Pyrroloiminoquinone Alkaloids: Total Synthesis of Makaluvamines A and K

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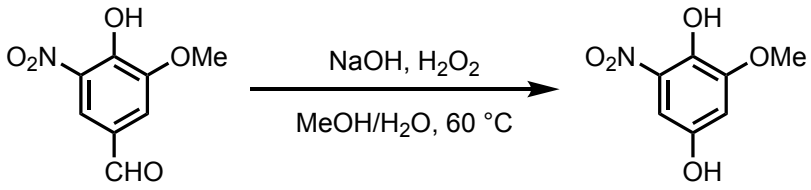
I. GENERAL INFORMATION

Unless otherwise stated, all reactions were performed in flame- or oven-dried (~120 °C) glassware under a nitrogen (N_2) atmosphere, using reagents as received from the manufacturers. The 3 Å molecular sieves (MS) were activated in the following manner: MS were oven-dried (120°C) overnight. The MS were then allowed to cool to room temperature (rt, usually 23°C) under a high vacuum (<1 Torr). The MS were then heated in a microwave oven for 1 min. Again, MS were allowed to cool to rt under a high vacuum. Lastly, the MS were flame-dried under vacuum and used once they had returned to rt. Abbreviations for common solvents are as follows: EtOAc = ethyl acetate, MeCN = acetonitrile, MeOH = methanol, EtOH = ethanol, t-BuOH = tert-butyl alcohol, THF = tetrahydrofuran, CH_2Cl_2 = methylene chloride Et_2O = diethyl ether. The argon (Ar) used was ultra-high purity (UHP, 99.999%) as was the oxygen (O_2, 99.993%). The reactions were monitored, and, where noted, analytical samples purified by, normal phase thin layer chromatography (TLC) using Millipore glass-backed 60 Å plates (indicator F-254, 250 μM). THF, CH_2Cl_2, MeCN, benzene, toluene, and Et_2O were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. MeOH was simply dried with activated 4 Å molecular sieves (MS), degassed by sparging, and stored under Ar. Manual flash column chromatography was performed using the indicated solvent systems with Silicycle SiliaFlash P60® (230-400 mesh) silica gel as the stationary phase. All Medium Pressure Liquid Chromatography (MPLC) purifications were performed on either a Teledyne RF+ UV-Vis or a Teledyne CombiFlash NextGen 300+ RF using the indicated solvent systems and Teledyne RediSep® Rf normal phase disposable columns. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker Avance™ 300, Bruker Ascend™ 400 autosampler or a Bruker Ascend™ 600 autosampler. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent resonance and coupling constants (*J*) are reported in hertz (Hz). NMR spectra were calibrated relative to their respective residual NMR solvent peaks; $CDCl_3$ = 7.26 ppm (^{1}H NMR) / 77.16 ppm (^{13}C NMR), Methanol-d4 = 3.31 ppm (^{1}H NMR) / 49.00 ppm (^{13}C NMR), DMSO-d6 = 2.50 ppm (^{1}H NMR) / 39.52 ppm (^{13}C NMR). NMR peak pattern abbreviations are as follows: s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, dt = doublet of triplets, tt = triplet of triplets, q = quartet, m = multiplet. Infrared (IR) spectra were recorded on a Bruker Platinum-ATR IR spectrometer using a diamond window. High Resolution mass spectra (HRMS) were obtained in the Baylor University Mass Spectrometry Center on a Thermo Scientific LTQ Orbitrap Discovery spectrometer using positive electrospray ionization (+ESI) and reported for the molecular ion ([M+H]+, [M+Na]+, or both). Optical rotations were obtained on a Rudolph Research Analytical Autopol IV Automatic Polarimeter using either Fisher Chemical Chloroform (HPLC grade; approx. 0.75% Ethanol as preservative) or Fisher Chemical Methanol (Optima® LC/MS). Melting points were taken on an Electrothermal Melting point measuring instrument 1101D Mel-Temp.

II. EXPERIMENTAL SECTION

Preparation of Hydroquinone 14



5-nitrovanillin (50.0 g, 253.0 mmol, 1.0 equiv) and MeOH/H_2O (1000 mL, 1:1 mixture, 0.25 M with respect to 5-nitrovanillin) were added to a 2 L round-bottom flask. Aqueous 1M NaOH (280 mL, 280.0 mmol, 1.1 equiv) and aqueous H_2O_2 (160 mL, 1,420 mmol, 5.6 equiv, 30% in H_2O, d = ~1 g/mL) were added sequentially to the reaction mixture. The solution was placed in a heating mantle and stirred for 3 h at 60 °C, at which point complete consumption of starting material was observed by TLC. The solution was cooled to rt, concentrated *in vacuo*, and the precipitate that formed was filtered, washed with ice water (3 x 200 mL), and dried under vacuum to give hydroquinone **14** (45.5 g, 96% yield) as a bright orange solid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 10.46 (s, 1H), 7.10 (d, J = 2.8 Hz, 1H), 6.77 (d, J = 2.8 Hz, 1H), 5.00 (apparent s, 1H; exact chemical shift of this proton varied with concentration between 5.00-4.75), 3.93 (s, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$) δ 151.0, 147.8, 141.6, 133.3, 108.3, 99.8, 56.9.

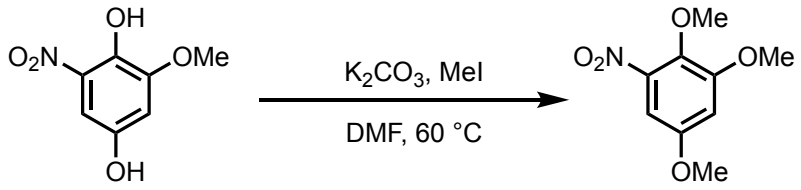
HRMS (ESI-): calculated for $C_7H_6NO_5^-$ $[M-H]^-$ 184.0251, found: 184.0243

FTIR: (thin film): 3445 (br), 1542, 1450, 1397, 1341, 1277, 1225, 1199, 1169, 1134, 1059, 989, 923, 812, 774, 762, 608 cm^{-1}

TLC: R_f = 0.13 (30% EtOAc/hexanes)

Melting point: 139-141 °C

Preparation of Trimethoxy-nitrobenzene 15



Hydroquinone **14** (45.5 g, 246.0 mmol, 1.0 equiv), K_2CO_3 (101.9 g, 737.0 mmol, 3.0 equiv), and DMF (450 mL, 0.5 M with respect to **14**) were added to a flame-dried 1 L round-bottom flask. MeI (46 mL, 737.0 mmol, 3.0 equiv) was added in one portion and the solution was placed in a heating mantle (60 °C) and stirred for 2 h, at which point complete consumption of starting material was observed by TLC. The solution was cooled to rt and H_2O (500 mL) was added. The solution was extracted with EtOAc (3 x 300 mL) and the combined organic extracts were washed with H_2O (5 x 200 mL), brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give trimethoxy-nitrobenzene **15** (42.0 g, 80% yield) as a yellow solid.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.81 (d, *J* = 2.9 Hz, 1H), 6.67 (d, *J* = 2.9 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.81 (s, 3H).

^{13}C NMR: ($CDCl_3$): δ 155.6, 155.0, 144.9, 137.5, 104.8, 98.9, 62.2, 56.5, 56.1.

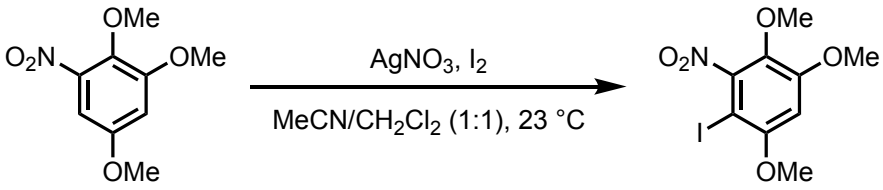
HRMS (ESI+): calculated for $C_9H_{11}NNaO_5^+$ $[M+Na]^+$ 236.0529, found: 236.0529.

FTIR (thin film): 2944, 1620, 1584, 1531, 1499, 1456, 1430, 1360, 1282, 1240, 1218, 1196, 1152, 1062, 1048, 996, 946, 921, 841, 786, 769, 623 cm^{-1}

TLC: R_f = 0.21 (20% EtOAc/hexanes)

Melting point: 79-81 °C

Preparation of Iodo-nitrobenzene 16



Trimethoxy-nitrobenzene **15** (35.0 g, 164.0 mmol, 1.0 equiv) and CH_2Cl_2/MeCN (1.60 L, 1:1 mixture, 0.1 M with respect to **15**) were added to a flame dried 2 L round-bottom flask. $AgNO_3$ (30.7 g, 180.0 mmol, 1.1 equiv) and I_2 (45.7 g, 180.0 mmol, 1.1 equiv) were added and the mixture was stirred in the dark for 3 h (Note: The reaction should be halted immediately after observing complete consumption of the starting material by TLC as unidentified byproducts were observed when the reaction was allowed to stir for longer periods). The mixture was filtered through a short bed of celite and washed with CH_2Cl_2 until the washings were colorless. Saturated aqueous $Na_2S_2O_3$ (500 mL) was added to the filtrate and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 200 mL) and the combined organic extracts were washed with H_2O (500 mL), brine (500 mL), and concentrated *in vacuo*. The precipitate that formed was filtered and washed with hexanes (3 x 100 mL) to give iodo-nitrobenzene **16** (50.7 g, 91% yield) as a yellow solid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.55 (s, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 3.84 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ 155.7, 154.5, 151.5, 135.6, 98.0, 65.7, 62.6, 57.4, 56.7.

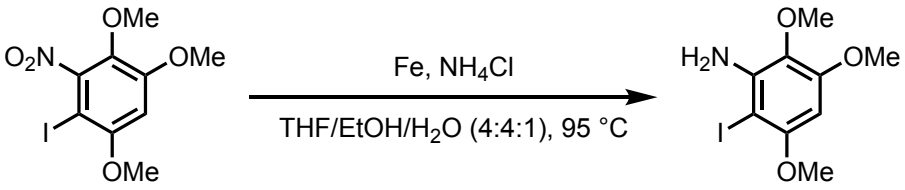
HRMS: (ESI+): calculated for $C_9H_{10}INNaO_5^+$ $[M+Na]^+$ 361.9496, found: 361.9496.

FTIR: (thin film): 2977, 2945, 2847, 1596, 1567, 1533, 1490, 1464, 1435, 1369, 1328, 1279, 1241, 1208, 1092, 1052, 999, 919, 836, 819, 763, 745, 745, 584 cm^{-1}.

TLC: R_f = 0.34 (20% EtOAc/hexanes).

Melting point: 166-172 °C

Preparation of Iodoaniline 11



Iodo-nitrobenzene **16** (15.0 g, 44.2 mmol, 1.0 equiv), Fe powder (24.7 g, 442.0 mmol, 10 equiv), NH_4Cl (11.8 g, 221.0 mmol, 5.0 equiv) and THF/EtOH/H_2O (295 mL, 4:4:1 mixture, 0.15 M with respect to **16**) were added to a 1 L round-bottom flask. The mixture was placed in a heating mantle and stirred for 1h at reflux (mantle temp = 95 °C), at which point full consumption of starting material was observed by TLC. The mixture cooled to rt and filtered through a short bed of celite. The filtrate was washed with CH_2Cl_2 (3 x 200 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography on silica gel (hexanes/EtOAc 70:30) to give iodoaniline **11** (11.5 g, 85% yield) as a white amorphous solid. Due to the instability of this product, it was used immediately or stored in the freezer (-20 °C) under Ar.

^{1}H NMR: (300 MHz, $CDCl_3$) δ 6.00 (s, 1H), 4.39 (br s, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H).

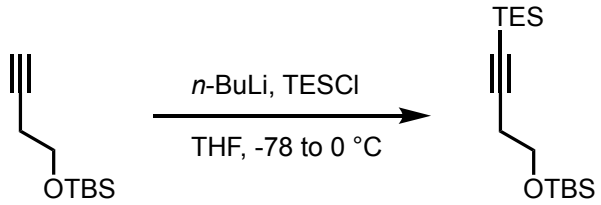
^{13}C NMR: (75 MHz, $CDCl_3$) δ 155.1, 153.2, 142.3, 129.9, 87.1, 65.7, 60.3, 56.7, 56.1.

HRMS: (ESI+): calculated for $C_9H_{13}INO_3^+$ $[M+H]^+$ 309.9935, found: 309.9932.

FTIR: (thin film): 3468, 3365, 2934, 2839, 1600, 1576, 1485, 1460, 1425, 1342, 1228, 1203, 1176, 1115, 1056, 1000, 975, 952, 773, 577, 416 cm^{-1}.

TLC: R_f = 0.24 (20% EtOAc/hexanes; stains yellow with Vanillin).

Preparation of Alkyne 12



The TBS-protected alkyne **18** was prepared according to a literature protocol.[1] TBS-protected alkyne **18** (20 g, 108.0 mmol, 1.0 equiv) and THF (120 mL, 0.9 M with respect to **18**) were added to a flame-dried 500 mL round-bottom flask under Ar. The solution was cooled to -78 °C and *n*-BuLi (48 mL, 119.0 mmol, 1.1 equiv, 2.5 M in hexanes) was added dropwise. The solution was stirred for 0.5 h at -78 °C and warmed to 0 °C. After stirring for 0.5 h at 0 °C, the solution was once again cooled to -78 °C and TESCl (15.1 mL, 119.0 mmol, 1.1 equiv) was added dropwise. The reaction stirred for an additional 0.5 h and quenched with saturated $NaHCO_3$ (100 mL) at -78 °C. After warming to rt, the organic and aqueous layers were separated, and the aqueous layer was further extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the crude silylated alkyne **12** (31.6 g) as a pale-yellow liquid. This material was carried forward without further purification. For characterization purposes, the crude material could be purified by flash column chromatography on silica gel (hexanes/EtOAc/Et_3N 90:6:4).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 3.72 (t, *J* = 7.1 Hz, 2H), 2.46 (t, *J* = 7.1 Hz, 2H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.90 (s, 9H), 0.57 (q, *J* = 7.9 Hz, 6H), 0.07 (s, 6H).

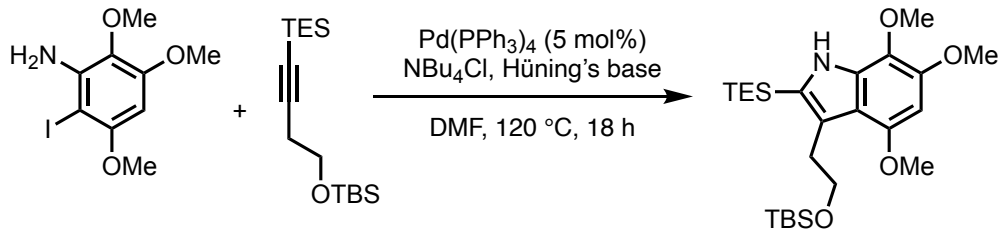
^{13}C NMR: (126 MHz, $CDCl_3$) δ 105.4, 82.9, 62.2, 26.0, 24.5, 18.5, 7.6, 4.6, -5.1.

HRMS (ESI+): calculated for $C_{16}H_{34}NaOSi_2$ $[M+H]^+$ 321.2040, found: 321.2041.

FTIR (thin film): 2954, 2931, 2875, 2176, 1462, 1415, 1382, 1361, 1253, 1106, 1046, 1006, 916, 835, 776, 724, 608 cm^{-1}.

TLC: R_f = 0.15 (hexanes; $KMnO_4$).

Preparation of Indole 10



Iodoaniline **11** (11.0 g, 35.6 mmol, 1.0 equiv), silylated alkyne **12** (15.9 g, 53.4 mmol, 1.5 equiv), and DMF (120 mL, 0.3 M with respect to **11**) were added to a flame-dried 500 mL round-bottom flask under Ar. The solution was sparged with Ar for ~10 min and Hünig's base (18.6 mL, 0.106 mol, 3.0 equiv), NBu_4Cl (9.88 g, 35.6 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (2.06 g, 1.78 mmol, 5 mol%) were added each in one portion. The solution was placed in a heating mantle (120 °C) and stirred for 18 h, at which point full consumption of starting material was observed by TLC. The solution was cooled to rt and diluted with Et_2O (100 mL) and saturated NH_4Cl (100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 100 mL) and the combined organic extracts were washed with H_2O (5 x 100 mL), brine (3 x 100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography on silica gel (hexanes/EtOAc 90:10) to give indole **10** (16.3 g, 95% yield) as a waxy yellow solid.

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 6.20 (s, 1H), 3.93 (s, 6H), 3.90 (s, 3H), 3.81-3.78 (m, 2H), 3.10-3.07 (m, 2H), 1.01-0.98 (m, 9H), 0.92 (s, 9H), 0.92-0.88 (m, 6H), 0.08 (s, 6H).

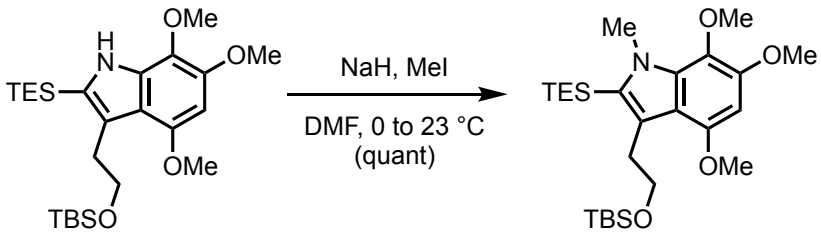
^{13}C NMR: (126 MHz, $CDCl_3$) δ 150.0, 147.1, 134.3, 130.2, 128.9, 122.6, 115.5, 90.2, 65.8, 61.1, 58.2, 55.5, 31.7, 26.3, 18.7, 7.6, 4.0, -5.0.

HRMS (ESI+): calculated for $C_{25}H_{45}NNaO_4Si_2^+$ $[M+Na]^+$ 502.2779, found: 502.2778.

FTIR: (thin film): 3485, 3357, 2953, 2933, 2875, 1626, 1594, 1525, 1464, 1417, 1338, 1233, 1204, 1135, 1089, 1041, 1002, 977, 902, 836, 777, 734 cm^{-1}.

TLC: R_f = 0.19 (10% EtOAc/hexanes; stains blue with vanillin).

Preparation of N-Methylated Indole 19



Indole **10** (1.0 g, 2.08 mmol, 1.0 equiv), MeI (0.16 mL, 2.70 mmol, 1.3 equiv), and DMF (10.4 mL, 0.2 M with respect to **10**) were added to a flame-dried 100 mL round-bottom flask. The solution was cooled to 0 °C and NaH (0.10 g, 2.50 mmol, 1.2 equiv, 60% dispersion in mineral oil) was added in one portion. The cooling bath was removed and the mixture was stirred for 1 h at rt, at which point full consumption of starting material was observed by TLC. H_2O (10 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were washed with H_2O (5 x 10 mL), brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography on silica gel (hexanes/EtOAc 95:5) to give N-methylated indole **19** (1.03 g, quant) as a white waxy solid.

Note: Due to sodium hydride (NaH) being moisture sensitive and flammable solid, proper caution should be implemented.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.20 (s, 1H), 4.02 (s, 3H), 3.93 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.77-3.73 (m, 2H), 3.17-3.13 (m, 2H), 1.03-0.95 (m, 15H), 0.93 (s, 9H), 0.08 (s, 6H).

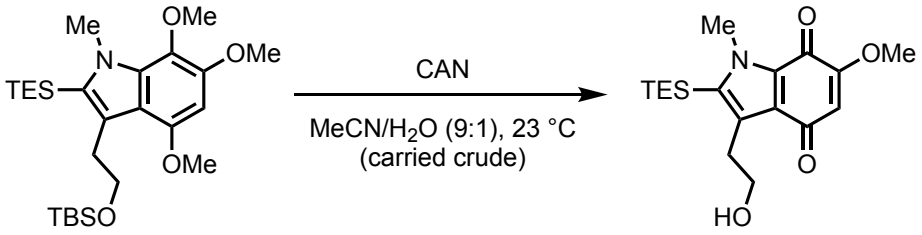
^{13}C NMR: (101 MHz, $CDCl_3$) 150.1, 148.6, 134.4, 133.8, 130.4, 123.6, 115.9, 89.9, 66.4, 61.9, 58.2, 55.4, 35.3, 30.7, 26.2, 18.6, 7.8, 5.1, -5.0.

HRMS (ESI+): calculated for $C_{26}H_{47}NNaO_4Si_2^+$ $[M+Na]^+$ 516.2936, found: 516.2936.

FTIR (thin film): 2953, 2931, 2875, 1610, 1516, 1463, 1341, 1287, 1255, 1215, 1154, 1117, 1085, 1020, 1003, 982, 930, 865, 836, 776, 733, 418cm^{-1}.

TLC: R_f = 0.33 (10% EtOAc/hexanes; stains purple with vanillin).

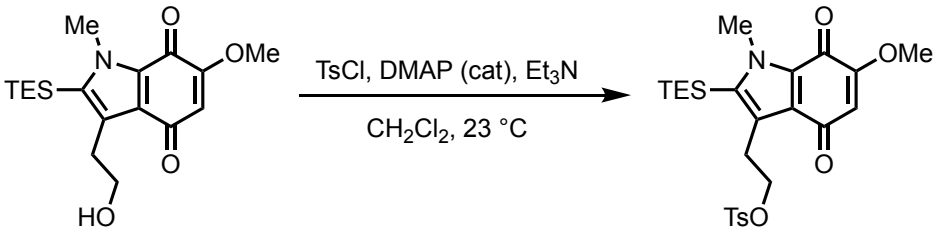
Preparation Indoloquinone 20



N-methyl indole **19** (0.53 g, 1.08 mmol, 1.0 equiv), CAN (1.48 g, 2.70 mmol, 2.5 equiv) and MeCN/H_2O (14 mL, 9:1 mixture, 0.07 M with respect to **19**) were added to a 50 mL round-bottom flask. The mixture was stirred for 0.5 h, at which point full consumption of starting material was observed by TLC. The reaction was then quenched by the addition of H_2O (100 mL) added and the aqueous layer was extracted with CH_2Cl_2 (5 x 50 mL). The combined organic extracts were washed with H_2O (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give indoloquinone **20**. The crude mixture was carried forward without further purification.

^{1}H NMR: (300 MHz, $CDCl_3$): δ 5.67 (s, 1H), 4.05 (s, 3H), 3.81 (s, 3H), 3.78 (t, J = 6.3 Hz, 2H; overlaps with s at 3.81 ppm), 3.11 (t, J = 6.4 Hz, 2H), 1.00-0.93 (m, 15).

Preparation of Ts-Indoloquinone 21



Crude indoloquinone **20** (0.47 g, 1.0 equiv, ~1.35 mmol), TsCl (0.51 g, 2.70 mmol, 2.0 equiv), DMAP (0.033 g, 0.27 mmol, 20 mol%), and DCM (4.5 mL, 0.2M with respect to **20**) were added to a flame-dried 10 mL round-bottom flask. Et_3N (0.38 mL, 2.70 mmol, 2.0 equiv) was added dropwise and the solution was stirred for 2 h. The reaction was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with H_2O (20 mL), brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography on silica gel (hexanes/EtOAc 70:30) to give indoloquinone **21** (0.342 g, 63% yield over two steps) as an orange foam.

^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.65-7.63 (m, 2H), 7.24-7.21 (m, 2H), 5.57 (s, 1H), 4.20 (t, J = 6.7 Hz, 2H), 4.02 (s, 3H), 3.80 (s, 3H), 3.13 (t, J = 6.7 Hz, 2H), 2.38 (s, 3H), 1.00-0.89 (m, 15H).

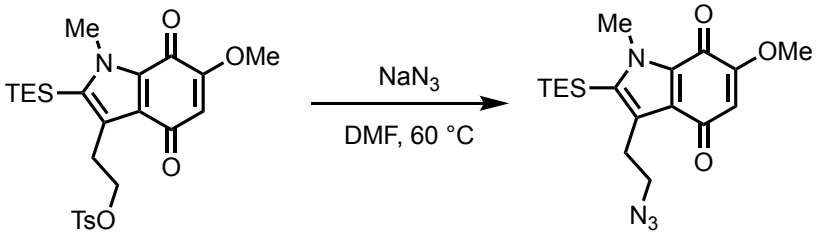
^{13}C NMR: (126 MHz, $CDCl_3$) δ 183.9, 171.9, 159.9, 144.5, 141.2, 133.0, 131.6, 130.4, 129.6, 128.0, 124.0, 107.3, 69.9, 56.7, 36.7, 25.7, 21.6, 7.6, 4.6.

HRMS (ESI+): calculated for $C_{25}H_{33}NNaO_6SSi^+$ $[M+Na]^+$ 526.1690, found: 526.1693.

FTIR (thin film): 2956, 2876, 1663, 1638, 1601, 1519, 1455, 1413, 1357, 1336, 1243, 1210, 1187, 1173, 1109, 1068, 1036, 1000, 959, 901, 843, 814, 782, 728, 662, 569, 553, 522, 494, 452 cm^{-1}.

TLC: R_f = 0.15 (40% EtOAc/hexanes).

Preparation of Azidoindoloquinone 9



Indoloquinone **21** (0.34 g, 0.678 mmol, 1.0 equiv), NaN_3 (0.221 g, 3.4 mmol, 5 equiv), and DMF (4 mL, 0.16 mmol/mL with respect to **21**) were added to a flame-dried 10 mL round-bottom flask. The mixture was placed in a heating mantle and stirred for 24 h at 60 °C. The mixture was cooled to rt and diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with H_2O (3 x 10 mL), brine (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography on silica gel (hexanes/EtOAc 70:30) to give azainodoloquinone **9** (0.143 g, 57% yield) as an orange oil that solidifies in the freezer (~-20 °C).

Note: Due to sodium azide being heat, shock, and friction sensitive, proper caution should be implemented.

^{1}H NMR: (400 MHz, $CDCl_3$): δ 5.67 (s, 1H), 4.05 (s, 3H), 3.80 (s, 3H), 3.45-3.42 (m, 2H), 3.10-3.06 (m, 2H), 1.01-0.90 (m, 15H).

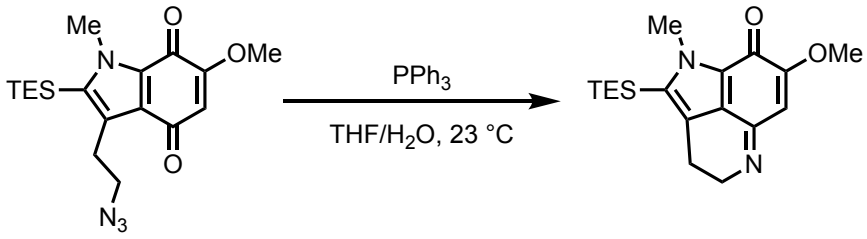
^{13}C NMR: (101 MHz, $CDCl_3$): δ 184.2, 172.1, 160.1, 140.6, 132.4, 131.8, 124.3, 107.5, 56.7, 51.8, 36.7, 26.0, 7.6, 4.6.

HRMS (ESI+): calculated for $C_{18}H_{26}N_4NaO_3Si^+$ $[M+Na]^+$ 397.1666, found: 397.1671.

FTIR (thin film): 2955, 2876, 2094, 1665, 1641, 1603, 1519, 1456, 1413, 1337, 1242, 1211, 1110, 1054, 1034, 1002, 925, 892, 844, 794, 735, 486, 456, 426 cm^{-1}.

TLC: R_f = 0.22 (20% EtOAc/hexanes).

Preparation of Vinylogous Imidate 6b



Azidoindoloquinone **9** (0.14 g, 0.382 mmol, 1.0 equiv), PPh_3 (0.20 g, 0.764 mmol, 2.0 equiv), and THF/H_2O (2.2 mL, 9:1 mixture, 0.2 M with respect to **9**) were added to a 6-dram vial. The mixture stirred for 16 h, at which point complete consumption of starting material was observed by TLC. The contents of the vial were transferred to a flask (rinsing the sides of the vial with CH_2Cl_2), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH 97:3) to give vinylogous imidate **6b** (0.082 g, 65% yield) as a dark purple oil.

Note: We have found the vinylogous imidate **6b** to be unstable as an impurity (<10%) quickly starts to form over time. We have found that the impurity does not impede the overall reactivity of the next step (aminolysis) and could be readily separated at that point. In addition, we have discovered that this two-step sequence (Staudinger reduction and aminolysis) could be accomplished in one-pot to obtain the desired vinylogous amidine **22** in comparable yields.

Two-step, one-pot sequence: Azaindoloquinone **9** (0.027 g, 0.072 mmol, 1.0 equiv), PPh_3 (0.038 g, 0.144 mmol, 2.0 equiv), and THF/H_2O (0.4 mL, 9:1 mixture) were added to a 6-dram vial. The mixture stirred for 16 h and Na_2SO_4 was added. The contents of the vial were filtered into a 6-dram vial and concentrated *in vacuo*. The crude mixture was carried forward without further purification.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.05 (s, 1H), 4.11 (t, *J* = 7.8 Hz, 2H), 4.04 (s, 3H), 3.81 (s, 3H), 2.79 (t, *J* = 7.8 Hz, 2H), 0.99-0.95 (m, 9H), 0.90-0.86 (m, 6H).

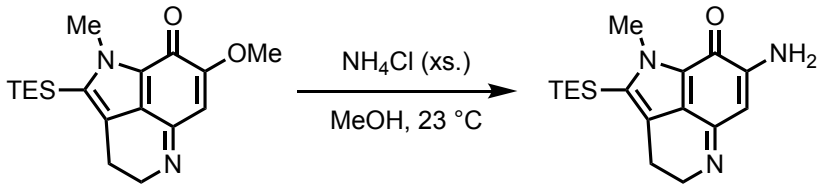
^{13}C NMR: (101 MHz, $CDCl_3$) δ 171.6, 158.7, 156.8, 137.8, 127.18, 127.16, 121.1, 105.9, 56.6, 50.9, 35.9, 20.8, 7.5, 4.0.

HRMS (ESI+): calculated for $C_{18}H_{27}N_2O_2Si^+$ $[M+H]^+$ 331.1836, found: 331.1834.

FTIR (thin film): 2953, 2875, 1654, 1614, 1571, 1452, 1320, 1282, 1218, 1179, 1129, 1044, 1007, 921, 837, 792, 734, 698, 585, 421 cm^{-1}.

TLC: R_f = 0.33 (5% MeOH/CH_2Cl_2).

Preparation of Vinylogous Amidine 22



Vinylogous imidate **6b** (0.071 g, 0.214 mmol, 1.0 equiv), NH_4Cl (0.11 g, 2.14 mmol, 10 equiv), and MeOH (1 mL, 0.2 M with respect to **6b**) were added to a 2-dram vial. The mixture was stirred for 16 h, at which point,full consumption of the starting material was observed by TLC. The reaction was concentrated *in vacuo* and the crude mixture was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH 90:10) to give vinylogous amidine **22** (0.038 g, 56% yield) as a dark green solid.

Two-step, one-pot sequence: crude vinylogous imidate **6b**, NH_4Cl (0.039 g, 0.72 mmol, 10.0 equiv) and MeOH (0.3 mL) were added to a 6-dram vial. The mixture was stirred for 16 h and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH 90:10) to give vinylogous amidine **22** (0.012 g, 53% yield over two steps)

Note: The ^{1}H NMR peak corresponding to the -NH_2 of the vinylogous amidine is presumed to be exchange-broadened and is not observed in the spectral data reported below.

^{1}H NMR: (600 MHz, methanol-*d4*) δ 5.65 (s, 1H), 4.07 (s, 3H), 3.82 (t, *J* = 7.6 Hz, 2H), 3.01 (t, *J* = 7.6 Hz, 2H), 1.04-0.95 (m, 15H).

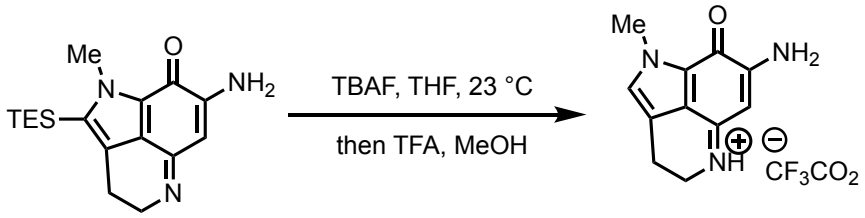
^{13}C NMR: (151 MHz, methanol-*d4*) δ 169.8, 160.0, 157.8, 142.5, 129.9, 128.8, 123.3, 87.9, 43.9, 37.1, 21.8, 7.6, 4.5.

HRMS (ESI+): calculated for $C_{17}H_{26}N_3OSi^+$ $[M+H]^+$ 316.1840, found: 316.1841.

FTIR (thin film): 2955, 2875, 1676, 1607, 1530, 1455, 1392, 1343, 1295, 1253, 1223, 1139, 1004, 967, 846, 726 cm^{-1}.

TLC: R_f = 0.18 (4% MeOH/CH_2Cl_2).

Preparation of Makaluvamine A (1)



Makaluvamine A

Vinylogous amidine **22** (0.013 g, 0.041 mmol, 1.0 equiv) and THF (0.2 mL, 0.2 M with respect to **22**) were added to flame-dried 2-dram vial. The solution was cooled to 0 °C and TBAF (0.08 mL, 0.082 mmol, 2.0 equiv, 1M solution in THF) was added dropwise. The reaction was warmed to rt (by removing ice bath) and the solution was stirred for 1 h at this temperature, at which point full consumption of starting material was observed by TLC. The reaction was concentrated *in vacuo* and the crude mixture was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH/NH_4OH 89:10:1) to give makaluvamine A (**1**), which was redissolved in MeOH (5 mL) and TFA (0.1 mL) was added. The resulting solution concentrated to give the corresponding TFA salt as dark purple solid (0.009 g, 69% yield).[2]

^{1}H NMR: (600 MHz, DMSO-*d6*) δ 10.40 (s, 1H), 9.09 (s, 1H), 8.40 (s, 1H), 7.31 (s, 1H), 5.60 (s, 1H), 3.89 (s, 3H), 3.76 (td, = 7.6, 2.7 Hz, 2H), 2.84 (t, = 7.6 Hz, 2H).

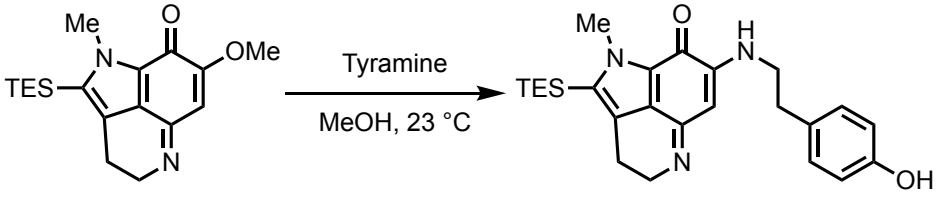
^{13}C NMR: (151 MHz, DMSO-*d6*) δ 168.3, 156.8, 156.1, 131.1, 123.1, 122.4, 117.9, 86.5, 42.1, 35.9, 18.1.

HRMS (ESI+): calculated for $C_{11}H_{12}N_3O^+$ $[M+H]^+$ 202.0975, found: 202.0975.

FTIR (thin film): 3470 (br), 2953, 2930, 2856, 1759, 1644, 1542, 1462, 1440, 1376, 1319, 1254, 1204, 1143, 1110, 1007, 894, 836, 808, 776, 698, 650, 588, 544, 491, 435, 424 cm^{-1}.

TLC: R_f = 0.15 (10% MeOH/CH_2Cl_2).

Preparation of Secondary Vinylogous Amidine 23



Vinylogous imidate **6b** (0.37 g, 1.12 mmol, 1.0 equiv), tyramine (0.23 g, 1.68 mmol, 1.5 equiv), and MeOH (5.5 mL, 0.2M with respect to **6b**) were added to a 10 mL round-bottom flask. The mixture was stirred for 16 h, at which point full consumption of the starting material was observed by TLC. The reaction was concentrated *in vacuo* and the crude mixture was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH 90:10) to give secondary vinylogous amidine **23** (0.21 g, 43% yield) as a dark brown film.

^{1}H NMR: (500 MHz, methanol-*d4*) δ 7.07 (d, *J* = 8.5 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 5.42 (s, 1H), 4.06 (s, 3H), 3.82 (t, *J* = 7.6 Hz, 2H), 3.54 (t, *J* = 7.3 Hz, 2H), 3.00 (t, *J* = 7.7 Hz, 2H), 2.88 (t, *J* = 7.0 Hz, 2H), 1.04-0.95 (m, 15H).

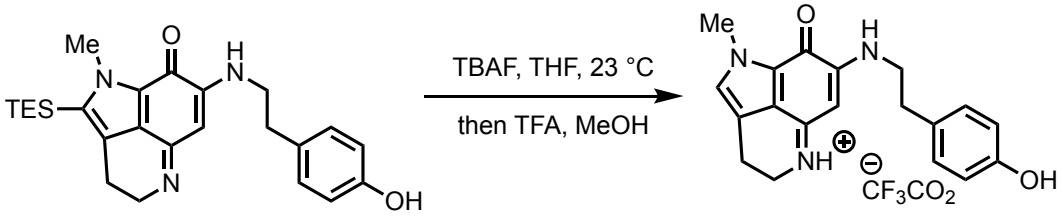
^{13}C NMR: (125 MHz, methanol-*d4*) δ 169.3, 159.4, 157.4, 154.7, 142.8, 130.9, 130.0, 129.9, 128.8, 123.3 116.5, 85.5, 46.5, 44.1, 37.1, 34.4, 21.8, 7.6, 4.5.

HRMS (ESI+)**:** (ESI+): calculated for $C_{25}H_{34}N_3OSi^+$ $[M+H]^+$ 436.2415, found: 436.2414.

FTIR (thin film): 3202, 2954, 2926, 2874, 1726, 1672, 1599, 1544, 1515, 1452, 1345, 1254, 1138, 1064, 1005, 968, 832, 738 cm^{-1}.

TLC: R_f = 0.16 (10% MeOH/CH_2Cl_2).

Preparation of Makaluvamine K (4)



Makaluvamine K

Vinylgous amidine **23** (0.050 g, 0.114 mmol, 1.0 equiv) and THF (0.6 mL, [0.2 M] in respect to **23**) were added to flame-dried 2-dram vial. The solution was cooled to 0 °C and TBAF (0.17 mL, 0.172 mmol, 1.5 equiv, 1M solution in THF) was added dropwise. The reaction warmed to rt (by removing ice bath), and the solution stirred for 1 h, at which point, full consumption of starting material was observed by TLC. The reaction was concentrated *in vacuo* and the crude mixture was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH/TFA 89:10:1) to give makaluvamine K (**4**), which was redissolved in MeOH (5 mL) and TFA (0.1 mL) was added. The resulting solution concentrated to give the corresponding TFA salt as red brown solid (0.025 g, 51% yield).[3]

^{1}H NMR: (400 MHz, DMSO-*d6*) δ 10.53 (s, 1H), 9.29 (br s, 1H), 8.95 (t, *J* = 6.3 Hz, 1H), 7.33 (s, 1H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2 H), 5.50 (s, 1H), 3.90 (s, 3H), 3.78 (td, *J* = 7.7, 2.4 Hz, 2H), 3.50-3.40 (m, 2H), 2.85 (t, = 7.6 Hz, 2H), 2.78 (t, *J* = 7.6 Hz, 2H).

^{13}C NMR: (125 MHz, DMSO-*d6*) δ 167.7, 156.5, 156.0, 152.9, 131.4, 129.6, 128.2, 123.1, 122.3, 118.1, 115.3, 84.2, 45.1, 42.2, 35.9, 32.4, 18.1.

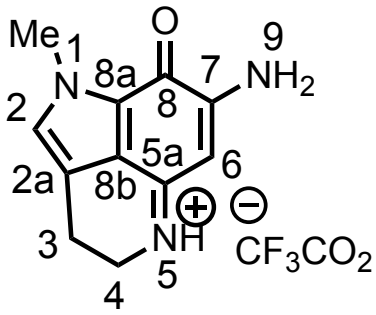
HRMS (ESI+): calculated for $C_{19}H_{20}N_3O_2^+$ $[M+H]^+$ 322.1550, found: 322.1551.

FTIR (thin film): 3239 (br), 2923, 2853, 1676, 1599, 1557, 1517, 1436, 1352, 1318, 1200, 1133, 970, 837, 801, 722 cm^{-1}.

TLC: R_f = 0.30 (1% TFA/10% MeOH/CH_2Cl_2).

III. SPECTRAL COMPARISONS FOR NATURAL PRODUCTS

Table S1. Tabular collation of $^{1}H/^{13}C$ NMR data for synthetic and natural makaluvamine A (1)



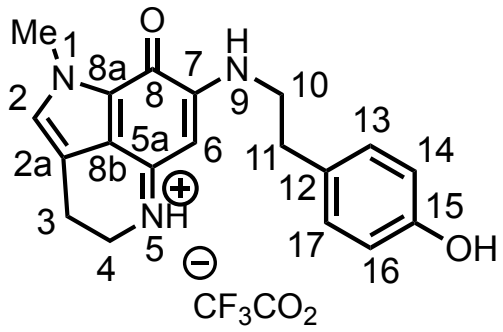
Makaluvamine A
(1)

Position	Synthetic δ ^{1}H (600 MHz)	Natural δ ^{1}H (500 MHz)	Δ_{ppm}
N-Me	3.89 (s)	3.88 (s)	+0.01
2	7.31 (s)	7.30 (s)	+0.01
3	2.84 (t, *J* = 7.6 Hz)	2.83 (t, *J* = 7.5 Hz)	+0.01
4	3.76 (td, *J* = 7.6, 2.7 Hz)	3.75 (t, *J* = 7.5 Hz)	+0.01
5	10.40 (s)	10.44 (s)	-0.04
6	5.60 (s)	5.61 (s)	-0.01
9	9.09, 8.40	9.09, 8.37	+0.03

Position	Synthetic δ ^{13}C (151 MHz)	Natural δ ^{13}C (125 MHz)	Δ_{ppm}
N-Me	35.9	35.8	+0.1
2	131.1	131.0	+0.1
2a	117.9	117.8	+0.1
3	18.1	18.0	+0.1
4	42.1	42.0	+0.1
5a	156.1	156.0	+0.1
6	86.5	86.4	+0.1
7	156.8	156.7	+0.1
8	168.3	168.2	+0.1
8a	123.1	123.0	+0.1
8b	122.4	122.3	+0.1

Figure SI. Stacked plots of (A) literature ^{1}H NMR for makaluvamine A (see ref. 2, main text, 500 MHz) and (B) synthetic makaluvamine A (**1**) ^{1}H NMR spectra (600 MHz).

Table S2. Tabular collation of $^{1}H/^{13}C$ NMR data for synthetic and natural makaluvamine K (4)



Makaluvamine K
(4)

Position	Synthetic δ ^{1}H (400 MHz)	Natural δ ^{1}H (400 MHz)	Δ_{ppm}
N-Me	3.90 (s)	3.89 (s)	+0.01
2	7.34 (s)	7.33 (s)	+0.01
3	2.85 (t, *J* = 7.6 Hz)	2.84 (t, *J* = 7.5 Hz)	+0.01
4	3.78 (td, *J* = 7.7, 2.7 Hz)	3.78 (t, *J* = 7.5 Hz)	0
5	10.44 (s)	10.47 (br s)	-0.03
6	5.48 (s)	5.47 (s)	+0.01
9	8.96 (t, *J* = 6.4 Hz)	8.97 (t, *J* = 6 Hz)	-0.01
10	3.47 (m)	3.48 (m)	-0.01
11	2.78 (t, *J* = 7.5 Hz)	2.77 (t, *J* = 7 Hz)	+0.01
13,17	7.04 (d, *J* = 8.1 Hz)	7.03 (d, *J* = 8 Hz)	+0.01
14, 16	6.70 (d, *J* = 8.2 Hz)	6.68 (d, *J* = 8 Hz)	+0.02
15 (OH)	9.28 (br s)	9.30 (br s)	+0.02

Position	Synthetic δ ^{13}C (151 MHz)	Natural δ ^{13}C (100.6 MHz)	Δ_{ppm}
N-Me	35.9	35.9	0
2	131.4	131.4	0
2a	118.1	118.0	+0.1
3	18.1	18.0	+0.1
4	42.2	42.2	0
5a	156.5	156.5	0
6	84.2	84.2	0
7	152.9	152.9	0
8	167.7	167.7	0
8a	123.1	123	+0.1
8b	122.3	122.3	0
10	45.1	45.1	0
11	32.4	32.4	0
12	128.2	128.2	0
13,17	129.6	129.6	0
14, 16	115.3	115.3	0
15	156.0	156.0	0

IV. SPECTRAL DATA FOR NEW COMPOUNDS

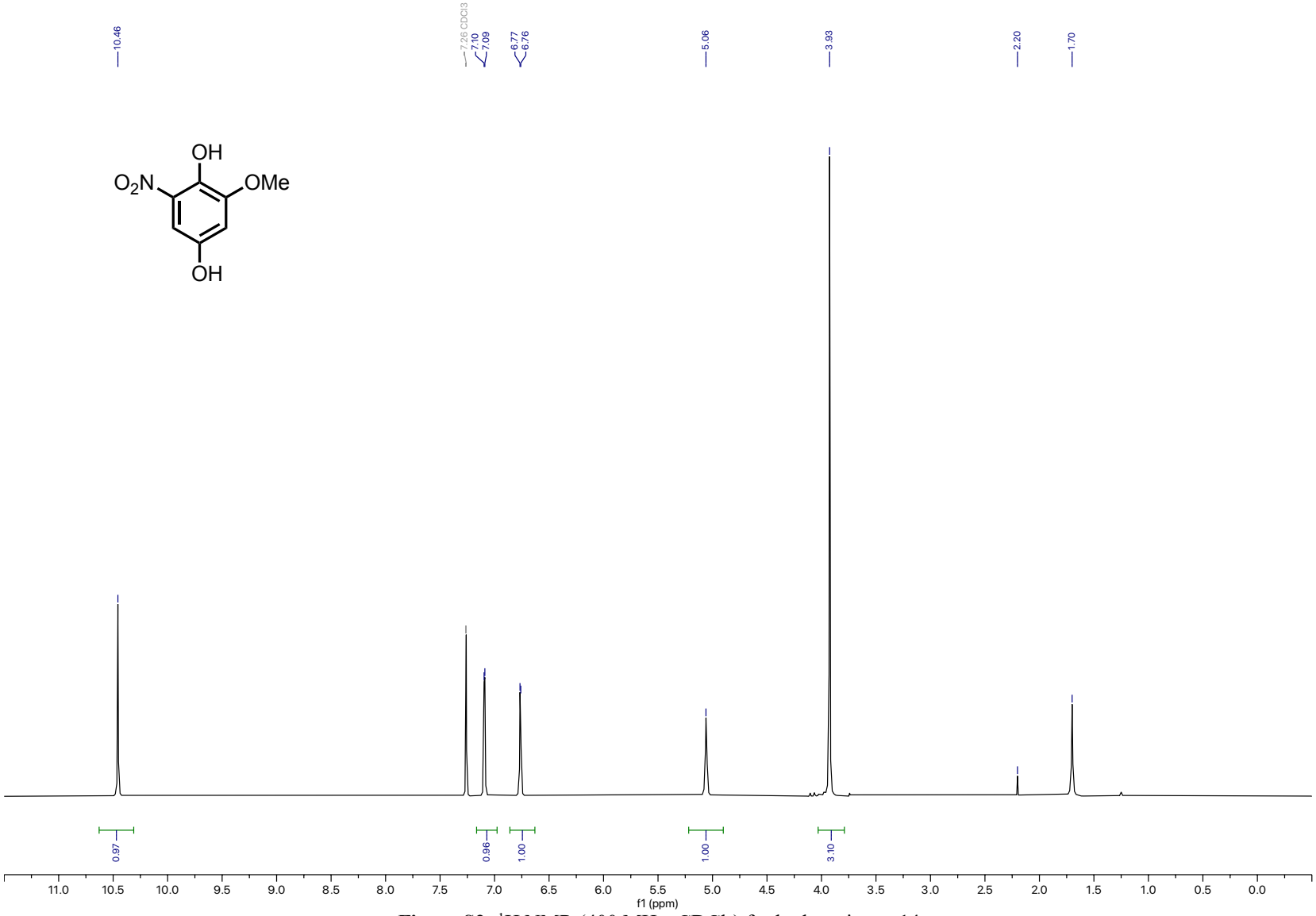


Figure S2: ^{1}H NMR (400 MHz, $CDCl_3$) for hydroquinone **14**

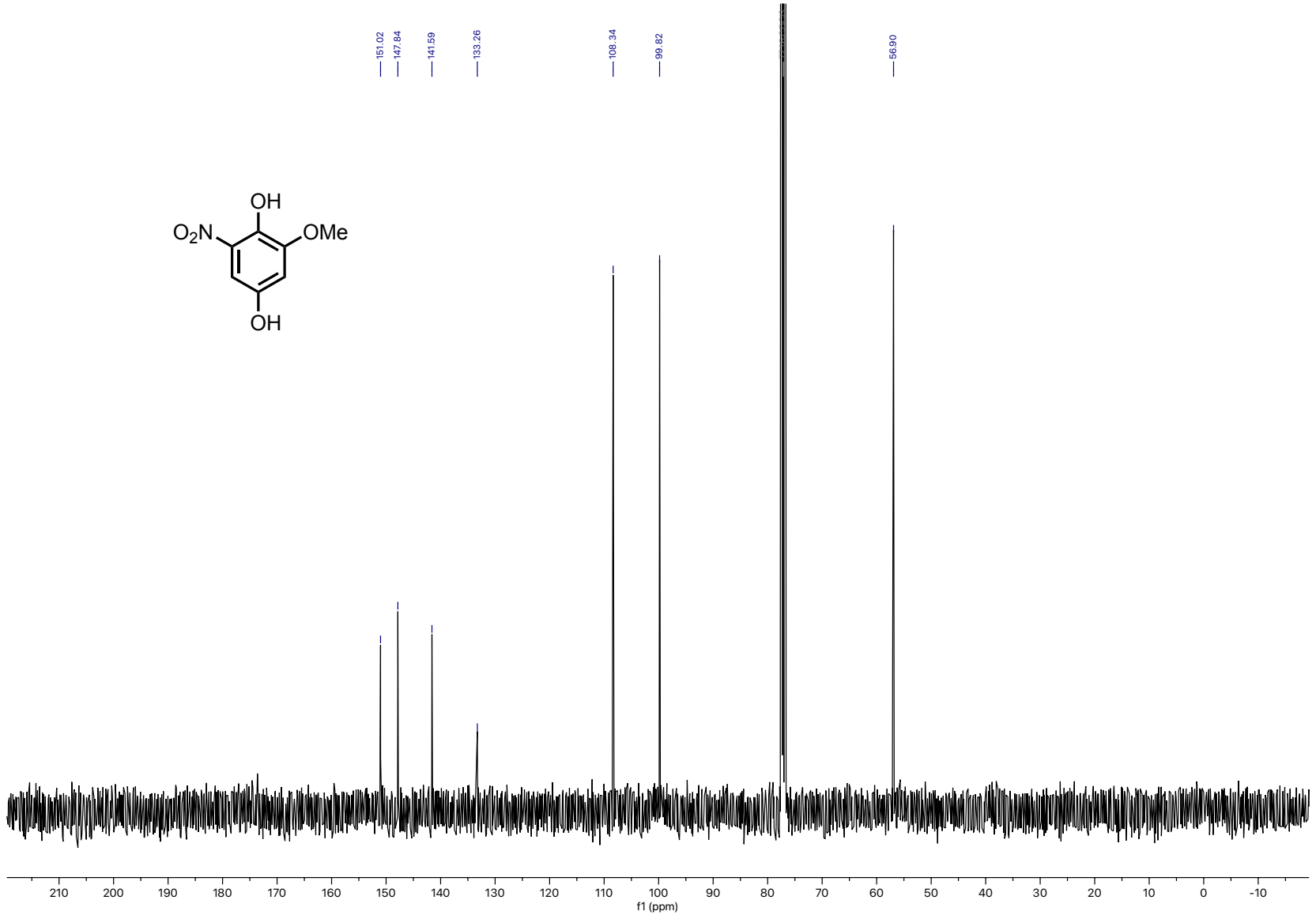


Figure S3: ^{13}C NMR (101 MHz, $CDCl_3$) for hydroquinone **14**

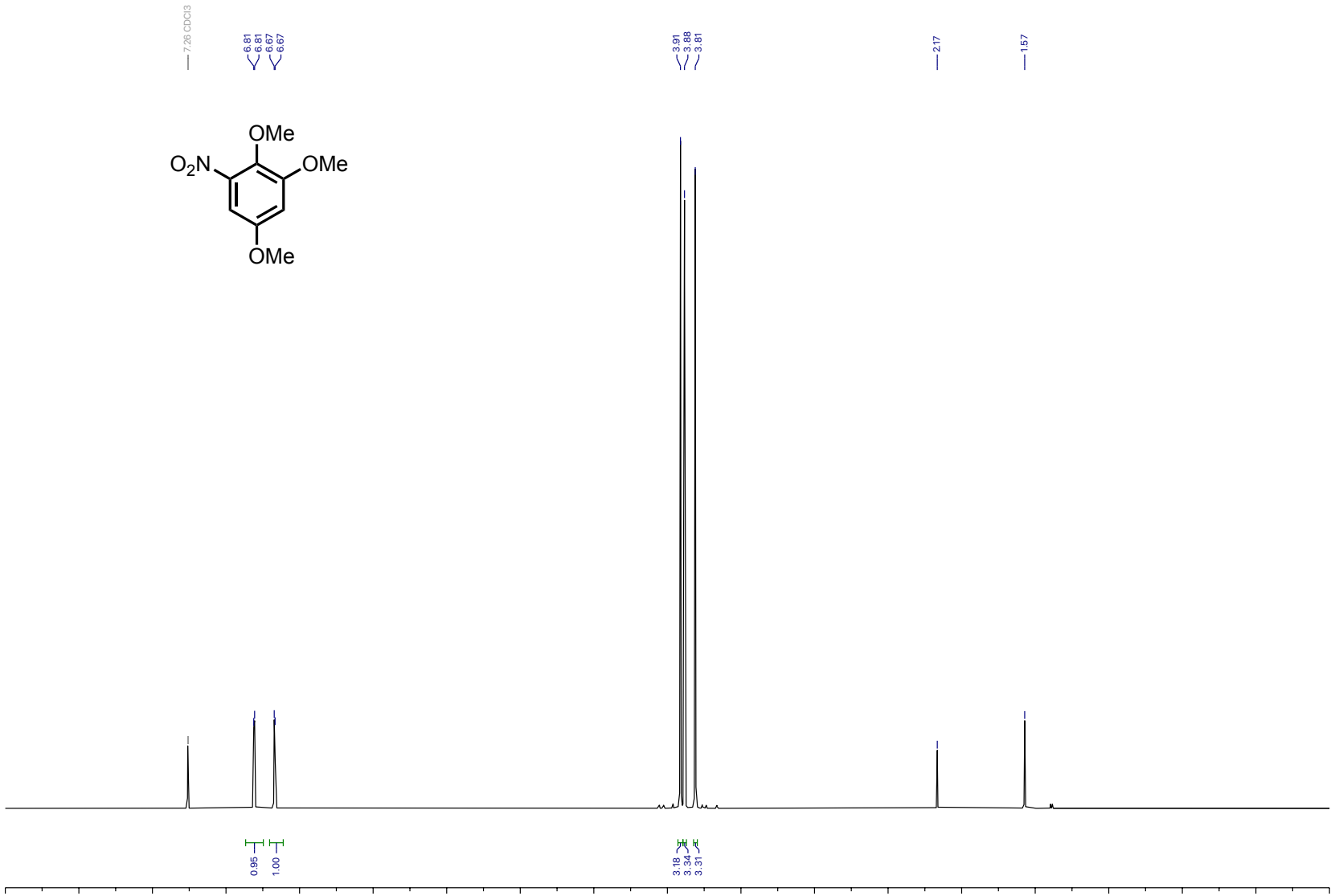


Figure S4: ^{1}H NMR (500 MHz, $CDCl_3$) for trimethoxy arene **15**

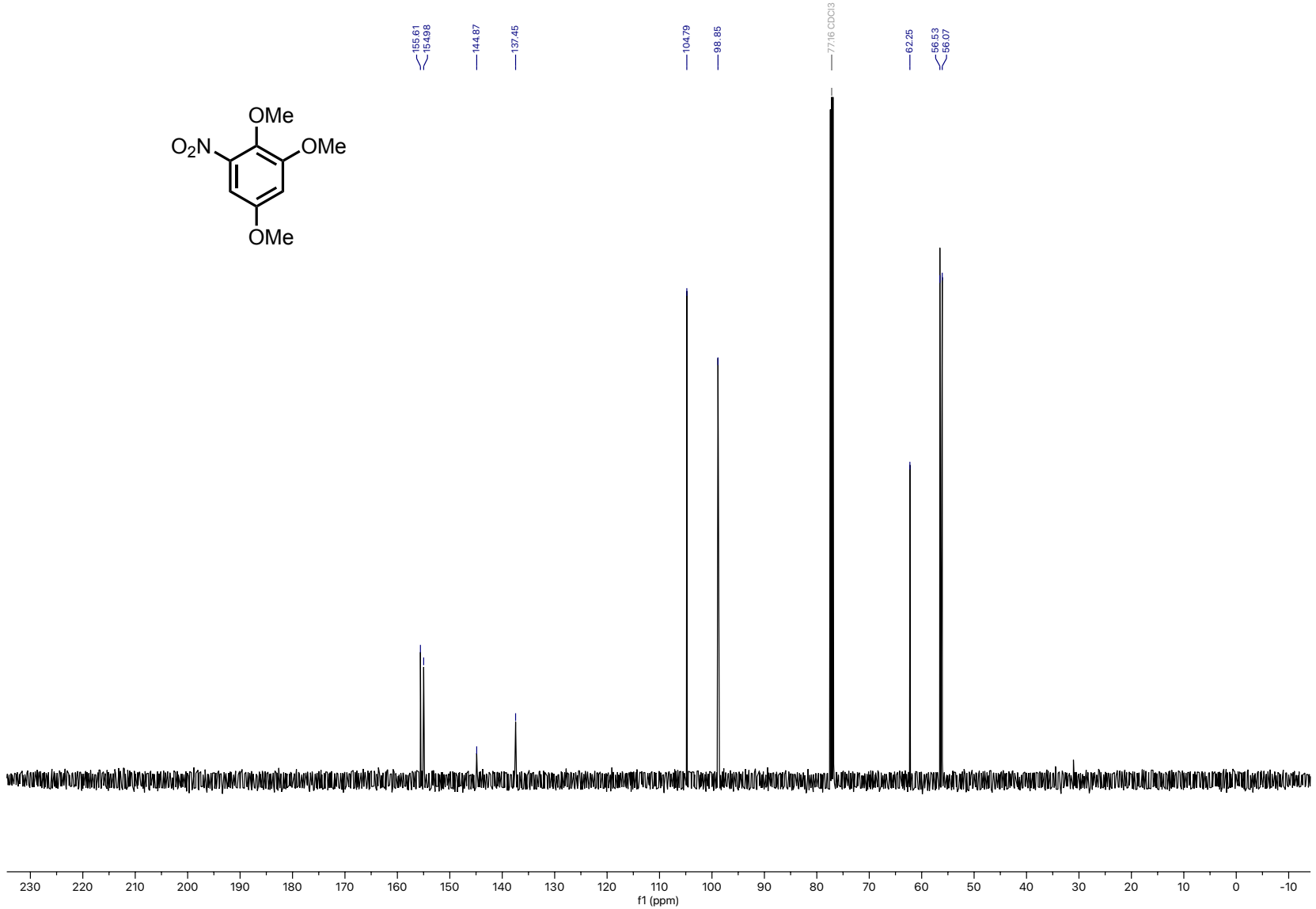


Figure S5: ^{13}C NMR (126 MHz, $CDCl_3$) for trimethoxy arene **15**

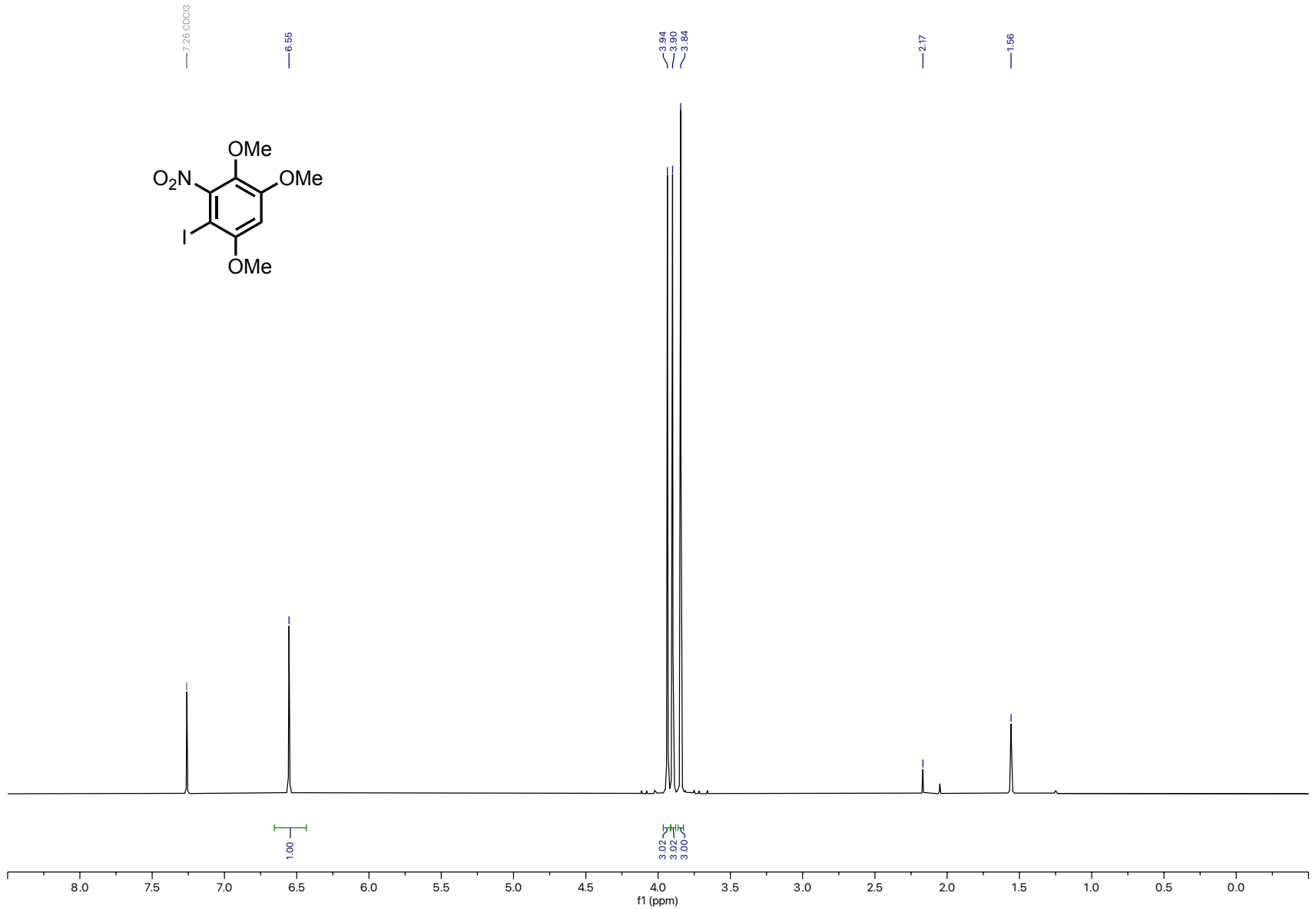


Figure S6: ^{1}H NMR (500 MHz, $CDCl_3$) for aryl iodide **16**

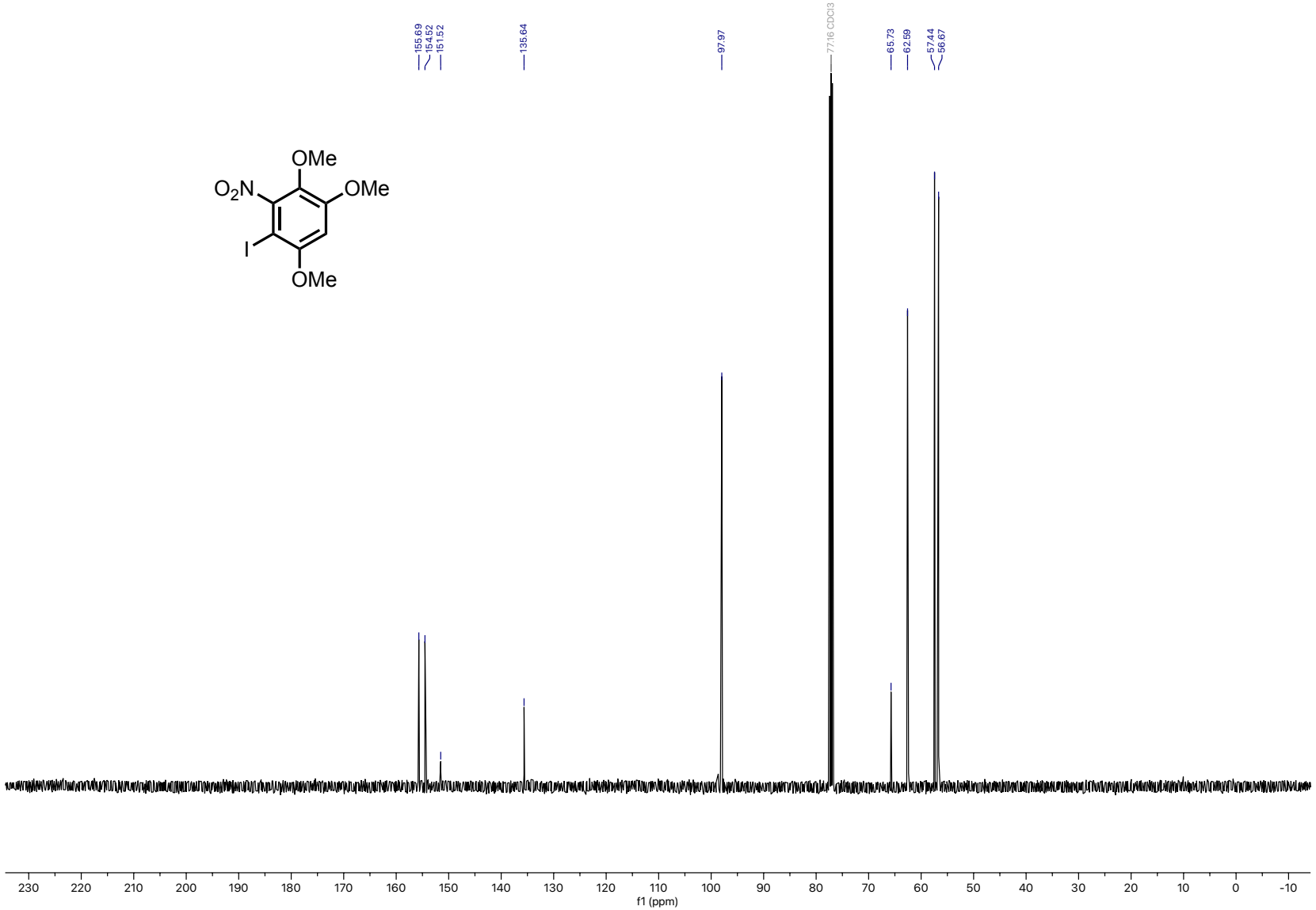


Figure S7: ^{13}C NMR (126 MHz, $CDCl_3$) for aryl iodide **16**

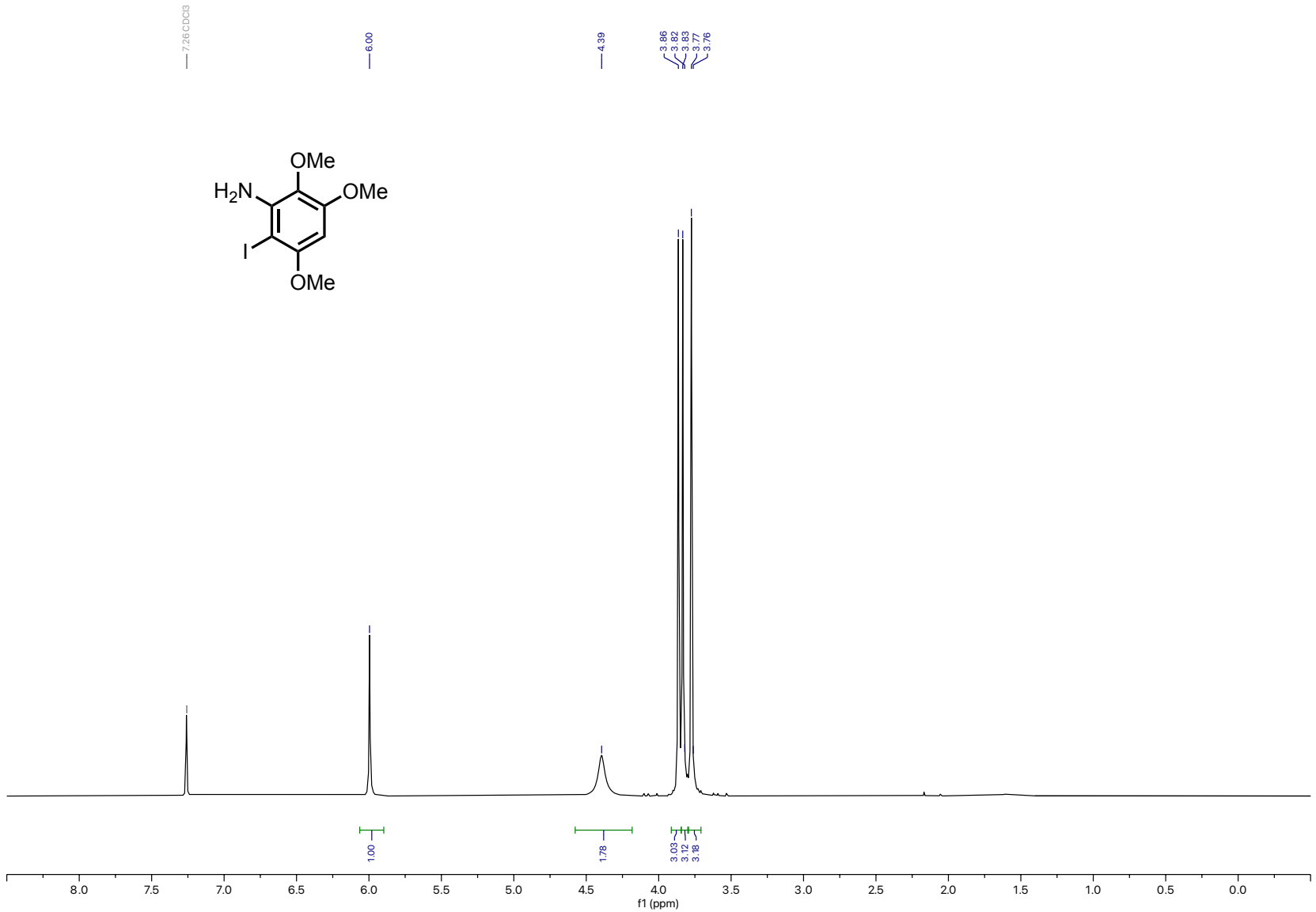


Figure S8: ^{1}H NMR (300 MHz, $CDCl_3$) for iodoaniline **11**

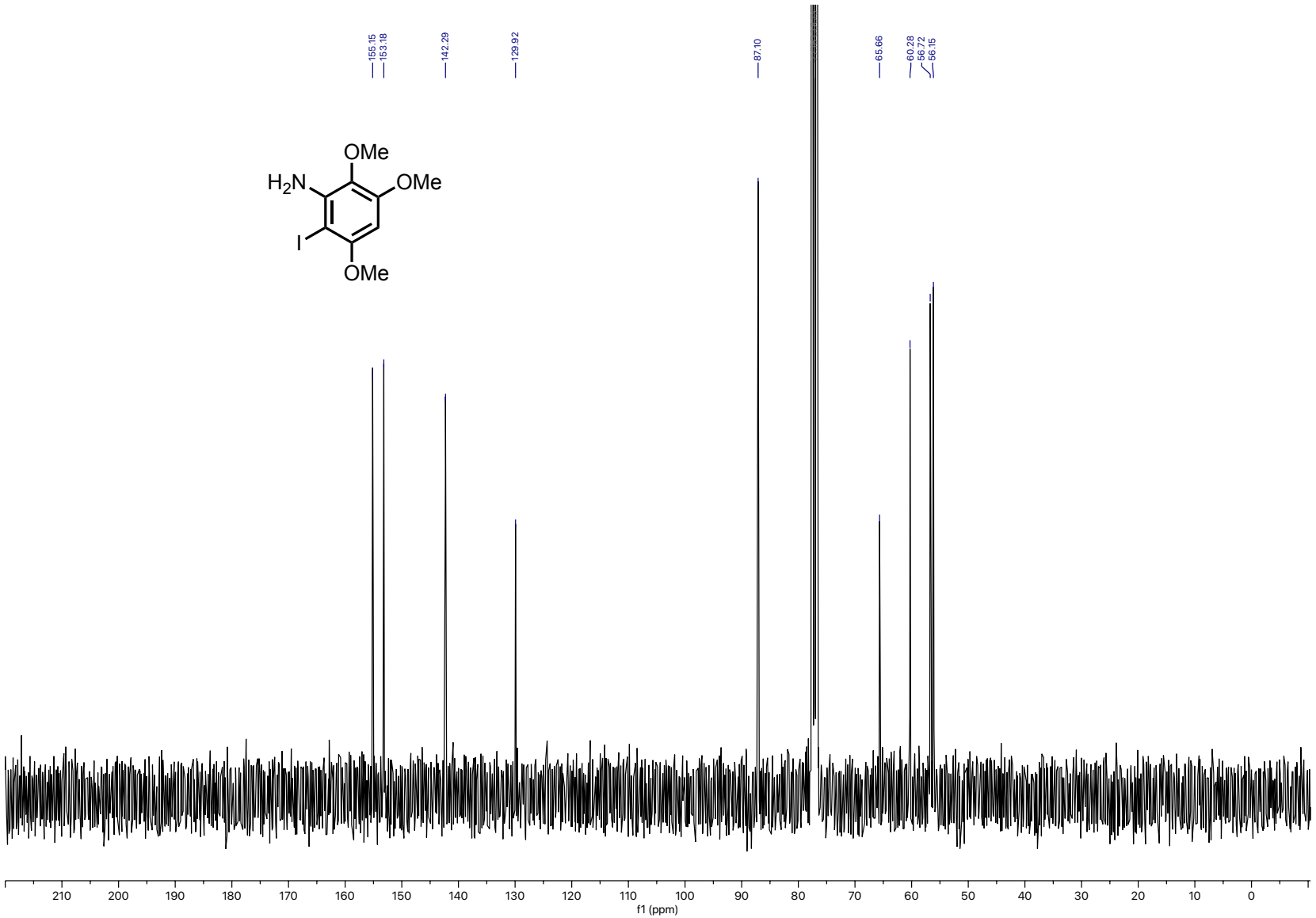


Figure S9: ^{13}C NMR (76 MHz, $CDCl_3$) for iodoaniline **11**

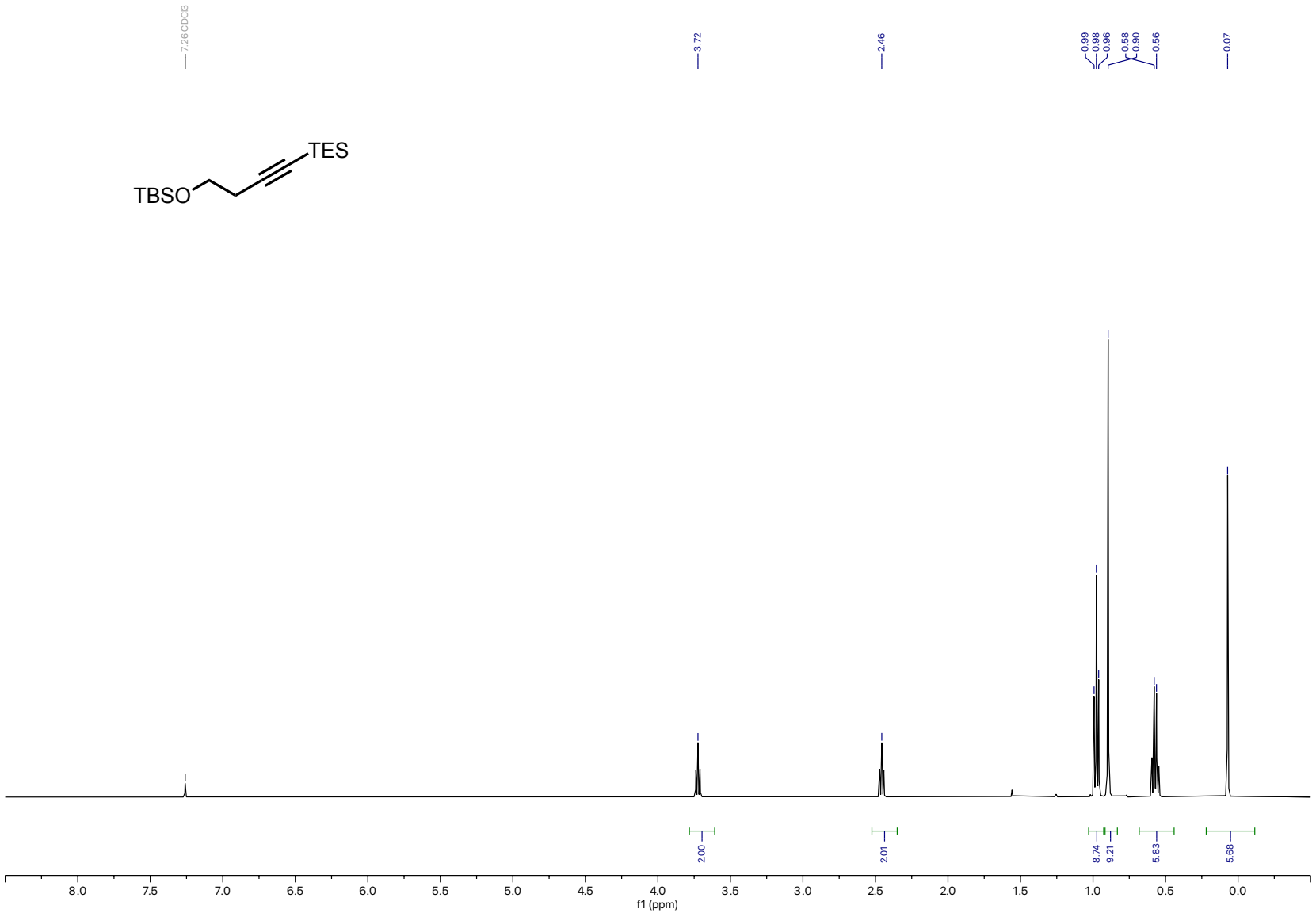


Figure S10: ^{1}H NMR (500 MHz, $CDCl_3$) for alkyne **12**

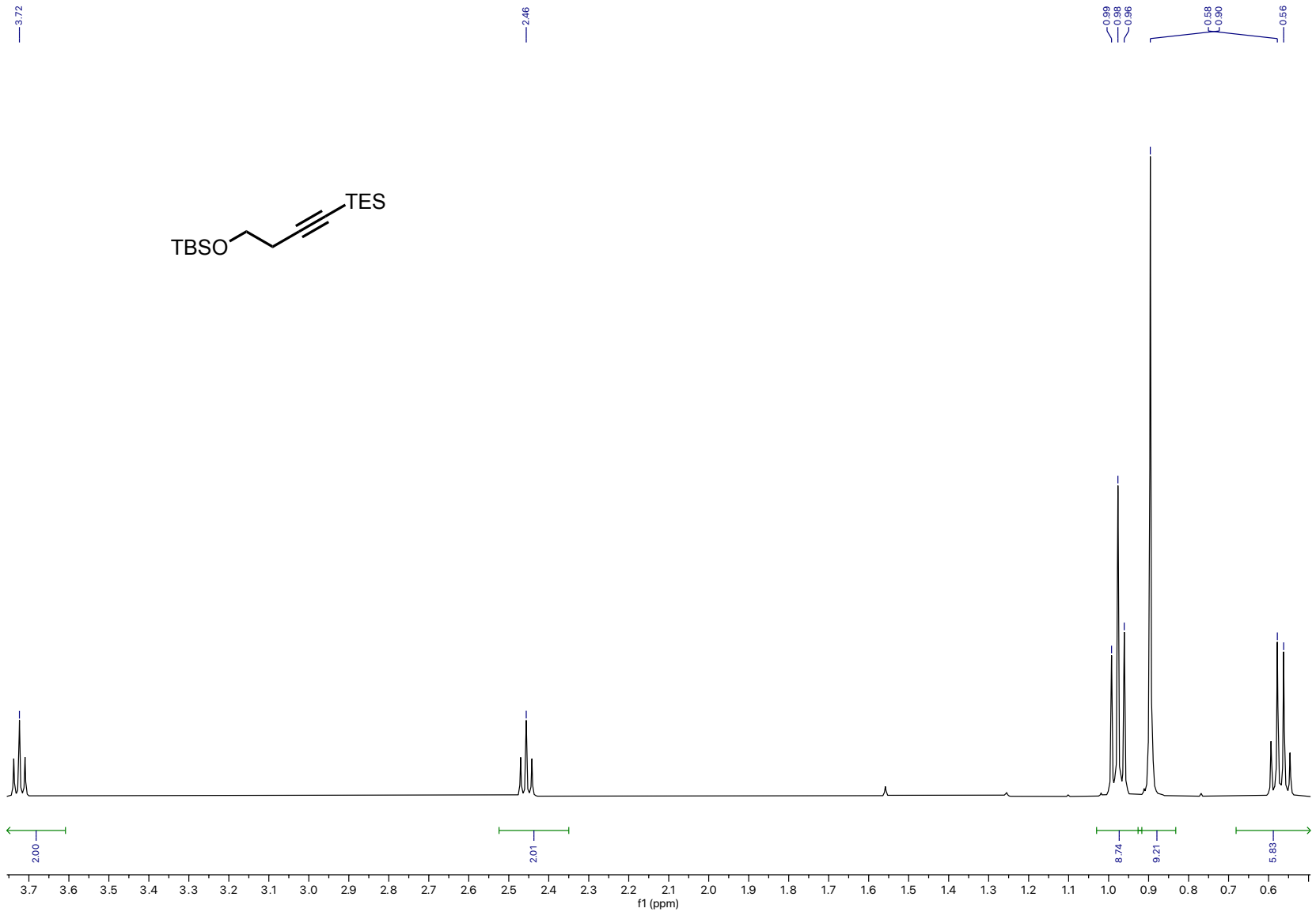


Figure S11: ^{1}H NMR (500 MHz, $CDCl_3$) for alkyne **12** (3.75-0.5 ppm inset)

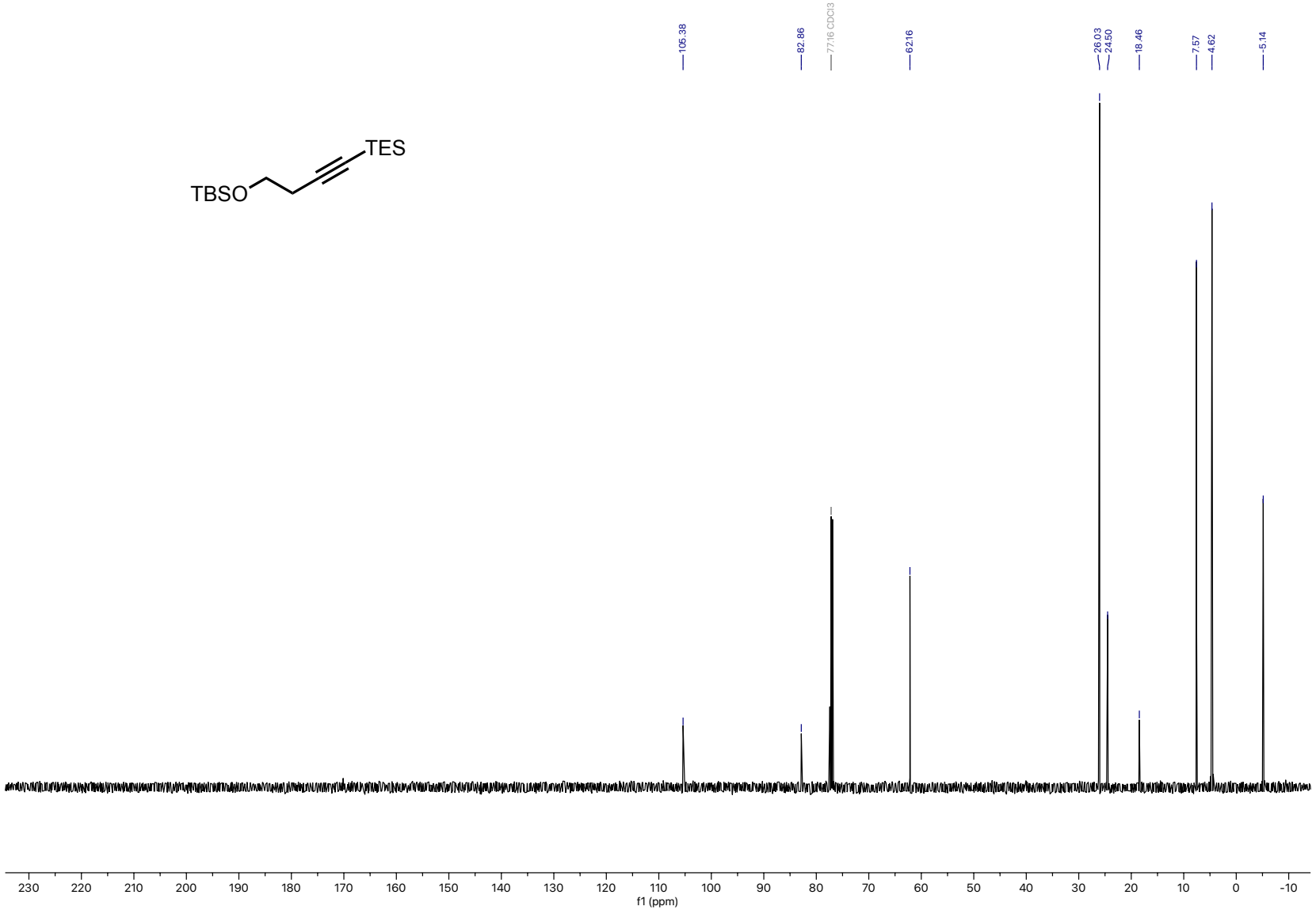


Figure S12: ^{13}C NMR (126 MHz, $CDCl_3$) for alkyne **12**

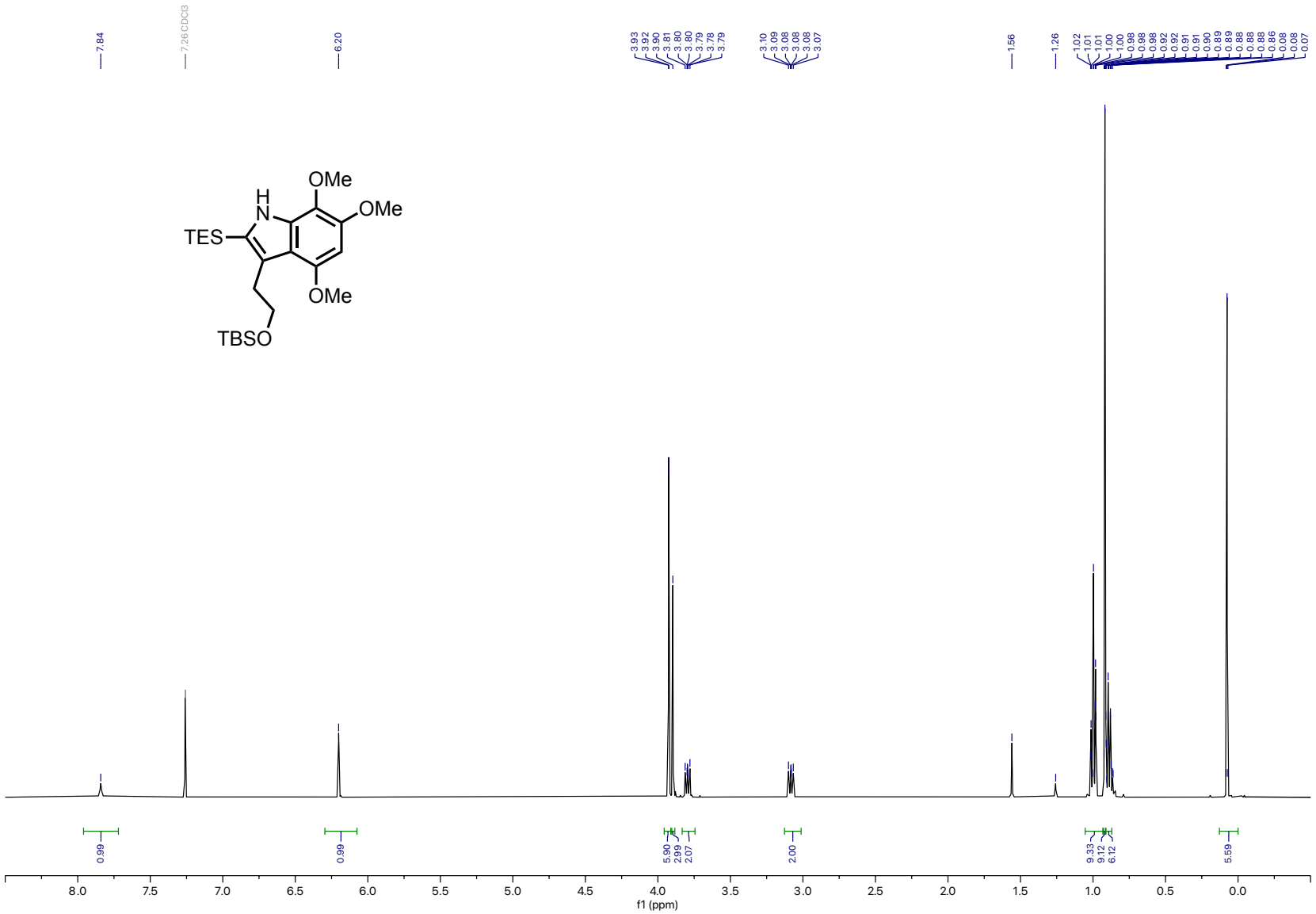


Figure S13: ^{1}H NMR (500 MHz, $CDCl_3$) for trimethoxyindole **10**

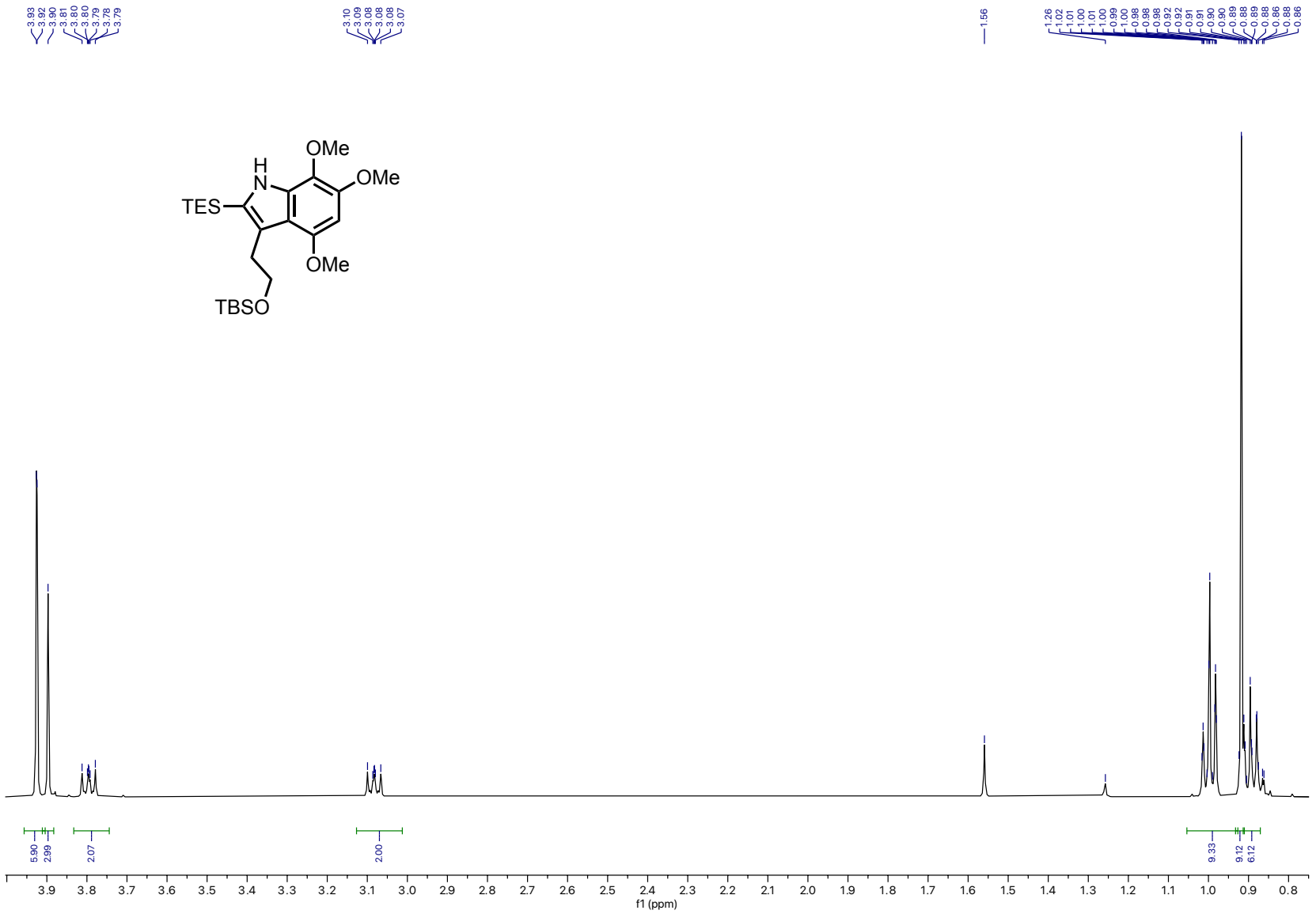


Figure S14: ^{1}H NMR (500 MHz, $CDCl_3$) for trimethoxyindole **10** (4.0-0.75 ppm inset)

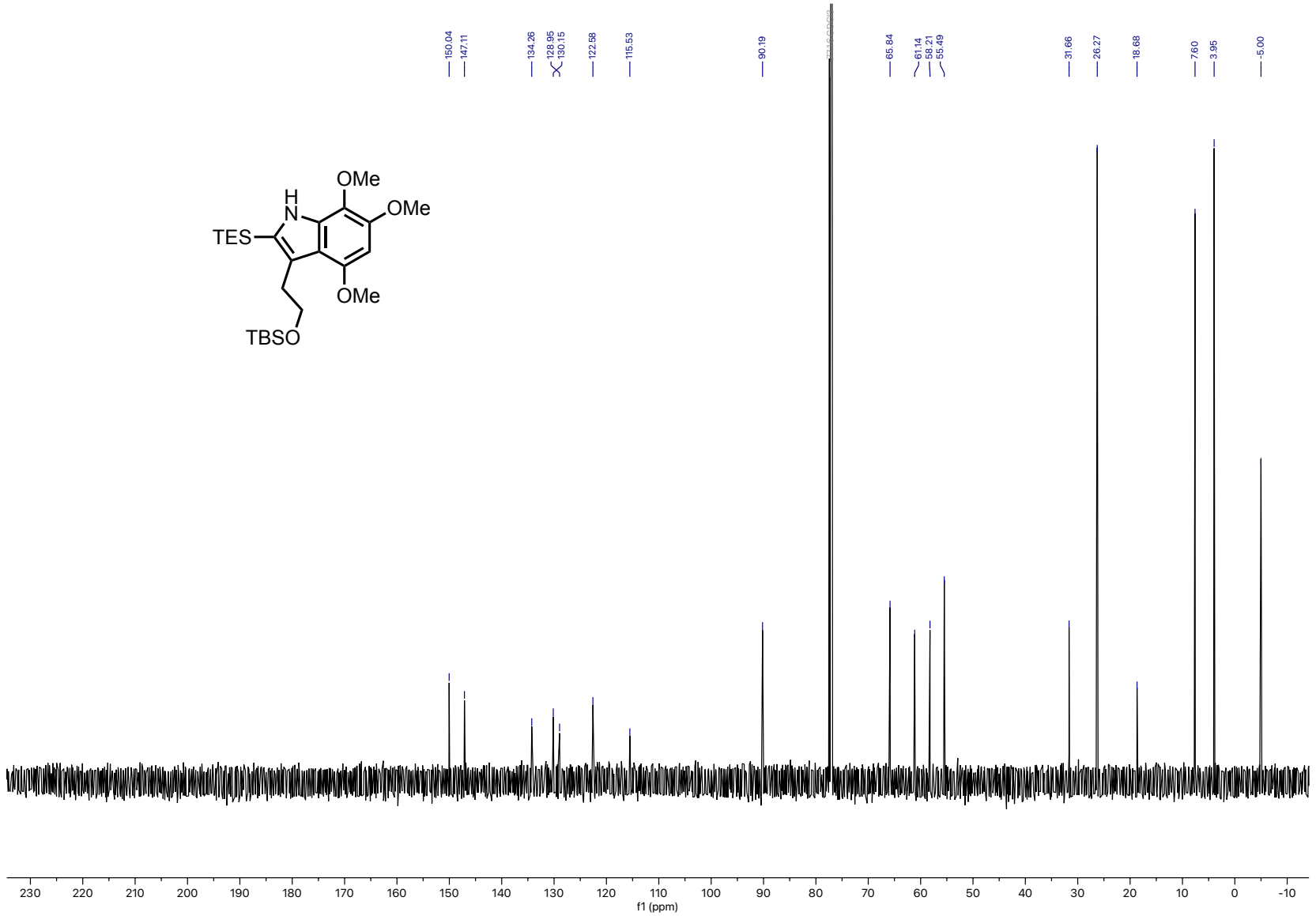


Figure S15: ^{13}C NMR (126 MHz, $CDCl_3$) for trimethoxyindole **10**

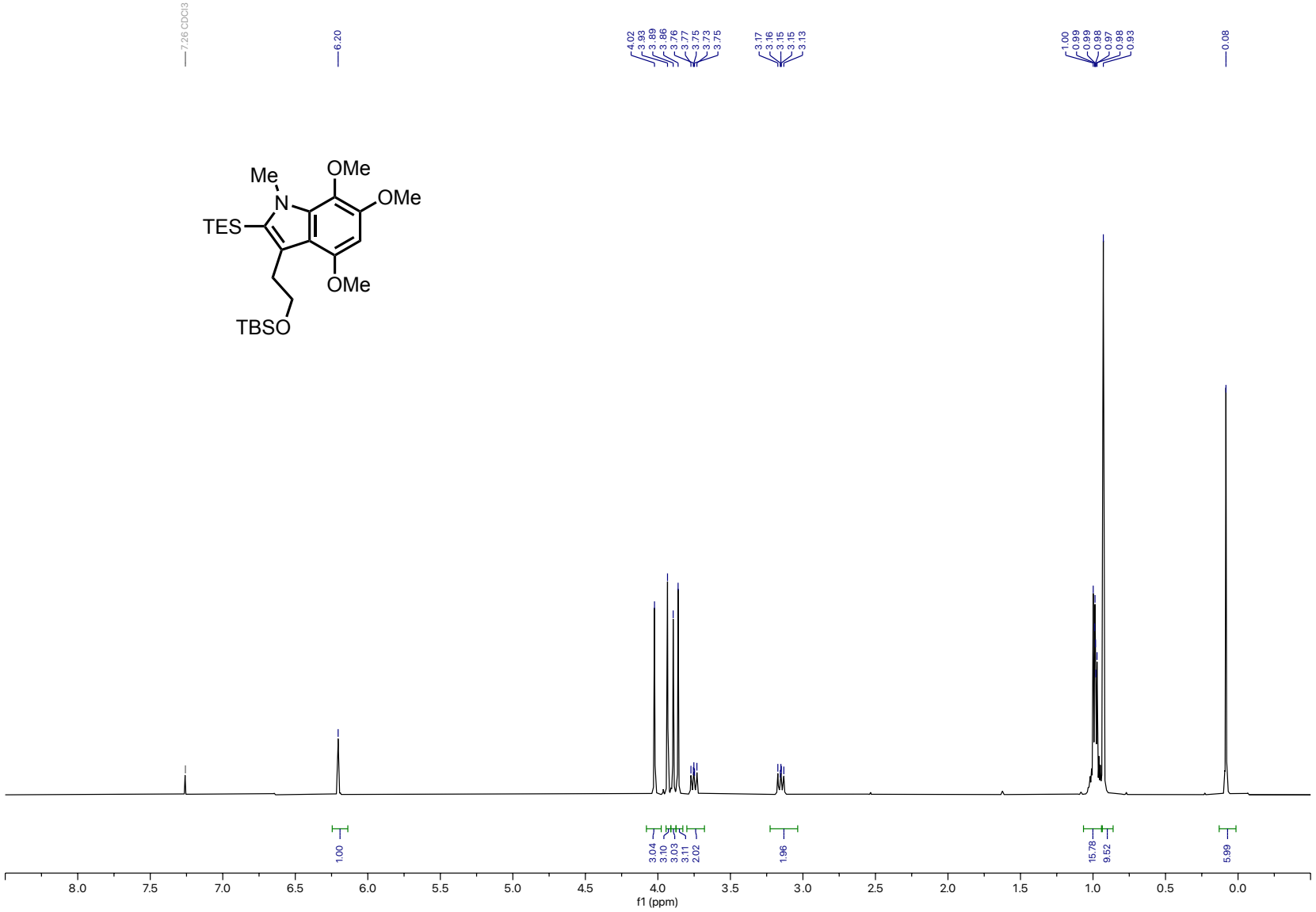


Figure S16: ^{1}H NMR (400 MHz, $CDCl_3$) for N-methylindole **19**

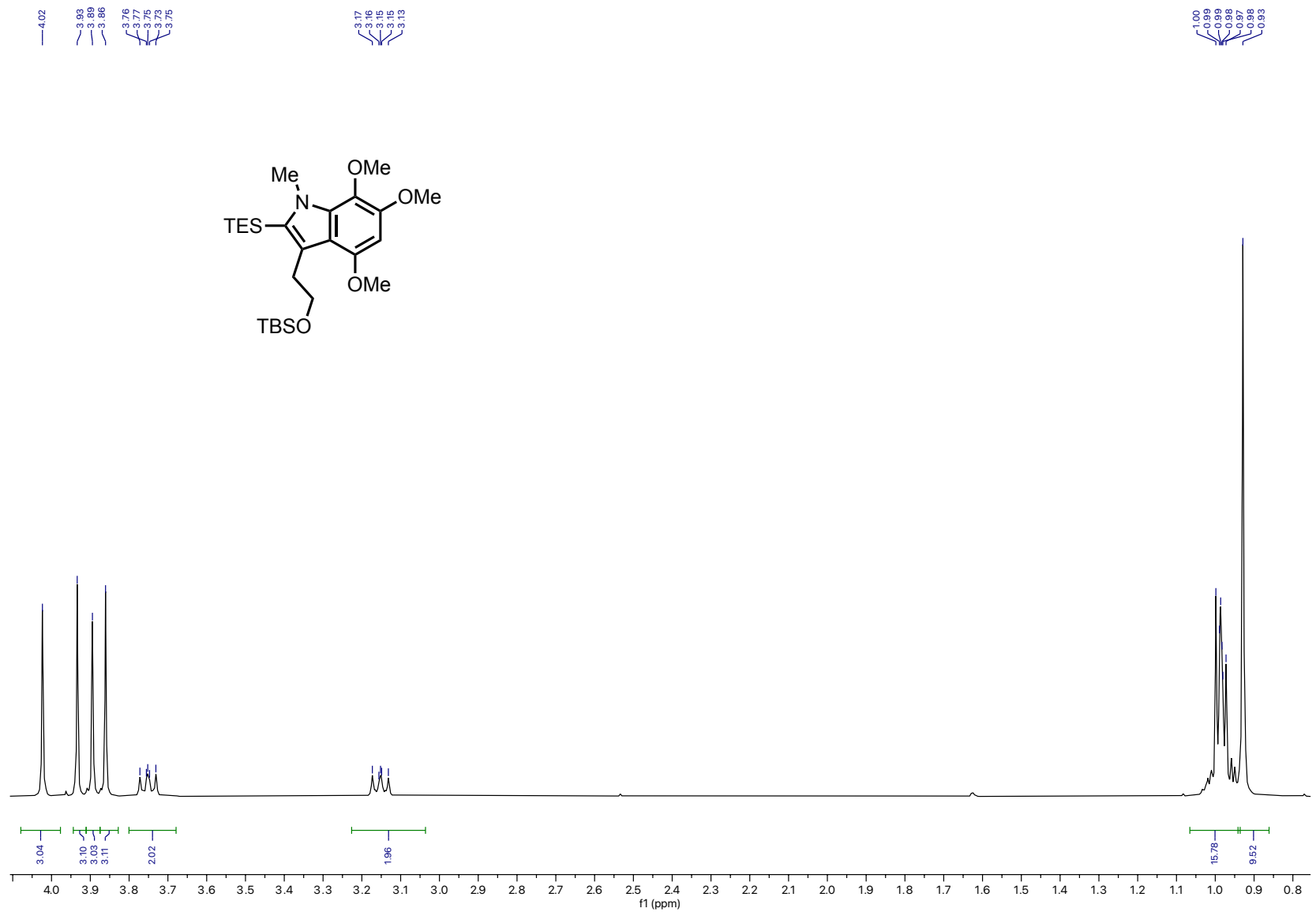


Figure S17: ^{1}H NMR (400 MHz, $CDCl_3$) for N-methylindole **19** (4.20-0.75 ppm inset)

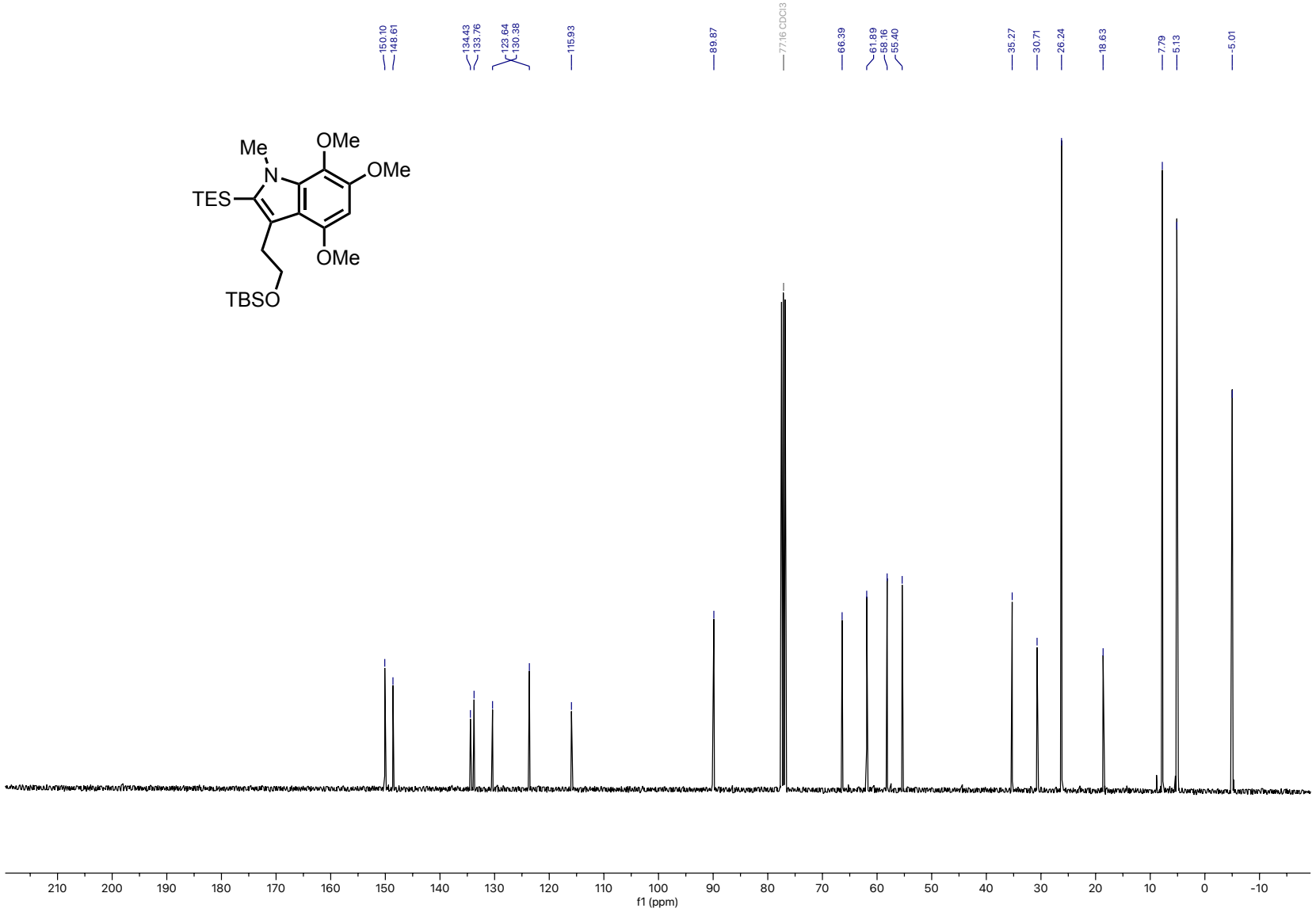


Figure S18: ^{13}C NMR (101 MHz, $CDCl_3$) for N-methylindole **19**

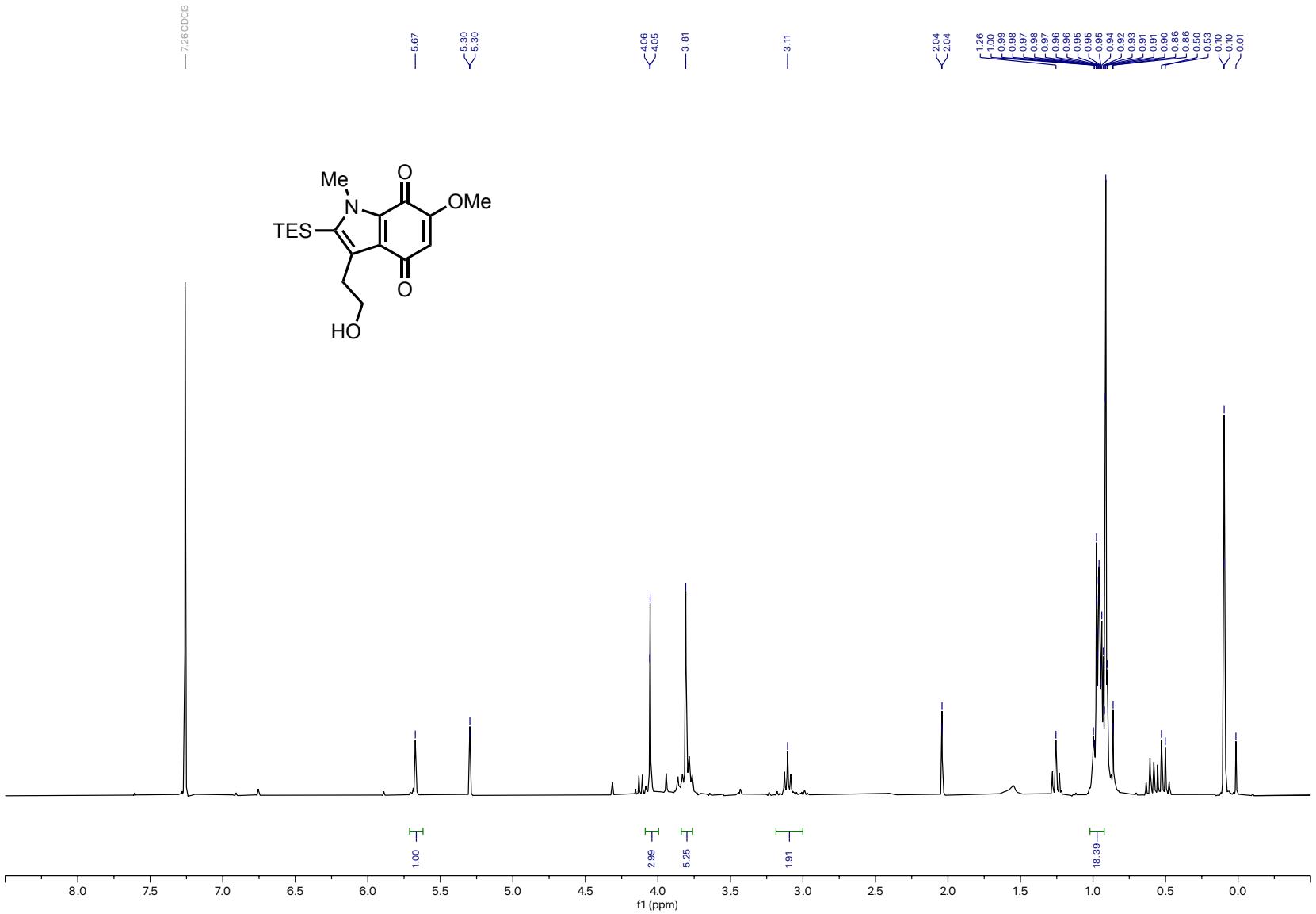


Figure S19: ^{1}H NMR (300 MHz, $CDCl_3$) for crude indoloquinone **20**

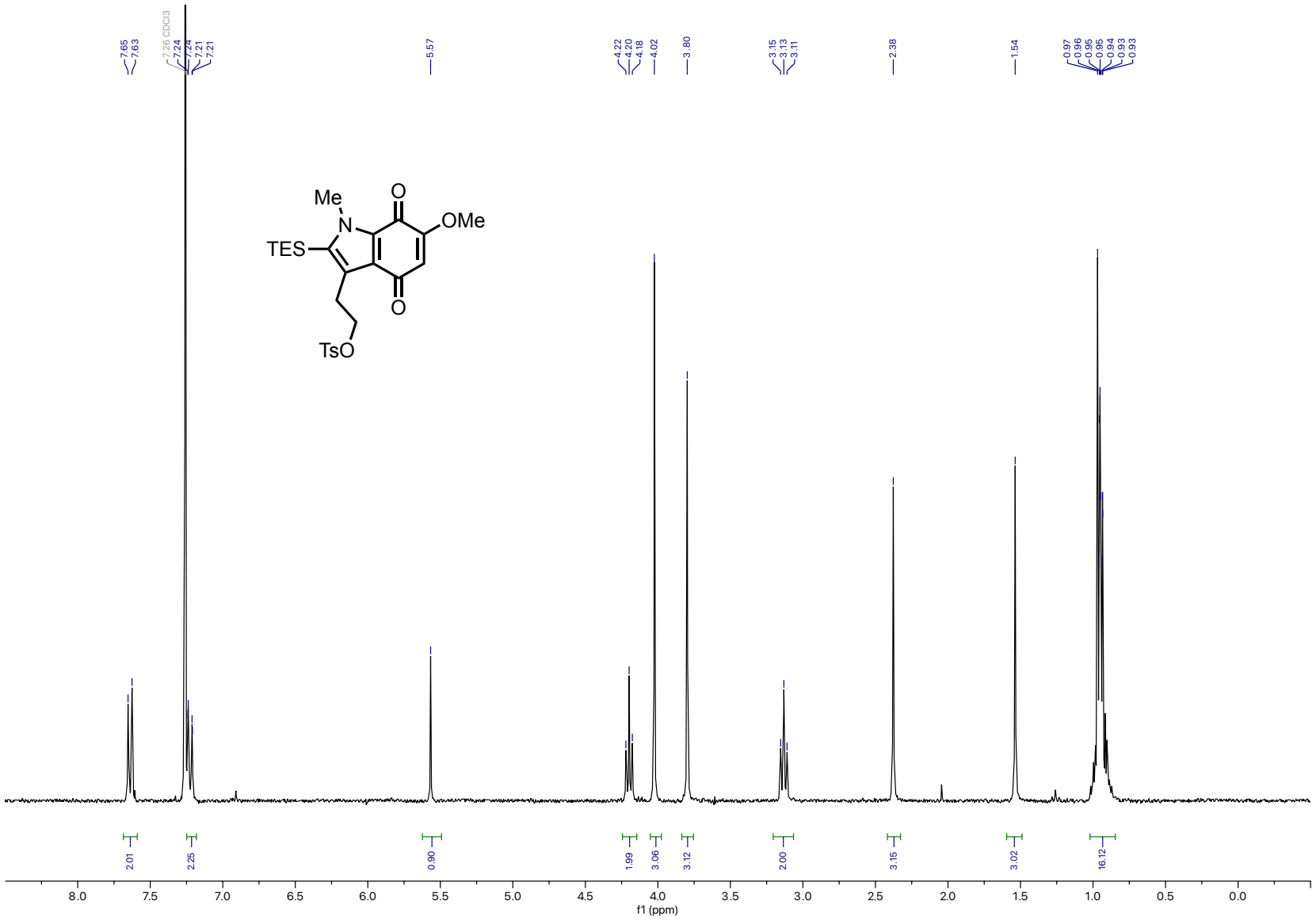


Figure S20: ^{1}H NMR (300 MHz, $CDCl_3$) for tosylate **21**

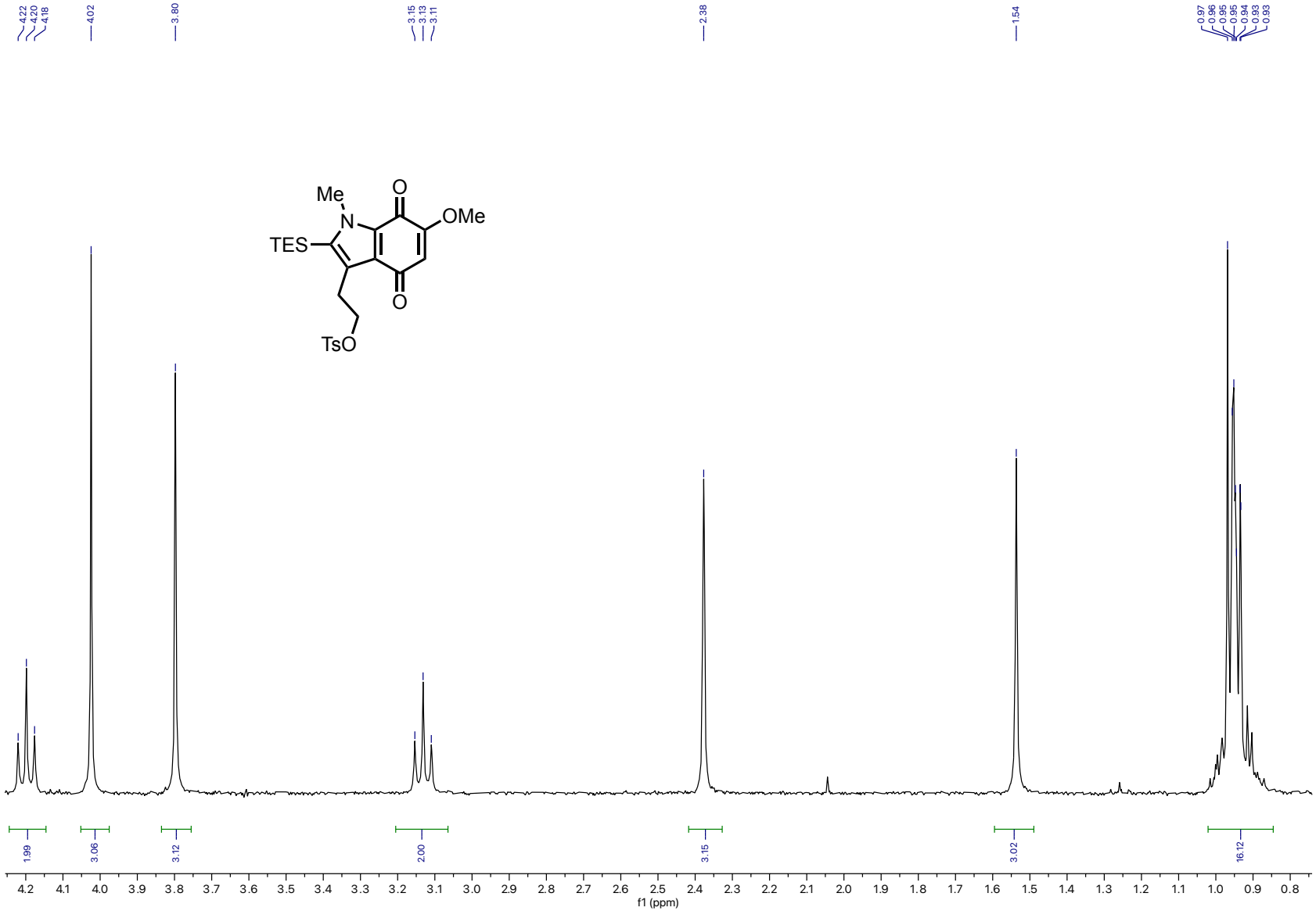


Figure S21: ^{1}H NMR (300 MHz, $CDCl_3$) for tosylate **21** (4.25-0.75 ppm inset)

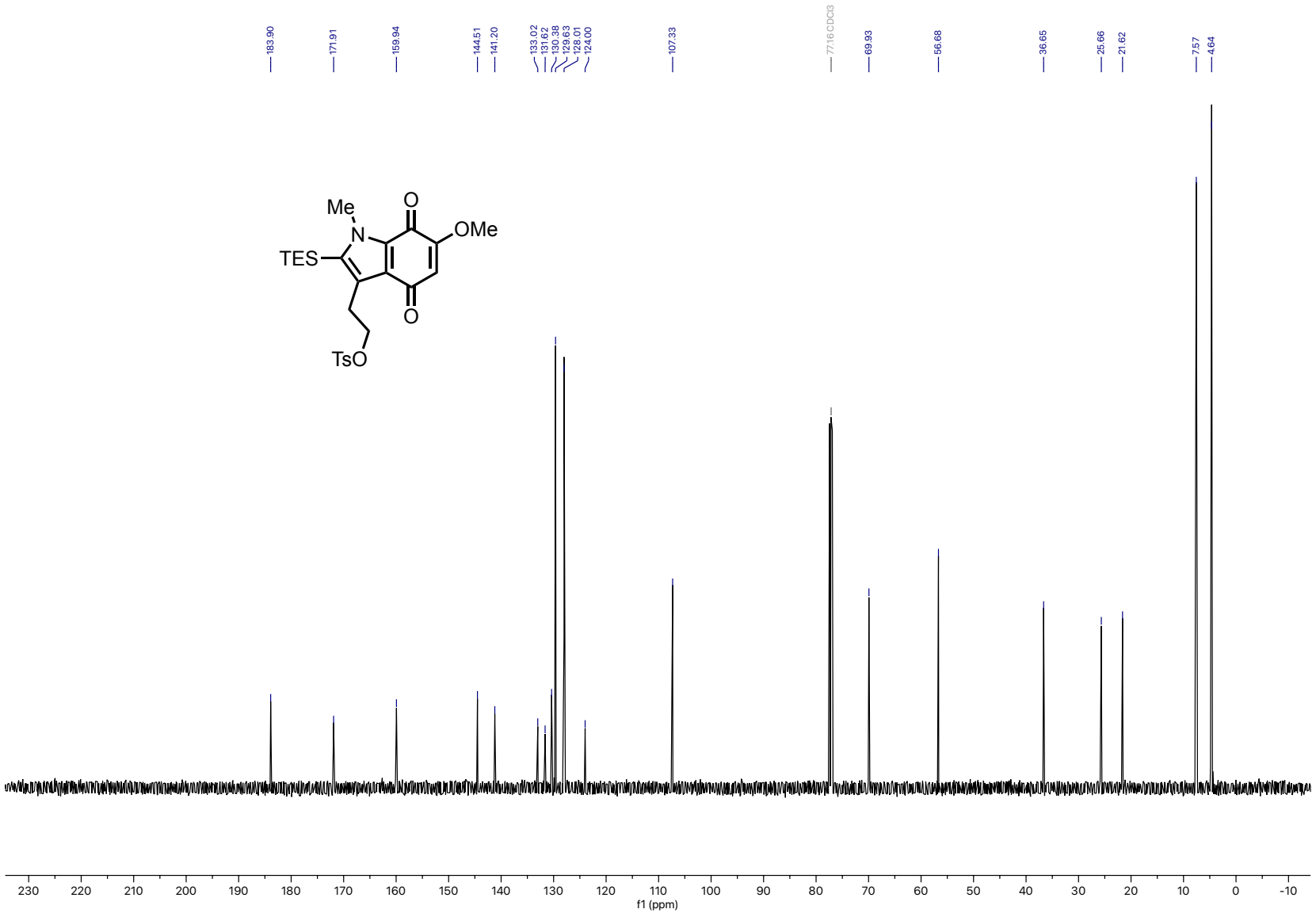


Figure S22: ^{13}C NMR (126 MHz, $CDCl_3$) for tosylate **21**

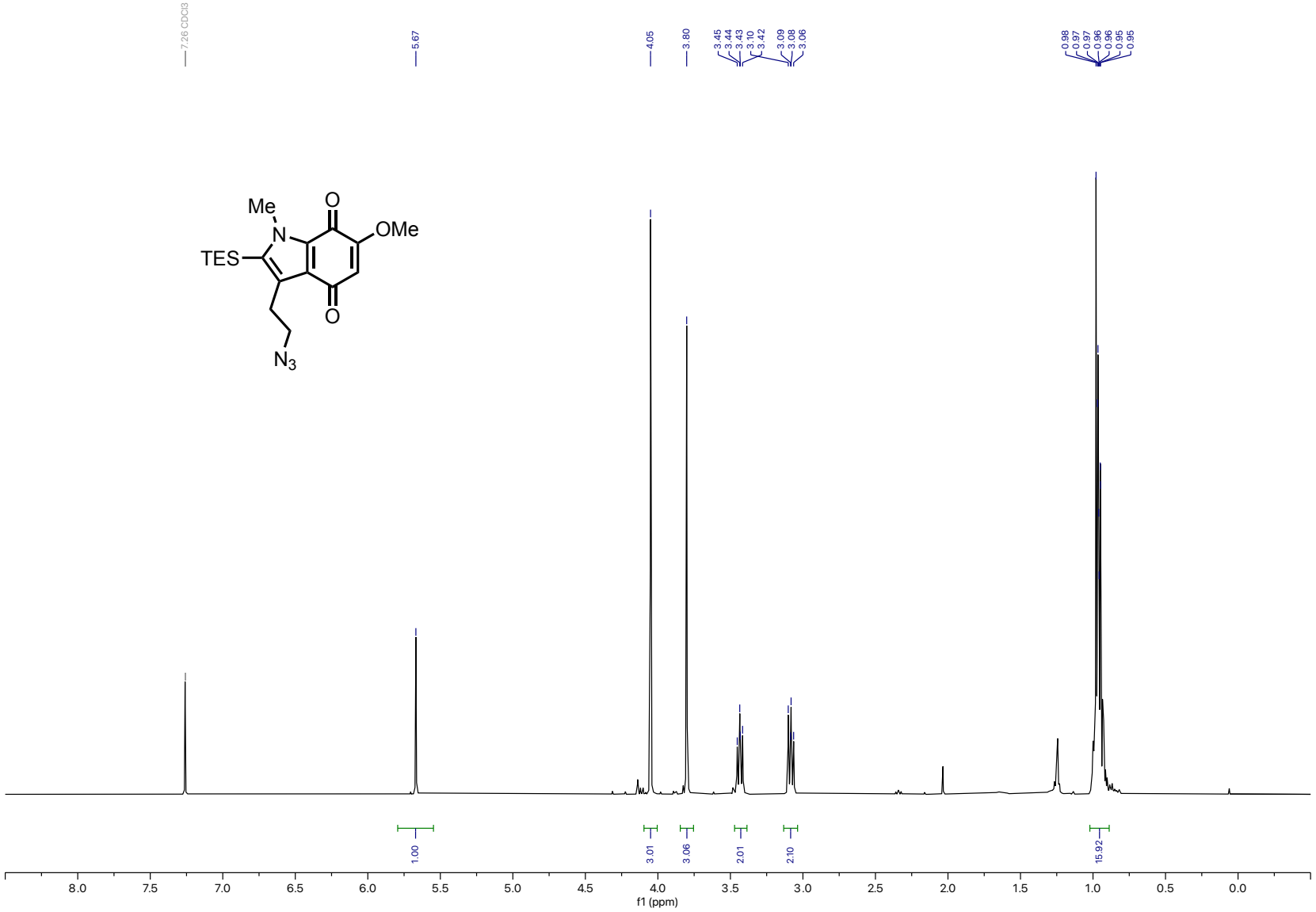


Figure S23: ^{1}H NMR (400 MHz, $CDCl_3$) for azidoinodoloquinone **9**

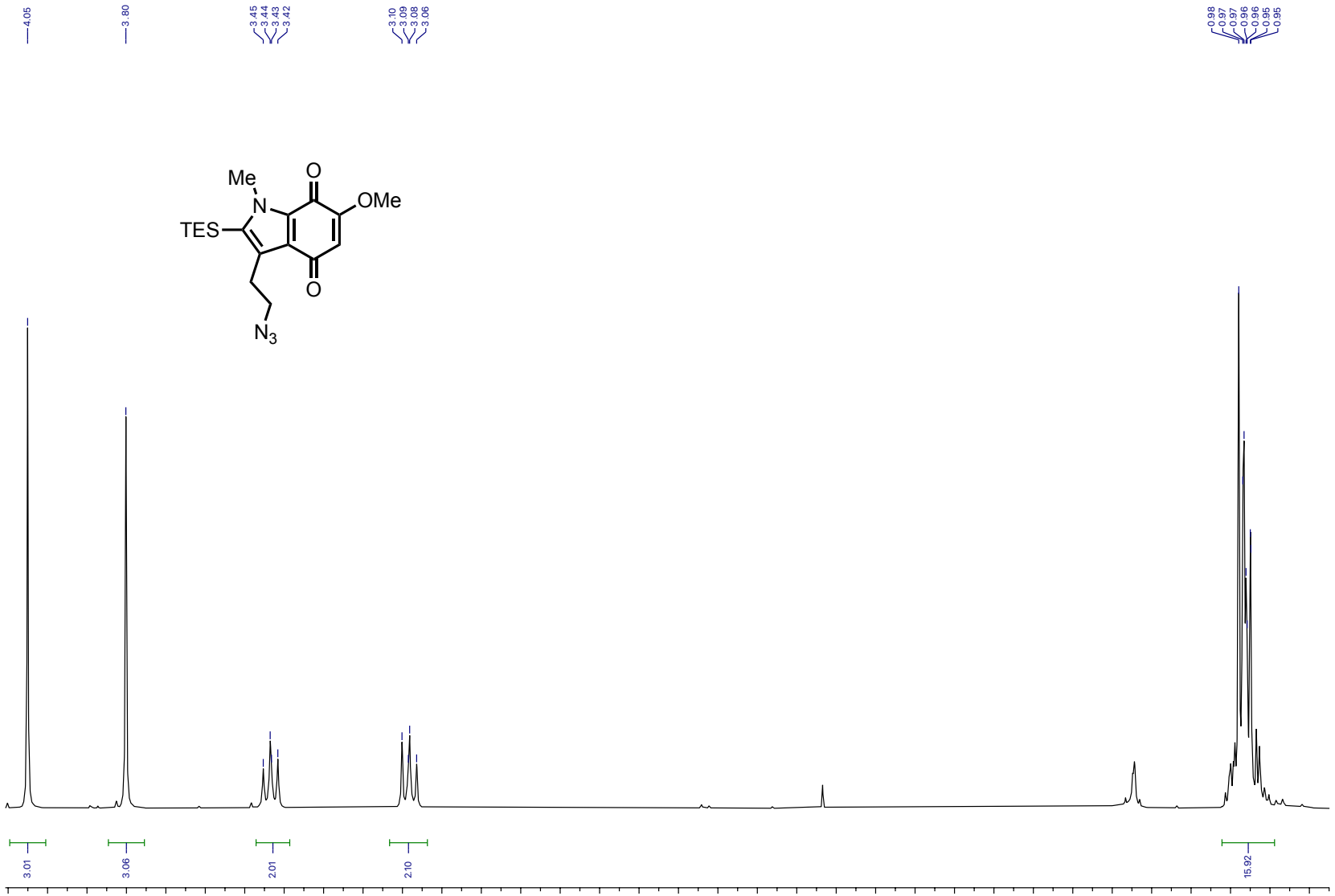


Figure S24: ^{1}H NMR (400 MHz, $CDCl_3$) for azidoindoloquinone **9** (4.10-0.75 ppm inset)

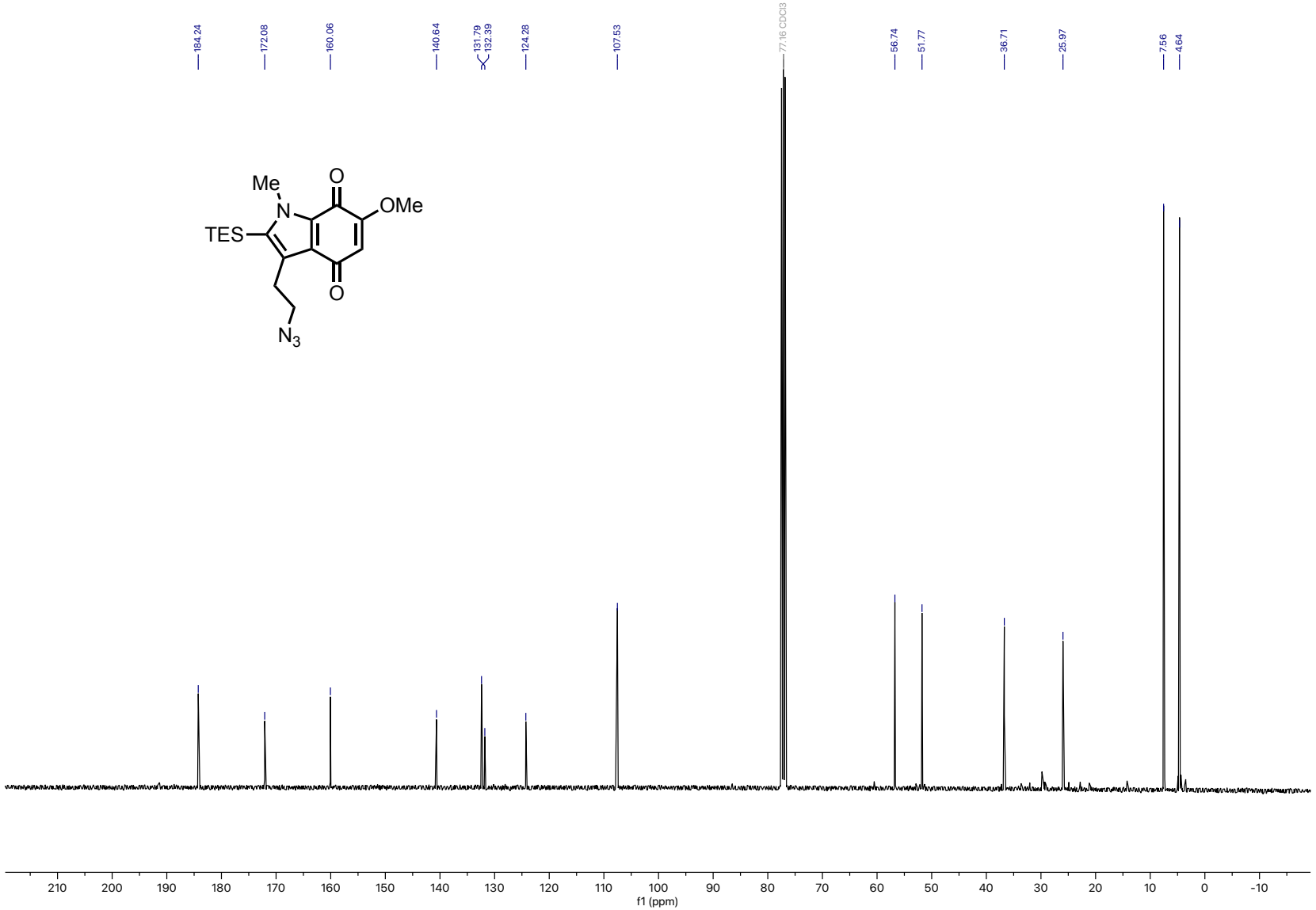


Figure S25: ^{13}C NMR (101 MHz, $CDCl_3$) for azidoindoloquinone **9**

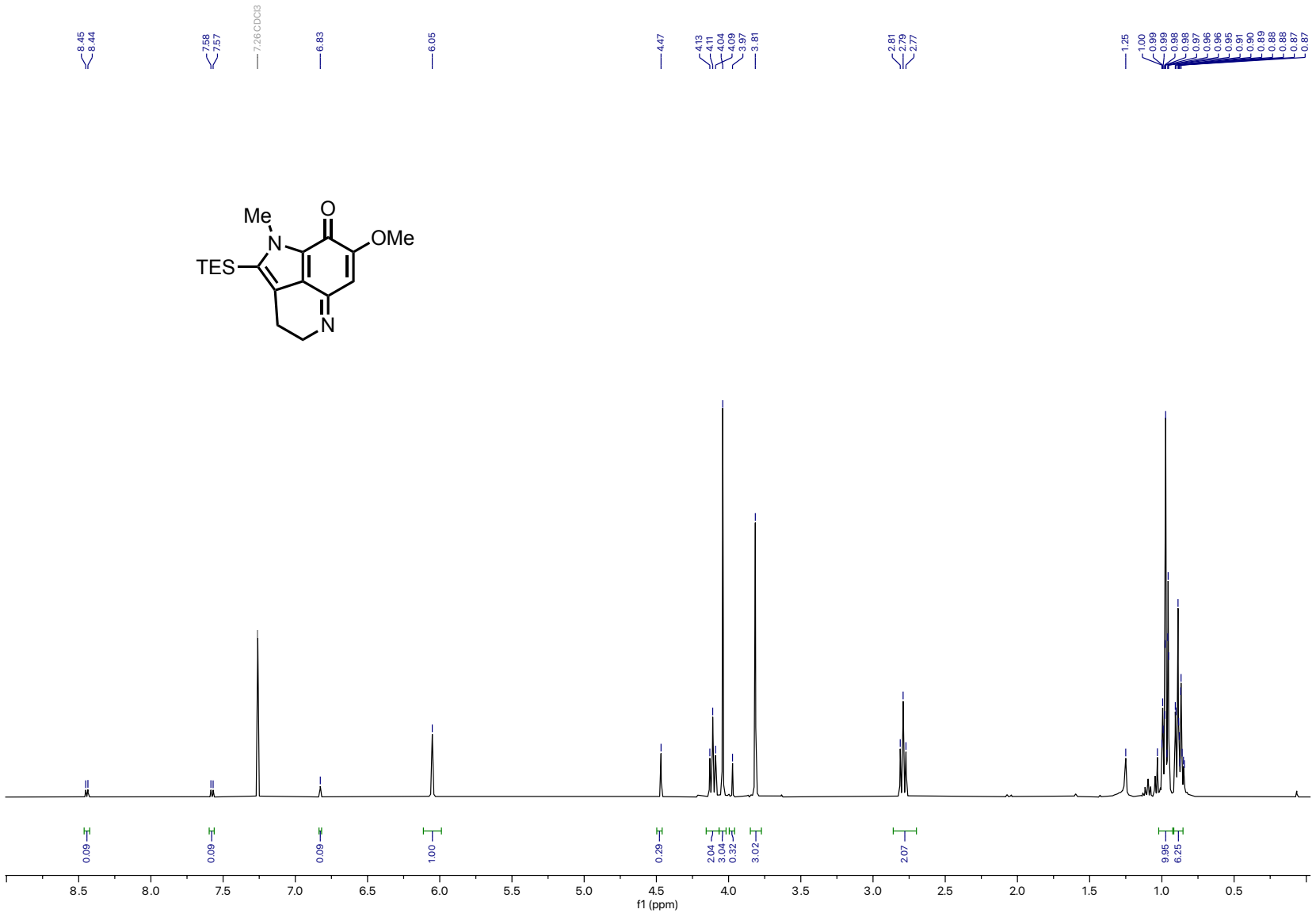


Figure S26: ^{1}H NMR (400 MHz, $CDCl_3$) for vinylogous imidate **6b**

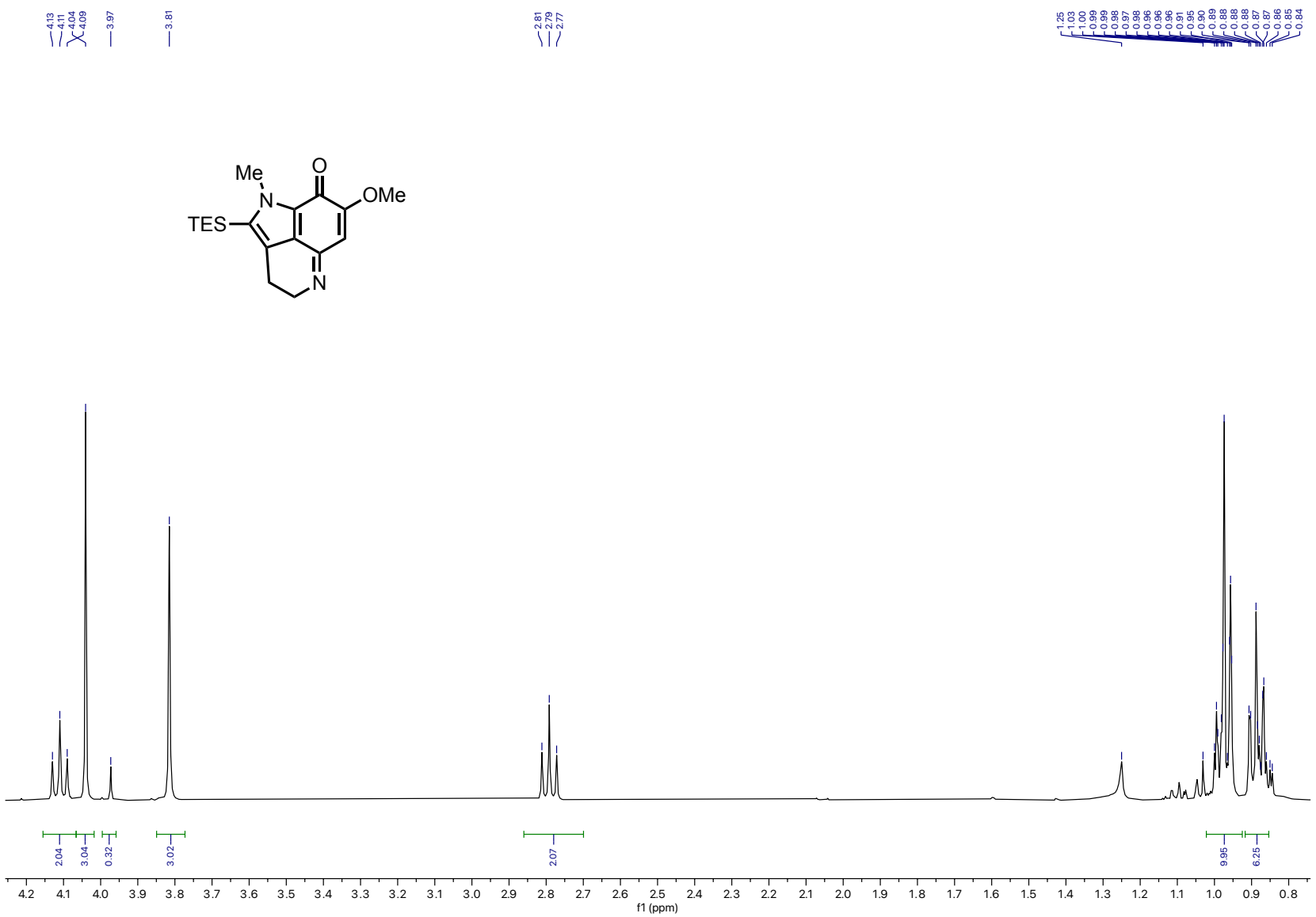


Figure S27: ^{1}H NMR (400 MHz, $CDCl_3$) for vinylogous imidate **6b** (4.25-0.75 ppm inset)

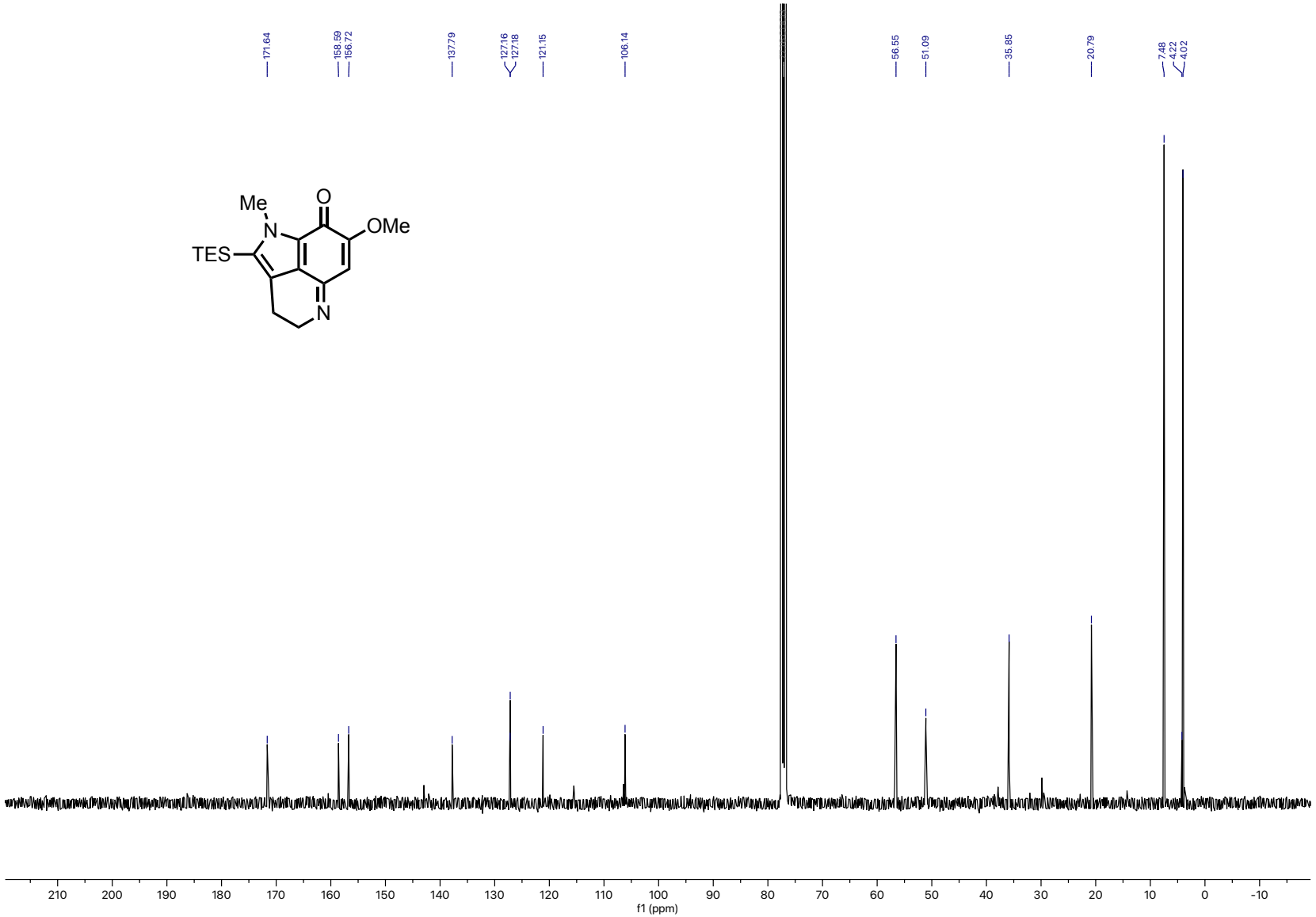


Figure S28: ^{13}C NMR (101 MHz, $CDCl_3$) for vinylogous imidate **6b**

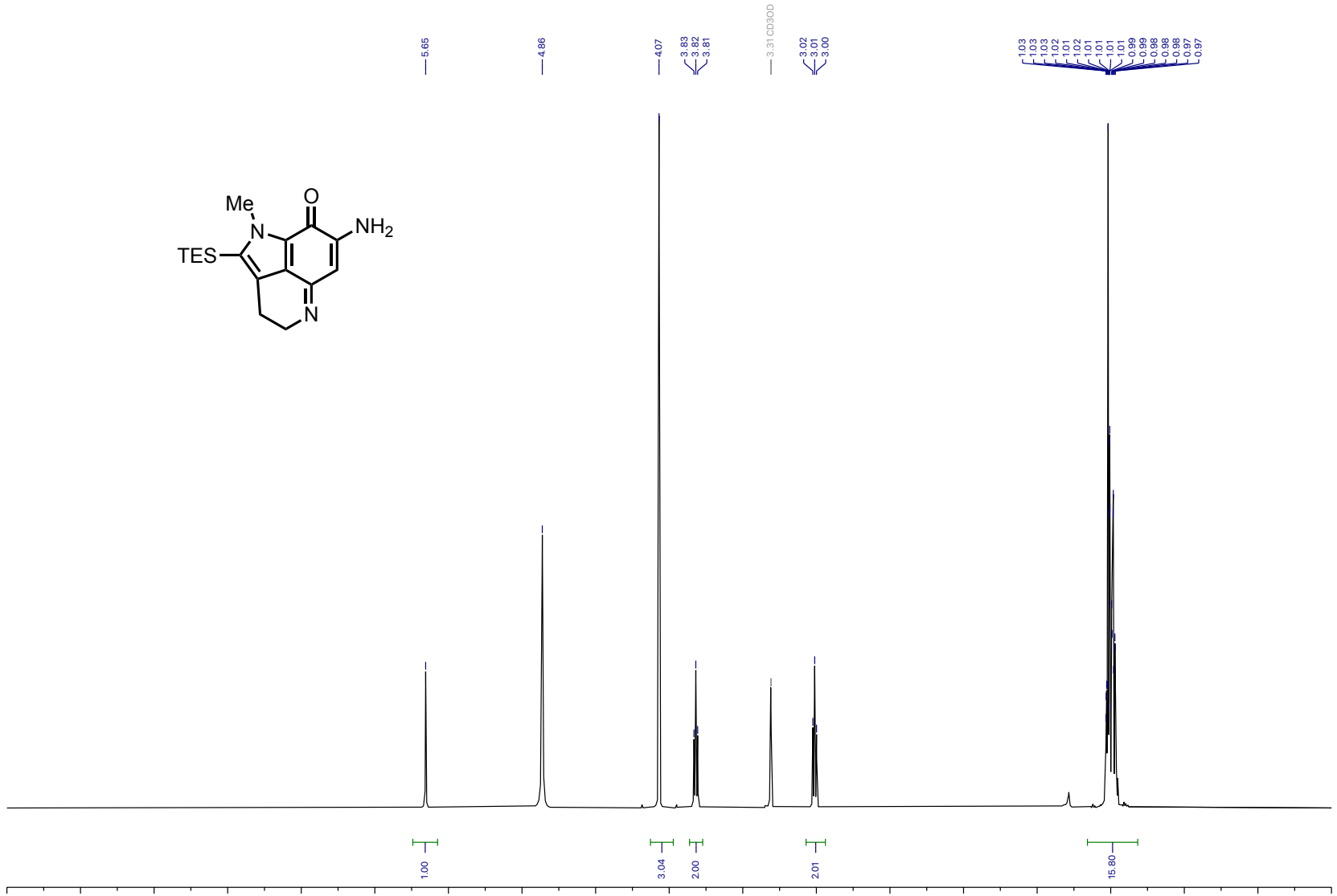


Figure S29: ^{1}H NMR (600 MHz, CD_3OD) for vinylogous amidine **22**

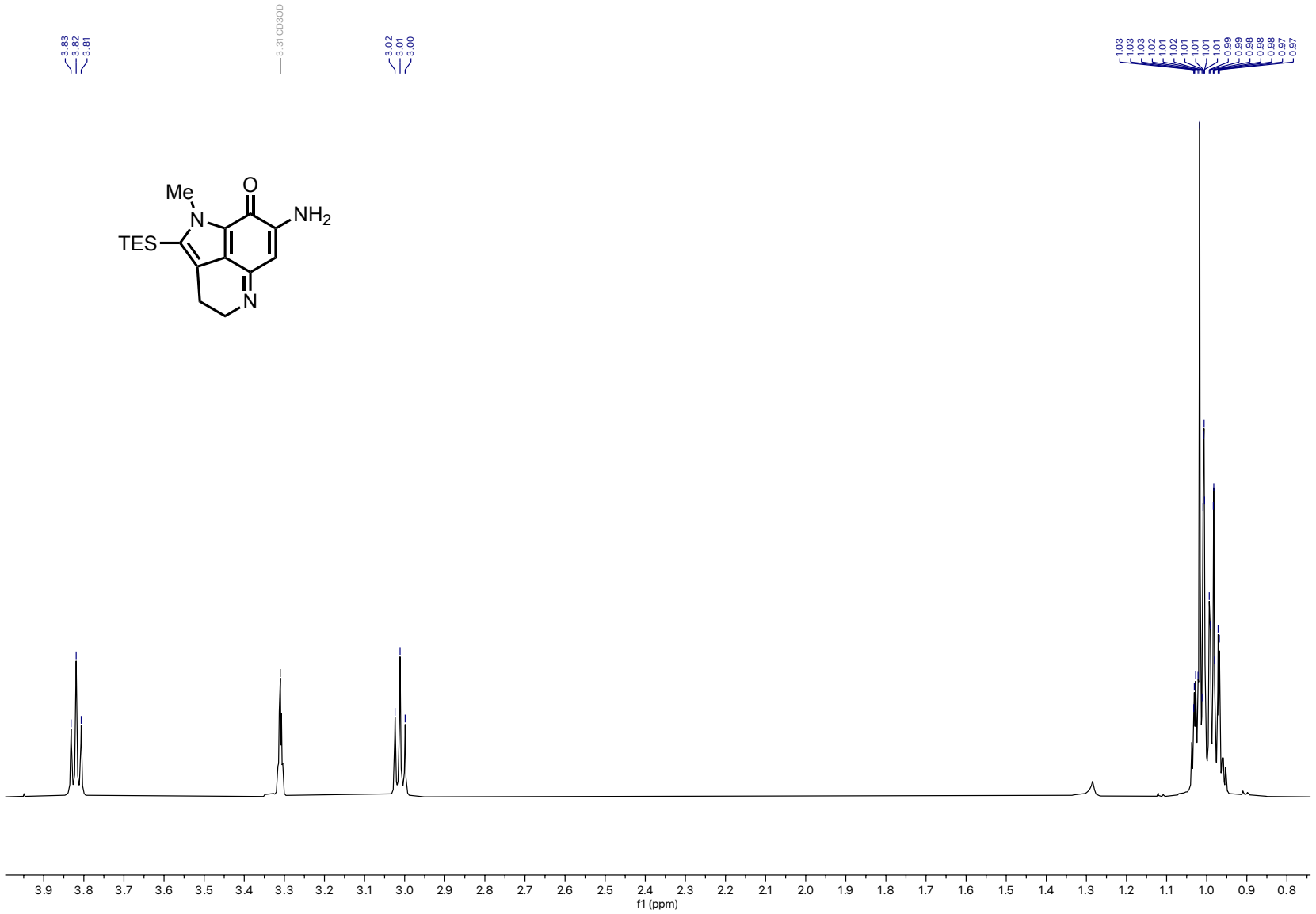


Figure S30: ^{1}H NMR (600 MHz, CD_3OD) for vinylogous amidine **22** (4.0-0.75 ppm inset)

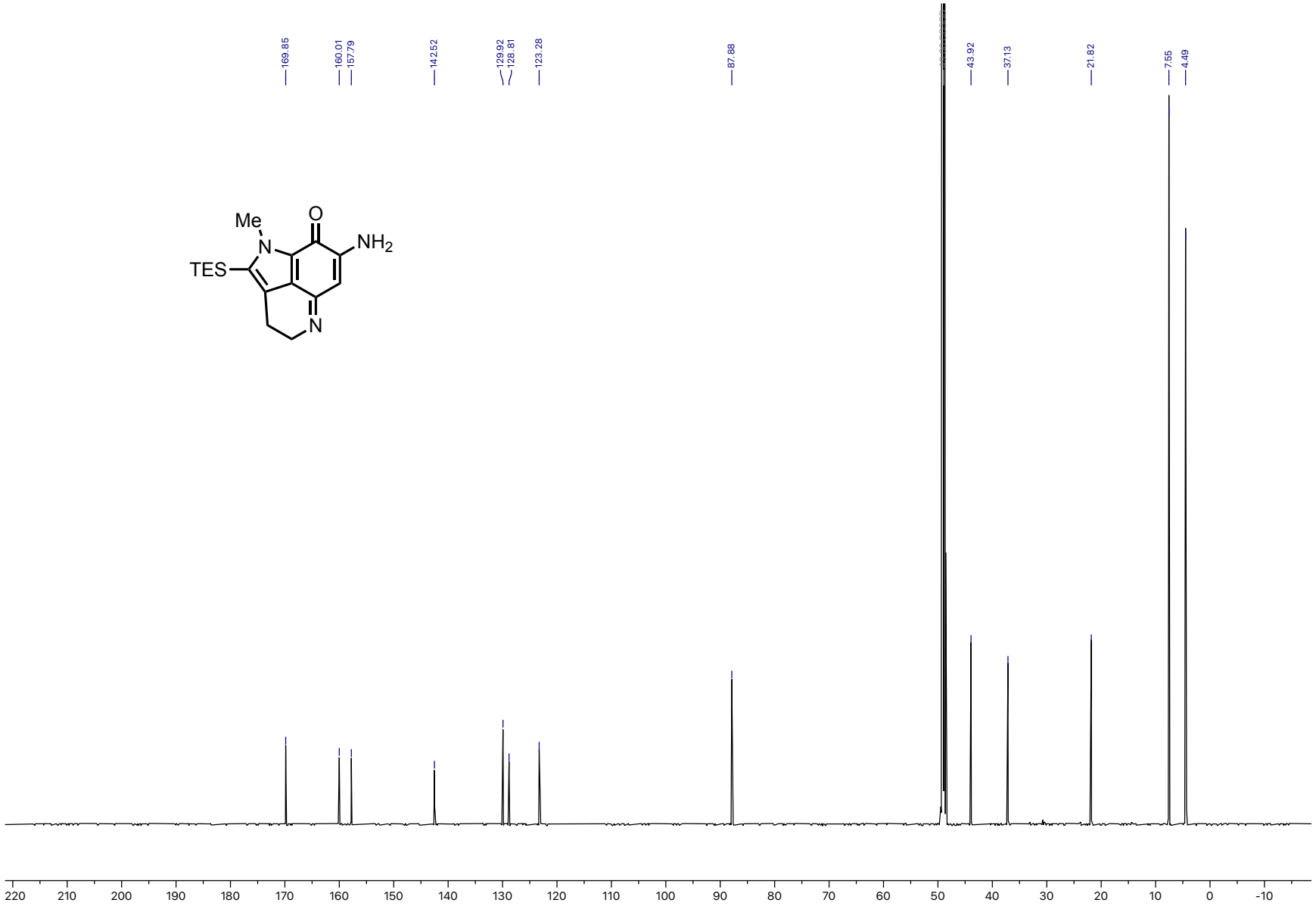


Figure S31: ^{13}C NMR (151 MHz, CD_3OD) for vinylogous amidine **22**

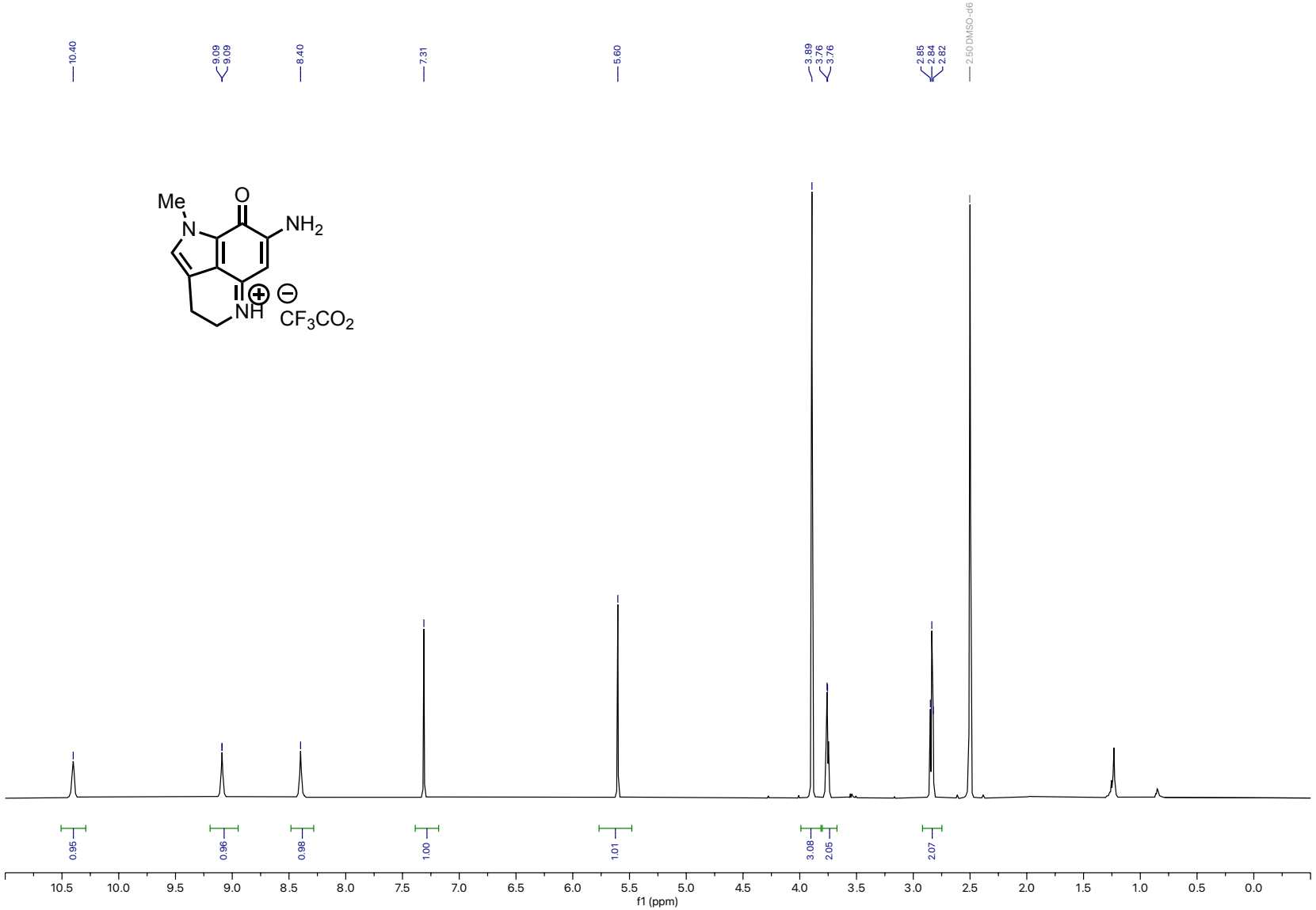


Figure S32: ^{1}H NMR (600 MHz, DMSO-d6) for makaluvamine A trifluoroacetate **(1)**

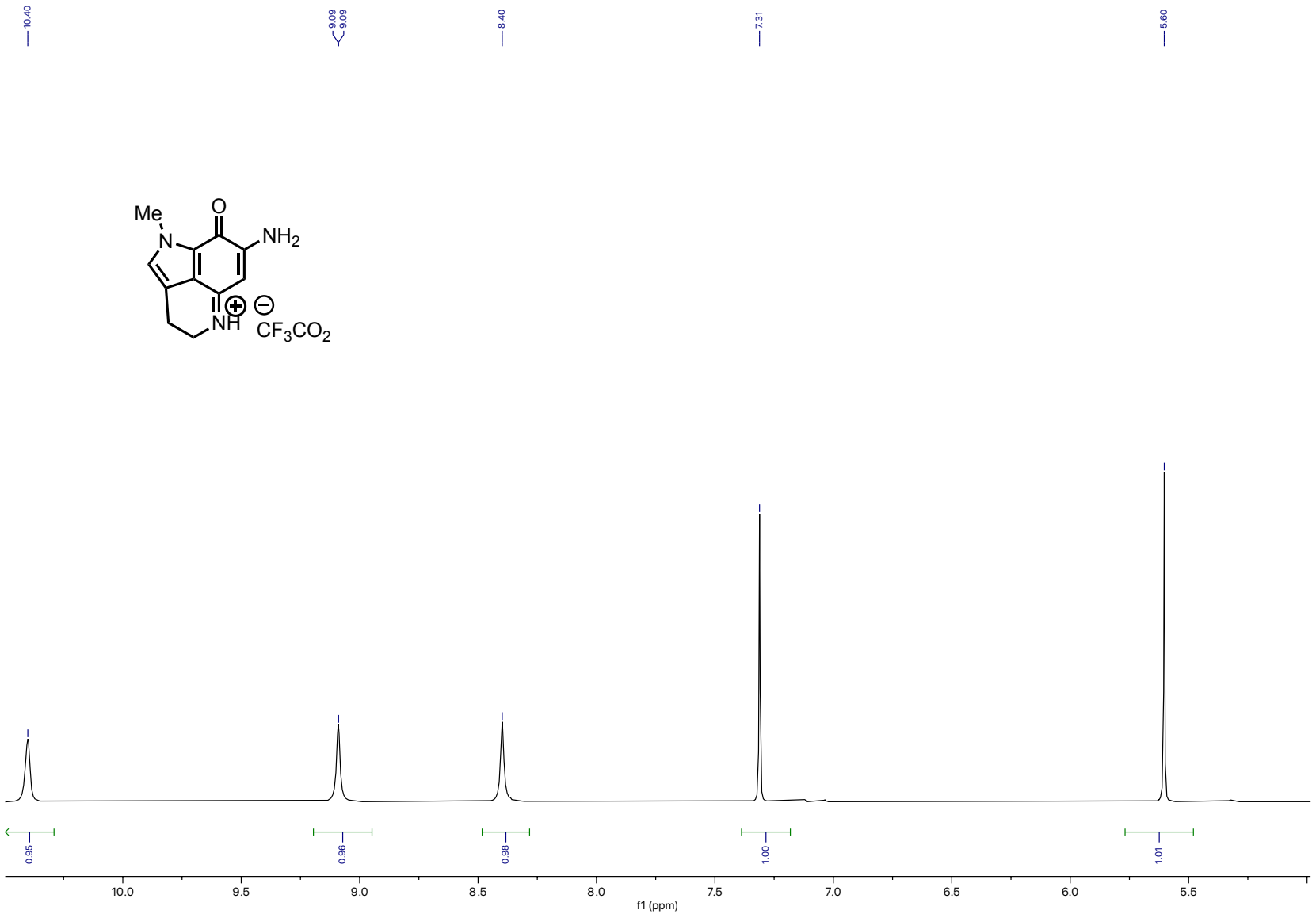


Figure S33: [1]H NMR (600 MHz, DMSO-d6) for makaluvamine A trifluoroacetate **(1)** (10.5-5.0 ppm inset)

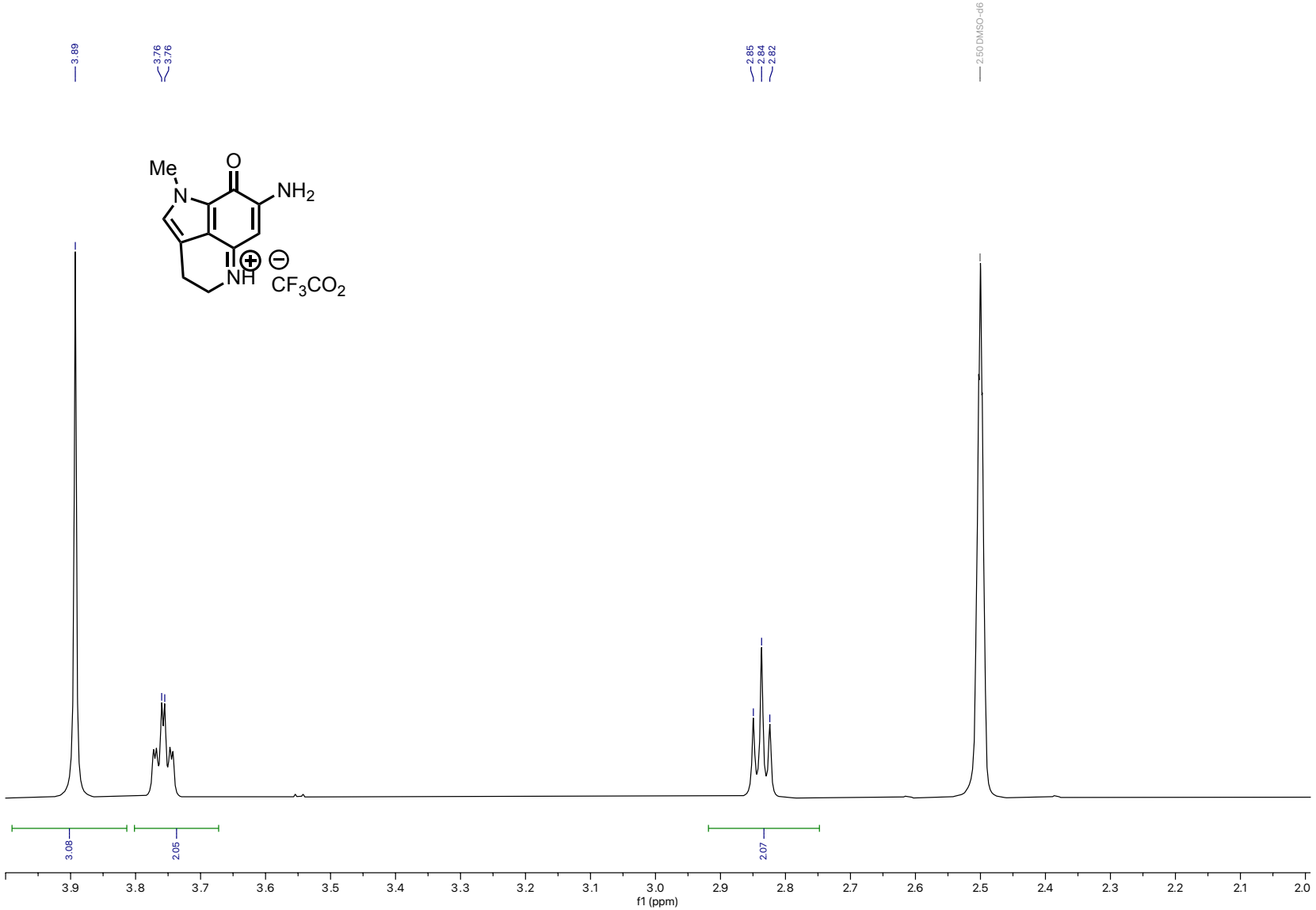


Figure S34: ^{1}H NMR (600 MHz, DMSO-d6) for makaluvamine A trifluoroacetate **(1)** (4.0-2.0 ppm inset)

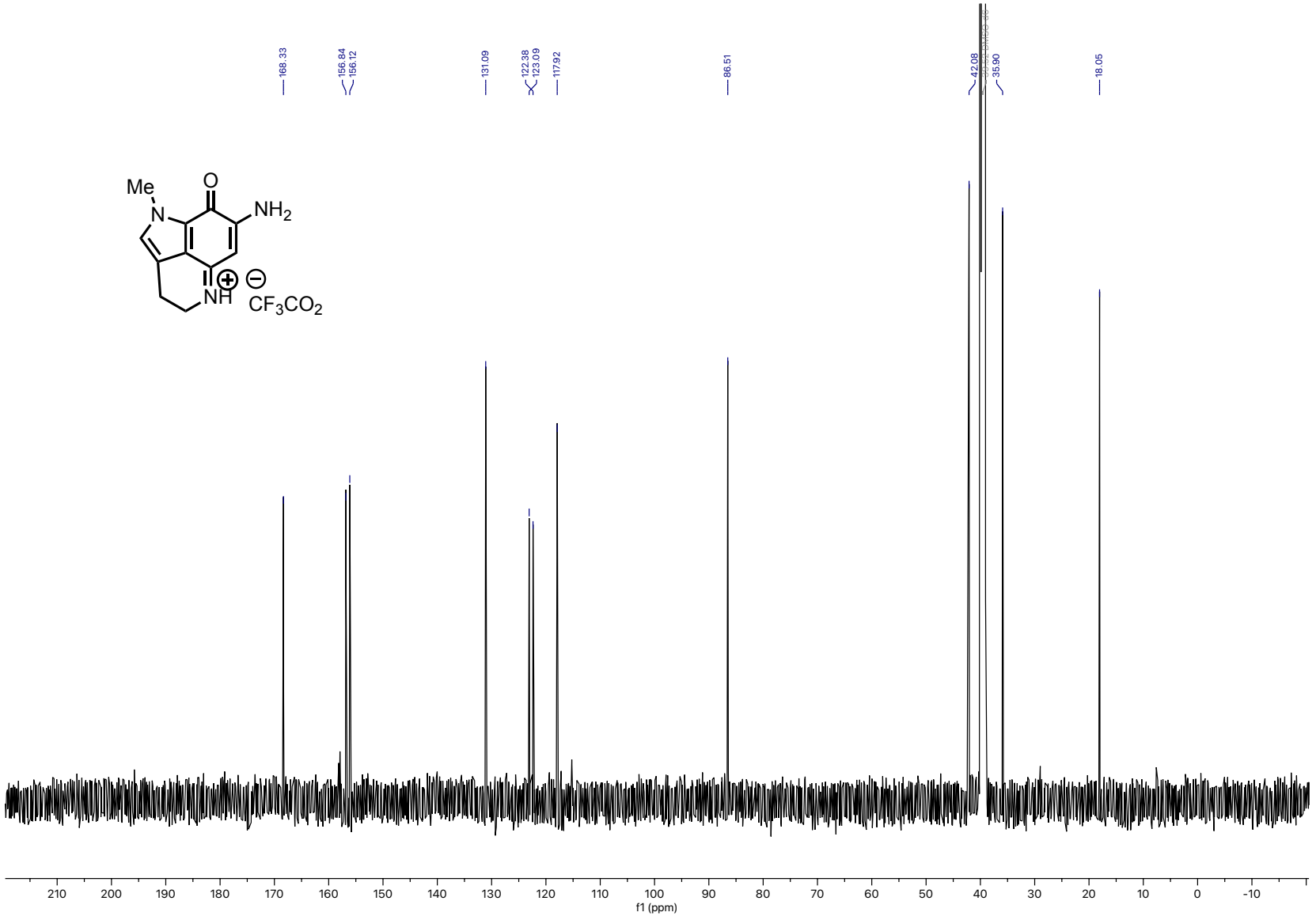


Figure S35: ^{13}C NMR (151 MHz, DMSO-d6) for makaluvamine A trifluoroacetate **(1)**

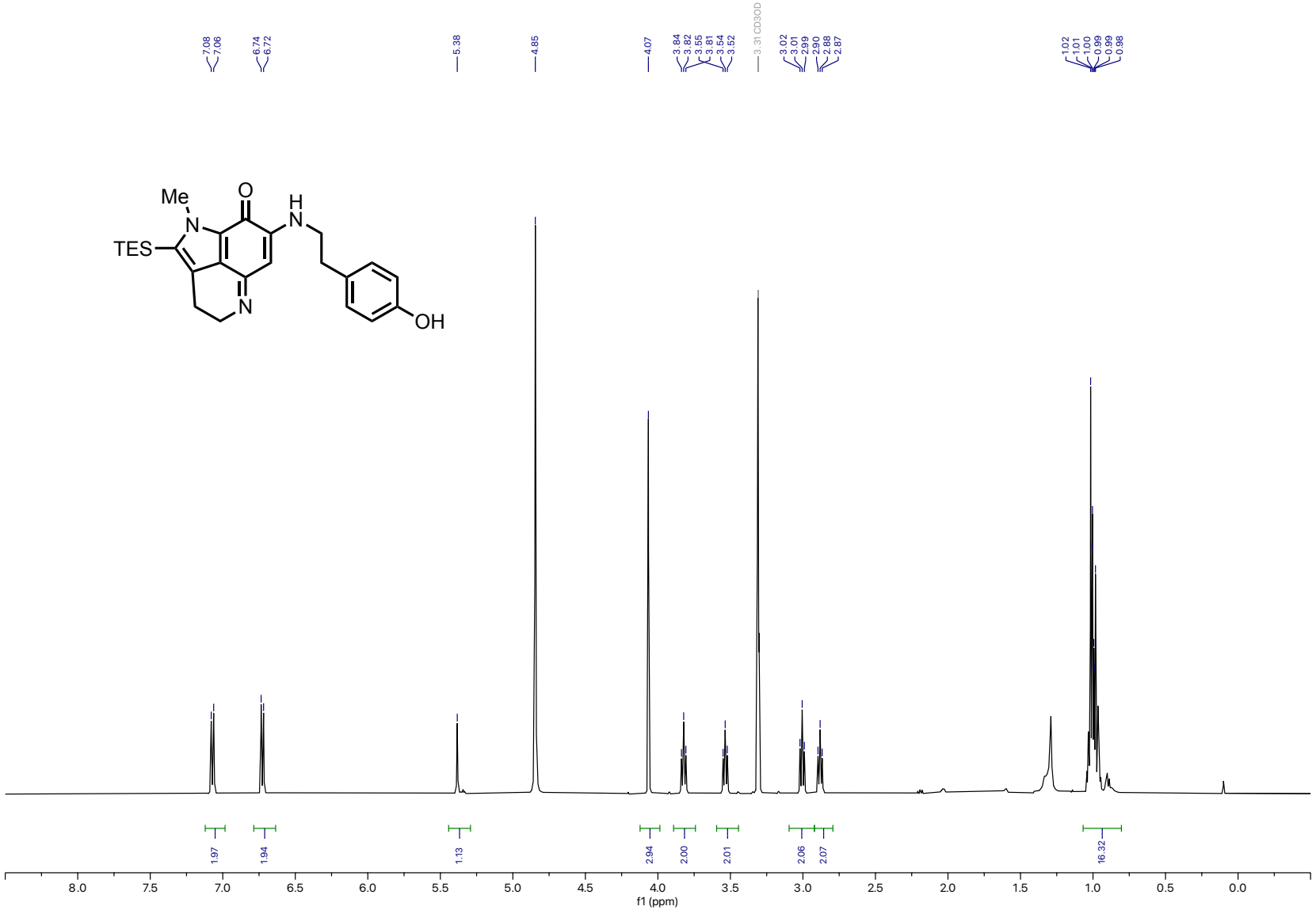


Figure S36: ^{1}H NMR (500 MHz, CD_3OD) for secondary vinylogous amidine **23**

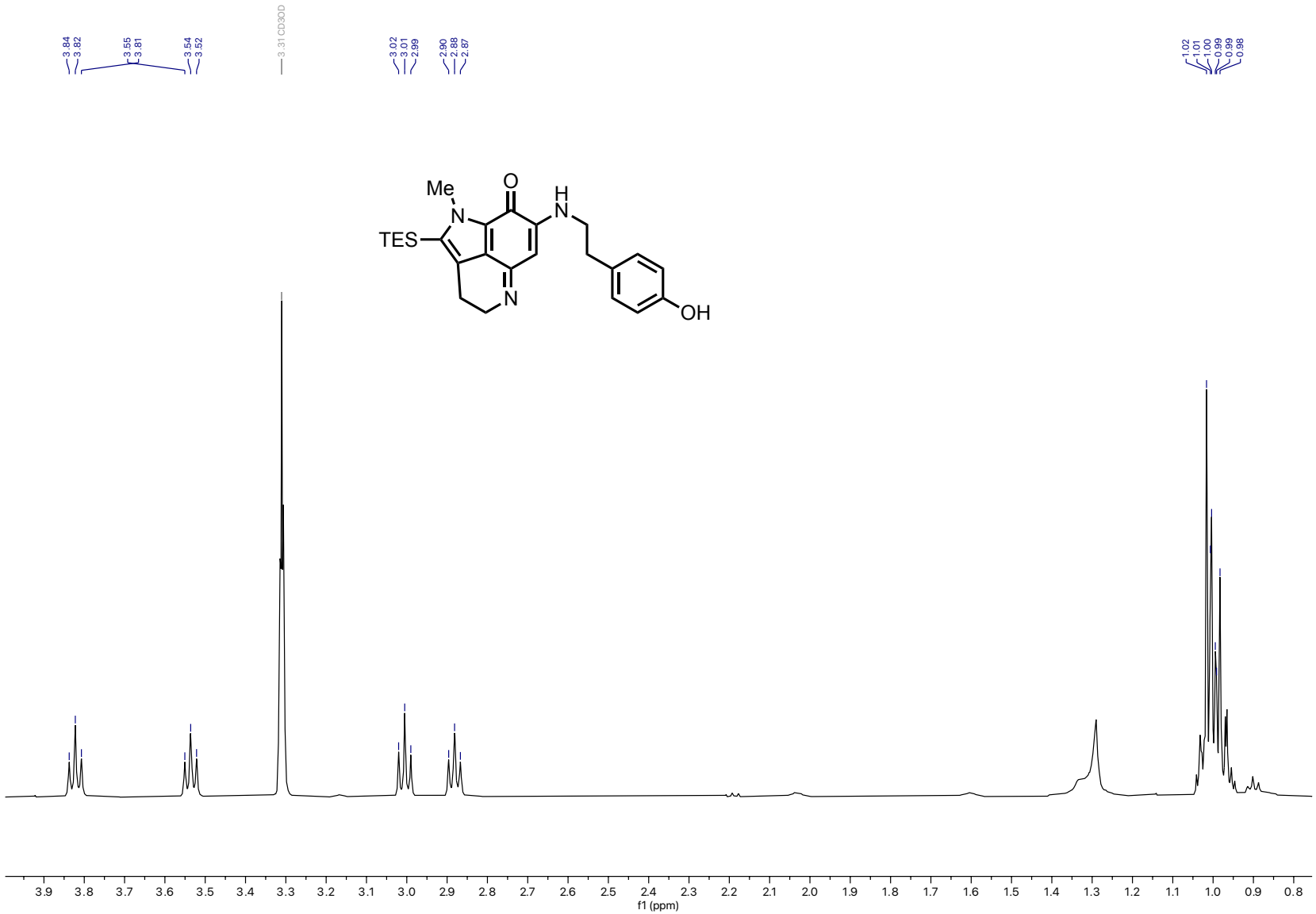


Figure S37: ^{1}H NMR (500 MHz, CD_3OD) for secondary vinylogous amidine **23** (4.0- 0.75 ppm inset)

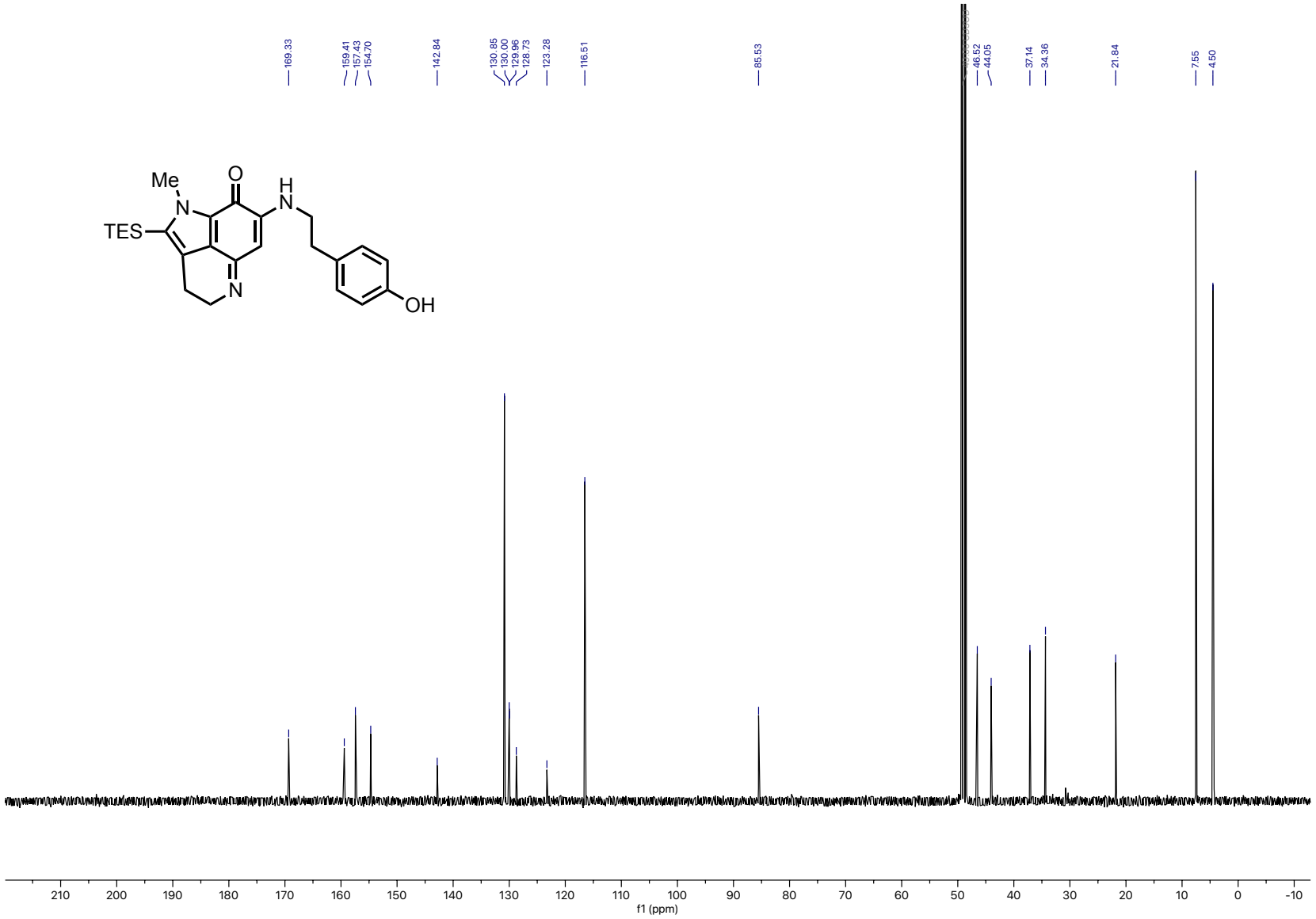


Figure S38: ^{13}C NMR (126 MHz, CD_3OD) for secondary vinylogous amidine **23**

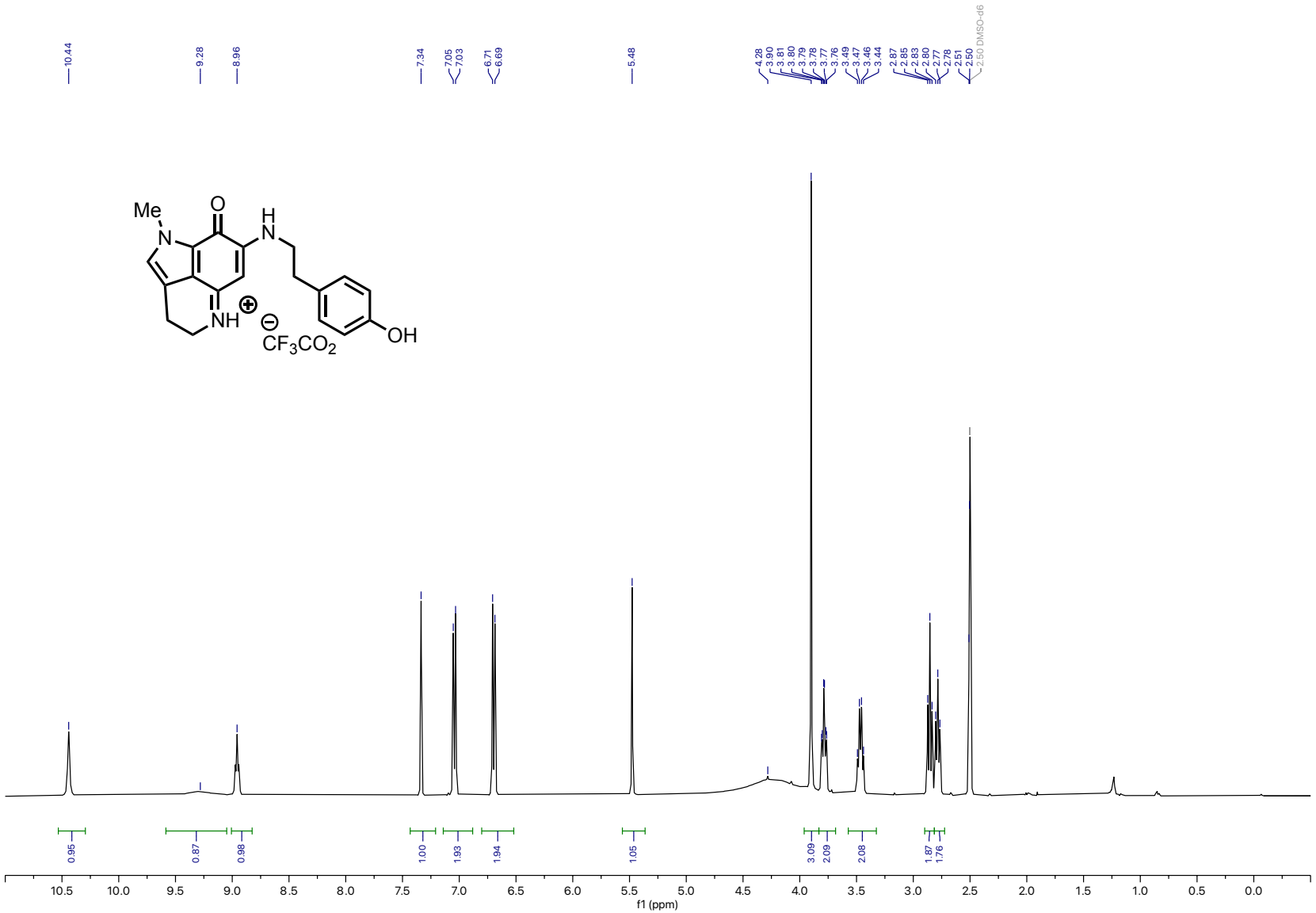


Figure S39: ^{1}H NMR (500 MHz, DMSO-d6) for makaluvamine K trifluoroacetate **(4)**

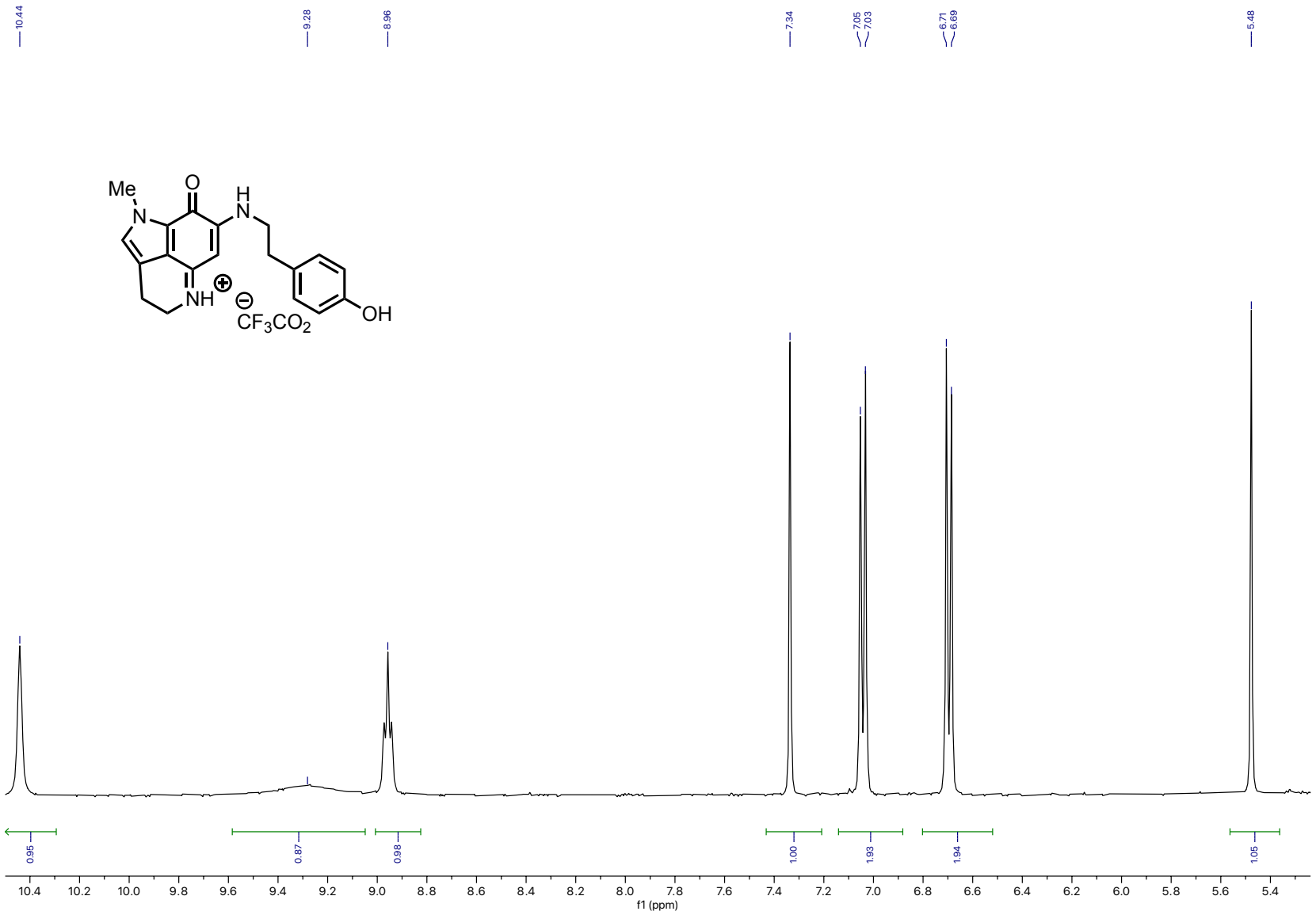


Figure S40: ^{1}H NMR (500 MHz, DMSO-d6) for makaluvamine K trifluoroacetate **(4)** (10.5-5.25 ppm inset)

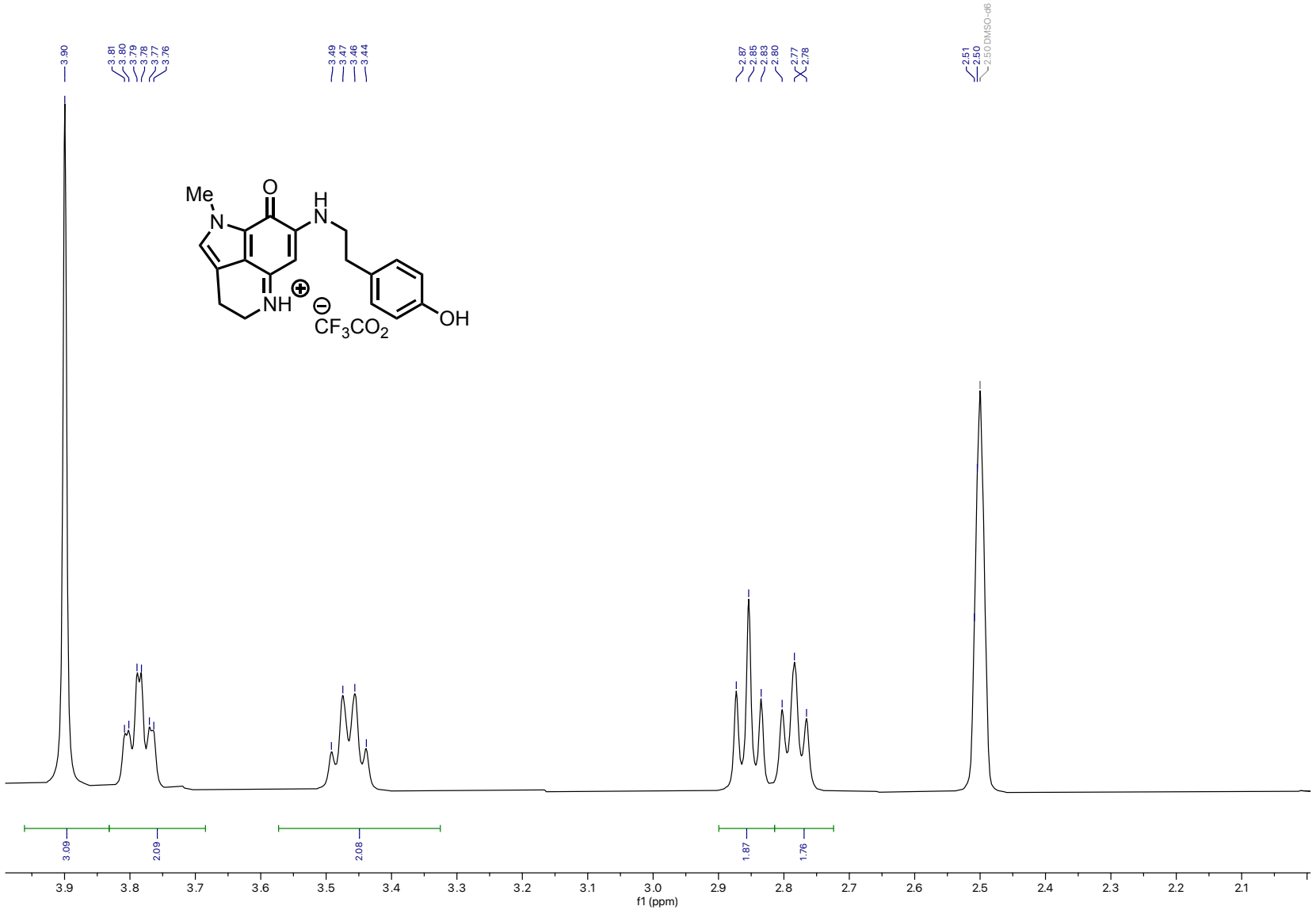


Figure S41: [1]H NMR (500 MHz, DMSO-d6) for makaluvamine K trifluoroacetate **(4)** (4.0-2.0 ppm inset)

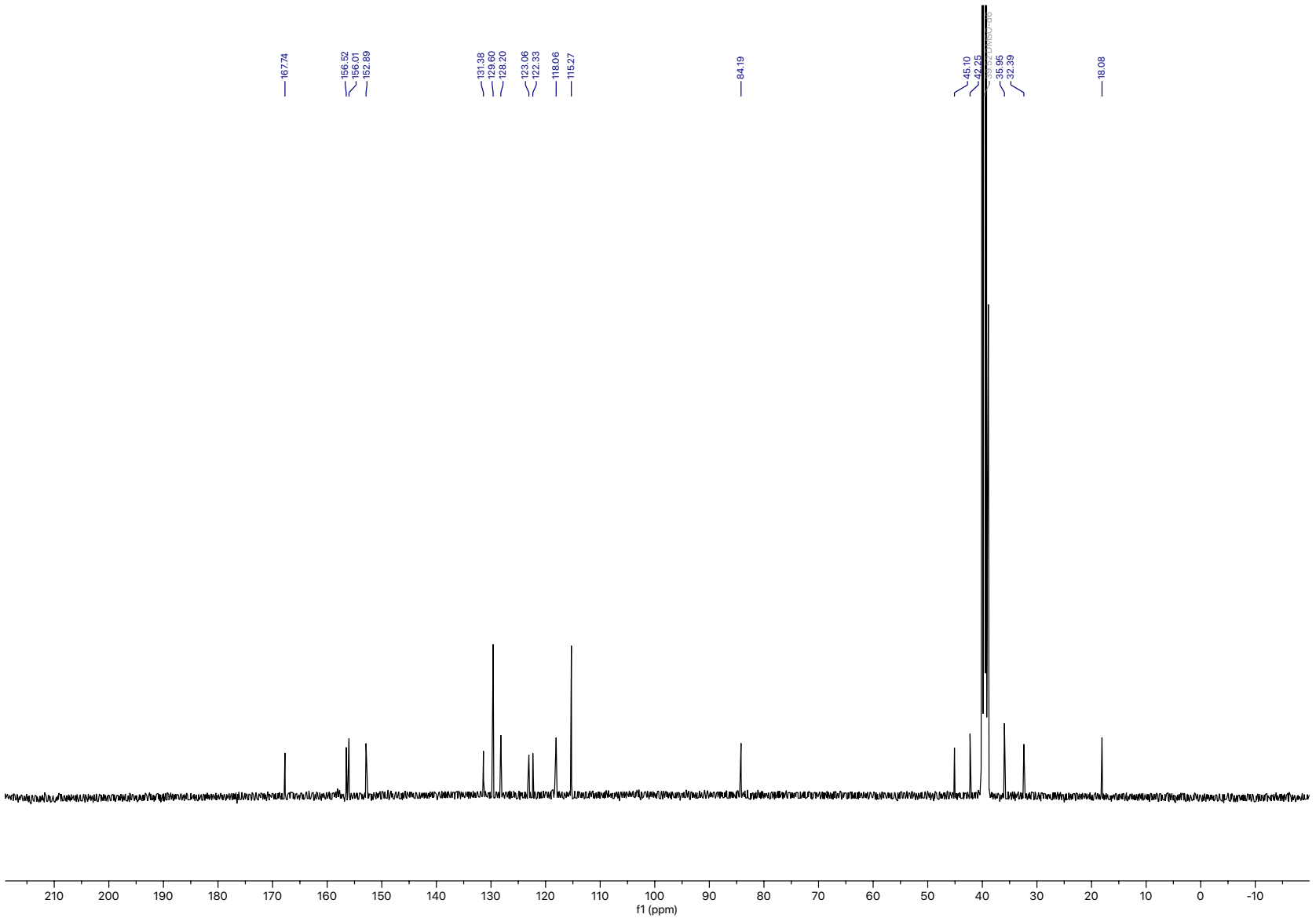


Figure S42: ^{13}CNMR (125 MHz, DMSO-d6) for makaluvamine K trifluoroacetate (**4**)

VI. REFERENCES

1) Sneddon, H. F.; Gaunt, M. J.; Ley, S. V.; *Org. Lett.* **2003**, *5*, 1147-1150.
2) Radisky, D. C.; Radisky, E. S.; Barrows, L. R.; Copp, B. R.; Kramer, R. A.; Ireland, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 1632-1638.
3) Schmidt, E. W.; Harper, M. K.; Faulkner, D. J *J. Nat. Prod.* **1995**, *58*, 1861-1867.