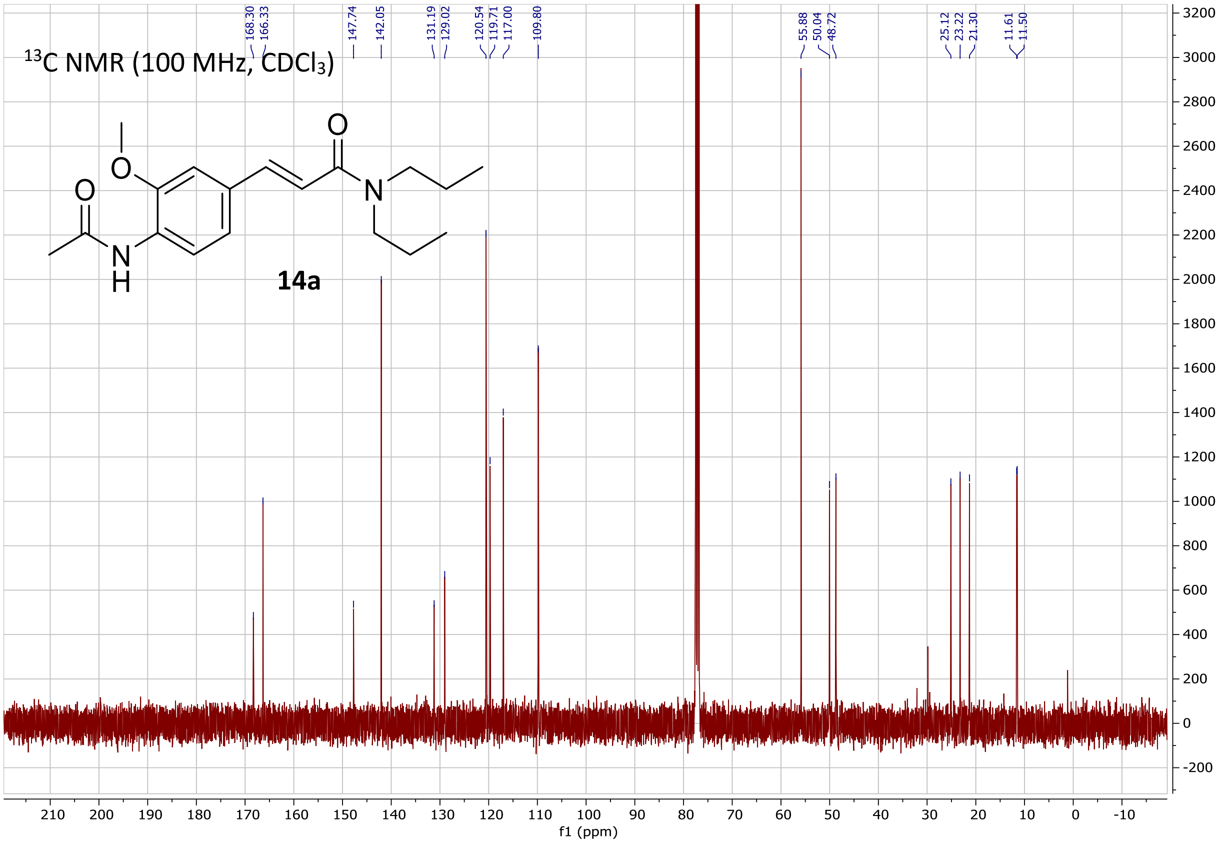
13c

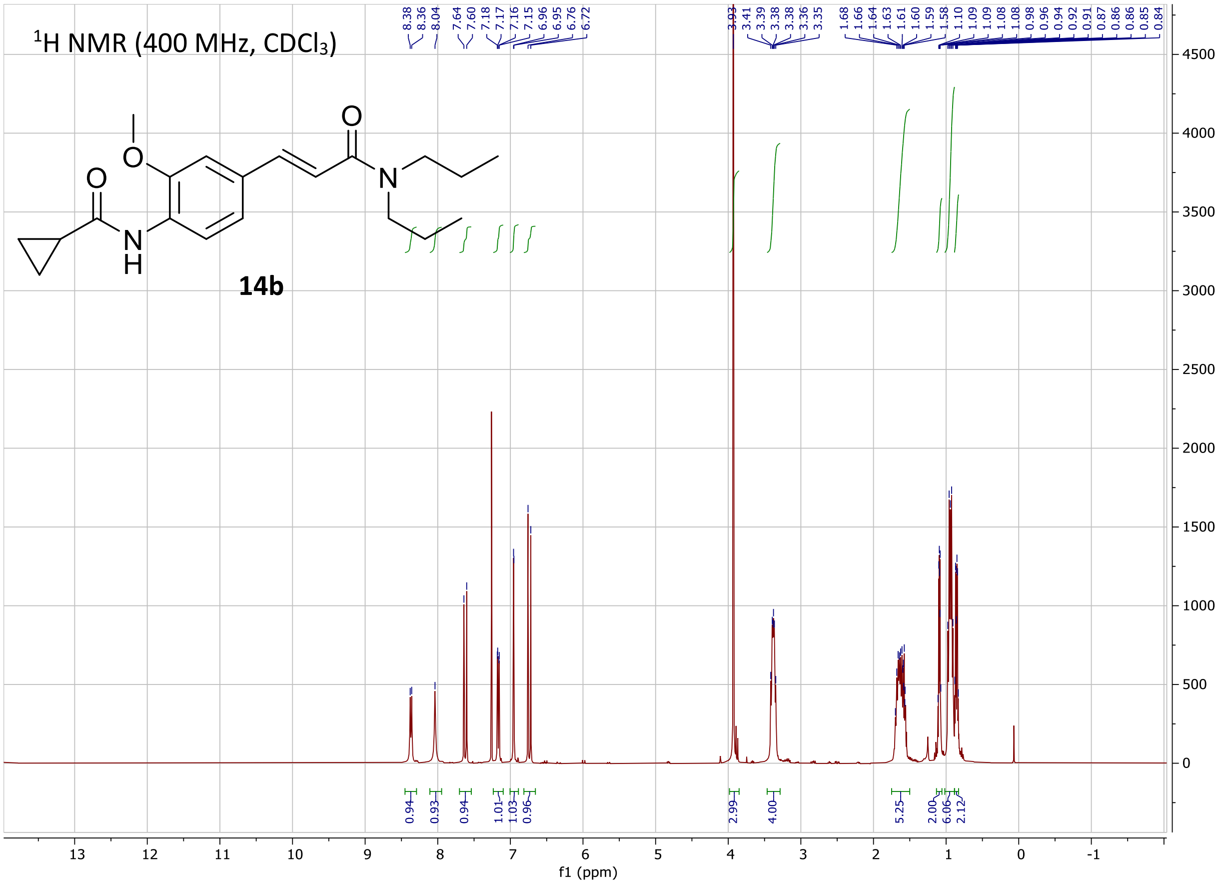

^{1}H NMR (400 MHz, CDCl$_3$)
13d
7.88
7.88
7.88
7.69
7.65
7.31
7.29
7.24
7.23
7.23
7.22
7.21
7.18
7.18
7.13
7.12
6.87
6.83
3.89
3.43
3.42
3.41
3.40
3.39
3.38
3.37
1.71
1.69
1.67
1.66
1.65
1.64
1.64
1.64
1.63
1.62
1.62
1.60
1.49
1.47
1.46
1.45
1.44
0.99
0.97
0.95
0.94
0.92
0.85
0.95
1.08
1.90
0.91
0.93
0.96
2.93
4.00
4.05
2.68
6.16
f1 (ppm)

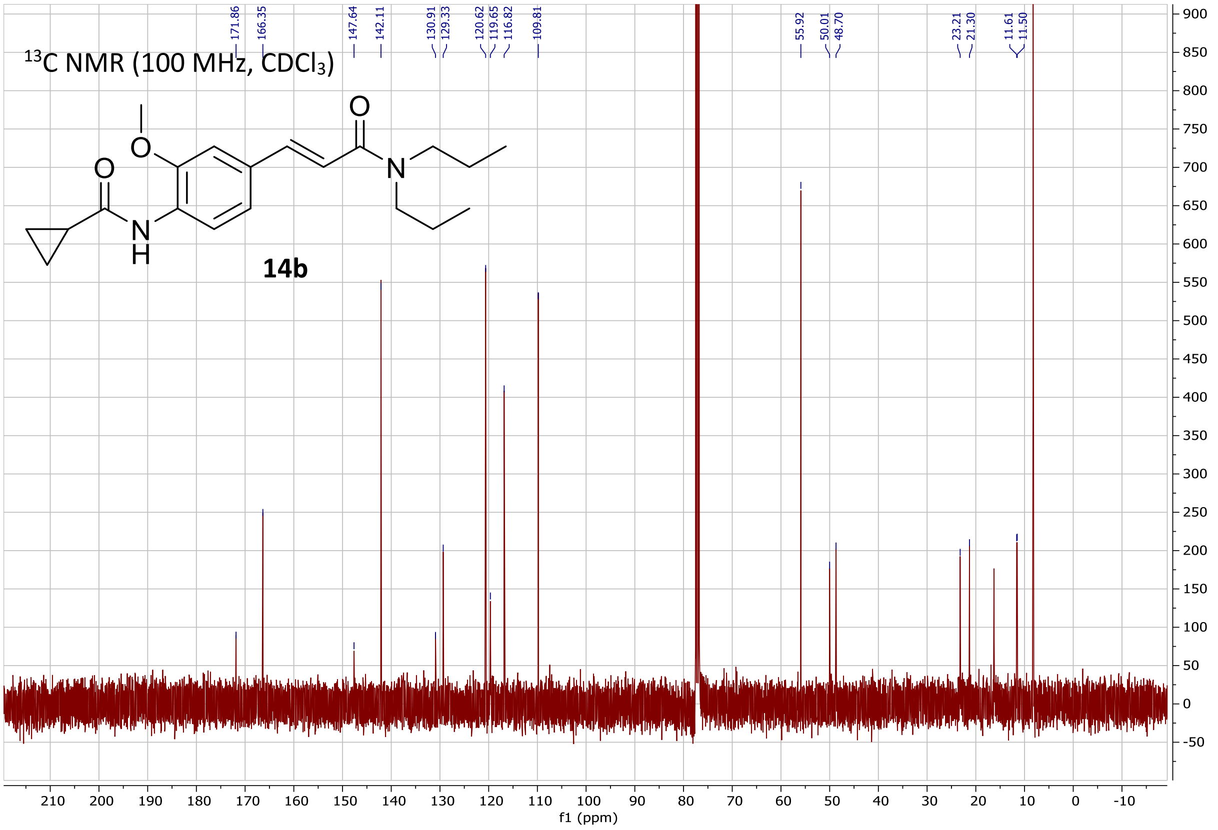

^{13}C NMR (100 MHz, CDCl$_3$)
13d
165.86
152.66
140.97
137.78
136.69
128.60
127.12
125.64
120.35
120.13
119.53
112.08
56.10
50.07
48.76
23.23
21.25
11.60
11.48
f1 (ppm)

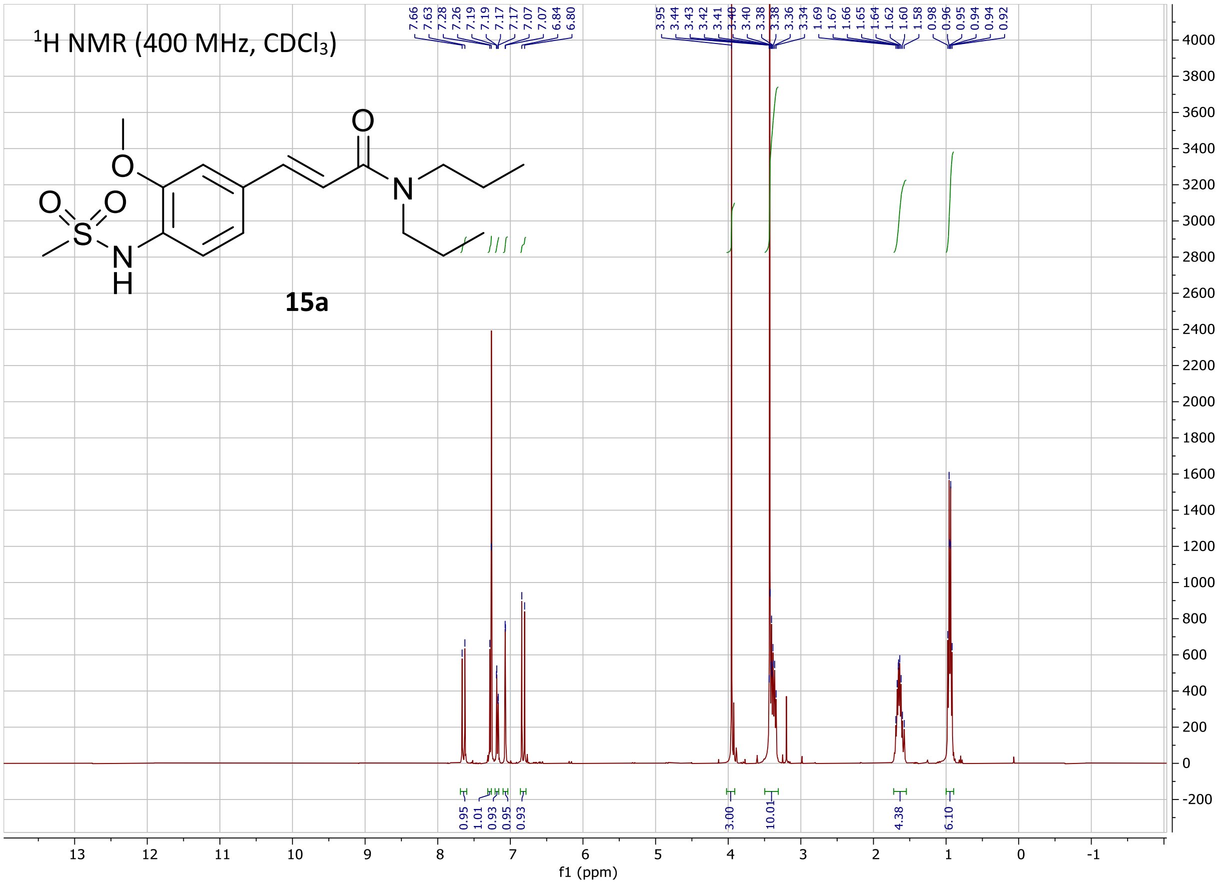

^1H NMR (400 MHz, $CDCl_3$)

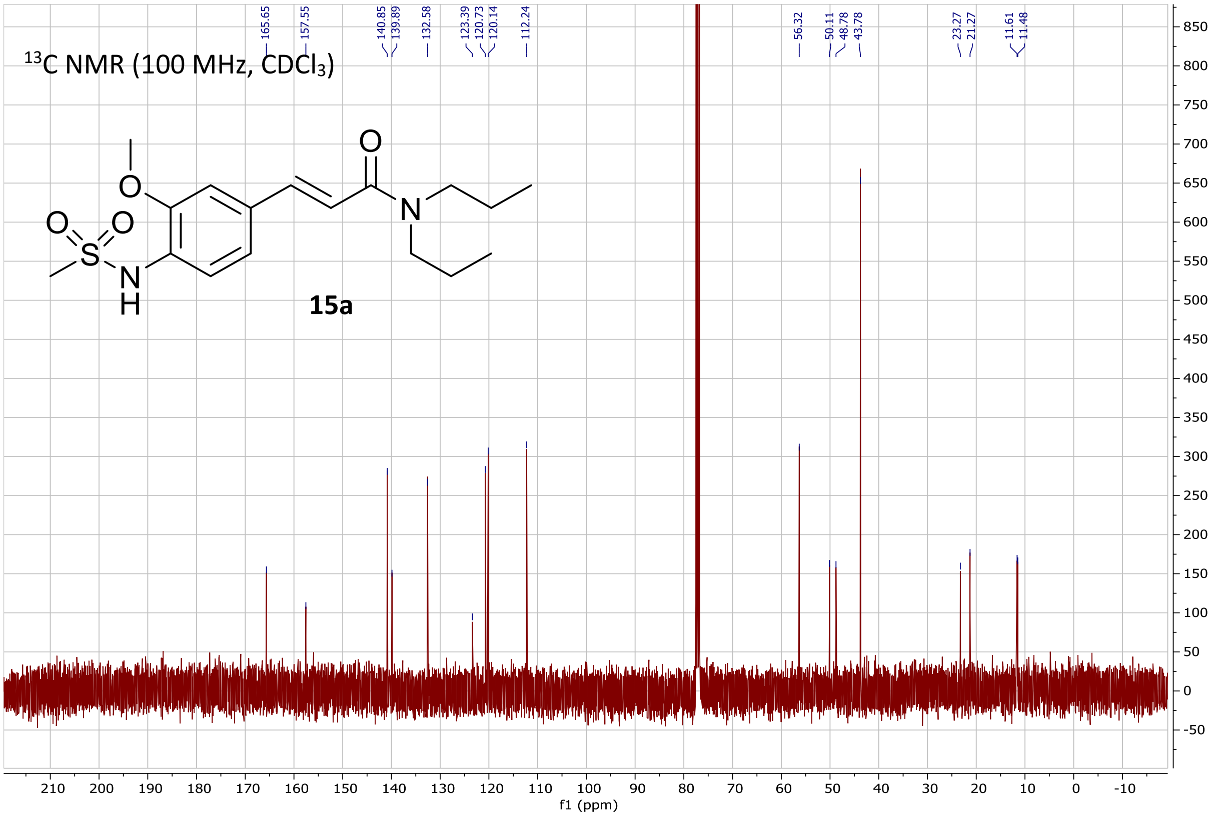
14a


^{13}C NMR (100 MHz, CDCl$_3$)
14a
168.30
166.33
147.74
142.05
131.19
129.02
120.54
119.71
117.00
109.80
55.88
50.04
48.72
25.12
23.22
21.30
11.61
11.50
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

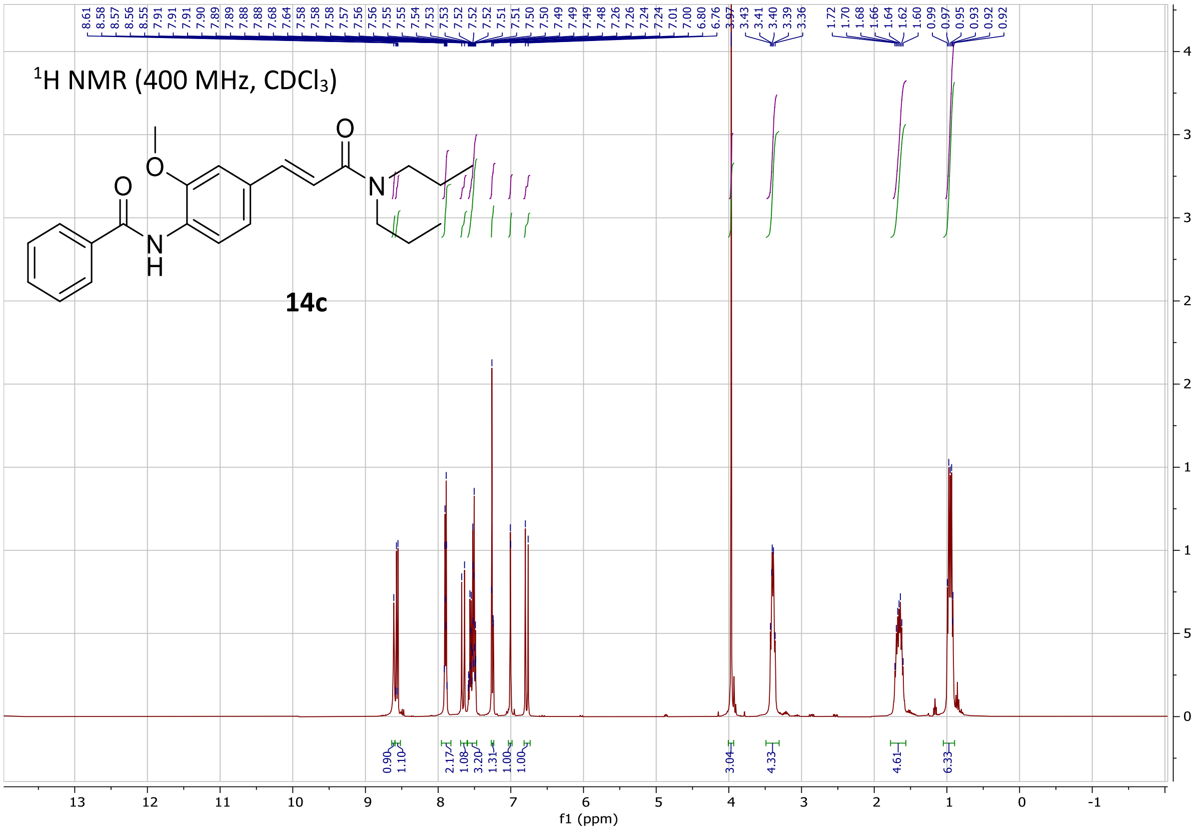

^1H NMR (400 MHz, CDCl$_3$)
14b
8.38
8.36
8.04
7.64
7.60
7.18
7.17
7.16
7.15
6.96
6.95
6.76
6.72
3.93
3.41
3.39
3.38
3.38
3.36
3.35
1.68
1.66
1.64
1.63
1.61
1.60
1.59
1.58
1.10
1.09
1.09
1.08
1.08
1.08
0.98
0.96
0.94
0.92
0.91
0.87
0.86
0.86
0.85
0.84
0.94
0.93
0.94
1.01
1.03
0.96
2.99
4.00
5.25
2.00
6.06
2.12
f1 (ppm)

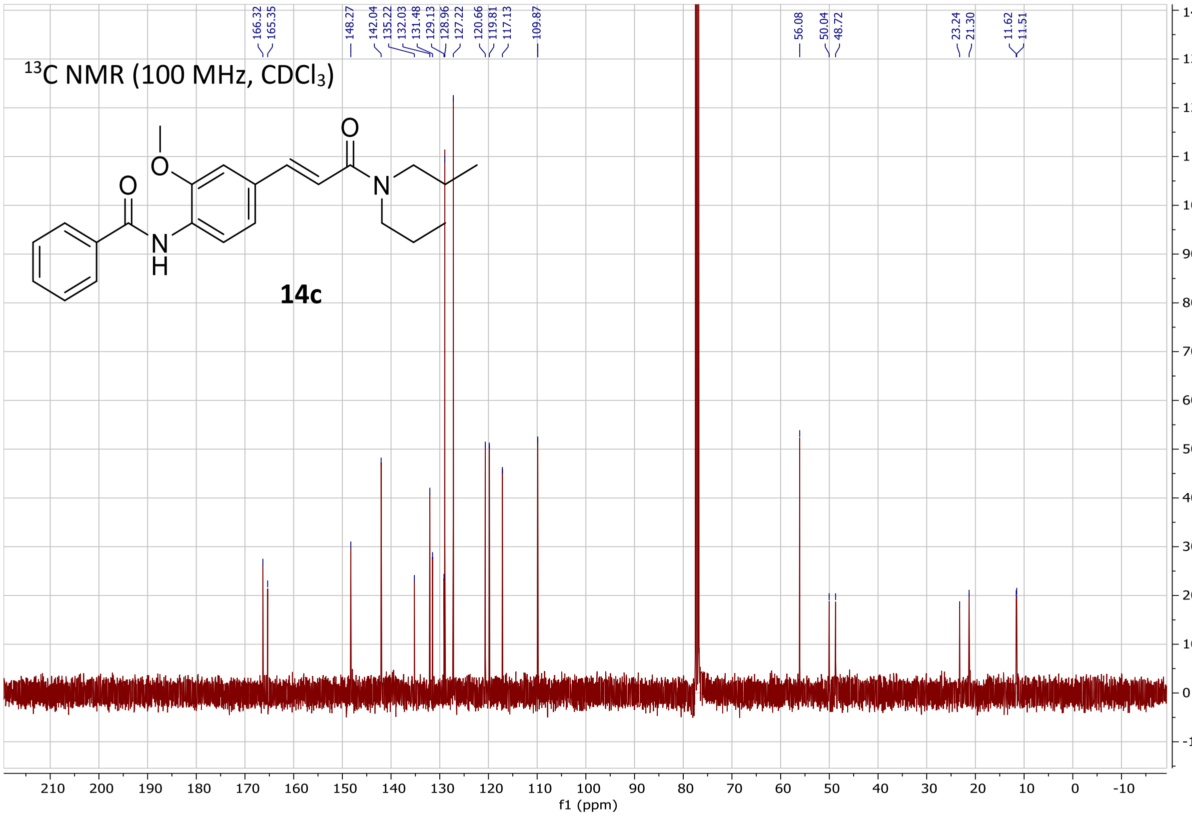

^{13}C NMR (100 MHz, CDCl$_3$)
14b
171.86
166.35
147.64
142.11
130.91
129.33
120.62
119.65
116.82
109.81
55.92
50.01
48.70
23.21
21.30
11.61
11.50
f1 (ppm)

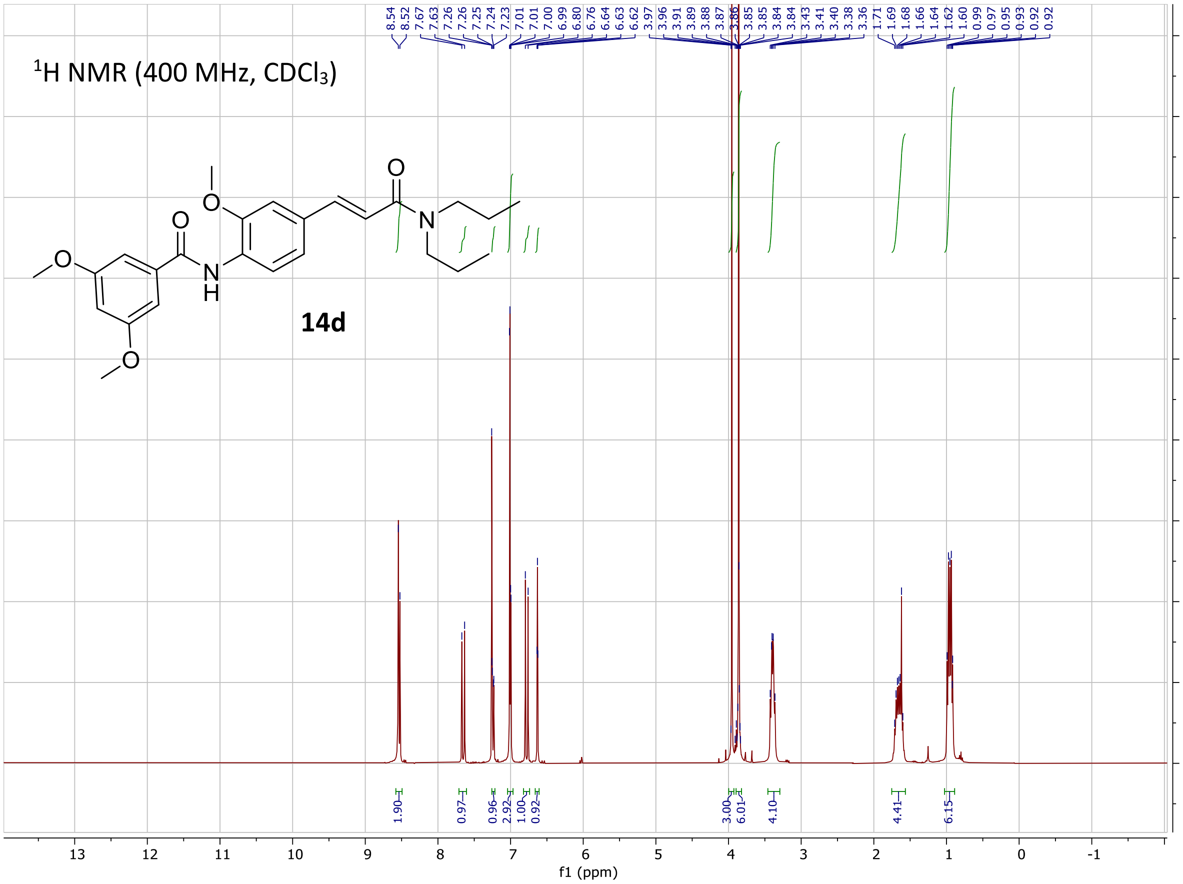

^{1}H NMR (400 MHz, CDCl$_3$)
15a
7.66, 7.63, 7.28, 7.26, 7.19, 7.17, 7.17, 7.07, 7.07, 6.84, 6.80
3.95, 3.44, 3.43, 3.42, 3.41, 3.40, 3.40, 3.38, 3.38, 3.36, 3.34, 1.69, 1.67, 1.66, 1.65, 1.64, 1.62, 1.60, 1.58, 0.98, 0.96, 0.95, 0.94, 0.94, 0.92
0.95, 1.01, 0.93, 0.95, 0.93, 3.00, 10.01, 4.38, 6.10
f1 (ppm)

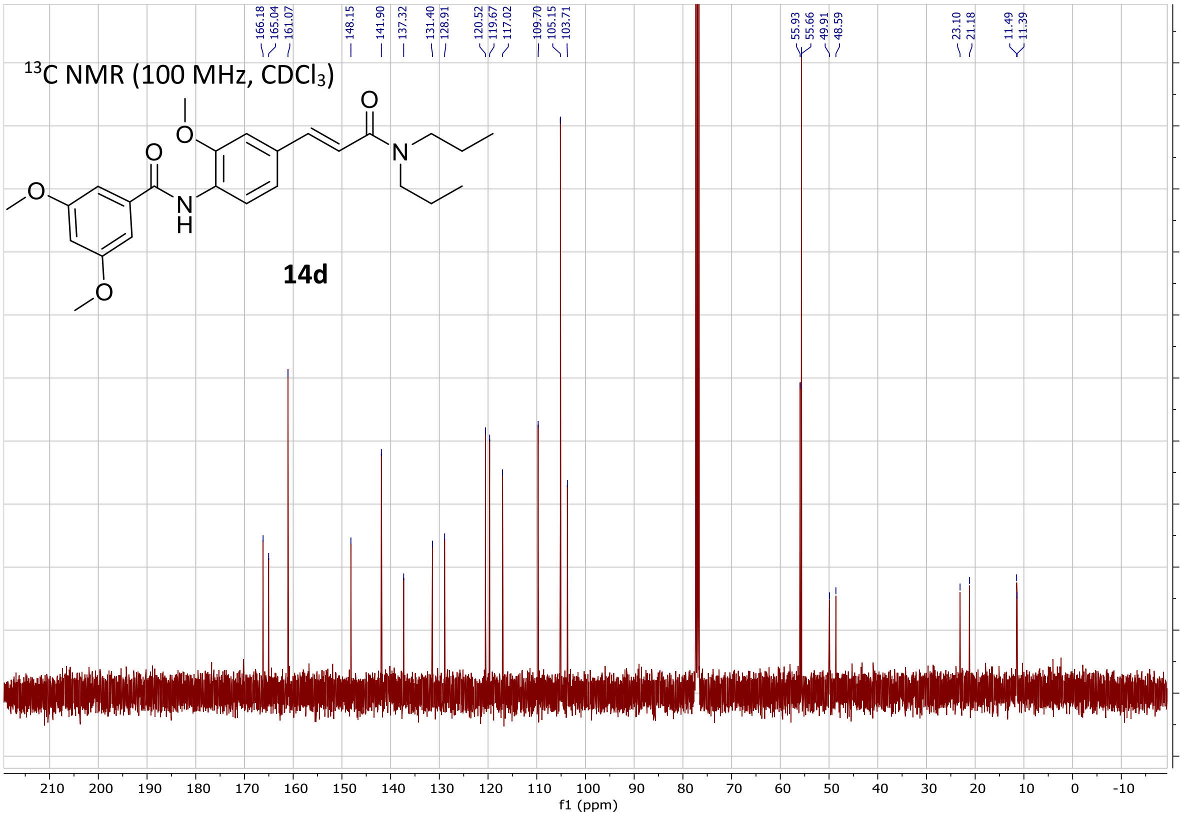

^{13}C NMR (100 MHz, CDCl$_3$)
15a
165.65, 157.55, 140.85, 139.89, 132.58, 123.39, 120.73, 120.14, 112.24
56.32, 50.11, 48.78, 43.78, 23.27, 21.27, 11.61, 11.48
f1 (ppm)

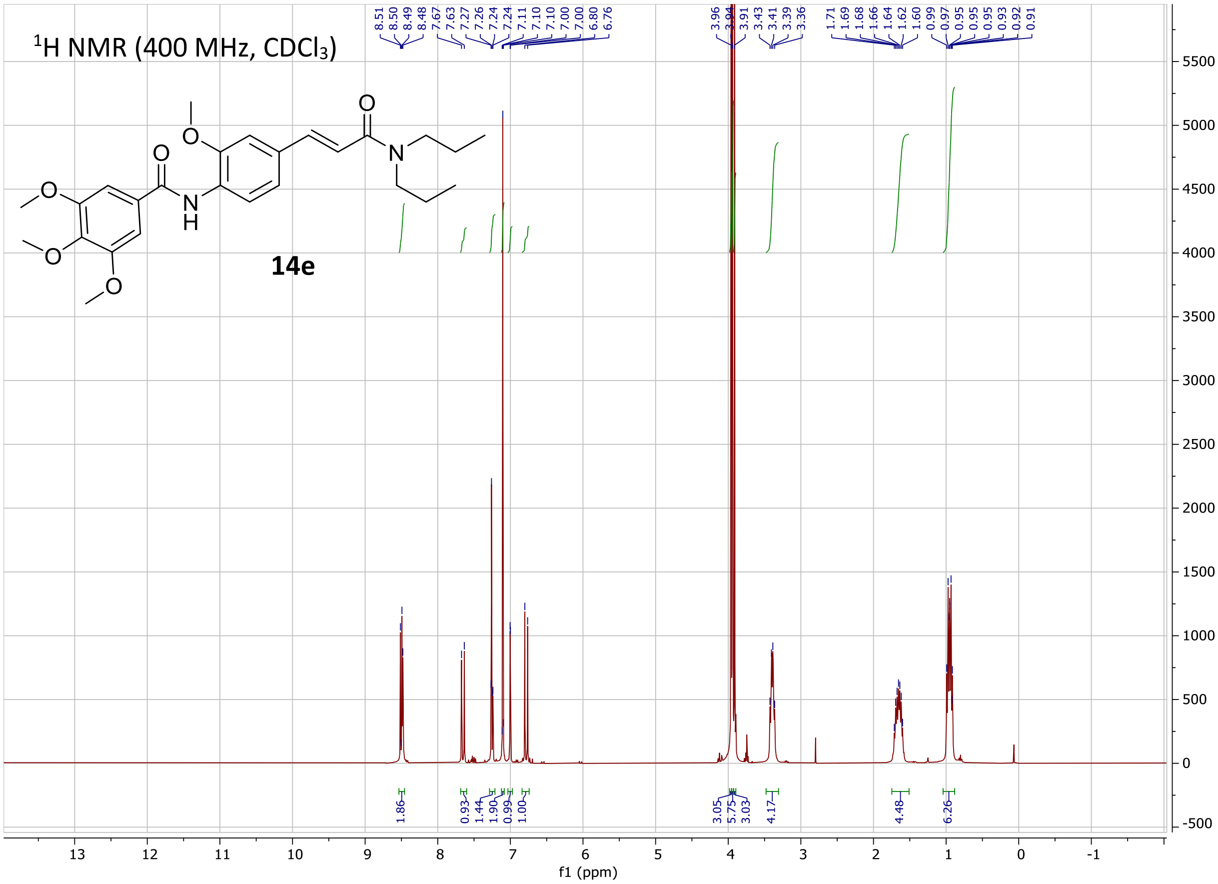
4.3 Series 3 compounds.



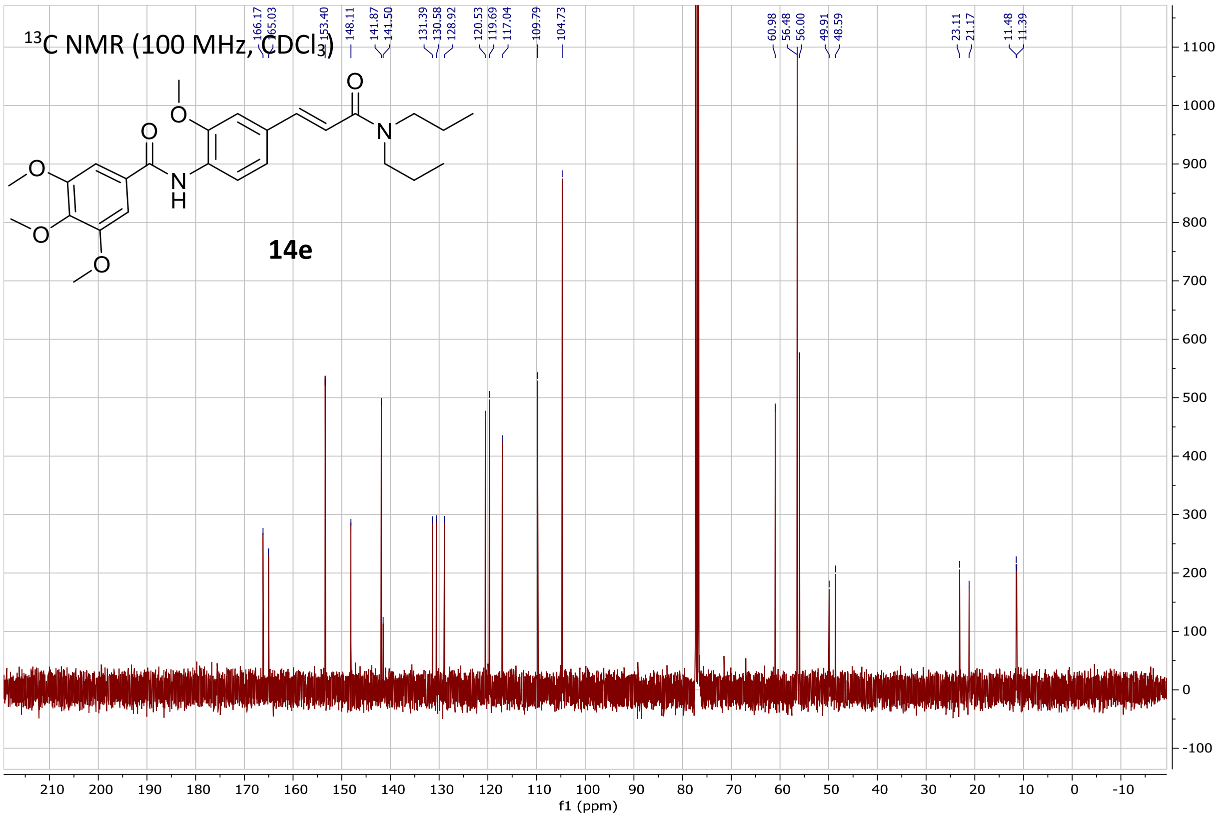



^{1}H NMR (400 MHz, CDCl$_3$)
14d
8.54
8.52
7.67
7.63
7.26
7.26
7.25
7.24
7.23
7.01
7.01
7.00
6.99
6.80
6.76
6.64
6.63
6.62
3.97
3.96
3.91
3.89
3.88
3.87
3.86
3.85
3.85
3.84
3.84
3.43
3.41
3.40
3.38
3.36
1.71
1.69
1.68
1.66
1.64
1.62
1.60
0.99
0.97
0.95
0.93
0.92
0.92
1.90
0.97
0.96
2.92
1.00
0.92
3.00
6.01
4.10
4.41
6.15
f1 (ppm)

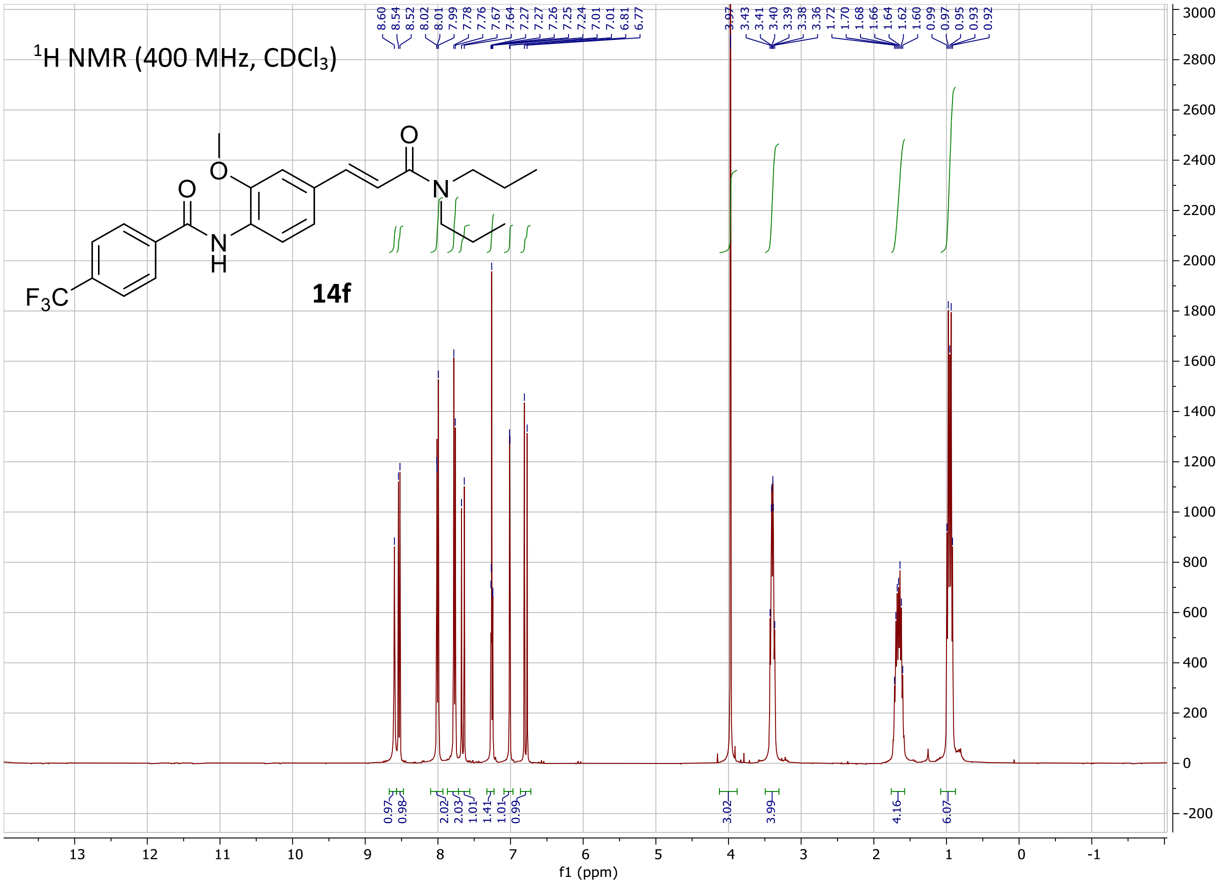

^{13}C NMR (100 MHz, CDCl$_3$)
14d
166.18
165.04
161.07
148.15
141.90
137.32
131.40
128.91
120.52
119.67
117.02
109.70
105.15
103.71
55.93
55.66
49.91
48.59
23.10
21.18
11.49
11.39
f1 (ppm)



^{1}H NMR (400 MHz, CDCl$_3$)
14e
8.51 8.50 8.49 8.48 7.67 7.63 7.27 7.26 7.24 7.24 7.11 7.10 7.10 7.00 7.00 6.80 6.76
3.96 3.94 3.91 3.43 3.41 3.39 3.36
1.71 1.69 1.68 1.66 1.64 1.62 1.60 0.99 0.97 0.95 0.95 0.95 0.93 0.92 0.91
1.86 0.93 1.44 1.90 0.99 1.00 3.05 5.75 3.03 4.17 4.48 6.26
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)
5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0 -500

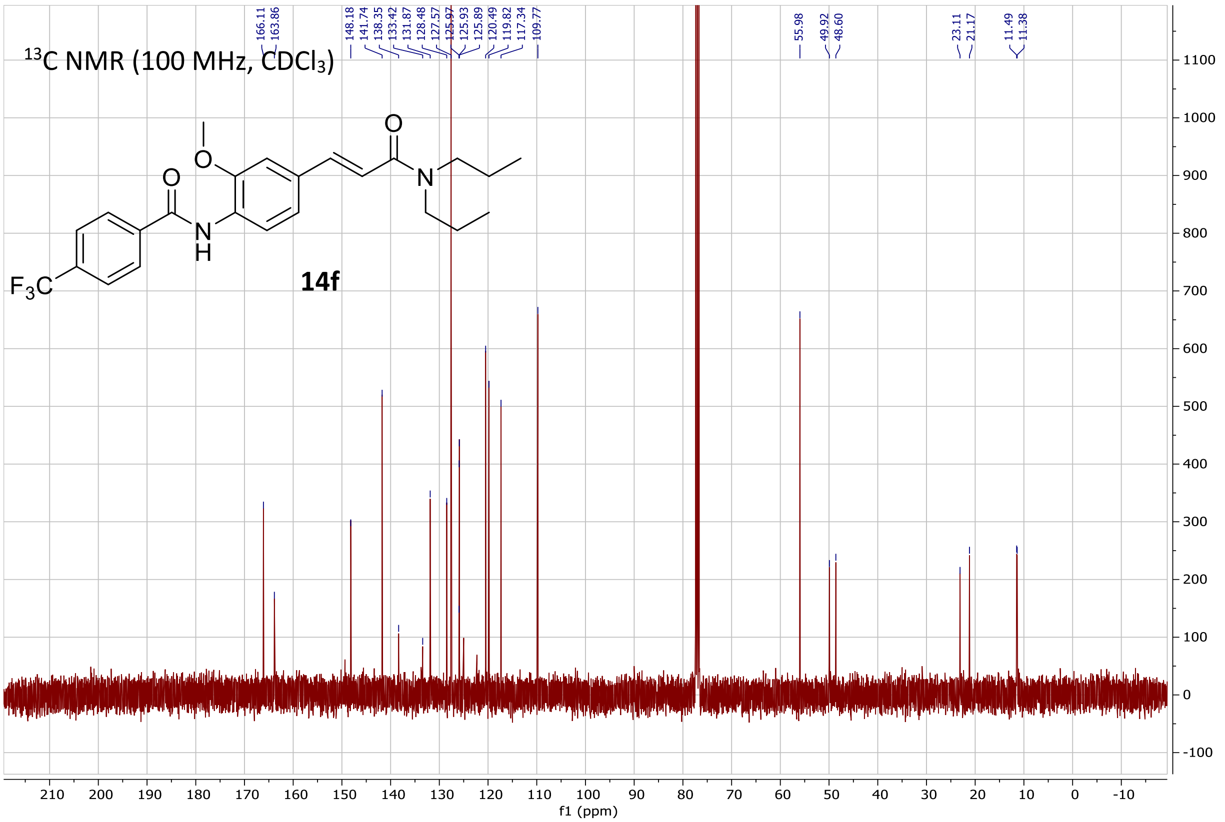


^{13}C NMR (100 MHz, CDCl$_3$)
14e
166.17 165.03 153.40 148.11 141.87 141.50 131.39 130.58 128.92 120.53 119.69 117.04 109.79 104.73
60.98 56.48 56.00 49.91 48.59 23.11 21.17 11.48 11.39
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
1100 1000 900 800 700 600 500 400 300 200 100 0 -100



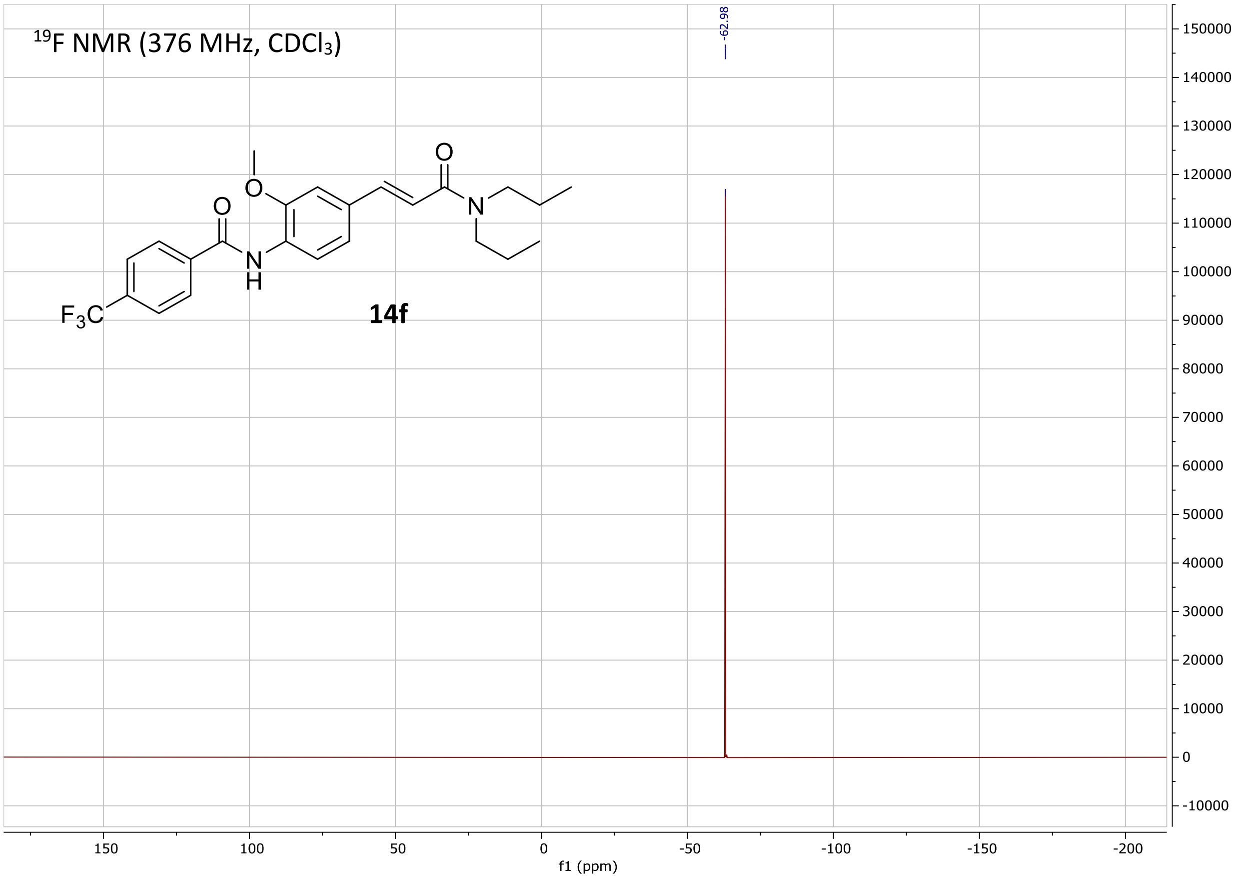
^{1}H NMR (400 MHz, $CDCl_3$)

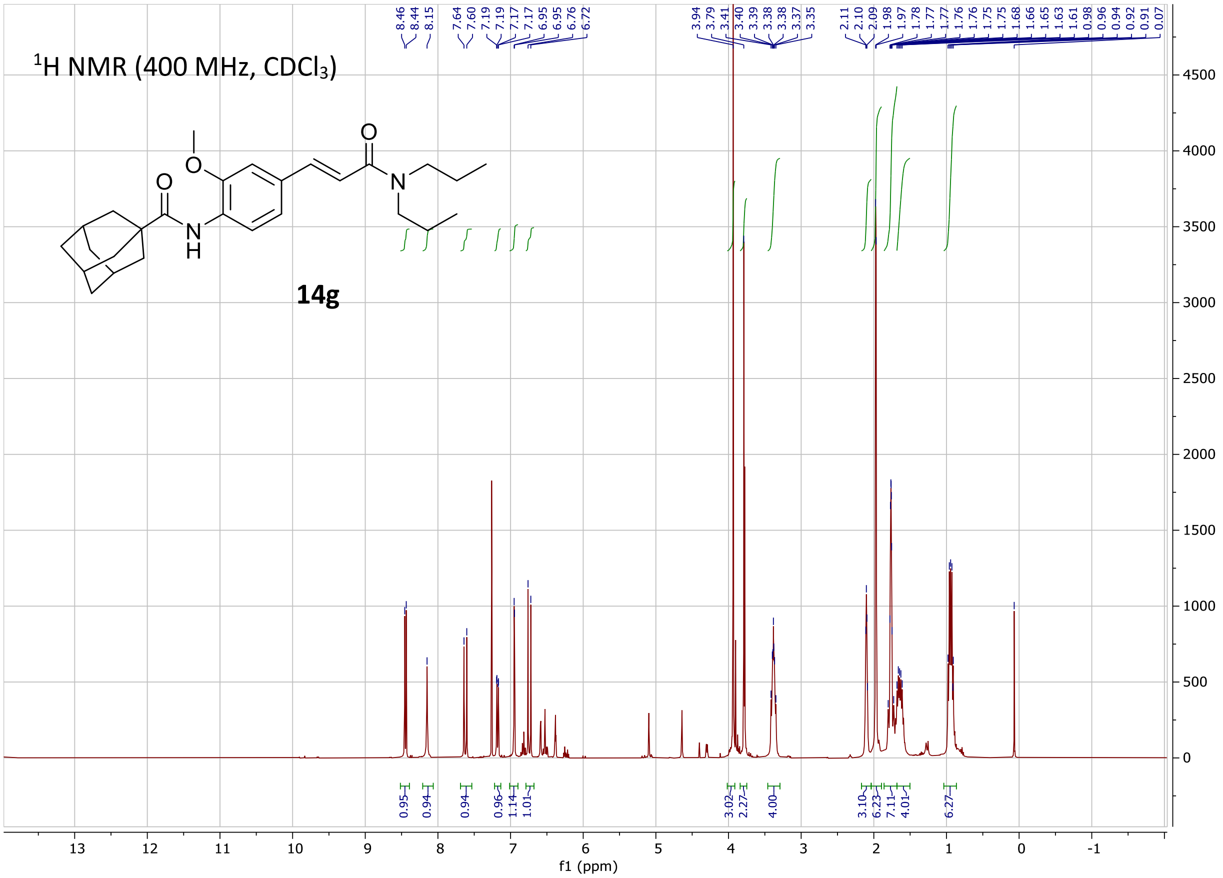
14f



^{13}C NMR (100 MHz, $CDCl_3$)

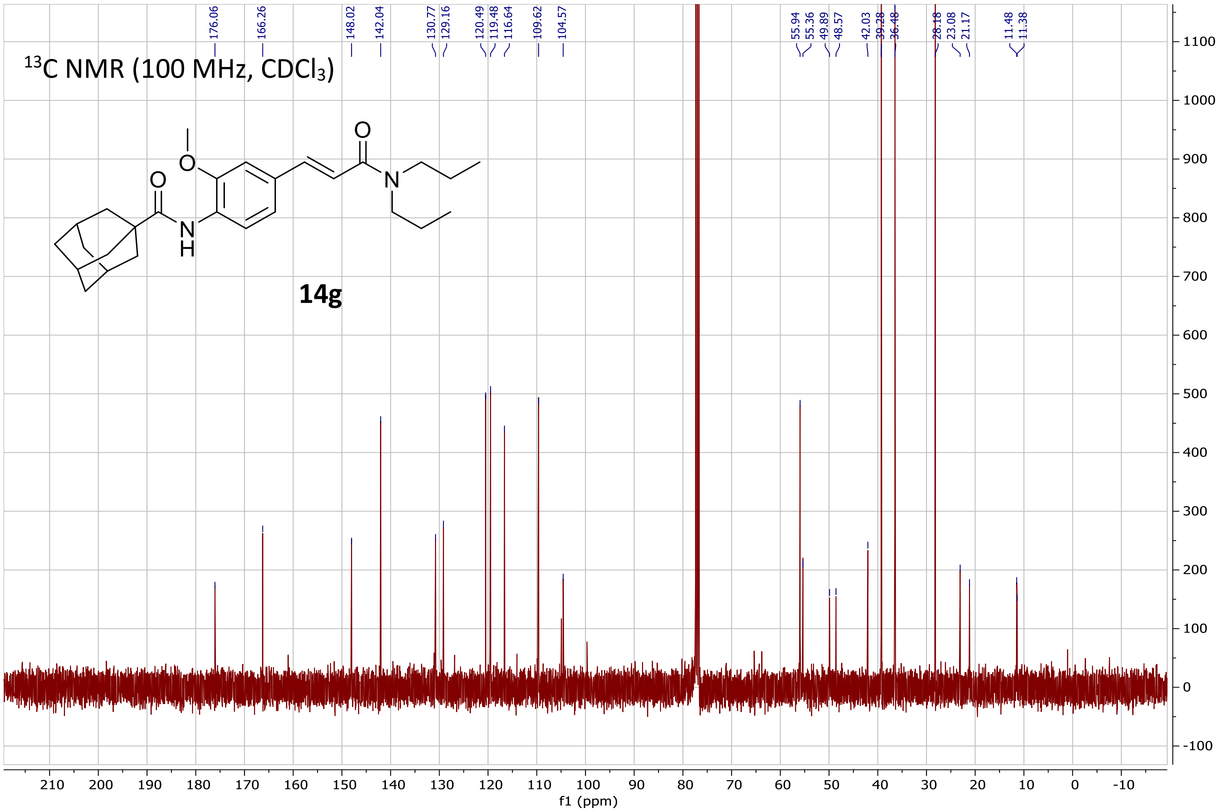
14f


^{19}F NMR (376 MHz, CDCl$_3$)
-62.98
F$_3$C
O
N
H
O
O
N
14f
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
150
100
50
0
-50
-100
-150
-200
f1 (ppm)



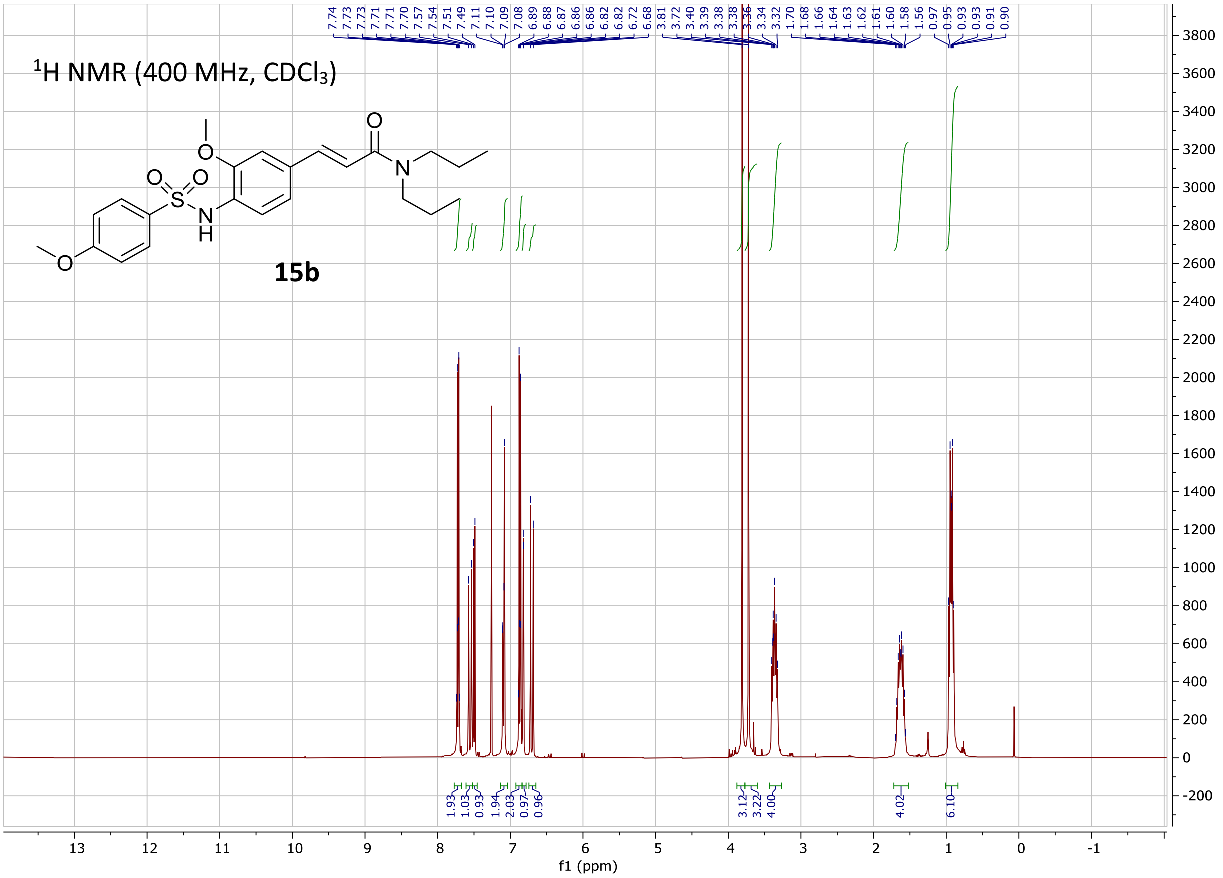
^{1}H NMR (400 MHz, $CDCl_3$)

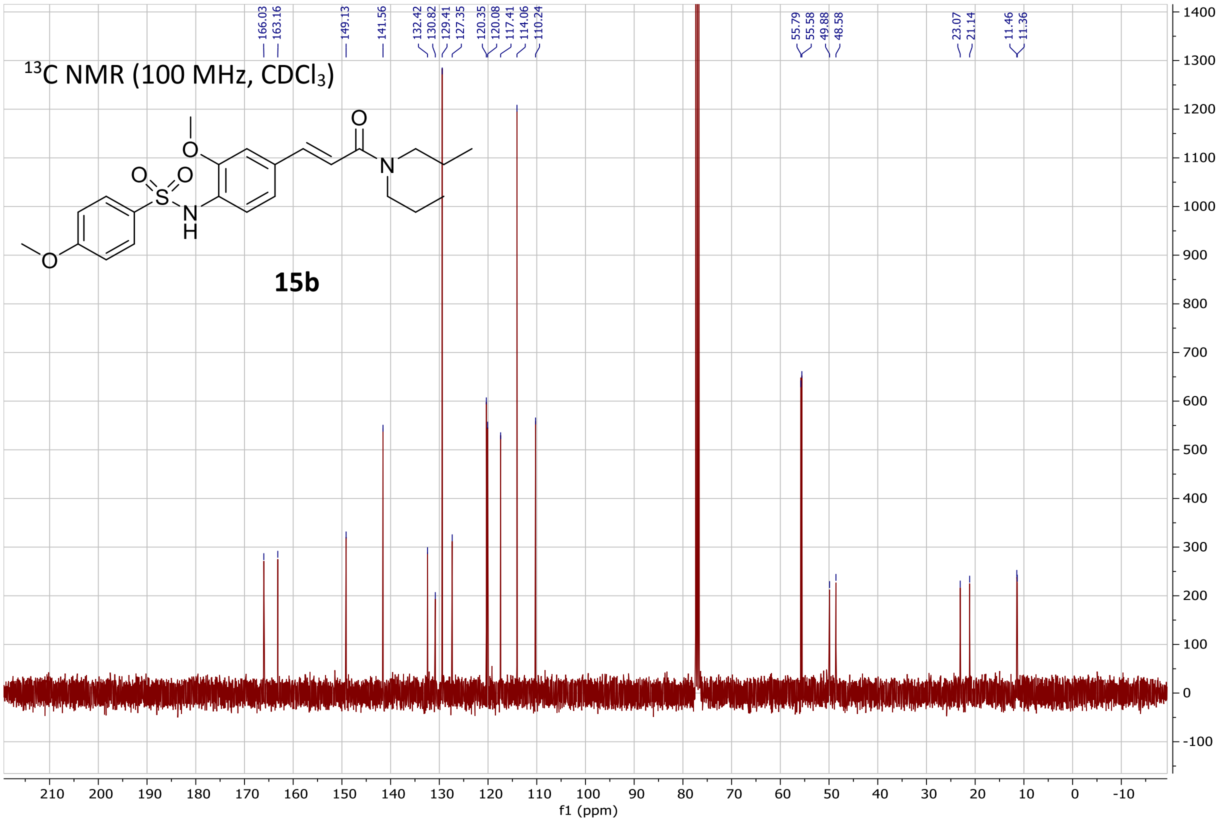
14g

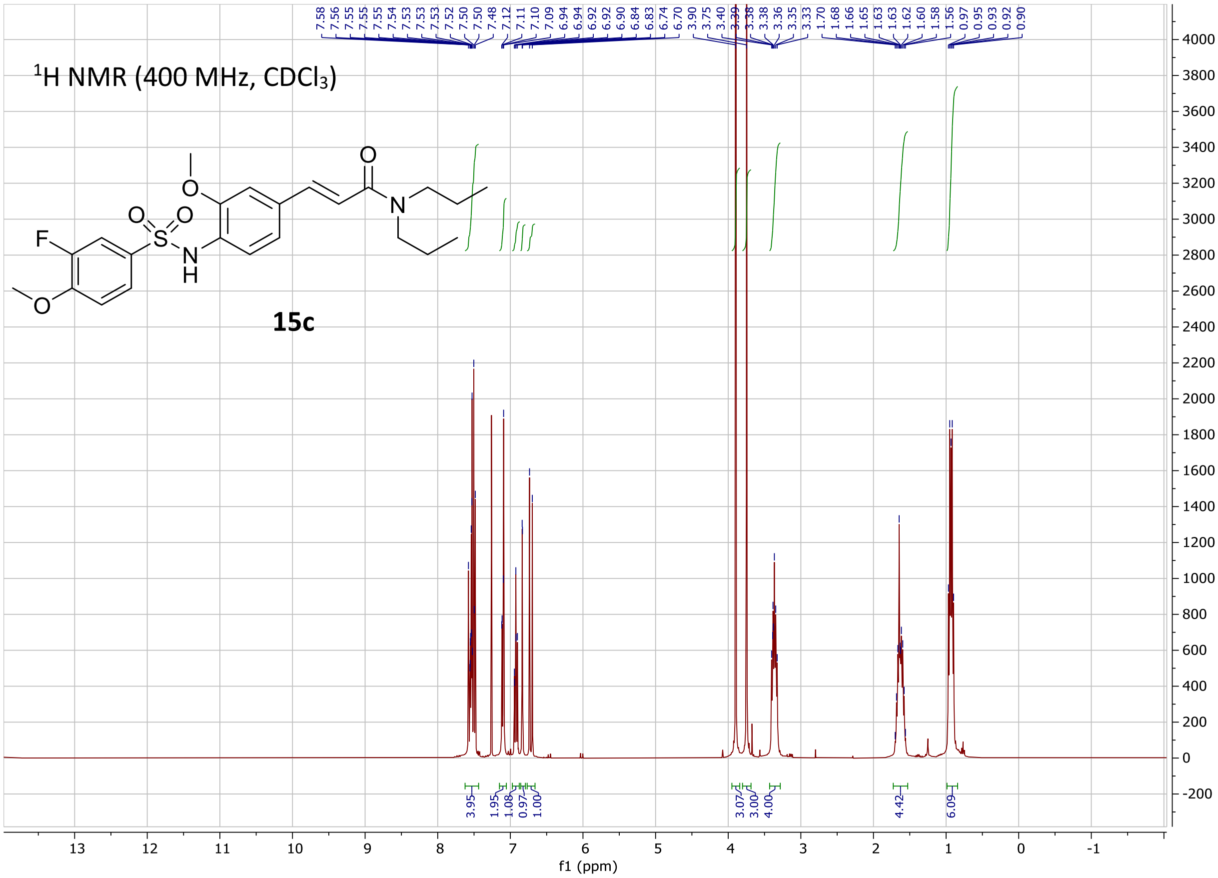


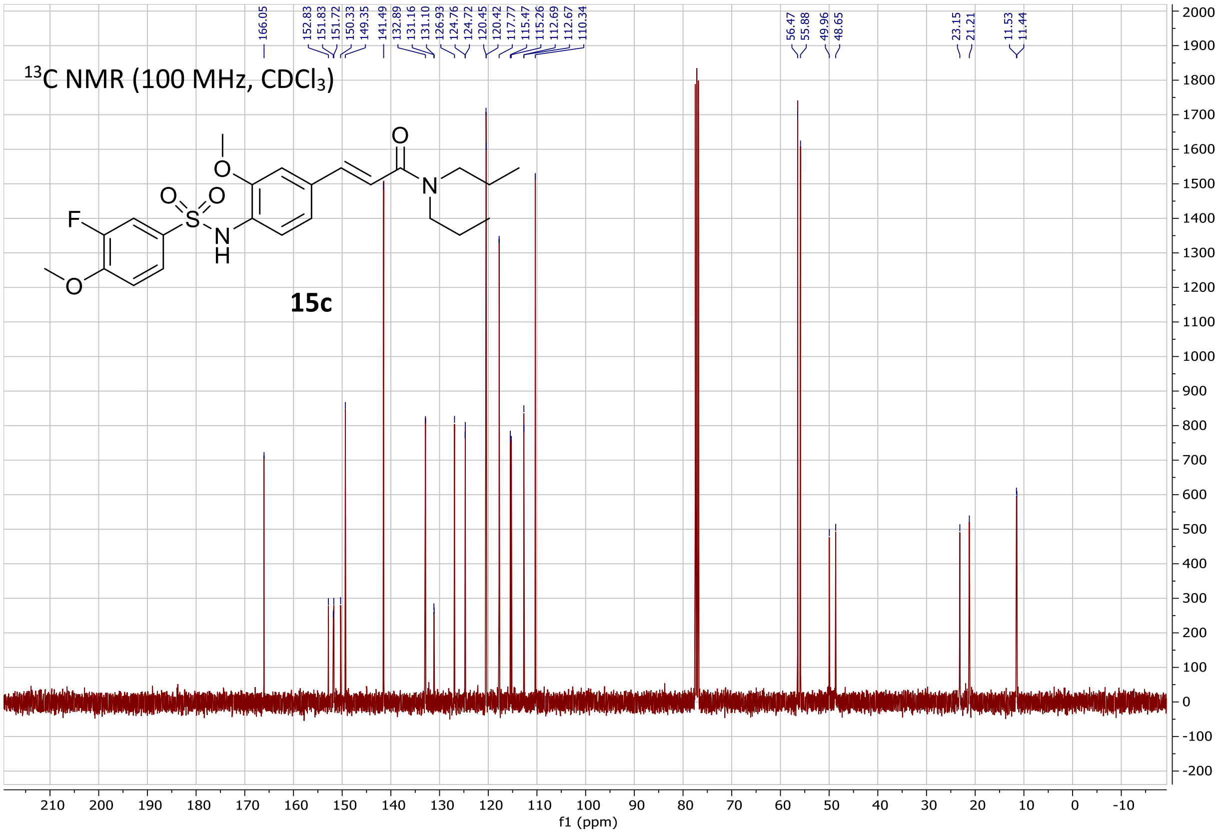
^{13}C NMR (100 MHz, $CDCl_3$)

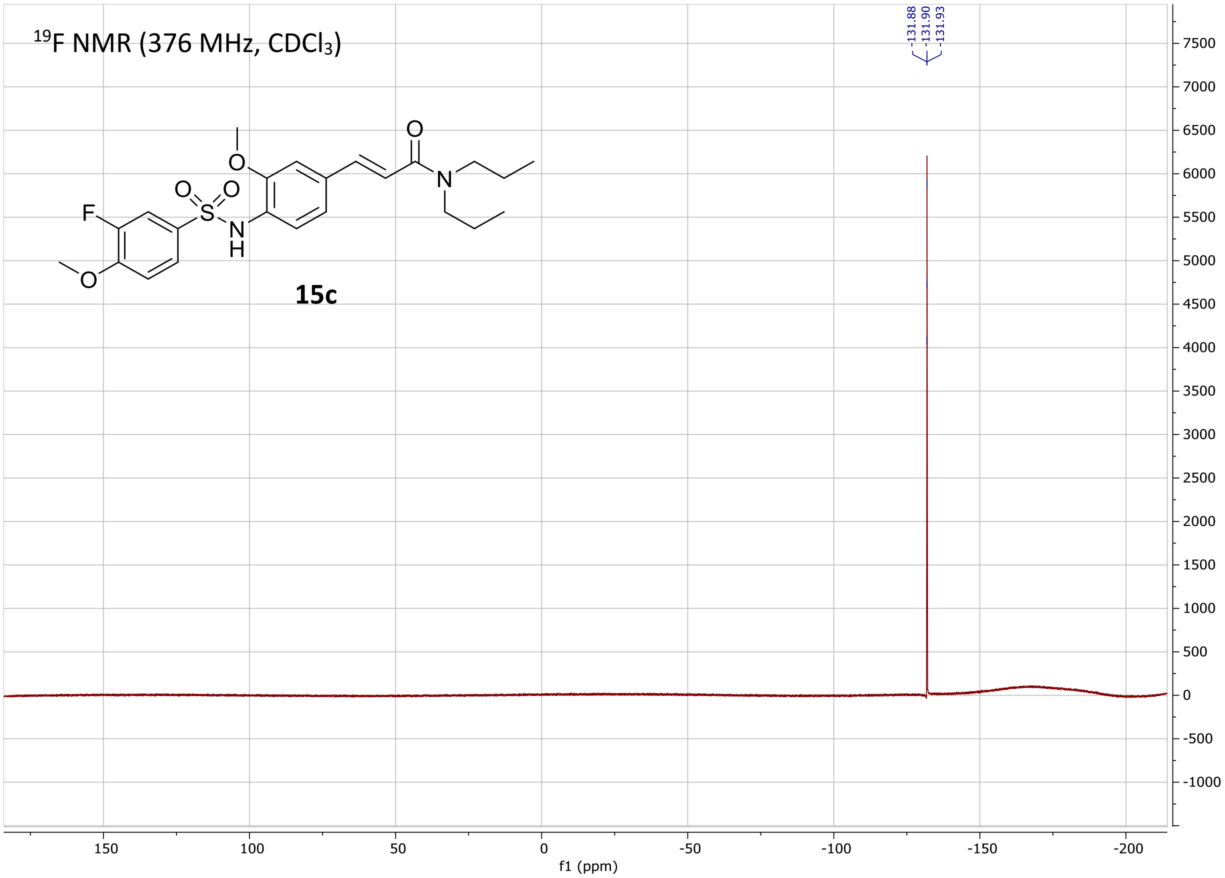
14g


^{1}H NMR (400 MHz, CDCl$_3$)
15b
7.74
7.73
7.73
7.71
7.71
7.70
7.57
7.54
7.51
7.49
7.11
7.10
7.09
7.08
6.89
6.88
6.87
6.86
6.86
6.82
6.82
6.72
6.68
3.81
3.72
3.40
3.39
3.38
3.38
3.36
3.34
3.32
1.70
1.68
1.66
1.64
1.63
1.62
1.61
1.60
1.58
1.56
0.97
0.95
0.93
0.93
0.91
0.90
1.93
1.03
0.93
1.94
2.03
0.97
0.96
3.12
3.22
4.00
4.02
6.10
f1 (ppm)


^{13}C NMR (100 MHz, CDCl$_3$)
15b
166.03
163.16
149.13
141.56
132.42
130.82
129.41
127.35
120.35
120.08
117.41
114.06
110.24
55.79
55.58
49.88
48.58
23.07
21.14
11.46
11.36
f1 (ppm)

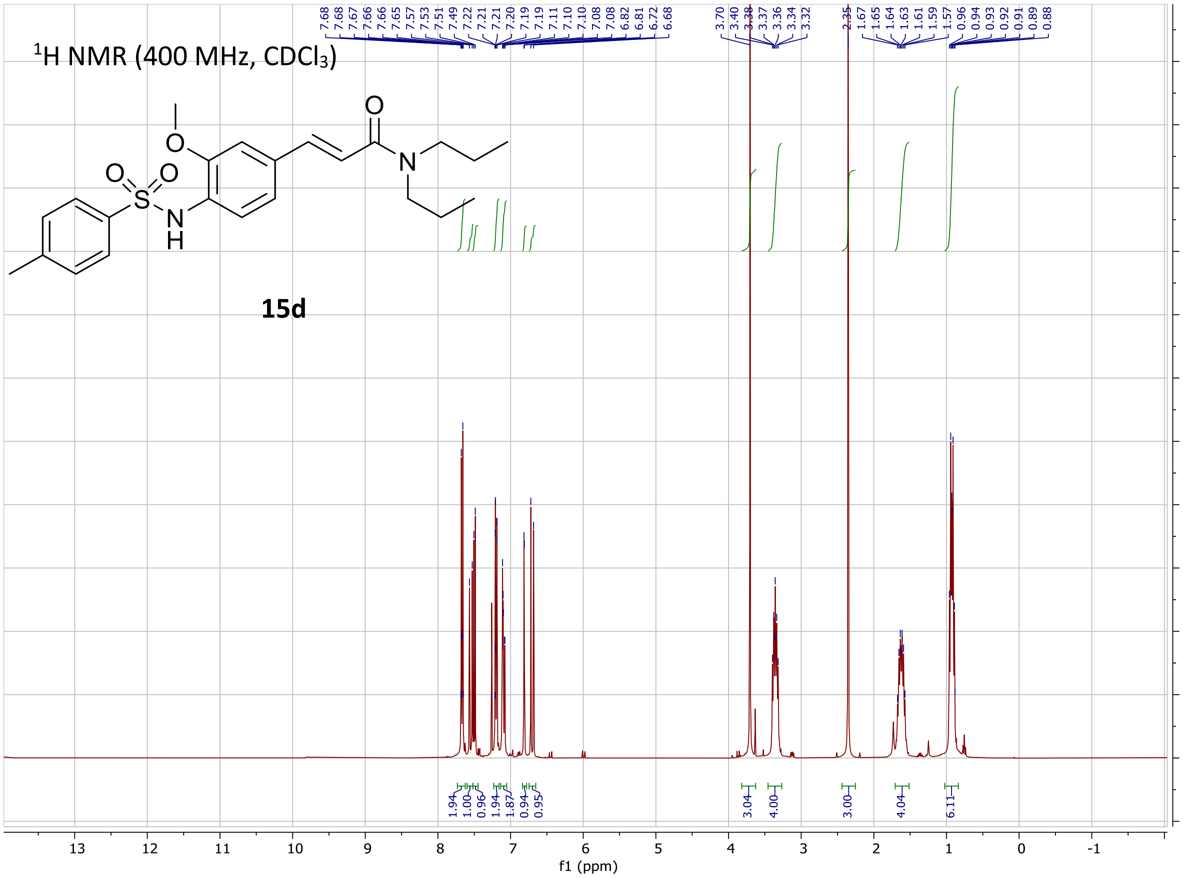

^{1}H NMR (400 MHz, CDCl$_3$)
15c
O
O
S
O
F
N
H
O
O
N
7.58 7.56 7.55 7.55 7.54 7.53 7.53 7.53 7.52 7.50 7.50 7.48 7.12 7.11 7.10 7.09 6.94 6.94 6.92 6.92 6.90 6.84 6.83 6.74 6.70 3.90 3.75 3.40 3.39 3.38 3.38 3.36 3.35 3.33 1.70 1.68 1.66 1.65 1.63 1.63 1.62 1.60 1.58 1.56 0.97 0.95 0.93 0.92 0.90
3.95 1.95 1.08 0.97 1.00 3.07 3.00 4.00 4.42 6.09
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)
4000 3800 3600 3400 3200 3000 2800 2600 2400 2200 2000 1800 1600 1400 1200 1000 800 600 400 200 0 -200

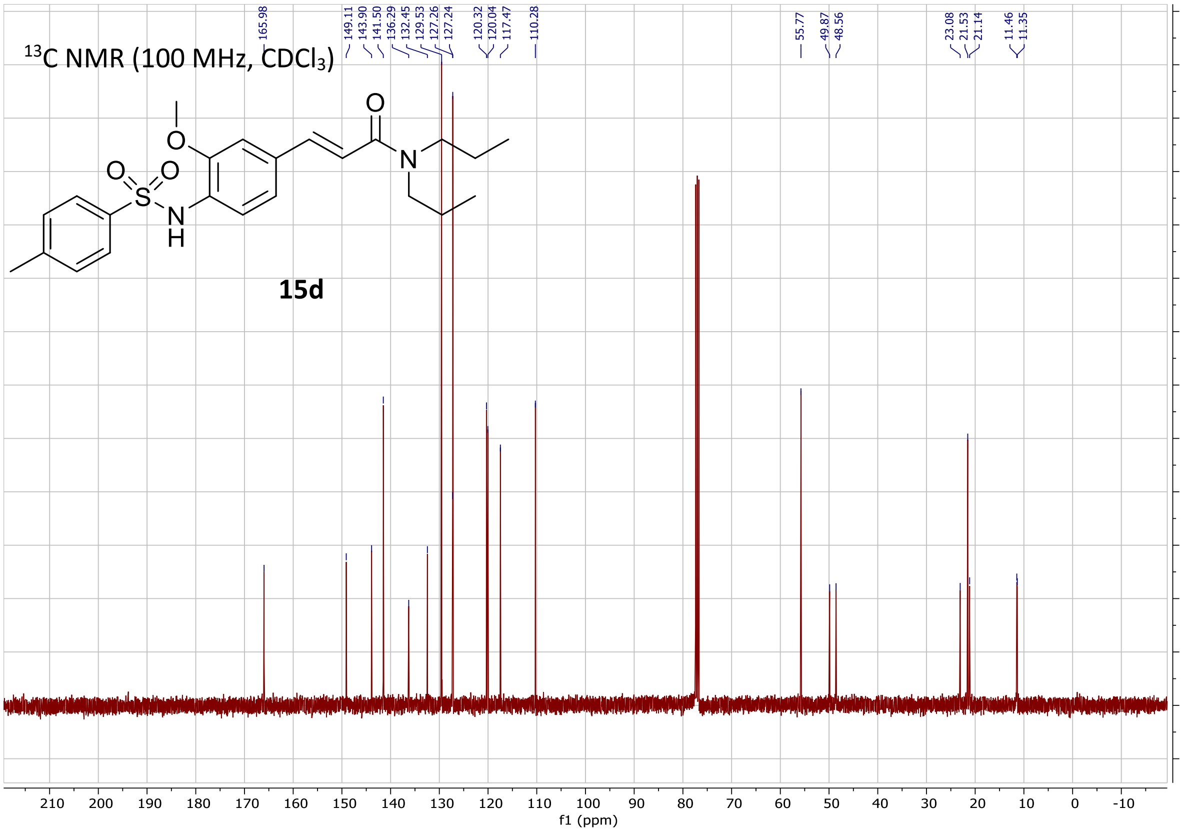

^{13}C NMR (100 MHz, CDCl$_3$)
15c
O
O
S
O
F
N
H
O
O
N
166.05 152.83 151.83 151.72 150.33 149.35 141.49 132.89 131.16 131.10 126.93 124.76 124.72 120.45 120.42 117.77 115.47 115.26 112.69 112.67 110.34 56.47 55.88 49.96 48.65 23.15 21.21 11.53 11.44
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100 -200

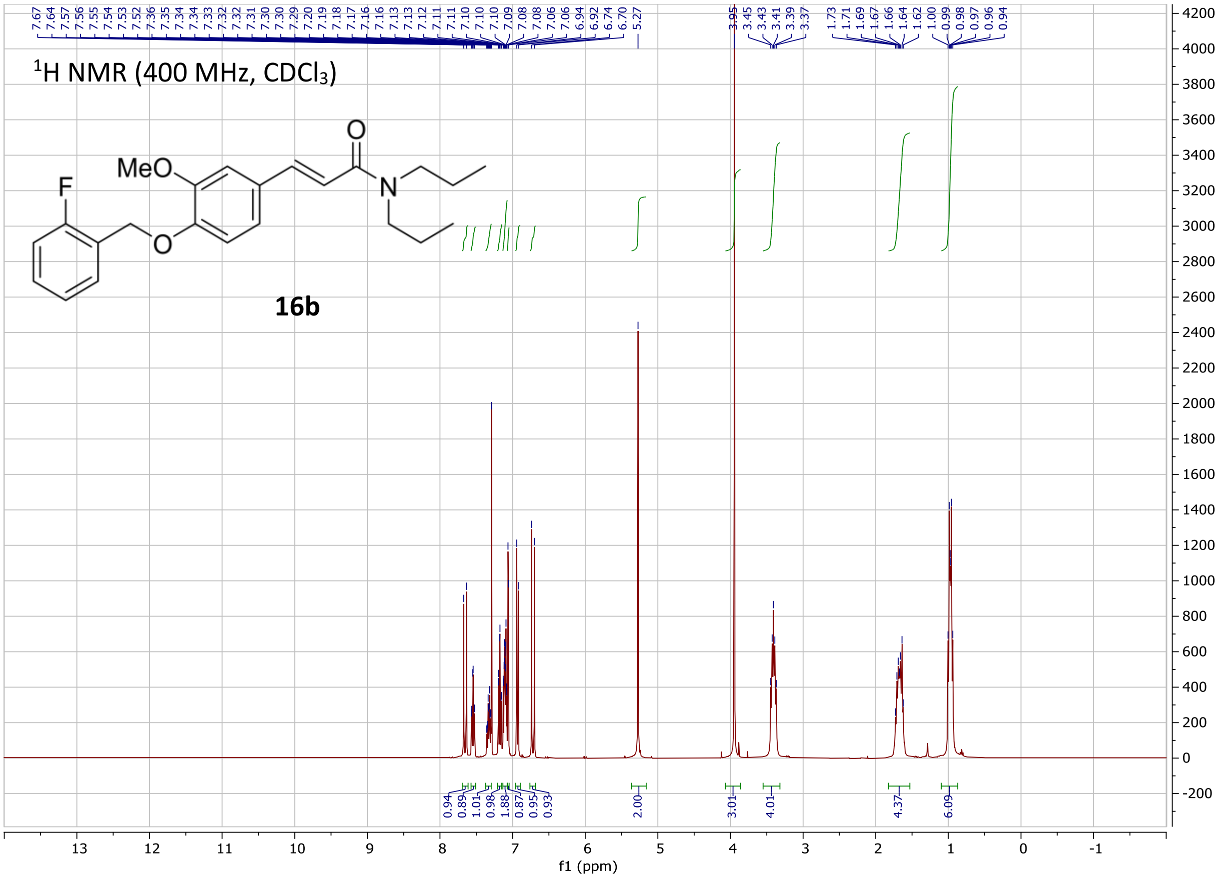


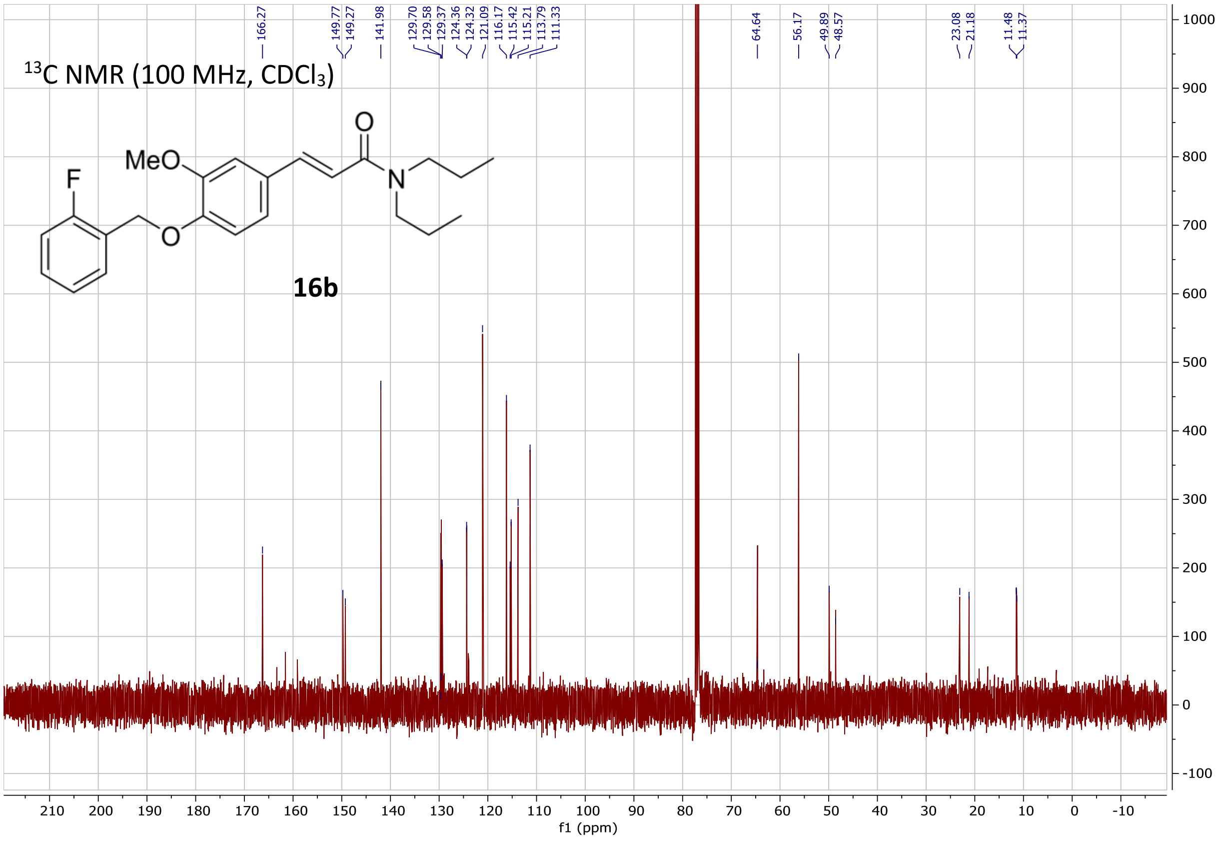
^{19}F NMR (376 MHz, $CDCl_3$)

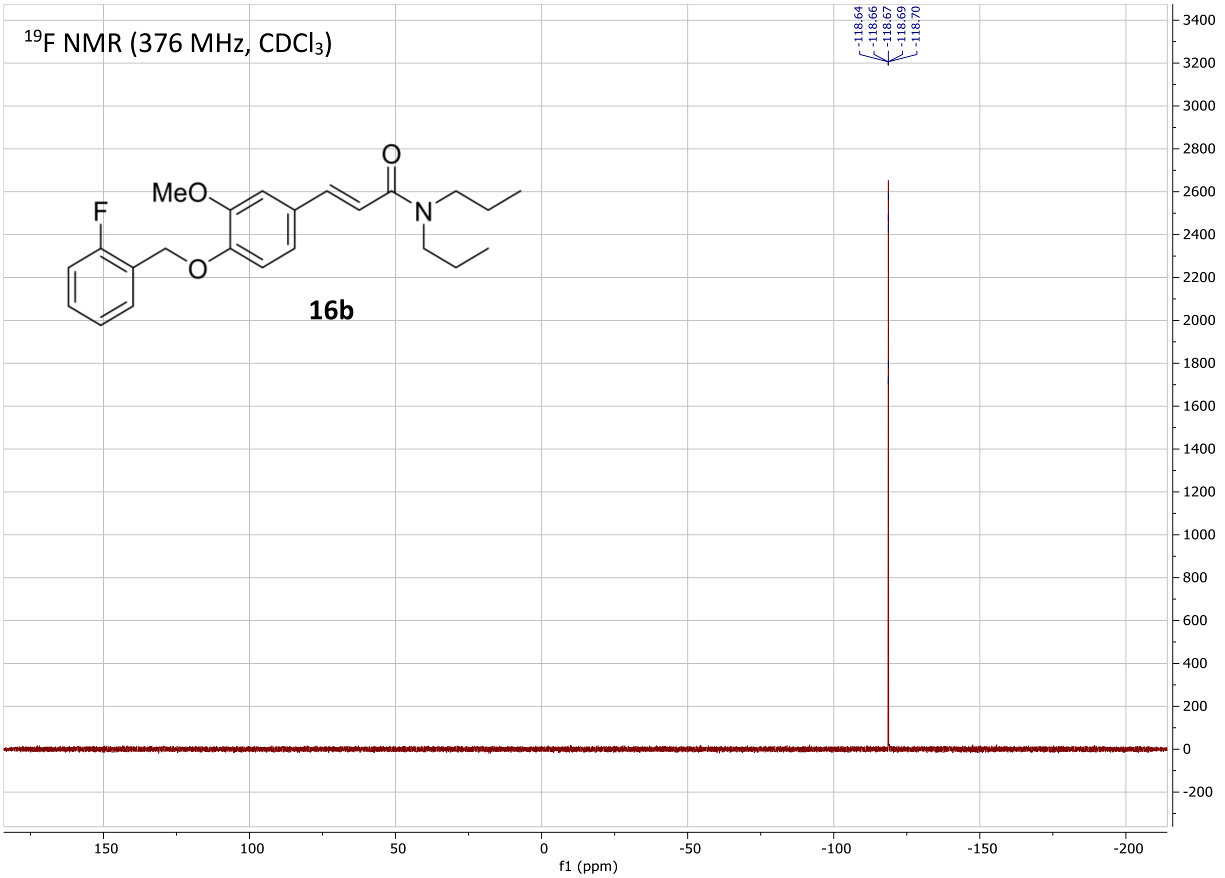
15c


1H NMR (400 MHz, CDCl3)
15d
7.68
7.68
7.67
7.66
7.66
7.65
7.57
7.53
7.51
7.49
7.22
7.21
7.21
7.20
7.19
7.19
7.11
7.10
7.10
7.08
7.08
6.82
6.81
6.72
6.68
3.70
3.40
3.38
3.37
3.36
3.34
3.32
2.35
1.67
1.65
1.64
1.63
1.61
1.59
1.57
0.96
0.94
0.93
0.92
0.91
0.89
0.88
1.94
1.00
0.96
1.94
1.87
0.94
0.95
3.04
4.00
3.00
4.04
6.11
f1 (ppm)

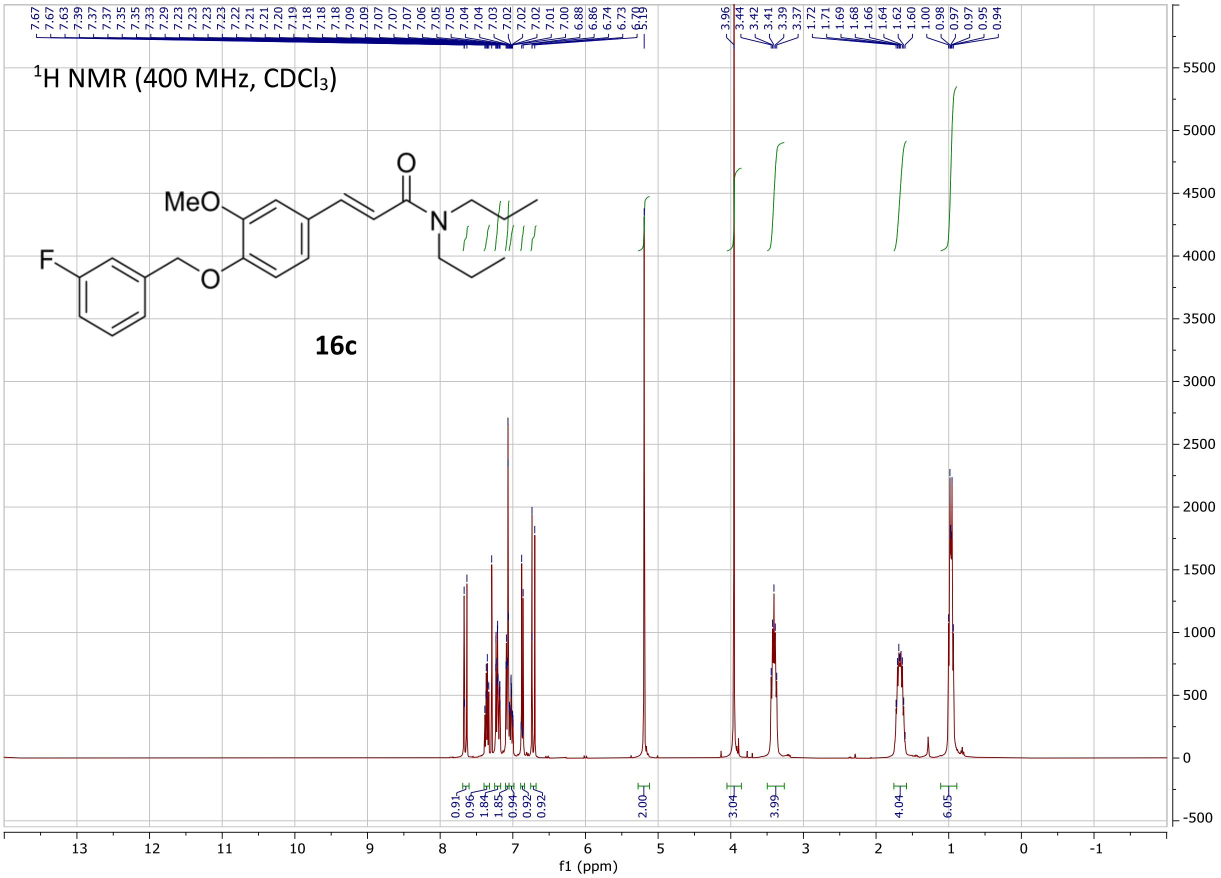

13C NMR (100 MHz, CDCl3)
15d
165.98
149.11
143.90
141.50
136.29
132.45
129.53
127.26
127.24
120.32
120.04
117.47
110.28
55.77
49.87
48.56
23.08
21.53
21.14
11.46
11.35
f1 (ppm)

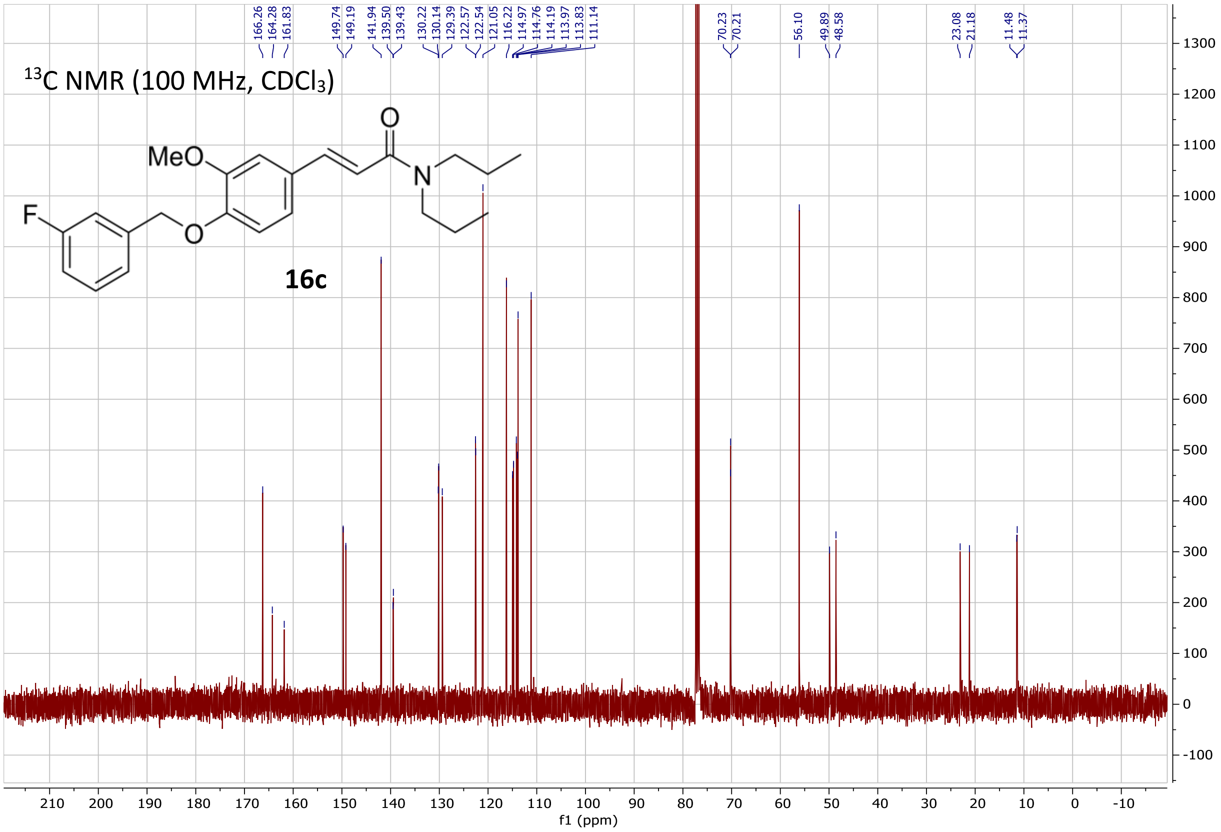

7.67
7.64
7.57
7.56
7.55
7.54
7.53
7.52
7.36
7.35
7.34
7.34
7.33
7.32
7.32
7.31
7.30
7.30
7.29
7.20
7.19
7.18
7.17
7.16
7.16
7.13
7.13
7.12
7.11
7.11
7.10
7.10
7.10
7.09
7.08
7.08
7.06
7.06
6.94
6.92
6.74
6.70
5.27
3.95
3.45
3.43
3.41
3.39
3.37
1.73
1.71
1.69
1.67
1.66
1.64
1.62
1.00
0.99
0.98
0.97
0.96
0.94
^{1}H NMR (400 MHz, CDCl$_3$)
MeO
F
O
O
N
16b
0.94
0.89
1.01
0.98
1.88
0.87
0.95
0.93
2.00
3.01
4.01
4.37
6.09
f1 (ppm)

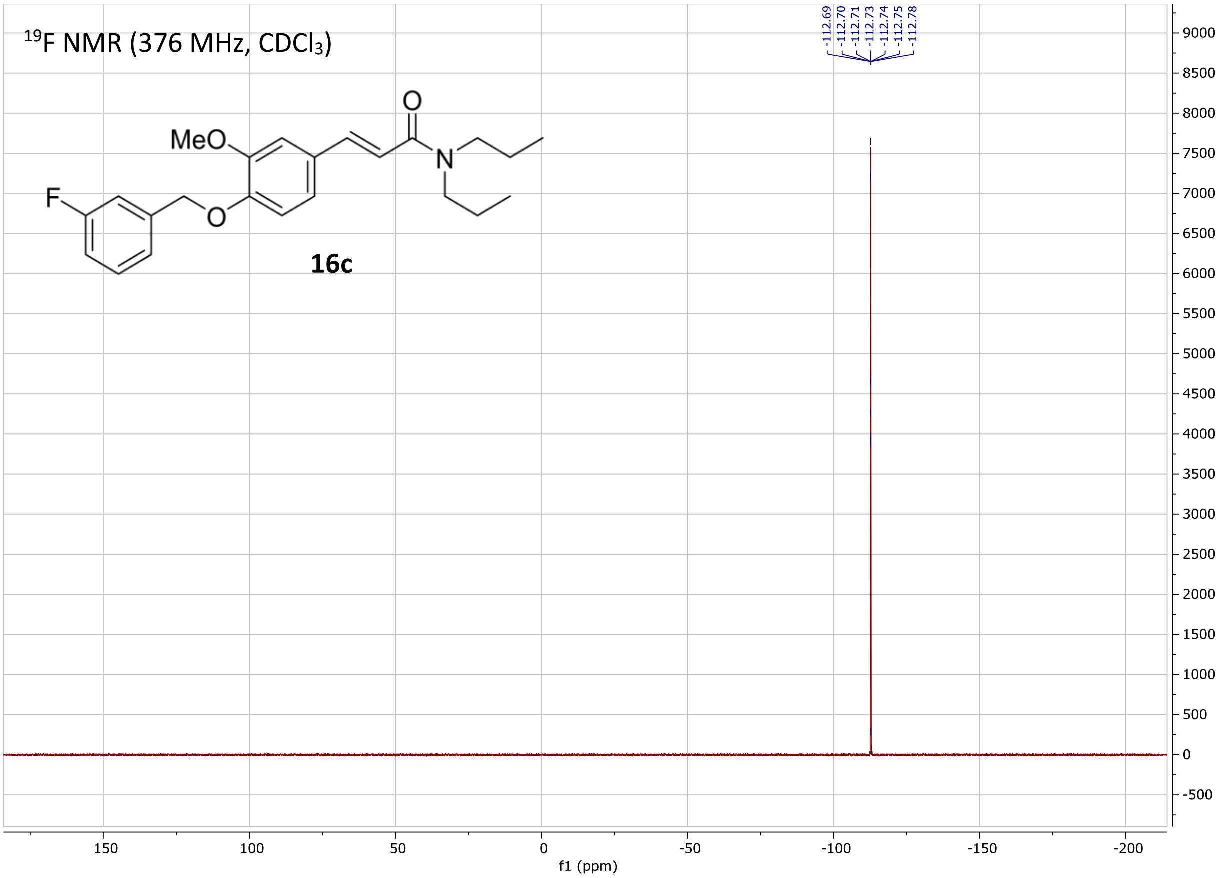

166.27
149.77
149.27
141.98
129.70
129.58
129.37
124.36
124.32
121.09
116.17
115.42
115.21
113.79
111.33
64.64
56.17
49.89
48.57
23.08
21.18
11.48
11.37
^{13}C NMR (100 MHz, CDCl$_3$)
MeO
F
O
O
N
16b
f1 (ppm)

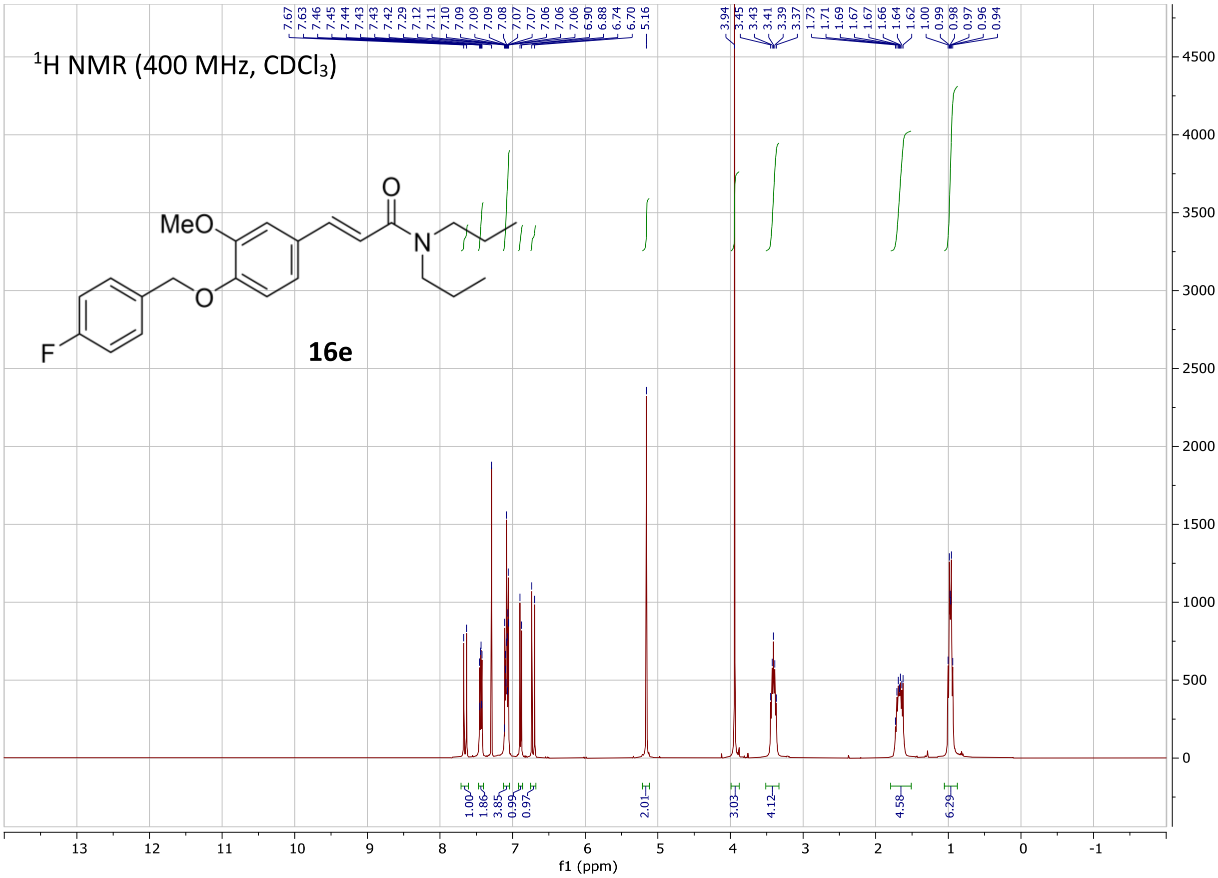

^{19}F NMR (376 MHz, $CDCl_3$)

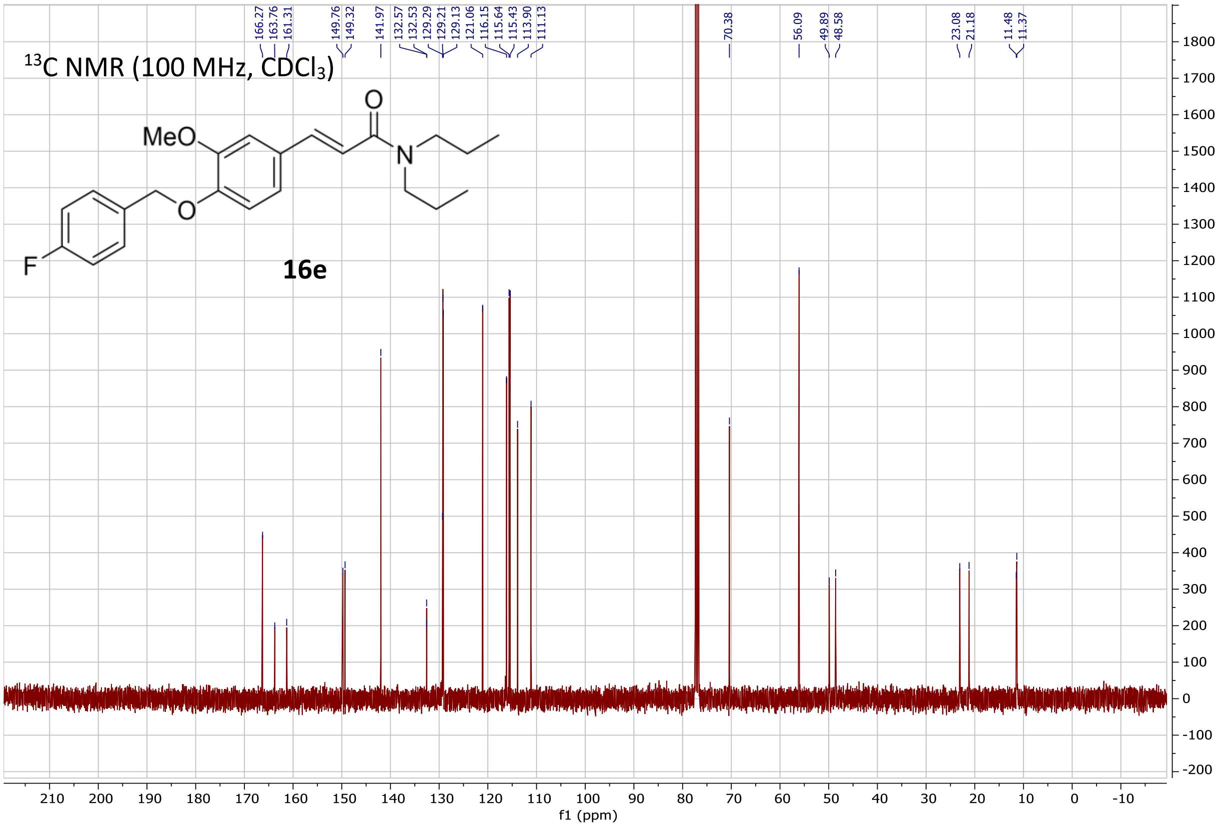
16b

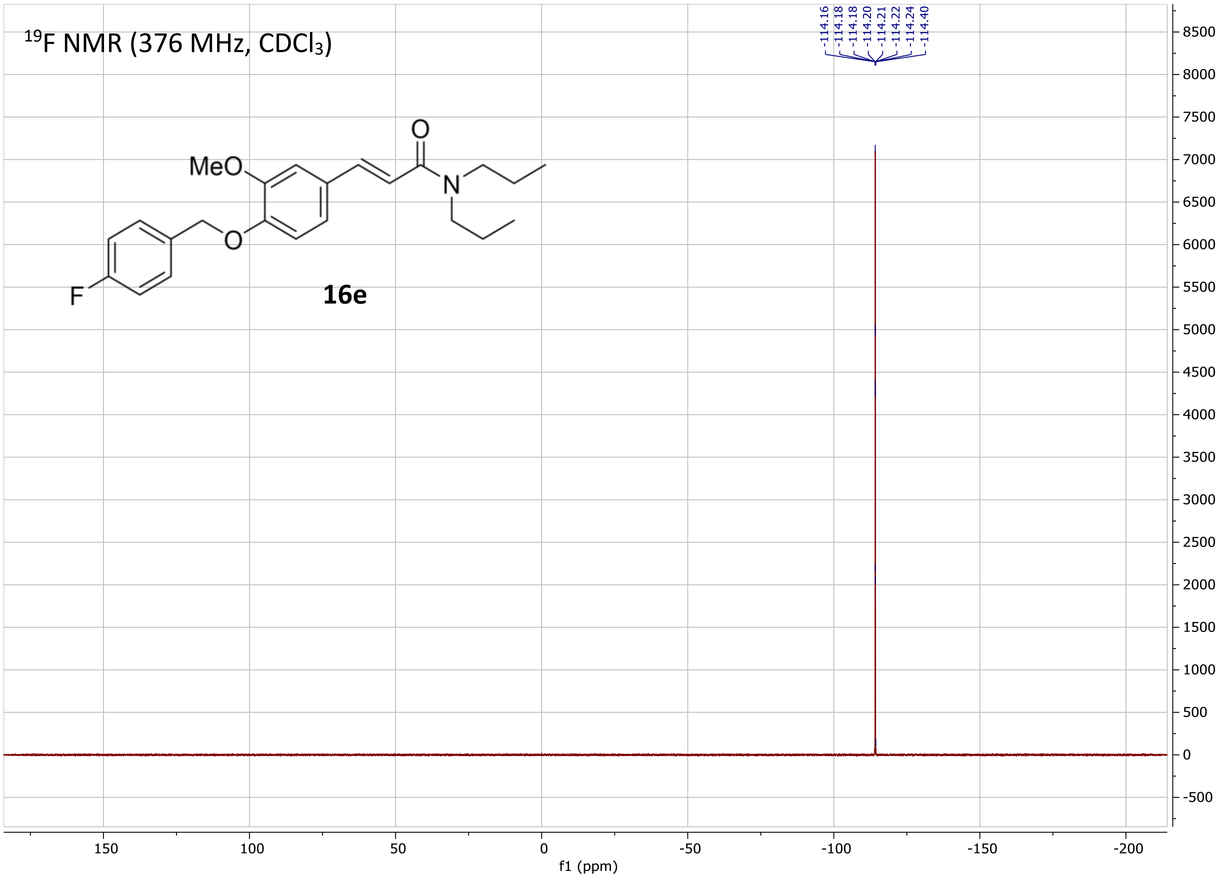

^{1}H NMR (400 MHz, CDCl$_3$)
MeO
F
O
O
N
16c
7.67 7.67 7.63 7.39 7.37 7.37 7.35 7.35 7.33 7.29 7.23 7.23 7.23 7.23 7.22 7.21 7.20 7.19 7.18 7.18 7.09 7.09 7.07 7.07 7.07 7.06 7.05 7.05 7.04 7.04 7.03 7.02 7.02 7.02 7.01 7.00 6.88 6.86 6.74 6.73 6.70 5.19
3.96 3.44 3.42 3.41 3.39 3.37 1.72 1.71 1.69 1.68 1.66 1.64 1.62 1.60 1.00 0.98 0.97 0.97 0.95 0.94
0.91 0.96 1.84 1.85 0.94 0.92 0.92 2.00 3.04 3.99 4.04 6.05
f1 (ppm)


^{13}C NMR (100 MHz, CDCl$_3$)
MeO
F
O
O
N
16c
166.26 164.28 161.83 149.74 149.19 141.94 139.50 139.43 130.22 130.14 129.39 122.57 122.54 121.05 116.22 114.97 114.76 114.19 113.97 113.83 111.14
70.23 70.21 56.10 49.89 48.58 23.08 21.18 11.48 11.37
f1 (ppm)


^{19}F NMR (376 MHz, CDCl$_3$)
16c
MeO
F
O
N
-112.69
-112.70
-112.71
-112.73
-112.74
-112.75
-112.78
9000
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
150
100
50
0
-50
-100
-150
-200
f1 (ppm)

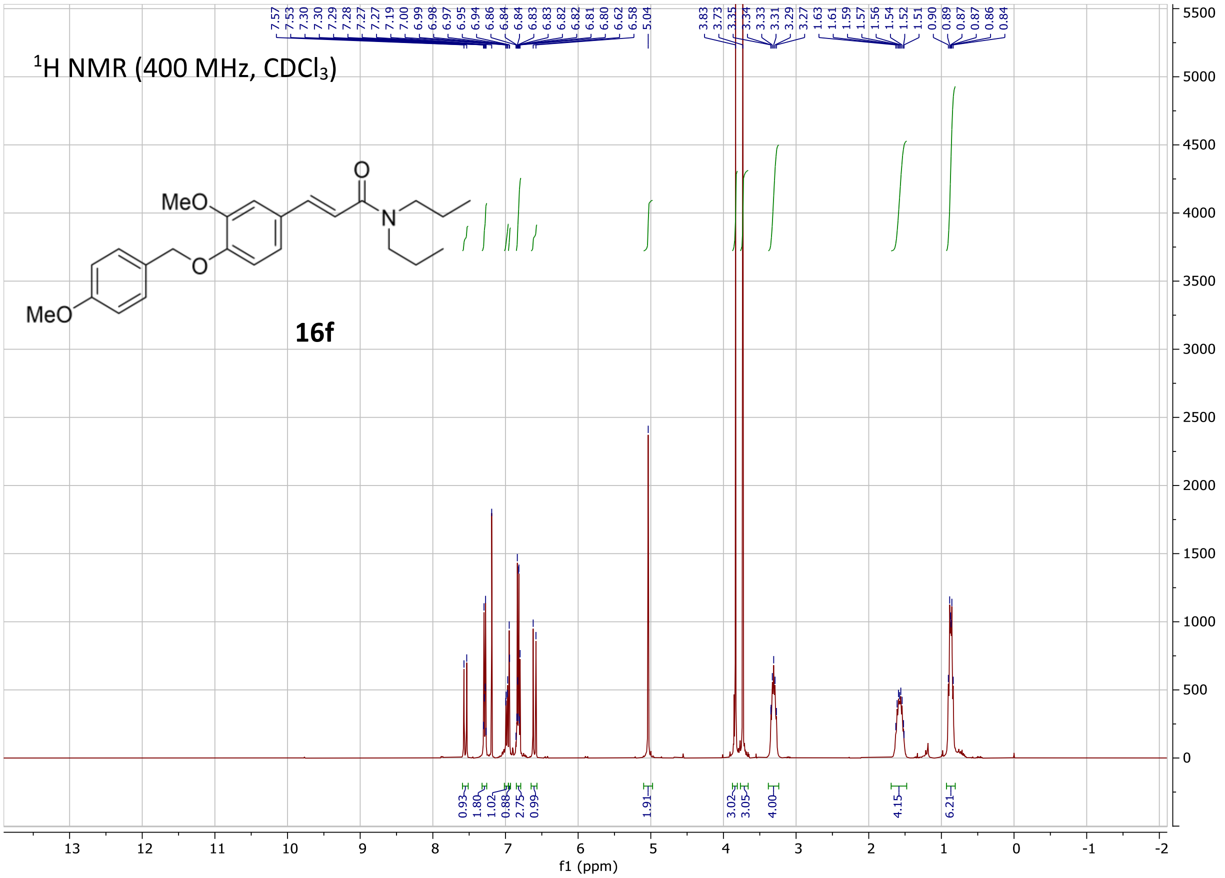

^{1}H NMR (400 MHz, CDCl$_3$)
MeO
O
N
O
F
16e
7.67 7.63 7.46 7.45 7.44 7.43 7.43 7.42 7.29 7.12 7.11 7.10 7.09 7.09 7.09 7.08 7.07 7.07 7.06 7.06 7.06 6.90 6.88 6.74 6.70 5.16
3.94 3.45 3.43 3.41 3.39 3.37 1.73 1.71 1.69 1.67 1.67 1.66 1.64 1.62 1.00 0.99 0.98 0.97 0.96 0.94
1.00 1.86 3.85 0.99 0.97 2.01 3.03 4.12 4.58 6.29
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)
4500 4000 3500 3000 2500 2000 1500 1000 500 0


^{13}C NMR (100 MHz, CDCl$_3$)
MeO
O
N
O
F
16e
166.27 163.76 161.31 149.76 149.32 141.97 132.57 132.53 129.29 129.21 129.13 121.06 116.15 115.64 115.43 113.90 111.13
70.38 56.09 49.89 48.58 23.08 21.18 11.48 11.37
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100 -200

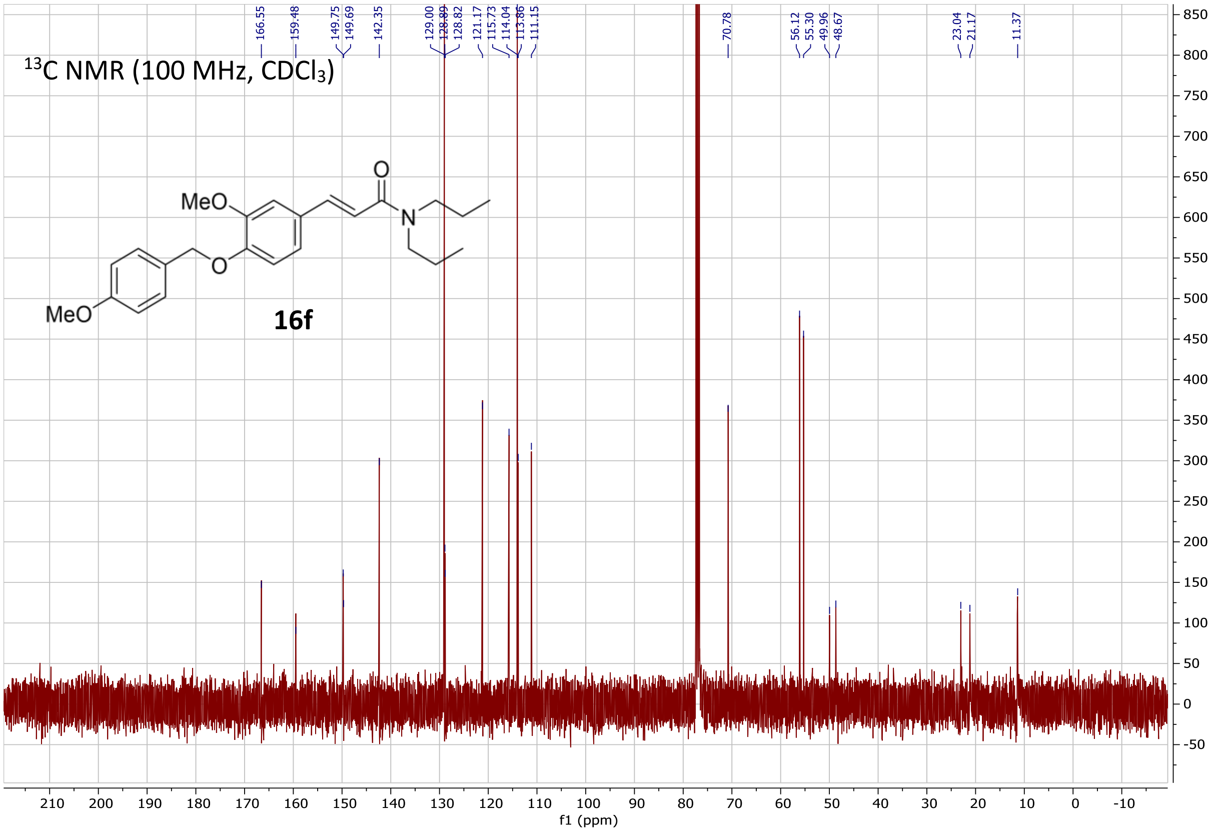


^{19}F NMR (376 MHz, $CDCl_3$)

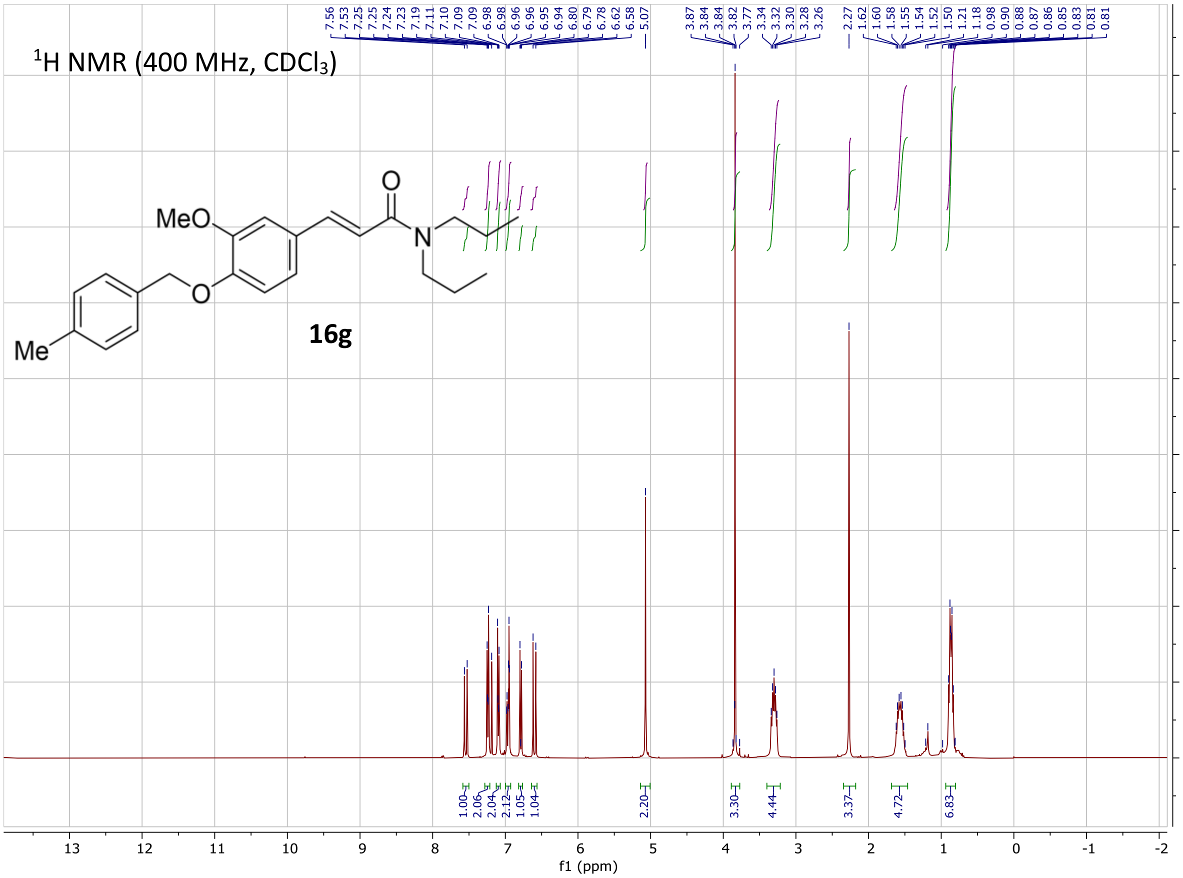
16e



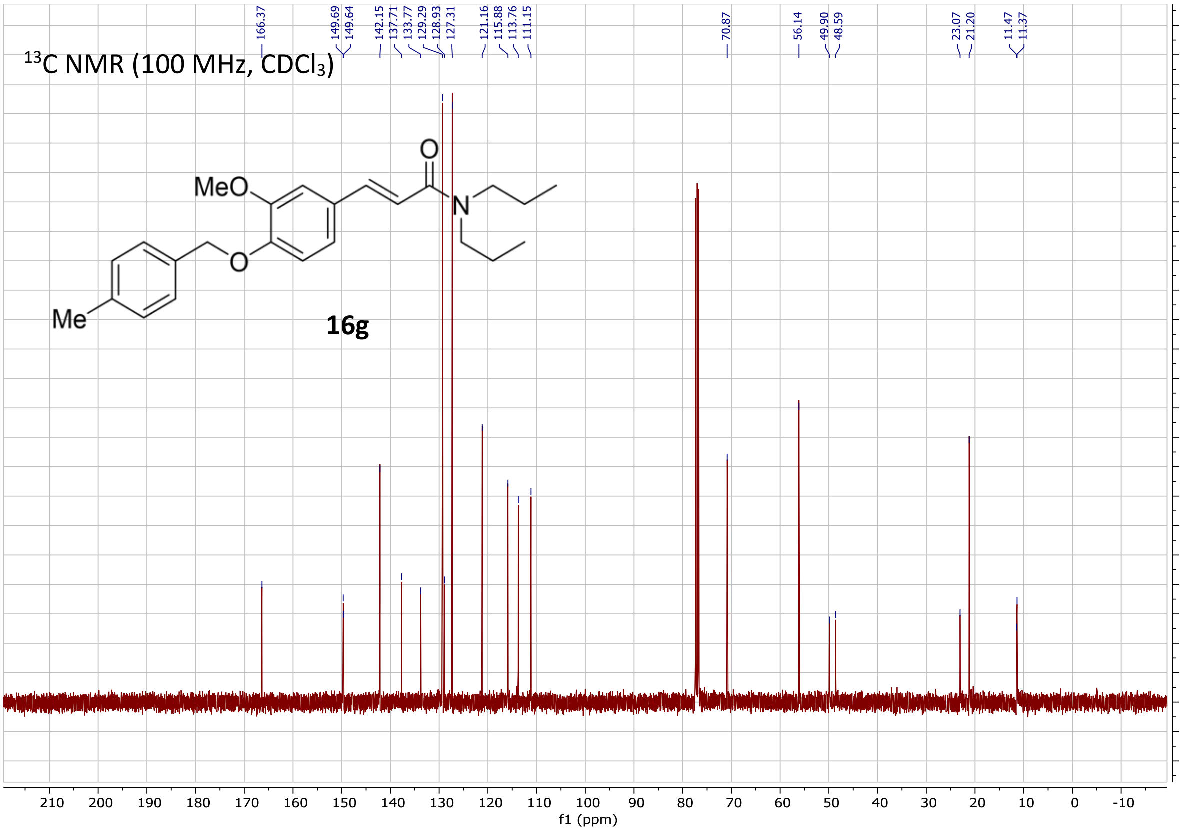
^{1}H NMR (400 MHz, CDCl$_3$)
16f
MeO
MeO
O
N
O
7.57 7.53 7.30 7.30 7.29 7.28 7.27 7.27 7.19 7.00 6.99 6.98 6.97 6.95 6.94 6.86 6.84 6.84 6.83 6.83 6.82 6.82 6.81 6.80 6.62 6.58 5.04
3.83 3.73 3.35 3.34 3.33 3.31 3.29 3.27 1.63 1.61 1.59 1.57 1.56 1.54 1.52 1.51 0.90 0.89 0.87 0.87 0.86 0.84
0.93 1.80 1.02 0.88 2.75 0.99 1.91 3.02 3.05 4.00 4.15 6.21
f1 (ppm)



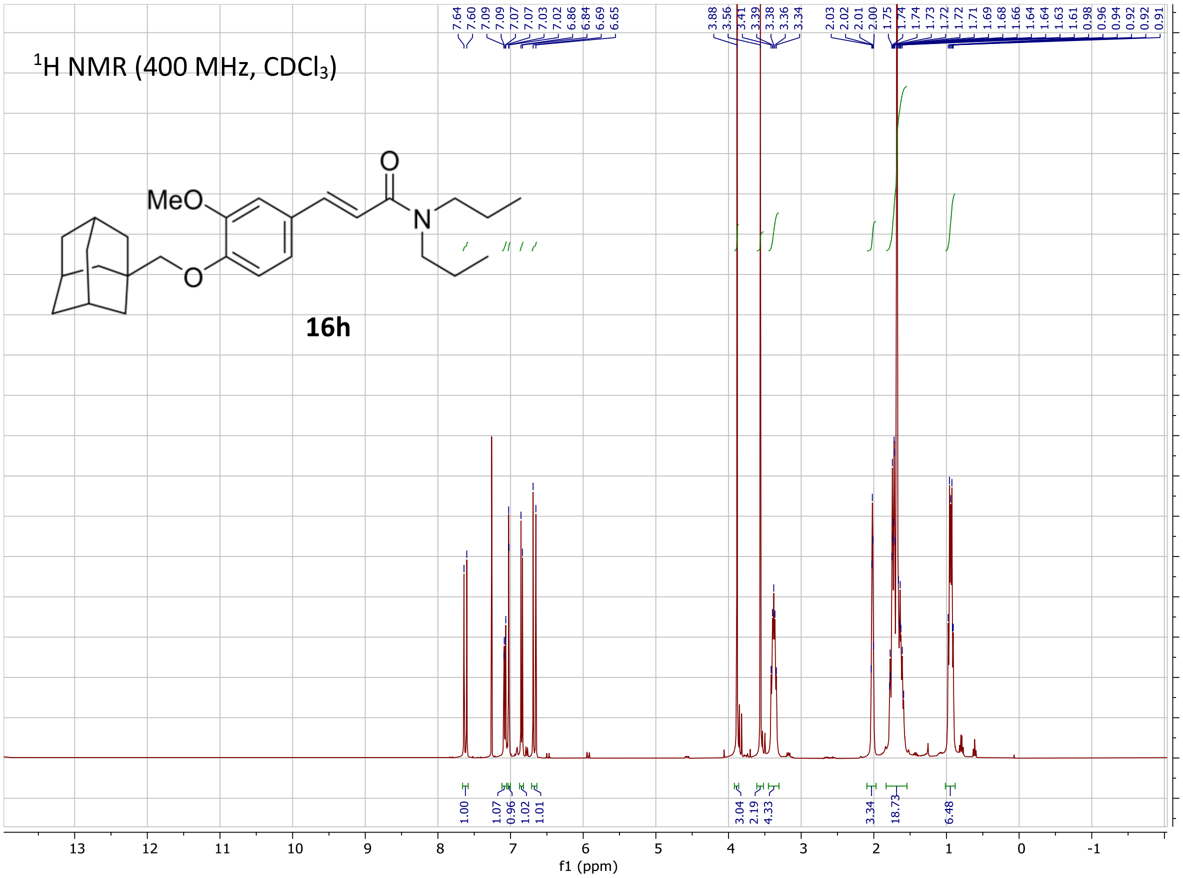
^{13}C NMR (100 MHz, CDCl$_3$)
16f
MeO
MeO
O
N
O
166.55 159.48 149.75 149.69 142.35 129.00 128.89 128.82 121.17 115.73 114.04 113.86 111.15 70.78 56.12 55.30 49.96 48.67 23.04 21.17 11.37
f1 (ppm)

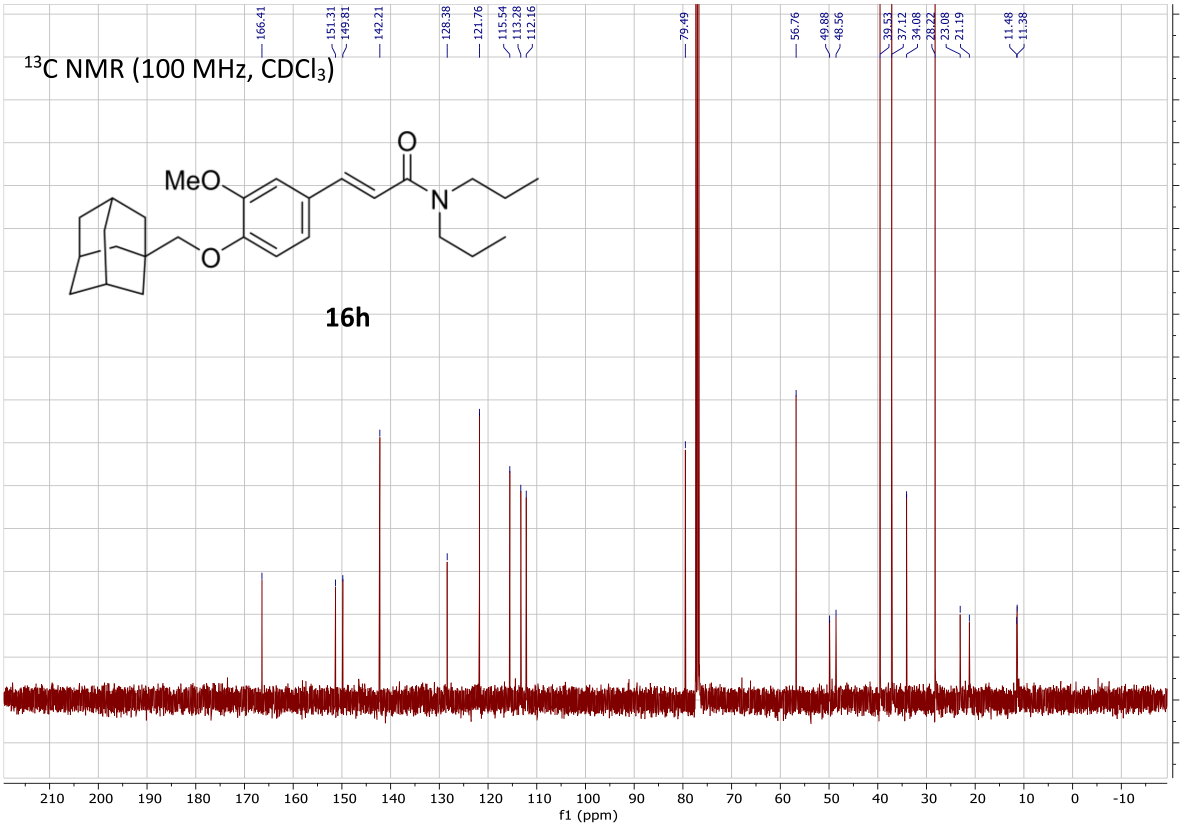


^{1}H NMR (400 MHz, CDCl$_3$)
MeO
O
N
Me
16g
7.56 7.53 7.25 7.25 7.24 7.23 7.19 7.11 7.10 7.09 6.98 6.98 6.96 6.96 6.95 6.94 6.80 6.79 6.78 6.62 6.58 5.07 3.87 3.84 3.84 3.82 3.77 3.34 3.32 3.30 3.28 3.26 2.27 1.62 1.60 1.58 1.55 1.54 1.52 1.50 1.21 1.18 0.98 0.90 0.88 0.87 0.86 0.85 0.83 0.81 0.81
1.00 2.06 2.04 2.12 1.05 1.04 2.20 3.30 4.44 3.37 4.72 6.83
f1 (ppm)

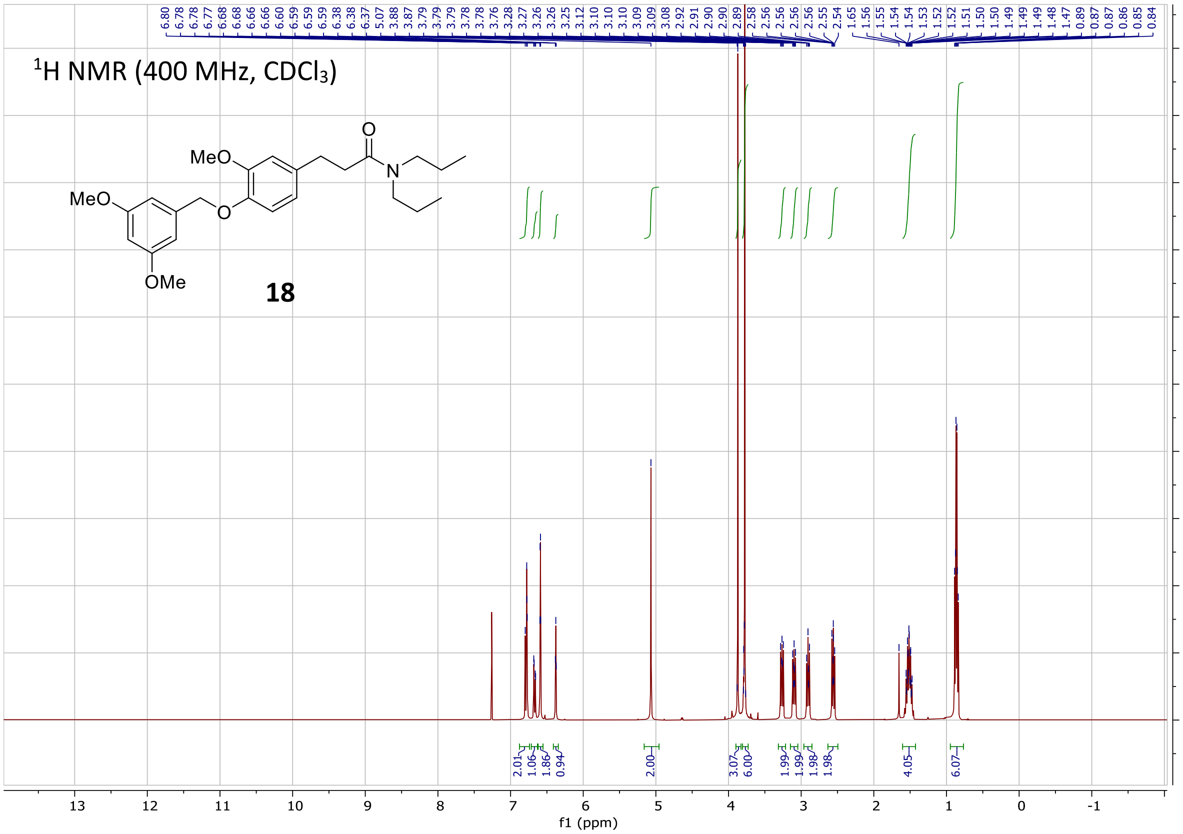


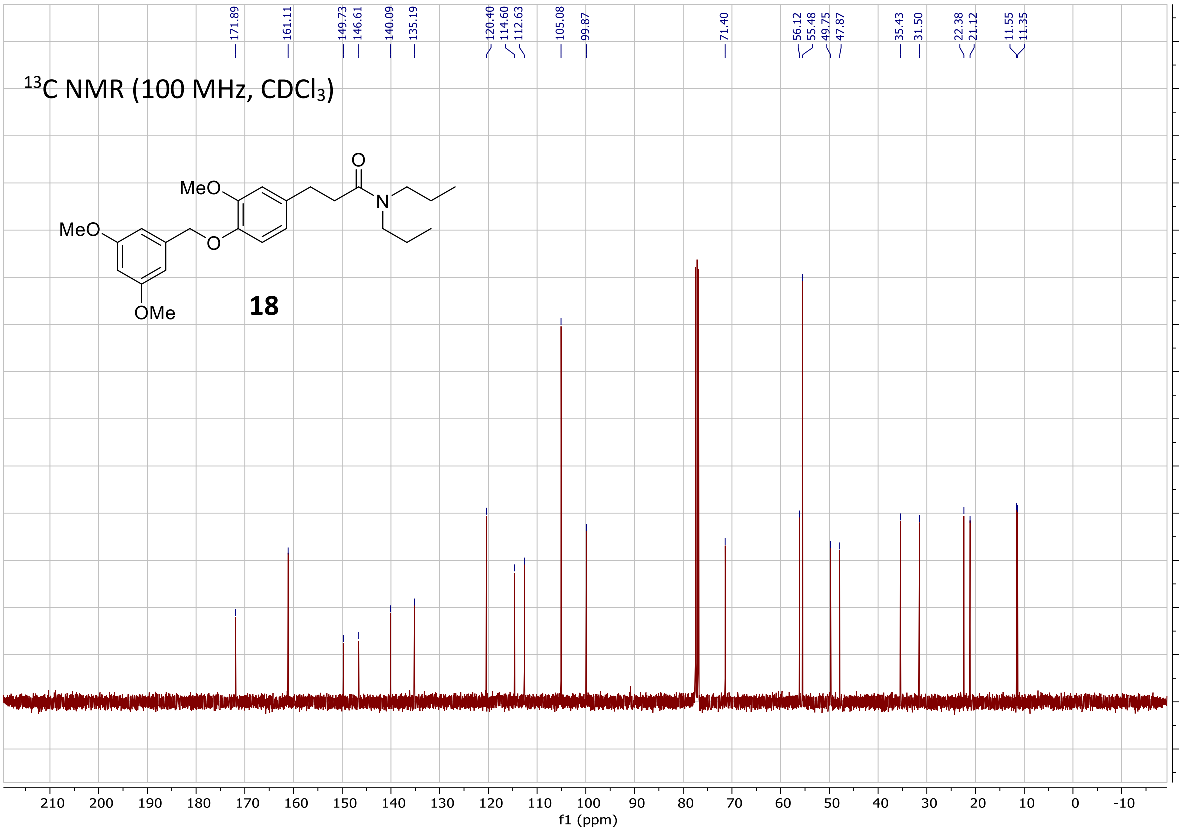
^{13}C NMR (100 MHz, CDCl$_3$)
MeO
O
N
Me
16g
166.37 149.69 149.64 142.15 137.71 133.77 129.29 128.93 127.31 121.16 115.88 113.76 111.15 70.87 56.14 49.90 48.59 23.07 21.20 11.47 11.37
f1 (ppm)

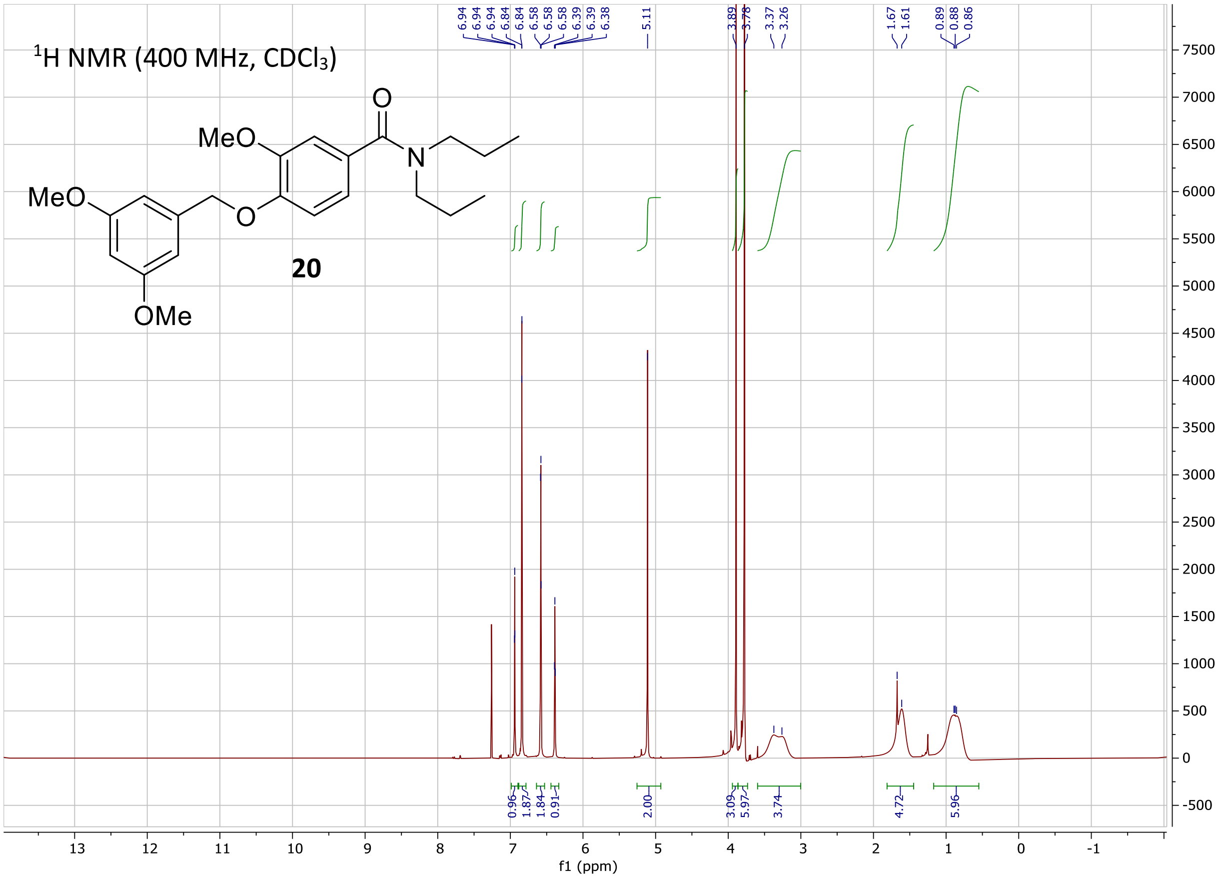

1H NMR (400 MHz, CDCl3)
MeO
O
N
O
16h
7.64
7.60
7.09
7.09
7.07
7.07
7.03
7.02
6.86
6.84
6.69
6.65
3.88
3.56
3.41
3.39
3.38
3.36
3.34
2.03
2.02
2.01
2.00
1.75
1.74
1.74
1.73
1.72
1.72
1.71
1.69
1.68
1.66
1.64
1.64
1.63
1.61
0.98
0.96
0.94
0.92
0.92
0.91
1.00
1.07
0.96
1.02
1.01
3.04
2.19
4.33
3.34
18.73
6.48
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200

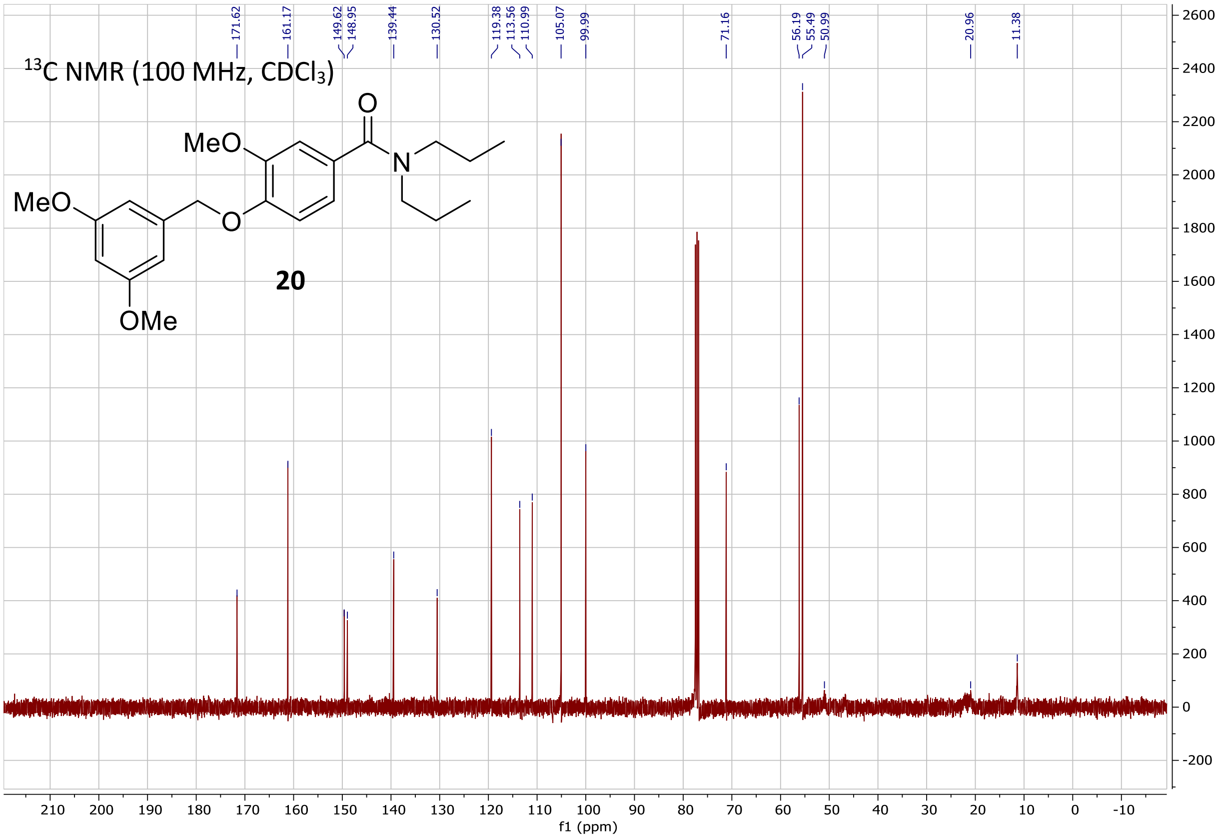

13C NMR (100 MHz, CDCl3)
MeO
O
N
O
16h
166.41
151.31
149.81
142.21
128.38
121.76
115.54
113.28
112.16
79.49
56.76
49.88
48.56
39.53
37.12
34.08
28.22
23.08
21.19
11.48
11.38
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100

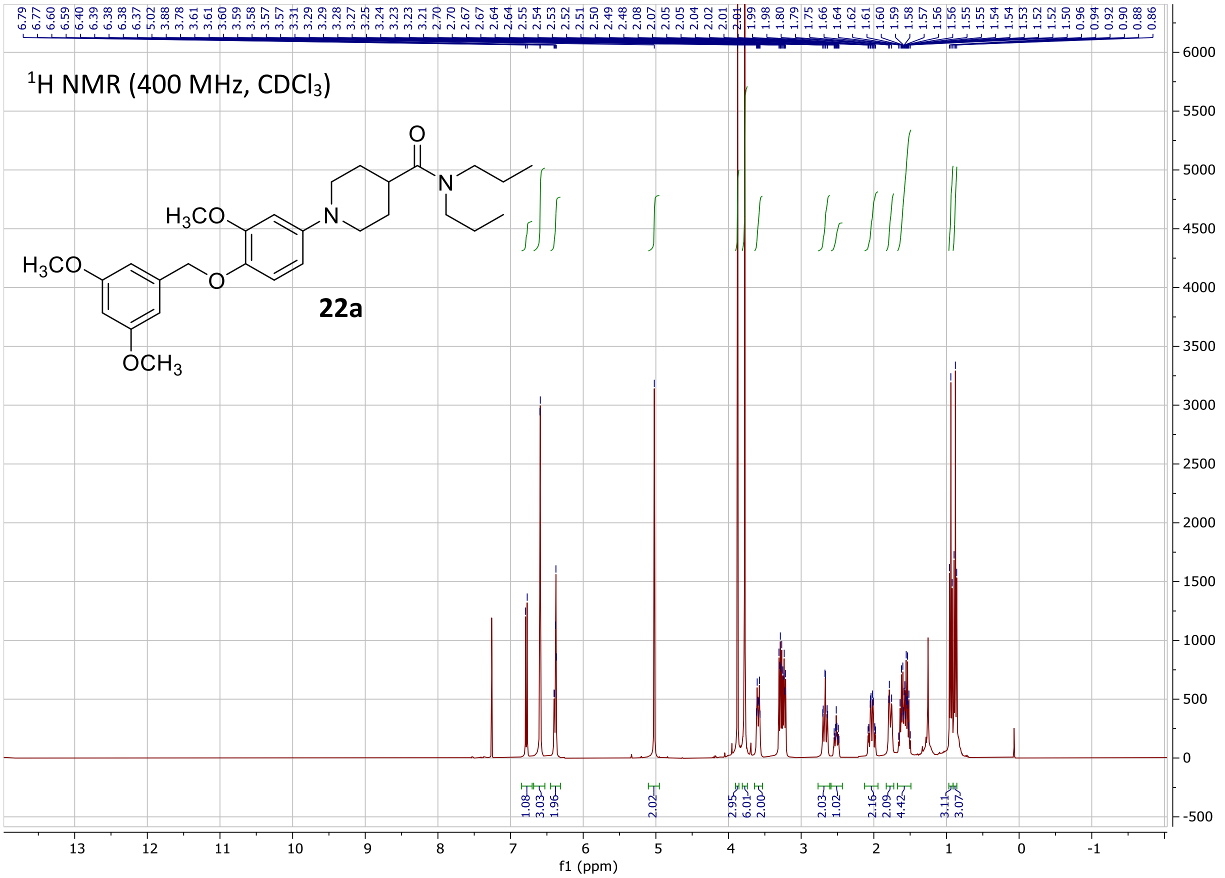
4.4 Series 4 compounds.

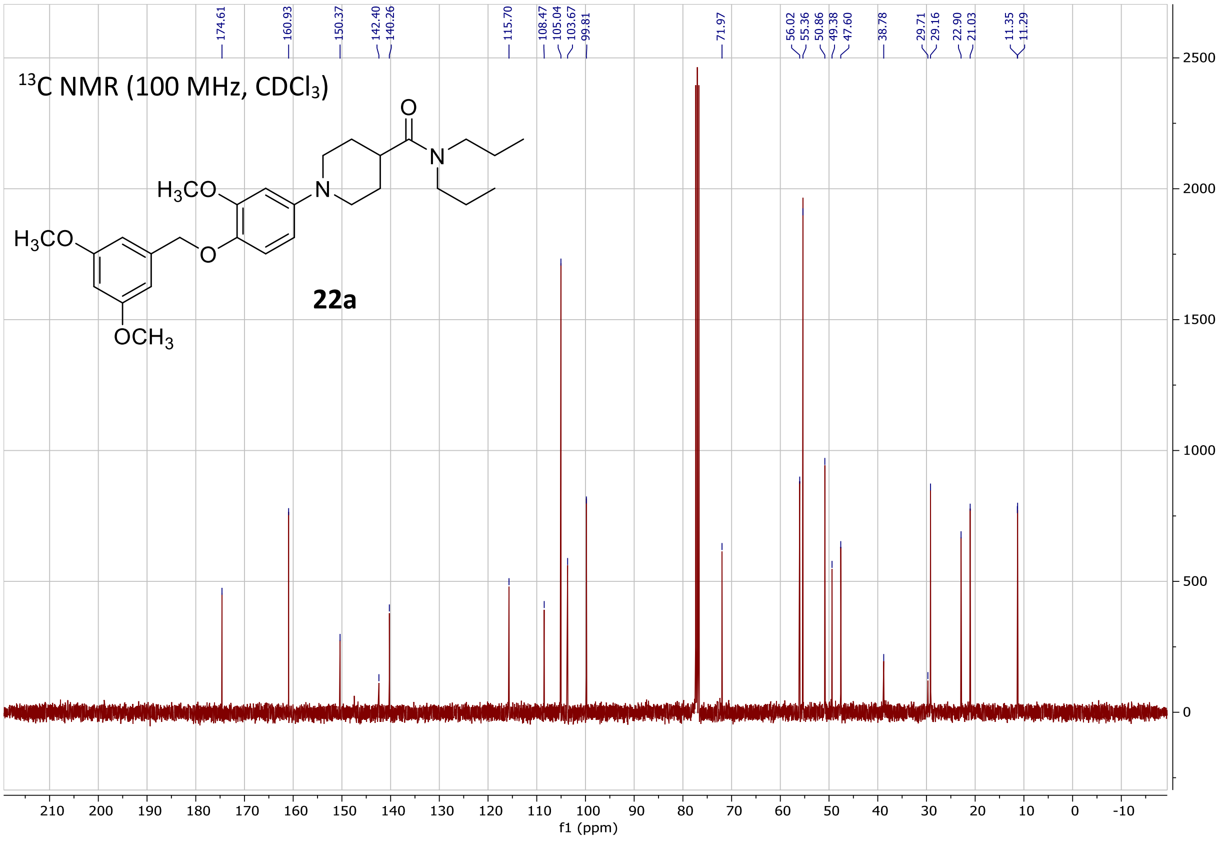


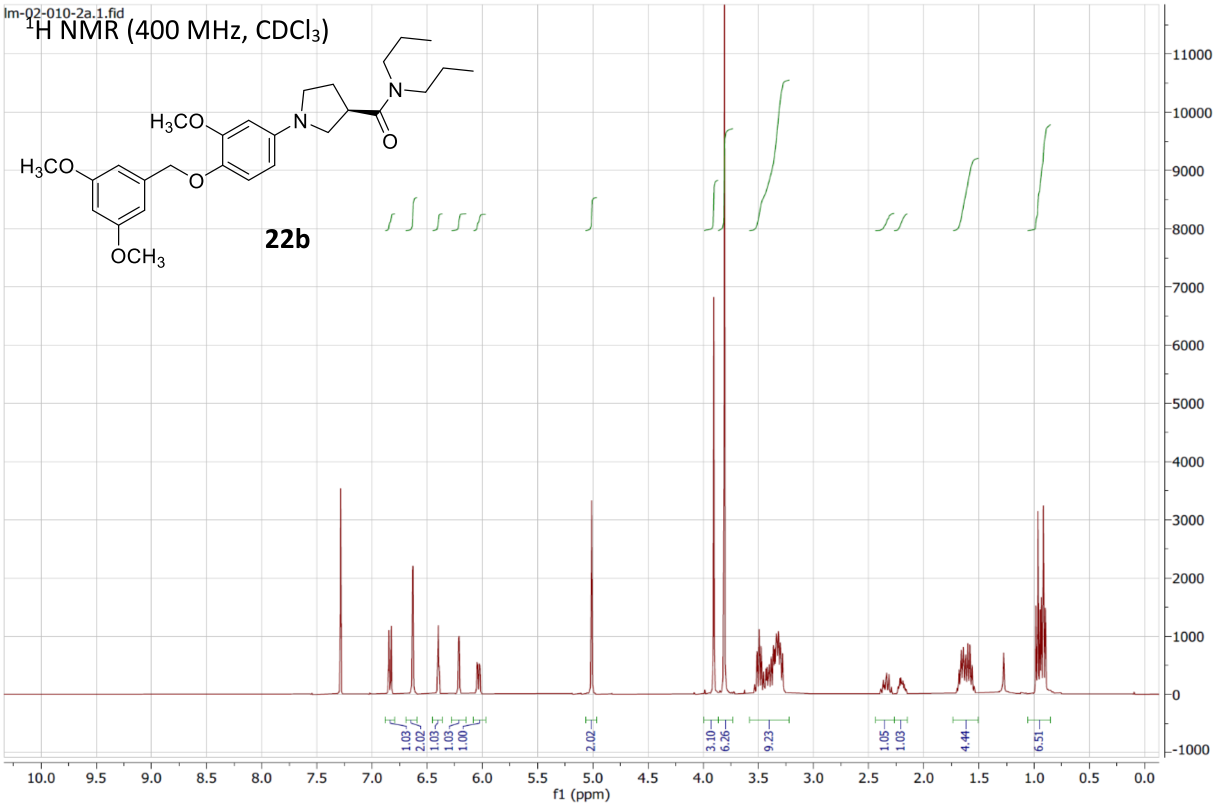


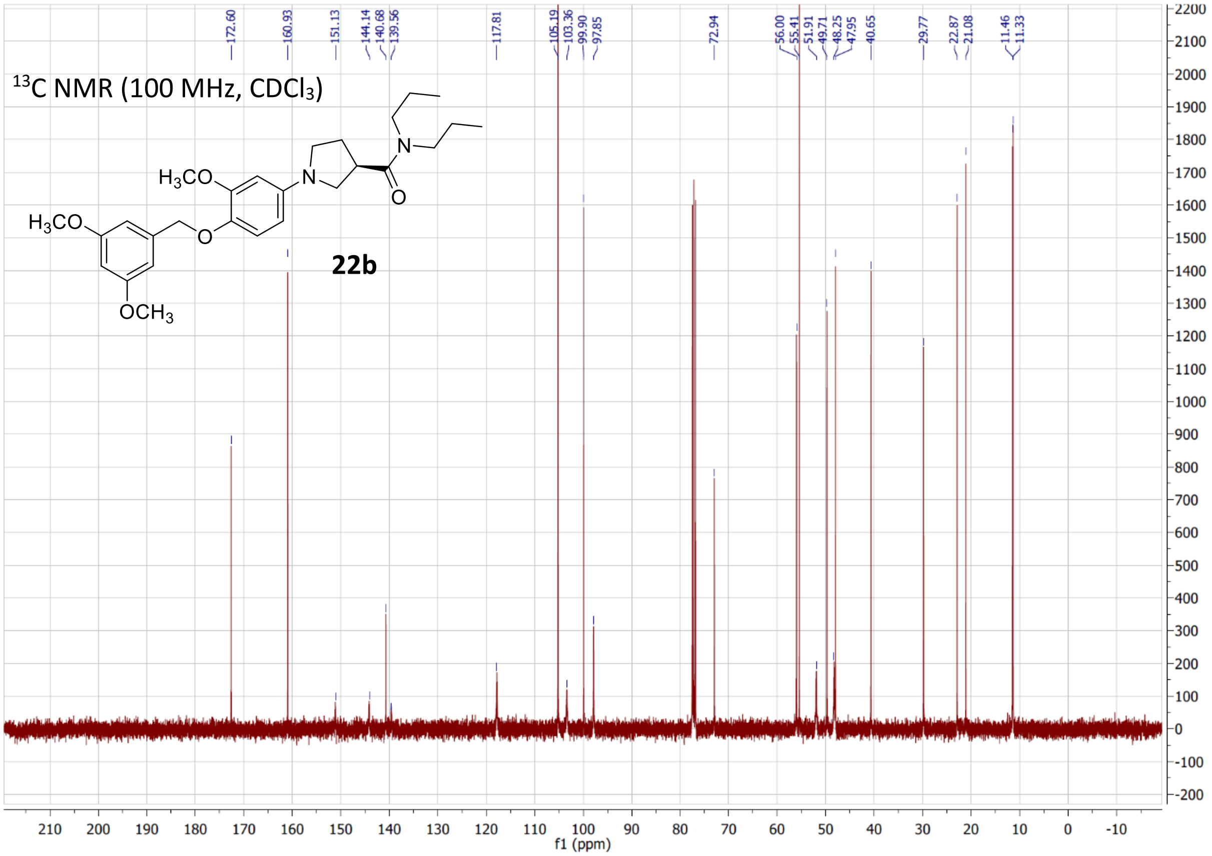

^{1}H NMR (400 MHz, CDCl$_3$)
MeO
MeO
OMe
O
N
O
20
6.94
6.94
6.94
6.84
6.84
6.58
6.58
6.58
6.39
6.39
6.38
5.11
3.89
3.78
3.37
3.26
1.67
1.61
0.89
0.88
0.86
0.96
1.87
1.84
0.91
2.00
3.09
5.97
3.74
4.72
5.96
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500

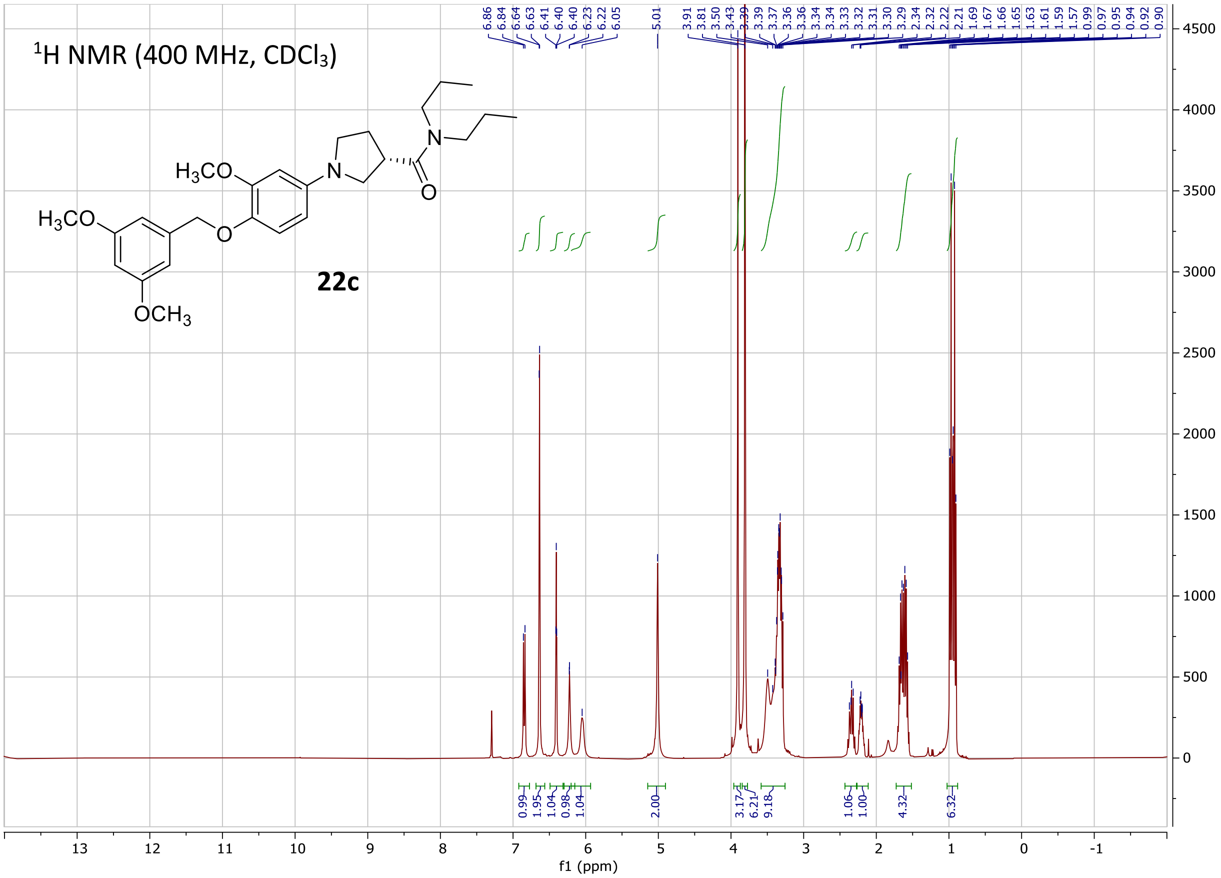

^{13}C NMR (100 MHz, CDCl$_3$)
MeO
MeO
OMe
O
N
O
20
171.62
161.17
149.62
148.95
139.44
130.52
119.38
113.56
110.99
105.07
99.99
71.16
56.19
55.49
50.99
20.96
11.38
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200

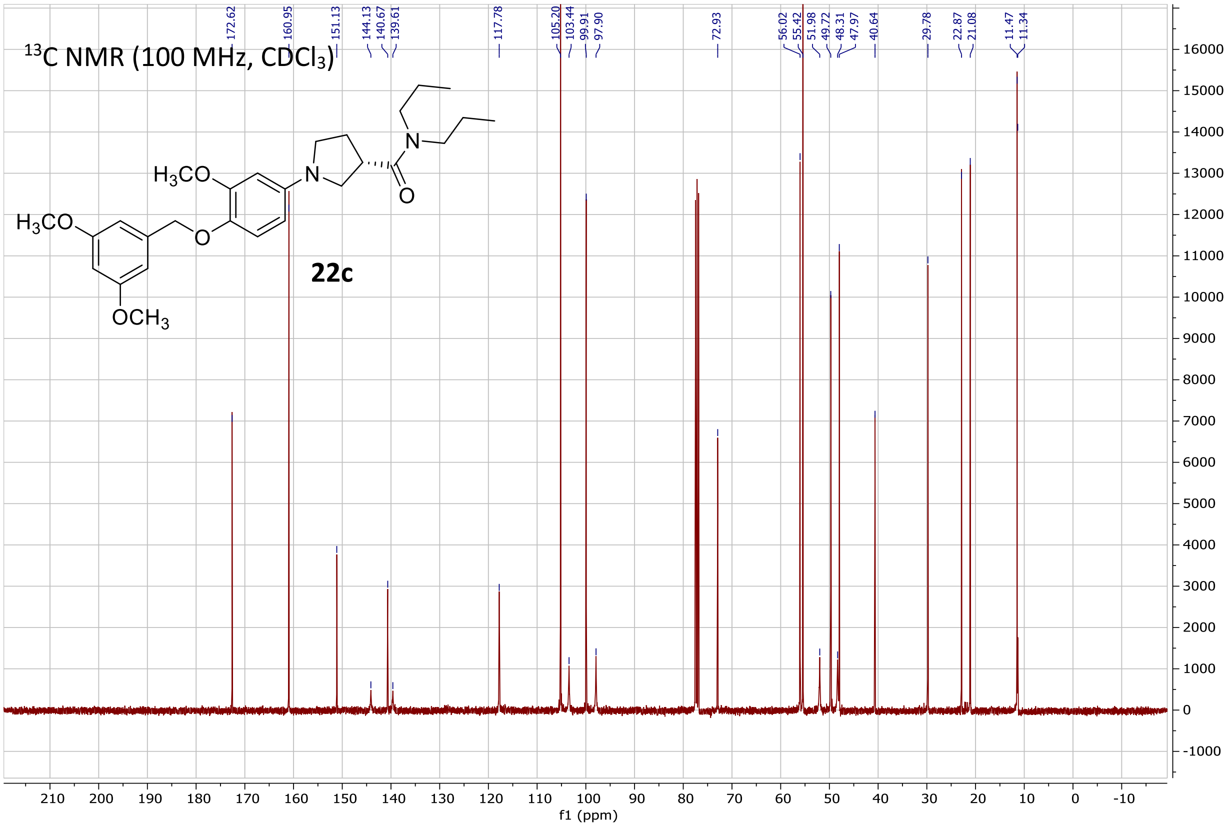

6.79 6.77 6.60 6.59 6.40 6.39 6.38 6.38 6.37 5.02 3.88 3.78 3.61 3.61 3.60 3.59 3.58 3.57 3.57 3.31 3.29 3.29 3.28 3.27 3.25 3.24 3.23 3.23 3.21 2.70 2.70 2.67 2.67 2.64 2.55 2.54 2.53 2.52 2.51 2.50 2.49 2.48 2.08 2.07 2.05 2.05 2.04 2.02 2.01 2.01 1.99 1.98 1.80 1.79 1.75 1.66 1.64 1.62 1.61 1.60 1.59 1.58 1.57 1.56 1.56 1.55 1.55 1.54 1.54 1.53 1.52 1.52 1.50 0.96 0.94 0.92 0.90 0.88 0.86
^{1}H NMR (400 MHz, CDCl$_3$)
O
N
N
H$_3$CO
H$_3$CO
O
OCH$_3$
22a
1.08 3.03 1.96 2.02 2.95 6.01 2.00 2.03 1.02 2.16 2.09 4.42 3.11 3.07
6000 5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0 -500
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)

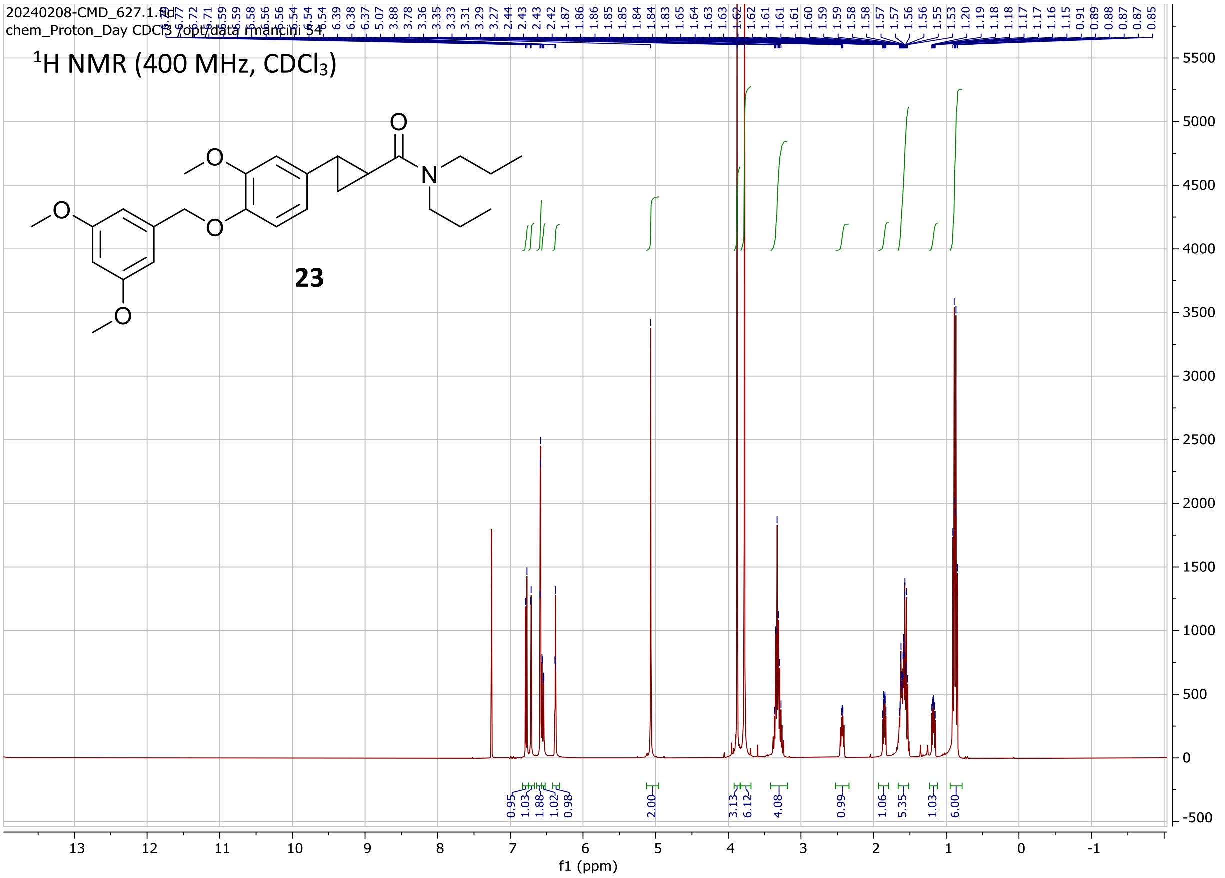

174.61 160.93 150.37 142.40 140.26 115.70 108.47 105.04 103.67 99.81 71.97 56.02 55.36 50.86 49.38 47.60 38.78 29.71 29.16 22.90 21.03 11.35 11.29
^{13}C NMR (100 MHz, CDCl$_3$)
O
N
N
H$_3$CO
H$_3$CO
O
OCH$_3$
22a
2500 2000 1500 1000 500 0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

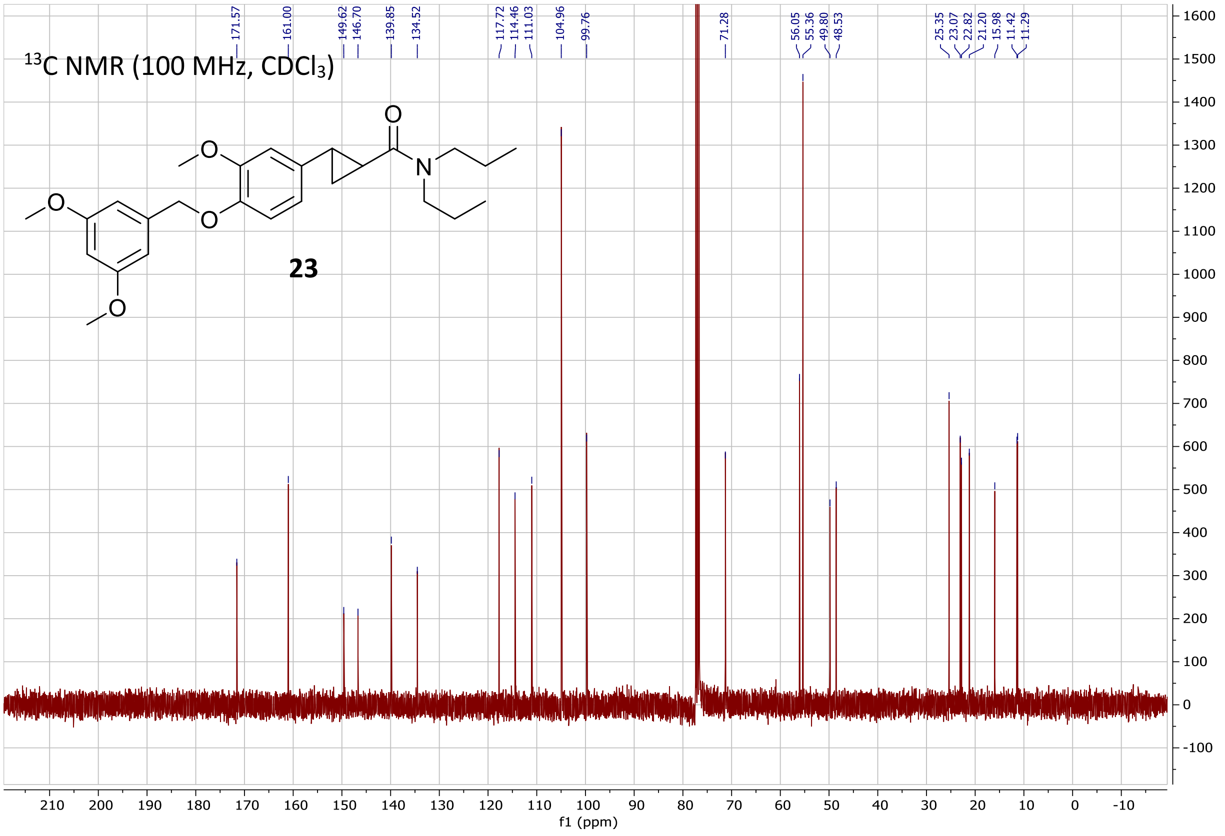

lm-02-010-2a.1.fid
1H NMR (400 MHz, CDCl3)
H3CO
H3CO
N
N
O
O
OCH3
22b
1.03
2.02
1.03
1.03
1.00
2.02
3.10
6.26
9.23
1.05
1.03
4.44
6.51
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000


172.60
160.93
151.13
144.14
140.68
139.56
117.81
105.19
103.36
99.90
97.85
72.94
56.00
55.41
51.91
49.71
48.25
47.95
40.65
29.77
22.87
21.08
11.46
11.33
13C NMR (100 MHz, CDCl3)
H3CO
H3CO
N
N
O
O
OCH3
22b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200


^{1}H NMR (400 MHz, CDCl$_3$)
22c
H$_3$CO
H$_3$CO
OCH$_3$
N
N
O
O
6.86 6.84 6.64 6.63 6.41 6.40 6.40 6.23 6.22 6.05
5.01
3.91 3.81 3.50 3.43 3.39 3.39 3.37 3.36 3.36 3.34 3.34 3.33 3.32 3.31 3.30 3.29
2.34 2.32 2.22 2.21 1.69 1.67 1.66 1.65 1.63 1.61 1.59 1.57 0.99 0.97 0.95 0.94 0.92 0.90
0.99 1.95 1.04 0.98 1.04
2.00
3.17 6.21 9.18
1.06 1.00
4.32
6.32
4500 4000 3500 3000 2500 2000 1500 1000 500 0
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


^{13}C NMR (100 MHz, CDCl$_3$)
22c
H$_3$CO
H$_3$CO
OCH$_3$
N
N
O
O
172.62
160.95
151.13
144.13 140.67 139.61
117.78
105.20 103.44 99.91 97.90
72.93
56.02 55.42 51.98 49.72 48.31 47.97 40.64
29.78 22.87 21.08 11.47 11.34
16000 15000 14000 13000 12000 11000 10000 9000 8000 7000 6000 5000 4000 3000 2000 1000 0 -1000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


20240208-CMD_627.1.fid
chem_Proton_Day CDCl3 /opt/data mancini 54
^{1}H NMR (400 MHz, CDCl$_3$)
23
O
N
O
O
O
O
6.72
6.71
6.59
6.58
6.56
6.56
6.54
6.54
6.54
6.39
6.38
6.37
5.07
3.88
3.78
3.36
3.35
3.33
3.31
3.29
3.27
2.44
2.43
2.43
2.42
1.87
1.86
1.85
1.85
1.84
1.84
1.83
1.65
1.64
1.63
1.63
1.62
1.62
1.61
1.61
1.61
1.60
1.59
1.59
1.58
1.58
1.57
1.57
1.56
1.56
1.55
1.53
1.20
1.19
1.18
1.18
1.17
1.17
1.16
1.15
0.91
0.89
0.88
0.87
0.87
0.85
0.95
1.03
1.88
1.02
0.98
2.00
3.13
6.12
4.08
0.99
1.06
5.35
1.03
6.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500


^{13}C NMR (100 MHz, CDCl$_3$)
23
O
N
O
O
O
O
171.57
161.00
149.62
146.70
139.85
134.52
117.72
114.46
111.03
104.96
99.76
71.28
56.05
55.36
49.80
48.53
25.35
23.07
22.82
21.20
15.98
11.42
11.29
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100