Re-engineering of Yohimbine's Biological Activity through Ring Distortion: Identification and Structure-Activity Relationships of a New Class of Antiplasmodial Agents

Nicholas G. Paciaroni[†], David J. Perry[‡], Verrill M. Norwood IV[†], Claribel Murillo-Solano[‡], Jennifer Collins[‡], Srinivasarao Tenneti[†], Debopam Chakrabarti[‡*], Robert W. Huigens III[†*]

[†]Department of Medicinal Chemistry and Center for Natural Product Drug Discovery & Development (CNPD3), College of Pharmacy, University of Florida, Gainesville, FL; [‡]Division of Molecular Microbiology, Burnett School of Biomedical Sciences, University of Central Florida, Orlando, FL.

* Corresponding authors e-mail addresses: rhuigens@cop.ufl.edu, dchak@ucf.edu

Supporting Information

Table of Contents

1. General Information. **S3**

2. Chemical Synthesis & Characterization. (Y1 series, then Y7 series) **S4**

3. Supporting Figure 1. Dose-dependent antiplasmodial activity for selected yohimbine analogues in chloroquine-resistant (Dd2) cells. **S20**

4. Supporting Figure 2. Dose-dependent antiplasmodial activity for selected yohimbine analogues in chloroquine-sentitive (3D7) cells. **S21**

5. Supporting Table 1. **S22**

6. Kill Kinetics for Y1f, DHA and Atovaquone. **S23**

7. Stage Specific Activity for Y1f. **S24**

8. NMR Spectra. **S25**

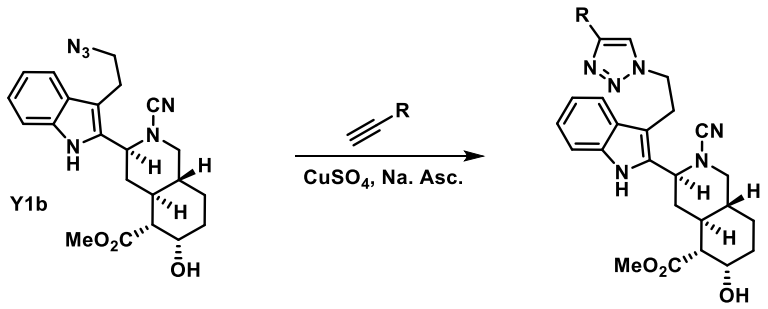
1. General Information.

All synthetic reactions were carried out under an inert atmosphere of argon unless otherwise specified. All reagents for chemical synthesis were purchased from commercial sources and used without further purification. Reagents were purchased at ≥ 95% purity and commercially available controls were used in our biological investigations without further purification. Analytical thin layer chromatography (TLC) was performed using 250 μm Silica Gel 60 F254 pre-coated plates (EMD Chemicals Inc.). Flash column chromatography was performed using 230-400 Mesh 60Å Silica Gel from Sorbent Technologies. All melting points were obtained, uncorrected, using a Mel-Temp capillary melting point apparatus from Laboratory Services, Inc.

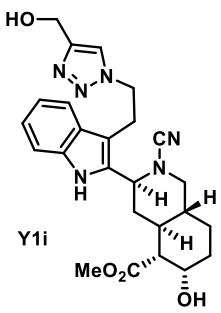
NMR experiments were recorded using broadband probes on Varian Mercury-Plus 400 MHz spectrometer (400 MHz for ^{1}H NMR; 100 MHz for ^{13}C NMR), Bruker Avance II 500 MHz spectrometer (500 MHz for ^{1}H NMR; 125 MHz for ^{13}C NMR), or Bruker Avance II 600 MHz spectrometer (600 MHz for ^{1}H NMR; 150 MHz for ^{13}C NMR). All spectra are presented using MestReNova 11.0 (Mnova) software and are displayed without the use of the signal suppression function. Spectra were obtained in deuterated chloroform or DMSO (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). NMR samples where the respective solvent peaks were buried in the sample signals referenced TMS at 0.00 ppm for ^{1}H NMR experiments. NMR experiments were performed at room temperature unless otherwise indicated. Chemical shift values (δ) 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, p = pentet, m = multiplet, br = broad. Melting points were obtained on a Mel-Temp II capillary melting point apparatus and were uncorrected. High-resolution mass spectra were obtained from the Mass Spectrometry Facility in the Chemistry Department at the University of Florida.

All biological experiments, including: antiplasmodial screen & dose-response assays (with Dd2 and 3D7 strains), stage-specific activity assays, kill kinetics and mammalian cytotoxicity assays (with HepG2 cells) were performed using experimental protocols described in Roberts, B. F.; Zheng, Y.; Cleaveland, J.; Lee, S.; Lee, E.; Ayong, L.; Yuan, Y.; Chakrabarti, D. *Int. J. Parasitol. Drugs Drug Resist.* **2017**, *7*, 120 – 129.

2. Chemical Synthesis & Characterization.



General procedure for the synthesis of indole-triazoles Y1i and Y1j. Anhydrous copper sulfate (6.9 mg, 0.04 mmol) and sodium ascorbate (26.9 mg, 0.14 mmol) were added to a reaction vial and dissolved in a 1:2 *tert*-butanol:water solution (2.4 mL). The resulting mixture was added to a round-bottom flask containing **Y1b** (39.0 mg, 0.09 mmol). Then, propargyl alcohol (16.1 µL, 0.28 mmol, 3.0 equiv) was added to the reaction followed by dichloromethane (0.8 mL). The reaction was vigorously stirred at room temperature for 2 hours. Upon completion, the biphasic mixture was then quenched with brine and the crude product was extracted with dichloromethane using a separatory funnel. The organic layers were collected, dried with sodium sulfate, filtered and concentrated. The crude product was then purified via column chromatography using 99:1 ethyl acetate:triethylamine to ethyl acetate:methanol:triethylamine 97.5:1.5:1 to afford **Y1i** (21.5 mg, 49%) as a colorless foam.



Yield: 49%; 21.5 mg of **Y1i** isolated as a colorless foam.

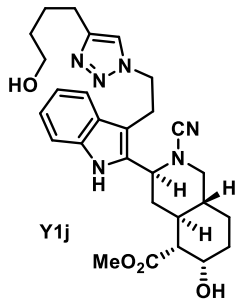
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.1 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.24 (t, *J* = 8.1 Hz, 1H), 7.11 (s, 1H), 4.73 – 4.55 (m, 4H), 4.20 (m, 1H), 4.14 (dd, *J* = 11.9, 3.6 Hz, 1H), 3.84 (s, 3H), 3.84 (m, 1H, buried under singlet), 3.52 (br m, 1H), 3.29 – 3.21 (m, 2H), 2.75 (dd, *J* = 13.4, 11.2 Hz, 1H), 2.20 (d, *J* = 11.6 Hz, 1H), 2.06 (q, *J* = 12.0 Hz, 1H), 1.97 (m, 1H), 1.79 (dt, *J* = 12.6, 3.4 Hz, 1H), 1.65 – 1.40 (m, 3H), 1.25 (m, 1H), 0.87 (q, *J* = 12.0 Hz, 1H).

^{1}H NMR: (500 MHz, d_6-DMSO) δ 8.11 (d, *J* = 7.6 Hz, 1H), 7.76 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 6.7 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 5.09 (m, 1H), 4.72 (d, *J* = 4.2 Hz, 1H), 4.63 – 4.57 (m, 2H), 4.50 – 4.43 (m, 3H), 4.11 (m, 1H), 4.05 (dd, *J* = 14.1, 3.5 Hz, 1H), 3.67 (s, 3H), 3.25 – 3.18 (m, 2H), 2.76 (dd, *J* = 14.0, 12.1 Hz, 1H), 2.20 (dd, *J* = 11.5, 2.7 Hz, 1H), 2.14 (dt, *J* = 12.3, 3.3 Hz, 1H), 2.00 (qd, *J* = 11.3, 2.8 Hz, 1H), 1.76 (m, 1H), 1.53 (tt, *J* = 12.5, 2.1 Hz, 1H), 1.44 (qd, *J* = 12.5, 2.4 Hz, 1H), 1.32 (m, 1H), 1.25 (m, 1H), 1.17 (m, 1H), 0.78 (q, *J* = 11.9 Hz, 1H).

^{13}C NMR: (125 MHz, d_6-DMSO) δ 172.4, 148.7, 147.8, 137.9, 132.0, 129.9, 122.7, 122.3, 121.3, 119.0, 112.0, 104.0, 66.4, 54.9, 59.2, 54.3, 51.7, 51.2, 49.2, 45.4, 34.9, 34.0, 32.0, 25.2, 22.2.

HRMS (ESI): calc. for $C_{25}H_{31}N_6O_4$ $[M+H]^+$: 479.2401, found: 479.2411.

MP: 179 – 181 °C.



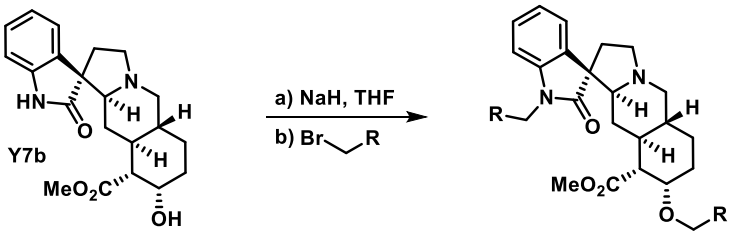
Yield: 69%; 32.3 mg of **Y1j** isolated as a colorless foam.

^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.49 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.32 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.25 (m, 1H), 6.71 (s, 1H), 4.64 (dt, *J* = 13.6, 6.0 Hz, 1H), 4.52 (ddd, *J* = 13.8, 7.7, 6.4 Hz, 1H), 4.21 (q, *J* = 2.5 Hz, 1H), 4.05 (dd, *J* = 11.7, 3.7 Hz, 1H), 3.90 (dd, *J* = 13.6, 4.5 Hz, 1H), 3.82 (s, 3H), 3.58 – 3.54 (m, 2H), 3.28 – 3.23 (m, 2H), 3.13 (br s, 1H), 2.77 (dd, *J* = 13.6, 11.3 Hz, 1H), 2.65 – 2.54 (m, 2H), 2.19 (dd, *J* = 11.6, 2.1 Hz, 1H), 2.09 (qd, *J* = 11.5, 3.0 Hz, 1H), 2.07 – 1.94 (m, 2H), 1.65 – 1.38 (m, 8H), 1.23 (m, 1H), 0.85 (q, *J* = 12.0 Hz, 1H).

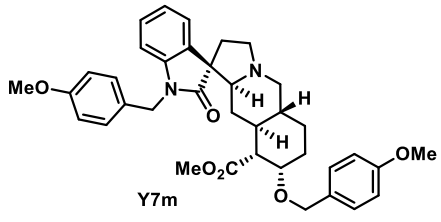
^{13}C NMR: (150 MHz, $CDCl_3$) δ 175.1, 150.7, 147.8, 137.8, 132.1, 130.7, 123.6, 122.3, 121.9, 118.7, 112.4, 104.6, 66.8, 62.4, 54.8, 52.4, 52.3, 49.9, 46.1, 40.0, 35.2, 35.1, 32.3, 31.2, 26.1, 25.9, 25.3, 22.8.

HRMS (ESI): calc. for $C_{28}H_{37}N_6O_4$ $[M+H]^+$: 521.2870, found: 521.2873.

MP: 94 – 96 °C.



General procedure for the synthesis of di-alkylated products Y7m – Y7v. Tetrahydrofuran (2 mL) was added to a round-bottom flask followed by sodium hydride (29.8 mg, 0.74 mmol, 60% dispersion in mineral oil) and cooled to 0 °C. Next, a solution of **Y7b** (67.3 mg, 0.18 mmol) in 0.5 mL of tetrahydrofuran was added to the reaction mixture, which was allowed to stir for 10 minutes. Then, a solution of 4-methoxybenzyl bromide (76.7 mg, 0.38 mmol) dissolved in 0.5 mL of tetrahydrofuran was added to the reaction mixture, which was slowly warmed to room temperature over 13 hours. Upon completion, the reaction was quenched via brine and extracted with ethyl acetate using a separatory funnel. The organic layers were collected, dried with sodium sulfate, filtered and concentrated. The crude mixture was then purified via column chromatography using hexanes:ethyl acetate:triethylamine 66:33:1 to 49.5:49.5:1 to elute **Y7m** (23.5 mg, 21%) as a pale-yellow film.



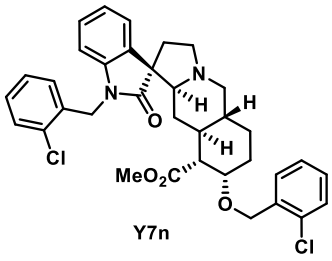
Yield: 21%; 23.5 mg of **Y7m** isolated as a pale-yellow film.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.4 Hz, 1H), 7.22 – 7.14 (m, 4H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.89 – 6.81 (m, 4H), 6.67 (d, *J* = 7.7 Hz, 1H), 5.05 (d, *J* = 15.4 Hz, 1H), 4.60 (d, *J* = 15.4 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.22 (d, *J* = 11.8 Hz, 1H), 3.88 (m, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.47 (s, 3H), 3.28 (t, *J* = 8.5 Hz, 1H), 3.10 (dd, *J* = 10.8, 3.4 Hz, 1H), 2.66 (d, *J* = 11.0 Hz, 1H), 2.53 (q, *J* = 8.7 Hz, 1H), 2.41 (m, 1H), 2.13 – 1.91 (m, 4H), 1.80 (qd, *J* = 11.0, 3.2 Hz, 1H), 1.66 – 1.16 (m, 5H), 0.42 (q, *J* = 11.6 Hz, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 179.4, 172.6, 159.2, 159.1, 142.5, 133.9, 130.9, 129.2, 128.7, 128.4, 127.5, 124.9, 122.3, 114.4, 113.8, 108.9, 74.6, 72.2, 70.2, 59.1, 56.4, 55.5, 55.4, 53.9, 52.7, 51.3, 43.5, 40.5, 36.1, 35.3, 31.1, 28.1, 23.8.

HRMS (ESI): calc. for $C_{37}H_{43}N_2O_6$ $[M+H]^+$: 611.3116, found: 611.3132.

MP: 53 – 55 °C.



Y7n

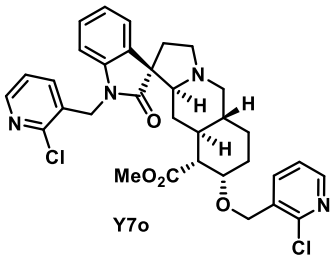
Yield: 89%; 61.5 mg of **Y7n** isolated as a colorless foam.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.38 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.32 – 7.25 (m, 2H), 7.24 – 7.16 (m, 3H), 7.14 (td, *J* = 7.8, 1.3 Hz, 1H), 7.06 – 6.99 (m, 2H), 6.64 (d, *J* = 7.7 Hz, 1H), 5.18 (d, *J* = 16.6 Hz, 1H), 4.89 (d, *J* = 16.6 Hz, 1H), 4.64 (d, *J* = 13.2 Hz, 1H), 4.34 (d, *J* = 13.2 Hz, 1H), 4.00 (m, 1H), 3.51 (s, 3H), 3.32 (t, *J* = 7.9 Hz, 1H), 3.13 (dd, *J* = 10.8, 3.5 Hz, 1H), 2.71 (d, *J* = 11.3 Hz, 1H), 2.56 (q, *J* = 8.7 Hz, 1H), 2.44 (m, 1H), 2.20 (dt, *J* = 10.7, 3.1 Hz, 1H), 2.16 – 2.03 (m, 2H), 1.98 (t, *J* = 10.7 Hz, 1H), 1.88 (qd, *J* = 11.3, 3.2 Hz, 1H), 1.57 (dt, *J* = 12.0, 3.0 Hz, 1H), 1.51 – 1.35 (m, 3H), 1.29 (m, 1H), 0.53 (q, *J* = 11.5 Hz, 1H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 179.7, 172.6, 142.2, 136.5, 133.7, 133.4, 133.0, 132.3, 129.7, 129.0, 128.9, 128.8, 128.5, 128.1, 127.7, 127.6, 127.0, 124.9, 122.7, 108.7, 75.9, 72.1, 67.5, 59.1, 56.5, 53.9, 52.7, 51.4, 41.3, 40.5, 36.2, 35.5, 31.2, 28.1, 23.8.

HRMS (ESI): calc. for $C_{35}H_{37}Cl_2N_2O_4$ $[M+H]^+$: 619.2124, found: 619.2151.

MP: 78 – 80 °C.



Y7o

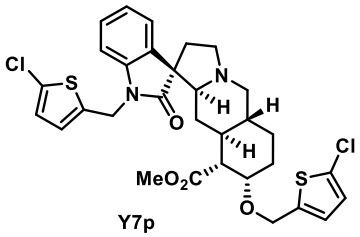
Yield: 37%; 31.4 mg of **Y7o** isolated as a colorless foam.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.34 – 8.25 (m, 2H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.3 Hz, 1H), 7.36 (d, *J* = 7.7 Hz, 1H), 7.31 – 7.20 (m, 2H), 7.17 (t, *J* = 7.7 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 7.7 Hz, 1H), 5.18 (d, *J* = 16.9 Hz, 1H), 4.85 (d, *J* = 16.9 Hz, 1H), 4.62 (d, *J* = 13.9 Hz, 1H), 4.27 (d, *J* = 13.9 Hz, 1H), 4.05 (m, 1H), 3.51 (s, 3H), 3.31 (t, *J* = 9.0 Hz, 1H), 3.14 (d, *J* = 10.6 Hz, 1H), 2.68 (d, *J* = 10.6 Hz, 1H), 2.54 (q, *J* = 8.7 Hz, 1H), 2.43 (dd, *J* = 12.9, 10.6 Hz, 1H), 2.27 – 2.03 (m, 3H), 1.96 (t, *J* = 10.4 Hz, 1H), 1.84 (q, *J* = 10.7 Hz, 1H), 1.53 (dt, *J* = 12.1, 2.8 Hz, 1H), 1.50 – 1.22 (m, 4H), 0.51 (q, *J* = 11.5 Hz, 1H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 179.9, 172.5, 150.0, 148.8, 148.7, 148.2, 141.7, 137.2, 137.0, 133.6, 133.5, 130.4, 127.9, 125.1, 123.4, 123.1, 123.0, 108.5, 76.5, 72.3, 66.6, 59.1, 56.6, 54.0, 52.4, 51.5, 40.8, 40.3, 36.2, 35.4, 31.2, 28.0, 23.8.

HRMS (ESI): calc. for $C_{33}H_{35}Cl_2N_4O_4$ $[M+H]^+$: 621.2030, found: 621.2020.

MP: 79 – 81 °C.



Y7p

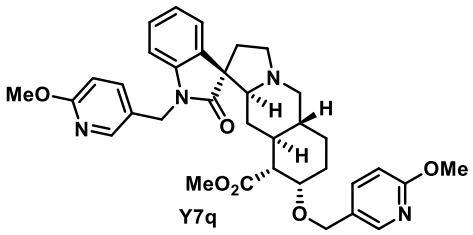
Yield: 34%; 29.2 mg of **Y7p** isolated as a pale-yellow foam.

^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.4 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.83 – 6.77 (m, 2H), 6.75 – 6.71 (m, 2H), 6.66 (d, *J* = 3.7 Hz, 1H), 5.11 (d, *J* = 15.7 Hz, 1H), 4.76 (d, *J* = 15.9 Hz, 1H), 4.56 (d, *J* = 12.9 Hz, 1H), 4.34 (d, *J* = 12.8 Hz, 1H), 3.93 (s, 1H), 3.54 (s, 3H), 3.26 (t, *J* = 8.4 Hz, 1H), 3.09 (d, *J* = 10.7 Hz, 1H), 2.62 (d, *J* = 11.0 Hz, 1H), 2.51 (q, *J* = 8.8 Hz, 1H), 2.37 (dd, *J* = 14.4, 11.4 Hz, 1H), 2.08 – 1.89 (m, 4H), 1.74 (q, *J* = 11.3 Hz, 1H), 1.45 – 1.18 (m, 5H), 0.42 (q, *J* = 11.6 Hz, 1H)

^{13}C NMR: (150 MHz, $CDCl_3$) δ 179.0, 172.5, 141.7, 140.5, 137.8, 133.8, 130.2, 129.6, 127.6, 126.1, 125.8, 125.7, 125.3, 125.1, 122.7, 108.4, 75.0, 72.0, 65.5, 59.0, 56.3, 53.8, 52.8, 51.6, 40.5, 39.2, 36.0, 35.4, 31.1, 28.2, 23.8.

HRMS (ESI): calc. for $C_{31}H_{33}Cl_2N_2O_4S_2$ $[M+H]^+$: 631.1253, found: 631.1240.

MP: 54 – 56 °C.



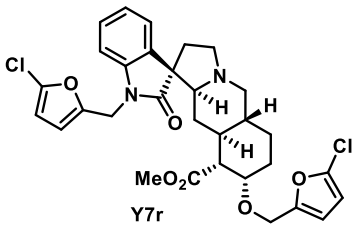
Y7q

Yield: 39%; 32.6 mg of **Y7q** isolated as a colorless, amorphous solid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 2.4 Hz, 1H), 7.98 (d, *J* = 2.4 Hz, 1H), 7.48 (d, *J* = 2.1 Hz, 1H), 7.46 (d, *J* = 2.1 Hz, 1H), 7.35 (d, *J* = 7.3 Hz, 1H), 7.12 (td, *J* = 7.7, 1.3 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.76 – 6.67 (m, 3H), 5.03 (d, *J* = 15.4 Hz, 1H), 4.57 (d, *J* = 15.4 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.18 (d, *J* = 11.9 Hz, 1H), 3.90 (s, 3H), 3.87 (m, 1H; signal partially buried), 3.87 (s, 3H), 3.47 (s, 3H), 3.27 (td, *J* = 8.5, 2.3 Hz, 1H), 3.09 (dd, *J* = 10.7, 3.5 Hz, 1H), 2.62 (dd, *J* = 11.2, 2.5 Hz, 1H), 2.51 (q, *J* = 8.8 Hz, 1H), 2.38 (ddd, *J* = 12.0, 9.4, 2.2 Hz, 1H), 2.10 – 1.96 (m, 3H), 1.93 (t, *J* = 10.5 Hz, 1H), 1.74 (qd, *J* = 11.3, 3.1 Hz, 1H), 1.46 – 1.30 (m, 4H), 1.22 (m, 1H), 0.37 (q, *J* = 11.6 Hz, 1H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 179.5, 172.5, 164.0, 163.9, 146.1, 145.7, 141.9, 139.0, 138.4, 133.7, 127.6, 126.8, 124.9, 124.8, 122.6, 111.9, 110.9, 108.5, 74.8, 72.2, 67.8, 59.0, 56.4, 53.8, 53.6, 53.6, 52.5, 51.4, 40.9, 40.3, 36.0, 35.2, 31.0, 28.1, 23.8.

HRMS (ESI): calc. for $C_{35}H_{41}N_4O_6$ $[M+H]^+$: 613.3021, found: 613.3006.



Y7r

Yield: 32%; 29.9 mg of **Y7r** isolated as a colorless foam.

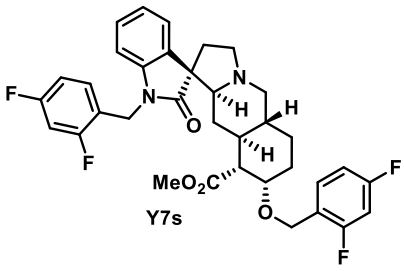
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.21 (d, *J* = 3.3 Hz, 1H), 6.19 (d, *J* = 3.3 Hz, 1H), 6.07 (d, *J* = 3.3 Hz, 1H), 6.05 (d, *J* = 3.3 Hz, 1H), 4.87 (d, *J* = 16.2 Hz, 1H), 4.75 (d, *J* = 16.2 Hz, 1H), 4.37 (d, *J* = 13.5 Hz, 1H), 4.18 (d, *J* = 13.5 Hz, 1H), 3.91 (m, 1H), 3.49 (s, 3H), 3.25 (t, *J* = 8.5 Hz, 1H), 3.08 (dd, *J* = 10.8, 3.4 Hz, 1H), 2.58 (d, *J* = 11.2 Hz, 1H), 2.50 (q, *J* = 8.8 Hz, 1H), 2.35 (ddd, *J* = 12.0, 9.3, 2.2 Hz,

1H), 2.06 – 1.96 (m, 3H), 1.93 (t, *J* = 10.7 Hz, 1H), 1.70 (qd, *J* = 11.4, 3.1 Hz, 1H), 1.43 – 1.28 (m, 4H), 1.21 (m, 1H), 0.41 (q, *J* = 11.6 Hz, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 179.0, 172.5, 151.9, 149.5, 142.0, 136.5, 135.8, 133.6, 127.7, 125.0, 122.6, 111.5, 110.5, 108.6, 107.4, 107.0, 74.9, 72.0, 62.5, 59.0, 56.3, 53.8, 52.6, 51.5, 40.4, 37.1, 36.0, 35.4, 31.1, 28.0, 23.8.

HRMS (ESI): calc. for $C_{31}H_{33}Cl_2N_2O_6$ $[M+H]^+$: 599.1710, found: 599.1701.

MP: 49 – 51 °C.



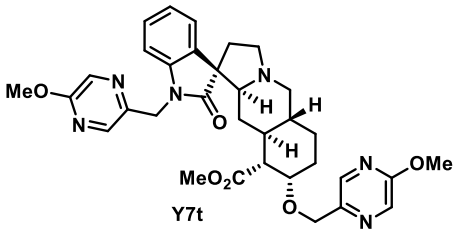
Yield: 51%; 50.2 mg of **Y7s** isolated as a colorless foam.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.4 Hz, 1H), 7.32 (q, *J* = 8.0 Hz, 1H), 7.20 (q, *J* = 7.7 Hz, 1H), 7.15 (t, *J* = 7.9 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.92 – 6.83 (m, 2H), 6.80 (m, 1H), 6.77 – 6.70 (m, 2H), 5.08 (d, *J* = 15.8 Hz, 1H), 4.72 (d, *J* = 15.8 Hz, 1H), 4.54 (d, *J* = 12.3 Hz, 1H), 4.28 (d, *J* = 12.3 Hz, 1H), 3.92 (m, 1H), 3.46 (s, 3H), 3.29 (t, *J* = 8.6 Hz, 1H), 3.10 (dd, *J* = 11.0, 3.5 Hz, 1H), 2.65 (d, *J* = 11.3 Hz, 1H), 2.52 (q, *J* = 8.8 Hz, 1H), 2.40 (m, 1H), 2.12 (dt, *J* = 11.1, 3.2 Hz, 1H), 2.06 – 1.98 (m, 2H), 1.94 (t, *J* = 10.7 Hz, 1H), 1.77 (qd, *J* = 11.3, 3.2 Hz, 1H), 1.44 – 1.32 (m, 4H), 1.24 (m, 1H), 0.39 (q, *J* = 11.5 Hz, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 179.6, 172.3, 162.7 (dd, *J* = 248, 12.2 Hz), 162.5 (dd, *J* = 248, 12.2 Hz), 159.7, 159.6, 141.9, 133.7, 131.0 (dd, *J* = 9.8, 5.9 Hz), 130.7 (dd, *J* = 9.9, 5.1 Hz), 127.7, 125.0, 122.7, 121.7 (d, *J* = 14.1 Hz), 119.3 (d, *J* = 13.1 Hz), 112.4 (dd, *J* = 21.3, 3.5 Hz), 111.4 (dd, *J* = 20.8, 3.5 Hz), 108.3, 103.9 (t, *J* = 25.5 Hz), 103.6 (t, *J* = 25.5 Hz), 75.4, 72.3, 63.6, 59.0, 56.4, 53.8, 52.4, 51.3, 40.4, 36.5, 36.0, 35.2, 31.0, 27.9, 23.7.

HRMS (ESI): calc. for $C_{35}H_{35}F_4N_2O_4$ $[M+H]^+$: 623.2527, found: 623.2546.

MP: 61 – 63 °C.

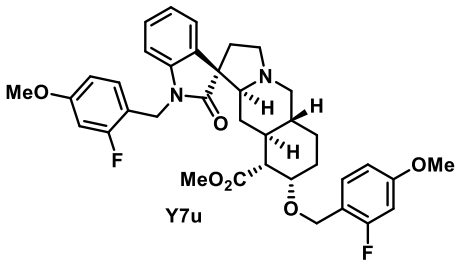


Yield: 46%; 49.5 mg of **Y7t** isolated as a colorless, amorphous solid.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.11 (s, 1H), 8.09 (s, 1H), 7.97 (s, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.14 (t, *J* = 7.7 Hz, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.10 (d, *J* = 15.8 Hz, 1H), 4.85 (d, *J* = 15.8 Hz, 1H), 4.60 (d, *J* = 12.7 Hz, 1H), 4.34 (d, *J* = 12.7 Hz, 1H), 3.98 (m, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.56 (s, 3H), 3.27 (t, *J* = 8.2 Hz, 1H), 3.09 (dd, *J* = 10.9, 3.5 Hz, 1H), 2.63 (d, *J* = 11.2 Hz, 1H), 2.51 (q, *J* = 8.8 Hz, 1H), 2.39 (ddd, *J* = 12.1, 9.2, 2.3 Hz, 1H), 2.12 (dt, *J* = 10.6, 3.1 Hz, 1H), 2.07 (dd, *J* = 11.7, 2.9 Hz, 1H), 2.04 – 1.88 (m, 2H), 1.79 (qd, *J* = 11.4, 3.2 Hz, 1H), 1.45 – 1.32 (m, 4H), 1.24 (m, 1H), 0.45 (q, *J* = 11.5 Hz, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 179.3, 172.7, 160.0, 159.9, 145.3, 143.0, 142.2, 139.6, 139.3, 135.0, 134.2, 133.7, 127.6, 125.0, 122.6, 108.8, 76.2, 72.0, 69.6, 59.0, 56.4, 53.8, 53.8, 53.8, 52.8, 51.5, 43.1, 40.4, 36.1, 35.4, 31.1, 28.3, 23.8.

HRMS (ESI): calc. for $C_{33}H_{39}N_6O_6$ $[M+H]^+$: 615.2956, found: 615.2955.



Y7u

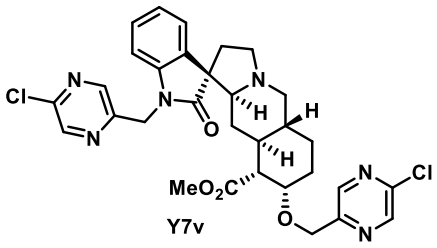
Yield: 55%; 32.4 mg of **Y7u** isolated as a colorless foam.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 8.5 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 8.5 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.70 – 6.64 (m, 2H), 6.61 – 6.53 (m, 2H), 5.02 (d, *J* = 15.6 Hz, 1H), 4.73 (d, *J* = 15.6 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.27 (d, *J* = 12.0 Hz, 1H), 3.89 (m, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.45 (s, 3H), 3.27 (t, *J* = 8.1 Hz, 1H), 3.09 (dd, *J* = 10.7, 3.5 Hz, 1H), 2.64 (d, *J* = 10.9 Hz, 1H), 2.52 (q, *J* = 8.8 Hz, 1H), 2.39 (ddd, *J* = 11.9, 9.3, 2.2 Hz, 1H), 2.11 (dd, *J* = 13.7, 3.1 Hz, 1H), 2.05 – 1.98 (m, 2H), 1.94 (t, *J* = 10.9 Hz, 1H), 1.77 (qd, *J* = 11.3, 3.2 Hz, 1H), 1.47 – 1.37 (m, 2H), 1.37 – 1.28 (m, 2H), 1.24 (m, 1H), 0.40 (q, *J* = 11.5 Hz, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 179.6, 172.5, 161.4 (d, *J* = 246 Hz), 161.2 (d, *J* = 245 Hz), 160.6 (d, *J* = 10.8 Hz), 160.5 (d, *J* = 10.9 Hz), 142.2, 133.7, 131.1 (d, *J* = 6.2 Hz), 130.3 (d, *J* = 5.8 Hz), 127.6, 124.8, 122.5, 117.6 (d, *J* = 15.7 Hz), 115.2 (d, *J* = 15.0 Hz), 111.0 (d, *J* = 2.2 Hz), 109.9 (d, *J* = 2.6 Hz), 108.5, 101.6 (d, *J* = 5.0 Hz), 101.4 (d, *J* = 4.9 Hz), 74.9, 72.1, 63.7, 59.1, 56.4, 55.7, 55.7, 53.9, 52.7, 51.3, 40.5, 36.6, 36.1, 35.4, 31.1, 28.0, 23.8.

HRMS (ESI): calc. for $C_{37}H_{41}F_2N_2O_6$ $[M+H]^+$: 647.2927, found: 647.2932.

MP: 61 – 63 °C.



Y7v

Yield: 60%; 75.0 mg of **Y7v** isolated as a colorless film.

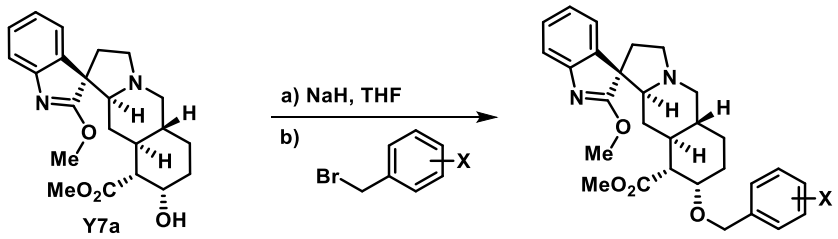
^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.64 (s, 0.6H, major rotamer), 8.55 (s, 1H), 8.46 (s, 0.4H, minor rotamer), 8.42 (m, 1H), 8.29 (m, 1H), 7.39 (d, *J* = 7.3 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.73 (dd, *J* = 7.8, 4.0 Hz, 1H), 5.18 (dd, *J* = 16.1, 11.4 Hz, 1H), 4.89 (t, *J* = 16.1 Hz, 1H), 4.67 (t, *J* = 14.0 Hz, 1H), 4.40 (t, *J* = 13.8 Hz, 1H), 4.01 (s, 1H), 3.59 (m, 3H, due to rotameric mixture), 3.29 (m, 1H), 3.11 (dd, *J* = 10.8, 3.4 Hz, 1H), 2.64 (m, 1H), 2.53 (q, *J* = 8.8 Hz, 1H), 2.41 (m, 1H), 2.19 – 2.07 (m, 2H), 2.07 – 1.88 (m, 2H), 1.81 (m, 1H), 1.52 – 1.20 (m, 5H), 0.44 (q, *J* = 11.6 Hz, 1H). **Note:** We believe several ^{1}H NMR signals in this spectrum are complicated by rotamers and have added some elevated temperature NMRs in d_6-DMSO in the spectra section of this supporting information document (NMR tabulation not present for these additional spectra).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 179.4, 172.5, 152.6, 152.3, 150.2, 149.9, 148.6, 148.2, 147.2, 146.1, 144.3, 143.8, 143.6, 143.3, 142.9, 142.8, 141.7, 141.7, 140.0, 139.5, 133.6, 127.7, 125.1, 122.9, 108.4, 76.8, 72.0, 69.4, 58.8, 56.4, 53.7, 52.6, 51.7, 51.7, 42.8, 40.3, 36.0, 35.3, 31.0, 28.1, 23.7. **Note:** This

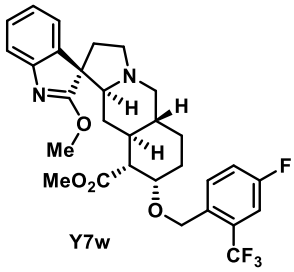
spectrum shows a mixture of rotational isomers (ten additional carbon signals correspond to eight additional aromatic carbons for the pyrazine fragments and two additional aliphatic carbons for the benzylic methylene carbons).

HRMS (ESI): calc. for $C_{31}H_{33}Cl_2N_6O_4$ $[M+H]^+$: 623.1935, found: 623.1925.

MP: 68 – 70 °C.



General procedure for the synthesis of *O*-alkylated imino methyl ether products Y7w – Y7z. Tetrahydrofuran (1 mL) was added to a round-bottom flask followed by sodium hydride (22.8 mg, 0.57 mmol, 60% dispersion in mineral oil). The mixture was cooled to 0 °C and then a solution of **Y7a** (104.2 mg, 0.27 mmol) in 1.0 mL of tetrahydrofuran was added and allowed to stir for 10 minutes. Then, 4-fluoro-2-(trifluoromethyl)benzyl bromide (46.0 µL, 0.30 mmol) was added and the reaction mixture was slowly warmed to room temperature over 14 hours. Upon completion, the reaction was quenched via brine and extracted with ethyl acetate using a separatory funnel. The organic layers were then collected, dried with sodium sulfate, filtered and concentrated. The crude mixture was purified via column chromatography using hexanes:ethyl acetate:triethylamine 66:33:1 to 49.5:49.5:1 to afford **Y7w** (115.4 mg, 76%) as a colorless film.



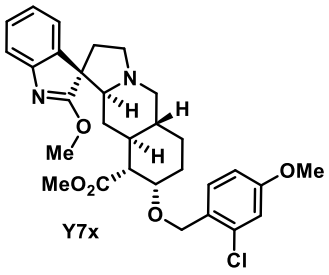
Yield: 76%; 115.4 mg of **Y7w** isolated as a colorless residue.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 8.6, 5.6 Hz, 1H), 7.35 (d, *J* = 7.3 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.24 – 7.18 (m, 2H), 7.02 (t, *J* = 7.4 Hz, 1H), 4.65 (d, *J* = 13.0 Hz, 1H), 4.35 (d, *J* = 13.0 Hz, 1H), 4.05 (s, 3H), 3.95 (m, 1H), 3.50 (s, 3H), 3.27 (td, *J* = 8.6, 2.3 Hz, 1H), 3.11 (dd, *J* = 10.7, 3.4 Hz, 1H), 2.55 (dd, *J* = 11.2, 2.6 Hz, 1H), 2.41 (q, *J* = 8.8 Hz, 1H), 2.26 (ddd, *J* = 11.9, 9.2, 2.3 Hz, 1H), 2.14 (m, 1H), 2.11 (dd, *J* = 11.3, 2.4 Hz, 1H), 2.00 (m, 1H), 1.90 (t, *J* = 10.6 Hz, 1H), 1.75 (qd, *J* = 11.3, 3.2 Hz, 1H), 1.45 – 1.17 (m, 5H), 0.48 (q, *J* = 11.6 Hz, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 182.3, 172.5, 161.4 (d, J = 248 Hz), 152.6, 141.0, 133.3 (q, *J* = 2.0 Hz), 131.3 (d, *J* = 7.8 Hz), 128.9 (qd, *J* = 31.8, 7.7 Hz), 127.7, 123.6, 123.6 (qd, *J* = 274, 2.8 Hz), 123.3, 118.9 (dd, *J* = 20.5, 0.8 Hz), 118.2, 113.2 (dq, *J* = 25.2, 5.8 Hz), 76.3, 69.8, 66.0 (q, *J* = 2.8 Hz), 59.8, 59.1, 56.6, 53.6, 52.4, 51.4, 40.4, 36.3, 33.1, 30.7, 28.1, 23.7.

HRMS (ESI): calc. for $C_{30}H_{33}F_4N_2O_4$ $[M+H]^+$: 561.2371, found: 561.2384.

MP: 117 – 119 °C.



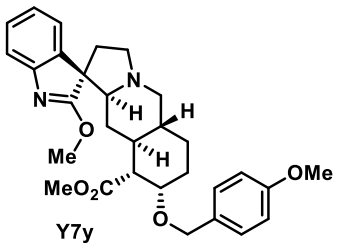
Yield: 73%; 102.1 mg of **Y7x** isolated as a colorless film.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.2 Hz, 1H), 7.32 – 7.24 (m, 2H), 7.21 (td, *J* = 7.6, 1.3 Hz, 1H), 7.03 (td, *J* = 7.4, 1.2 Hz, 1H), 6.86 (d, *J* = 2.6 Hz, 1H), 6.78 (dd, *J* = 8.5, 2.6 Hz, 1H), 4.55 (d, *J* = 12.3 Hz, 1H), 4.28 (d, *J* = 12.3 Hz, 1H), 4.05 (s, 3H), 3.92 (m, 1H), 3.77 (s, 3H), 3.48 (s, 3H), 3.27 (t, *J* = 8.2 Hz, 1H), 3.11 (dd, *J* = 10.8, 3.4 Hz, 1H), 2.55 (d, *J* = 11.3 Hz, 1H), 2.41 (q, *J* = 8.8 Hz, 1H), 2.26 (ddd, *J* = 11.8, 9.1, 2.3 Hz, 1H), 2.17 (dt, *J* = 11.2, 2.8 Hz, 1H), 2.07 (dd, *J* = 11.6, 3.0 Hz, 1H), 2.00 (m, 1H), 1.90 (t, *J* = 10.6 Hz, 1H), 1.74 (qd, *J* = 11.4, 3.2 Hz, 1H), 1.51 – 1.21 (m, 5H), 0.47 (q, *J* = 11.6 Hz, 1H). **Note:** This spectrum referenced TMS at 0.00 ppm.

^{13}C NMR: (100 MHz, $CDCl_3$) δ 182.4, 172.5, 159.6, 152.5, 141.0, 133.7, 130.5, 128.3, 127.6, 123.6, 123.3, 118.1, 114.6, 113.0, 75.2, 69.9, 67.2, 59.7, 59.2, 56.6, 55.7, 53.7, 52.4, 51.5, 40.4, 36.2, 33.2, 30.7, 28.0, 23.8.

HRMS (ESI): calc. for $C_{30}H_{36}ClN_2O_5$ $[M+H]^+$: 539.2307, found: 539.2323.

MP: 170 – 172 °C.

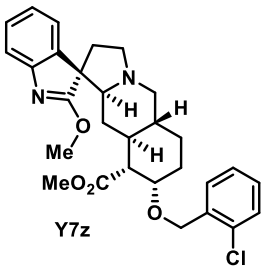


Yield: 55%; 50.2 mg of **Y7y** isolated as a colorless, amorphous solid. **Note:** **Y7y** was purified via column chromatography using alumina neutral act I with hexanes:ethyl acetate.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.1 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.20 (td, *J* = 7.6, 1.3 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 2H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.19 (d, *J* = 11.8 Hz, 1H), 4.04 (s, 3H), 3.87 (m, 1H), 3.77 (s, 3H), 3.45 (s, 3H), 3.26 (t, *J* = 8.8 Hz, 1H), 3.10 (d, *J* = 9.5 Hz, 1H), 2.54 (d, *J* = 11.0 Hz, 1H), 2.40 (q, *J* = 9.4 Hz, 1H), 2.25 (ddd, *J* = 11.8, 9.2, 2.2 Hz, 1H), 2.11 – 1.94 (m, 3H), 1.90 (t, *J* = 10.0 Hz, 1H), 1.72 (q, *J* = 10.8 Hz, 1H), 1.49 – 1.21 (m, 5H), 0.45 (q, *J* = 11.4 Hz, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 182.4, 172.5, 159.2, 152.5, 141.0, 130.7, 129.3, 127.6, 123.6, 123.3, 118.1, 113.8, 74.4, 70.1, 69.9, 59.7, 59.2, 56.6, 55.4, 53.7, 52.4, 51.4, 40.4, 36.1, 33.1, 30.6, 28.0, 23.8.

HRMS (ESI): calc. for $C_{30}H_{37}N_2O_5$ $[M+H]^+$: 505.2697, found: 505.2696.



Yield: 79%; 56.1 mg of **Y7z** isolated as a colorless foam.

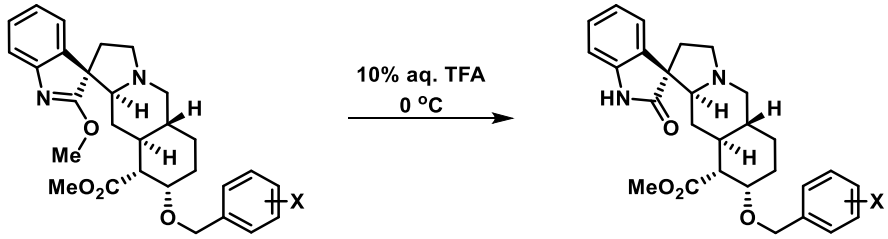
^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.25 – 7.19 (m, 2H), 7.18 (td, *J* = 7.7, 1.8 Hz, 1H), 7.04 (t, *J* = 7.4 Hz, 1H), 4.62 (d, *J* = 13.0 Hz, 1H), 4.33 (d, *J* = 13.0 Hz, 1H), 4.05 (s, 3H), 3.96 (m, 1H), 3.48 (s, 3H), 3.27 (t, *J* = 7.5 Hz, 1H), 3.12 (d, *J* = 9.3 Hz, 1H), 2.56 (d, *J* = 9.6 Hz, 1H), 2.42 (q, *J* = 8.8 Hz, 1H), 2.26 (m, 1H), 2.18 (dt, *J* = 10.6, 2.9

Hz, 1H), 2.10 (dd, *J* = 11.7, 3.0 Hz, 1H), 2.01 (m, 1H), 1.92 (t, *J* = 10.8 Hz, 1H), 1.77 (qd, *J* = 11.3, 1.8 Hz, 1H), 1.46 – 1.33 (m, 4H), 1.29 (m, 1H), 0.48 (q, *J* = 12.0 Hz, 1H).

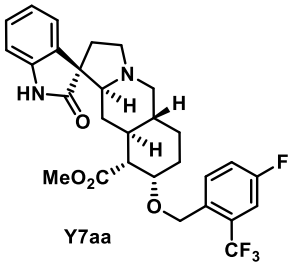
^{13}C NMR: (150 MHz, $CDCl_3$) δ 182.4, 172.5, 152.6, 141.0, 136.4, 132.7, 129.2, 129.2, 128.6, 127.7, 127.0, 123.7, 123.3, 118.2, 75.8, 69.9, 67.5, 59.8, 59.1, 56.7, 53.6, 52.5, 51.5, 40.5, 36.3, 33.2, 30.7, 28.1, 23.8.

HRMS (ESI): calc. for $C_{29}H_{34}ClN_2O_4$ $[M+H]^+$: 509.2202, found: 509.2193.

MP: 131 – 133 °C.



General procedure for the synthesis of free amides Y7aa – Y7ad. **Y7w** (110.0 mg, 0.20 mmol) was first added to a round-bottom flask followed by the addition of solution of 10% aqueous trifluoroacetic acid (4.0 mL, 0.05 M) at 0 °C. The reaction was allowed to stir at 0 °C for 3.25 hours before being quenched with a 3 M ammonium hydroxide solution. The crude product was then extracted with ethyl acetate in a separatory funnel. The organic layers were then washed with brine, dried with sodium sulfate, filtered and concentrated. The crude mixture was purified via column chromatography using hexanes:ethyl acetate:triethylamine 66:33:1 to 49.5:49.5:1 to afford **Y7aa** (89.4 mg, 83%) as a colorless film.



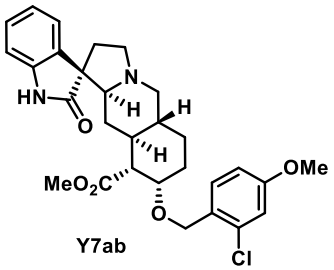
Yield: 83%; 89.4 mg of **Y7aa** isolated as a colorless film.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.64 (t, *J* = 6.6 Hz, 1H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.28 (m, 1H), 7.22 (t, *J* = 8.1 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 4.67 (d, *J* = 13.1 Hz, 1H), 4.35 (d, *J* = 13.1 Hz, 1H), 3.98 (m, 1H), 3.50 (s, 3H), 3.27 (t, *J* = 8.6 Hz, 1H), 3.11 (d, *J* = 10.6 Hz, 1H), 2.61 (d, *J* = 11.1 Hz, 1H), 2.50 (q, *J* = 8.9 Hz, 1H), 2.38 (t, *J* = 11.2 Hz, 1H), 2.18 – 2.09 (m, 2H), 2.01 (q, *J* = 10.5 Hz, 1H), 1.94 (t, *J* = 10.5 Hz, 1H), 1.84 (q, *J* = 10.5 Hz, 1H), 1.51 (d, *J* = 12.1 Hz, 1H), 1.46 – 1.35 (m, 3H), 1.29 (m, 1H), 0.55 (q, *J* = 11.7 Hz, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 182.2, 172.7, 161.3 (d, *J* = 247 Hz), 140.7, 134.2, 133.4, 131.1 (d, *J* = 7.7 Hz), 128.6 (qd, *J* = 31.7, 7.7 Hz), 127.6, 125.0, 123.6 (qd, *J* = 274, 2.8 Hz), 122.3, 118.9 (d, *J* = 20.5 Hz), 113.1 (dq, *J* = 25.2, 5.9 Hz), 109.9, 76.5, 71.7, 65.9 (q, *J* = 2.9 Hz), 59.0, 56.9, 53.8, 52.7, 51.4, 40.4, 36.2, 35.6, 31.0, 28.2, 23.8.

HRMS (ESI): calc. for $C_{29}H_{31}F_4N_2O_4$ $[M+H]^+$: 547.2214, found: 547.2204.

MP: 73 – 75 °C.



Y7ab

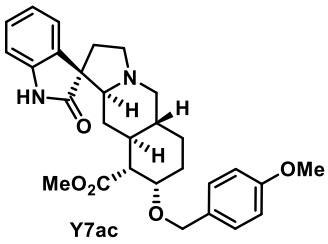
Yield: 98%; 93.0 mg of **Y7ab** isolated as a colorless film.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.36 (d, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.85 (s, 1H), 6.78 (d, *J* = 8.7 Hz, 1H), 4.55 (d, *J* = 12.3 Hz, 1H), 4.27 (d, *J* = 12.3 Hz, 1H), 3.94 (m, 1H), 3.75 (s, 3H), 3.49 (s, 3H), 3.26 (t, *J* = 8.7 Hz, 1H), 3.10 (d, *J* = 10.7 Hz, 1H), 2.60 (d, *J* = 10.9 Hz, 1H), 2.49 (q, *J* = 8.9 Hz, 1H), 2.37 (t, *J* = 11.4 Hz, 1H), 2.15 (d, *J* = 11.0 Hz, 1H), 2.09 (d, *J* = 11.0 Hz, 1H), 2.00 (q, *J* = 11.0 Hz, 1H), 1.94 (t, *J* = 10.9 Hz, 1H), 1.81 (q, *J* = 11.0 Hz, 1H), 1.50 (d, *J* = 12.3 Hz, 1H), 1.46 – 1.32 (m, 3H), 1.27 (m, 1H), 0.52 (q, *J* = 11.7 Hz, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 182.0, 172.7, 159.5, 140.7, 134.1, 133.4, 130.2, 128.4, 127.6, 125.0, 122.2, 114.6, 112.9, 109.8, 75.5, 71.7, 67.2, 59.0, 56.9, 55.6, 53.7, 52.8, 51.4, 40.4, 36.1, 35.6, 31.0, 28.1, 23.8.

HRMS (ESI): calc. for $C_{29}H_{34}ClN_2O_5$ $[M+H]^+$: 525.2150, found: 525.2149.

MP: 83 – 85 °C.



Y7ac

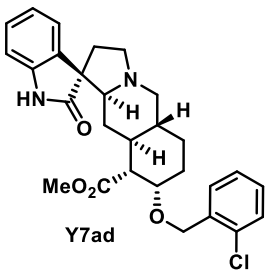
Yield: 54%; 12.2 mg of **Y7ac** isolated as a pale-yellow film.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.21 – 7.12 (m, 3H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.88 – 6.79 (m, 3H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.21 (d, *J* = 11.8 Hz, 1H), 3.89 (m, 1H), 3.78 (s, 3H), 3.47 (s, 3H), 3.25 (t, *J* = 8.4 Hz, 1H), 3.08 (d, *J* = 9.8 Hz, 1H), 2.57 (d, *J* = 10.7 Hz, 1H), 2.47 (q, *J* = 8.7 Hz, 1H), 2.37 (t, *J* = 11.1 Hz, 1H), 2.13 – 1.87 (m, 4H), 1.79 (q, *J* = 11.3 Hz, 1H), 1.50 – 1.18 (m, 5H), 0.48 (q, *J* = 11.6 Hz, 1H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 181.4, 172.8, 159.2, 140.4, 134.2, 130.8, 129.2, 127.6, 125.2, 122.4, 113.8, 109.5, 74.6, 71.9, 70.2, 59.0, 56.8, 55.5, 53.8, 52.8, 51.5, 40.5, 36.0, 35.6, 31.1, 28.2, 23.8.

HRMS (ESI): calc. for $C_{29}H_{35}N_2O_5$ $[M+H]^+$: 491.2540, found: 491.2536.

MP: 87 – 89 °C.



Y7ad

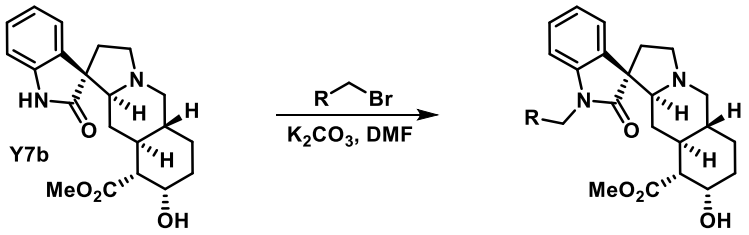
Yield: 53%; 16.8 mg of **Y7ad** isolated as a colorless film.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.32 – 7.22 (m, 2H), 7.22 – 7.15 (m, 2H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 4.63 (d, *J* = 13.2 Hz, 1H), 4.33 (d, *J* = 13.2 Hz, 1H), 3.99 (m, 1H), 3.50 (s, 3H), 3.27 (t, *J* = 8.5 Hz, 1H), 3.11 (dd, *J* = 11.0, 3.5 Hz, 1H), 2.60 (d, *J* = 10.9 Hz, 1H), 2.50 (q, *J* = 8.7 Hz, 1H), 2.38 (ddd, *J* = 11.6, 9.2, 2.1 Hz, 1H), 2.19 (m, 1H), 2.12 (dd, *J* = 11.7, 2.8 Hz, 1H), 2.02 (m, 1H), 1.95 (t, *J* = 10.6 Hz, 1H), 1.85 (qd, *J* = 11.2, 1.9 Hz, 1H), 1.51 (dt, *J* = 12.2, 2.9 Hz, 1H), 1.47 – 1.34 (m, 3H), 1.27 (m, 1H), 0.52 (q, *J* = 11.6 Hz, 1H). **Note:** This spectrum referenced TMS at 0.00 ppm.

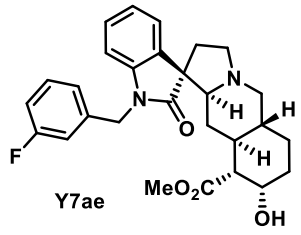
^{13}C NMR: (100 MHz, $CDCl_3$) δ 181.6, 172.8, 140.5, 136.5, 134.2, 132.3, 129.0, 128.9, 128.5, 127.7, 127.0, 125.2, 122.4, 109.6, 76.0, 71.9, 67.5, 59.0, 56.8, 53.8, 52.8, 51.5, 40.5, 36.2, 35.6, 31.1, 28.2, 23.8.

HRMS (ESI): calc. for $C_{28}H_{32}ClN_2O_4$ $[M+H]^+$: 495.2045, found: 495.2044.

MP: 97 – 99 °C.



General procedure for the synthesis of *N*-alkylated products Y7ae – Y7ai. **Y7b** (45.7 mg, 0.12 mmol) and potassium carbonate (42.6 mg, 0.31 mmol) were added to a round bottom flask, then dissolved with *N,N*-dimethylformamide (3 mL, 0.04 M). 3-Fluorobenzyl bromide (16.6 µL, 0.14 mmol) was added and the reaction mixture, which was then allowed to stir at room temperature for 24 hours. Upon completion, the reaction was quenched via brine, extracted with ethyl acetate and washed with additional brine (4x) in a separatory funnel. The organic layers were then collected, dried with sodium sulfate, filtered and concentrated. The crude product was then purified via column chromatography using hexanes:ethyl acetate:triethylamine 66:33:1 to 49.5:49.5:1 to afford **Y7ae** (46.6 mg, 79%) as a colorless foam.



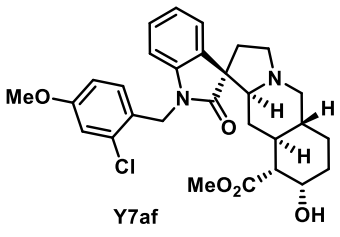
Yield: 79%; 46.6 mg of **Y7ae** isolated as a colorless foam.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.4 Hz, 1H), 7.27 (q, *J* = 7.7, 1H), 7.14 (t, *J* = 7.7 Hz, 1H), 7.06 – 6.98 (m, 2H), 6.96 – 6.86 (m, 2H), 6.65 (d, *J* = 7.7 Hz, 1H), 5.06 (d, *J* = 15.9 Hz, 1H), 4.70 (d, *J* = 15.9 Hz, 1H), 4.08 (m, 1H), 3.52 (s, 3H), 3.28 (td, *J* = 8.8, 2.5 Hz, 1H), 3.10 (dd, *J* = 10.9, 3.6 Hz, 1H), 3.03 (br. s, 1H), 2.60 (d, *J* = 11.6 Hz, 1H), 2.53 (q, *J* = 8.8 Hz, 1H), 2.40 (ddd, *J* = 12.3, 9.3, 2.5 Hz, 1H), 2.09 (dd, *J* = 11.6, 1.0 Hz, 1H), 2.06 – 1.87 (m, 3H), 1.73 (qd, *J* = 11.5, 3.4 Hz, 1H), 1.54 (m, 1H), 1.48 – 1.34 (m, 2H), 1.27 (m, 1H), 1.01 (dt, *J* = 12.2, 3.1 Hz, 1H), 0.66 (q, *J* = 11.7 Hz, 1H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 179.4, 175.4, 163.1 (d, *J* = 247 Hz), 142.0, 138.9 (d, *J* = 7.0 Hz), 133.5, 130.6 (d, *J* = 8.3 Hz), 127.7, 125.1, 122.9 (d, *J* = 2.9 Hz), 122.8, 114.7 (d, *J* = 21 Hz), 114.2 (d, *J* = 22 Hz), 108.7, 71.6, 66.9, 58.9, 56.4, 53.5, 52.6, 51.7 (d, *J* = 1.9 Hz), 43.6 (d, *J* = 1.7 Hz), 40.5, 36.2, 35.7, 31.6, 30.7, 23.5.

HRMS (ESI): calc. for $C_{28}H_{32}FN_2O_4$ $[M+H]^+$: 479.2341, found: 479.2332.

MP: 111 – 113 °C.



Y7af

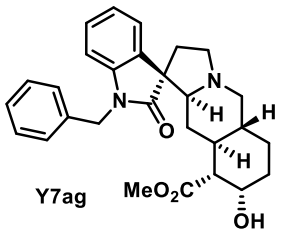
Yield: 80%; 62.3 mg of **Y7af** isolated as a colorless film.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 5.4 Hz, 1H), 7.15 (td, *J* = 7.7, 1.3 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 6.92 (d, *J* = 2.6 Hz, 1H), 6.74 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 5.07 (d, *J* = 16.1 Hz, 1H), 4.84 (d, *J* = 16.1 Hz, 1H), 4.09 (m, 1H), 3.76 (s, 3H), 3.54 (s, 3H), 3.31 (t, *J* = 8.0 Hz, 1H), 3.13 (d, *J* = 8.9 Hz, 1H), 2.91 (s, 1H), 2.63 (d, *J* = 11.3 Hz, 1H), 2.55 (q, *J* = 9.4 Hz, 1H), 2.41 (ddd, *J* = 12.0, 9.3, 2.4 Hz, 1H), 2.11 (dd, *J* = 11.7, 2.0 Hz, 1H), 2.08 – 1.89 (m, 3H), 1.75 (qd, *J* = 11.5, 2.5 Hz, 1H), 1.61 – 1.21 (m, 4H), 1.04 (dt, *J* = 12.2, 3.0 Hz, 1H), 0.68 (d, *J* = 12.3 Hz, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 179.6, 175.2, 159.6, 142.2, 133.6, 133.4, 129.2, 127.7, 125.4, 124.9, 122.7, 115.0, 113.6, 108.8, 71.8, 66.9, 59.0, 56.5, 55.6, 53.7, 52.7, 51.7, 40.9, 40.5, 36.2, 35.5, 31.6, 30.7, 23.5.

HRMS (ESI): calc. for $C_{29}H_{34}ClN_2O_5$ $[M+H]^+$: 525.2150, found, 525.2155.

MP: 63 – 65 °C.



Y7ag

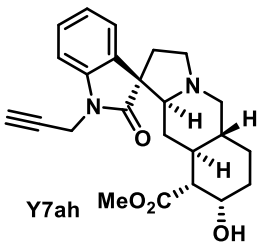
Yield: 93%; 46.8 mg of **Y7ag** isolated as a colorless foam.

^{1}H NMR: (500 MHz,$CDCl_3$) δ 7.40 (d, *J* = 7.3 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.25 – 7.21 (m, 3H), 7.13 (t, *J* = 7.7 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 5.09 (d, *J* = 15.6 Hz, 1H), 4.70 (d, *J* = 15.6 Hz, 1H), 4.08 (m, 1H), 3.50 (s, 3H), 3.29 (td, *J* = 8.7, 2.4 Hz, 1H), 3.11 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.00 (br. s, 1H), 2.61 (dd, *J* = 11.3, 2.5 Hz, 1H), 2.54 (q, *J* = 8.8 Hz, 1H), 2.41 (ddd, *J* = 12.3, 9.4, 2.5 Hz, 1H), 2.08 (dd, *J* = 11.7, 2.0 Hz, 1H), 2.02 (dt, *J* = 12.9, 8.4 Hz, 1H), 1.97 – 1.89 (m, 2H), 1.74 (qd, *J* = 11.5, 3.4 Hz, 1H), 1.55 (m, 1H), 1.44 (dt, *J* = 13.5, 3.0 Hz, 1H), 1.38 (m, 1H), 1.29 (m, 1H), 1.00 (dt, *J* = 12.3, 3.1 Hz, 1H), 0.64 (q, *J* = 11.7 Hz, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 179.5, 175.4, 142.4, 136.4, 133.6, 128.9, 127.7, 127.6, 127.4, 124.9, 122.6, 108.8, 71.8, 66.9, 59.0, 56.5, 53.7, 52.7, 51.7, 44.0, 40.6, 36.3, 35.4, 31.5, 30.7, 23.6.

HRMS (ESI): calc. for $C_{28}H_{33}N_2O_4$ $[M+H]^+$: 461.2434, found: 461.2456.

MP: 155 – 157 °C.



Y7ah

Yield: 82%; 72.5 mg of **Y7ah** isolated as a tan foam.

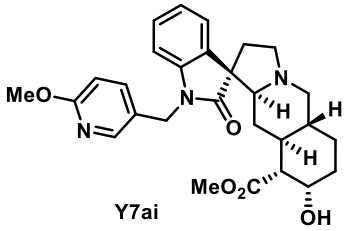
^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.4 Hz, 1H), 7.27 (m, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 4.55 (dd, *J* = 17.7, 2.5 Hz, 1H), 4.40 (dd, *J* = 17.7, 2.5 Hz, 1H), 4.06 (m, 1H), 3.52 (s, 3H), 3.26 (t, *J* = 9.0 Hz, 1H), 3.12 (s, 1H), 3.08 (dd, *J* = 11.3, 3.5 Hz, 1H), 2.54 – 2.43 (m, 2H), 2.34 (ddd, *J* = 12.4, 9.4, 2.5 Hz, 1H), 2.17 (t, *J* = 2.5 Hz, 1H), 2.06 (dd, *J* = 11.5, 2.0 Hz, 1H), 1.97 (dt, *J* = 13.2,

8.5 Hz, 1H), 1.93 – 1.85 (m, 2H), 1.68 (qd, *J* = 11.4, 3.3 Hz, 1H), 1.52 (m, 1H), 1.41 (d, *J* = 14.2 Hz, 1H), 1.36 (m, 1H), 1.25 (q, *J* = 10.8 Hz, 1H), 0.94 (dt, *J* = 12.5, 3.0 Hz, 1H), 0.59 (q, *J* = 11.7 Hz, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 178.4, 175.7, 141.3, 133.3, 127.7, 124.9, 123.0, 108.8, 77.4, 72.1, 71.8, 66.7, 58.9, 56.4, 53.5, 52.5, 51.6, 40.6, 36.3, 35.1, 31.4, 30.5, 29.5, 23.5.

HRMS (ESI): calc. for $C_{24}H_{29}N_2O_4$ $[M+H]^+$: 409.2122, found: 409.2112.

MP: 56 – 58 °C.



Y7ai

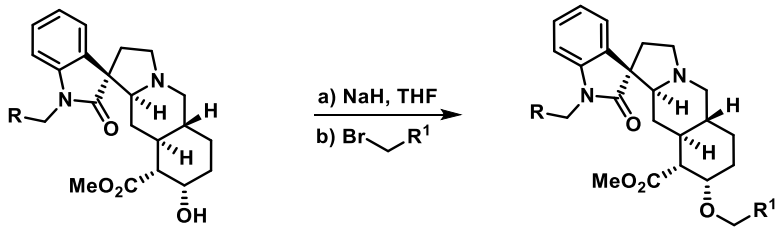
Yield: 47%; 40.1 mg of **Y7ai** isolated as a colorless film.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 2.4 Hz, 1H), 7.48 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.15 (td, *J* = 7.7, 1.3 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 8.5 Hz, 1H), 4.99 (d, *J* = 15.5 Hz, 1H), 4.63 (d, *J* = 15.5 Hz, 1H), 4.07 (m, 1H), 3.87 (s, 3H), 3.53 (s, 3H), 3.28 (t, *J* = 8.3 Hz, 1H), 3.10 (dd, *J* = 10.9, 3.6 Hz, 1H), 3.00 (br s, 1H), 2.57 (d, *J* = 11.2 Hz, 1H), 2.52 (q, *J* = 8.8 Hz, 1H), 2.38 (ddd, *J* = 12.4, 9.4, 2.5 Hz, 1H), 2.06 (dd, *J* = 11.6, 2.1 Hz, 1H), 2.00 (m, 1H), 1.96 – 1.87 (m, 2H), 1.71 (qd, *J* = 11.5, 3.5 Hz, 1H), 1.52 (qd, *J* = 12.3, 2.8 Hz, 1H), 1.43 (dt, *J* = 13.6, 3.0 Hz, 1H), 1.36 (m, 1H), 1.25 (m, 1H), 0.93 (dt, *J* = 12.2, 3.1 Hz, 1H), 0.59 (q, *J* = 11.7 Hz, 1H).

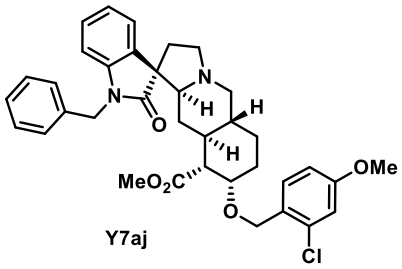
^{13}C NMR: (125 MHz, $CDCl_3$) δ 179.4, 175.4, 163.9, 145.7, 141.9, 138.3, 133.6, 127.7, 125.1, 124.7, 122.8, 111.6, 108.6, 71.8, 66.9, 59.0, 56.4, 53.6, 53.6, 52.6, 51.7, 41.0, 40.5, 36.3, 35.3, 31.5, 30.6, 23.6.

HRMS (ESI): calc. for $C_{28}H_{34}N_3O_5$ $[M+H]^+$: 492.2493, found: 492.2486.

MP: 49 – 51 °C.



General procedure for the synthesis of mixed functionalized products Y7aj – Y7am. Tetrahydrofuran (1.7 mL) was added to a round-bottom flask followed by sodium hydride (8.4 mg, 0.21 mmol, 60% dispersion in mineral oil). The mixture was cooled to 0 °C and then **Y7ag** (64.3 mg, 0.14 mmol) dissolved in 0.3 mL of tetrahydrofuran was added and allowed to stir for 10 minutes. Then, 2-chloro-4-methoxybenzyl bromide (36.2 mg, 0.15 mmol) was added to the reaction mixture, which was allowed to stir while warming to room temperature over 7 hours. Upon completion, the reaction was quenched via brine and extracted with ethyl acetate. The organic layers were then collected, dried with sodium sulfate, filtered and concentrated. The crude product was purified via column chromatography using hexanes:ethyl acetate:triethylamine 66:33:1 to 49.5:49.5:1 to afford **Y7aj** (62.0 mg, 72%) as a colorless foam.



Y7aj

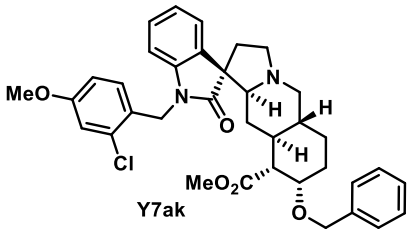
Yield: 72%; 62.0 mg of **Y7aj** isolated as a colorless film.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.2 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.25 – 7.19 (m, 3H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.87 (s, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 5.13 (d, *J* = 15.6 Hz, 1H), 4.67 (d, *J* = 15.6 Hz, 1H), 4.57 (d, *J* = 12.4 Hz, 1H), 4.29 (d, *J* = 12.4 Hz, 1H), 3.96 (m, 1H), 3.78 (s, 3H), 3.50 (s, 3H), 3.29 (t, *J* = 7.2 Hz, 1H), 3.12 (d, *J* = 10.6 Hz, 1H), 2.69 (d, *J* = 10.9 Hz, 1H), 2.55 (q, *J* = 8.9 Hz, 1H), 2.43 (t, *J* = 11.2 Hz, 1H), 2.16 (d, *J* = 12.7 Hz, 1H), 2.11 – 2.01 (m, 2H), 1.97 (t, *J* = 11.3 Hz, 1H), 1.84 (q, *J* = 11.6 Hz, 1H), 1.50 (d, *J* = 12.4 Hz, 1H), 1.47 – 1.32 (m, 3H), 1.27 (m, 1H), 0.47 (q, *J* = 11.7 Hz, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 179.5, 172.5, 159.6, 142.5, 136.3, 133.8, 133.4, 130.2, 129.0, 128.4, 127.6, 127.5, 127.3, 124.8, 122.4, 114.7, 112.9, 108.8, 75.5, 72.1, 67.2, 59.1, 56.4, 55.7, 53.9, 52.8, 51.4, 44.0, 40.5, 36.1, 35.4, 31.1, 28.1, 23.8.

HRMS (ESI): calc. for $C_{36}H_{40}ClN_2O_5$ $[M+H]^+$: 615.2620, found: 615.2602.

MP: 63 – 65 °C.



Y7ak

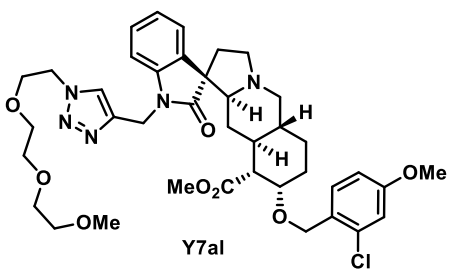
Yield: 79%; 26.4 mg of **Y7ak** isolated as a colorless film.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.3 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.28 – 7.23 (m, 3H), 7.13 (t, *J* = 7.7 Hz, 1H), 7.03 – 6.97 (m, 2H), 6.92 (d, *J* = 2.6 Hz, 1H), 6.81 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.68 (d, *J* = 7.7 Hz, 1H), 5.12 (d, *J* = 16.1 Hz, 1H), 4.81 (d, *J* = 16.1 Hz, 1H), 4.56 (d, *J* = 12.2 Hz, 1H), 4.29 (d, *J* = 12.2 Hz, 1H), 3.93 (m, 1H), 3.75 (s, 3H), 3.48 (s, 3H), 3.31 (t, *J* = 8.7 Hz, 1H), 3.12 (dd, *J* = 10.7, 3.4 Hz, 1H), 2.70 (d, *J* = 11.0 Hz, 1H), 2.55 (q, *J* = 8.8 Hz, 1H), 2.43 (ddd, *J* = 11.9, 9.5, 2.2 Hz, 1H), 2.11 – 2.01 (m, 3H), 1.98 (t, *J* = 10.7 Hz, 1H), 1.85 (q, *J* = 10.9 Hz, 1H), 1.53 (dd, *J* = 12.0, 2.8 Hz, 1H), 1.45 (m, 1H), 1.40 – 1.21 (m, 3H), 0.48 (q, *J* = 11.6 Hz, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 179.6, 172.5, 159.5, 142.3, 138.7, 133.6, 133.4, 129.2, 128.4, 127.6, 127.6, 127.5, 125.3, 124.8, 122.5, 114.9, 113.9, 108.8, 74.9, 72.1, 70.4, 59.0, 56.5, 55.6, 53.8, 52.6, 51.3, 40.7, 40.4, 36.0, 35.4, 31.1, 28.0, 23.8.

HRMS (ESI): calc. for $C_{36}H_{40}ClN_2O_5$ $[M+H]^+$: 615.2620, found: 615.2640.

MP: 54 – 56 °C.



Y7al

Yield: 57%; 37.9 mg of **Y7al** isolated as a colorless, amorphous solid.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.33 (m, 1H), 7.28 (m, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.85 (s, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 5.08 (d, *J* = 15.8 Hz, 1H), 4.91 (d, *J* = 15.8 Hz, 1H), 4.58 – 4.45 (m, 3H), 4.26 (d, *J* = 12.5

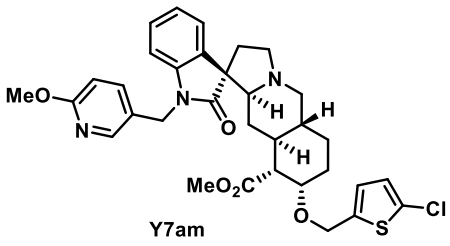
Hz, 1H), 3.94 (m, 1H), 3.87 – 3.80 (m, 2H), 3.77 (s, 3H), 3.59 – 3.48 (m, 8H), 3.45 (s, 3H), 3.35 (s, 3H), 3.27 (t, *J* = 8.5 Hz, 1H), 3.09 (d, *J* = 10.7 Hz, 1H), 2.58 (d, *J* = 11.1 Hz, 1H), 2.49 (q, *J* = 9.4, 8.8 Hz, 1H), 2.34 (t, *J* = 11.3 Hz, 1H), 2.14 (d, *J* = 11.9 Hz, 1H), 2.07 – 1.88 (m, 4H), 1.75 (q, *J* = 11.6 Hz, 1H), 1.43 – 1.30 (m, 3H), 1.23 (m, 1H), 0.37 (q, *J* = 11.8 Hz, 1H).

^{1}H NMR: (500 MHz, d_6-DMSO) δ 7.88 (s, 1H), 7.32 – 7.25 (m, 2H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), 7.01 – 6.97 (m, 2H), 6.91 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.96 (d, *J* = 15.0 Hz, 1H), 4.91 (d, *J* = 15.0 Hz, 1H), 4.52 – 4.41 (m, 3H), 4.19 (d, *J* = 11.9 Hz, 1H), 3.87 (m, 1H), 3.78 (m, 1H), 3.76 (s, 3H), 3.49 – 3.37 (m, 12H), 3.22 (s, 3H), 3.07 (d, *J* = 10.6 Hz, 1H), 2.40 – 2.29 (m, 2H), 2.20 (t, *J* = 11.1 Hz, 1H), 2.15 (d, *J* = 11.9 Hz, 1H), 2.07 (d, *J* = 13.5 Hz, 1H), 1.85 (m, 1H), 1.78 (t, *J* = 10.0 Hz, 1H), 1.50 (q, *J* = 10.5 Hz, 1H), 1.39 (t, *J* = 12.5 Hz, 1H), 1.34 – 1.17 (m, 5H), 0.32 (q, *J* = 11.6 Hz, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 179.2, 172.5, 159.6, 143.3, 141.9, 133.5, 130.3, 128.3, 127.7, 124.7, 123.5, 122.5, 114.6, 112.9, 109.0, 75.3, 72.4, 72.1, 70.7, 70.7, 70.7, 69.5, 67.1, 59.2, 59.1, 56.3, 55.7, 54.0, 52.4, 51.4, 50.3, 40.4, 36.1, 35.8, 35.1, 30.9, 28.0, 23.8. **Note:** Missing one aromatic ^{13}C NMR signal, most likely due to signal overlap.

^{13}C NMR: (125 MHz, d_6-DMSO) δ 177.8, 171.8, 159.4, 142.0, 141.7, 133.0, 132.9, 130.9, 127.6, 127.4, 124.1, 123.3, 122.1, 114.3, 113.0, 108.8, 74.7, 71.5, 71.2, 69.6, 69.5, 69.5, 68.6, 66.5, 58.5, 58.0, 55.5, 55.4, 53.0, 51.0, 50.9, 49.4, 35.8, 34.8, 34.6, 30.1, 26.9, 23.2. **Notes:** Missing one aliphatic ^{13}C NMR signal. Have HSQC of this compound in d_6-DMSO.

HRMS (ESI): calc. for $C_{39}H_{51}ClN_5O_8$ $[M+H]^+$: 752.3421, found: 752.3453.



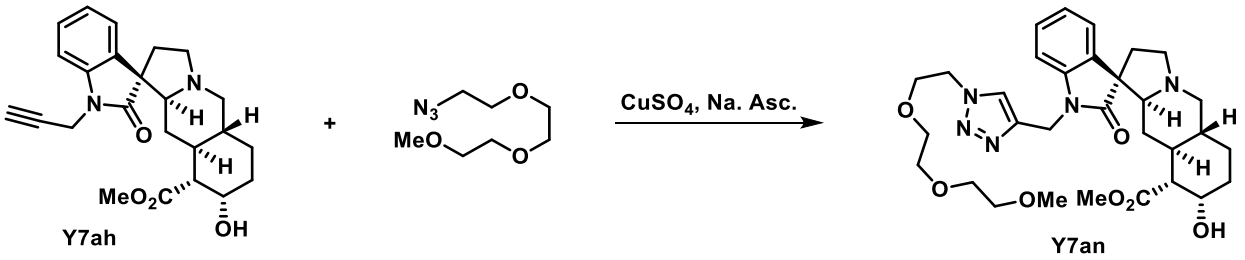
Y7am

Yield: 75%; 18.4 mg of **Y7am** isolated as a colorless, amorphous solid.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 2.4 Hz, 1H), 7.48 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.35 (d, *J* = 7.4 Hz, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 8.6 Hz, 1H), 6.73 (d, *J* = 3.7 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.66 (d, *J* = 3.7 Hz, 1H), 5.04 (d, *J* = 15.4 Hz, 1H), 4.59 (d, *J* = 15.4 Hz, 1H), 4.57 (d, *J* = 12.8 Hz, 1H), 4.34 (d, *J* = 12.8 Hz, 1H), 3.93 (m, 1H), 3.89 (s, 3H), 3.53 (s, 3H), 3.27 (t, *J* = 7.8 Hz, 1H), 3.09 (d, *J* = 9.5 Hz, 1H), 2.63 (d, *J* = 11.0 Hz, 1H), 2.52 (q, *J* = 8.4 Hz, 1H), 2.39 (t, *J* = 11.2 Hz, 1H), 2.07 – 1.97 (m, 3H), 1.94 (t, *J* = 11.1 Hz, 1H), 1.74 (q, *J* = 11.6 Hz, 1H), 1.45 – 1.28 (m, 4H), 1.22 (m, 1H), 0.37 (q, *J* = 11.6 Hz, 1H).

^{13}C NMR: (125 MHz, $CDCl_3$) δ 179.5, 172.3, 164.0, 145.8, 142.0, 140.4, 138.5, 133.8, 130.3, 127.6, 125.7, 125.4, 125.0, 124.9, 122.6, 112.0, 108.6, 74.8, 72.2, 65.4, 59.0, 56.4, 53.8, 53.6, 52.5, 51.6, 41.0, 40.4, 36.0, 35.2, 31.0, 28.0, 23.7.

HRMS (ESI): calc. for $C_{33}H_{37}ClN_3O_5S$ $[M+H]^+$: 622.2136, found: 622.2167.



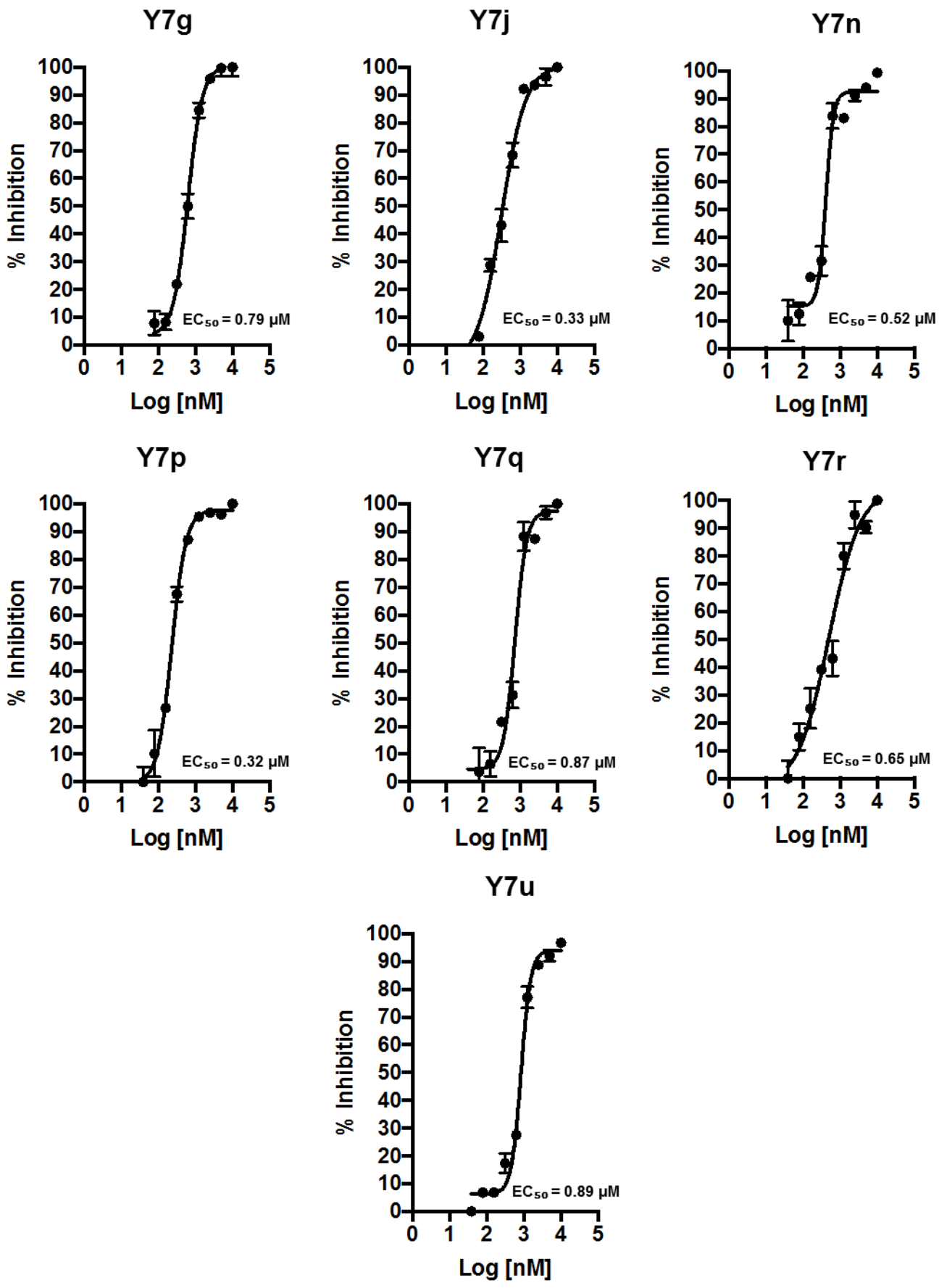
Procedure for the synthesis of intermediate Y7an. Anhydrous copper sulfate (11.7 mg, 0.07 mmol) and sodium ascorbate (45.3 mg, 0.23 mmol) were added to a vial and dissolved in a 1:2 solution of *tert*-butanol:water (4.2 mL). This mixture was then added to a round-bottom flask containing **Y7ah** (63.5 mg, 0.16 mmol). Then, PEG-azide (88.2 mg, 0.47 mmol) was added to the reaction, followed by dichloromethane (3 mL). The reaction was then vigorously stirred at room temperature for 20 hours. Upon completion, the biphasic reaction mixture was quenched with brine and the product was extracted with dichloromethane using a separatory funnel. The organic layers were then collected, dried with sodium sulfate, filtered and concentrated. The crude product was purified via column chromatography using 99:1 ethyl acetate:triethylamine to ethyl acetate:methanol:triethylamine 97.5:1.5:1 to afford **Y7an** (54.2 mg, 58%) as a colorless, amorphous solid.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 5.01 – 4.90 (m, 2H), 4.46 (t, *J* = 5.1 Hz, 2H), 4.06 (s, 1H), 3.81 (t, *J* = 5.2 Hz, 2H), 3.59 – 3.52 (m, 6H), 3.52 – 3.49 (m, 2H), 3.48 (s, 3H), 3.34 (s, 3H), 3.24 (t, *J* = 8.8 Hz, 1H), 3.07 (d, *J* = 10.8 Hz, 1H), 2.95 (s, 1H), 2.52 – 2.42 (m, 2H), 2.31 (t, *J* = 11.2 Hz, 1H), 2.03 (d, *J* = 11.7 Hz, 1H), 1.95 (q, *J* = 10.3 Hz, 1H), 1.91 – 1.83 (m, 2H), 1.64 (q, *J* = 11.5 Hz, 1H), 1.48 (m, 1H), 1.41 (m, 1H), 1.34 (m, 1H), 1.23 (q, *J* = 8.7 Hz, 1H), 0.86 (d, *J* = 12.3 Hz, 1H), 0.51 (q, *J* = 11.9 Hz, 1H).

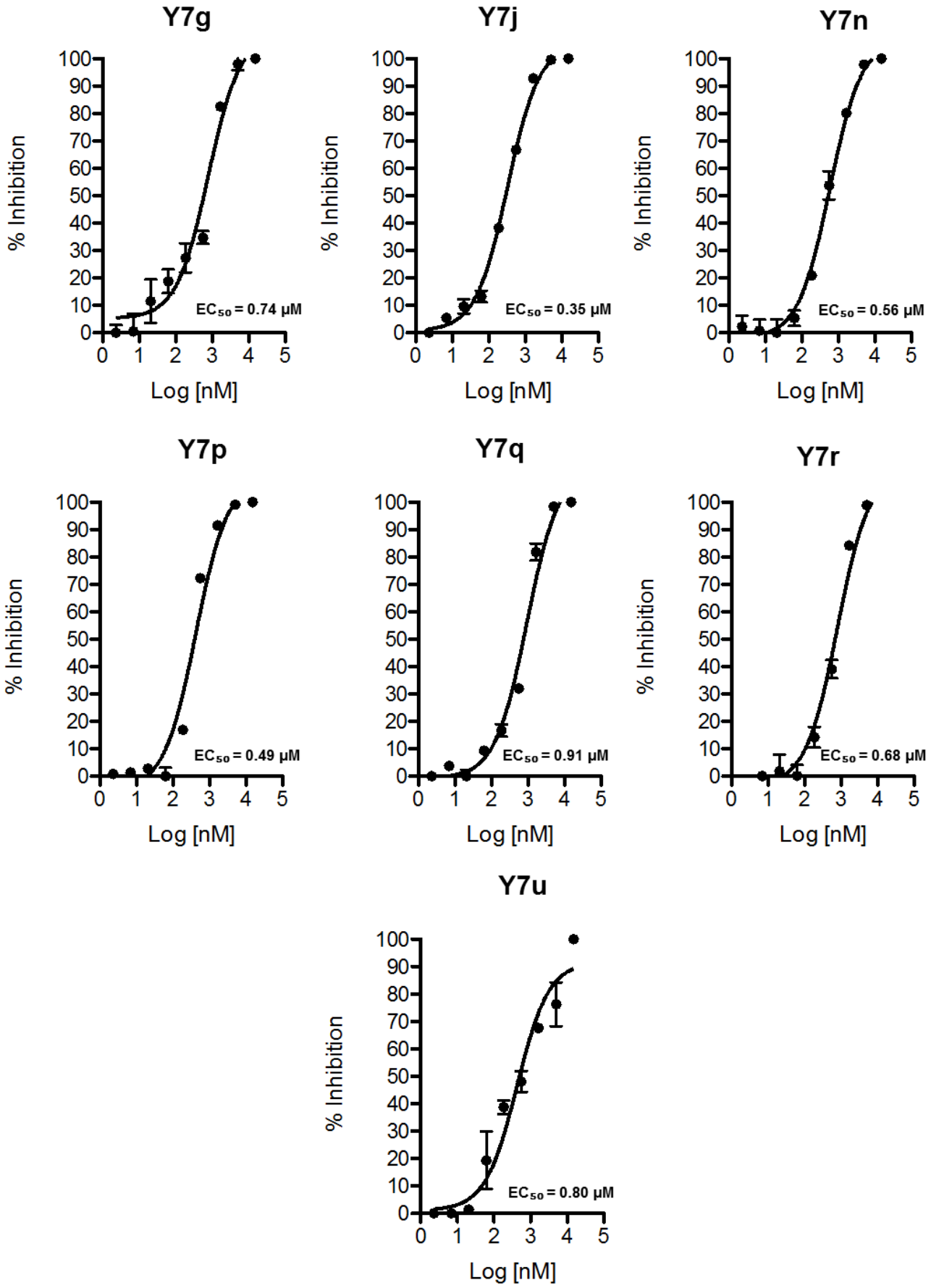
^{13}C NMR: (125 MHz, $CDCl_3$) δ 179.0, 175.2, 143.1, 141.9, 133.2, 127.8, 124.7, 123.6, 122.6, 109.0, 72.0, 72.0, 70.7, 70.6, 70.6, 69.5, 66.9, 59.1, 59.0, 56.3, 53.7, 52.5, 51.6, 50.4, 40.5, 36.1, 35.7, 35.0, 31.6, 30.5, 23.5.

HRMS (ESI): calc. for $C_{31}H_{44}N_5O_7$ $[M+H]^+$: 598.3235, found: 598.3255.

3. Supporting Figure 1. Dose-dependent antiplasmodial activity for selected yohimbine analogues in chloroquine-resistant (Dd2) cells.



4. Supporting Figure 2. Dose-dependent antiplasmodial activity for selected yohimbine analogues in chloroquine-sensitive (3D7) cells.



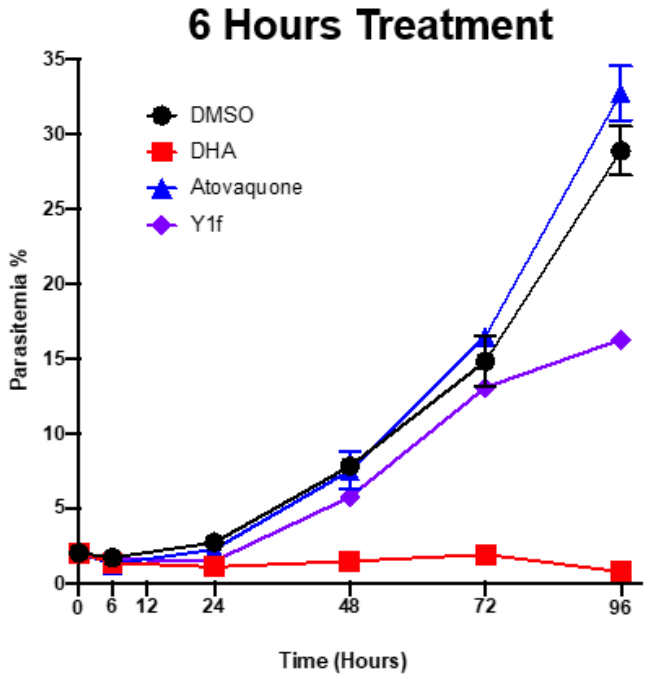
5. Supporting Table 1. Summary of antiplasmodial activities and cytotoxicity against HepG2 (liver) cells for **Y** and relevant **Y1** and **Y7** analogues. All concentrations are reported in micromolar (µM).

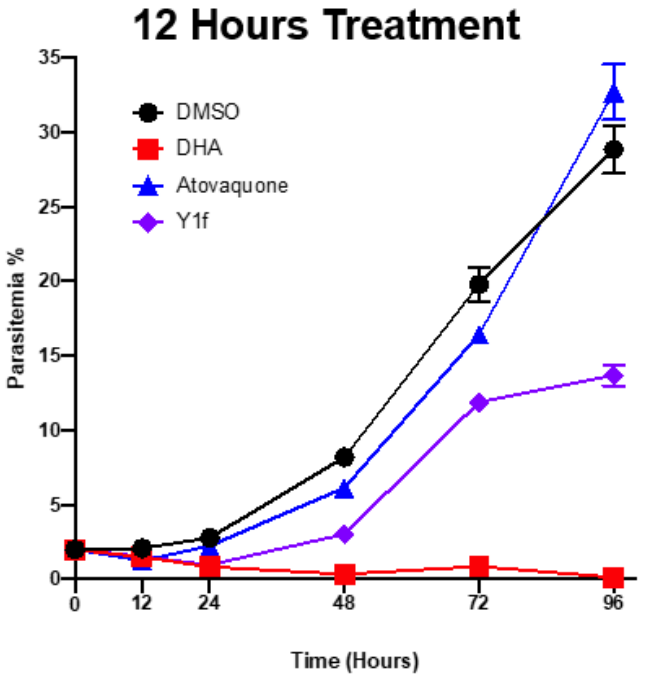
Y Code	EC_{50} Dd2 cells (µM)	EC_{50} 3D7 cells (µM)	EC_{50} HepG2 cells (µM)	Selectivity Index (SI)	Stage-Specific Activity
Y	76.7 ± 0.74	-	> 100	-	n.a.
Y1c	2.58 ± 0.07	-	-	-	-
Y1d	5.18 ± 0.10	-	-	-	-
Y1e	2.98 ± 0.20	-	-	-	-
Y1f	1.60 ± 0.16	-	18.9	12	A
Y1g	3.18 ± 0.11	-	-	-	-
Y1h	3.47 ± 0.11	-	-	-	-
Y1i	> 20	-	-	-	-
Y1j	> 20	-	-	-	-
Y7e	1.50 ± 0.09	-	-	-	-
Y7f	1.41 ± 0.23	-	-	-	-
Y7g	0.79 ± 0.06	0.74 ± 0.07	> 40	> 51	A
Y7h	1.05 ± 0.08	-	-	-	-
Y7i	0.85 ± 0.05	-	-	-	-
Y7j	0.33 ± 0.03	0.35 ± 0.03	> 40	> 121	A
Y7k	0.64 ± 0.07	0.68 ± 0.07	-	-	-
Y7l	2.57 ± 0.05	-	-	-	-
Y7m	1.51 ± 0.06	-	-	-	-
Y7n	0.52 ± 0.04	0.56 ± 0.04	> 40	> 77	-
Y7o	3.51 ± 0.32	-	-	-	-
Y7p	0.32 ± 0.02	0.49 ± 0.05	> 40	> 125	A
Y7q	0.87 ± 0.04	0.91 ± 0.03	> 40	> 46	-
Y7r	0.65 ± 0.07	0.68 ± 0.09	> 40	> 62	-
Y7s	1.32 ± 0.07	1.13 ± 0.09	-	-	-
Y7t	3.08 ± 0.20	4.31 ± 0.16	-	-	-
Y7u	0.89 ± 0.05	0.80 ± 0.09	> 40	> 45	-
Y7v	8.30 ± 0.10	-	-	-	-
Y7x	> 20	-	-	-	-
Y7aa	> 20	-	-	-	-
Y7ab	> 20	-	-	-	-
Y7ac	> 20	-	-	-	-
Y7ad	> 20	-	-	-	-
Y7ae	> 20	-	-	-	-
Y7af	> 20	-	-	-	-
Y7aj	2.38 ± 0.24	-	-	-	-
Y7ak	0.94 ± 0.10	-	-	-	-
Y7al	> 20	-	-	-	-
Y7am	2.71 ± 0.07	3.00 ± 0.13	-	-	-

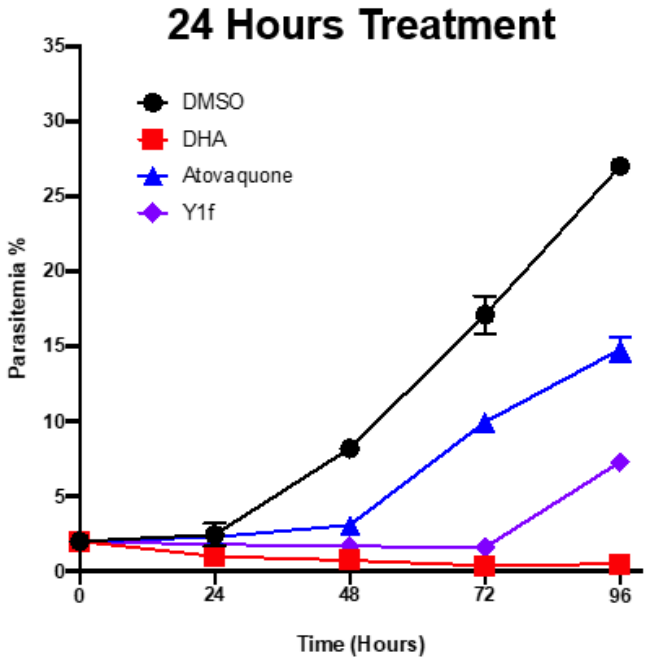
Notes: "A" = stage-specific activity at the late ring/trophozoite phase of asexual blood stage *P*. *falciparum.* "n.a." = yohimbine (Y), which is inactive against *P. falciparum.* "-" = noted for analogues that were not tested for stage specific activity. Selectivity Index (SI) was generated according to EC_{50} against HepG2 cells divided by EC_{50} against Dd2 cells. All values reported in this table resulted from three independent experiments.

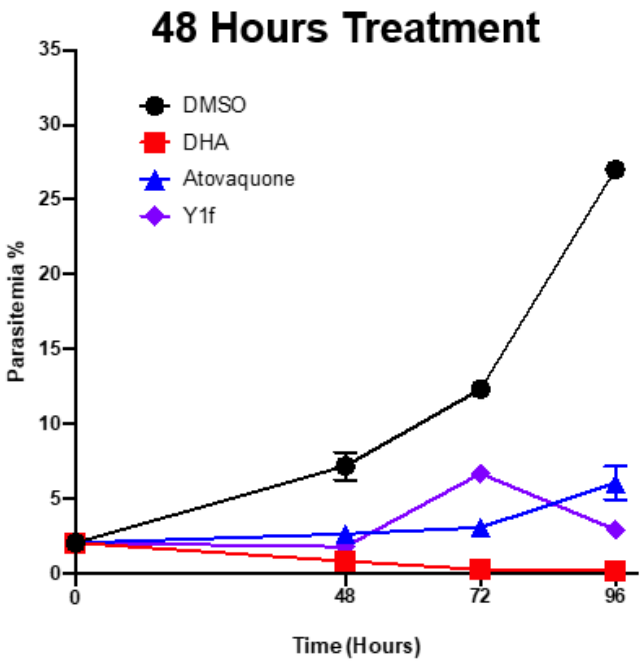
6. Kill Kinetics for Y1f, DHA and Atovaquone.

Kill kinetics for analogue **Y1f** and comparator agents DHA and Atovaquone tested against Dd2 cells are included below. Each compound was tested at 5 x EC_{50} value in these experiments (test concentrations: DHA, 50 nM; Atovaquone, 6.6 nM).



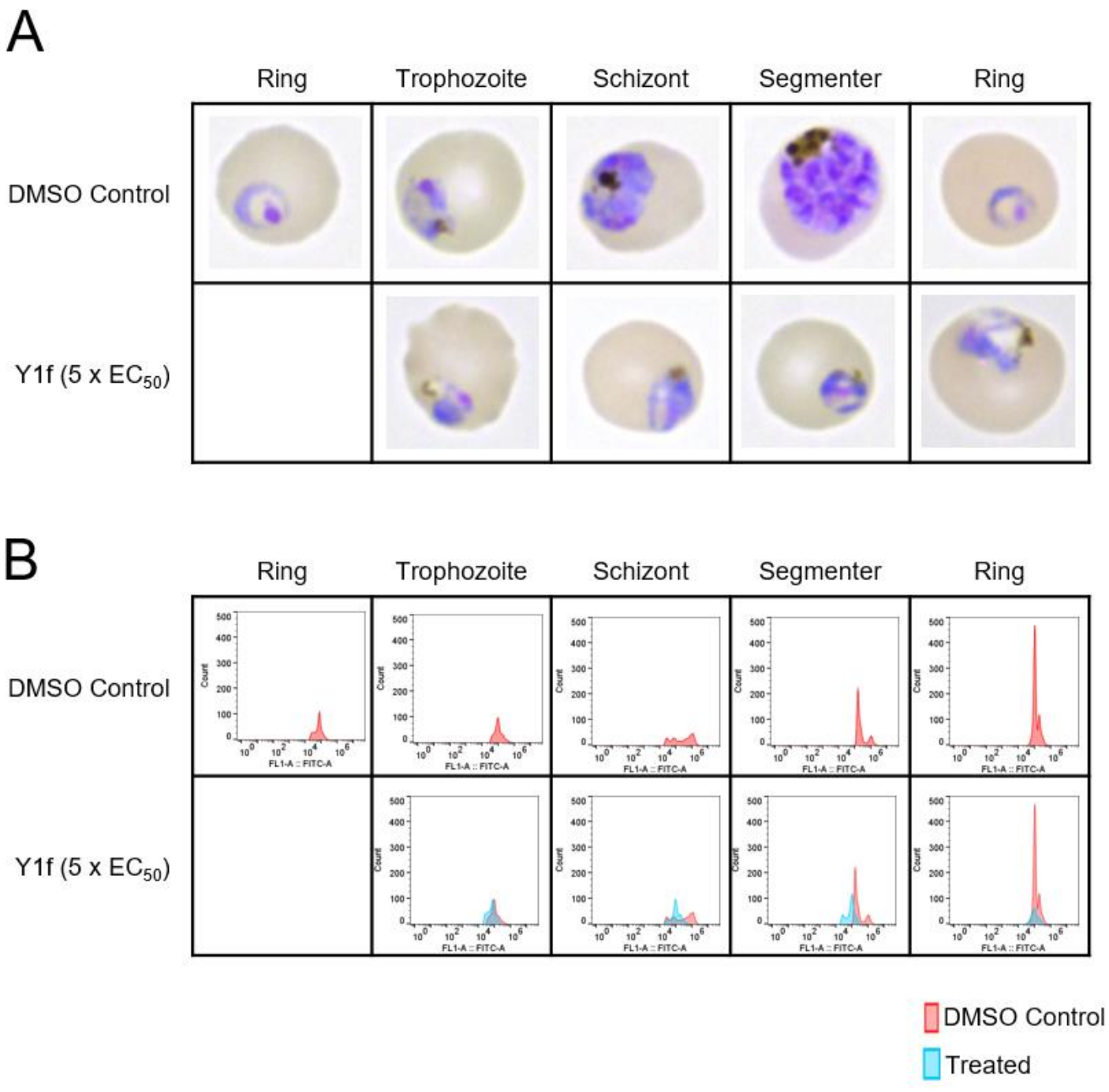




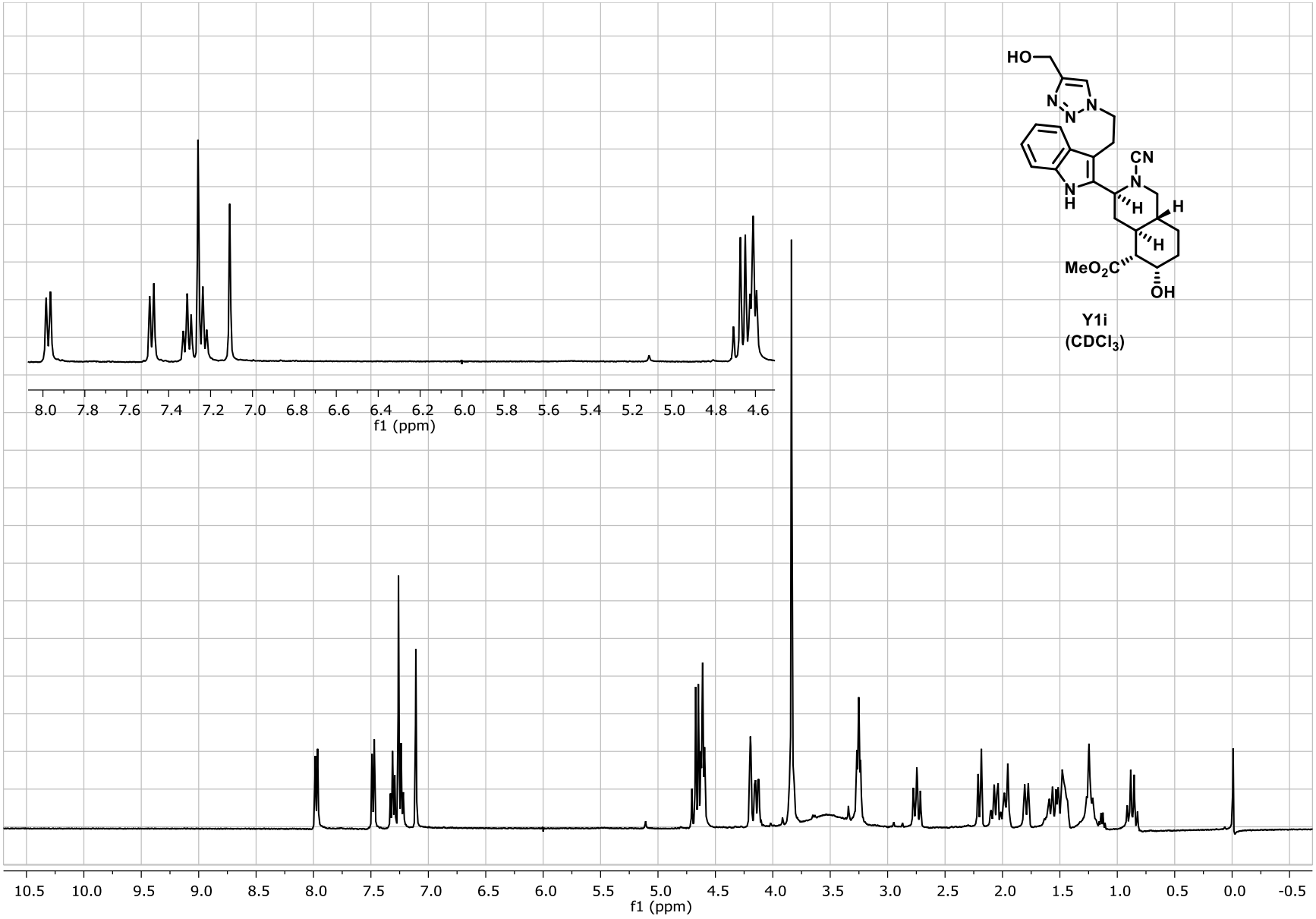


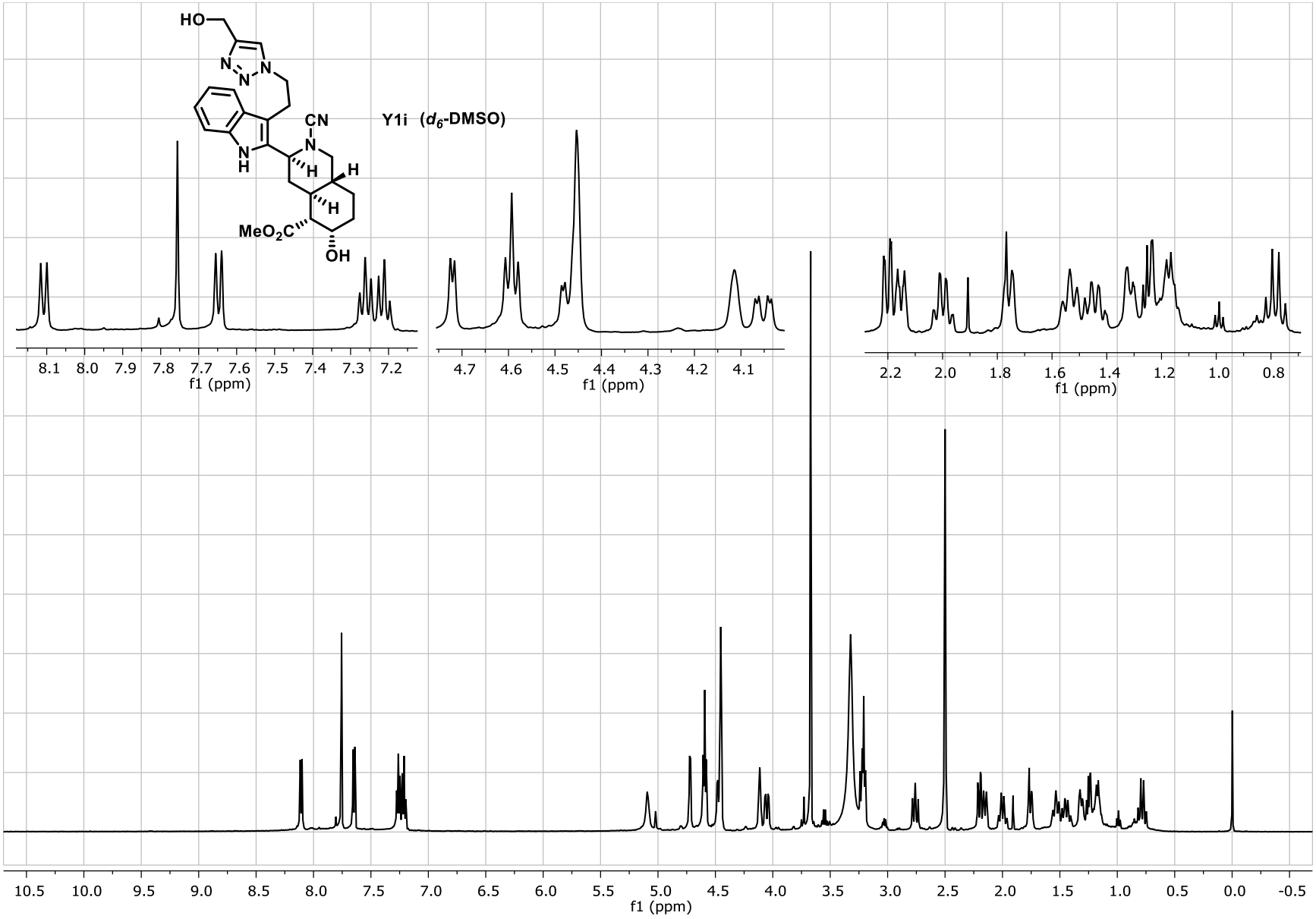
7. Stage Specific Activity for Y1f.

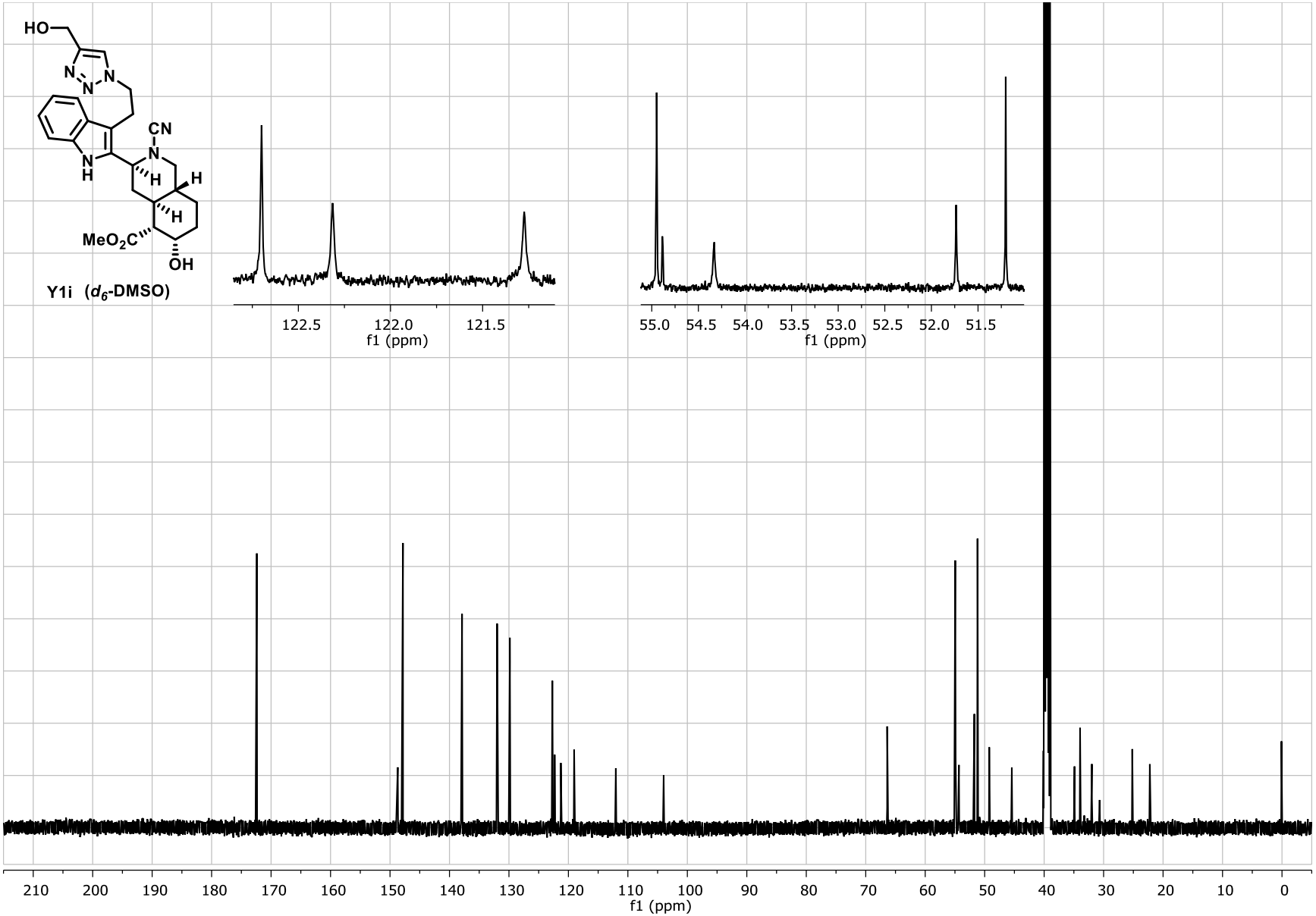
Y1f reports the same stage specific action as **Y7j** (late ring/trophozoite phase of asexual blood stage *P. falciparum*). In addition, **Y1f** also induces vacuolization in these experiments.

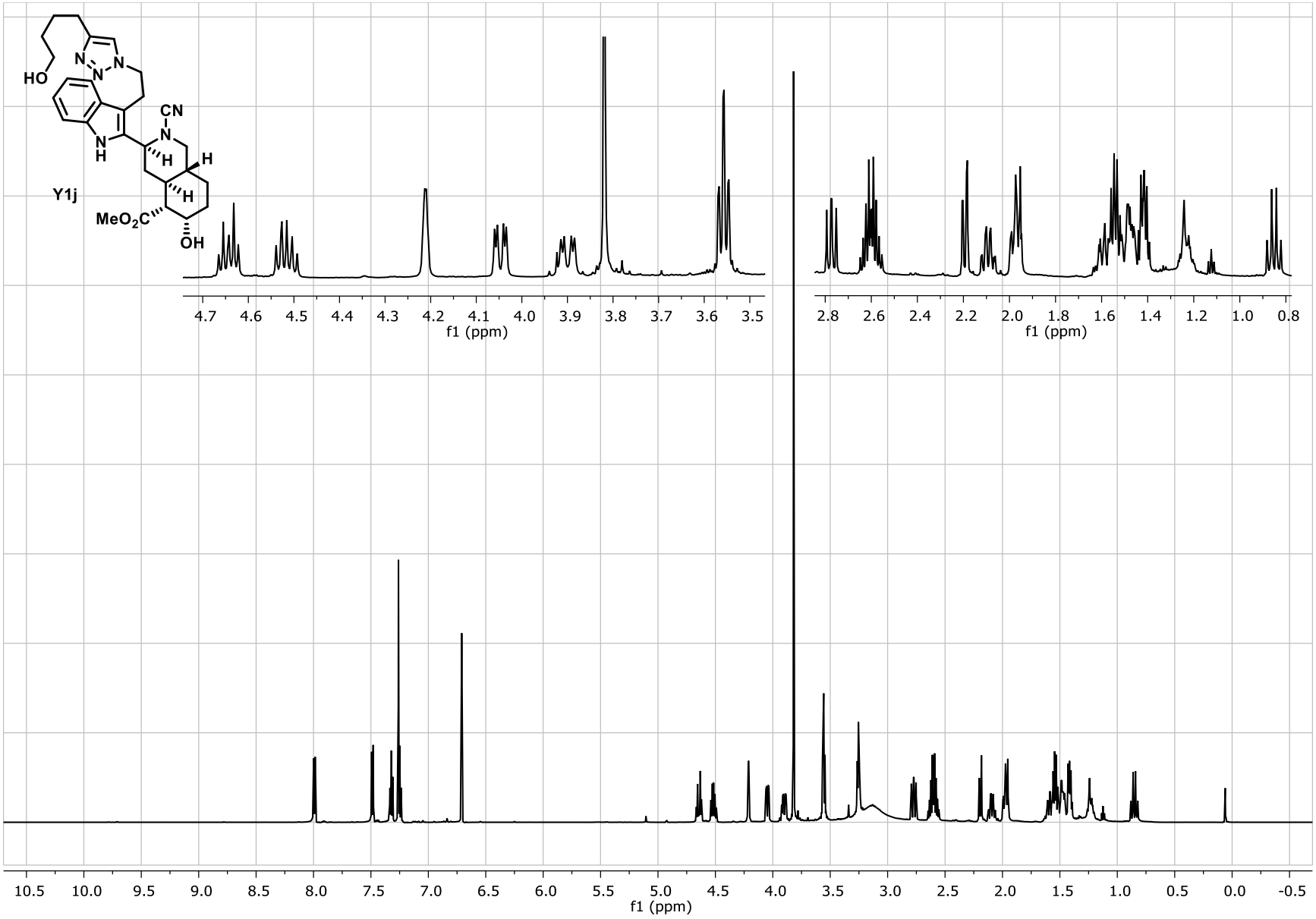


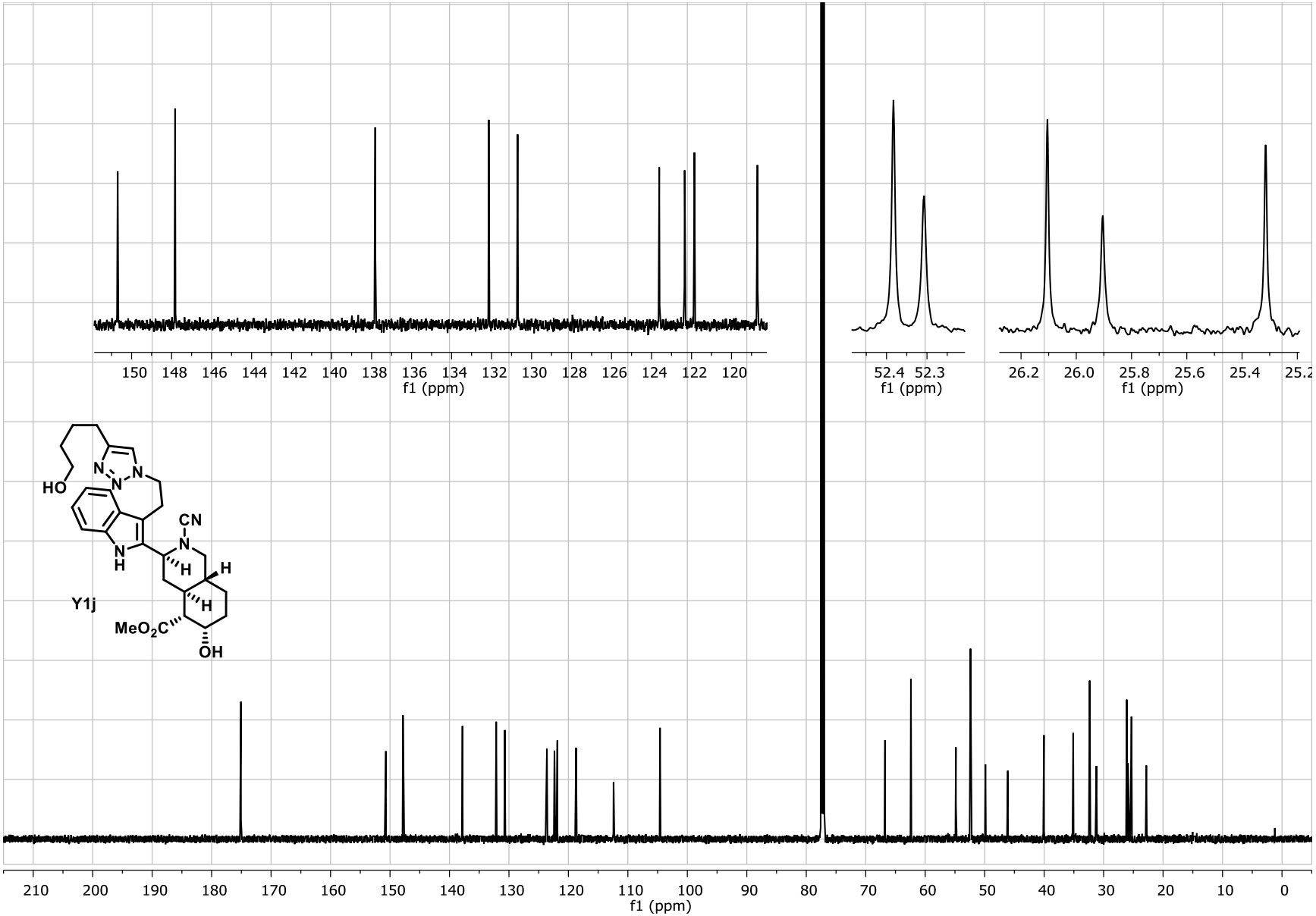
8. NMR Spectra.

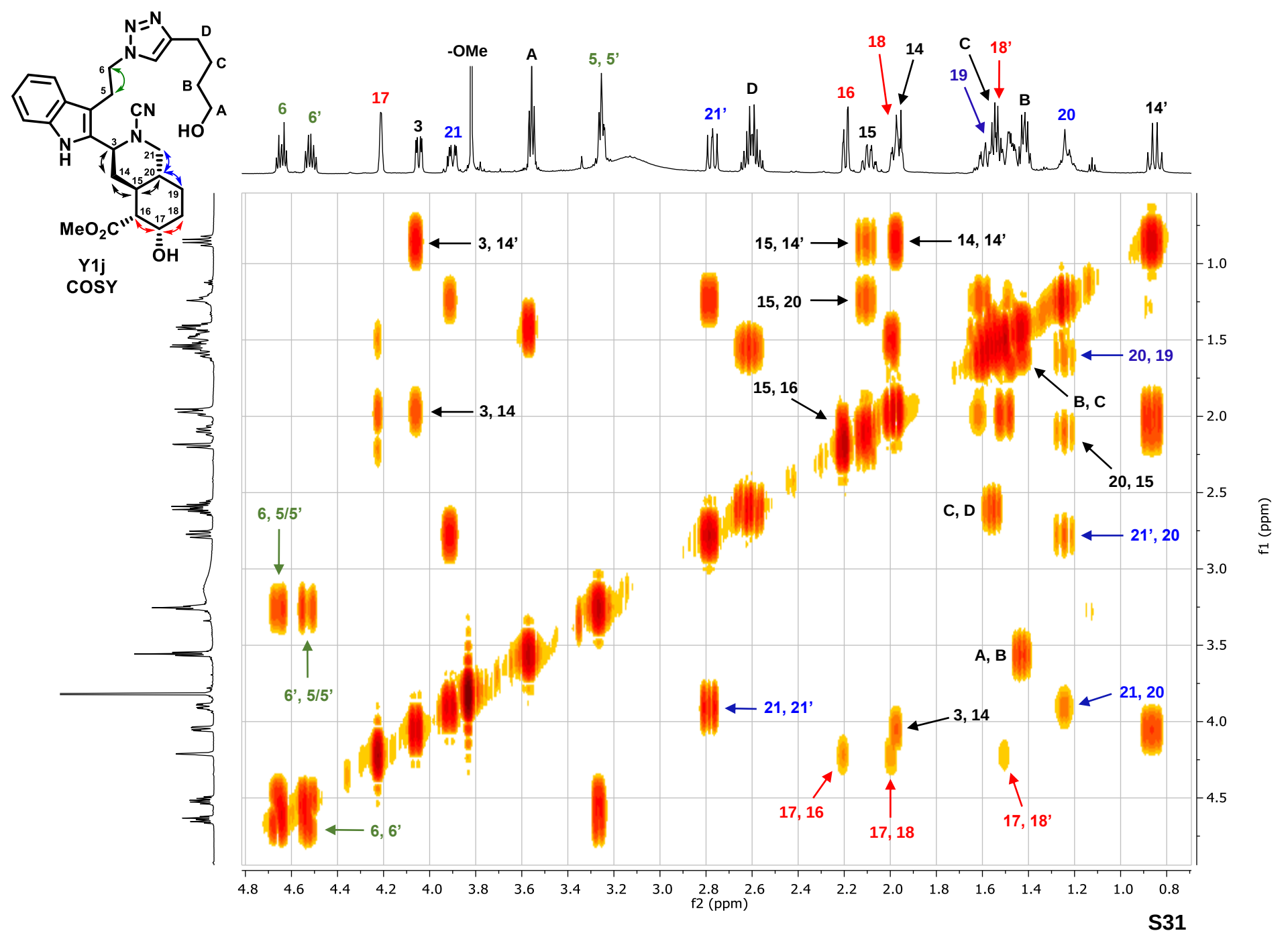

HO
N
N
N
N
H
CN
N
H
H
H
MeO2C
OH
Y1i
(CDCl3)
8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6
f1 (ppm)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


HO
N
N
N
CN
N
H
H
H
H
MeO2C
OH
Y1i (d6-DMSO)
8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2
f1 (ppm)
4.7 4.6 4.5 4.4 4.3 4.2 4.1
f1 (ppm)
2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f1 (ppm)
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
f1 (ppm)


HO
N
N
N
CN
N
H
H
H
H
MeO2C
OH
Y1i (d6-DMSO)
122.5
122.0
121.5
f1 (ppm)
55.0
54.5
54.0
53.5
53.0
52.5
52.0
51.5
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

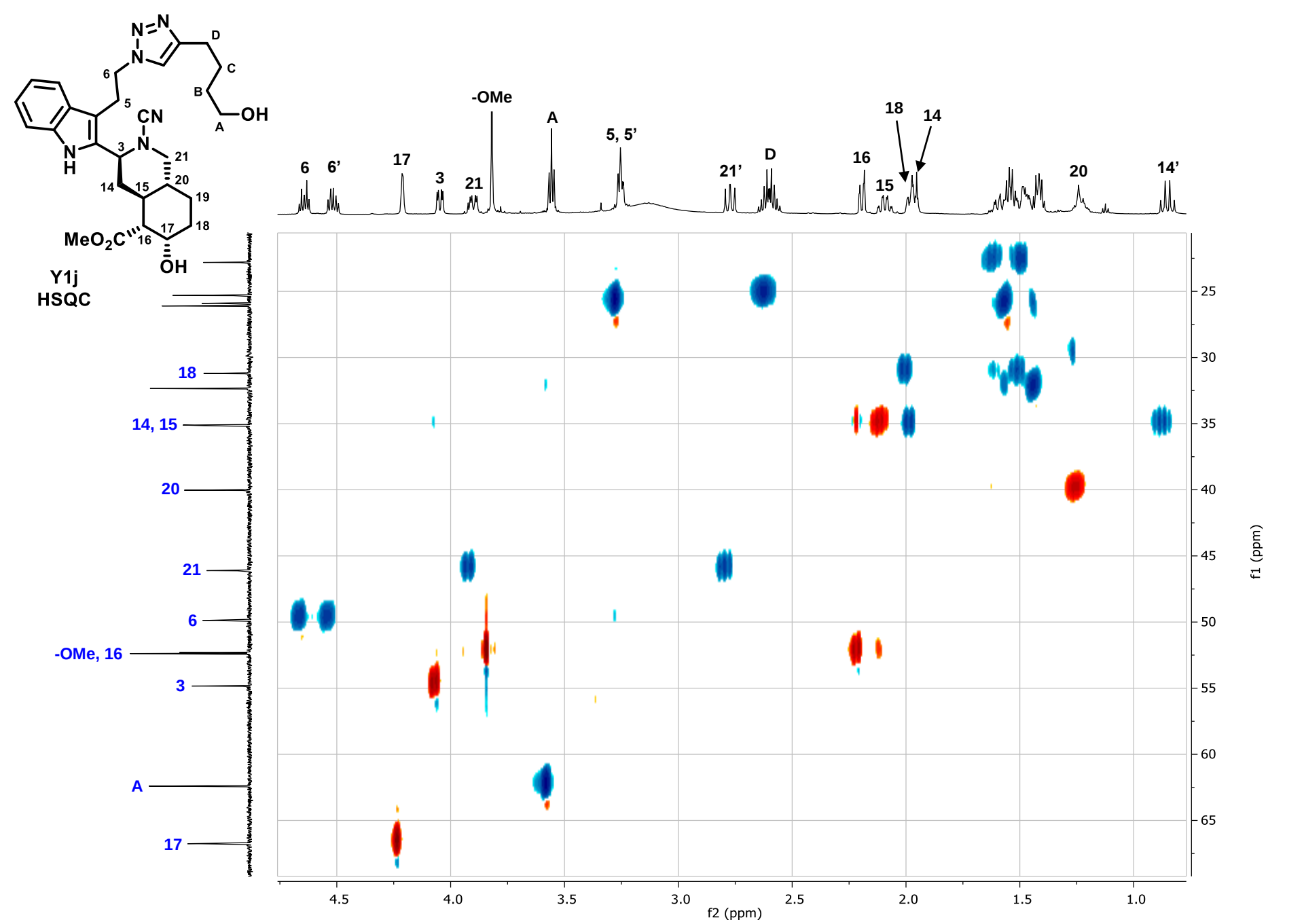

HO
N
N
N
CN
N
H
H
H
H
Y1j
MeO2C
OH
4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5
f1 (ppm)
2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f1 (ppm)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

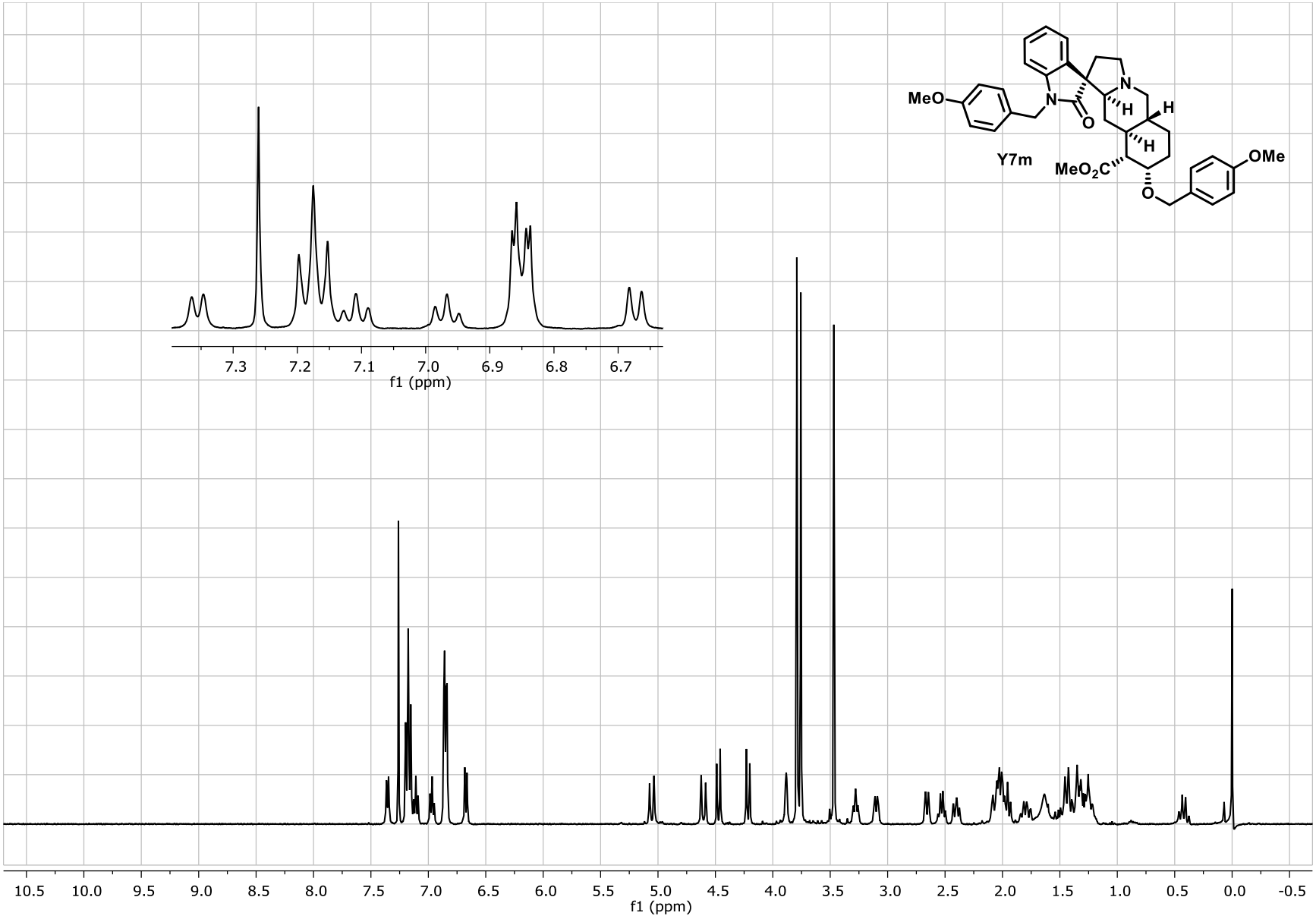

HO
N
N
N
CN
N
H
H
H
H
Y1j
MeO2C
OH
150 148 146 144 142 140 138 136 134 132 130 128 126 124 122 120
f1 (ppm)
52.4 52.3
f1 (ppm)
26.2 26.0 25.8 25.6 25.4 25.2
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

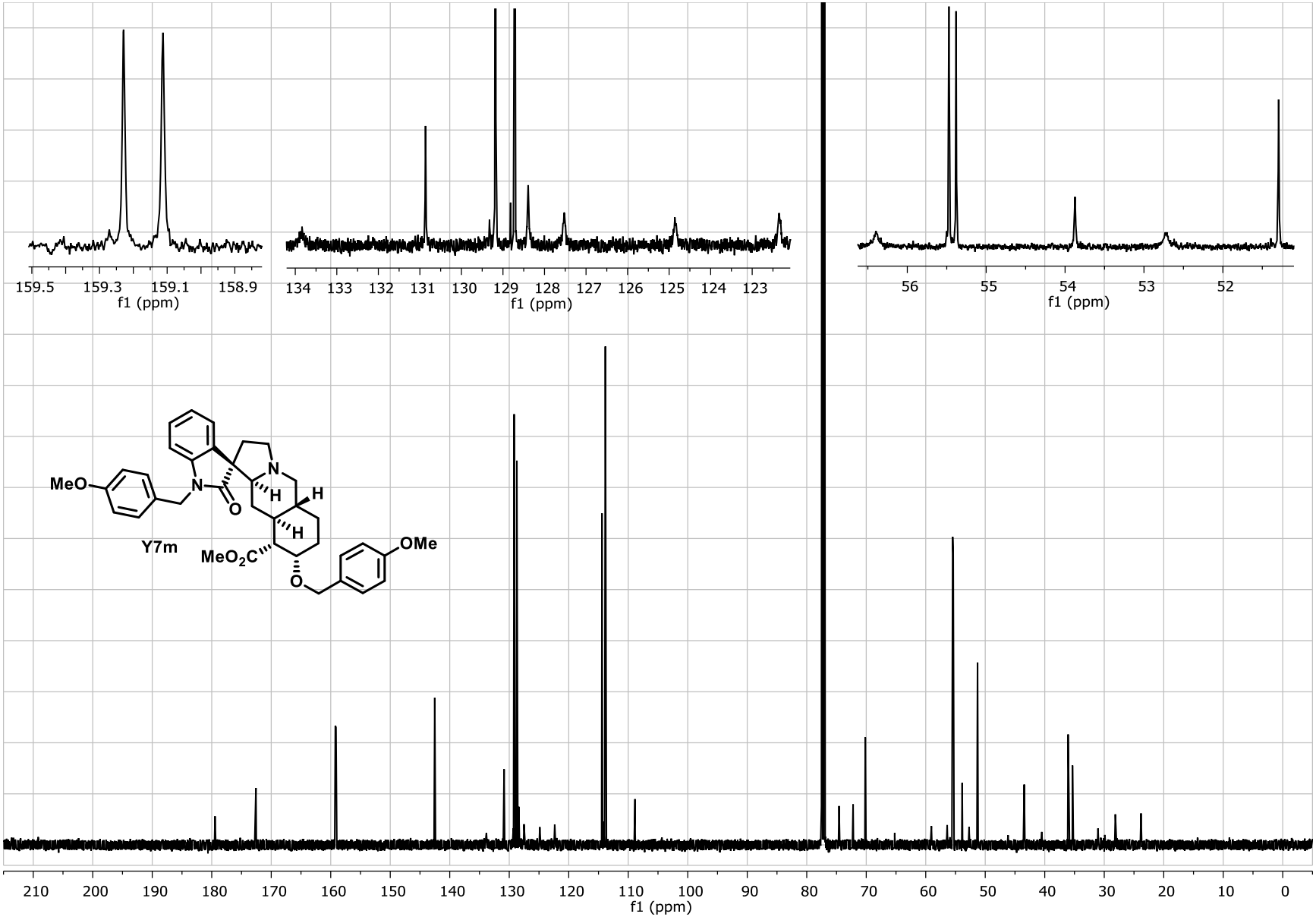


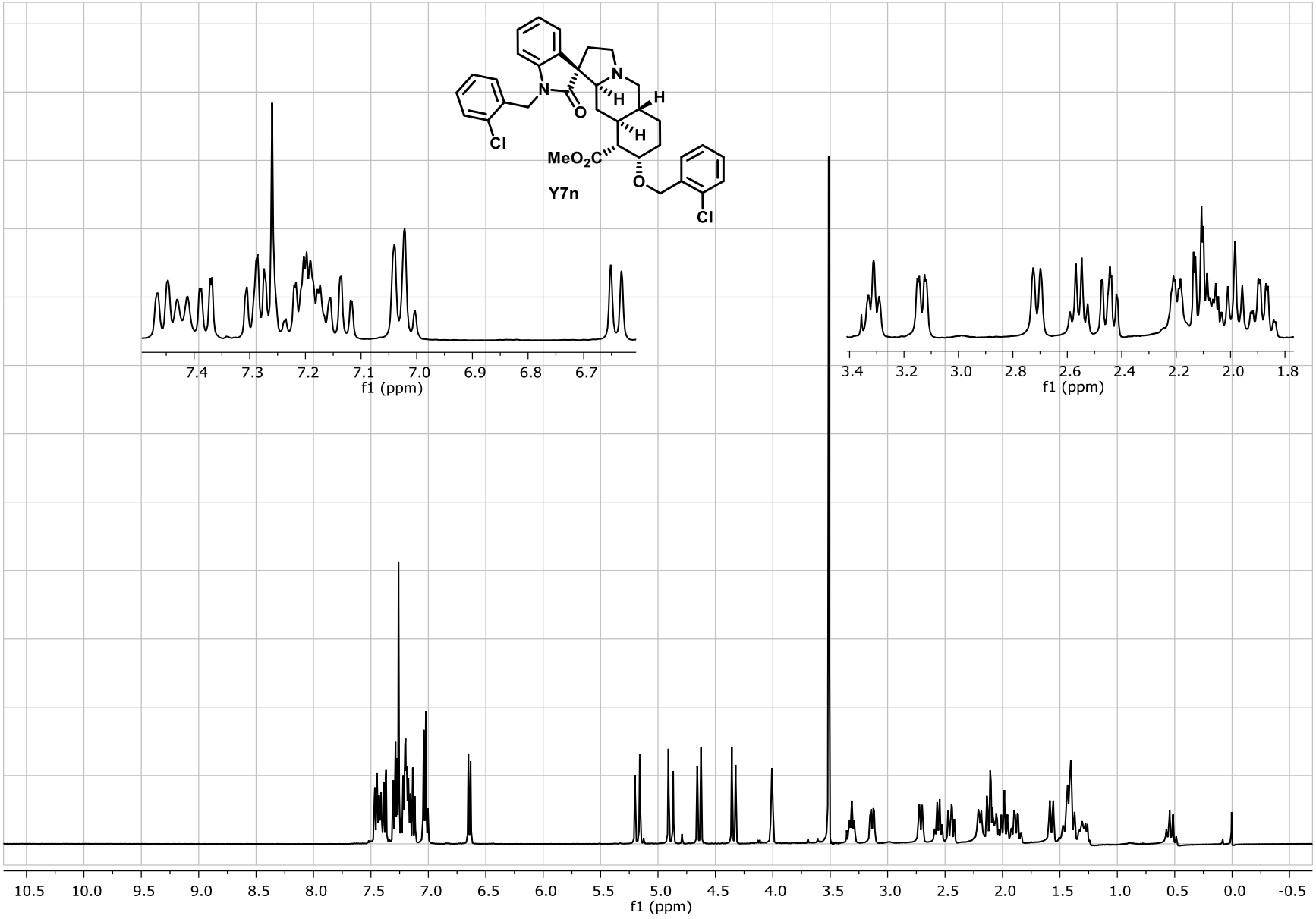
S31

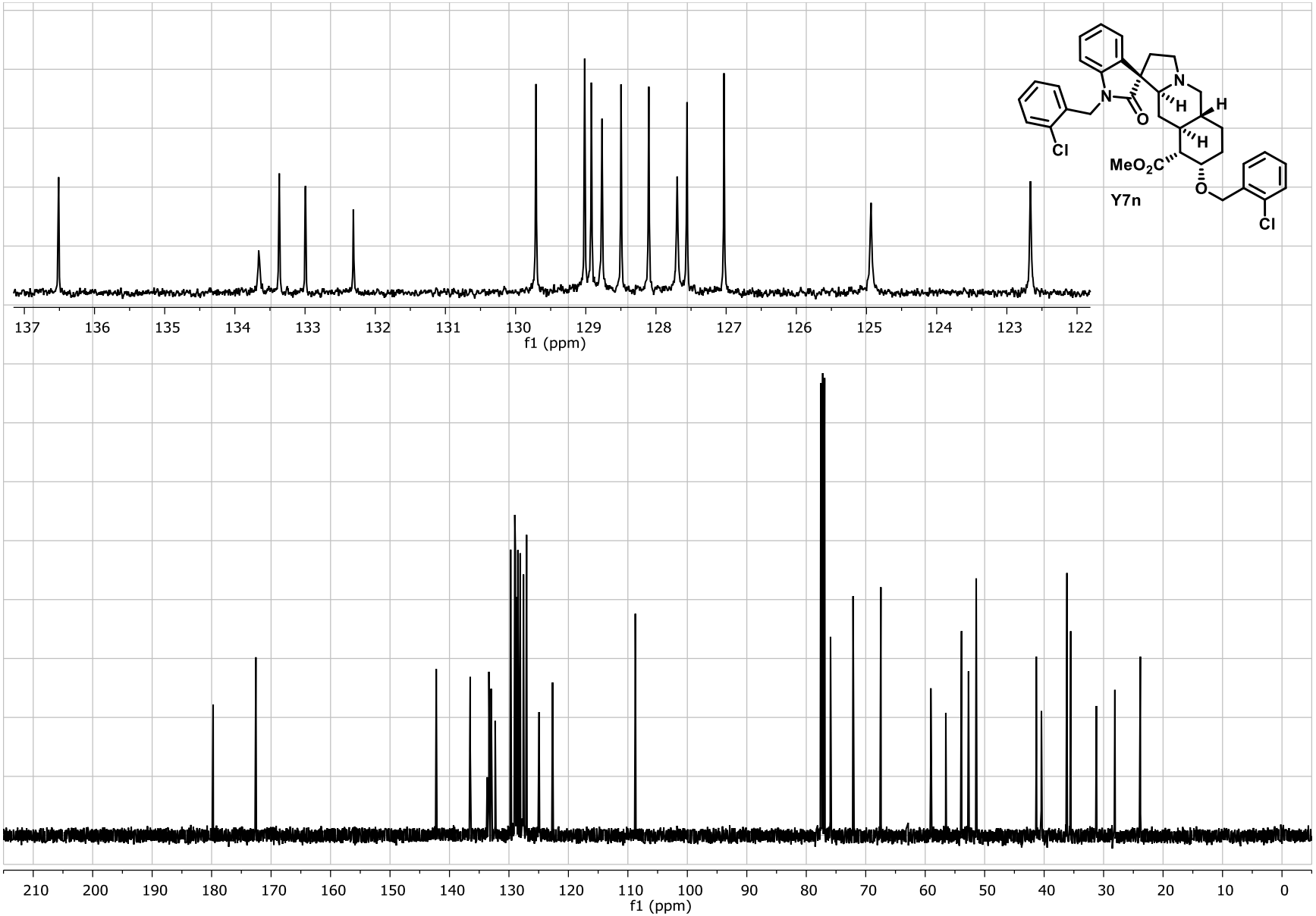
Note: COSY correlations between positions 15 & 16 can be viewed as well.

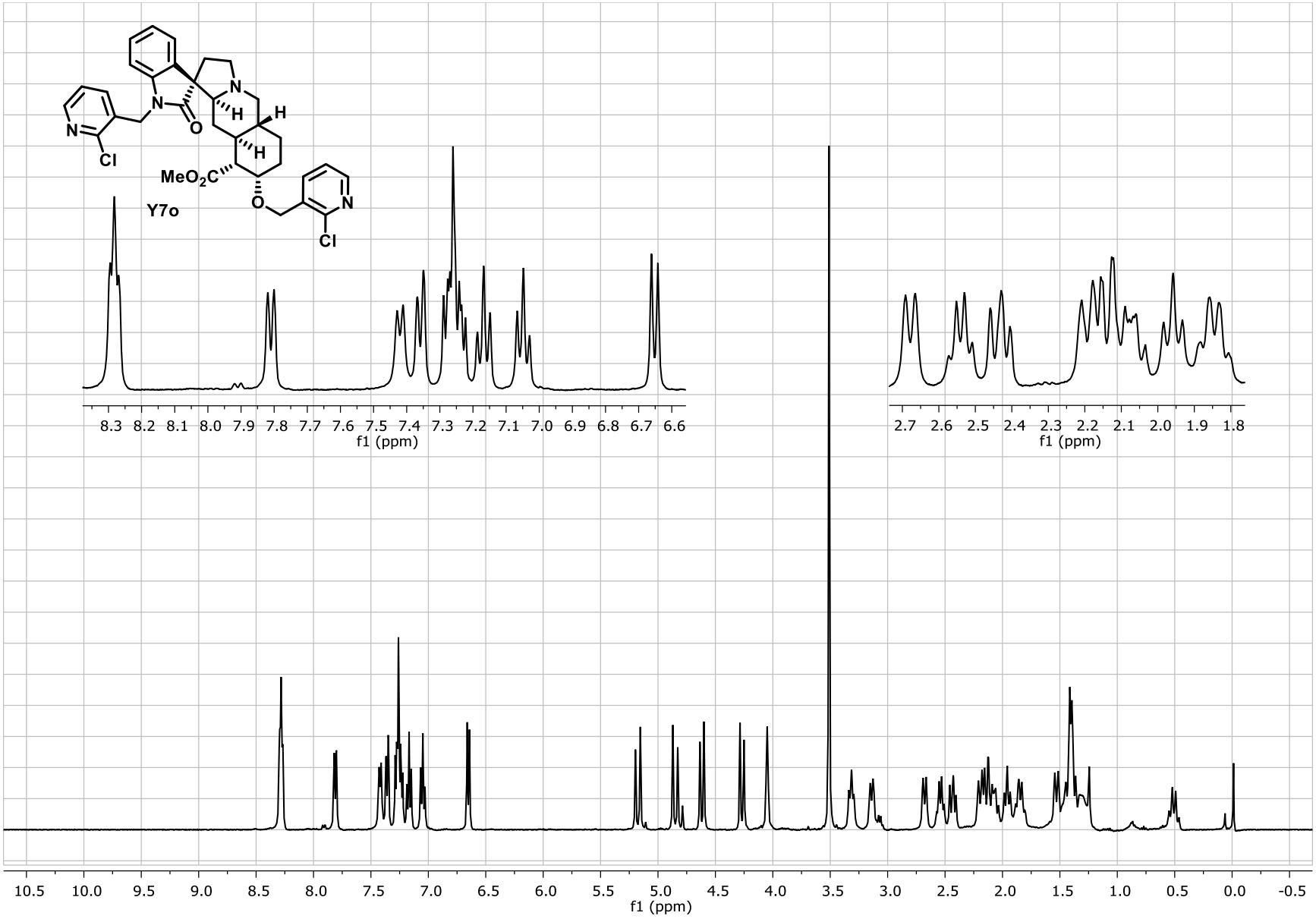

Y1j
HSQC
-OMe
A
5, 5'
D
21'
16
18
14
15
20
14'
6
6'
17
3
21
f2 (ppm)
f1 (ppm)

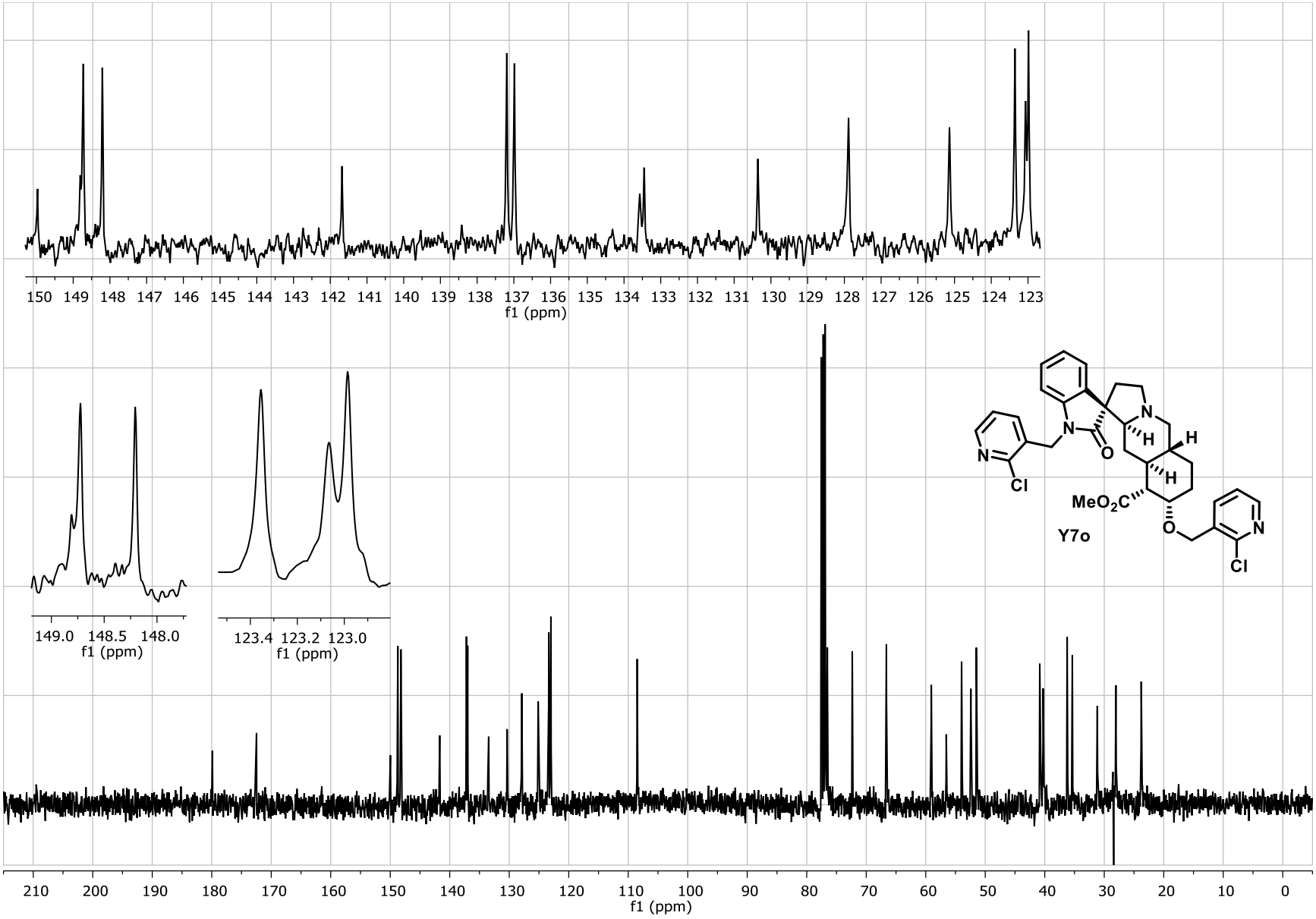

MeO
N
O
N
H
H
H
Y7m
MeO2C
O
OMe
7.3
7.2
7.1
7.0
6.9
6.8
6.7
f1 (ppm)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

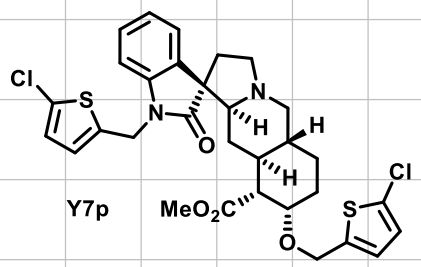

159.5
159.3
159.1
158.9
f1 (ppm)
134
133
132
131
130
129
128
127
126
125
124
123
f1 (ppm)
56
55
54
53
52
f1 (ppm)
MeO
N
O
H
H
H
N
Y7m
MeO2C
O
OMe
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
N
O
N
H
H
H
MeO2C
O
Cl
Y7n
7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7
f1 (ppm)
3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8
f1 (ppm)
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
f1 (ppm)


137
136
135
134
133
132
131
130
129
128
127
126
125
124
123
122
f1 (ppm)
Cl
N
O
H
H
H
MeO2C
O
Cl
Y7n
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

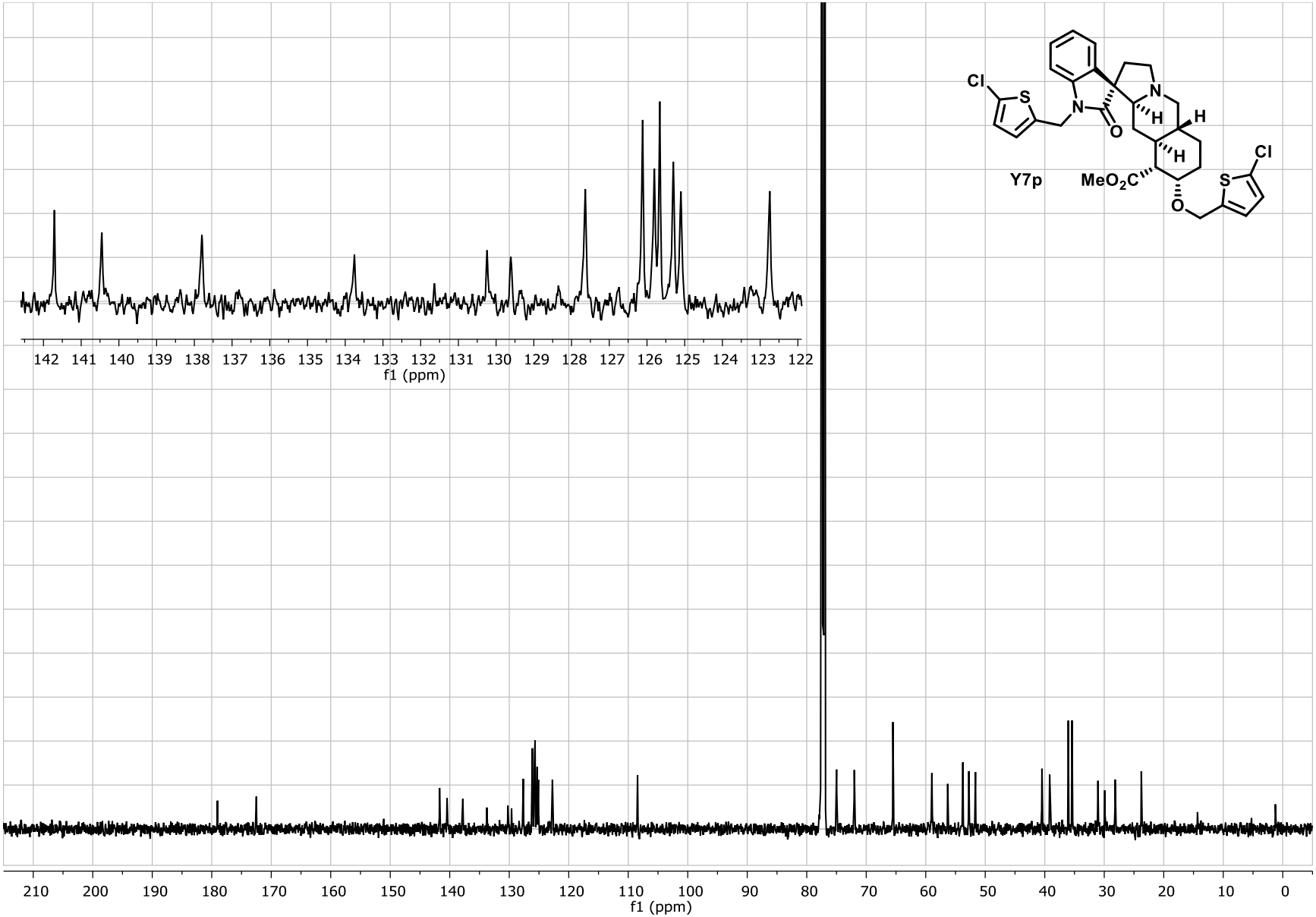

Y7o
f1 (ppm)
f1 (ppm)
f1 (ppm)

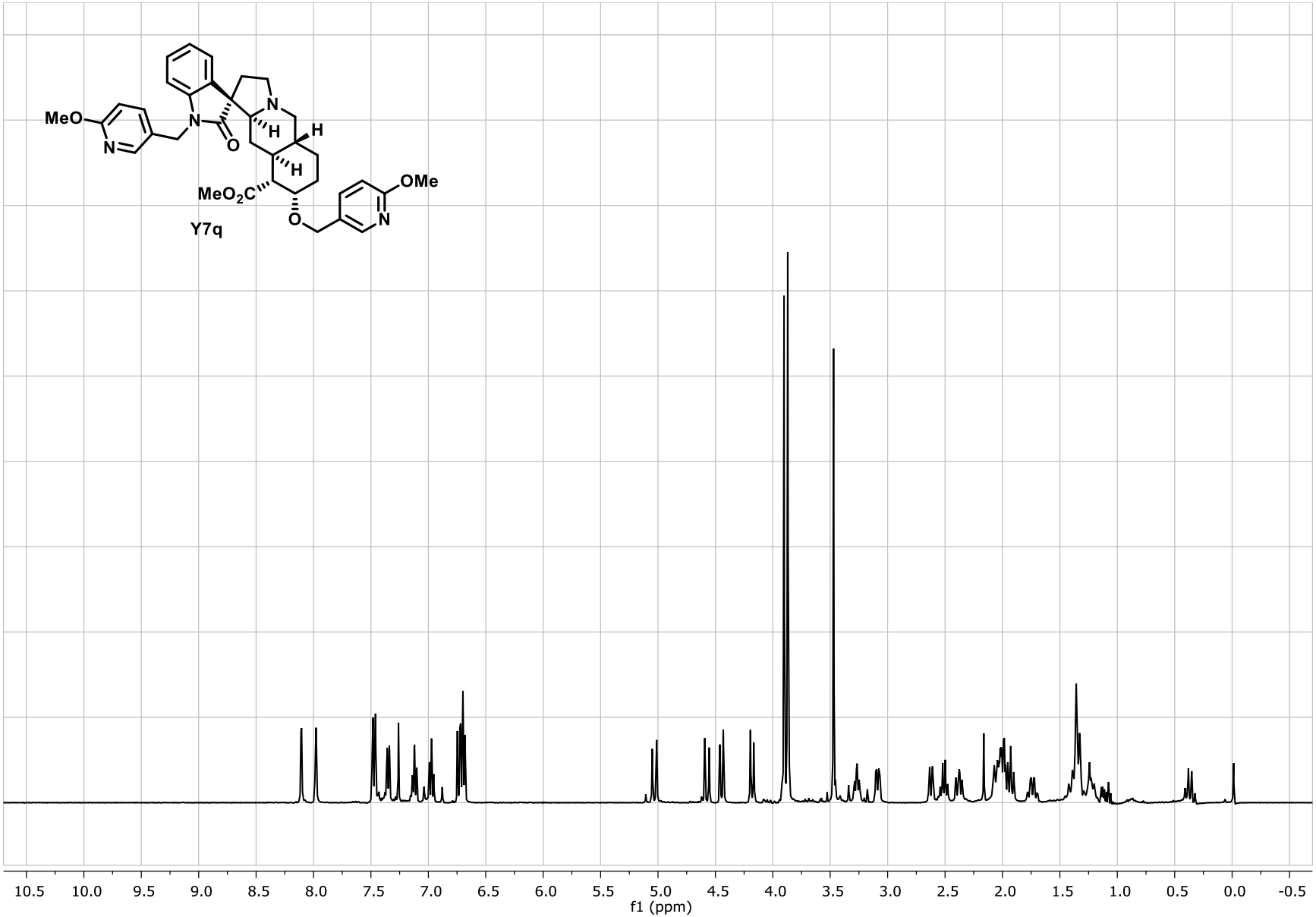

150 149 148 147 146 145 144 143 142 141 140 139 138 137 136 135 134 133 132 131 130 129 128 127 126 125 124 123
f1 (ppm)
149.0 148.5 148.0
f1 (ppm)
123.4 123.2 123.0
f1 (ppm)
N
Cl
N
O
N
H
H
H
MeO2C
O
N
Cl
Y7o
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

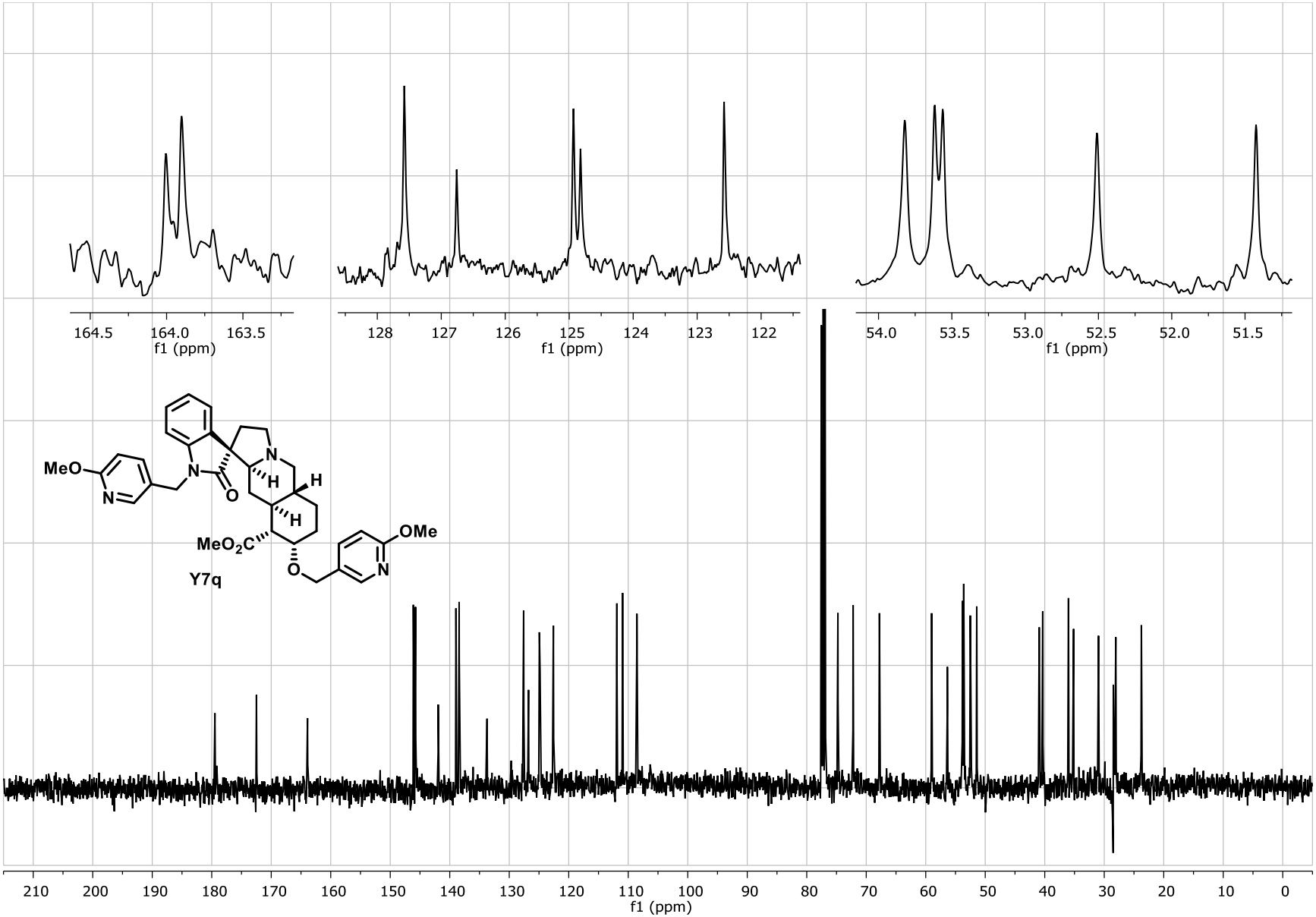

Cl
S
N
O
N
H
H
H
Cl
S
O
MeO2C

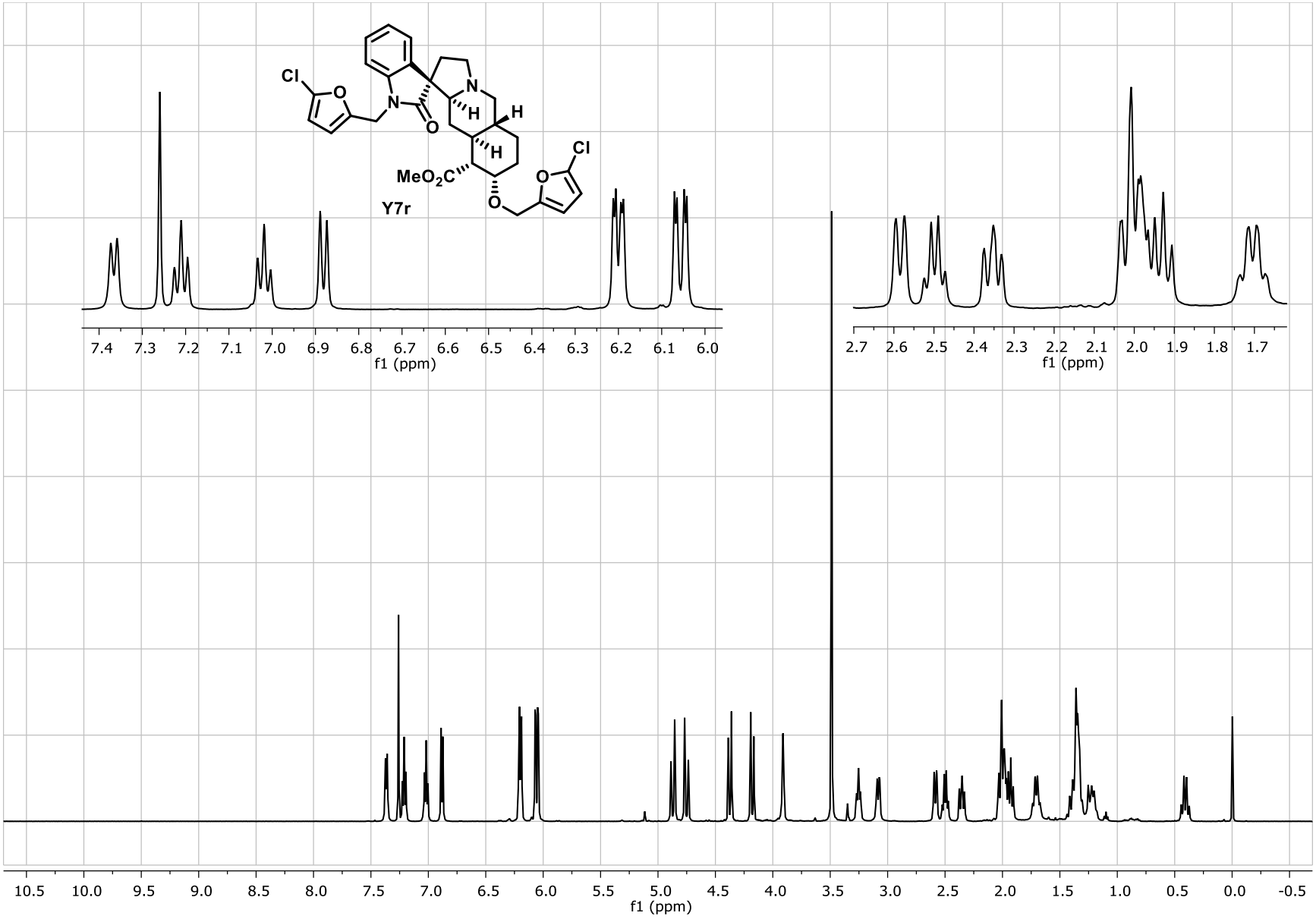
Y7p

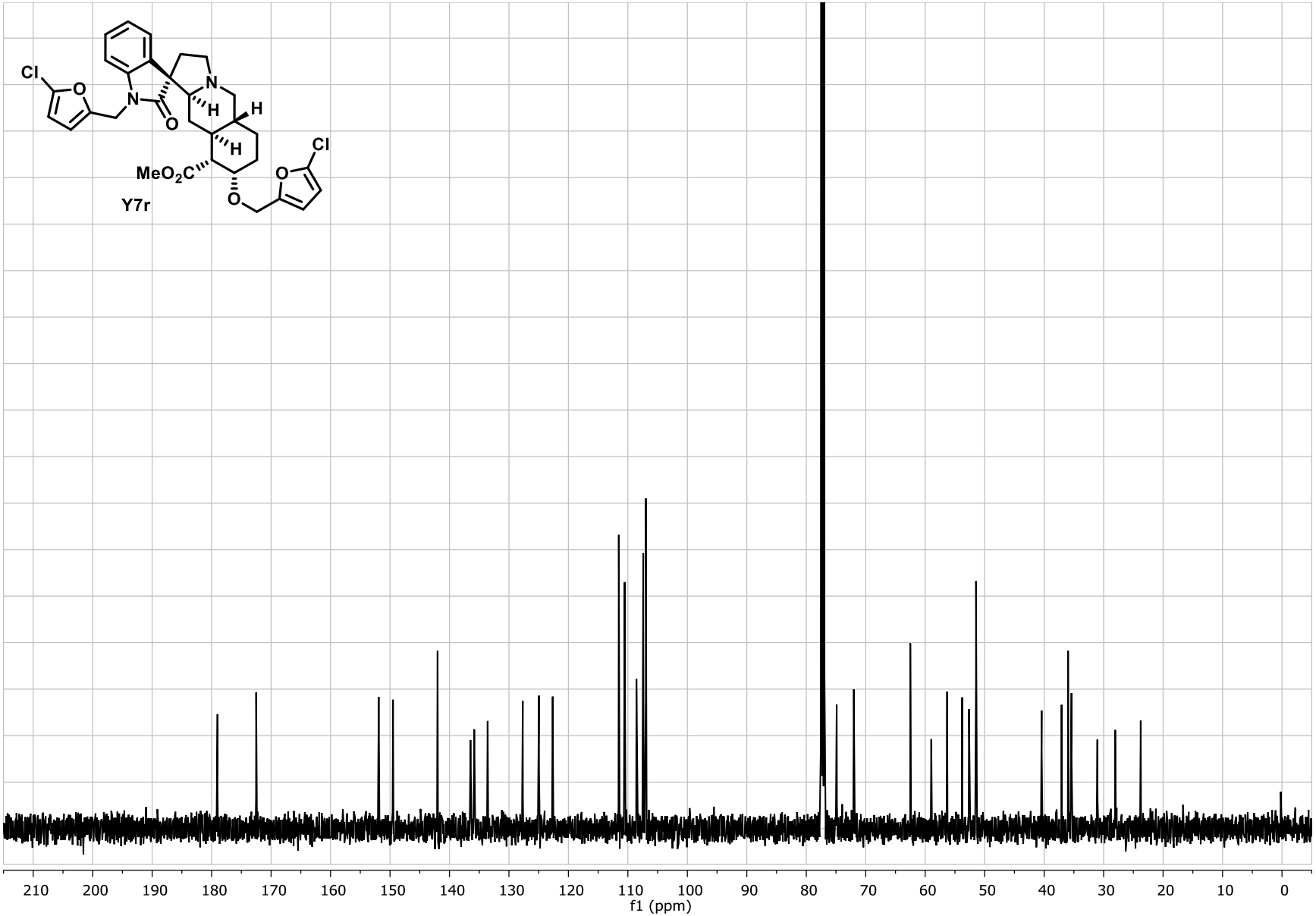
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

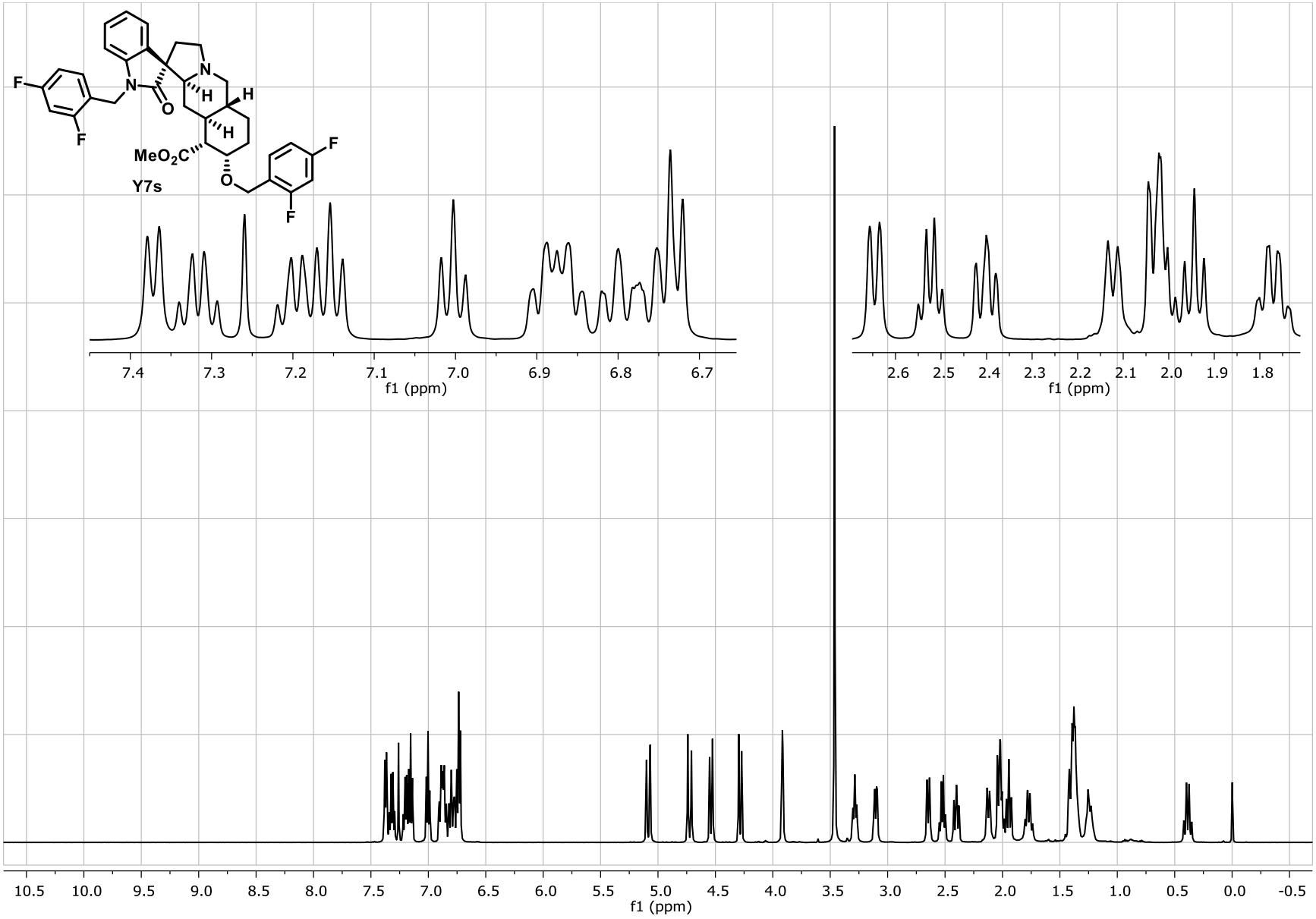

Cl
S
N
O
N
H
H
H
Cl
S
O
Y7p
MeO2C
142 141 140 139 138 137 136 135 134 133 132 131 130 129 128 127 126 125 124 123 122
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

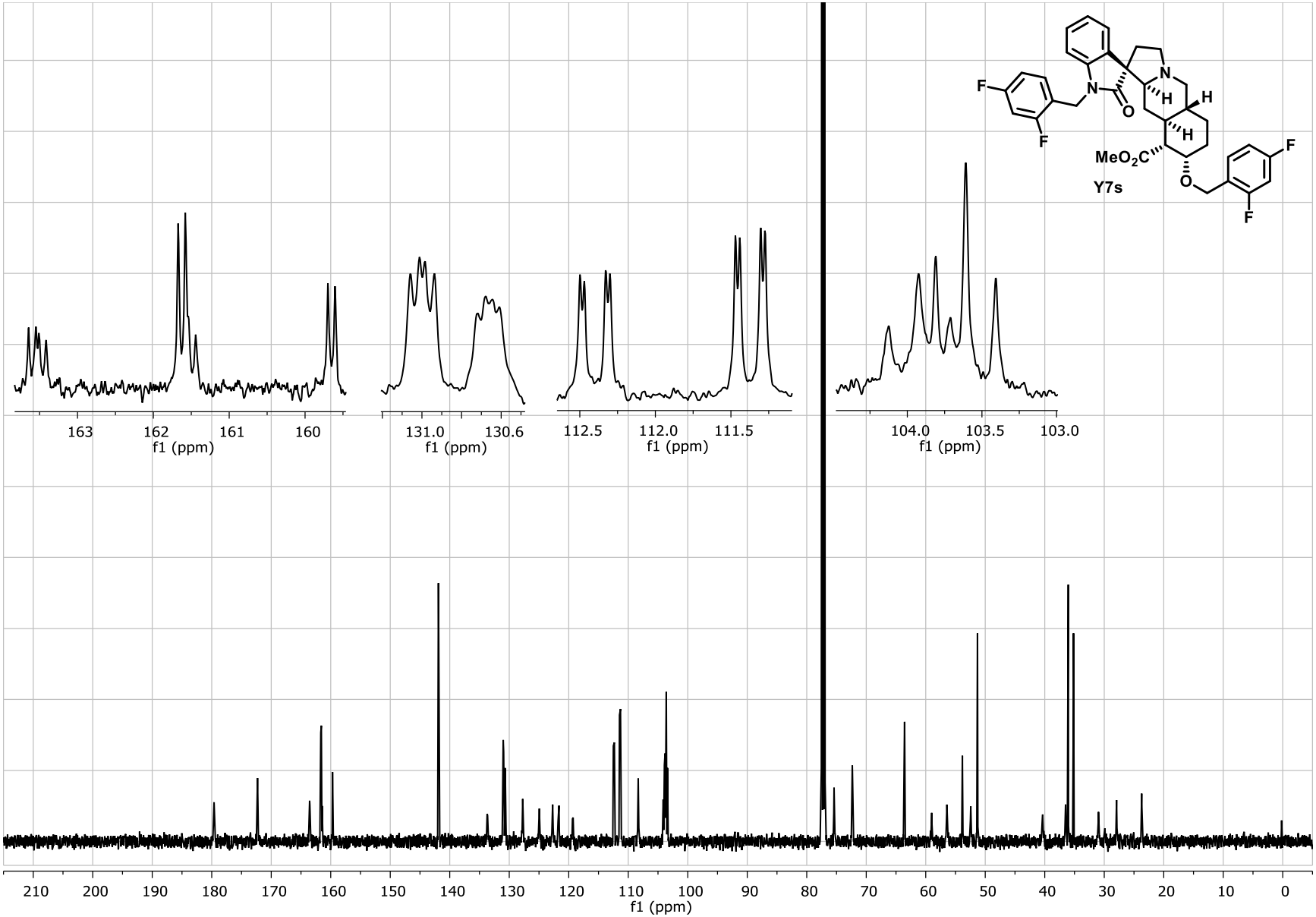

MeO
N
N
O
H
H
H
N
MeO2C
O
OMe
N
Y7q
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

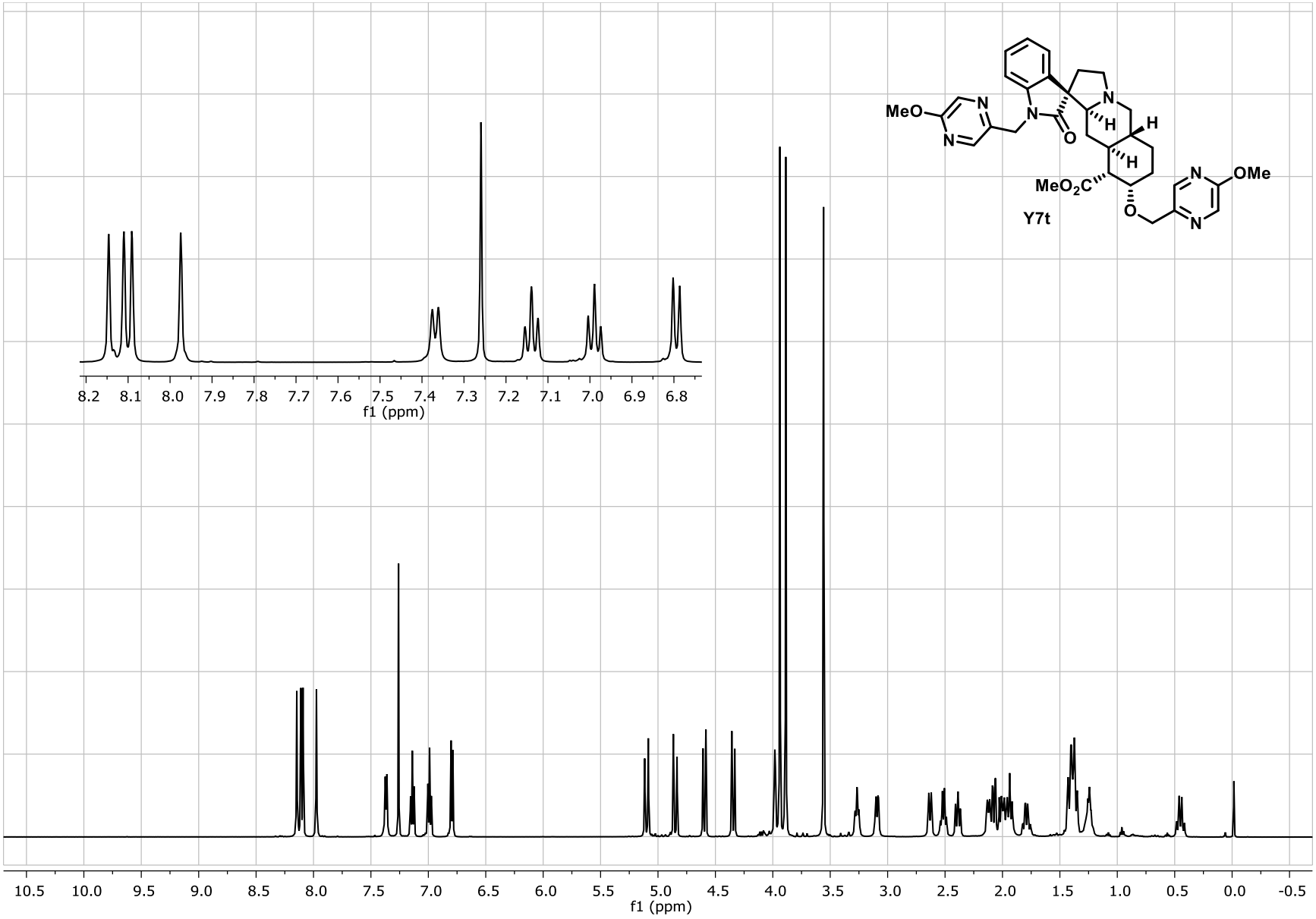

164.5
164.0
163.5
f1 (ppm)
128
127
126
125
124
123
122
f1 (ppm)
54.0
53.5
53.0
52.5
52.0
51.5
f1 (ppm)
MeO
N
N
O
N
H
H
H
MeO2C
O
OMe
N
Y7q
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

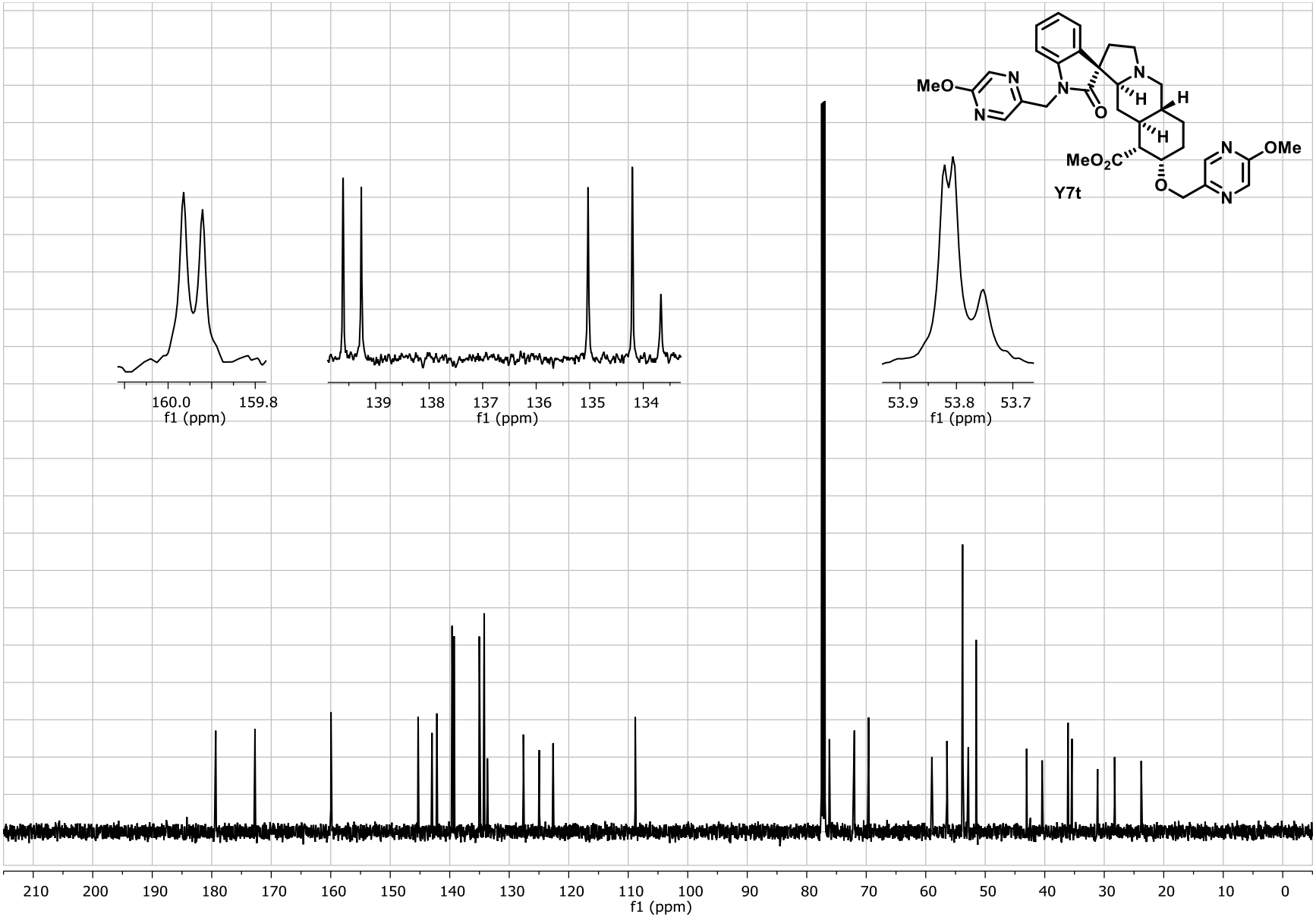

Cl
O
N
O
N
H
H
H
MeO2C
O
O
Cl
Y7r
7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 6.3 6.2 6.1 6.0
f1 (ppm)
2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7
f1 (ppm)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

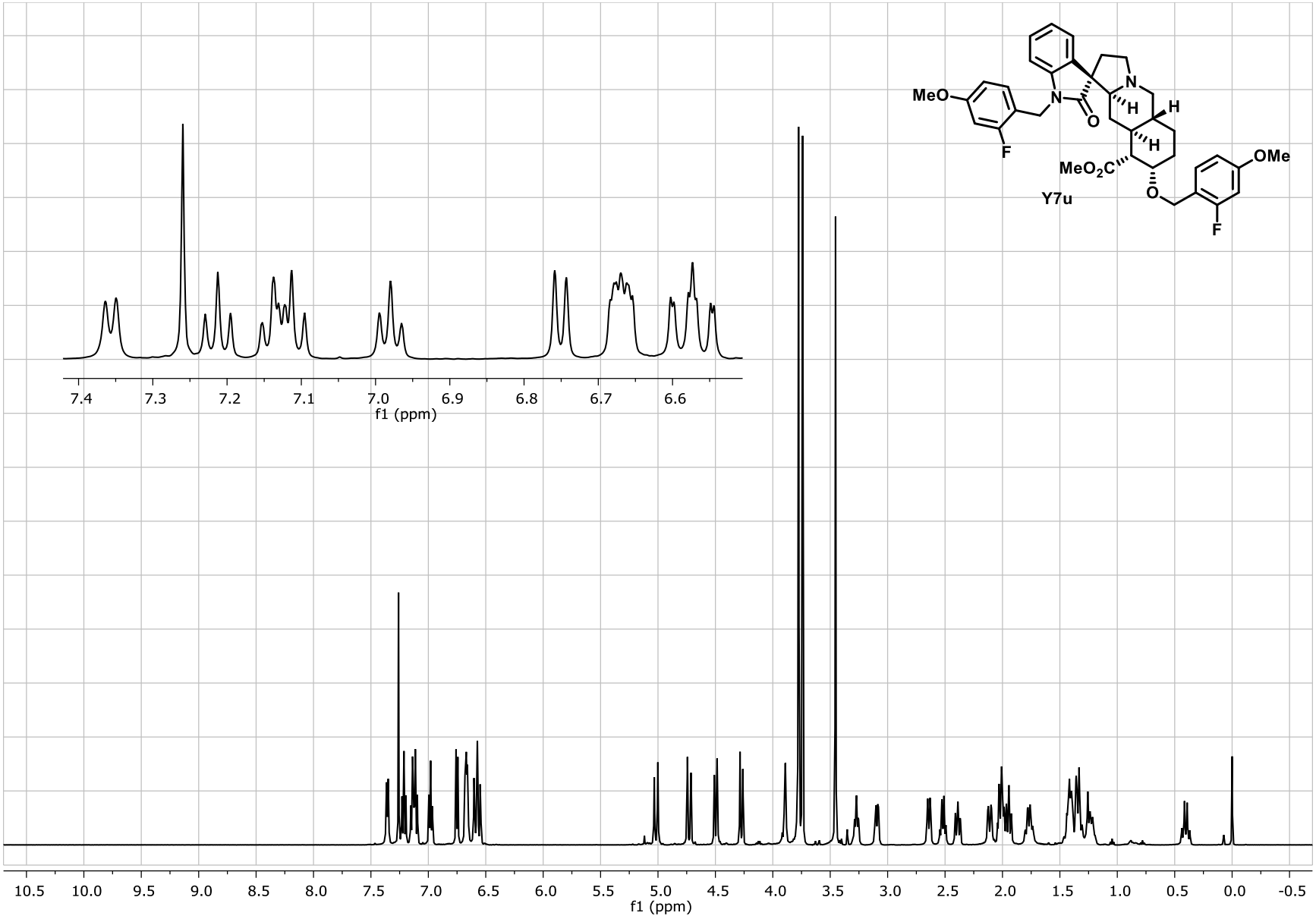

Cl
O
N
O
N
H
H
H
MeO2C
O
O
Cl
Y7r
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

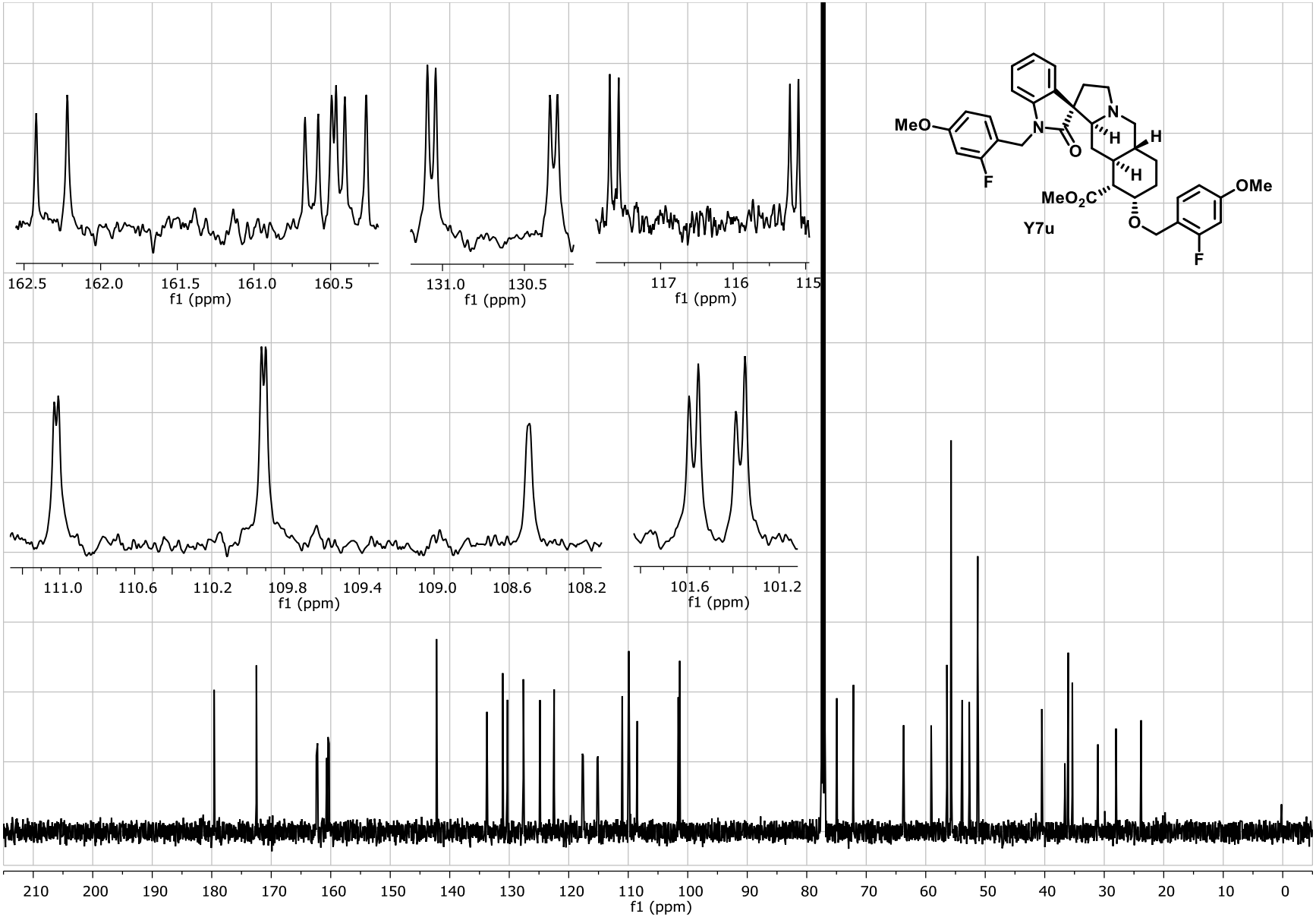

F
F
N
O
N
H
H
H
MeO2C
O
F
F
Y7s
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
f1 (ppm)
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
f1 (ppm)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

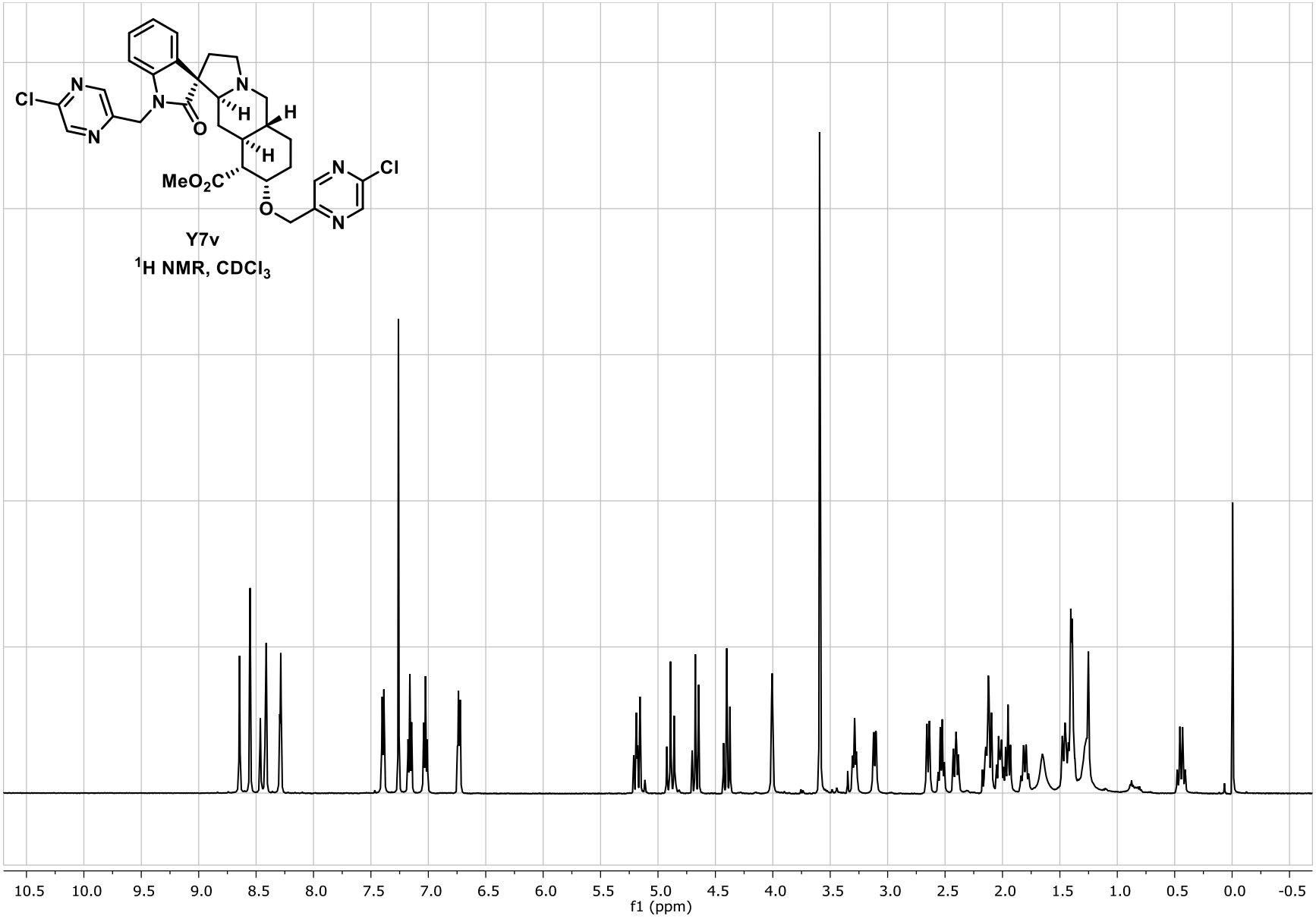

F
F
N
O
N
H
H
H
MeO2C
O
F
F
Y7s
163
162
161
160
f1 (ppm)
131.0
130.6
f1 (ppm)
112.5
112.0
111.5
f1 (ppm)
104.0
103.5
103.0
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

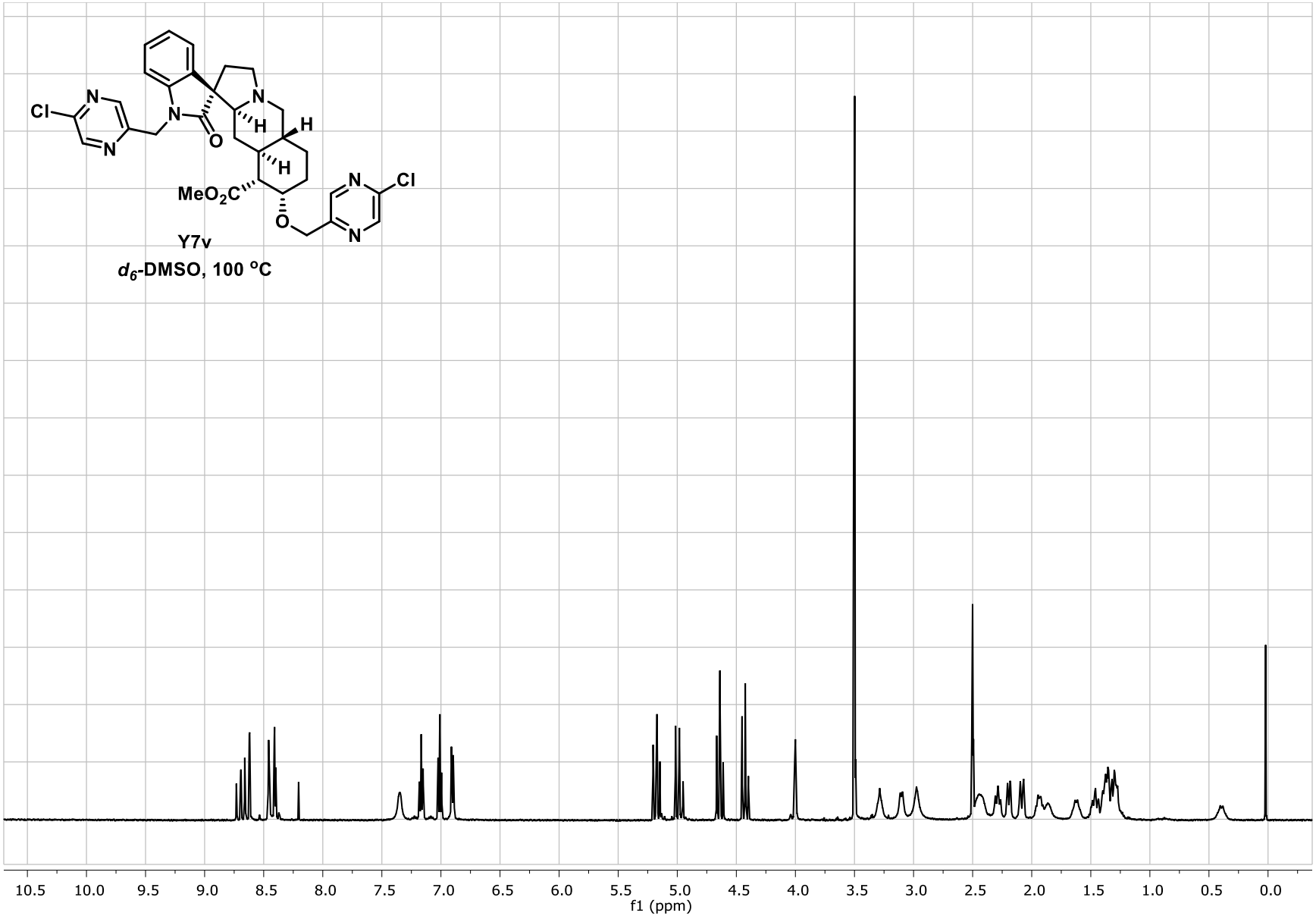

MeO
N
N
N
N
O
H
H
H
MeO2C
O
N
OMe
N
Y7t
8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8
f1 (ppm)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

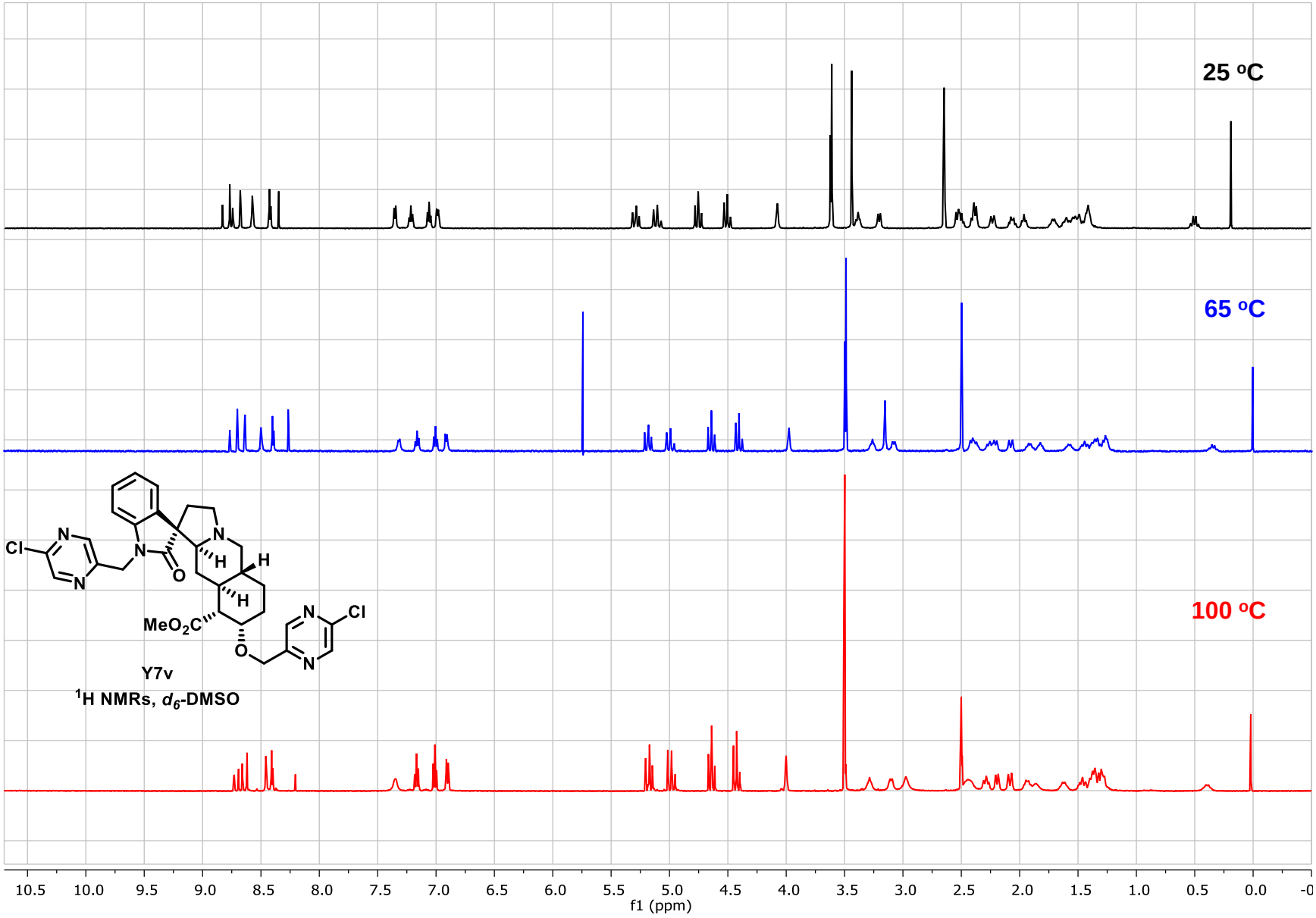

MeO
N
N
N
O
H
H
H
MeO2C
O
N
OMe
N
Y7t
160.0
159.8
f1 (ppm)
139
138
137
136
135
134
f1 (ppm)
53.9
53.8
53.7
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

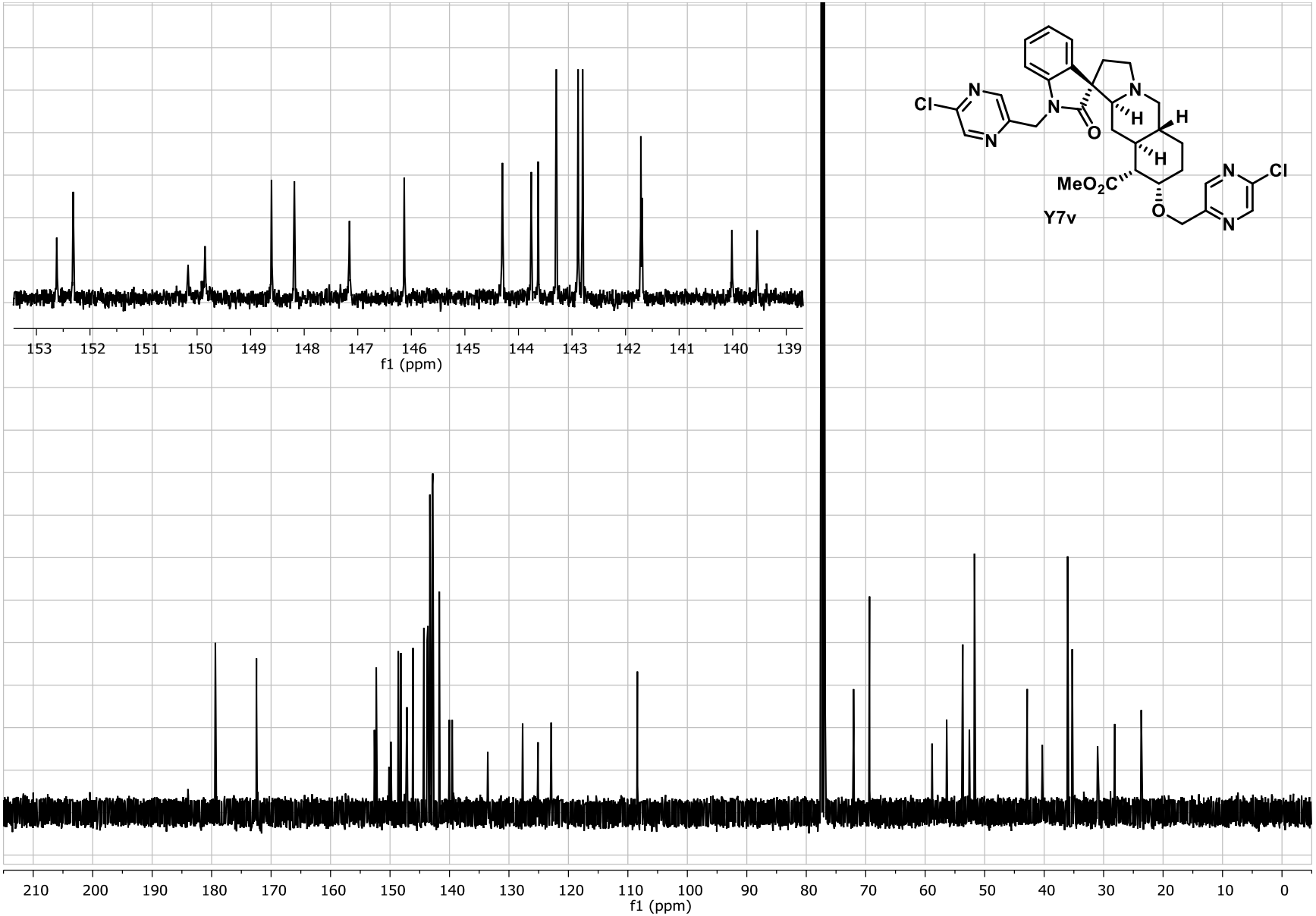

MeO
F
N
O
N
H
H
H
MeO2C
O
OMe
F
Y7u
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
f1 (ppm)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

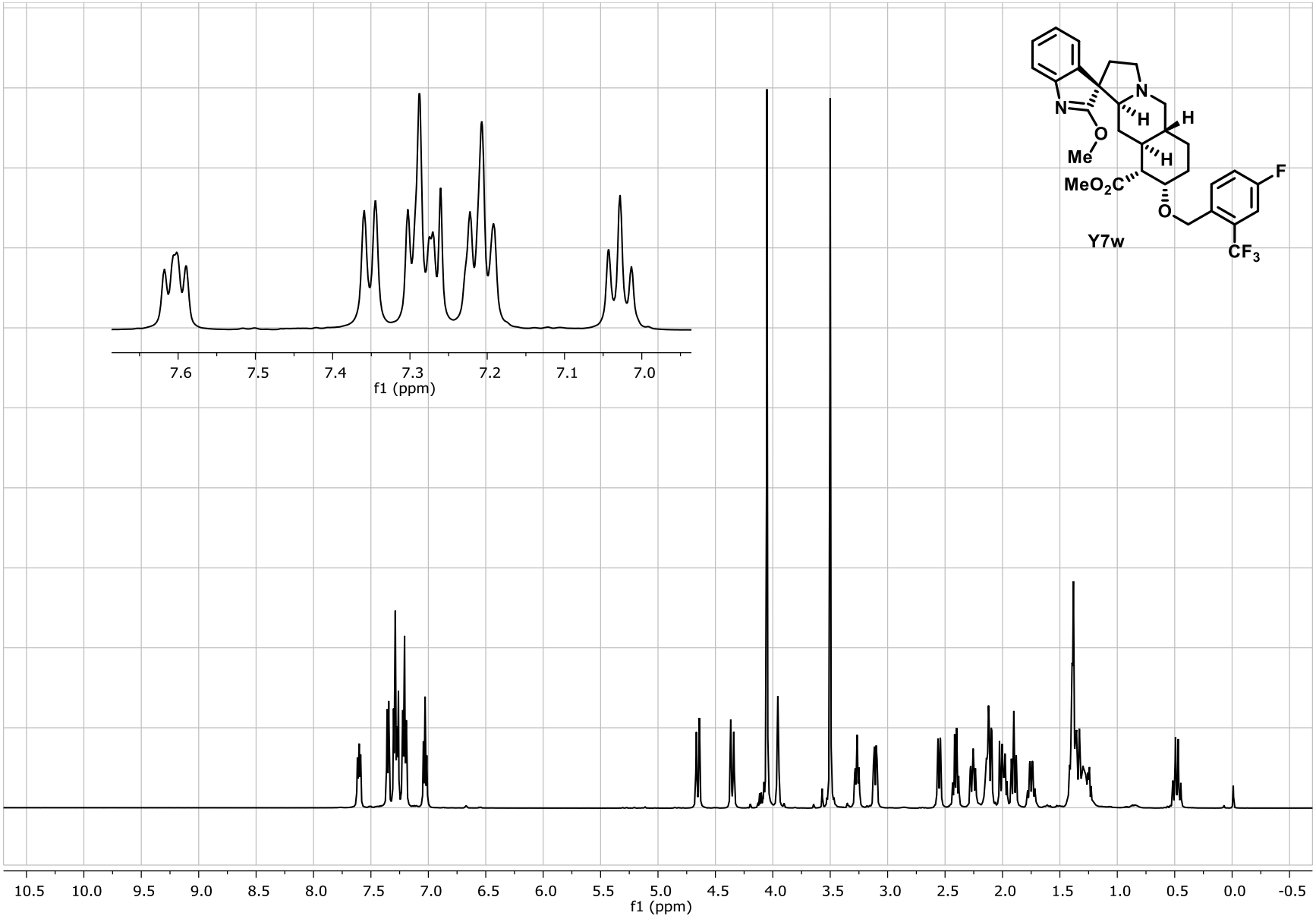

MeO
F
N
N
O
H
H
H
MeO2C
O
OMe
F
Y7u
162.5
162.0
161.5
161.0
160.5
f1 (ppm)
131.0
130.5
f1 (ppm)
117
116
115
f1 (ppm)
111.0
110.6
110.2
109.8
109.4
109.0
108.6
108.2
f1 (ppm)
101.6
101.2
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

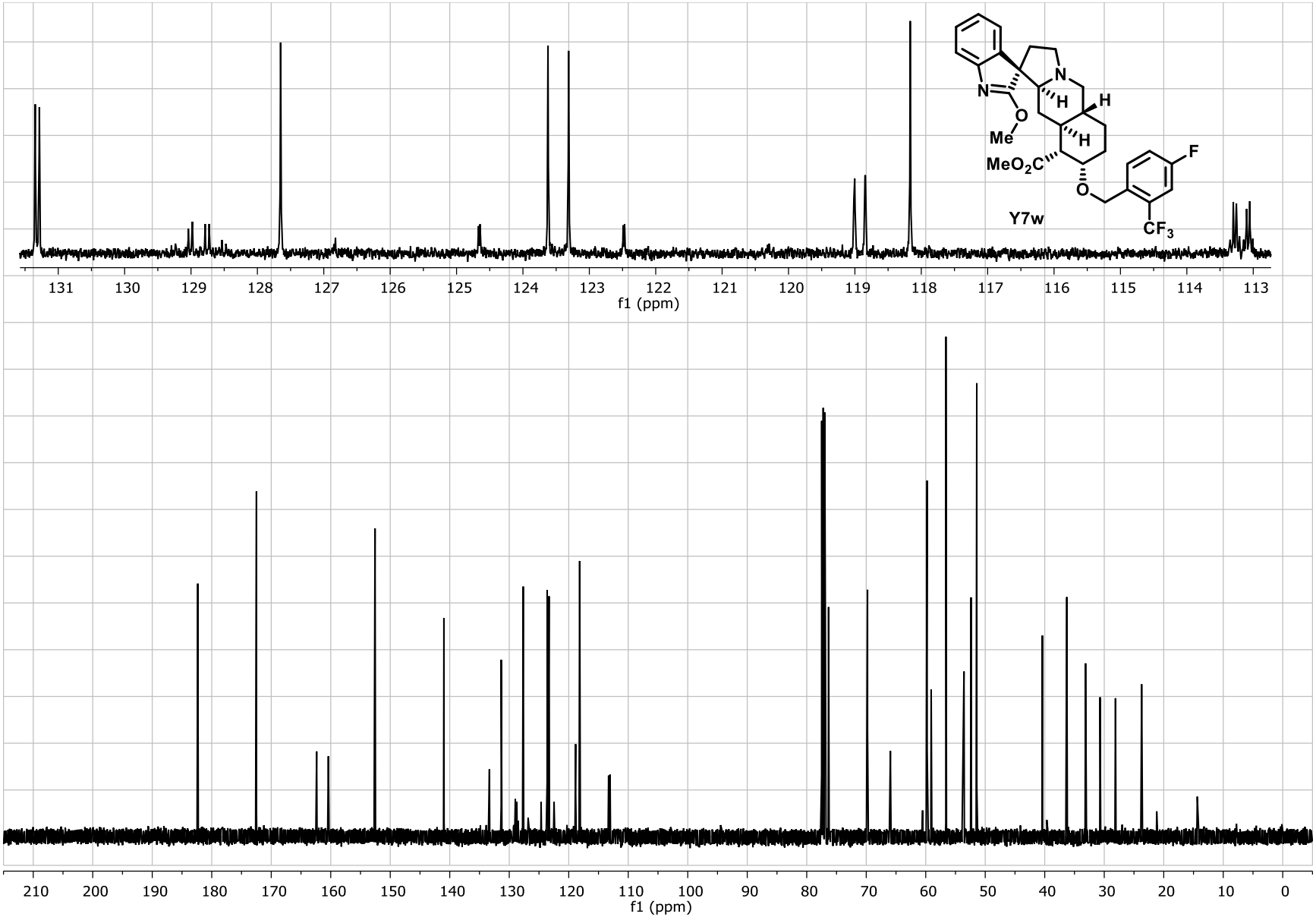

Cl
N
N
N
O
H
H
H
MeO2C
O
N
N
Cl
Y7v
1H NMR, CDCl3
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

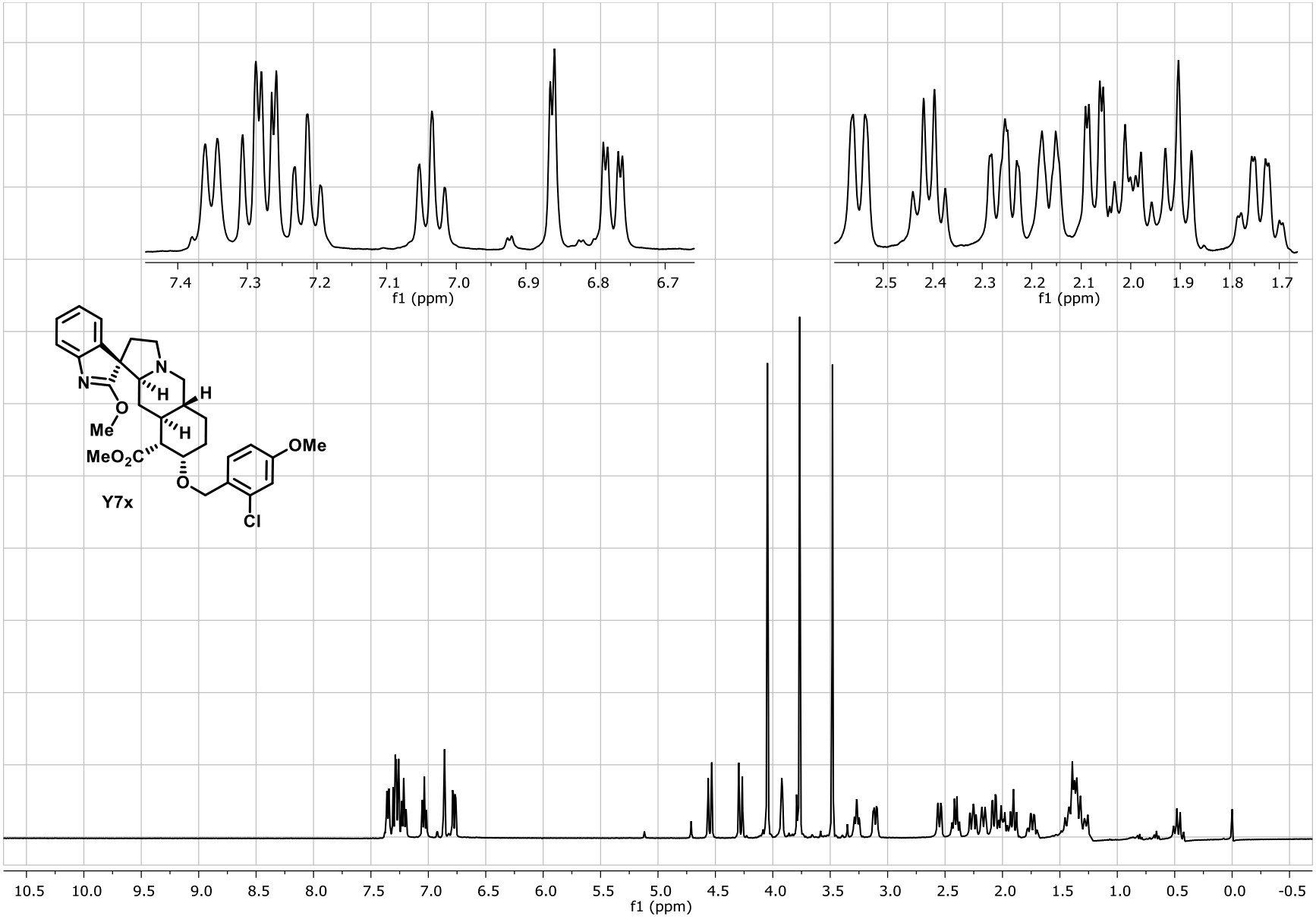

Cl
N
N
N
O
H
H
H
MeO2C
O
N
N
Cl
Y7v
d6-DMSO, 100 °C
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

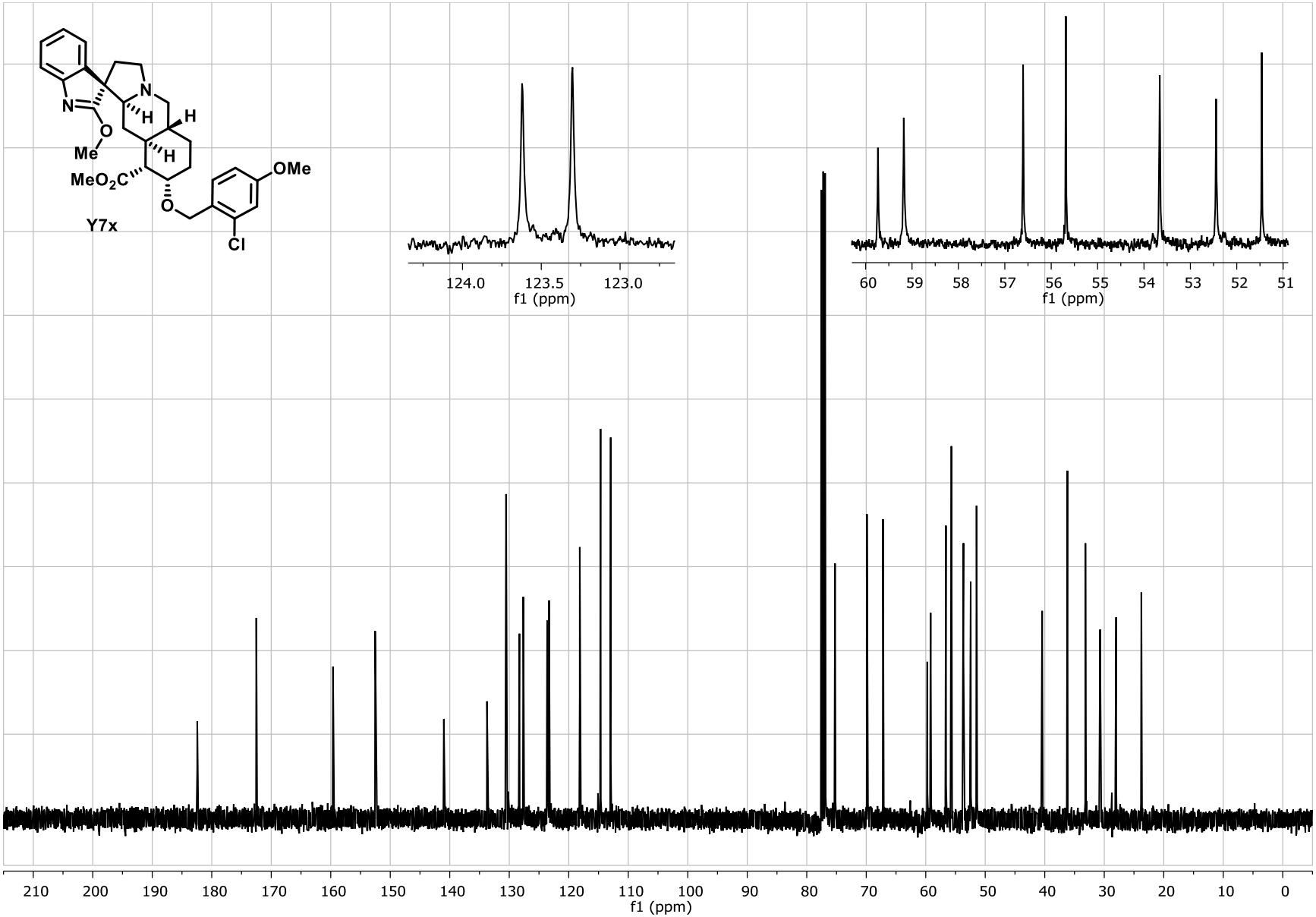

25 °C
65 °C
100 °C
Cl
N
N
N
O
H
H
H
MeO2C
O
N
Cl
N
Y7v
1H NMRs, d6-DMSO
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

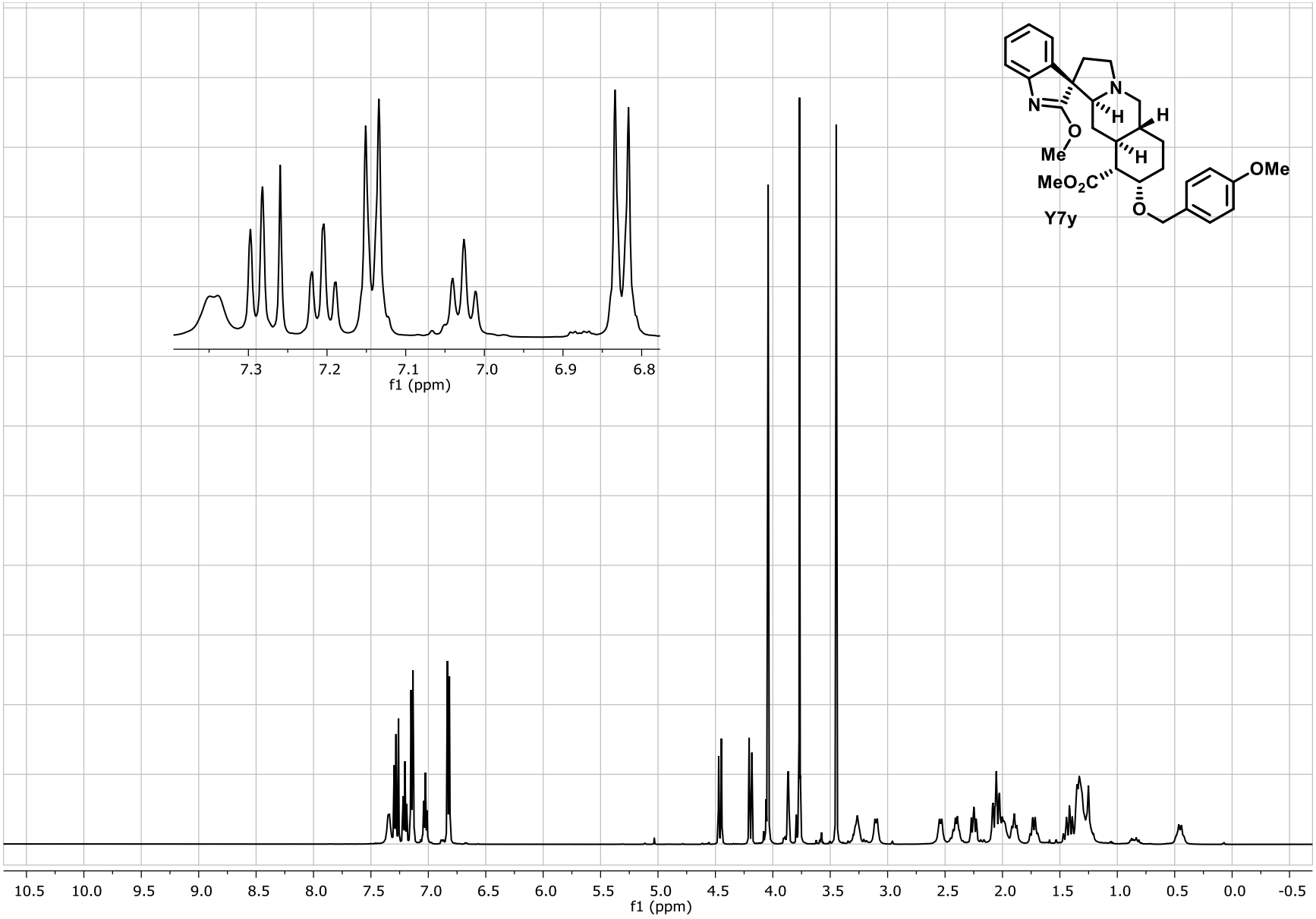

Cl
N
N
N
O
N
H
H
H
MeO2C
O
N
N
Cl
Y7v
153 152 151 150 149 148 147 146 145 144 143 142 141 140 139
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

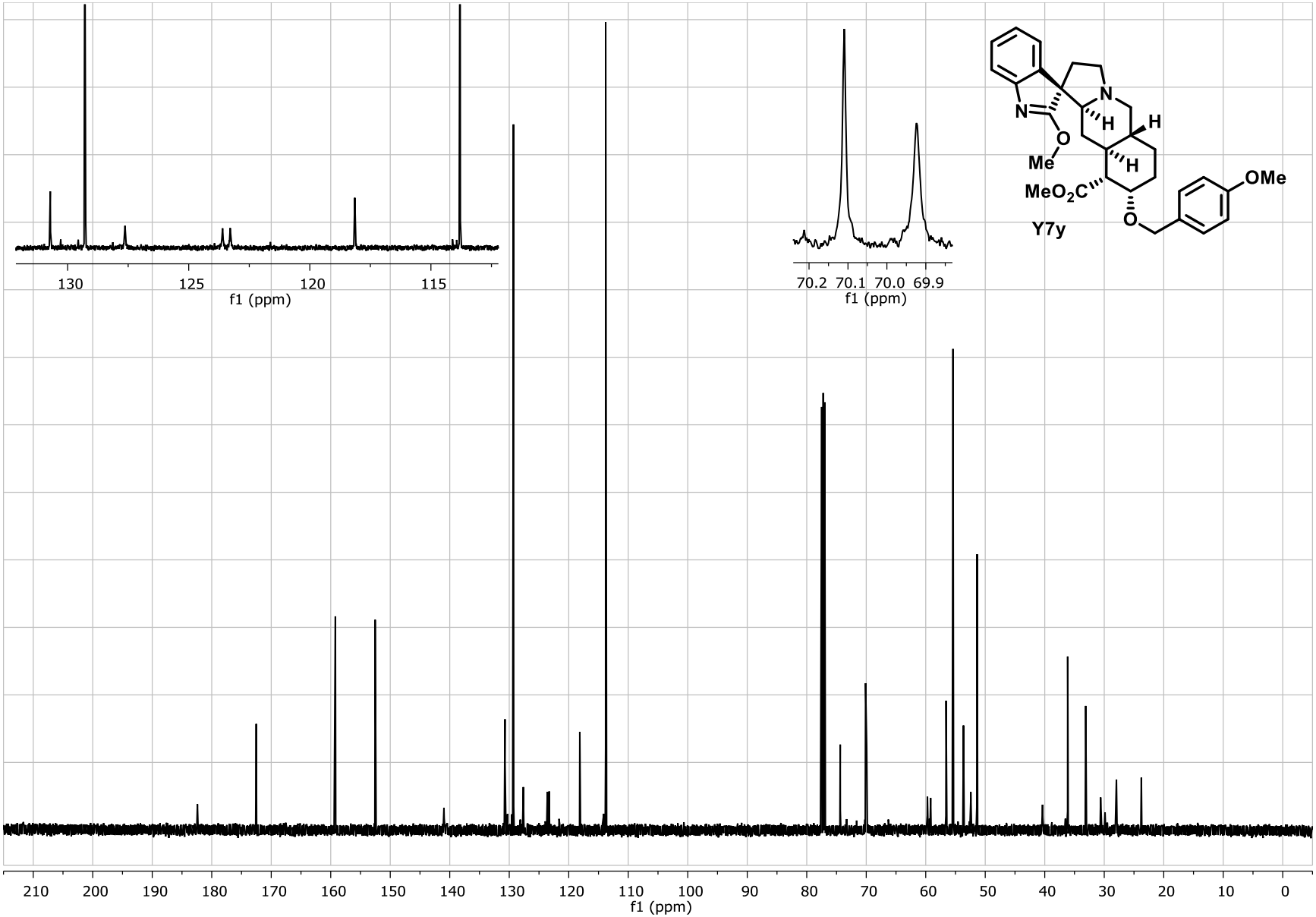

7.6
7.5
7.4
7.3
7.2
7.1
7.0
f1 (ppm)
N
O
Me
N
H
H
H
MeO2C
O
F
CF3
Y7w
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

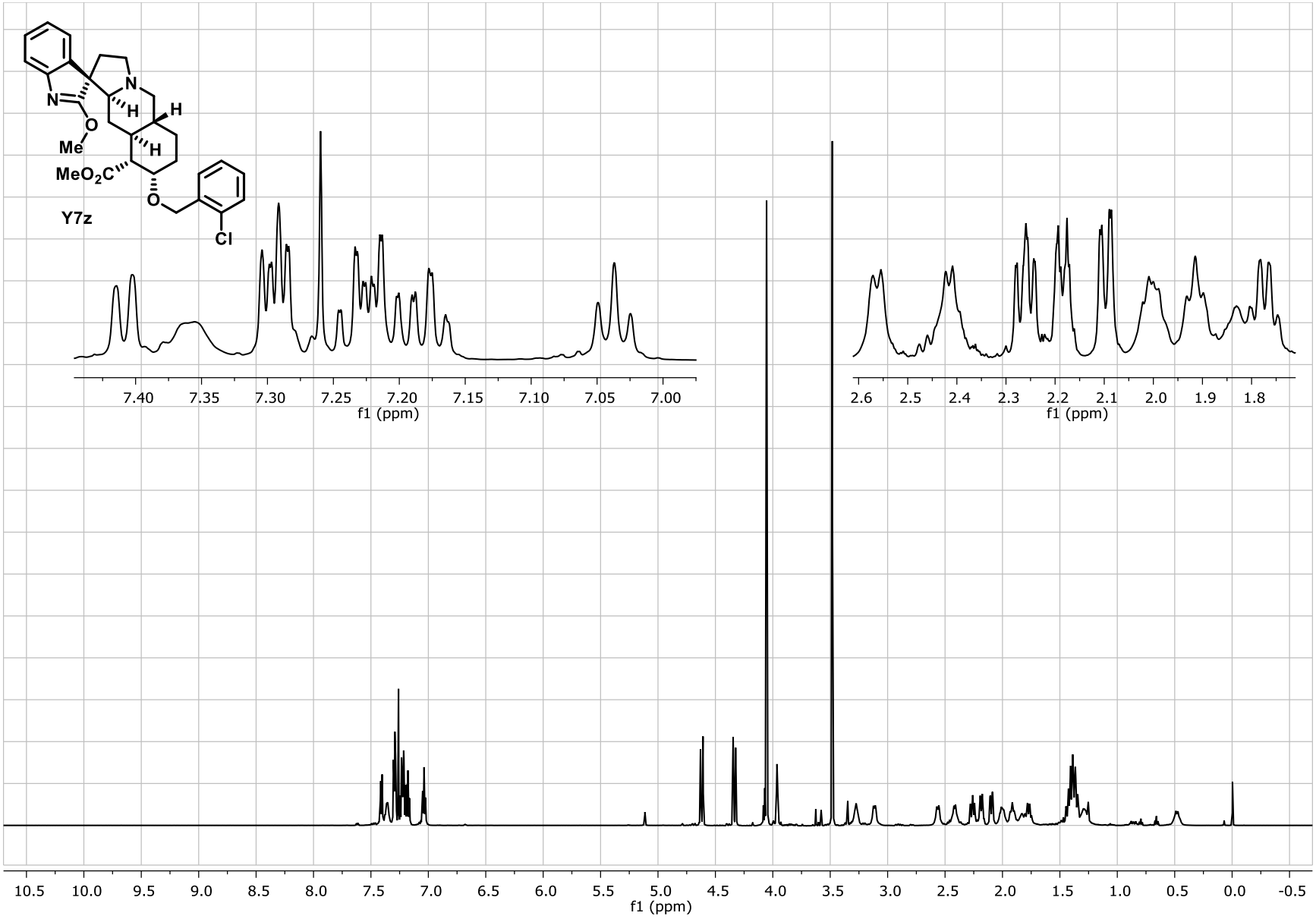

Y7w
f1 (ppm)
f1 (ppm)

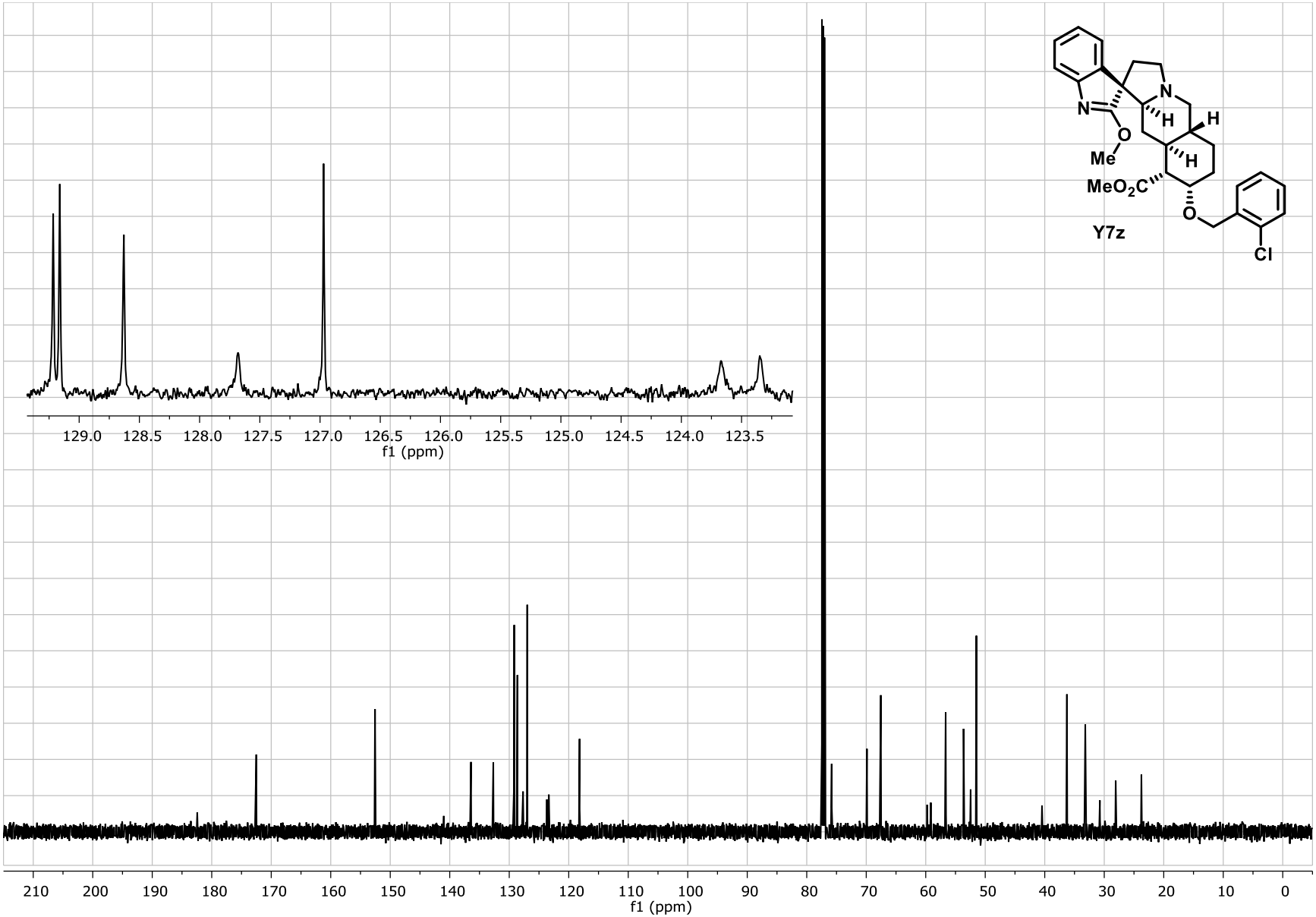

7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
f1 (ppm)
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
f1 (ppm)
N
H
H
H
N
O
Me
MeO2C
O
OMe
Cl
Y7x
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

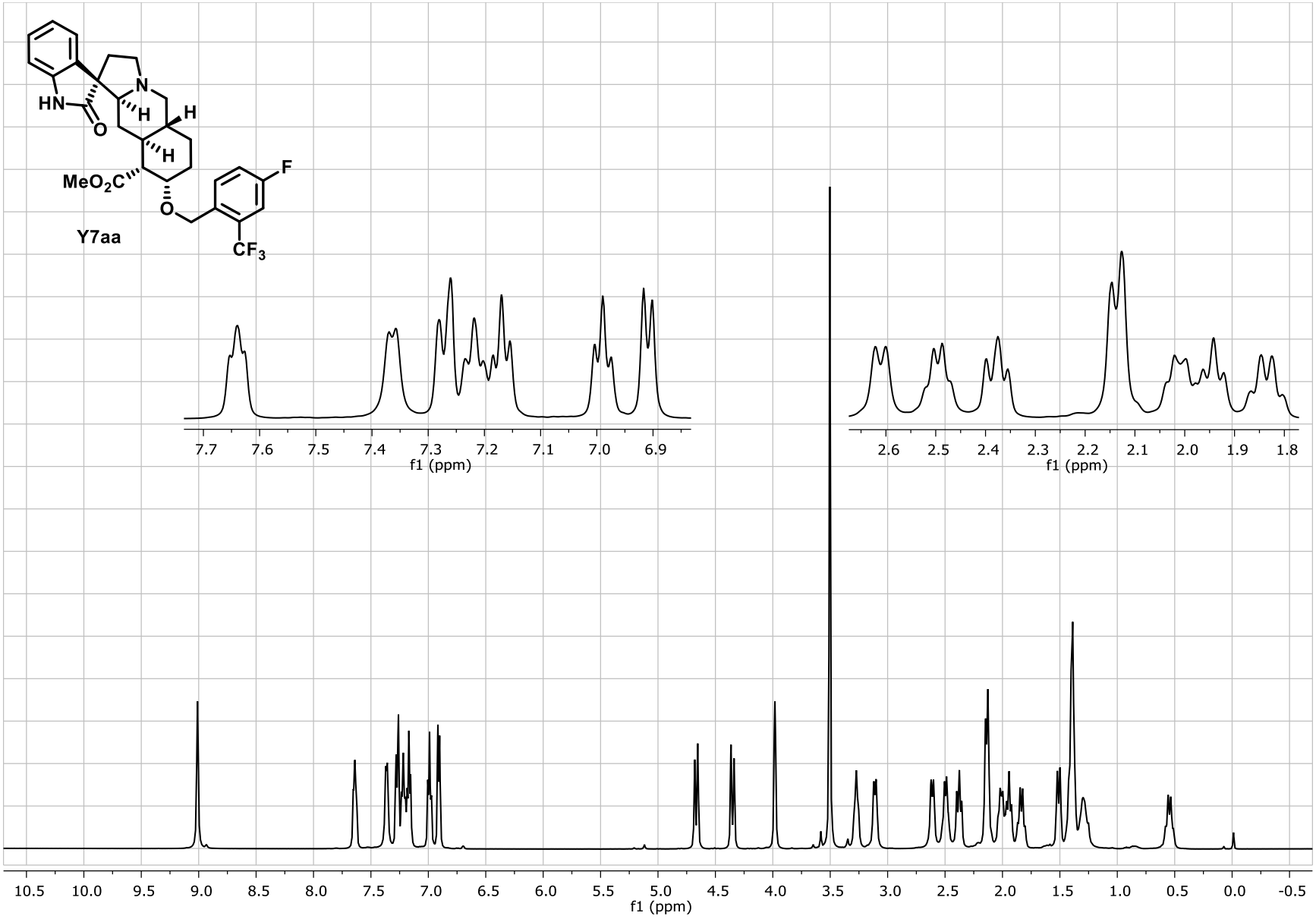

Y7x
Me
MeO2C
OMe
Cl
124.0
123.5
123.0
f1 (ppm)
60
59
58
57
56
55
54
53
52
51
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

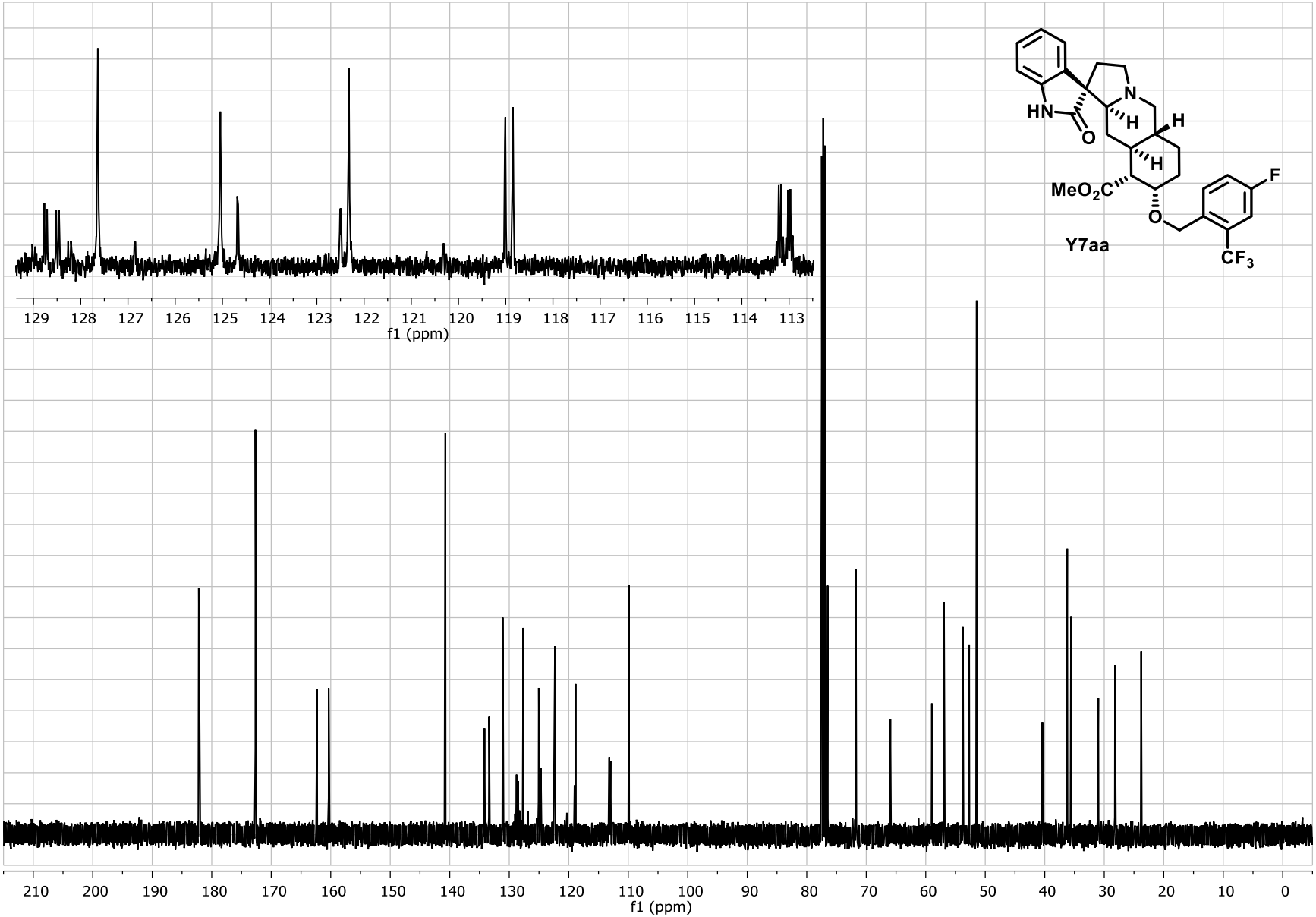

7.3
7.2
7.1
7.0
6.9
6.8
f1 (ppm)
N
N
O
Me
H
H
H
MeO2C
O
OMe
Y7y
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

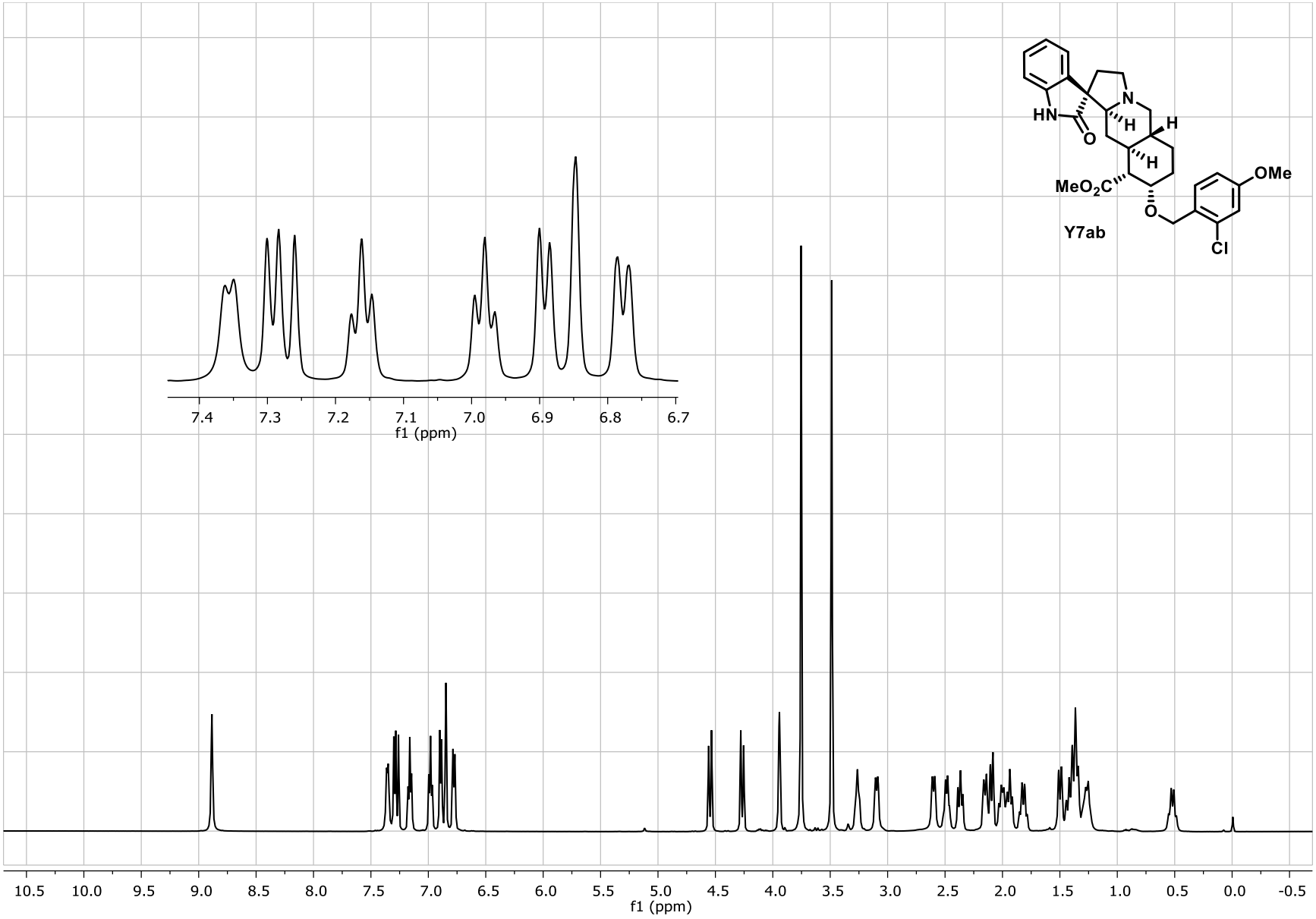

130
125
120
115
f1 (ppm)
70.2
70.1
70.0
69.9
f1 (ppm)
N
N
H
H
H
O
Me
MeO2C
O
OMe
Y7y
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

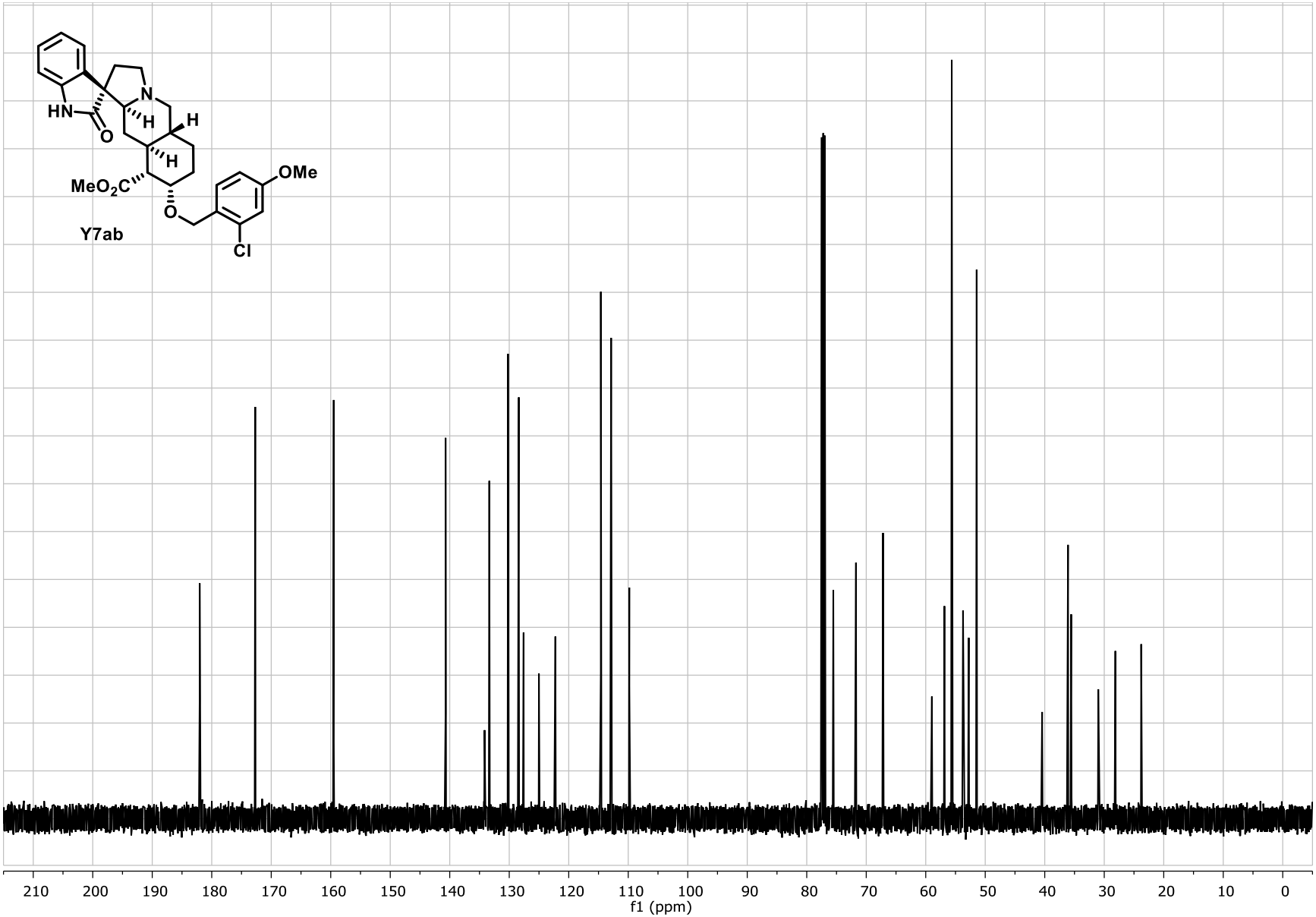

Y7z
Me
MeO2C
Cl
7.40 7.35 7.30 7.25 7.20 7.15 7.10 7.05 7.00
f1 (ppm)
2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8
f1 (ppm)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

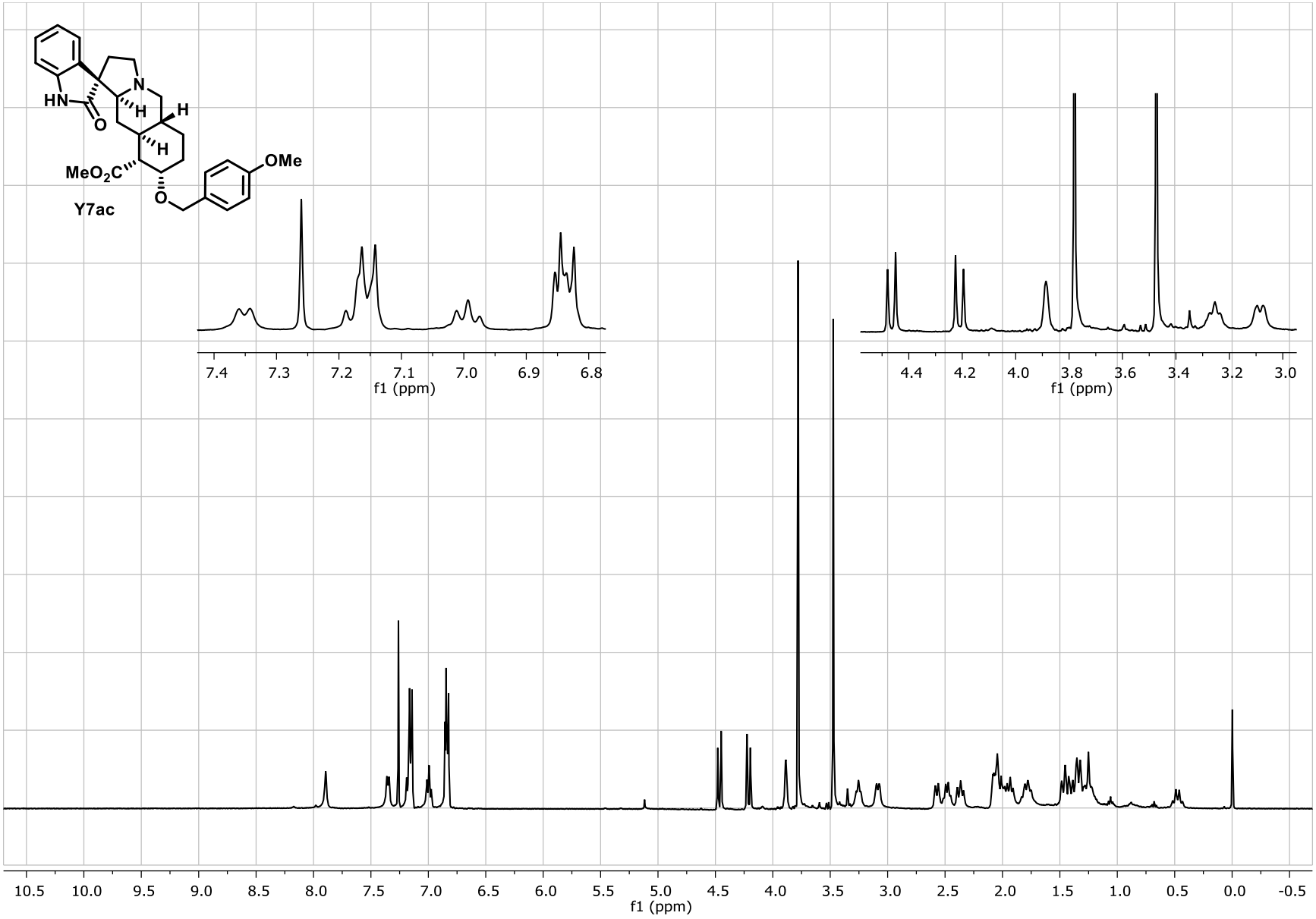

129.0
128.5
128.0
127.5
127.0
126.5
126.0
125.5
125.0
124.5
124.0
123.5
f1 (ppm)
N
N
O
Me
H
H
H
MeO2C
O
Cl
Y7z
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

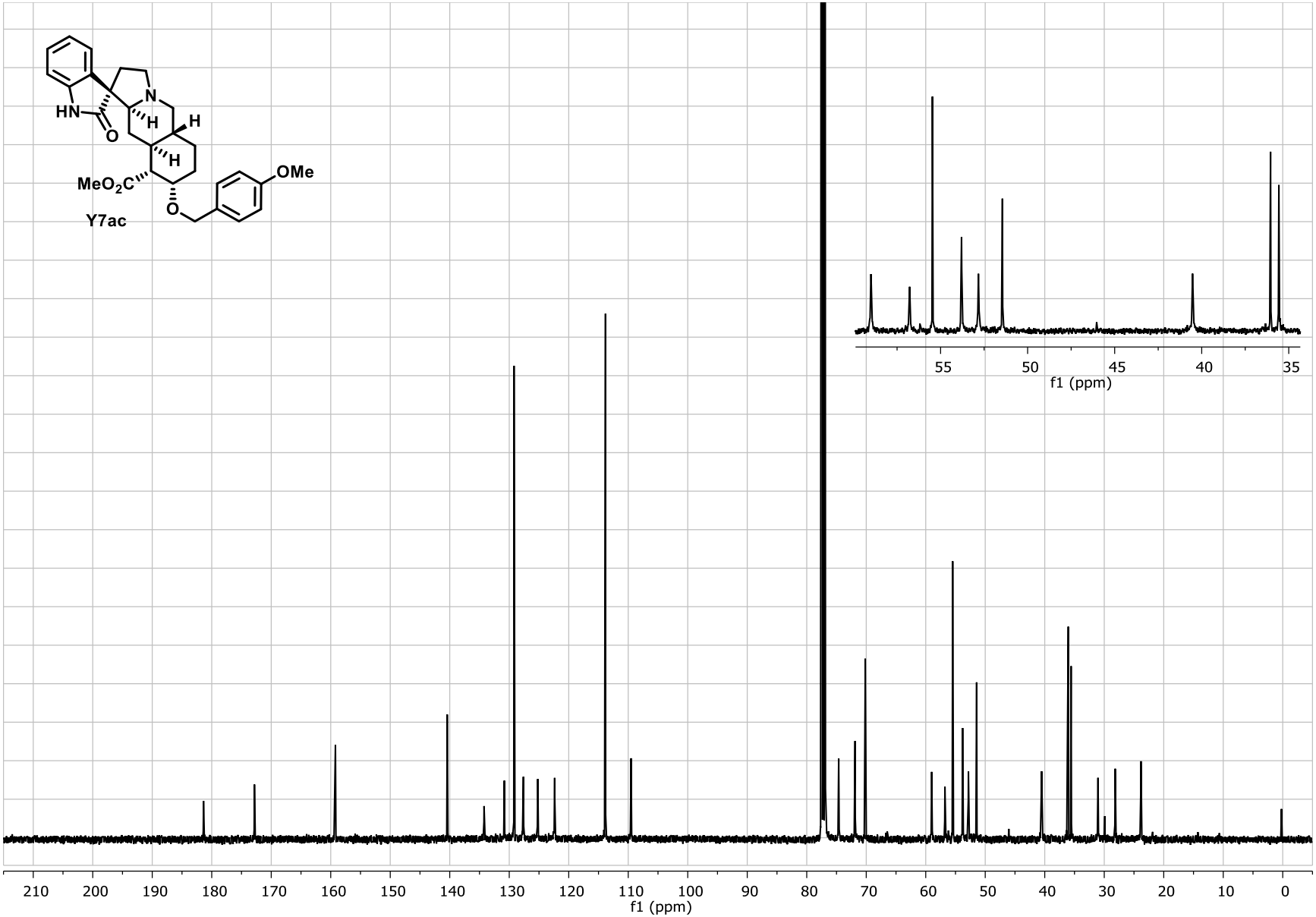

HN
O
N
H
H
H
MeO2C
O
F
CF3
Y7aa
7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9
f1 (ppm)
2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8
f1 (ppm)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

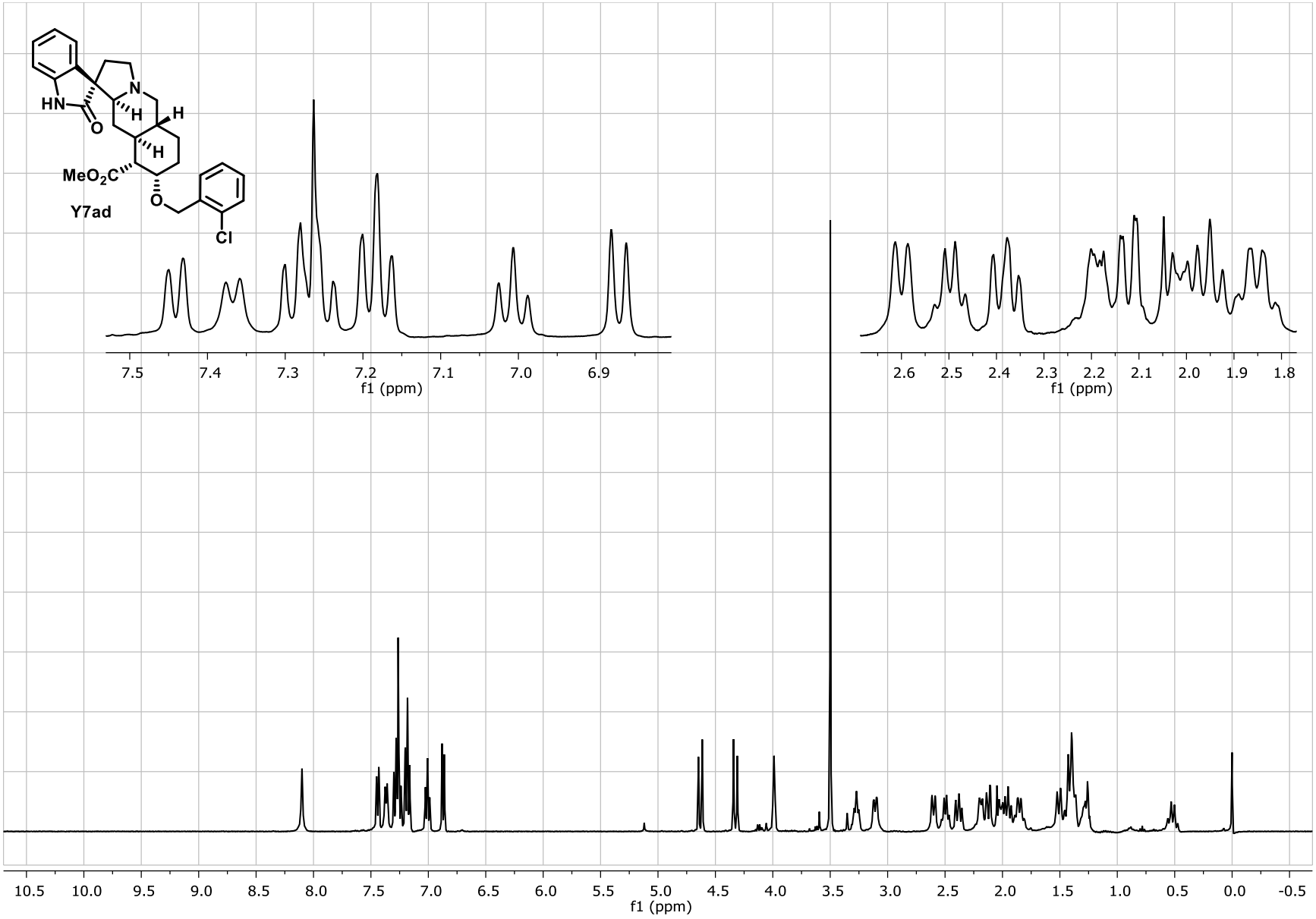

HN
O
N
H
H
H
MeO2C
O
F
CF3
Y7aa
129 128 127 126 125 124 123 122 121 120 119 118 117 116 115 114 113
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

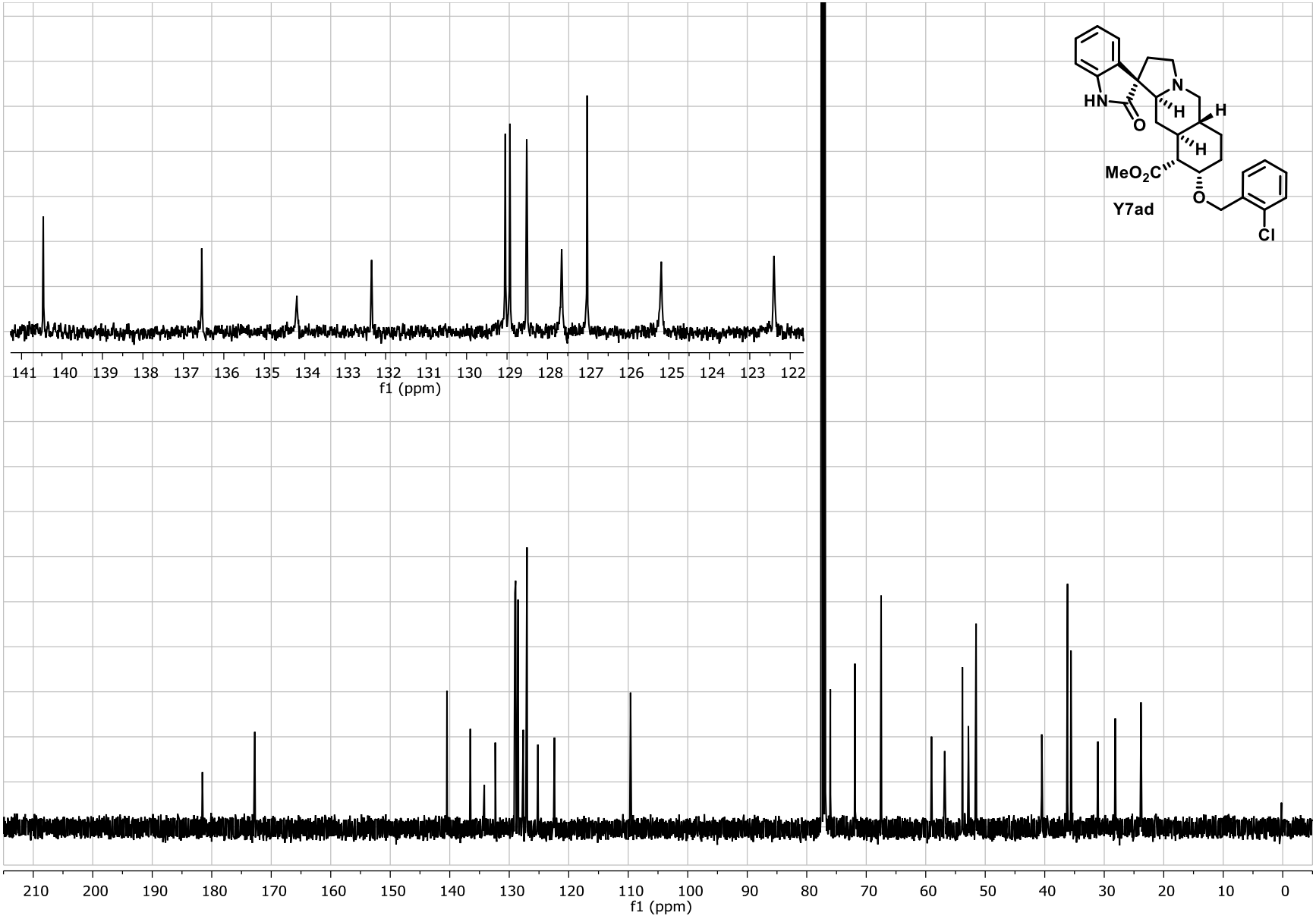

HN
O
N
H
H
H
MeO2C
O
OMe
Cl
Y7ab
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
f1 (ppm)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

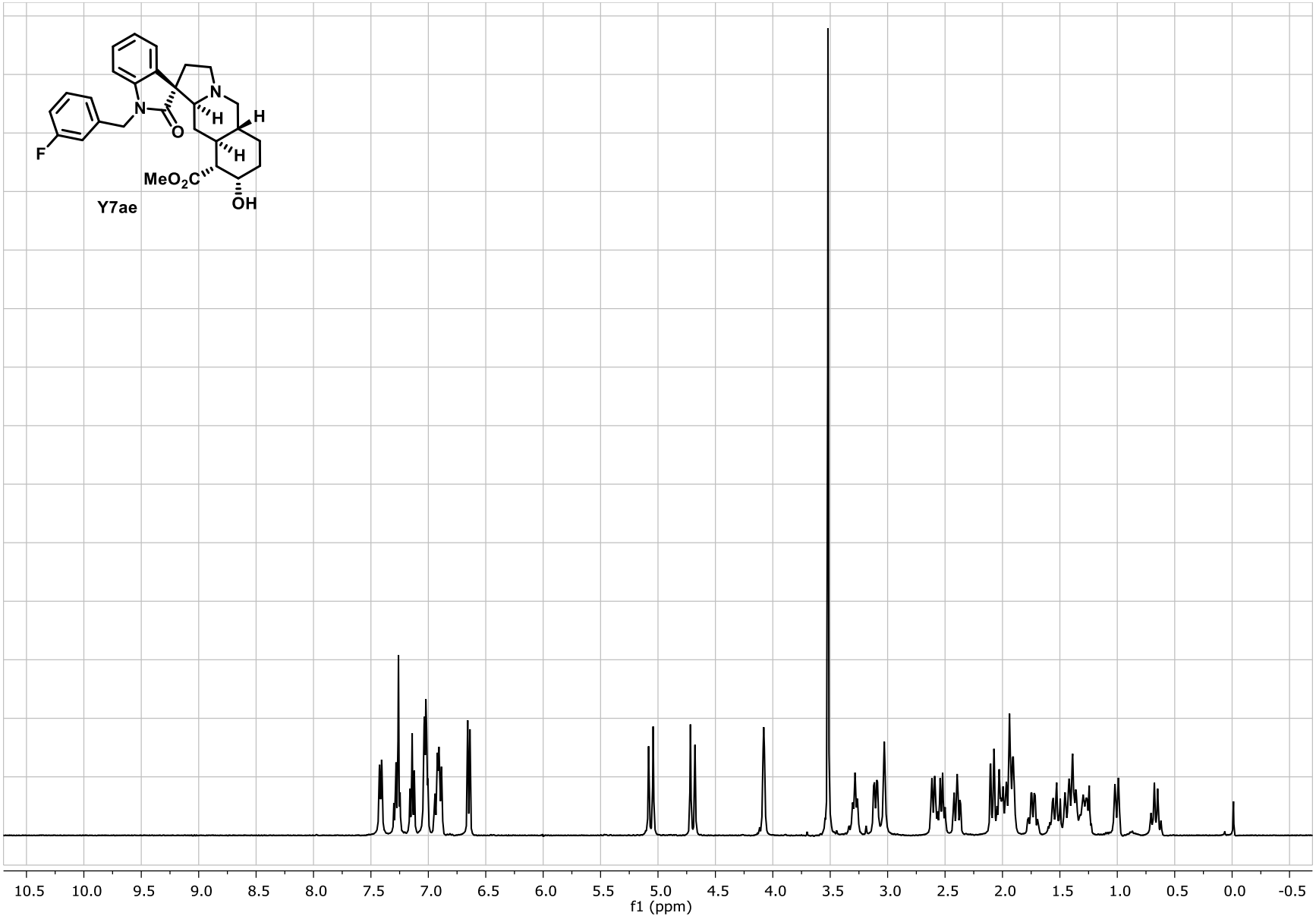

HN
O
N
H
H
H
MeO2C
O
OMe
Cl
Y7ab
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

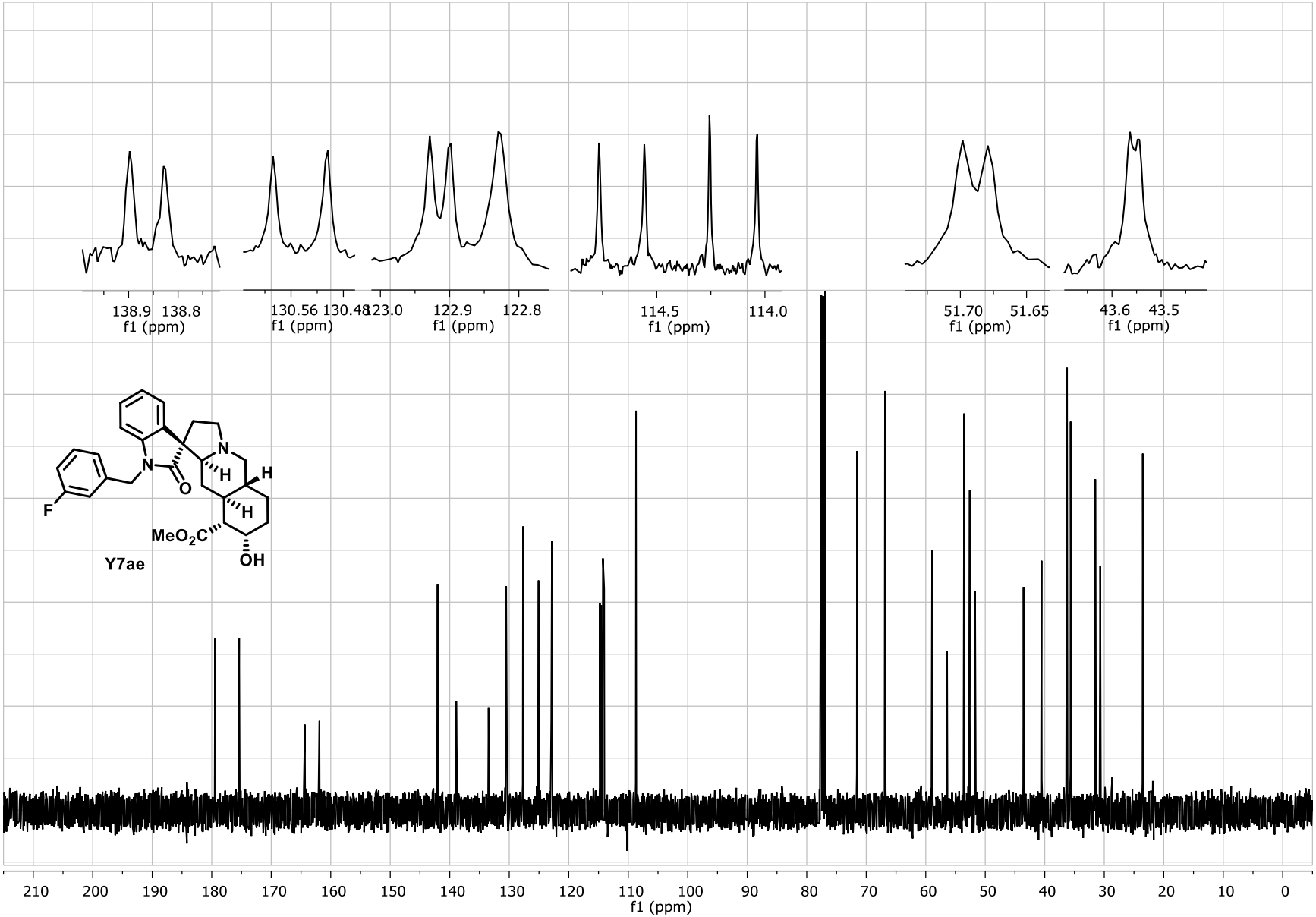

HN
O
N
H
H
H
MeO2C
O
OMe
Y7ac
7.4
7.3
7.2
7.1
7.0
6.9
6.8
f1 (ppm)
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
f1 (ppm)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

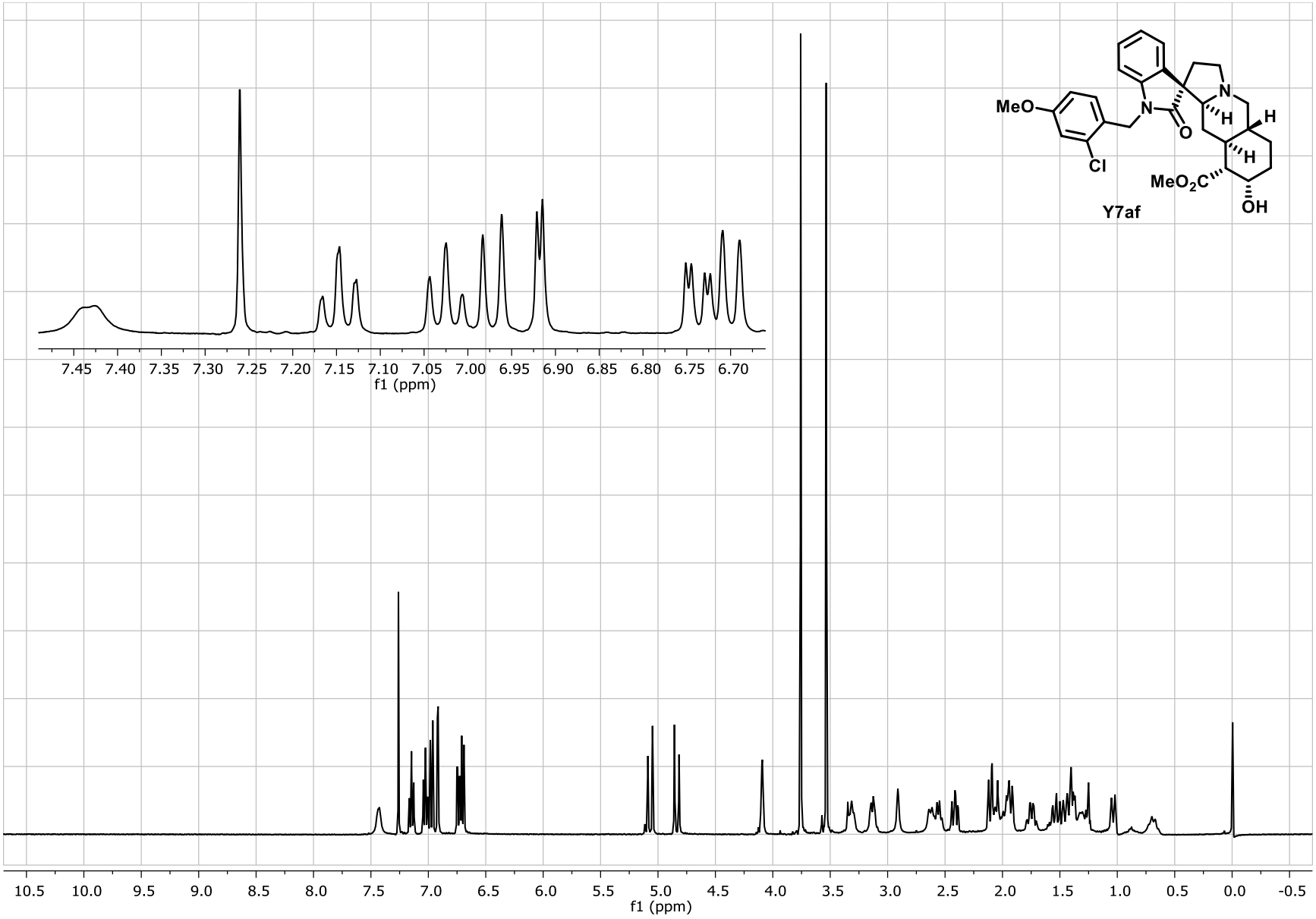

HN
O
N
H
H
H
MeO2C
O
OMe
Y7ac
55
50
45
40
35
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

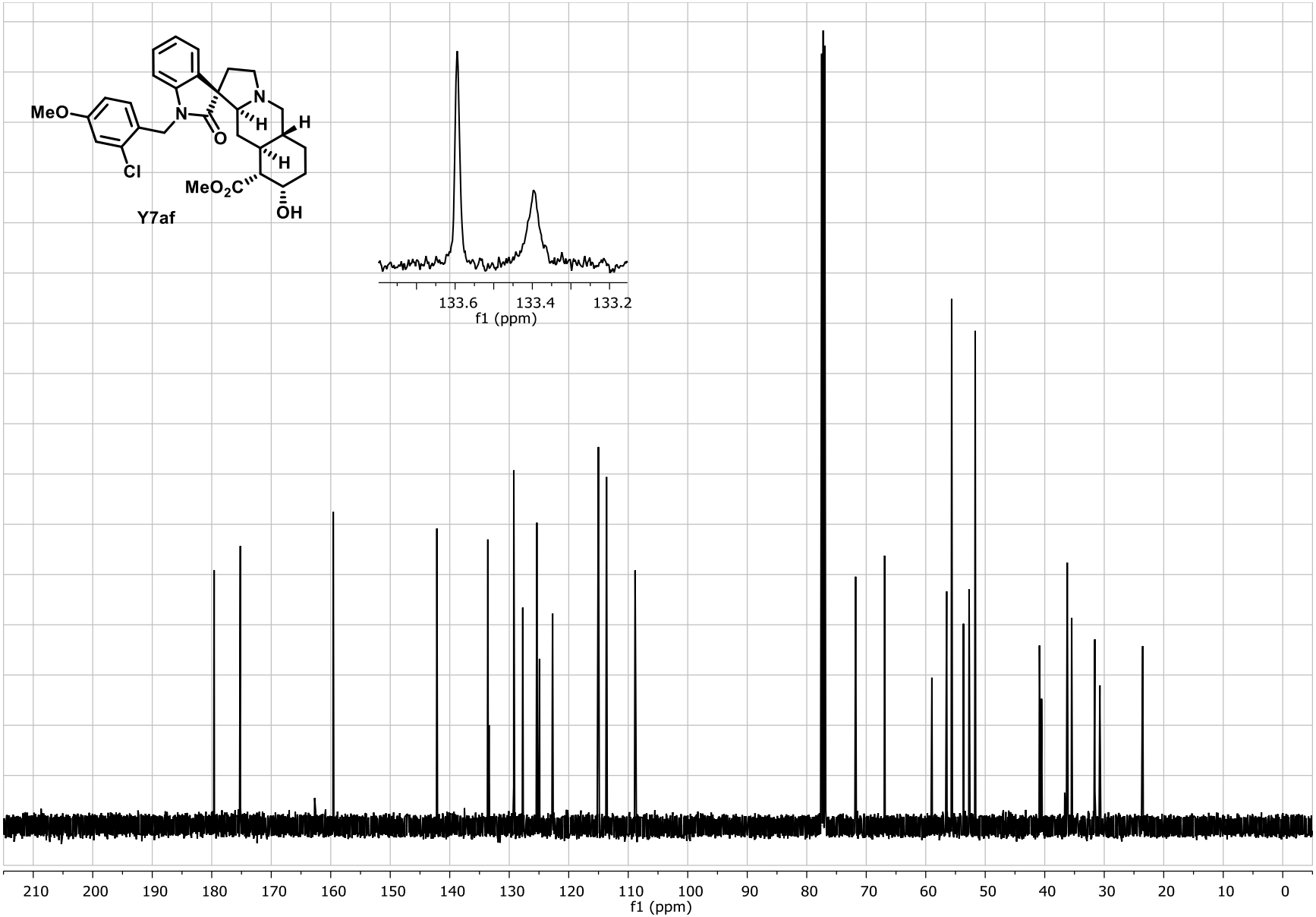

HN
O
N
H
H
H
MeO2C
O
Cl
Y7ad
7.5
7.4
7.3
7.2
7.1
7.0
6.9
f1 (ppm)
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
f1 (ppm)
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

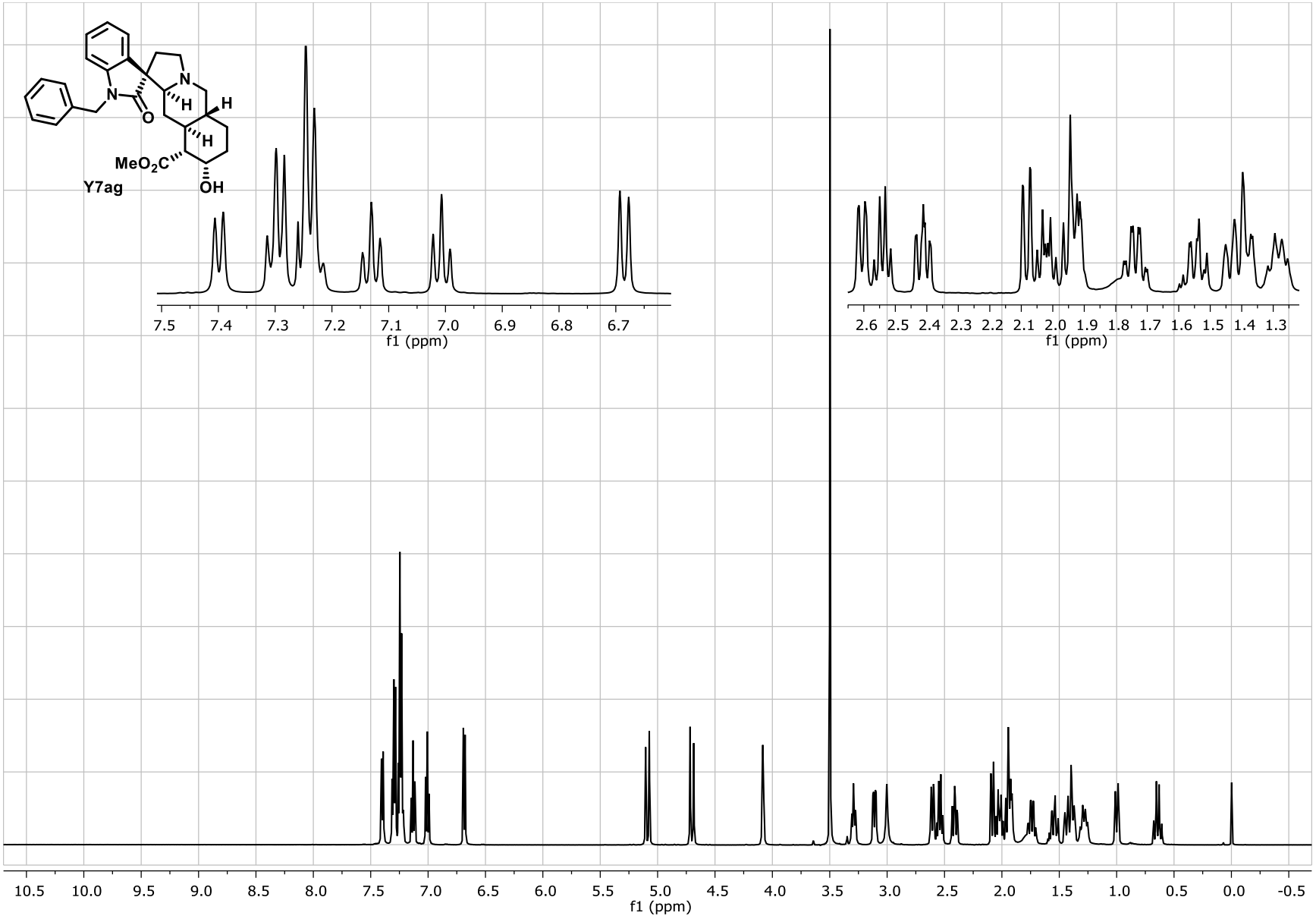

HN
O
N
H
H
H
MeO2C
O
Cl
Y7ad
141 140 139 138 137 136 135 134 133 132 131 130 129 128 127 126 125 124 123 122
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

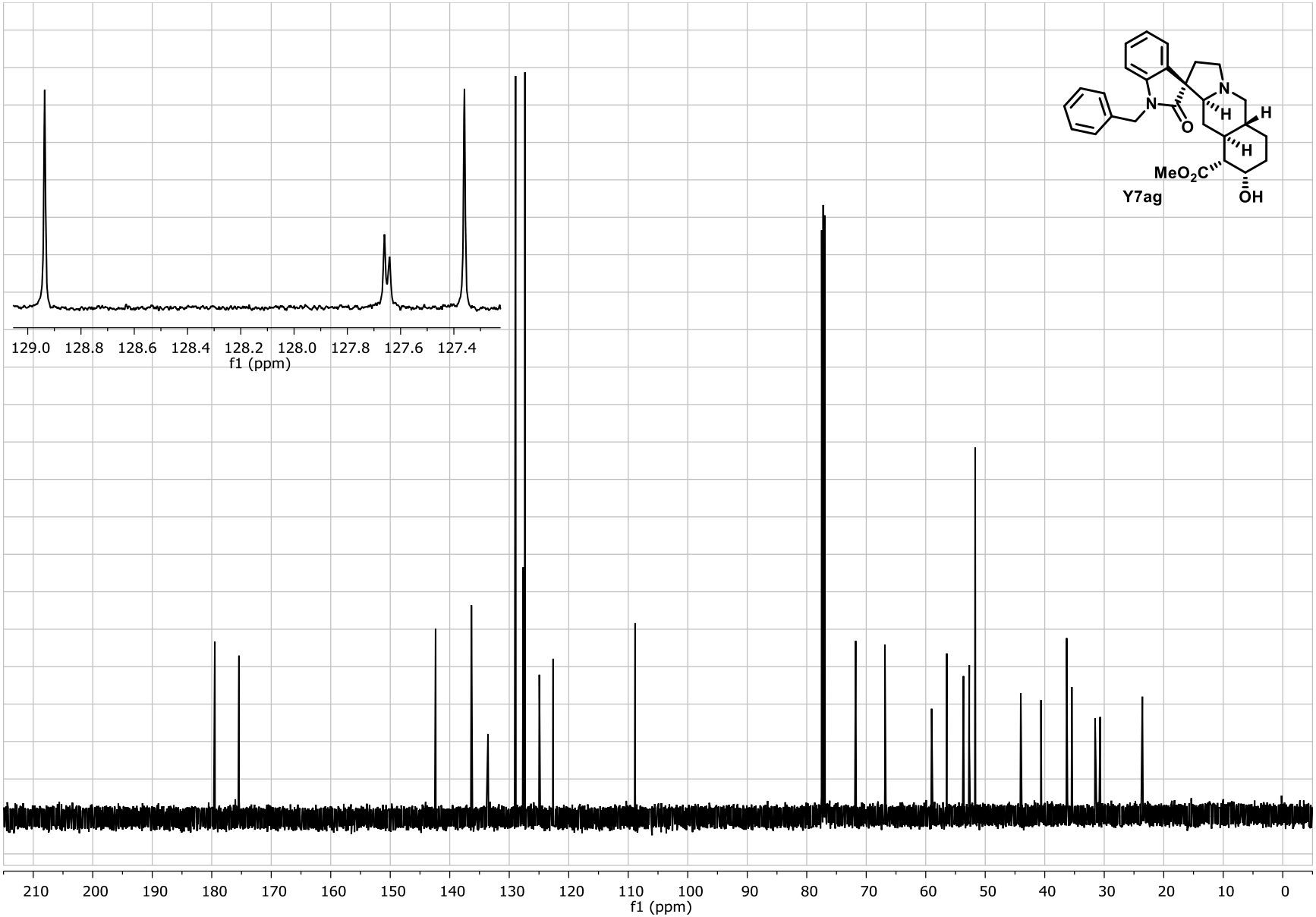

F
N
O
N
H
H
H
MeO2C
OH
Y7ae
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

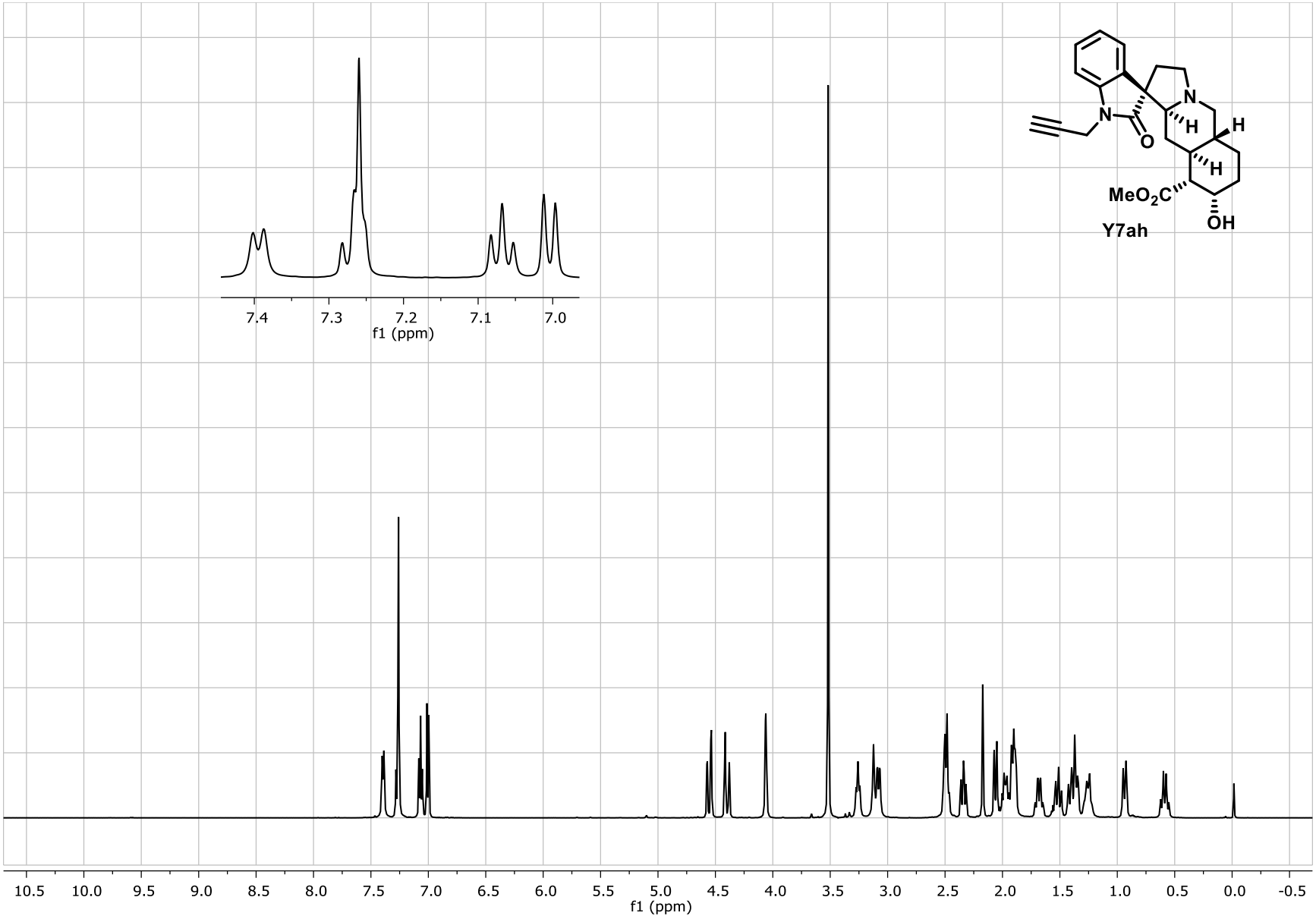

138.9 138.8
f1 (ppm)
130.56 130.48
f1 (ppm)
123.0 122.9 122.8
f1 (ppm)
114.5 114.0
f1 (ppm)
51.70 51.65
f1 (ppm)
43.6 43.5
f1 (ppm)
F
N
O
N
H
H
H
MeO2C
OH
Y7ae
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

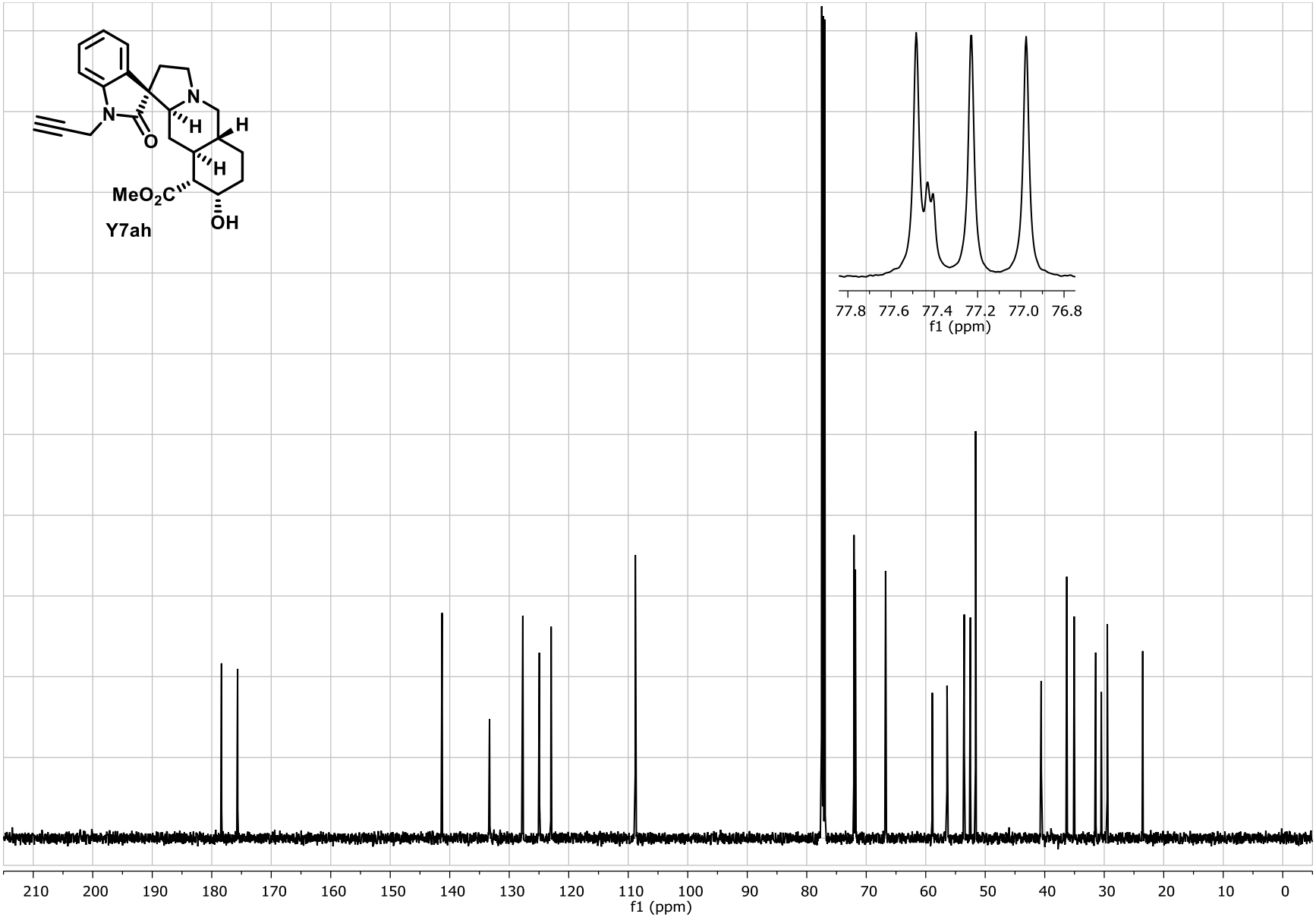

MeO
Cl
N
O
N
H
H
H
MeO2C
OH
Y7af
7.45 7.40 7.35 7.30 7.25 7.20 7.15 7.10 7.05 7.00 6.95 6.90 6.85 6.80 6.75 6.70
f1 (ppm)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

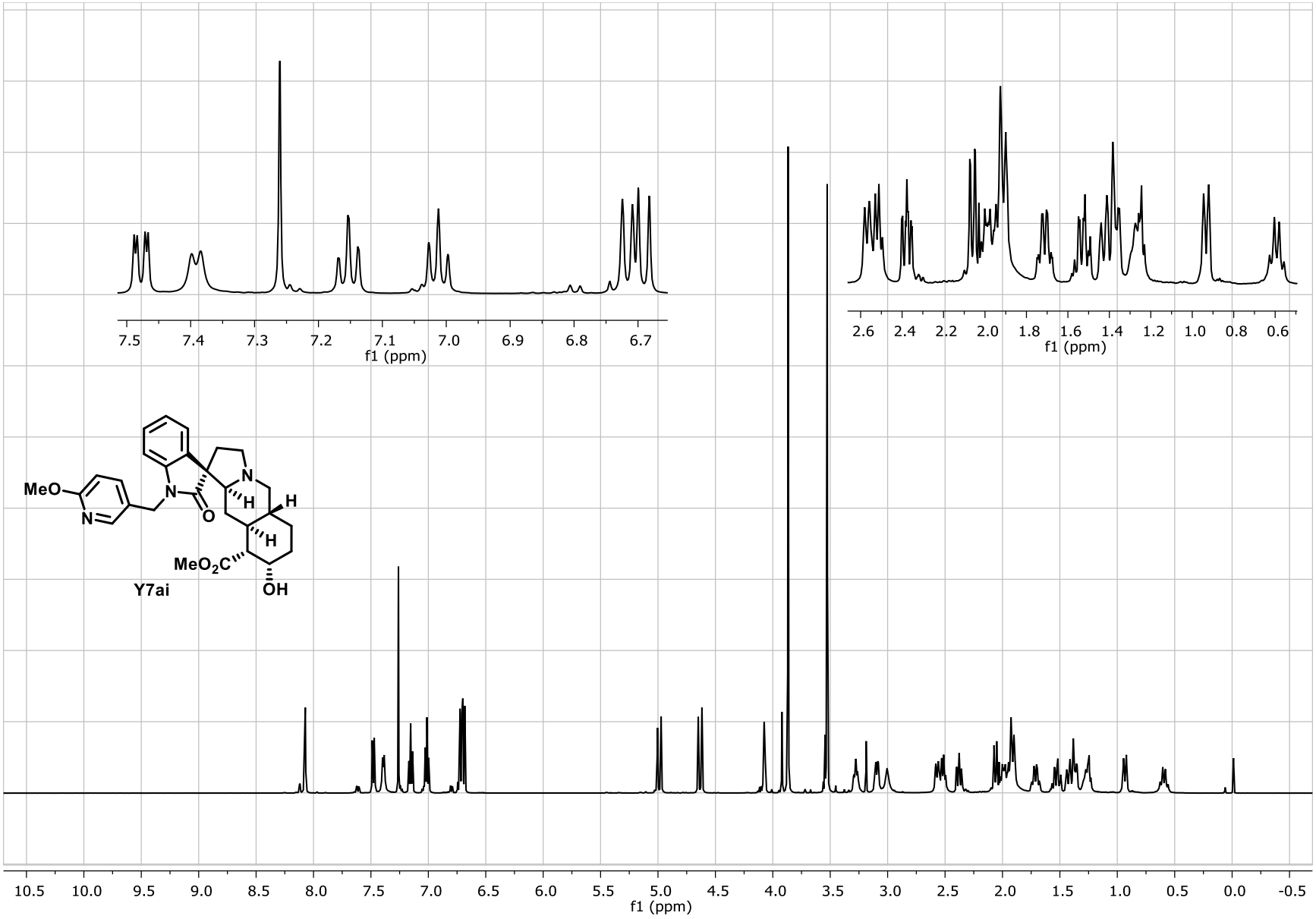

MeO
N
O
Cl
N
H
H
H
MeO2C
OH
Y7af
133.6
133.4
133.2
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

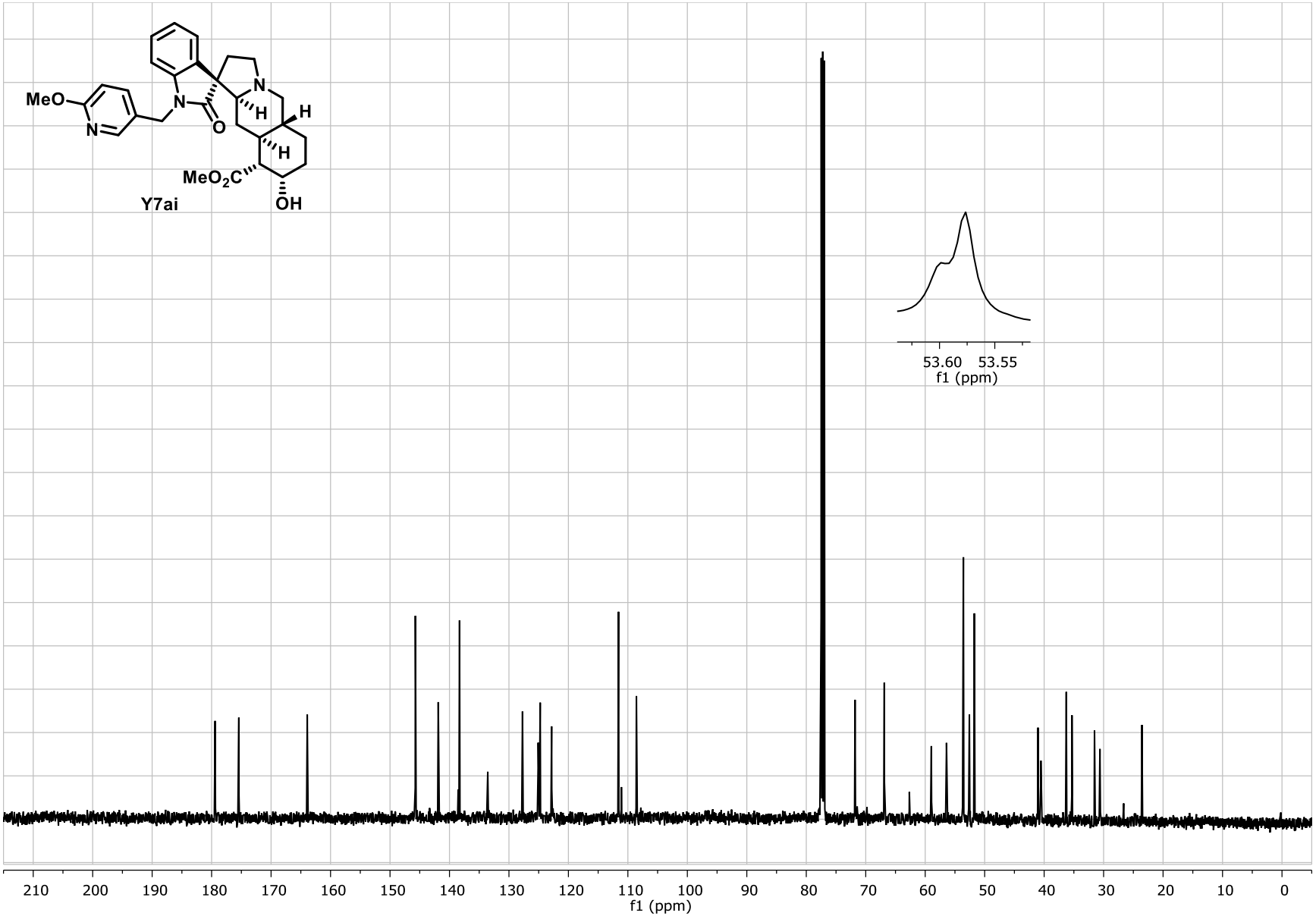

Y7ag
MeO2C
OH
H
H
H
N
N
O
7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7
f1 (ppm)
2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3
f1 (ppm)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

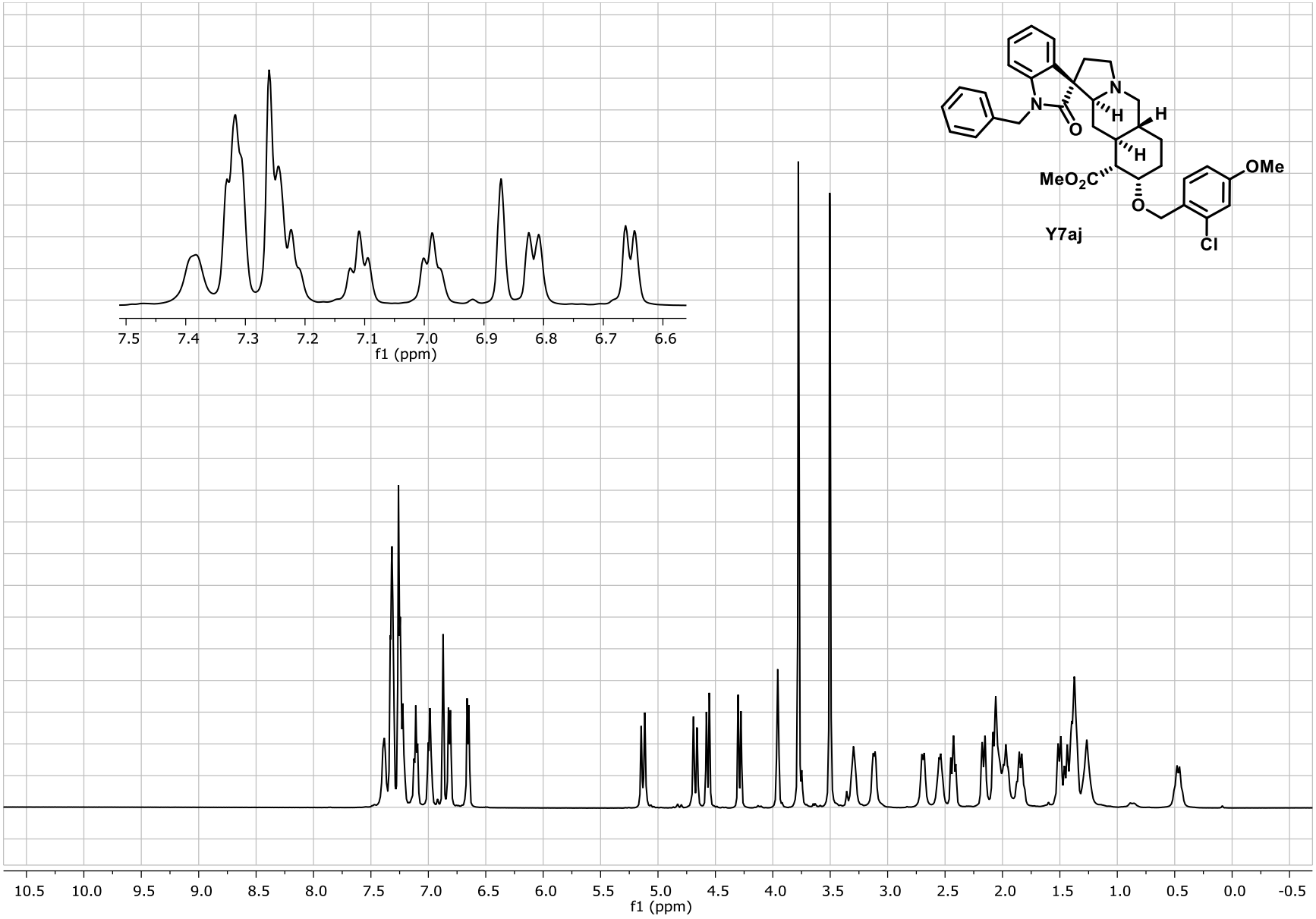

129.0 128.8 128.6 128.4 128.2 128.0 127.8 127.6 127.4
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
N
O
N
H
H
H
MeO2C
OH
Y7ag

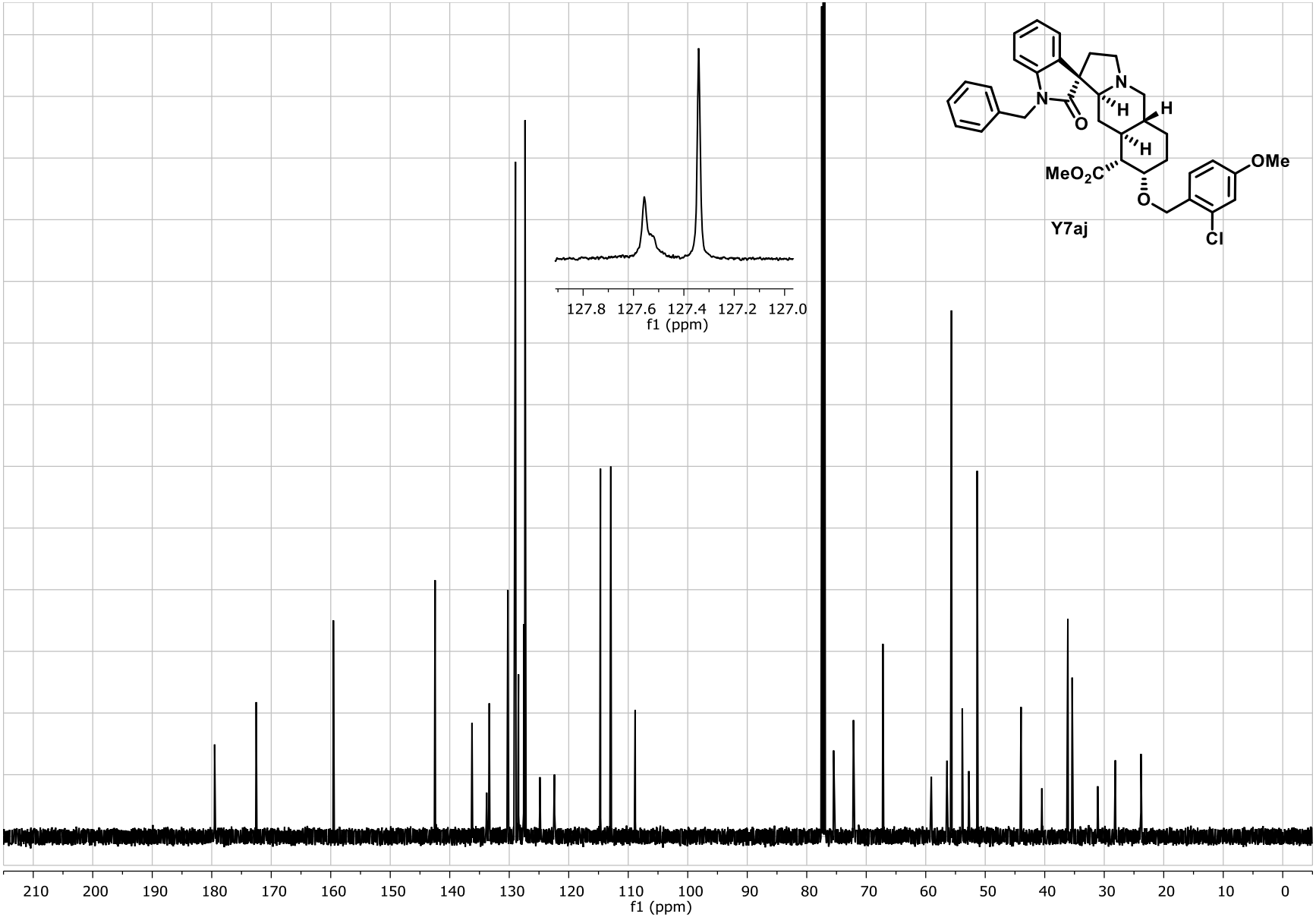

7.4
7.3
7.2
7.1
7.0
f1 (ppm)
N
N
O
H
H
H
MeO2C
OH
Y7ah
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

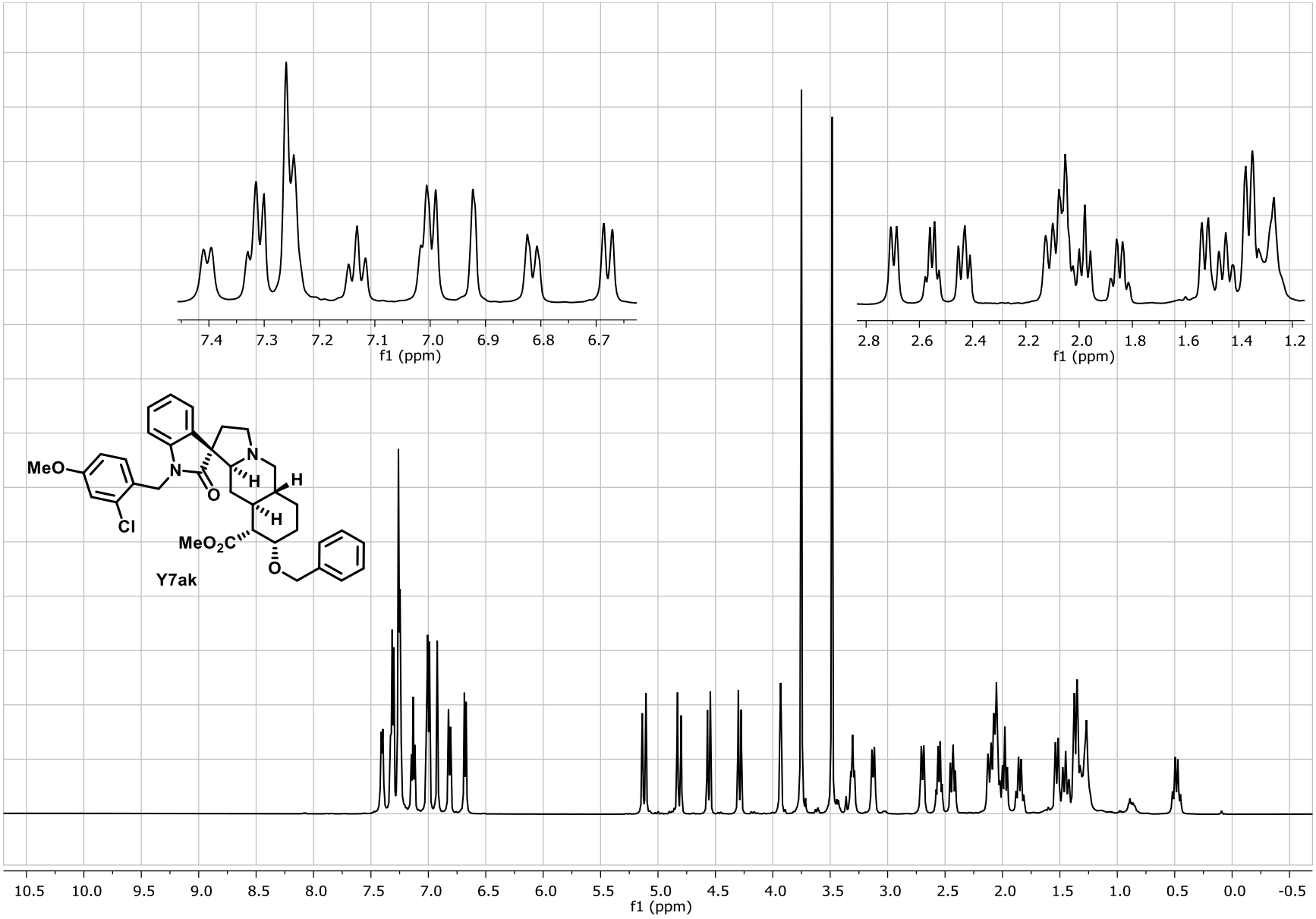

MeO2C
OH
Y7ah
77.8 77.6 77.4 77.2 77.0 76.8
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

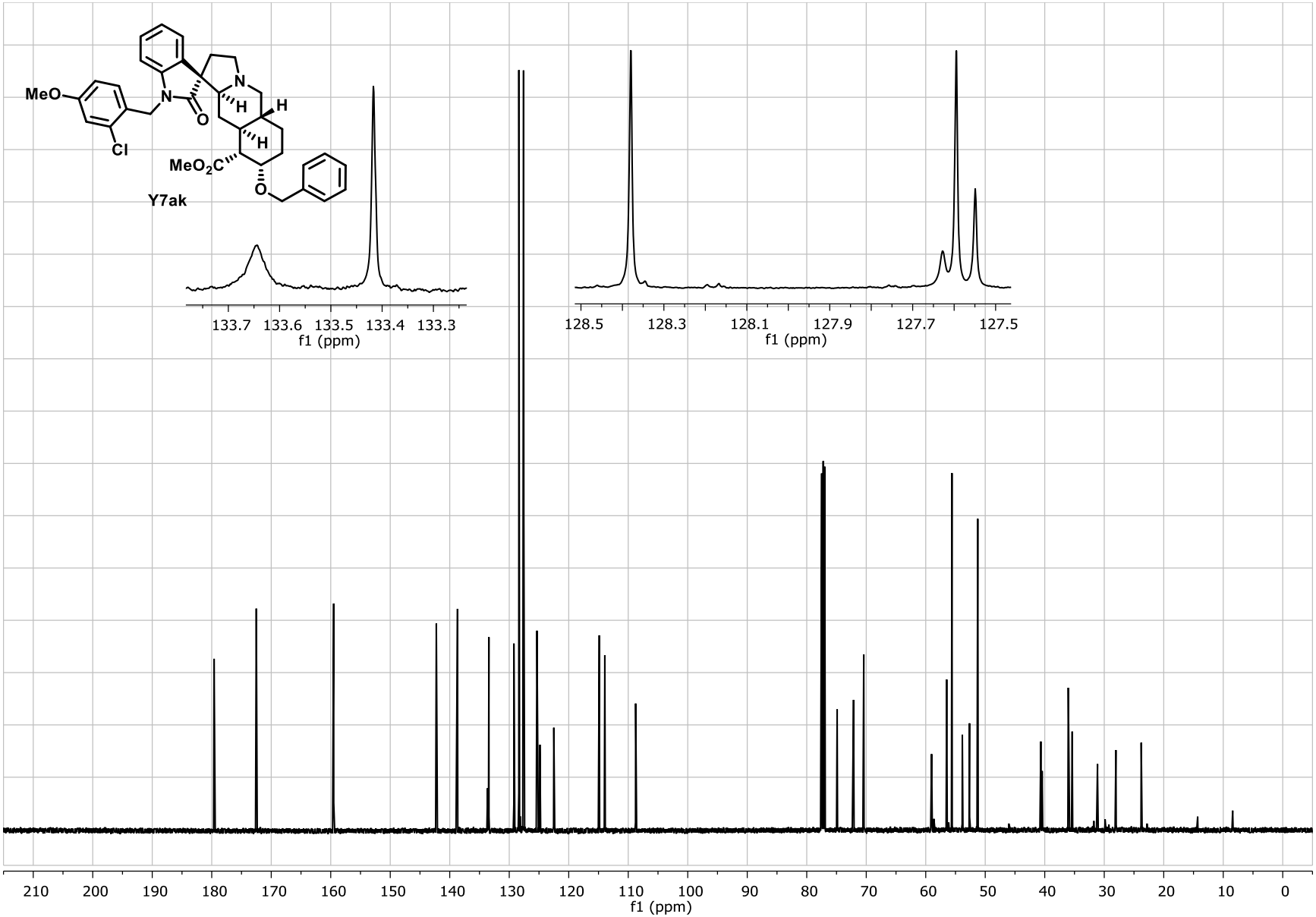

MeO
N
N
O
N
H
H
H
MeO2C
OH
Y7ai
7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7
f1 (ppm)
2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
f1 (ppm)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

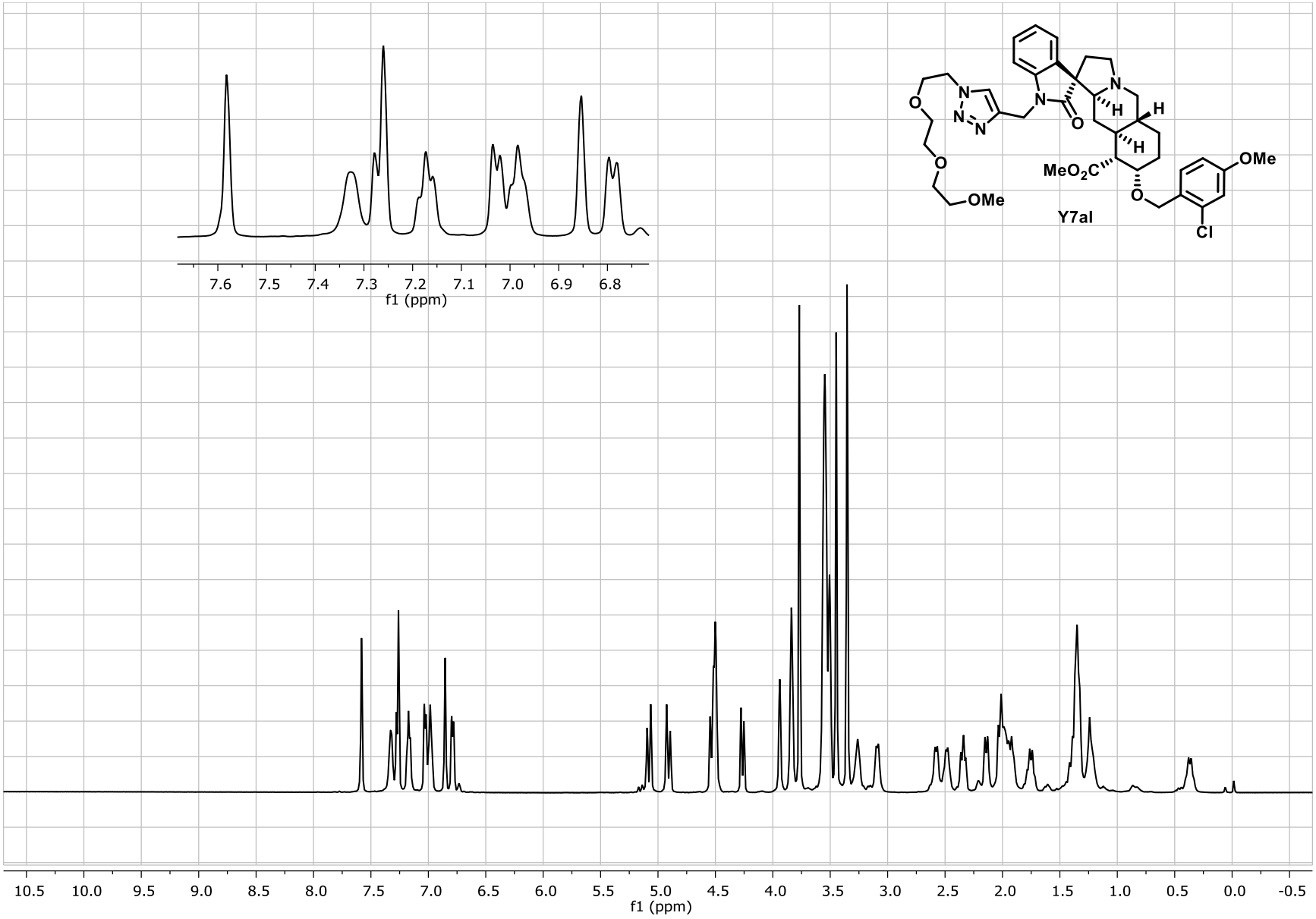

MeO
N
N
O
N
H
H
H
MeO2C
OH
Y7ai
53.60
53.55
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

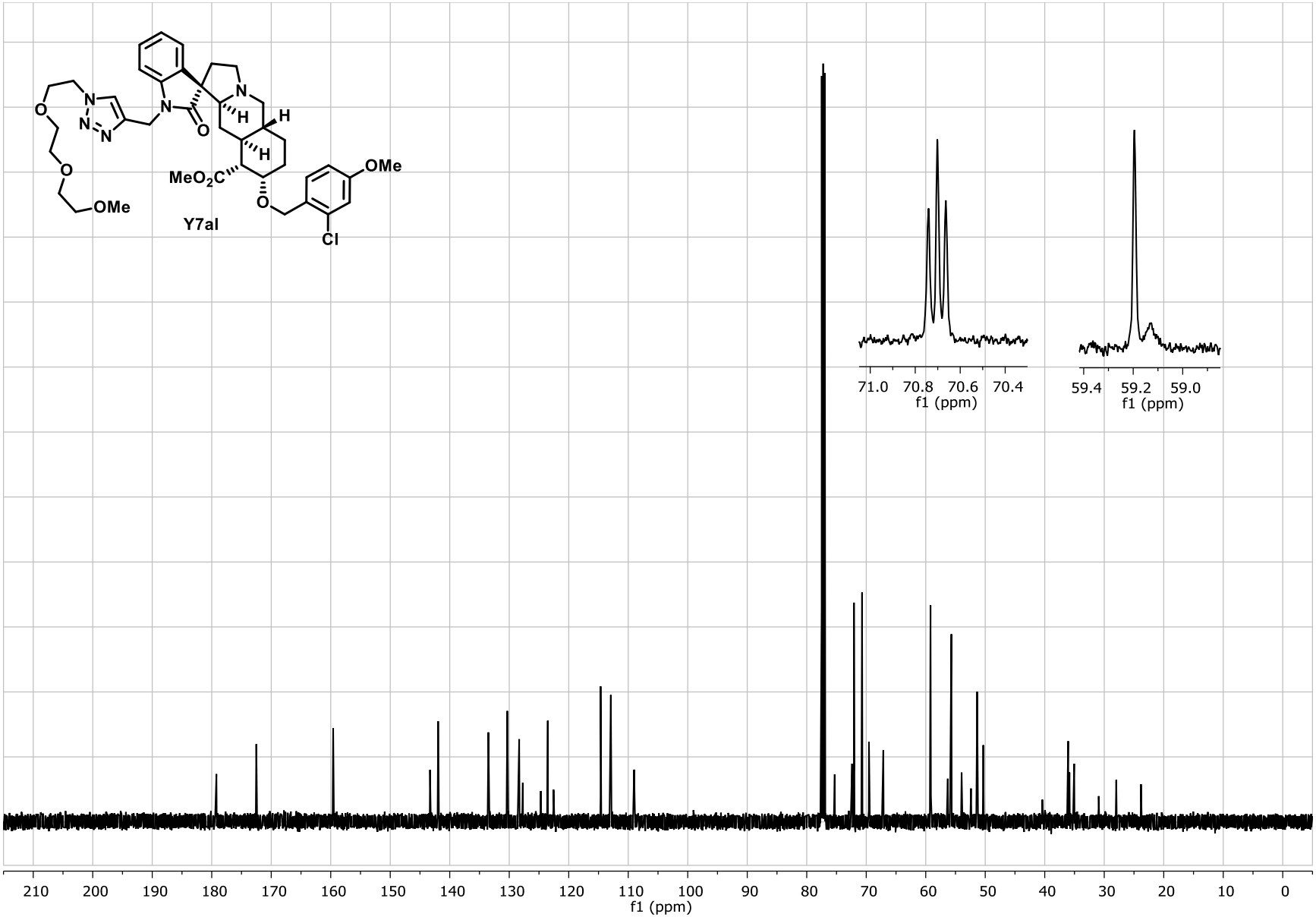

7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
f1 (ppm)
N
N
O
H
H
H
MeO2C
O
OMe
Cl
Y7aj
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

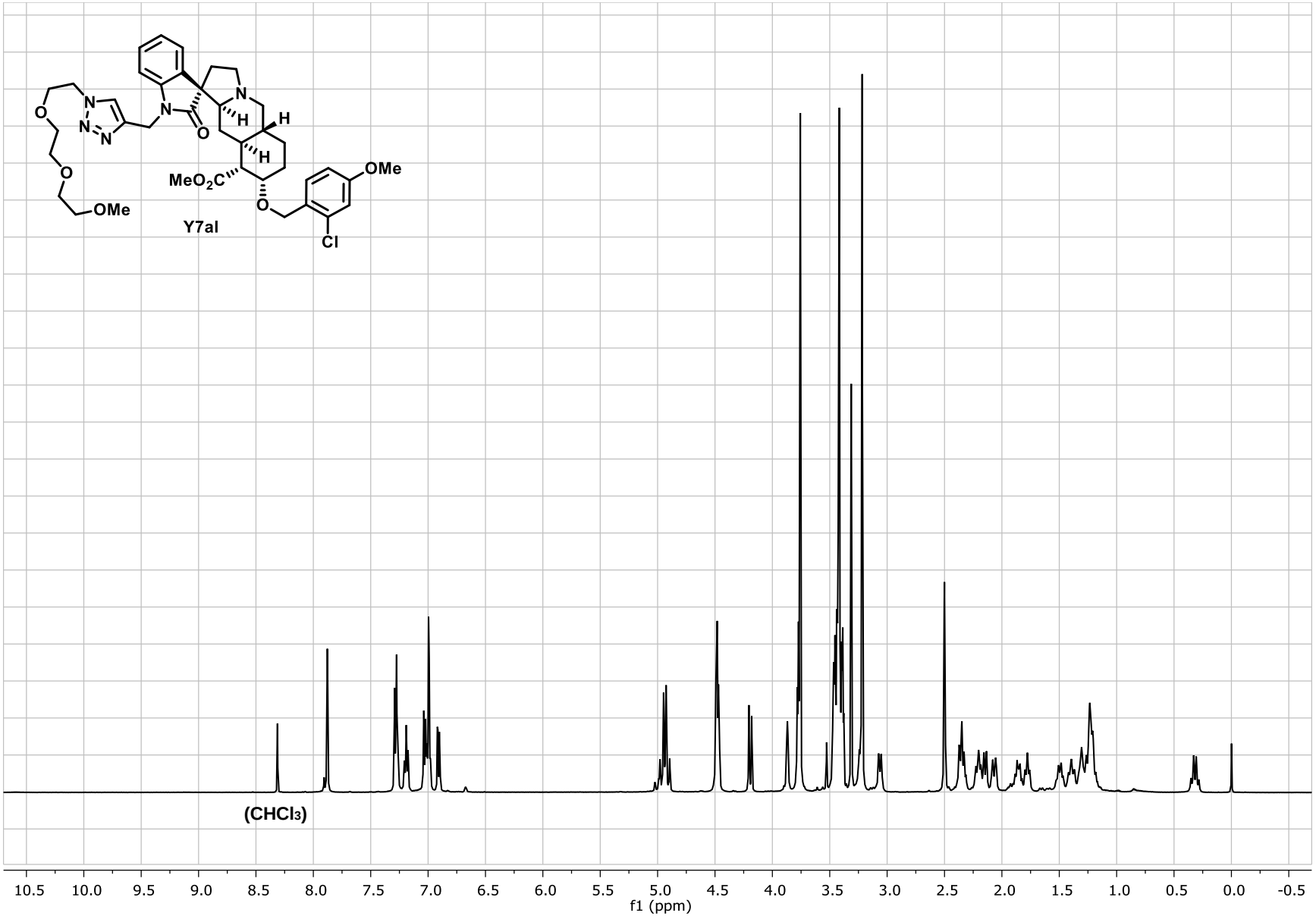

127.8 127.6 127.4 127.2 127.0
f1 (ppm)
N
O
H
H
H
MeO_2C
O
OMe
Cl
Y7aj
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

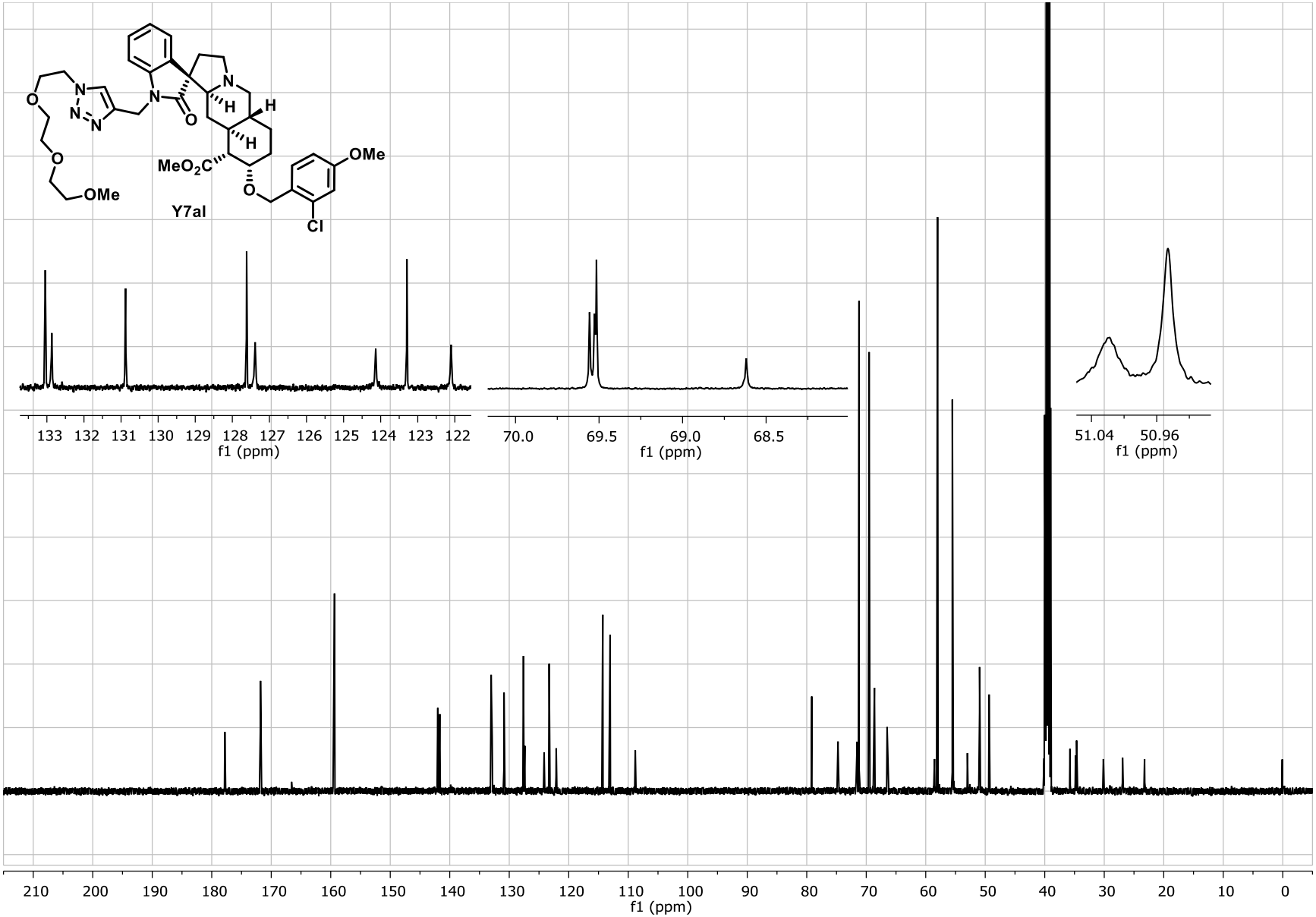

7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7
f1 (ppm)
2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2
f1 (ppm)
MeO
Cl
N
O
N
H
H
H
MeO2C
O
Y7ak
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

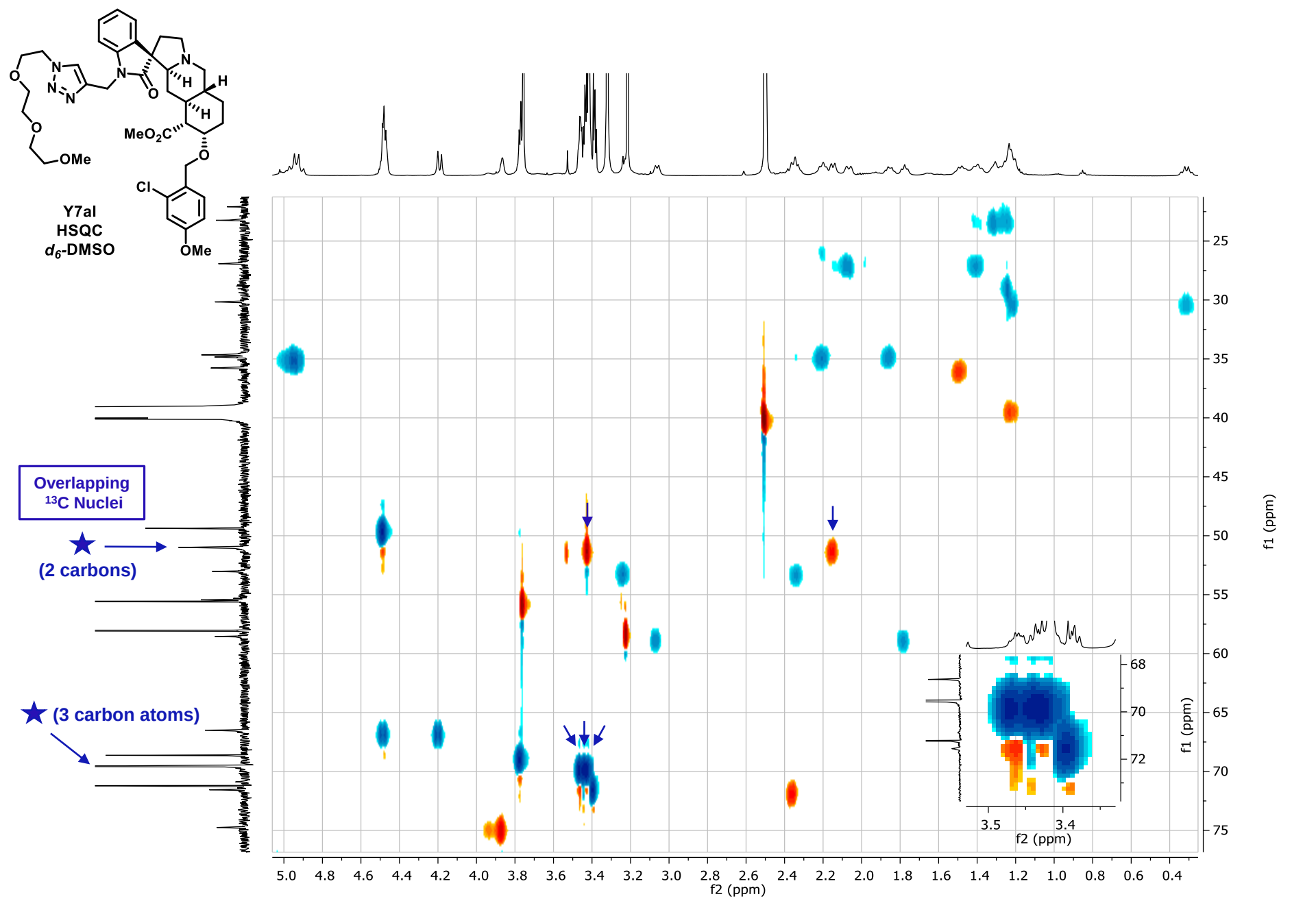

MeO
Cl
N
O
H
H
H
MeO_2C
O
Y7ak
133.7 133.6 133.5 133.4 133.3
f1 (ppm)
128.5 128.3 128.1 127.9 127.7 127.5
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

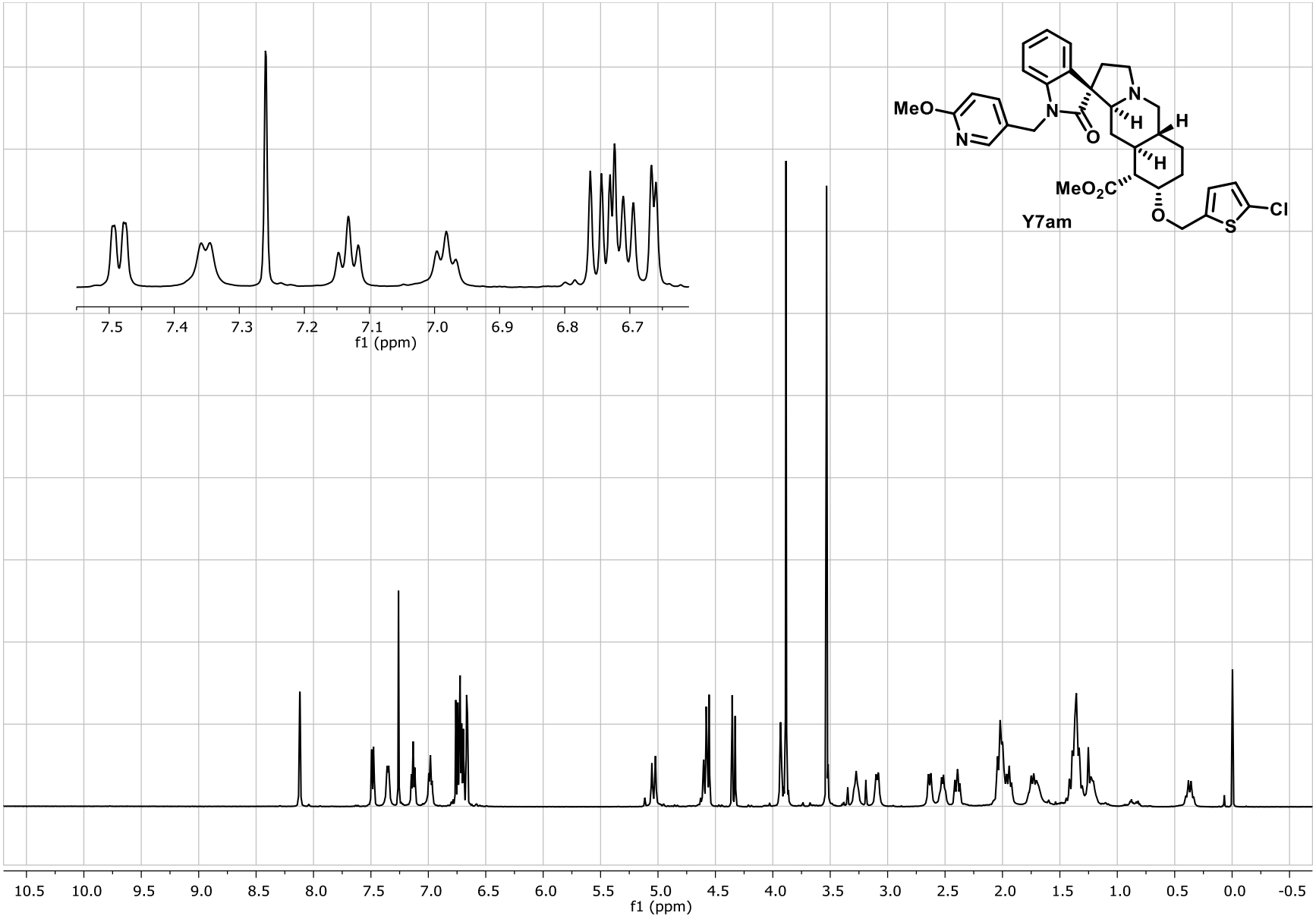

7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8
f1 (ppm)
OMe
MeO2C
OMe
Cl
Y7al
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

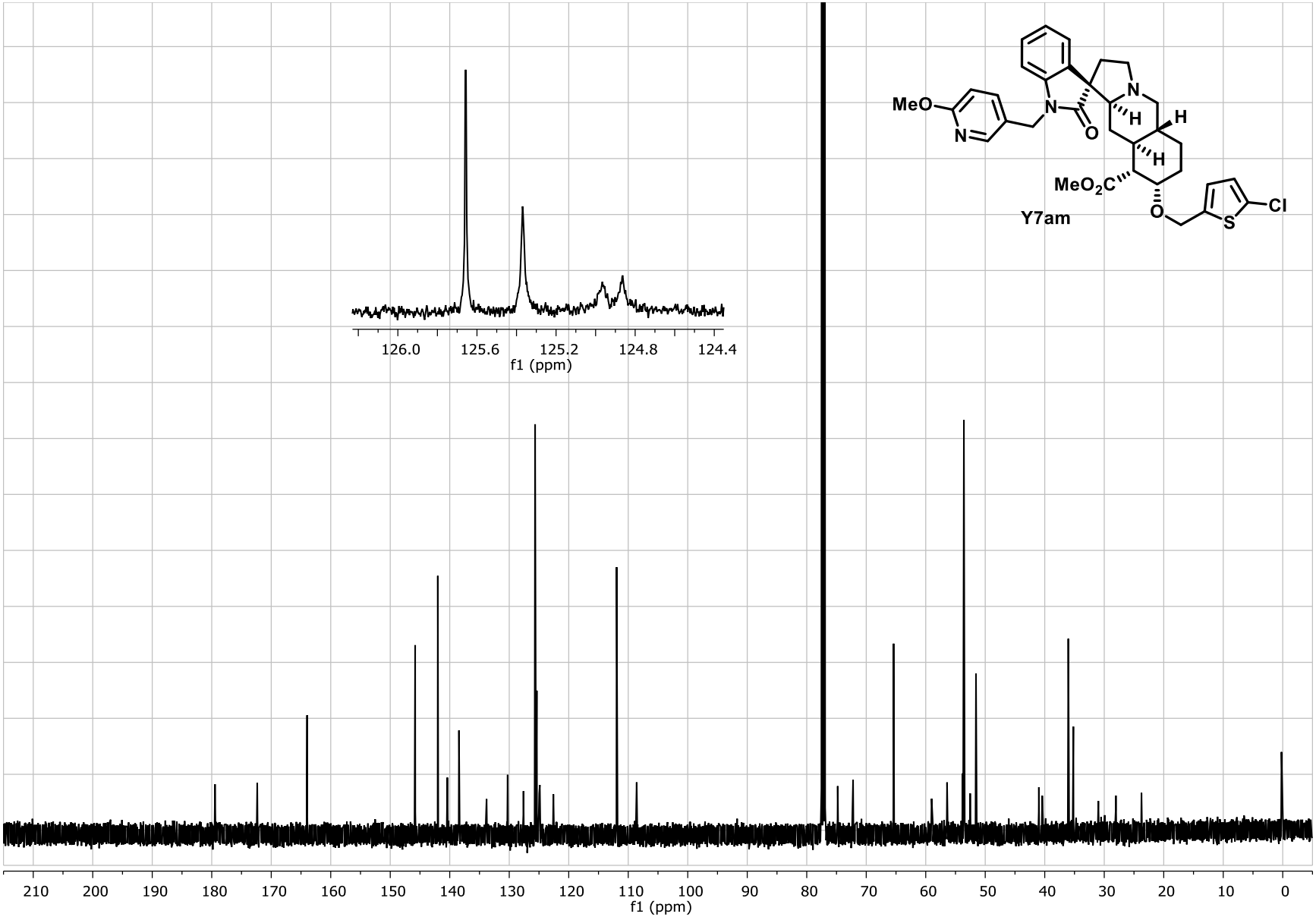

Y7al
71.0 70.8 70.6 70.4
f1 (ppm)
59.4 59.2 59.0
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

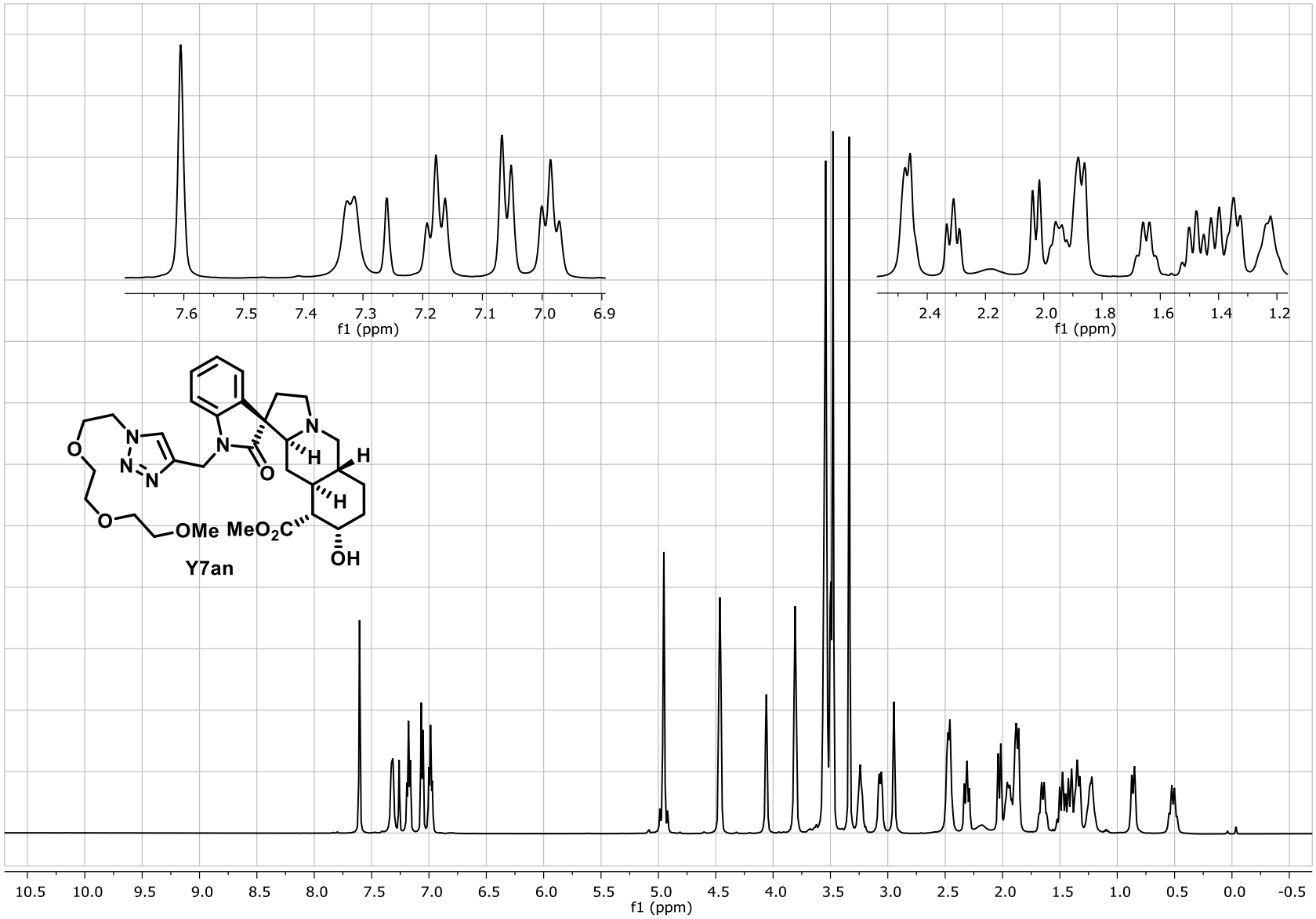

Y7al
(CHCl3)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

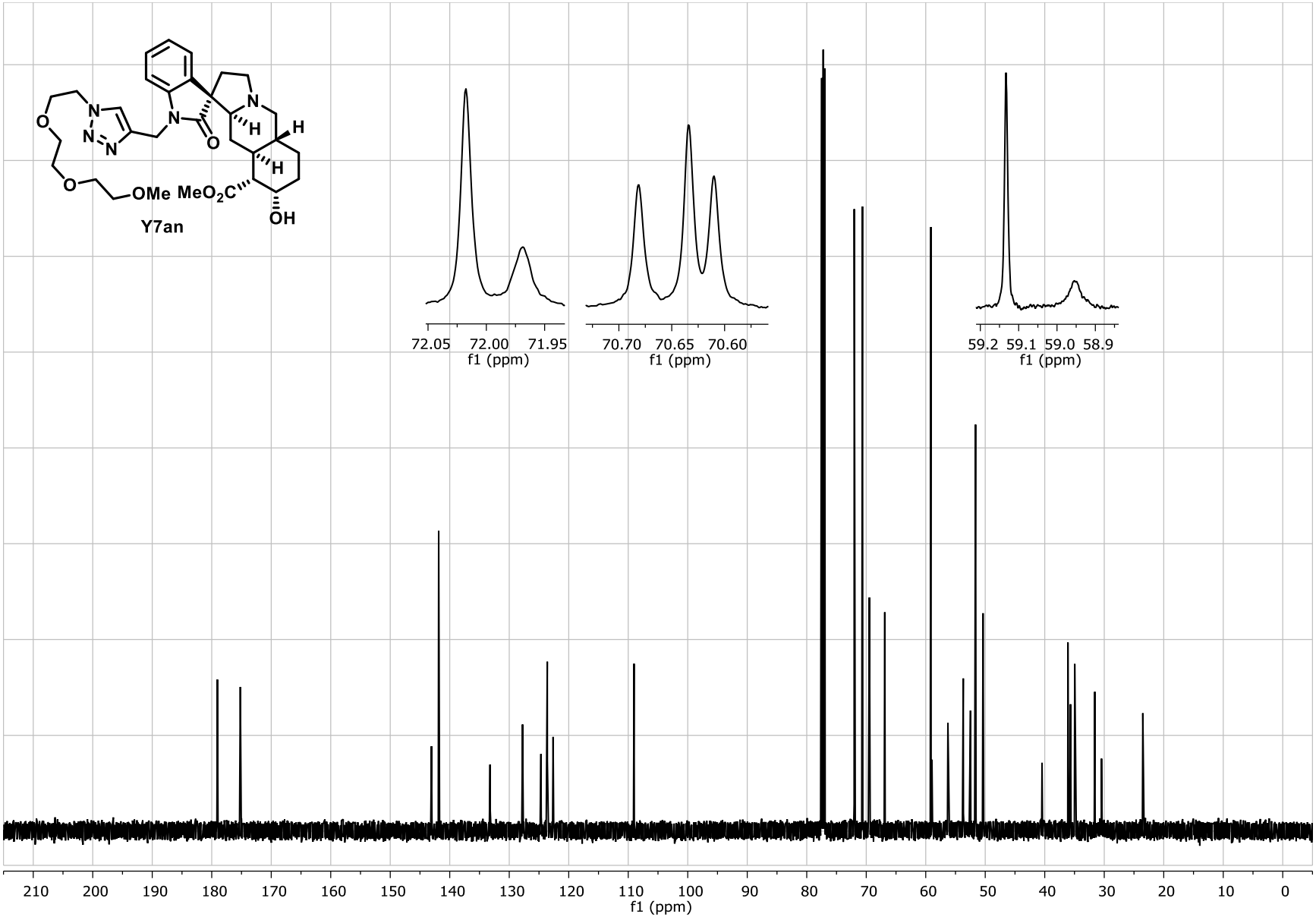

Y7al
133 132 131 130 129 128 127 126 125 124 123 122
f1 (ppm)
70.0 69.5 69.0 68.5
f1 (ppm)
51.04 50.96
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Y7al
HSQC
d_6-DMSO
Overlapping
^{13}C Nuclei
(2 carbons)
(3 carbon atoms)
f2 (ppm)
f1 (ppm)


MeO
N
N
O
N
H
H
H
MeO2C
O
S
Cl
Y7am
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
f1 (ppm)
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
f1 (ppm)


MeO
N
N
O
N
H
H
H
MeO2C
O
S
Cl
Y7am
126.0
125.6
125.2
124.8
124.4
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9
f1 (ppm)
2.4 2.2 2.0 1.8 1.6 1.4 1.2
f1 (ppm)
Y7an
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
f1 (ppm)


Y7an
72.05 72.00 71.95
f1 (ppm)
70.70 70.65 70.60
f1 (ppm)
59.2 59.1 59.0 58.9
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)