ESI

Synthesis of 3-substituted 2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-ones by sequential reactions of 2-indolylmethyl acetates with α-amino acids

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1. GENERAL INFORMATION

All of the commercially available reagents, catalysts, bases and solvents were used as purchased, without further purification. Starting materials **1**, **7** and reaction products **5**, **8**, **10**-**13** were purified, when needed, by flash chromatography using SiO_2 as stationary phase, eluting with *n*-hexane/ethyl acetate (EtOAc) mixtures. α-amino acid methyl esters **4a-d** were obtained by corresponding commercially available chloro hydrates. ^{1}H NMR (400.13 MHz), ^{13}C NMR (100.6 MHz), and ^{19}F spectra (376.5 MHz) were recorded with a Bruker Avance 400 spectrometer. Splitting patterns are designed as s (singlet), d (doublet), t (triplet), dt (doublets of triplets), td (triplet of doublets), triplets of triplets (tt), q (quartet), m (multiplet), or br s (broad singlet). IR spectra were recorded with a Jasco FT/IR 6800 (ATR). HRMS of samples were recorded on Orbitrap Exactive (Thermo Fisher) (compounds **1** and **7**, **11**, **8a**, **8g**, **12**, **13**) and Orbitrap Fusion Lumos (Thermo Fisher) (compounds **5**, **8**, **10**) and Orbitrap Exactive (Thermo Fisher). Source ESI positive as well negative. Data were collected on Xcalibur (Thermo Scientific, Bremen, Germany). Melting points were determined with a Büchi B-545 apparatus and are uncorrected.

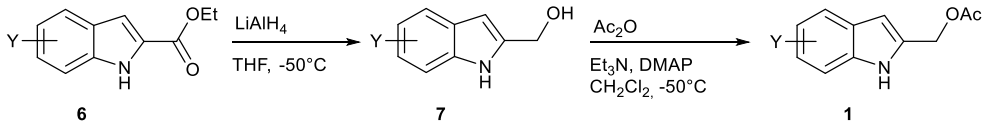
2. SYNTHETIC PROCEDURES FOR STARTING MATERIALS

2.1. Typical procedure for the preparation of substituted (1*H*-indol-2-yl)methyl acetate 1(a-e)

The (1*H*-indol-2-yl)methyl acetates (**1a-d**) and 3-phenyl-2-(1*H*-indol-2-yl)methyl acetates (**1e**) were previously synthesized in our laboratory [1] according to the procedures reported below.

2.1.a Typical procedure for the preparation of (1*H*-indol-2-yl)methyl acetate 1

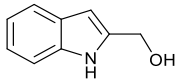
(1*H*-indol-2-yl)methyl acetate **1a-d** were prepared according to the two-steps sequence outlined in Scheme 1.



Scheme 1

***STEP 1*: *synthesis of (1H-indol-2-yl)methanol* 7**

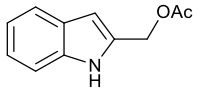
A flame dried three-necked round bottom flask, equipped with a magnetic stirring bar, was charged with ethyl 1*H*-indole-2-carboxylate **6** (1.50 g, 8.00 mmol, 1.0 equiv.) dissolved in anhydrous THF (30 mL) under argon. Then, a solution of $LiAlH_4$ in THF (2 M, 4.4 mL, 8.8 mmol, 1.1 equiv.) was added dropwise at 0°C and the mixture was stirred at room temperature until the disappearance of the starting material, monitoring by TLC (mobile phase for TLC: n-hexane-EtOAc, 80:20). The reaction was cooled down to 0°C and quenched with an 80 percent aqueous MeOH solution. The mixture was extracted with Et_2O, washed with a solution of $NaHSO_4$ (10% w/w) and with brine. The organic layer was dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The resulting crude product was used in the next step without further purification (1.15 g, 98% yield).



(1*H*-indol-2-yl)methanol 7a: known compound; 98% yield (1.15 g); yellow solid; mp: 72-74 °C; lit.[2] mp: 72-73 °C; R_f = 0.23 (*n*-hexane-EtOAc, 80:20); IR (neat): 3373, 2856, 1617, 1453, 1289, 1004 cm^{-1}; ^{1}H NMR: (400.13 MHz) (DMSO-d_6): δ 11.0 (s, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.33 (dd, J_1 = 7.8 Hz, J_2 = 0.7 Hz, 1H), 7.03 (td, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 6.94 (td, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 6.27 (d, J = 1.2 Hz, 1H), 5.22 (t, J = 5.6 Hz, 1H), 4.61 (d, J = 5.6 Hz, 2H); ^{13}C NMR (100.6 MHz) (DMSO-d_6): δ 140.6 (C), 136.7 (C), 128.3 (C), 121.0 (CH), 120.1 (CH), 119.1 (CH), 111.5 (CH), 98.9 (CH), 57.4 (CH_2); HRMS: *m/z* $[M + H]^+$ calcd for $C_9H_{10}NO$: 146.0611; found: 146.0599.

***STEP 2*: *synthesis of (1H-indol-2-yl)methyl acetate* 1a**

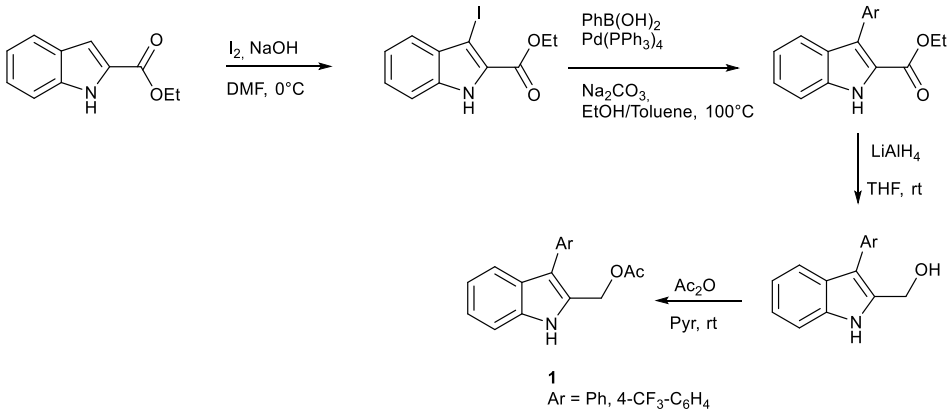
To a stirred solution of (1*H*-indol-2-yl)methanol **7a** (1.00 g, 6.80 mmol, 1.0 equiv.) in pyridine (3mL) was added acetic anhydride (706 µL, 7.48 mmol, 1.1 equiv.) were added at 0 °C and the resulting reaction mixture was stirred for 1h. After the consumption of substrate (TLC, *n*-hexane-EtOAc, 85:15), the reaction was diluted with Et_2O, washed with a saturated $NaHCO_3$ solution and with brine. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting compound **1a** was used in the next step without further purification (1.25 g, 98% yield).



(1*H*-indol-2-yl)methyl acetate (1a): known compound; 98% yield (1.25 g); yellow solid**;** mp: 104-106 °C; lit.[2] mp: 112 °C; R_f = 0.27 (*n*-hexane-EtOAc, 85:15); IR (neat): 3303, 1726, 1454, 1274, 1045, 805 cm^{-1}; ^1H (400.13 MHz) ($CDCl_3$): δ = 8.51 (br s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.46 (s, 1H), 5.15 (s, 2H), 2.03 (s, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ = 172.3 (C), 136.6 (C), 133.0 (C), 127.5 (C), 122.8 (CH), 120.9 (CH), 120.1 (CH), 111.1 (CH), 103.9 (CH), 59.8 (CH_2), 21.0 (CH_3); HRMS: *m/z* $[M + H]^+$ calcd for $C_{11}H_{10}NO_2$: 188.0717; found: 188.0705.

2.1.b Typical procedure for the preparation of (3-phenyl-1*H*-phenyl-2-yl)methyl acetate (1e)

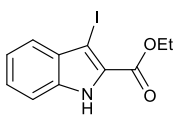
(3-phenyl-1*H*-indol-2-yl)methyl acetate **1e** was prepared according to the four-steps sequence outlined in Scheme 2.



Scheme 2

STEP 1: synthesis of ethyl 3-iodo-1H-indole-2-carboxylate

To a solution of ethyl 1*H*-indole-2-carboxylate (1.50 g, 7.92 mmol, 1.0 equiv.) in DMF (9.0 mL) KOH (2.22 g, 39.6 mmol, 5.0 equiv.) was added at 0°C and the resulting mixture was stirred for 10 minutes before a solution of iodine (1.02 g, 8.03 mmol, 1.1 equiv.) in DMF (10.0 mL) was added dropwise over 5 minutes. After 3h, the mixture was poured into a saturated solution of NH_4Cl and $Na_2S_2O_3$ to precipitate the product. The solid material was filtered off, solubilized in Et_2O, washed with water and dried over Na_2SO_4. After filtration, the mixture was concentrated under reduced pressure to give ethyl 3-iodo-1*H*-indole-2-carboxylate as an off-white powder (2.37 g, 95% yield).

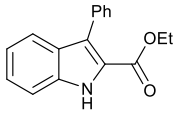


ethyl 3-iodo-1*H*-indole-2-carboxylate: known compound; 95% yield (2.37 g); white solid; mp: 133-135 °C; lit.[3] mp: 137-139 °C; R_f = 0.23 (*n*-hexane-EtOAc, 80:20); IR (neat): 3289, 2896, 1686, 1505, 1255, 859 cm^{-1}; ^1H NMR: (400.13 MHz) ($CDCl_3$): δ 9.42 (br s, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.43-7.38 (m, 2H), 7.28-7.24 (m, 1H),

4.50 (q, *J* = 6.9 Hz, 2H), 1.50 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 161.1 (C), 136.3 (C), 131.6 (C), 127.3 (C), 126.7 (CH), 123.6 (CH), 121.8 (CH), 112.2 (CH), 66.2 (C), 61.7 (CH_2), 14.5 (CH_3); HRMS: *m/z* $[M + H]^+$ calcd for $C_{11}H_{10}INO_2Na$: 337.9648; found: 337.9644.

STEP 2*: *synthesis of ethyl 3-phenyl-1H-indole-2-carboxylate

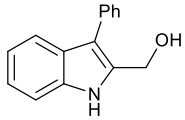
In a three-necked round bottom flask, equipped with a condenser and magnetic stirring bar, $[Pd(PPh_3)_4]$ (439.2 mg, 0.380 mmol, 0.05 equiv) was dissolved at room temperature in 25,0 mL of EtOH/Toluene (2:1) under argon; then, ethyl 3-iodo-1*H*-indole-2-carboxylate (2.37 g, 7.520 mmol, 1.0 equiv), phenylboronic acid (2.76 g, 22.60 mmol, 3.0 equiv), and Na_2CO_3 (2.39 g, 22.6 mmol, 3.0 equiv) were added and the mixture was refluxed for 16 hours. After this time, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (25-40 µm), eluting with an 80/20 (v/v) *n*-hexane-AcOEt mixture (R_f = 0.22) to obtain the ethyl 3-phenyl-1*H*-indole-2-carboxylate (1.69 g, 85% yield).



ethyl 3-phenyl-1*H*-indole-2-carboxylate: known compound; 85% yield (1.69 g); yellow solid; mp: 133-135 °C; lit.[4] mp: 133-135 °C; R_f = 0.23 (*n*-hexane-EtOAc, 80:20); IR (neat): 3331, 2916, 1675, 1383, 1254 cm^{-1}; ^{1}H NMR (400.13 MHz) ($CDCl_3$): δ 9.04 (br s, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.58-7.55 (m, 2H), 7.48-7.44 (m, 3H), 7.41-7.35 (m, 2H), 7.18-7.14 (m, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 162.1 (C), 135.8 (C), 130.8 (C), 128.1 (CH), 127.9 (CH), 127.3 (CH), 125.9 (CH), 124.4 (C), 122.9 (C), 121.9 (CH), 121.0 (CH), 111.8 (CH), 61.0 (CH), 14.2 (CH_2); HRMS: *m/z* $[M + Na]^+$ calcd for $C_{17}H_{15}NO_2Na$: 288.0995; found: 288.0991.

***STEP* 3: *synthesis of (3-phenyl-1H-indol-2-yl)methanol* 7e**

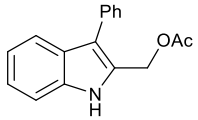
(3-phenyl-1*H*-indol-2-yl)methanol was synthetized according to the typical procedures outlined for (1*H*-indol-2-yl)methanol.



(3-phenyl-1*H*-indol-2-yl)methanol (7e): known compound; 81% yield (1.15 g); brown solid; mp: 88-90 °C; lit.[1a] mp: 88-90. R_f = 0.25 (*n*-hexane-EtOAc, 70:30); IR (neat): 3391, 2917, 1730, 1456, 1384, 1231 cm^{-1}; ^{1}H NMR (400.13 MHz) ($CDCl_3$): δ 8.56 (br s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.48-7.46 (m, 4H), 7.37-7.33 (m, 2H), 7.24 (dt, J_1 = 8.0 Hz, J_2 = 1.1 Hz, 1H), 7.16 (dt, J_1 = 8.0 Hz, J_2 = 1.1 Hz, 1H), 4.89 (s, 2 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 135.7 (C), 134.6 (C), 133.7 (C), 129.5 (CH), 128.8 (CH), 127.4 (C), 126.5 (CH), 122.7 (CH), 120.4 (CH), 119.7 (CH), 115.4 (C), 111.2 (CH), 57.2 (CH_2); HRMS: *m/z* $[M + H]^+$ calcd for $C_{15}H_{12}NO$: 222.0924; found: 222.0917.

***STEP* 4: *synthesis of (3-phenyl-1H-indol-2-yl)methyl acetate* (1e)**

(3-phenyl-1*H*-indol-2-yl)methyl acetate **1e** was synthesized according to the typical procedures outlined for **1a**, *step 2*.

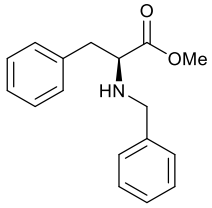


(3-phenyl-1*H*-indol-2-yl)methyl acetate (1e): quantitative yield (1.37 g); yellow solid; mp: 133-135 °C; lit.[1a] mp: 133-135 °C; R_f = 0.25 (*n*-hexane-EtOAc, 80:20); IR (neat): 3391, 2917, 1730, 1456, 1384, 1231 cm^{-1}; ^{1}H NMR (400.13 MHz) ($CDCl_3$): δ 8.71 (br s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.5

Hz, 2H), 7.30 (t, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 7.0 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 5.19 (s, 2H), 2.06 (s, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 172.8 (C), 135.8 (C), 134.2 (C), 129.8 (CH), 129.4 (C), 128.8 (CH), 126.8 (CH), 126.7 (C) 123.5 (CH), 120.4 (CH), 120.2(CH), 118.8 (C), 111.4(CH), 58.5 (CH_2), 21.2 (CH_3); HRMS: *m/z* $[M + H]^+$ calcd for $C_{17}H_{14}NO_2$: 288.0995; found: 288.0997.

2.2. Typical procedure for the preparation of methyl *N*-benzil L-phenylalaninate 9 [5]

A round bottom flask, equipped with a magnetic stirring bar, was charged with L-Phenylalanine methyl ester hydrochloride (1 g, 5.12 mmol, 1.0 equiv.), triethylamine (644 µL, 5.12 mmol, 1.0 equiv.), benzaldehyde (521 µL, 5.63 mmol, 1.1 equiv.) and MeOH (10 mL) were added and the mixture was stirred for 2 hours. Then, $NaBH_4$ (387 mg, 10.24 mmol, 2.0 equiv.) was added portion wise at 0°C and the mixture was stirred for 3h. The resulting mixture was diluted with EtO_2 and washed with brine. The organic layer was dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The resulting crude product was used in the next step without further purification (960 mg, 81% yield).

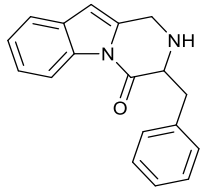


methyl benzyl-L-phenylalaninate 9a: 80% yield (1.1 g); white oil; R_f = 0.21 (*n*-hexane-EtOAc, 90:10); IR (neat): 3030, 1733, 1453, 1200, 749 cm^{-1}; ^{1}H NMR (400.13 MHz) ($CDCl_3$): δ 7.29 - 7.15 (m, 10H), 3.81 (d, *J* = 13.2 Hz, 1H), 3.642 (d, *J* = 13.2 Hz, 1H), 3.640 (s, 1H), 3.55 (t, *J* = 6.9 Hz, 1H), 2.97 (d, *J* = 7.6 Hz, 2H), 2.23 (s, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 175.1 (C), 139.6 (C), 137.3 (C), 129.3 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH) 127.1 (CH), 126.7 (CH), 62.1 (CH), 52.0 (CH_2), 51.7 (CH), 19.4 (CH_2), 39.8 (CH_2). HRMS: *m/z* $[M + H]^+$ calcd for $C_{17}H_{20}NO_2$: 270.1489; found: 270.1487.

3. SYNTHETIC PROCEDURES FOR FINAL COMPOUNDS

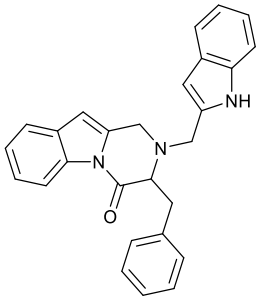
3.1. Typical procedure for the preparation of 3-benzyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 5:

In a 50 mL Carousel Tube Reactor (Radely Discovery Technology) containing a magnetic stirring bar (1*H*-indol-2-yl)methyl acetate **1a** (76.4 mg, 0.404 mmol, 1.00 equiv.) was dissolved at room temperature with 2.0 mL of anhydrous MeCN. Then, methyl L-phenylalaninate **4a** (357.5 mg, 2.020 mmol, 5.0 equiv.), K_2CO_3 (112.0 mg, 0.808 mmol, 2.0 equiv.), and 1.0 mL of solvent were added. The mixture was stirred for 18h at 120 °C. After this time, the reaction mixture was cooled to room temperature, diluted with Et_2O, washed with a saturated $NaHCO_3$ solution and with brine. The organic extract was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (25-40 µm), eluting with a 80/20 (v/v) *n*-hexane/AcOEt mixture (R_f = 0.21) to obtain 81.0 mg (73% yield) of 3-benzyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one **5a** and 7.0 mg (8% yield) of 2-((1*H*-indol-2-yl)methyl)-3-benzyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one **8a**.



3-benzyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 5a: 73% yield (81.0 mg); brown solid; mp: 120-123 °C; R_f = 0.21 (*n*-hexane-EtOAc, 80:20); IR (neat): 2989, 2796, 1444, 1272, 1183, 941, 734 cm^{-1}; ^{1}H NMR (400.13 MHz) ($CDCl_3$): δ 8.36 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.27-7.16 (m, 7H), 6.17 (s, 1H), 4.11 (d, *J* = 16

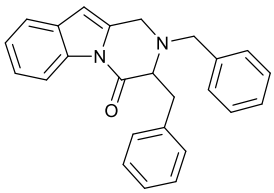
Hz, 1H), 3.88 (d, J = 16 Hz, 1H), 3.79 (dd, J_1 = 8.7 Hz, J_2 = 4.0 Hz, 1H), 3.44 (dd, J_1 = 14 Hz, J_2 = 4.0 Hz, 1H), 3.06 (dd, J_1= 14.0 Hz, J_2 = 8.7 Hz, 1H), 1.79 (s, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 169.1 (C), 137.5 (C), 136.6 (C), 134.7 (C), 129.5 (CH), 128.8 (CH), 127.0 (CH), 124.5 (CH), 124.2 (CH), 120.2 (CH), 116.3 (CH), 103.1 (CH), 61.3 (CH), 41.9 (CH_2), 36.3 (CH_2); HRMS: *m/z* $[M + H]^+$ calcd for $C_{15}H_{17}NO_2$: 277.1335; found: 277.1336.



2-((1*H*-indol-2-yl)methyl)-3-benzyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 8a: 8% yield (7.0 mg); yellow solid; mp: 107-110 °C; R_f = 0.22 (*n*-hexane-EtOAc, 85:15); IR (neat): 3361, 2986, 2808, 1692, 1356, 1188, 691 cm^{-1}; ^{1}H NMR (400.13 MHz) ($CDCl_3$): δ 8.40 (d, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 6.8 Hz, 1H), 7.41 - 7.18 (m, 10H), 7.06 - 7.02 (m, 1H), 7.00 - 6.94 (m, 2H), 6.36 (s, 1H), 6.11 (s, 1H), 4.43 (dd, J_1 = 16.7, J_2 = 1.8 Hz, 1H), 3.89 - 3.82 (m, 2H), 3.74 - 3.69 (m, 2H), 3.25 (dd, J_1 = 14.1, J_2 = 4.3 Hz, 1H), 3.09 (dd, J_1 = 14.2, J_2 = 11.5 Hz, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 168.8 (C), 138.3 (C), 136.0 (C), 134.9 (C), 134.6 (C), 133.9 (C), 129.7 (C), 129.5 (CH), 128.8 (CH), 128.3 (C), 127.1 (CH), 124.9 (CH), 124.6 (CH), 121.7 (CH), 120.5 (CH), 120.2 (CH), 119.7 (CH), 116.5 (CH), 111.0 (CH), 105.8 (CH), 101.5 (CH), 64.6 (CH), 52.0 (CH_2), 43.5 (CH_2), 35.6 (CH_2). HRMS: *m/z* $[M + H]^+$ calcd for $C_{27}H_{24}N_3O$: 406.1914; found: 406.1915.

3.2. Typical procedure for the preparation of 2,3-dibenzyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 10:

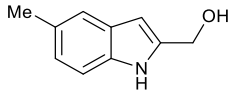
In a 50 mL Carousel Tube Reactor (Radely Discovery Technology) containing a magnetic stirring bar (1*H*-indol-2-yl)methyl acetate (54.9 mg, 0.290 mmol, 1.0 equiv.) was dissolved at room temperature with 2.0 mL of anhydrous MeCN. Then, methyl benzyl L-phenylalaninate (369.8 mg, 1.450 mmol, 5.0 equiv.), K_2CO_3 (80.0 mg, 0.580 mmol, 2.0 equiv.), and 1.0 mL of solvent were added. The mixture was stirred for 24h at 120 °C. After this time, the reaction mixture was cooled to room temperature, diluted with Et_2O, washed with a saturated $NaHCO_3$ solution, and with brine. The organic extract was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (25-40 µm), eluting with a 96/4 (v/v) *n*-hexane/AcOEt mixture *(*R_f = 0.21) to obtain 89.2 mg (84% yield) of 2,3-dibenzyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one **10a**.



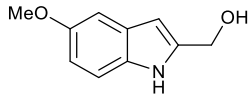
2,3-dibenzyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 10a: 84% yield (89.2 mg); pale pink solid; mp: 115-116 °C; R_f = 0.21 (*n*-hexane-EtOAc, 96:4); IR (neat): 3024, 1782, 1450, 1373, 695 cm^{-1}; ^{1}H NMR (400.13 MHz) ($CDCl_3$): δ 8.54 (d, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 7.2 1H), 7.43 - 7.31 (m, 7H), 7.29 - 7.22 (m, 3H), 7.05 - 7.03 (m, 2H), 6.41 (s, 1H), 4.39 (dd, J_1 = 16.9, J_2 = 1.7 Hz, 1H), 3.93 (d, *J* = 4.4 Hz, 1H), 3.90 (d, *J* = 7.2 Hz, 1H), 3.82 (d, *J* = 13.3 Hz, 1H), 3.66 (d, *J* = 13.3 Hz, 1H), 3.35 (dd, J_1 = 14.4, J_2 = 4.9 Hz, 1H), 3.25 (dd, J_1 = 14.4, J_2 = 10.1 Hz, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 169.4 (C), 138.2 (C), 137.6 (C), 134.9 (C), 134.6 (C), 129.7 (C), 129.4 (CH), 128.8 (CH), 128.4 overlapping (CH), 127.5 (CH), 126.7 (CH), 124.6 (CH), 124.3 (CH), 120.3 (CH), 116.5 (CH), 105.4 (CH), 66.4 (CH), 58.1 (CH_2), 43.1 (-CH_2), 35.5 (CH_2); HRMS: *m/z* $[M + H]^+$ calcd for $C_{25}H_{23}N_2O$: 367.1805; found: 367.1804.

4. CHARACTERIZATION DATA OF STARTING MATERIALS

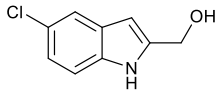
4.1. Characterization data of (1*H*-indol-2-yl)methanols 7



(5-methyl-1*H*-indol-2-yl)methanol 7b: known compound; 98% yield (1.25 g); orange solid; mp: 77-79 °C; lit.[2] mp: 77-79 °C; R_f = 0.25 (*n*-hexane-EtOAc, 75:25); IR (neat): 3346, 2932, 1623, 1487, 1197, 1025 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.15 (br s, 1H), 7.28 (s, 1H), 7.12 (d, *J* = 8.3 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 6.23 (br s, 1H), 4.67 (s, 2H), 2.36 (s, 3H), 1.94 (br s, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 137.6 (C), 134.7 (C), 129.2 (C), 128.4 (C), 123.8 (CH), 120.3 (CH), 110.6 (CH), 100.1 (CH), 58.8 (CH_2), 21.4 (CH_3); HRMS: *m/z* $[M + H]^+$ calcd for $C_{10}H_{12}NO$: 162.0913; found: 162.0917.

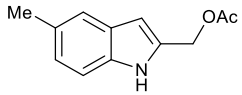


(5-methoxy-1*H*-indol-2-yl)methanol 7c: known compound; 97% yield (1.363 g); mp: 64 -66 °C; lit.[6] mp: 67-69 °C; orange solid; R_f = 0.18 (*n*-hexane-EtOAc, 80:20); IR (neat): 3463, 3279, 2932, 1312, 1016, 788 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.18 (bs, 1H), 7.12 (d, J = 8.7 Hz, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.76 (dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz, 1H), 6.25 (s, 1H), 4.69 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 154.2 (C), 138.3 (C), 131.5 (C), 128.6 (C), 112.4 (CH), 111.7 (CH), 102.4 (CH), 100.4 (CH), 58.8 (CH_2), 55.9 (CH_3); HRMS: *m/z* $[M + H]^+$ calcd for $C_{10}H_{12}NO_2$: 178.0863; found: 178.0860.

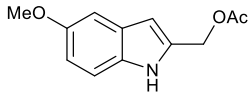


(5-chloro-1*H*-indol-2-yl)methanol 7d: known compound; 98% yield (1.41 g); yellow solid; mp: 102-104 °C; lit.[7] mp: 101.9-103.8 °C; R_f = 0.23 (*n*-hexane-EtOAc, 75:25); IR (neat): 3383, 3097, 2916, 1450, 1384, 1017 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.39 (br s, 1H), 7.45 (s, 1H), 7.18 (d, *J* = 7.4 Hz, 1H), 7.04 (dd, J_1 = 8.6 Hz, J_2 = 2.0 Hz, 1H), 6.26 (d, 1H), 5.30 (t, *J* = 5.5 Hz, 1H), 4.73 (s, 2H), 2.00 (br s, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 139.1 (C), 134.8 (C), 129.3 (C), 125.6 (C), 122.6 (CH), 120.1 (CH), 112.0 (CH), 100.2 (CH), 58.7 (CH_2); HRMS: *m/z* $[M + H]^+$ calcd for C_9H_9ClNO: 182.0367; found: 182.0366.

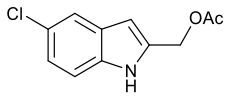
4.2. Characterization data of 1 (1*H*-indol-2-yl)methyl acetates 1



(5-methyl-1*H*-indol-2-yl)methyl acetate 1b: known compound; brown solid**;** 98% yield (1.49 g); mp: 84-86 °C; lit.[2] mp: 87-88 °C; R_f = 0.24 (*n*-hexane-EtOAc, 75:25); IR (neat): 3427, 1718, 1361, 806 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.42 (br s, 1H), 7.31 (q, *J* = 0.80 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 6.96 (dd, J_1 = 8.2 Hz, J_2 = 1.6 Hz, 1H), 6.38 (d, *J* = 1.6 Hz, 1H), 5.14 (s, 2H), 2.36 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 172.3 (C), 134.9 (C), 133.1 (C), 129.2 (C), 127.8 (C), 124.5 (CH), 120.5 (CH), 110.8 (CH), 103.4 (CH), 59.8 (CH_2), 21.5 (CH_3), 21.0 (CH_3); HRMS: *m/z* $[M + Na]^+$ calcd for $C_{12}H_{15}NO_2Na$: 226.0838; found: 226.0838.

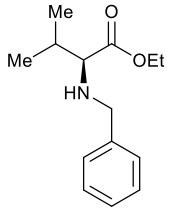


(5-methoxy-1*H*-indol-2-yl)methyl acetate 1c: known compound; 98% yield (7.47 mmol scale, 1.606 g); pink solid; mp: 87-89 °C; lit.[8] mp: 87-88 °C; R_f = 0.27 (*n*-hexane-EtOAc, 75:25); IR (neat): 3383, 1711, 1487, 1225, 1018, 790 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.40 (br s, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 6.97 (d, *J* = 2.5 Hz, 1H), 6.80 (dd, J_1 = 8.8 Hz, J_2 = 2.5 Hz, 1H), 6.39 (d, *J* = 1.5 Hz, 1H), 5.12 (s, 2H), 3.76 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 172.3 (C), 154.3 (C), 133.7 (C), 131.8 (C), 128.0 (C), 113.3 (CH), 111.9 (CH), 103.7 (CH), 102.3 (CH), 59.8 (CH_2), 55.8 (CH_3), 21.0 (CH_3); HRMS: *m/z* $[M + H]^+$ calcd for $C_{12}H_{13}NO_3$: 218.0823; found: 218.0818.

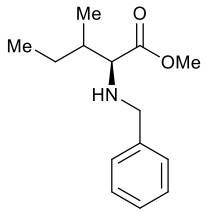


(5-chloro-1*H*-indol-2-yl)methyl acetate 1d: 98% yield (1.64 g); yellow solid; mp: 93-95 °C; R_f = 0.25 (*n*-hexane-EtOAc, 85:15); IR (neat): 3362, 2919, 1445, 1383, 1238 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.65 (br s, 1H), 7.56 (d, *J* = 1.6 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 1H), 7.15 (dd, J_1 = 8.5 Hz, J_2 = 2.1 Hz, 1H), 6.47 (d, *J* = 1.6 Hz, 1H), 5.20 (s, 2H), 2.12 (s, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 172.5 (C), 135.0 (C), 134.6 (C), 128.7 (C), 125.7 (C), 123.2 (CH), 120.4 (CH), 112.3 (CH), 103.6 (CH), 59.7 (CH_2), 21.1 (CH_3); HRMS: *m/z* $[M + H]^-$ calcd for $C_{11}H_{10}ClNO_2$: 222.0327; found: 222.0320.

4.3. Characterization data of *N*-benzil α-amino acids alkyl esters 9



ethyl benzyl-L-valinate 9b: 82% yield (0.976 g); pale yellow oil; R_f = 0.22 (*n*-hexane-EtOAc, 90:10); IR (neat): 2945, 1718, 1462, 1110, 751 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.27 - 7.13 (m, 5H), 4.11 - 4.07 (m, 2H), 3.75 (d, *J* = 13.1 Hz, 1H), 3.51 (d, *J* = 13.1 Hz, 1H), 2.91 (d, *J* = 6.1 Hz, 1H), 1.86 - 1.80 (m, 1H), 1.72 (s, 1H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.88 - 0.85 (m, 6H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 175.3 (C), 140.3 (C), 128.3 (CH), 128.3 (CH), 127.0 (CH), 66.7 (CH), 60.4 (CH_2), 52.6 (CH_2), 31.8 (CH), 19.4 (CH_3), 18.7 (CH_3), 14.5 (CH_3). HRMS: *m/z* $[M + H]^+$ calcd for $C_{14}H_{22}NO_2$: 236.1645; found: 236.1645.

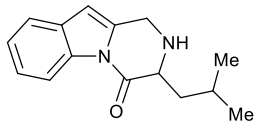


methyl (2S)-2-(benzylamino)-3-methylpentanoate 9c: 84% yield (1.01 g); pale yellow oil; R_f = 0.22 (*n*-hexane-EtOAc, 90:10); IR (neat): 2960, 1729, 1458, 1109, 748 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.38 - 7.25 (m, 5H), 3.85 (d, *J* = 13.0 Hz, 1H), 3.74 (s, 3H), 3.62 (d, *J* = 13.1 Hz, 1H), 3.13 (d, *J* = 6.2 Hz, 1H), 1.91 (s, 1H), 1.77 - 1.56 (m, 1H), 1.30 - 1.18 (m, 1H), 0.93 - 0.87 (m, 6H); ^{13}C NMR (101 MHz) ($CDCl_3$) δ 175.8 (C), 140.1 (C), 128.32 (C),

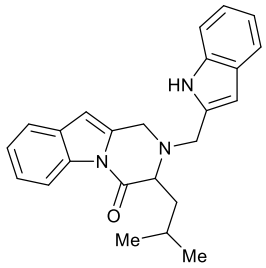
128.31 (CH), 127.0 (CH), 65.5 (CH), 52.6 (CH_2), 51.4 (CH_3), 38.4 (CH), 25.6 (CH_2), 15.7 (CH_3), 11.5 (CH_3); HRMS: *m/z* $[M + H]^+$ calcd for $C_{14}H_{22}NO_2$: 236.1645; found: 236.1645.

5. CHARACTERIZATION DATA OF FINAL PRODUCTS

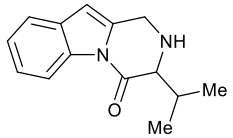
5.1. Characterization data of 3-substituted-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-ones 5, 8, 11-13



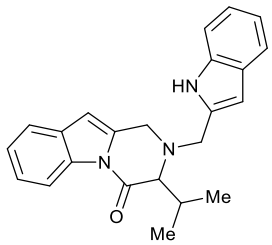
3-isobutyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 5b: 59% yield (57.7 mg); brown solid; mp: 126-128 °C; R_f = 0.21 (*n*-hexane-EtOAc, 80:20); IR (neat): 2976, 2808, 1704, 1260, 1210, 941, 733 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.38 (d, *J* = 7.9 Hz, 1H), 7.46 (d, *J* = 7.1 Hz, 1H), 7.29 - 7.22 (m, 2H), 6.24 (s, 1H), 4.20 (d, *J* = 16.5 Hz, 1H), 4.01 (d, *J* = 16.5 Hz, 1H), 3.64 (dd, J_1 = 9.8, J_2 = 3.9 Hz, 1H), 2.05 - 1.89 (m, 2H), 1.87 (br s, 1H), 1.65 - 1.58 (m, 1H), 1.00 (t, *J* = 6.3 Hz, 6H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 170.9 (C), 137.1 (C), 134.8 (C), 129.5 (C), 124.4 (CH), 124.1(CH), 120.2 (CH), 116.3 (CH), 102.7 (CH), 58.1 (CH), 41.0 (CH_2), 39.1 (CH_2), 24.9 (CH), 23.4 (CH_3), 21.4 (CH_3); HRMS: *m/z* $[M + H]^+$ calcd for $C_{15}H_{15}N_2O$: 243.1492; found: 243.1492.



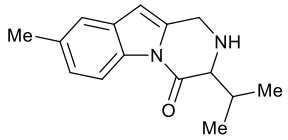
2-((1H-indol-2-yl)methyl)-3-isobutyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 8b: 32% yield (23.9 mg); pale yellow solid ; mp: 96-100 °C; R_f = 0.21 (*n*-hexane-EtOAc, 90:10); IR (neat): 3413, 2995, 2814, 1702, 1365, 1160, 683 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.36 (d, *J* = 8.0 Hz, 1H), 8.20 (br s, 1H), 7.48 - 7.42 (m, 2H), 7.27 - 7.17 (m, 3H), 7.10 (t, *J* = 7.0 Hz, 1H), 7.02 (t, *J* = 7.0 Hz, 1H), 6.24 (s, 2H), 4.11 (d, *J* = 18.6 Hz, 1H), 3.86 - 3.74 (m, 3H), 3.63 - 3.59 (m, 1H), 1.92 - 1.89 (m, 1H), 1.84 - 1.76 (m, 1H), 1.70 - 1.63 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 170.1 (C), 136.3 (C), 134.9 (C), 134.8 (C), 133.9 (C), 129.7 (C), 128.4 (C), 124.7(CH), 124.4 (CH), 122.1 (CH), 120.5 (CH), 120.3 (CH), 120.0 (CH), 116.6 (CH), 110.9 (CH), 105.6 (CH), 102.6 (CH), 63.4 (CH), 51.6 (CH_2), 42.7 (CH_2), 38.2 (CH_2), 25.2 (CH), 23.2 (CH_3), 21.8 (CH_3); HRMS: *m/z* $[M + Na]^+$ calcd for $C_{24}H_{25}N_3ONa$: 394.1890; found: 394.1890.



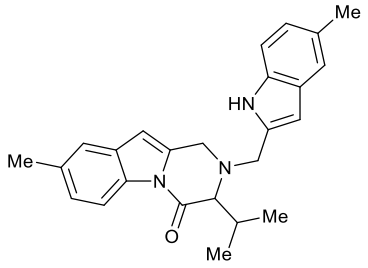
3-isopropyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 5c: 71% yield (65.4 mg); brown solid; mp: 116-118 °C; R_f = 0.21 (*n*-hexane-EtOAc, 86:14); IR (neat): 2978, 2901, 1694, 1271, 1220, 957, 740 cm^{-1}; ^1H (400.13 MHz) ($CDCl_3$): δ 8.43 (d, *J* = 7.9 Hz, 1H), 7.50 - 7.42 (d, *J* = 8.6 Hz, 1H), 7.33 - 7.24 (m, 2H), 6.28 (s, 1H), 4.29 (d, *J* = 16.2 Hz, 1H), 4.02 (d, *J* = 16.2 Hz, 1H), 3.48 (d, *J* = 4.0 Hz, 1H), 2.75 - 2.67 (m, 1H), 1.85 (br s, 1H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 169.8 (C), 137.2 (C), 134.8 (C), 129.6 (CH), 124.4 (CH), 124.2 (CH), 120.2 (CH), 116.4 (CH), 102.7 (CH), 65.5 (CH), 42.0 (CH_2), 28.3 (CH), 20.0 (CH_3), 17.5 (CH_3); HRMS: *m/z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O$: 229.1335; found: 229.1334.



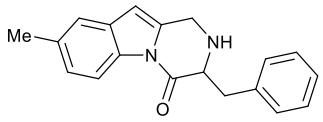
2-((1*H*-indol-2-yl)methyl)-3-isopropyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 8c: 13 % yield (10.0 mg); brown wax; R_f = 0.22 (*n*-hexane-EtOAc, 90:10); IR (neat): 3339, 2998, 2814, 1682, 1266, 1180, 688 cm^{-1}; ^1H (400.13 MHz) ($CDCl_3$): δ 8.49 (d, *J* = 8Hz, 1H), 8.32 (br s, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.40 -7.28 (m, 3H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.35 (s, 2H), 4.30 (d, *J* = 17.0 Hz, 1H), 3.99 - 3.88 (m, 3H), 3.14 (d, *J* = 10.0 Hz,1H), 2.27 - 2.20 (m, 1H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.16 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 168.9 (C), 136.2 (C), 134.8 (C), 134.7 (C), 133.9 (C), 129.6 (C), 128.3 (C), 124.5 (CH), 124.2 (CH), 121.9 (CH), 120.4 (CH), 120.1 (CH), 119.8 (CH), 116.5 (CH), 110.7 (CH), 105.2 (CH), 102.4 (CH), 71.3 (CH), 52.5 (CH_2), 42.4 (CH_2), 28.6 (CH), 21.1 (CH_3), 20.0 (CH_3); HRMS: *m/z* $[M + Na]^+$ calcd for $C_{25}H_{15}N_3ONa$: 380.1733; found: 380.1733.



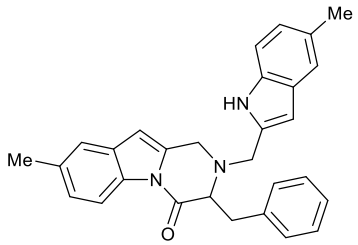
3-isopropyl-8-methyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 5d: 76% yield (74.4 mg); pale brown solid; mp: 91-93 °C; R_f = 0.22 (*n*-hexane-EtOAc, 85:15); IR (neat): 2996, 2891, 1697, 1282, 1243, 949, 731 cm^{-1}; ^1H (400.13 MHz) ($CDCl_3$): δ 8.28 (d, *J* = 8.3 Hz, 1H), 7.26 (s, 1H), 7.11 (d, *J* = 8.3 Hz, 1H), 6.19 (s, 1H), 4.24 (d, *J* = 16.3 Hz, 1H), 3.98 (d, *J* = 16.3 Hz, 1H), 3.43 (d, *J* = 4.5 Hz, 1H), 2.73 - 2.65 (m, 1H), 2.43 (s, 3H), 1.87 (br s, 1H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 169.5 (C), 137.2 (C), 133.7 (C), 132.9 (C), 129.8 (C), 125.6 (CH), 120.2 (CH), 115.9 (CH), 102.4 (CH), 65.3 (CH), 41.9 (CH_2), 28.1 (CH_3), 21.5 (CH), 20.0 (CH_3), 17.4 (CH_3); HRMS: *m/z* $[M + H]^+$ calcd for $C_{15}H_{15}N_2O$: 243.1492; found: 243.14920.



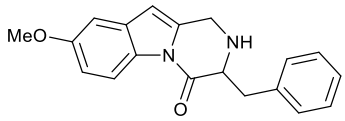
2-((1*H*-indol-2-yl)methyl)-3-isopropyl-8-methyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 8d: 19% yield (15.0 mg); yellow oil; R_f = 0.21 (*n*-hexane-EtOAc, 98:2); IR (neat): 3409, 2984, 2793, 1702, 1256, 1208, 699 cm^{-1}; ^1H (400.13 MHz) ($CDCl_3$): δ 8.24 (d, *J* = 8.3 Hz, 1H), 8.11 (br s, 1H), 7.25 - 7.16 (m, 3H), 7.07 (d, *J* = 8.3 Hz, 1H), 6.93 (d, *J* = 7.1 Hz, 1H), 6.14 (s, 2H), 4.16 (d, *J* = 17.2 Hz, 1H), 3.83 - 3.72 (m, 3H), 3.0 (d, *J* = 9.6 Hz, 1H), 2.36 (d, *J* = 6.0 Hz, 6H), 2.12 (m, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 168.7 (C), 134.9 (C), 134.5 (C), 134.0 (C), 133.7 (C), 132.9 (C), 129.8 (C), 129.1 (C), 128.6 (C), 125.7 (CH), 123.5 (CH), 120.2 (CH), 120.1 (CH), 116.1 (CH), 110.4 (CH), 105.0 (CH), 101.9 (CH), 71.2 (CH), 52.6 (CH_2), 42.4 (CH_2), 28.6 (CH), 21.5 (CH_3), 21.4 (CH_3), 21.2 (CH_3), 20.0 (CH_3); HRMS: *m/z* $[M + H]^+$ calcd for $C_{25}H_{28}N_3O$: 386.2227; found: 386.2227; HRMS: *m/z* $[M + H]^+$ calcd for $C_{25}H_{28}N_3O$: 386.2227; found: 386.2227.



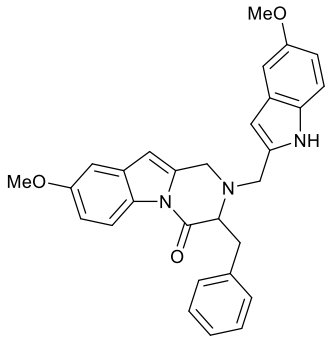
3-benzyl-8-methyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 5e: 44% yield (51.6 mg); brown solid mp: 123-126 °C; R_f = 0.20 (*n*-hexane-EtOAc, 85:15); IR (neat): 2998, 2917, 1692, 1286, 1252, 945, 737 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.24 (d, *J* = 8.3 Hz, 1H), 7.29 - 7.18 (m, 6H), 7.08 (d, *J* = 8.3, 1H), 6.16 (s, 1H), 4.16 (dd, J_1 = 15.9, J_2 = 1.7 Hz, 1H), 3.94 (dd, J_1 = 15.9, J_2 = 1.7 Hz, 1H), 3.83 (dd, J_1 = 12.8, J_2 = 8.3 Hz, 1H), 3.47 (dd, J_1 = 14.1, J_2 = 4.0 Hz, 1H), 3.11 (dd, J_1 = 14.1, J_2 = 8.3 Hz, 1H), 2.38 (s, 3H) 1.78 (br s, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 169.0 (C), 137.6 (C), 136.7 (C), 133.9 (C), 132.9 (C), 129.9 (C), 129.6 (CH), 128.9 (CH), 127.1 (CH), 125.7 (CH), 120.3 (CH), 116.0 (CH), 103.0 (CH), 61.3 (CH), 42.0 (CH_2), 36.4 (CH_2), 21.6 (CH_3); HRMS: *m/z* $[M + H]^+$ calcd for $C_{19}H_{18}N_2O$: 291.1492; found: 291.1492.



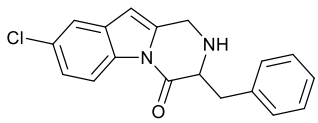
3-benzyl-8-methyl-2-((5-methyl-1*H*-indol-2-yl)methyl)-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 8e: 20% yield (17.1 mg); white solid; mp: 191-193°C; R_f = 0.20 (*n*-hexane-EtOAc, 90:10); IR (neat): 3389, 2992, 2801, 1686, 1260, 687 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.32 (d, *J* = 8.3 Hz, 1H), 7.43 - 7.41 (m, 3H), 7.33 (br s, 1H), 7.28 - 7.25 (m, 3H), 7.19 - 7.17 (m, 2H), 6.95 - 6.90 (m, 2H), 6.36 (s, 1H), 6.09 (s, 1H), 4.48 (dd, J_1 = 16.0, J_2 = 1.4 Hz, 1H), 3.93 - 3.87 (m, 2H), 3.78 - 3.73 (m, 2H), 3.30 (dd, J_1 = 14.1 Hz, J_2 = 4.2 Hz, 1H), 3.18 - 3.12 (m, 1H), 2.47 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 168.6 (C), 138.4 (C), 134.7 (C), 134.3 (C), 134.2 (C), 134.0 (C), 133.0 (C), 129.9 (CH), 129.5 (C), 129.4 (CH), 128.9 (C), 128.7 (CH), 128.6 (CH), 127.0 (CH), 126.0 (CH), 123.2 (CH), 120.5 (CH), 119.9 (CH), 116.1 (CH), 110.6 (CH), 105.6 (CH), 101.1 (CH), 65.5 (CH), 52.0 (CH_2), 43.6 (CH_2), 35.7 (CH_2), 21.6 (CH_3), 21.5 (CH_3); HRMS: *m/z* $[M + H]^+$ calcd for $C_{29}H_{28}N_3O$: 434.2227; found: 434.2225.



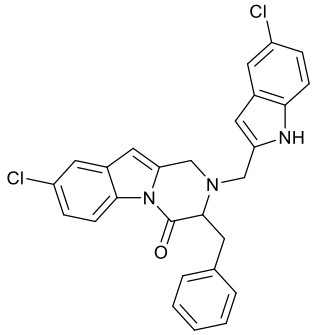
3-benzyl-8-methoxy-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 5f: 67% yield (82.9 mg); brown solid mp: 136-139 °C; R_f = 0.23 (*n*-hexane-EtOAc, 85:15); IR (neat): 3002, 2900, 1683, 1297, 1266, 951, 729 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.27 (d, *J* = 8.9 Hz, 1H), 7.30 - 7.17 (m, 5H), 6.89 (d, *J* = 2.4 Hz, 1H), 6.85 (dd, J_1 = 8.9, J_2 = 2.6 Hz, 1H), 6.14 (s, 1H), 4.12 (d, *J* = 16.0, 1H), 3.90 (dd, J_1 = 16.0, J_2 = 1.7 Hz, 1H), 3.82 - 3.79 (m, 1H), 3.79 (s, 3H), 3.46 (dd, J_1 = 14.0, J_2 = 4.0 Hz, 1H), 3.08 (dd, J_1 = 14.0, J_2 = 8.8 Hz, 1H), 1.78 (br s, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 168.8 (C), 157.0 (C), 137.6 (C), 137.5 (C), 130.7 (C), 129.6 (C), 129.4 (CH), 128.9 (CH), 127.0 (CH), 117.0 (CH), 112.4 (CH), 103.6 (CH), 103.1 (CH), 61.2 (CH), 55.7 (CH_3), 42.0 (CH_2), 36.4 (CH_2); HRMS: *m/z* $[M + H]^+$ calcd for $C_{19}H_{19}N_2O_2$: 307.1441; found: 307.1441.



3-benzyl-8-methoxy-2-((5-methoxy-1*H*-indol-2-yl)methyl)-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 8f: 15 % yield (14.1 mg); brown solid; mp: 120-122 °C; R_f = 0.22 (*n*-hexane-EtOAc, 90:10); IR (neat): 3400, 2996, 2791, 1695, 1244, 1219, 703 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.34 (d, *J* = 8.9 Hz, 1H), 7.45 - 7.39 (m, 3H), 7.28 - 7.26 (m, 3H), 7.15 (br s, 1H), 7.02 (d, *J* = 2.4 Hz, 1H), 6.97 - 6.84 (m, 3H), 6.77 (dd, J_1 = 8.8, J_2 = 2.4 Hz, 1H), 6.36 (s, 1H), 6.11 (s, 1H), 4.50 (dd, J_1 = 16.8, J_2 = 1.7 Hz, 1H), 3.94 - 3.90 (m, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.78 (d, J = 14.2 Hz, 1H), 3.76 - 3.71 (m, 1H), 3.30 (dd, J = 14.2, J_2 = 4.2 Hz, 1H), 3.15 (dd, J_1 = 14.2, J_2 = 11.5 Hz, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 168.4 (C), 157.3 (C), 154.2 (C), 138.5 (C), 135.4 (C), 134.8 (C), 131.1 (C), 130.9 (C), 129.5 (CH), 128.8 (CH), 128.7 (CH), 127.1 (CH), 117.3 (CH), 112.8 (CH), 111.9 (CH), 111.7 (CH), 105.7 (CH), 103.8 (CH), 102.1 (CH), 101.4 (CH), 65.5 (CH), 55.99 (CH_3), 55.91 (CH_3), 52.2 (CH_2), 43.7 (CH_2), 35.7 (CH_2); HRMS: *m/z* $[M + H]^+$ calcd for $C_{29}H_{28}N_3O_3$: 466.2125; found: 466.2125.

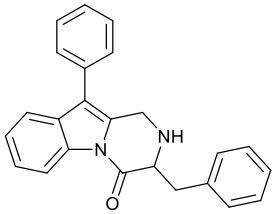


3-benzyl-8-chloro-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 5g: 58% yield (72.8 mg); brown solid; mp: 131-134 °C; R_f = 0.22 (*n*-hexane-EtOAc, 85:15); IR (neat): 2988, 2925, 1701, 1264, 1234, 927, 728 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.29 (d, *J* = 8.8 Hz, 1H), 7.36 (d, *J* = 2.1 Hz, 1H), 7.29 - 7.18 (m, 6H), 6.14 (s, 1H), 4.15 (d, *J* = 16.1 Hz, 1H), 3.92 (d, *J* = 16.1 Hz, 1H), 3.82 (dd, J_1 = 8.8, J_2 = 4.0 Hz, 1H), 3.46 (dd, J_1 = 14.0, J_2 = 4.0 Hz, 1H), 3.07 (dd, J_1 = 14.0, J_2 = 8.8 Hz, 1H), 1.83 (br s, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 169.0 (C), 138.2 (C), 137.4 (C), 133.1 (C), 130.9 (C), 129.8 (C), 129.6 (CH), 128.9 (CH), 127.1 (CH), 124.5 (CH), 120.0 (CH), 117.3 (CH), 102.4 (CH), 61.3 (CH), 42.0 (CH_2), 36.3 (CH_2); HRMS: *m/z* $[M + H]^+$ calcd for $C_{18}H_{16}ClN_2O$: 311.0946; found: 311.0943.

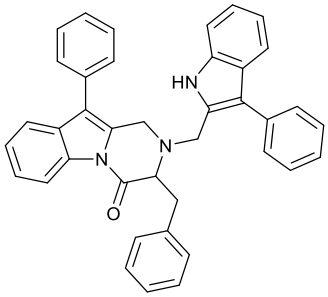


3-benzyl-8-chloro-2-((5-chloro-1*H*-indol-2-yl)methyl)-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 8g: 6**%** yield [yield calculated from ^1H NMR analysis; the chromatographic fraction containing **1d** and **8g** was further purified by semi-preparative HPLC under normal phase condition using a Nucleodur 100-5 column (762007.100) and eluiting with *n*-hexane-EtOAc, 95:5 to obtain suitable characterization data]; white solid;

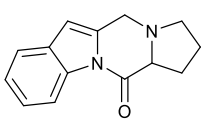
mp: 131-134 °; R_f = 0.22 (*n*-hexane-EtOAc, 95:5); IR (neat): 3388, 2988, 2941, 1681, 1255, 1229, 913 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$) δ 8.37 (d, *J* = 8.7 Hz, 1H), 7.51 (d, *J* = 2.1 Hz, 1H), 7.45 - 7.38 (m, 4H), 7.32 (dd, J_1 = 8.7, J_2 = 2.0 Hz, 1H), 7.26 - 7.23 (m, 3H), 7.05 (dd, J_1 = 8.7, J_2 = 2.0 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 6.39 (s, 1H), 6.12 (s, 1H), 4.53 (d, *J* = 16.9 Hz, 1H), 3.95 (d, *J* = 16.9 Hz, 1H), 3.90 (d, *J* = 14.4 Hz, 1H), 3.78 (d, *J* = 14.4 Hz, 1H), 3.73 (dd, J_1 = 16.9, J_2 = 1.8 Hz, 1H), 3.30 (dd, J_1 = 14.1, J_2 = 4.2 Hz, 1H), 3.16 (dd, J_1 = 14.1, J_2 = 11.6 Hz, 1H). ^{13}C NMR (100.6 MHz) ($CDCl_3$): inadequate amount for the analysis. HRMS: *m/z* $[M + H]^+$ calcd for $C_{27}H_{22}Cl_2N_3O$: 474.1134; found: 474.1134.



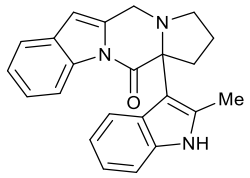
3-benzyl-10-phenyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 5h: 68% yield (101.0 mg); brown oil; R_f = 0.22 (*n*-hexane-EtOAc, 80:20); IR (neat): 3025, 2972, 1702, 1250, 1236, 939, 730 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.49 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.57 - 7.17 (m, 12H), 4.25 (d, *J* = 16.9 Hz, 1H), 4.04 (d, *J* = 16.9 Hz, 1H), 4.00 (dd, J_1 = 12.7, J_2 = 4.0 Hz, 1H), 3.48 (dd, J_1 = 13.9, J_2 = 4.0 Hz, 1H), 3.14 (dd, J_1 = 13.9, J_2 = 8.7 Hz, 1H), 1.78 (br s, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 169.3 (C), 137.5 (C), 134.8 (C), 132.7 (C), 132.6 (C), 129.7 (CH), 129.3 (C), 129.1 (CH), 128.9 (CH), 127.5 (CH), 127.1 (CH), 125.1 (CH), 124.5 (CH), 119.3 (CH), 117.6 (CH) 116.6 (CH), 61.5 (CH), 41.3 (CH_2), 36.4 (CH_2). HRMS: *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}N_2O$: 353.1648; found: 353.1647.



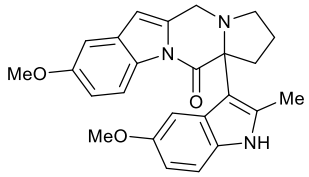
3-benzyl-10-phenyl-2-((3-phenyl-1*H*-indol-2-yl)methyl)-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 8h: 8% yield (9.0 mg); yellow solid; mp: 131-134 °C; R_f = 0.20 (*n*-hexane-EtOAc, 85:15); IR (neat): 3356, 2998, 1697, 1258, 1248, 923 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.54 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.57 - 7.27 (m, 16H), 7.19 - 7.11 (m, 4H), 7.04 (t, *J* = 1.1 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 4.59 (d, *J* = 17.0 Hz, 1H), 4.07 - 3.99 (m, 2H), 3.92 - 3.85 (m, 2H), 3.41 (dd, J_1 = 14.1, J_2 = 4.3 Hz, 1H), 3.24 (dd, J_1 = 14.1, J_2 = 11.8 Hz, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 168.8 (C), 161.6 (C), 138.5 (C), 135.1 (C), 134.9 (C), 134.3 (C), 131.0 (C), 129.63 (C), 129.56 (CH), 129.44 (CH), 129.41 (C), 129.13 (CH), 129.08 (CH), 129.00 (CH), 128.7 (CH), 127.8 (C), 127.7 (CH), 127.2 (CH), 126.2 (CH), 125.4 (CH), 124.7 (CH), 122.1 (CH), 120.5 (C), 119.9 (CH), 119.5 (CH), 119.2 (CH), 116.7 (CH), 116.0 (C), 111.0 (CH), 66.6 (CH), 50.8 (CH_2), 42.4 (CH_2), 35.9 (CH_2). HRMS: *m/z* $[M + H]^+$ calcd for $C_{39}H_{32}N_3O$: 558.2540; found: 558.2540.



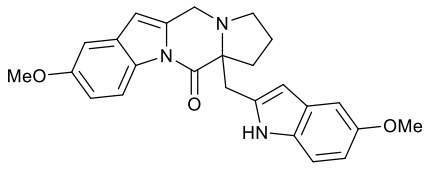
1,2,3,12a-tetrahydro-5*H*,12*H*-pyrrolo[1',2':4,5]pyrazino[1,2-*a*]indol-12-one 11a: 76 % yield (69.0 mg); yellow solid; mp: 130-132 °C; R_f = 0.20 (*n*-hexane-EtOAc, 85:15); IR (neat): 2986, 1704, 1238, 1110, 940 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.44 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.35 - 7.26 (m, 2H), 6.39 (s, 1H), 4.31 (d, *J* = 15.2 Hz, 1H), 3.88 (d, *J* = 15.2 Hz, 1H), 3.47 (t, *J* = 7.4 Hz, 1H), 3.02 (q, *J* = 6.6 Hz, 1H), 2.67 (q, *J* = 8.1 Hz, 1H), 2.35 - 2.30 (m, 2H), 1.97 - 1.89 (m, 2H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 169.7 (C), 135.8 (C), 134.6 (C), 129.9 (C), 124.5 (CH), 124.1 (CH), 120.2 (CH), 116.2 (CH), 104.6 (CH), 65.7 (CH), 52.6 (CH_2), 47.7 (CH_2), 26.3 (CH_2), 22.3 (CH_2). HRMS: *m/z* $[M + H]^+$ calcd for $C_{14}H_{15}N_2O$: 227.1179; found: 227.1180.



12a-(2-methyl-1*H*-indol-3-yl)-1,2,3,12a-tetrahydro-5*H*,12*H*-pyrrolo[1',2':4,5]pyrazino[1,2-*a*]indol-12-one 12a: 8% yield (5.6 mg); yellow solid; mp: 141-139 °C; R_f = 0.20 (*n*-hexane-EtOAc, 90:10); IR (neat): 3397, 3026, 1687, 1245, 933 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.56 (d, *J* = 7.9 Hz, 1H), 7.96 (d, *J* = 7.5 Hz, 1H), 7.72 (br s, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.36 - 7.23 (m, 3H), 7.14 - 7.03 (m, 2H), 6.26 (s, 1H), 4.12 (dd, J_1 = 14.0, J_2 = 1.2 Hz, 1H), 3.96 (d, *J* = 17.1 Hz, 1H), 3.30 (td, *J* = 9.0, 2.8 Hz, 1H), 3.09 - 3.02 (m, 1H), 2.81 (q, *J* = 9.0 Hz, 1H), 2.61 - 2.52 (m, 1H), 2.21 (s, 3H), 2.20 - 2.08 (m, 1H), 1.94 - 1.86 (m, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 172.4(C), 136.6 (C), 135.0 (C), 132.7 (C), 130.1 (C), 128.0 (C), 124.3 (CH), 124.1 (CH), 121.5 (CH), 120.9 (CH), 120.1 (CH), 119.5 (CH), 116.5 (CH), 110.3 (CH), 107.8 (C), 104.8 (CH), 71.3 (C), 49.8 (CH_2), 41.8 (CH_2), 34.7 (CH_2), 21.8 (CH_2), 13.3 (CH_3). HRMS: *m/z* $[M + H]^+$ calcd for $C_{23}H_{22}N_3O$: 356.1757; found: 356.1757.

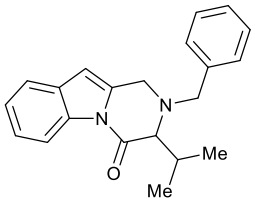


8-methoxy-12a-(5-methoxy-2-methyl-1*H*-indol-3-yl)-1,2,3,12a-tetrahydro-5*H*,12*H* pyrrolo[1',2':4,5]pyrazino[1,2-*a*]indol-12-one 12b: 39 % yield (32.8 mg); yellow oil; R_f = 0.20 (*n*-hexane-EtOAc, 90:10); IR (neat): 3356, 2998, 1696, 1233, 1222, 799 cm^{-1}; ^1H NMR (400.13 MHz) (DMSO-d_6) δ 10.81 (br s, 1H), 8.33 (d, *J* = 8.9 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 7.08 (s, 2H), 6.93 (dd, J_1 = 8.9, J_2 = 2.6 Hz, 1H), 6.64 (dd, J_1 = 8.9, J_2 = 2.6 Hz, 1H), 6.35 (s, 1H), 4.04 (d, *J* = 17.2 Hz, 1H), 3.95 - 3.84 (m, 1H), 3.79 (s, 3H), 3.74 (m, 1H), 3.59 (s, 3H), 3.26 (t, *J* = 2.4 Hz, 1H), 2.96 - 2.85 (m, 1H), 2.50 (s, 3H), 2.44 - 2.32 (m, 1H), 2.14 - 1.97 (m, 1H), 1.91 - 1.71 (m, 1H); ^{13}C NMR (100.6 MHz) (DMSO-d_6) δ 171.5 (C), 156.5 (C), 152.7 (C), 136.9 (C), 134.1 (C), 130.9 (C), 130.0 (C), 128.6 (C), 127.4 (C), 116.3 (CH), 111.9 (CH), 111.0 (CH), 109.5 (CH), 105.2 (CH), 104.5 (CH), 103.6 (CH), 70.3 (C), 55.3 (CH_3), 55.1 (CH_3), 49.2 (CH_2), 40.8 (CH_2), 33.9 (CH_2), 21.2 (CH_2), 12.6 (CH_3). HRMS: *m/z* $[M + H]^+$ calcd for $C_{25}H_{26}N_3O_3$: 416.1969; found: 416.1970.

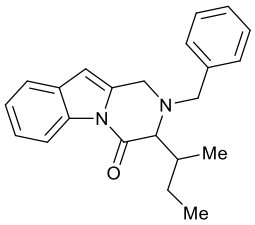


8-methoxy-12a-((5-methoxy-1H-indol-2-yl)methyl)-1,2,3,12a-tetrahydro-5*H*,12*H*-pyrrolo[1',2':4,5]pyrazino[1,2-*a*]indol-12-one 13b 12 % yield (10.0 mg); brown solid; mp: 133-135 °C; R_f = 0.20 (*n*-hexane-EtOAc, 85:15); IR (neat): 3339, 2987, 1709, 1238, 940, 726 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 9.21 (br s, 1H), 8.25 (d, *J* = 8.9 Hz, 1H), 7.17 - 7.14 (m, 2H), 6.95 -6.91 (m, 2H), 6.86 (dd, J_1 = 8.9, J_2 = 2.4 Hz, 1H), 6.73 (dd, J_1 = 8.9, J_2 = 2.4 Hz, 1H), 6.29 (s, 1H), 6.23 (s, 1H), 4.40 (d, *J* =17.0, 1H), 4.13 (d, *J* = 17.0 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.35 (d, *J* = 15.4 Hz, 1H), 3.21 (d, *J* = 15.4 Hz, 1H), 3.17 - 3.07 (m, 1H), 2.71 (q, *J* = 8.9 Hz, 1H), 2.47 - 2.35 (m, 1H), 1.94 - 1.82 (m, 1H) 1.20 - 1.17 (m, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 172.2 (C), 157.1 (C), 154.1 (C), 135.8 (C), 135.0 (C), 131.4 (C), 130.8 (C), 129.5 (C), 128.7 (C), 117.1 (CH), 112.5 (CH), 111.4 (CH), 111.3 (CH), 105.8 (CH), 103.6 (CH), 102.9 (CH), 102.0 (CH), 70.4 (C), 55.9 (CH_3), 55.7 (CH_3), 52.1 (CH_2), 41.7 (CH_2), 33.2 (CH_2), 31.8 (CH_2), 21.7 (CH_2). HRMS: *m/z* $[M + H]^+$ calcd for $C_{25}H_{26}N_3O_3$: 416.1969; found: 416.1968.

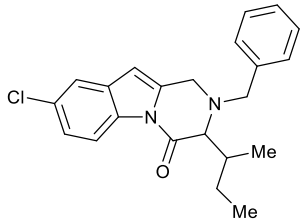
5.2. Characterization data of 2-benzyl-3-substituted 2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-ones 10



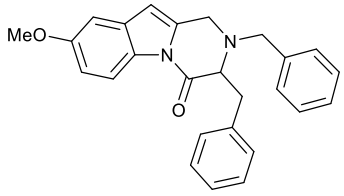
2-benzyl-3-isopropyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 10b: 71 % yield (66.0mg); dark yellow oil; R_f = 0.22 (*n*-hexane-EtOAc, 95:5); IR (neat): 2965, 1699, 1459, 1348, 1326, 719 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.43 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 6.7 Hz, 1H), 7.31 - 7.21 (m, 7H), 6.26 (s, 1H), 4.21 (dd, J_1 = 17.3, J_2 = 1.9 Hz, 1H), 3.77 (d, *J* = 17.3 Hz, 1H), 3.72 (d, *J* = 13.3 Hz, 1H), 3.67 (d, *J* = 13.3 Hz, 1H), 3.02 (d, *J* = 9.0 Hz, 1H), 2.14 (m, 1H), 1.16 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 169.7 (C), 138.2 (C) , 135.0 (C), 134.9 (C), 129.7 (C), 129.0 (CH), 128.6 (CH), 127.6 (CH), 124.5 (CH), 124.1 (CH), 120.2 (CH), 116.6 (CH), 104.9 (CH), 71.6 (CH), 59.2 (CH_2), 42.3 (CH_2), 28.7 (CH), 21.2 (CH_3), 20.2 (CH_3); HRMS: *m/z* $[M + H]^+$ calcd for $C_{25}H_{23}N_2O$: 319.1805; found: 319.1804.



2-benzyl-3-(sec-butyl)-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 10c: 67 % yield (64.5 mg); dark yellow oil; R_f = 0.21 (*n*-hexane-EtOAc, 95:5); IR (neat): 2955, 1679, 1450, 1340, 1310, 739 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.46 (d, *J* = 8.1 Hz, 1H), 7.50 (d, *J* = 6.8 Hz, 1H), 7.34 - 7.23 (m, 7H), 6.29 (s, 1H), 4.24 (dd, J_1 = 17.3 Hz, J_2 = 1.5 Hz, 1H), 3.80 (d, *J* = 17.3 Hz, 1H), 3.73 (s, 2H), 3.18 (d, *J* = 11.1 Hz, 1H), 2.07 - 1.97 (m, 1H), 1.95 - 1.85 (m, 1H), 1.46 - 1.35 (m, 1H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 170.0 (C), 138.1 (C), 134.9 (C), 129.8 (C), 129.1 (C), 128.6 overlapping (CH), 127.7 (CH), 124.5 (CH), 124.1 (CH), 120.2 (CH), 116.7 (CH), 105.0 (CH), 77.5 (CH), 77.2 (CH), 76.8 (CH), 69.9 (CH), 59.3 (CH_2), 42.3 (CH_2), 34.3 (CH), 26.6 (CH_2), 16.2 (CH_3), 10.4 (CH_3); HRMS: *m/z* $[M + H]^+$ calcd for $C_{22}H_{25}N_2O$: 333.1961; found: 333.1961.



2-benzyl-3-(sec-butyl)-8-chloro-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 10d: 54 % yield (57.3 mg); pale orange oil; R_f = 0.22 (*n*-hexane-EtOAc, 99:1); IR (neat): 2922, 1702, 1447, 1342, 733, 698 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.37 (d, *J* = 8.7 Hz, 1H), 7.46 (d, *J* = 2.1 Hz, 1H), 7.35 - 7.24 (m, 6H), 6.24 (s, 1H), 4.22 (dd, J_1 =17.4, J_2 = 1.9 Hz, 1H), 3.79 (d, *J* = 17.4 Hz, 1H), 3.72 (s, 2H), 3.18 (d, *J* = 10.0 Hz, 1H), 2.07 - 1.97 (m, 1H), 1.95 - 1.85 (m, 1H), 1.46 - 1.35 (m, 1H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 169.8 (C), 137.9 (-C), 136.5 (C), 133.2 (C), 131.1 (C), 129.7 (C), 129.0 (CH), 128.6 (CH), 127.7 (CH), 124.5 (CH), 119.9 (CH), 117.5 (CH), 104.2 (CH), 69.7 (CH), 59.4 (CH_2), 42.3 (CH_2), 34.2 (CH), 26.6 (CH_2), 16.1 (CH_3), 10.4 (CH_3); HRMS: *m/z* $[M + H]^+$ calcd for $C_{22}H_{24}ClN_2O$: 367.1572; found: 367.1571.

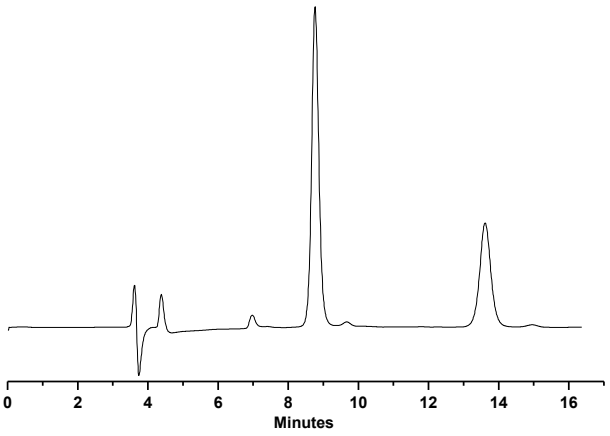


2,3-dibenzyl-8-methoxy-2,3-dihydropyrazino[1,2-a]indol-4(1H)-one 10e: 68% yield (78.1 mg); orange solid; mp:116-118 °C; R_f = 0.22 (*n*-hexane-EtOAc, 96:4); IR (neat): 3020, 2810, 1682, 1373, 1163, 695 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.35 (d, *J* = 8.8 Hz, 1H), 7.36 - 7.18 (m, 8H), 7.00 - 6.93 (m, 4H), 6.29 (s, 1H), 4.33 (dd, J_1 = 16.9, J_2 = 1.1 Hz, 1H), 3.88 (s, 3H), 3.86 (d, *J* = 5.3 Hz, 1H), 3.83 (d, *J* = 5.3 Hz, 1H), 3.77 (d, *J* = 13.3 Hz, 1H), 3.61 (d, *J* = 13.3 Hz, 1H), 3.29 (dd, J_1 = 14.4, J_2 = 4.8 Hz, 1H), 3.20 (dd, J_1 = 14.4, J_2 = 10.0 Hz, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 169.0 (C), 157.1 (C), 138.3 (C), 137.6 (C), 135.4 (C), 130.9 (C), 129.5 (C), 129.4 (CH), 128.8 overlapping (CH), 128.4 (CH), 127.5 (CH), 126.7 (CH), 117.2 (CH), 112.5 (CH), 105.3 (CH), 103.7 (CH), 66.3 (CH), 58.2 (CH_2), 55.8 (CH_3), 43.0 (CH_2), 35.5 (CH_2); HRMS: *m/z* $[M + H]^+$ calcd for $C_{26}H_{25}N_2O_2$: 397.1910; found: 397.1910.

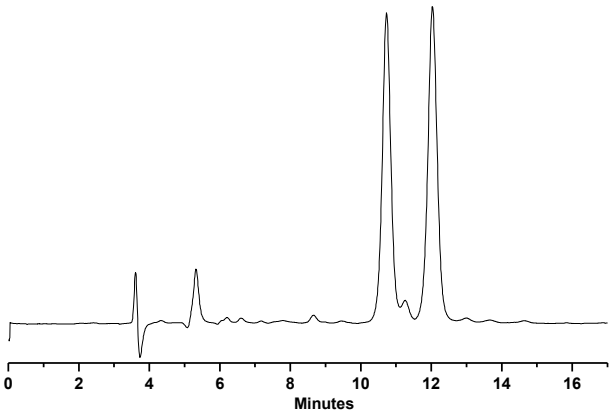
6. HPLC DATA AND CHROMATOGRAMS: EFFECT OF REACTION TEMPERATURE IN ENANTIOMERIC EXCESS

Enantiomeric ratios were determined on JASCO HPLC system equipped with a UV/CD detector. Chiralpak IA column (250x4.6 mm L.xI.D. 5µm), *n*-hexane/DCM 80/20 + 1% MeOH, 1 mL/min, UV detection at 254 nm (product **5f**) or 280 nm (product **8f**), room temperature. Analytical conditions have been optimized on racemic version of product **5f** (k_1 = 1.43, K_2 = 2.78, α = 1.94) and **8f** (k_1 = 1.97, K_2=2.33, α = 1.18)**.**

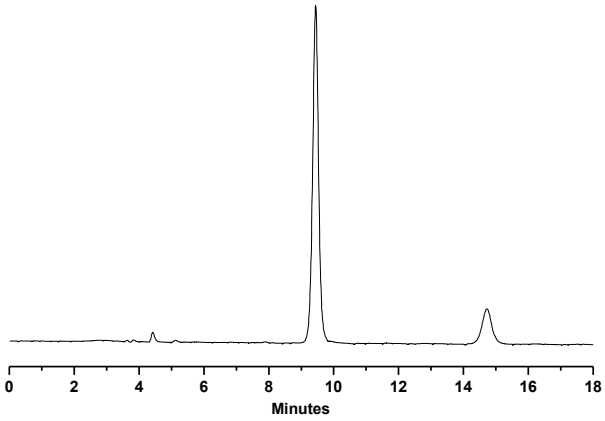
Chromatogram of product 5f obtained using the reaction conditions reported in Table 5, **at 120 °C** (entry 1, see article).
Area ratio of enantiomers was 68:32



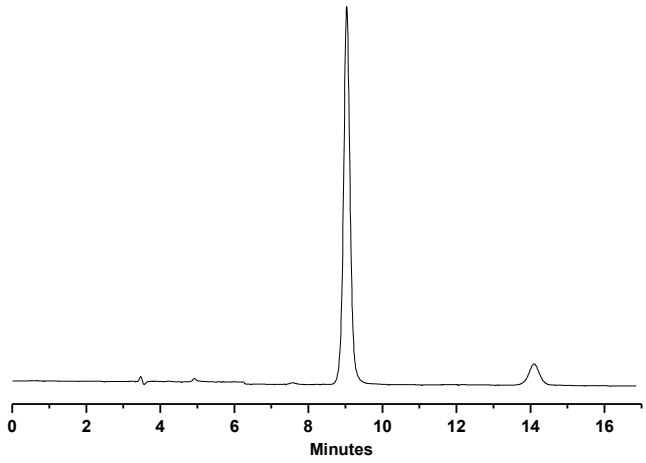
Chromatogram of product 8f obtained using the reaction conditions reported in Table 5, **at 120 °C** (entry 1, see article).
Area ratio of enantiomers was 46:54



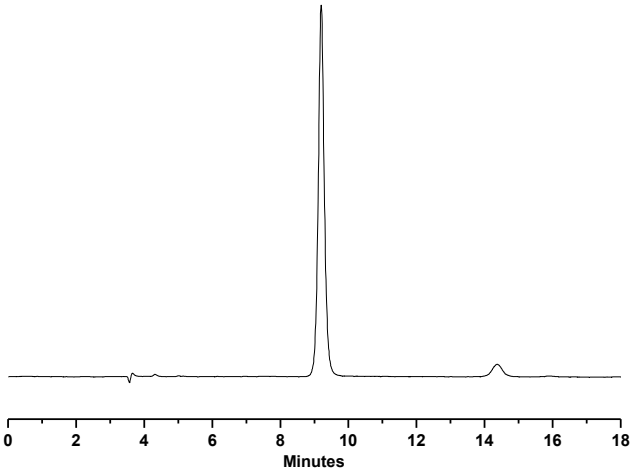
Chromatogram of product 5f obtained using the reaction conditions reported in Table 5, **at 90 °C** (entry 2, see article).
Area ratio of enantiomers was 85:15



Chromatogram of product 5f obtained using the reaction conditions reported in Table 5, **at 70 °C** (entry 3, see article).
Area ratio of enantiomers was 92:8



Chromatogram of product 5f obtained using the reaction conditions reported in Table 5, **at 70 °C** (entry 4, see article).
Area ratio of enantiomers was 95:5


0
2
4
6
8
10
12
14
16
18
Minutes

7. REFERENCES

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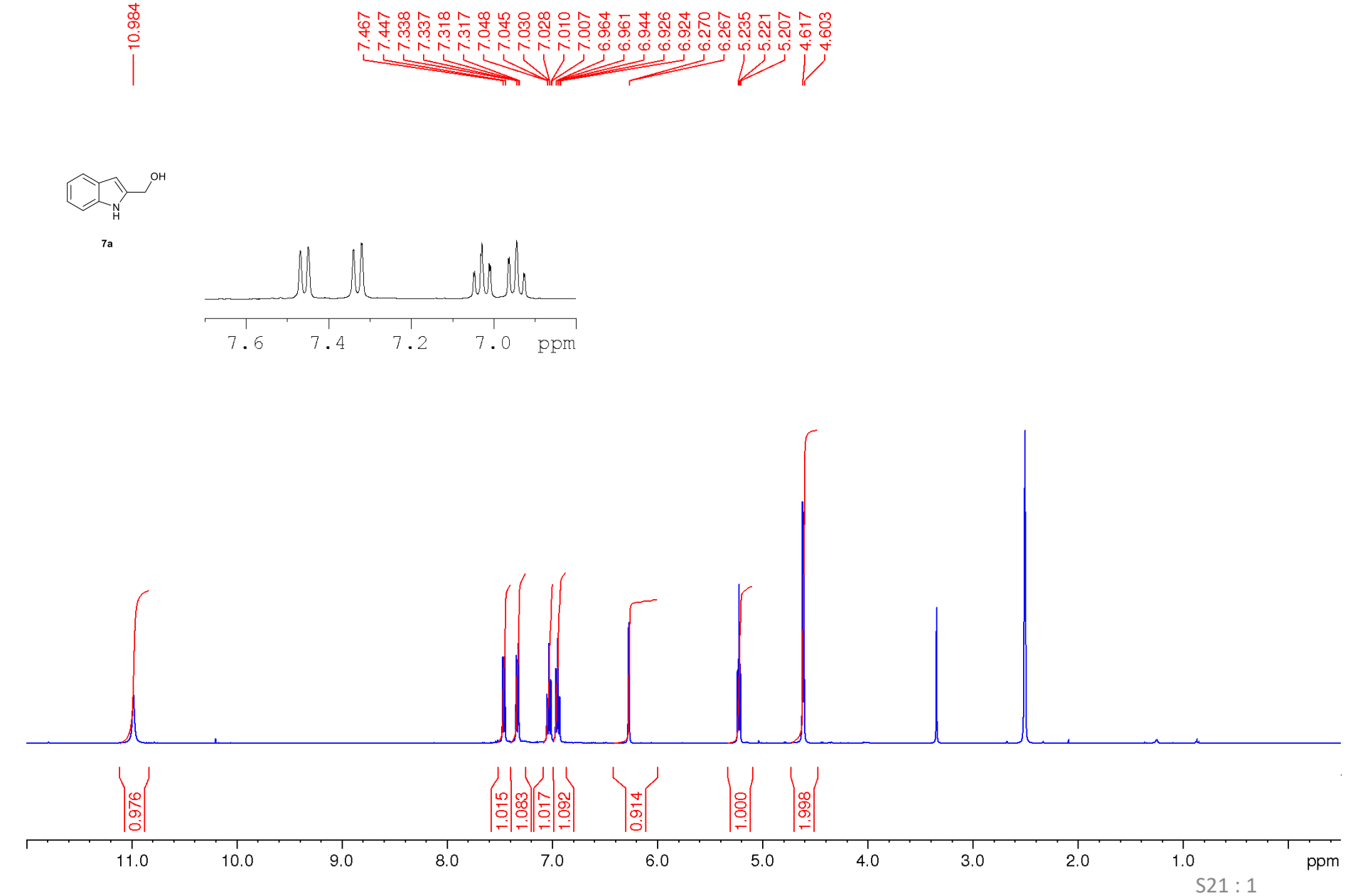
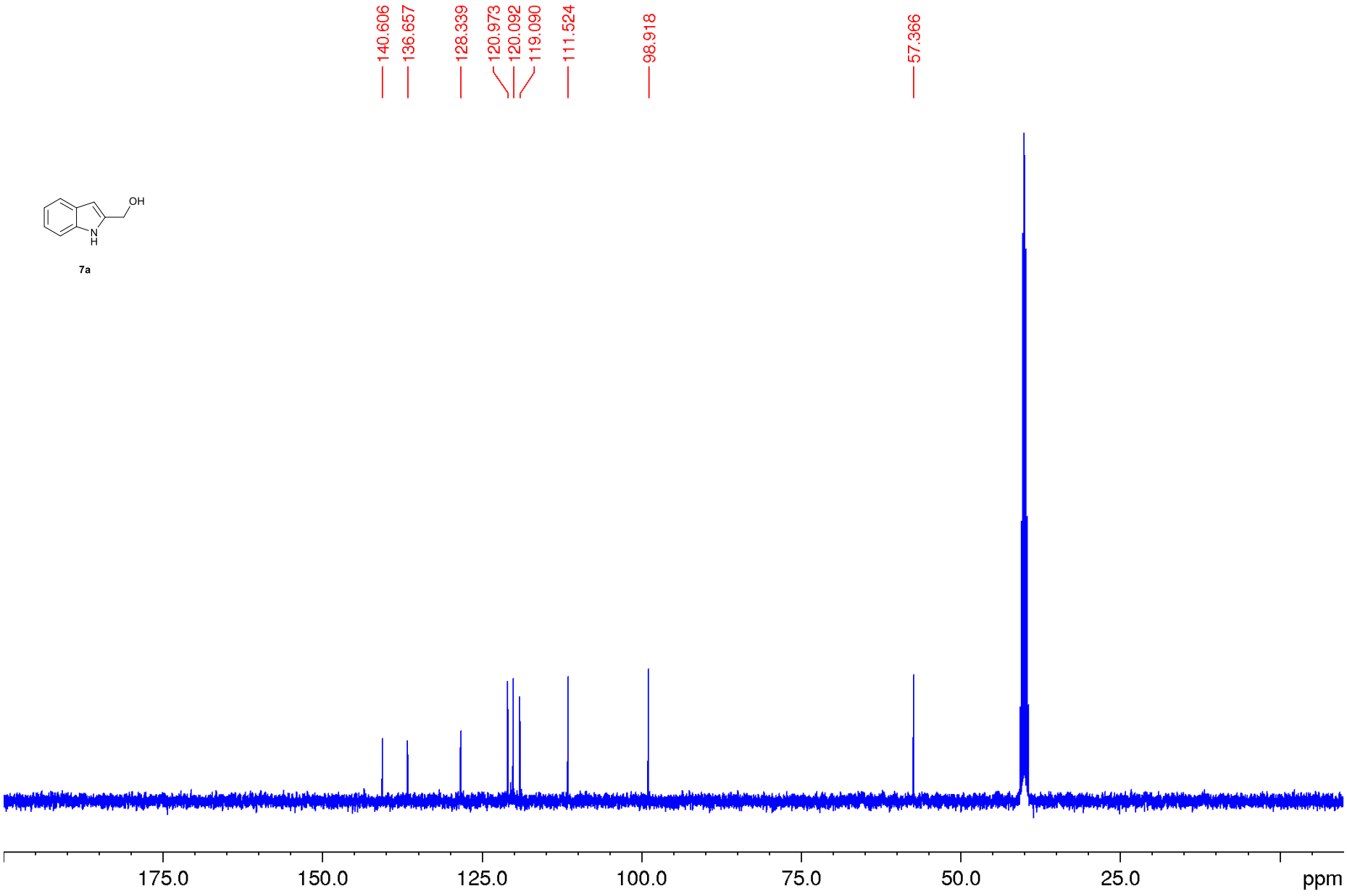
8.· COPIES OF NMR SPECTRA

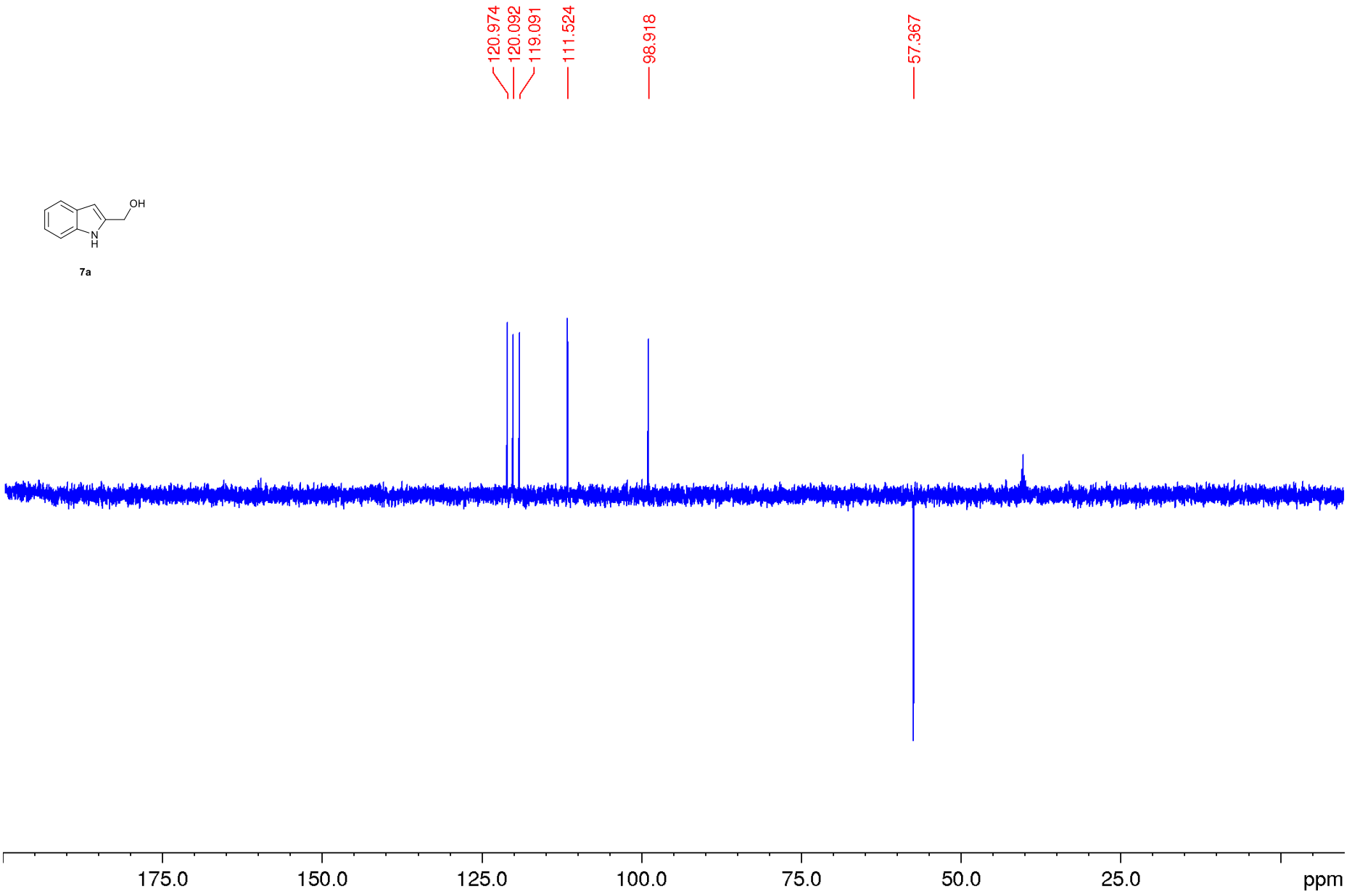
^{1}H NMR-spectrum (400.13 MHz) (DMSO-d_6)



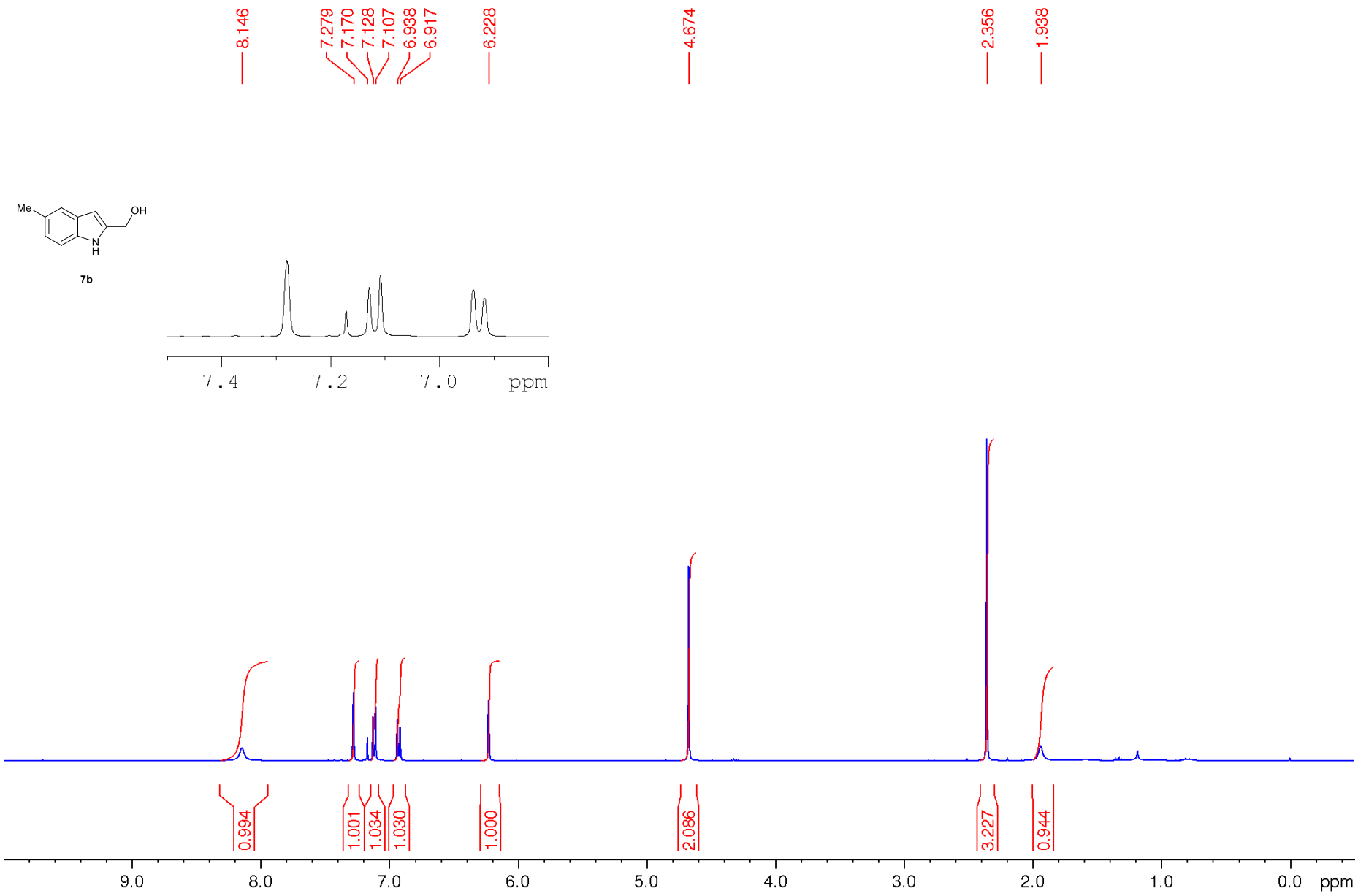
^{13}C NMR-spectrum (100.6 MHz) (DMSO-d_6)



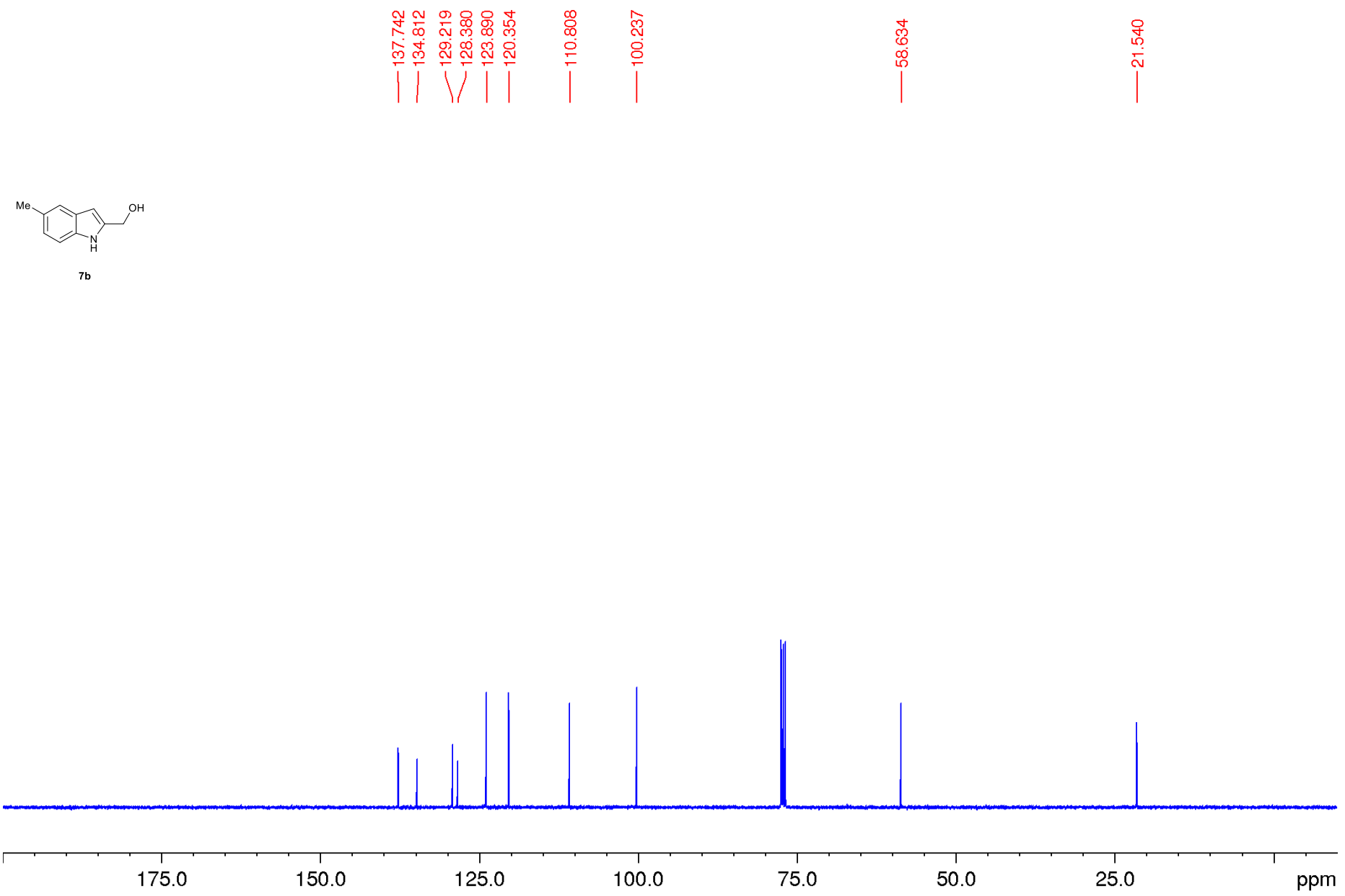
DEPT 135 NMR-spectrum (DMSO-d_6)



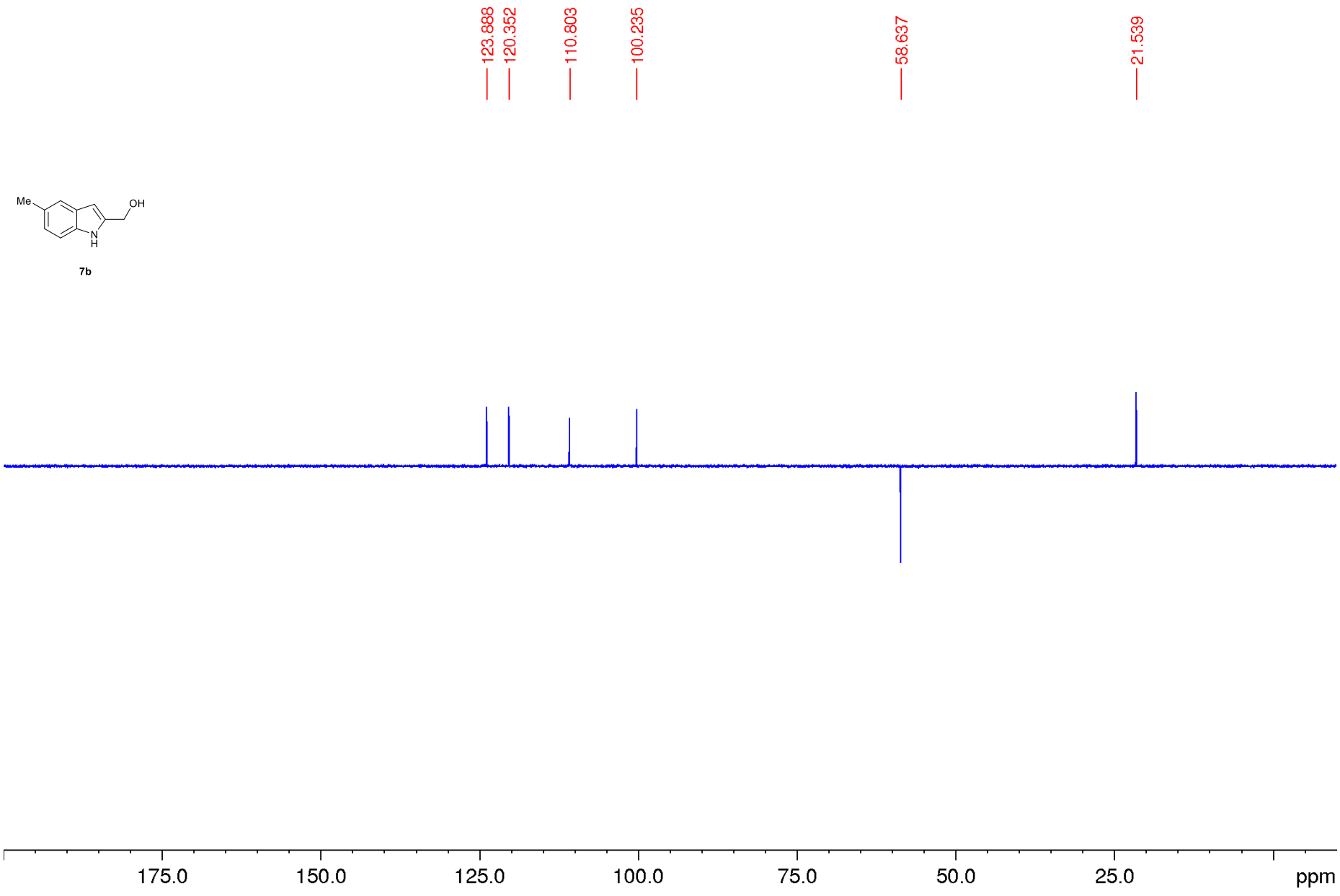
^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



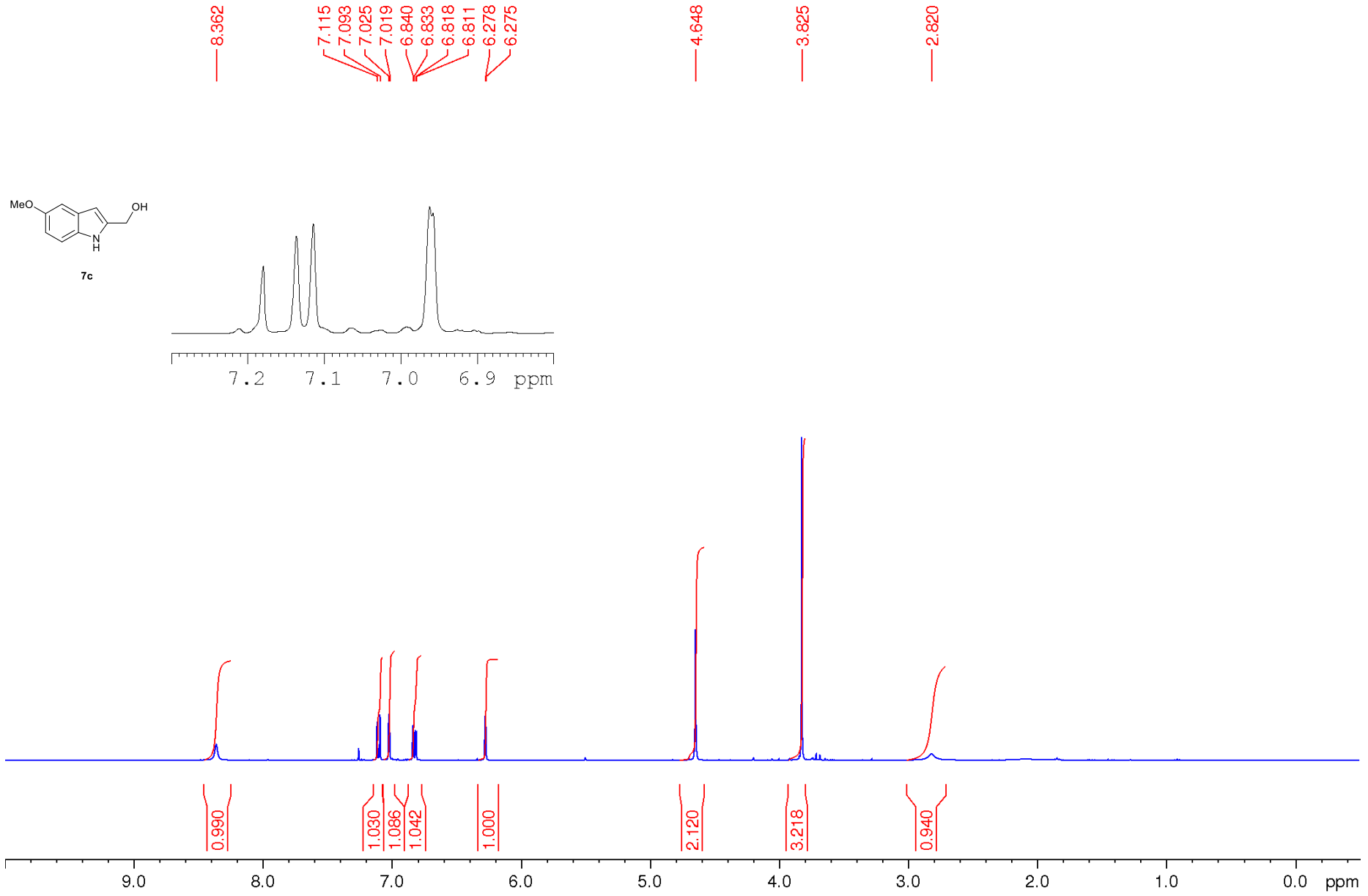
^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



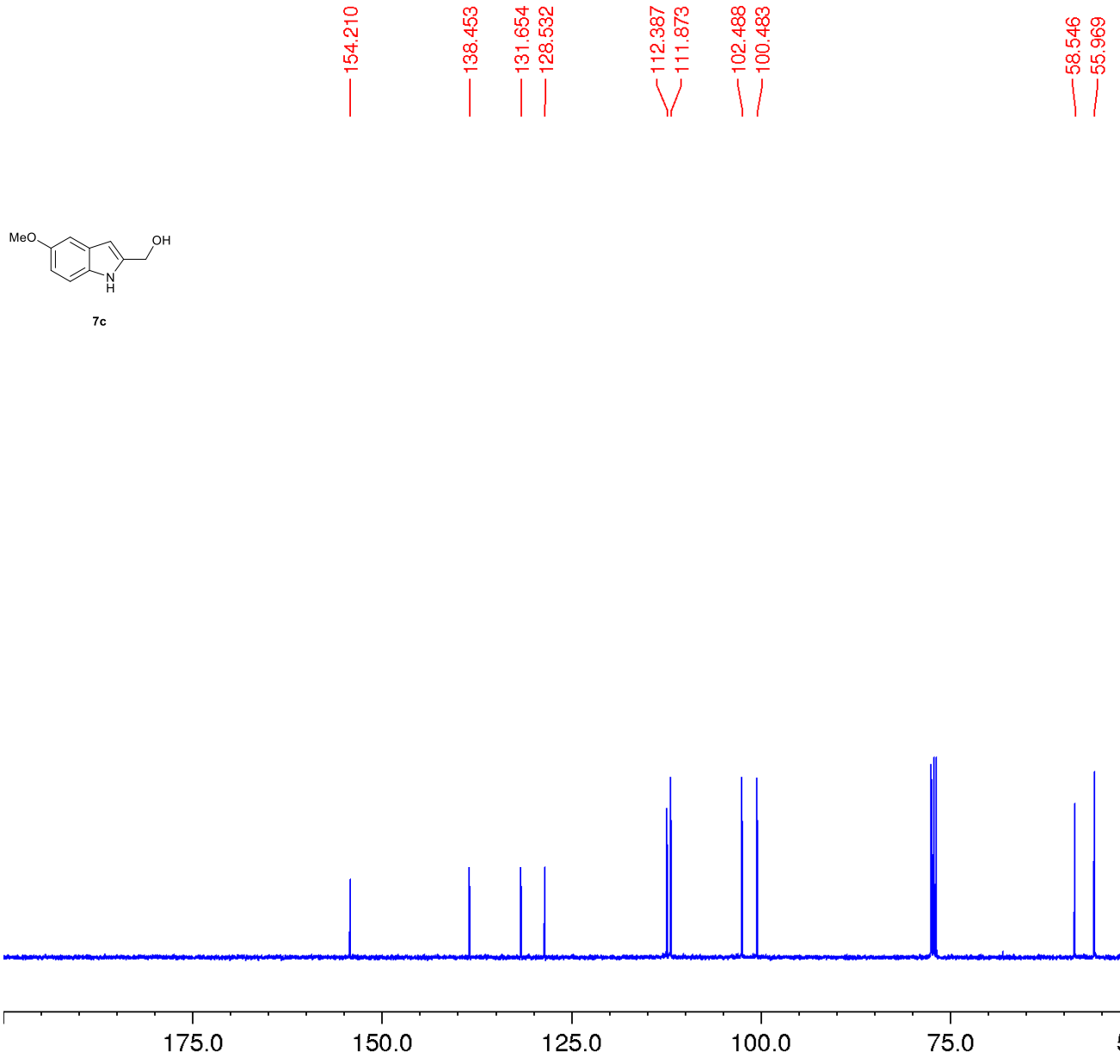
DEPT 135 NMR-spectrum ($CDCl_3$)



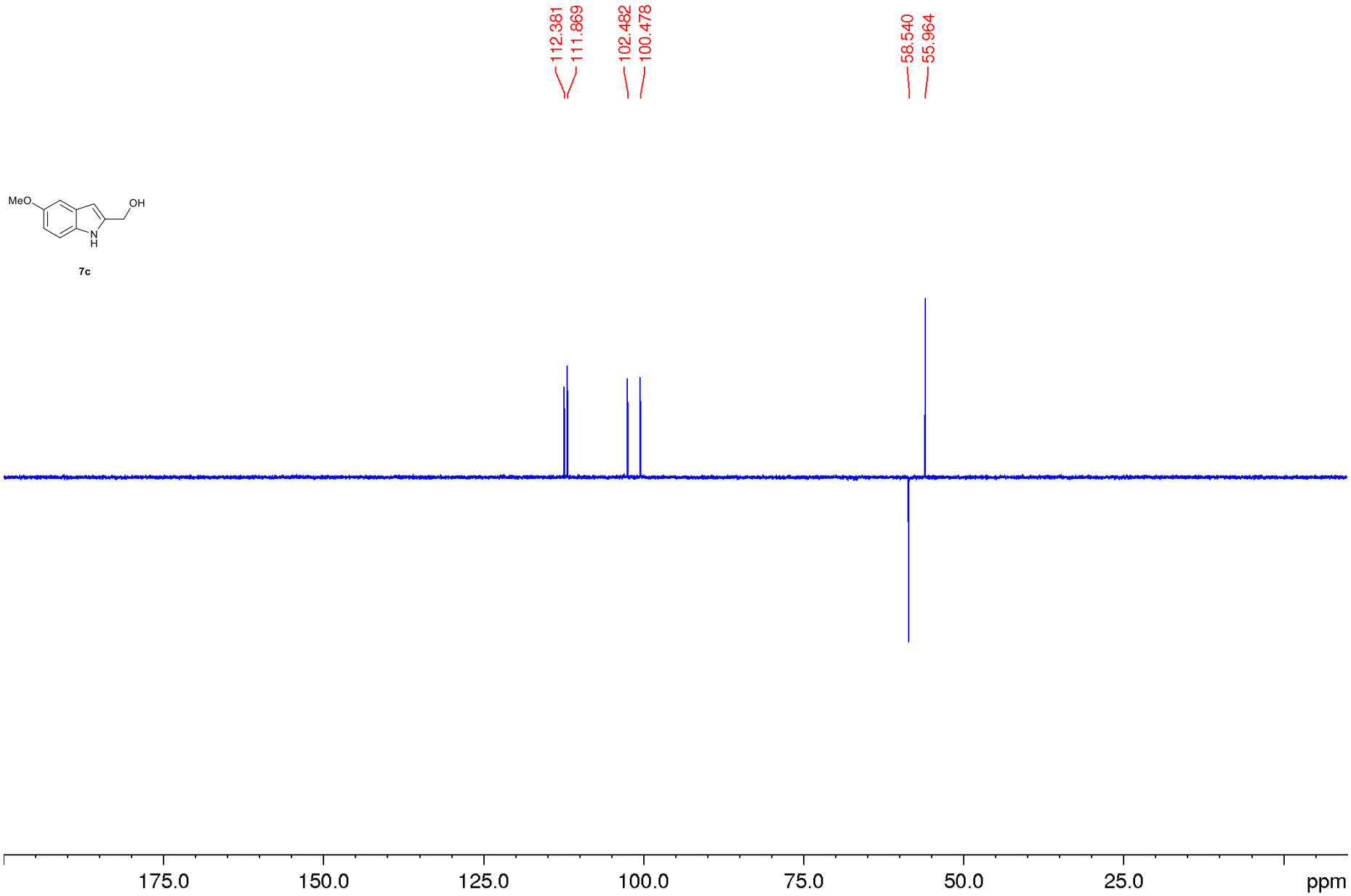
^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



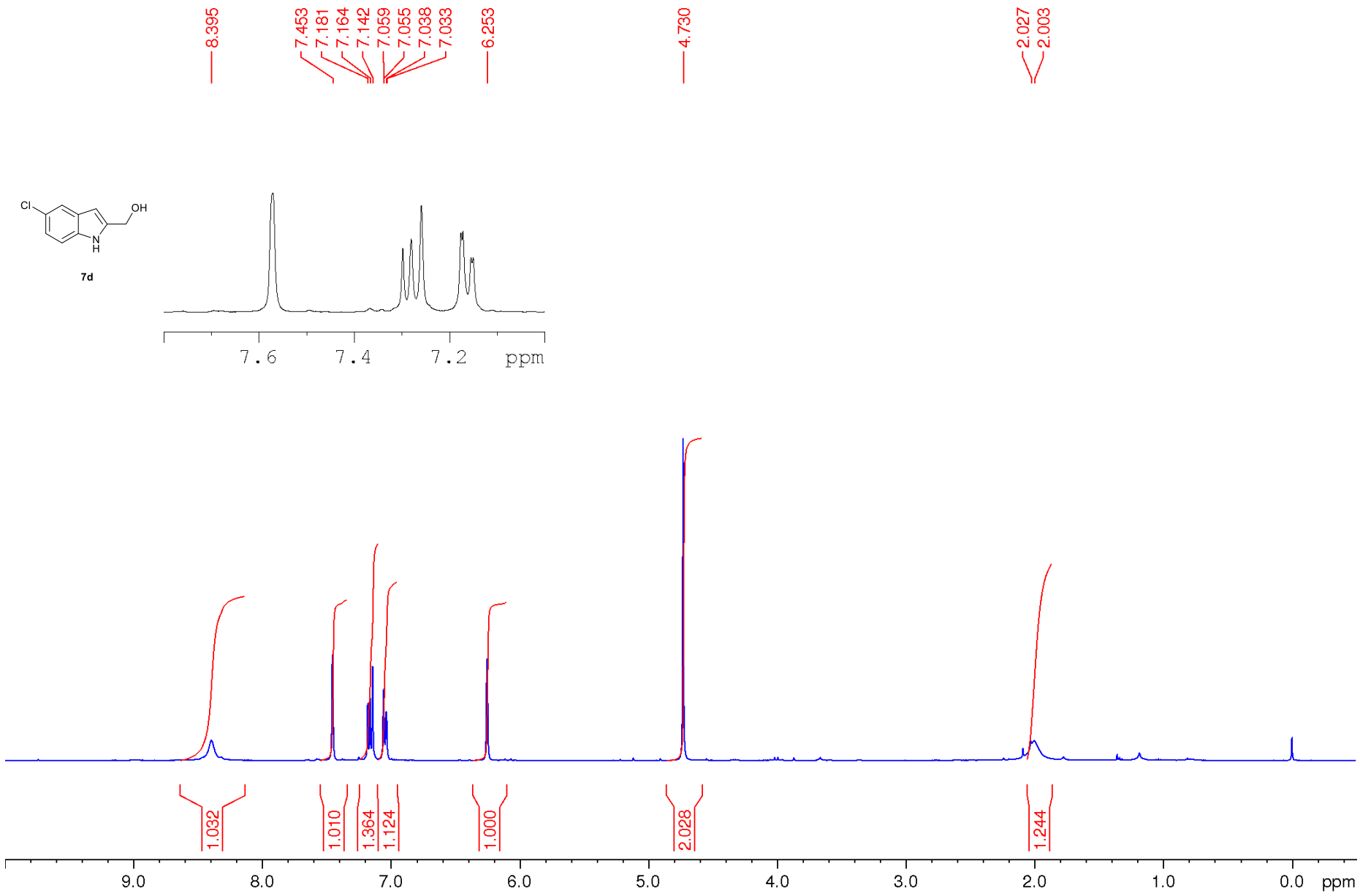
^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



DEPT 135 NMR-spectrum ($CDCl_3$)



^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



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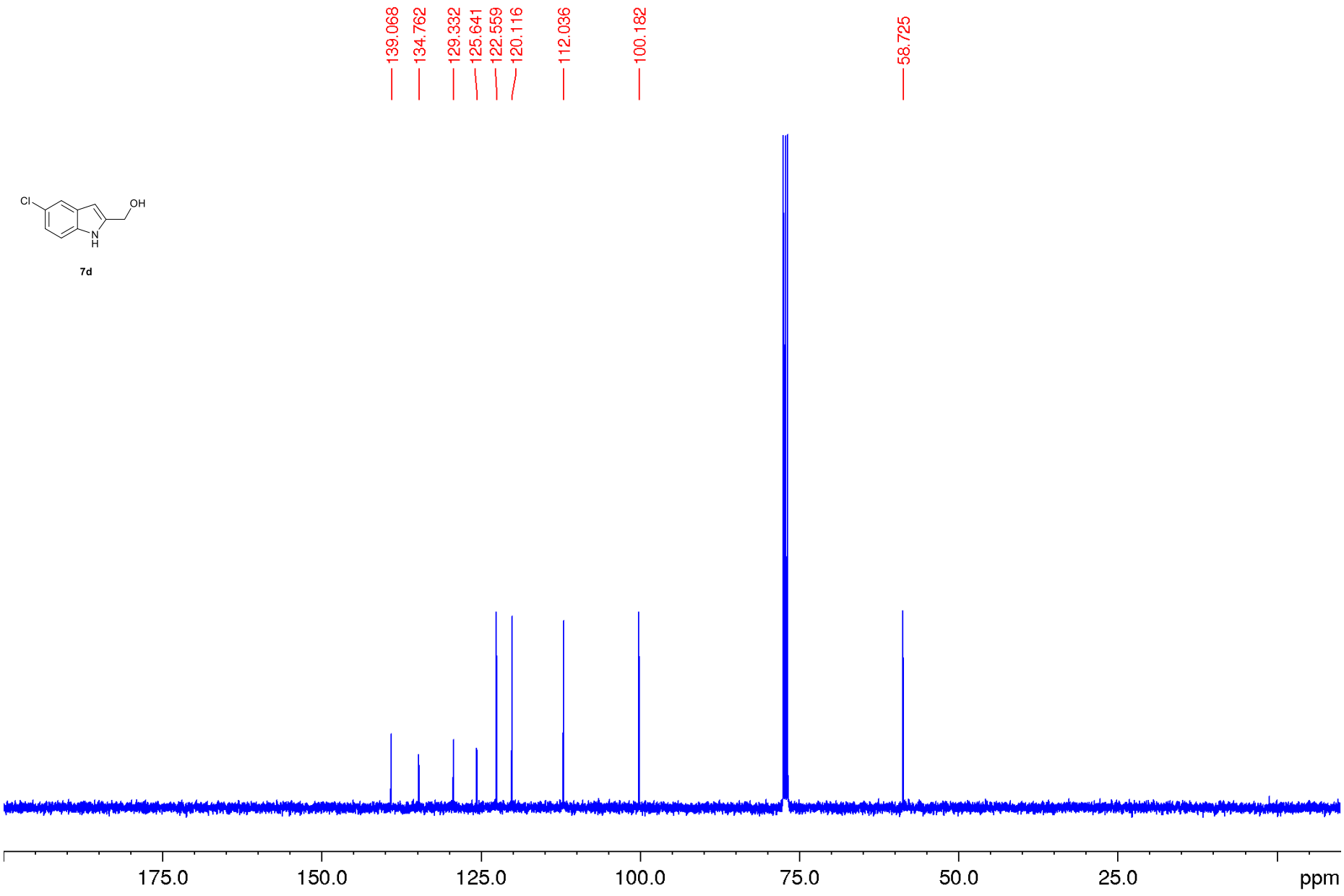

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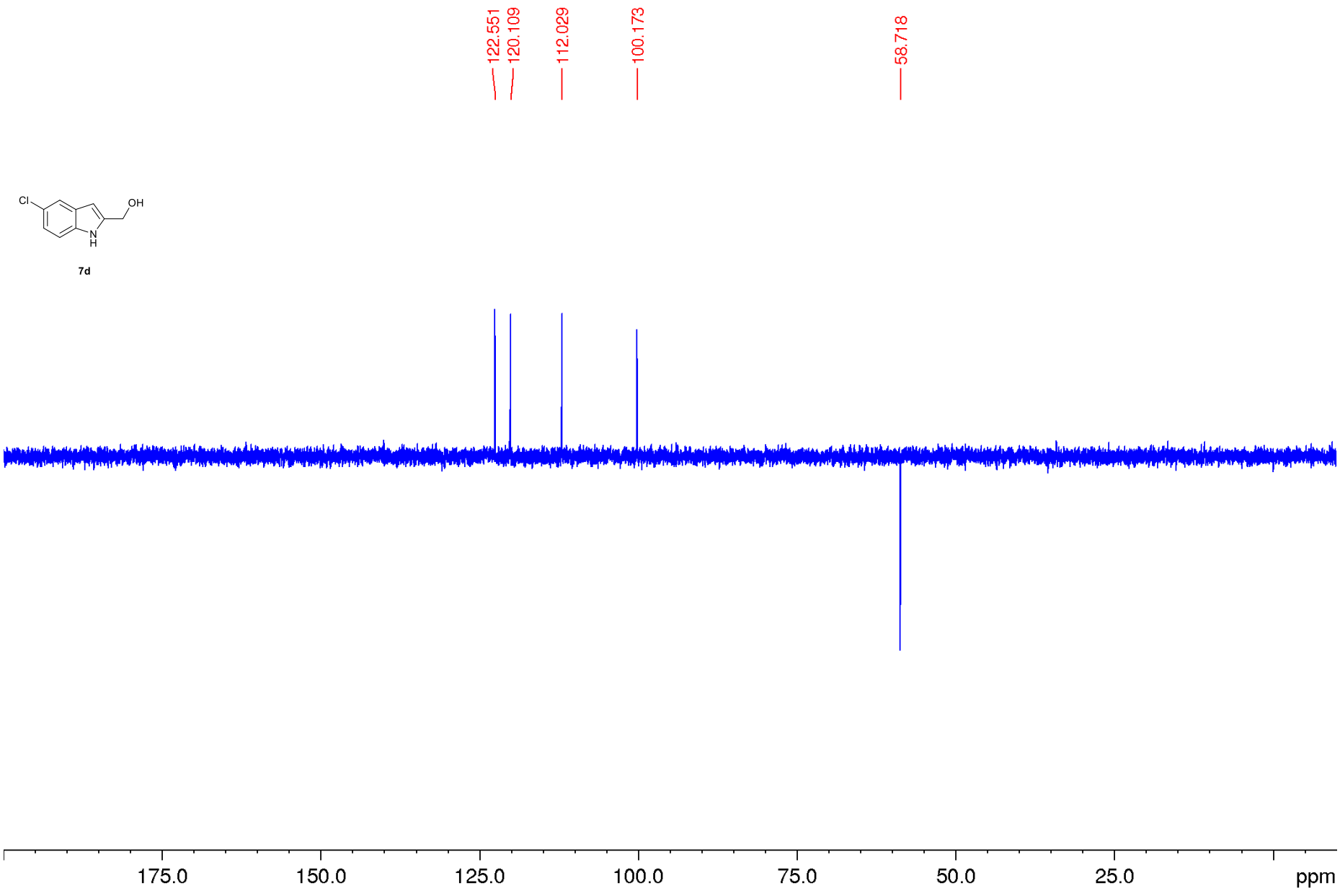
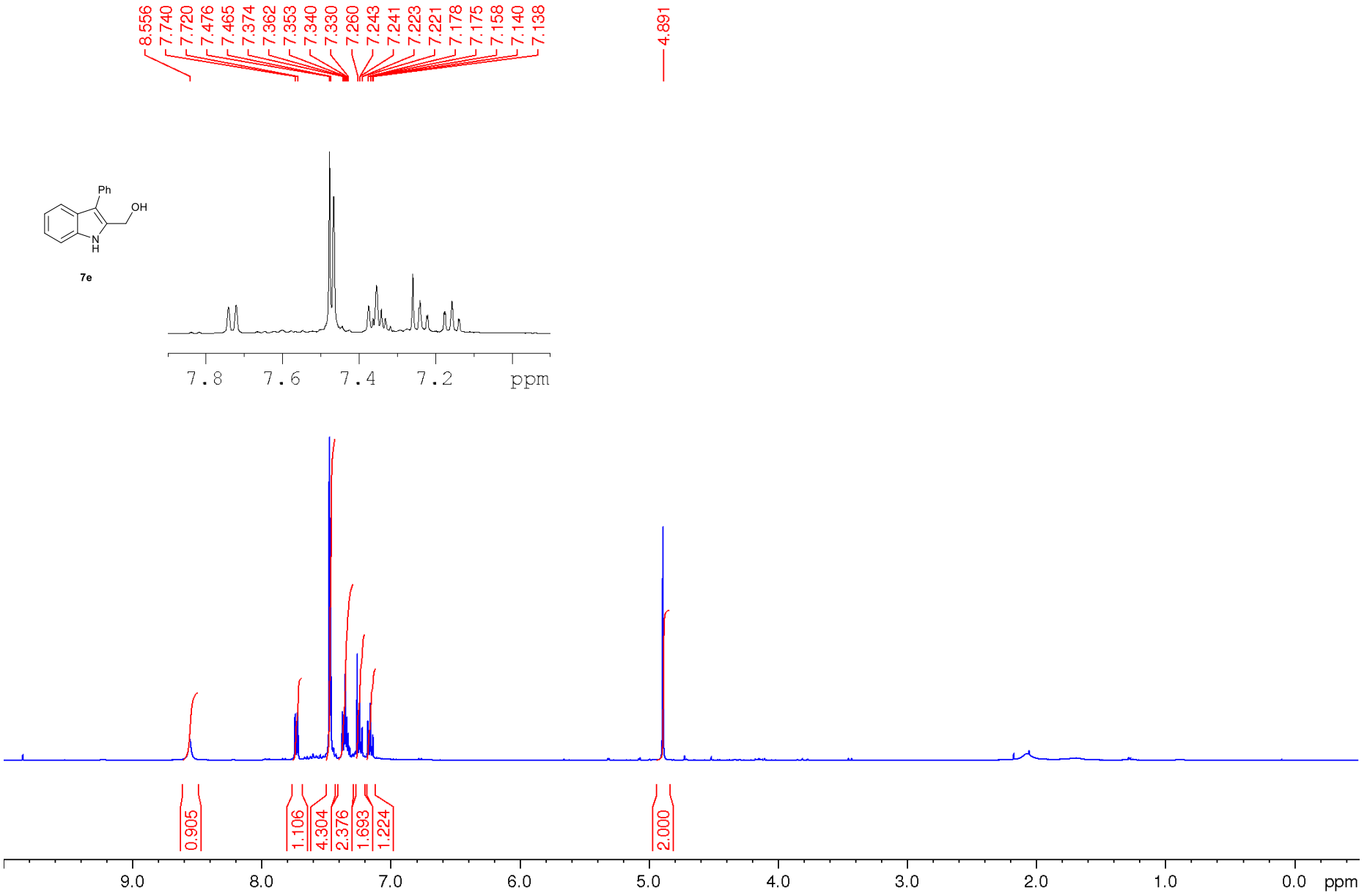


^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



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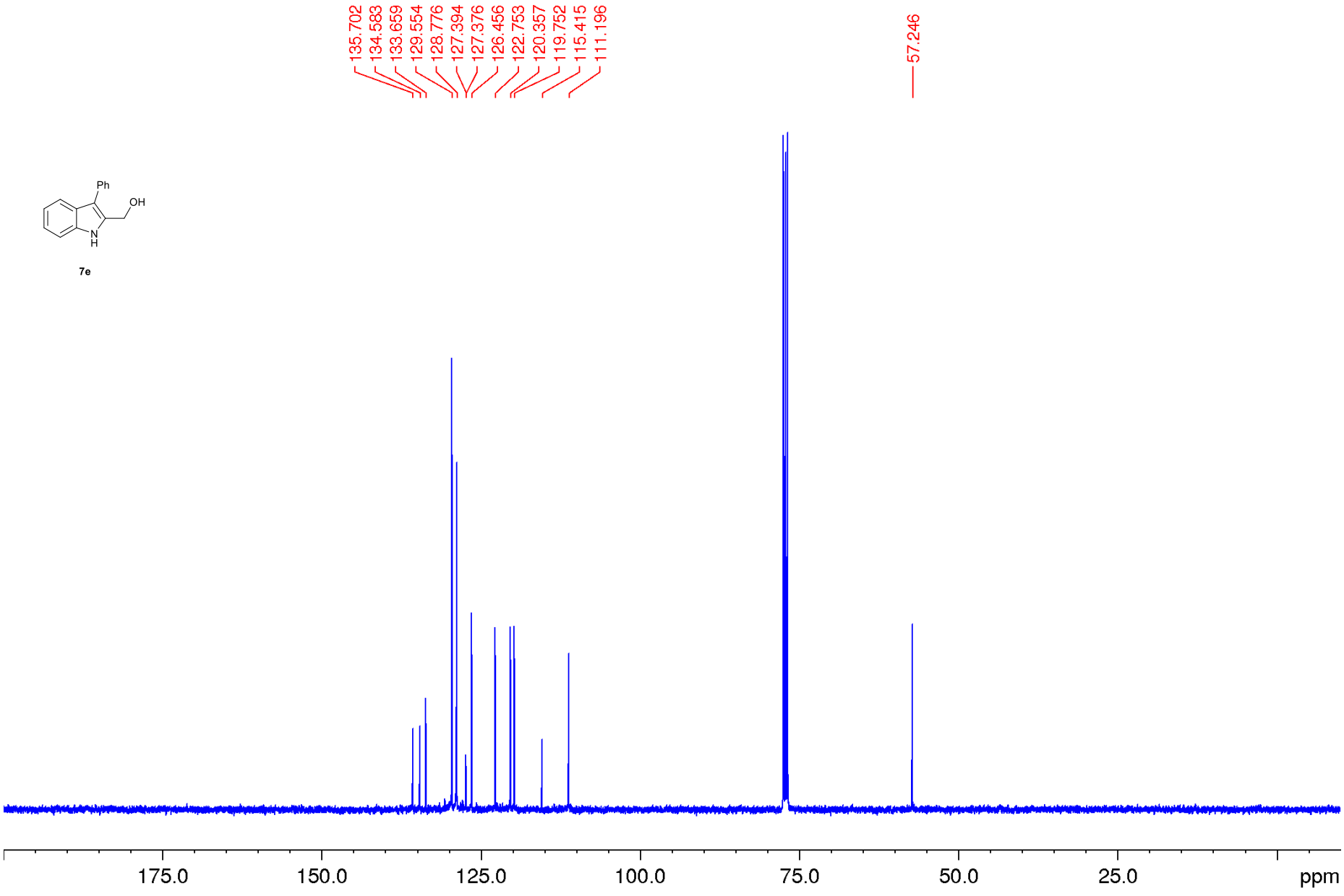

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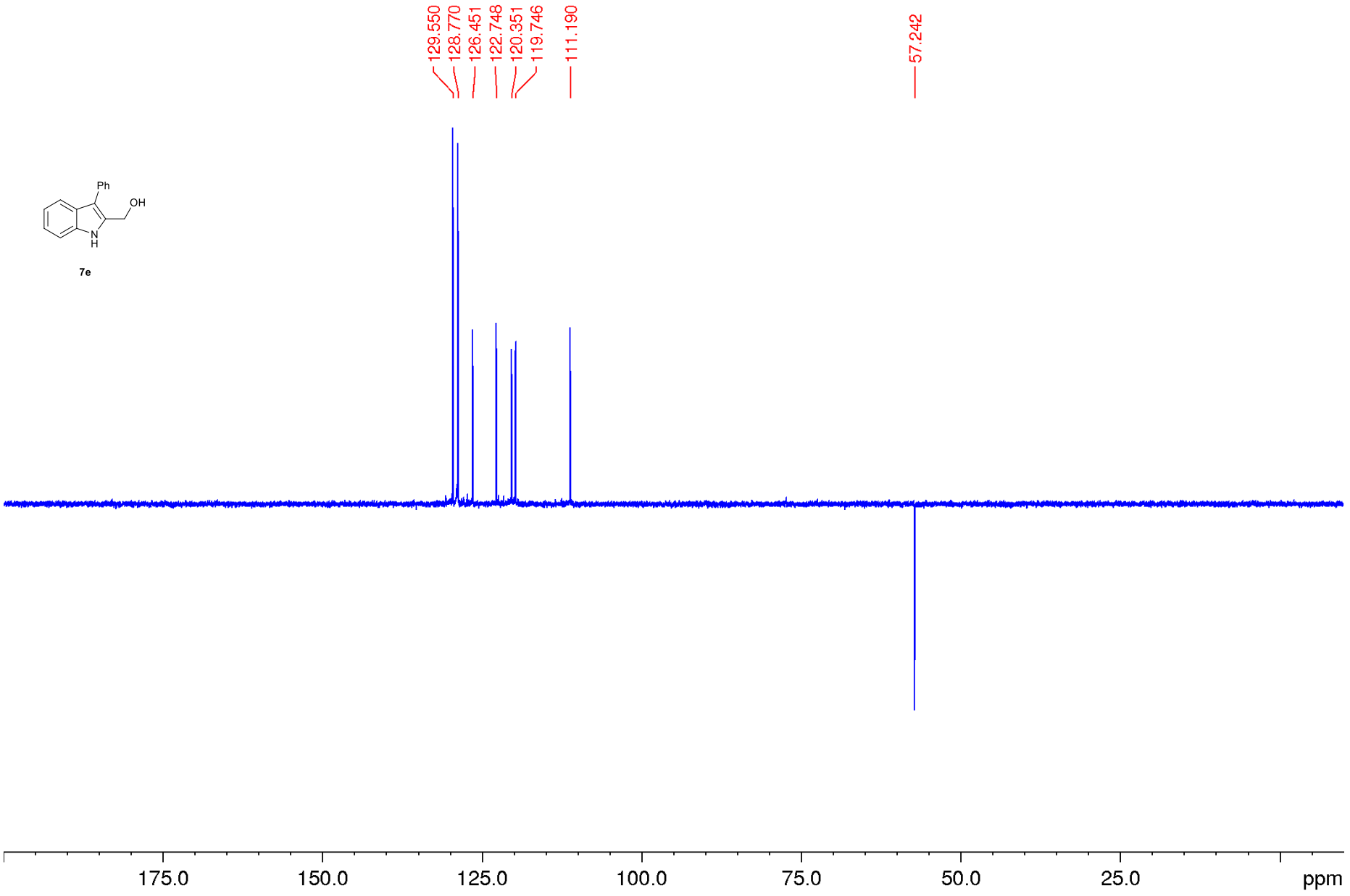

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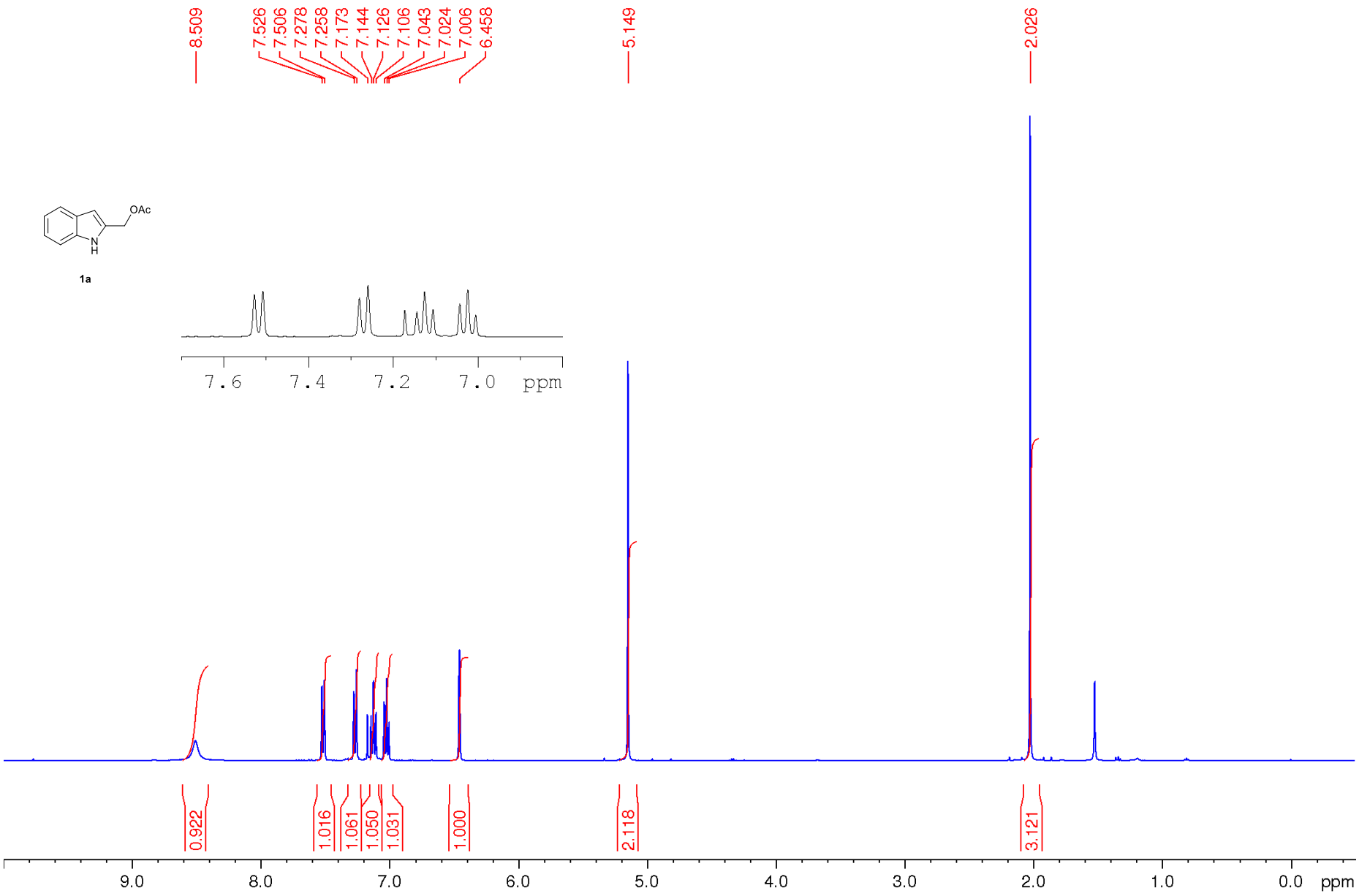
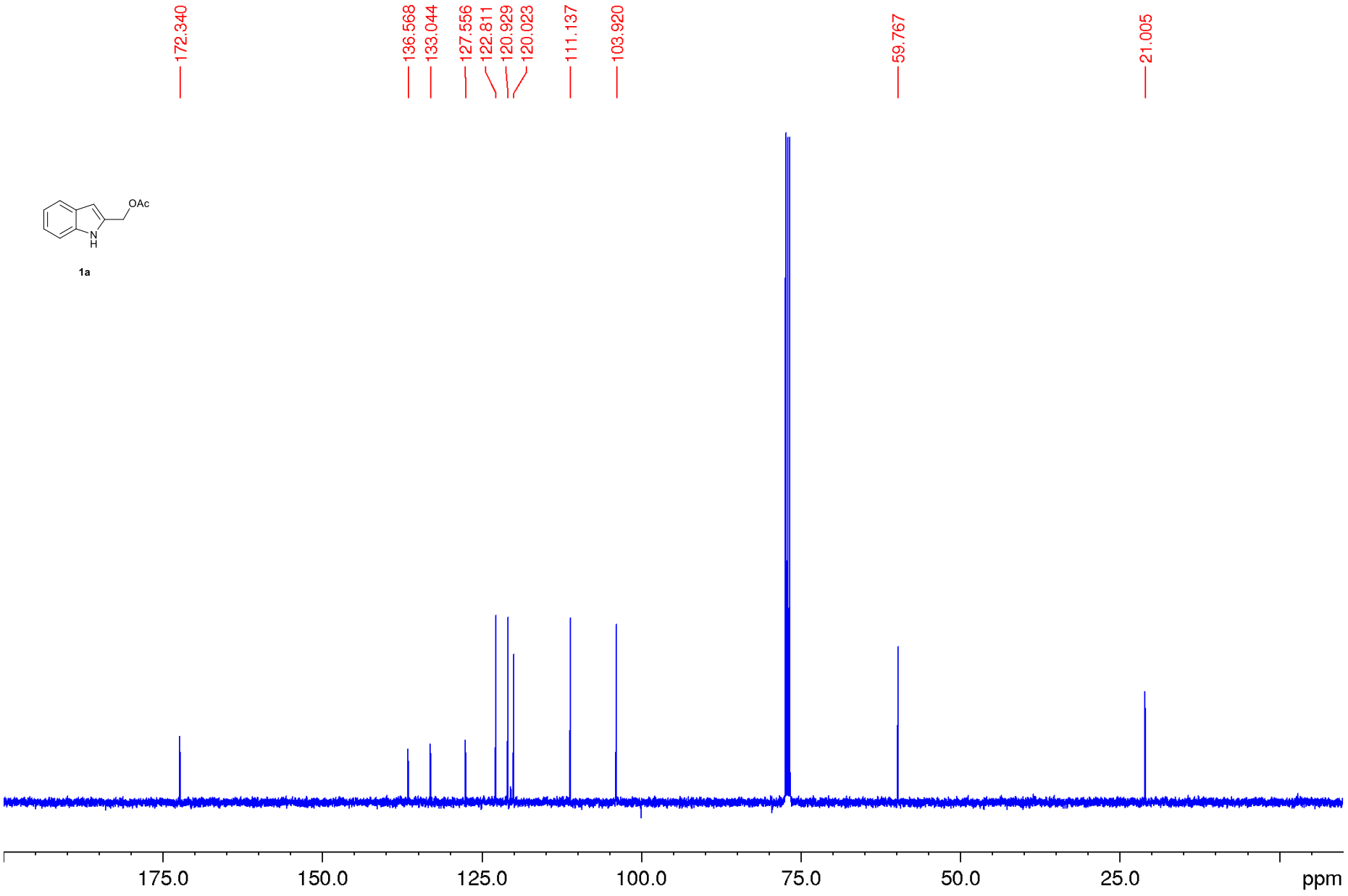


^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



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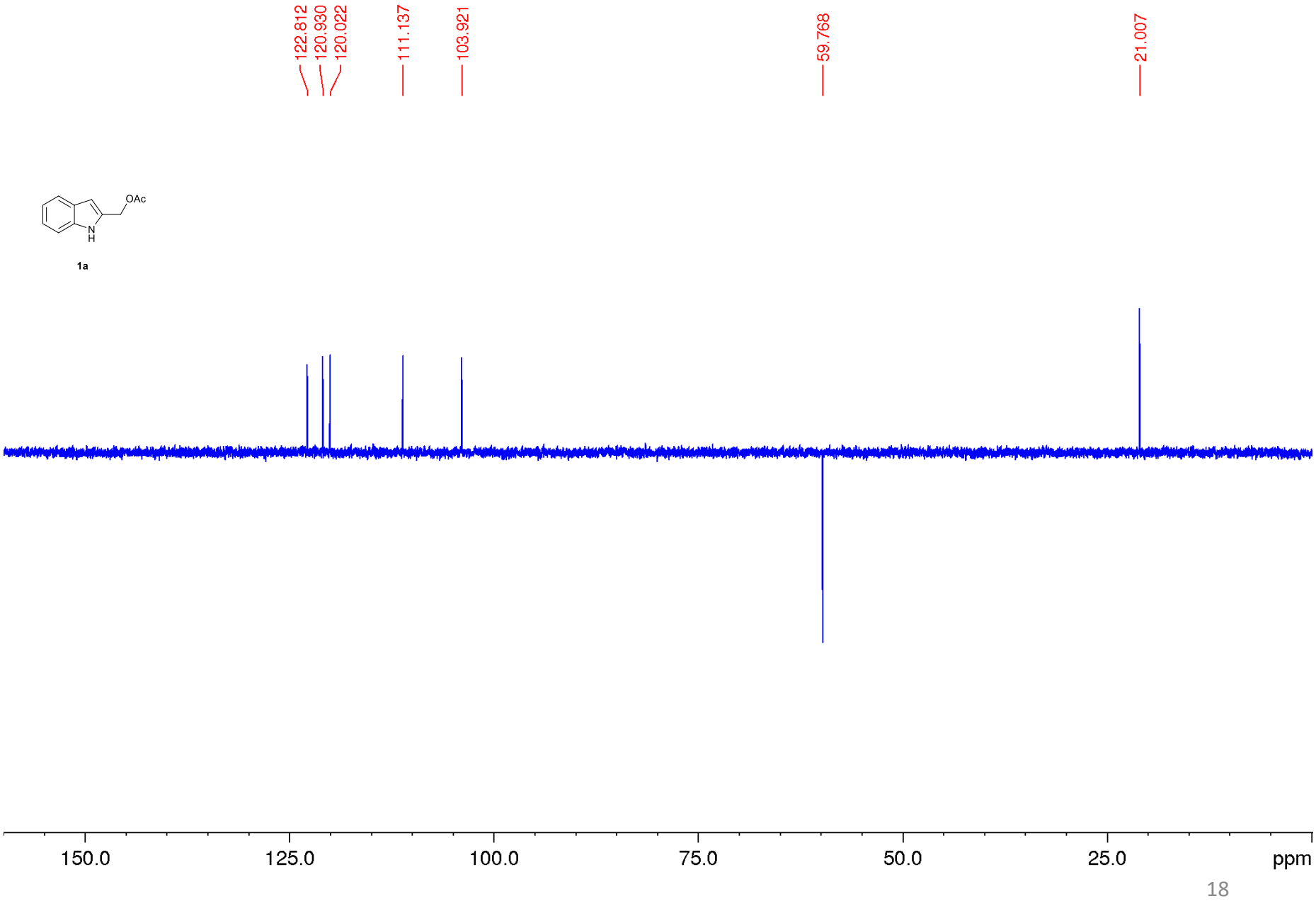

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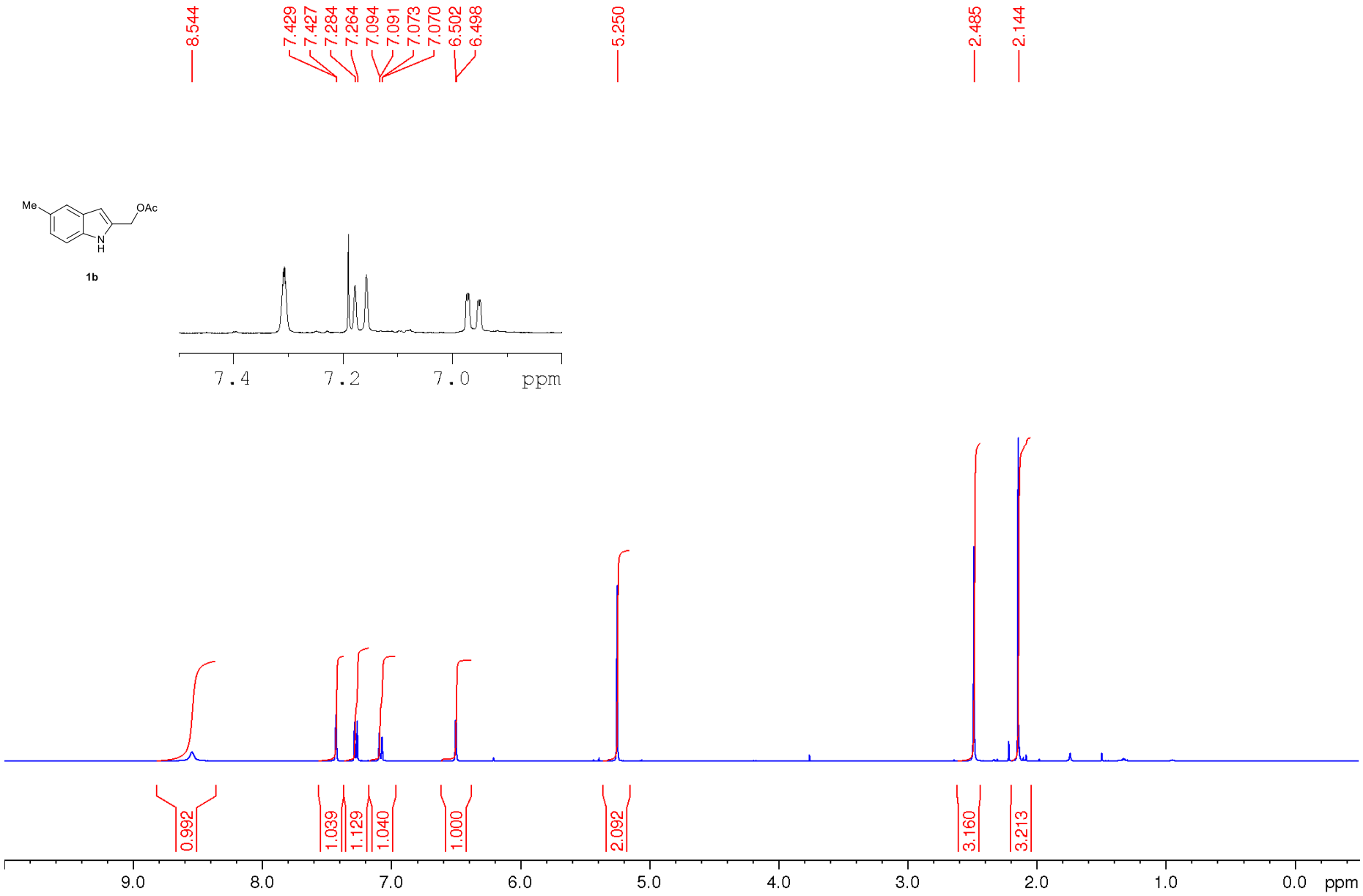
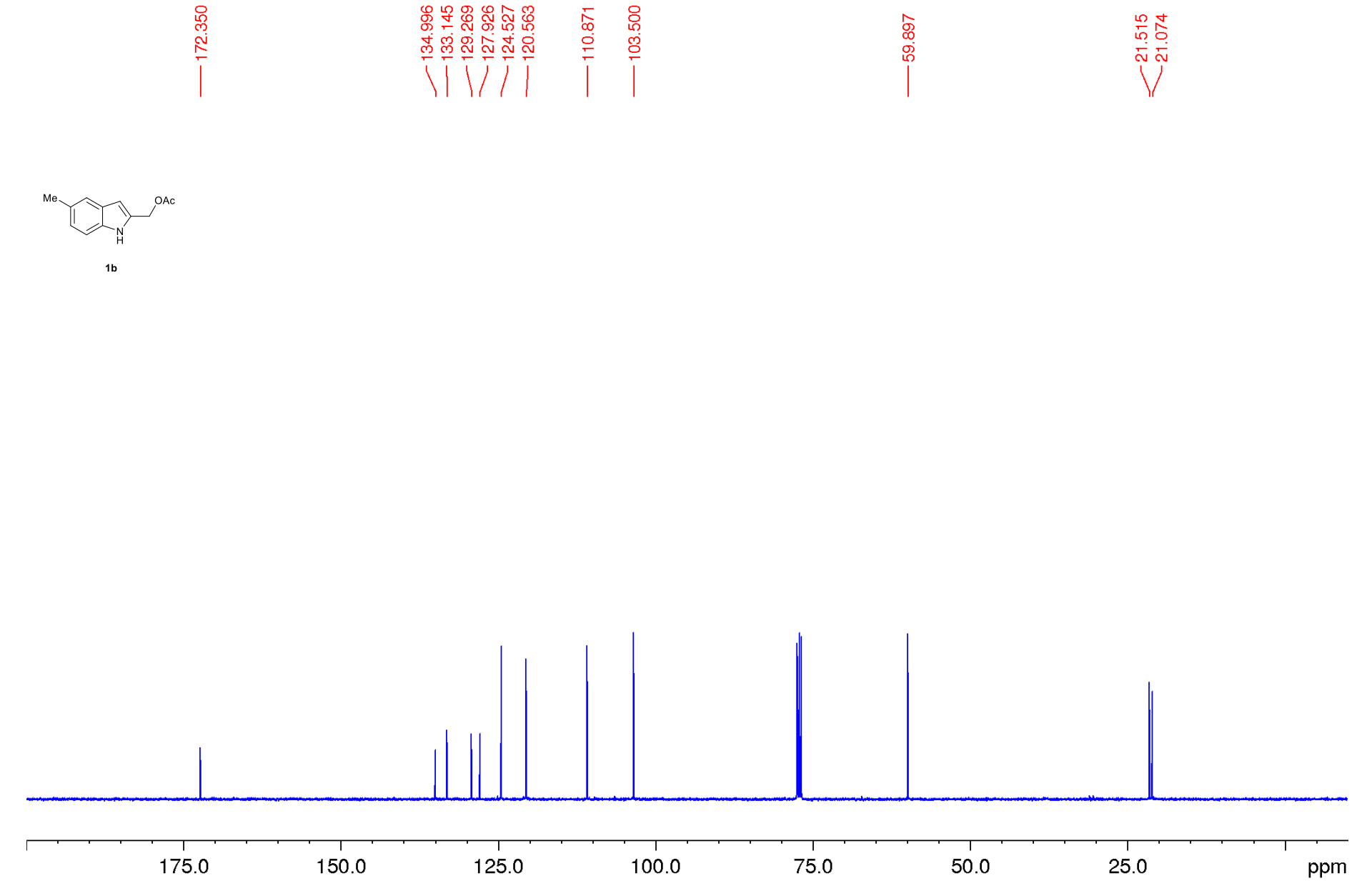


^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



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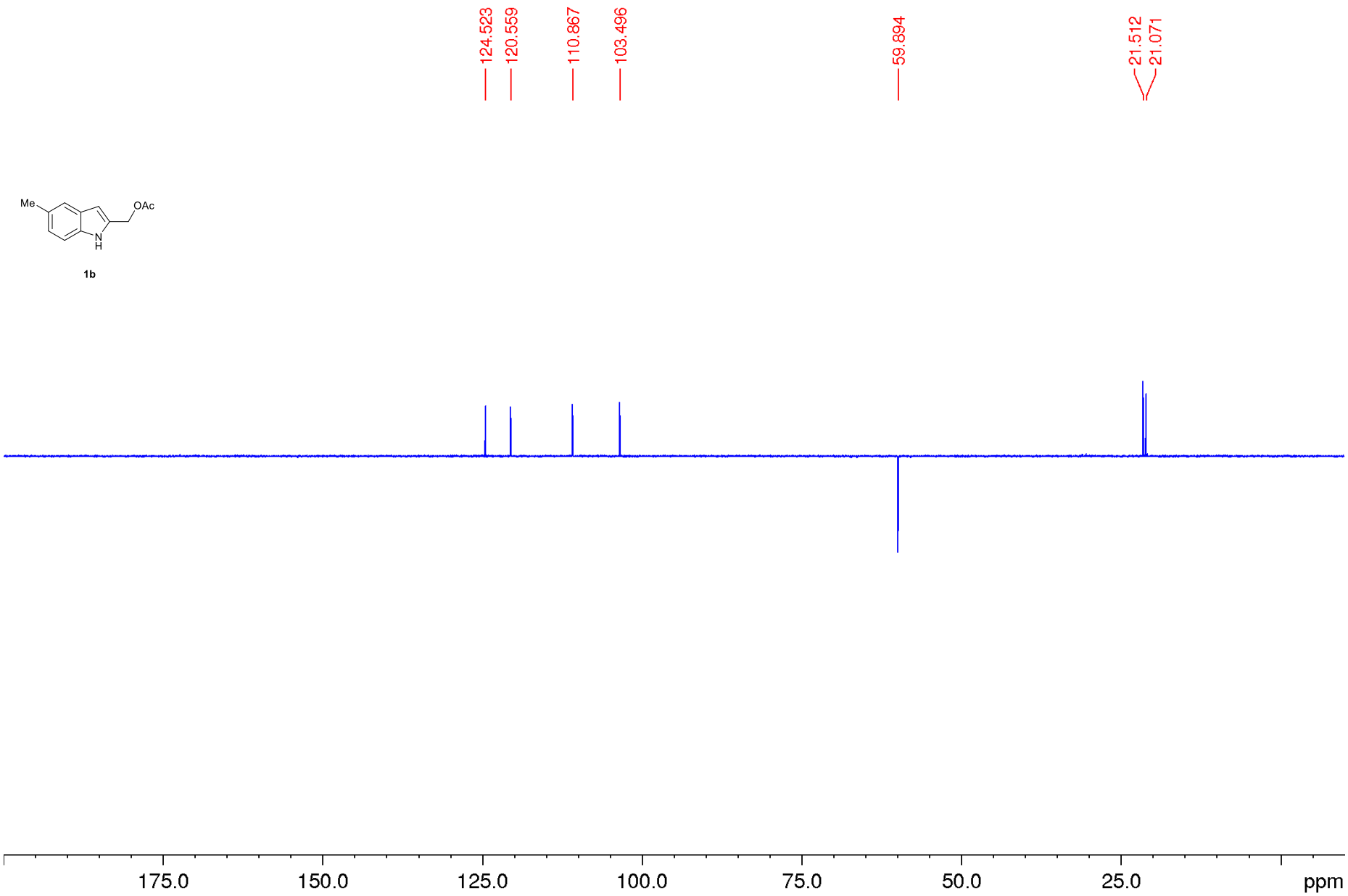

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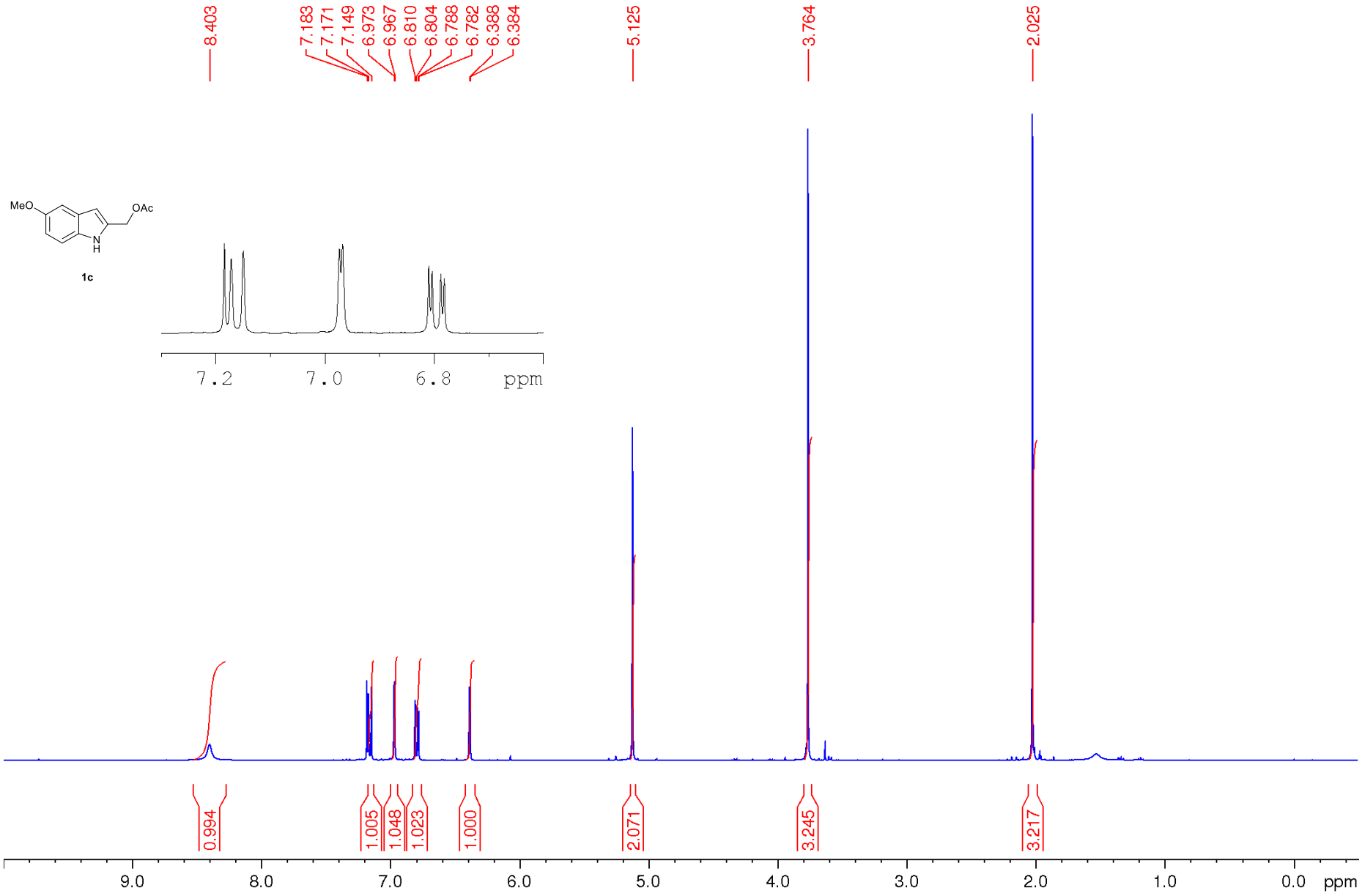
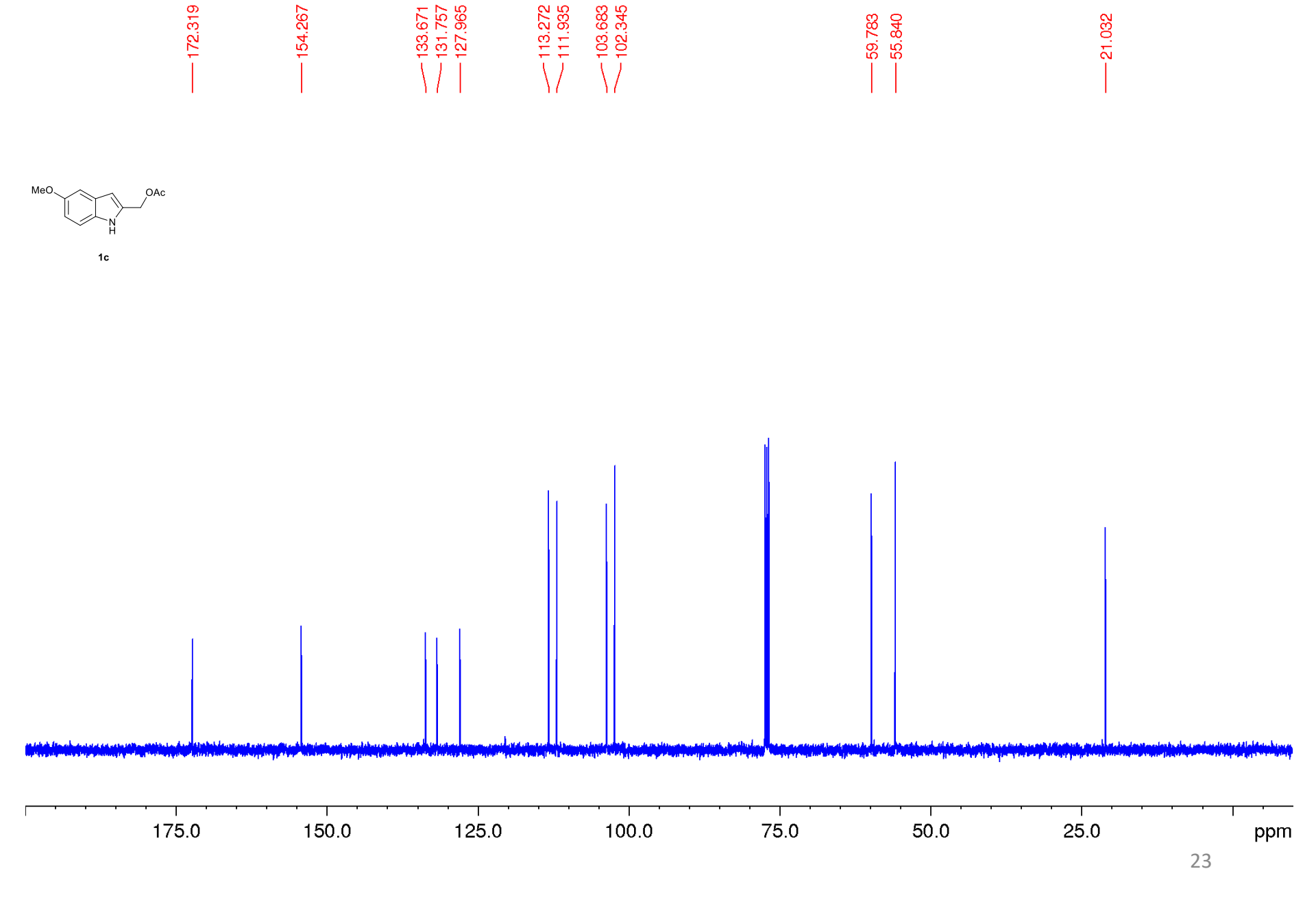


^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



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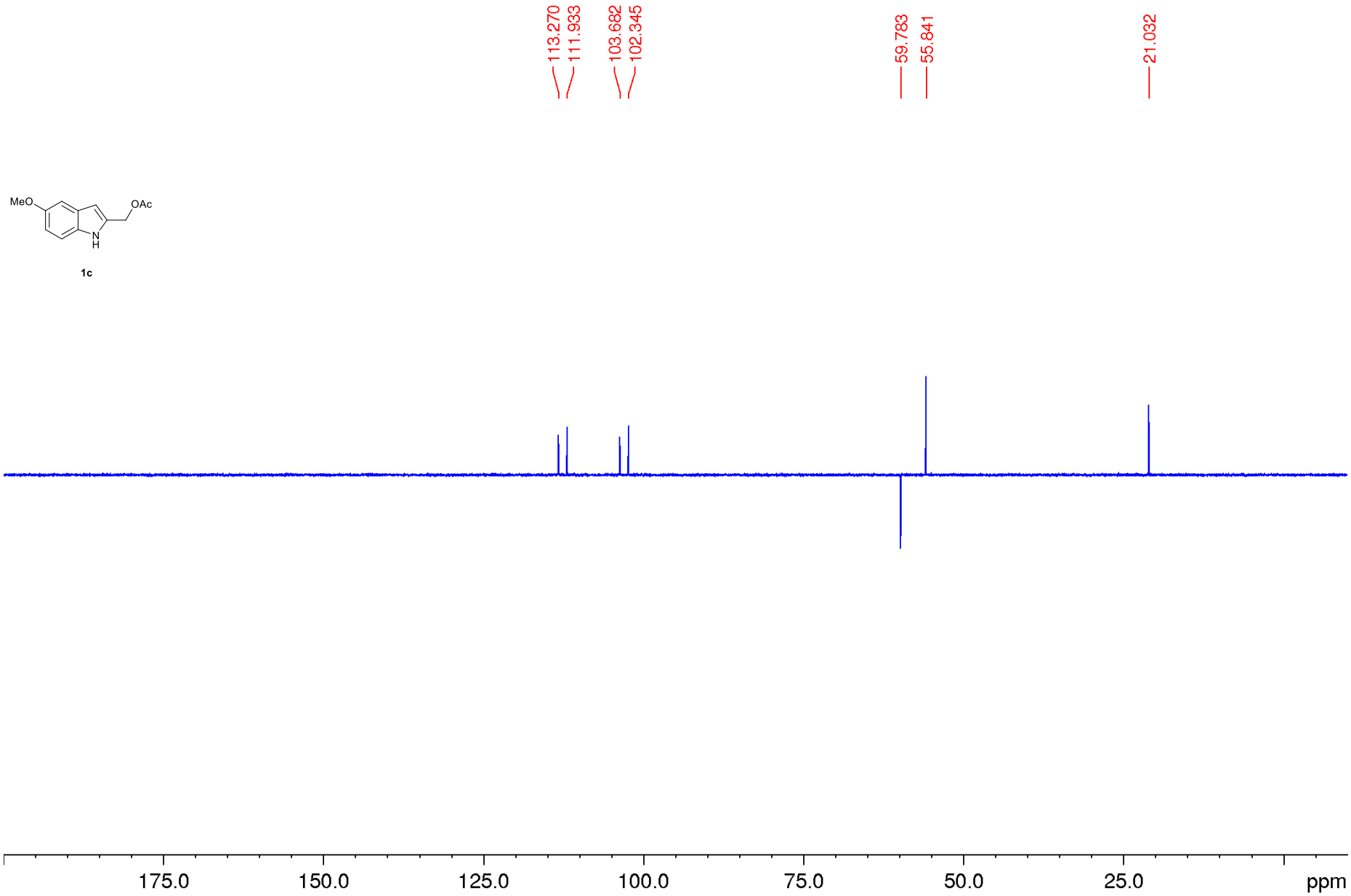

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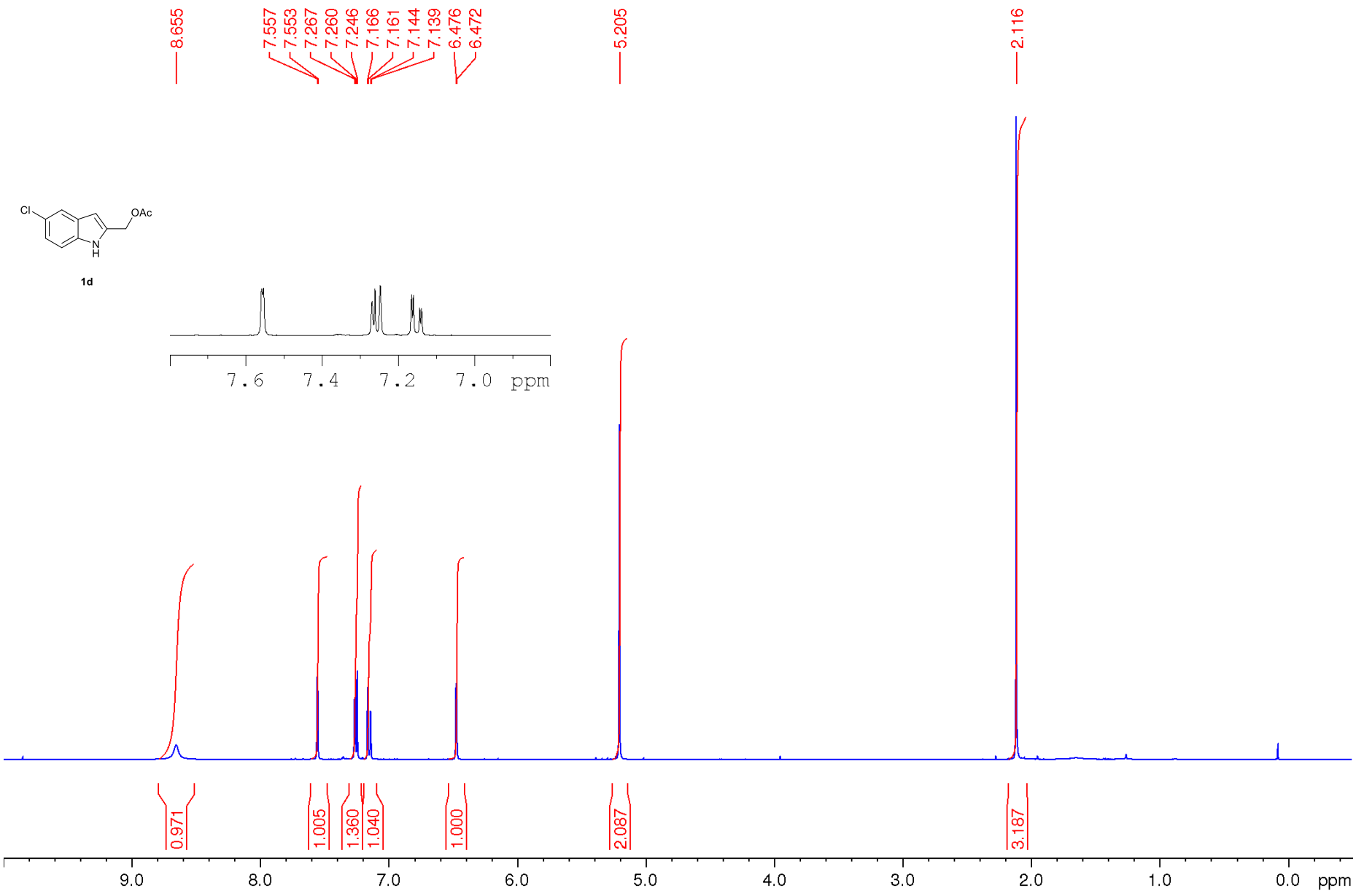

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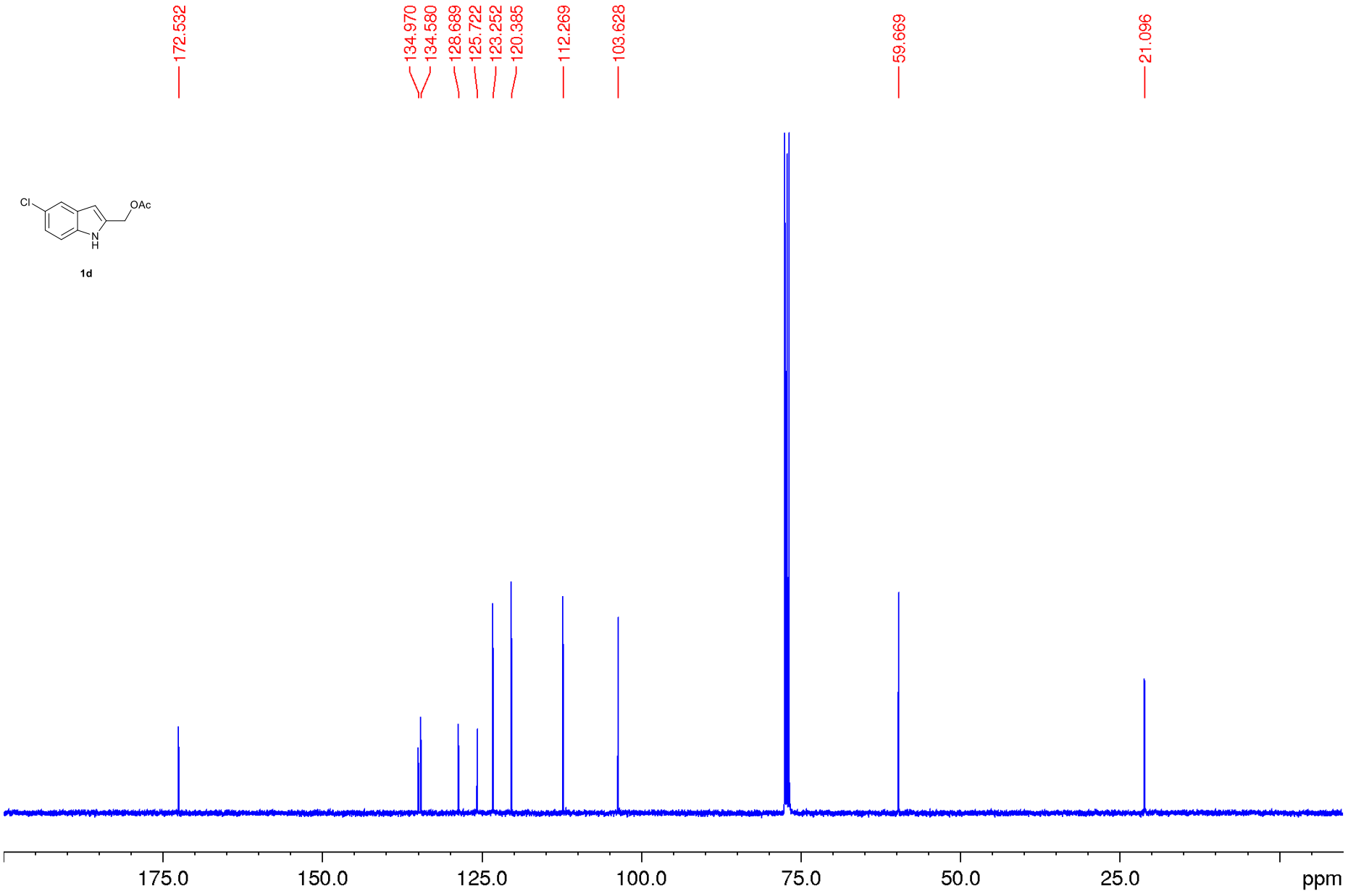

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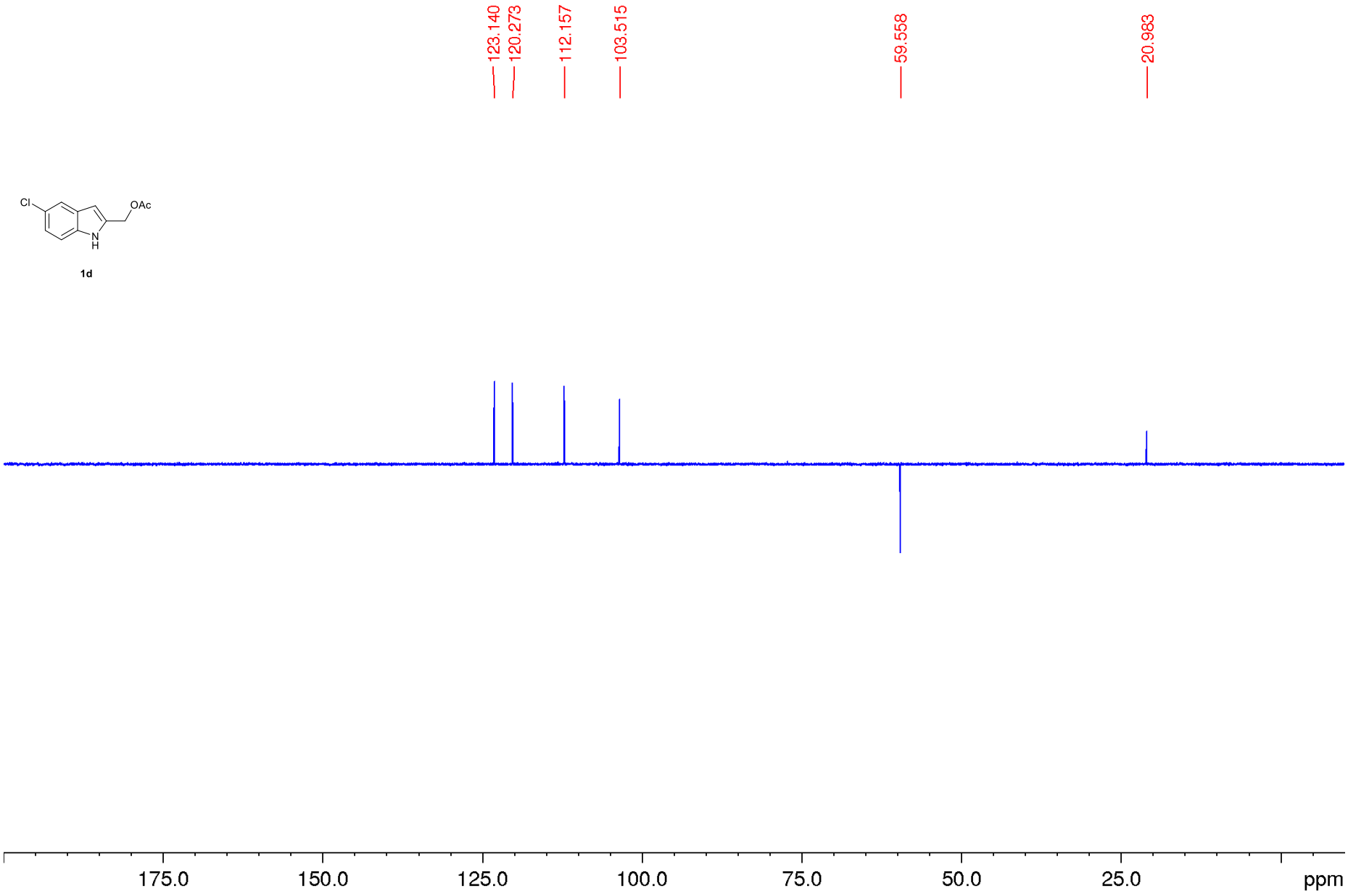

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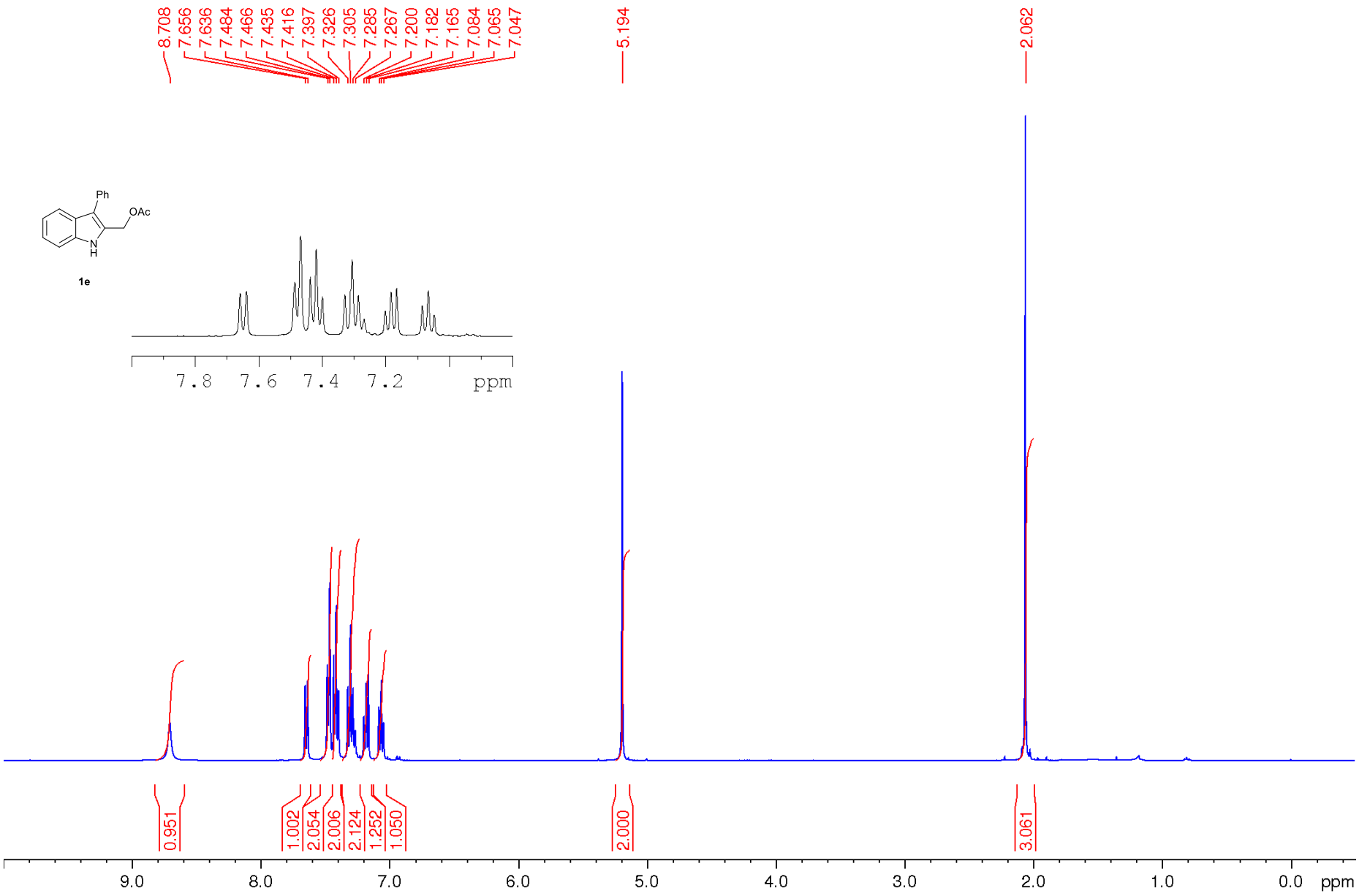

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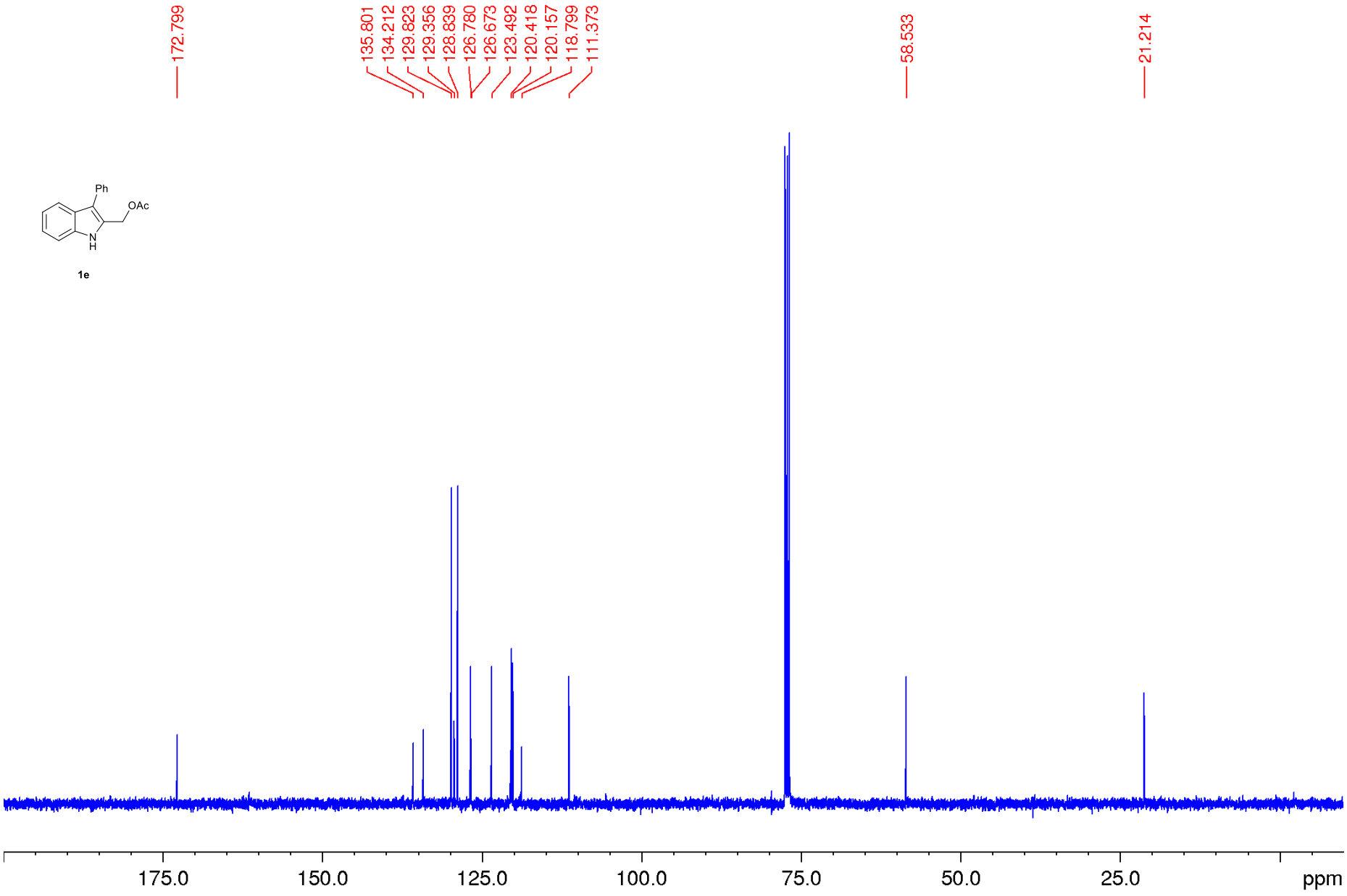

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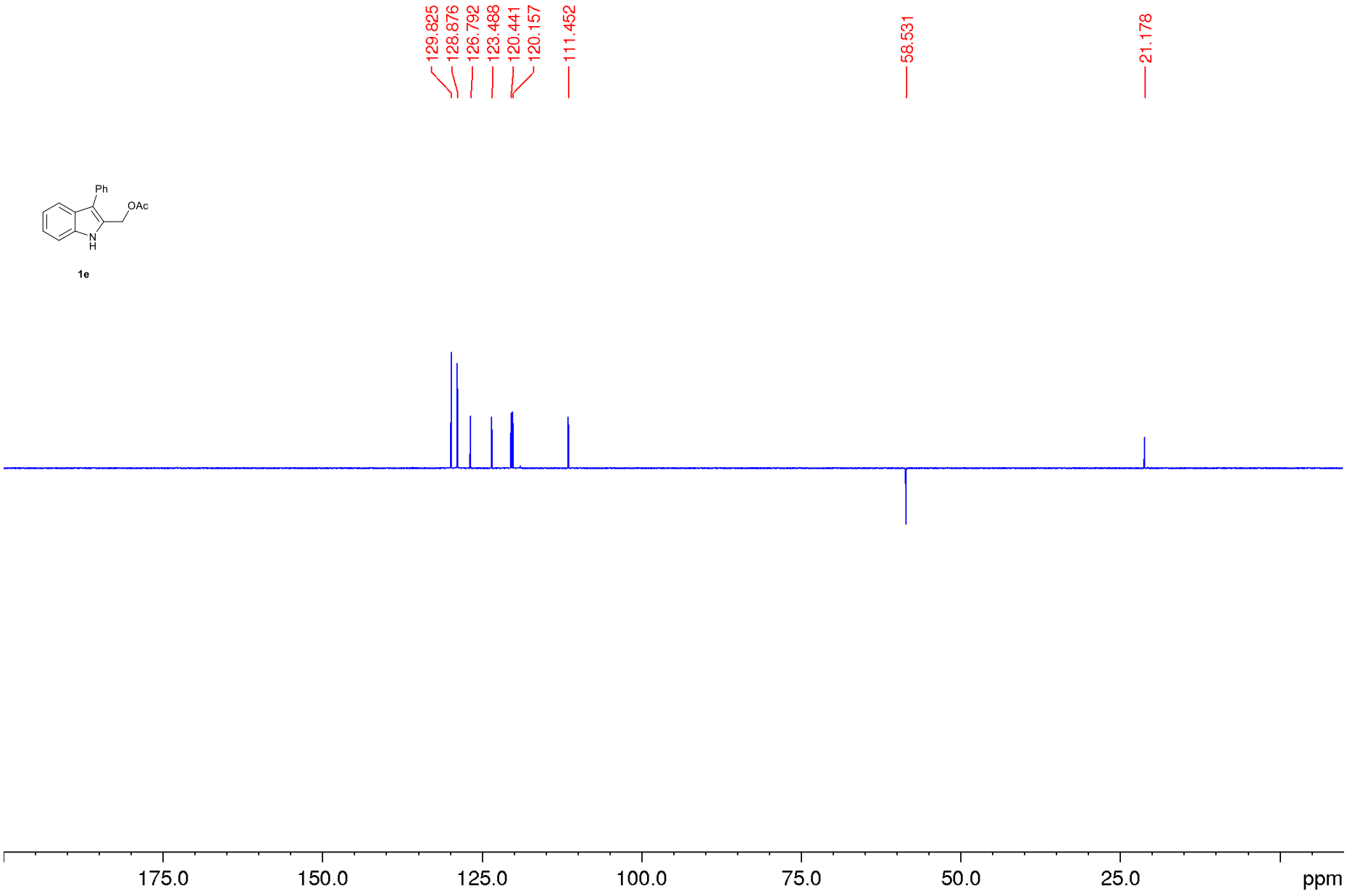

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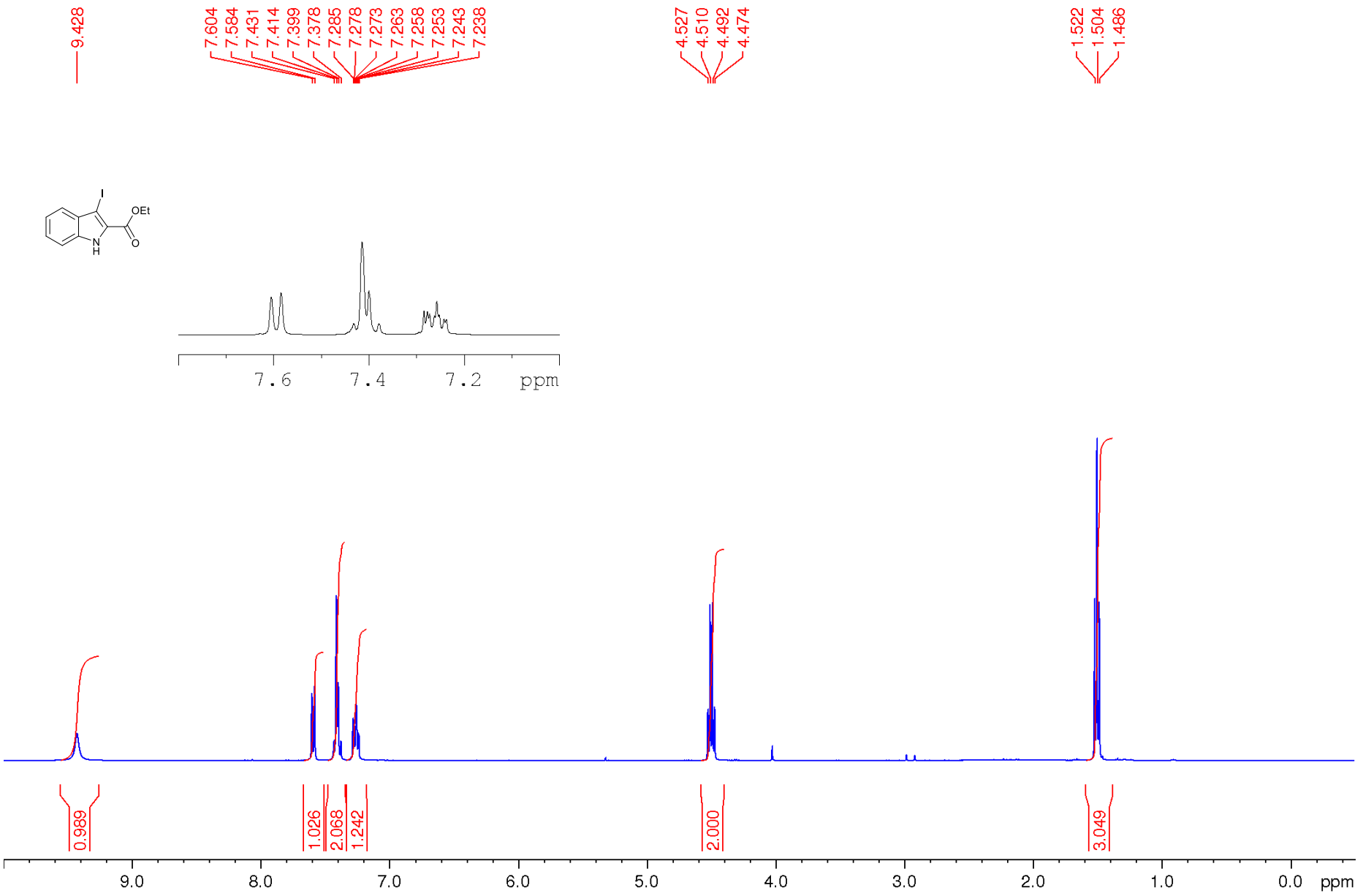

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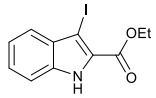

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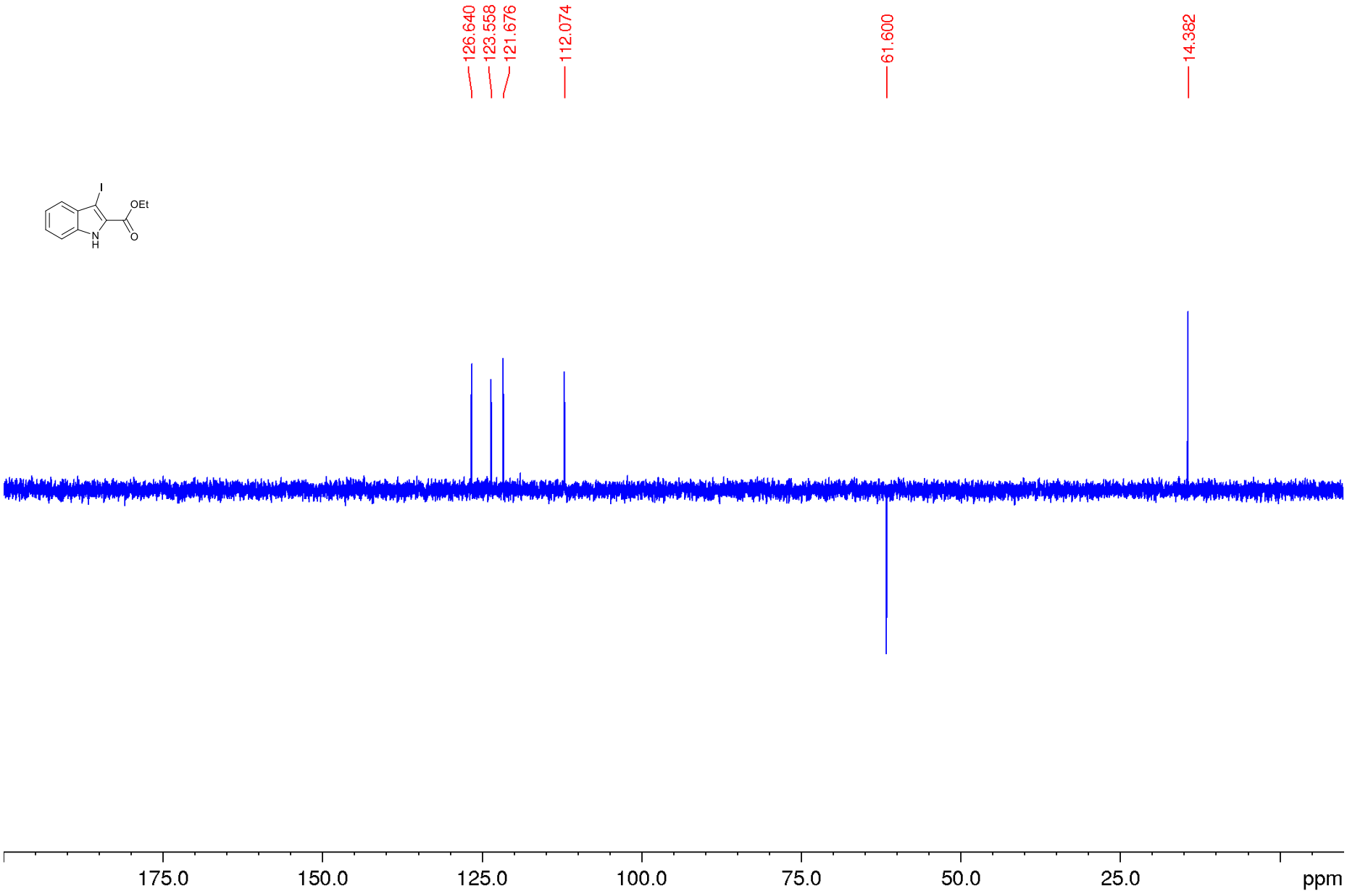
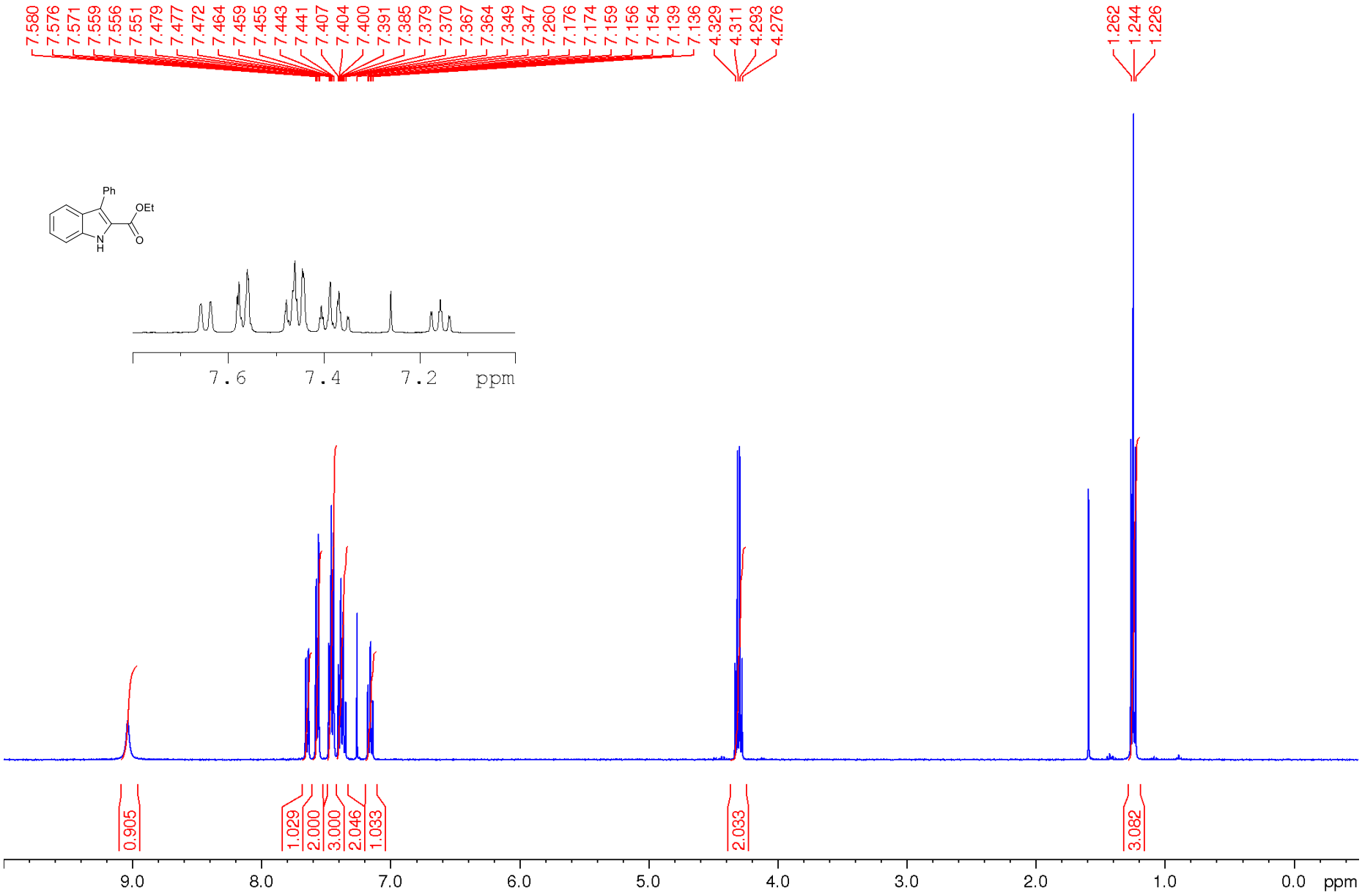
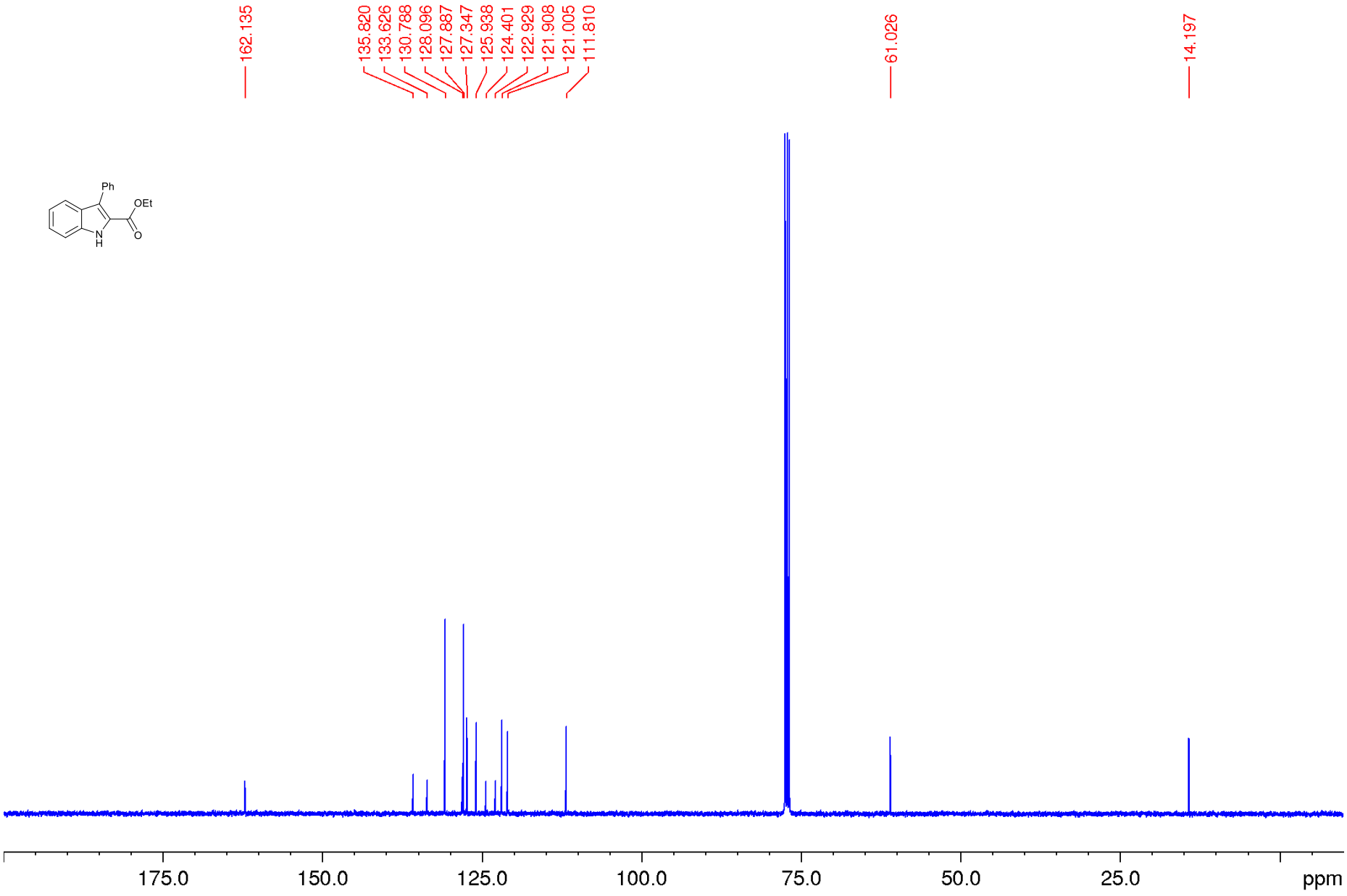


^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



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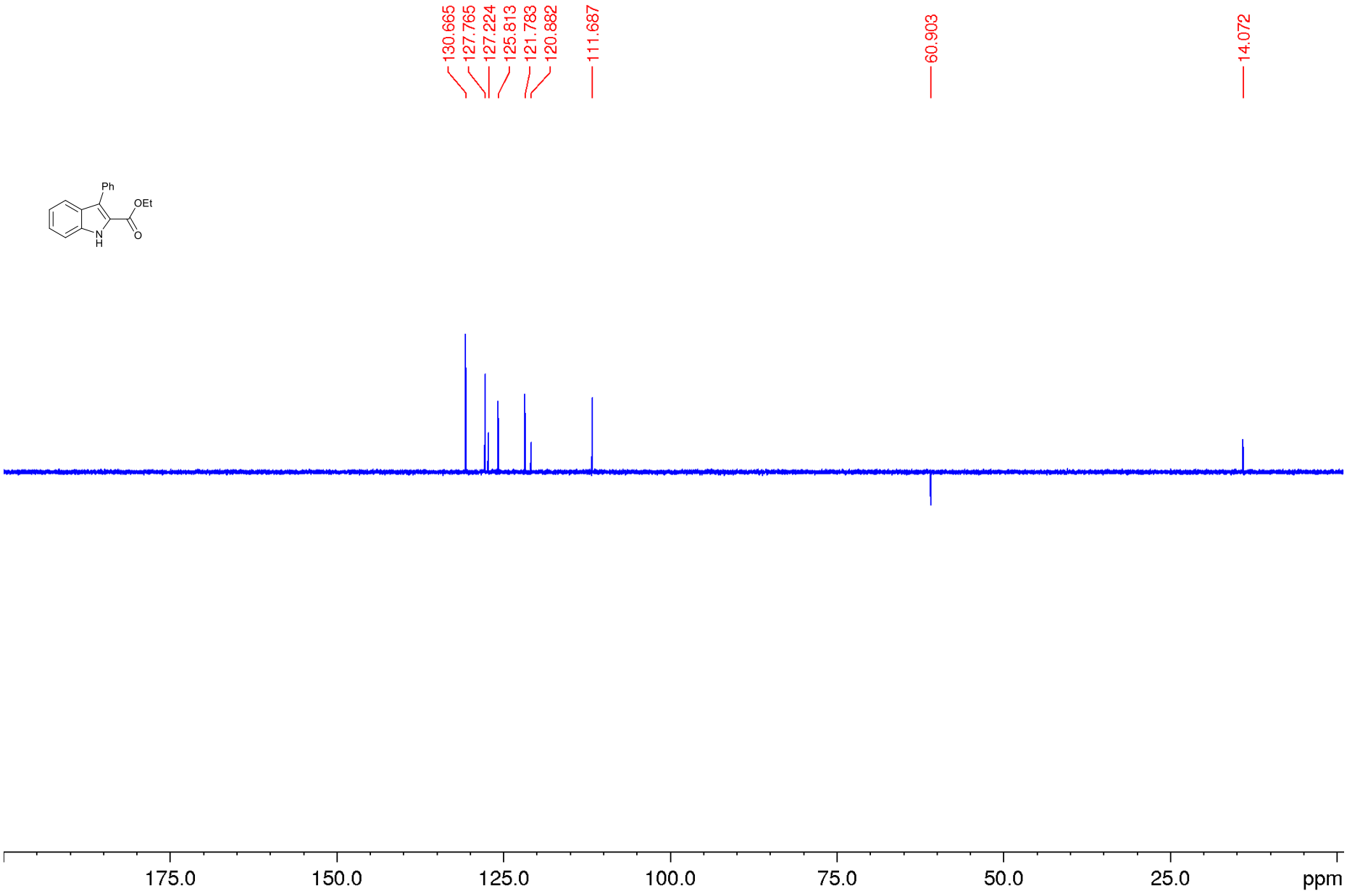

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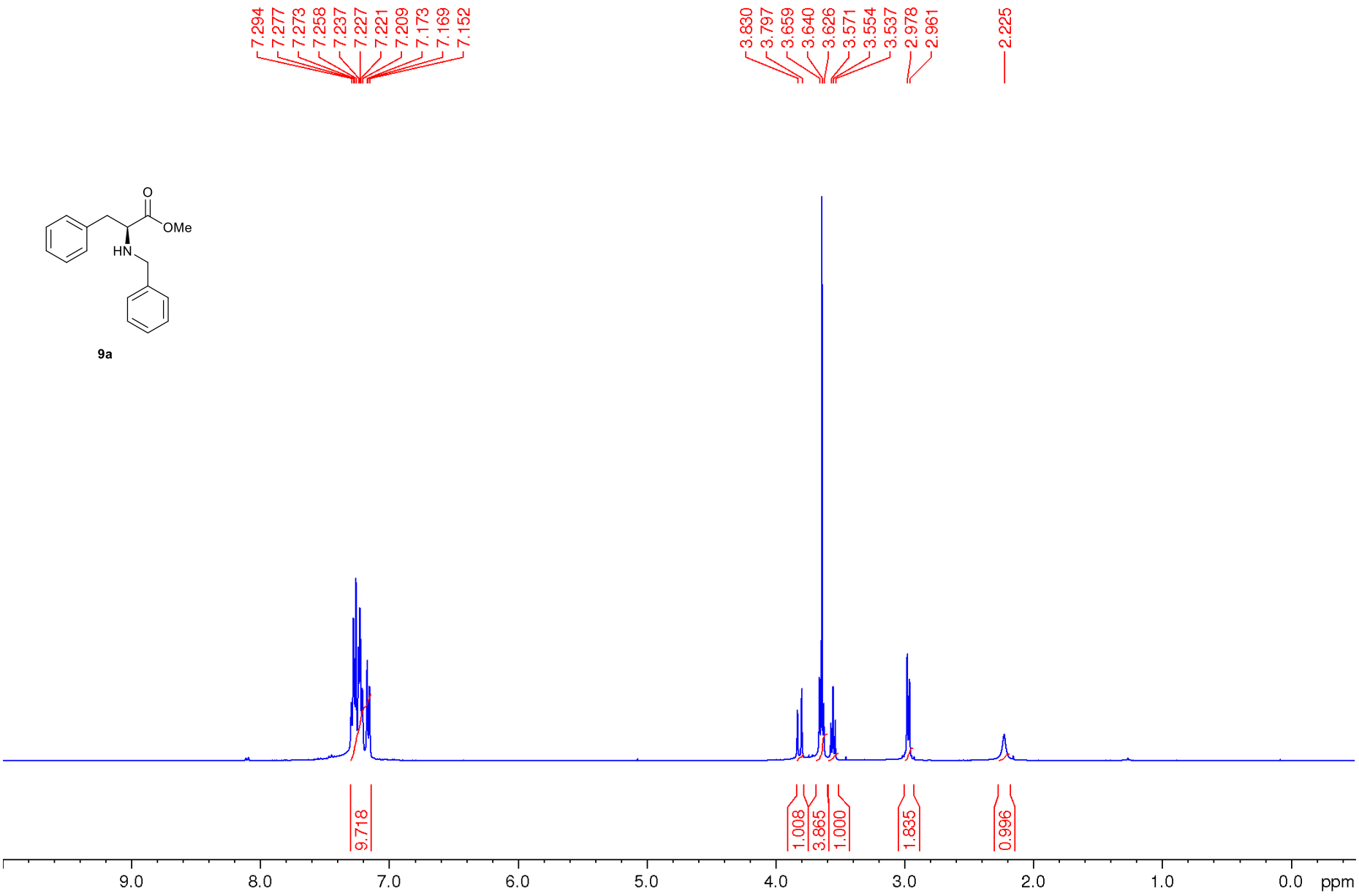
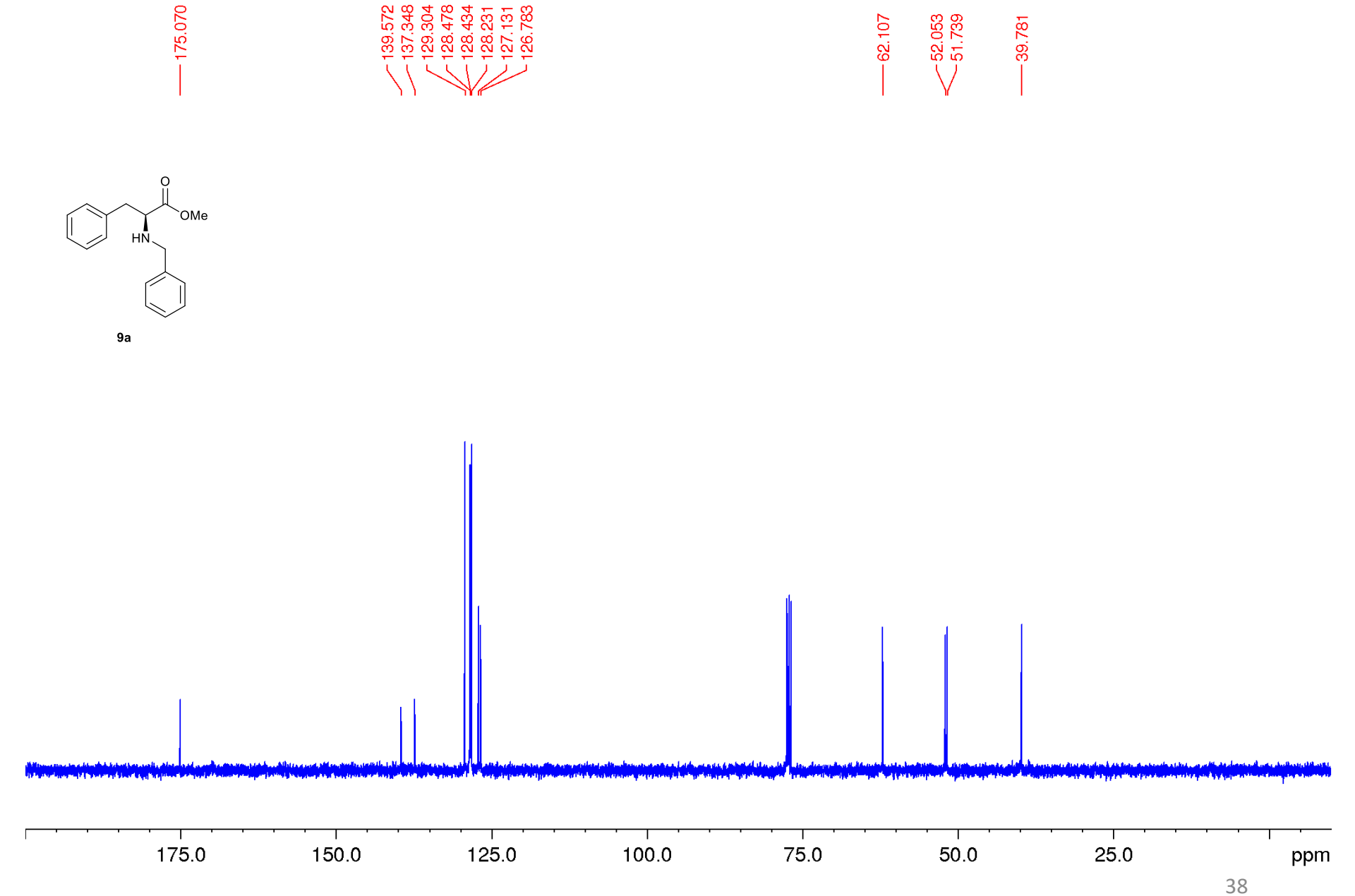


^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



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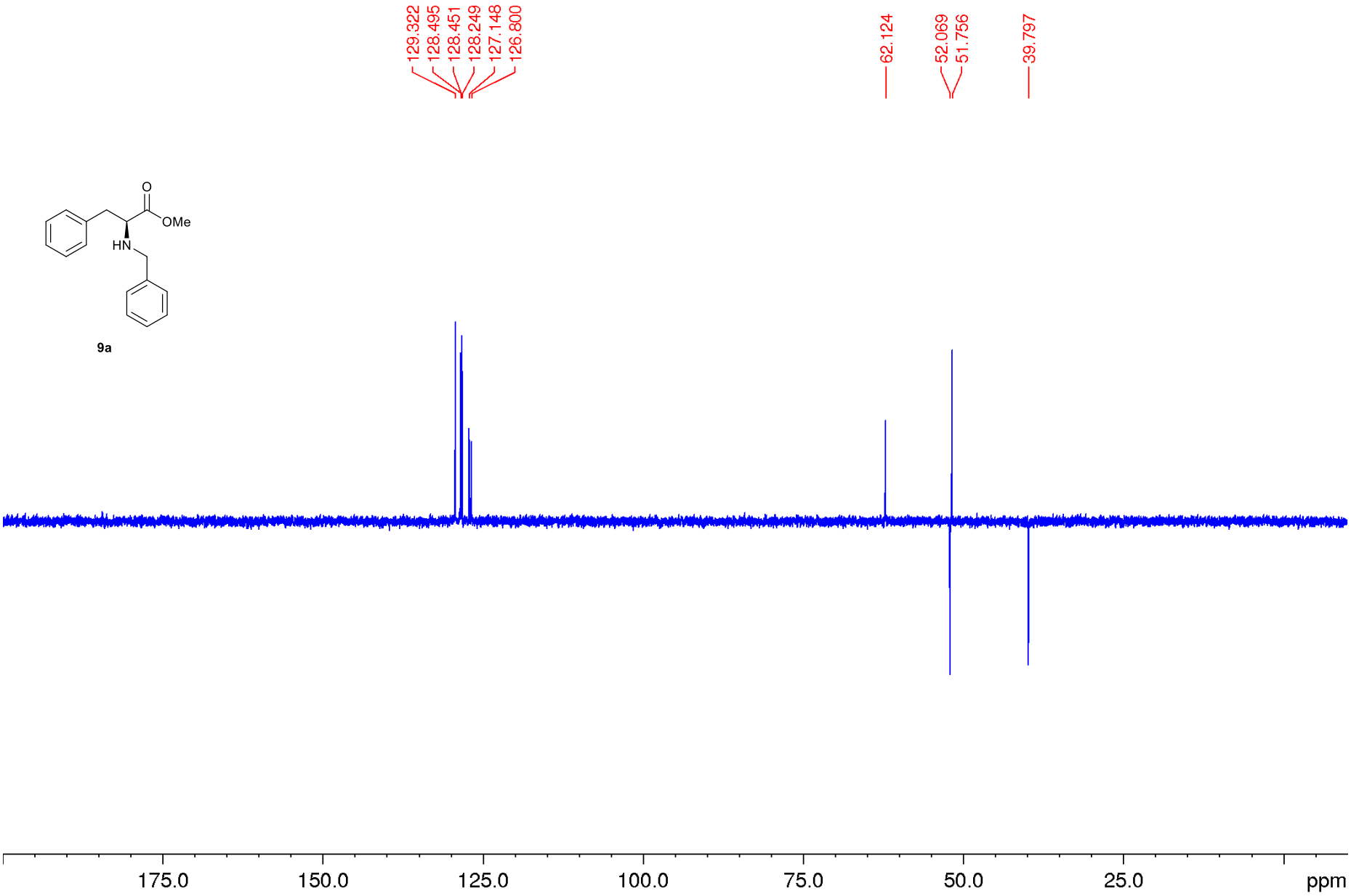
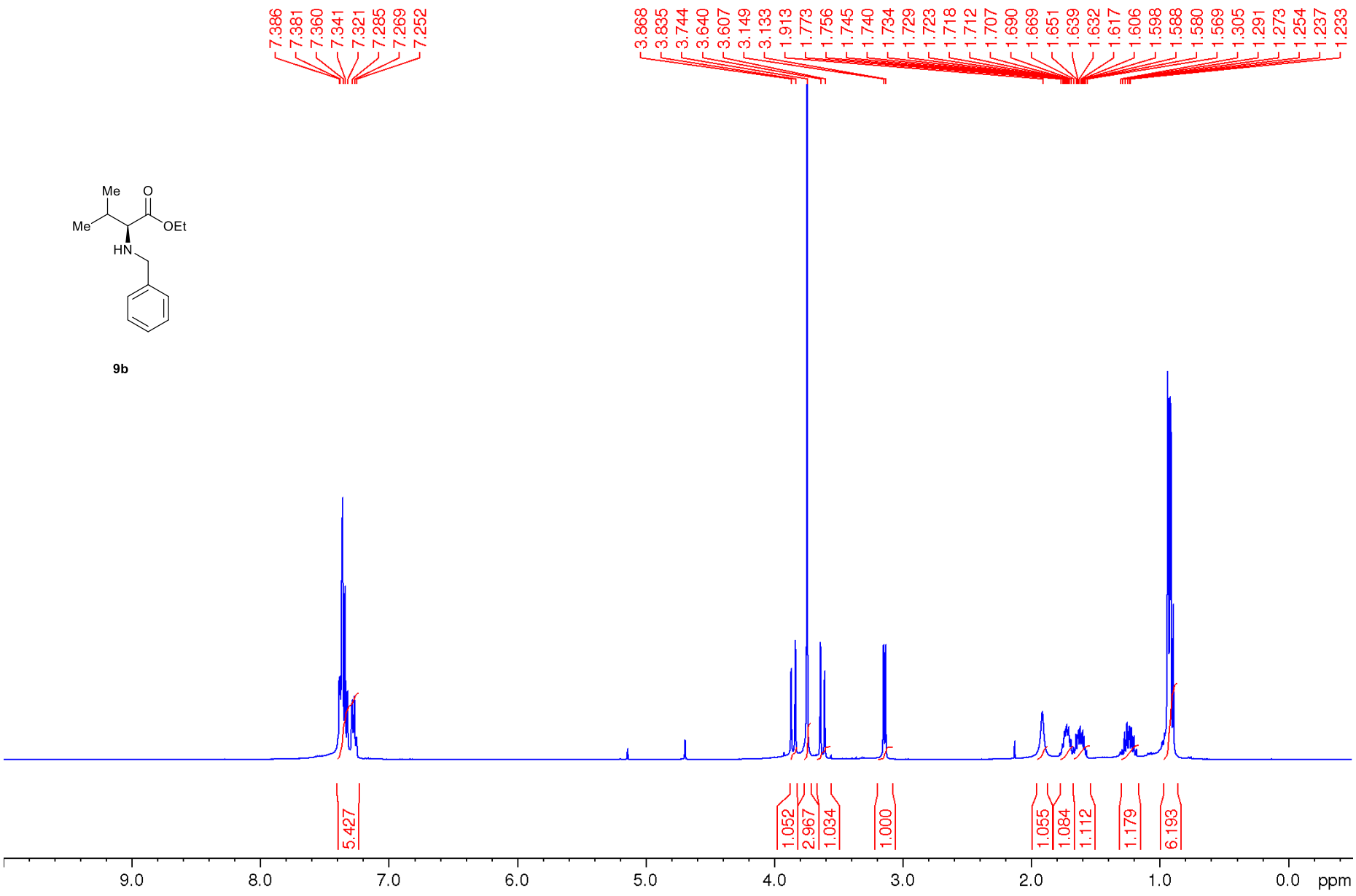
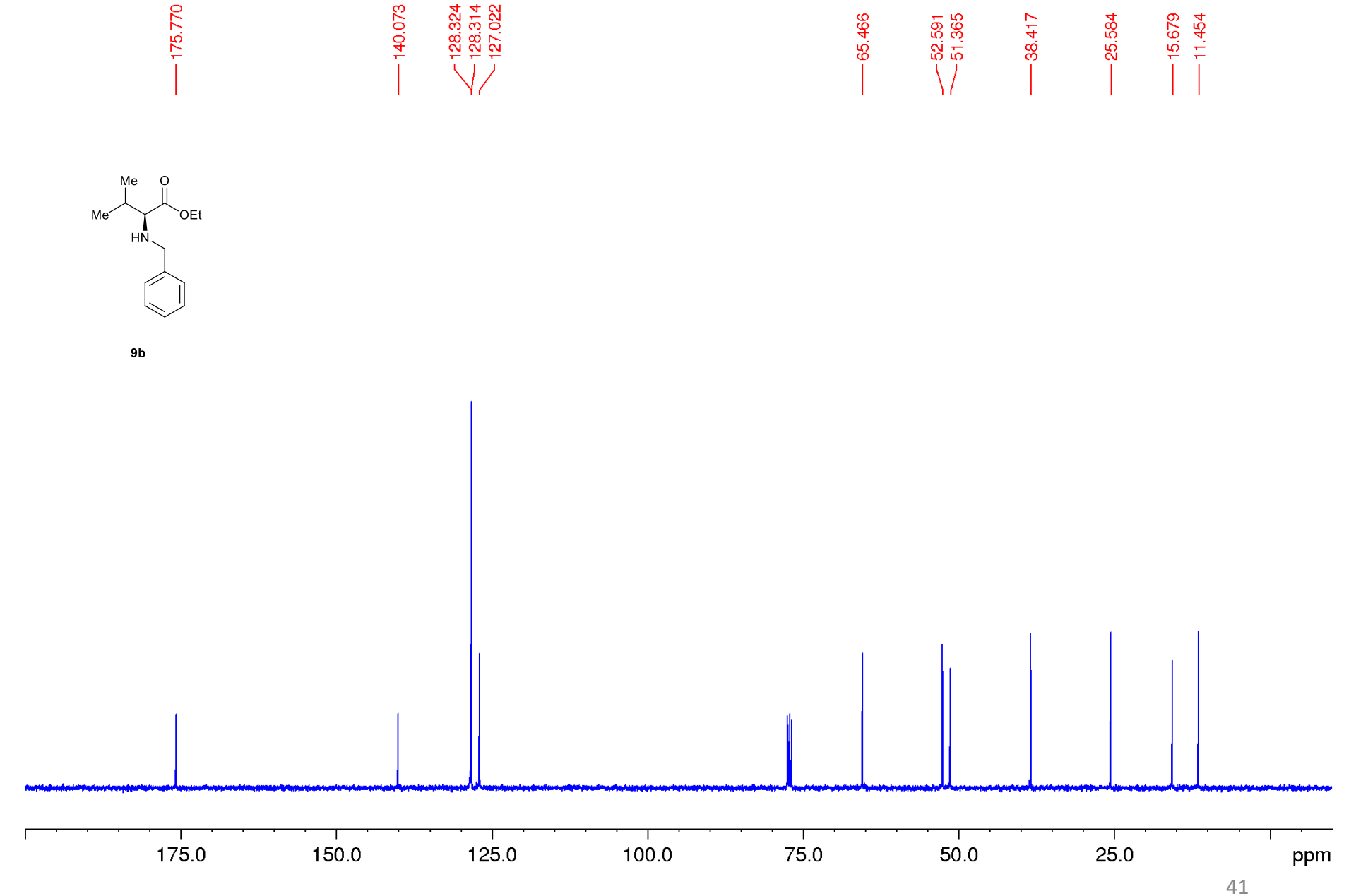


^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)

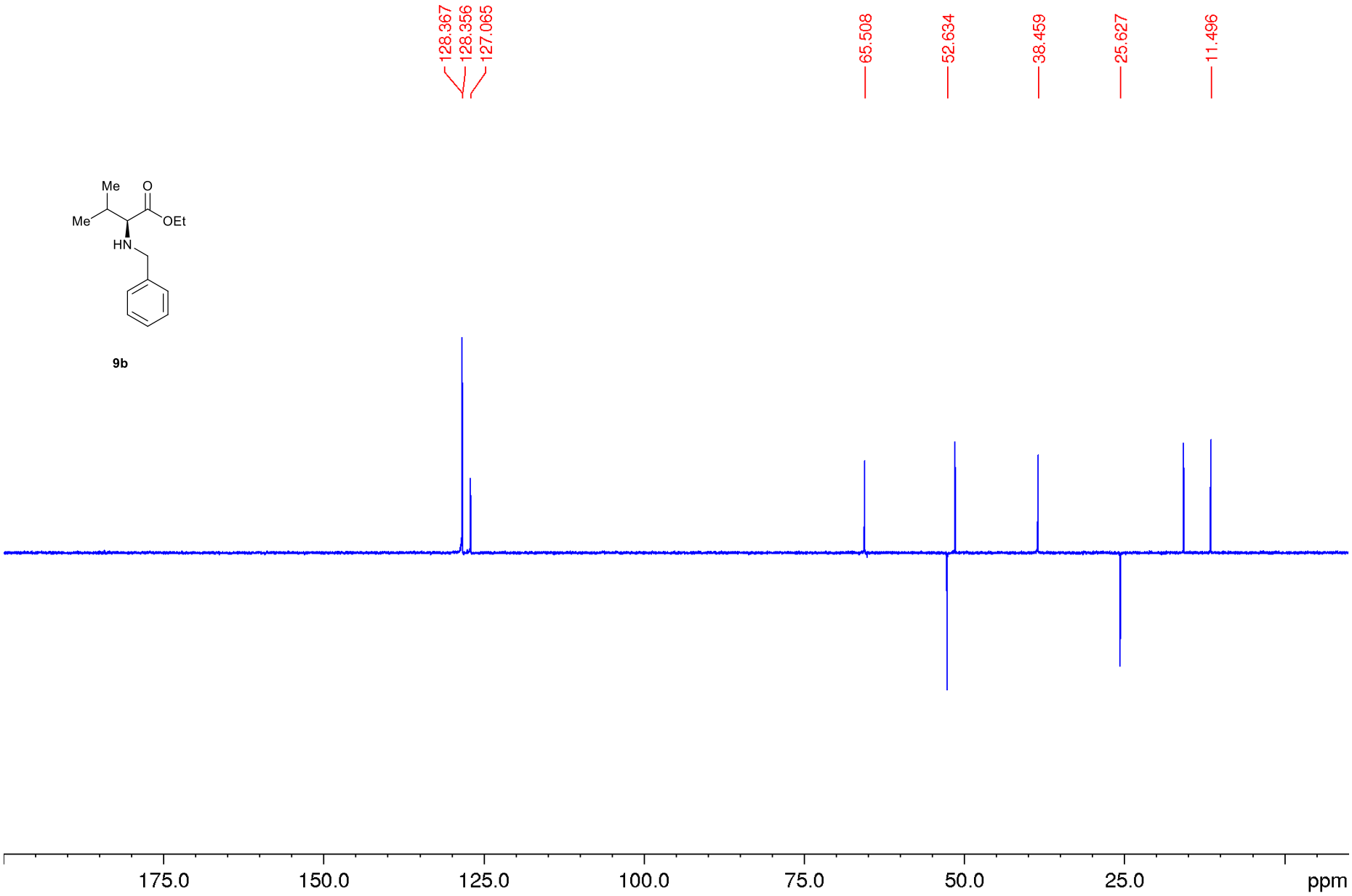


^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)

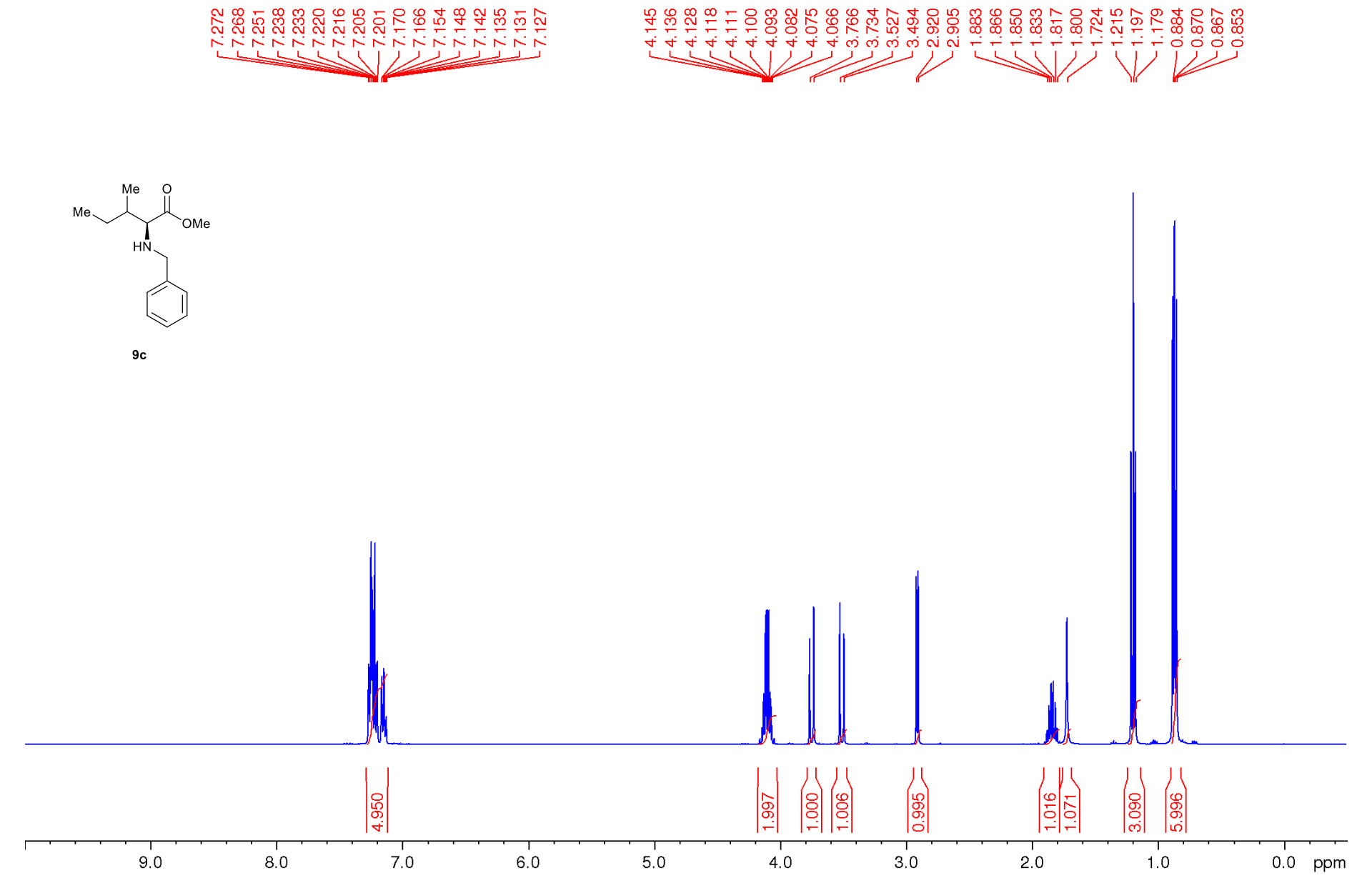


9b

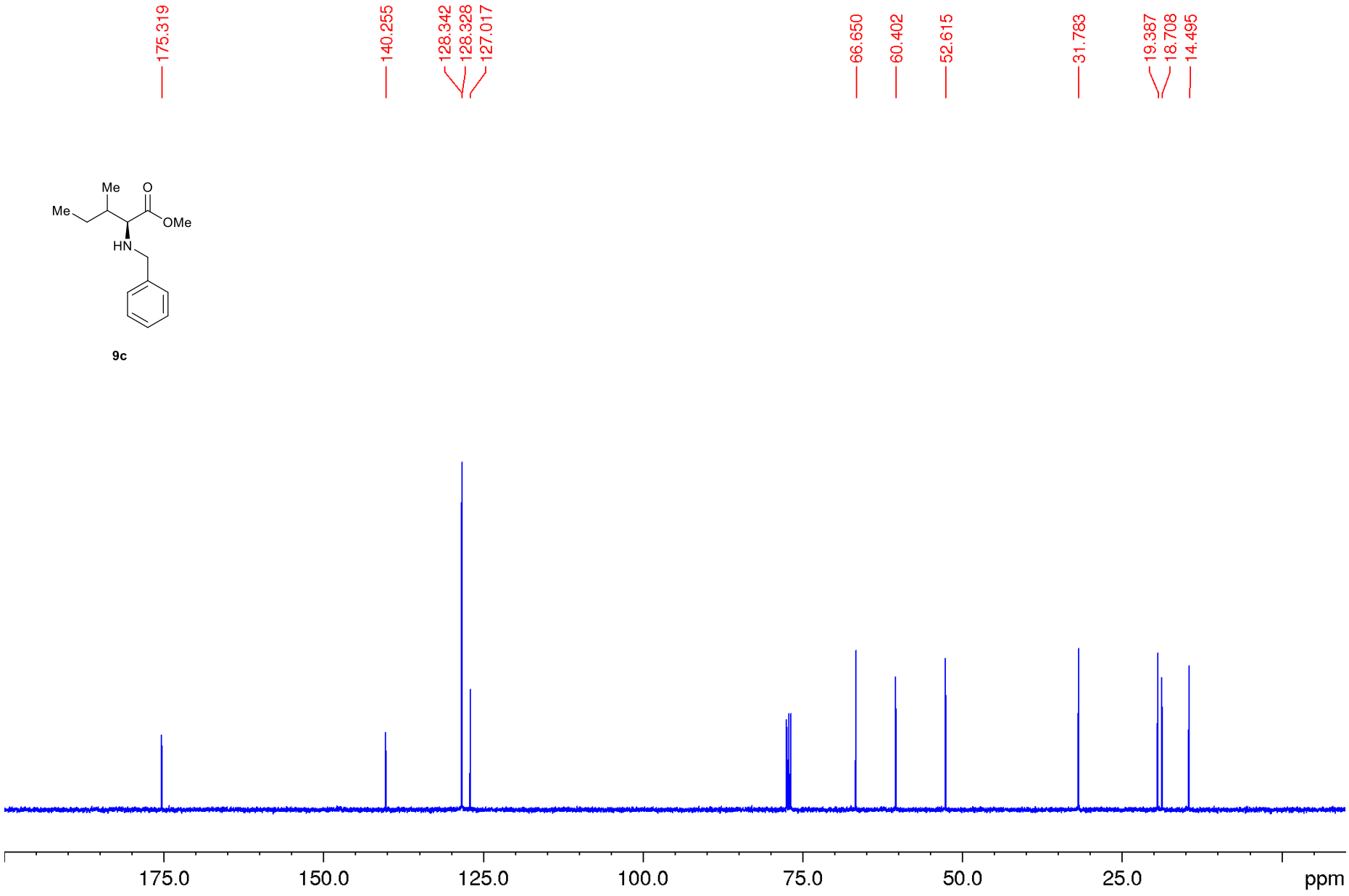
DEPT 135 NMR-spectrum ($CDCl_3$)



^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



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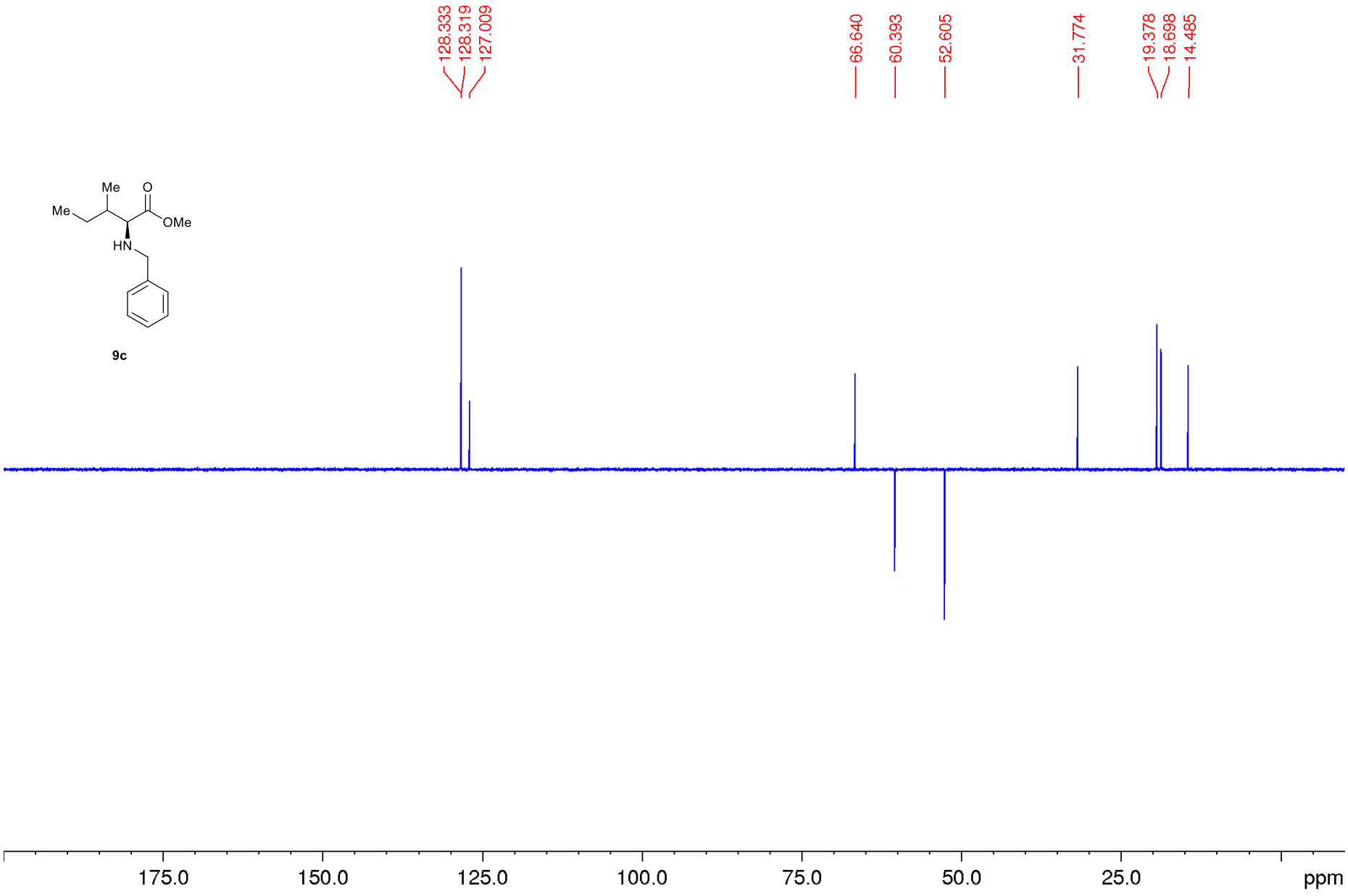
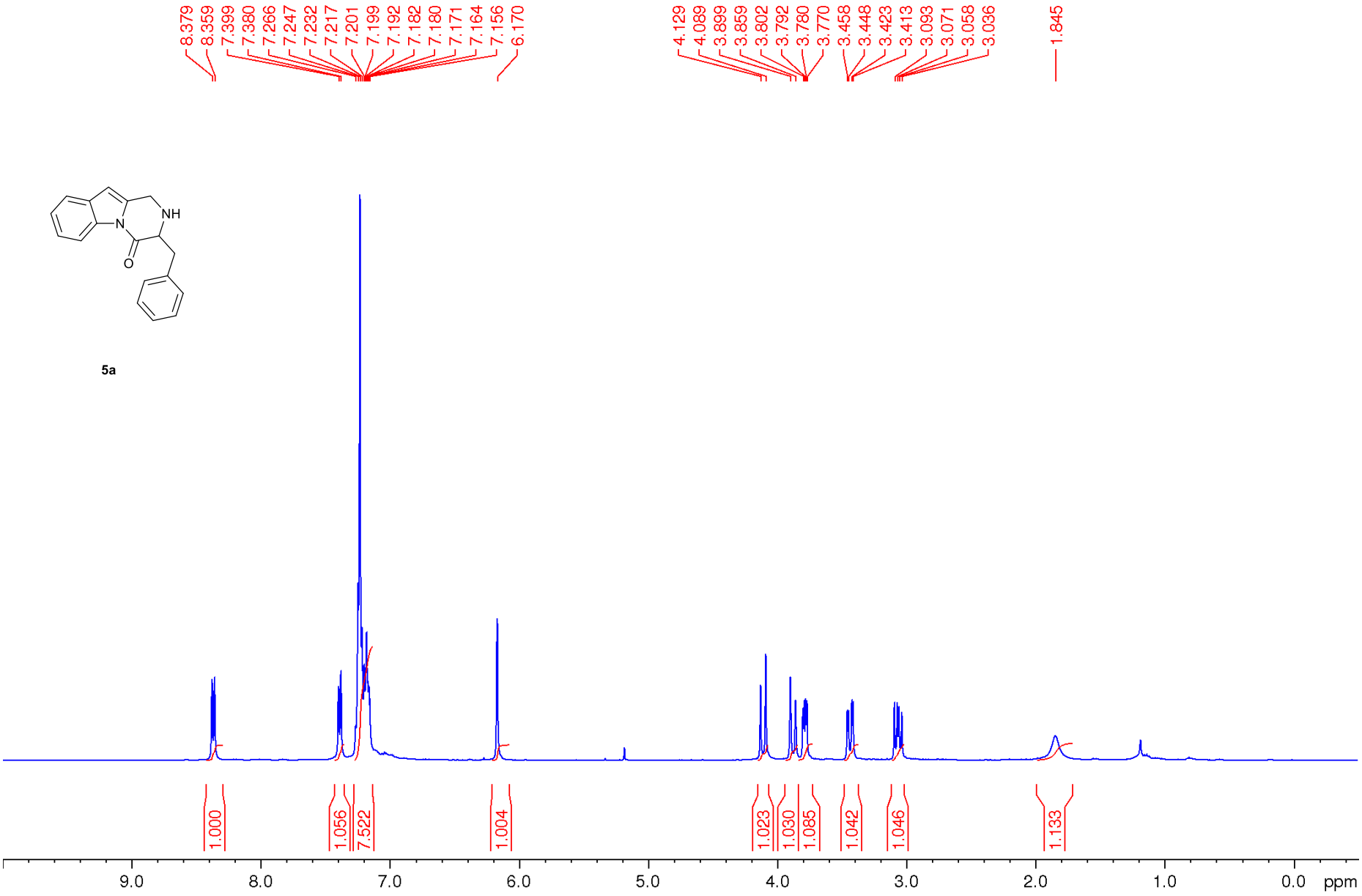
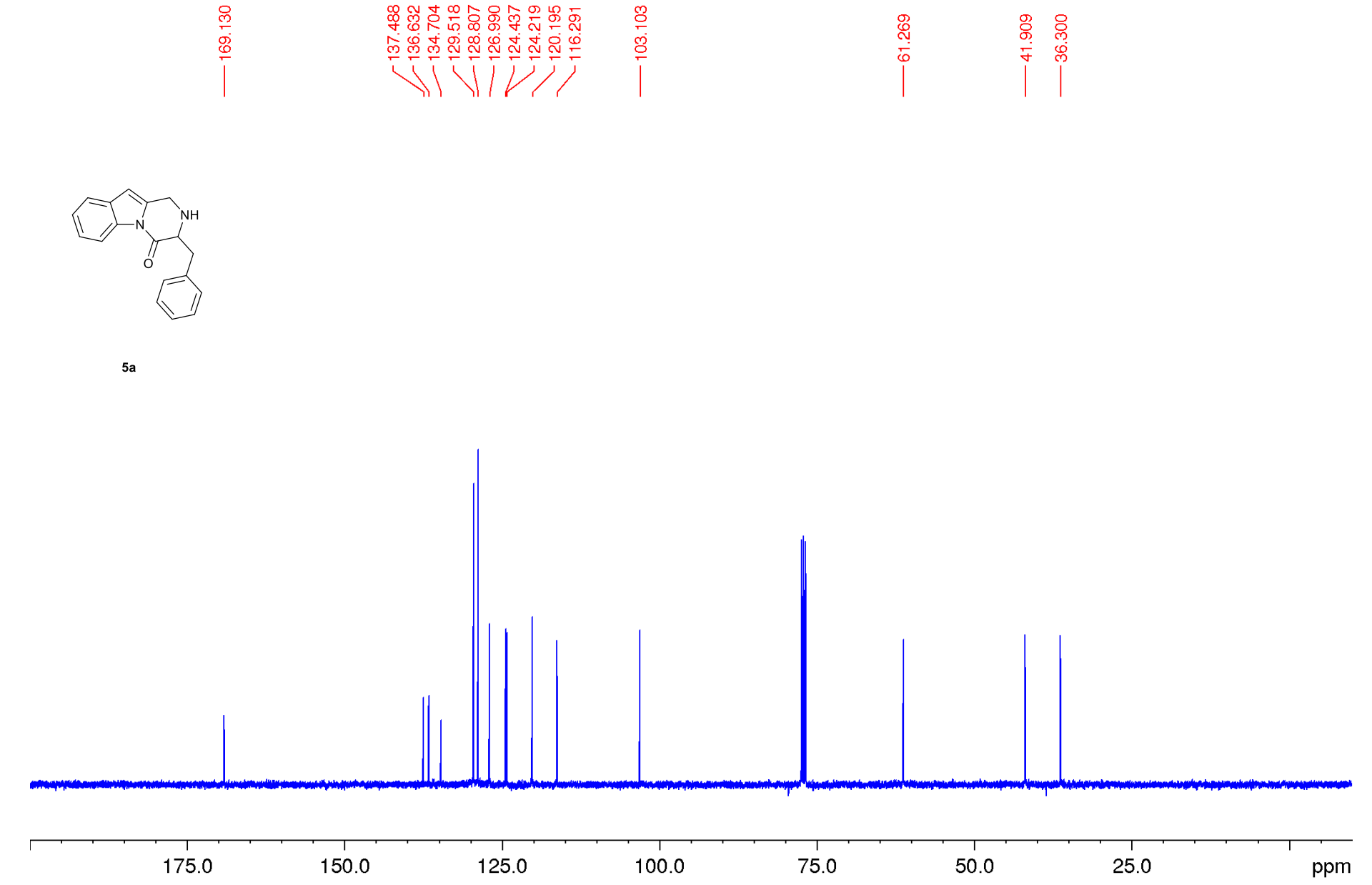


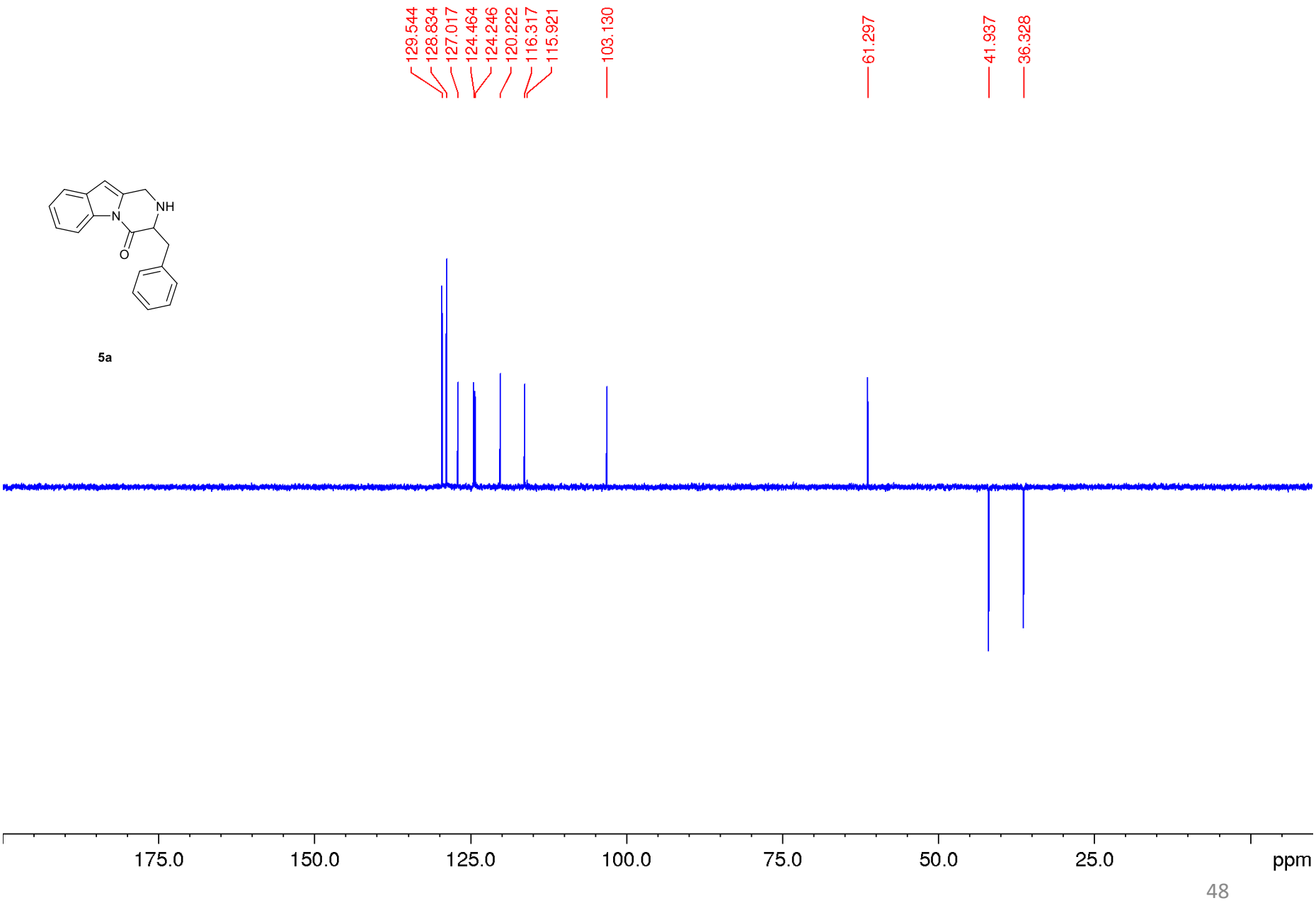
^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



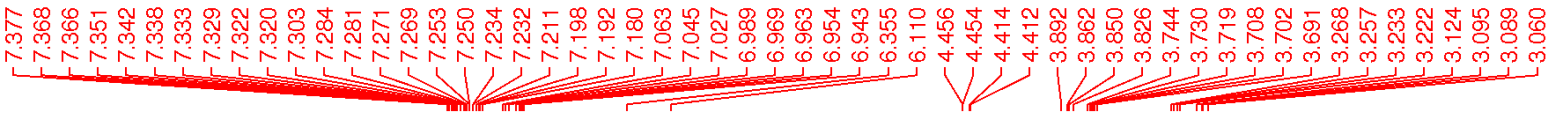
^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)

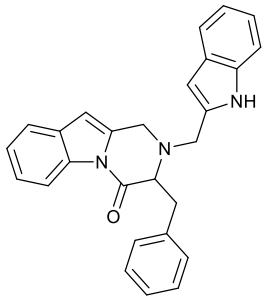


DEPT 135 NMR-spectrum ($CDCl_3$)

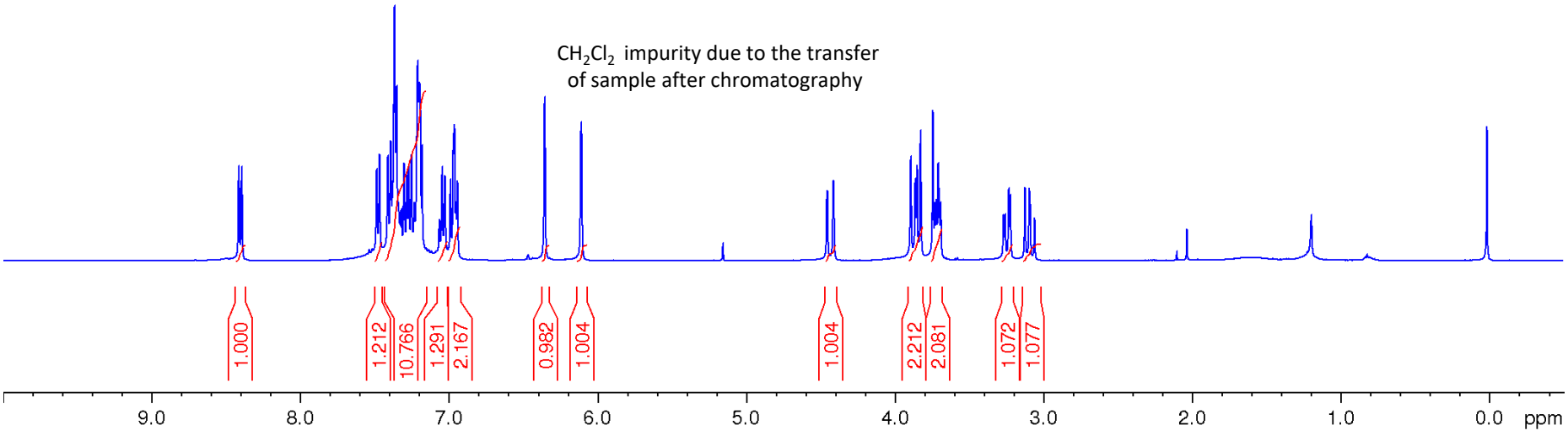


^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)

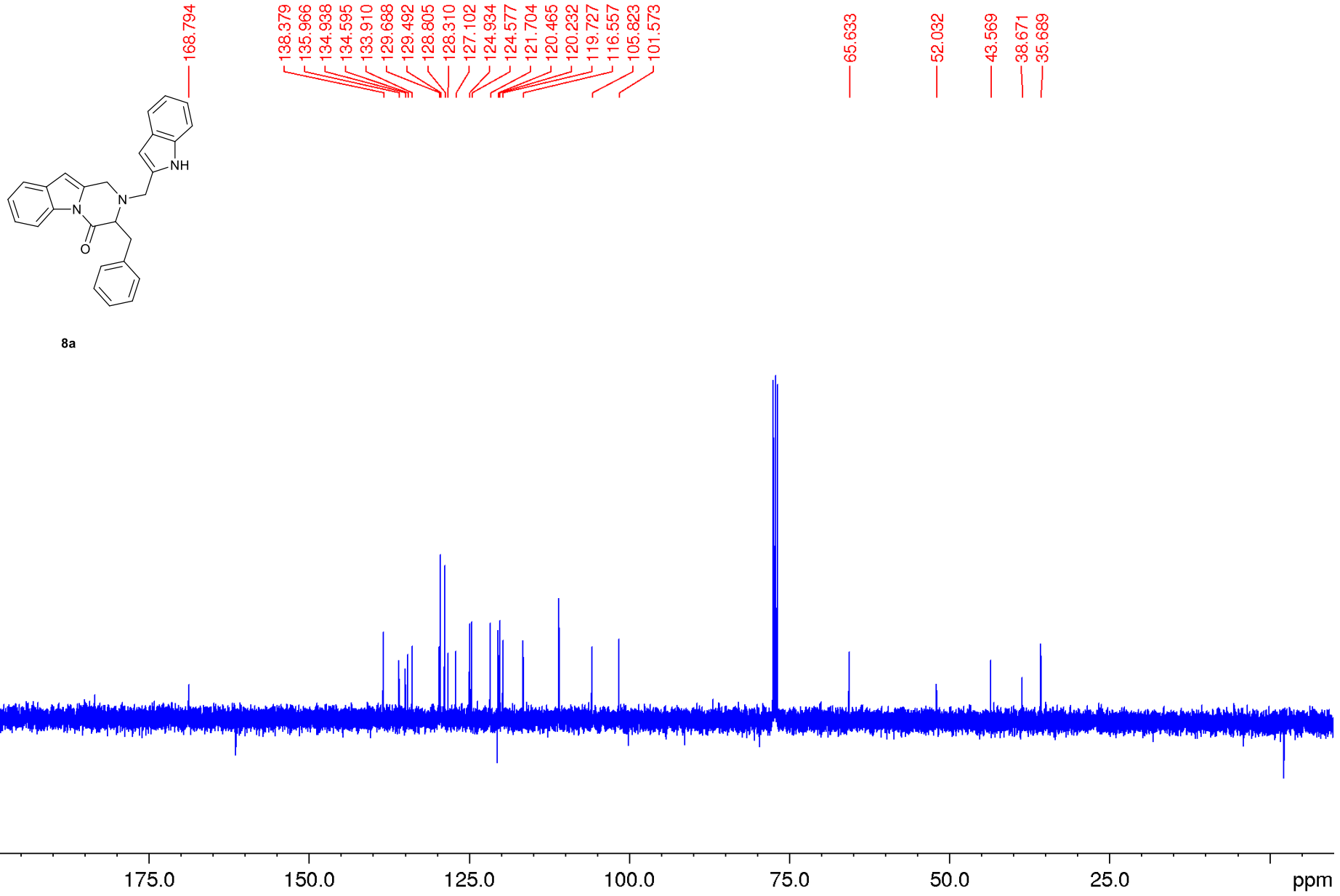




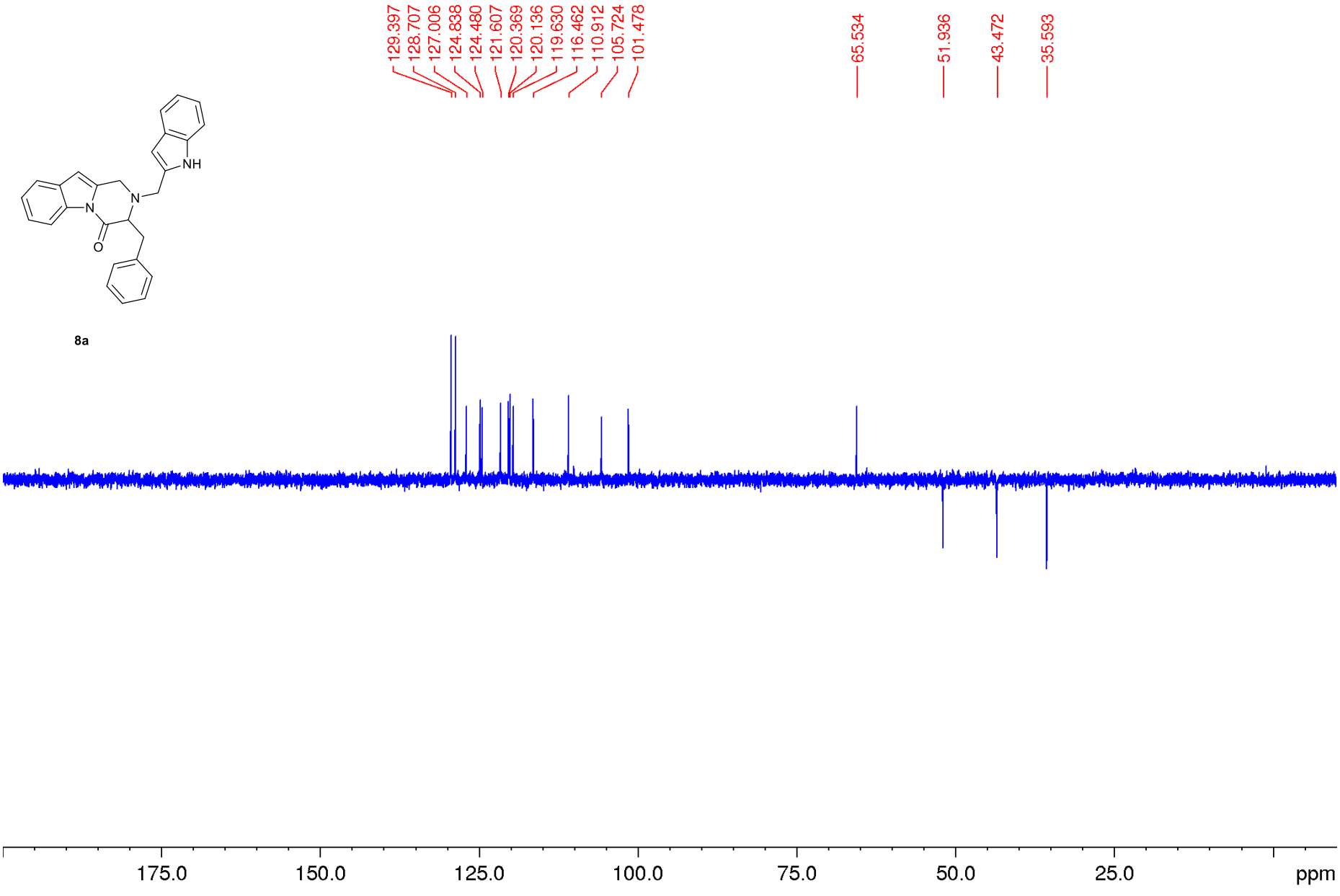
8a



^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



DEPT 135 NMR-spectrum ($CDCl_3$)



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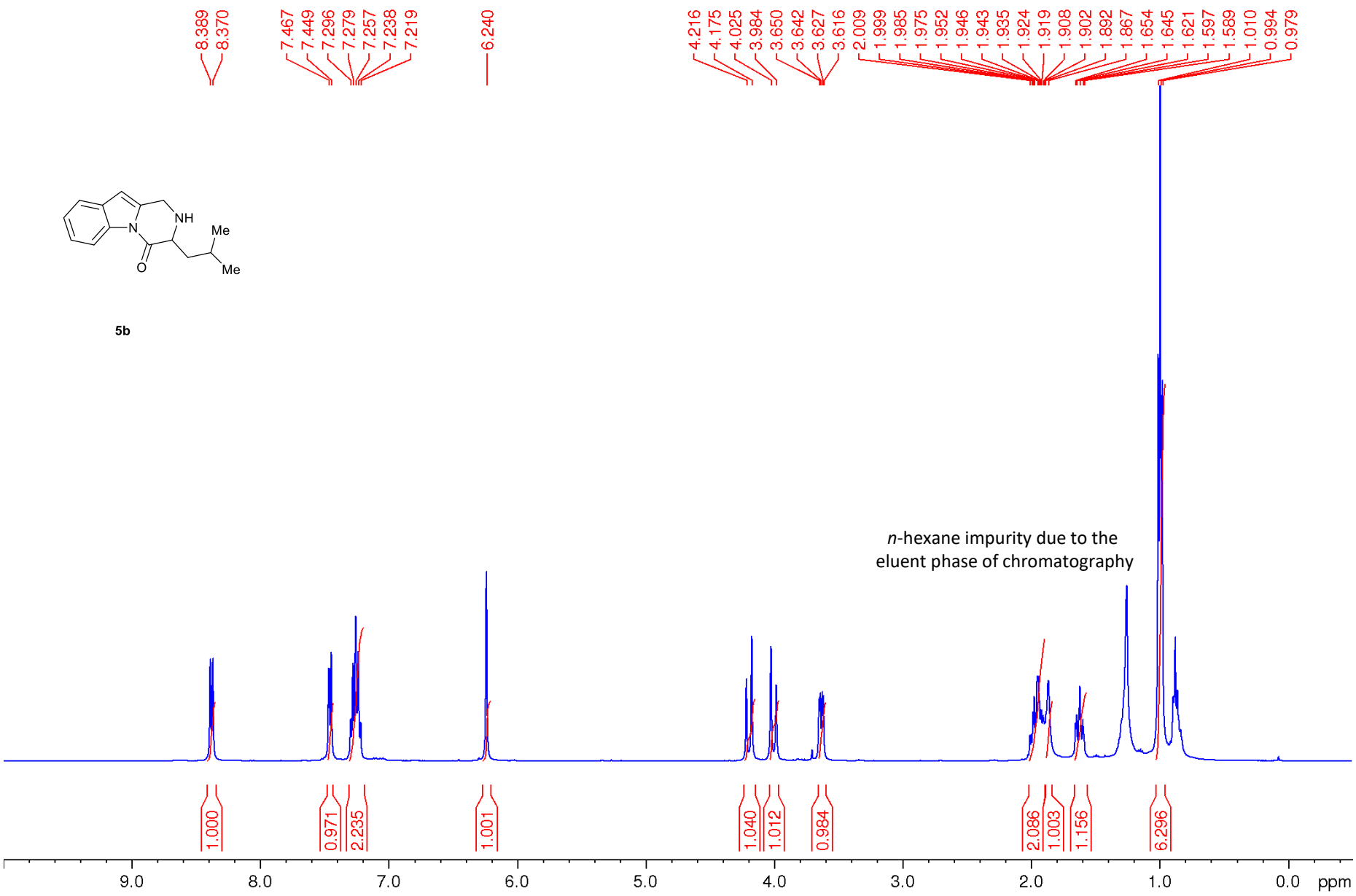
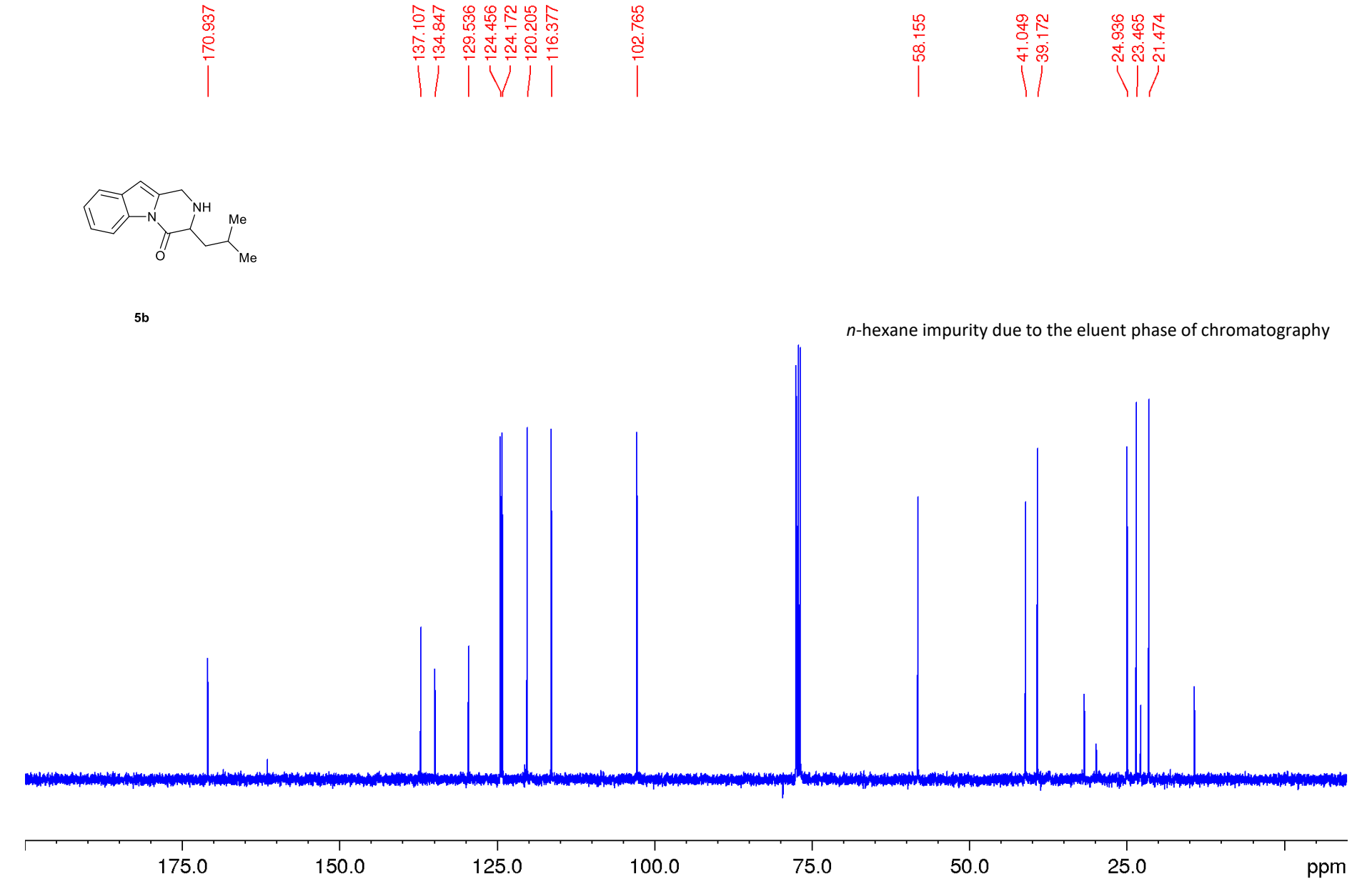
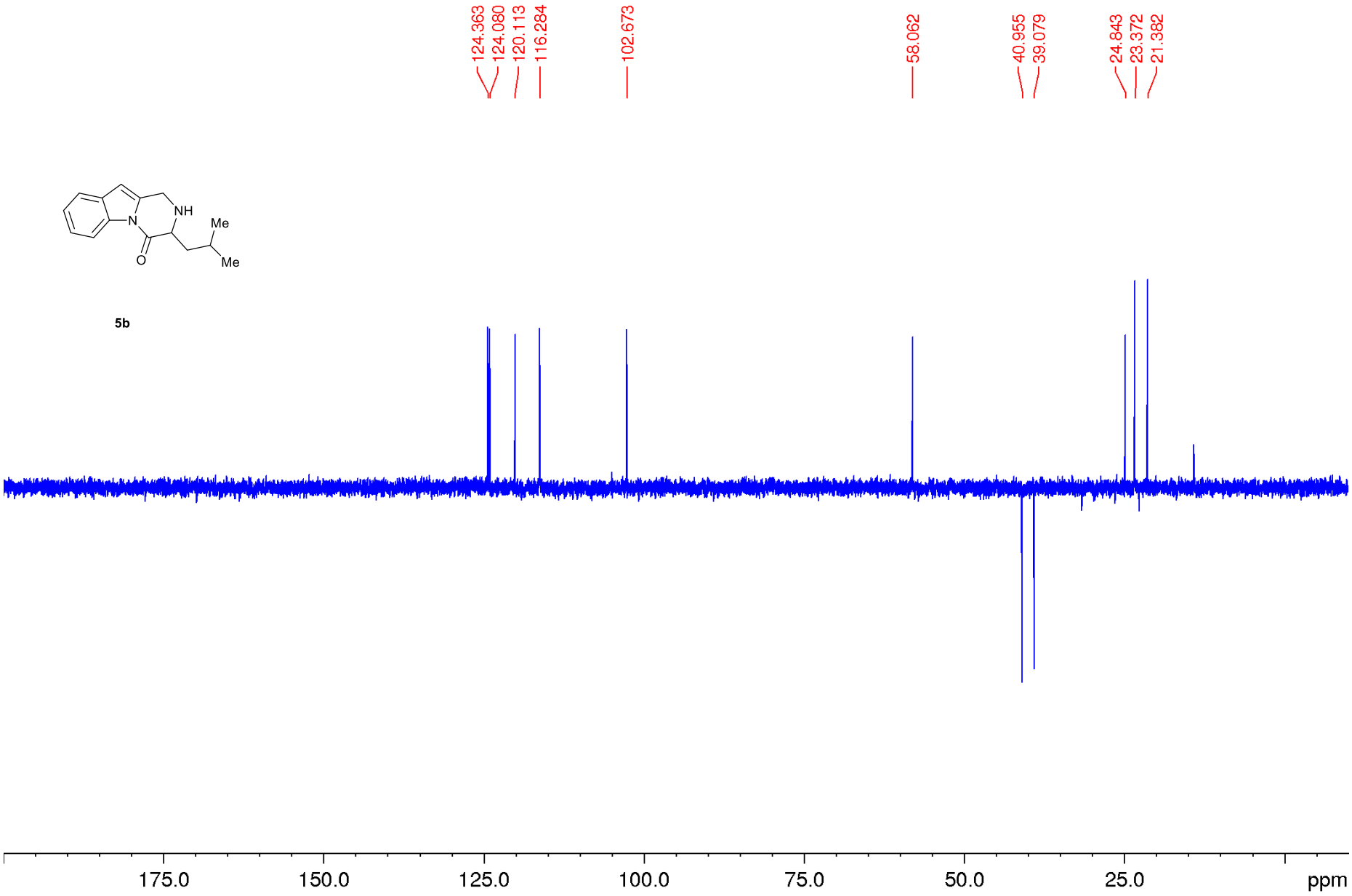


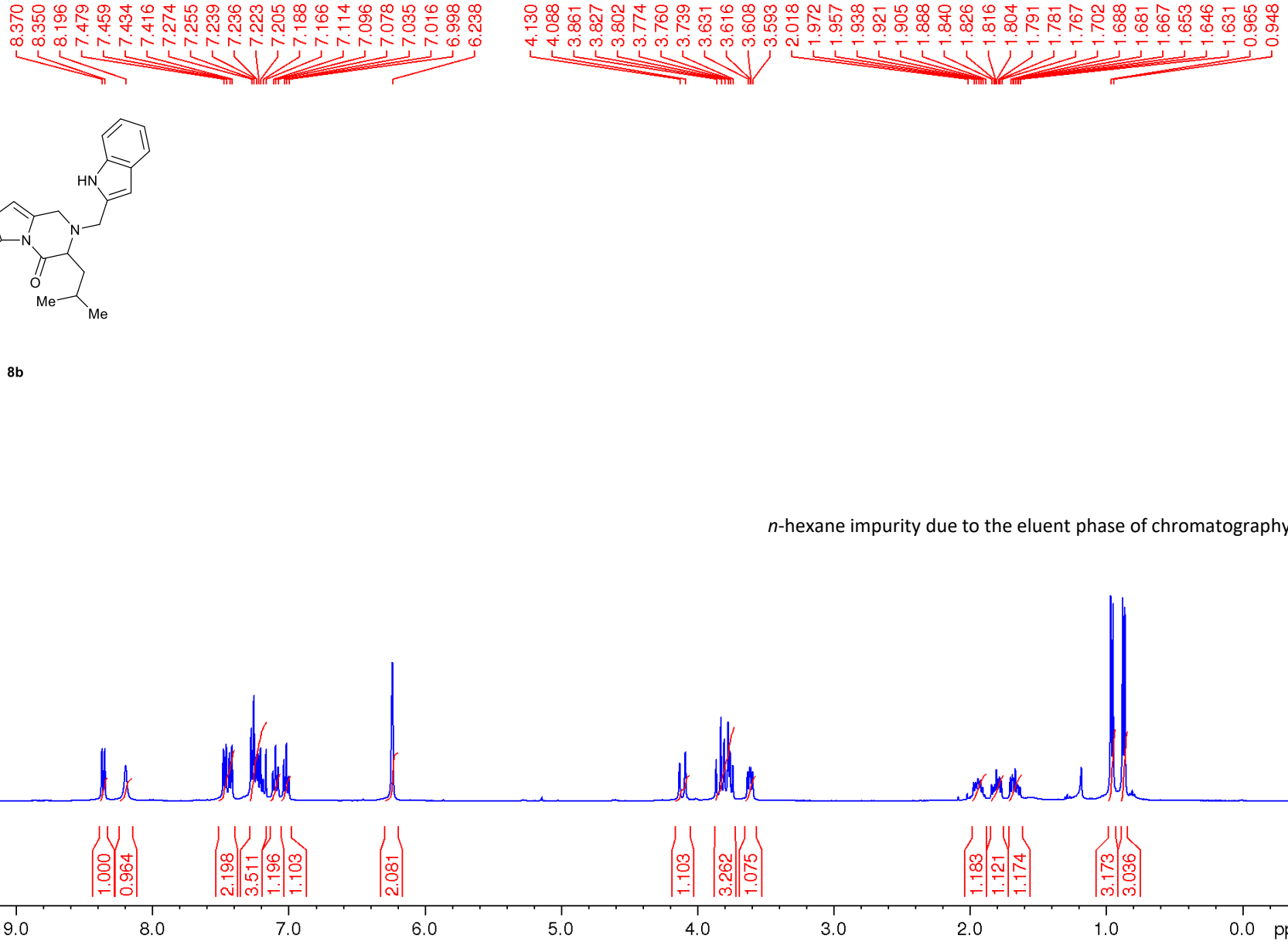
^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



DEPT 135 NMR-spectrum ($CDCl_3$)



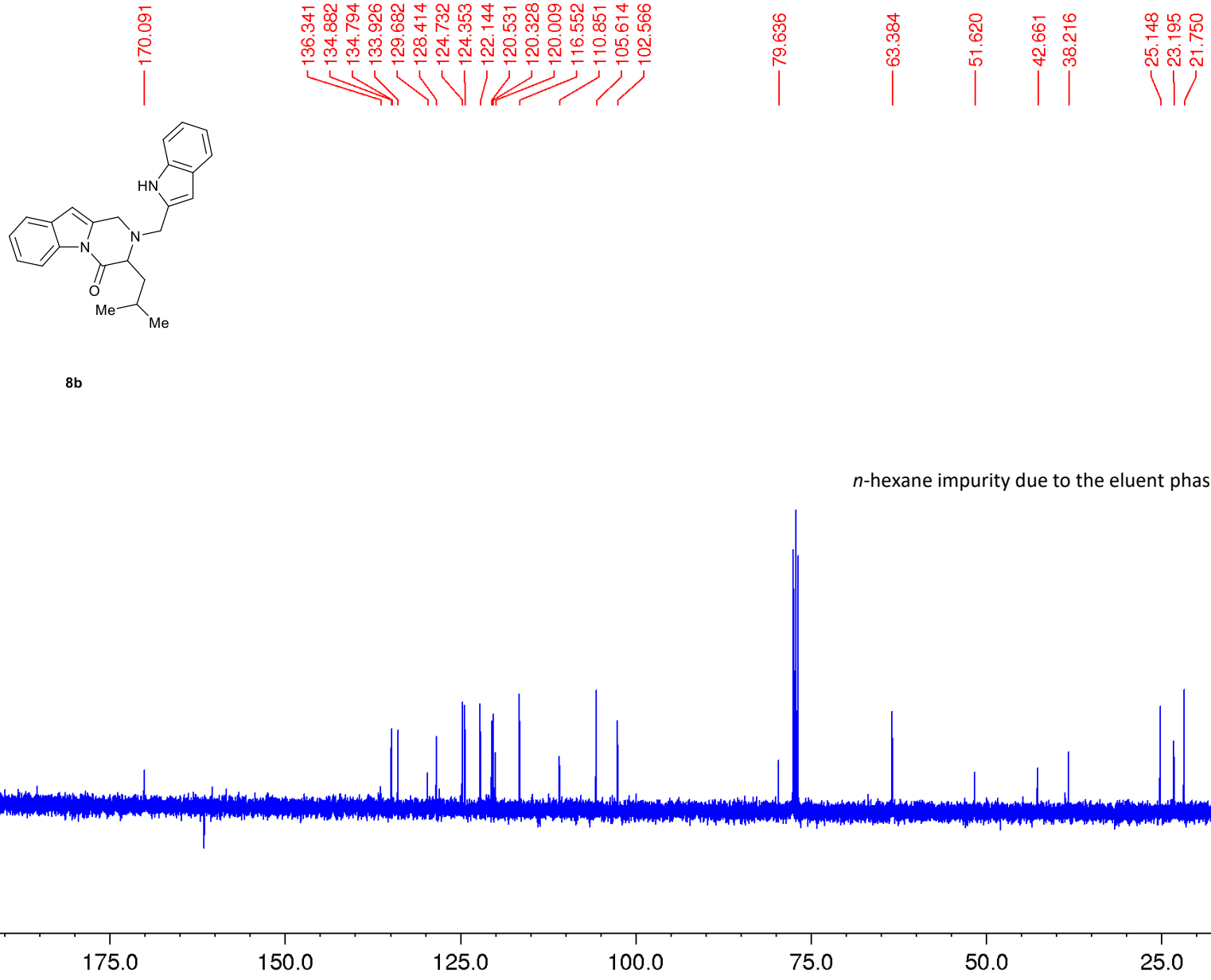
^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



8b

n-hexane impurity due to the eluent phase of chromatography

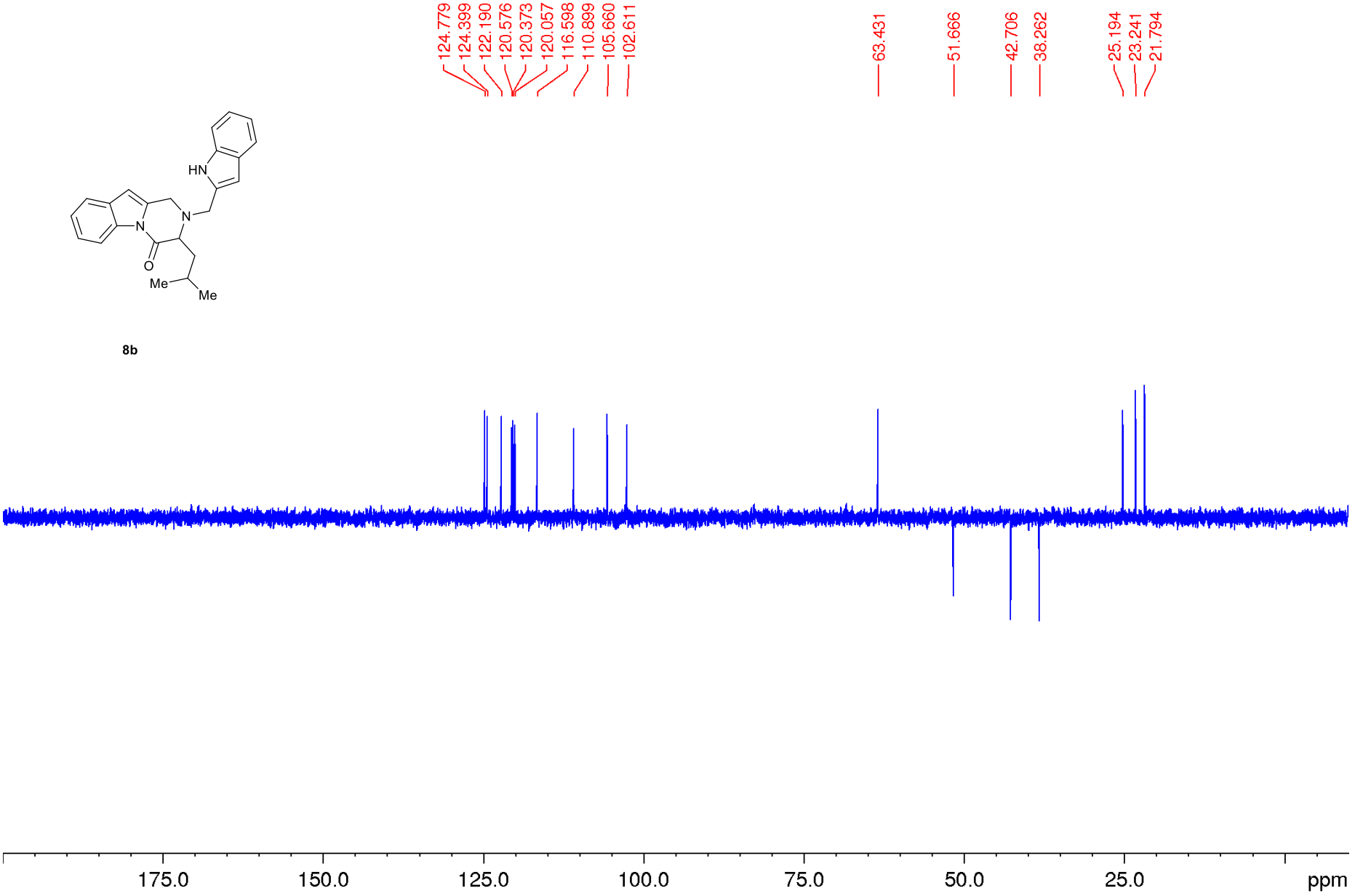
^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



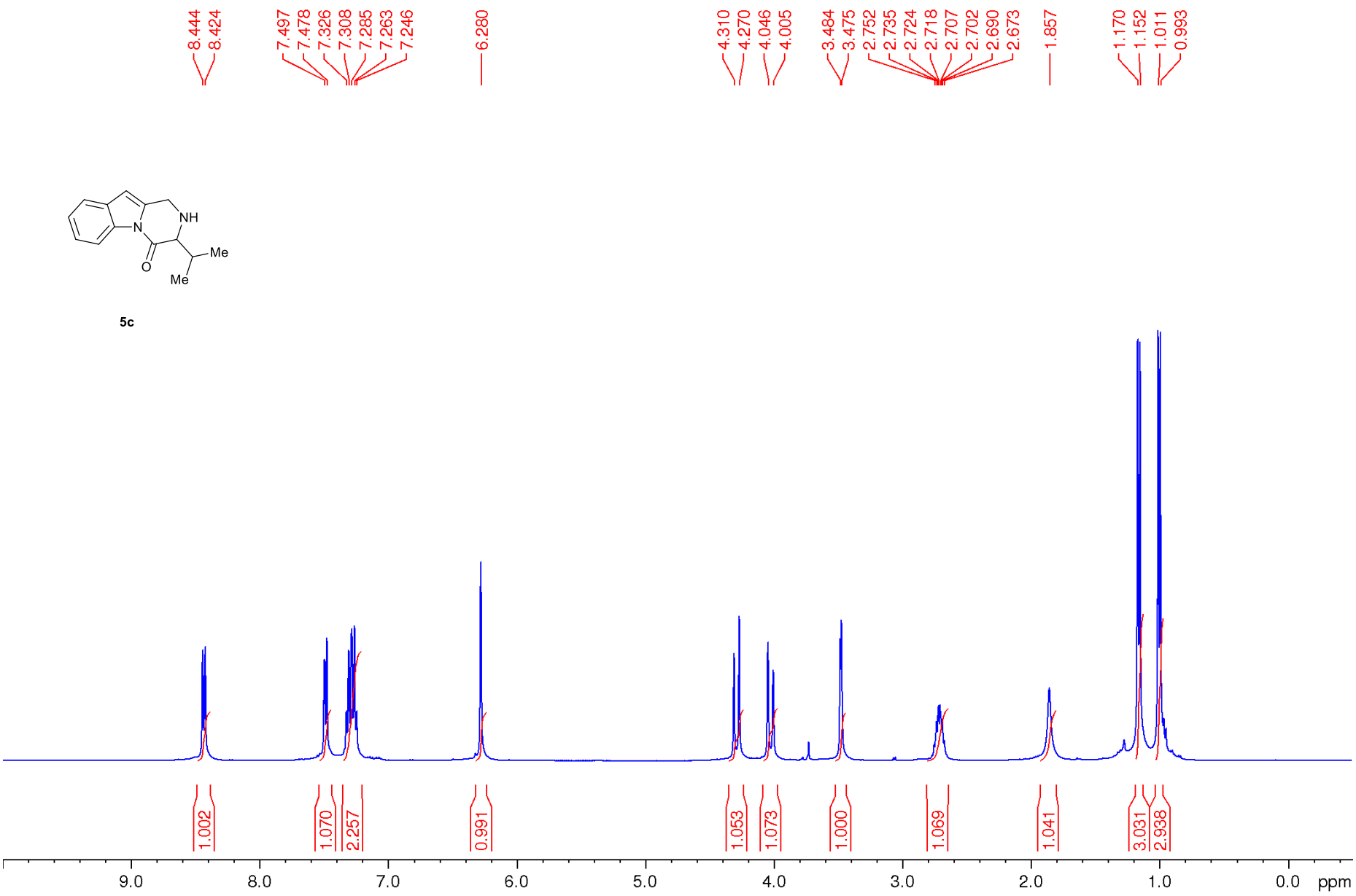
8b

n-hexane impurity due to the eluent phase of chromatography

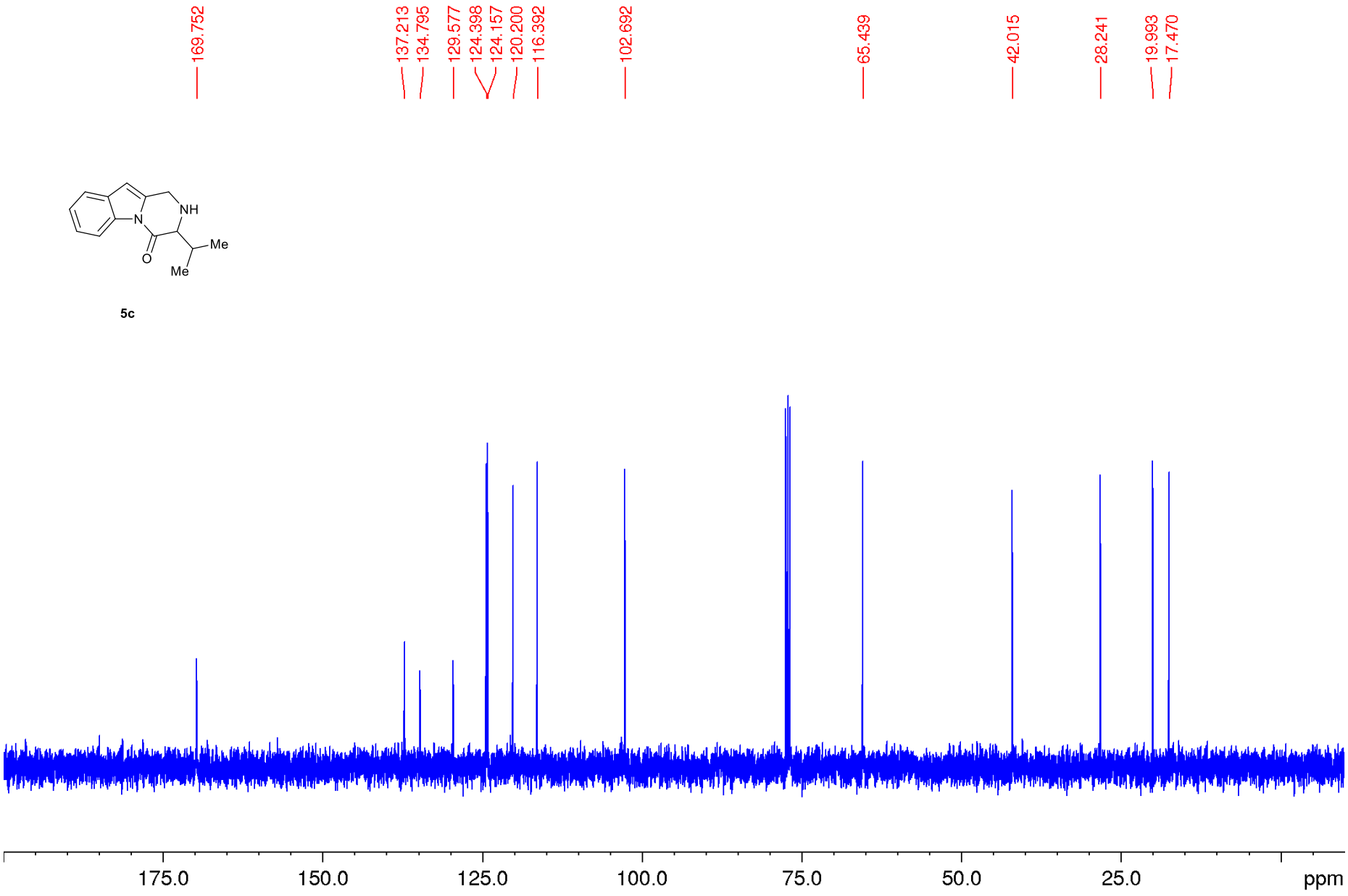
DEPT 135 NMR-spectrum ($CDCl_3$)



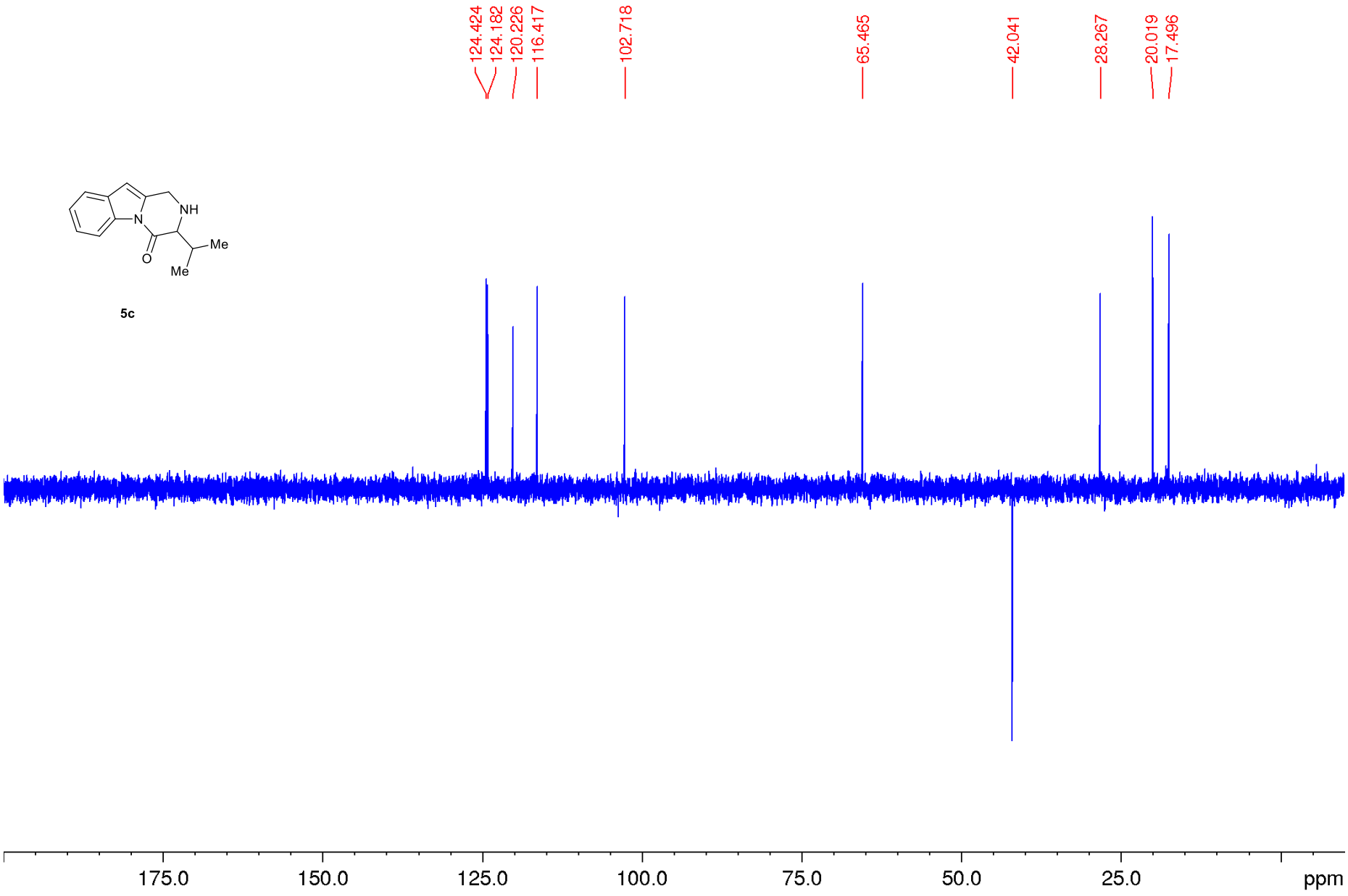
^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



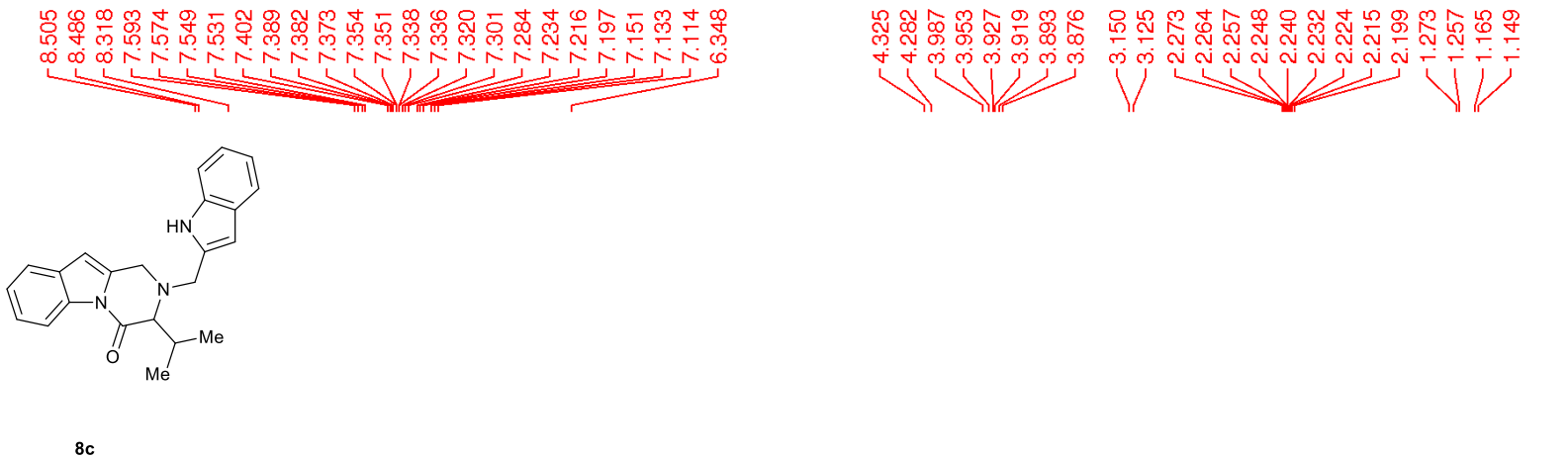
^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



DEPT 135 NMR-spectrum ($CDCl_3$)

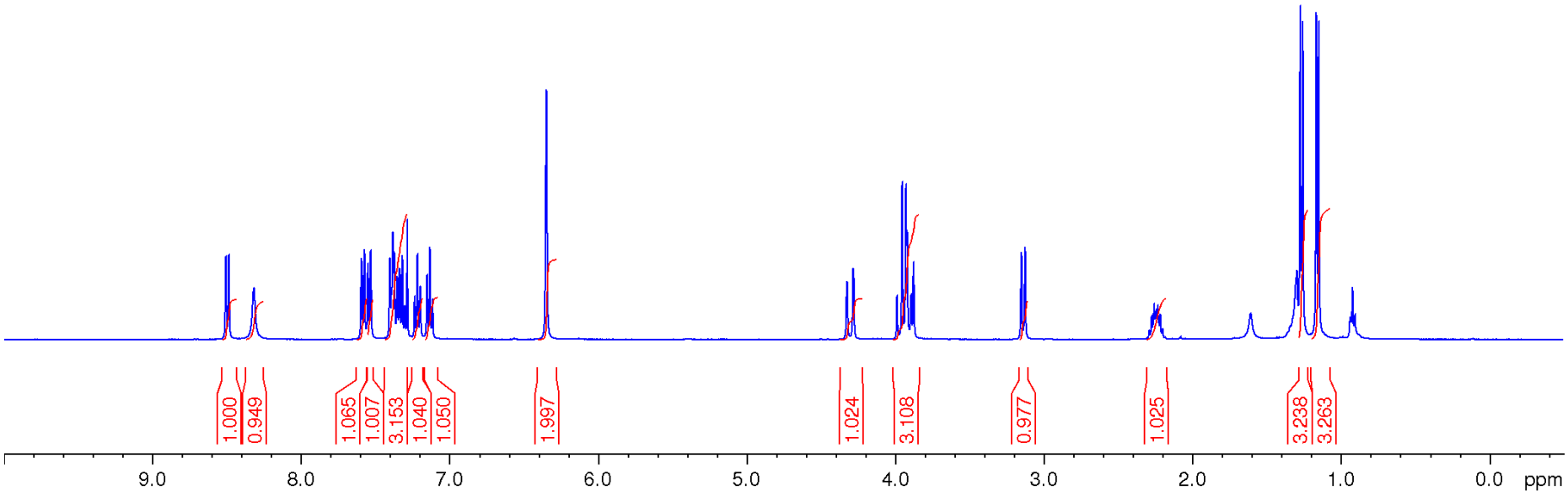


^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)

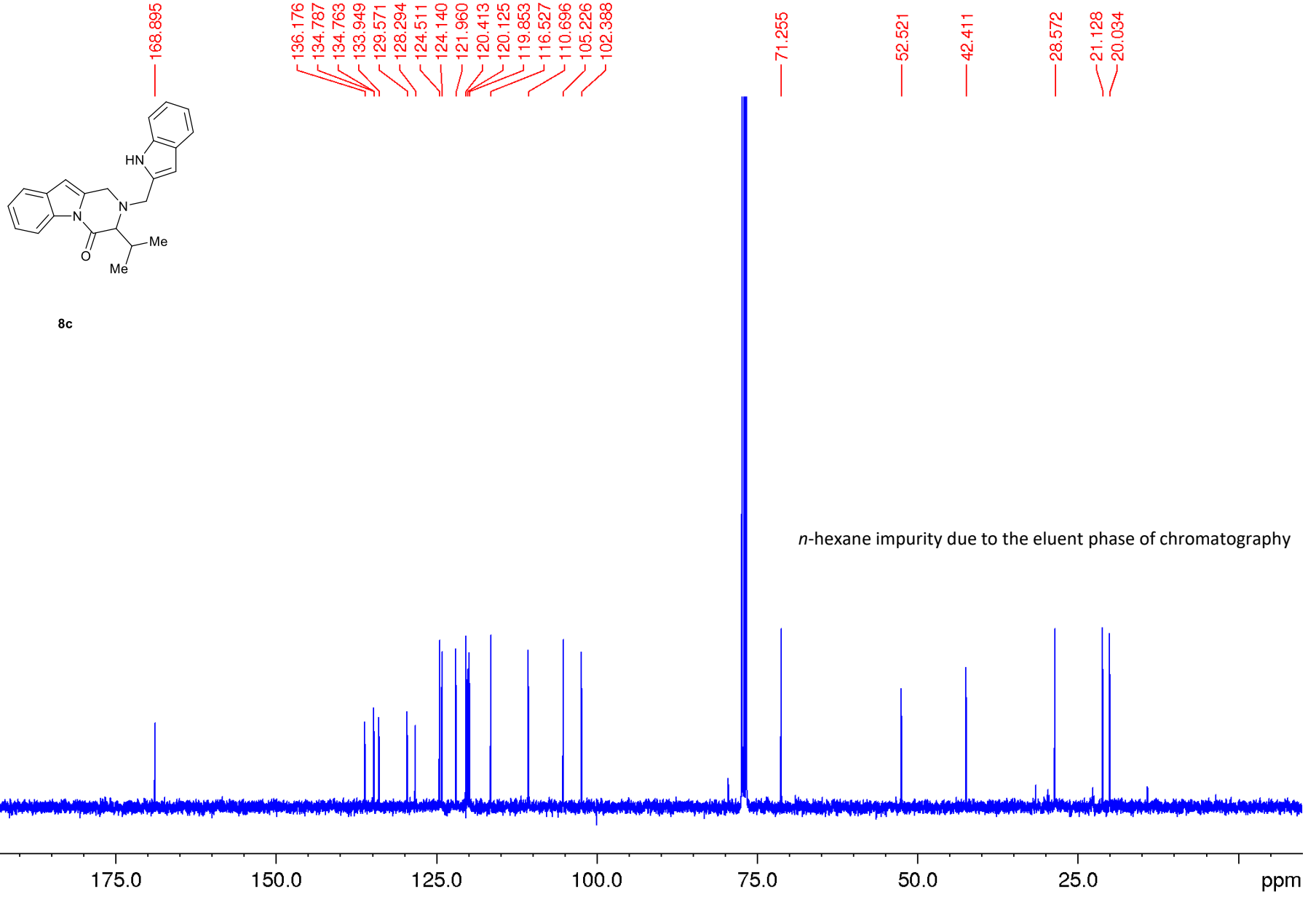


8c

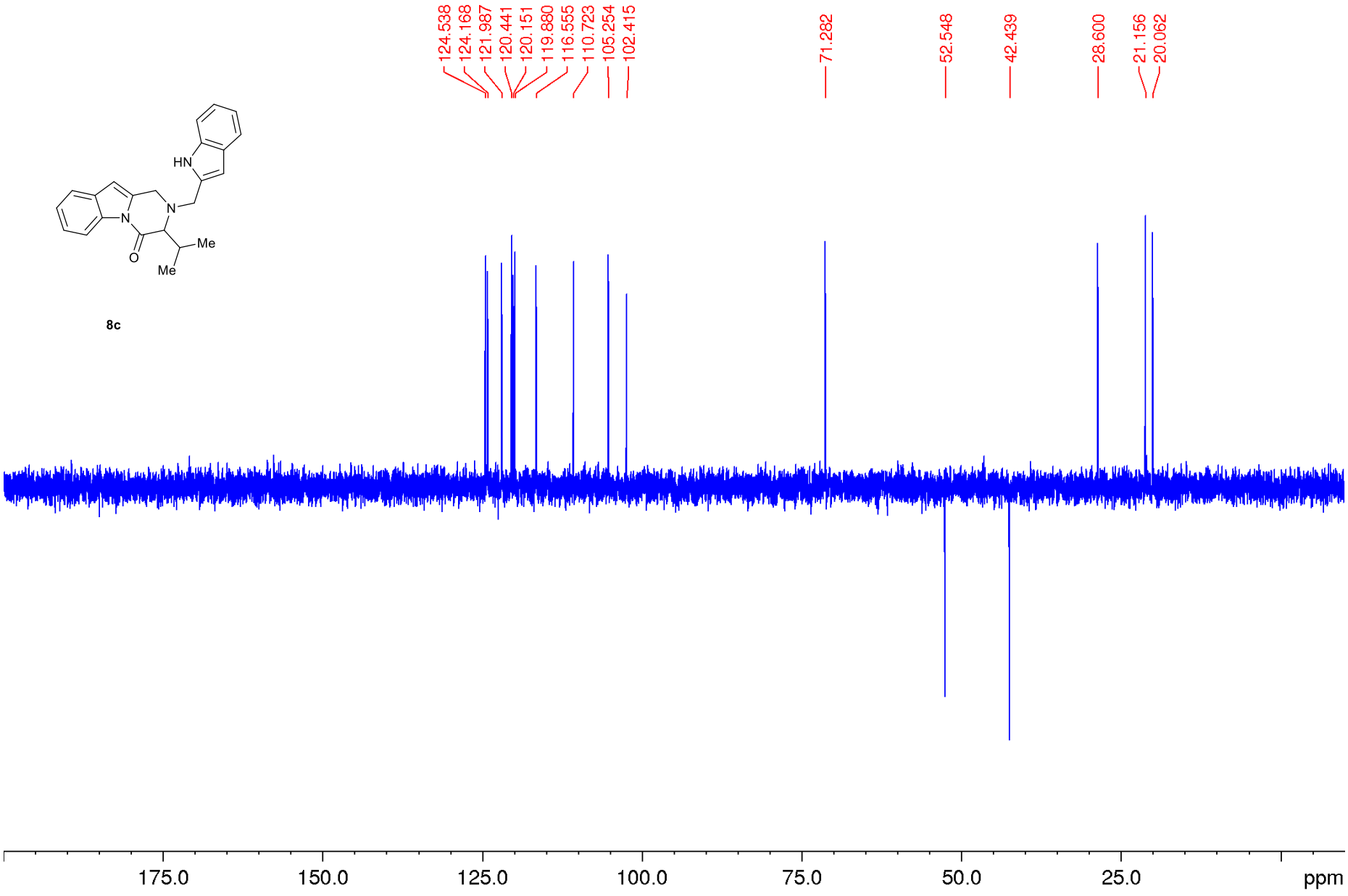
n-hexane impurity due to the eluent phase of chromatography



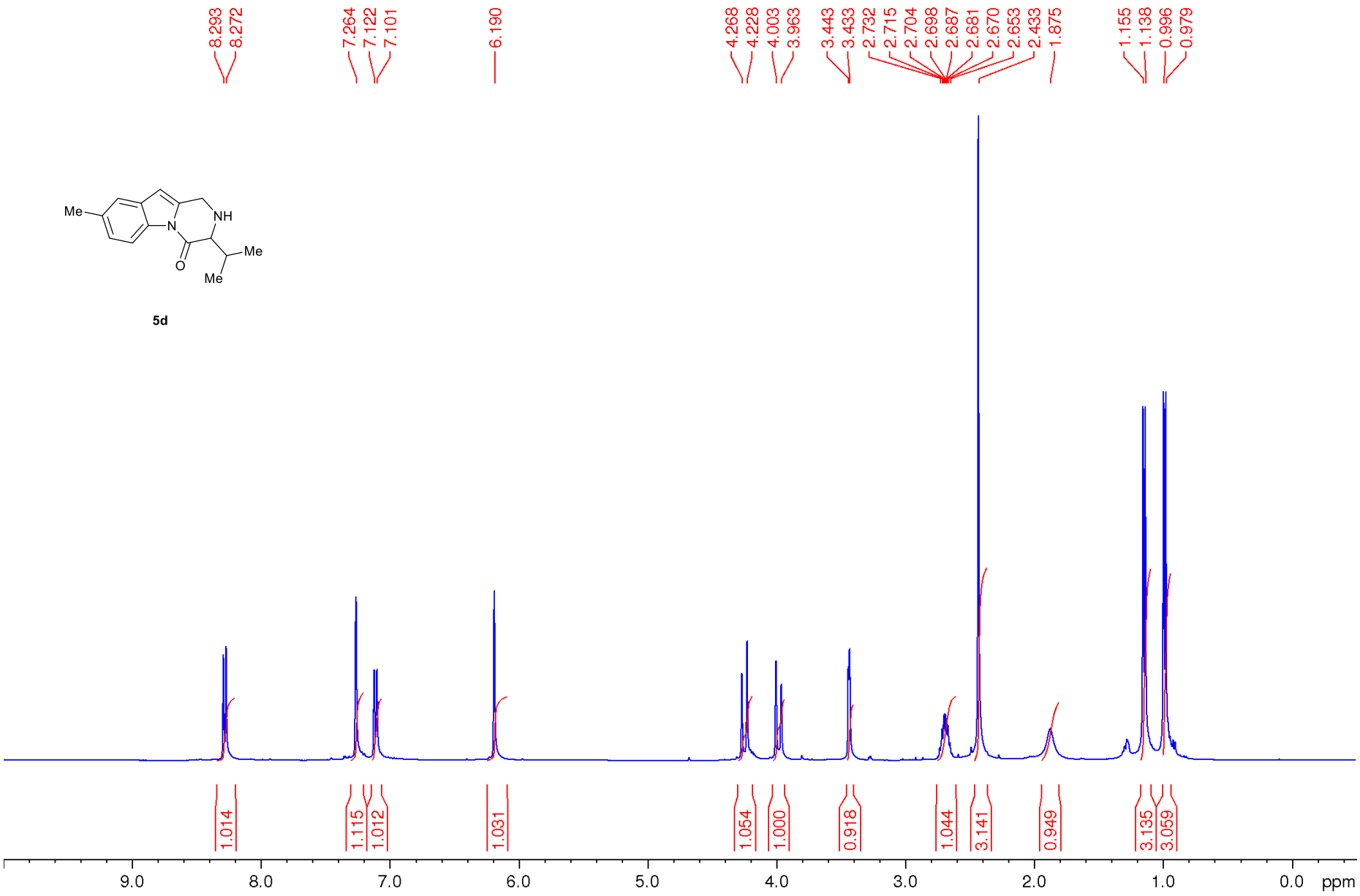
^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



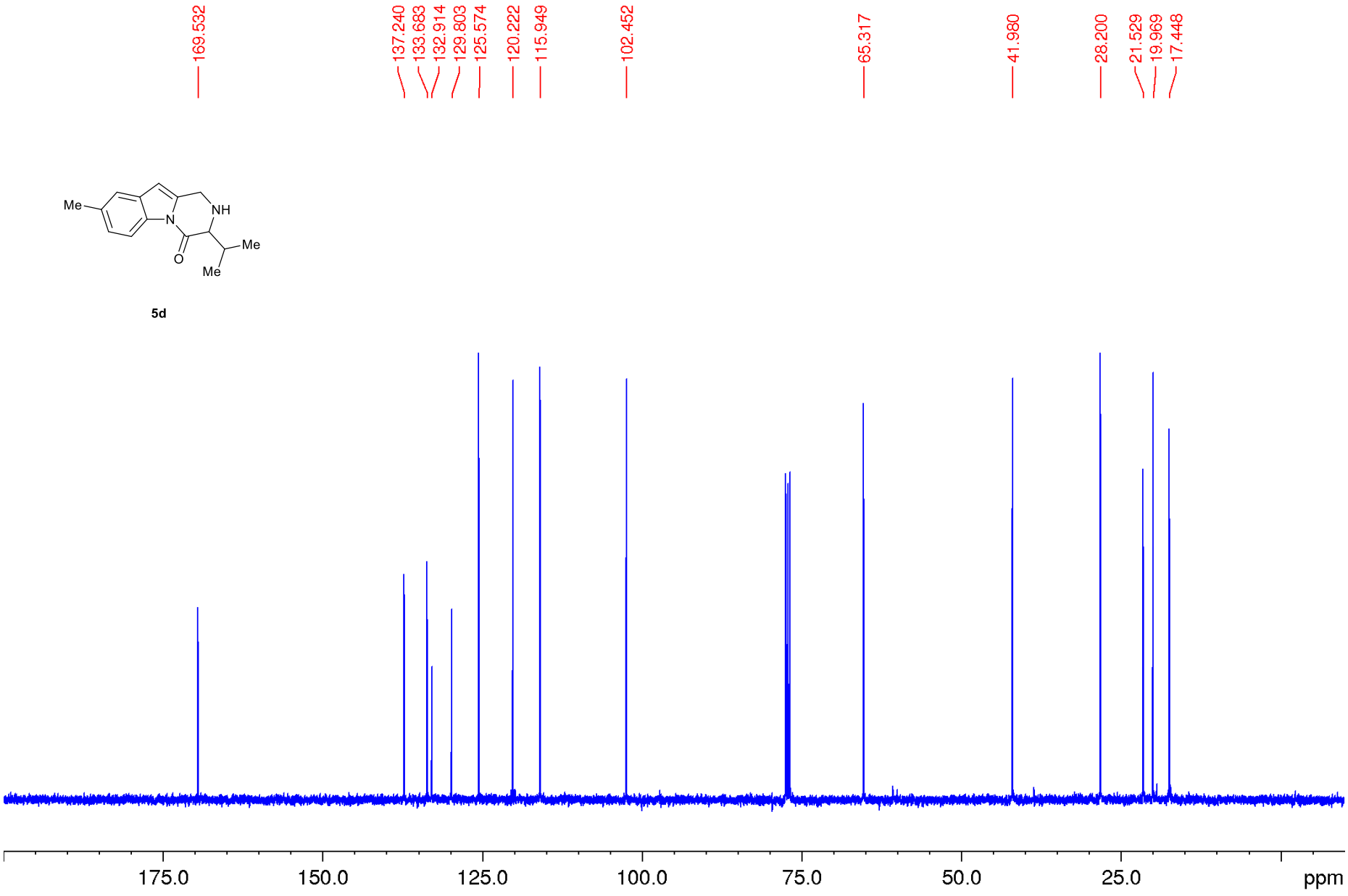
DEPT 135 NMR-spectrum ($CDCl_3$)



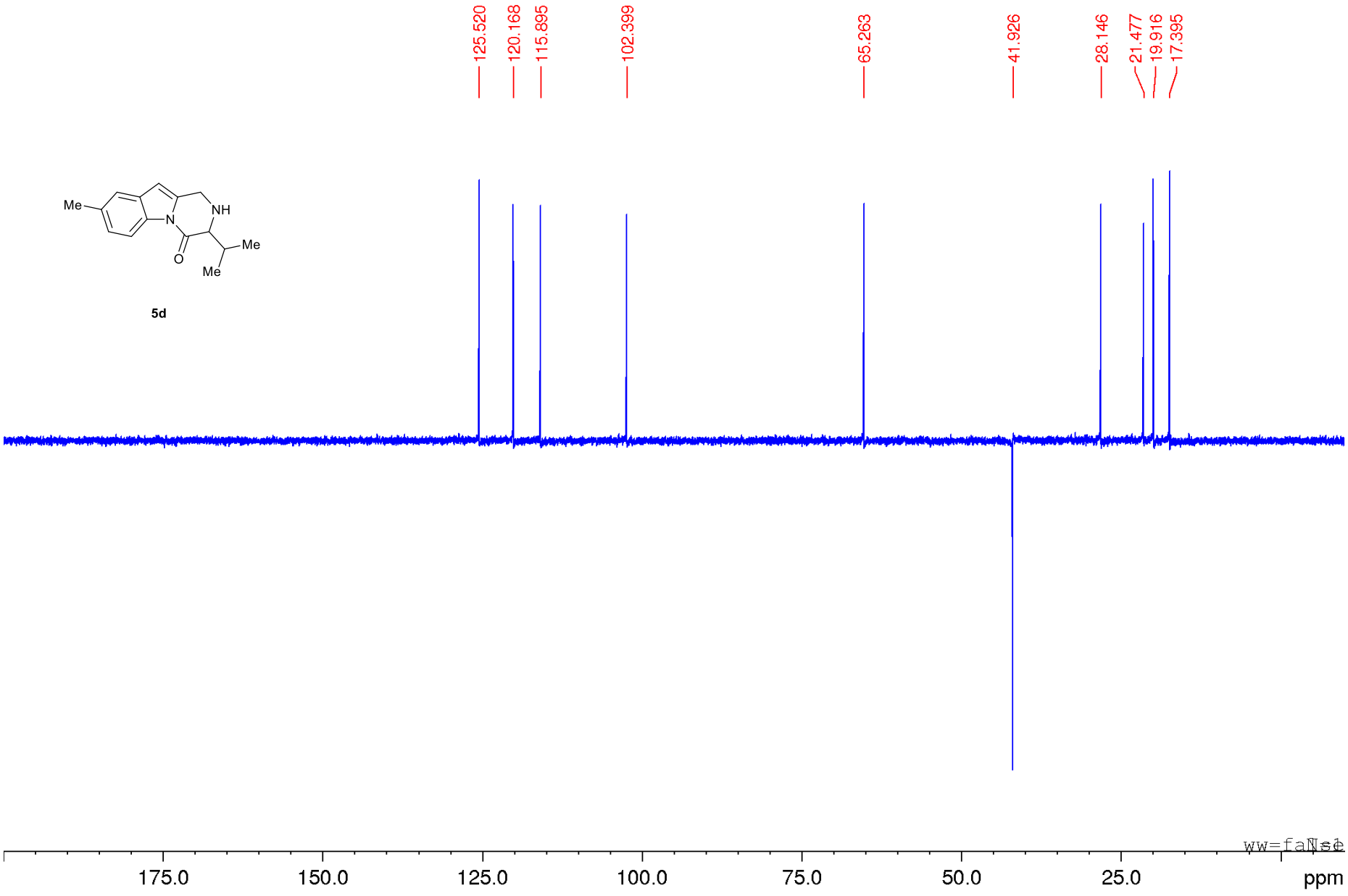
^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



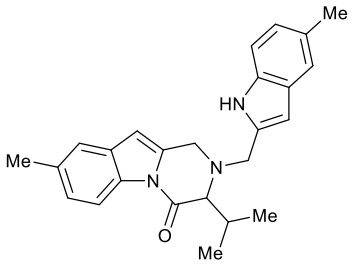
^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



DEPT 135 NMR-spectrum ($CDCl_3$)



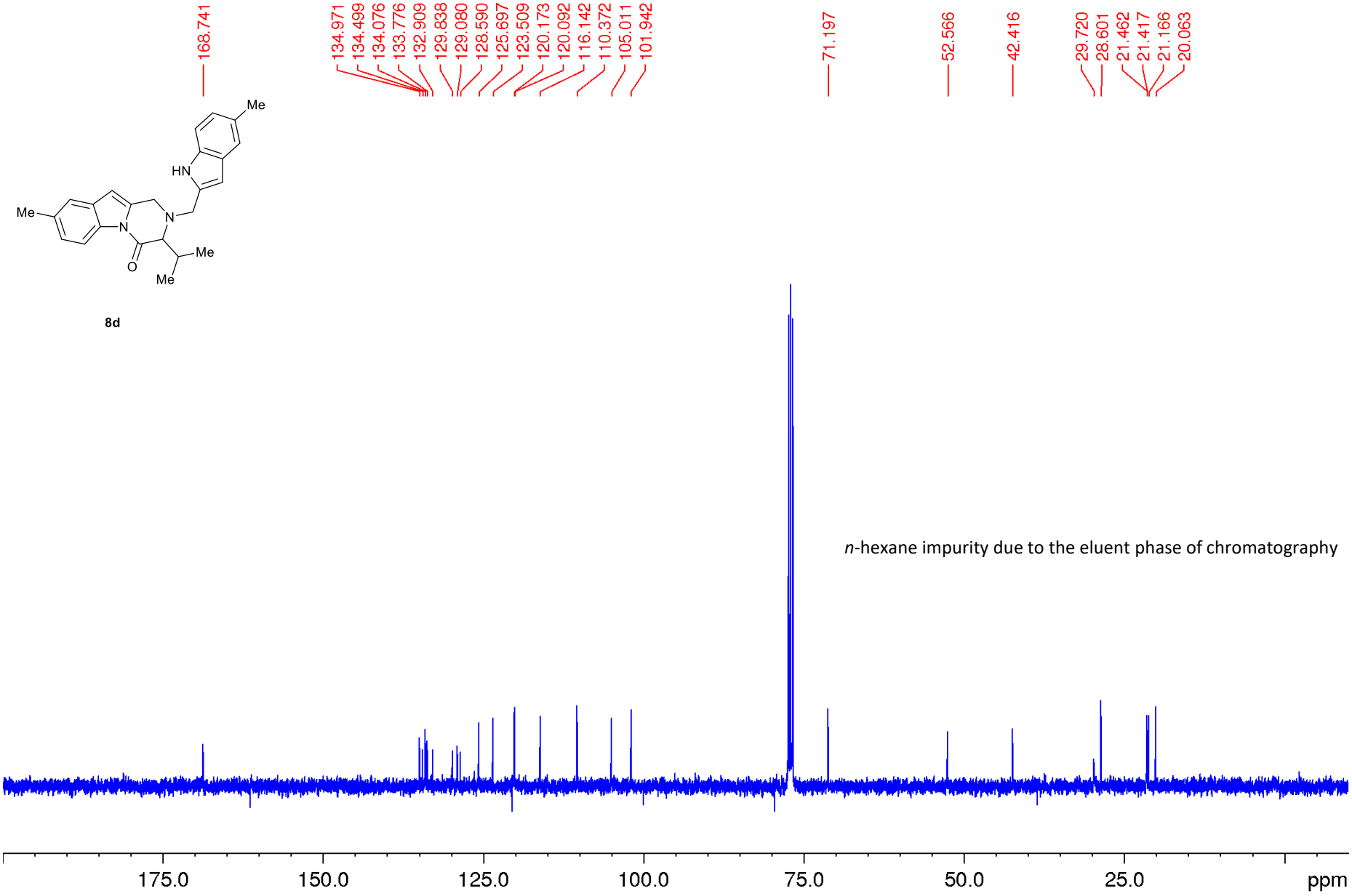
^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



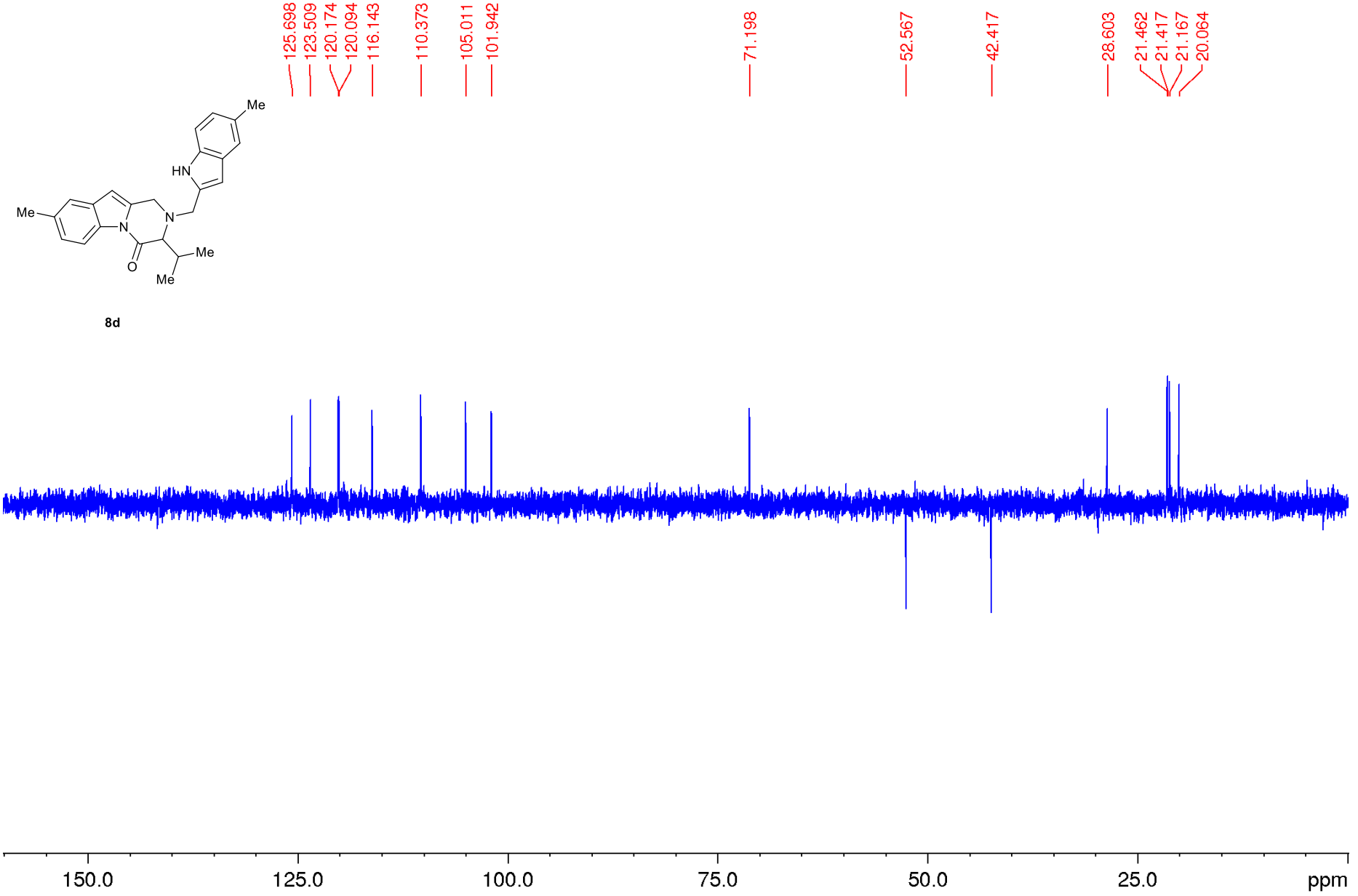
8d

n-hexane impurity due to the eluent phase of chromatography

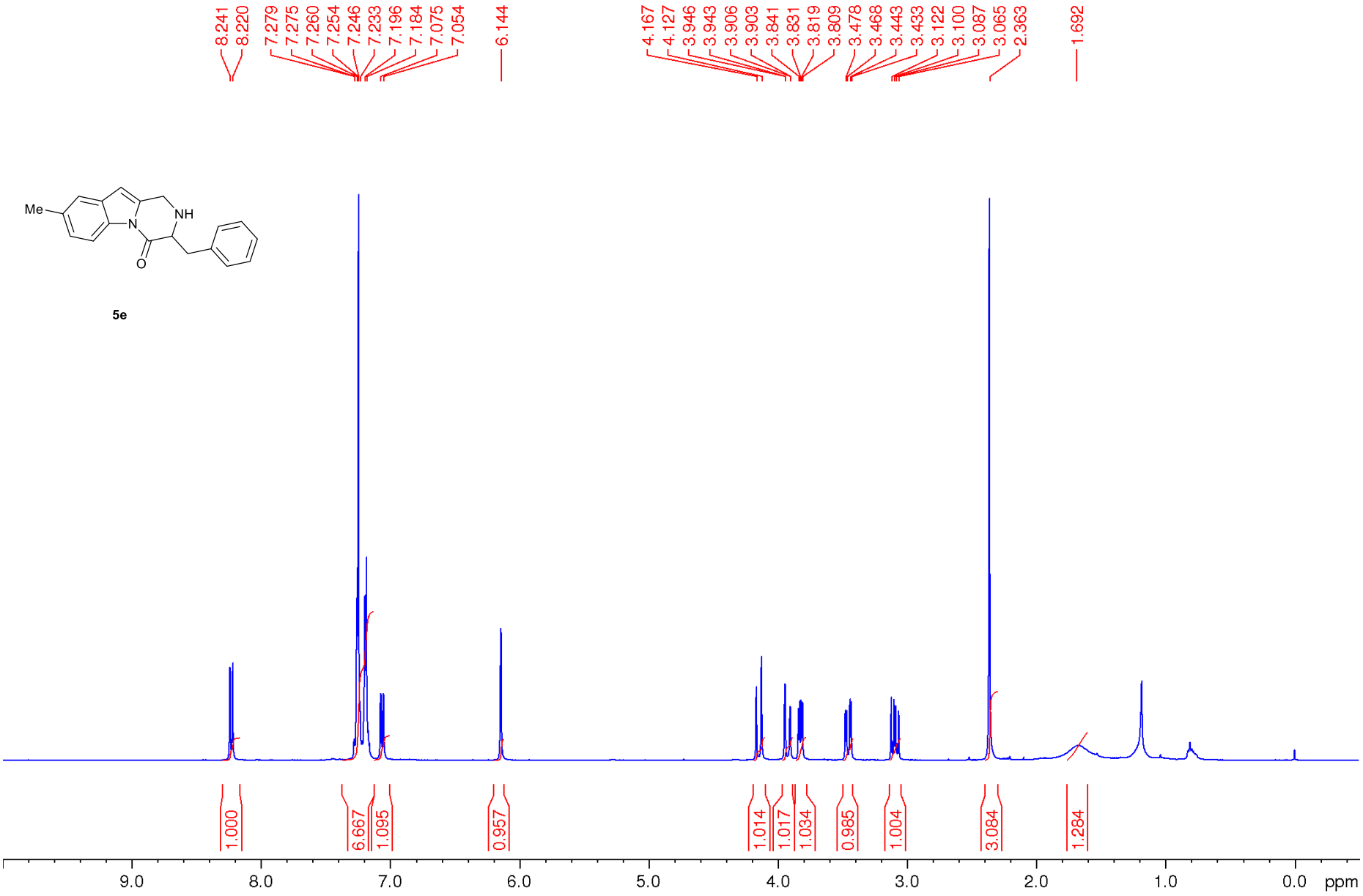
^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



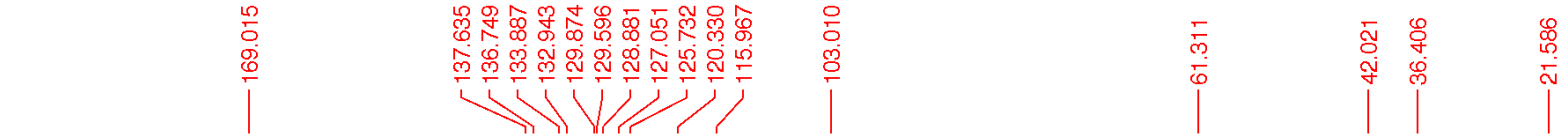
DEPT 135 NMR-spectrum ($CDCl_3$)

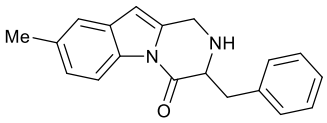


^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)

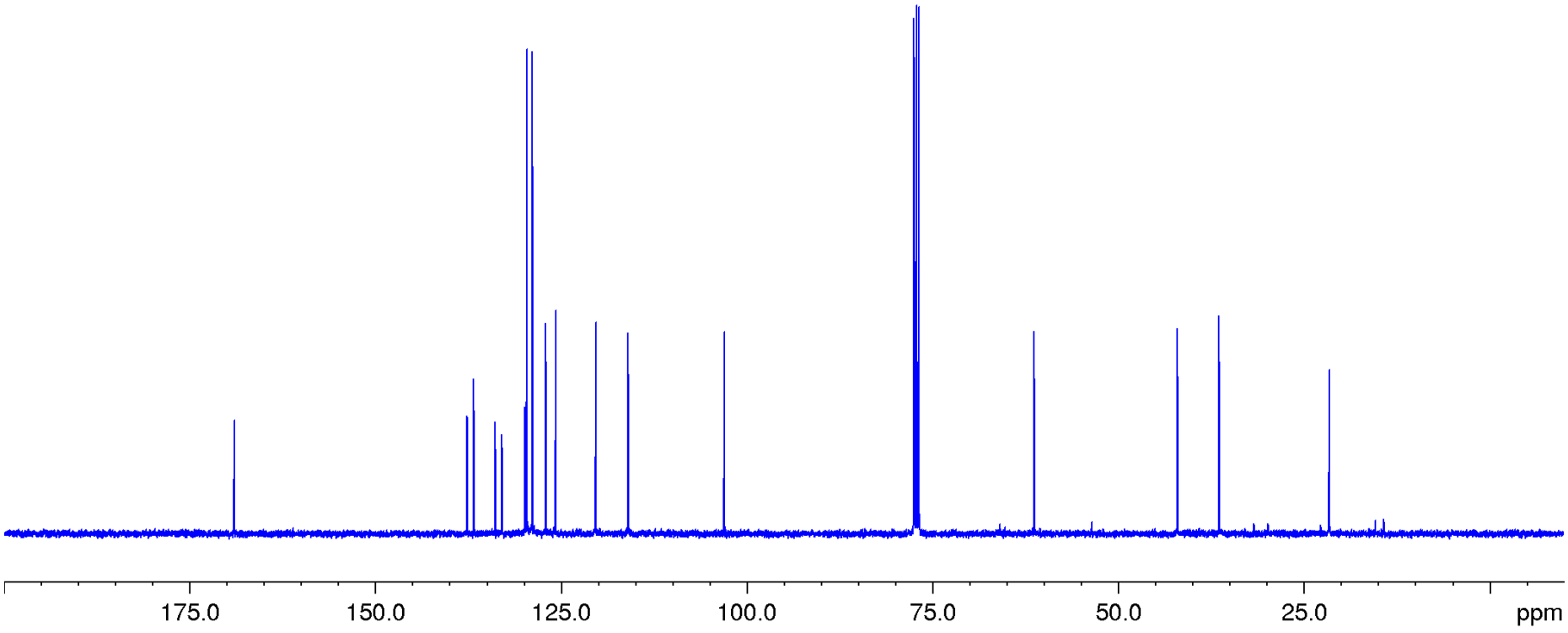


^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)

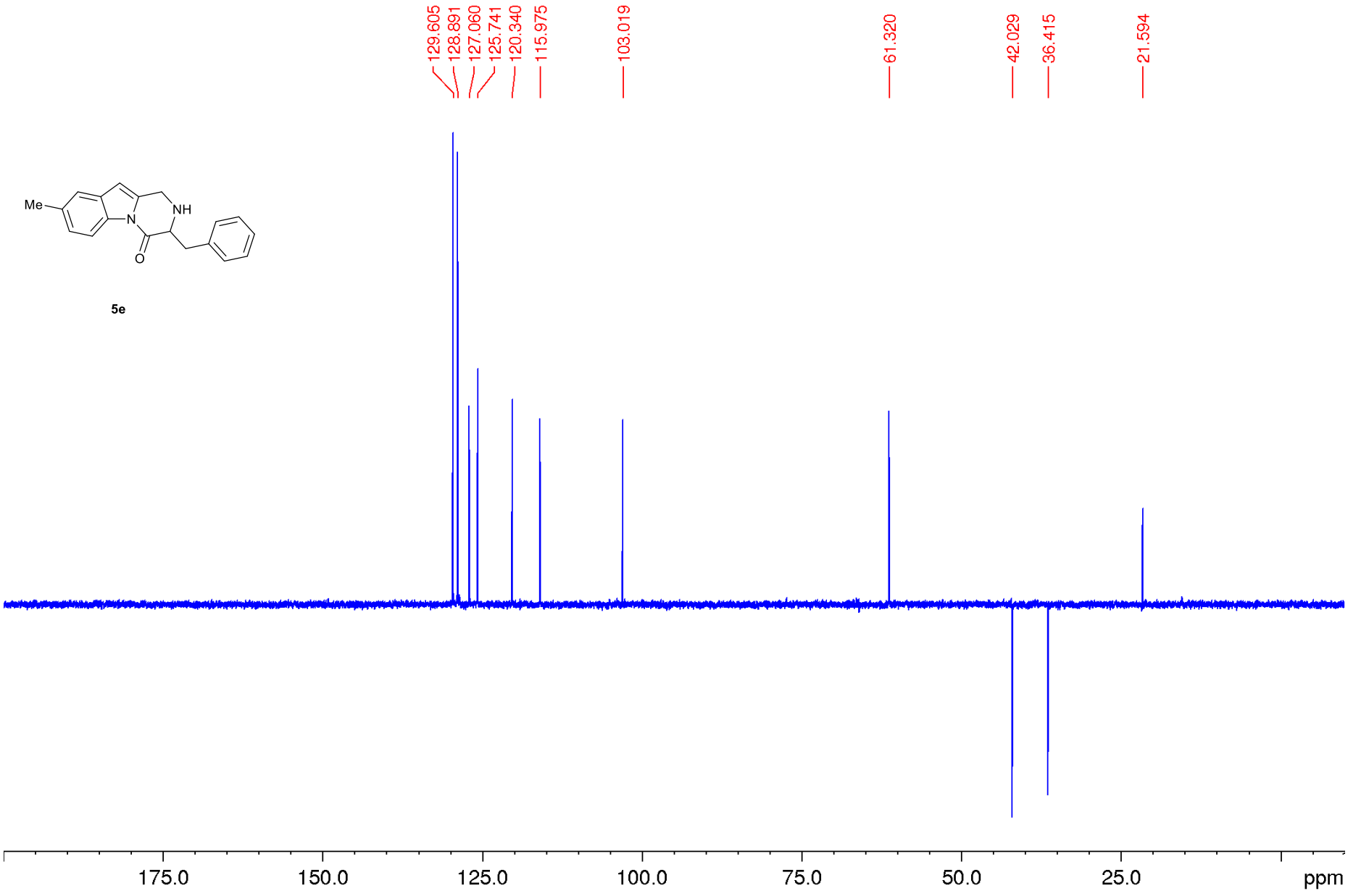




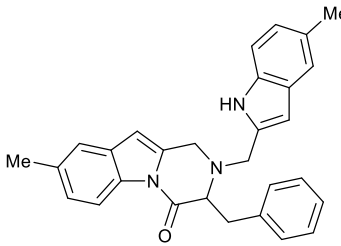
5e



DEPT 135 NMR-spectrum ($CDCl_3$)



^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



8e

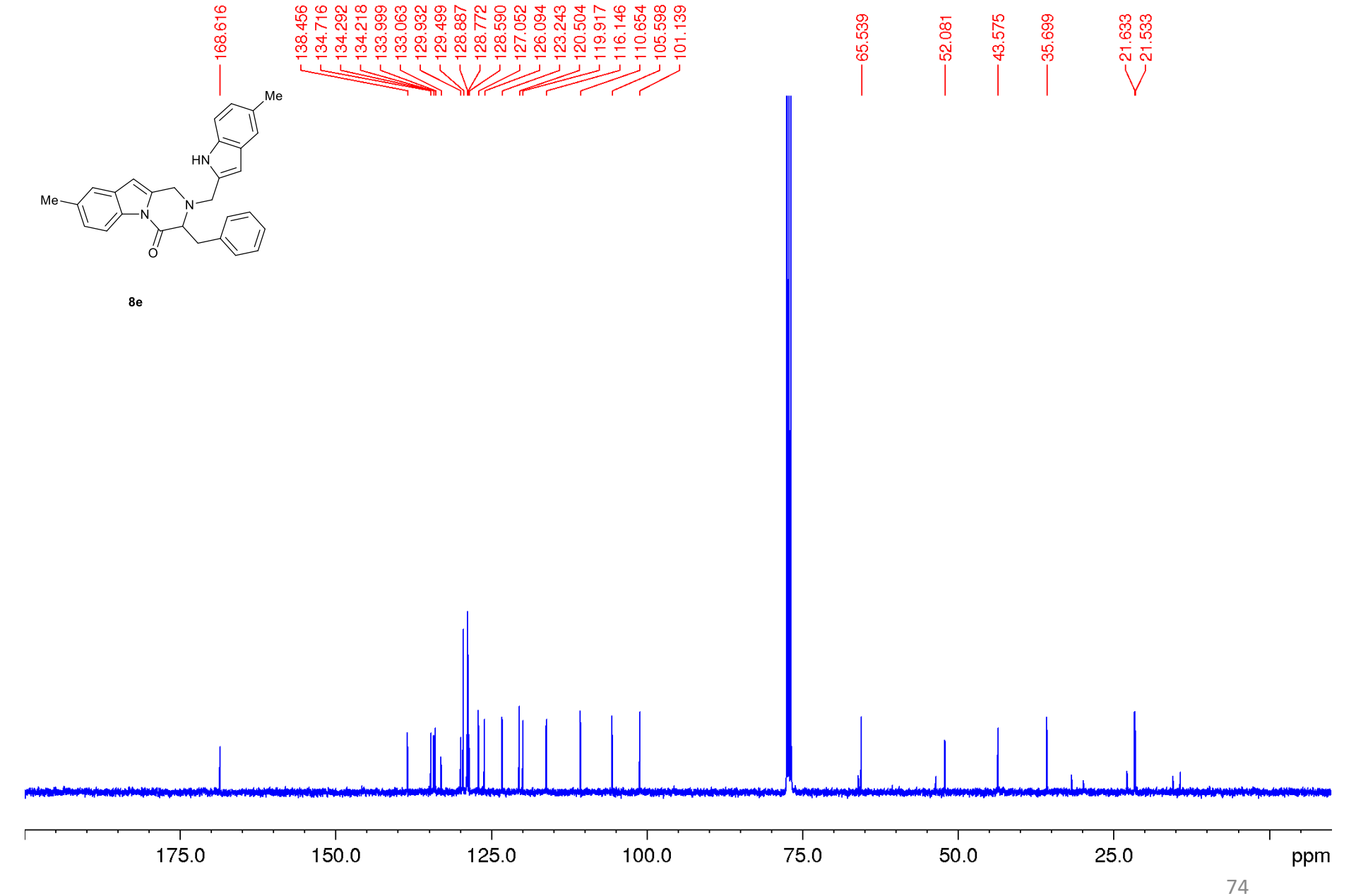
8.325 8.305 7.428 7.424 7.416 7.411 7.328 7.278 7.274 7.255 7.250 7.187 7.169 6.948 6.944 6.927 6.924 6.918 6.897 6.346 6.090 4.509 4.506 4.467 4.464 3.936 3.906 3.894 3.871 3.788 3.770 3.759 3.752 3.742 3.731 3.324 3.313 3.288 3.278 3.187 3.158 3.152 3.123 2.468 2.404

H_2O impurity

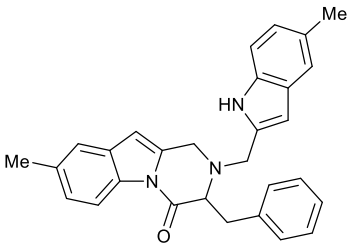
1.000 3.055 1.042 4.924 1.889 1.894 0.949 0.916 0.956 2.002 1.977 0.999 0.976 2.998 2.904

9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0 ppm

^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)

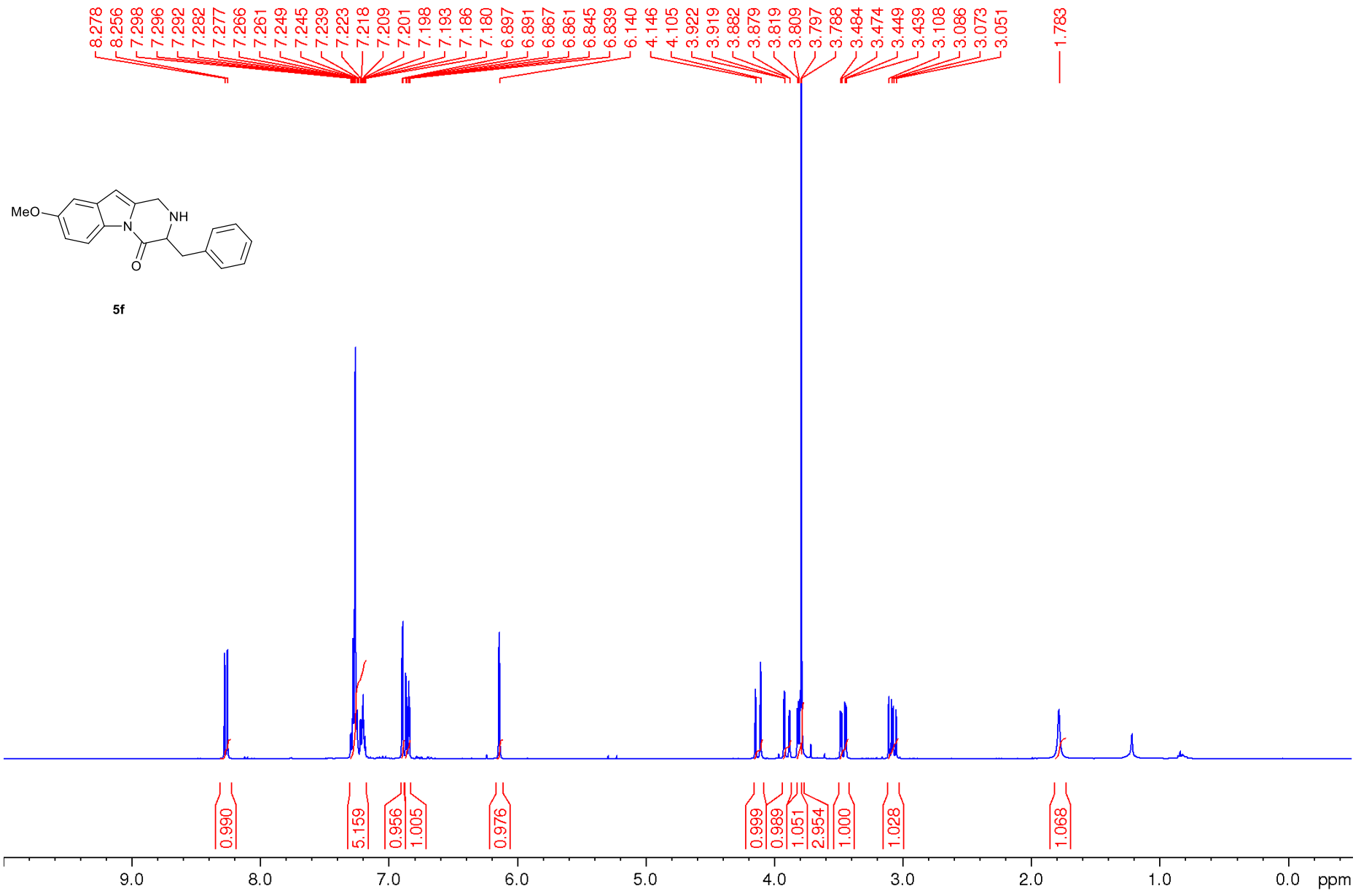


DEPT 135 NMR-spectrum ($CDCl_3$)



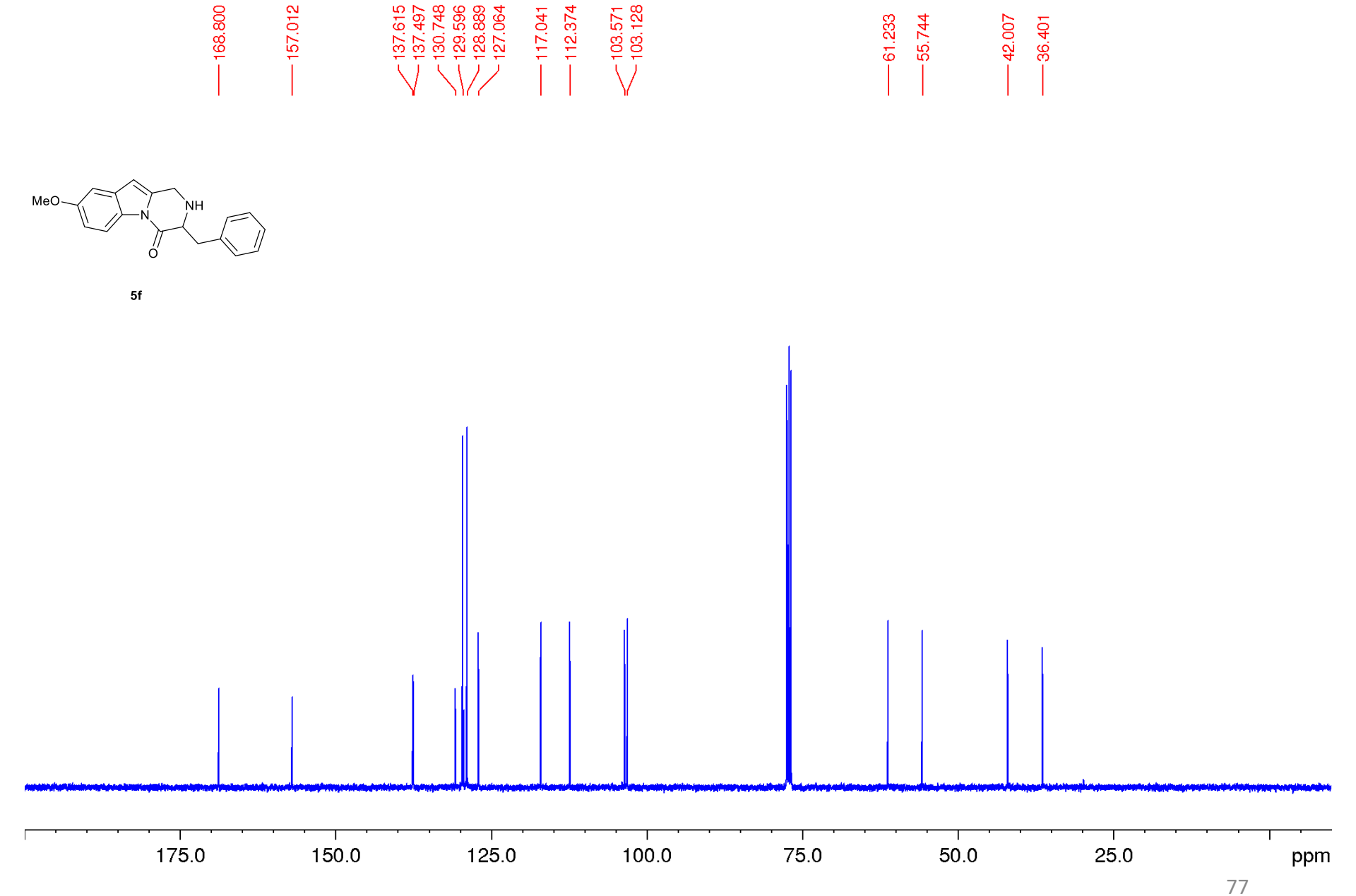
8e

^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)

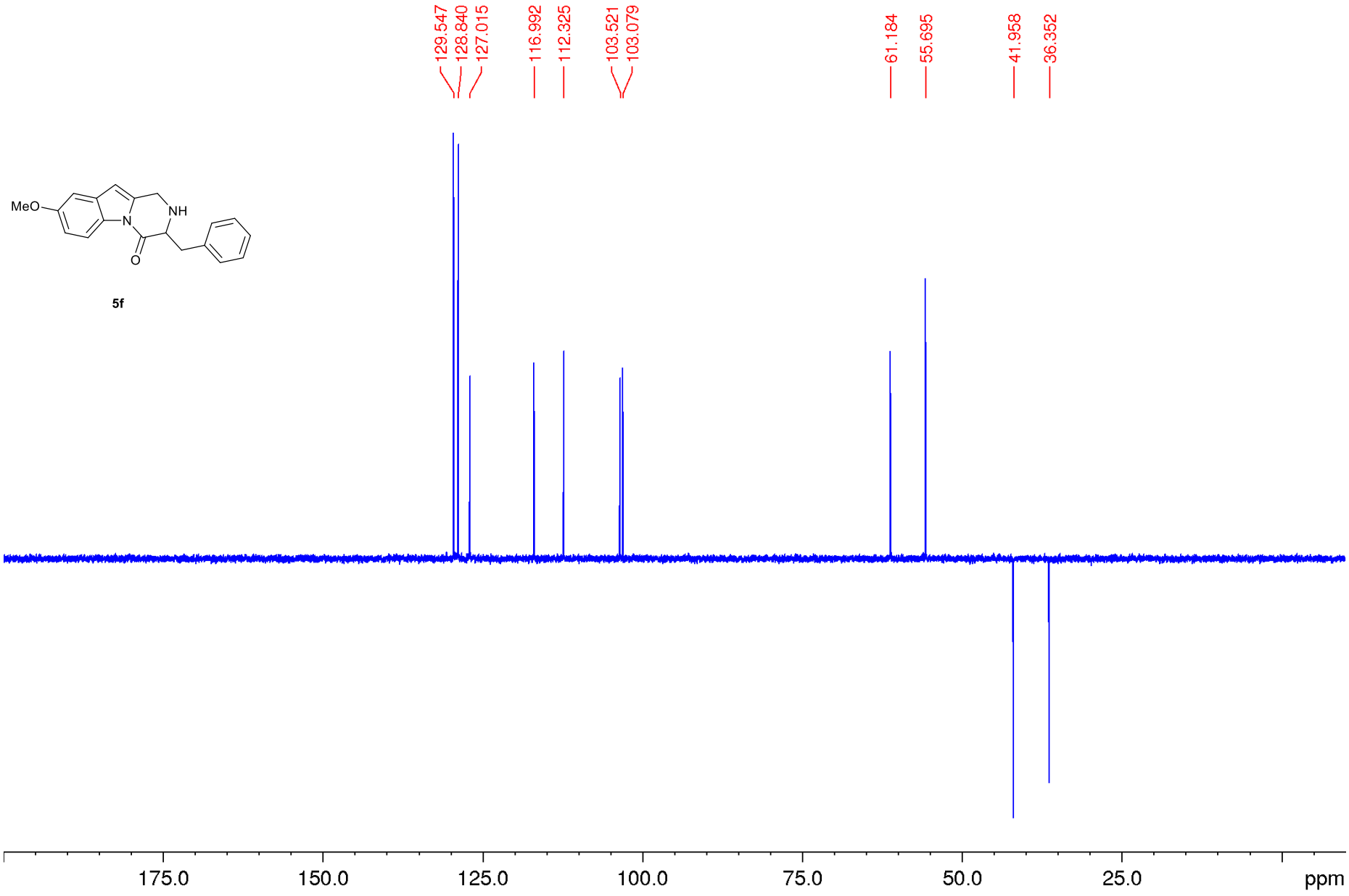


5f

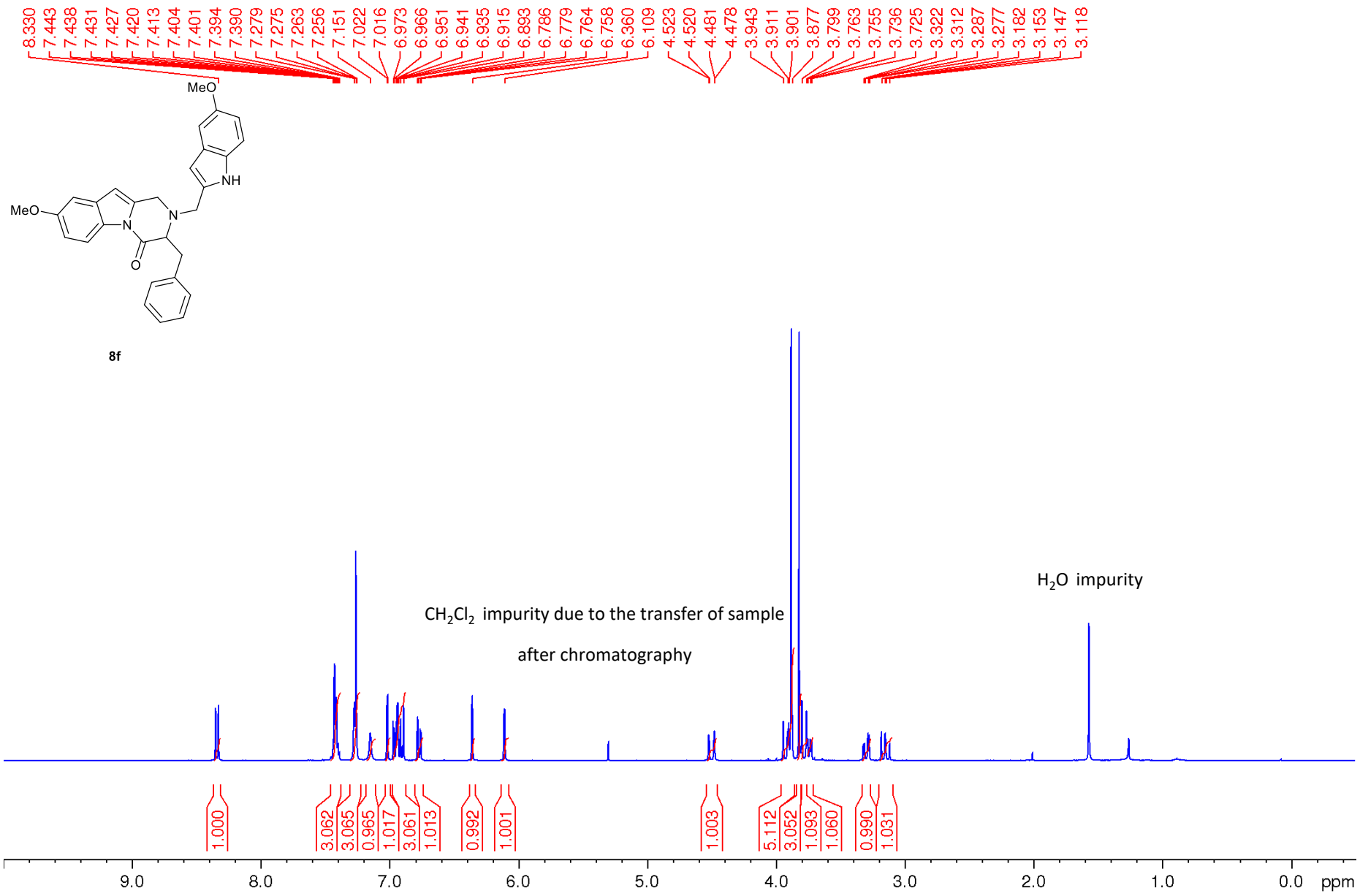
^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



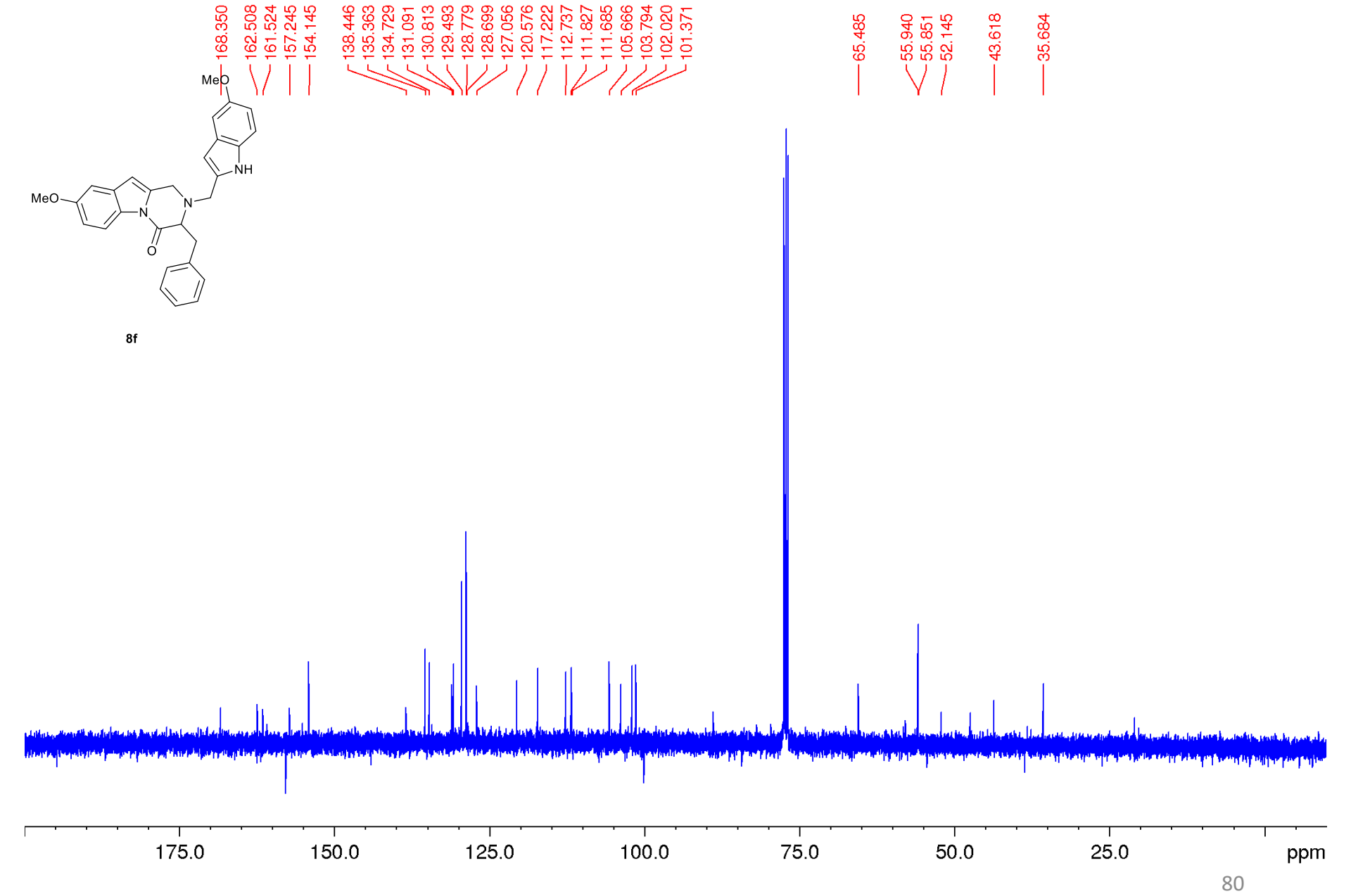
DEPT 135 NMR-spectrum ($CDCl_3$)



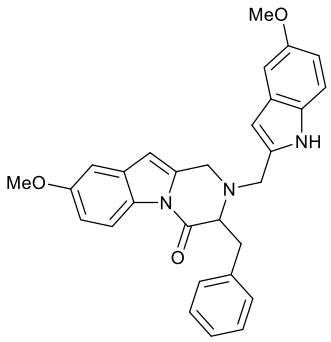
^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)

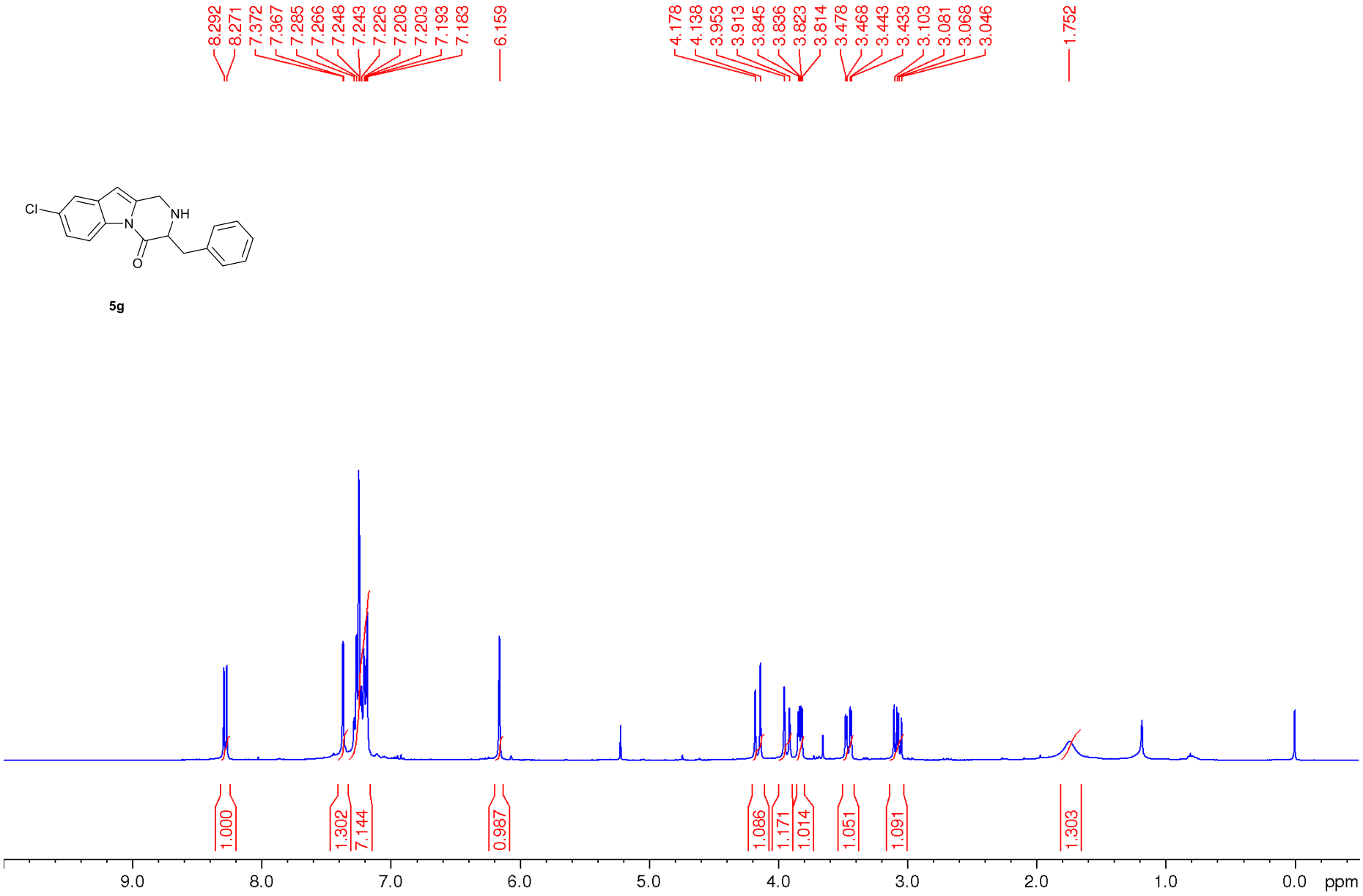


DEPT 135 NMR-spectrum ($CDCl_3$)



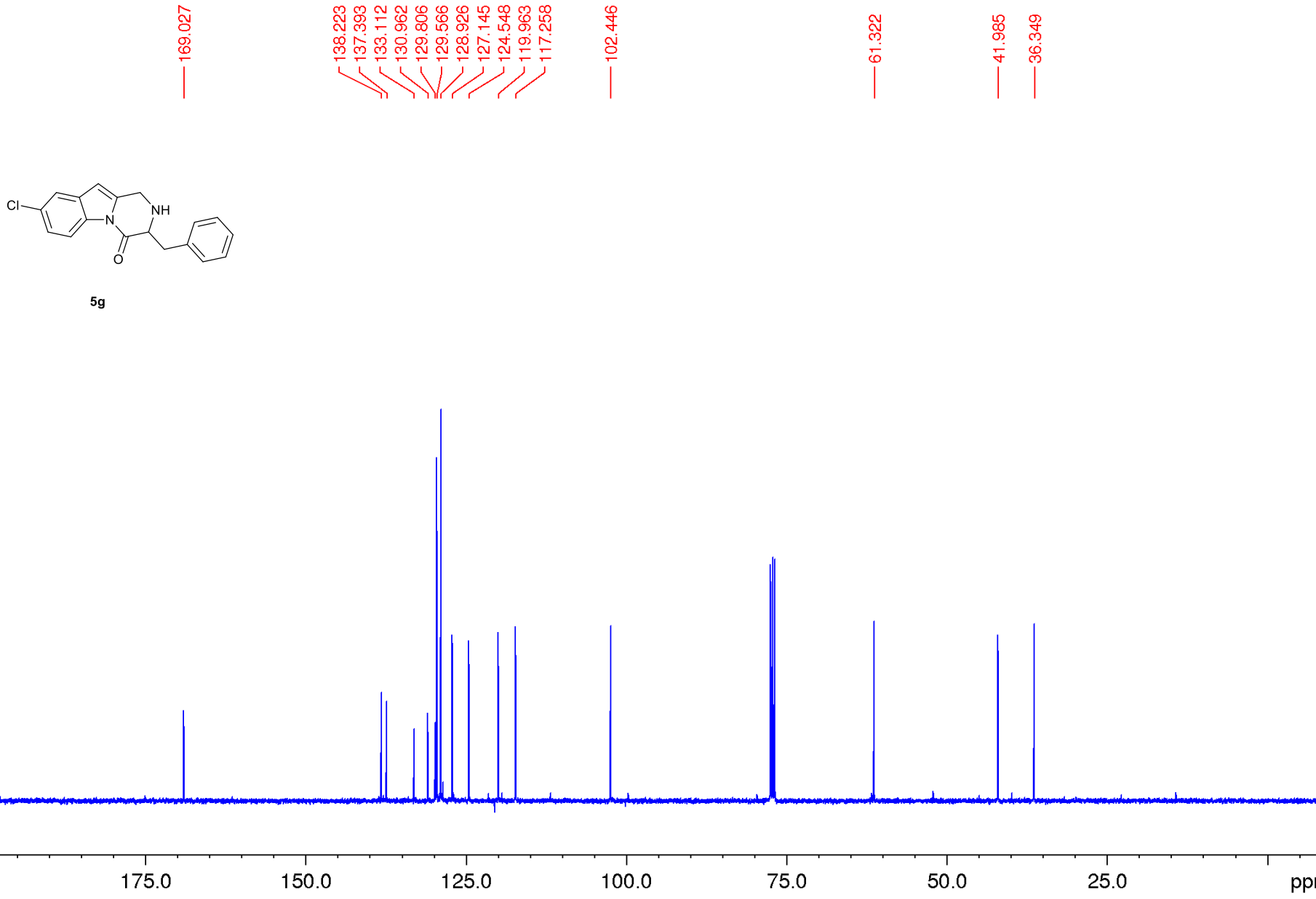
8f

^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)

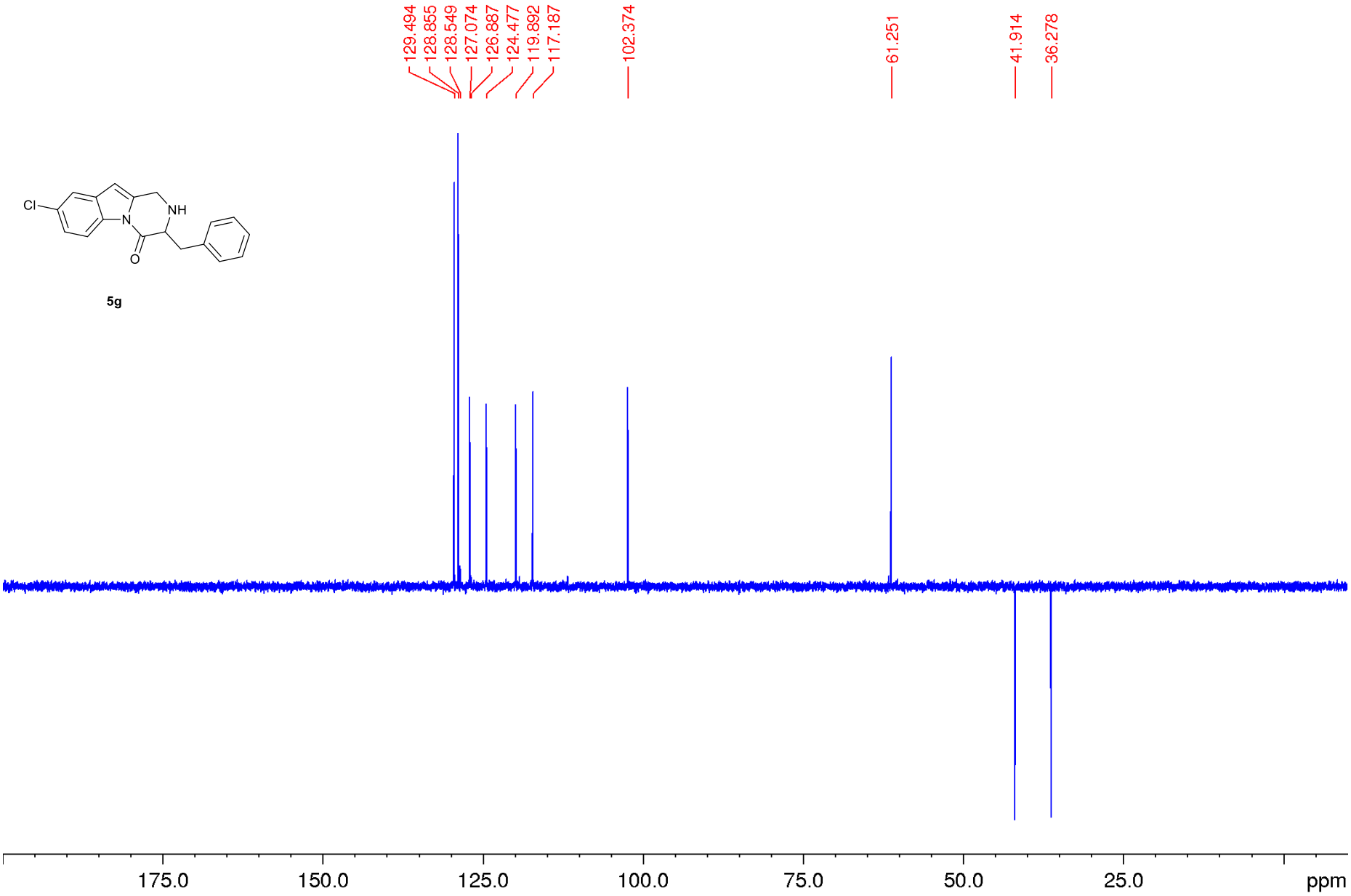


5g

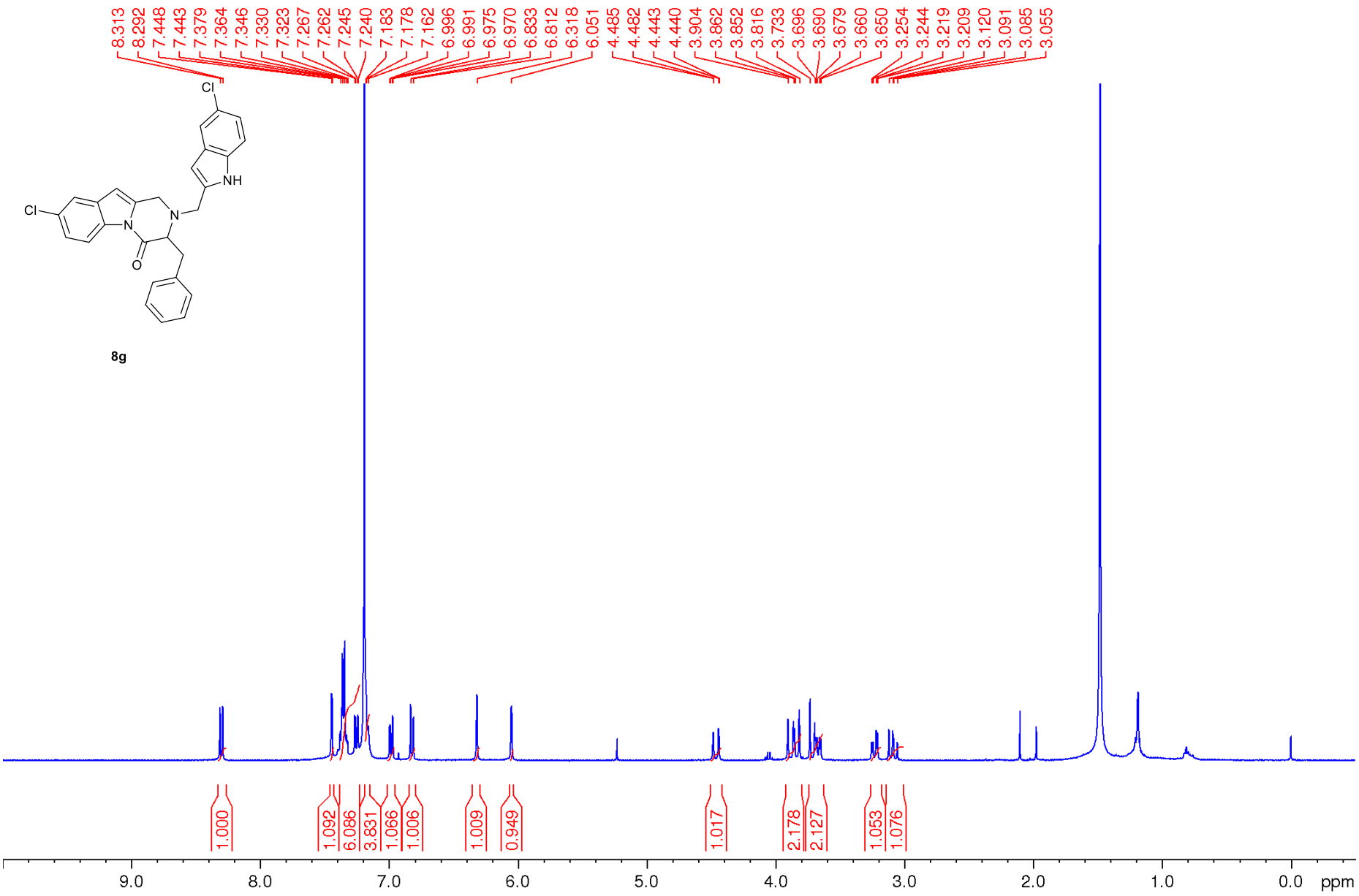
^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



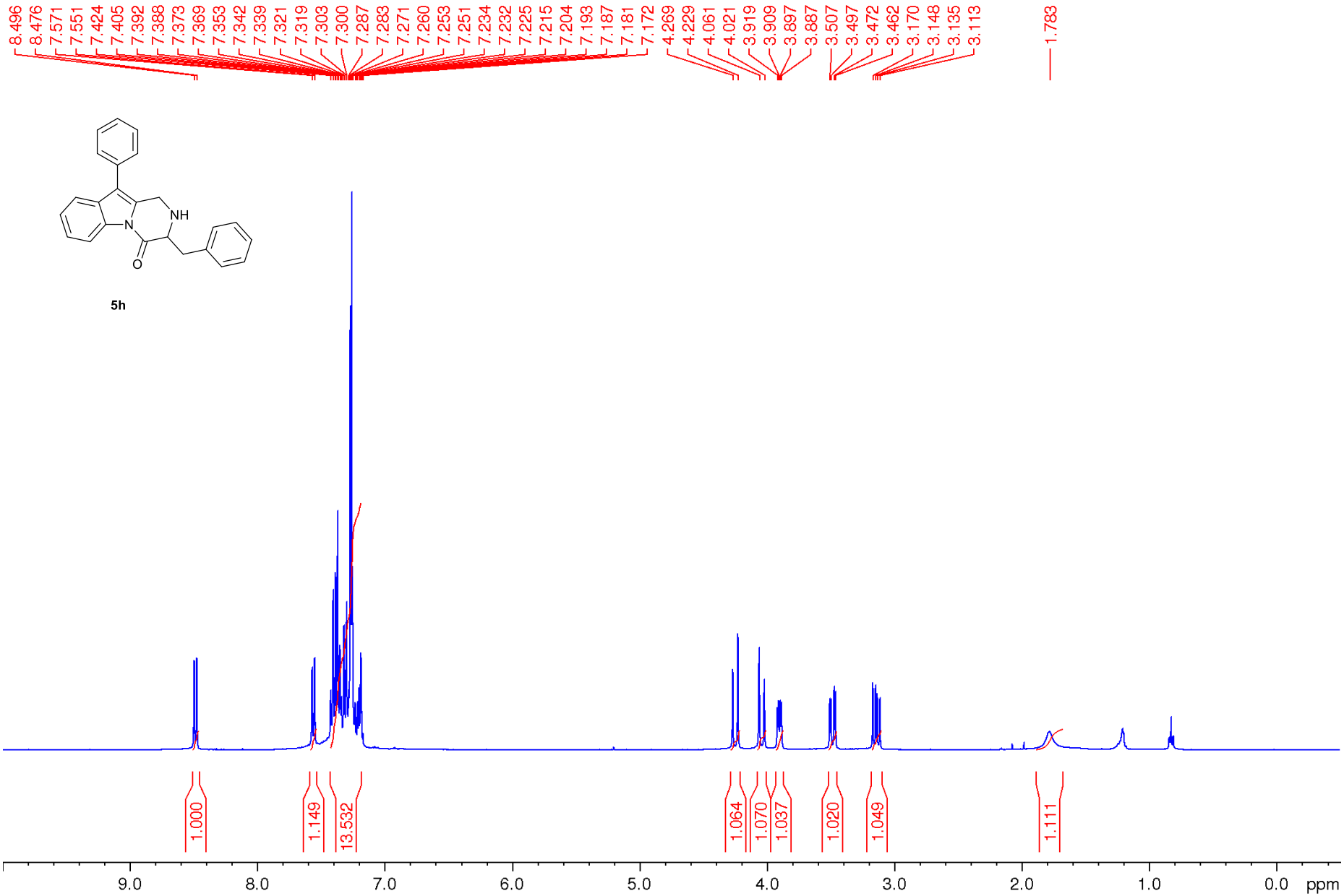
DEPT 135 NMR-spectrum ($CDCl_3$)



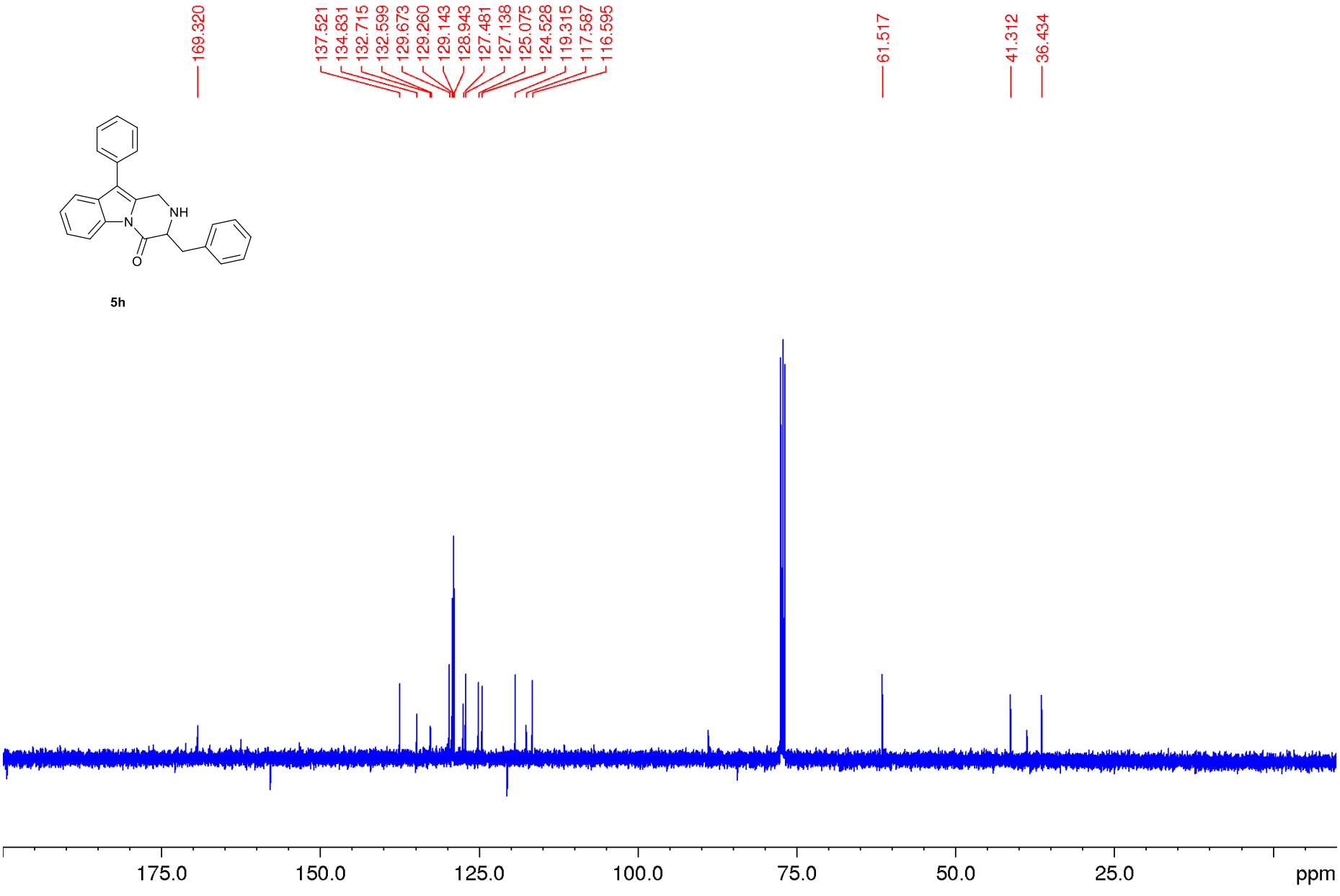
^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



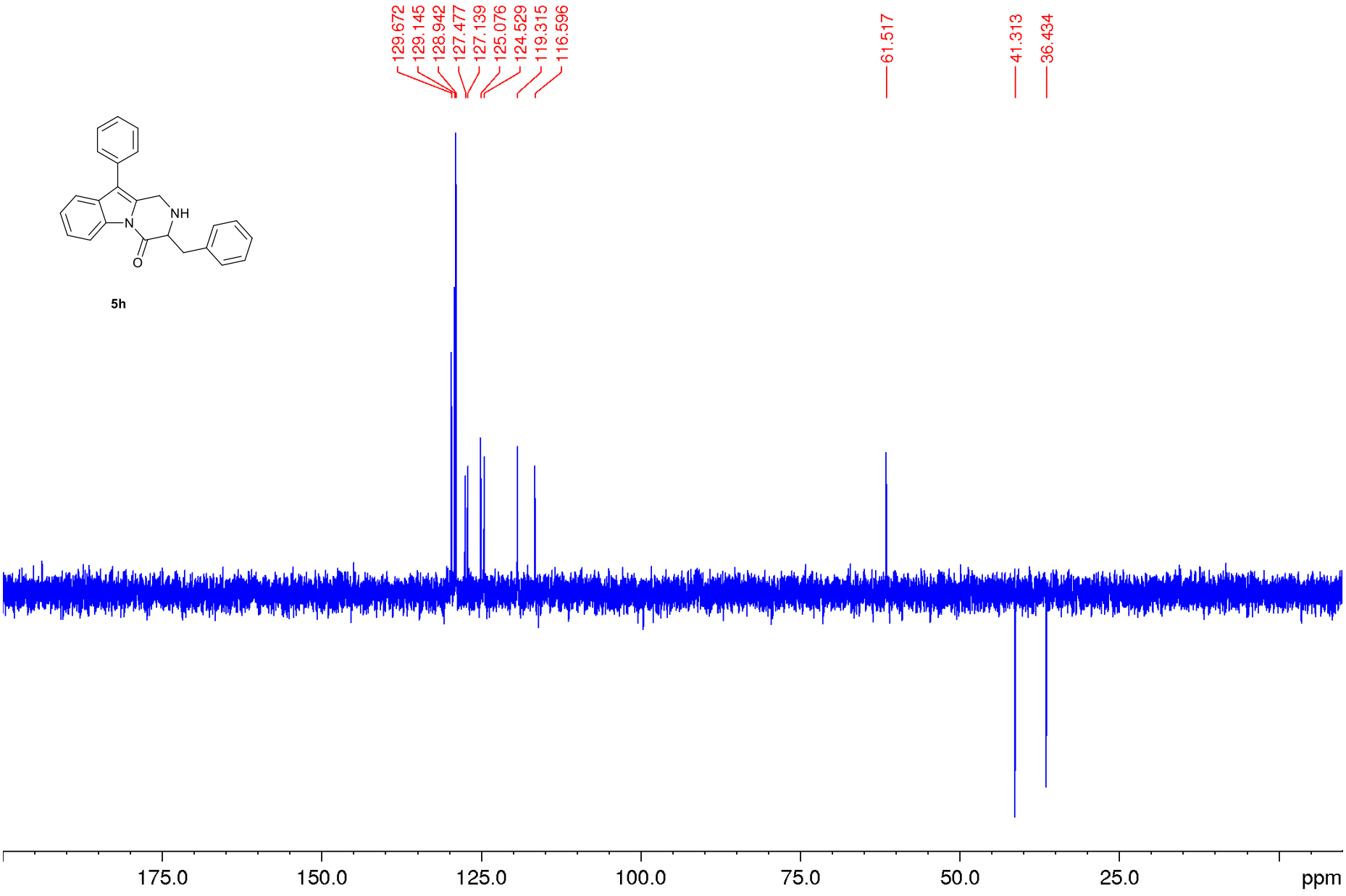
^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



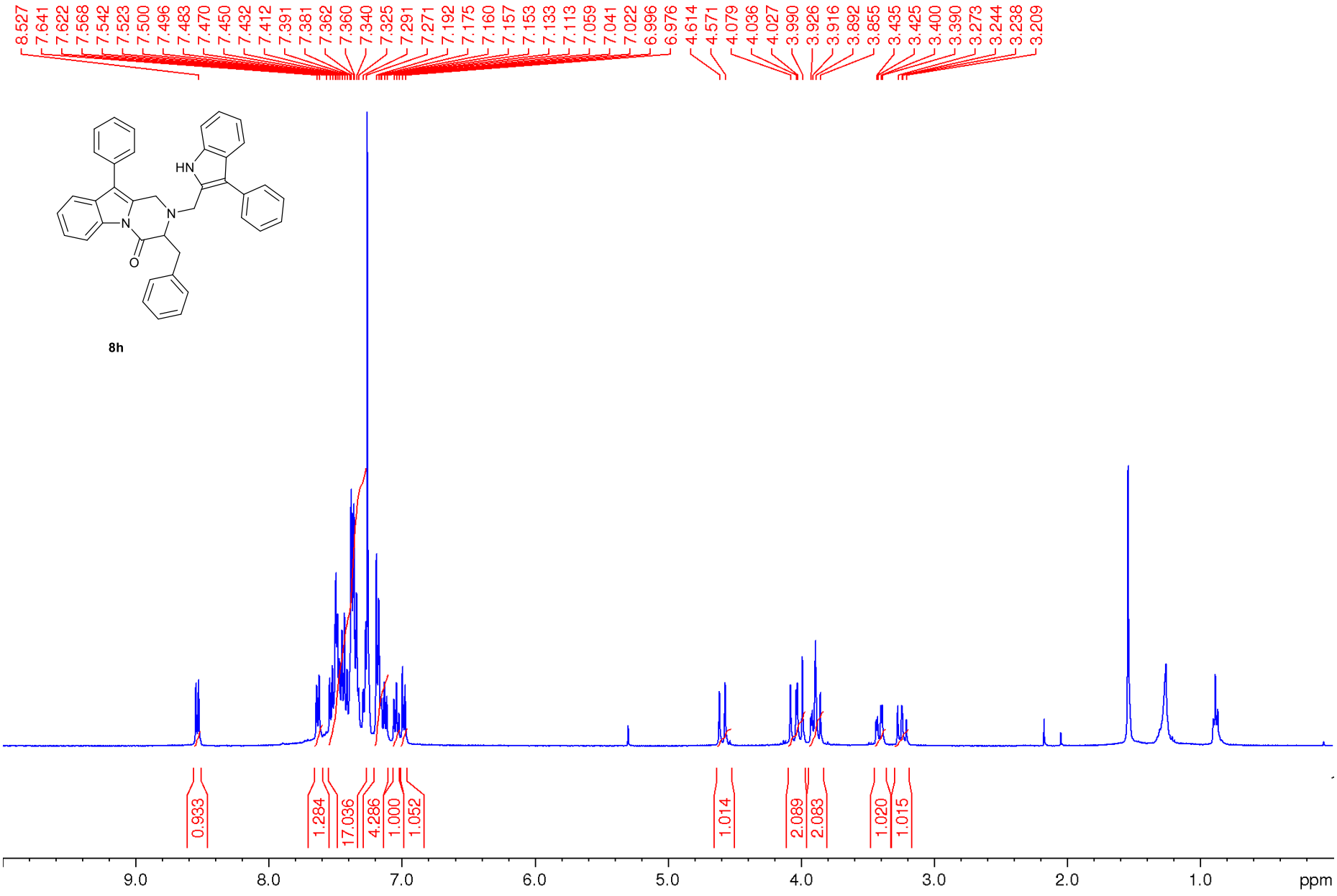
^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



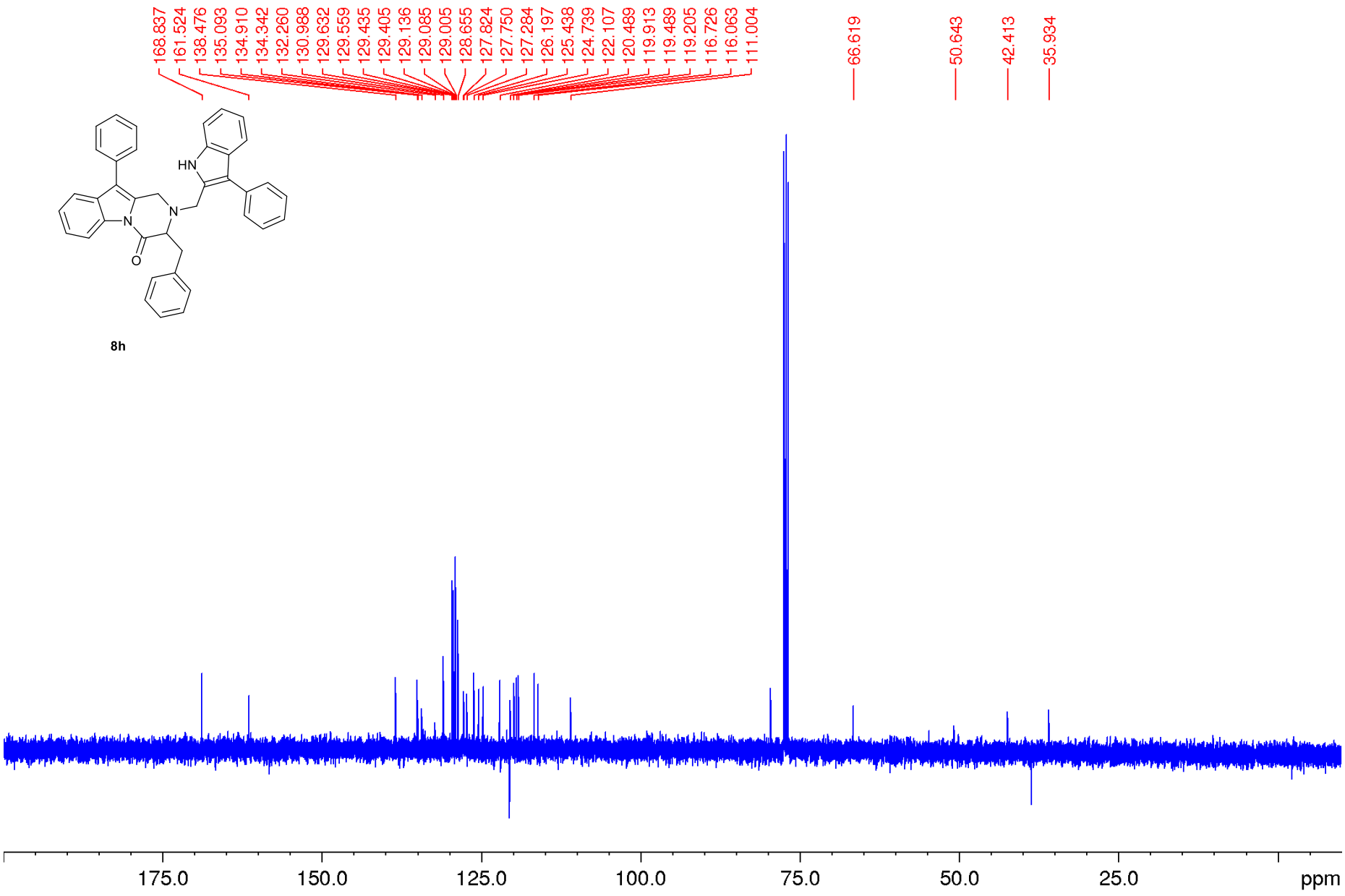
DEPT 135 NMR-spectrum ($CDCl_3$)



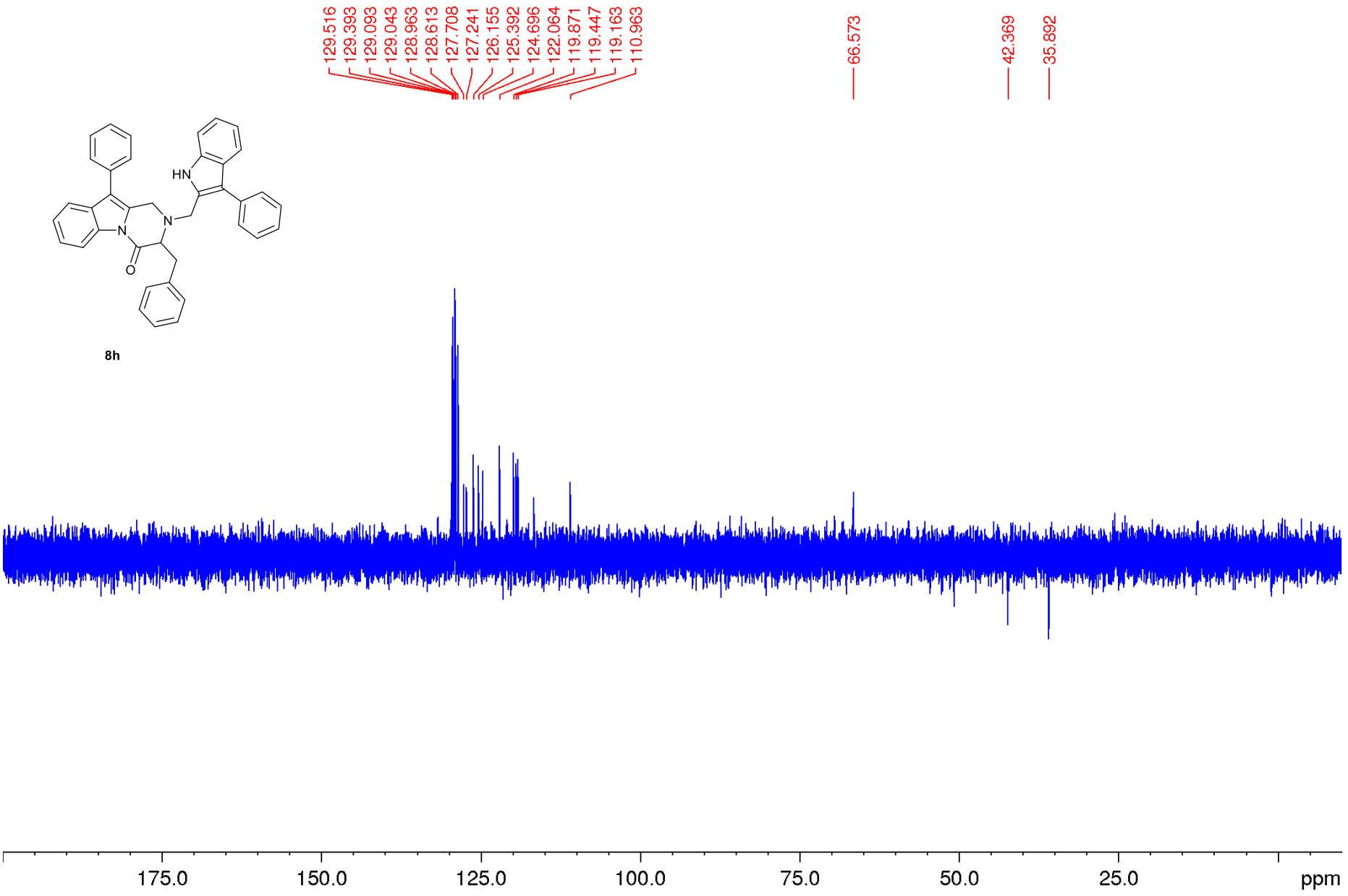
^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



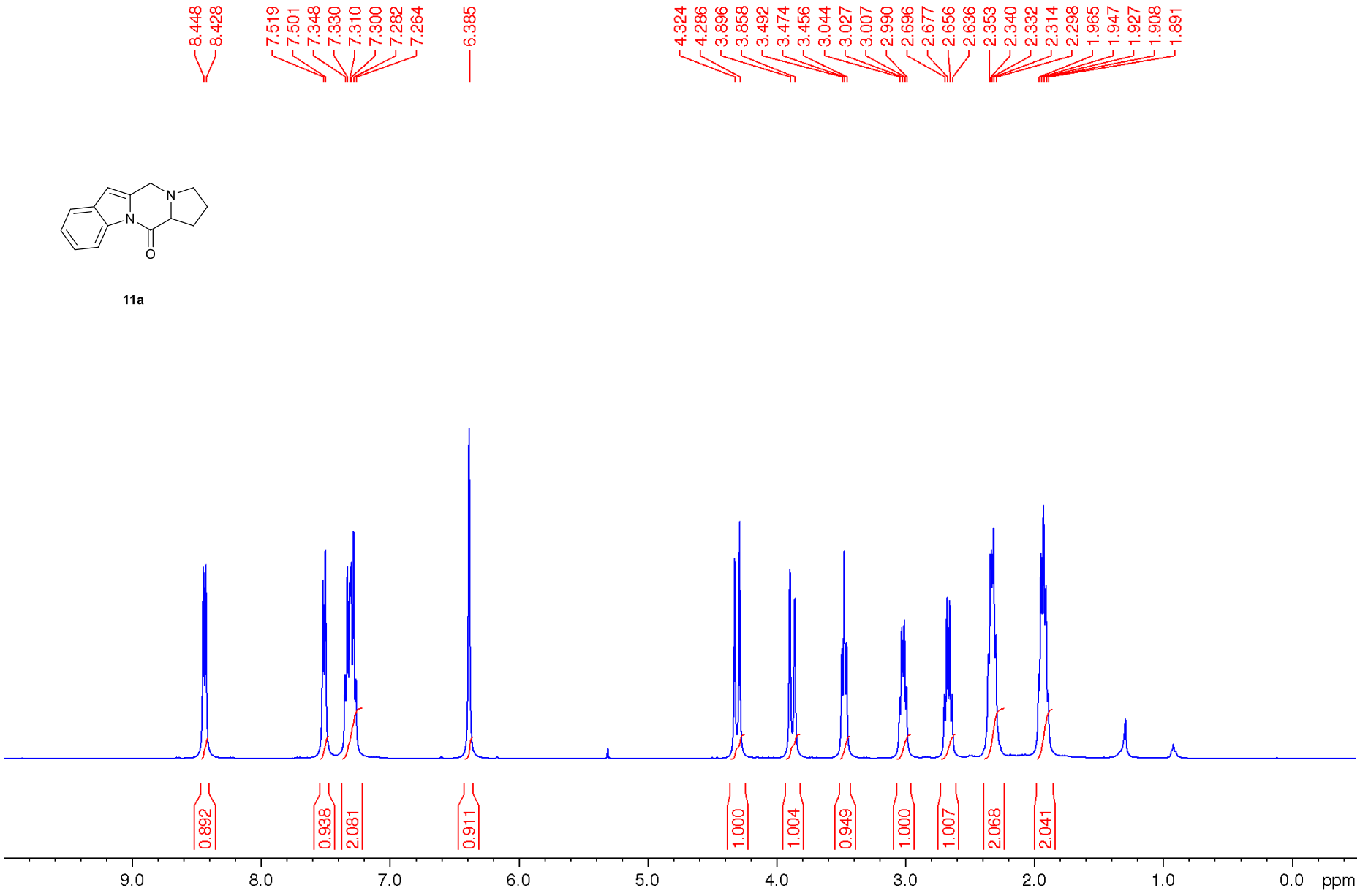
^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



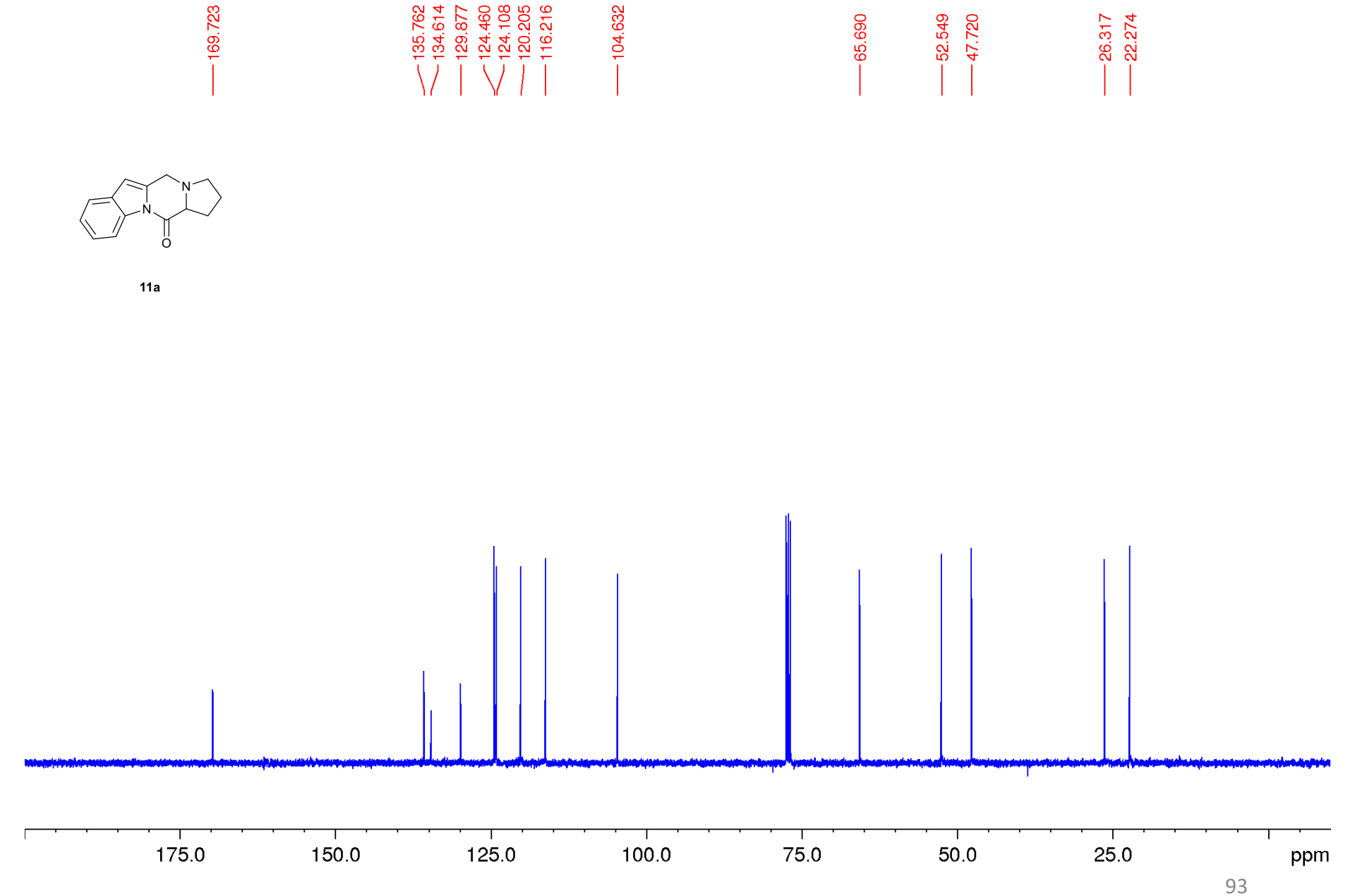
DEPT 135 NMR-spectrum ($CDCl_3$)



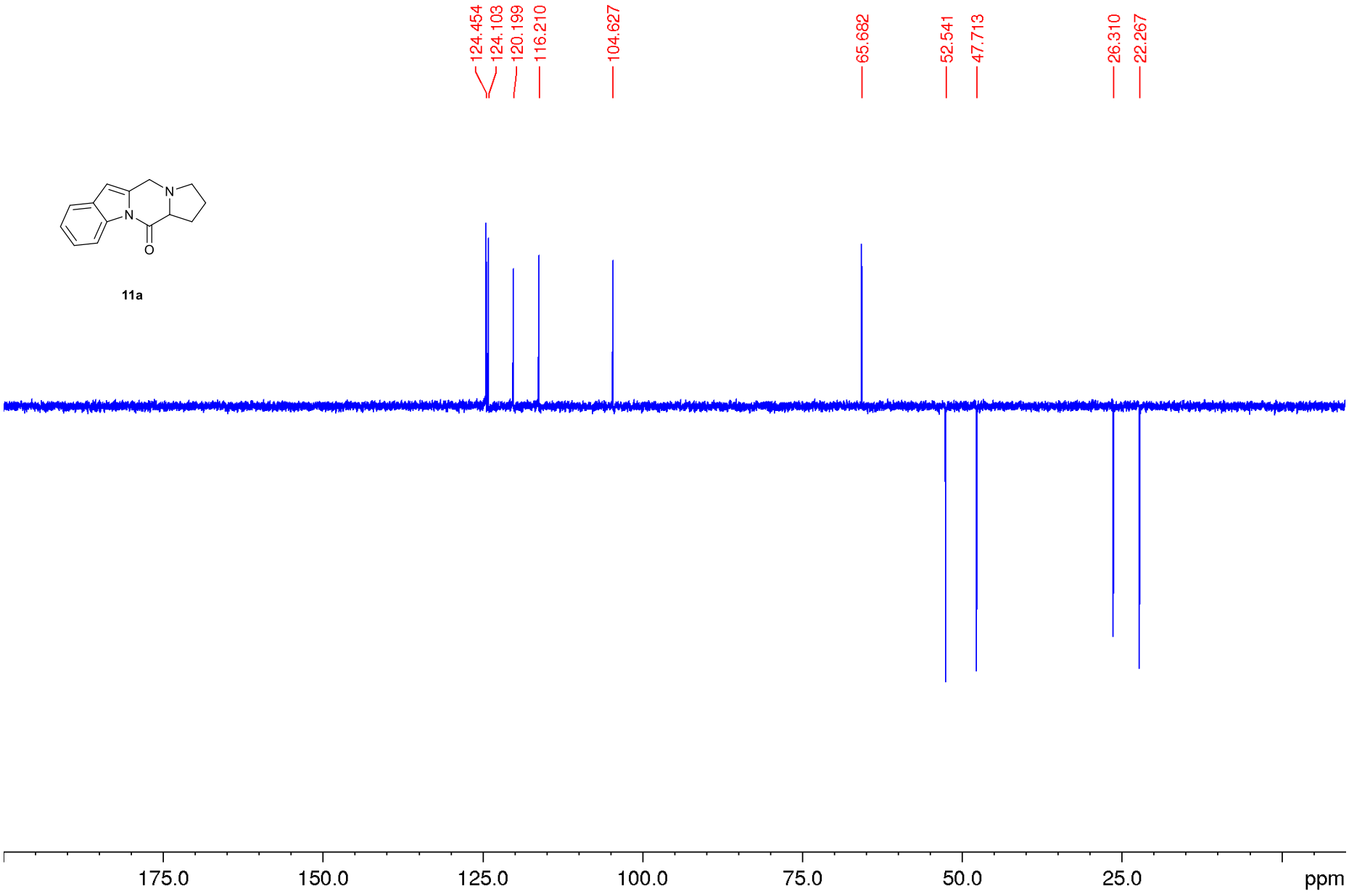
^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



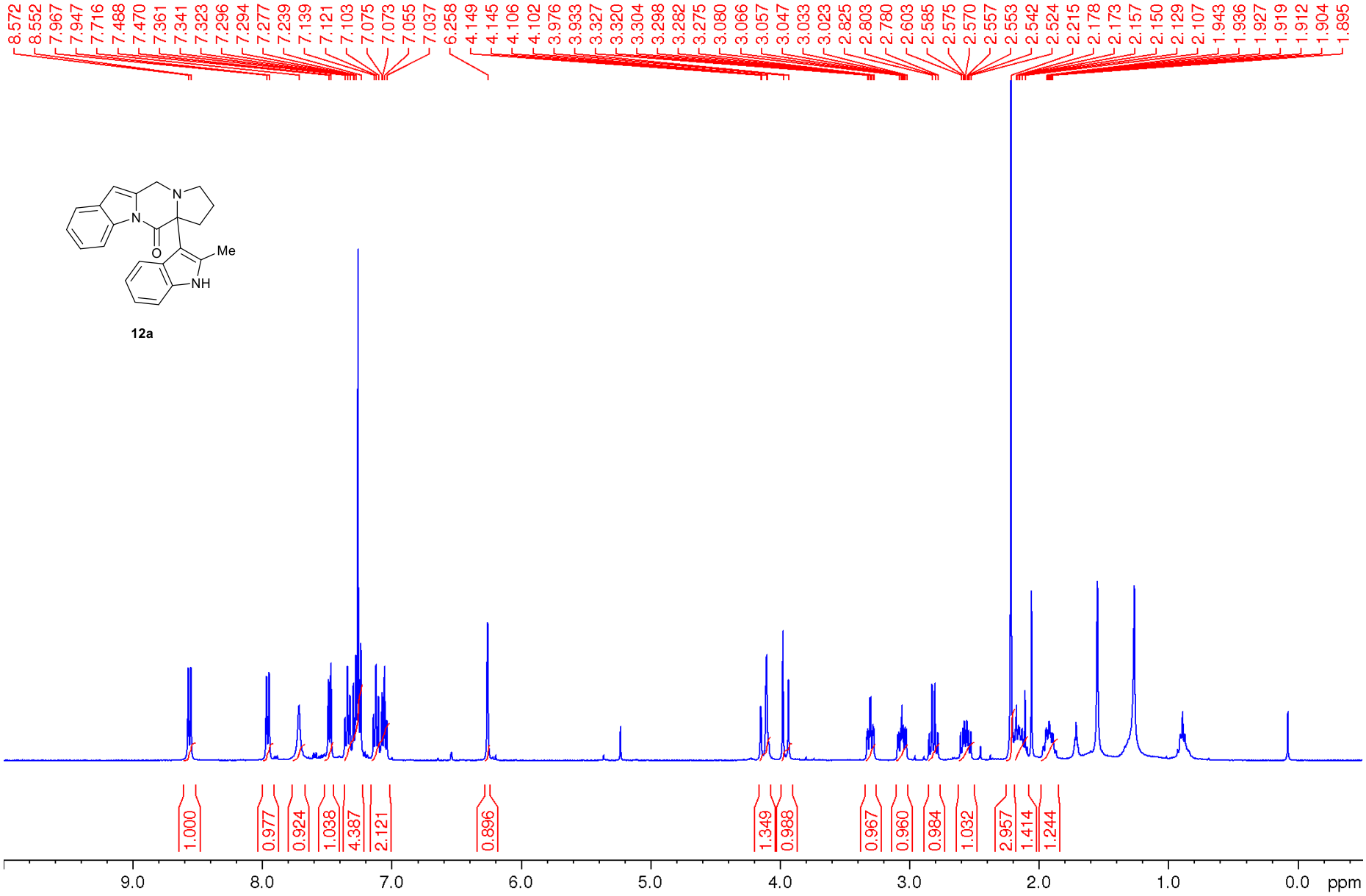
^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



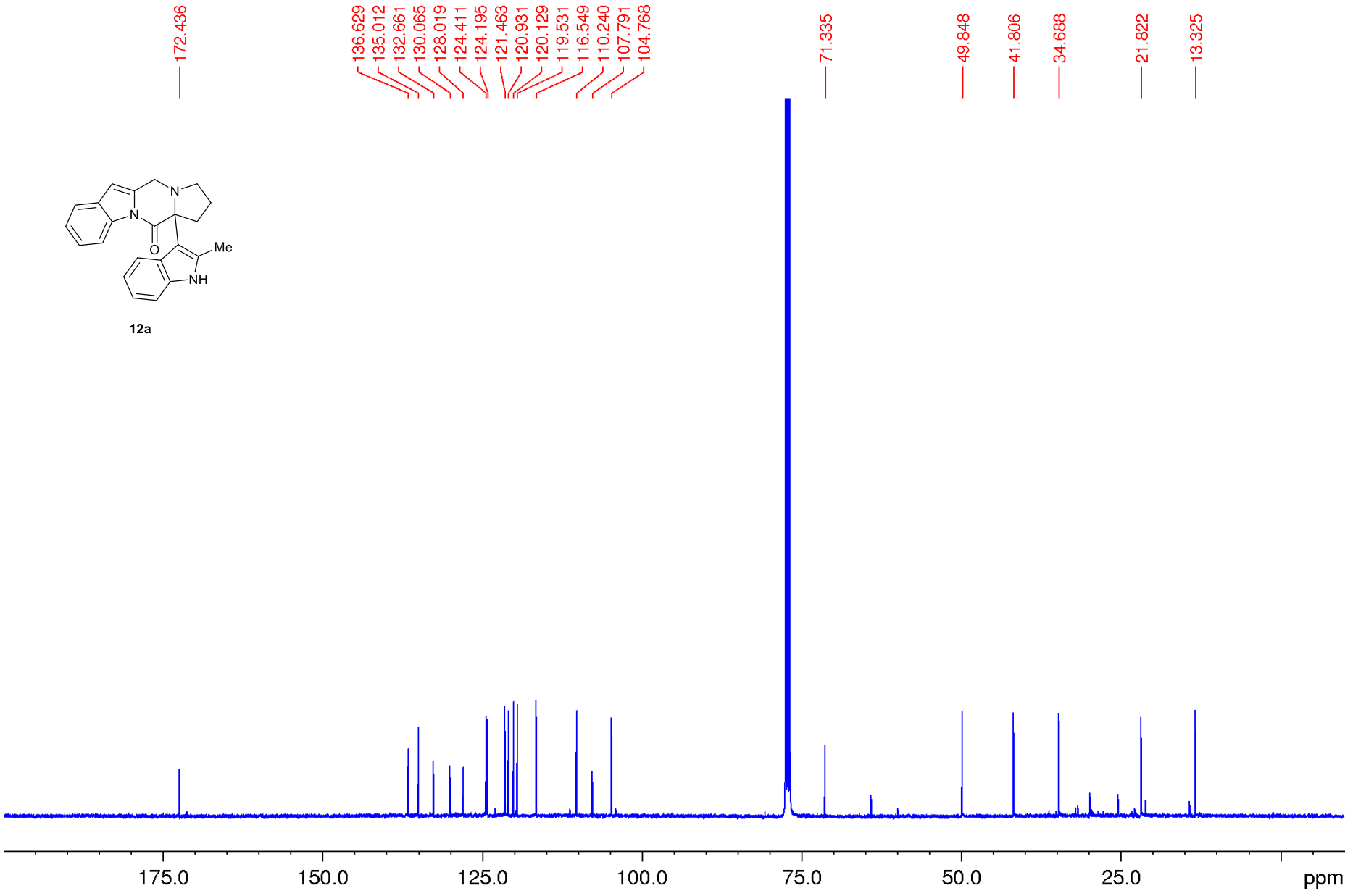
DEPT 135 NMR-spectrum ($CDCl_3$)



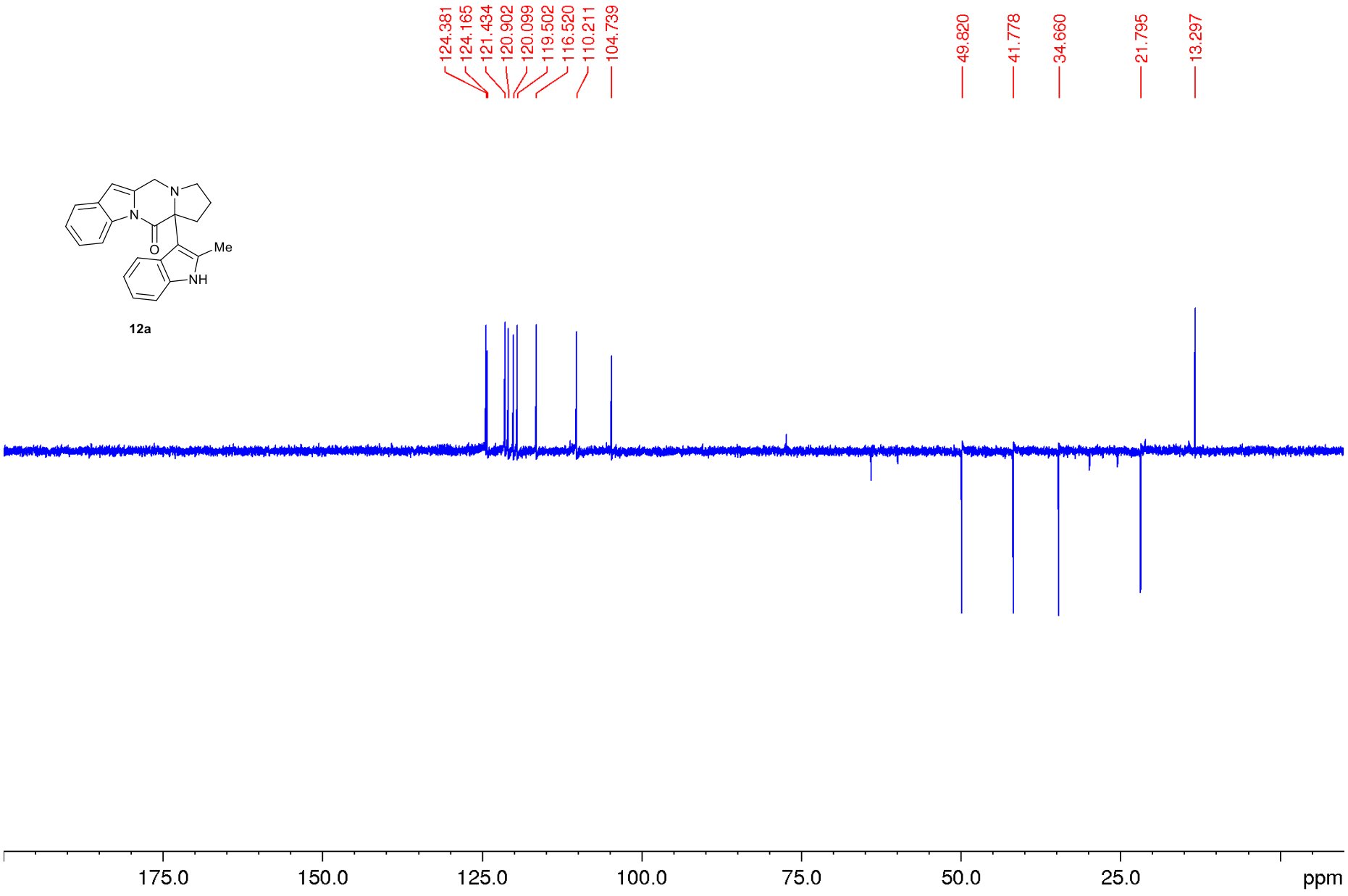
^{1}H NMR-spectrum (400.13 MHz) (DMSO-d_6)



^{13}C NMR-spectrum (100.6 MHz) (DMSO-d_6)

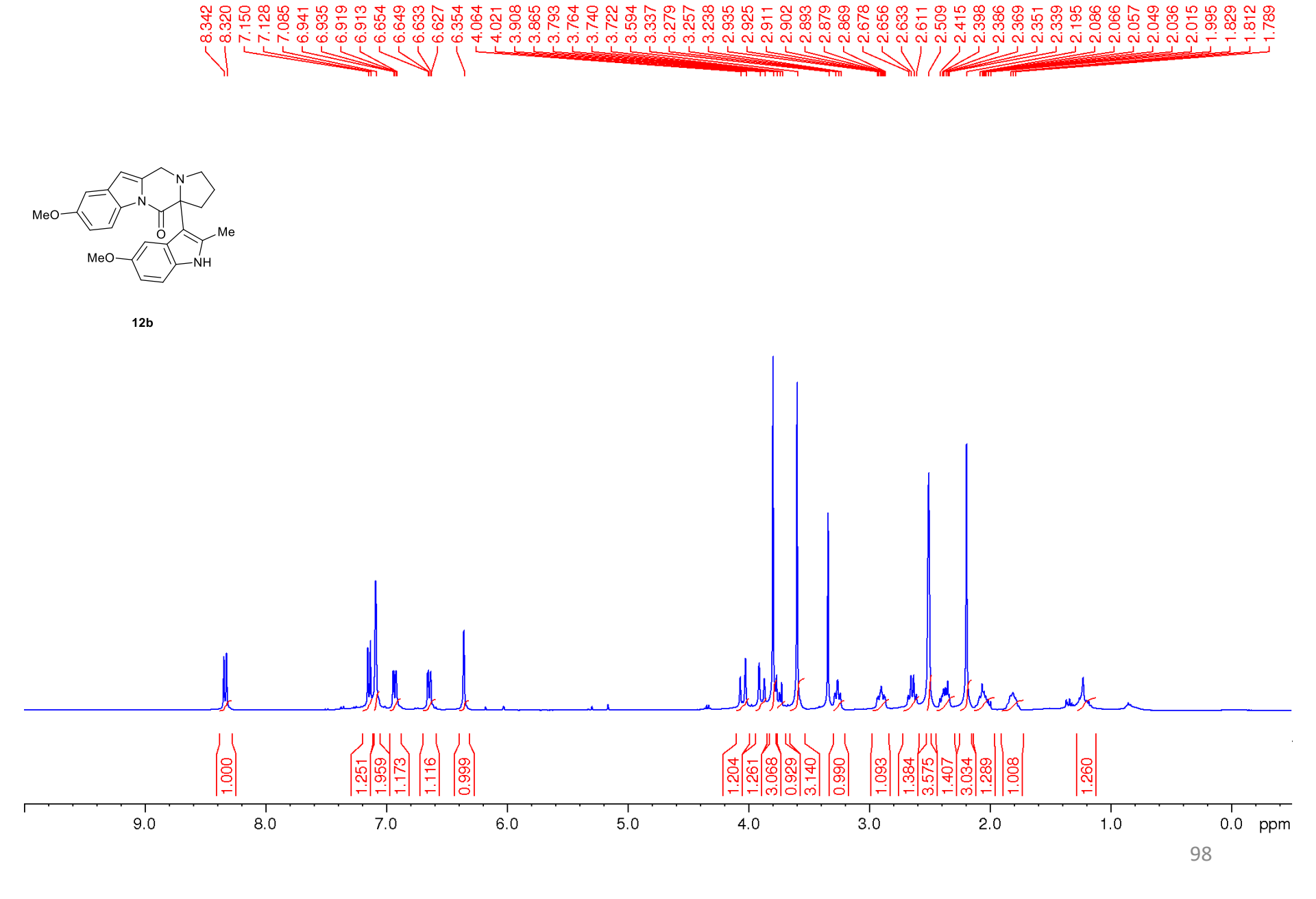


DEPT 135 NMR-spectrum (DMSO-d_6)

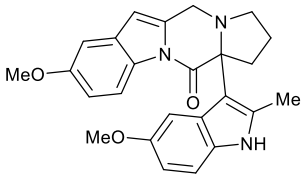


12a

^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)

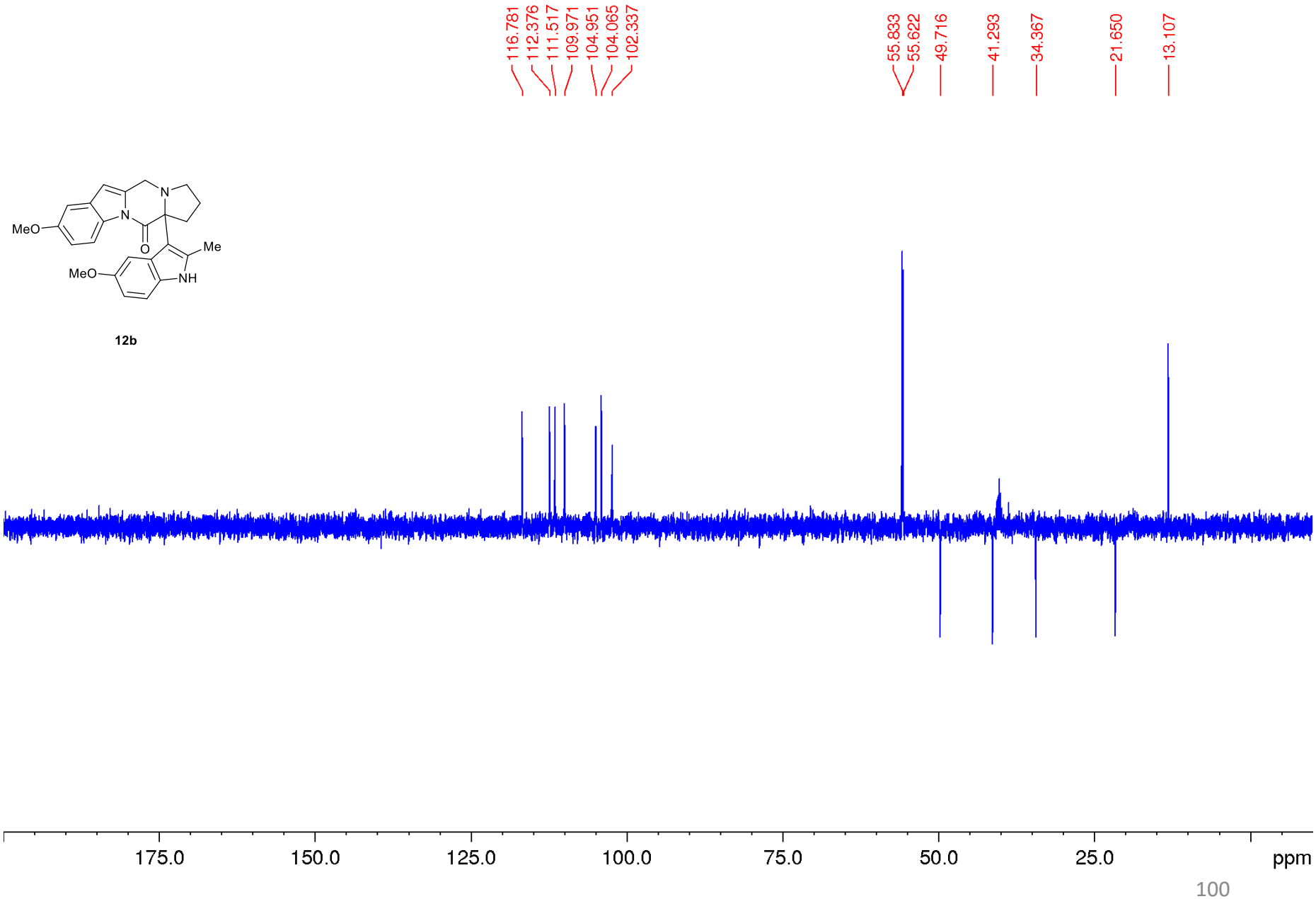


12b

171.453
156.455
152.647
136.920
134.130
130.859
129.953
128.578
127.339
116.274
111.868
111.008
109.462
105.152
104.443
103.556
70.257
55.323
55.113
49.208
33.857
21.141
12.597

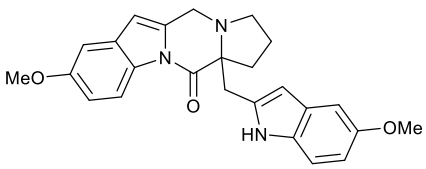
175.0 150.0 125.0 100.0 75.0 50.0 25.0 ppm

DEPT 135 NMR-spectrum ($CDCl_3$)



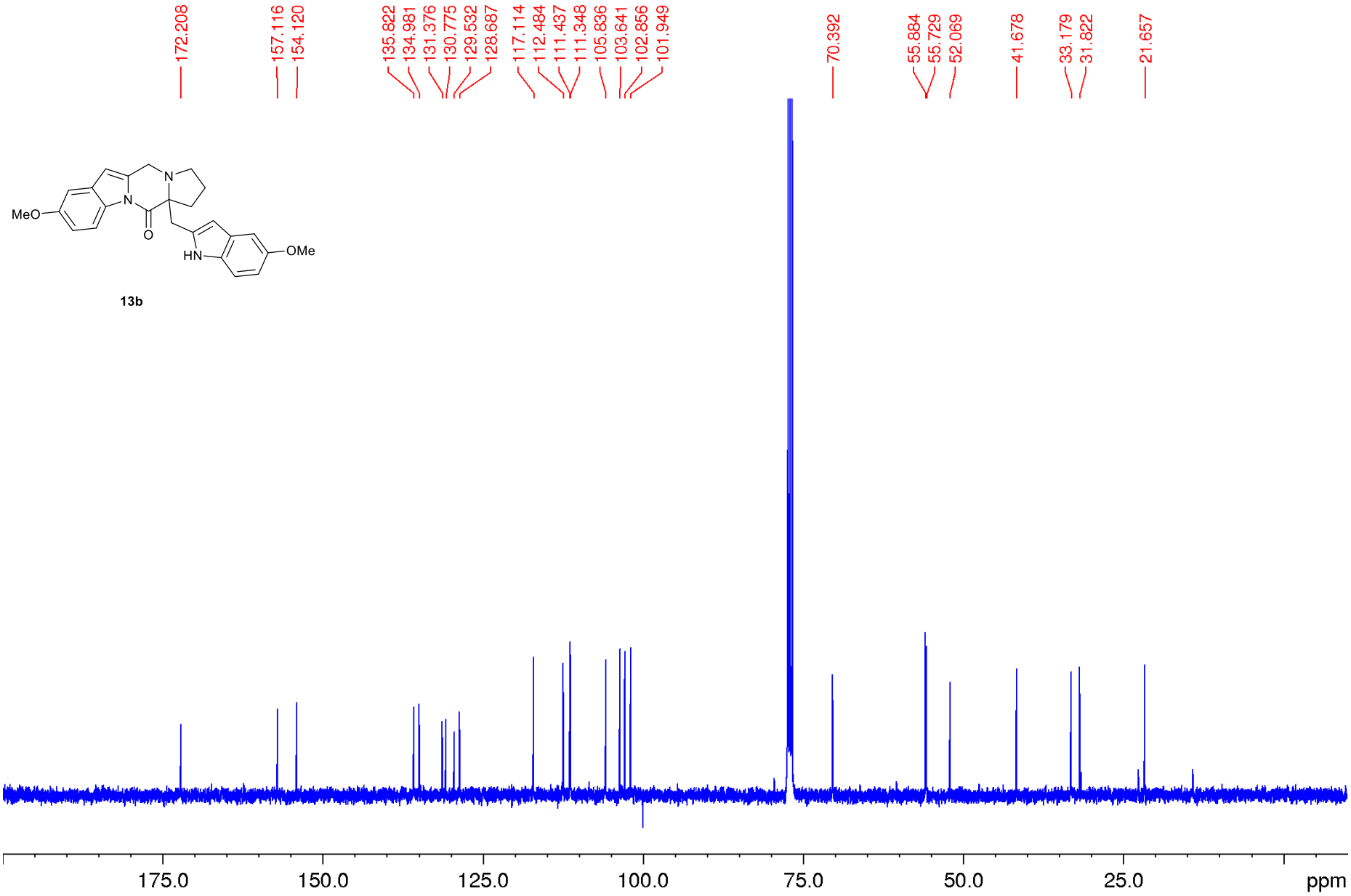
12b

^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)

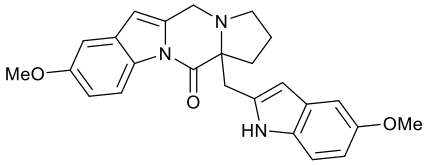


13b

^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)

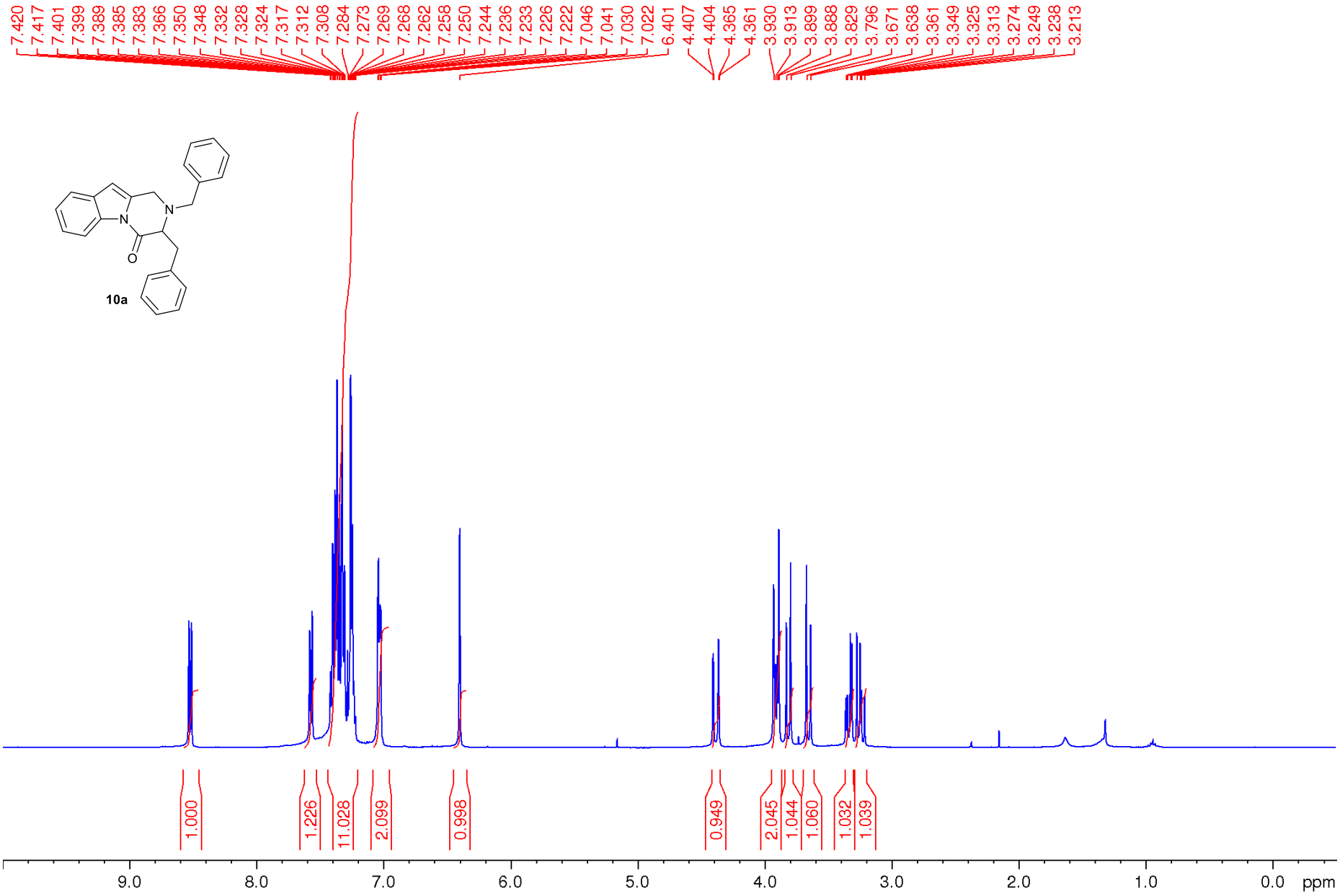


DEPT 135 NMR-spectrum ($CDCl_3$)

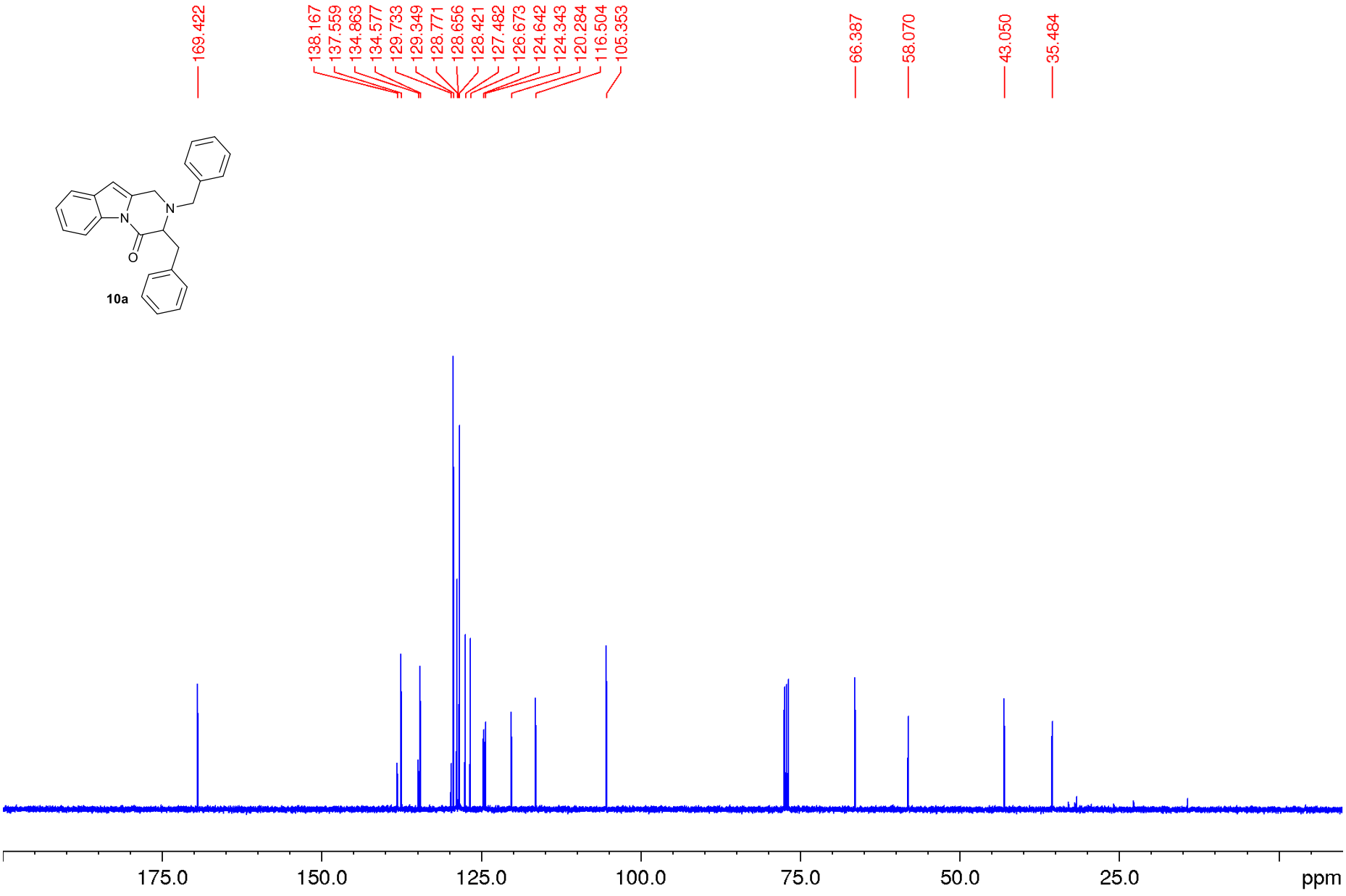


13b

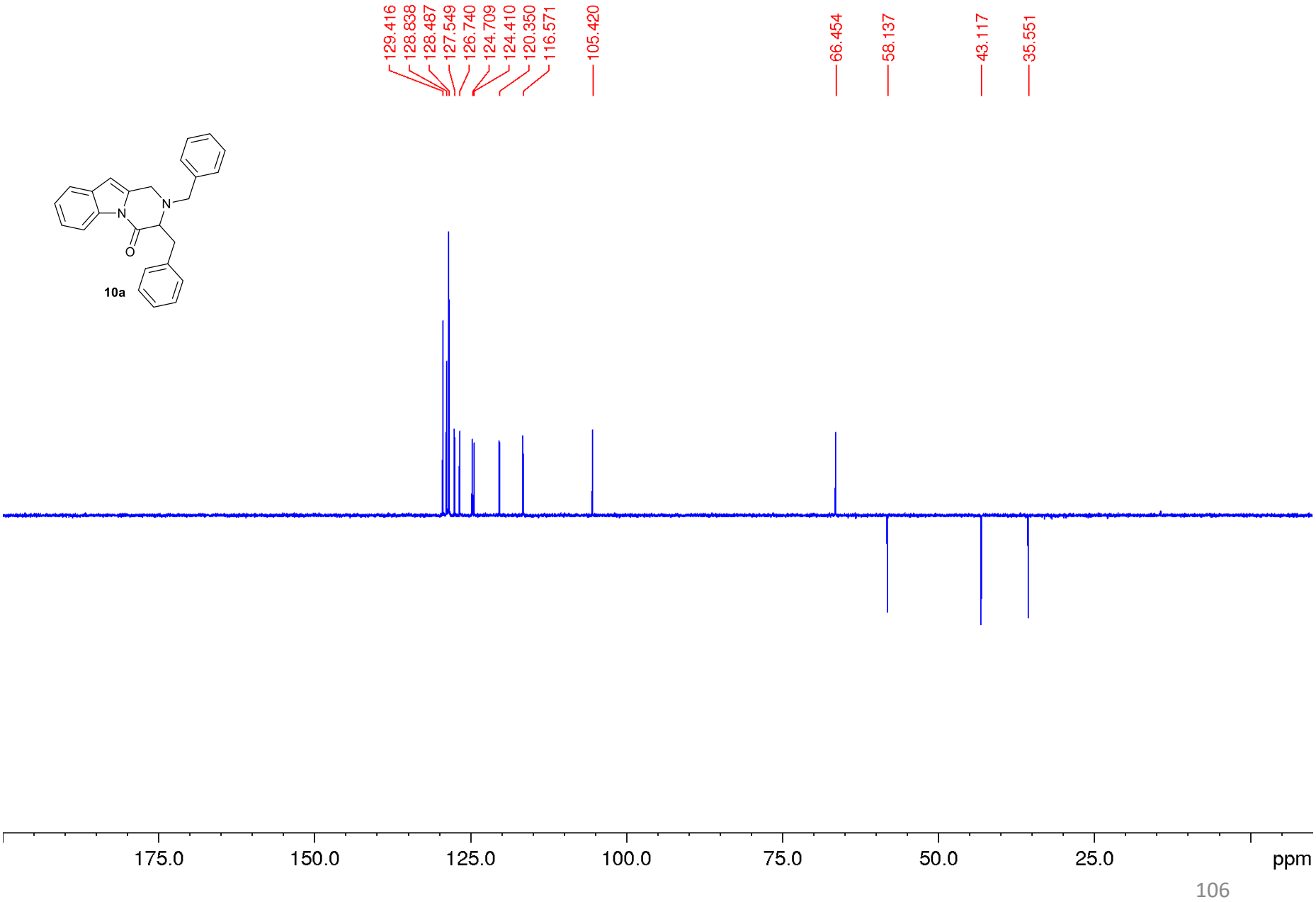
^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



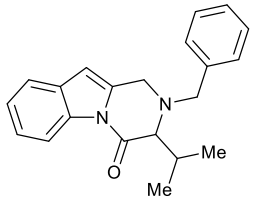
^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



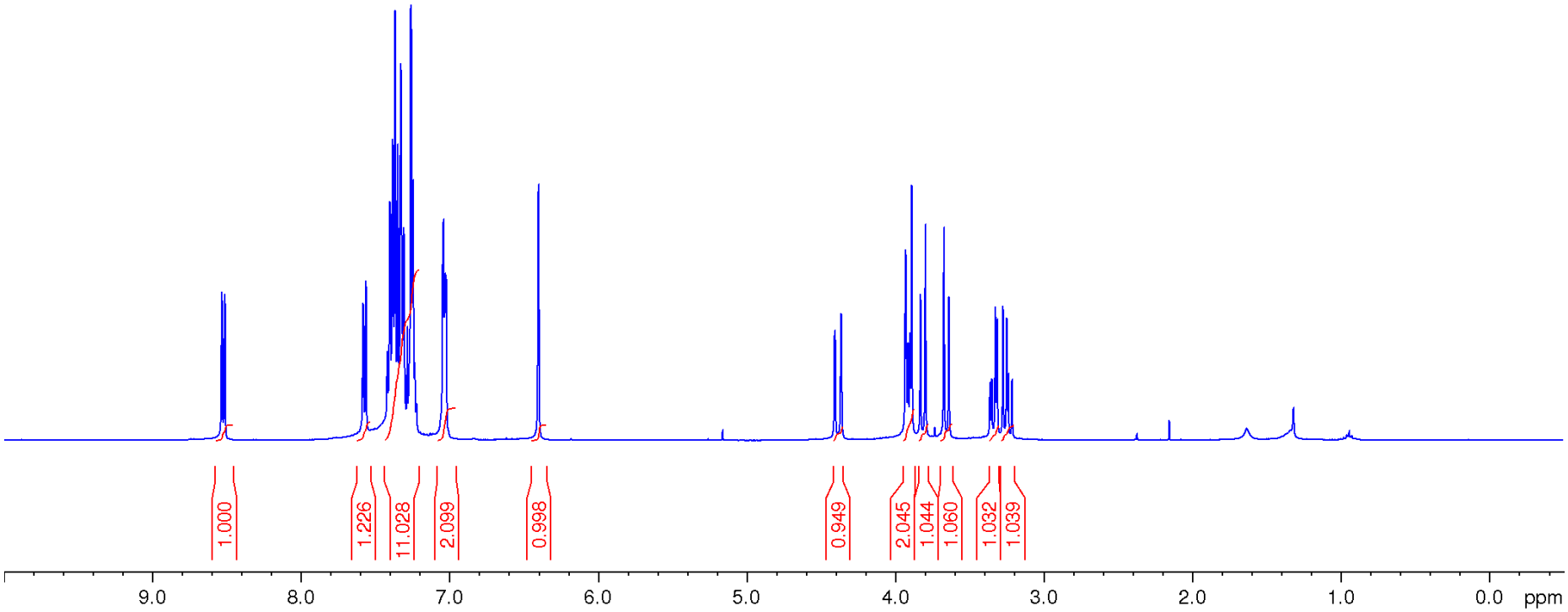
DEPT 135 NMR-spectrum ($CDCl_3$)



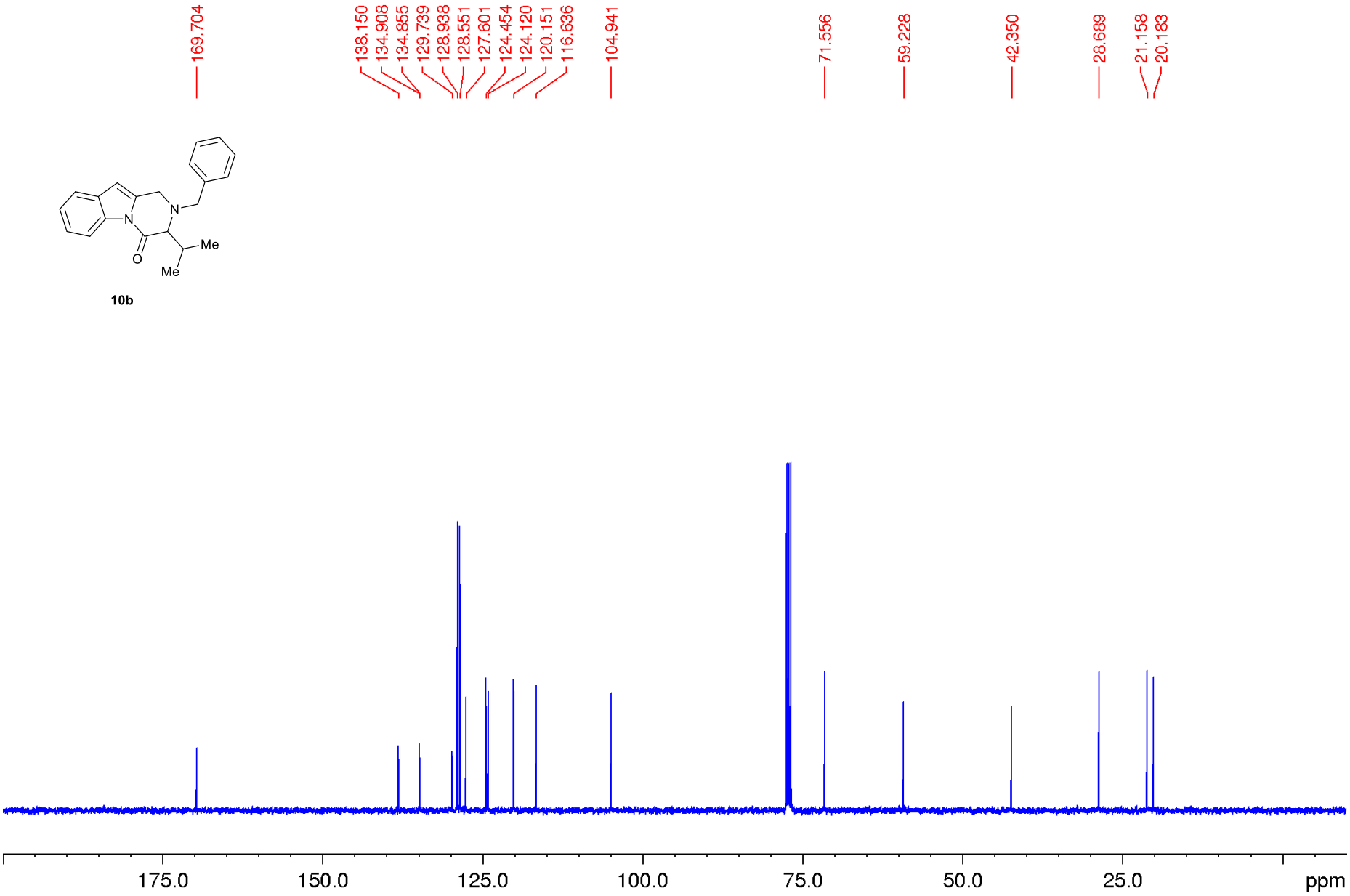
^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



10b

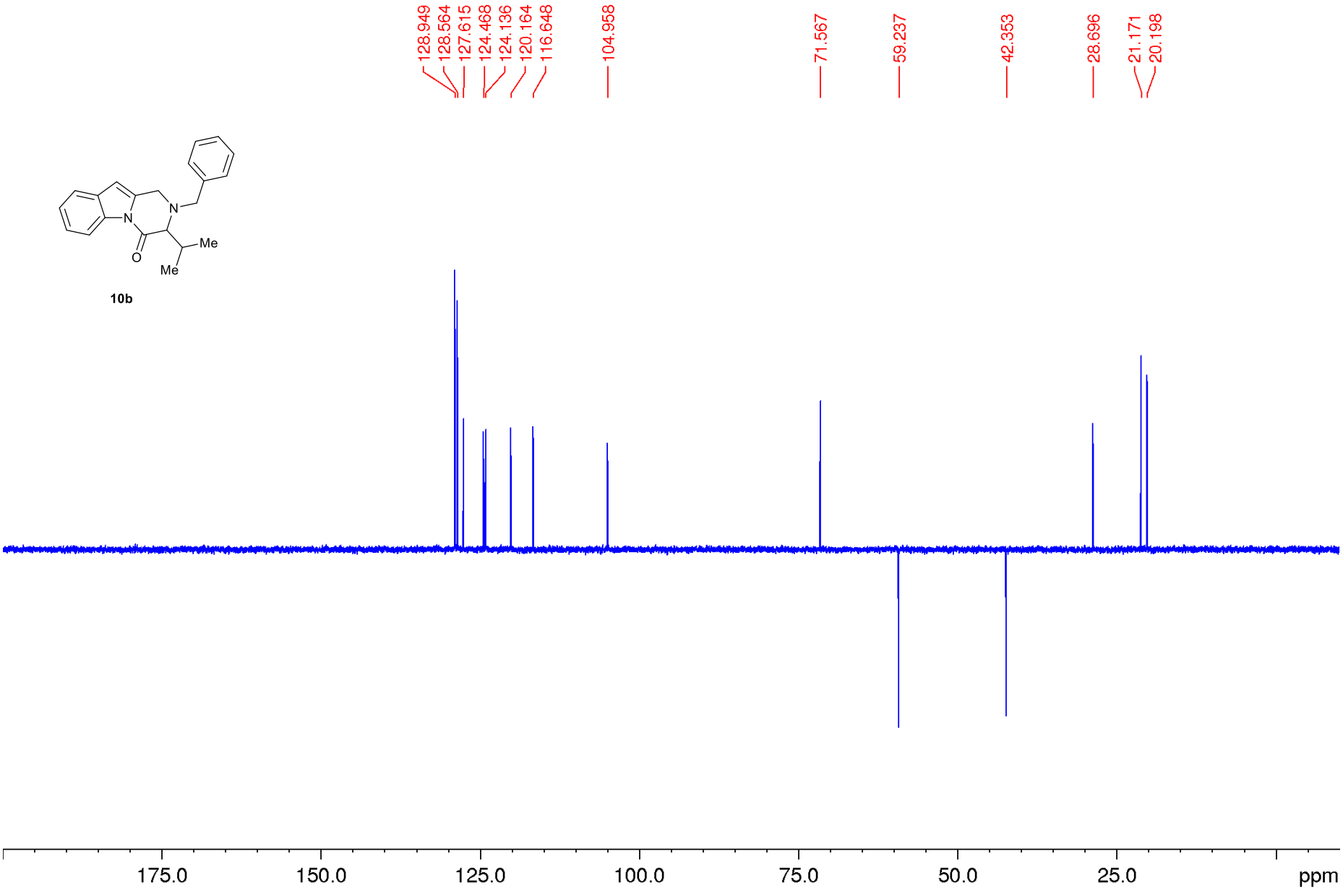


^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)

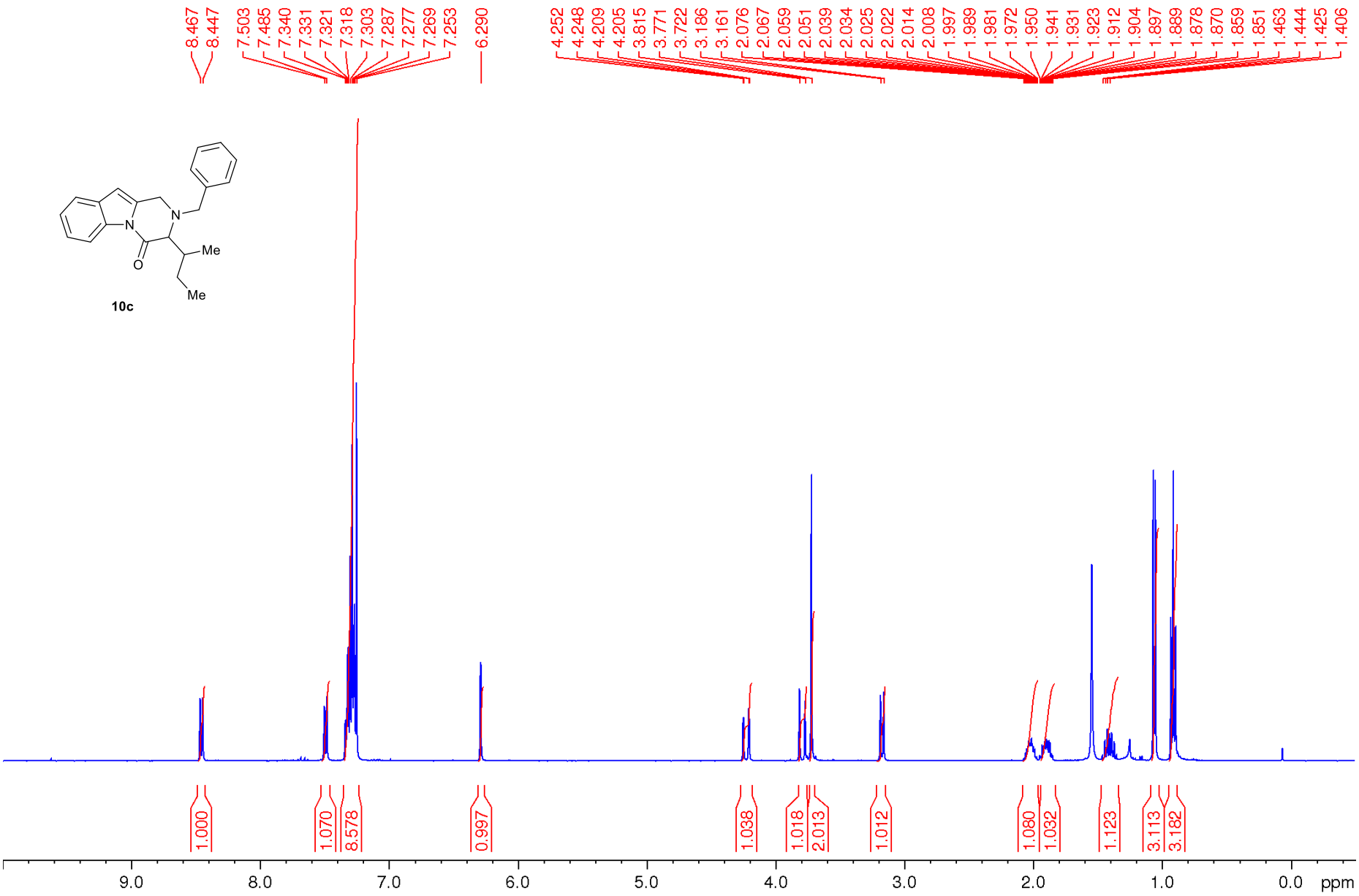


10b

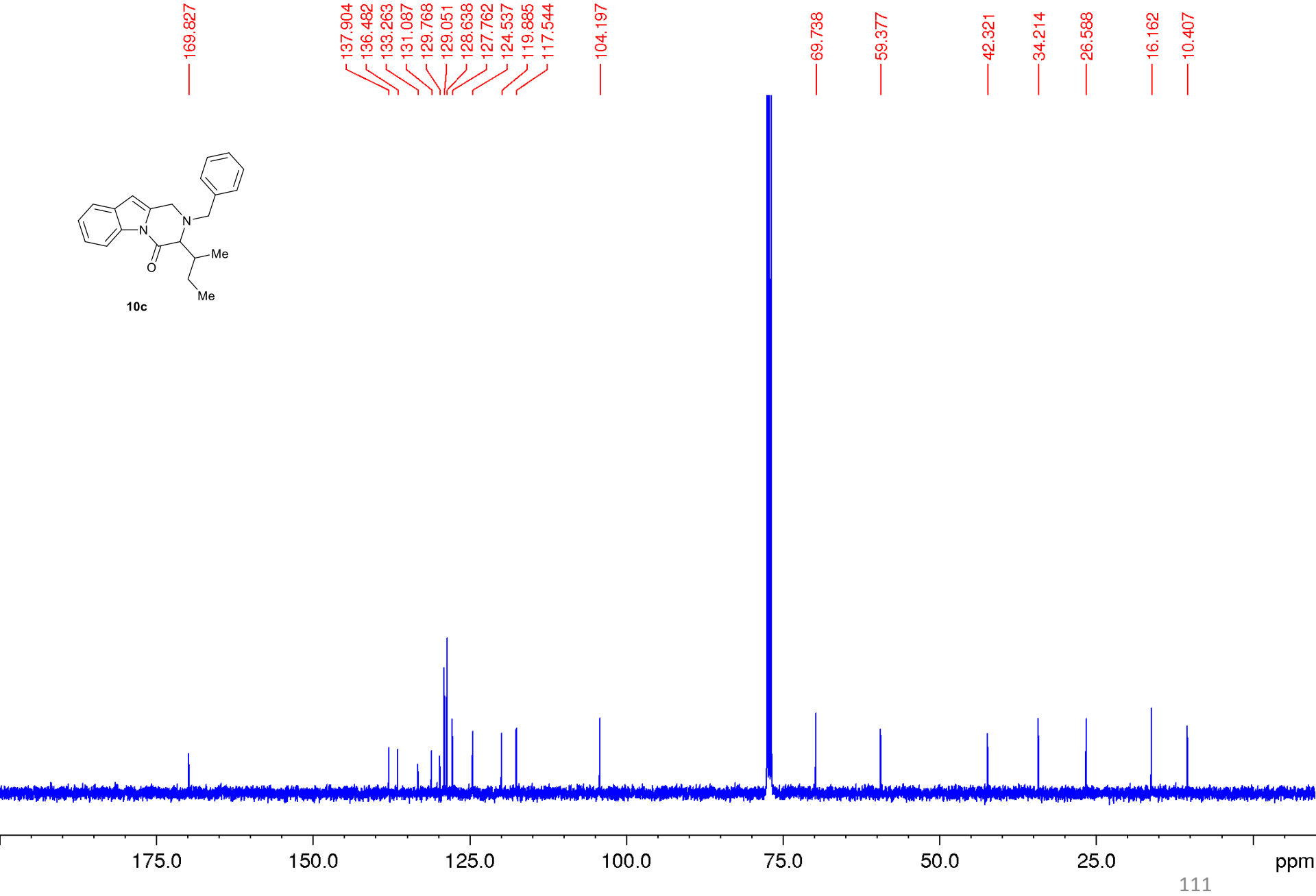
DEPT 135 NMR-spectrum ($CDCl_3$)



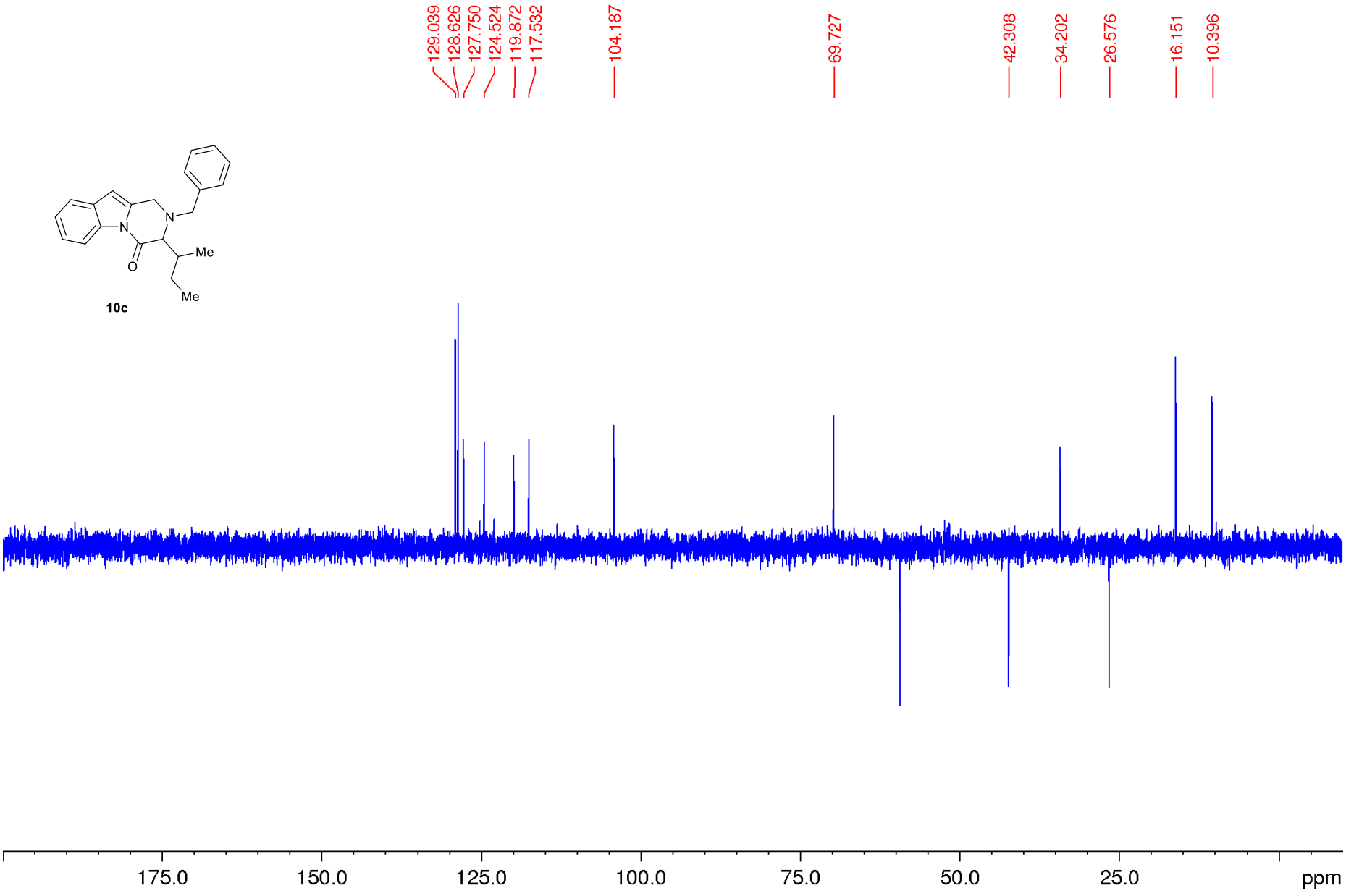
^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



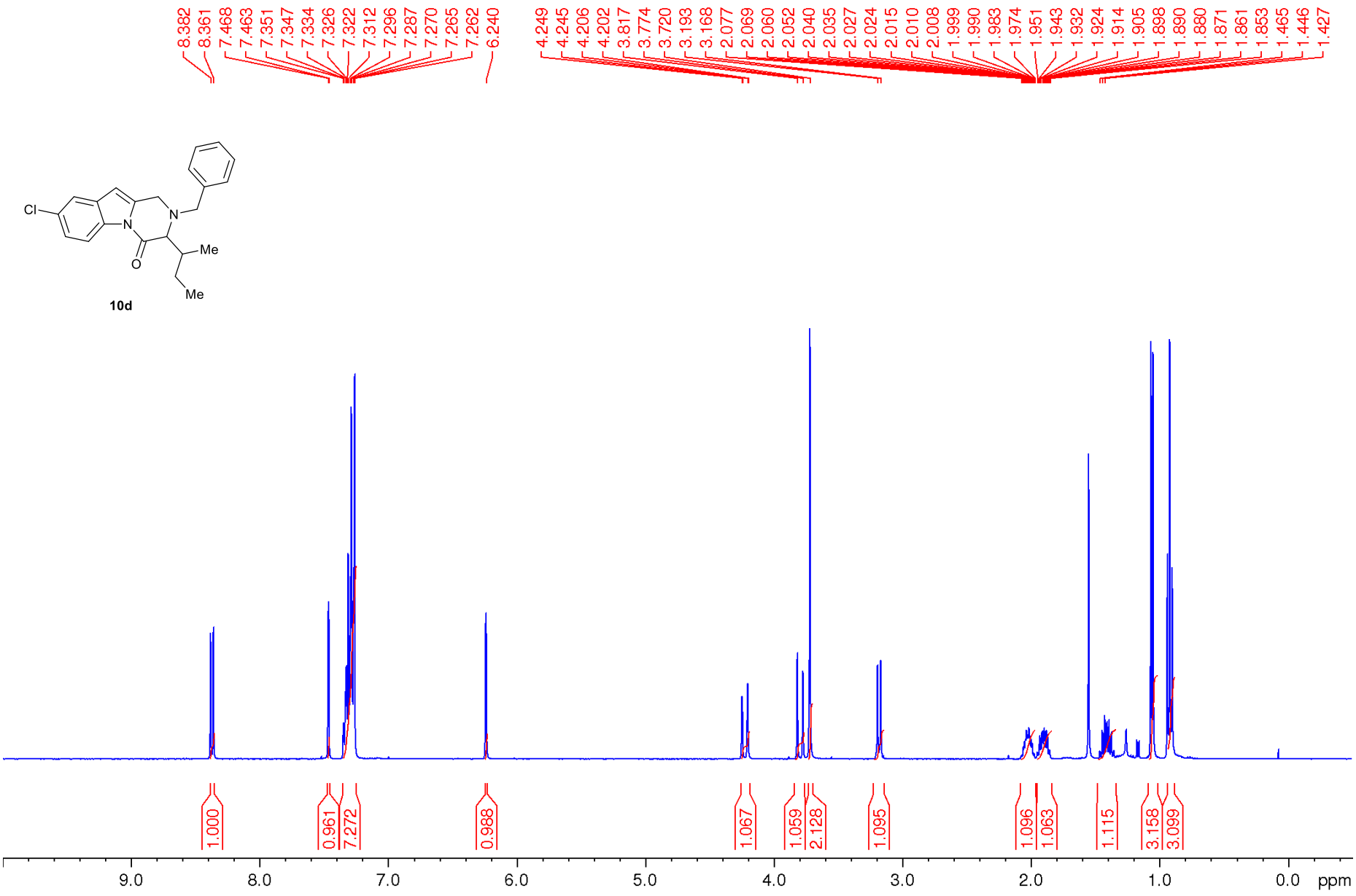
^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



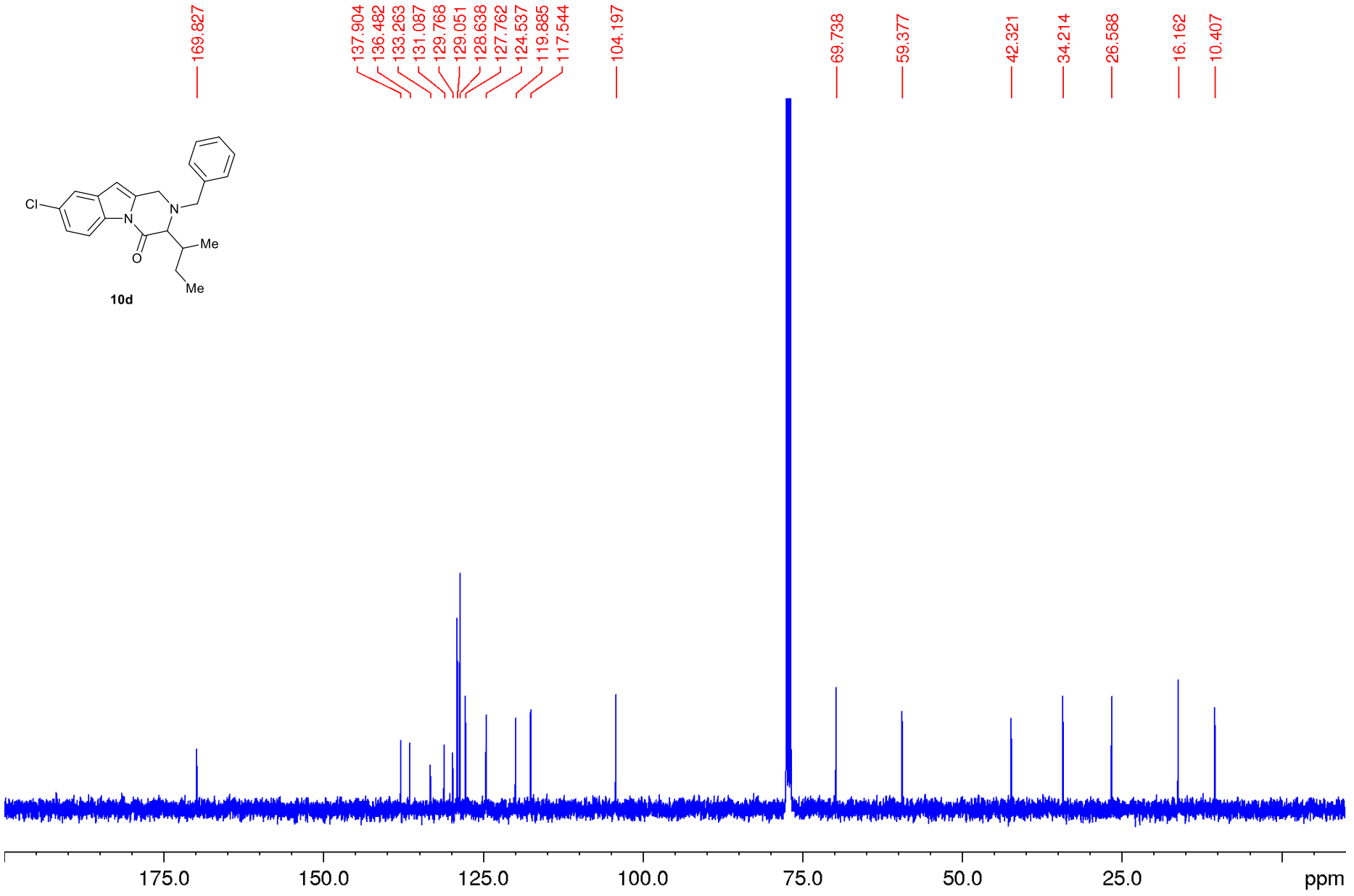
DEPT 135 NMR-spectrum ($CDCl_3$)



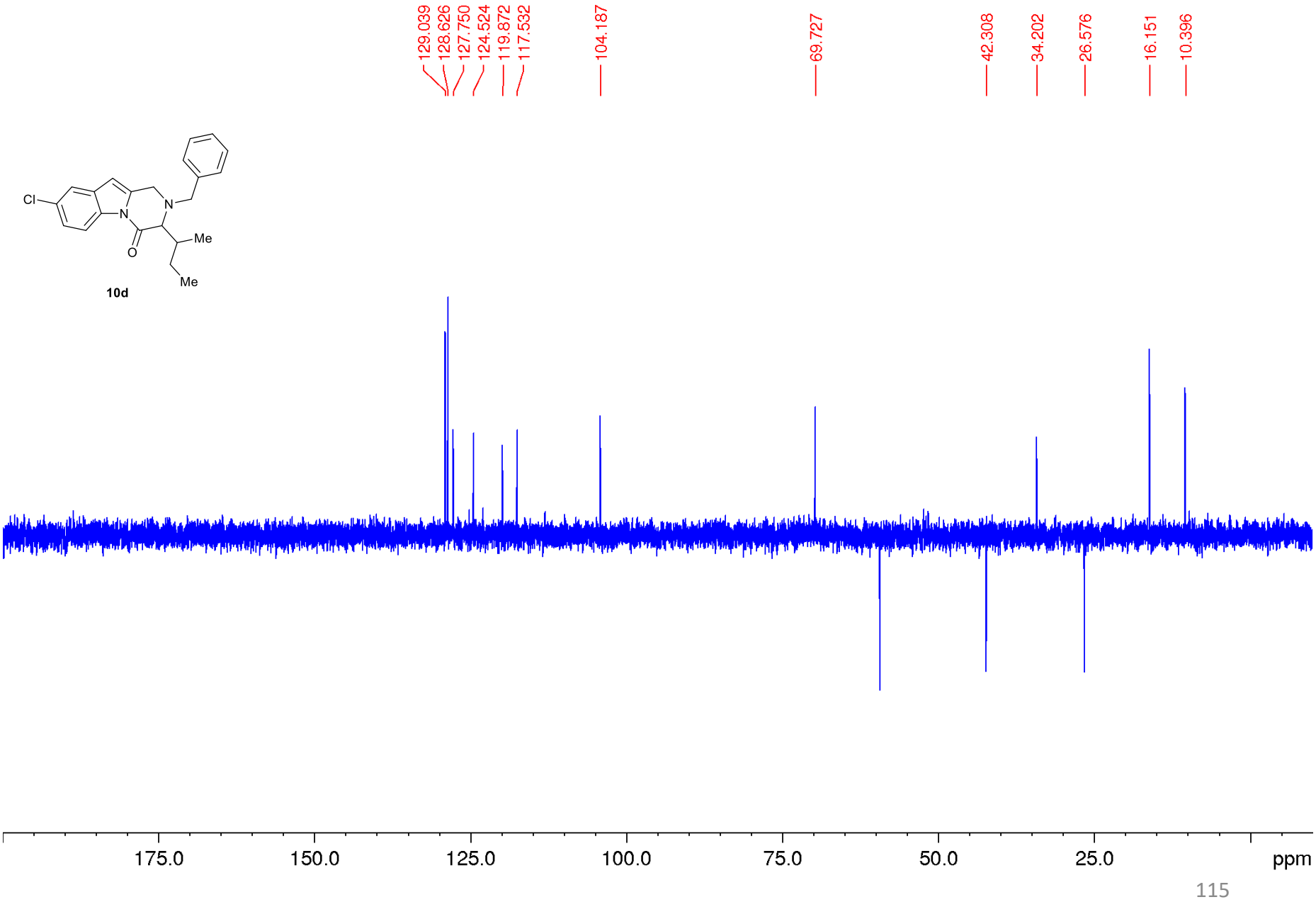
^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



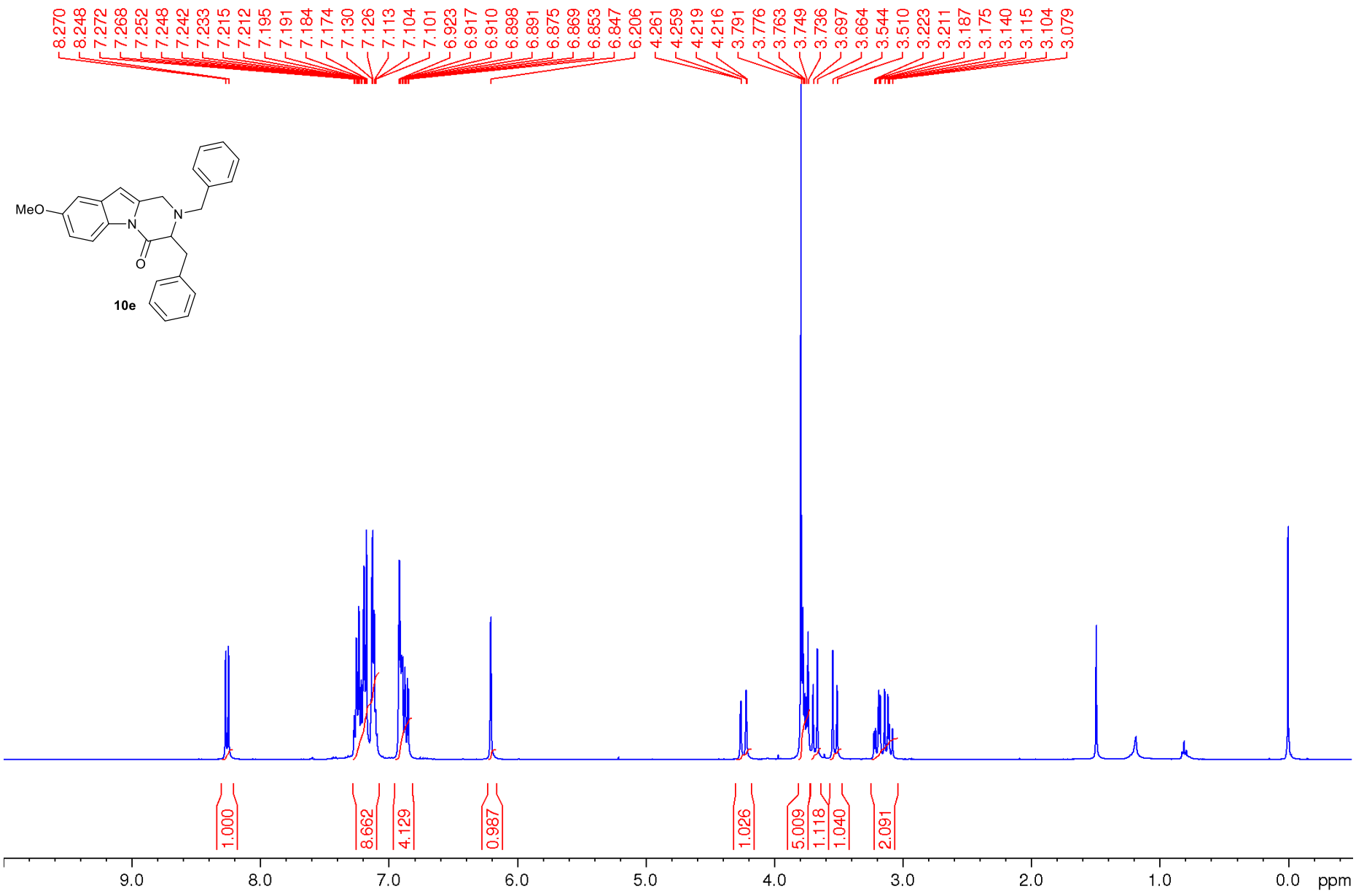
^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



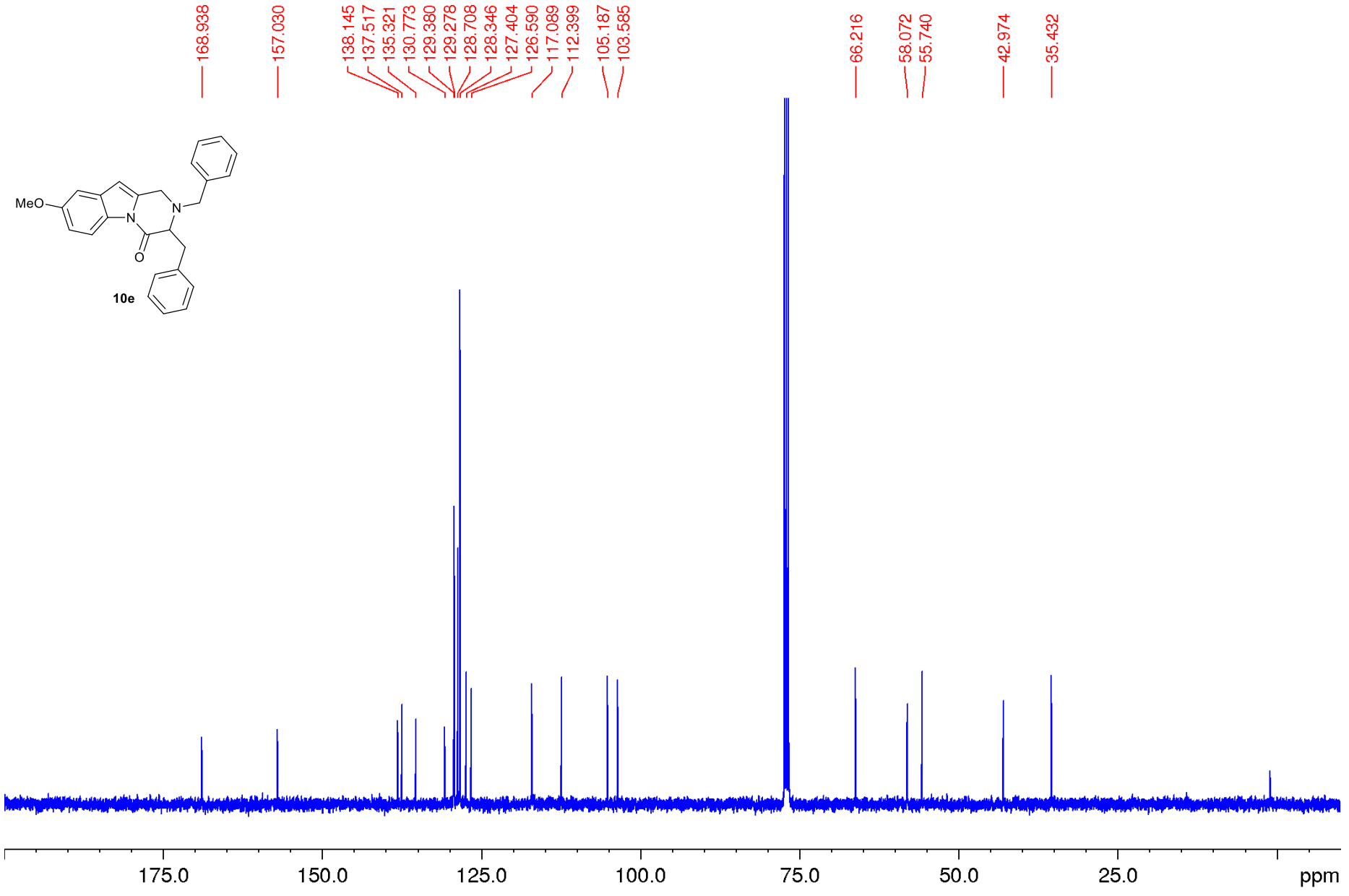
DEPT 135 NMR-spectrum ($CDCl_3$)



^{1}H NMR-spectrum (400.13 MHz) ($CDCl_3$)



^{13}C NMR-spectrum (100.6 MHz) ($CDCl_3$)



DEPT 135 NMR-spectrum ($CDCl_3$)