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Supporting information

Synthesis and biological evaluation of 3-nitro-4-chromanone derivatives as potential antiproliferative agents for castration-resistant prostate cancer

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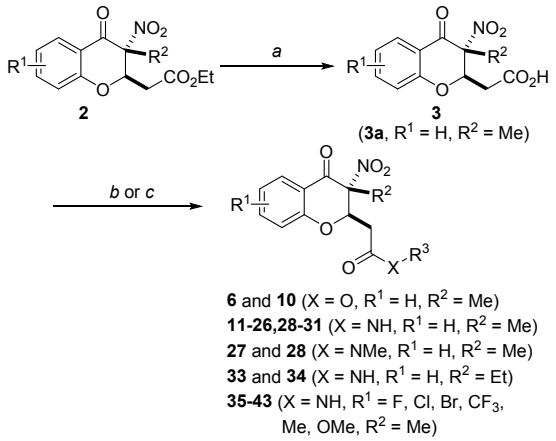
1. General experimental details

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. All the solvents were treated according to general methods. The progress of reactions was monitored by silica gel thin layer chromatography (TLC) plates, visualized under UV. Flash column chromatography was performed using Qingdao Haiyang 200-300 mesh silica gel. Proton, carbon, and fluorine magnetic resonance spectra (^{1}H NMR, ^{13}C NMR and ^{19}F NMR) were recorded on a Bruker Ascend or AVANCE III spectrometer (^{1}H NMR at 400 MHz, 500 MHz or 600 MHz; ^{13}C NMR at 100 MHz, 125 MHz or 150 MHz; and ^{19}F NMR at 375 MHz or 565 MHz). Chemical shifts (δ) are reported in ppm from the solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 pm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm, DMSO-d_6 at 39.5 pm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet), coupling constants (Hz) and integration. High resolution mass spectra were performed using a Bruker micrOTOF II high resolution mass spectrometer. Melting points were uncorrected and were recorded on a WRR melting point apparatus.

2. General procedure and spectral data

2.1 General Procedure



Scheme S1 General synthetic route of compound **3-43**. Reagent and conditions: (a) 6N HCl/1,4-dioxane, 100 °C, 95% for **3a**; (b) alcohols, $SOCl_2$, 1,4-dioxane, 70 °C, 68-81%; (c) amines, HOBt, EDCI, DIPEA, DCM, rt, 64-88%.

Compounds **2** were synthesized according to procedures which were previously described by our group[1].

General procedure for the synthesis of 3

A solution of Compound **2** (2 mmol, 1 equiv.) in 10 mL of 1,4-dioxane and 10 mL of 6 N hydrochloric acid was heated to reflux at 100 °C for 12 h under nitrogen atmosphere. The reaction was monitored by means of TLC analysis. It was then cooled to room temperature. The reaction mixture was extracted with EtOAc. The combined organic phase was dried over Na_2SO_4, reduced to a residue. Then the crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate/acetic acid = 100:20:1) to afford the title compound **3**.

General procedure for the synthesis of 6 and 10

To a suspension of crude carboxylic acid **3a** and alcohol substrate (2 mmol, 2 equiv.) in 1,4-dioxane (10 mL), thionyl chloride (3 mmol, 3 equiv.) was added and the resulting mixture was stirred at 70 °C for 4 h. The reaction mixture was cooled to 0 °C and water (2 mL) were added. The reaction mixture was concentrated and the residue was distributed between EtOAc (30 mL) and water (30 mL) and the phases were separated. The aqueous layer was extracted with EtOAc (30 mL) and the combined organic layers were dried over Na_2SO_4, filtered and evaporated in vacuo to a residue. Then the crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate) to afford esters **6** and **10**.

General procedure for the synthesis of 11-43

To the solution of carboxylic acid **3** (1 mmol, 1 equiv.) in DCM (10 mL) was added HOBt (162 mg, 1.2 mmol, 1.2 equiv.), EDCI (230 mg, 1.2 mmol, 1.2 equiv.), DIPEA (322 mg, 2.5 mmol, 2.5 equiv.) and amine substrate (1.2 mmol, 1.2 equiv.). The reaction mixture was stirred at room temperature for 18 h. It was then quenched with NH_4Cl solution, extracted with EtOAc. The combined organic phase was dried over Na_2SO_4, reduced to a residue. Then the crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate) to afford the product amide **11-43**.

Reference

1 H. Q. Chen, J. Xie, D. Xing, J. P. Wang, J. Tang, Z. F. Yi, F. Xia, W. W. Qiu and F. Yang, *Org. Biomol. Chem.*, 2019, **17**, 1062.

2.2 Spectral Data of Products

2-((2*R,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetic acid (3a)**

White solid, 95% yield. m.p. 132-135 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.81 (br, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.69 (dd, J = 8.0, 7.5 Hz, 1H), 7.23 (dd, J = 7.8, 7.3 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 5.26 (d, J = 10.2 Hz, 1H), 3.25 (d, J = 16.6 Hz, 1H), 2.53 (dd, J = 16.7, 10.2 Hz, 1H), 1.81 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 182.54, 170.57, 160.09, 137.18, 127.79, 122.96, 119.67, 117.88, 90.28, 79.01, 35.10, 15.81. HRMS (ESI): Calcd for $C_{12}H_{11}NNaO_6$ $[M+Na]^+$: 288.0479. Found: 288.0496.

prop-2-yn-1-yl 2-((2*R,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetate (6)**

Colorless oil, 68% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (dd, J = 7.9, 1.3 Hz, 1H), 7.61-7.57 (m, 1H), 7.17-7.14 (m, 1H), 7.04 (d, J = 8.4 Hz, 1H), 5.61 (dd, J = 10.2, 2.3 Hz, 1H), 4.77 (d, J = 2.4 Hz, 2H), 2.93 (dd, J = 16.2, 10.2 Hz, 1H), 2.52-2.48 (m, 2H), 1.75 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.72, 167.67, 159.52, 137.54, 128.45, 123.22 (2C), 118.14, 92.01, 77.67, 76.88, 75.50, 52.83, 34.22, 14.28. HRMS (ESI): Calcd for $C_{15}H_{13}NNaO_6$ $[M+Na]^+$: 326.0635. Found: 326.0643.

benzyl 2-((2*R,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetate (10)**

Colorless oil, 77% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.2 Hz, 1H), 7.60-

7.56 (m, 1H), 7.37 (s, 5H), 7.15 (dd, *J* = 7.6, 7.4 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 5.63 (dd, *J* = 10.1, 1.9 Hz, 1H), 5.22-5.21 (m, 2H), 2.93 (dd, *J* = 16.0, 10.3 Hz, 1H), 2.50 (dd, *J* = 16.0, 1.9 Hz, 1H), 1.75 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.85, 168.24, 159.55, 137.49, 135.18, 128.64 (2C), 128.53, 128.46, 128.37 (2C), 123.17, 118.16, 118.11, 92.07, 77.90, 67.22, 34.50, 14.30. HRMS (ESI): Calcd for $C_{19}H_{17}NNaO_6$ $[M+Na]^+$: 378.0948. Found: 378.0933.

2-((2*R,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (11)**

White solid, 87% yield. m.p. 179-181 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.88 (d, *J* = 7.8 Hz, 1H), 7.73 (dd, *J* = 7.9, 7.6 Hz, 1H), 7.54 (s, 1H), 7.23 (dd, *J* = 7.6, 7.5 Hz, 1H), 7.16-7.12 (m, 2H), 5.53 (dd, *J* = 7.5, 2.2 Hz, 1H), 2.68 (dd, *J* = 15.5, 9.8 Hz, 1H), 2.35 (dd, *J* = 15.6, 2.5 Hz, 1H), 1.70 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 184.71, 169.00, 159.17, 138.16, 127.71, 123.13, 118.34, 117.86, 92.22, 78.82, 34.28, 14.70. HRMS (ESI): Calcd for $C_{12}H_{12}N_2NaO_5$ $[M+Na]^+$: 287.0638. Found: 287.0653.

***N*-methyl-2-((2*R**,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (12)**

White solid, 83% yield. m.p. 128-130 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.57-7.53 (m, 1H), 7.15 (dd, *J* = 7.2, 7.2 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 5.83 (s, 1H), 4.97 (dd, *J* = 9.1, 2.7 Hz, 1H), 2.90 (d, *J* = 4.8 Hz, 3H), 2.88-2.86 (m, 1H), 2.68 (dd, *J* = 15.3, 9.2 Hz, 1H), 1.83 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.91, 167.64, 159.45, 137.47, 128.44, 123.14, 118.30, 118.17, 92.17, 78.45, 35.90, 26.66, 14.54. HRMS (ESI): Calcd for $C_{13}H_{14}N_2NaO_5$ $[M+Na]^+$: 301.0795. Found: 301.0787.

***N*-ethyl-2-((2*R**,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (13)**

White solid, 80% yield. m.p. 134-136 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.60-7.56 (m, 1H), 7.15 (dd, *J* = 7.6, 7.4 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 5.64 (dd, *J* = 9.9, 2.3 Hz, 1H), 5.58 (s, 1H), 3.35 (dq, *J* = 7.2, 2.4 Hz, 2H), 2.62 (dd, *J* = 14.9, 9.9 Hz, 1H), 2.34 (dd, *J* = 15.0, 2.2 Hz, 1H), 1.75 (s, 3H), 1.17 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 185.00, 166.96, 159.50, 137.47, 128.31, 123.05, 118.21, 118.12, 92.22, 78.50, 35.92, 34.72, 14.64, 14.47. HRMS (ESI): Calcd for $C_{14}H_{16}N_2NaO_5$ $[M+Na]^+$: 315.0951. Found: 315.0970.

2-((2*R,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)-*N*-(prop-2-yn-1-yl)acetamide (14)**

White solid, 82% yield. m.p. 101-102 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.59-7.55 (m, 1H), 7.13 (dd, *J* = 7.6, 7.4 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.39 (t, *J* = 4.8 Hz, 1H), 5.62 (dd, *J* = 10.0, 2.1 Hz, 1H), 4.07 (dd, *J* = 4.7, 1.9 Hz, 2H), 2.72 (dd, *J* = 15.1, 10.0 Hz, 1H), 2.36 (dd, *J* = 15.1, 2.0 Hz, 1H), 2.23 (t, *J* = 2.4 Hz, 1H), 1.72 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.93, 167.08, 159.43, 137.55, 128.36, 123.15, 118.19, 118.15, 92.19, 78.96, 78.24, 71.90, 35.66, 29.46, 14.42. HRMS (ESI): Calcd for $C_{15}H_{14}N_2NaO_5$ $[M+Na]^+$: 325.0795. Found: 325.0785.

***N*-butyl-2-((2*R**,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (15)**

White solid, 78% yield. m.p. 106-108 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.8 Hz, 1H), 7.60-7.56 (m, 1H), 7.15 (dd, *J* = 7.6, 7.5 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 5.65-5.62

(m, 2H), 3.36-3.25 (m, 2H), 2.62 (dd, *J* = 14.8, 10.1 Hz, 1H), 2.34 (dd, *J* = 14.9, 2.1 Hz, 1H), 1.75 (s, 3H), 1.55-1.47 (m, 2H), 1.41-1.32 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.87, 166.93, 159.43, 137.45, 128.45, 123.13, 118.36, 118.09, 92.15, 78.61, 39.60, 36.10, 31.52, 19.96, 14.59, 13.70. HRMS (ESI): Calcd for $C_{16}H_{20}N_2NaO_5$ $[M+Na]^+$: 343.1264. Found: 343.1256.

***N*-(*tert*-butyl)-2-((2*R**,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (16)**

White solid, 78% yield. m.p. 192-193 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.9 Hz, 1H), 7.60-7.57 (m, 1H), 7.15 (dd, *J* = 7.6, 7.4 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 5.61 (dd, *J* = 9.9, 2.4 Hz, 1H), 5.42 (s, 1H), 2.54 (dd, *J* = 14.8, 9.9 Hz, 1H), 2.28 (dd, *J* = 14.8, 2.4 Hz, 1H), 1.74 (s, 3H), 1.37 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.86, 166.16, 159.46, 137.41, 128.46, 123.10, 118.47, 118.07, 92.13, 78.84, 51.89, 36.90, 28.71 (3C), 14.68. HRMS (ESI): Calcd for $C_{16}H_{20}N_2NaO_5$ $[M+Na]^+$: 343.1264. Found: 343.1267.

***N*-octyl-2-((2*R**,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (17)**

White solid, 82% yield. m.p. 93-95 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.8 Hz, 1H), 7.58 (dd, *J* = 7.6, 7.4 Hz, 1H), 7.14 (dd, *J* = 7.8, 7.3 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 5.67 (s, 1H), 5.63 (dd, *J* = 10.1, 2.4 Hz, 1H), 3.33-3.26 (m, 2H), 2.62 (dd, *J* = 14.9, 10.1 Hz, 1H), 2.33 (dd, *J* = 14.8, 2.4 Hz, 1H), 1.74 (s, 3H), 1.30-1.27 (m, 12H), 0.87 (t, *J* = 6.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.88, 166.91, 159.43, 137.43, 128.44, 123.12, 118.35, 118.10, 92.15, 78.60, 39.91, 36.09, 31.75, 29.48, 29.20 (2C), 26.83, 22.61, 14.58, 14.07. HRMS (ESI): Calcd for $C_{20}H_{28}N_2NaO_5$ $[M+Na]^+$: 399.1890. Found: 399.1902.

***N*-cyclohexyl-2-((2*R**,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (18)**

White solid, 82% yield. m.p. 142-145 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.60-7.56 (m, 1H), 7.17-7.13 (m, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 5.62 (dd, *J* = 10.0, 2.5 Hz, 1H), 5.46 (d, *J* = 7.4 Hz, 1H), 3.87-3.78 (m, 1H), 2.59 (dd, *J* = 14.8, 10.0 Hz, 1H), 2.33 (dd, *J* = 14.8, 2.5 Hz, 1H), 1.98-1.90 (m, 2H), 1.75 (s, 3H), 1.72-1.70 (m, 2H), 1.41-1.34 (m, 2H), 1.22-1.11 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.83, 165.97, 159.42, 137.43, 128.44, 123.11, 118.44, 118.09, 92.15, 78.72, 48.63, 36.25, 33.11, 32.96, 25.42, 24.76, 24.73, 14.64. HRMS (ESI): Calcd for $C_{18}H_{22}N_2NaO_5$ $[M+Na]^+$: 369.1421. Found: 369.1439.

***N*-(adamantan-1-yl)-2-((2*R**,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (19)**

White solid, 84% yield. m.p. 161-163 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.7 Hz, 1H), 7.58 (dd, *J* = 7.5, 7.2 Hz, 1H), 7.14 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 5.59 (d, *J* = 9.3 Hz, 1H), 5.29 (s, 1H), 2.55 (dd, *J* = 14.5, 10.0 Hz, 1H), 2.28 (dd, *J* = 14.7, 2.5 Hz, 1H), 2.09-2.08 (m, 3H), 2.01-2.00 (m, 6H), 1.74 (s, 3H), 1.68-1.68 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.89, 165.90, 159.47, 137.39, 128.42, 123.06, 118.45, 118.11, 92.16, 78.85, 52.56, 41.54 (3C), 36.95, 36.22 (3C), 29.35 (3C), 14.68. HRMS (ESI): Calcd for $C_{22}H_{26}N_2NaO_5$ $[M+Na]^+$: 421.1734. Found: 421.1748.

2-((2*R,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)-*N*-phenylacetamide (20)**

White solid, 68% yield. m.p. 91-93 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.8 Hz, 1H), 7.60-7.56 (m, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.33 (dd, *J* = 7.8, 7.5 Hz, 2H), 7.15 (dd,

J = 13.5, 6.9 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 5.72 (d, *J* = 10.0 Hz, 1H), 2.85 (dd, *J* = 15.1, 10.1 Hz, 1H), 2.51 (dd, *J* = 15.1, 1.6 Hz, 1H), 1.77 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.85, 165.33, 159.40, 137.58, 137.24, 129.11 (2C), 128.49, 124.89, 123.27, 120.00 (2C), 118.26, 118.13, 92.17, 78.32, 36.98, 14.53. HRMS (ESI): Calcd for $C_{18}H_{16}N_2NaO_5$ $[M+Na]^+$: 363.0951. Found: 363.0962.

***N*-benzyl-2-((2*R**,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (21)**

White solid, 85% yield. m.p. 187-189 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.63 (dd, *J* = 5.3, 5.2 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.74 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.35 (d, *J* = 7.4, 7.4 Hz, 2H), 7.27 (d, *J* = 7.6 Hz, 2H), 7.24 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 1H), 5.59 (d, *J* = 9.9 Hz, 1H), 4.38 (dd, *J* = 15.2, 6.0 Hz, 1H), 4.26 (dd, *J* = 15.2, 5.5 Hz, 1H), 2.79 (dd, *J* = 15.1, 10.2 Hz, 1H), 2.49 (dd, *J* = 15.1, 1.6 Hz, 1H), 1.72 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 184.57, 167.14, 159.05, 139.06, 138.19, 128.30 (2C), 127.76, 127.15 (2C), 126.86, 123.18, 118.23, 117.93, 92.18, 79.00, 42.24, 34.58, 14.74. HRMS (ESI): Calcd for $C_{19}H_{18}N_2NaO_5$ $[M+Na]^+$: 377.1108. Found: 377.1112.

2-((2*R,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)-*N*-(thiazol-2-yl)acetamide (22)**

Prepared according to the general procedure B to provide the title compound as a yellow solid, 73% yield. m.p. 182-183 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.29 (brs, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.58-7.54 (m, 1H), 7.37 (d, *J* = 3.5 Hz, 1H), 7.15 (dd, *J* = 7.6, 7.4 Hz, 1H), 7.06 (d, *J* = 3.6 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 5.80 (dd, *J* = 9.9, 1.9 Hz, 1H), 3.05 (dd, *J* = 15.4, 10.0 Hz, 1H), 2.68 (dd, *J* = 15.4, 1.9 Hz, 1H), 1.82 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.52, 165.49, 159.68, 159.30, 137.59, 135.91, 128.47, 123.35, 118.27, 118.17, 114.52, 91.96, 77.84, 35.71, 14.72. HRMS (ESI): Calcd for $C_{15}H_{13}N_3NaO_5S$ $[M+Na]^+$: 370.0468. Found: 370.0474.

2-((2*R,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)-*N*-(pyrimidin-2-yl)acetamide (23)**

Prepared according to the general procedure B to provide the title compound as a yellow solid, 72% yield. m.p. 217-219 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 10.98 (s, 1H), 9.34 (s, 1H), 8.42 (dd, *J* = 2.5, 1.5 Hz, 1H), 8.39 (d, *J* = 2.5 Hz, 1H), 7.90 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.73-7.70 (m, 1H), 7.24 (dd, *J* = 7.4, 7.3 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 5.67 (dd, *J* = 9.8, 2.7 Hz, 1H), 3.17 (dd, *J* = 15.9, 9.9 Hz, 1H), 2.81 (dd, *J* = 15.8, 2.7 Hz, 1H), 1.75 (s, 3H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 184.45, 167.34, 159.00, 148.35, 142.69, 140.09, 138.18, 136.22, 127.73, 123.24, 118.37, 117.88, 92.07, 78.36, 35.21, 14.74. HRMS (ESI): Calcd for $C_{16}H_{14}N_4NaO_5$ $[M+Na]^+$: 365.0856. Found: 365.0864.

***N*-(1*H*-indol-5-yl)-2-((2*R**,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (24)**

Prepared according to the general procedure B to provide the title compound as a yellow solid, 77% yield. m.p. 184-187 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 9.94 (s, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.85 (s, 1H), 7.72 (dd, *J* = 8.1, 7.4 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.31 (s, 1H), 7.24 (dd, *J* = 7.7, 7.4 Hz, 1H), 7.17 (d, *J* = 7.9 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 1H), 6.38 (s, 1H), 5.66 (dd, *J* = 9.5, 2.3 Hz, 1H), 2.94 (dd, *J* = 15.4, 9.7 Hz, 1H), 2.67 (dd, *J* = 15.4, 2.2 Hz, 1H), 1.77 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 184.67, 165.25, 159.16, 138.20, 132.83, 130.75, 127.75, 127.43, 126.01, 123.20, 118.39, 117.94, 114.73, 111.23,

110.83, 101.12, 92.25, 78.88, 35.55, 14.82. HRMS (ESI): Calcd for $C_{20}H_{17}N_3NaO_5$ $[M+Na]^+$: 402.1060. Found: 402.1071.

***N*-(benzo[d]thiazol-2-yl)-2-((2*R**,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (25)**

White solid, 79% yield. m.p. 122-125 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 12.41 (brs, 1H), 7.87 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.1 Hz, 1H), 7.54 (dd, J = 7.4, 7.4 Hz, 1H), 7.49 (dd, J = 7.7, 7.7 Hz, 1H), 7.38 (dd, J = 7.7, 7.5 Hz, 1H), 7.10 (dd, J = 7.7, 7.5 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 5.76 (d, J = 9.9 Hz, 1H), 2.95 (dd, J = 15.5, 10.2 Hz, 1H), 2.61 (d, J = 15.5 Hz, 1H), 1.45 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 184.51, 166.47, 159.93, 159.19, 147.18, 137.54, 131.81, 128.43, 126.82, 124.61, 123.33, 122.00, 120.10, 118.02, 117.93, 91.91, 77.63, 36.12, 14.16. HRMS (ESI): Calcd for $C_{19}H_{15}N_3NaO_5S$ $[M+Na]^+$: 420.0625. Found: 420.0643.

***N′*-(benzo[*d*]thiazol-2-yl)-2-((2*R**,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetohydrazide (26)**

White solid, 72% yield. m.p. 208-210 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 (d, J = 7.7 Hz, 1H), 7.82 (dd, J = 11.9, 8.4 Hz, 2H), 7.58 (dd, J = 7.3, 7.3 Hz, 1H), 7.46 (dd, J = 7.6, 7.0 Hz, 1H), 7.34 (dd, J = 7.3, 7.3 Hz, 1H), 7.15 (dd, J = 7.5, 7.4 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 5.83 (d, J = 9.3 Hz, 1H), 4.86 (s, 2H), 3.73 (dd, J = 16.6, 9.8 Hz, 1H), 2.91 (d, J = 16.7 Hz, 1H), 1.86 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 185.07, 169.87, 159.87, 159.75, 147.64, 137.46, 133.74, 128.47, 126.30, 124.41, 123.10, 121.49, 121.39, 118.25, 118.22, 92.33, 77.49, 34.19, 14.57. HRMS (ESI): Calcd for $C_{19}H_{16}N_4NaO_5S$ $[M+Na]^+$: 435.0734. Found: 435.0739.

***N*-cyclohexyl-*N*-methyl-2-((2*R**,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (27)**

White solid, 83% yield. m.p. 88-90 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.7 Hz, 1H), 7.58-7.54 (m, 1H), 7.15-7.11 (m, 1H), 7.04 (d, J = 7.9 Hz, 1H), 5.78-5.75 (m, 1H), 4.48-4.44 (m, 0.6H), 3.43-3.38 (m, 0.4H), 2.96-2.88 (m, 1H), 2.86 (s, 1.2H), 2.82 (s, 1.8H), 2.35-2.29 (m, 1H), 1.86-1.81 (m, 2H), 1.78 (s, 3H), 1.68-1.63 (m, 4H), 1.40-1.08 (m, 4H), reflecting an amide conformer mixture in about 3:2 ratio. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 185.28, 166.52, 159.90, 137.32, 128.36, 122.88, 118.25, 92.44, 78.43, 56.83, 52.90, 33.39, 32.72, 29.81, 29.74, 29.55, 27.66, 25.13, 14.73. HRMS (ESI): Calcd for $C_{19}H_{24}N_2NaO_5$ $[M+Na]^+$: 383.1577. Found: 383.1589.

***N,N*-dimethyl-2-((2*R**,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (28)**

White solid, 87% yield. m.p. 87-89 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) 8.00 (d, J = 7.9, 1.4 Hz, 1H), 7.57-7.52 (m, 1H), 7.14 (dd, J = 7.8, 7.4 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 5.13 (dd, J = 8.0, 2.7 Hz, 1H), 3.11 (s, 3H), 3.04 (s, 3H), 3.03 (dd, J = 16.3, 8.1 Hz, 1H), 2.89 (dd, J = 16.4, 2.6 Hz, 1H), 1.83 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 182.61, 168.10, 160.76, 136.79, 128.39, 122.89, 119.66, 118.07, 89.79, 80.20, 37.33, 35.90, 33.79, 16.59. HRMS (ESI): Calcd for $C_{14}H_{16}N_2NaO_5$ $[M+Na]^+$: 315.0951. Found: 315.0970.

***N*-cyclopentyl-2-((2*R**,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (29)**

White solid, 67% yield. m.p. 203-205 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (dd, J = 7.9, 1.6 Hz, 1H), 7.60-7.56 (m, 1H), 7.17-7.13 (m, 1H), 7.01 (d, J = 8.3 Hz, 1H), 5.62 (dd, J =

10.0, 2.4 Hz, 1H), 5.56-5.55 (m, 1H), 4.30-4.21 (m, 1H), 2.60 (dd, *J* = 14.9, 10.0 Hz, 1H), 2.32 (dd, *J* = 14.9, 2.4 Hz, 1H), 2.04-1.99 (m, 2H), 1.75 (s, 3H), 1.65-1.63 (m, 6H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 184.84, 166.50, 159.41, 137.45, 128.46, 123.13, 118.42, 118.08, 92.14, 78.67, 51.59, 36.13, 33.15, 32.98, 23.66 (2C), 14.63. HRMS (ESI): Calcd for $C_{17}H_{20}N_2NaO_5$ $[M+Na]^+$: 355.1264. Found: 355.1266.

methyl (1*R*,4*r*)-4-(2-((2*R,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamido)cyclohex-ane-1-carboxylate (30)**

White solid, 73% yield. m.p. 215-217 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.61-7.56 (m, 1H), 7.17-7.13 (m, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 5.61 (dd, *J* = 10.0, 2.5 Hz, 1H), 5.43 (d, *J* = 8.1 Hz, 1H), 3.84-3.77 (m, 1H), 3.67 (s, 3H), 2.60 (dd, *J* = 14.9, 10.0 Hz, 1H), 2.33 (dd, *J* = 14.8, 2.4 Hz, 1H), 2.28-2.24 (m, 1H), 2.10-2.01 (m, 4H), 1.75 (s, 3H), 1.62-1.54 (m, 2H), 1.19-1.12 (m, 2H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 184.80, 175.58, 166.25, 159.39, 137.48, 128.49, 123.18, 118.38, 118.05, 92.13, 78.59, 51.72, 48.19, 42.25, 36.19, 32.11, 31.97, 27.63, 27.61, 14.59. HRMS (ESI): Calcd for $C_{20}H_{24}N_2NaO_7$ $[M+Na]^+$: 427.1476. Found: 427.1471.

***N*-(cyclohexylmethyl)-2-((2*R**,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (31)**

White solid, 60% yield. m.p. 138-140 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.60-7.56 (m, 1H), 7.17-7.13 (m, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 5.67 (s, 1H), 5.63 (dd, *J* = 10.2, 2.3 Hz, 1H), 3.24-3.17 (m, 1H), 3.14-3.07 (m, 1H), 2.62 (dd, *J* = 14.8, 10.2 Hz, 1H), 2.35 (dd, *J* = 14.8, 2.2 Hz, 1H), 1.75 (s, 3H), 1.73-1.67 (m, 5H), 1.53-1.45 (m, 1H), 1.29-1.17 (m, 5H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 184.85, 167.00, 159.41, 137.44, 128.49, 123.15, 118.40, 118.05, 92.14, 78.70, 46.03, 37.88, 36.20, 30.71 (2C), 26.30, 25.74, 25.73, 14.60. HRMS (ESI): Calcd for $C_{19}H_{24}N_2NaO_5$ $[M+Na]^+$: 383.1577. Found: 383.1574.

***N*-(3,5-dimethyladamantan-1-yl)-2-((2*R**,3*R**)-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (32)**

White solid, 62% yield. m.p. 131-133 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.61-7.57 (m, 1H), 7.17-7.13 (m, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 5.59 (dd, *J* = 9.8, 2.5 Hz, 1H), 5.30 (s, 1H), 2.54 (dd, *J* = 14.9, 9.8 Hz, 1H), 2.28 (dd, *J* = 14.9, 2.5 Hz, 1H), 2.17-2.14 (m, 1H), 1.86-1.84 (m, 2H), 1.74 (s, 3H), 1.68-1.65 (m, 4H), 1.40-1.37 (m, 2H), 1.31-1.28 (m, 2H), 1.17-1.16 (m, 2H), 0.86 (s, 6H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 184.86, 165.99, 159.45, 137.41, 128.44, 123.08, 118.45, 118.12, 92.13, 78.82, 54.17, 50.46, 47.49, 47.47, 42.53 (2C), 40.09, 36.96, 32.40 (2C), 30.04, 30.00 (2C), 14.71. HRMS (ESI): Calcd for $C_{24}H_{30}N_2NaO_5$ $[M+Na]^+$: 449.2047. Found: 449.2054.

***N*-(adamantan-1-yl)-2-((2*R**,3*R**)-3-ethyl-3-nitro-4-oxochroman-2-yl)acetamide (33)**

Hydrolysis of corresponding ester **2** (2 mmol, 1 equiv.) in 10 mL of 1,4-dioxane and 10 mL of 6 N hydrochloric acid gave the crude acid product according to general procedure for the synthesis of **3**. Then it was used for next step directly to give title product following the general condensation procedure. White solid, 81% yield. m.p. 186-188 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.8 Hz, 1H), 7.57 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.13 (dd, *J* = 7.7, 7.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 5.62 (dd, *J* = 9.9, 2.3 Hz, 1H), 5.23 (s, 1H), 2.51 (dd, *J* =

14.8, 10.1 Hz, 1H), 2.27 (dd, *J* = 14.9, 2.5 Hz, 1H), 2.18 (dd, *J* = 14.7, 7.3 Hz, 2H), 2.10-2.08 (m, 3H), 2.01-1.99 (m, 6H), 1.68-1.66 (m, 6H), 1.03 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 183.81, 165.94, 158.82, 137.21, 128.12, 122.87, 119.21, 118.11, 94.96, 79.26, 52.56, 41.52 (3C), 36.50, 36.21 (3C), 29.34 (3C), 21.93, 8.22. HRMS (ESI): Calcd for $C_{23}H_{28}N_2NaO_5$ $[M+Na]^+$: 435.1890. Found: 435.1866.

***N*-cyclohexyl-2-((2*R**,3*R**)-3-ethyl-3-nitro-4-oxochroman-2-yl)acetamide (34)**

Following the procedure for synthesis of **33**.White solid, 78% yield. m.p. 156-158 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.58-7.54 (m, 1H), 7.15-7.11 (m, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 5.64 (dd, *J* = 10.4, 2.4 Hz, 1H), 5.46 (d, *J* = 7.6 Hz, 1H), 3.84-3.76 (m, 1H), 2.56 (dd, *J* = 14.9, 10.2 Hz, 1H), 2.32 (dd, *J* = 14.8, 2.6 Hz, 1H), 2.21-2.16 (m, 2H), 1.96-1.88 (m, 2H), 1.73-1.68 (m, 2H), 1.60-1.59 (m, 1H), 1.42-1.31 (m, 2H), 1.18-1.09 (m, 3H), 1.03 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 183.79, 166.04, 158.78, 137.26, 128.11, 122.92, 119.17, 118.08, 94.98, 79.15, 48.62, 35.77, 33.08, 32.93, 25.38, 24.73, 24.72, 21.82, 8.22. HRMS (ESI): Calcd for $C_{19}H_{24}N_2NaO_5$ $[M+Na]^+$: 383.1577. Found: 383.1565.

***N*-(adamantan-1-yl)-2-((2*R**,3*R**)-3-methyl-3-nitro-4-oxo-6-(trifluoromethyl)chroman-2-yl)acetamide (35)**

Following the procedure for synthesis of **33**. White solid, 64% yield. m.p. 115-117 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.78 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 1H), 5.37 (s, 1H), 4.98 (dd, *J* = 8.9, 2.9 Hz, 1H), 2.85 (dd, *J* = 15.2, 3.0 Hz, 1H), 2.62 (dd, *J* = 15.2, 9.0 Hz, 1H), 2.11-2.09 (m, 3H), 2.04-2.02 (m, 6H), 1.84 (s, 3H), 1.70-1.68 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 181.54, 166.40, 162.41, 133.07, 133.04, 126.25, 126.21, 119.45, 119.00, 89.39, 80.63, 52.72, 41.53 (3C), 38.13, 36.20 (3C), 29.34 (3C), 16.22. **^{19}F NMR** (375 MHz, $CDCl_3$) δ -62.43. HRMS (ESI): Calcd for $C_{23}H_{25}F_3N_2NaO_5$ $[M+Na]^+$: 489.1608. Found: 489.1633.

***N*-(adamantan-1-yl)-2-((2*R**,3*R**)-6-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (36)**

Following the procedure for synthesis of **33**. White solid, 77% yield. m.p. 169-171 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.8, 3.0 Hz, 1H), 7.33-7.28 (m, 1H), 7.02 (dd, *J* = 9.1, 4.0 Hz, 1H), 5.58 (dd, *J* = 9.6, 2.4 Hz, 1H), 5.25 (s, 1H), 2.53 (dd, *J* = 14.9, 9.7 Hz, 1H), 2.27 (dd, *J* = 14.9, 2.4 Hz, 1H), 2.08-2.6 (m, 3H), 2.01-1.99 (m, 6H), 1.73 (s, 3H), 1.68-1.65 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.19, 165.65, 157.99 (d, *J* = 243.3 Hz), 155.78, 125.06 (d, *J* = 24.5 Hz), 120.01 (d, *J* = 7.5 Hz), 119.19 (d, *J* = 7.0 Hz), 113.32 (d, *J* = 23.8 Hz), 91.93, 79.25, 52.65, 41.61 (3C), 36.80, 36.25 (3C), 29.40 (3C), 14.76. **^{19}F NMR** (375 MHz, $CDCl_3$) δ -118.51. HRMS (ESI): Calcd for $C_{22}H_{25}FN_2NaO_5$ $[M+Na]^+$: 439.1640. Found: 439.1635.

***N*-(adamantan-1-yl)-2-((2*R**,3*R**)-6-chloro-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (37)**

Following the procedure for synthesis of **33**. White solid, 72% yield. m.p. 142-144 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 2.3 Hz, 1H), 7.44 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.93

(d, *J* = 8.9 Hz, 1H), 5.46 (s, 1H), 4.65 (dd, *J* = 9.3, 2.0 Hz, 1H), 2.77 (dd, *J* = 15.0, 2.1 Hz, 1H), 2.55 (dd, *J* = 15.0, 9.5 Hz, 1H), 2.08-2.06 (m, 3H), 2.05-2.02 (m, 6H), 1.68-1.65 (m, 6H), 1.26 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.89, 168.14, 159.25, 136.44, 127.60, 127.00, 119.53, 118.85, 80.44, 72.30, 52.29, 41.62 (3C), 36.74, 36.28 (3C), 29.39 (3C), 18.15. HRMS (ESI): Calcd for $C_{22}H_{25}ClN_2NaO_5$ $[M+Na]^+$: 455.1344. Found: 455.1345.

_N_-(adamantan-1-yl)-2-((2_R_*,3_R_*)-6-bromo-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (38)

Following the procedure for synthesis of **33**. White solid, 79% yield. m.p. 138-140 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 2.1 Hz, 1H), 7.64 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 5.59 (dd, *J* = 9.6, 2.4 Hz, 1H), 5.32 (s, 1H), 2.53 (dd, *J* = 14.9, 9.7 Hz, 1H), 2.28 (dd, *J* = 14.9, 2.4 Hz, 1H), 2.09-2.07 (m, 3H), 1.98- (s, 6H), 1.72 (s, 3H), 1.67-1.65 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 183.66, 165.59, 158.31, 140.01, 130.57, 120.19, 119.81, 115.72, 91.70, 79.08, 52.61, 41.49 (3C), 36.64, 36.18 (3C), 29.32 (3C), 14.81. HRMS (ESI): Calcd for $C_{22}H_{25}BrN_2NaO_5$ $[M+Na]^+$: 499.0839. Found: 499.0817.

_N_-(adamantan-1-yl)-2-((2_R_*,3_R_*)-3,6-dimethyl-3-nitro-4-oxochroman-2-yl)acetamide (39)

Following the procedure for synthesis of **33**. White solid, 82% yield. m.p. 119-121 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 5.54-5.52 (m, 1H), 5.41 (s, 1H), 2.57-2.51 (m, 1H), 2.32 (s, 3H), 2.24 (dd, *J* = 14.8, 2.5 Hz, 1H), 2.07-20.5 (m, 3H), 1.99-1.97 (m, 6H), 1.71 (s, 3H), 1.67-1.65 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 185.08, 166.04, 157.55, 138.52, 132.72, 127.78, 117.97, 117.85, 92.26, 78.78, 52.45, 41.46 (3C), 36.89, 36.19 (3C), 29.31 (3C), 20.39, 14.63. HRMS (ESI): Calcd for $C_{23}H_{28}N_2NaO_5$ $[M+Na]^+$: 435.1890. Found: 435.1903.

_N_-(adamantan-1-yl)-2-((2_R_*,3_R_*)-6-methoxy-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (40)

Following the procedure for synthesis of **33**. White solid, 83% yield. m.p. 156-158 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 2.9 Hz, 1H), 7.18 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.59 (d, *J* = 9.0 Hz, 1H), 5.53 (dd, *J* = 9.9, 2.2 Hz, 1H), 5.26 (s, 1H), 3.82 (s, 3H), 2.53 (dd, *J* = 14.8, 9.9 Hz, 1H), 2.25 (dd, *J* = 14.8, 2.2 Hz, 1H), 2.09-2.07 (m, 3H), 2.04-2.00 (m, 6H), 1.73 (s, 3H), 1.68-1.65 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 185.01, 165.95, 155.19, 154.19, 126.83, 119.43, 118.42, 108.23, 92.30, 79.07, 55.88, 52.55, 41.57 (3C), 36.99, 36.24 (3C), 29.37 (3C), 14.72. HRMS (ESI): Calcd for $C_{23}H_{28}N_2NaO_6$ $[M+Na]^+$: 451.1840. Found: 451.1850.

_N_-(adamantan-1-yl)-2-((2_R_*,3_R_*)-5-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (41)

White solid, 54% yield. m.p. 76-78 °C. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.54-7.50 (m, 1H), 6.84-6.81 (m, 2H), 5.62 (dd, *J* = 9.7, 2.7 Hz, 1H), 5.24 (s, 1H), 2.52 (dd, *J* = 14.9, 9.6 Hz, 1H), 2.30 (dd, *J* = 14.9, 2.8 Hz, 1H), 2.09-2.08 (m, 3H), 2.01-2.00 (m, 6H), 1.74 (s, 3H), 1.69-1.68 (m, 6H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 181.89, 165.60, 162.29 (d, *J* = 267.9 Hz), 159.94 (d, *J* = 2.0 Hz), 137.50 (d, *J* = 11.6 Hz), 113.91 (d, *J* = 3.8 Hz), 110.47 (d, *J* = 20.4 Hz), 109.01

(d, J = 9.8 Hz), 92.11, 78.80, 52.65, 41.56 (3C), 36.72, 36.23 (3C), 29.37 (3C), 14.98. **^{19}F NMR** (565 MHz, $CDCl_3$) δ -107.97 (dd, J = 9.7, 6.0 Hz, 1F). HRMS (ESI): Calcd for $C_{22}H_{25}FN_2NaO_5$ $[M+Na]^+$: 439.1640. Found: 439.1637.

***N*-(adamantan-1-yl)-2-((2*R**,3*R**)-7-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (42)**

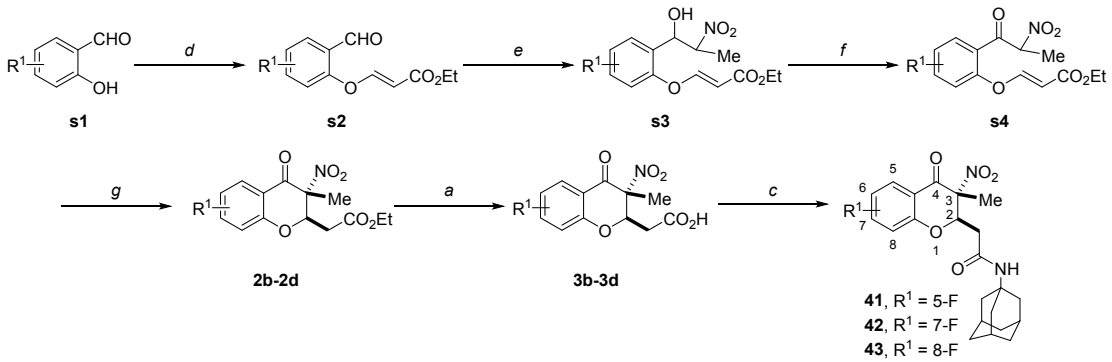
White solid, 75% yield. m.p. 126-128 °C. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.98 (dd, J = 8.8, 6.3 Hz, 1H), 6.88-6.85 (m, 1H), 6.72 (dd, J = 9.3, 2.3 Hz, 1H), 5.63 (dd, J = 9.7, 2.6 Hz, 1H), 5.24 (s, 1H), 2.53 (dd, J = 14.9, 9.7 Hz, 1H), 2.29 (dd, J = 14.9, 2.6 Hz, 1H), 2.09-2.08 (m, 3H), 2.01-2.00 (m, 6H), 1.73 (s, 3H), 1.69-1.68 (m, 6H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 183.56, 168.20 (d, J = 258.6 Hz), 165.57, 161.27 (d, J = 13.8 Hz), 131.09 (d, J = 11.3 Hz), 115.38, 111.74 (d, J = 22.6 Hz), 105.20 (d, J = 24.6 Hz), 91.83, 79.37, 52.67, 41.59 (3C), 36.84, 36.23 (3C), 29.38 (3C), 14.79. **^{19}F NMR** (565 MHz, $CDCl_3$) δ -96.93 (dd, J = 15.9, 8.2 Hz, 1F). HRMS (ESI): Calcd for $C_{22}H_{25}FN_2NaO_5$ $[M+Na]^+$: 439.1640. Found: 439.1652.

***N*-(adamantan-1-yl)-2-((2*R**,3*R**)-8-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetamide (43)**

White solid, 65% yield. m.p. 90-92 °C. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.74-7.73 (m, 1H), 7.40-7.37 (m, 1H), 7.11-7.08 (m, 1H), 5.62 (dd, J = 9.9, 2.5 Hz, 1H), 5.47 (s, 1H), 2.62 (dd, J = 14.8, 10.0 Hz, 1H), 2.29 (dd, J = 14.8, 2.5 Hz, 1H), 2.09-2.08 (m, 3H), 2.01-2.00 (m, 6H), 1.76 (s, 3H), 1.69-1.68 (m, 6H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 184.02 (d, J = 3.0 Hz), 165.61, 151.31 (d, J = 249.5 Hz), 147.76 (d, J = 12.1 Hz), 123.46 (d, J = 3.9 Hz), 123.28 (d, J = 17.1 Hz), 122.79 (d, J = 6.0 Hz), 120.57, 92.07, 79.79, 52.63, 41.43 (3C), 37.09, 36.25 (3C), 29.39 (3C), 14.64. **^{19}F NMR** (565 MHz, $CDCl_3$) δ -133.50 (dd, J = 10.0, 3.8 Hz, 1F). HRMS (ESI): Calcd for $C_{22}H_{25}FN_2NaO_5$ $[M+Na]^+$: 439.1640. Found: 439.1627.

***N*-(adamantan-1-yl)-2-((2*R**,3*R**)-6-fluoro-3-methyl-3-amino-4-oxochroman-2-yl)acetamide (44)**

A suspension of **36** (83 mg, 0.2 mmol, 1.0 equiv) in ethanol (5 mL) was heated at reflux. Iron powder (110 mg, 2.0 mmol) and an aqueous solution of NH_4Cl (100 mg dissolved in 0.8 mL of water) were added. The reaction was stirred at reflux to completeness. The warm mixture was filtered through a Celite patch and the remaining solids were washed several times with warm EtOH. The filtrates were combined and concentrated. The residue was purified by column chromatography (dichloromethane/methanol = 50:1) on silica gel to afford compound **44**. White solid, 79% yield. m.p. 93-95 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52-7.50 (m, 1H), 7.22-7.18 (m, 1H), 6.94-6.92 (m, 1H), 5.58 (s, 1H), 4.57 (d, J = 8.9 Hz, 1H), 2.82 (d, J = 14.9 Hz, 1H), 2.50 (dd, J = 14.5, 9.2 Hz, 1H), 2.08-2.07 (m, 3H), 2.03-2.02 (m, 6H), 1.86 (s, 3H), 1.69-1.68 (m, 6H), 1.18 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.98 (d, J = 0.9 Hz), 168.67, 157.51 (d, J = 241.0 Hz), 156.69 (d, J = 2.5 Hz), 123.64 (d, J = 24.5 Hz), 119.33 (d, J = 7.5 Hz), 119.22 (d, J = 6.6 Hz), 112.75 (d, J = 23.2 Hz), 81.54, 57.66, 52.19, 41.61 (3C), 37.44, 36.29 (3C), 29.38 (3C), 18.67. **^{19}F NMR** (375 MHz, $CDCl_3$) δ -120.69. HRMS (ESI): Calcd for $C_{22}H_{28}FN_2O_3$ $[M+H]^+$: 387.2078. Found: 387.2062.



Scheme S2 General synthetic route of compound **41-43**. Reagent and conditions: (d) ethyl propiolate, 4-methylmorpholine, DCM, 0 °C - rt, 77-88%; (e) $EtNO_2$, 4-methylmorpholine, KF, *i*PrOH, 0 °C - rt, 80-98%;(f) DMP, DCM, 0 °C - rt, 85-91%;(g) *t*BuOK, THF, -40 °C, 75-94%; (a) 6N HCl/1,4-dioxane, 100 °C, 65-97%; (c) amines, HOBt, EDCI, DIPEA, DCM, rt, 54-75%.

Compounds **s1**, **s2**, **s3**, **s4** and **2** were synthesized according to procedures which were previously described by our group[1].

General procedure for the synthesis of s2b-s2d

To a mixture of fluoro-substituted 2-hydroxybenzaldehyde **s1** (560 mg, 4 mmol, 1 equiv.) and ethyl propiolate (440 mg, 4.4 mmol, 1.1 equiv.) in DCM (20 mL) at 0 °C was added 4-methylmorpholine (80 mg, 0.8 mmol, 0.2 equiv.) under N_2 atmosphere. The mixture was allowed to rise to room temperature and stirred for another 2 h. The mixture was quenched with 1N HCl and extracted 3 times with EtOAc. Combined organic phases were dried over sodium sulfate, filtered and purified by column chromatography (petroleum ether/ethyl acetate) on silica gel to afford **s2b-s2d**.

General procedure for the synthesis of s3b-s3d

To a mixture of fluoro-substituted ethyl (*E*)-3-(2-formylphenoxy)acrylate derivatives **s2b-s2d** (830 mg, 3.5 mmol, 1 equiv.) and nitroethane (790 mg, 10.5 mmol, 3 equiv.) in *i*PrOH (20 mL) at 0 °C was added 4-methylmorpholine (35 mg, 0.35 mmol, 0.1 equiv.) and KF (20 mg, 0.35 mmol, 0.1 equiv.) under N_2 atmosphere. The mixture was allowed to rise to room temperature and stirred for another 18 h. The mixture was quenched with 1N HCl and extracted 3 times with EtOAc. Combined organic phases were dried over sodium sulfate, filtered and purified by column chromatography (petroleum ether/ethyl acetate) on silica gel to afford **s3b-s3d**.

General procedure for the synthesis of s4b-s4d

To a solution of fluoro-substituted ethyl (*E*)-3-(2-(1-hydroxy-2-nitropropyl)phenoxy)-acrylate **s3b-s3d** (626 mg, 2 mmol, 1 equiv.) in DCM (20 mL) at 0 °C was added Dess-Martin periodinane (1020 mg, 2.4 mmol, 1.2 equiv.) under N_2 atmosphere. The mixture was allowed to rise to room temperature and stirred for another 18 h. The slurry was purified directly by column chromatography (dichloromethane/acetic acid = 100:1) on silica gel. The eluent fractions were collected and washed with water. Combined organic phases were dried over sodium sulfate and concentrated. Removal of the residual acetic acid in vacuo to afford

compound **s4b-s4d**.

General procedure for the synthesis of 2b-2d

A catalytic amount of *t*BuOK (11 mg, 0.1 mmol, 0.1 equiv.) was added to the corresponding α-nitro-acetophenone **s4b-s4d** (1 mmol, 1 equiv.) dissolved in THF (5 mL) at -40 °C. The reaction was monitored by TLC analysis and was completed in 4 h. To the crude reaction mixture was added 1N HCl (1 mL) and extracted with EtOAc. Combined organic phases were dried over sodium sulfate, filtered and purified by column chromatography (petroleum ether/ethyl acetate) on silica gel to afford 2**b-2d**.

ethyl (*E*)-3-(3-fluoro-2-formylphenoxy)acrylate (s2b)

Column chromatography eluent petroleum ether/ethyl acetate = 5:1. Yellow oil, 88% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 7.75 (d, J = 12.2 Hz, 1H), 7.61-7.56 (m, 1H), 7.05-7.00 (m, 1H), 6.96 (d, J = 8.7 Hz, 1H), 5.64 (d, J = 12.2 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 185.40 (d, J = 3.4 Hz), 166.31, 163.20 (d, J = 262.3 Hz), 157.42, 157.00 (d, J = 4.5 Hz), 136.07 (d, J = 11.2 Hz), 115.96 (d, J = 9.3 Hz), 114.16 (d, J = 3.5 Hz), 113.28 (d, J = 21.5 Hz), 104.49, 60.37, 14.19. **^{19}F NMR** (565 MHz, $CDCl_3$) δ -113.86 (dd, J = 15.4, 11.8 Hz, 1F). HRMS (ESI): Calcd for $C_{12}H_{11}FNaO_4$ $[M+Na]^+$: 261.0534. Found: 261.0523.

ethyl (*E*)-3-(5-fluoro-2-formylphenoxy)acrylate (s2c)

Column chromatography eluent petroleum ether/ethyl acetate = 10:1. Colorless oil, 87% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.29 (s, 1H), 7.98-7.94 (m, 1H), 7.78 (d, J = 12.2 Hz, 1H), 7.03-6.99 (m, 1H), 6.88 (d, J = 9.2 Hz, 1H), 5.72 (d, J = 12.2 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 186.58, 167.00 (d, J = 261.7 Hz), 166.15, 158.98 (d, J = 10.8 Hz), 156.64, 131.27 (d, J = 10.9 Hz), 123.16 (d, J = 3.0 Hz), 112.80 (d, J = 21.7 Hz), 105.70 (d, J = 25.0 Hz), 105.45, 60.56, 14.24. **^{19}F NMR** (565 MHz, $CDCl_3$) δ -98.35 (dd, J = 15.1, 7.3 Hz, 1F). HRMS (ESI): Calcd for $C_{12}H_{11}FNaO_4$ $[M+Na]^+$: 261.0534. Found: 261.0551.

ethyl (*E*)-3-(6-fluoro-2-formylphenoxy)acrylate (s2d)

Column chromatography eluent petroleum ether/ethyl acetate = 10:1. Colorless oil, 77% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.23 (s, 1H), 7.81 (d, J = 12.3 Hz, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.48-7.44 (m, 1H), 7.37-7.32 (m, 1H), 5.35 (d, J = 12.3 Hz, 1H), 4.18 (q, J = 7.0 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 186.93, 166.17, 160.10, 153.99 (d, J = 252.2 Hz), 144.08 (d, J = 12.5 Hz), 129.76, 126.89 (d, J = 6.9 Hz), 124.17 (d, J = 3.3 Hz), 122.98 (d, J = 18.6 Hz), 102.40, 60.40, 14.20. **^{19}F NMR** (565 MHz, $CDCl_3$) δ -129.23 (dd, J = 9.4, 3.1 Hz, 1F). HRMS (ESI): Calcd for $C_{12}H_{11}FNaO_4$ $[M+Na]^+$: 261.0534. Found: 261.0546.

ethyl (*E*)-3-(3-fluoro-2-(1-hydroxy-2-nitropropyl)phenoxy)acrylate (s3b)

Column chromatography eluent petroleum ether/ethyl acetate = 10:1. Yellow oil, 80% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.1 Hz, 1H), 7.41-7.37 (m, 1H), 7.00-6.97 (m, 1H), 6.92 (d, J = 5.6 Hz, 1H), 5.70 (d, J = 8.1 Hz, 1H), 5.52 (d, J = 7.2 Hz, 1H), 5.13-5.10

(m, 1H), 4.20 (q, *J* = 4.8 Hz, 2H), 3.14 (s, 1H), 1.34 (d, *J* = 4.6 Hz, 3H), 1.29 (t, *J* = 4.8 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.60, 161.27 (d, *J* = 248.1 Hz), 157.28, 154.64 (d, *J* = 7.2 Hz), 131.25 (d, *J* = 10.3 Hz), 116.56 (d, *J* = 15.8 Hz), 113.78 (d, *J* = 3.1 Hz), 113.00, 112.85, 104.63, 86.53 (d, *J* = 2.8 Hz), 68.10 (d, *J* = 2.8 Hz), 68.09, 60.57, 16.28, 14.21. **^{19}F NMR** (565 MHz, $CDCl_3$) δ -112.81 (m, 1F). HRMS (ESI): Calcd for $C_{14}H_{16}FNaO_6$ $[M+Na]^+$: 336.0854. Found: 336.0873.

ethyl (*E*)-3-(5-fluoro-2-(1-hydroxy-2-nitropropyl)phenoxy)acrylate (s3c)

Column chromatography eluent petroleum ether/ethyl acetate = 10:1. Yellow oil, 90% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.1 Hz, 1H), 7.61-7.58 (m, 1H), 6.98-6.95 (m, 1H), 6.81 (d, *J* = 6.0 Hz, 1H), 5.66 (d, *J* = 8.1 Hz, 1H), 5.62 (s, 1H), 4.74-4.72 (m, 1H), 4.20 (q, *J* = 4.7 Hz, 2H), 3.12 (s, 1H), 1.44 (d, *J* = 4.6 Hz, 3H), 1.29 (t, *J* = 4.8 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.49, 163.01 (d, *J* = 248.5 Hz), 156.77, 152.49 (d, *J* = 9.8 Hz), 129.34 (d, *J* = 9.6 Hz), 124.55 (d, *J* = 3.4 Hz), 112.19 (d, *J* = 21.2 Hz), 105.05 (d, *J* = 25.1 Hz), 104.55, 84.96, 68.49, 60.55, 14.22, 11.67. **^{19}F NMR** (565 MHz, $CDCl_3$) δ -109.57 (dd, *J* = 14.6, 7.4 Hz, 1F). HRMS (ESI): Calcd for $C_{14}H_{16}FNaO_6$ $[M+Na]^+$: 336.0854. Found: 336.0851.

ethyl (*E*)-3-(6-fluoro-2-(1-hydroxy-2-nitropropyl)phenoxy)acrylate (s3d)

Column chromatography eluent petroleum ether/ethyl acetate = 10:1. Yellow oil, 98% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.41 (d, *J* = 5.2 Hz, 1H), 7.29-7.25 (m, 1H), 7.19-7.16 (m, 1H), 5.60 (s, 1H), 5.33 (d, *J* = 8.2 Hz, 1H), 4.76-4.72 (m, 1H), 4.16 (q, *J* = 4.8 Hz, 2H), 3.17 (d, *J* = 2.6 Hz, 1H), 1.44 (d, *J* = 4.6 Hz, 3H), 1.26 (t, *J* = 4.8 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.56, 159.53, 154.48 (d, *J* = 250.8 Hz), 138.50 (d, *J* = 12.9 Hz), 132.96, 126.94 (d, *J* = 7.6 Hz), 123.02, 117.17 (d, *J* = 17.9 Hz), 101.59, 84.89, 68.59, 60.45, 14.18, 11.54. **^{19}F NMR** (565 MHz, $CDCl_3$) δ -129.45 (m, 1F). HRMS (ESI): Calcd for $C_{14}H_{16}FNaO_6$ $[M+Na]^+$: 336.0854. Found: 336.0835.

ethyl (*E*)-3-(3-fluoro-2-(2-nitropropanoyl)phenoxy)acrylate (s4b)

Column chromatography eluent dichloromethane/acetic acid = 100:1. Yellow oil, 88% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 12.2 Hz, 1H), 7.54-7.50 (m, 1H), 7.04-7.02 (m, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 5.75 (q, *J* = 7.0 Hz, 1H), 5.70 (d, *J* = 12.1 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 1.80 (d, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 187.97, 166.16, 160.11 (d, *J* = 253.3 Hz), 156.33, 153.95 (d, *J* = 5.8 Hz), 134.00 (d, *J* = 10.2 Hz), 116.65 (d, *J* = 17.8 Hz), 113.25 (d, *J* = 3.3 Hz), 112.77 (d, *J* = 21.6 Hz), 105.49, 89.13, 60.52, 14.86, 14.22. **^{19}F NMR** (565 MHz, $CDCl_3$) δ -111.67 (m, 1F). HRMS (ESI): Calcd for $C_{14}H_{14}FNaO_6$ $[M+Na]^+$: 334.0697. Found: 334.0716.

ethyl (*E*)-3-(5-fluoro-2-(2-nitropropanoyl)phenoxy)acrylate (s4c)

Column chromatography eluent dichloromethane/acetic acid = 100:1. Yellow oil, 91% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.8, 6.4 Hz, 1H), 7.68 (d, *J* = 12.1 Hz, 1H), 7.04-7.01 (m, 1H), 6.87 (dd, *J* = 9.1, 2.3 Hz, 1H), 5.94 (q, *J* = 7.0 Hz, 1H), 5.84 (d, *J* = 12.2 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.81 (d, *J* = 7.1 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -98.91 (m, 1F). HRMS (ESI): Calcd for $C_{14}H_{14}FNaO_6$ $[M+Na]^+$:

334.0697. Found: 334.0705.

ethyl (*E*)-3-(6-fluoro-2-(2-nitropropanoyl)phenoxy)acrylate (s4d)

Column chromatography eluent dichloromethane/acetic acid = 100:1. Yellow oil, 85% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.68 (dd, J = 12.3, 2.9 Hz, 1H), 7.64-7.62 (m, 1H), 7.47-7.44 (m, 1H), 7.36-7.33 (m, 1H), 5.88 (q, J = 7.0 Hz, 1H), 5.50 (d, J = 12.2 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 1.80 (d, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 188.57 (d, J = 2.9 Hz), 165.94, 158.83 (d, J = 3.2 Hz), 153.92 (d, J = 252.0 Hz), 141.44 (d, J = 12.7 Hz), 129.48, 127.03 (d, J = 7.4 Hz), 126.27 (d, J = 3.6 Hz), 122.51 (d, J = 18.7 Hz), 103.38, 87.58, 60.57, 15.50, 14.18. **^{19}F NMR** (565 MHz, $CDCl_3$) δ -127.61. HRMS (ESI): Calcd for $C_{14}H_{14}FNaO_6$ $[M+Na]^+$: 334.0697. Found: 334.0671.

ethyl 2-((2*R,3*R**)-5-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetate (2b)**

Column chromatography eluent petroleum ether/ethyl acetate = 10:1. Yellow oil, 94% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55-7.50 (m, 1H), 6.85-6.81 (m, 2H), 5.61 (d, J = 9.8 Hz, 1H), 4.22 (q, J = 7.0 Hz, 2H), 2.83 (dd, J = 16.0, 10.1 Hz, 1H), 2.46 (d, J = 16.1 Hz, 1H), 1.75 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 181.95, 168.18, 162.29 (d, J = 267.9 Hz), 160.01 (d, J = 2.5 Hz), 137.67 (d, J = 11.5 Hz), 113.87 (d, J = 4.0 Hz), 110.57 (d, J = 20.3 Hz), 108.68 (d, J = 9.6 Hz), 92.07, 77.88, 61.58, 34.30, 14.51, 14.07. **^{19}F NMR** (375 MHz, $CDCl_3$) δ -107.86. HRMS (ESI): Calcd for $C_{14}H_{14}FNaO_6$ $[M+Na]^+$: 334.0697. Found: 334.0697.

ethyl 2-((2*R,3*R**)-7-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetate (2c)**

Column chromatography eluent petroleum ether/ethyl acetate = 10:1. Yellow oil, 75% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00-7.97 (m, 1H), 6.90-6.86 (m, 1H), 6.73 (d, J = 9.2 Hz, 1H), 5.63 (d, J = 10.0 Hz, 1H), 4.23 (q, J = 7.0 Hz, 2H), 2.85 (dd, J = 15.9, 10.2 Hz, 1H), 2.45 (d, J = 16.1 Hz, 1H), 1.74 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 183.55, 168.26 (d, J = 258.4 Hz), 168.18, 161.32 (d, J = 13.7 Hz), 131.14 (d, J = 11.4 Hz), 115.13 (d, J = 2.4 Hz), 111.89 (d, J = 22.8 Hz), 105.21 (d, J = 24.9 Hz), 91.75, 78.51, 61.62, 34.38, 14.43, 14.10. **^{19}F NMR** (375 MHz, $CDCl_3$) δ -96.67. HRMS (ESI): Calcd for $C_{14}H_{14}FNaO_6$ $[M+Na]^+$: 334.0697. Found: 334.0696.

ethyl 2-((2*R,3*R**)-8-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetate (2d)**

Column chromatography eluent petroleum ether/ethyl acetate = 10:1. Yellow oil, 89% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.9 Hz, 1H), 7.41-7.36 (m, 1H), 7.12-7.10 (m, 1H), 5.66 (d, J = 9.9 Hz, 1H), 4.23 (q, J = 7.0 Hz, 2H), 2.91 (dd, J = 15.7, 10.0 Hz, 1H), 2.49 (d, J = 16.0 Hz, 1H), 1.77 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.00 (d, J = 3.3 Hz), 168.03, 151.27 (d, J = 250.0 Hz), 148.95 (d, J = 12.2 Hz), 123.49 (d, J = 7.3 Hz), 123.38 (d, J = 6.0 Hz), 122.82 (d, J = 6.3 Hz), 120.33, 91.93, 78.85, 61.68, 34.39, 14.44, 14.04. **^{19}F NMR** (375 MHz, $CDCl_3$) δ -133.36. HRMS (ESI): Calcd for $C_{14}H_{14}FNaO_6$ $[M+Na]^+$: 334.0697. Found: 334.0701.

2-((2*R,3*R**)-5-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetic acid (3b)**

Column chromatography eluent petroleum ether/ethyl acetate/acetic acid = 100:20:1.

Yellow solid, 85% yield. m.p. 157-160 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.84 (s, 1H), 7.75-7.70 (m, 1H), 7.07-7.02 (m, 1H), 7.99 (d, J = 8.4 Hz, 1H), 5.55 (d, J = 9.8 Hz, 1H), 2.79 (dd, J = 16.6, 10.0 Hz, 1H), 2.66 (d, J = 16.5 Hz, 1H), 1.72 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 182.02, 170.08, 161.36 (d, J = 264.1 Hz), 159.64 (d, J = 2.4 Hz), 138.73 (d, J = 11.8 Hz), 114.26 (d, J = 3.6 Hz), 110.33 (d, J = 20.0 Hz), 108.06 (d, J = 9.7 Hz), 92.30, 78.13, 33.83, 14.47. **^{19}F NMR** (375 MHz, DMSO-d_6) δ -109.89. HRMS (ESI): Calcd for $C_{12}H_{10}FNaO_6$ $[M+Na]^+$: 306.0384. Found: 306.0377.

2-((2*R,3*R**)-7-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetic acid (3c)**

Column chromatography eluent petroleum ether/ethyl acetate/acetic acid = 100:20:1. Yellow solid, 97% yield. m.p. 146-147 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02-7.98 (m, 1H), 6.92-6.88 (m, 1H), 6.77 (d, J = 9.1 Hz, 1H), 5.63 (d, J = 10.0 Hz, 1H), 2.93 (dd, J = 16.3, 10.4 Hz, 1H), 2.53 (d, J = 16.6 Hz, 1H), 1.76 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 183.42, 173.80, 168.31(d, J = 258.7 Hz), 161.22 (d, J = 13.7 Hz), 131.24 (d, J = 11.5 Hz), 115.02 (d, J = 2.4 Hz), 112.08 (d, J = 22.8 Hz), 105.28 (d, J = 25.1 Hz), 91.66, 78.07, 34.11, 14.37. **^{19}F NMR** (375 MHz, DMSO-d_6) δ -97.71. HRMS (ESI): Calcd for $C_{12}H_{10}FNaO_6$ $[M+Na]^+$: 306.0384. Found: 306.0364.

2-((2*R,3*R**)-8-fluoro-3-methyl-3-nitro-4-oxochroman-2-yl)acetic acid (3d)**

Column chromatography eluent petroleum ether/ethyl acetate/acetic acid = 100:20:1. Yellow solid, 65% yield. m.p. 142-144 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.89 (s, 1H), 7.74-7.69 (m, 2H), 7.25-7.20 (m, 1H), 5.62 (d, J = 9.6 Hz, 1H), 2.84 (dd, J = 16.5, 10.1 Hz, 1H), 2.70 (d, J = 16.4 Hz, 1H), 1.75 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 184.01 (d, J = 3.3 Hz), 169.98, 150.65 (d, J = 246.4 Hz), 147.33 (d, J = 12.2 Hz), 124.94 (d, J = 17.3 Hz), 123.24 (d, J = 3.8 Hz), 123.16 (d, J = 6.8 Hz), 119.93, 92.08, 79.13, 33.92, 14.41. **^{19}F NMR** (375 MHz, DMSO-d_6) δ -134.32. HRMS (ESI): Calcd for $C_{12}H_{10}FNaO_6$ $[M+Na]^+$: 306.0384. Found: 306.0384.

3. Biology materials and methods

3.1 Cell lines and culture conditions

Human fibroblast cell line HAF and human prostate cancer cell lines PC3M, DU145, PC3, LNCaP and 22RV1 were obtained from the American Type Culture Collection (ATCC). DU145, PC3, LNCaP and 22RV1 cell lines were cultured in RPMI 1640 medium (Gibco), and PC3M cell lines wer maintained in Dulbecco's modified Eagle's medium (Gibco, Cleveland, OH). Both media were supplemented with 10% FBS (Wisent, St. Bruno, QC, Canada). Moreover, the human fibroblast cell line HAF was cultured in DMEM medium with 10% FBS and an additional final concentration of 2 mM L-glutamine. All cells were incubated at 37 ^{o}C and 5% CO_2 incubator.

3.2 Cell viability assay

The cell viability of cell lines in the presence of this series of compounds was determined by Sulforhodamine B (SRB) assay (Sigma Aldrich) which was described previously.[1] Cells were seeded in 96-well plates (3000 cells/well) after 24 h and incubated with compounds of which 8 concentrations were set at 100, 33, 11, 3.7, 1.2, 0.41, 0.14 and 0.05 μM. After incubation for 96 h, the cells were then fixed with 25 μl cold 50% trichloroacetic acid for 1 h at 4°C, stained with 50 μl 0.4% SRB (Sigma Aldrich, Argentina, Cat# S1402) for 10-20min at room temperature, and OD value was measured by a microplate spectrophotometer at 515nm. The IC_{50} (half maximal inhibitory concentration) value was calculated using GraphPad software.

3.3 Transwell migration assay

Transwell migration assay was performed as previously reported[1]. The inhibition of tumor cell migration was assessed by the Boyden chamber (Corning Falcon) migration assay in 24-well cell culture plate with 8.0 μm pore. Briefly, the top chambers were seeded with 8×10^4 DU145 cells in 200 μl of serum-free medium containing different dose of compound. The bottom chambers were filled with 500 μl of complete medium supplemented with different dose of compound. After 24 h incubation, non-migrated cells were removed with cotton swabs, and migrated cells were fixed with cold 4% paraformaldehyde for 20 min and stained with 0.2% crystal violet for 3 min. Then the chambers were washed using water, and the membrane was left to dry. Images were taken with an inverted microscope (Olympus) and cells from three random areas per filter were counted. The percentage of migrated cells was normalized to untreated control cells.

3.4 Wound healing migration assay

DU145 cells were seeded in a 6-well plate at a density that after 24 h of growth, and they were allowed to reach 95% confluence in complete medium. A single scratch wound was created on the confluent monolayers using a micropipette tip across the center of the well and a straight line was scratched in one direction. Then, wounded monolayers were washed with phosphate buffer saline (PBS) to remove the detached cells, and each assay was carried out

three times. After washing, fresh media with FBS was added, 10 μM of **36** were added to their respective wells, and then they were incubated for 24 h. The medium in each well was discarded and washed several times with PBS. Cells migrated to the wound surface and the average distance of migrating cells was determined under an inverted microscope at designated time points. Pictures of three different regions of each wound were taken. The experiment was performed three times.

3.5 Colony formation assay

Prostate cancer cells DU145, PC3 and PC3M were seeded 2000 per well in 6-well plate and allowed to grow for 24 hours. Then cells were treated with indicated concentrations of cisplatin or compound **36** for 7 days. Colonies were fixed with 4% paraformaldehyde for 30 min, stained with 0.1% crystal violet for 5 min. Colonies were visualized and all the fields were imaged and counted. Colony formation as a percentage of vehicle control for each cell line is presented.

3.6 Cell cycle analysis

Cell cycle analysis was conducted by propidium iodide (PI) staining as described previously[2]. Briefly, cells were treated with different concentrations of compound **36** for 24h followed by PBS washing, then fixed with cold 70% ethanol at 4℃ for at least 12h. After washing twice with PBS, cells were incubated in the dark with 50 mg/mL PI and 10 mg/L RNase for 30min. Cell cycle distribution was analyzed by flow cytometry (FACS Calibur, BD biosciences).

3.7 Cell apoptosis assay

Apoptosis was measured using the apoptosis detection kit (BD Biosciences) with flow cytometry. DU145 cells (2.0×10^5/well) were cultured in 6-well plate with concentrations of 0 μM, 2.5 μM, 5 μM and 10 μM of compound 36 or cisplatin for 48h. Cells were collected and washed with PBS, then resuspended in binding buffer and incubated with Annexin V-FITC and propidium iodide. About 15min later, cells were analyzed immediately with flow cytometry (FACS Calibur, BD Biosciences).

3.8 Western Blot Analysis

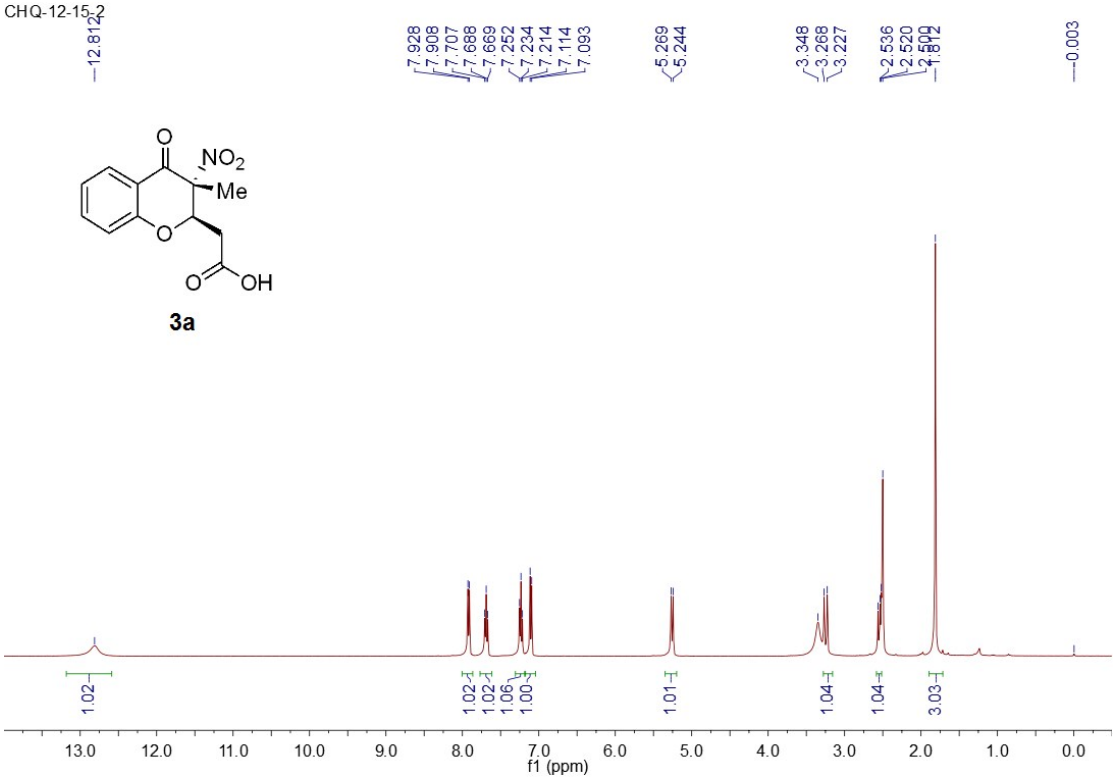
Cells were lysed in cell lysis buffer (50 mM Tris-HCl, pH 7.5, 150 mM NaCl, 1% Nonidet P-40, 0.5% sodium deoxycholate and 1% protease inhibitor cocktails) and boiled for 10 min with loading buffer (2% SDS, 10% glycerol, 10% β-Mercaptoethanol, Bromphenol Blue and Tris-HCl, pH 6.8). Lysates were fractionated on polyacrylamide gels and transferred to nitrocellulose. The blots were probed with specific antibodies followed by secondary antibody, then membranes were examined by the LI-COR Odyssey infrared imaging system (LI-COR Biotechnology, Lincoln NE). PARP antibody (Catalog #9542) was from Cell Signaling Technology and β-actin antibody (Catalog #A5441) was from Sigma. The secondary antibody was conjugated with IRDye 680/800 (Catalog #926-32221, #926-32210, Millennium Science).

References

1 Y. Y. Wang, Y. He, L. F. Yang, S. H. Peng, X. L. He, J. H. Wang, F. Lv, Y. Hao, M. Y. Liu, Z. F. Yi and W. W. Qiu, *Eur. J. Med. Chem.*, 2016, **120**, 13.

2 J. Wu, L. X. Yu, F. F. Yang, J. J. Li, P. Wang, W. B. Zhou, L. W. Qin, Y. Q. Li, J. Luo, Z. F. Yi, M. Y. Liu and Y. H. Chen, *Eur. J. Med. Chem.*, 2014, **80**, 340.

4. NMR charts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1.02
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1.01
1.04
1.04
3.03
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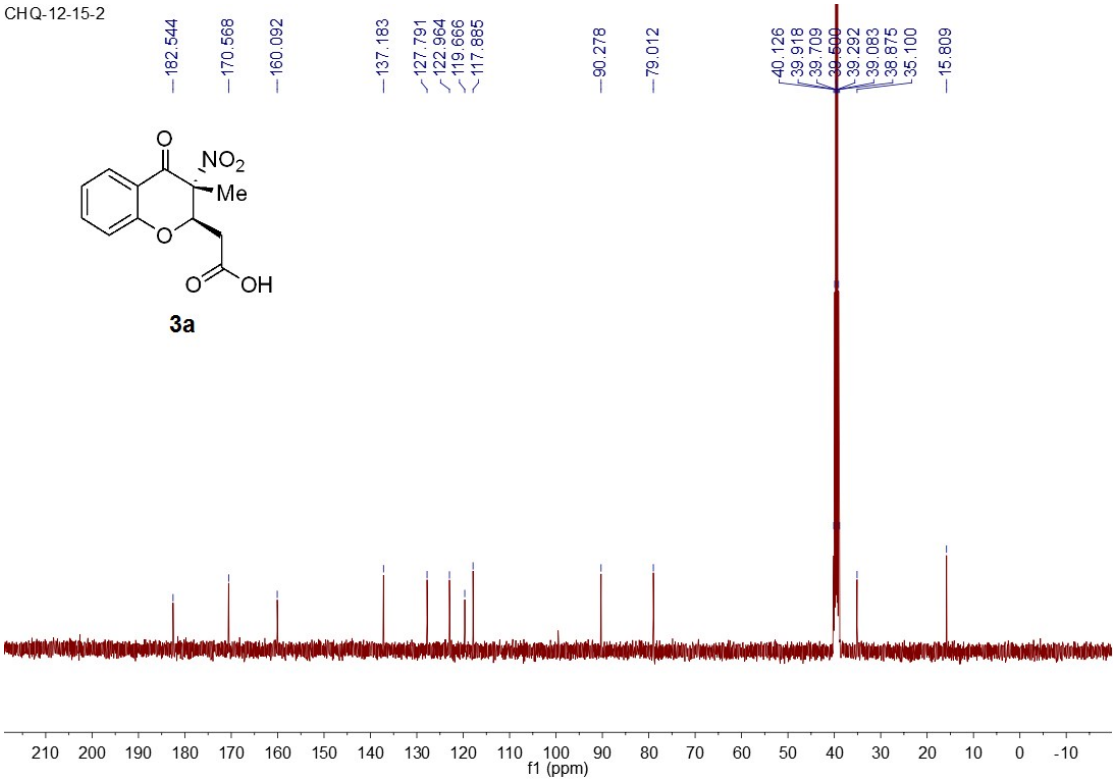
f1 (ppm)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f1 (ppm)

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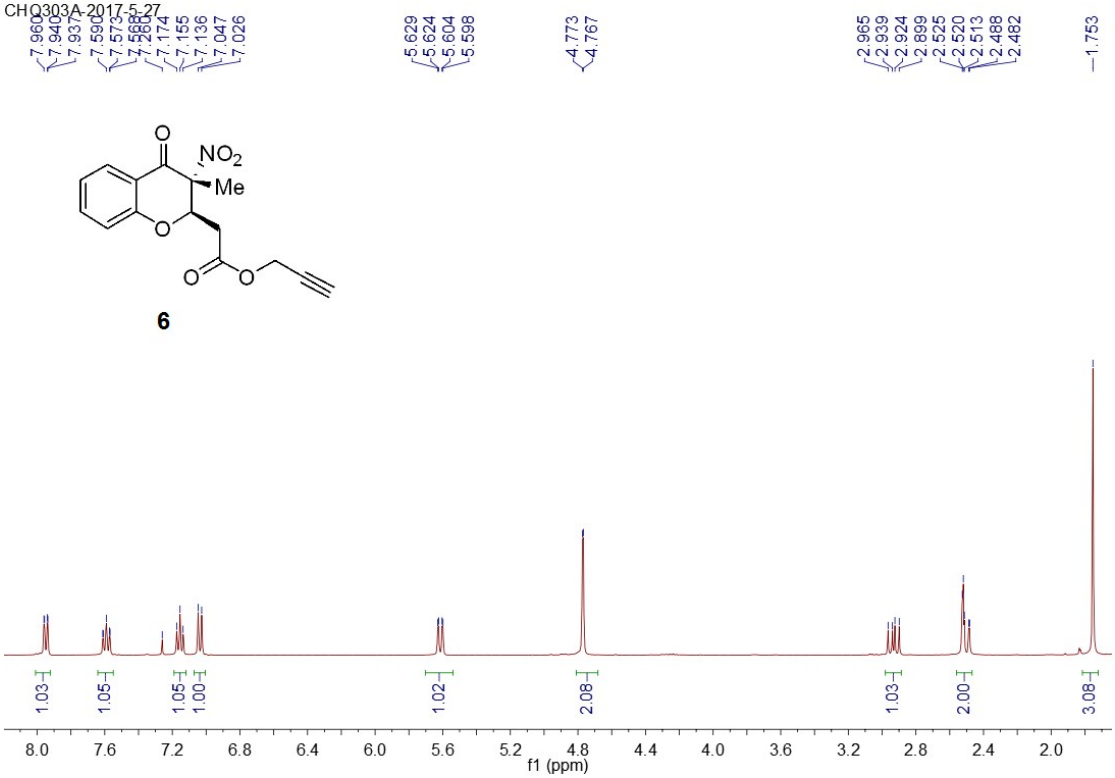

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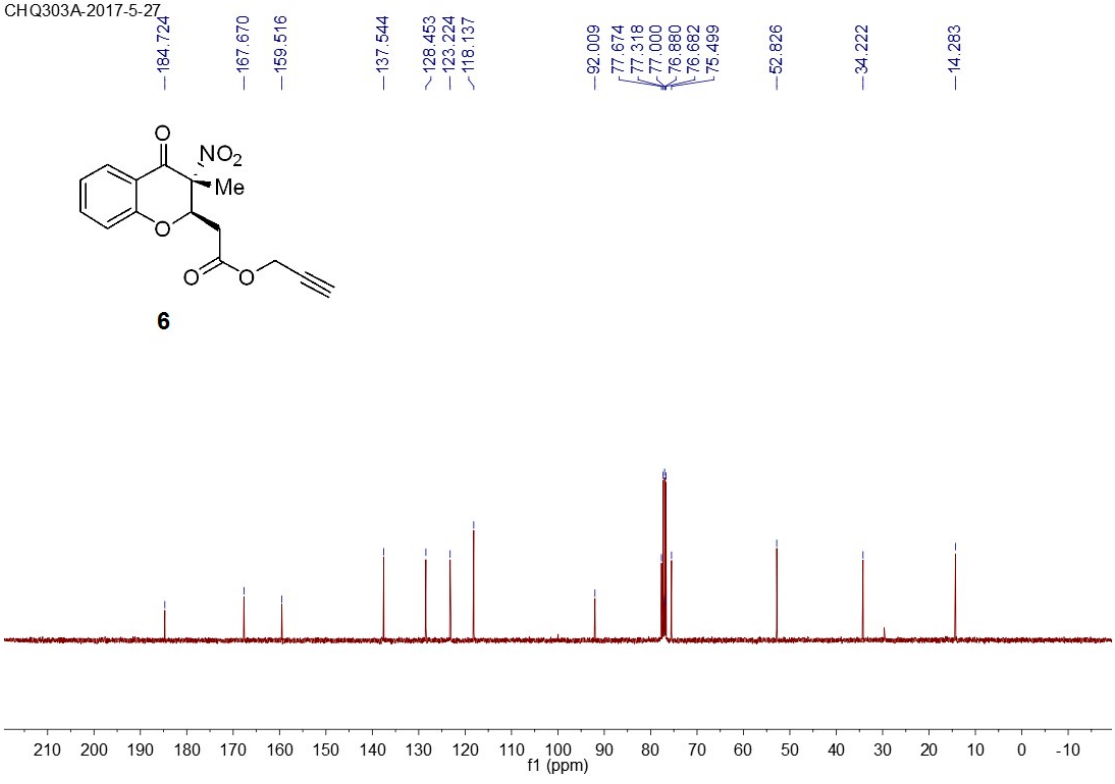

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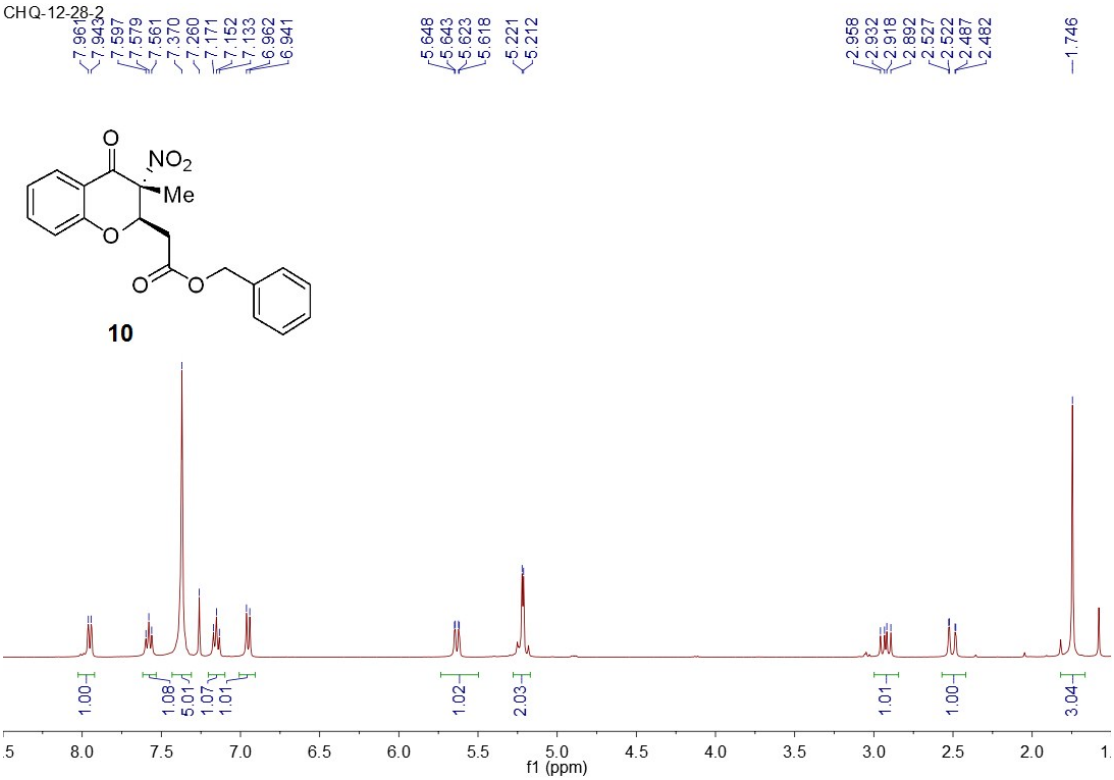

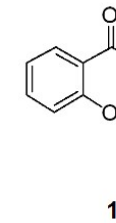

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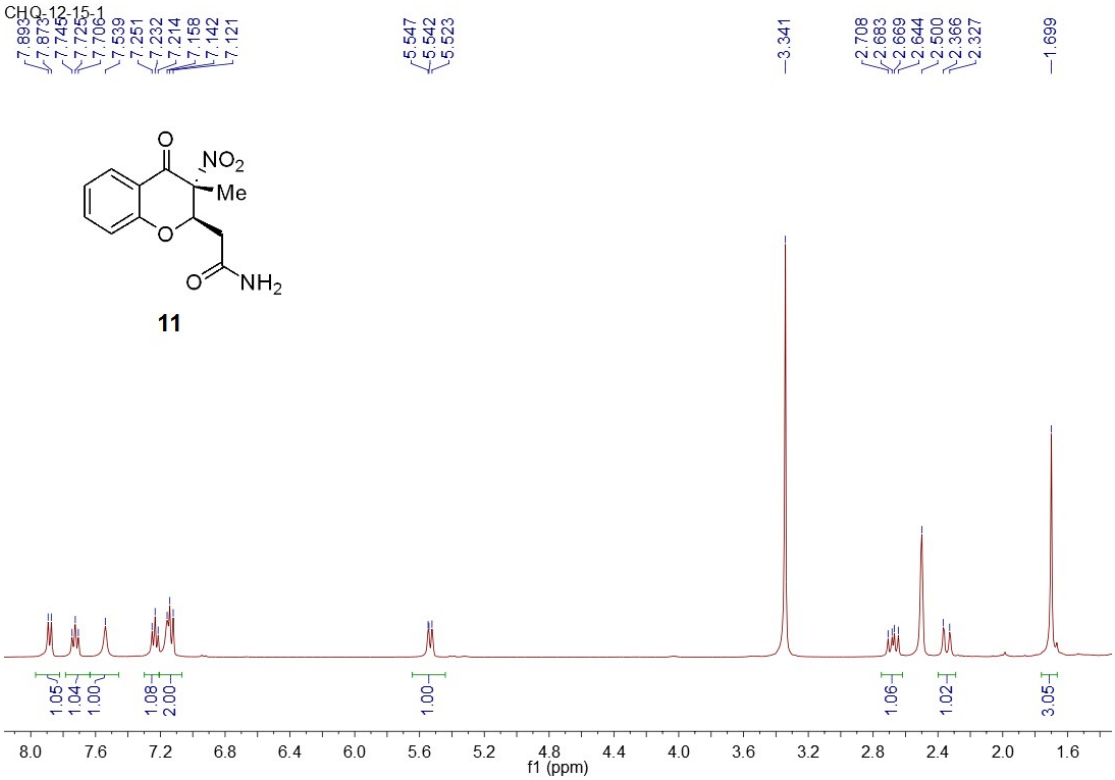
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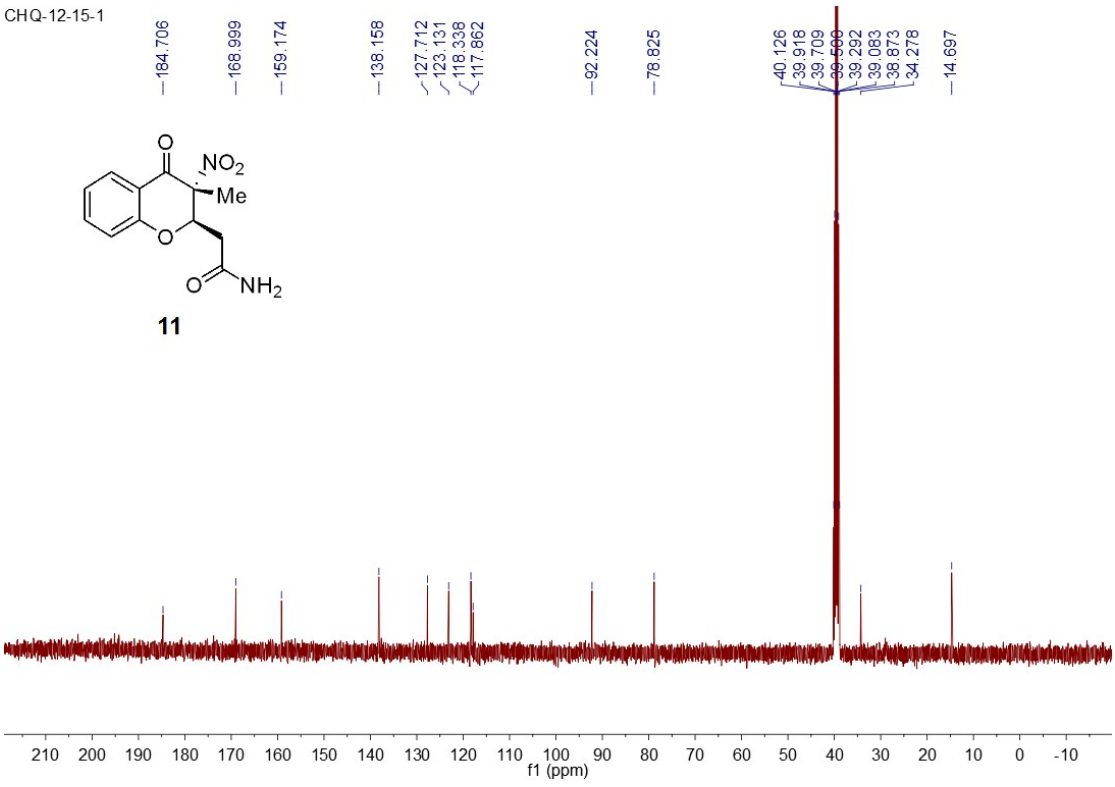
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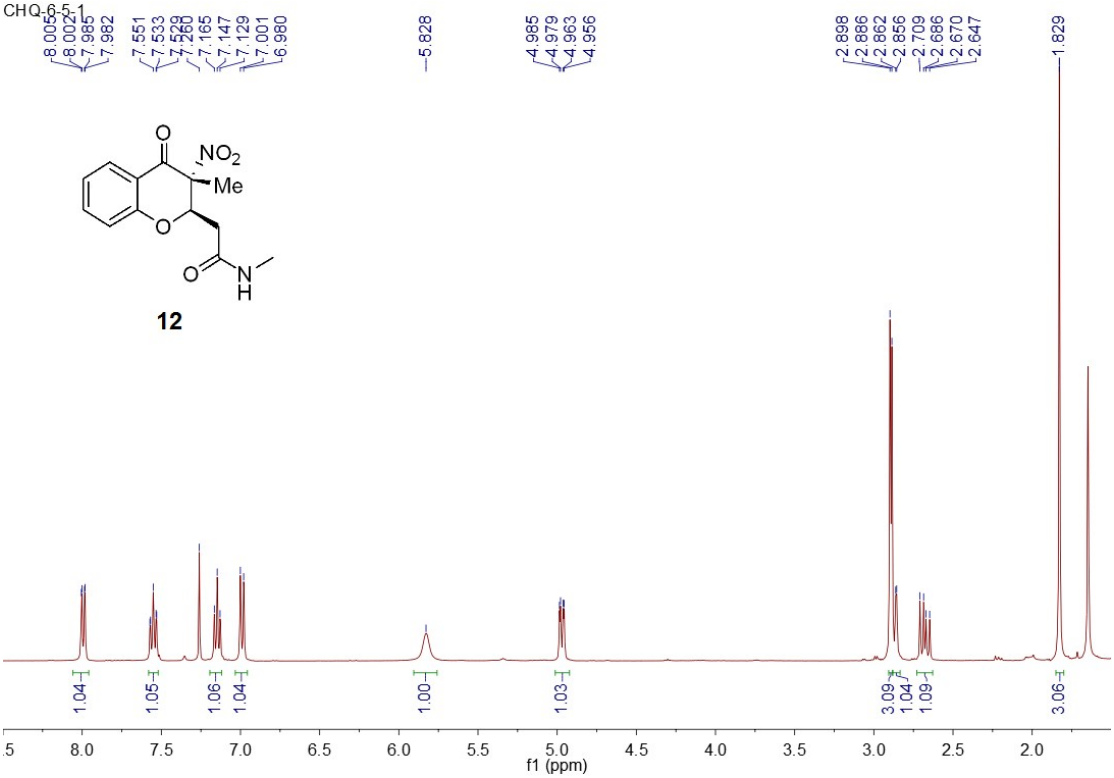

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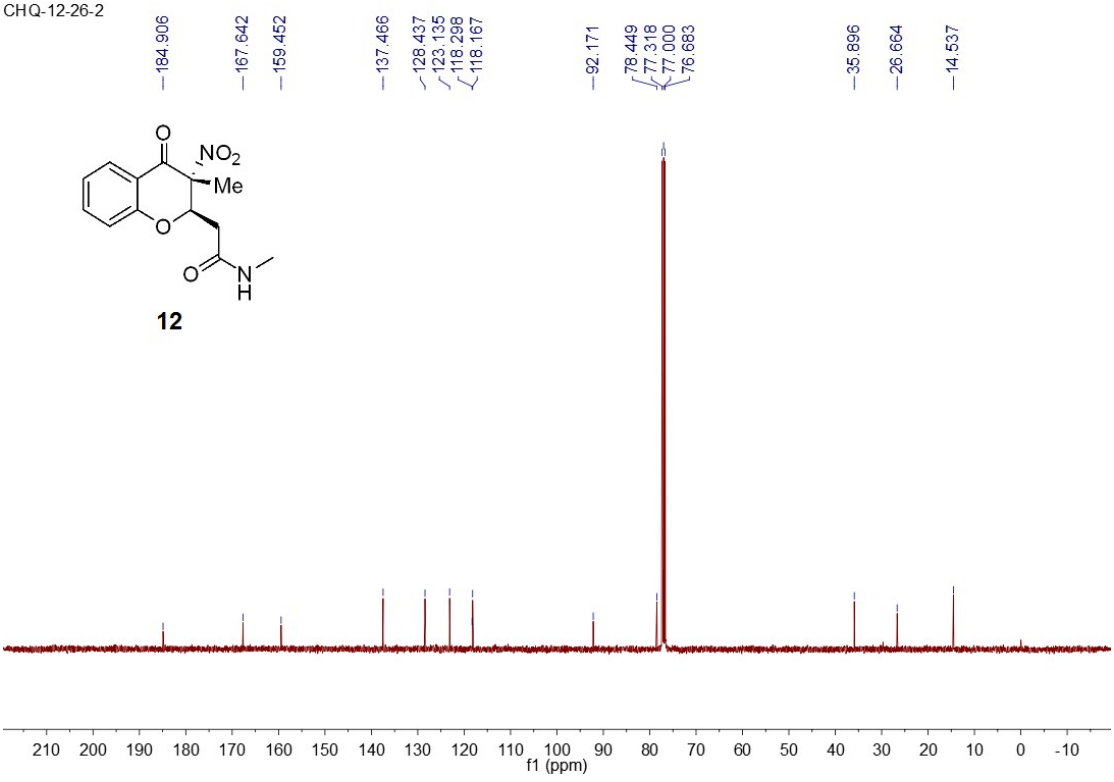

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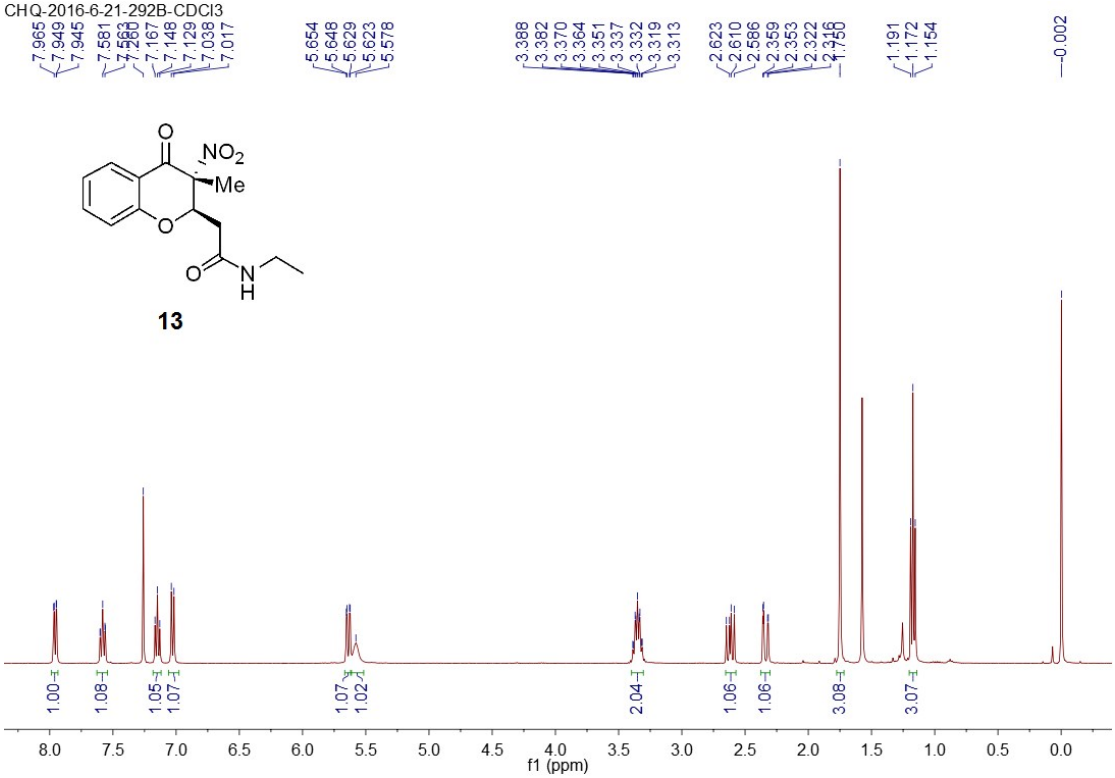

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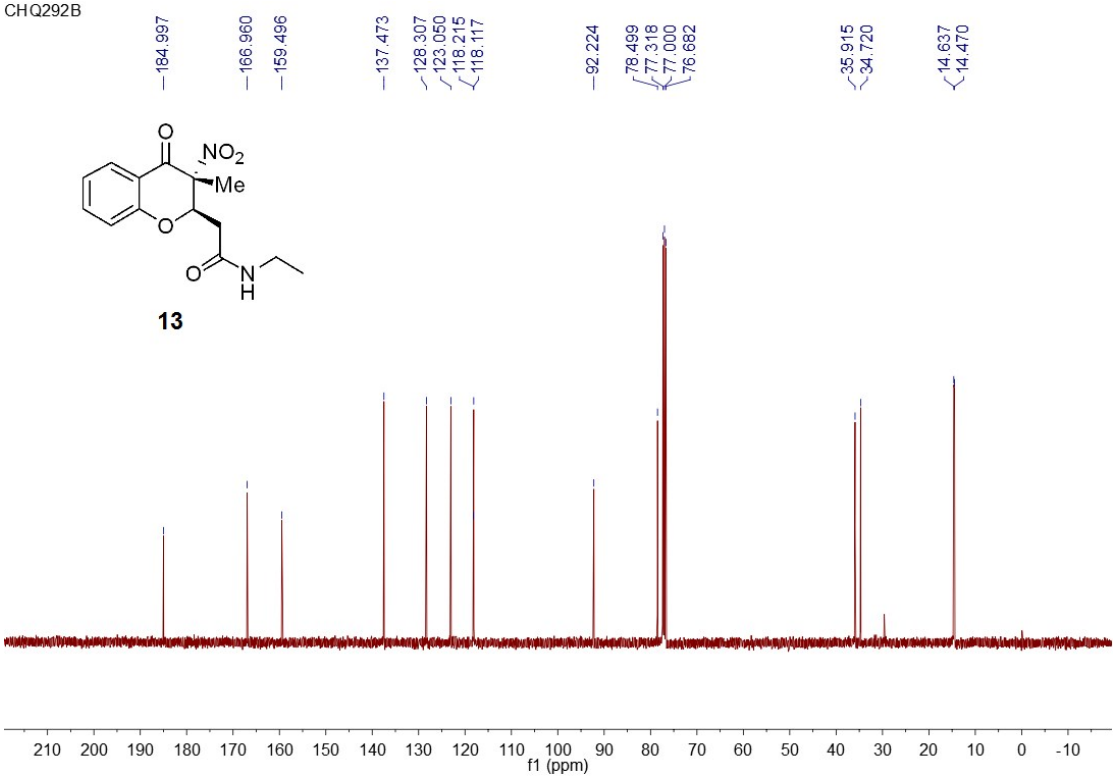

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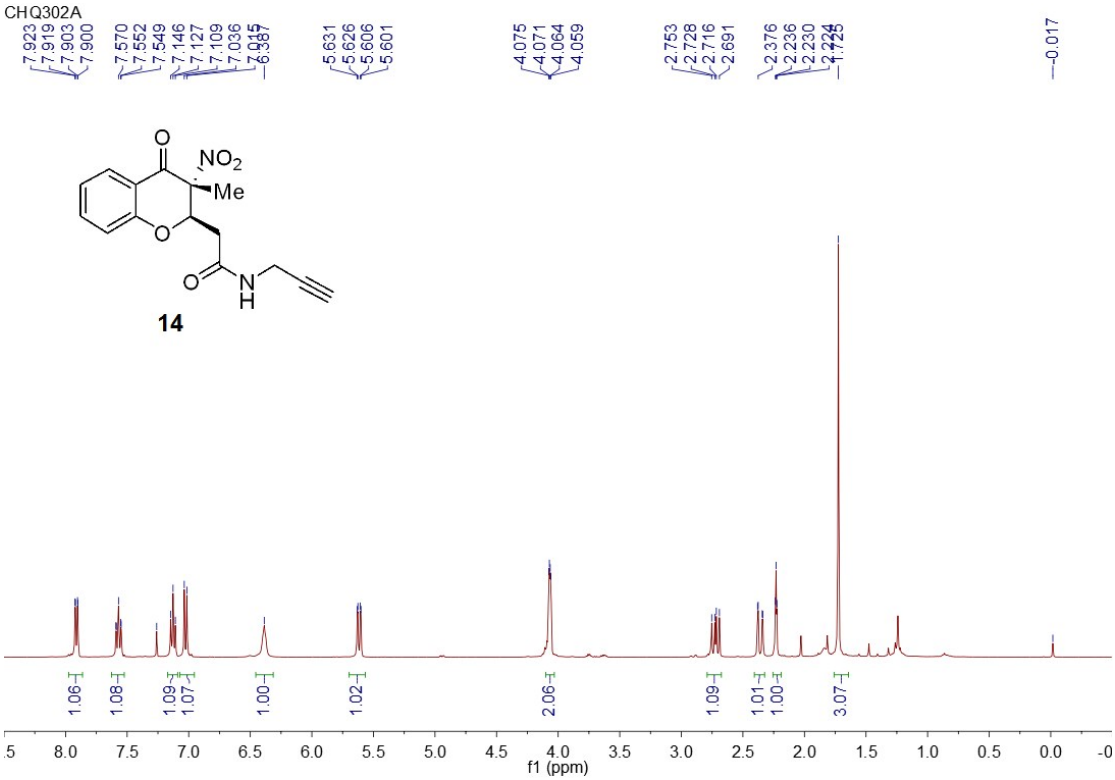
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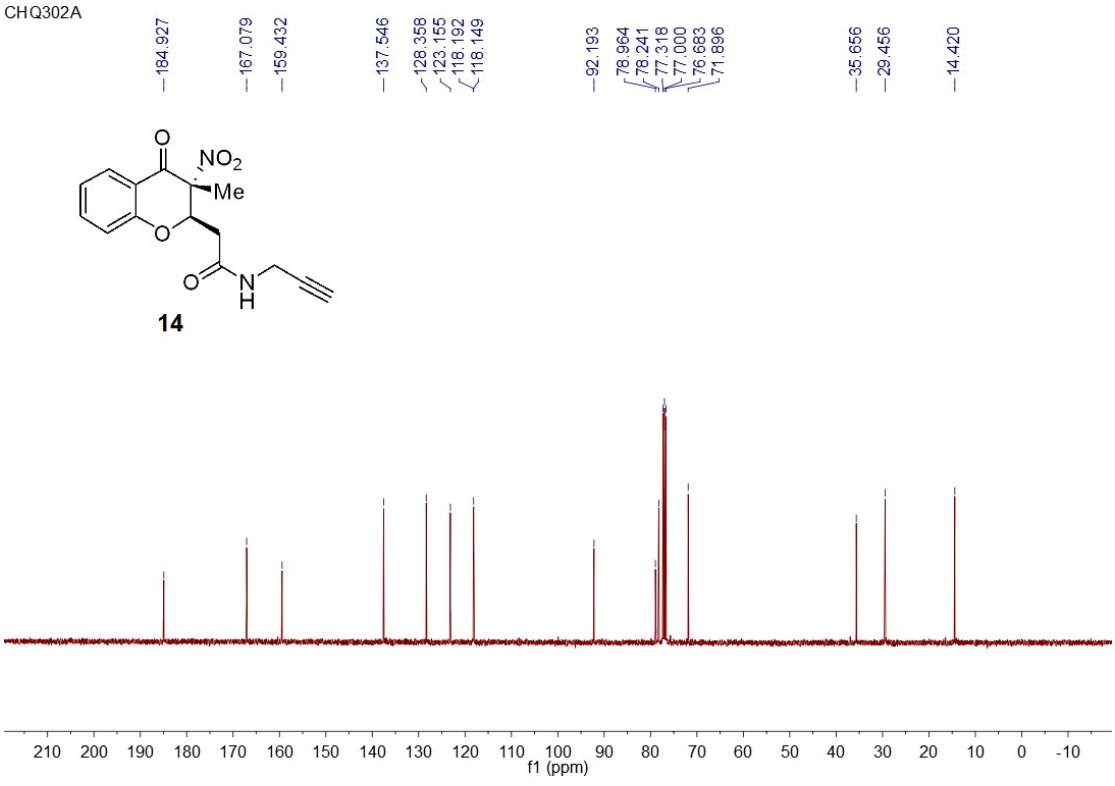
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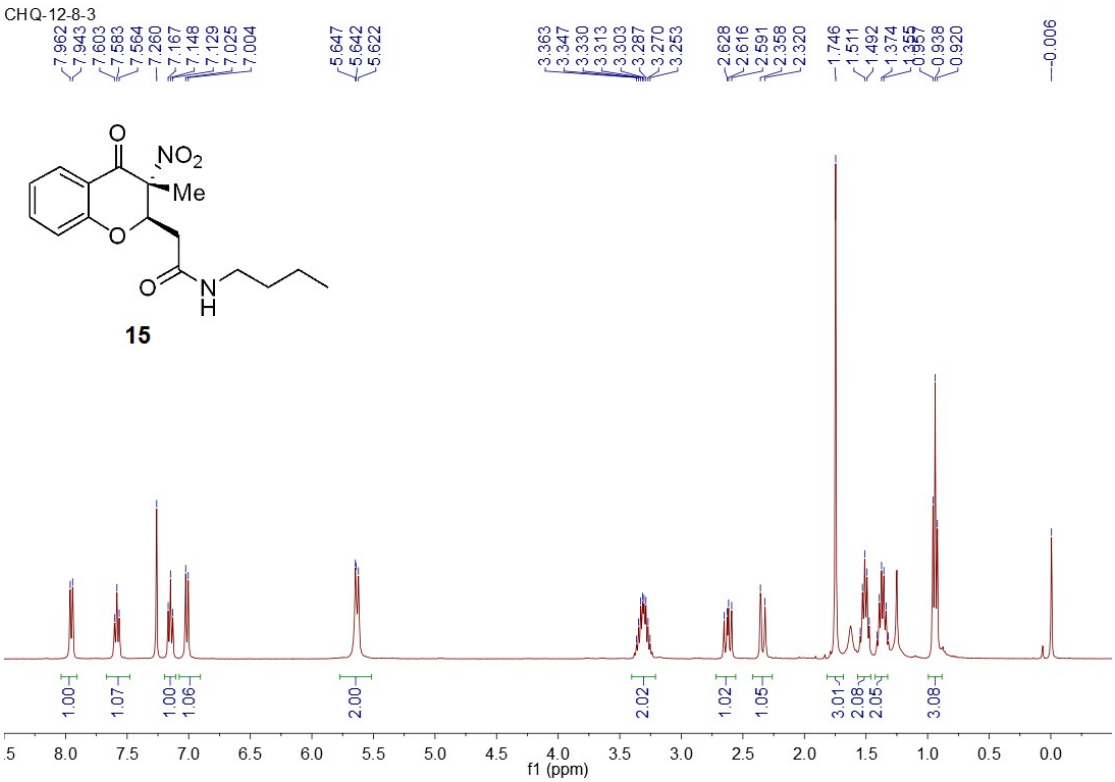
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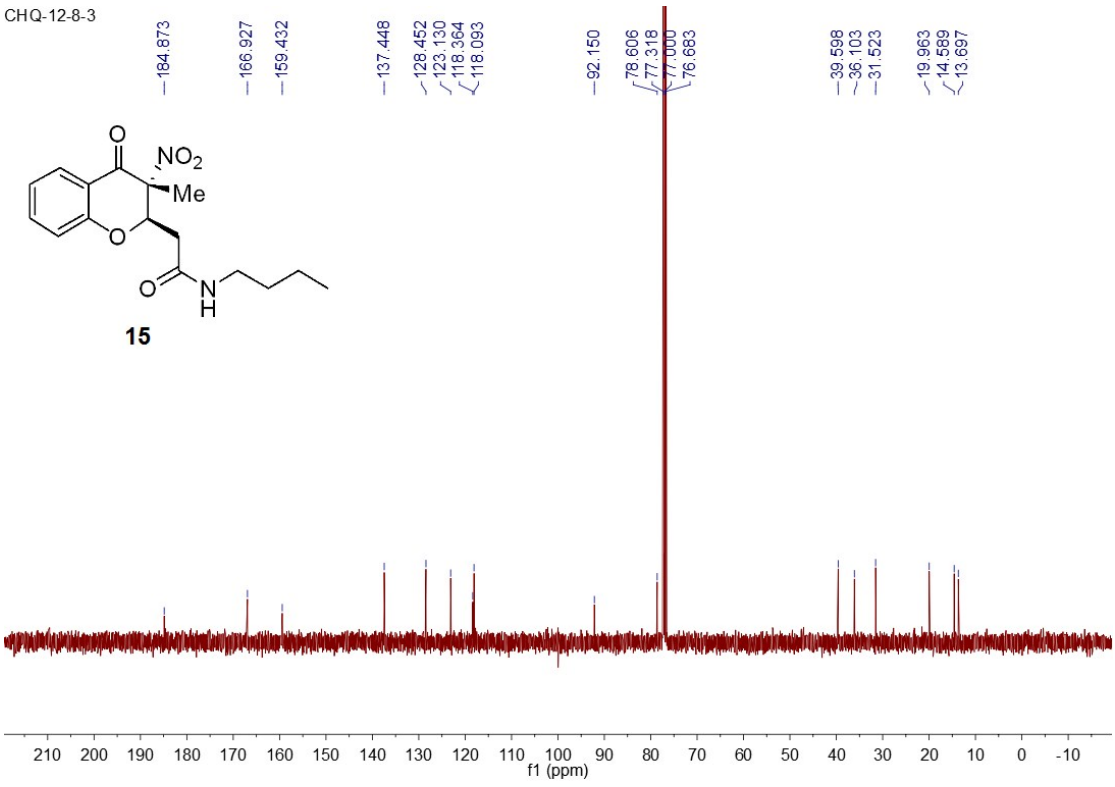
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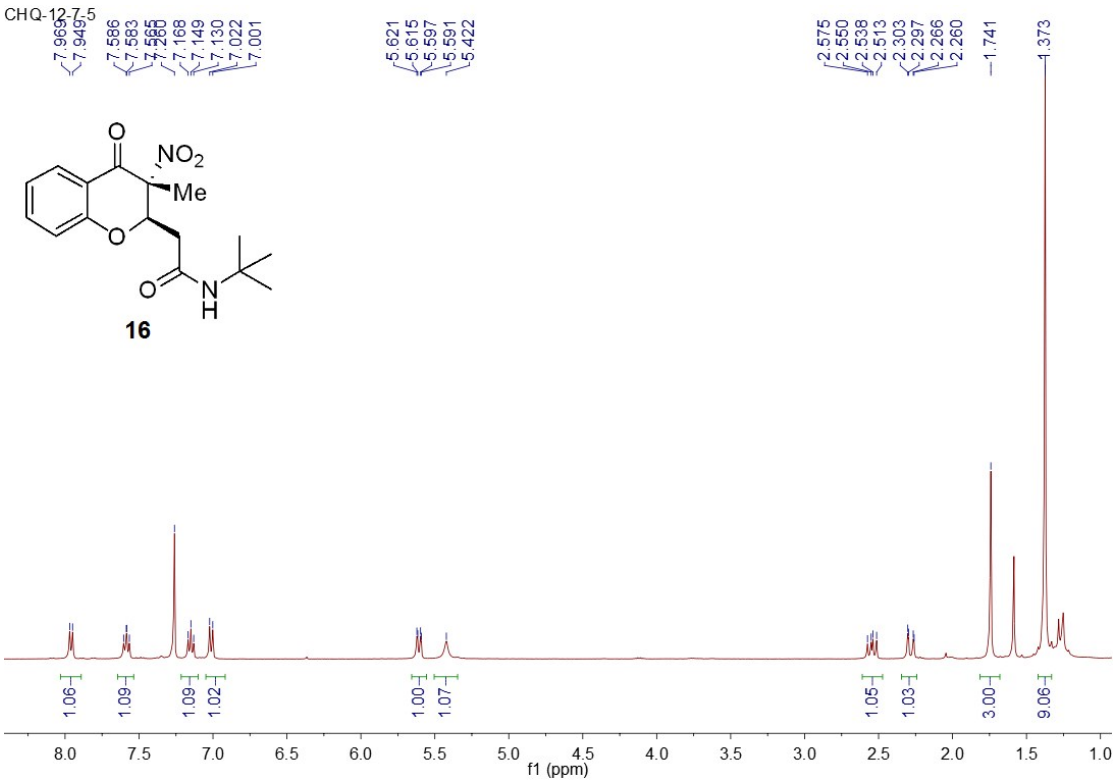
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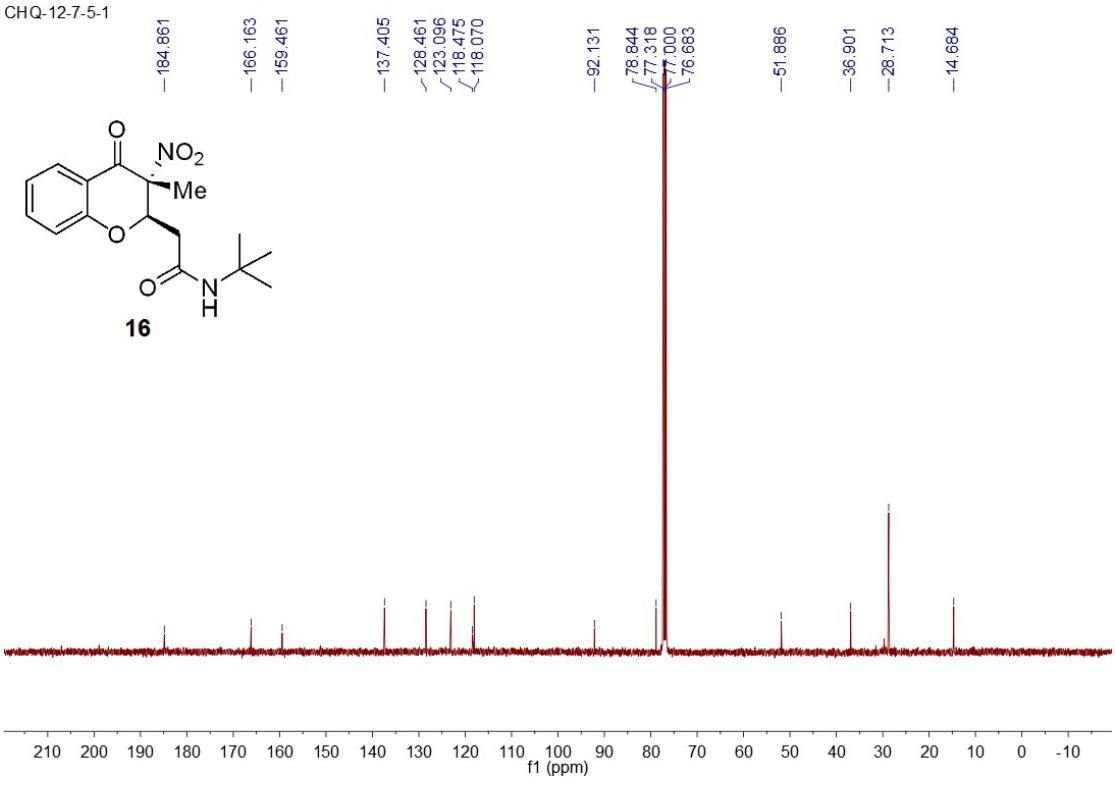
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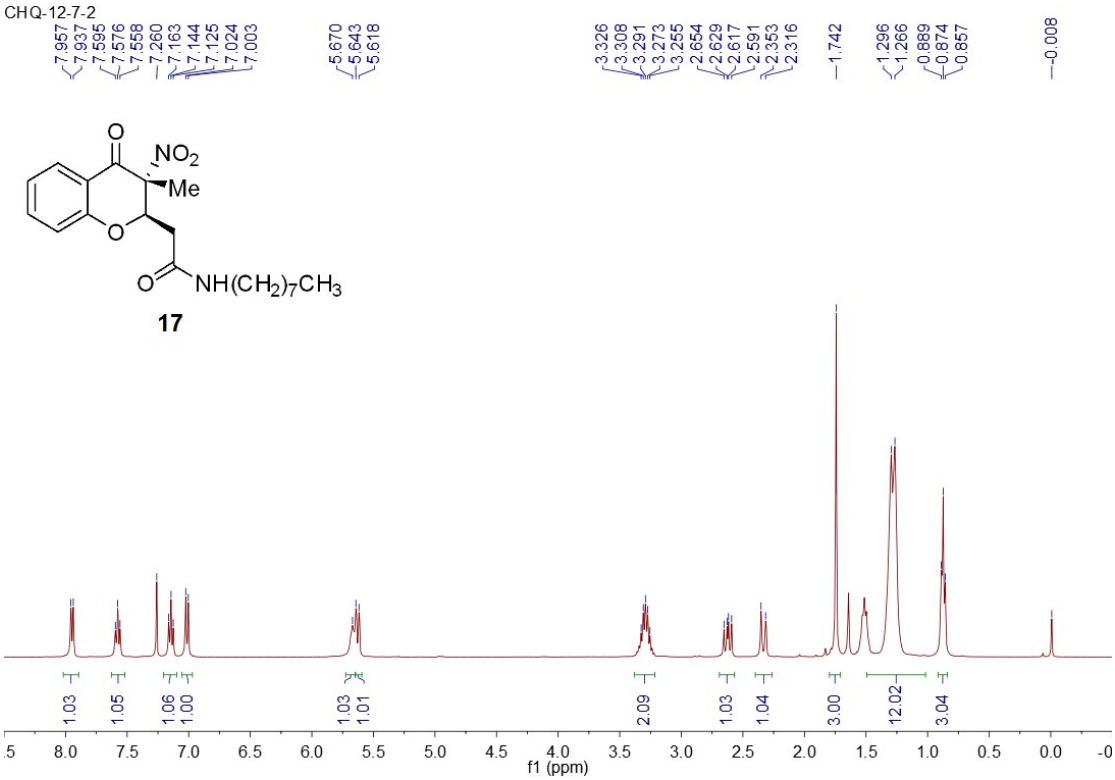
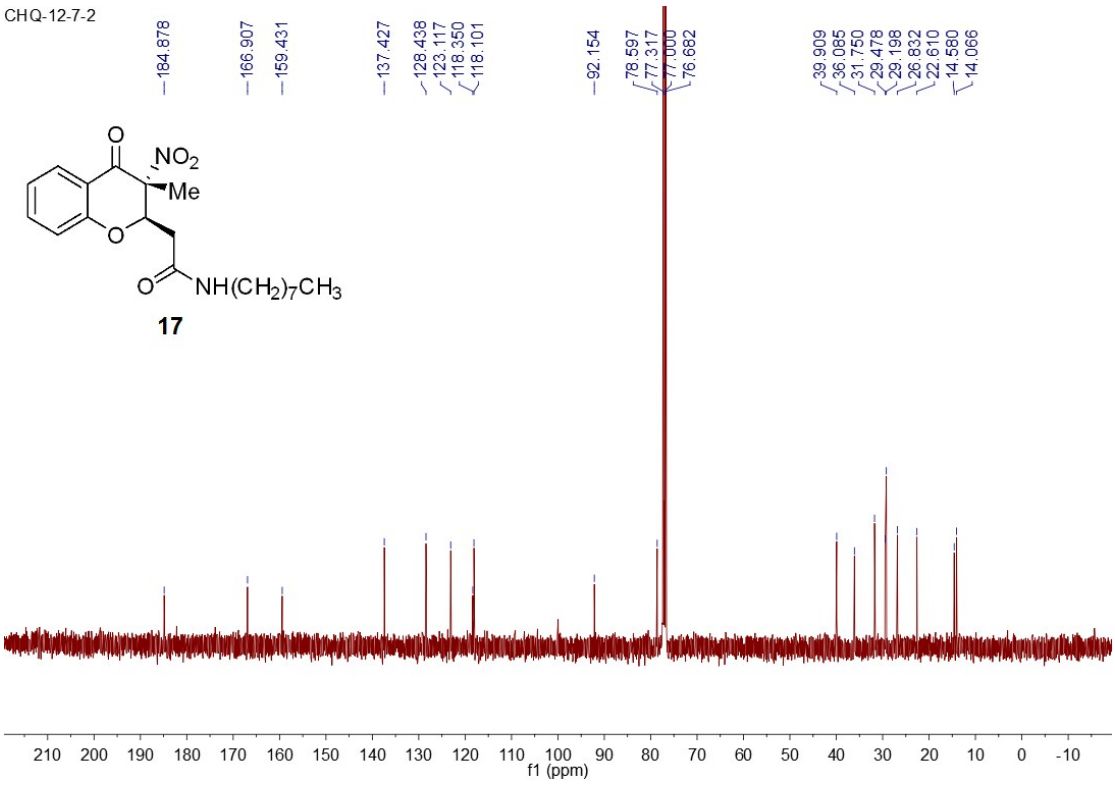
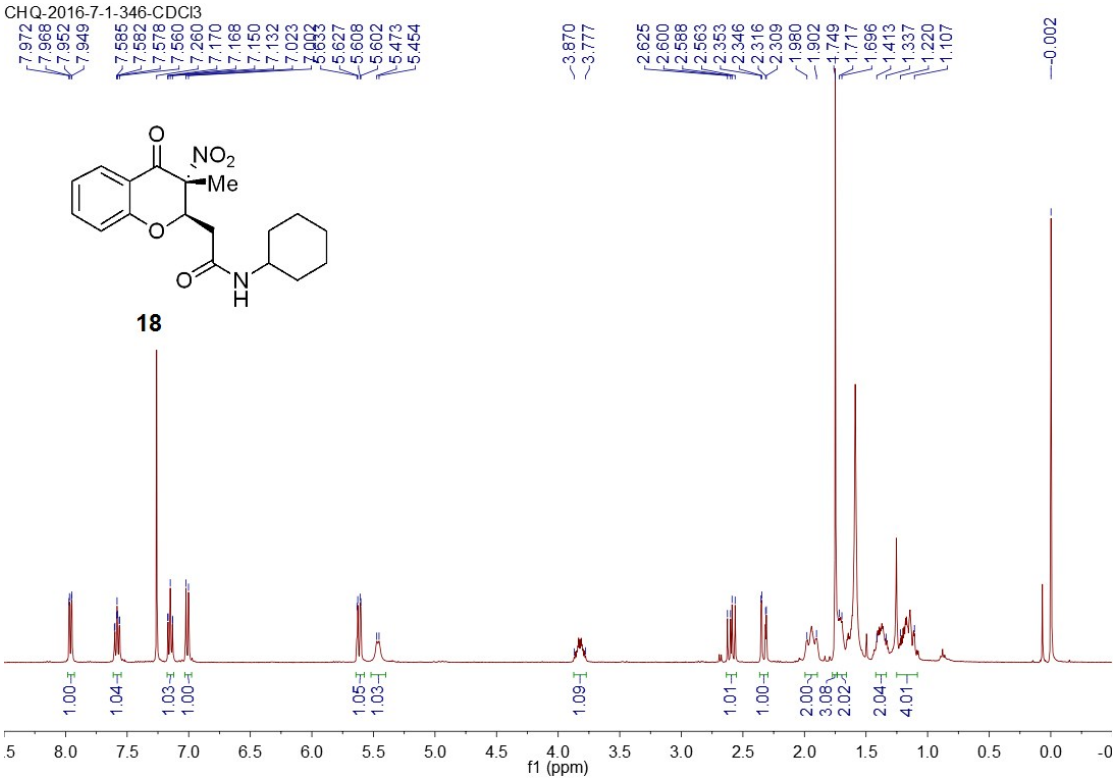
-10
f1 (ppm)


CHQ-12-7-2
7.957
7.937
7.595
7.576
7.558
7.260
7.163
7.144
7.125
7.024
7.003
5.670
5.643
5.618
3.326
3.308
3.291
3.273
3.255
2.654
2.629
2.617
2.591
2.353
2.316
1.742
1.296
1.266
0.889
0.874
0.857
0.008
NO2
Me
O
NH(CH2)7CH3
17
1.03
1.05
1.06
1.00
1.03
1.01
2.09
1.03
1.04
3.00
12.02
3.04
f1 (ppm)

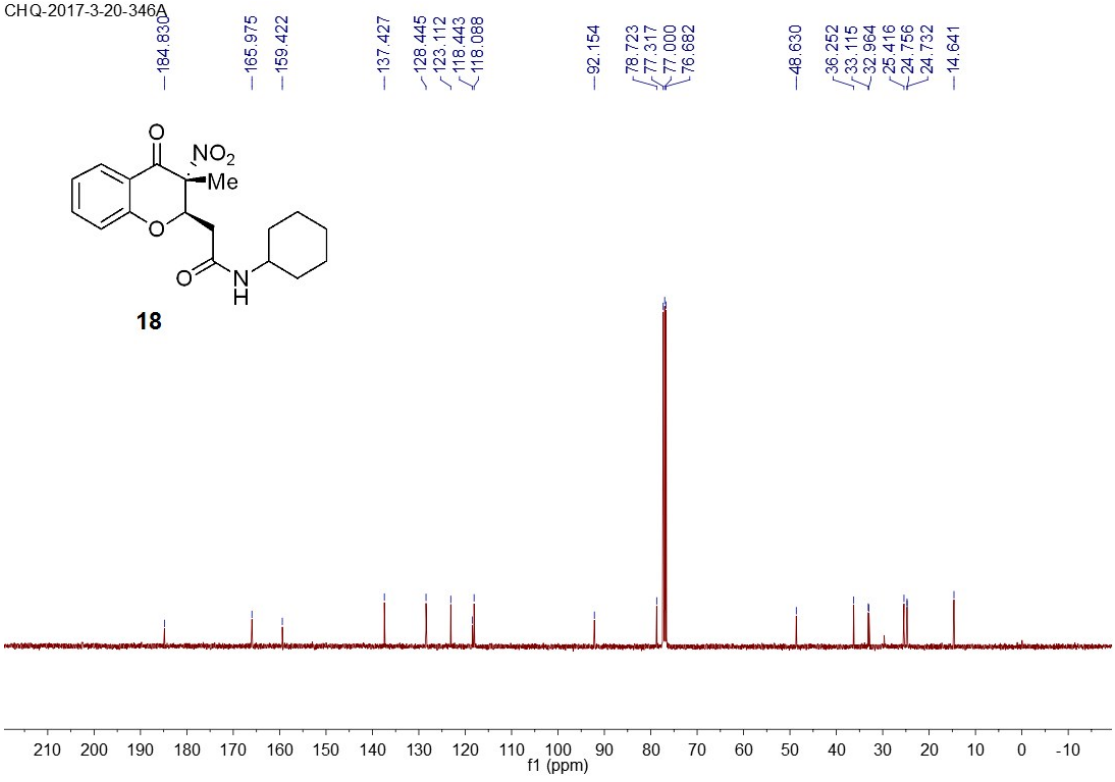

CHQ-12-7-2
184.878
166.907
159.431
137.427
128.438
123.117
118.350
118.101
92.154
78.597
77.317
77.000
76.682
39.909
36.085
31.750
29.478
29.198
26.832
22.610
14.580
14.066
NO2
Me
O
NH(CH2)7CH3
17
f1 (ppm)

CHQ-2016-7-1-346-CDCl3



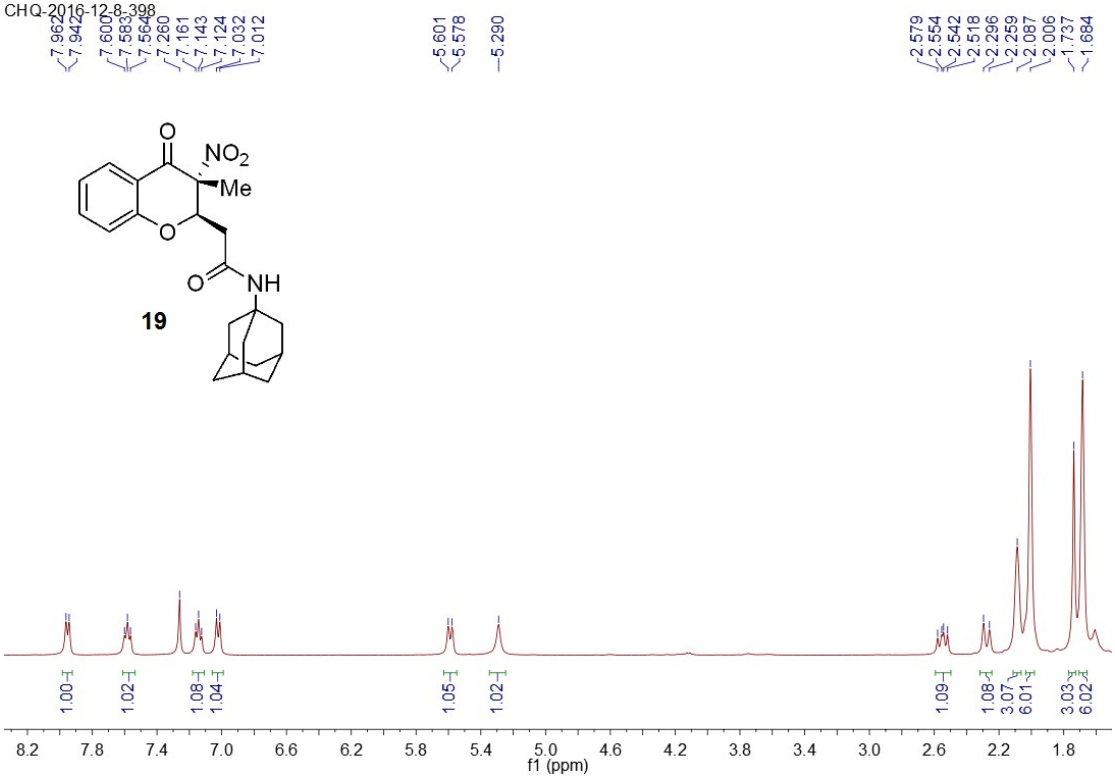
18

CHQ-2017-3-20-346A

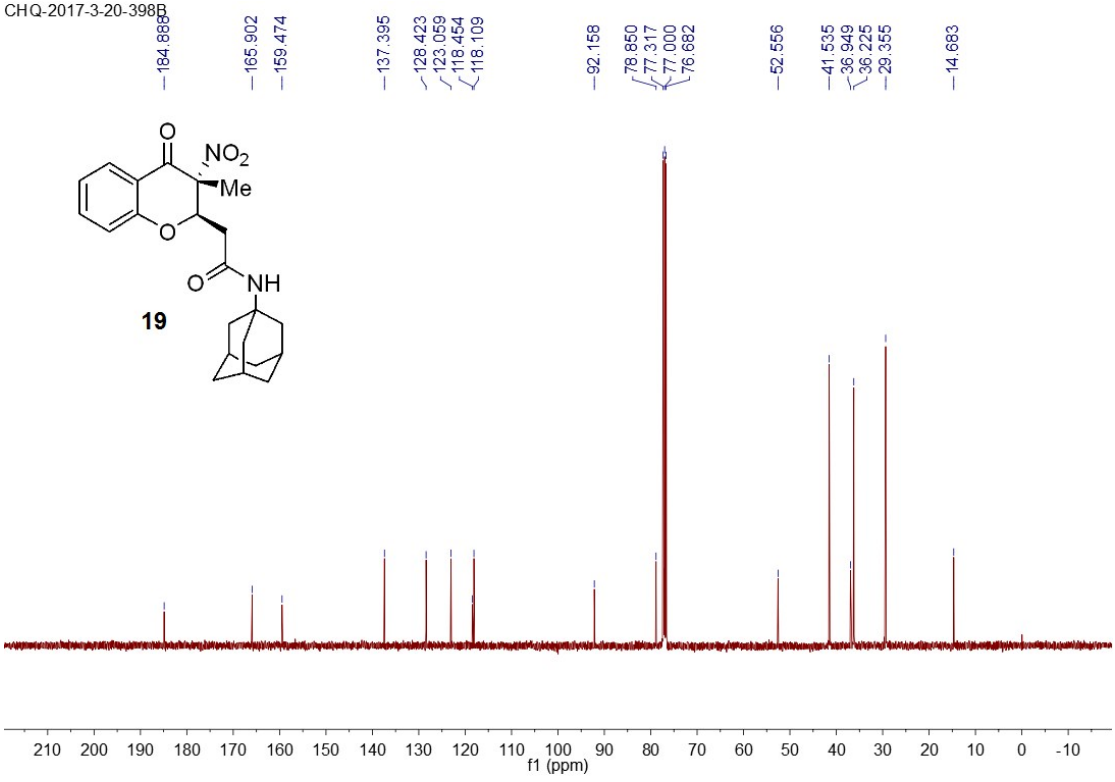


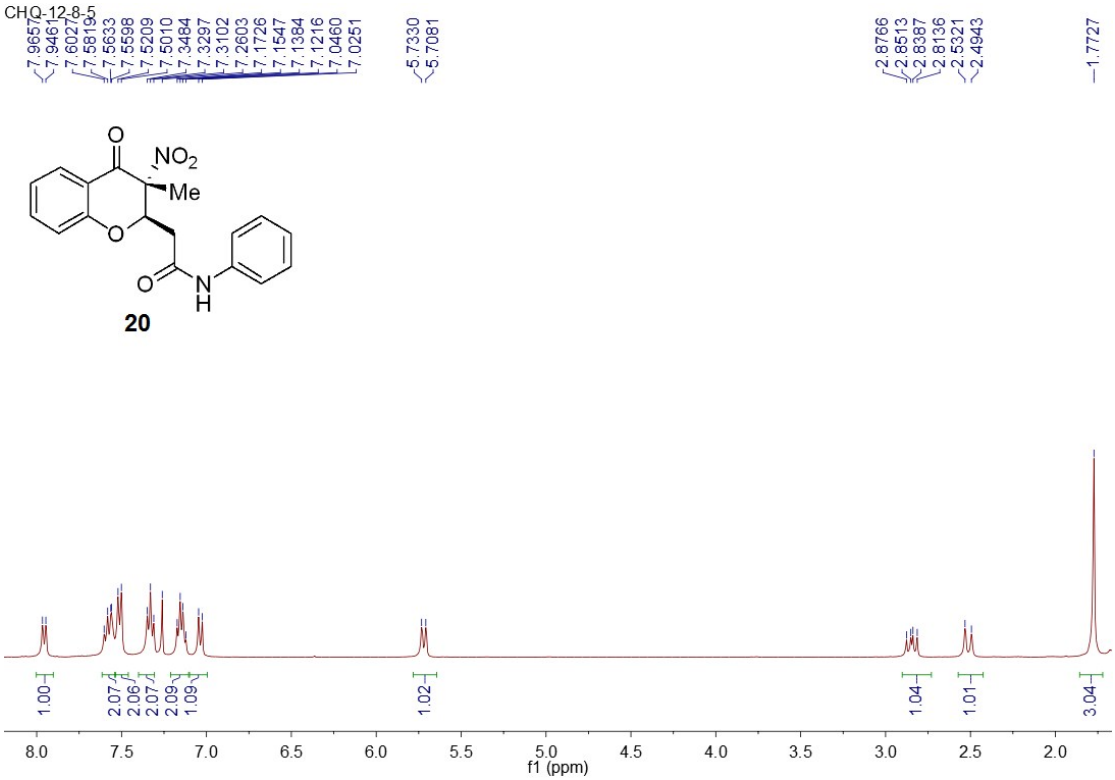
18

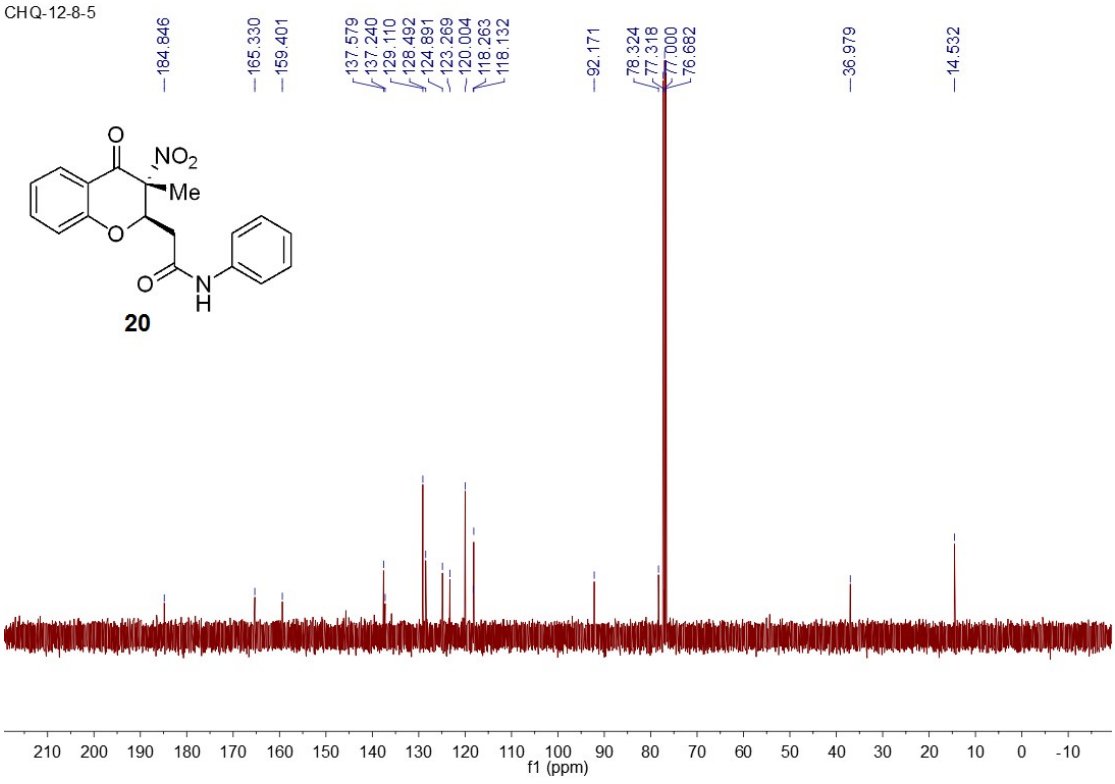
CHQ-2016-12-8-398

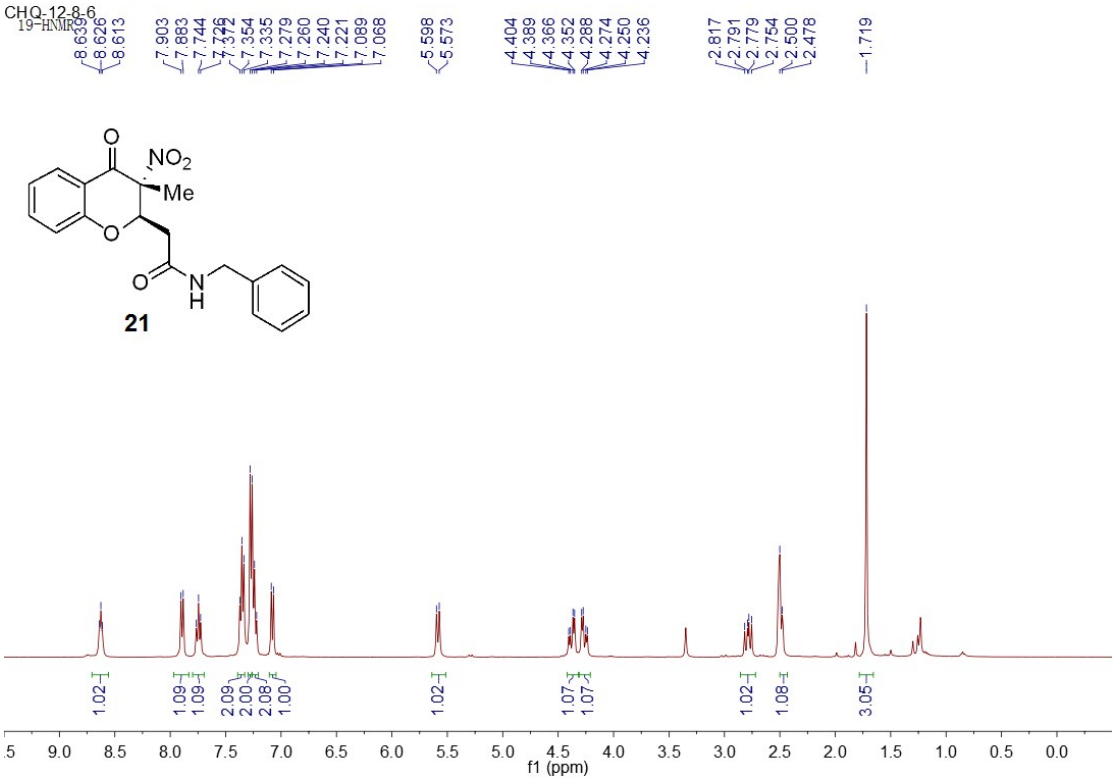


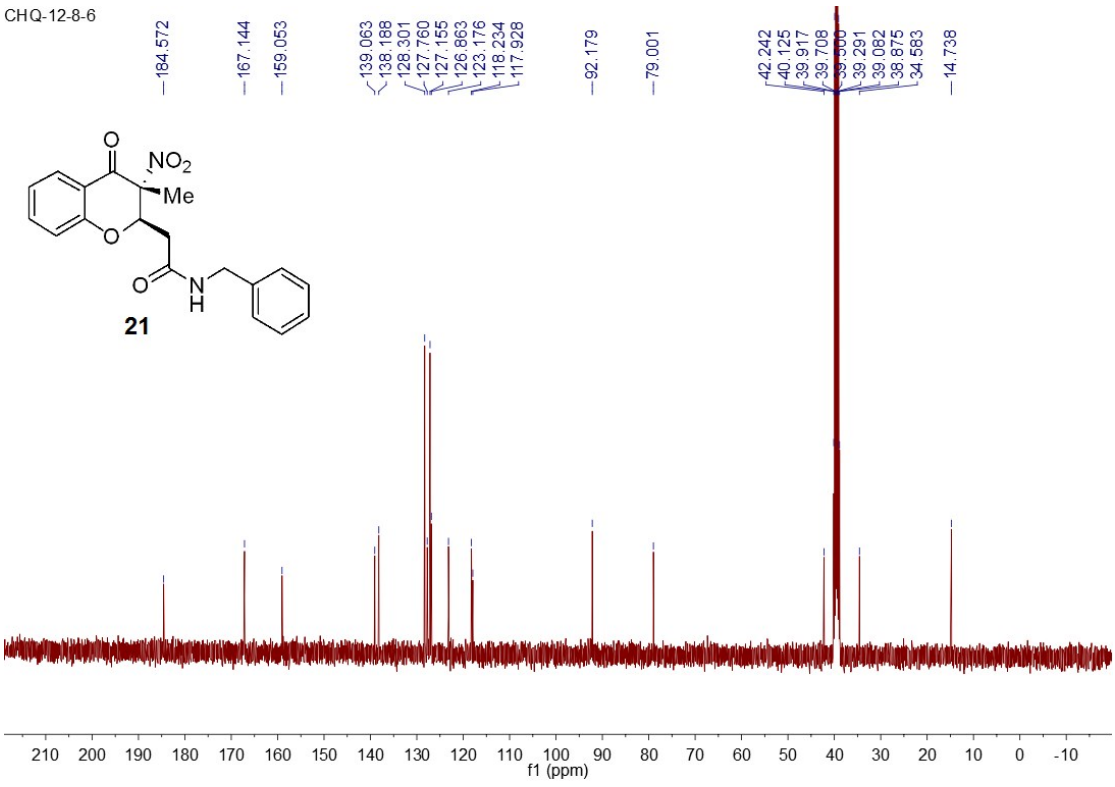
CHQ-2017-3-20-398B



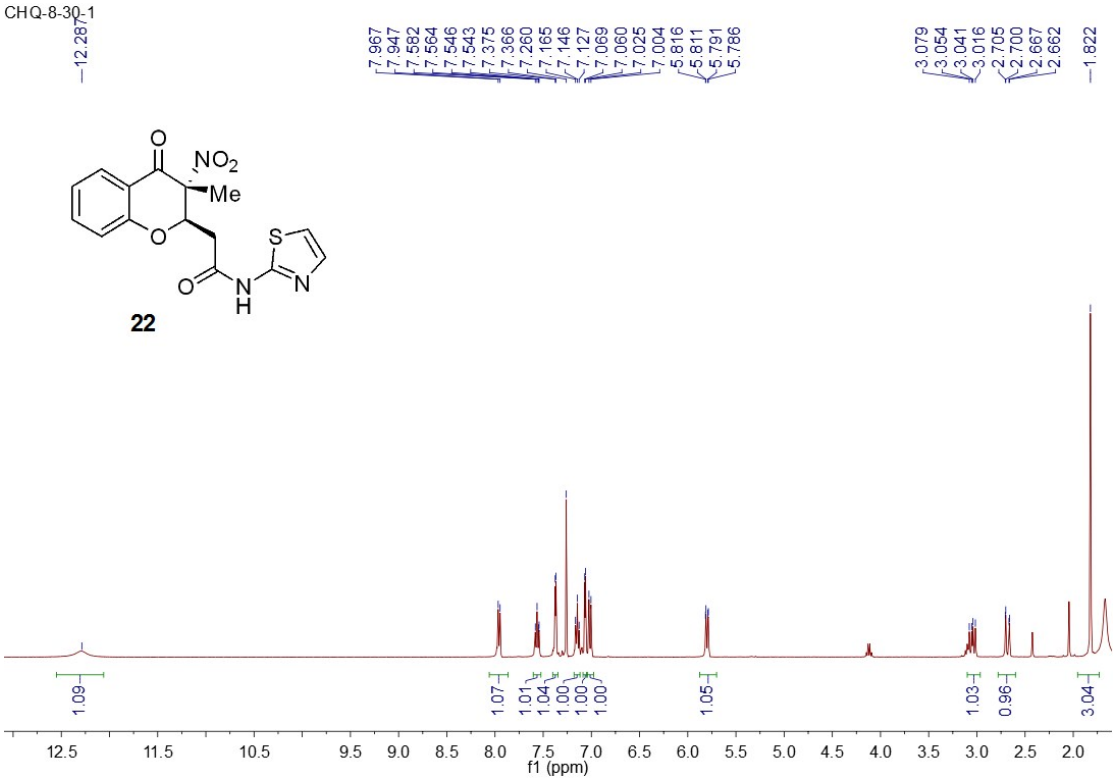

CHQ-12-8-5
7.9657
7.9461
7.6027
7.5819
7.5633
7.5598
7.5209
7.5010
7.3484
7.3297
7.3102
7.2603
7.1726
7.1547
7.1384
7.1216
7.0460
7.0251
5.7330
5.7081
2.8766
2.8513
2.8387
2.8136
2.5321
2.4943
1.7727
NO2
Me
O
N
H
20
1.00
2.07
2.06
2.07
2.09
1.09
1.02
1.04
1.01
3.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)


CHQ-12-8-5
184.846
165.330
159.401
137.579
137.240
129.110
128.492
124.891
123.269
120.004
118.263
118.132
92.171
78.324
77.318
77.000
76.682
36.979
14.532
NO2
Me
O
N
H
20
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)


CHQ-12-8-6
19-HNMR
8.639
8.626
8.613
7.903
7.883
7.744
7.372
7.354
7.335
7.279
7.260
7.240
7.221
7.089
7.068
5.598
5.573
4.404
4.389
4.366
4.352
4.288
4.274
4.250
4.236
2.817
2.791
2.779
2.754
2.500
2.478
1.719
NO2
Me
O
N
H
21
1.02
1.09
1.09
2.09
2.00
2.08
1.00
1.02
1.07
1.07
1.02
1.08
3.05
f1 (ppm)

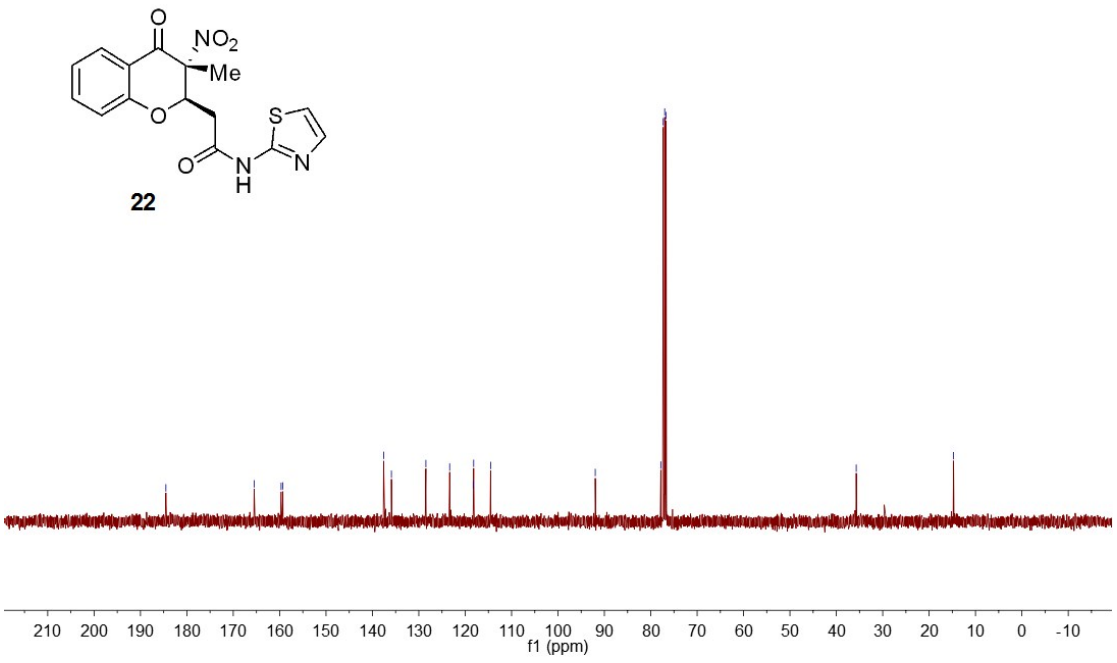

CHQ-12-8-6
184.572
167.144
159.053
139.063
138.188
128.301
127.760
127.155
126.863
123.176
118.234
117.928
92.179
79.001
42.242
40.125
39.917
39.708
39.500
39.291
39.082
38.875
34.583
14.738
NO2
Me
O
N
H
21
f1 (ppm)

CHQ-8-30-1

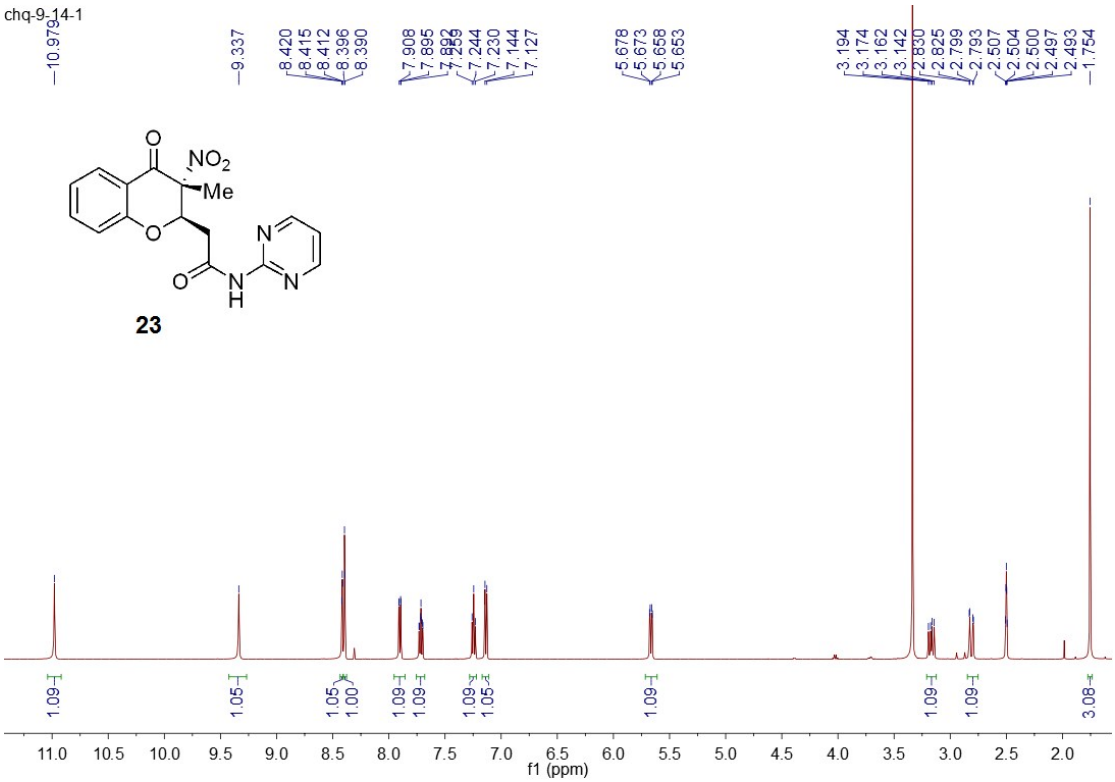


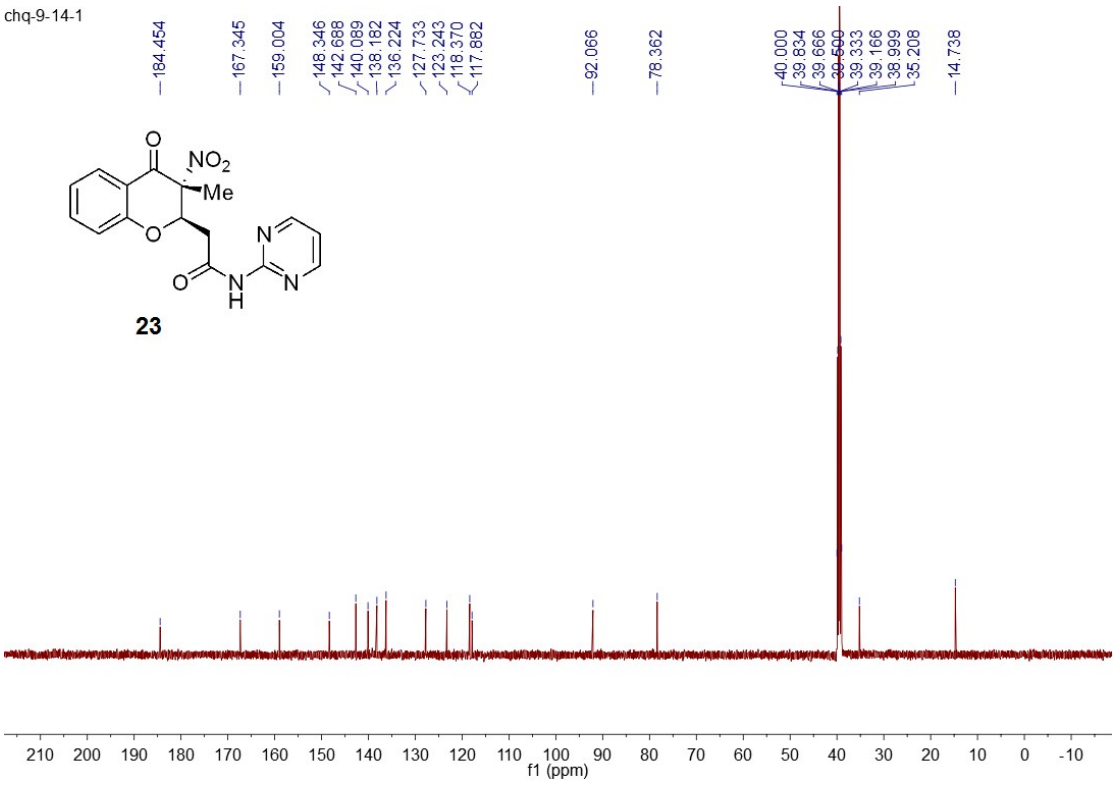
22

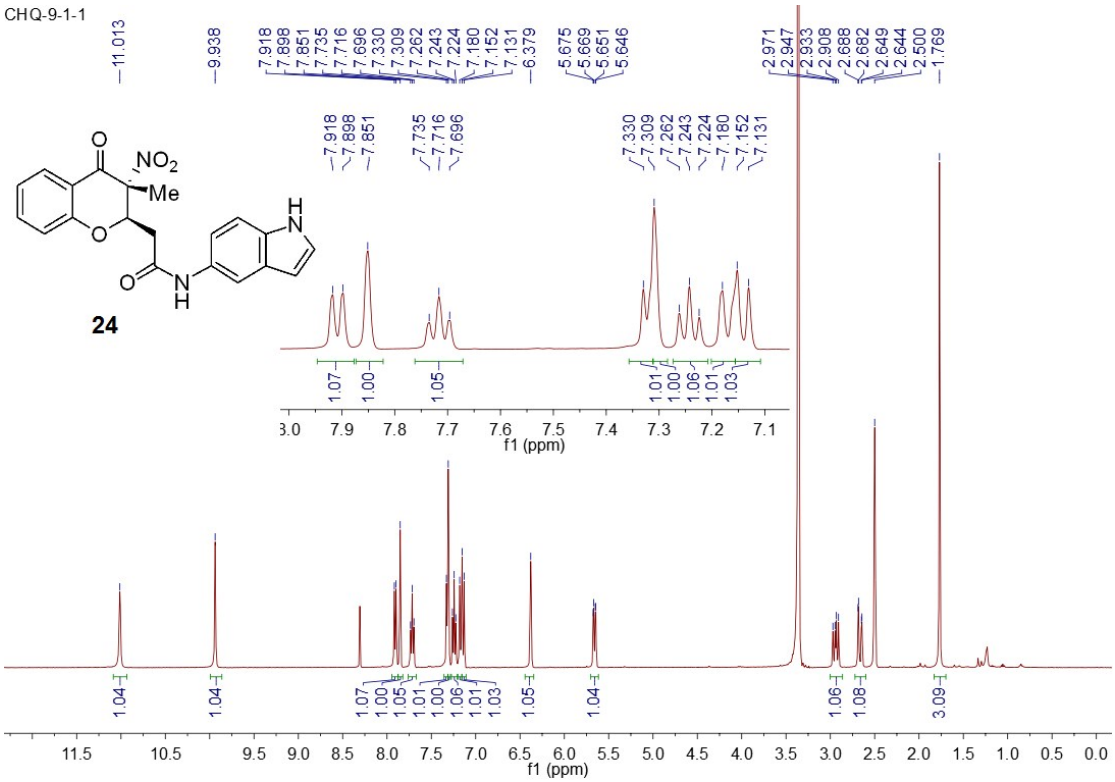
CHQ-9-3-1

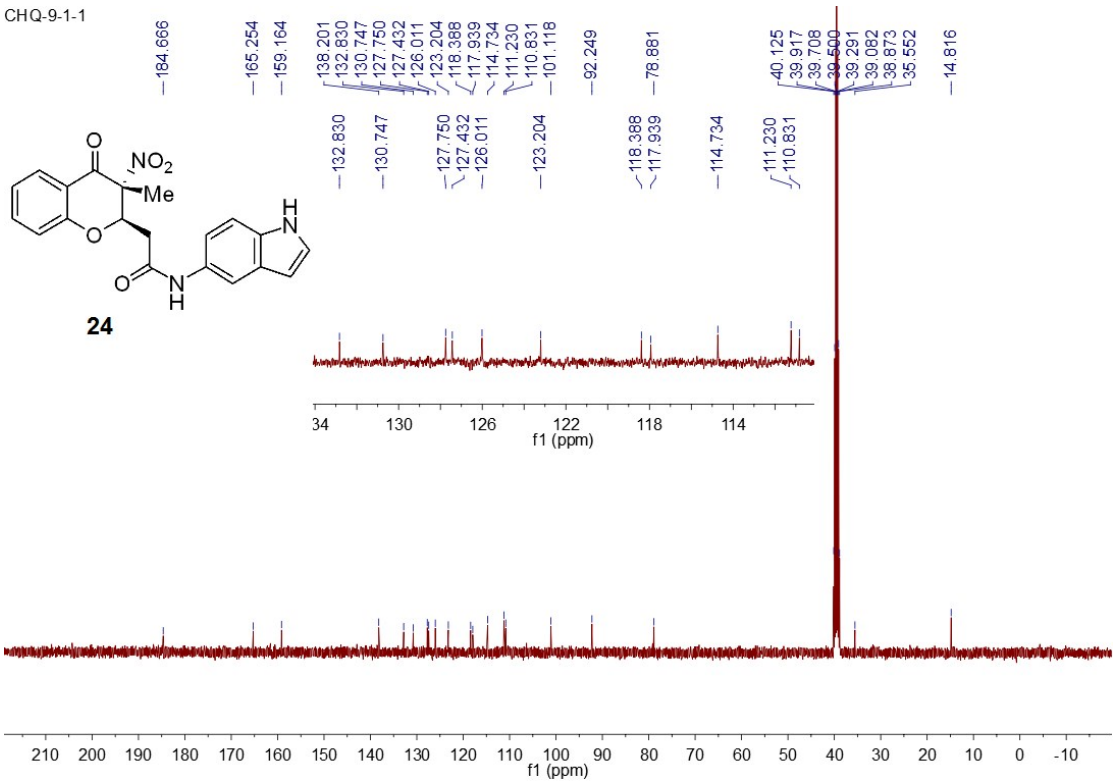


22

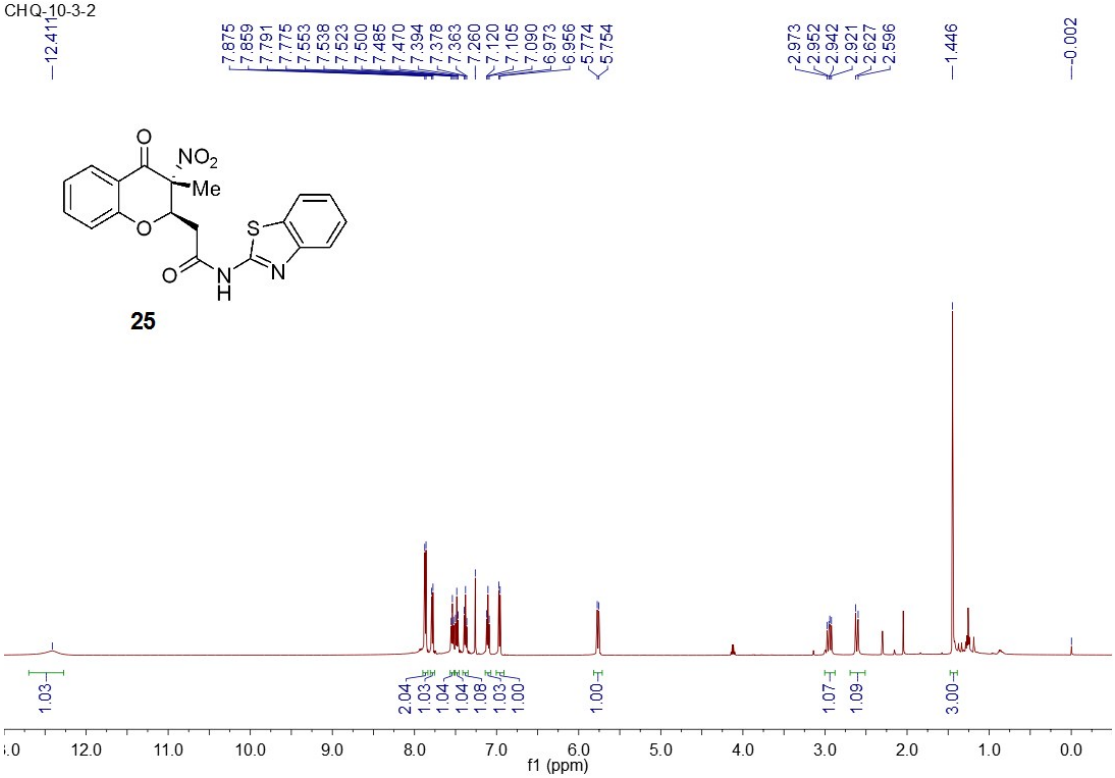

chq-9-14-1
10.979
9.337
8.420
8.415
8.412
8.396
8.390
7.908
7.895
7.244
7.230
7.144
7.127
5.678
5.673
5.658
5.653
3.194
3.174
3.162
3.142
2.830
2.825
2.799
2.793
2.507
2.504
2.500
2.497
2.493
1.754
NO2
Me
O
N
H
23
1.09
1.05
1.05
1.00
1.09
1.09
1.09
1.05
1.09
1.09
1.09
3.08
11.0 10.5 10.0 9.5 9.0 8.5 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
f1 (ppm)


chq-9-14-1
184.454
167.345
159.004
148.346
142.688
140.089
138.182
136.224
127.733
123.243
118.370
117.882
92.066
78.362
40.000
39.834
39.666
39.500
39.333
39.166
38.999
35.208
14.738
NO2
Me
O
N
H
23
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)


CHQ-9-1-1
24
f1 (ppm)

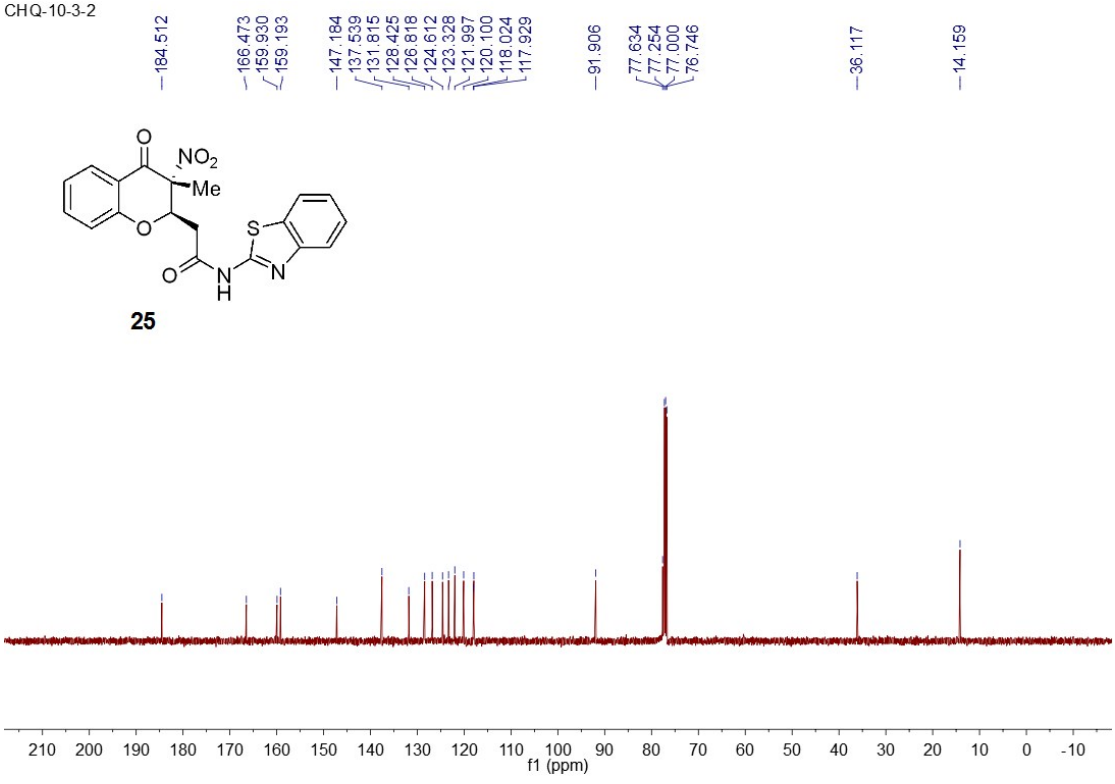

CHQ-9-1-1
24
f1 (ppm)

CHQ-10-3-2

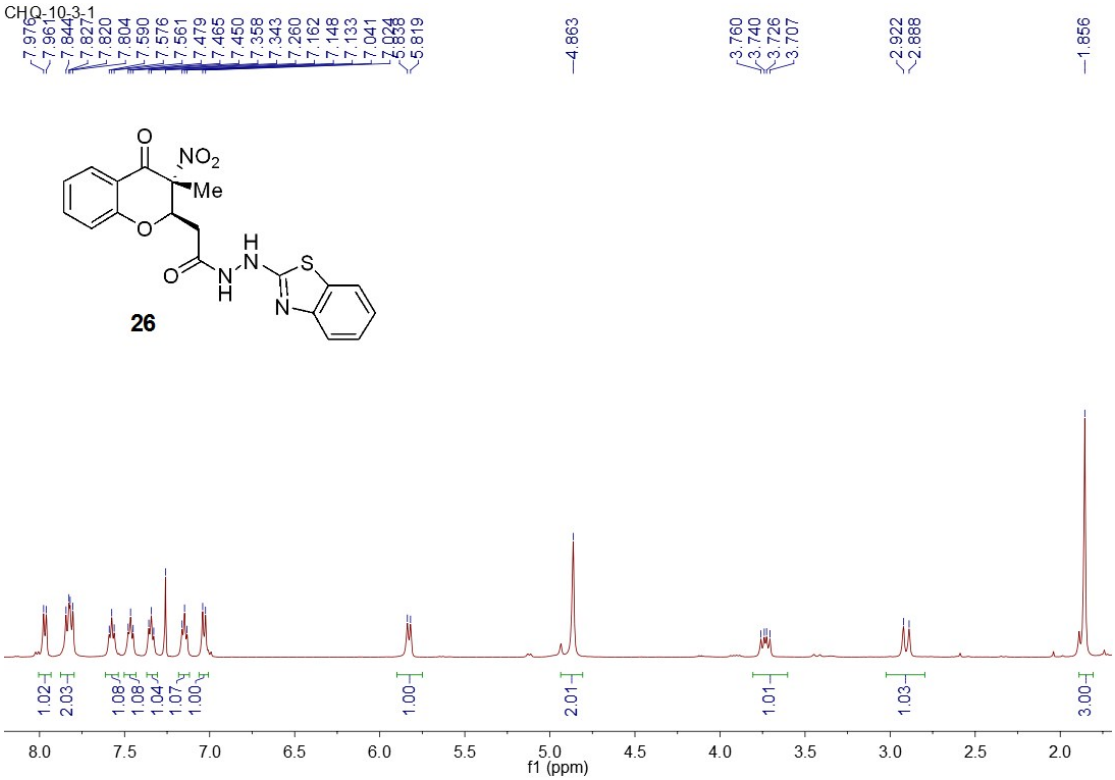


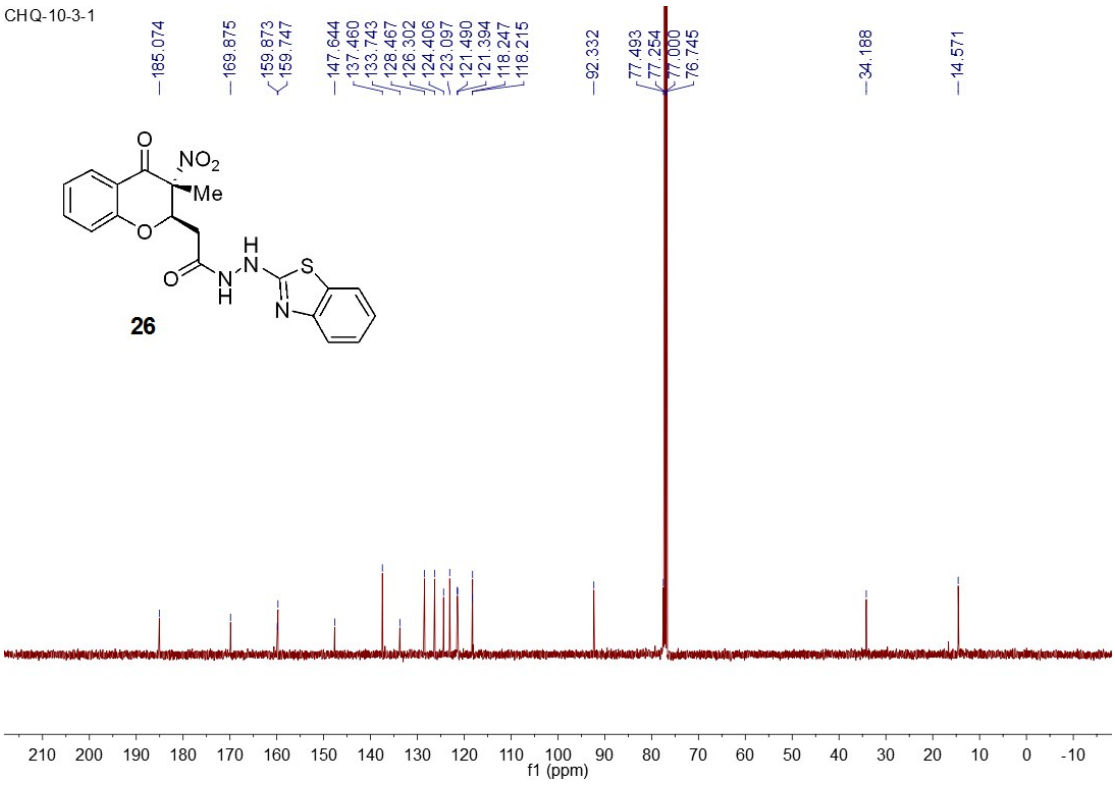
25

CHQ-10-3-2

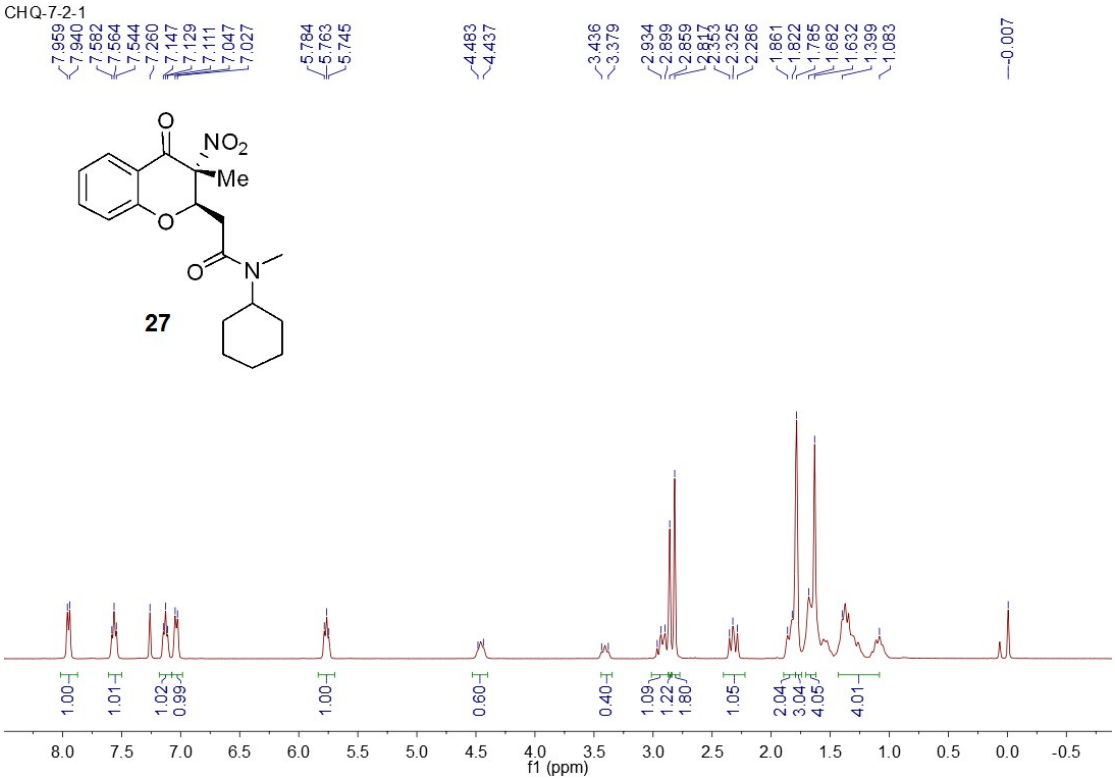


25

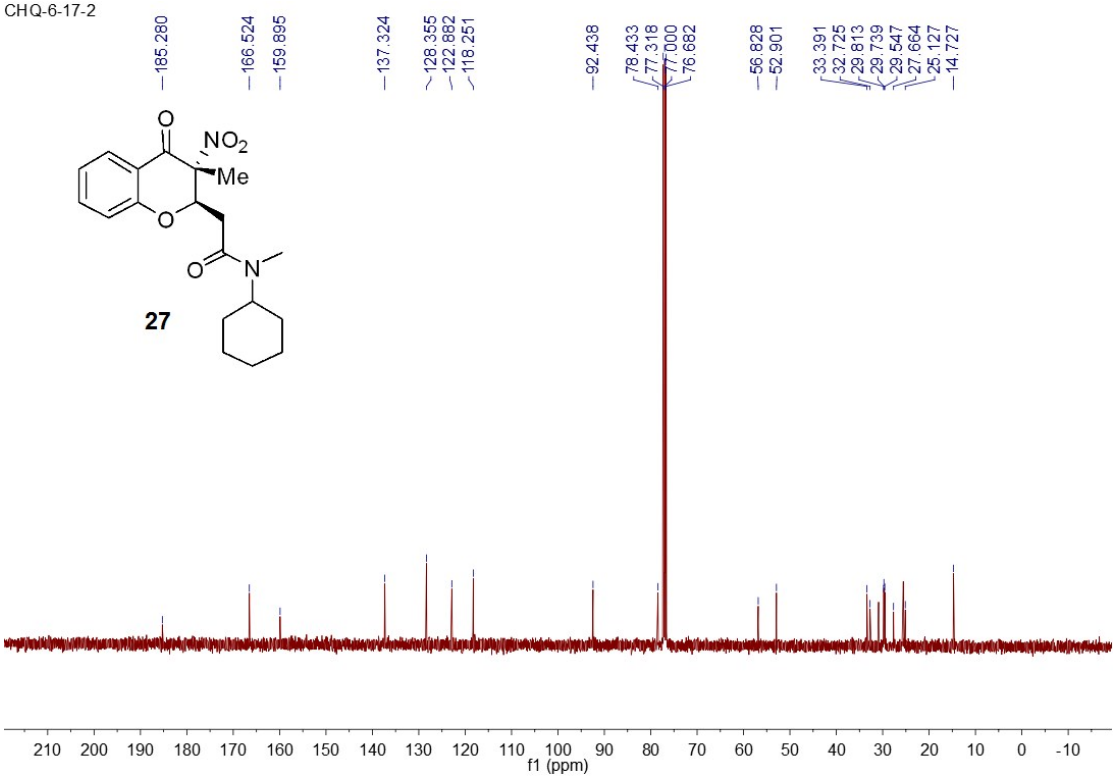

CHQ-10-3-1
7.976
7.961
7.844
7.827
7.820
7.804
7.590
7.576
7.561
7.479
7.465
7.450
7.358
7.343
7.260
7.162
7.148
7.133
7.041
7.024
6.838
5.819
4.863
3.760
3.740
3.726
3.707
2.922
2.888
1.856
O
NO2
Me
O
H
N
S
O
N
H
N
26
1.02
2.03
1.08
1.08
1.04
1.07
1.00
1.00
2.01
1.01
1.03
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

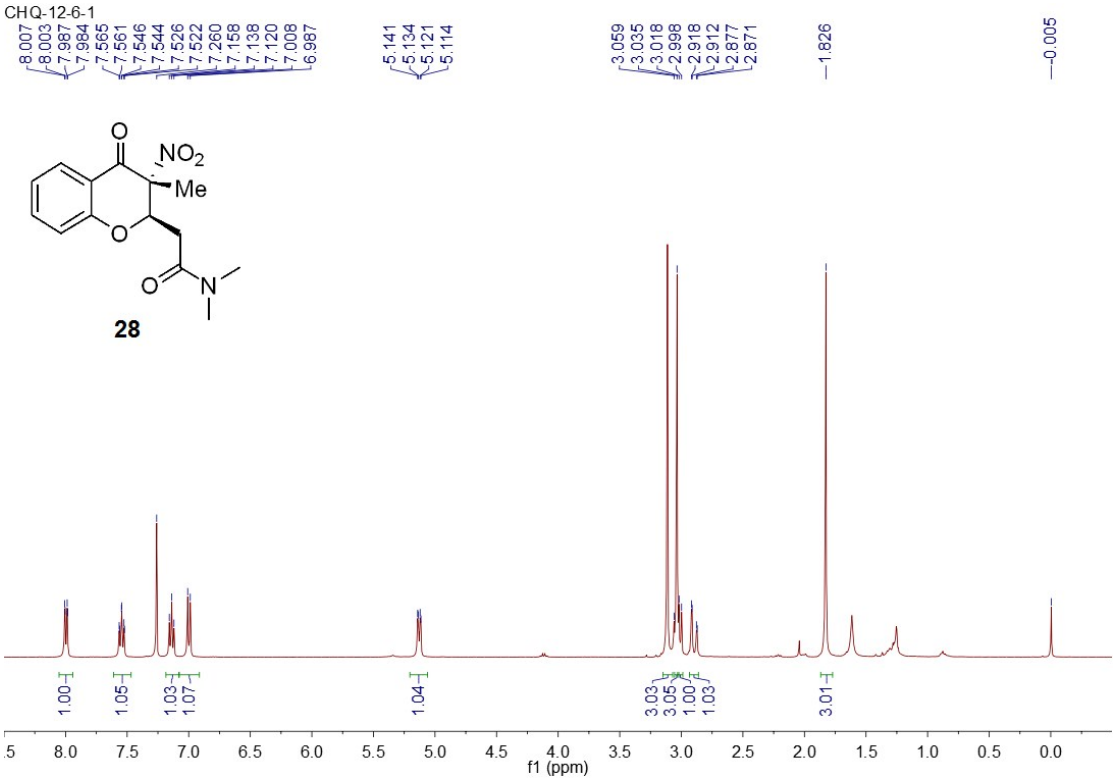

CHQ-10-3-1
185.074
169.875
159.873
159.747
147.644
137.460
133.743
128.467
126.302
124.406
123.097
121.490
121.394
118.247
118.215
92.332
77.493
77.254
77.000
76.745
34.188
14.571
O
NO2
Me
O
H
N
S
O
N
H
N
26
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

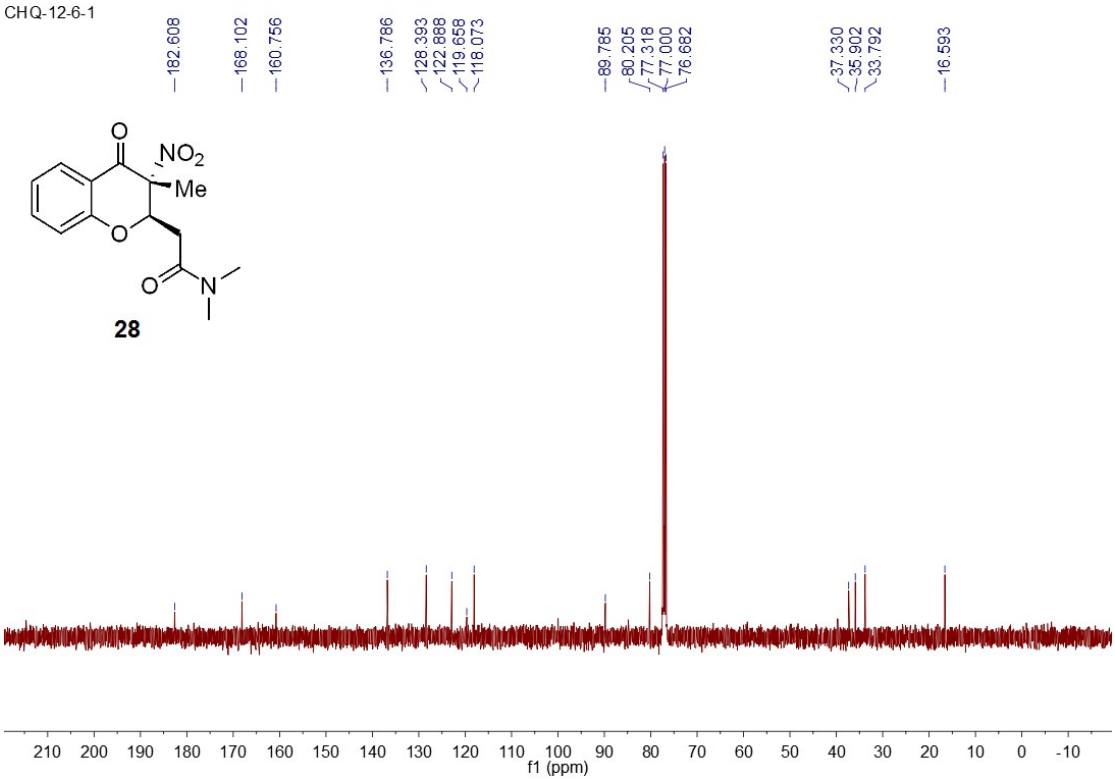
CHQ-7-2-1

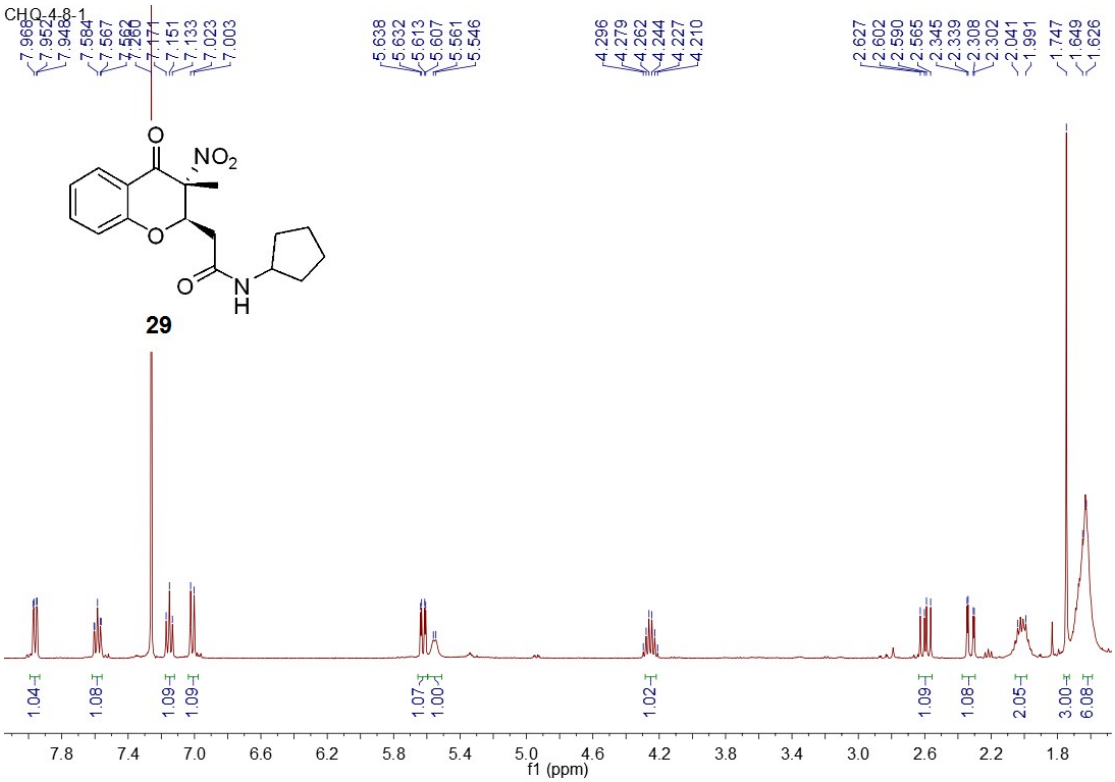


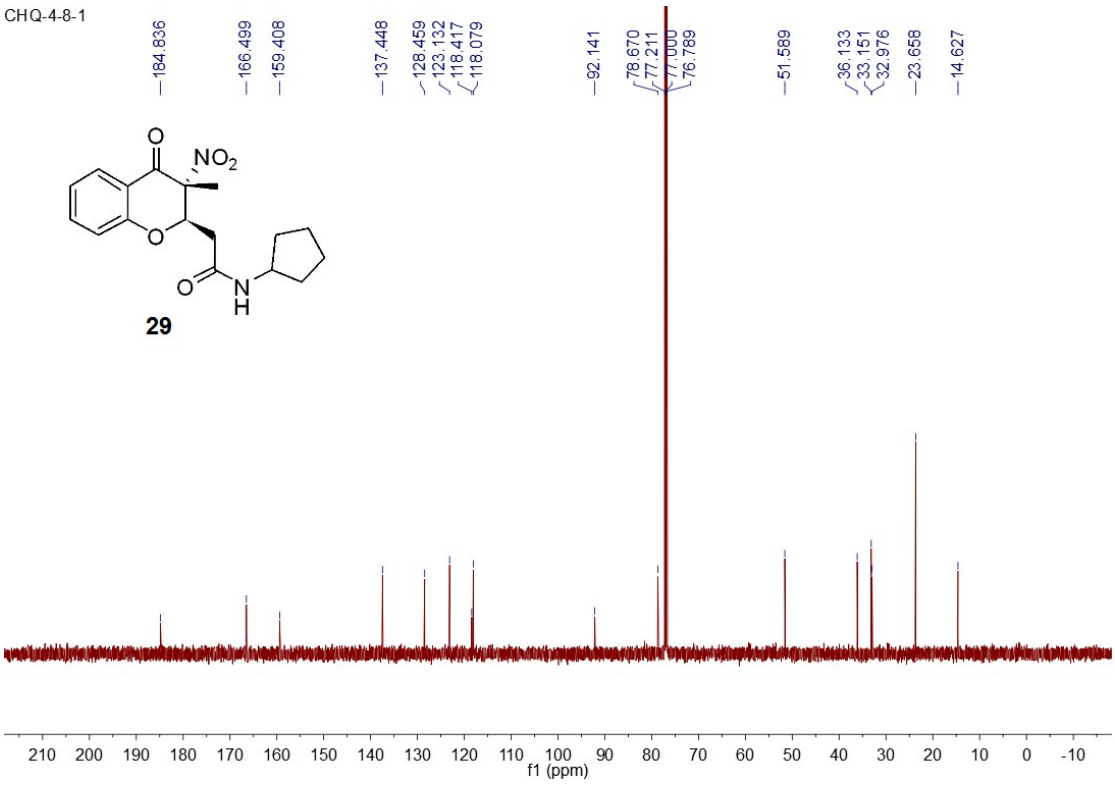
CHQ-6-17-2

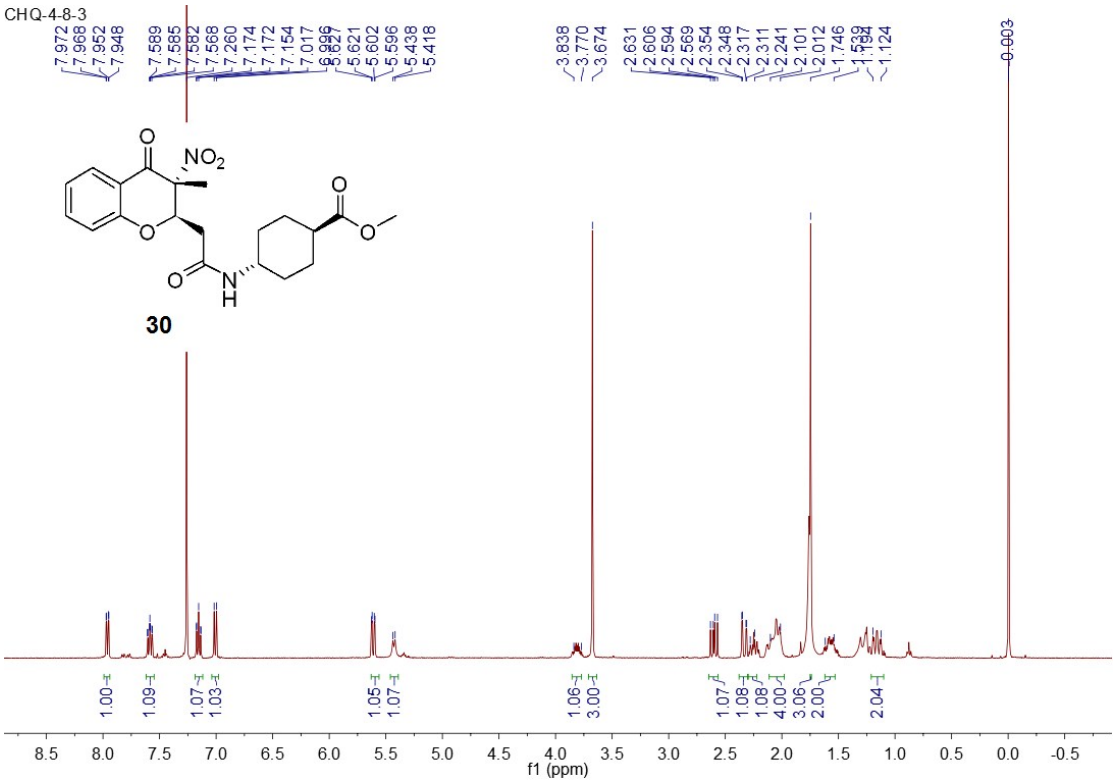


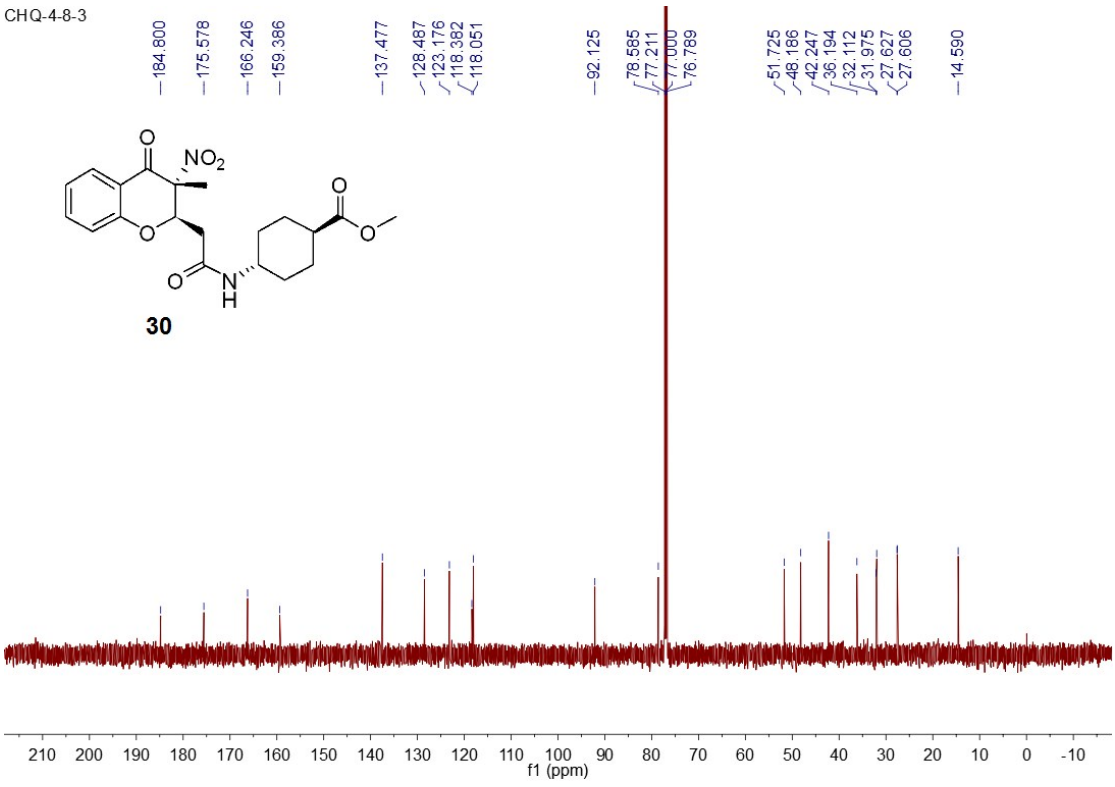

CHQ-12-6-1
8.007
8.003
7.987
7.984
7.565
7.561
7.546
7.544
7.526
7.522
7.260
7.158
7.138
7.120
7.008
6.987
5.141
5.134
5.121
5.114
3.059
3.035
3.018
2.998
2.918
2.912
2.877
2.871
1.826
0.005
NO2
Me
O
N
28
1.00
1.05
1.03
1.07
1.04
3.03
3.05
1.00
1.03
3.01
f1 (ppm)

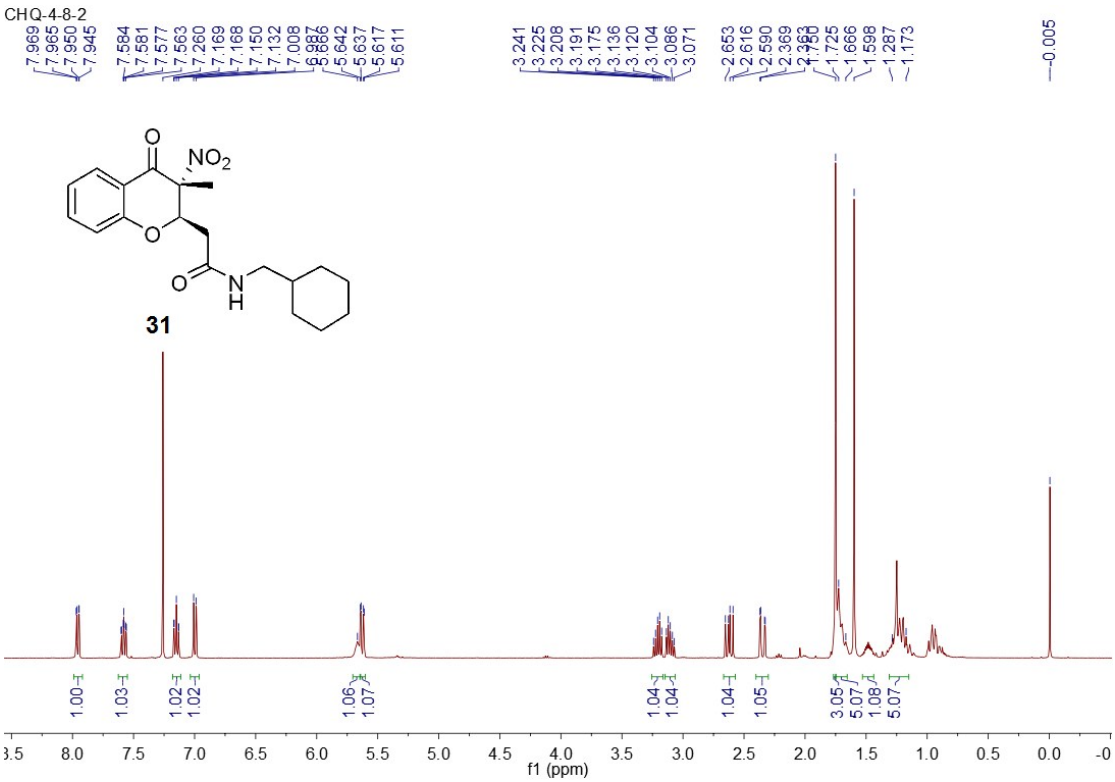

CHQ-12-6-1
182.608
168.102
160.756
136.786
128.393
122.888
119.658
118.073
89.785
80.205
77.318
77.000
76.682
37.330
35.902
33.792
16.593
NO2
Me
O
N
28
f1 (ppm)

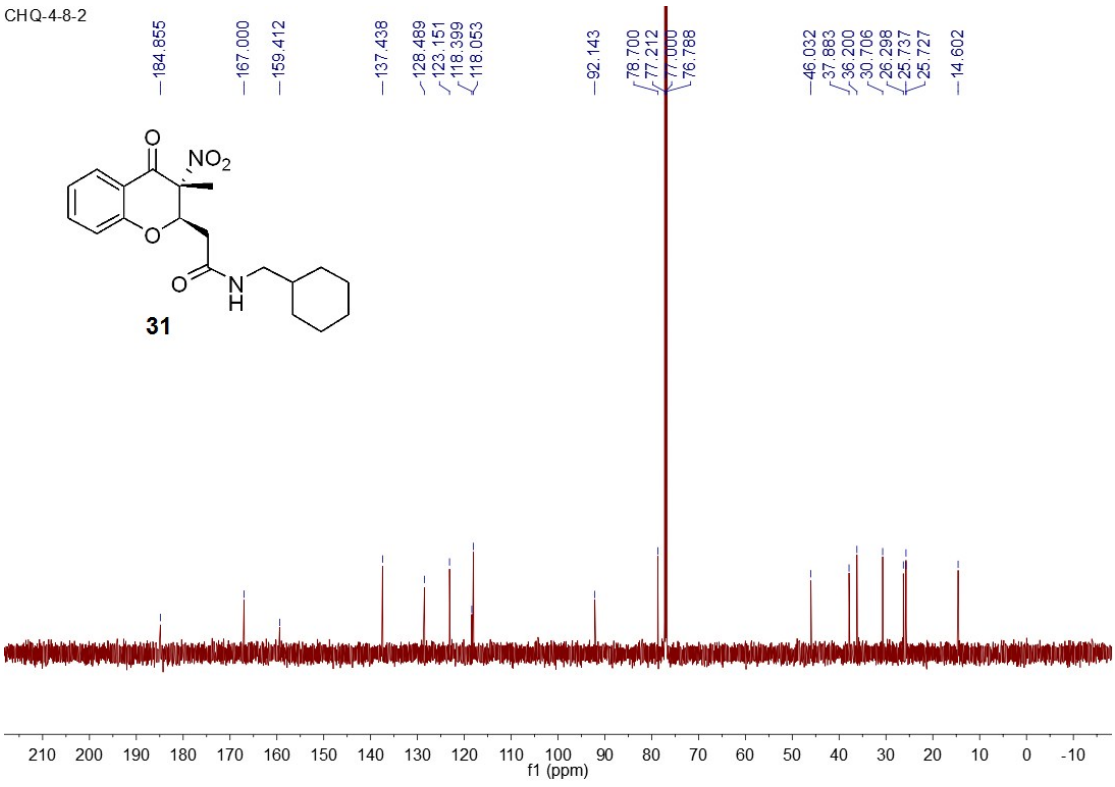

CHQ-4-8-1
7.968
7.952
7.948
7.584
7.567
7.562
7.260
7.171
7.151
7.133
7.023
7.003
5.638
5.632
5.613
5.607
5.561
5.546
4.296
4.279
4.262
4.244
4.227
4.210
2.627
2.602
2.590
2.565
2.345
2.339
2.308
2.302
2.041
1.991
1.747
1.649
1.626
O
NO2
O
O
N
H
29
1.04
1.08
1.09
1.09
1.07
1.00
1.02
1.09
1.08
2.05
3.00
6.08
7.8
7.4
7.0
6.6
6.2
5.8
5.4
5.0
4.6
4.2
3.8
3.4
3.0
2.6
2.2
1.8
f1 (ppm)

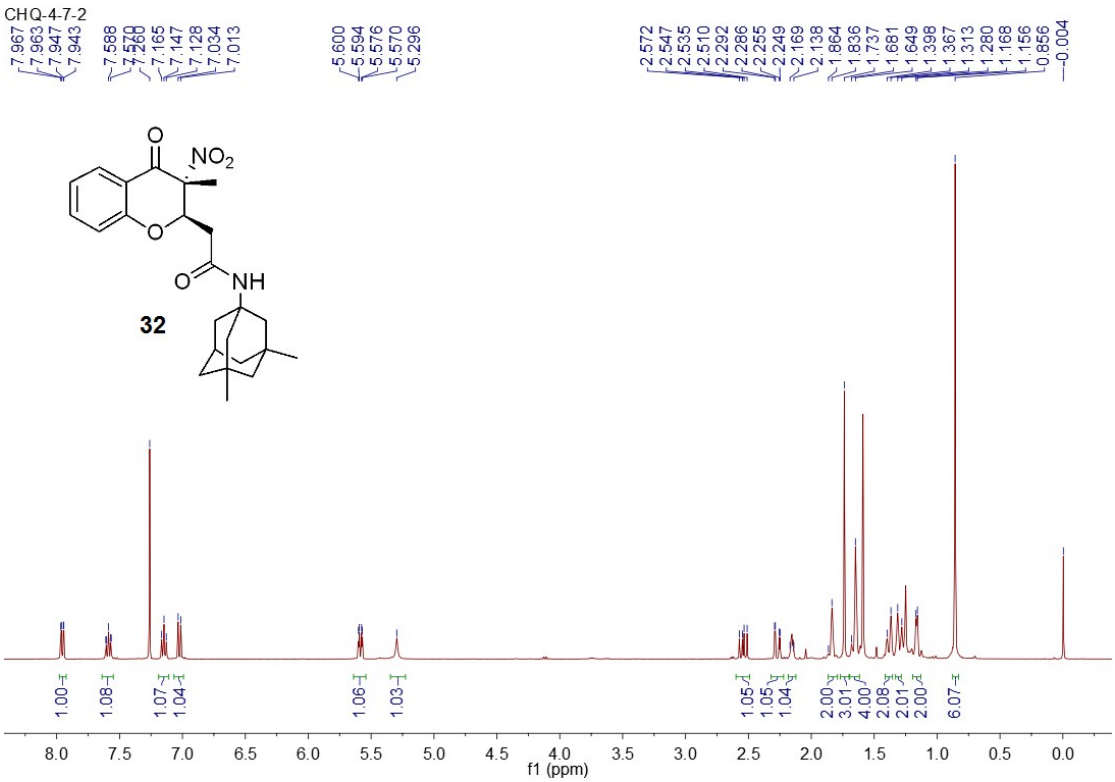

CHQ-4-8-1
184.836
166.499
159.408
137.448
128.459
123.132
118.417
118.079
92.141
78.670
77.211
77.000
76.789
51.589
36.133
33.151
32.976
23.658
14.627
O
NO2
O
O
N
H
29
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

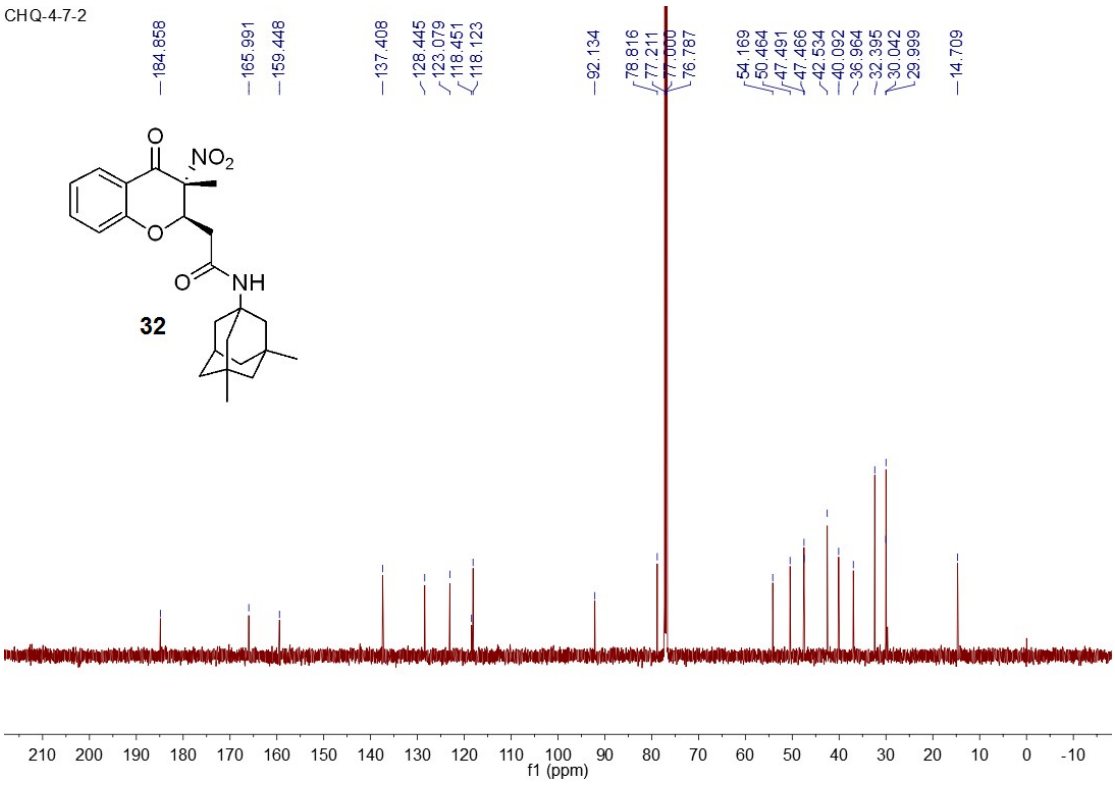

CHQ-4-8-3
7.972
7.968
7.952
7.948
7.589
7.585
7.582
7.568
7.260
7.174
7.172
7.154
7.017
5.621
5.602
5.596
5.438
5.418
3.838
3.770
3.674
2.631
2.606
2.594
2.569
2.354
2.348
2.317
2.311
2.241
2.101
2.012
1.746
1.124
0.903
NO2
O
O
O
O
N
H
30
1.00
1.09
1.07
1.03
1.05
1.07
1.06
3.00
1.07
1.08
1.08
4.00
3.06
2.00
2.04
f1 (ppm)

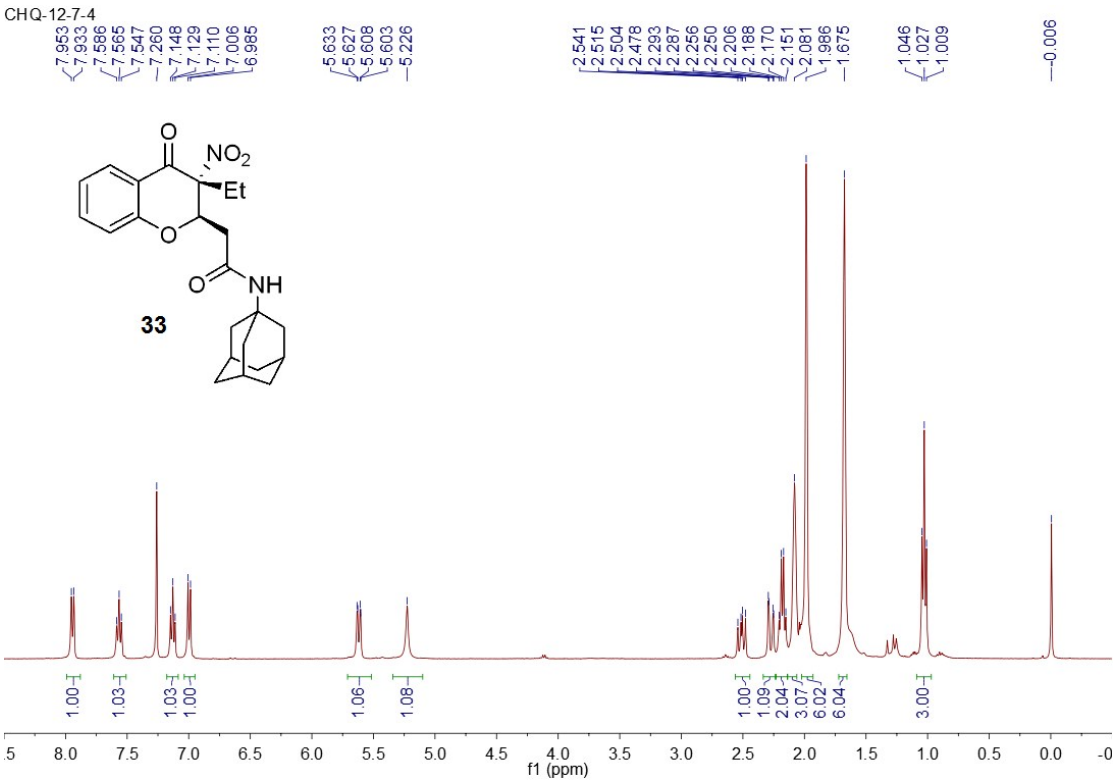

CHQ-4-8-3
184.800
175.578
166.246
159.386
137.477
128.487
123.176
118.382
118.051
92.125
78.585
77.211
77.000
76.789
51.725
48.186
42.247
36.194
32.112
31.975
27.627
27.606
14.590
NO2
O
O
O
O
N
H
30
f1 (ppm)

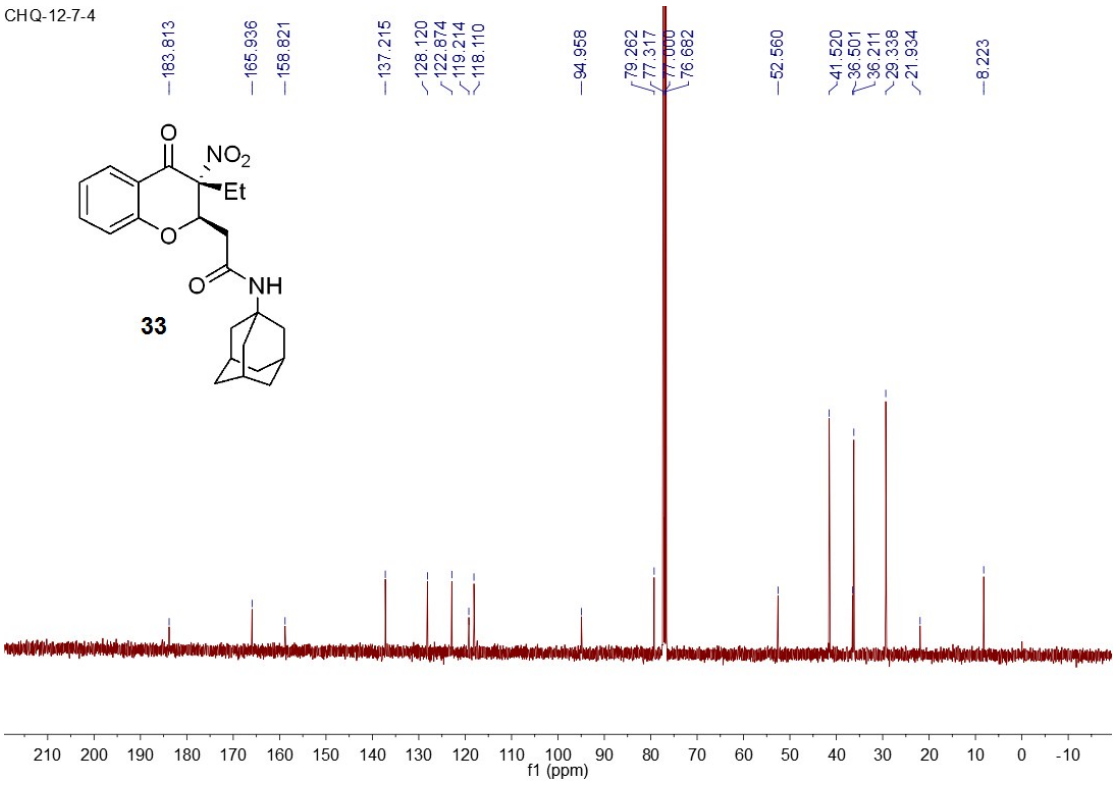

CHQ-4-8-2
7.969
7.965
7.950
7.945
7.584
7.581
7.577
7.563
7.260
7.169
7.168
7.150
7.132
7.008
6.988
6.986
5.642
5.637
5.617
5.611
3.241
3.225
3.208
3.191
3.175
3.136
3.120
3.104
3.086
3.071
2.653
2.616
2.590
2.369
1.725
1.666
1.598
1.287
1.173
0.005
NO2
O
O
O
N
H
31
1.00
1.03
1.02
1.02
1.06
1.07
1.04
1.04
1.04
1.05
3.05
5.07
1.08
5.07
f1 (ppm)

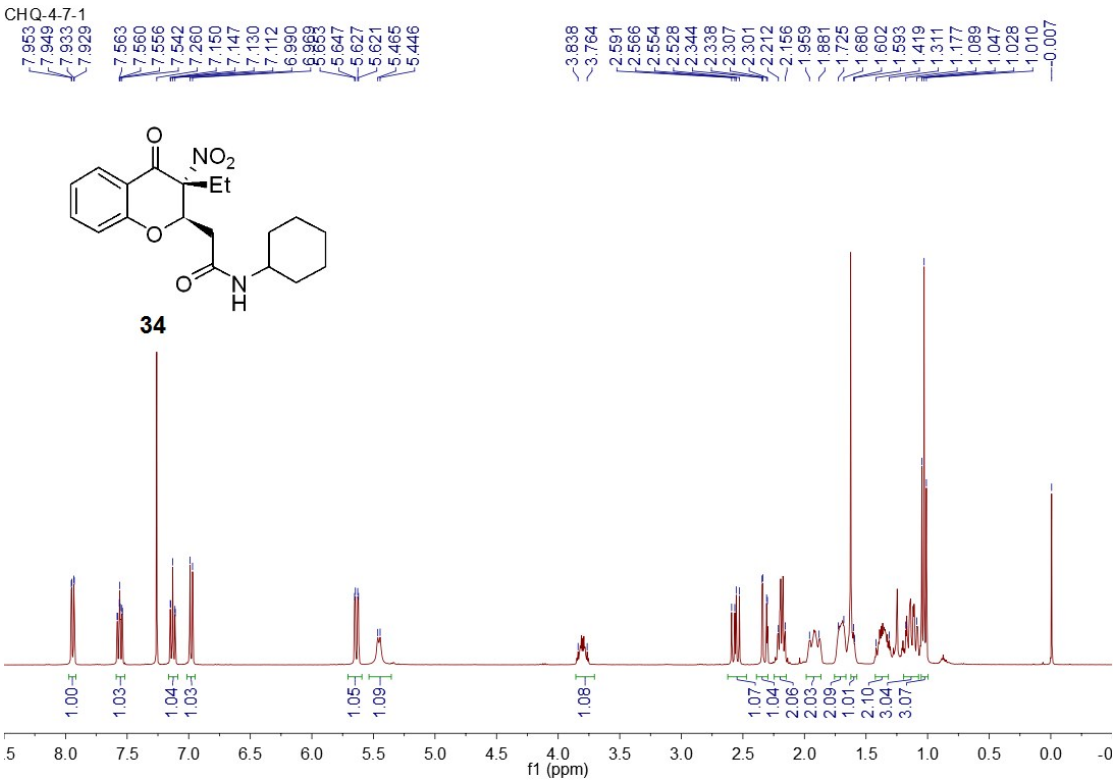

CHQ-4-8-2
184.855
167.000
159.412
137.438
128.489
123.151
118.399
118.053
92.143
78.700
77.212
77.000
76.788
46.032
37.883
36.200
30.706
26.298
25.737
25.727
14.602
NO2
O
O
O
N
H
31
f1 (ppm)

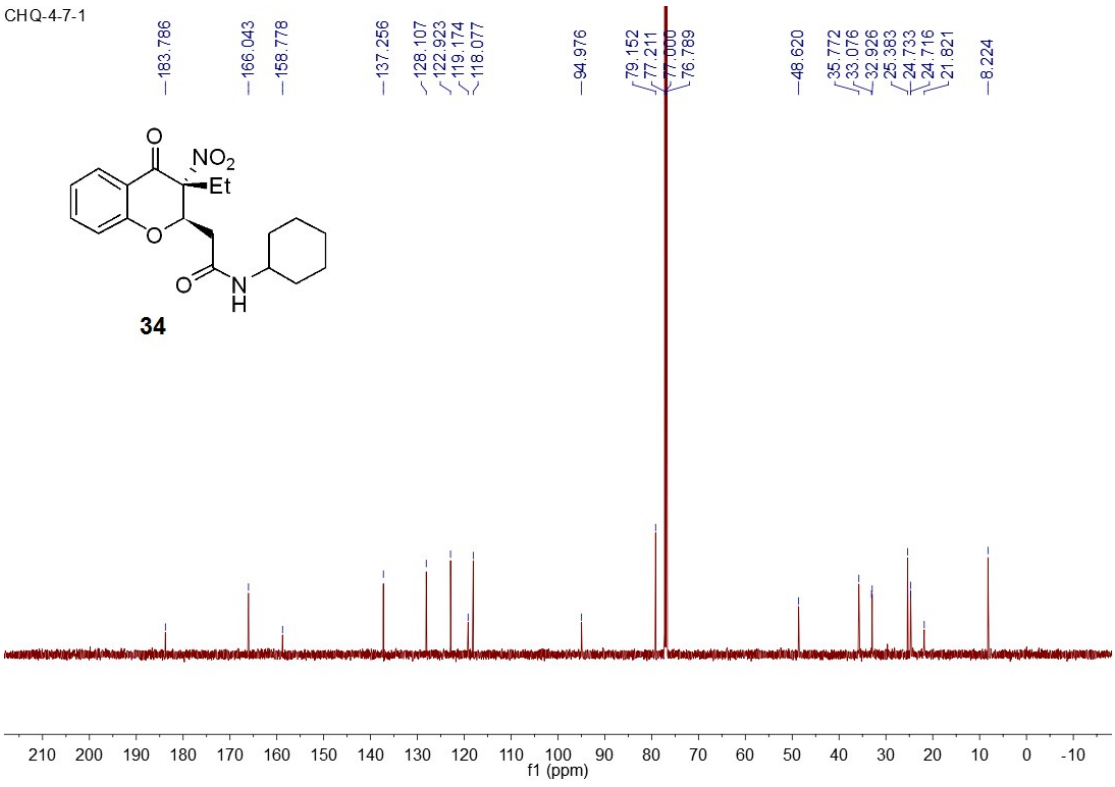

CHQ-4-7-2
7.967
7.963
7.947
7.943
7.588
7.570
7.560
7.165
7.147
7.128
7.034
7.013
5.600
5.594
5.576
5.570
5.296
2.572
2.547
2.535
2.510
2.292
2.286
2.255
2.249
2.169
2.138
1.864
1.836
1.737
1.681
1.649
1.398
1.367
1.313
1.280
1.168
1.156
0.856
0.004
O
NO2
O
O
NH
32
1.00
1.08
1.07
1.04
1.06
1.03
1.05
1.05
1.04
2.00
3.01
4.00
2.08
2.01
2.00
6.07
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)


CHQ-4-7-2
184.858
165.991
159.448
137.408
128.445
123.079
118.451
118.123
92.134
78.816
77.211
77.000
76.787
54.169
50.464
47.491
47.466
42.534
40.092
36.964
32.395
30.042
29.999
14.709
O
NO2
O
O
NH
32
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)

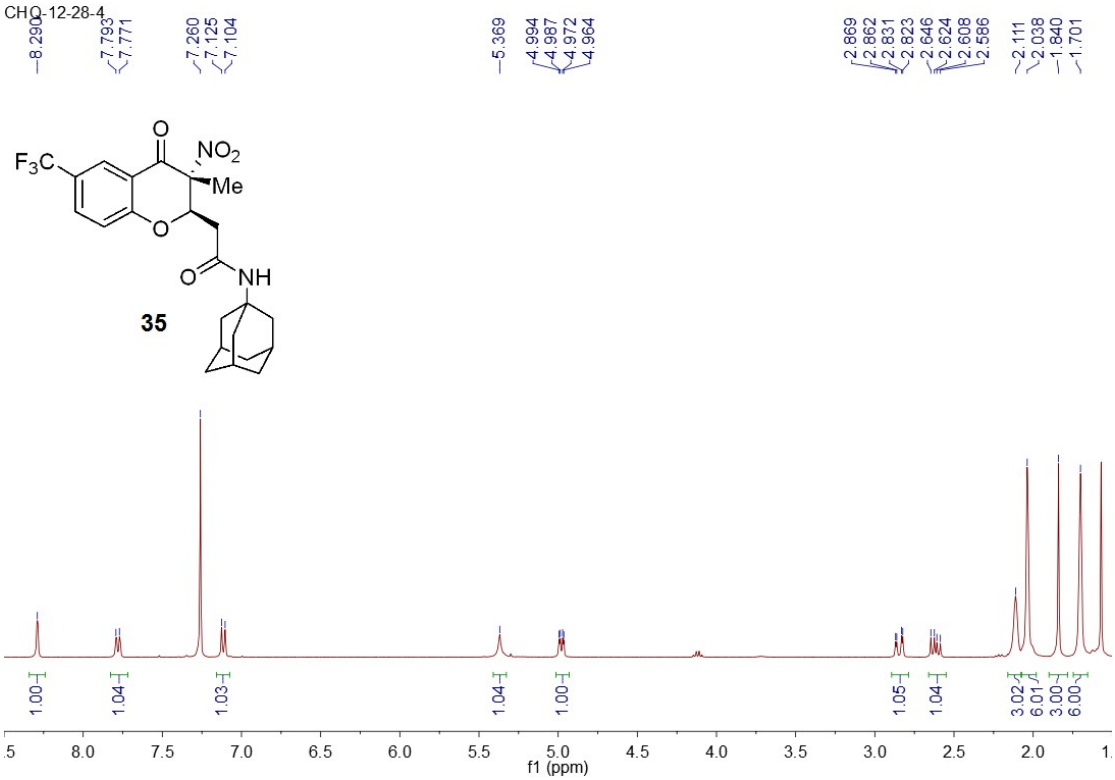

CHQ-12-7-4
7.953
7.933
7.586
7.565
7.547
7.260
7.148
7.129
7.110
7.006
6.985
5.633
5.627
5.608
5.603
5.226
2.541
2.515
2.504
2.478
2.293
2.287
2.256
2.250
2.206
2.188
2.170
2.151
2.081
1.986
1.675
1.046
1.027
1.009
0.006
O
NO2
Et
O
O
NH
33
1.00
1.03
1.03
1.00
1.06
1.08
1.00
1.09
2.04
3.07
6.02
6.04
3.00
f1 (ppm)


CHQ-12-7-4
183.813
165.936
158.821
137.215
128.120
122.874
119.214
118.110
94.958
79.262
77.317
77.000
76.682
52.560
41.520
36.501
36.211
29.338
21.934
8.223
O
NO2
Et
O
O
NH
33
f1 (ppm)


CHQ-4-7-1
7.953
7.949
7.933
7.929
7.563
7.560
7.556
7.542
7.260
7.150
7.147
7.130
7.112
6.990
6.969
6.883
5.647
5.627
5.621
5.465
5.446
3.838
3.764
2.591
2.566
2.554
2.528
2.344
2.338
2.307
2.301
2.212
2.156
1.959
1.881
1.725
1.680
1.602
1.593
1.419
1.311
1.177
1.089
1.047
1.028
1.010
0.007
NO2
Et
O
N
H
34
1.00
1.03
1.04
1.03
1.05
1.09
1.08
1.07
1.04
2.06
2.03
2.09
1.01
2.10
3.04
3.07
f1 (ppm)

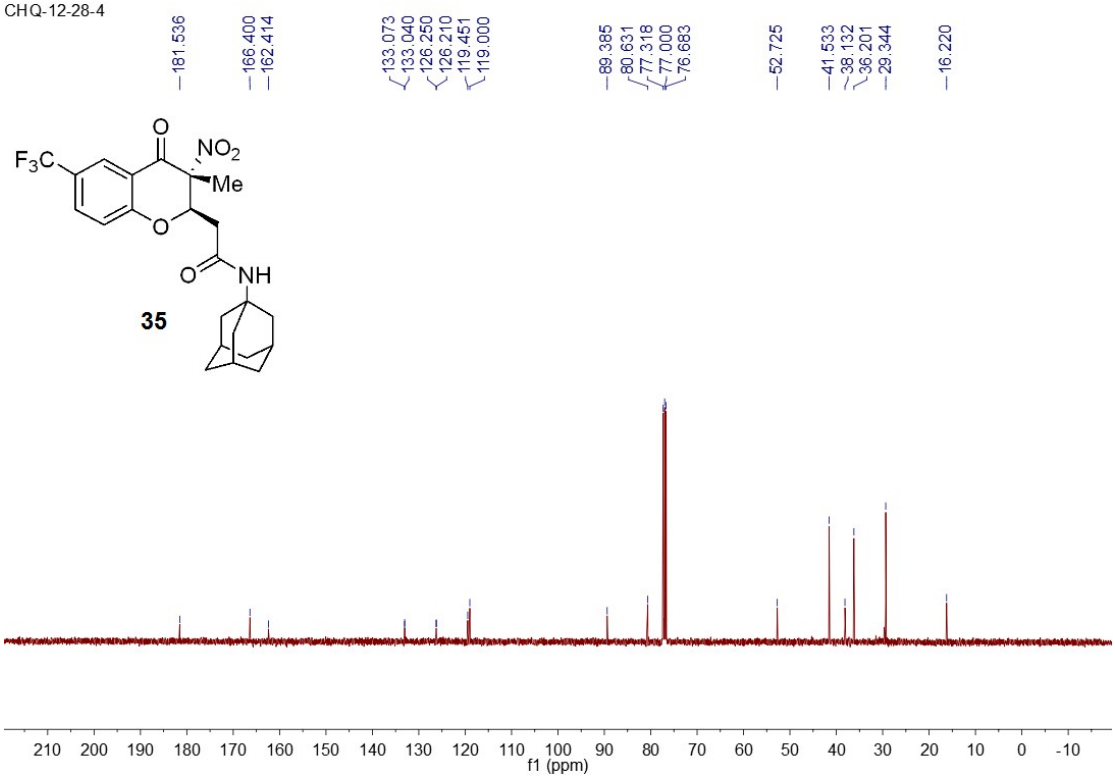

CHQ-4-7-1
183.786
166.043
158.778
137.256
128.107
122.923
119.174
118.077
94.976
79.152
77.211
77.000
76.789
48.620
35.772
33.076
32.926
25.383
24.733
24.716
21.821
8.224
NO2
Et
O
N
H
34
f1 (ppm)

CHQ-12-28-4



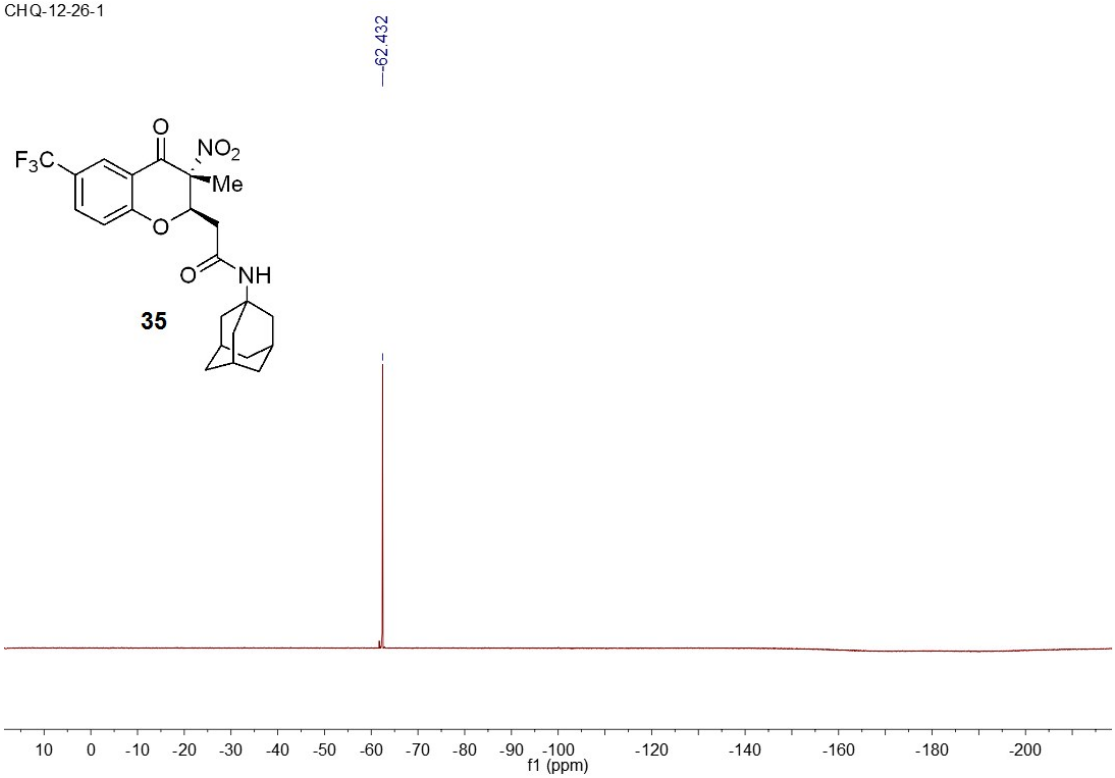
35

CHQ-12-28-4

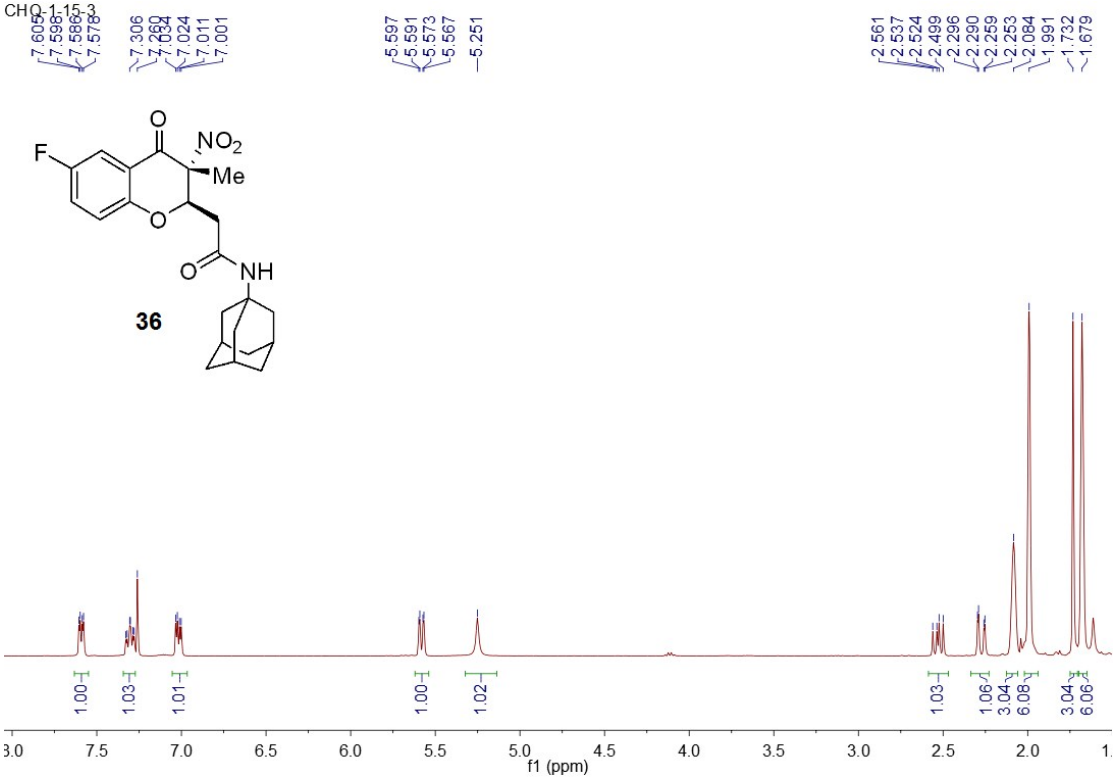


35

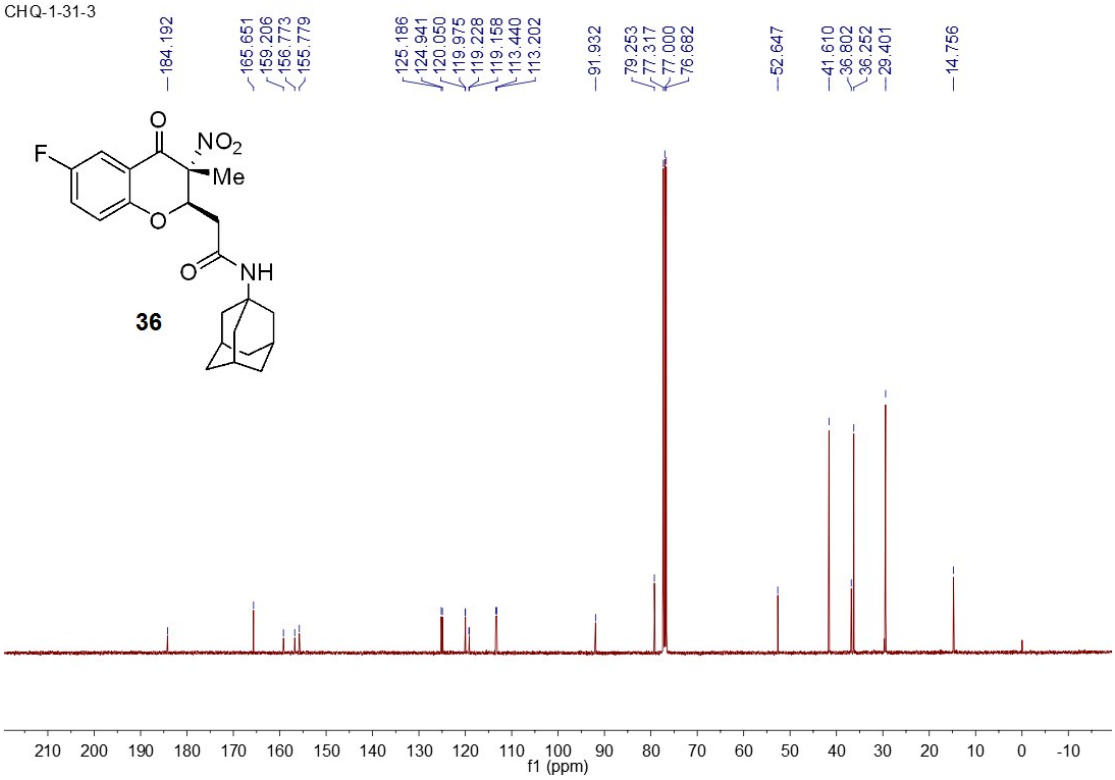
CHQ-12-26-1


-62.432
O
NO2
F3C
Me
O
O
NH
35
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)

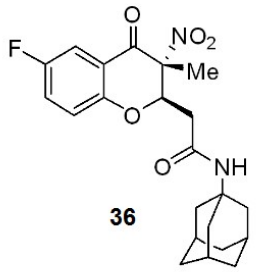
CHQ-1-15-3



CHQ-1-31-3

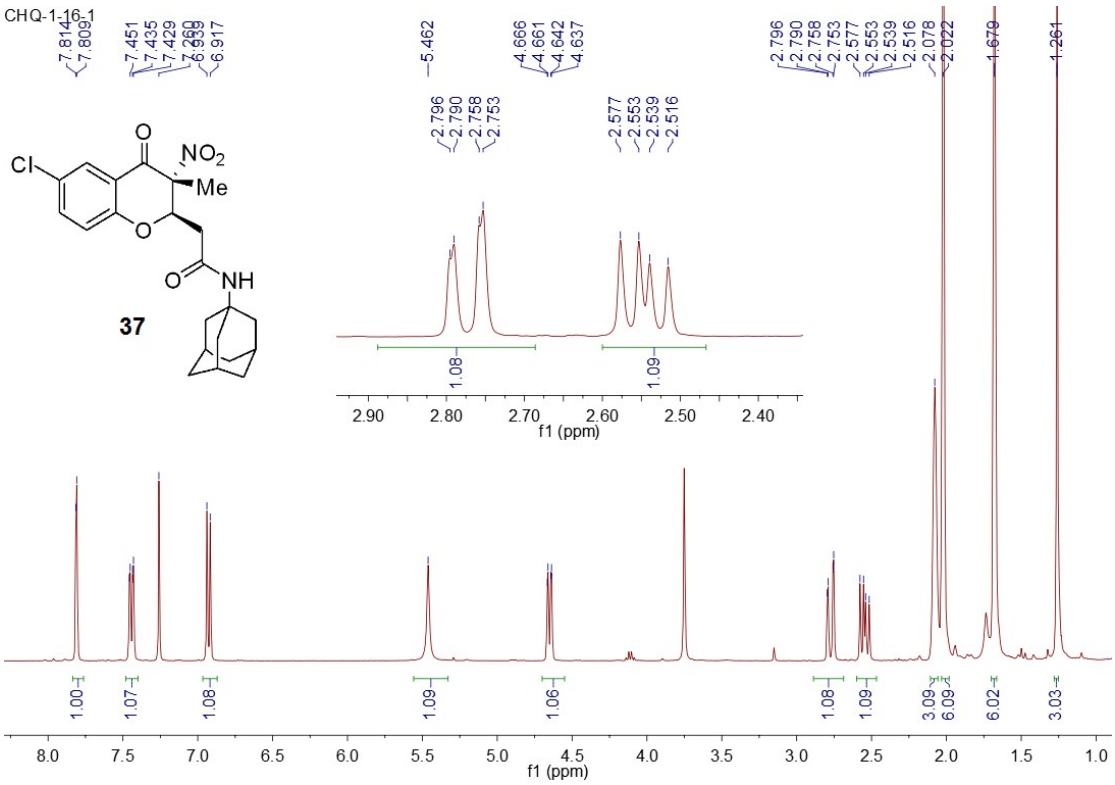


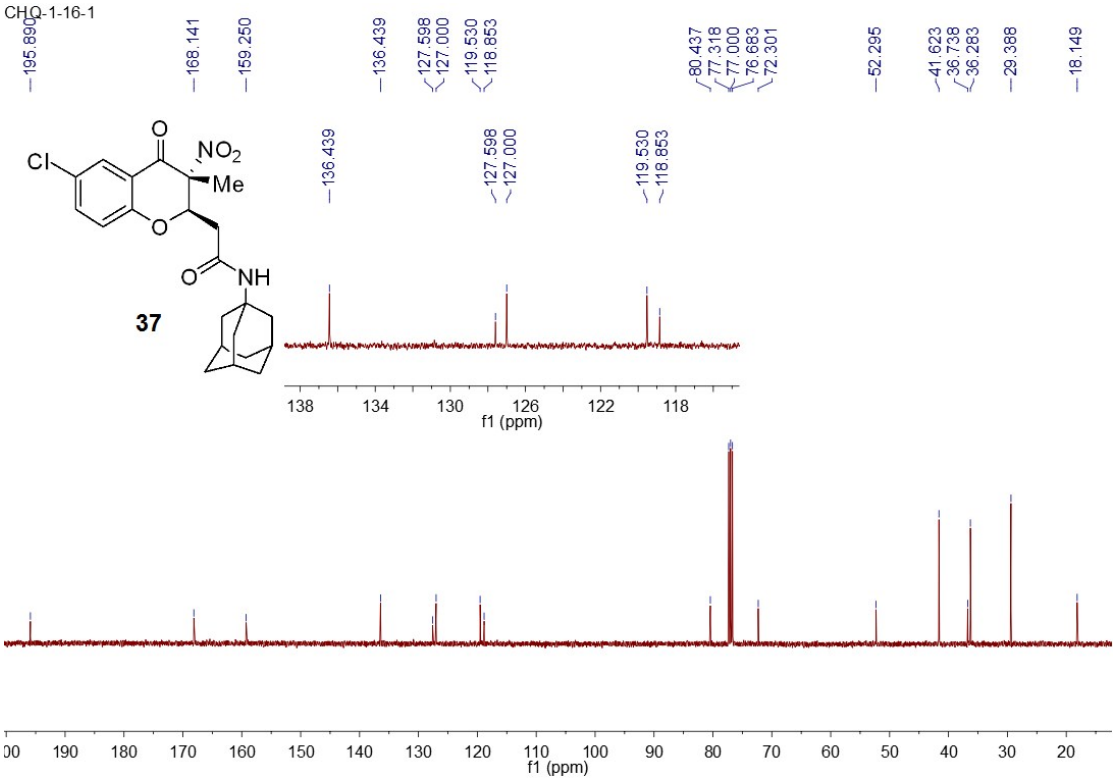
CHQ-1-14-1

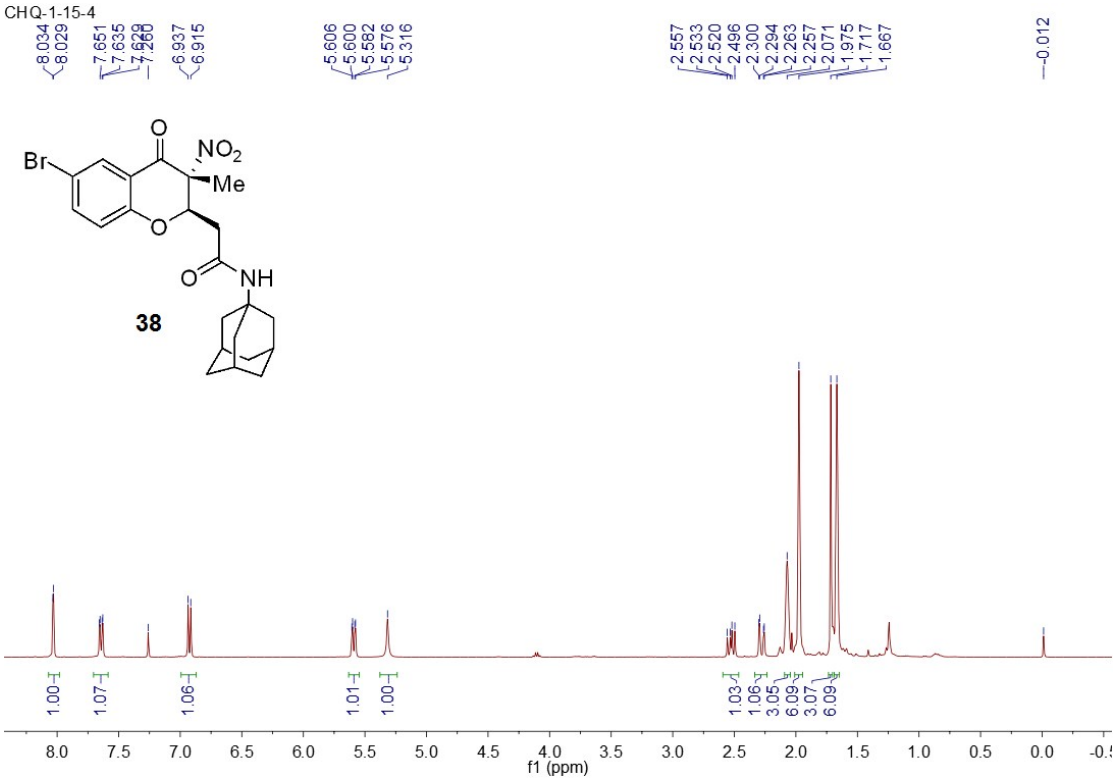

O
NO2
F
Me
O
O
NH

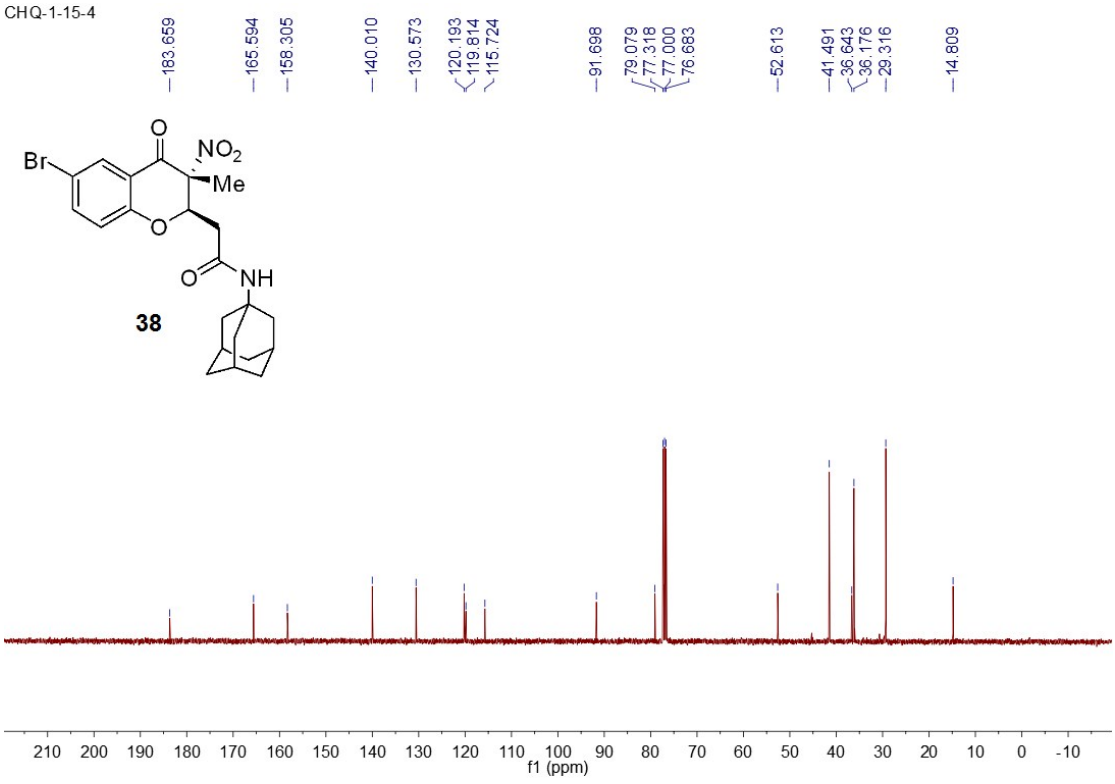
36

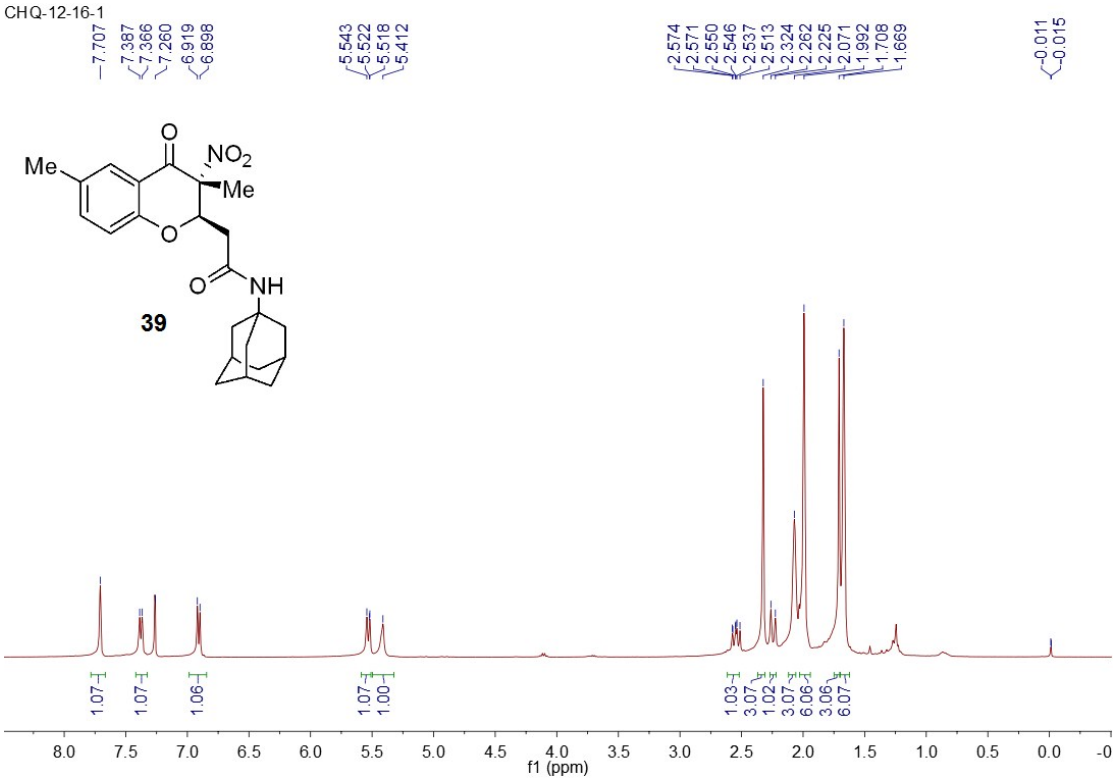
118.505
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)

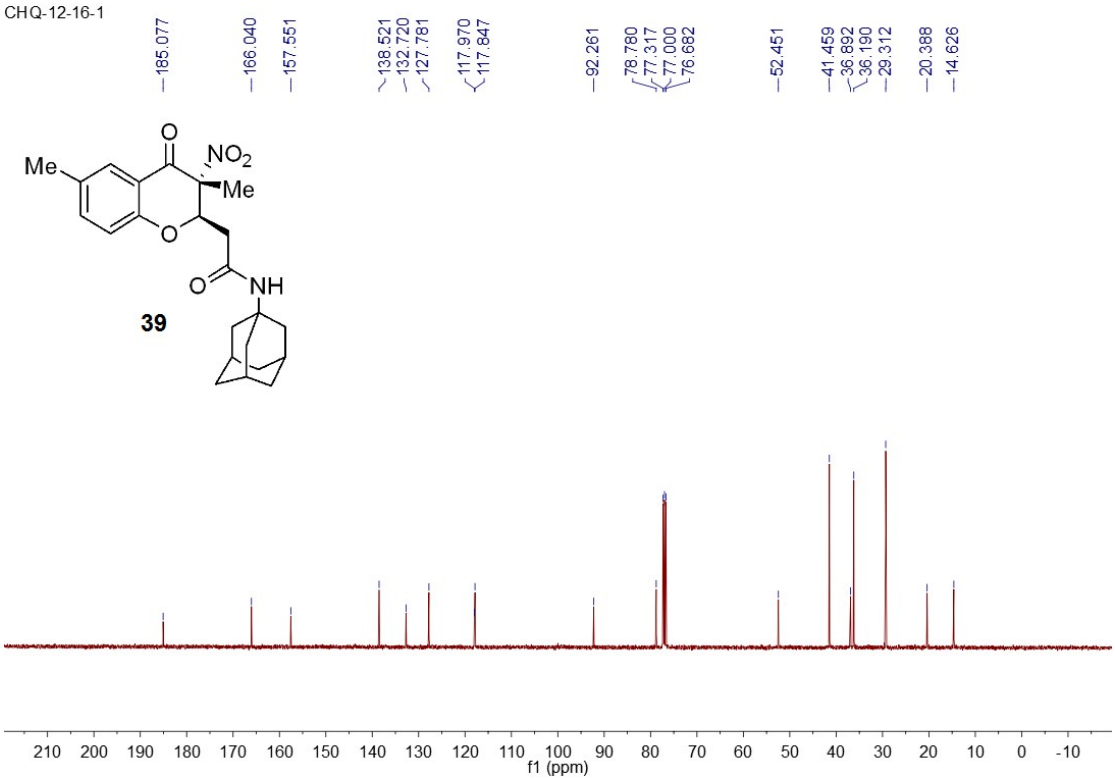

CHQ-1-16-1
37
f1 (ppm)


CHQ-1-16-1
37
f1 (ppm)

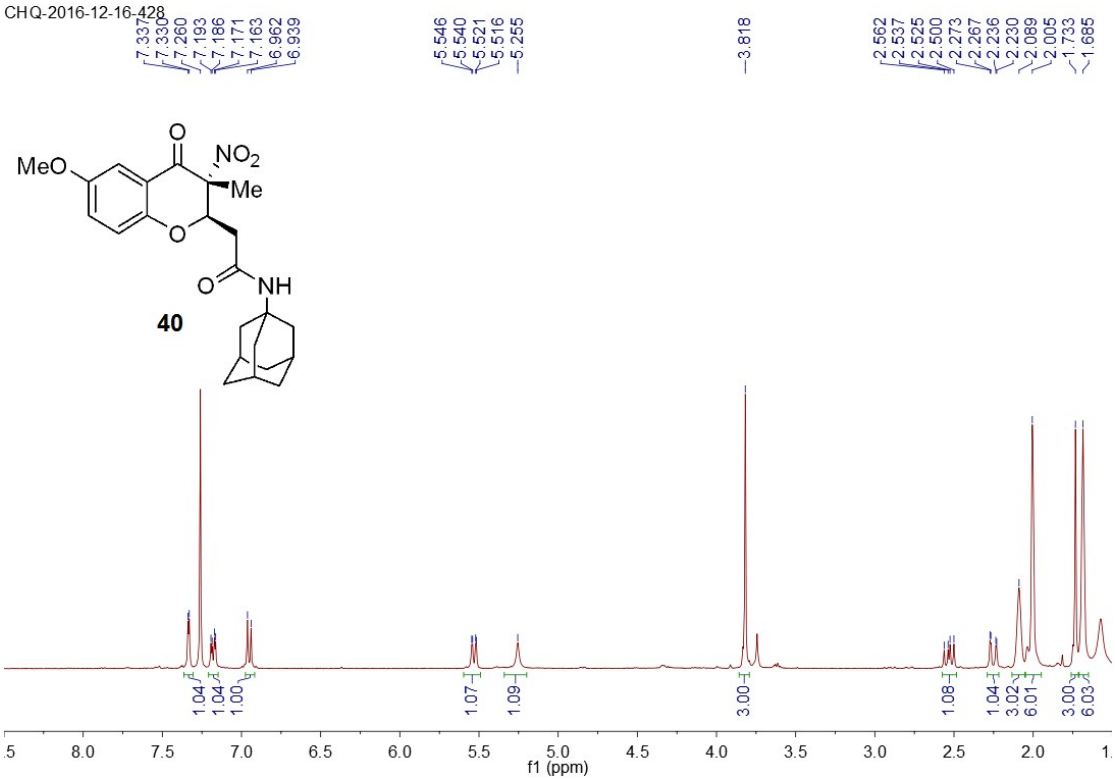

CHQ-1-15-4
8.034
8.029
7.651
7.635
7.260
6.937
6.915
5.606
5.600
5.582
5.576
5.316
2.557
2.533
2.520
2.496
2.300
2.294
2.263
2.257
2.071
1.975
1.717
1.667
0.012
Br
O
NO2
Me
O
O
NH
38
1.00
1.07
1.06
1.01
1.00
1.03
1.06
3.05
6.09
3.07
6.09
f1 (ppm)


CHQ-1-15-4
183.659
165.594
158.305
140.010
130.573
120.193
119.814
115.724
91.698
79.079
77.318
77.000
76.683
52.613
41.491
36.643
36.176
29.316
14.809
Br
O
NO2
Me
O
O
NH
38
f1 (ppm)

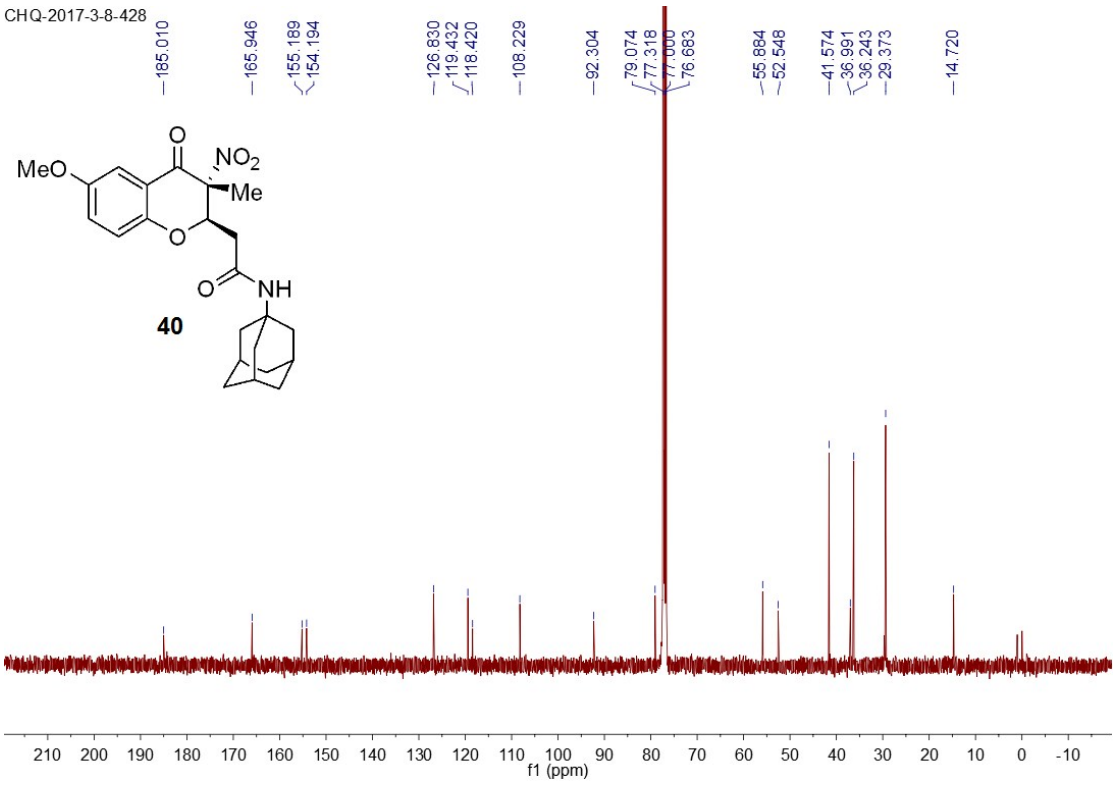

CHQ-12-16-1
7.707
7.387
7.366
7.260
6.919
6.898
5.543
5.522
5.518
5.412
2.574
2.571
2.550
2.546
2.537
2.513
2.324
2.262
2.225
2.071
1.992
1.708
1.669
0.011
0.015
Me
NO2
Me
O
O
NH
39
1.07
1.07
1.06
1.07
1.00
1.03
3.07
1.02
3.07
6.06
3.06
6.07
f1 (ppm)

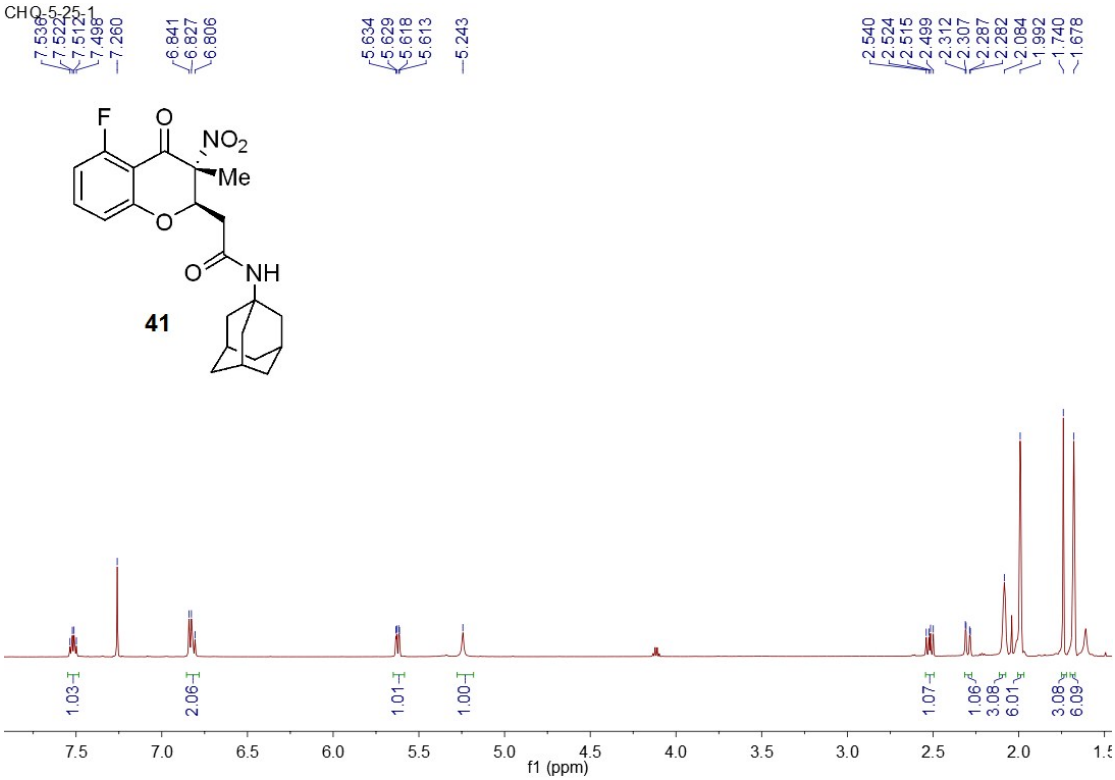

CHQ-12-16-1
185.077
166.040
157.551
138.521
132.720
127.781
117.970
117.847
92.261
78.780
77.317
77.000
76.682
52.451
41.459
36.892
36.190
29.312
20.388
14.626
Me
NO2
Me
O
O
NH
39
f1 (ppm)

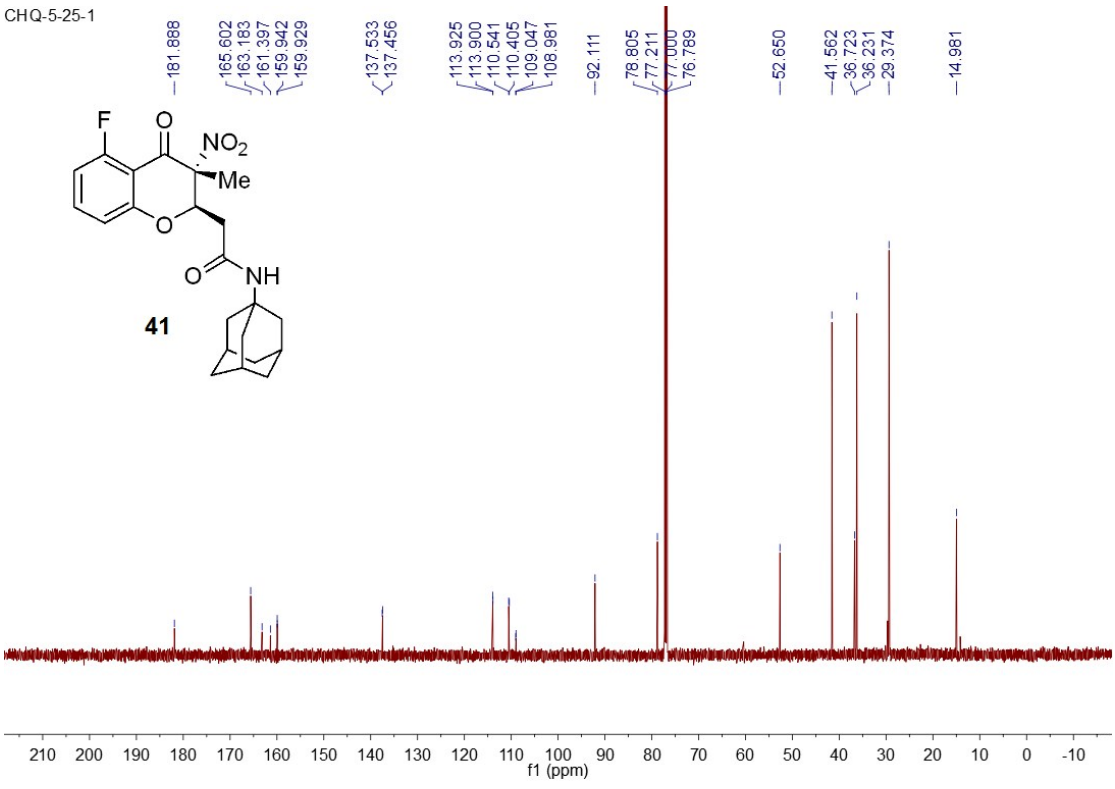
CHQ-2016-12-16-428



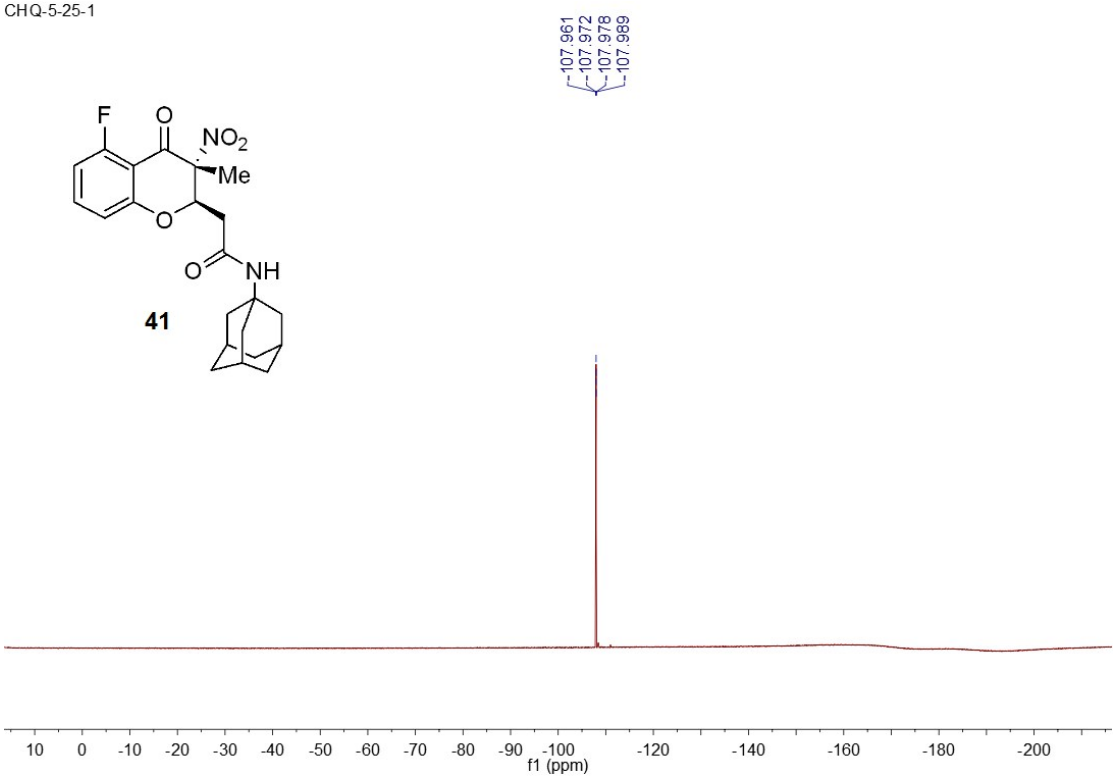
CHQ-2017-3-8-428

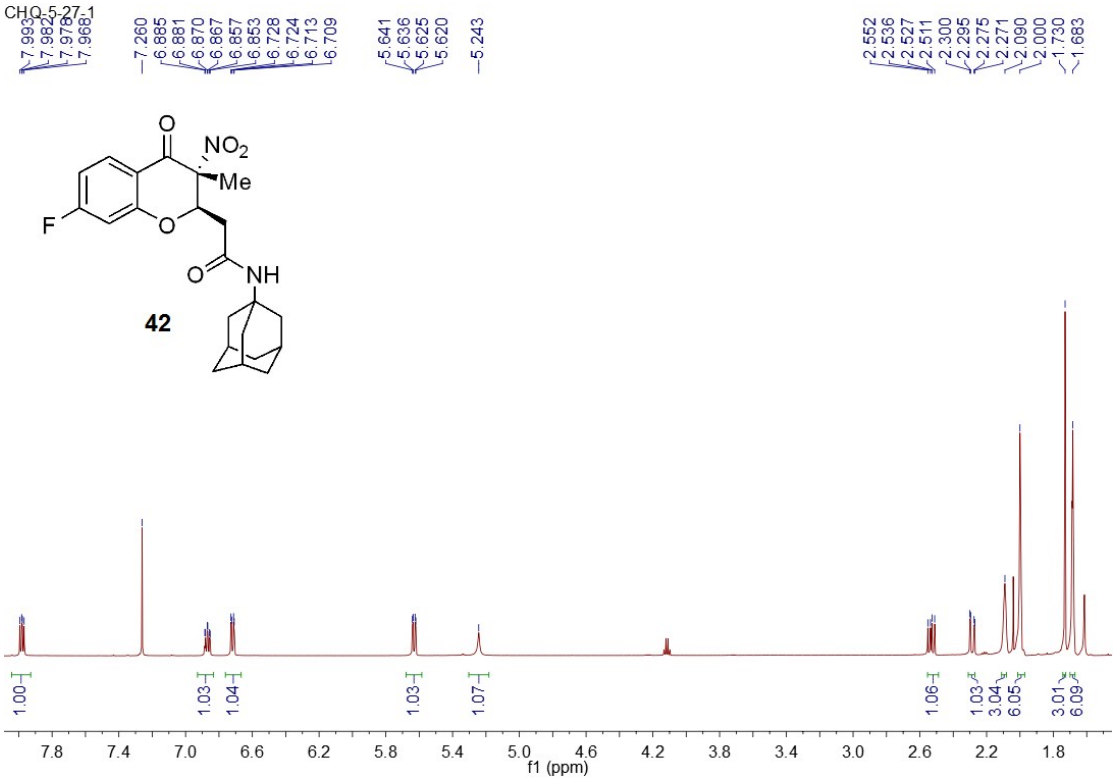


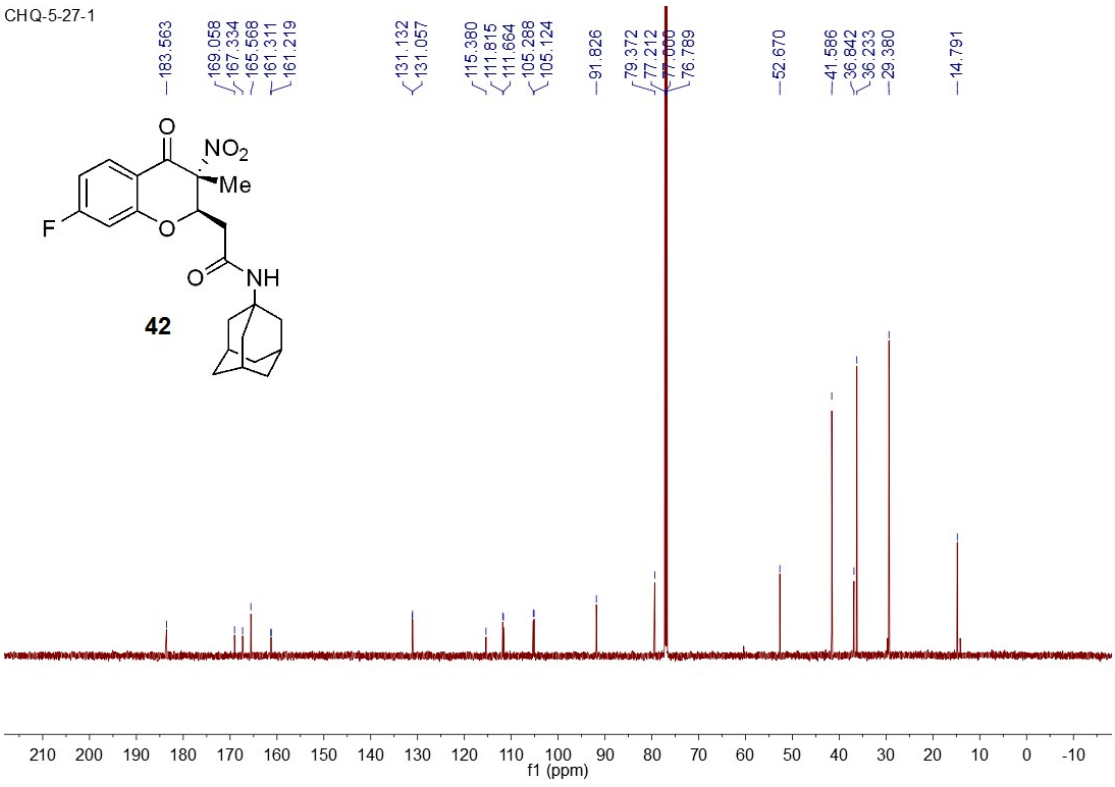

CHQ-5-25-1
7.536
7.522
7.512
7.498
7.260
6.841
6.827
6.806
5.634
5.629
5.618
5.613
5.243
2.540
2.524
2.515
2.499
2.312
2.307
2.287
2.282
2.084
1.992
1.740
1.678
F
O
NO2
Me
O
O
NH
41
1.03
2.06
1.01
1.00
1.07
1.06
3.08
6.01
3.08
6.09
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)


CHQ-5-25-1
181.888
165.602
163.183
161.397
159.942
159.929
137.533
137.456
113.925
113.900
110.541
110.405
109.047
108.981
92.111
78.805
77.211
77.000
76.789
52.650
41.562
36.723
36.231
29.374
14.981
F
O
NO2
Me
O
O
NH
41
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)

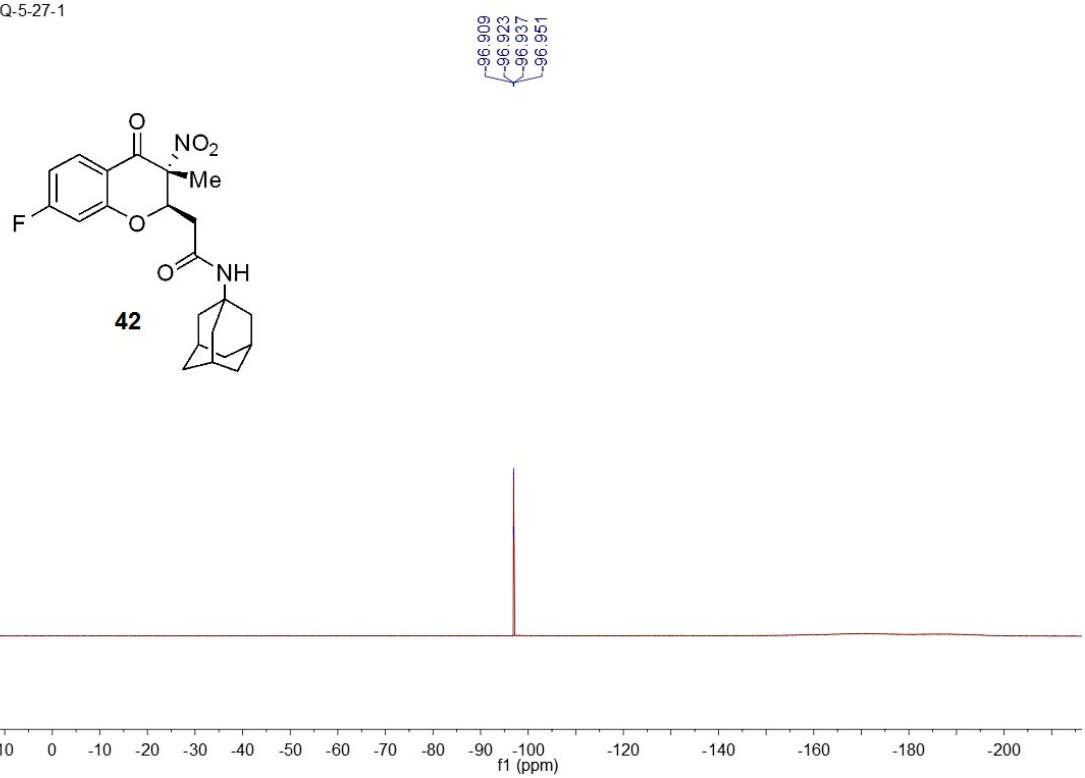
CHQ-5-25-1

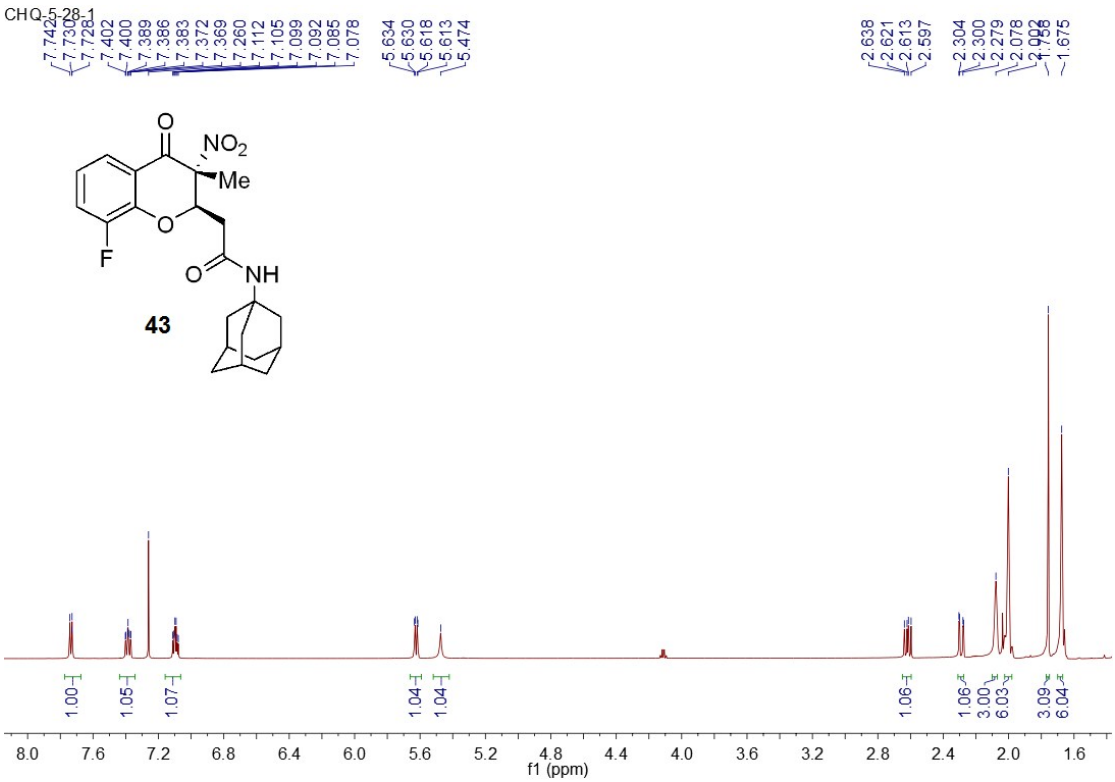

-107.961
-107.972
-107.978
-107.989
F
O
NO2
Me
O
O
NH
41
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)

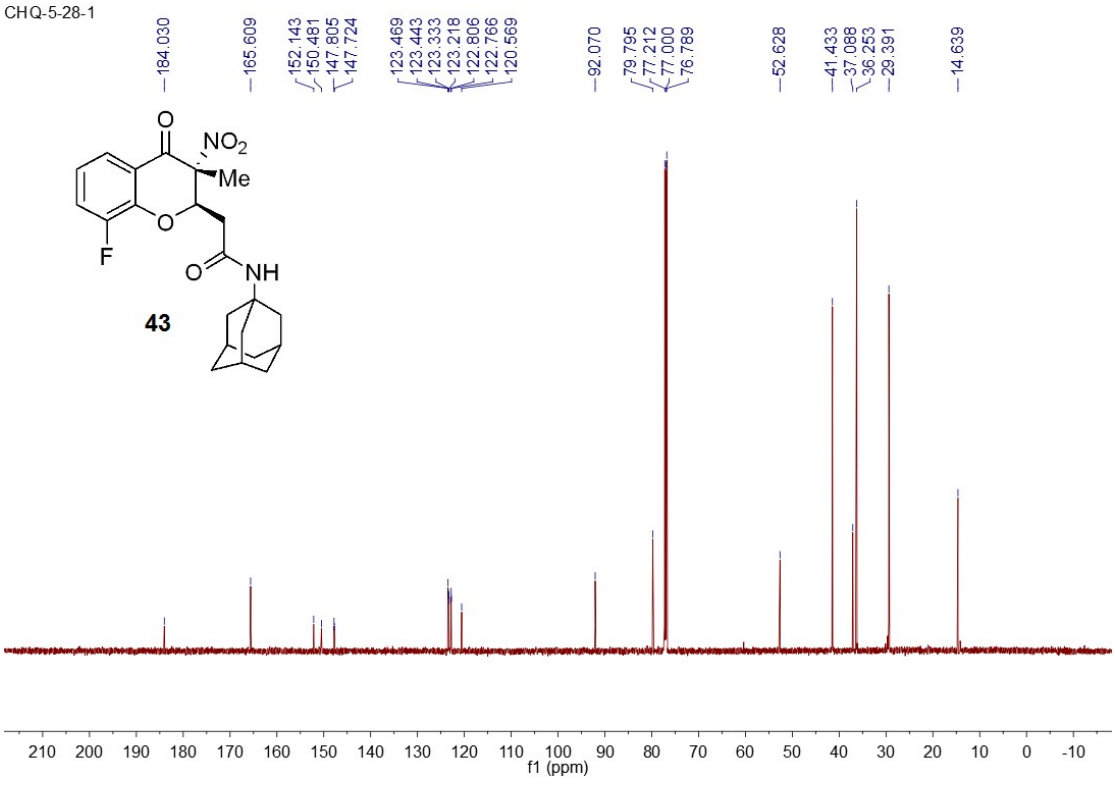

CHQ-5-27-1
7.993
7.982
7.978
7.968
7.260
6.885
6.881
6.870
6.867
6.857
6.853
6.728
6.724
6.713
6.709
5.641
5.636
5.625
5.620
5.243
2.552
2.536
2.527
2.511
2.300
2.295
2.275
2.271
2.090
2.000
1.730
1.683
O
NO2
Me
F
O
O
NH
42
1.00
1.03
1.04
1.03
1.07
1.06
1.03
3.04
6.05
3.01
6.09
7.8
7.4
7.0
6.6
6.2
5.8
5.4
5.0
4.6
4.2
3.8
3.4
3.0
2.6
2.2
1.8
f1 (ppm)


CHQ-5-27-1
183.563
169.058
167.334
165.568
161.311
161.219
131.132
131.057
115.380
111.815
111.664
105.288
105.124
91.826
79.372
77.212
77.000
76.789
52.670
41.586
36.842
36.233
29.380
14.791
O
NO2
Me
F
O
O
NH
42
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)

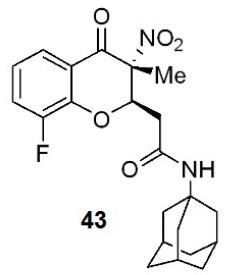
CHQ-5-27-1


-96.909
-96.923
-96.937
-96.951
O
NO2
Me
F
O
O
NH
42
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)


CHQ-5-28-1
7.742
7.730
7.728
7.402
7.400
7.389
7.386
7.383
7.372
7.369
7.260
7.112
7.105
7.099
7.092
7.085
7.078
5.634
5.630
5.618
5.613
5.474
2.638
2.621
2.613
2.597
2.304
2.300
2.279
2.078
1.758
1.675
O
NO2
Me
O
F
O
NH
43
1.00
1.05
1.07
1.04
1.04
1.06
1.06
3.00
6.03
3.09
6.04
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
f1 (ppm)

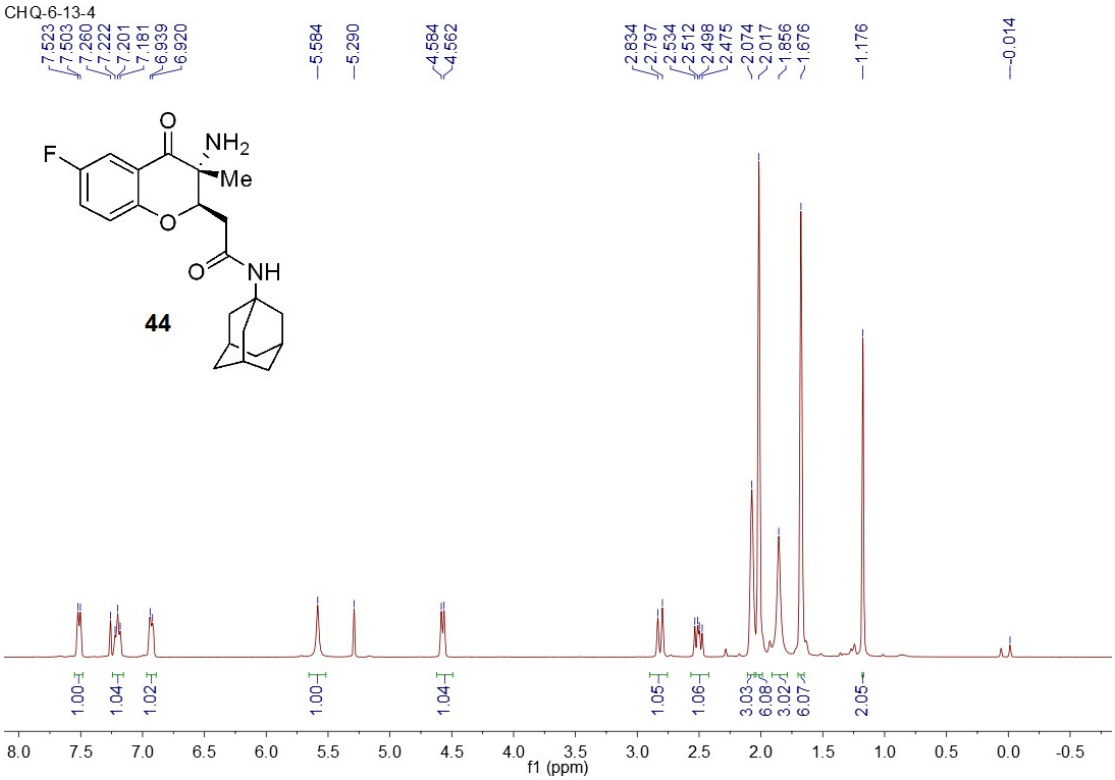

CHQ-5-28-1
184.030
165.609
152.143
150.481
147.805
147.724
123.469
123.443
123.333
123.218
122.806
122.766
120.569
92.070
79.795
77.212
77.000
76.789
52.628
41.433
37.088
36.253
29.391
14.639
O
NO2
Me
O
F
O
NH
43
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

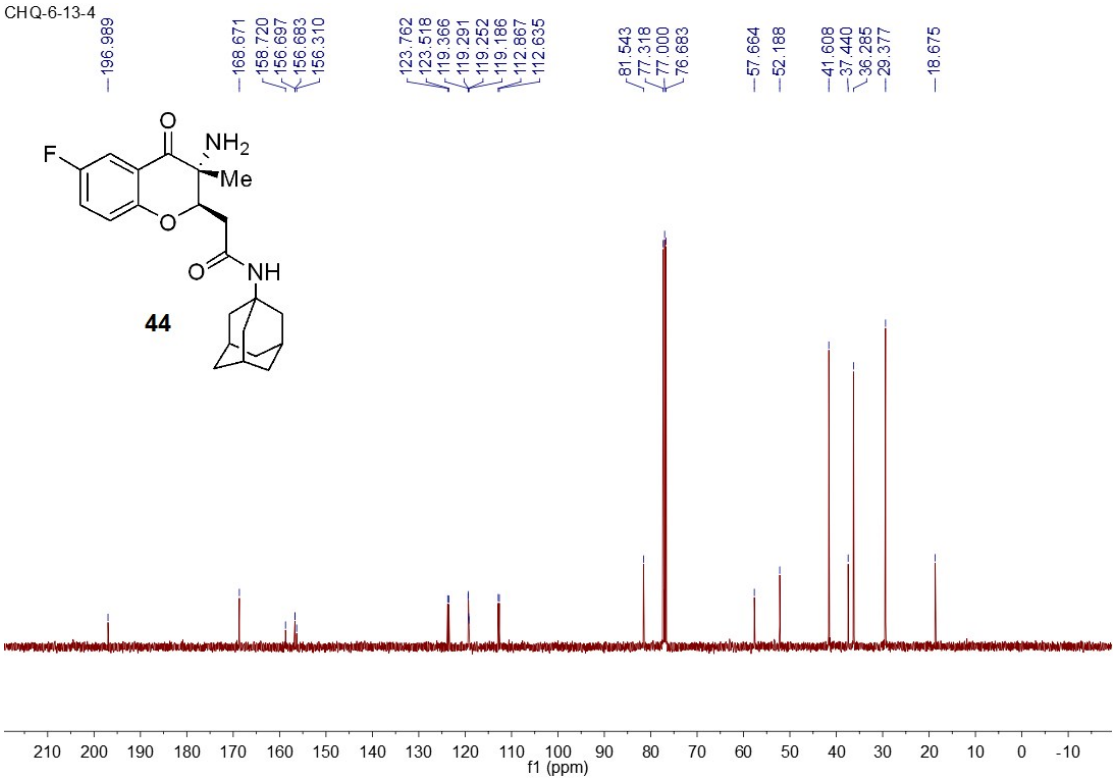
CHQ-5-28-1


O
NO2
Me
O
F
O
NH

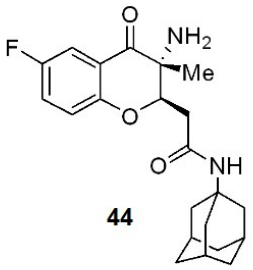
43

-133.484
-133.491
-133.502
-133.509
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)


CHQ-6-13-4
7.523
7.503
7.260
7.222
7.201
7.181
6.939
6.920
5.584
5.290
4.584
4.562
2.834
2.797
2.534
2.512
2.498
2.475
2.074
2.017
1.856
1.676
1.176
0.014
F
O
NH2
Me
O
O
NH
44
1.00
1.04
1.02
1.00
1.04
1.05
1.06
3.03
6.08
3.02
6.07
2.05
f1 (ppm)


CHQ-6-13-4
196.989
168.671
158.720
156.697
156.683
156.310
123.762
123.518
119.366
119.291
119.252
119.186
112.867
112.635
81.543
77.318
77.000
76.683
57.664
52.188
41.608
37.440
36.285
29.377
18.675
F
O
NH2
Me
O
O
NH
44
f1 (ppm)

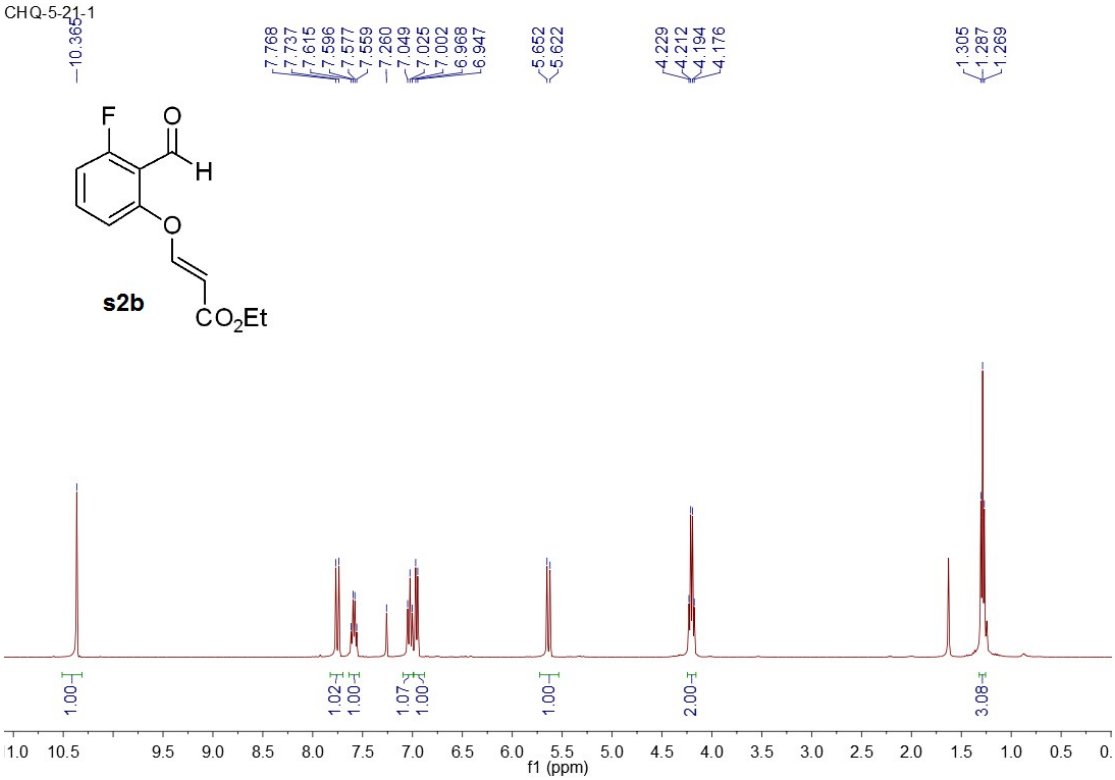
CHQ-6-13-4


O
NH2
F
Me
O
O
NH

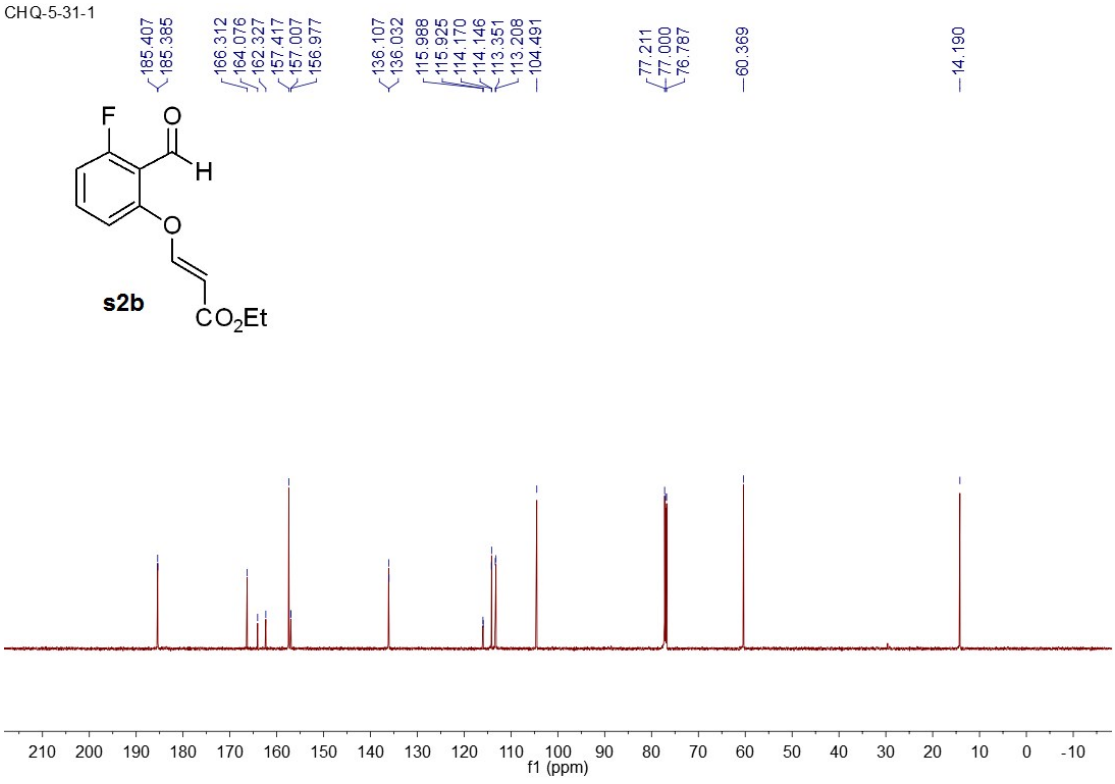
44

120.691
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)

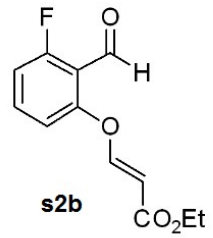
CHQ-5-21-1



CHQ-5-31-1

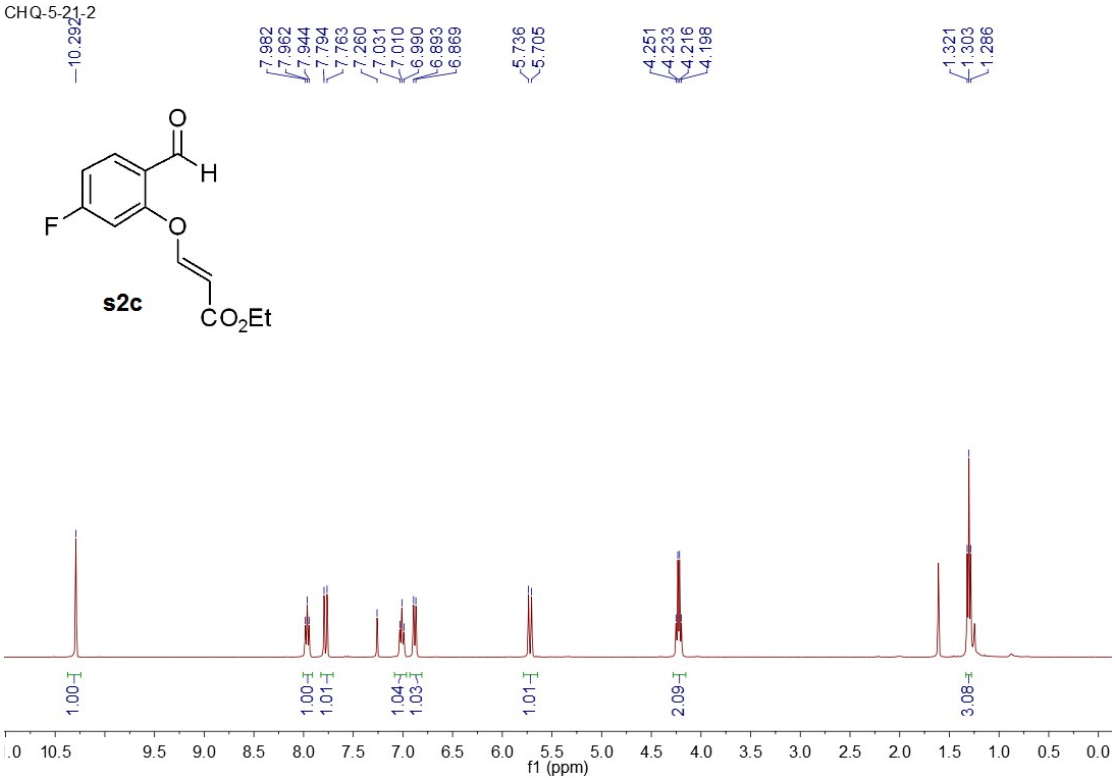


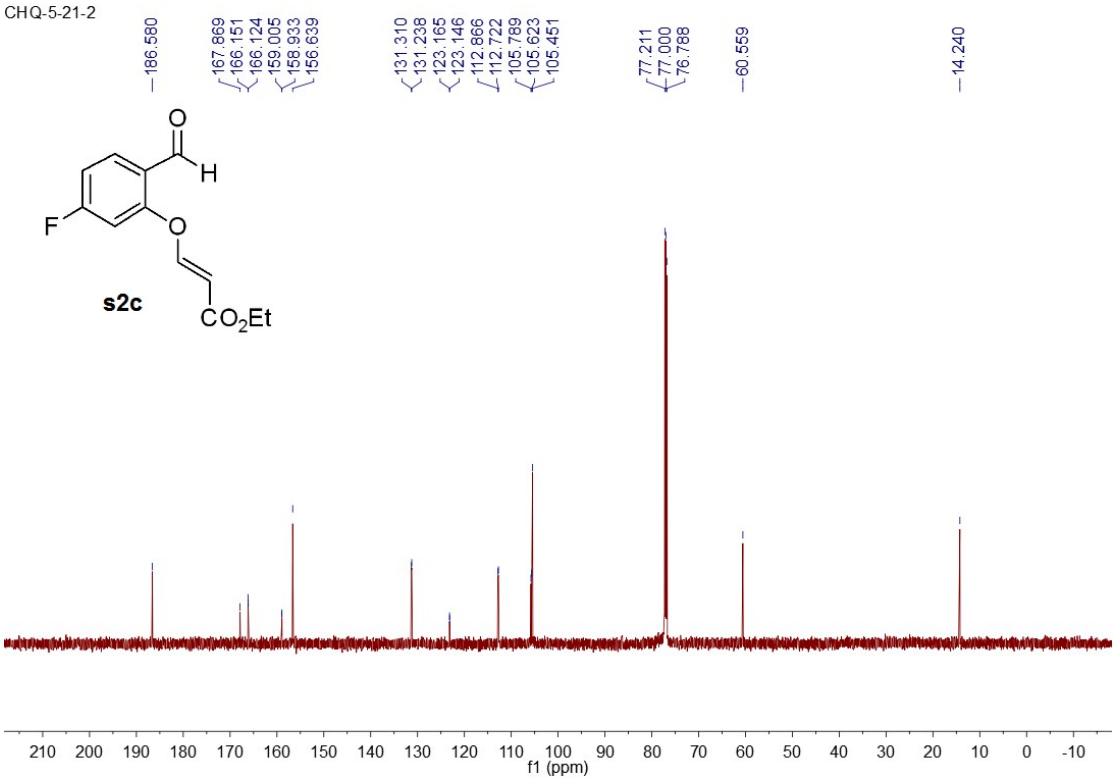
CHQ-5-21-1


F
O
H
O
CO2Et

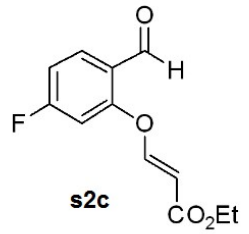
s2b

-113.861
-113.867
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)


CHQ-5-21-2
10.292
7.982
7.962
7.944
7.794
7.763
7.260
7.031
7.010
6.990
6.893
6.869
5.736
5.705
4.251
4.233
4.216
4.198
1.321
1.303
1.286
O
H
F
O
s2c
CO2Et
1.00
1.00
1.01
1.04
1.03
1.01
2.09
3.08
f1 (ppm)

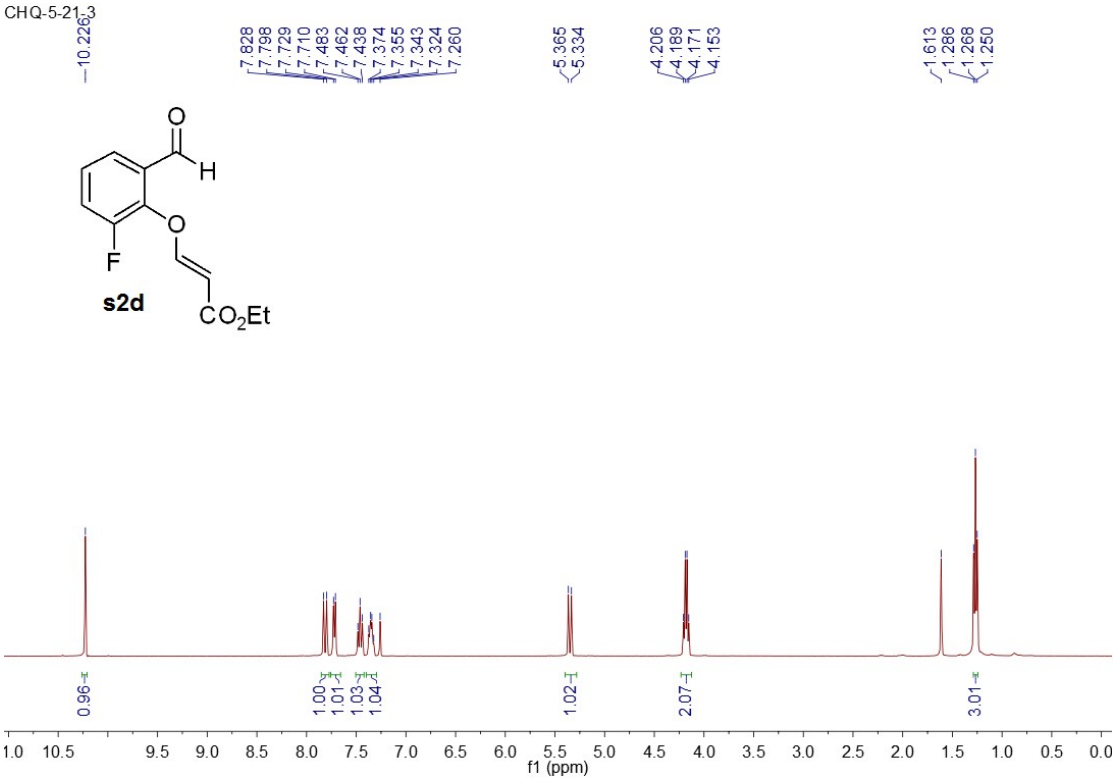

CHQ-5-21-2
186.580
167.869
166.151
166.124
159.005
158.933
156.639
131.310
131.238
123.165
123.146
112.866
112.722
105.789
105.623
105.451
77.211
77.000
76.788
60.559
14.240
O
H
F
O
s2c
CO2Et
f1 (ppm)

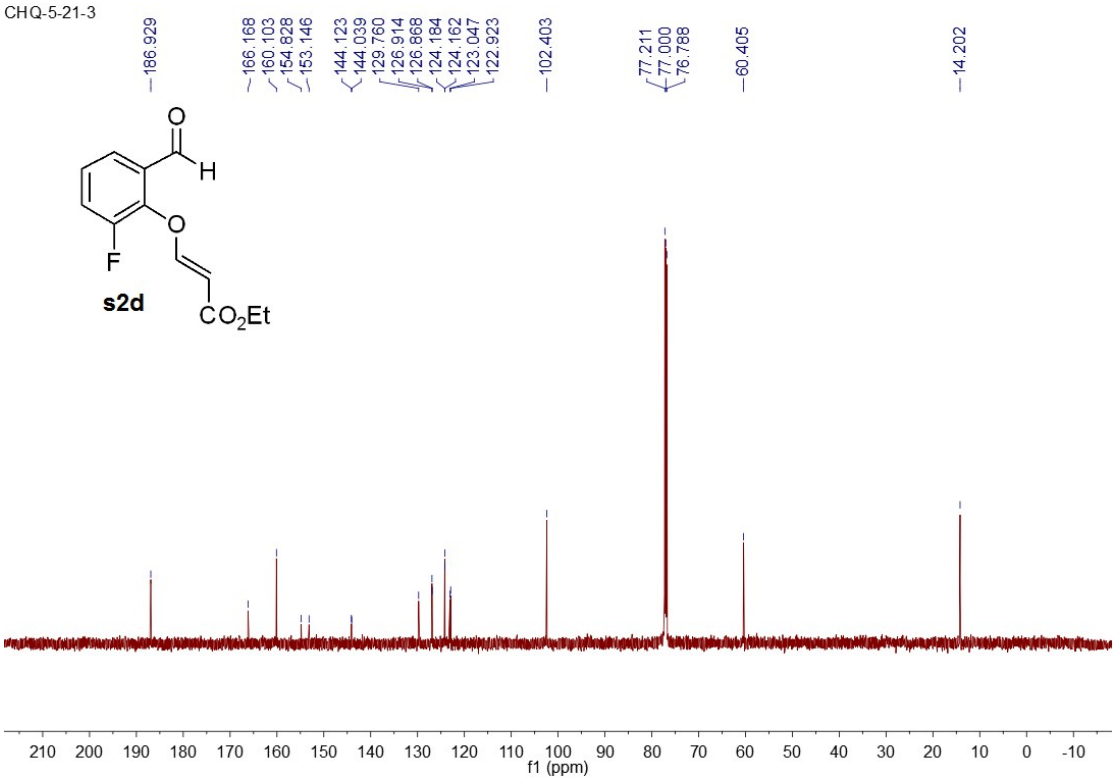
CHQ-5-21-2


O
H
F
O
CO2Et

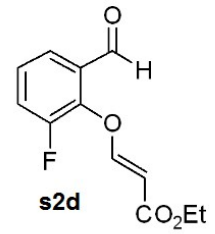
s2c

-98.329
-98.342
-98.356
-98.369
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)


CHQ-5-21-3
10.226
7.828
7.798
7.729
7.710
7.483
7.462
7.438
7.374
7.355
7.343
7.324
7.260
5.365
5.334
4.206
4.189
4.171
4.153
1.613
1.286
1.268
1.250
O
H
O
F
s2d
CO2Et
0.96
1.00
1.01
1.03
1.04
1.02
2.07
3.01
f1 (ppm)

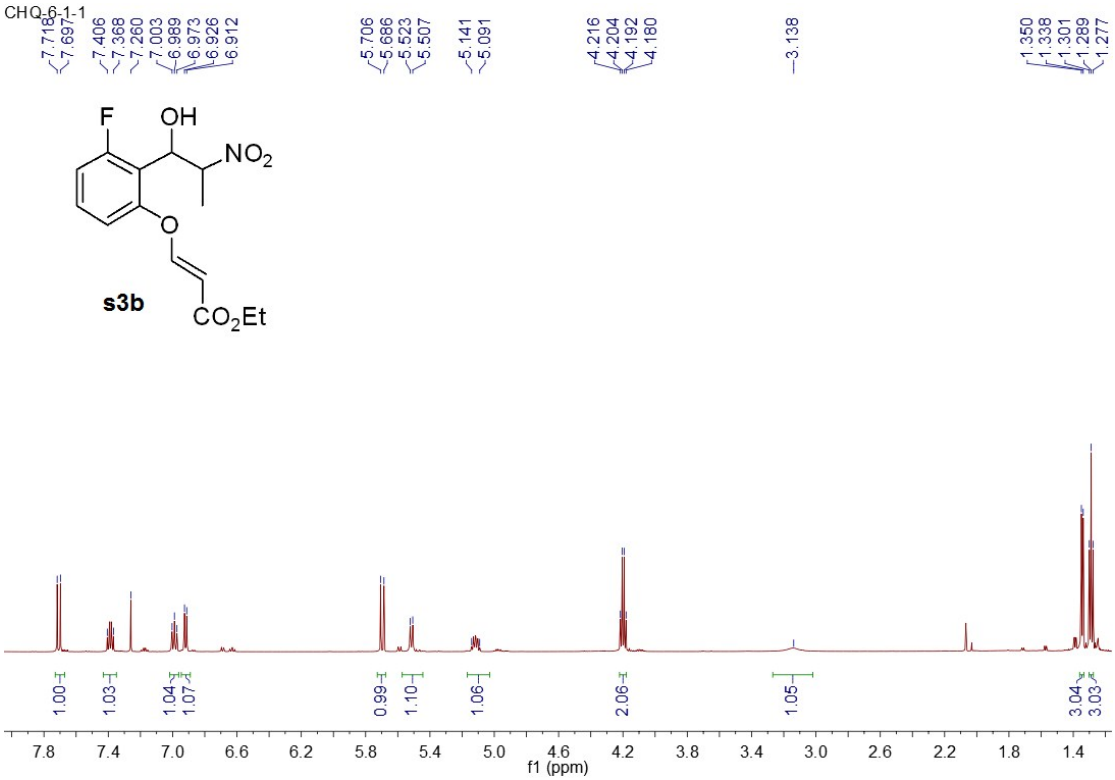

CHQ-5-21-3
186.929
166.168
160.103
154.828
153.146
144.123
144.039
129.760
126.914
126.868
124.184
124.162
123.047
122.923
102.403
77.211
77.000
76.788
60.405
14.202
O
H
O
F
s2d
CO2Et
f1 (ppm)

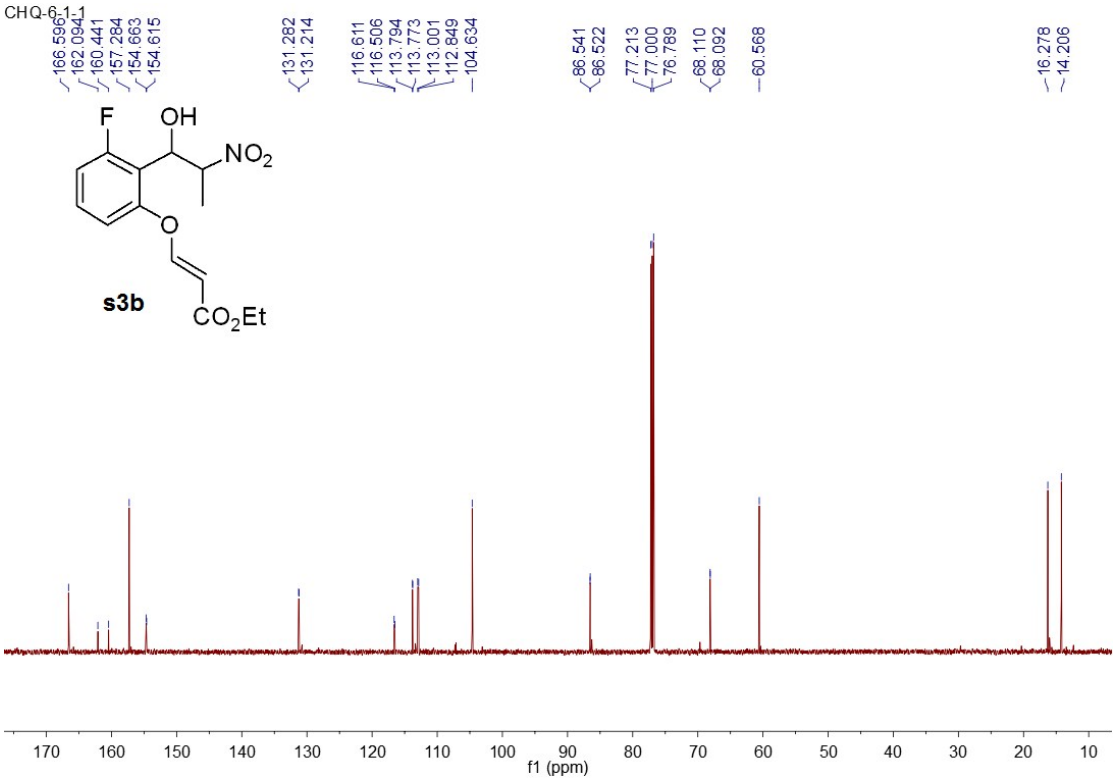
CHQ-5-21-3


O
H
O
F
CO2Et

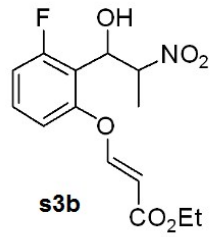
s2d

129.224
129.230
129.241
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)


CHQ-6-1-1
7.718
7.697
7.406
7.368
7.260
7.003
6.989
6.973
6.926
6.912
5.706
5.686
5.523
5.507
5.141
5.091
4.216
4.204
4.192
4.180
3.138
1.350
1.338
1.301
1.289
1.277
F
OH
NO2
O
s3b
CO2Et
1.00
1.03
1.04
1.07
0.99
1.10
1.06
2.06
1.05
3.04
3.03
7.8
7.4
7.0
6.6
6.2
5.8
5.4
5.0
4.6
4.2
3.8
3.4
3.0
2.6
2.2
1.8
1.4
f1 (ppm)


CHQ-6-1-1
166.596
162.094
160.441
157.284
154.663
154.615
131.282
131.214
116.611
116.506
113.794
113.773
113.001
112.849
104.634
86.541
86.522
77.213
77.000
76.789
68.110
68.092
60.568
16.278
14.206
F
OH
NO2
O
s3b
CO2Et
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

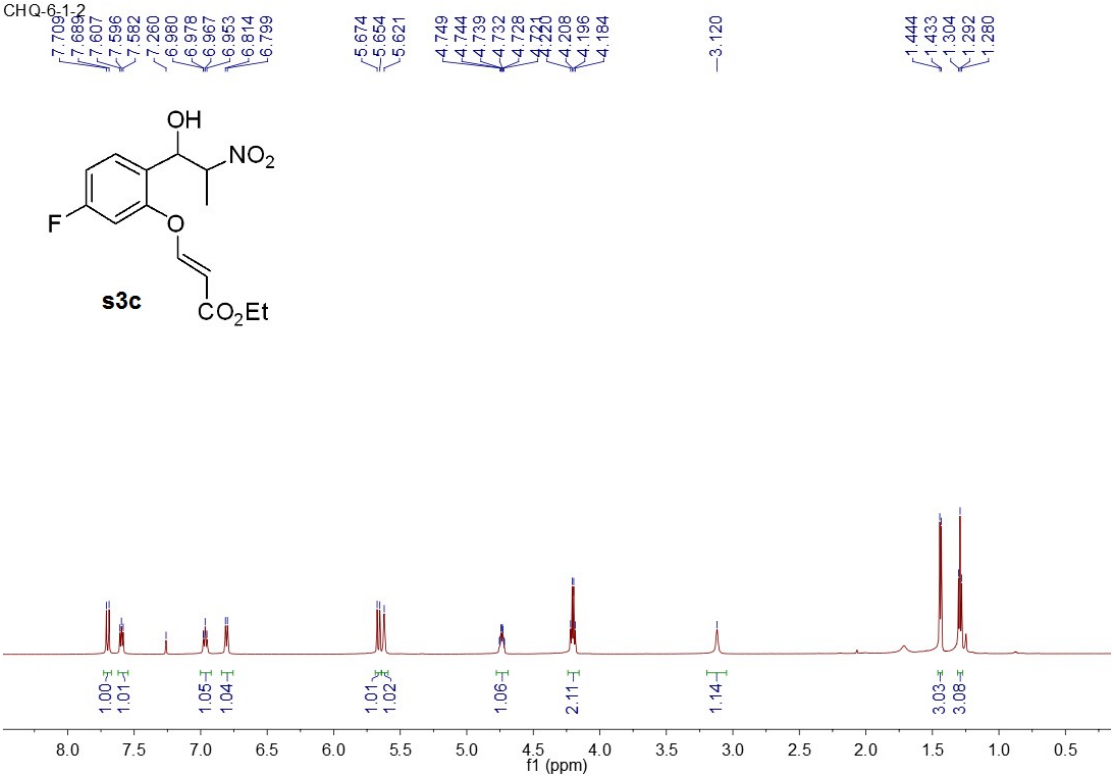
CHQ-6-1-1


F
OH
NO2
O
CO2Et

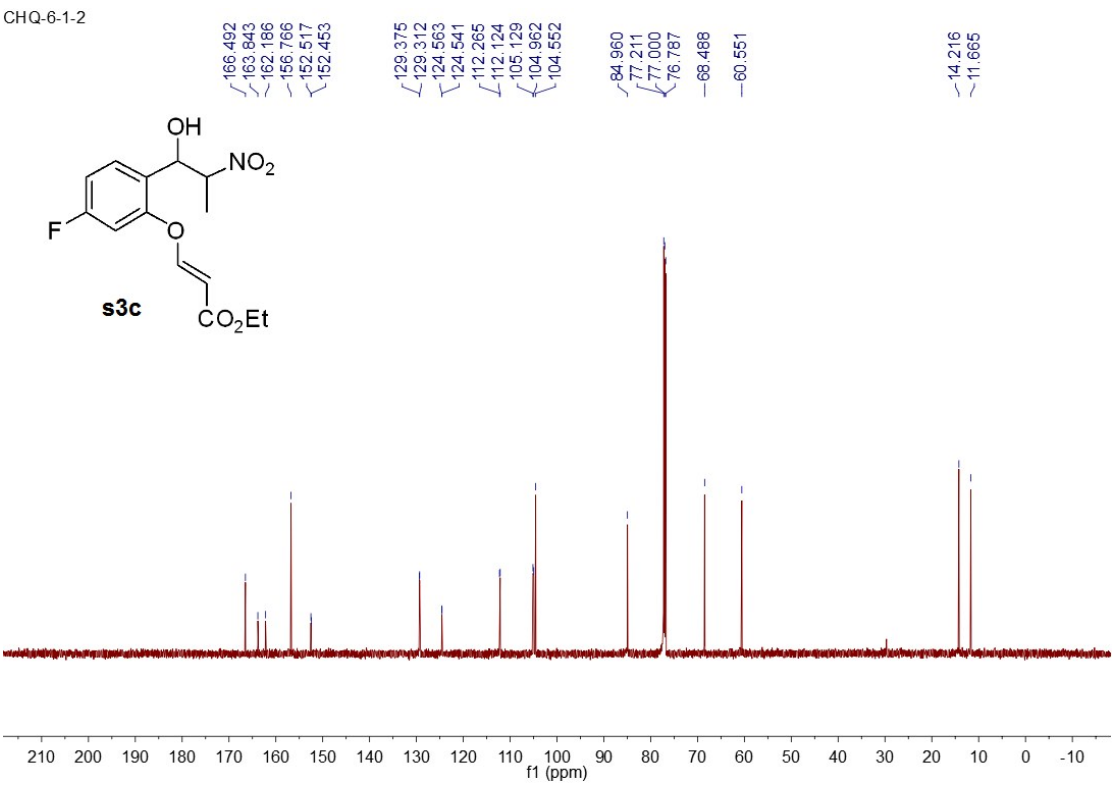
s3b

-112.791
-112.805
-112.819
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)

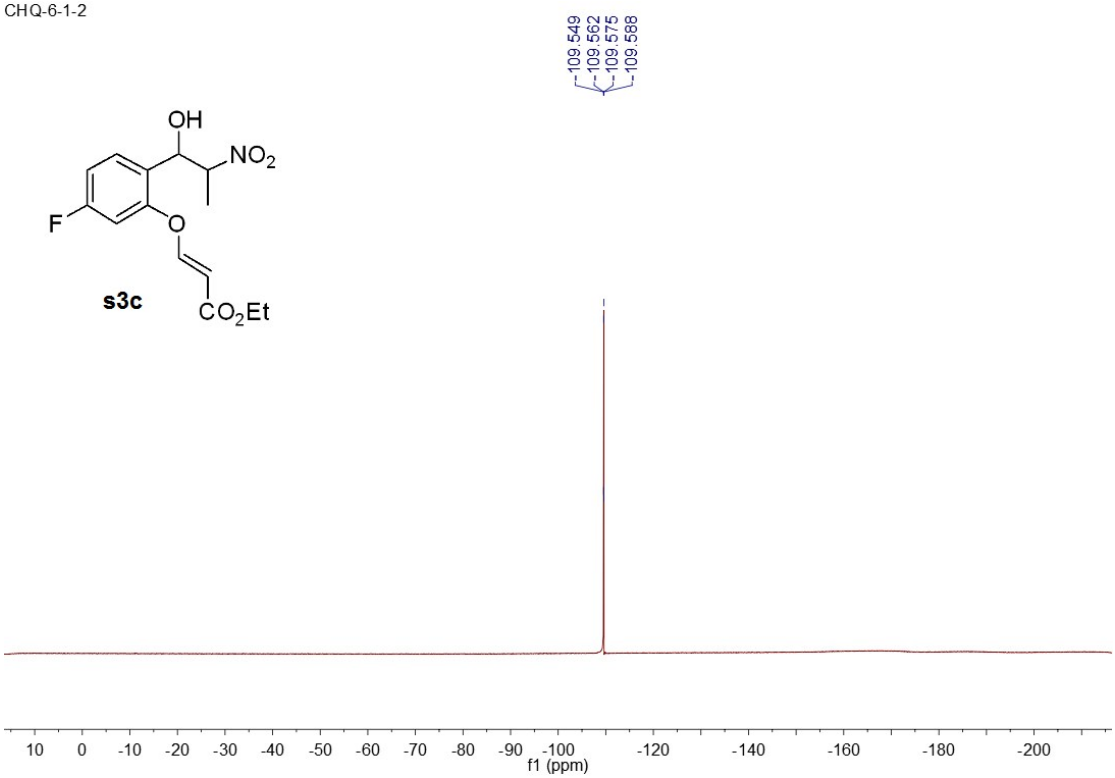
CHQ-6-1-2

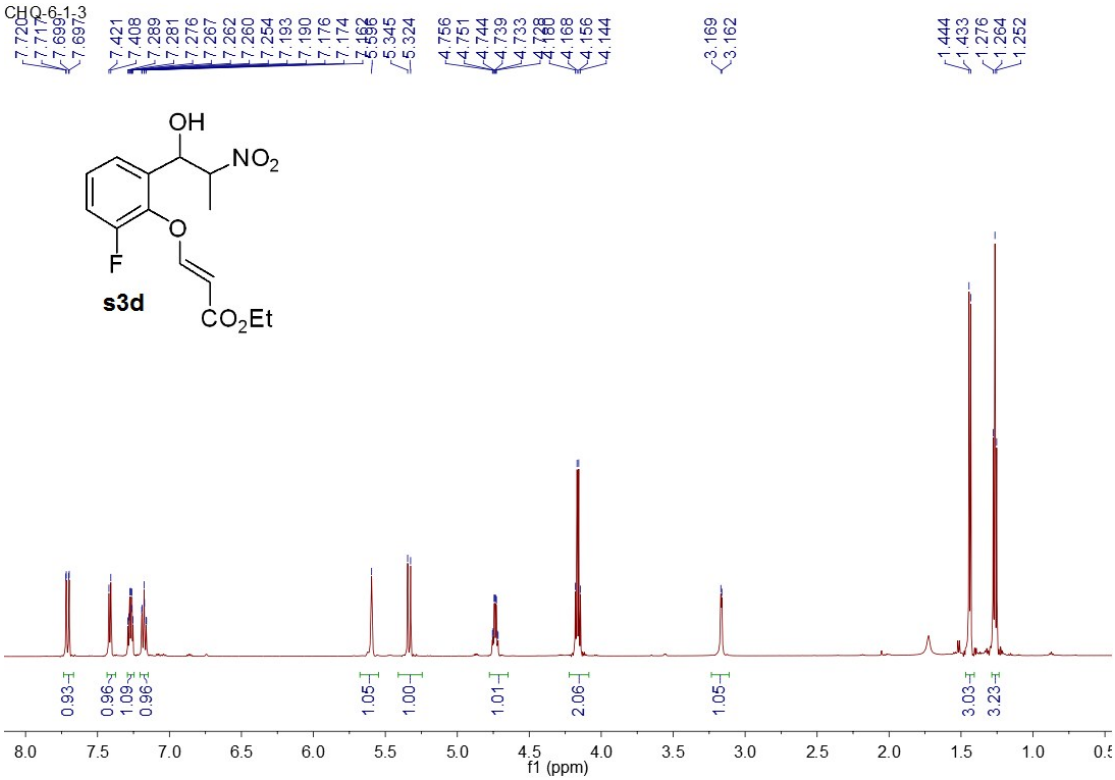


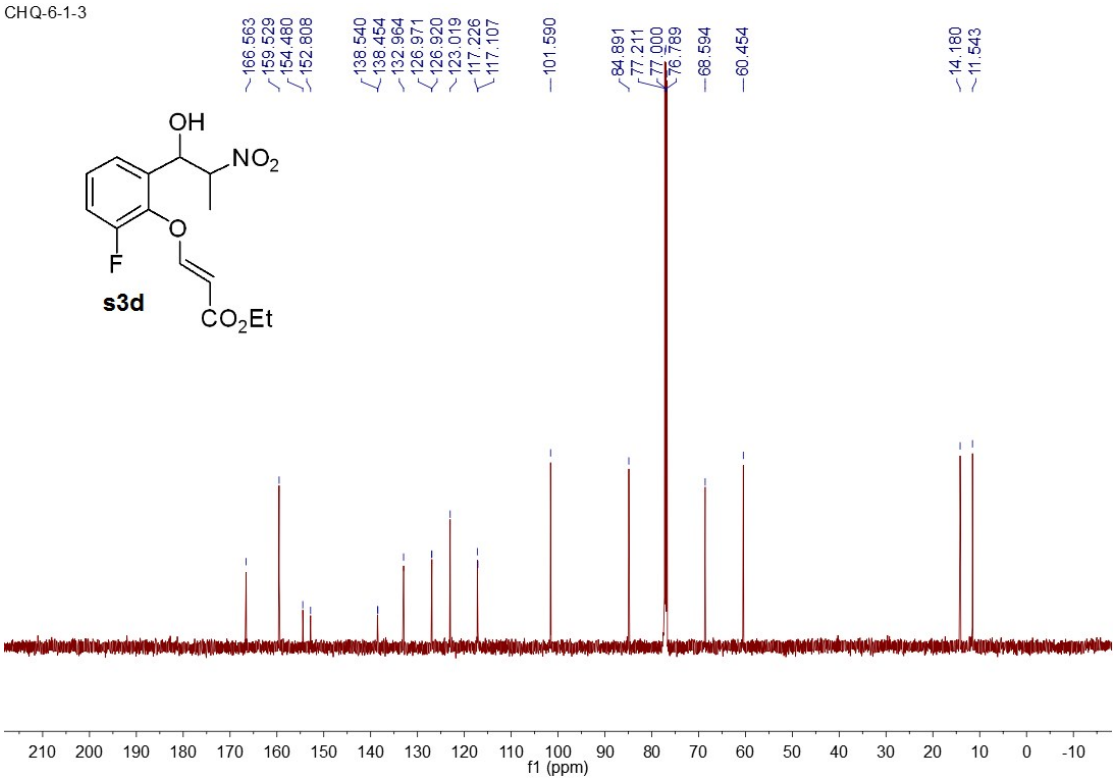
CHQ-6-1-2



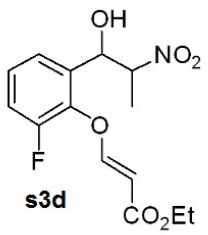
CHQ-6-1-2


109.549
109.562
109.575
109.588
OH
NO2
F
O
s3c
CO2Et
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)


CHQ-6-1-3
7.720
7.717
7.699
7.697
7.421
7.408
7.289
7.281
7.276
7.267
7.262
7.260
7.254
7.193
7.190
7.176
7.174
5.345
5.324
4.756
4.751
4.744
4.739
4.733
4.168
4.156
4.144
3.169
3.162
1.444
1.433
1.276
1.264
1.252
OH
NO2
O
F
s3d
CO2Et
0.93
0.96
1.09
0.96
1.05
1.00
1.01
2.06
1.05
3.03
3.23
f1 (ppm)


CHQ-6-1-3
166.563
159.529
154.480
152.808
138.540
138.454
132.964
126.971
126.920
123.019
117.226
117.107
101.590
84.891
77.211
77.000
76.789
68.594
60.454
14.180
11.543
OH
NO2
O
F
s3d
CO2Et
f1 (ppm)

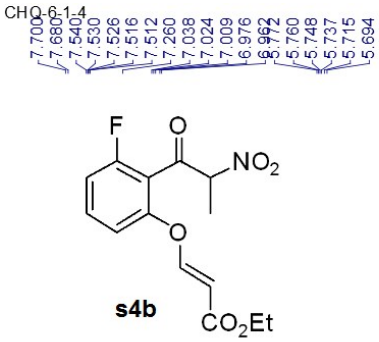
CHQ-6-1-3

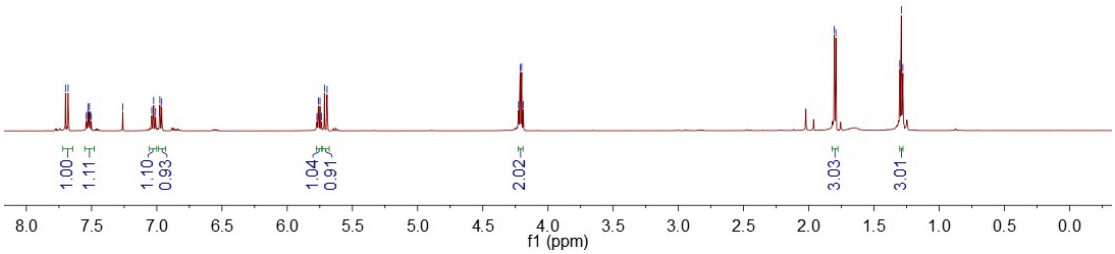

OH
NO2
O
F
CO2Et

s3d

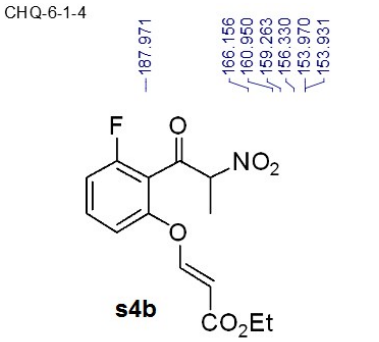
-129.445
-129.449
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)

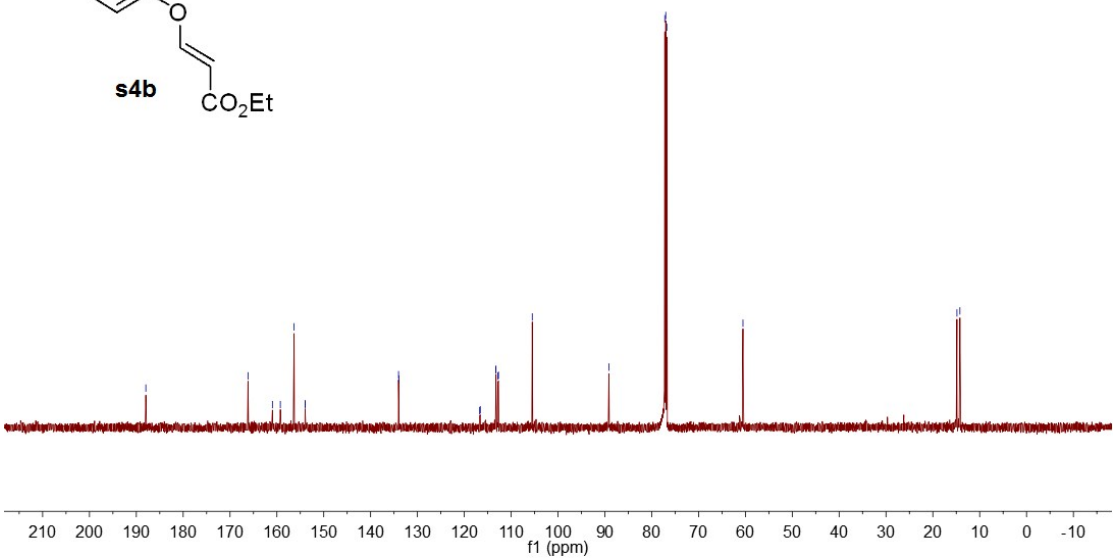
CHQ-6-1-4



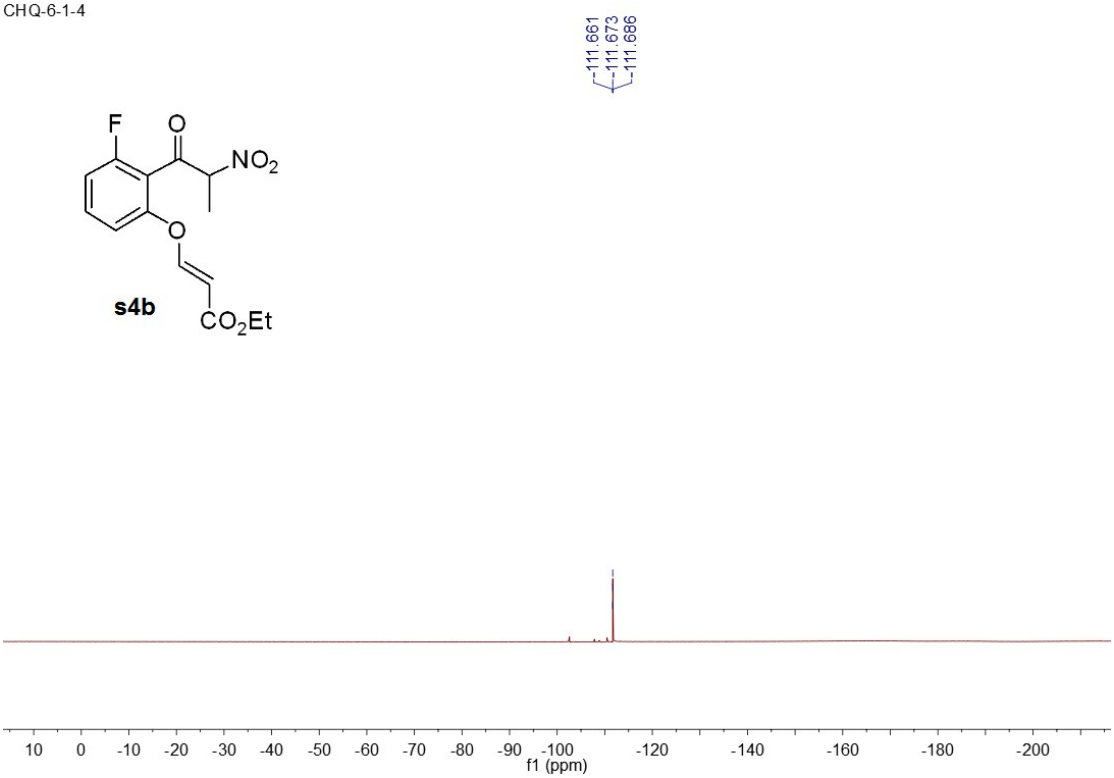


CHQ-6-1-4

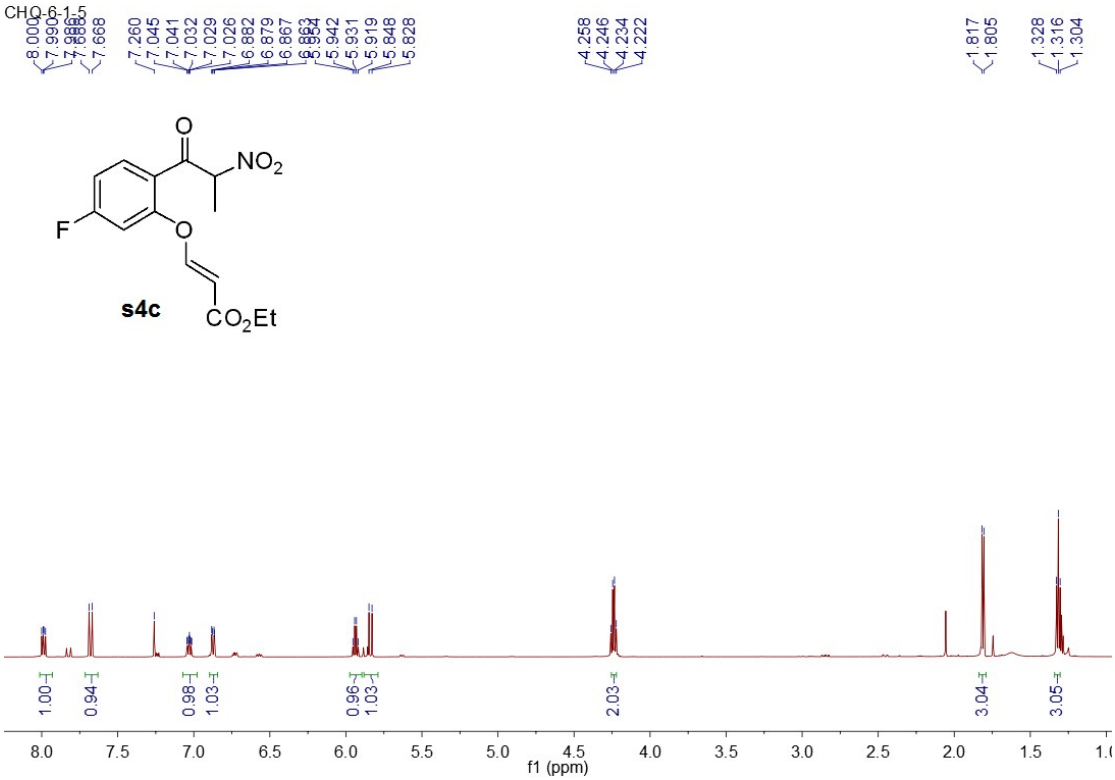




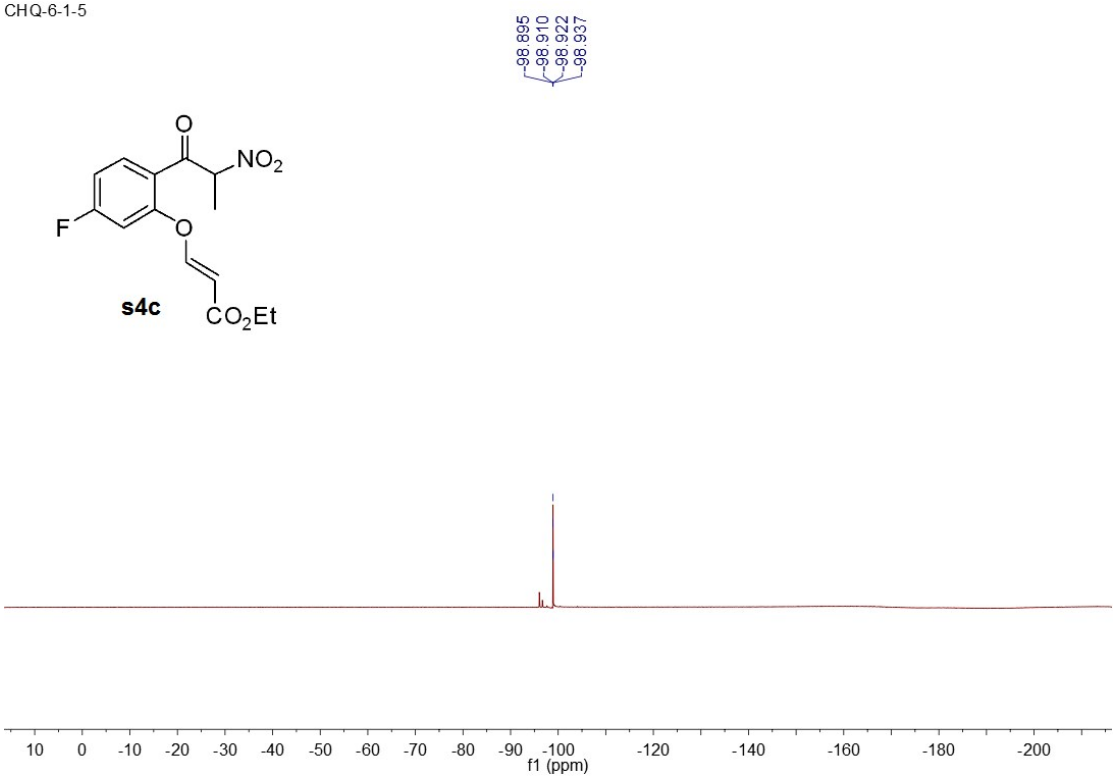
CHQ-6-1-4


-111.661
-111.673
-111.686
F
O
NO2
O
s4b
CO2Et
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)

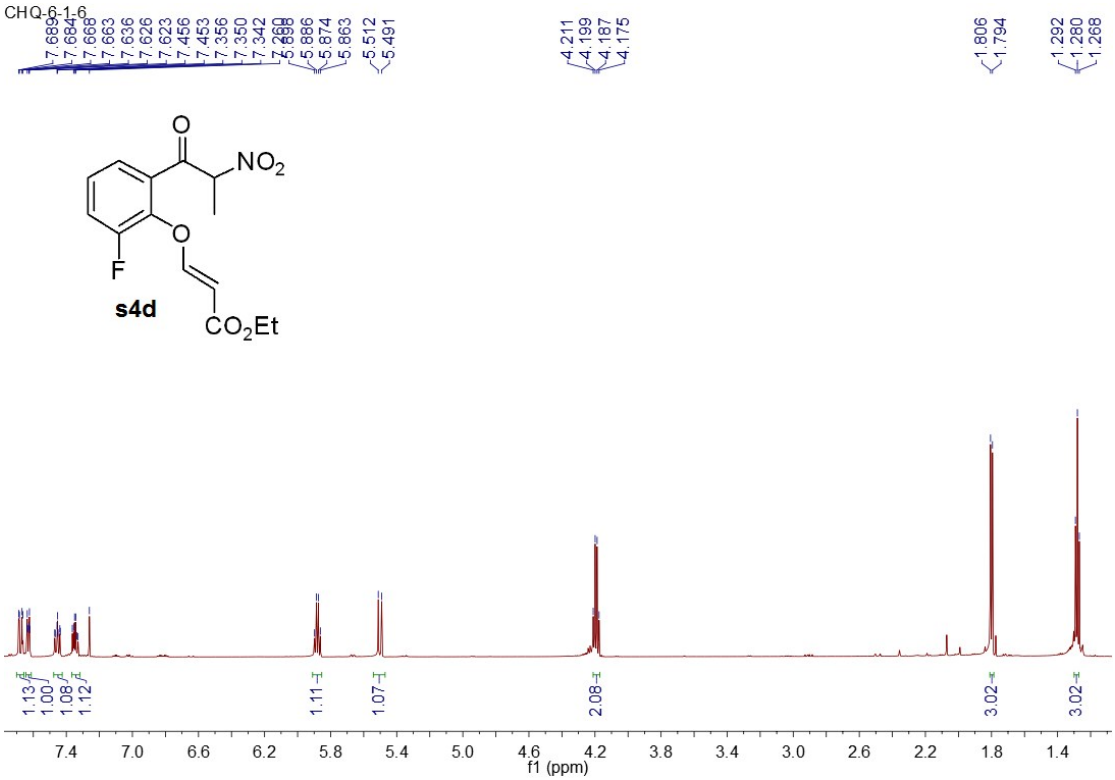
CHQ-6-1-5



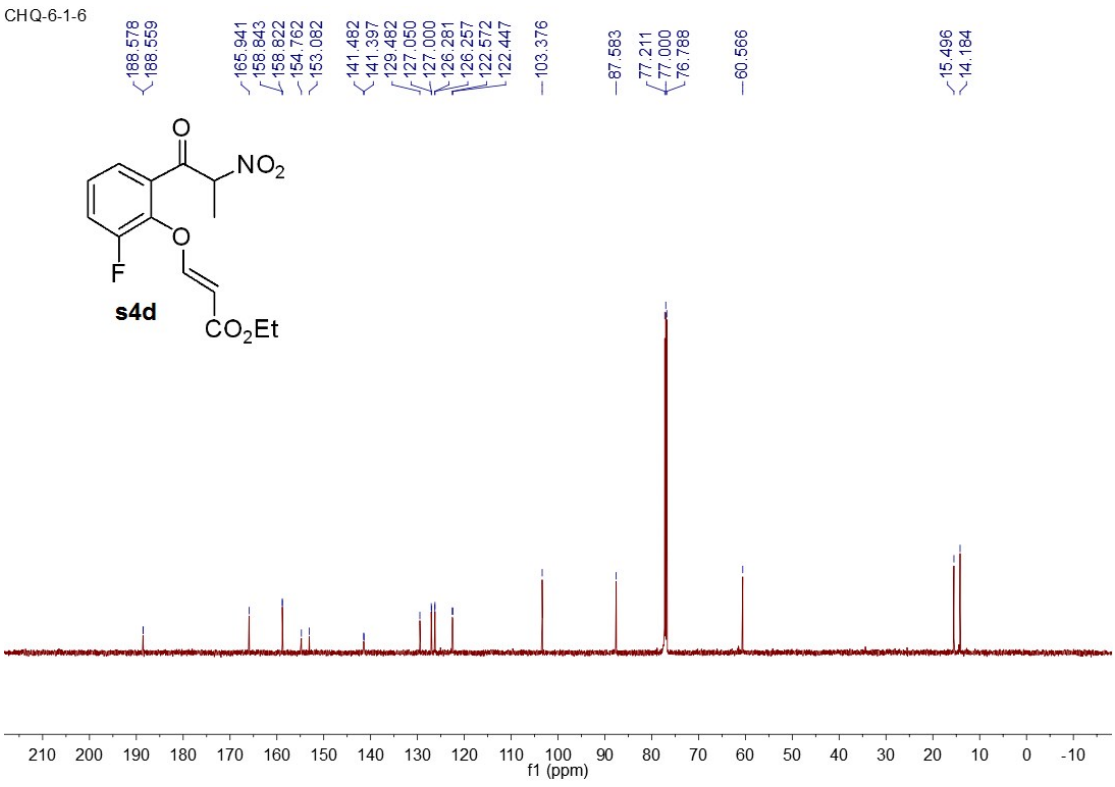
CHQ-6-1-5



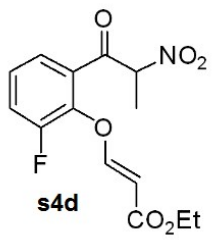
CHQ-6-1-6



CHQ-6-1-6

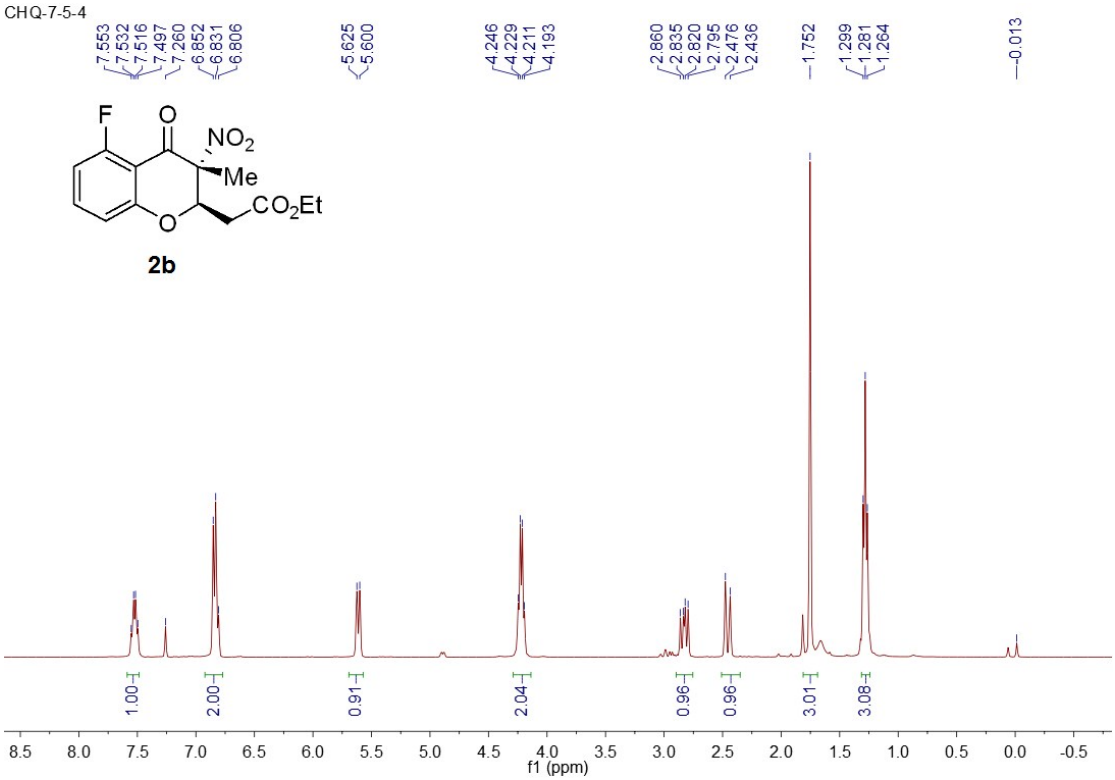


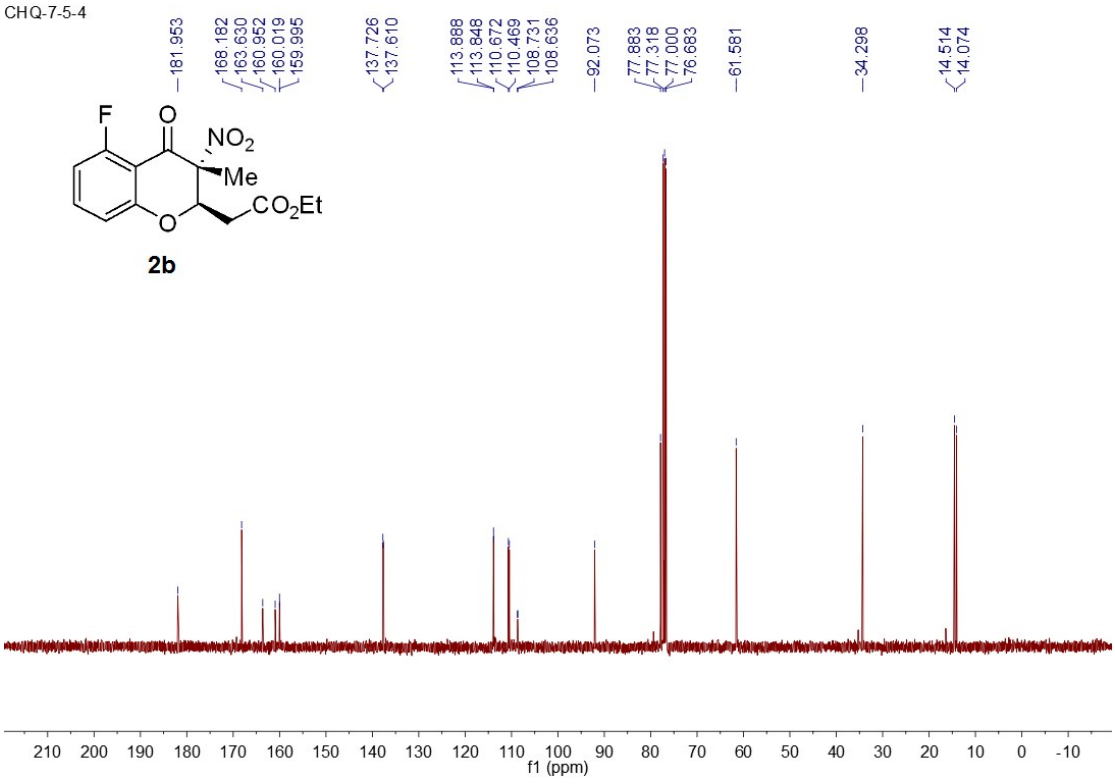
CHQ-6-1-6


O
NO2
O
F
CO2Et

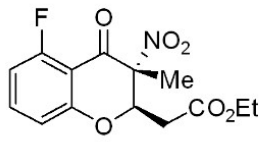
s4d

-127.608
-127.624
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)


CHQ-7-5-4
7.553
7.532
7.516
7.497
7.260
6.852
6.831
6.806
5.625
5.600
4.246
4.229
4.211
4.193
2.860
2.835
2.820
2.795
2.476
2.436
1.752
1.299
1.281
1.264
0.013
F
O
NO2
Me
CO2Et
O
2b
1.00
2.00
0.91
2.04
0.96
0.96
3.01
3.08
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 -0.5
f1 (ppm)

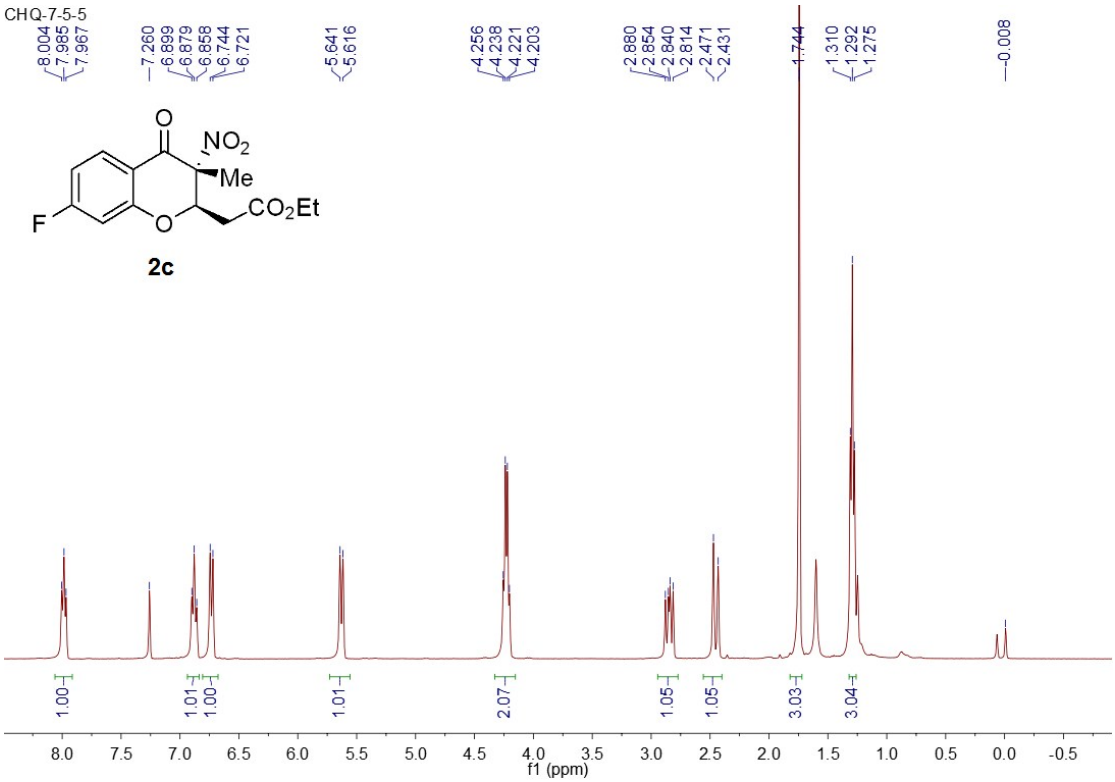

CHQ-7-5-4
181.953
168.182
163.630
160.952
160.019
159.995
137.726
137.610
113.888
113.848
110.672
110.469
108.731
108.636
92.073
77.883
77.318
77.000
76.683
61.581
34.298
14.514
14.074
F
O
NO2
Me
CO2Et
O
2b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

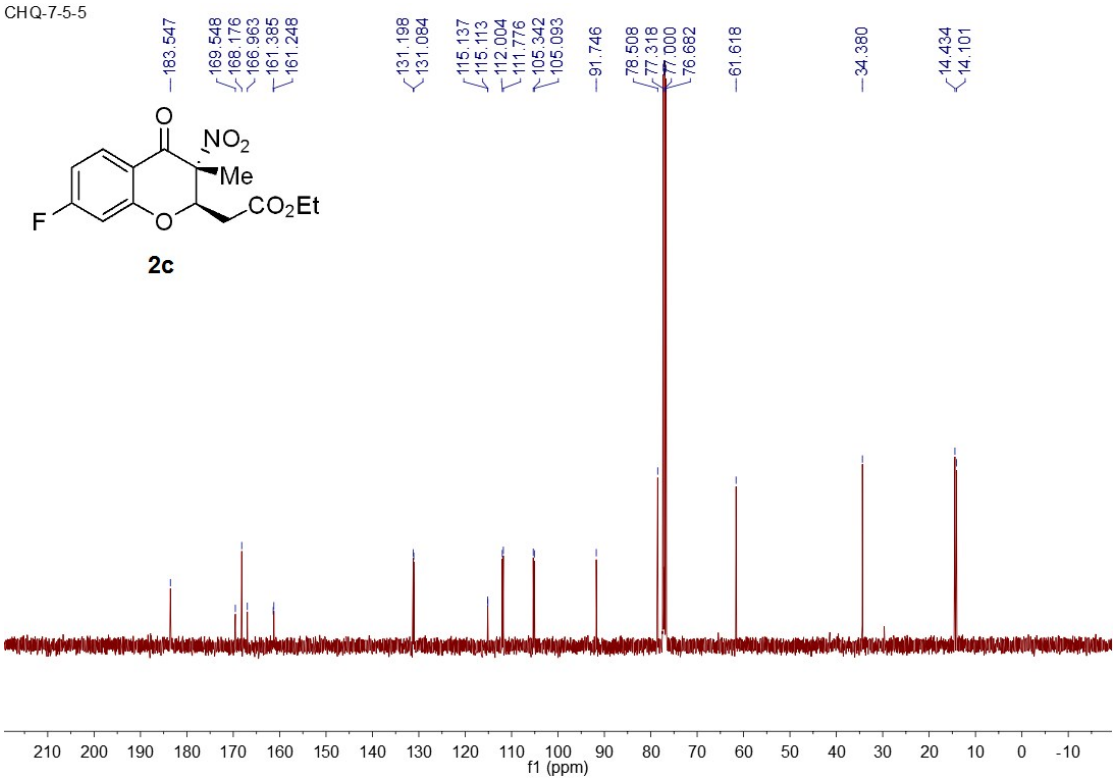
CHQ-7-5-4


F
O
NO2
Me
CO2Et
O

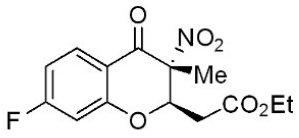
2b

-107.856
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)


CHQ-7-5-5
8.004
7.985
7.967
7.260
6.899
6.879
6.858
6.744
6.721
5.641
5.616
4.256
4.238
4.221
4.203
2.880
2.854
2.840
2.814
2.471
2.431
1.744
1.310
1.292
1.275
0.008
O
NO2
Me
CO2Et
F
O
2c
1.00
1.01
1.00
1.01
2.07
1.05
1.05
3.03
3.04
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
-0.5
f1 (ppm)


CHQ-7-5-5
183.547
169.548
168.176
166.963
161.385
161.248
131.198
131.084
115.137
115.113
112.004
111.776
105.342
105.093
91.746
78.508
77.318
77.000
76.682
61.618
34.380
14.434
14.101
O
NO2
Me
CO2Et
F
O
2c
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)

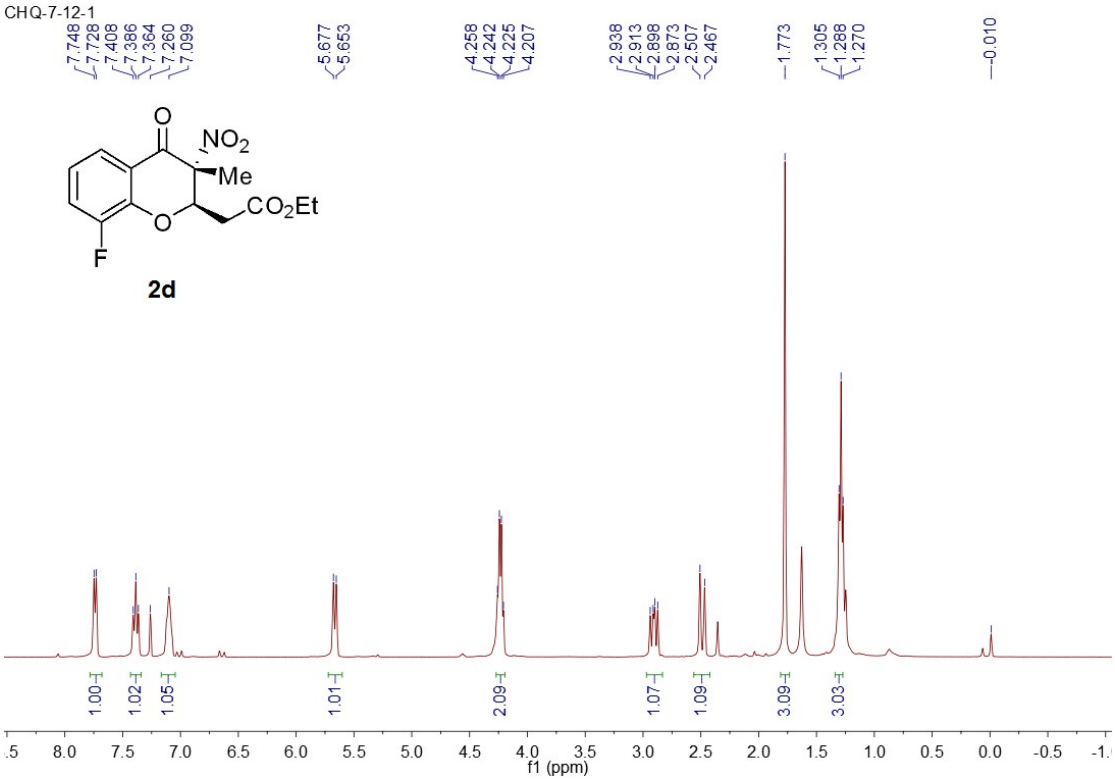
CHQ-7-5-5


O
NO2
Me
CO2Et
F
O

2c

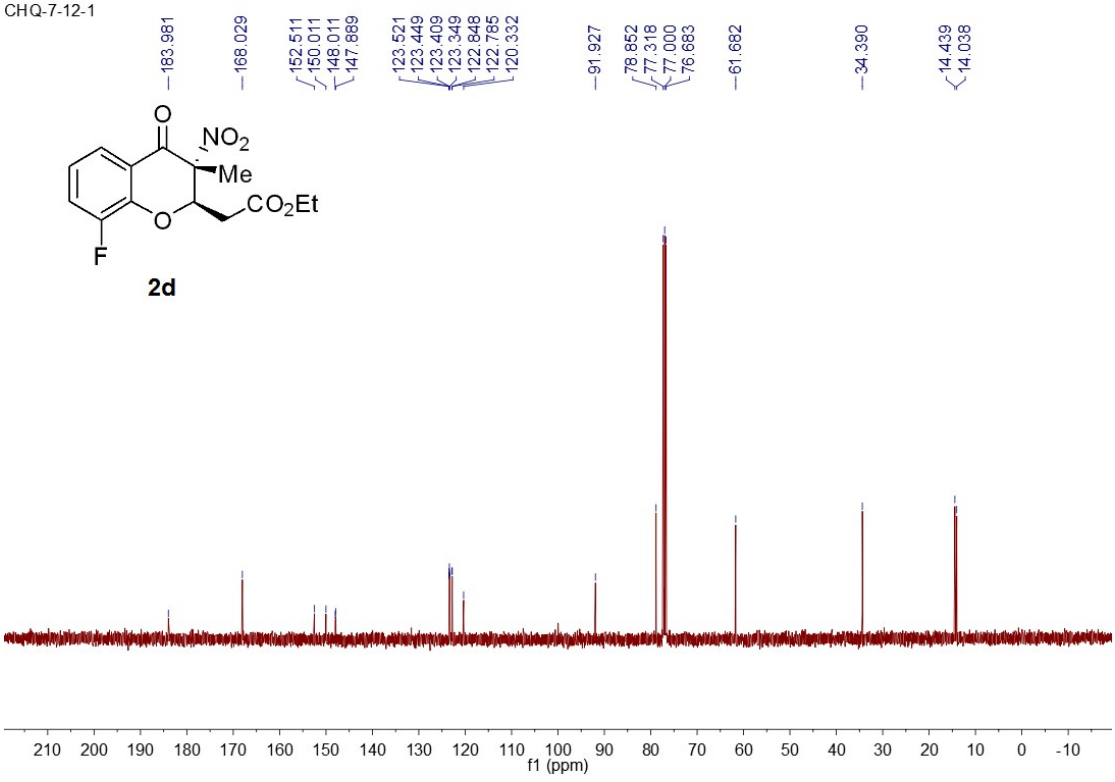
-96.699
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)

CHQ-7-12-1



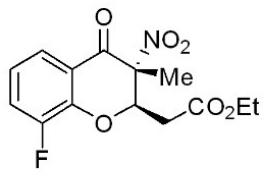
2d

CHQ-7-12-1



2d

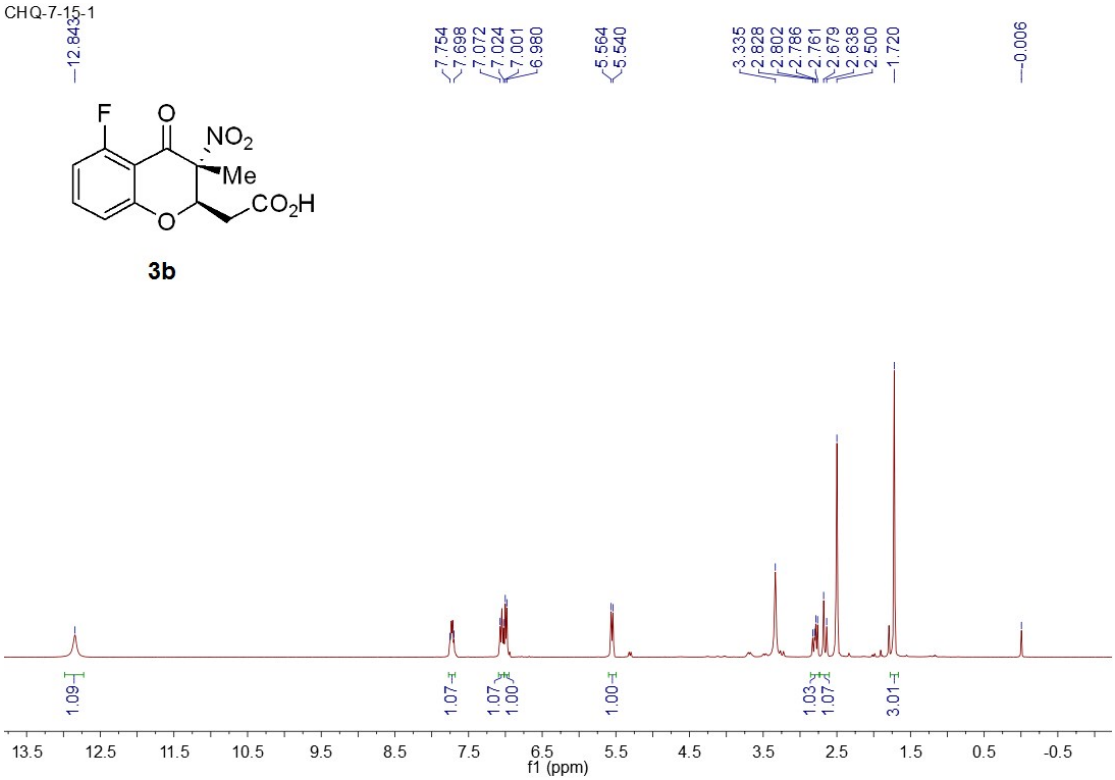
CHQ-7-5-6


O
NO2
Me
CO2Et
O
F

2d

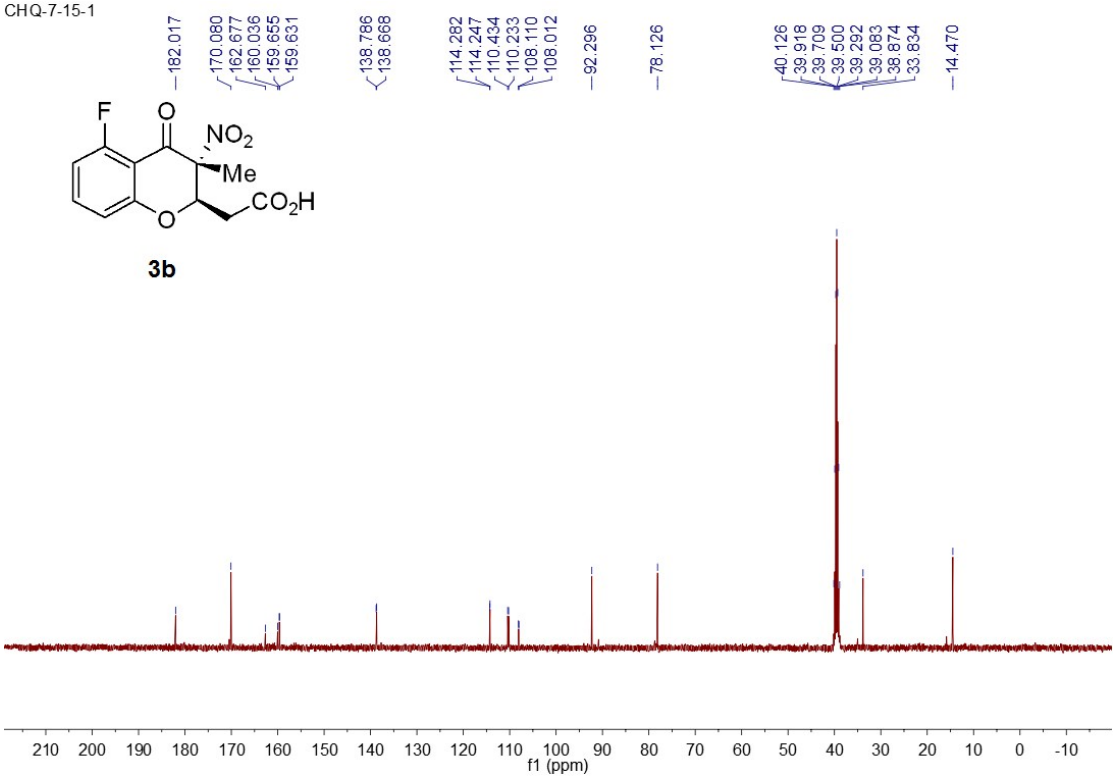
-133.359
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)

CHQ-7-15-1



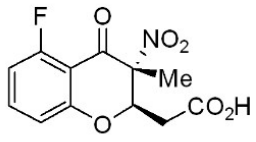
3b

CHQ-7-15-1



3b

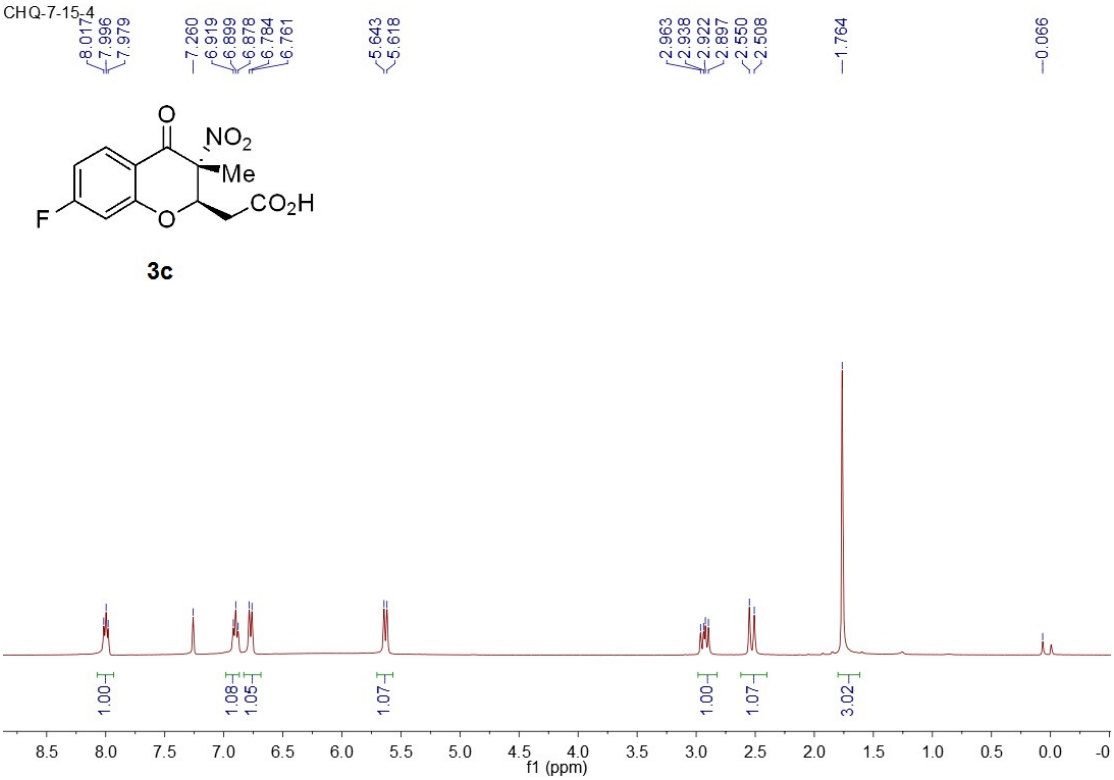
CHQ-7-2-2


F
O
NO2
Me
CO2H
O

3b

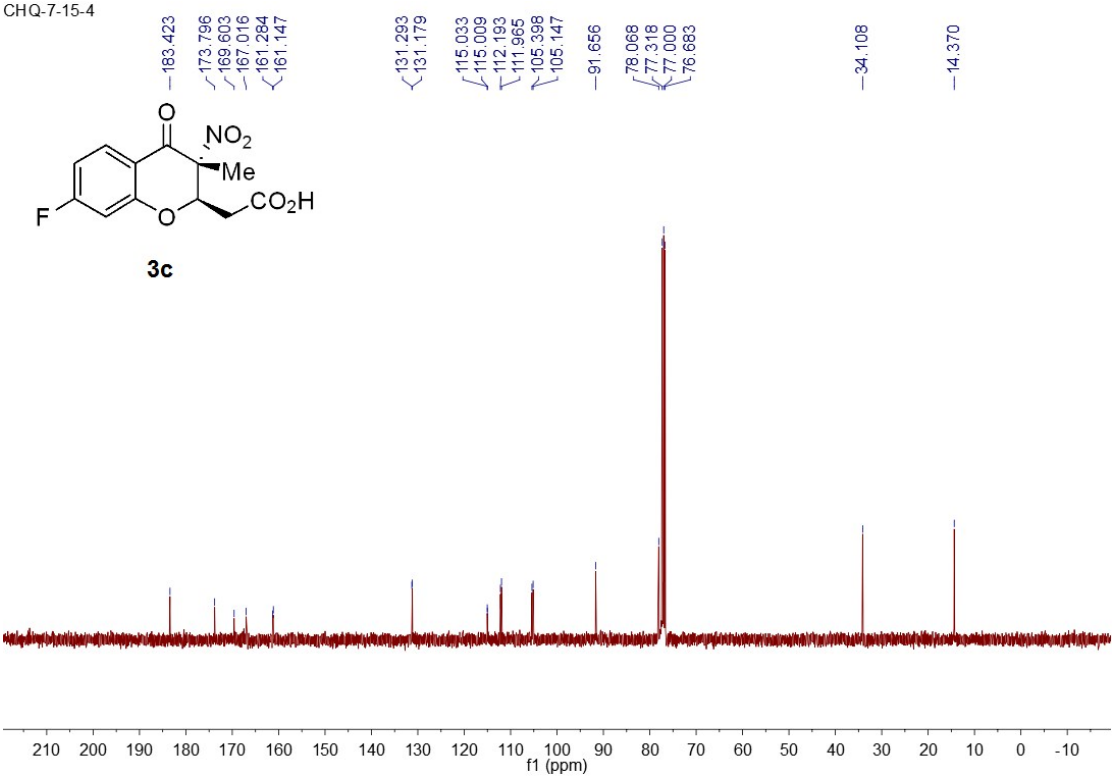
-109.888
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)

CHQ-7-15-4



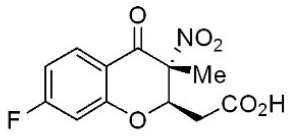
3c

CHQ-7-15-4



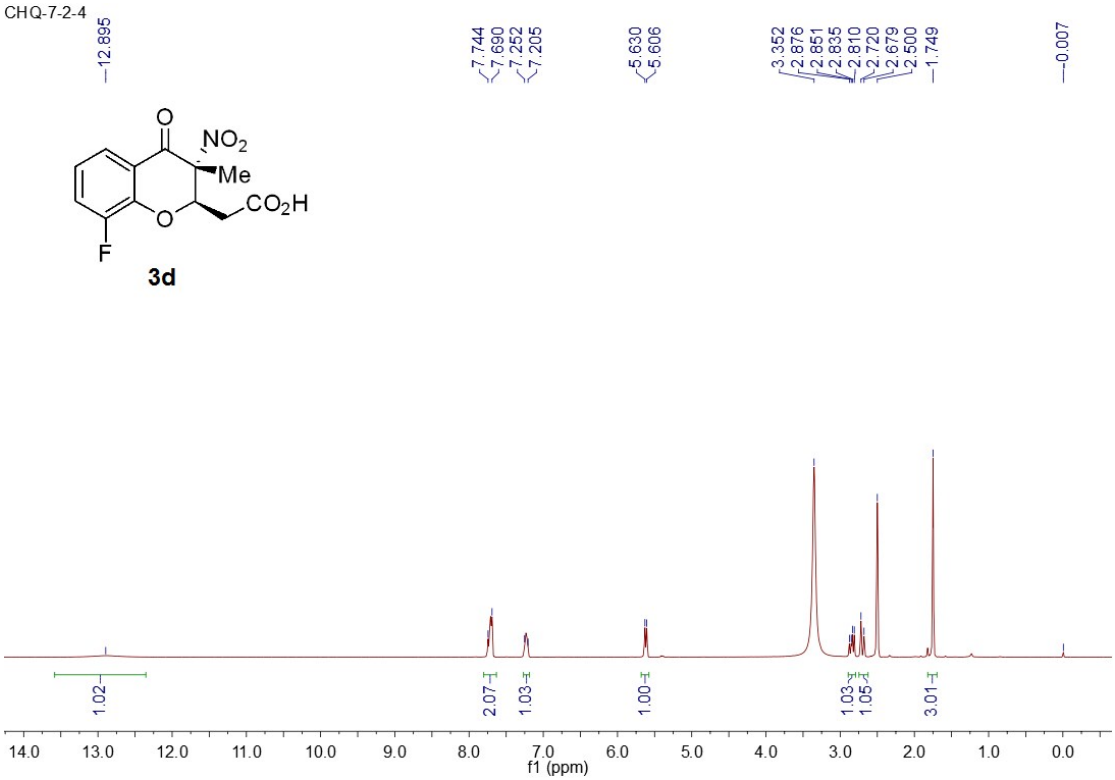
3c

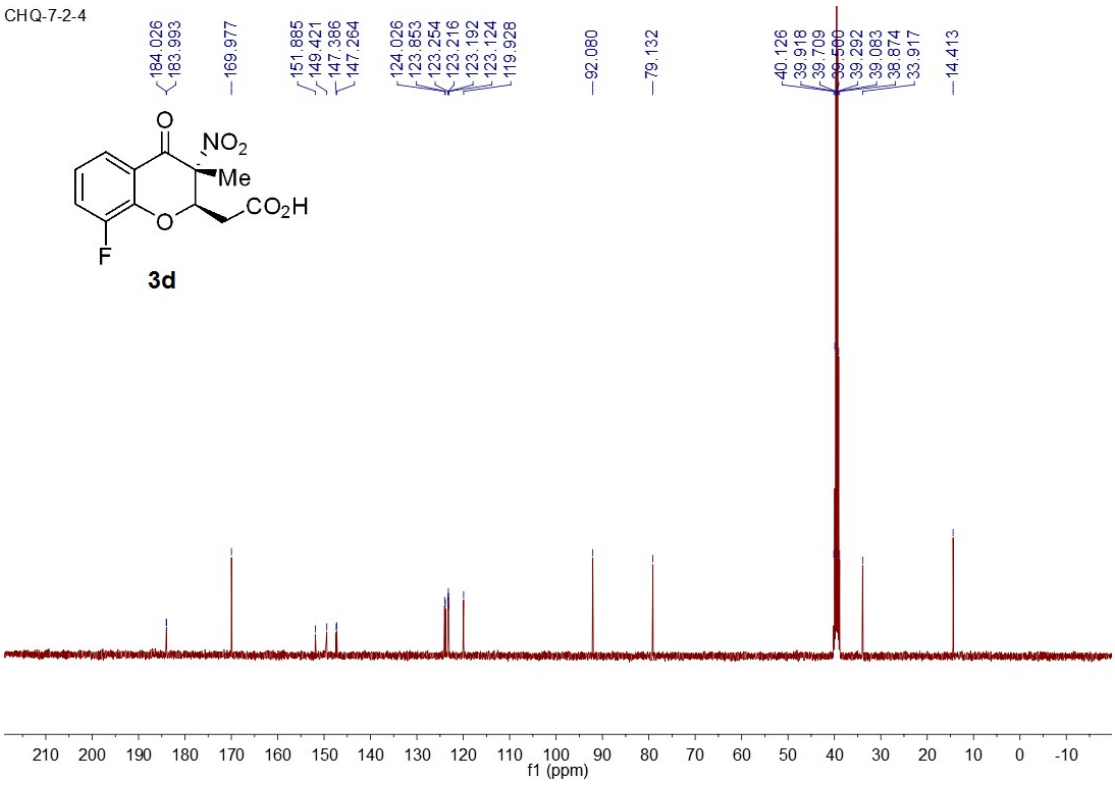
CHQ-7-2-3


O
NO2
Me
CO2H
F
O

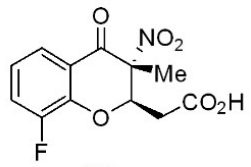
3c

-97.711
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)


CHQ-7-2-4
12.895
7.744
7.690
7.252
7.205
5.630
5.606
3.352
2.876
2.851
2.835
2.810
2.720
2.679
2.500
1.749
0.007
O
NO2
Me
CO2H
O
F
3d
1.02
2.07
1.03
1.00
1.03
1.05
3.01
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


CHQ-7-2-4
184.026
183.993
169.977
151.885
149.421
147.386
147.264
124.026
123.853
123.254
123.216
123.192
123.124
119.928
92.080
79.132
40.126
39.918
39.709
39.500
39.292
39.083
38.874
33.917
14.413
O
NO2
Me
CO2H
O
F
3d
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)

CHQ-7-2-4


O
NO2
Me
CO2H
O
F

3d

-134.315
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
f1 (ppm)