# A Ring Distortion Strategy to Construct Stereochemically Complex and Structurally Diverse Compounds from Natural Products

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# Supplementary Information

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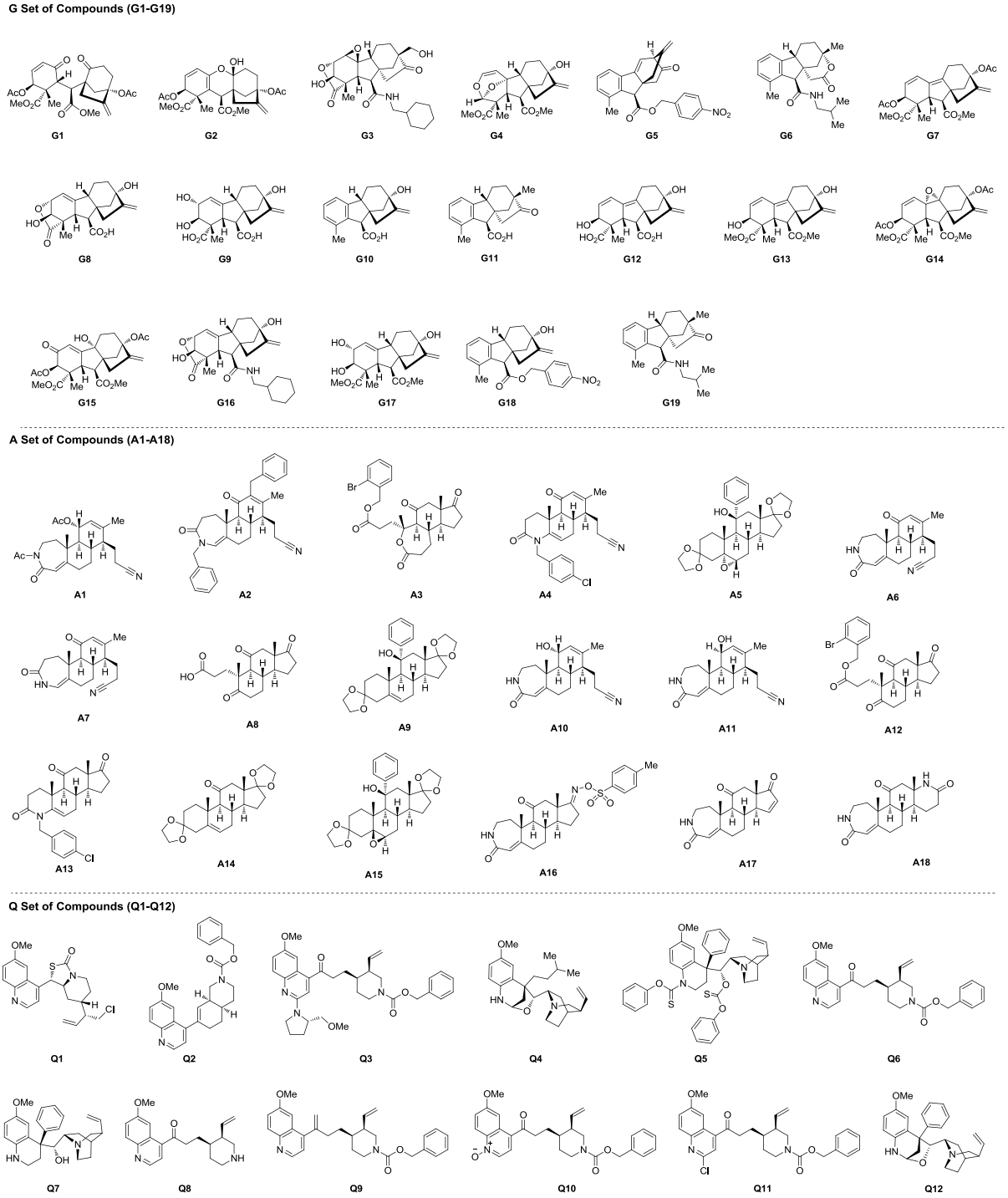
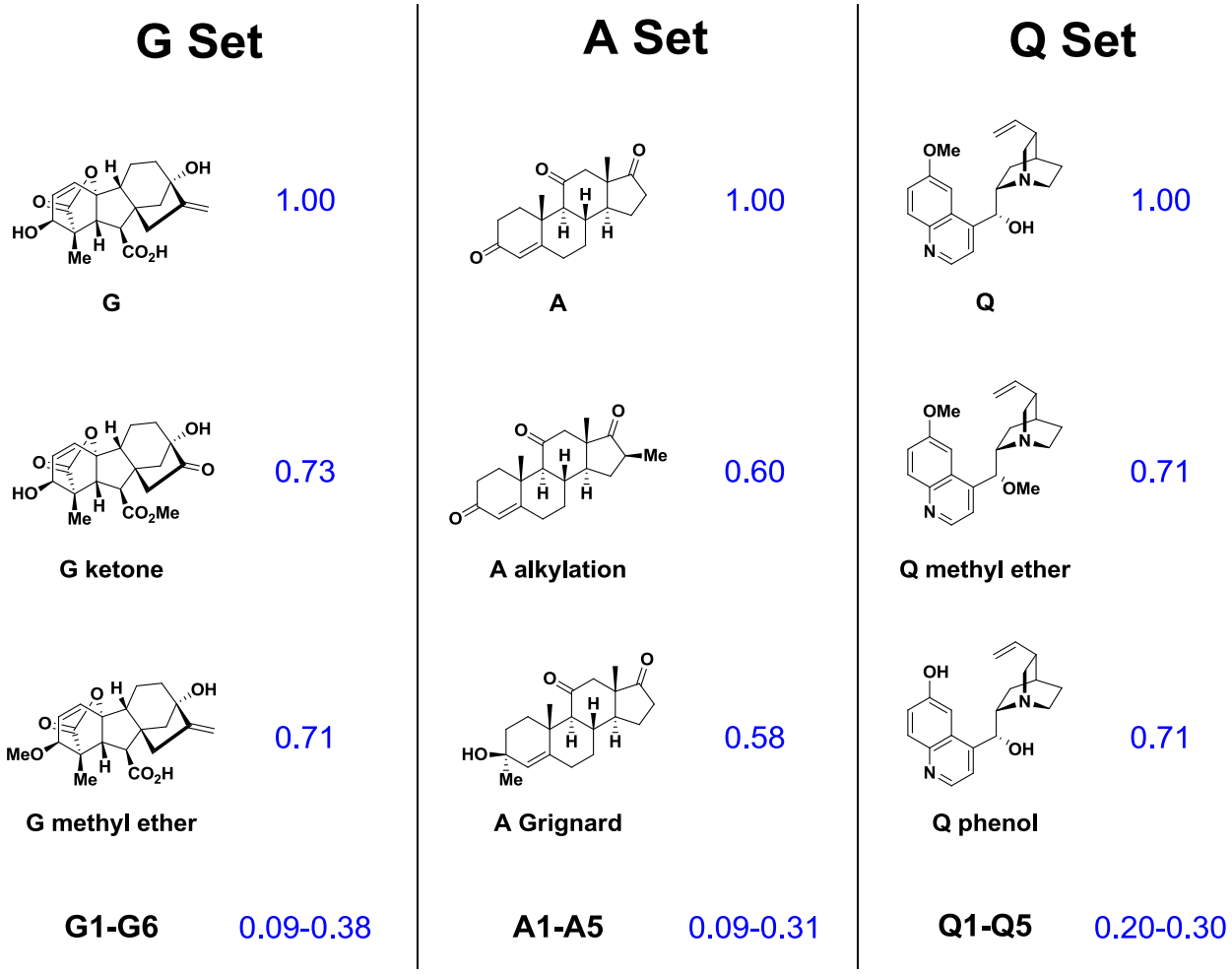
## 1.) Supplementary Figure 1: Full Compound Set



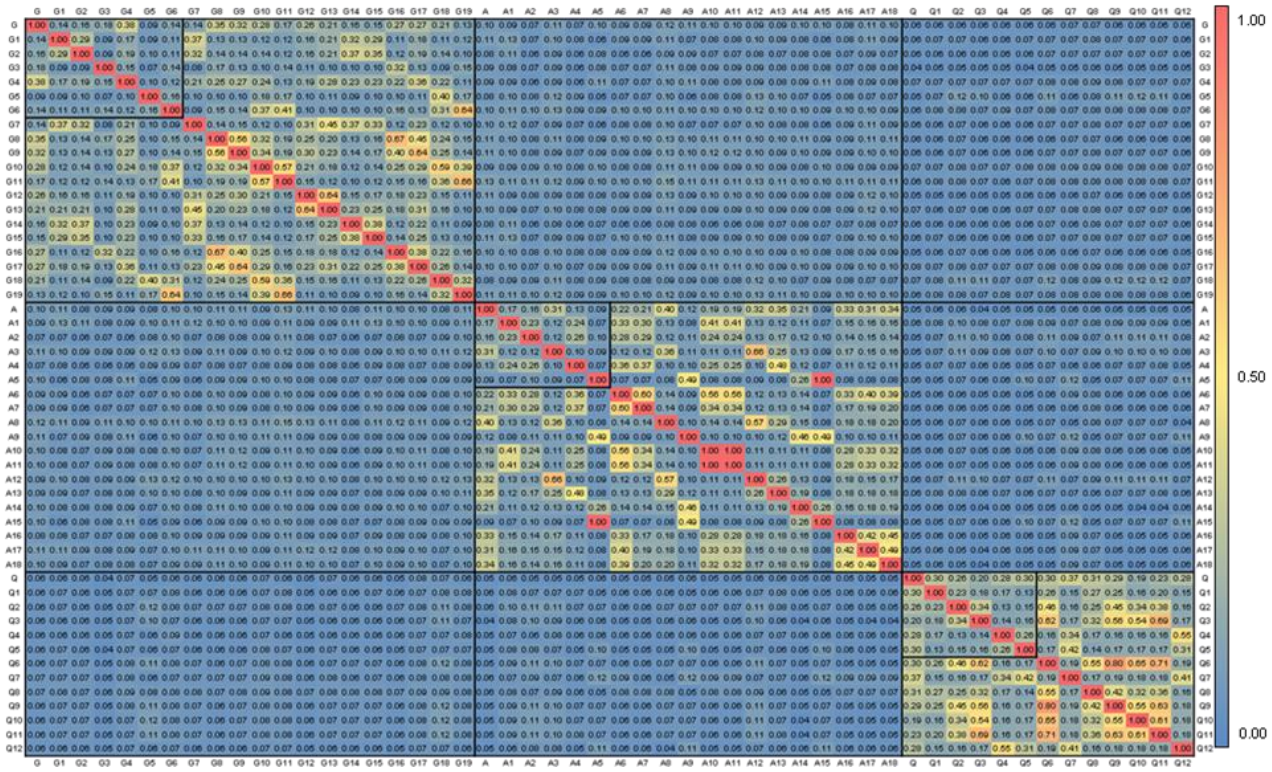

**Supplementary Figure 1:** Chemical structures of 49 compounds produced through the Complexity-to-Diversity method.

**2.) Supplementary Figure 2: Tanimoto Similarity for Peripheral Transformations**



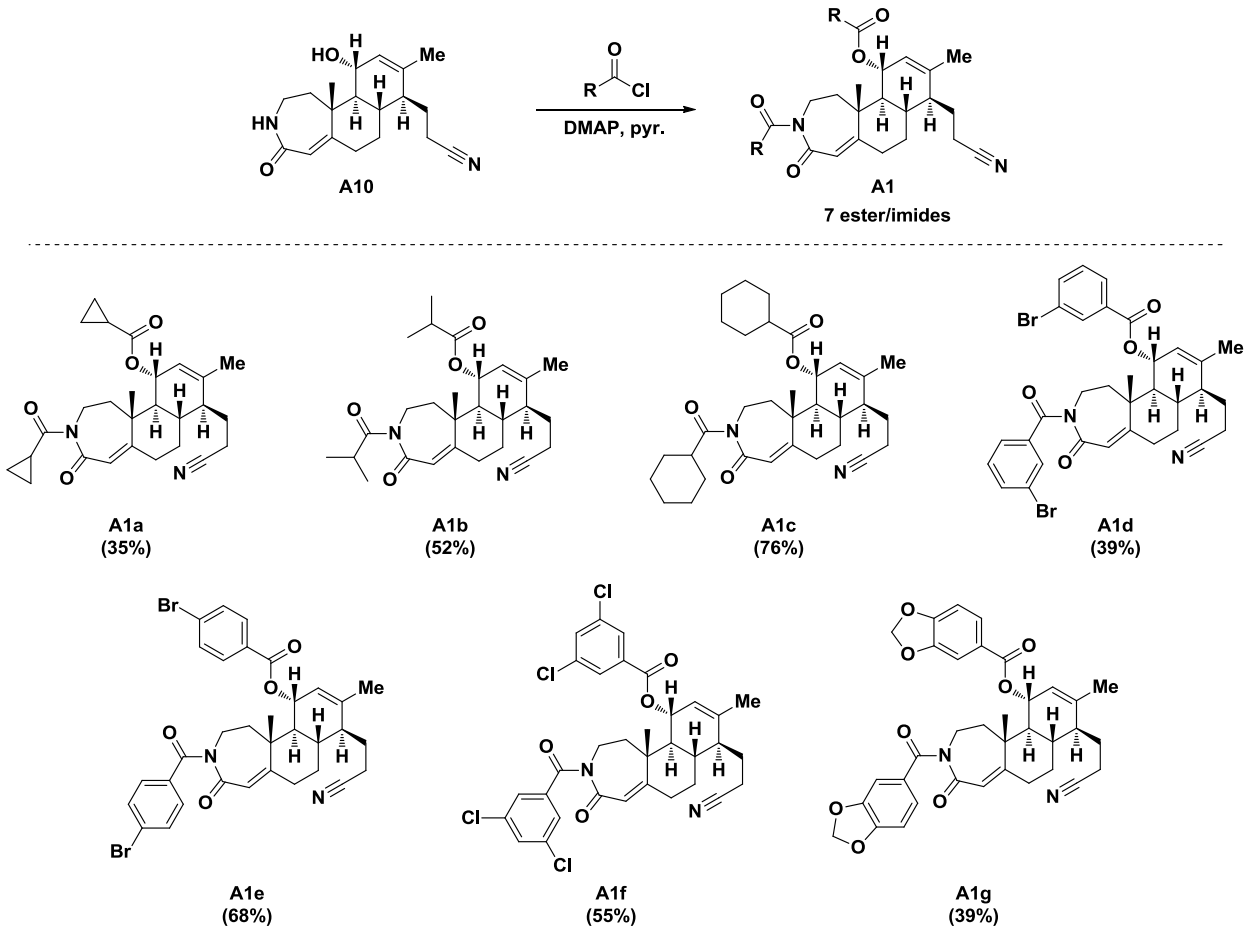

**Supplementary Figure 2:** Tanimoto similarity coefficients for compounds with peripheral transformations of the three natural products, as compared to Tanimoto coefficients for the G, A, and Q sets.

## 3.) Supplementary Figure 3: Tanimoto Similarity Matrix for Full Compound Set

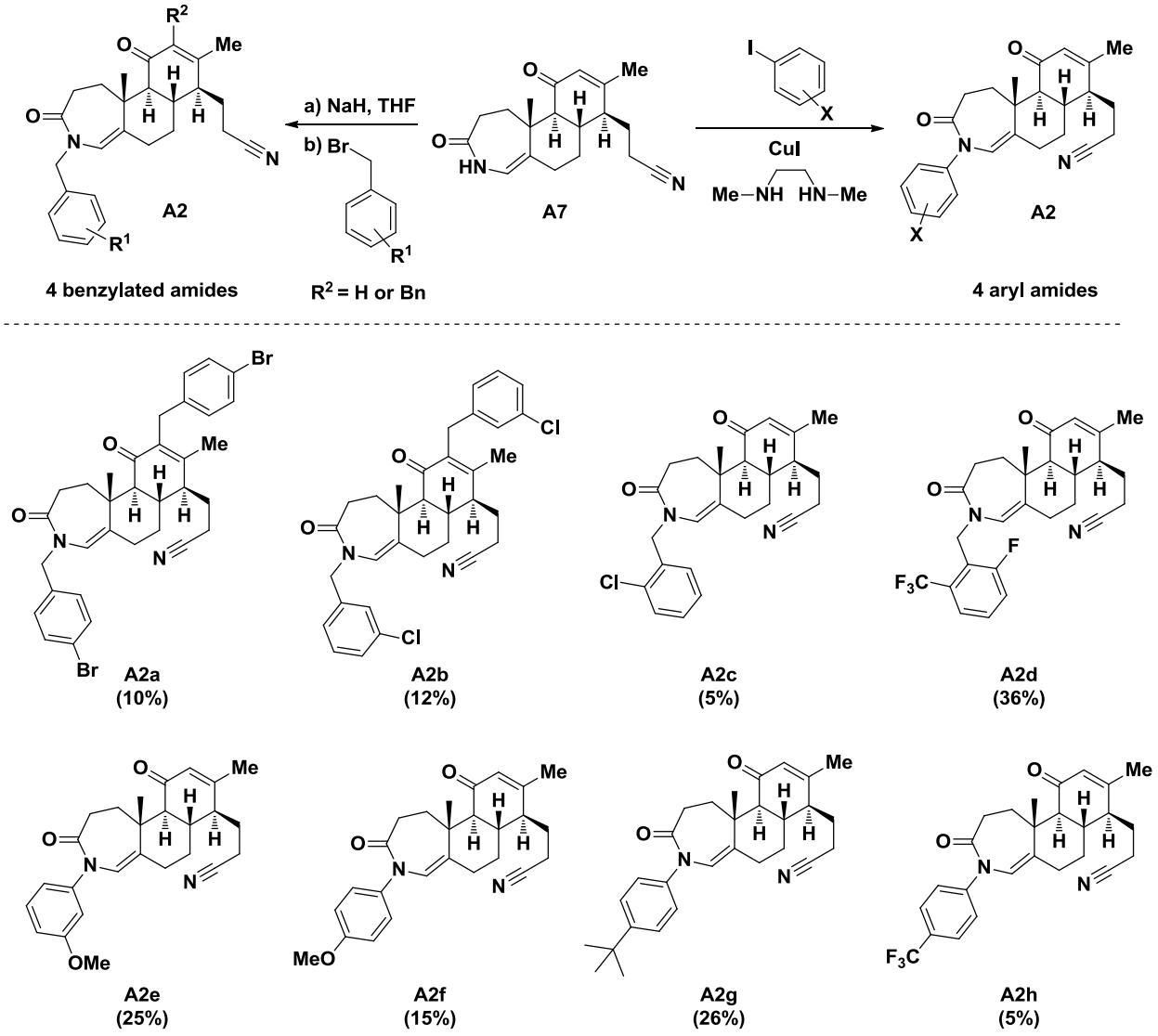



**Supplementary Figure 3.** Tanimoto similarity matrix for the full 49 compound set synthesized by the Complexity-to-Diversity method. Each compound was used as the reference input for every other compound and Tanimoto coefficient was calculated in Discovery Studio (Accelrys) based on ECFP_6 molecular fingerprints. Target compounds shown in Fig 1 (i.e. **G1**-**G6**, **A1**-**A5**, **Q1**-**Q5**) are indicated by additional frames. Note that diastereomeric compound pairs (**A5** & **A15**, **A10** & **A11**) appear identical by this connectivity-based analysis.

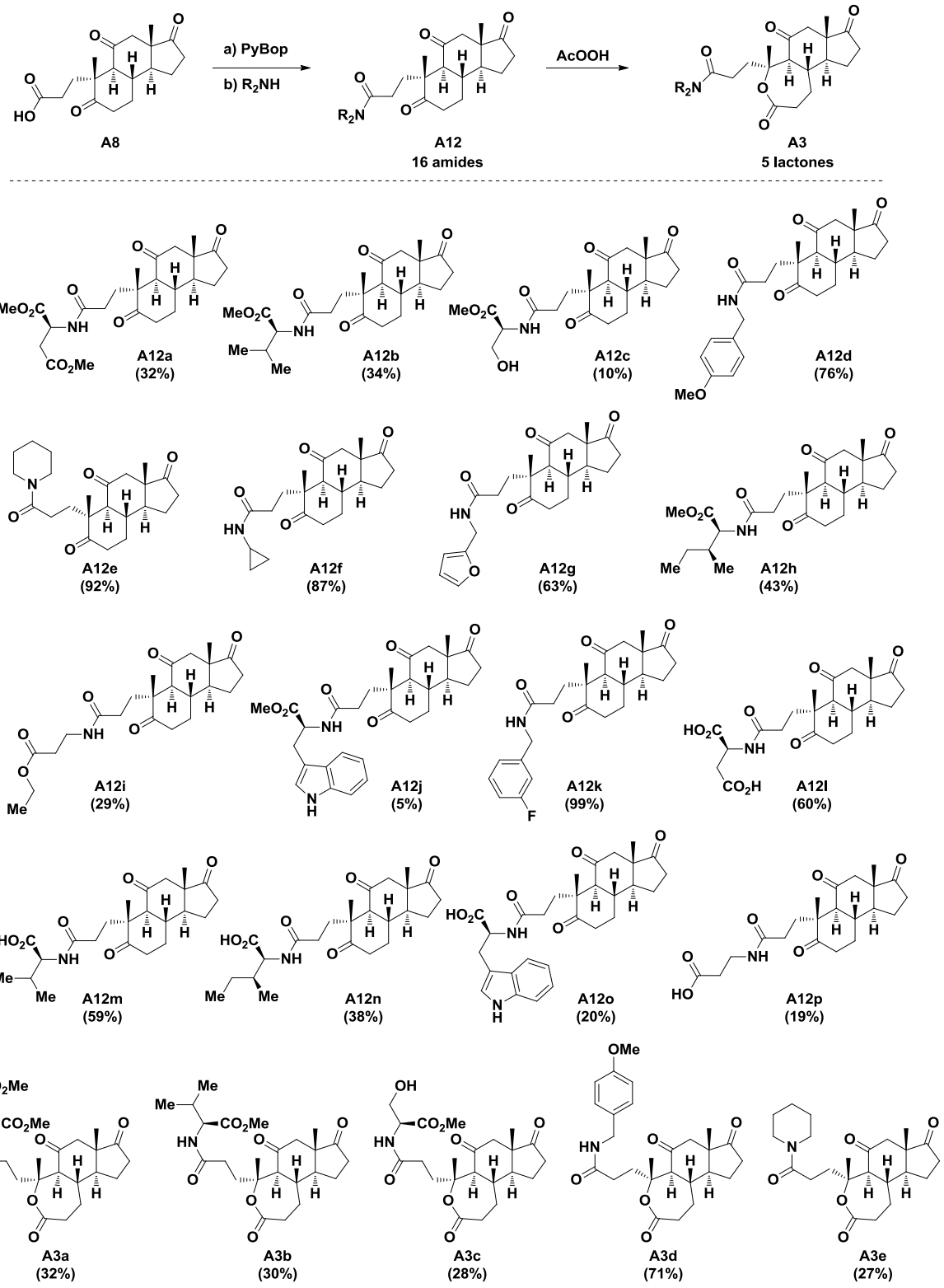
## 4.) Supplementary Figure 4: CtD Library Synthesis



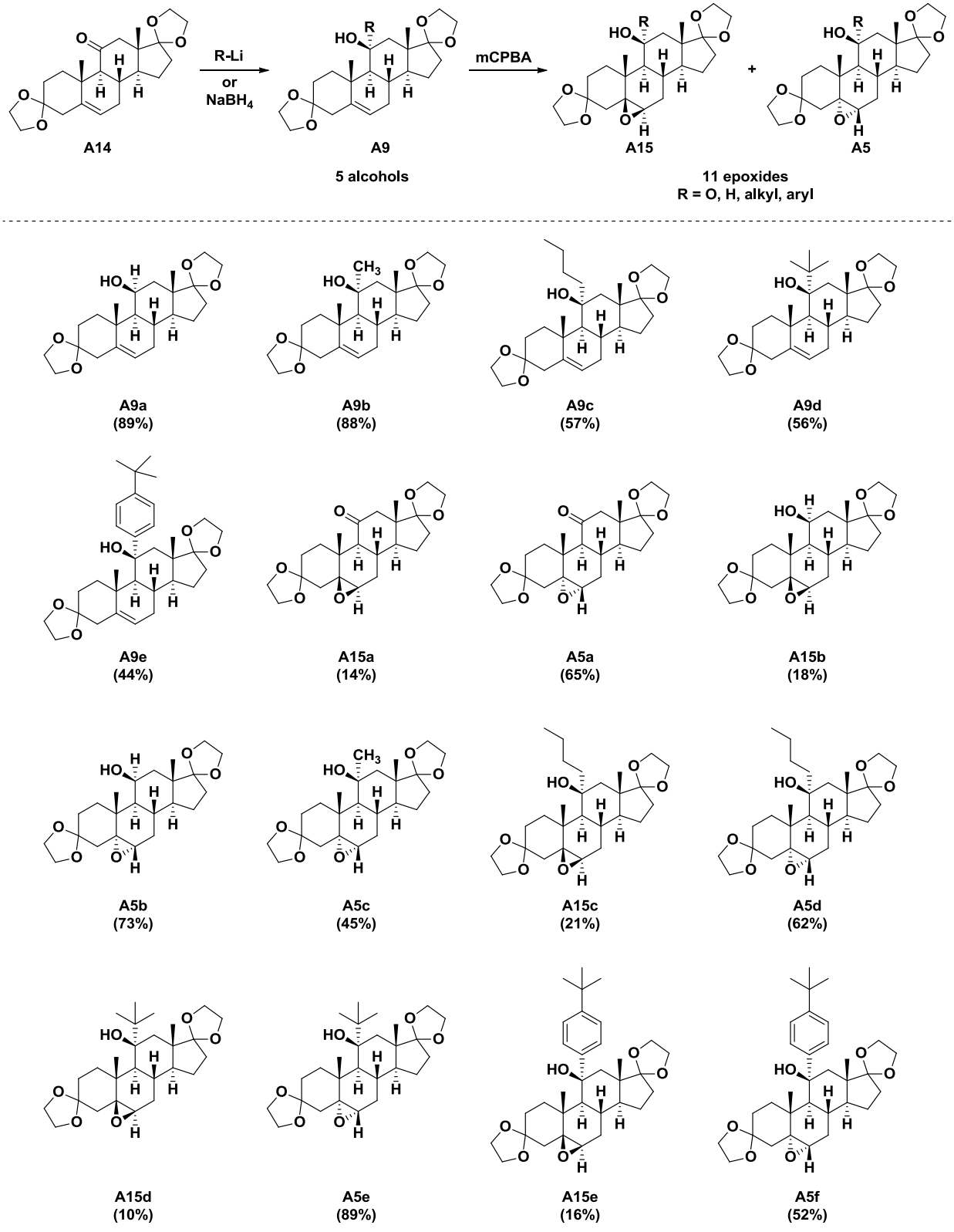

**Supplementary Figure 4a.** Synthesis of **A1** derivatives.



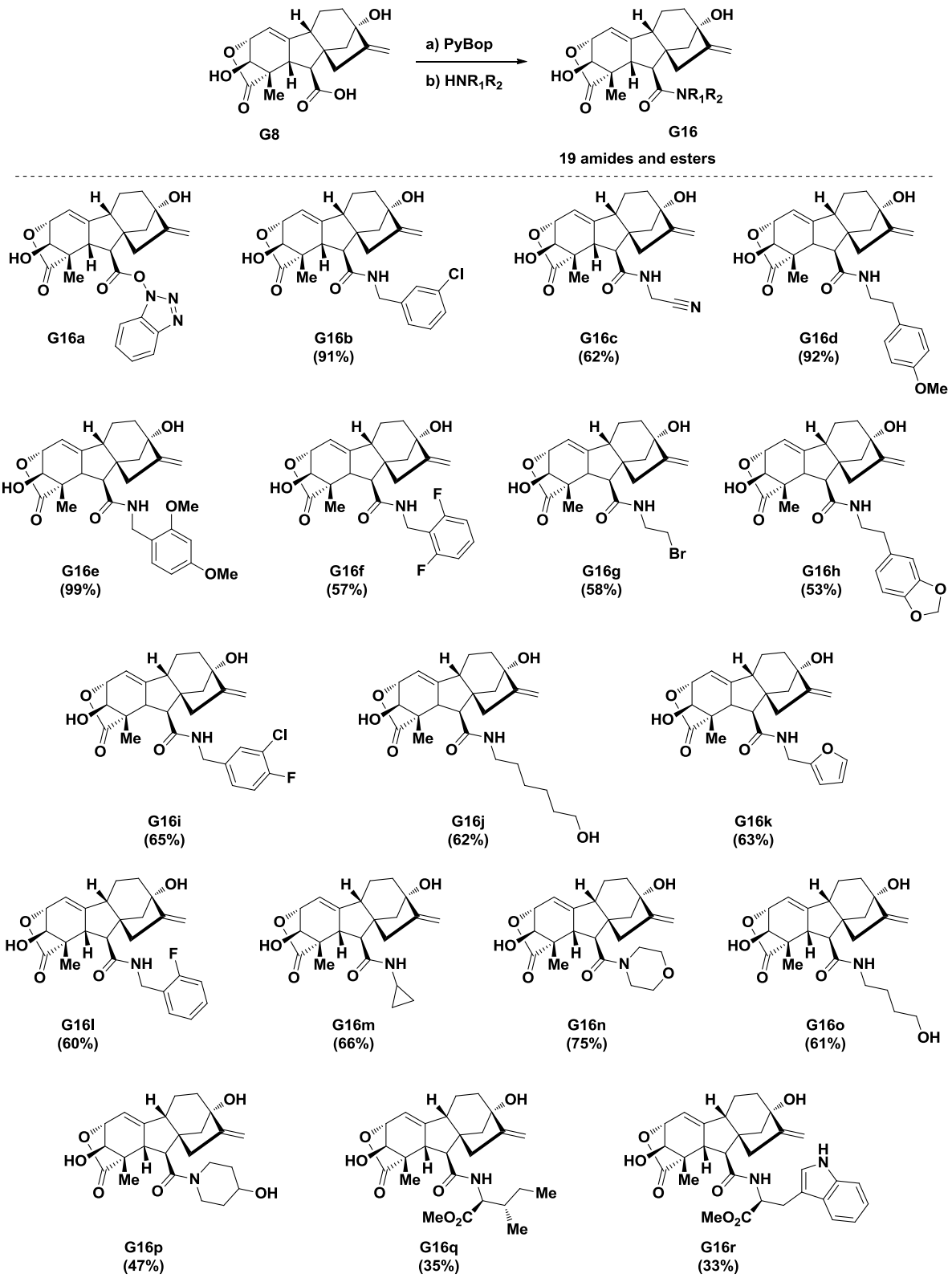

**Supplementary Figure 4b.** Synthesis of **A2** derivatives.



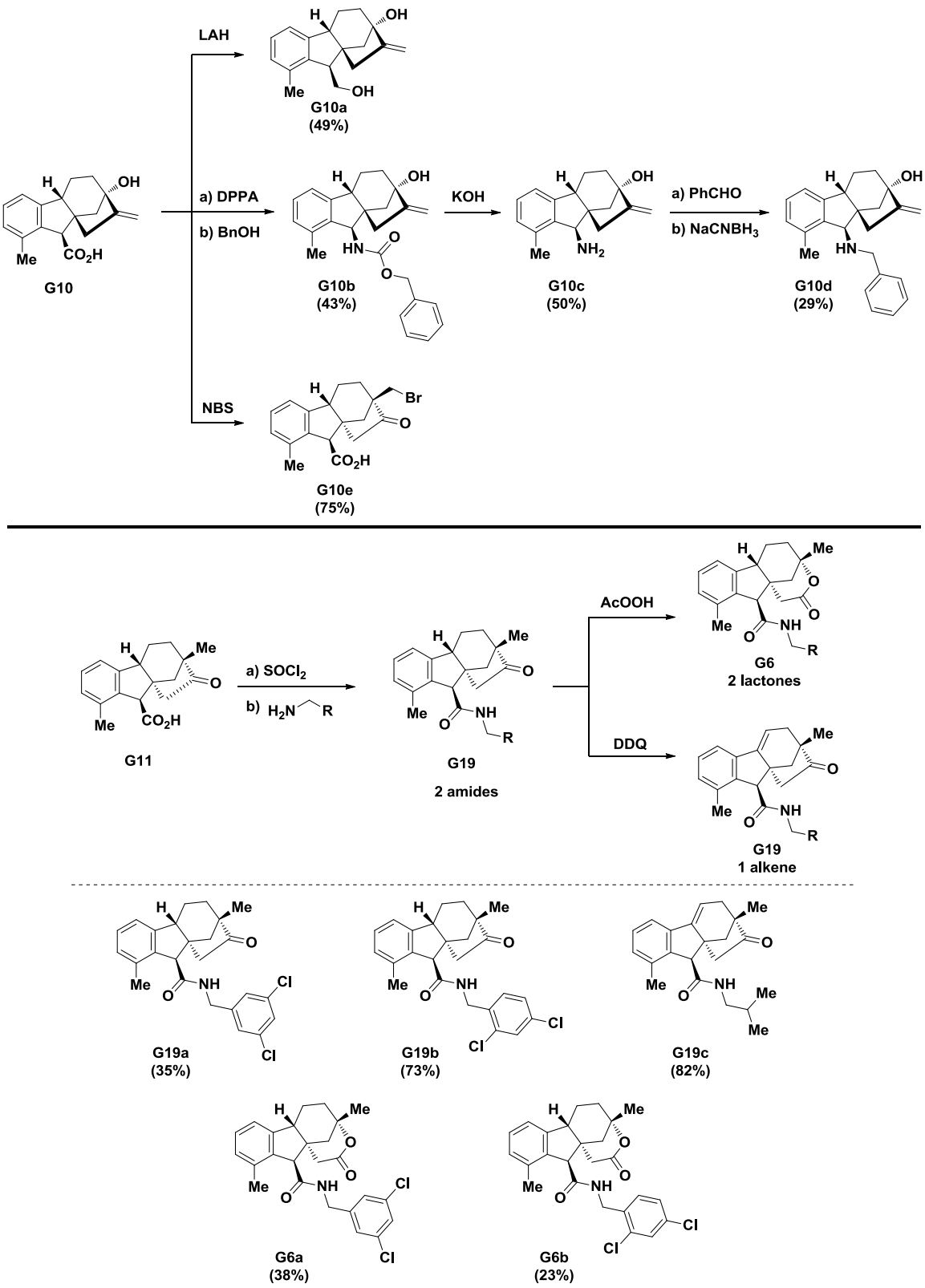

**Supplementary Figure 4c.** Synthesis of **A12** and **A3** derivatives.



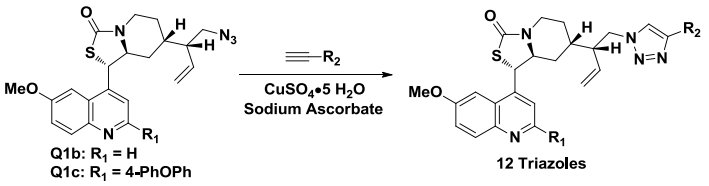

**Supplementary Figure 4d.** Synthesis of **A9**, **A5**, and **A15** derivatives.

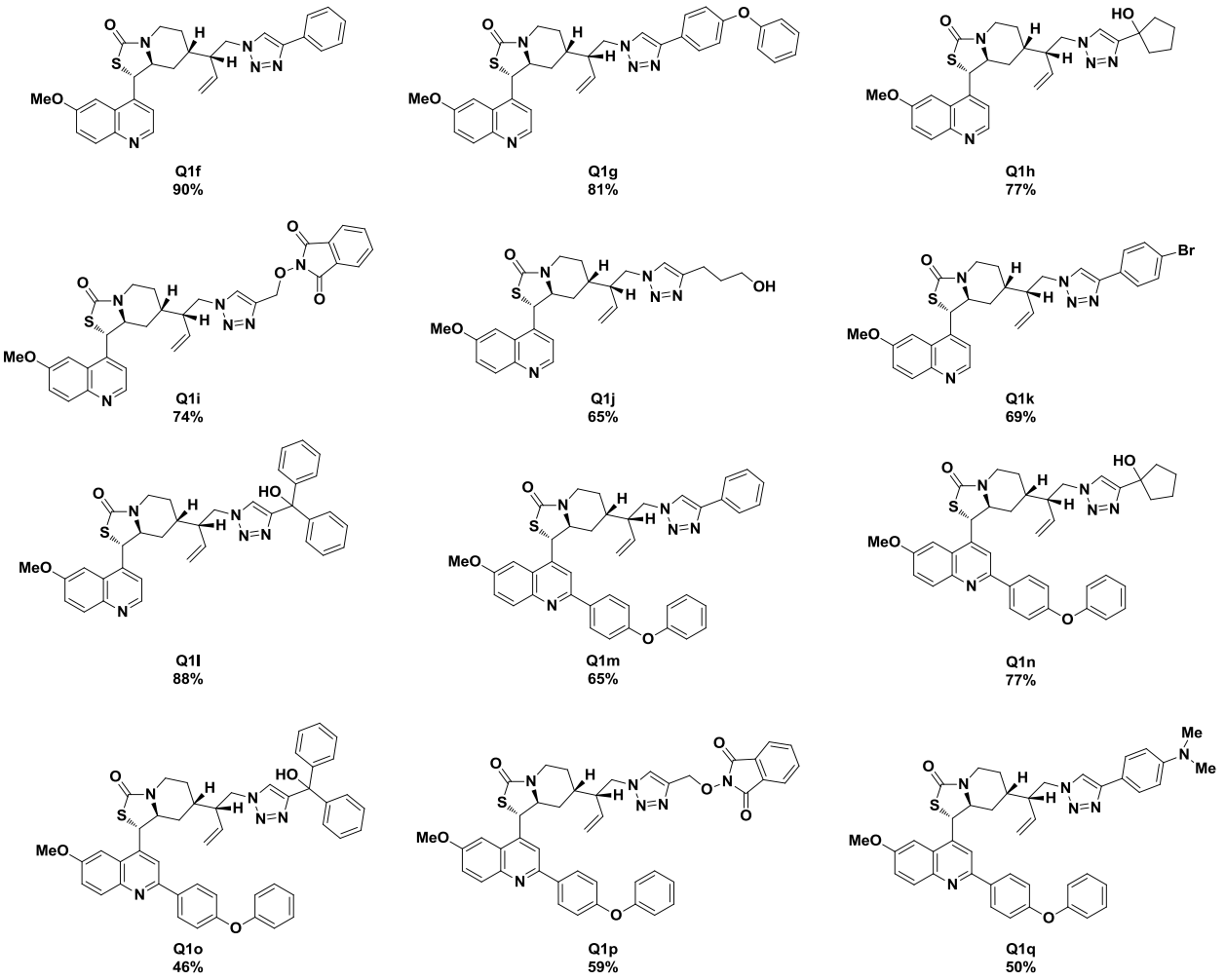



**Supplementary Figure 4e.** Synthesis of **G16** derivatives.

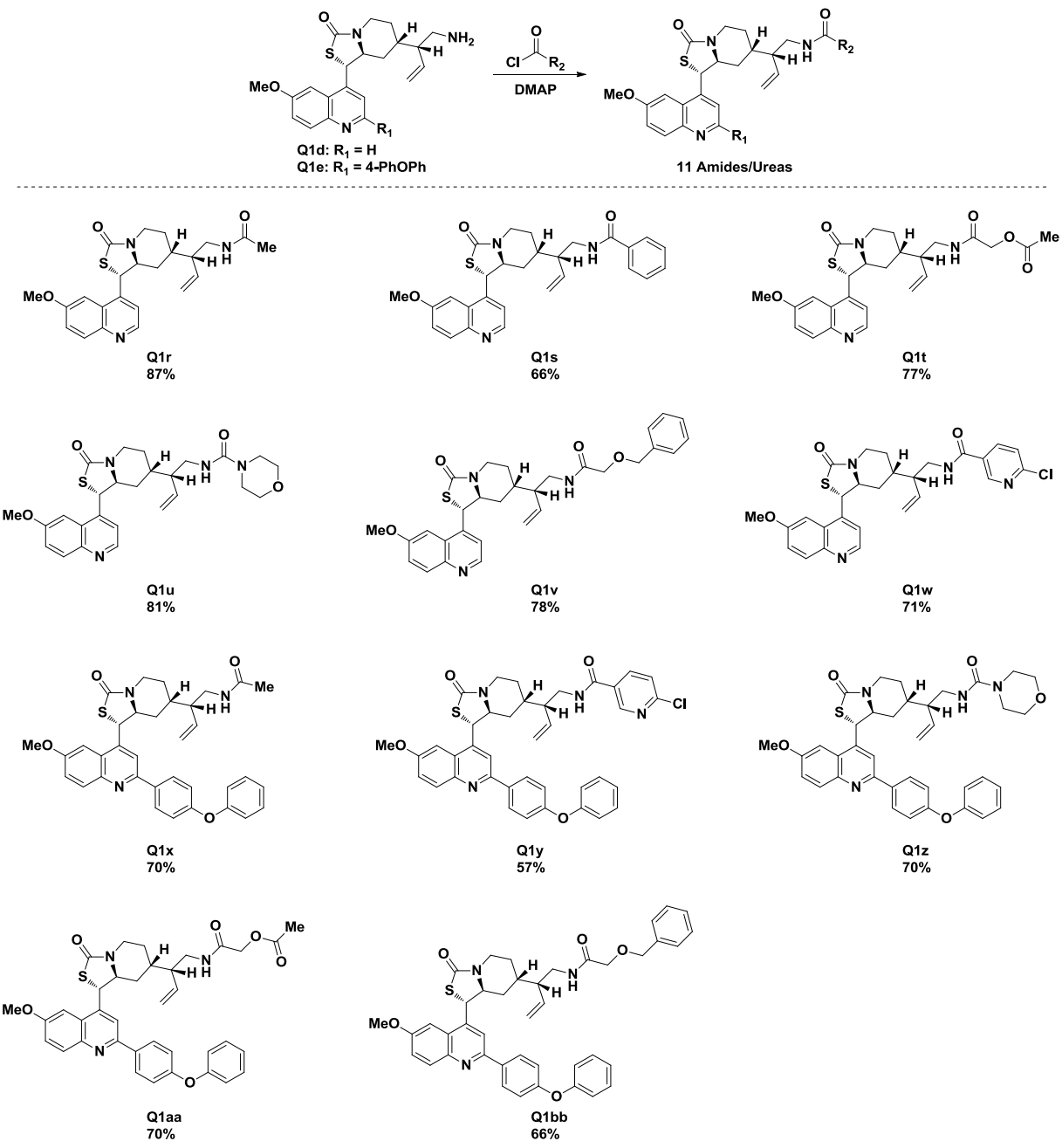



**Supplementary Figure 4f.** Synthesis of **G10**, **G19**, and **G6** derivatives.

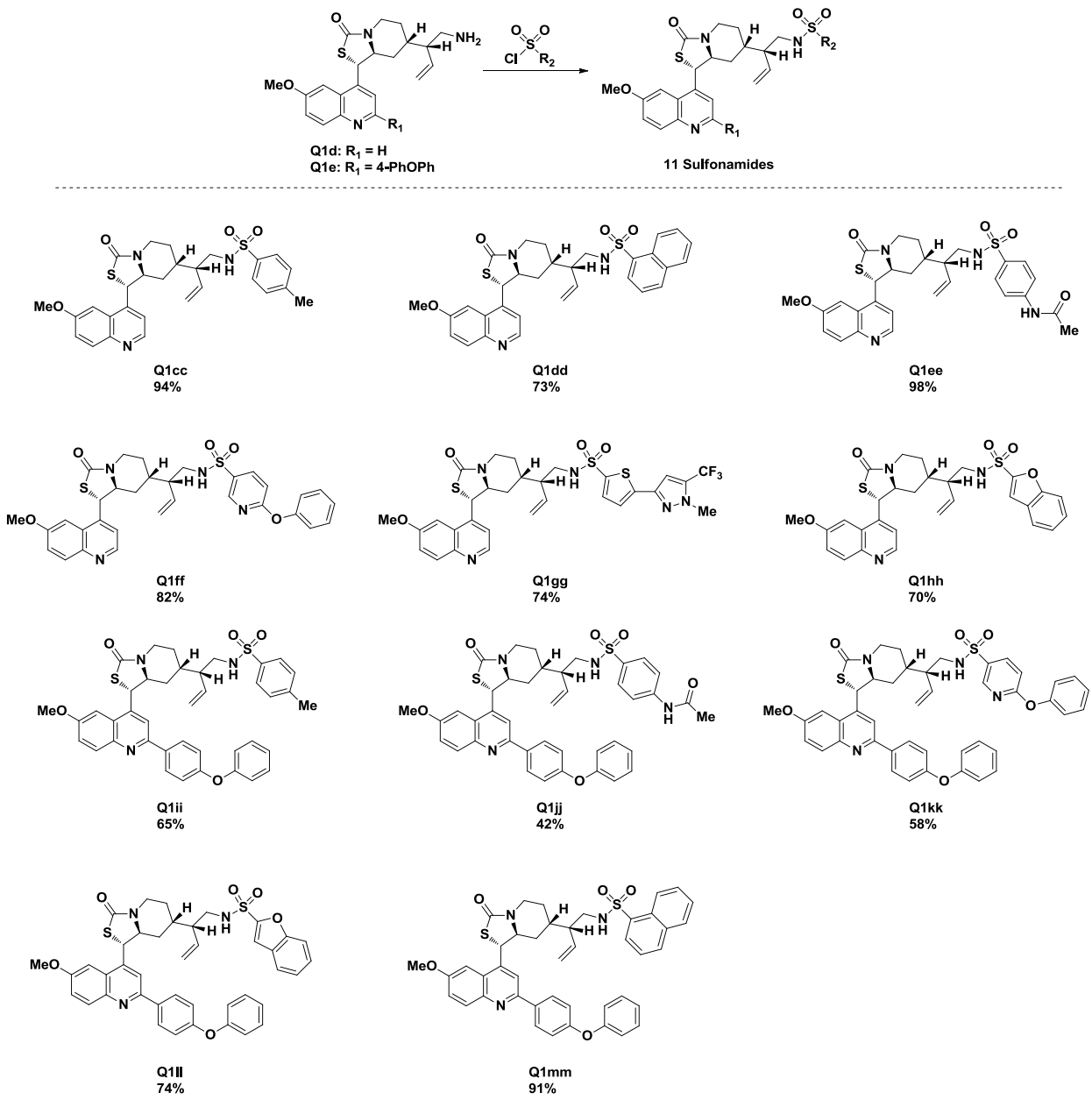



**Supplementary Figure 4g.** Synthesis of **Q1** triazoles.

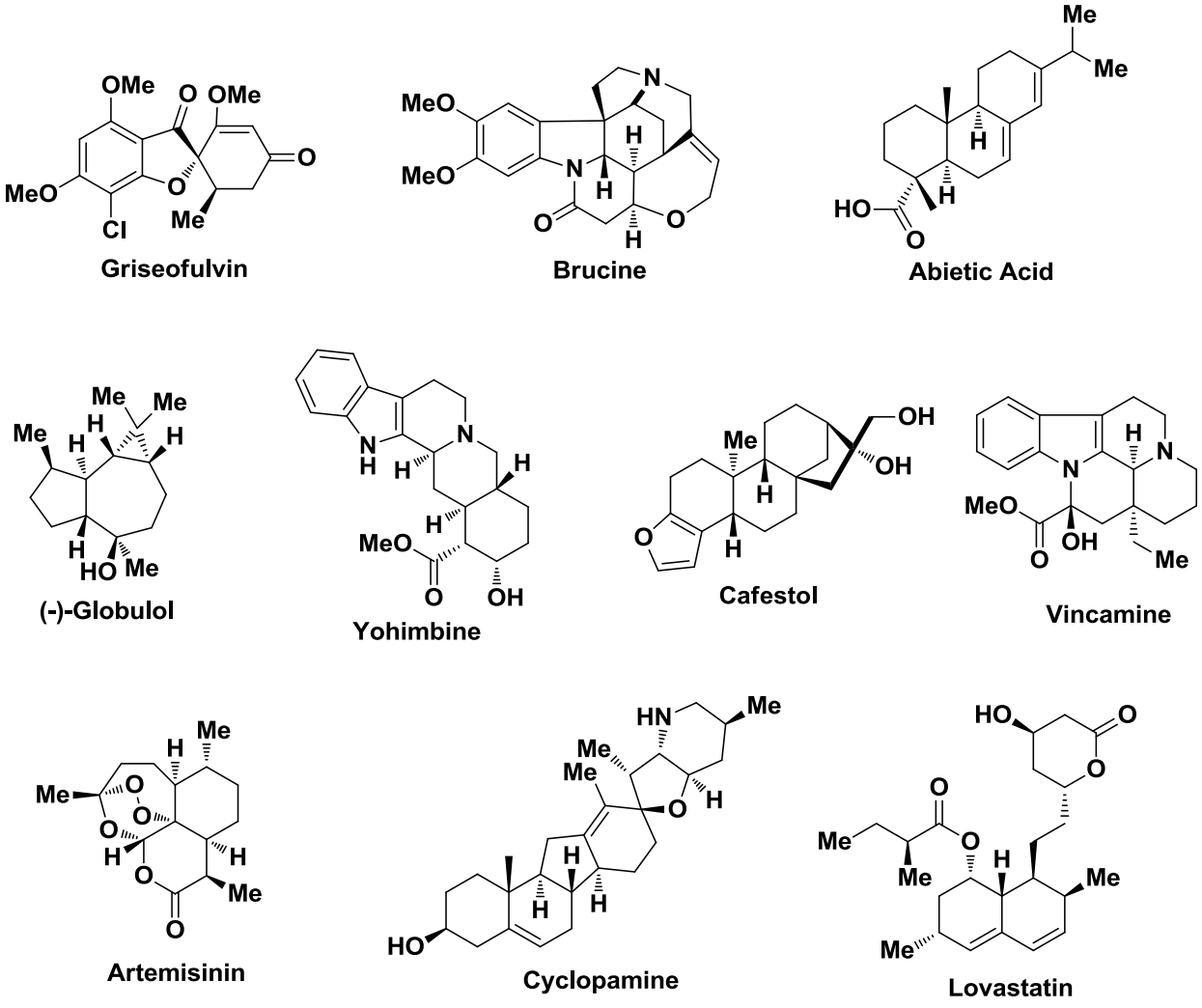



**Supplementary Figure 4h.** Synthesis of **Q1** amides and ureas.




**Supplementary Figure 4i.** Synthesis of **Q1** sulfonamides.

**5.) Supplementary Figure 5: Representative Natural Products Suitable for CtD Approach**




**Supplementary Figure 5.** Representative natural products amenable to modification by a Complexity-to-Diversity approach based on structural complexity and availability.

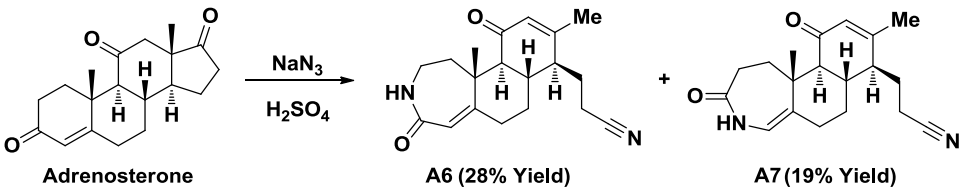
## 6.) Materials and Methods

Chemical reagents were purchased from commercial sources and used without further purification. Quinine and adrenosterone were purchased from Sigma-Aldrich (at ≥98.0% purity for both natural products) and gibberellic acid (90% purity) was purchased from AK Scientific. These three natural products can be purchased for between $2 and $20 per gram. Anhydrous solvents used during these studies were dried after being passed through columns with activated alumina.

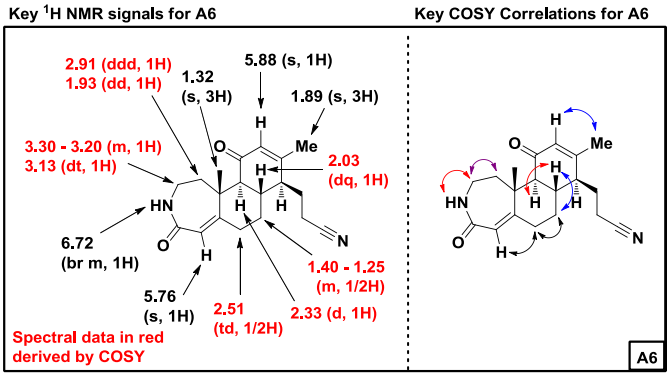
All G, A and Q compounds from Supplementary Figure 1 have $^{1}$H NMR, $^{13}$C NMR and HRMS (all spectra shown in separate NMR file). Various 2-D NMR experiments were conducted on these compounds as necessary. All library compounds derived from the G, A and Q compound sets have $^{1}$H NMR and HRMS (representative spectra shown in separate NMR file).

$^{1}$H NMR and $^{13}$C NMR experiments were recorded on Varian Unity spectrometers at 400 MHz and 500 MHz and 125 MHz, respectively. Spectra were obtained in the following solvents (reference peaks also included for $^{1}$H and $^{13}$C NMRs): $CDCl_3$ ($^{1}$H NMR: 7.26 ppm; $^{13}$C NMR: 77.23 ppm), $d_6$-DMSO ($^{1}$H NMR: 2.50 ppm; $^{13}$C NMR: 39.52 ppm), $d_6$-acetone ($^{1}$H NMR: 2.05 ppm; $^{13}$C NMR: 206.26 ppm), $d_6$-benzene ($^{1}$H NMR: 7.16 ppm; $^{13}$C NMR: 128.06 ppm), $CD_3OD$ ($^{1}$H NMR: 3.31 ppm). NMR experiments were performed at room temperature unless otherwise indicated. Chemical shift values are reported in parts per million (ppm) for all $^{1}$H NMR and $^{13}$C NMR spectra. $^{1}$H NMR multiplicities are reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. All melting points were uncorrected and obtained using a Digimelt MPA 160.

## 7.) Adrenosterone Derived Compounds: Synthesis and Characterization




**Procedure:** Adrenosterone (107.3 mg, 0.357 mmol) was dissolved in concentrated sulfuric acid (1 mL) at room temperature before cooling to 0 °C. Sodium azide (70 mg, 1.072 mmol) was then added to the reaction slowly and the resulting reaction mixture was allowed to stir for 1 hour at 0 °C. After this time, ice was added to quench the reaction and stirring continued for an additional 3 minutes before being transferred to a separatory funnel and partitioned between brine and dichloromethane. Dichloromethane was used to extract the desired Schmidt products (3x). The organic layers were combined, dried with magnesium sulfate and concentrated under reduced pressure to give a crude white foam. The two products were purified via column chromatography using 100:0 to 95:5 ethyl acetate/methanol to afford 31.7 mg (28% yield) of lactam **A6** as a white foam and 21.4 mg of enamide **A7** (19% yield) as a white foam.



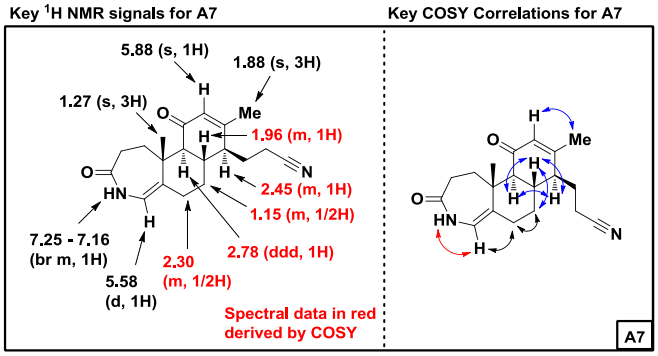

**$^{1}$H NMR** ($CDCl_3$, 500 MHz): δ 6.72 (br m, 1H), 5.88 (s, 1H), 5.76 (s, 1H), 3.30 - 3.20 (m, 1H), 3.13 (dt, *J* = 14.7, 6.8 Hz, 1H), 2.91 (ddd, *J* = 15.0, 8.3, 2.8 Hz, 1H), 2.51 (td, *J* = 13.7, 4.0 Hz, 1H), 2.33 (d, *J* = 11.5 Hz, 1H), 2.32 - 2.08 (m, 7H), 2.03 (dq, *J* = 16.0, 5.0 Hz, 1H), 1.93 (dd, *J* = 19.0, 11.5 Hz, 1H), 1.89 (s, 3H), 1.40 - 1.25 (m, 1H), 1.32 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 198.0, 169.8, 158.4, 156.4, 131.1, 120.3, 119.3, 57.9, 46.3, 43.8, 41.2, 37.0, 36.3, 35.2, 33.1, 24.1, 21.5, 21.4, 12.6.

**HRMS (ESI):** *m/z* calc. for $C_{19}H_{25}N_2O_2$ $[M+H]^+$: 313.1916, found: 313.1917.

**IR** ($cm^{-1}$ NaCl plates, thin film in $CDCl_3$): 3262 (b, m), 2943 (b, m), 2245 (m), 1658 (s), 1607 (m), 1440 (m), 1380 (m).

**Melting point:** 63-65 °C.



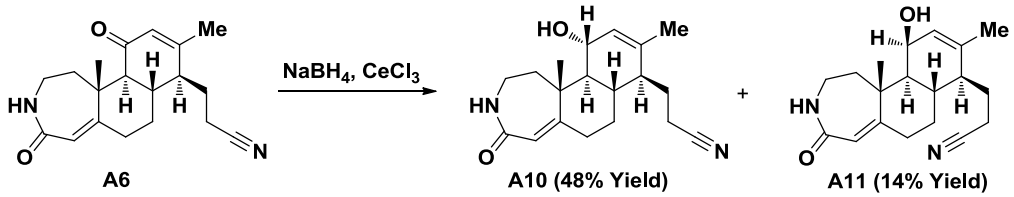

**$^{1}$H NMR** ($CDCl_3$, 500 MHz): δ 7.25 - 7.16 (br m, 1H), 5.88 (s, 1H), 5.58 (d, *J* = 5.8 Hz, 1H), 2.78 (ddd, *J* = 14.5, 6.5, 3.9 Hz, 1H), 2.47 (m, 2H), 2.36 - 2.06 (m, 8H), 2.03 - 1.87 (m, 3H), 1.88 (s, 3H), 1.27 (s, 3H), 1.19 (dq, *J* = 13.5, 4.0 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 198.5, 177.4, 156.2, 131.2, 128.9, 119.4, 115.8, 57.3, 46.3, 41.2, 36.7, 33.5, 32.9, 31.9, 31.7, 24.2, 21.6, 20.6, 12.7.

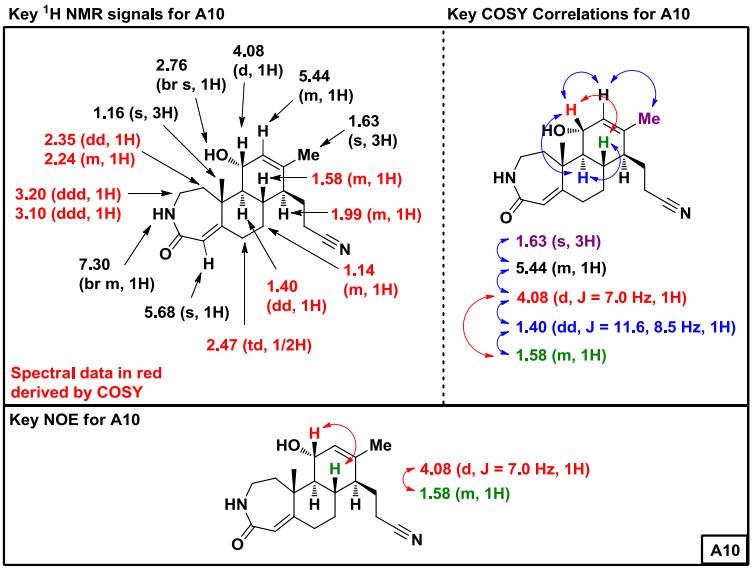
**HRMS(ESI):** *m/z* calc. for $C_{19}H_{25}N_2O_2$ $[M+H]^+$: 313.1916, found: 313.1918.

**IR** ($cm^{-1}$ NaCl plates, thin film in $CDCl_3$): 3242 (b, m), 2928 (b, m), 2245 (m), 1660 (s), 1437 (m), 1380 (m).

**Melting point:** 63-65 °C.



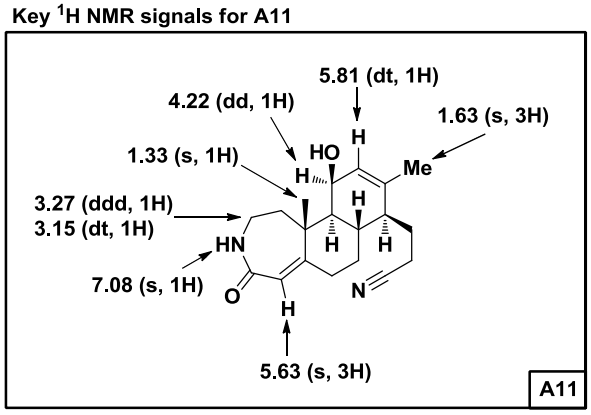

**Procedure:** Lactam **A6** (299 mg, 0.957 mmol) was dissolved in anhydrous methanol (6 mL) at room temperature. Then cerium(III) chloride (428 mg, 1.15 mmol) was added to the reaction vial and dissolved before the solution was cooled to 0 °C. After the reaction was cooled, sodium borohydride (354 mg, 9.57 mmol) was added in three portions at the start of the reaction. The reaction was allowed to stir at 0 °C for 2 hours before warming to room temperature on its own accord (ice bath was not removed) overnight. After 16 hours, a saturated solution of ammonia chloride was added slowly to the reaction vial to quench the reaction. The contents of the reaction mixture were transferred to a separatory funnel where dichloromethane was used to extract the product (3x). The organic layers were combined, dried with magnesium sulfate and concentrated to give a crude white foam. The crude diastereomers were purified via column chromatography using 100:0 to 95:5 dichloromethane/methanol to afford 144 mg (48% yield) of **A10** as a white foam and 43 mg (14% yield) of **A11** as a white foam.




**$^{1}$H NMR** ($CDCl_3$, 500 MHz): δ 7.30 (br m, 1H), 5.68 (s, 1H), 5.44 (m, 1H), 4.08 (d, *J* = 7.0 Hz, 1H), 3.20 (ddd, *J* = 13.6, 7.8, 4.8 Hz, 1H), 3.10 (ddd, *J* = 14.1, 8.9, 5.3 Hz, 1H), 2.76 (br s, 1H), 2.47 (td, *J* = 13.4, 4.3 Hz, 1H), 2.35 (dd, *J* = 15.0, 8.6 Hz, 1H), 2.22 - 2.05 (m, 5H), 2.04 - 1.93 (m, 3H), 1.63 (s, 3H), 1.58 (m, 1H), 1.40 (dd, *J* = 11.6, 8.5 Hz, 1H), 1.16 (s, 3H), 1.14 (m, 1H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 170.4, 160.6, 134.0, 131.2, 120.1, 119.4, 67.5, 53.9, 45.1, 44.5, 43.3, 37.0, 35.8, 34.4, 33.2, 24.1, 22.4, 20.9, 12.1.

**HRMS(ESI):** *m/z* calc. for $C_{19}H_{27}N_2O_2$ $[M+H]^+$: 315.2073, found: 315.2072.

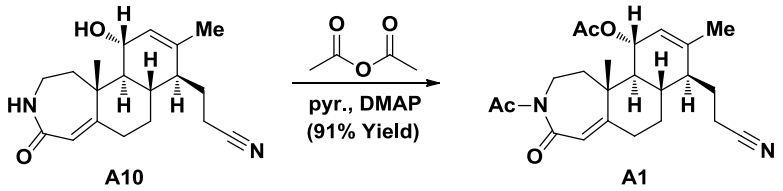



**$^{1}$H NMR** ($CDCl_3$, 500 MHz): δ 7.08 (s, 1H), 5.81 (dt, *J* = 6.4, 1.6 Hz, 1H), 5.63 (s, 1H), 4.22 (dd, *J* = 6.5, 2.4 Hz, 1H), 3.27 (ddd, *J* = 13.6, 9.0, 4.2 Hz, 1H), 3.15 (dt, *J* = 14.5, 7.1 Hz, 1H), 2.57 (td, *J* = 13.5, 4.5 Hz, 1H), 2.38 (ddd, *J* = 17.2, 10.0, 5.8 Hz, 1H), 2.28 - 1.82 (m, 9H), 1.63 (s, 3H), 1.33 (s, 3H), 1.26 (dd, *J* = 12.2, 2.5 Hz, 1H), 1.21 - 1.08 (m, 1H).

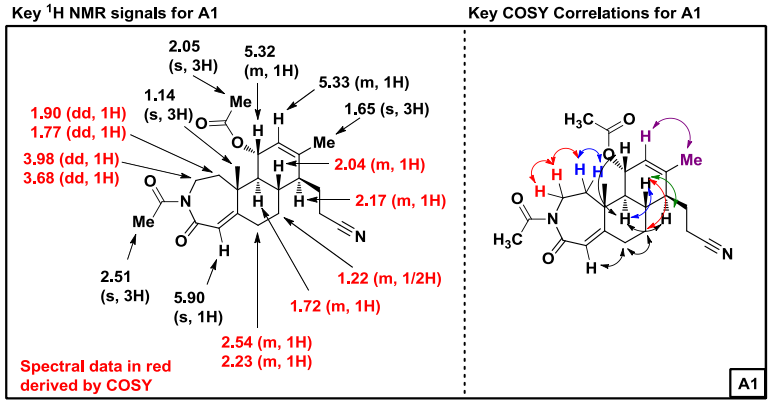
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 170.4, 161.0, 137.7, 128.7, 120.6, 118.0, 63.7, 51.3, 46.1, 44.8, 42.2, 36.6, 35.8, 35.1, 29.4, 25.4, 24.3, 21.2, 12.5.

**HRMS(ESI):** *m/z* calc. for $C_{19}H_{27}N_2O_2$ $[M+H]^+$: 315.2073, found: 315.2073.

**Melting point:** 55-57 °C.




**Procedure:** Alcohol **A10** (41.9 mg, 0.133 mmol) was taken up in anhydrous pyridine (500 µL) and catalytic 4-(dimethylamino)-pyridine (2 mg, 0.016 mmol) was added. After 2 minutes of stirring at room temperature, all solids were completely dissolved. Acetic anhydride (500 µL, 5.29 mmol) was then added to the stirring solution and allowed to run overnight at room temperature. After 25 hours, the reaction was quenched with a saturated solution of sodium bicarbonate and extracted with dichloromethane (3x). The organic layer was then washed with a 5% solution of aqueous hydrochloric acid followed by brine (1x each). The organic layer was then collected, dried with magnesium sulfate and concentrated under reduced pressure. The desired target compound **A1** was purified via flash chromatography using 1:1 hexanes/ethyl acetate to yield 48.5 mg (91% yield) as a white foam.

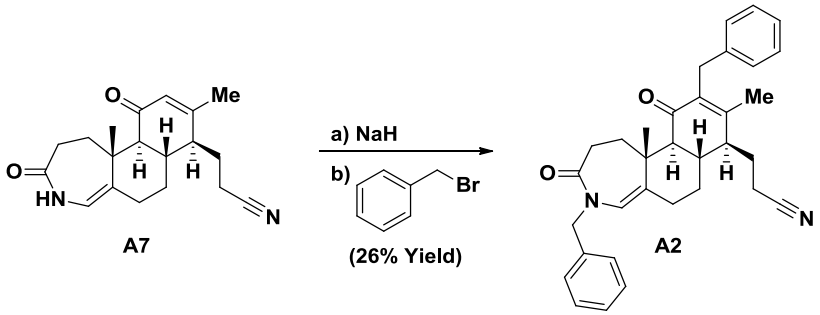



**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 5.90 (s, 1H), 5.33 (m, 1H), 5.32 (m, 1H), 3.98 (dd, *J* = 15.0, 8.4 Hz, 1H), 3.68 (dd, *J* = 14.9, 8.5 Hz, 1H), 2.53 - 2.47 (m, 1H), 2.51 (s, 3H), 2.29 - 2.06 (m, 4H), 2.05 (s, 3H), 2.02 (m, 3H), 1.90 (dd, *J* = 15.4, 8.7 Hz, 1H), 1.77 (dd, *J* = 15.0, 8.0 Hz, 1H), 1.68 (m, 2H), 1.65 (s, 3H), 1.22 (m, 1H), 1.14 (s, 3H).

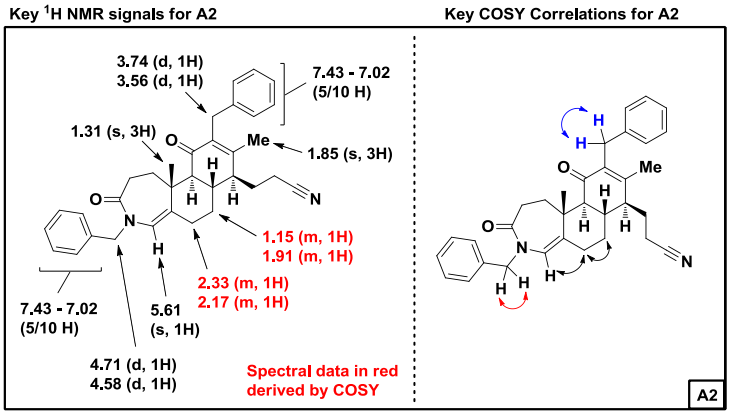
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 172.6, 170.6, 168.7, 159.8, 136.4, 126.1, 121.1, 119.9, 70.2, 49.7, 44.5, 44.1, 41.1, 36.4, 35.1, 34.2, 32.9, 27.7, 24.1, 21.9, 21.8, 20.8, 12.2.

**HRMS(ESI):** *m/z* calc. for $C_{23}H_{31}N_2O_4$ $[M+H]^+$: 399.2284, found: 399.2288.

**Melting point:** 57-58 °C.



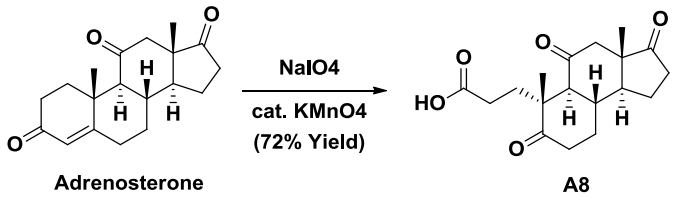

**Procedure:** Enamide **A7** (77.0 mg, 0.246 mmol dissolved in 0.8 mL tetrahydrofuran) was added dropwise to a stirring suspension of sodium hydride (50 mg, 0.986 mmol) in tetrahydrofuran (1.2 mL) at 0 °C. The resulting mixture was allowed to stir for 30 minutes before benzyl bromide (59 µL, 0.493 mmol) was added to the reaction. The reaction was allowed to stir at 0 °C for an additional 20 minutes before the ice bath was removed and the reaction stirred at room temperature for 16 hours. Upon completion of the reaction (monitored by TLC) a saturated solution of ammonia chloride was added to quench the reaction and ethyl acetate was used to extract the product. The ethyl acetate layer was then washed with brine (2x), dried with magnesium sulfate and concentrated under reduced pressure. The crude material was purified by column chromatography using 10:1 to 2:1 hexanes/ethyl acetate to afford 27.4 mg enamide **A2** (26% yield) as a white foam.



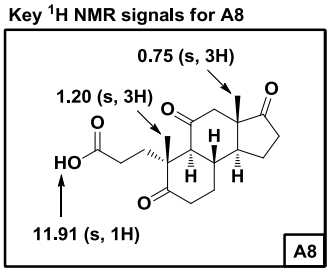

**$^{1}$H NMR** ($CDCl_3$, 500 MHz): δ 7.43 - 7.13 (m, 8H), 7.12 - 7.02 (m, 2H), 5.61 (s, 1H), 4.71 (d, *J* = 15.0 Hz, 1H), 4.58 (d, *J* = 15.0 Hz, 1H), 3.74 (d, *J* = 14.9 Hz, 1H), 3.56 (d, *J* = 14.9 Hz, 1H), 2.58 - 2.42 (m, 3H), 2.39 - 2.22 (m, 2H), 2.21 - 1.83 (m, 9H), 1.85 (s, 3H), 1.31 (s, 3H), 1.15 (m, 1H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 198.6, 174.8, 149.3, 140.0, 139.2, 137.7, 130.9, 128.8 (2), 128.7 (2), 128.2 (2), 127.8 (2), 127.5, 126.3, 121.6, 119.6, 56.3, 51.3, 47.5, 41.2, 35.4, 34.3, 34.0, 32.5, 32.4, 32.2, 25.6, 21.1, 18.5, 12.7.

**HRMS(ESI):** *m/z* calc. for $C_{33}H_{37}N_2O_2$ $[M+H]^+$: 493.2855, found: 493.2859.



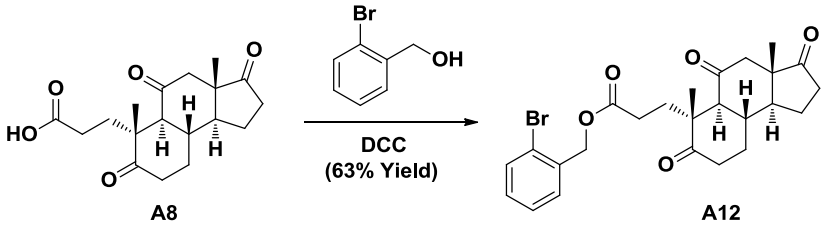

**Procedure:** Adrenosterone (2.29 g, 7.61 mmol) was dissolved in isopropanol (30 mL) and sodium carbonate (914 mg, 8.62 mmol) was added to the resulting solution. The reaction mixture was heated to reflux. A solution of sodium periodate (9.14 g, 42.7 mmol) and catalytic potassium permanganate (69 mg, 0.44 mmol) in water (25 mL) was preheated at 75 °C and added to the reaction mixture dropwise using a slow addition funnel over a 30 minute period. The slow addition funnel was then removed and a reflux condenser was placed on the reaction flask. The reaction was allowed to stir for an additional 2.5 hours before being cooled to room temperature. The reaction was filtered and the remaining solids were washed with water. The isopropanol was then removed under reduced pressure and the remaining aqueous solution was acidified with concentrated hydrochloric acid to pH 2. This aqueous solution was extracted with dichloromethane (3x). The organic layers were collected, dried using magnesium sulfate and concentrated under reduced pressure to give 1.75 grams (72% yield) of the desired acid **A8** as a white foam.




**$^{1}$H NMR** ($d_6$-DMSO, 500 MHz): δ 11.91 (s, 1H), 2.65 (td, *J* = 14.4, 6.4 Hz, 1H), 2.56 - 2.45 (m, 4H), 2.30 - 1.89 (m, 10H), 1.64 (m, 1H), 1.43 (dq, *J* = 13.5, 4.5 Hz, 1H), 1.20 (s, 3H), 0.75 (s, 3H).

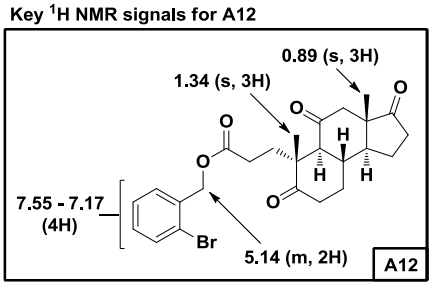
**$^{13}$C NMR** ($d_6$-DMSO, 125 MHz): δ 217.0, 212.1, 208.2, 174.6, 55.9, 49.9, 49.5, 49.1, 47.9, 36.8, 35.7, 34.6, 29.5, 28.9, 28.7, 21.1, 20.1, 14.4.

**HRMS(ESI):** *m/z* calc. for $C_{18}H_{24}O_5Na$ $[M+Na]^+$: 343.1521, found: 343.1519.




**Procedure:** Acid **A8** (215 mg, 0.672 mmol) was dissolved in anhydrous dichloromethane (7 mL) and cooled to 0 °C before 2-bromobenzyl alcohol (126 mg, 0.672 mmol) was added. *N,N'*-Dicyclohexylcarbodiimide (125 mg, 0.605 mmol) and 4-dimethylaminopyridine (8 mg, 0.067 mmol)

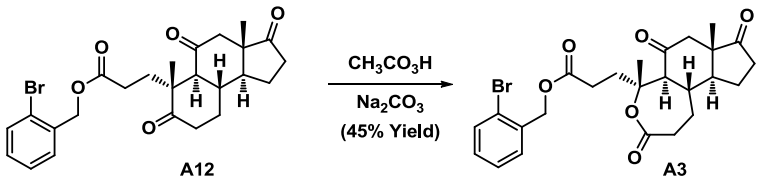
were added to the reaction which was allowed to warm to room temperature and stirred for 21 hours. The reaction contents were then directly passed through a half-inch plug of silica gel eluting with ethyl acetate. The product was further purified by flash chromatography by using 5:1 to 1:1 hexanes/ethyl acetate to give 208.3 mg ester **A12** (63% yield) as a white amorphous solid.




**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.55 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.41 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.31 (td, *J* = 7.5, 1.2 Hz, 1H), 7.17 (td, *J* = 7.7, 1.8 Hz, 1H), 5.14 (m, 2H), 2.66 - 2.53 (m, 2H), 2.48 (d, *J* = 13.2 Hz, 1H), 2.42 - 2.10 (m, 11H), 1.90 (ddd, *J* = 12.5, 10.5, 5.9 Hz, 1H), 1.71 (tt, *J* = 12.5, 9.2 Hz, 1H), 1.53 - 1.36 (m, 1H), 1.34 (s, 3H), 0.89 (s, 3H).

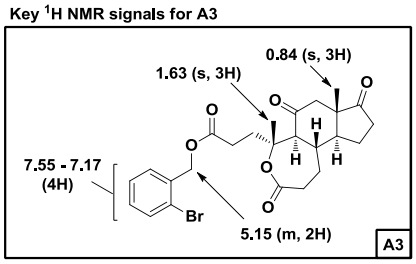
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 216.7, 212.0, 207.2, 173.4, 135.6, 133.0, 130.2, 129.9, 127.7, 123.6, 66.0, 57.7, 50.6, 50.1, 50.0, 49.9, 37.2, 36.1, 35.7, 30.3, 29.9, 28.8, 21.8, 20.5, 15.0.

**HRMS(ESI):** *m/z* calc. for $C_{25}H_{30}O_5Br$ $[M+H]^+$: 489.1277, found: 489.1274.




**Procedure: A12** (100.8 mg, 0.206 mmol) was dissolved in anhydrous dichloromethane (2 mL). Then sodium carbonate (122 mg, 1.15 mmol) was added to the solution and cooled to 0 °C. After cooling, a solution of peracetic acid (147 μL of a 32% by weight peracetic acid solution in dilute acetic acid, 0.618 mmol) was added dropwise to the reaction mixture. The reaction slowly warmed to room temperature over several hours and was quenched with a saturated solution sodium bicarbonate of after 19.5 hours. The reaction was then transferred to a separatory funnel and extracted with dichloromethane (3x). The organic layers were collected, dried with magnesium sulfate and concentrated under reduced pressure to give the crude product. The desired lactone was purified via column chromatography using 9:1 to 3:5 hexanes/ethyl acetate to give 46.8 mg (45% yield) **A3** as a white foam in addition to 14.8 mg (15% yield) of starting material **A12**.

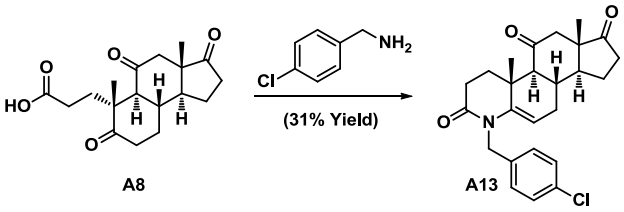
Key $^1$H NMR signals for A3




**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.55 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.39 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.30 (td, *J* = 7.5, 1.2 Hz, 1H), 7.17 (td, *J* = 7.7, 1.8 Hz, 1H), 5.15 (m, 2H), 2.80 (ddd, *J* = 16.4, 6.9, 1.9 Hz, 1H), 2.68 - 2.40 (m, 7H), 2.34 - 2.18 (m, 3H), 2.16 - 2.06 (m, 2H), 2.05 - 1.92 (m, 2H), 1.70 - 1.61 (m, 1H), 1.63 (s, 3H), 1.58 - 1.44 (m, 1H), 0.84 (s, 3H).

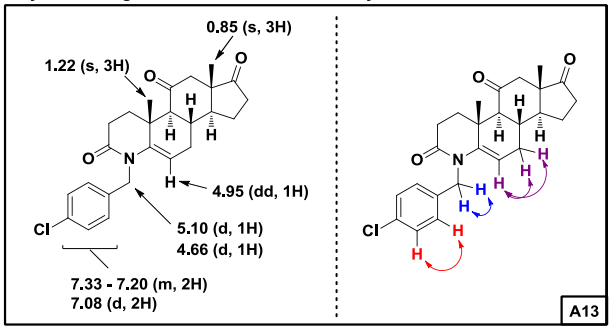
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 215.8, 207.6, 173.9, 173.0, 135.4, 133.0, 130.3, 129.9, 127.7, 123.7, 83.7, 66.1, 62.6, 50.7, 50.4, 50.3, 39.7, 36.7, 35.7, 35.4, 28.6, 27.1, 22.2, 22.0, 14.6.

**HRMS(ESI):** *m/z* calc. for $C_{25}H_{30}O_6Br$ $[M+H]^+$: 505.1226, found: 505.1223.




**Procedure:** Acid **A8** (235.5 mg, 0.739 mmol) was dissolved in ethanol (2 mL) in a sealed tube and 4-chlorobenzylamine (447 µL, 3.678 mmol) was added the solution. The tube was sealed and heated to 125 °C for 6.5 hours before being cooled to room temperature (TLC indicated that the starting material was consumed at this time). A 5% solution of aqueous hydrochloric acid solution was added to the reaction vessel and allowed to stir for 5 minutes before being transferred to a separatory funnel where dichloromethane was used to extract the mixture (3x). The organic layers were combined, dried with magnesium sulfate and concentrated under reduced pressure. The product was purified by flash column chromatography using 9:1 to 3:2 hexanes/ethyl acetate to yield 97.9 mg enamide **A13** (31% yield) as a white foam.

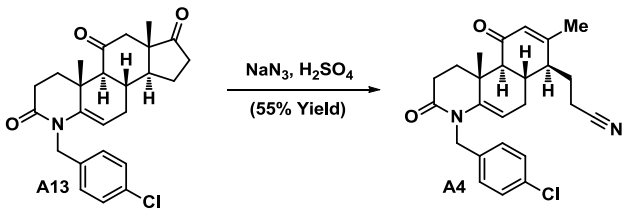
Key $^1$H NMR signals for A13 | Key COSY Correlations for A13



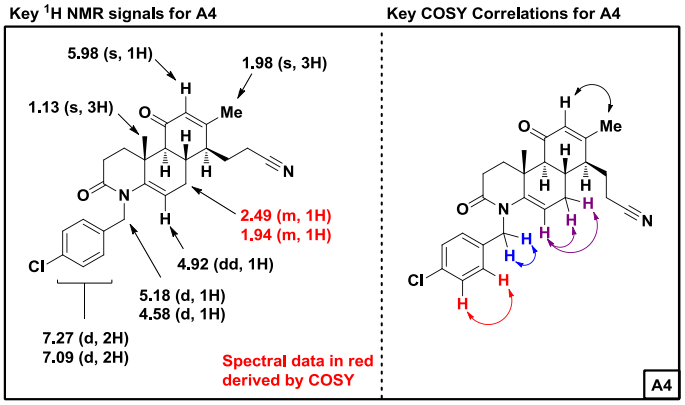
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.33 - 7.20 (m, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 5.10 (d, *J* = 15.9 Hz, 1H), 4.95 (dd, *J* = 5.8, 2.0 Hz, 1H), 4.66 (d, *J* = 15.8 Hz, 1H), 2.80 - 2.45 (m, 5H), 2.44 - 2.15 (m, 3H), 2.10 (ddd, *J* = 13.6, 8.7, 5.5 Hz, 1H), 2.06 - 1.83 (m, 4H), 1.67 (tt, *J* = 12.3, 9.3 Hz, 1H), 1.54 - 1.37 (m, 1H), 1.22 (s, 3H), 0.85 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 217.3, 207.9, 169.2, 143.7, 136.4, 132.8, 128.9 (2), 128.2(2), 104.0, 59.8, 50.5, 50.1, 49.9, 47.5, 36.3, 36.0, 32.1, 30.7, 30.4, 29.0, 21.9, 18.1, 15.0.

**HRMS(ESI):** *m/z* calc. for $C_{25}H_{29}NO_3Cl$ $[M+H]^+$: 426.1836, found: 426.1832.



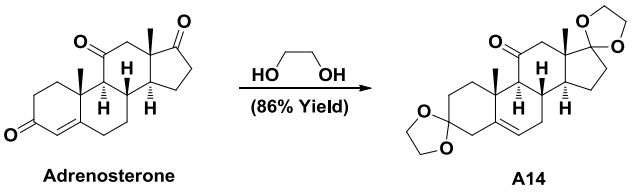

**Procedure: A13** (24.2 mg, 0.057 mmol) was dissolved in concentrated sulfuric acid (400 µL) at room temperature and cooled to 0 °C. Sodium azide (7.4 mg, 0.114 mmol) was then added to the solution and the reaction was allowed to stir for 1 hour at 0 °C. After this time, ice was added to quench the reaction and the solution was allowed to stir for an additional 3 minutes before being transferred to a separatory funnel and partitioned between brine and dichloromethane. Dichloromethane was used to extract the desired product (3x). The organic layers were combined, dried with magnesium sulfate and concentrated under reduced pressure to give a crude white foam. The product was purified via column chromatography using 1:1 to 3:1 ethyl acetate/hexanes to afford 13.3 mg of enamide **A4** (55% yield) as a white foam.




**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.27 (d, *J* = 7.6 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 5.98 (s, 1H), 5.18 (d, *J* = 15.9 Hz, 1H), 4.92 (dd, *J* = 5.5, 2.0 Hz, 1H), 4.58 (d, *J* = 15.9 Hz, 1H), 3.08 (ddd, *J* = 13.3, 6.6, 1.9 Hz, 1H), 2.80 - 2.59 (m, 2H), 2.55 - 2.42 (m, 1H), 2.39 - 2.27 (m, 2H), 2.26 - 2.02 (m, 4H), 2.06 - 1.89 (m, 2H), 1.98 (s, 3H), 1.58 (td, *J* = 13.1, 6.4 Hz, 1H), 1.13 (s, 3H).

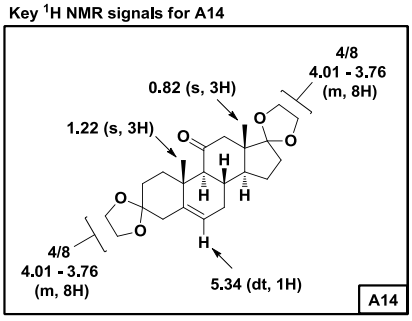
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 197.6, 169.4, 157.6, 143.4, 136.4, 132.8, 131.5, 129.0, 128.1, 119.2, 103.1, 54.6, 47.6, 44.9, 36.3, 32.1, 31.7, 30.8, 29.0, 24.4, 21.8, 17.9, 13.0.

**HRMS(ESI):** *m/z* calc. for $C_{25}H_{28}N_2O_2Cl$ $[M+H]^+$: 423.1839, found: 423.1838.




Adrenosterone A14

**Procedure:** Adrenosterone (2.95 g, 9.83 mmol) was dissolved in toluene (250 mL). A catalytic amount of *p*-toluenesulfonic acid (129 mg, 0.678 mmol) was added to the reaction solution followed by ethylene glycol (25 mL). A Dean-Stark trap was fitted to the reaction flask and the reaction was heated at 145 °C for 6 hours. At this time, the reaction was cooled to room temperature, concentrated under reduced pressure to a third of its original volume and transferred to a separatory funnel. A saturated solution of sodium bicarbonate was added to the separatory funnel and the crude product was extracted with chloroform (3x). The organic layers were then combined, dried with magnesium sulfate and concentrated under reduced pressure to give a crude solid. This product was then purified via recrystallization using petroleum ether and ether to give 3.29 g (86% yield) of the desired ketone **A14** as a white crystalline solid. **A14** has been previously described in the literature.[1]

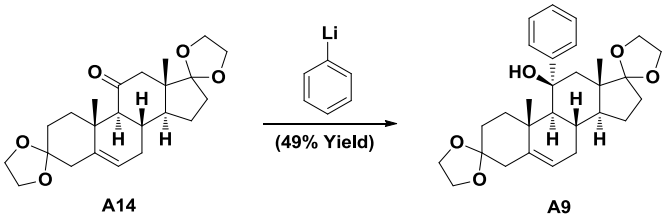



**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 5.34 (dt, *J* = 5.4, 2.0 Hz, 1H), 4.01 - 3.89 (m, 6H), 3.85 - 3.76 (m, 2H), 2.68 - 2.53 (m, 3H), 2.17 - 1.75 (m, 11H), 1.64 (dq, *J* = 13.8, 3.5 Hz, 1H), 1.43 - 1.29 (m, 1H), 1.25 - 1.19 (m, 1H), 1.22 (s, 3H), 0.82 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 211.3, 141.4, 120.8, 118.2, 109.3, 65.6, 64.8, 64.6, 64.4, 60.6, 50.4, 49.1, 48.8, 41.8, 37.3, 35.3, 34.6, 34.1, 32.1, 31.0, 22.8, 18.2, 15.1.

**HRMS(ESI):** *m/z* calc. for $C_{23}H_{33}O_5$ $[M+H]^+$: 389.2328, found: 389.2327.

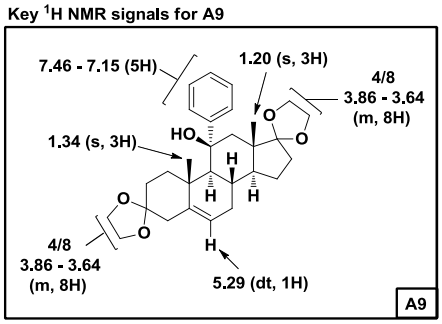
**Melting point:** 180-182 °C.




A14 A9

**Procedure:** Phenyllithium (3.75 mL of a 1.8 M solution in dibutyl ether, 6.76 mmol) was slowly added to a stirring solution of **A14** (877 mg, 2.25 mmol) in anhydrous toluene at room temperature. The reaction continued to stir for an additional two hours before being cooled to 0 °C and slowly quenched with a saturated solution of ammonium chloride. The contents of the reaction were then transferred to a separatory funnel and extracted with dichloromethane (3x). The organic layers were then combined, dried with magnesium sulfate and concentrated under reduced pressure to give a crude white foam. This reaction does not go to completion and has been previously described.[2] The desired alcohol **A9** and starting ketone **A14** are readily separated via column chromatography using 7:1 to 2:1 hexanes/ethyl acetate to give 514 mg of alcohol **A9** (49% yield) as a white foam and 229 mg of ketone **A14** (26% recovery).

**Note:** Our spectra (room temperature) and melting point obtained for **A9** were identical to previously published values. Here we report $^{1}$H NMR and $^{13}$C NMR spectra for **A9** at 50 °C. The NMR sample we report was highly concentrated and $CDCl_3$ is buried under the multiplet at 7.30 - 7.22 ppm.

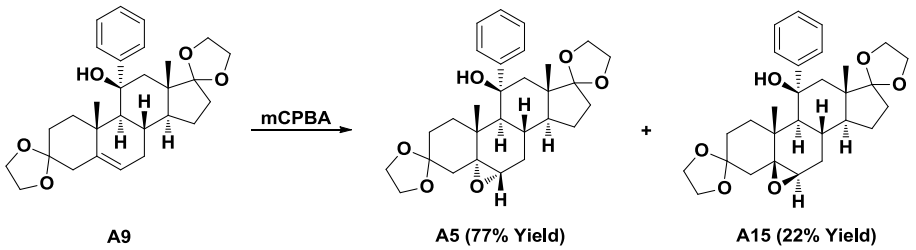



**$^{1}$H NMR** ($CDCl_3$, 500 MHz, 50 °C): δ 7.46 (m, 2H), 7.30 - 7.22 (m, 2H), 7.15 (td, *J* = 7.2, 1.3 Hz, 1H), 5.29 (dt, *J* = 4.6, 2.1 Hz, 1H), 3.86 - 3.64 (m, 8H), 2.51 (dq, *J* = 14.8, 3.0 Hz, 1H), 2.23 (d, *J* = 14.5 Hz, 1H), 2.18 (m, 1H), 2.14 - 1.96 (m, 4H), 1.93 - 1.76 (m, 3H), 1.68 (td, *J* = 11.5, 6.1 Hz, 1H), 1.57 (s, 1H), 1.50 (td, *J* = 14.0, 4.5 Hz, 1H), 1.44 - 1.17 (m, 2H), 1.34 (s, 3H buried in multiplet), 1.26 - 1.17 (m, 1H) 1.20 (s, 3H buried in multiplet) 0.98 (dt, *J* = 13.6, 3.8 Hz, 1H), 0.67 (td, *J* = 13.9, 4.1 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz, 50 °C): δ 153.0, 141.9, 128.0, 126.0, 125.2, 121.2, 119.8, 109.0, 79.8, 65.2, 64.7, 64.5, 64.2, 57.2, 52.9, 51.7, 45.3, 41.7, 40.7, 37.9, 34.5, 32.9, 31.5, 31.2, 23.7, 22.2, 16.3.

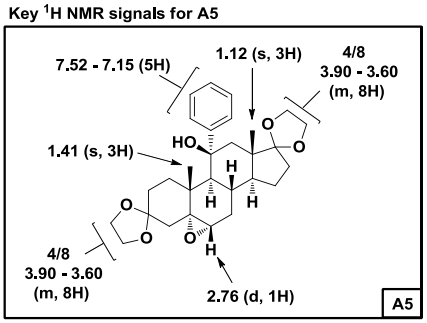
**HRMS(ESI):** *m/z* calc. for $C_{29}H_{39}O_5$ $[M+H]^+$: 467.2797, found: 467.2790.

**Melting point:** 181-182 °C.



**Procedure:** *m*-Chloroperoxybenzoic acid (112 mg, 0.449 mmol calculated at 77% purity, dissolved in 1 mL of anhydrous dichloromethane) was added at room temperature to stirring solution of **A9** (258.6 mg, 0.203 mmol) in anhydrous dichloromethane (2.6 mL). The reaction continued to stir for 40 minutes before a saturated solution of sodium bicarbonate was added to quench the reaction. The reaction contents were then extracted three times with dichloromethane. The combined organic layers were then washed once more with a saturated solution of sodium bicarbonate. The organic layer was then collected, dried with magnesium sulfate and concentrated to give a crude mixture. The epoxide diastereomers were then separated via column chromatography using 5:1 to 1:1 hexanes/ethyl acetate to afford 206.1 mg of **A5** (77% yield) as a white solid and 60.1 mg of **A15** (22% yield) as a white solid.

**Note:** The β/α-stereochemistry of steroidal epoxides (at C5-C6) is well studied and routinely assigned based on the chemical shift of the $^{1}$H NMR at C6 (δ = 3.15 - 3.00 ppm corresponds to the β-epoxide; δ = 2.95 - 2.75 ppm corresponds to the α-epoxide).[3-4]

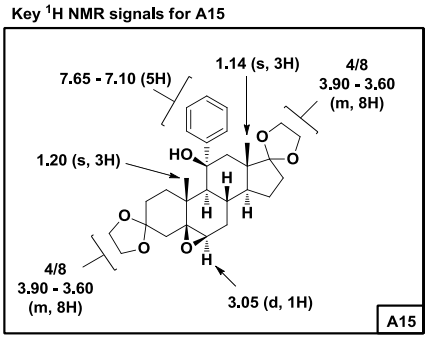



**$^{1}$H NMR** ($CDCl_3$, 500 MHz): δ 7.52 (m, 1H), 7.32 (m, 1H), 7.28 (m, 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 3.90 - 3.71 (m, 6H), 3.70 - 3.60 (m, 2H), 2.76 (d, *J* = 3.7 Hz, 1H), 2.38 (d, *J* = 10.5 Hz, 1H), 2.33 (d, *J* = 14.0 Hz, 1H), 2.14 - 1.95 (m, 4H), 1.84 - 1.68 (m, 3H), 1.66 - 1.56 (m, 2H), 1.47 (s, 1H), 1.41 (s, 3H), 1.36 - 1.32 (m, 2H), 1.22 (d, *J* = 14.6 Hz, 1H), 1.14 - 1.08 (m, 1H), 1.12 (s, 3H), 1.04 (dd, *J* = 14.5, 3.0, 1H), 0.79 (td, *J* = 13.9, 4.2 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 153.0, 128.2, 128.0, 126.6, 125.9, 123.1, 119.4, 108.3, 79.7, 66.0, 65.2, 64.6, 64.6, 64.1, 57.0, 53.1, 51.5, 48.2, 45.4, 39.1, 38.2, 34.2, 33.2, 31.1, 29.3, 29.0, 23.3, 18.7, 16.0.

**HRMS(ESI):** *m/z* calc. for $C_{29}H_{39}O_6$ $[M+H]^+$: 483.2747, found: 483.2746.

**Melting point:** 272-274 °C.

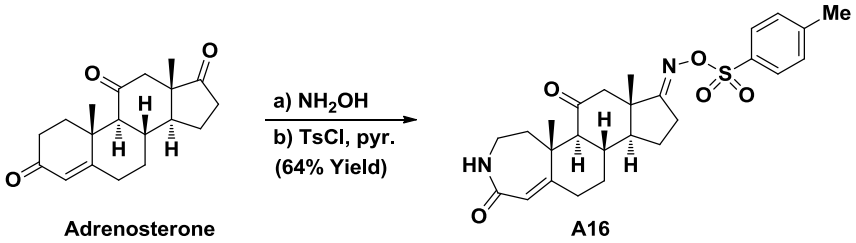



**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.65 (s, 1H), 7.30 - 7.24 (m, 3H), 7.21 - 7.10 (m, 1H), 3.90 - 3.60 (m, 8H), 3.05 (d, *J* = 3.1 Hz, 1H), 2.29 - 2.19 (m, 1H), 2.25 (d, *J* = 13.5 Hz, 1H), 2.16 (dd, *J* = 11.0, 4.0 Hz, 1H), 2.12 (d, *J* = 14.0 Hz, 1H), 2.10 - 1.96 (m, 1H), 1.86 - 1.68 (m, 3H), 1.82 (s, 1H partially buried in multiplet), 1.59 (d, *J* = 11.0 Hz, 1H), 1.57 - 1.47 (m, 2H), 1.48 - 1.09 (m, 3H), 1.31 (d, *J* = 14.0 Hz, 1H buried in multiplet), 1.20 (s, 3H buried in multiplet), 1.14 (s, 3H buried in multiplet), 1.04 (dd, *J* = 13.8, 2.7 Hz, 1H), 0.95 (dt, *J* = 13.7, 4.1 Hz, 1H).

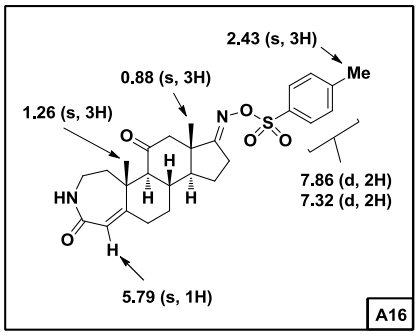
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 150.2, 127.6, 126.3, 124.5, 119.7, 108.9, 79.8, 65.1, 64.7, 64.4, 64.3, 63.8, 62.8, 58.7, 51.7, 51.4, 45.6, 41.8, 38.5, 38.0, 34.4, 31.1, 30.7, 28.8, 23.3, 18.2, 16.8.

**HRMS(ESI):** *m/z* calc. for $C_{29}H_{39}O_6$ $[M+H]^+$: 483.2747, found: 483.2753.

**Melting point:** 182-183 °C.



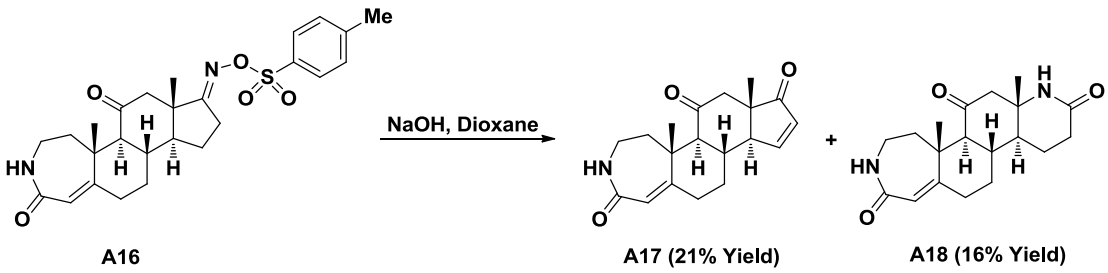

**Procedure:** Adrenosterone (129.6 mg, 0.431 mmol), hydroxylamine hydrochloride (240 mg, 3.451 mmol) and sodium acetate (283 mg, 3.451 mmol) were added to a round bottom flask and dissolved in ethanol (4 mL). The reaction was then refluxed for 2 hours. After this time, the reaction was cooled to room temperature and poured into ice water. Dichloromethane was then used to extract the intermediate oxime (3x). The organic layers were then combined, dried with magnesium sulfate and concentrated. This crude oxime was directly dissolved in pyridine (4 mL) before adding *p*-toluenesulfonyl chloride (164 mg, 0.862 mmol). The reaction was allowed to stir at room temperature for 4 hours before being diluted with ethyl acetate and washed with a 5% aqueous solution of hydrochloric acid followed by brine (1x each). The organic layers were then combined, dried with magnesium sulfate and concentrated. Lactam **A16** was purified by column chromatography using 100:0 to 95:5 dichloromethane/methanol to afford 133.6 mg (64% yield) as a white foam.



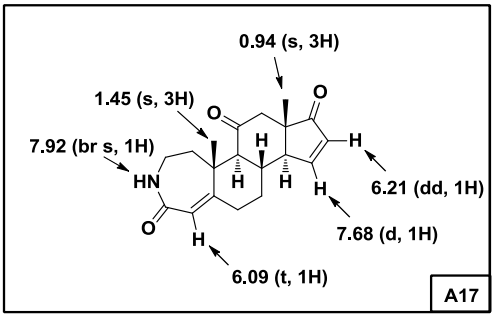

**$^{1}$H NMR** ($CDCl_3$, 500 MHz): δ 7.86 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.79 (s, 1H), 2.96 (dt, *J* = 17.6, 3.8 Hz, 1H), 2.70 - 2.49 (m, 4H), 2.43 (s, 3H), 2.39 - 2.17 (m, 3H), 2.05 - 1.85 (m, 3H), 1.83 - 1.70 (m, 2H), 1.49 (tt, *J* = 12.3, 9.3 Hz, 1H), 1.34 - 1.10 (m, 3H), 1.26 (s, 3H, buried in multiplet), 0.88 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 208.3, 168.2, 163.5, 159.3, 144.9, 133.1, 129.7 (2), 129.0 (2), 116.6, 63.5, 52.8, 52.5, 46.8, 38.0, 36.4, 33.0, 32.2, 31.9, 25.5, 23.1, 21.9, 20.4, 18.3, 17.5.

**HRMS(ESI):** *m/z* calc. for $C_{26}H_{33}N_2O_5S$ $[M+H]^+$: 485.2110, found: 485.2110.



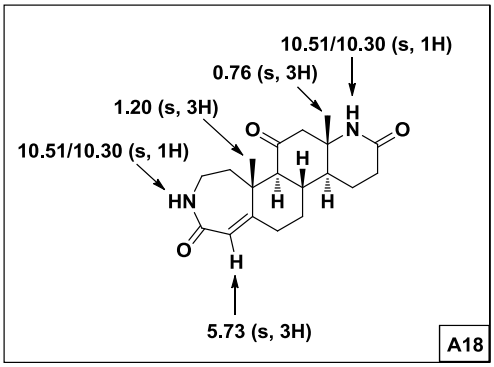

**Procedure:** Lactam **A16** (300 mg, 0.619 mmol) was taken up in a 4:3 water/dioxane solution (18 mL). A 10% NaOH (aq) solution (1.26 mL) was then added and the reaction was heated to 65 °C for 8 hours. The reaction was then cooled to room temperature, quenched with brine and extracted with dichloromethane (3x). The organic layer was collected, dried with magnesium sulfate and concentrated. Enone **A17** and bis-lactam **A18** were separated via column chromatography using 100:0 to 95:5 dichloromethane/methanol to afford 41 mg **A17** (21% yield) as a white solid and 32.4 mg **A18** (16% yield) as a white solid.



**$^{1}$H NMR** ($CDCl_3$, 500 MHz): δ 7.92 (br s, 1H), 7.68 (d, *J* = 10.3 Hz, 1H), 6.21 (dd, *J* = 10.3, 2.0 Hz, 1H), 6.09 (t, *J* = 1.8 Hz, 1H), 2.68 - 2.57 (m, 3H), 2.52 (tdd, *J* = 13.6, 4.9, 1.6 Hz, 1H), 2.48 - 2.37 (m, 2H), 2.20 - 2.12 (m, 1H), 2.06 (td, *J* = 11.3, 3.6 Hz, 1H), 2.03 - 1.94 (m, 2H), 1.77 (ddd, *J* = 12.6, 10.7, 6.1 Hz, 1H), 1.54 (tt, *J* = 12.5, 9.3 Hz, 1H), 1.45 (s, 3H), 1.28 (m, 1H), 0.94 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 207.9, 186.5, 167.8, 166.1, 155.1, 128.0, 125.1, 61.2, 52.5, 52.4, 47.0, 42.6, 36.1, 33.1, 32.3, 25.5, 23.2, 19.1, 18.5.

**HRMS(ESI):** *m/z* calc. for $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.1756, found: 314.1757.

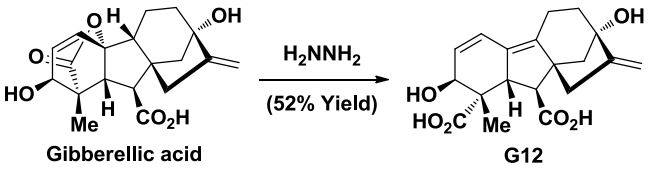



**$^{1}$H NMR** ($d_6$-DMSO, 500 MHz): δ 10.51 (s, 1H), 10.30 (s, 1H), 5.73 (s, 1H), 2.79 (dt, *J* = 16.8, 4.0 Hz, 1H), 2.55 (d, *J* = 6.0 Hz, 1H), 2.52 - 2.38 (m, 4H), 2.36 - 2.17 (m, 3H), 2.06 (d, *J* = 11.0 Hz, 1H), 1.98 (ddd, *J* = 17.0, 14.2, 5.0 Hz, 1H), 1.93 - 1.77 (m, 3H), 1.43 (m, 1H), 1.32 - 1.01 (m, 2H), 1.20 (s, 3H), 0.76 (s, 3H).

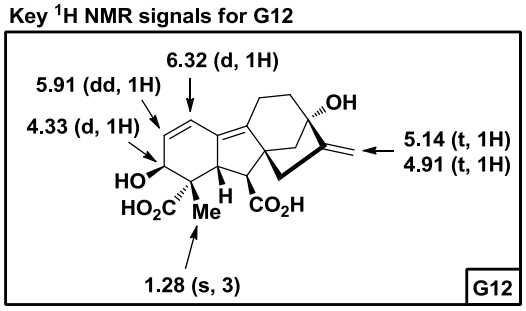
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 208.7, 168.5, 156.8, 153.3, 118.7, 63.9, 52.9, 52.7, 46.8, 38.0, 36.5, 33.5, 32.2, 32.0, 25.7, 23.1, 18.8, 18.3, 17.8.

**HRMS(ESI):** *m/z* calc. for $C_{19}H_{27}N_2O_3$ $[M+H]^+$: 331.2022, found: 331.2022.

## 8.) Gibberellic Acid Derived Compounds: Synthesis and Characterization




**Procedure:** Gibberellic acid (3.99 g, 11.5 mmol) was added to a round bottom flask with stir bar, and suspended in hydrazine monohydrate (18 mL). The reaction refluxed at 110 °C for 30 minutes, after which the reaction was cooled for 5 minutes in an ice bath. Following cooling, the reaction was diluted in ice water and acidified to pH 3 with concentrated hydrochloric acid. The aqueous phases were extracted with ethyl acetate (5x), and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. White solid precipitated out during the concentration process to afford known compound **G12** as a white solid (2.06 g, 51.6% yield).[5]

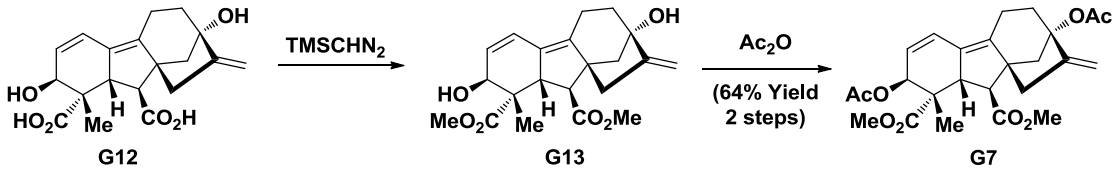



**$^1$H NMR** ($d_6$-acetone, 500 MHz): δ 6.32 (d, *J* = 9.7 Hz, 1H), 5.91 (dd, *J* = 9.7, 5.5 Hz, 1H), 5.14 (t, *J* = 2.4 Hz, 1H), 4.91 (t, *J* = 2.4 Hz, 1H), 4.33 (d, *J* = 5.6 Hz, 1H), 3.98 (s, 1H), 3.72 (d, *J* = 8.5 Hz, 1H), 3.57 (dd, *J* = 8.5, 4.4 Hz, 1H), 2.61 (dd, *J* = 16.1, 6.2 Hz, 1H), 2.51 (dt, *J* = 16.5, 3.0 Hz, 1H), 2.20 (t, *J* = 3.5 Hz, 1H), 2.18 (dd, *J* = 9.0, 2.5 Hz, 1H), 2.11 - 1.98 (m, 2H), 1.79 - 1.63 (m, 3H), 1.28 (s, 3H).

**$^{13}$C NMR** ($d_6$-acetone, 125 MHz): δ 176.4, 175.9, 156.2, 139.8, 130.5, 128.2, 124.1, 105.7, 79.2, 69.8, 56.4, 53.1, 50.0, 49.8, 48.5, 40.7, 40.0, 21.2, 20.5.

**HRMS(ESI)**: *m/z* calc. for $C_{19}H_{22}O_6Na$ $[M+Na]^+$: 369.1314, found: 369.1315.

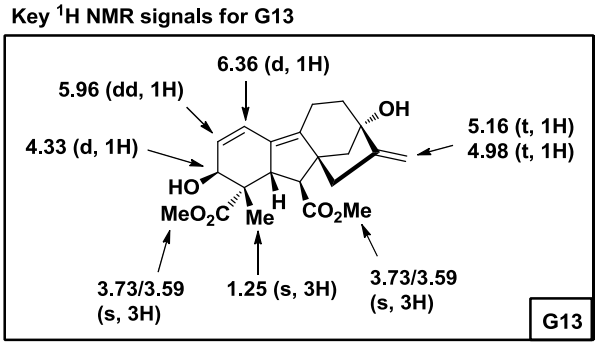
**Melting point:** 189-191 °C.




**Procedure:** In an oven-dried round bottom flask with stir bar under argon, **G12** (521 mg, 1.50 mmol) was dissolved in toluene (18 mL) and methanol (3 mL). (Trimethylsilyl)diazomethane (2 M in hexanes, 1.8 mL, 3.60 mmol) was added dropwise at room temperature, and the reaction was stirred for 1 hour at room

temperature. The reaction was concentrated, and then dissolved in pyridine (9 mL). Acetic anhydride (1.5 mL, 15.9 mmol) and 4-(dimethylamino)-pyridine (53.1 mg, 0.43 mmol) were added, and the reaction was allowed to stir overnight at room temperature. After 14 hours, the reaction was quenched with chilled hydrochloric acid to pH 3. The aqueous phase was extracted with ethyl acetate (4x), and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. Purification by flash silica chromatography (5:1 hexanes/ethyl acetate) afforded **G7** as a white solid (445 mg, 65% yield).

**Note: G13** could be isolated and purified following esterification with (trimethylsilyl)diazomethane by flash silica chromatography (3:1 hexanes/ethyl acetate) to afford pure product.

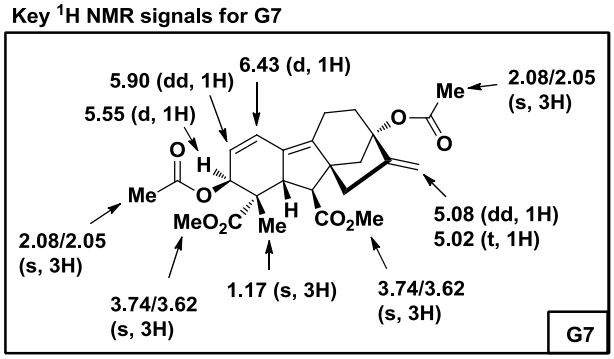



**$^{1}$H NMR** ($CDCl_3$, 500 MHz): δ 6.36 (d, *J* = 9.5 Hz, 1H), 5.96 (dd, *J* = 9.7, 5.6 Hz, 1H), 5.16 (t, *J* = 2.5 Hz, 1H), 4.98 (t, *J* = 2.2 Hz, 1H), 4.33 (d, *J* = 5.5 Hz, 1H), 3.73 (s, 3H), 3.63 (d, *J* = 8.4 Hz, 1H), 3.59 (s, 3H), 3.49 (dd, *J* = 8.4, 4.4 Hz, 1H), 2.61 (dd, *J* = 16.3, 6.4 Hz, 1H), 2.30 (dt, *J* = 16.5, 2.8 Hz, 1H), 2.24 (dq, *J* = 16.5, 2.1 Hz, 1H), 2.19 (dd, *J* = 10.4, 2.8 Hz, 1H), 2.13 - 2.02 (m, 1H), 1.84 (td, *J* = 11.9, 6.4 Hz, 1H), 1.77 - 1.58 (br s, partially buried, 1H), 1.76 (dd, *J* = 10.4, 2.4 Hz, 1H), 1.74 - 1.70 (m, 2H), 1.25 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 175.1, 174.9, 154.5, 140.3, 128.6, 126.8, 124.8, 106.4, 79.3, 69.9, 56.3, 52.6, 52.0, 51.8, 49.7, 49.3, 48.1, 39.4, 39.2, 20.9, 19.9.

**HRMS(ESI)**: *m/z* calc. for $C_{21}H_{26}O_6Na$ $[M+Na]^+$: 397.1627, found: 397.1629.

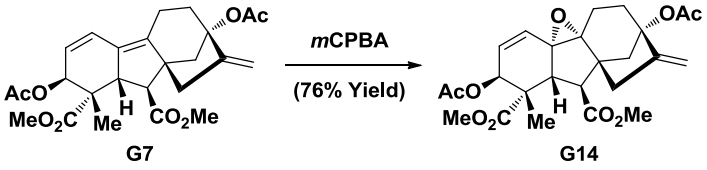
**Melting point:** 81-82 °C.



**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 6.43 (d, *J* = 9.6 Hz, 1H), 5.90 (dd, *J* = 9.6, 5.6 Hz, 1H), 5.55 (d, *J* = 5.6 Hz, 1H), 5.08 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.02 (t, *J* = 2.0 Hz, 1H), 3.74 (s, 3H), 3.70 (d, *J* = 8.6 Hz, 1H), 3.64 - 3.59 (m, 1H), 3.62 (s, 3H), 2.69 (dd, *J* = 10.5, 2.9 Hz, 1H), 2.62 (dd, *J* = 16.2, 6.3 Hz, 1H), 2.39 - 2.29 (m, 2H), 2.25 (dd, *J* = 16.1, 2.1 Hz, 1H), 2.21 - 2.11 (m, 2H), 2.08 (s, 3H), 2.05 (s, 3H), 1.70 (ddd, *J* = 10.8, 7.1, 2.6 Hz, 1H), 1.17 (s, 3H).

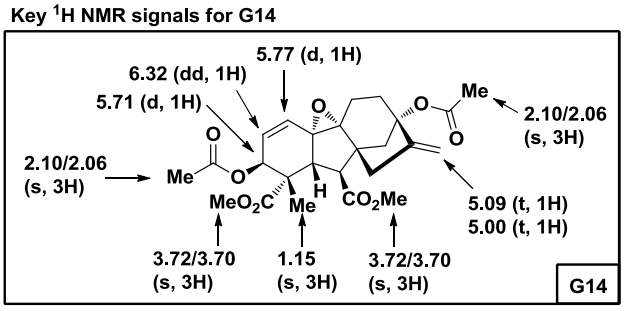
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 175.0, 173.8, 170.6, 169.9, 150.6, 140.6, 126.8, 126.2, 125.3, 106.7, 85.9, 71.2, 57.2, 52.0, 52.0, 49.0, 48.9, 48.5, 47.9, 38.9, 36.9, 22.3, 21.3, 20.7, 19.9.

**HRMS(ESI)**: *m/z* calc. for $C_{25}H_{30}O_8Na$ $[M+Na]^+$: 481.1838, found: 481.1837.




**Procedure:** In an oven-dried vial with stir bar, **G7** (120 mg, 0.26 mmol) was dissolved in dichloromethane (10.5 mL). Sodium bicarbonate (89 mg, 1.06 mmol) and *m*-chloroperoxybenzoic acid (69 mg, 0.31 mmol calculated at 77% purity) were added sequentially, and the reaction was allowed to stir at room temperature for 7 hours. The reaction was washed sequentially with saturated aqueous sodium thiosulfate, saturated aqueous sodium bicarbonate, and brine, dried over magnesium sulfate, and concentrated. Flash silica chromatography (3:1 hexanes/ethyl acetate) afforded **G14** as a white solid (95 mg, 76% yield).

**Note:** Although the absolute stereochemistry could not be directly determined for this compound, the product of the oxidation and allylic rearrangement of **G14** following treatment with PCC afforded **G15**, whose stereochemistry could be assigned.



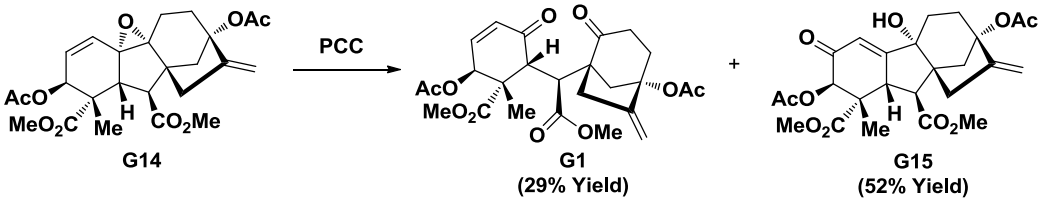

**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 6.32 (dd, *J* = 9.8, 5.1 Hz, 1H), 5.77 (d, *J* = 9.0 Hz, 1H), 5.71 (d, *J* = 5.6 Hz, 1H), 5.09 (t, *J* = 2.6 Hz, 1H), 5.00 (t, *J* = 2.3 Hz, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.06 (d, *J* = 10.5 Hz, 1H), 2.94 (d, *J* = 10.5 Hz, 1H), 2.56 (tt, *J* = 12.5, 6.1 Hz, 1H), 2.47 (dd, *J* = 10.8, 1.6 Hz, 1H), 2.44 (dd, *J* = 10.8, 2.3 Hz, 1H), 2.25 (dd, *J* = 17.2, 2.4 Hz, 1H), 2.17 (t, *J* = 2.4 Hz, 1H), 2.14 - 2.07 (m, 1H buried under methyl), 2.10 (s, 3H), 2.06 (s, 3H), 1.64 (td, *J* = 14.3, 12.3, 5.9 Hz, 2H), 1.15 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 173.7, 173.4, 170.3, 169.7, 149.3, 134.7, 125.2, 106.7, 85.8, 72.1, 70.4, 65.7, 52.3, 52.2, 51.4, 47.6, 44.5, 44.3, 41.9, 35.4, 35.0, 22.1, 22.1, 21.2, 19.5.

**HRMS(ESI)**: *m/z* calc. for $C_{25}H_{31}O_9$ $[M+H]^+$: 475.1968, found: 475.1971.

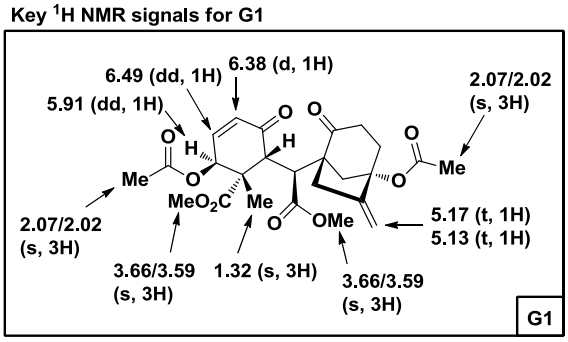
**HRMS(ESI)**: *m/z* calc. for $C_{25}H_{30}O_9Na$ $[M+Na]^+$: 497.1788, found: 497.1790.

**Melting point:** 62-64 °C.




**Procedure:** In an oven-dried round bottom flask with stir bar, dissolved **G14** (97.6 mg, 0.21 mmol) in dichloromethane (7 mL) and added powdered molecular sieves (160 mg) followed by pyridinium chlorochromate (97.5 mg, 0.45 mmol). The reaction was refluxed at 45 °C for 2.5 hours, and was then diluted with ether and filtered over a silica plug to remove the chromium. Purification by flash silica chromatography (4:1 to 3:1 hexanes/ethyl acetate) afforded **G1** as a white solid (29.0 mg, 29% yield in 90% purity determined by $^1$H NMR integrations) and **G15**, which is the product of allylic oxidation and rearrangement, was also recovered as a pure white solid (52.8 mg, 52%).

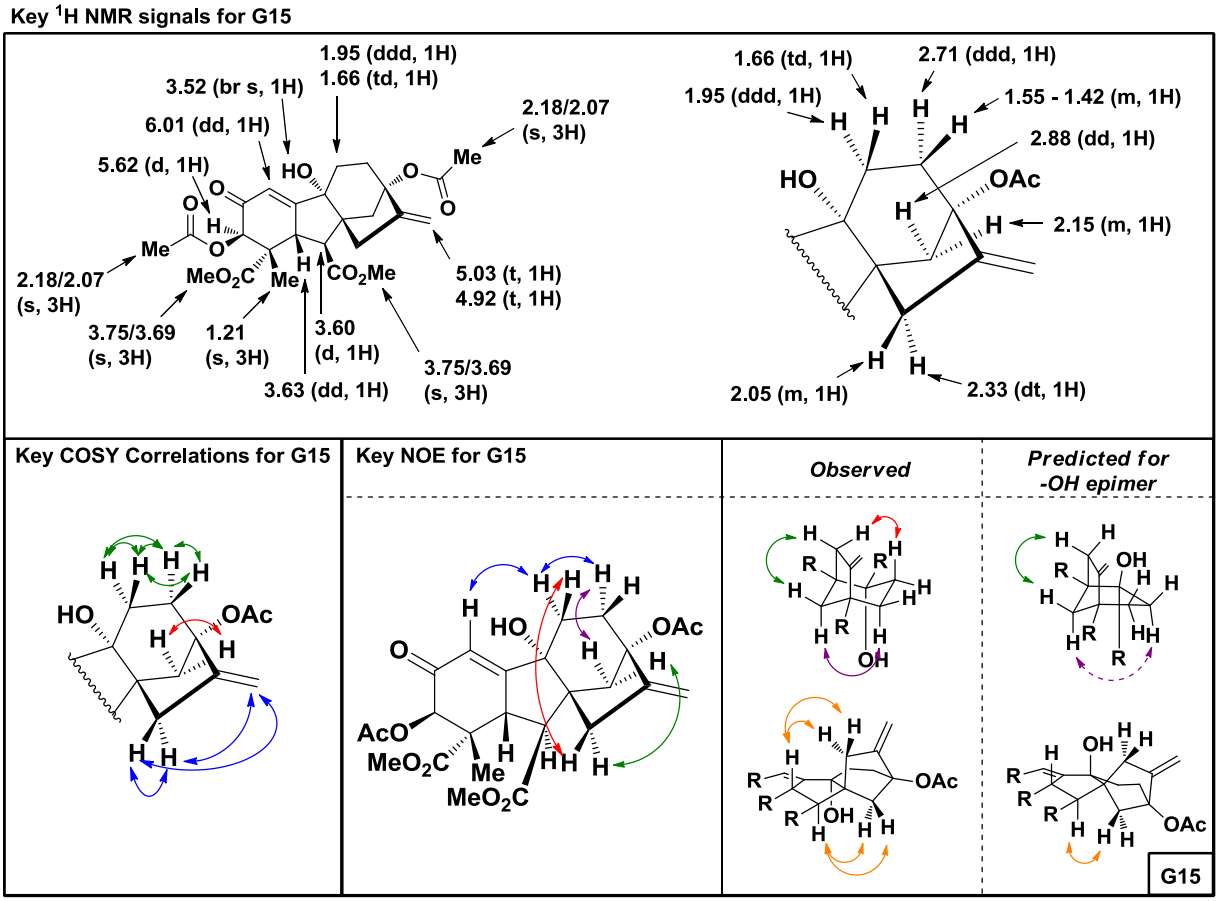
**Note: G1** was not stable to chromatography or storage at room temperature, and would gradually convert to **G2** over time. There was a significant contaminant signal in the $^{13}$C NMR spectra for **G1** that could not be removed at 56.4 ppm. **G15** was used for assigning the absolutely stereochemistry of the precursor epoxide **G14**. The assignment of the stereochemistry of the tertiary alcohol is based on the NOEs observed across the C/D bicycle. A comparison is provided to the opposite diastereomer to identify the interactions that are not observed but would be expected if the alcohol was in the opposite configuration.




**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 6.49 (dd, *J* = 10.3, 2.1 Hz, 1H), 6.38 (t, *J* = 2.2 Hz, 1H), 5.91 (dd, *J* = 10.3, 2.1, Hz, 1H), 5.17 (t, *J* = 2.6 Hz, 1H), 5.13 (t, *J* = 2.2 Hz, 1H), 3.79 (d, *J* = 11.8 Hz, 1H), 3.66 (s, 3H), 3.59 (s, 3H), 3.12 (dt, *J* = 17.5, 2.5 Hz, 1H), 3.04 (dq, *J* = 17.5, 1.5 Hz, 1H), 2.92 (d, *J* = 11.7 Hz, 1H), 2.55 - 2.38 (m, 2H), 2.29 - 2.18 (m, 2H), 2.07 (s, 3H), 2.02 (m, 3H singlet buried in multiplet, 4H), 1.79 (ddd, *J* = 10.3, 7.1, 3.5 Hz, 1H), 1.32 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 209.2, 198.7, 172.5, 172.2, 170.0, 169.9, 148.8, 141.7, 130.4, 107.2, 84.5, 69.8, 55.1, 52.7, 51.9, 51.6, 45.3, 43.8, 36.7, 35.6, 33.6, 29.9, 22.1, 21.1, 19.1.

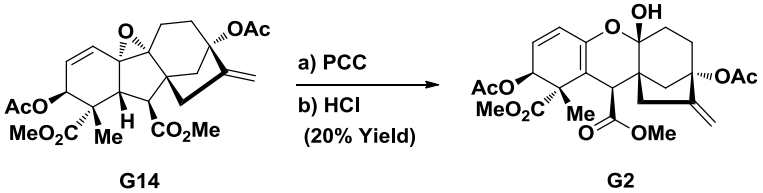
**HRMS(ESI)**: *m/z* calc. for $C_{25}H_{30}O_{10}Na$ $[M+Na]^+$: 513.1737, found: 513.1746.




**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 6.01 (d, *J* = 2.6, 0.9 Hz, 1H), 5.62 (d, *J* = 0.9 Hz, 1H), 5.03 (t, *J* = 2.5 Hz, 1H), 4.92 (t, *J* = 2.1 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.63 (dd, *J* = 11.1, 2.7 Hz, 1H), 3.60 (d, *J* = 11.1 Hz, 1H), 3.52 (br s, 1H), 2.88 (dd, *J* = 10.8, 2.6 Hz, 1H), 2.71 (ddd, *J* = 12.7, 11.7, 5.2 Hz, 1H), 2.33 (dt, *J* = 17.7, 2.8 Hz, 1H), 2.19 - 2.14 (m, 1H buried under methyl), 2.18 (s, 3H), 2.07 (s, 3H), 2.07 - 2.01 (m, 1H buried under methyl), 1.95 (ddd, *J* = 14.0, 5.3, 1.8 Hz, 1H), 1.66 (td, *J* = 13.4, 5.7 Hz, 1H), 1.55 - 1.42 (m, 1H), 1.21 (s, 3H).

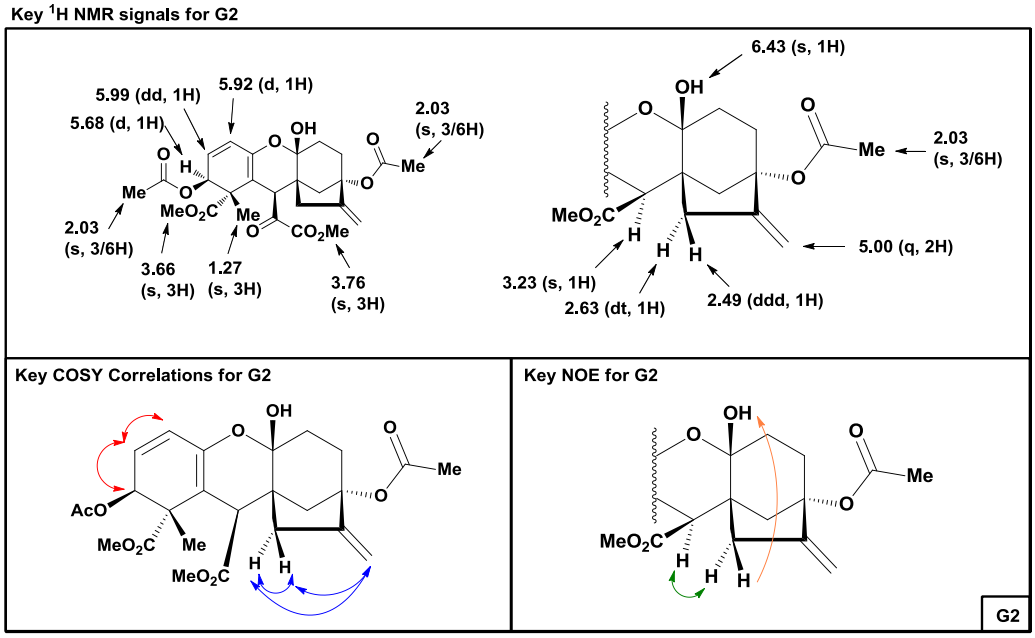
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 192.0, 174.8, 173.2, 171.1, 169.8, 169.6, 148.7, 121.5, 105.7, 86.3, 79.9, 74.2, 55.1, 53.3, 52.5, 47.0, 45.1, 37.5, 35.1, 33.5, 29.9, 27.9, 22.3, 21.0, 19.7.

**HRMS(ESI)**: *m/z* calc. for $C_{25}H_{31}O_{10}$ $[M+H]^+$: 491.1917, found: 491.1916.




G14 G2

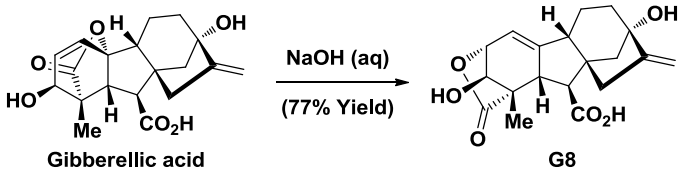
**Procedure:** In an oven-dried round bottom flask with stir bar, dissolved **G14** (100.3 mg, 0.21 mmol) in dichloromethane (7 mL) and added powdered molecular sieves (100 mg) followed by pyridinium chlorochromate (98.0 mg, 0.46 mmol). The reaction was refluxed for 2.5 hours, at which point hydrochloric acid (1 M, 8 mL) was added. The reaction stirred overnight at room temperature, and was then extracted with dichloromethane (3x). Purification by flash silica chromatography (4:1 to 3:1 hexanes/ethyl acetate) afforded **G2** as a white solid (20.4 mg, 20% yield).



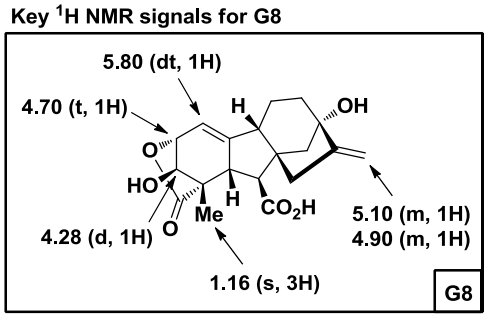

**$^{1}$H NMR** ($CDCl_3$, 500 MHz): δ 6.43 (s, 1H), 5.99 (dd, *J* = 9.9, 4.4 Hz, 1H), 5.92 (d, *J* = 9.9 Hz, 1H), 5.68 (d, *J* = 4.5 Hz, 1H), 5.00 (q, *J* = 2.6 Hz, 2H), 3.76 (s, 3H), 3.66 (s, 3H), 3.23 (s, 1H), 2.63 (dt, *J* = 16.7, 3.0 Hz, 1H), 2.49 (ddd, *J* = 16.7, 3.7, 2.0 Hz, 1H), 2.28 - 2.20 (m, 3H), 2.12 - 2.05 (m, 1H), 2.03 (s, 6H), 1.84 (td, *J* = 13.9, 6.6 Hz, 1H), 1.61 - 1.55 (m, 1H), 1.27 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 176.6, 174.0, 170.4, 169.6, 149.4, 145.1, 127.6, 126.8, 106.0, 103.0, 98.7, 85.2, 71.2, 53.1, 52.7, 50.3, 48.5, 45.1, 44.9, 35.7, 35.0, 32.8, 22.2, 21.1, 15.9.

**HRMS(ESI)**: *m/z* calc. for $C_{25}H_{30}O_{10}Na$ $[M+Na]^+$: 513.1737, found: 513.1741.



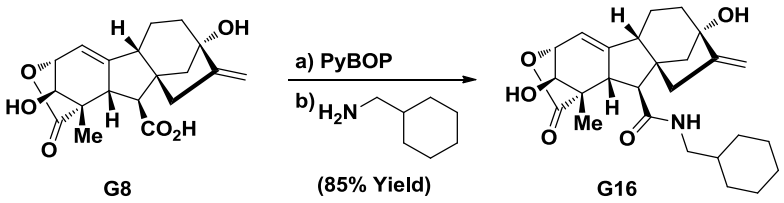

**Procedure:** Gibberellic acid (1.002 g, 2.89 mmol) and sodium hydroxide (954 mg, 23.9 mmol) were dissolved in water (500 mL) in a round bottom flask. After stirring at room temperature for 1.5 hours, the reaction was acidified to pH 3 and extracted with ethyl acetate (5x). The organic layers were dried over magnesium sulfate and concentrated to afford known compound **G8** as a white solid (771 mg, 77% yield).[6]



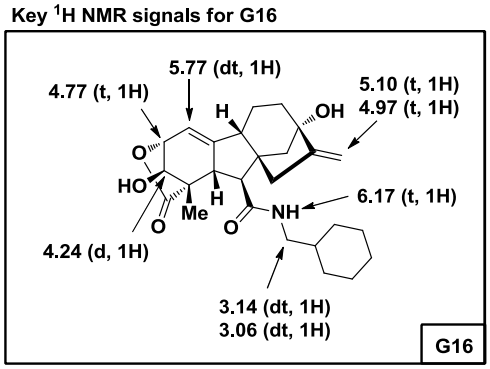

**$^{1}$H NMR** ($d_6$-acetone, 500 MHz): δ 5.80 (dt, *J* = 5.2, 2.6 Hz, 1H), 5.10 - 5.06 (m, 1H), 4.93 - 4.90 (m, 1H), 4.70 (t, *J* = 5.3 Hz, 1H), 4.28 (d, *J* = 5.3 Hz, 1H), 3.33 (dd, *J* = 6.1, 2.7 Hz, 1H), 2.81 (br s, 1H), 2.68 (dt, *J* = 16.4, 3.0 Hz, 1H), 2.61 - 2.55 (m, 1H), 2.44 (d, *J* = 6.1 Hz, 1H), 2.33 - 2.24 (m, 1H), 1.99 - 1.89 (m, 1H), 1.77 - 1.62 (m, 3H), 1.51 (dd, *J* = 11.0, 3.1 Hz, 1H), 1.49 - 1.42 (m, 1H), 1.34 (ddd, *J* = 10.9, 2.8, 1.1 Hz, 1H), 1.16 (s, 3H).

**$^{13}$C NMR** ($d_6$-acetone, 125 MHz): δ 177.5, 176.0, 155.7, 151.9, 114.6, 106.3, 79.0, 75.8, 74.9, 49.9, 49.8, 49.6, 49.1, 46.7, 46.3, 39.9, 38.6, 19.4, 17.4.

**HRSM(ESI)**: *m/z* calc. for $C_{19}H_{22}O_6Na$ $[M+Na]^+$: 369.1314, found: 369.1317.



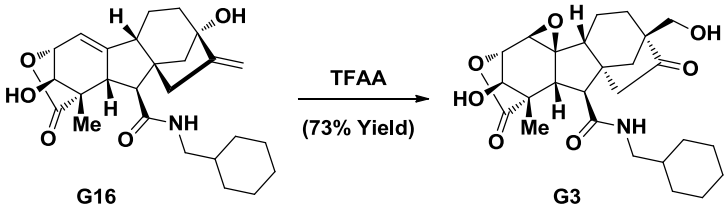

**Procedure:** In an oven-dried flask, **G8** (128.4 mg, 0.37 mmol) and benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (213.0 mg, 0.41 mmol) were dissolved in dichloromethane (4 mL). Diisopropylethylamine (200 µL, 1.15 mmol) was added, and the reaction was stirred at room temperature for 2 hours. After complete complexation by TLC, cyclohexanemethylamine (50 µL, 0.38 mmol) and additional diisopropylethylamine (50 µL, 0.29 mmol) were added, and the reaction was allowed to stir at room temperature for 16 hours. The reaction was quenched with water, extracted with ethyl acetate (3x), and concentrated. Purification by flash silica chromatography (1:1 to 1:2 hexanes/ethyl acetate) afforded pure **G16** as a white solid (138.4 mg, 85% yield).



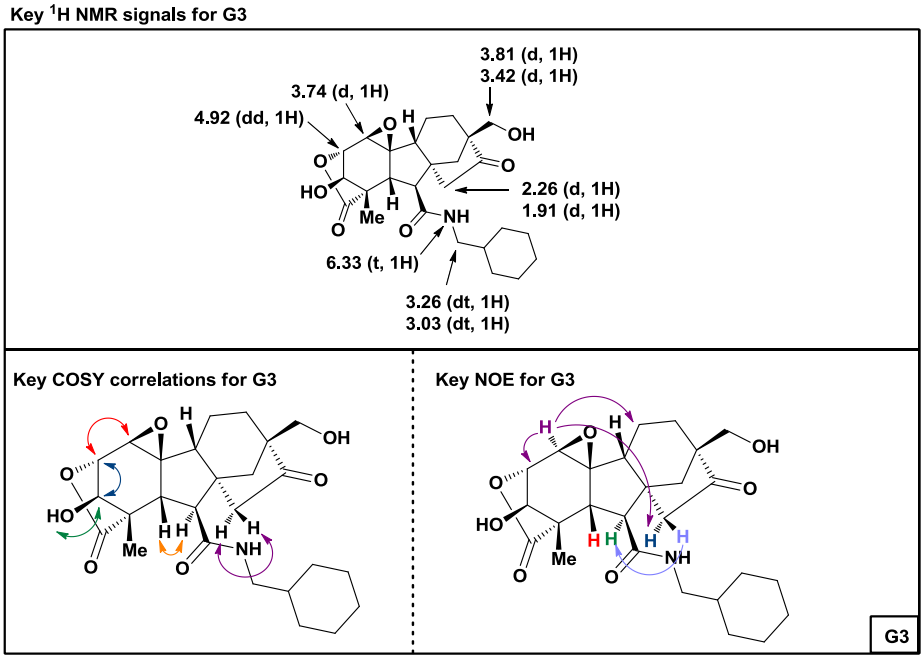

**$^{1}$H NMR** ($CDCl_3$, 500 MHz): δ 6.17 (t, *J* = 5.9 Hz, 1H), 5.77 (dt, *J* = 5.0, 2.4 Hz, 1H), 5.10 (t, *J* = 2.5 Hz, 1H), 4.97 (t, *J* = 2.0 Hz, 1H), 4.77 (t, *J* = 5.3 Hz, 1H), 4.24 (d, *J* = 5.3 Hz, 1H), 3.33 (dd, *J* = 5.9, 2.6 Hz, 1H), 3.14 (dt, *J* = 13.3, 6.6 Hz, 1H), 3.06 (dt, *J* = 13.3, 6.0 Hz, 1H), 2.82 - 2.74 (m, 1H), 2.51 (dt, *J* = 16.5, 2.9 Hz, 1H), 2.38 - 2.28 (m, 1H), 2.30 - 2.05 (br s, buried, 1H), 2.24 (d, *J* = 5.9 Hz, 1H), 1.97 - 1.86 (m, 1H), 1.78 - 1.62 (m, 7H), 1.58 - 1.52 (m, 1H), 1.51 (dd, *J* = 11.1, 2.7 Hz, 1H), 1.46 (ddp, *J* = 11.0, 7.0, 3.6 Hz, 1H), 1.34 (dd, *J* = 11.0, 2.7 Hz, 1H), 1.29 - 1.10 (m, 3H singlet buried, 7H), 1.00 - 0.85 (m, 2H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 177.9, 174.0, 153.9, 153.4, 113.1, 107.0, 79.2, 75.8, 74.3, 51.4, 49.5, 49.0, 48.7, 46.3, 45.7, 45.7, 39.1, 38.1, 37.5, 31.1 (2), 26.6, 26.0 (2), 18.9, 17.2.

**HRMS(ESI)**: *m/z* calc. for $C_{26}H_{36}NO_5$ $[M+H]^+$: 442.2593, found: 442.2585.



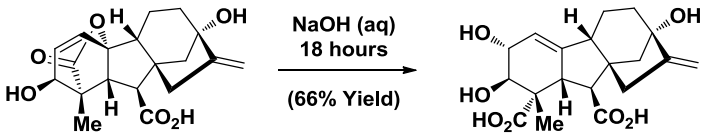

**Procedure:** In a vial with a stir bar, loaded hydrogen peroxide (30% in water, 15.4 µL, 0.14 mmol), trifluoroacetic anhydride (100 µL, 0.72 mmol), and trifluoroacetic acid (110 µL, 1.44 mmol) were dissolved in dichloromethane. Amide **G16** was added in one portion and allowed to react for 15 minutes. The reaction was then washed with water (2x) and saturated aqueous sodium bicarbonate. Purification by flash silica chromatography (1:1 to 1:2 hexanes/ethyl acetate) afforded pure **G3** as a white solid (14.8 mg, 73% yield).




**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 6.33 (t, *J* = 5.8 Hz, 1H), 4.92 (dd, *J* = 5.7, 3.4 Hz, 1H), 4.22 (br s, 1H), 4.01 (br s, 1H), 3.81 (d, *J* = 11.6 Hz, 1H), 3.74 (d, *J* = 3.4 Hz, 1H), 3.42 (d, *J* = 11.6 Hz, 1H), 3.26 (dt, *J* = 13.5, 6.9 Hz, 1H), 3.22 (d, *J* = 3.7 Hz, 1H), 3.03 (dt, *J* = 13.5, 5.7 Hz, 1H), 2.99 (dd, *J* = 12.5, 5.0 Hz, 1H), 2.76 (d, *J* = 3.8 Hz, 1H), 2.26 (dd, *J* = 11, 8 Hz, 1H), 2.26 (d, *J* = 18.8 Hz, 1H), 1.91 (d, *J* = 18.8 Hz, 1H), 1.76 - 1.56 (m, 7H), 1.52 - 1.45 (m, 1H), 1.40 - 1.32 (m, 1H), 1.27 - 1.12 (m, buried methyl, 8H), 1.02 - 0.90 (m, 3H).

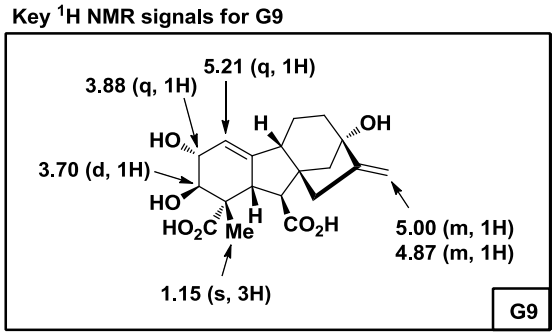
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 219.1, 177.6, 172.8, 76.9, 71.5, 67.9, 63.8, 56.4, 56.3, 50.5, 48.7, 46.6, 46.4, 46.0, 45.2, 43.6, 40.6, 38.0, 31.1 (2), 30.6, 26.6, 26.0 (2), 19.2, 17.7.

**HRMS(ESI)**: *m/z* calc. for $C_{26}H_{36}NO_7$ $[M+H]^+$: 474.2492, found: 474.2493.




Gibberellic acid G9

**Procedure:** Gibberellic acid (2.008 g, 5.80 mmol) and sodium hydroxide (955 mg, 23.9 mmol) were dissolved in water (230 mL, 0.1 M NaOH) and stirred at room temperature for 17.5 hours. The reaction was cooled in an ice bath and quenched with hydrogen chloride (1 M, 40 mL) to a final pH of 2. The reaction was extracted with ethyl acetate (5x) and concentrated. The organic layer was then triturated with hexanes to afford known compound **G9** as a white solid (1.403 g, 66% yield).[7]

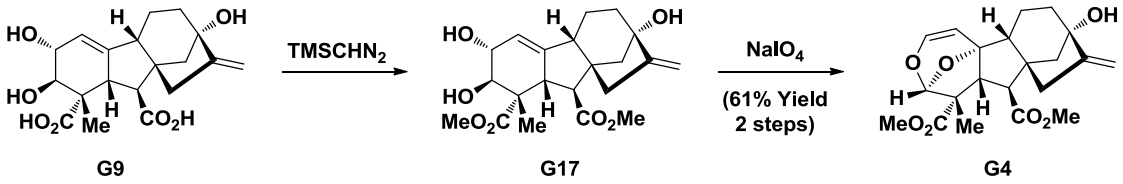



**$^{1}$H NMR** ($d_6$-DMSO, 500 MHz): δ 12.32 (s, 2H), 5.21 (q, *J* = 2.9 Hz, 1H), 5.08 (br m, 1H), 5.00 (m, 1H), 4.87 (m, 1H), 4.76 (s, 1H), 3.88 (q, *J* = 2.8 Hz, 1H), 3.70 (d, *J* = 3.1 Hz, 1H), 2.88 - 2.83 (m, 1H), 2.75 (d, *J* = 6.0 Hz, 1H), 2.55 - 2.45 (m, 1H), 2.36 - 2.31 (m, 1H), 2.13 (dd, *J* = 16.1, 2.6 Hz, 1H), 1.85 - 1.78 (m, 1H), 1.63 (dd, *J* = 11.1, 2.7 Hz, 1H), 1.61 - 1.48 (m, 2H), 1.42 - 1.35 (m, 1H), 1.31 (d, *J* = 10.5 Hz, 1H), 1.15 (s, 3H).

**$^{13}$C NMR** ($d_6$-acetone, 125 MHz): δ 177.1, 176.2, 155.7, 143.2, 115.6, 105.4, 78.7, 75.2, 71.2, 50.0, 49.6, 48.9, 47.3, 46.7, 46.6, 39.5, 38.2, 21.2, 18.8.

**HRMS(ESI)**: *m/z* calc. for $C_{19}H_{24}O_7Na$ $[M+Na]^+$: 387.1420, found: 387.1420.

**Melting point:** 143-145 °C.

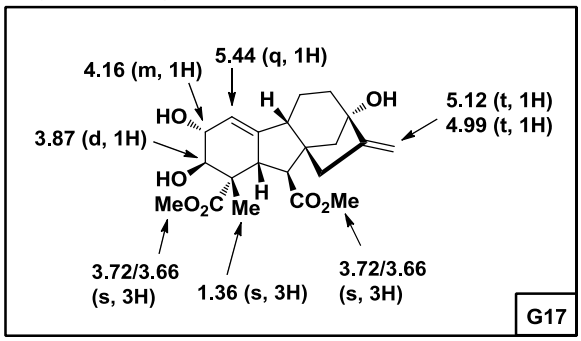



**G9** **G17** **G4**

**Procedure:** In an oven-dried round bottom flask with a stir bar under argon, loaded **G9** (55.4 mg, 0.15 mmol) and dissolved in toluene (1.5 mL) and methanol (0.5 mL). Added trimethylsilyldiazomethane (2 M in hexanes, 160 µL, 0.32 mmol) and allowed to stir for 1 hour, at which point the reaction was concentrated. The solid residual was redissolved in dichloromethane (1.5 mL) and water (0.5 mL). Sodium periodate (65.2 mg, 0.31 mmol) was added in a single portion, and the reaction was heated at 40 °C for 6 hours. The reaction was then cooled, extracted with ethyl acetate (3x) and concentrated. Purification by flash silica chromatography (2:1 hexanes/ethyl acetate) afforded pure **G4** as a white solid (36.2 mg, 61% yield).

**Note: G17** could be isolated and purified following esterification with (trimethylsilyl)diazomethane by flash silica chromatography (2:1 hexanes/ethyl acetate) to afford pure product.

Key $^1$H NMR signals for G17

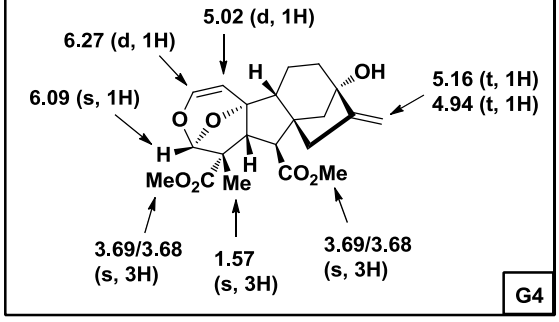



**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 5.44 (q, *J* = 2.3 Hz, 1H), 5.12 (t, *J* = 2.5 Hz, 1H), 4.99 (t, *J* = 2.1 Hz, 1H), 4.16 (m, 1H), 3.87 (d, *J* = 4.5 Hz, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 3.10 (d, *J* = 6.6 Hz, 1H), 2.59 - 2.48 (m, 3H), 2.28 - 2.15 (m, 2H), 1.97 (dd, *J* = 14.4, 6.1 Hz, 1H), 1.80 (td, *J* = 11.4, 6.1 Hz, 1H), 1.75 - 1.67 (m, 1H), 1.65 (dd, *J* = 10.7, 2.9 Hz, 1H), 1.61 - 1.49 (m, 3H), 1.39 - 1.35 (m, 1H), 1.36 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 176.4, 175.4, 154.0, 142.6, 116.2, 106.8, 79.2, 75.2, 70.3, 52.2, 52.0, 50.9, 49.7, 48.9, 48.0, 47.3, 46.1, 39.1, 37.7, 20.3, 18.9.

**HRMS(ESI)**: *m/z* calc. for $C_{21}H_{28}O_7Na$ $[M+Na]^+$: 415.1733, found: 415.1734.

Key $^1$H NMR signals for G4

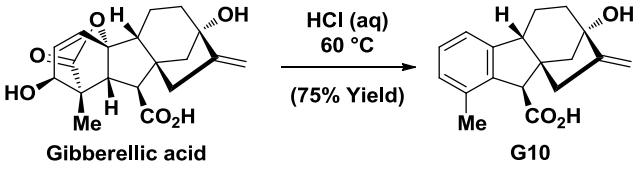



**$^1$H NMR** ($CDCl_3$, 125 MHz): δ 6.27 (d, *J* = 5.9 Hz, 1H), 6.09 (s, 1H), 5.16 (t, *J* = 1.4 Hz, 1H), 5.02 (d, *J* = 5.9 Hz, 1H), 4.94 (t, *J* = 2.0 Hz, 1H), 3.69 (s, 3H), 3.68 (s, 3H), 3.11 (d, *J* = 6.6 Hz, 1H), 2.42 - 2.36 (m, 2H), 2.27 (dt, *J* = 15.8, 3.0 Hz, 1H), 2.11 - 2.02 (m, 1H), 2.00 - 1.85 (m, 2H), 1.77 (dd, *J* = 7.8, 5.5 Hz, 1H), 1.71 - 1.63 (m, 2H), 1.63 - 1.58 (m, 1H), 1.57 (s, 3H), 1.52 - 1.46 (m, 1H).

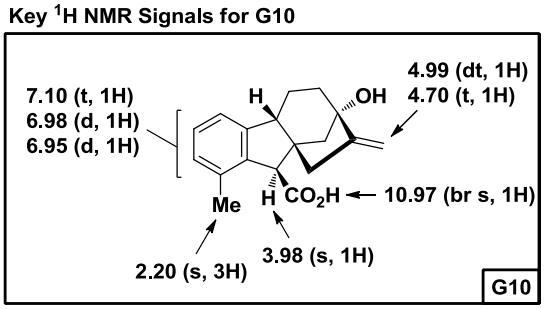
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 174.6, 173.4, 155.6, 142.8, 108.1, 106.9, 103.9, 92.7, 78.8, 66.7, 63.4, 54.5, 52.1, 52.0, 51.6, 49.6, 48.1, 42.3, 38.7, 22.3, 18.1.

**HRMS (ESI)**: *m/z* calc. for $C_{21}H_{26}O_7Na$ $[M+Na]^+$: 413.1576, found: 413.1578.

**Melting point:** 136-137 °C.




**Procedure:** Gibberellic acid (1.404 g, 4.05 mmol) was dissolved in hydrochloric acid (1.2 M, 20 mL) in a round bottom flask and heated for 2.75 hours at 65 °C. The reaction was cooled, and the solid precipitate was filtered and washed with water. **G10**, a known compound, was isolated as a white solid (863 mg, 75% yield).[8]



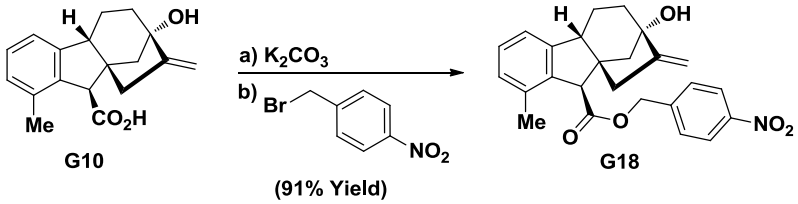

**$^1$H NMR** ($d_6$-acetone, 500 MHz): δ 10.97 (br s, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.4 Hz, 1H), 4.99 (dt, *J* = 2.7, 1.4 Hz, 1H), 4.70 (t, *J* = 2.0 Hz, 1H), 3.98 (s, 1H), 2.88 (dd, *J* = 12.6, 5.0 Hz, 1H), 2.31 - 2.21 (m, 3H), 2.20 (s, 3H), 2.08 - 1.99 (m, 2H), 1.93 (td, *J* = 12.2, 5.1 Hz, 1H), 1.89 (dd, *J* = 10.3, 2.6 Hz, 1H), 1.71 - 1.62 (m, 1H), 1.54 (qd, *J* = 12.7, 5.1 Hz, 1H).

**$^{13}$C NMR** ($d_6$-acetone, 125 MHz): δ 172.7, 155.9, 145.7, 139.7, 135.8, 129.3, 127.9, 120.3, 103.1, 80.6, 55.2, 53.8, 52.7, 49.1, 40.7, 34.9, 22.8, 20.0.

**HRMS(ESI)**: *m/z* calc. for $C_{18}H_{21}O_3$ $[M+H]^+$: 285.1491, found: 285.1491.

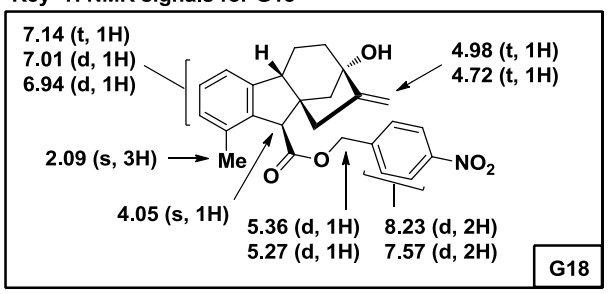
**HRMS(ESI)**: *m/z* calc. for $C_{18}H_{20}O_3Na$ $[M+Na]^+$: 307.1310, found: 307.1307.

**Melting point:** 188-190 °C.




**Procedure:** In an oven-dried vial with stir bar, **G10** (48.7 mg, 0.17 mmol) and 4-nitrobenzyl bromide (92.0 mg, 0.43 mmol) were dissolved in acetone (1 mL). Potassium carbonate (120.9 mg, 0.88 mmol) was then added, and the reaction stirred at room temperature for 15.5 hours. The reaction was diluted with water and extracted with ethyl acetate (2x). Purification by flash silica chromatography (4:1 to 3:1 hexanes/ethyl acetate) afforded pure **G18** as a white solid (65.3 mg, 91% yield).

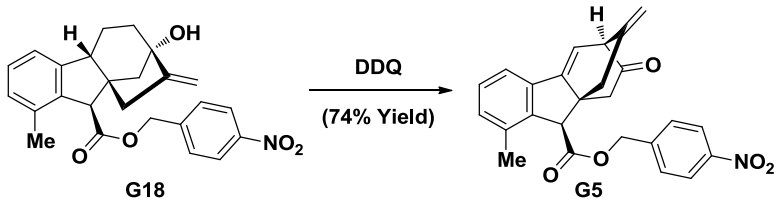
Key $^1$H NMR signals for G18




**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.23 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.4 Hz, 1H), 5.36 (d, *J* = 13.2 Hz, 1H), 5.27 (d, *J* = 13.2 Hz, 1H), 4.98 (t, *J* = 2.7 Hz, 1H), 4.72 (t, *J* = 2.2 Hz, 1H), 4.05 (s, 1H), 2.85 (dd, *J* = 12.6, 4.9 Hz, 1H), 2.25 (ddt, *J* = 12.6, 5.2, 2.7 Hz, 1H), 2.16 (dd, *J* = 6.6, 2.5 Hz, 1H), 2.13 (d, *J* = 2.5 Hz, 1H), 2.09 (s, 3H), 2.05 (dt, *J* = 18, 3.0 Hz, 1H), 1.97 (dd, *J* = 12.4, 4.3 Hz, 1H), 1.95 - 1.92 (m, 1H), 1.73 (ddd, *J* = 9.6, 5.3, 2.3 Hz, 1H), 1.63 (dd, *J* = 12.7, 5.2 Hz, 1H), 1.57 (dd, *J* = 12.6, 5.0 Hz, 1H).

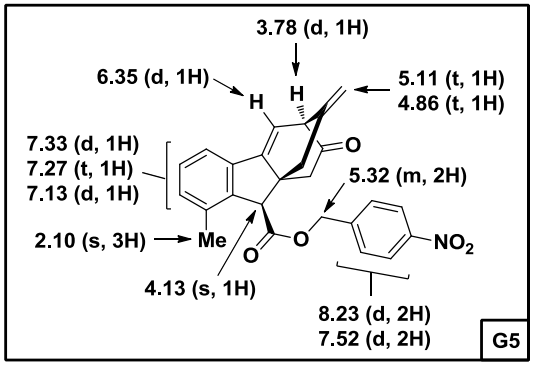
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 171.1, 154.11, 148.0, 144.5, 143.0, 138.0, 135.0, 129.2, 129.0, 127.8, 124.0 (2), 120.0, 103.5, 80.6, 65.3, 65.3, 54.7, 53.7, 52.3, 49.0, 39.6, 34.3, 22.1, 20.0.

**HRMS(ESI)**: *m/z* calc. for $C_{25}H_{26}NO_5$ $[M+H]^+$: 420.1811, found: 420.1810.




**Procedure:** In an oven-dried vial with stir bar, **G18** (35.0 mg, 0.083 mmol) and 2,3-dichloro-5,6-dicyanobenzoquinone (39.0 mg, 0.172 mmol) were dissolved in toluene (1.5 mL) and heated at 80 °C for 15 hours. The reaction was cooled and diluted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride (2x) and water (4x), and concentrated. Purification by flash silica chromatography (4:1 to 3:1 hexanes/ethyl acetate) afforded pure **G5** as a white solid (25.5 mg, 74% yield).

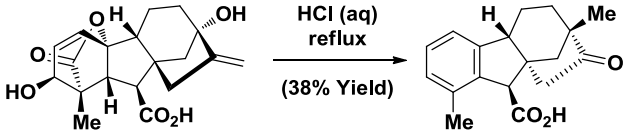
Key $^1$H NMR signals for G5



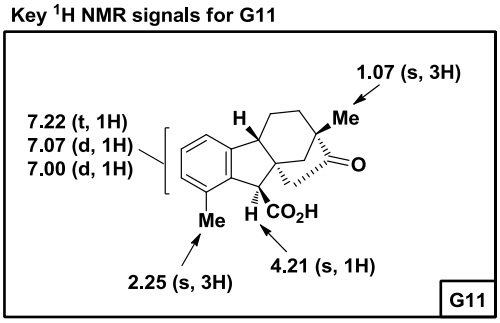
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.23 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.4 Hz, 1H), 6.35 (d, *J* = 6.4 Hz, 1H), 5.32 (m, 2H), 5.11 (t, *J* = 2.5 Hz, 1H), 4.86 (t, *J* = 2.5 Hz, 1H), 4.13 (s, 1H), 3.78 (d, *J* = 6.5 Hz, 1H), 2.51 (d, *J* = 17.8 Hz, 1H), 2.39 (dt, *J* = 15.7, 2.1 Hz, 1H), 2.34 (dq, *J* = 15.7, 2.5 Hz, 1H), 2.22 (dd, *J* = 17.8, 3.1 Hz, 1H), 2.10 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 205.7, 171.1, 153.2, 148.1, 142.6, 142.0, 139.7, 136.5, 136.0, 131.0, 129.3, 129.3 (2), 124.0 (2), 119.3, 112.9, 111.7, 65.5, 60.3, 55.5, 48.9, 45.7, 35.5, 19.0.

**HRMS(ESI)**: *m/z* calc. for $C_{25}H_{22}NO_5$ $[M+H]^+$: 416.1498, found: 416.1494.




**Procedure:** Gibberellic acid (959 mg, 2.77 mmol) was suspended in aqueous hydrochloric acid (2.4 M, 150 mL) in a round bottom flask and refluxed for 2 hours. The solid crust that formed during the course of the reaction was periodically broken up with a glass rod. After refluxing, the reaction was filtered hot, and the solid was washed with water to provide known compound **G11** as a white solid (298 mg, 38% yield).[8]

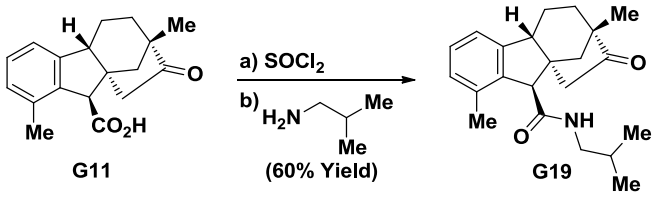



**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.22 (t, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 4.21 (s, 1H), 3.04 (t, *J* = 7.8 Hz, 1H), 2.74 (d, *J* = 17.9 Hz, 1H), 2.51 (dd, *J* = 17.8, 3.6 Hz, 1H), 2.25 (s, 3H), 2.15 - 2.07 (m, 1H), 2.05 (dd, *J* = 12.1, 3.8 Hz, 1H), 1.90 (dq, *J* = 14.3, 8.1 Hz, 1H), 1.83 - 1.73 (m, 1H), 1.64 (ddd, *J* = 13.5, 7.5, 5.5 Hz, 1H), 1.40 (d, *J* = 12.1 Hz, 1H), 1.07 (s, 3H).

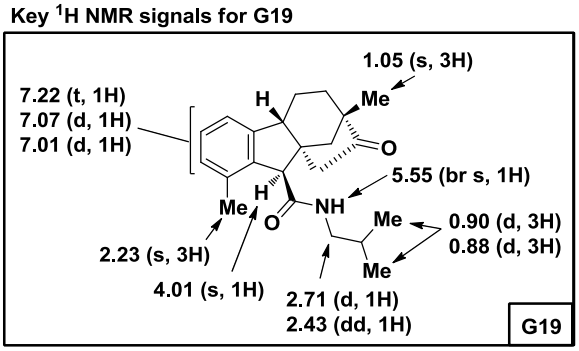
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 221.6, 177.0, 146.2, 137.2, 135.4, 129.2, 128.6, 120.7, 55.8, 51.4, 50.7, 50.0, 48.2, 39.1, 34.6, 23.0, 21.8, 19.7.

**HRMS(ESI)**: *m/z* calc. for $C_{18}H_{21}O_3$ $[M+H]^+$: 285.1491, found: 285.1492.

**HRMS(ESI)**: *m/z* calc. for $C_{18}H_{20}O_3Na$ $[M+Na]^+$: 307.1310, found: 307.1312.




**Procedure:** In an oven-dried round bottom flask, **G11** (799.5 mg, 2.81 mmol) was dissolved in tetrahydrofuran (60 mL). Thionyl chloride (450 μL, 6.20 mmol) was added, and the reaction was refluxed for 50 minutes. The reaction was then cooled in an ice bath, at which point triethylamine (900 μL, 6.46 mmol) and isobutylamine (950 μL, 9.47 mmol) were added and the reaction was allowed to warm to room temperature for 1 hour. The reaction was quenched with water, extracted with ethyl acetate (3x), and purified by flash silica chromatography using 4:1 to 3:1 hexanes/ethyl acetate to afford pure **G19** as a white solid (569.6 mg, 60% yield).

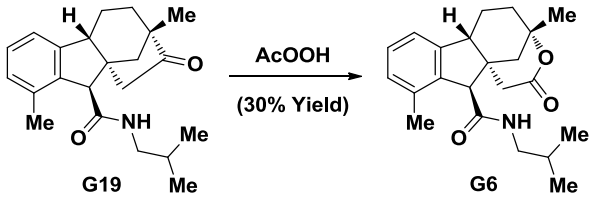



**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.22 (t, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 5.55 (br s, 1H), 4.01 (s, 1H), 3.12 (t, *J* = 6.4 Hz, 2H), 2.94 (t, *J* = 8.0 Hz, 1H), 2.71 (d, *J* = 17.7 Hz, 1H), 2.43 (dd, *J* = 17.7, 3.7 Hz, 1H), 2.23 (s, 3H), 2.10 (dq, *J* = 9.0, 7.8 Hz, 1H), 1.96 (dd, *J* = 12.0, 3.7 Hz, 1H), 1.87 - 1.71 (m, 3H), 1.68 - 1.59 (m, 1H), 1.47 (d, *J* = 12.0 Hz, 1H), 1.05 (s, 3H), 0.90 (d, *J* = 2.2 Hz, 3H), 0.88 (d, *J* = 2.2 Hz, 3H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 222.0, 171.4, 147.2, 137.9, 135.6, 129.4, 128.7, 121.1, 58.5, 52.0, 51.6, 49.4, 48.1, 47.3, 38.6, 34.5, 29.9, 28.6, 23.5, 21.8, 20.5, 19.5.

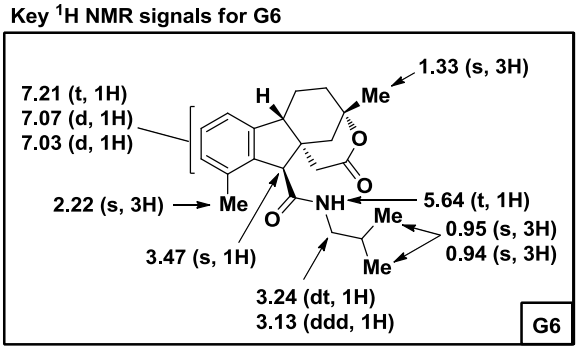
**HRMS(ESI)**: *m/z* calc. for $C_{22}H_{30}NO_2$ $[M+H]^+$: 340.2277, found: 340.2267.

**Melting point:** 168-170 °C.




**Procedure:** An oven-dried vial with stir bar was loaded with **G19** (51.4 mg, 0.15 mmol) and dissolved in dichloromethane (4 mL). The reaction was cooled to 0 °C in an ice bath, and sodium carbonate (127.1

mg, 1.20 mmol) and peracetic acid (32% in acetic acid, 170 µL, 0.81 mmol) were added. The reaction stirred for 15 hours, during which time it was allowed to warm to room temperature. Saturated aqueous sodium bicarbonate was added to quench the reaction. The reaction was acidified to pH 3, and the aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. Purification by flash silica chromatography (3:1 to 2:1 hexanes/ethyl acetate) afforded **G6** as a white solid (16.0 mg, 30% yield). Unreacted starting material was also recovered as a white solid (7.7 mg).

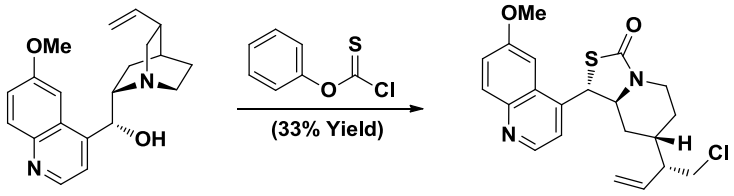



**$^{1}$H NMR** ($CDCl_3$, 500 MHz): δ 7.21 (t, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 5.64 (t, *J* = 6.0 Hz, 1H), 3.47 (s, 1H), 3.24 (dt, *J* = 13.1, 6.4 Hz, 1H), 3.13 (ddd, *J* = 13.2, 7.1, 5.8 Hz, 1H), 2.95 (d, *J* = 17.5 Hz, 1H), 2.90 (d, *J* = 6.5 Hz, 1H), 2.72 (dd, *J* = 17.5, 2.8 Hz, 1H), 2.35 - 2.19 (m, 1H), 2.22 (s, 3H), 1.94 (ddt, *J* = 15.3, 12.1, 5.8 Hz, 1H), 1.89 - 1.77 (m, 2H), 1.68 (dd, *J* = 14.0, 2.9 Hz, 1H), 1.49 - 1.37 (m, 2H), 1.33 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 171.5, 169.2, 144.4, 137.9, 136.0, 129.9, 128.1, 119.8, 81.8, 60.2, 48.3, 47.5, 46.9, 40.6, 35.9, 33.1, 29.9, 29.1, 28.6, 20.5, 19.6, 19.0.

**HRMS(ESI)**: *m/z* calc. for $C_{22}H_{30}NO_3$ $[M+H]^+$: 356.2226, found: 356.2219.

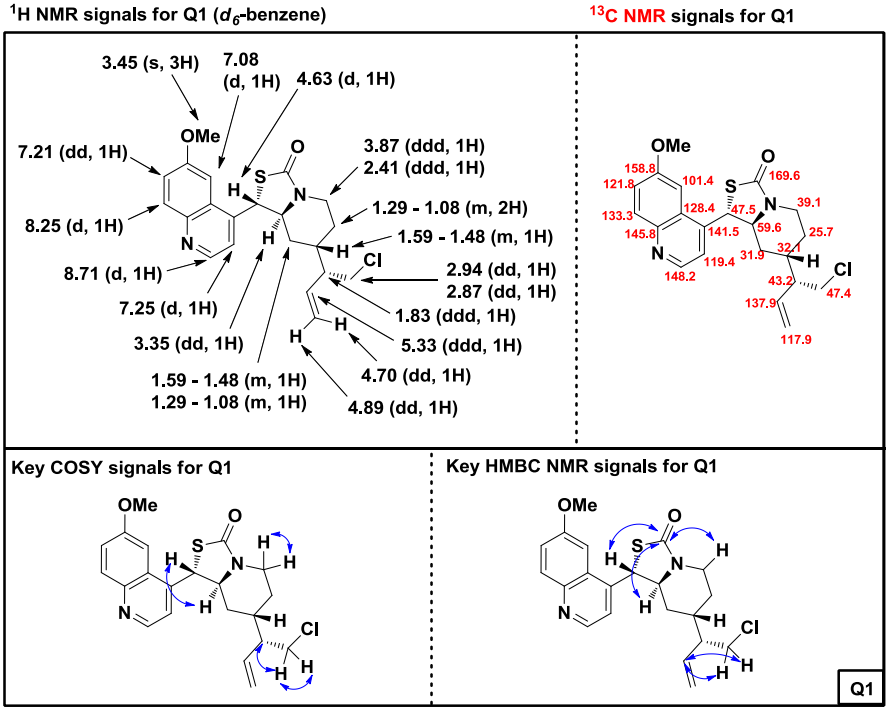
## 9.) Quinine Derived Compounds: Synthesis and Characterization




Quinine Q1

**Procedure:** *O*-phenyl chlorothionoformate (448.8 mg, 2.60 mmol) was added to a stirring solution of quinine (324.4 mg, 1.00 mmol) in anhydrous dichloromethane (10 mL) at room temperature. The resulting reaction was allowed to stir for 2.5 hours before the reaction was diluted with dichloromethane and quenched with a saturated solution of sodium bicarbonate. The contents of the quenched reaction were then transferred to a separatory funnel. The biphasic mixture was separated and the organic layer washed with brine, dried with magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography 3:2 chloroform/ethyl acetate to provide 133.3 mg (33% yield) of *S*-thiocarbamate **Q1** as a tan foam. Co-crystallization with benzene provided colorless crystals of suitable quality for x-ray diffraction analysis.

**Note:** Spectral data for **Q1** is reported in both $CDCl_3$ and $d_6$-benzene. This was required to attain optimal spectra to fully characterize **Q1** in 1-D and 2-D NMR experiments.




**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.81 (d, *J* = 4.6 Hz, 1H), 8.16 (d, *J* = 9.2 Hz, 1H), 7.64 (d, *J* = 4.7 Hz, 1H), 7.47 (dd, *J* = 9.3, 2.6 Hz, 1H), 7.25 (d, *J* = 3.1 Hz, 1H), 5.69 (ddd, *J* = 17.0, 10.1, 9.0 Hz, 1H), 5.21 (dd, *J* = 10.2, 1.4 Hz, 1H), 5.18 - 5.10 (m, 2H), 4.05 - 3.96 (m, 2H), 3.98 (s, 3H), 3.53 (dd, *J* = 11.2, 3.4

Hz, 1H), 3.42 (dd, *J* = 11.2, 4.8 Hz, 1H), 2.97 (ddd, *J* = 13.3, 13.3, 3.4 Hz, 1H), 2.61 (ddd, *J* = 14.3, 9.1, 4.1 Hz, 1H), 2.20 - 2.13 (m, 1H), 2.07 - 2.00 (m, 1H), 1.88 (ddd, *J* = 13.8, 11.8, 4.7 Hz, 1H), 1.85 - 1.79 (m, 1H), 1.68 (dddd, *J* = 13.9, 13.9, 4.9, 4.9 Hz, 1H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 170.4, 158.7, 147.8, 144.8, 141.8, 137.5, 132.4, 127.8, 122.4, 119.6, 118.6, 100.7, 60.4, 55.9, 47.7, 47.6, 44.0, 39.2, 32.7, 32.0, 26.0.

**$^{1}$H NMR** (*$d_6$*-benzene, 500 MHz): δ 8.71 (d, *J* = 4.5 Hz, 1H), 8.25 (d, *J* = 9.2 Hz, 1H), 7.25 (d, *J* = 4.5 Hz, 1H), 7.21 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.08 (d, *J* = 2.7 Hz, 1H), 5.33 (ddd, *J* = 17.1, 10.2, 9.1 Hz, 1H), 4.89 (dd, *J* = 10.2, 1.7 Hz, 1H), 4.70 (dd, 17.1, 1.0 Hz, 1H), 4.66 (d, *J* = 7.2 Hz, 1H), 3.89 (ddd, *J* = 13.6, 5.1, 2.6 Hz, 1H), 3.45 (s, 3H), 3.37 (dd, *J* = 14.4, 5.1 Hz, 1H), 2.97 (dd, *J* = 11.2, 3.1 Hz, 1H), 2.90 (dd, *J* = 11.2, 4.8 Hz, 1H), 2.44 (td, *J* = 13.2, 3.5 Hz, 1H), 1.83 (ddd, *J* = 9.6, 9.0, 4.6 Hz, 1H), 1.59 - 1.48 (m, 2H), 1.29 - 1.08 (m, 3H).

**$^{13}$C NMR** (*$d_6$*-benzene, 125 MHz): δ 169.6, 158.8, 148.2, 145.8, 141.5, 137.9, 133.3, 128.4, 121.8, 119.4, 117.9, 101.4, 59.6, 55.3, 47.5, 47.4, 43.2, 39.1, 32.1, 31.9, 25.7.

**HRMS(ESI)**: *m/z* calc. for $C_{21}H_{24}ClN_2O_2S$ $[M+H]^+$: 403.1247, found: 403.1244.

**Melting Point:** 158-160 °C.

**X-ray Crystallographic Data for Q1:**

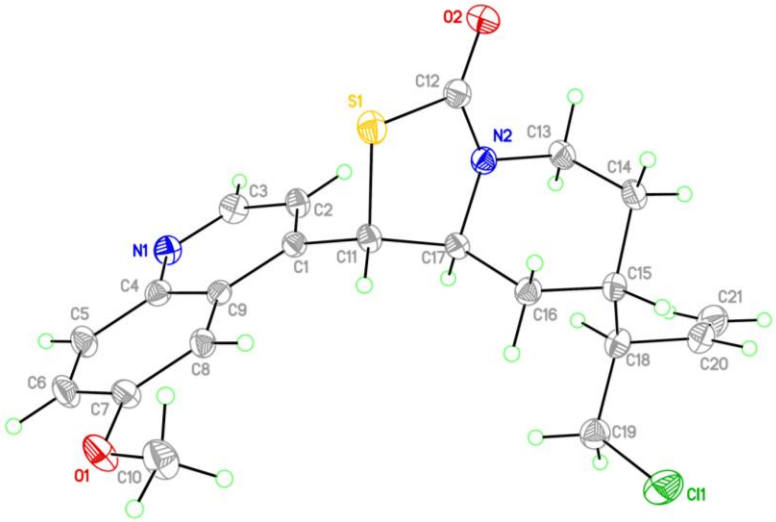
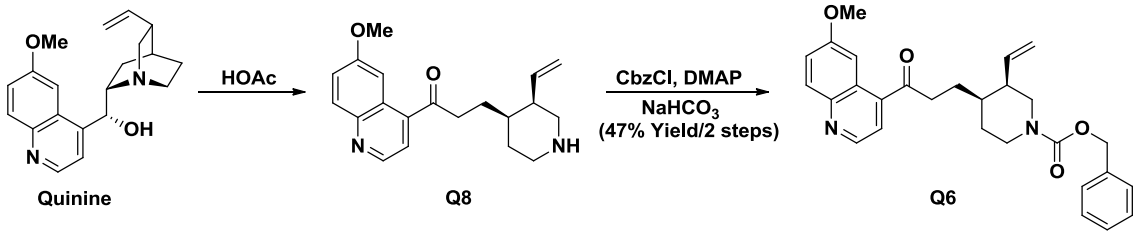



**Table S1.** Crystal data and structure refinement for bm28ras.

| | |
|---|---|
| Identification code | bm28ras |
| Empirical formula | $C_{21}$ $H_{23}$ Cl $N_2$ $O_2$ S |
| Formula weight | 559.14 |
| Temperature | 193(2)K |
| Wavelength | 0.71073 Å |
| Crystal system | Monoclinic |
| Space group | P2(1) |

| | | |
|---|---|---|
| Unit cell dimensions | a = 10.774(2)Å | α= 90° |
| | b = 9.935(2)Å | β= 103.813(2) |
| | c = 14.000(3)Å | γ= 90° |
| Volume | 1455.1(5) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.276 $g/cm^3$ | |
| Absorption coefficient | 0.236 $mm^{-1}$ | |
| F(000) | 592 | |
| Crystal size | 0.436 x 0.20 x 0.165 $mm^3$ | |
| Theta range for data collection | 1.95 to 25.36° | |
| Index ranges | -12<=h<=12, -11<=k<=11, -16<=l<=16 | |
| Reflections collected | 15549 | |
| Independent reflections | 5290 [R(int) = 0.0377] | |
| Completeness to theta = 25.36° | 99.5 % | |
| Absorption correction | Integration | |
| Max. and min. transmission | 0.8628 and 0.8386 | |
| Refinement method | Full-matrix least-squares on F2 | |
| Data / restraints / parameters | 5290 / 295 / 415 | |
| Goodness-of-fit on $F^2$ | 1.039 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0336, wR2 = 0.0727 | |
| R indices (all data) | R1 = 0.0402, wR2 = 0.0764 | |
| Absolute structure (Flack) parameter | -0.01(4) | |
| Largest diff. peak and hole | 0.162 and -0.159 e. $Å^{-3}$ | |

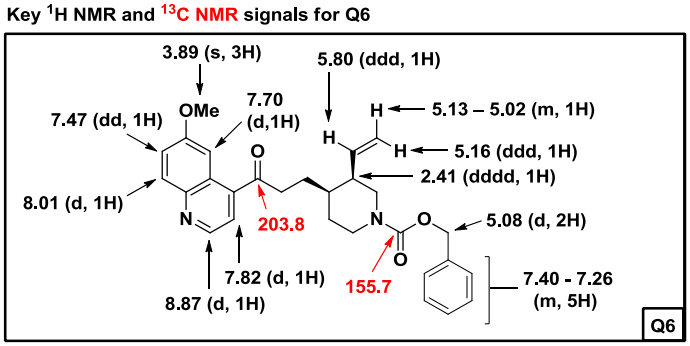
Crystallographic data have been deposited at the Cambridge Crystallographic Centre, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number CCDC 872159.




**Procedure:** Quinine (10 g, 30.8 mmol) was dissolved in a 1.2 M solution of acetic acid (140 mL) and stirred at 102 °C for 72 hours before cooling to room temperature. The reaction mixture was diluted with ethyl acetate followed by addition of 1 M sodium hydroxide until basic. The solution was transferred to a separatory funnel and extracted with ethyl acetate (3x). The combined organic layers were concentrated under reduced pressure to provide crude quinotoxine **Q8** which was directly carried on to the next step. Quinotoxine **Q8** was dissolved in a 1:1 mixture of ethyl acetate and a saturated solution sodium bicarbonate (460 mL) along with 4-(dimethylamino)-pyridine (40 mg, 0.329 mmol) and cooled to 0 °C with stirring. Benzyl chloroformate (4.43 g, 37.0 mmol) was added to the stirring reaction dropwise and the reaction mixture was warmed to room temperature and allowed to stir overnight. The reaction mixture was then transferred to a separatory funnel and the carbamate product extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried with magnesium sulfate and concentrated *in*

*vacuo* to afford a tan residue. Purification by column chromatography using 49:1 ethyl acetate/triethylamine provided 6.70 g (47% yield over two steps) of carbamate **Q6** as a tan oil.

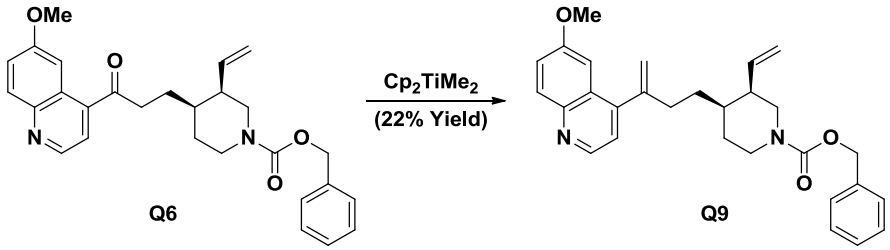
**Note:** Best yields for this reaction sequence were obtained when quinotoxine **Q8** was carried on without chromatographic purification; however, flash column chromatography using 3:2:0.1 ethyl acetate/methanol/aqueous ammonium hydroxide afforded **Q8** in 66% yield. Spectral data obtained for **Q8** were identical to that previously reported and are not reported here.[9] Reaction of pure **Q8** with benzyl chloroformate provided **Q6** in 60% yield.




**$^{1}$H NMR** ($d_6$-DMSO, 500 MHz, 80 °C): δ 8.87 (d, *J* = 4.4 Hz, 1H), 8.01 (d, *J* = 9.2 Hz, 1H), 7.82 (d, *J* = 4.4 Hz, 1H), 7.70 (d, *J* = 2.9 Hz, 1H), 7.47 (dd, *J* = 9.2, 2.9 Hz, 1H), 7.40 - 7.26 (m, 5H), 5.80 (ddd, *J* = 17.4, 10.5, 8.6 Hz, 1H), 5.16 (ddd, *J* = 17.4, 2.2, 1.1 Hz, 1H), 5.13 - 5.02 (m, 1H), 5.08 (d, *J* = 6.5 Hz, 2H), 4.01 - 3.95 (m, 1H), 3.95 - 3.84 (m, 1H), 3.89 (s, 3H), 3.15 - 3.06 (m, 3H), 2.92 (ddd, *J* = 12.5, 11.3, 3.30 Hz, 1H), 2.41 (dddd, *J* = 7.6, 3.6, 3.5, 3.5 Hz, 1H), 1.74 (dddd, *J* = 10.8, 7.2, 3.7, 3.7 Hz, 1H), 1.69 - 1.57 (m, 2H), 1.54 (dddd, *J* = 13.4, 3.4, 3.4, 3.4 Hz, 1H), 1.38 (dddd, *J* = 13.5, 11.2, 11.2, 4.5 Hz, 1H).

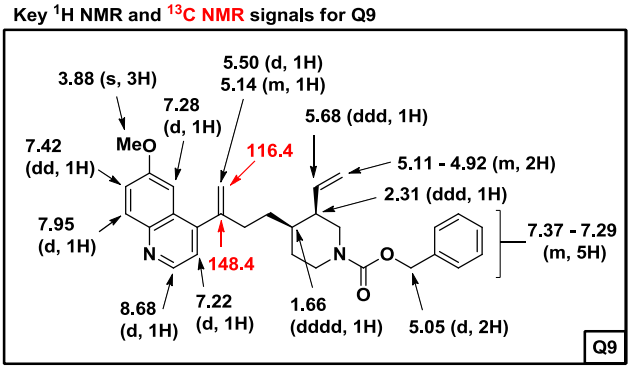
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 203.8, 159.6, 155.7, 147.1, 145.9, 140.5, 137.0, 135.4, 131.6, 128.6, 128.1, 128.0, 125.3, 123.0, 120.2, 117.6, 103.2, 67.2, 55.8, 49.2, 44.1, 42.8, 39.3, 38.5, 27.9, 27.6.

**HRMS(ESI):** *m/z* calc. for $C_{28}H_{31}N_2O_4$ $[M+H]^+$: 459.2284, found: 459.2286.




**Procedure**: Carbamate **Q6** (610 mg, 1.33 mmol) was added to a solution of 12% w/w dimethyl titanocene in toluene (5 mL, 2.5 mmol) containing titanocene dichloride (44 mg, 0.18 mmol).[10] The reaction mixture was heated at 80 °C for 6 hours before cooling to room temperature. Sodium bicarbonate (600 mg), methanol (6 mL), and water (1 mL) were added to the reaction mixture followed by heating at 40 °C for 18 hours to decompose and precipitate the remaining organotitanium residues. The reaction was cooled, filtered, washed with water (3x) and brine, dried with $MgSO_4$, and concentrated under reduced

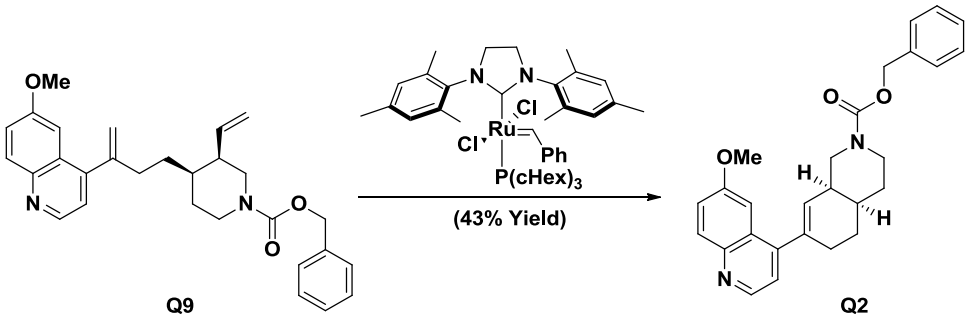
pressure. The crude material was purified by column chromatography using 1:1 hexane/ethyl acetate to yield 135 mg (22% yield) of the desired olefin **Q9** as a tan oil.



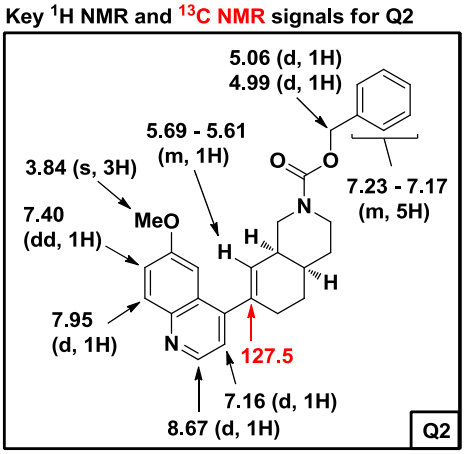

**$^{1}$H NMR** ($d_6$-DMSO, 500 MHz, 80 °C): δ 8.68 (d, *J* = 4.3 Hz, 1H), 7.95 (d, *J* = 9.1 Hz, 1H), 7.42 (dd, *J* = 9.1, 2.9 Hz, 1H), 7.37 - 7.29 (m, 5H), 7.28 (d, *J* = 2.9 Hz, 1H), 7.22 (d, *J* = 4.3 Hz, 1H), 5.68 (ddd, *J* = 17.3, 11.3, 9.1 Hz, 1H), 5.50 (d, *J* = 1.6 Hz, 1H), 5.14 (m, 1H), 5.11 - 4.92 (m, 2H), 5.05 (d, *J* = 6.9 Hz, 2H), 3.93 (ddd, *J* = 13.3, 3.8, 3.8 Hz, 1H), 3.90 - 3.78 (m, 1H), 3.88 (s, 3H), 3.03 (dd, *J* = 13.0, 3.1 Hz, 1H), 2.87 (dd, *J* = 12.4, 12.4 Hz, 1H), 2.58 - 2.51 (m, 2H), 2.31 (ddd, *J* = 7.5, 3.6, 3.6 Hz, 1H), 1.66 (dddd, *J* = 10.1, 3.4, 3.4, 3.2 Hz, 1H), 1.43 (dd, *J* = 13.3, 3.1 Hz, 1H), 1.39 - 1.23 (m, 2H).

**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 157.8, 155.6, 148.4, 147.5, 146.7, 144.8, 137.0, 135.5, 131.5, 128.5, 128.0, 127.9, 127.5, 121.8, 120.0, 117.2, 116.4, 103.6, 67.1, 55.6, 49.1, 44.2, 42.5, 38.5, 34.9, 31.6, 27.6.

**HRMS(ESI):** *m/z* calc. for $C_{29}H_{33}N_2O_3$ $[M+H]^+$: 457.2491, found: 457.2482.



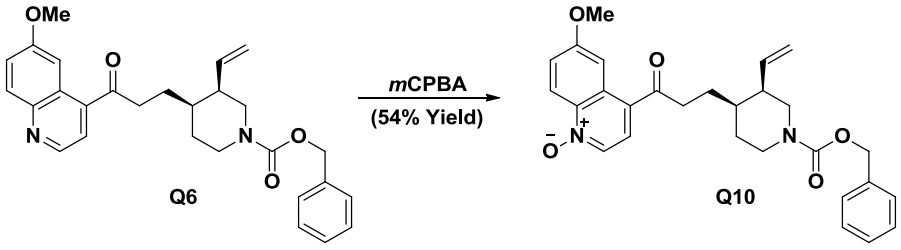

**Procedure**: To a solution of **Q9** (70 mg, 0.15 mmol) in anhydrous dichloromethane (38 mL) was added Grubbs second-generation catalyst (19.5mg, 0.023 mmol). The reaction mixture was heated to 40 °C and allowed to stir 24 hours. The reaction was then cooled to room temperature and the solvent was removed *in vacuo* and the crude mixture purified by column chromatography using 9:1 ethyl acetate/hexane to provide 28.4 mg (43% yield) of the desired [4.4.0]-bicycle **Q2** as a tan oil.




**$^1$H NMR** ($d_6$-DMSO, 500 MHz, 80 °C): δ 8.67 (d, *J* = 4.4 Hz, 1H), 7.95 (d, *J* = 9.1 Hz, 1H), 7.40 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.23 (d, *J* = 2.8 Hz, 1H), 7.23 - 7.17 (m, 5H), 7.16 (d, *J* = 4.4 Hz, 1H), 5.69 - 5.61 (m, 1H), 5.06 (d, *J* = 12.7 Hz, 1H), 4.99 (d, *J* = 12.7 Hz, 1H), 3.84 (s, 3H), 3.80 - 3.65 (m, 2H), 3.46 (dd, *J* = 13.3, 4.2 Hz, 1H), 3.25 (ddd, *J* = 10.6, 9.7, 5.1 Hz, 1H), 2.58 (ddddd, *J* = 7.8, 5.4, 5.4, 3.0, 3.0 Hz, 1H), 2.40 - 2.34 (m, 2H), 2.11 (dddd, *J* = 11.1, 8.5, 4.6, 4.6 Hz, 1H), 1.94 (dddd, *J* = 12.4, 6.0, 5.9, 5.9 Hz, 1H), 1.83 (dddd, *J* = 13.6, 7.2, 7.1, 3.5 Hz, 1H), 1.77 - 1.58 (m, 2H).

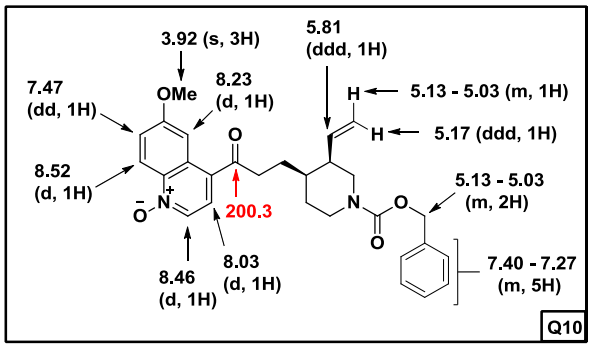
**$^{13}$C NMR** ($d_6$-DMSO, 125 MHz, 80 °C): δ 156.9, 154.3, 147.9, 147.1, 143.9, 136.6, 136.3, 130.6, 129.1, 127.7, 127.1, 126.8, 126.4, 120.8, 119.3, 103.2, 65.6, 54.9, 46.8, 41.9, 35.0, 30.2, 26.8, 26.4, 24.8.

**HRMS(ESI)**: *m/z* calc. for $C_{27}H_{29}N_2O_3$ $[M+H]^+$: 429.2178, found: 429.2178.




**Procedure:** Carbamate **Q6** (1.00 g, 2.18 mmol) was dissolved in dichloromethane (50 mL) at room temperature. Sodium bicarbonate (1.48 g, 14.0 mmol) was added and the solution was cooled to 0 °C. *m*-Chloroperoxybenzoic acid (600 mg, 2.68 mmol calculated at 77% purity) was added and the reaction was stirred overnight. Upon warming to room temperature, the reaction was diluted with dichloromethane (50 mL) and quenched with a saturated solution of sodium bicarbonate (50 mL). The reaction mixture was transferred to a separatory funnel and extracted with dichloromethane (3x). The combined organic layers were washed with brine, dried with magnesium sulfate, and concentrated under reduced pressure. The crude material was purified by column chromatography using 9:1 chloroform/acetone to provide 555 mg (54%) of *N*-oxide **Q10** as a yellow oil.

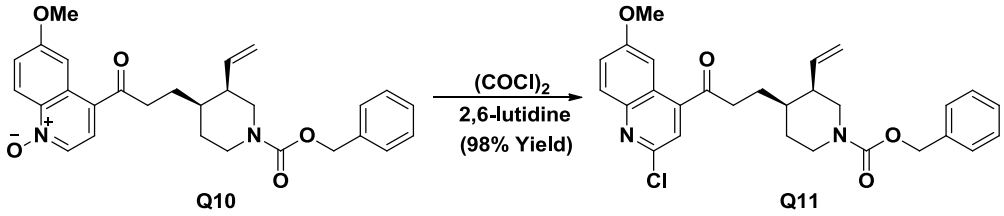
Key $^{1}$H NMR and $^{13}$C NMR signals for Q10




**$^{1}$H NMR** ($d_6$-DMSO, 500 MHz, 80 °C): δ 8.52 (d, *J* = 9.5 Hz, 1H), 8.46 (d, *J* = 6.5 Hz, 1H), 8.23 (d, *J* = 2.8 Hz, 1H), 8.03 (d, *J* = 6.5 Hz, 1H), 7.47 (dd, *J* = 9.6, 2.8 Hz, 1H), 7.40 - 7.27 (m, 5H), 5.81 (ddd, *J* = 17.3, 10.5, 8.5 Hz, 1H), 5.17 (ddd, *J* = 17.3, 2.1, 1.0 Hz, 1H), 5.13 - 5.03 (m, 3H), 4.01 - 3.95 (m, 1H), 3.95 - 3.87 (m, 1H), 3.92 (s, 3H), 3.15 - 3.07 (m, 3H), 2.94 (ddd, *J* = 13.8, 11.5, 3.5 Hz, 1H), 2.42 (ddd, *J* = 7.9, 4.0, 4.0 Hz, 1H), 1.74 (dddd, *J* = 11.1, 7.4, 3.8, 3.8 Hz, 1H), 1.70 - 1.51 (m, 3H), 1.39 (dddd, *J* = 13.6, 11.4, 11.3, 4.5 Hz, 1H).

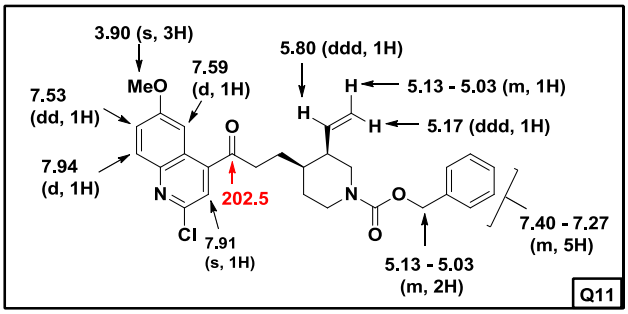
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 200.3, 161.3, 155.6, 138.3, 137.0, 135.5, 132.3, 129.5, 128.5, 128.1, 128.0, 127.9, 123.6, 123.0, 121.3, 117.6, 105.1, 67.1, 55.9, 49.1, 44.1, 42.8, 38.5, 38.2, 27.8, 27.6.

**HRMS(ESI):** *m/z* calc. for $C_{28}H_{31}N_2O_5$ $[M+H]^+$: 475.2233, found: 475.2234.




**Procedure:** To a solution of *N*-oxide **Q10** (50.0 mg, 0.105 mmol) in dichloromethane (0.525 mL) at 0 °C was added 2,6-lutidine (28.1 mg, 0.263 mmol) followed by dropwise addition of oxalyl chloride (19.9 mg, 0.157 mmol). The reaction warmed to room temperature and stirred 2 hours. Upon completion, the reaction was quenched by cooling to 0 °C followed by careful addition of a cold saturated solution of sodium bicarbonate. The reaction mixture was then transferred to a separatory funnel, washed with additional saturated solution of sodium bicarbonate, and extracted with dichloromethane (3x). The combined organic extracts were washed with brine, dried with magnesium sulfate, and evaporated. The crude product was purified by column chromatography using 9:1 ethyl acetate/hexane to provide 50.8 mg (98% yield) of chloride **Q11** as a bright yellow oil.

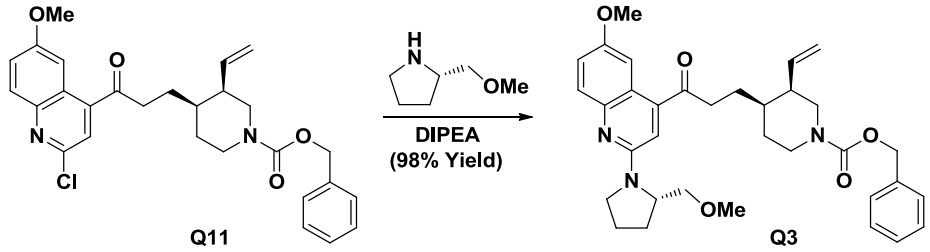
Key $^{1}$H and $^{13}$C NMR signals for Q11




**$^{1}$H NMR** ($d_6$-DMSO, 500 MHz, 80 °C): δ 7.94 (d, *J* = 9.1 Hz, 1H), 7.91 (s, 1H), 7.59 (d, *J* = 2.8 Hz, 1H), 7.53 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.40 - 7.27 (m, 5H), 5.80 (ddd, *J* = 17.3, 10.5, 8.6 Hz, 1H), 5.17 (ddd, *J* = 17.3, 2.1, 1.0 Hz, 1H), 5.13 - 5.03 (m, 3H), 4.03 - 3.94 (m, 1H), 3.94 - 3.90 (m, 1H), 3.90 (s, 3H), 3.14 (m, 2H), 3.11 (dd, *J* = 13.2, 3.3 Hz, 1H), 2.94 (ddd, *J* = 13.7, 12.6, 3.4 Hz, 1H), 2.43 (dddd, *J* = 7.4, 3.5, 3.5, 3.5 Hz, 1H), 1.74 (ddddd, *J* = 11.0, 7.4, 3.9, 3.7, 3.7 Hz, 1H), 1.69 - 1.51 (m, 3H), 1.38 (dddd, *J* = 13.4, 11.2, 11.2, 4.5 Hz, 1H).

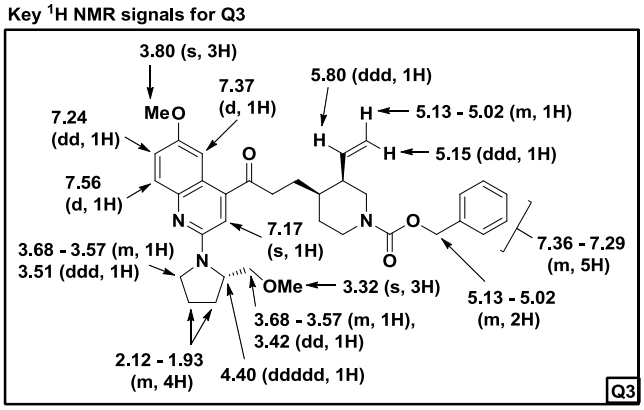
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 202.5, 159.7, 155.7, 147.4, 145.4, 143.7, 137.0, 135.4, 130.6, 128.6, 128.1, 128.0, 124.3, 123.9, 121.5, 117.8, 103.6, 67.2, 55.9, 49.3, 44.1, 42.8, 39.5, 38.5, 27.6, 27.5.

**HRMS (ESI):** *m/z* calc. for $C_{28}H_{30}ClN_2O_4$ $[M+H]^+$: 493.1894, found: 493.1901.




**Procedure:** A solution of chloride **Q11** (100 mg, 0.203 mmol), (*S*)-2-(methoxymethyl)pyrrolidine (47 mg, 0.408 mmol), and *N*,*N*-disoproylethylamine (130 mg, 1.01 mmol) in *N*-methyl-2-pyrrolidone (0.910 mL) was heated at 140 °C in a sealed tube with stirring for 24 hours. The reaction contents were directly purified by column chromatography using 96:3:1 chloroform/acetone/triethylamine to provide 113 mg (98% yield) of the desired amine **Q3** as a yellow oil.

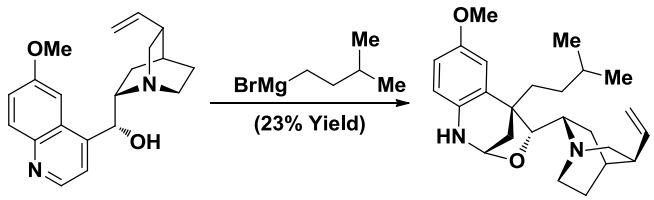
Key $^1$H NMR signals for Q3




**$^1$H NMR** ($d_6$-DMSO, 500 MHz, 80 °C): δ 7.56 (d, *J* = 9.1 Hz, 1H), 7.37 (d, *J* = 2.9 Hz, 1H), 7.36 - 7.29 (m, 5H), 7.24 (dd, *J* = 9.1, 2.9 Hz, 1H), 7.17 (s, 1H), 5.80 (ddd, *J* = 17.3, 10.5, 8.6 Hz, 1H), 5.15 (ddd, *J* = 17.3, 2.1, 1.1 Hz, 1H), 5.13 - 5.02 (m, 3H), 4.40 (ddddd, *J* = 9.2, 3.2, 3.2, 2.4, 2.4 Hz, 1H), 4.02 - 3.94 (m, 1H), 3.91 (ddd, *J* = 13.0, 3.6, 1.7 Hz, 1H), 3.80 (s, 3H), 3.68 - 3.57 (m, 2H), 3.51 (ddd, *J* = 10.2, 8.8, 6.6 Hz, 1H), 3.42 (dd, *J* = 9.6, 6.9 Hz, 1H), 3.32 (s, 3H), 3.14 - 3.02 (m, 2H), 2.98 - 2.89 (m, 1H), 2.41 (dddd, *J* = 7.7, 3.7, 3.7, 3.7 Hz, 1H), 2.12 - 1.93 (m, 5H), 1.73 (dddd, *J* = 11.1, 7.4, 3.8, 3.8 Hz, 1H), 1.67 - 1.57 (m, 2H), 1.57 - 1.50 (m, 1H), 1.38 (dddd, *J* = 13.5, 11.3, 11.3, 4.4 Hz, 1H).

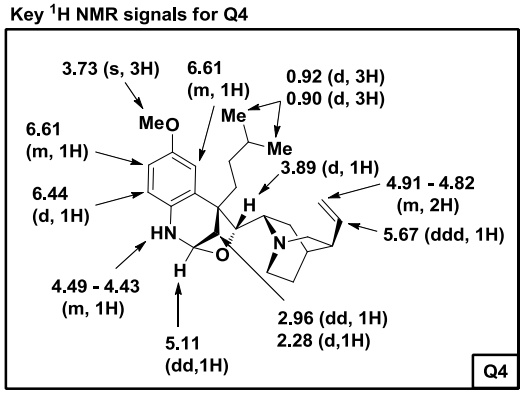
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 204.7, 155.7, 155.6, 154.1, 145.3, 143.6, 137.1, 135.5, 128.6, 128.1, 128.0, 121.8, 118.8, 117.9, 117.6, 109.7, 104.0, 74.0, 67.2, 59.4, 57.5, 55.7, 49.3, 48.0, 44.1, 42.8, 39.6, 38.5, 28.9, 28.0, 27.6, 23.9.

**HRMS(ESI):** *m/z* calc. for $C_{34}H_{42}N_3O_5$ $[M+H]^+$: 572.3124, found: 572.3117.




**Procedure:** A flame dried three necked flask was charged with magnesium (2.43 g, 100 mmol) and heated to 130 °C under vacuum for 30 minutes. The flask was then cooled and flushed with argon. Anhydrous THF (10 mL) and diisobutylaluminum hydride (0.6 mL, 1.0 M in tetrahydrofuran) were then added. Isoamyl bromide (2.40 mL, 20 mmol) was then added dropwise until an exotherm was observed then slow addition maintained a gentle reflux. After complete addition, the reaction mixture was refluxed 2h and cooled to provide a 0.9 M solution of isoamylmagnesium bromide in tetrahydrofuran (titrated with menthol/2,2'-bipyridine). To a flame dried round bottom flask charged with dry toluene (20 mL) was added isoamylmagnesium bromide (5.0 mL, 0.9 M in tetrahydrofuran, 4.5 mmol) followed by addition of quinine (292 mg, 0.9 mmol) as a single portion with vigorous stirring. The mixture was stirred at 70 °C for 3 hours at which point a second portion of isoamylmagnesium bromide (1.5 mL, 0.9 M in tetrahydrofuran, 1.2 mmol) was added. The reaction was refluxed an additional 12 hours and then cooled to 0°C, diluted with methyl *tert*-butyl ether, and quenched by careful addition of a saturated solution of

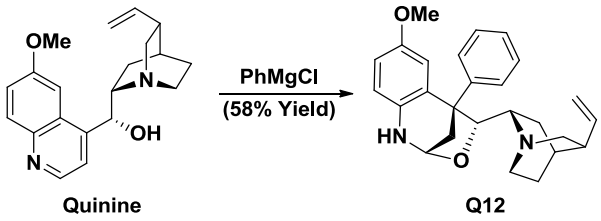
ammonium chloride. The biphasic mixture was separated and the organic layer was washed with additional ammonium chloride followed by water. The organic layer was then collected from a separatory funnel, dried with magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography using 49:1 ethyl acetate/triethylamine provided 83.1 mg (23% yield) of aminal **Q4** as a tan oil.




**$^1$H NMR** (500 MHz, $CDCl_3$): δ 6.61 (m, 2H), 6.44 (d, *J* = 9.1 Hz, 1H), 5.67 (ddd, *J* = 17.7, 9.8, 7.9 Hz, 1H), 5.11 (dd, *J* = 5.1, 3.2 Hz, 1H), 4.91 - 4.82 (m, 2H), 4.49 - 4.43 (m, 1H), 3.89 (d, *J* = 5.1 Hz, 1H), 3.73 (s, 3H), 2.96 (dd, *J* = 13.7, 10.0 Hz, 1H), 2.92 - 2.83 (m, 1H), 2.63 - 2.52 (m, 1H), 2.41 (ddd, *J* = 13.7, 4.6, 2.4 Hz, 1H), 2.38 - 2.32 (m, 1H), 2.28 (d, *J* = 10.9 Hz, 1H), 2.19 (ddd, *J* = 13.2, 13.1, 3.6 Hz, 1H), 2.15 - 1.99 (m, 2H), 1.65 - 1.46 (m, 4H), 1.40 - 1.30 (m, 2H), 1.23 - 1.07 (m, 2H), 1.00 (ddd, *J* = 13.7, 8.5, 3.4 Hz, 1H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H).

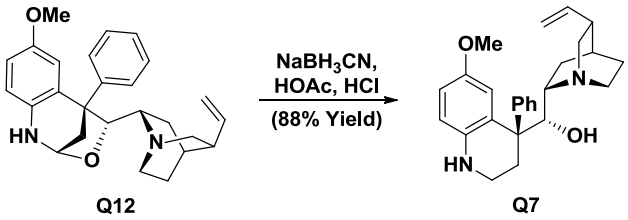
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 153.2, 142.5, 136.8, 129.1, 116.2, 113.8, 113.1, 112.7, 96.9, 83.8, 57.2, 56.1, 55.9, 47.9, 42.6, 40.5, 37.8, 34.6, 29.8, 28.9, 27.9, 27.6, 23.5, 22.8, 22.8.

**HRMS(ESI)**: *m/z* calc. for $C_{25}H_{37}N_2O_2$ $[M+H]^+$: 397.2855, found: 397.2853.

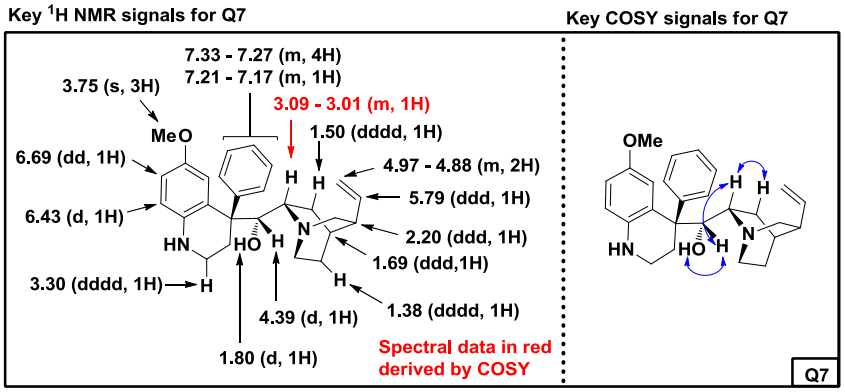



**Procedure:** To a flame dried round bottom flask charged with anhydrous toluene (20 mL) was added phenyl magnesium chloride (4.65 mL, 2.0 M in tetrahydrofuran, 9.29 mmol) followed by addition of quinine (600 mg, 1.85 mmol) as a single portion with vigorous stirring. The mixture was stirred at 70 °C for 3 hours and an additional portion of phenyl magnesium chloride (4.65 mL, 2.0 M in tetrahydrofuran, 9.29 mmol) was added. The reaction was refluxed an additional 1.5 hours and then cooled to 0 °C, diluted with methyl *tert*-butyl ether, and quenched by careful addition of a saturated solution of ammonium chloride. The biphasic mixture was separated and the organic layer was washed with ammonium chloride and then water. The organic layer was then dried with magnesium sulfate and

concentrated under reduced pressure. Purification by column chromatography using 47:2:1 ethyl acetate/methanol/triethylamine afforded 434 mg (58% yield) of aminal **Q12** as a tan crystalline powder that had identical spectra to those that were previously published ($^{1}$H NMR and $^{13}$C NMR) for this compound.[11]




**Procedure**: Aminal **Q12** (400 mg, 1.00 mmol) was dissolved in a solution of glacial acetic acid (0.25 mL) and methanol (2 mL) at 0 °C. Sodium cyanoborohydride (126 mg, 2.00 mmol) was added and the reaction was stirred 2.5 hours before concentrated hydrochloric acid (0.60 mL) was added and stirred for an additional 12 hours. The reaction was quenched by the addition of 2 M sodium hydroxide until pH >9 and transferred to a separatory funnel. The crude mixture was extracted with ethyl acetate (3x), washed with brine, dried with magnesium sulfate, and concentrated under reduced pressure. Purification by column chromatography using 49:1 ethyl acetate/triethylamine yielded 352 mg (88% yield) of tetrahydroquinoline **Q7** as a white foam.

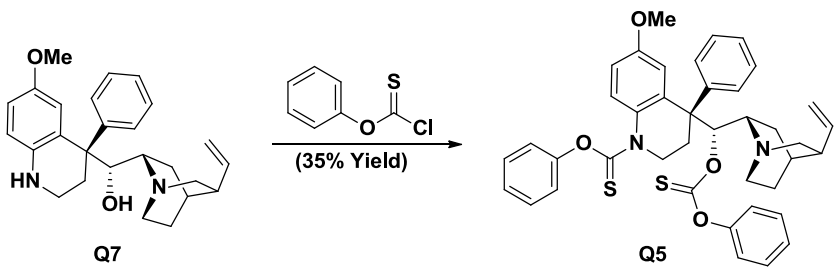



**$^{1}$H NMR** ($CDCl_3$, 500 MHz): δ 7.33 - 7.27 (m, 4H), 7.21 - 7.17 (m, 1H), 6.98 (d, *J* = 2.8 Hz, 1H), 6.69 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.43 (d, *J* = 8.6 Hz, 1H), 5.79 (ddd, *J* = 17.1, 10.4, 7.9 Hz, 1H), 4.97 - 4.88 (m, 2H), 4.39 (d, *J* = 4.5 Hz, 1H), 3.75 (s, 3H), 3.59 - 3.48 (m, 1H), 3.30 (dddd, *J* = 11.4, 5.7, 3.0, 3.0 Hz, 1H), 3.22 - 3.09 (m, 2H), 3.09 - 3.01 (m, 2H), 2.68 - 2.55 (m, 2H), 2.49 (ddd, *J* = 13.7, 5.4, 2.4 Hz, 1H), 2.20 (ddd, *J* = 8.0, 8.0, 7.8 Hz, 1H), 1.93 - 1.82 (m, 2H), 1.80 (d, *J* = 4.6 Hz, 1H), 1.72 - 1.60 (m, 2H), 1.50 (dddd, *J* = 13.4, 10.4, 3.2, 3.2 Hz, 1H), 1.38 (dddd, *J* = 15.5, 10.7, 5.3, 2.9 Hz, 1H).

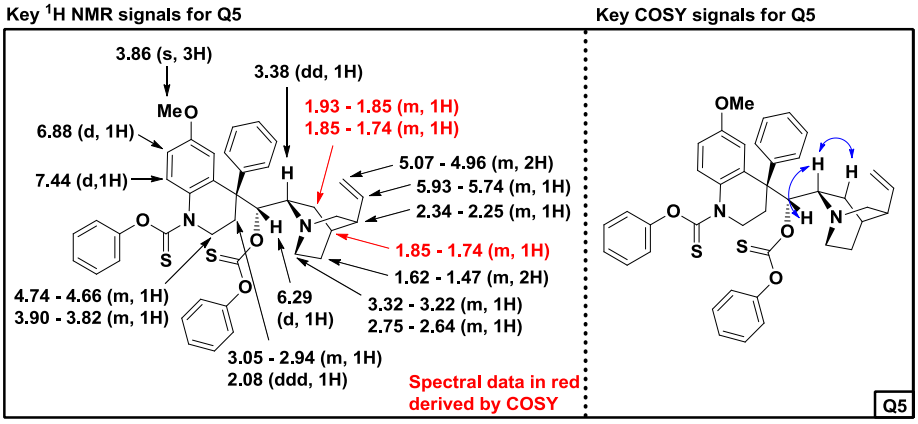
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 151.4, 145.0, 142.6, 139.1, 128.6, 128.5, 126.6, 125.6, 115.7, 114.8, 114.4, 114.0, 79.7, 57.0, 56.4, 56.3, 50.5, 42.8, 40.7, 39.0, 28.6, 27.7, 26.8, 22.2.

**HRMS(ESI)**: *m/z* calc. for $C_{26}H_{33}N_2O_2$ $[M+H]^+$: 405.2542, found: 405.2542.

**Melting point:** 143-146 °C.




**Procedure**: Tetrahydroquinoline **Q7** (202 mg, 0.50 mmol) was dissolved in anhydrous dichloromethane (7 mL) and cooled to 0 °C. *O*-phenyl chlorothionoformate (190 mg, 2.20 mmol) was added and the reaction was warmed to room temperature and stirred for 7.5 hours. The reaction mixture was then diluted with dichloromethane, quenched with a saturated solution of sodium bicarbonate and transferred to a separatory funnel. The biphasic mixture was separated and the organic layer washed with brine, dried with magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography using 100:0 to 90:10 chloroform/ethyl acetate to provide 119 mg (35% yield) of *O*-thiocarbonate **Q5** as a white solid.




**$^{1}$H NMR** ($CDCl_3$, 500 MHz): δ 7.44 (d, *J* = 9.1 Hz, 1H), 7.39 - 7.32 (m, 3H), 7.31 - 7.22 (m, 8H), 7.15 (dd, *J* = 8.4, 6.3 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 6.88 - 6.81 (m, 2H), 6.64 (d, *J* = 7.8 Hz, 2H), 6.29 (d, *J* = 2.6 Hz, 1H), 5.85 (ddd, *J* = 17.4, 10.0, 7.4 Hz, 1H), 5.07 - 4.96 (m, 2H), 4.74 - 4.66 (m, 1H), 3.90 - 3.82 (m, 1H), 3.86 (s, 3H), 3.38 (dd, *J* = 8.7, 8.7 Hz, 1H), 3.32 - 3.22 (m, 1H), 3.12 (dd, *J* = 11.9, 11.9 Hz, 1H), 3.05 - 2.94 (m, 1H), 2.75 - 2.64 (m, 1H), 2.63 - 2.54 (m, 1H), 2.34 - 2.25 (m, 1H), 2.08 (ddd, *J* = 12.0, 10.9, 6.1 Hz, 1H), 1.93 - 1.85 (m, 1H) 1.85 - 1.74 (m, 2H), 1.62 - 1.47 (m, 2H).

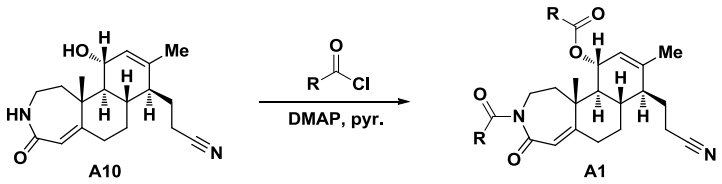
**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 187.0, 157.6, 155.9, 154.0, 153.4, 141.9, 139.6, 130.1, 129.8, 129.6, 129.2, 128.2, 127.3, 126.7, 125.9, 122.6, 122.0, 120.7, 115.6, 114.6, 113.2, 112.0, 88.3, 57.6, 56.3, 55.8, 51.4, 47.8, 42.8, 40.0, 29.3, 28.0, 27.7, 23.3.

**HRMS(ESI)**: *m/z* calc. for $C_{40}H_{41}N_2O_4S_2$ $[M+H]^+$: 677.2508, found: 677.2514.

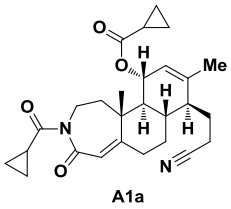
**Melting point:** 169-171 °C.

## 10.) Adrenosterone Derived Libraries: Synthesis and Characterization

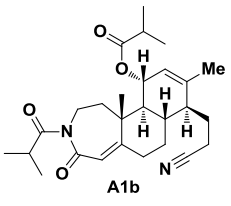
### Synthesis of A1 Derivatives



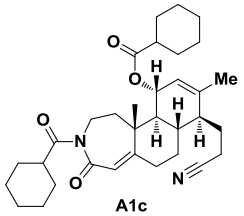

**General procedure for the preparation of A1 ester imides:** Acid chloride (10 equiv.) was added to a solution of pyridine (800 µL) and 4-(dimethylamino)-pyridine (5 equiv.) at room temperature and allowed to stir for one hour. After this time, **A10** (25 mg, 0.080 mmol), dissolved in 200 µL pyridine, was added to the reaction mixture and allowed to stir for 12 hours at room temperature before being quenched with a saturated aqueous solution of sodium bicarbonate and extracted with dichloromethane (3x). The organic layer was washed with a 5% aqueous solution of hydrochloric acid followed by brine (1x each). The organic layers were combined, dried with magnesium sulfate and concentrated. Ester imide **A1** derivatives were purified by column chromatography using hexanes/ethyl acetate to elute. (Note: The scale of this reaction ranged from 6 to 50 milligrams of **A10**.)




**A1a:** Prepared from cyclopropanecarbonyl chloride.
**Yield:** 3.3 mg, 35%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 5.97 (d, *J* = 1.1 Hz, 1H), 5.36 (m, 1H), 5.35 (m, 1H), 3.90 (dd, *J* = 14.8, 7.9 Hz, 1H), 3.82 (dd, *J* = 14.0, 8.5 Hz, 1H), 2.98 (tt, *J* = 7.9, 4.7 Hz, 1H), 2.54 (m, 1H), 2.31 - 2.21 (m, 2H), 2.21 - 2.10 (m, 2H), 2.10 - 1.95 (m, 4H), 1.88 - 1.74 (m, 2H), 1.71 (m, 1H),1.67 (s, 3H), 1.59 (tt, *J* = 7.9, 4.7 Hz, 1H), 1.26 (m, 1H), 1.17 (s, 3H), 1.12 - 1.08 (m, 2H), 1.03 - 0.98 (m, 2H), 0.97 - 0.92 (m, 3H), 0.88 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{27}H_{35}N_2O_4$ $[M+H]^+$: 451.2597, found: 451.2588.

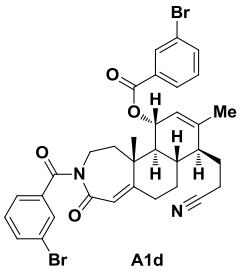



**A1b:** Prepared from isobutyryl chloride.
**Yield:** 17.2 mg, 52%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 5.92 (s, 1H), 5.36 (dd, *J* = 5.0,1.5 Hz, 1H), 5.28 (d, *J* = 1.0 Hz, 1H), 3.96 (dd, *J* = 14.8, 8.3 Hz, 1H), 3.70 (m, 2H), 2.59 - 2.43 (m, 2H), 2.31 - 2.09 (m, 4H), 2.04 (m, 3H), 1.91 (dd, *J* = 15.4, 8.5 Hz, 1H), 1.82 - 1.62 (m, 3H), 1.66 (s, 3H), 1.25 (m, 1H), 1.20 - 1.10 (m, 15H).
**HRMS(ESI):** *m/z* calc. for $C_{27}H_{39}N_2O_4$ $[M+H]^+$: 455.2910, found: 455.2903.



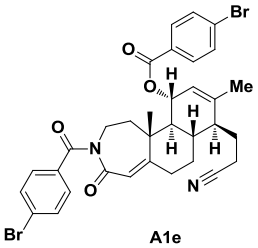

**A1c:** Prepared from cyclohexanecarbonyl chloride.
**Yield:** 35.8 mg, 76%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 5.90 (s, 1H), 5.35 (m, 1H), 5.26 (m, 1H), 3.98 (dd, *J* = 14.7, 8.4 Hz, 1H), 3.59 (dd, *J* = 14.9, 8.4 Hz, 1H), 3.43 (tt, *J* = 11.0, 3.2 Hz, 1H), 2.51 (td, *J* = 12.5, 3.5 Hz, 1H), 2.30 - 2.07 (m, 4H), 2.03 (m, 3H), 1.96 - 1.81 (m, 5H), 1.81 - 1.71 (m, 5H), 1.70 - 1.59 (m, 4H), 1.65 (s, 3H), 1.49 - 1.17 (m, 12H),

1.15 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{33}H_{47}N_2O_4$ $[M+H]^+$: 535.3536, found: 535.3528.



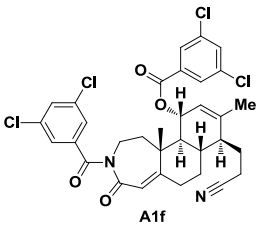
A1d

**A1d:** Prepared from 3-bromobenzoyl chloride.
**Yield:** 20.6 mg, 39%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.17 (t, *J* = 1.8 Hz, 1H), 7.96 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.72 (ddt, *J* = 7.9, 2.0, 1.1 Hz, 1H), 7.61 (t, *J* = 1.8 Hz, 1H), 7.57 (ddt, *J* = 7.9, 2.0, 1.0 Hz, 1H), 7.39 (m, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.24 (t, *J* = 7.9 Hz, 1H), 5.90 (s, 1H), 5.68 (dq, *J* = 8.8, 2.1 Hz, 1H), 5.46 (q, *J* = 1.9 Hz, 1H), 3.96 (dd, *J* = 14.9, 8.4 Hz, 1H), 3.71 (dd, *J* = 14.9, 8.7 Hz, 1H), 2.59 (td, *J* = 13.6, 4.5 Hz, 1H), 2.33 (m, 1H), 2.27 (dt, *J* = 14.0, 3.7 Hz, 1H), 2.24 - 2.18 (m, 2H), 2.18 - 2.03 (m, 4H), 2.00 (dd, *J* = 11.8, 8.9 Hz, 1H), 1.94 (dd, *J* = 15.5, 8.3 Hz, 1H), 1.82 (qd, *J* = 11.9, 3.9 Hz, 1H), 1.70 (m, 3H), 1.33 (m, 1H), 1.28 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{33}H_{33}N_2O_4Br_2$ $[M+H]^+$: 679.0807, found: 679.0804.



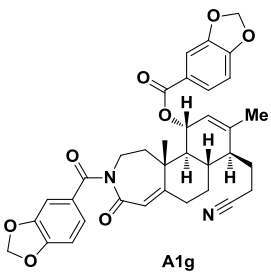
A1e

**A1e:** Prepared form 4-bromobenzoyl chloride
**Yield:** 39.0 mg, 68%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.89 (m, 2H), 7.62 (m, 2H), 7.51 (m, 2H), 7.37 (m, 2H), 5.89 (s, 1H), 5.67 (dq, *J* = 8.7, 2.0 Hz, 1H), 5.46 (q, *J* = 1.9 Hz, 1H), 3.94 (dd, *J* = 14.9, 8.3 Hz, 1H), 3.72 (dd, *J* = 14.8, 8.6 Hz, 1H), 2.59 (m, 1H), 2.34 (m, 1H), 2.27 (m, 1H), 2.24 - 2.16 (m, 2H), 2.15 - 2.03 (m, 4H), 1.99 - 1.92 (m, 2H), 1.82 (ddd, *J* = 12.9, 9.4, 3.9 Hz, 1H), 1.69 (s, 3H), 1.36 - 1.24 (m, 1H), 1.27 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{33}H_{33}N_2O_4Br_2$ $[M+H]^+$: 679.0807, found: 679.0816.



A1f

**A1f:** Prepared from 3,5-dichlorobenzoyl chloride.
**Yield:** 7.6 mg, 55%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.89 (d, *J* = 2.0 Hz, 2H), 7.59 (t, *J* = 1.9 Hz, 1H), 7.41 (t, *J* = 1.9 Hz, 1H), 7.31 (d, *J* = 1.9 Hz, 2H), 5.90 (s, 1H), 5.68 (dq, *J* = 8.6, 2.1 Hz, 1H), 5.45 (d, *J* = 1.5 Hz, 1H), 3.99 (dd, *J* = 14.9, 8.3 Hz, 1H), 3.68 (dd, *J* = 14.9, 8.6 Hz, 1H), 2.60 (td, *J* = 13.5, 4.0 Hz, 1H), 2.35 (dq, *J* = 12.4, 3.9 Hz, 1H), 2.29 (m, 1H), 2.25 - 2.18 (m, 2H), 2.18 - 1.96 (m, 5H), 1.91 (dd, *J* = 15.6, 8.3 Hz, 1H), 1.88 - 1.77 (m, 1H), 1.71 (s, 3H), 1.33 (m, 1H), 1.28 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{33}H_{31}N_2O_4Cl_4$ $[M+H]^+$: 659.1038, found: 659.1027.

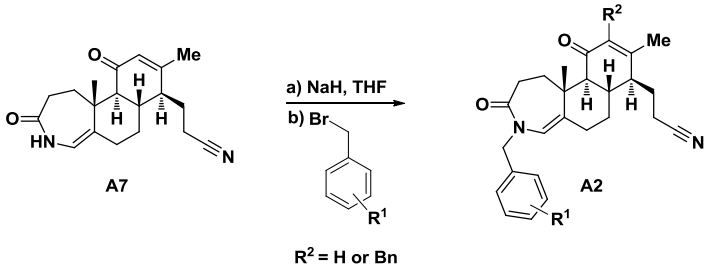


A1g

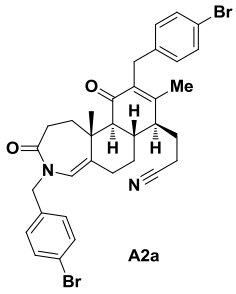
**A1g:** Prepared from piperonyloyl chloride.
**Yield:** 19.7 mg, 39%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.63 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.44 (d, *J* = 1.7 Hz, 1H), 7.16 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.02 (d, *J* = 1.7 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.05 (d, *J* = 1.0 Hz, 1H), 6.03 (d, *J* = 1.5 Hz, 1H), 6.02 - 5.98 (m, 2H), 5.90 (s, 1H), 5.63 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.45 (q, *J* = 1.9 Hz, 1H), 3.86 (dd, *J* = 14.9, 8.3 Hz, 1H), 3.68 (dd, *J* = 14.9, 8.7 Hz, 1H), 2.58 (td, *J* = 13.7, 4.5 Hz, 1H), 2.32 (dq, *J* = 12.3, 3.9 Hz, 1H), 2.26 (dt, *J* =

13.4, 3.5 Hz, 1H), 2.24 - 2.04 (m, 6H), 2.02 - 1.88 (m, 2H), 1.86 - 1.72 (m, 1H), 1.68 (s, 3H), 1.32 (m, 1H), 1.26 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{35}H_{35}N_2O_8$ $[M+H]^+$: 611.2393, found: 611.2392.

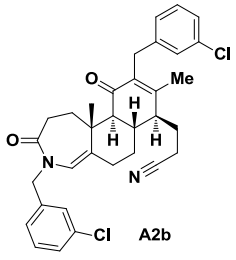
**Synthesis of A2 Derivatives**



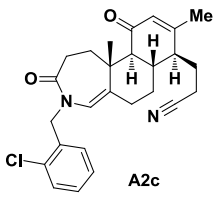

**General procedure for the preparation of A2 *N*-benzylated enamides:** Enamide **A7** (70 mg, 0.224 mmol dissolved in 0.8 mL tetrahydrofuran) was added dropwise to a stirring suspension of sodium hydride (50 mg, 0.986 mmol) in tetrahydrofuran (1.2 mL) at 0 °C. The resulting mixture was allowed to stir for 30 minutes before a benzyl bromide derivative (2 equiv.) was added to the reaction. The reaction was allowed to stir at 0 °C for an additional 20 minutes before the ice bath was removed and the reaction stirred at room temperature for 16 hours. Upon completion of the reaction a saturated solution of aqueous ammonia chloride was added to quench the reaction and ethyl acetate was used to extract the product. The ethyl acetate layer was then washed with brine (2x), dried with magnesium sulfate and concentrated under reduced pressure. The crude material was purified by column chromatography using hexanes/ethyl acetate to afford a benzylated enamide.




**A2a:** Prepared from 4-bromobenzyl bromide.
**Yield:** 15.1 mg, 10%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.43 (d, *J* = 7.9 Hz, 2H), 7.36 (d, *J* = 7.9 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 5.57 (s, 1H), 4.58 (m, 2H), 3.66 (d, *J* = 15.0 Hz, 1H), 3.50 (d, *J* = 15.0 Hz, 1H), 2.70 - 2.42 (m, 3H), 2.33 (m, 2H), 2.26 - 2.03 (m, 5H), 2.03 - 1.73 (m, 4H), 1.85 (s, 3H), 1.29 (s, 3H), 1.14 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{33}H_{35}N_2O_2Br_2$ $[M+H]^+$: 649.1065, found: 649.1057.

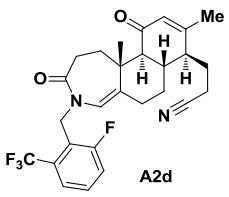



**A2b:** Prepared from 3-chlorobenzyl bromide.
**Yield:** 15.9 mg, 12%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.25 - 7.12 (m, 5H), 7.10 (dt, *J* = 6.9, 1.9 Hz, 1H), 7.02 (m, 1H), 6.93 (dt, *J* = 7.2, 1.6 Hz, 1H), 5.58 (s, 1H), 4.66 - 4.56 (m, 2H), 3.71 (d, *J* = 15.0 Hz, 1H), 3.53 (d, *J* = 15.0 Hz, 1H), 2.58 - 2.45 (m, 3H), 2.36 (m, 1H), 2.33 (dd, *J* = 13.5, 3.0 Hz, 1H), 2.24 - 1.87 (m, 9H), 1.86 (s, 3H), 1.32 (s, 3H), 1.16 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{33}H_{35}N_2O_2Cl_2$ $[M+H]^+$: 561.2076, found: 561.2083.



A2c

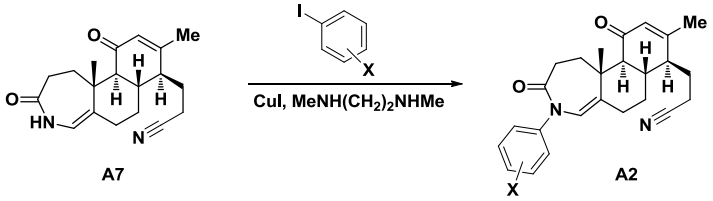
**A2c:** Prepared from 2-chlorobenzyl bromide.
**Yield:** 4.4 mg, 5%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.44 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.34 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.28 (m, 1H), 7.19 (td, *J* = 7.6, 1.6 Hz, 1H), 5.69 (s, 1H), 5.65 (d, *J* = 1.7 Hz, 1H), 4.86 (d, *J* = 16.5 Hz, 1H), 4.80 (d, *J* = 16.6 Hz, 1H), 3.54 (dd, *J* = 12.5, 12.0 Hz, 1H), 2.78 - 2.47 (m, 6H), 2.47 - 2.42 (m, 1H), 2.09 (dd, *J* = 10.0, 2.0 Hz, 1H), 2.01 (m, 1H), 1.96 - 1.83 (m, 2H), 1.92 (s, 3H), 1.59 - 1.45 (m, 2H), 1.29 - 1.24 (m, 1H), 1.27 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{26}H_{30}N_2O_2Cl$ $[M+H]^+$: 437.1996, found: 437.1997.



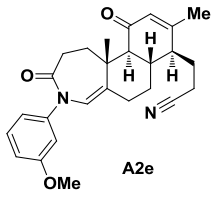
A2d

**A2d:** Prepared from 2-fluoro-6-(trifluoromethyl)benzyl bromide.
**Yield:** 31.4 mg, 36%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.49 (d, *J* = 7.8 Hz, 1H), 7.40 (td, *J* = 8.1, 5.2 Hz, 1H), 7.25 (t, *J* = 8.5 Hz, 1H), 5.86 (dd, *J* = 2.5, 1.4 Hz, 1H), 5.49 (s, 1H), 4.99 (d, *J* = 15.5 Hz, 1H), 4.89 (d, *J* = 15.5 Hz, 1H), 2.62 - 2.36 (m, 3H), 2.32 - 2.15 (m, 3H), 2.15 - 2.00 (m, 6H), 1.96 - 1.84 (m, 1H), 1.87 (s, 3H), 1.79 (dt, *J* = 13.6, 3.6 Hz, 1H), 1.18 (s, 3H), 0.96 (qd, *J* = 13.0, 4.0 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{27}H_{29}N_2O_2F_4$ $[M+H]^+$: 489.2165, found: 489.2156.

**Synthesis of A2 Derivatives**

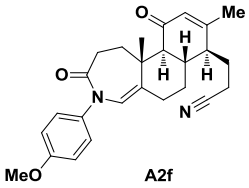



**General procedure for the preparation of A2 *N*-aryl enamides:** Enamide **A7** (35 mg, 0.112 mmol) and aryl iodide (1.2 equiv.) were dissolved in dry acetonitrile (0.5 mL) and stirred under argon at 70 °C for 20 minutes before potassium carbonate (2 equiv.), *N*,*N*′-dimethylethylenediamine (0.8 equiv.) and copper (I) iodide (0.4 equiv.) were added. The reaction vial was sealed and the reaction was refluxed for 15 hours before being cooled to room temperature and quenched with brine and extracted with ethyl acetate. The organic layer was collected, dried with magnesium sulfate and concentrated. The desired aryl enamides were purified using column chromatography using hexanes/ethyl acetate.



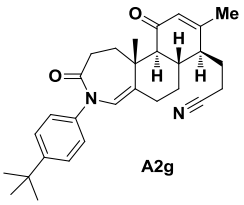
A2e

**A2e:** Prepared from 3-iodoanisole.
**Yield:** 8.7 mg, 25%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.30 (t, *J* = 8.1 Hz, 1H), 6.84 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 6.81 (ddd, *J* = 7.8, 2.0, 0.9 Hz, 1H), 6.76 (t, *J* = 2.2 Hz, 1H), 5.92 (dd, *J* = 2.6, 1.4 Hz, 1H), 5.82 (d, *J* = 1.3 Hz, 1H), 3.80 (s, 3H), 2.75 (dd, *J* = 14.5, 9.5 Hz, 1H), 2.69 - 2.56 (m, 2H), 2.42 - 2.11 (m, 9H), 2.06 - 1.95 (m, 2H), 1.92 (s, 3H), 1.34 (s, 3H), 1.32 - 1.20 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{26}H_{31}N_2O_3$ $[M+H]^+$: 419.2335, found: 419.2344.



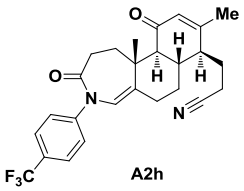
A2f

**A2f:** Prepared from 4-iodoanisole.
**Yield:** 9.7 mg, 15%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.12 (m, 2H), 6.91 (m, 2H), 5.91 (dd, *J* = 2.7, 1.4 Hz, 1H), 5.79 (m, 1H), 3.81 (s, 3H), 2.73 (m, 1H), 2.68 - 2.53 (m, 2H), 2.43 - 2.31 (m, 2H), 2.31 - 2.07 (m, 7H), 2.07 - 1.94 (m, 2H), 1.91 (s, 3H), 1.34 (s, 3H), 1.26 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{26}H_{31}N_2O_3$ $[M+H]^+$: 419.2335, found: 419.2338.



A2g

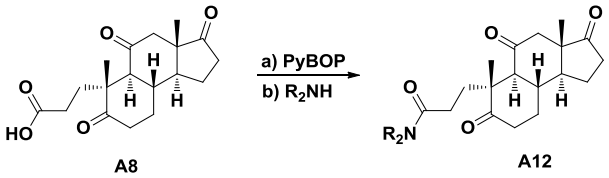
**A2g:** Prepared from 4-*tert*-butyliodobenzene.
**Yield:** 15.9 mg, 26%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.41 (m, 2H), 7.14 (m, 2H), 5.91 (dd, *J* = 2.6, 1.4 Hz, 1H), 5.82 (s, 1H), 2.74 (dd, *J* = 14.0, 9.5 Hz, 1H), 2.69 - 2.53 (m, 2H), 2.43 - 2.31 (m, 2H), 2.30 - 2.07 (m, 7H), 2.06 - 1.95 (m, 2H), 1.91 (s, 3H), 1.34 (s, 3H), 1.31 (s, 9H), 1.30 - 1.20 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{29}H_{37}N_2O_2$ $[M+H]^+$: 445.2855, found: 455.2846.



A2h

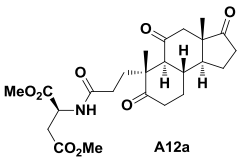
**A2h:** Prepared from 4-iodobenzotrifluoride.
**Yield:** 4.5 mg, 5%.
**$^1$H NMR** ($CDCl_3$,500 MHz): δ 7.65 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 5.92 (dd, *J* = 2.6, 1.4 Hz, 1H), 5.79 (m, 1H), 2.76 (m, 1H), 2.71 - 2.57 (m, 2H), 2.46 - 2.13 (m, 9H), 2.10 - 1.97 (m, 2H), 1.92 (s, 3H), 1.36 (s, 3H), 1.34 - 1.23 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{26}H_{28}N_2O_2F_3$ $[M+H]^+$: 457.2103, found: 457.2107.

**Synthesis of Compounds based on A12**



A8 A12

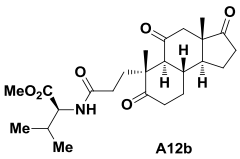
**General procedure for the preparation of A12 amides:** In an oven-dried vial, **A8** (1 equiv.) and benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (1.2 equiv.) were dissolved in dichloromethane (0.1 M). Diisopropylethylamine (1 equiv.) was added, and the reaction was stirred at room temperature for 1-2 hours. After complete complexation by TLC, an amine (1-3 equiv.) and additional diisopropylethylamine (1-3 equiv.) were added, and the reaction was allowed to stir at room temperature for 12-16 hours. The reaction was concentrated under reduce pressure and purified by flash chromatography on silica gel (hexanes/ethyl acetate or dichloromethane/methanol) to provide the amide**.**



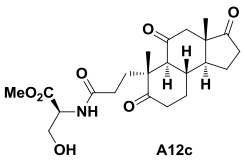
A12a

**A12a**: Prepared from L- aspartic acid dimethyl ester hydrochloride.
**Yield:** 75.1 mg, 32%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 6.62 (d, *J* = 8.1 Hz, 1H), 4.75 (dt, *J* = 8.5, 4.5 Hz, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 2.98 (dd, *J* = 17.2, 4.4 Hz, 1H), 2.83 (dd, *J* = 17.2,

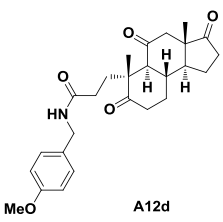
4.6 Hz, 1H), 2.62 - 2.43 (m, 3H), 2.40 - 1.92 (m, 12H), 1.70 (tt, *J* = 12.4, 9.2 Hz, 1H), 1.53 (tdd, *J* = 13.4, 11.7, 4.8 Hz, 1H), 1.29 (s, 3H), 0.87 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{24}H_{34}NO_8$ $[M+H]^+$: 464.2284, found: 464.2279.



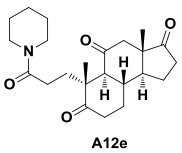

**A12b:** Prepared from L-valine methyl ester hydrochloride.
**Yield:** 113.6 mg, 34%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 6.24 (d, *J* = 8.7 Hz, 1H), 4.42 (dd, *J* = 8.7, 5.0 Hz, 1H), 3.69 (s, 3H), 2.63 - 2.50 (m, 2H), 2.44 (d, *J* = 13.1 Hz, 1H), 2.39 - 1.89 (m, 13H), 1.68 (tt, *J* = 12.4, 9.2 Hz, 1H), 1.50 (qd, *J* = 13.0, 4.5 Hz, 1H), 1.29 (s, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 7.5 Hz, 3H), 0.86 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{24}H_{36}NO_6$ $[M+H]^+$: 434.2543, found: 434.2534.



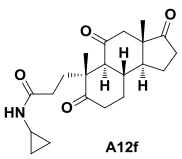

**A12c:** Prepared from L-serine methyl ester hydrochloride.
**Yield:** 43.6 mg, 10%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 6.62 (d, *J* = 6.6 Hz, 1H), 4.43 (dt, *J* = 6.4, 3.1 Hz, 1H), 3.94 (dd, *J* = 12.0, 3.0 Hz, 1H), 3.85 (dd, *J* = 11.5, 3.0 Hz, 1H), 3.77 (s, 3H), 2.92 (d, *J* = 11.0 Hz, 1H), 2.61 - 2.50 (m, 2H), 2.48 (d, *J* = 13.5 Hz, 1H), 2.46 - 2.22 (m, 6H), 2.22 - 2.09 (m, 4H), 2.08 - 1.93 (m, 2H), 1.68 (dtt, *J* = 16.5, 11.8, 7.0 Hz, 2H), 1.26 (s, 3H), 0.88 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{22}H_{32}NO_7$ $[M+H]^+$: 422.2179, found: 422.2185.



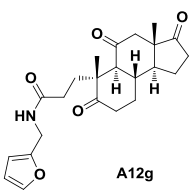

**A12d:** Prepared from 4-methoxybenzylamine.
**Yield:** 25.0 mg, 76%.
**$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.20 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.89 (t, *J* = 5.8 Hz, 1H), 4.32 (dd, *J* = 14.4, 5.6 Hz, 1H), 4.27 (dd, *J* = 14.4, 5.2 Hz, 1H), 3.79 (s, 3H), 2.66 - 1.86 (m, 15H), 1.70 (tt, *J* = 12.5, 9.2 Hz, 1H), 1.52 (tdd, *J* = 13.6, 11.5, 4.7 Hz, 1H), 1.31 (s, 3H), 0.88 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{26}H_{34}NO_5$ $[M+H]^+$: 440.2437, found: 440.2445.



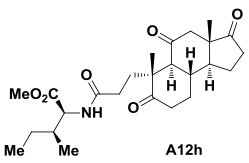

**A12e:** Prepared from piperidine.
**Yield:** 144 mg, 92%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 3.52 - 3.30 (m, 4H), 2.65 (d, *J* = 11.1 Hz, 1H), 2.61 - 2.47 (m, 2H), 2.46 - 2.31 (m, 3H), 2.31 - 1.95 (m, 8H), 1.68 (tt, *J* = 12.3, 9.2 Hz, 1H), 1.62 - 1.51 (m, 4H), 1.50 - 1.42 (m, 2H), 1.40 - 1.32 (m, 2H), 1.28 (s, 3H), 0.85 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{23}H_{34}NO_4$ $[M+H]^+$: 388.2488, found: 388.2498.



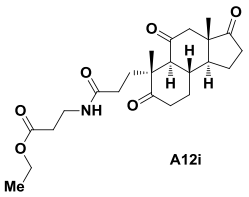

**A12f:** Prepared from cyclopropylamine.
**Yield:** 25.4 mg, 87%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 5.79 (br s, 1H), 2.65 - 2.46 (m, 5H), 2.39 (ddd, *J* = 15.2, 4.8, 2.4 Hz, 1H), 2.37 - 2.13 (m, 7H), 2.02 - 1.88 (m, 3H), 1.75 - 1.61 (m, 2H), 1.30 (s, 3H), 0.89 (s, 3H), 0.75 - 0.69 (m, 2H), 0.50 - 0.45 (m, 2H).
**HRMS(ESI):** *m/z* calc. for $C_{21}H_{30}NO_4$ $[M+H]^+$: 360.2175, found: 360.2180.



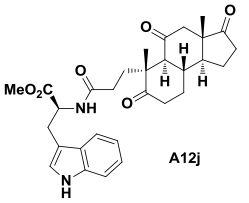
**A12g**: Prepared from furfurylamine.
**Yield:** 18.7 mg, 63%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.34 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.31 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.22 (dd, *J* = 3.1, 0.9 Hz, 1H), 5.95 (t, *J* = 5.5 Hz, 1H), 4.40 (dd, *J* = 15.5, 5.5 Hz, 1H), 4.36 (dd, *J* = 15.5, 5.5 Hz, 1H), 2.66 - 2.53 (m, 2H), 2.49 (d, *J* = 13.2 Hz, 1H), 2.43 (d, *J* = 11.2 Hz, 1H), 2.39 (ddd, *J* = 15.1, 4.8, 2.4 Hz, 1H), 2.36 - 1.90 (m, 10H), 1.71 (tt, *J* = 12.5, 9.2 Hz, 1H), 1.58 - 1.47 (m, 1H), 1.32 (s, 3H), 0.89 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{23}H_{30}NO_5$ $[M+H]^+$: 400.2124, found: 400.2121.



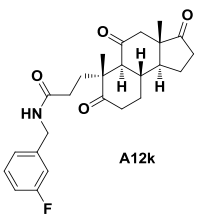
**A12h**: Prepared from L-isoleucine methyl ester hydrochloride.
**Yield:** 60.0 mg, 43%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 6.37 (d, *J* = 8.5 Hz, 1H), 4.44 (dd, *J* = 8.5, 5.1 Hz, 1H), 3.68 (s, 3H), 2.62 - 2.48 (m, 2H), 2.41 (d, *J* = 13.1 Hz, 1H), 2.38 - 1.77 (m, 12H), 1.82 (tdd, *J* = 11.4, 5.8, 2.2 Hz, 1H), 1.68 (tt, *J* = 12.4, 9.2 Hz, 1H), 1.57 - 1.46 (m, 1H), 1.38 (dtd, *J* = 14.8, 7.4, 4.6 Hz, 1H), 1.27 (s, 3H), 1.13 (ddt, *J* = 14.5, 9.0, 7.3 Hz, 1H), 0.89 (m, 6H) 0.85 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{25}H_{38}NO_6$ $[M+H]^+$: 448.2699, found: 448.2698.



**A12i**: Prepared from β-alanine ethyl ester hydrochloride.
**Yield:** 70.4 mg, 29%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 6.28 - 6.14 (t, *J* = 5.5 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.46 - 3.40 (m, 2H), 2.62 - 2.52 (m, 2H), 2.51 – 2.44 (m, 4H), 2.41 - 2.11 (m, 8H), 2.05 - 1.89 (m, 3H), 1.70 (tt, *J* = 12.5, 9.2 Hz, 1H), 1.59 - 1.47 (m, 1H), 1.29 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.87 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{23}H_{34}NO_6$ $[M+H]^+$: 420.2386, found: 420.2378.



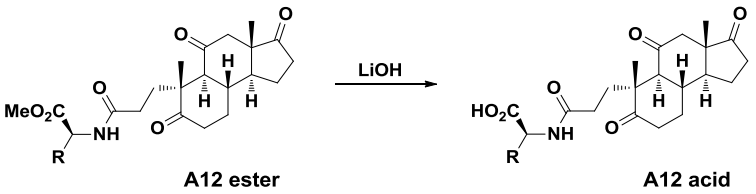
**A12j**: Prepared from L-tryptophan methyl ester hydrochloride.
**Yield:** 30.0 mg, 5%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.56 (d, *J* = 2.4 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.30 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.16 - 7.11 (m, 1H), 7.09 - 7.03 (m, 1H), 7.04 (d, *J* = 2.0 Hz, 1H), 6.26 (d, *J* = 7.8 Hz, 1H), 4.84 (dt, *J* = 7.5, 5.5 Hz, 1H), 3.64 (s, 3H), 3.30 (dd, *J* = 15.0, 5.5 Hz, 1H), 3.25 (dd, *J* = 15.0, 6.0 Hz, 1H), 2.59 - 2.49 (m, 2H), 2.43 (d, *J* = 13.1 Hz, 1H), 2.36 - 1.90 (m, 11H), 1.84 - 1.76 (m, 1H), 1.65 (tt, *J* = 12.3, 9.2 Hz, 1H), 1.43 (qd, *J* = 13.0, 5.0 Hz, 1H), 1.26 (s, 3H), 0.85 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{30}H_{37}N_2O_6$ $[M+H]^+$: 521.2652, found: 521.2648.



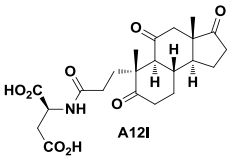
**A12k:** Prepared from 3-fluorobenzylamine.
**Yield:** 40.7 mg, 99%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.30 - 7.25 (m, 1H), 7.05 (ddd, *J* = 7.6, 1.7, 0.9 Hz, 1H), 6.98 (dt, 10.0, 1.5 Hz, 1H), 6.94 (td, *J* = 8.5, 2.0 Hz, 1H), 6.10 (t, *J* = 5.5 Hz, 1H), 4.39 (dd, *J* = 15.0, 6.0 Hz, 1H), 4.34 (dd, *J* = 15.0, 5.5 Hz, 1H), 2.65 - 2.53 (m, 2H), 2.48 (d, *J* = 13.2 Hz, 1H), 2.44 (d, *J* = 11.2 Hz, 1H), 2.38 (ddd, *J* = 15.0, 4.7, 2.4 Hz,

1H), 2.35 - 1.90 (m, 10H), 1.78 - 1.65 (tt, *J* = 12.5, 9.5 Hz, 1H), 1.59 - 1.47 (m, 1H), 1.31 (s, 3H), 0.89 (s, 3H).

**HRMS(ESI):** *m/z* calc. for $C_{25}H_{31}NO_4F$ $[M+H]^+$: 428.2237, found: 428.2237.




**General procedure for the preparation of acids from A12 amides:** In a vial with stir bar, amide (1 equiv.) and lithium hydroxide (20-30 equiv.) were dissolved in a 1:1 mixture of tetrahydrofuran and water (0.005 M), and stirred at room temperature for 12-16 hours. The reaction mixture was acidified to pH 2 with concentrated hydrochloric acid and extracted with ethyl acetate (3x). The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol/formic acid) to yield the desired acid.

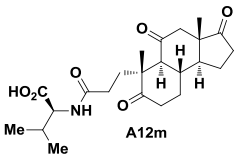



**A12l**: Prepared from **A12a**.

**Yield:** 17.6 mg, 60%.

**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.45 (br s, 1H), 4.75 (br s, 1H), 2.97 (d, *J* = 16.5 Hz, 1H), 2.85 (d, *J* = 16.5 Hz, 1H), 2.70 - 2.06 (m, 15H), 1.75 - 1.50 (m, 2H), 1.28 (s, 3H), 0.86 (s, 3H).

**HRMS(ESI):** *m/z* calc. for $C_{22}H_{30}NO_8$ $[M+H]^+$: 436.1971, found: 436.1968.

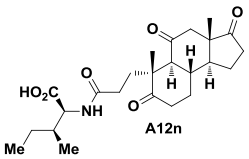



**A12m**: Prepared from **A12b**.

**Yield:** 23.3 mg, 59%.

**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 6.46 (d, *J* = 8.5 Hz, 1H), 4.41 (dd, *J* = 8.4, 5.0 Hz, 1H), 2.65 - 2.52 (m, 2H), 2.47 (d, *J* = 13.2 Hz, 1H), 2.44 - 1.93 (m, 13H), 1.71 (tt, *J* = 12.4, 9.2 Hz, 1H), 1.53 (qd, *J* = 13.0, 4.5 Hz, 1H), 1.31 (s, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 7.5 Hz, 3H), 0.89 (s, 3H).

**HRMS(ESI):** *m/z* calc. for $C_{23}H_{34}NO_6$ $[M+H]^+$: 420.2386, found: 420.2390.

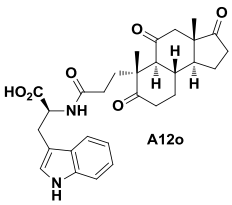



**A12n**: Prepared from **A12h**.

**Yield:** 21.8 mg, 38%.

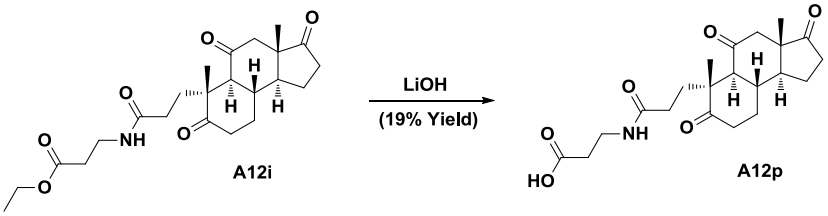
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 6.45 (d, *J* = 8.3 Hz, 1H), 4.47 (dd, *J* = 8.3, 4.9 Hz, 1H), 2.65 - 2.52 (m, 2H), 2.47 (d, *J* = 13.2 Hz, 1H), 2.44 - 1.88 (m, 13H), 1.71 (tt, *J* = 12.4, 9.2 Hz, 1H), 1.58 - 1.45 (m, 2H), 1.31 (s, 3H), 1.21 (ddd, *J* = 13.5, 9.3, 7.1 Hz, 1H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.92 (t, 7.0 Hz, 3H), 0.88 (s, 3H).

**HRMS(ESI):** *m/z* calc. for $C_{24}H_{36}NO_6$ $[M+H]^+$: 434.2543, found: 434.2535.




**A12o**: Prepared from **A12j**.
**Yield:** 5.1 mg, 20%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.66 (br s, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.29 - 7.25 (m, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.07 - 6.99 (m, 2H), 6.51 (s, 1H), 4.79 (d, *J* = 7.3 Hz, 1H), 3.36 - 3.19 (m, 2H), 2.60 - 1.82 (m, 13H), 1.74 - 1.52 (m, 2H), 1.48 - 1.23 (m, 2H), 1.21 (s, 3H), 0.81 (s, 3H).

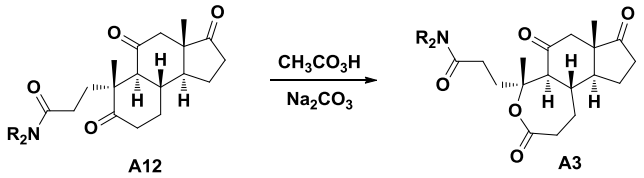
**HRMS(ESI):** *m/z* calc. for $C_{29}H_{35}N_2O_6$ $[M+H]^+$: 507.2495, found: 507.2499.



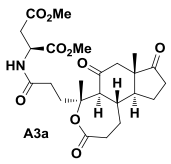

**Procedure:** In a vial with stir bar, **A12i** (106.0 mg, 0.253 mmol) and lithium hydroxide hydrate (306.2 mg, 7.30 mmol) were dissolved in a tetrahydrofuran (10 mL) and methanol (10 mL), and stirred at room temperature for 12 hours. The reaction was diluted with water (10 mL), acidified to pH 2 with concentrated hydrochloric acid, and extracted with ethyl acetate (3x). The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol 9:1) to yield **A12p** (19.0 mg, 19.2%).

**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 6.50 (t, *J* = 6.1 Hz, 1H), 3.51 - 3.39 (m, 2H), 2.64 - 2.11 (m, 14H), 2.08 - 1.95 (m, 3H), 1.70 (tt, *J* = 12.3, 9.2 Hz, 1H), 1.56 (tdd, *J* = 13.2, 11.6, 4.8 Hz, 1H), 1.30 (s, 3H), 0.88 (s, 3H).

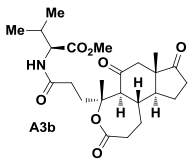
**HRMS(ESI):** *m/z* calc. for $C_{21}H_{30}NO_6$ $[M+H]^+$: 392.2073, found: 392.2079.



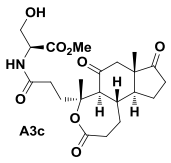

**General procedure for the preparation of A3 lactones from A12 amides:** An A12 amide (1 equiv.) was dissolved in anhydrous dichloromethane (0.1 M). Then sodium carbonate (5 equiv.) was added to the solution and cooled to 0 °C. After cooling, a solution of peracetic acid of a 32% by weight peracetic acid solution in dilute acetic acid (3 equiv.) was added dropwise to the reaction mixture. The reaction slowly warmed to room temperature over several hours and was quenched with a saturated solution sodium bicarbonate after 16-20 hours. The reaction was then transferred to a separatory funnel and extracted with dichloromethane (3x). The organic layers were collected, dried with magnesium sulfate and concentrated under reduced pressure to give the crude product. The desired lactone was purified via column chromatography on silica gel (hexanes/ethyl acetate).



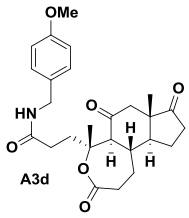

**A3a:** Prepared from **A12a**.
**Yield:** 13.9 mg, 33.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 6.46 (d, *J* = 8.1 Hz, 1H), 4.83 (dt, *J* = 8.5, 4.4 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.01 (dd, *J* = 17.3, 4.5 Hz, 1H), 2.88 - 2.79 (m, 2H), 2.74 - 2.53 (m, 3H), 2.49 (s, 2H), 2.38 (t, *J* = 7.6 Hz, 2H), 2.33 - 1.97 (m, 8H), 1.67 (tt, *J* = 12.5, 9.5 Hz, 1H), 1.63 (s, 3H), 0.86 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{24}H_{33}NO_9$ $[M+H]^+$: 480.2234, found: 480.2230.



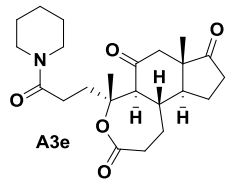

**A3b:** Prepared from **A12b**.
**Yield:** 15.8 mg, 30%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 5.96 (d, *J* = 8.0 Hz, 1H), 4.50 (dd, *J* = 8.7, 5.0 Hz, 1H), 3.73 (s, 3H), 2.83 (ddd, *J* = 16.4, 6.9, 1.9 Hz, 1H), 2.69 (d, *J* = 10.9 Hz, 1H), 2.67 - 2.54 (m, 2H), 2.49 (s, 2H), 2.46 - 2.23 (m, 4H), 2.19 - 1.96 (m, 6H), 1.67 (tt, *J* = 12.5, 9.5 Hz, 1H), 1.63 (s, 3H), 1.60 - 1.50 (m, 1H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.85 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{24}H_{36}NO_7$ $[M+H]^+$: 450.2492, found: 450.2492.




**A3c**: Prepared from **A12c**.
**Yield:** 12.7 mg, 28%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 6.49 (d, *J* = 6.9 Hz, 1H), 4.58 (dt, *J* = 6.3, 2.9 Hz, 1H), 4.01 (dd, *J* = 11.6, 3.0 Hz, 1H), 3.89 (dd, *J* = 11.7, 3.0 Hz, 1H), 3.80 (s, 3H), 2.86 (d, *J* = 10.5 Hz, 1H), 2.82 (ddd, *J* = 16.5, 7.0, 2.0 Hz, 1H), 2.68 - 2.55 (m, 2H), 2.50 (s, 2H), 2.39 - 2.23 (m, 5H), 2.18 - 1.97 (m, 4H), 1.67 (tt, *J* = 12.5, 9.0 Hz, 1H), 1.65 (s, 3H), 1.63 - 1.50 (m, 1H), 0.86 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{22}H_{32}NO_8$ $[M+H]^+$: 438.2128, found: 438.2134.

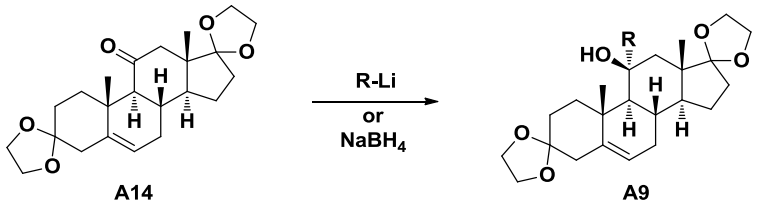



**A3d:** Prepared from **A12d**
**Yield:** 32.7 mg, 71%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.25 - 7.19 (m, 2H), 6.90 - 6.84 (m, 2H), 5.85 (t, *J* = 5.8 Hz, 1H), 4.37 (dd, *J* = 14.0, 5.5 Hz, 1H), 4.30 (dd, *J* = 14.5, 5.5 Hz, 1H), 3.81 (s, 3H), 2.83 (ddd, *J* = 16.6, 6.9, 1.9 Hz, 1H), 2.69 - 2.62 (m, 2H), 2.59 (dd, *J* = Hz, 1H) 2.52 - 2.42 (m, 2H), 2.42 - 2.17 (m, 5H), 2.17 - 2.08 (m, 2H), 2.08 - 1.97 (m, 1H), 1.90 (td, *J* = 11.6, 11.2, 5.7 Hz, 1H), 1.77 - 1.59 (m, 1H), 1.64 (s, 3H), 1.53 (q, *J* = 12.9 Hz, 1H), 0.86 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{26}H_{34}NO_6$ $[M+H]^+$: 456.2386, found: 456.2390.



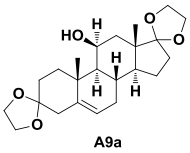

**A3e:** Prepared from **A12e**.
**Yield:** 34.8 mg, 27%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 3.52 (dt, *J* = 11.7, 5.3 Hz, 1H), 3.45 - 3.29 (m, 3H), 2.86 - 2.75 (m, 2H), 2.69 - 2.49 (m, 3H), 2.49 - 2.35 (m, 3H), 2.32 - 2.19 (m, 2H), 2.19 - 1.96 (m, 5H), 1.70 - 1.41 (m, 8H), 1.63 (s, 3H), 0.83 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{23}H_{34}NO_5$ $[M+H]^+$: 404.2437, found: 404.2441.

**Synthesis of A9 Derivatives**

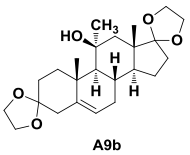



**General procedure for the preparation of A9 alcohols using organolithium reagent:** Organolithium (3 equiv.) was slowly added to a stirring solution of **A14** (250 mg, 0.644 mmol) in anhydrous tetrahydrofuran at room temperature. The reaction continued to stir for an additional thirty minutes to four hours (depending on organolithium) before being slowly quenched with a saturated solution of ammonium chloride. The contents of the reaction were then transferred to a separatory funnel and extracted with dichloromethane (3x). The organic layers were combined, dried with magnesium sulfate and concentrated under reduced pressure to give a crude product which was purified via column chromatography using hexanes/ethyl acetate to elute. (Notes: The scale for this reaction was typically between 200 and 800 milligrams of **A14**. The organolithium of 4-*tert*-butyliodobenzene was generated using 1.0 equiv. of *n*-butyllithium in ether for 30 minutes at room temperature before cannulation to **A14** in toluene. The other organolithium reagents used are commercially available).

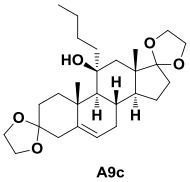
**Sodium borohydride procedure: A14** (950 mg, 2.45 mmol) was dissolved in 1:1:1 solution of tetrahydrofuran/*t*-butanol/water (45 mL) and cooled to 0 °C. Then sodium borohydride (1.85 g, 48.91 mmol) was added slowly and the reaction was allowed to stir at 0 °C for 2 hours before removal of the ice bath. The reaction continued to stir for an additional 20 hours before being quenched with a saturated solution of aqueous ammonium chloride. Ethyl acetate was used to extract the alcohol product and the organic layer was washed with water and brine (1x each). The organic layer was collected, dried with magnesium sulfate and concentrated. The alcohol was purified by column chromatography using 5:1 to 1:1 hexanes/ethyl acetate to give 847 mg (89% yield) **A9a**.


A9a

**A9a:** Prepared from sodium borohydride.
**Yield:** 847 mg, 89%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 5.22 (dt, *J* = 4.6, 2.4 Hz, 1H), 4.43 (q, J = 3.3 Hz, 1H), 4.00 - 3.76 (m, 8H), 2.60 (dq, *J* = 14.7, 3.3 Hz, 1H), 2.20 - 1.64 (m, 11H), 1.56 (dd, J = 13.8, 2.6 Hz, 1H), 1.54 - 1.30 (m, 4H), 1.28 (s, 3H), 1.18 (dd, *J* = 11.7, 3.8 Hz, 1H), 1.09 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{23}H_{35}O_5$ $[M+H]^+$: 391.2484, found: 391.2482.

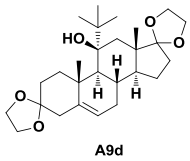

A9b

**A9b:** Prepared from methyllithium.
**Yield:** 226 mg, 88%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 5.29 (m, 1H), 4.01 - 3.77 (m, 8H), 2.65 - 2.55 (m, 1H), 2.24 (dt, *J* = 13.0, 2.5 Hz, 1H), 2.14 - 1.94 (m, 3H), 1.90 (d, *J* = 14.0 Hz, 1H), 1.87 - 1.65 (m, 6H), 1.61 (td, *J* = 13.6, 4.1 Hz, 1H), 1.44 (s, 3H), 1.40 - 1.22 (m, 4H), 1.35 (s, 3H), 1.05 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{24}H_{37}O_5$ $[M+H]^+$: 405.2641, found: 405.2646.



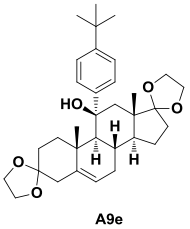
A9c

**A9c:** Prepared from *n*-butyllithium.
**Yield:** 545 mg, 57%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 5.30 (dt, *J* = 5.6, 2.0 Hz, 1H), 4.02 - 3.79 (m, 8H), 2.59 (dq, *J* = 14.5, 2.5 Hz, 1H), 2.21 (m, 1H), 2.09 (dd, *J* = 14.5, 3.0 Hz, 1H), 2.07 - 1.91 (m, 3H), 1.88 - 1.56 (m, 8H), 1.43 - 1.18 (m, 9H), 1.37 (s, 3H), 1.04 (s, 3H), 0.88 (td, *J* = 6.9, 1.4 Hz, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{29}H_{43}O_5$ $[M+H]^+$: 447.3110, found: 447.3108.



A9d

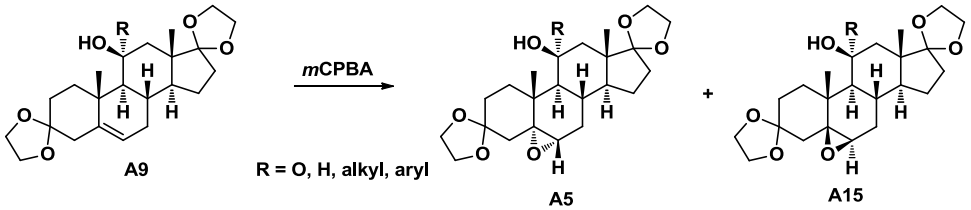
**A9d:** Prepared from *tert*-butyllithium.
**Yield:** 152 mg, 56%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 5.40 (m, 1H), 4.01 - 3.78 (m, 8H), 2.81 (d, *J* = 14.9 Hz, 1H), 2.54 (dq, *J* = 14.5, 2.7 Hz, 1H), 2.30 (dt, *J* = 12.3, 3.2 Hz, 1H), 2.11 (dd, *J* = 14.3, 2.9 Hz, 1H), 1.89 (m, 2H), 1.85 - 1.52 (m, 10H), 1.45 (s, 3H), 1.23 (m, 1H), 1.03 (s, 3H), 0.96 (s, 9H).
**HRMS(ESI):** *m/z* calc. for $C_{27}H_{43}O_5$ $[M+H]^+$: 447.3110, found: 447.3110.



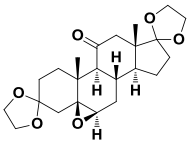
A9e

**A9e:** Prepared from 4-*tert*-butylphenyllithium.
**Yield:** 154 mg, 44%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.49 - 7.19 (m, 4H), 5.31 (dt, *J* = 4.9, 2.1 Hz, 1H), 3.97 - 3.63 (m, 8H), 2.52 (dq, *J* = 14.6, 2.9 Hz, 1H), 2.32 - 2.12 (m, 2H), 2.12 - 1.97 (m, 3H), 1.92 (d, *J* = 10.9 Hz, 1H), 1.88 - 1.75 (m, 3H), 1.65 (td, *J* = 11.7, 6.2 Hz, 1H), 1.55 - 1.45 (m, 2H), 1.39 (m, 1H), 1.32 (s, 3H), 1.30 (s, 9H), 1.25 - 1.06 (m, 1H), 1.19 (s, 3H), 0.90 (dt, *J* = 13.7, 3.7 Hz, 1H), 0.63 (td, *J* = 14.0, 4.1 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{33}H_{47}O_5$ $[M+H]^+$: 523.3424, found: 523.3422.

**Synthesis of A5 and A15 Derivatives**

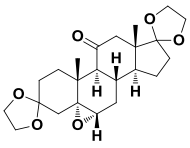



**General procedure for the preparation of A15 and A5 epoxides:** *m*-Chloroperoxybenzoic acid (0.9 equiv. calc. at 77% purity, dissolved in 1 mL of anhydrous dichloromethane) was added at room temperature to stirring solution of **A9** alkene (0.15 mmol) in anhydrous dichloromethane (2 mL). The reaction continued to stir for 40 minutes before a saturated solution of sodium bicarbonate was added to quench the reaction. The reaction contents were then extracted with dichloromethane (3x). The combined organic layers were then washed once more with a saturated solution of sodium bicarbonate. The organic layer was then collected, dried with magnesium sulfate and concentrated to give a crude mixture. The epoxide diastereomers were then separated via column chromatography using hexanes/ethyl acetate. The β/α-stereochemistry of steroidal epoxides (at C5-C6) is well studied and assigned according to the chemical shift of the $^1$H NMR at C6 (as in **A5** and **A15**).



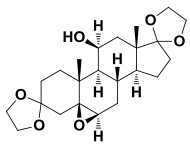
A15a

**A15a:** Prepared from **A14**.
**Yield:** 13.1 mg, 14%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 3.95 - 3.85 (m, 6H), 3.84 - 3.77 (m, 2H), 3.10 (d, *J* = 1.9 Hz, 1H), 2.49 (d, *J* = 14.0 Hz, 1H), 2.41 - 2.35 (m, 1H), 2.34 (d, *J* = 14.0 Hz, 1H), 2.23 (dt, *J* = 14.5, 2.8 Hz, 1H), 2.10 (d, *J* = 14.1 Hz, 1H), 2.07 - 1.97 (m, 1H), 1.95 - 1.80 (m, 3H), 1.76 - 1.50 (m, 6H), 1.36 (m, 1H), 1.25 (dd, *J* = 15.5, 1.8 Hz, 1H), 1.24 (s, 3H), 0.78 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{23}H_{33}O_6$ $[M+H]^+$: 405.2277, found: 405.2290.



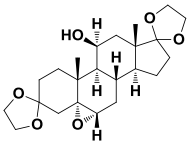
A5a

**A5a:** Prepared from **A14**.
**Yield:** 60.1 mg, 65%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 4.05 - 3.72 (m, 8H), 2.83 (d, *J* = 4.3 Hz, 1H), 2.57 - 2.48 (m, 2H), 2.37 (d, *J* = 14.1 Hz, 1H), 2.31 (m, 1H), 2.12 - 1.69 (m, 10H), 1.48 (td, *J* = 13.8, 4.1 Hz, 1H), 1.27 (m, 1H), 1.22 (s, 3H), 1.16 (dd, *J* = 14.1, 2.8 Hz, 1H), 0.73 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{23}H_{33}O_6$ $[M+H]^+$: 405.2277, found: 405.2290.



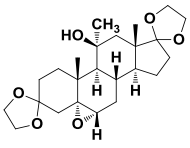
A15b

**A15b:** Prepared from **A9a**.
**Yield:** 12.5 mg, 18%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 4.26 (q, *J* = 3.0 Hz, 1H), 3.98 - 3.78 (m, 8H), 3.07 (d, *J* = 3.0 Hz, 1H), 2.36 (d, *J* = 13.8 Hz, 1H), 2.21 (dt, J = 14.7, 3.9 Hz, 1H), 2.02 (m, 1H), 1.91 (dq, *J* = 11.0, 4.5 Hz, 1H), 1.84 (dt, *J* = 13.0, 5.0 Hz, 1H), 1.78 - 1.51 (m, 8H), 1.46 - 1.06 (m, 3H), 1.41 (dd, *J* = 15.0, 11.5 Hz, 1H), 1.29 (s, 3H), 1.08 (s, 3H), 0.89 (dd, *J* = 11.6, 2.4 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{23}H_{35}O_6$ $[M+H]^+$: 407.2434, found: 407.2425.



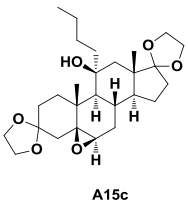
A5b

**A5b:** Prepared from **A9a**.
**Yield:** 52.0 mg, 73%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 4.28 (q, *J* = 3.3 Hz, 1H), 4.04 - 3.74 (m, 8H), 2.77 (d, *J* = 3.5, 1H), 2.42 (d, *J* = 14.1 Hz, 1H), 2.05 - 1.94 (m, 2H), 1.92 - 1.64 (m, 10H), 1.61 (dd, J = 12.0, 3.5 Hz, 1H), 1.49 - 1.38 (m, 2H), 1.33 (s, 3H), 1.33 - 1.22 (m, 1H), 1.17 (dd, *J* = 14.1, 2.8 Hz, 1H), 1.03 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{23}H_{35}O_6$ $[M+H]^+$: 407.2434, found: 407.2432.



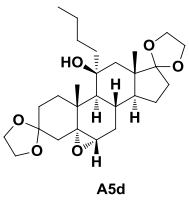
A5c

**A5c:** Prepared from **A9b**.
**Yield:** 34.3 mg, 45%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 4.05 - 3.78 (m, 8H), 2.76 (d, *J* = 4.4 Hz, 1H), 2.40 (d, *J* = 14.1 Hz, 1H), 2.19 - 2.10 (m, 1H), 2.04 - 1.67 (m, 9H), 1.65 (d, *J* = 11.3 Hz, 1H), 1.54 (dd, *J* = 15.4, 10.1 Hz, 1H), 1.42 (s, 3H), 1.42 (s, 3H), 1.36 - 1.18 (m, 3H), 1.14 (dd, *J* = 14.1, 2.9 Hz, 1H), 1.00 (s, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{24}H_{37}O_6$ $[M+H]^+$: 421.2590, found: 421.2586.



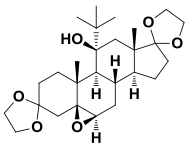
A15c

**A15c:** Prepared from **A9c**.
**Yield:** 16.4 mg, 21%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 3.98 - 3.76 (m, 8H), 3.06 (d, *J* = 3.1 Hz, 1H), 2.42 (d, *J* = 13.8 Hz, 1H), 2.16 (dt, *J* = 14.6, 3.7 Hz, 1H), 2.09 (dt, *J* = 12.8, 3.5 Hz, 1H), 2.06 - 1.92 (m, 2H), 1.76 (m, 3H), 1.71 - 1.53 (m, 6H), 1.47 - 1.36 (m, 2H), 1.40 (s, 3H), 1.35 - 1.16 (m, 6H), 1.12 (dd, *J* = 13.9, 2.6 Hz, 1H), 1.05 (s, 3H), 0.98 - 0.87 (m, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{27}H_{43}O_6$ $[M+H]^+$: 463.3060, found: 463.3065.



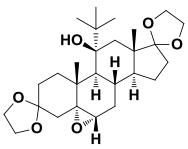
A5d

**A5d:** Prepared from **A9c**.
**Yield:** 49.0 mg, 62%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 4.03 - 3.93 (m, 2H), 3.93 - 3.76 (m, 6H), 2.74 (dd, *J* = 4.7, 1.2 Hz, 1H), 2.37 (dd, *J* = 14.0, 1.2 Hz, 1H), 2.14 (dd, *J* = 8.4, 2.9 Hz, 1H), 2.01 - 1.64 (m, 11H), 1.60 (ddd, *J* = 13.6, 12.0, 5.1 Hz, 1H), 1.49 (dd, *J* = 15.4, 10.6 Hz, 1H), 1.42 (s, 3H), 1.36 (m, 1H), 1.31 - 1.13 (m, 6H), 1.11 (dd, *J* = 14.0, 2.5 Hz, 1H), 0.97 (s, 3H), 0.88 (t, *J* = 7.0 Hz, 3H).
**HRMS(ESI):** *m/z* calc. for $C_{27}H_{43}O_6$ $[M+H]^+$: 463.3060, found: 463.3068.



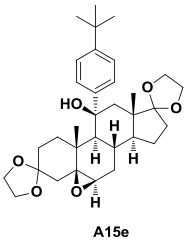
A15d

**A15d:** Prepared from **A9d**.
**Yield:** 6.5 mg, 10%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 4.01 - 3.81 (m, 8H), 3.02 (m, 1H), 2.74 (d, *J* = 14.9 Hz, 1H), 2.36 - 2.25 (m, 2H), 2.04 (dt, *J* = 14.0, 2.5 Hz, 1H), 1.95 - 1.60 (m, 7H), 1.57 (d, *J* = 9.0 Hz, 1H), 1.50 (m, 1H), 1.45 (s, 3H), 1.40 (ddd, *J* = 14.0, 11.4, 1.3 Hz, 1H), 1.32 (d, *J* = 14.3 Hz, 1H), 1.29 - 1.21 (m, 2H), 1.00 (s, 3H), 0.97 (s, 9H).
**HRMS(ESI):** *m/z* calc. for $C_{27}H_{43}O_6$ $[M+H]^+$: 463.3060, found: 463.3071.



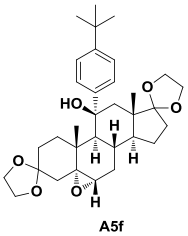
A5e

**A5e:** Prepared from **A9d**.
**Yield:** 59.5 mg, 89%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 4.03 - 3.78 (m, 8H), 2.90 (d, *J* = 5.5 Hz, 1H), 2.70 (d, *J* = 14.8 Hz, 1H), 2.41 (d, *J* = 14.0 Hz, 1H), 2.25 (dt, *J* = 12.1, 3.3 Hz, 1H), 2.02 (d, *J* = 10.0 Hz, 1H), 2.01 - 1.85 (m, 5H), 1.85 - 1.70 (m, 3H), 1.66 (dt, *J* = 7.8, 3.9 Hz, 1H), 1.52 (s, 3H), 1.44 (dd, *J* = 13.5, 13.5 Hz, 1H), 1.33 (td, *J* = 11.6, 7.5 Hz, 1H), 1.21 (m, 1H), 1.13 (dd, *J* = 14.0, 2.0 Hz, 1H), 0.99 (s, 3H), 0.95 (s, 9H).
**HRMS(ESI):** *m/z* calc. for $C_{27}H_{43}O_6$ $[M+H]^+$: 463.3060, found: 463.3066.



A15e

**A15e:** Prepared from **A9e**.
**Yield:** 13.2 mg, 16%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.70 - 6.98 (m, 4H), 3.96 - 3.60 (m, 8H), 3.05 (d, *J* = 3.2 Hz, 1H), 2.31 - 2.20 (m, 2H), 2.20 - 2.10 (m, 2H), 2.10 - 1.96 (m, 1H), 1.88 - 1.68 (m, 3H), 1.68 - 1.47 (m, 3H), 1.39 (m, 1H), 1.35 - 1.07 (m, 3H), 1.30 (s, 9H), 1.22 (s, 3H), 1.15 (s, 3H) 1.05 (dd, *J* = 14.0, 3.0 Hz, 1H) 0.86 (dt, *J* = 13.5, 3.5 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{33}H_{47}O_6$ $[M+H]^+$: 539.3373, found: 539.3381.

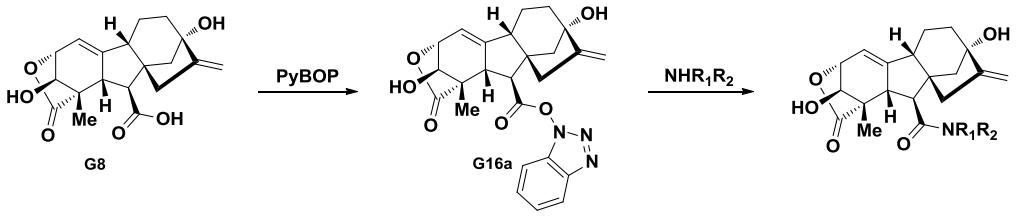


A5f

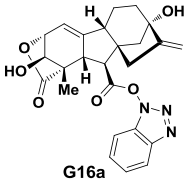
**A5f:** Prepared from **A9e**.
**Yield:** 42.7 mg, 52%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.46 - 7.14 (m, 4H), 3.92 - 3.60 (m, 8H), 2.76 (d, *J* = 3.8 Hz, 1H), 2.40 - 2.28 (m, 2H), 2.15 - 1.93 (m, 4H), 1.88 - 1.67 (m, 3H), 1.65 - 1.52 (m, 2H), 1.40 (s, 3H), 1.38 - 1.17 (m, 3H), 1.30 (s, 9H), 1.14 - 1.07 (m, 1H), 1.12 (s, 3H), 1.05 (dd, *J* = 14.5, 3.0 Hz, 1H) 0.79 (td, *J* = 14.0, 4.2 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{33}H_{47}O_6$ $[M+H]^+$: 539.3373, found: 539.3375.

## 11.) Gibberellic Acid Derived Libraries: Synthesis and Characterization

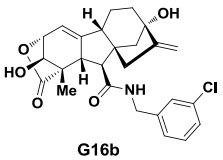
### Synthesis of G16 Derivatives



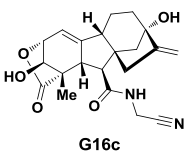

**General procedure for the preparation of G16 amides:** In an oven-dried vial, **G8** (1 equiv.) and benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (1.2 equiv.) were dissolved in dichloromethane (0.1 M). Diisopropylethylamine (1 equiv.) was added, and the reaction was stirred at room temperature for 1-2 hours. After complete complexation by TLC, amine (1-3 equiv.) and additional diisopropylethylamine (1-3 equiv.) were added, and the reaction was allowed to stir at room temperature for 12-16 hours. The reaction was concentrated and purified by flash silica chromatography (hexanes/ethyl acetate) to provide the amide. (Note: **G16a** can be isolated and purified prior to the addition of amine.)




**G16a:** Prepared from **G8**.
**Yield:** N.A./aliquot purified for screening.
**$^1$H NMR** ($d_6$-acetone, 500 MHz): δ 8.10 (dt, *J* = 8.5, 0.9 Hz, 1H), 7.73 - 7.66 (m, 2H), 7.54 (ddd, *J* = 8.5, 6.5, 1.5 Hz, 1H), 5.95 (dt, *J* = 5.0, 2.5 Hz, 1H), 5.21 (d, *J* = 5.2 Hz, 1H), 5.17 (ddd, *J* = 3.1, 1.9, 0.9 Hz, 1H), 5.07 - 5.05 (m, 1H), 4.80 (t, *J* = 5.3 Hz, 1H), 4.41 (t, *J* = 5.2 Hz, 1H), 4.05 (s, 1H), 3.41 (ddt, *J* = 6.3, 2.6, 0.8 Hz, 1H), 3.07 - 3.00 (m, 2H), 2.67 (d, *J* = 5.9 Hz, 1H), 2.56 (ddt, *J* = 15.5, 2.5, 1.0 Hz, 1H), 2.03 - 1.98 (m, 1H), 1.81 - 1.72 (m, 2H), 1.64 (dd, *J* = 10.9, 2.9 Hz, 1H), 1.58 (ddd, *J* = 10.8, 2.7, 1.1 Hz, 1H), 1.54 (tt, *J* = 4.2, 1.6 Hz, 1H), 1.39 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{25}H_{26}N_3O_6$ $[M+H]^+$: 464.1822, found: 464.1823.

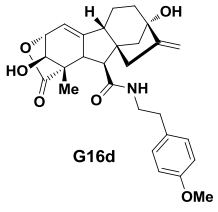



**G16b:** Prepared from 3-chlorobenzylamine.
**Yield:** 130.0 mg, 91%.
**$^1$H NMR** ($CD_3OD$, 500 MHz): δ 7.35 (t, *J* = 1.8 Hz, 1H), 7.33 - 7.22 (m, 4H), 5.78 (dt, *J* = 5.5, 2.0 Hz, 1H), 5.05 (t, *J* = 2.5Hz, 1H), 4.91 (t, *J* = 1.9 Hz, 1H), 4.70 (t, *J* = 5.3 Hz, 1H), 4.38 (d, *J* = 15.0 Hz, 1H), 4.34 (d, *J* = 15.0 Hz, 1H), 4.19 (d, *J* = 5.3 Hz, 1H), 3.38 - 3.33 (m, 1H), 2.68 (d, *J* = 6.0 Hz, 1H), 2.49 (dt, *J* = 16.3, 3.0 Hz, 1H), 2.38 (d, *J* = 6.0 Hz, 1H), 2.16 (ddt, *J* = 16.0, 2.0, 1.0 Hz, 1H), 2.02 - 1.88 (m, 1H), 1.76 - 1.62 (m, 2H), 1.51 - 1.46 (m, 1H) 1.46 (dd, *J* = 11.0, 3.0 Hz, 1H), 1.36 (dd, *J* = 11.0, 2.5Hz, 1H), 1.15 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{26}H_{29}NO_5Cl$ $[M+H]^+$: 470.1734, found: 470.1740.

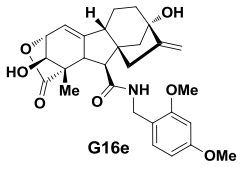



**G16c**: Prepared from aminoacetonitrile bisulfate.
**Yield:** 36.0 mg, 63%.
**$^1$H NMR** ($d_6$-acetone, 500 MHz): δ 8.20 (t, *J* = 5.7 Hz, 1H), 5.76 (dt, *J* = 4.9, 2.1 Hz, 1H), 5.05 (dt, *J* = 3.0, 1.5 Hz, 1H), 4.96 (d, *J* = 5.1 Hz, 1H), 4.89 - 4.86 (m, 1H), 4.68 (t, *J* = 5.3 Hz, 1H), 4.28 (d, *J* = 4.5 Hz, H), 4.27 (d, *J* = 4.5, 1H), 4.26 - 4.22 (m, 1H),

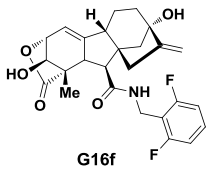
3.84 (s, 1H), 3.37 (dd, *J* = 5.9, 2.7 Hz, 1H), 2.64 (d, *J* = 5.5 Hz, 1H), 2.58 (dt, *J* = 16.4, 3.0 Hz, 1H), 2.33 (d, *J* = 5.9 Hz, 1H), 2.21 (ddt, *J* = 16.0, 2.5, 1.5 Hz, 1H), 1.96 - 1.88 (m, 1H), 1.73 - 1.60 (m, 2H), 1.48 - 1.41 (m, 1H),1.43 (dd, *J* = 10.9, 2.9 Hz, 1H), 1.31 (dd, *J* = 10.0, 2.0 Hz, 1H), 1.09 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{21}H_{24}N_2O_5Na$ $[M+Na]^+$: 407.1583, found: 407.1594.



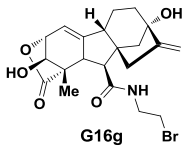

**G16d**: Prepared from 4-methoxyphenethylamine.
**Yield:** 70 mg, 92%.
**$^1$H NMR** ($d_6$-acetone, 500 MHz): δ 7.56 (t, *J* = 5.7 Hz, 1H), 7.16 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.71 (dt, *J* = 5.5, 2.0 Hz, 1H), 5.02 (p, *J* = 1.0 Hz, 1H), 4.95 (d, *J* = 5.2 Hz, 1H), 4.85 - 4.83 (m, 1H), 4.64 (t, *J* = 5.3 Hz, 1H), 4.21 (t, *J* = 5.0 Hz, 1H), 3.78 (s, 1H), 3.74 (s, 3H), 3.75 - 3.72 (m, 1H), 3.51 - 3.45 (m, 2H), 3.37 (dd, *J* = 5.8, 2.7 Hz, 1H), 2.78 (t, *J* = 7.2 Hz, 2H), 2.64 (d, *J* = 7.0 Hz, 1H), 2.42 (dt, *J* = 16.5, 2.9 Hz, 1H), 2.18 (d, *J* = 5.8 Hz, 1H), 1.92 - 1.83 (m, 1H), 1.72 - 1.52 (m, 2H), 1.44 - 1.39 (m, 1H), 1.38 (dd, *J* = 10.8, 2.9 Hz, 1H), 1.23 (dd, *J* = 10.5, 2.0 Hz, 1H), 1.05 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{28}H_{34}NO_6$ $[M+H]^+$: 480.2386, found: 480.2381.




**G16e**: Prepared from 2,4-dimethoxybenzylamine.
**Yield:** 84.4 mg, 99%.
**$^1$H NMR** ($d_6$-acetone, 500 MHz): δ 7.71 (t, *J* = 5.6 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 6.52 (d, *J* = 2.4 Hz, 1H), 6.45 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.71 (dt, *J* = 5.5, 2.0 Hz, 1H), 5.02 (dt, *J* = 2.5, 2.0 Hz, 1H), 4.96 (d, *J* = 5.4 Hz, 1H), 4.87 - 4.79 (m, 1H), 4.64 (t, *J* = 5.3 Hz, 1H), 4.32 (d, *J* = 5.5 Hz, 2H), 4.20 (t, *J* = 4.9 Hz, 1H), 3.81 (s, 3H), 3.79 - 3.77 (m, 1H), 3.77 (s, 3H), 3.40 (dd, *J* = 5.8, 2.6 Hz, 1H), 2.64 (d, *J* = 7.0 Hz, 1H), 2.53 (dt, *J* = 16.6, 3.0 Hz, 1H), 2.29 (d, *J* = 5.8 Hz, 1H), 2.14 - 2.11 (m, 1H), 1.88 (dd, *J* = 13.5, 5.5 Hz, 1H), 1.71 - 1.55 (m, 2H), 1.45 - 1.40 (m, 1H), 1.38 (dd, *J* = 10.9, 2.9 Hz, 1H), 1.29 (dd, *J* = 11.1, 2.0 Hz, 1H), 1.08 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{28}H_{34}NO_7$ $[M+H]^+$: 496.2335, found: 496.2333.

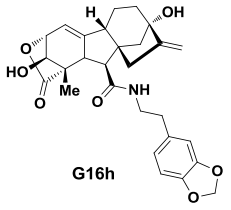



**G16f**: Prepared from 2,6-difluorobenzylamine.
**Yield:** 40.8 mg, 57%.
**$^1$H NMR** ($d_6$-acetone, 500 MHz): δ 7.87 (t, *J* = 5.2 Hz, 1H), 7.42 - 7.30 (m, 1H), 7.04 - 6.94 (m, 2H), 5.71 (dt, *J* = 5.5, 2.0 Hz, 1H), 5.01 (dt, *J* = m.0, 1.5 Hz, 1H), 4.92 (br s, 1H), 4.82 - 4.80 (m, 1H), 4.63 (t, *J* = 5.3 Hz, 1H), 4.53 (ddt, *J* = 14.0, 5.5, 1.0 Hz, 1H), 4.48 (ddt, *J* = 12.0, 5.5, 1.5 Hz, 1H) 4.41 (s, 1H), 4.19 (d, *J* = 5.4 Hz, 1H), 3.38 (dd, *J* = 6.0, 2.5 Hz, 1H), 2.62 (d, *J* = 7.5 Hz, 1H), 2.50 (dt, *J* = 16.5, 2.9 Hz, 1H), 2.26 (d, *J* = 5.8 Hz, 1H), 2.00 - 1.91 (m, 1H), 1.91 - 1.84 (m, 1H), 1.71 - 1.56 (m, 2H), 1.45 - 1.39 (m, 1H), 1.38 (dd, *J* = 10.9, 2.9 Hz, 1H), 1.26 (dd, *J* = 10.9, 2.8 Hz, 1H) 1.04 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{26}H_{28}NO_5F_2$ $[M+H]^+$: 472.1936, found: 472.1938.



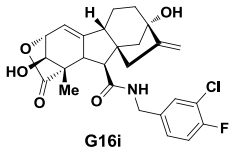

**G16g**: Prepared from 2-bromoethylamine hydrobromide.
**Yield:** 40.2 mg, 58%.
**$^1$H NMR** ($d_6$-acetone, 500 MHz): δ 7.86 (t, *J* = 5.0 Hz, 1H), 5.74 (dt, *J* = 5.5, 3.0 Hz, 1H), 5.06 - 5.03 (m, 1H), 4.91 (d, *J* = 5.6 Hz, 1H), 4.89 - 4.86 (m, 1H), 4.66 (t, *J* = 5.3 Hz, 1H), 4.22 (t, *J* = 5.4 Hz, 1H), 3.77 (s, 1H), 3.67 - 3.61 (m, 2H), 3.61 - 3.51 (m, 2H),

3.38 (dd, *J* = 5.9, 2.8 Hz, 1H), 2.69 - 2.62 (m, 1H), 2.28 (d, *J* = 5.8 Hz, 1H), 2.20 (ddt, *J* = 16.5, 2.5, 2.0 Hz, 1H), 1.93 - 1.87 (m, 1H), 1.73 - 1.58 (m, 2H), 1.46 - 1.38 (m, 2H), 1.32 - 1.26 (m, 2H), 1.11 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{21}H_{27}NO_5Br$ $[M+H]^+$: 452.1073, found: 452.1077.



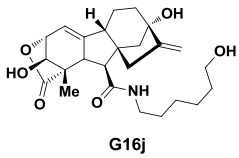
G16h

**G16h**: Prepared from 3,4-methylenedioxyphenethylamine.
**Yield:** 52.9 mg, 70%.
**$^1$H NMR** ($d_6$-acetone, 500 MHz): δ 7.53 (t, *J* = 5.7 Hz, 1H), 6.78 (d, *J* = 1.6 Hz, 1H), 6.76 - 6.68 (m, 2H), 5.92 (dd, *J* = 1.5, 1.0 Hz, 2H), 5.71 (dt, *J* = 5.9, 2.5 Hz, 1H), 5.02 (dt, *J* = 2.5, 1.0 Hz, 1H), 4.95 (d, *J* = 5.5 Hz, 1H), 4.86 - 4.84 (m, 1H), 4.64 (t, *J* = 5.3 Hz, 1H), 4.20 (t, *J* = 5.4 Hz, 1H), 3.77 (s, 1H), 3.52 - 3.42 (m, 2H), 3.37 (dd, *J* = 5.8, 2.7 Hz, 1H), 2.78 (d, *J* = 7.1, 1H), 2.76 (d, *J* = 7.1 Hz, 1H), 2.63 (d, *J* = 7.0 Hz, 1H), 2.42 (dt, *J* = 16.6, 3.0 Hz, 1H), 2.17 (d, *J* = 5.7 Hz, 1H), 2.11 (m, 1H), 1.90 - 1.85 (m, 1H), 1.71 - 1.53 (m, 2H), 1.45 - 1.39 (m, 1H), 1.38 (dd, *J* = 10.9, 2.9 Hz, 1H), 1.22 (dd, *J* = 10.9, 2.8 Hz, 1H), 1.05 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{28}H_{32}NO_7$ $[M+H]^+$: 494.2179, found: 494.2177.



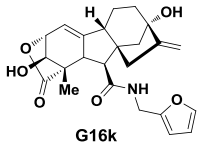
G16i

**G16i**: Prepared from 3-chloro-4-fluorobenzylamine.
**Yield:** 47.6 mg, 65%.
**$^1$H NMR** ($d_6$-acetone, 500 MHz): δ 8.09 (t, *J* = 6.1 Hz, 1H), 7.50 (dd, *J* = 7.2, 2.2 Hz, 1H), 7.35 (ddd, *J* = 8.4, 4.6, 2.2 Hz, 1H), 7.26 (dd, *J* = 9.3, 8.5 Hz, 1H), 5.74 (dt, *J* = 5.2, 2.1 Hz, 1H), 5.03 (dt, *J* = 2.5, 2.0 Hz, 1H), 4.93 (d, *J* = 5.5 Hz, 1H), 4.85 - 4.83 (m, 1H), 4.66 (t, *J* = 5.3 Hz, 1H), 4.46 (dd, *J* = 14.5, 6.0 Hz, 1H), 4.40 (dd, *J* = 15.0, 6.0 Hz, 1H), 4.23 (t, *J* = 5.4 Hz, 1H), 3.39 (dd, *J* = 5.8, 2.7 Hz, 1H), 2.95 (s, 1H), 2.65 (d, *J* = 6.5 Hz, 1H), 2.51 (dt, *J* = 16.4, 3.0 Hz, 1H), 2.29 (d, *J* = 5.8 Hz, 1H), 2.19 - 2.12 (m, 1H), 1.15 (ddt, *J* = 16.5, 2.5, 1.5 Hz, 1H), 1.72 - 1.58 (m, 2H), 1.46 - 1.43 (m, 1H), 1.41 (dd, *J* = 10.8, 3.0 Hz, 1H), 1.28 (dd, *J* = 10.9, 2.8 Hz, 1H), 1.09 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{26}H_{28}NO_5ClF$ $[M+H]^+$: 488.1640, found: 488.1640.



G16j

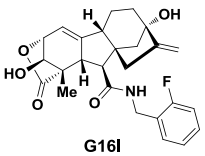
**G16j**: Prepared from 6-amino-1-hexanol.
**Yield:** 42.6 mg, 62%.
**$^1$H NMR** ($d_6$-acetone, 500 MHz): δ 7.55 (t, *J* = 5.7 Hz, 1H), 5.72 (dt, *J* = 5.2, 2.1 Hz, 1H), 5.04 (dt, *J* = 2.0, 1.0 Hz, 1H), 4.96 (d, *J* = 5.5 Hz, 1H), 4.89 - 4.86 (m, 1H), 4.65 (t, *J* = 5.3 Hz, 1H), 4.22 (t, *J* = 5.4 Hz, 1H), 3.81 (s, 1H), 3.55 - 3.47 (m, 3H), 3.38 (dd, *J* = 5.8, 2.7 Hz, 1H), 3.24 (td, *J* = 6.9, 5.7 Hz, 2H), 2.97 (s, 1H), 2.66 (d, *J* = 4.0 Hz, 1H), 2.57 (dt, *J* = 16.4, 3.0 Hz, 1H), 2.24 - 2.18 (m, 2H), 1.91 - 1.86 (m, 1H), 1.72 - 1.57 (m, 2H), 1.56 - 1.47 (m, 4H), 1.46 - 1.40 (m, 1H), 1.40 - 1.34 (m, 4H), 1.28 (dd, *J* = 10.9, 2.8 Hz, 1H), 1.09 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{25}H_{36}NO_6$ $[M+H]^+$: 446.2543, found: 446.3536.



G16k

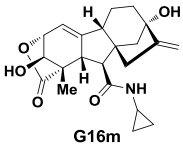
**G16k**: Prepared from furfurylamine.
**Yield:** 52.9 mg, 83%.
**$^1$H NMR** ($d_6$-acetone, 500 MHz): δ 7.94 (t, *J* = 5.7 Hz, 1H), 7.46 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.36 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.27 - 6.25 (m, 1H), 5.74 (dt, *J* = 5.9, 2.5 Hz, 1H), 5.03 (dt, *J* = 3.0, 1.5 Hz, 1H), 4.94 (d, *J* = 5.5 Hz, 1H), 4.86 - 4.83 (m, 1H), 4.66 (t, *J* = 5.3 Hz, 1H), 4.45 (dd, *J* = 15.5, 5.5 Hz, 1H), 4.41 (dd, *J* = 15.5, 5.5 Hz, 1H), 4.23 (t, *J* = 5.4 Hz, 1H), 3.79

(s, 1H), 3.41 (dd, *J* = 5.8, 2.7 Hz, 1H), 2.65 (d, *J* = 6.5 Hz, 1H), 2.53 (dt, *J* = 16.5, 3.0 Hz, 1H), 2.31 (d, *J* = 5.8 Hz, 1H), 2.14 (ddt, *J* = 16.5, 2.5, 1.5 Hz, 1H), 1.93 - 1.87 (m, 1H), 1.73 - 1.57 (m, 2H), 1.47 - 1.43 (m, 1H), 1.41 (dd, *J* = 11.0, 2.5 Hz, 1 H), 1.30 (dd, *J* = 11.0, 2.5 Hz, 1H), 1.09 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{24}H_{28}NO_6$ $[M+H]^+$: 426.1917, found: 426.1913.



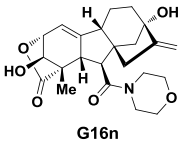
G16l

**G16l**: Prepared from 2-fluorobenzylamine.
**Yield:** 21.0 mg, 60%.
**$^1$H NMR** ($d_6$-acetone, 500 MHz): δ 8.00 - 7.93 (m, 1H), 7.45 (td, *J* = 7.7, 1.7 Hz, 1H), 7.34 - 7.27 (m, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 8.5 Hz, 1H), 5.74 - 5.71 (m, 1H), 5.02 (dt, *J* = 3.3, 1.6 Hz, 1H), 4.94 - 4.88 (m, 1H), 4.83 - 4.80 (m, 1H), 4.65 (t, *J* = 5.3 Hz, 1H), 4.51 (dd, *J* = 15.0, 6.0 Hz, 1H), 4.45 (dd, *J* = 15.0, 5.5 Hz, 1H), 4.21 (t, *J* = 5.0 Hz, 1H), 3.78 - 3.74 (m, 1H), 3.40 (dd, *J* = 6.0, 2.6 Hz, 1H), 2.90 - 2.80 (m, 1H), 2.64 (d, *J* = 5.5 Hz, 1H), 2.52 (dt, *J* = 16.5, 3.0 Hz, 1H), 2.31 (d, *J* = 5.8 Hz, 1H), 2.11 (ddt, *J* = 16.5, 3.0, 1.5 Hz, 1H), 1.93 - 1.86 (m, 1H), 1.72 - 1.56 (m, 2H), 1.45 - 1.41 (m, 1H), 1.40 (dd, *J* = 11.0, 2.5 Hz, 1H), 1.28 (dd, *J* = 10.8, 2.6 Hz, 1H), 1.08 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{26}H_{29}NO_5F$ $[M+H]^+$: 454.2030, found: 454.2034.



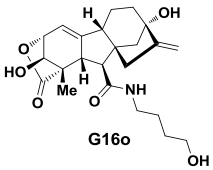
G16m

**G16m**: Prepared from cyclopropylamine.
**Yield:** 19.3 mg, 66%.
**$^1$H NMR** ($d_6$-acetone, 500 MHz): δ 7.56 (d, *J* = 2.5 Hz, 1H), 5.72 (dt, *J* = 5.0, 2.0 Hz, 1H), 5.04 (ddd, *J* = 3.3, 2.0, 1.2 Hz, 1H), 4.92 (d, *J* = 5.6 Hz, 1H), 4.89 - 4.87 (m, 1H), 4.65 (t, *J* = 5.3 Hz, 1H), 4.21 (t, *J* = 5.5 Hz, 1H), 3.76 (s, 1H), 3.38 (dd, *J* = 5.5, 2.5 Hz, 1H), 2.79 - 2.73 (m, 1H), 2.64 (d, *J* = 6.0 Hz, 1H), 2.53 (dt, *J* = 16.4, 3.0 Hz, 1H), 2.20 (ddt, *J* = 16.5, 2.5, 2.0 Hz, 1H), 2.14 (d, *J* = 5.8 Hz, 1H), 1.92 - 1.85 (m, 1H), 1.71 - 1.58 (m, 2H), 1.46 - 1.40 (m, 1H), 1.39 (dd, *J* = 10.8, 2.9 Hz, 1H), 1.24 (dd, *J* = 10.9, 2.9 Hz, 1H), 1.07 (s, 3H), 0.71 - 0.64 (m, 2H), 0.53 - 0.44 (m, 2H).
**HRMS(ESI)**: *m/z* calc. for $C_{22}H_{28}NO_5$ $[M+H]^+$: 386.1967, found: 386.1961.



G16n

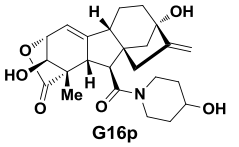
**G16n**: Prepared from morpholine.
**Yield:** 23.9 mg, 75%.
**$^1$H NMR** ($CD_3OD$, 500 MHz): δ 5.80 (dt, *J* = 5.0, 2.5 Hz, 1H), 5.11 - 5.07 (m, 1H), 5.00 - 4.96 (m, 1H), 4.72 (t, *J* = 5.3 Hz, 1H), 4.20 (d, *J* = 5.3 Hz, 1H), 3.76 - 3.55 (m, 8H), 3.45 (dd, *J* = 6.5, 2.6 Hz, 1H), 2.84 (d, *J* = 6.5 Hz, 1H), 2.68 (d, *J* = 3.0 Hz, 1H), 2.42 (dt, *J* = 16.0, 2.5 Hz, 1H), 2.24 (ddt, *J* = 16.0, 2.5, 2.0 Hz, 1H), 1.98 - 1.92 (m, 1H), 1.78 - 1.66 (m, 2H), 1.54 - 1.48 (m, 2H), 1.40 (dd, *J* = 11.0, 1.5 Hz, 1H), 1.38 - 1.34 (m, 2H), 1.10 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{23}H_{30}NO_6$ $[M+H]^+$: 416.2073, found: 416.2067.



G16o

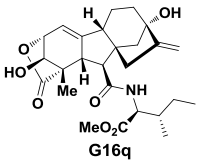
**G16o**: Prepared from 4-amino-1-butanol.
**Yield:** 19.4 mg, 61%.
**$^1$H NMR** ($d_6$-acetone, 500 MHz): δ 7.53 (t, *J* = 5.7 Hz, 1H), 5.72 (dt, *J* = 5.5, 3.0 Hz, 1H), 5.04 (ddd, *J* = 3.3, 2.0, 1.2 Hz, 1H), 4.93 (d, *J* = 5.4 Hz, 1H), 4.88 - 4.86 (m, 1H), 4.65 (t, *J* = 5.3 Hz, 1H), 4.22 (t, *J* = 5.2 Hz, 1H), 3.78 (s, 1H), 3.59 - 3.50 (m, 2H), 3.39 (dd, *J* = 5.8, 2.7 Hz, 1H), 3.30 - 3.20 (m, 2H), 2.66 (d, *J* = 6.6 Hz, 1H), 2.57 (dt, *J* = 16.4, 3.0

Hz, 1H), 2.30 - 2.17 (m, 2H), 1.92 - 1.86 (m, 1H), 1.72 - 1.51 (m, 7H), 1.46 - 1.42 (m, 1H), 1.41 (dd, *J* = 10.9, 2.9 Hz, 1H), 1.28 (dd, *J* = 10.9, 2.8, Hz, 1H), 1.09 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{23}H_{32}NO_6$ $[M+H]^+$: 418.2230, found: 418.2238.



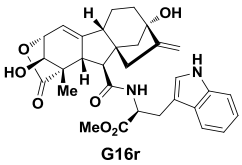
G16p

**G16p**: Prepared from 4-hydroxypiperidine.
**Yield:** 15.5 mg, 47%.
**$^1$H NMR** ($d_6$-DMSO, 500 MHz): δ 5.87 (t, *J* = 5.0 Hz, 1H), 5.70 (dt, *J* = 5.1, 2.4 Hz, 1H), 5.01 - 4.97 (m, 1H), 4.87 (d, *J* = 14.5 Hz, 1H), 4.83 - 4.80 (m, 2H), 4.67 (t, *J* = 5.0 Hz, 1H), 4.10 (q, *J* = 5.0 Hz, 1H), 3.94 - 3.64 (m, 3H), 3.36 - 3.24 (m, 2H), 3.18 (ddd, *J* = 13.2, 9.2, 3.1 Hz, 1H), 2.91 (ddd, *J* = 13.4, 10.8, 3.1 Hz, 1H), 2.68 (t, *J* = 7.0 Hz, 1H), 2.27 (ddt, *J* = 24.5, 16.5, 2.5 Hz, 1H), 2.08 (s, 1H), 1.87 - 1.64 (m, 3H), 1.61 - 1.44 (m, 2H), 1.39 - 1.10 (m, 5H), 0.96 (d, *J* = 13.7 Hz, 3H). Note: The doublet at 0.96 ppm gave partial coalescence at 95 °C. Higher temperatures were not attempted.
**HRMS(ESI)**: *m/z* calc. for $C_{24}H_{32}NO_6$ $[M+H]^+$: 430.2230, found: 430.2233.



G16q

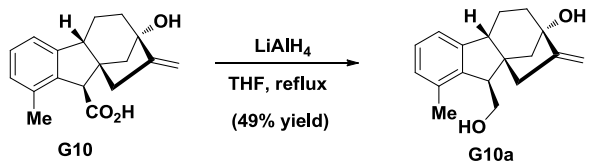
**G16q**: Prepared from L-isoleucine methyl ester hydrochloride.
**Yield:** 36.7 mg, 25%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 6.75 (d, *J* = 8.7 Hz, 1H), 5.76 (dt, *J* = 5.0, 2.2 Hz, 1H), 5.08 (t, *J* = 2.5 Hz, 1H), 4.94 (t, *J* = 2.0 Hz, 1H), 4.76 (t, *J* = 5.3 Hz, 1H), 4.56 (dd, *J* = 8.7, 5.3 Hz, 1H), 4.23 (d, *J* = 5.4 Hz, 1H), 3.74 (s, 3H), 3.32 (dd, *J* = 5.8, 2.6 Hz, 1H), 2.79 (br s, 1H), 2.73 (d, *J* = 6.7 Hz, 1H), 2.59 (dt, *J* = 16.6, 3.0 Hz, 1H), 2.40 (d, *J* = 5.8 Hz, 1H), 2.23 (ddt, *J* = 17.0, 3.0, 2.0 Hz, 1H), 1.96 - 1.86 (m, 2H), 1.78 - 1.63 (m, 2H), 1.57 - 1.50 (m, 1H), 1.51 (dd, *J* = 10.8, 2.8 Hz, 1H), 1.46 - 1.35 (m, 2H), 1.27 - 1.11 (m, 2H), 1.20 (s, 3H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 6.5, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{26}H_{36}NO_7$ $[M+H]^+$: 474.2492, found: 474.2499.



G16r

**G16r**: Prepared from L-tryptophan methyl ester hydrochloride.
**Yield:** 60.6 mg, 33%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.64 (br s, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 7.09 (t, *J* = 7.0, 2H), 6.98 (d, *J* = 2.3 Hz, 1H), 5.69 (dt, *J* = 5.2, 2.1 Hz, 1H), 5.04 (t, *J* = 2.4 Hz, 1H), 4.97 - 4.90 (m, 1H), 4.90 (s, 1H), 4.66 (t, *J* = 5.3 Hz, 1H), 4.02 (d, *J* = 5.4 Hz, 1H), 3.70 (s, 3H), 3.31 (dd, *J* = 15.0, 4.5 Hz, 1H) 3.28 - 3.19 (m, 2H), 2.68 - 2.59 (m, 2H), 2.26 (d, *J* = 5.7 Hz, 1H), 2.18 (d, *J* = 17.0 Hz, 1H), 1.85 (d, *J* = 9.1 Hz, 1H), 1.69 - 1.56 (m, 2H), 1.53 - 1.50 (m, 1H), 1.42 - 1.39 (m, 2H), 0.84 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{31}H_{35}N_2O_7$ $[M+H]^+$: 547.2444, found: 547.2438.

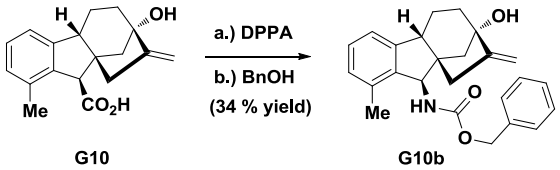
**Synthesis of G10 Derivatives**



**Procedure:** In an oven-dried round bottom flask with a stir bar under nitrogen, loaded **G10** (39.7 mg, 0.140 mmol) and dissolved in tetrahydrofuran (2.0 mL). Added lithium aluminum hydride (103.7 mg, 2.73 mmol) and refluxed for 16 hours. The reaction was cooled to 0°C and quenched with water (0.12 mL), followed by 15% aqueous sodium hydroxide (0.12 mL) and additional water (3.0 mL). The mixture stirred for 15 minutes, at which point anhydrous magnesium sulfate was added. After an additional 15 minutes of stirring, the solids were filtered and washed thoroughly with ethyl acetate. The aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1:4 hexanes/ethyl acetate) to yield the product as a white solid (18.4 mg, 49%).

**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.09 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 5.02 (t, *J* = 2.6 Hz, 1H), 4.79 (t, *J* = 2.2 Hz, 1H), 4.33 (dd, *J* = 11.1, 4.4 Hz, 1H), 4.06 (dd, *J* = 11.1, 7.3 Hz, 1H), 3.26 (dd, *J* = 7.5, 4.5 Hz, 1H), 2.71 (dd, *J* = 12.6, 5.0 Hz, 1H), 2.47 (dt, *J* = 17.0, 3.0 Hz, 1H), 2.39 (s, 3H), 2.32 (dd, *J* = 10.1, 2.5 Hz, 1H), 2.22 (dtd, *J* = 13.1, 5.1, 1.7 Hz, 1H), 2.16 - 2.06 (m, 2H), 2.00 - 1.91 (m, 2H), 1.84 (dd, *J* = 10.1, 2.6 Hz, 1H), 1.73 (ddt, *J* = 11.7, 5.1, 2.0 Hz, 1H), 1.55 (qd, *J* = 12.7, 5.3 Hz, 1H).

**HRMS(ESI)**: *m/z* calc. for $C_{18}H_{23}O_2$ $[M+H]^+$: 271.1698, found: 271.1704.

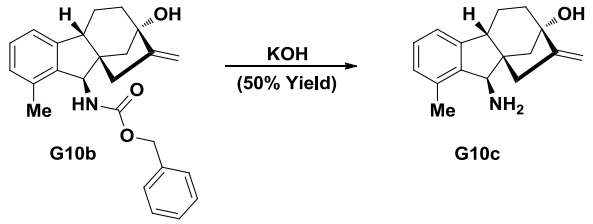



G10 G10b

**Procedure:** In an oven-dried round bottom flask with a stir bar under nitrogen, loaded **G10** (321.0 mg, 1.13 mmol) and dissolved in benzene (11 mL). Added triethylamine (170 µL, 1.22 mmol) and diphenylphosphoryl azide (250 µL, 1.21 mmol) and refluxed. When **G10** had fully dissolved, benzyl alcohol (240 µL, 2.32 mmol) was added and the reaction refluxed for 14 hours. The reaction was cooled to room temperature, quenched with water (10 mL), extracted with ethyl acetate (3x), washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (9:1 to 1:9 hexanes/ethyl acetate) to yield the product as a white solid (151.2 mg, 34%).

**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.41 - 7.30 (m, 5H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.97 - 6.91 (m, 2H), 5.31 (d, *J* = 10.3 Hz, 1H), 5.21 (d, *J* = 12.1 Hz, 1H), 5.13 (d, *J* = 12.2 Hz, 1H), 5.04 (t, *J* = 2.5 Hz, 1H), 4.97 (d, *J* = 10.3 Hz, 1H), 4.79 (t, *J* = 2.1 Hz, 1H), 2.75 (dd, *J* = 12.5, 5.2 Hz, 1H), 2.34 - 2.19 (m, 2H), 2.27 (s, 3H), 2.06 (dd, *J* = 10.5, 2.5 Hz, 1H), 1.95 (td, *J* = 12.0, 5.0 Hz, 1H), 1.90 - 1.84 (m, 2H), 1.77 - 1.68 (m, 2H), 1.55 (qd, *J* = 12.8, 5.2 Hz, 1H).

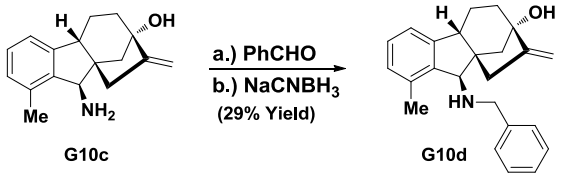
**HRMS(ESI)**: *m/z* calc. for $C_{25}H_{28}NO_3$ $[M+H]^+$: 390.2069, found: 390.2063.




**Procedure:** In a round bottom flask with a stir bar, dissolved **G10** (41.5 mg, 0.107 mmol) and potassium hydroxide (237.3 mg, 4.23 mmol) in methanol (2 mL) and water (2 mL). The reaction was refluxed for 24 hours, and then the reaction was cooled to room temperature, extracted with dichloromethane (3x), washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (98:1:1 to 97:2:1 dichloromethane/methanol/triethylamine) to yield the product as a white solid (13.6 mg, 50%).

**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.08 (t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 7.0 Hz, 1H), 5.02 (t, *J* = 2.6 Hz, 1H), 4.79 (t, *J* = 2.2 Hz, 1H), 4.29 (s, 1H), 2.66 (dd, *J* = 12.3, 4.9 Hz, 1H), 2.49 (s, 3H), 2.40 (dt, *J* = 17.0, 2.9 Hz, 1H), 2.25 (dtd, *J* = 13.1, 5.2, 1.7 Hz, 1H), 2.09 (dd, *J* = 10.3, 2.3 Hz, 1H), 1.97 (td, *J* = 12.2, 5.2 Hz, 1H), 1.80 (q, *J* = 2.0 Hz, 1H), 1.77 (q, *J* = 2.4 Hz, 1H), 1.74 (q, *J* = 2.5 Hz, 1H), 1.72 (q, *J* = 2.5 Hz, 1H), 1.56 (qd, *J* = 12.7, 5.3 Hz, 1H).

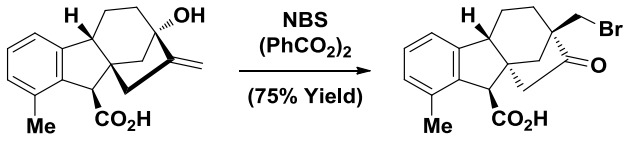
**HRMS(ESI)**: *m/z* calc. for $C_{17}H_{22}NO$ $[M+H]^+$: 256.1701, found: 256.1712.




**Procedure:** In an oven-dried vial with a stir bar under $N_2$, **G10c** (10.5 mg, 0.0411 mmol) and benzaldehyde (8.0 μL, 1.76 mmol) were dissolved in methanol (0.5 mL) and stirred at room temperature for 20 minutes. Sodium cyanoborohydride (14.1 mg, 5.45 mmol) was added and the reaction continued to stir for 8 hours. The reaction was quenched with aqueous saturated sodium bicarbonate, extracted with dichloromethane (3x), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (196:3 to 97:3 dichloromethane/ethyl acetate) to yield a white solid (4.1 mg, 29%).

**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.45 - 7.41 (m, 2H), 7.38 - 7.32 (m, 2H), 7.29 - 7.24 (m, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 7.3 Hz, 1H), 5.04 (t, *J* = 2.6 Hz, 1H), 4.83 (t, *J* = 1.0 Hz, 1H), 4.24 (s, 1H), 4.12 (d, *J* = 13.1 Hz, 1H), 4.07 (d, *J* = 13.1 Hz, 1H), 2.64 (dd, *J* = 12.5, 5.1 Hz, 1H), 2.57 (t, *J* = 2.9 Hz, 1H), 2.53 (s, 3H), 2.25 (dtd, *J* = 13.0, 5.5, 1.5 Hz, 1H) 2.21 (dd, *J* = 10.0, 2.0 Hz, 1H), 1.95 (td, *J* = 12.2, 5.2 Hz, 1H), 1.89 - 1.82 (m, 2H), 1.75 - 1.67 (m, 2H), 1.57 (td, *J* = 12.8, 5.3 Hz, 1H).

**HRMS(ESI)**: *m/z* calc. for $C_{24}H_{28}NO$ $[M+H]^+$: 346.2171, found: 346.2169.



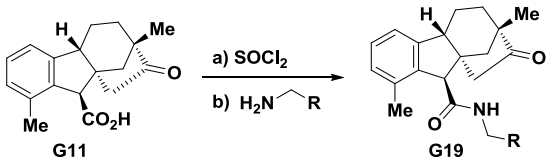

G10 G10e

**Procedure:** In an oven-dried 7 mL vial with stir bar, **G10** (20.7 mg, 0.073 mmol), *N*-bromosuccinamide (15.8 mg, 0.089 mmol), and benzoyl peroxide (0.1 mg, 0.0004 mmol) were dissolved in carbon tetrachloride (0.5 mL). The reaction was heated at 67 °C for 24 hours, after which the reaction was concentrated and purified directly using flash silica chromatography (3:1 hexanes/ethyl acetate to ethyl acetate) to afford **G10e** as a white solid (19.8 mg, 75%).

**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.23 (t, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 4.25 (s, 1H), 3.57 (d, *J* = 10.4 Hz, 1H), 3.35 (d, *J* = 10.4 Hz, 1H), 3.06 (t, *J* = 7.8 Hz, 1H), 2.76 (d, *J* = 17.8 Hz, 1H), 2.57 (dd, *J* = 17.8, 3.5 Hz, 1H), 2.27 (s, 3H), 2.18 (td, *J* = 7.0, 3.4 Hz, 1H), 2.14 (dd, *J* = 12.2, 3.5 Hz, 1H), 1.93 - 1.81 (m, 3H), 1.81 - 1.72 (m, 1H).

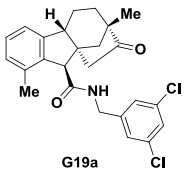
**HRMS(ESI)**: *m/z* calc. for $C_{18}H_{20}O_3Br$ $[M+H]^+$: 363.0596, found: 363.0586.

**Synthesis of G19 Derivatives**



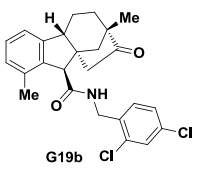

G11 G19

**General procedure for the preparation of amides from G11:** In an oven-dried round bottom flask with stir bar, **G11** (1 equiv.) was dissolved in tetrahydrofuran (0.05 M). Thionyl chloride (1.2 equiv.) was added, and the reaction was refluxed for 30 minutes. The reaction was then cooled in an ice bath, at which point triethylamine (2.2 equiv.) and amine (1.5 equiv.) were added and the reaction was allowed to warm to room temperature for 1 hour. The reaction was quenched with water, extracted with ethyl acetate (3x), and purified by flash silica chromatography (hexanes/ethyl acetate) to provide the amide.




G19a

**G19a:** Prepared from 3,5-dichlorobenzylamine.
**Yield:** 26.6 mg, 35%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.27 (t, *J* = 1.9 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.20 (s, 1H), 7.19 (s, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 5.90 (br s, 1H), 4.49 (dd, *J* = 14.9, 6.4 Hz, 1H), 4.36 (dd, *J* = 14.9, 6.0 Hz, 1H), 4.07 (s, 1H), 2.95 (t, *J* = 8.5 Hz, 1H), 2.70 (d, *J* = 15.1 Hz, 1H), 2.44 (dd, *J* = 17.6, 3.7 Hz, 1H), 2.17 (s, 3H), 2.10 (tt, *J* = 7.3, 3.5 Hz, 1H), 1.89 (dd, *J* = 11.9, 3.5 Hz, 1H), 1.83 - 1.72 (m, 2H), 1.63 (dt, *J* = 6.4, 3.3 Hz, 1H), 1.38 (d, *J* = 11.5 Hz, 1H), 1.04 (s, 3H).
**HRMS(ESI)**: *m/z* calc. for $C_{25}H_{26}NO_2Cl_2$ $[M+H]^+$: 442.1341, found: 442.1342.




**G19b**: Prepared from 2,4-dichlorobenzylamine.

**Yield:** 202.9 mg, 73%.

**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.46 (d, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 2.1 Hz, 1H), 7.23, (dd, *J* = 8.2, 2.1 Hz, 1H) 7.21 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 5.98 (s, 1H), 4.51 (dd, *J* = 14.8, 6.2 Hz, 1H), 4.48 (dd, *J* = 14.8, 6.2 Hz, 1H), 3.99 (s, 1H), 2.92 (t, *J* = 8.0 Hz, 1H), 2.65 (d, *J* = 17.7 Hz, 1H), 2.42 (dd, *J* = 17.6, 3.7 Hz, 1H), 2.12 - 2.06 (m, 1H), 2.08 (s, 3H), 1.85 - 1.69 (m, 3H), 1.64 - 1.54 (m, 1H), 1.17 (d, *J* = 12.0 Hz, 1H), 0.96 (s, 3H).

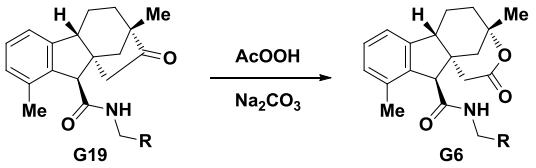
**HRMS(ESI)**: *m/z* calc. for $C_{25}H_{26}NO_2Cl_2$ $[M+H]^+$: 442.1341, found: 442.1350.


**Procedure:** In an oven-dried vial with stir bar, **G19** (15.3 mg, 0.048 mmol) and 2,3-dichloro-5,6-dicyanobenzoquinone (12.2 mg, 0.054 mmol) were dissolved in toluene (0.5 mL) and refluxed for 20 hours. The reaction was then diluted with ethyl acetate, washed with saturated aqueous ammonium chloride (2x) and water (2x), and concentrated. Purification by flash silica chromatography (4:1 hexanes/ethyl acetate) afforded **G19c** as a white solid (12.4 mg, 82%).

**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.32 (d, *J* = 7.7 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.4 Hz, 1H), 5.97 (t, *J* = 3.6 Hz, 1H), 4.96 (t, *J* = 6.1 Hz, 1H), 3.90 (s, 1H), 3.08 (dt, *J* = 13.4, 6.7 Hz, 1H), 2.89 (ddd, *J* = 12.8, 6.8, 5.5 Hz, 1H), 2.49 (d, *J* = 17.4 Hz, 1H), 2.43 (dd, *J* = 17.4, 3.3 Hz, 1H), 2.34 - 2.23 (m, 3H), 2.27 (s, 3H), 1.86 (dd, *J* = 11.3, 3.3 Hz, 1H), 1.69 - 1.58 (m, 1H), 1.20 (s, 3H), 0.76 (d, *J* = 6.5 Hz, 3H), 0.75 (d, *J* = 6.5 Hz, 3H).

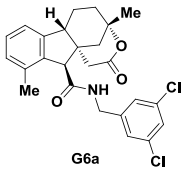
**HRMS(ESI)**: *m/z* calc. for $C_{22}H_{28}NO_2$ $[M+H]^+$: 338.2120, found: 338.2112.

**Synthesis of G6 Derivatives**




**General procedure for the preparation of lactones from G19:** In oven-dried vial with stir bar, **G19a** or **G19b** (1 equiv.) was dissolved in dichloromethane (0.05 M). The reaction was cooled to 0 °C in an ice bath, and sodium carbonate (7.5 equiv.) and peracetic acid (32% in acetic acid, 5 equiv.) were added. The reaction stirred for 15 hours, during which time it was allowed to warm to room temperature. Saturated aqueous sodium bicarbonate was added to quench the reaction. The reaction was acidified to pH 3, and the aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were washed with

brine, dried over magnesium sulfate, and concentrated. Purification by flash silica chromatography (hexanes/ethyl acetate) afforded the lactone along with unreacted starting material.

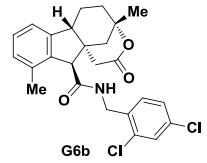



**G6a:** Prepared from **G19a**.

**Yield:** 10.4 mg, 38%, 79% brsm.

**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.29 (t, *J* = 1.9 Hz, 1H), 7.23 (s, 1H), 7.22 (s, 1H), 7.20 (t, *J* = 7.9 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.29 (br s, 1H), 4.60 (dd, *J* = 14.8, 6.8 Hz, 1H), 4.31 (dd, *J* = 14.9, 5.4 Hz, 1H), 3.55 (s, 1H), 2.92 (d, *J* = 17.6 Hz, 1H), 2.89 (s, 1H), 2.70 (dd, *J* = 17.6, 2.8 Hz, 1H), 2.22 (ddt, *J* = 15.1, 5.0, 2.4 Hz, 1H), 2.14 (s, 3H), 1.92 (ddt, *J* = 15.1, 12.0, 5.8 Hz, 1H), 1.84 (dq, *J* = 14.0, 2.6 Hz, 1H), 1.64 (d, *J* = 14.0 Hz, 1H), 1.45 - 1.39 (m, 1H), 1.39 - 1.35 (m, 1H), 1.31 (s, 3H).

**HRMS(ESI)**: *m/z* calc. for $C_{25}H_{26}NO_3Cl_2$ $[M+H]^+$: 458.1290, found: 458.1291.



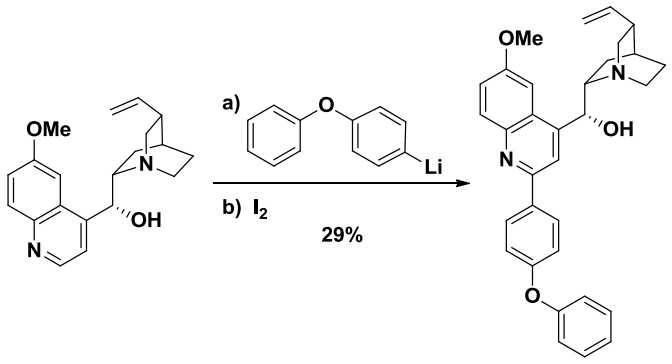

**G6b:** Prepared from **G19b**.

**Yield:** 9.1 mg, 23%, 34% brsm.

**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.46 (d, *J* = 8.2 Hz, 1H), 7.40 (d, *J* = 2.1 Hz, 1H), 7.24 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.16 (t, *J* = 5.4 Hz, 1H), 4.61 (dd, *J* = 14.4, 6.4 Hz, 1H), 4.47 (dd, *J* = 14.4, 5.6 Hz, 1H), 3.49 (s, 1H), 2.90 (d, *J* = 17.6 Hz, 1H), 2.89 (s, 1H), 2.69 (dd, *J* = 17.6, 2.8 Hz, 1H), 2.29 - 2.14 (m, 2H), 2.04 (s, 3H), 1.91 (ddt, *J* = 15.2, 12.1, 5.9 Hz, 1H), 1.85 - 1.77 (m, 1H), 1.56 (d, *J* = 14.2 Hz, 1H), 1.38 (td, *J* = 13.5, 5.4 Hz, 1H), 1.25 (s, 3H).

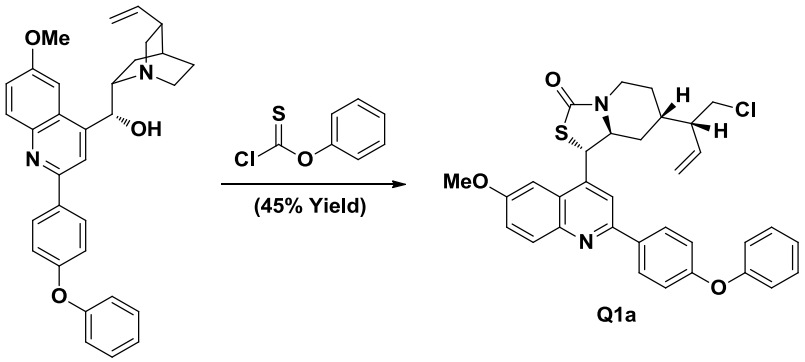
**HRMS(ESI)**: *m/z* calc. for $C_{25}H_{26}NO_3Cl_2$ $[M+H]^+$: 458.1290, found: 458.1290.

**12.) Quinine Derived Libraries: Synthesis and Characterization**




PhOPh-Q

**Procedure:** To a flame dried round bottom flask under argon containing a suspension of quinine (3.153 g, 9.7 mmol) in methyl *t*-butyl ether (58 mL) at -10 °C was added (4-phenoxyphenyl)lithium (5.142 g, 29.2 mmol). The reaction mixture was stirred for 20 min at -10 °C, warmed to room temperature for 1 h, and quenched by dropwise addition of acetic acid at 0 °C. Upon dilution with water and ethyl acetate, solid iodine (~700 mg) was added with vigorous stirring until a dark brown color persisted. A saturated aqueous solution of sodium metabisulfite was then added to quench excess iodine. The reaction mixture was basified with 25% aqueous ammonia and extracted with dichloromethane (3x). The organic layer was washed with brine, dried with magnesium sulfate, and evaporated. Purification by column chromatography using 1:9 methanol/toluene with 2% triethylamine provided 1.406 g (29%) of **PhOPh-Q** as a white solid. Spectral data for **PhOPh-Q** ($^{1}$H NMR, $^{13}$C NMR, and HRMS) matched previously reported spectra.[12]



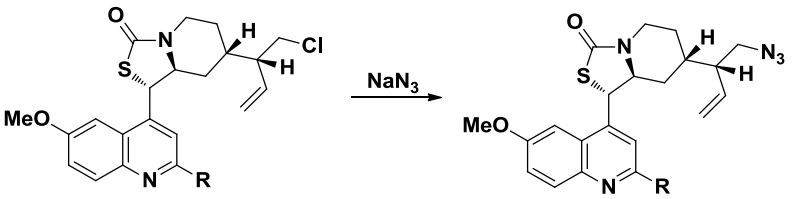

PhOPh-Q

Q1a

**Procedure**: To a solution of **PhOPh-Q** (700 mg, 1.42 mmol) in dry dichloromethane (28.4 mL) at 0 °C under argon was added *O*-Phenyl chlorothionoformate (295.2 mg, 1.71 mmol). The reaction was warmed to room temperature and stirred overnight. Upon cooling to 0 °C, the reaction was quenched by slow addition of aqueous sodium bicarbonate and transferred to a separatory funnel. The crude mixture was washed 3 times with 1 M NaOH to remove phenol then washed with brine, dried with magnesium sulfate, and evaporated. Purification by column chromatography using 1:12 to 0:1 hexanes/chloroform provided **Q1a** (368 mg, 45%) as a yellow powder.

**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.16 - 8.10 (m, 3H), 8.07 (s, 1H), 7.44 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.39 - 7.35 (m, 2H), 7.25 (d, *J* = 2.7 Hz, 1H), 7.18 - 7.12 (m, 3H), 7.10 - 7.06 (m, 2H), 5.68 (dt, *J* = 17.1, 9.7 Hz, 1H), 5.21 (dd, *J* = 10.1, 1.5 Hz, 1H), 5.18 (d, *J* = 7.3 Hz, 1H), 5.13 (dd, *J* = 17.0, 1.4 Hz, 1H), 4.06 - 3.99 (m, 2H), 3.99 (s, 3H), 3.52 (dd, *J* = 11.2, 3.4 Hz, 1H), 3.40 (dd, *J* = 11.1, 5.1 Hz, 1H), 2.97 (td, *J* = 13.3, 3.4 Hz, 1H), 2.61 (dq, *J* = 14.4, 4.5 Hz, 1H), 2.19 - 2.12 (m, 1H), 2.09 (dd, *J* = 14.1, 2.5 Hz, 1H), 1.95 - 1.87 (m, 1H), 1.86 - 1.80 (m, 1H), 1.73 - 1.64 (m, 1H).

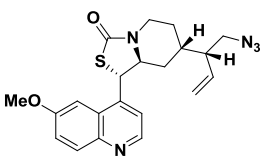
**HRMS(ESI):** *m/z* calc. for $C_{33}H_{32}N_2O_3SCl$ $[M+H]^+$: 571.1822, found: 571.1811.




**Q1: R = H**
**Q1a: R = 4-PhOPh**

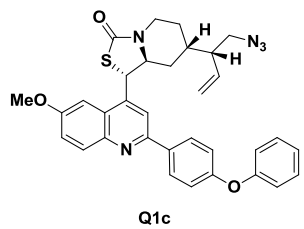
**Q1b: R = H, 89% Yield**
**Q1c: R = 4-PhOPh, 95% Yield**

**General procedure for the preparation of Q1 azides:** To a solution of chloride **Q1** or **Q1a** (0.26 mmol) in *N*,*N*-dimethylformamide (2.6 mL) was added sodium azide (51.4 mg, 0.79 mmol). The reaction mixture was heated to 50 °C and stirred 24 h. Upon cooling, the reaction was poured into brine and extracted with ethyl acetate. Washing the organic layer with brine (4x), drying with magnesium sulfate, and evaporation of solvent provided pure azide. (Note: This procedure was performed at several scales 0.22 - 1.66 mmol.)




Q1b

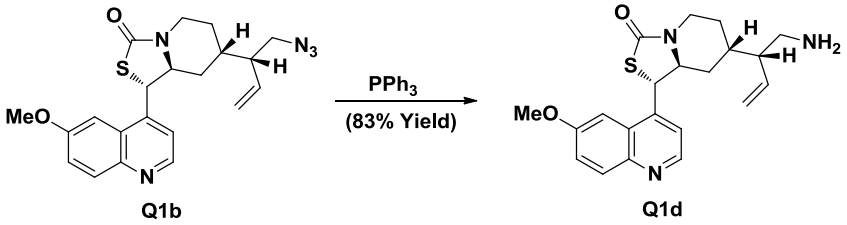
**Q1b**: Prepared from **Q1.**
**Yield:** 451.7 mg, 89% yield.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.79 (d, *J* = 4.6 Hz, 1H), 8.08 (d, *J* = 9.2 Hz, 1H), 7.60 (d, *J* = 4.6 Hz, 1H), 7.43 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.25 (d, *J* = 2.7 Hz, 1H), 5.59 (ddd, *J* = 16.9, 10.2, 9.4 Hz, 1H), 5.20 (dd, *J* = 10.2, 1.5 Hz, 1H), 5.16 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.12 (d, *J* = 7.8 Hz, 1H), 4.03 - 3.96 (m, 2H), 3.96 (s, 3H), 3.26 (dd, *J* = 12.3, 4.7 Hz, 1H), 3.20 (dd, *J* = 12.3, 5.8 Hz, 1H), 2.95 (td, *J* = 13.2, 3.3 Hz, 1H), 2.48 (tt, *J* = 10.5, 5.3 Hz, 1H), 2.02 - 1.94 (m, 2H), 1.85 - 1.77 (m, 2H), 1.62 (tt, *J* = 13.7, 4.8 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{21}H_{24}N_5O_2S$ $[M+H]^+$: 410.1651, found: 410.1655.




Q1c

**Q1c**: Prepared from **Q1a.**
**Yield:** 143 mg, 95%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.17 - 8.10 (m, 3H), 8.09 (s, 1H), 7.45 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.40 - 7.34 (m, 2H), 7.26 (d, *J* = 2.3 Hz, 1H), 7.18 - 7.12 (m, 3H), 7.10 - 7.05 (m, 2H), 5.59 (dt, *J* = 17.1, 9.8 Hz, 1H), 5.23 - 5.13 (m, 3H), 4.07 - 4.00 (m, 2H), 3.98 (s, 3H), 3.27 (dd, *J* = 12.3, 4.7 Hz, 1H), 3.19 (dd, *J* = 12.3, 5.9 Hz, 1H), 2.96 (td, *J* = 13.3, 3.3 Hz, 1H), 2.48 (tt, *J* = 10.4, 5.3 Hz, 1H), 2.08 - 2.01 (m, 1H), 2.02 - 1.95 (m, 1H), 1.90 - 1.79 (m, 2H), 1.64 (tt, *J* = 13.7, 4.8 Hz, 1H).

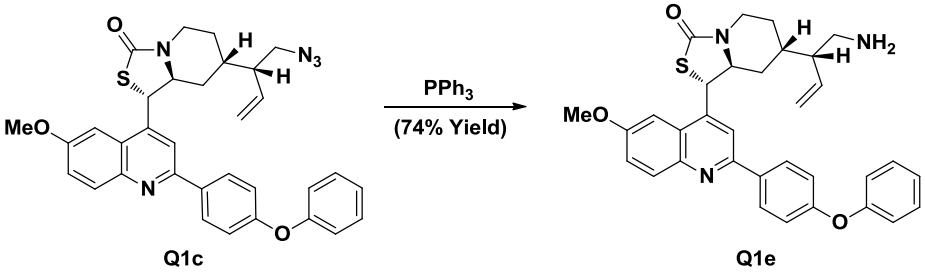
**HRMS(ESI):** *m/z* calc. for $C_{33}H_{32}N_5O_3S$ $[M+H]^+$: 578.2226, found: 578.2220.




**Procedure:** A solution of azide **Q1b** (481.8 mg, 1.18 mmol) and triphenylphosphine (926 mg, 3.53 mmol) in tetrahydrofuran (30 mL) and water (2 mL) was stirred at 50 °C for 6 hours. The reaction was then cooled to room temperature, washed with brine, dried with magnesium sulfate, and evaporated. Purification by column chromatography using a gradient of 1:49 to 3:22 methanol/ethyl acetate with 2% triethylamine provided amine **Q1d** (377.3 mg, 83%) as a white solid.

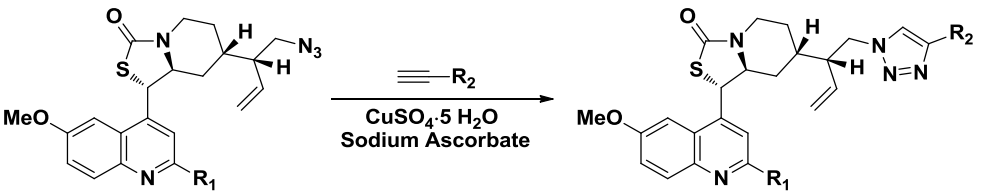
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.74 (d, *J* = 4.6 Hz, 1H), 8.02 (d, *J* = 9.2 Hz, 1H), 7.55 (d, *J* = 4.6 Hz, 1H), 7.38 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.21 (d, *J* = 2.7 Hz, 1H), 5.39 (dt, *J* = 17.0, 9.7 Hz, 1H), 5.18 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.13 - 5.06 (m, 2H), 4.01 (ddd, *J* = 11.5, 8.0, 3.0 Hz, 1H), 3.96 - 3.92 (m, 1H), 3.92 (s, 3H), 2.95 (td, *J* = 13.2, 3.1 Hz, 1H), 2.63 (dd, *J* = 12.1, 3.5 Hz, 1H), 2.33 (dd, *J* = 12.0, 9.2 Hz, 1H), 2.29 - 2.20 (m, 1H), 1.96 - 1.90 (m, 1H), 1.85 - 1.69 (m, 3H), 1.56 (tt, *J* = 13.5, 4.5 Hz, 1H).

**HRMS(ESI):** *m/z* calc. for $C_{21}H_{26}N_3O_2S$ $[M+H]^+$: 384.1746, found: 384.1750.

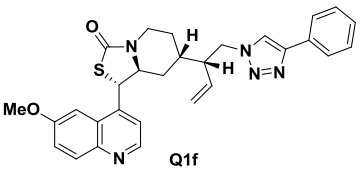



**Procedure:** A solution of azide **Q1c** (135 mg, 0.234 mmol) and triphenylphosphine (67 mg, 0.257 mmol) in tetrahydrofuran (1.17 mL) and water (5 μL) was stirred at room temperature for 36 hours. The reaction was then evaporated and purified by column chromatography using a gradient of 1:49 to 2:23 methanol/ethyl acetate with 2% triethylamine provided amine **Q1e** (96 mg, 74%) as a white solid.

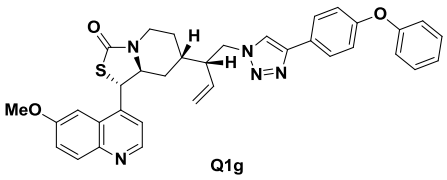
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.15 - 8.09 (m, 3H), 8.07 (s, 1H), 7.43 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.39 - 7.34 (m, 2H), 7.25 (d, *J* = 2.9 Hz, 1H), 7.18 - 7.11 (m, 3H), 7.10 - 7.04 (m, 2H), 5.44 (dt, *J* = 17.0, 9.8 Hz, 1H), 5.21 (dd, *J* = 10.2, 1.8 Hz, 1H), 5.16 (d, *J* = 7.9 Hz, 1H), 5.13 (dd, *J* = 17.1, 1.8 Hz, 1H), 4.12 - 4.05 (m, 1H), 4.03 - 3.98 (m, 1H), 3.97 (s, 3H), 3.00 (td, *J* = 13.1, 3.1 Hz, 1H), 2.67 (dd, *J* = 12.1, 3.5 Hz, 1H), 2.38 (dd, *J* = 12.0, 9.2 Hz, 1H), 2.28 (qd, *J* = 9.5, 3.3 Hz, 1H), 2.07 - 2.00 (m, 1H), 1.91 - 1.77 (m, 3H), 1.63 (td, *J* = 8.8, 4.3 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{33}H_{34}N_3O_3S$ $[M+H]^+$: 552.2321, found: 552.2311.



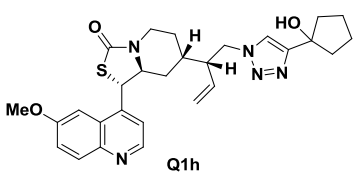

**General procedure for the preparation of Q1 triazoles:** To a vial containing azide **Q1b** or **Q1c** (0.017 mmol) was added a solution of copper sulfate pentahydrate (2 mg, 0.0080 mmol) and sodium ascorbate (5 mg, 0.025 mmol) in 2:1 water/*t*-butanol (600 μL) followed by alkyne (0.051 mmol). Dichloromethane (200 μL) was then added to vials containing **Q1c** to help dissolve the azide. The reaction was stirred at room temperature for 24 hours then diluted with water and extracted with chloroform. The organic layer was washed, dried with magnesium sulfate, evaporated, and purified by preparative TLC (hexanes/ethyl acetate) to provide the triazole. (Note: This procedure was performed at scales from 0.017 - 0.147 mmol azide)




**Q1f**: Prepared from phenylacetylene.
**Yield:** 32.3 mg, 90%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.86 - 8.76 (m, 1H), 8.18 (d, *J* = 8.8 Hz, 1H), 7.83 - 7.71 (m, 3H), 7.68 (s, 1H), 7.49 - 7.26 (m, 5H), 5.53 (dt, *J* = 16.5, 9.8 Hz, 1H), 5.24 - 5.10 (m, 2H), 5.01 (d, *J* = 16.5 Hz, 1H), 4.47 (dd, *J* = 13.7, 3.4 Hz, 1H), 4.32 - 4.24 (m, 1H), 4.20 (dd, *J* = 13.7, 7.8 Hz, 1H), 4.03 - 3.92 (m, 1H), 3.98(s, 3H), 3.07 - 2.97 (m, 1H), 2.99 - 2.89 (m, 1H), 2.24 (d, *J* = 13.5 Hz, 1H), 2.10 - 1.88 (m, 2H), 1.89 - 1.76 (m, 1H), 1.76 - 1.60 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{29}H_{30}N_5O_2S$ $[M+H]^+$: 512.2120, found: 512.2119.



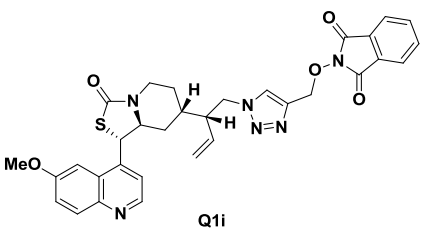

**Q1g**: Prepared from 1-ethynyl-4-phenoxybenzene.
**Yield:** 71.6 mg, 81%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.80 (d, *J* = 4.6 Hz, 1H), 8.05 (d, *J* = 9.2 Hz, 1H), 7.75 - 7.69 (m, 2H), 7.64 (d, *J* = 4.6 Hz, 1H), 7.59 (s, 1H), 7.41 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.36 - 7.30 (m, 2H), 7.25 (d, *J* = 2.7 Hz, 1H), 7.15 - 7.07 (m, 1H), 7.05 - 6.99 (m, 4H), 5.50 (dt, *J* = 17.0, 9.9 Hz, 1H), 5.19 - 5.09 (m, 2H), 4.98 (dd, *J* = 17.0, 1.2 Hz, 1H), 4.41 (dd, *J* = 13.9, 3.8 Hz, 1H), 4.23 (ddd, *J* = 11.3, 7.9, 3.0 Hz, 1H), 4.15 (dd, *J* = 13.8, 8.2 Hz, 1H), 3.97 - 3.89 (m, 1H), 3.95 (s, 3H), 2.99 (td, *J* = 13.5, 3.3 Hz, 1H), 2.95 - 2.86 (m, 1H), 2.26 - 2.17 (m, 1H), 2.00 - 1.93 (m, 1H), 1.89 (ddd, *J* = 13.9, 11.9, 4.6 Hz, 1H), 1.85 - 1.77 (m, 1H), 1.65 (tt, *J* = 13.6, 4.8 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{35}H_{34}N_5O_3S$ $[M+H]^+$: 604.2382, found: 604.2382.




**Q1h**: Prepared from 1-ethynylcyclopentanol.
**Yield:** 58.5 mg, 77%.
**$^1$H NMR** ($d_6$-DMSO, 500 MHz, 80 °C): δ 8.79 (d, *J* = 4.6 Hz, 1H), 7.99 (d, *J* = 9.1 Hz, 1H), 7.81 (s, 1H), 7.78 (d, *J* = 4.6 Hz, 1H), 7.49 (d, *J* = 2.7 Hz, 1H), 7.46 (dd, *J* = 9.1, 2.7 Hz, 1H), 5.59 (d, *J* = 6.5 Hz, 1H), 5.49 (dt,

*J* = 16.7, 10.1 Hz, 1H), 4.96 - 4.94 (m, 1H), 4.94 - 4.90 (m, 1H), 4.61 - 4.49 (m, 1H), 4.34 (dd, *J* = 13.7, 4.1 Hz, 1H), 4.23 (dd, *J* = 13.7, 9.5 Hz, 1H), 3.94 (s, 3H), 3.79 - 3.70 (m, 1H), 3.20 - 3.06 (m, 2H), 2.09 - 2.02 (m, 1H), 1.97 - 1.83 (m, 4H), 1.82 - 1.72 (m, 4H), 1.73 - 1.66 (m, 1H), 1.66 - 1.58 (m, 2H), 1.58 - 1.49 (m, 1H).

**HRMS(ESI):** *m/z* calc. for $C_{28}H_{34}N_5O_3S$ $[M+H]^+$: 520.2382, found 520.2390.



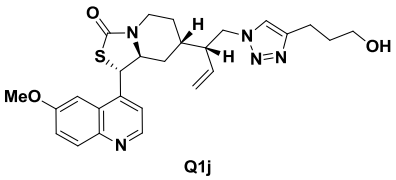
Q1i

**Q1i**: Prepared from *N*-(propargyloxy)phthalimide.

**Yield:** 66.6 mg, 74%.

**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.77 (d, *J* = 5.0 Hz, 1H), 8.05 (d, *J* = 9.2 Hz, 1H), 7.77 - 7.66 (m, 5H), 7.62 (d, *J* = 4.6 Hz, 1H), 7.39 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.23 (d, *J* = 2.7 Hz, 1H), 5.50 (dt, *J* = 16.9, 9.8 Hz, 1H), 5.28 (s, 2H), 5.18 - 5.08 (m, 2H), 4.97 (dd, *J* = 17.1, 1.5 Hz, 1H), 4.39 (dd, *J* = 13.9, 3.7 Hz, 1H), 4.23 - 4.13 (m, 2H), 3.98 - 3.92 (m, 1H), 3.93 (s, 3H), 2.98 (td, *J* = 13.3, 3.4 Hz, 1H), 2.88 - 2.78 (m, 1H), 2.21 - 2.13 (m, 1H), 1.93 - 1.84 (m, 2H), 1.83 - 1.77 (m, 1H), 1.66 (ddq, *J* = 13.4, 9.3, 4.4 Hz, 1H).

**HRMS(ESI):** *m/z* calc. for $C_{32}H_{31}N_6O_5S$ $[M+H]^+$: 611.2077, found: 611.2071.



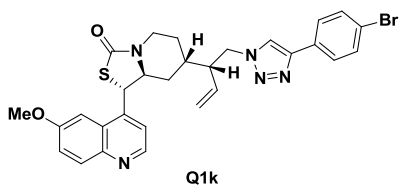
Q1j

**Q1j**: Prepared from 4-pentyn-1-ol.

**Yield:** 47.0 mg, 65%.

**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.78 (d, *J* = 4.7 Hz, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.64 (d, *J* = 4.6 Hz, 1H), 7.40 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.23 (d, *J* = 2.7 Hz, 1H), 7.16 (s, 1H), 5.44 (dt, *J* = 17.0, 9.9 Hz, 1H), 5.13 (d, *J* = 8.0 Hz, 1H), 5.08 (dd, *J* = 10.1, 1.4 Hz, 1H), 4.92 (dd, *J* = 17.0, 1.4 Hz, 1H), 4.32 (dd, *J* = 13.9, 3.9 Hz, 1H), 4.21 (ddd, *J* = 11.2, 7.9, 3.1 Hz, 1H), 4.06 (dd, *J* = 13.8, 8.2 Hz, 1H), 3.94 (s, 3H), 3.93 - 3.87 (m, 1H), 3.63 (t, *J* = 6.1 Hz, 2H), 2.96 (td, *J* = 13.3, 3.4 Hz, 1H), 2.84 (tt, *J* = 12.8, 3.8 Hz, 1H), 2.73 (t, *J* = 7.3 Hz, 2H), 2.18 - 2.09 (m, 1H), 1.91 (dd, *J* = 12.3, 4.2 Hz, 2H), 1.88 - 1.83 (m, 2H), 1.83 - 1.75 (m, 1H), 1.63 (tt, *J* = 13.6, 4.9 Hz, 1H).

**HRMS(ESI):** *m/z* calc. for $C_{26}H_{32}N_5O_3S$ $[M+H]^+$: 494.2226, found: 494.2230.



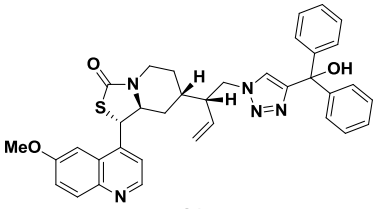
Q1k

**Q1k**: Prepared from 1-bromo-4-ethynylbenzene.

**Yield:** 60.0 mg, 69%.

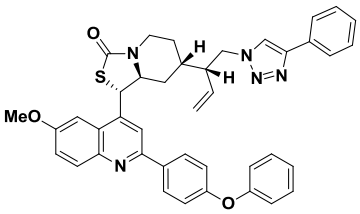
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.87 - 8.62 (m, 1H), 8.14 - 7.96 (m, 1H), 7.72 - 7.57 (m, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.36 - 7.18 (m, 5H), 7.14 - 6.94 (m, 1H), 5.40 (dt, *J* = 16.4, 9.7 Hz, 1H), 5.12 (d, *J* = 7.9 Hz, 1H), 5.06 (d, *J* = 10.1 Hz, 1H), 4.88 (d, *J* = 16.9 Hz, 1H), 4.40 - 4.29 (m, 1H), 4.26 - 4.16 (m, 1H), 4.04 - 3.85 (m, 2H), 3.92 (s, 3H), 3.02 - 2.89 (m, 1H), 2.89 - 2.76 (m, 1H), 2.19 - 2.04 (m, 1H), 2.00 - 1.81 (m, 2H), 1.81 - 1.74 (m, 1H), 1.64 (tt, *J* = 13.2, 4.8 Hz, 1H).

**HRMS(ESI):** *m/z* calc. for $C_{29}H_{29}N_5O_2SBr$ $[M+H]^+$: 590.1225, found: 590.1223.



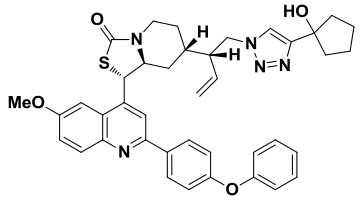
Q1l

**Q1l**: Prepared from 1,1-diphenyl-2-propyn-1-ol.
**Yield:** 80.2 mg, 88%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ $^1$H NMR (500 MHz, $CDCl_3$) δ 8.79 (d, *J* = 4.6 Hz, 1H), 8.05 (d, *J* = 9.2 Hz, 1H), 7.66 - 7.58 (m, 8H), 7.51 - 7.46 (m, 4H), 7.41 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.24 (d, *J* = 2.7 Hz, 1H), 5.49 (dt, *J* = 17.0, 9.8 Hz, 1H), 5.16 - 5.10 (m, 2H), 4.97 (dd, *J* = 17.1, 1.5 Hz, 1H), 4.41 (dd, *J* = 13.9, 3.8 Hz, 1H), 4.21 (ddd, *J* = 11.4, 8.0, 3.0 Hz, 1H), 4.14 (dd, *J* = 13.9, 8.3 Hz, 1H), 3.94 (s, 3H), 3.94 - 3.90 (m, 1H), 2.98 (td, *J* = 13.3, 3.3 Hz, 1H), 2.94 - 2.85 (m, 1H), 2.18 (dd, *J* = 13.9, 2.4 Hz, 1H), 1.99 - 1.93 (m, 1H), 1.89 (ddd, *J* = 13.9, 11.8, 4.6 Hz, 1H), 1.80 (dt, *J* = 14.0, 2.7 Hz, 1H), 1.65 (tt, *J* = 13.9, 4.9 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{36}H_{36}N_5O_3S$ $[M+H]^+$: 618.2539, found: 618.2543.



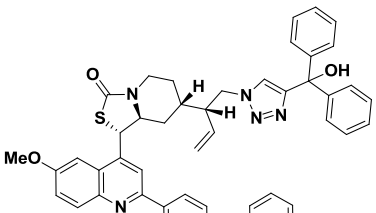
Q1m

**Q1m**: Prepared from phenylacetylene.
**Yield:** 7.6 mg, 65%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.20 (d, *J* = 8.7 Hz, 2H), 8.18 - 8.09 (m, 2H), 7.75 - 7.70 (m, 2H), 7.57 (s, 1H), 7.44 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.42 - 7.37 (m, 2H), 7.37 - 7.31 (m, 3H), 7.28 (d, *J* = 2.6 Hz, 1H), 7.19 - 7.14 (m, 2H), 7.14 - 7.10 (m, 1H), 7.06 (dd, *J* = 8.6, 1.1 Hz, 2H), 5.51 (dt, *J* = 17.1, 9.8 Hz, 1H), 5.23 (d, *J* = 7.7 Hz, 1H), 5.13 (dd, *J* = 10.0, 1.2 Hz, 1H), 4.97 (d, *J* = 17.1 Hz, 1H), 4.44 (dd, *J* = 13.7, 3.7 Hz, 1H), 4.30 (td, *J* = 7.9, 4.0 Hz, 1H), 4.16 (dd, *J* = 13.8, 8.3 Hz, 1H), 4.05 - 3.99 (m, 1H), 3.98 (s, 3H), 3.00 (td, *J* = 13.3, 3.3 Hz, 1H), 2.98 - 2.87 (m, 1H), 2.36 - 2.29 (m, 1H), 2.03 - 1.94 (m, 2H), 1.84 (d, *J* = 14.2 Hz, 1H), 1.76 - 1.66 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{41}H_{38}N_5O_3S$ $[M+H]^+$: 680.2695, found: 680.2709.



Q1n

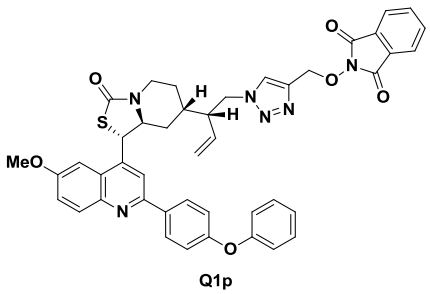
**Q1n**: Prepared from 1-ethynylcyclopentanol.
**Yield:** 9.0 mg, 77%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.18 (d, *J* = 8.4 Hz, 2H), 8.14 - 8.11 (m, 2H), 7.47 - 7.41 (m, 1H), 7.40 - 7.33 (m, 2H), 7.30 - 7.22 (m, 2H), 7.17 - 7.09 (m, 3H), 7.09 - 7.04 (m, 2H), 5.47 (dt, *J* = 16.9, 9.8 Hz, 1H), 5.21 (d, *J* = 7.9 Hz, 1H), 5.11 (d, *J* = 10.2 Hz, 1H), 4.93 (d, *J* = 16.8 Hz, 1H), 4.36 (dd, *J* = 13.7, 3.7 Hz, 1H), 4.28 (ddd, *J* = 11.1, 7.9, 3.2 Hz, 1H), 4.08 (dd, *J* = 13.8, 8.4 Hz, 1H), 4.03 - 3.97 (m, 1H), 3.98 (s, 3H), 3.00 (td, *J* = 13.2, 3.5 Hz, 1H), 2.92 - 2.83 (m, 1H), 2.32 - 2.23 (m, 1H), 2.14 - 1.86 (m, 8H), 1.86 - 1.59 (m, 4H).
**HRMS(ESI):** *m/z* calc. for $C_{40}H_{42}N_5O_4S$ $[M+H]^+$: 688.2958, found: 688.2944.



Q1o

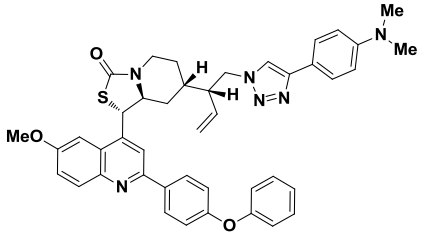
**Q1o**: Prepared from 1,1-diphenyl-2-propyn-1-ol.
**Yield:** 6.1 mg, 46%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.18 (d, *J* = 8.7 Hz, 2H), 8.14 - 8.05 (m, 2H), 7.42 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.34 (dd, *J* = 8.6, 7.3 Hz, 2H), 7.26 (q, *J* = 2.5, 1.7 Hz, 11H), 7.17 - 7.11 (m, 3H), 7.06 (dd, *J* = 8.4, 1.1 Hz, 2H), 6.92 (s, 1H), 5.42 (dt, *J* = 17.0, 9.9 Hz, 1H), 5.21 (d, *J* = 8.1 Hz, 1H), 5.08 (dd, *J* = 10.1, 1.4 Hz, 1H), 4.89 (dd, *J* = 17.2, 1.3 Hz, 1H), 4.40 (dd, *J* = 13.7, 3.8 Hz, 1H), 4.33 - 4.26 (m, 1H), 4.05 - 3.95 (m,

2H), 3.96 (s, 3H), 2.99 (td, *J* = 13.1, 3.4 Hz, 1H), 2.95 - 2.83 (m, 1H), 2.24 (d, *J* = 14.5 Hz, 1H), 2.01 (dd, *J* = 34.3, 8.1 Hz, 2H), 1.84 (d, *J* = 13.9 Hz, 1H), 1.69 (d, *J* = 16.9 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{48}H_{44}N_5O_4S$ $[M+H]^+$: 786.3114, found: 786.3118.



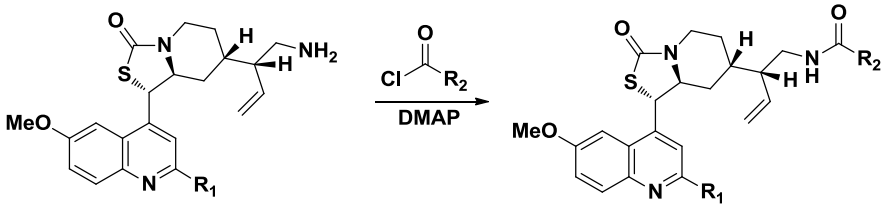
Q1p

**Q1p**: Prepared from *N*-(propargyloxy)phthalimide.
**Yield:** 7.8 mg, 59%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.20 - 8.02 (m, 4H), 7.73 (dddd, *J* = 18.5, 5.1, 3.3, 2.0 Hz, 4H), 7.68 (d, *J* = 1.7 Hz, 1H), 7.43 (dt, *J* = 9.2, 2.3 Hz, 1H), 7.39 - 7.32 (m, 2H), 7.27 (d, *J* = 2.3 Hz, 1H), 7.13 (ddd, *J* = 6.6, 4.1, 1.5 Hz, 3H), 7.06 (ddd, *J* = 8.3, 2.0, 1.0 Hz, 2H), 5.51 (dtd, *J* = 17.1, 9.9, 1.9 Hz, 1H), 5.27 (s, 2H), 5.21 (d, *J* = 7.5 Hz, 1H), 5.12 (d, *J* = 10.0 Hz, 1H), 4.97 (d, *J* = 17.1 Hz, 1H), 4.43 - 4.34 (m, 1H), 4.28 - 4.13 (m, 2H), 4.05 - 3.97 (m, 1H), 3.97 (s, 3H), 3.05 - 2.94 (m, 1H), 2.90 - 2.78 (m, 1H), 2.27 - 2.21 (m, 1H), 2.01 - 1.88 (m, 2H), 1.86 - 1.78 (m, 1H), 1.71 (d, *J* = 13.9 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{44}H_{39}N_6O_6S$ $[M+H]^+$: 779.2652, found: 779.2640.



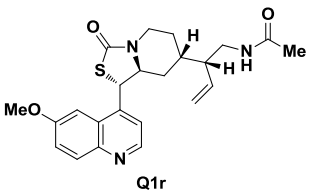
Q1q
50%

**Q1q**: Prepared from 4-ethynyl-*N*,*N*-dimethylaniline.
**Yield:** 6.1 mg, 50%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.21 - 8.17 (m, 2H), 8.15 (s, 1H), 8.13 (d, *J* = 9.5 Hz, 1H), 7.62 - 7.57 (m, 2H), 7.45 - 7.42 (m, 1H), 7.42 (s, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 3.3 Hz, 1H), 7.16 (dd, *J* = 8.6, 1.3 Hz, 2H), 7.14 - 7.10 (m, 1H), 7.06 (d, *J* = 7.9 Hz, 2H), 6.73 (d, *J* = 8.2 Hz, 2H), 5.51 (dt, *J* = 16.8, 9.8 Hz, 1H), 5.21 (d, *J* = 7.6 Hz, 1H), 5.12 (d, *J* = 10.1 Hz, 1H), 4.97 (d, *J* = 17.0 Hz, 1H), 4.38 (dd, *J* = 13.9, 3.7 Hz, 1H), 4.31 - 4.22 (m, 1H), 4.16 (dd, *J* = 13.8, 7.9 Hz, 1H), 4.02 (t, *J* = 3.8 Hz, 1H), 3.98 (s, 3H), 3.09 (q, *J* = 7.2 Hz, 1H), 2.98 (d, *J* = 1.3 Hz, 6H), 2.88 (d, *J* = 9.3 Hz, 1H), 2.36 - 2.26 (m, 1H), 1.97 (t, *J* = 11.6 Hz, 2H), 1.83 (d, *J* = 15.7 Hz, 1H), 1.75 - 1.65 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{43}H_{43}N_6O_3S$ $[M+H]^+$: 723.3117, found: 723.3124.

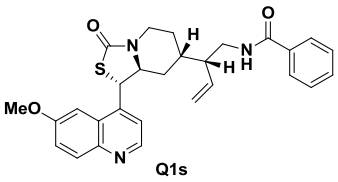


Q1d: $R_1$ = H
Q1e: $R_1$ = 4-PhOPh

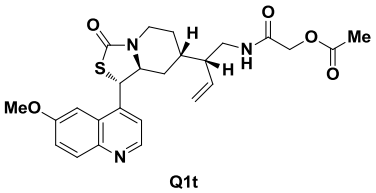
**General procedure for the preparation of Q1 amides/ureas:** To a solution of amine **Q1d** or **Q1e**, *N*,*N*-dimethylaminopyridine (1 mg, 0.008 mmol), and triethylamine (7.5 μL, 0.054 mmol) in dichloromethane (2 mL) was added acyl chloride (0.036 mmol). The reaction was stirred at room temperature 24 hours, quenched with methanol, evaporated, and purified by preparative TLC (hexanes/ethyl acetate) to provide the amide/urea. (Note: This procedure was performed at several scales: 0.018 - 0.104 mmol amine)



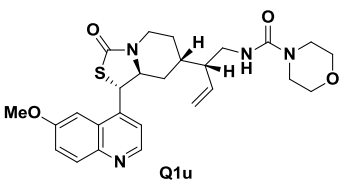

**Q1r**: prepared from acetyl chloride.
**Yield:** 38.6 mg, 87%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.82 (d, *J* = 4.6 Hz, 1H), 8.03 (d, *J* = 9.2 Hz, 1H), 7.80 (d, *J* = 4.7 Hz, 1H), 7.38 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.21 (d, *J* = 2.7 Hz, 1H), 5.86 - 5.69 (m, 1H), 5.45 (dt, *J* = 16.9, 9.8 Hz, 1H), 5.21 (dd, *J* = 10.1, 1.7 Hz, 1H), 5.14 - 5.07 (m, 2H), 4.34 (ddd, *J* = 12.0, 9.0, 3.1 Hz, 1H), 3.95 (s, 3H), 3.96 - 3.88 (m, 1H), 3.67 (ddd, *J* = 13.0, 7.3, 3.1 Hz, 1H), 2.97 (td, *J* = 13.2, 3.1 Hz, 1H), 2.60 (ddd, *J* = 12.8, 10.1, 4.6 Hz, 1H), 2.56 - 2.47 (m, 1H), 2.19 (dd, *J* = 13.8, 2.6 Hz, 1H), 1.95 (s, 3H), 1.88 - 1.77 (m, 2H), 1.74 - 1.64 (m, 1H), 1.66 - 1.56 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{23}H_{28}N_3O_3S$ $[M+H]^+$: 426.1851, found: 426.1854.




**Q1s**: Prepared from benzoyl chloride.
**Yield:** 33.6 mg, 66%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.86 (d, *J* = 4.6 Hz, 1H), 8.05 (d, *J* = 9.2 Hz, 1H), 7.89 (d, *J* = 4.7 Hz, 1H), 7.76 - 7.67 (m, 2H), 7.53 - 7.46 (m, 1H), 7.45 - 7.37 (m, 3H), 7.24 (d, *J* = 2.7 Hz, 1H), 6.44 - 6.37 (m, 1H), 5.54 (dt, *J* = 17.0, 9.9 Hz, 1H), 5.25 (dd, *J* = 10.1, 1.7 Hz, 1H), 5.18 - 5.09 (m, 2H), 4.42 (ddd, *J* = 11.9, 8.8, 3.0 Hz, 1H), 3.96 (s, 3H), 3.99 - 3.93 (m, 1H), 3.89 (ddd, *J* = 13.2, 7.3, 3.4 Hz, 1H), 2.99 (td, *J* = 13.3, 3.2 Hz, 1H), 2.82 (ddd, *J* = 13.1, 10.1, 4.7 Hz, 1H), 2.73 - 2.63 (m, 1H), 2.28 (dd, *J* = 13.8, 2.6 Hz, 1H), 1.93 - 1.82 (m, 2H), 1.75 (ddd, *J* = 13.7, 11.8, 4.3 Hz, 1H), 1.65 (ddt, *J* = 13.3, 8.7, 4.8 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{28}H_{30}N_3O_3S$ $[M+H]^+$: 488.2008, found: 488.2005.

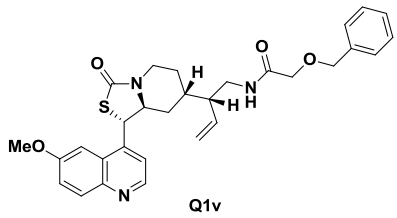



**Q1t**: Prepared from acetoxyacetyl chloride.
**Yield:** 29.1 mg, 77%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.83 (dd, *J* = 4.6, 0.9 Hz, 1H), 8.06 (dd, *J* = 9.2, 0.8 Hz, 1H), 7.77 (d, *J* = 4.6 Hz, 1H), 7.41 (ddd, *J* = 9.2, 2.7, 0.9 Hz, 1H), 7.22 (d, *J* = 2.6 Hz, 1H), 6.32 - 6.21 (m, 1H), 5.49 (dt, *J* = 17.3, 9.8 Hz, 1H), 5.28 - 5.22 (m, 1H), 5.18 - 5.08 (m, 2H), 4.55 (d, *J* = 3.9 Hz, 2H), 4.31 (ddd, *J* = 11.8, 8.7, 3.0 Hz, 1H), 4.00 - 3.94 (m, 1H), 3.96 (s, 3H), 3.73 (ddd, *J* = 13.1, 7.4, 3.3 Hz, 1H), 2.98 (td, *J* = 13.3, 3.1 Hz, 1H), 2.68 (ddd, *J* = 13.2, 10.3, 4.5 Hz, 1H), 2.54 (qd, *J* = 10.2, 9.6, 3.1 Hz, 1H), 2.18 (dd, *J* = 13.8, 2.6 Hz, 1H), 2.13 (s, 3H), 1.91 - 1.79 (m, 2H), 1.74 (ddd, *J* = 13.7, 11.8, 4.2 Hz, 1H), 1.65 (tt, *J* = 13.5, 4.8 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{25}H_{30}N_3O_5S$ $[M+H]^+$: 484.1906, found: 484.1897.



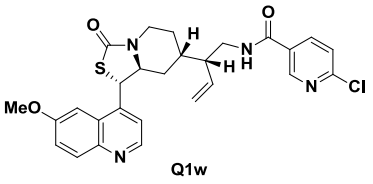

**Q1u**: Prepared from 4-morpholinecarbonyl chloride.
**Yield:** 31.5 mg, 81%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.83 (d, *J* = 4.6 Hz, 1H), 8.06 (d, *J* = 9.2 Hz, 1H), 7.86 (d, *J* = 4.4 Hz, 1H), 7.40 (dd, *J* = 9.3, 2.5 Hz, 1H), 7.22 (d, *J* = 2.6 Hz, 1H), 5.48 (dt, *J* = 17.1, 9.7 Hz, 1H), 5.23 (dt, *J* = 10.1, 1.7 Hz, 1H), 5.18 - 5.01 (m, 2H), 4.60 (dd, *J* = 8.0, 3.9 Hz, 1H), 4.40 (ddd, *J* = 11.9, 8.9, 3.0 Hz, 1H), 3.97 (s, 3H), 4.00 - 3.94 (m, 1H), 3.74 - 3.65 (m, 1H), 3.68 (td, *J* = 4.9, 1.5 Hz, 4H), 3.31 (td, *J* = 4.5, 1.5 Hz, 4H),

2.99 (td, *J* = 13.4, 3.1 Hz, 1H), 2.65 - 2.49 (m, 2H), 2.24 (dt, *J* = 13.7, 2.5 Hz, 1H), 1.90 - 1.79 (m, 2H), 1.71 (ddd, *J* = 13.6, 11.9, 4.2 Hz, 1H), 1.67 - 1.59 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{26}H_{33}N_4O_4S$ $[M+H]^+$: 497.2223, found: 497.2230.



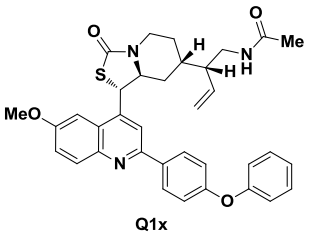
Q1v

**Q1v**: Prepared from benzyloxyacetyl chloride.
**Yield:** 32.4 mg, 78%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.83 (d, *J* = 4.6 Hz, 1H), 8.06 (d, *J* = 9.2 Hz, 1H), 7.78 (d, *J* = 4.7 Hz, 1H), 7.40 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.38 - 7.27 (m, 5H), 7.22 (d, *J* = 2.7 Hz, 1H), 6.75 (s, 1H), 5.47 (dt, *J* = 17.0, 9.9 Hz, 1H), 5.22 (dd, *J* = 10.2, 1.7 Hz, 1H), 5.17 - 5.05 (m, 2H), 4.55 (s, 2H), 4.31 (ddd, *J* = 11.7, 8.6, 3.0 Hz, 1H), 3.97 (d, *J* = 3.2 Hz, 2H), 4.02 - 3.93 (m, 1H), 3.96 (s, 3H), 3.69 (ddd, *J* = 13.2, 7.4, 3.4 Hz, 1H), 2.98 (td, *J* = 13.4, 3.1 Hz, 1H), 2.71 (ddd, *J* = 13.1, 10.1, 4.8 Hz, 1H), 2.53 (qd, *J* = 10.2, 3.3 Hz, 1H), 2.19 (dd, *J* = 13.8, 2.6 Hz, 1H), 1.90 - 1.80 (m, 2H), 1.73 (ddd, *J* = 13.8, 11.8, 4.2 Hz, 1H), 1.68 - 1.58 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{30}H_{34}N_3O_4S$ $[M+H]^+$: 532.2270, found: 532.2280.



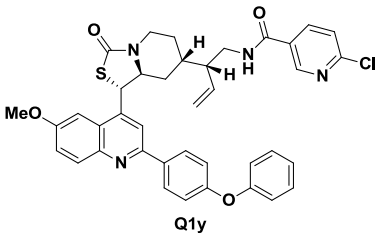
Q1w

**Q1w**: Prepared from 6-chloronicotinoyl chloride.
**Yield:** 28.8 mg, 71%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.83 (s, 1H), 8.69 (d, *J* = 2.5 Hz, 1H), 8.10 - 8.01 (m, 2H), 7.84 (d, *J* = 4.7 Hz, 1H), 7.48 - 7.34 (m, 2H), 7.24 (d, *J* = 2.7 Hz, 1H), 6.63 (s, 1H), 5.53 (dt, *J* = 17.1, 9.8 Hz, 1H), 5.24 (dd, *J* = 10.1, 1.7 Hz, 1H), 5.18 - 5.09 (m, 2H), 4.38 (ddd, *J* = 12.0, 9.0, 3.1 Hz, 1H), 3.96 (s, 3H), 3.97 - 3.91 (m, 1H), 3.85 (ddd, *J* = 13.2, 7.0, 3.3 Hz, 1H), 2.99 (td, *J* = 13.3, 3.2 Hz, 1H), 2.84 (ddd, *J* = 13.4, 10.3, 4.9 Hz, 1H), 2.67 (ddd, *J* = 20.4, 10.2, 3.1 Hz, 1H), 2.23 (dd, *J* = 13.7, 2.6 Hz, 1H), 1.94 - 1.81 (m, 2H), 1.80 - 1.70 (m, 1H), 1.65 (ddt, *J* = 22.7, 9.4, 4.5 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{27}H_{28}N_4O_3SCl$ $[M+H]^+$: 523.1571, found: 523.1581.

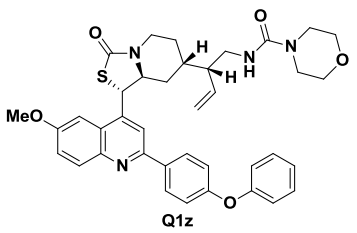


Q1x

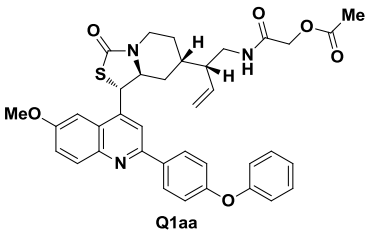
**Q1x**: Prepared from acetyl chloride.
**Yield:** 7.5 mg, 70%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.25 - 8.14 (m, 3H), 8.11 (dd, *J* = 9.3, 0.8 Hz, 1H), 7.42 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.39 - 7.33 (m, 2H), 7.25 (d, *J* = 2.6 Hz, 1H), 7.17 - 7.10 (m, 3H), 7.10 - 7.05 (m, 2H), 5.54 - 5.41 (m, 2H), 5.21 (dd, *J* = 10.2, 1.7 Hz, 1H), 5.17 (d, *J* = 8.2 Hz, 1H), 5.10 (dd, *J* = 17.0, 1.7 Hz, 1H), 4.39 (ddd, *J* = 11.3, 8.2, 3.1 Hz, 1H), 4.02 - 3.97 (m, 1H), 3.99 (s, 3H), 3.53 (ddd, *J* = 12.9, 6.4, 3.4 Hz, 1H), 3.01 (td, *J* = 13.3, 3.1 Hz, 1H), 2.69 (ddd, *J* = 13.0, 10.0, 5.0 Hz, 1H), 2.58 (qd, *J* = 10.1, 3.2 Hz, 1H), 2.21 (dd, *J* = 13.5, 2.7 Hz, 1H), 1.88 (s, 3H), 1.87 - 1.76 (m, 3H), 1.65 (ddt, *J* = 18.4, 9.6, 4.8 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{35}H_{36}N_3O_4S$ $[M+H]^+$: 594.2427, found: 594.2434.



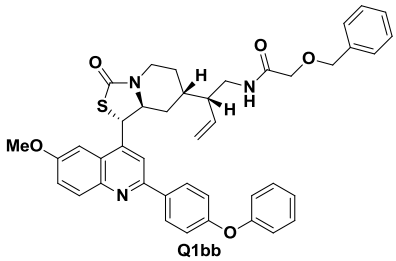

**Q1y**: Prepared from 6-chloronicotinoyl chloride.
**Yield:** 7.1 mg, 57%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.60 - 8.56 (m, 1H), 8.26 - 8.18 (m, 3H), 8.11 (d, *J* = 9.3 Hz, 1H), 7.86 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.42 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.37 - 7.32 (m, 2H), 7.31 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.27 (d, *J* = 2.8 Hz, 1H), 7.18 - 7.11 (m, 1H), 7.08 - 7.00 (m, 4H), 6.29 - 6.20 (m, 1H), 5.52 (dt, *J* = 16.8, 9.8 Hz, 1H), 5.25 - 5.20 (m, 2H), 5.11 (dd, *J* = 17.0, 1.7 Hz, 1H), 4.45 (ddd, *J* = 11.8, 8.8, 3.0 Hz, 1H), 4.04 - 4.00 (m, 1H), 3.99 (s, 3H), 3.75 (ddt, *J* = 9.8, 6.7, 2.9 Hz, 1H), 3.03 (td, *J* = 13.5, 3.2 Hz, 1H), 2.84 - 2.75 (m, 1H), 2.70 (qd, *J* = 10.3, 3.0 Hz, 1H), 2.29 - 2.19 (m, 1H), 1.95 - 1.84 (m, 2H), 1.85 - 1.74 (m, 1H), 1.74 - 1.52 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{39}H_{36}N_4O_4SCl$ $[M+H]^+$: 691.2146, found: 619.2155.




**Q1z**: Prepared from 4-morpholinecarbonyl chloride.
**Yield:** 8.4 mg, 70%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.31 - 8.15 (m, 3H), 8.10 (d, *J* = 9.1 Hz, 1H), 7.41 (dd, *J* = 9.3, 2.5 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.27 - 7.23 (m, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.08 (dd, *J* = 10.5, 8.0 Hz, 4H), 5.45 (dt, *J* = 16.8, 9.6 Hz, 1H), 5.25 - 5.15 (m, 2H), 5.09 (dd, *J* = 17.3, 1.8 Hz, 1H), 4.53 - 4.42 (m, 2H), 4.03 - 3.97 (m, 1H), 3.98 (s, 3H), 3.63 - 3.52 (m, 5H), 3.25 - 3.14 (m, 4H), 3.11 - 2.98 (m, 1H), 2.68 - 2.51 (m, 2H), 2.29 - 2.17 (m, 1H), 1.84 (dd, *J* = 9.9, 5.2 Hz, 2H), 1.79 - 1.68 (m, 1H), 1.70 - 1.59 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{38}H_{41}N_4O_5S$ $[M+H]^+$: 665.2798, found: 665.2802.

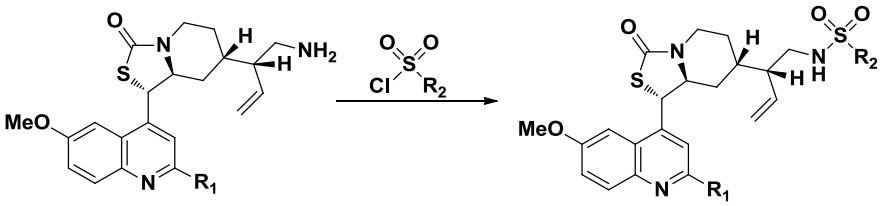



**Q1aa**: Prepared from acetoxyacetyl chloride.
**Yield:** 7.8 mg, 66%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.21 - 8.14 (m, 3H), 8.11 (d, *J* = 9.2 Hz, 1H), 7.42 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.39 - 7.33 (m, 2H), 7.24 (d, *J* = 2.7 Hz, 1H), 7.17 - 7.10 (m, 3H), 7.10 - 7.04 (m, 2H), 6.13 (t, *J* = 5.7 Hz, 1H), 5.48 (dt, *J* = 16.8, 10.0 Hz, 1H), 5.23 (dd, *J* = 10.1, 1.7 Hz, 1H), 5.17 (d, *J* = 8.0 Hz, 1H), 5.15 - 5.08 (m, 1H), 4.52 - 4.38 (m, 2H), 4.37 - 4.27 (m, 1H), 4.04 - 4.00 (m, 1H), 3.99 (s, 3H), 3.56 (ddd, *J* = 13.1, 6.7, 3.5 Hz, 1H), 3.12 - 2.93 (m, 1H), 2.76 (ddd, *J* = 13.1, 10.1, 5.0 Hz, 1H), 2.56 (ddt, *J* = 13.6, 10.2, 6.2 Hz, 1H), 2.25 - 2.15 (m, 1H), 2.10 (s, 3H), 1.94 - 1.74 (m, 3H), 1.75 - 1.57 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{37}H_{38}N_3O_6S$ $[M+H]^+$: 652.2481, found: 652.2490.

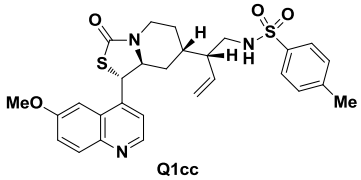



**Q1bb**: Prepared from benzyloxyacetyl chloride.
**Yield:** 7.7 mg, 61%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.20 - 8.14 (m, 3H), 8.11 (d, *J* = 9.3 Hz, 1H), 7.42 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.39 - 7.29 (m, 5H), 7.28 - 7.22 (m, 3H), 7.16 - 7.09 (m, 3H), 7.09 - 7.03 (m, 2H), 6.67 - 6.60 (m, 1H), 5.47 (dt, *J* = 17.1, 9.8 Hz, 1H), 5.26 - 5.13 (m, 2H), 5.09 (d, *J* = 17.1 Hz, 1H), 4.49 (s, 2H), 4.33 (td, *J* = 8.3, 4.1 Hz, 1H), 4.03 - 3.99 (m, 1H), 3.98 (s, 3H), 3.88 (d, *J* = 2.4 Hz, 2H), 3.52 (ddd, *J* = 13.1, 6.9, 3.7 Hz, 1H), 3.00 (td, *J* = 13.2,

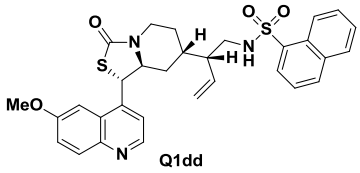
3.3 Hz, 1H), 2.82 (ddd, *J* = 13.5, 10.2, 5.5 Hz, 1H), 2.57 (qd, *J* = 9.8, 3.4 Hz, 1H), 2.25 - 2.15 (m, 1H), 1.93 - 1.77 (m, 3H), 1.71 - 1.61 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{42}H_{42}N_3O_5S$ $[M+H]^+$: 700.2845, found: 700.2849.



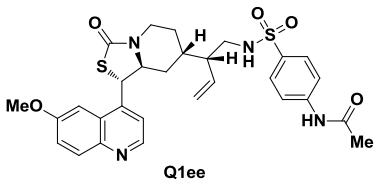

**General procedure for the preparation of Q1 sulfonamides:** To a solution of amine **Q1d** or **Q1e** and triethylamine (7.5 μL, 0.054 mmol) in dichloromethane (2 mL) was added sulfonyl chloride (0.036 mmol). The reaction was stirred at room temperature 24 hours, quenched with methanol, evaporated, and purified by preparative TLC (hexanes/ethyl acetate) to provide the sulfonamide. (note: This procedure was performed at several scales: 0.018 - 0.078 mmol amine)



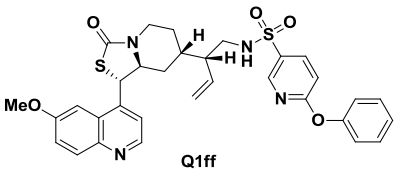

**Q1cc**: Prepared from p-toluenesulfonyl chloride.
**Yield:** 39.3 mg, 94%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.85 (d, *J* = 4.8 Hz, 1H), 8.19 (d, *J* = 9.2 Hz, 1H), 7.82 (d, *J* = 4.7 Hz, 1H), 7.52 - 7.48 (m, 2H), 7.45 (dd, *J* = 9.3, 2.6 Hz, 1H), 7.28 (d, *J* = 2.6 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 2H), 5.44 - 5.30 (m, 1H), 5.23 (dd, *J* = 10.2, 1.6 Hz, 1H), 5.20 - 5.12 (m, 2H), 5.13 - 5.02 (m, 1H), 4.25 (t, *J* = 9.4 Hz, 1H), 3.99 (s, 3H), 3.98 - 3.93 (m, 1H), 3.11 - 3.03 (m, 1H), 2.95 (td, *J* = 13.4, 3.1 Hz, 1H), 2.61 - 2.47 (m, 2H), 2.36 (s, 3H), 2.13 (d, *J* = 13.4 Hz, 1H), 1.87 - 1.70 (m, 3H), 1.60 (tt, *J* = 13.5, 4.8 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{28}H_{32}N_3O_4S_2$ $[M+H]^+$: 538.1834, found: 538.1840.



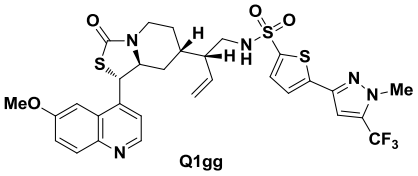

**Q1dd**: Prepared from 1-naphthalenesulfonyl chloride.
**Yield:** 32.6 mg, 73%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.82 (d, *J* = 4.6 Hz, 1H), 8.54 - 8.48 (m, 1H), 8.13 (d, *J* = 9.2 Hz, 1H), 7.95 - 7.90 (m, 1H), 7.90 - 7.86 (m, 1H), 7.78 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.67 (d, *J* = 4.7 Hz, 1H), 7.62 - 7.54 (m, 2H), 7.45 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.25 - 7.18 (m, 2H), 5.24 (dt, *J* = 16.9, 9.8 Hz, 1H), 5.14 (dd, *J* = 10.2, 1.6 Hz, 1H), 5.07 (d, *J* = 8.6 Hz, 1H), 4.95 - 4.86 (m, 2H), 4.04 (ddd, *J* = 11.7, 8.6, 3.0 Hz, 1H), 3.97 (s, 3H), 3.92 - 3.85 (m, 1H), 3.12 - 3.04 (m, 1H), 2.77 (td, *J* = 13.3, 3.1 Hz, 1H), 2.45 (ddd, *J* = 13.3, 9.7, 3.5 Hz, 1H), 2.36 - 2.26 (m, 1H), 1.86 (dd, *J* = 13.7, 2.6 Hz, 1H), 1.73 - 1.66 (m, 2H), 1.61 (ddd, *J* = 13.6, 11.8, 4.2 Hz, 1H), 1.58 - 1.46 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{31}H_{32}N_3O_4S_2$ $[M+H]^+$: 574.1834, found: 574.1838.



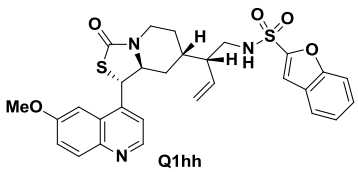

**Q1ee**: Prepared from *N*-acetylsulfanilyl chloride.
**Yield:** 44.6 mg, 98%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.78 (d, *J* = 4.6 Hz, 1H), 8.44 (s, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.68 (d, *J* = 4.6 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.45 - 7.42 (m, 2H), 7.41 (dd, *J* = 9.2, 2.6 Hz, 2H), 5.34 (dt, *J* = 16.9, 9.4 Hz, 1H), 5.22 (dd, *J* = 10.1, 1.7 Hz, 1H), 5.18 - 5.10 (m, 2H), 5.10 - 5.01 (m, 1H), 4.17 - 4.08 (m, 1H), 3.96 (s, 3H), 3.96 - 3.90 (m, 1H), 3.00 (t, *J* = 9.4 Hz, 1H), 2.90 (td, *J* = 13.4, 3.1 Hz, 1H), 2.47 (dtd, *J* = 18.9, 12.1, 11.4, 8.5 Hz, 2H), 2.19 (s, 3H), 2.01 - 1.92 (m, 1H), 1.83 - 1.74 (m, 2H), 1.74 - 1.63 (m, 1H), 1.63 - 1.53 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{29}H_{33}N_4O_5S_2$ $[M+H]^+$: 581.1892, found: 581.1895.




**Q1ff**: Prepared from 6-phenoxypyridine-3-sulfonyl chloride.
**Yield:** 39.6 mg, 82%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.78 (d, *J* = 4.5 Hz, 1H), 8.42 - 8.37 (m, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.77 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.64 (d, *J* = 4.6 Hz, 1H), 7.48 - 7.41 (m, 2H), 7.39 (dd, *J* = 9.3, 2.6 Hz, 1H), 7.30 - 7.25 (m, 1H), 7.23 (d, *J* = 2.7 Hz, 1H), 7.15 - 7.10 (m, 2H), 6.87 (d, *J* = 8.7 Hz, 1H), 5.40 - 5.31 (m, 1H), 5.24 (dd, *J* = 10.1, 1.7 Hz, 1H), 5.21 - 5.15 (m, 1H), 5.13 (d, *J* = 8.5 Hz, 1H), 5.00 (dd, *J* = 9.0, 3.1 Hz, 1H), 4.12 (ddd, *J* = 11.7, 8.6, 3.0 Hz, 1H), 3.99 - 3.93 (m, 1H), 3.95 (s, 3H), 3.07 (t, *J* = 9.2 Hz, 1H), 2.93 (td, *J* = 13.3, 3.1 Hz, 1H), 2.58 - 2.44 (m, 2H), 1.97 (dd, *J* = 13.7, 2.6 Hz, 1H), 1.87 - 1.68 (m, 3H), 1.60 (ddq, *J* = 16.9, 9.2, 4.5 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{29}H_{33}N_4O_5S_2$ $[M+H]^+$: 617.1892, found: 617.1896.

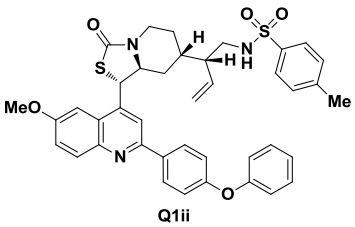



**Q1gg**: Prepared from 5-[1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]thiophene-2-sulfonyl chloride.
**Yield:** 58.5 mg, 74%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.87 (s, 1H), 8.12 (d, *J* = 9.2 Hz, 1H), 7.71 (s, 1H), 7.44 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.26 - 7.25 (m, 2H), 7.09 (d, *J* = 3.9 Hz, 1H), 6.81 (s, 1H), 5.39 (dt, *J* = 16.8, 9.7 Hz, 1H), 5.29 (dd, *J* = 10.1, 1.7 Hz, 1H), 5.19 (dd, *J* = 16.9, 1.7 Hz, 1H), 5.13 (d, *J* = 8.7 Hz, 1H), 4.78 (d, *J* = 7.4 Hz, 1H), 4.20 (ddd, *J* = 11.9, 8.7, 2.9 Hz, 1H), 4.01 (s, 3H), 3.98 (s, 3H), 3.97 - 3.93 (m, 1H), 3.24 (ddd, *J* = 12.7, 9.0, 3.4 Hz, 1H), 2.94 (td, *J* = 13.4, 3.1 Hz, 1H), 2.64 (ddd, *J* = 13.0, 9.6, 3.5 Hz, 1H), 2.55 (qd, *J* = 9.5, 3.3 Hz, 1H), 2.09 - 2.01 (m, 1H), 1.89 - 1.78 (m, 2H), 1.74 (ddd, *J* = 13.9, 11.9, 4.3 Hz, 1H), 1.64 (ddt, *J* = 13.4, 8.8, 4.8 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{30}H_{31}N_5O_4F_3S_3$ $[M+H]^+$: 678.1490, found: 678.1483.

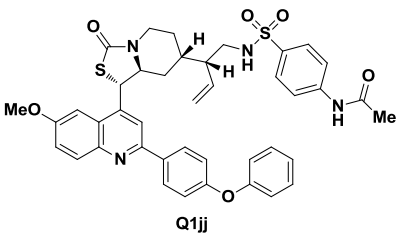



**Q1hh**: Prepared from benzofuran-2-sulfonyl chloride.
**Yield:** 30.8 mg, 70%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.87 (d, *J* = 4.6 Hz, 1H), 8.14 (d, *J* = 9.2 Hz, 1H), 7.73 (d, *J* = 4.7 Hz, 1H), 7.59 - 7.53 (m, 1H), 7.50 - 7.41 (m, 2H), 7.36 - 7.27 (m, 2H), 7.25 (d, *J* = 3.0 Hz, 1H), 7.03 (s, 1H), 5.37 (dt, *J* = 16.9, 9.8 Hz, 1H), 5.27 (dd, *J* = 10.0, 1.8 Hz, 1H), 5.17 - 5.08 (m, 2H), 5.03 - 4.96 (m, 1H), 4.15 (ddd, *J* = 11.8, 8.6, 3.0 Hz, 1H), 3.98 (s, 3H), 3.94 - 3.86 (m, 1H), 3.34 (ddd, *J* = 13.2, 9.1, 3.5 Hz, 1H), 2.77

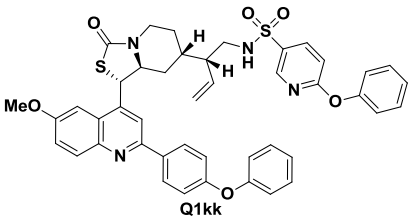
(td, *J* = 13.4, 3.4 Hz, 1H), 2.69 (ddd, *J* = 13.6, 10.0, 3.6 Hz, 1H), 2.49 - 2.38 (m, 1H), 2.05 (dt, *J* = 14.3, 2.8 Hz, 1H), 1.85 - 1.67 (m, 3H), 1.61 (ddd, *J* = 13.4, 8.4, 4.6 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{29}H_{30}N_3O_5S_2$ $[M+H]^+$: 564.1627, found: 564.1617.



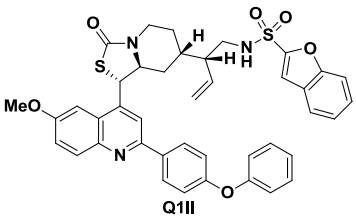

**Q1ii**: Prepared from *p*-toluenesulfonyl chloride.
**Yield:** 8.3 mg, 65%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.23 - 8.09 (m, 4H), 7.47 (dd, *J* = 9.2, 2.0 Hz, 1H), 7.38 - 7.31 (m, 2H), 7.28 (s, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.16 - 7.08 (m, 3H), 7.04 (dd, *J* = 7.5, 1.0 Hz, 2H), 7.00 (d, *J* = 7.9 Hz, 2H), 5.33 (dt, *J* = 17.4, 9.8 Hz, 1H), 5.26 - 5.15 (m, 2H), 5.11 (dd, *J* = 16.9, 2.1 Hz, 1H), 4.38 (dd, *J* = 8.9, 4.2 Hz, 1H), 4.10 - 4.02 (m, 1H), 4.00 (s, 3H), 3.97 - 3.92 (m, 1H), 2.99 - 2.82 (m, 2H), 2.47 (ddd, *J* = 13.1, 9.1, 4.0 Hz, 1H), 2.43 - 2.33 (m, 1H), 2.30 (s, 3H), 2.02 - 1.92 (m, 1H), 1.87 - 1.70 (m, 3H), 1.67 - 1.58 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{40}H_{40}N_3O_5S_2$ $[M+H]^+$: 706.2409, found: 706.2415.




**Q1jj**: Prepared from *N*-acetylsulfanilyl chloride.
**Yield:** 5.7 mg, 42%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.23 - 8.07 (m, 4H), 7.48 (dd, *J* = 9.3, 2.6 Hz, 1H), 7.39 (s, 1H), 7.38 - 7.33 (m, 2H), 7.33 - 7.20 (m, 5H), 7.17 - 7.08 (m, 3H), 7.07 - 7.00 (m, 2H), 5.34 (dt, *J* = 16.7, 9.7 Hz, 1H), 5.28 - 5.16 (m, 2H), 5.11 (dd, *J* = 17.0, 1.8 Hz, 1H), 4.45 (dd, *J* = 8.8, 4.0 Hz, 1H), 4.06 - 3.99 (m, 1H), 3.99 (s, 3H), 3.98 - 3.92 (m, 1H), 2.89 (qd, *J* = 12.6, 3.1 Hz, 2H), 2.48 (ddd, *J* = 13.2, 9.3, 3.9 Hz, 1H), 2.35 (qd, *J* = 9.8, 3.5 Hz, 1H), 2.15 (s, 3H), 2.01 - 1.90 (m, 1H), 1.85 - 1.67 (m, 3H), 1.62 (ddt, *J* = 15.6, 11.5, 3.6 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{41}H_{41}N_4O_6S_2$ $[M+H]^+$: 749.2468, found: 749.2476.

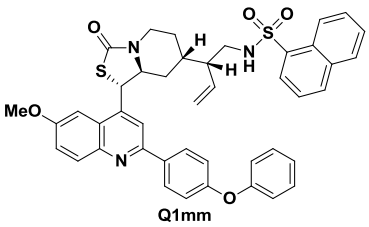



**Q1kk**: Prepared from 6-phenoxypyridine-3-sulfonyl chloride.
**Yield:** 8.2 mg, 58%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.26 (d, *J* = 2.6 Hz, 1H), 8.18 (s, 1H), 8.13 (d, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 9.4 Hz, 1H), 7.48 (dt, *J* = 8.9, 1.8 Hz, 1H), 7.46 - 7.40 (m, 3H), 7.38 - 7.32 (m, 2H), 7.30 - 7.26 (m, 2H), 7.16 - 7.07 (m, 5H), 7.04 (dd, *J* = 8.6, 1.2 Hz, 2H), 6.75 (d, *J* = 8.7 Hz, 1H), 5.40 - 5.30 (m, 1H), 5.29 - 5.14 (m, 3H), 4.50 (dd, *J* = 8.9, 3.0 Hz, 1H), 4.14 - 4.05 (m, 1H), 4.01 (dd, *J* = 5.1, 2.6 Hz, 1H), 3.97 (s, 3H), 2.94 (td, *J* = 11.6, 10.1, 4.0 Hz, 2H), 2.54 - 2.40 (m, 2H), 1.96 (d, *J* = 13.6 Hz, 1H), 1.87 - 1.73 (m, 3H), 1.70 - 1.58 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{44}H_{41}N_4O_6S_2$ $[M+H]^+$: 785.2468, found: 785.2478.




**Q1ll:** Prepared from benzofuran-2-sulfonyl chloride.
**Yield:** 9.7 mg, 74%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.24 - 8.11 (m, 4H), 7.50 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.46 - 7.40 (m, 2H), 7.39 (dd, *J* = 2.4, 1.2 Hz, 1H), 7.36 (dd, *J* = 8.6, 7.1 Hz, 2H), 7.29 (d, *J* = 3.1 Hz, 1H), 7.27 - 7.23 (m, 1H), 7.17 - 7.11 (m, 3H), 7.07 - 7.02 (m, 2H), 6.64 (s, 1H), 5.38 (dt, *J* = 16.8, 9.7 Hz,

1H), 5.27 (dd, *J* = 10.1, 1.6 Hz, 1H), 5.22 (d, *J* = 7.5 Hz, 1H), 5.17 (dd, *J* = 16.8, 1.7 Hz, 1H), 4.80 (dd, *J* = 8.6, 3.9 Hz, 1H), 4.09 - 4.03 (m, 1H), 4.02 (s, 3H), 3.99 - 3.90 (m, 1H), 3.18 (ddd, *J* = 12.9, 8.7, 3.3 Hz, 1H), 2.78 (td, *J* = 13.3, 3.3 Hz, 1H), 2.66 (ddd, *J* = 13.6, 9.7, 4.0 Hz, 1H), 2.43 - 2.32 (m, 1H), 2.04 (d, *J* = 13.6 Hz, 1H), 1.91 - 1.80 (m, 2H), 1.77 (d, *J* = 13.4 Hz, 1H), 1.65 (dt, *J* = 18.1, 6.5 Hz, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{41}H_{38}N_3O_6S_2$ $[M+H]^+$: 732.2202, found: 732.2191.




**Q1mm**: Prepared from 1-naphthalenesulfonyl chloride.
**Yield:** 12.1 mg, 91%.
**$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.45 - 8.39 (m, 1H), 8.25 - 8.15 (m, 4H), 7.83 - 7.74 (m, 2H), 7.59 - 7.49 (m, 2H), 7.49 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.43 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.32 (dd, *J* = 8.6, 7.3 Hz, 2H), 7.28 - 7.26 (m, 1H), 7.16 - 7.09 (m, 3H), 7.05 - 6.98 (m, 3H), 5.24 (dt, *J* = 16.9, 9.8 Hz, 1H), 5.18 - 5.08 (m, 2H), 4.90 (dd, *J* = 17.0, 1.7 Hz, 1H), 4.65 (dd, *J* = 9.0, 3.6 Hz, 1H), 3.99 (s, 3H), 3.98 - 3.95 (m, 1H), 3.92 (ddd, *J* = 13.6, 5.0, 2.4 Hz, 1H), 2.92 (ddd, *J* = 12.8, 8.9, 3.3 Hz, 1H), 2.78 (td, *J* = 13.2, 3.2 Hz, 1H), 2.39 (ddd, *J* = 13.3, 9.5, 3.6 Hz, 1H), 2.24 (qd, *J* = 9.7, 3.0 Hz, 1H), 1.84 (dd, *J* = 12.7, 2.8 Hz, 1H), 1.77 - 1.62 (m, 3H), 1.57 - 1.48 (m, 1H).
**HRMS(ESI):** *m/z* calc. for $C_{43}H_{40}N_3O_5S_2$ $[M+H]^+$: 742.2409, found: 742.2419.

## 13.) Computational Analysis

### *Molecular Property Distribution Histograms*

Library data for the MicroFormat Library was obtained via the ChemBridge website. Molecular properties were calculated in Discovery Studio Client 2.5 (Accelrys, San Diego CA) using the Analyze Small Molecules toolset. Fsp3 values were calculated using the electrotopological state (E-State) counts for all possible carbon configurations. Histograms were generated in Excel (Microsoft, Redmond WA) using the Analysis ToolPak.

### *Tanimoto Similarity Analysis*

Compound structure sets were converted to .sdf library format in ChemDraw (Cambridgesoft, Cambridge MA). Tanimoto similarity coefficients were calculated using Discovery Studio Client 2.5 (Accelrys, San Diego CA). Each structure was saved as an individual .sdf file and used as an input reference ligand for the Library Analysis protocol "Find Similar Molecules by Fingerprints", setting the minimum similarity to 0 and using ECFP_6 molecular fingerprints. This was repeated for all compounds and the resulting Tanimoto coefficients were arranged in a similarity matrix. Heatmaps were generated in Excel (Microsoft, Redmond WA) using a three-color scale set to 0.0 (blue), 0.5 (yellow), and 1.0 (red).

## 14.) References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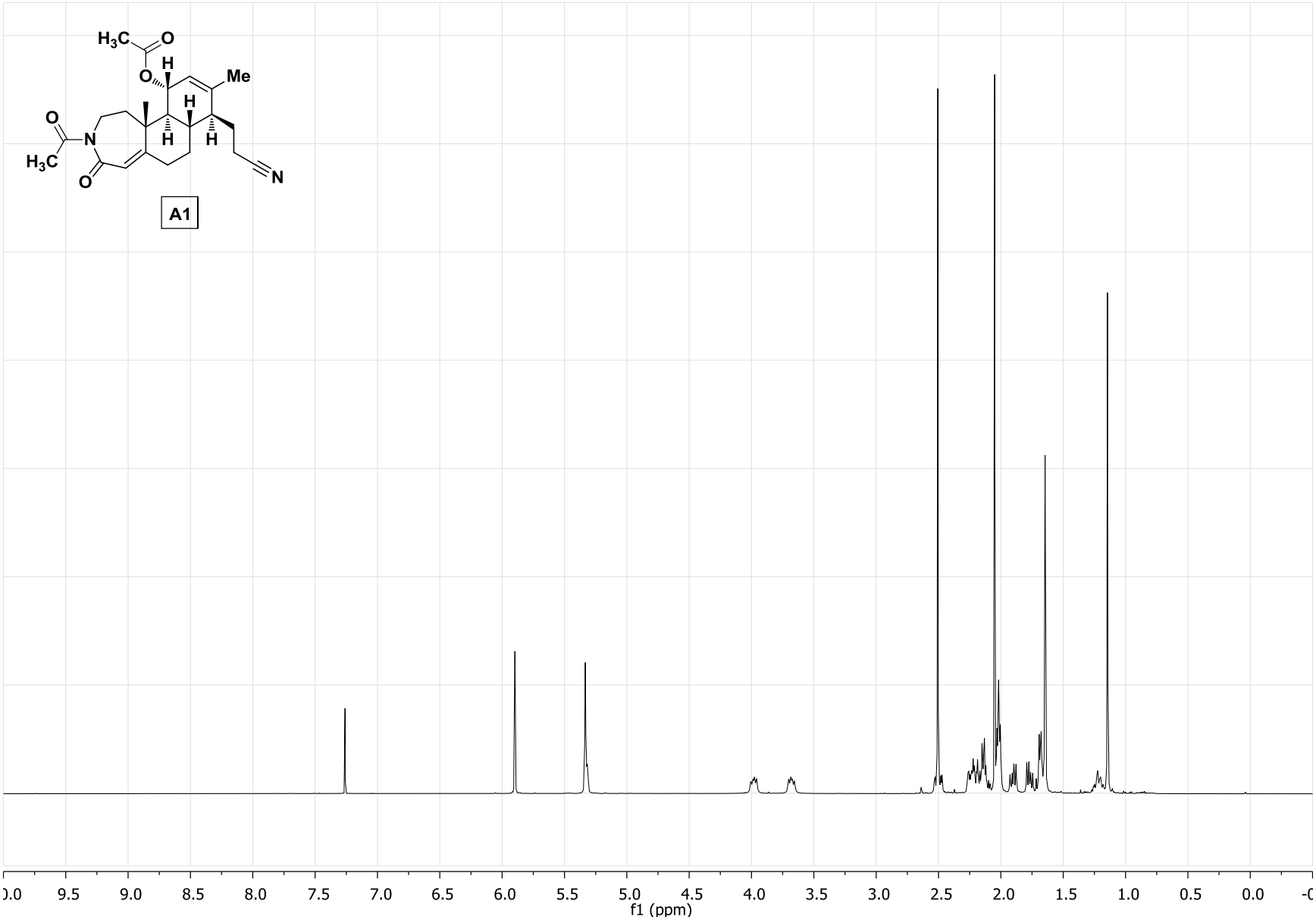
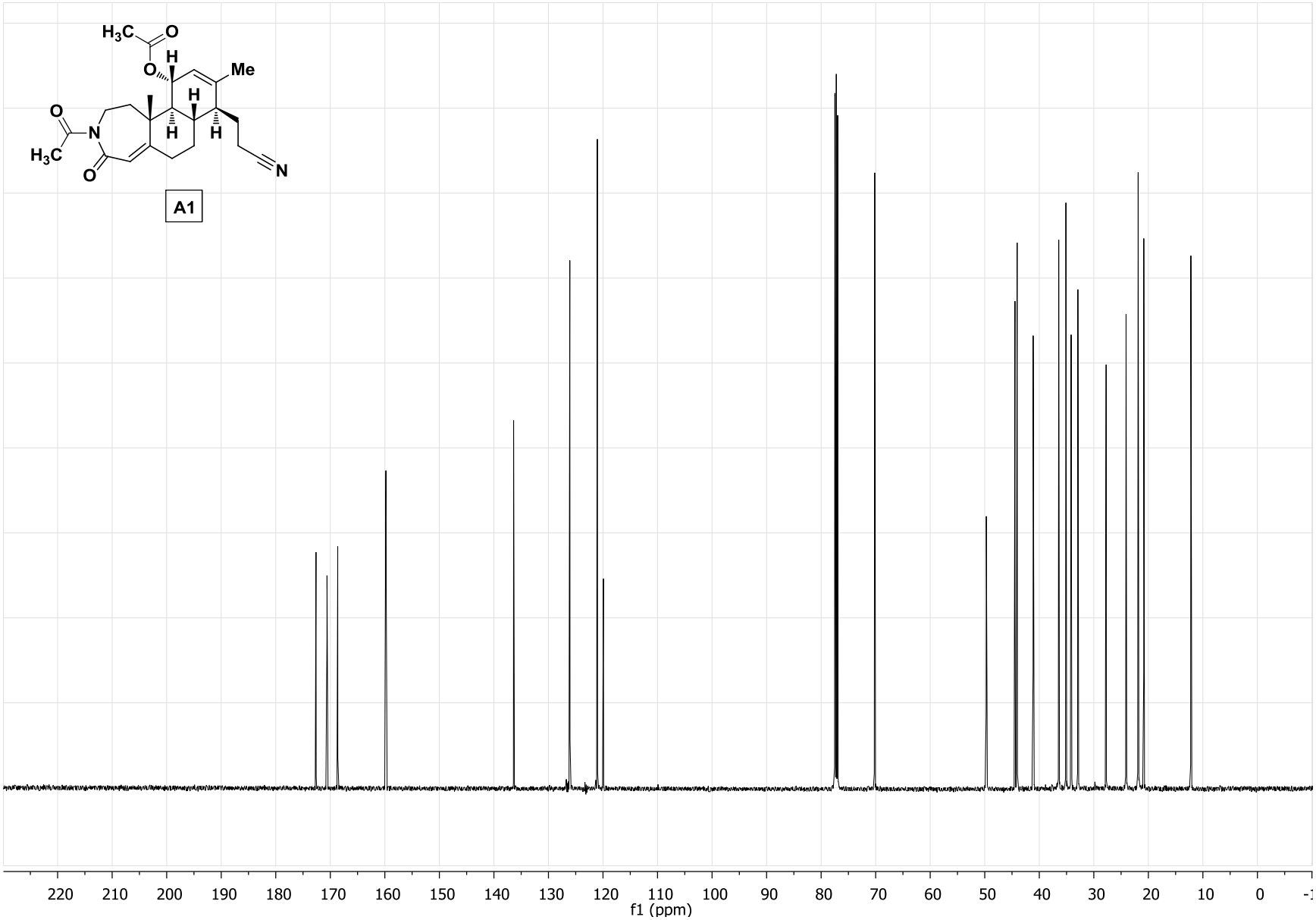
12 Seiple, I. B., Su, S., Rodriguez, R. A., Gianatassio, R., Fujiwara, Y., Sobel, A. L. & Baran, P. S. Direct C−H arylation of electron-deficient heterocycles with arylboronic acids. *J. Am. Chem. Soc.* **132**, 13194-13196, (2010).

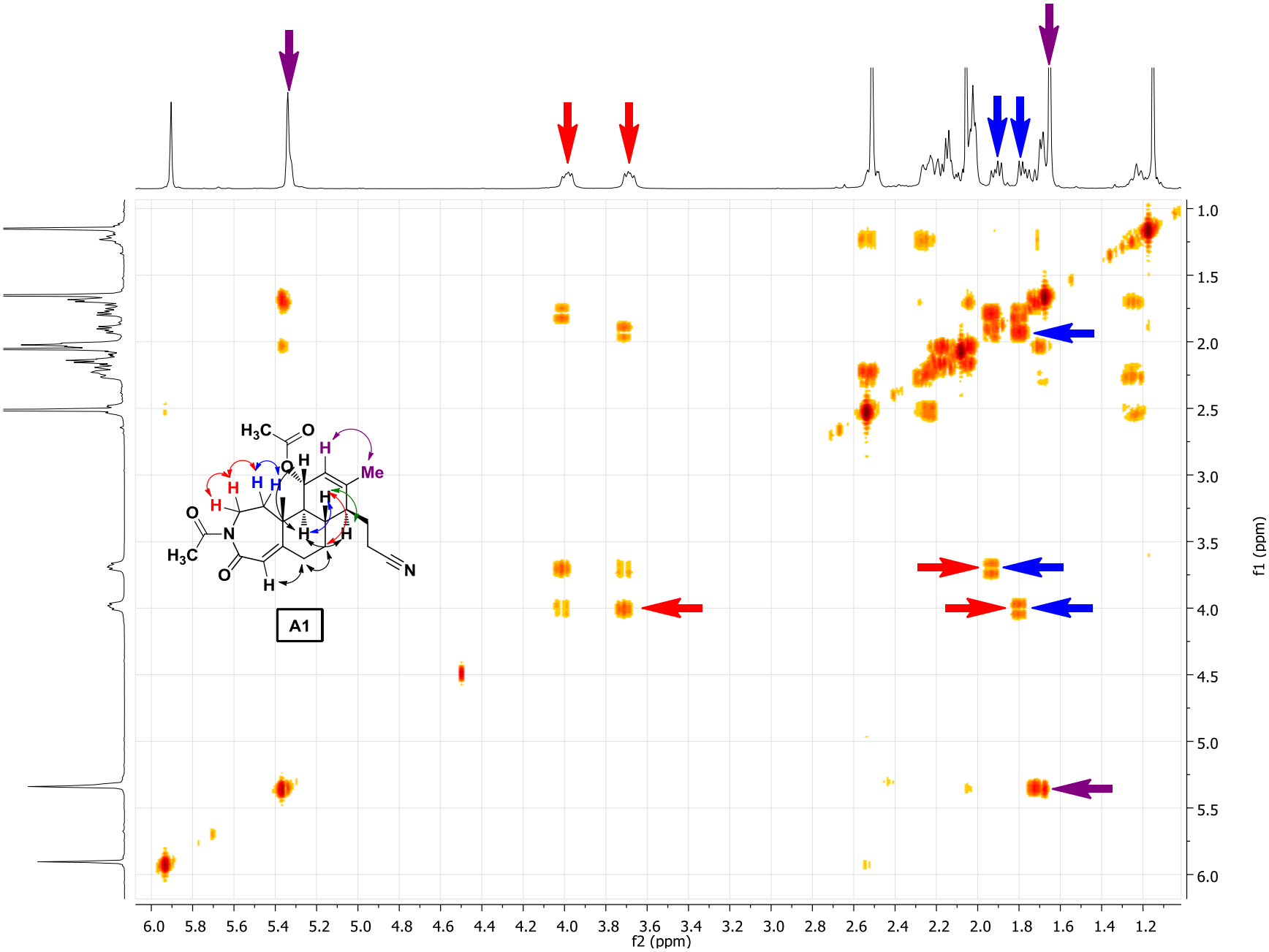

## 15.) NMR Spectra



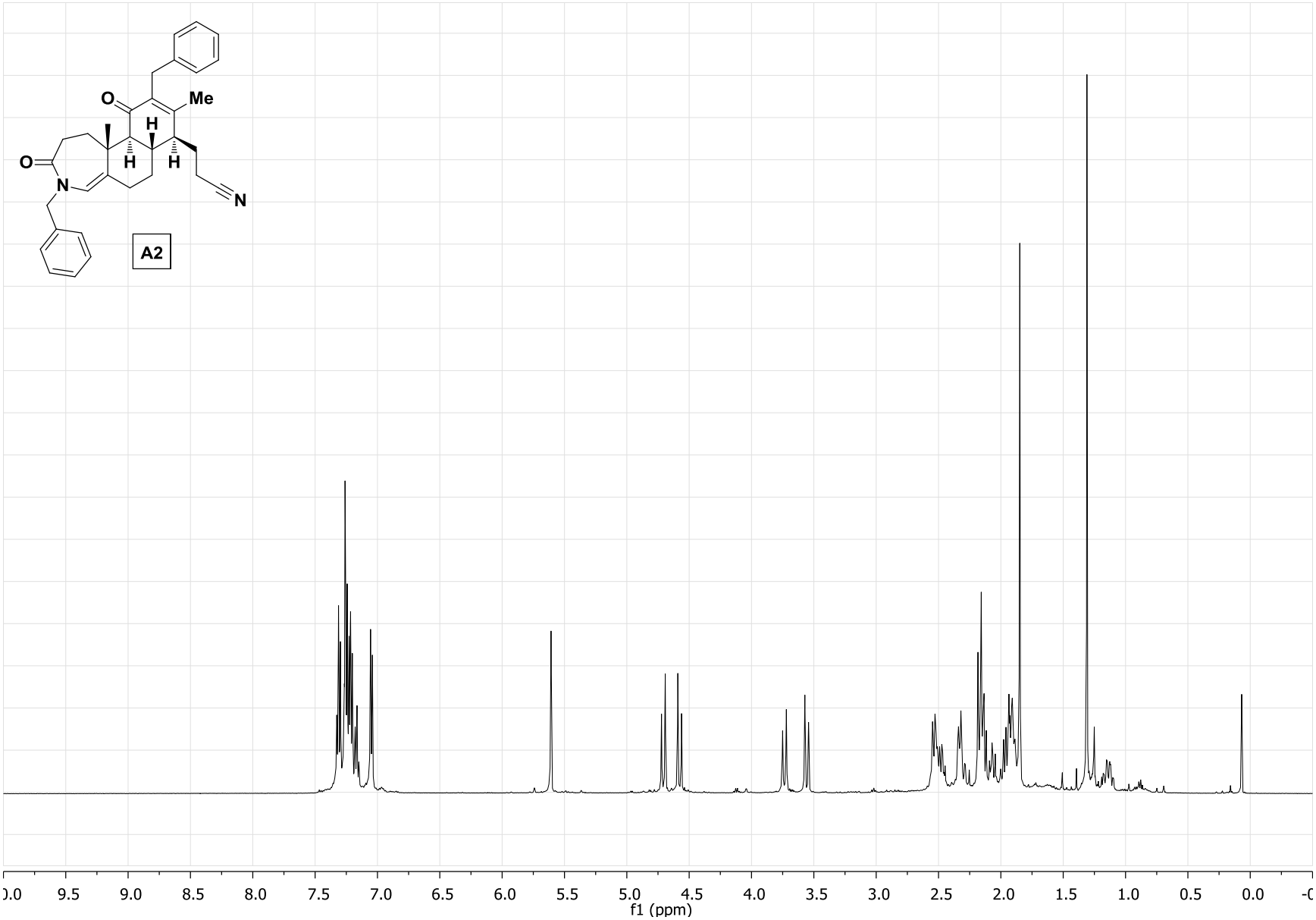

NMR1

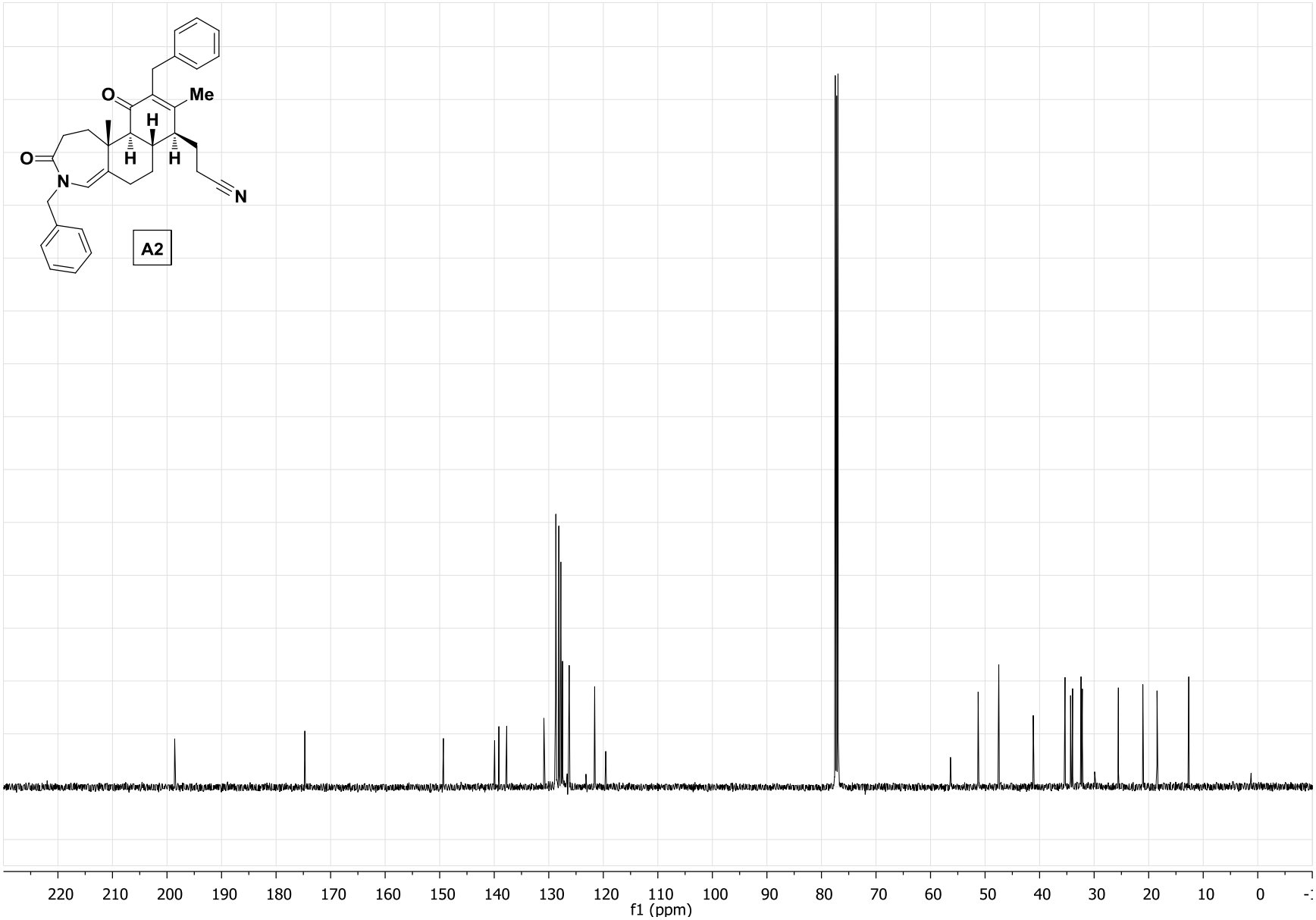


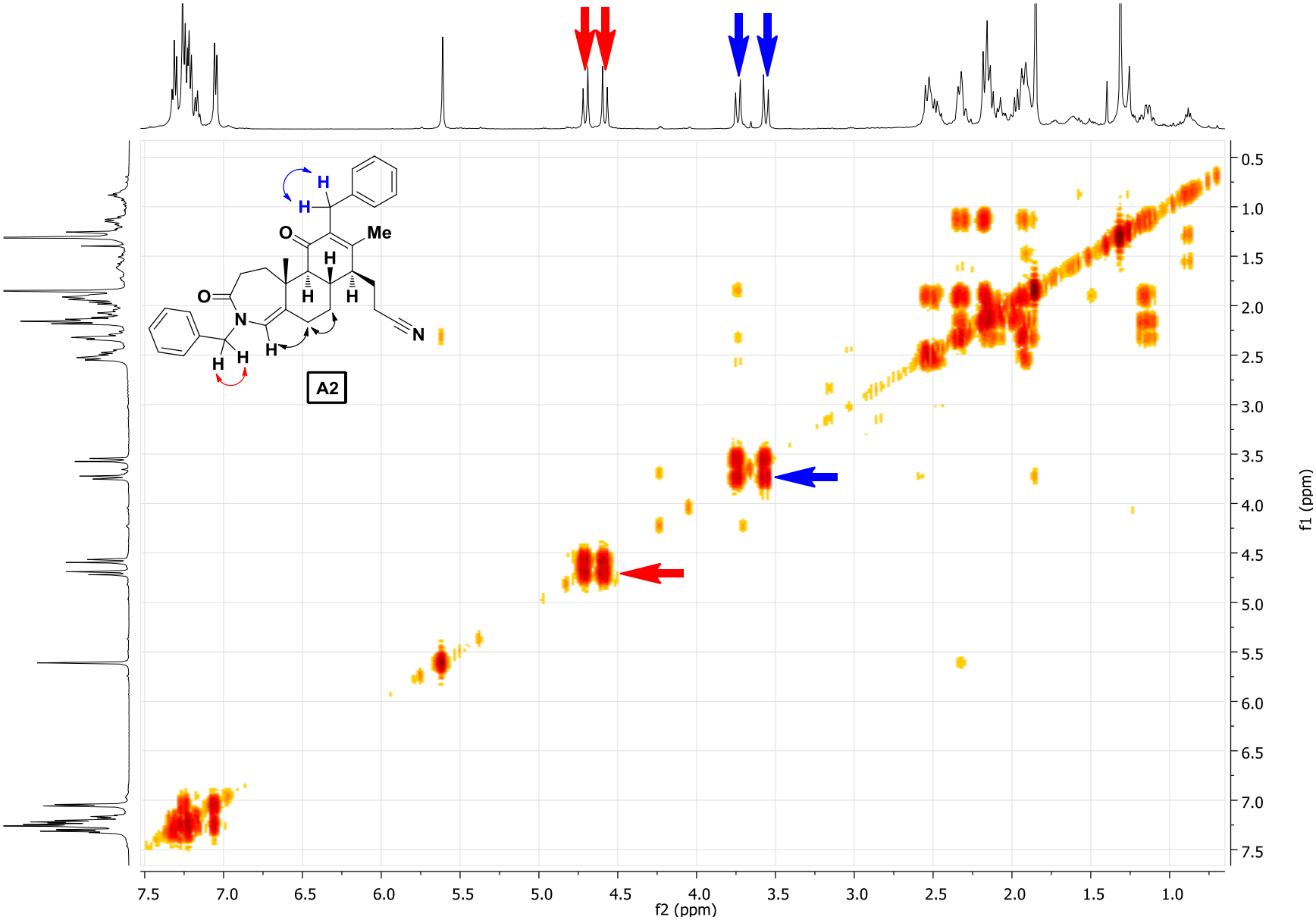

NMR2

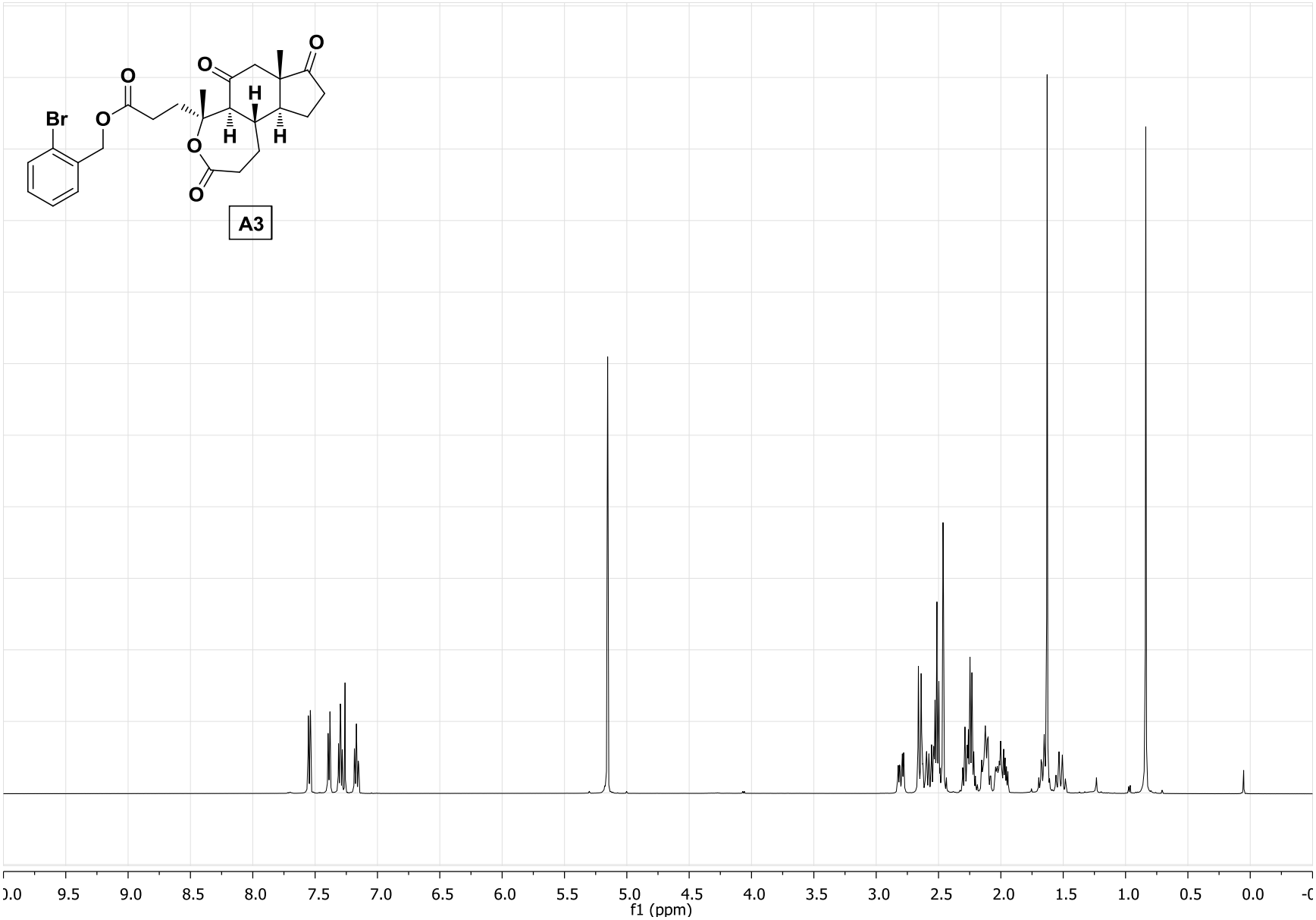



NMR3

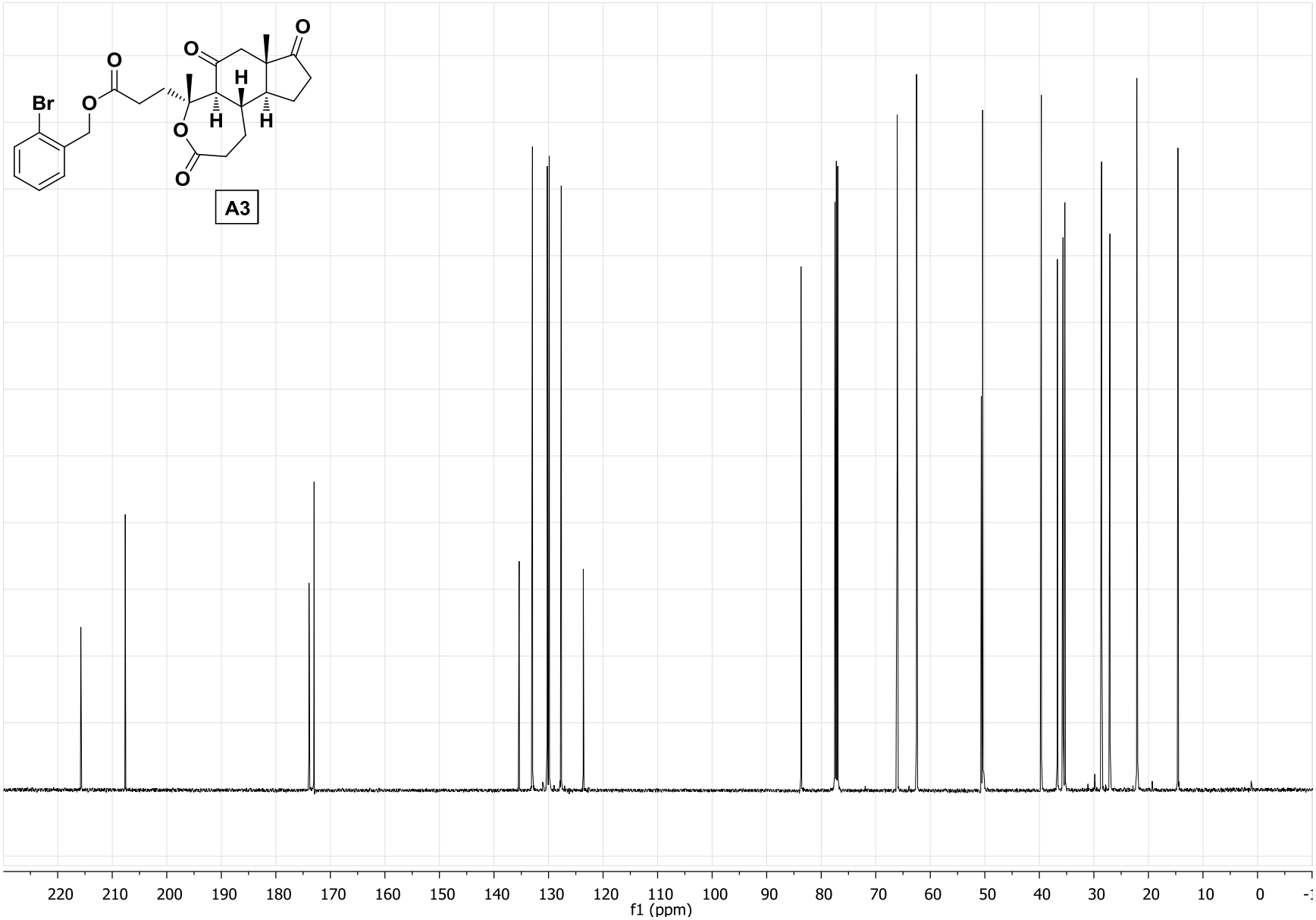

O
Me
H
O
H
H
N
N
A2
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

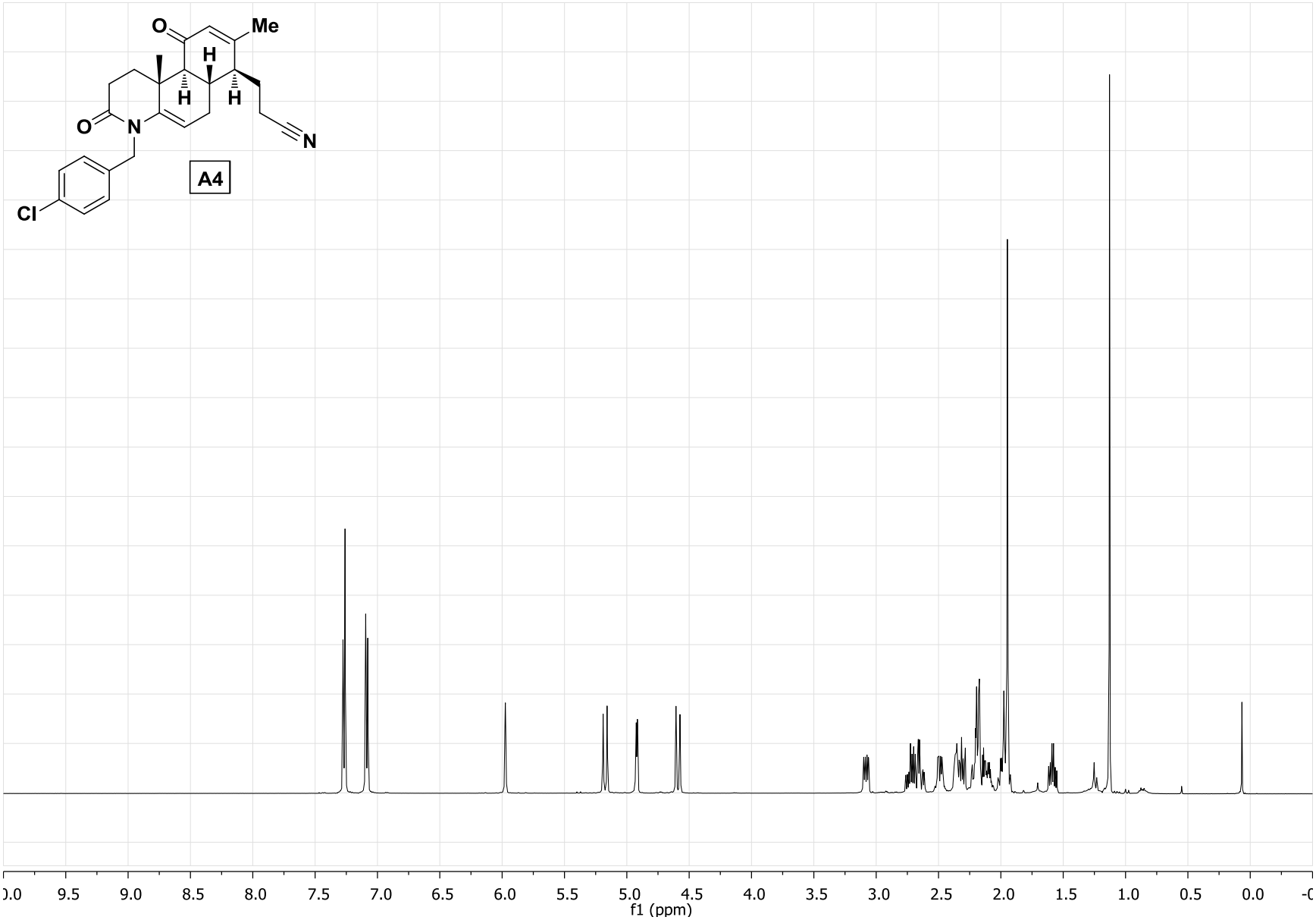

O
Me
H
O
H
H
N
N
A2
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H
H
O
Me
H
O
H
H
N
H
H
H
N
A2
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
f2 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)


Br
O
O
O
O
O
O
H
H
H
A3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

NMR7


Br
O
O
O
O
O
O
H
H
H
O
A3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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Me
H
H
H
O
N
N
A4
Cl
9.5
9.0
8.5
8.0
7.5
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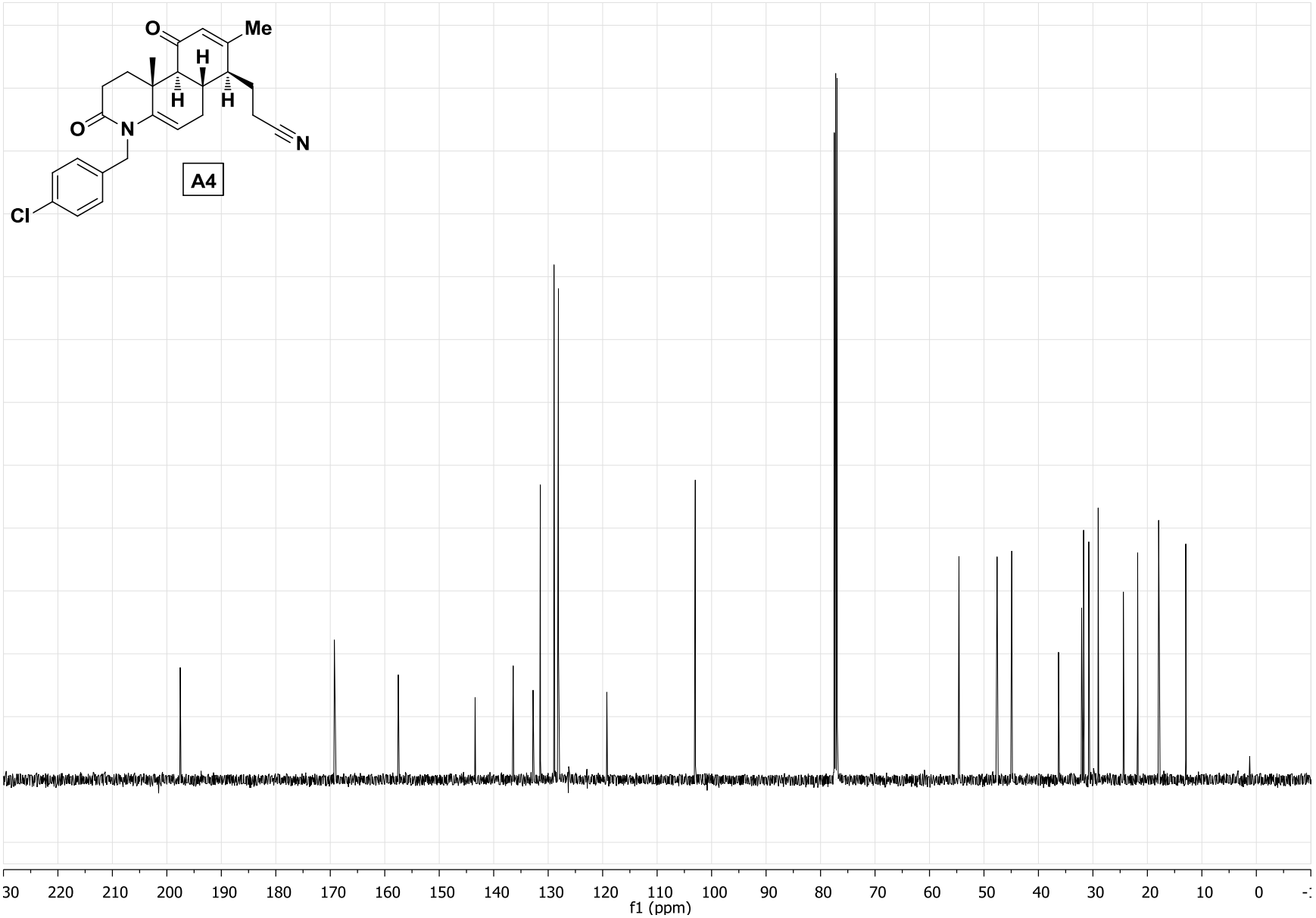
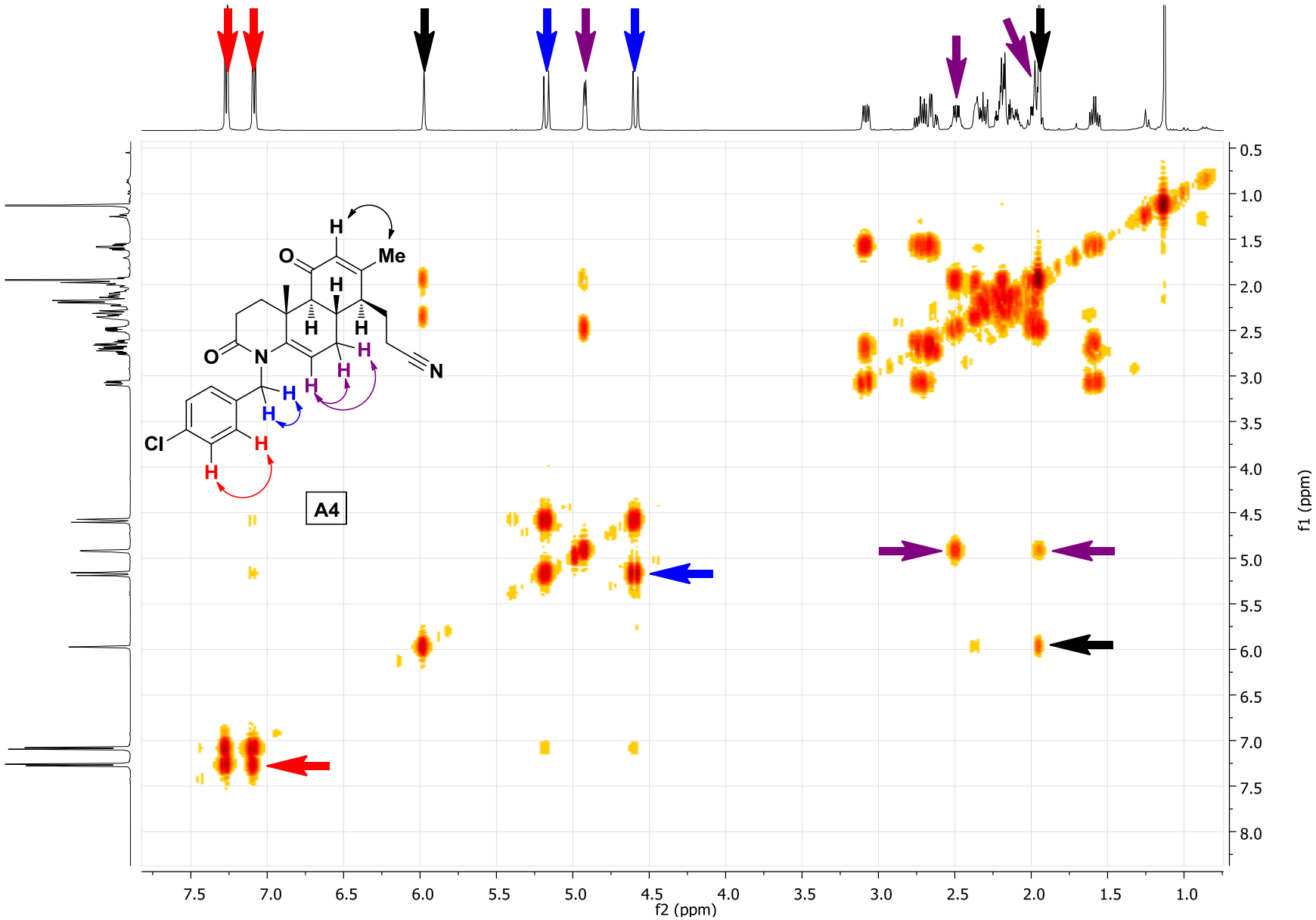
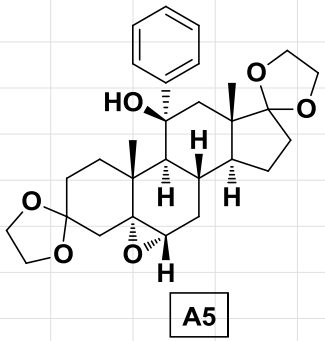
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
Me
H
H
H
O
N
N
A4
Cl
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

NMR10

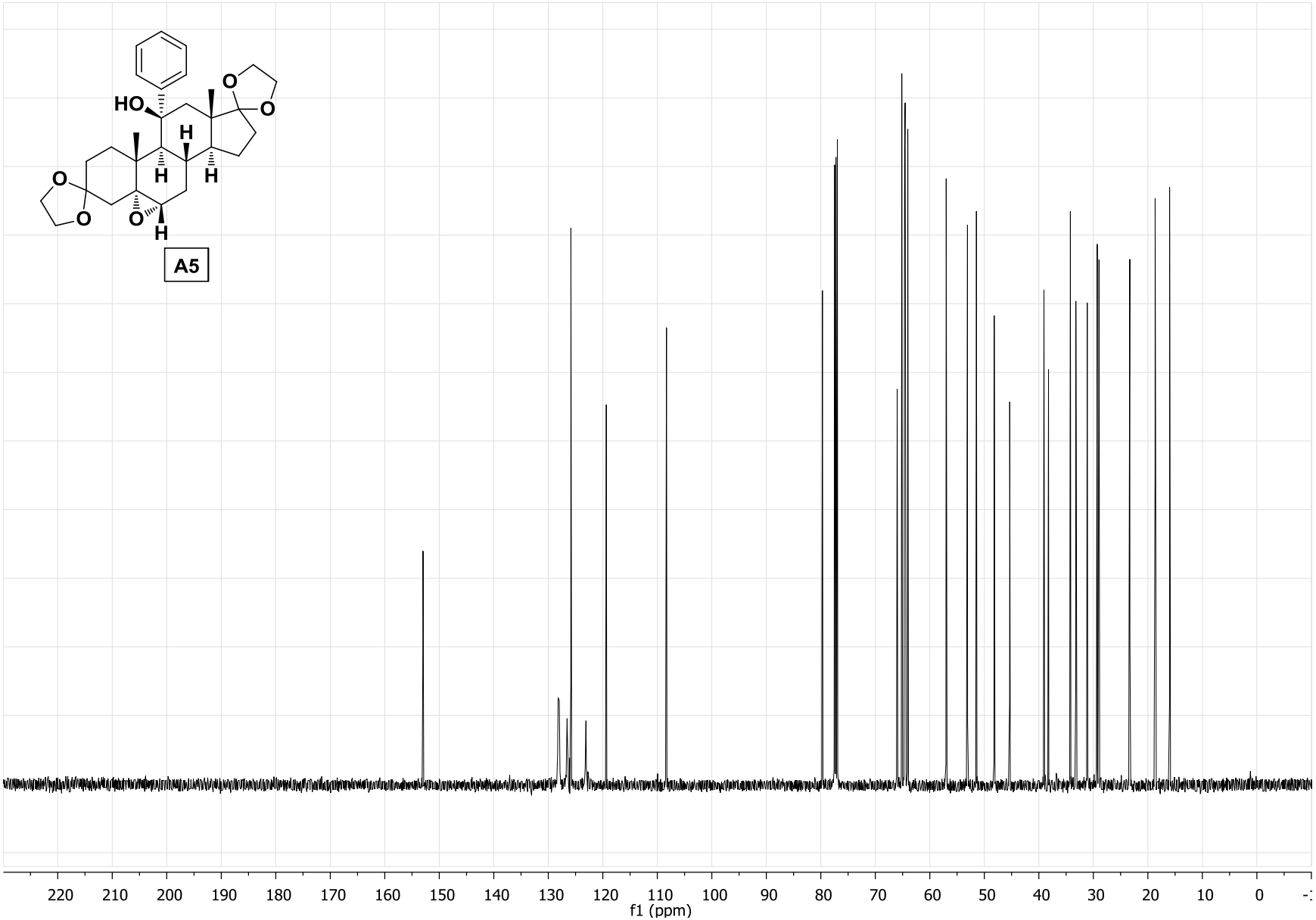



NMR11

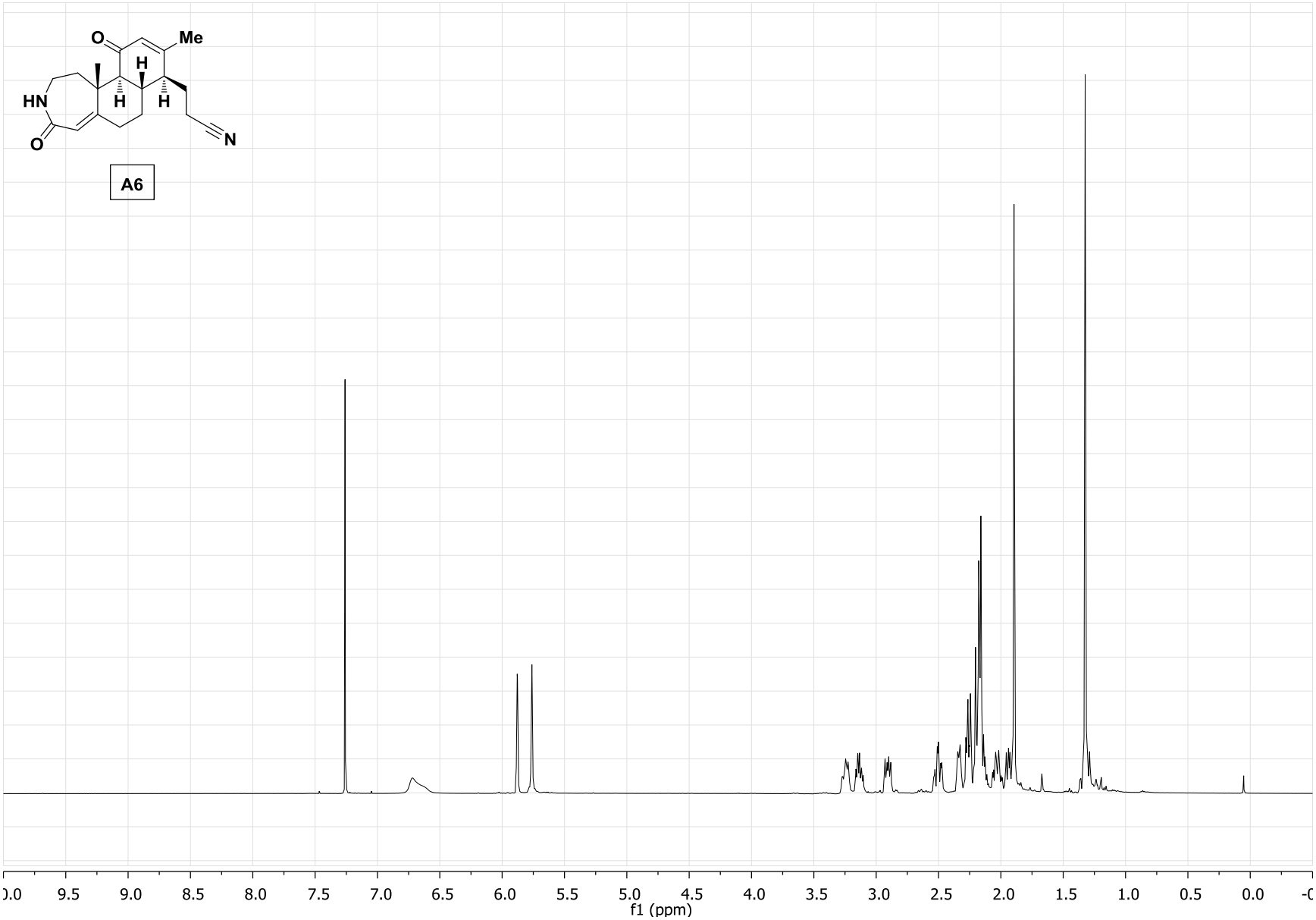

HO
O
O
H
H
H
O
O
O
H

A5

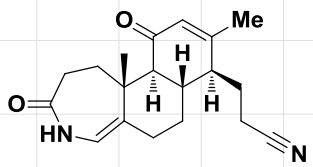

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


HO
O
O
H
H
H
O
O
O
H
A5
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

NMR13

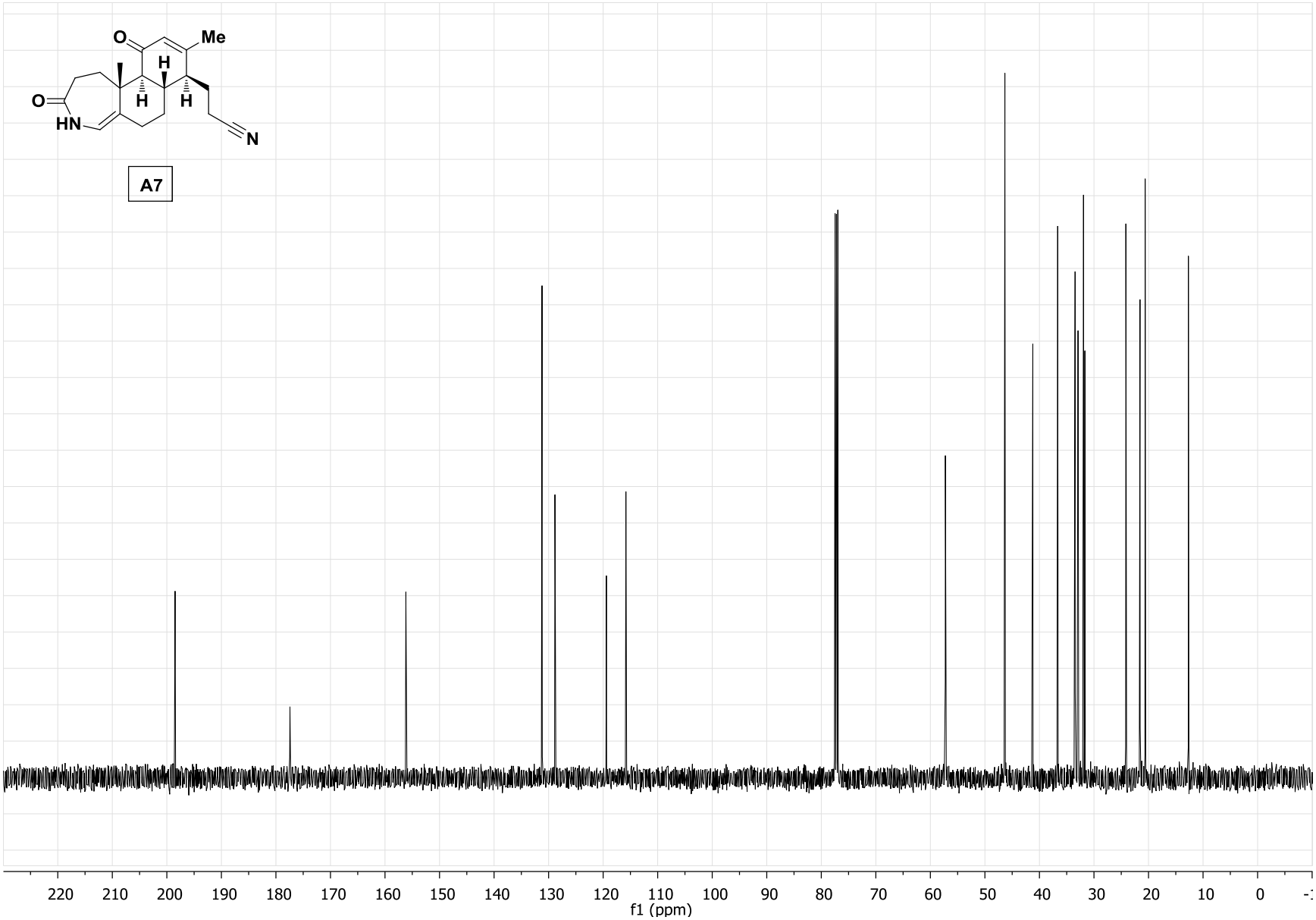



NMR14

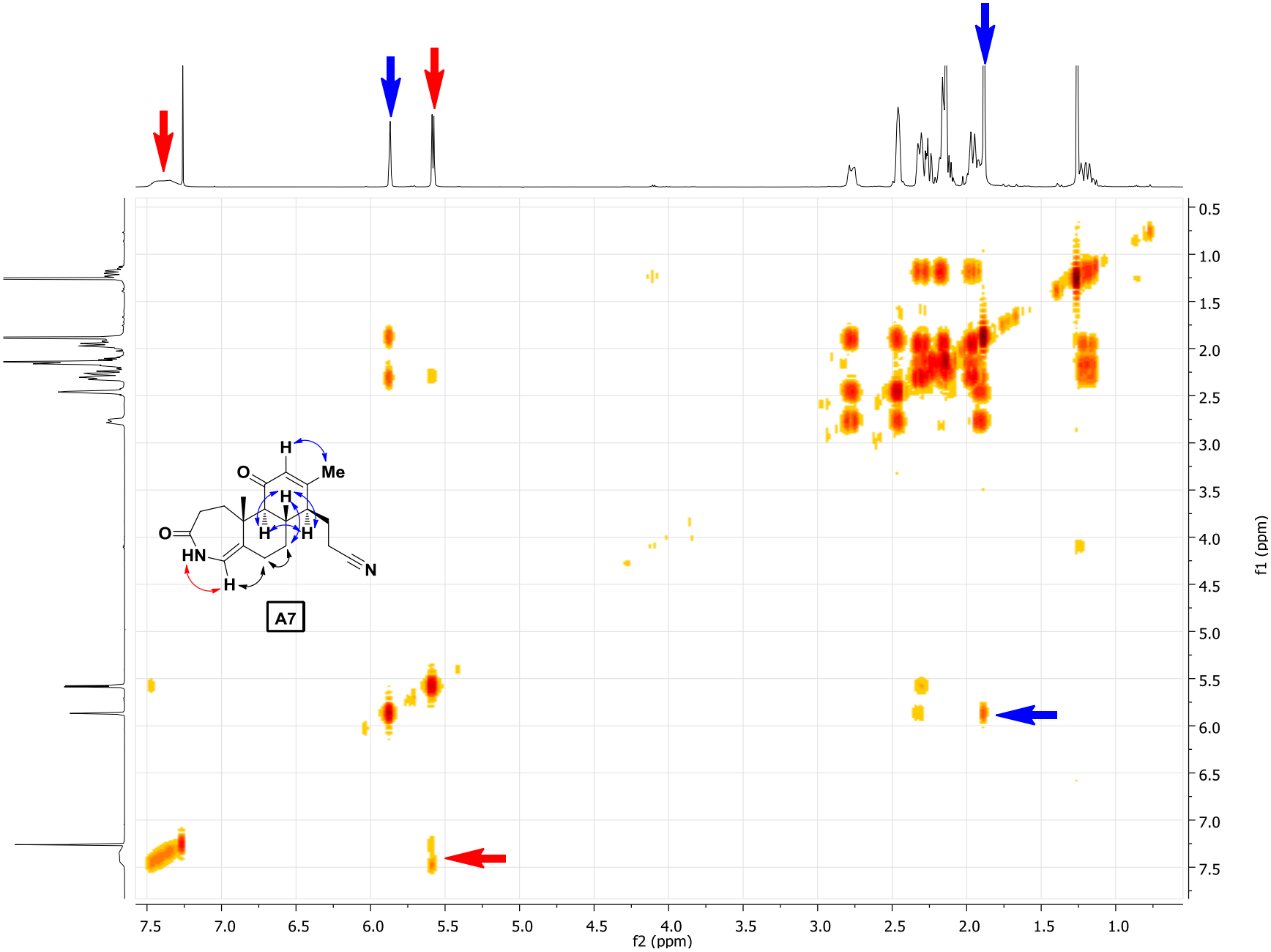

O
Me
H
O
H
H
HN
N

A7

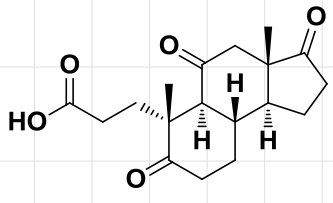

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
Me
H
O
H
H
HN
N
A7
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

NMR16

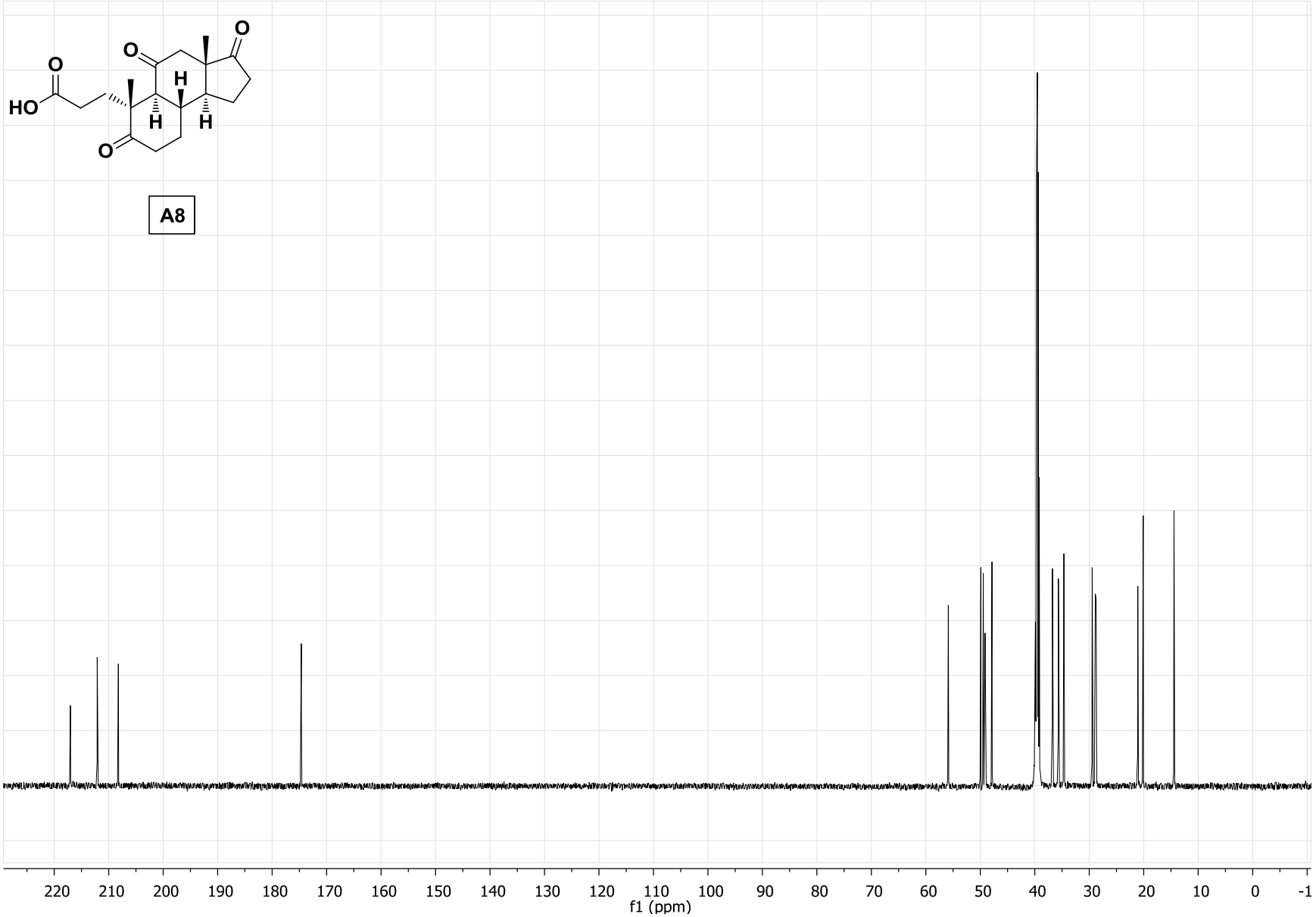

H
Me
O
H
O
H
H
H
HN
H
N
A7
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)

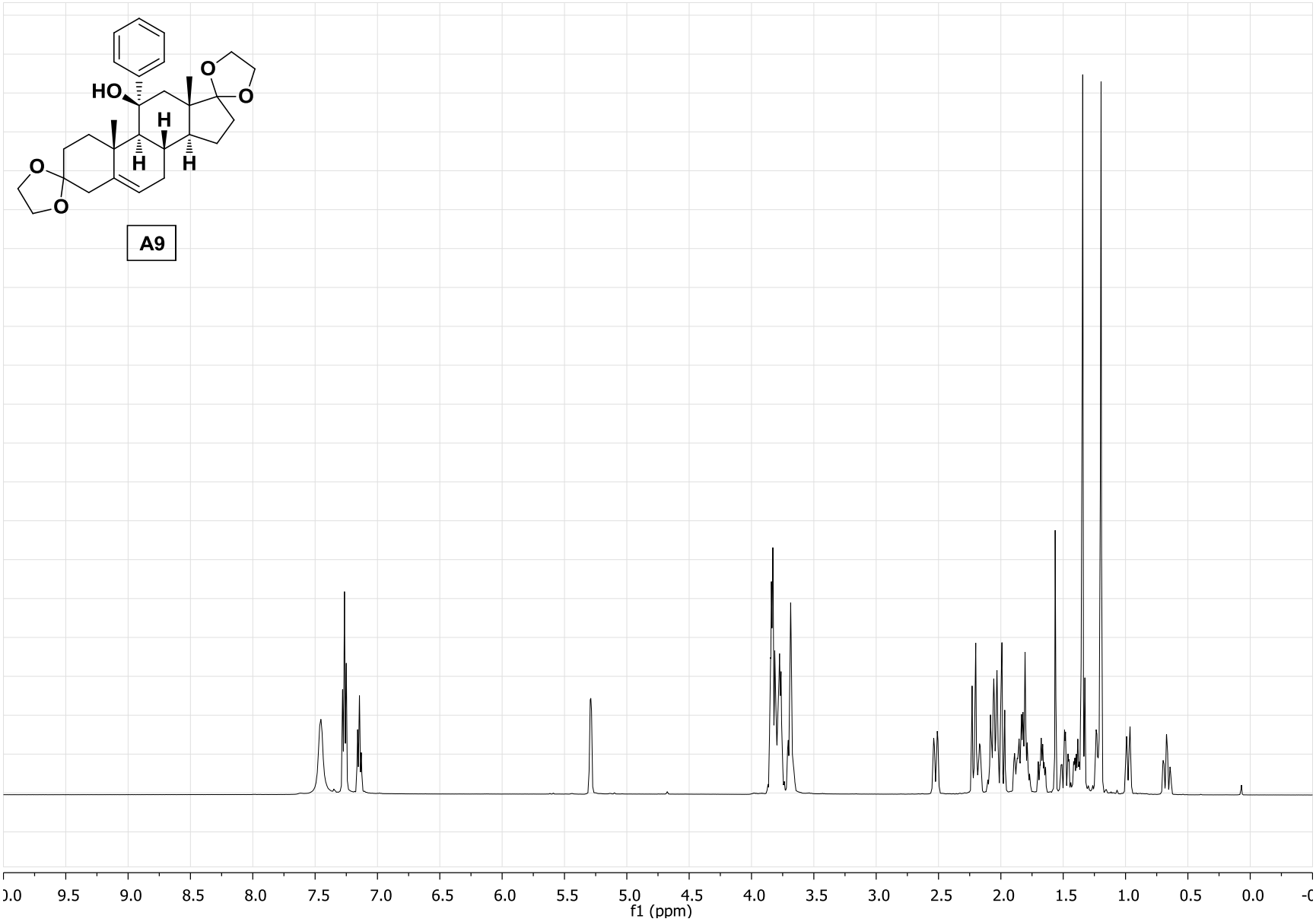
NMR17


O
HO
O
O
H
H
H
O

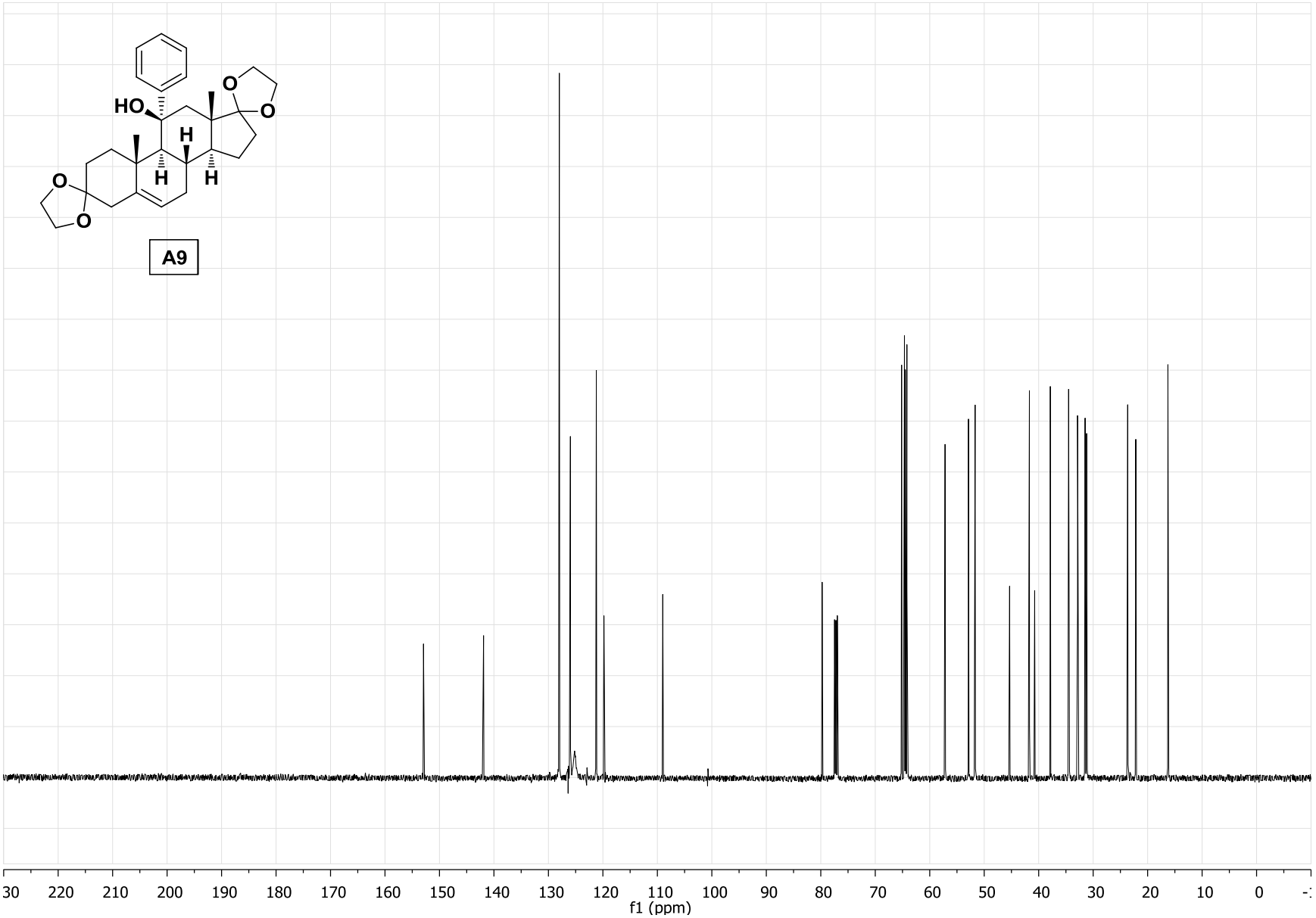
A8


2.5 12.0 11.5 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 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2.0 -2
f1 (ppm)

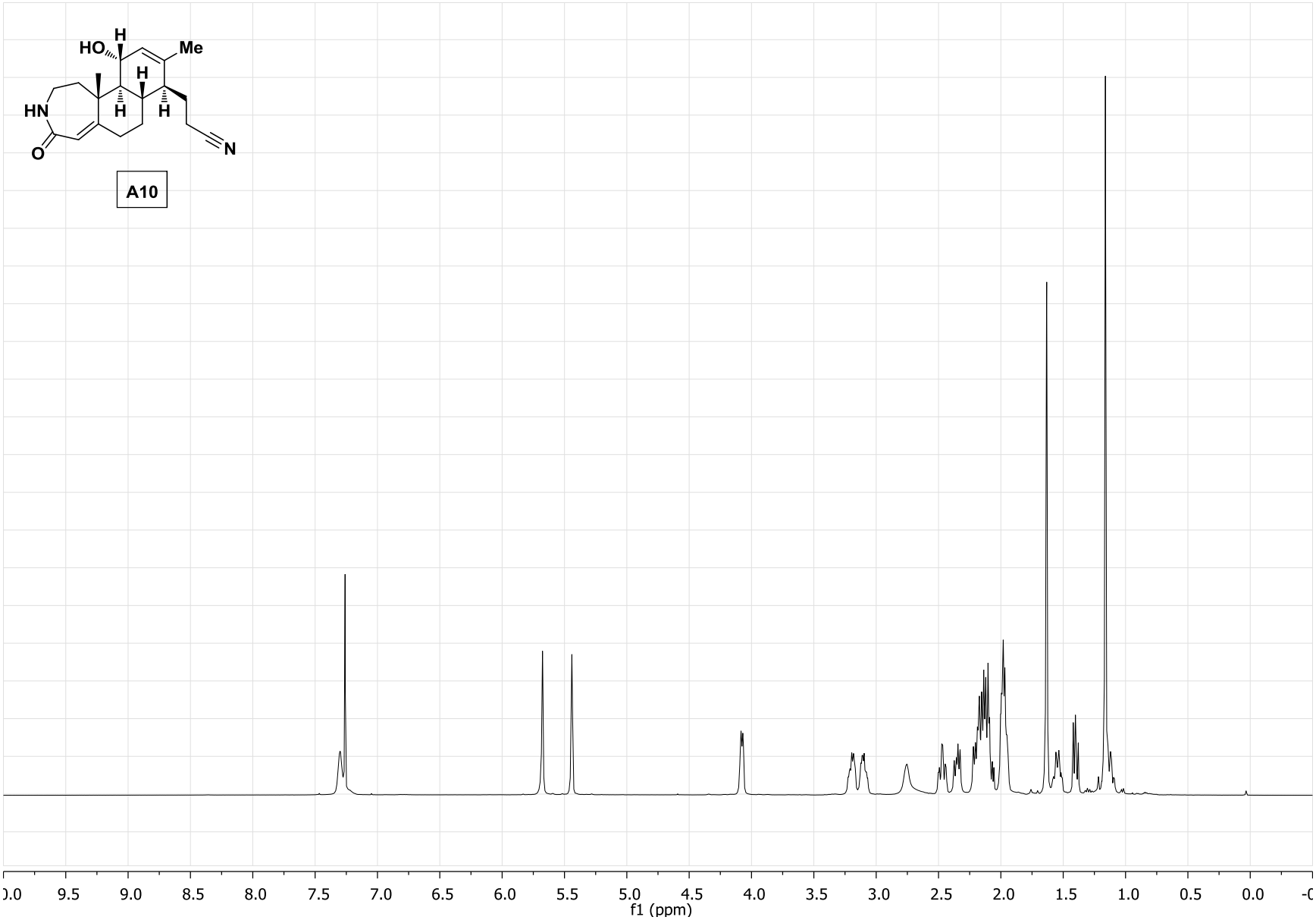

O
O
HO
H
H
H
O
O
A8
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)


HO
O
O
H
H
H
O
O
A9
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

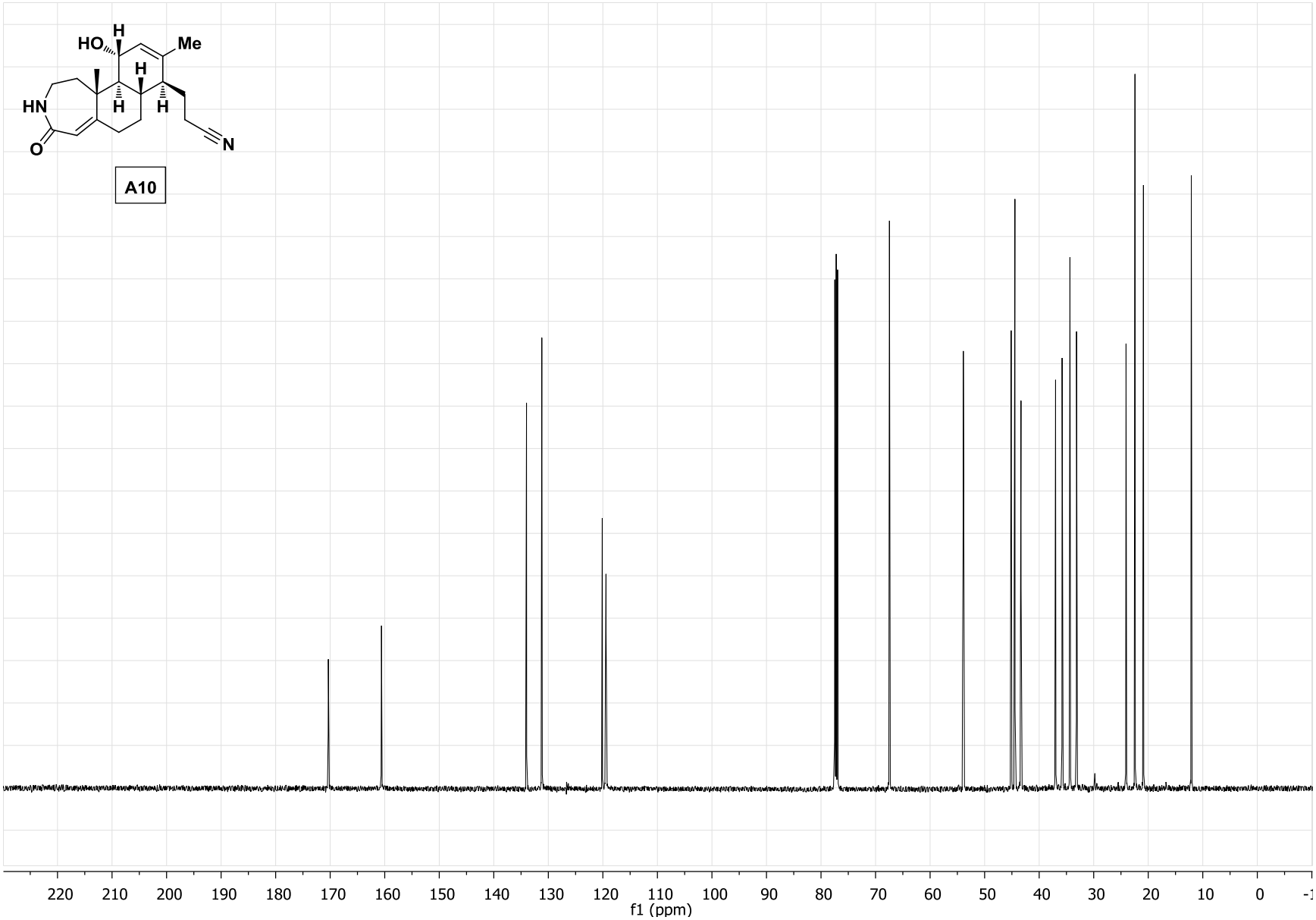
NMR20


HO
O
O
H
H
H
O
O
A9
30
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

NMR21




NMR22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H
Me
H
HN
H
H
O
N
A10
220
210
200
190
180
170
160
150
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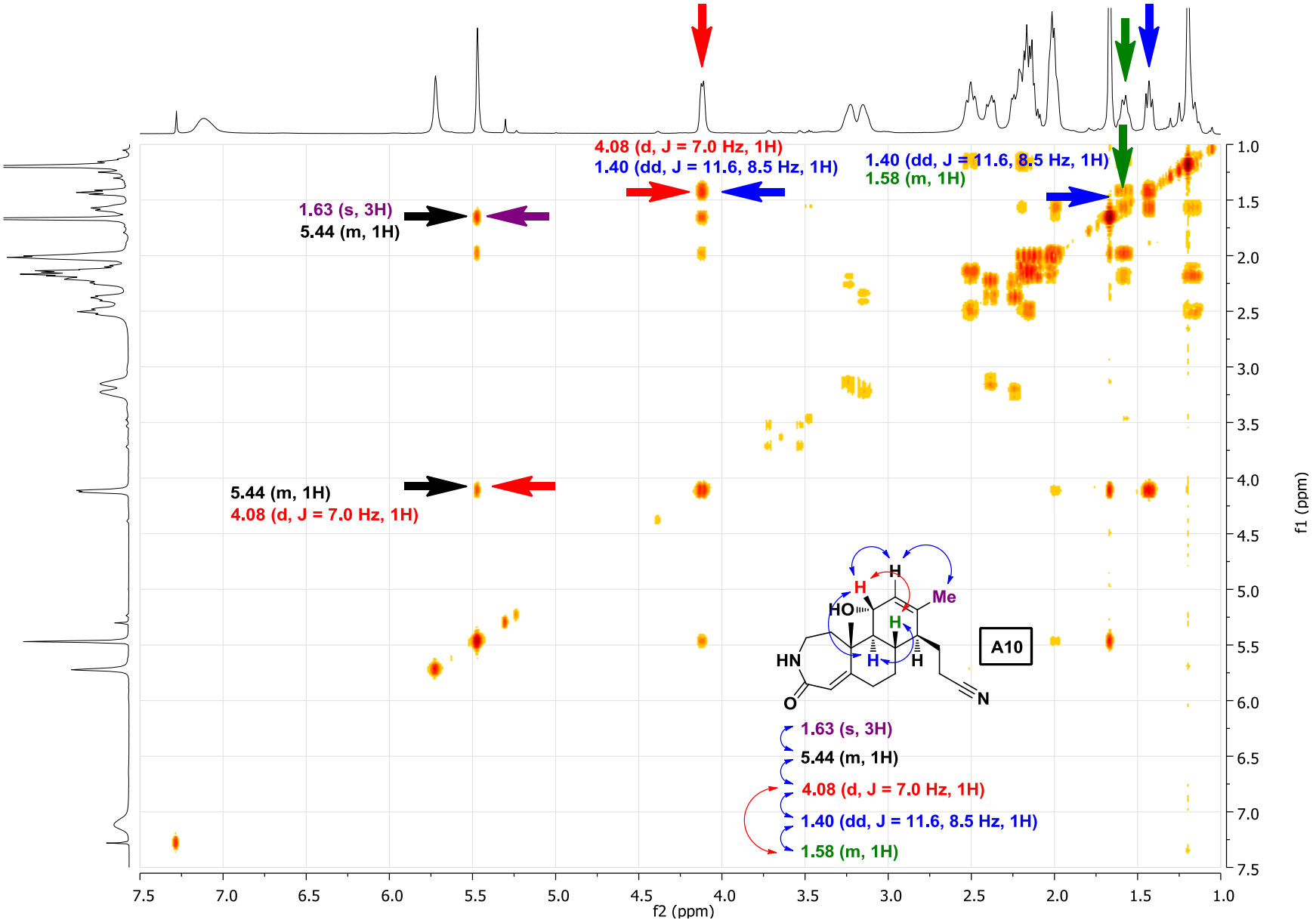
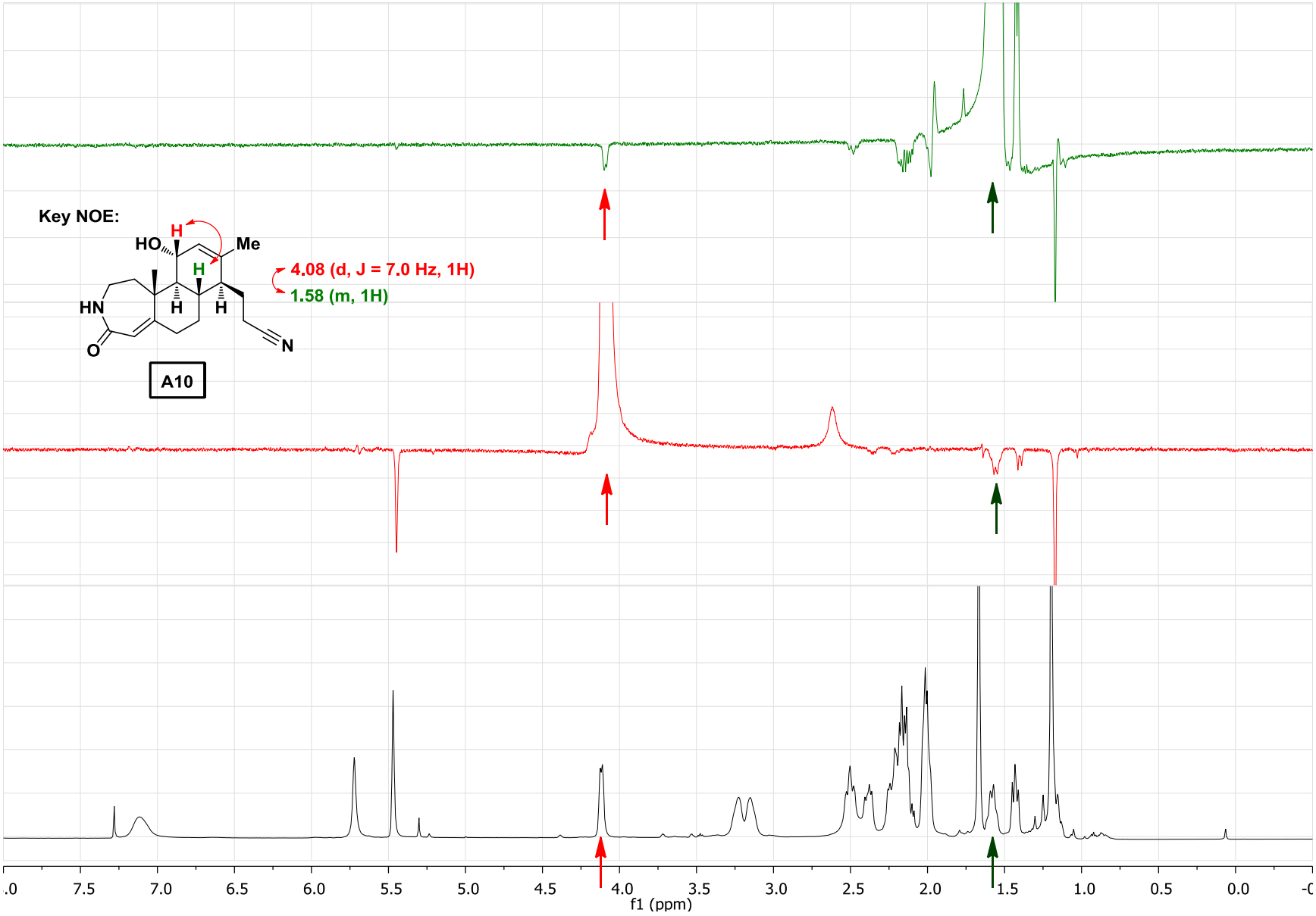
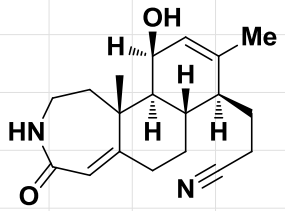
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

NMR23


4.08 (d, J = 7.0 Hz, 1H)
1.40 (dd, J = 11.6, 8.5 Hz, 1H)
1.40 (dd, J = 11.6, 8.5 Hz, 1H)
1.58 (m, 1H)
1.63 (s, 3H)
5.44 (m, 1H)
5.44 (m, 1H)
4.08 (d, J = 7.0 Hz, 1H)
A10
1.63 (s, 3H)
5.44 (m, 1H)
4.08 (d, J = 7.0 Hz, 1H)
1.40 (dd, J = 11.6, 8.5 Hz, 1H)
1.58 (m, 1H)
f2 (ppm)
f1 (ppm)

NMR24


Key NOE:
HO
H
Me
H
HN
H
H
O
N
A10
4.08 (d, J = 7.0 Hz, 1H)
1.58 (m, 1H)
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)


OH
H
Me
H
HN
H
H
O
N

A11


0.0
9.5
9.0
8.5
8.0
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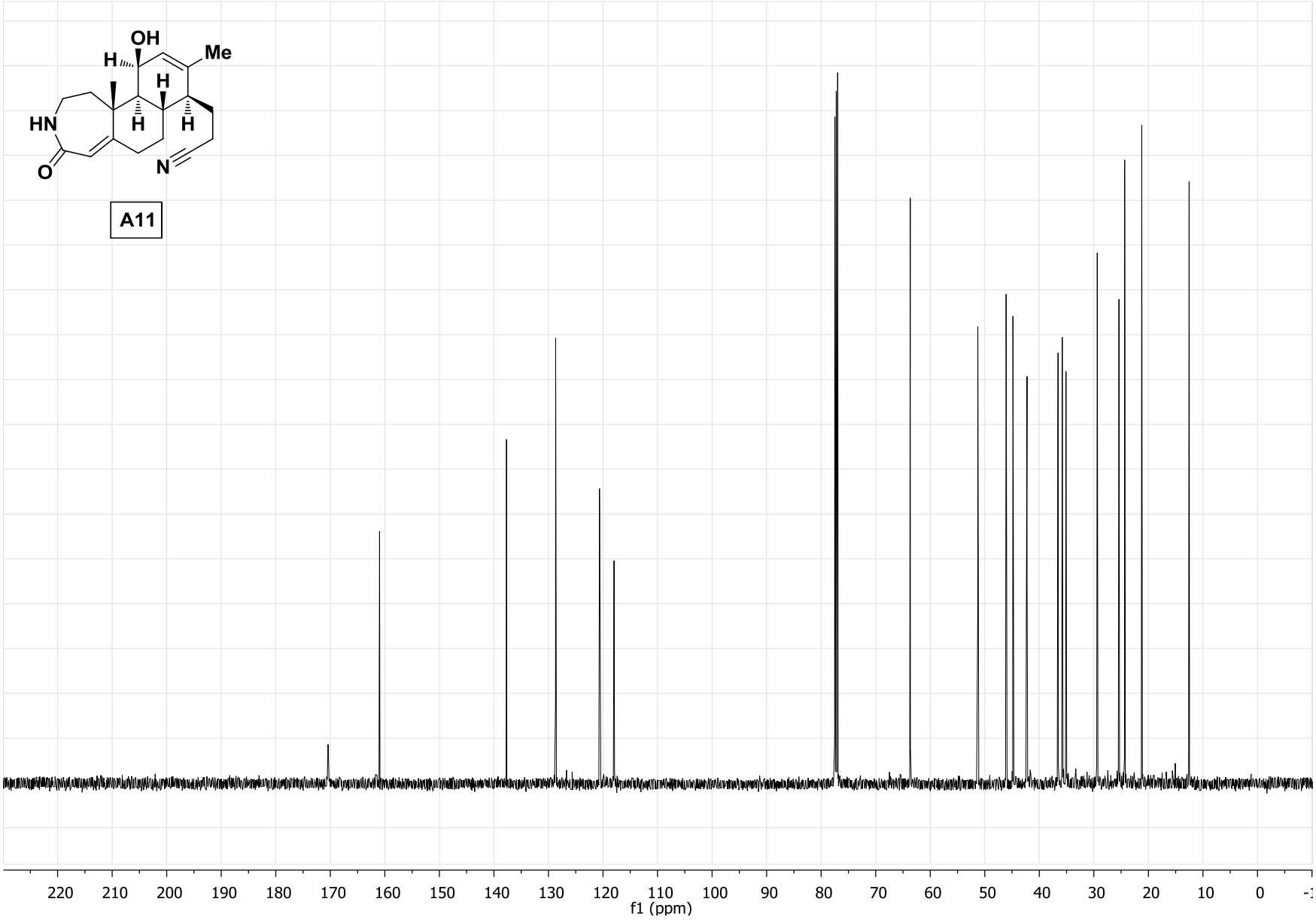
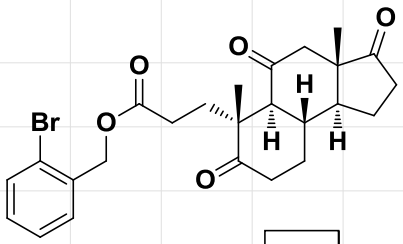
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

NMR26

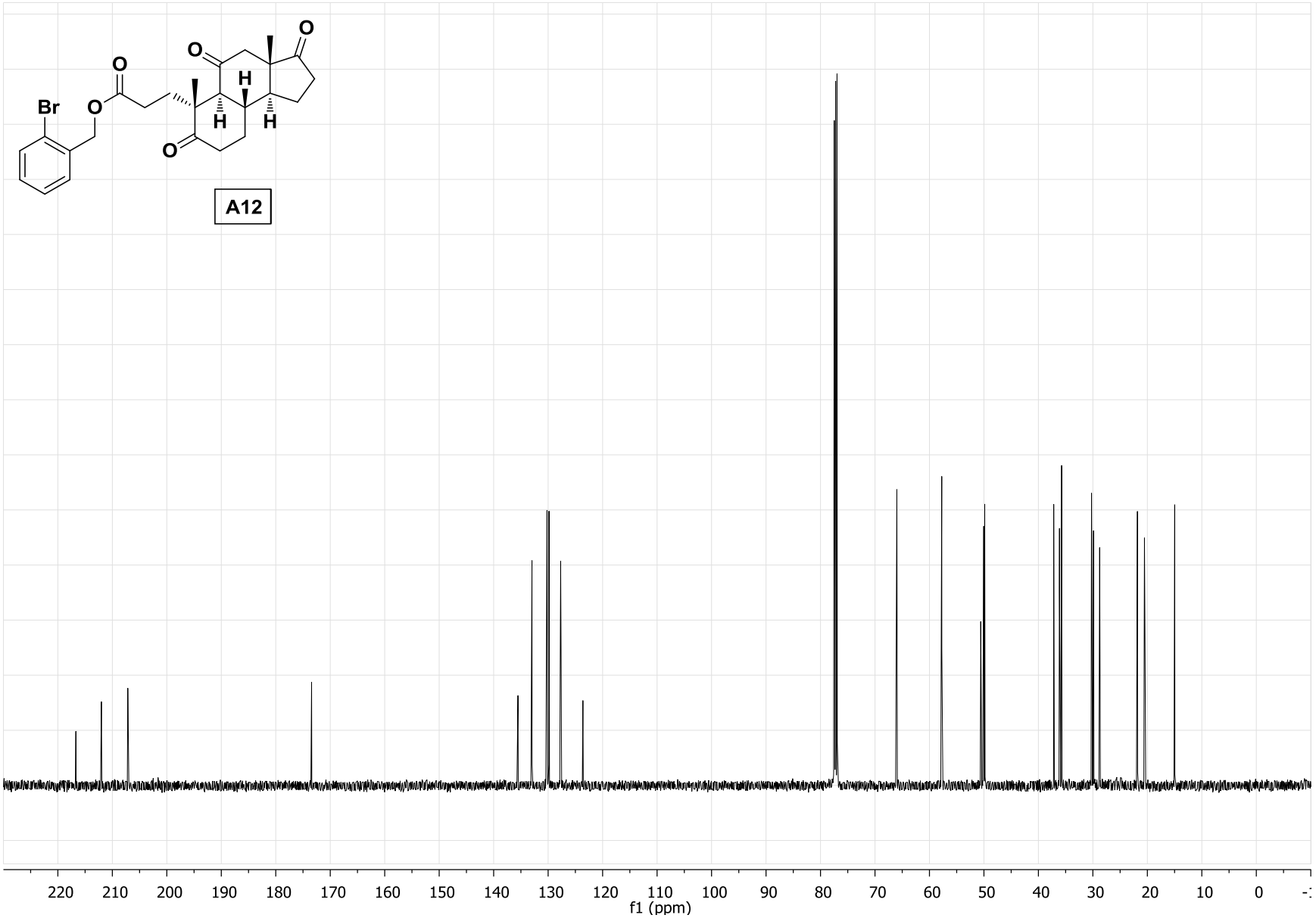

OH
H
Me
H
HN
H
H
O
N
A11
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

NMR27

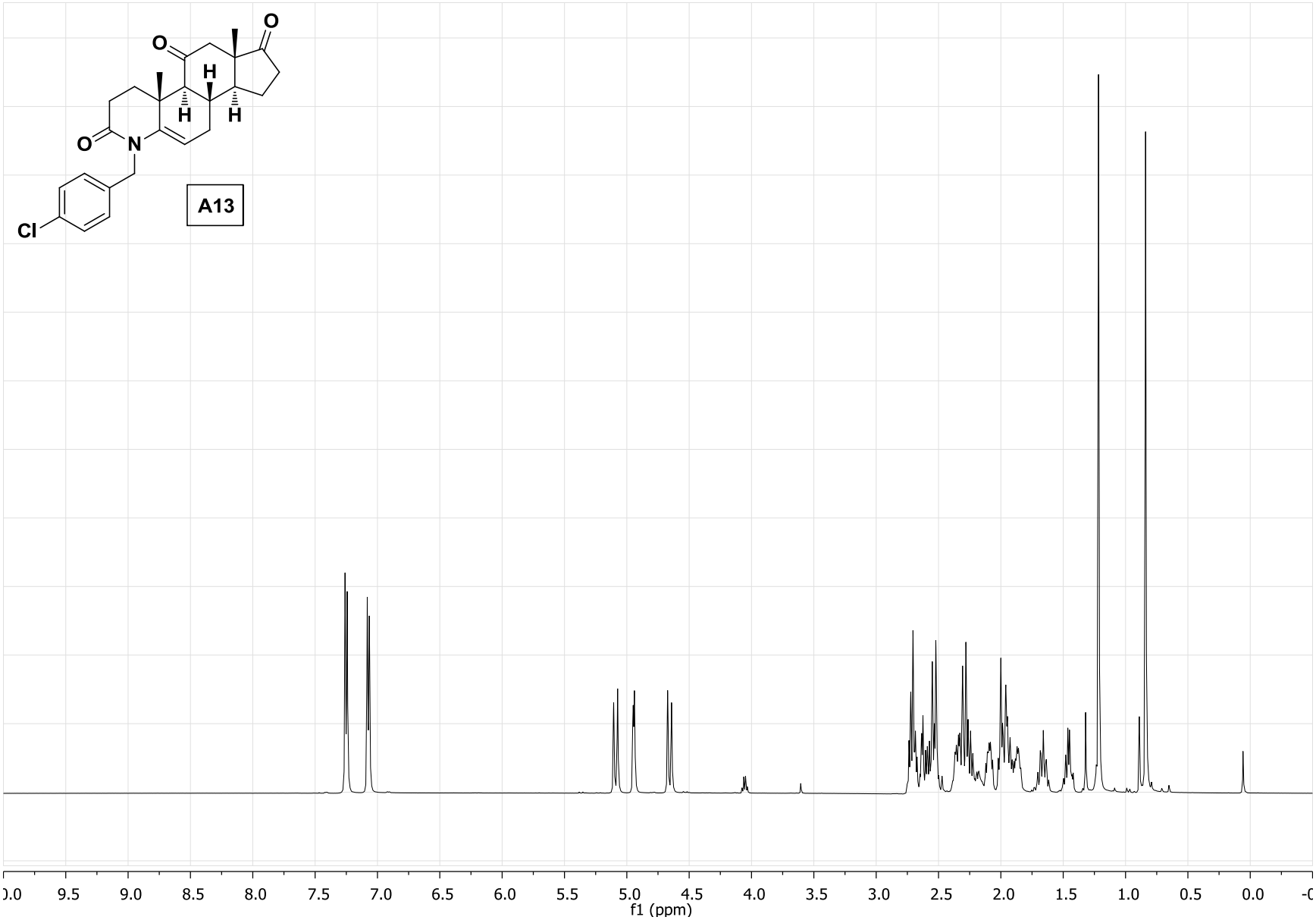

Br
O
O
O
O
H
H
H
O

A12

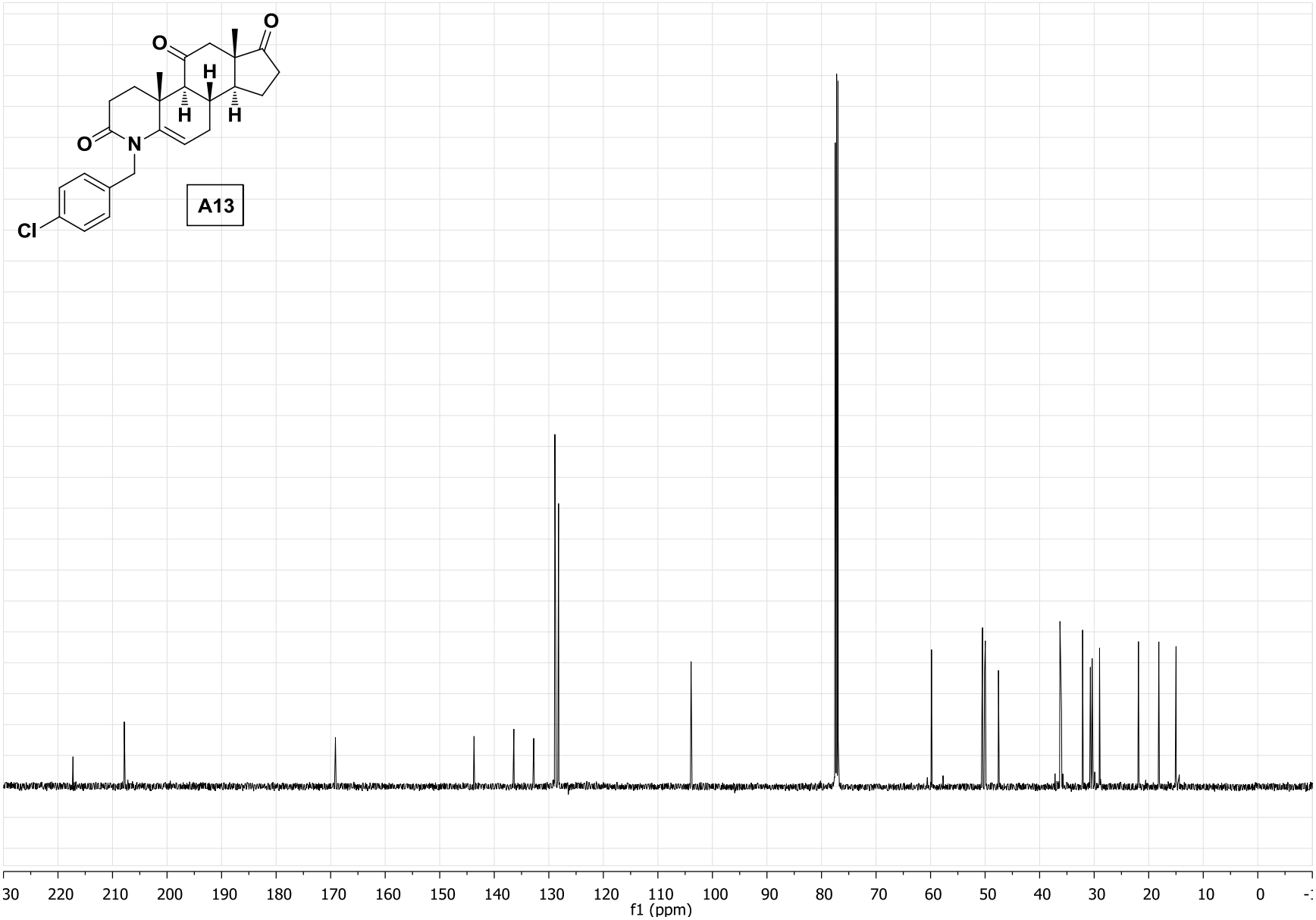

0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0
f1 (ppm)


Br
O
O
O
O
O
H
H
H
A12
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

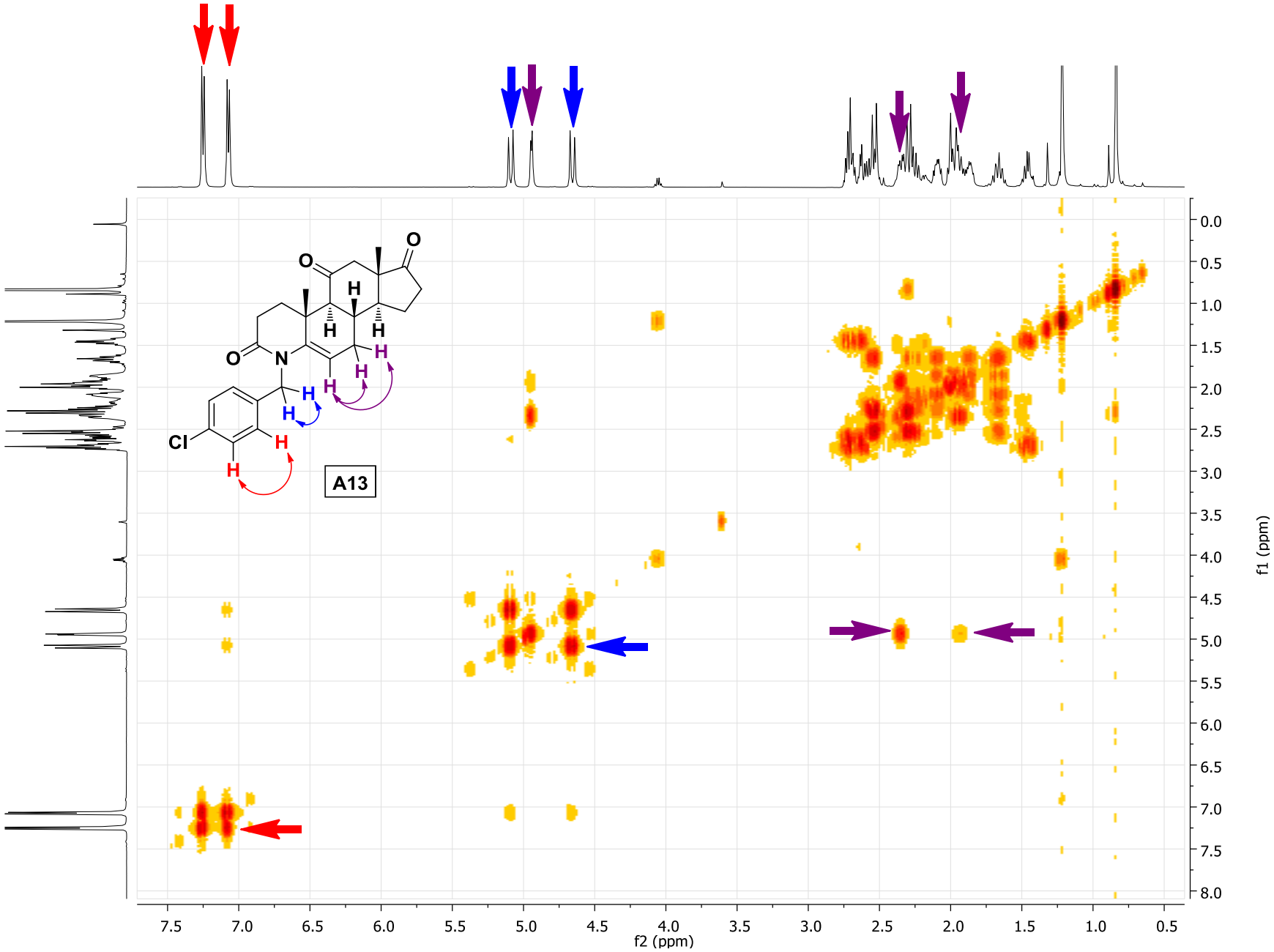
NMR29



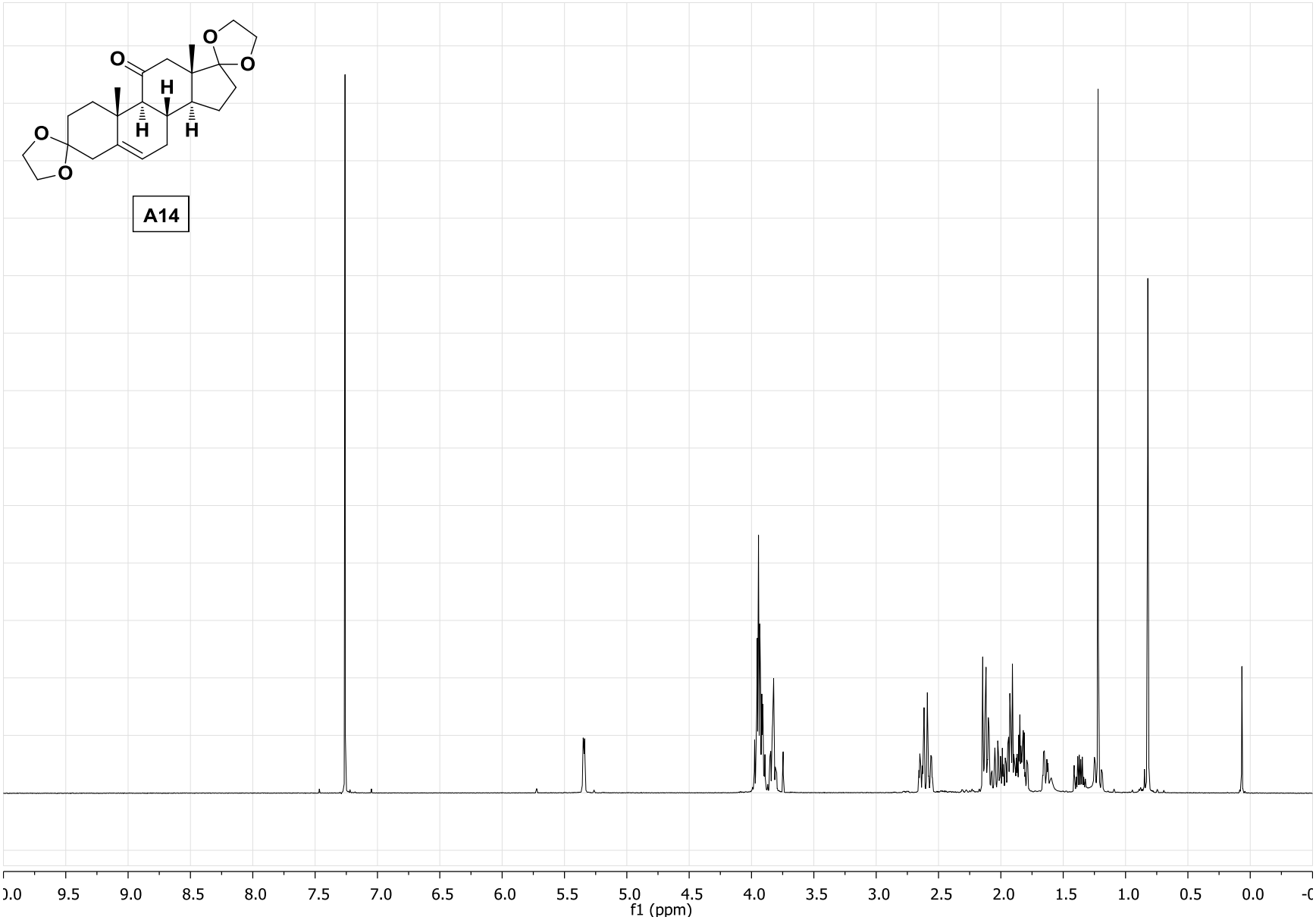

NMR30


O
O
H
H
H
O
N
Cl
A13
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

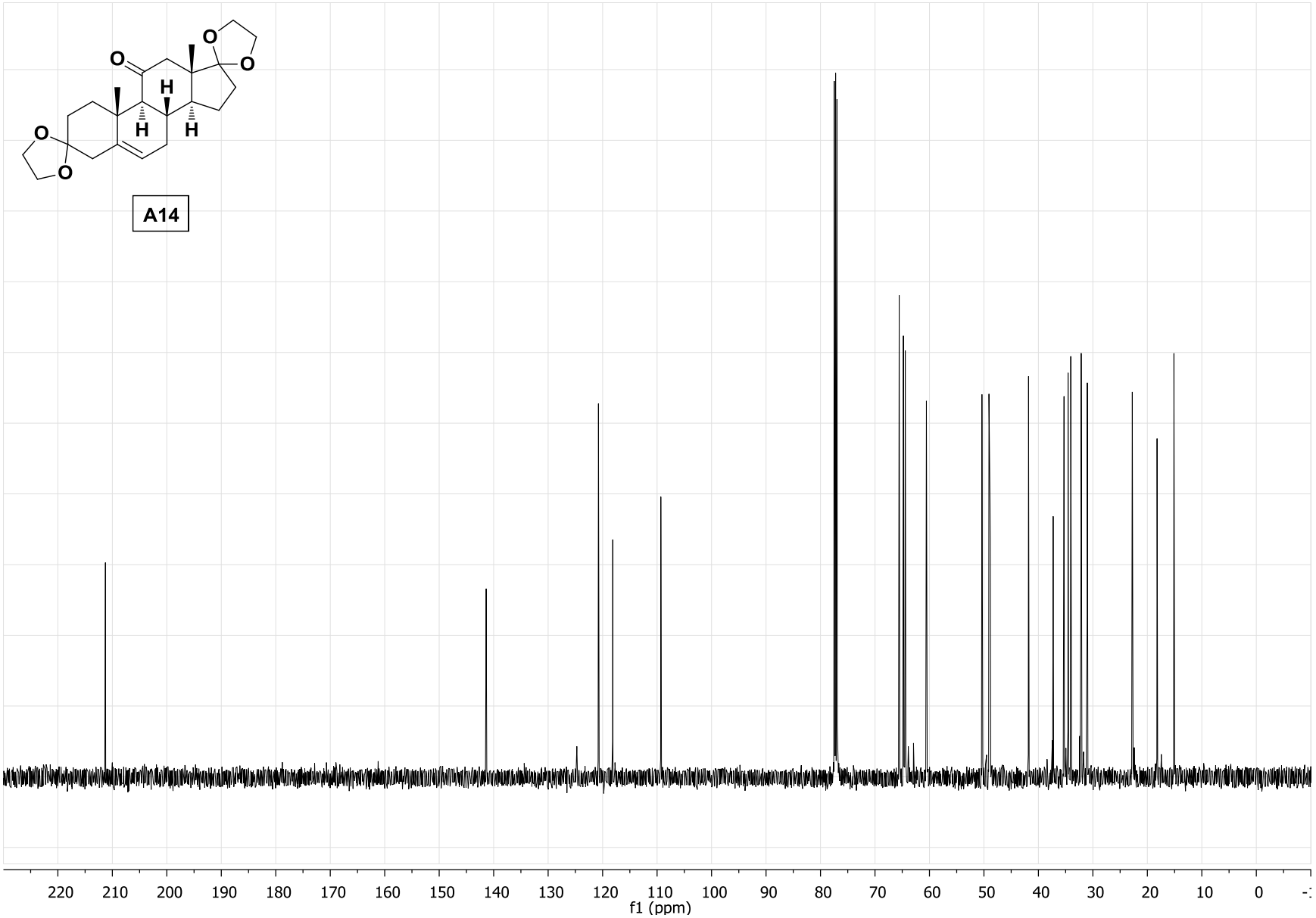
NMR31



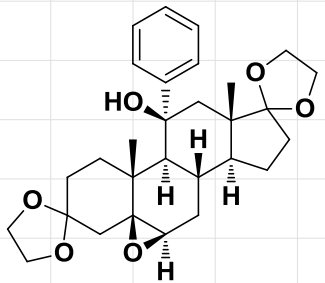

NMR32




NMR33

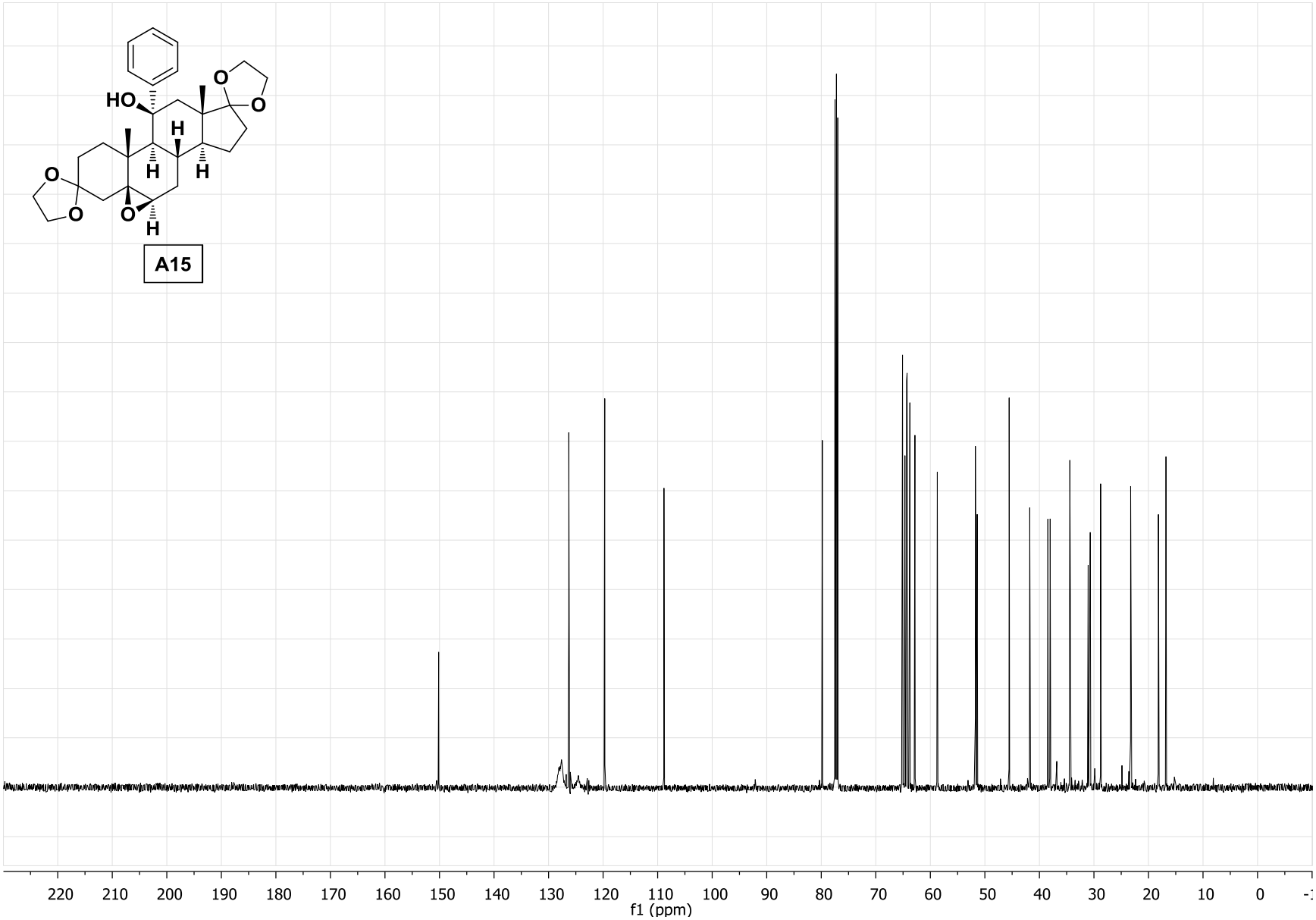

O
O
O
O
H
H
H
O
O
A14
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

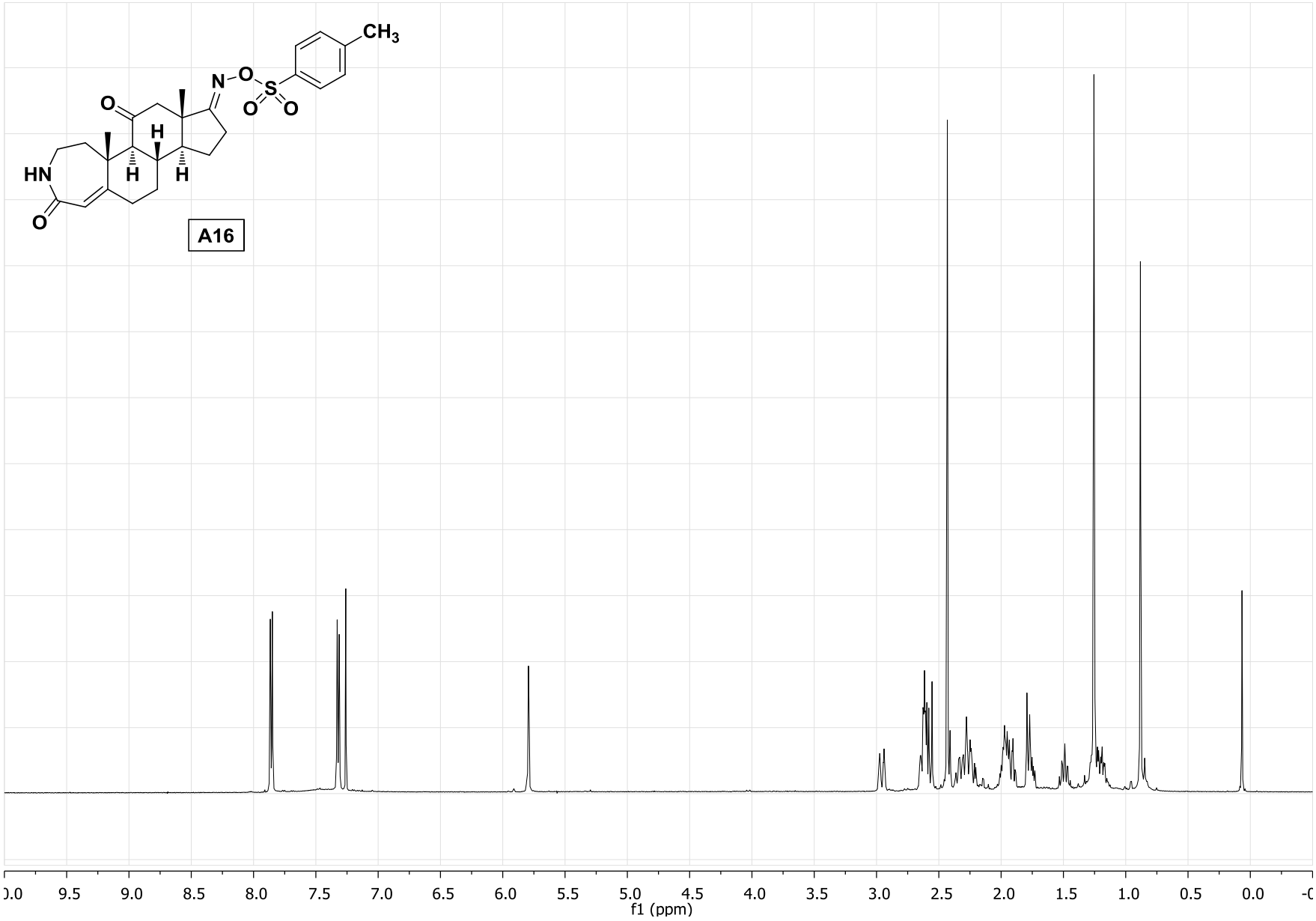
NMR34

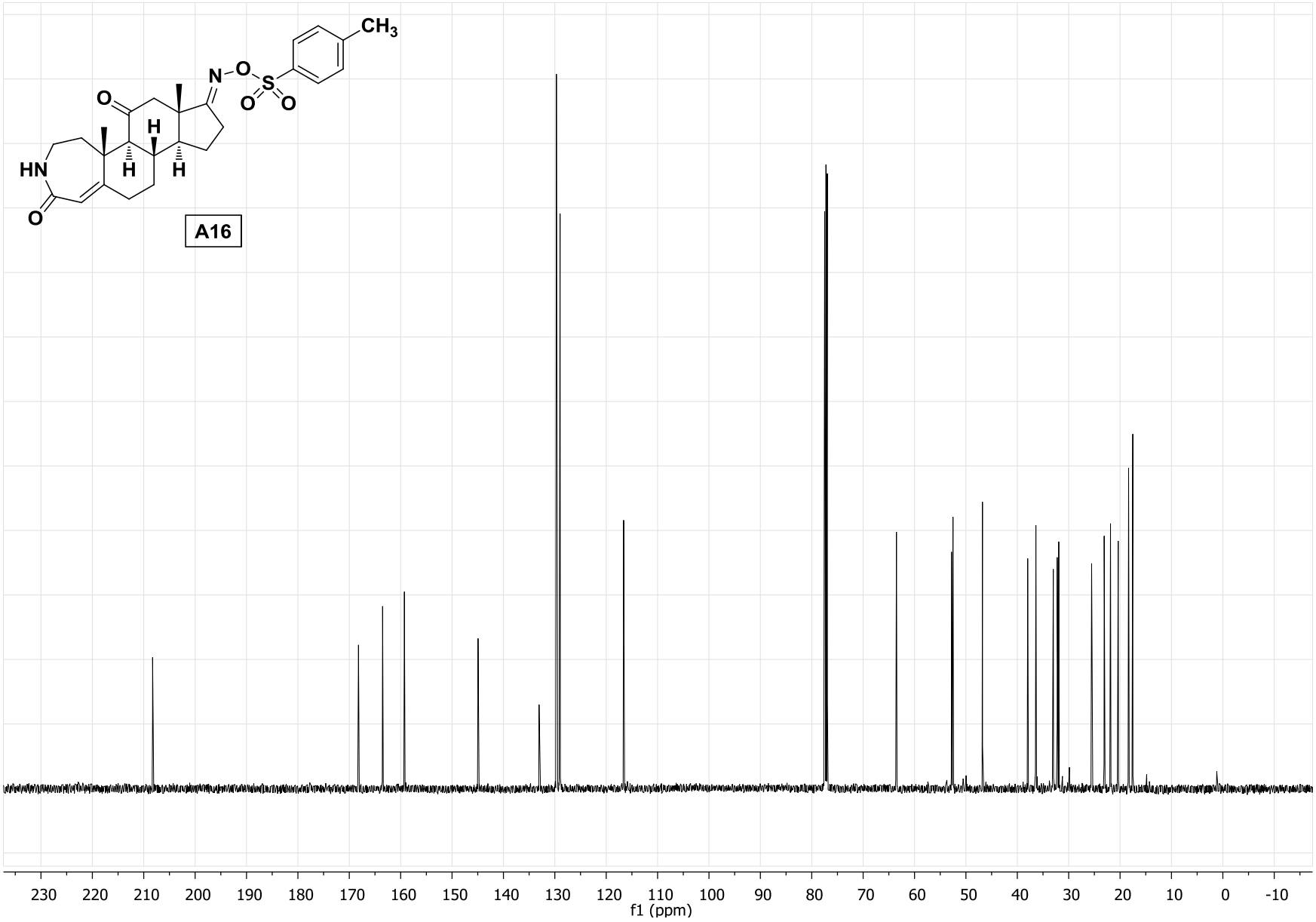

HO
O
O
H
H
H
O
O
O
H

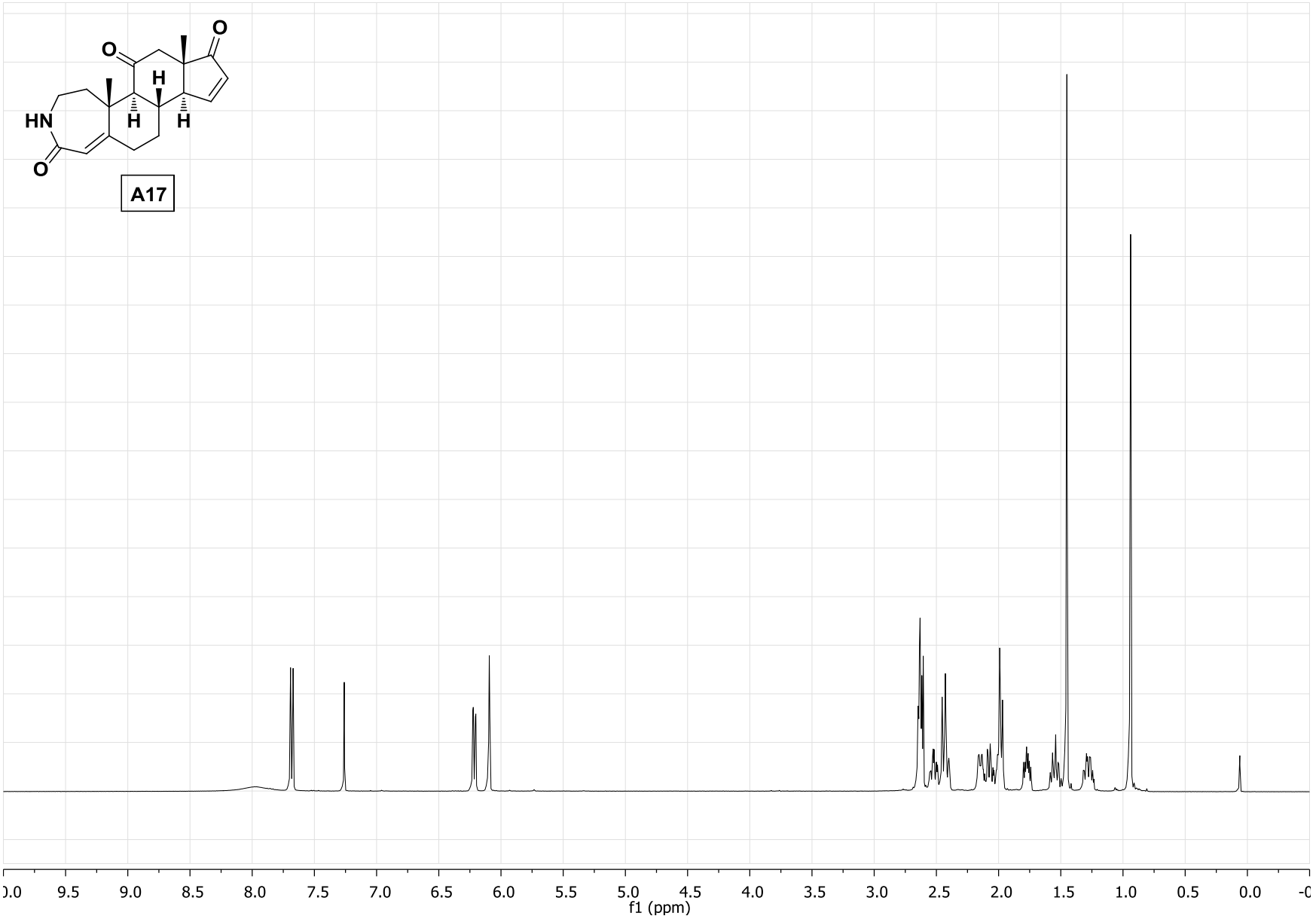
A15

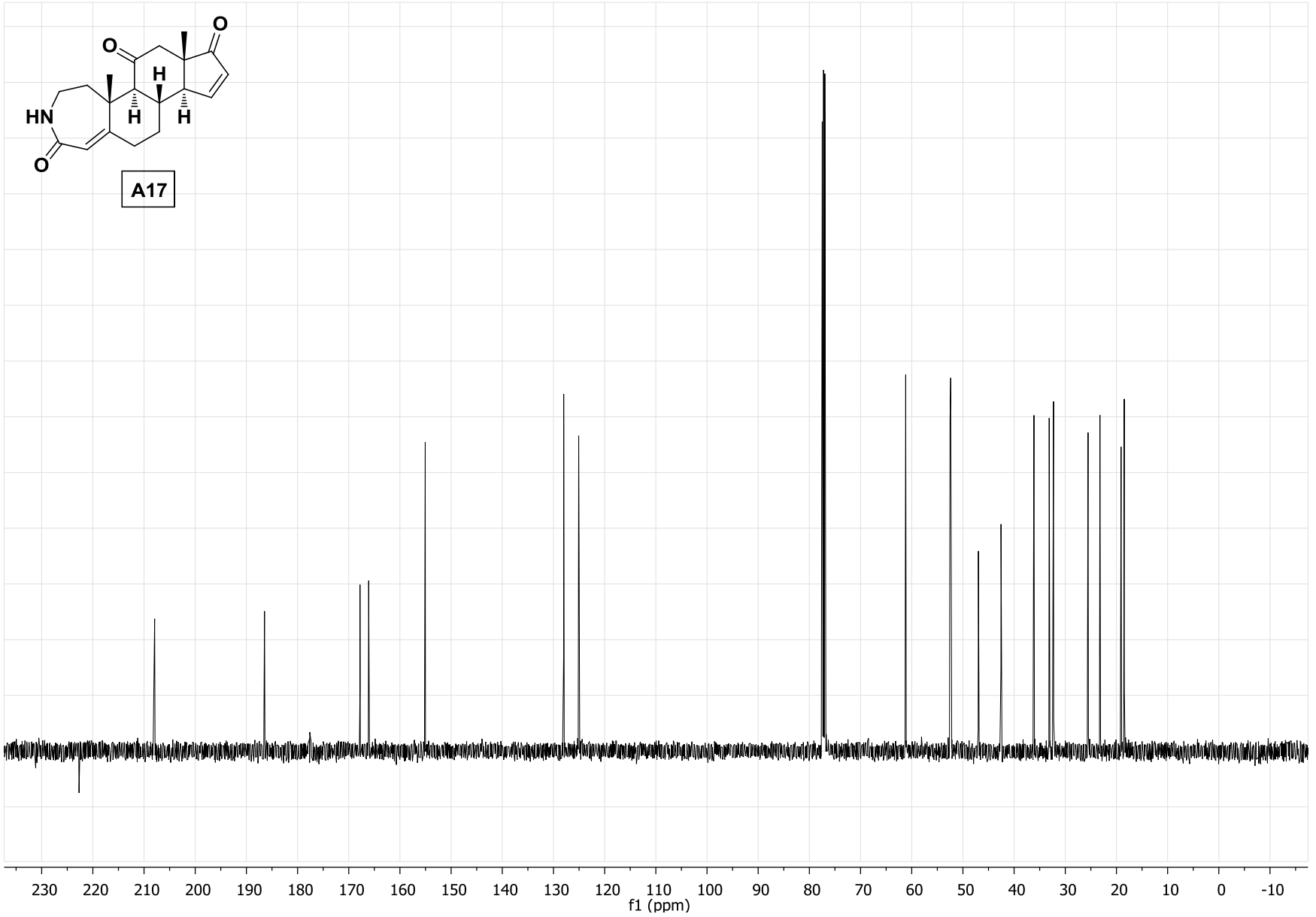

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

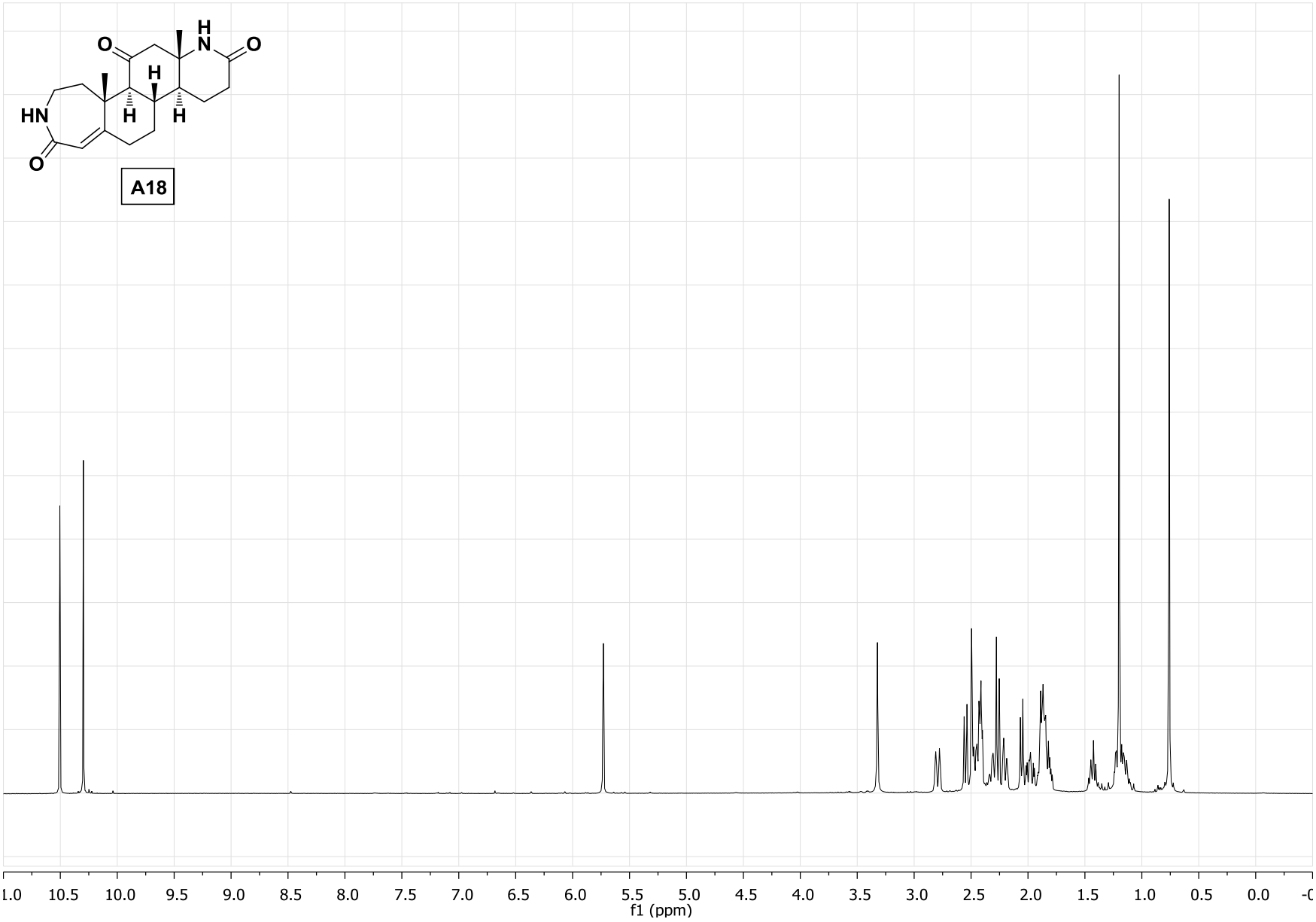

HO
O
O
H
H
H
O
O
O
H
A15
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CH3
N
O
S
O
O
O
H
HN
H
H
O
A16
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

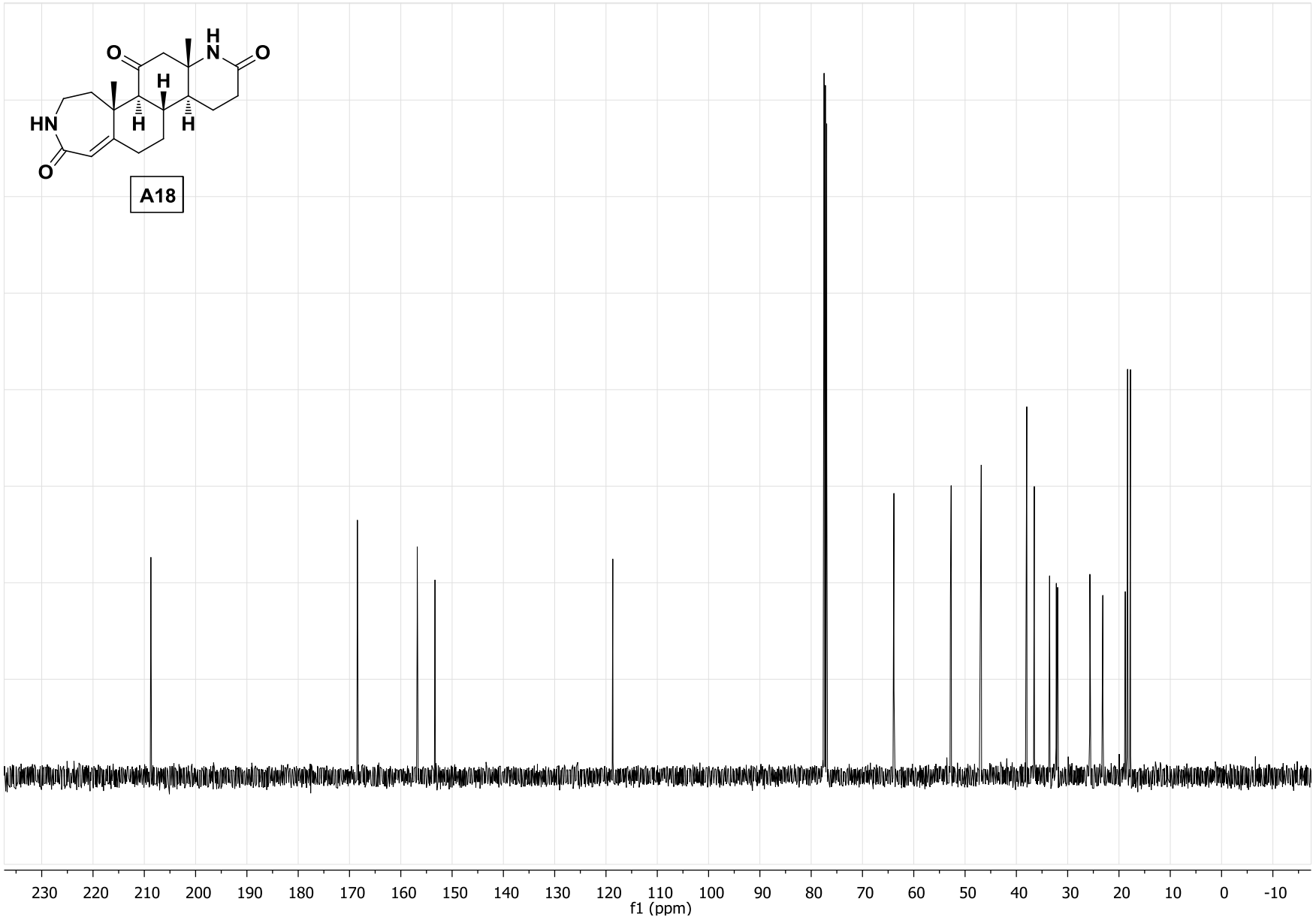

CH3
N
O
S
O
O
O
H
HN
H
H
O
A16
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

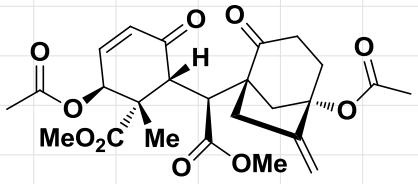

O
O
H
HN
H
H
O
A17
f1 (ppm)


O
O
H
HN
H
H
O
A17
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
H
N
O
H
HN
H
H
O
A18
1.0
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
1.5
1.0
0.5
0.0
f1 (ppm)

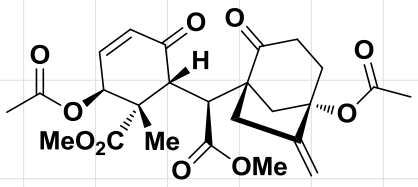
NMR41


O
H
N
O
H
HN
H
H
O
A18
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O
H
O
O
O
O
MeO2C
Me
O
OMe

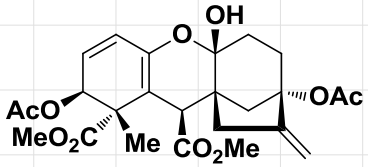
G1


0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
O
H
O
O
O
O
MeO2C
Me
O
OMe

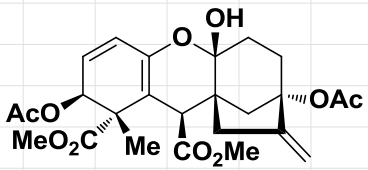
G1


30
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OH
O
AcO
OAc
MeO2C
Me
CO2Me

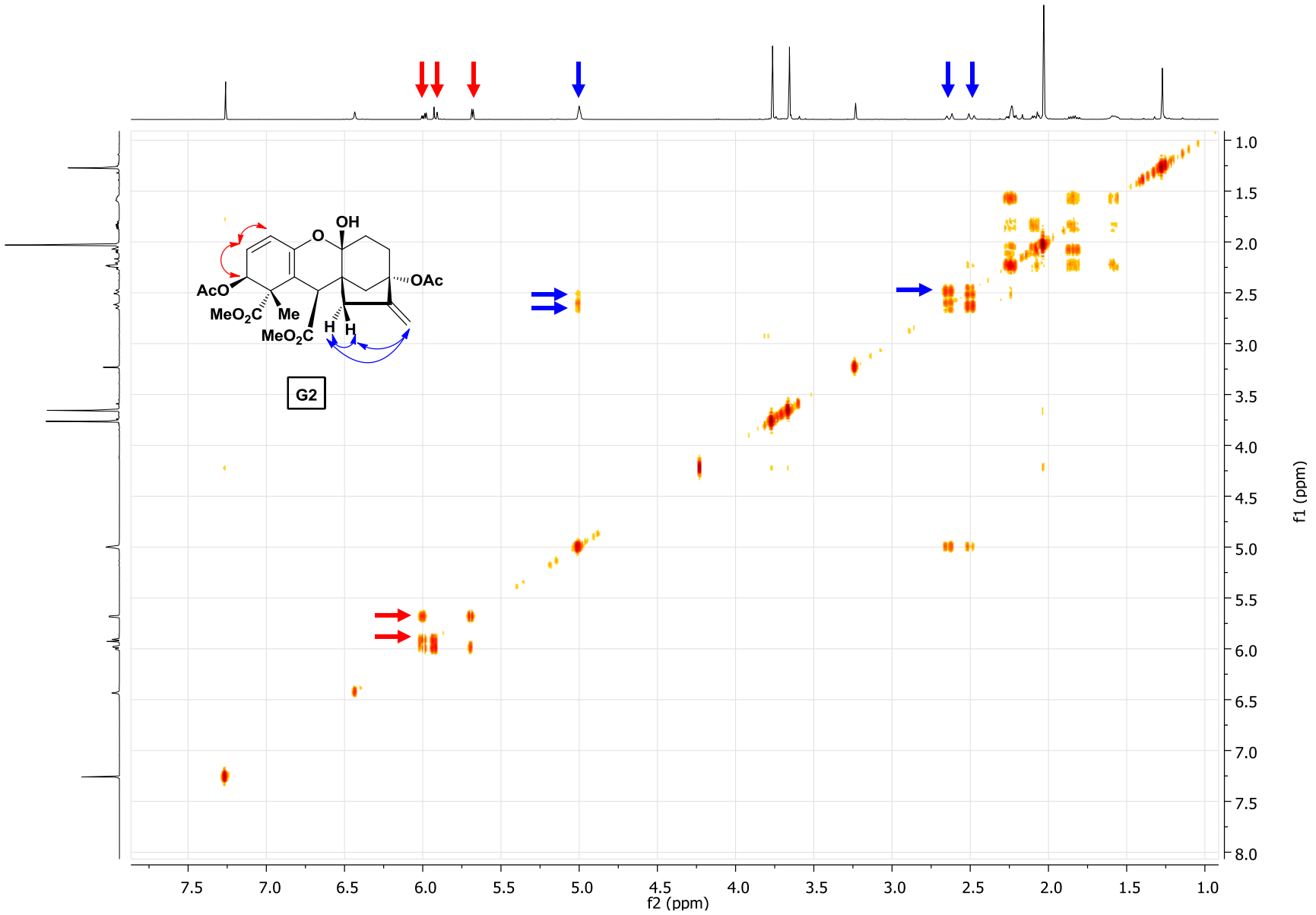
G2


0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

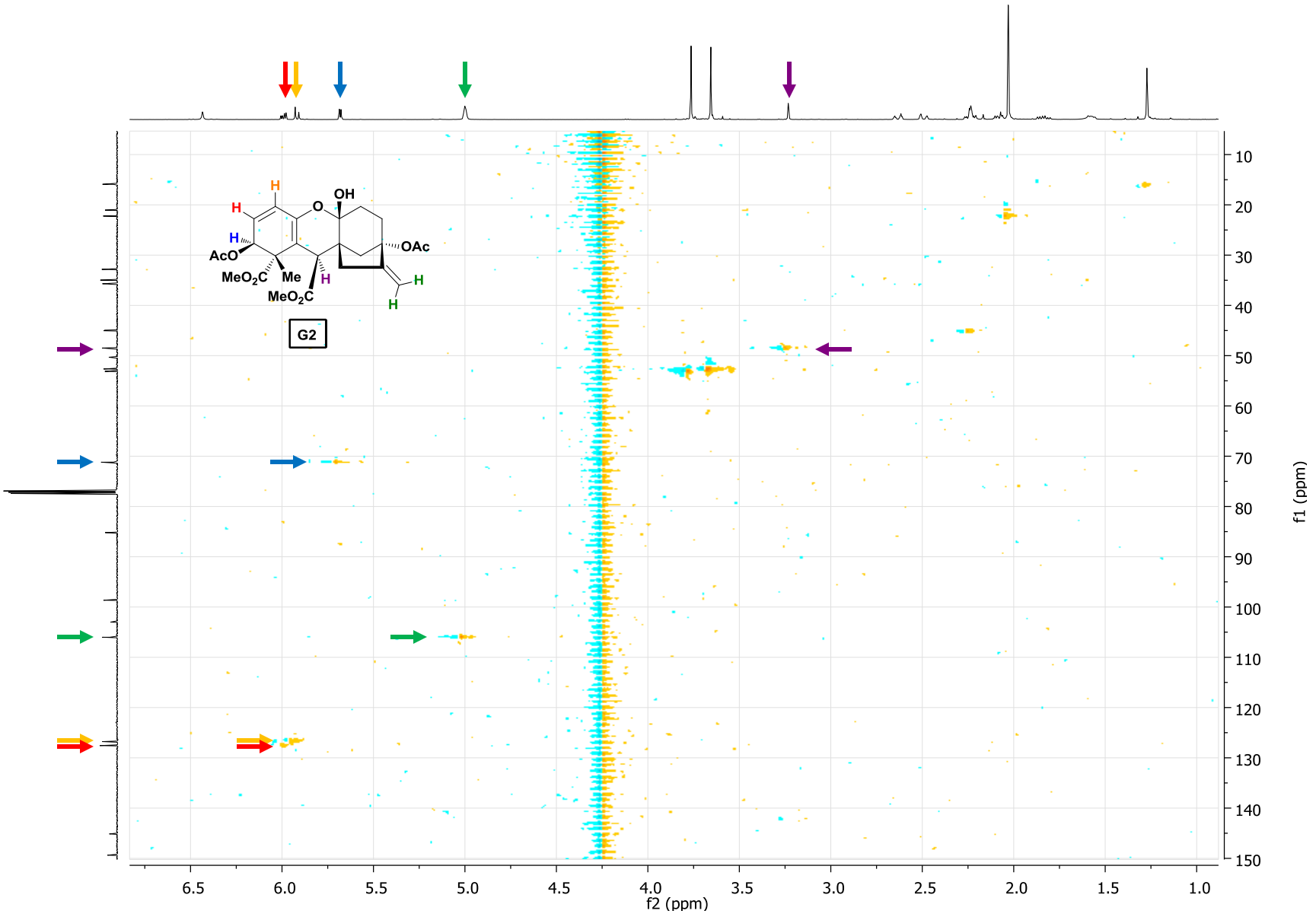

OH
O
AcO
OAc
MeO2C
Me
CO2Me

G2

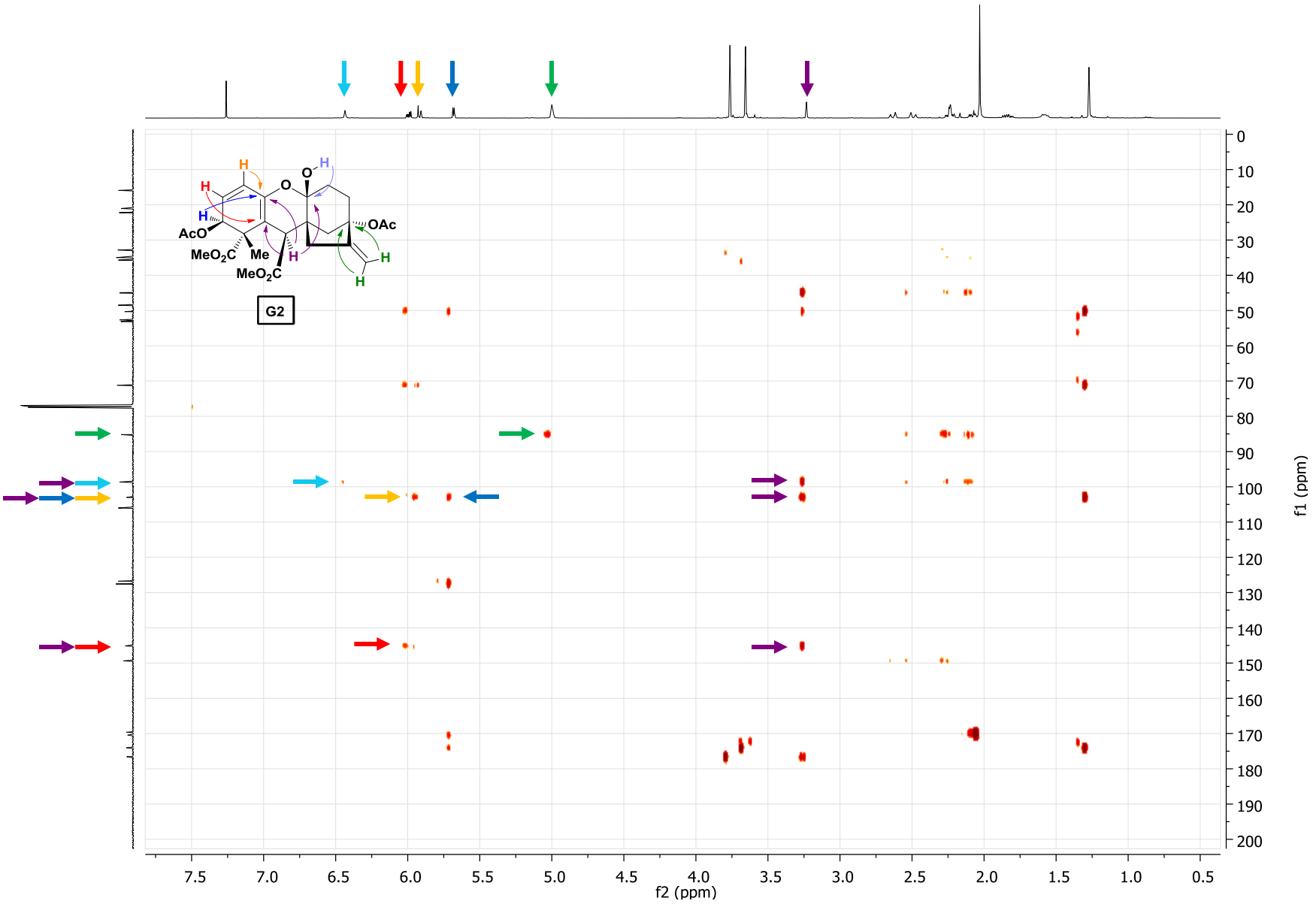

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OH
O
AcO
OAc
MeO2C
Me
MeO2C
H
H
G2
f2 (ppm)
f1 (ppm)
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

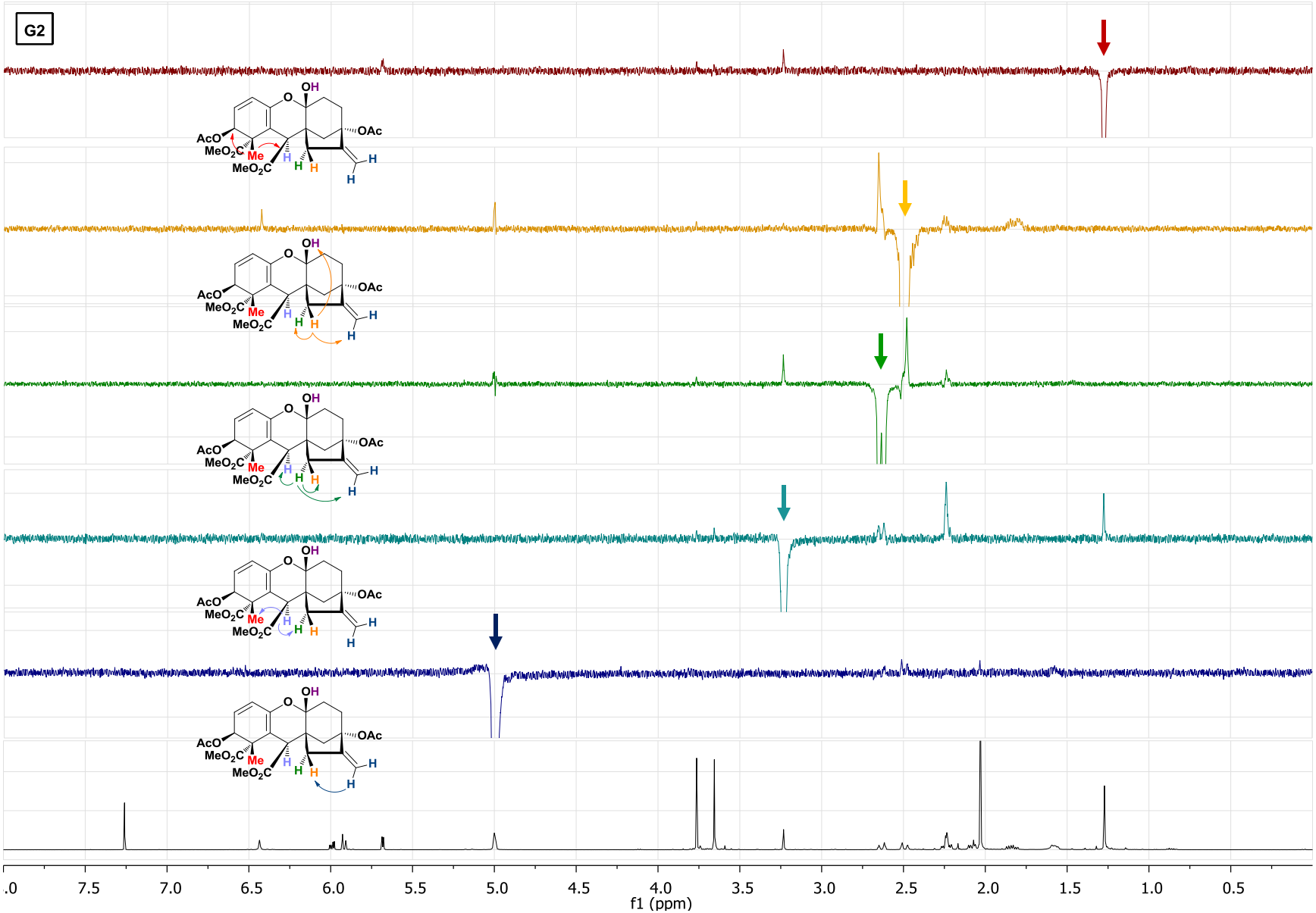
NMR47


H
H
O
OH
H
AcO
OAc
MeO2C
Me
H
MeO2C
H
H
G2
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)

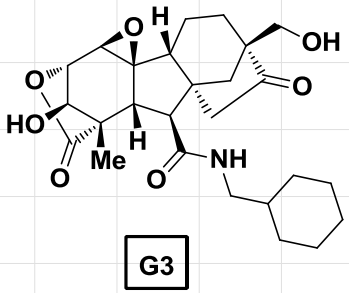
NMR48




NMR49


G2
OH
O
AcO
OAc
MeO2C
Me
MeO2C
H
H
H
H
H
f1 (ppm)
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

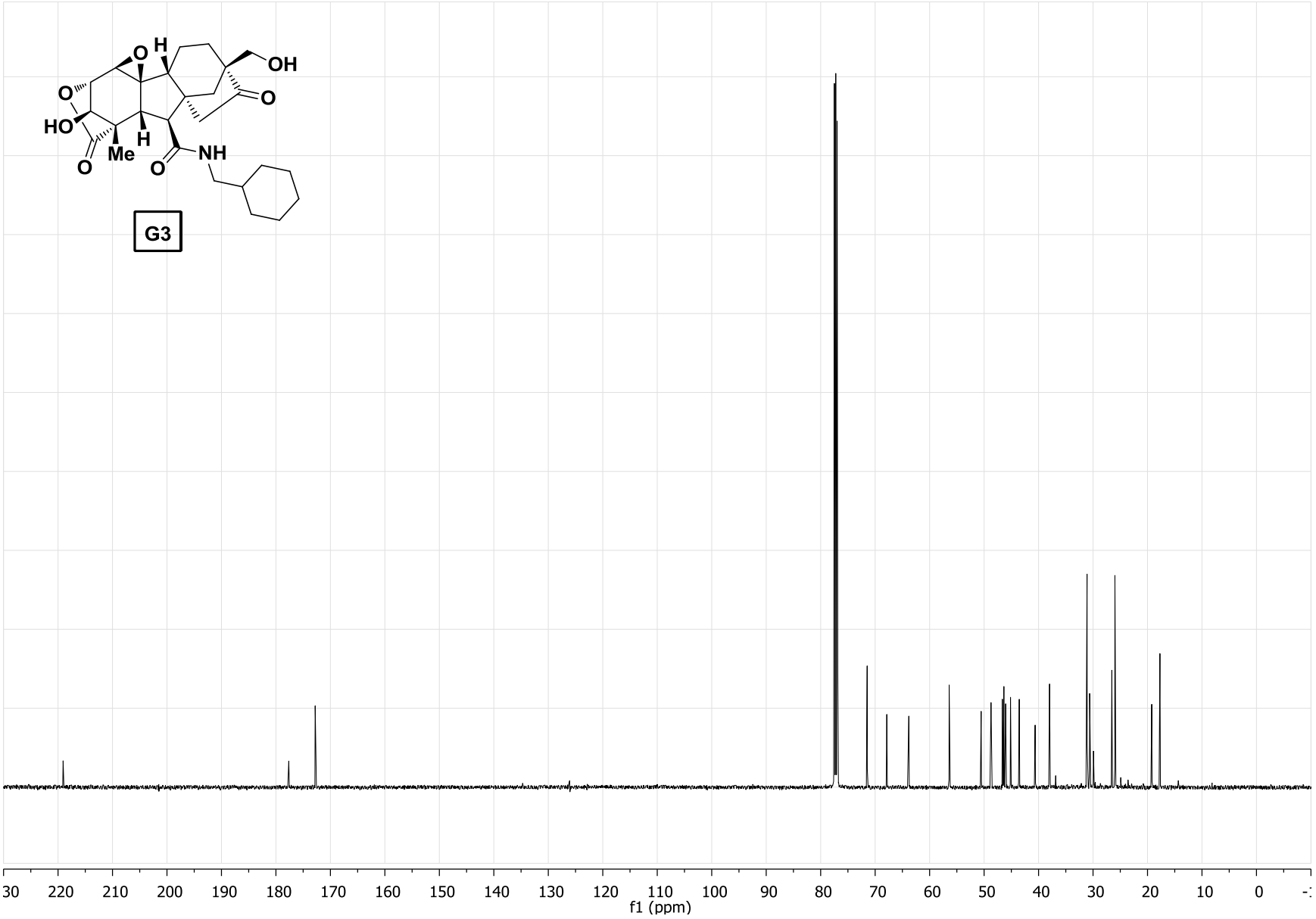
NMR50

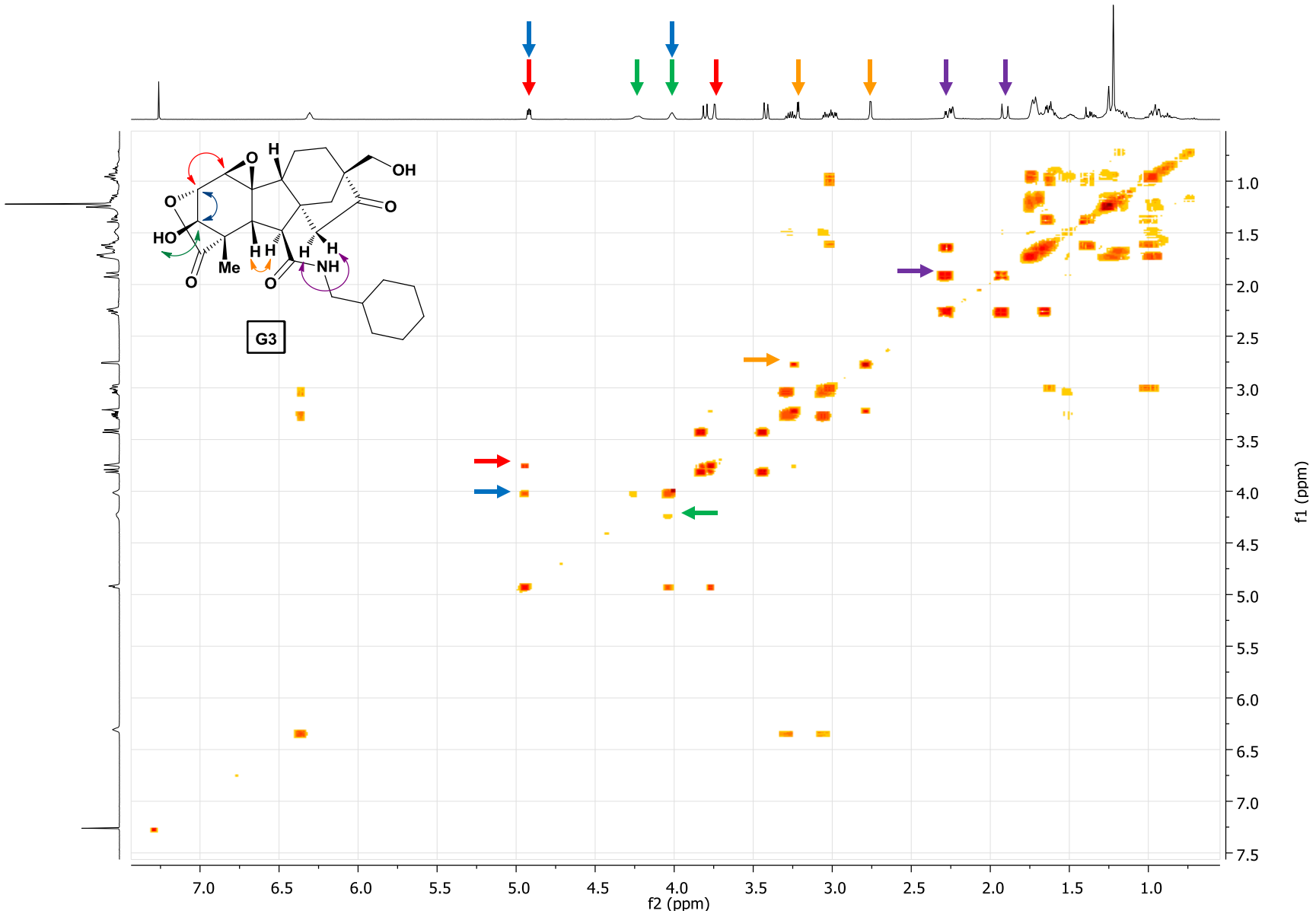



G3

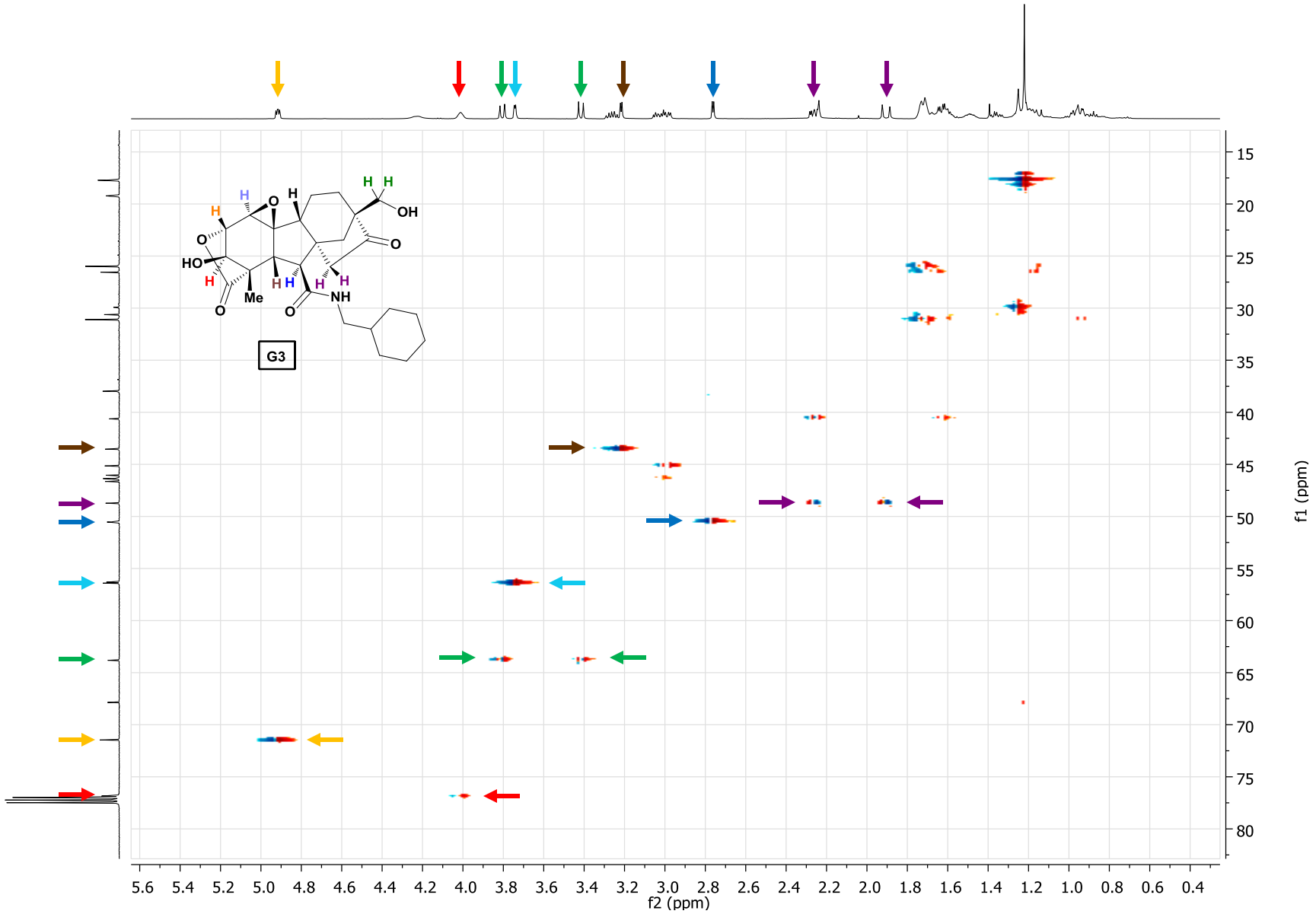



NMR51

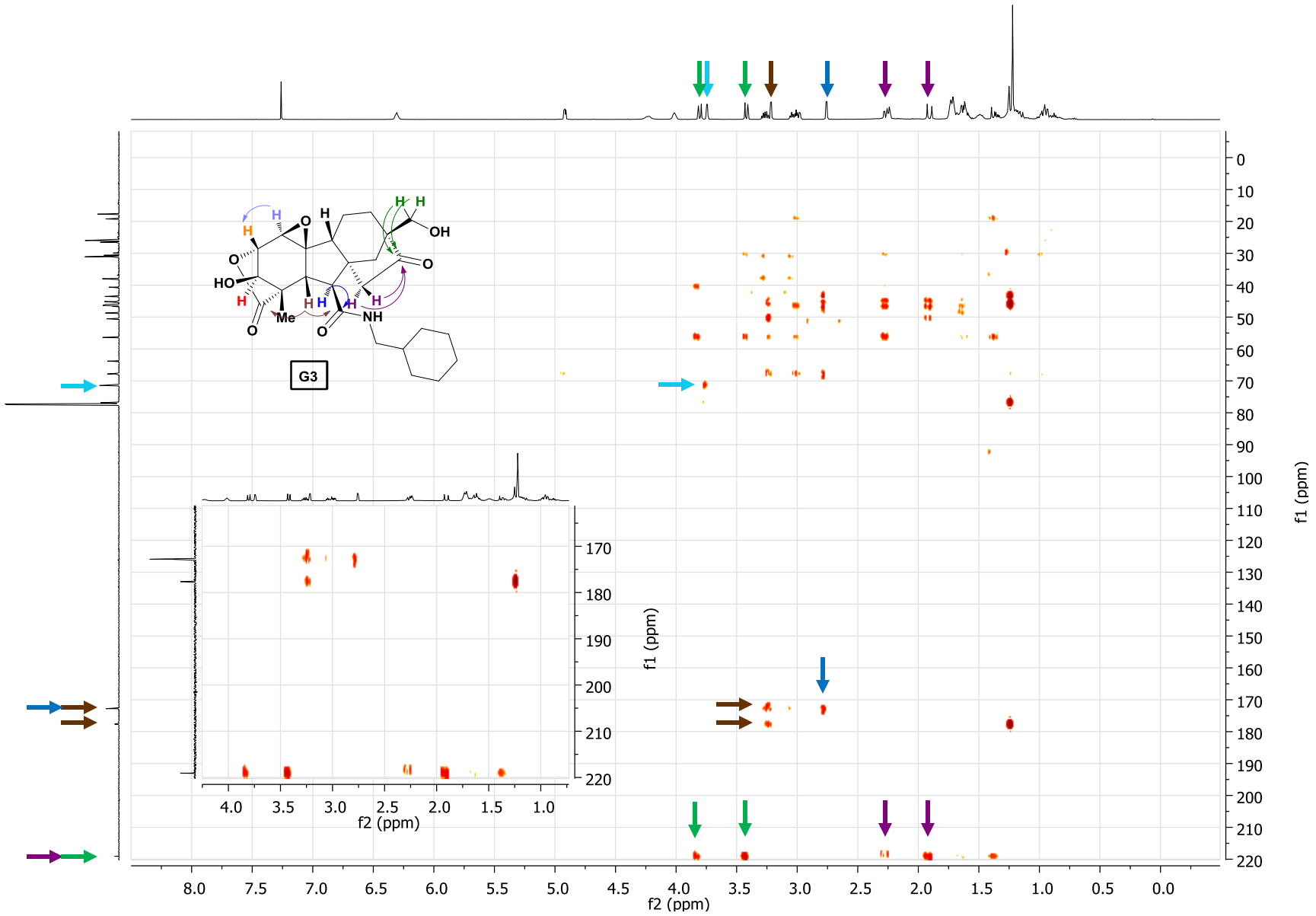

O
H
OH
O
HO
H
Me
O
O
NH
G3
30
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
H
OH
O
O
HO
H H
H
H
Me
O
NH
G3
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
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)

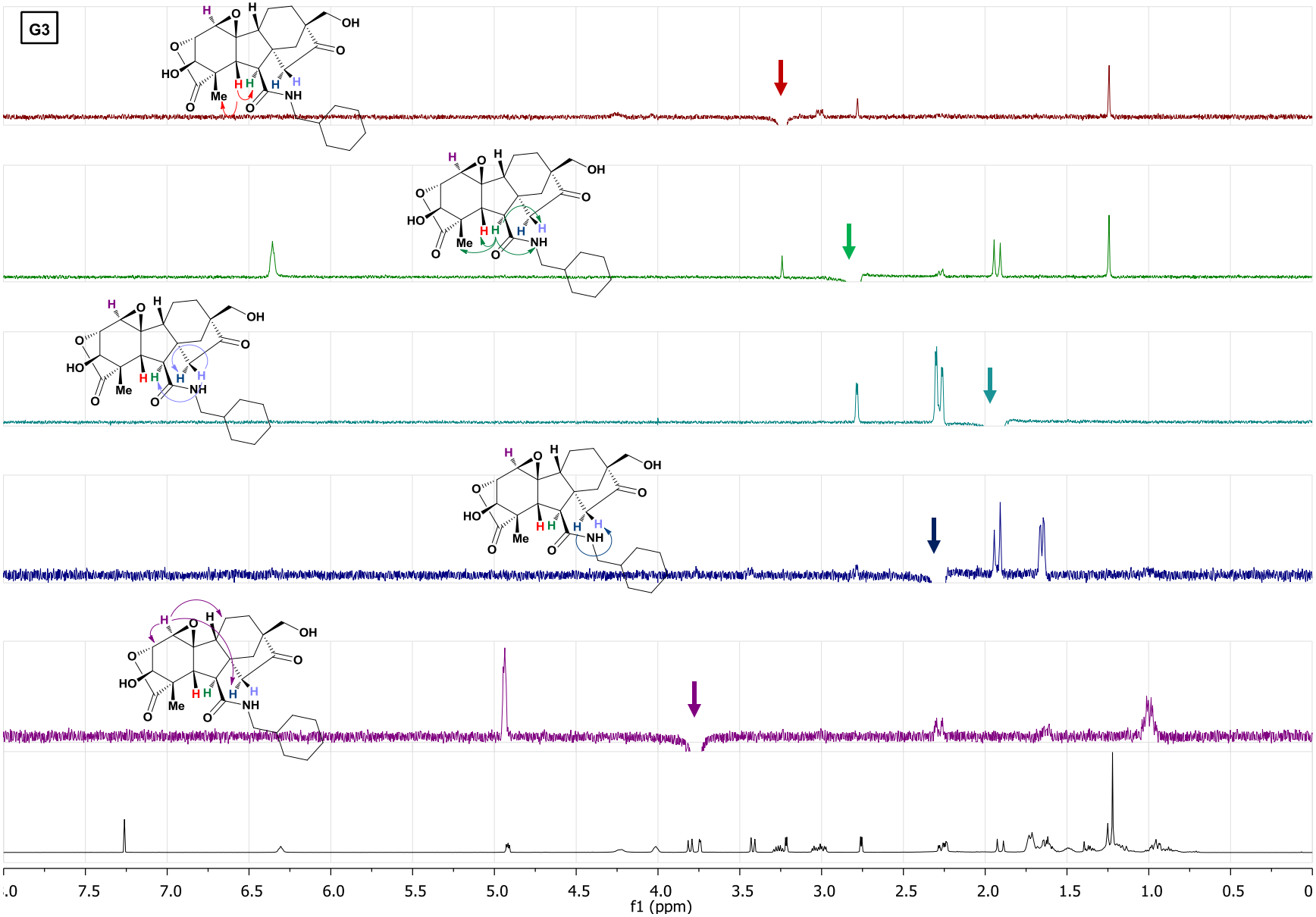
NMR53



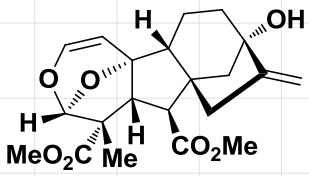

NMR54




NMR55

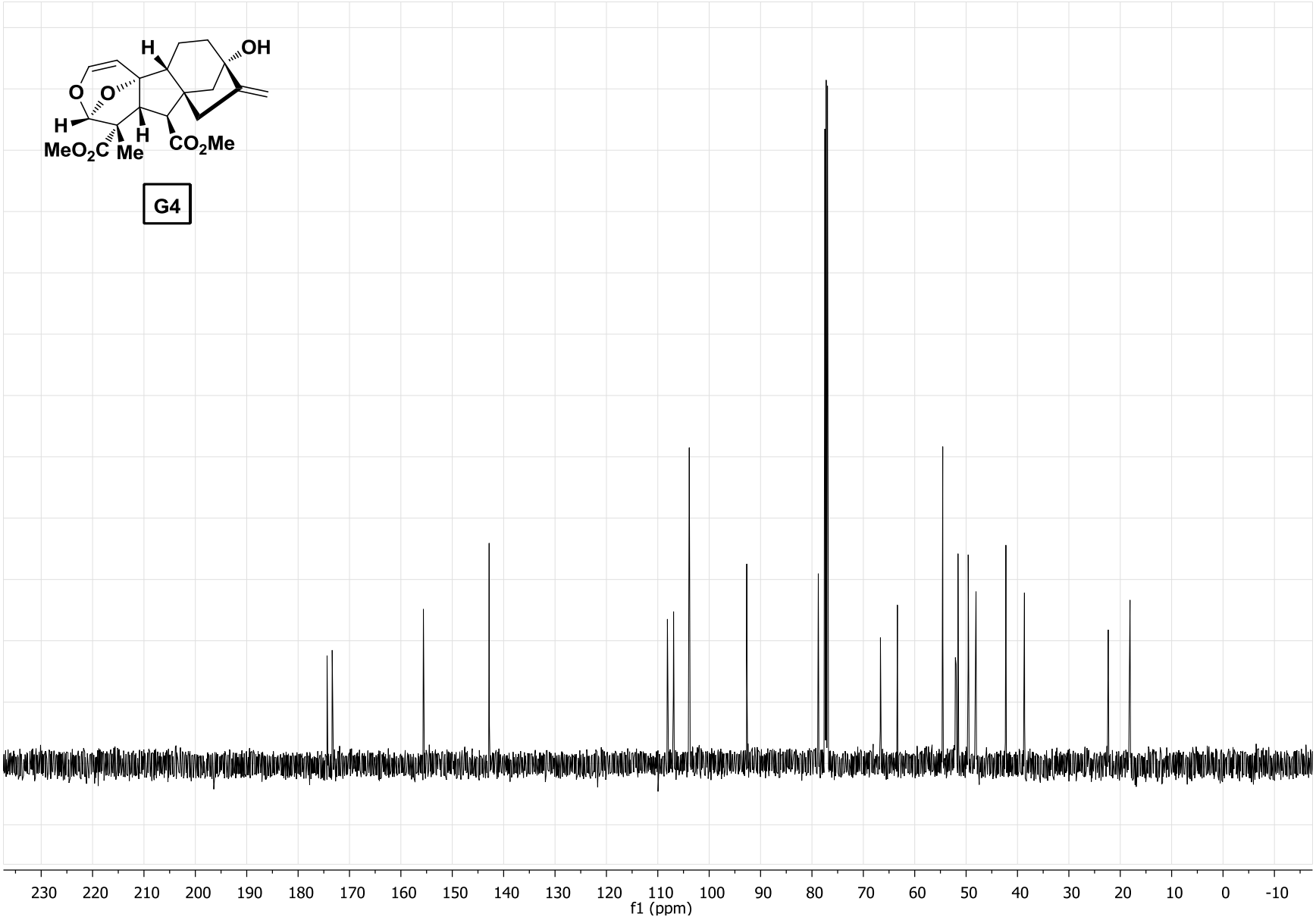



NMR56

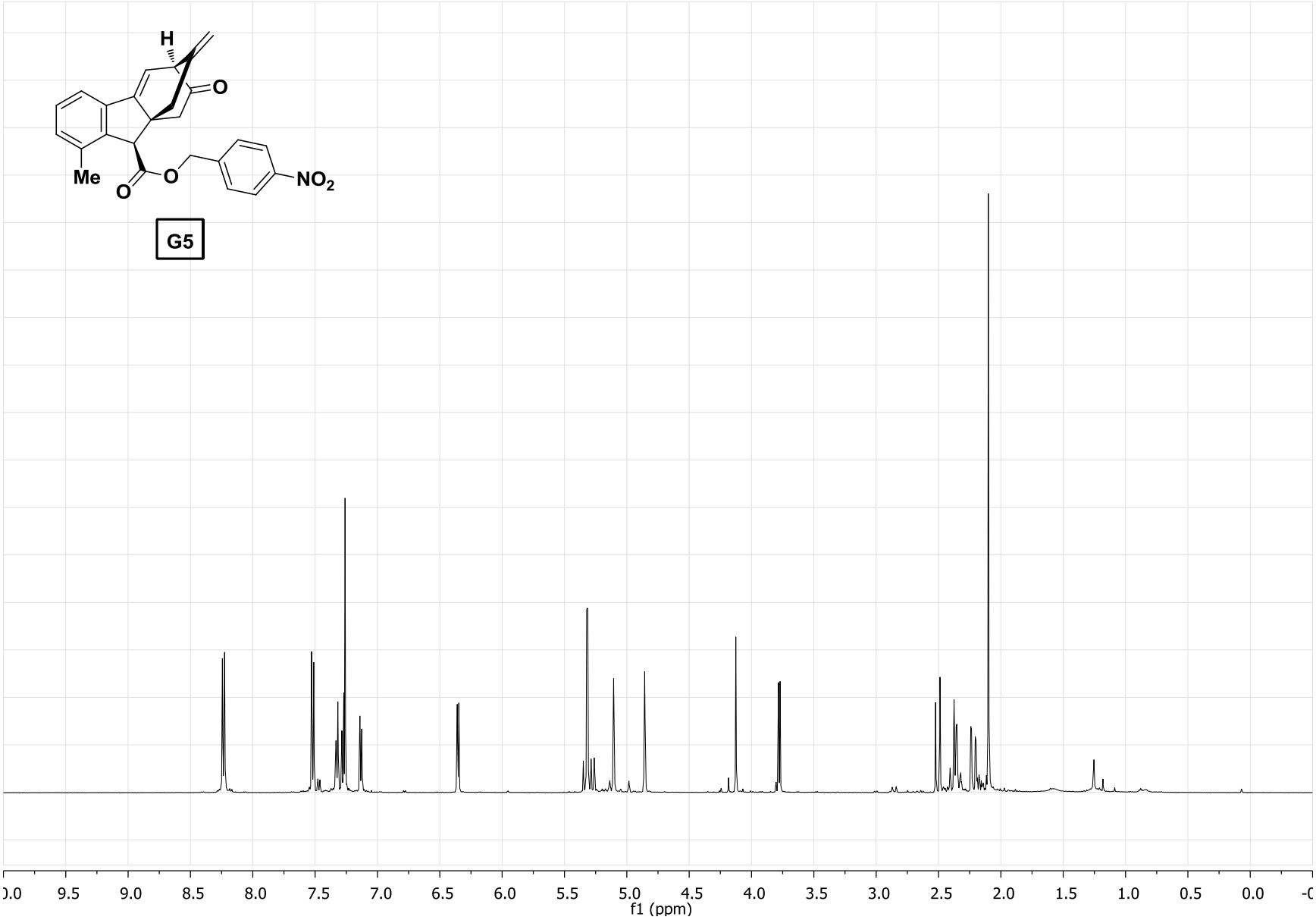

H
OH
O
O
H
H
MeO2C
Me
CO2Me

G4

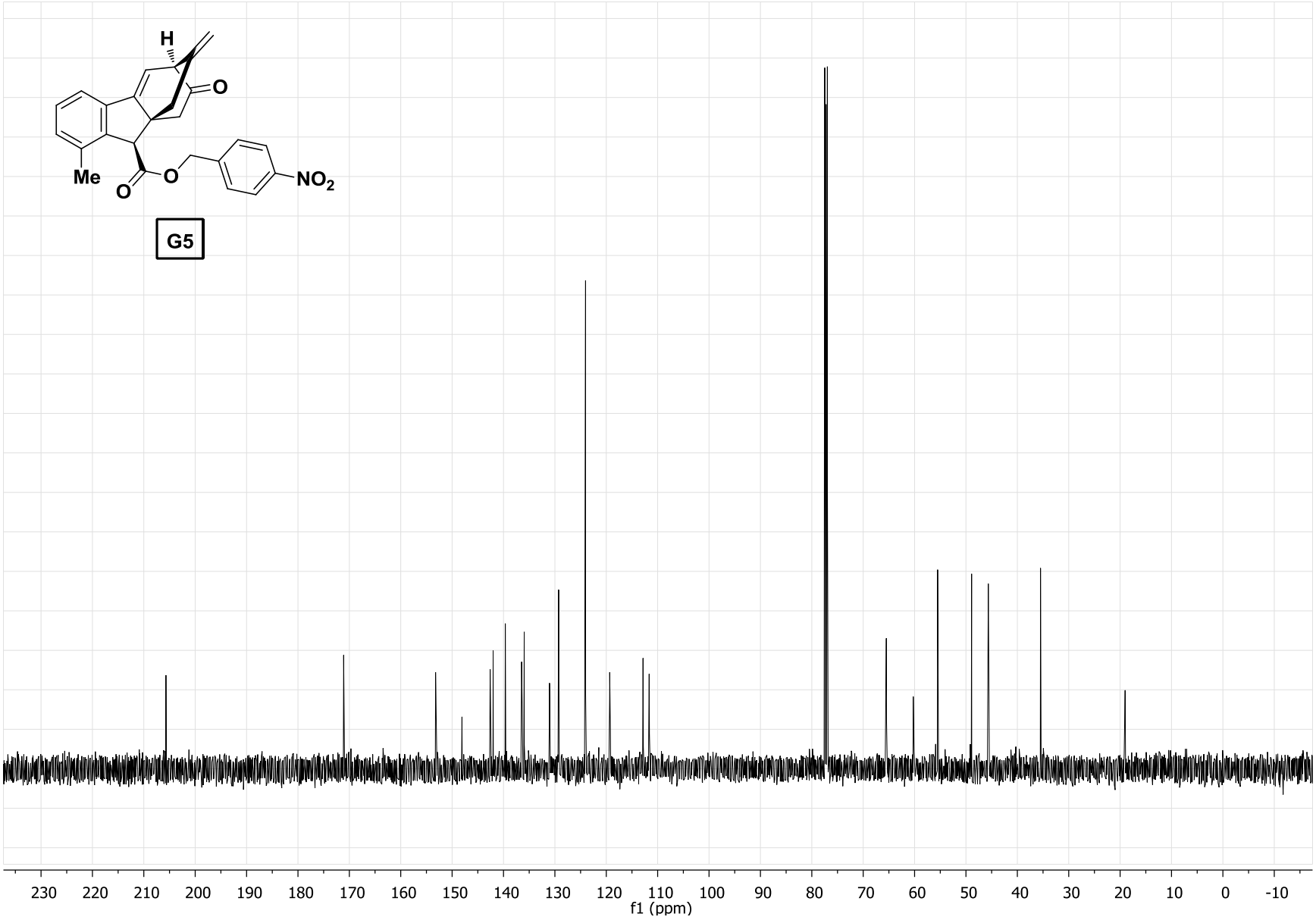

0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


H
OH
O
O
H
H
MeO2C
Me
CO2Me
G4
230
220
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)

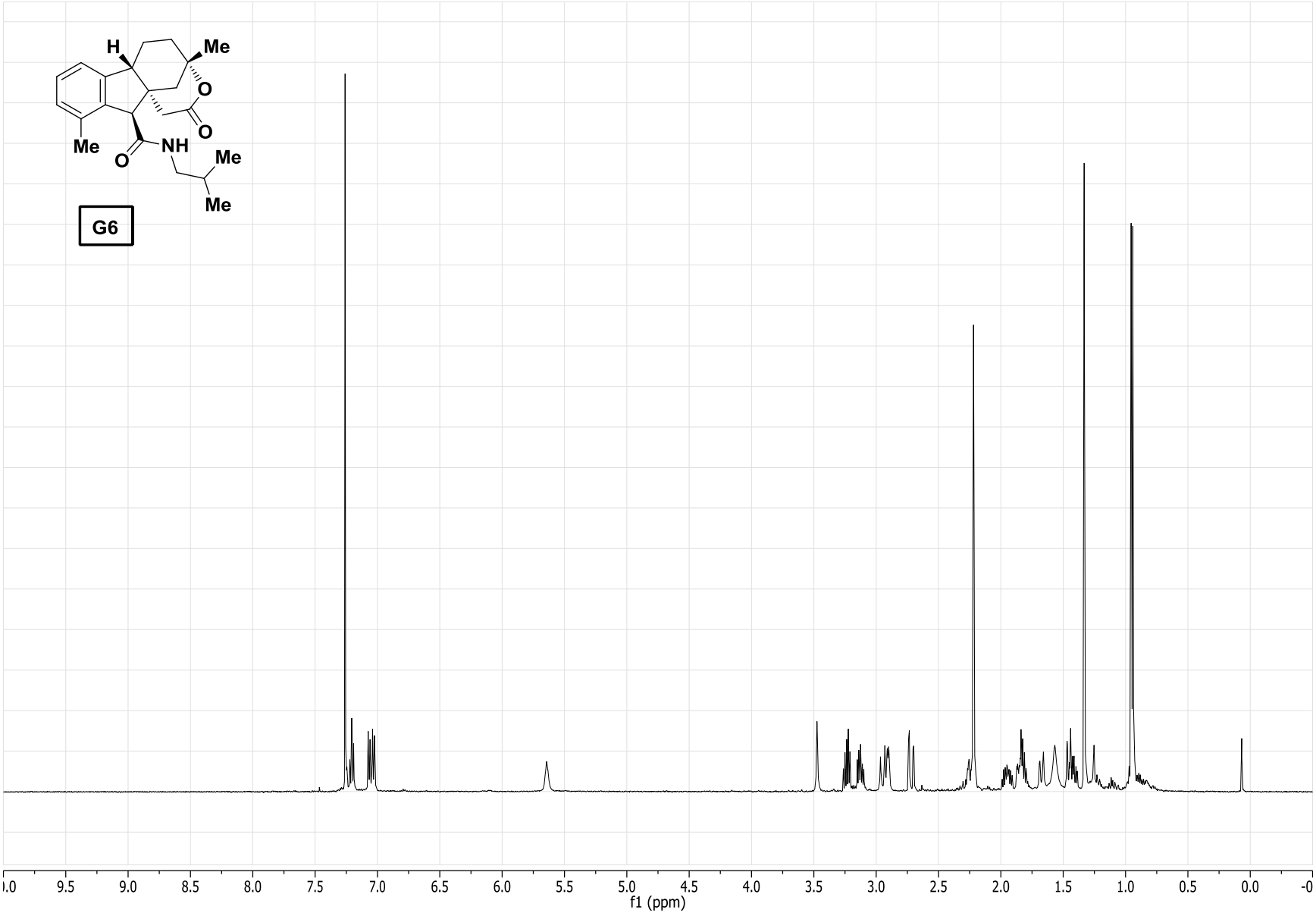
NMR58


H
O
Me
O
O
NO2
G5
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

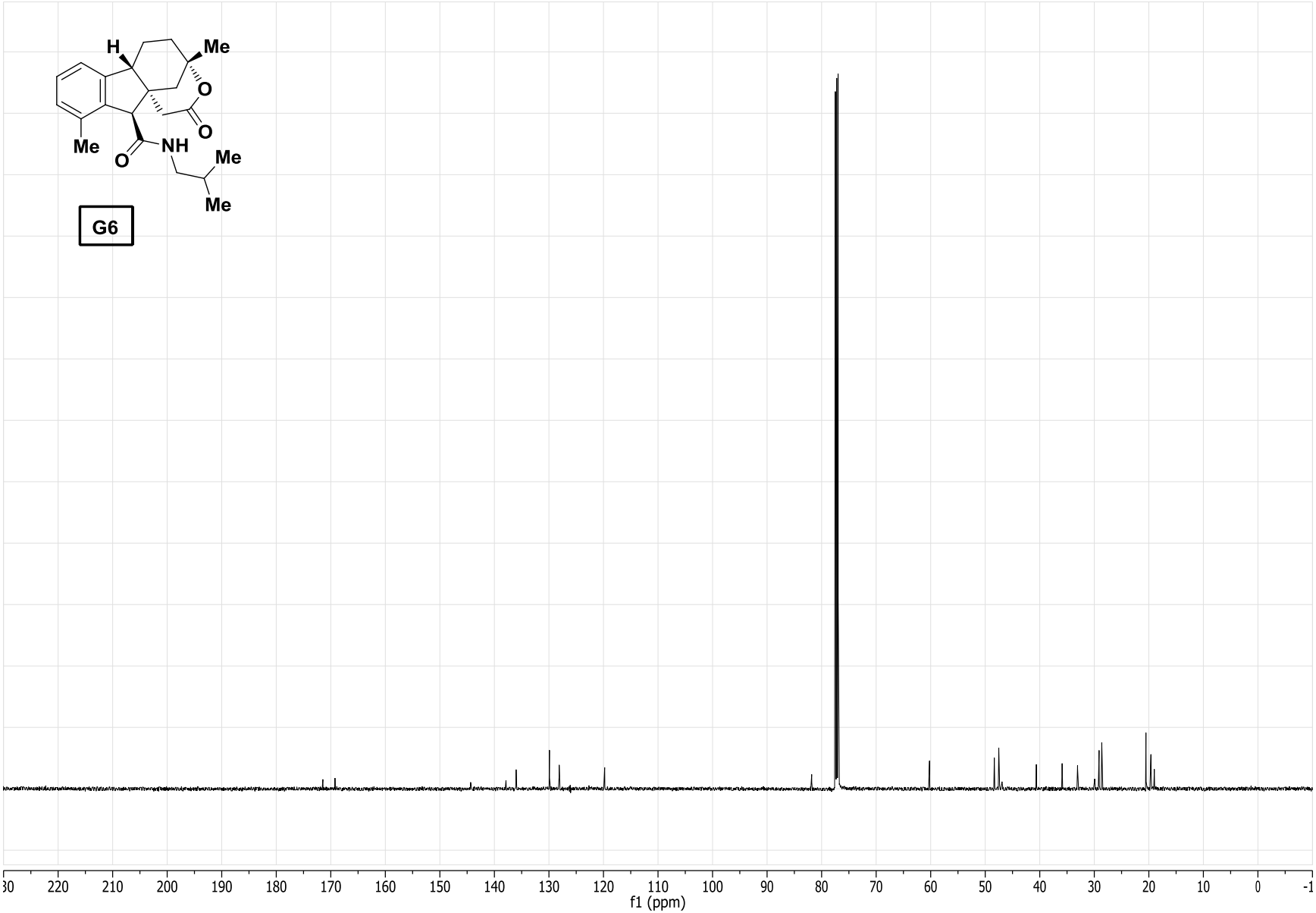
NMR59

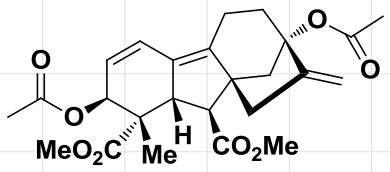

H
O
Me
O
O
NO2
G5
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

NMR60


H
Me
O
O
Me
NH
Me
O
Me
G6
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

NMR61

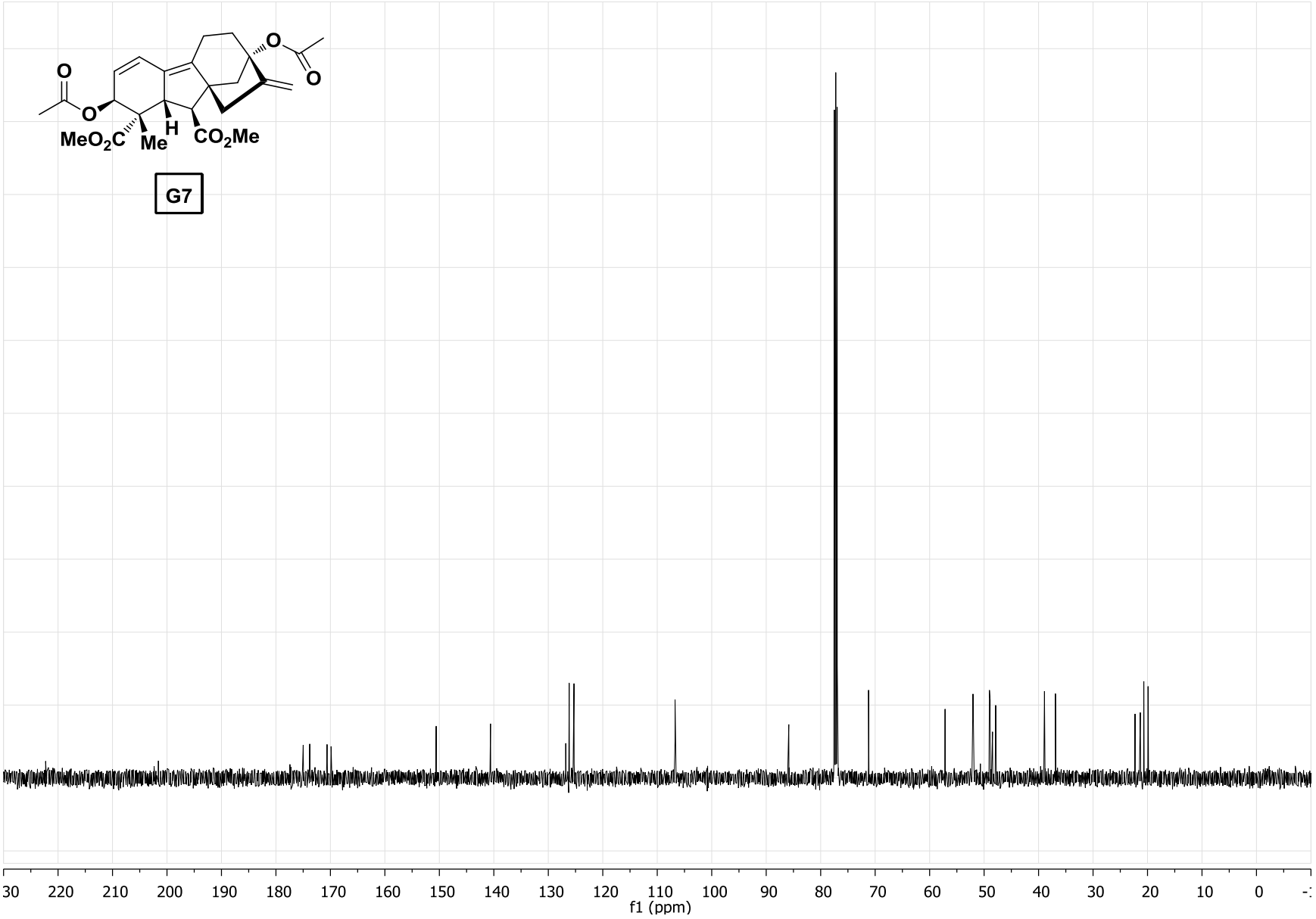

H
Me
O
O
Me
O
NH
Me
Me
G6
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
O
O
O
MeO2C
Me
H
CO2Me

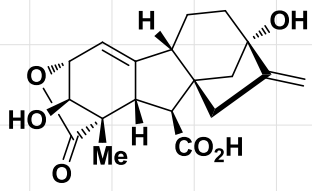
G7


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

NMR63


O
O
MeO2C
Me
H
CO2Me
O
O
G7
30
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

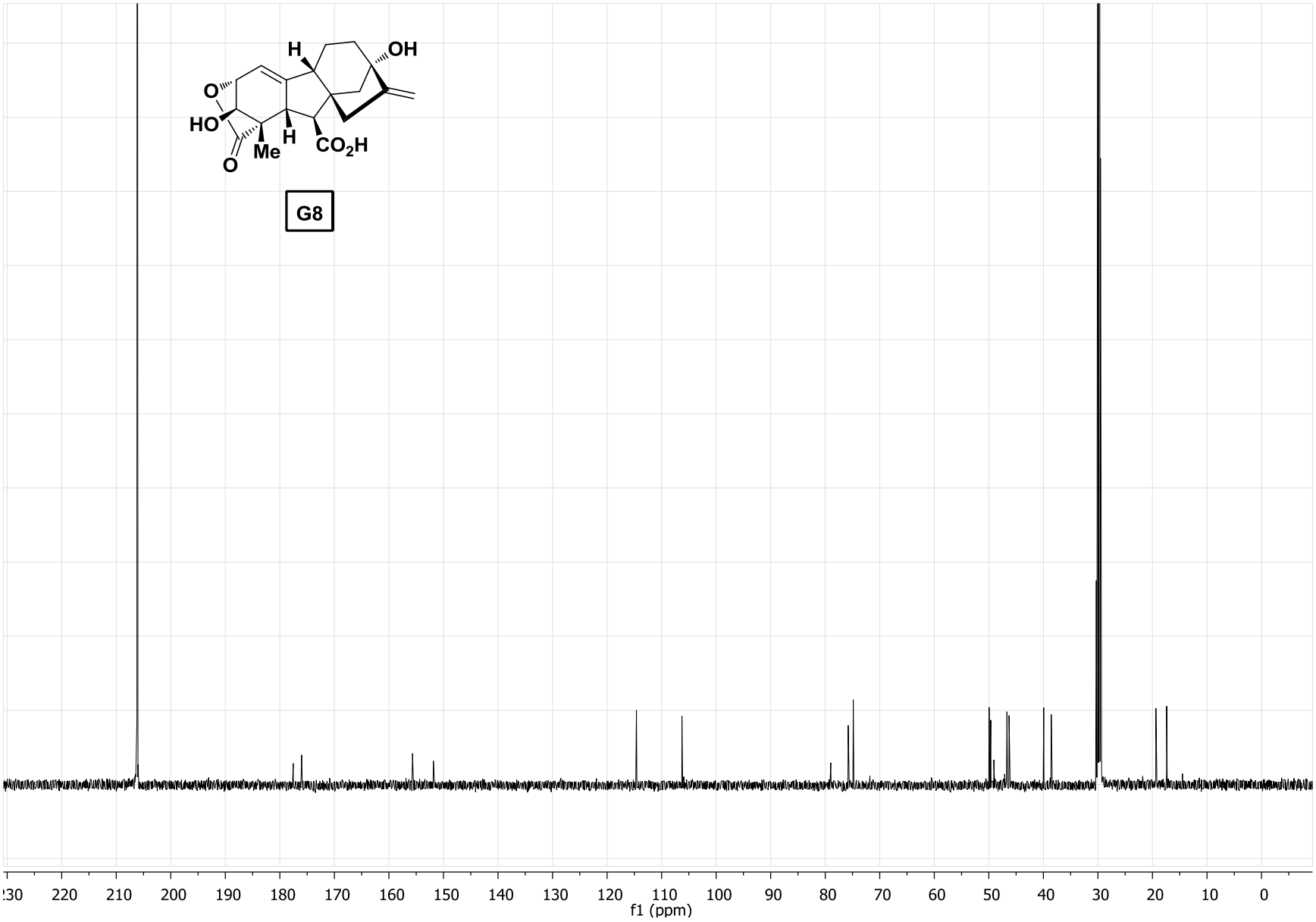
NMR64


H
OH
O
HO
H
Me
CO2H
O

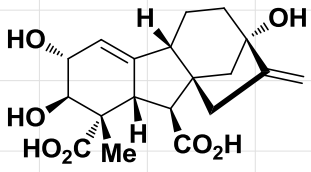
**G8**


0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

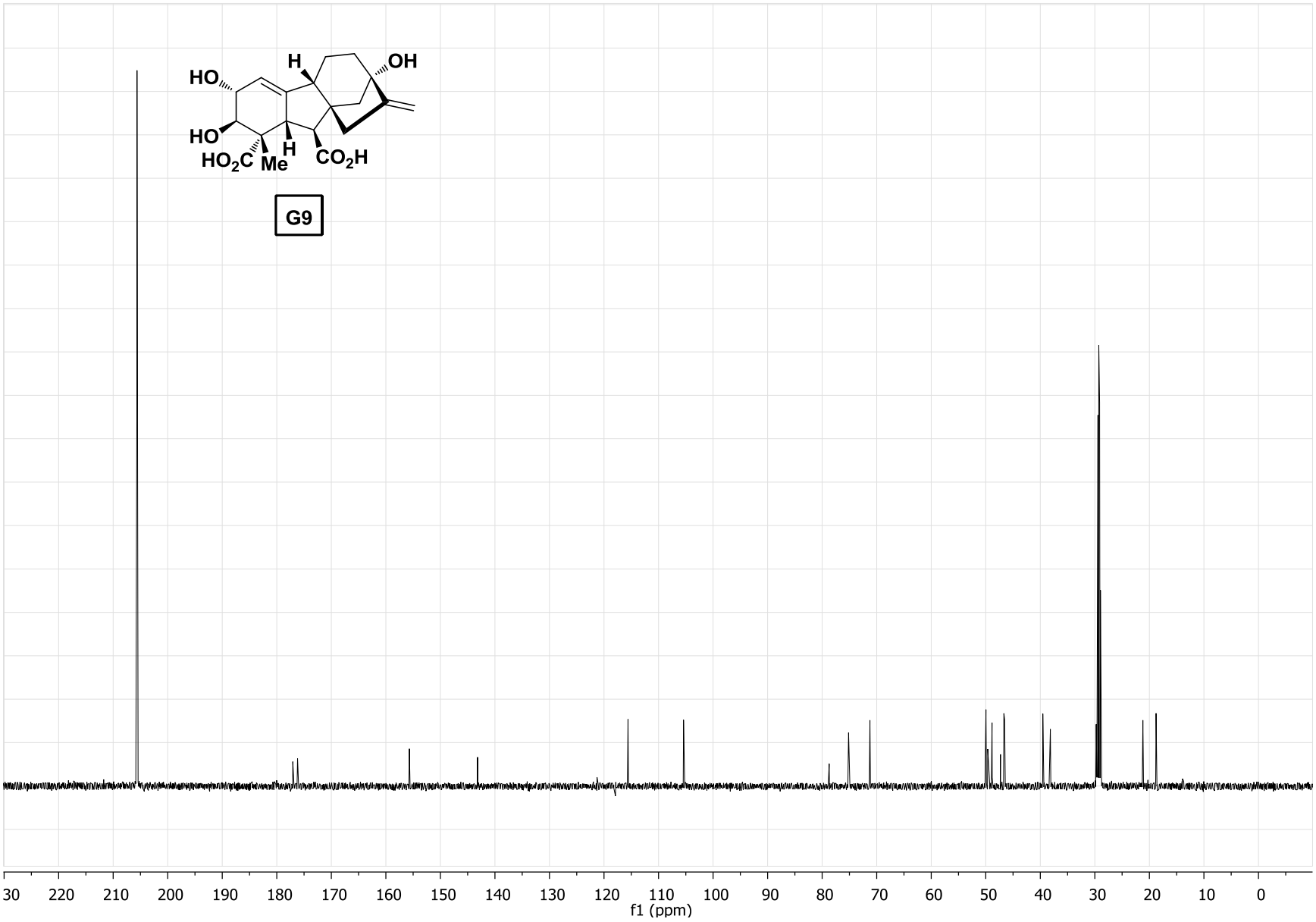
NMR65

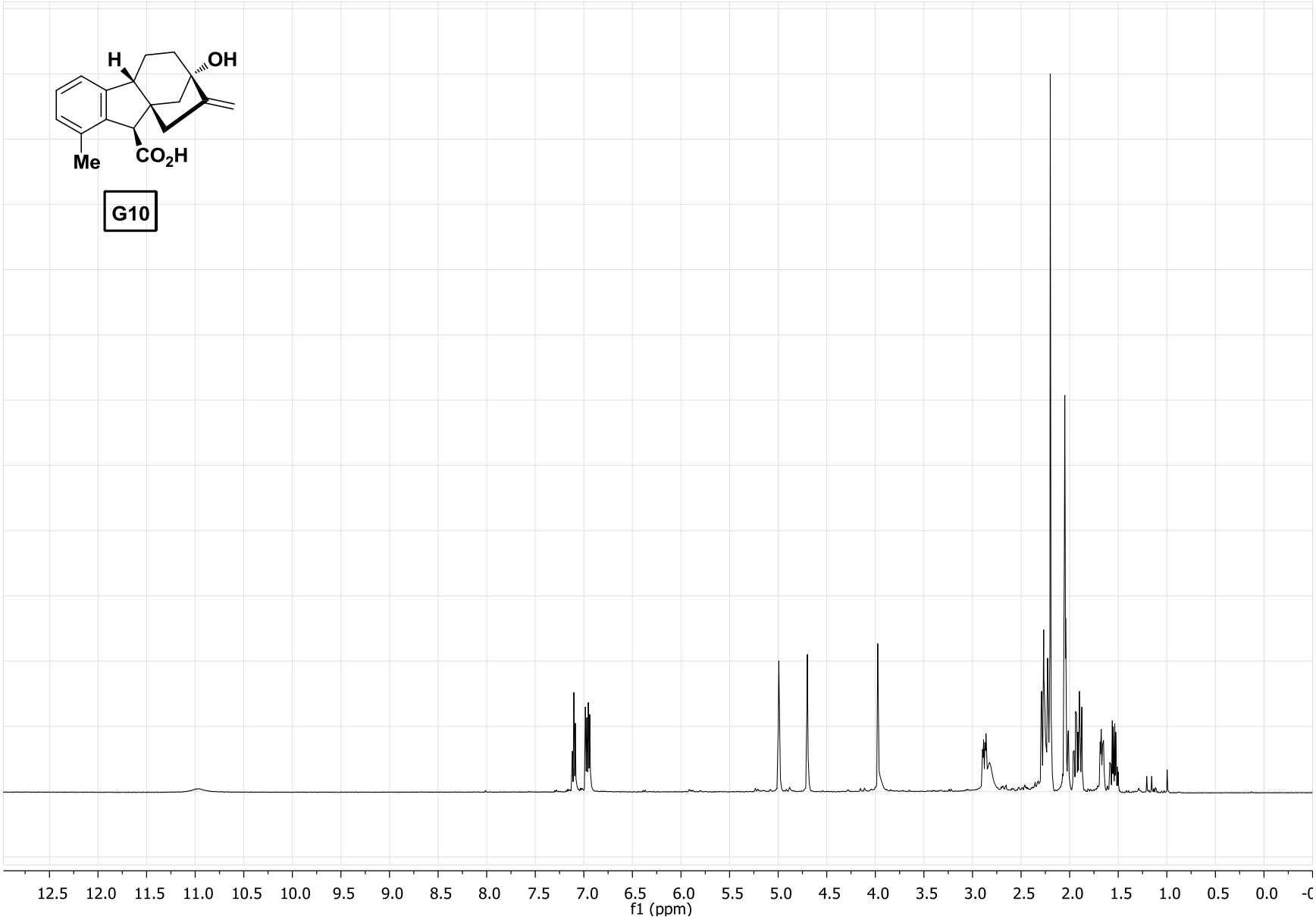

H
OH
O
HO
Me
H
CO2H
O
G8
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

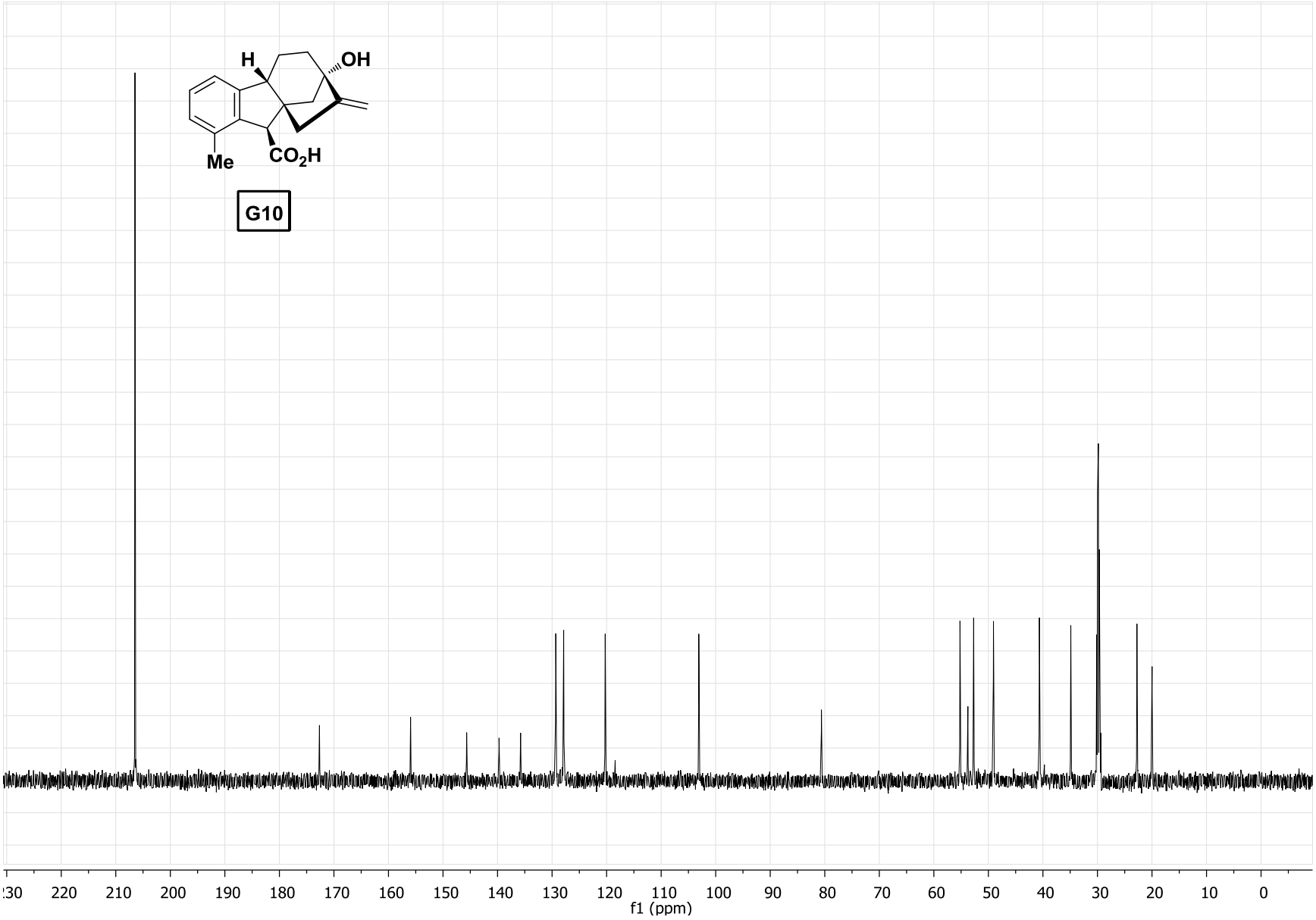
NMR66

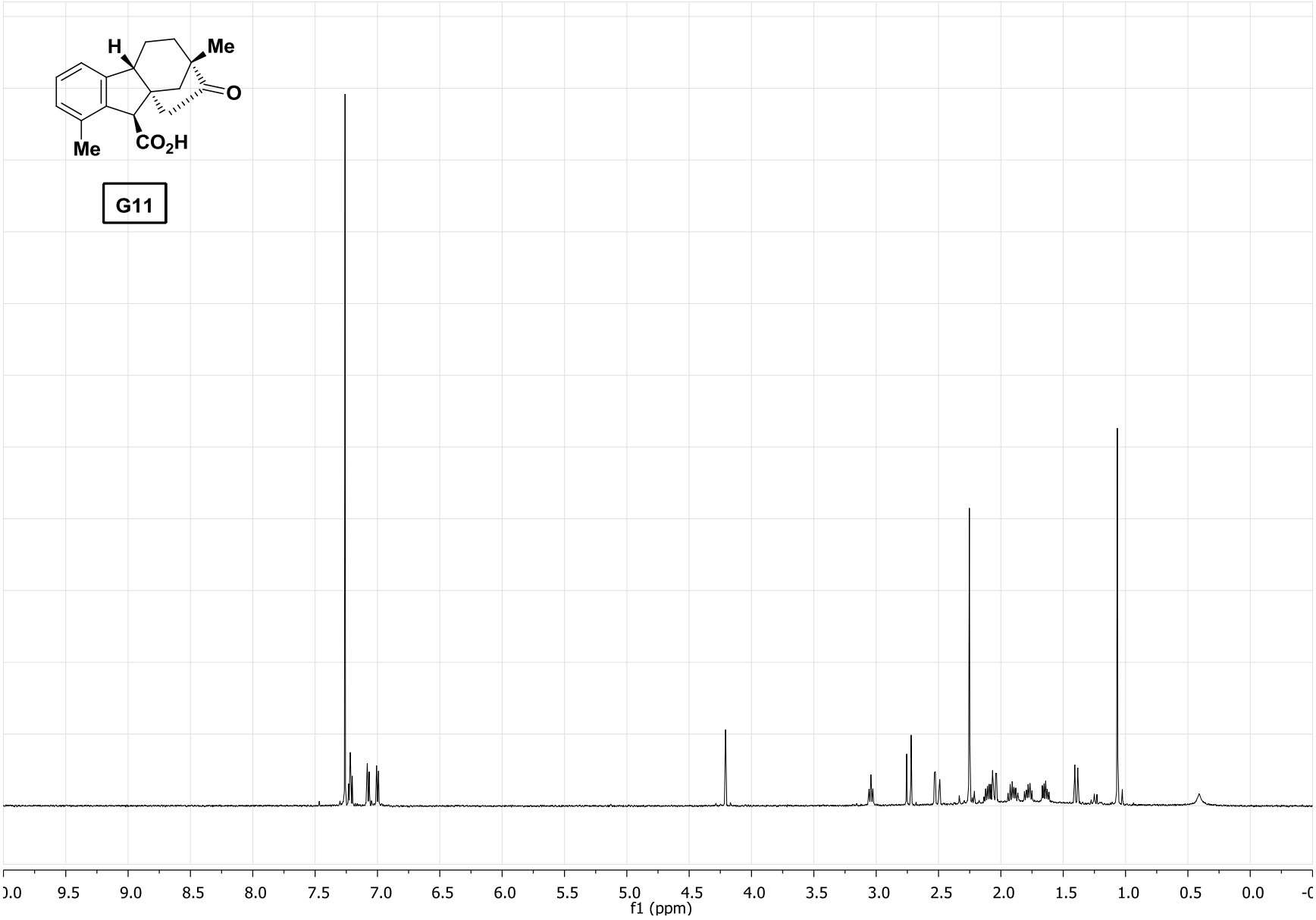



G9

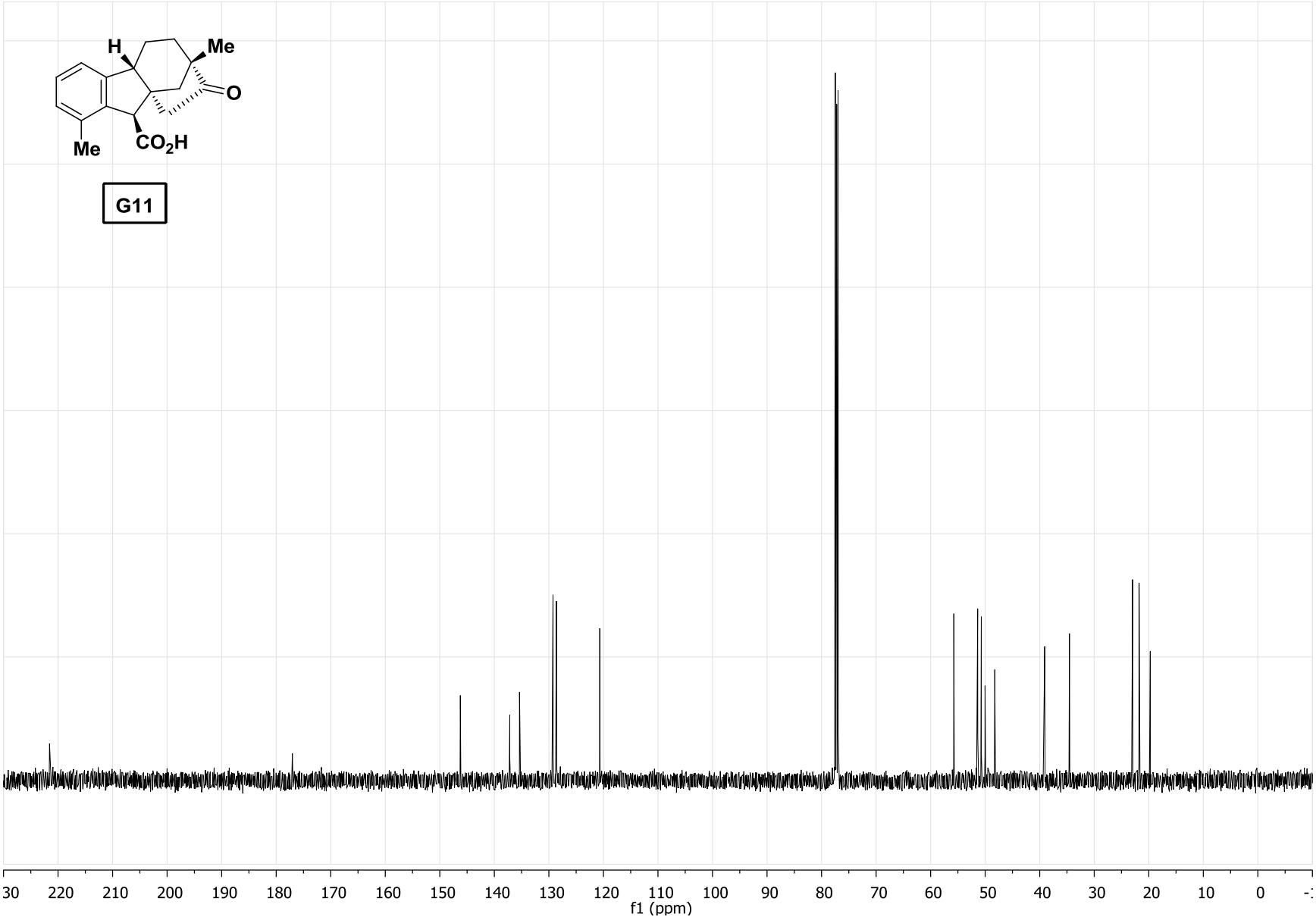

HO
H
OH
HO
HO2C
Me
H
CO2H
G9
30
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H
OH
Me
CO2H
G10
12.5 12.0 11.5 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 1.5 1.0 0.5 0.0
f1 (ppm)

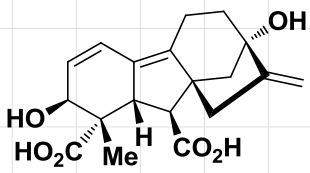

H
OH
Me
CO2H
G10
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)




NMR71


H
Me
O
Me
CO2H
G11
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

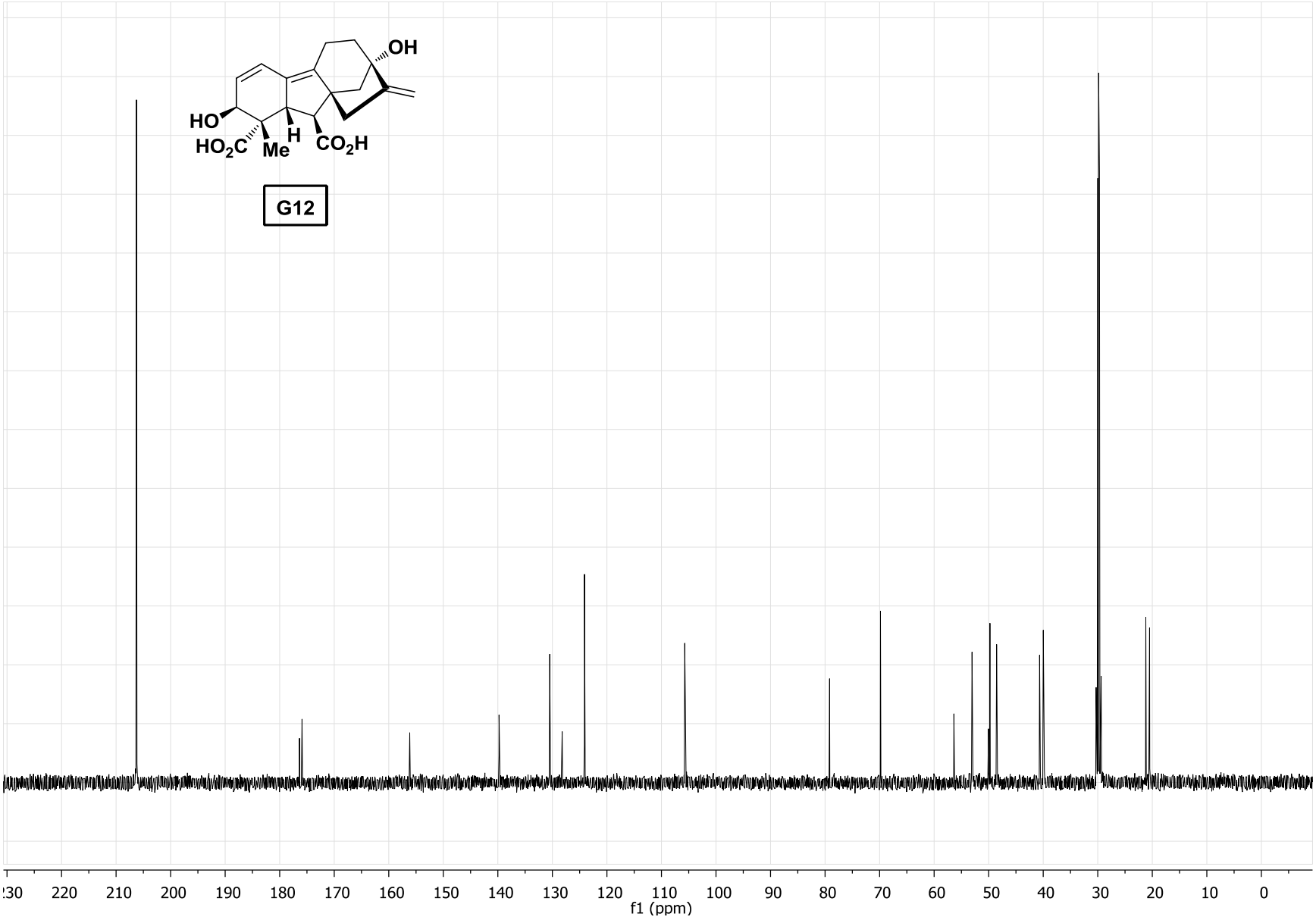
NMR72

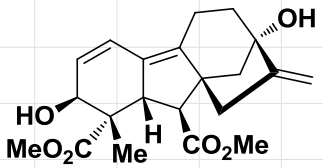

OH
HO
HO2C
Me
H
CO2H

G12


12.5 12.0 11.5 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 1.5 1.0 0.5 0.0
f1 (ppm)

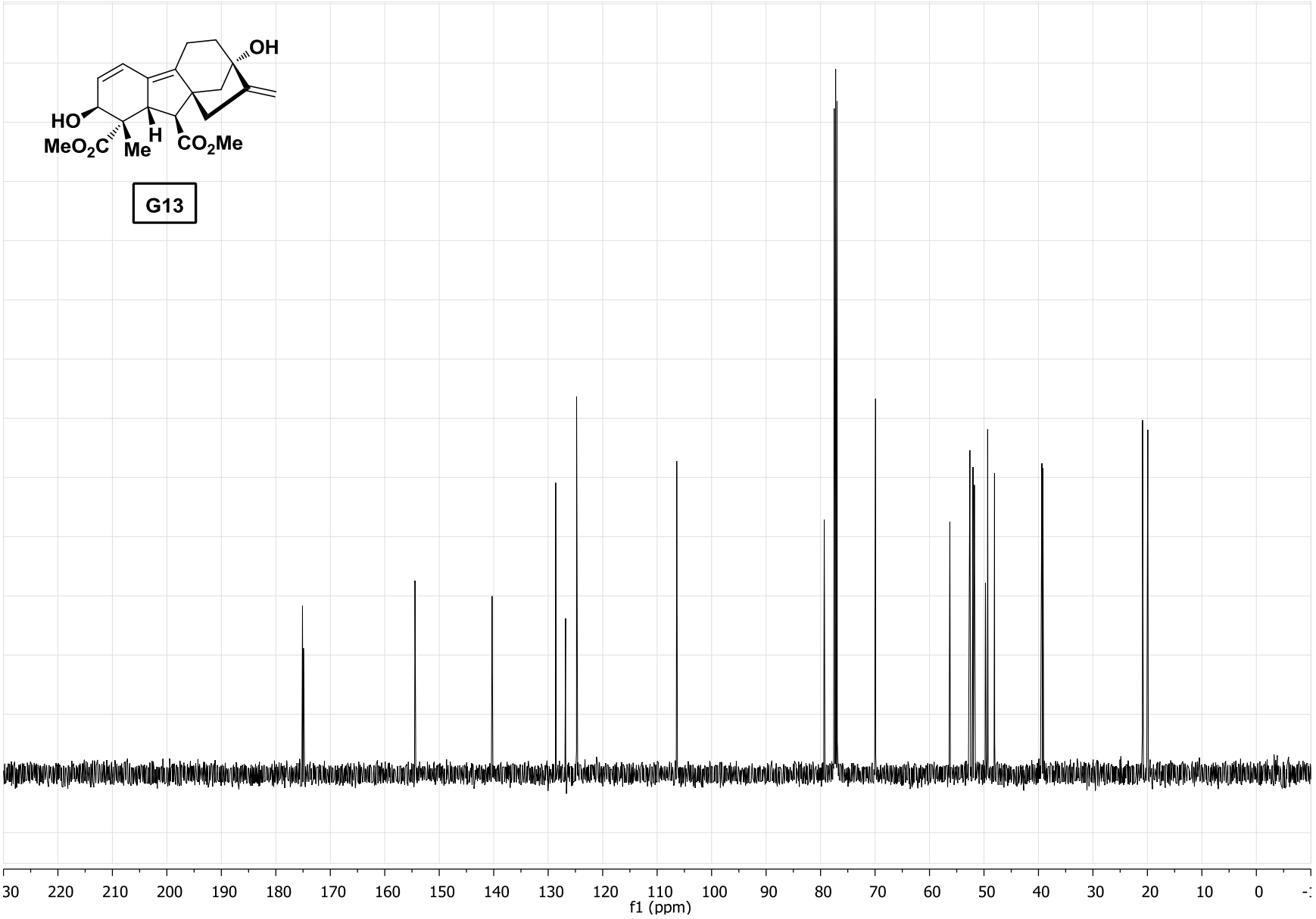
NMR73

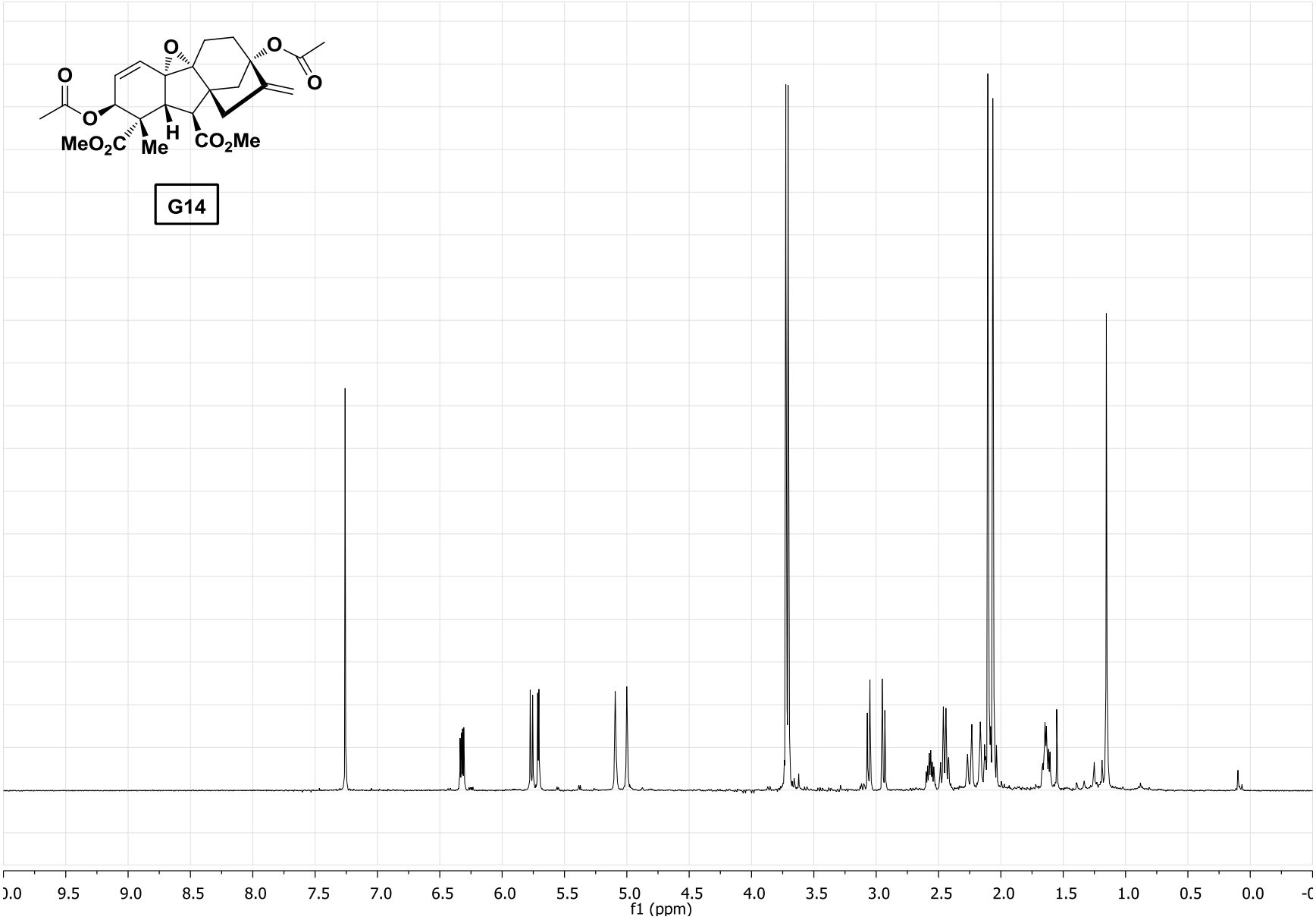

OH
HO
HO2C
Me
H
CO2H
G12
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OH
HO
MeO2C
Me
H
CO2Me

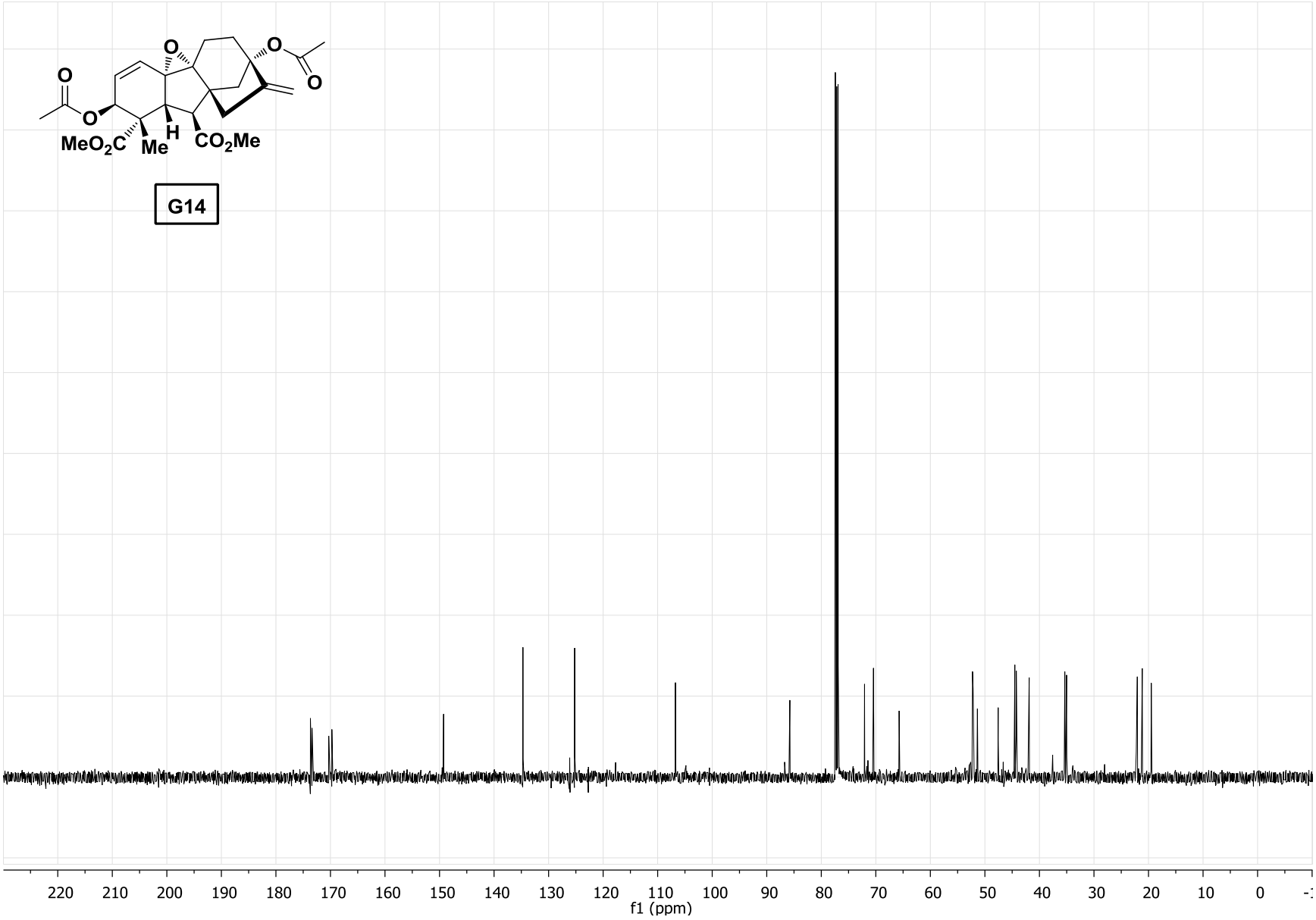
G13

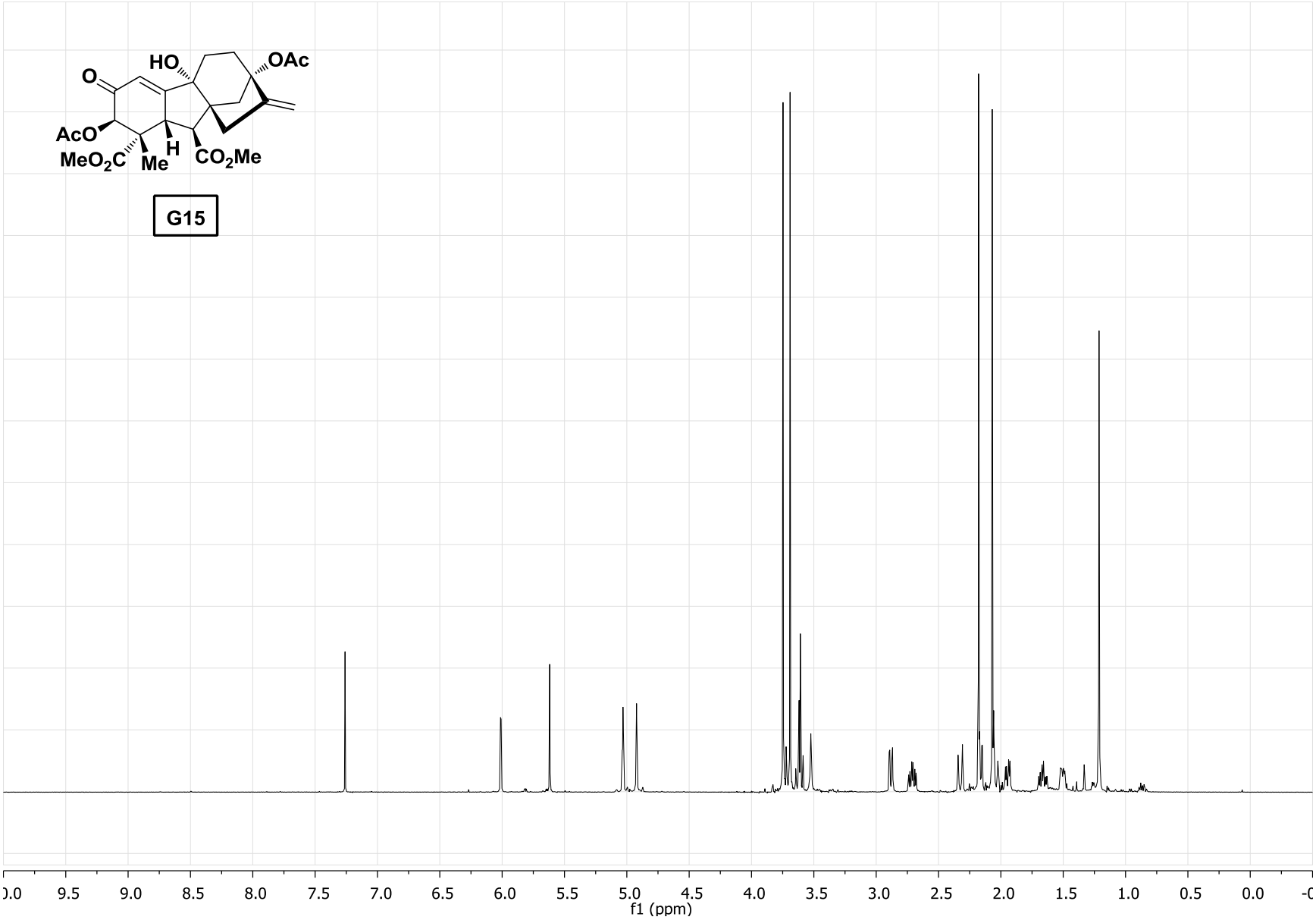

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OH
HO
MeO2C
Me
H
CO2Me
G13
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

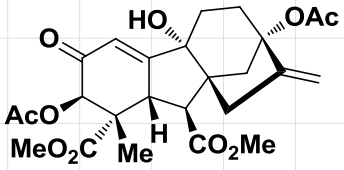



NMR77


O
O
O
O
O
MeO2C
Me
H
CO2Me
G14
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

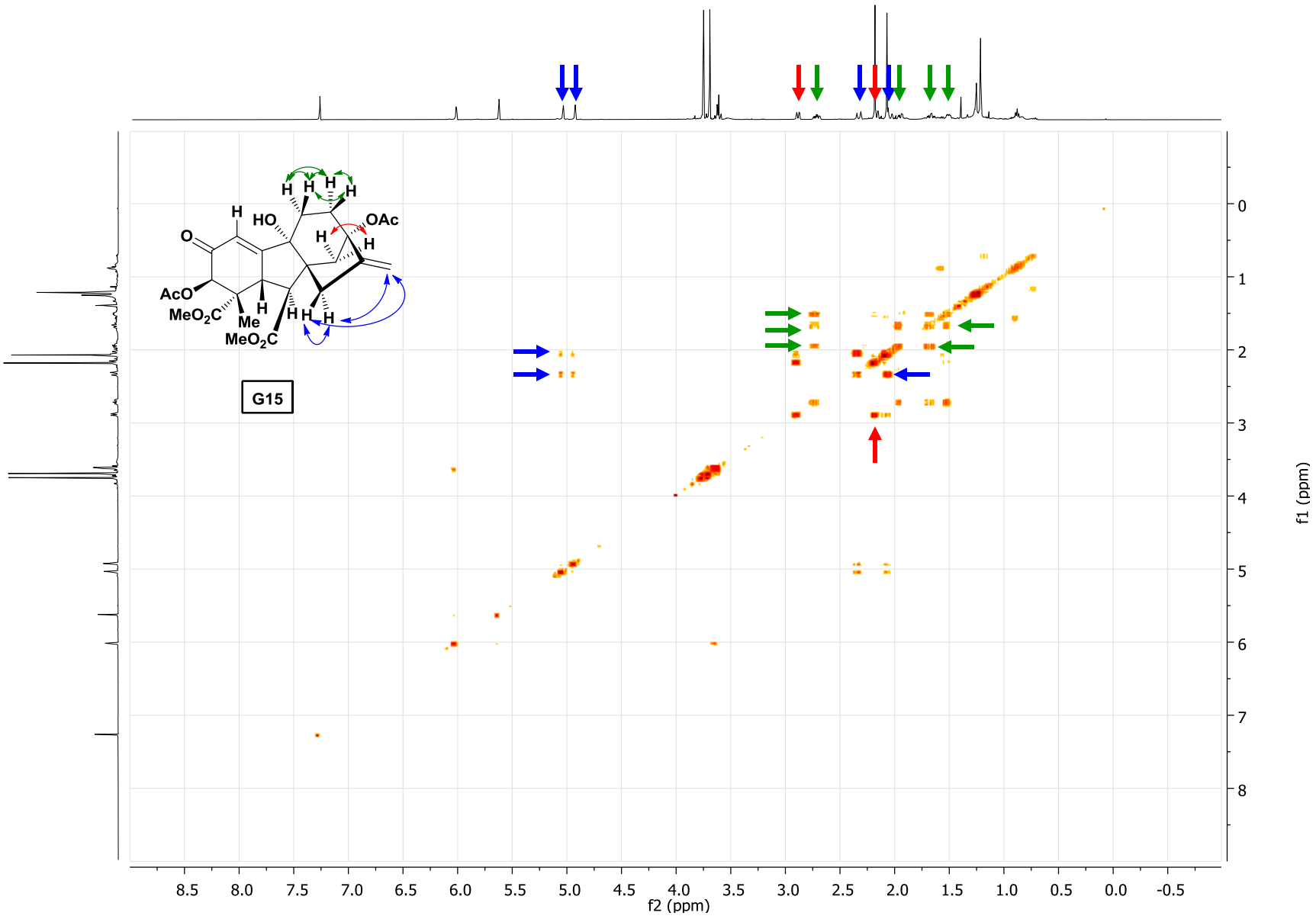



NMR79

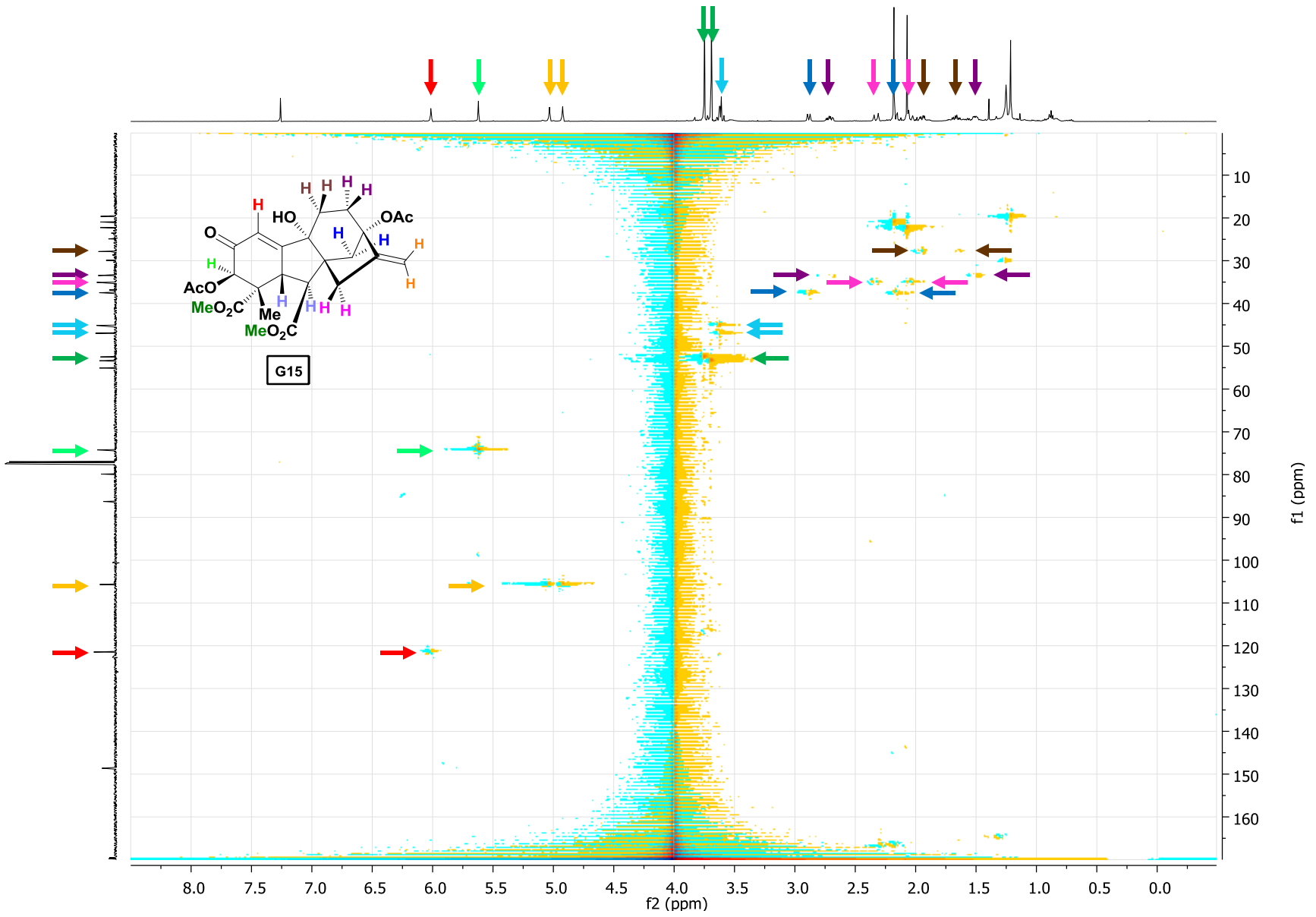

HO
OAc
O
AcO
MeO2C
Me
H
CO2Me

G15

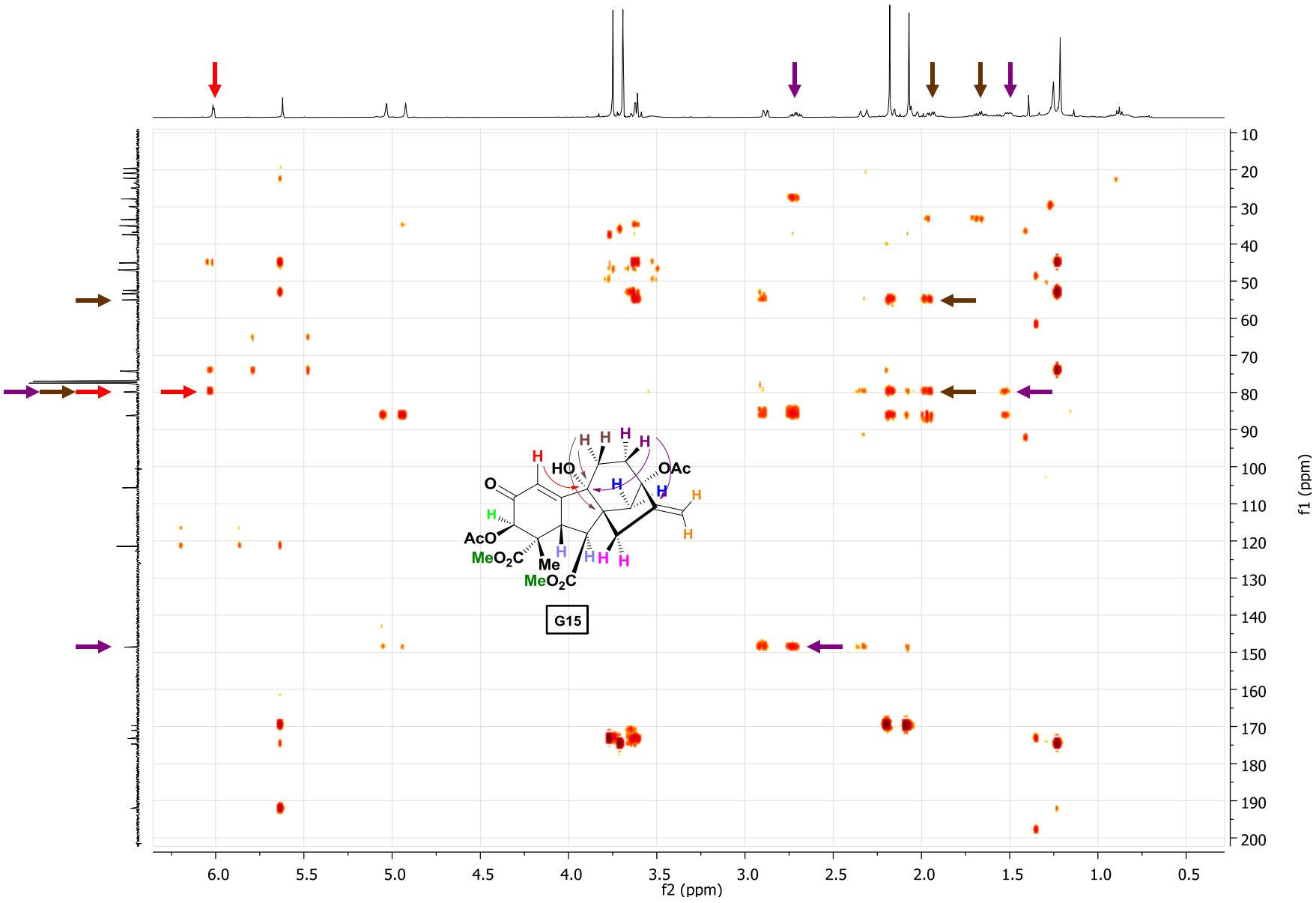

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)



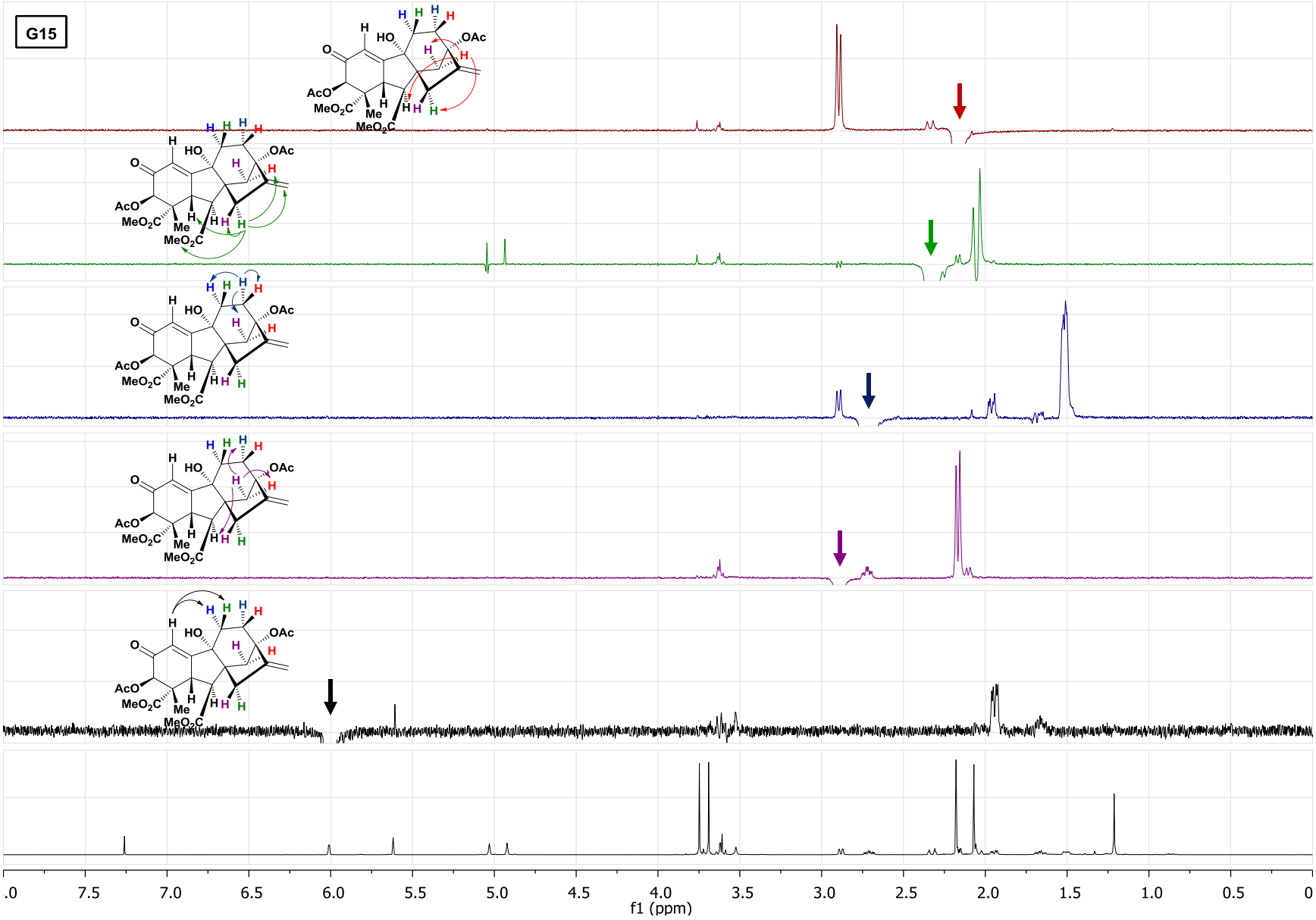

NMR81



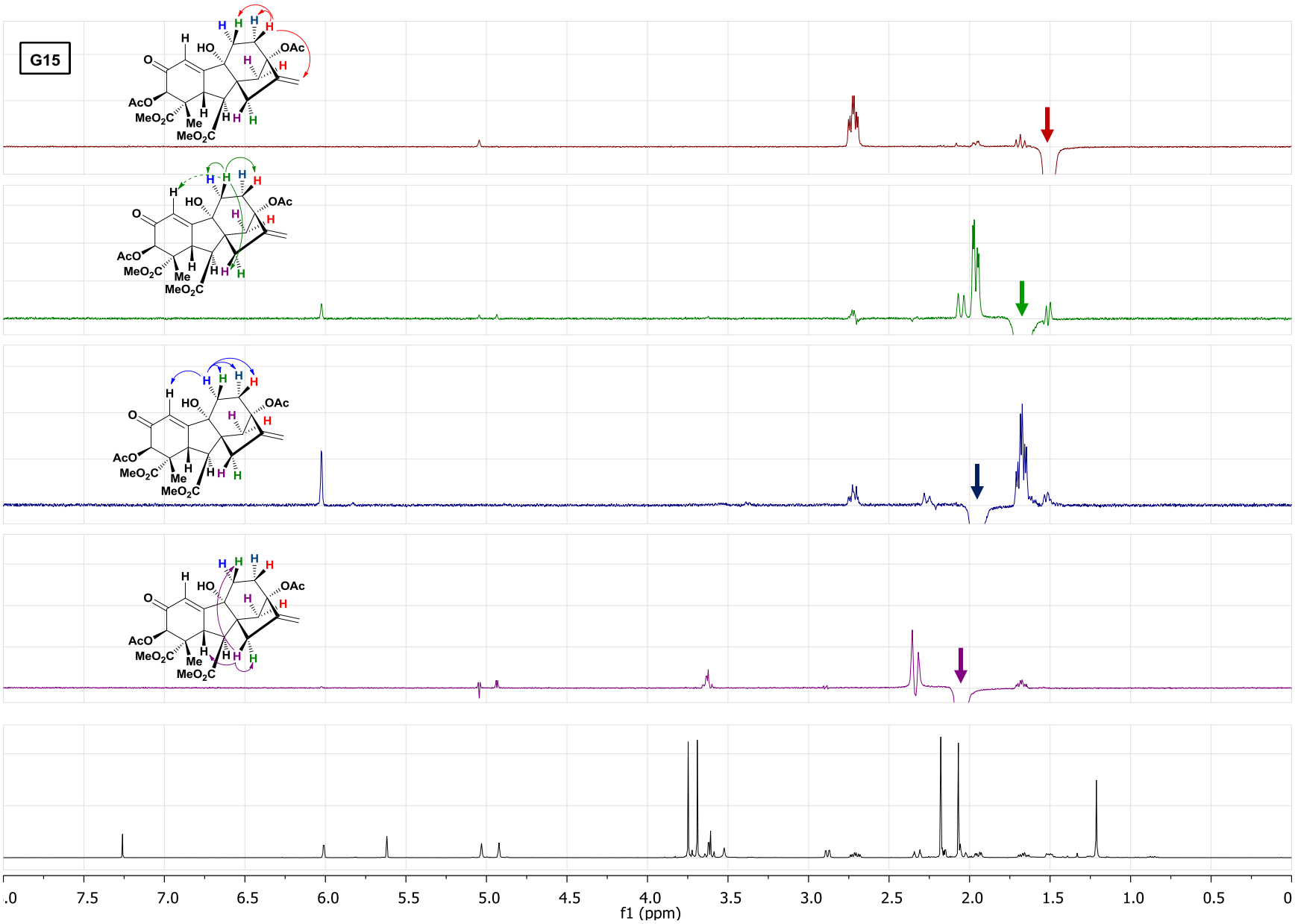

NMR82


f2 (ppm)
f1 (ppm)
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
HO
OAc
O
AcO
MeO2C
Me
MeO2C
G15

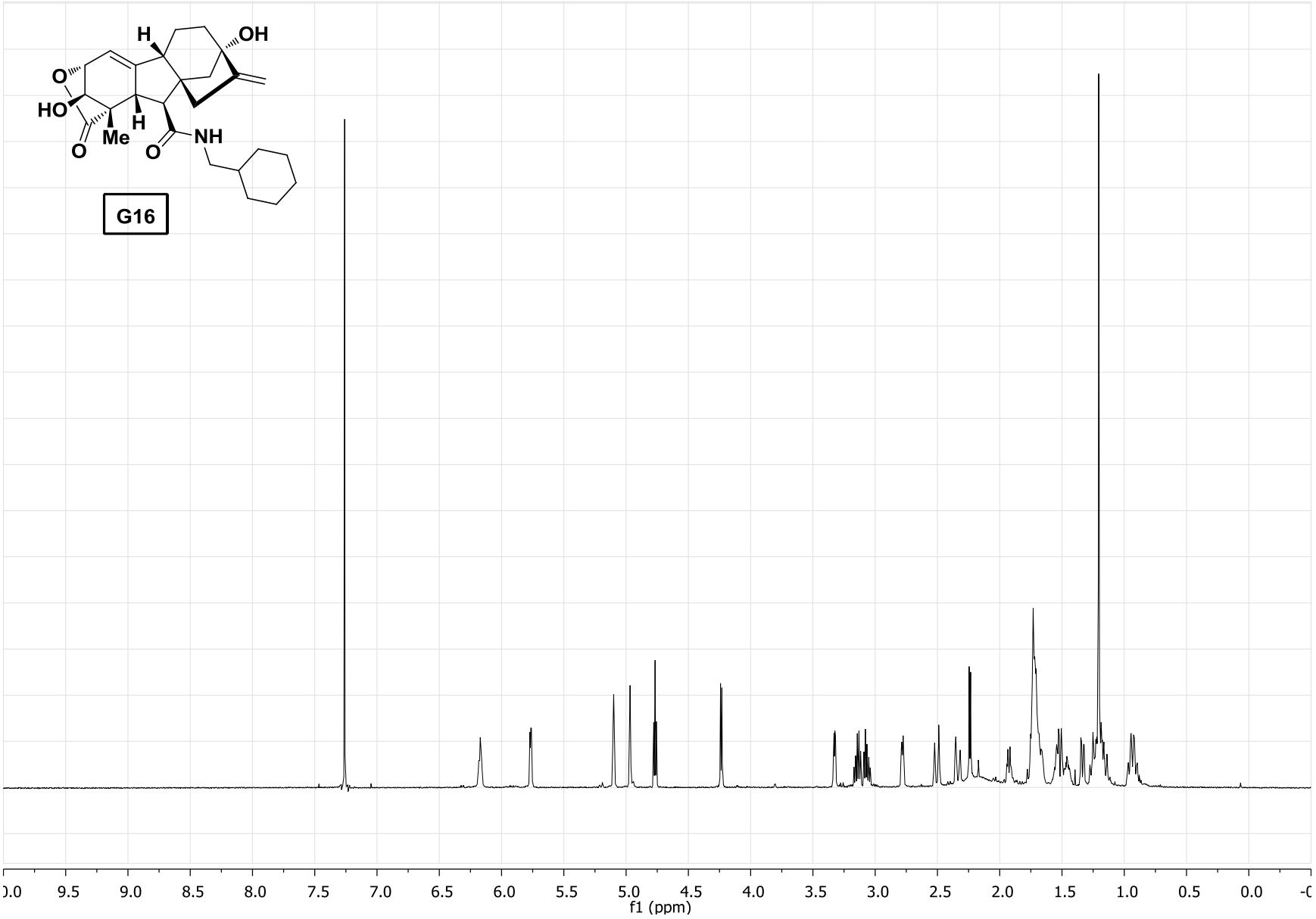
NMR83



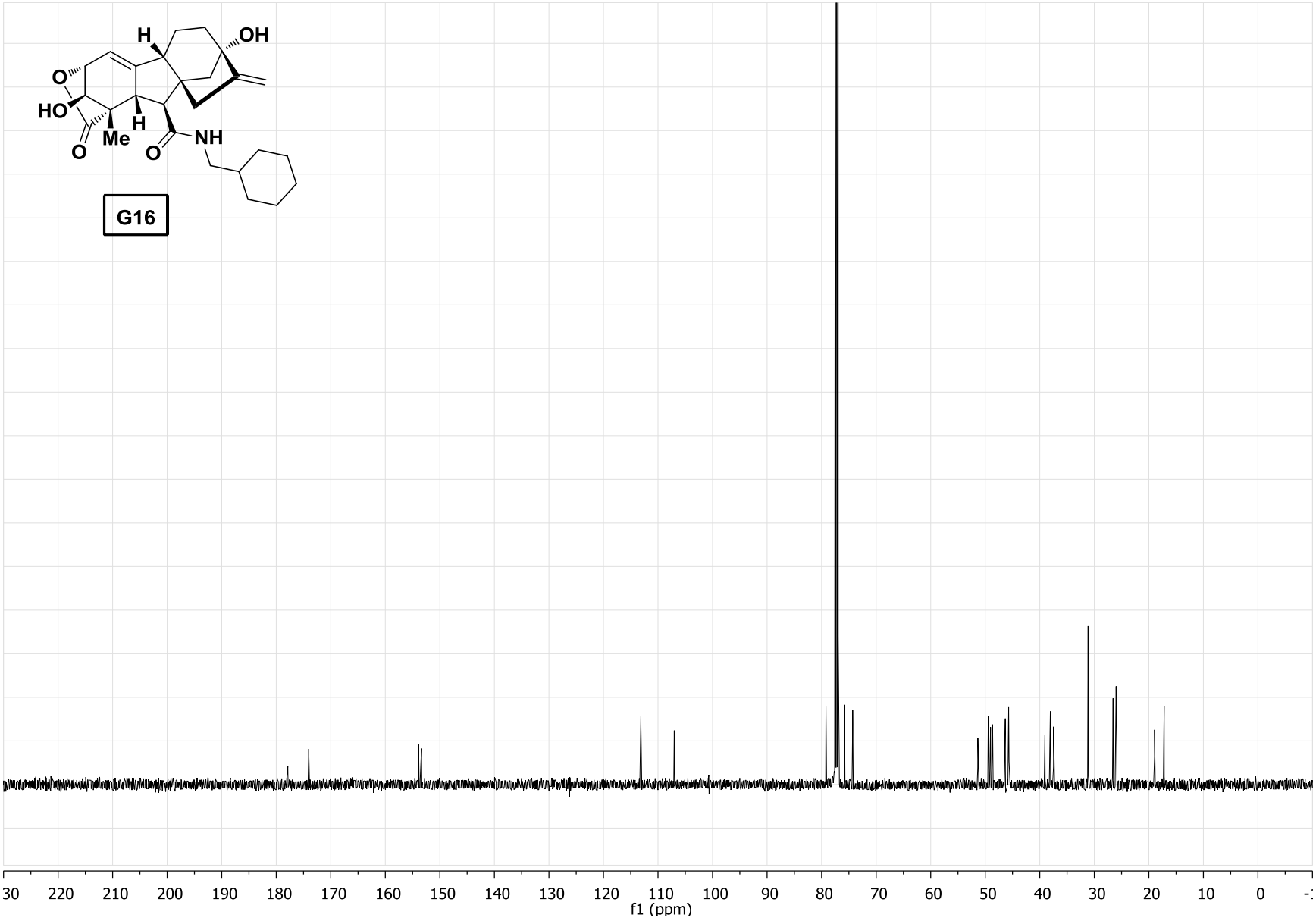

NMR84



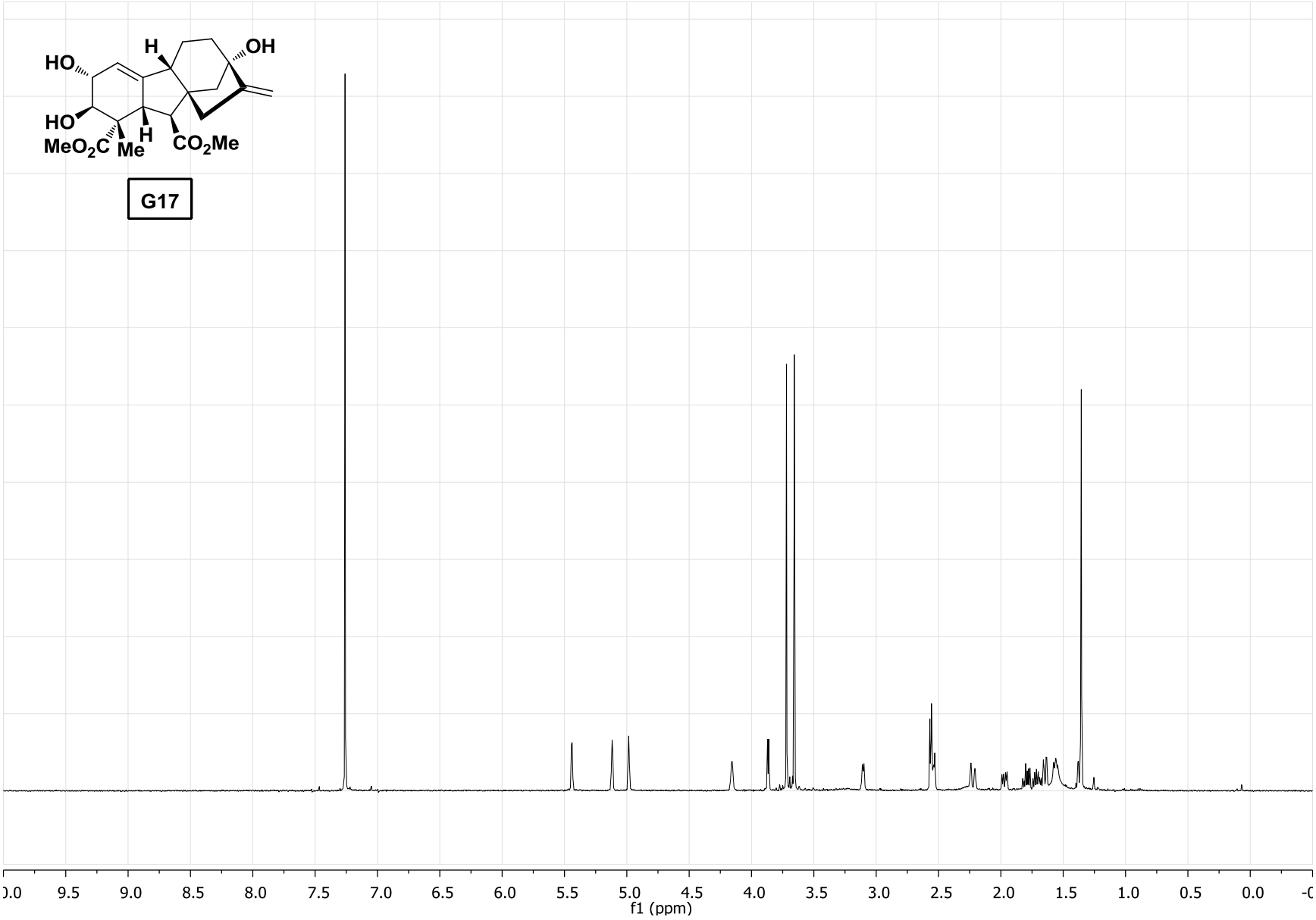

NMR85


H
OH
O
HO
Me
H
O
O
NH
G16
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

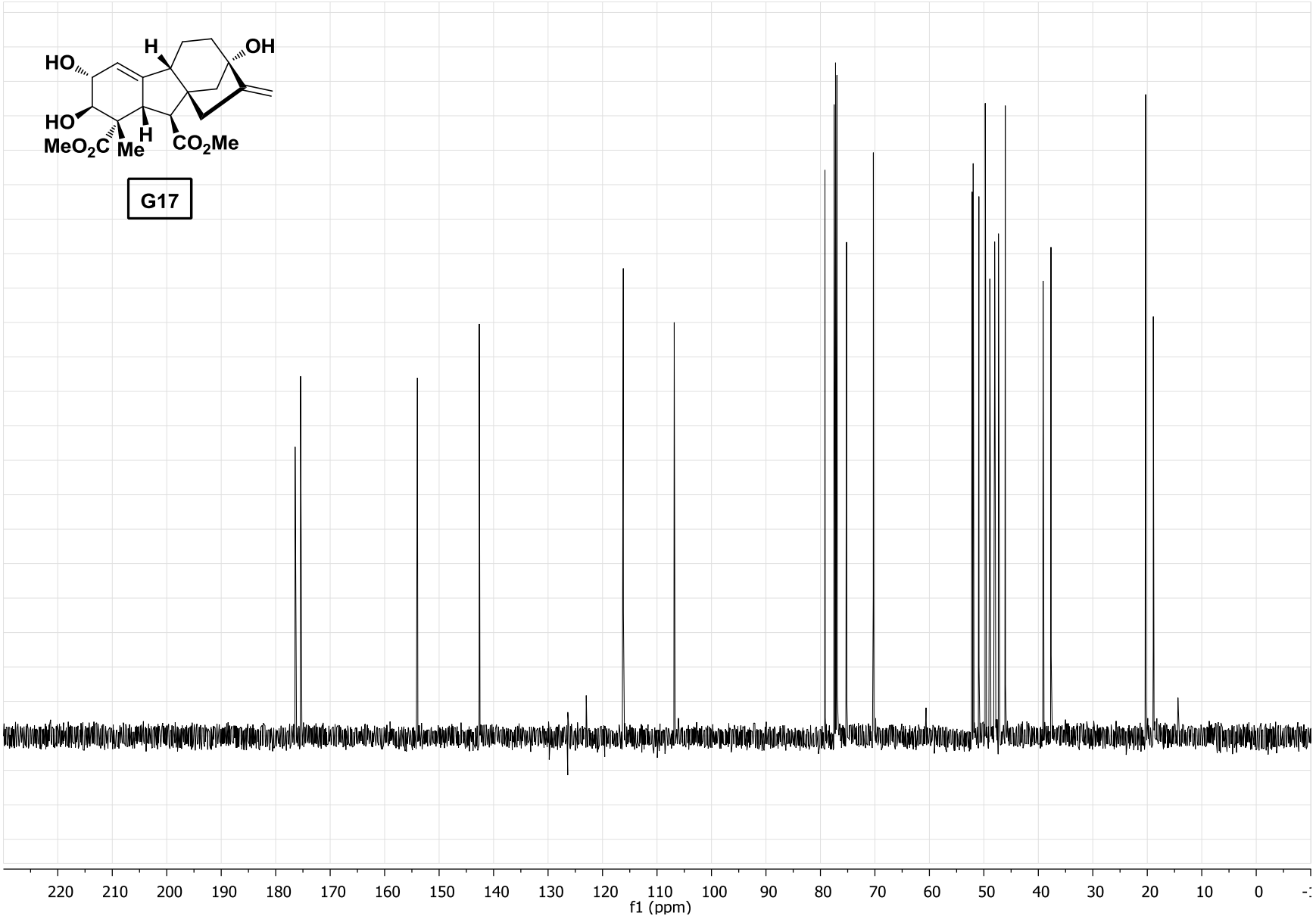
NMR86


H
OH
O
HO
Me
H
O
O
NH
G16
30
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

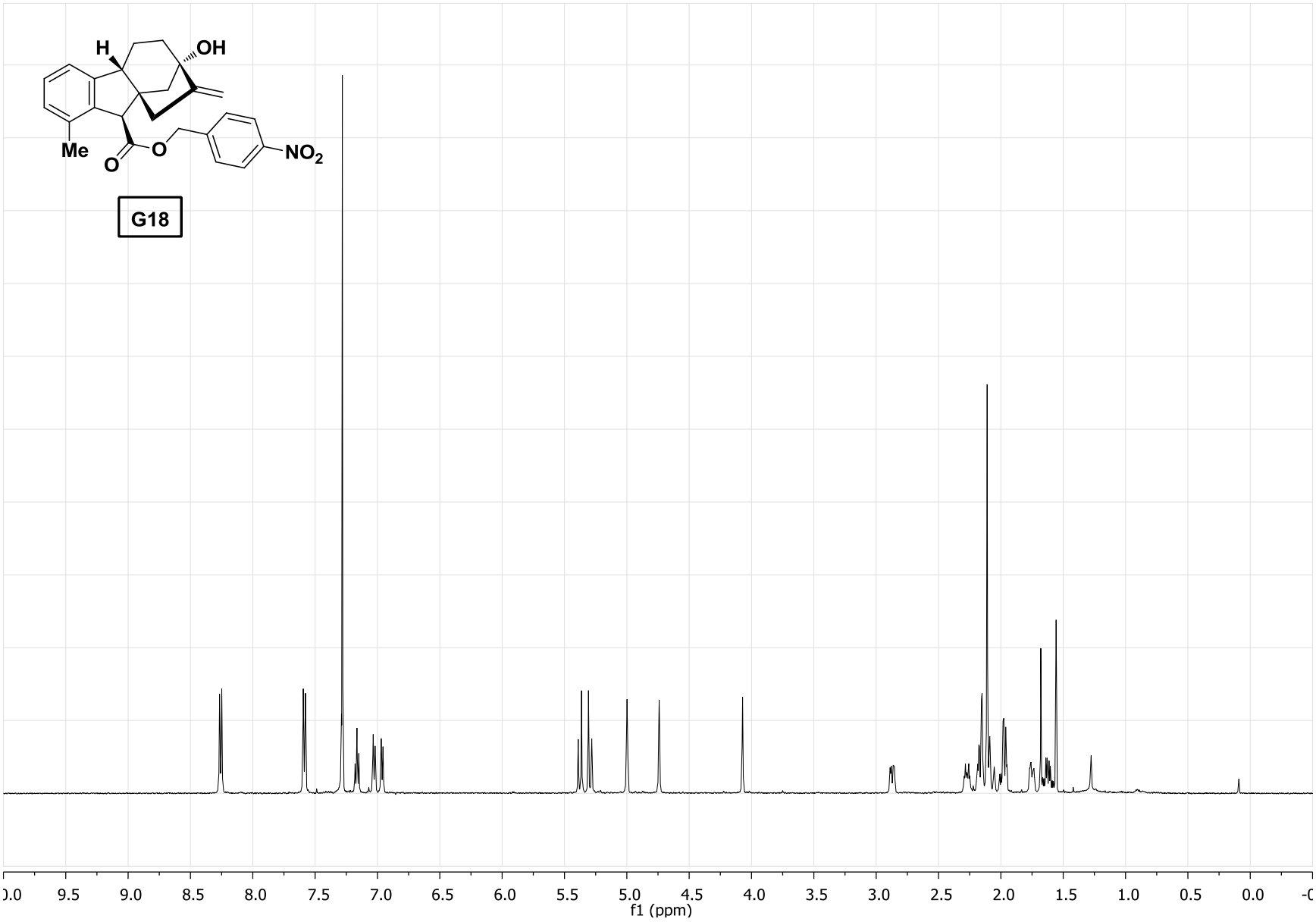
NMR87


HO
H
OH
HO
MeO2C
Me
H
CO2Me
G17
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

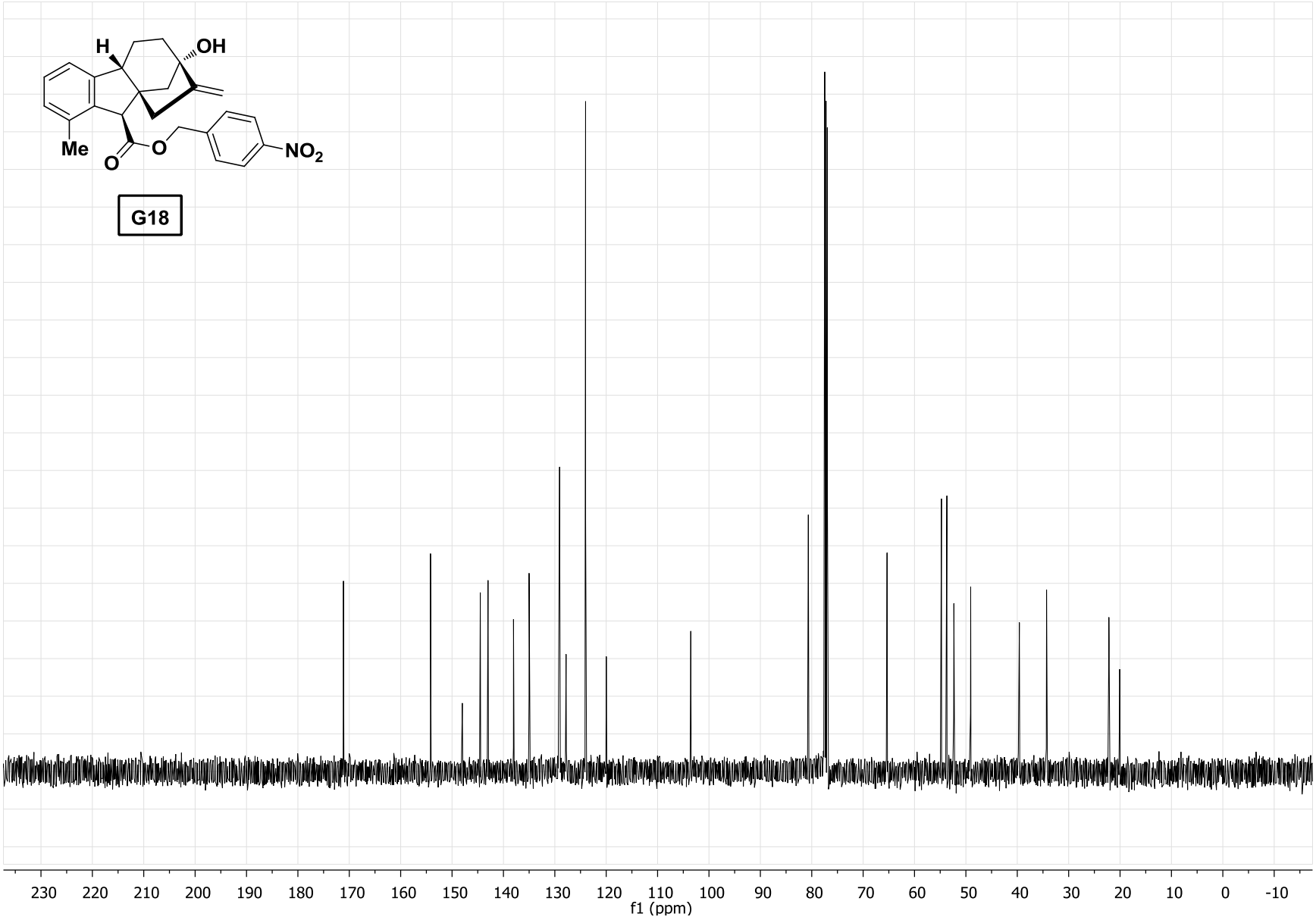
NMR88


HO
H
OH
HO
MeO2C
Me
H
CO2Me
G17
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

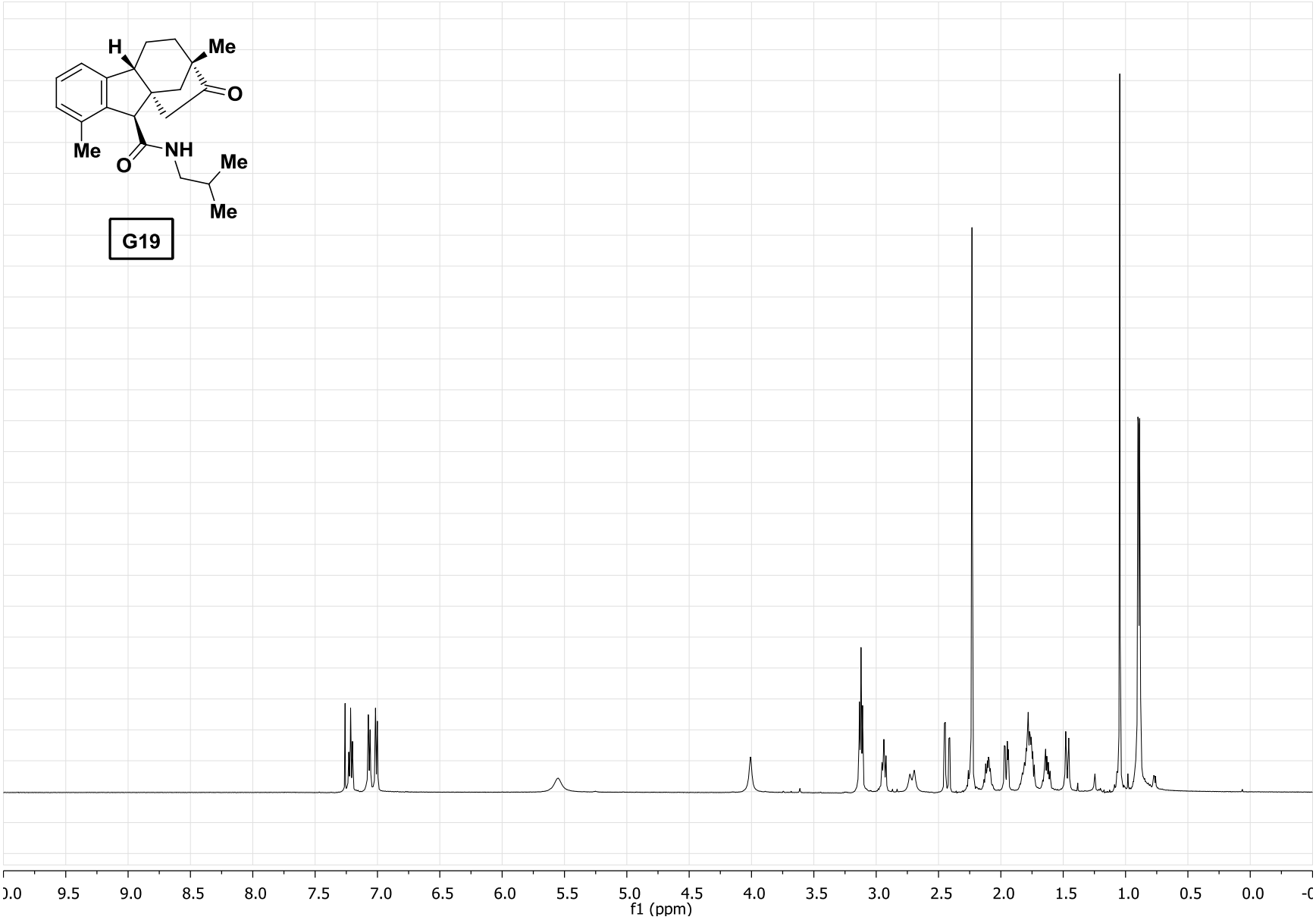
NMR89


H
OH
Me
O
O
NO2
G18
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

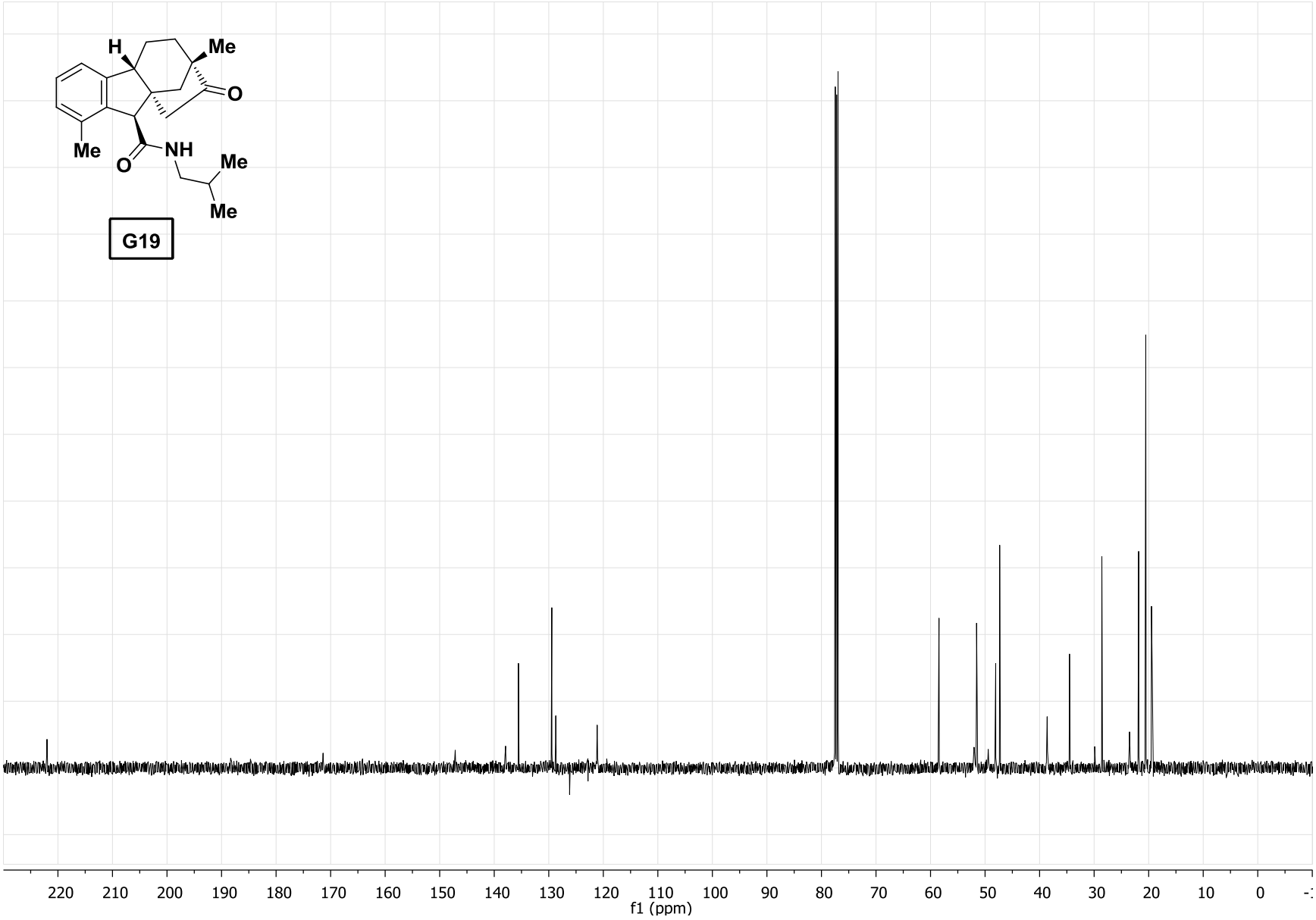
NMR90


H
OH
Me
O
O
NO2
G18
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

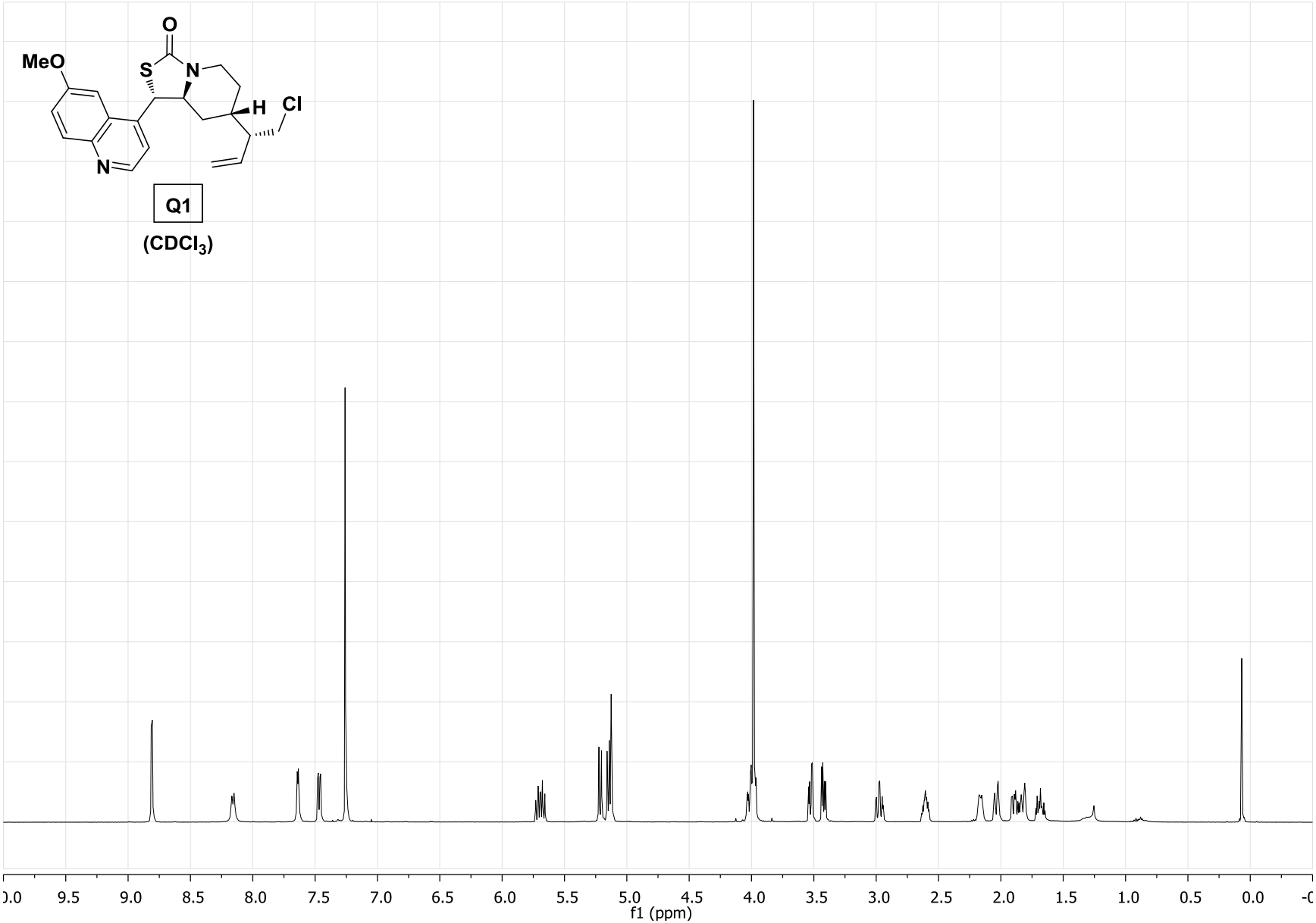
NMR91



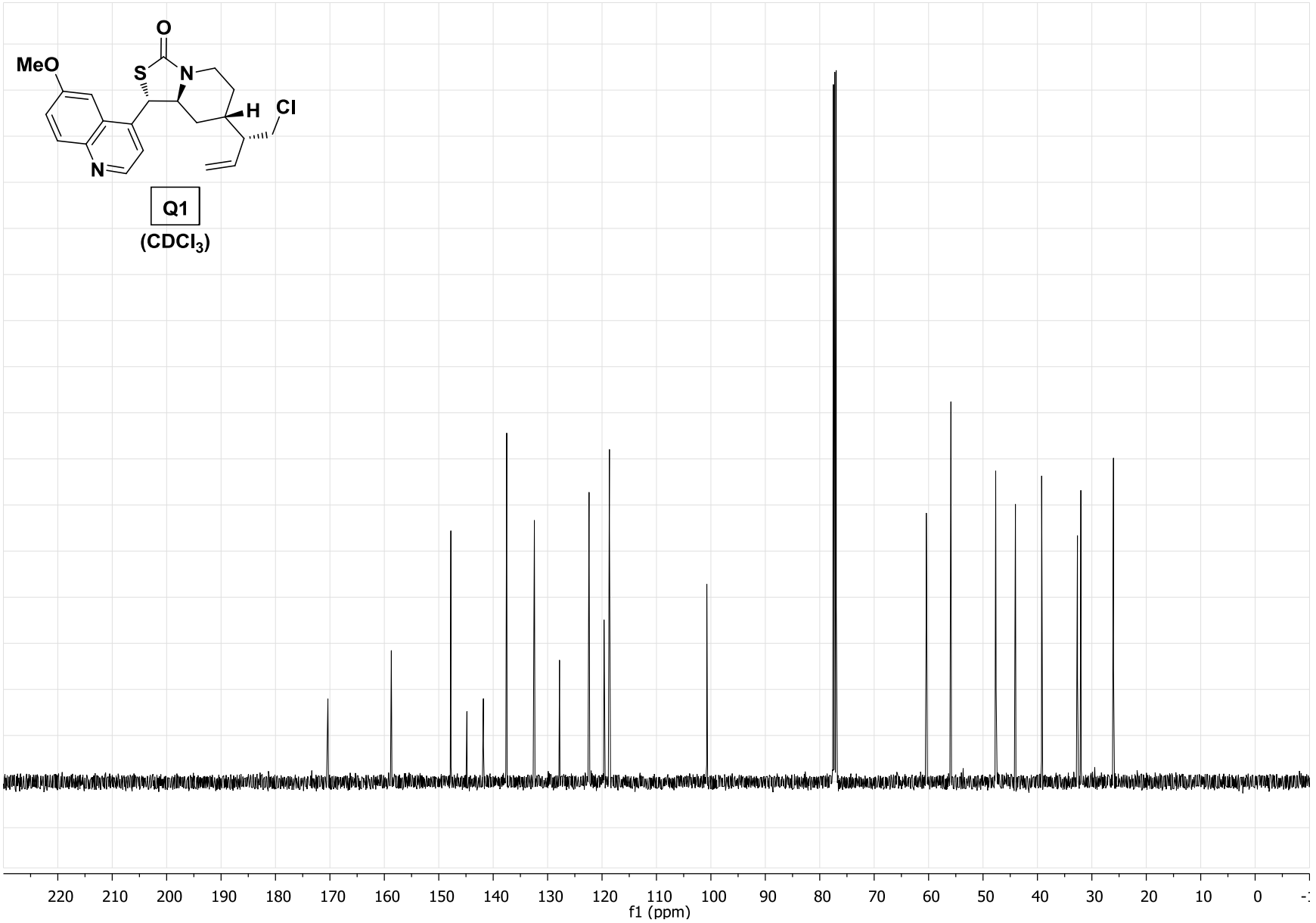

NMR92

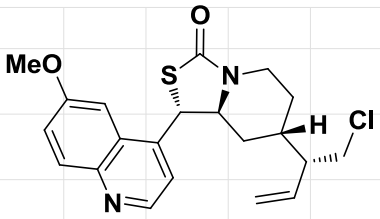

H
Me
O
Me
NH
O
Me
Me
G19
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

NMR93


MeO
O
S
N
H
Cl
N
Q1
(CDCl3)
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

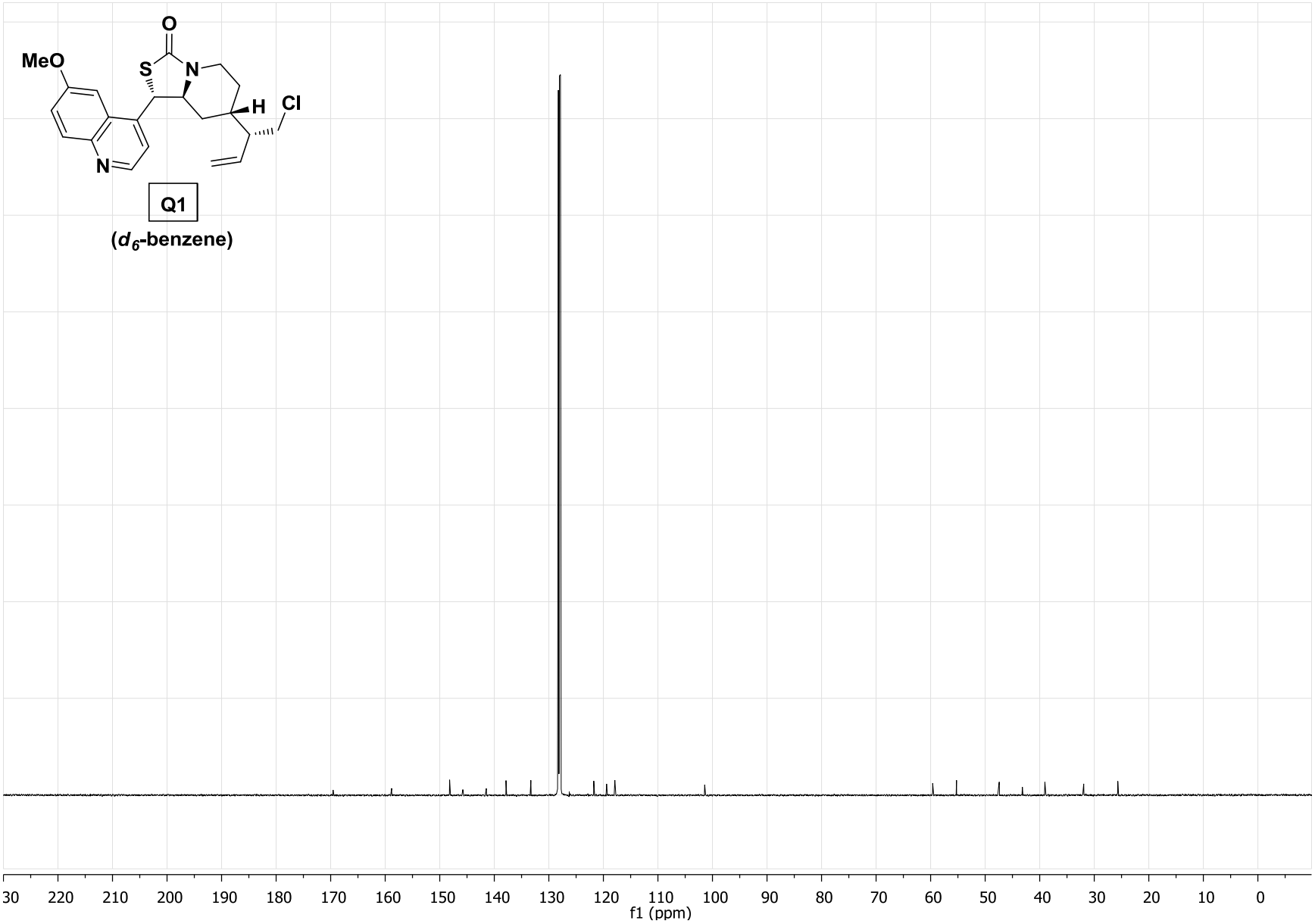
NMR94

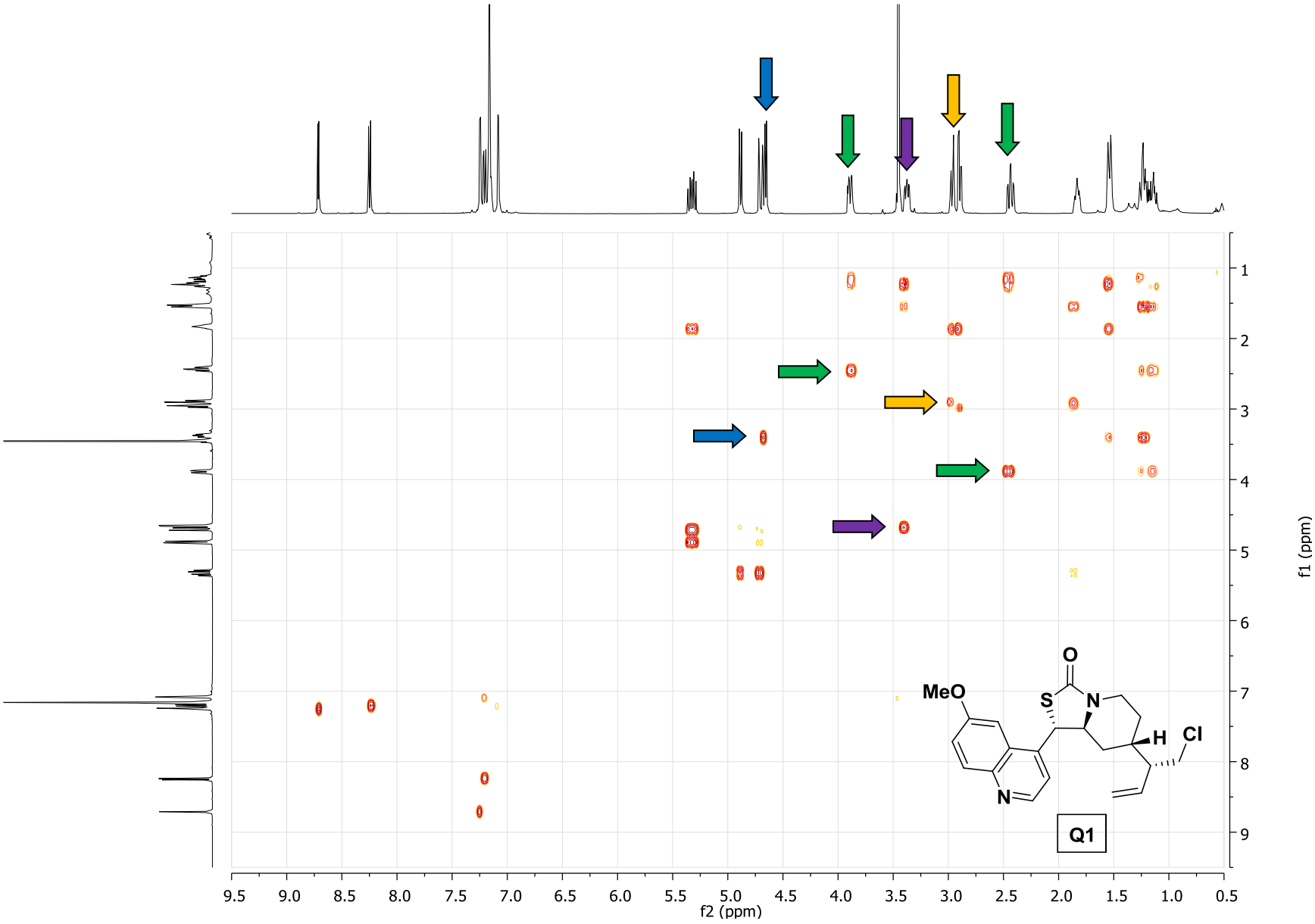

MeO
O
S
N
H
Cl
N
Q1
(CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

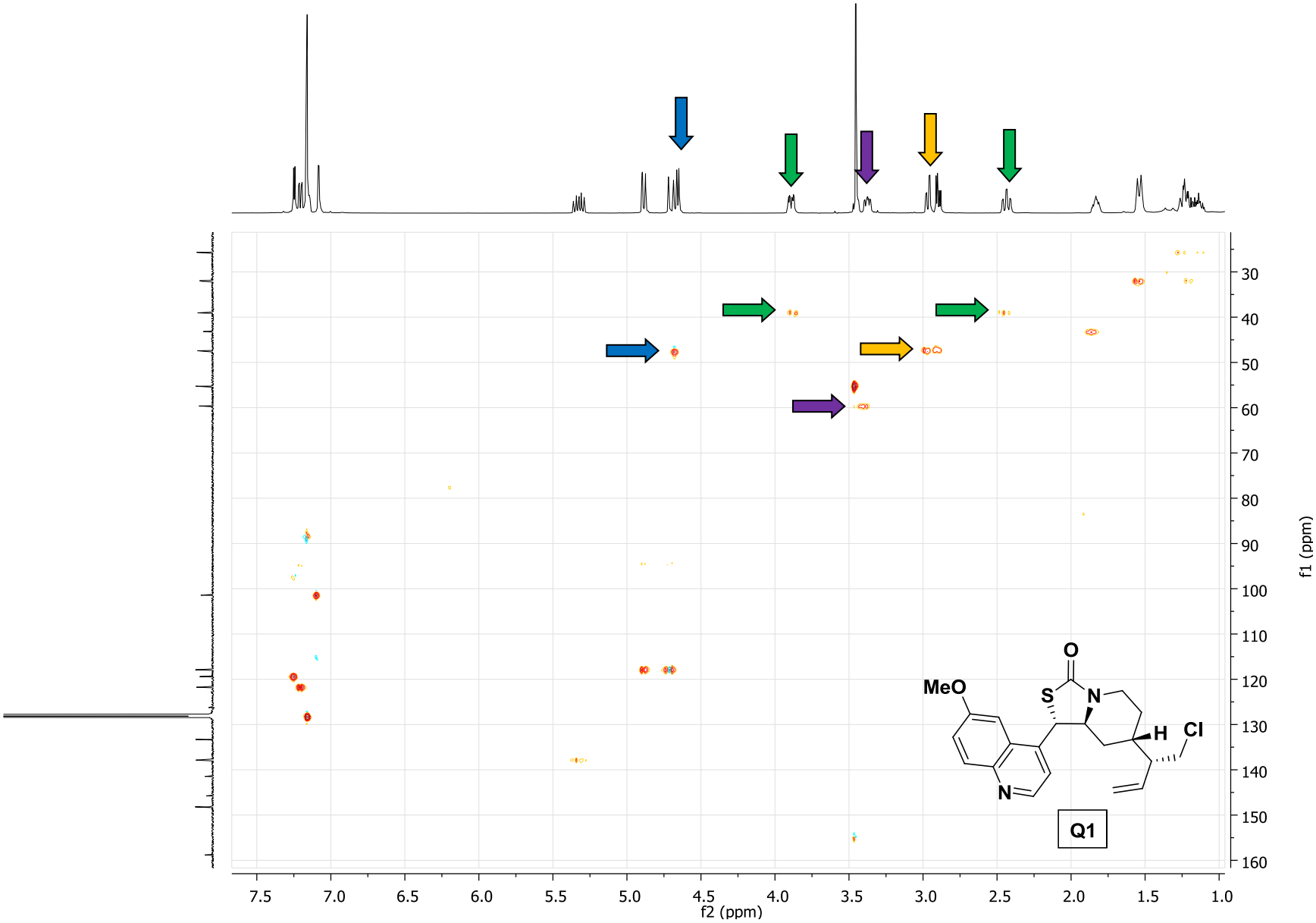



**Q1**

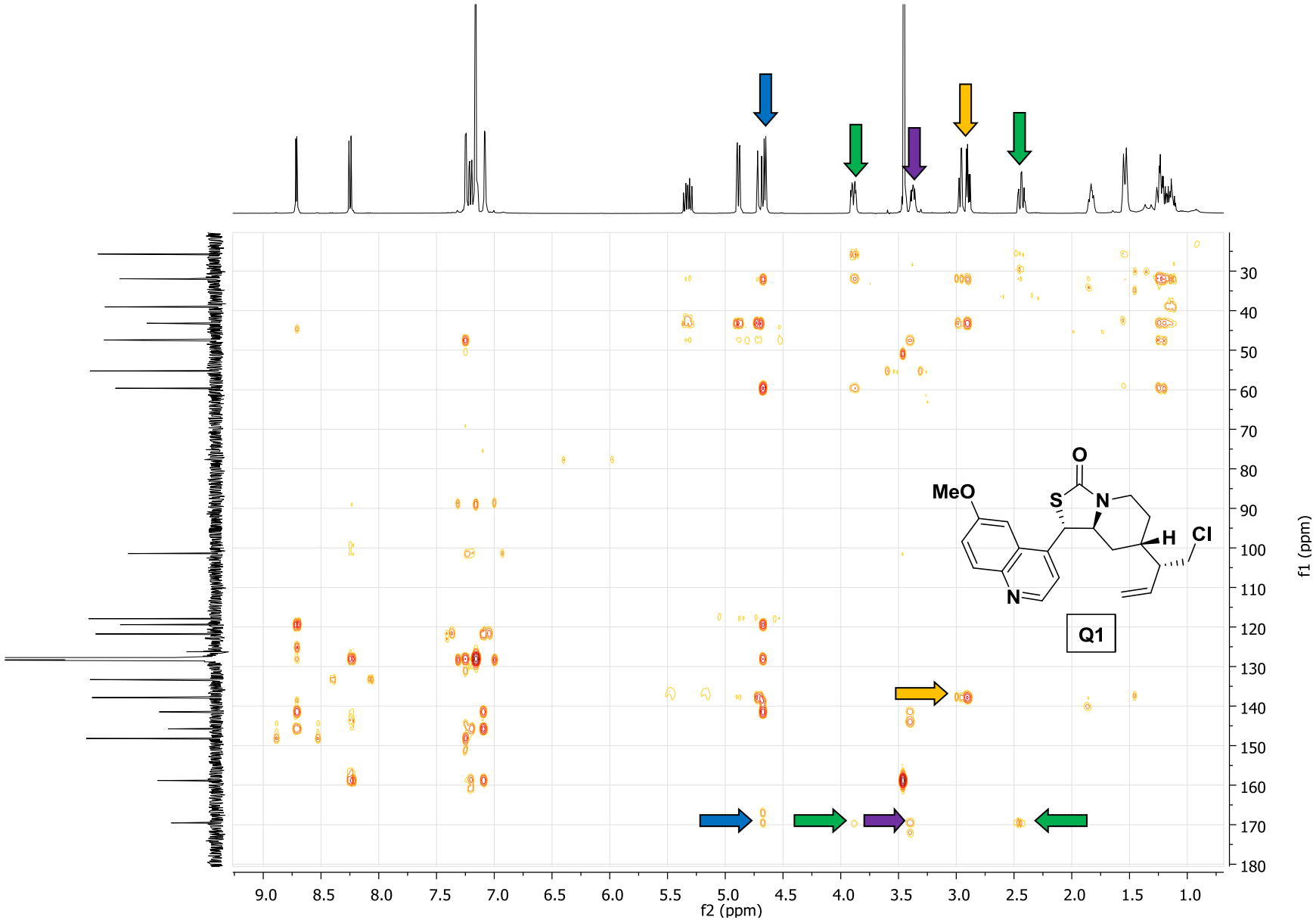
**($d_6$-benzene)**

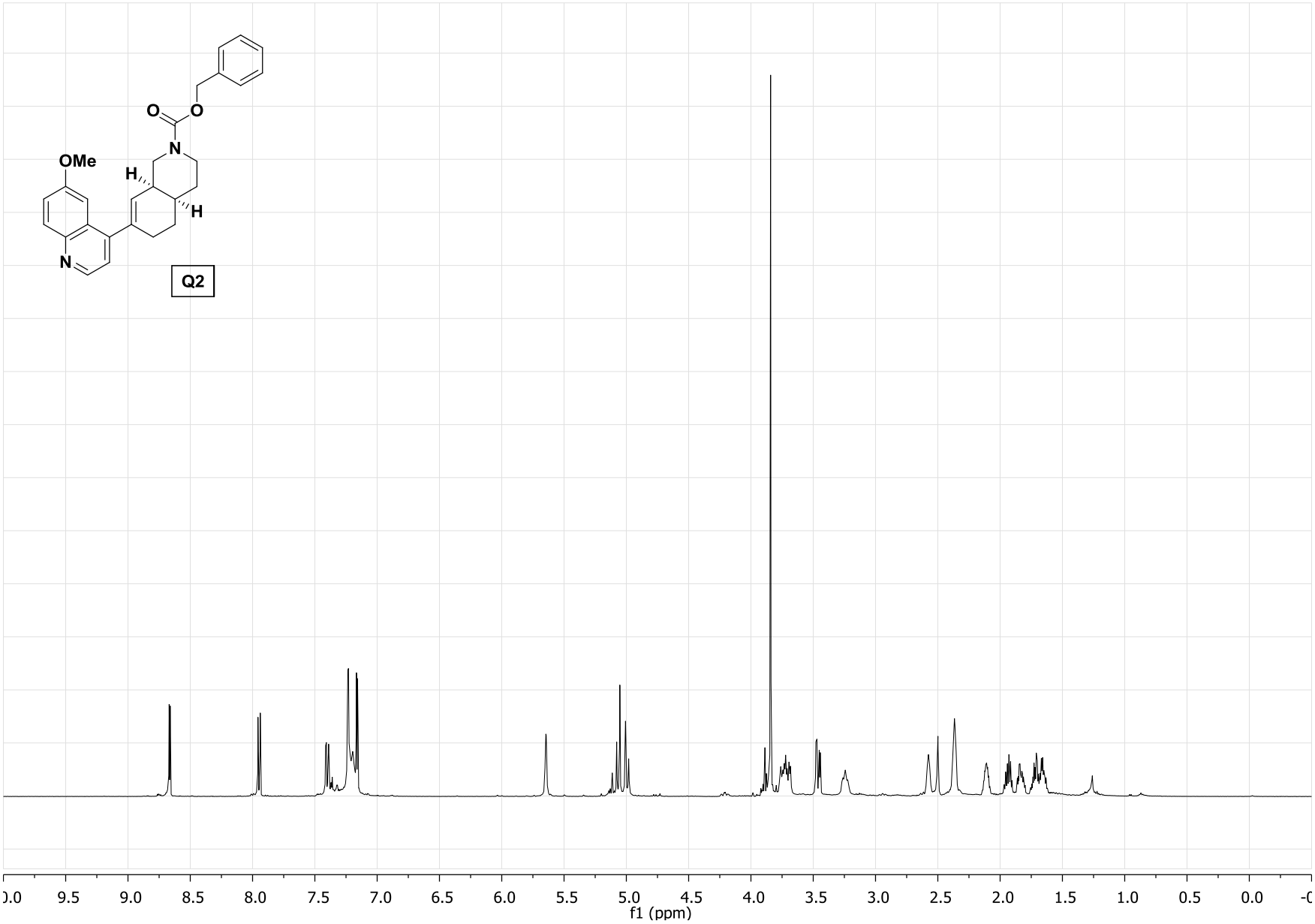

MeO
O
S
N
H
Cl
N
Q1
($d_6$-benzene)
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


f2 (ppm)
f1 (ppm)
MeO
O
S
N
H
Cl
N
Q1

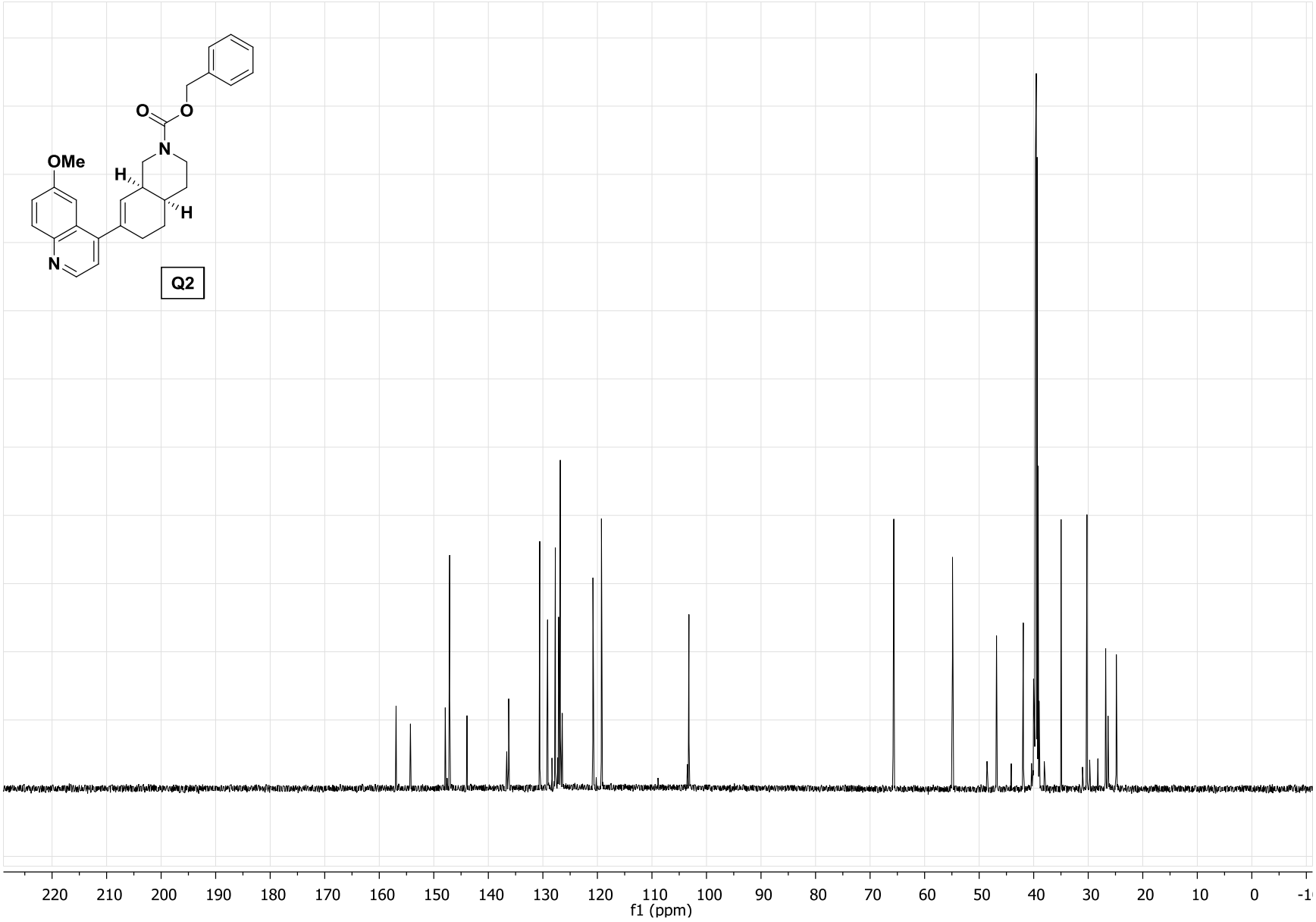


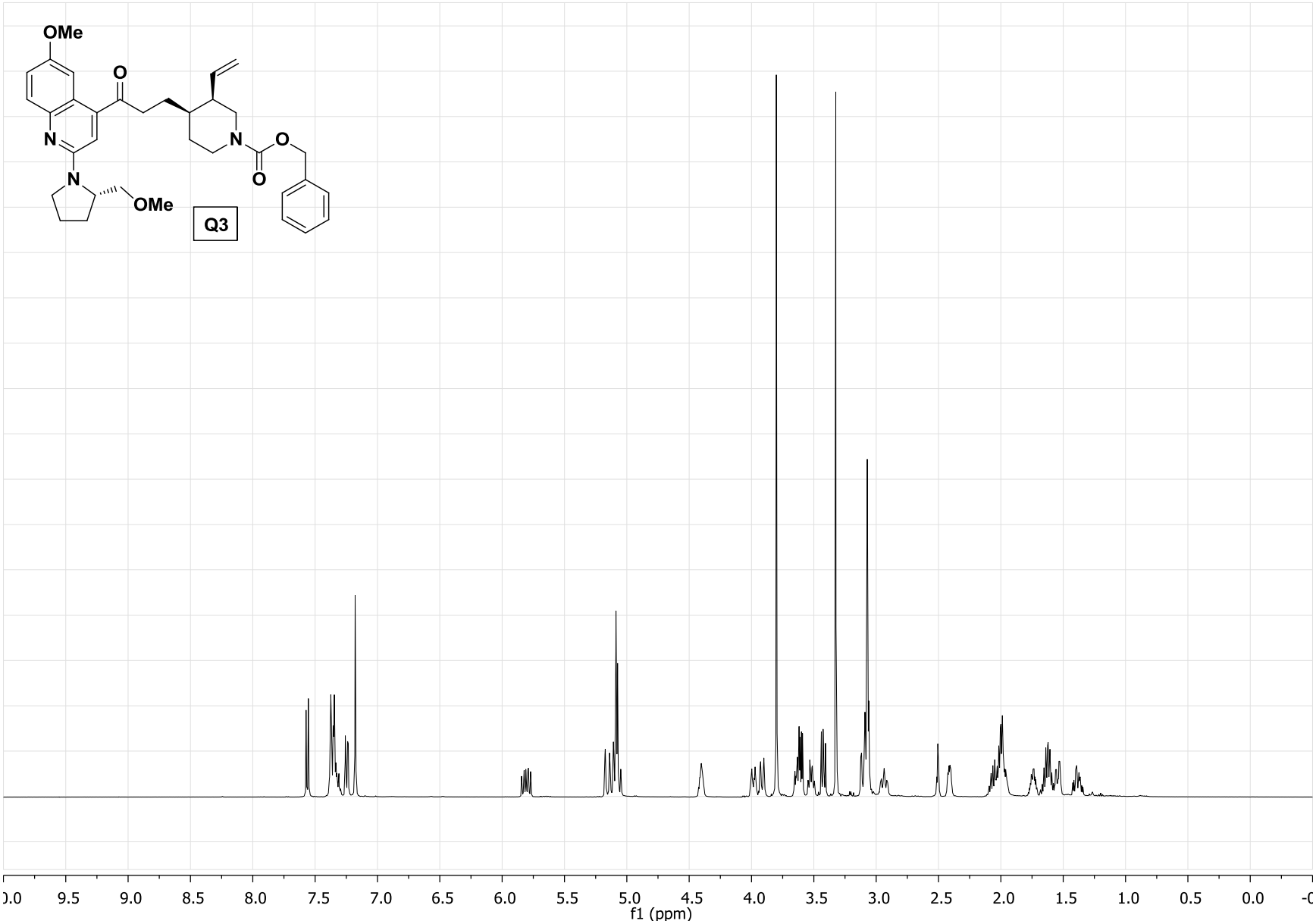

NMR99


MeO
O
S
N
H
Cl
N
Q1
f2 (ppm)
f1 (ppm)

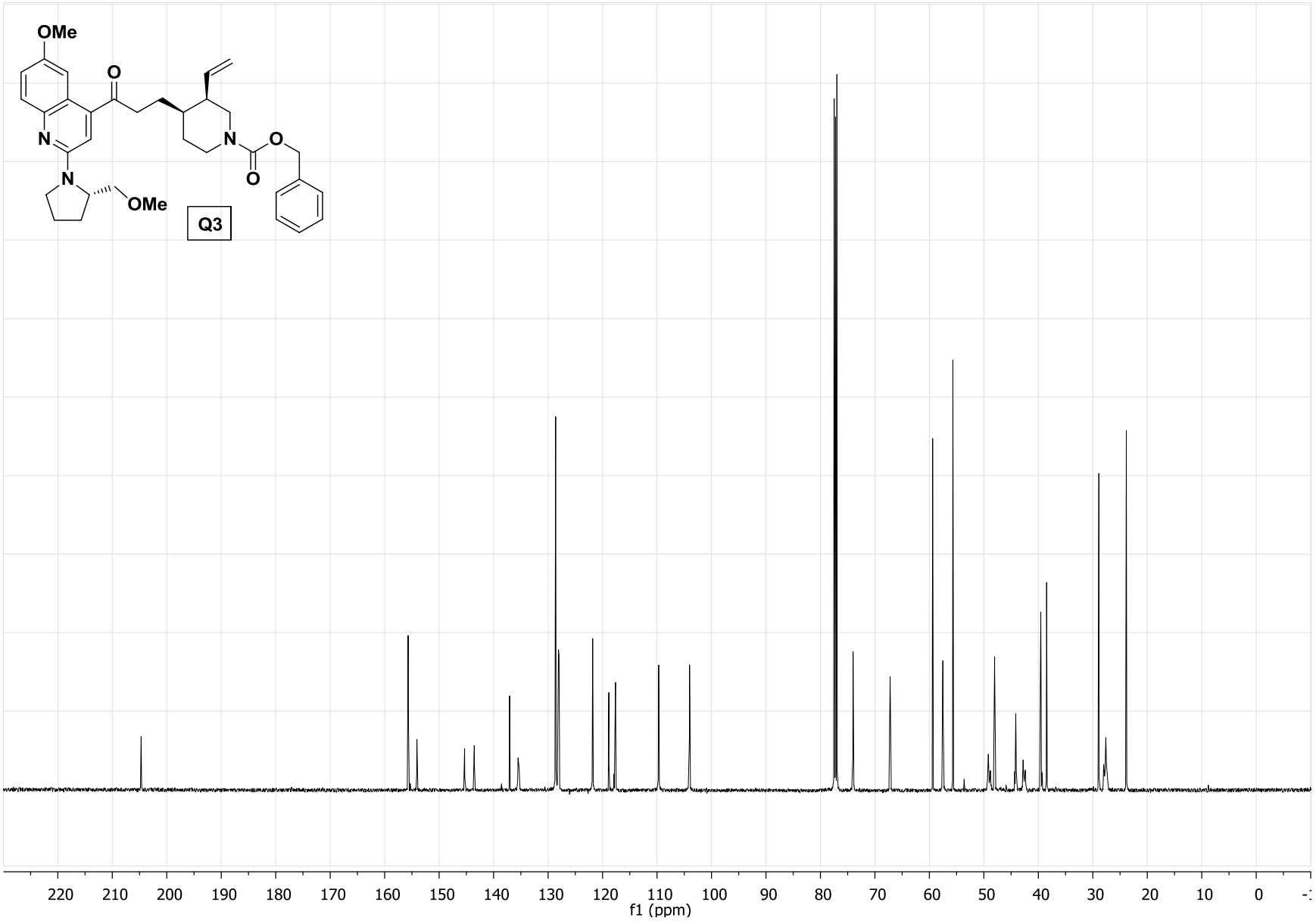

OMe
H
H
O
O
N
N
Q2
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

NMR101

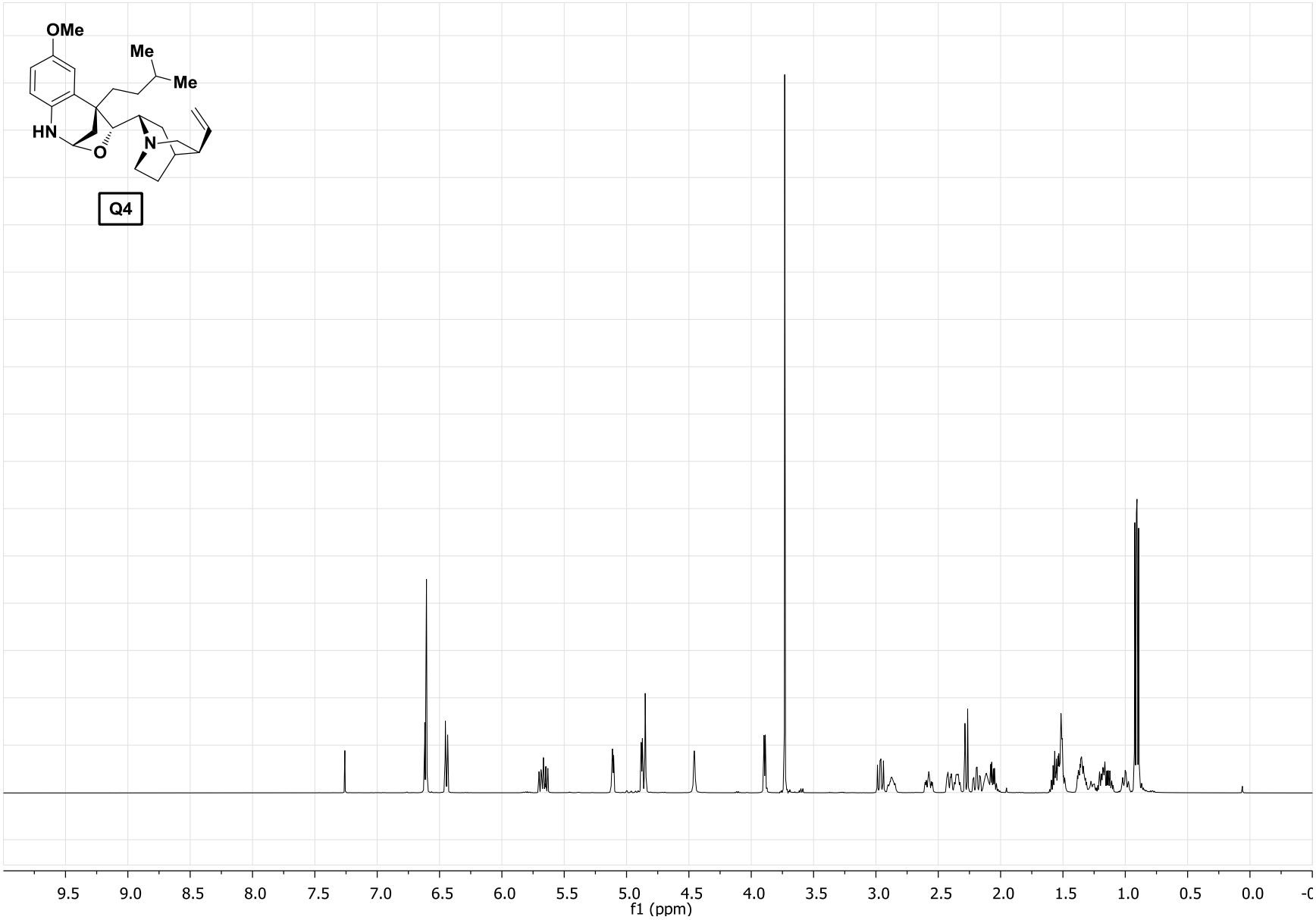

OMe
H
H
O
O
N
N
Q2
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



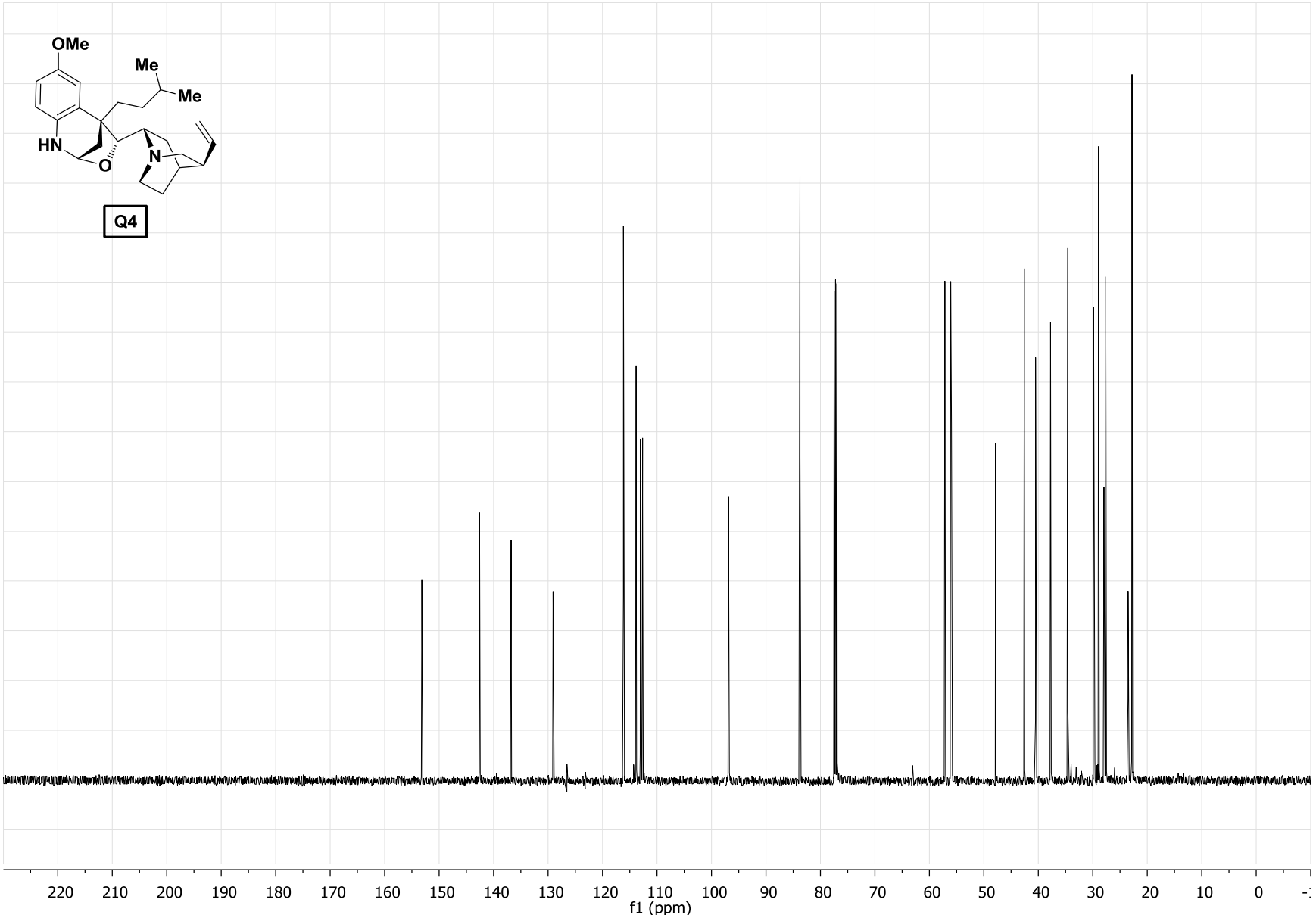

NMR103


OMe
O
N
N
OMe
N
O
O
Q3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

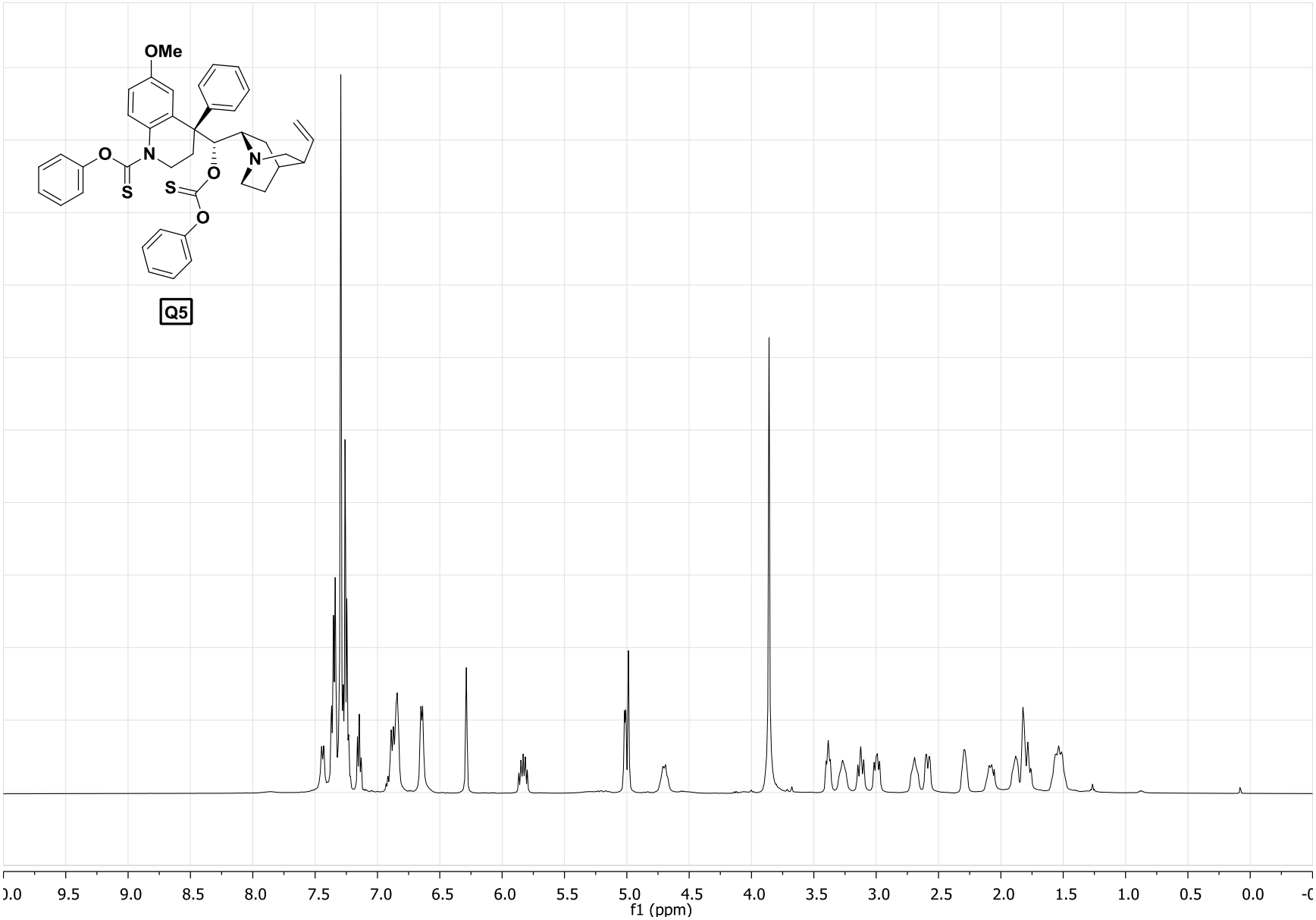
NMR104


OMe
Me
Me
HN
O
N
Q4
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

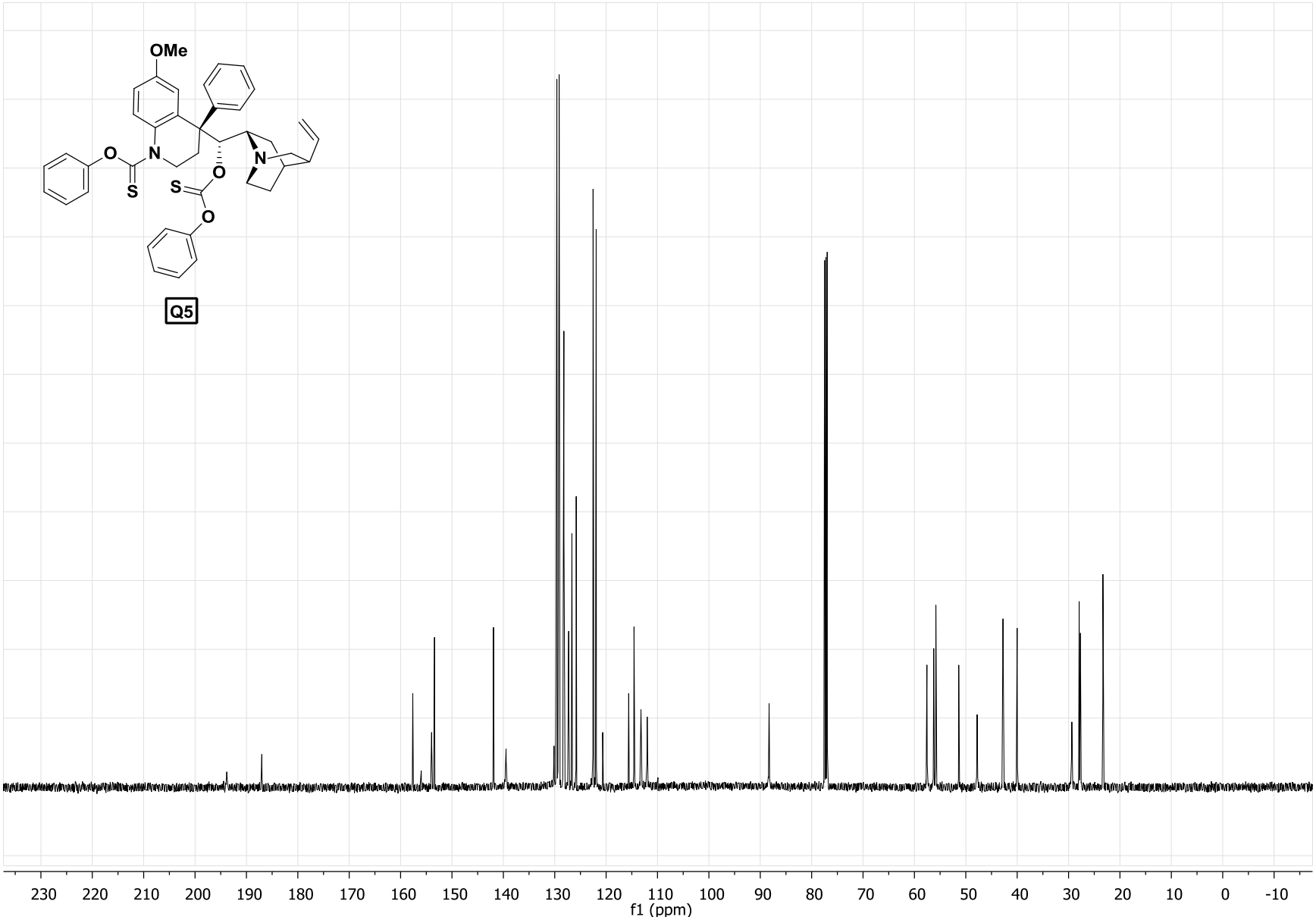
NMR105

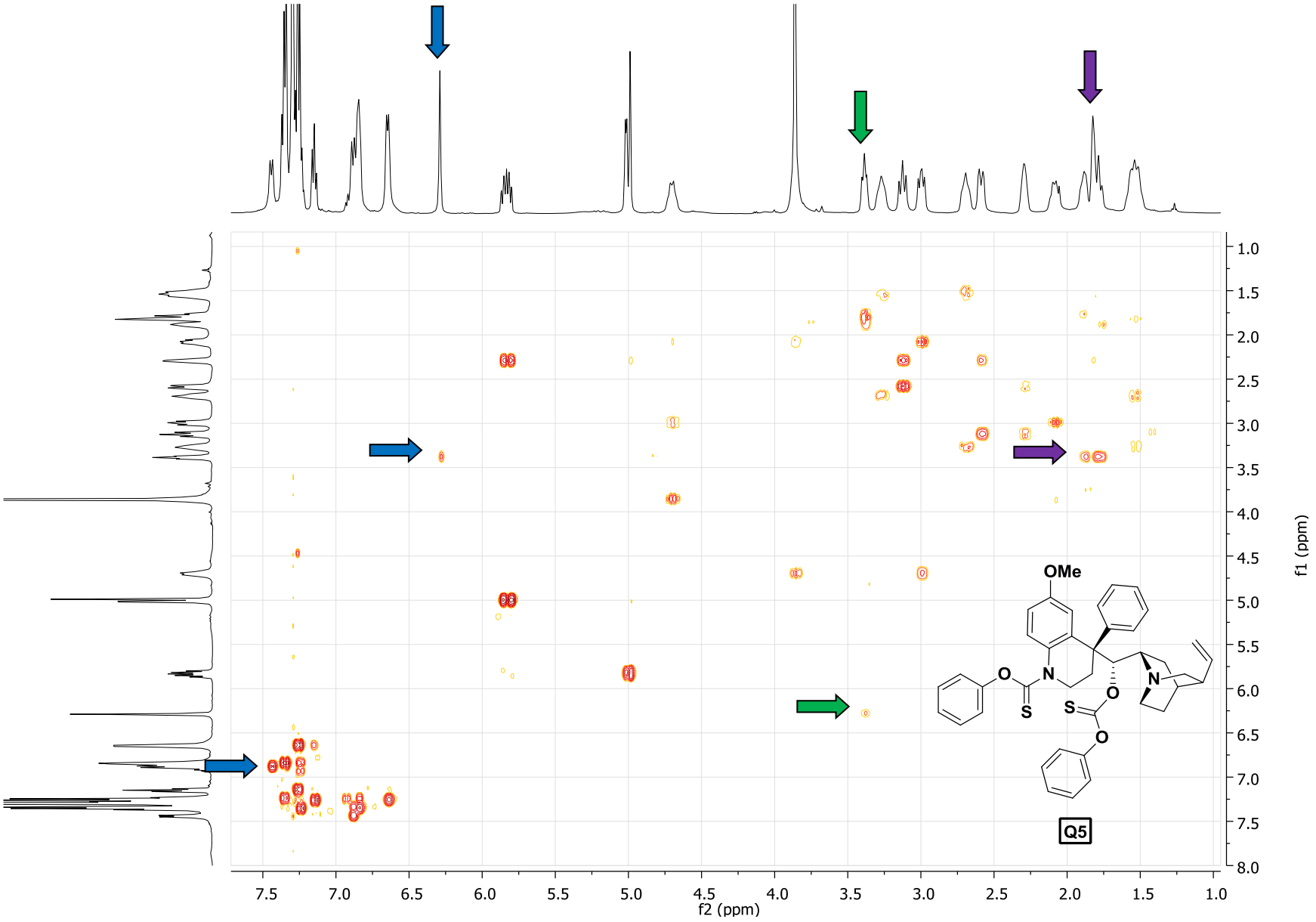

OMe
Me
Me
HN
O
N
Q4
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

NMR106

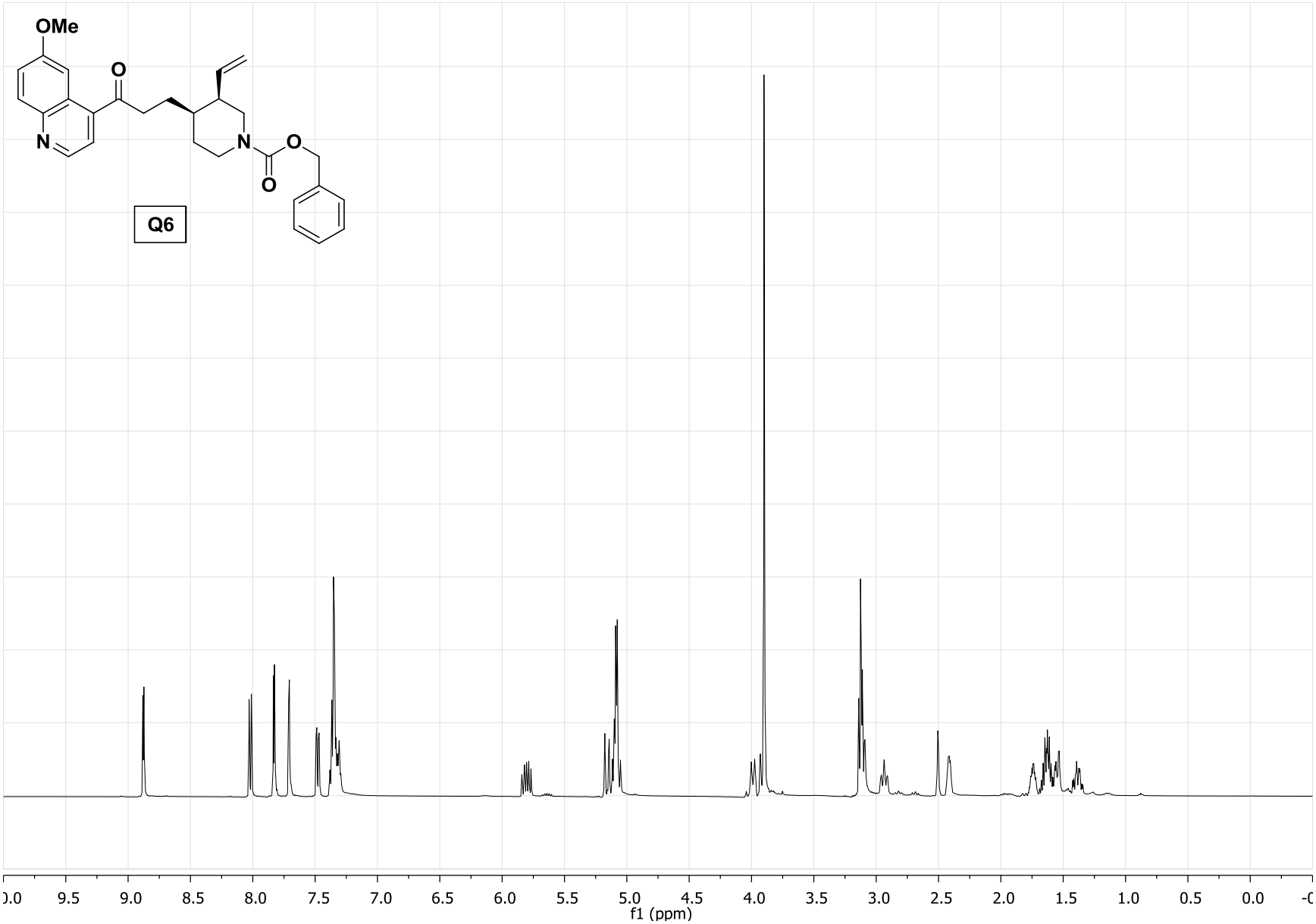


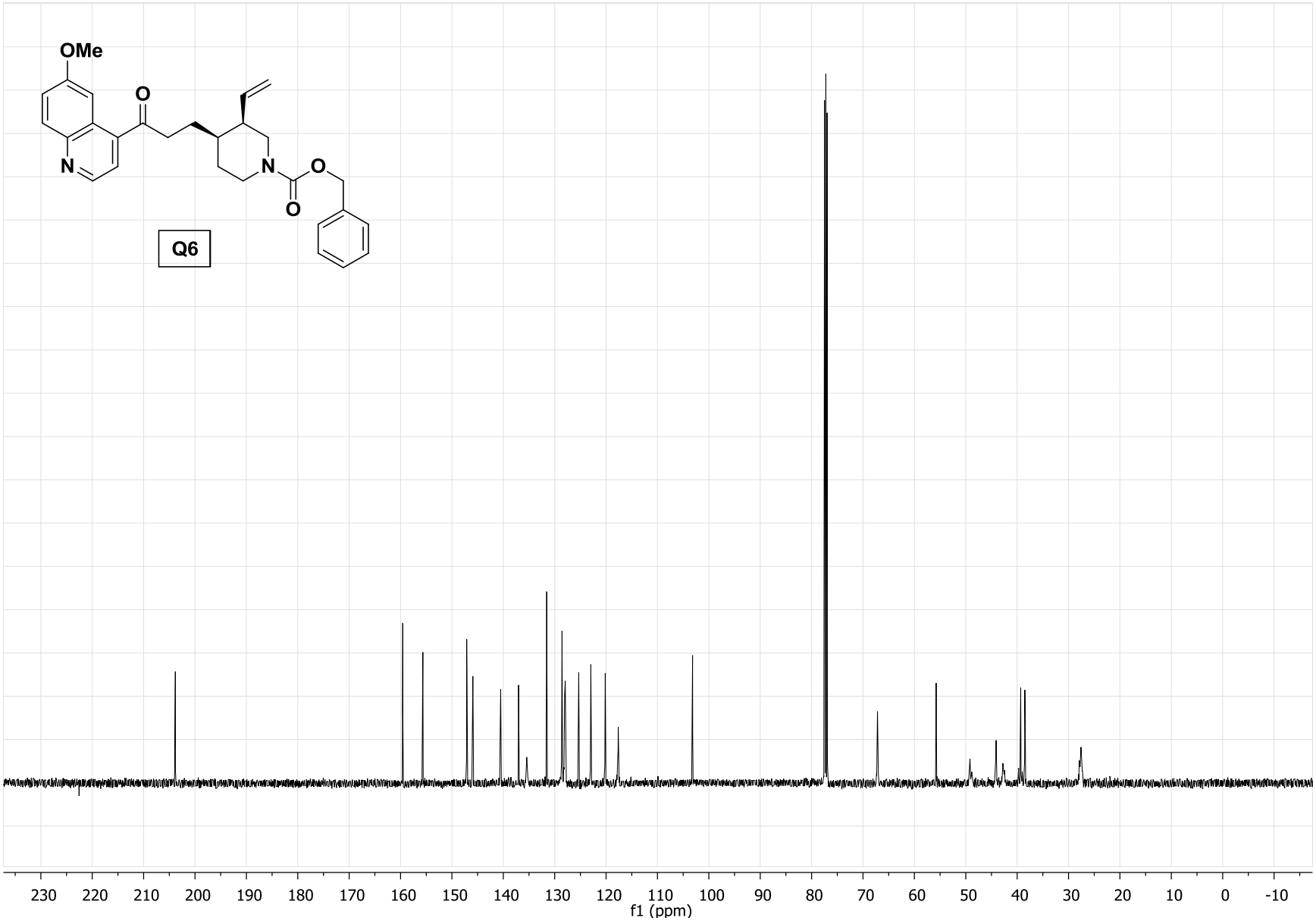

NMR107


OMe
O
N
S
O
S
O
N
Q5
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

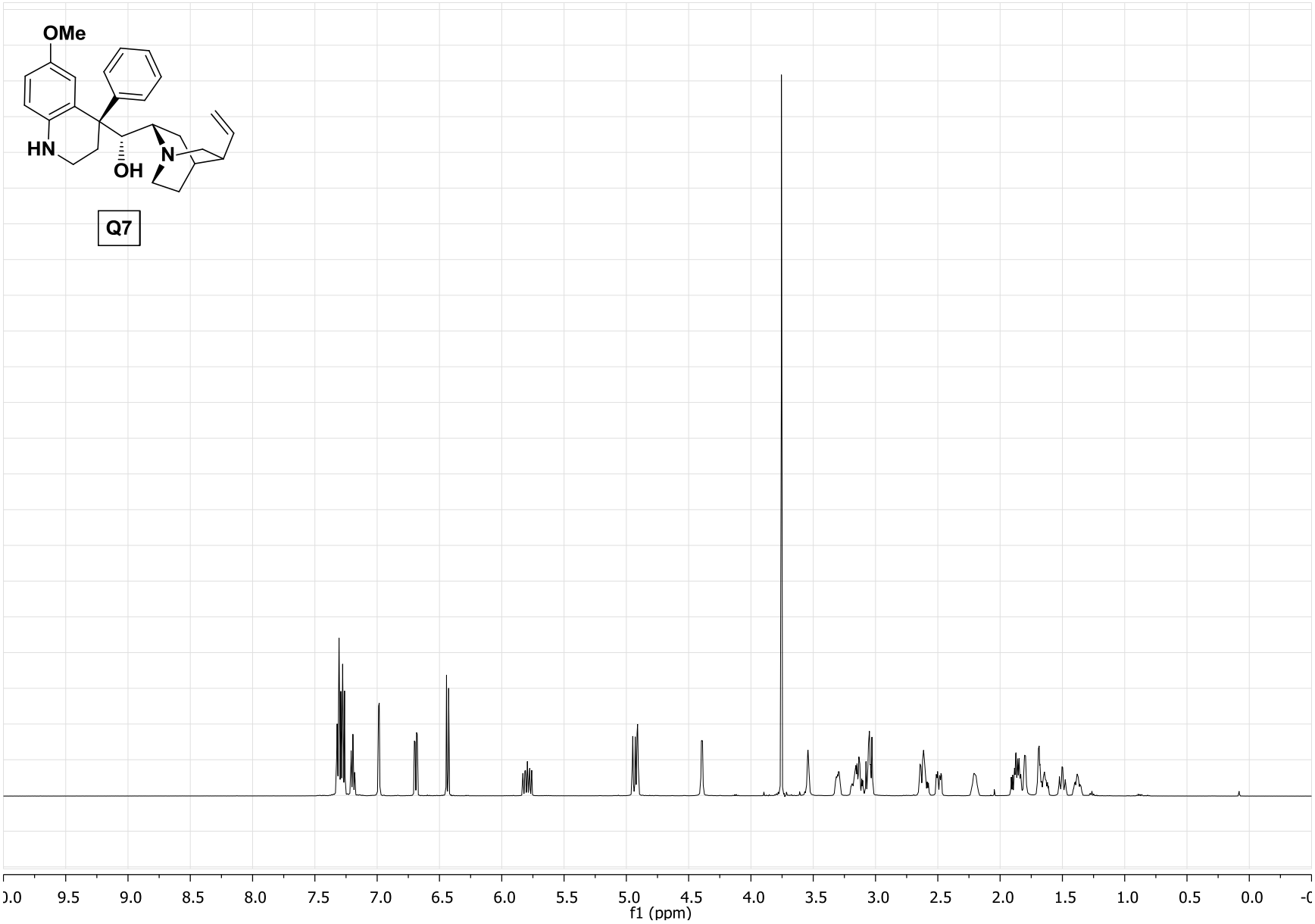



NMR109

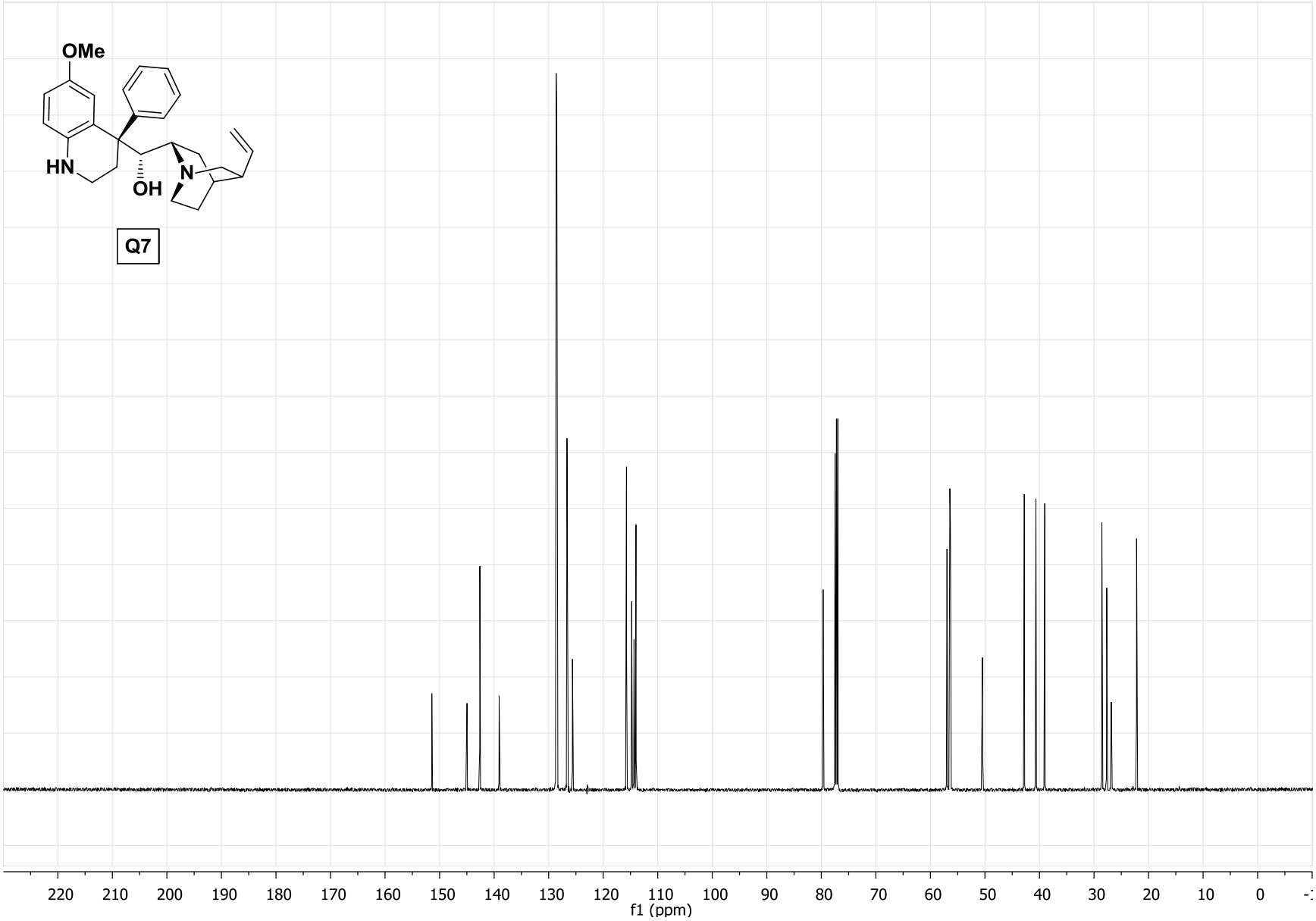

OMe
O
N
N
O
O
Q6
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OMe
O
N
N
O
O
Q6
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

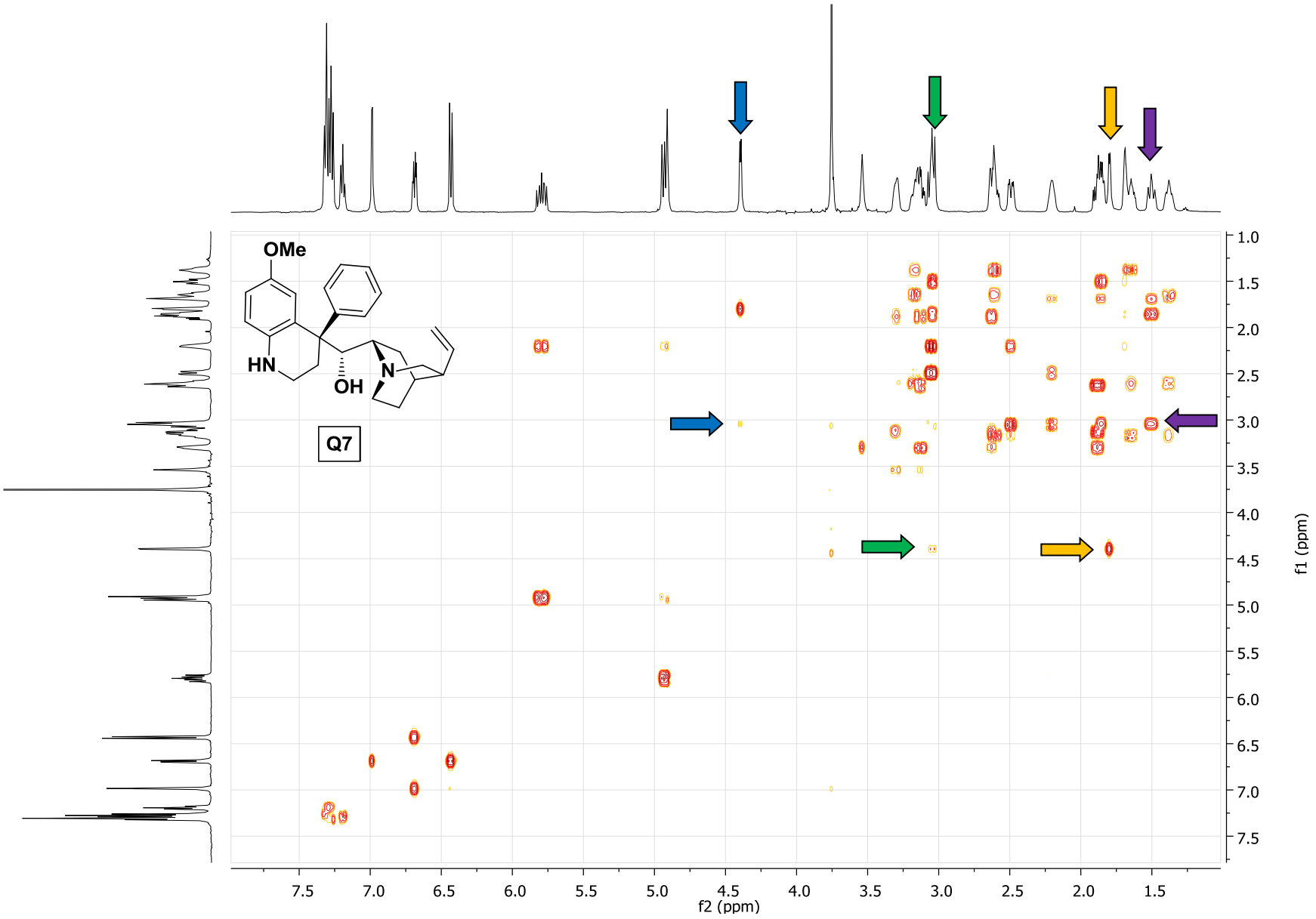
NMR111



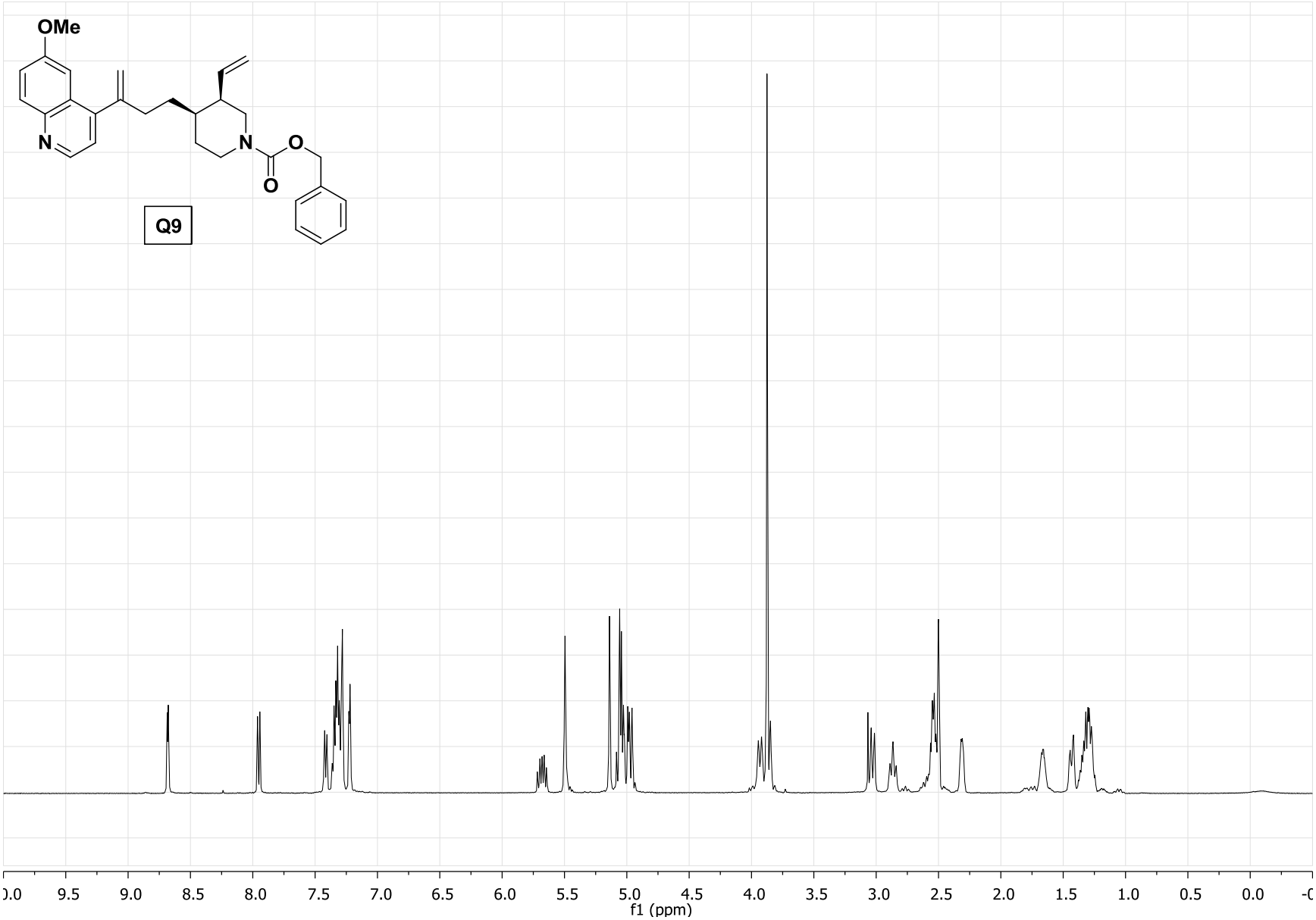

NMR112


OMe
HN
OH
N
Q7
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

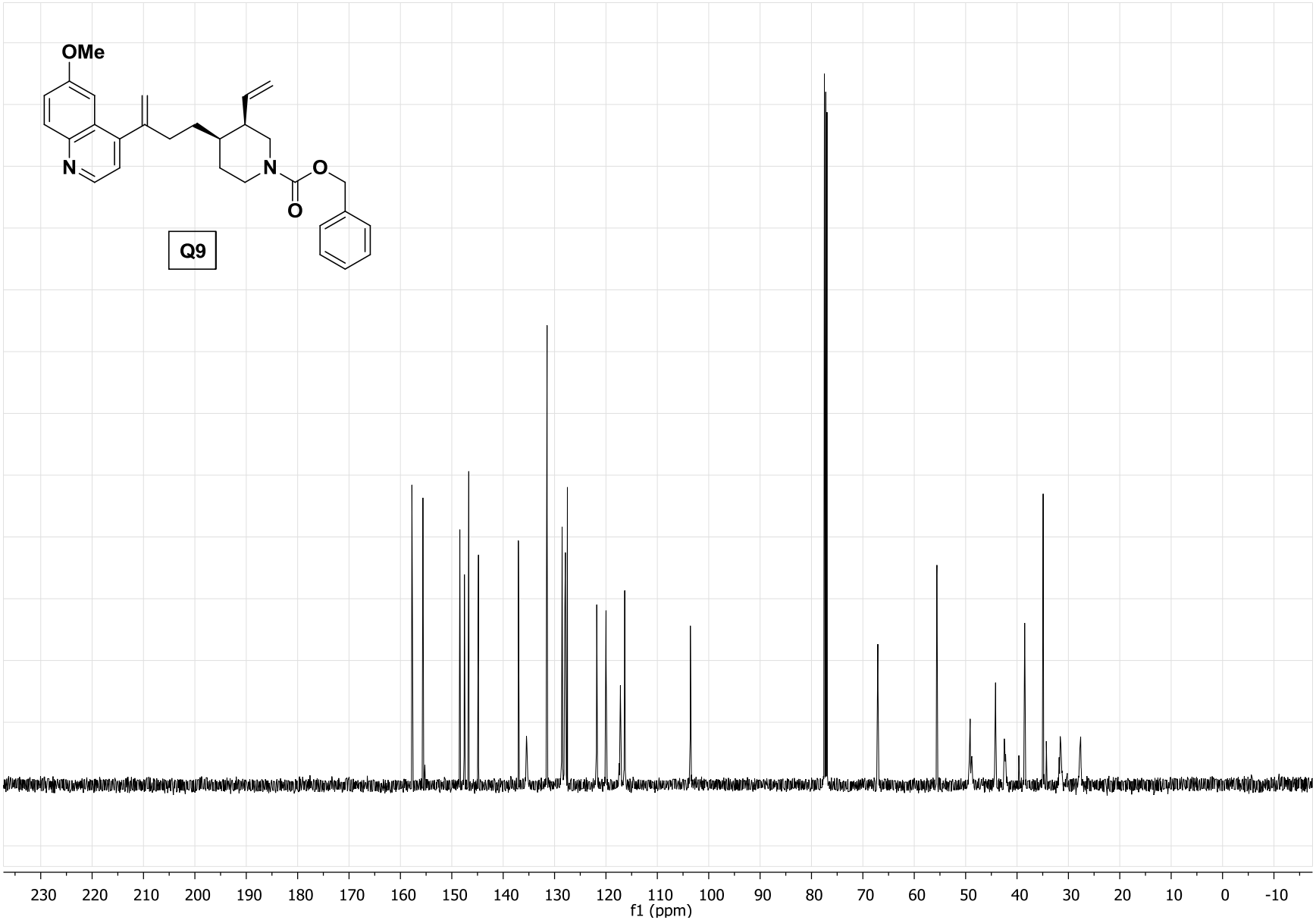
NMR113



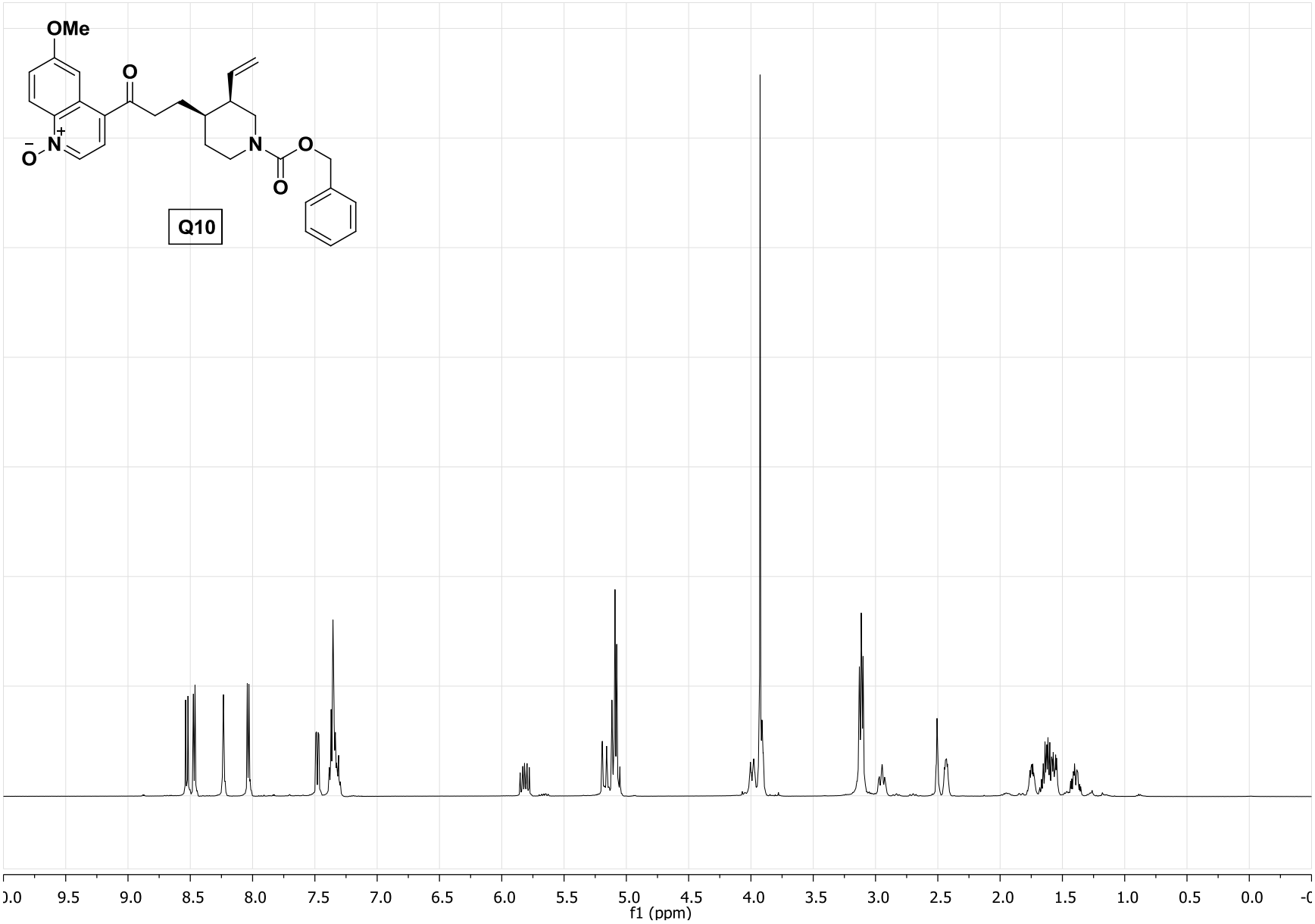

NMR114


OMe
N
N
O
O
Q9
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

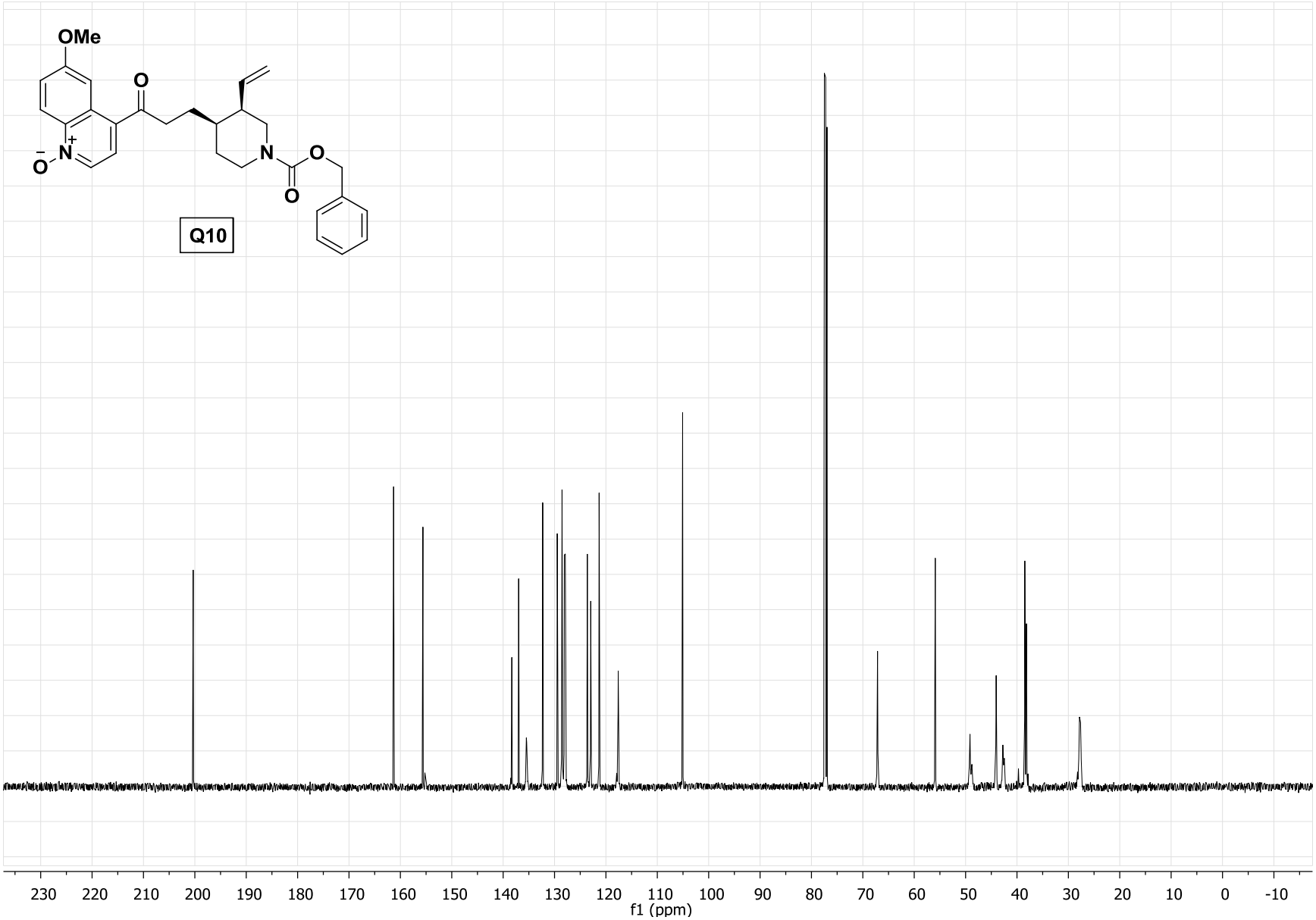
NMR115


OMe
N
N
O
O
Q9
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

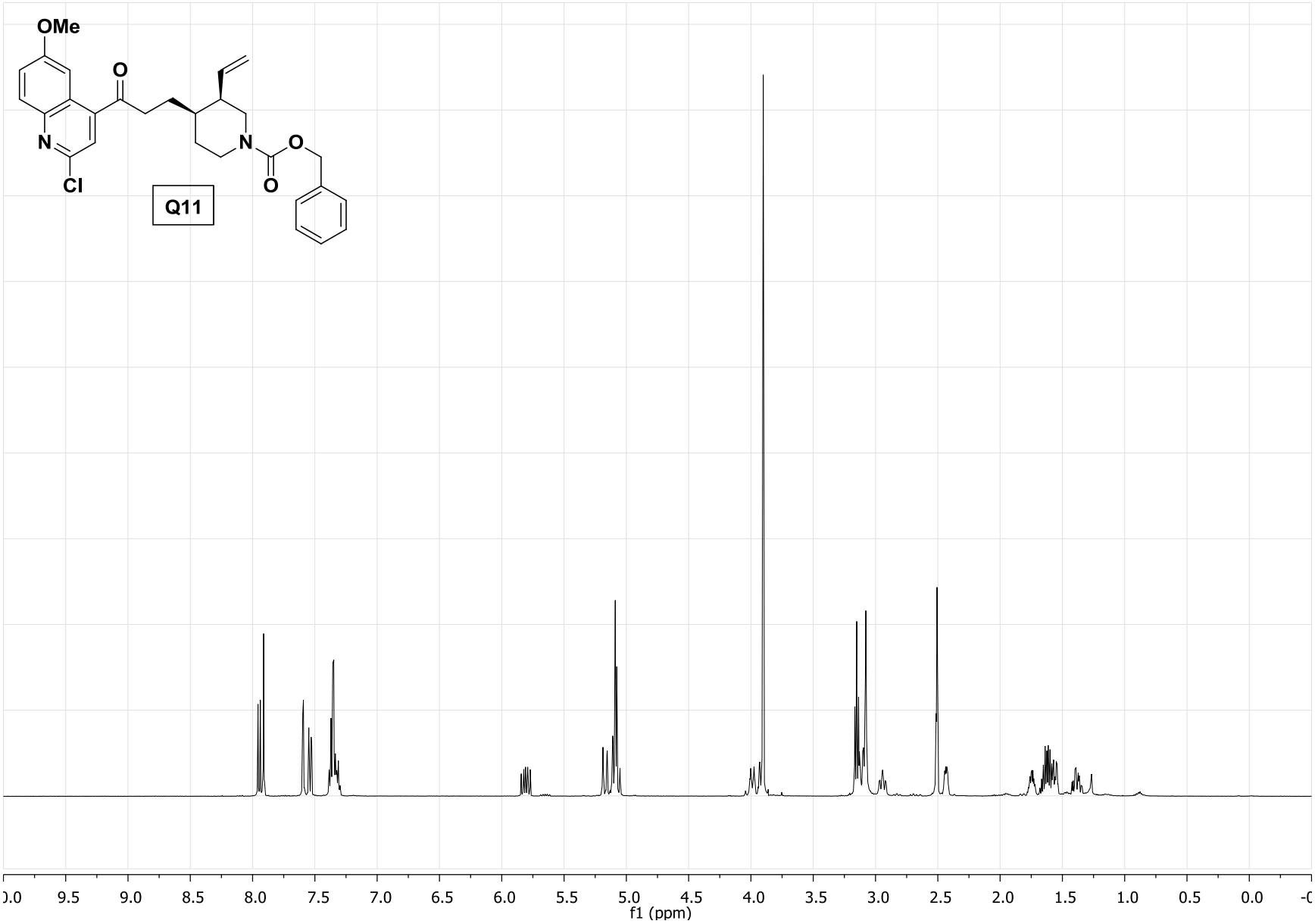
NMR116



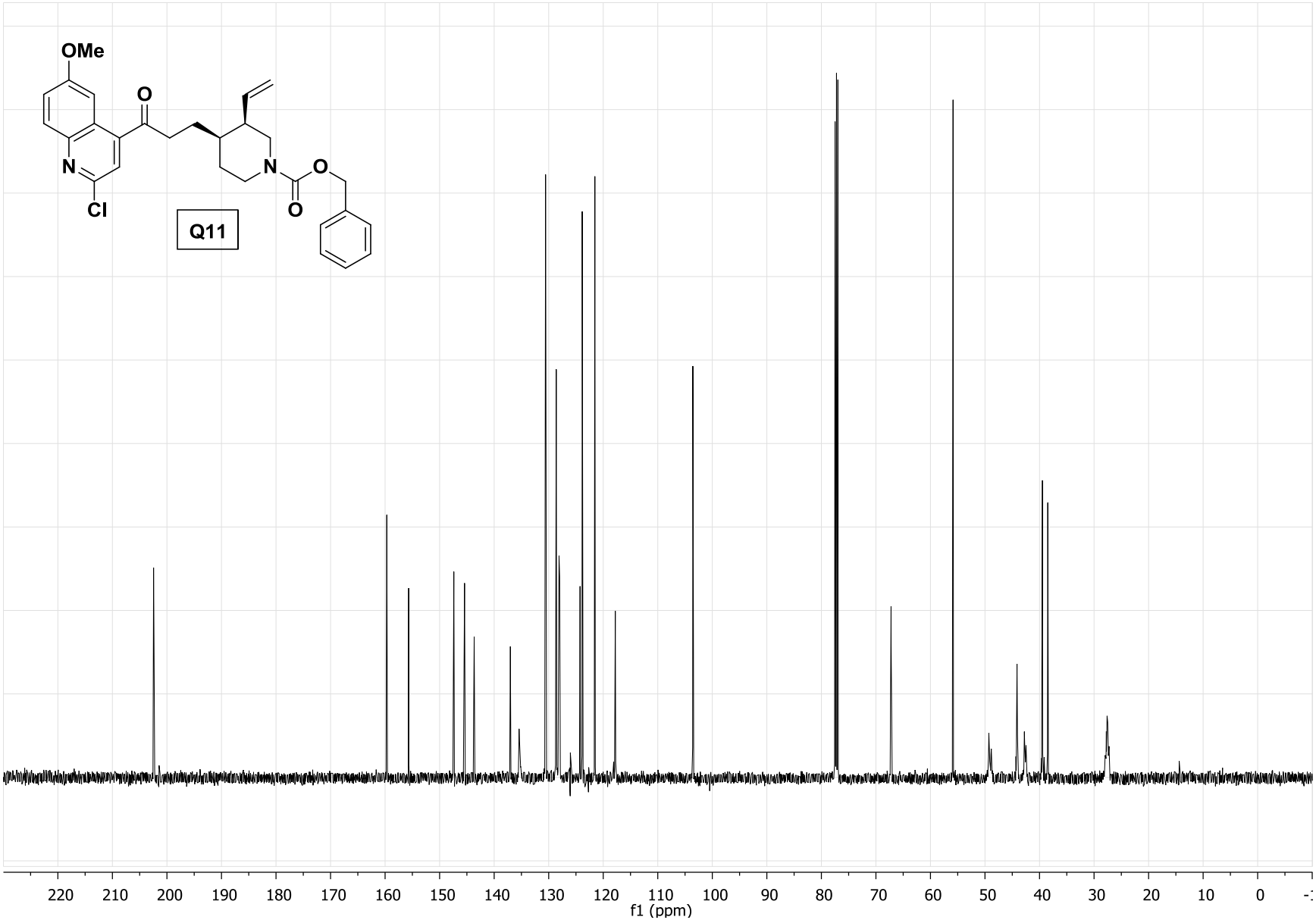

NMR117


OMe
O
N
O
N
O
O
Q10
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

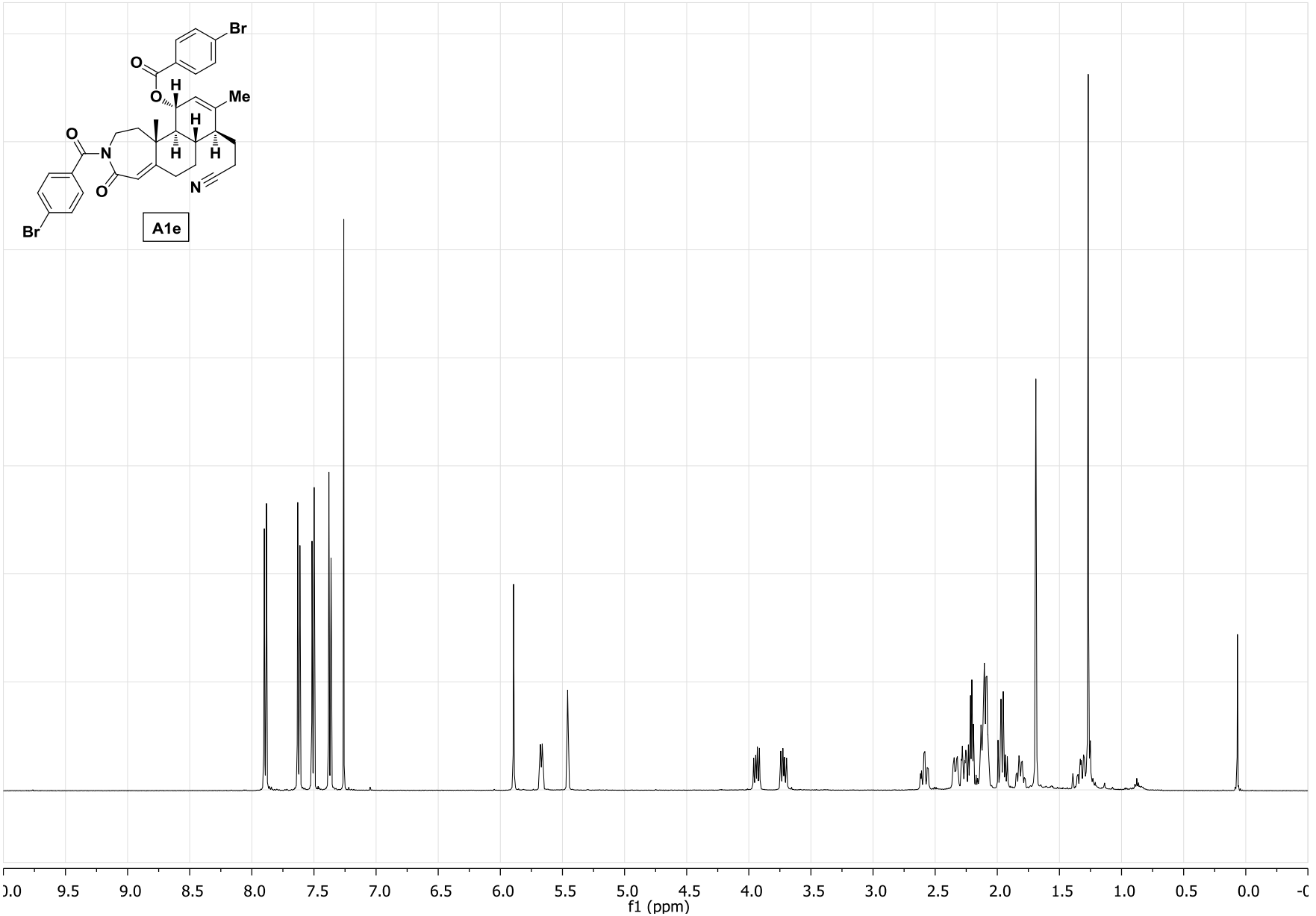
NMR118


OMe
O
N
Cl
N
O
O
Q11
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

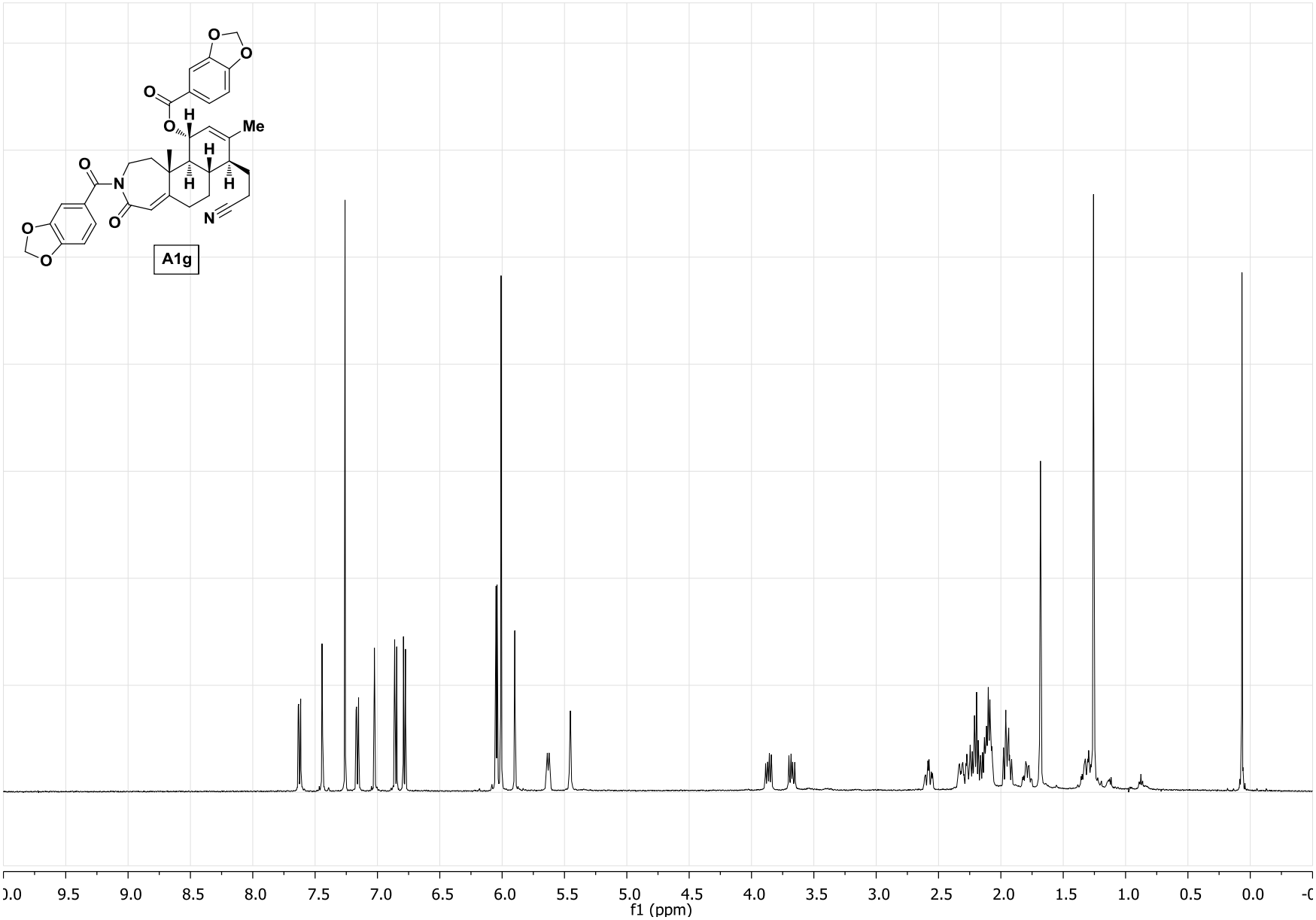
NMR119


OMe
O
N
Cl
N
O
O
Q11
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

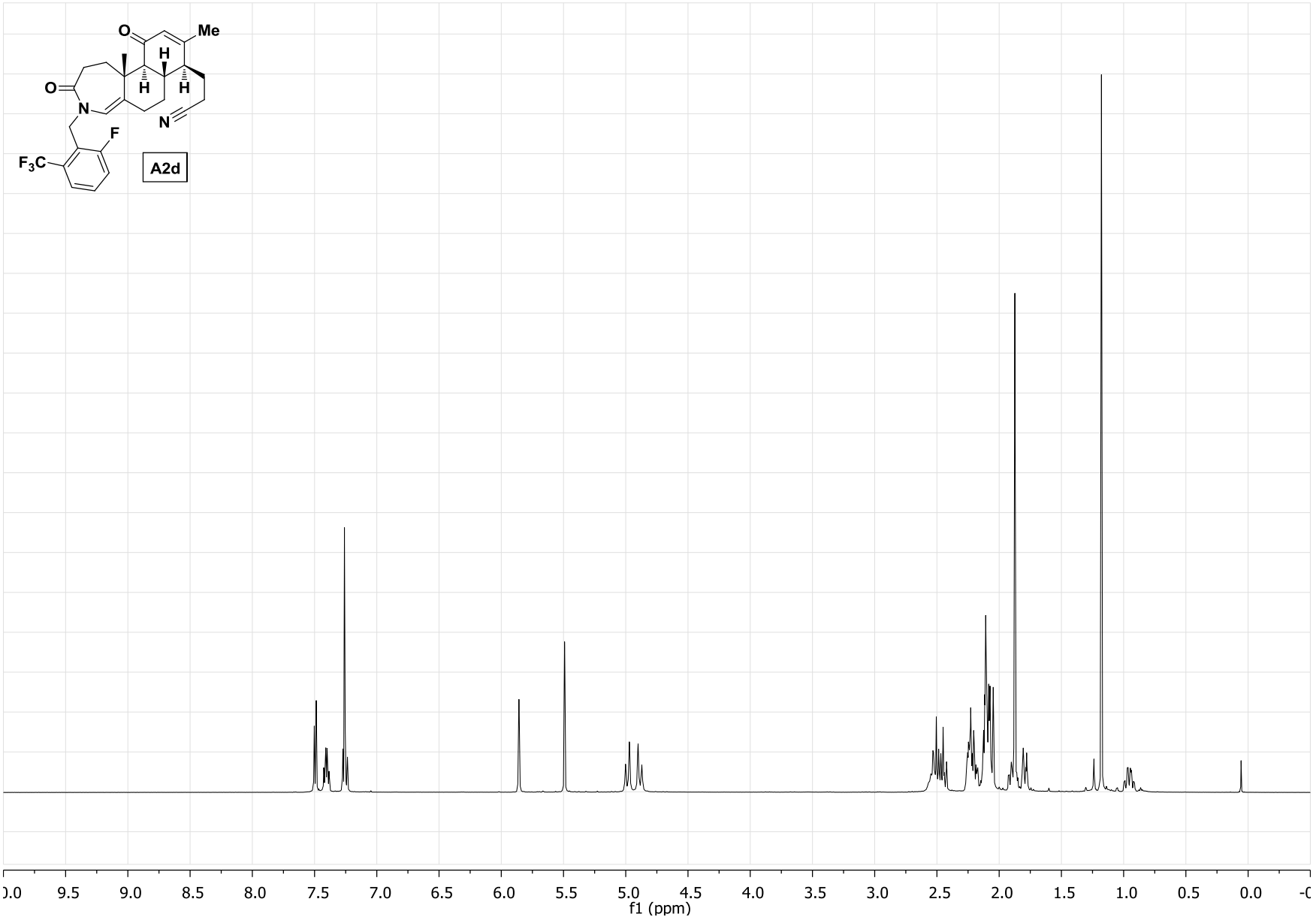
NMR120

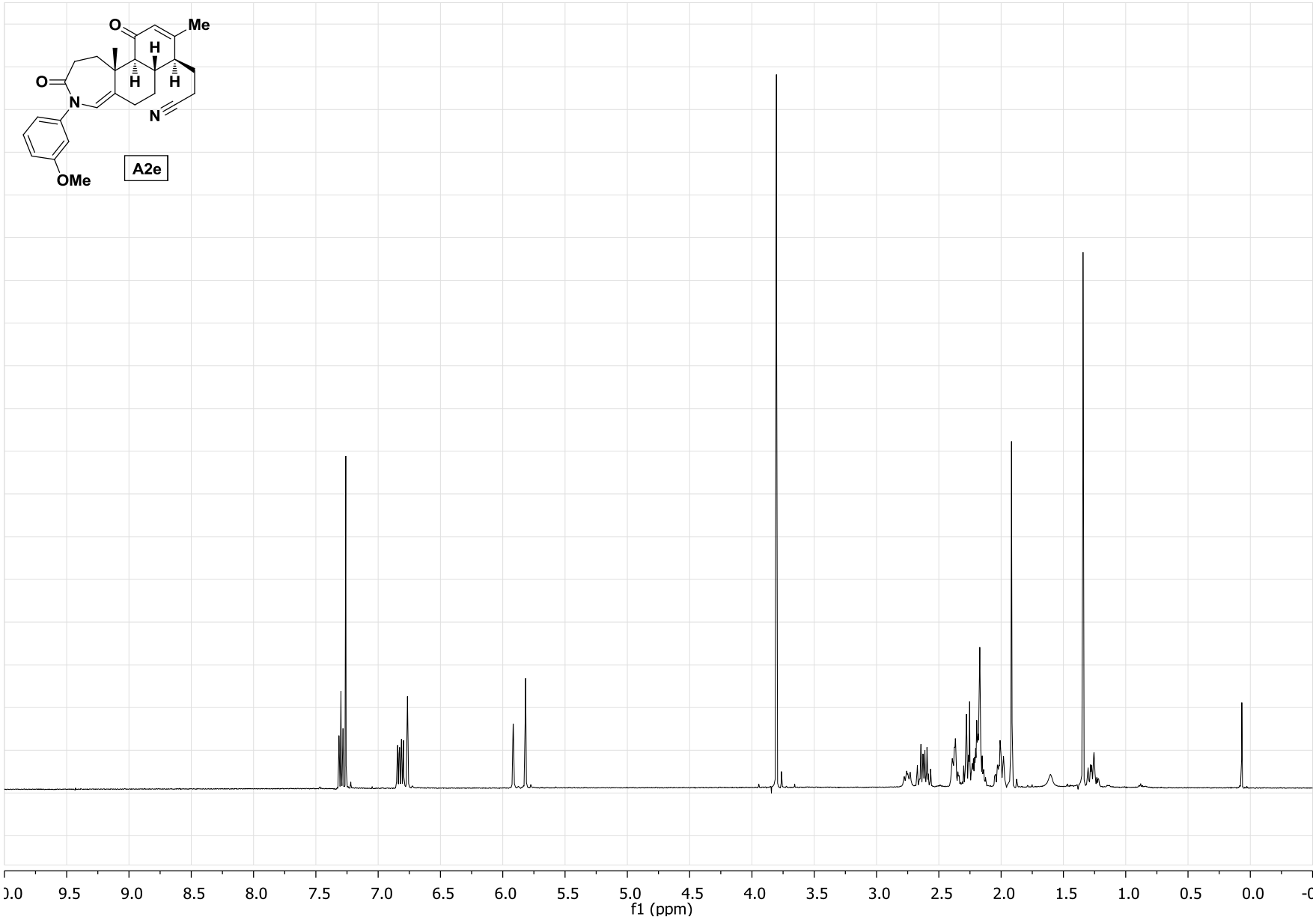

Br
O
O
H
Me
O
N
H
H
H
O
N
Br
A1e
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

NMR121

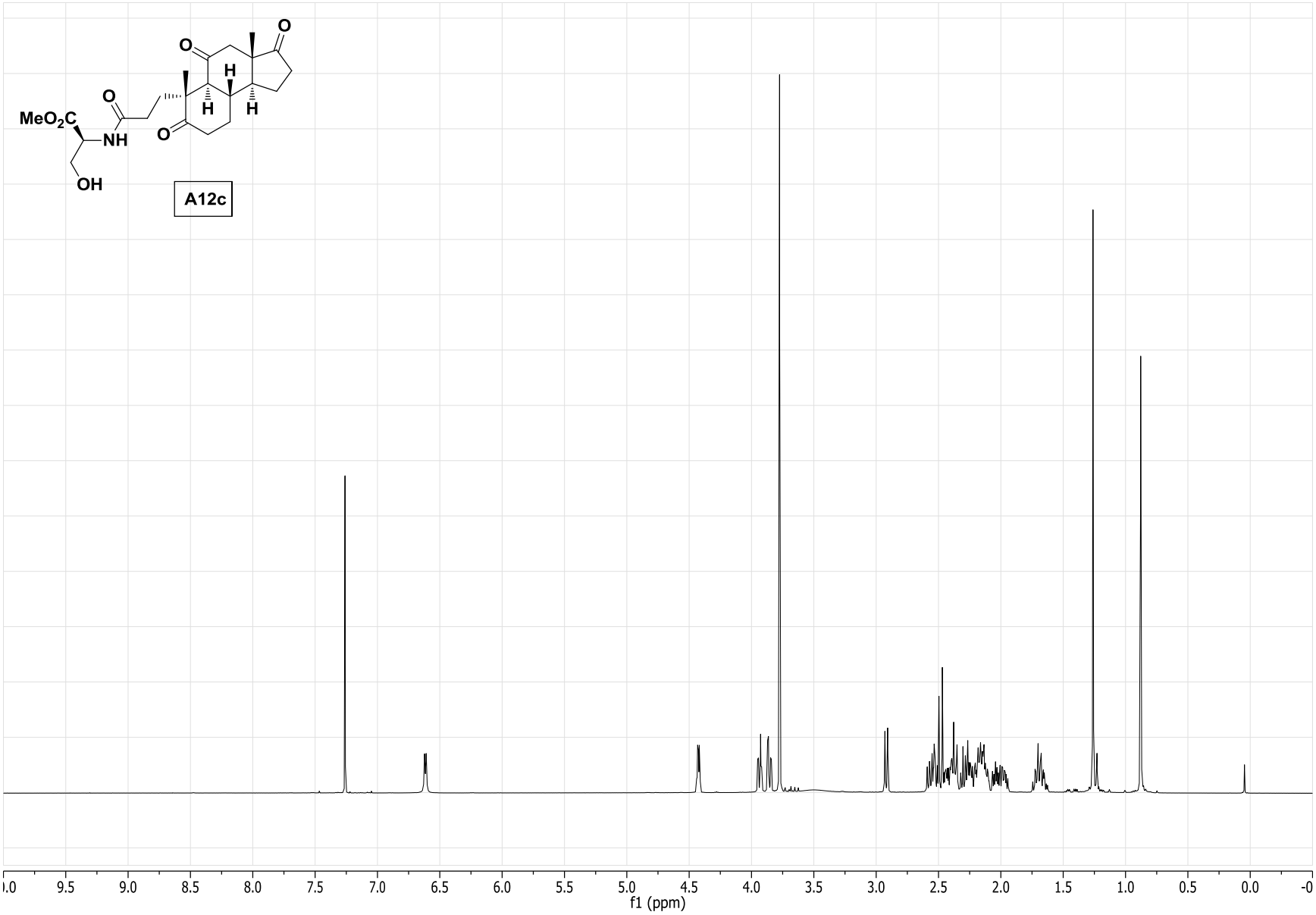



NMR122

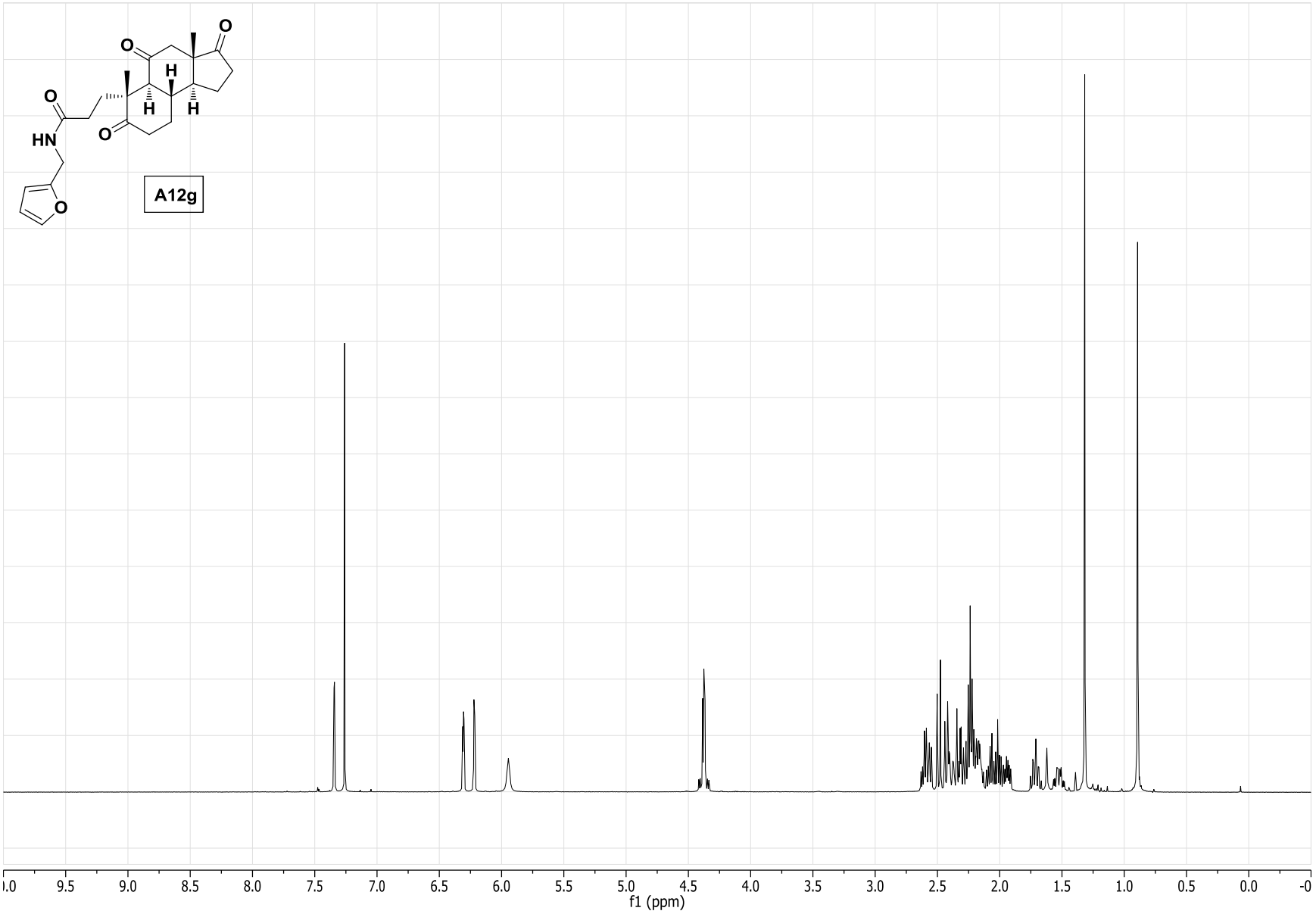

O
Me
H
O
H
H
N
N
F
F3C
A2d
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

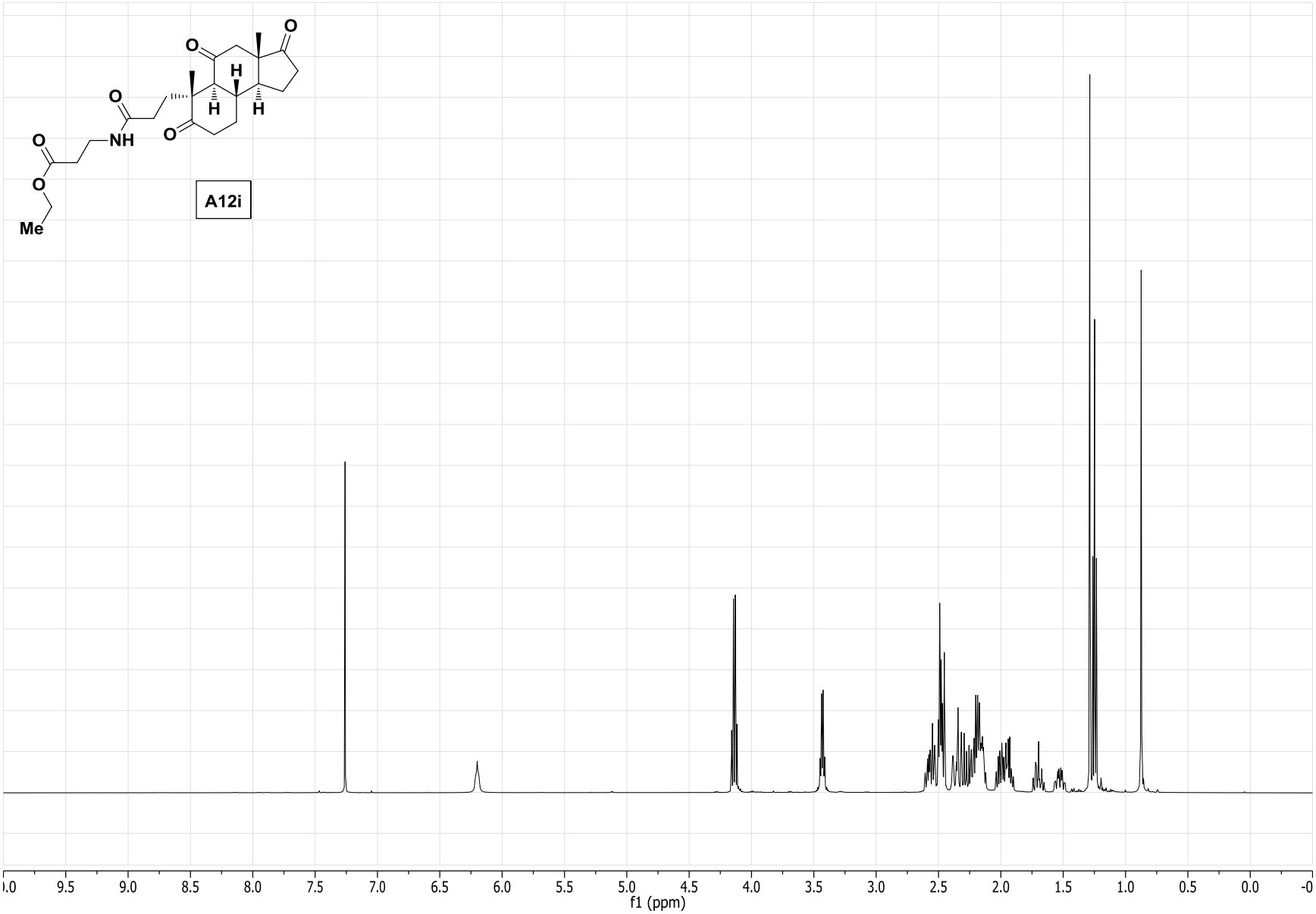



NMR124

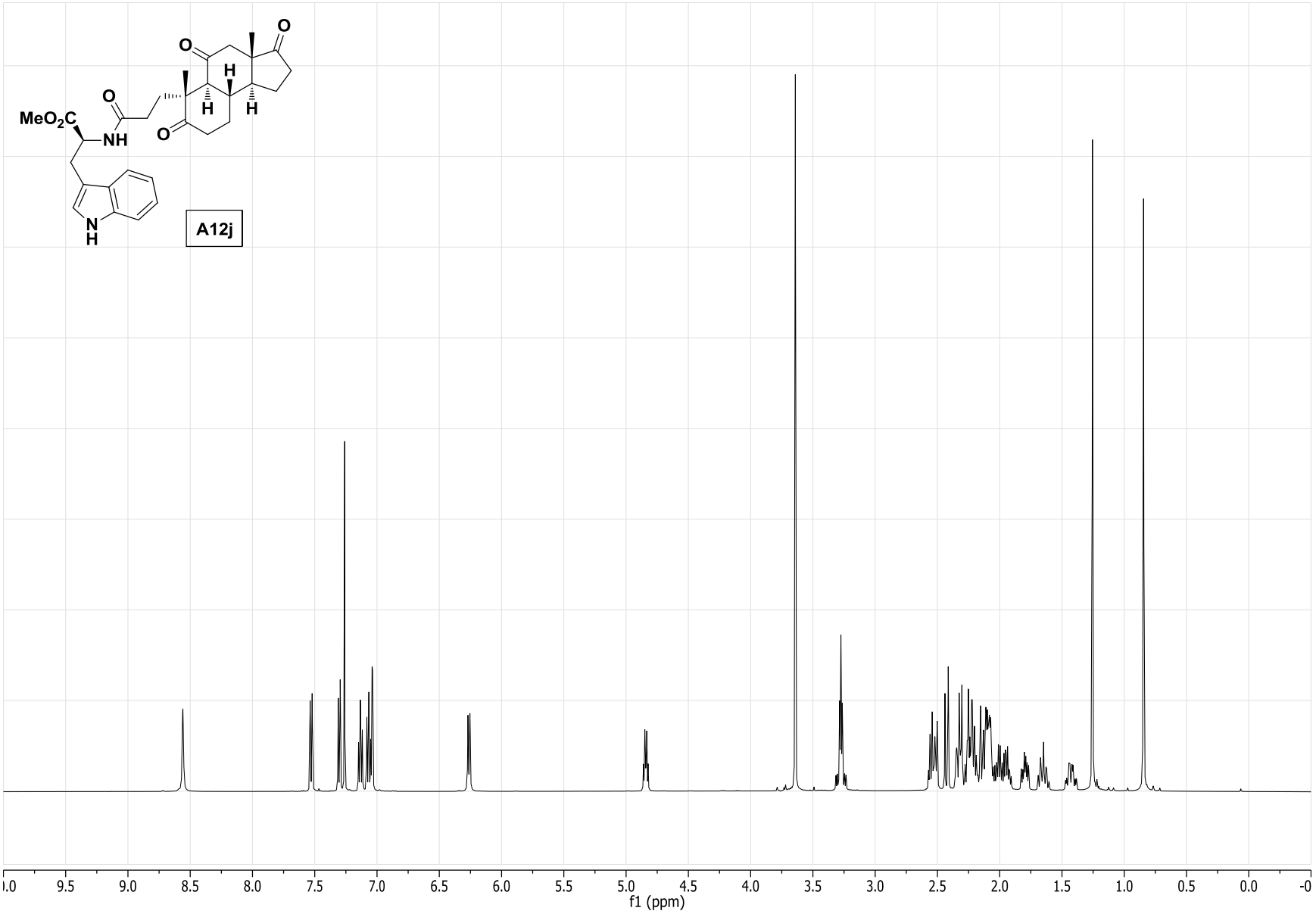


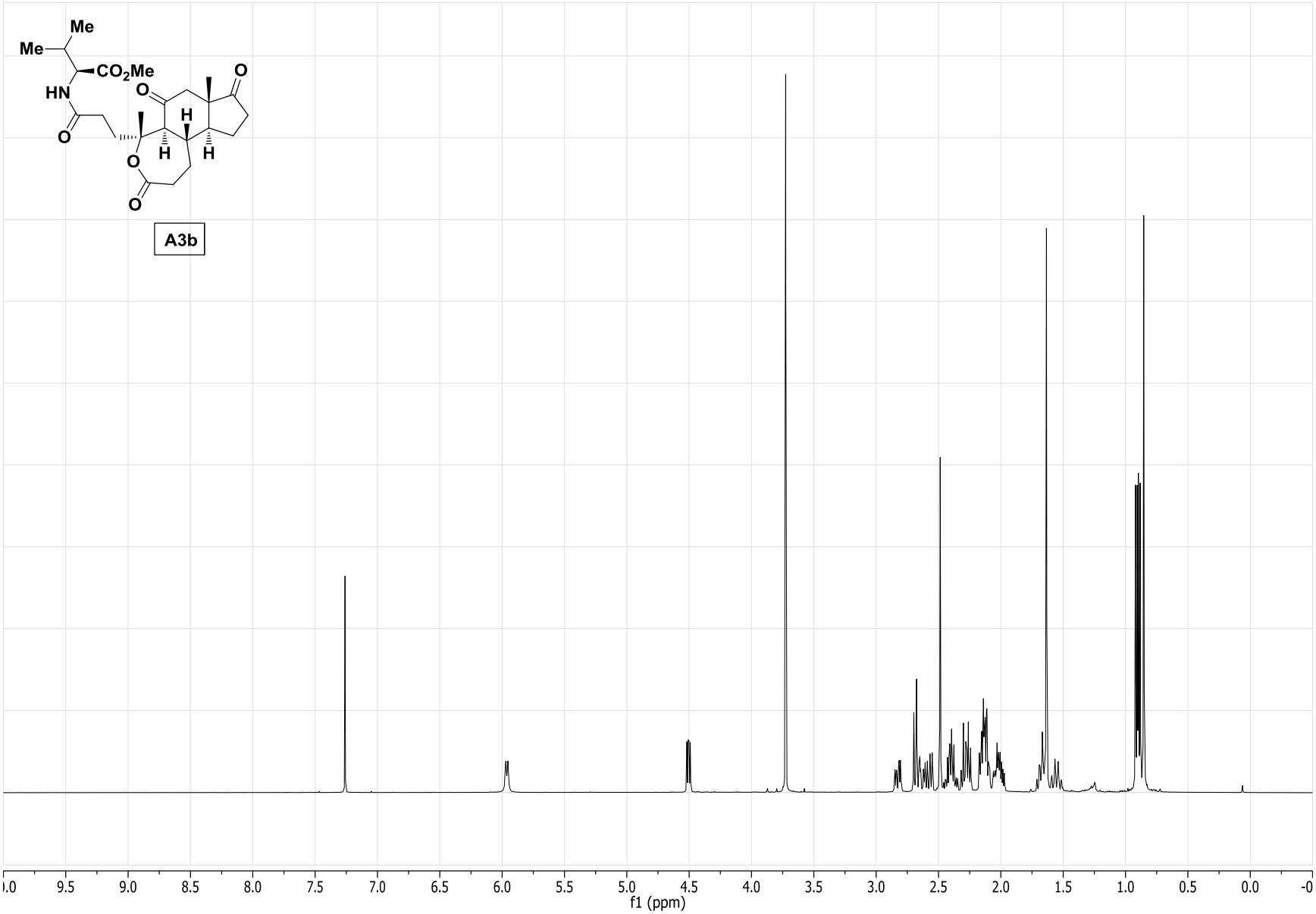

NMR125


A12g
f1 (ppm)

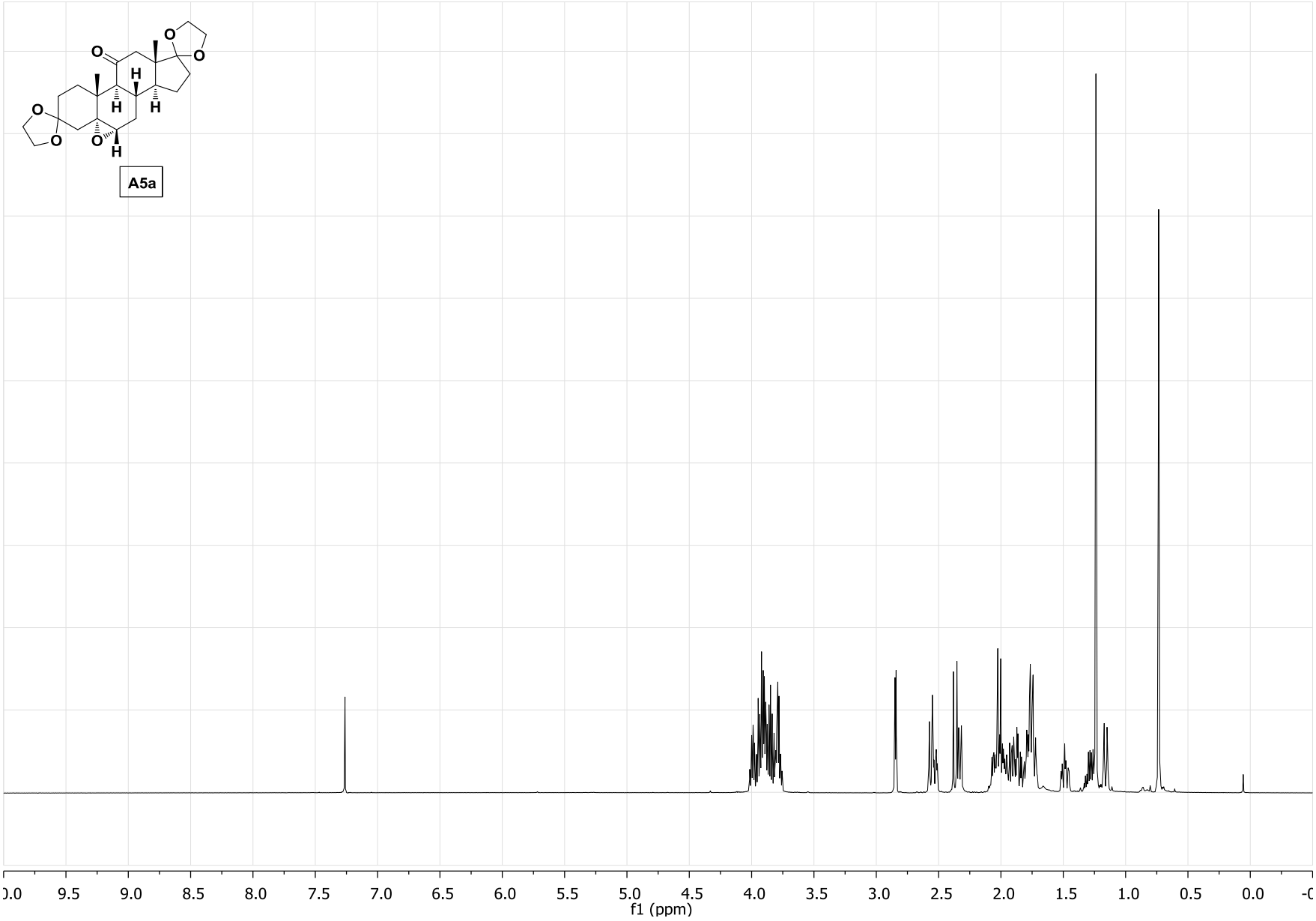



NMR127

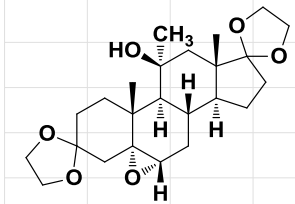

A12j
f1 (ppm)




NMR129



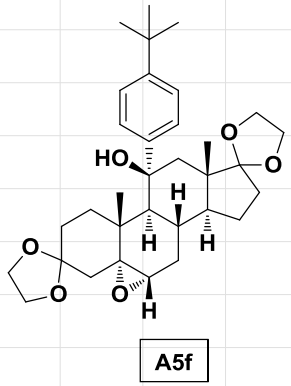

NMR130


HO
CH3
O
O
H
H
H
O
O
O
H

A5c


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

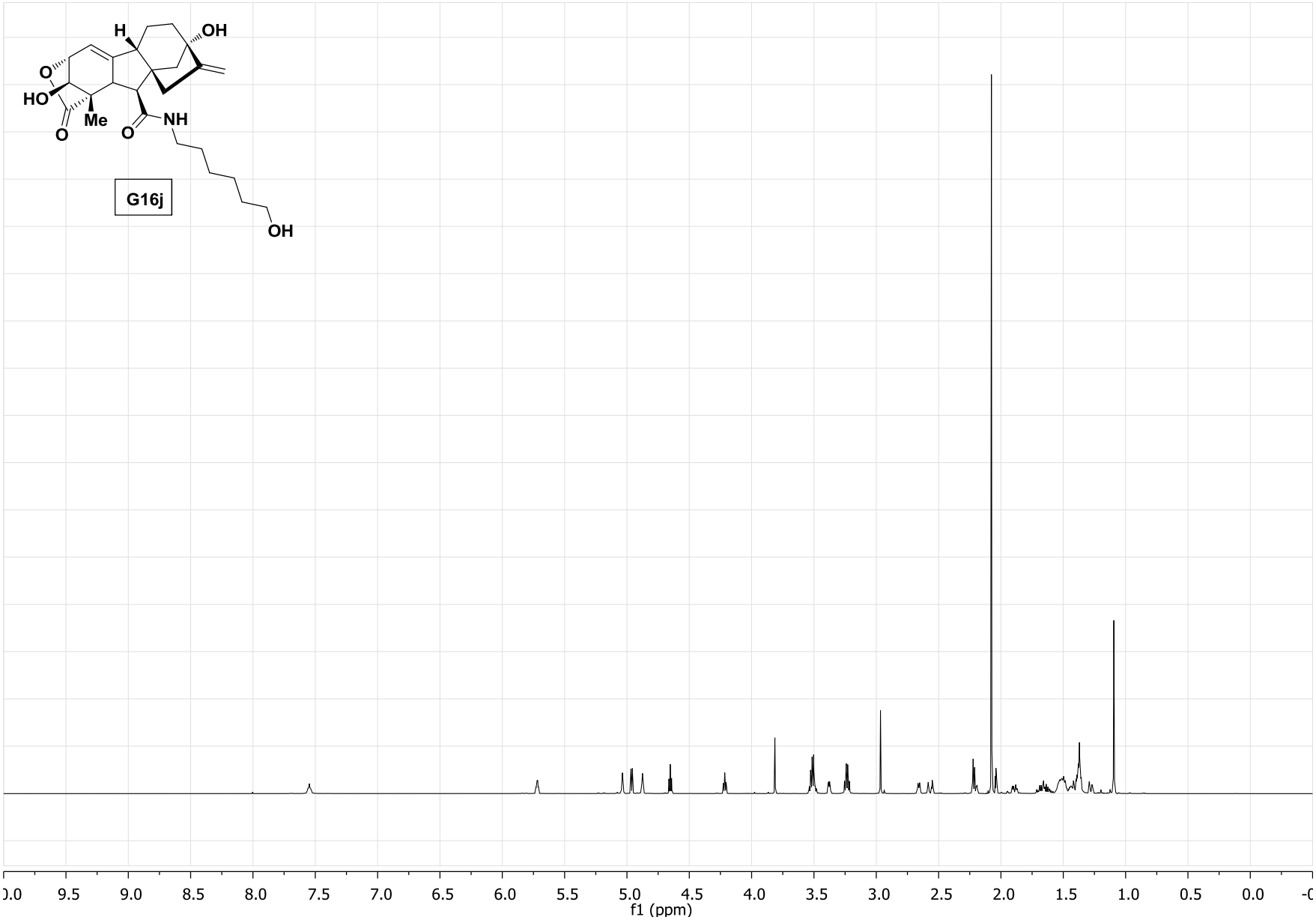
NMR131

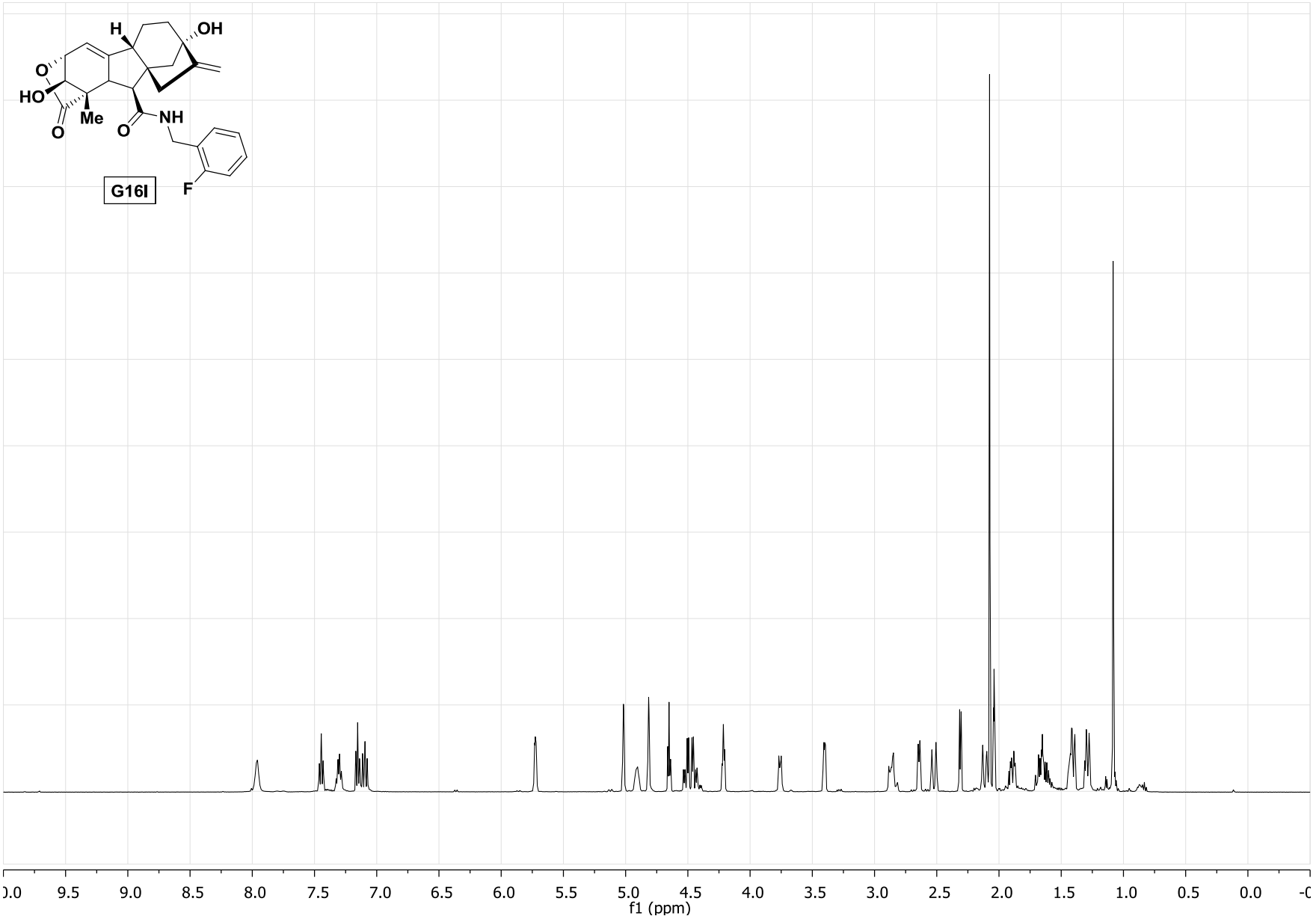

HO
O
O
H
H
H
O
O
O
H

A5f

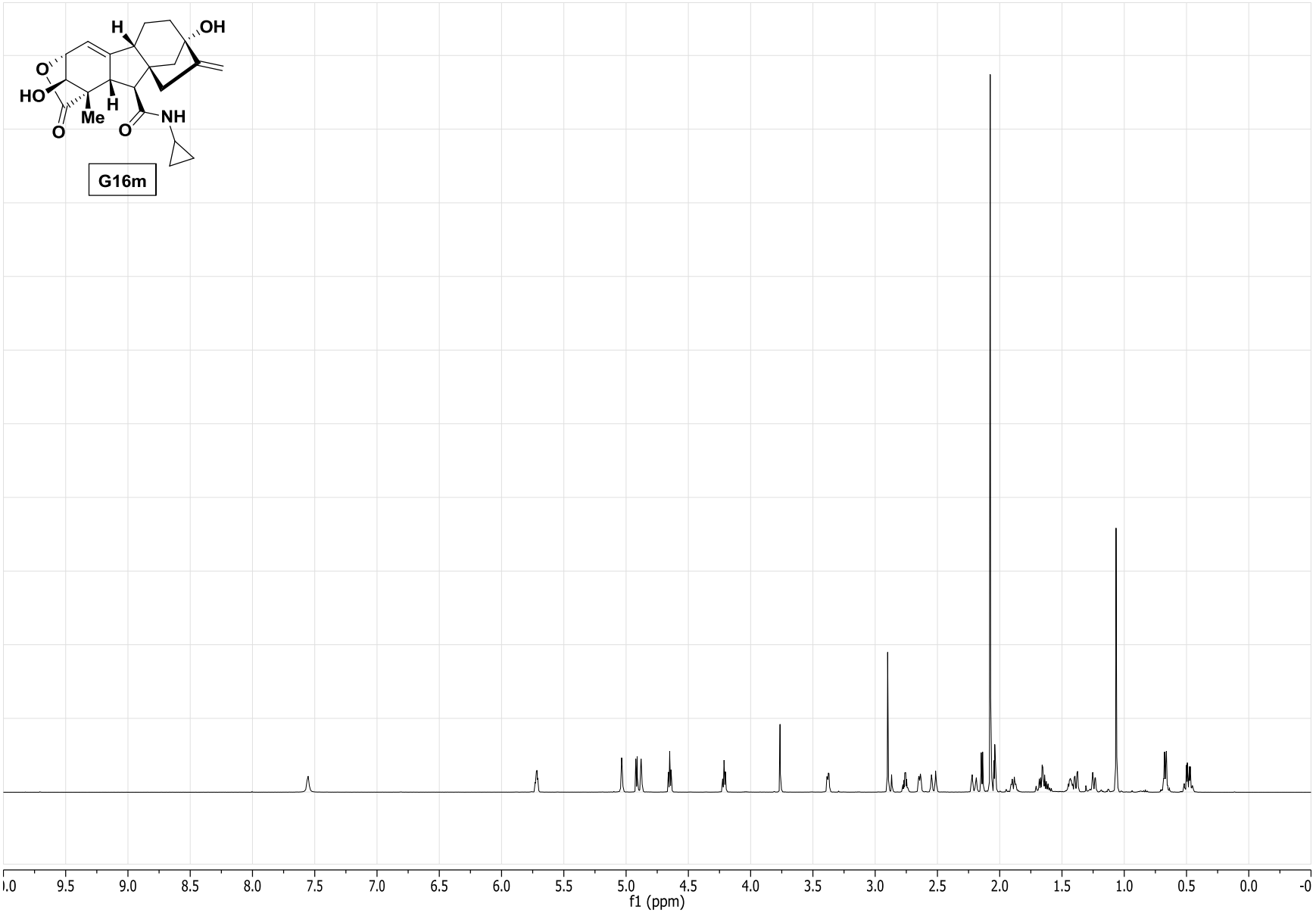

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

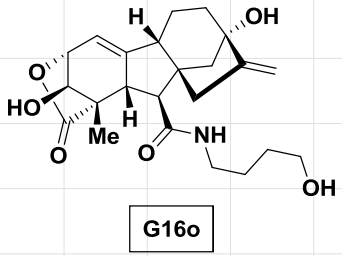
NMR132


H
OH
O
HO
Me
O
O
NH
G16j
OH
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)




NMR134

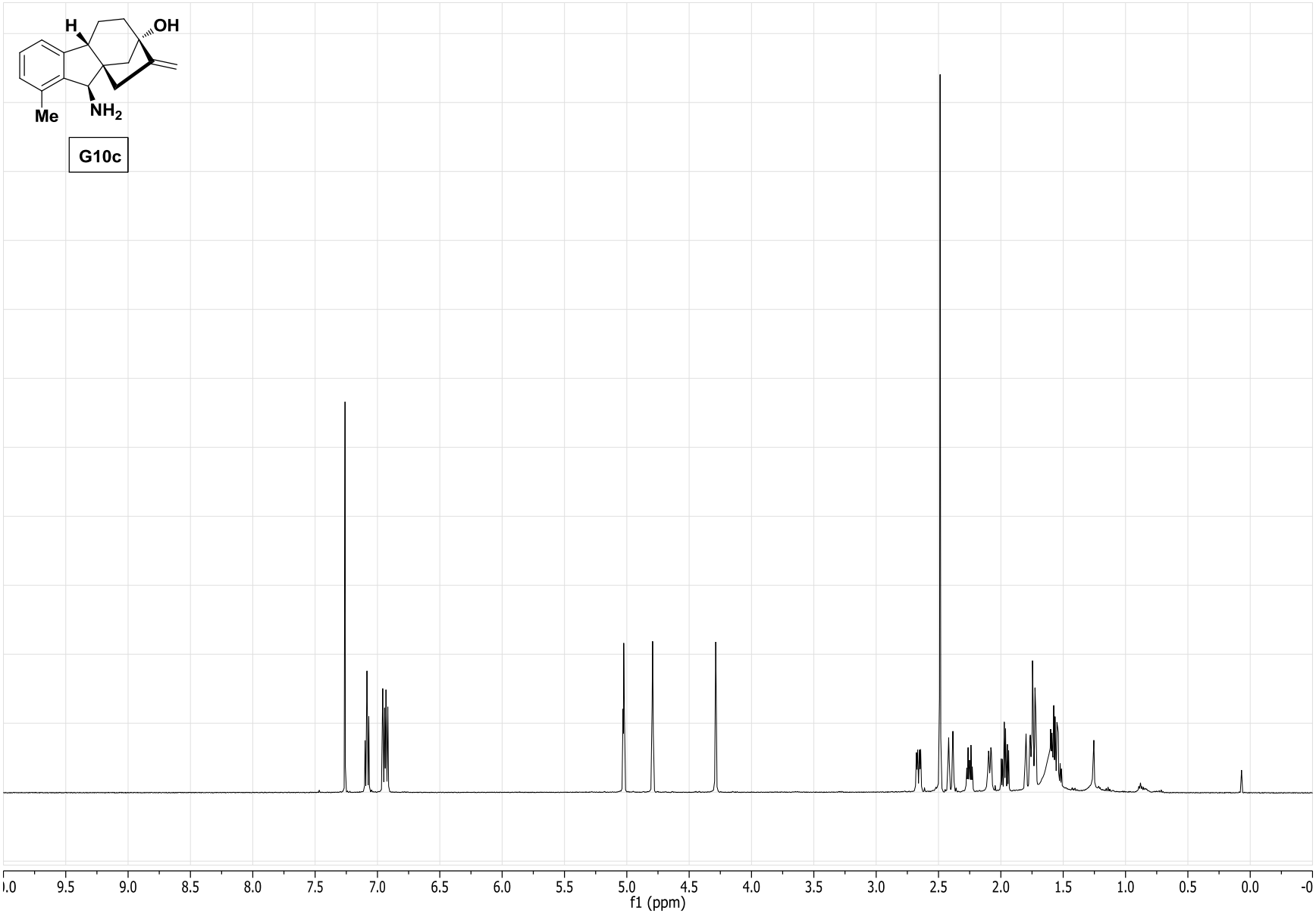

H
OH
O
HO
Me
H
O
O
NH
G16m
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


H
OH
O
HO
H
Me
O
O
NH
OH

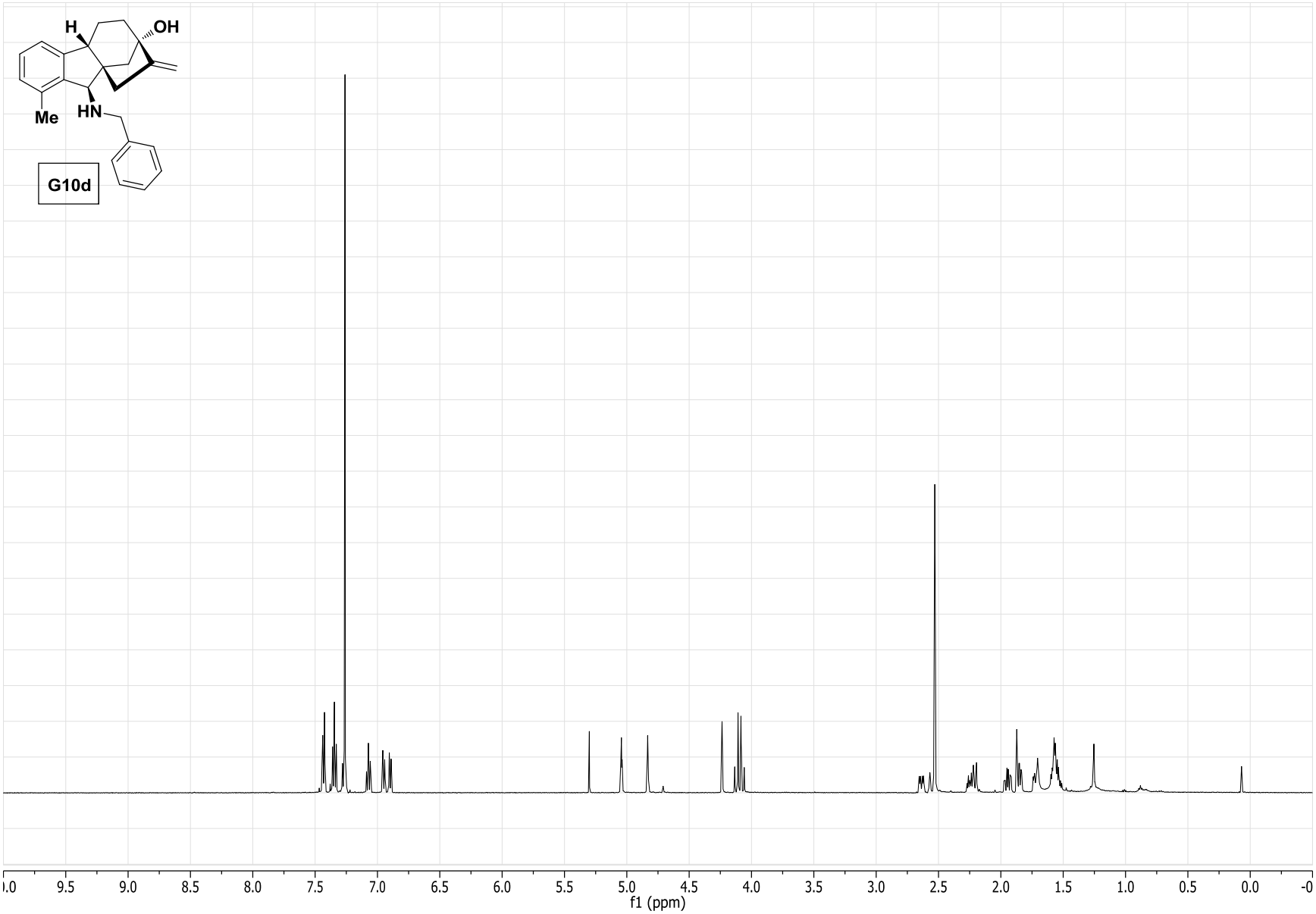
G16o


0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

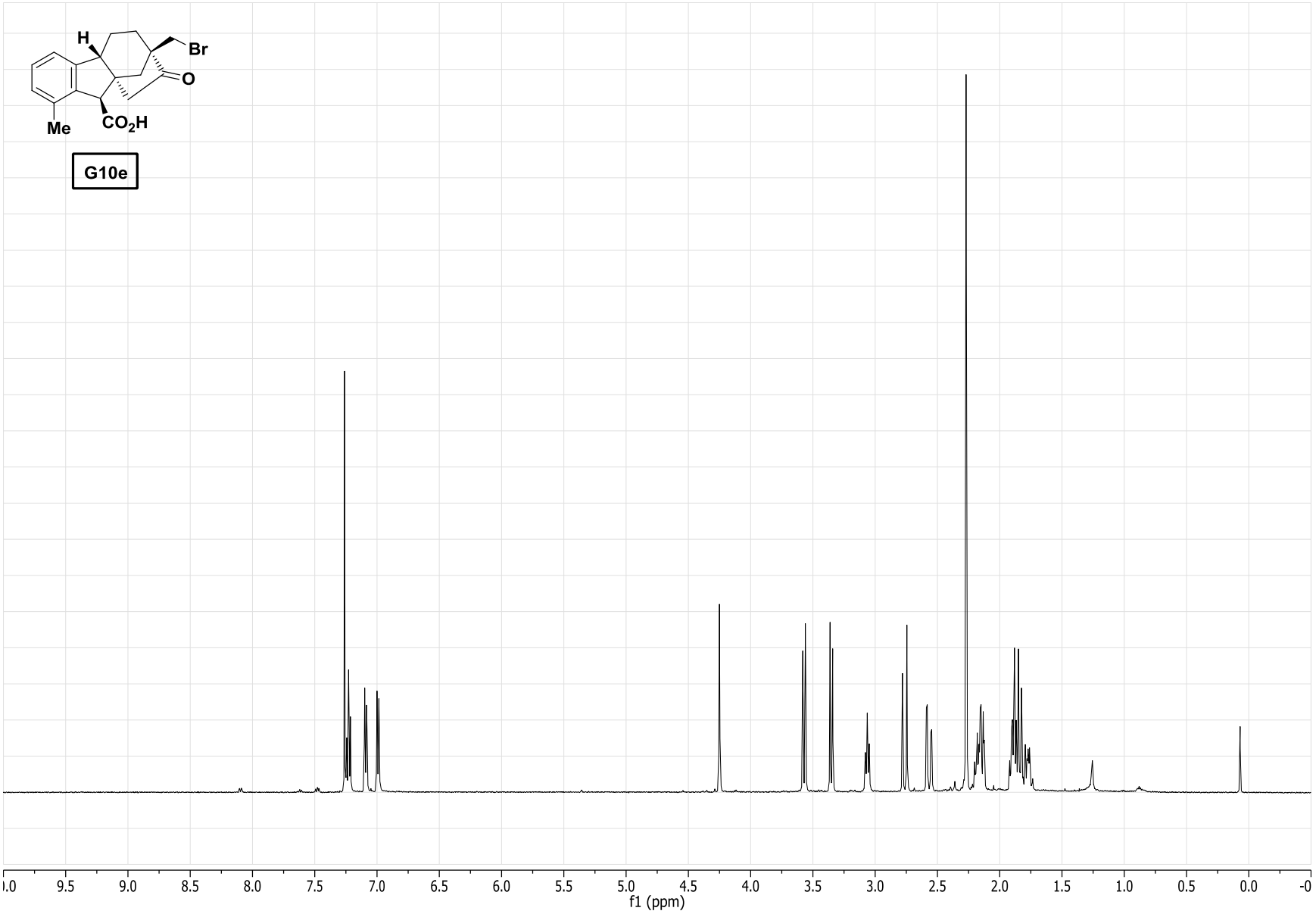
NMR136



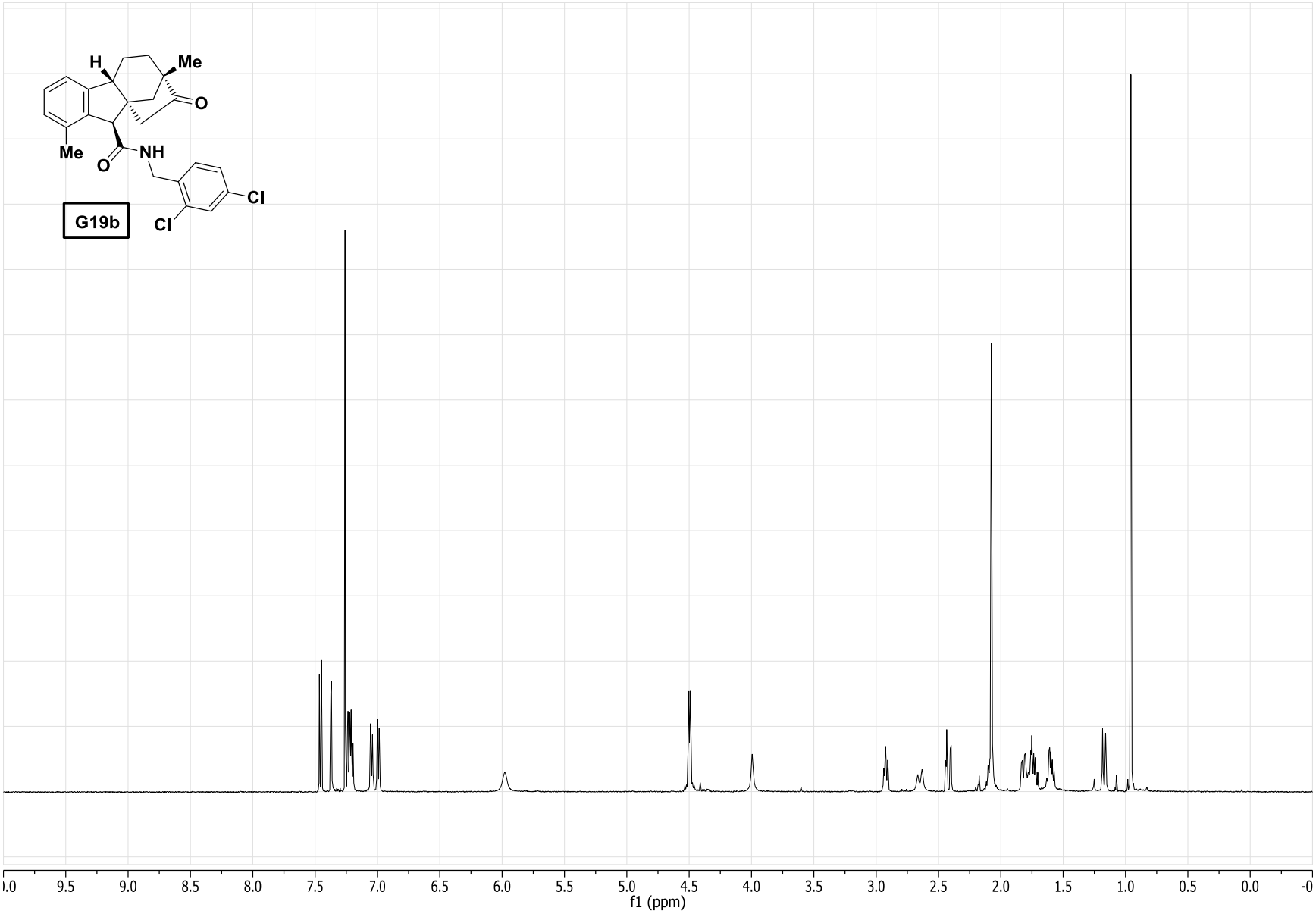

NMR137

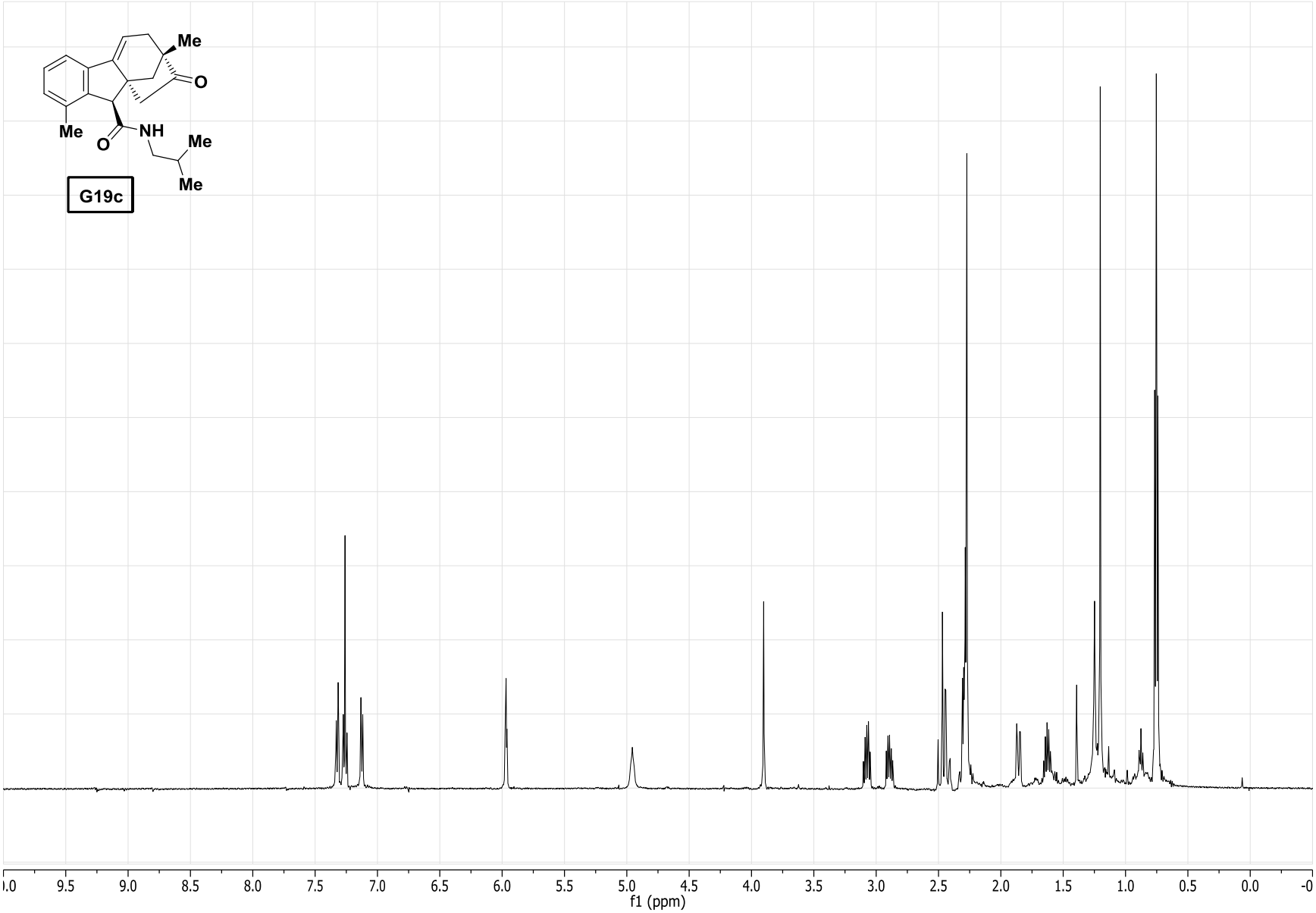



NMR138

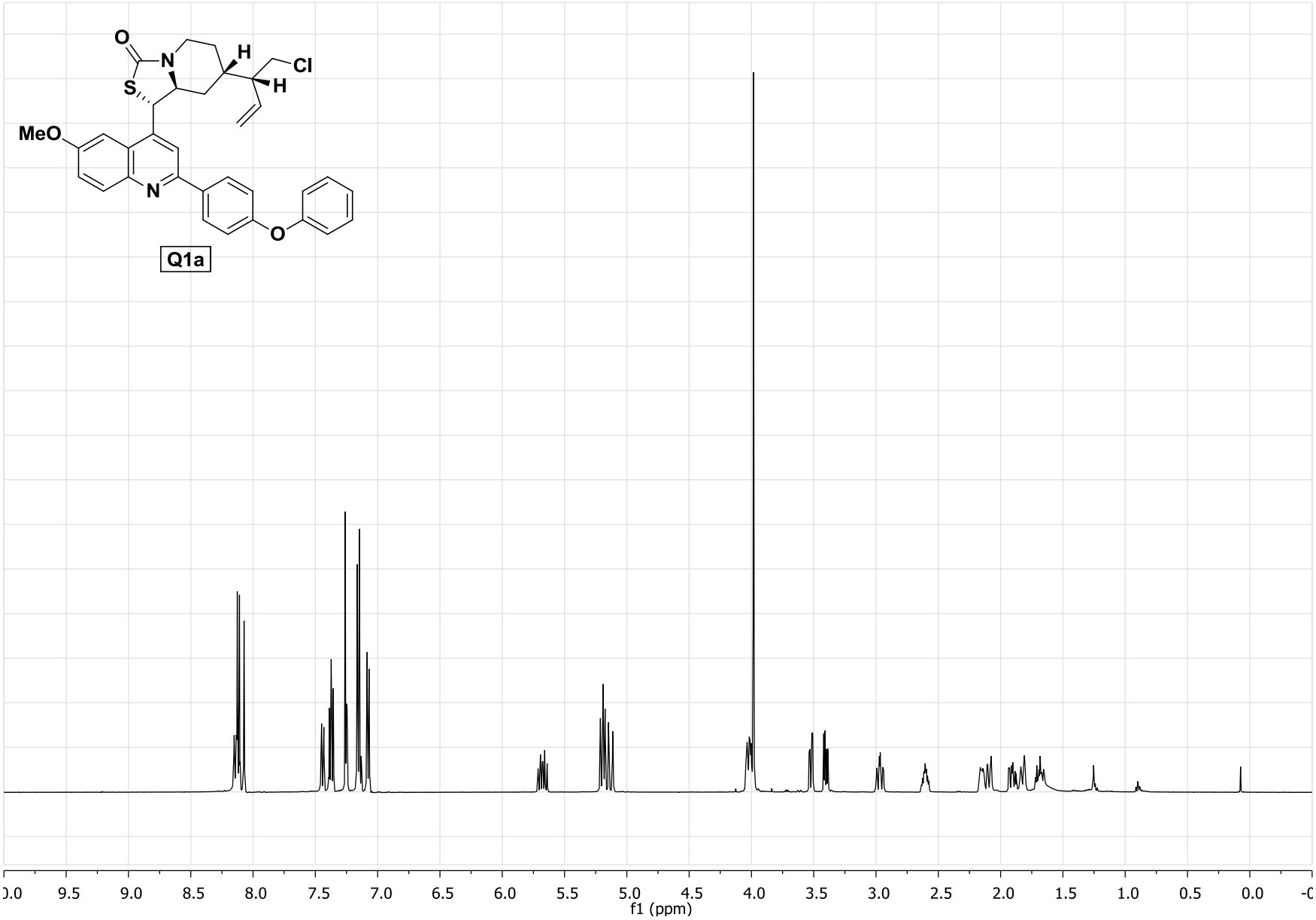



NMR139

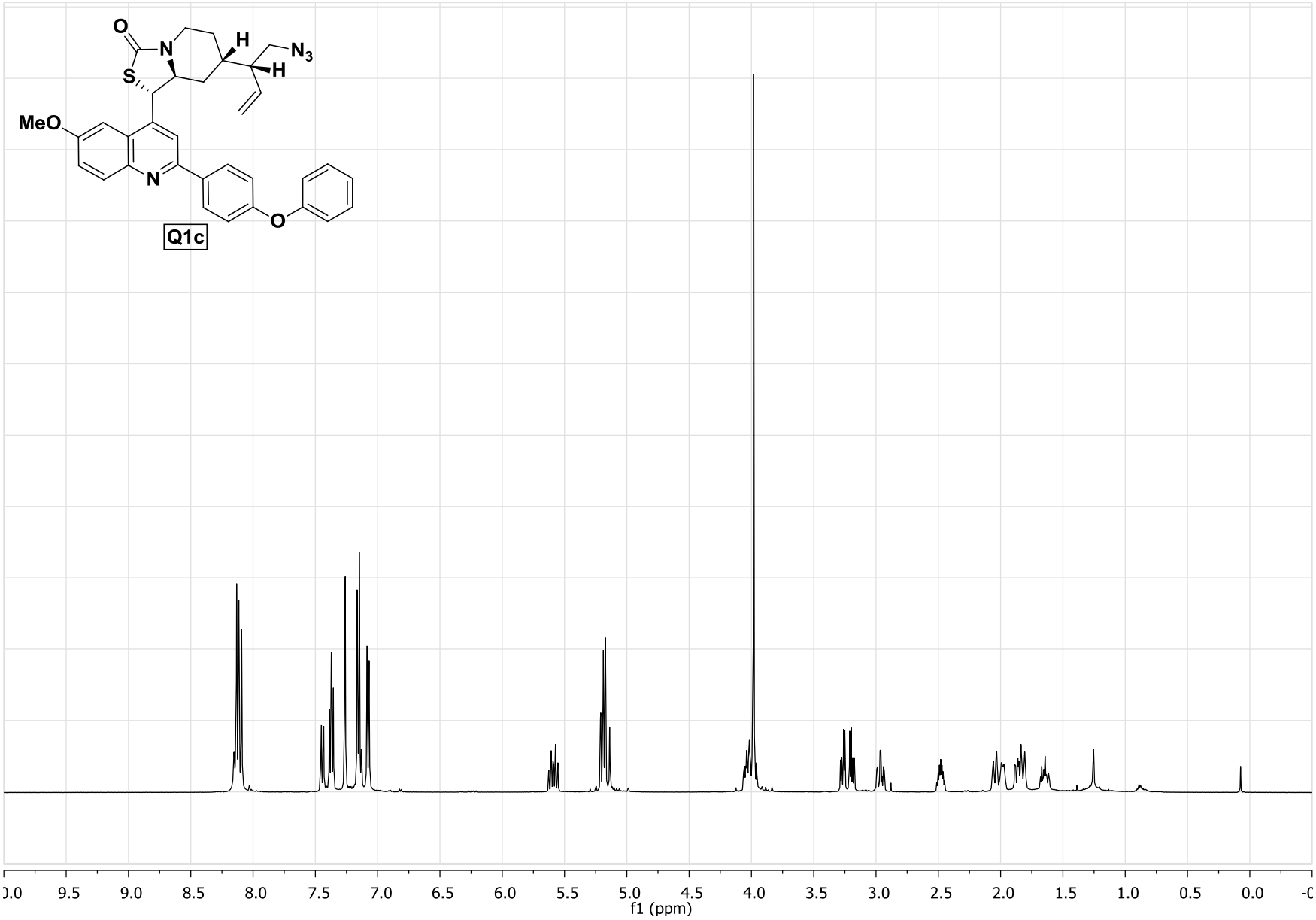

H
Me
O
Me
O
NH
Cl
Cl
G19b
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



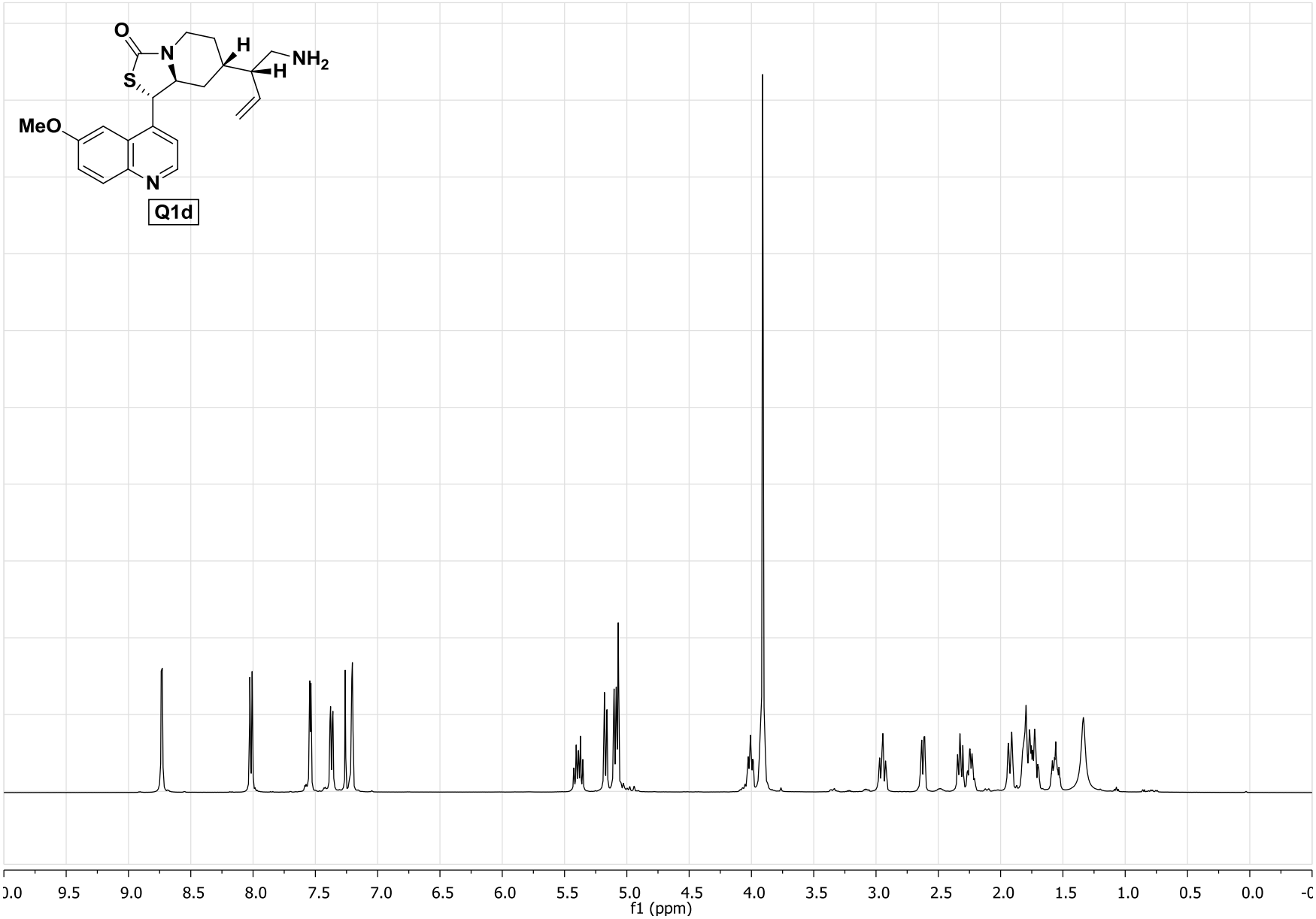

NMR141


O
N
H
Cl
S
H
MeO
N
O
Q1a
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

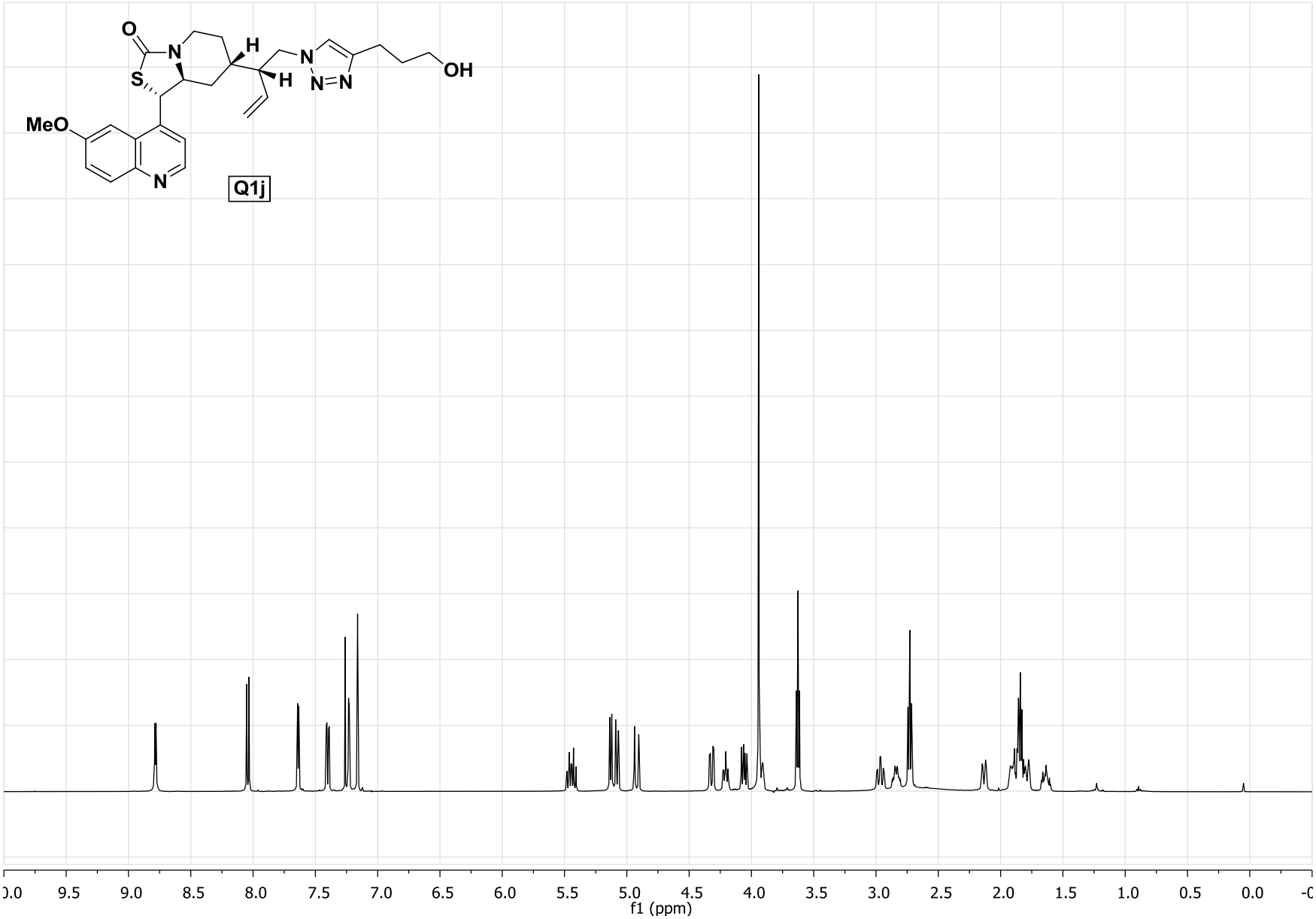
NMR142


O
N
H
N3
S
H
MeO
N
O
Q1c
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

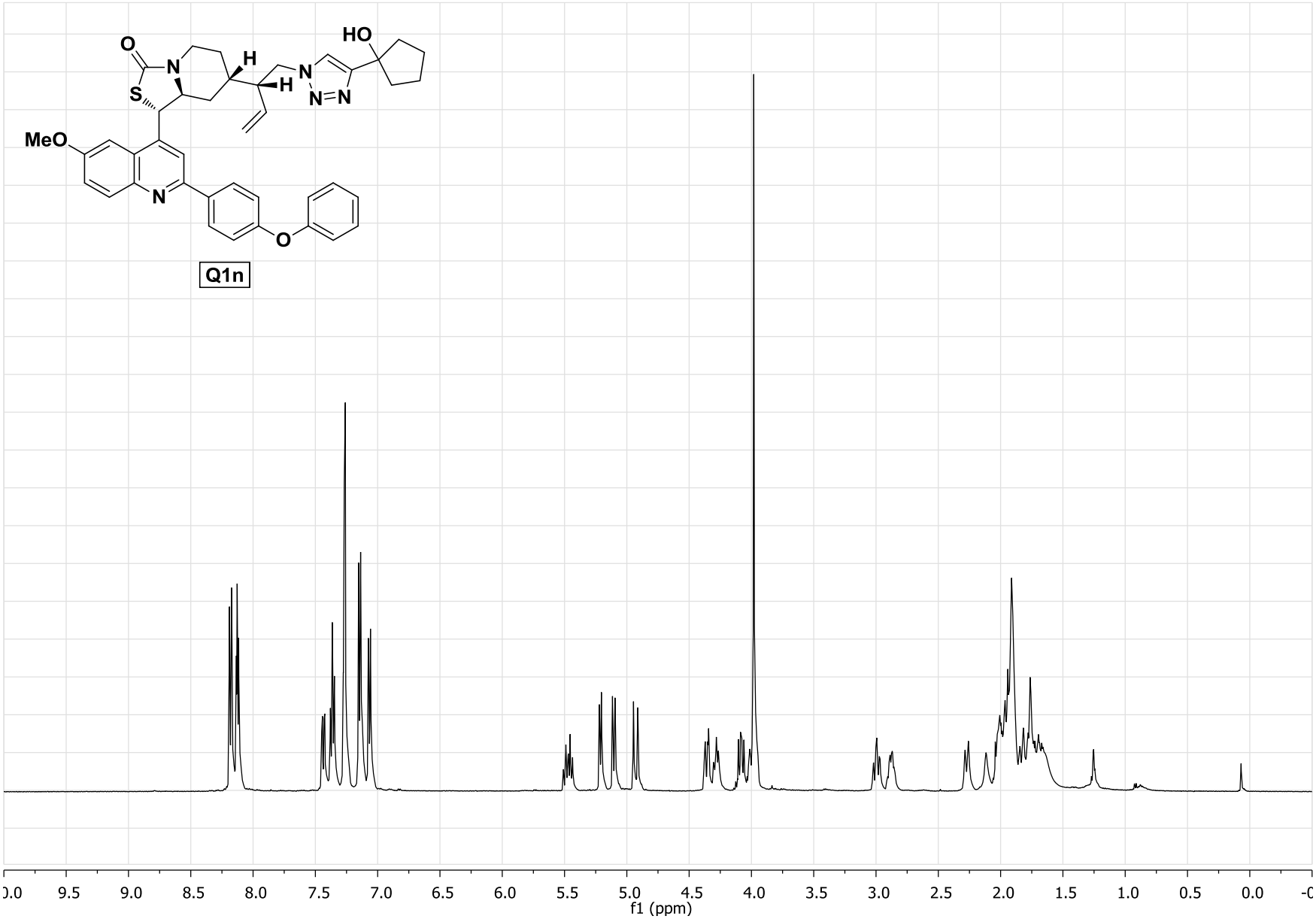
NMR143


O
N
S
H
H
NH2
MeO
N
Q1d
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

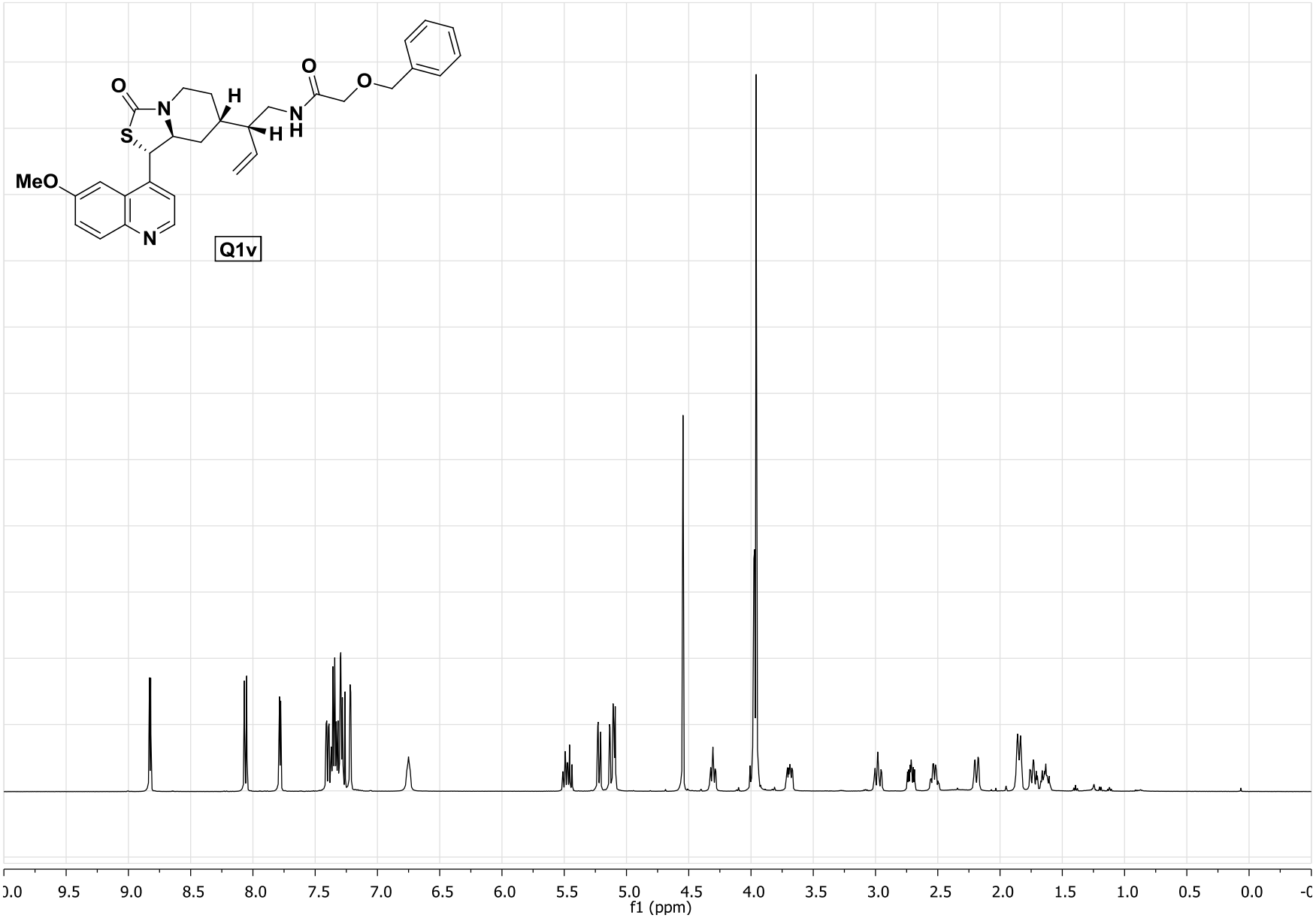
NMR144


O
N
S
H
H
N
N=N
OH
MeO
N
Q1j
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

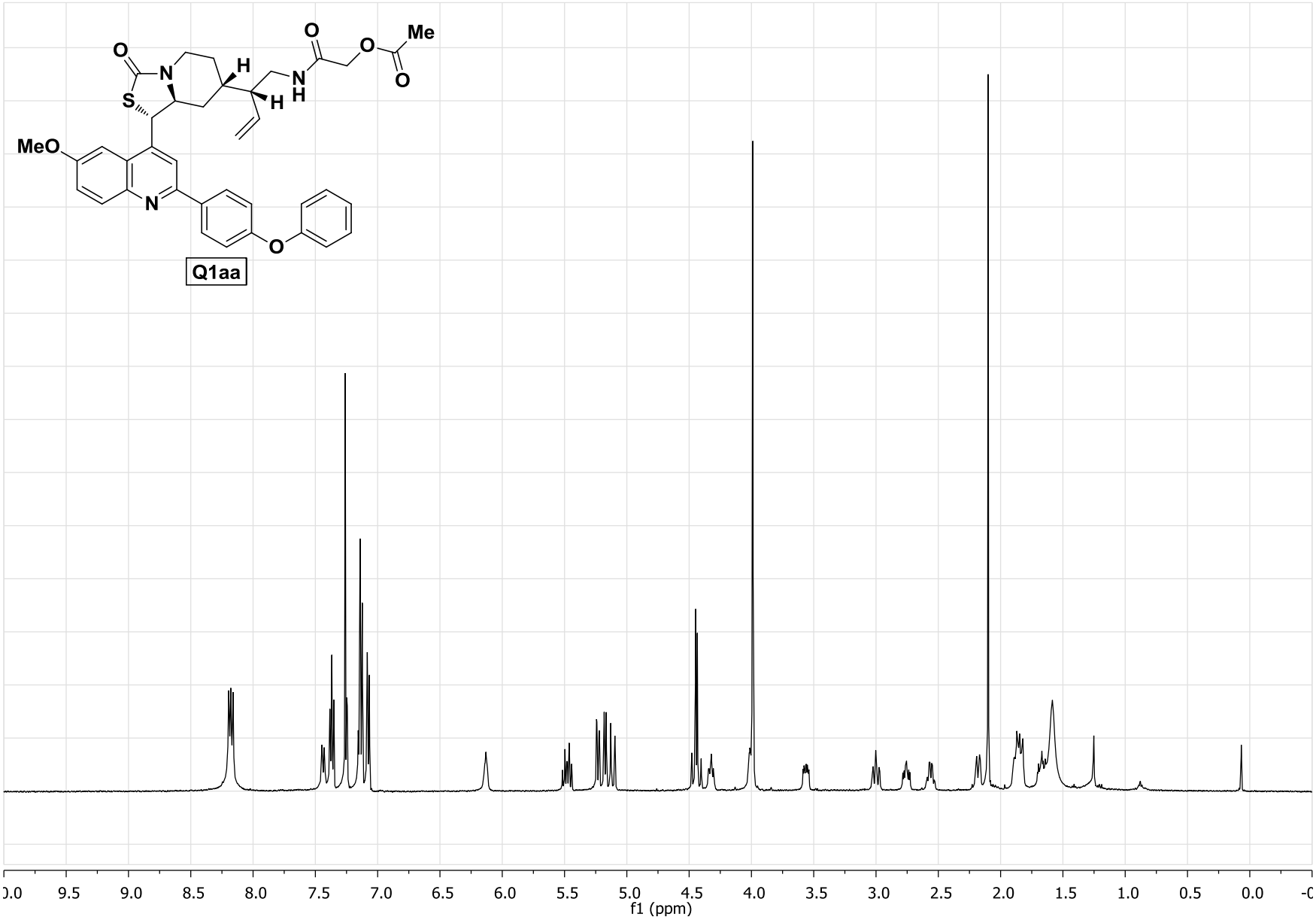
NMR145



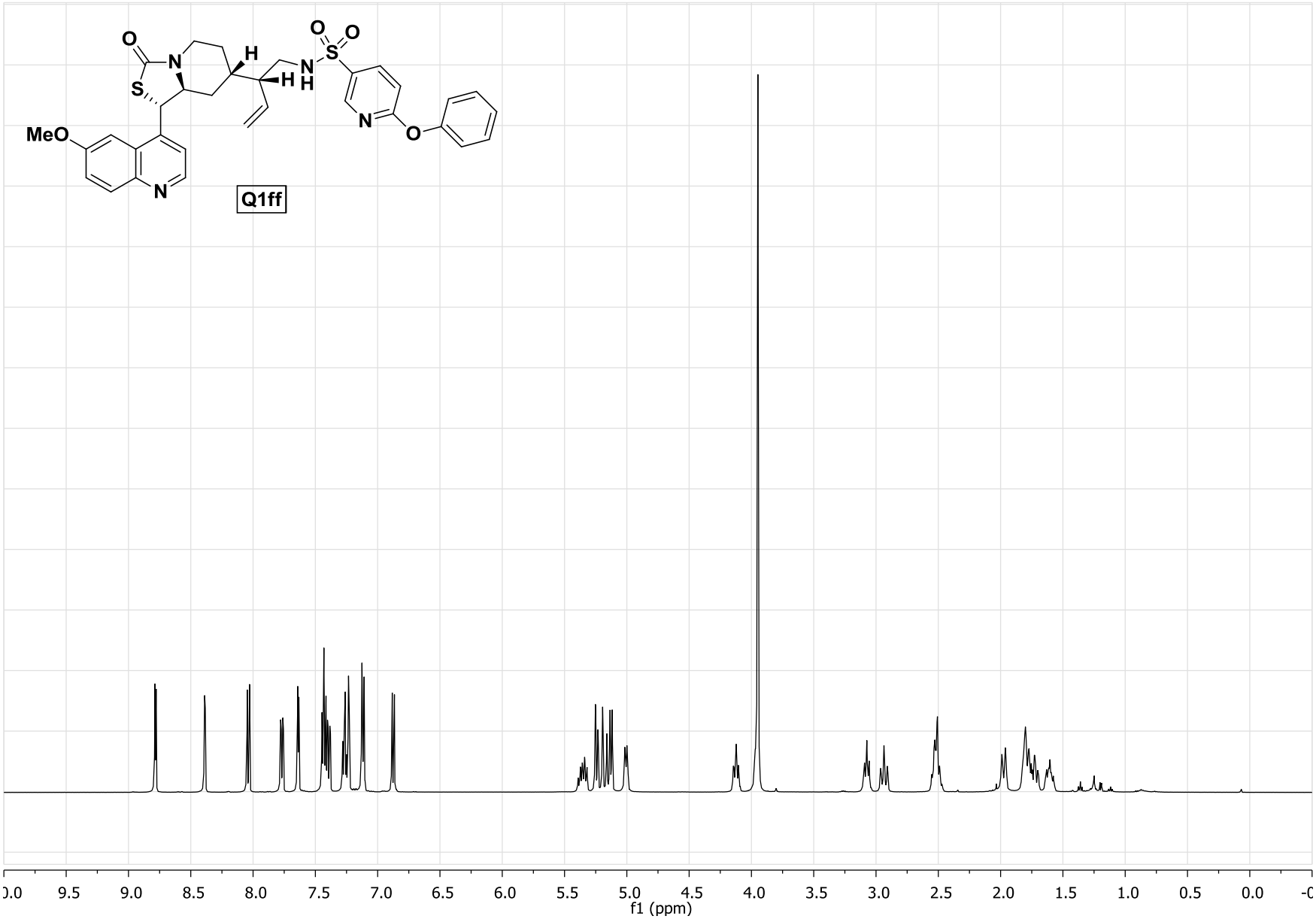

NMR146



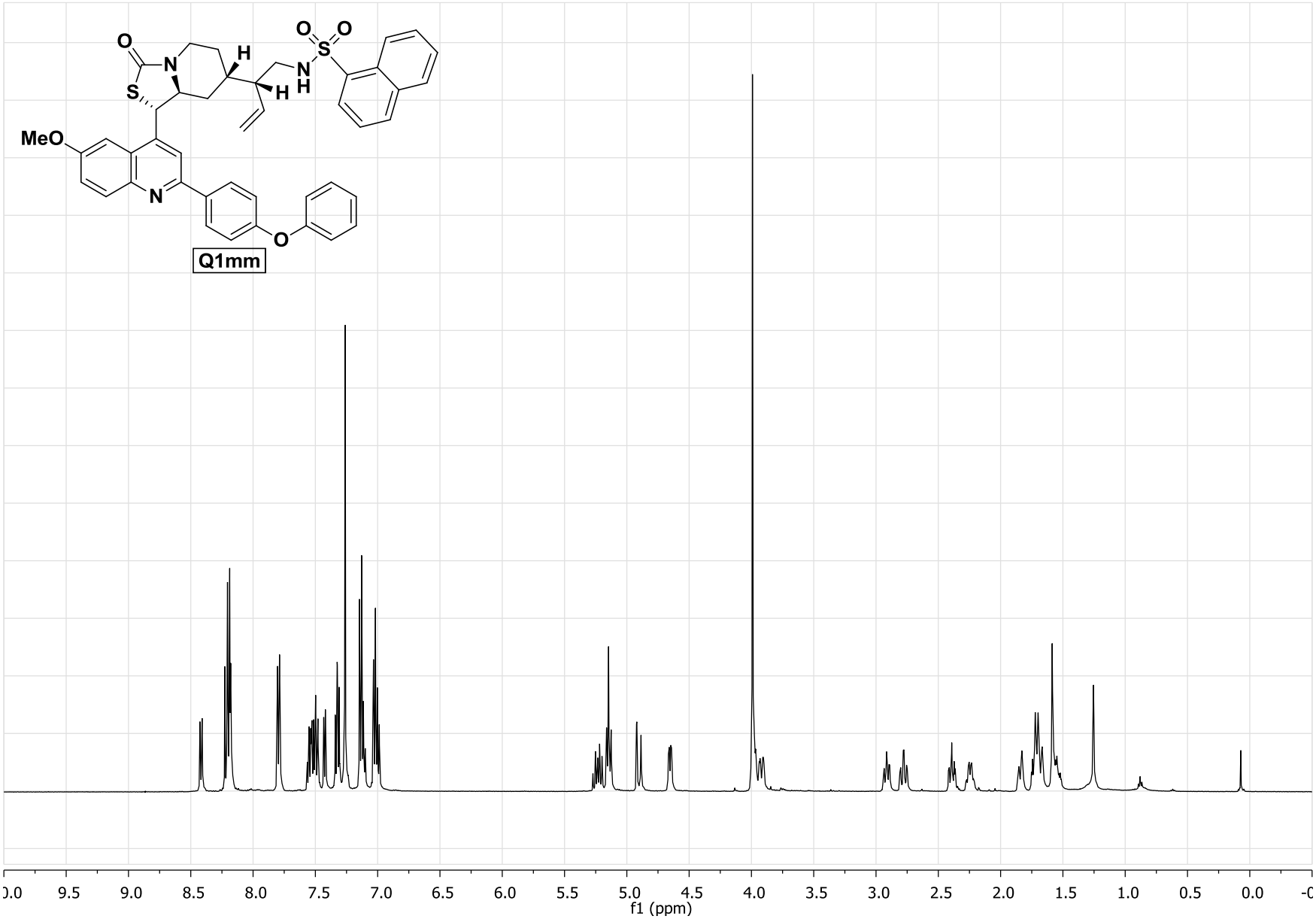

NMR147


MeO
Q1aa
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

NMR148




NMR149




NMR150