Electronic Supplementary Material (ESI) for RSC Advances.

Discovery of Indolizines Lactones as Anticancer agents and their Optimization through Late-Stage Functionalization.

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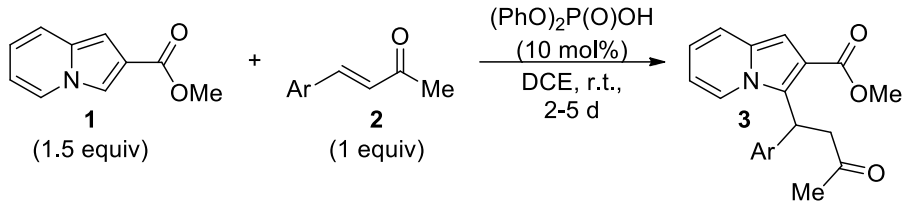
1. General information

Unless otherwise noted, commercially available chemicals and solvents were used without further purification All reactions were performed under ambient atmosphere in oven-dried open-flask glassware with magnetic stirring. Reaction progress was monitored by thin-layer chromatography (TLC) performed on silica gel (aluminum foils). The TLC plates were visualized with UV light (254 nm and/or 365 nm) and sulfuric vanillin followed by heating. Products purifications were carried out by flash column chromatography using silica gel (230–400 mesh). ^{1}H NMR and proton-decoupled ^{13}C NMR spectra were measured at 250, 400, 500 MHz ^{1}H NMR and 63, 101,126 MHz for ^{13}C NMR, in $CDCl_3$, CD_3CN at room temperature. Chemical shifts (δ) were reported in ppm and the coupling constants (J) in Hertz (Hz). Signal multiplicity was assigned as singlet (s), doublet (d), double doublet (dd), double triplet (dt), double of double doublet (ddd), triplet (t), triple doublet (td), multiplet (m), and broad singlet (bs). High- resolution mass spectrometry (HRMS) of unknown compounds was performed using electrospray ionization (ESI) on a Thermo Scientific® Q Exactive® Quadrupole-Orbitrap mass spectrometer. Melting points were uncorrected. Methyl indolizine-2-carboxylate **1** and methyl cinnamyl enones **2** were synthetized according to previous procedures.[1]

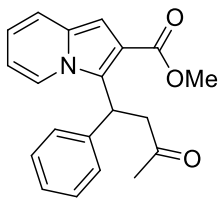
2. Supplementary methods

Synthesis of the conjugate adducts 3



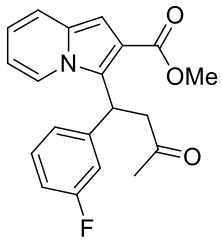
In a 4 mL dram vial, methyl indolizine-2-carboxylate **1** (87.6 mg, 0.5 mmol, 1.5 equiv.), enone **2** (0.33 mmol, 1.0 equiv.) and diphenyl phosphoric acid (8.34 mg, 0.033 mmol, 0.1 equiv.) were dissolved in 1,2-dichloroethane (0.5 mL) and stirred at room temperature for the indicated time . The organic solvent was removed under reduced pressure and the crude residue purified by column chromatography.

Methyl 3-(3-oxo-1-phenylbutyl)indolizine-2-carboxylate (3a)[1]



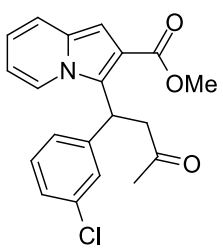
Reaction time: 2 days. **Purification**: Hexane/Ethyl Acetate 90:10. **Yield**: 67% (71,8 mg) as a viscous pale yellow oil. **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.70 (dd, *J* = 7.3, 0.8 Hz, 1H), 7.34 (dt, *J* = 9.1, 1.1 Hz, 1H), 7.26 – 7.24 (m, 2H), 7.20 – 7.18 (m, 3H) 7.19 (d, *J* = 7.5 Hz, 1H), 6.89 (s, 1H), 6.63 (ddd, *J* = 9.0, 6.4, 0.8 Hz, 1H), 6.42 (ddd, *J* = 7.6, 6.5, 1.3 Hz, 1H), 6.00 (t, *J* = 7.2 Hz, 1H), 3.88 (s, 3H), 3.57 (dd, *J* = 16.7, 7.4 Hz, 1H), 3.39 (dd, *J* = 16.7, 7.1 Hz, 1H), 2.16 (s, 3H). **NMR ^{13}C (101 MHz, $CDCl_3$)** δ 206.93, 166.15, 140.24, 131.80, 128.69, 127.11, 126.60, 123.00, 120.59, 117.66, 116.92, 112.13, 101.63, 51.51, 45.76, 35.30, 29.81.

Methyl 3-(1-(3-fluorophenyl)-3-oxobutyl)indolizine-2-carboxylate (3b)



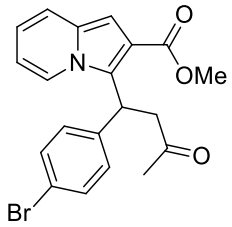
Reaction time: 2 days. **Purification:** Hex/Ethyl acetate 90:10 **Yield**: 57% (64.6 mg) as a viscous colorless oil. **NMR ^{1}H (250 MHz, $CDCl_3$)** δ 7.70 (dd, *J* = 7.3, 0.8 Hz, 1H), 7.35 (dt, *J* = 9.1, 1.2 Hz, 1H), 7.23 – 7.17 (m, 1H), 7.07 – 6.80 (m, 1H), 6.66 (ddd, *J* = 9.1, 6.5, 0.8 Hz, 1H), 6.46 (ddd, *J* = 7.7, 6.6, 1.3 Hz, 1H), 5.94 (t, *J* = 7.0 Hz, 1H), 3.56 (dd, *J* = 17.0, 7.3 Hz, 1H), 3.40 (dd, *J* = 17.0, 6.9 Hz, 1H), 2.15 (s, 1H). **NMR ^{13}C (63 MHz, $CDCl_3$)** δ 206.61 (s), 166.10 (s), 163.15 (d, *J* = 246.0 Hz), 143.18 (d, *J* = 6.8 Hz), 131.95 (s), 130.15 (d, *J* = 8.3 Hz), 128.06 (s), 122.83 (s), 122.78 (s), 120.73 (s), 117.86 (s), 117.06 (s), 114.37 (d, *J* = 22.1 Hz), 113.64 (d, *J* = 21.1 Hz), 112.44 (s), 101.83 (s), 51.63 (s), 45.84 (s), 35.01 (d, *J* = 1.7 Hz), 29.94 (s). **HRMS** (ESI, m/z): calcd for $C_{20}H_{19}FNO_3^+$, 340.13435 $[M + H]^+$; found, 340.13404.

Methyl 3-(1-(3-chlorophenyl)-3-oxobutyl)indolizine-2-carboxylate (3c)[1]



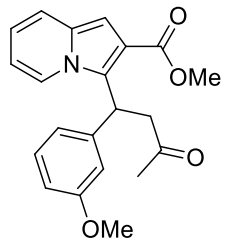
Reaction Time: 2 days. **Purification**: 90:10 Hexane/Ethyl acetate. **Yield**: starting from 51.3 mg of **2c** (0.284 mmol), 54% (54.6 mg) as a viscous pale yellow oil. **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.71 (d, *J* = 7.4 Hz, 1H), 7.36 (dt, *J* = 9.1, 1.0 Hz, 1H), 7.19 – 7.15 (m, 3H), 6.66 (ddd, *J* = 9.0, 6.5, 0.8 Hz, 1H), 6.47 (ddd, *J* = 7.5, 6.5, 1.2 Hz, 1H), 5.90 (t, *J* = 6.8 Hz, 1H), 3.88 (s, 3H), 3.55 (dd, *J* = 17.1, 7.2 Hz, 1H), 3.41 (dd, *J* = 17.1, 7.0 Hz, 1H), 2.15 (s, 3H). **NMR ^{13}C (101 MHz, $CDCl_3$)** δ 206.52, 166.07, 142.66, 134.63, 131.96, 129.92, 127.91, 127.43, 126.93, 125.43, 122.78, 120.74, 117.89, 117.09, 112.49, 101.88, 51.63, 45.81, 34.97, 29.96.

Methyl 3-(1-(4-bromophenyl)-3-oxobutyl)indolizine-2-carboxylate (3d)[1]



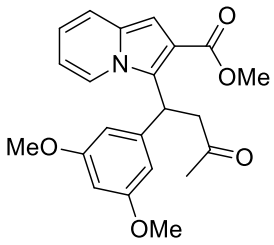
Reaction Time: 2 days. **Purification**: 90:10 Hexane/Ethyl acetate **Yield**: 61% (81,5 mg) as a viscous incolor oil. **NMR ^{1}H (250 MHz, $CDCl_3$)** δ 7.71 (dd, *J* = 7.3, 0.7 Hz, 1H), 7.43 – 7.30 (m, 3H), 7.15 – 7.01 (m, 2H), 6.88 (s, 1H), 6.65 (ddd, *J* = 9.0, 6.5, 0.8 Hz, 1H), 6.46 (ddd, *J* = 7.7, 6.6, 1.3 Hz, 1H), 5.85 (t, *J* = 7.1 Hz, 1H), 3.87 (s, 3H), 3.55 (dd, *J* = 17.1, 7.3 Hz, 1H), 3.40 (dd, *J* = 17.1, 6.9 Hz, 1H), 2.14 (s, 3H). **NMR ^{13}C (63 MHz, $CDCl_3$)** δ 206.69, 166.08, 139.55, 131.90, 131.74, 129.01, 128.15, 122.76, 120.71, 120.52, 117.86, 116.96, 112.45, 101.84, 51.62, 45.87, 34.80, 29.95.

Methyl 3-(1-(3-methoxyphenyl)-3-oxobutyl)indolizine-2-carboxylate (3e)[1]



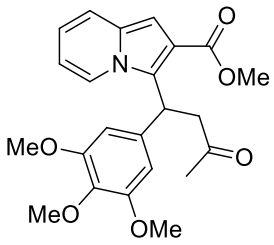
Reaction Time: 2 days. **Purification**: 75:25 - 80:20 Hexane/Ethyl acetate. **Yield**: 62% (72,3 mg) as a colorless oil. **NMR ^{1}H (500 MHz, $CDCl_3$)** δ 7.69 (d, *J* = 7.3 Hz, 1H), 7.33 (d, *J* = 9.0 Hz, 1H), 7.18 (t, *J* = 7.9 Hz, 1H), 6.87 (s, 1H), 6.81 – 6.69 (m, 3H), 6.63 (dd, *J* = 8.7, 6.7 Hz, 1H), 6.43 – 6.39 (m, 1H), 5.98 (t, *J* = 6.8 Hz, 1H), 3.89 (s, 3H), 3.72 (s, 3H), 3.54 (dd, *J* = 16.7, 7.5 Hz, 1H), 3.36 (dd, *J* = 16.6, 7.0 Hz, 1H), 2.15 (s, *J* = 53.1 Hz, 3H). **NMR ^{13}C (126 MHz, $CDCl_3$)** δ 206.93, 166.24, 159.97, 141.98, 131.88, 129.72, 128.50, 123.13, 120.64, 119.52, 117.72, 116.98, 113.59, 112.20, 111.57, 101.66, 55.24, 51.58, 45.82, 35.38, 29.85.

Methyl 3-(1-(3,5-dimethoxyphenyl)-3-oxobutyl)indolizine-2-carboxylate (3f)



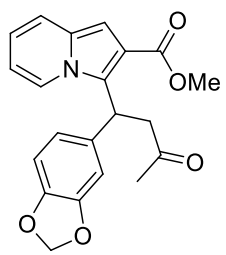
Reaction Time: 2 days. **Purification**: 85:15 Hexane/Ethyl acetate. **Yield**: 70% (88,4 mg) as a colorless oil. **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.69 (dd, *J* = 7.3, 0.6 Hz, 1H), 7.32 (dt, *J* = 9.1, 1.0 Hz, 1H), 6.86 (s, 1H), 6.62 (ddd, *J* = 9.0, 6.5, 0.8 Hz, 1H), 6.41 (ddd, *J* = 7.6, 6.5, 1.3 Hz, 1H), 6.36 (dd, *J* = 2.2, 0.7 Hz, 2H), 6.28 (t, *J* = 2.2 Hz, 1H), 5.96 (t, *J* = 7.2 Hz, 1H), 3.88 (s, *J* = 6.7 Hz, 3H), 3.69 (s, 6H), 3.50 (dd, *J* = 16.6, 7.5 Hz, 1H), 3.31 (dd, *J* = 16.6, 7.0 Hz, 1H), 2.14 (s, 3H). **NMR ^{13}C (101 MHz, $CDCl_3$)** δ 206.82, 166.24, 161.09, 142.78, 131.87, 128.25, 123.19, 120.59, 117.70, 116.96, 112.18, 105.71, 101.60, 98.09, 55.31, 51.55, 45.74, 35.55, 29.78. **HRMS** (ESI, m/z): calcd for $C_{22}H_{24}NO_5$, 382.16490 $[M + H]^+$; found, 382.16509

Methyl 3-(3-oxo-1-(3,4,5-trimethoxyphenyl)butyl)indolizine-2-carboxylate (3g)



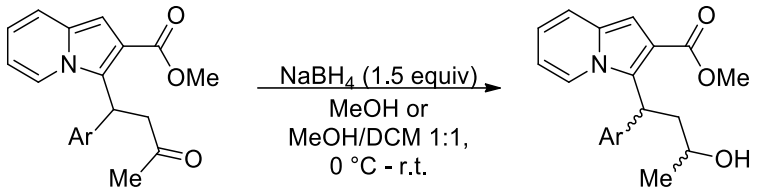
Reaction Time: 3 days. **Yield**: 66% (90,5 mg) as a colorless oil. **Purification**: Hexane/Ethyl acetate 80:20 to 70:30. **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.74 (d, *J* = 7.3 Hz, 1H), 7.36 (dt, *J* = 9.1, 1.1 Hz, 1H), 6.89 (s, 1H), 6.66 (ddd, *J* = 8.9, 6.4, 0.6 Hz, 1H), 6.53 – 6.45 (m, 3H), 5.88 (t, *J* = 7.1 Hz, 1H), 3.91 (s, 3H), 3.80 (s, 3H), 3.76 (s, 6H), 3.52 (dd, *J* = 16.6, 7.7 Hz, 1H), 3.40 (dd, *J* = 16.6, 6.7 Hz, 1H), 2.17 (s, 3H). **NMR ^{13}C (101 MHz, $CDCl_3$)** δ 207.04, 166.23, 153.33, 136.75, 136.06, 131.76, 128.26, 123.03, 120.53, 117.69, 116.80, 112.19, 104.57, 101.64, 60.80, 56.14, 51.53, 46.50, 35.78, 29.73. **HRMS** (ESI, m/z): calcd for $C_{23}H_{26}NO_5$, 412.17546 $[M + H]^+$; found, 412.17491.

Methyl 3-(1-(benzo[d][1,3]dioxol-5-yl)-3-oxobutyl)indolizine-2-carboxylate (3h)[1]



Reaction Time: 5 days. **Yield**: 55% (67,2 mg) de um óleo incolor **Purification**: 80:20 Hexane/Ethyl acetate. **NMR ^{1}H (500 MHz, $CDCl_3$)** δ 7.72 (dd, *J* = 7.4, 0.6 Hz, 1H), 7.34 (dt, *J* = 9.1, 1.0 Hz, 1H), 6.87 (d, *J* = 4.4 Hz, 1H), 6.71 – 6.67 (m, 3H), 6.64 (ddd, *J* = 9.0, 6.4, 0.8 Hz, 1H), 6.44 (ddd, *J* = 7.6, 6.6, 1.3 Hz, 1H), 5.88 - 5.87 (m, 3H), 3.89 (s, *J* = 2.5 Hz, 3H), 3.51 (dd, *J* = 16.7, 7.6 Hz, 1H), 3.34 (dd, *J* = 16.7, 6.9 Hz, 1H), 2.14 (s, *J* = 2.7 Hz, 3H). **NMR ^{13}C (126 MHz, $CDCl_3$)** δ 206.95, 166.23, 148.13, 146.31, 134.19, 131.85, 128.67, 123.05, 120.66, 119.94, 117.73, 116.84, 112.25, 108.25, 108.13, 101.68, 101.10, 51.61, 46.12, 35.19, 29.86.

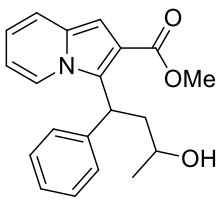
Synthesis of hydroxyesters 5



3 **5**

To a solution of conjugate adduct **3** in methanol (0.1M) or dichloromethane/methanol (1:1, 0.1M) was added sodium borohydride (1.5 equiv.) in portions at 0 °C and the reaction was stirred at room temperature until the total consumption of starting material (15 to 60 min). A saturated solution of ammonium chloride was added and the aqueous phase washed with dichloromethane (3x). The organic phase was combined, dried with Na_2SO_4, concentrated under reduced pressure and purified by column chromatography to afford the *syn* and *anti* hydroxyesters **5**. *Note: The relative configuration of* **5** *was assigned on the lactonization step*. *The diastereoisomeric ratio (d.r.) was determinate by analysis of the crude NMR mixture.*

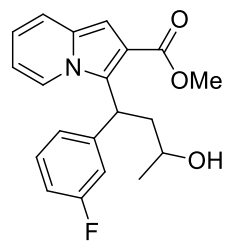
Methyl 3-(3-hydroxy-1-phenylbutyl)indolizine-2-carboxylate (**5a**)



Reaction Time: 1 hour. **Diastereoisomeric ratio:** 68:32 (*syn*/*anti*) **Purification**: 80:20 – 70:30 Hexane/Ethyl Acetate **Yield**: Starting from **3a** (48.7 mg, 0.152 mmol): syn-**3a** was obtained as a colorless oil (27.0 mg, 55% yield); *anti*-**3a** was obtained as a colorless oil (11.3 mg, 23% yield). *Syn-**5a*** **NMR ^{1}H (500 MHz, $CDCl_3$)** δ 7.53 (dd, *J* = 7.3, 0.9 Hz, 1H), 7.34 (dt, *J* = 9.1, 1.0 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.23 – 7.16 (m, 3H), 6.87 (s, 1H), 6.61 (ddd, *J* = 9.0, 6.4, 0.7 Hz, 1H), 6.33 (ddd, *J* = 7.6, 6.6, 1.3 Hz, 1H), 5.80 (dd, *J* = 9.2, 5.9 Hz, 1H), 3.91 (s, 3H), 3.84 (sext, *J* = 6.1 Hz, 1H), 2.58 (dt, *J* = 13.8, 5.6 Hz, 1H), 2.35 (ddd, *J* = 13.7, 9.2, 6.9 Hz, 1H), 1.24 (d, *J* = 6.2 Hz, 3H). *Syn-**5a*** **NMR ^{13}C (126 MHz, $CDCl_3$)** δ 166.95, 140.60, 132.00, 129.53, 128.76, 127.26, 126.50, 123.69, 120.71, 117.74, 116.93, 111.91, 101.15, 67.31, 51.68, 39.51, 36.61, 23.47. **HRMS** (ESI, m/z): calcd for $C_{20}H_{22}NO_3^+$, 324.15942 $[M + H]^+$; found, 324.15913 . *Anti-**5a*** **NMR ^{1}H (500 MHz, $CDCl_3$)** δ 7.41 (dd, *J* = 7.4, 0.9 Hz, 1H), 7.38 (dt, *J* = 9.1, 1.0 Hz, 1H), 7.33 – 7.26 (m, 2H), 7.23 – 7.16 (m, 3H), 6.90 (s, 1H), 6.64 (ddd, *J* = 9.1, 6.4, 0.9 Hz, 1H), 6.30 (ddd, *J* = 7.4, 6.6, 1.3 Hz, 1H), 5.83 (dd, *J* = 12.8, 3.8 Hz, 1H), 3.97 (s, 3H), 3.42 (dqd, *J* = 10.3, 6.2, 1.5 Hz, 1H), 2.43 (ddd, *J* = 13.4, 10.4, 4.0 Hz, 1H), 2.32 (td, *J* = 13.1, 1.7 Hz, 1H), 1.21 (d, *J* = 6.2 Hz, 3H). *Anti-**5a*** **NMR ^{13}C (101 MHz, CDCl3)** δ 168.41, 140.54, 132.32, 128.80, 128.45, 127.20, 126.53, 123.85, 120.81, 118.06, 117.86, 111.87,

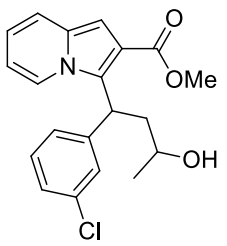
100.91, 65.03, 52.16, 38.71, 36.25, 23.11. **HRMS** (ESI, m/z): calcd for $C_{20}H_{22}NO_3^+$, 324.15942 $[M + H]^+$; found, 324.15902.

Methyl 3-(1-(3-fluorophenyl)-3-hydroxybutyl)indolizine-2-carboxylate (5b)



Reaction Time: 15 min. **Diastereoisomeric ratio:** 66:34 (*syn*/*anti*) **Purification**: 80:20 – 70:30 Hexane/Ethyl Acetate. **Yield**: Starting from **3b** (57.5 mg, 0.166 mmol): syn-**5b** was obtained as a white solid (30.0 mg, 51% yield), m.p.: 160 - 162°C; *anti*-**3b** was obtained as a colorless oil (14.5 mg, 25% yield). *Syn*-**5b NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.50 (dd, *J* = 7.3, 0.9 Hz, 1H), 7.35 (dt, *J* = 9.1, 1.0 Hz, 1H), 7.28 – 7.18 (m, 1H), 7.02 – 6.97 (m, 1H), 6.95 – 6.83 (m, 3H), 6.63 (ddd, *J* = 9.1, 6.5, 0.7 Hz, 1H), 6.36 (ddd, *J* = 7.6, 6.6, 1.3 Hz, 1H), 5.79 (dd, *J* = 9.0, 6.1 Hz, 1H), 3.91 (s, 3H), 3.1 (sex, *J* = 6.1 Hz, 1H), 2.53 (dt, *J* = 13.7, 5.6 Hz, 1H), 2.34 (ddd, *J* = 13.8, 9.2, 6.9 Hz, 1H), 1.23 (d, *J* = 6.2 Hz, 3H). *Syn*-**5b NMR ^{13}C (63 MHz, $CDCl_3$)** δ 166.87 (s), 163.27 (d, *J* = 245.9 Hz), 143.51 (d, *J* = 6.7 Hz), 132.13 (s), 130.19 (d, *J* = 8.3 Hz), 128.72 (s), 123.49 (s), 122.90 (d, *J* = 2.8 Hz), 120.83 (s), 117.91 (s), 117.06 (s), 114.40 (d, *J* = 22.0 Hz), 113.50 (d, *J* = 21.1 Hz), 112.17 (s), 101.28 (s), 67.16 (s), 51.73 (s), 39.43 (s), 36.44 (d, *J* = 1.6 Hz), 23.51 (s). *Syn*-**5b NMR ^{19}F (235 MHz, $CDCl_3$)** δ -112.64. **HRMS** (ESI, m/z): calcd for $C_{20}H_{21}FNO_3^+$, 342.15000 $[M + H]^+$; found, 342.14995. *Anti*-**5b NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.40 – 7.33 (m, 2H), 7.25 – 7.18 (m, 1H), 6.94 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.91 – 6.84 (m, 3H), 6.68 – 6.59 (m, 1H), 6.37 – 6.26 (m, 1H), 5.79 (dd, *J* = 12.5, 4.1 Hz, 1H), 4.27 (s, 1H), 3.94 (s, 3H), 3.45 – 3.34 (m, 1H), 2.36 (ddd, *J* = 14.3, 10.1, 4.2 Hz, 1H), 2.28 (td, *J* = 13.0, 2.0 Hz, 1H), 1.18 (d, *J* = 6.2 Hz, 3H). *Anti*-**5b NMR ^{13}C (63 MHz, $CDCl_3$)** δ 168.34 (s), 163.32 (d, *J* = 246.1 Hz), 143.47 (d, *J* = 6.7 Hz), 132.44 (s), 130.24 (d, *J* = 8.3 Hz), 127.59 (s), 123.61 (s), 122.84 (d, *J* = 2.8 Hz), 120.92 (s), 118.16 (s), 118.02 (s), 114.32 (d, *J* = 22.1 Hz), 113.53 (d, *J* = 21.1 Hz), 112.15 (s), 101.05 (s), 64.91 (s), 52.21 (s), 38.70 (s), 36.14 (d, *J* = 1.5 Hz), 23.10 (s). *Anti*-**5b NMR ^{19}F (235 MHz, $CDCl_3$)** δ -112.65. **HRMS** (ESI, m/z): calcd for $C_{20}H_{21}FNO_3^+$, 342.15000 $[M + H]^+$; found,.342.14985.

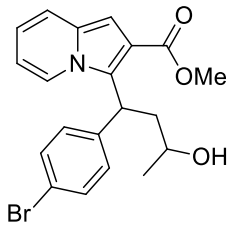
Methyl 3-(1-(3-chlorophenyl)-3-hydroxybutyl)indolizine-2-carboxylate (5c)



Reaction Time: 1 hour. **Diastereoisomeric ratio:** 61:39 (*syn*/*anti*) **Purification**: 80:20 – 75:25 Hexane/Ethyl Acetate **Yield**: Starting from **3c** (59.2 mg, 0.169 mmol): *syn*-**5c** was obtained as colorless oil that slowly solidifies under refrigeration (30.4 mg, 51% yield); *anti*-**5c** was obtained as a colorless oil (19.2 mg, 32%). *Syn*-**5c NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.51 (dd, *J* = 7.3, 0.9 Hz, 1H), 7.35 (dt, *J* = 9.1, 1.0 Hz, 1H), 7.23 (m, 1H), 7.22 – 7.14 (m, 2H), 7.10 – 7.05 (m, 1H), 6.88 (s, 1H), 6.63 (ddd, *J* = 9.1, 6.4, 0.8 Hz, 1H), 6.37 (ddd, *J* = 7.7, 6.6, 1.3 Hz, 1H), 5.77 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.91 (s, 3H), 3. 79 (t, *J* = 6.2 Hz, 1H), 2.52 (dt, *J* = 13.7, 5.7 Hz, 1H), 2.33 (ddd, *J* = 13.7, 9.2, 6.9 Hz, 1H), 1.22 (d, *J* = 6.2

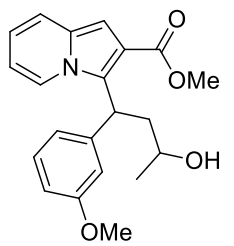
Hz, 3H). *Syn*-**5c NMR ^{13}C (101 MHz, $CDCl_3$)** δ 166.84, 142.95, 134.76, 132.14, 129.97, 128.54, 127.47, 126.81, 125.54, 123.41, 120.84, 117.93, 117.10, 112.23, 101.33, 67.11, 51.73, 39.34, 36.43, 23.52. **HRMS** (ESI, m/z): calcd for $C_{20}H_{21}ClNO_3^+$, 358.12045 $[M + H]^+$; found, 358.12040. *Anti*-**5c NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.39 – 7.34 (m, 2H), 7.20 – 7.16 (m, 3H), 7.05 – 6.98 (m, 1H), 6.88 (s, 1H), 6.67 – 6.61 (m, 1H), 6.32 (ddd, *J* = 7.7, 6.5, 1.2 Hz, 1H), 5.78 (dd, *J* = 12.3, 4.3 Hz, 1H), 4.25 (bs, 1H), 3.94 (s, 3H), 3.43 – 3.31 (m, 1H), 2.39 - 2.32 (m, 1H), 2.28 (td, *J* = 13.0, 2.0 Hz, 1H), 1.18 (d, *J* = 6.2 Hz, 3H). *Anti*-**5c NMR ^{13}C (101 MHz, $CDCl_3$)** δ 168.31, 142.90, 134.85, 132.45, 130.01, 127.42, 127.36, 126.85, 125.49, 123.54, 120.95, 118.18, 118.05, 112.22, 101.10, 64.92, 52.21, 38.61, 36.10, 23.09. **HRMS** (ESI, m/z): calcd for $C_{20}H_{21}ClNO_3^+$, 358.12045 $[M + H]^+$; found, 358.12046.

Methyl 3-(1-(4-bromophenyl)-3-hydroxybutyl)indolizine-2-carboxylate (5d)



Reaction Time: 1 hour. **Diastereoisomeric ratio:** 67:33 (*syn*/*anti*) **Purification**: 80:20 Hexane/Ethyl Acetate. **Yield**: Starting from **5d** (77.3 mg, 0.193 mmol): *syn*-**5d** was obtained as a viscous pale yellow oil (40.3 mg, 52% yield); *anti*-**5d** was obtained as viscous pale yellow oil (21.2 mg, 27% yield). *Syn*-**5d NMR ^{1}H (250 MHz, $CDCl_3$)** δ 7.52 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.44 – 7.34 (m, 3H), 7.12 (m, 2H), 6.90 (s, 1H), 6.66 (ddd, *J* = 9.1, 6.5, 0.8 Hz, 1H), 6.39 (ddd, *J* = 7.7, 6.5, 1.3 Hz, 1H), 5.75 (dd, *J* = 9.0, 6.1 Hz, 1H), 3.93 (s, 3H), 3.82 (sext, *J* = 6.1 Hz, 1H), 2.62 – 2.47 (m, 1H), 2.35 (ddd, *J* = 13.7, 9.1, 6.9 Hz, 1H), 1.25 (d, *J* = 6.2 Hz, 3H). *Syn*-**5d NMR ^{13}C (63 MHz, $CDCl_3$)** δ 166.87, 139.79, 132.11, 131.82, 129.08, 128.74, 123.43, 120.83, 120.41, 117.91, 117.03, 112.20, 101.29, 67.15, 51.74, 39.45, 36.22, 23.54. **HRMS** (ESI, m/z): calcd for $C_{20}H_{21}BrNO_3^+$, 402.06993 $[M + H]^+$; found, 402.07068. *Anti*-**5d NMR ^{1}H (500 MHz, $CDCl_3$)** δ 7.40 – 7.36 (m, 3H), 7.34 - 7.33 (m, 1H), 7.03 (dd, *J* = 8.6, 0.9 Hz, 2H), 6.88 (s, 1H), 6.64 (ddd, *J* = 9.1, 6.5, 0.9 Hz, 1H), 6.31 (ddd, *J* = 7.5, 6.5, 1.3 Hz, 1H), 5.74 (dd, *J* = 12.4, 3.7 Hz, 1H), 4.26 (bs, 1H), 3.94 (s, 3H), 3.42 – 3.34 (m, 1H), 2.37 - 2.32 (m, 1H), 2.27 (td, *J* = 13.1, 1.6 Hz, 1H), 1.18 (d, *J* = 6.2 Hz, 3H). *Anti*-**5d NMR ^{13}C (126 MHz, $CDCl_3$)** δ 168.31, 139.72, 132.43, 131.86, 128.97, 127.60, 123.59, 120.93, 120.43, 118.15, 118.02, 112.17, 101.06, 64.94, 52.21, 38.71, 35.90, 23.11. **HRMS** (ESI, m/z): calcd for $C_{20}H_{21}BrNO_3^+$, 402.06993 $[M + H]^+$; found, 402.07035.

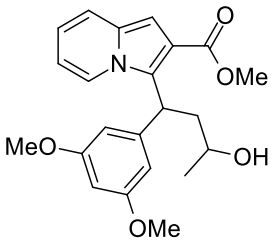
Methyl 3-(3-hydroxy-1-(3-methoxyphenyl)butyl)indolizine-2-carboxylate (5e)



Reaction Time: 30 min. **Diastereoisomeric ratio:** 68:32 (*syn*/*anti*) **Purification**: 75:25 Hexane/Ethyl Acetate **Yield**: Starting from **3e** (68.0 mg, 0.194 mmol): *syn*-**5e** was obtained as colorless oil that slowly solidify under refrigeration (40.3 mg, 39% yield); *anti*-**5e** was obtained as colorless oil that slowly solidify under refrigeration (15.1 mg, 22% yield). Additionally, 7.1 mg (10% yield) of a fraction containing both diastereoisomers was obtained. *Syn*-**5e NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.55 (dq, *J* = 7.3,

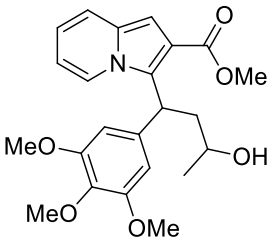
1.1 Hz, 1H), 7.33 (dt, *J* = 9.0, 1.2 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 6.86 (d, *J* = 0.9 Hz, 1H), 6.82 – 6.77 (m, 2H), 6.74 – 6.71 (m, 1H), 6.61 (ddd, *J* = 9.0, 6.5, 1.0 Hz, 1H), 6.33 (ddd, *J* = 7.6, 6.5, 1.3 Hz, 1H), 5.76 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.91 (s, 3H), 3.82 (sex, *J* = 6.2 Hz, 1H), 3.73 (s, 3H), 2.55 (ddd, *J* = 13.7, 6.0, 5.2 Hz, 1H), 2.32 (ddd, *J* = 13.7, 9.1, 6.9 Hz, 1H), 1.23 (d, *J* = 6.2 Hz, 3H). *Syn*-**5e NMR ^{13}C (63 MHz, $CDCl_3$)** δ 166.94, 159.99, 142.37, 132.02, 129.70, 129.39, 123.77, 120.70, 119.68, 117.76, 116.90, 113.77, 111.94, 111.23, 101.14, 67.29, 55.27, 51.68, 39.53, 36.61, 23.49. **HRMS** (ESI, m/z): calcd for $C_{21}H_{24}NO_4^+$, 354.16998 $[M + H]^+$; found, 354.16969. *Anti*-**5e NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.41 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.35 (dt, *J* = 9.2, 1.2 Hz, 1H), 7.18 (dd, *J* = 9.0, 7.4 Hz, 1H), 6.86 (s, 1H), 6.78 – 6.68 (m, 3H), 6.61 (ddd, *J* = 9.2, 6.5, 1.0 Hz, 1H), 6.28 (ddd, *J* = 7.6, 6.5, 1.4 Hz, 1H), 5.77 (dd, *J* = 12.8, 3.9 Hz, 1H), 4.33 (sl, 1H), 3.94 (s, 3H), 3.73 (s, 3H), 3.44 – 3.30 (m, 1H), 2.38 (ddd, *J* = 13.3, 10.3, 4.1 Hz, 1H), 2.27 (td, *J* = 13.0, 1.9 Hz, 1H), 1.18 (d, *J* = 6.2 Hz, 3H). *Anti*-**5e NMR ^{13}C (63 MHz, $CDCl_3$)** δ 168.41, 160.02, 142.33, 132.31, 129.74, 128.29, 123.92, 120.79, 119.64, 118.01, 117.87, 113.67, 111.90, 111.24, 100.89, 64.98, 55.31, 52.15, 38.73, 36.21, 23.09. **HRMS** (ESI, m/z): calcd for $C_{21}H_{24}NO_4^+$, 354.16998 $[M + H]^+$; found, 354.16972.

Methyl 3-(1-(3,5-dimethoxyphenyl)-3-hydroxybutyl)indolizine-2-carboxylate (5f)



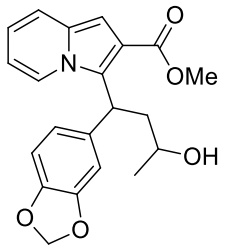
Reaction Time: 30 min. **Diastereoisomeric ratio:** 66:34 (*syn*/*anti*) **Purification**: 75:25 – 70:30 Hexane/Ethyl Acetate. **Yield**: Starting from **3f** (76.2 mg, 0.2 mmol) in MeOH/DCM (1:1, 0.1 M): *syn*-**5f** was obtained as a colorless viscous oil that slowly solidifies under refrigeration (36.6 mg, 46% yield); *anti*-**5f** was obtained as a colorless viscous oil that slowly solidifies under refrigeration (15.6 mg, 20% yield). *Syn*-**5f NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.58 (dq, *J* = 7.3, 1.0 Hz, 1H), 7.32 (dt, *J* = 9.1, 1.3 Hz, 1H), 6.85 (d, *J* = 0.9 Hz, 1H), 6.60 (ddd, *J* = 9.1, 6.4, 1.0 Hz, 1H), 6.38 (dd, *J* = 2.2, 1.0 Hz, 2H), 6.34 (ddd, *J* = 7.3, 6.4, 1.4 Hz, 1H), 6.29 (td, *J* = 2.3, 0.6 Hz, 1H), 5.71 (dd, *J* = 8.9, 6.2 Hz, 1H), 3.90 (s, 3H), 3.80 (sex, *J* = 6.3 Hz, 1H), 3.70 (s, 6H), 2.52 (ddd, *J* = 13.7, 6.1, 5.3 Hz, 1H), 2.28 (ddd, *J* = 13.7, 9.1, 6.9 Hz, 1H), 1.21 (d, *J* = 6.2 Hz, 3H). *Syn*-**5f NMR ^{13}C (63 MHz, $CDCl_3$)** δ 166.91, 161.09, 143.23, 132.01, 129.22, 123.85, 120.64, 117.77, 116.86, 111.95, 105.86, 101.12, 97.81, 67.19, 55.35, 51.66, 39.52, 36.73, 23.47. **HRMS** (ESI, m/z): calcd for $C_{22}H_{26}NO_5^+$, 384.18055 $[M + H]^+$; found, 384.18039. *Anti*-**5f NMR ^{1}H (250 MHz, CDCl3)** δ 7.45 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.40 – 7.28 (m, 1H), 6.85 (s, 1H), 6.62 (ddd, *J* = 9.1, 6.5, 1.0 Hz, 1H), 6.34 – 6.26 (m, 4H), 5.72 (dd, *J* = 12.2, 4.4 Hz, 1H), 4.31 (sl, 1H), 3.93 (s, 3H), 3.70 (s, 6H), 3.44 – 3.21 (m, 1H), 2.40 – 2.17 (m, 2H), 1.16 (d, *J* = 6.2 Hz, 3H). *Anti*-**5f NMR ^{13}C (63 MHz, $CDCl_3$)** δ 168.41, 161.14, 143.23, 132.31, 128.12, 124.01, 120.75, 117.96, 117.89, 111.95, 105.78, 100.88, 97.86, 64.96, 55.41, 52.15, 38.74, 36.33, 23.07. **HRMS** (ESI, m/z): calcd for $C_{22}H_{26}NO_5^+$, 384.18055 $[M + H]^+$; found, 384.18039.

Methyl 3-(3-hydroxy-1-(3,4,5-trimethoxyphenyl)butyl)indolizine-2-carboxylate (5g)



Reaction Time: 30 min. **Diastereoisomeric ratio:** 64:36 (*syn*/*anti*) **Purification**: 70:30 – 50:50 Hexane/Ethyl Acetate. **Yield**: Starting from **3g** (83.6 mg, 0.203 mmol) in MeOH:DCM (1:1, 0.1 M): *syn*-**5g** was obtained as a colorless viscous oil that slowly solidifies under refrigeration (37.6 mg, 45% yield); *anti*-**5g** was obtained as a colorless viscous oil that slowly solidifies under refrigeration (24.7 mg, 29% yield). *Syn*-**5g NMR ^{1}H (400 MHz, CDCl3**) δ 7.62 – 7.55 (m, 1H), 7.34 (dt, *J* = 9.2, 1.2 Hz, 1H), 6.86 (d, *J* = 1.0 Hz, 1H), 6.63 (ddd, *J* = 9.1, 6.5, 0.9 Hz, 1H), 6.43 (d, *J* = 0.9 Hz, 2H), 6.37 (ddd, *J* = 7.7, 6.5, 1.3 Hz, 1H), 5.67 (dd, *J* = 9.3, 6.0 Hz, 1H), 3.90 (s, 3H), 3.79 (s, 3H), 3.74 – 3.72 (m, 7H), 2.51 (dt, *J* = 13.7, 5.8 Hz, 1H), 2.33 (ddd, *J* = 13.6, 9.3, 6.7 Hz, 1H), 1.23 (d, *J* = 6.2 Hz, 3H). *Syn*-**5g NMR ^{13}C (63 MHz, CDCl$_3$)** δ 166.87, 153.43, 136.77, 136.48, 132.03, 129.07, 123.86, 120.68, 117.81, 116.99, 112.00, 104.63, 101.22, 67.15, 60.95, 56.29, 51.69, 39.87, 36.78, 23.51. **HRMS** (ESI, m/z): calcd for $C_{23}H_{28}NO_6^+$, 414.19111 $[M + H]^+$; found, 414.19104. *Anti*-**5g NMR ^{1}H (400 MHz, CDCl$_3$)** δ 7.44 – 7.32 (m, 3H), 7.35 (s, 0H), 6.87 (s, 1H), 6.64 (ddd, *J* = 9.0, 6.5, 1.0 Hz, 1H), 6.35 – 6.29 (m, 3H), 5.73 (dd, *J* = 12.6, 4.0 Hz, 1H), 4.30 (sl, 1H), 3.94 (s, 3H), 3.80 (s, 3H), 3.71 (s, 6H), 3.43 – 3.30 (m, 1H), 2.34 (ddd, *J* = 13.2, 10.3, 4.0 Hz, 1H), 2.23 (td, *J* = 12.9, 1.8 Hz, 1H), 1.17 (d, *J* = 6.2 Hz, 3H). *Anti*-**5g NMR ^{13}C (63 MHz, CDCl$_3$)** δ 168.35, 153.50, 136.76, 136.30, 132.34, 128.03, 124.11, 120.75, 118.02, 117.95, 111.97, 104.45, 100.93, 65.03, 61.00, 56.32, 52.17, 39.09, 36.32, 23.09. **HRMS** (ESI, m/z): calcd for $C_{23}H_{28}NO_6^+$, 414.19111 $[M + H]^+$; found, 414.19112.

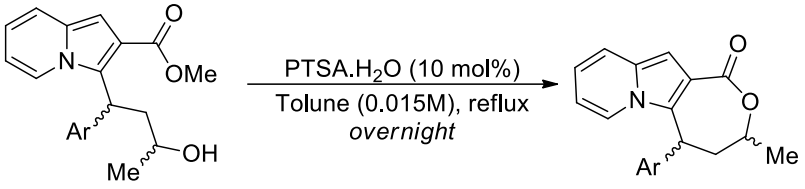
Methyl 3-(1-(benzo[d][1,3]dioxol-5-yl)-3-hydroxybutyl)indolizine-2-carboxylate (5h)



Reaction Time: 30 min. **Diastereoisomeric ratio:** 65:35 (*syn*/*anti*) **Purification**: 75:25 – 70:30 Hexane/Ethyl Acetate. **Yield**: Starting from **3h** (47.5 mg, 0.13 mmol) in MeOH/DCM (1:1, 0.1 M); *syn*-**5h** was obtained as a colorless viscous oil (23.8 mg, 50% yield); *anti*-**5h** was obtained as a colorless viscous oil (12.2 mg, 26% yield). *Syn*-**5h NMR ^{1}H (250 MHz, CDCl$_3$)** δ 7.58 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.33 (dt, *J* = 9.2, 1.1 Hz, 1H), 6.86 (s, 1H), 6.74 – 6.71 (m, 2H), 6.68 (d, *J* = 1.1 Hz, 1H), 6.62 (ddd, *J* = 9.1, 6.4, 1.0 Hz, 1H), 6.36 (ddd, *J* = 7.7, 6.5, 1.4 Hz, 1H), 5.91 – 5.87 (m, 2H), 5.68 (dd, *J* = 9.1, 6.1 Hz, 1H), 3.91 (s, 3H), 3.79 (sext, *J* = 6.1 Hz, 1H), 2.59 – 2.41 (m, 1H), 2.30 (ddd, *J* = 13.7, 9.1, 6.9 Hz, 1H), 1.22 (d, *J* = 6.2 Hz, 3H). *Syn*-**5h NMR ^{13}C (63 MHz, CDCl$_3$)** δ 166.91, 148.18, 146.16, 134.54, 132.01, 129.49, 123.72, 120.72, 119.87, 117.77, 116.83, 111.97, 108.24, 108.18, 101.16, 101.09, 67.19, 51.69, 39.74, 36.37, 23.51. **HRMS** (ESI, m/z): calcd for $C_{21}H_{22}NO_5^+$, 368.14925 $[M + H]^+$; found, 368.14910. *Anti*-**5h NMR ^{1}H (250 MHz, CDCl$_3$)** δ 7.51 – 7.39 (m, 1H), 7.35 (dt, *J* = 9.1, 1.0 Hz, 1H), 6.86 (s, 1H), 6.74 – 6.61 (m, 3H), 6.63 – 6.55 (m, 1H), 6.31 (ddd, *J* = 7.3, 6.5, 1.4 Hz, 1H), 5.95 – 5.86 (m, 2H), 5.69 (dd, *J* = 11.6, 5.1 Hz,

1H), 4.31 (sl, 1H), 3.94 (s, 3H), 3.36 (ddt, *J* = 9.1, 6.0, 3.1 Hz, 1H), 2.41 – 2.11 (m, 2H), 1.17 (d, *J* = 6.2 Hz, 3H). *Anti*-**5h NMR ^{13}C (63 MHz, $CDCl_3$)** δ 168.39, 148.23, 146.15, 134.51, 132.33, 128.42, 123.88, 120.82, 119.79, 117.94, 117.89, 111.95, 108.30, 108.04, 101.12, 100.90, 65.01, 52.17, 38.98, 35.97, 23.10. **HRMS** (ESI, m/z): calcd for $C_{21}H_{22}NO_5^+$, 368.14925 [M + H]$^+$; found, 368.14925.

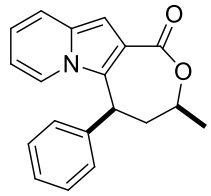
Synthesis of *cis* and *trans* lactones 4



syn-**5** or *anti*-**5** **4**

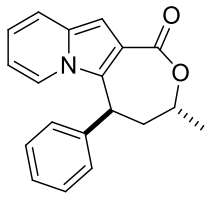
A solution of hydroxyester **5** in toluene (0.015 M) containing *p*-Toluenesulfonic acid (10 mol%) was refluxed overnight. After cooled to room temperature, the excess of solvent was removed under reduced pressure and the crude mixture purified by column chromatography to afford lactones **4**.

***cis*-3-methyl-5-phenyl-4,5-dihydrooxepino[3,4-b]indolizin-1(3H)-one (*cis*-4a)**



Purification: 85:15 Hexane/Ethyl Acetate. **Yield**: Starting from *syn*-**5a** (67.4 mg, 0.208 mmol), *cis*-**4a** was obtained as viscous colorless oil (51.7 mg, 85% yield) **NMR ^{1}H (500 MHz, $CDCl_3$)** δ 7.40 (dt, *J* = 9.1, 1.2 Hz, 1H), 7.31 – 7.19 (m, 4H), 7.06 (s, 1H), 7.01 – 6.96 (m, 2H), 6.67 (ddd, *J* = 9.1, 6.4, 1.0 Hz, 1H), 6.36 (ddd, *J* = 7.5, 6.4, 1.3 Hz, 1H), 4.72 (quint, *J* = 6.7 Hz, 1H), 4.50 (dd, *J* = 12.0, 7.6 Hz, 1H), 2.55 (dd, *J* = 15.7, 7.6 Hz, 1H), 2.34 (ddd, *J* = 15.8, 12.0, 7.6 Hz, 1H), 1.49 (d, *J* = 6.6 Hz, 3H). **NMR ^{13}C (101 MHz, $CDCl_3$)** δ 167.33, 141.74, 132.54, 129.51, 127.49, 126.90, 124.58, 123.06, 120.36, 118.33, 117.99, 112.31, 103.81, 73.81, 45.37, 43.71, 22.44. **HRMS** (ESI, m/z): calcd $C_{19}H_{18}NO_2^+$, 292.13321 [M + H]$^+$; found, 292.13273.

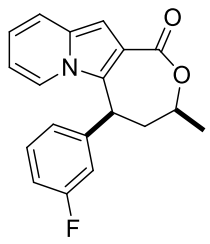
***cis*-3-methyl-5-phenyl-4,5-dihydrooxepino[3,4-b]indolizin-1(3H)-one (*trans*-4a)**



Purification: 85:15 Hexane/Ethyl Acetate. **Yield**: Starting from *anti*-**5a** (43.9 mg, 0.136 mmol), *trans*-**4a** was obtained as viscous colorless oil (29.3 mg, 74% yield) (29,3 mg). **NMR ^{1}H (250 MHz, $CDCl_3$)** δ 7.42 (dt, *J* = 9.2, 1.2 Hz, 1H), 7.38 – 7.21 (m, 3H), 7.19 – 7.11 (m, 2H), 6.99 – 6.89 (m, 1H), 6.68 (ddd, *J* = 9.2, 6.4, 1.0 Hz, 1H), 6.37 (ddd, *J* = 7.6, 6.5, 1.3 Hz, 1H), 4.70 (p, *J* = 6.7 Hz, 1H), 4.51 (dd, *J* = 5.0, 2.9 Hz, 1H), 2.73 (ddd, *J* = 15.4, 7.4, 5.0 Hz, 1H), 2.32 (dd, *J* = 15.3, 2.9 Hz, 1H), 1.30 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR (63 MHz, $CDCl_3$)** δ 166.89, 141.58, 132.77, 129.96, 128.28, 128.04, 124.77, 123.92, 120.96, 119.45, 118.83, 113.00,

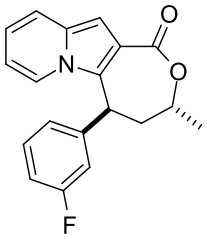
105.20, 71.46, 42.56, 41.89, 23.69. **HRMS** (ESI, m/z): calcd $C_{19}H_{18}NO_2^+$, 292.13321 $[M + H]^+$; found, 292.13275.

***cis*-5-(3-fluorophenyl)-3-methyl-4,5-dihydrooxepino[3,4-b]indolizin-1(3H)-one (*cis*-4b)**



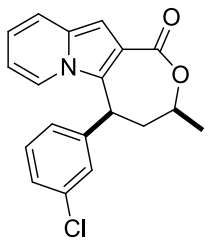
Purification: 100% DCM **Yield**: Starting from *syn*-**5b** (24.9 mg, 0.073 mmol), *cis*-**4b** was obtained as a yellow solid (20.0 mg, 88% yield). mp. 159 – 161°C (degradation). **NMR ^{1}H (500 MHz, $CDCl_3$)** δ 7.42 (d, *J* = 9.1 Hz, 1H), 7.29 – 7.21 (m, 2H), 7.06 (s, 1H), 6.96 – 6.89 (m, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.73 – 6.66 (m, 2H), 6.41 (ddd, *J* = 7.5, 6.5, 1.3 Hz, 1H), 4.71 (quint, *J* = 6.7 Hz, 1H), 4.51 (dd, *J* = 12.0, 7.6 Hz, 1H), 2.56 (dd, *J* = 15.7, 7.6 Hz, 1H), 2.33 (ddd, *J* = 15.5, 11.9, 7.4 Hz, 1H), 1.49 (d, *J* = 6.5 Hz, 3H). **NMR ^{13}C (126 MHz, $CDCl_3$)** δ 167.08, 163.48 (d, *J* = 247.9 Hz), 144.38 (d, *J* = 6.6 Hz), 132.67, 131.17 (d, *J* = 8.2 Hz), 123.67, 122.84, 122.50 (d, *J* = 3.0 Hz), 120.48, 118.51, 118.09, 114.60 (d, *J* = 21.1 Hz), 113.94 (d, *J* = 21.9 Hz), 112.58, 103.98, 73.67, 45.05, 43.33 (d, *J* = 1.4 Hz), 22.42. **HRMS** (ESI, m/z): calculated for $C_{19}H_{18}FNO_2$ $[M+H]^+$: 310.12378, found: 310.12333.

***trans*-5-(3-fluorophenyl)-3-methyl-4,5-dihydrooxepino[3,4-b]indolizin-1(3H)-one (*trans*-4b)**



Purification: 75:25 – 70:30 Hexane/Ethyl Acetate. **Yield**: Starting from *anti*-**5b** (14.2 mg, 0.043 mmol), *trans*-**4b** was obtained as a colorless viscous oil (11.2 mg, 87% yield). **NMR ^{1}H (500 MHz, $CDCl_3$)** δ 7.43 (d, *J* = 9.1 Hz, 1H), 7.32 – 7.24 (m, 1H), 7.18 (s, 1H), 7.13 (d, *J* = 7.3 Hz, 1H), 6.97 (td, *J* = 8.5, 2.0 Hz, 1H), 6.77 – 6.62 (m, 3H), 6.45 – 6.38 (m, 1H), 4.67 (quint, *J* = 6.8 Hz, 1H), 4.54 – 4.47 (m, 1H), 2.74 (ddd, *J* = 15.3, 7.5, 5.1 Hz, 1H), 2.31 (dd, *J* = 15.5, 2.9 Hz, 1H), 1.32 (d, *J* = 6.5 Hz, 3H). **NMR ^{13}C (126 MHz, $CDCl_3$)** δ 166.12, 163.48 (d, *J* = 247.6 Hz), 143.84 (d, *J* = 6.5 Hz), 132.40, 131.10 (d, *J* = 8.4 Hz), 123.40 (d, *J* = 2.8 Hz), 123.34, 123.16, 120.58, 119.05, 118.50, 114.84 (d, *J* = 11.9 Hz), 114.67 (d, *J* = 10.9 Hz), 112.77, 104.90, 70.81, 41.85, 41.15 (d, *J* = 1.8 Hz), 23.17. **HRMS** (ESI, m/z): calculated for $C_{19}H_{18}FNO_2$ $[M+H]^+$: 310.12378, found: 310.12332.

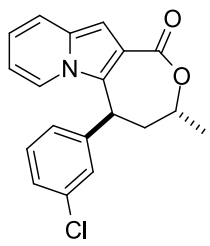
***cis*-5-(3-chlorophenyl)-3-methyl-4,5-dihydrooxepino[3,4-b]indolizin-1(3H)-one (*cis*-4c)**



Purification: 80:20 – 70:30 Hexane/Ethyl Acetate. **Yield**: Starting from *syn*-**5c** (29.4 mg, 0.082 mmol), *cis*-**4c** was obtained as a yellow viscous oil (16.1 mg, 60% yield). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.42 (dt, *J* = 9.1, 1.3 Hz, 1H), 7.27 – 7.23 (m, sinal do solvente sobreposto, 1H,), 7.21 – 7.18 (m, 2H), 7.07 – 7.03 (m, 2H), 6.81 (dt, *J* = 6.5, 2.0 Hz, 1H), 6.71 (ddd, *J* = 9.1, 6.5, 1.0 Hz, 1H), 6.44 – 6.39 (m, 1H), 4.70 (quint, *J* = 6.7 Hz, 1H), 4.49 (dd, *J* = 12.0, 7.6 Hz, 1H), 2.55 (dd, *J* = 15.7, 7.6 Hz, 1H), 2.31 (ddd, *J* = 15.7, 12.0, 7.6 Hz, 1H), 1.48 (d, *J* = 6.5 Hz, 3H). **NMR ^{13}C (63 MHz, $CDCl_3$)** δ 167.10, 143.88, 135.30, 132.68, 130.89,

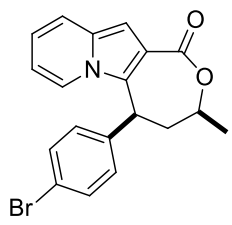
127.85, 127.17, 124.91, 123.49, 122.80, 120.49, 118.55, 118.12, 112.65, 103.98, 73.66, 45.12, 43.28, 22.40. **HRMS** (ESI, m/z): calcd $C_{19}H_{17}ClNO_2^+$, 326.09423 $[M + H]^+$; found, 326.09377.

***trans-5-(3-chlorophenyl)-3-methyl-4,5-dihydrooxepino[3,4-b]indolizin-1(3H)-one* (*trans*-4c)**



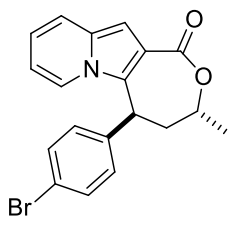
Purification: 80:20 - 75:25 Hexane/Ethyl Acetate. **Yield**: Starting from *anti*-**5c** (17.9 mg, 0.05 mmol), *trans*-**4c** was obtained as a yellow solid (8.7 mg, 53% yield). mp.: 235°C (degradation) **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.43 (dt, *J* = 9.1, 1.2 Hz, 1H), 7.28 – 7.18 (m, 2H), 7.18 (m, 1H), 7.13 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.02 (s, 1H), 6.76 (d, *J* = 7.0 Hz, 1H), 6.71 (ddd, *J* = 9.1, 6.5, 1.0 Hz, 1H), 6.43 (ddd, *J* = 7.6, 6.5, 1.3 Hz, 1H), 4.67 (quint, *J* = 6.9 Hz, 1H), 4.49 (dd, *J* = 5.0, 2.9 Hz, 1H), 2.74 (ddd, *J* = 15.5, 7.5, 5.1 Hz, 1H), 2.35 – 2.24 (m, 1H), 1.32 (d, *J* = 6.6 Hz, 3H). **NMR ^{13}C (63 MHz, $CDCl_3$)** δ 166.09, 143.32, 135.47, 132.42, 130.75, 127.97, 127.94, 125.89, 123.14, 120.60, 119.12, 118.53, 112.84, 104.94, 70.77, 41.84, 41.14, 23.18. **HRMS** (ESI, m/z): calcd $C_{19}H_{17}ClNO_2^+$, 326.09423 $[M + H]^+$; found, 326.09382.

***cis-5-(4-bromophenyl)-3-methyl-4,5-dihydrooxepino[3,4-b]indolizin-1(3H)-one* (*cis*-4d)**



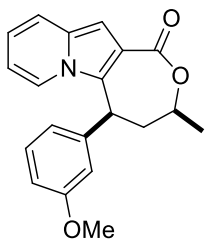
Purification: 80:20 – 75:25 Hexane/Ethyl Acetate. **Yield**: Starting from *syn*-**5d** (39.2 mg, 0.097 mmol), cis-**4d** was obtained as a pale yellow oil (36.1 mg, 77% yield). **NMR ^{1}H (250 MHz, $CDCl_3$)** δ 7.46 – 7.34 (m, 3H), 7.23 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.07 – 7.03 (m, 1H), 6.90 – 6.82 (m, 2H), 6.70 (ddd, *J* = 9.1, 6.5, 1.0 Hz, 1H), 6.40 (ddd, *J* = 7.3, 6.5, 1.3 Hz, 1H), 4.70 (quint, *J* = 6.7 Hz, 1H), 4.48 (dd, *J* = 11.9, 7.7 Hz, 1H), 2.54 (dd, *J* = 15.6, 7.7 Hz, 1H), 2.28 (ddd, *J* = 15.7, 11.9, 7.5 Hz, 1H), 1.48 (d, *J* = 6.6 Hz, 3H). **NMR ^{13}C (63 MHz, $CDCl_3$)** δ 167.09, 140.79, 132.66, 128.61, 123.75, 122.82, 121.29, 120.46, 118.50, 118.08, 112.59, 103.93, 73.67, 45.13, 43.06, 22.40. **HRMS** (ESI, m/z): calculated for $C_{19}H_{17}BrNO_2^+$: 370.04372 $[M + H]^+$, found: 370.04341.

***trans-5-(4-bromophenyl)-3-methyl-4,5-dihydrooxepino[3,4-b]indolizin-1(3H)-one* (*trans*-4d)**



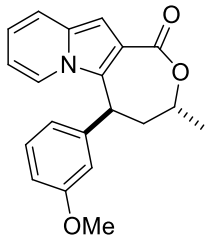
Purification: 75:25 Hexane/Ethyl Acetate **Yield**: Starting from *anti*-**4d** (21.3 mg, 0.053 mmol), *trans*-**4d** was obtained as a yellow oil (14.4 mg, 73% yield). **NMR ^{1}H (250 MHz, $CDCl_3$)** δ 7.48 – 7.37 (m, 3H), 7.17 (s, 1H), 7.11 (dd, *J* = 7.2, 1.1 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 2H), 6.71 (ddd, *J* = 9.2, 6.5, 1.0 Hz, 1H), (m, 2H), 6.48 – 6.35 (m, 1H), 4.63 (quint, *J* = 6.7 Hz, 1H), 4.47 (dd, *J* = 5.0, 2.9 Hz, 1H), 2.74 (ddd, *J* = 15.5, 7.5, 5.0 Hz, 1H), 2.27 (dd, *J* = 15.4, 2.9 Hz, 1H), 1.31 (d, *J* = 6.5 Hz, 3H). **NMR ^{13}C (63 MHz, $CDCl_3$)** δ 166.11, 140.14, 132.64, 132.38, 129.49, 123.40, 123.17, 121.51, 120.57, 119.05, 118.49, 112.78, 104.87, 70.76, 41.86, 40.87, 23.19. **HRMS** (ESI, m/z): calculated for $C_{19}H_{17}BrNO_2^+$: 370.04372 $[M + H]^+$, found: 370.04347.

***cis*-5-(3-methoxyphenyl)-3-methyl-4,5-dihydrooxepino[3,4-b]indolizin-1(3H)-one (*cis*-4e)**



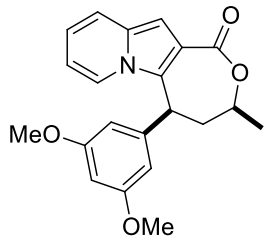
Purification: 75:25 Hexane/Ethyl Acetate. **Yield**: Starting from *syn*-**5e** (24.6 mg, 0.07 mmol), *cis*-**4e** was obtained as a white solid (16.3 mg, 73% yield) **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.39 (dt, *J* = 9.2, 1.2 Hz, 1H), 7.31 (dq, *J* = 7.3, 1.0 Hz, 1H), 7.21 – 7.16 (m, 1H), 7.04 (d, *J* = 0.8 Hz, 1H), 6.76 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 6.68 (ddd, *J* = 9.1, 6.5, 1.0 Hz, 1H), 6.59 – 6.55 (m, 1H), 6.54 – 6.51 (m, 1H), 6.38 (ddd, *J* = 7.7, 6.5, 1.3 Hz, 1H), 4.69 (quint, *J* = 6.8 Hz, 1H), 4.46 (dd, *J* = 12.0, 7.5 Hz, 1H), 3.70 (s, 3H), 2.55 (dd, *J* = 15.6, 7.5 Hz, 1H), 2.35 (ddd, *J* = 15.7, 12.0, 7.5 Hz, 1H), 1.48 (d, *J* = 6.6 Hz, 3H). **NMR ^{13}C (63 MHz, $CDCl_3$)** δ 167.31, 160.47, 143.40, 132.52, 130.58, 124.44, 123.12, 120.32, 119.18, 118.35, 117.92, 112.80, 112.49, 112.34, 103.81, 73.81, 55.34, 45.18, 43.73, 22.44. **HRMS** (ESI, m/z): calcd $C_{20}H_{20}NO_3^+$, 322.14377 $[M + H]^+$; found, 322.14348.

***trans*-5-(3-methoxyphenyl)-3-methyl-4,5-dihydrooxepino[3,4-b]indolizin-1(3H)-one (*trans*-4e)**



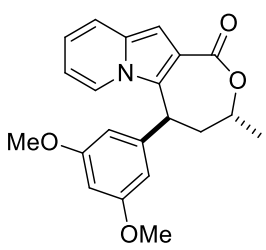
Purification: 75:25 Hexane/Ethyl Acetate. **Yield**: Starting from *anti*-**5e** (15.1 mg, 0.043 mmol), *trans*-**4e** was obtained as colorless oil (12.4 mg, 91% yield). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.40 (dt, *J* = 9.1, 1.2 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.19 – 7.15 (m, 2H), 6.82 – 6.76 (m, 1H), 6.68 (ddd, *J* = 9.1, 6.5, 1.0 Hz, 1H), 6.55 – 6.45 (m, 2H), 6.39 (ddd, *J* = 7.1, 6.4, 1.3 Hz, 1H), 4.72 (quint, *J* = 6.8 Hz, 1H), 4.46 (dd, *J* = 5.1, 2.9 Hz, 1H), 3.74 (s, 3H), 2.71 (ddd, *J* = 15.4, 7.5, 5.1 Hz, 1H), 2.31 (dd, *J* = 15.4, 2.9 Hz, 1H), 1.31 (d, *J* = 6.6 Hz, 3H). **NMR ^{13}C (63 MHz, $CDCl_3$)** δ 166.38, 160.39, 142.83, 132.25, 130.49, 124.17, 123.41, 120.43, 120.03, 118.88, 118.34, 114.00, 112.51, 112.20, 104.68, 71.04, 55.33, 41.94, 41.41, 23.20. **HRMS** (ESI, m/z): calcd $C_{20}H_{20}NO_3^+$, 322.14377 $[M + H]^+$; found, 322.14336.

***cis*-5-(3,5-dimethoxyphenyl)-3-methyl-4,5-dihydrooxepino[3,4-b]indolizin-1(3H)-one (*cis*-4f)**



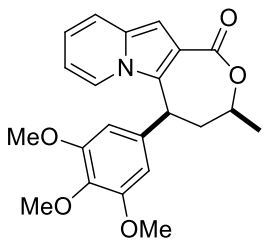
Purification: 75:25 Hexane/Ethyl Acetate. **Yield**: Starting from *syn*-**5f** (33.6 mg, 0.088 mmol), *cis*-**4f** was obtained as a colorless oil (26.6 mg, 86% yield). **NMR ^{1}H (250 MHz, $CDCl_3$)** δ 7.45 – 7.29 (m, 2H), 7.03 (d, *J* = 0.9 Hz, 1H), 6.68 (ddd, *J* = 9.1, 6.5, 1.0 Hz, 1H), 6.39 (ddd, *J* = 7.2, 6.5, 1.4 Hz, 1H), 6.31 (t, *J* = 2.2 Hz, 1H), 6.13 (d, *J* = 2.2 Hz, 2H), 4.67 (quint, *J* = 6.7 Hz, 1H), 4.41 (dd, *J* = 11.9, 7.6 Hz, 1H), 3.67 (s, 5H), 2.54 (dd, *J* = 15.6, 7.5 Hz, 1H), 2.35 (ddd, *J* = 15.7, 12.0, 7.4 Hz, 1H), 1.47 (d, *J* = 6.6 Hz, 3H). **NMR ^{13}C (63 MHz, $CDCl_3$)** δ 167.31, 161.68, 144.27, 132.51, 124.28, 123.19, 120.27, 118.38, 117.87, 112.38, 104.98, 103.80, 98.91, 73.82, 55.44, 44.99, 43.97, 22.44. **HRMS** (ESI, m/z): calcd $C_{21}H_{22}NO_4^+$, 352.15433 $[M + H]^+$; found, 352.15372.

***trans-5-(3,5-dimethoxyphenyl)-3-methyl-4,5-dihydrooxepino[3,4-b]indolizin-1(3H)-one* (*trans*-4f)**



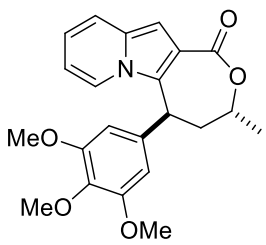
Purification: 75:25 – 70:30 Hexane/Ethyl Acetate. **Yield**: Starting from *anti*-**5f** (12.6 mg, (0.033 mmol), *trans*-**4f** was obtained as a yellow solid (9.1 mg, 79% yield). mp.: 219 – 223°C. **NMR ^{1}H (250 MHz, $CDCl_3$)** δ 7.40 (dt, *J* = 9.1, 1.3 Hz, 1H), 7.20 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.15 (s, 1H), 6.69 (ddd, *J* = 9.1, 6.5, 1.0 Hz, 1H), 6.41 (ddd, *J* = 7.2, 6.5, 1.3 Hz, 1H), 6.34 (t, *J* = 2.3 Hz, 1H), 6.09 (s, 2H), 4.76 (quint, *J* = 6.7 Hz, 1H), 4.40 (dd, *J* = 5.1, 2.9 Hz, 1H), 3.71 (s, 6H), 2.70 (ddd, *J* = 15.4, 7.4, 5.1 Hz, 1H), 2.30 (dd, *J* = 15.3, 2.9 Hz, 1H), 1.33 (d, *J* = 6.5 Hz, 3H). **NMR ^{13}C (63 MHz, $CDCl_3$)** δ 166.38, 161.60, 143.77, 132.26, 124.06, 123.44, 120.42, 118.88, 118.37, 112.55, 106.06, 104.68, 98.60, 71.14, 55.44, 41.84, 41.63, 23.22. **HRMS** (ESI, m/z): calculated for $C_{21}H_{22}NO_4^+$: 352.15433 $[M + H]^+$; found: 352.15423.

***cis-3-methyl-5-(3,4,5-trimethoxyphenyl)-4,5-dihydrooxepino[3,4-b]indolizin-1(3H)-one* (*cis*-4g)**



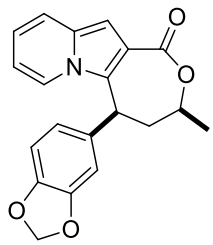
Purification: 70:30 – 60:40 Hexane/Ethyl Acetate. **Yield**: Starting from *syn*-**5g** (36.0 mg, (0.087 mmol), *cis*-**4g** was obtained as a yellow solid (27.9 mg, 84% yield). **NMR ^{1}H (250 MHz, $CDCl_3$)** δ 7.40 (dt, *J* = 9.3, 1.2 Hz, 1H), 7.31 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.04 (s, 1H), 6.70 (ddd, *J* = 9.2, 6.5, 1.0 Hz, 1H), 6.41 (ddd, *J* = 8.5, 6.5, 1.3 Hz, 1H), 6.16 (s, 2H), 4.68 (quinta-feira, *J* = 6.7 Hz, 1H), 4.42 (dd, *J* = 11.9, 7.5 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 6H), 2.55 (dd, *J* = 15.7, 7.5 Hz, 1H), 2.35 (ddd, *J* = 15.7, 11.9, 7.4 Hz, 1H), 1.48 (d, *J* = 6.5 Hz, 3H). **NMR ^{13}C (63 MHz, $CDCl_3$)** δ 167.33, 154.08, 137.49, 137.15, 132.53, 124.25, 123.20, 120.26, 118.44, 117.88, 112.43, 103.82, 103.62, 73.81, 60.93, 56.28, 45.21, 44.08, 22.43. **HRMS** (ESI, m/z): calcd $C_{22}H_{24}NO_5^+$, 382.16490 $[M + H]^+$; found, 382.16434.

***trans-3-methyl-5-(3,4,5-trimethoxyphenyl)-4,5-dihydrooxepino[3,4-b]indolizin-1(3H)-one* (*trans*-4g)**



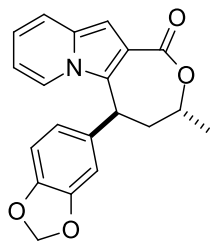
Purification: 60:40 Hexane/Ethyl Acetate. **Yield**: Starting from *anti*-**5g** (21.5 mg, 0.052 mmol), *trans*-**4g** was obtained as yellow viscous oil (16.4 mg, 83% yield). **NMR ^{1}H (400 MHz, $CDCl_3$)** δ 7.40 (dt, *J* = 9.1, 1.2 Hz, 1H), 7.18 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.15 (s, 1H), 6.70 (ddd, *J* = 9.1, 6.5, 1.0 Hz, 1H), 6.42 (ddd, *J* = 7.6, 6.5, 1.3 Hz, 1H), 6.11 (s, 2H), 4.73 (quint, *J* = 6.7 Hz, 1H), 4.42 (dd, *J* = 5.0, 3.0 Hz, 1H), 3.83 (s, 3H), 3.69 (s, 6H), 2.70 (ddd, *J* = 15.3, 7.5, 5.0 Hz, 1H), 2.31 (dd, *J* = 15.3, 3.0 Hz, 1H), 1.35 (d, *J* = 6.5 Hz, 3H). **NMR ^{13}C (101 MHz, $CDCl_3$)** δ 166.34, 153.99, 137.24, 136.87, 132.25, 124.07, 123.48, 120.38, 118.91, 118.43, 112.58, 104.69, 104.62, 71.19, 60.96, 56.29, 42.05, 41.64, 23.20. **HRMS** (ESI, m/z): calcd $C_{22}H_{24}NO_5^+$, 382.16490 $[M + H]^+$; found, 382.16429.

***cis*-5-(benzo[d][1,3]dioxol-5-yl)-3-methyl-4,5-dihydrooxepino[3,4-b]indolizin-1(3H)-one (*cis*-4h)**



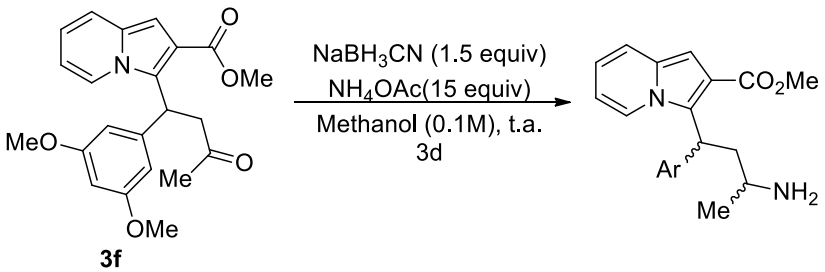
Purification: 70:30 Hexane/Ethyl Acetate. **Yield**: Starting from *syn*-**5h** (22.8 mg, 0.062 mmol), *cis*-**4h** was obtained as a pale yellow solid (13.9 mg, 67% yield). mp.: 192-196 °C. **NMR ^{1}H (250 MHz, $CDCl_3$)** δ 7.40 (dt, *J* = 9.1, 1.1 Hz, 1H), 7.35 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.04 (d, *J* = 0.7 Hz, 1H), 6.76 – 6.62 (m, 2H), 6.51 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.46 – 6.36 (m, 2H), 5.97 – 5.85 (m, 2H), 4.67 (quint, *J* = 6.7 Hz, 1H), 4.42 (dd, *J* = 11.9, 7.6 Hz, 1H), 2.52 (dd, *J* = 15.7, 7.6 Hz, 1H), 2.31 (ddd, *J* = 15.7, 11.9, 7.4 Hz, 1H), 1.48 (d, *J* = 6.6 Hz, 3H). **NMR ^{13}C (63 MHz, $CDCl_3$)** δ 167.27, 148.60, 146.92, 135.61, 132.57, 124.53, 123.14, 120.38, 120.12, 118.37, 117.86, 112.37, 109.00, 107.10, 103.82, 101.33, 73.73, 45.49, 43.40, 22.44. **HRMS** (ESI, m/z): calculated for $C_{20}H_{18}NO_4^+$, 336.12303 $[M + H]^+$, found: 336.12250.

***trans*-5-(benzo[d][1,3]dioxol-5-yl)-3-methyl-4,5-dihydrooxepino[3,4-b]indolizin-1(3H)-one (*trans*-4h)**



Purification: 80:20 – 70:30 Hexane/Ethyl Acetate. **Yield**: Starting from *anti*-**5h** (18.8 mg, 0.051 mmol), *trans*-**4h** was obtained as yellow solid (12.9 mg, 75% yield) mp.: 210-212°C (degradation). **NMR ^{1}H (250 MHz, $CDCl_3$)** δ 7.41 (dt, *J* = 9.1, 1.1 Hz, 1H), 7.20 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.15 (s, 1H), 6.75 – 6.65 (m, 2H), 6.50 – 6.30 (m, 3H), 5.98 – 5.93 (m, 2H), 4.71 (quint, *J* = 6.7 Hz, 1H), 4.41 (dd, *J* = 4.9, 2.9 Hz, 1H), 2.69 (ddd, *J* = 15.4, 7.4, 4.9 Hz, 1H), 2.26 (dd, *J* = 15.3, 2.9 Hz, 1H), 1.33 (d, *J* = 6.5 Hz, 3H). **NMR ^{13}C (63 MHz, $CDCl_3$)** δ 166.32, 148.62, 146.96, 134.95, 132.27, 124.28, 123.45, 120.90, 120.46, 118.84, 118.37, 112.55, 108.99, 108.03, 104.68, 101.42, 70.90, 42.17, 41.08, 23.22. **HRMS** (ESI, m/z): calculated for $C_{20}H_{18}NO_4^+$: 336.12303 $[M + H]^+$, found: 336.12245.

Synthesis of *cis* and *trans* amino esters 6

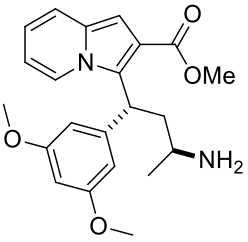


3f

To a solution of conjugate adduct **3f** (63.7 mg, 0.167 mmol, 1 equiv) in methanol (0.1 M) was sequentially added at room temperature ammonium acetate (193.2 mg, 2.51 mmol, 15 equiv) and sodium cyanoborohydride (15.7 mg, 0.250 mmol, 1.5 equiv). The reaction was left stirring for 3 days, then a saturated ammonium chloride solution (15 mL) was added, and the aqueous phase extracted with dichloromethane (3 x 10 mL). The organic fractions were combined, dried with sodium sulfate, concentrated under reduced pressure, and purified by column chromatography (SiO_2, DCM/MeOH

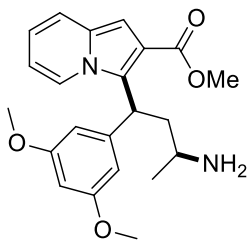
19:1 to 9:1) to afford a separable mixture of the *syn* and *anti* amino esters **6** as colorless oils in a global yield of 50% (*anti*-**6**, 20.0 mg, 31% yield; and *syn*-**6**, 12.4 mg, 0.032 mmol, 19% yield.). *The absolute conFiguretions of syn and anti*-**6** *were assigned afer lactamization.*

***methyl 3-(3-amino-1-(3,5-dimethoxyphenyl)butyl)indolizine-2-carboxylate* (*anti*-6)**



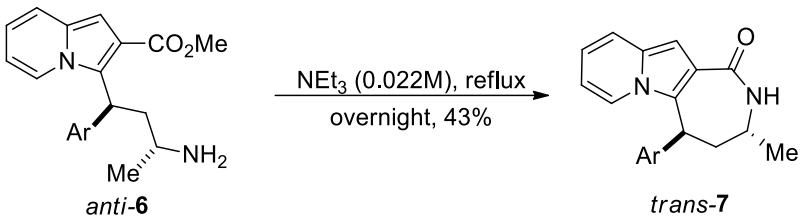
H NMR (250 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.3 Hz, 1H), 7.37 – 7.33 (m, 1H), 6.86 (s, 1H), 6.67 – 6.57 (m, 1H), 6.46 – 6.24 (m, 4H), 5.75 (dd, *J* = 11.7, 3.5 Hz, 1H), 4.50 (sl, 2H), 3.91 (s, 3H), 3.69 (s, 7H), 2.66 – 2.27 (m, 2H), 1.22 (d, *J* = 6.0 Hz, 3H). **^{13}C NMR (63 MHz, $CDCl_3$)** δ 167.8, 161.1, 142.7, 132.4, 127.6, 124.0, 120.8, 117.9, 117.9, 112.1, 105.7, 101.2, 98.1, 55.4, 52.0, 45.9, 38.0, 36.4, 22.8. **HRMS** (ESI, m/z) calcd for $C_{22}H_{26}N_2O_4H^+$, 383.19653 $[M + H]^+$; found, 383.19624.

***methyl 3-(3-amino-1-(3,5-dimethoxyphenyl)butyl)indolizine-2-carboxylate* (*anti*-6)**



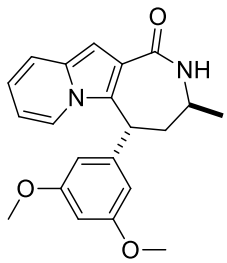
^{1}H NMR (250 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 9.1 Hz, 1H), 6.86 (s, 1H), 6.60 (dd, *J* = 9.1, 6.1 Hz, 1H), 6.40 (d, *J* = 1.7 Hz, 2H), 6.38 – 6.26 (m, 2H), 5.74 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.90 (s, 3H), 3.73 – 3.65 (m, 7H), 2.51 – 2.14 (m, 2H), 1.16 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR** (63 MHz, $CDCl_3$) δ 166.6, 161.1, 143.4, 132.0, 129.0, 124.0, 120.7, 117.7, 117.2, 112.0, 105.9, 101.2, 97.9, 55.4, 51.6, 46.2, 39.7, 36.9, 23.4. **HRMS** (ESI, m/z) calcd for $C_{22}H_{26}N_2O_4H^+$, 383.19653 $[M + H]^+$; found, 383.19645.

Synthesis of lactam *trans*-7



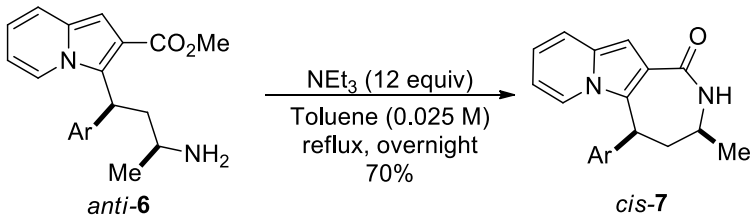
A solution of anti-**6** (16.7 mg, 0.044 mmol) in fresh distilled NEt_3 (2 mL, 0.022 M) was refluxed overnight. After cooling to room temperature, NEt_3 was removed under reduced pressure and the crude mixture purified by column chromatography (pure EtOAc) to afford lactam *trans*-**7** as a brownish foam (6.5 mg, 43% yield).

5-(3,5-dimethoxyphenyl)-3-methyl-2,3,4,5-tetrahydro-1H-azepino[3,4-b]indolizin-1-one (trans-7)



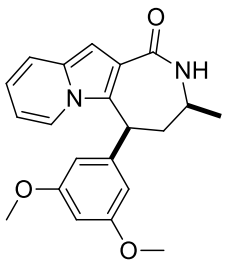
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dt, *J* = 9.1, 1.0 Hz, 1H), 7.27 – 7.24 (m, 1H, superimposed with $CDCl_3$ peak), 7.15 (s, 1H), 6.65 (ddd, *J* = 9.1, 6.4, 0.8 Hz, 1H), 6.40 – 6.36 (m, 1H), 6.32 (t, *J* = 2.2 Hz, 1H), 6.12 (s, 2H), 5.80 (bs, 1H), 4.44 (t, *J* = 4.1 Hz, 1H), 3.75 – 3.67 (m, 7H, 6H corresponding to OMe groups, and 1H refers to the α-amido ^{1}H peak according to HSQC), 2.47 (ddd, *J* = 13.7, 8.9, 4.6 Hz, 1H), 2.25 (dd, *J* = 14.3, 3.6 Hz, 1H), 1.19 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.8 (C), 161.4 (C), 144.7 (C), 131.9 (C), 123.1 (CH), 121.8 (C), 120.4 (CH), 117.7 (CH), 112.0 (CH), 106.3 (CH), 102.8 (CH), 98.5 (CH), 55.4 (CH3), 43.7 (CH), 42.2 (CH), 42.2 (CH_2), 23.5 (CH3). **HRMS** (ESI, m/z) calcd for $C_{21}H_{22}N_2O_3Na^+$, 373.15226 $[M + Na]^+$; found, 373.15163.

Synthesis of lactam *cis*-7



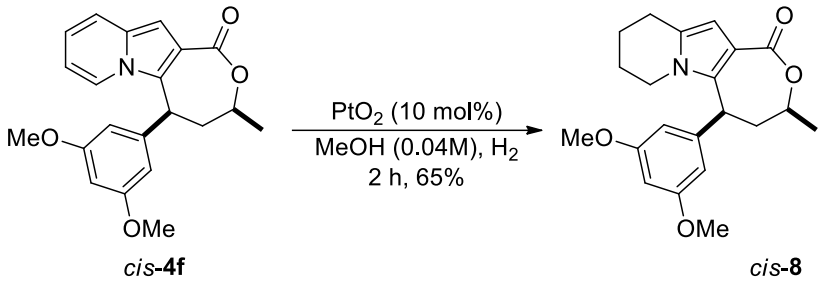
In a sealed tube, NEt_3 (45.5 μL**,** 0.33 mmol, 12 equiv) was added to a solution of *syn*-**6** (10.4 mg, 0.027 mmol) in dry toluene (1 mL, 0.027 M) and the reaction was keeping under reflux overnight. After cooling to room temperature, the reaction solution was directly purified by column chromatography (pure EtOAC) to furnish lactam *cis*-**7** as a milky semi-solid (6.8 mg, 70% yield).

5-(3,5-dimethoxyphenyl)-3-methyl-2,3,4,5-tetrahydro-1H-azepino[3,4-b]indolizin-1-one (cis-7)



^{1}H NMR (500 MHz, CD_3CN) δ 7.44 (d, *J* = 7.4 Hz, 1H), 7.44 – 7.39 (m, 1H), 6.88 (s, 1H), 6.68 (ddd, *J* = 9.1, 6.4, 1.0 Hz, 1H), 6.44 – 6.38 (m, 1H), 6.31 (t, *J* = 2.2 Hz, 1H), 6.24 (s, 1H), 6.12 (d, *J* = 2.2 Hz, 2H), 4.54 (dd, *J* = 11.5, 7.7 Hz, 1H), 3.70 – 3.63 (m, 7H, 6H corresponding to OMe groups, and 1H refers to the α-amido ^{1}H peak according to the HSQC, TOCSY and NOESY), 2.50 (dd, *J* = 14.4, 7.7 Hz, 1H), 2.04 (ddd, *J* = 14.4, 11.6, 8.5 Hz, 1H), 1.28 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, CD_3CN) δ 162.4 (C), 146.9 (C), 132.8 (C), 125.2 (C), 124.4 (CH), 122.9 (C), 120.6 (CH), 118.6 (CH), 112.1 (CH), 105.9 (CH), 102.4 (CH), 99.1 (CH), 55.9 (CH3), 48.0 (CH2), 47.7 (CH), 44.8 (CH), 22.3 (CH3). **HRMS** (ESI, m/z) calcd for $C_{21}H_{23}N_2O_3^+$, 351.17032 $[M + H]^+$; found, 351.17055.

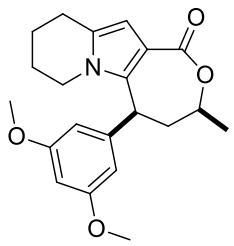
Synthesis of 5,6,7,8-tetrahydro-indolizine cis-(8) [2]



cis-**4f** *cis*-**8**

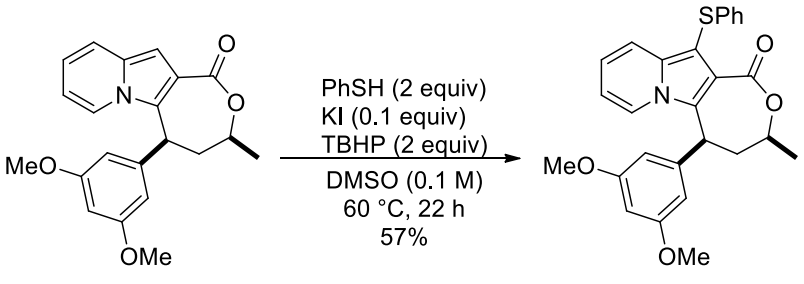
A 5 mL round bottom flask containing *cis*-**4f** (14.8 mg, 0.042 mmol) in methanol (1 mL, 0.04 M) was purged with nitrogen followed by the addition of PtO_2 (0.96 mg, 10 mol%). The reaction atmosphere was changed to hydrogen gas (balloon) and the heterogenous mixture was stirred for 2 hours, then it was poured on a celite pad, filtered, and the rection solvent removed under reduced pressure. The crude mixture was purified by column chromatography (Hex/EtOAc 75:25) to yield indolizine lactone *cis*-**8** as a colorless oil (9.7 mg, 65% yield).

***5-(3,5-dimethoxyphenyl)-3-methyl-4,5,7,8,9,10-hexahydrooxepino[3,4-b]indolizin-1(3H)-one* (*cis*-8)**



^{1}H NMR (500 MHz, $CDCl_3$) δ 6.40 – 6.38 (m, 1H), 6.31 (t, *J* = 2.2 Hz, 1H), 6.14 (d, *J* = 2.2 Hz, 2H), 4.58 (p, *J* = 6.7 Hz, 1H), 4.15 (dd, *J* = 11.8, 7.7 Hz, 1H), 3.72 (s, 6H), 3.62 – 3.53 (m, 1H), 3.09 – 3.01 (m, 1H), 2.76 (dt, *J* = 16.2, 5.4 Hz, 1H), 2.72 – 2.64 (m, 1H), 2.35 (dd, *J* = 15.6, 7.6 Hz, 1H), 2.16 (ddd, *J* = 15.7, 11.9, 7.6 Hz, 1H), 1.82 – 1.68 (m, 4H), 1.40 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.5 (C), 161.5 (C),146.0 (C), 134.0 (C), 130.6 (C), 112.9 (C), 108.7 (CH), 105.2 (CH), 98.6 (CH), 73.3 (CH), 55.5 (CH3), 45.2 (CH2), 44.3 (overlapped CH_2 and CH signals, see HSQC), 23.4 (CH2), 23.4 (CH2), 22.4 (CH3), 20.4 (CH2). **HRMS** (ESI,m/z): calcd for $C_{21}H_{25}NO_4Na$, 378,16758 $[M+H]^+$; found, 378,16703.

Synthesis of thiolated analogue cis-9 [3]

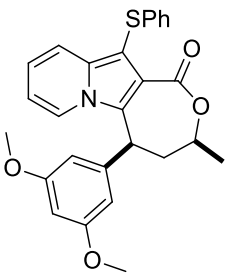


cis-**4f** *cis*-**9**

In a 4 mL dram vial, indolizine lactone *cis*-**4f** (23.8 mg, 0.068 mmol) was dissolved in DMSO (680 μL, 0.1 M) and thiophenol (14.9 mg, 13.8 μL, 0.135 mmol, 2 equiv), potassium iodide (1.1 mg, 0.007 mmol, 0.1 equiv) and tert-butyl hydroperoxide (5 M in decane, 27 μL, 0.135 mmol, 2 equiv) were sequentially

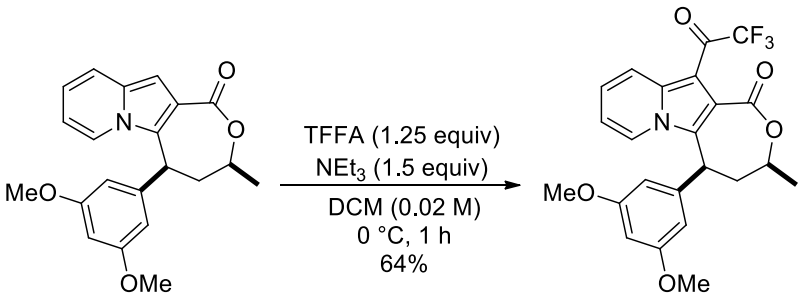
added. The vial was tightly sealed, and reaction was heated to 60 °C for 22 hours. After cooling to room temperature, distilled water was added (10 mL) and the aqueous phase extracted with EtOAc (3 x 15 mL). The organic phases were combined, dired wiht Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography (Hex/EtOAc 70:30) to yield cis-**9** as an orange wax (17.7 mg, 57% yield)

5-(3,5-dimethoxyphenyl)-3-methyl-11-(phenylthio)-4,5-dihydrooxepino[3,4-b]indolizin-1(3H)-one (cis-9)



^{1}H NMR (250 MHz, $CDCl_3$) δ 7.65 (d, *J* = 9.1 Hz, 1H), 7.54 (d, *J* = 7.1 Hz, 1H), 7.21 – 6.99 (m, 5H), 6.85 (dd, *J* = 8.7, 6.6 Hz, 1H), 6.63 – 6.50 (m, 1H), 6.33 (t, *J* = 2.2 Hz, 1H), 6.20 (d, *J* = 2.2 Hz, 2H), 4.67 (p, *J* = 6.7 Hz, 1H), 4.51 (dd, *J* = 11.4, 8.3 Hz, 1H), 3.70 (s, 6H), 2.60 (dd, *J* = 15.7, 8.3 Hz, 1H), 2.37 (ddd, *J* = 15.7, 11.4, 7.7 Hz, 1H), 1.44 (d, *J* = 6.5 Hz, 3H**). ^{13}C NMR** (63 MHz, $CDCl_3$) δ 164.5, 161.8, 143.9, 140.0, 137.0, 128.7, 126.2, 125.6, 124.9, 123.4, 120.9, 120.0, 119.2, 113.6, 105.0, 100.9, 99.1, 73.4, 55.4, 44.6, 43.6, 22.0. **HRMS** (ESI, m/z): calcd for $C_{27}H_{26}NO_4S^+$, 460.15771 [M + Na]$^+$; found, 460.15772.

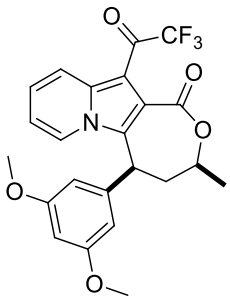
Synthesis of trifluoromethylated indolizine lactone *cis*-10



cis-**4f** *cis*-**10**

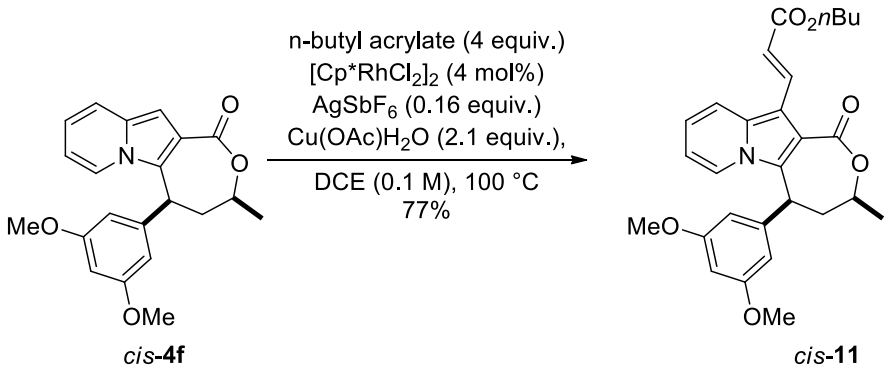
Under a positive nitrogen pressure, indolizine lactone *cis*-**5f** (28.1 mg, 0.08 mmol) was dissolved in dry dichloromethane (1 mL, 0.08 M), followed by the addition of NEt_3 (17 μL, 0.12 mmol, 1.5 equiv). The system was cooled to 0 ° C in an ice-water bath, and trifluoroacetic anhydride (13 μ, 20 mg, 0.096 mmol, 1.2 equiv) was added. Reaction was stirred at the same temperature for 1 hour then, diluted in dichloromethane (10 mL) and washed with $NaHCO_3$ (3 x 5 mL). The organic phase was dried with Na_2SO_4, filtered, and the organic solvent removed under reduced pressure leading to a residue that was purified by column chromatography (Hex/EtOAc 80:20 to 70:30). Lactone *cis*-**10** was obtained as a white foam (22.8 mg, 64% yield).

***5-(3,5-dimethoxyphenyl)-3-methyl-11-(2,2,2-trifluoroacetyl)-4,5-dihydrooxepino[3,4-b]indolizin-1(3H)-one* (*cis*-10)**



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 9.1 Hz, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.27 – 7.21 (m, 1H), 6.78 (td, *J* = 6.9, 1.3 Hz, 1H), 6.33 (t, *J* = 2.2 Hz, 1H), 6.18 (d, *J* = 2.2 Hz, 2H), 4.93 – 4.86 (m, 1H), 4.49 (dd, *J* = 10.9, 8.7 Hz, 1H), 3.69 (s, 3H), 2.65 (dd, *J* = 15.9, 8.7 Hz, 1H), 2.34 (ddd, *J* = 15.9, 10.9, 8.3 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 178.66 (q, *J* = 35.9 Hz), 165.1, 162.0, 142.9, 138.4, 126.8, 124.4, 119.7, 119.5, 116.4 (q, *J* = 290.3 Hz), 115.4, 108.0, 104.9, 99.3, 73.9, 55.5, 44.4, 42.7, 21.8. **HRMS** (ESI, m/z): calcd for $C_{23}H_{20}F_3NO_5Na^+$, 470.11858 [M + Na]$^+$; found, 470.11791

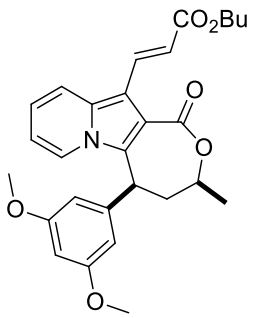
Procedure for Rh (III) catalyzed olefination [4]



cis-**4f** *cis*-**11**

A Schlenk tube was charged with indolizine lactone *cis*-5f (37.9 mg, 0.108 mmol), $Cu(OAc)_2.H_2O$ (45.2 mg, 0.227 mmol, 2.1 equiv), $AgSbF_6$ (5.93 mg, 0.017 mmol, 0.16 equiv), and the rhodium catalyst $[Cp^*RhCl_2]_2$ (2.64 mg, 4 mol %). The system was subject to three vacuum/nitrogen cycles, then 1,2-dichloroethane (1 ml) and *n*butyl acrylate (62.1 μl, 55.3 mg, 0.431 mmol, 4 equiv) were added under a positive nitrogen pressure. The Schlenk tube was sealed and the reaction was maintained under stirring at 100 °C for 24 hours. After cooling to room temperature, the reaction mixture were filtered on a small column (SiO_2, pure EtOAc), concentrade under reduced pressure and the crude purified by column chromatography (Hex/EtOAc 75:30 to 65:35) yielding olefinated analogue *cis*-**11** s a yellow solid (39.5 mg, 0.083 mmol, 77% yield). mp: 73-75 °C.

(E)-butyl 3-(5-(3,5-dimethoxyphenyl)-3-methyl-1-oxo-1,3,4,5-tetrahydrooxepino[3,4-b]indolizin-11-yl)acrylate (cis-11)



m.p. 73-75 °C. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.33 (d, *J* = 16.2 Hz, 1H), 7.84 (d, *J* = 9.2 Hz, 1H), 7.53 (d, *J* = 7.2 Hz, 1H), 6.96 (dd, *J* = 9.2, 6.5 Hz, 1H), 6.60 (t, *J* = 6.8 Hz, 1H), 6.37 (d, *J* = 16.3 Hz, 1H), 6.31 (t, *J* = 2.1 Hz, 1H), 6.17 (d, *J* = 2.2 Hz, 2H), 4.68 (p, *J* = 6.6 Hz, 1H), 4.44 (dd, *J* = 11.3, 8.4 Hz, 1H), 4.25 – 4.17 (m, 2H), 3.69 (s, 6H), 2.59 (dd, *J* = 15.7, 8.4 Hz, 1H), 2.36 (ddd, *J* = 15.7, 11.4, 8.0 Hz, 1H), 1.73 – 1.66 (m, 2H), 1.49 – 1.42 (m, 5H), 0.96 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 168.1, 165.9, 161.8, 143.6, 137.2, 132.8, 126.1, 123.7, 121.9, 119.6, 117.0, 116.1, 113.9, 110.8, 105.0, 99.1, 73.6, 64.2, 55.5, 44.5, 43.4, 31.0, 22.0, 19.4, 14.0. **HRMS** (ESI,m/z): calcd for $C_{28}H_{32}NO_6^+$, 478.22241 $[M+H]^+$; found, 478.22245.

Cytotoxicity essays

To evaluate the cytotoxicity of the compounds the following cell lines were purchased from American Type Culture Collection (ATCC, Manassas, Virginia, EUA) or Rio de Janeiro Cell Bank (BCRJ, Rio de Janeiro, Brazil), and used in the citotoxicity assays: **i**) Human prostate epithelial tumour cell (DU-145, ATCC: HTB-81); **ii**) Human breast epithelial tumour cell (MDA-MB-231, ATCC: HTB-26); **iii**) Non-tumour mouse liver fibroblast (FC3H, BCRJ: 0082); **iv**) Human non-tumour skin fibroblast (HFF-1, ATCC: SCRC-1041); **v**) Human prostate epithelial non-tumour cell (RWPE-1, BCRJ: 0389); **vi**) Human breast epithelial non-tumour cell (MCF-10A, ATCC: CRL-10317).

Cells **i** and **iii** were maintained in RPMI 1640 culture medium (Roswell Park Memorial Intitute – Cultilab®, Campinas, São Paulo, Brazil). Cells **ii** and **iv** in DMEM (Dulbecco's modified eagle medium – Cultilab®, Campinas, São Paulo, Brazil). Both were supplemented with 10% fetal bovine serum (FBS, Gibco™, Waltham, Massachusetts, USA). Cells **v** in serum-free keratinocyte medium (keratinocyte serum-free medium, K-SFM, Gibco™, Grand Island, New York, USA), supplemented with bovine pituitary extract (0.05 mg/mL, Thermo Fisher Scientific, Waltham, Massachusetts, EUA, catalog No.: 13028014) and recombinant human epidermal growth factor (5 ng/mL, Merck KGaA, Darmstadt, Germany, CAS No.: 62253-63-8). Finally, **vi** cells were cultured in DMEM/F12 (Thermo Fisher Scientific, Waltham, Massachusetts, EUA, catalog No.: 11320033) medium with the addition of 5% horse serum (Thermo Fisher Scientific, Waltham, Massachusetts, EUA, catalog No.: 26050088), epidermal growth factor (20 ng/mL, Merck KGaA, Darmstadt, Germany, CAS No.: 62253-63-8), hidrocortisona (0.5 µg/mL, Sigma-Aldrich®, Burlington, Massachusetts, EUA, CAS No.: 50-23-7) and insulin (10 µg/mL, Sigma-Aldrich®, Burlington, Massachusetts, EUA, CAS No.: 11061-68-0). In all the aforementioned cases, penicillin (200 U/mL, CAS No.: 69-57-8), streptomycin (100 µg/mL, CAS No.: 3810-74-0) and L-

glutamine (2 mM, CAS No.: 56-85-9) (Sigma-Aldrich®, Burlington, Massachusetts, United States) were added.

Cells in culture were maintained in an incubator at 37°C and 5% CO_2 until 75-90% confluence was reached. In order to ensure that the cells used in the assays were in similar conditions, a cell stock was initially established by freezing at their respective passage numbers. Freezing was performed by adding 3 x 10^6 cells in a solution of FBS containing 5% dimethyl sulfoxide (DMSO, Merck KGaA, Darmstadt, Germany, CAS No.: 67-68-5). Cell suspension was placed in cryotubes in a freezer at -80°C for 24h, which ensured the gradual reduction of temperature. After freezing, the cells were stored in dewar with liquid nitrogen (-196°C). All procedures involving the manipulation of cells were performed under aseptic conditions. The materials were manipulated in tissue culture hood previously exposed to ultraviolet light for 15 minutes and disinfected with 70% ethanol. To perform the assays, the cells were thawed in a 37°C thermal bath and cultured in 75 cm^2 culture bottles (Corning®, Corning, New York, USA, catalog No.: 430168). Once cell monolayer confluence was reached, the cells were sub-cultured and, when necessary, frozen and/or plated.

The antiproliferative activities of the lactones, colchicine (Sigma-Aldrich®, Burlington, Massachusetts, United States, CAS No.: 64-86-8) and doxorubicin (Sigma-Aldrich®, Burlington, Massachusetts, United States, CAS No.: 25316-40-9) were determined by a standard resazurin (Sigma-Aldrich®, Burlington, Massachusetts, United States, CAS No.: 62758-13-8) assay.[5,6] In brief, cells were seeded into 96-well plates at a density of 4×10^3 log phase cells per well and they were incubated at 37°C in an atmosphere containing 5% CO_2. 24h later, eleven drug dilutions (100 to 0.097 μM) were distributed in triplicate and cells were incubated for 72h. All the compounds were prepared in DMSO at 10 mM concentration and 100-fold dilutions were performed in each respectively growth medium. Final DMSO concentrations did not reach 1% v/v. Then, the drug-containing medium was removed and replaced with 100 μL of the respectively fresh medium (without phenol red and FBS) plus 20 μL resazurin solution in 1× phosphate-buffered saline (Gibco™, Grand Island, New York, USA, catalog No.: 10010023). After 4h of incubation, the fluorescence was measured at 488 nm by a microplate spectrophotometer (SpectraMax Gemini EM, Molecular Devices, Silicon Valley, California, USA). The data were calculated and plotted as the per cent nonviability compared to the control. The 50% inhibitory concentration (IC_{50}) values were determined using a curve-fitting program within the GraphPad Prism software [3]. The IC_{50} was defined as the concentration that reduced the fluorescence of the untreated wells by 50% of the vehicle in the resazurin assay. At least three independent assays were performed. Doxorubicin [IC_{50} (DU-145) = 0.095±0.005 μM; IC_{50} (MDA-MB-231) = 0.383±0.025 μM; CC_{50} (FC3H) = 0.445 ± 0.012 μM; CC_{50} (HFF-1) = 0.468 ± 0.009 μM] and colchicine [IC_{50} (DU-145) = 0.014 ± 0.002 μM; IC_{50} (MDA-

MB-231) = 0.009 ± 0.001 μM; CC_{50} (FC3H) 0.019 ± 0.001 μM; CC_{50} (HFF-1) = 0.024 ± 0.003 μM] were used as positive controls.

3. References

1 J. T. M. Correia, B. List and F. Coelho, *Angew. Chemie Int. Ed.*, 2017, **56**, 7967.

2 B. V. M. Teodoro, J. T. M. Correia and F. Coelho, *J. Org. Chem.*, 2015, **80**, 2529.

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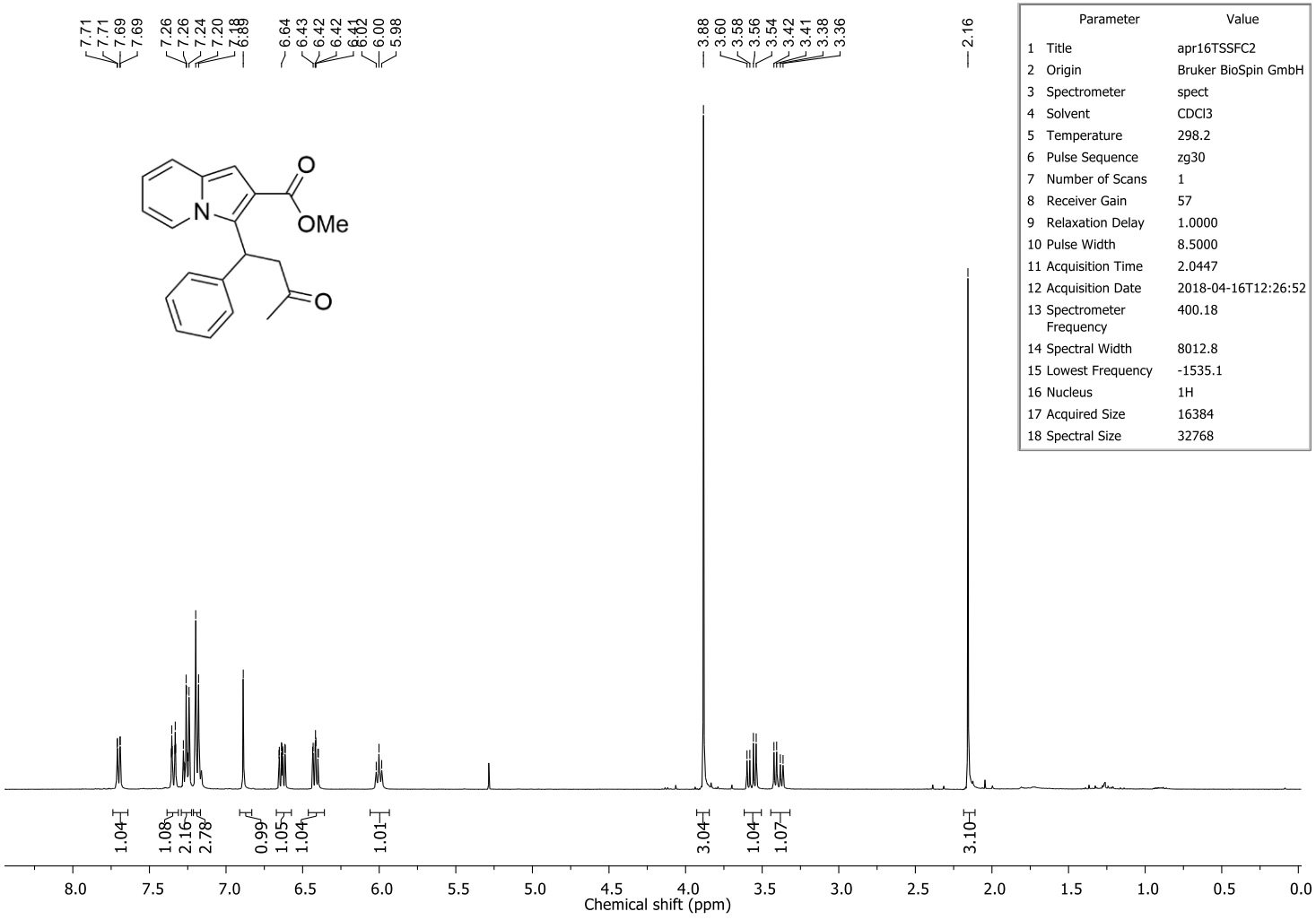
5 R. D. Fields and M. V Lancaster, *Am. Biotechnol. Lab.*, 1993, **11**, 48.

6 M. Lopez-Lazaro, *Curr. Med. Chem.*, 2015, 22, 1324–1334.

4. Copies of ^{1}H and ^{13}C NMR spectra



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3	Spectrometer	spect
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9	Relaxation Delay	1.0000
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16	Nucleus	1H
17	Acquired Size	16384
18	Spectral Size	32768

Figure 1. ^{1}H NMR spectrum of compound **3a**.

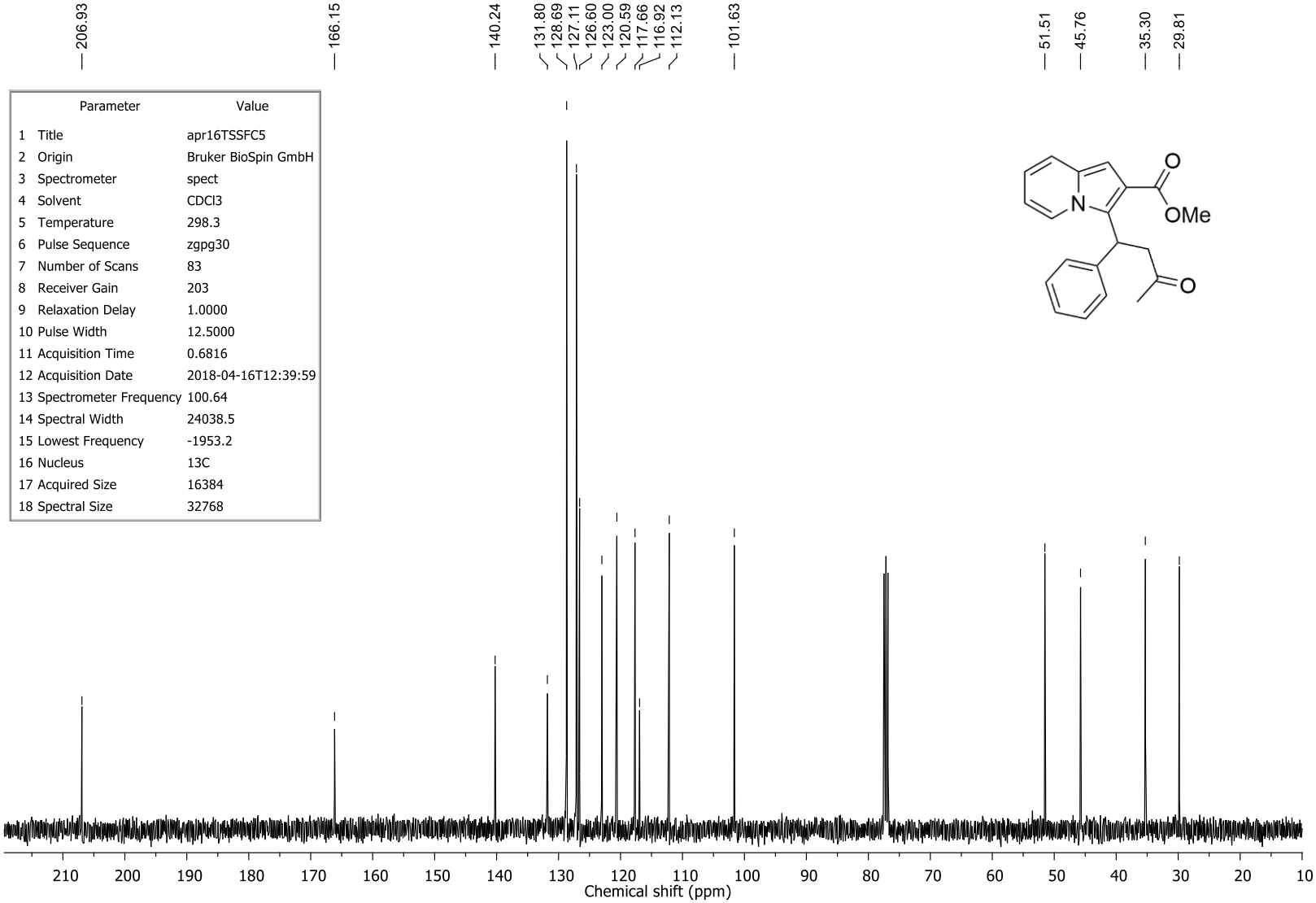

Figure 2. ^{13}C NMR spectrum of compound **3a**

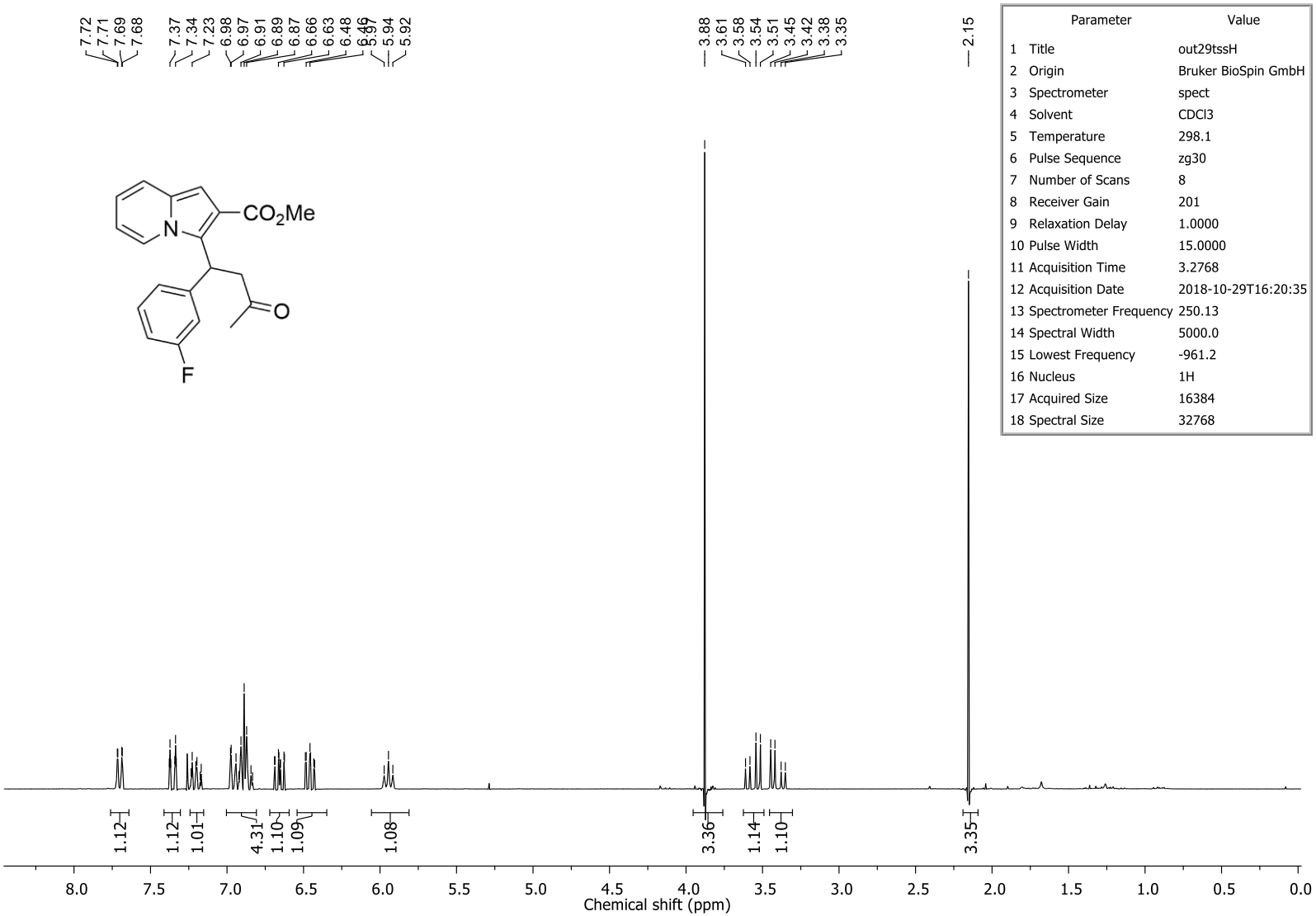

Figure 3. ^{1}H NMR spectrum of compound **3b.**

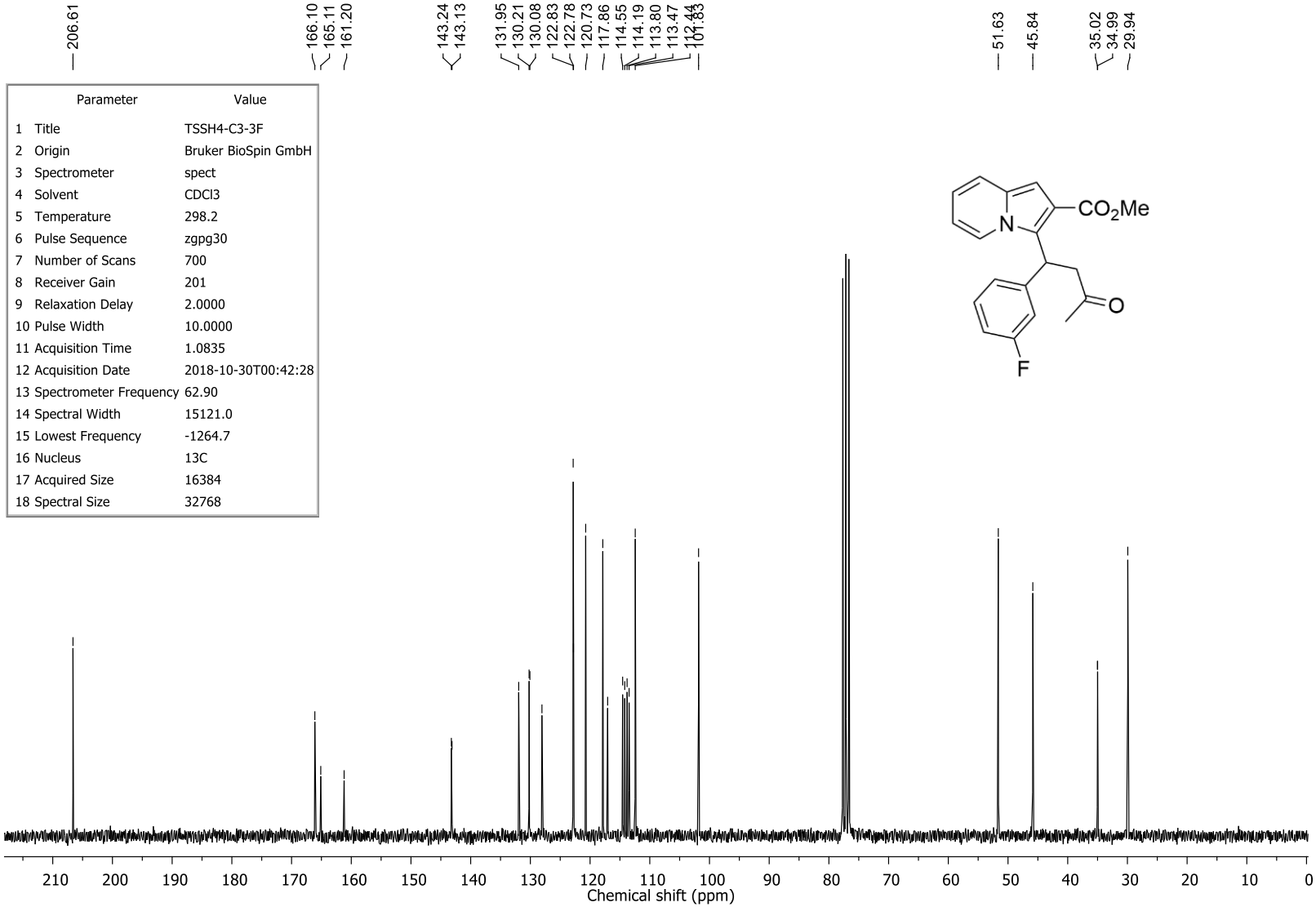

Figure 4. ^{13}C NMR spectrum of compound **3b.**

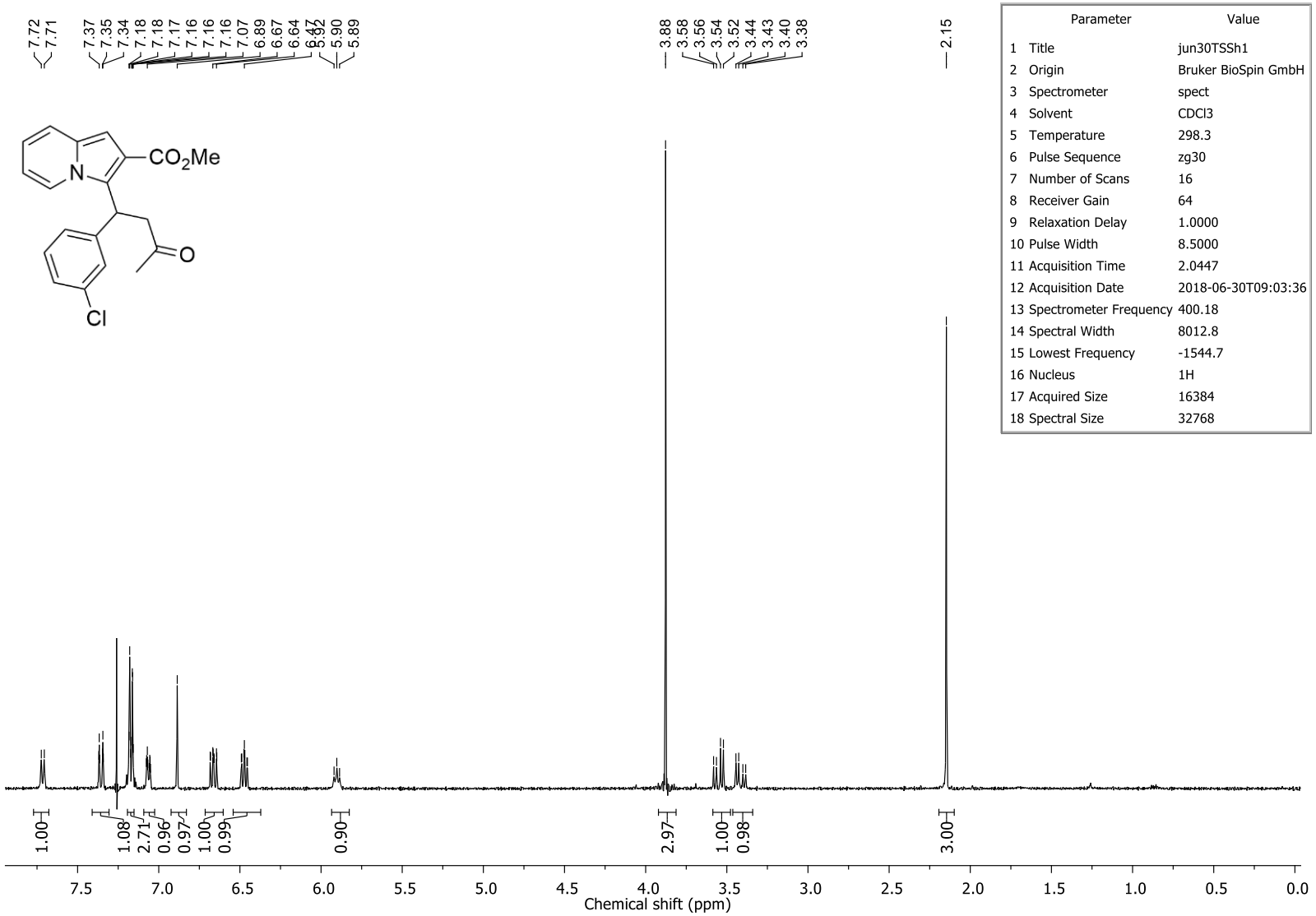

Figure 5. ^{1}H NMR spectrum of compound **3c.**

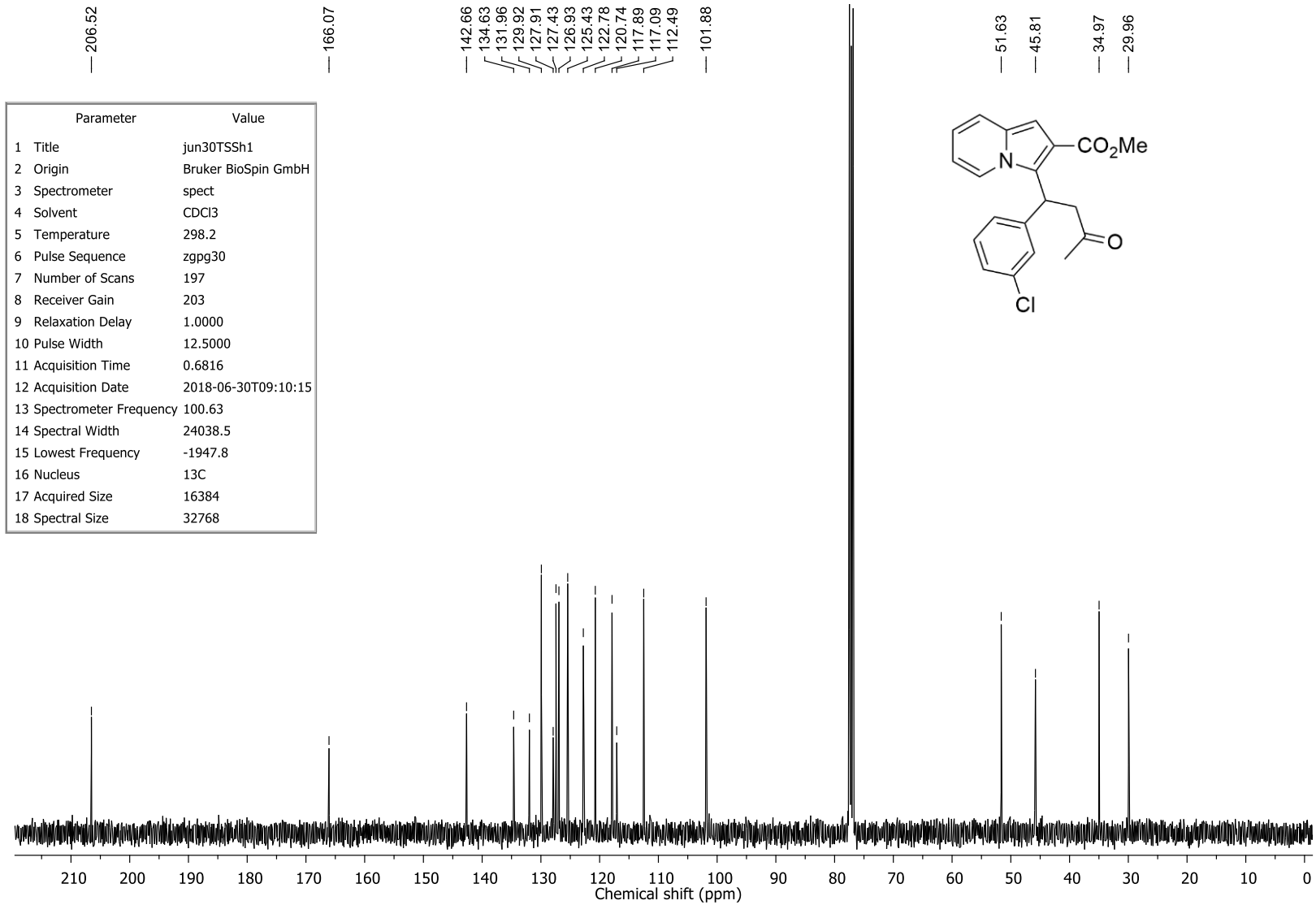

Figure 6. ^{13}C NMR spectrum of compound **3c.**

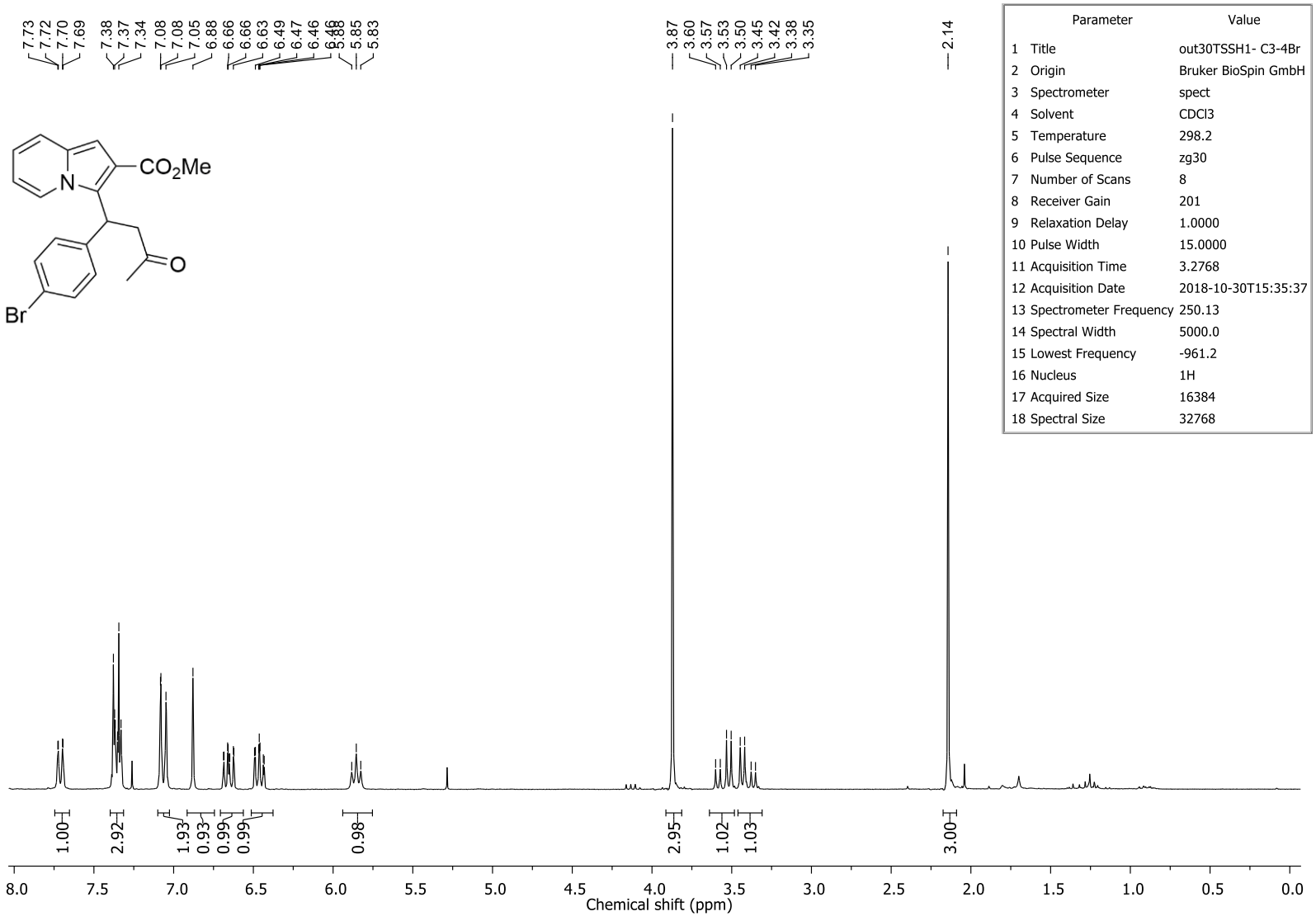

Figure 7. ^{1}H NMR spectrum of compound **3d.**

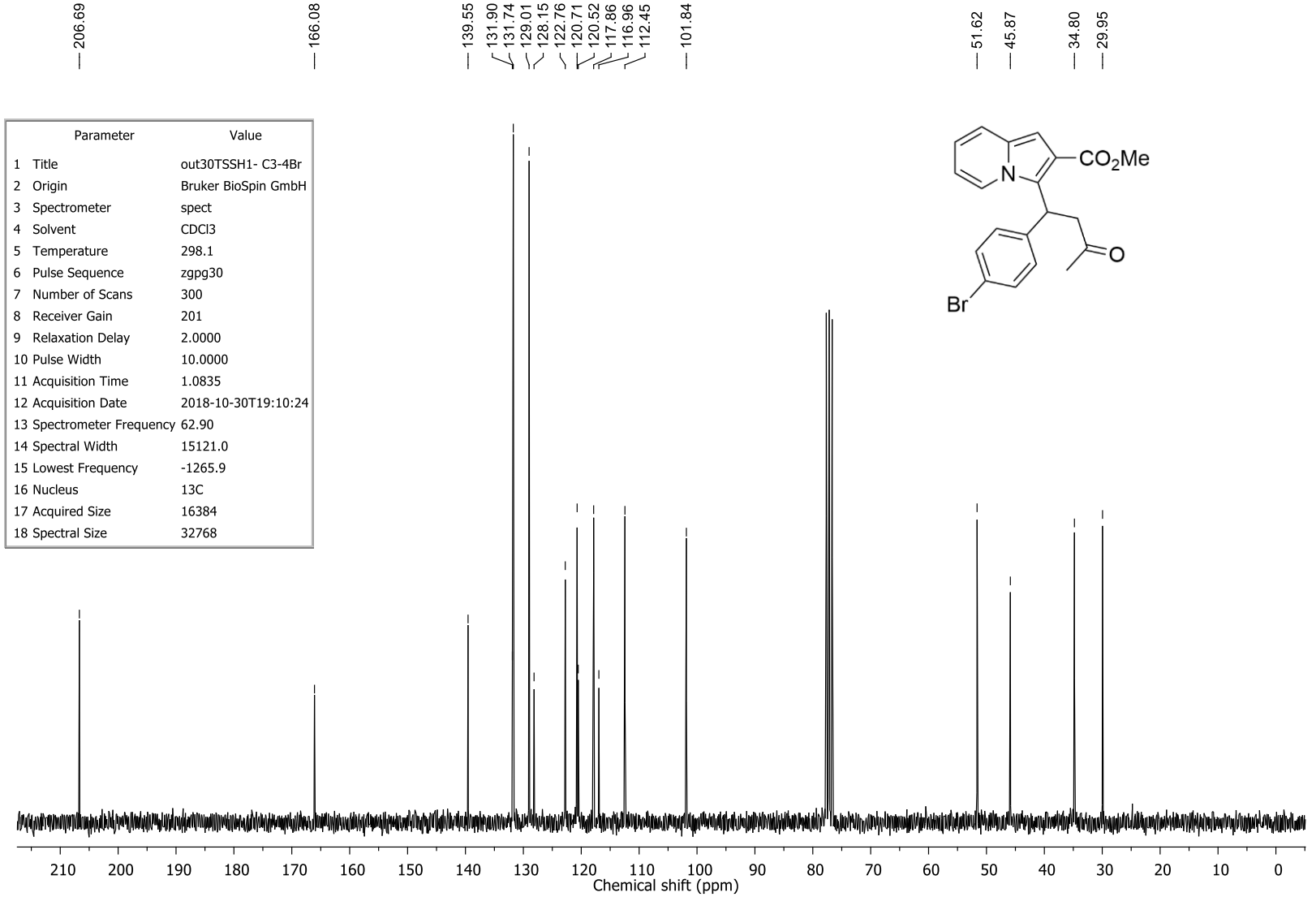

Figure 8. ^{13}C NMR spectrum of compound **3d.**

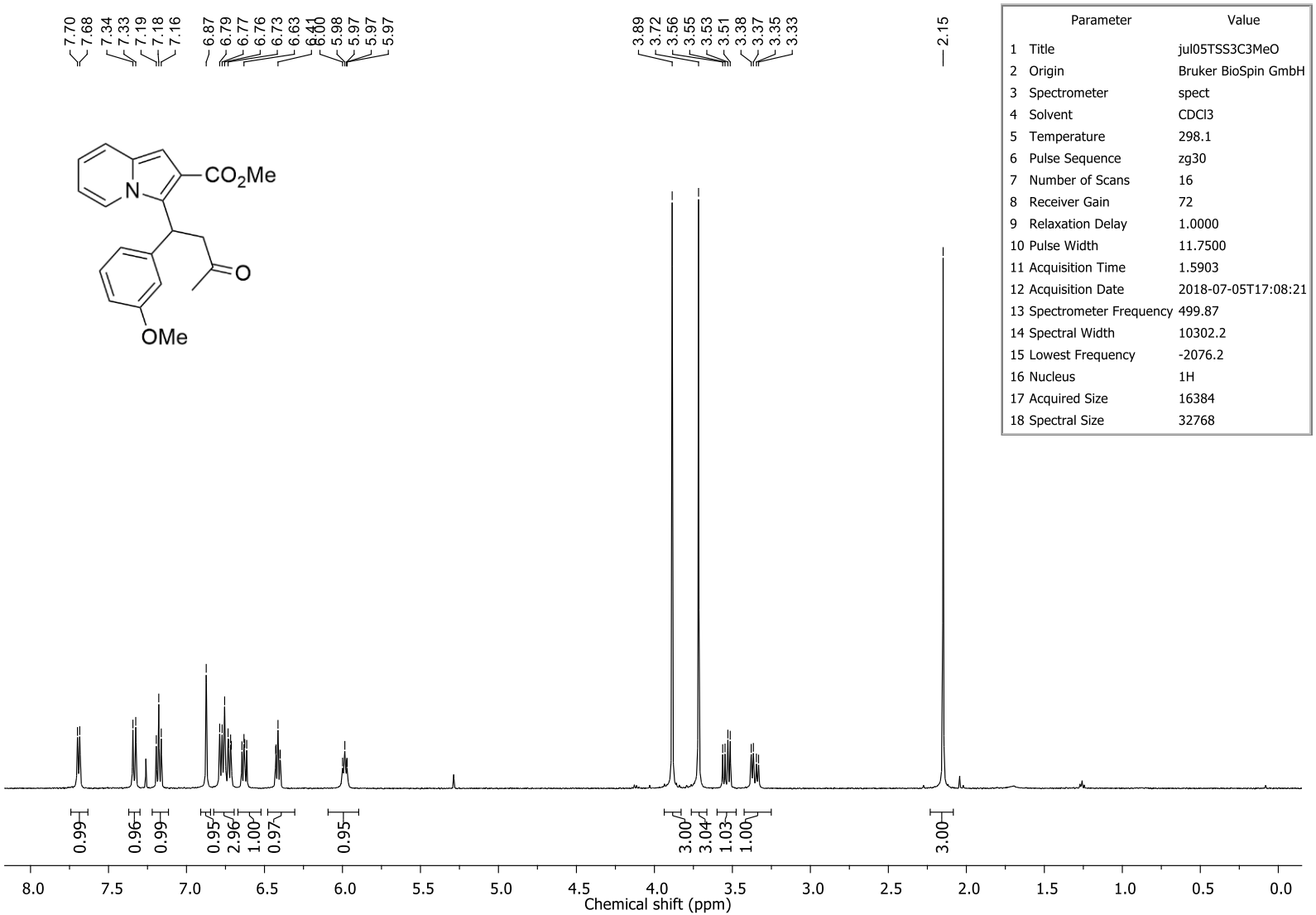

Figure 9. ^{1}H NMR spectrum of compound **3e.**

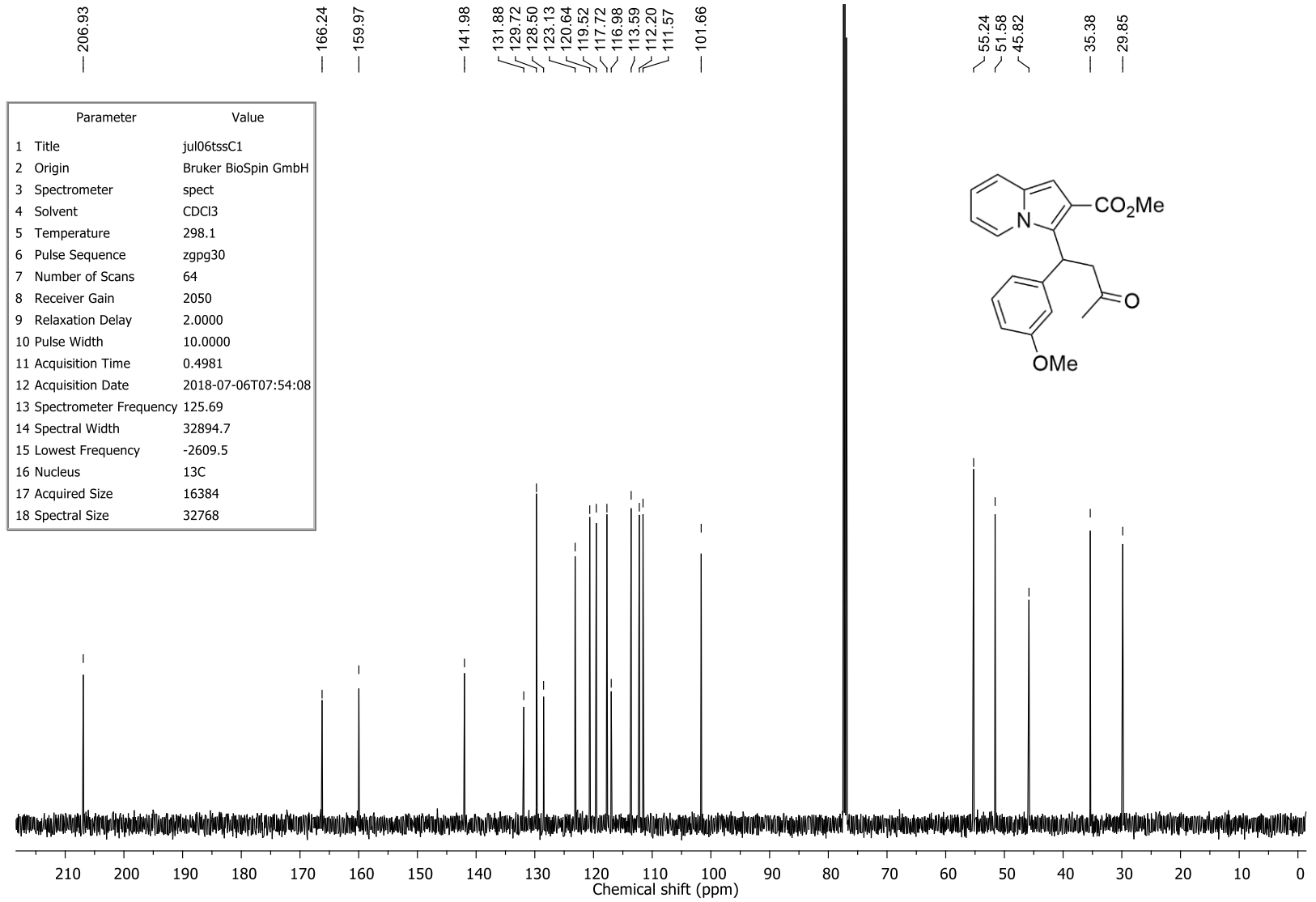

Figure 10. ^{13}C NMR spectrum of compound **3e.**

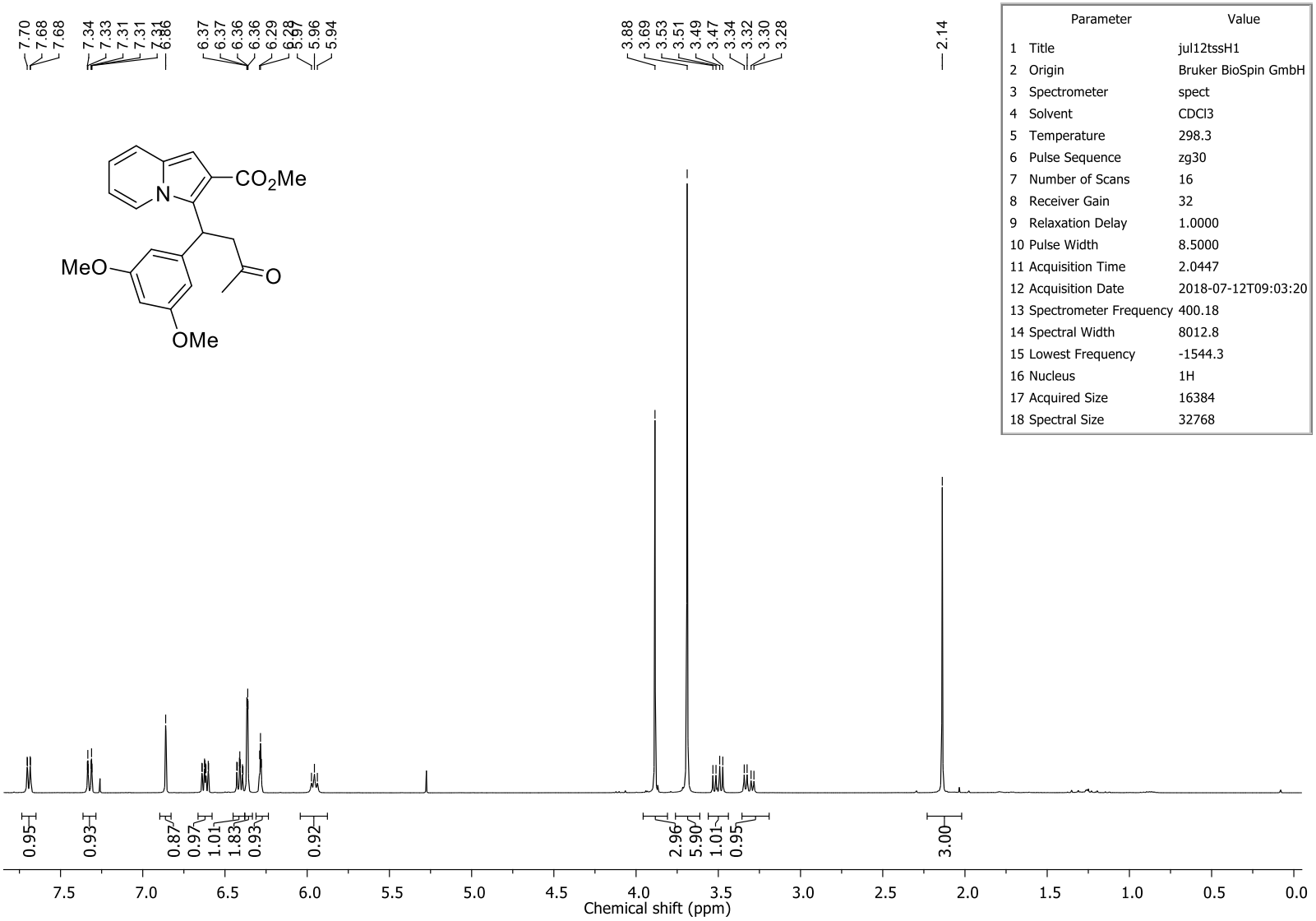

Figure 11. ^{1}H NMR spectrum of compound **3f.**

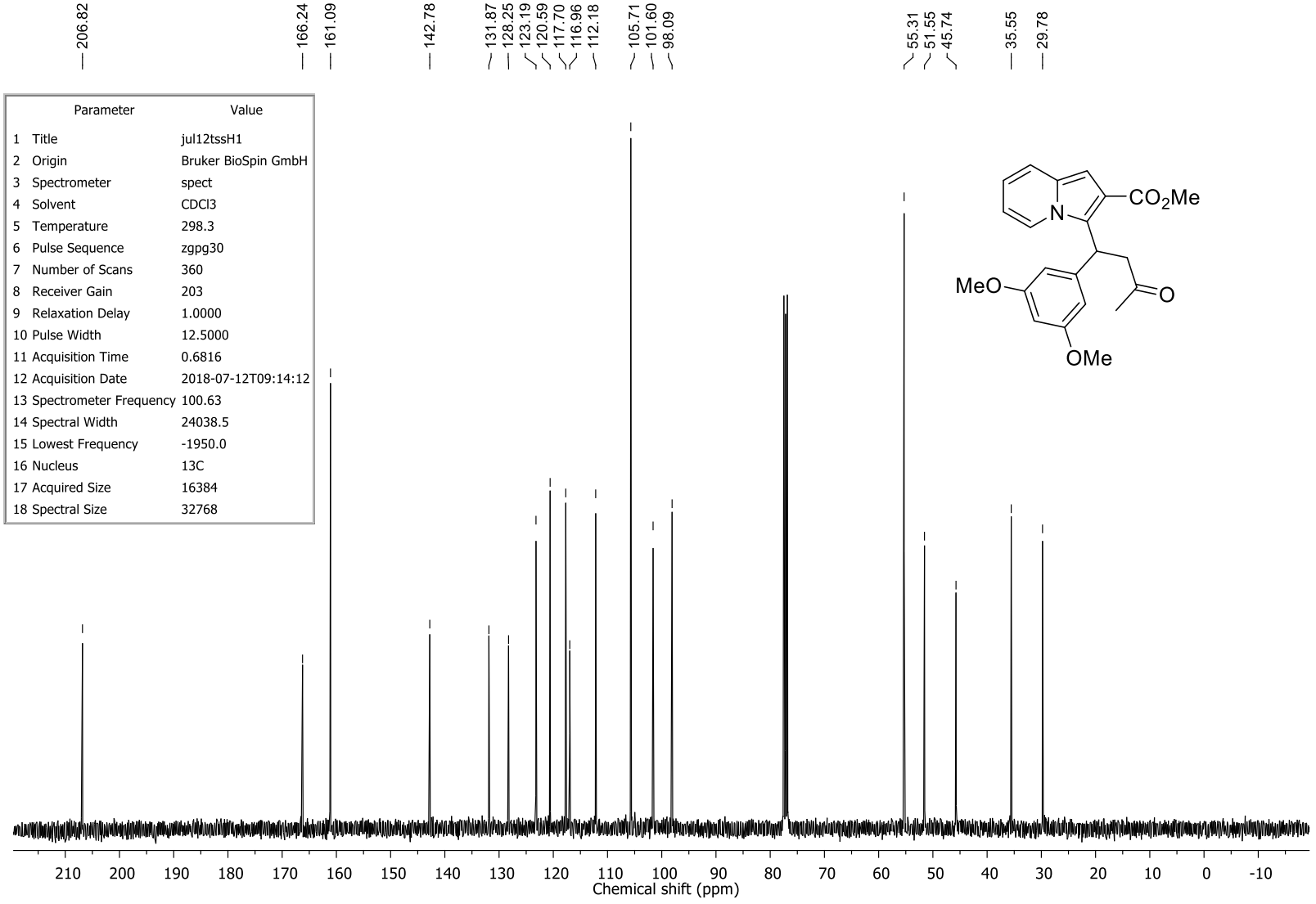

Figure 12. ^{13}C NMR spectrum of compound **3f.**

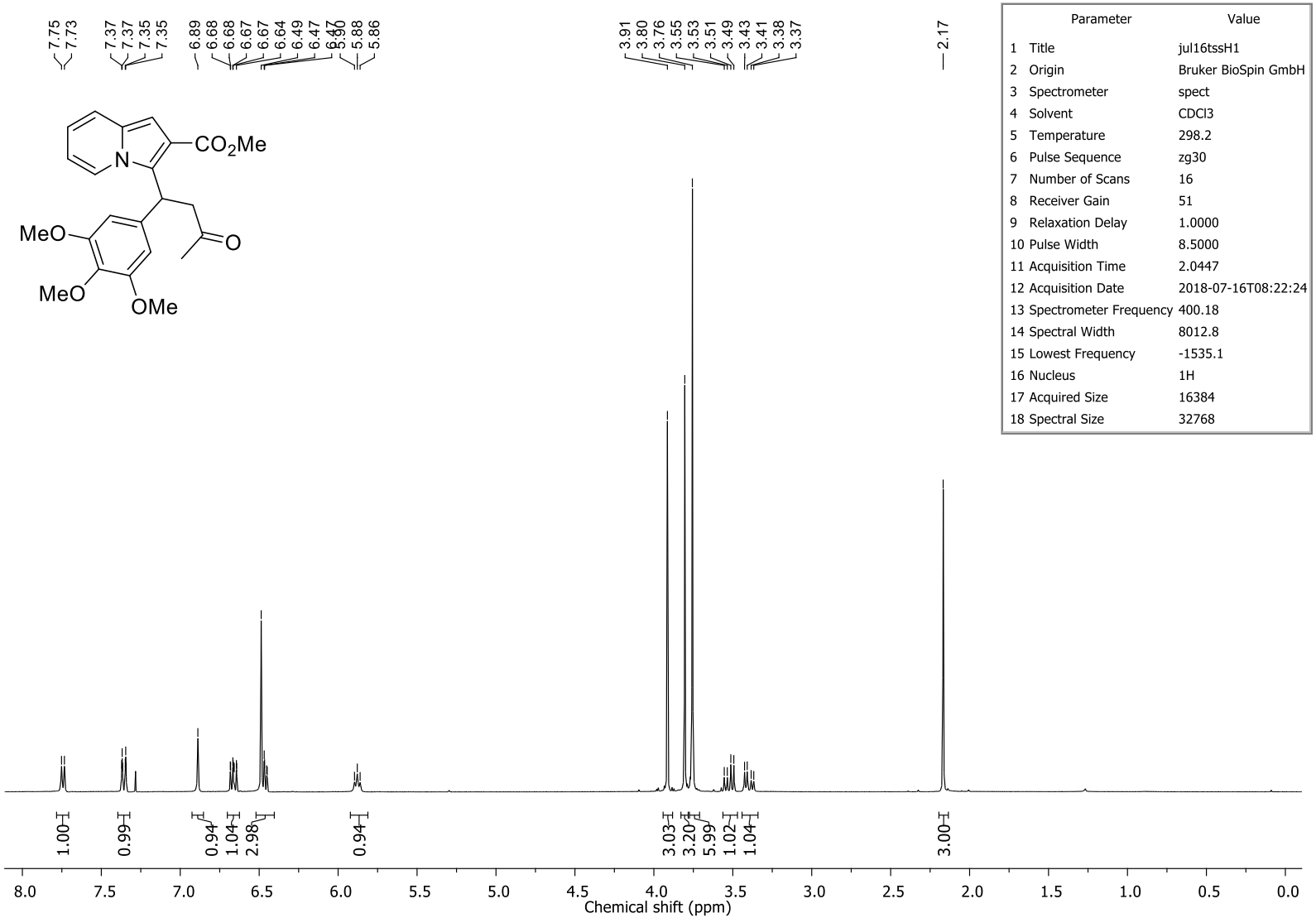

Figure 13. ^{1}H NMR spectrum of compound **3g.**

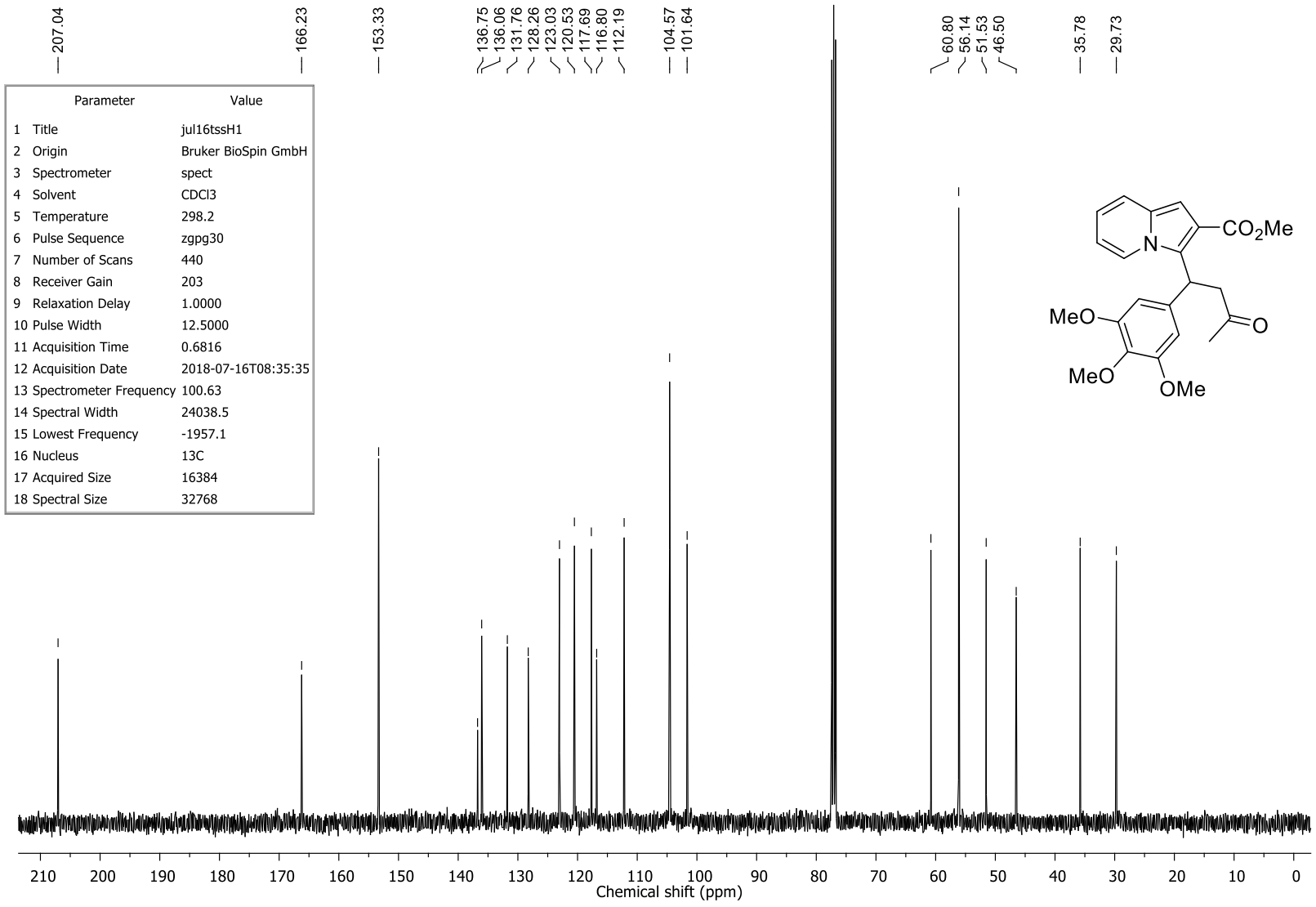

Figure 14. ^{13}C NMR spectrum of compound **3g.**

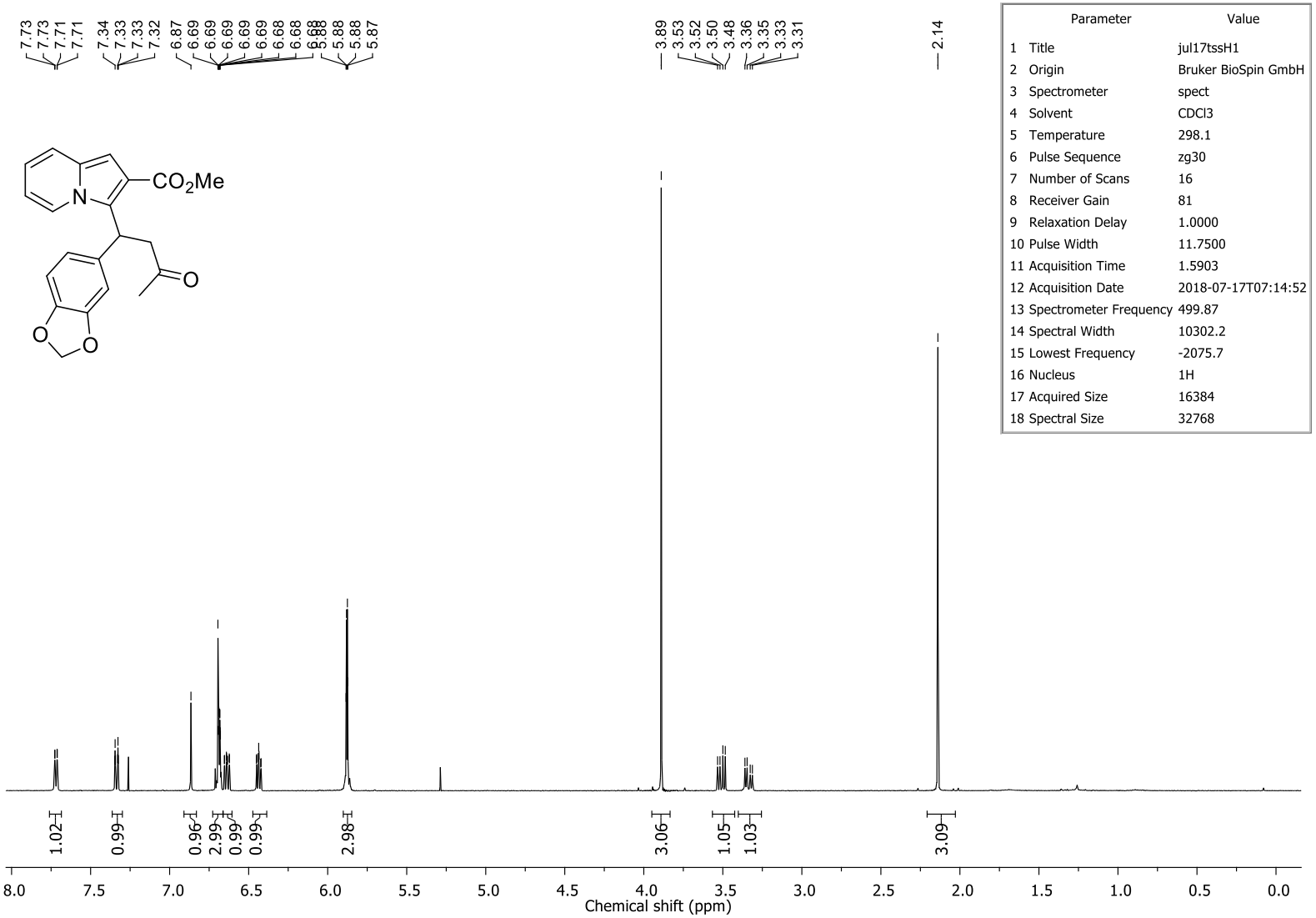

Figure 15. ^{1}H NMR spectrum of compound **3h.**

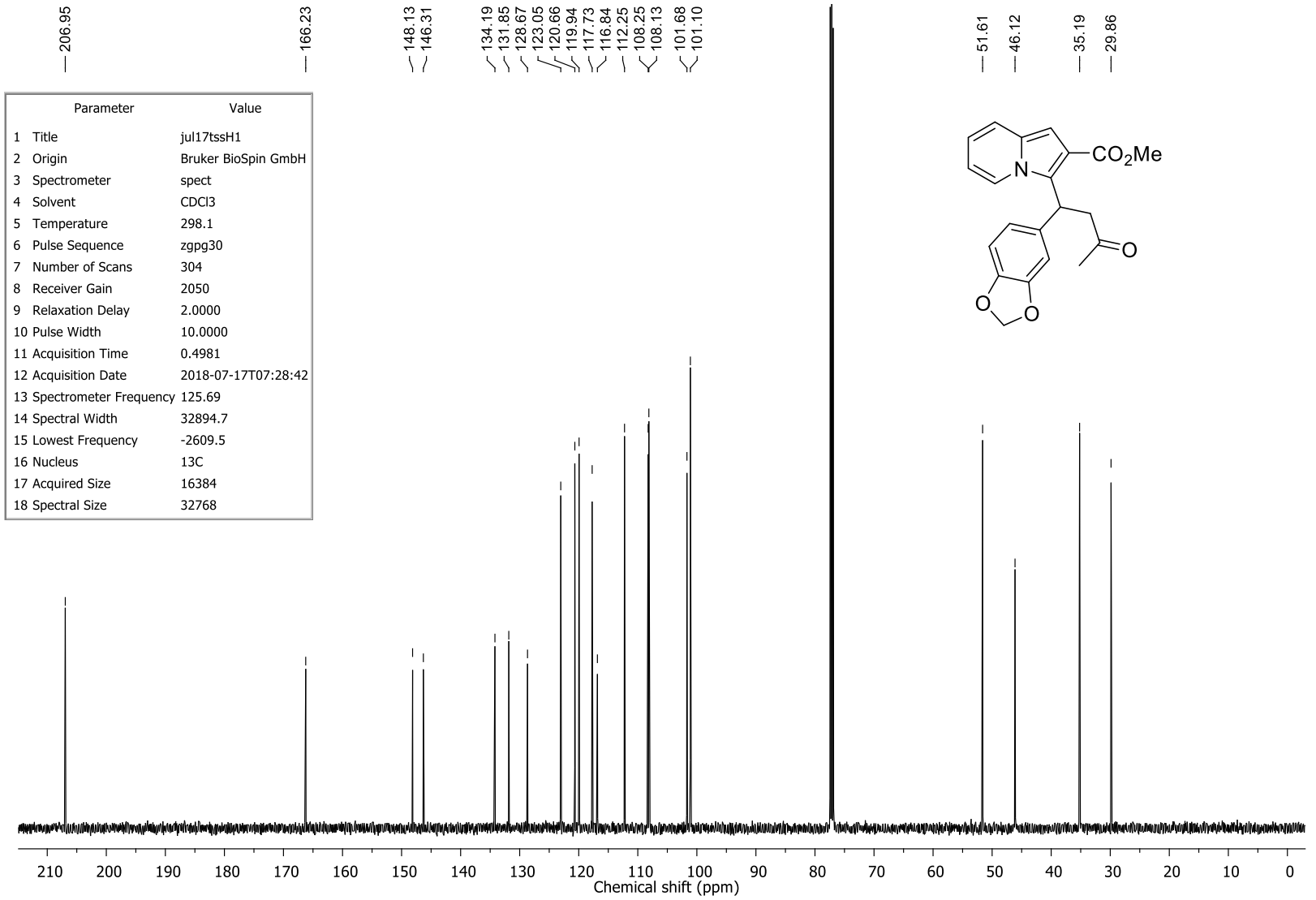

Figure 16. ^{13}C NMR spectrum of compound **3h.**

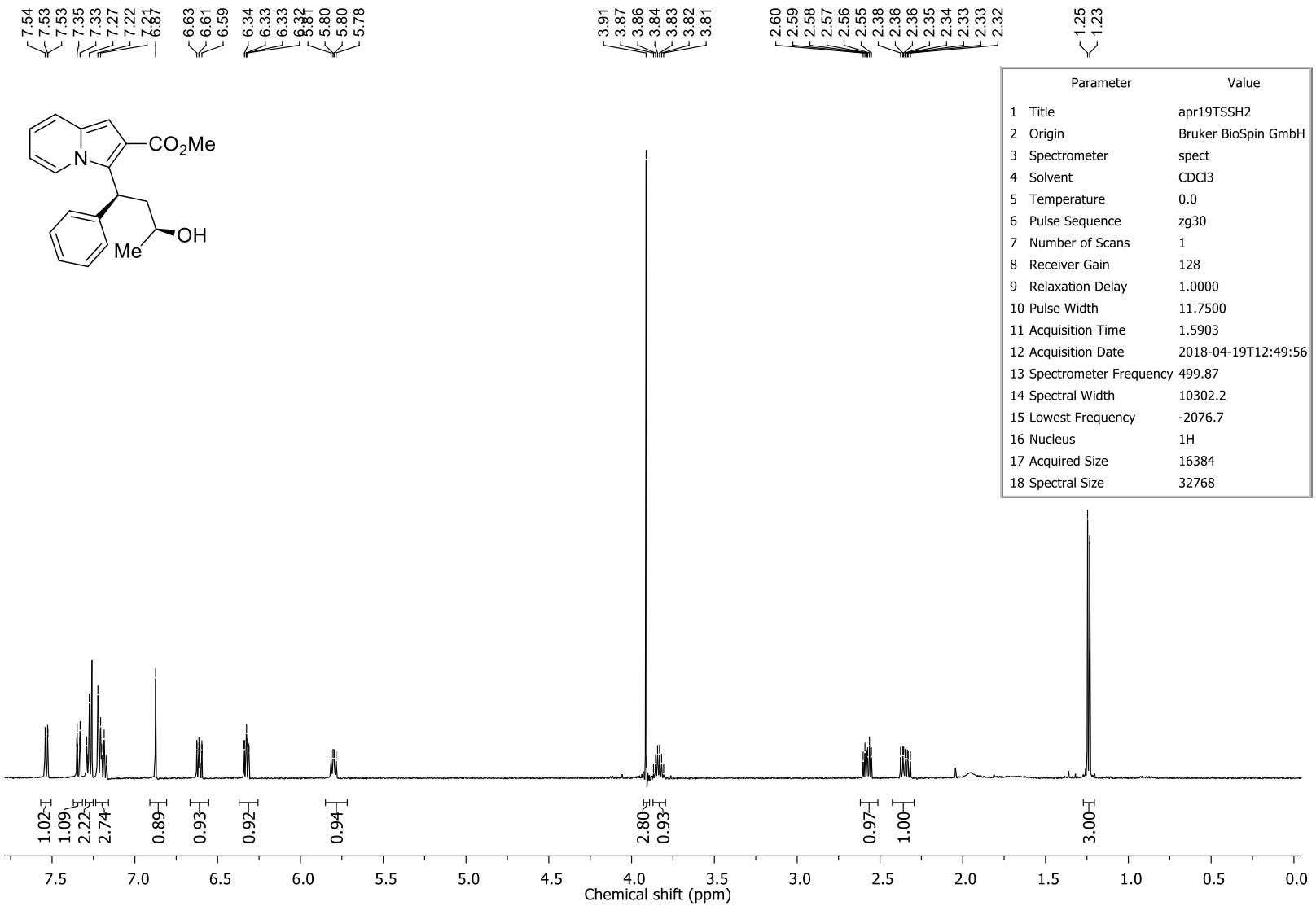

Figure 17. ^{1}H NMR spectrum of compound *syn*-**5a.**

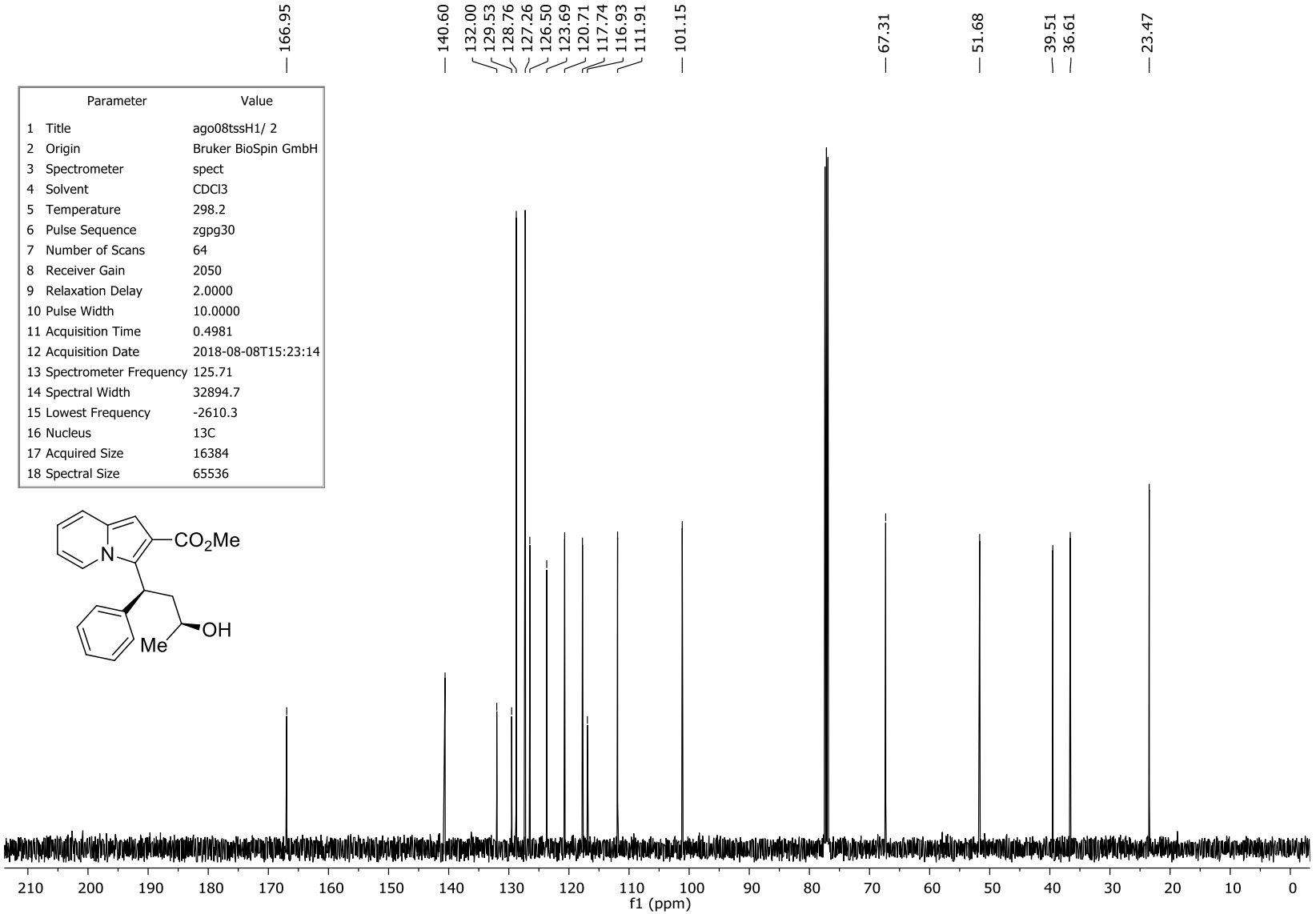

Figure 18. ^{13}C NMR spectrum of compound *syn*-**5a.**

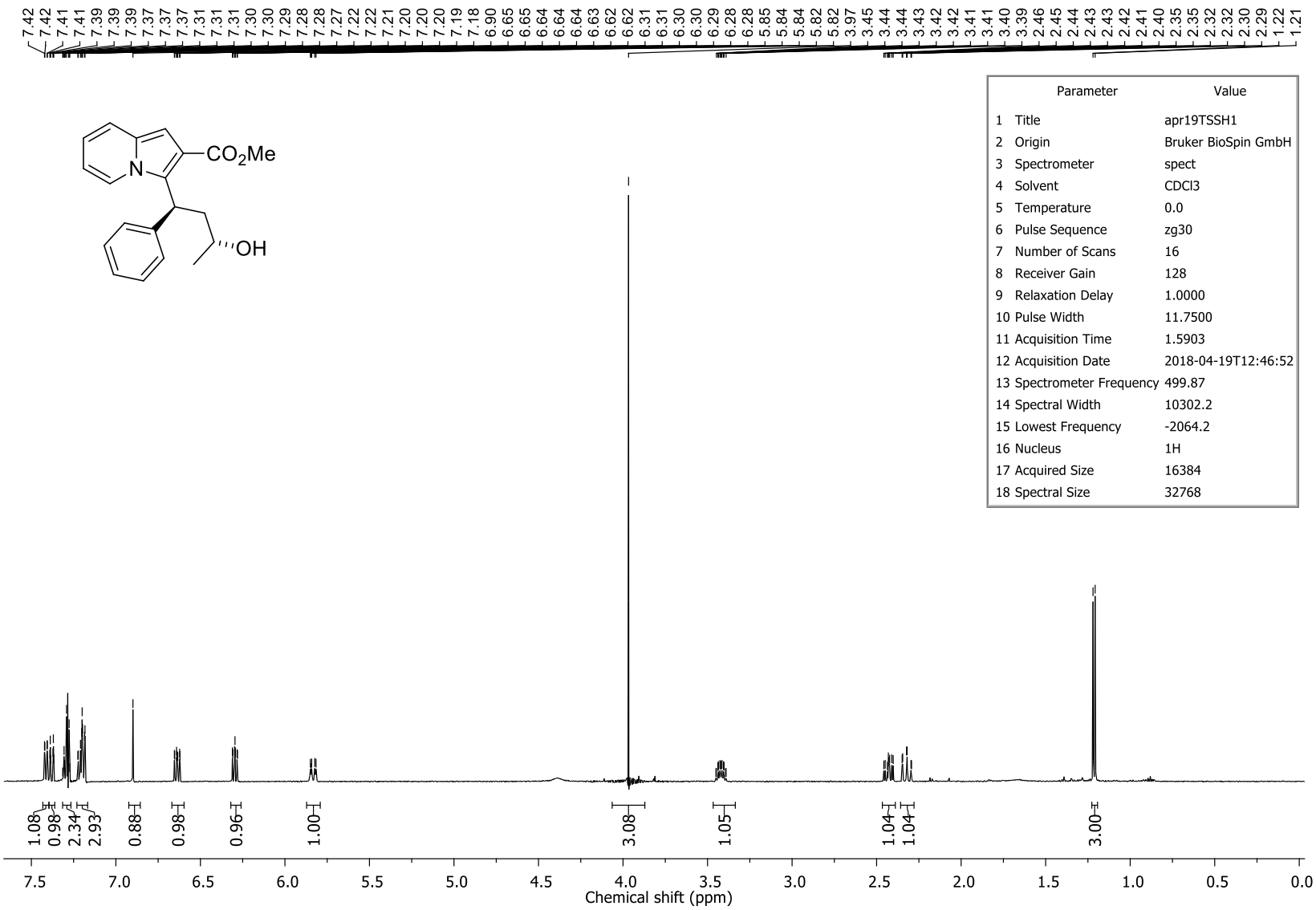

Figure 19. ^{1}H NMR spectrum of compound *anti*-**5a.**

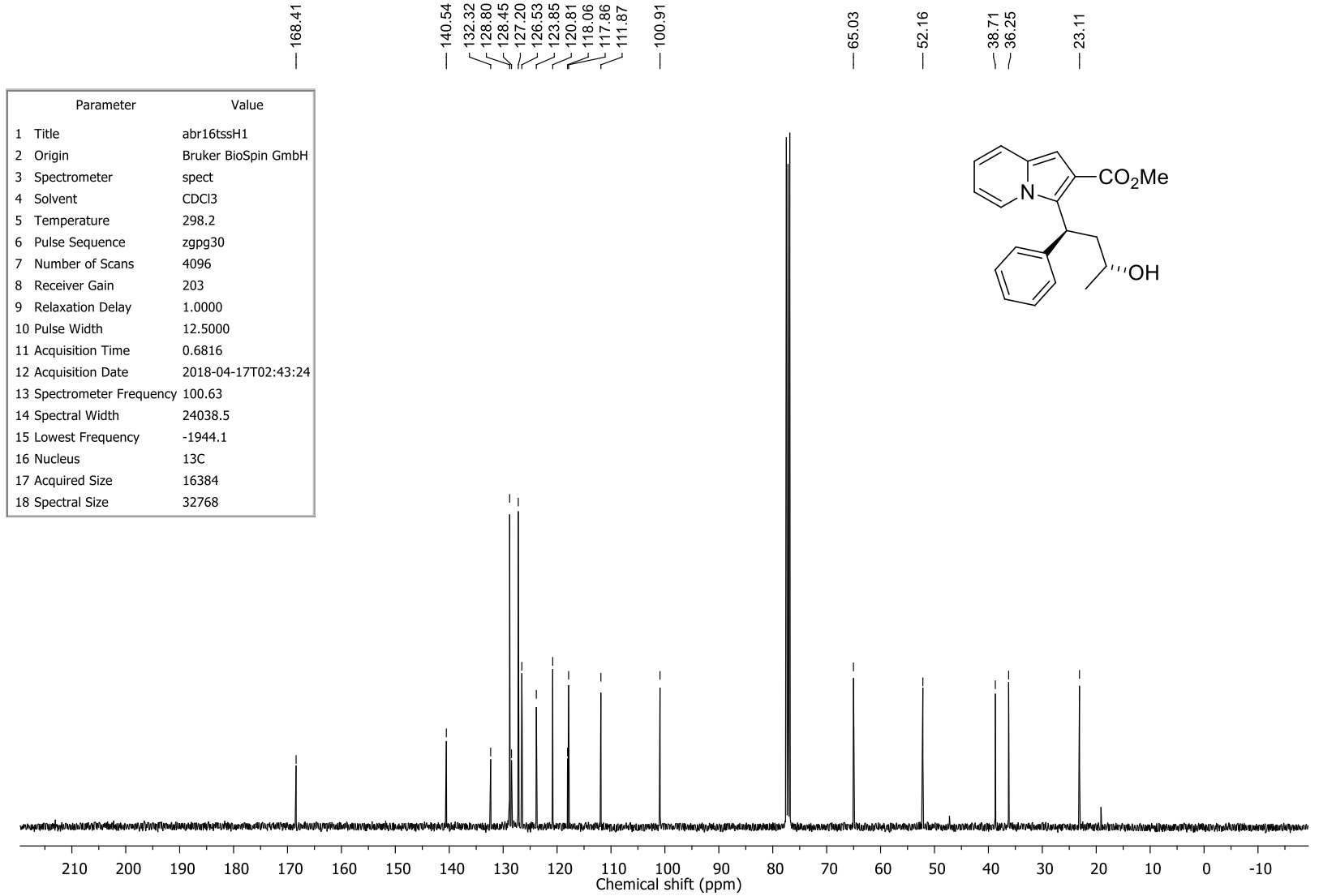

Figure 20. ^{1}H NMR spectrum of compound *anti*-**5a.**

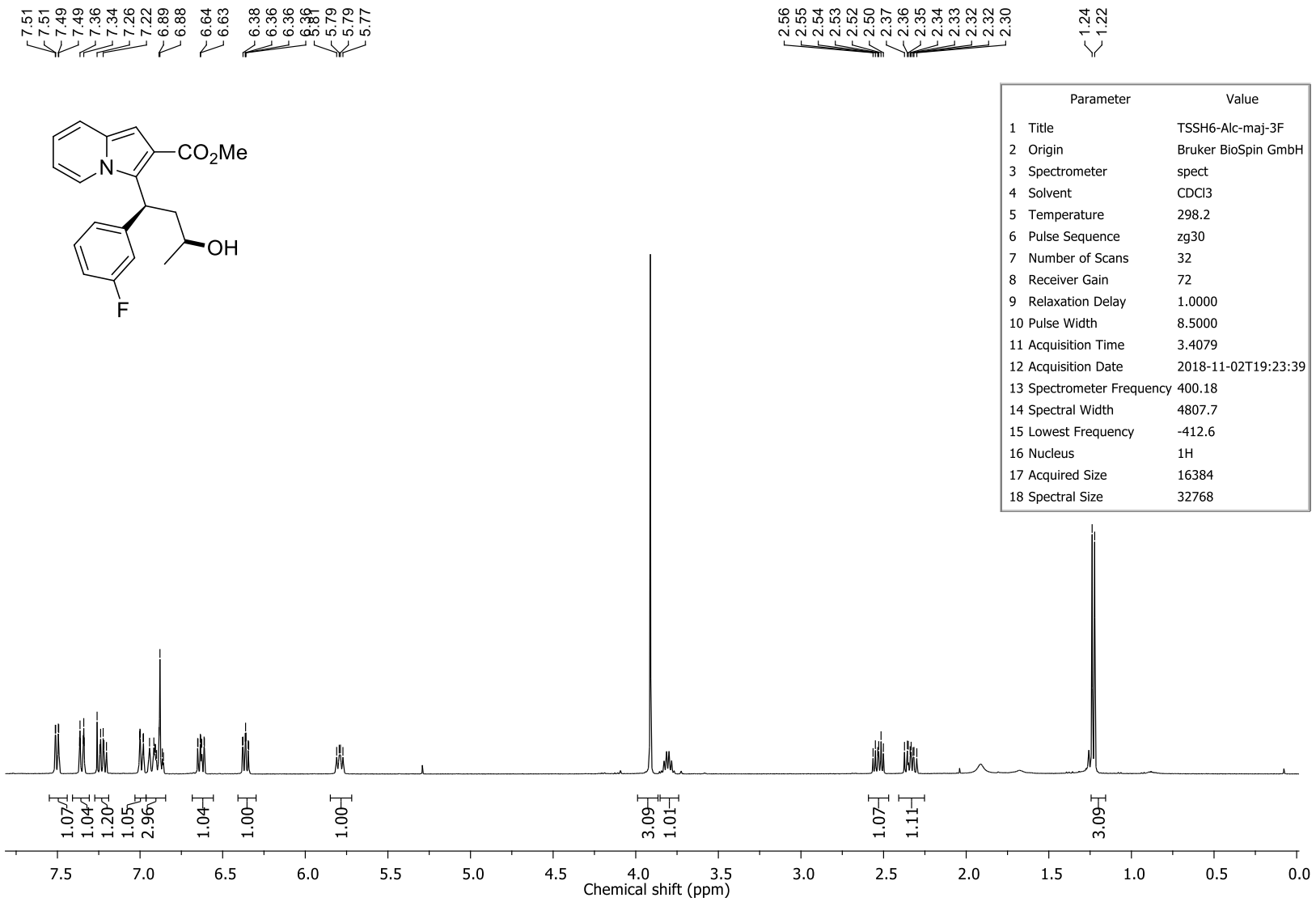

Figure 21. ^{1}H NMR spectrum of compound *syn*-**5b.**

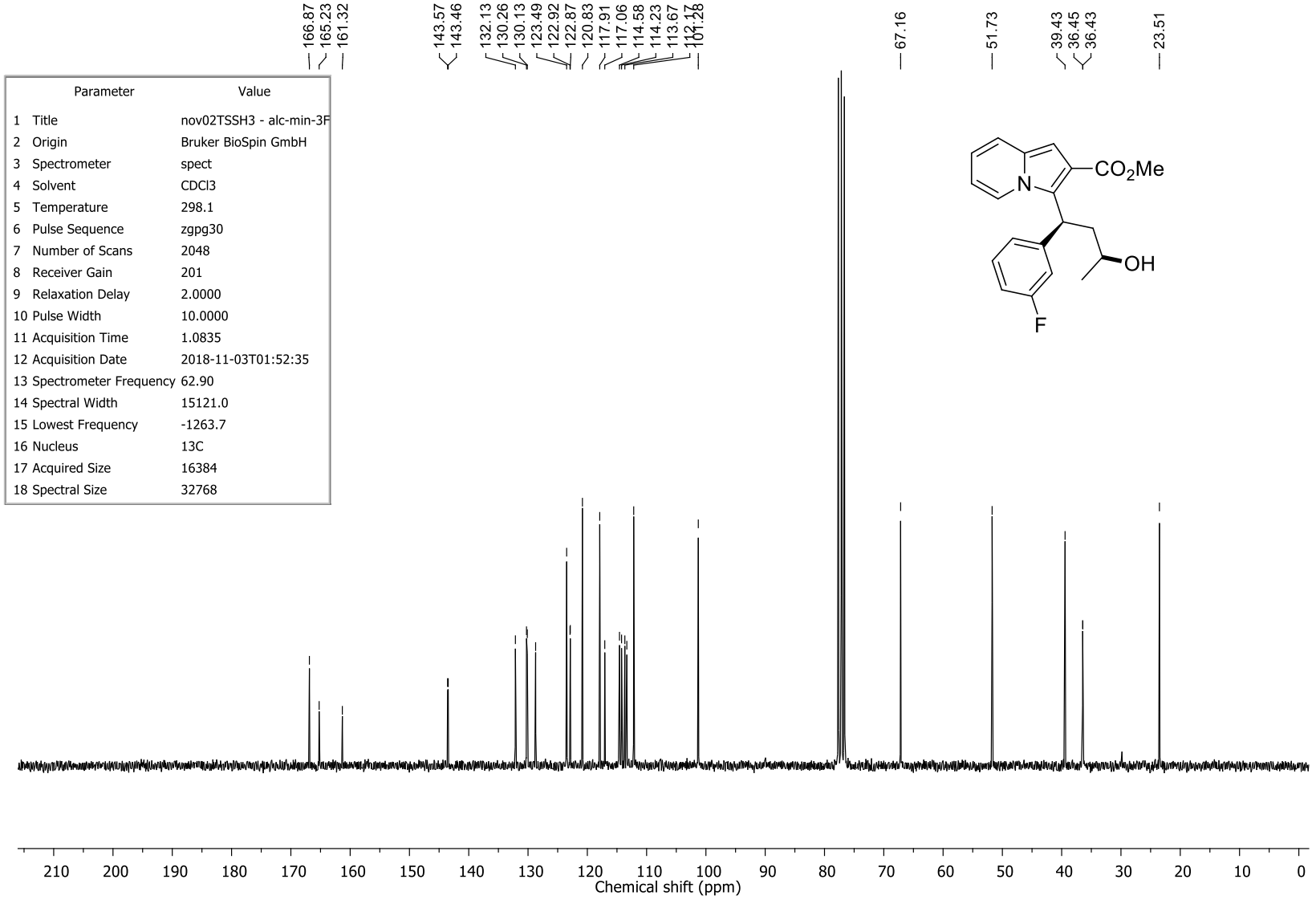

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Figure 22. ^{13}C NMR spectrum of compound *syn*-**5b.**

	Parameter	Value
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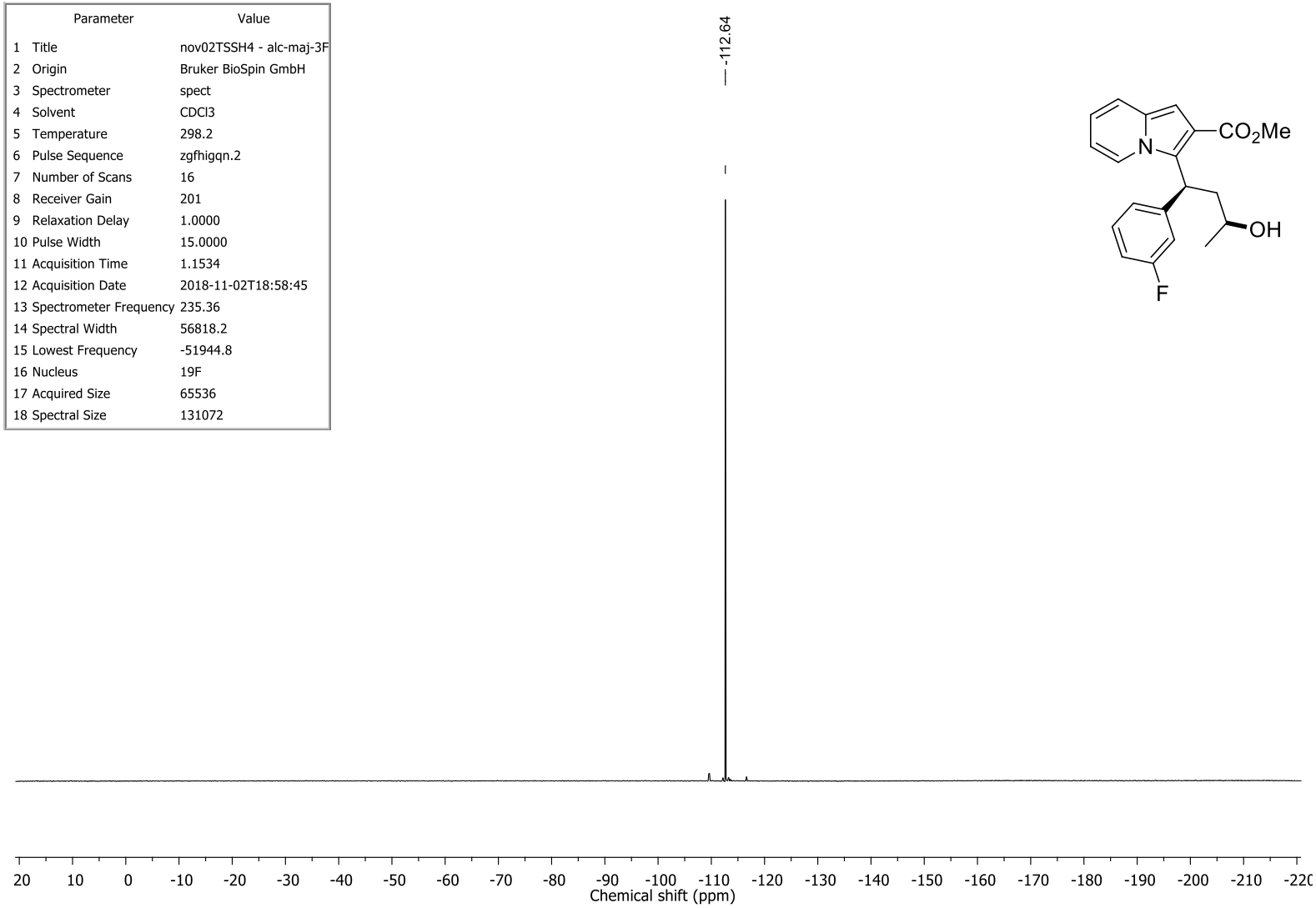

Figure 23. ^{19}F NMR spectrum of compound *syn*-**5b.**

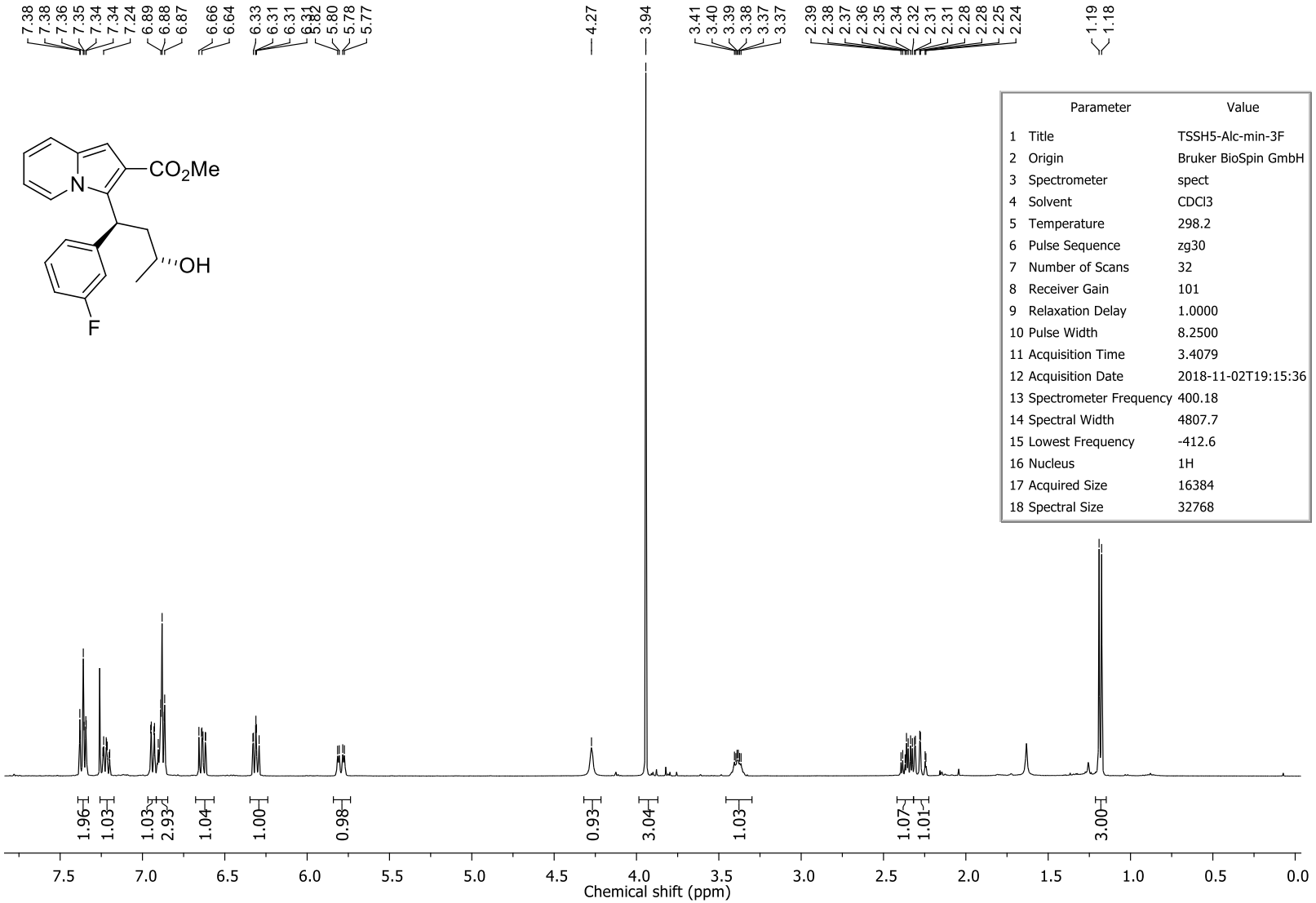

Figure 24. ^{1}H NMR spectrum of compound *anti*-**5b**.

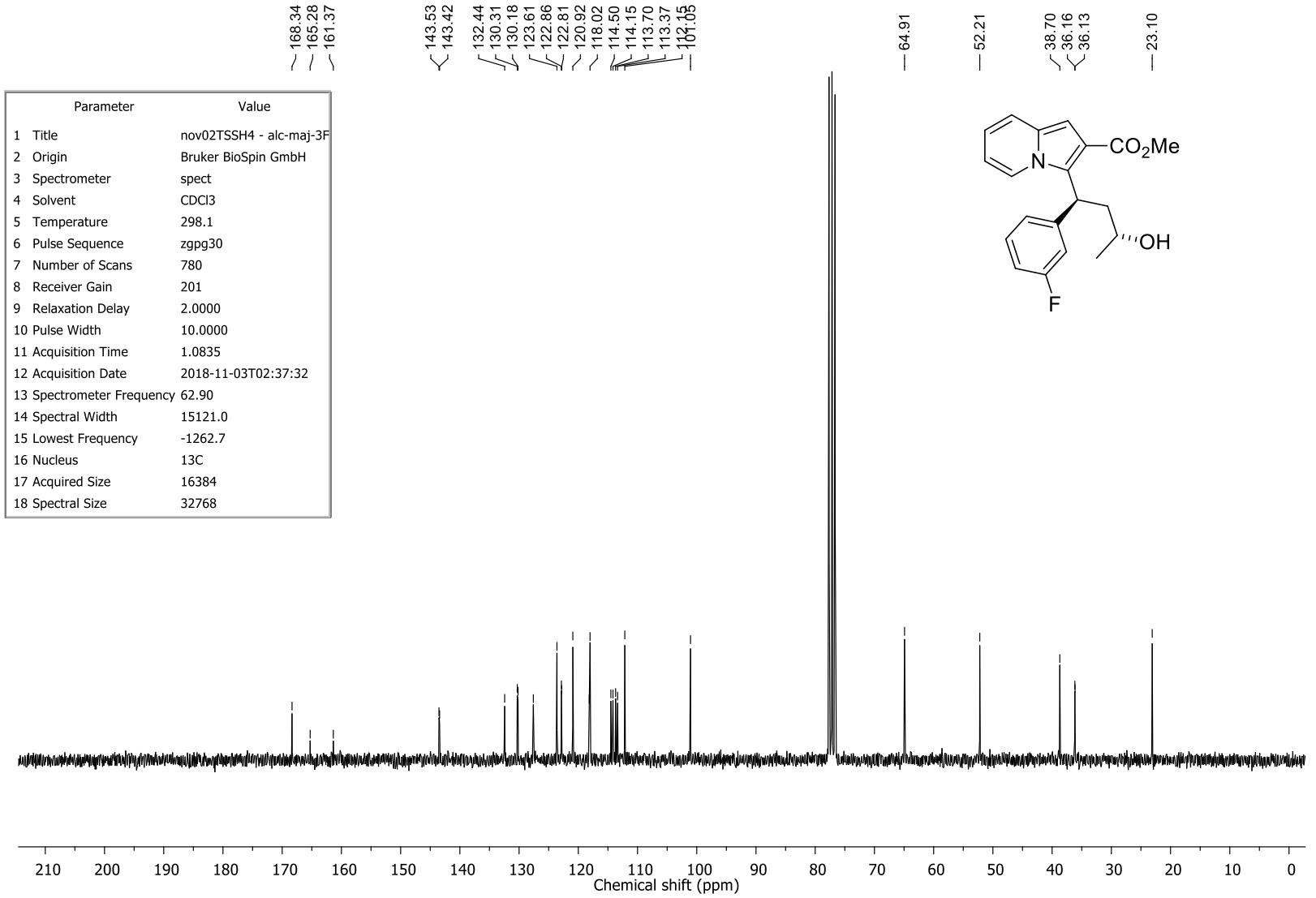

Figure 25. ^{13}C NMR spectrum of compound *anti*-**5b**.

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7	Number of Scans	16
8	Receiver Gain	201
9	Relaxation Delay	1.0000
10	Pulse Width	15.0000
11	Acquisition Time	1.1534
12	Acquisition Date	2018-11-02T18:54:14
13	Spectrometer Frequency	235.36
14	Spectral Width	56818.2
15	Lowest Frequency	-51944.8
16	Nucleus	19F
17	Acquired Size	65536
18	Spectral Size	131072

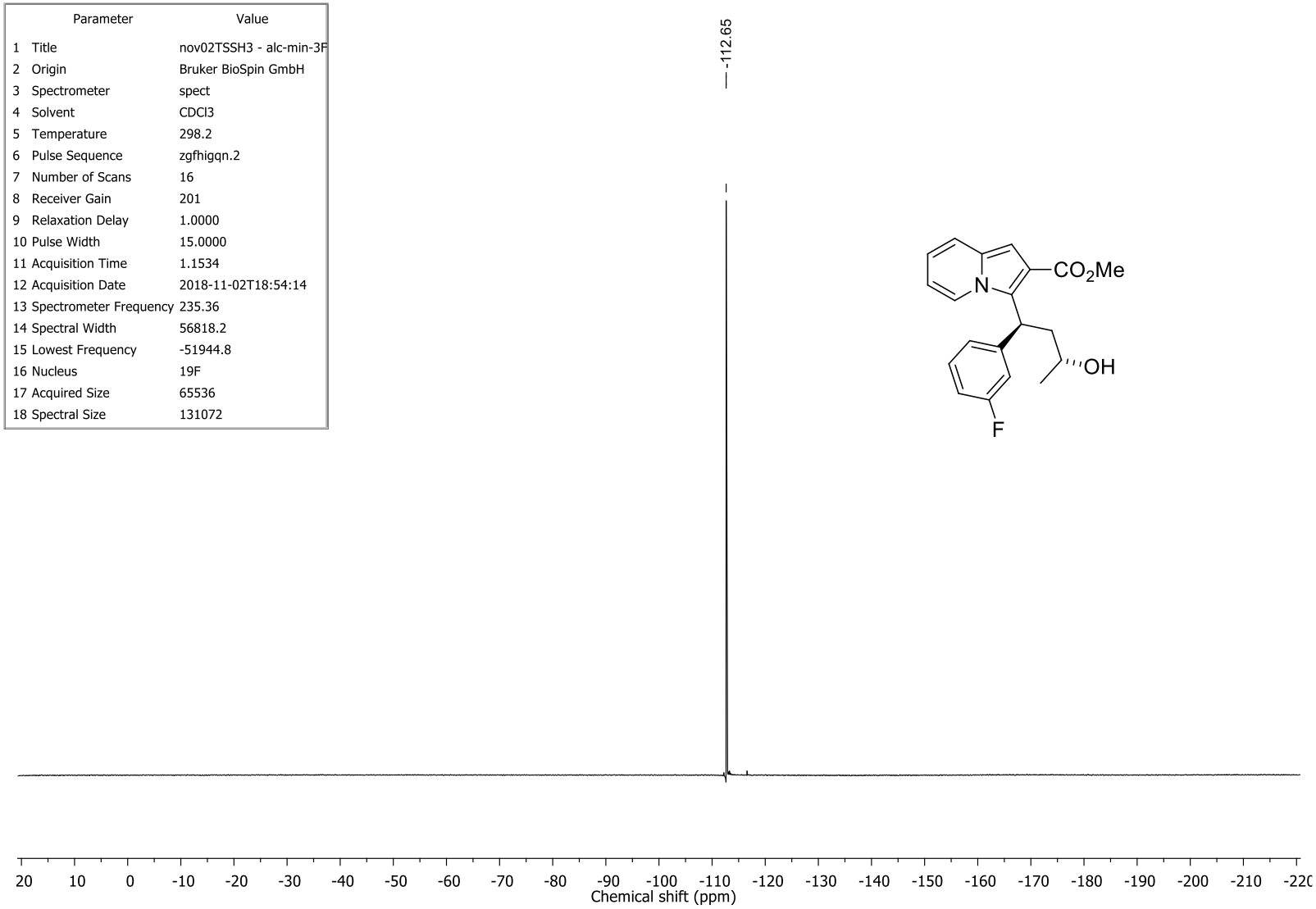


Figure 26. ^{19}F NMR spectrum of compound *anti*-**5b**.

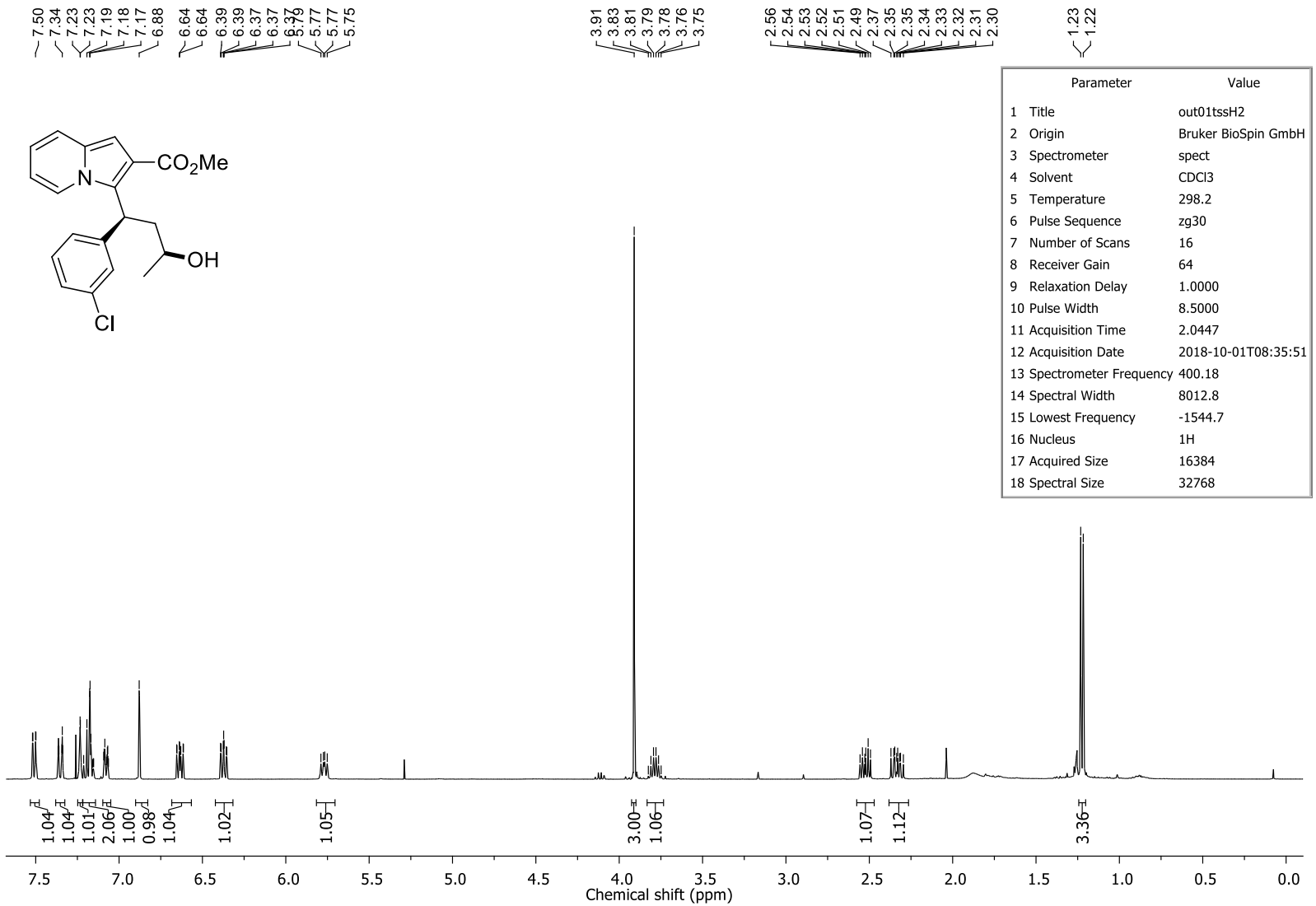


Figure 27. ^{1}H NMR spectrum of compound *syn*-**5c**.

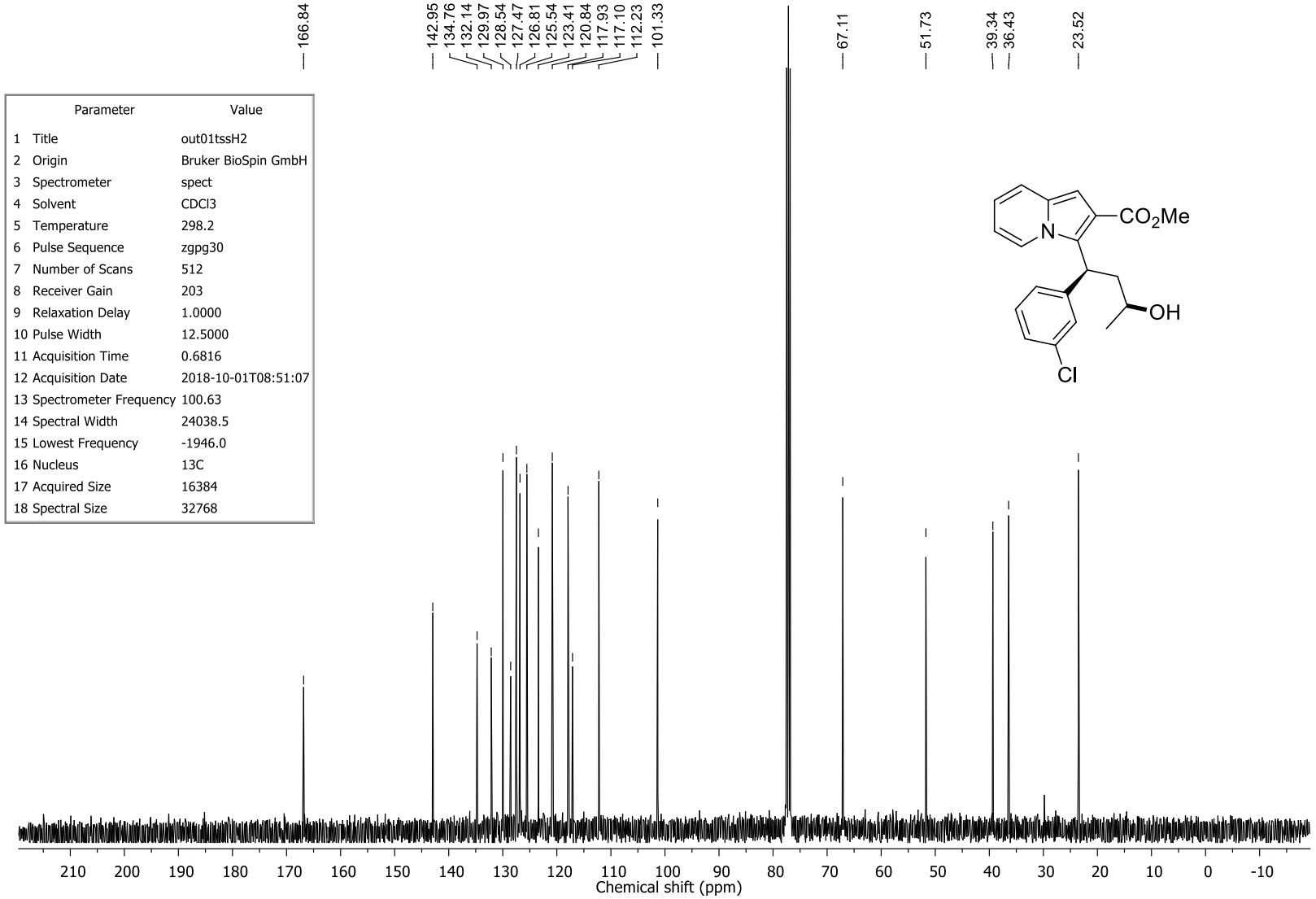


Figure 28. ^{13}C NMR spectrum of compound *syn*-**5c**.

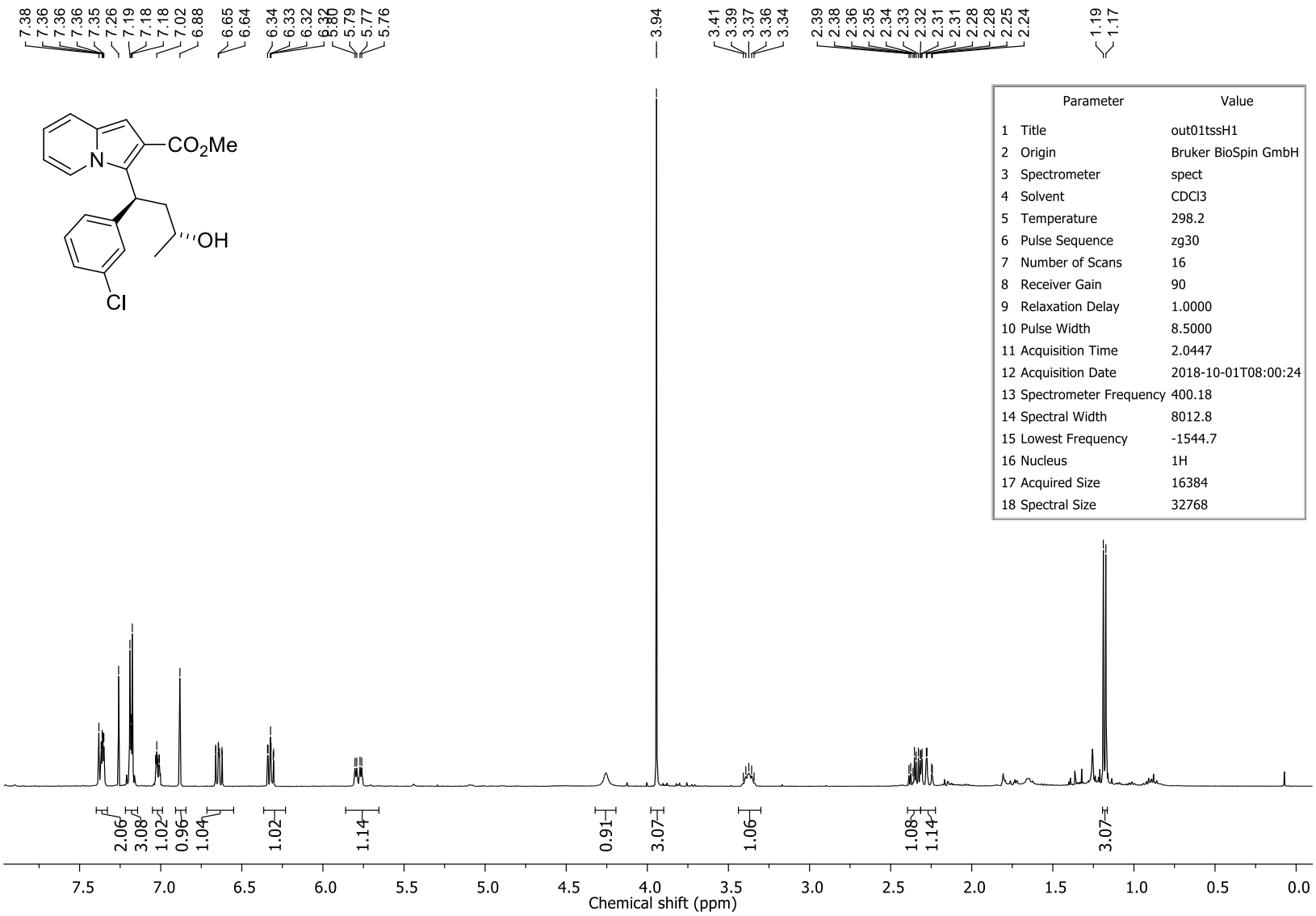


Figure 29. ^{1}H NMR spectrum of compound *anti*-**5c**.

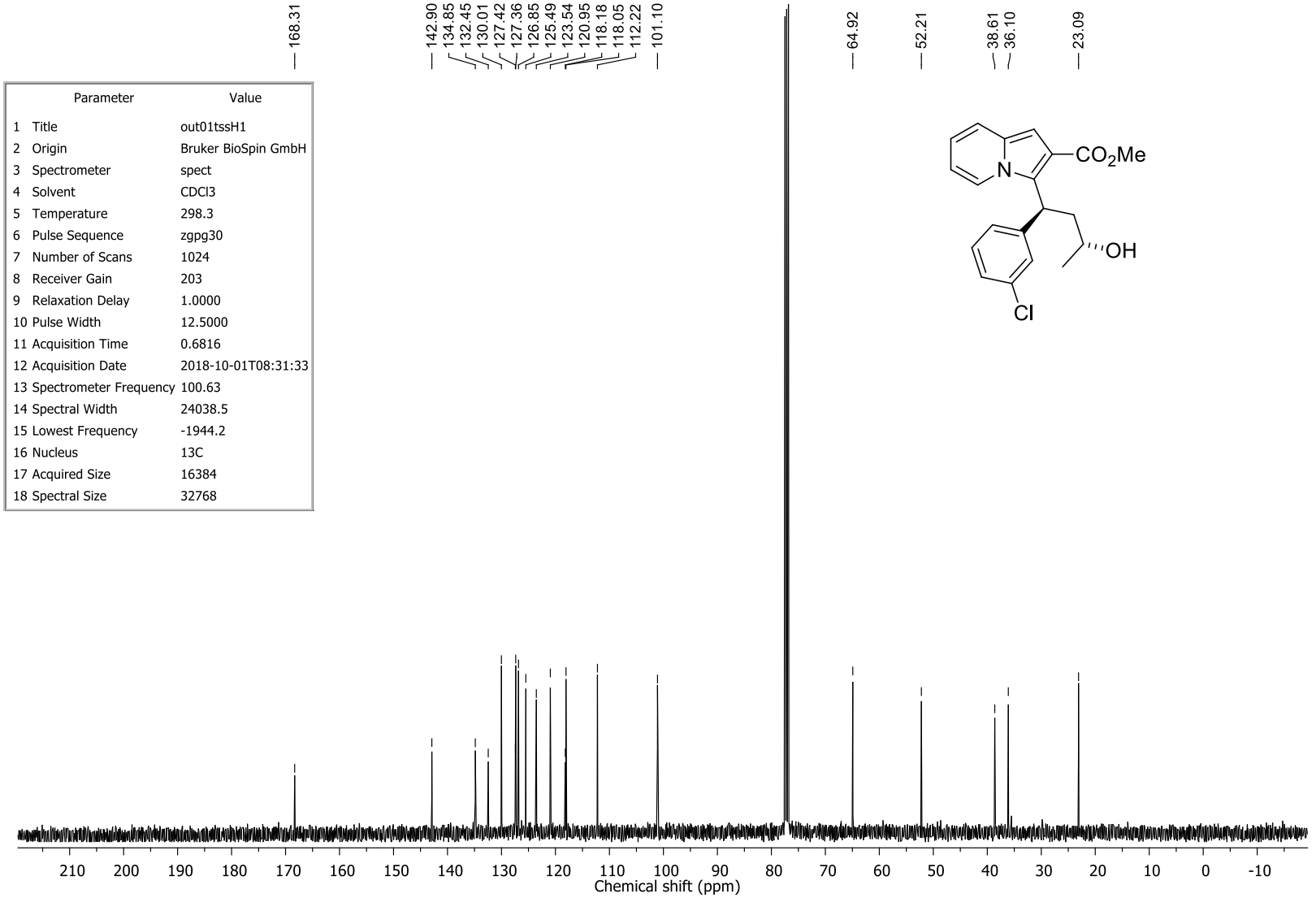


Figure 30. ^{13}C NMR spectrum of compound *anti*-**5c**.

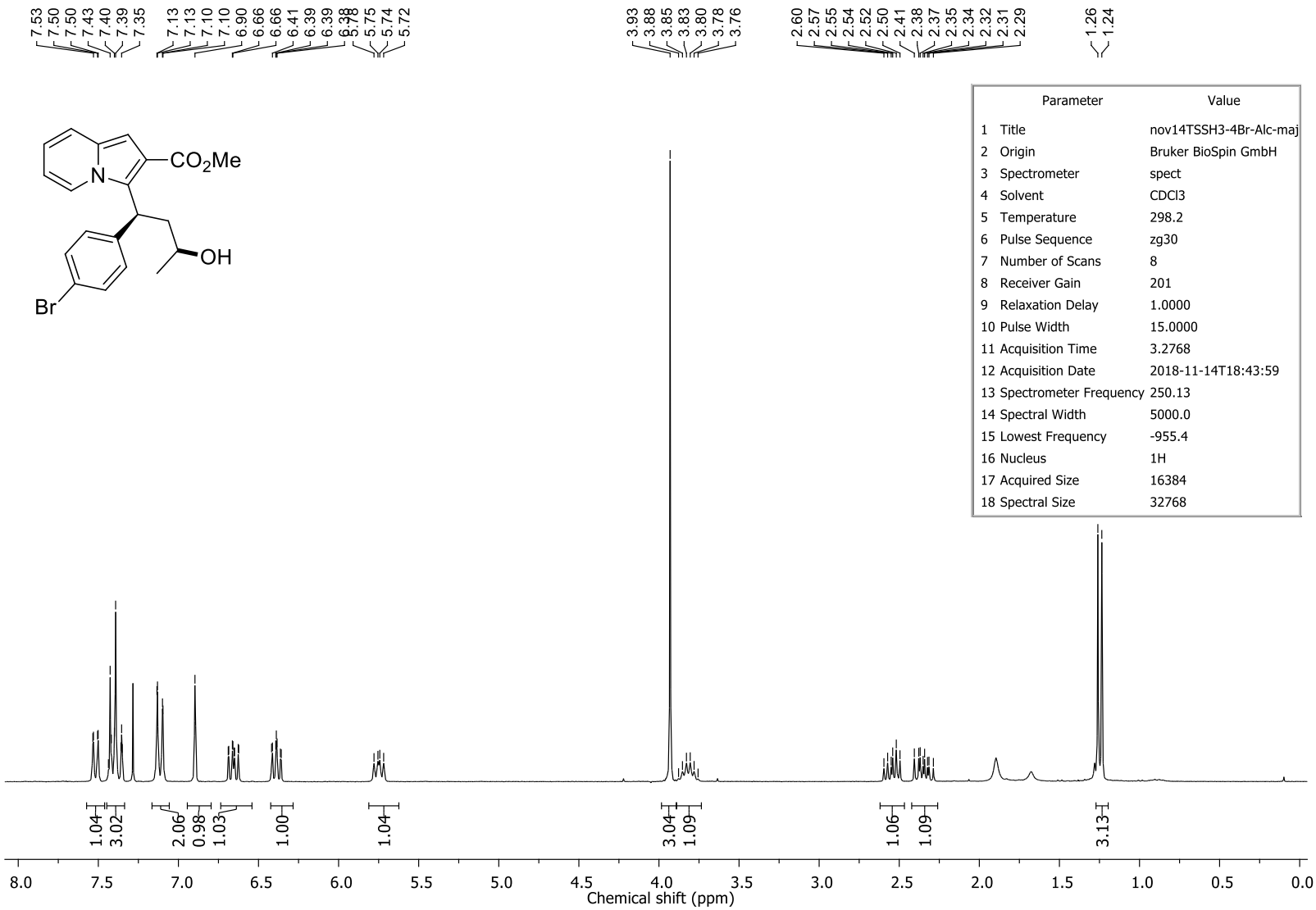
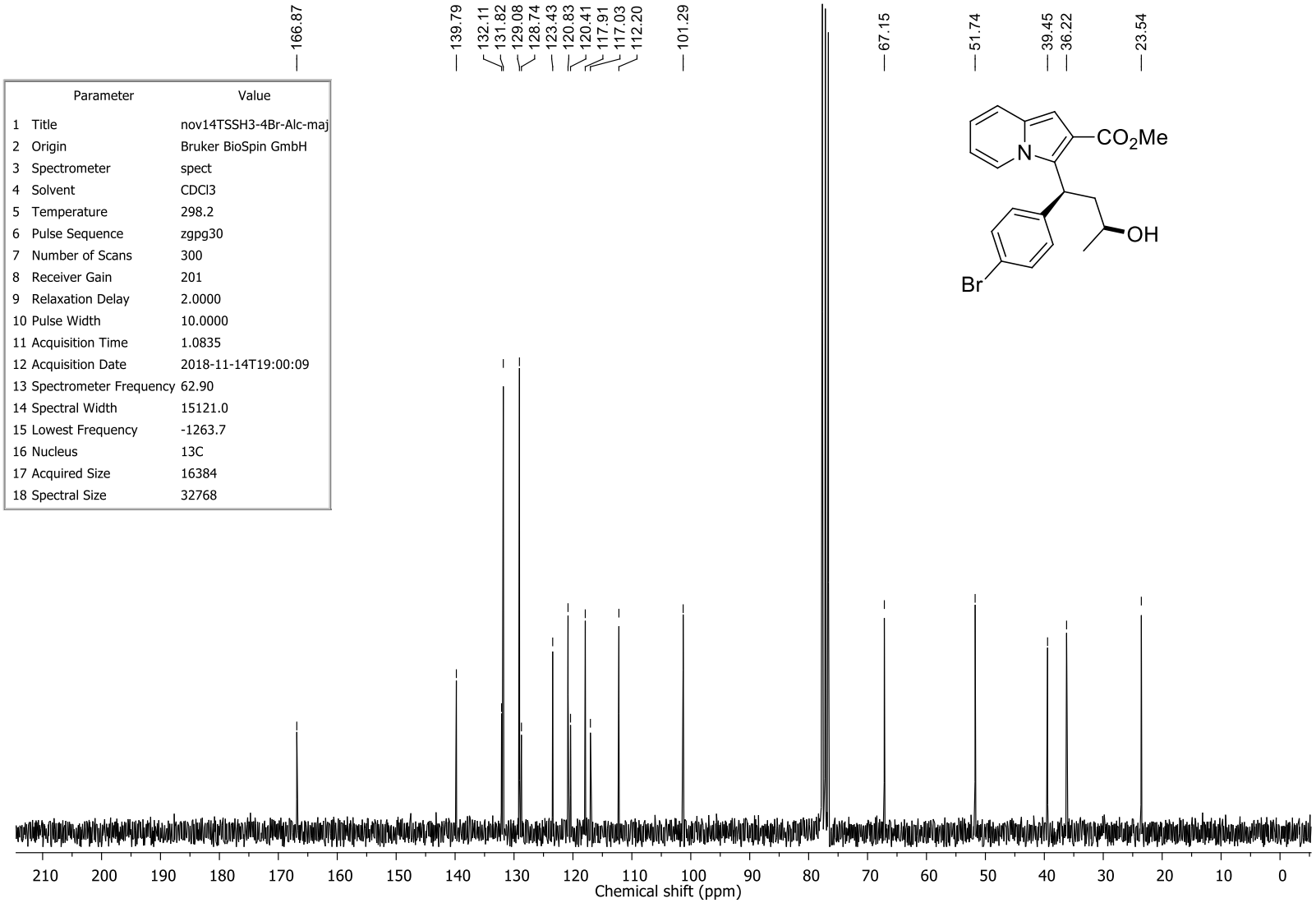


Figure 31. ^{1}H NMR spectrum of compound *syn*-**5d**.



	Parameter	Value
1	Title	nov14TSSH3-4Br-Alc-maj
2	Origin	Bruker BioSpin GmbH
3	Spectrometer	spect
4	Solvent	CDCl3
5	Temperature	298.2
6	Pulse Sequence	zgpg30
7	Number of Scans	300
8	Receiver Gain	201
9	Relaxation Delay	2.0000
10	Pulse Width	10.0000
11	Acquisition Time	1.0835
12	Acquisition Date	2018-11-14T19:00:09
13	Spectrometer Frequency	62.90
14	Spectral Width	15121.0
15	Lowest Frequency	-1263.7
16	Nucleus	13C
17	Acquired Size	16384
18	Spectral Size	32768

Figure 32. ^{13}C NMR spectrum of compound *syn*-**5d**.

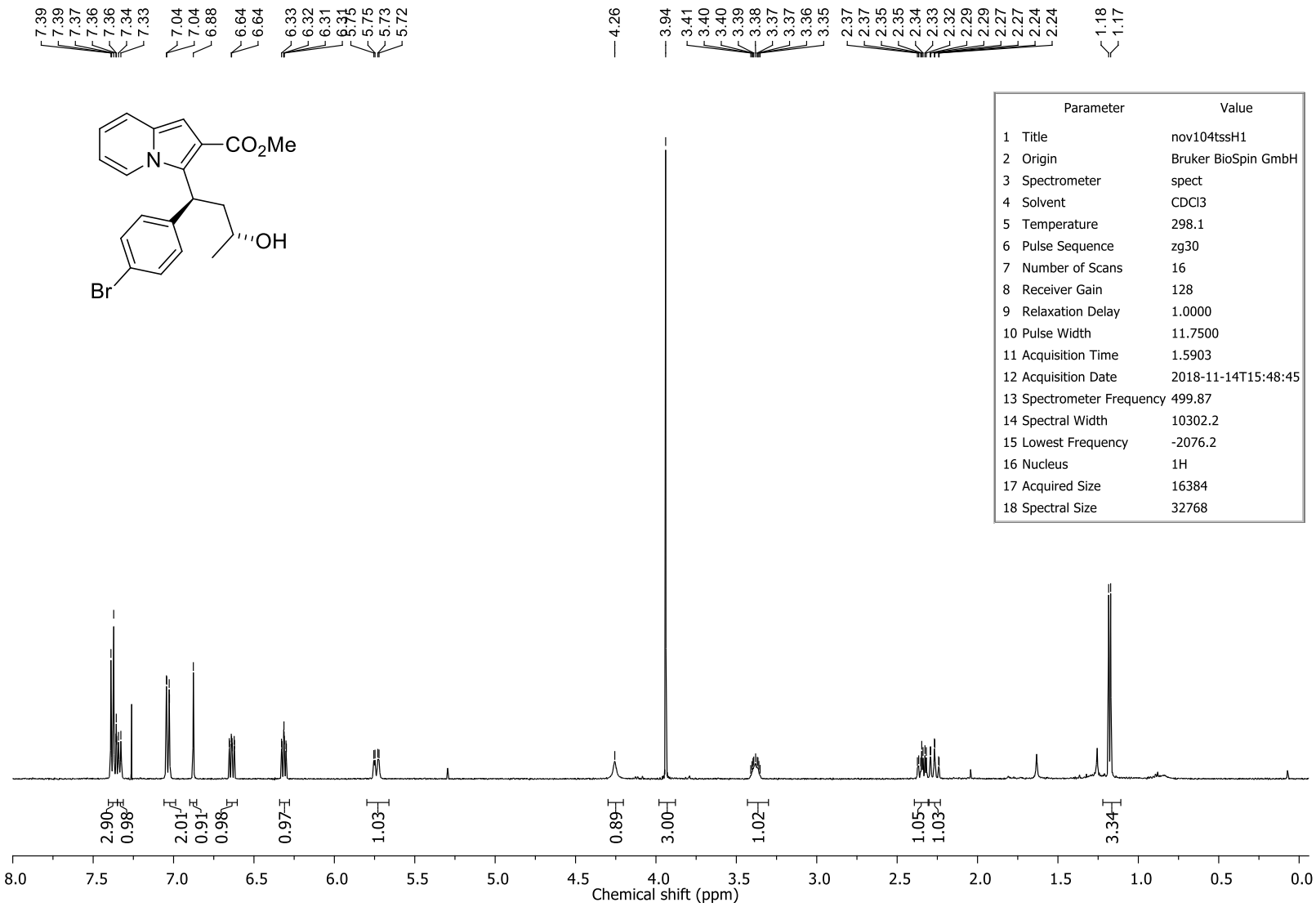


Figure 33. ^{1}H NMR spectrum of compound *anti*-**5d**.

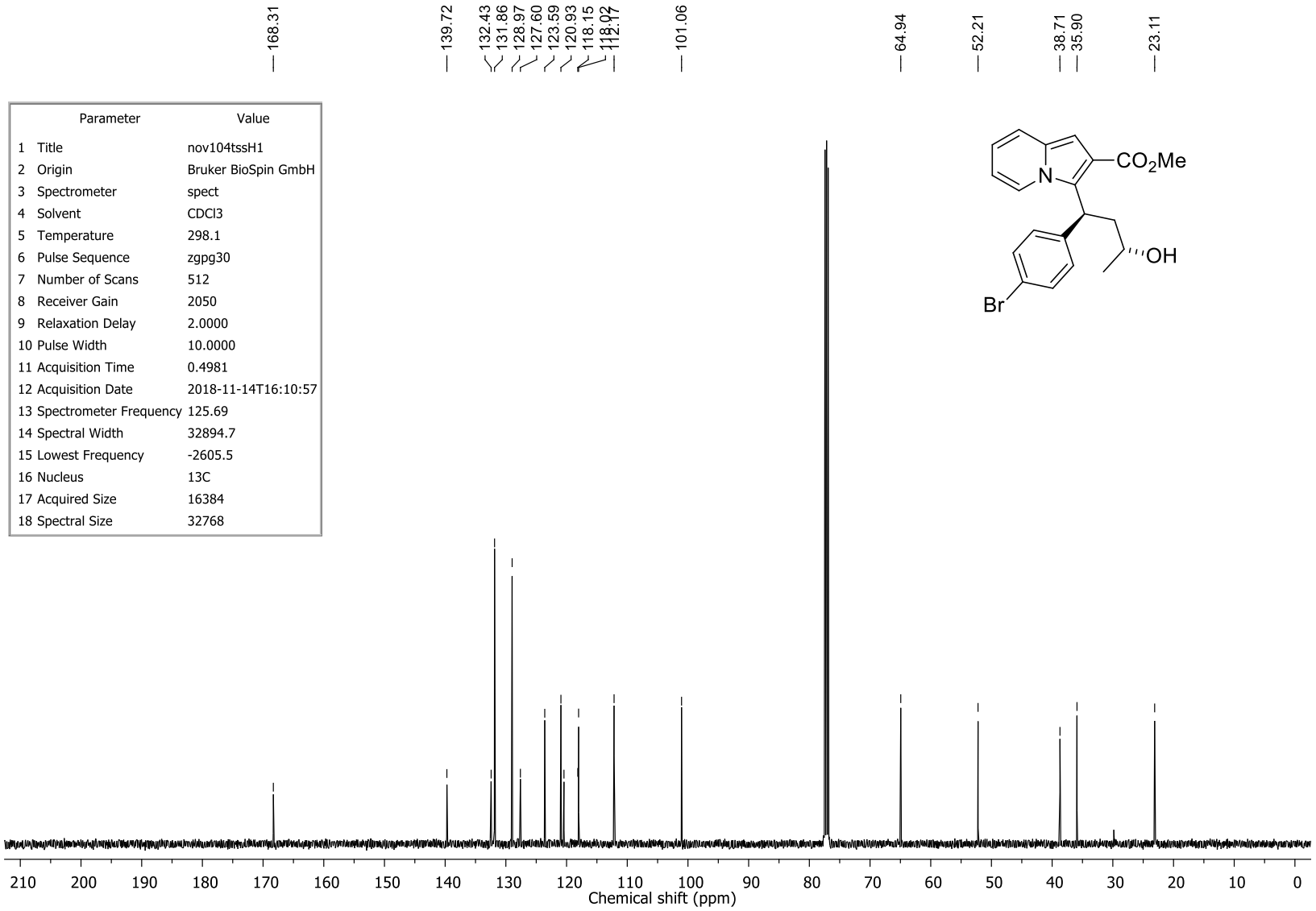


Figure 34. ^{13}C NMR spectrum of compound *anti*-**5d**.

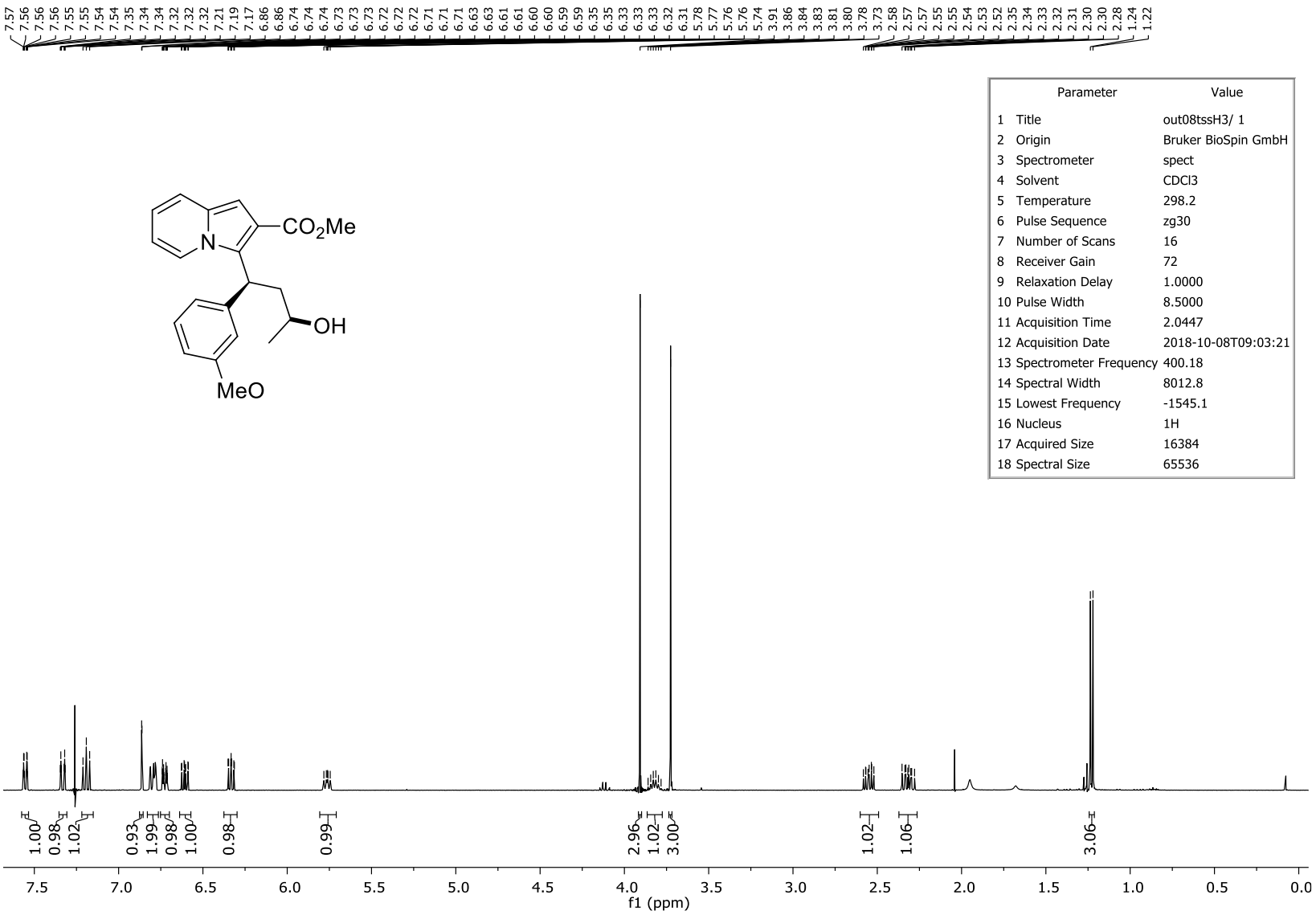


Figure 35. ^{1}H NMR spectrum of compound *syn*-**5e**.

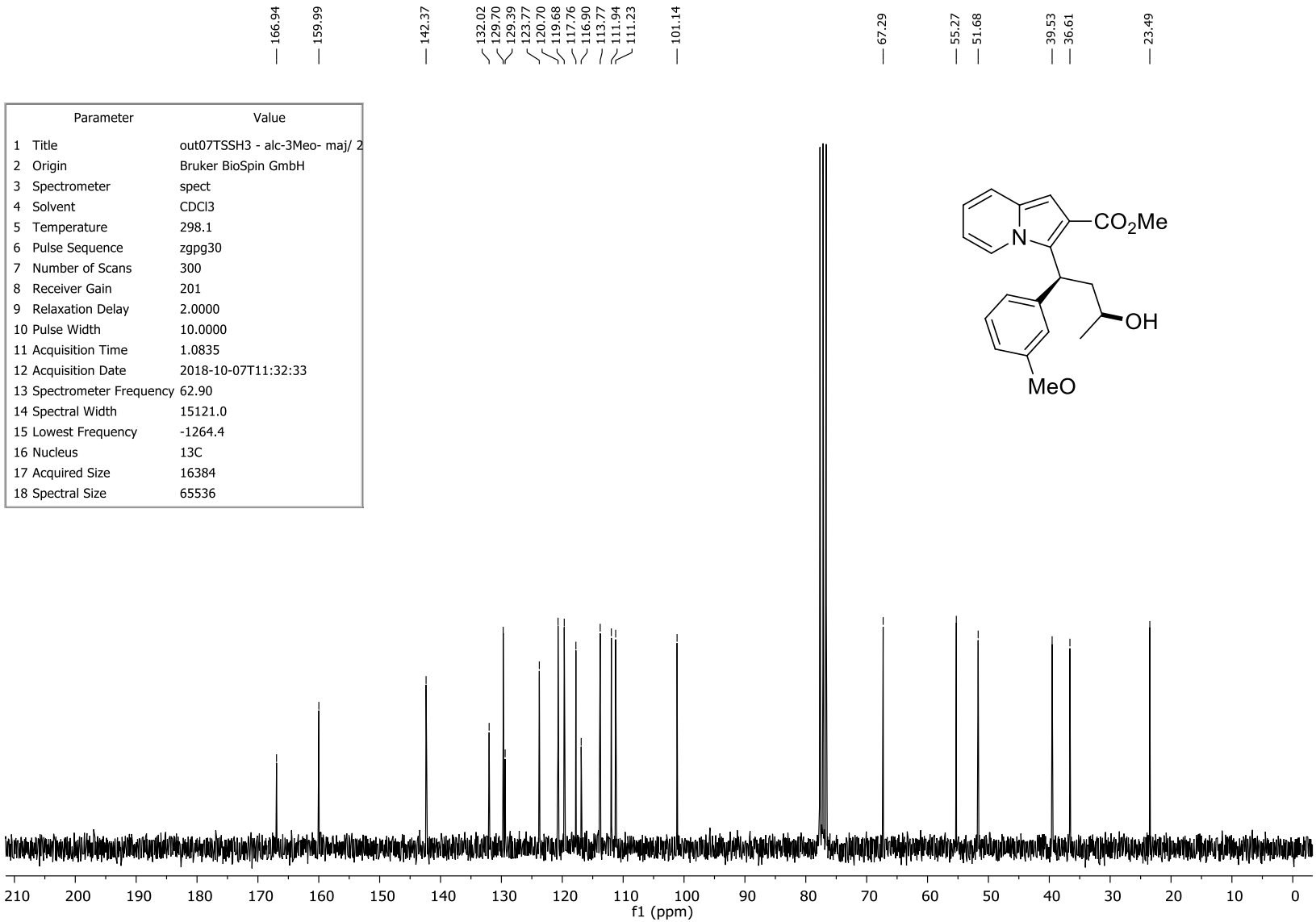


Figure 36. ^{13}C NMR spectrum of compound *syn*-**5e**.

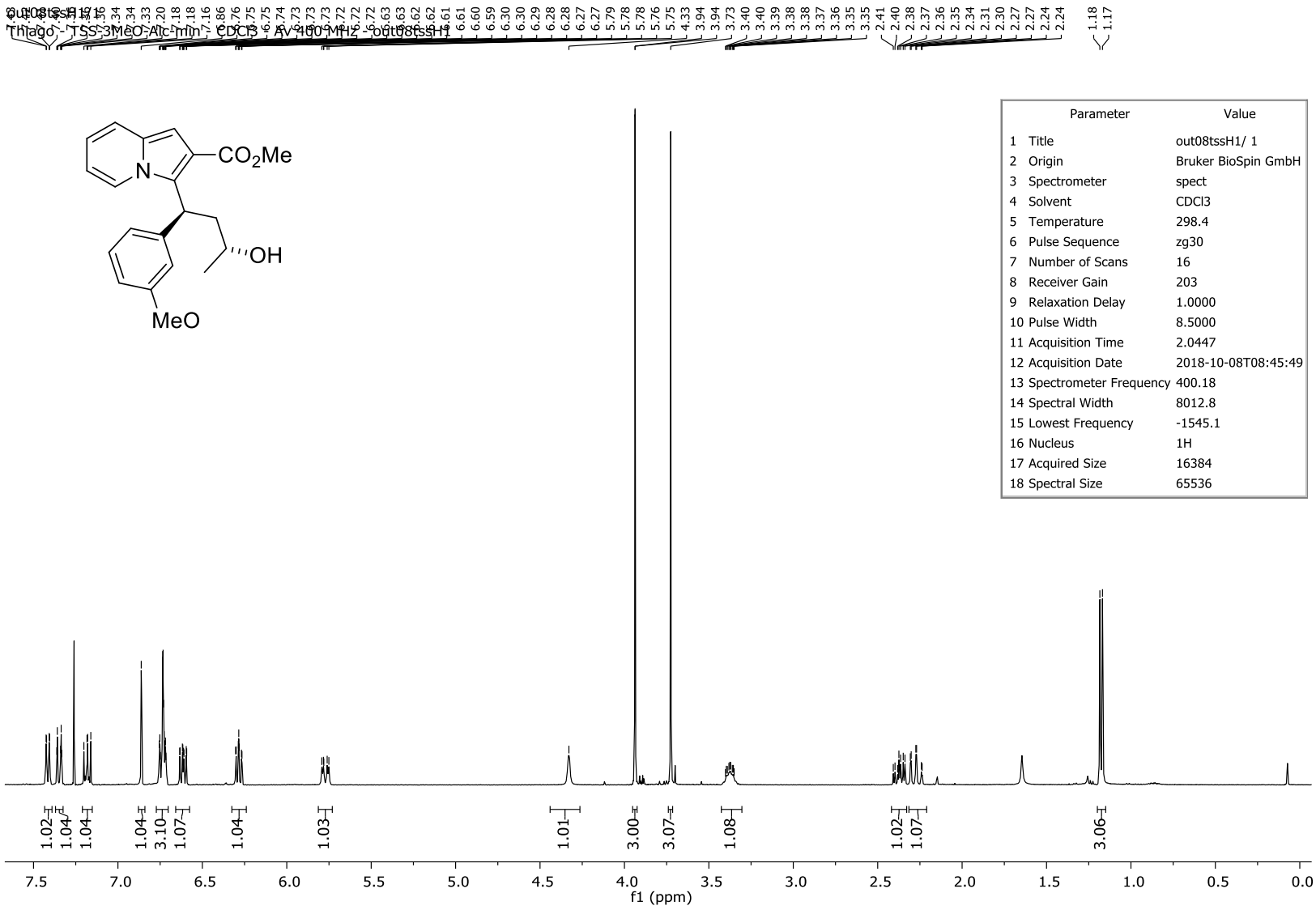


Figure 37. ^{1}H NMR spectrum of compound *anti*-**5e**.

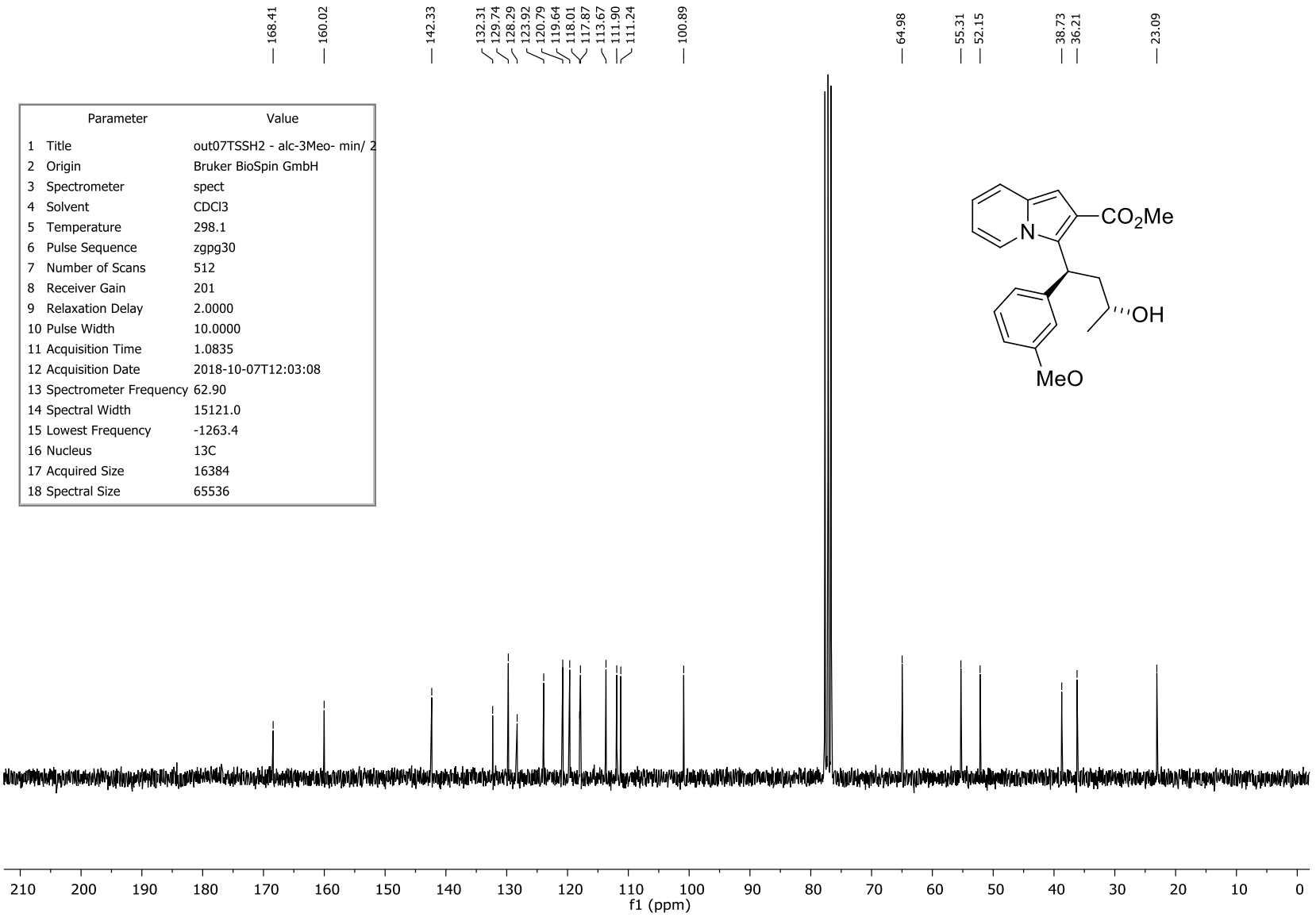


Figure 38. ^{1}H NMR spectrum of compound *anti*-**5e**.

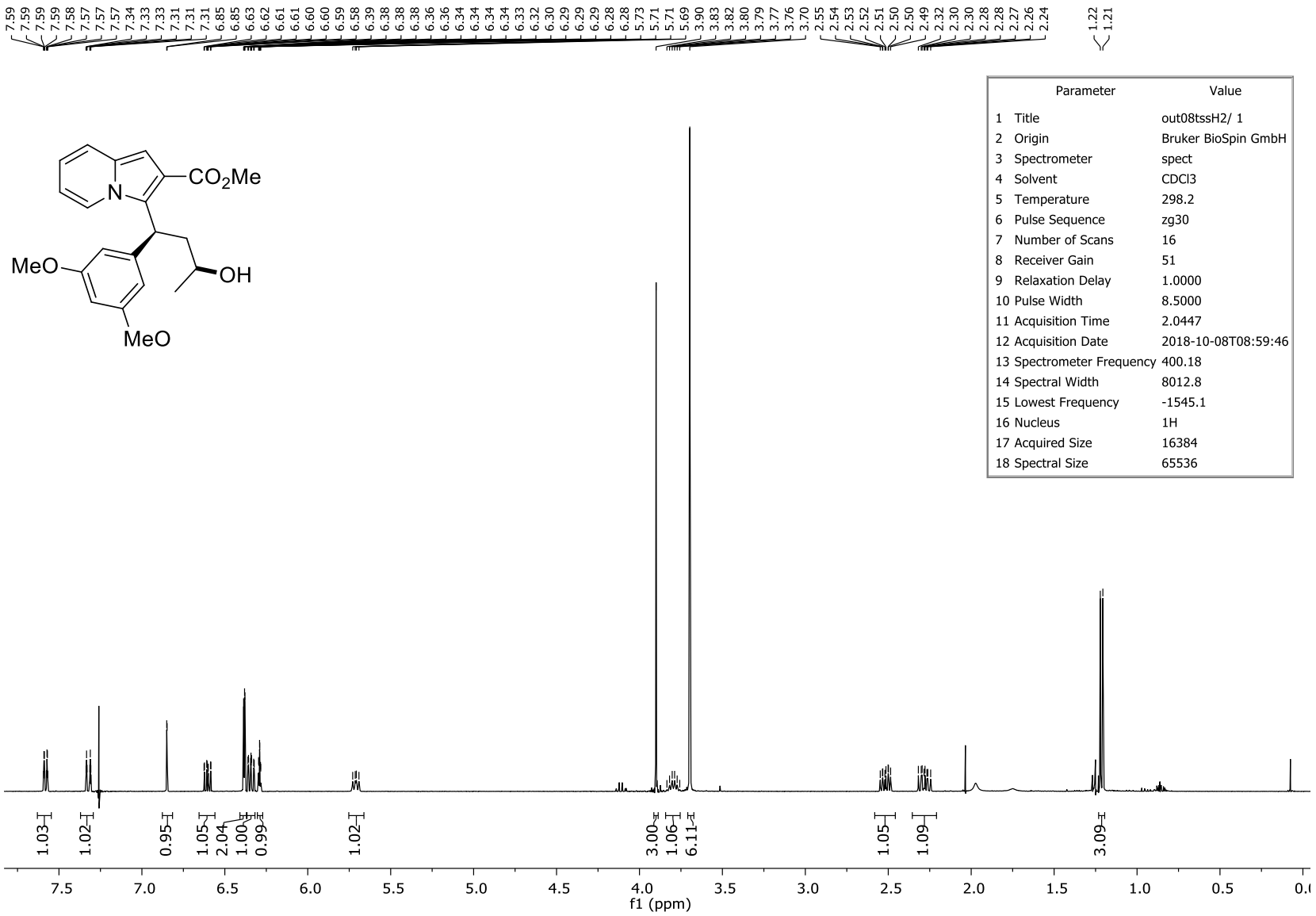


Figure 39. ^{1}H NMR spectrum of compound *syn*-**5f**.

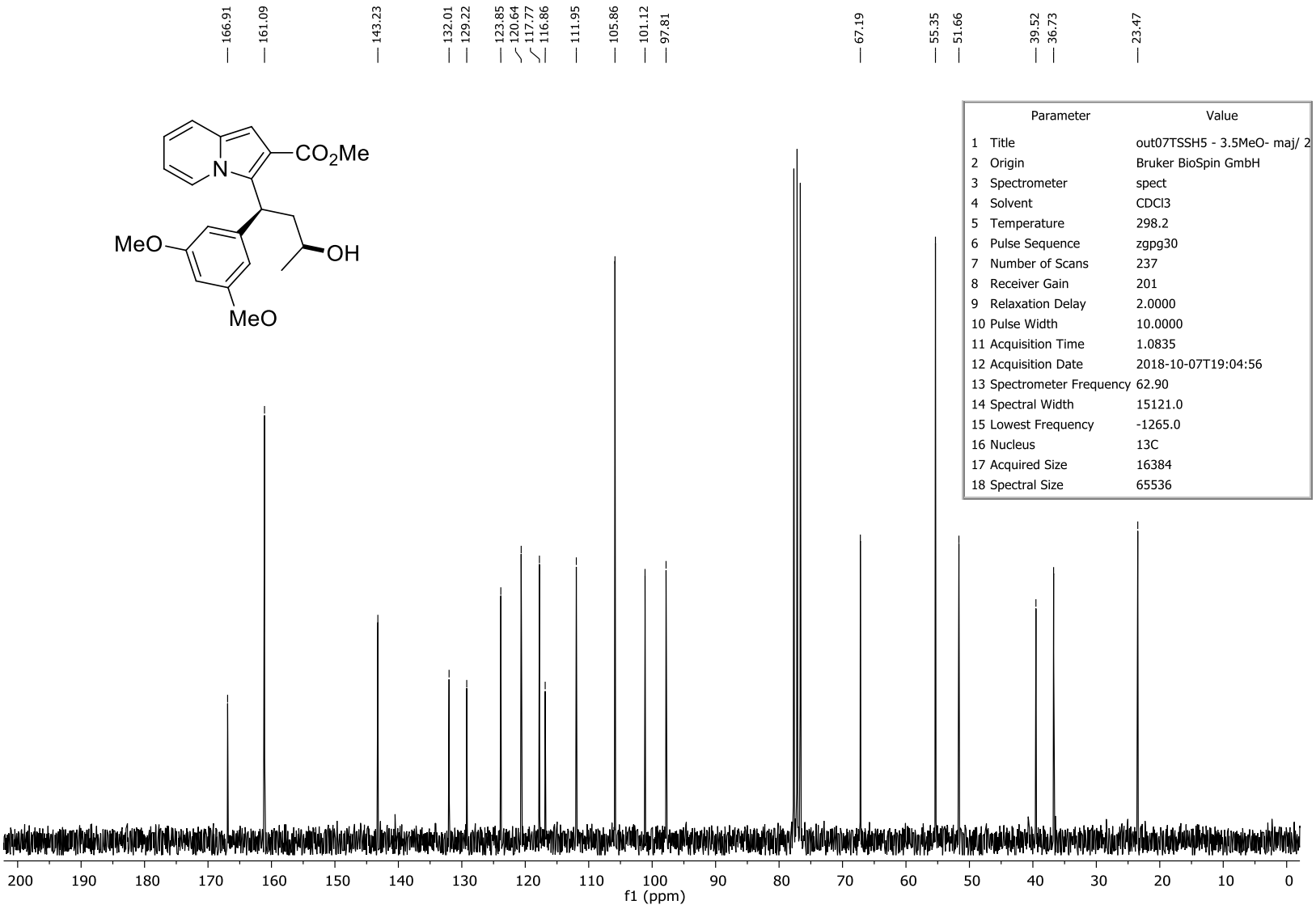


Figure 40. ^{13}C NMR spectrum of compound *syn*-**5f**.

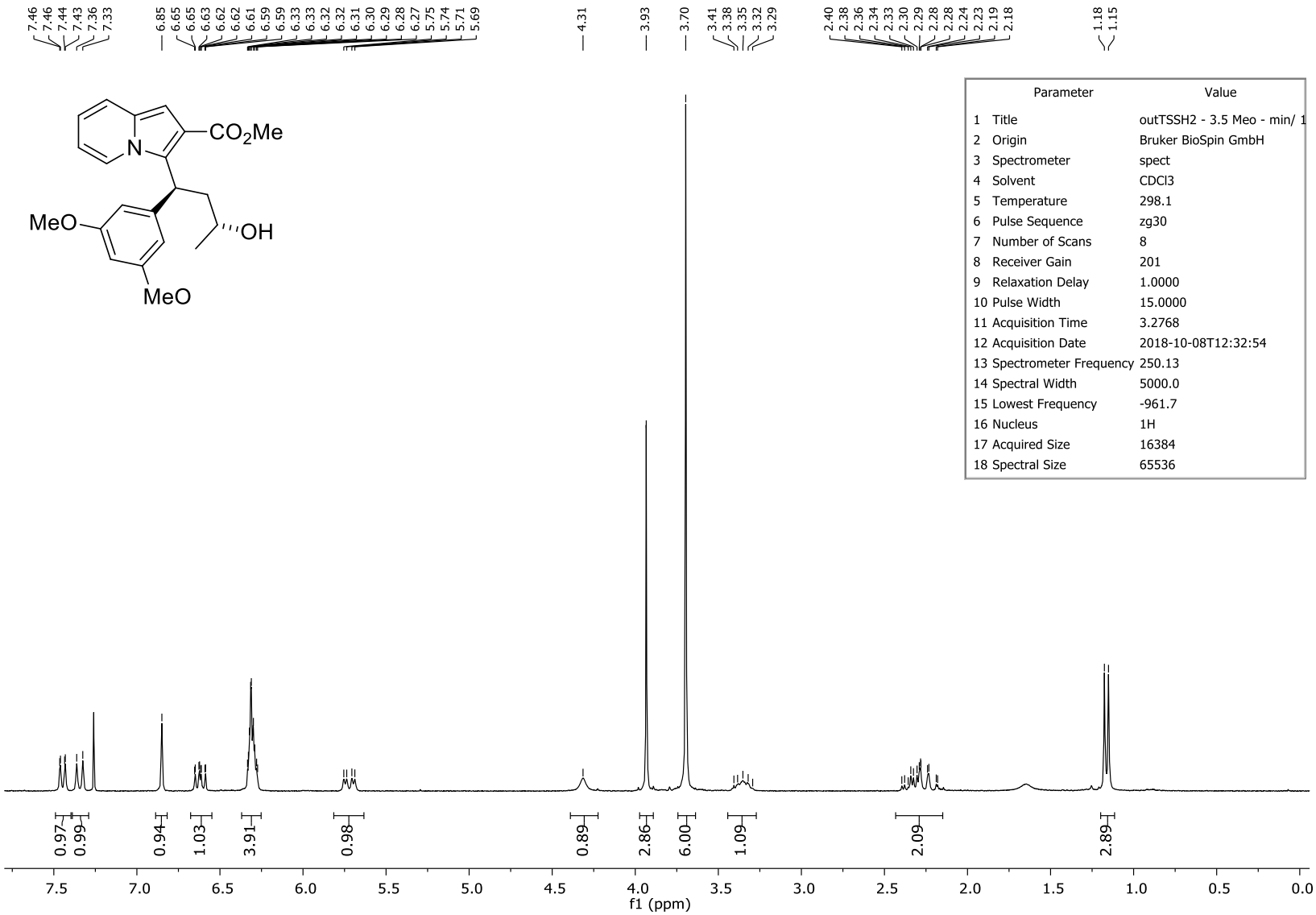


Figure 41. ^{1}H NMR spectrum of compound *anti*-**5f**.

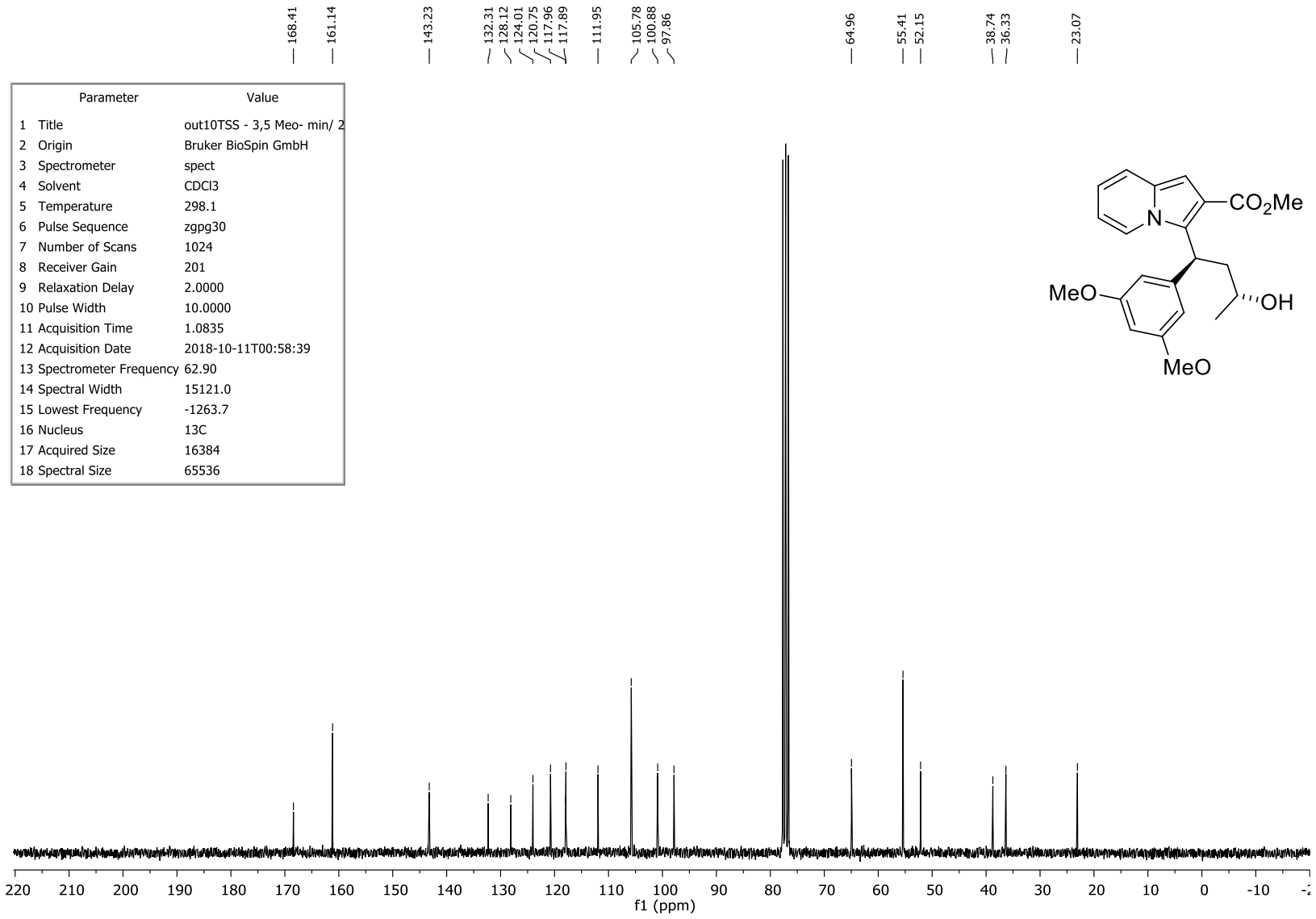


Figure 42. ^{13}C NMR spectrum of compound *anti*-**5f**.

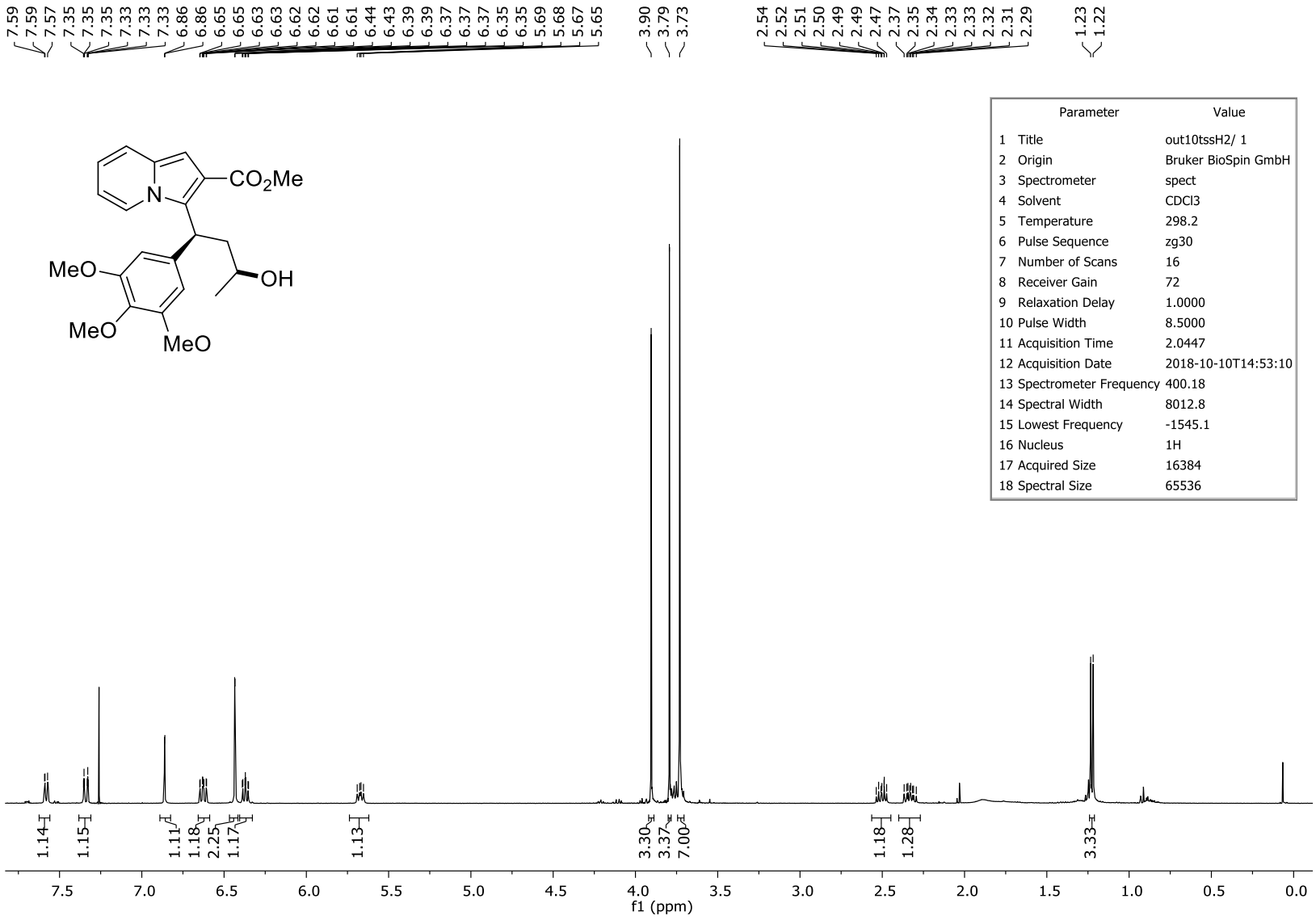


Figure 43. ^{1}H NMR spectrum of compound *syn*-**5g**.

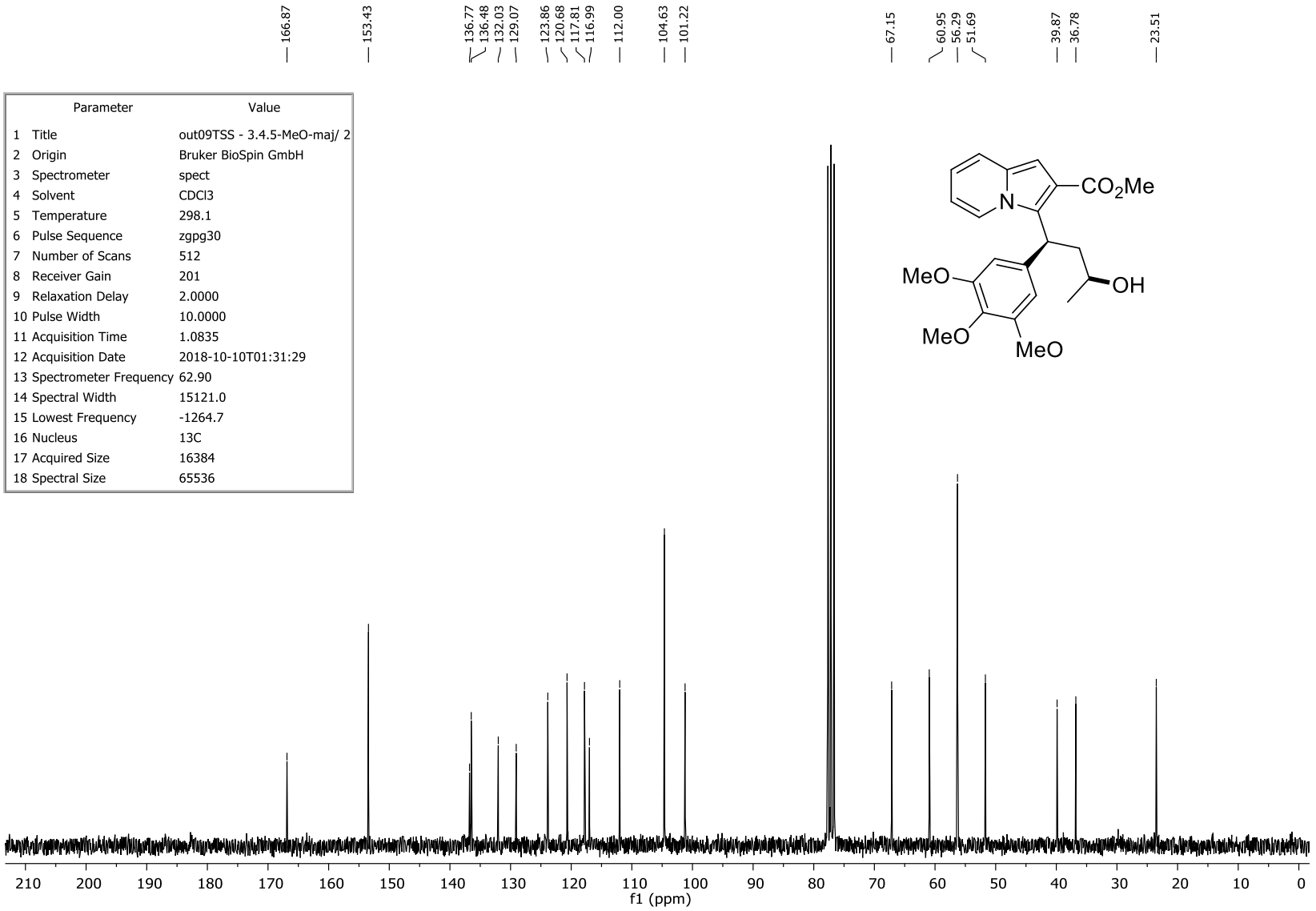


Figure 44. ^{13}C NMR spectrum of compound *syn*-**5g**.

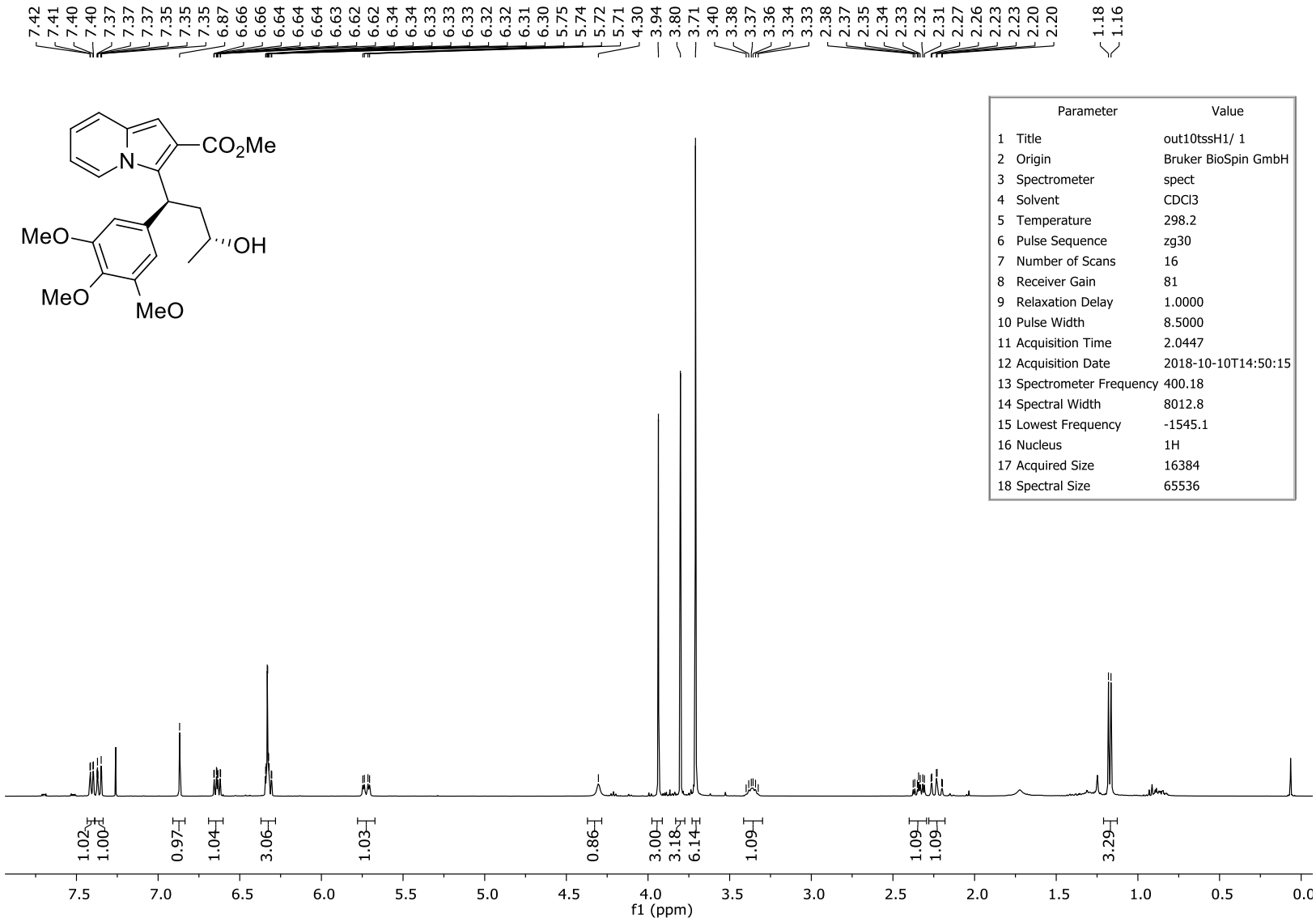


Figure 45. ^{1}H NMR spectrum of compound *anti*-**5g**.

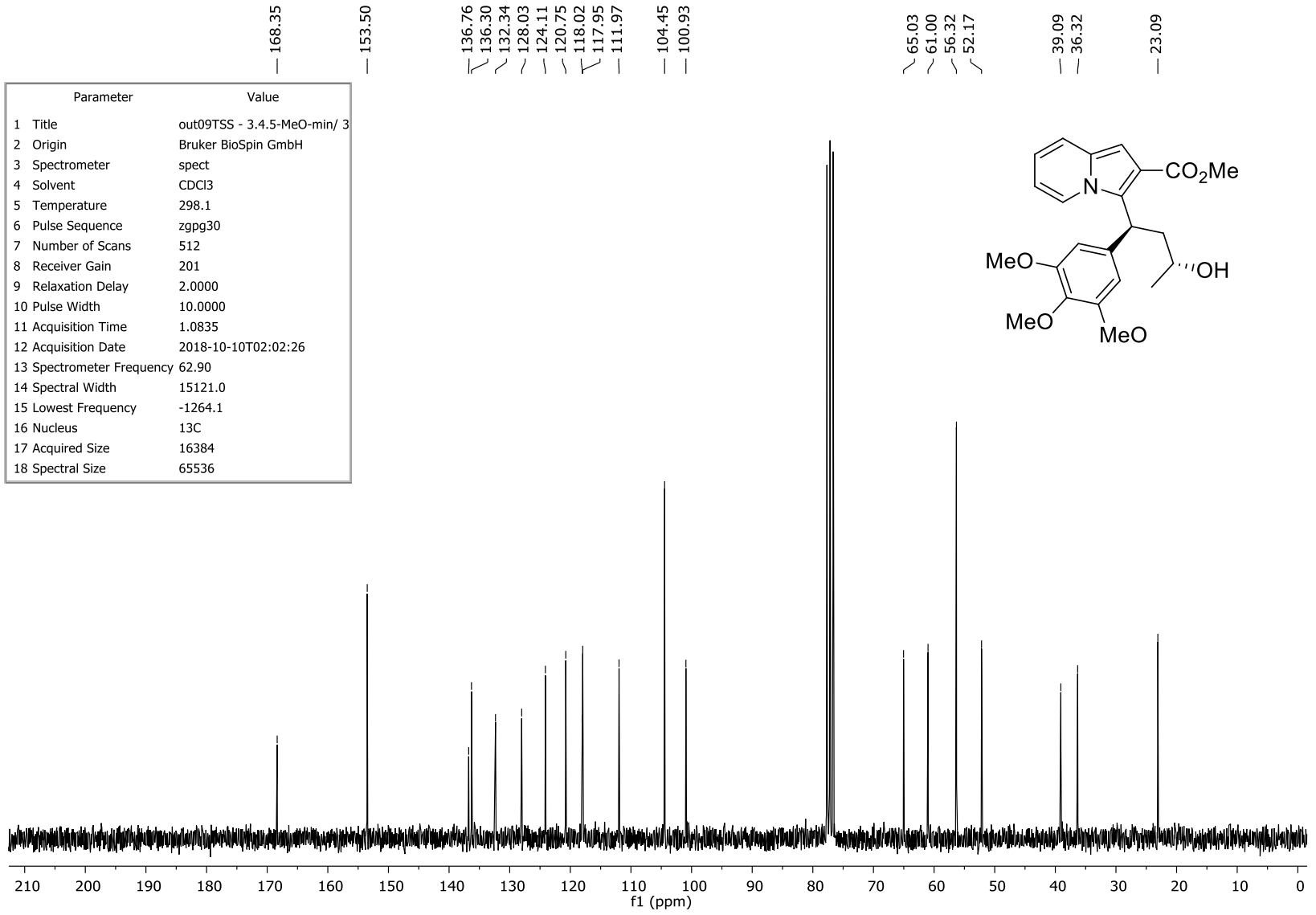


Figure 46. ^{13}C NMR spectrum of compound *anti*-**5g**.

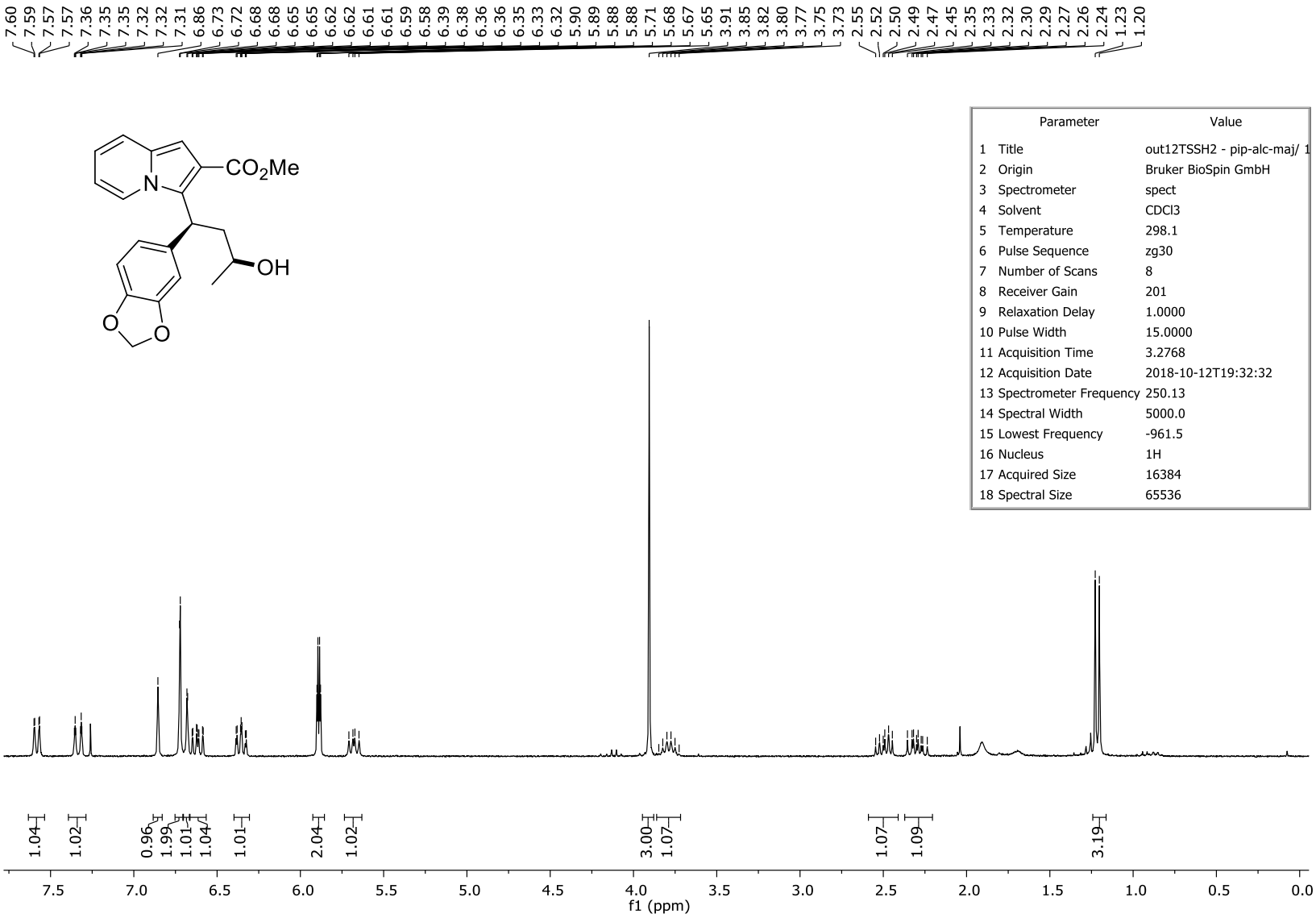


Figure 47. ^{1}H NMR spectrum of compound *syn*-**5h**.

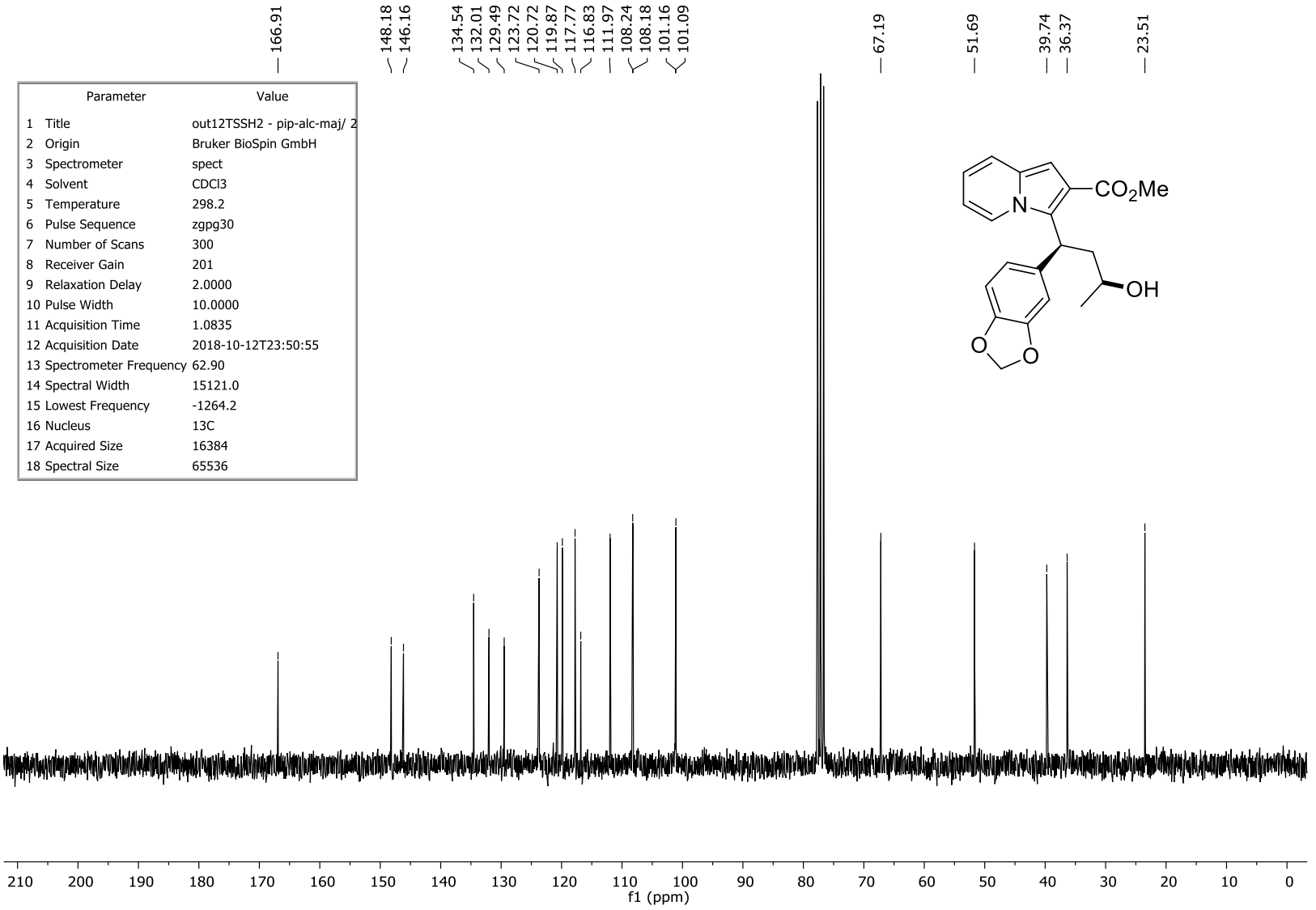


Figure 48. ^{13}C NMR spectrum of compound *syn*-**5h**.

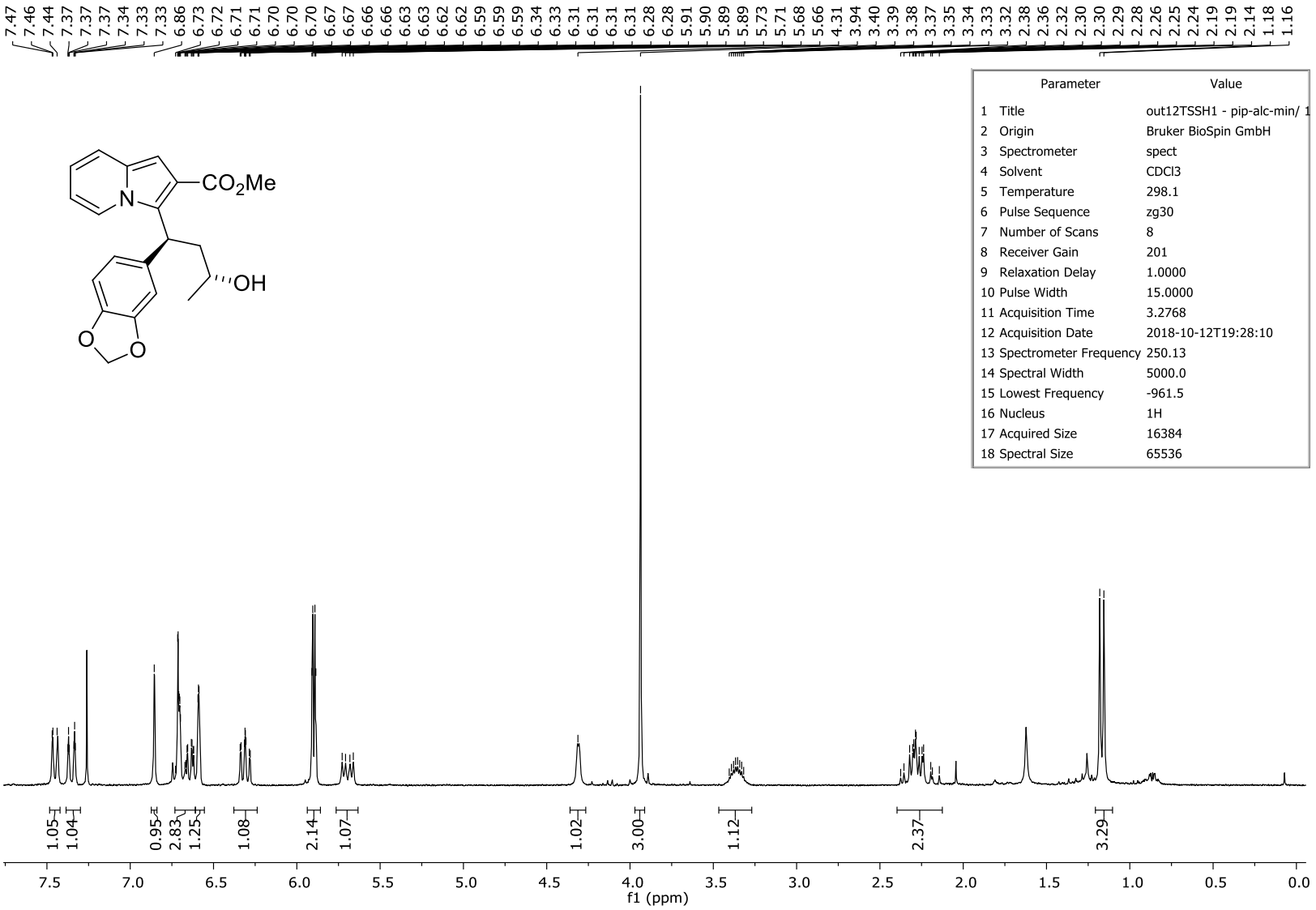


Figure 49. ^{1}H NMR spectrum of compound *anti*-**5h**.

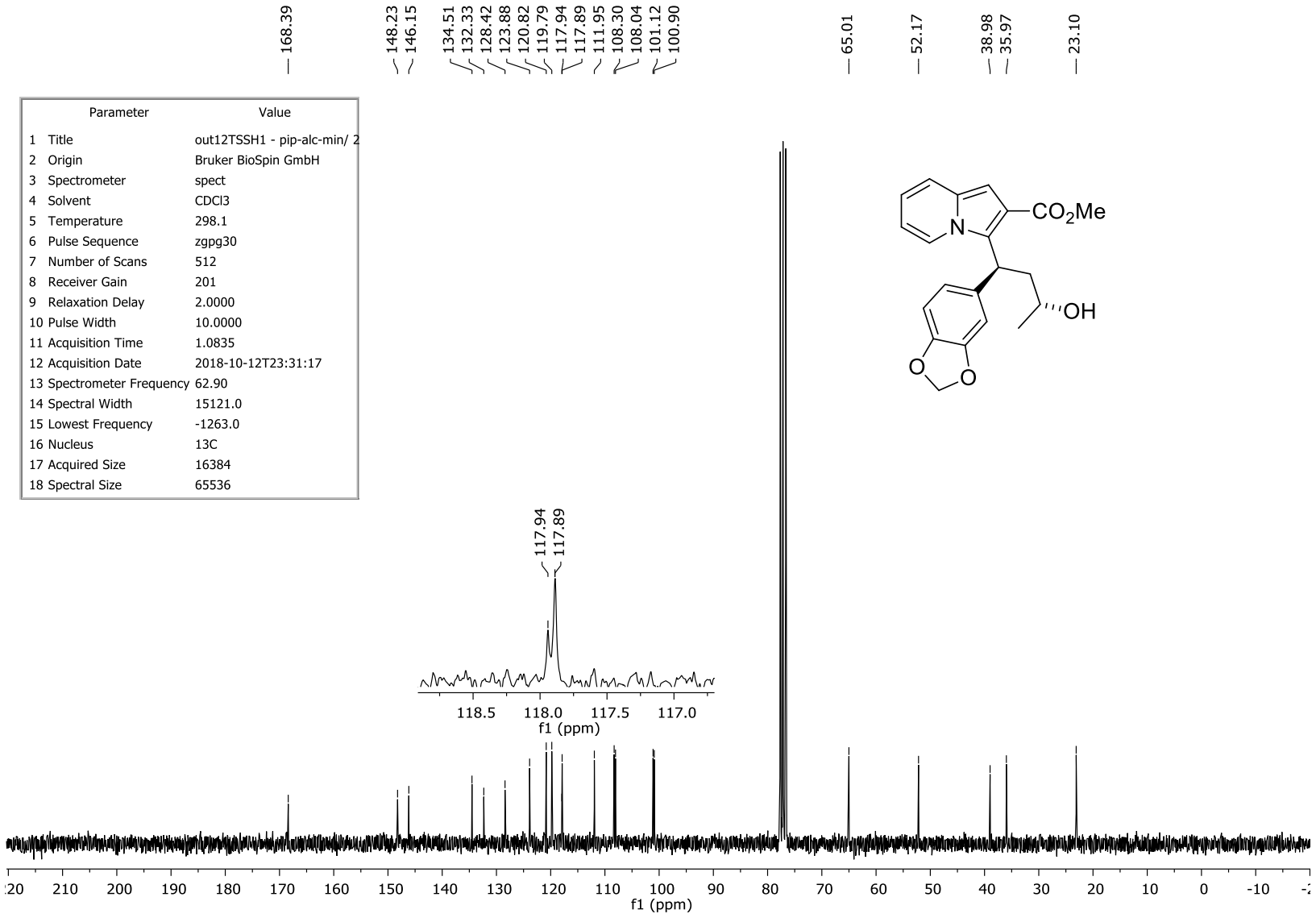


Figure 50. ^{13}C NMR spectrum of compound *anti*-**5h**.

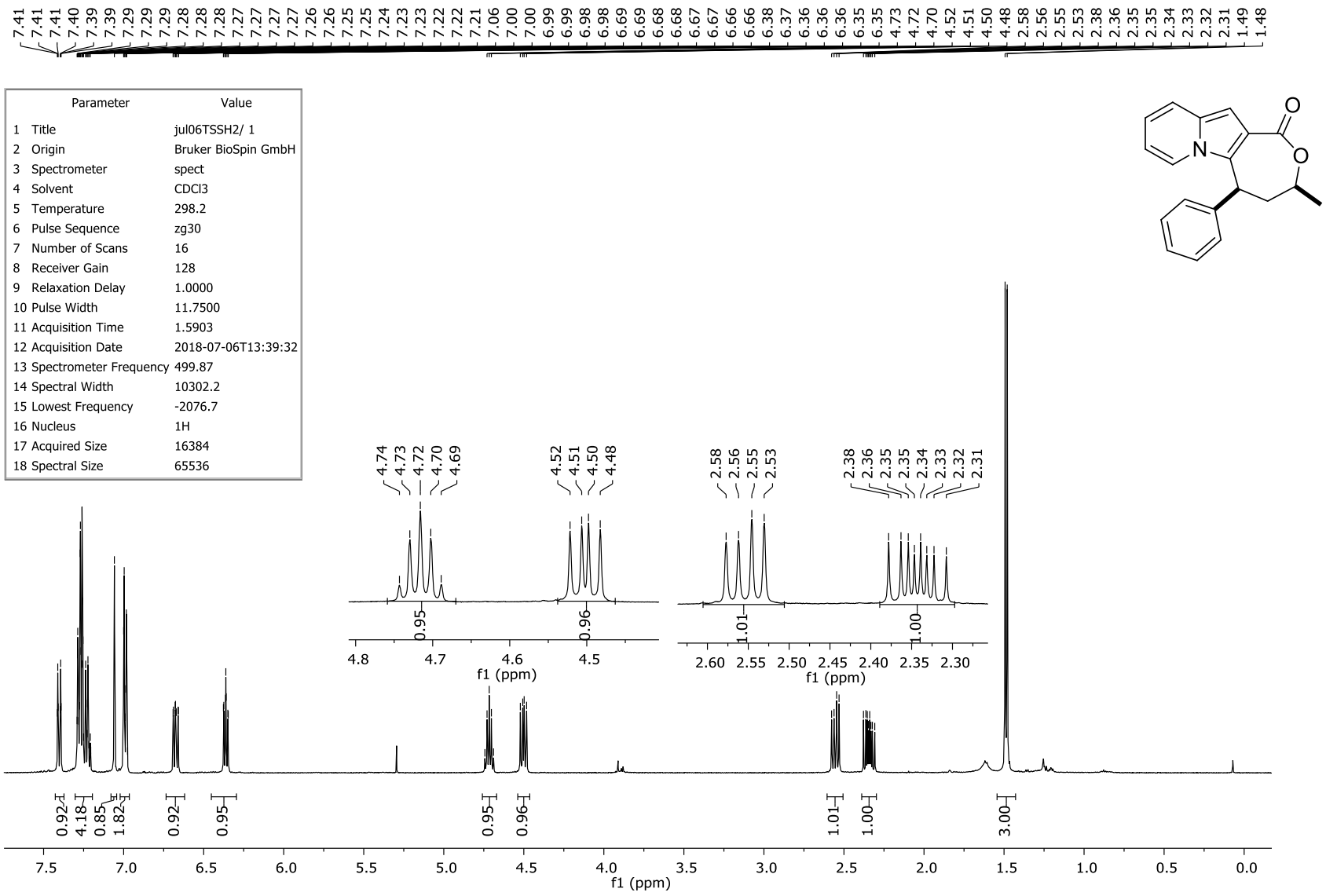


Figure 51. ^{1}H NMR spectrum of compound *cis*-**4a**.

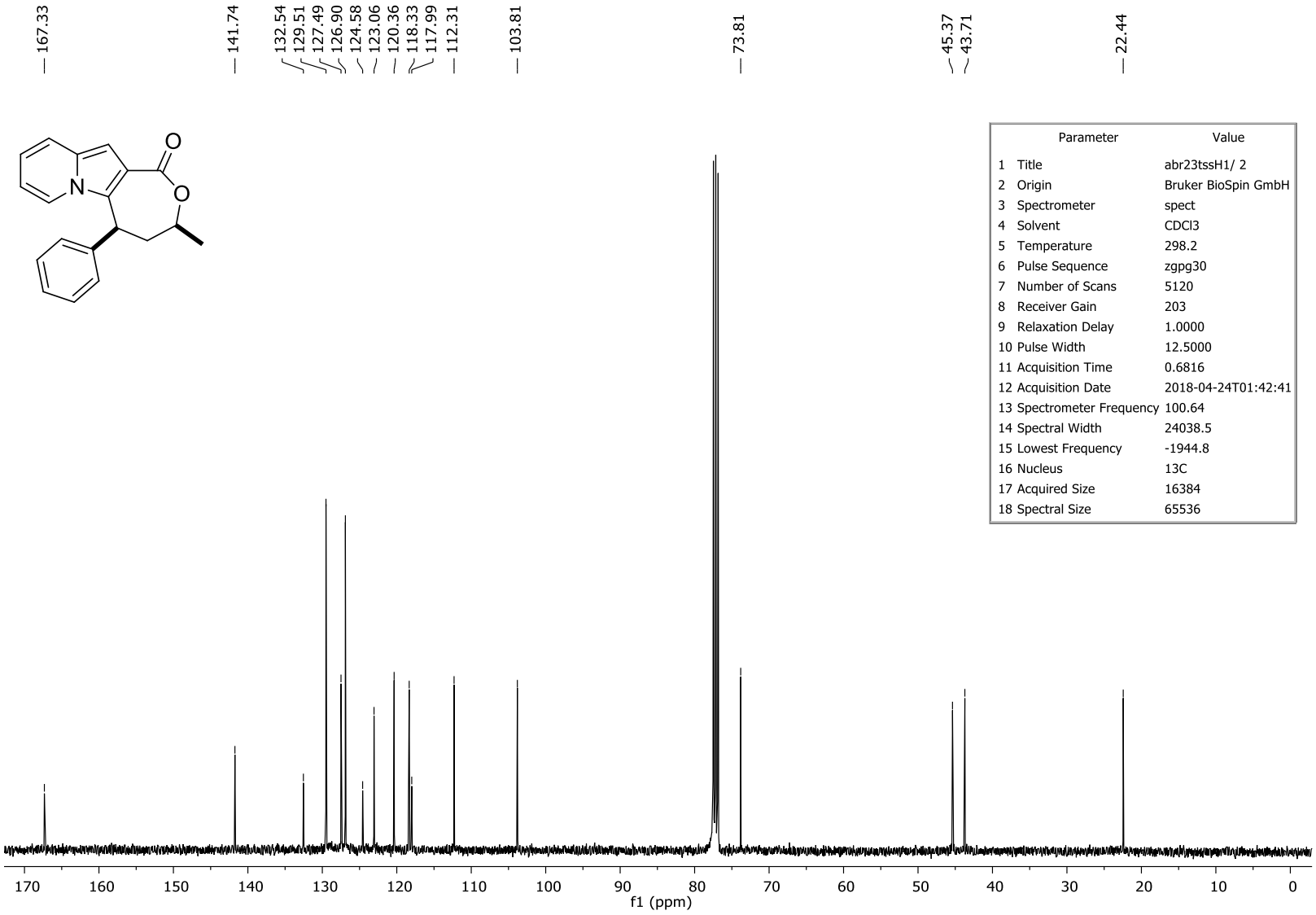


Figure 52. ^{13}C NMR spectrum of compound *cis*-**4a**.

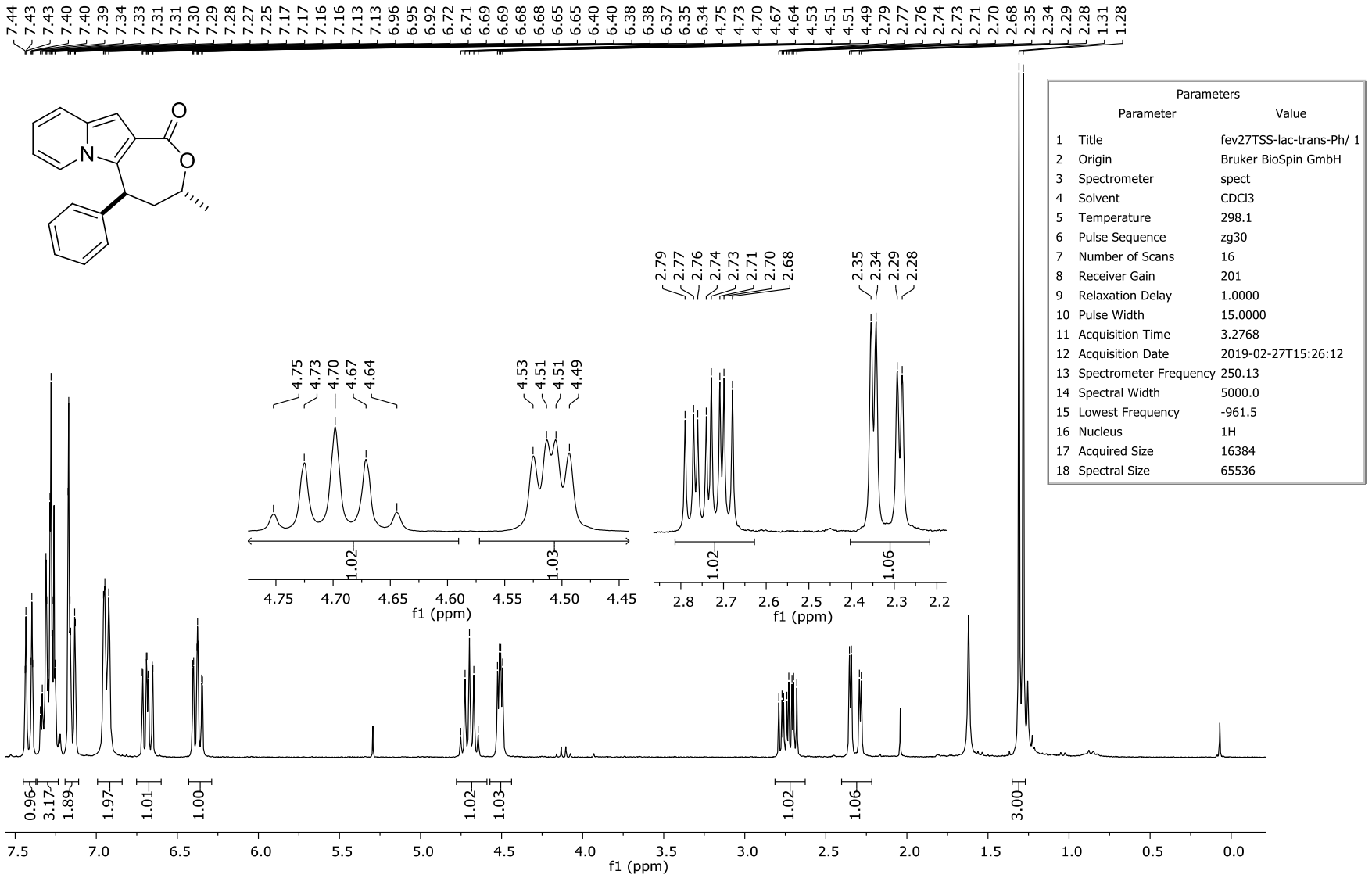


Figure 53. ^{1}H NMR spectrum of compound *trans*-**4a**.

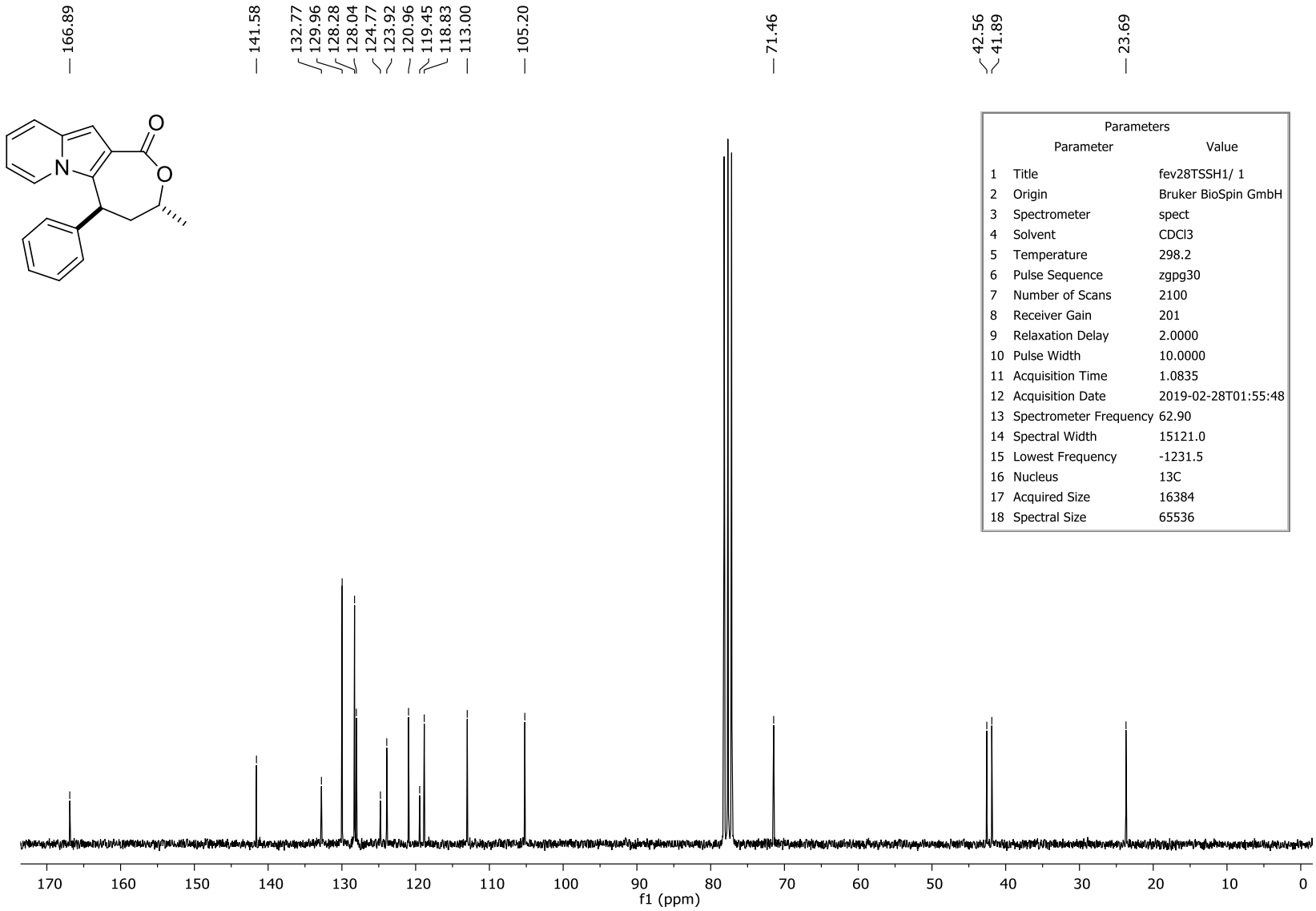


Figure 54. ^{13}C NMR spectrum of compound *trans*-**4a**.

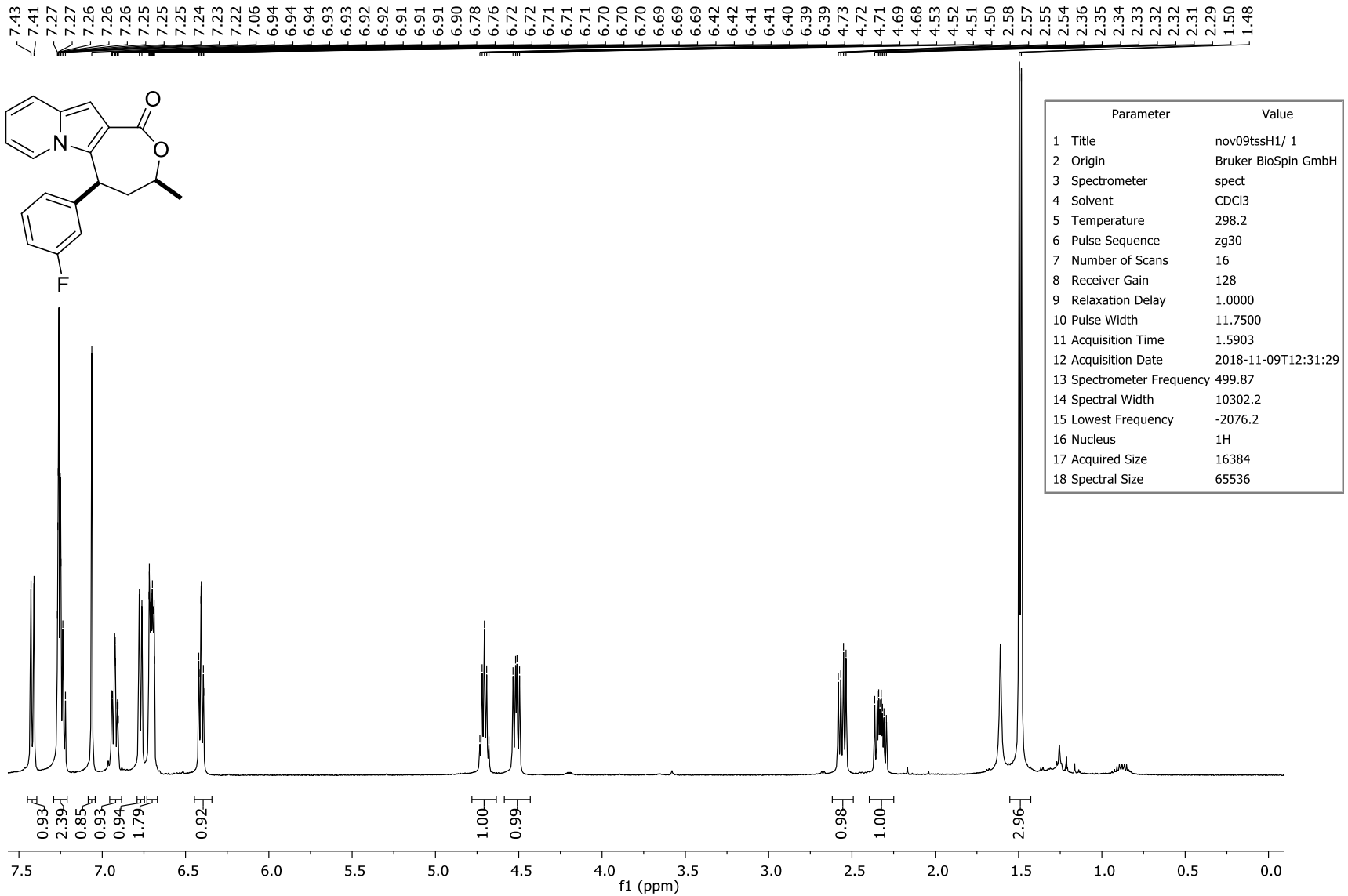


Figure 55. ^{1}H NMR spectrum of compound *cis*-**4b**.

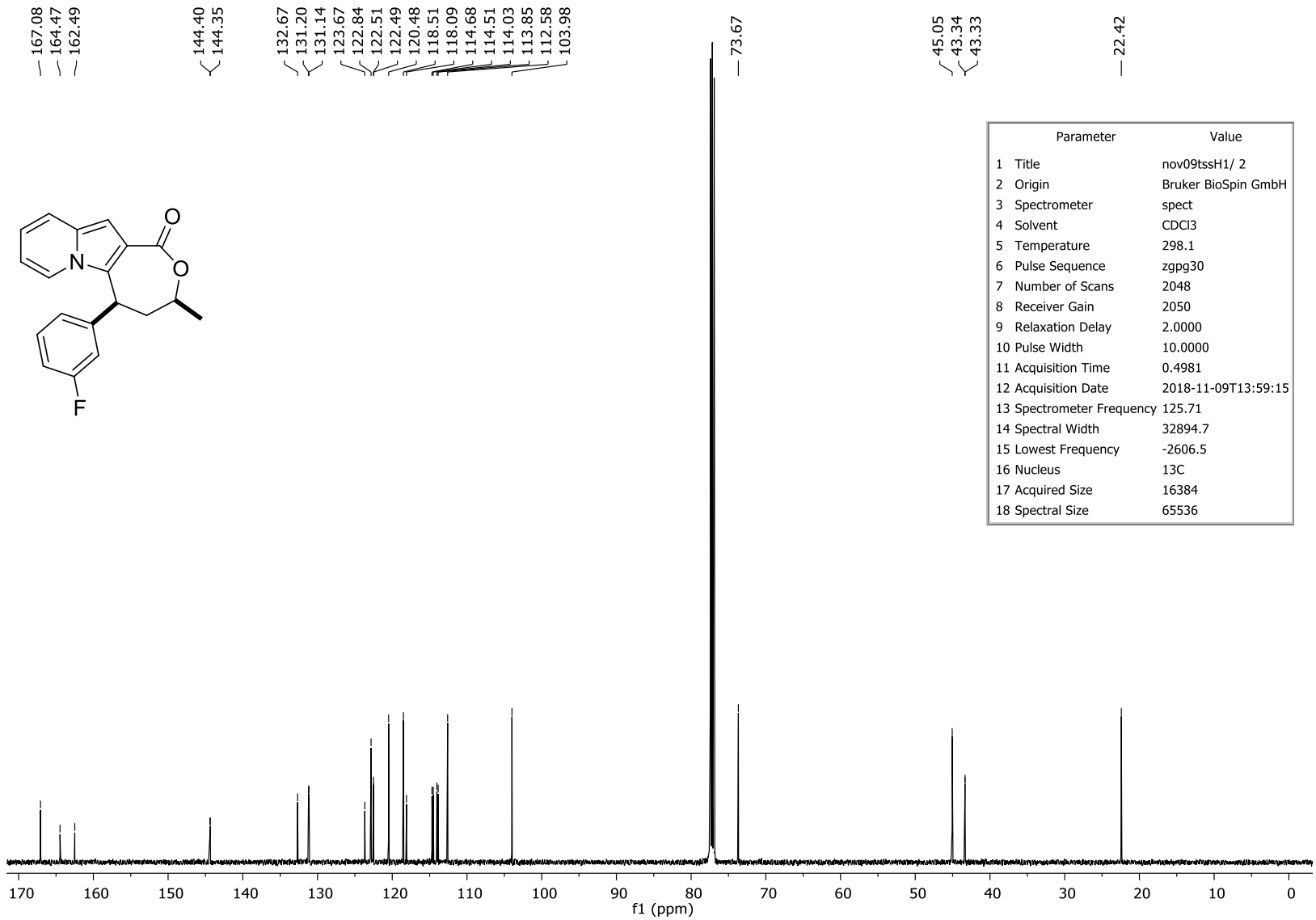


Figure 56. ^{13}C NMR spectrum of compound *cis*-**4b**.

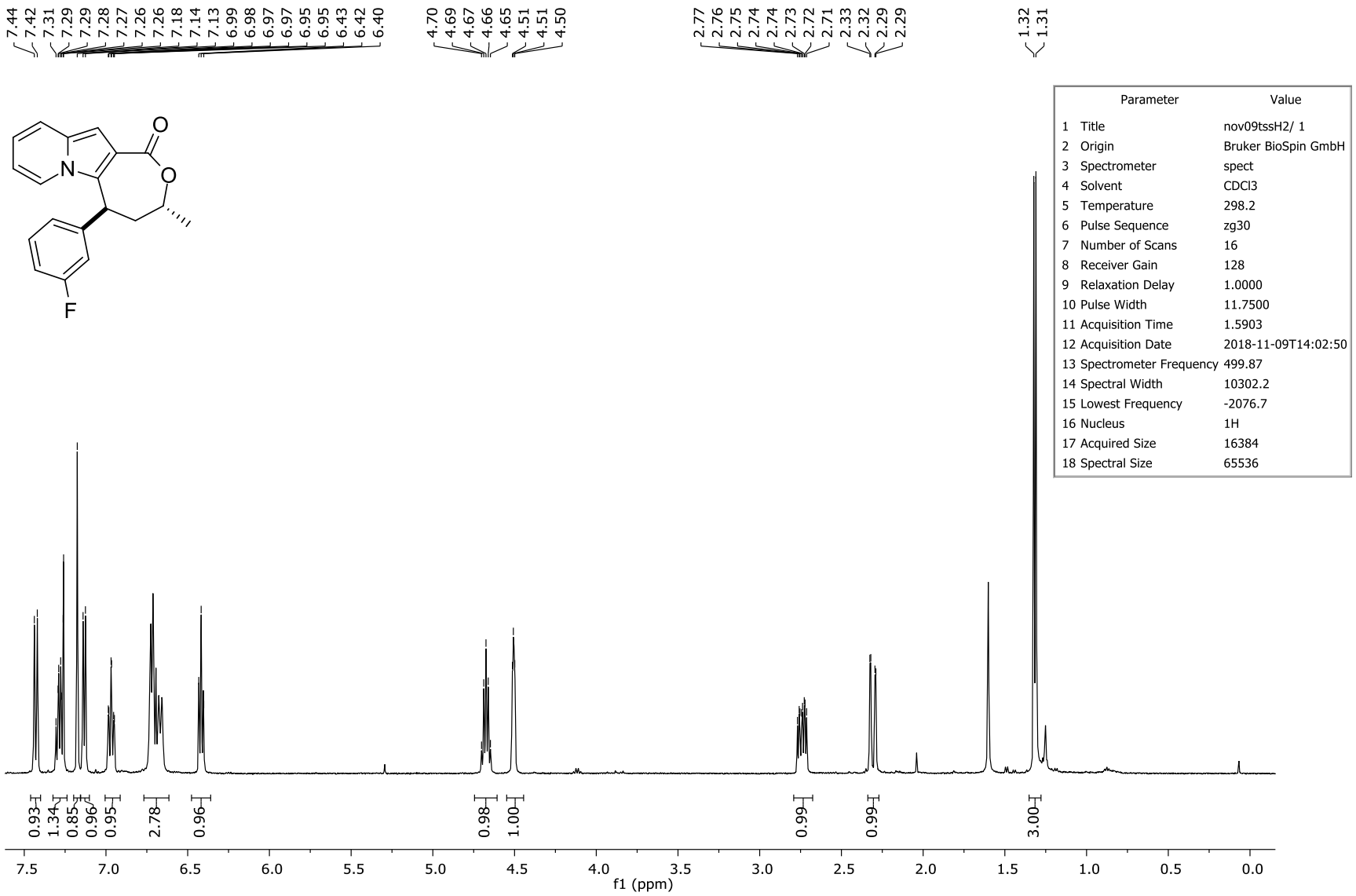


Figure 57. ^{1}H NMR spectrum of compound *trans*-**4b**.

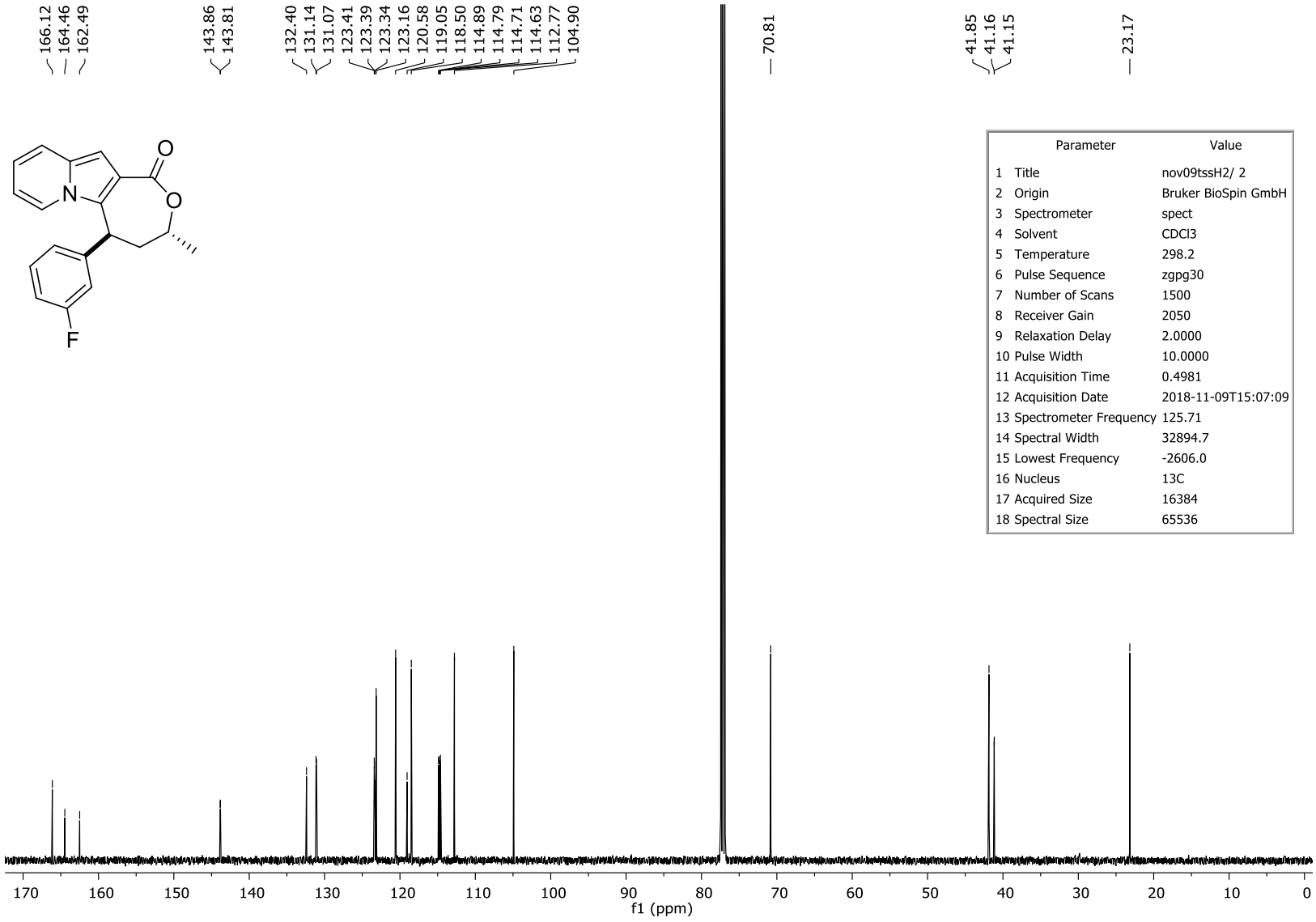


Figure 58. ^{1}H NMR spectrum of compound *trans*-**4b**.

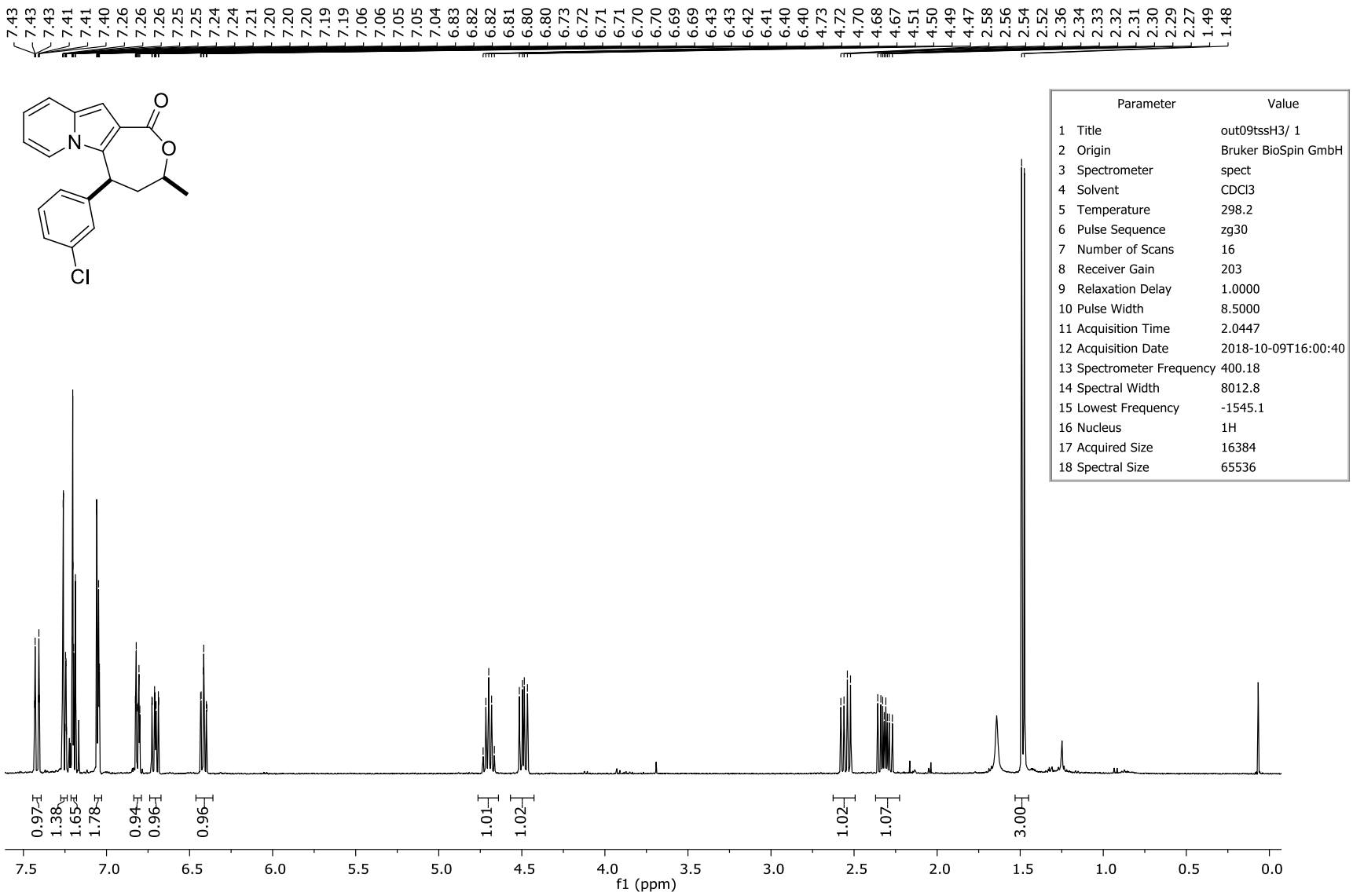


Figure 59. ^{1}H NMR spectrum of compound *cis*-**4c**.

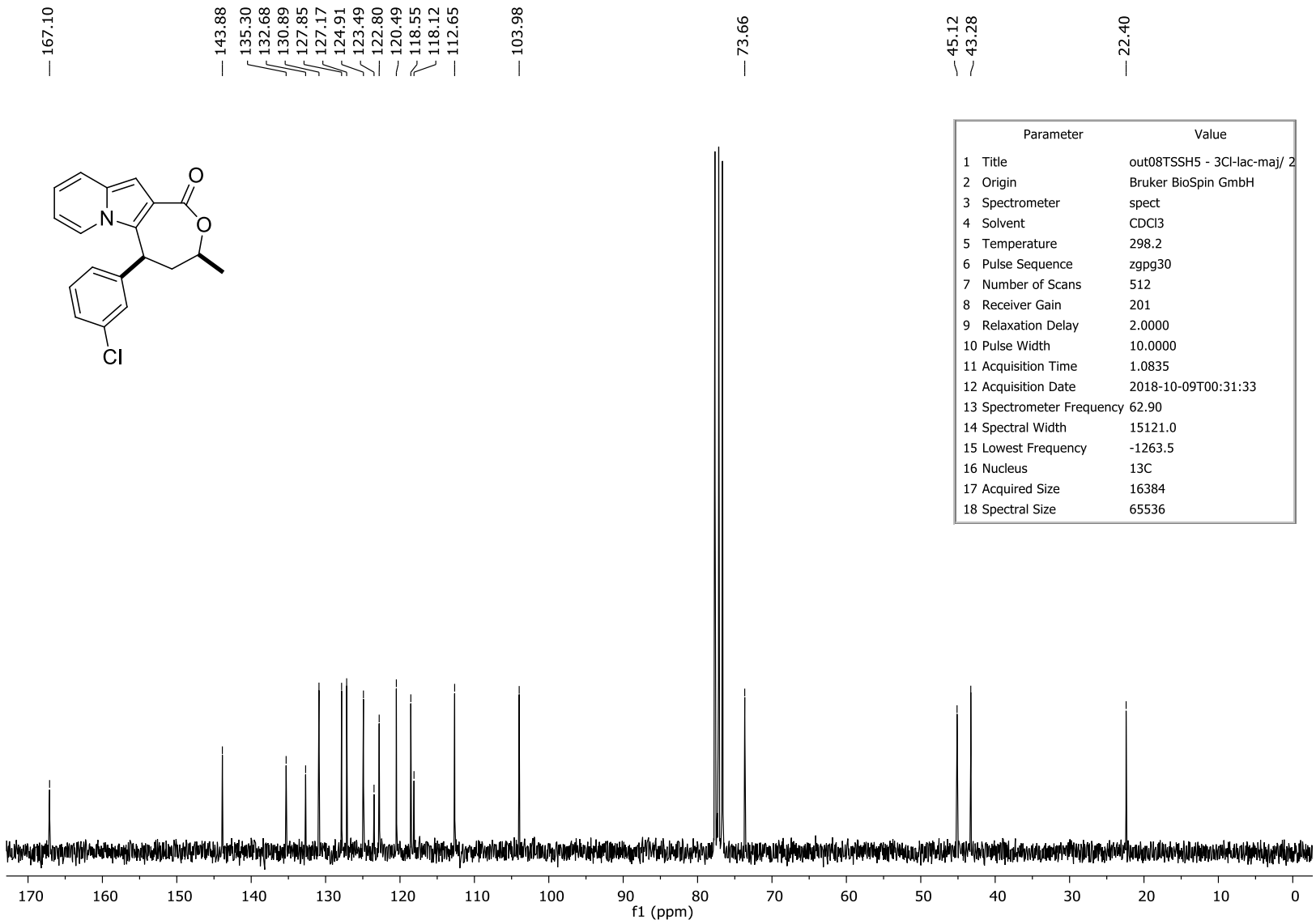


Figure 60. ^{13}C NMR spectrum of compound *cis*-**4c.**

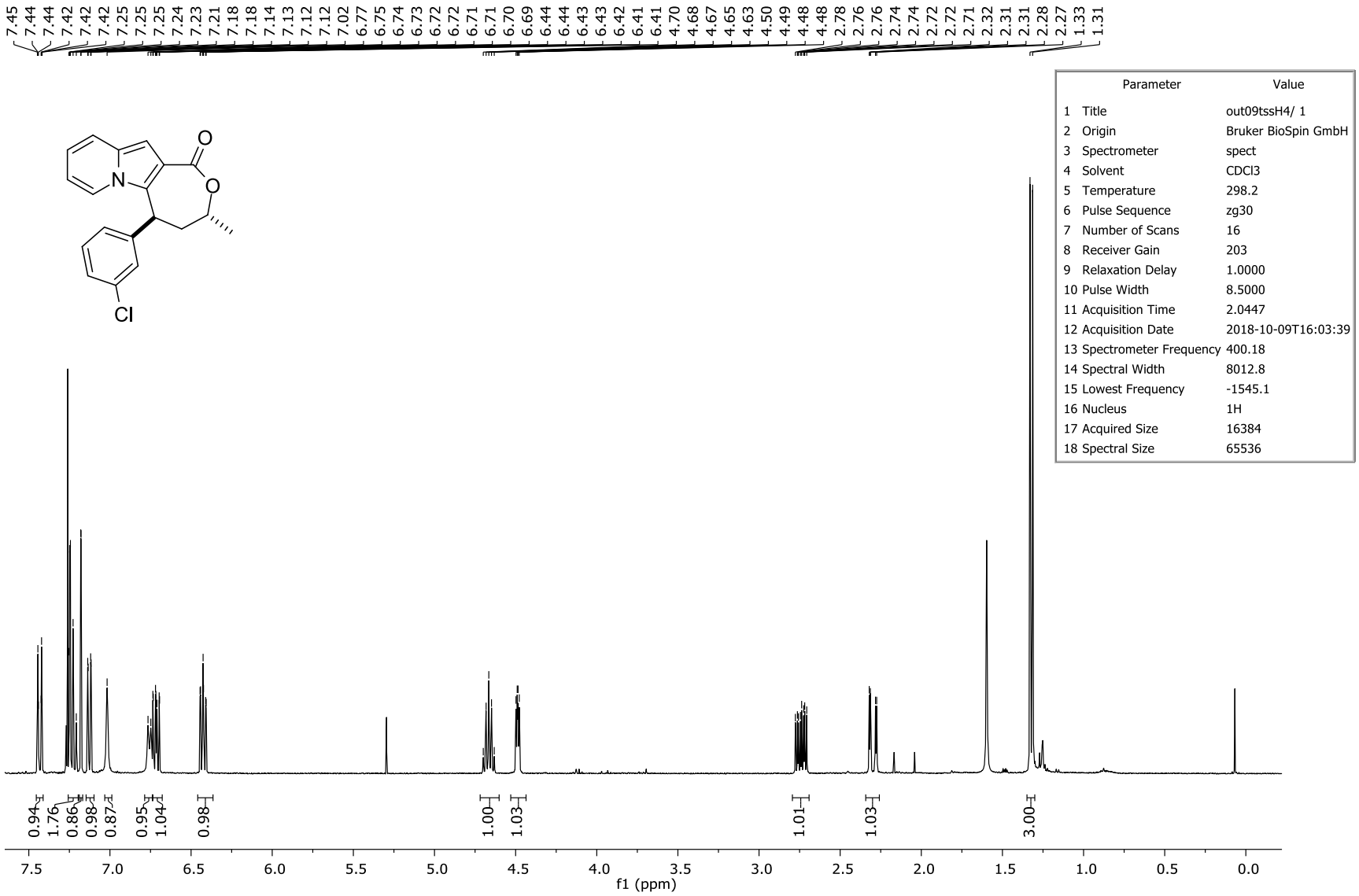


Figure 61. ^{1}H NMR spectrum of compound *trans*-**4c**

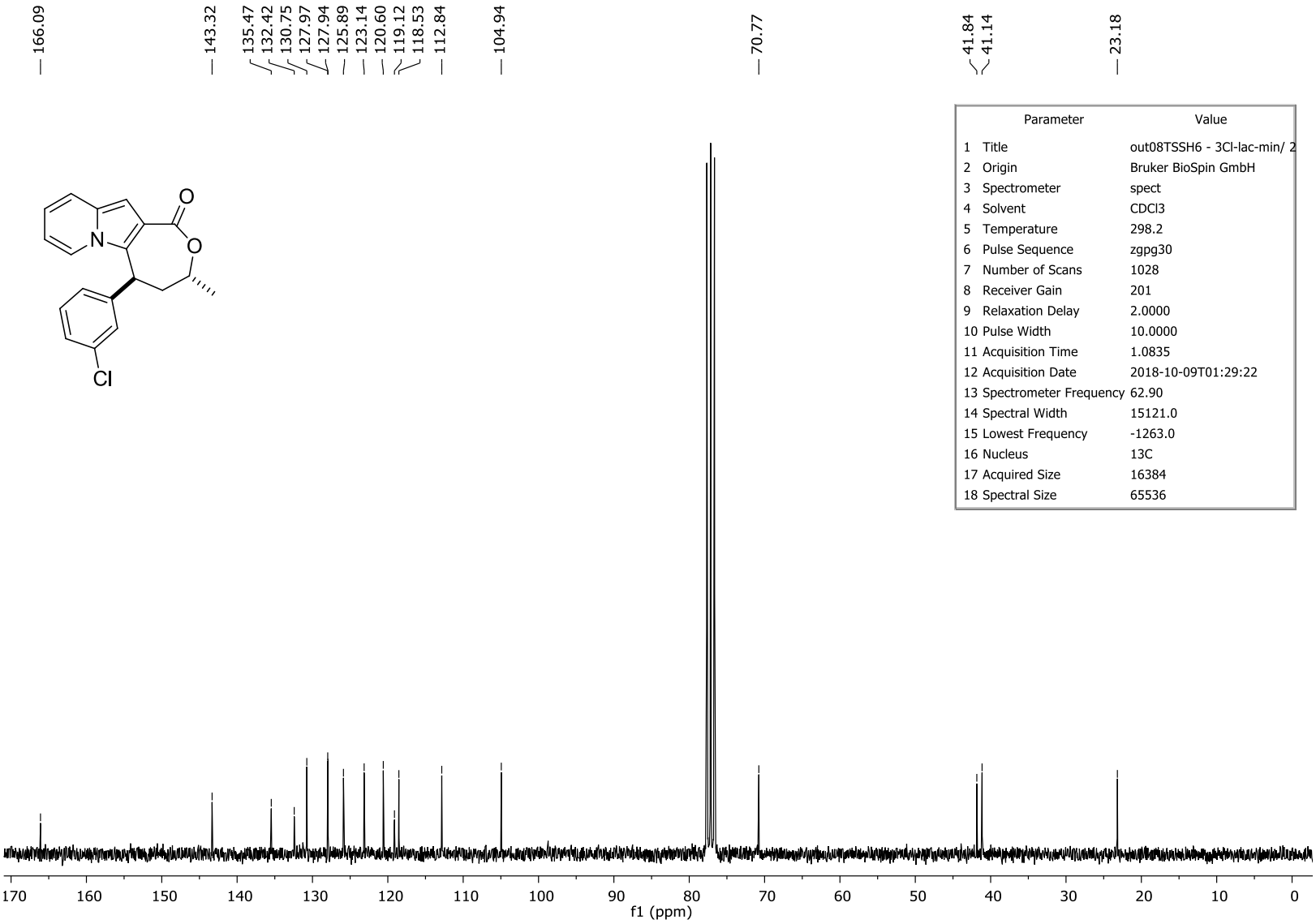


Figure 62. ^{13}C NMR spectrum of compound *trans*-**4c**.

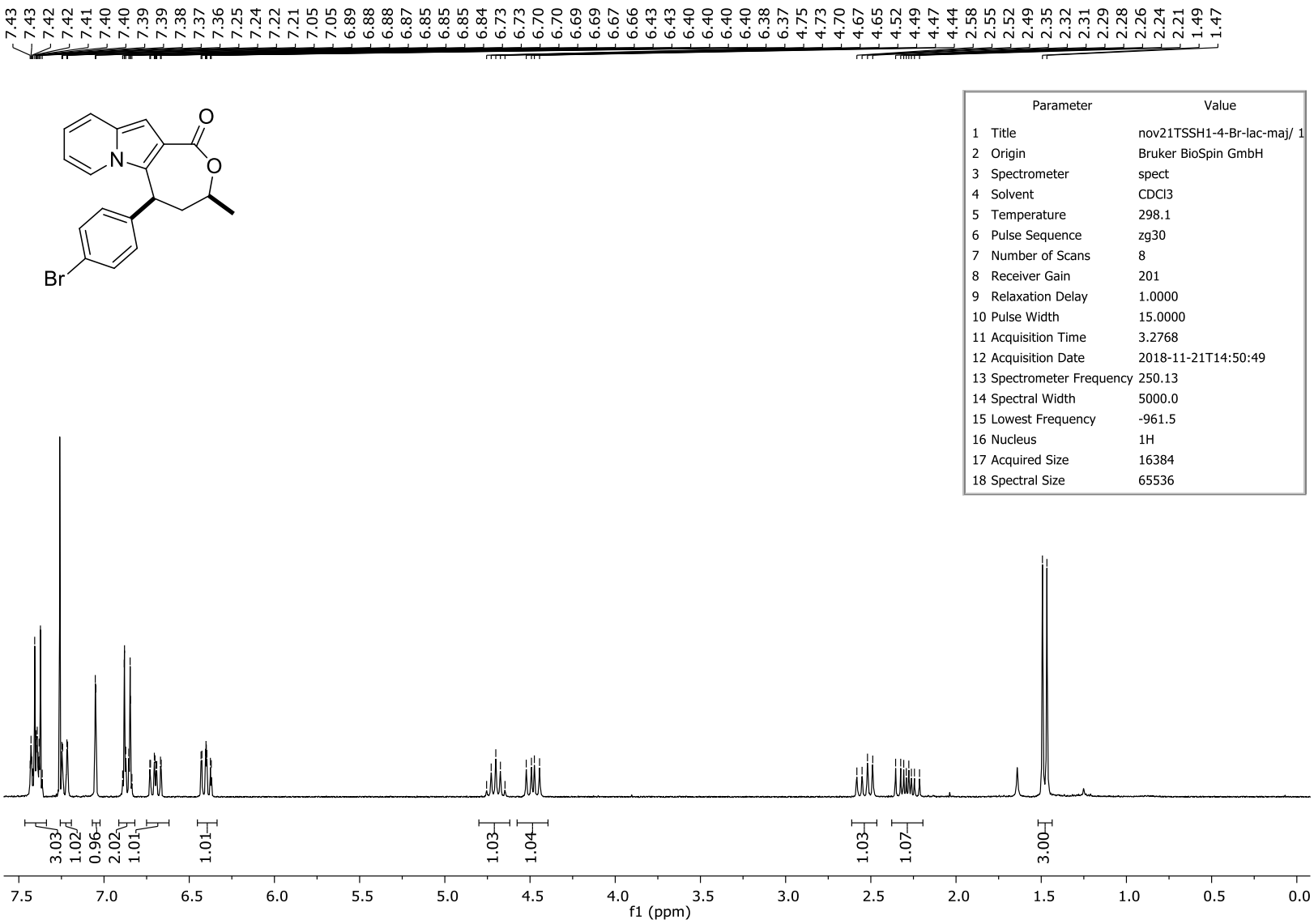


Figure 63. ^{1}H NMR spectrum of compound *cis*-**4d**.

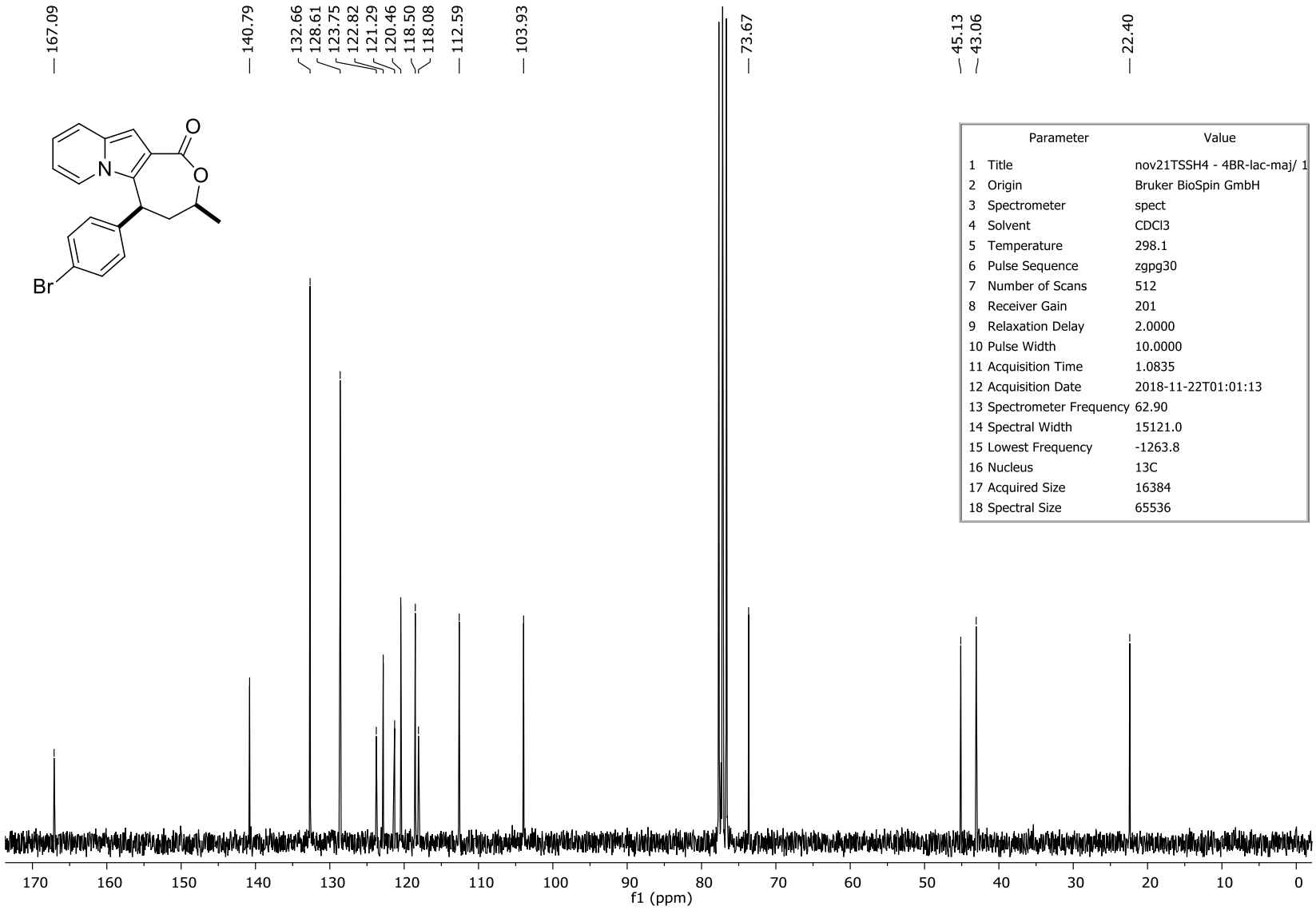


Figure 64. ^{13}C NMR spectrum of compound *cis*-**4d**.

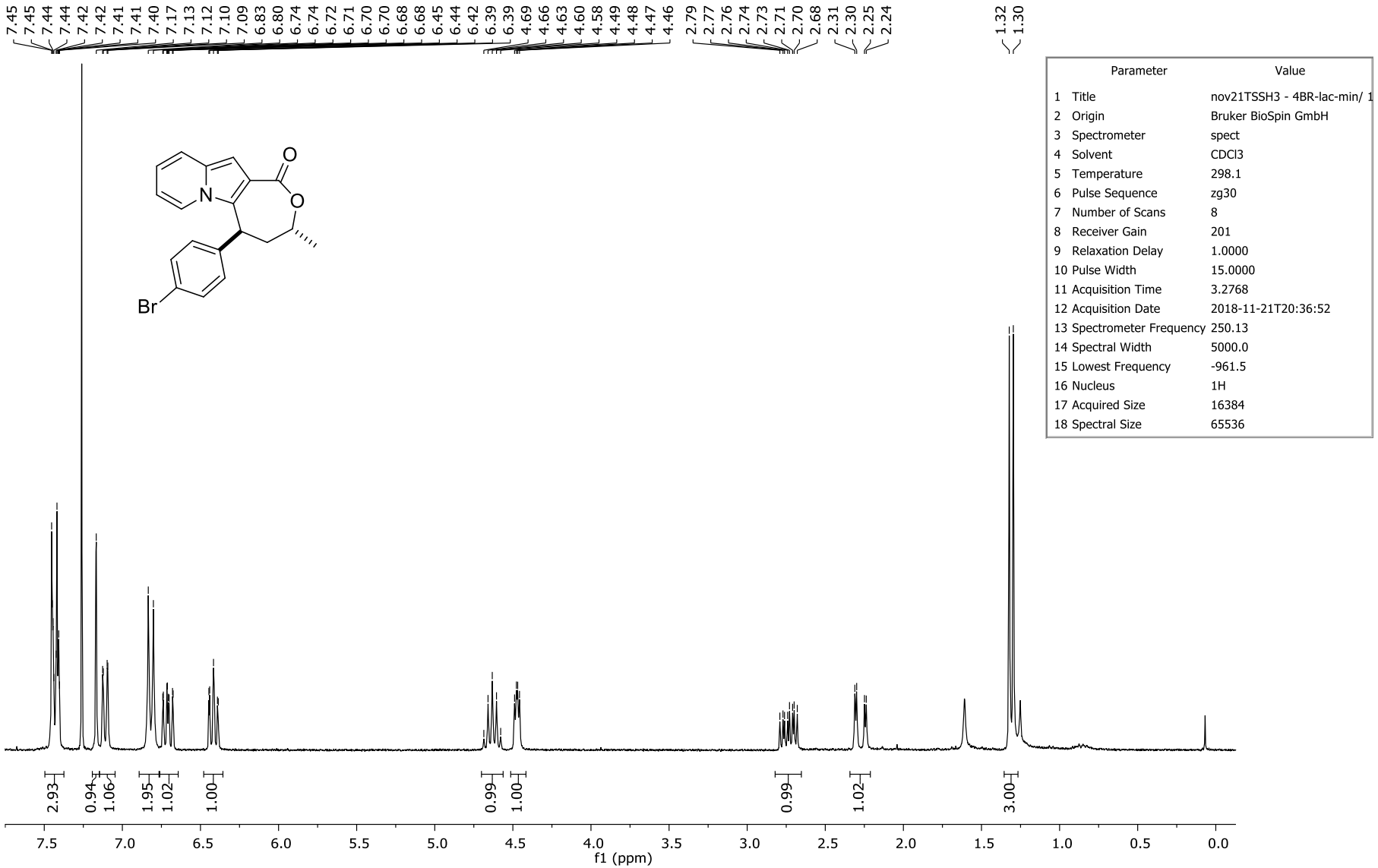


Figure 65. ^{1}H NMR spectrum of compound *trans*-**4d**.

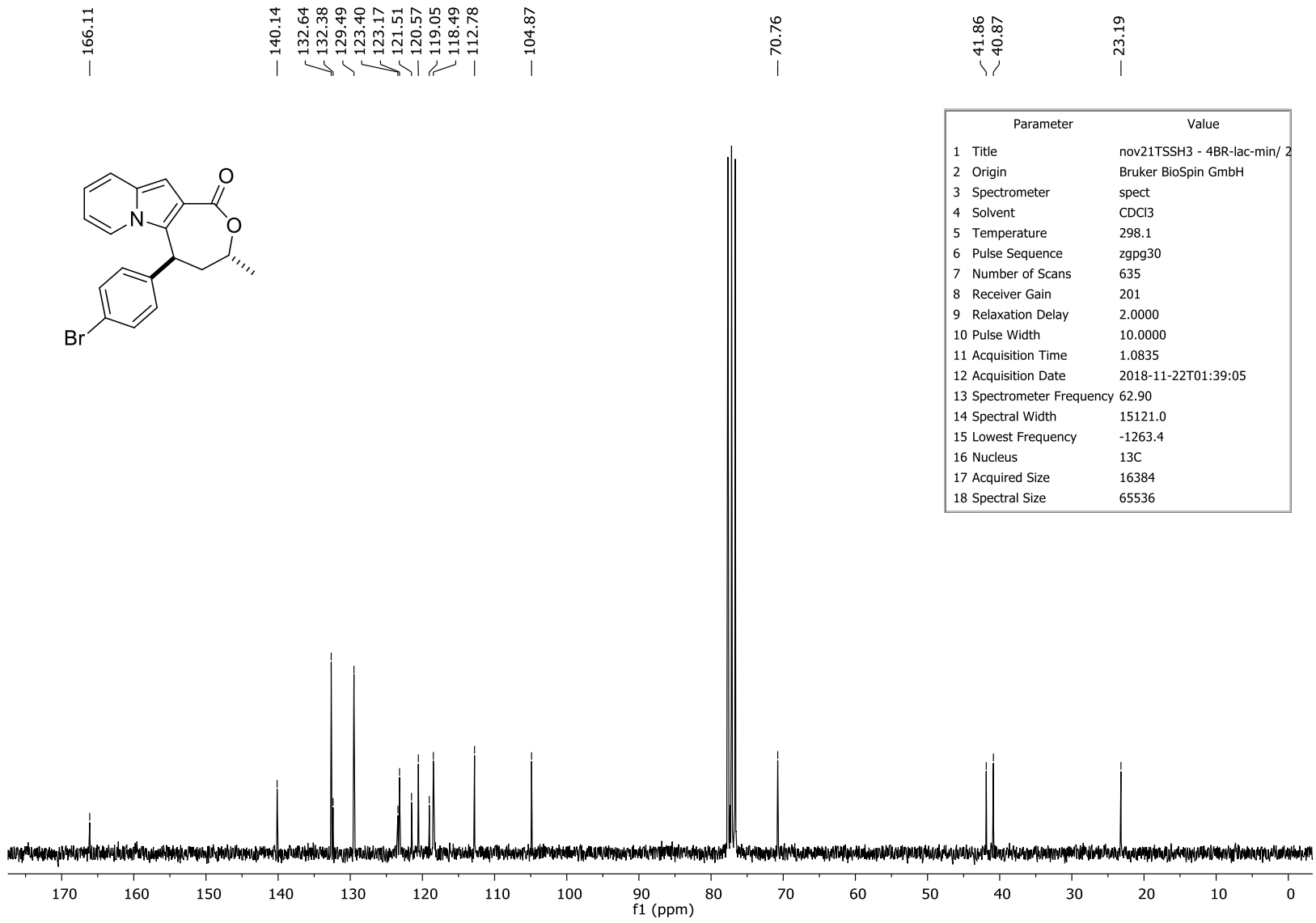


Figure 66. ^{13}C NMR spectrum of compound *trans*-**4d**.

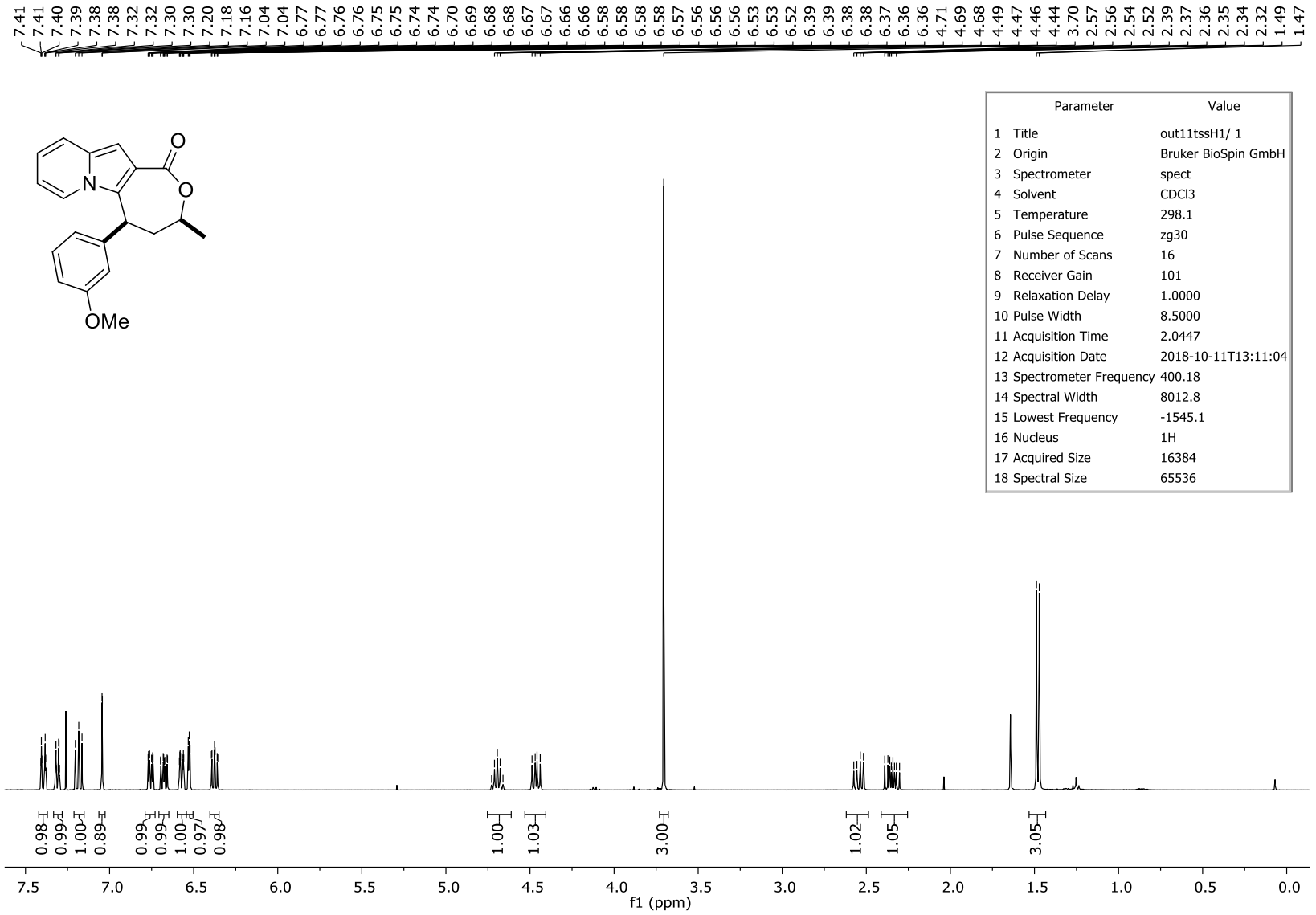


Figure 67. ^{1}H NMR spectrum of compound *cis*-**4e**.

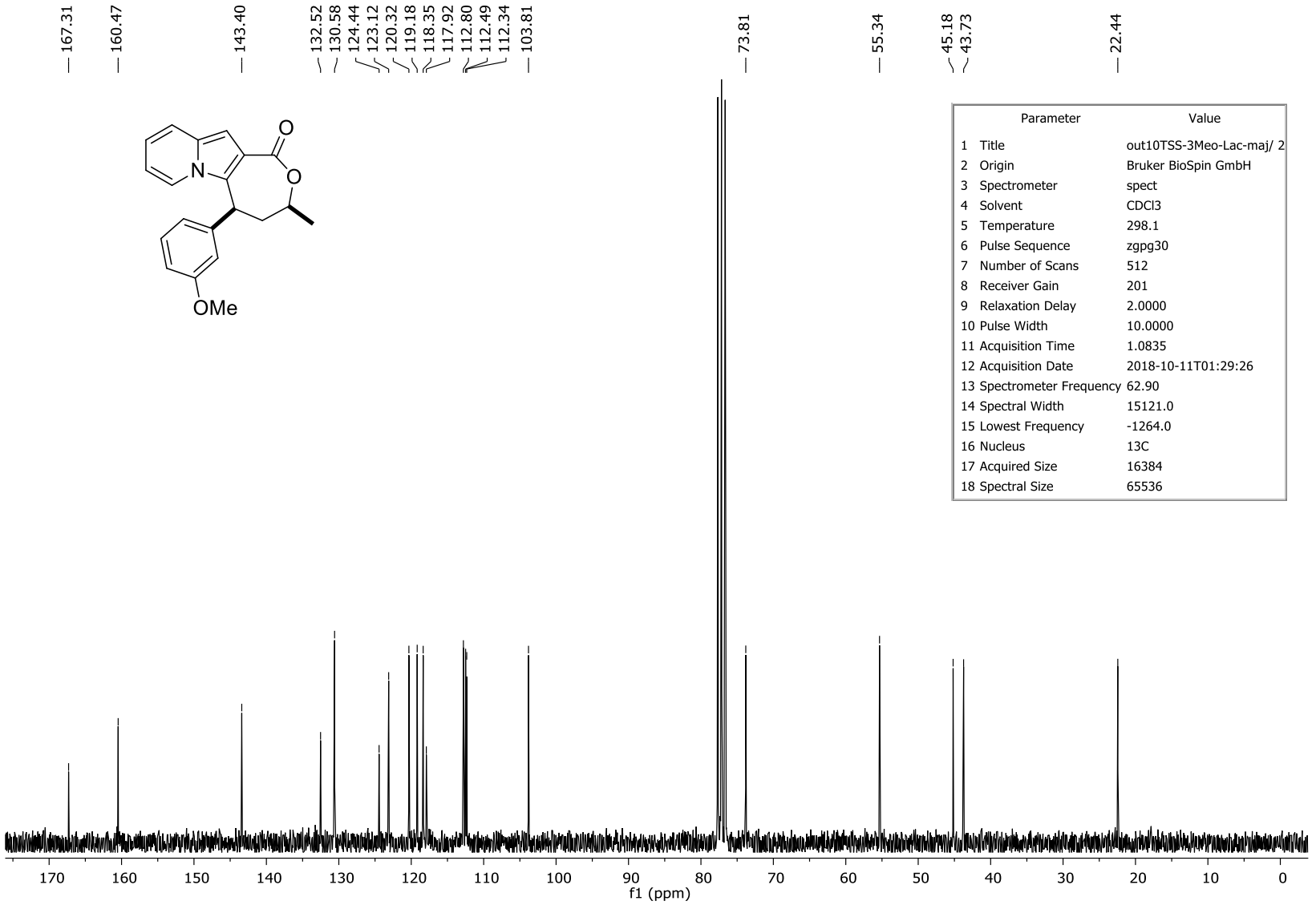


Figure 68. ^{13}C NMR spectrum of compound *cis*-**4e**.

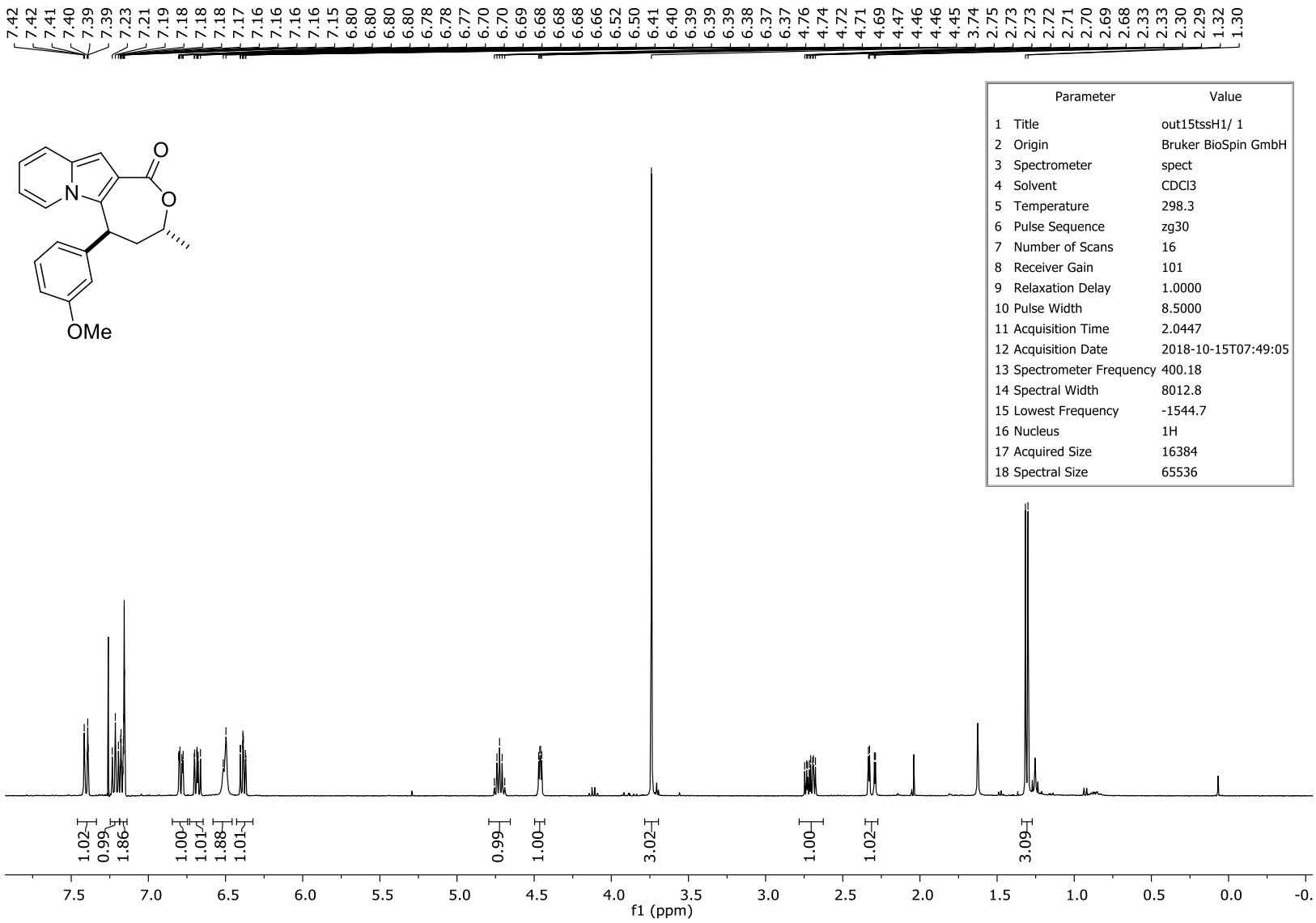


Figure 69. ^{1}H NMR spectrum of compound *trans*-**4e**.

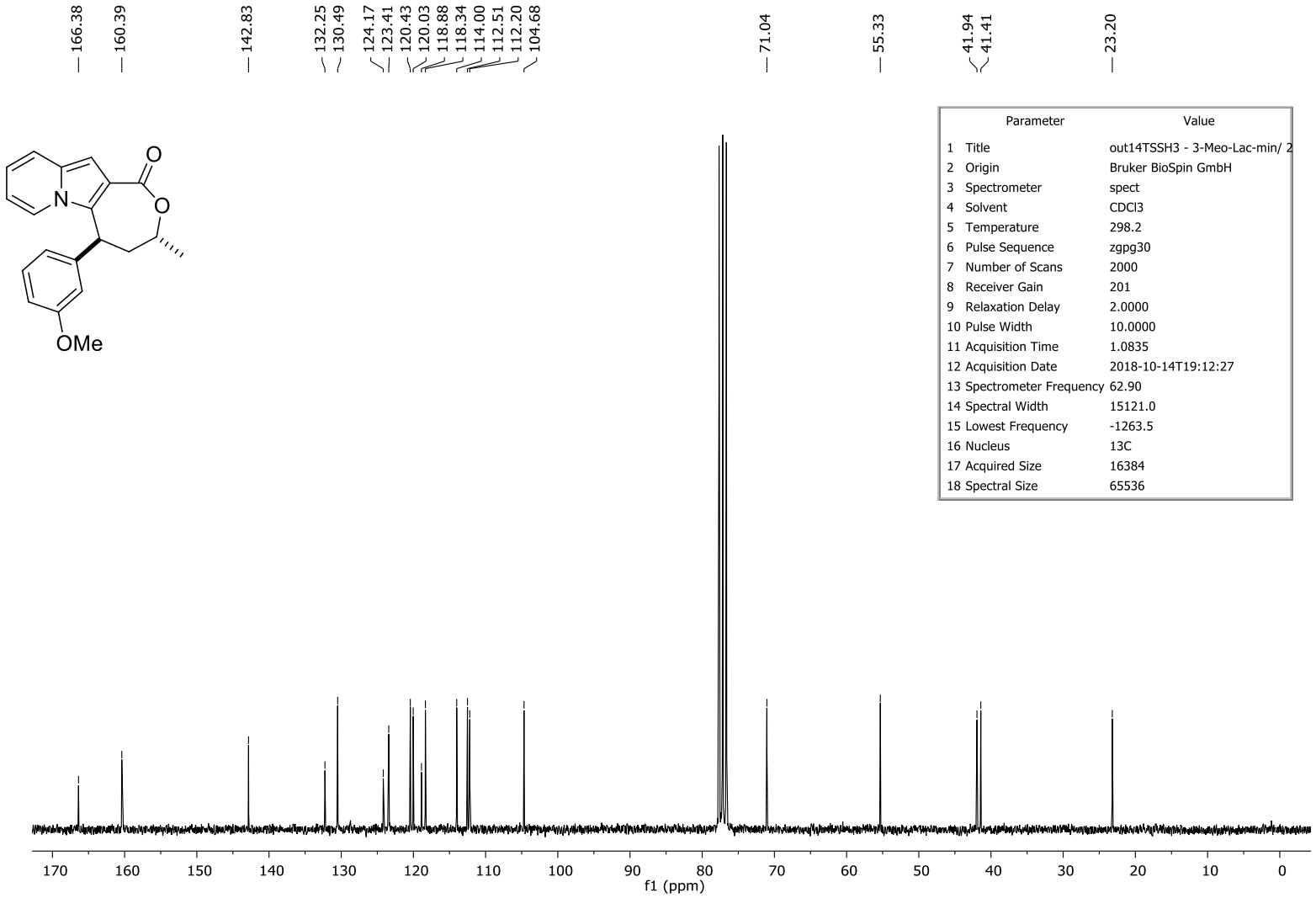


Figure 70. ^{13}C NMR spectrum of compound *trans*-**4e**.

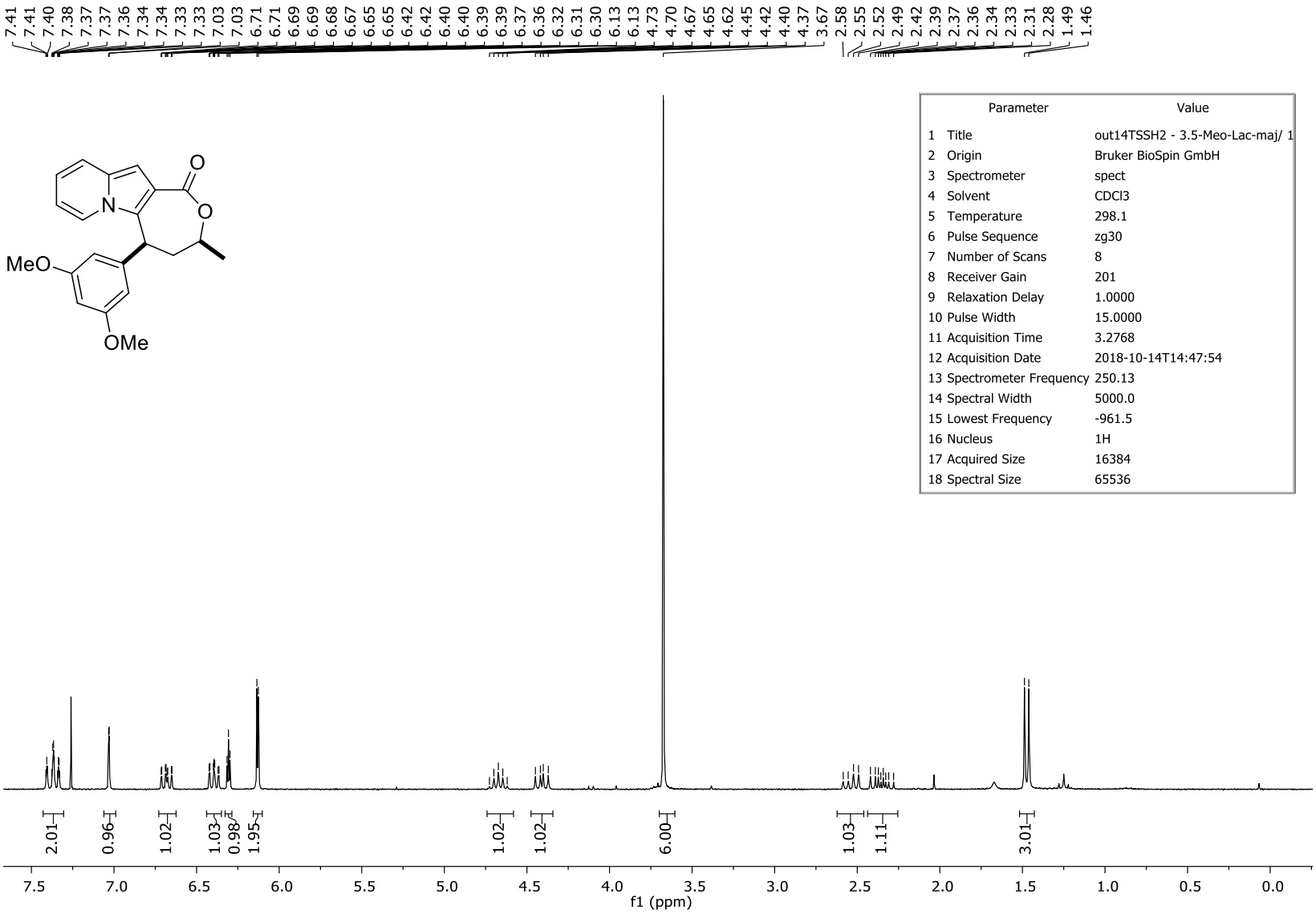


Figure 71. ^{1}H NMR spectrum of compound *cis*-**4f**

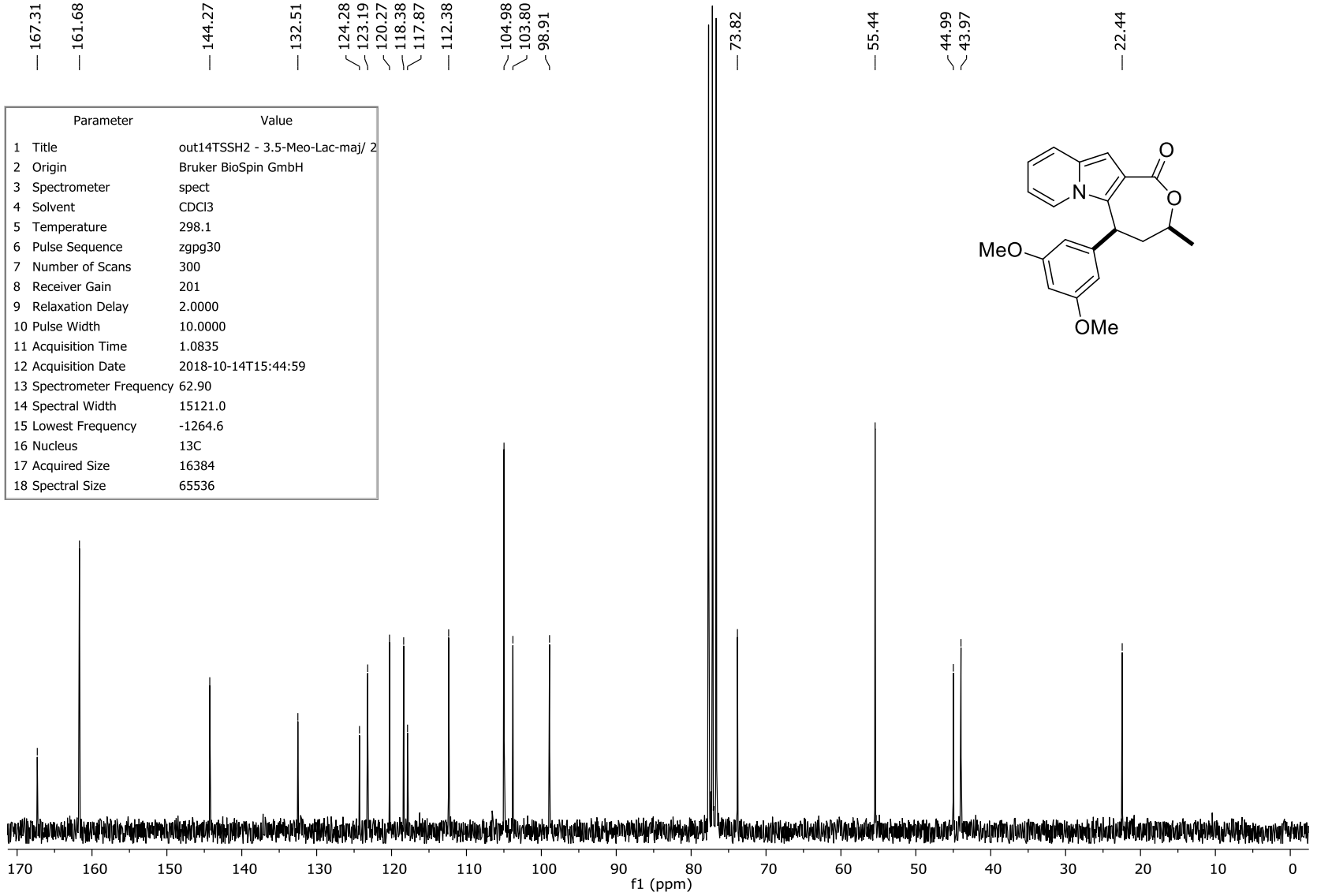


Figure 72. ^{13}C NMR spectrum of compound *cis*-**4f**.

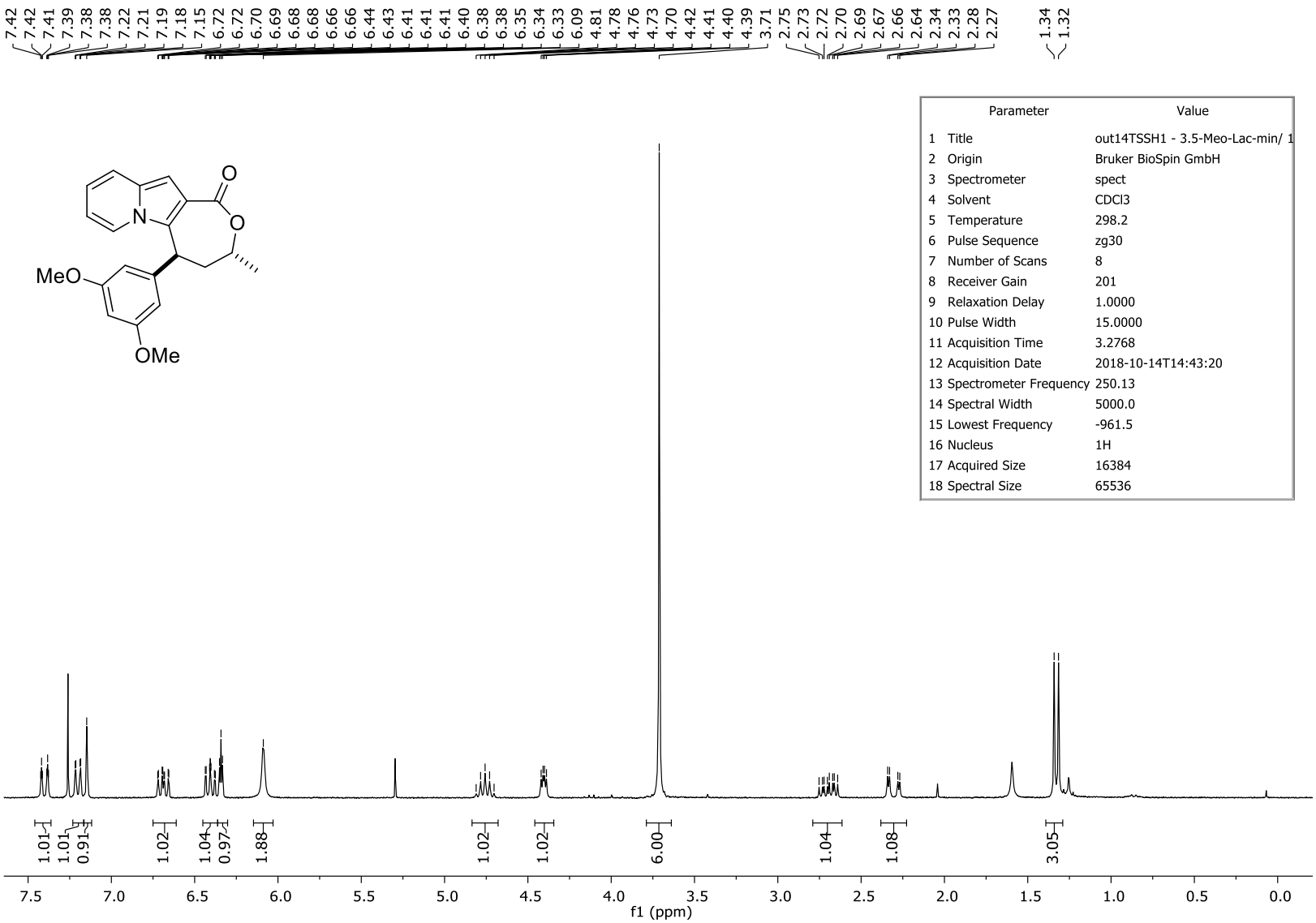


Figure 73. ^{1}H NMR spectrum of compound *trans*-**4f**.

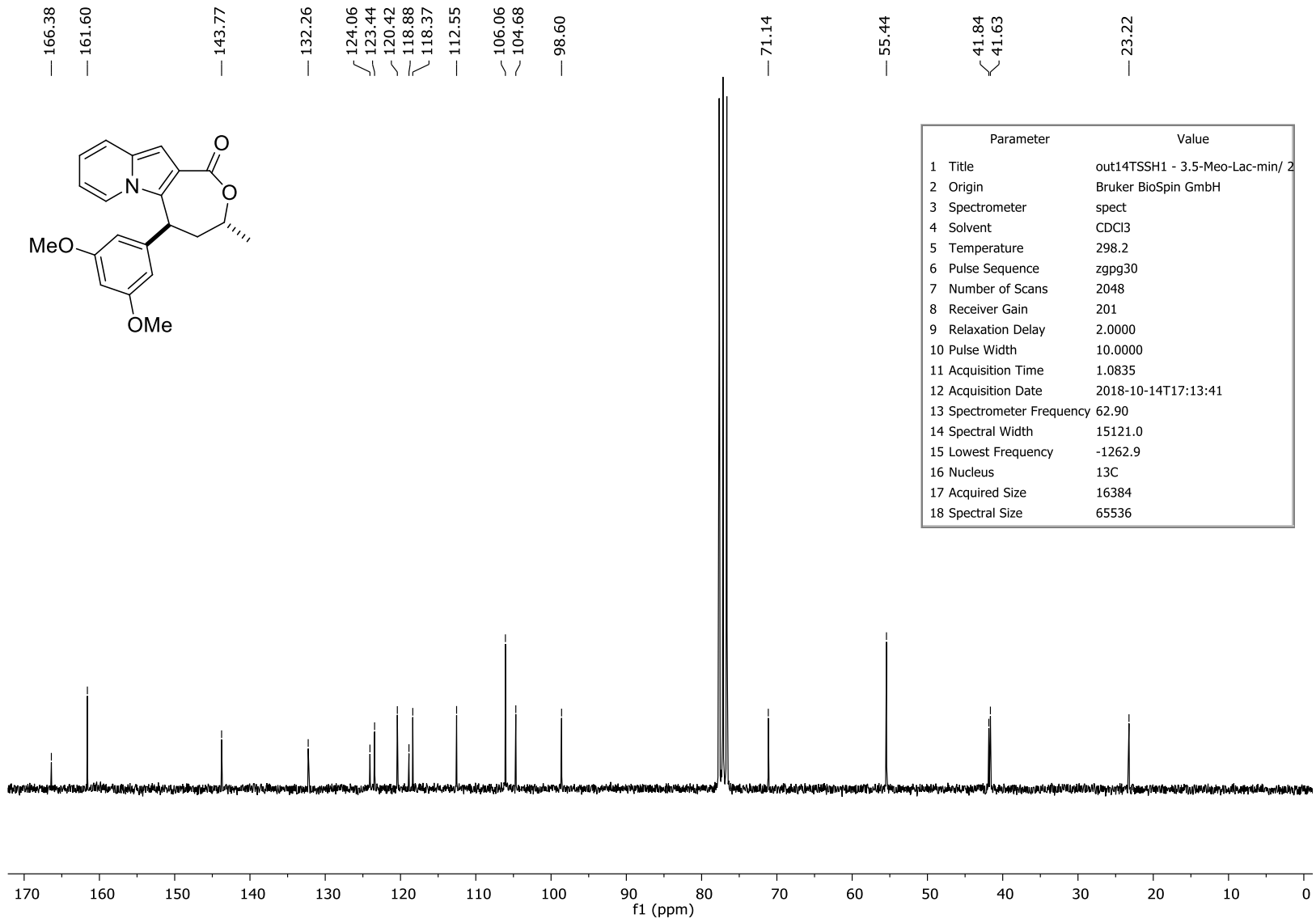


Figure 74. ^{13}C NMR spectrum of compound *trans*-**4f**.

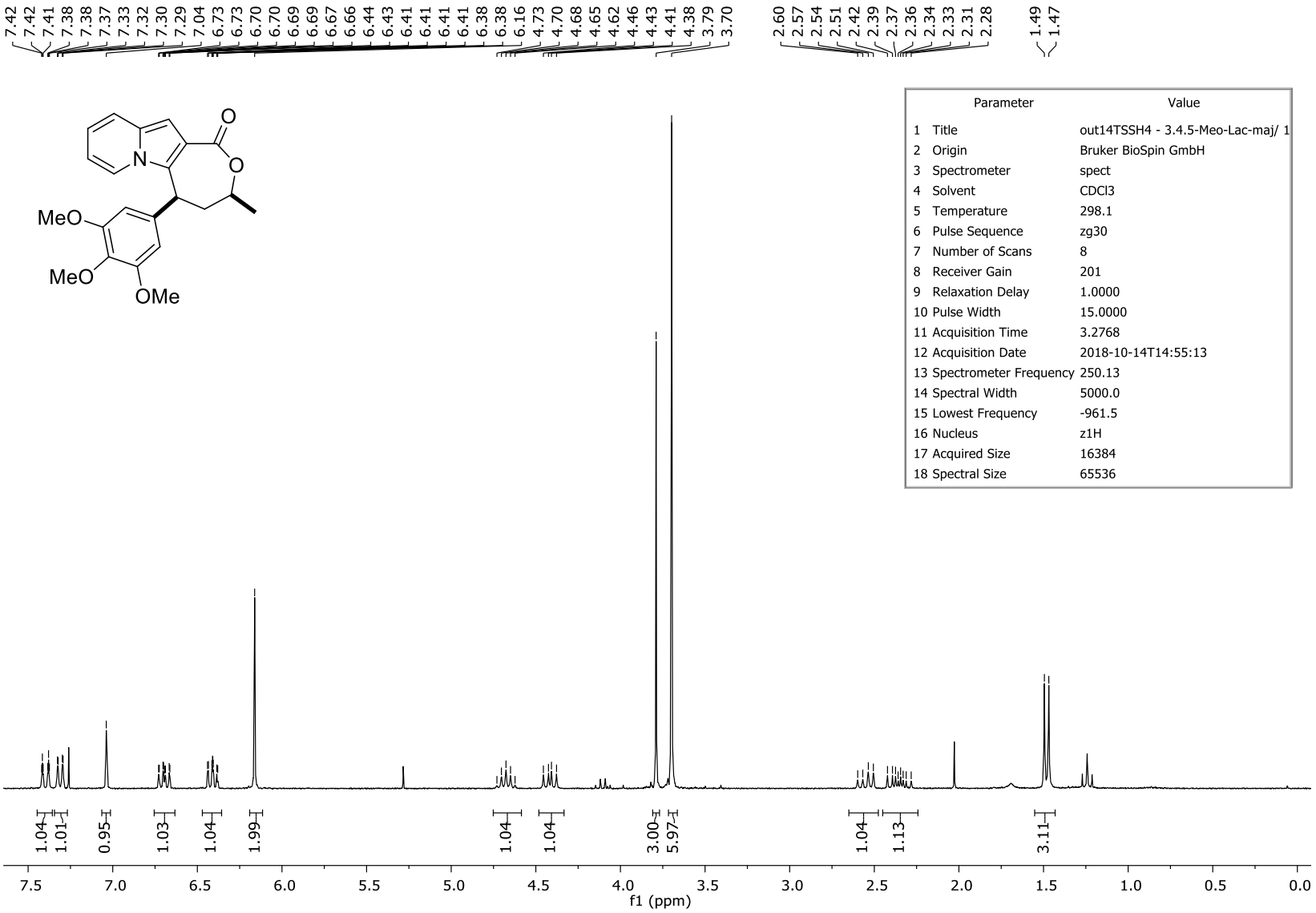


Figure 75. ^{1}H NMR spectrum of compound *cis*-**4g**.

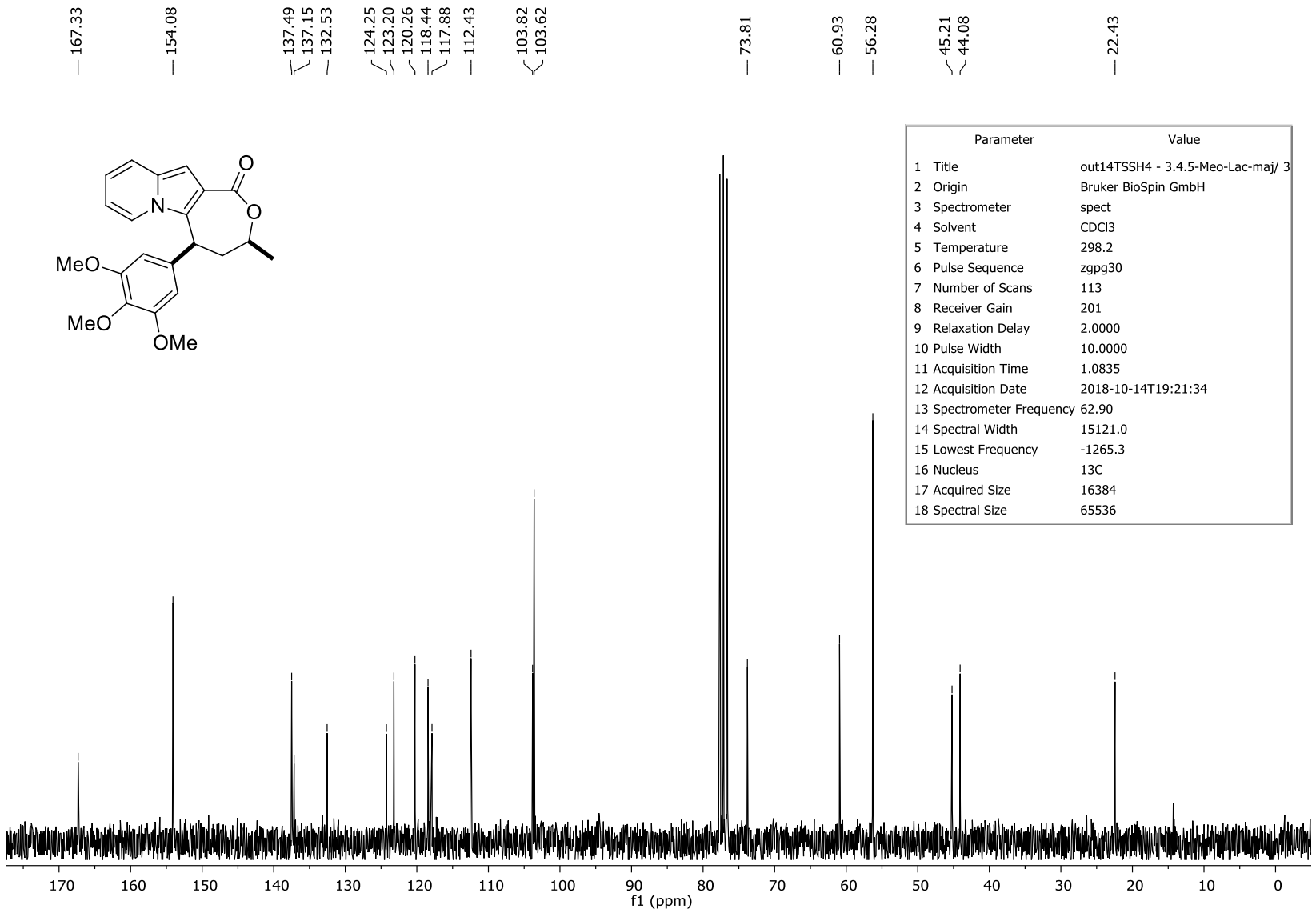


Figure 76. ^{13}C NMR spectrum of compound *cis*-**4g**.

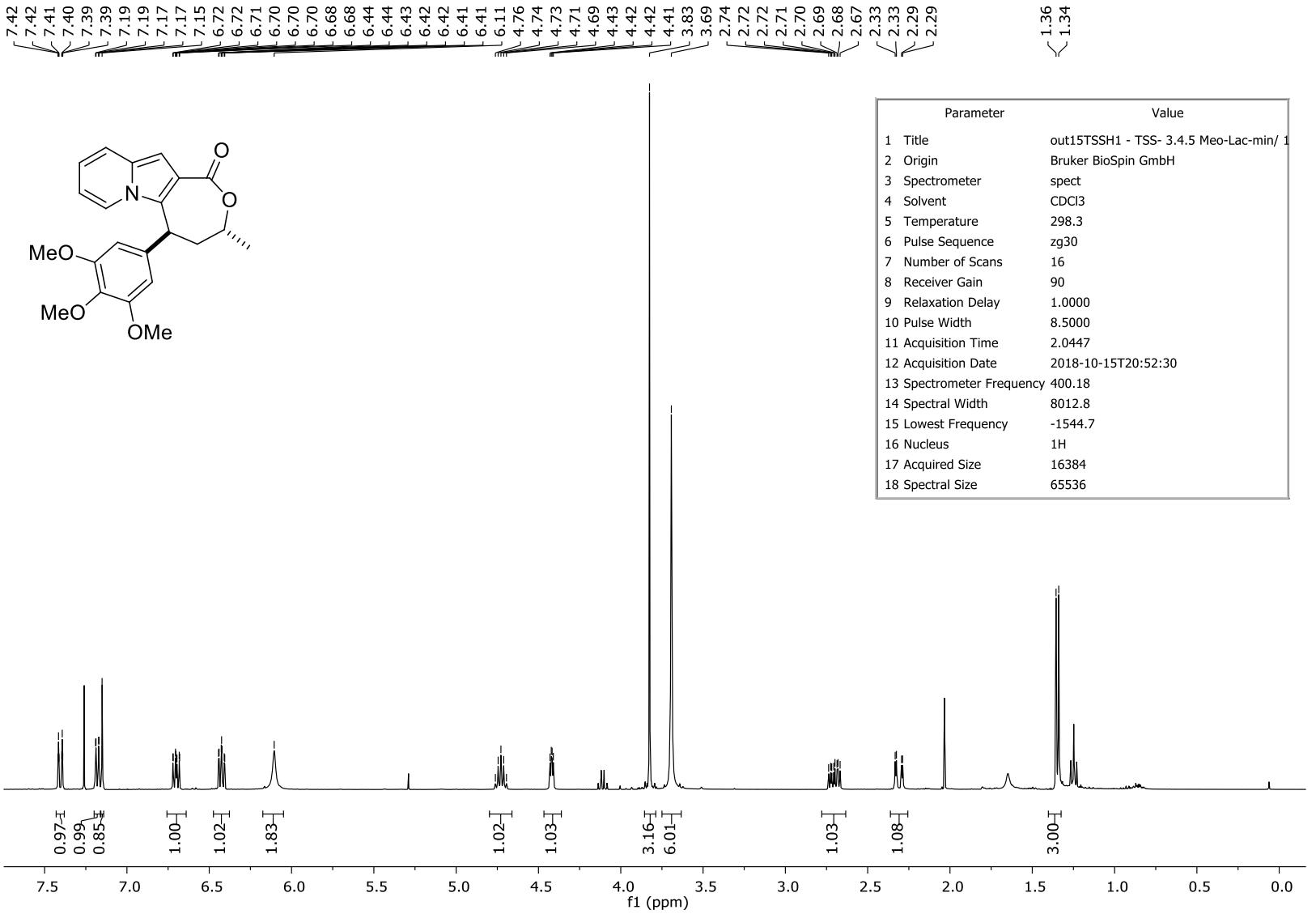


Figure 77. ^{1}H NMR spectrum of compound *anti*-**4g**.

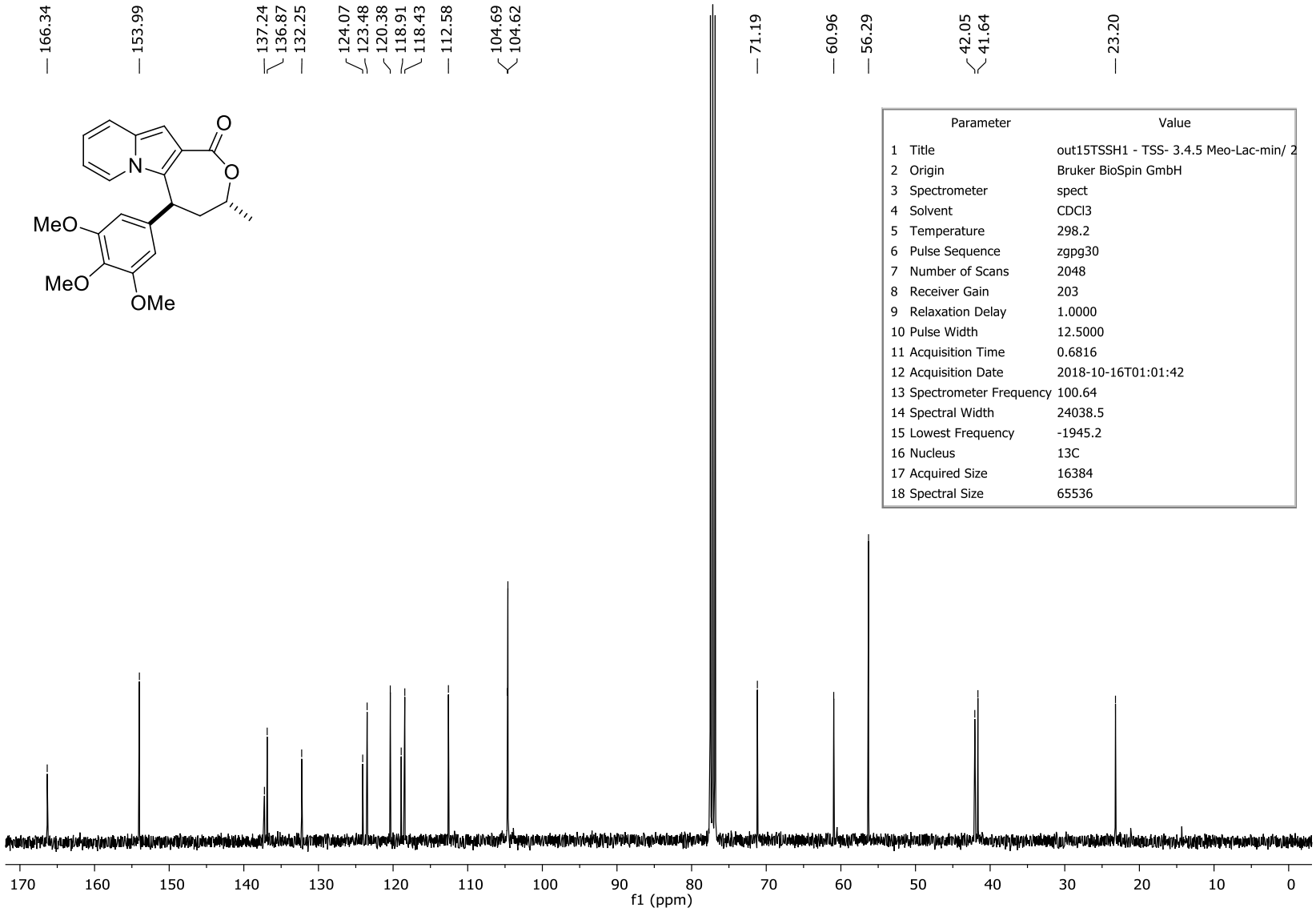


Figure 78. ^{13}C NMR spectrum of compound *anti*-**4g**.

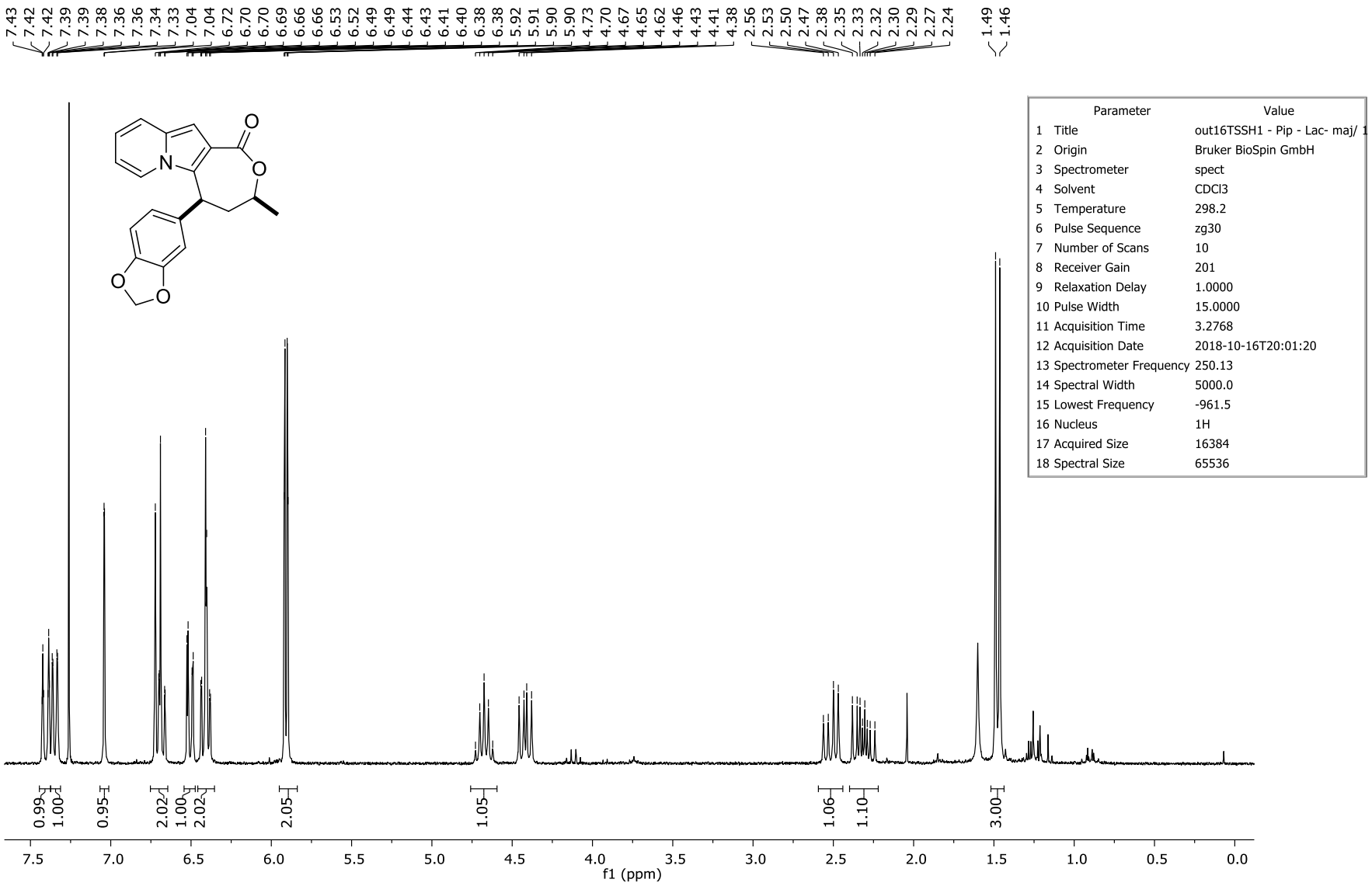


Figure 79. ^{1}H NMR spectrum of compound *cis*-**4h**.

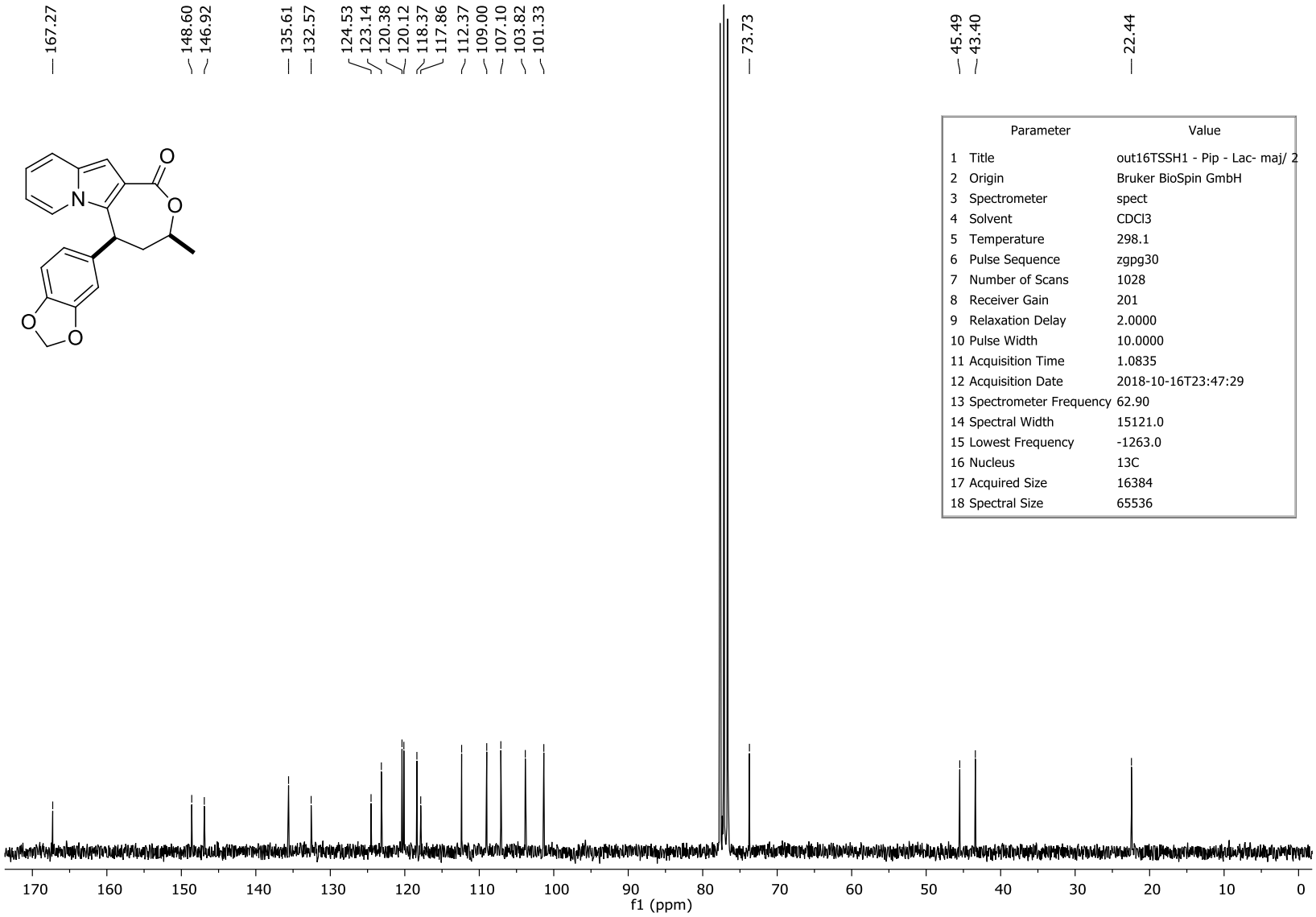


Figure 80. ^{13}C NMR spectrum of compound *cis*-**4h**.

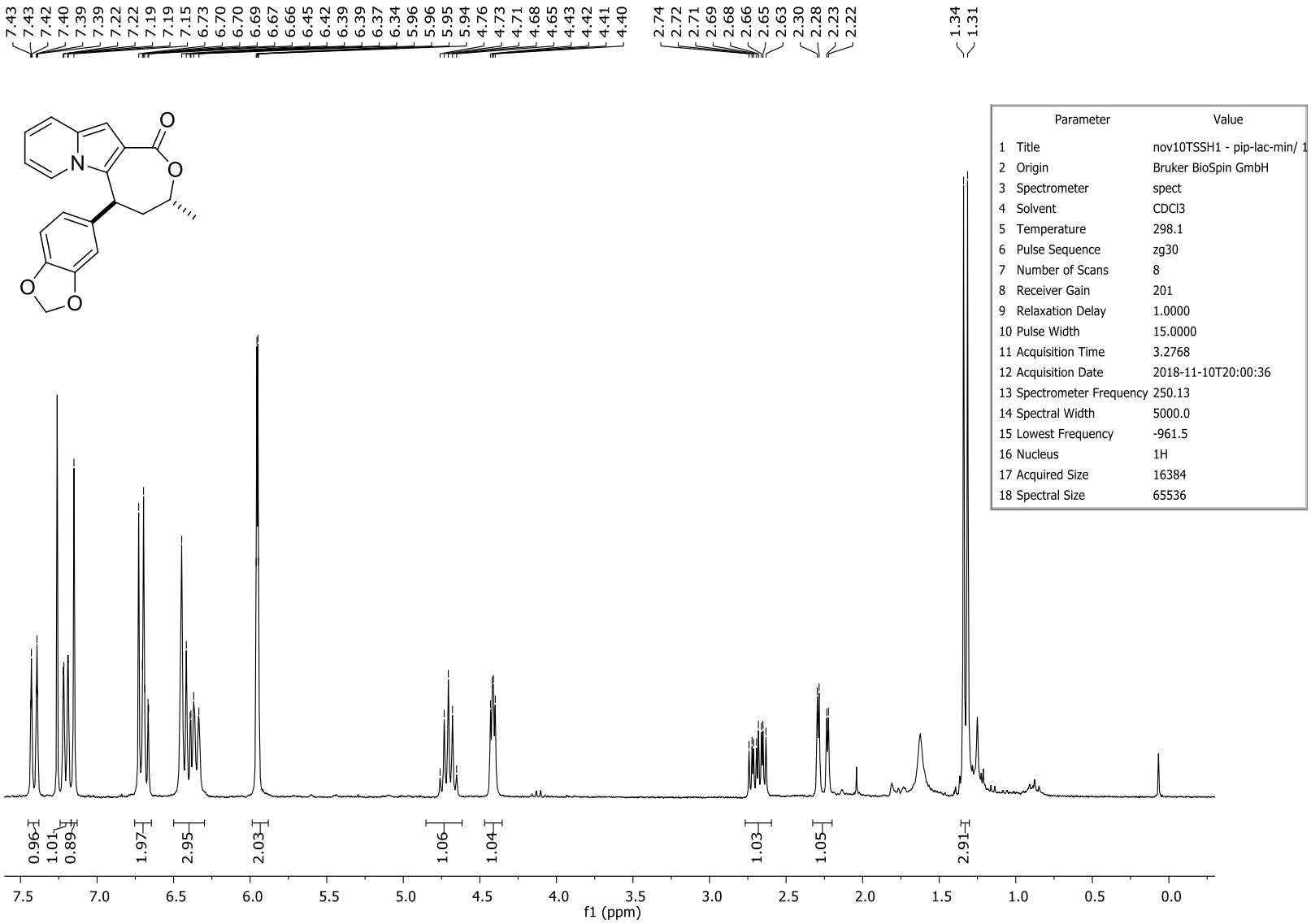


Figure 81. ^{1}H NMR spectrum of compound *trans*-**4h**.

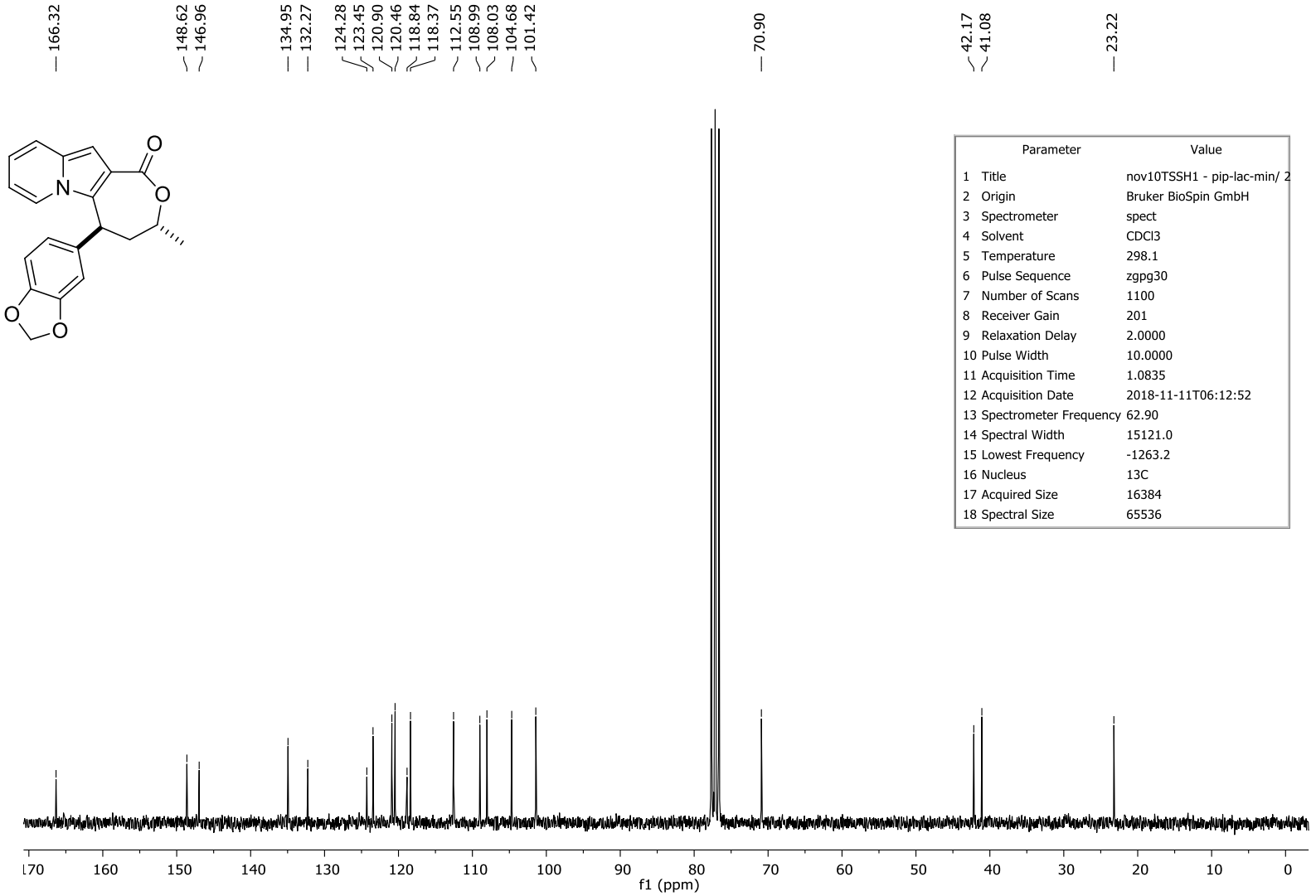


Figure 82. ^{13}C NMR spectrum of compound *trans*-**4h**.

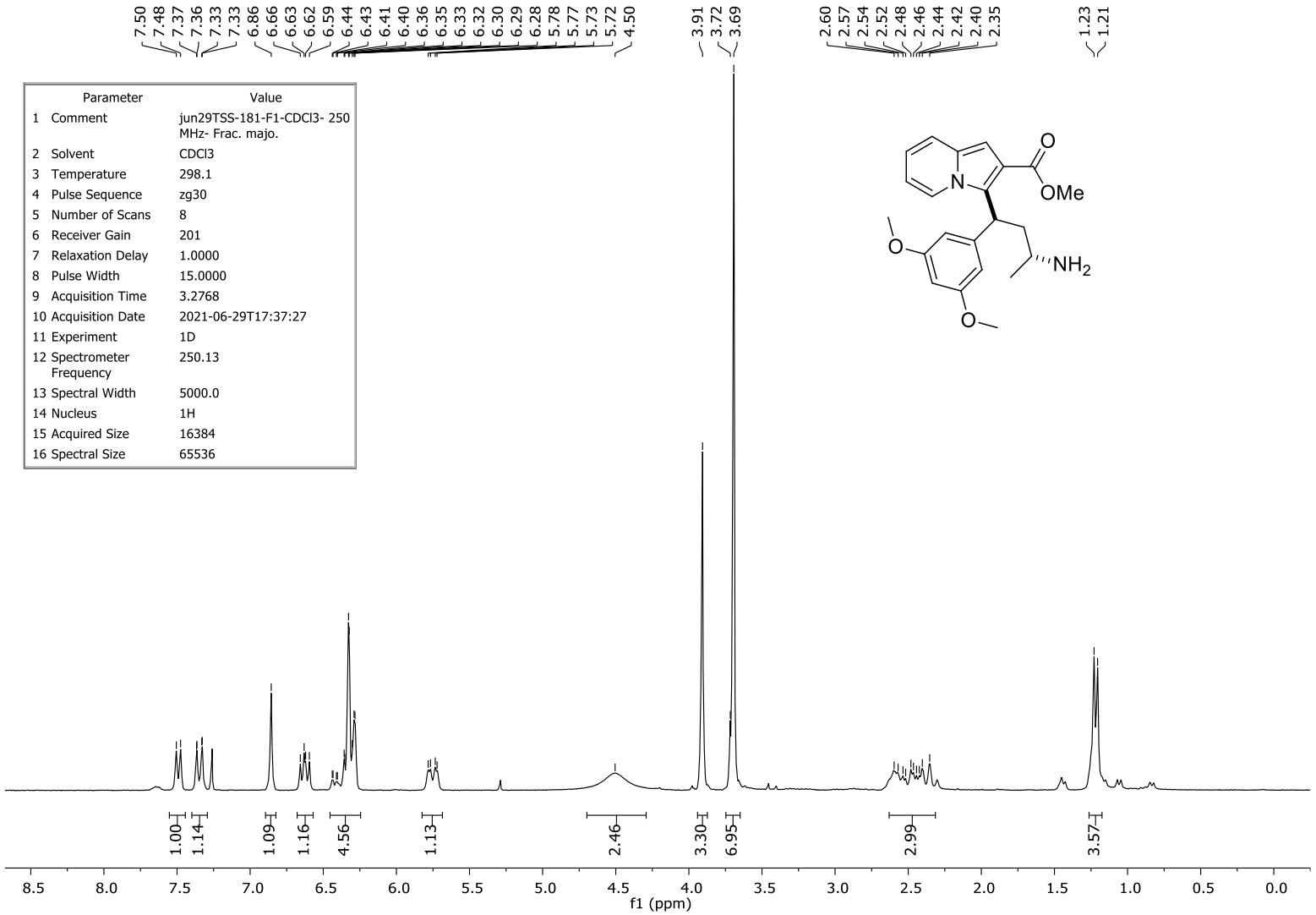


Figure 83. ^{1}H NMR spectrum of compound *anti*-**6**.

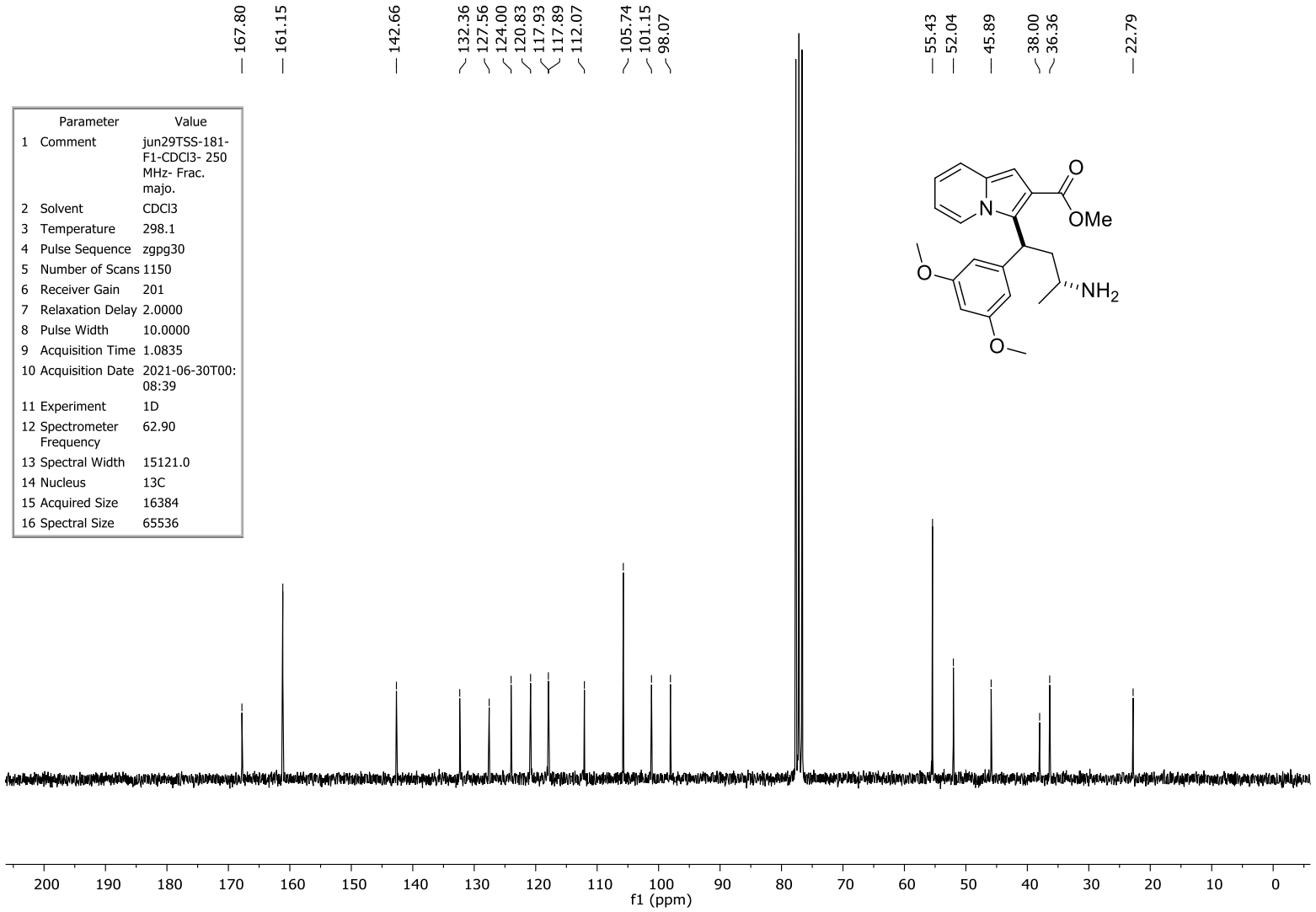


Figure 84. ^{13}C NMR spectrum of compound *anti*-**6**.

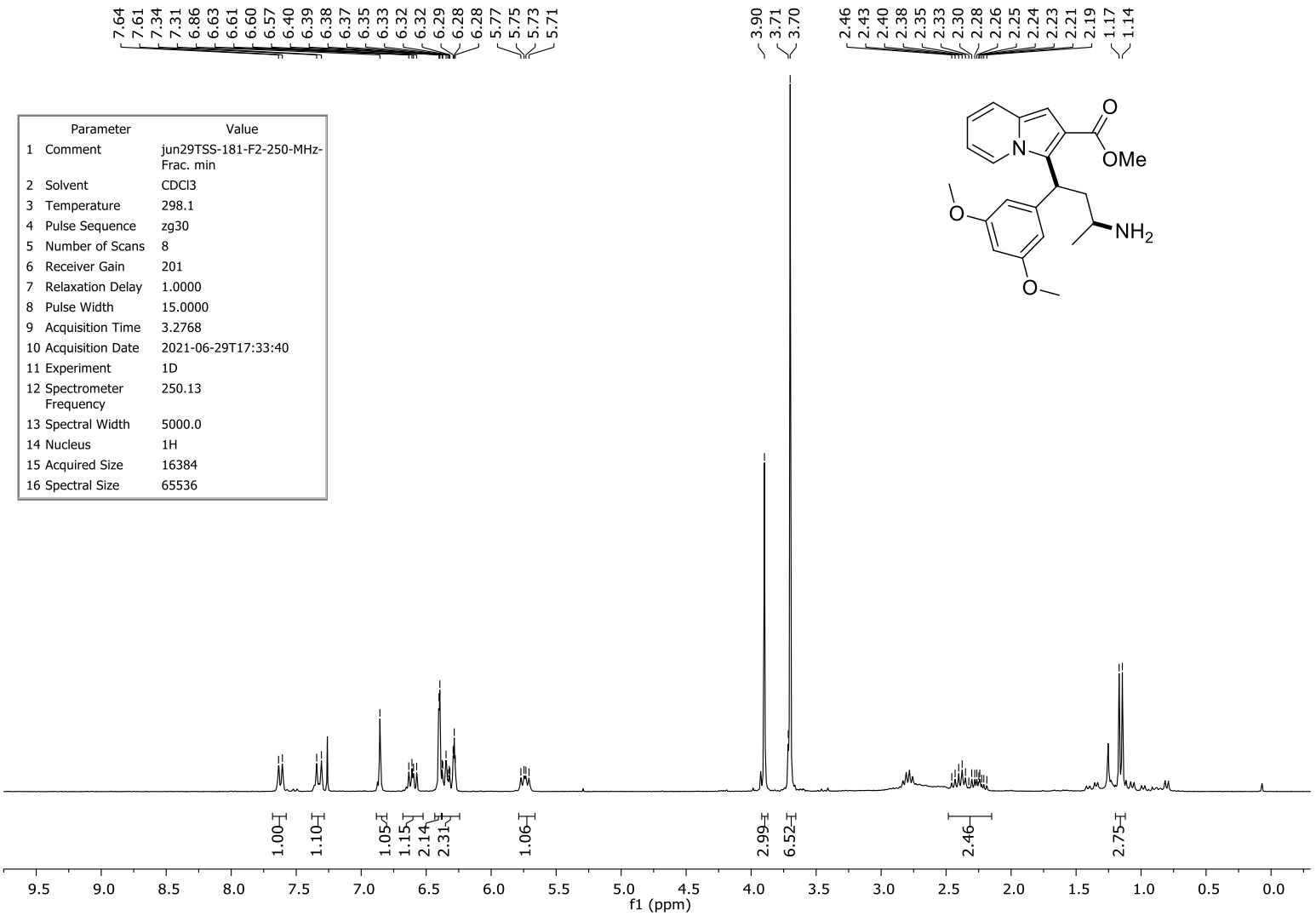


Figure 85. ^{1}H NMR spectrum of compound *syn*-**6**.

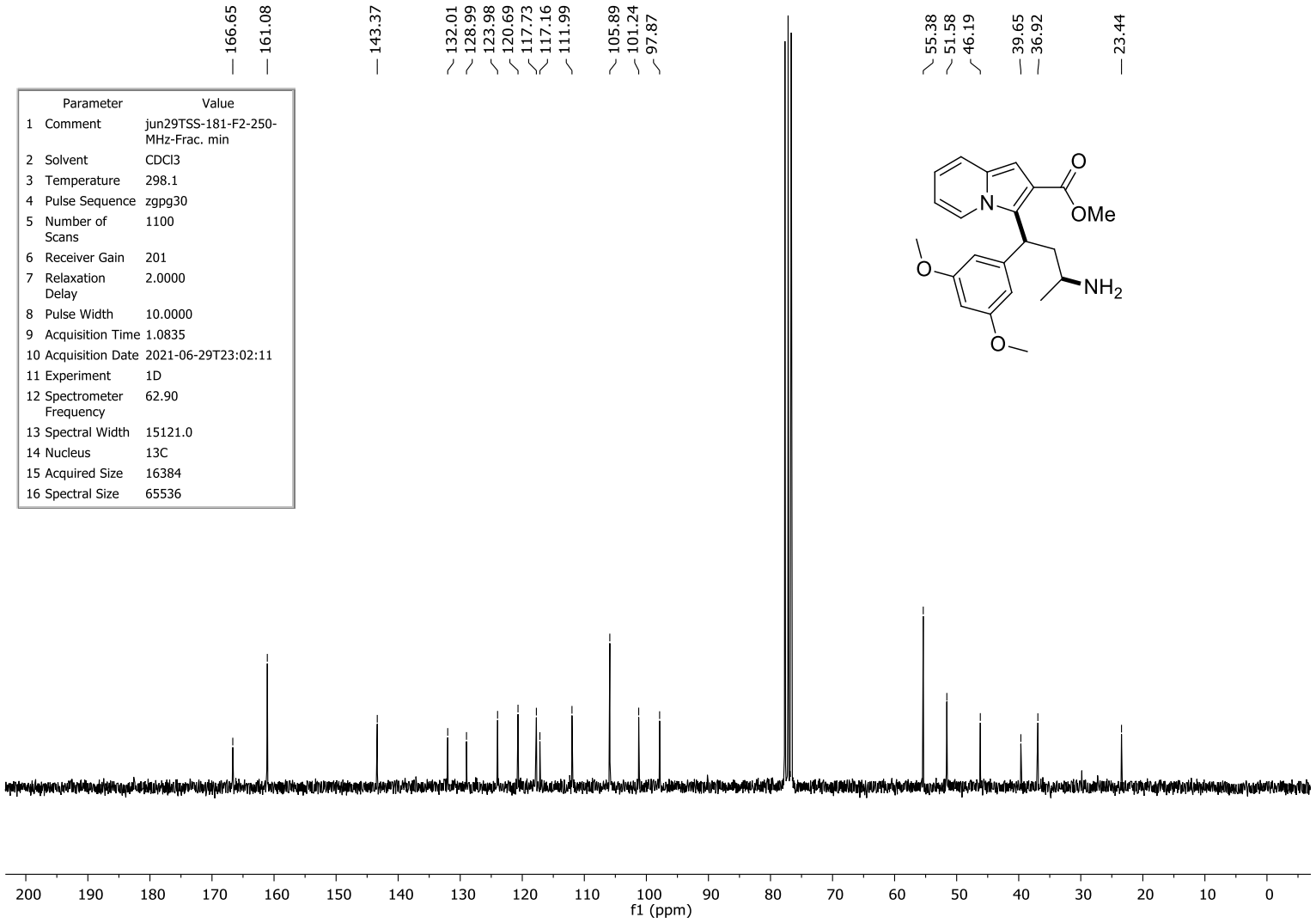


Figure 86. ^{1}H NMR spectrum of compound *syn*-**6**.

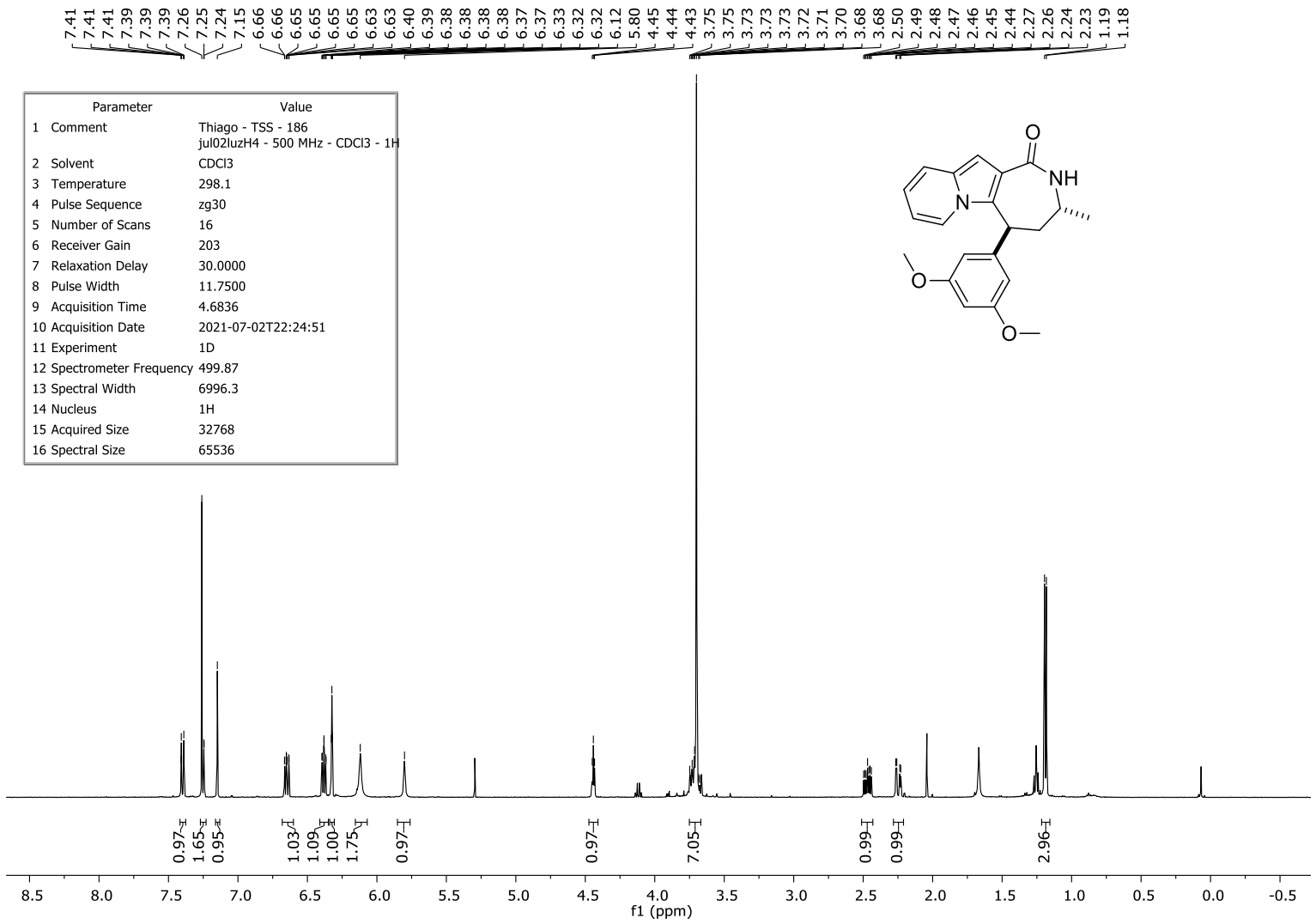


Figure 87. ^{1}H NMR spectrum of compound *trans*-**7**.

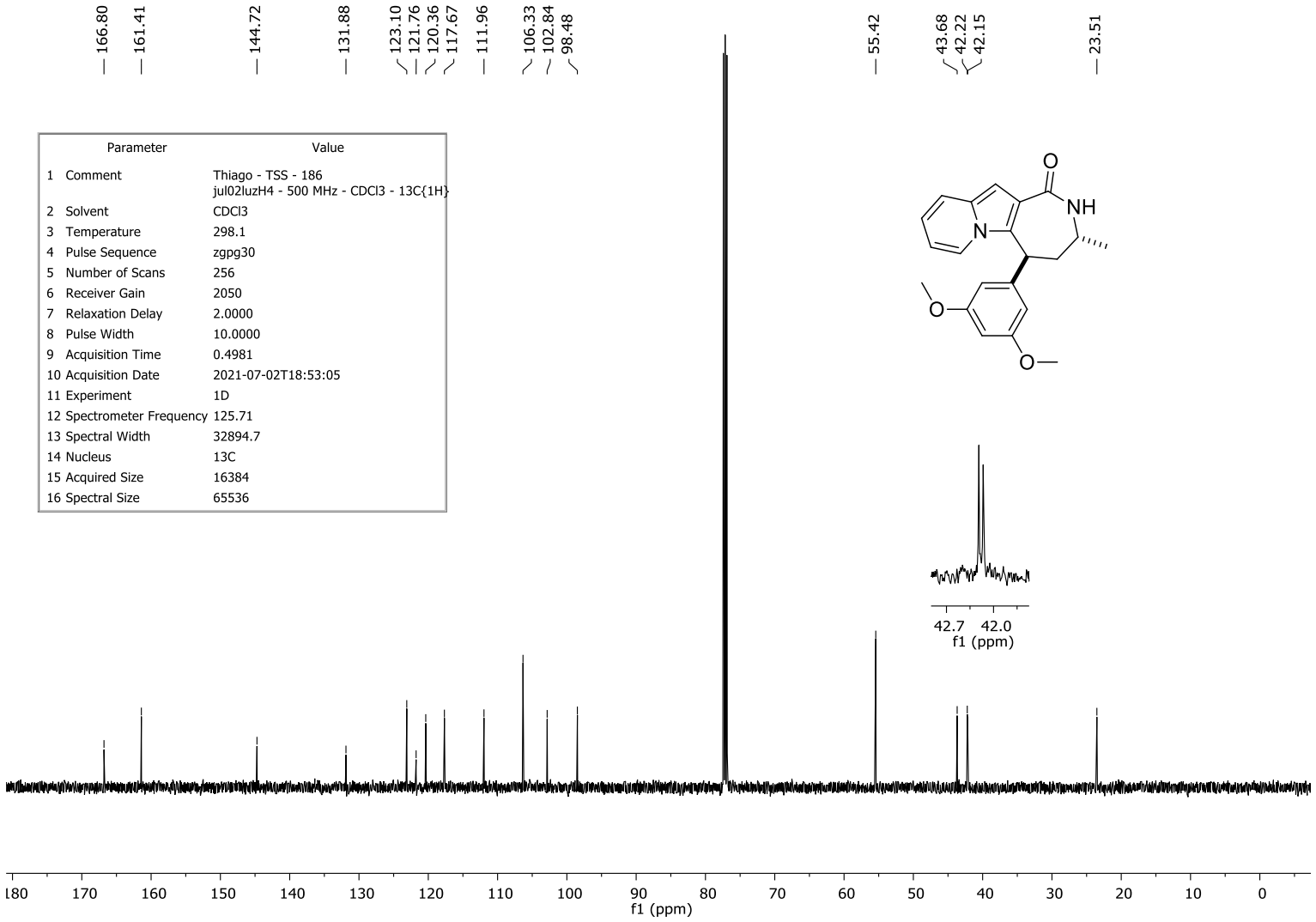


Figure 88. ^{13}C NMR spectrum of compound *trans*-**7**.

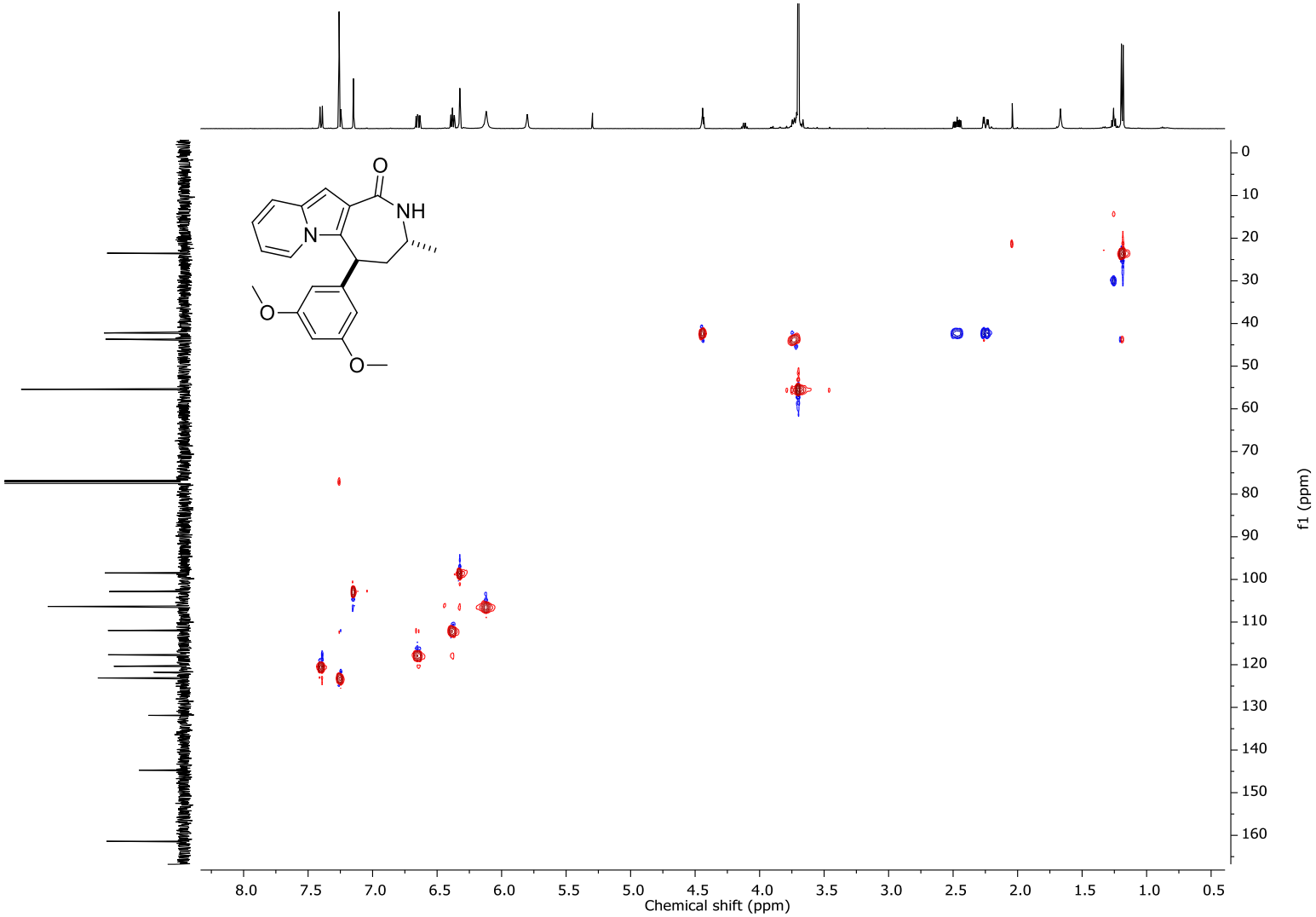


Figure 89. ^{1}H-^{13}C HSQC of *trans*-**7**.

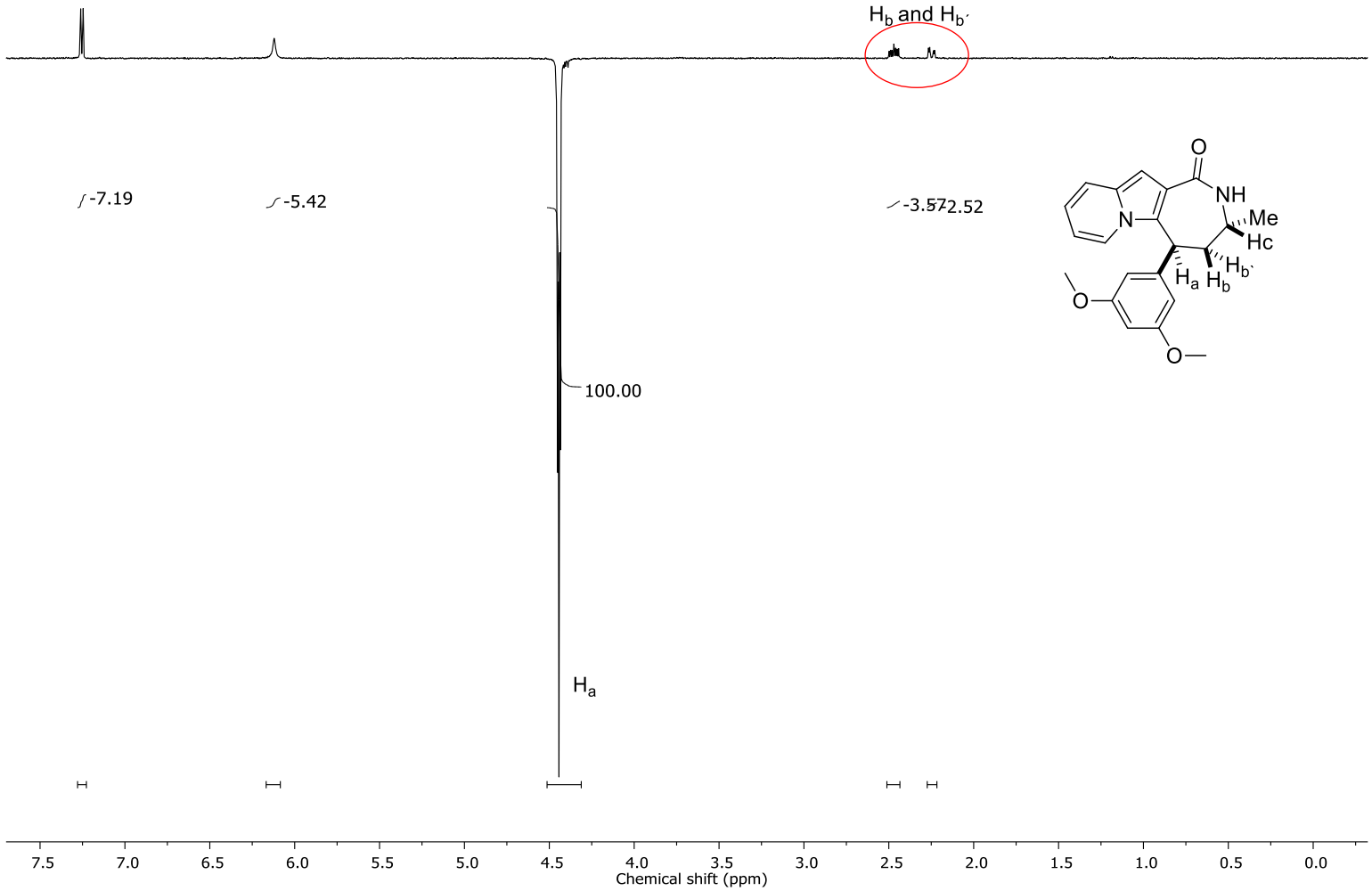


Figure 90. NOESY spectrum of *trans*-**7**.

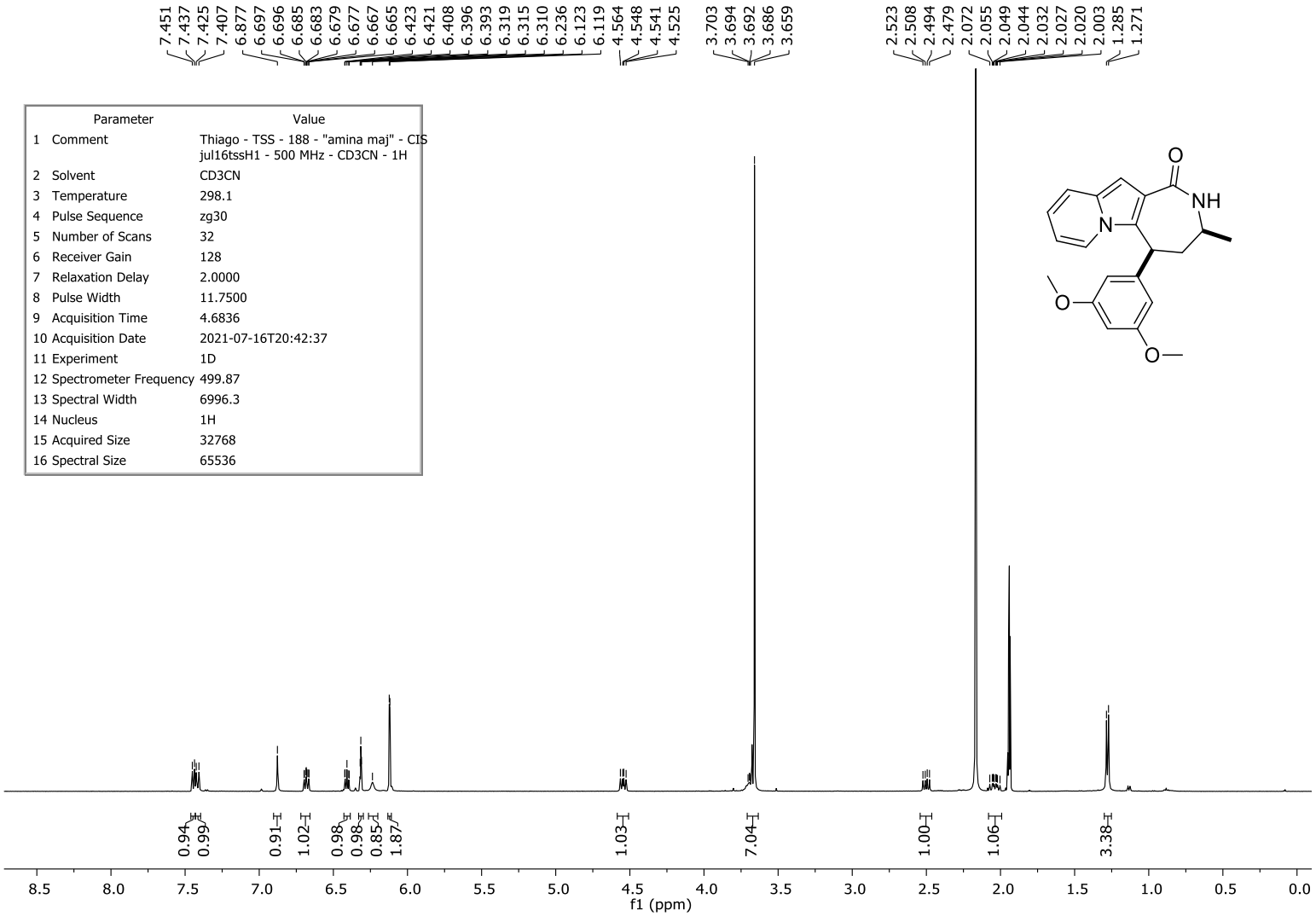


Figure 91. ^{1}H NMR spectrum of compound *cis*-**7**.

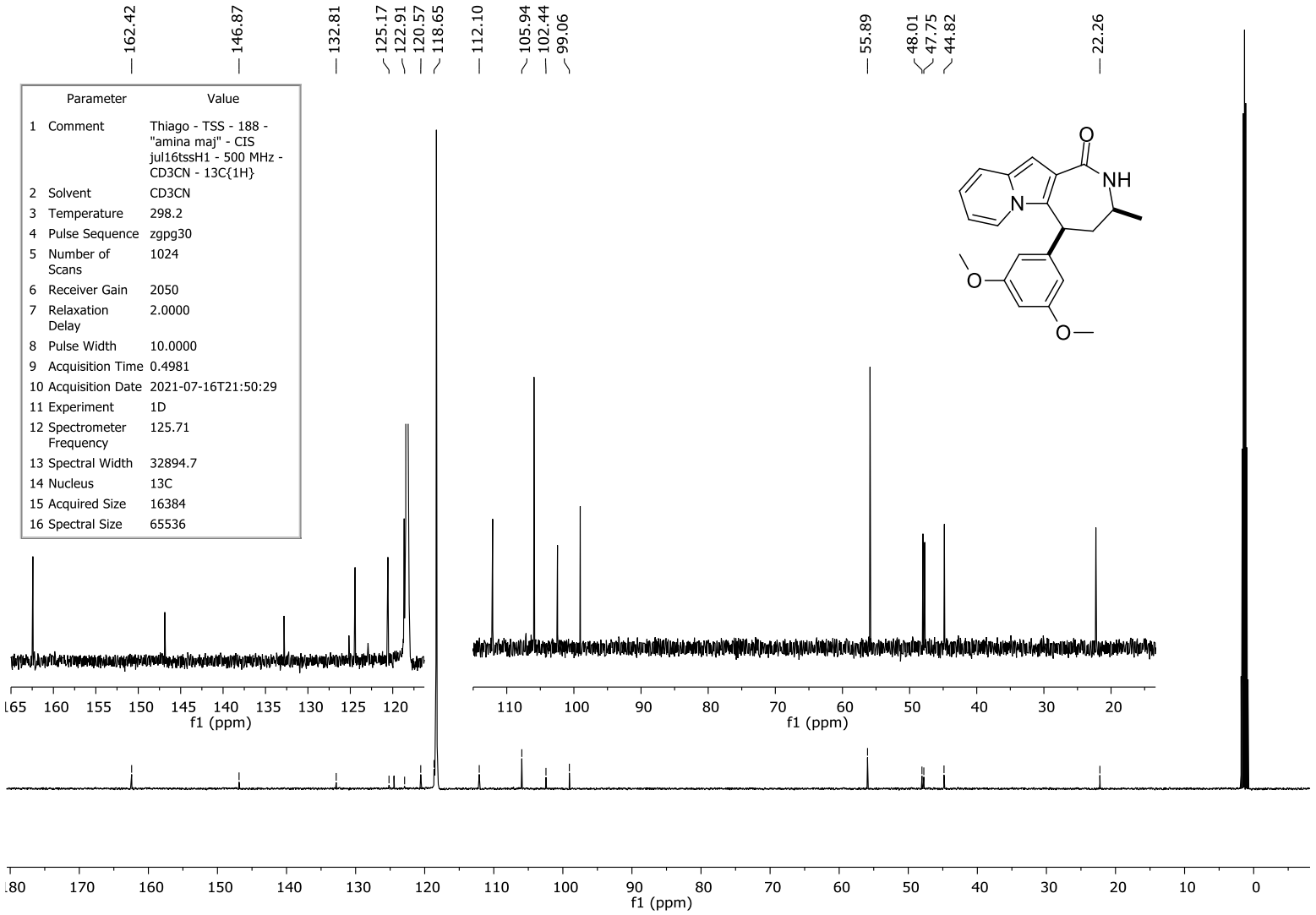


Figure 92. ^{13}C NMR spectrum of compound *cis*-**7**.

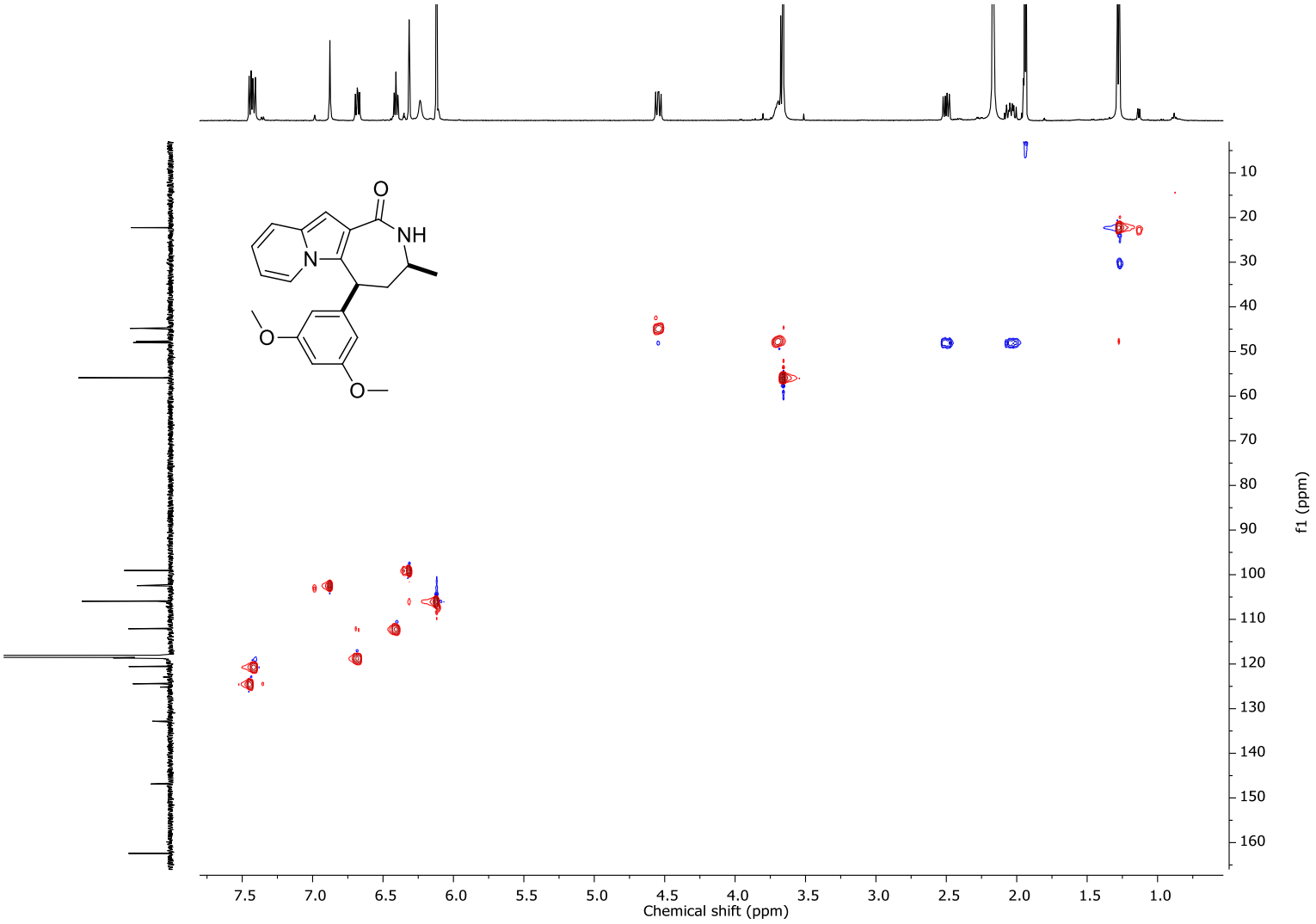


Figure 93. ^{1}H-^{13}C HSQC of *cis*-**7**

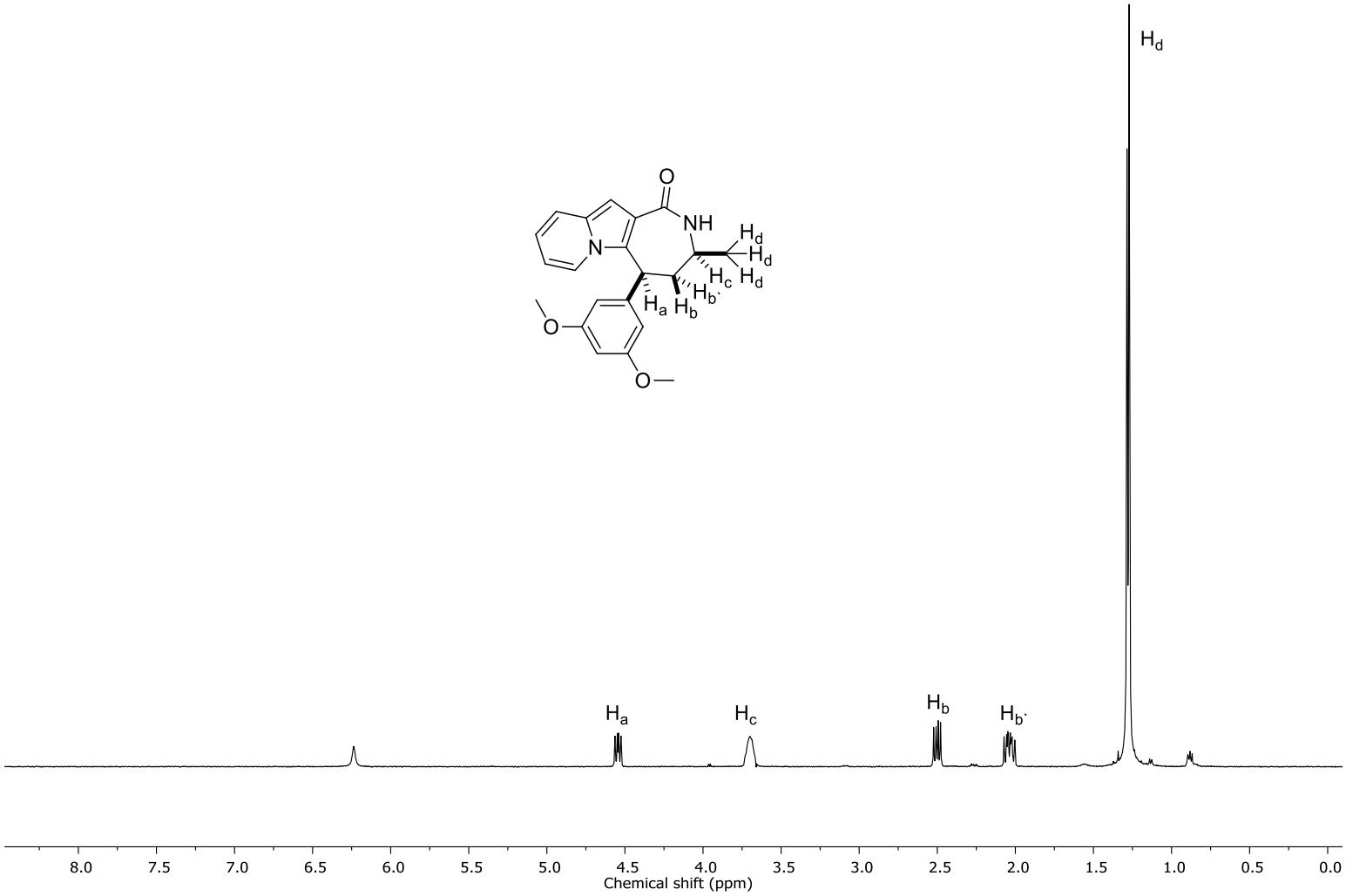


Figure 94. Selective TOCSY (1.3 ppm) of *cis*-**7**.

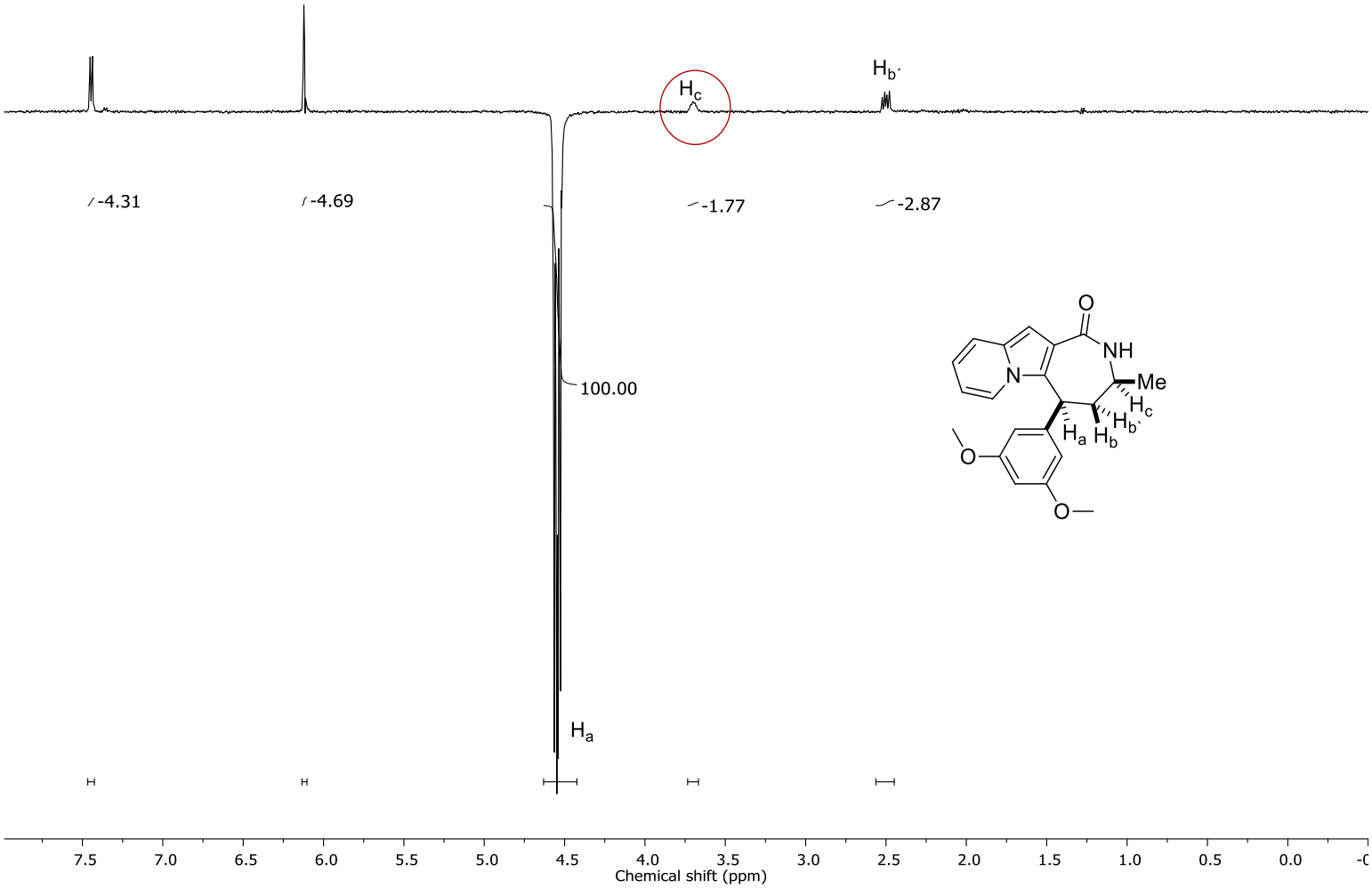


Figure 95. NOESY spectrum of *cis*-**7**.

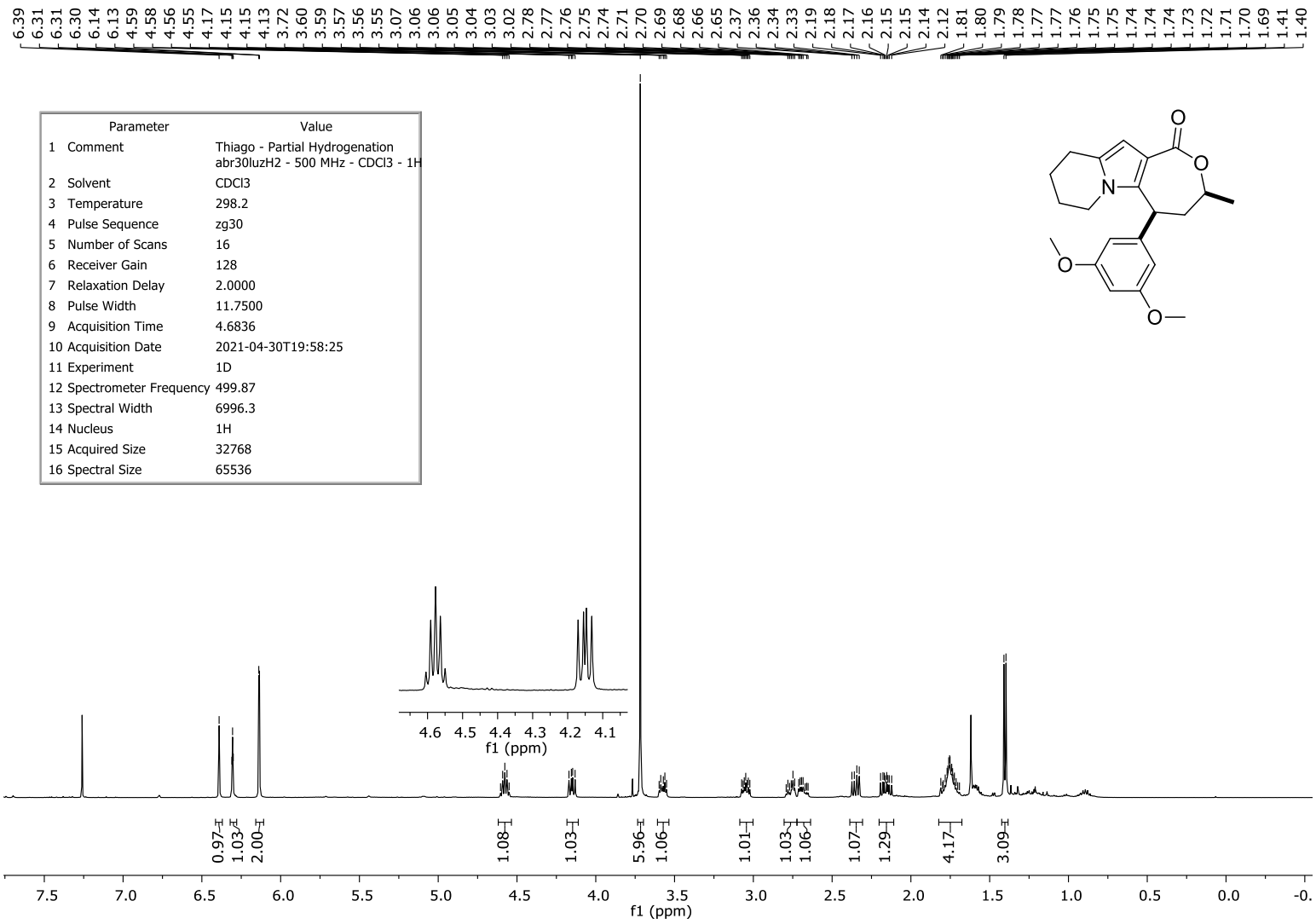


Figure 96. ^{1}H NMR spectrum of compound *cis*-**8**.

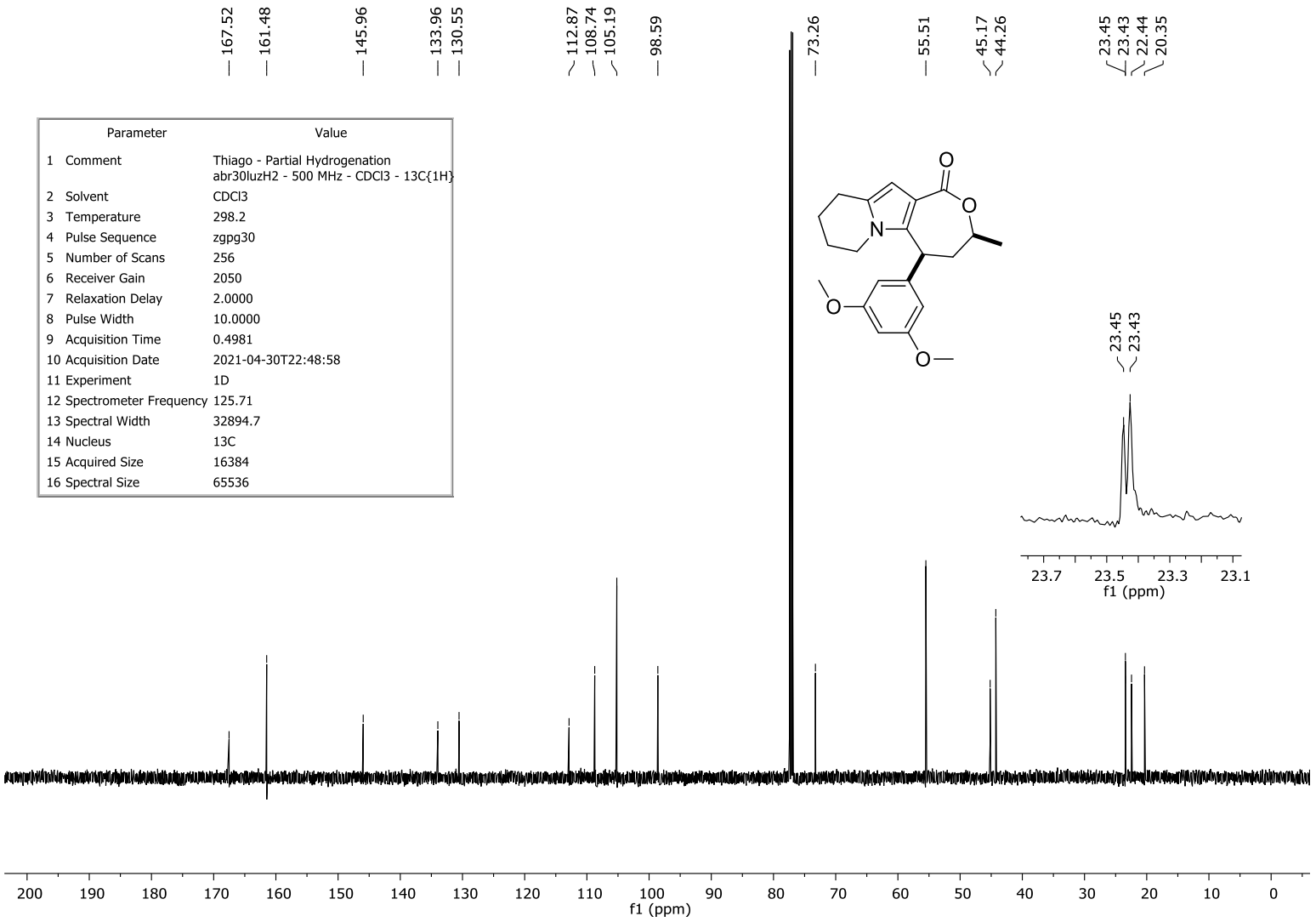


Figure 97. ^{13}C NMR spectrum of compound *cis*-**8**.

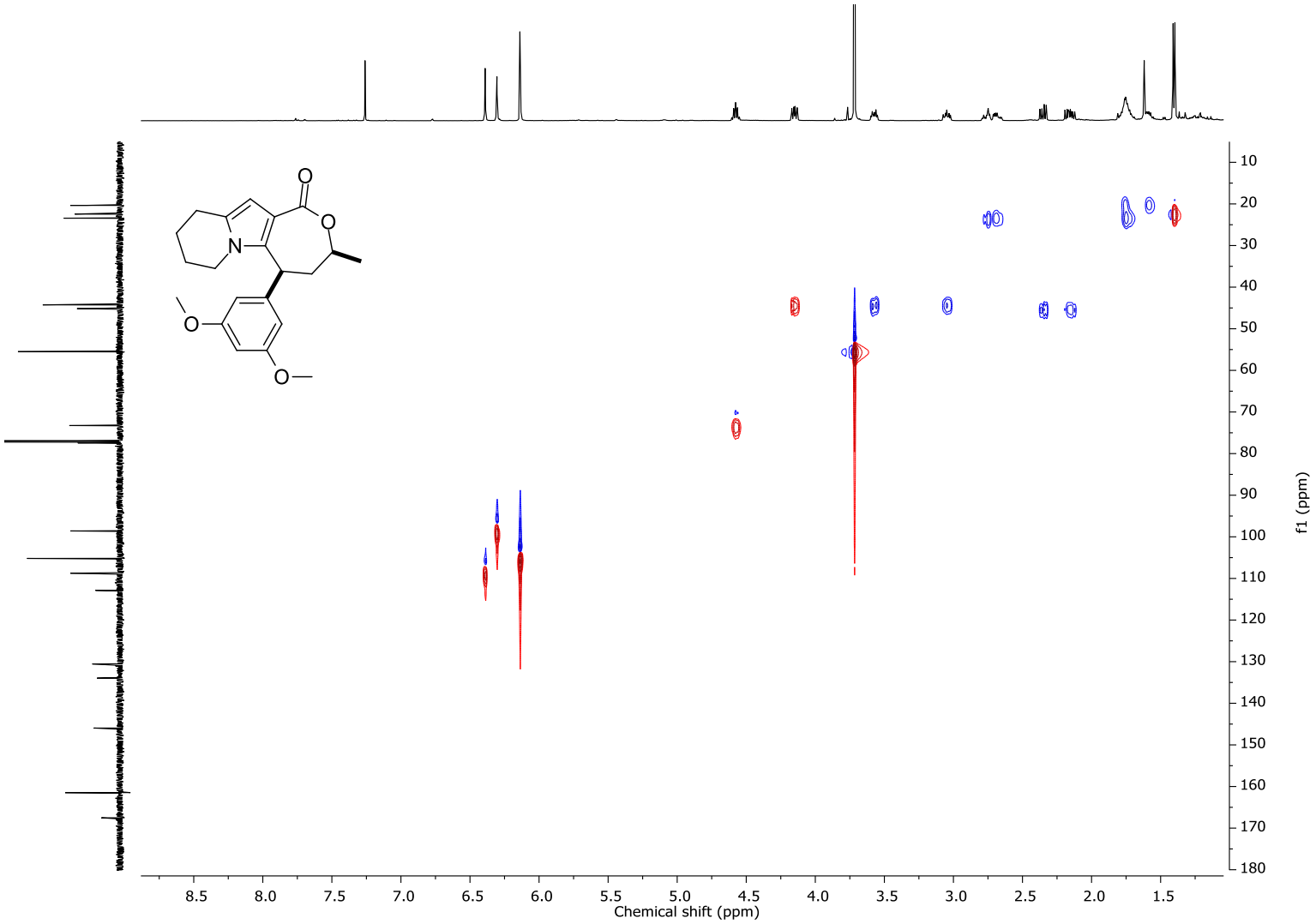


Figure 98. ^{1}H-^{13}C HSQC of *cis*-**8**.

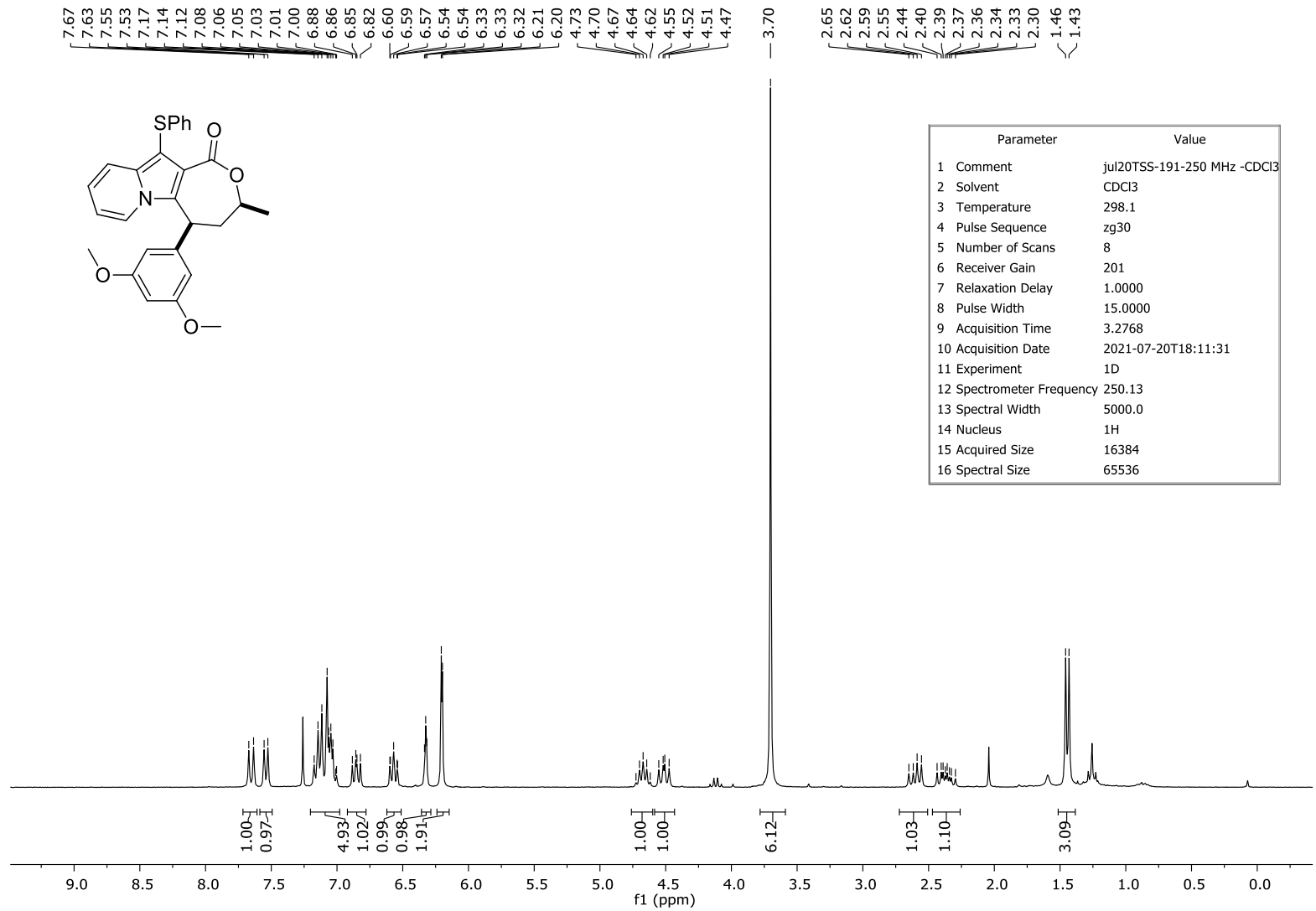


Figure 99. ^{1}H NMR spectrum of compound *cis*-**9**.

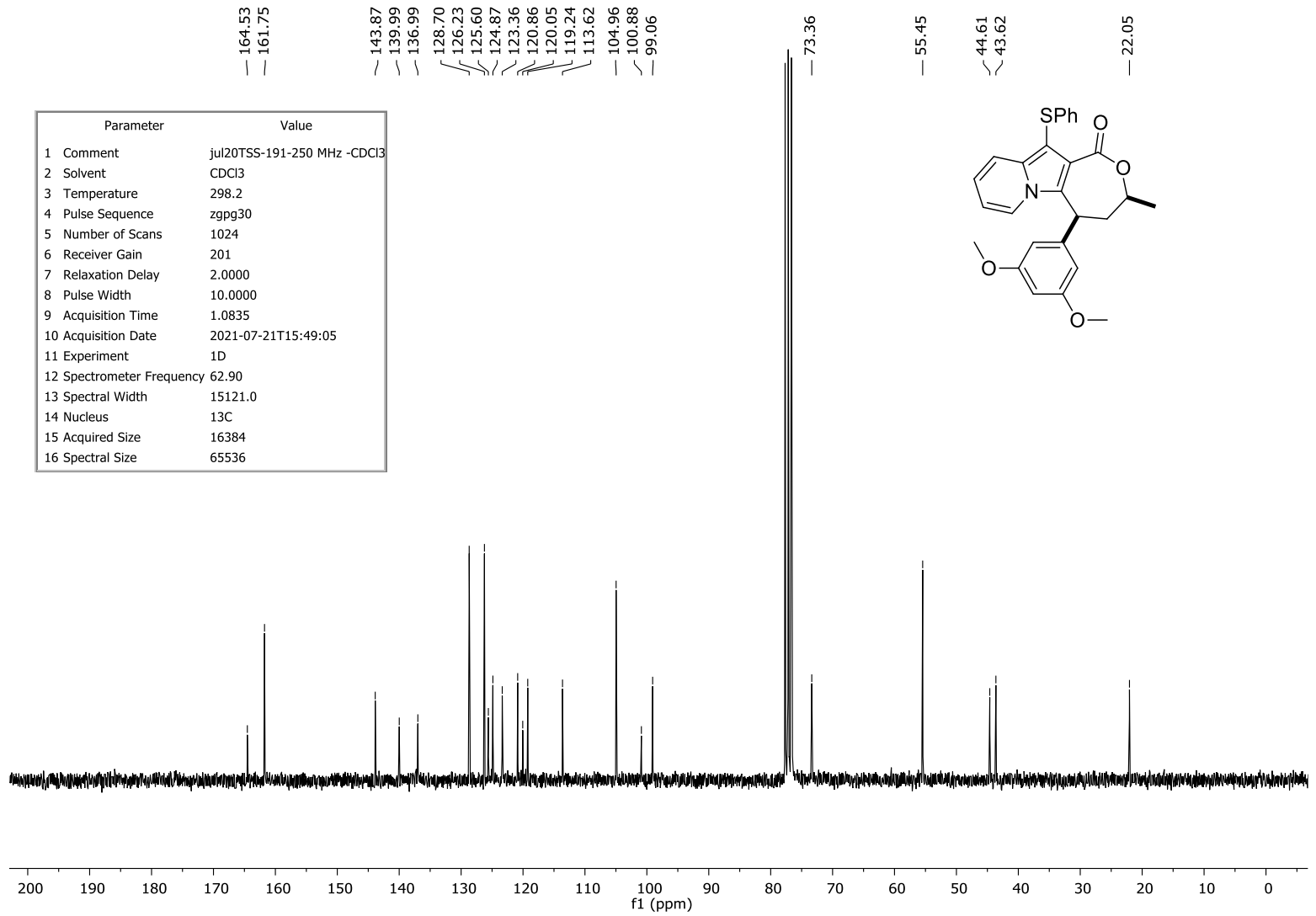


Figure100. ^{13}C NMR spectrum of compound *cis*-**9**.

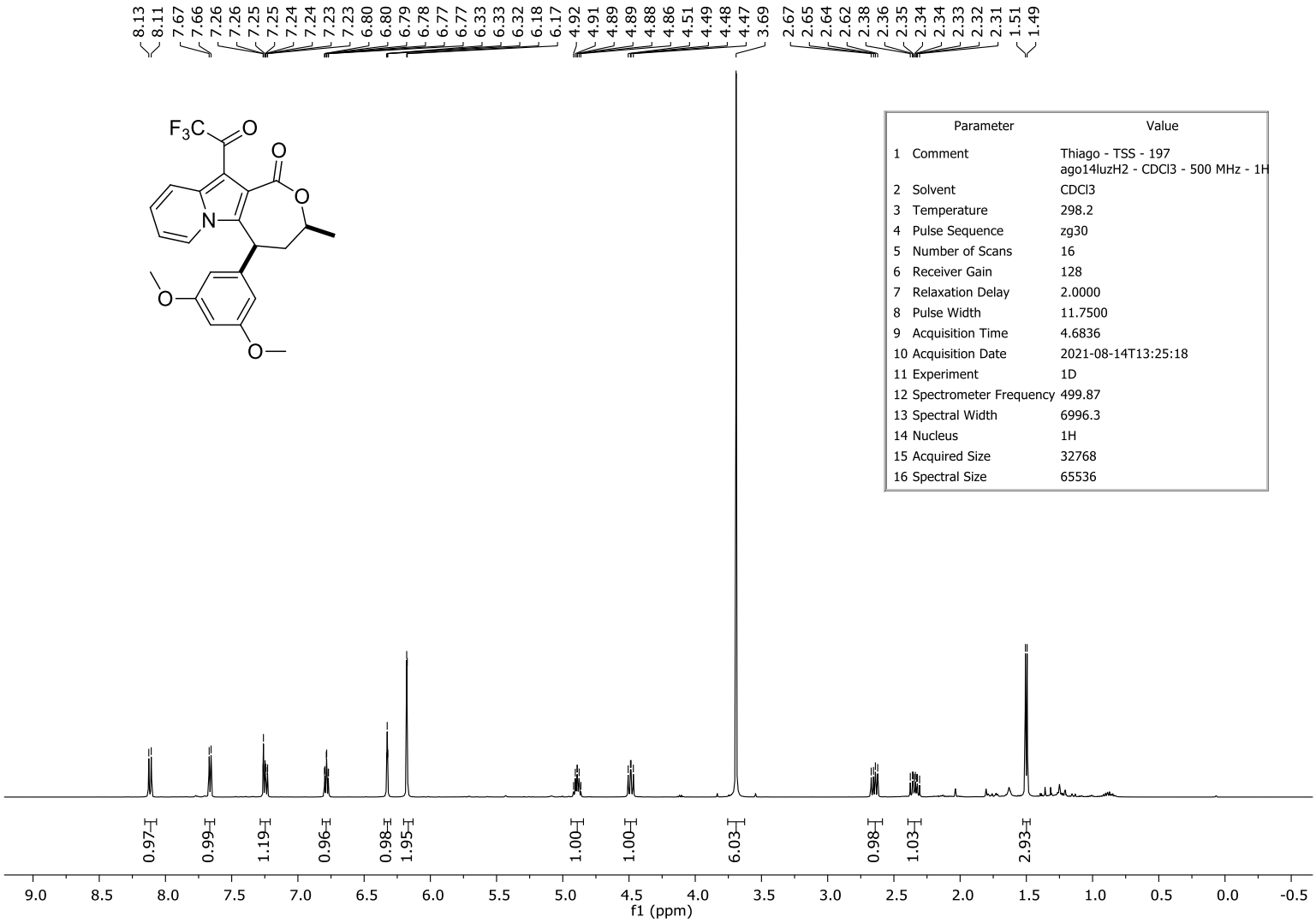


Figure 101. ^{1}H NMR spectrum of compound *cis*-**10**.

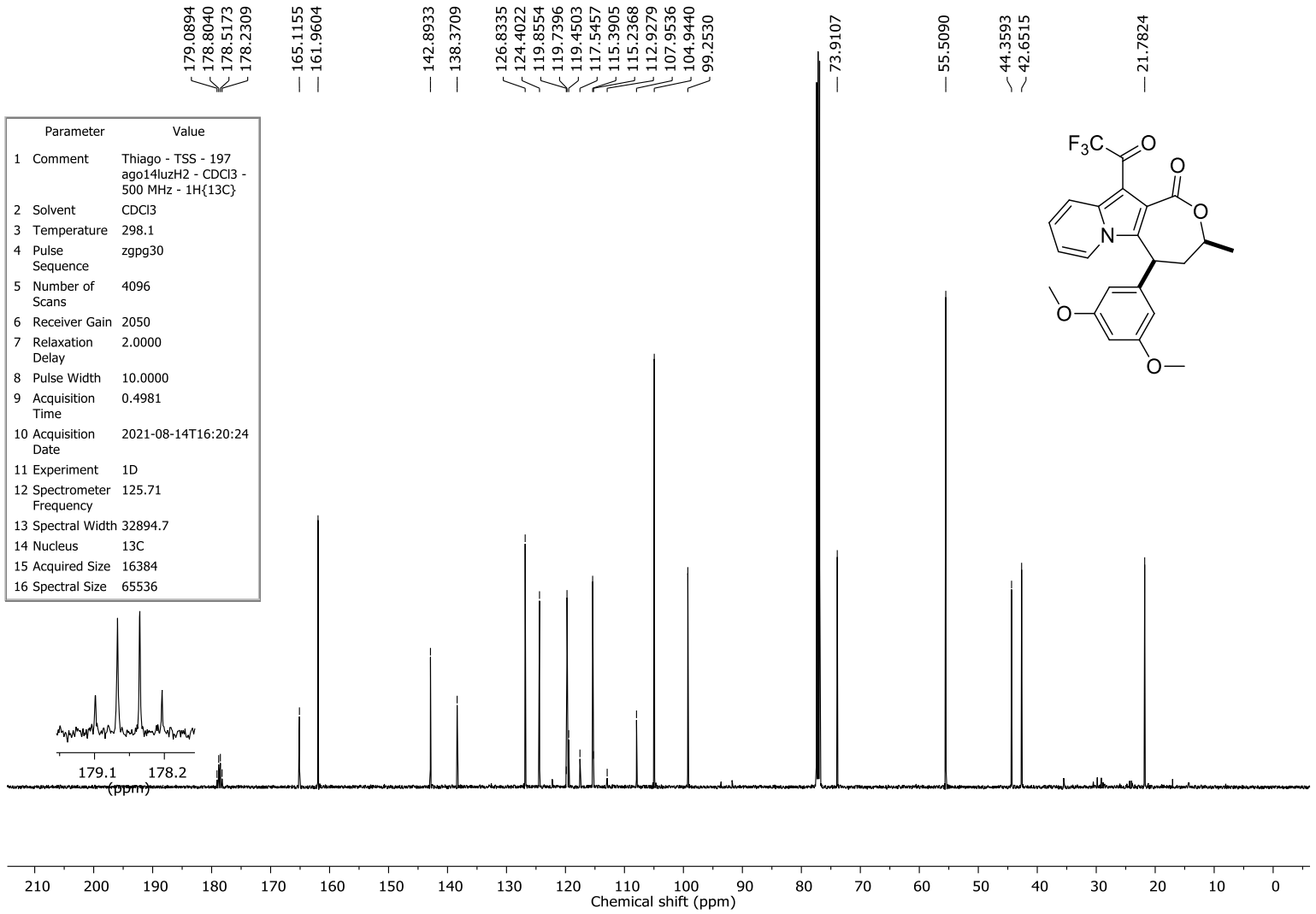


Figure 102. ^{13}C NMR spectrum of compound *cis*-**10**.

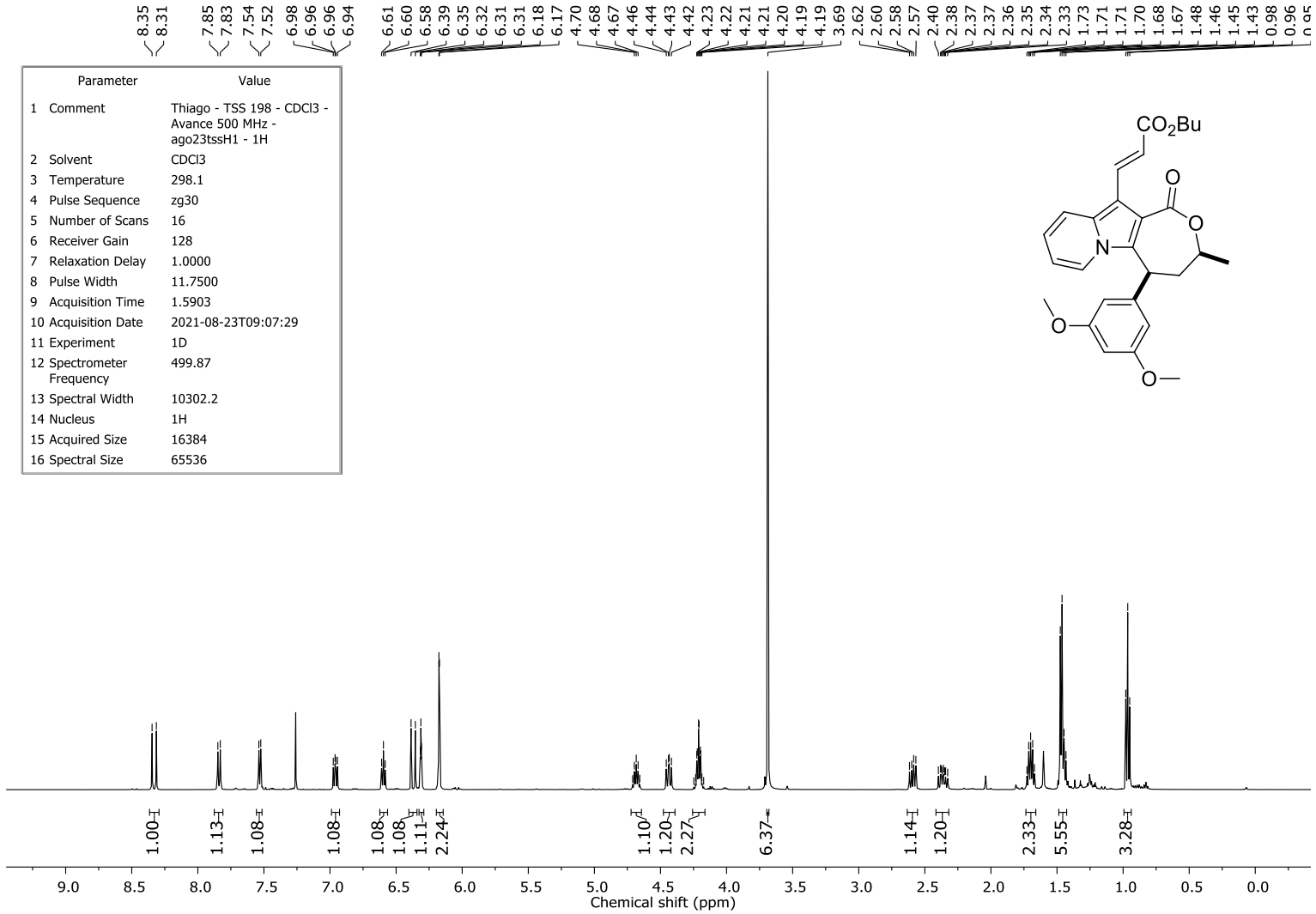


Figure 103. ^{1}H NMR spectrum of compound *cis*-**11**.

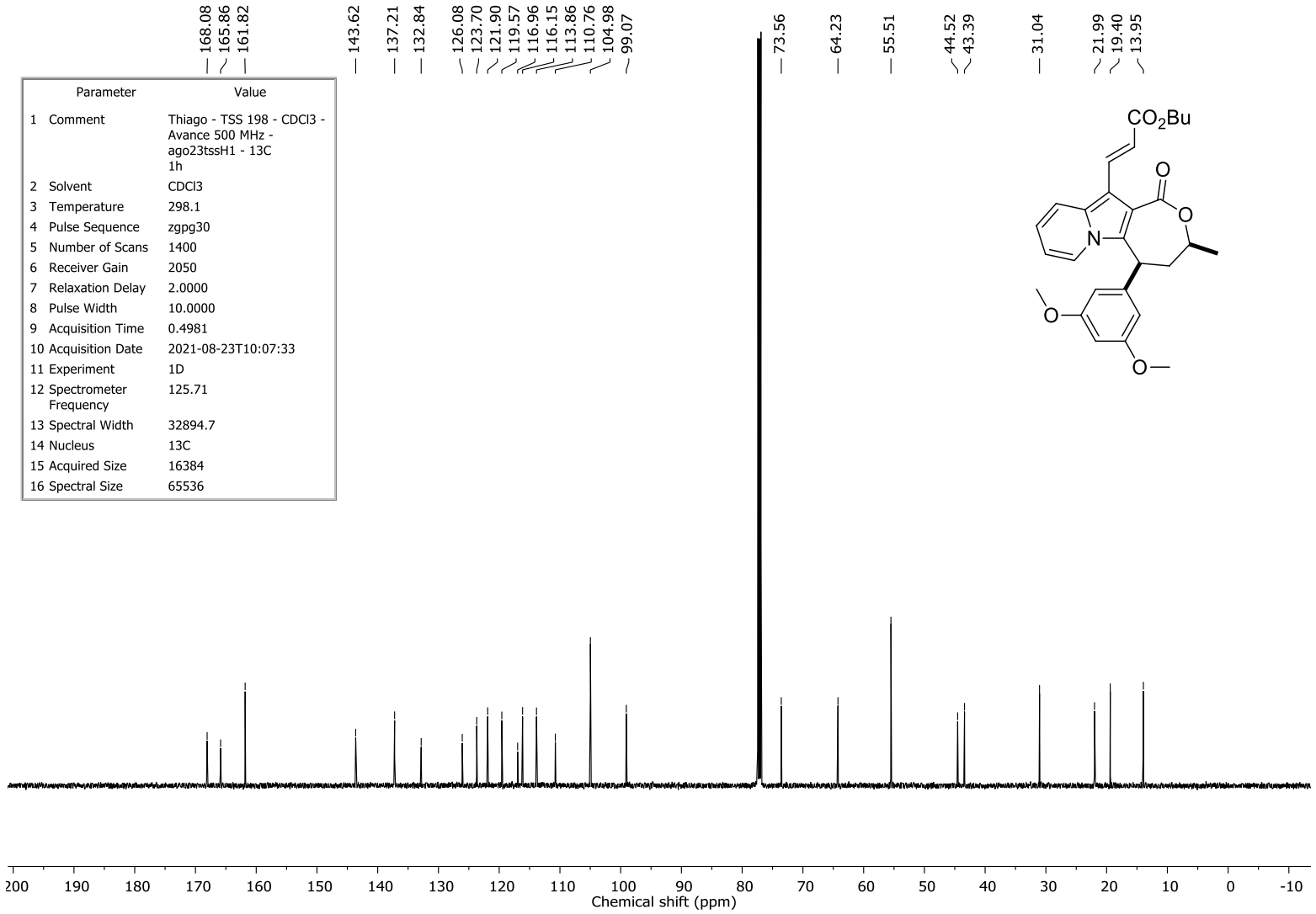


Figure 104. ^{13}C NMR spectrum of compound *cis*-**11**.