Electronic Supplementary Material (ESI) for ChemComm.


# Supporting Information

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# *I. Materials and Methods*

All reagents and solvents were used as purchased from commercial suppliers or were purified/dried according to W. L. F. Armarego and C. L. L. Chai (Purification of Laboratory Chemicals, 6th edition, Elsevier). Purifications by column chromatography on silica gel were performed using Merck Silica Gel 60 (70-230 mesh) and purifications by preparative thin layer chromatography on silica gel using Merck Silica Gel 60 $PF_{254}$. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker ARX500 instrument using $CDCl_3$, acetone-$d_6$, or $CD_3OD$ as internal references. Chemical shifts (δ values) are given in parts per million (ppm), coupling constants (*J* values) are given in Hertz (Hz), and multiplicity of signals are reported as follows: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quadruplet; dd, doublet of doublets; m, multiplet. HRMS analyses were obtained using a Waters LCT Premier instrument by ElectroSpray Ionization (ESI) or by Atmospheric Pressure Photo-Ionization (APPI). Melting points were measured with a Büchi Melting Point B-540 apparatus. Optical rotation, $[\alpha]_D^{20}$values, were measured using an Anton Paar MCP 300 instrument and are expressed in $deg.cm^3.g^{-1}.dm^{-1}$ for a concentration of compound in $g.cm^{-1}$. Chiral HPLC was performed using a Daicel Chiralpak® IB column (5 µm, 4.6 x 250 mm) on a Waters Alliance 2695 apparatus.

# *II. Molecular Modelling*

Molecular docking was carried out using GOLD 5.2[1] with standard parameters. The receptor was a conformer of Bcl-xL that is appropriate for the interaction with the meiogynin A family, generated previously using a ligand-driven conformer selection from molecular dynamics simulations (see below for a detailed description of this procedure).[2] The binding site was defined as a sphere with a 17 A□ radius around the OH group of Tyr101.

The 3D structures of the ligands were constructed with CORINA 3.44 (Molecular Networks GmbH).

The image representing the docking complexes was generated using Pymol (http://www.pymol.org/).

[1] M. L. Verdonk, J. C. Cole, M. J. Hartshorn, C. W. Murray and R. D. Taylor, *Proteins* **2003**, *52*, 609.

[2] C. Colas, F. Roussi, B. I. Iorga, "Focused ligand libraries as tools for *in silico* design of anti-apoptotic proteins inhibitors" in *Chemistry for Life Sciences*, eds. T. Kiss and A. Perczel, Medimond, Bologna **2011**, 41-46.

**Ligand-driven conformer selection for Bcl-xL**

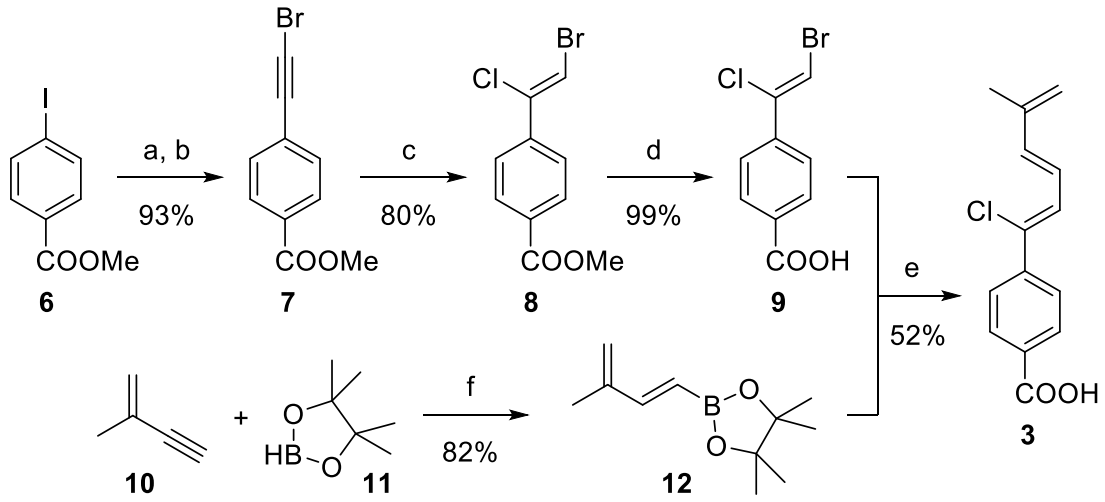
In order to explore the conformational flexibility of Bcl-xL, molecular dynamics (MD) simulations were performed using four representative X-ray structures of this protein as initial conformations: the apo form (1MAZ) and the complexes with ABT-737 (2YXJ), W119542 (3INQ) and the peptide Bim (3FDL). The fragment containing the helix α1 and the loop α1-α2 being not present in all X-ray structures available, it was removed from all structures used in this study.

The MD simulations (20 ns in each case) were performed with GROMACS 4.5.4[3] using the OPLS-AA force field.[4] All MD simulations were concatenated and clustered with the g_cluster module, in order to generate an ensemble containing 40 representative protein conformations that was used for the subsequent molecular docking step.

Meiogynin A and three of its diastereoisomers[5] were used in flexible docking with Gold 5.0[1] on the ensemble of conformers generated in the previous step. The binding site was defined as a sphere with 17 Å radius around the OH group of Tyr101. GoldScore scoring function was used, while all other parameters had default values, to generate 200 docking conformations for each ligand. It was found that only one conformer from the ensemble of 40 conformers generated previously is able to correctly recognize the three active compounds and discriminate against the fourth inactive compound. Therefore, this conformer was used throughout the present study as representative conformation of Bcl-xL able to bind compounds from the meiogynin A family.

[3] Hess, B., Kutzner, C., van der Spoel, D., Lindahl, E. *J. Chem. Theory Comput.* **2008**, *4*, 435-447.
[4] Kaminski, G. A., Friesner, R. A., Tirado-Rives, J., Jorgensen,W. L. *J. Phys. Chem. B* **2001**, *105*, 6474-6487.
[5] Fotsop, D. F., Roussi, F., Leverrier, A., Breteche, A., Gueritte, F. *J. Org. Chem.* **2010**, *75*, 7412-7415.

# *III. Synthesis of the Triene **3***




Methyl 4-(bromoethynyl)benzoate **7**

To a mixture of methyl 4-iodobenzate **6** (13.1 g, 50 mmol, 1 eq), copper iodide (1.9 g, 10 mmol, 0.2 eq), and bis(triphenylphosphine)palladium (II) dichloride (1,8 g, 2.5 mmol, 0.05 eq) in $Et_3N$ (100 mL) under Ar atm. was added dropwise (triisopropylsilyl)acetylene (11,8 mL, 53 mmol, 1.05 eq). After 18 h at RT, the reaction mixture was quenched with a saturated solution of $NH_4Cl$ and the product was extracted with MTBE (3 times). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using heptane to obtain a colorless oil (15.8 g, 50 mmol, 99%). To a solution of this compound in MeCN (250 mL) were added NBS (9.8 g, 55 mmol, 1.1 eq) and AgF (7.0 g, 55 mmol, 1.1 eq) in the dark. The reaction mixture was stirred at RT for 18 h and then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using heptane/EtOAc 9:1 to obtain a white solid (11.1 g, 46 mmol, 93%). $R_f$ = 0.55 (heptane/EtOAc 9:1); Mp = 97 °C; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.4 Hz, 2 H), 7.52 (d, *J* = 8.4 Hz, 2 H), 3.93 (s, 3 H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ 166.4, 131.9 (2 C), 130.0, 129.5 (2 C), 127.3, 79.4, 53.3, 52.2 ppm; HRMS (APPI): *m/z* calcd. for $C_{10}H_7BrO_2$ $[M]^{+\bullet}$ 237.9624; found 237.9620.

Methyl (*Z*)-4-(2-bromo-1-chlorovinyl)benzoate **8**

To a solution of methyl 4-(bromoethynyl)benzoate **7** (10.7 g, 45 mmol, 1 eq), LiCl (3.8 g, 90 mmol, 2 eq) in AcOH (100 mL) were added allylpalladium (II) chloride dimer (820 mg, 2.2 mmol, 0.05 eq) and *cis,cis*-1,5-cyclooctadiene (550 µL, 4.5 mmol, 0.1 eq). After 18 h at 80 °C, the reaction mixture was cooled down and

water was added. The product was then extracted with MTBE (3 times) and the combined organic phases were washed with a saturated solution of $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using heptane/EtOAc 95:5 to obtain a yellow solid (9.9 g, 36 mmol, 80%). $R_f$ = 0.3 (heptane/EtOAc 95:5); Mp = 78 °C; $^1$H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.4 Hz, 2 H), 7.58 (d, *J* = 8.4 Hz, 2 H), 7.00 (s, 1 H), 3.91(s, 3 H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ 166.1, 140.2, 137.4, 131.7, 129.8 (2 C), 126.4 (2 C), 107.4, 52.2 ppm; HRMS (APPI): *m/z* calcd. for $C_{10}H_8BrClO_2$ $[M]^{+\bullet}$ 273.9396; found 273.9381.

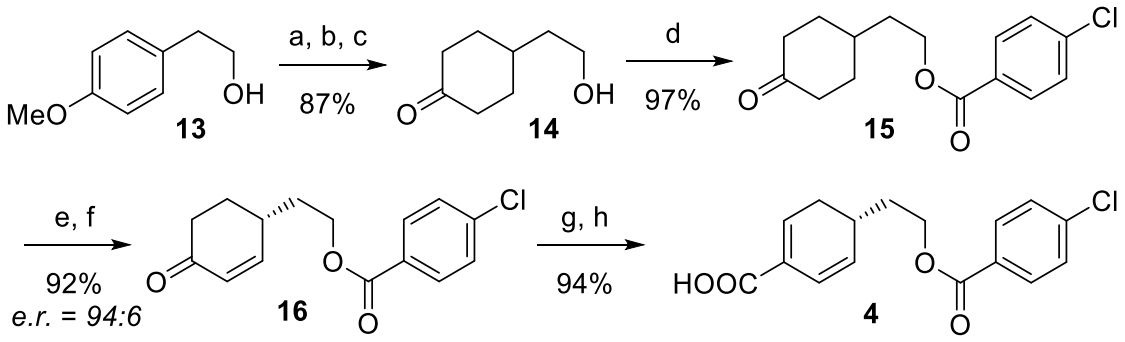
(*Z*)-4-(2-Bromo-1-chlorovinyl)benzoic acid **9**

To a solution of methyl (*Z*)-4-(2-bromo-1-chlorovinyl)-benzoate **8** (3.0 g, 11 mmol, 1 eq) in THF/water 2:1 (50 mL) was added $LiOH.H_2O$ (2.3 g, 54 mmol, 5 eq). The mixture was stirred 6 h at RT and water was added. The aqueous phase was washed twice with MTBE and acidified with a 2 M solution of HCl. The product was then extracted with MTBE (3 times) and the combined organic phases dried over $MgSO_4$ and concentrated under reduced pressure to obtain the benzoic acid as white solid (2.8 g, 11 mmol, 99%). $R_f$ = 0.2 (heptane/EtOAc/AcOH 80:19:1); Mp = 206 °C; $^1$H NMR (500 MHz, acetone-$d_6$): δ 12.50-10.50 (brs, 1 H), 8.08 (d, *J* = 8.4 Hz, 2 H), 7.81 (d, *J* = 8.4 Hz, 2 H), 7.56 (s, 1 H) ppm; $^{13}$C NMR (125 MHz, acetone-$d_6$): δ 166.9, 140.9, 137.7, 132.3, 130.8 (2 C), 127.6 (2 C), 109.5 ppm; HRMS (ESI): *m/z* calcd. for $C_9H_5BrClO_2$ $[M-H]^-$ 258.9167; found 258.9153.

4-[(1*Z*,3*E*)-1-chloro-5-methylhexa-1,3,5-trien-1-yl]benzoic acid **3**

To a solution of benzoic acid **9** (1.0 g, 3.8 mmol, 1 eq) and boronic ester **12** (2.2 g, 11.5 mmol, 3 eq) in THF/water 2:1 (60 mL) were added tetrakis(triphenylphosphine) palladium(0) (220 mg, 0.2 mmol, 0.05 eq) and $K_3PO_4$ (4.05 g, 2.0 mmol, 5 eq) in the dark. The mixture was stirred 6 h at 50 °C and a saturated solution of $NH_4Cl$ was added. The product was then extracted with MTBE (3 times) and the combined organic phases dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was then purified by column chromatography on silica gel using heptane/EtOAc/AcOH 80:19:1 to obtain a light yellow solid (490 mg, 2.0 mmol, 52%). $R_f$ = 0.3 (heptane/EtOAc/AcOH 70:29:1); Mp = degradation at 165 °C; $^1$H NMR (500 MHz, acetone-$d_6$): δ 12.00-10.50 (brs, 1 H), 8.06 (d, *J* = 8.4 Hz, 2 H), 7.87 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.3 Hz, 1 H), 6.82-6.74 (m, 2 H), 5.20 (s, 2 H), 1.98 (s, 3 H) ppm; $^{13}$C NMR (125 MHz, acetone-$d_6$): δ 167.0, 143.1, 142.4, 141.4, 131.7, 131.4, 130.7 (2 C), 129.0, 126.9 (2 C), 125.7, 120.2, 18.4 ppm; HRMS (ESI): *m/z* calcd. for $C_{14}H_{12}ClO_2$ $[M-H]^-$ 247.0531; found 247.0533.

# *IV. Synthesis of the Dienophile **4***




4-(2-Hydroxyethyl)cyclohexan-1-one **14**

To a solution of *p*-methoxyphenethyl alcohol **13** (10 g, 65.7 mmol, 1 eq) and *tert*-butanol (20 mL) in liquid $NH_3$ at -78 °C was added Li (2.8 g, 394 mmol, 6 eq) portionwise. After 5 h at this temperature, the reaction mixture was slowly quenched with $NH_4Cl$ (28 g, 526 mmol, 8 eq) and the cooling bath removed. The mixture was stirred overnight at RT with a flow of $N_2$ to evaporate the residual $NH_3$ and water was added. The product was then extracted with MTBE (3 times). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to obtain a yellow oil. To a solution of this crude product in THF/water 2:1 (75 mL) at 0 °C was added conc. $H_2SO_4$ (2 mL). The reaction mixture was stirred 2 h at this temperature and water was added. The compound was then extracted with $CH_2Cl_2$ (6 times) and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The above product was then dissolved in EtOAc and Pd-C (500 mg) was added. The suspension was stirred under $H_2$ atm. at RT for 18 h. After filtration through Celite, followed by concentration under reduced pressure, the crude product was purified by column chromatography on silica gel using heptane/EtOAc 6:4 to obtain a colorless oil (8.0 g, 56 mmol, 87%). $R_f$ = 0.05 (heptane/EtOAc 1:1); $^1$H NMR (500 MHz, $CDCl_3$): δ 3.75 (t, *J* = 6.5 Hz, 2 H), 2.43-2.30 (m, 4 H), 2.13-2.04 (m, 2 H), 1.99-1.88 (m, 1 H), 1.60 (q, *J* = 6.5 Hz, 2 H), 1.45 (qd, *J* = 12.3, 5.0 Hz, 2 H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ 212.2, 60.5, 40.7 (2 C), 38.2, 32.6 (2 C), 32.5 ppm; HRMS (ESI): *m/z* calcd. for $C_{10}H_{18}NO_2$ $[M+MeCN+H]^+$ 184.1332; found 184.1330.

2-(4-Oxocyclohexyl)ethyl 4-chlorobenzoate **15**

To a solution of 4-(2-hydroxyethyl)cyclohexan-1-one **14** (8.0 g, 56 mmol, 1 eq) in $CH_2Cl_2$ (100 mL) at 0 °C under Ar atm. was added $Et_3N$ (23.5 mL, 169 mmol, 3 eq) and 4-chlorobenzoyl chloride (7.6 mL, 59 mmol, 1.05 eq). The mixture was allowed to warm to RT overnight and quenched with a saturated solution of $NH_4Cl$. The product

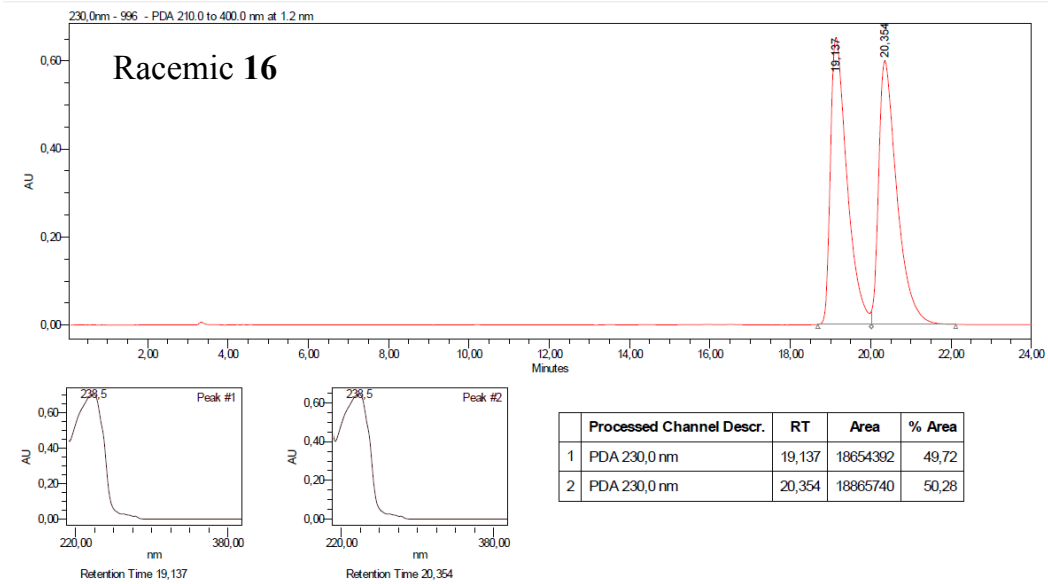
was then extracted with MTBE (3 times) and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using heptane/EtOAc 8:2 to obtain the ester as a white solid (15.3 g, 55 mmol, 97%). $R_f$ = 0.2 (heptane/EtOAc 8:2); Mp = 58 °C; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.6 Hz, 2 H), 7.40 (d, *J* = 8.6 Hz, 2 H), 4.39 (t, *J* = 6.7 Hz, 2 H), 2.42-2.29 (m, 4 H), 2.15-2.08 (m, 2 H), 1.97-1.88 (m, 1 H), 1.79 (q, *J* = 6.7 Hz, 2 H), 1.48 (dq, *J* = 5.0, 12.3 Hz, 2 H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ 211.3, 165.6, 139.4, 130.9 (2 C), 128.7 (2 C), 128.6, 63.2, 40.6 (2 C), 34.3, 33.1, 32.5 (2 C) ppm; HRMS (ESI): *m/z* calcd. for $C_{17}H_{21}ClNO_3$ $[M+MeCN+H]^+$ 322.1204; found 322.1202.

(*R*)-2-(4-Oxocyclohex-2-en-1-yl)ethyl 4-chlorobenzoate **16**

A 1.5 M solution of *n*-BuLi in hexanes (14.2 mL, 21.4 mmol, 1.2 eq) was added dropwise to a solution of bis[(*R*)-1-phenylethyl]amine (4.48 mL, 19.6 mmol, 1.1 eq) in THF (150 mL) at -78 °C under Ar atm. After 30 min, TMSCl (11 mL, 89 mmol, 5 eq) was added, followed by a solution of the cyclohexanone **15** (5.0 g, 17.8 mmol, 1 eq) in THF (30 mL) over a period of 1 h. After the addition was complete, the mixture was stirred for an additional 1 h at -78 °C and quenched with $Et_3N$ (20 mL). A saturated solution of $NaHCO_3$ (20 mL) was then added and the reaction mixture was allowed to warm to RT. After addition of water, the mixture was extracted with MTBE (3 times) and the combined organic phases were dried over $MgSO_4$. The solvent was then partially evaporated under reduced pressure and the residue was washed with a 0.5 M citric acid solution to remove the amine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give the silyl enol ether as a yellow oil. $Pd(OAc)_2$ (200 mg, 0.89 mmol, 0.05 eq) was then added to a solution of the crude product in dry DMSO (50 mL). $O_2$ was bubbled through for 5 min and the resulting black mixture was stirred at RT under $O_2$ atm. overnight. The reaction mixture was quenched with a saturated solution of $NH_4Cl$ and the product was extracted with MTBE (3 times). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was then purified by column chromatography on silica gel using heptane/EtOAc 8:2 to give the cyclohexenone **16** as a white solid (4.56 g, 16.4 mmol, 92%) with an *e.r.* of 94:6. $R_f$ = 0.2 (heptane/EtOAc 7:3); Mp = 44 °C; $[\alpha]_D^{20}$ = -45.0 ° (*c* 2.0, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.3 Hz, 2 H), 7.41 (d, *J* = 8.3 Hz, 2 H), 6.88 (d, *J* = 10.0 Hz, 1 H), 6.01 (d, *J* = 10.0 Hz, 1 H), 4.49-4.40 (m, 2 H), 2.68-2.59 (m, 1 H), 2.56-2.48 (m, 1 H), 2.43-2.33 (m, 1 H), 2.24-2.16 (m, 1 H), 2.06-1.97 (m, 1 H), 1.93-1.85 (m, 1 H), 1.83-1.73 (m, 1 H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): δ 199.1, 165.5, 153.3, 139.5, 130.9 (2 C), 129.5, 128.8 (2 C), 128.4, 62.5, 36.7, 33.4, 33.2, 28.5 ppm; HRMS (ESI): *m/z* calcd. for $C_{15}H_{16}ClO_3$ $[M+H]^+$ 279.0782; found 279.0790.

Chiral HPLC

The *e.r.* of the cyclohexenone **16** was measured using a Daicel Chiralpak® IB column (5 µm, 4.6 x 250 mm) with a U.V. detection at 230 nm and at 25 °C. Flow = 1 mL/min with heptane/isopropanol 95:5.




| | Processed Channel Descr. | RT | Area | % Area |
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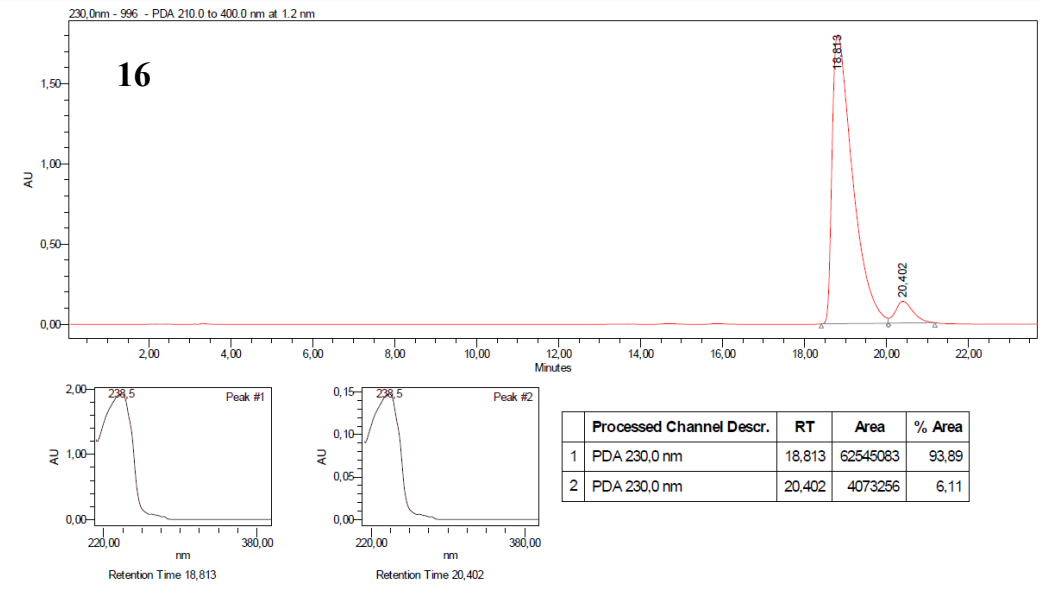
| 2 | PDA 230,0 nm | 20,354 | 18865740 | 50,28 |

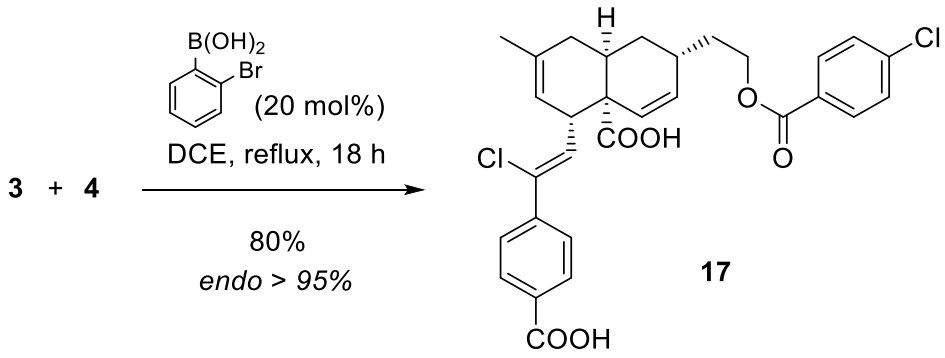



| | Processed Channel Descr. | RT | Area | % Area |
|---|---|---|---|---|
| 1 | PDA 230,0 nm | 18,813 | 62545083 | 93,89 |
| 2 | PDA 230,0 nm | 20,402 | 4073256 | 6,11 |

(*R*)-4-[2-(4-chlorobenzoyloxy)ethyl]cyclohexa-1,5-diene-1-carboxylic acid **4**

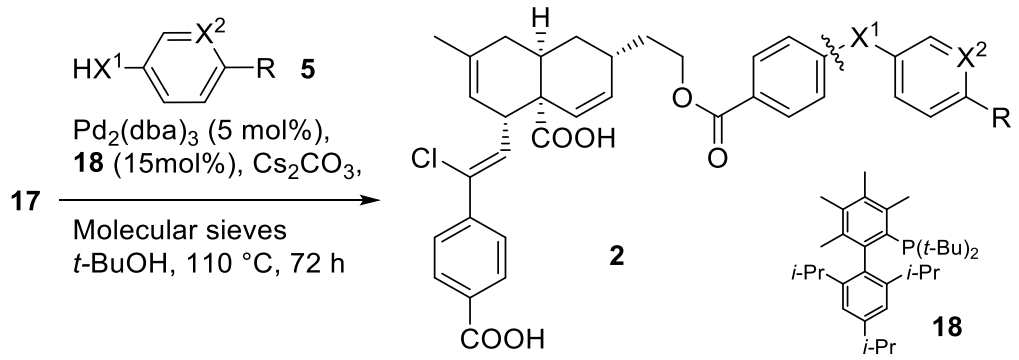
To a solution of the cyclohexenone **16** (6.46 g, 23.2 mmol, 1 eq) in dry THF (150 mL) at -78 °C was added a 1 M solution of NaHMDS in THF (47 mL, 46.3 mmol, 2 eq). After 30 min, the Comins'reagent (27.3 mL, 69.5 mmol, 3 eq) was added and the reaction mixture stirred for 3 h at -78 °C. A 10% solution of NaOH (50 mL) was then added and the mixture was allowed to warm to r.t. After addition of water, the mixture was extracted with MTBE (3 times) and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was then purified by column chromatography on silica gel using heptane/EtOAc 95:5 to obtain a light yellow oil (9.44 g, 23.0 mmol, **99%**).To a solution of the triflate obtained (5.10 g, 12.4 mmol, 1 eq) in dry DMF (150 mL) at RT was added AcOK (4.90 g, 50.0 mmol, 4 eq), $Pd(OAc)_2$ (140 mg, 0.6 mmol, 0.05 eq) and $PPh_3$ (330 mg, 1.2 mmol, 0.1 eq). The reaction mixture was stirred for 7 h under CO atm. before being degassed by bubbling Ar in the solution for 20 min. After addition of a 1 M solution of HCl, the product was extracted with MTBE (3 times) and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was then purified by column chromatography on silica gel using heptane/EtOAc/AcOH 90:9:1 to obtain the carboxylic acid as a white solid (3.58 g, 11.7 mmol, 94%). $R_f$ = 0.4 (heptane/EtOAc/AcOH 70:29:1); Mp = 123 °C; $[\alpha]_D^{20}$ = -47.8 ° (*c* 2.0, MeOH); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 13.00-9.00 (brs, 1 H), 7.98 (d, *J* = 8.6 Hz, 2 H), 7.44 (d, *J* = 8.6 Hz, 2 H), 7.12-7.07 (m, 1 H), 6.43 (d, *J* = 10.1 Hz, 1 H), 5.93 (dd, *J* = 10.1, 3.3 Hz, 1 H), 4.41 (t, *J* = 6.5 Hz, 2 H), 2.66-2.53 (m, 2 H), 2.37-2.26 (m, 1 H), 2.01-1.92 (m, 1 H), 1.89-1.81 (m, 1 H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 171.4, 165.7, 139.5, 138.7, 131.1, 130.9 (2 C), 128.7 (2 C), 128.6, 127.9, 121.5, 62.7, 33.1, 29.2, 28.9 ppm; HRMS (ESI): *m/z* calcd. for $C_{16}H_{14}ClO_4$ $[M-H]^-$ 305.0586; found 305.0583.

# *V. Diels-Alder Cycloaddition Reaction*




A solution of triene **3** (460 mg, 1.84 mmol, 1 eq), dienophile **4** (624 mg, 2.03 mmol, 1.1 eq) and 2-bromophenylboronic acid (74 mg, 0.37 mmol, 0.2 eq) in 1,2-dichloroethane (15 mL) was heated at reflux overnight. The reaction mixture was then concentrated under reduced pressure and purified by column chromatography on silica gel using $CH_2Cl_2$/AcOH 99:1 to obtain the decalin **17** as a white solid (818 mg, 1.47 mmol, 80%). $R_f$ = 0.15 ($CH_2Cl_2$/AcOH 99:1); Mp = 208 °C; $[\alpha]_D^{20}$ = -239.0 ° (*c* 0.5, MeOH); $^1$H NMR (500 MHz, acetone-$d_6$): δ 13.00-9.00 (brs, 2 H), 8.03 (d, *J* = 8.2 Hz, 4 H), 7.69 (d, *J* = 8.2 Hz, 2 H), 7.55 (d, *J* = 8.2 Hz, 2 H), 6.33 (d, *J* = 9.8 Hz, 1 H), 5.77 (dd, *J* = 9.9, 2.7 Hz, 1 H), 5.70 (d, *J* = 9.9 Hz, 1 H), 5.31-5.26 (m, 1 H), 4.46-4.36 (m, 2 H), 3.78-3.69 (m, 1 H), 2.77-2.69 (m, 1 H), 2.64-2.55 (m, 1 H), 2.10 (dd, *J* = 18.1, 7.2 Hz, 1 H), 1.99-1.83 (m, 4 H), 1.78-1.70 (m, 1 H), 1.65 (s, 3 H) ppm; $^{13}$C NMR (125 MHz, acetone-$d_6$): δ 175.6, 167.1, 165.9, 143.0, 139.6, 136.5, 133.1, 132.0 (2 C), 131.6, 131.4, 131.1, 130.7, 130.6 (2 C), 130.2, 129.7 (2 C), 127.3 (2 C), 117.9, 63.8, 48.6, 35.7, 32.5, 31.6, 30.4, 30.2, 29.7, 23.5 ppm; HRMS (ESI): *m/z* calcd. for $C_{30}H_{27}Cl_2O_6$ $[M-H]^-$ 553.1190; found 553.1199.

# *VI. Buchwald-Hartwig Coupling*




General procedure

A mixture of $Cs_2CO_3$ (83 mg, 0.22 mmol, 4 eq) and 3 Å molecular sieves in powder (400 mg) was heated for 1 h at 300 °C under *vacuum*. The flask was then cooled to RT under Ar atm. and the chlorinated compound **17** (30 mg, 0.05 mmol, 1 eq), $Pd_2(dba)_3$ (3 mg, 0.003 mmol, 0.05 eq), 2-di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl **18** (4 mg, 0.01 mmol, 0.15 eq), nucleophile **5** (0.11 mmol, 2 eq), and dry *t*-BuOH (1.5 mL) were successively added. The reaction mixture was heated at reflux for 72 h and then quenched with a 2 M HCl solution (3 mL). The molecular sieves was filtered off and washed with MTBE. Water was added to the filtrate and the product was extracted with MTBE (3 times). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was then purified by column chromatography on silica gel using $CH_2Cl_2$/AcOH 99:1 to $CH_2Cl_2$/MeOH/AcOH 97:2:1.

Compound **2a**

The coupling product **2a** was isolated as a white solid (28 mg, 0.05 mmol, 75%). $R_f$ = 0.2 ($CH_2Cl_2$/MeOH/AcOH 97:2:1); Mp = 164 °C; $[\alpha]_D^{20}$ = -172.3 ° (*c* 0.3, MeOH); $^1$H NMR (500 MHz, MeOD): δ 8.39 (brs, 2 H), 8.06 (d, *J* = 8.9 Hz, 2 H), 7.98 (d, *J* = 8.4 Hz, 2 H), 7.63 (d, *J* = 8.4 Hz, 2 H), 7.59-7.55 (m, 1 H), 7.49 (dd, *J* = 8.2, 4.8 Hz, 1 H), 7.10 (d, *J* = 8.9 Hz, 2 H), 6.19 (d, *J* = 9.5 Hz, 1 H), 5.73 (dd, *J* = 9.6, 3.0 Hz, 1 H), 5.66 (d, *J* = 9.6 Hz, 1 H), 5.28-5.24 (m, 1 H), 4.42-4.36 (m, 2 H), 3.71-3.66 (m, 1 H), 2.70-2.62 (m, 1 H), 2.58-2.49 (m, 1 H), 2.08 (dd, *J* = 18.7, 6.8 Hz, 1 H), 1.97-1.81 (m, 4 H), 1.77-1.69 (m, 1 H), 1.66 (s, 3 H) ppm; $^{13}$C NMR (125 MHz, MeOD): δ 178.1, 169.6, 167.3, 162.2, 154.5, 146.0, 143.5, 142.6, 136.8, 133.2, 133.0 (2 C), 132.4, 131.6 (2 C), 130.8 (2 C), 130.7, 129.0, 127.5 (2 C), 127.1, 126.4, 119.0 (2 C), 118.3, 64.1, 48.6, 46.3, 36.0, 32.8, 32.0, 30.7, 30.1, 23.5 ppm; HRMS (ESI): *m/z* calcd. for $C_{35}H_{31}ClNO_7$ $[M-H]^-$ 612.1785; found 612.1795.

Compound **2b**

The coupling product **2b** was isolated as a white solid (36 mg, 0.06 mmol, 89%). $R_f$ = 0.35 ($CH_2Cl_2$/MeOH/AcOH 97:2:1); Mp = 175 °C; $[\alpha]_D^{20}$ = -208.9 ° (*c* 0.3, MeOH); $^1$H NMR (500 MHz, acetone-$d_6$): δ 13.00-9.00 (brs, 2 H), 8.03 (d, *J* = 8.5 Hz, 2 H), 8.00 (d, *J* = 8.8 Hz, 2 H), 7.69 (d, *J* = 8.5 Hz, 2 H), 7.07 (d, *J* = 8.8 Hz, 2 H), 7.01 (d, *J* = 8.8 Hz, 2 H), 6.98 (d, *J* = 8.8 Hz, 2 H), 6.32 (d, *J* = 9.6 Hz, 1 H), 5.77 (dd, *J* = 10.0, 3.0 Hz, 1 H), 5.69 (d, *J* = 10.0 Hz, 1 H), 5.31-5.26 (m, 1 H), 4.42-4.32 (m, 2 H), 3.82 (s, 3 H), 3.75-3.69 (m, 1 H), 2.76-2.69 (m, 1 H), 2.63-2.54 (m, 1 H), 2.10 (dd, *J* = 18.1, 7.0 Hz, 1 H), 1.99-1.82 (m, 4 H), 1.76-1.67 (m, 1 H), 1.65 (s, 3 H) ppm; $^{13}$C NMR (125 MHz, acetone-$d_6$): δ 175.6, 167.1, 166.2, 163.8, 157.9, 149.5, 143.0, 136.5, 133.2, 132.4 (2 C), 131.6, 131.4, 131.1, 130.7, 130.6 (2 C), 127.3 (2 C), 125.2, 122.5 (2 C), 117.9, 117.2 (2 C), 116.1 (2 C), 63.3, 56.0, 48.6, 45.8, 35.8, 32.5, 31.7, 30.2, 30.1, 23.5 ppm; HRMS (ESI): *m/z* calcd. for $C_{37}H_{34}ClO_8$ $[M-H]^-$ 641.1948; found 641.1951.

Compound **2c**

The coupling product **2c** was isolated as a white solid (10 mg, 0.01 mmol, 20%). $R_f$ = 0.2 ($CH_2Cl_2$/MeOH/AcOH 97:2:1); Mp = 156 °C; $[\alpha]_D^{20}$ = -164.7 ° (*c* 0.3, MeOH); $^1$H NMR (500 MHz, MeOD): δ 8.00 (d, *J* = 8.8 Hz, 2 H), 7.99 (d, *J* = 8.4 Hz, 2 H), 7.67 (d, *J* = 8.8 Hz, 2 H), 7.63 (d, *J* = 8.4 Hz, 2 H), 7.12 (d, *J* = 8.6 Hz, 2 H), 7.07 (d, *J* = 8.8 Hz, 2 H), 7.01 (d, *J* = 8.8 Hz, 2 H), 6.94 (d, *J* = 8.6 Hz, 2 H), 6.19 (d, *J* = 9.6 Hz, 1 H), 5.73 (dd, *J* = 10.0, 3.0 Hz, 1 H), 5.66 (d, *J* = 10.0 Hz, 1 H), 5.28-5.23 (m, 1 H), 4.63 (s, 2 H), 4.40-4.34 (m, 2 H), 3.71-3.66 (m, 1 H), 2.69-2.62 (m, 1 H), 2.58-2.49 (m, 1 H), 2.28 (s, 3 H), 2.08 (dd, *J* = 18.1, 7.0 Hz, 1 H), 1.97-1.80 (m, 4 H), 1.76-1.68 (m, 1 H), 1.66 (s, 3 H) ppm; $^{13}$C NMR (125 MHz, MeOD): δ 178.1, 169.7, 169.5, 167.6, 163.7, 157.2, 153.6, 143.7, 136.8, 135.7, 133.3, 132.8 (2 C), 132.4, 132.3, 131.6, 131.1 (2 C), 130.8 (2 C), 130.7 (2 C), 127.5 (2 C), 125.8, 123.9 (2 C), 121.7 (2 C), 118.4, 118.1 (2 C), 115.9 (2 C), 68.9, 64.1, 48.6, 46.3, 36.1, 32.9, 32.0, 30.7, 30.2, 23.5, 20.6 ppm; HRMS (ESI): *m/z* calcd. for $C_{45}H_{43}ClNO_9$ $[M+H]^+$ 776.2621; found 776.2634.

Compound **2d**

The coupling product **2d** was isolated as a white solid (34 mg, 0.05 mmol, 86%). $R_f$ = 0.2 ($CH_2Cl_2$/MeOH/AcOH 97:2:1); Mp = 146 °C; $[\alpha]_D^{20}$ = -196.3 ° (*c* 0.3, MeOH); $^1$H NMR (500 MHz, acetone-$d_6$): δ 10.00-12.00 (brs, 2 H), 8.04 (d, *J* = 8.6 Hz, 2 H), 7.86 (d, *J* = 8.7 Hz, 2 H), 7.82 (brs, 1 H), 7.70 (d, *J* = 8.6 Hz, 2 H), 7.18-7.12 (m, 4 H), 7.04 (d, *J* = 8.7 Hz, 2 H), 6.33 (d, *J* = 9.6 Hz, 1 H), 5.78 (dd,

*J* = 10.0, 3.0 Hz, 1 H), 5.70 (d, *J* = 10.0 Hz, 1 H), 5.31-5.27 (m, 1 H), 4.38-4.29 (m, 2 H), 3.75-3.69 (m, 1 H), 2.76-2.69 (m, 1 H), 2.62-2.54 (m, 1 H), 2.30 (s, 3 H), 2.10 (dd, *J* = 18.1, 7.0 Hz, 1 H), 2.00-1.80 (m, 4 H), 1.74-1.67 (m, 1 H), 1.65 (s, 3 H) ppm; $^{13}$C NMR (125 MHz, acetone-$d_6$): δ 175.6, 167.0, 166.6, 150.4, 143.0, 139.8, 136.5, 133.3, 132.9, 132.1 (2 C), 131.6, 131.4, 131.0, 130.8, 130.7 (2 C), 130.6 (2 C), 127.3 (2 C), 121.6 (2 C), 121.0, 117.9, 114.6 (2 C), 62.7, 48.6, 45.8, 36.0, 32.5, 31.7, 30.2, 30.1, 23.5, 20.8 ppm; HRMS (ESI): *m/z* calcd. for $C_{37}H_{35}ClNO_6$ $[M-H]^-$ 624.2158; found 624.2158.

Compound **2e**

The coupling product **2e** was isolated as a white solid (18 mg, 0.03 mmol, 46%). $R_f$ = 0.2 ($CH_2Cl_2$/MeOH/AcOH 97:2:1); Mp = 136 °C; $[\alpha]_D^{20}$ = -188.4 ° (*c* 0.5, MeOH); $^1$H NMR (500 MHz, acetone-$d_6$): δ 12.00-10.0 (brs, 2 H), 8.03 (d, *J* = 8.5 Hz, 2 H), 7.78 (d, *J* = 8.8 Hz, 2 H), 7.69 (d, *J* = 8.5 Hz, 2 H), 7.39 (d, *J* = 7.3 Hz, 2 H), 7.33 (t, *J* = 7.3 Hz, 2 H), 7.24 (t, *J* = 7.3 Hz, 1 H), 6.70 (d, *J* = 8.8 Hz, 2 H), 6.33 (d, *J* = 9.6 Hz, 1 H), 6.30-6.20 (brs, 1 H), 5.76 (dd, *J* = 10.0, 3.0 Hz, 1 H), 5.68 (d, *J* = 10.0 Hz, 1 H), 5.31-5.26 (m, 1 H), 4.45 (s, 2 H), 4.34-4.25 (m, 2 H), 3.75-3.68 (m, 1 H), 2.77-2.69 (m, 1 H), 2.60-2.51 (m, 1 H), 2.09 (dd, *J* = 17.9, 7.1 Hz, 1 H), 1.99-1.78 (m, 4 H), 1.71-1.61 (m, 4 H) ppm; $^{13}$C NMR (125 MHz, acetone-$d_6$): δ 175.6, 167.0, 166.9, 153.6, 143.0, 140.3, 136.5, 133.3, 132.2, 132.0 (2 C), 131.6, 130.9, 130.7, 130.6 (2 C), 129.3 (2 C), 128.1 (2 C), 127.8, 127.3 (2 C), 118.7, 117.9, 112.4 (2 C), 62.5, 48.6, 47.6, 45.8, 36.0, 32.5, 31.7, 30.2, 30.1, 23.5 ppm; HRMS (ESI): *m/z* calcd. for $C_{37}H_{35}ClNO_6$ $[M-H]^-$ 624.2158; found 624.2154.

Compound **2f**

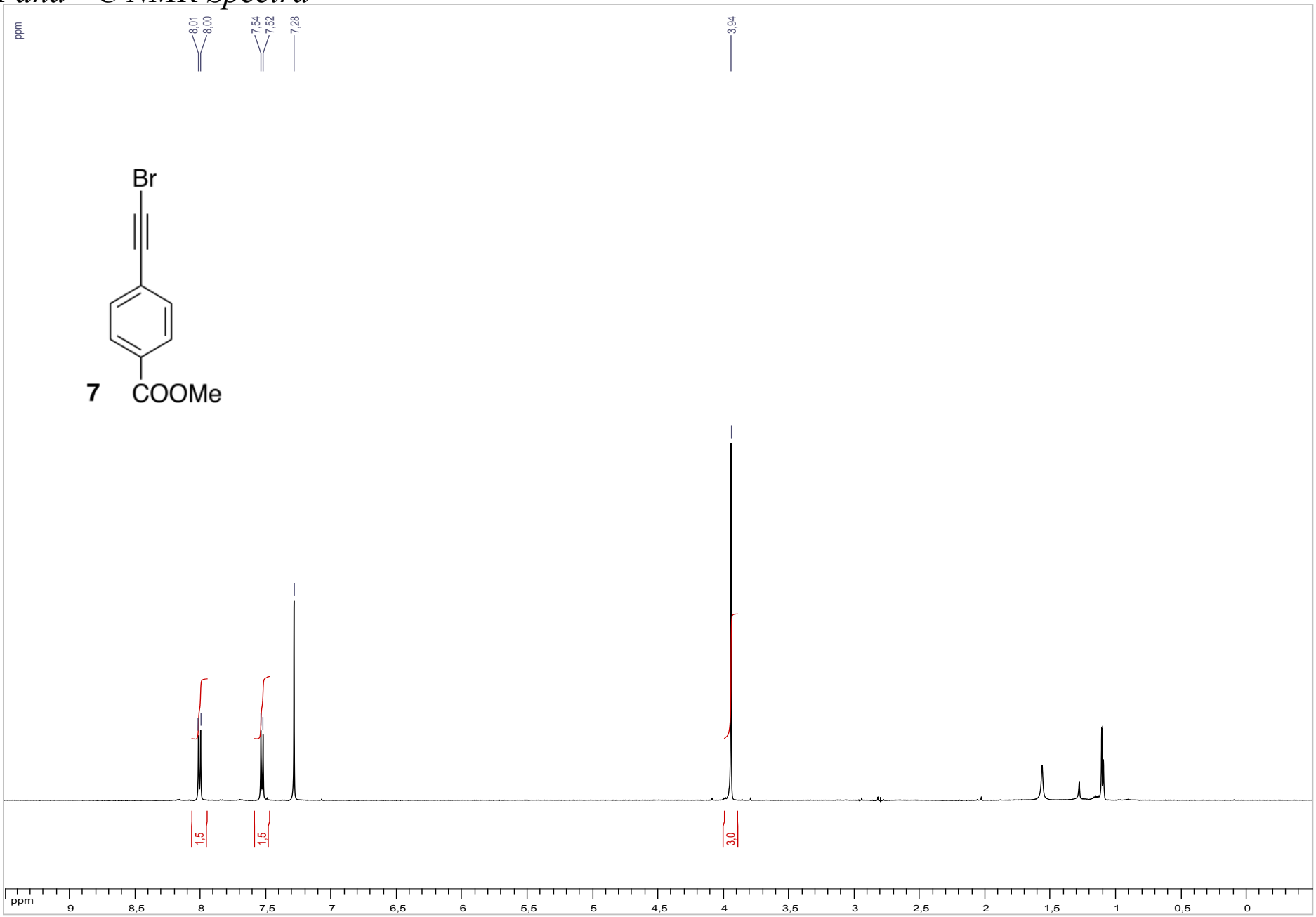
The coupling product **2f** was isolated as a white solid (32 mg, 0.05 mmol, 74%). $R_f$ = 0.3 ($CH_2Cl_2$/MeOH/AcOH 97:2:1); Mp = 219 °C; $[\alpha]_D^{20}$ = -201.6 ° (*c* 0.3, MeOH); $^1$H NMR (500 MHz, acetone-$d_6$): δ 13.00-10.50 (brs, 2 H), 9.43 (brs,1 H), 8.03 (d, *J* = 8.4 Hz, 2 H), 7.91 (d, *J* = 8.6 Hz, 2 H), 7.77 (d, *J* = 8.3 Hz, 2 H), 7.69 (d, *J* = 8.4 Hz, 2 H), 7.39-7.29 (m, 4 H), 6.32 (d, *J* = 9.5 Hz, 1 H), 5.75 (dd, *J* = 10.0, 3.0 Hz, 1 H), 5.68 (d, *J* = 10.0 Hz, 1 H), 5.32-5.24 (m, 1 H), 4.42-4.27 (m, 2 H), 3.75-3.67 (m, 1 H), 2.75-2.67 (m, 1 H), 2.60-2.52 (m, 1 H), 2.36 (s, 3 H), 2.08 (dd, *J* = 17.9, 7.0 Hz, 1 H), 1.97-1.80 (m, 4 H), 1.73-1.66 (m, 1 H), 1.64 (s, 3 H) ppm; $^{13}$C NMR (125 MHz, acetone-$d_6$): δ 175.6, 167.1, 166.2, 144.9, 143.4, 143.0, 137.9, 136.5, 133.2, 131.6 (2 C), 131.4, 131.1, 130.7 , 130.6 (4 C), 128.0 (2 C), 127.3 (2 C), 126.6, 119.5 (2 C), 117.2, 63.4, 48.6, 45.8, 35.8, 32.5, 31.6, 30.4, 30.2, 30.1, 23.5, 21.4 ppm; HRMS (ESI): *m/z* calcd. for $C_{37}H_{35}ClNO_8S$ $[M-H]^-$ 688.1777; found 688.1790.

Compound **2g**

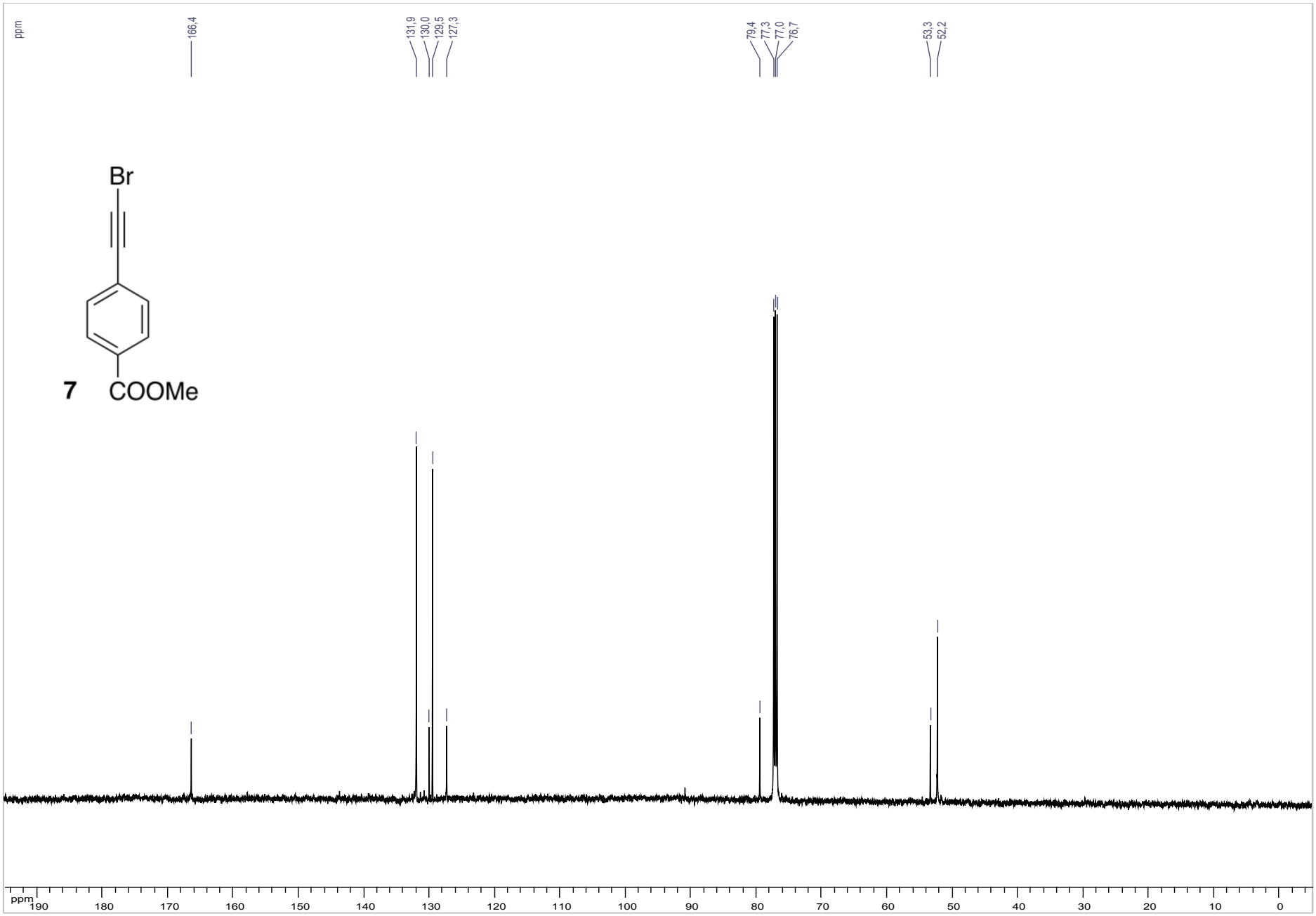
The coupling product **2g** was isolated as a white solid (17 mg, 0.03 mmol, 48%). $R_f$ = 0.3 ($CH_2Cl_2$/MeOH/AcOH 97:2:1); Mp = 216 °C; $[\alpha]_D^{20}$ = -195.0 ° (*c* 0.3, MeOH); $^1$H NMR (500 MHz, acetone-$d_6$): δ 13.00-9.50 (brs, 2 H), 9.72 (s,1 H), 8.06-7.97 (m, 8 H), 7.70 (d, *J* = 8.5 Hz, 2 H), 7.34 (d, *J* = 8.3 Hz, 2 H), 6.33 (d, *J* = 9.6 Hz, 1 H), 5.79 (dd, *J* = 10.0, 3.0 Hz, 1 H), 5.71 (d, *J* = 10.0 Hz, 1 H), 5.31-5.27 (m, 1 H), 4.44-4.35 (m, 2 H), 3.76-3.70 (m, 1 H), 2.77-2.71 (m, 1 H), 2.64-2.56 (m, 1 H), 2.40 (s, 3 H), 2.10 (dd, *J* = 18.1, 7.0 Hz, 1 H), 2.00-1.85 (m, 4 H), 1.77-1.69 (m, 1 H), 1.66 (s, 3 H) ppm; $^{13}$C NMR (125 MHz, acetone-$d_6$): δ 175.6, 167.1, 166.5, 166.4, 144.7, 143.2, 143.0, 136.5, 133.2, 133.1, 131.6, 131.4, 131.2 (2 C), 131.1, 130.6 (2 C), 129.9 (2 C), 128.5 (2 C), 127.3 (2 C), 126.2, 120.2 (2 C), 117.9, 63.3, 48.6, 45.8, 35.9, 32.5, 31.7, 30.4, 30.2, 30.1, 23.5, 21.4 ppm; HRMS (ESI): *m/z* calcd. for $C_{38}H_{35}ClNO_7$ $[M-H]^-$ 652.2108; found 652.2097.

## *VII. $^{1}H$ and $^{13}C$ NMR Spectra*

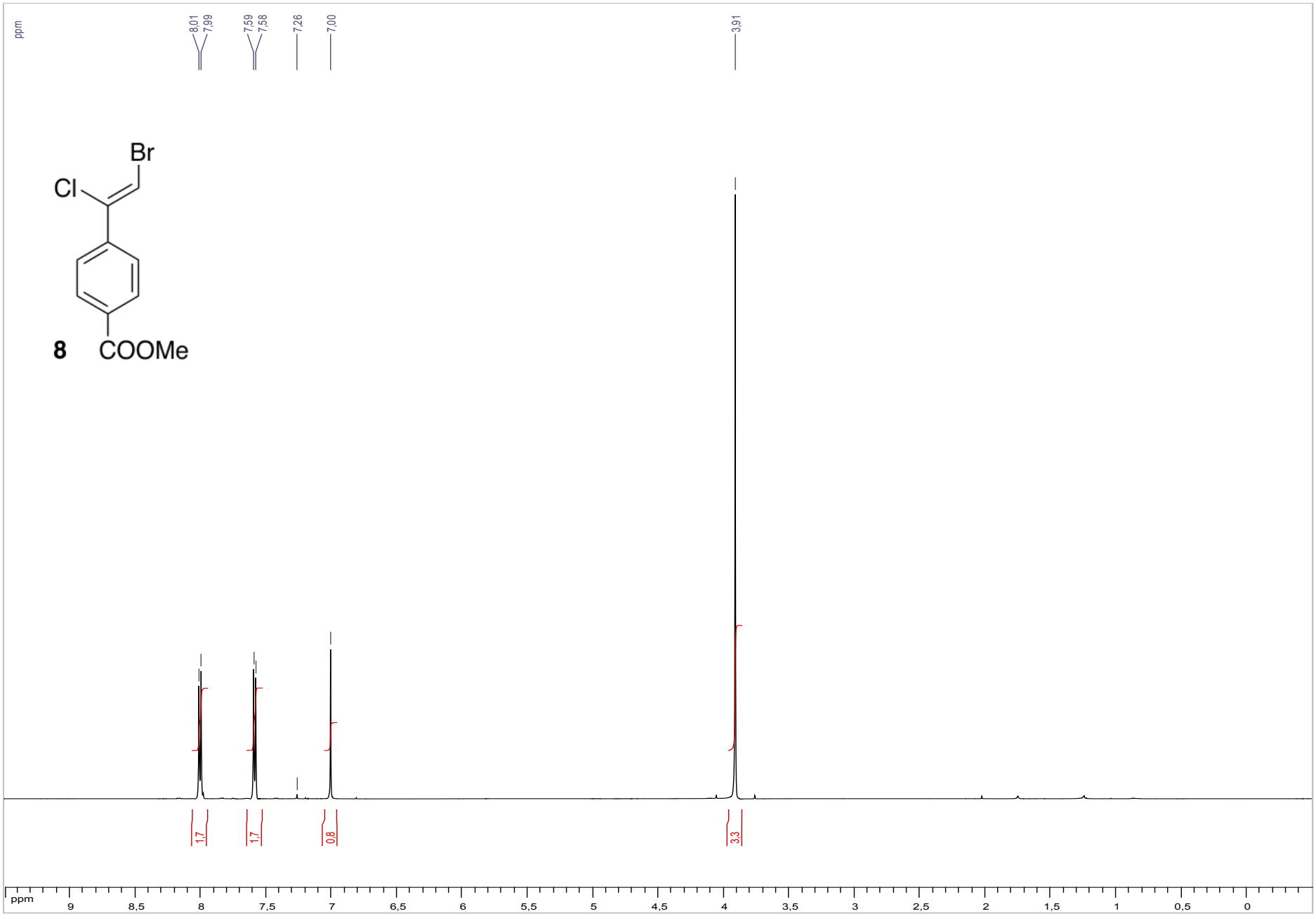
$^{1}H$ NMR $CDCl_3$ 500MHz



$^{13}C$ NMR $CDCl_3$ 125MHz



$^{1}$H NMR $CDCl_3$ 500MHz



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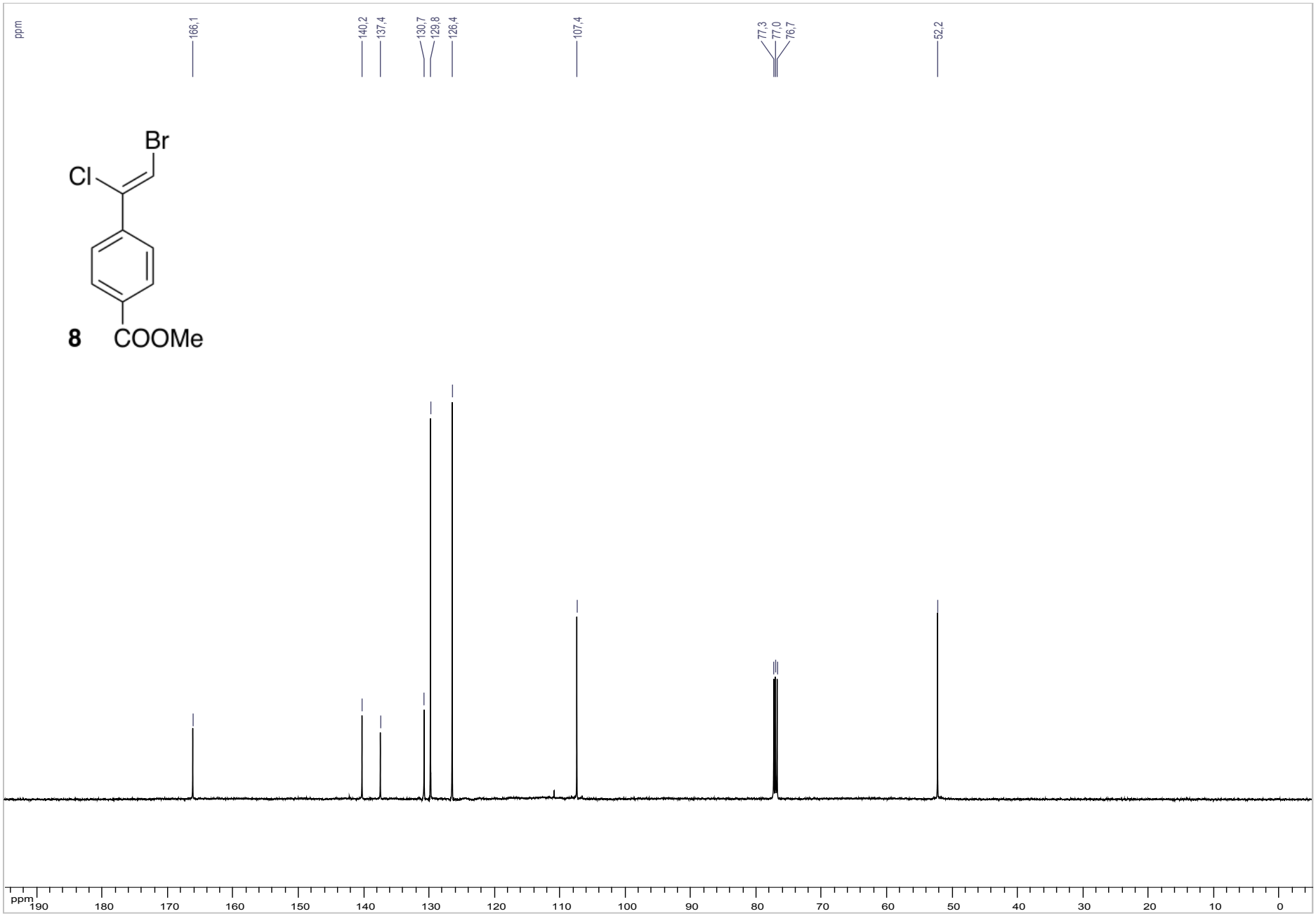
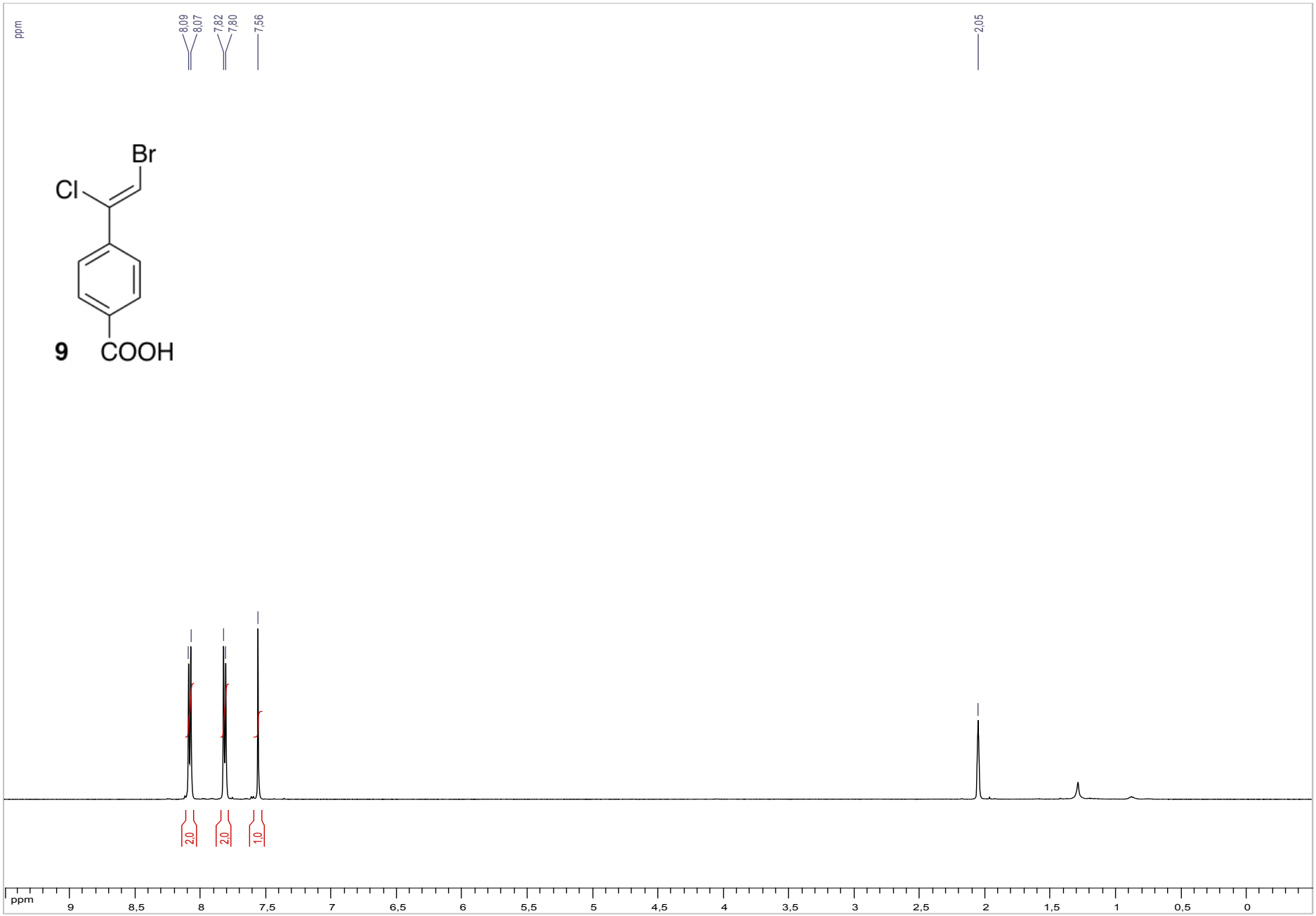
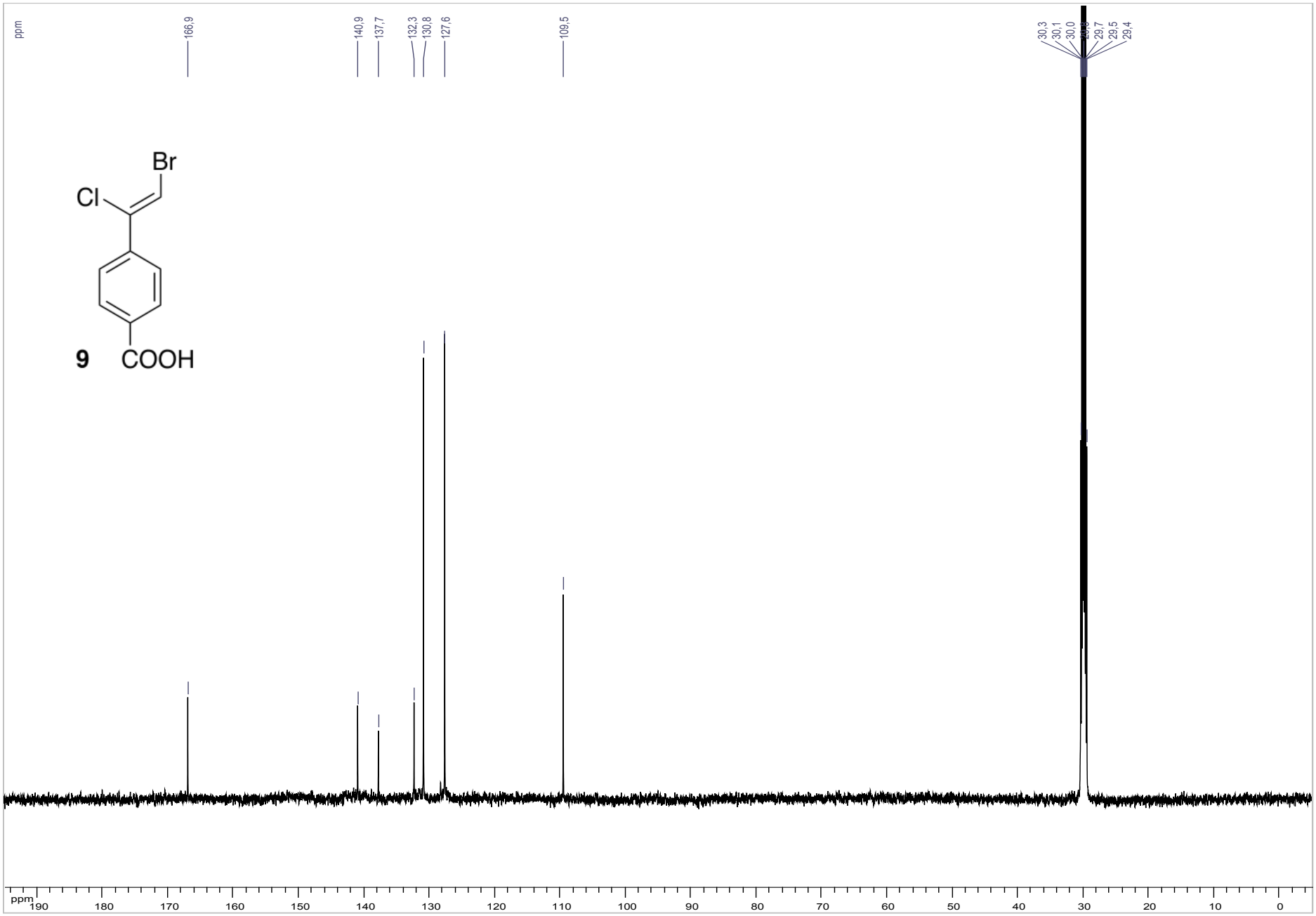


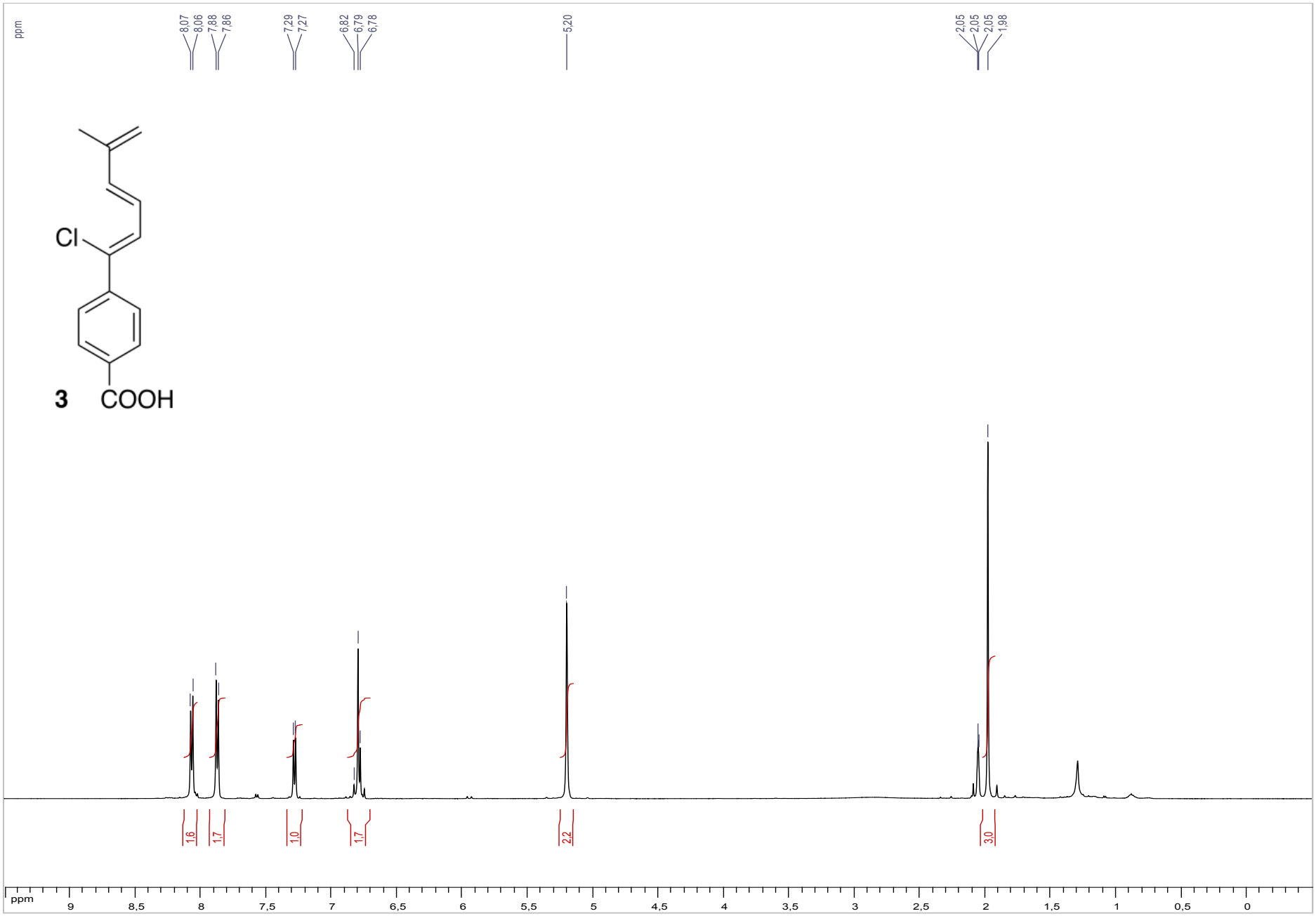
$^{1}$H NMR acetone-$d_6$ 500MHz



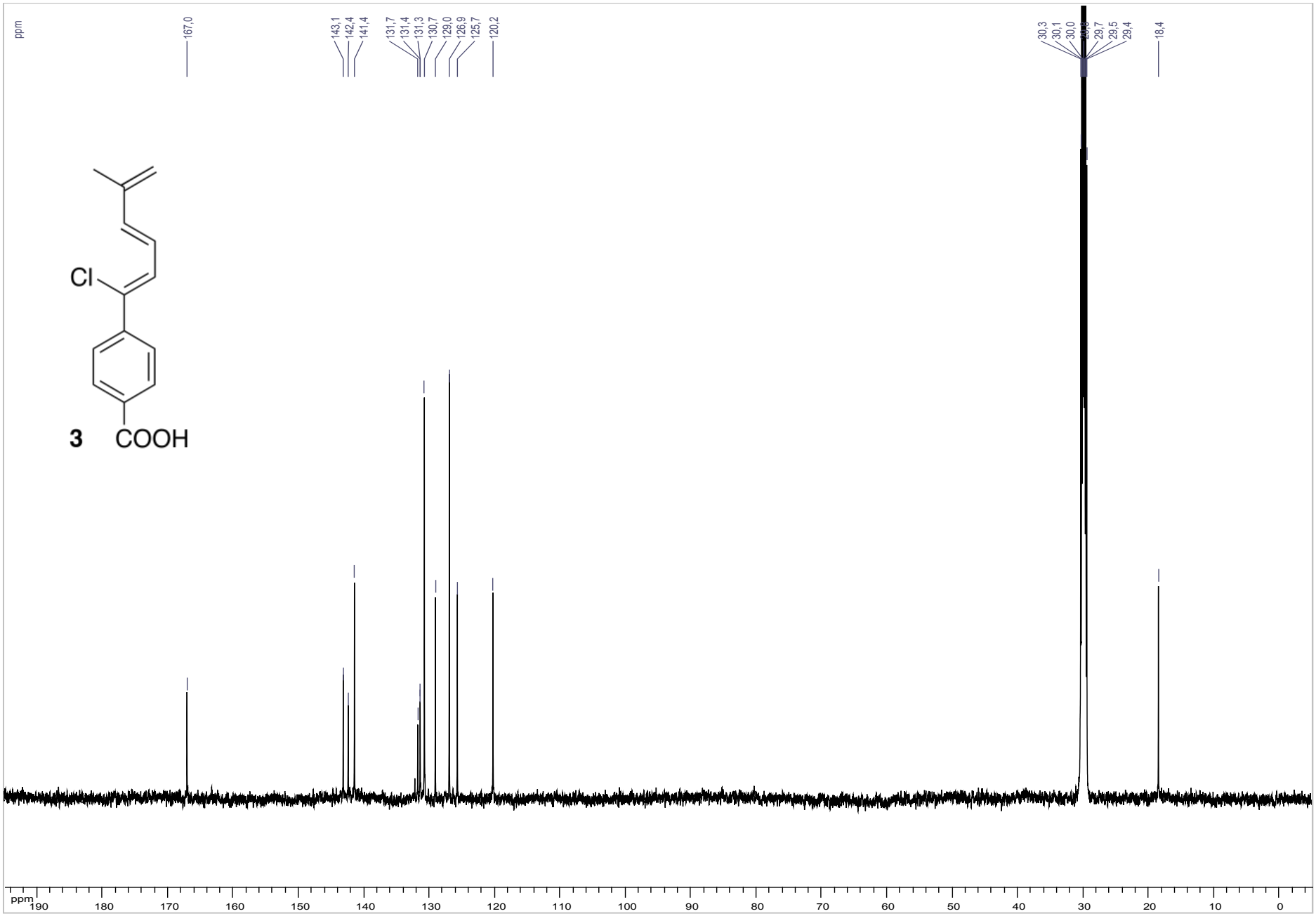
C NMR acetone-$a_6$ 125MHz



H NMR acetone-$a_6$ 500MHz



$^{13}$C NMR acetone-$d_6$ 125MHz



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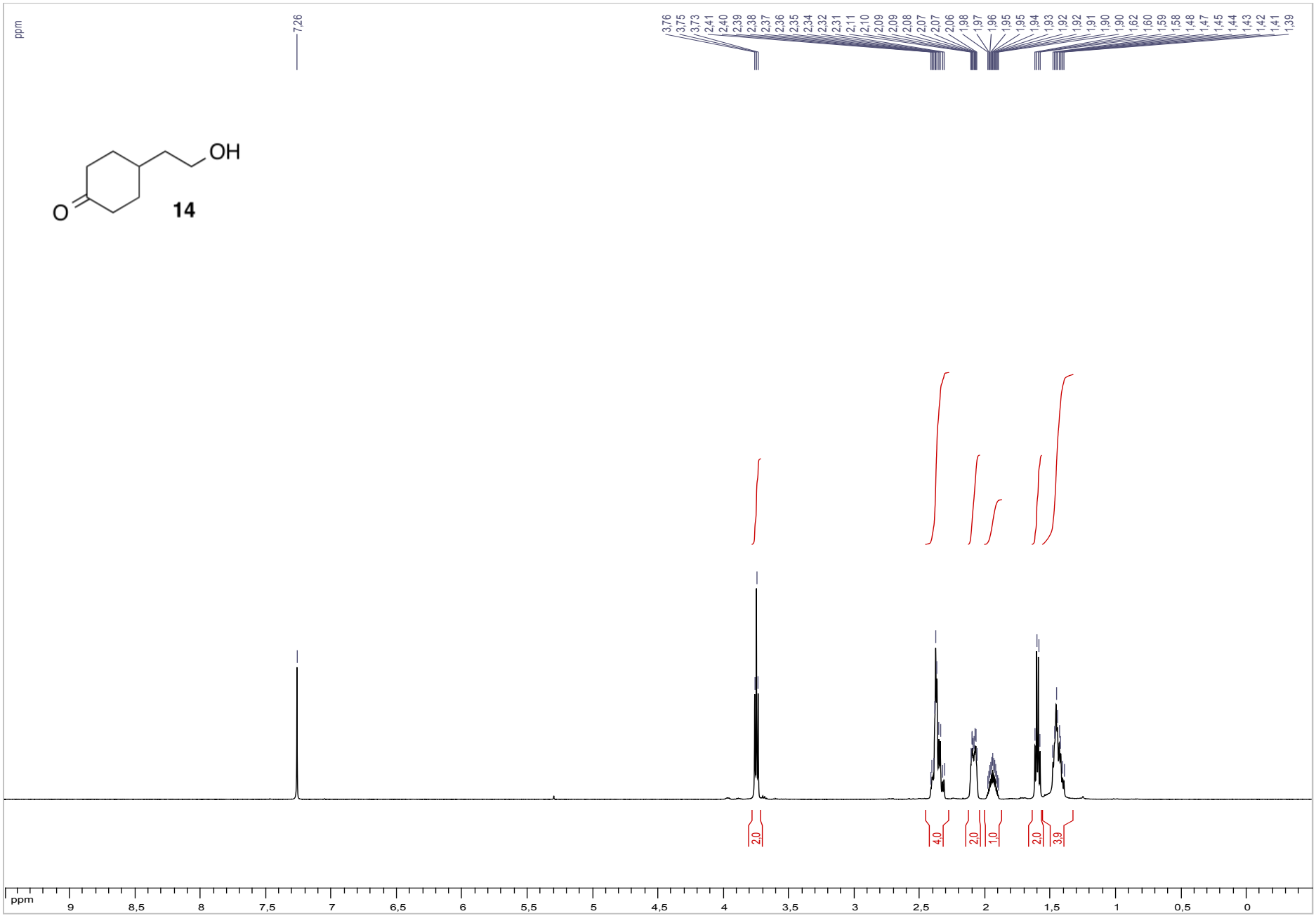

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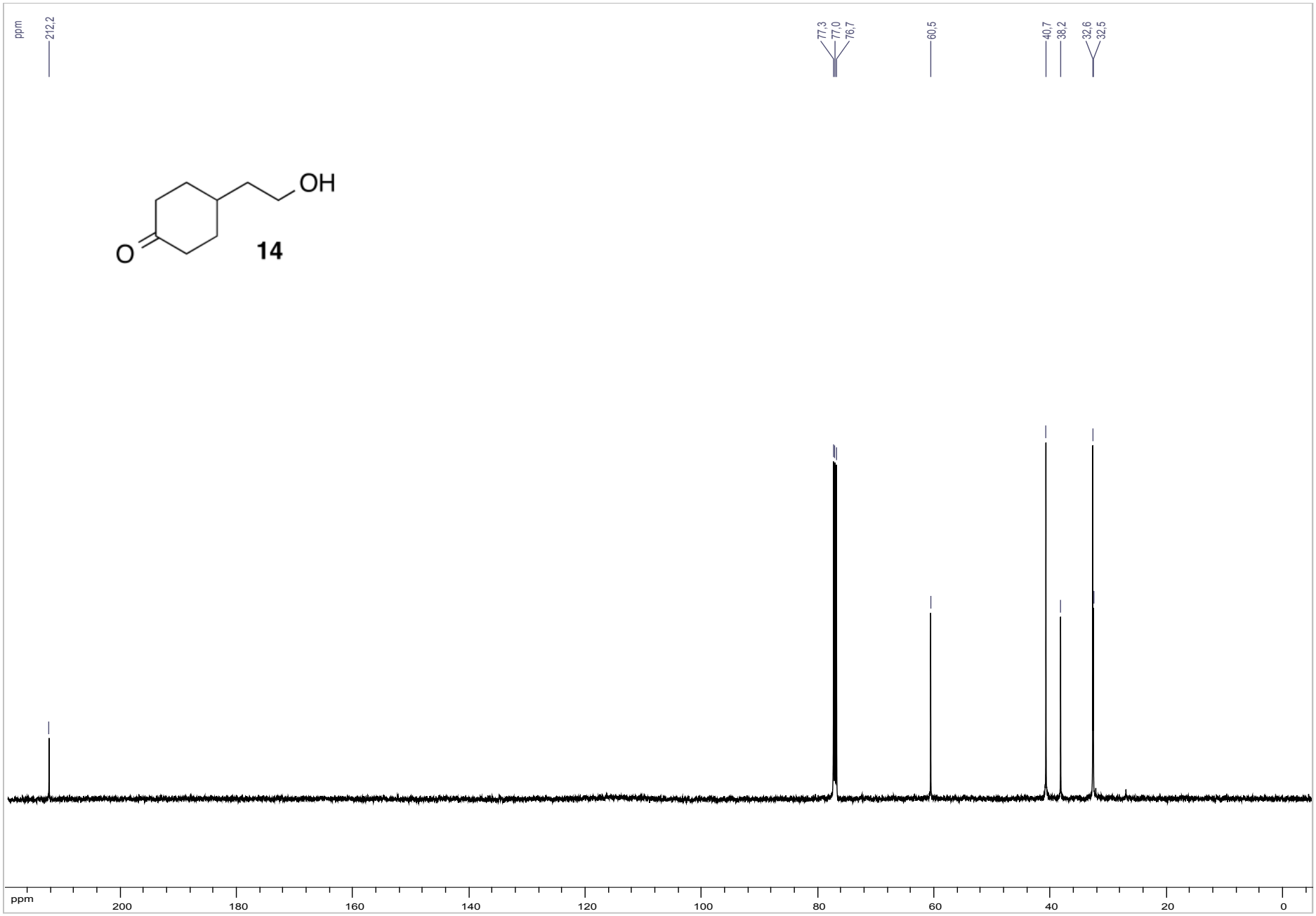
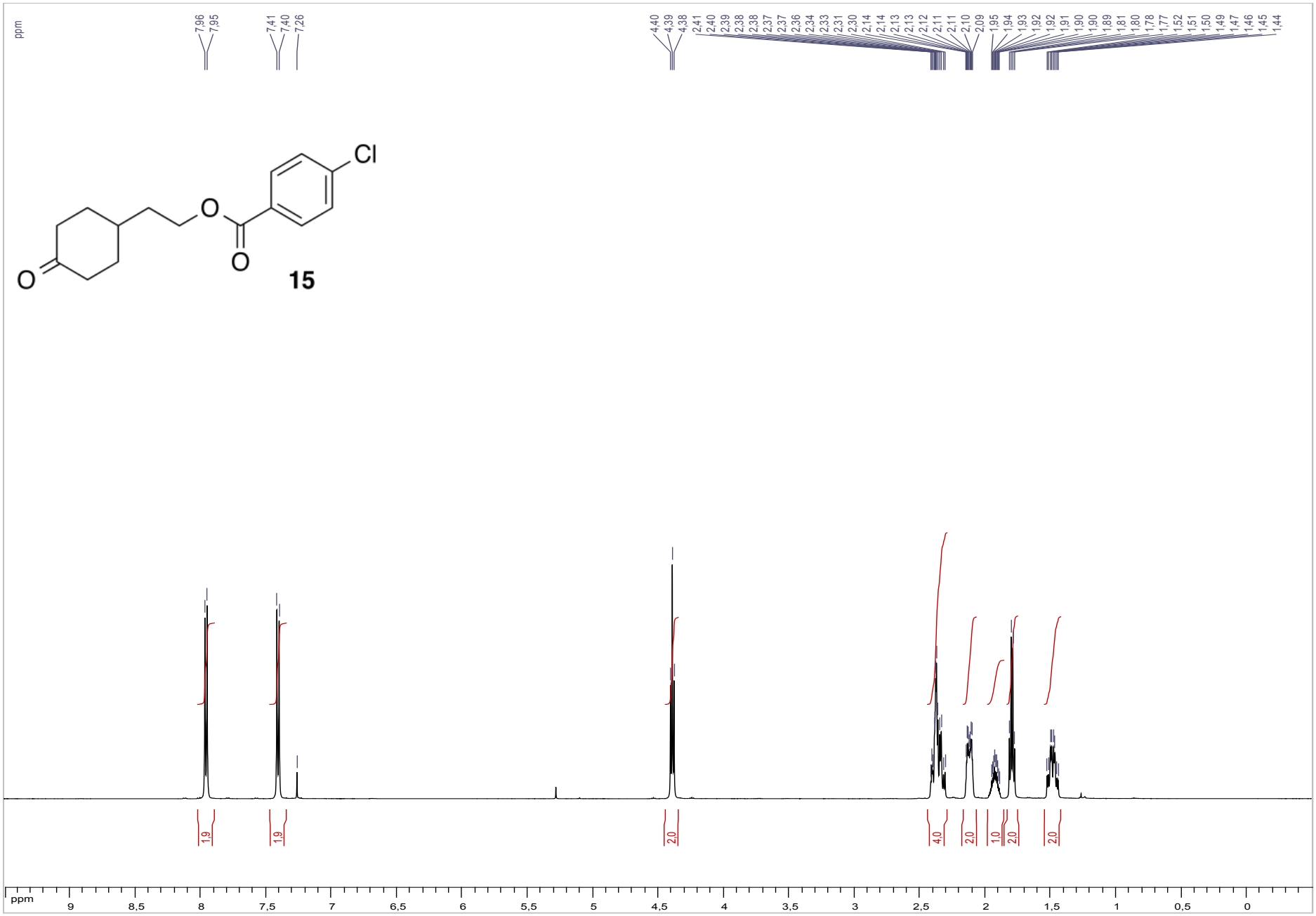


$^1$H NMR $CDCl_3$ 500MHz



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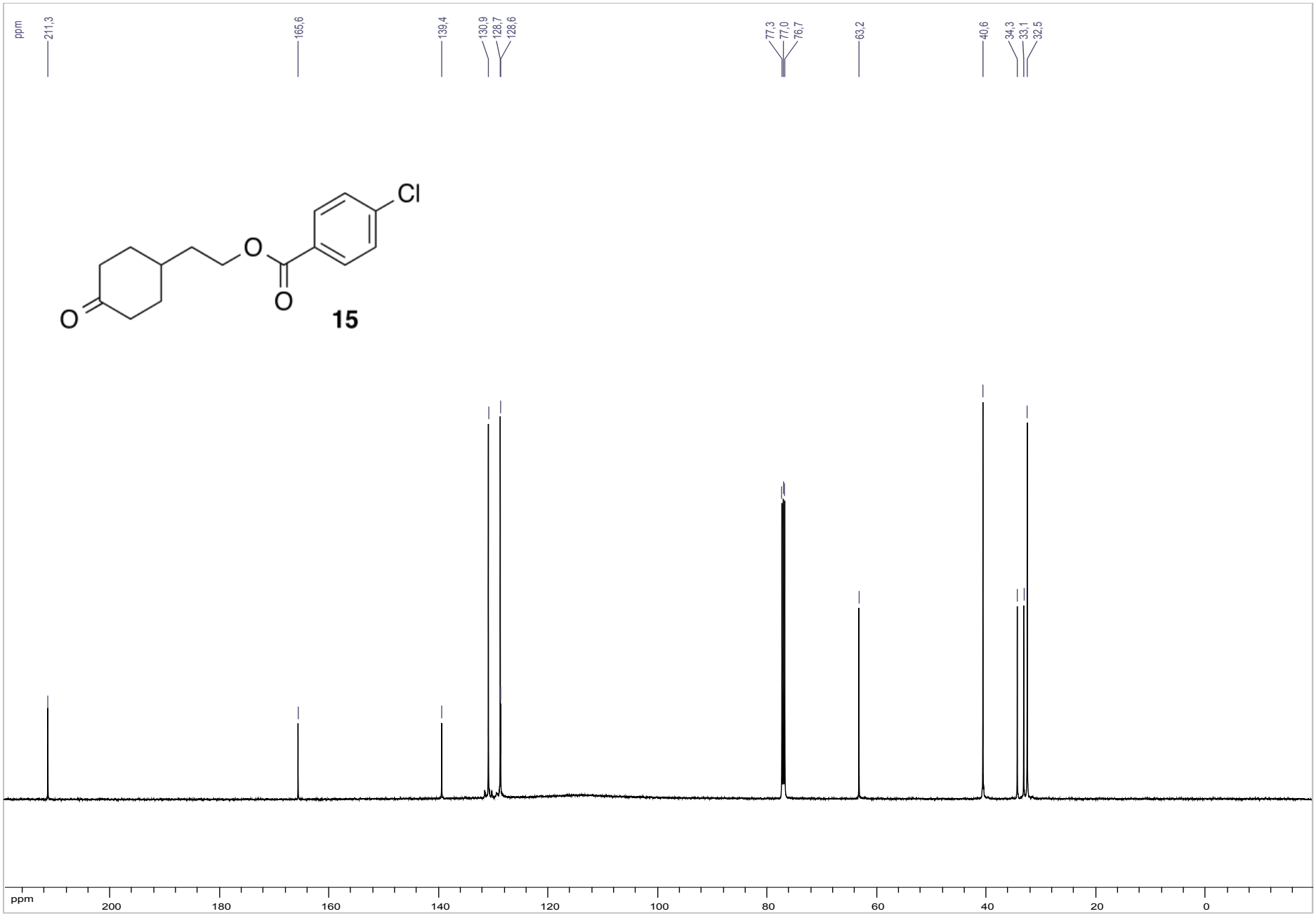

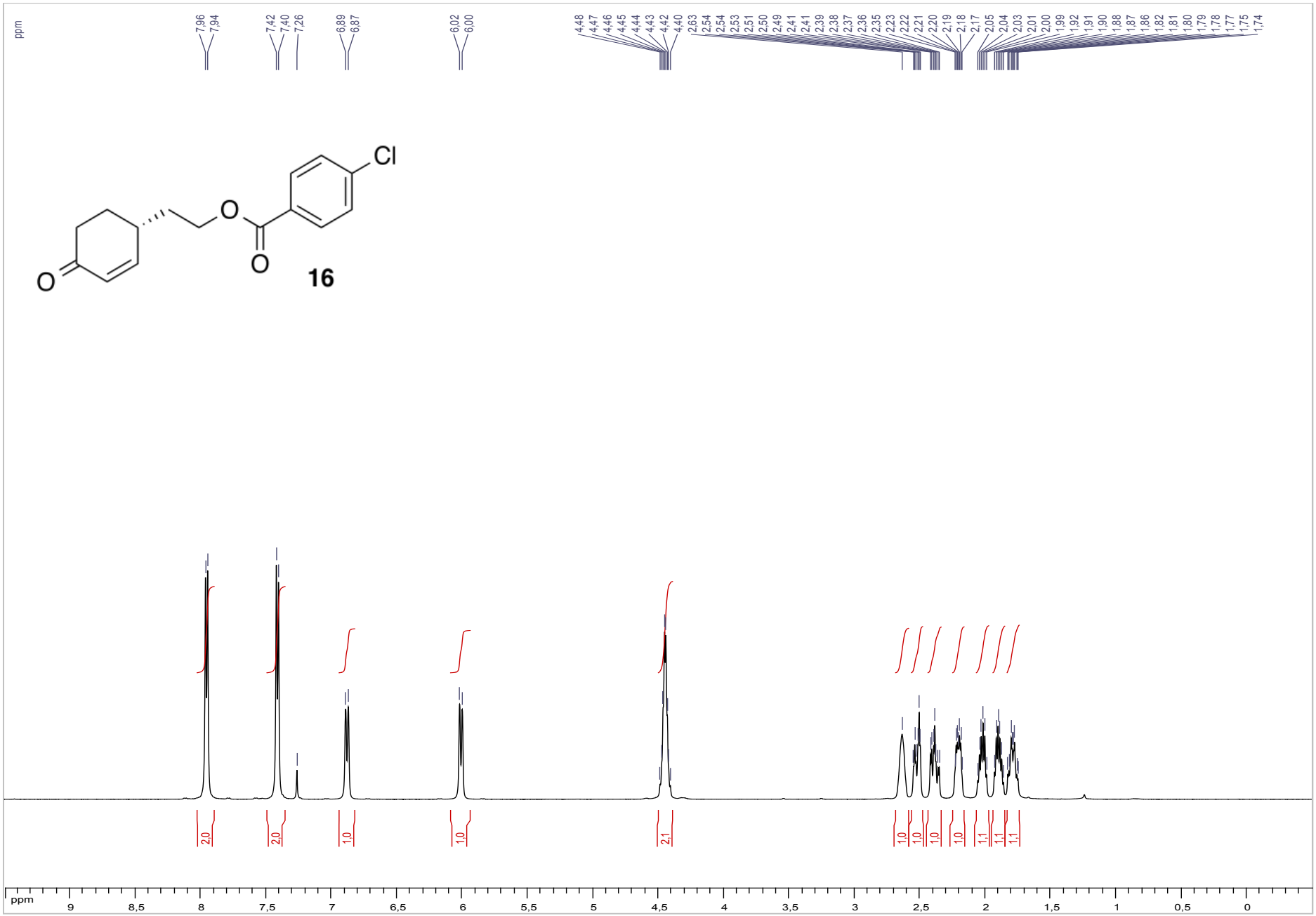
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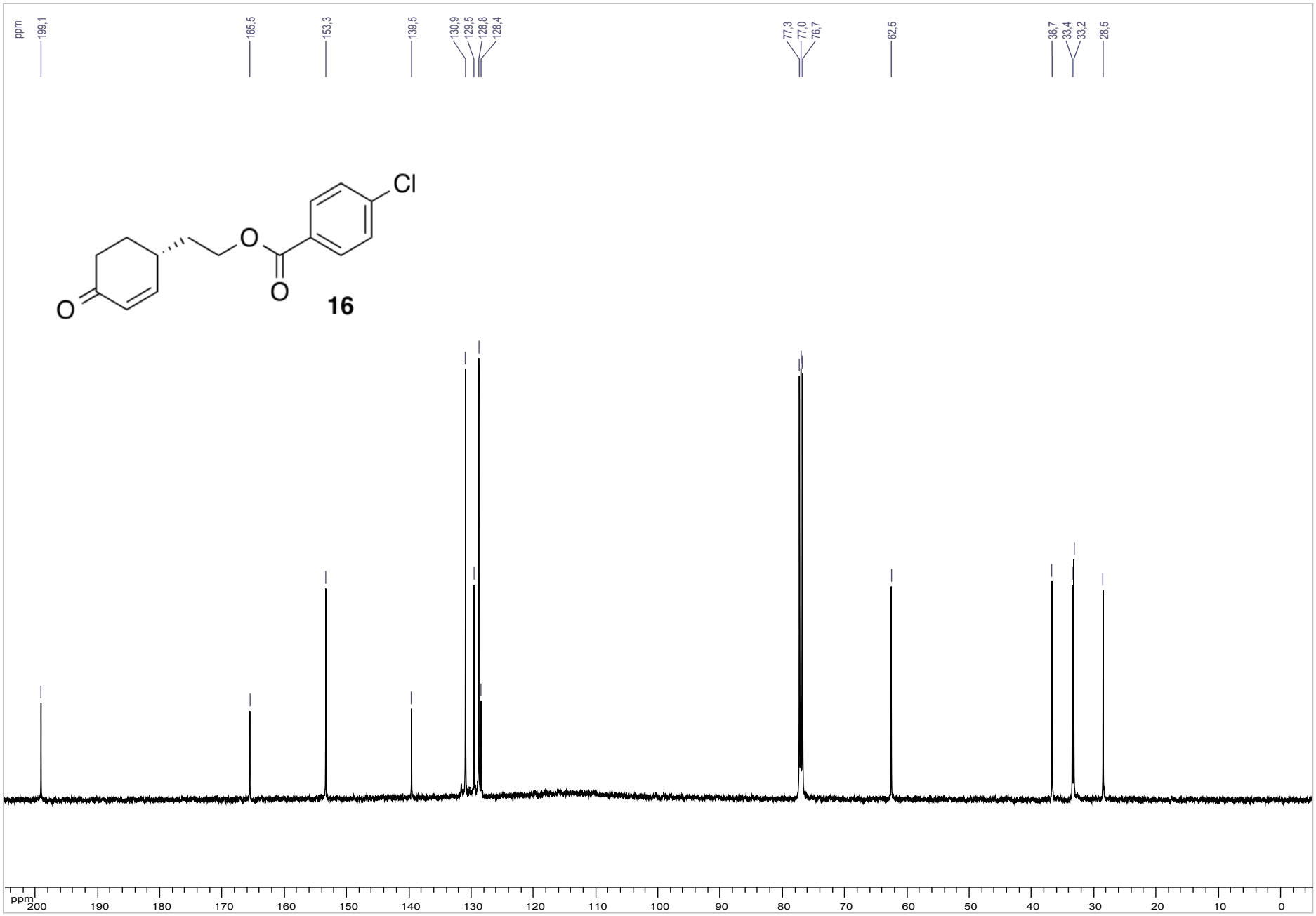
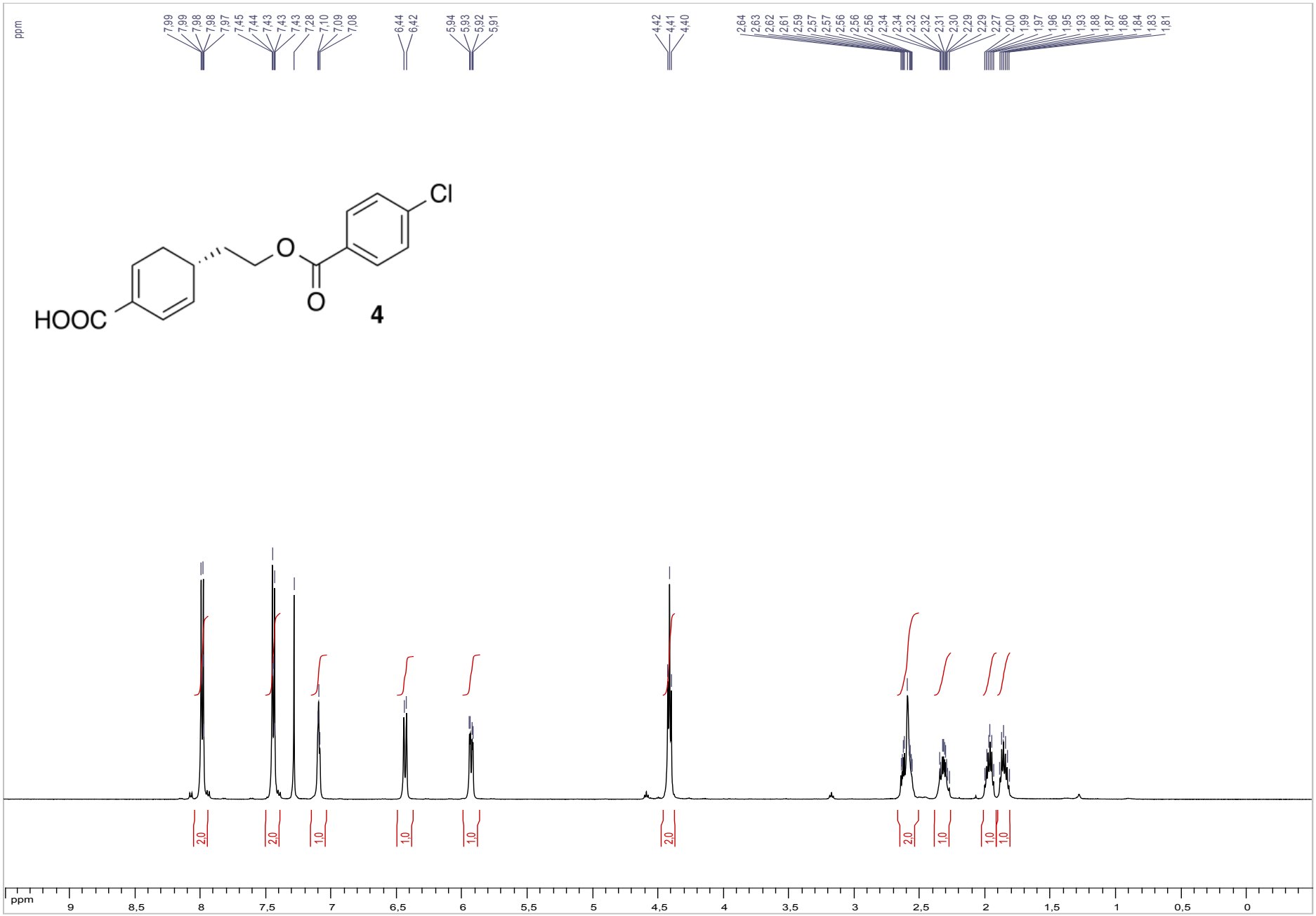
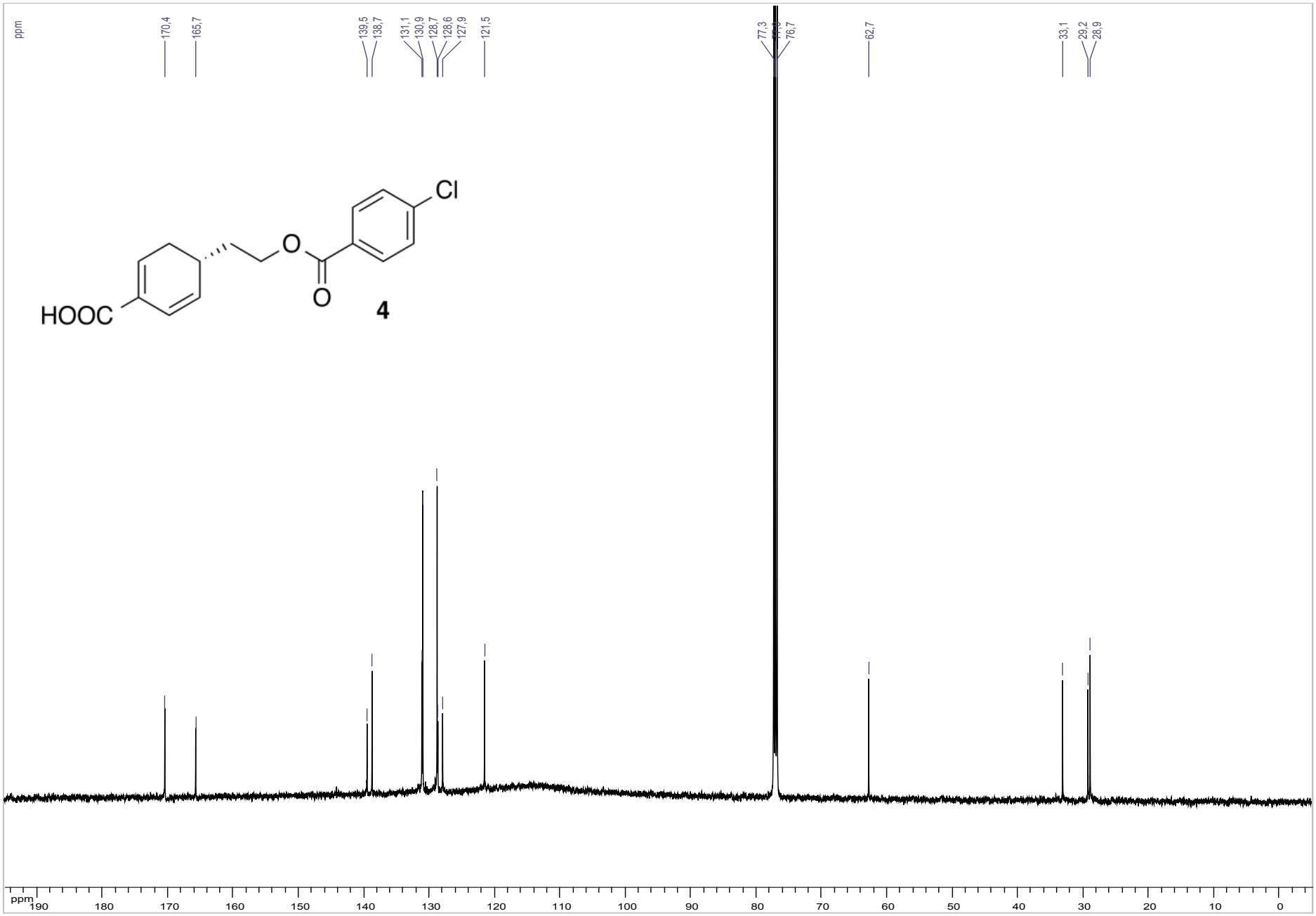
$^{13}C$ NMR $CDCl_3$ 125MHz



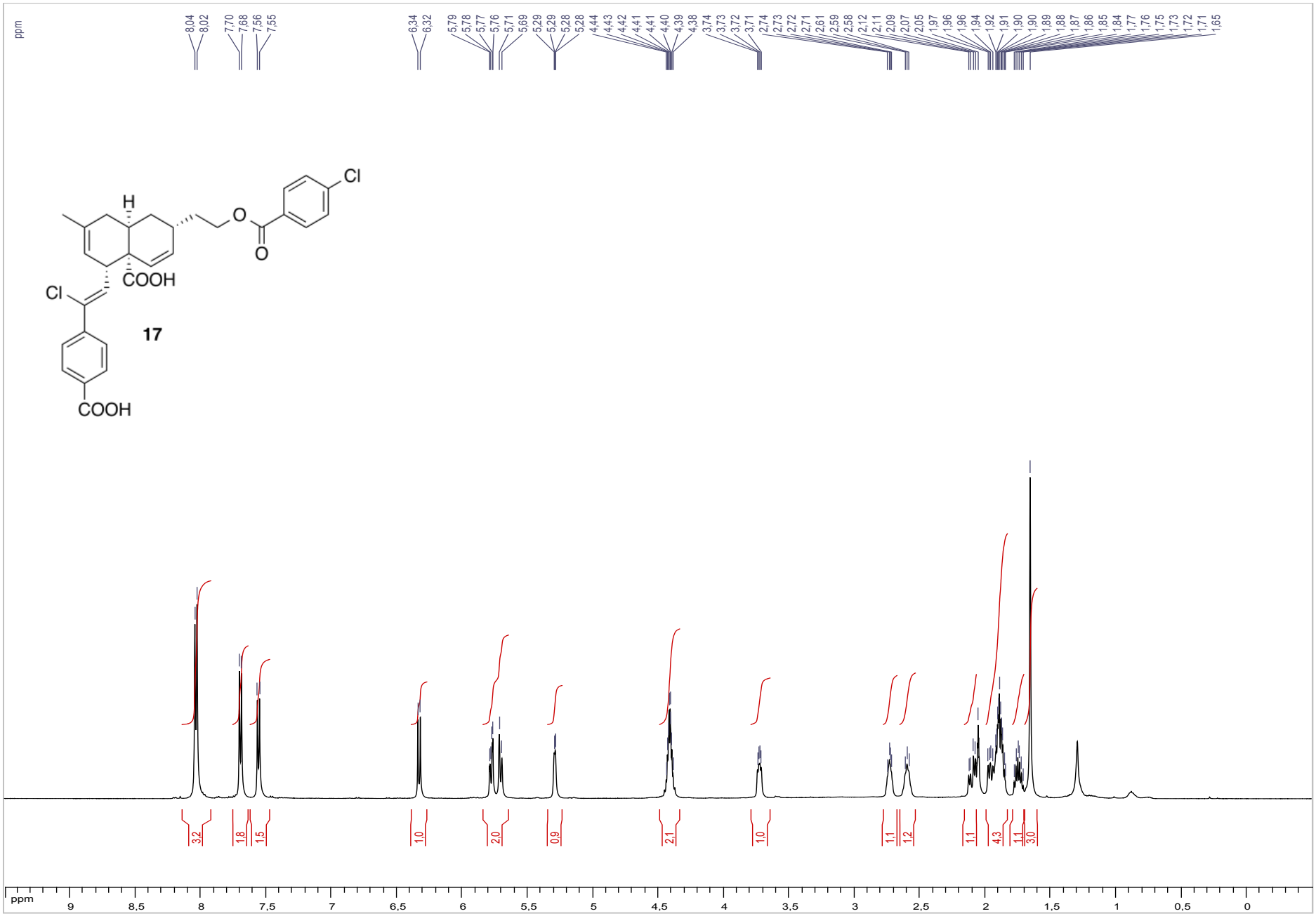
H NMR $CDCl_3$ 500MHz



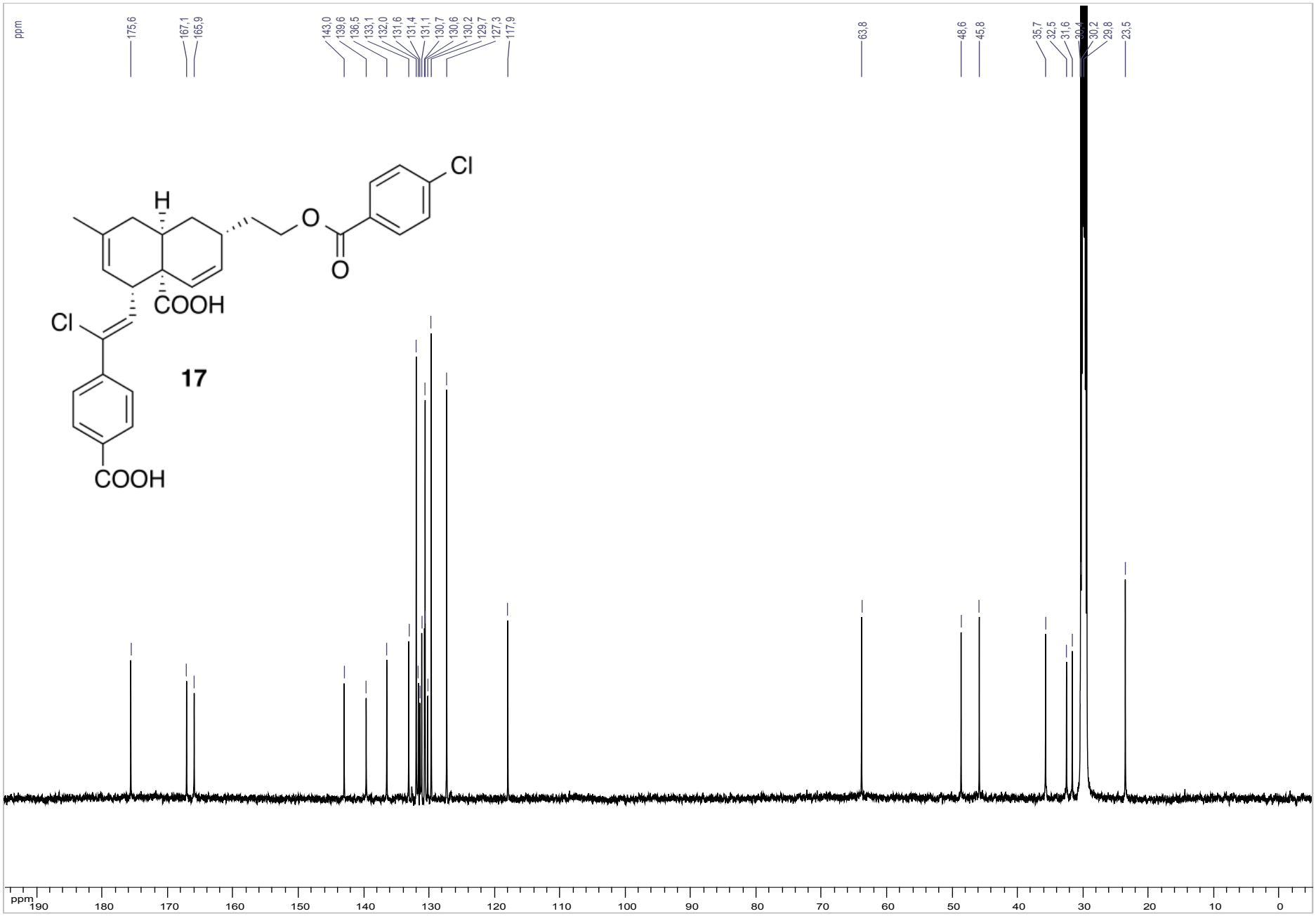
$^{13}C$ NMR $CDCl_3$ 125MHz



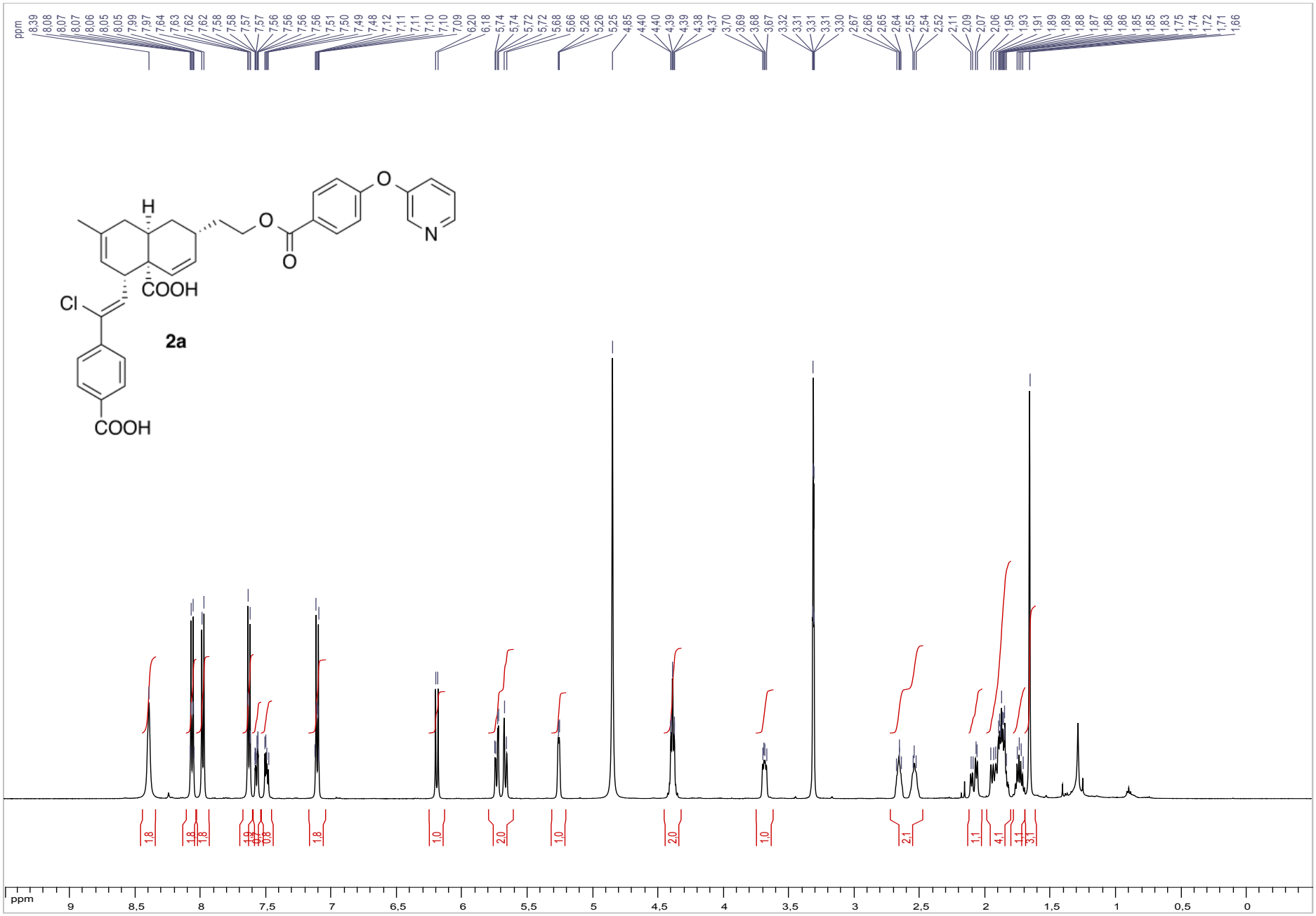
$^1$H NMR acetone-$d_6$ 500MHz



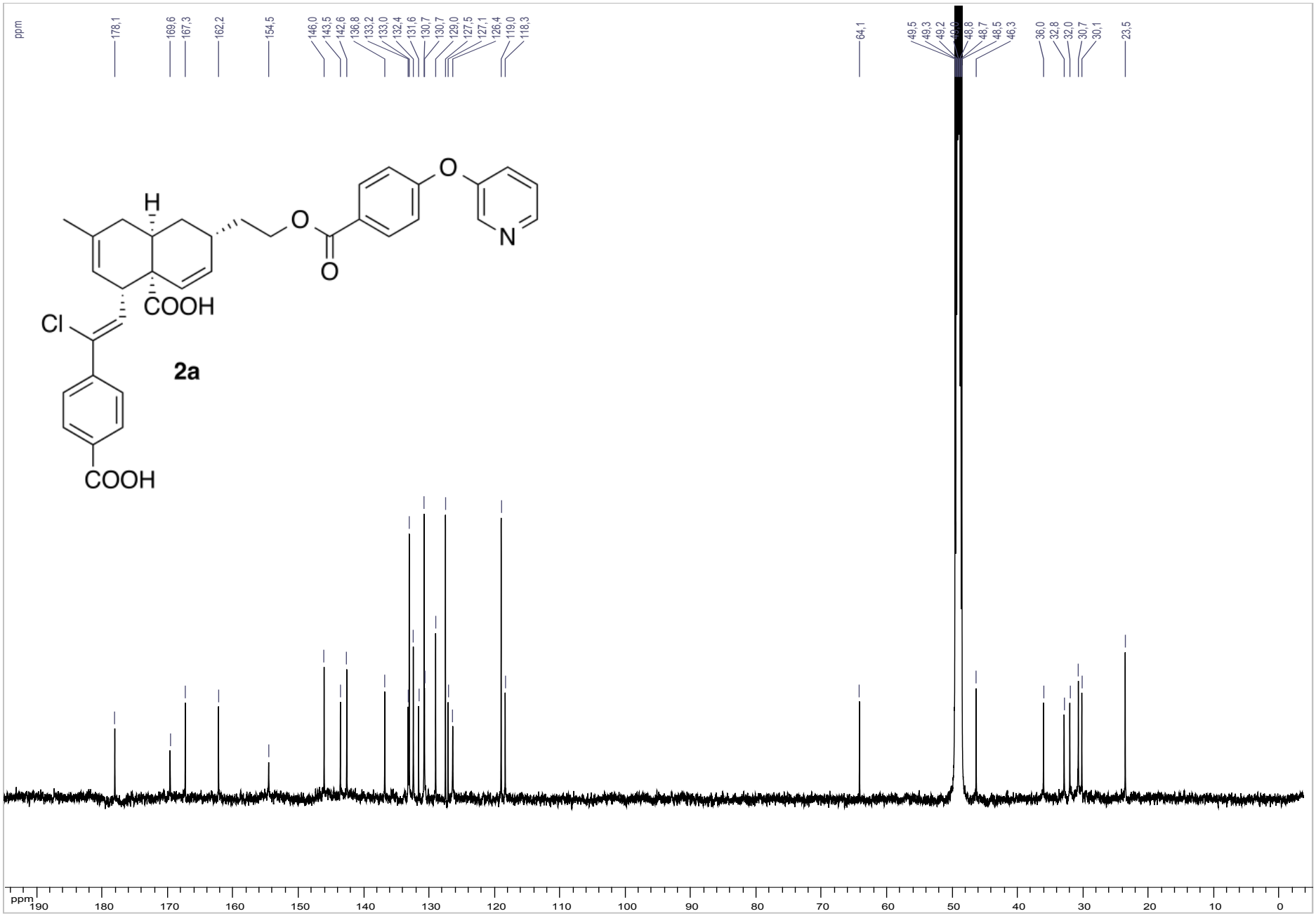
$^{13}$C NMR acetone-$d_6$ 125MHz



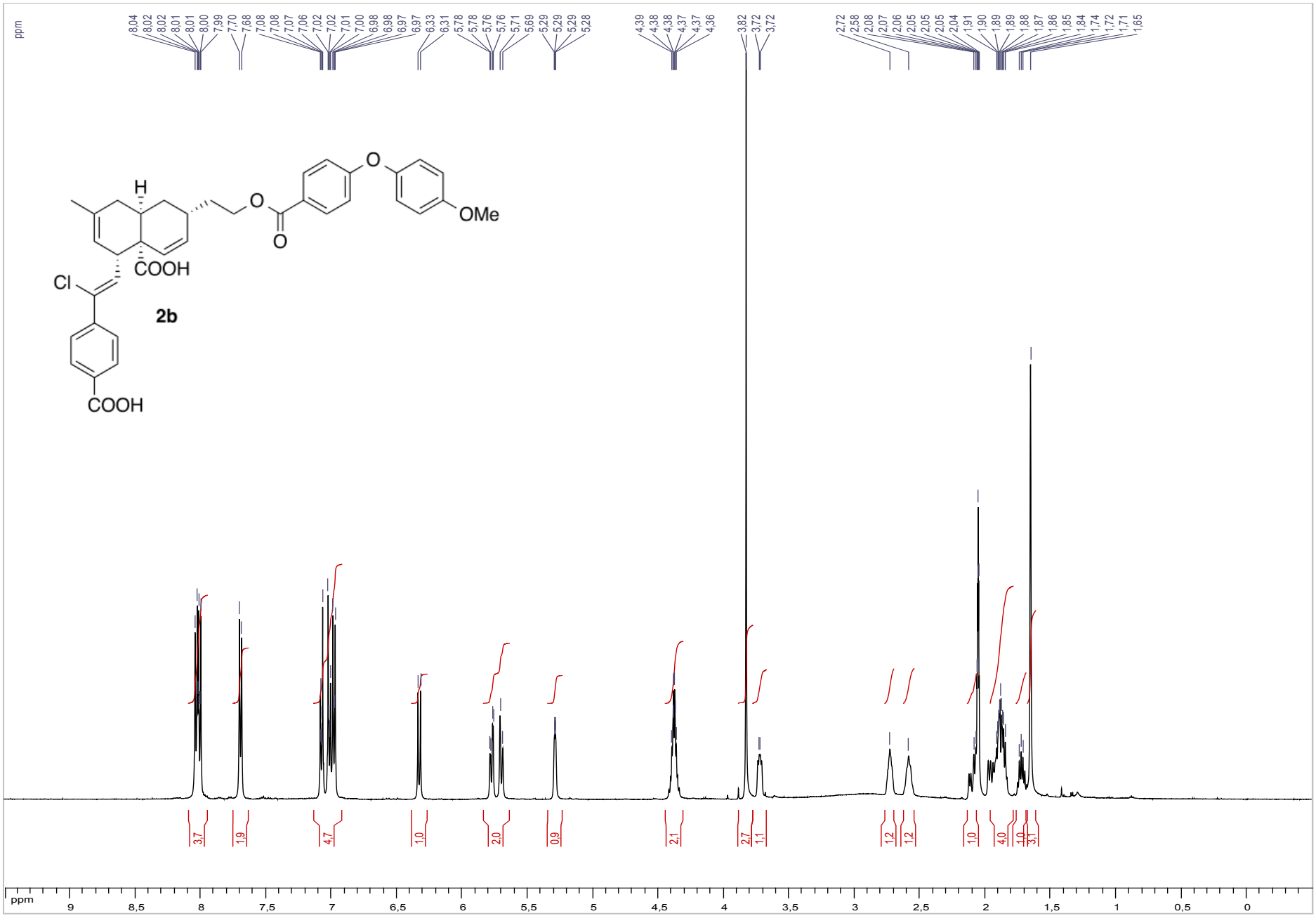
H NMR $CD_3OD$ 125MHz



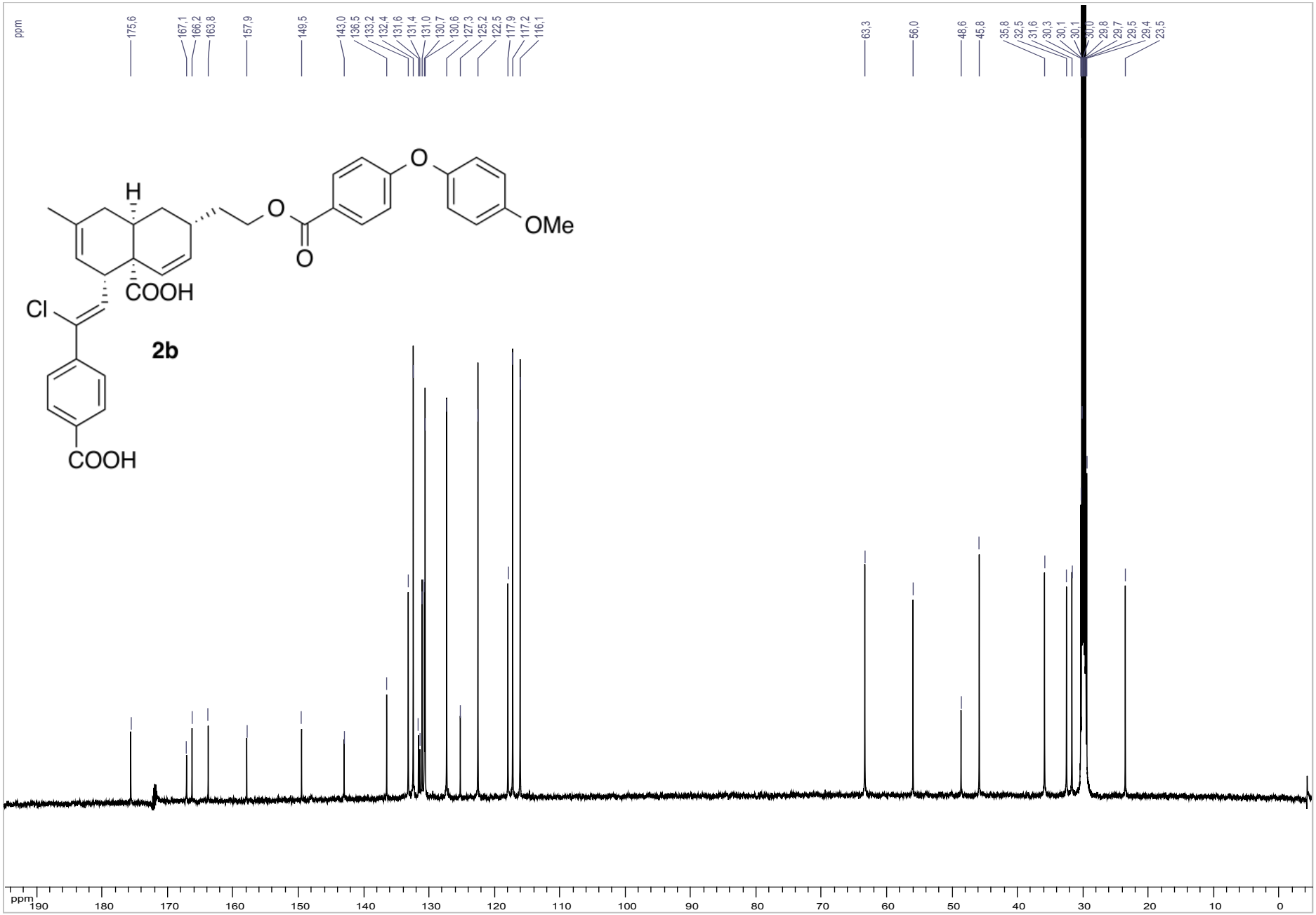
$^{13}$C NMR $CD_3OD$ 125MHz



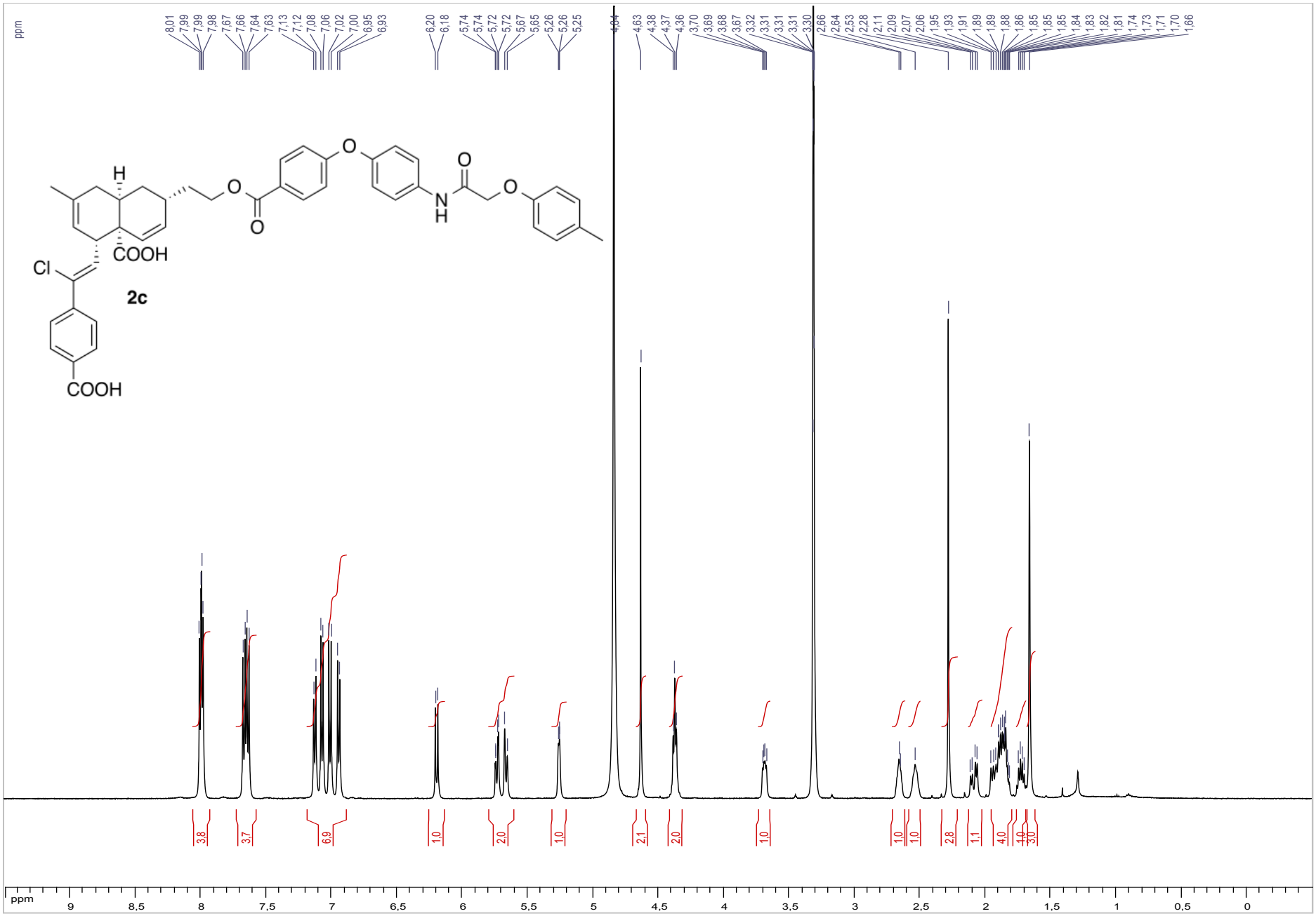
H NMR acetone-$d_6$ 500MHz



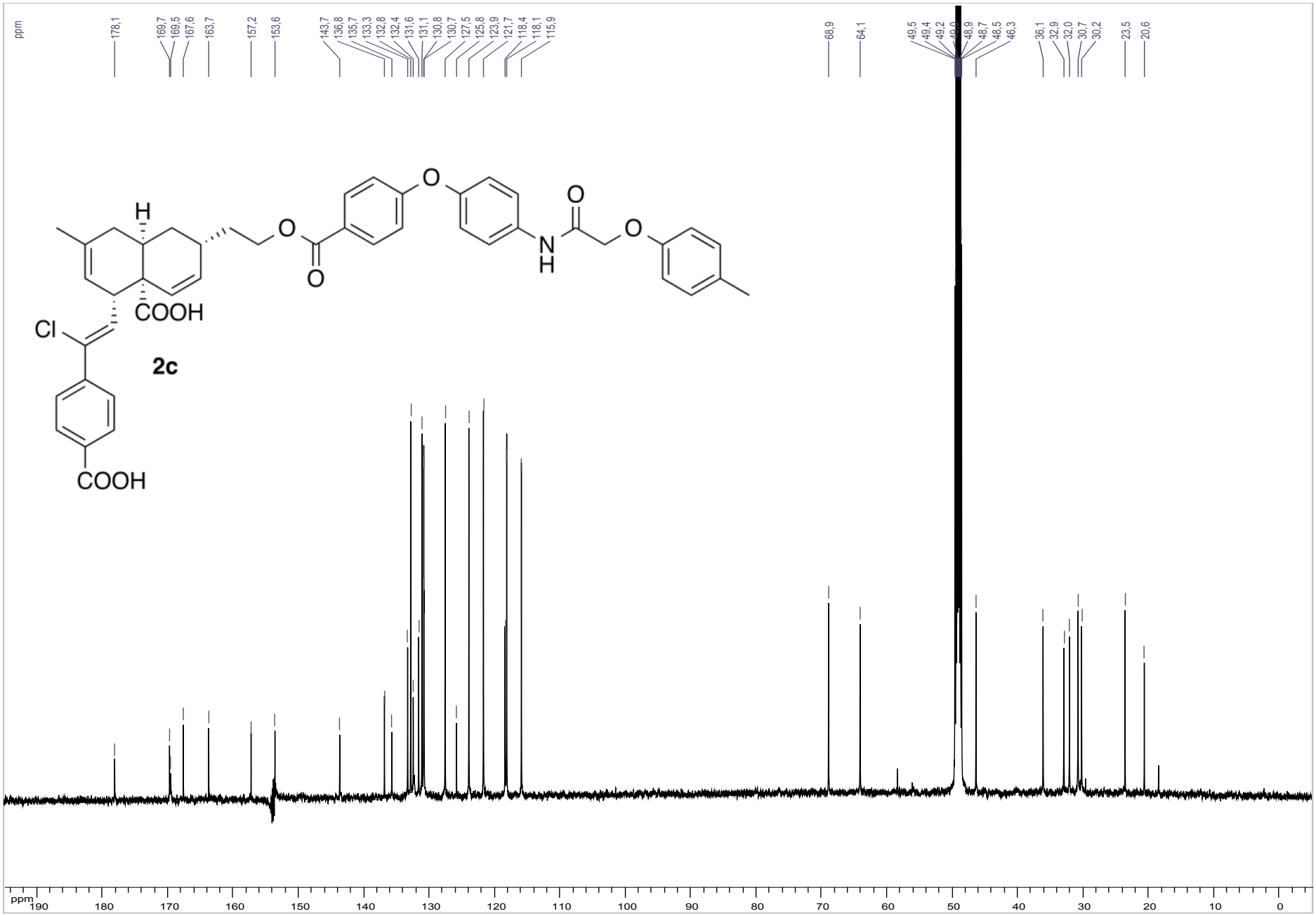
$^{13}$C NMR acetone-$d_6$ 125MHz



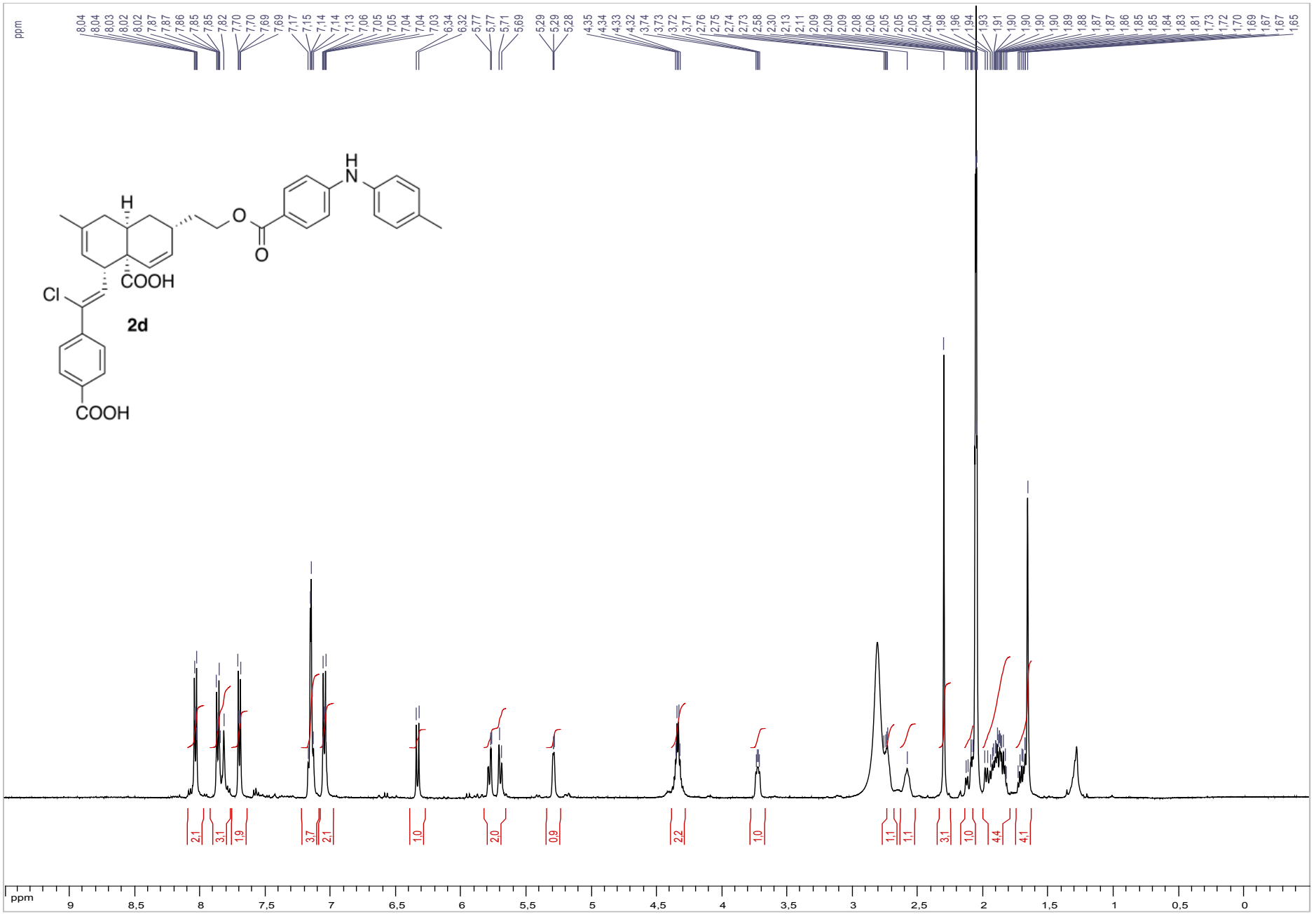
H NMR $CD_3OD$ 125MHz



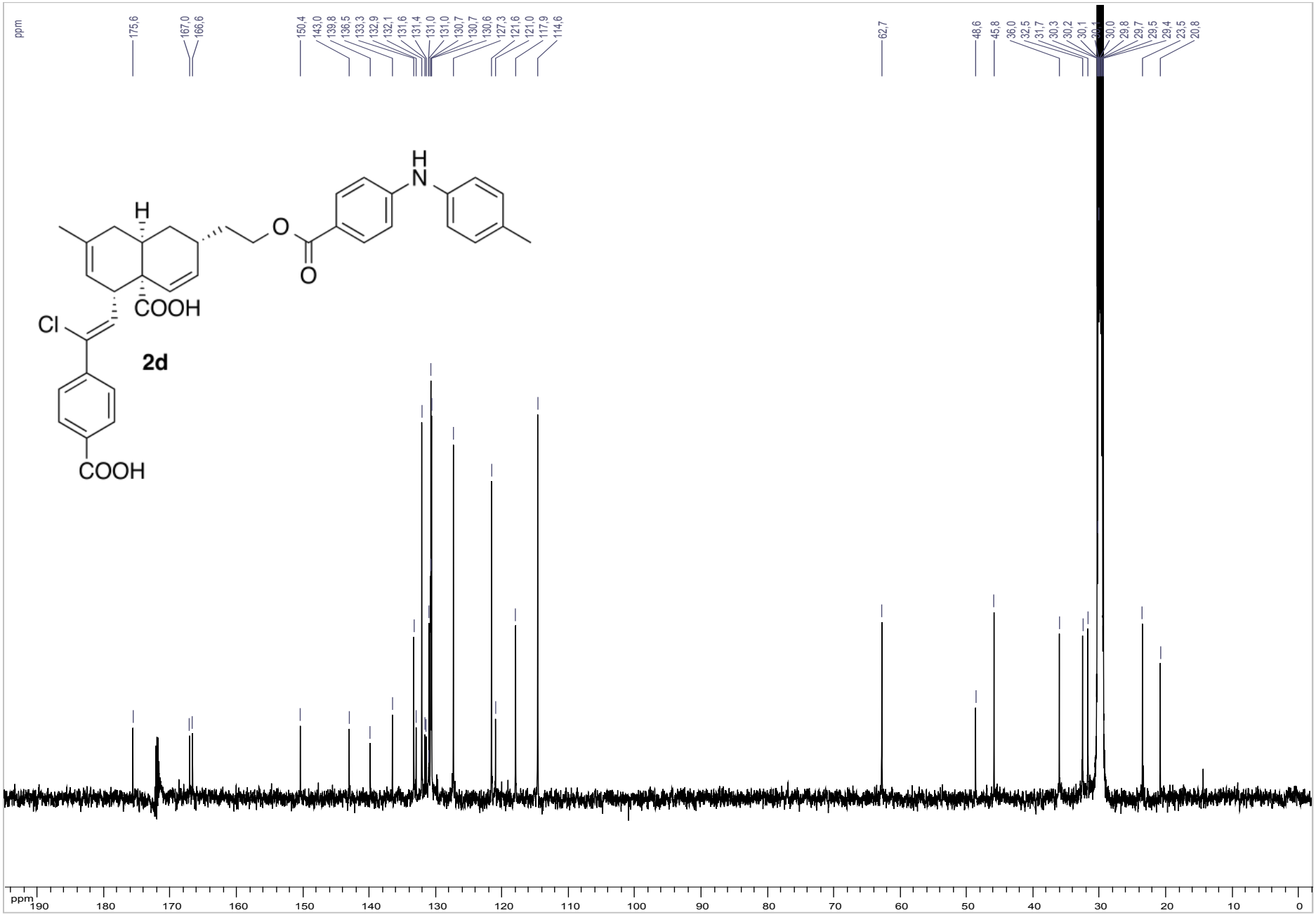
$^{13}$C NMR $CD_3OD$ 125MHz



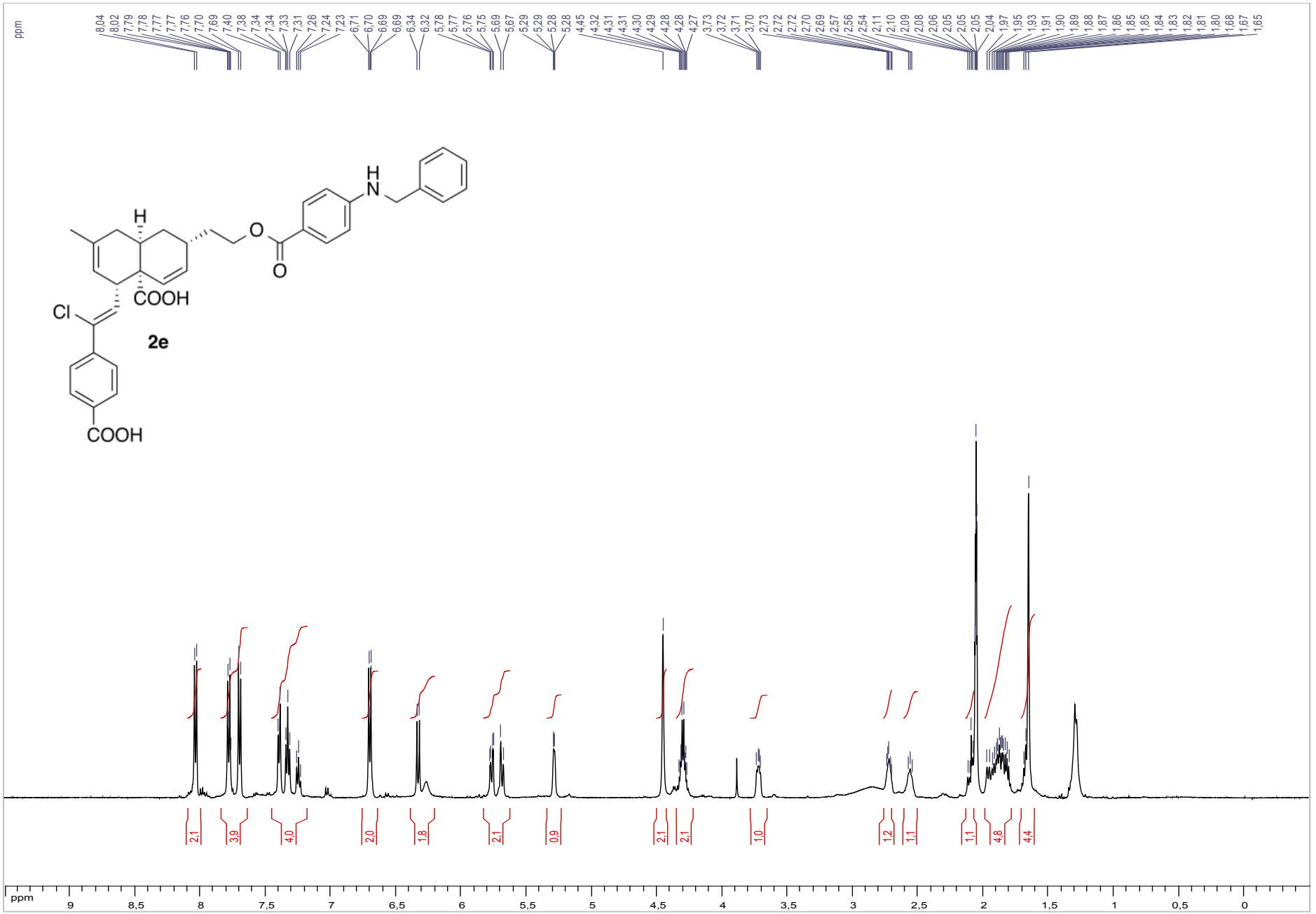
H NMR acetone-$a_6$ 500MHz



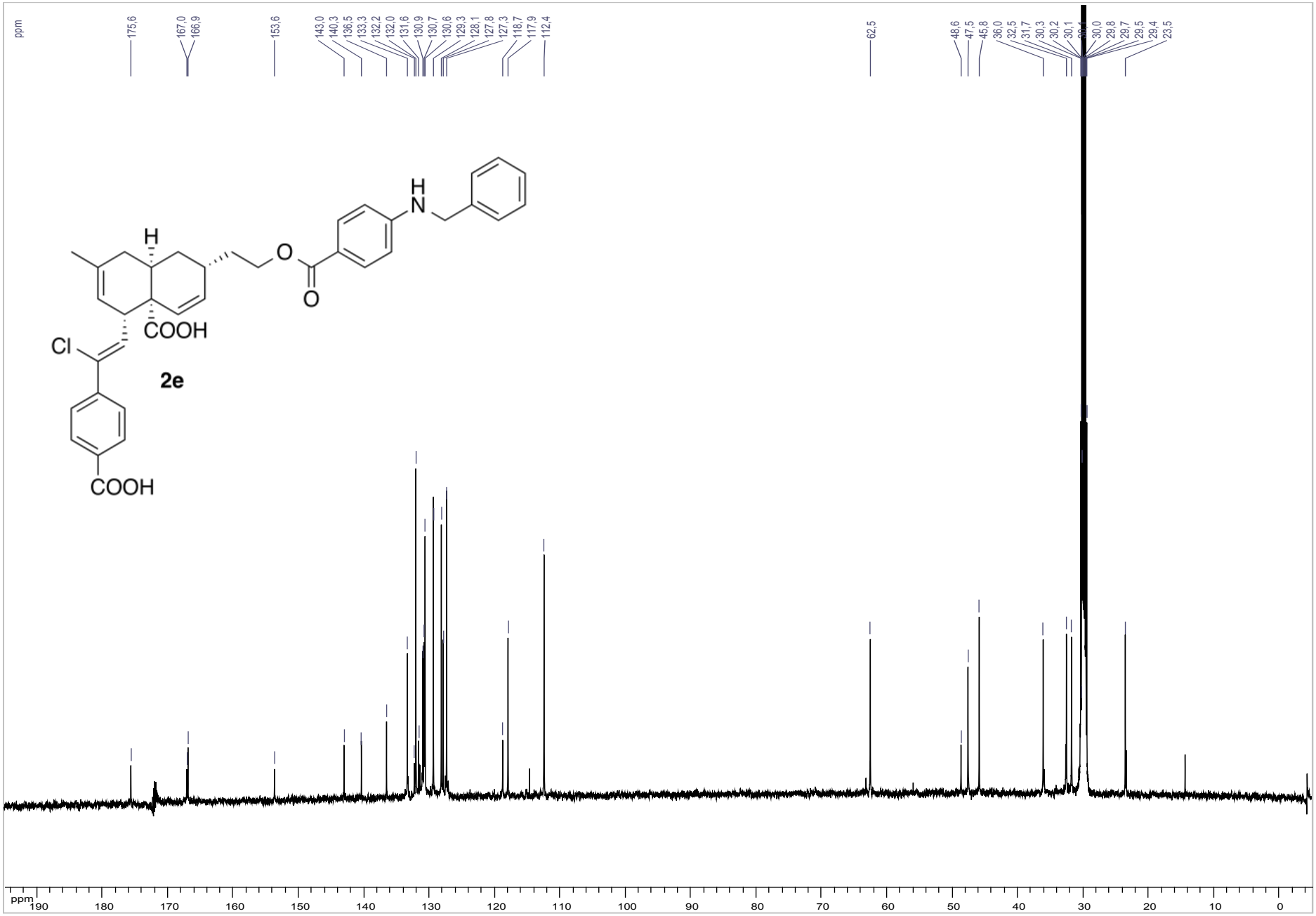
$^{13}$C NMR acetone-$d_6$ 125MHz



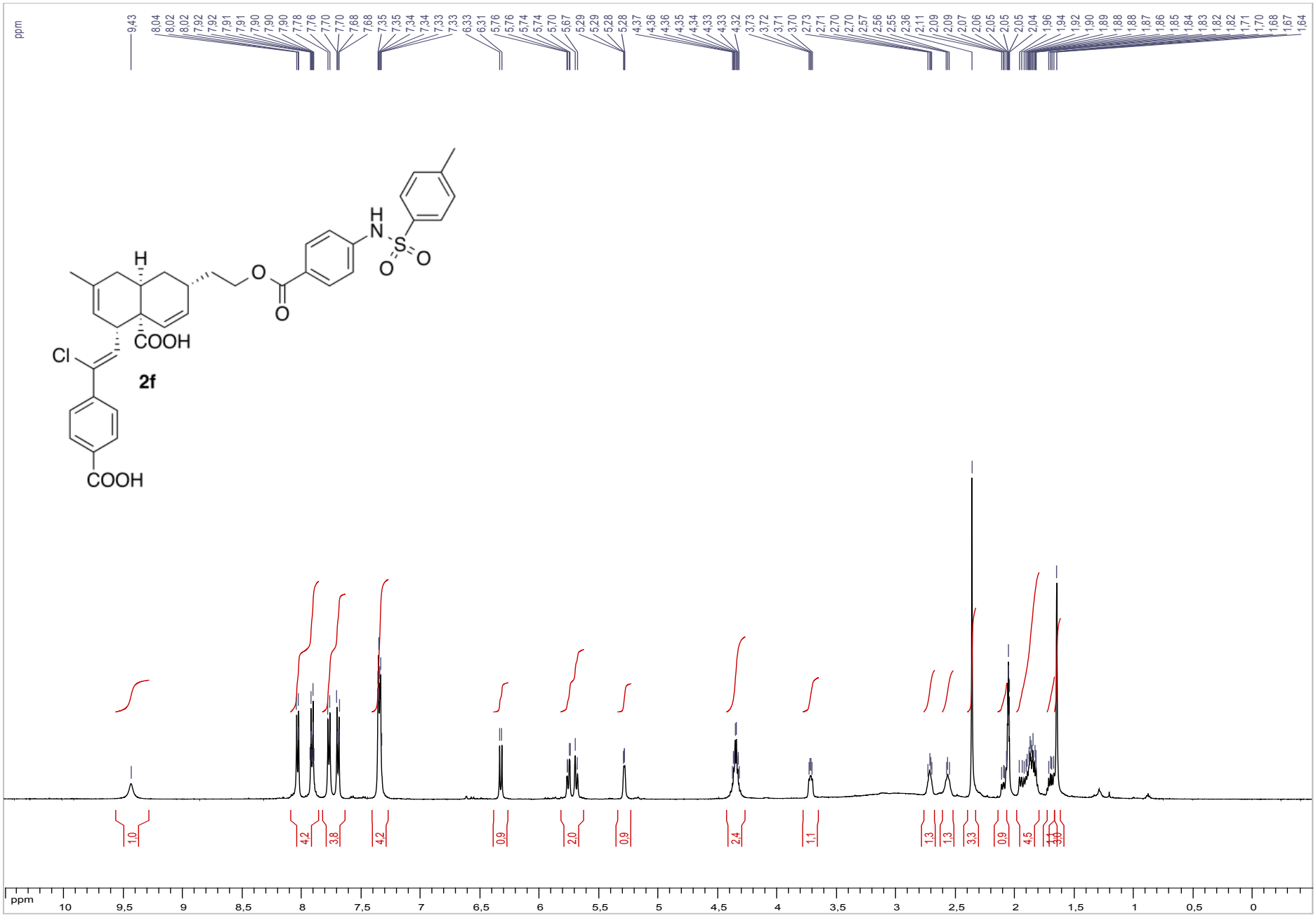
H NMR acetone-$d_6$ 500MHz



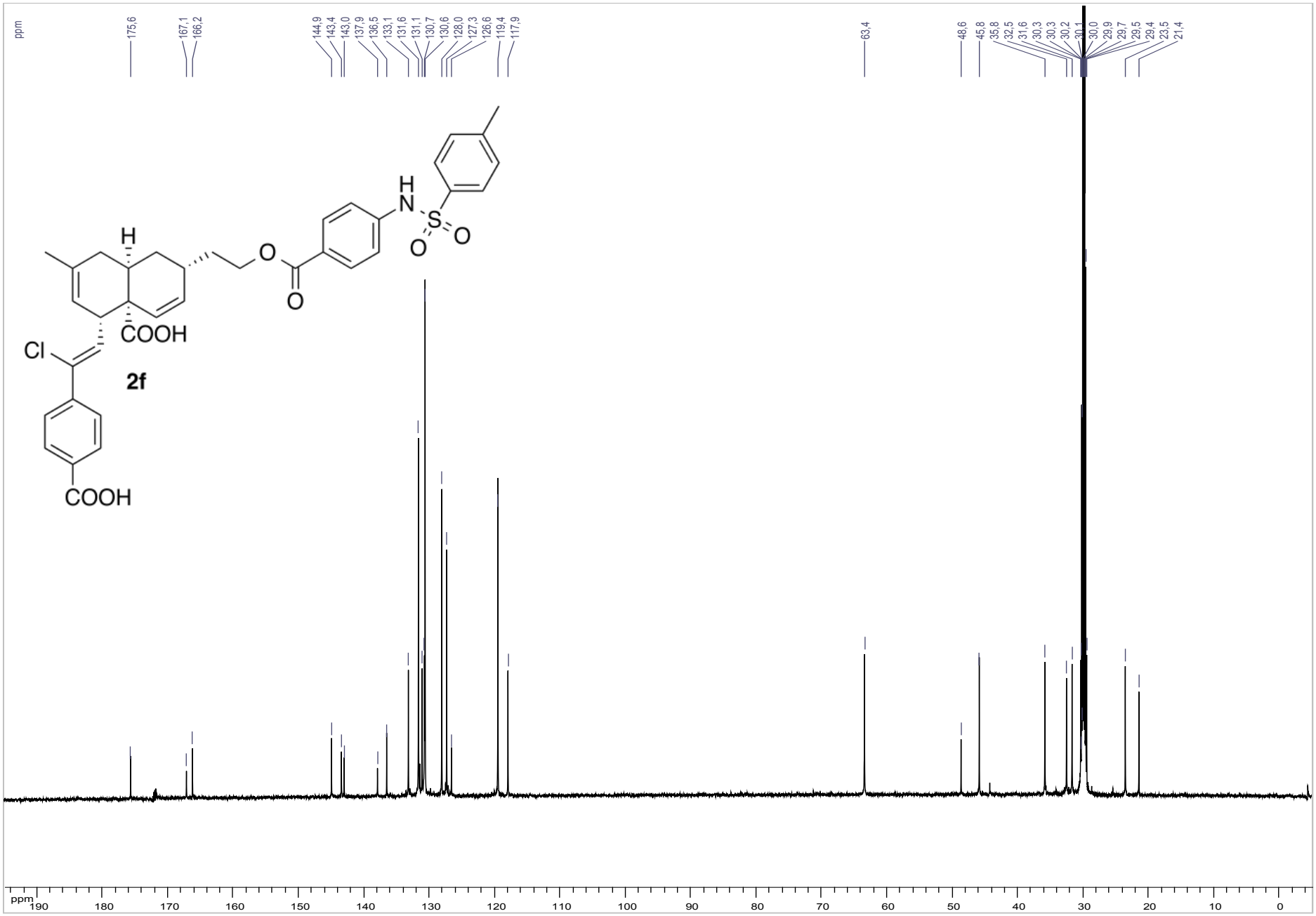
$^{13}$C NMR acetone-$d_6$ 125MHz



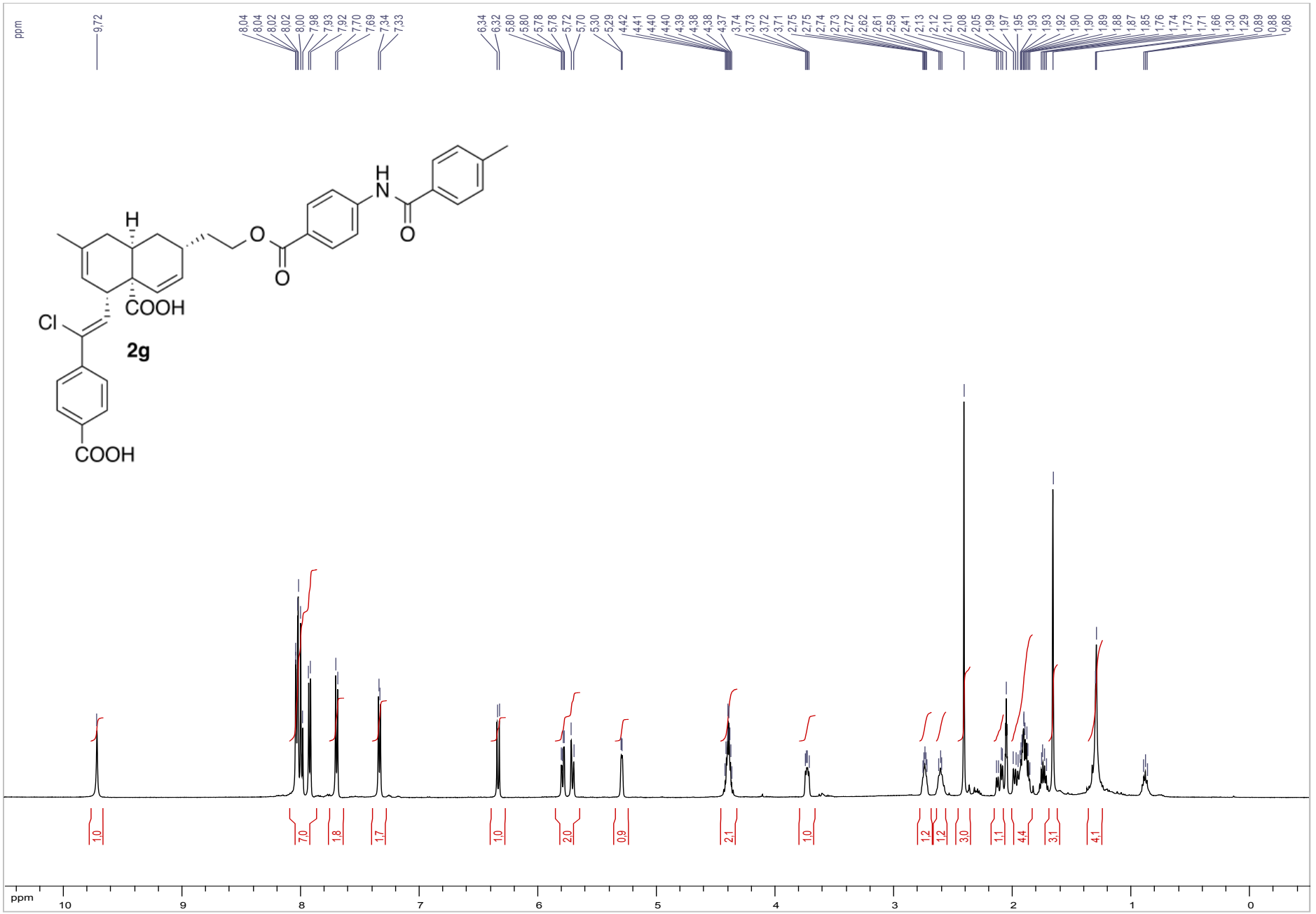
H NMR acetone-$d_6$ 500MHz



C NMR acetone-$a_6$ 125MHz



H NMR acetone-$d_6$ 500MHz



$^{13}$C NMR acetone-$d_6$ 125MHz