Phenotype-directed discovery of diverse, biologically-relevant molecular scaffolds

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1. General Experimental

Commercially available starting materials were obtained from SigmaAldrich, Fluorochem, Acros, Apollo Scientific, Alfa Aesar and Strem. Anhydrous acetonitrile was purchased from Acros. All solvents used in purification were of chromatography or analytical grade. Thin layer chromatography (TLC) was performed using aluminium backed silica (Merck silica gel 60 F254) plates obtained from Merck. An ultraviolet lamp (λ_{max}=254 nm) and $KMnO_4$ were used for visualization. Analytical LC-MS was performed using a system comprising a Waters Acquity H-CLASS UPLC with a PDA detector, evaporative light-scattering detector, and SQD2 with electrospray ionisation. The system ran with a positive and negative switching mode using a Waters Acquity UPLC BEH C18 (50 mm × 2.1 mm × 1.7 µm) column and gradient elution with a binary solvent system: MeCN plus 0.1% formic acid and H_2O plus 0.1% formic acid.

Mass directed auto-purification (MDAP) was performed using a Waters Autopurifcation system comprising a PDA detector, ELS detector and SQD2 with electrospray ionisation. The system ran in positive mode using a Waters XBridge Prep C18 (100 mm × 19 mm × 5 µm) or Waters XBridge Prep C18 (50 mm × 19 mm × 5 µm) column and gradient elution with a binary solvent system: MeCN plus 0.1% formic acid and H2O plus 0.1% formic acid. Flash column chromatography was performed using silica gel 60 (35-70 µm particles) supplied by Merck. A Bruker Daltonics micrOTOF spectrometer with electrospray (ES) ionisation source was used for high-resolution mass spectrometry (HRMS). It was not possible to secure mass spectrometry data for several diazo substrates and their immediate precursors. Proton (^{1}H) and carbon (^{13}C) NMR data was collected on Bruker 400 or 500 MHz spectrometers using $CDCl_3$, CD_3OD, CD_2Cl_2, acetone-d_6 or DMSO-d_6 as solvent. Data was collected at 298 K unless otherwise stated. Chemical shifts (δ) are given in parts per million (ppm) and they are referenced to the residual solvent peak. Coupling constants (*J*) are reported in Hertz (Hz) and splitting patterns are reported in an abbreviated manner: app. (apparent), s (singlet), d (doublet), t (triplet), q (quartet), pent (pentet), m (multiplet), br. (broad). Assignments and identifications were made using COSY, DEPT, HSQC, HMBC and NOESY experiments.

2. High-Throughput Experimentation

2.1 Execution of reaction array

Stock solutions in 1:1 MeCN–TFE and CH_2Cl_2 were prepared for each diazo compound (**S1-S8**) (0.25 M) and substrate (**C1-C8**) (0.3 M), $[Ru(bpz)_3](PF_6)_2$ (0.02 M) and $MesAcrBF_4$ (0.05 M). Stock solutions in CH_2Cl_2 were prepared for $Rh_2(pfb)_4$ (0.02 M) and $Rh_2(piv)_4$ (0.02 M).

All 288 combinations were explored for diazo compound and substrate with each catalyst and solvent. To each reaction vial in a 96-well plate was added a diazo compound (100 µL of stock solution, see above, 0.025 mmol), a substrate (80 µL of stock solution, see above, 0.02 mmol, limiting reagent) and a catalyst (20 µL of stock solution, see above). The final volume of each reaction was 200 µL. Each reaction vial was capped. The 192 reactions containing photocatalysts $[Ru(bpz)_3](PF_6)_2$ and $MesAcrBF_4$ were irradiated with 2x 40 W Kessil A160WE Tuna Blue lamps from a distance of 17 cm for 16 hr. A fan was used to avoid over-heating, and each corner of the plate was determined to be at a uniform temperature 25 °C after 16 h (see below for experimentalset-up). The 96 reactions with $Rh_2(pfb)_4$ and $Rh_2(piv)_4$ were kept in darkness for 16 hr.

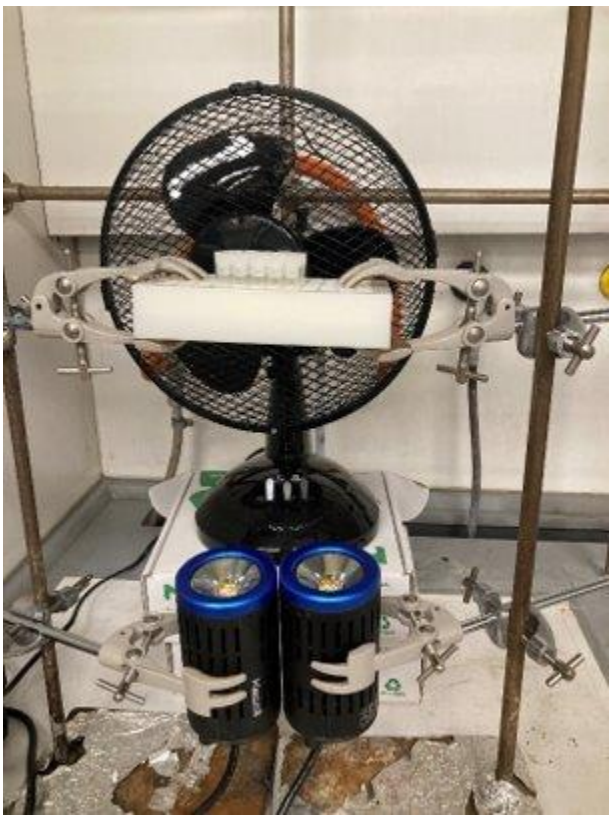


Figure S1: Experimental set-up of arrays of reactions containing the photocatalysts $[Ru(bpz)_3](PF_6)_2$ and $MesAcrBF_4$.

2.2 Method for the quantification of products formed in the reaction array

Analytical UPLC-MS was performed using a system comprising a Waters Acquity H-CLASS UPLC with a PDA detector, ELS detector and SQD2 with electrospray ionisation. The system ran with a positive and negative switching mode using

a Waters Acquity UPLC BEH C18 (50 mm × 2.1 mm × 1.7 μm) column. The column oven was set to 45 ^{o}C. The PDA scanned over a wavelength range of 210 to 500 nm. The ELSD nebuilser mode was set to cooling, the drift tube temperature set to 35 ^{o}C and the gas pressure set to 60 psi. The ELSD gain was set to 30 with the data collection rate set at 40 Hz. Gradient elution was performed with a binary LCMS-grade solvent system: MeCN plus 0.1% formic acid and H_2O plus 0.1% formic acid. The mobile phase flow-rate was set to 0.8 mL/min with a total run length of 3.5 min.

2.3 Calibration of quantification method

The calibration analytes were purchased from SigmaAldrich, Fluorochem and Fisher Scientific. The calibration mixes comprised of equal masses of 7-hydroxyethyl theophylline, hydrocortisone, dibenzyl 2,3-dihydroxysuccinate, dibenzyl succinate and dibenzyl phthalate. The calibration mixes were prepared at the following concentrations: 12.5, 10, 7.5, 5, 2.5, 1.0 and 0.5 mg/mL. The calibration mixes were all prepared by weighing on a calibrated 1 decimal place balance and diluted to volume in 10 ml volumetric flasks with dimethylsulfoxide:water (80:20). Where necessary, flasks were immersed in an ultrasonic bath in order to aid solubilisation.

1 μL of each of the seven calibration concentration mixes were injected in triplicate onto the UPLC-MS system and the ELSD peak areas and retention times were manually extracted from the generated results files. Three-dimensional calibration plots were produced in Origin with retention time (minutes) as the X-axis, log ELSD peak area as the Y-axis and log mass concentration as the Z-axis. The calibration surface produced, was described by the equation:[1]

$$\log(\text{concentration}) = A + B \times \text{retention time} + C \times \log 10(\text{response area}) + D \times \text{retention time}^2 + E \times \text{retention time} \times \log 10(\text{response area}) + F \times (\log 10(\text{response area}))^2$$

R^2 was calculated as a goodness-of-fit measure ($R^2 = 0.998$)

A series of test compounds (MWt. range 250-400) was prepared at concentrations (0.5-10 mg/mL). 1 μL of each test compound was injected onto the analytical system and the ELSD peak area and retention times extracted as before. Values were substituted into the described equation to give calculated concentrations. All test compounds returned calculated concentrations within 10% of the actual concentration.

2.4 Reactions selected for purification and evaluation and validation of the products

Combination of components	Target MW 1	Target MW 2	µmol of product	Active Combination?[a]	Validated?[b]	Bioactive product
S1 + C1 + MesAcrBF4 + MeCN/TFE	234		3.6			
S2 + C1 + MesAcrBF4 + MeCN/TFE	260		10.2			
S2 + C2 + MesAcrBF4 + MeCN/TFE	281		4			
S3 + C2 + Ru(bpz)3PF6 + MeCN/TFE	371		10.6			
S5 + C2 + Ru(bpz)3PF6 + MeCN/TFE	384		4.2			
S2 + C4 + Ru(bpz)3PF6 + MeCN/TFE	243		4.2			
S4 + C4 + MesAcrBF4 + MeCN/TFE	432		7.4	✓	X	
S5 + C4 + MesAcrBF4 + MeCN/TFE	323		14.2			
S4 + C6 + Ru(bpz)3PF6 + MeCN/TFE	354		2	✓	X	
S5 + C6 + Ru(bpz)3PF6 + MeCN/TFE	338		3.6			
S5 + C7 + MesAcrBF4 + MeCN/TFE	384	504	9	✓	X	
S6 + C7 + MesAcrBF4 + MeCN/TFE	290		4			
S4 + C1 + Ru(bpz)3PF6 + CH_2Cl_2	449	446	5.8			
S5 + C1 + Ru(bpz)3PF6 + CH_2Cl_2	340		6.6			
S3 + C2 + MesAcrBF4 + CH_2Cl_2	371		2.4	✓	✓	**4a/b**
S5 + C2 + Ru(bpz)3PF6 + CH_2Cl_2	359	361	6.6			
S4 + C3 + Ru(bpz)3PF6 + CH_2Cl_2	419		7.2	✓	✓	**8**
S5 + C3 + Ru(bpz)3PF6 + CH_2Cl_2	310		9.2			
S4 + C4 + Ru(bpz)3PF6 + CH_2Cl_2	430		5			
S5 + C4 + Ru(bpz)3PF6 + CH_2Cl_2	321		3.2	✓	X	
S3 + C5 + Ru(bpz)3PF6 + CH_2Cl_2	310		4	✓ (2 products)	X	
S5 + C5 + MesAcrBF4 + CH_2Cl_2	300		7	✓ (2 products)	X	
S4 + C7 + Ru(bpz)3PF6 + CH_2Cl_2	439		9.8	✓	✓	**5**
S3 + C8 + Ru(bpz)3PF6 + CH_2Cl_2	337		3.4			
S4 + C8 + Ru(bpz)3PF6 + CH_2Cl_2	436		4.4	✓	✓	**3**
S5 + C8 + Ru(bpz)3PF6 + CH_2Cl_2	327		11			
S6 + C8 + Ru(bpz)3PF6 + CH_2Cl_2	365		4			
S3 + C1 + Rh2(pfb)4 + CH_2Cl_2	358		3.6	✓	✓	**6**
S4 + C1 + Rh2(pfb)4 + CH_2Cl_2	261		4.4			
S6 + C1 + Rh2(pfb)4 + CH_2Cl_2	378	478	0.8	✓	✓	**7**
S3 + C2 + Rh2(pfb)4 + CH_2Cl_2	371		9.4			
S4 + C2 + Rh2(pfb)4 + CH_2Cl_2	470		6.8	✓	✓	**1**
S5 + C2 + Rh2(piv)4 + CH_2Cl_2	361		10.6	✓	✓	**2**

S6 + C2 + Rh2(piv)4 + CH_2Cl_2	399		6.2			
S3 + C3 + Rh2(piv)4 + CH_2Cl_2	320		4.6			
S6 + C3 + Rh2(piv)4 + CH_2Cl_2	348		2.4			
S3 + C4 + Rh2(pfb)4 + CH_2Cl_2	333		7			
S6 + C4 + Rh2(piv)4 + CH_2Cl_2	361		4			
S3 + C7 + Rh2(piv)4 + CH_2Cl_2	340		4.8			
S5 + C7 + Rh2(piv)4 + CH_2Cl_2	330		8.2			
S6 + C7 + Rh2(pfb)4 + CH_2Cl_2	368		2.6			

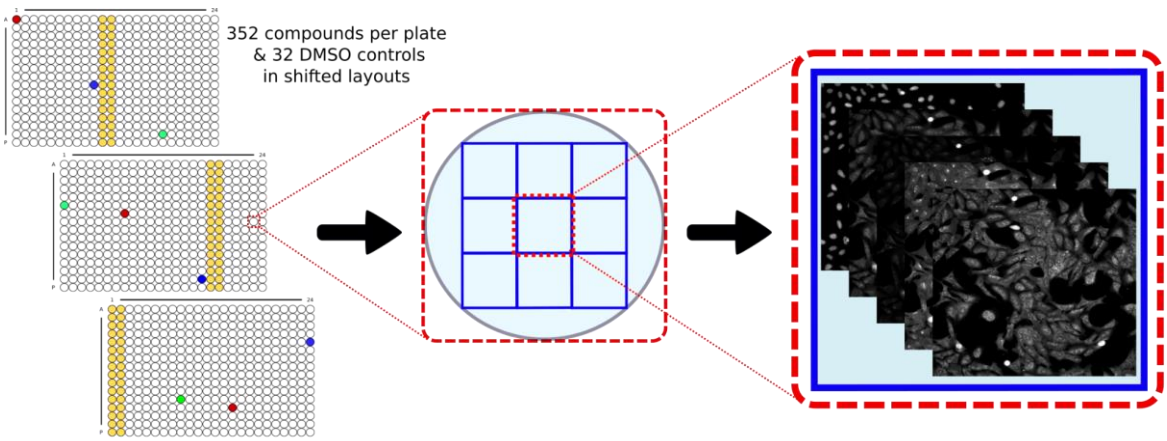
[a]>5% induction value in the cell painting assay (see main text). [b]Validation following reaction scale-up, structural elucidation/characterisation and re-evaluation in the cell painting assay (see main text).

3 Methods for Cell Painting Assay

The described assay follows closely the method described by Bray et al.[2]

Initially, 5 µl U2OS medium were added to each well of a 384-well plate (PerkinElmer CellCarrier-384 Ultra). Subsequently, U2OS cell were seeded with a density of 1600 cells per well in 20 µl medium. The plate was incubated for 10 min at the ambient temperature, followed by an additional 4 h incubation (37 °C, 5% CO2). Compound treatment was performed with the Echo 520 acoustic dispenser (Labcyte) at final concentrations of 10 µM, 3 µM or 1 µM. Incubation with compound was performed for 20 h (37 °C, 5% CO2). Subsequently, mitochondria were stained with Mito Tracker Deep Red (Thermo Fisher Scientific, Cat. No. M22426). The Mito Tracker Deep Red stock solution (1 mM) was diluted to a final concentration of 100 nM in prewarmed medium. The medium was removed from the plate leaving 10 µl residual volume and 25 µl of the Mito Tracker solution were added to each well. The plate was incubated for 30 min in darkness (37 °C, 5% CO2). To fix the cells 7 µl of 18.5 % formaldehyde in PBS were added, resulting in a final formaldehyde concentration of 3.7 %. Subsequently, the plate was incubated for another 20 min in darkness (RT) and washed three times with 70 µl of PBS. (Biotek Washer Elx405). Cells were permeabilized by addition of 25 µl 0.1% Triton X-100 to each well, followed by 15 min incubation (RT) in darkness. The cells were washed three times with PBS leaving a final volume of 10 µl. To each well 25 µl of a staining solution were added, which contains 1% BSA, 5 µl/ml Phalloidin (Alexa594 conjugate, Thermo Fisher Scientific, A12381), 25 µg/ml Concanavalin A (Alexa488 conjugate, Thermo Fisher Scientific, Cat. No. C11252), 5 µg/ml Hoechst 33342 (Sigma, Cat. No. B2261-25mg), 1.5 µg/ml WGA-Alexa594 conjugate (Thermo Fisher Scientific, Cat. No. W11262) and 1.5 µM SYTO 14 solution (Thermo Fisher Scientific, Cat. No. S7576). The plate is incubated for 30 min (RT) in darkness and washed three times with 70 µl PBS. After the final washing step, the PBS was not aspirated. The plates were sealed and centrifuged for 1 min at 500 rpm.

The plates were prepared in triplicates with shifted layouts to reduce plate effects and imaged using a Micro XL High-Content Screening System (Molecular Devices) in 5 channels (DAPI: Ex350-400/ Em410-480; FITC: Ex470-500/ Em510-540; Spectrum Gold: Ex520-545/ Em560-585; TxRed: Ex535-585/ Em600-650; Cy5: Ex605-650/ Em670-715) with 9 sites per well and 20x magnification (binning 2).



The generated images were processed with the *CellProfiler* package (https://cellprofiler.org/, version 3.0.0) on a computing cluster of the Max Planck Society to extract 1716 cell features per microscope site. The data was then further aggregated as medians per well (9 sites -> 1 well), then over the three replicates.

Further analysis was performed with custom *Python* (https://www.python.org/) scripts using the *Pandas* (https://pandas.pydata.org/) and *Dask* (https://dask.org/) data processing libraries as well as the *Scientific Python* (https://scipy.org/) package (separate publication to follow).

From the total set of 1716 features, a subset of highly reproducible and robust features was determined using the procedure described by Woehrmann et al. in the following way:[3]

Two biological repeats of one plate containing reference compounds were analysed. For every feature, its full profile over each whole plate was calculated. If the profiles from the two repeats showed a similarity >= 0.8 (see below), the feature was added to the set.

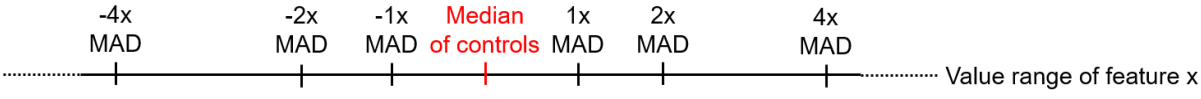
This procedure was only performed once and resulted in a set of 579 robust features out of the total of 1716 that was used for all further analyses.

Determination of reproducible Features

1716	*Determined by CellProfiler*
↓	*Keep features that have a minimum correlation of 0.80 between repeats for all cpds.*
579	*Final set of relevant features. Used for all further analyses*

The phenotypic profiles were compiled from the Z-scores of all individual cellular features, where the Z-score is a measure of how far away a data point is from a median value.

Specifically, Z-scores of test compounds were calculated relative to the Median of DMSO controls. Thus, the Z-score of a test compound defines how many MADs (Median Absolute Deviations) the measured value is away from the Median of the controls as illustrated by the following formula:



$$z\_score = \frac{value_{meas.} - Median_{Controls}}{MAD_{Controls}}$$

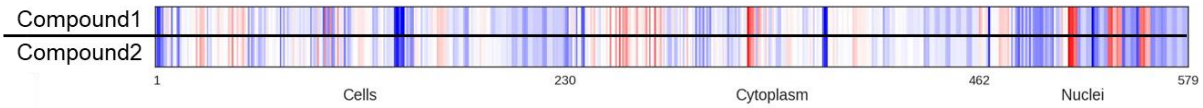
The phenotypic compound profile is then determined as the list of Z-scores of all features for one compound.

In addition to the phenotypic profile, an induction value was determined for each compound as the fraction of significantly changed features, in percent:

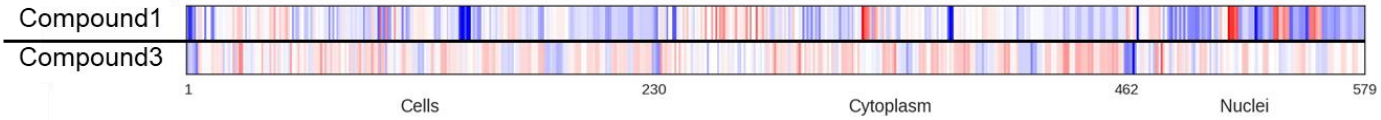
$$Induction\ [\%] = \frac{number\ of\ features\ with\ abs.\ values > 3}{total\ number\ of\ features}$$

Similarities of phenotypic profiles were calculated from the correlation distances between two profiles (https://docs.scipy.org/doc/scipy/reference/generated/scipy.spatial.distance.correlation.html; Similarity = 1 - Correlation Distance).

An example for two compounds with highly similar profiles (96% similarity):



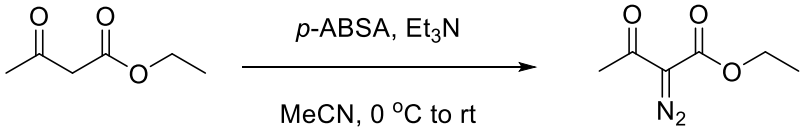
An example for two compounds with low similarity profiles (0% similarity):



Each colored band represents one Z-score of a feature.

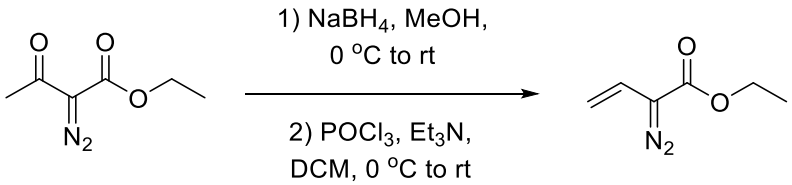
4 Synthetic chemistry experimental

Ethyl 2-diazo-3-oxobutanoate



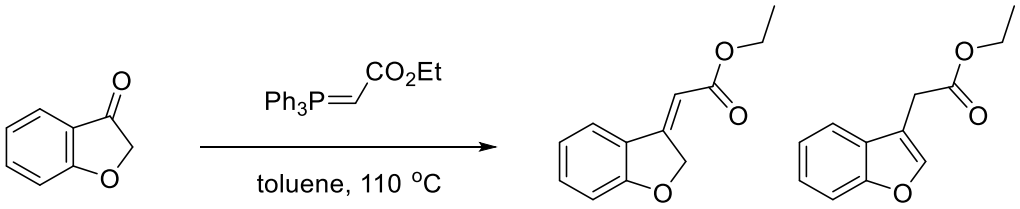
To a solution of ethyl acetoacetate (1 g, 7.70 mmol) and 4-acetamidobenzenesulfonyl azide (*p*-ABSA) (1.85 g, 7.70 mmol) in MeCN (60 mL) at 0 °C was added Et_3N (3.2 mL, 23.2 mmol). The mixture was warmed to room temperature and stirred for 16 h, then volatiles were removed *in vacuo*. The residue was triturated with Et_2O/hexane (1:1, 2 x 20 mL), and the extracts were combined and concentrated *in vacuo*. The crude residue was purified by column chromatography (90:10 hexane-EtOAc) to give ethyl 2-diazo-3-oxobutanoate (1.05 g, 87% yield) as a yellow oil. δ_H (500 MHz, $CDCl_3$) 4.29 (2H, q, *J* = 7.1 Hz, ethyl CH_2), 2.47 (3H, s, $COCH_3$), 1.32 (3H, t, *J* = 7.1 Hz, ethyl CH_3) ppm; δ_C (126 MHz, $CDCl_3$) 190.4 (ketone C=O), 161.6 (ester C=O), 61.6 (ethyl CH_2), 28.4 ($CO\mathit{C}H_3$), 14.5 (ethyl CH_3) ppm (signal for 2-C missing). Observed spectral data was consistent with data previously reported in literature.[4]

Ethyl 2-diazobut-3-enoate S2



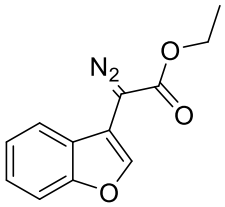
To a solution of ethyl 2-diazo-3-oxobutanoate (483 mg, 3.10 mmol) in MeOH (30 mL) at 0 °C was added $NaBH_4$ (236 mg, 6.20 mmol) portionwise. The mixture was stirred for 60 min then poured into sat. aq. $NaHCO_3$ (30 mL). The mixture was extracted with Et_2O (2x60 mL). Organics were combined, washed with water (60 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the intermediate alcohol, which was used immediately without further purification. To a solution of the intermediate alcohol in CH_2Cl_2 (30 mL) at 0 °C was added Et_3N (1.73 mL, 12.4 mmol) followed by a solution of $POCl_3$ (432 µL, 4.65 mmol) in CH_2Cl_2 (4 mL) dropwise. The reaction mixture was stirred overnight at room temperature. The organics were washed with ice-cooled water (3 x 40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (95:5 hexane-EtOAc) (note: product degrades on silica over prolonged exposure) to give ethyl 2-diazobut-3-enoate (262 mg, 78% yield). δ_H (500 MHz, $CDCl_3$) 6.17 (1H, dd, *J* = 17.4, 11.0 Hz, butenoate 3-H), 5.11 (1H, d, *J* = 11.0 Hz, butenoate 4-H_A), 4.85 (1H, d, *J* = 17.4 Hz, butenoate 4-H_B), 4.27 (2H, q, *J* = 7.1 Hz, ethyl CH_2), 1.30 (3H, t, *J* = 7.1 Hz, ethyl CH_3) ppm. Observed spectral data was consistent with data previously reported in literature.[5]

Ethyl 2-[(3*Z*)-2,3-dihydro-1-benzofuran-3-ylidene]acetate SI1a and ethyl 2-(1-benzofuran-3-yl)acetate SI1b



A mixture of benzofuran-3(2H)-one (1.00 g, 7.46 mmol) and (carbethoxymethylene)triphenylphosphorane (3.89 g, 11.2 mmol) in toluene (75 mL) was stirred at 110 °C for 72 h. The mixture was cooled to room temperature and volatiles were removed *in vacuo* to give the crude product. The crude product was purified by column chromatography (95:5 hexane-EtOAc) to give a 50:50 mixture of ester **SI1a** and ester **SI1b** (996 mg, 65% combined yield) as a yellow oil. Small amounts of ester **SI1a** and ester **SI1b** could be isolated individually. **SI1a:** δ_H (500 MHz, $CDCl_3$) 7.51 (1H, br. d, *J* = 7.4 Hz, dihydrobenzofuranyl 4-H), 7.37 (1H, br. t, *J* = 7.7 Hz, dihydrobenzofuranyl 6-H), 7.00-6.94 (2H, m, dihydrobenzofuranyl 5-H and 7-H), 6.17 (1H, t, *J* = 3.1 Hz, alkenyl 1-H), 5.52 (2H, d, *J* = 3.1 Hz, dihydrobenzofuranyl 2-H), 4.23 (2H, q, *J* = 7.1 Hz, ethyl CH_2), 1.33 (3H, t, *J* = 7.1 Hz, ethyl CH_3) ppm; δ_C (126 MHz, $CDCl_3$) 167.2 (C=O), 165.5 (dihydrobenzofuranyl C-7a), 156.1 (dihydrobenzofuranyl C-3), 133.7 (dihydrobenzofuranyl C-6), 124.2 (dihydrobenzofuranyl C-3a), 122.4 (dihydrobenzofuranyl C-4), 121.3 (dihydrobenzofuranyl C-5), 111.5 (dihydrobenzofuranyl C-7), 104.5 (alkenyl C-1), 76.8 (dihydrobenzofuranyl C-2), 60.3 (ethyl CH_2), 14.5 (ethyl CH_3) ppm; HRMS found M+H 205.0860. $C_{12}H_{13}O_3$ requires M+H 205.0859. **SI1b:** δ_H (500 MHz, $CDCl_3$) 7.63 (1H, t, 1.0 Hz, benzofuranyl 2-H), 7.58-7.55 (1H, m, benzofuranyl 4-H), 7.47 (1H, br. d, *J* = 8.1 Hz, benzofuranyl 7-H), 7.32-7.27 (1H, m, benzofuranyl 6-H), 7.27-7.22 (1H, m, benzofuranyl 5-H), 4.19 (2H, q, *J* = 7.1 Hz, ethyl CH_2), 3.69 (2H, d, *J* = 1.0 Hz, methylene CH_2), 1.27 (3H, t, *J* = 7.1 Hz, ethyl CH_3) ppm; δ_C (126 MHz, $CDCl_3$) 170.8 (C=O), 155.3 (benzofuranyl C-7a), 143.0 (benzofuranyl C-2), 127.8 (benzofuranyl C-3a), 124.6 (benzofuranyl C-6), 122.7 (benzofuranyl C-5), 119.8 (benzofuranyl C-4), 113.3 (benzofuranyl C-3), 111.6 (benzofuranyl C-7), 61.2 (ethyl CH_2), 30.0 (methylene C), 14.3 (ethyl CH_3) ppm; HRMS found 205.0857. $C_{12}H_{13}O_3$ requires M+H 205.0859.

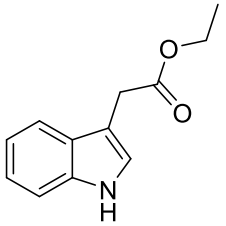
Ethyl 2-(1-benzofuran-3-yl)-2-diazoacetate S3



To a solution of *esters* **SI1a** and **SI1b** (850 mg, 4.17 mmol; 1:1 mixture) and 4-acetamidobenzenesulfonyl azide (*p*-ABSA) (1.20 g, 5.00 mmol) in MeCN (17 mL) was added DBU (870 µL, 6.03 mmol) dropwise at room temperature. The mixture was stirred for 16 h at room temperature, then diluted with CH_2Cl_2 (50 mL). Organics were washed with 10% aq. NH_4Cl (30 mL), water (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (95:5 hexane-Et_2O) to give *diazo* **S3** (557 mg, 58% yield) as a red solid. δ_H (500 MHz, $CDCl_3$) 7.99 (1H, br. s, benzofuranyl 2-H), 7.55-7.48 (2H, m, benzofuranyl 4-H and 7-H), 7.37-7.32 (1H, m, benzofuranyl 6-H), 7.29-7.23 (1H, m, benzofuranyl 5-H), 4.37 (2H, q, *J* = 7.1 Hz, ethyl CH_2), 1.36 (3H, t, *J* = 7.1 Hz, ethyl CH_3) ppm; δ_C (126 MHz, $CDCl_3$) 166.0 (C=O), 155.0 (benzofuranyl C-7a), 141.6 (benzofuranyl C-2), 125.1 (benzofuranyl

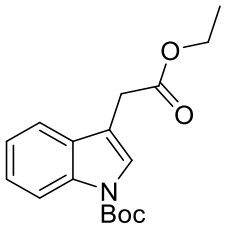
C-6), 124.5 (benzofuranyl C-3a), 123.1 (benzofuranyl C-5), 118.8 (benzofuranyl C-4), 112.1 (benzofuranyl C-7), 104.0 (benzofuranyl C-3), 61.7 (ethyl CH_2), 14.7 (ethyl CH_3) ppm (signal for 2-C missing).

Ethyl 2-(1H-indol-3-yl)acetate SI2



To a solution of indole-3-acetic acid (1.00 g, 5.71 mmol) in EtOH (25 mL) was added conc. H_2SO_4 (1 mL) and the reaction mixture was stirred at 80 °C for 2 h. The mixture was cooled to room temperature and neutralised with 10% w/v aq. NaOH. Volatiles were removed *in vacuo*, and the residue was diluted with CH_2Cl_2 (30 mL) and H_2O (30 mL). Layers were separated, and organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give *ester* **SI2** (1.10 g, 95% yield) as a brown oil. δ_H (500 MHz, $CDCl_3$) 8.11 (1H, br. s, N-H), 7.64 (1H, dt, *J* = 7.8, 1.0 Hz, indolyl 4-H), 7.35 (1H, dt, *J* = 8.1, 1.0 Hz, indolyl 7-H), 7.21 (1H, ddd, *J* = 8.1, 7.1, 1.0 Hz, indolyl 6-H), 7.17-7.12 (2H, m, indolyl 2-H and 5-H), 4.18 (2H, q, *J* = 7.1 Hz, ethyl CH_2), 3.78 (2H, d, *J* = 1.0 Hz, methylene CH_2), 1.28 (3H, t, *J* = 7.1 Hz, ethyl CH_3) ppm; δ_C (126 MHz, $CDCl_3$) 172.2 (C=O), 136.2 (indolyl C-7a), 127.4 (indolyl C-3a), 123.1 (indolyl C-2), 122.3 (indolyl C-6), 119.8 (indolyl C-5), 119.1 (indolyl C-4), 111.3 (indolyl C-7), 108.6 (indolyl C-3), 60.9 (ethyl CH_2), 31.6 (methylene CH_2), 14.4 (ethyl CH_3) ppm. Observed spectral data was consistent with data previously reported in literature.[6]

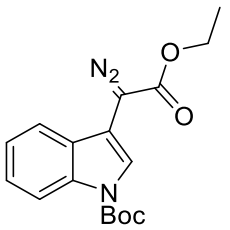
tert-Butyl 3-(2-ethoxy-2-oxoethyl)-1H-indole-1-carboxylate SI3



To a solution of ethyl 2-(1H-indol-3-yl)acetate (895 mg, 4.40 mmol) and Et_3N (918 µL, 6.60 mmol) in CH_2Cl_2 (9 mL), was added Boc_2O (1.51 mL, 6.60 mmol) and 4-dimethylaminopyridine (50 mg, 0.440 mmol) at room temperature. The mixture was stirred for 16 h then diluted with CH_2Cl_2 (20 mL). Organics were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (95:5 hexane-EtOAc) to give *N-Boc indolyl ester* **SI3** (1.11 g, 83% yield) as a colourless oil. δ_H (500 MHz, acetone-d_6) 8.15 (1H, br. d, *J* = 8.3 Hz, indolyl 7-H), 7.65 (1H, br. s, indolyl 2-H), 7.61-7.57 (1H, m, indolyl 4-H), 7.33 (1H, ddd, *J* = 8.3, 7.3, 1.1 Hz, indolyl 6-H), 7.25 (1H, ddd, *J* = 8.3, 7.3, 1.1 Hz, indolyl 5-H), 4.14 (2H, q, *J* = 7.1 Hz, ethyl CH_2), 3.76 (2H, d, *J* = 1.0 Hz, methylene CH_2), 1.68 (9H, s, Boc CH_3), 1.22 (3H, t, *J* = 7.1 Hz, ethyl CH_3) ppm; δ_C (126 MHz, acetone-D_6) 171.3 (ester C=O), 150.2 (Boc C=O), 136.3 (indolyl C-7a), 131.2 (indolyl C-3a), 125.3 (indolyl C-2 or C-6), 125.2 (indolyl C-2 or C-6), 123.3 (indolyl C-5), 120.2 (indolyl C-4), 115.8 (indolyl C-7), 114.7 (indolyl C-3), 84.3 (Boc C), 61.2 (ethyl CH_2), 31.3

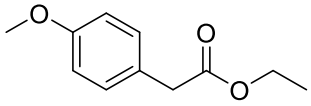
(methylene CH_2), 28.2 (Boc CH_3), 14.5 (ethyl CH_3) ppm. Observed spectral data was consistent with data previously reported in literature.[7]

tert-Butyl 3-(1-diazo-2-ethoxy-2-oxoethyl)-1H-indole-1-carboxylate S4



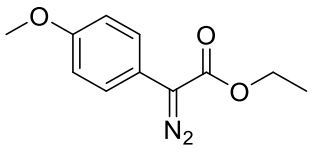
To a solution of *ester* **SI3** (1.62 g, 5.35 mmol) and 4-acetamidobenzenesulfonyl azide (*p*-ABSA) (1.54 g, 6.42 mmol) in MeCN (21 mL) was added DBU (1.11 mL, 7.49 mmol) dropwise at room temperature. The mixture was stirred for 16 h at room temperature, then diluted with CH_2Cl_2 (50 mL). Organics were washed with 10% aq. w/v NH_4Cl (30 mL), water (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (95:5 hexane-Et_2O) to give *diazo* **S4** (592 mg, 34% yield) as a red solid. δ_H (500 MHz, CD_2Cl_2) 8.20 (1H, br. d, *J* = 8.3 Hz, indolyl 7-H), 7.85 (1H, s, indolyl 2-H), 7.53-7.48 (1H, m, indolyl 4-H), 7.35 (1H, ddd, *J* = 8.3, 7.3, 1.0 Hz, indolyl 6-H), 7.25 (1H, ddd, *J* = 8.3, 7.3, 1.0 Hz, indolyl 5-H), 4.32 (2H, q, *J* = 7.1 Hz, ethyl CH_2), 1.66 (9H, s, Boc CH_3), 1.33 (3H, t, *J* = 7.1 Hz, ethyl CH_3) ppm; δ_C (126 MHz, CD_2Cl_2) 166.4 (ester C=O), 149.7 (Boc C=O), 135.7 (indolyl C-7a), 127.9 (indolyl C-3a), 125.2 (indolyl C-6), 124.1 (indolyl C-2), 123.2 (indolyl C-5), 119.0 (indolyl C-4), 115.9 (indolyl C-7), 103.6 (indolyl C-3), 84.5 (Boc C), 61.8 (ethyl CH_2), 57.9 (C=N_2), 28.3 (Boc CH_3), 14.7 (ethyl CH_3) ppm. Observed spectral data was consistent with data previously reported in literature.[8]

Ethyl 2-(4-methoxyphenyl)acetate SI4



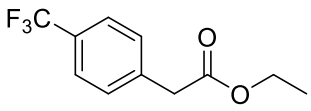
To a solution of 2-(4 methoxyphenyl)acetic acid (1.00 g, 6.02 mmol) in EtOH (25 mL) was added conc. H_2SO_4 (1 mL) and the reaction mixture was stirred at 78 °C for 2 h. The mixture was cooled to room temperature and neutralised with 10% aq. NaOH. Volatiles were removed *in vacuo*, and the residue was diluted with CH_2Cl_2 (30 mL) and H_2O (30 mL). Layers were separated, and organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give *ester* **SI4** (1.15 g, 98% yield) as a dark yellow oil. δ_H (500 MHz, $CDCl_3$) 7.22-7.18 (2H, m, aryl 2-H and 6-H), 6.89-6.84 (2H, m, aryl 3-H and 5-H), 4.14 (2H, q, *J* = 7.1 Hz, ethyl CH_2), 3.79 (3H, s, OCH_3), 3.55 (2H, s, methylene CH_2), 1.25 (3H, t, *J* = 7.1 Hz, ethyl CH_3) ppm; δ_C (126 MHz, $CDCl_3$) 172.1 (C=O), 158.8 (aryl C-4), 130.4 (aryl C-2 and C-6), 126.4 (C-1), 114.1 (aryl C-3 and C-5), 60.9 (ethyl CH_2), 55.4 (OCH_3), 40.7 (methylene C), 14.3 (ethyl CH_3) ppm. Observed spectral data was consistent with data previously reported in literature.[9]

Ethyl 2-diazo-2-(4-methoxyphenyl)acetate S5



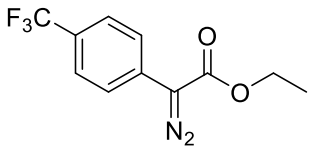
To a solution of *ester* **SI4** (700 mg, 3.61 mmol) and 4-acetamidobenzenesulfonyl azide (*p*-ABSA) (1.04 g, 4.33 mmol) in MeCN (14 mL) was added DBU (752 µL, 5.05 mmol) dropwise at room temperature. The mixture was stirred for 16 h at room temperature, then diluted with Et_2O (30 mL) and H_2O (30 mL). Layers were separated and the aqueous was extracted with Et_2O (30 mL). Organics were combined, washed with 10% aq. NH_4Cl (40 mL) and brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (95:5 hexane-Et_2O) to give *diazo* **S5** (303 mg, 38% yield) as a red solid. δ_H (500 MHz, $CDCl_3$) 7.41-7.36 (2H, m, aryl C-2 and C-6), 6.97-6.91 (2H, m, aryl 3-H and 5-H), 4.32 (2H, q, *J* = 7.1 Hz, ethyl CH_2), 3.81 (3H, s, OCH_3), 1.33 (3H, t, *J* = 7.1 Hz, ethyl CH_3) ppm; δ_C (126 MHz, $CDCl_3$) 166.0 (C=O), 158.2 (aryl C-4), 126.1 (aryl C-2 and C-6), 117.2 (aryl C-1), 114.8 (aryl C-3 and C-5), 62.5 ($C=N_2$), 61.1 (ethyl CH_2), 55.5 (OCH_3), 14.7 (ethyl CH_3) ppm. Observed spectral data was consistent with data previously reported in literature.[10]

Ethyl 2-[4-(trifluoromethyl)phenyl]acetate SI5



To a solution of 2-[4-(trifluoromethyl)phenyl]acetic acid (1.00 g, 4.90 mmol) in EtOH (25 mL) was added conc. H_2SO_4 (500 µL) and the reaction mixture was stirred at 78 °C for 2 h. The mixture was cooled to room temperature and neutralised with 10% aq. NaOH. Volatiles were removed *in vacuo*, and the residue was diluted with CH_2Cl_2 (30 mL) and H_2O (30 mL). Layers were separated, and organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give *ester* **SI5** as a colourless solid (1.05 g, 92% yield). δ_H (500 MHz, $CDCl_3$) 7.58 (2H, d, *J* = 8.1 Hz, aryl 3-H and 5-H), 7.41 (2H, d, *J* = 8.1 Hz, aryl 2-H and 6-H), 4.17 (2H, q, *J* = 7.1 Hz, ethyl CH_2), 3.67 (2H, s, methylene CH_2), 1.26 (3H, t, *J* = 7.1 Hz, ethyl CH_3) ppm; δ_C (126 MHz, $CDCl_3$) 170.9 (C=O), 138.2 (q, *J* = 1.2 Hz, aryl C-1), 129.8 (aryl C-2 and C-6), 129.6 (q, *J* = 32.5 Hz, aryl C-4), 125.6 (q, *J* = 3.8 Hz, aryl C-3 and C-5), 124.3 (q, *J* = 272 Hz, CF_3), 61.3 (ethyl CH_2), 41.3 (methylene C), 14.3 (ethyl CH_3) ppm; δ_F (376 MHz, $CDCl_3$) −62.6 ppm. Observed spectral data was consistent with data previously reported in literature.[11]

Ethyl 2-diazo-2-[4-(trifluoromethyl)phenyl]acetate S6



To a solution of *ester* **SI5** (1 g, 4.31 mmol) and 4-acetamidobenzenesulfonyl azide (*p*-ABSA) (1.24 g, 5.17 mmol) in MeCN (17 mL) was added DBU (900 µL, 6.03 mmol) dropwise at room temperature. The mixture was stirred for 16 h at room temperature, then diluted with CH_2Cl_2 (50 mL). Organics were washed with 10% aq. NH_4Cl (30 mL), water (30

mL) and brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (95:5 hexane-Et_2O) to give *diazo* **S6** (988 mg, 89% yield) as a yellow solid. δ_H (500 MHz, $CDCl_3$) 7.61 (4H, s, aryl 2-H, 3-H, 5-H and 6-H), 4.36 (2H, q, *J* = 7.1 Hz, ethyl CH_2), 1.36 (3H, t, *J* = 7.1 Hz, ethyl CH_3) ppm; δ_C (126 MHz, $CDCl_3$) 164.6 (C=O), 130.4 (q, *J* = 1.2 Hz, aryl C-1), 127.6 (q, *J* = 32.8 Hz, aryl C-4), 126.0 (q, *J* = 3.8 Hz, aryl C-3 and C-5), 124.2 (q, *J* = 272 Hz, CF_3), 123.6 (aryl C-2 and C-6), 63.9 ($C=N_2$), 61.5 (ethyl CH_2), 14.6 (ethyl CH_3) ppm; δ_F (376 MHz, $CDCl_3$) −62.5 ppm. Observed spectral data was consistent with data previously reported in literature.[12]

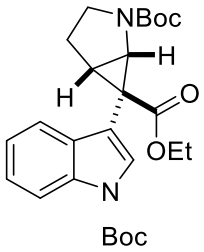
General Procedure A

A mixture of α-diazo ester (1.5 eq), co-subtrate (1 eq) and photocatalyst (2 mol% or 5 mol%) in solvent (0.1 M with respect to co-substrate) was stirred for 16 hr with a 40 W Kessil A160WE Tuna Blue lamp approximately 10 cm away. No external cooling was applied. Volatiles were removed *in vacuo* to give a crude product.

General Procedure B

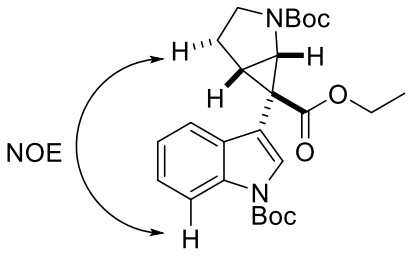
A solution of α-diazo ester (1.5 eq) in CH_2Cl_2 (0.3 M with respect to co-substrate) was added dropwise to a solution of co-substrate (1 eq) and Rh(II) catalyst (2 mol%) in CH_2Cl_2 (0.15 M with respect to co-substrate). The reaction was stirred for 16 hr at room temperature, then volatiles were removed *in vacuo* to give a crude product.

2-*tert*-Butyl 6-ethyl (1*S,5*S**,6*R**)-6-{1-[(tert-butoxy)carbonyl]-1H-indol-3-yl}-2-azabicyclo[3.1.0]hexane-2,6-dicarboxylate 1**

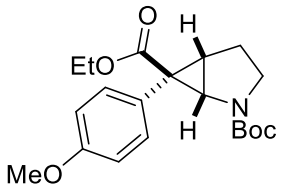


Following **General Procedure B**, α-diazo ester **S4** (49 mg, 0.150 mmol), co-substrate **C2** (16.9 mg, 0.100 mmol) and $Rh_2(pfb)_4$ (2.1 mg, 2 mol%) in CH_2Cl_2 (1 mL) gave a crude product which was purified by column chromatography (85:15 hexane-EtOAc) to give *cyclopropane* **1** (40.4 mg, 86% yield) as a yellow oil as a 55:45 mixture of rotamers. δ_H (500 MHz, CD_3OD) 8.16-8.08 (1H, m, indolyl 7-H), 7.60-7.52 (1H, m, indolyl 4-H), 7.50-7.41 (1H, m, indolyl 2-H), 7.34-7.28 (1H, m, indolyl 6-H), 7.26-7.18 (1H, m, indolyl 5-H), 4.20-4.12 (1H, m, 1-H), 4.10-4.00 (2H, m, ethyl CH_2), 3.40-3.32 (1H, m, 3-H_A), 2.82-2.74 (1H, m, 5-H), 2.38-2.23 (1H, m, 4-H_A), 2.22-2.08 (1H, m, 3-H_B), 2.00-1.82 (1H, m, 4-H_B), 1.68 (5H, s, indolyl Boc CH_3^{maj}), 1.68 (4H, s, indolyl Boc CH_3^{min}), 1.57 (4H, s, pyrrolidine Boc CH_3^{min}), 1.39 (5H, br. s, pyrrolidine Boc CH_3^{maj}), 1.09 (1.67H, t, *J* = 7.1 Hz, ethyl CH_3^{maj}), 1.07 (1.33H, t, *J* = 7.1 Hz, ethyl CH_3^{min}) ppm; δ_C (126 MHz, CD_3OD) 172.45, 172.43 (ester C=O), 156.9, 156.1 (pyrrolidine Boc C=O), 150.88, 150.85 (indolyl Boc C=O), 136.72, 136.69 (indolyl C-7a), 132.0, 131.9 (indolyl C-3a), 127.3, 126.8 (indolyl C-2), 125.6, 125.5 (indolyl C-6), 123.9, 123.8 (indolyl C-5), 120.8, 120.7 (indolyl C-4), 116.3, 116.2 (indolyl C-7), 113.7, 113.6 (indolyl C-3), 85.34, 85.30 (indolyl Boc C), 82.0, 81.6 (pyrrolidine Boc C), 62.4 (ethyl CH_2), 50.3 (C-1), 48.3 (C-3), 33.1, 32.0 (C-6), 28.9, 28.8, 28.42, 28.38 (indolyl Boc CH_3 and pyrrolidine Boc CH_3), 25.6, 24.6 (C-4), 14.4 (ethyl CH_3) ppm; HRMS Found M+H 471.2488. $C_{26}H_{35}N_2O_6$ requires M+H 471.2490.

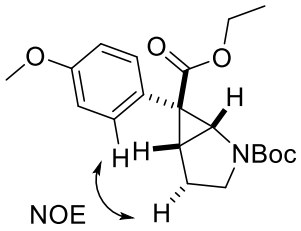
Several ^{13}C assignments were enabled by HSQC spectra. The relative configuration was determined through the observation of NOESY interactions between indolyl 7-H and pyrrolidine 4-H_A.



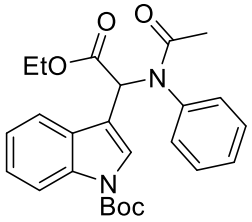
2-*tert*-Butyl 6-ethyl (1*S,5*S**,6*R**)-6-(4-methoxyphenyl)-2-azabicyclo[3.1.0]hexane-2,6-dicarboxylate 2**



Following **General Procedure B**, α-diazo ester **S5** (33 mg, 0.150 mmol), co-substrate **C2** (16.9 mg, 0.100 mmol) and $Rh_2(piv)_4$ (1.2 mg, 2 mol%) in CH_2Cl_2 (1 mL) gave a crude product which was purified by column chromatography (90:10 hexane-EtOAc) to give *cyclopropane* **2** (35.9 mg, 99% yield) as a colourless oil and a 55:45 mixture of rotamers. δ_H (500 MHz, $CDCl_3$) 7.19-7.15 (1.1H, m, aryl 2-H^{maj} and 6-H^{maj}), 7.15-7.10 (0.9H, m, aryl 2-H^{min} and 6-H^{min}), 6.88-6.83 (2H, m, aryl 3-H and 5-H), 4.13 (0.55H, d, *J* = 6.9 Hz, 1-H^{maj}), 4.06 (0.9H, q, *J* = 7.1 Hz, ethyl CH_2^{min}), 4.03 (0.45H, d, *J* = 6.9 Hz, 1-H^{min}), 4.02 (1.1H, qd, *J* = 7.1, 1.5 Hz, ethyl CH_2^{maj}), 3.81 (1.65H, s, OCH_3^{maj}), 3.79 (1.35H, s, OCH_3^{min}), 3.30 (0.45H, td, *J* = 11.0, 2.8 Hz, 3-H_A^{min}), 3.20 (0.55H, td, *J* = 11.0, 2.8 Hz, 3-H_A^{maj}), 2.59 (1H, br. t, *J* = 6.5 Hz, 5-H), 2.30-2.17 (1H, m, 4-H_A), 1.94-1.85 (1H, m, 4-H_B), 1.74 (0.45H, dt, *J* = 11.0, 9.0 Hz, 3-H_B^{min}), 1.67 (0.55H, dt, *J* = 11.0, 9.0 Hz, 3-H_B^{maj}), 1.55 (4.05H, s, Boc CH_3^{min}), 1.42 (4.95H, s, Boc CH_3^{maj}), 1.13 (1.35H, t, *J* = 7.1 Hz, ethyl CH_3^{min}), 1.11 (1.65H, t, *J* = 7.1 Hz, ethyl CH_3^{maj}) ppm; δ_C (126 MHz, $CDCl_3$) 171.9 (ester C=O^{min}), 171.6 (ester C=O^{maj}), 159.1 (aryl C-4^{min}), 159.0 (aryl C-4^{maj}), 155.5 (Boc C=O^{maj}), 154.6 (Boc C=O^{min}), 132.6 (aryl C-2^{min} and C-6^{min}), 132.1 (aryl C-2^{maj} and C-6^{maj}), 124.7 (aryl C-1^{maj}), 124.3 (aryl C-1^{min}), 114.3 (aryl C-3^{maj} and C-5^{maj}), 114.1 (aryl C-3^{min} and C-5^{min}), 80.2 (Boc C^{min}), 79.8 (Boc C^{maj}), 61.13 (ethyl CH_2^{maj}), 61.10 (ethyl CH_2^{min}), 55.30 (OCH_3^{maj}), 55.27 (OCH_3^{min}), 49.4 (C-1^{maj}), 49.3 (C-1^{min}), 46.2 (C-3^{maj}), 46.0 (C-3^{min}), 37.9 (C-6^{maj}), 37.7 (C-6^{min}), 31.9 (C-5^{min}), 31.0 (C-5^{maj}), 28.7 (Boc CH_3^{min}), 28.5 (Boc CH_3^{maj}), 24.7 (C-4^{maj}), 23.8 (C-4^{min}), 14.29 (ethyl CH_3^{min}), 14.28 (ethyl CH_3^{maj}) ppm; HRMS Found M+H 362.1964. $C_{20}H_{28}NO_5$ requires M+H 362.1962. The relative configuration was determined through the observation of NOESY interactions between aryl 2-H and pyrrolidine 4-H_A.

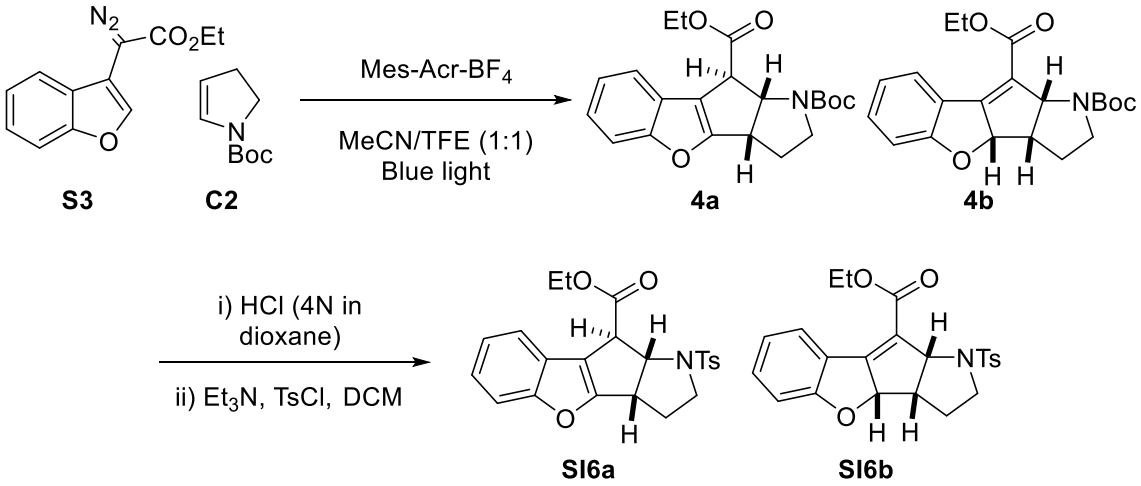


***tert*-Butyl 3-[2-ethoxy-2-oxo-1-(N-phenylacetamido)ethyl]-1H-indole-1-carboxylate 3**



Following **General Procedure A**, α-diazo ester **S4** (49 mg, 0.150 mmol), co-substrate **C8** (13.5 mg, 0.100 mmol) and $[Ru(bpz)_3][PF_6]_2$ (1.7 mg, 2 mol%) in CH_2Cl_2 (1 mL) gave a crude product which was purified by column chromatography (75:25 hexane-EtOAc) to give *N-H insertion product* **3** (10.8 mg, 25% yield) as a yellow oil. δ_H (500 MHz, CD_3OD) 8.02 (1H, br. d, *J* = 8.3 Hz, indolyl 7-H), 7.38 (1H, br. d, *J* = 8.3 Hz, indolyl 4-H), 7.45-6.76 (8H, m, indolyl 2-H, 5-H and 6-H and phenyl ArH x 5), 6.43 (1H, br. s, methine CH), 4.33-4.24 (2H, m, ethyl CH_2), 1.87 (3H, s, acetamide CH_3), 1.62 (9H, s, Boc CH_3), 1.27 (3H, t, *J* = 7.1 Hz, ethyl CH_3) ppm; δ_C (126 MHz, CD_3OD) 173.5 (acetamide C=O), 171.5 (ester C=O), 150.5 (Boc C=O), 141.3 (phenyl C), 136.3 (indolyl C-7a), 131.0 (2 x phenyl CH), 130.6 (indolyl C-3a), 130.1 (2 x phenyl CH), 129.7 (phenyl CH), 128.1 (indolyl C-2), 125.8 (indolyl C-6), 124.0 (indolyl C-5), 120.0 (indolyl C-4), 116.1 (indolyl C-7), 114.9 (indolyl C-3), 85.4 (Boc C), 62.9 (ethyl CH_2), 57.0 (methine CH), 28.3 (Boc CH_3), 23.0 (acetamide CH_3), 14.5 (ethyl CH_3) ppm; HRMS Found M+H 437.2067. $C_{25}H_{29}N_2O_5$ requires M+H 437.2071.

Ethyl 13-(4-methylbenzenesulfonyl)-8-oxa-13-azatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-1(9),2(7),3,5-tetraene-15-carboxylate SI6a and ethyl 13-(4-methylbenzenesulfonyl)-8-oxa-13-azatetracyclo[7.6.0.0^{2,7}.0^{10,14}]pentadeca-1(15),2(7),3,5-tetraene-15-carboxylate SI6b



Following **General Procedure A**, α-diazo ester **S3** (69 mg, 0.300 mmol), co-substrate **C2** (33.8 mg, 0.200 mmol) and Mes-Acr-BF_4 (5.8 mg, 5 mol%) in MeCN/2,2,2-TFE (1:1, 2 mL) gave a crude product which was purified by column chromatography (85:15 hexane-EtOAc) to give a 1:4 mixture of benzofuran and dihydrobenzofuran isomers **4a** and **4b** (51 mg, 46% yield) as yellow oils. In a separate experiment, the isomers were separated on a small scale by mass-directed HPLC to enable characterisation and biological evaluation.

4a: δ_H (400 MHz, CD_3OD, peaks reported for major rotamer) 7.50 (2H, m, 3-H and 6-H), 7.32–7.21 (2H, m, 4-H and 5-H), 5.23 (1H, dd, *J* = 6.8 and 1.3 Hz, 14-H), 4.20 (2H, m, ethyl CH_2), 4.10 (1H, br. s, 15-H), 3.92 (1H, br. d, *J* = 12.1 Hz,

10-H), 3.75 (1H, dt, *J* = 10.7 and 5.0 Hz, 12-H_a), 3.17-3.05 (1H, m, 12-H_b), 2.26–2.14 (2H, m, 11-H_a and 11-H_b), 1.52 (9H, s, Boc CH_3), 1.30 (3H, t, *J* = 7.1 Hz, ethyl CH_3) ppm; δ_C (151 MHz, CD_3OD, peaks reported for major rotamer) 172.4 (ester C=O), 161.1 (Boc C=O), 160.7 (C-9), 153.7 (C-7), 124.8 (C-2), 123.6, 122.9 (C-4 and C-5), 119.1 (C-3), 118.4 (C-1), 111.6 (C-6), 80.1 (Boc C), 68.4 (C-14), 60.9 (ethyl CH_2), 50.4 (C-15), 44.8 (C-12), 42.9 (C-10), 27.3 (Boc CH_3), 26.9 (C-11), 13.3 (ethyl CH_3) ppm. The compound was observed to exist as a *ca.* 10:1 mixture of rotamers. The relative configuration was assigned by comparison of the signal for 9-H to that in the corresponding tosylated derivative.

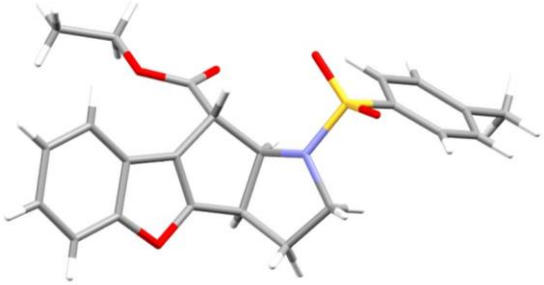
4b: δ_H (400 MHz, CD_3OD, peaks reported for major rotamer) 7.90 (1H, d, *J* = 7.7 Hz, 3-H), 7.39 (1H, dd, *J* = 8.8 and 7.5 Hz, 5-H), 7.02 (1H, t, *J* = 7.6 Hz, 4-H), 6.94 (1H, d, *J* = 8.3 Hz, 6-H), 5.68 (1H, d, *J* = 7.1 Hz, 14-H), 5.18 (1H, dd, *J* = 6.1 and 1.5 Hz, 9-H), 4.42-4.25 (2H, m, ethyl CH_2), 3.77 (1H, q, *J* = 11.0 Hz, 12-H_a), 3.69 (1H, dt, *J* = 11.2 and 5.6 Hz, 12-H_b), 3.39 (1H, q, J = 6.4 Hz, 10-H), 2.17 (1H, dd, *J* = 13.1 and 6.4 Hz, 11-H_a), 2.02 (1H, dddd, *J* = 13.2, 11.1, 9.3 and 6.0 Hz, 11-H_b), 1.46 (9H, s, Boc CH_3), 1.39 (3H, t, J = 7.1 Hz, ethyl CH_3) ppm; δ_C (101 MHz, CD_3OD, peaks reported for major rotamer) 167.9 (C-7), 133.2 (C-5), 126.1 (C-3), 124.6 (C-2), 121.3 (C-4), 120.8 (C-15), 111.2 (C-6), 95.3 (C-9), 80.1 (Boc C), 70.9 (C-14), 60.4 (ethyl CH_2), 47.5 (C-10 and C-12), 27.4 (Boc CH_3), 24.6 (C-11) and 13.4 (ethyl CH_3) ppm. The compound was observed to exist as a *ca.* 10:1 mixture of rotamers. The relative configuration was assigned by comparison of the signal for 9-H to that in the corresponding tosylated derivative. Upon standing in the MeCN–H_2O solution used for purification, the compound was observed to be susceptible to hydration. Peak broadening, caused by rotamer interconversion at room temperature, along with the overlap of the aliphatic region with the solvent peak, made it difficult to assign unambigiuously peaks for the following quaternary carbons: C=O ester, C=O Boc and C-1. The assignment of the signals for C-10, C-11 and C-12 was based on HSQC analyses, and that of the signal for the quaternary Boc carbon based on HMBC analysis.

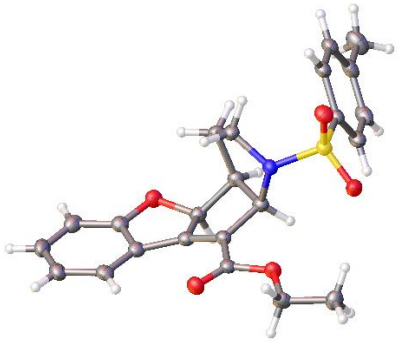
The mixture of the isomers **4a** and **4b** (51 mg, 0.137 mmol) was stirred in HCl (4 M in dioxane, 350 µL) for 2 h at room temperature. Volatiles were removed *in vacuo* and the residue was re-dissolved in CH_2Cl_2 (1.4 mL), before the addition of Et_3N (95 µL, 0.685 mmol) and TsCl (40 mg, 0.206 mmol). The mixture was stirred overnight at room temperature, then diluted with CH_2Cl_2 (5 mL) and sat. aq. $NaHCO_3$ (5 mL). Layers were separated and the organics were washed with 5% aq. citric acid (5 mL) and water (5 mL), then passed through a phase separator and concentrated *in vacuo*. The crude product was purified by column chromatography (90:10 to 80:20 hexane-EtOAc) to give *benzofuran* **SI6a** (4.6 mg, 5% yield over 3 steps) as an off-white solid and *dihydrobenzofuran* **SI6b** (23 mg, 27% yield over 3 steps) as an off-white solid (combined 27.6 mg, 32% yield over 3 steps).

Benzofuran **SI6a:** δ_H (500 MHz, $CDCl_3$) 7.83 (2H, d, *J* = 8.2 Hz, tosyl 2-H and 6-H), 7.58-7.53 (1H, m, 3-H), 7.43-7.39 (1H, m, 6-H), 7.38 (2H, d, *J* = 8.2 Hz, tosyl 3-H and 5-H), 7.26-7.22 (2H, m, 4-H and 5-H), 5.10 (1H, dd, *J* = 7.6, 1.9 Hz, 14-H), 4.33 (1H, t, *J* = 1.9 Hz, 15-H), 4.30-4.22 (2H, m, ethyl CH_2), 3.81-3.74 (1H, m, 10-H), 3.46 (1H, dt, *J* = 10.8, 6.6 Hz, 12-H_A), 3.30 (1H, dt, *J* = 10.8, 6.6 Hz, 12-H_B), 2.46 (3H, s, tosyl CH_3), 2.01-1.93 (1H, m, 11-H_A), 1.89-1.81 (1H, m, 11-H_B), 1.35 (3H, t, *J* = 7.1 Hz) ppm; δ_C (126 MHz, $CDCl_3$) 172.0 (ester C=O), 160.6, 160.2 (C-7 and C-9), 144.1 (tosyl C-4), 133.8 (tosyl C-1), 130.0 (tosyl C-3 and C-5), 128.1 (tosyl C-2 and C-6), 125.4 (C-2), 124.0, 123.4 (C-4 and C-5), 120.1 (C-3), 118.6 (C-1), 112.2 (C-6), 70.1 (C-14), 61.5 (ethyl CH_2), 51.0 (C-15), 49.7 (C-12), 43.2 (C-10), 28.8 (C-11), 21.8 (tosyl CH_3), 14.5 (ethyl CH_3) ppm; HRMS Found M+H 426.1376. $C_{23}H_{24}NO_5S$ requires M+H 426.1370.

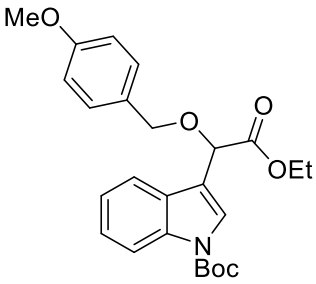
Dihydrobenzofuran **SI6b:** δ_H (500 MHz, $CDCl_3$) 8.13 (1H, br. d, *J* = 7.8 Hz, 3-H), 7.80 (2H, d, *J* = 8.2 Hz, tosyl 2-H and 6-H), 7.36 (1H, br. t, *J* = 7.2 Hz, 5-H), 7.33 (2H, d, *J* = 8.2 Hz, tosyl 3-H and 5-H), 7.03 (1H, br. t, *J* = 7.6 Hz, 4-H), 6.92 (1H, br. d, *J* = 8.2 Hz, 6-H), 5.67 (1H, dd, *J* = 5.6, 1.9 Hz, 14-H), 5.35 (1H, dd, *J* = 7.1, 1.9 Hz, 9-H), 4.38-4.27 (2H, m, ethyl CH_2), 3.57 (1H, ddd, *J* = 13.1, 9.0, 4.7 Hz, 12-H_A), 3.08 (1H, dt, *J* = 12.6, 8.3 Hz, 12-H_B), 2.88 (1H, dddd, *J* = 10.9, 7.1, 6.2, 5.6 Hz, 10-H), 2.45 (3H, s, tosyl CH_3), 1.79-1.70 (1H, m, 11-H_A), 1.56-1.47 (1H, m, 11-H_B), 1.41 (3H, t, *J* = 7.1 Hz, ethyl CH_3) ppm; δ_C (126 MHz, $CDCl_3$) 168.3 (C-7), 163.9 (ester C=O), 157.1 (C-1), 143.8 (tosyl C-4), 136.7 (tosyl C-1), 133.6 (C-5), 129.9 (tosyl C-3 and C-5), 127.9 (C-3), 127.7 (tosyl C-2 and C-6), 122.1 (C-4), 120.9 (C-2), 118.4 (C-15), 111.9 (C-6), 91.2 (C-9), 73.9 (C-14), 60.8 (ethyl CH_2), 47.9 (C-12), 45.5 (C-10), 23.7 (C-11), 21.7 (tosyl CH_3), 14.5 (ethyl CH_3) ppm; HRMS Found M+H 426.1374. $C_{23}H_{24}NO_5S$ requires M+H 426.1370.

The structures of **SI6a** and **SI6b** were confirmed by X-ray crystallography.





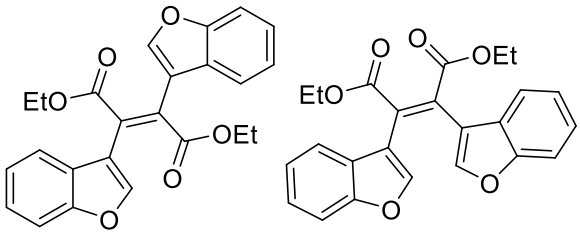
***tert*-Butyl 3-{2-ethoxy-1-[(4-methoxyphenyl)methoxy]-2-oxoethyl}-1H-indole-1-carboxylate 5**



Following **General Procedure A**, α-diazo ester **S4** (49 mg, 0.150 mmol), co-substrate **C7** (12.4 µL, 0.100 mmol) and $[Ru(bpz)_3][PF_6]_2$ (1.7 mg, 2 mol%) in CH_2Cl_2 (1 mL) gave a crude product which was purified by column chromatography (90:10 hexane-EtOAc) to give *O-H insertion product* **5** (11.6 mg, 26% yield) as a yellow oil. δ_H (500 MHz, CD_3OD) 8.12 (1H, d, *J* = 8.3 Hz, indolyl 7-H), 7.69-7.66 (2H, m, indolyl 2- and 4-H), 7.32 (1H, ddd, *J* = 8.3, 7.3, 1.0 Hz, indolyl 6-H), 7.29-7.22 (3H, m, phenol 2- and 6-H and indolyl 5-H), 6.91-6.86 (2H, m, phenol 3-H and 5-H), 5.24 (1H, d, *J* = 0.6 Hz, methine CH), 4.56 (1H, d, *J* = 11.3 Hz, methylene CH_AH$_B$), 4.52 (1H, d, *J* = 11.3 Hz, methylene CH$_A$*H*$_B$), 4.24-4.11 (2H, m, ethyl CH_2), 3.78 (3H, s, OCH_3), 1.68 (9H, s, Boc CH_3), 1.19 (3H, t, *J* = 7.1 Hz, ethyl CH_3) ppm; δ_C (126 MHz, CD_3OD) 172.3 (ester C=O), 161.1 (phenol C-4), 150.8 (Boc C=O), 137.0 (indolyl C-7a), 131.0 (phenol C-2 and C-6), 130.6 (phenol C-1), 129.6 (indolyl C-3a), 126.4 (indolyl C-2), 125.8 (indolyl C-6), 123.9 (indolyl C-5), 121.4 (indolyl C-4), 117.7 (indolyl C-3), 116.1 (indolyl C-7), 114.8 (phenol C-3 and C-5), 85.4 (Boc C), 74.5 (methine CH), 72.1 (methylene CH_2), 62.5 (ethyl CH_2),

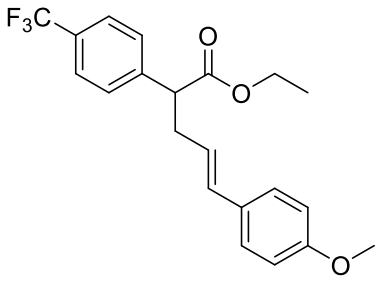
55.7 (OCH_3), 28.3 (Boc CH_3), 14.4 (ethyl CH_3) ppm; HRMS Found M+Na 462.1889. $C_{25}H_{29}NNaO_6$ requires M+Na 462.1887.

(2*E*)- and (2*Z*)-1,4-Diethyl 2,3-bis(1-benzofuran-3-yl)but-2-enedioate 6



Following **General Procedure B**, α-diazo ester **S3** (34.5 mg, 0.150 mmol), co-substrate **C1** (14.8 µL, 0.100 mmol) and $Rh_2(pfb)_4$ (2.1 mg, 2 mol%) in CH_2Cl_2 (1 mL) gave a crude product which was purified by column chromatography (90:10 to 85:15 hexane-EtOAc) to give *dimer* **6** (13.5 mg, 44% yield) as a yellow oil as a 50:50 mixture of geometric isomers. δ_H (500 MHz, CD_3OD) 8.09 (0.5H, s, benzofuranyl 2-H), 8.06 (0.5H, s, benzofuranyl 2-H), 7.63 (0.5H, dd, *J* = 7.7, 1.5 Hz, benzofuranyl 4-H), 7.59-7.54 (1H, m, benzofuranyl 6-H and 7-H), 7.49 (0.5H, app. dt, *J* = 8.3, 1.0 Hz, benzofuranyl 7-H), 7.32 (0.5H, dd, *J* = 8.4, 0.6 Hz, benzofuranyl 4-H), 7.29 (0.5H, ddd, *J* = 8.3, 7.3 and 1.5 Hz, benzofuranyl 5-H), 7.26 (0.5H, td, *J* = 7.6, 1.0 Hz, benzofuranyl 5-H), 7.22 (0.5H, ddd, *J* = 8.2, 7.3, 1.0 Hz, benzofuranyl 6-H), 4.30 (1H, q, *J* = 7.1 Hz, ethyl CH_2), 4.26 (1H, q, *J* = 7.1 Hz, ethyl CH_2), 1.31 (1.5H, t, *J* = 7.1 Hz, ethyl CH_3), 1.30 (1.5H, t, *J* = 7.1 Hz, ethyl CH_3) ppm; δ_C (126 MHz, CD_3OD) 168.1 (C=O), 159.6 (benzofuranyl C-7a), 156.4 (benzofuranyl C-7a), 154.9 (C=O), 154.8 (benzofuranyl C-2), 146.7 (benzofuranyl C-2), 135.9 (benzofuranyl C-4), 134.1 (benzofuranyl C-6), 128.3 (benzofuranyl C-3a), 126.3 (benzofuranyl C-6), 125.2 (benzofuranyl C-5), 123.6 (benzofuranyl C-5), 122.8 (benzofuranyl C-7), 118.3 (benzofuranyl C-4), 113.0 (benzofuranyl C-3), 112.1 (benzofuranyl C-7), 108.6 (benzofuranyl C-3), 86.5 (alkenyl C), 81.7 (alkenyl C), 63.3 (ethyl CH_2), 62.2 (ethyl CH_2), 14.6 (ethyl CH_3), 14.4 (ethyl CH_3) ppm, 23 of 24 expected signals observed. HRMS Found M+Na 427.1150. $C_{24}H_{20}NaO_6$ requires M+Na 427.1152.

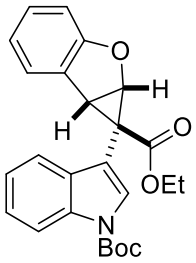
Ethyl (4*E*)-5-(4-methoxyphenyl)-2-[4-(trifluoromethyl)phenyl]pent-4-enoate 7



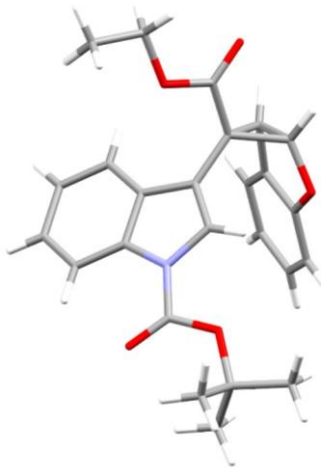
Following **General Procedure B**, α-diazo ester **S6** (156 mg, 0.600 mmol), co-substrate **C1** (59 µL, 0.400 mmol) and $Rh_2(pfb)_4$ (8.5 mg, 2 mol%) in CH_2Cl_2 (4 mL) gave a crude product which was purified by mass-directed purification, with a gradient of 45:55→25:75 H_2O (0.1% formic acid)/MeCN over 9 min to give *C-H insertion product* **7** (14.8 mg, 10% yield) as a colourless oil. δ_H (500 MHz, $CDCl_3$) 7.59 (2H, d, *J* = 8.2 Hz, CF_3-aryl 3-H and 5-H), 7.47 (2H, d, *J* = 8.2 Hz, CF_3-aryl 2-H and 6-H), 7.24-7.20 (2H, m, OMe-aryl 2-H and 6-H), 6.85-6.79 (2H, m, OMe-aryl 3-H and 5-H), 6.38 (1H, d,

J = 15.8 Hz, 5-H), 5.93 (1H, dt, *J* = 15.8, 7.2 Hz, 4-H), 4.20-4.07 (2H, m, ethyl CH_2), 3.79 (3H, s, OCH_3), 3.74 (1H, dd, *J* = 8.1, 7.2 Hz, 2-H), 3.00-2.92 (1H, m, 3-H_A), 2.65 (1H, dtd, *J* = 8.1, 7.2, 1.3 Hz, 3-H_B), 1.20 (3H, t, *J* = 7.1 Hz, ethyl CH_3) ppm; δ_C (126 MHz, $CDCl_3$) 172.9 (C=O), 159.2 (OMe-aryl C-4), 142.8 (CF_3-aryl C-1), 132.5 (C-5), 130.1 (OMe-aryl C-1), 129.8 (q, *J* = 32.3 Hz, CF_3-aryl C-4), 128.5 (CF_3-aryl C-2 and C-6), 127.4 (OMe-aryl C-2 and C-6), 125.7 (q, *J* = 3.7 Hz, CF_3-aryl C-3 and C-5), 124.3 (q, *J* = 272.2 Hz, CF_3), 124.1 (C-4), 114.1 (OMe-aryl C-3 and C-5), 61.2 (ethyl CH_2), 55.4 (OCH_3), 52.1 (C-2), 37.1 (C-3), 14.3 (ethyl CH_3) ppm; δ_F (376 MHz, $CDCl_3$) -62.5 ppm; HRMS Found M+H 379.1521. $C_{21}H_{22}F_3O_3$ requires 379.1516.

tert-Butyl 3-[(2*S,3*R**,4*S**)-3-(ethoxycarbonyl)-5-oxatricyclo[4.4.0.0^{2,4}]deca-1(6),7,9-trien-3-yl]-1H-indole-1-carboxylate 8**



Following **General Procedure A**, α-diazo ester **S4** (98 mg, 0.300 mmol), co-substrate **C3** (22 µL, 0.200 mmol) and $[Ru(bpz)_3][PF_6]_2$ (3.4 mg, 2 mol%) in CH_2Cl_2 (2 mL) gave a crude product which was purified by column chromatography (95:5 hexane-EtOAc) to give *cyclopropane* **8** (10.8 mg, 25% yield) as a yellow oil. δ_H (500 MHz, $CDCl_3$) 7.94 (1H, br.s, indolyl 7-H), 7.46 (1H, br. dd, *J* = 7.0, 1.0 Hz, indolyl 4-H), 7.24-7.13 (4H, m, 10-H and indolyl 2-H, 5-H and 6-H), 6.93-6.88 (1H, m, 8-H), 6.68 (1H, br. t, *J* = 7.0 Hz, 9-H), 6.56 (1H, d, *J* = 8.1 Hz, 7-H), 5.42 (1H, d, *J* = 5.0 Hz, 4-H), 4.21-4.09 (2H, m, ethyl CH_2), 3.89 (1H, d, *J* = 5.0 Hz, 2-H), 1.59 (9H, s, Boc CH_3), 1.14 (3H, t, *J* = 7.1 Hz, ethyl CH_3) ppm; δ_C (126 MHz, $CDCl_3$) 172.6 (ester C=O), 160.6 (C-6), 149.5 (Boc C=O), 134.8 (indolyl C-7a), 130.8 (indolyl C-3a), 128.2 (C-8), 128.1 (indolyl C-2), 125.8 (C-1), 125.2 (C-10), 124.1 (indolyl C-5 or C-6), 122.4 (indolyl C-5 or C-6), 121.9 (C-9), 119.4 (indolyl C-4), 115.0 (indolyl C-7), 109.7 (C-7), 109.5 (indolyl C-3), 83.5 (Boc C), 70.5 (C-4), 61.7 (ethyl CH_2), 37.6 (C-2), 28.3 (Boc CH_3), 23.0 (C-3), 14.4 (ethyl CH_3) ppm. HRMS Found M+H 420.1812. $C_{25}H_{26}NO_5$ requires M+H 420.1805. The relative configuration was determined by X-ray crystallography.

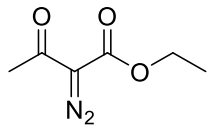


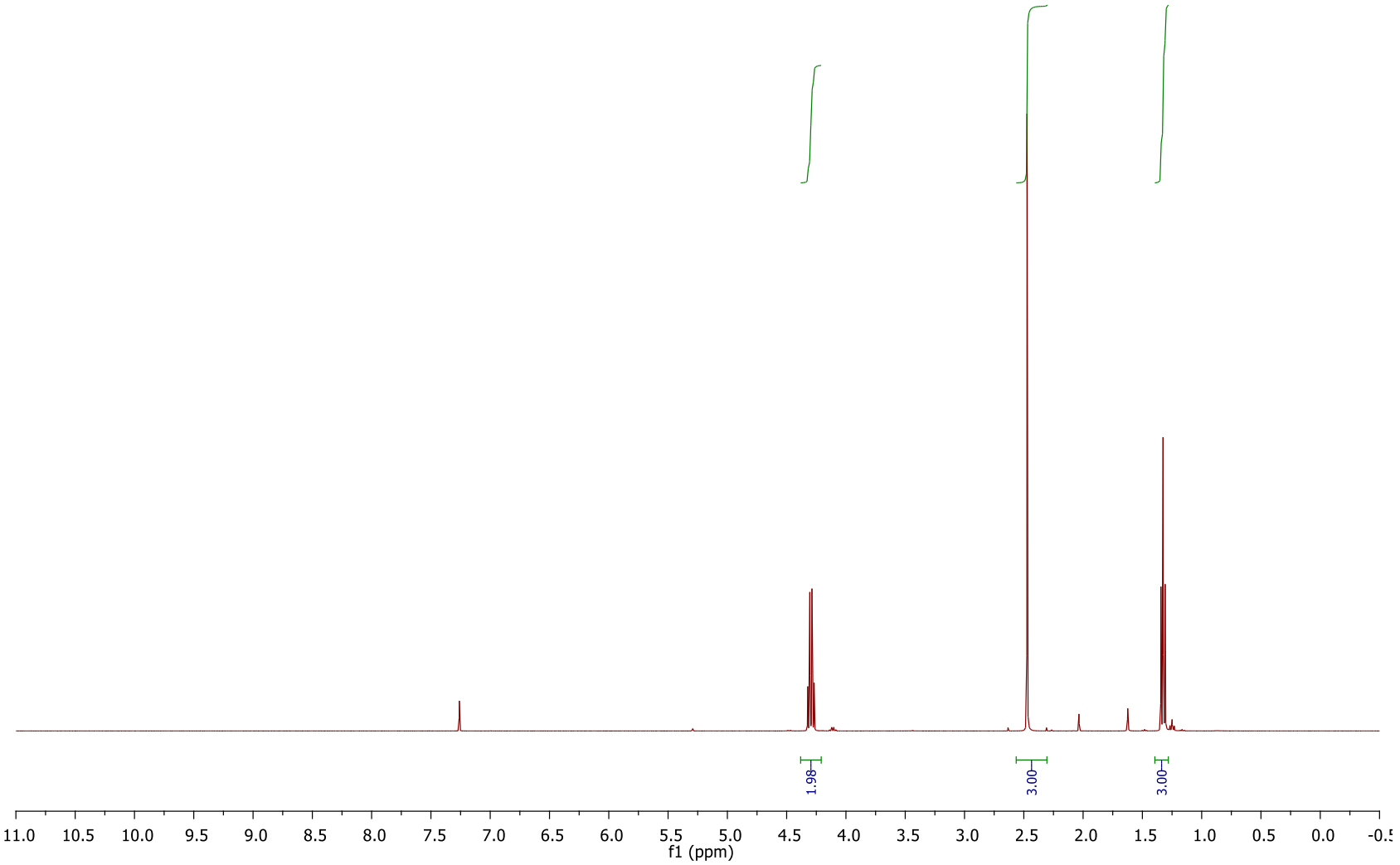
5 References

1. A. W. Squibb, M. R. Taylor, B. L. Parnas, G. Williams, R. Girdler, P. Waghorn, A. G. Wright and F. S. Pullen, *J. Chrom. A* 2008, **1189**, 101.
2. M.-A. Bray, S. Singh, H. Han, C. T. Davis, B. Borgeson, C. Hartland, M. Kost-Alimova, S. M. Gustafsdottir, C. Gibson, and A. E. *Nature Protocols* 2016, **11**, 1757.
3. M. H. Woehrmann, W. M. Bray, J. K. Durbin, S. C. Nisam, A. K. Michael, E. Glassey, J. M. Stuart and R. S. Lokey, *Mol. BioSyst.* 2013, **9**, 2604.
4. A. J. Boddy, D. P. Affron, C. J. Cordier, E. L. Rivers, A. C. Spivey and J. A. Bull, *Angew. Chem. Int.Ed.* 2019, **58**, 1458.
5. A. M. Jadhav, V. V. Pagar and R.-S. Liu, *Angew. Chem. Int. Ed.* 2012, **51**, 11809.
6. C. Empel, S. Jana, L. W. Ciszewski, K. Zawada, C. Pei, D. Gryko and R. M. Koenigs, *Chem. Eur. J.* 2023, **29**, e202300214.
7. P. Saxena and M. Kapur, *Chem. Asian J.* 2018, **13**, 861.
8. W.-W. Chan, S.-H. Yeung, Z. Zhou, A. S. C. Chan and W.-Y. Yu, *Org. Lett.* 2010, **12**, 604.
9. C. E. Katz and J. Aubé, *J. Am. Chem. Soc.* 2003, **125**, 13948.
10. S. Thurow, A. A. G. Fernandes, Y. Quevedo-Acosta, M. F. de Oliveira, M. G. de Oliveira, I. D. Jurberg, *Org. Lett.* 2019, **21**, 6909.
11. R. Claveau, B. Twamley and S. J. Connon, *Chem. Commun.* 2018, **54**, 3231.
12. N. Kumar, R. Venkatesh and J. Kandasamy, *Org. Biomol. Chem.* 2022, **20**, 6766.

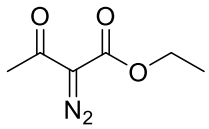
6. NMR spectra

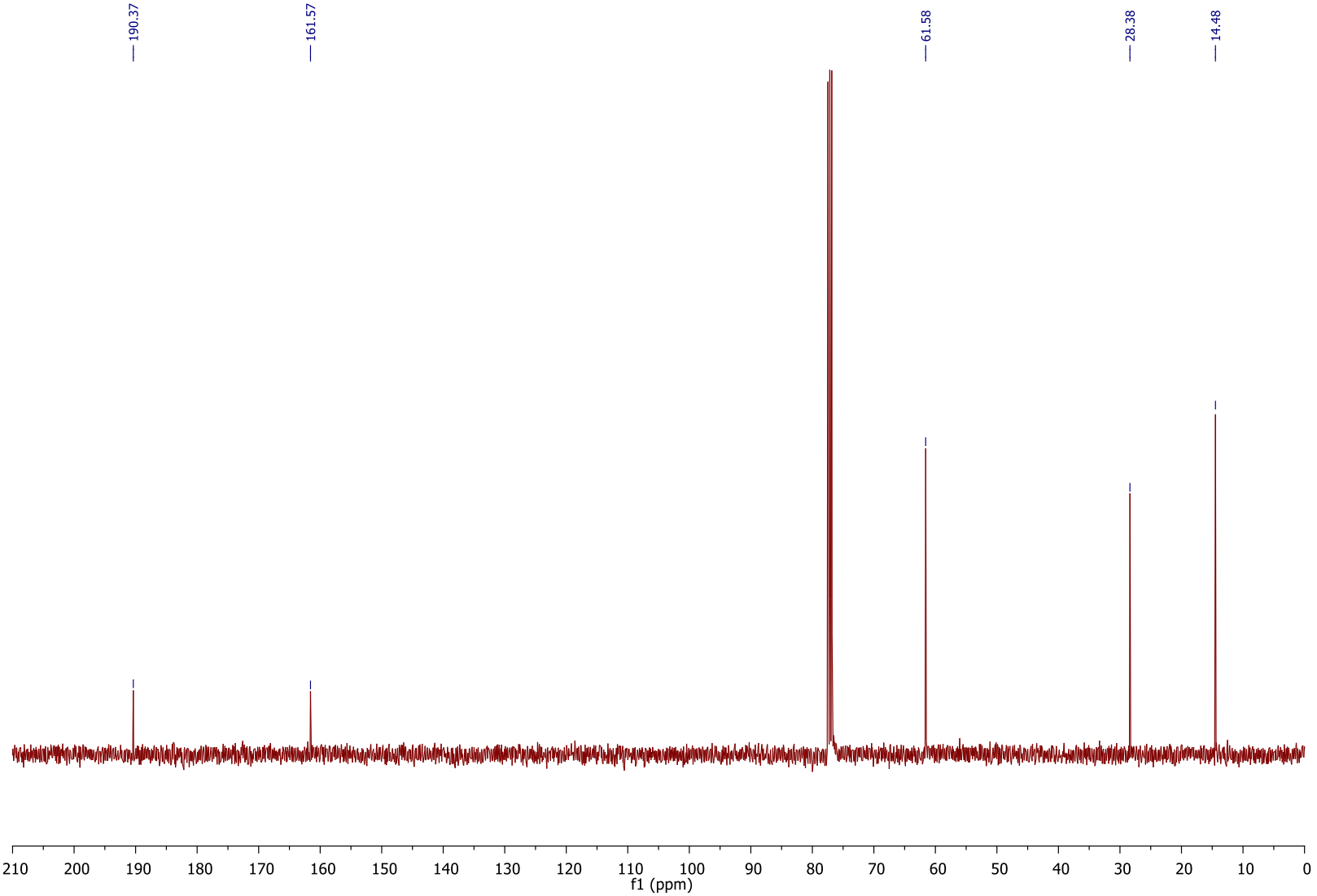
500 MHz ^{1}H spectrum in $CDCl_3$



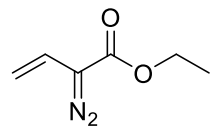


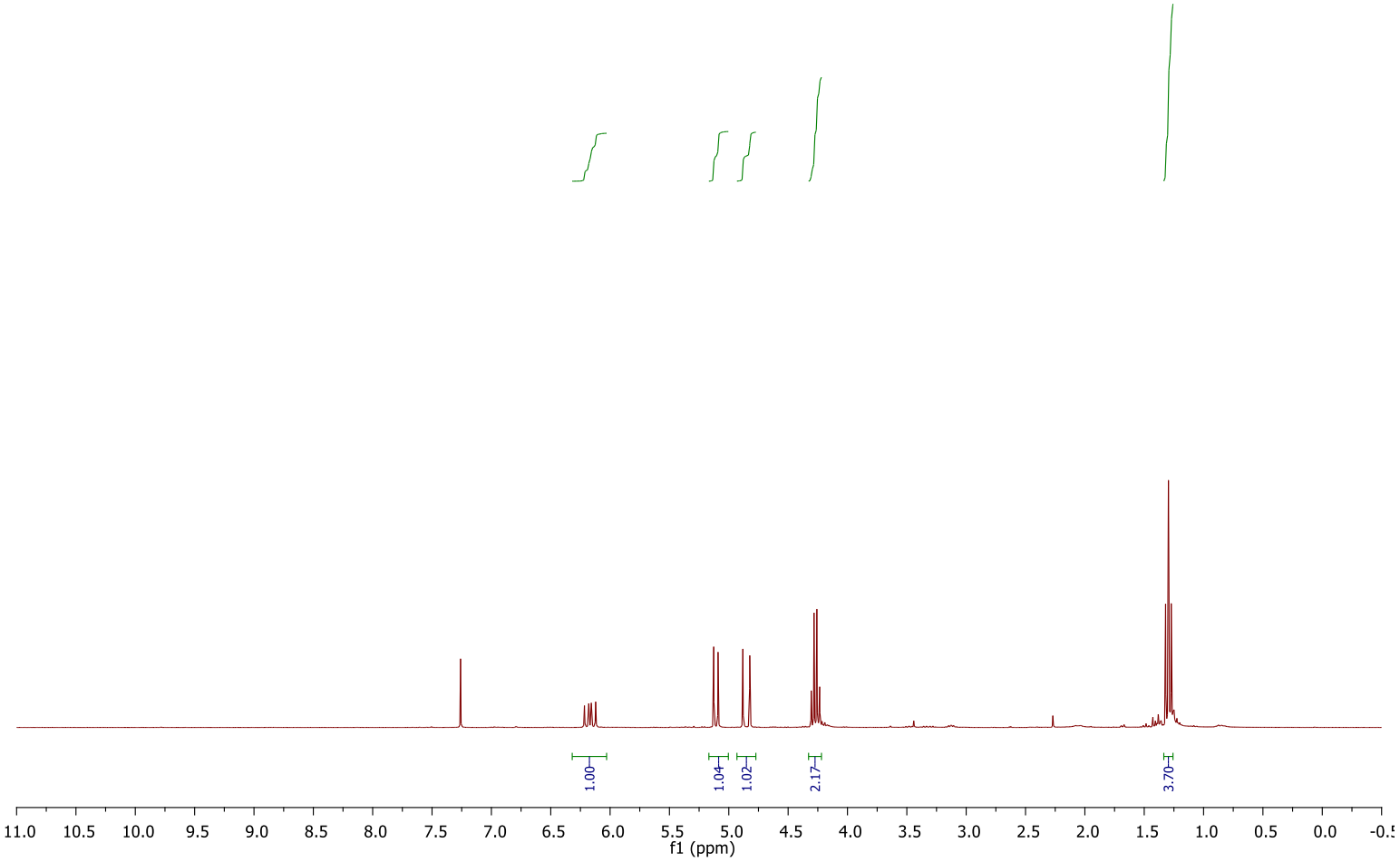
126 MHz ^{13}C spectrum in $CDCl_3$



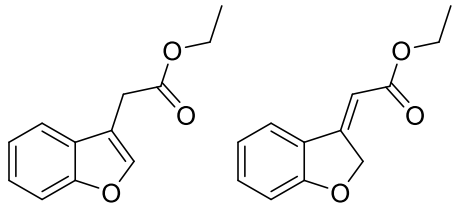


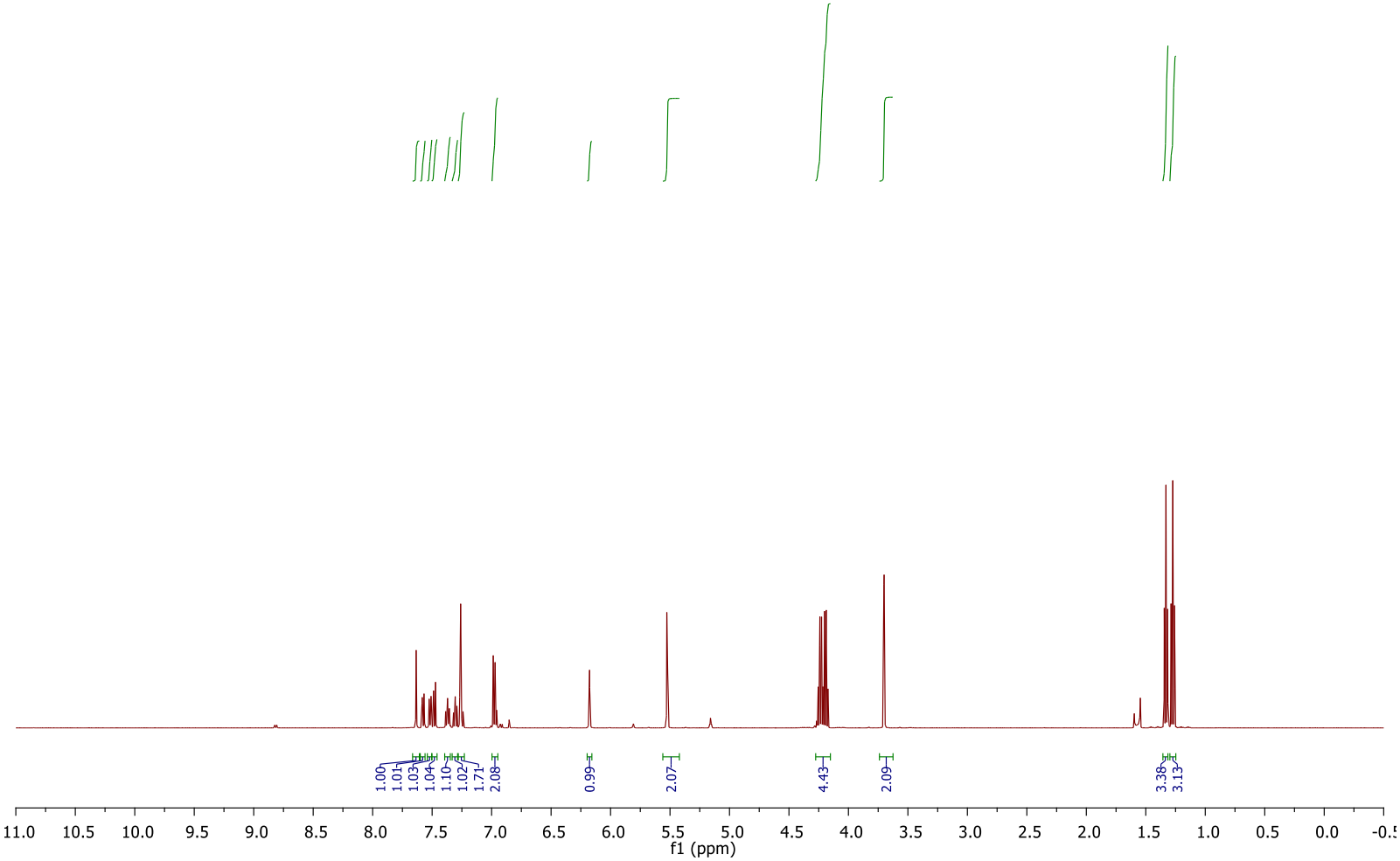
500 MHz ^{1}H spectrum in $CDCl_3$
Compound **S2**



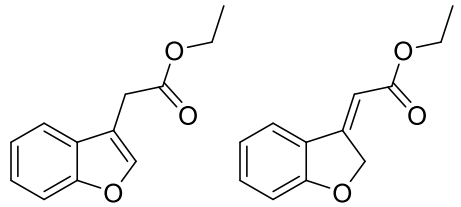


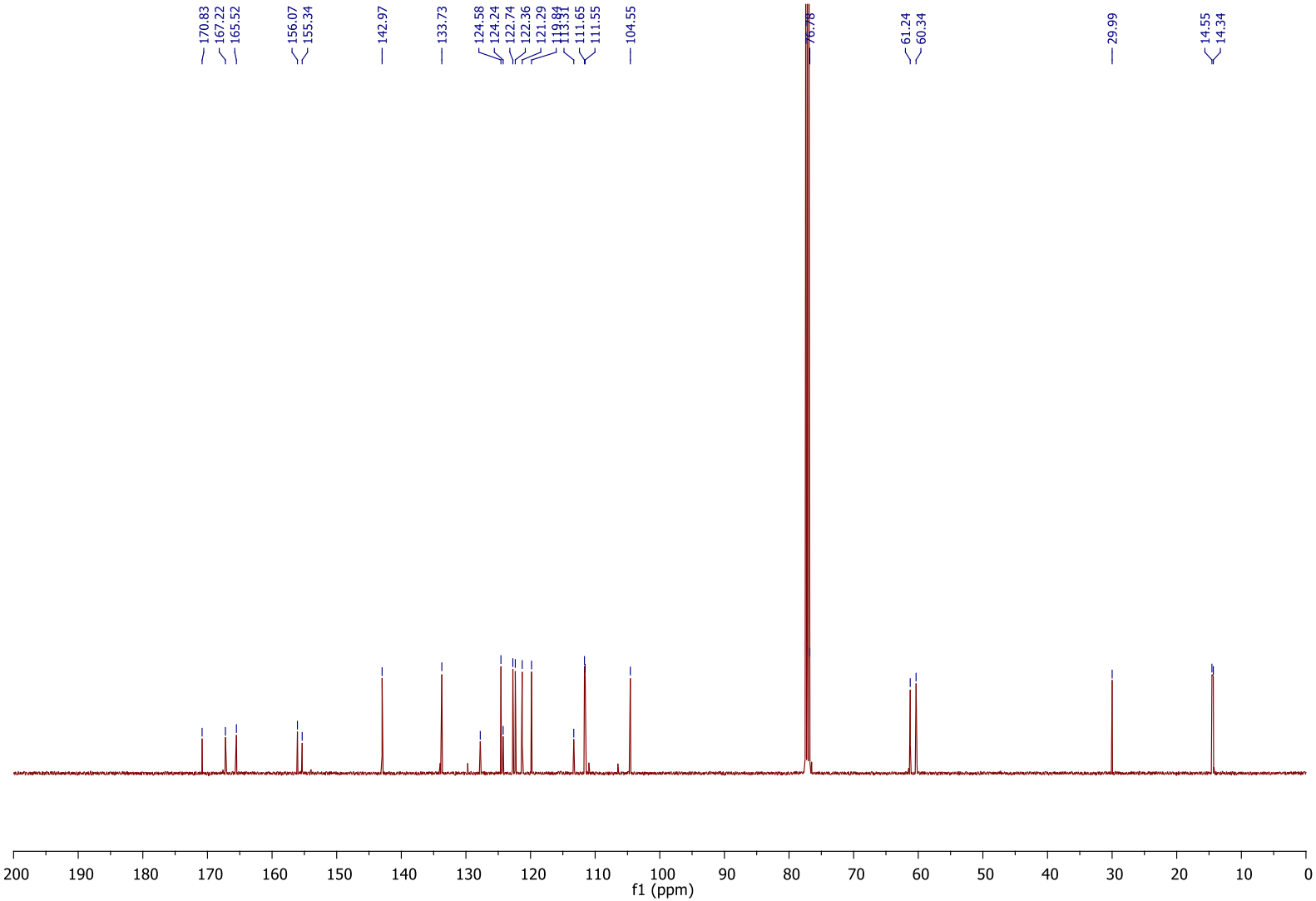
500 MHz ^{1}H spectrum in $CDCl_3$
Compound **SI1a/b**



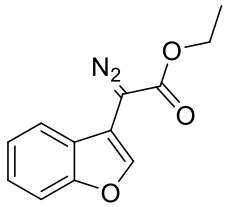


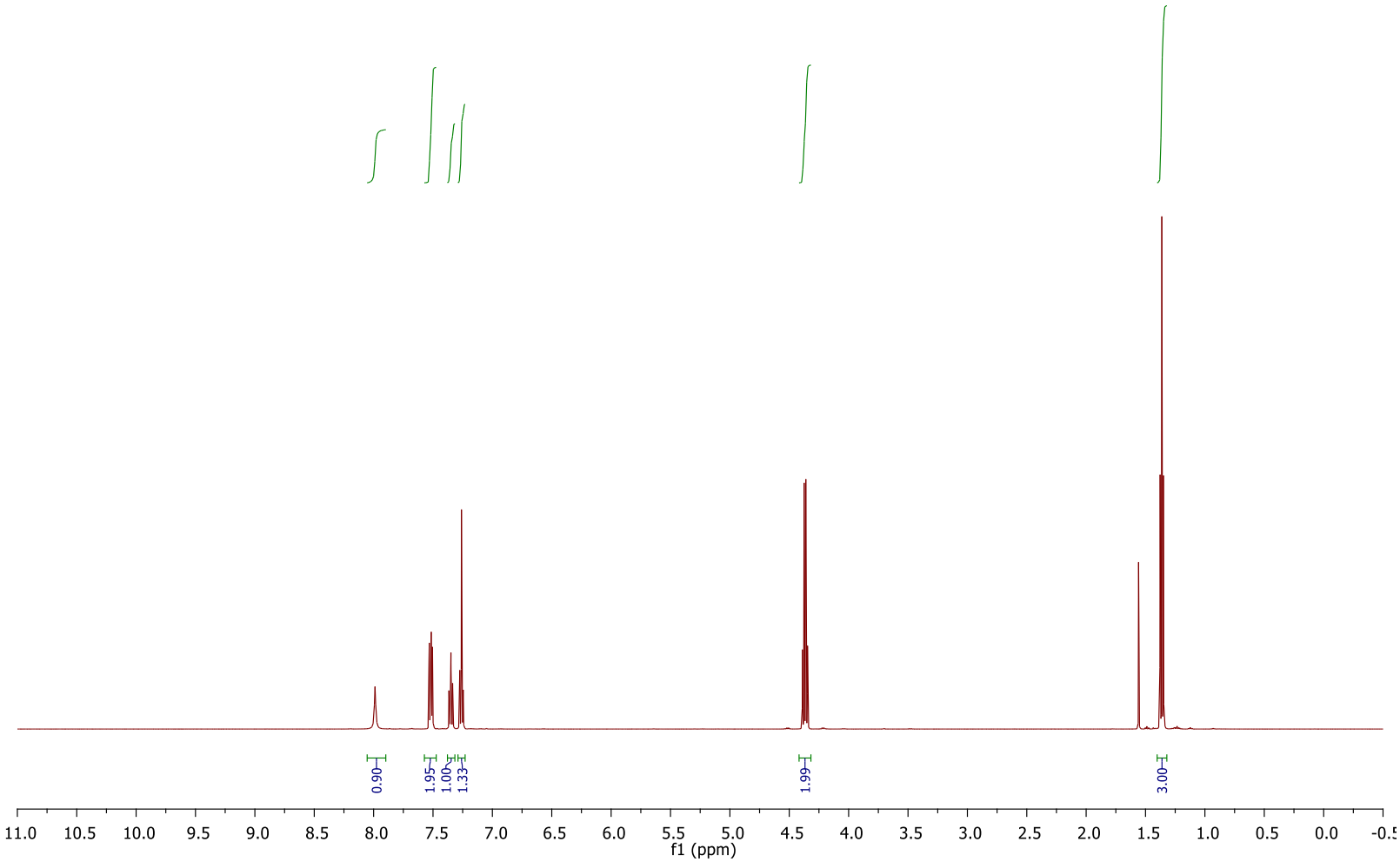
126 MHz ^{13}C spectrum in $CDCl_3$
Compound **SI1a/b**



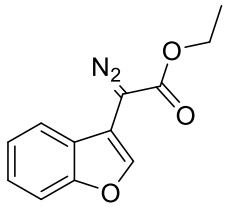


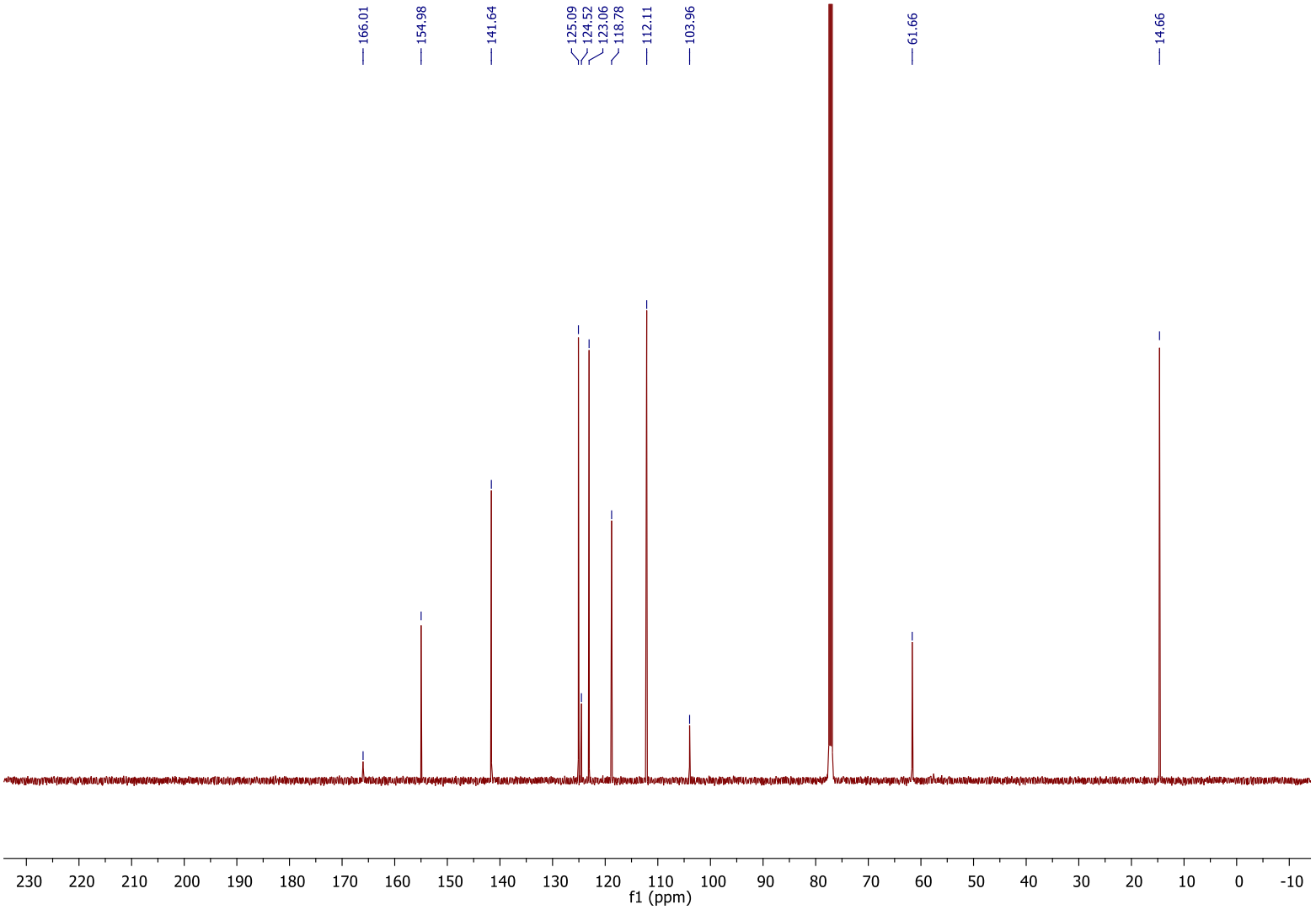
500 MHz ^{1}H spectrum in $CDCl_3$
Compound **S3**



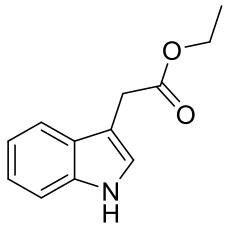


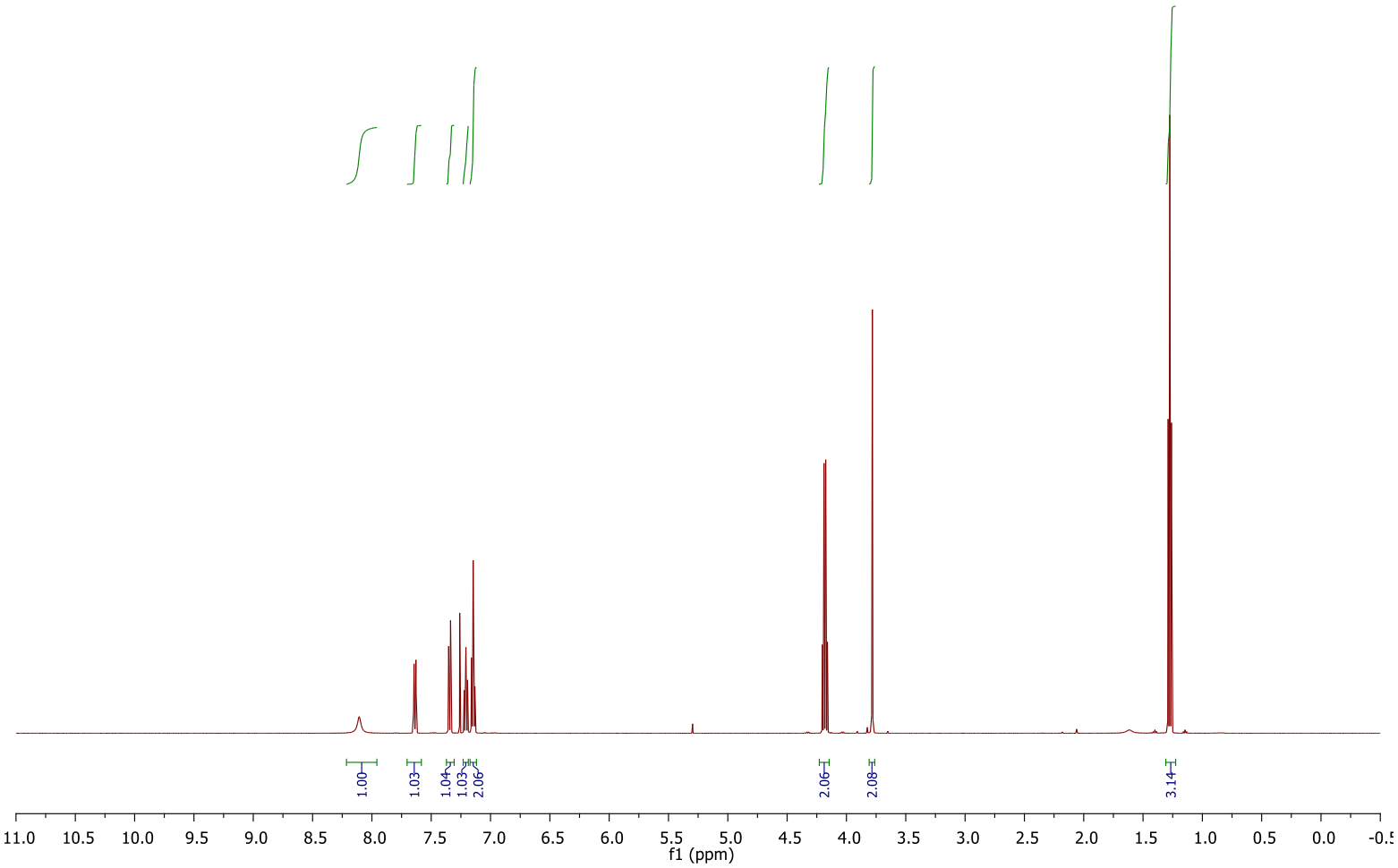
126 MHz ^{13}C spectrum in $CDCl_3$
Compound **S3**



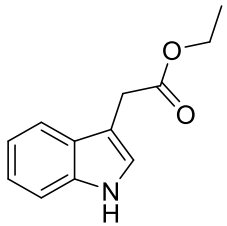


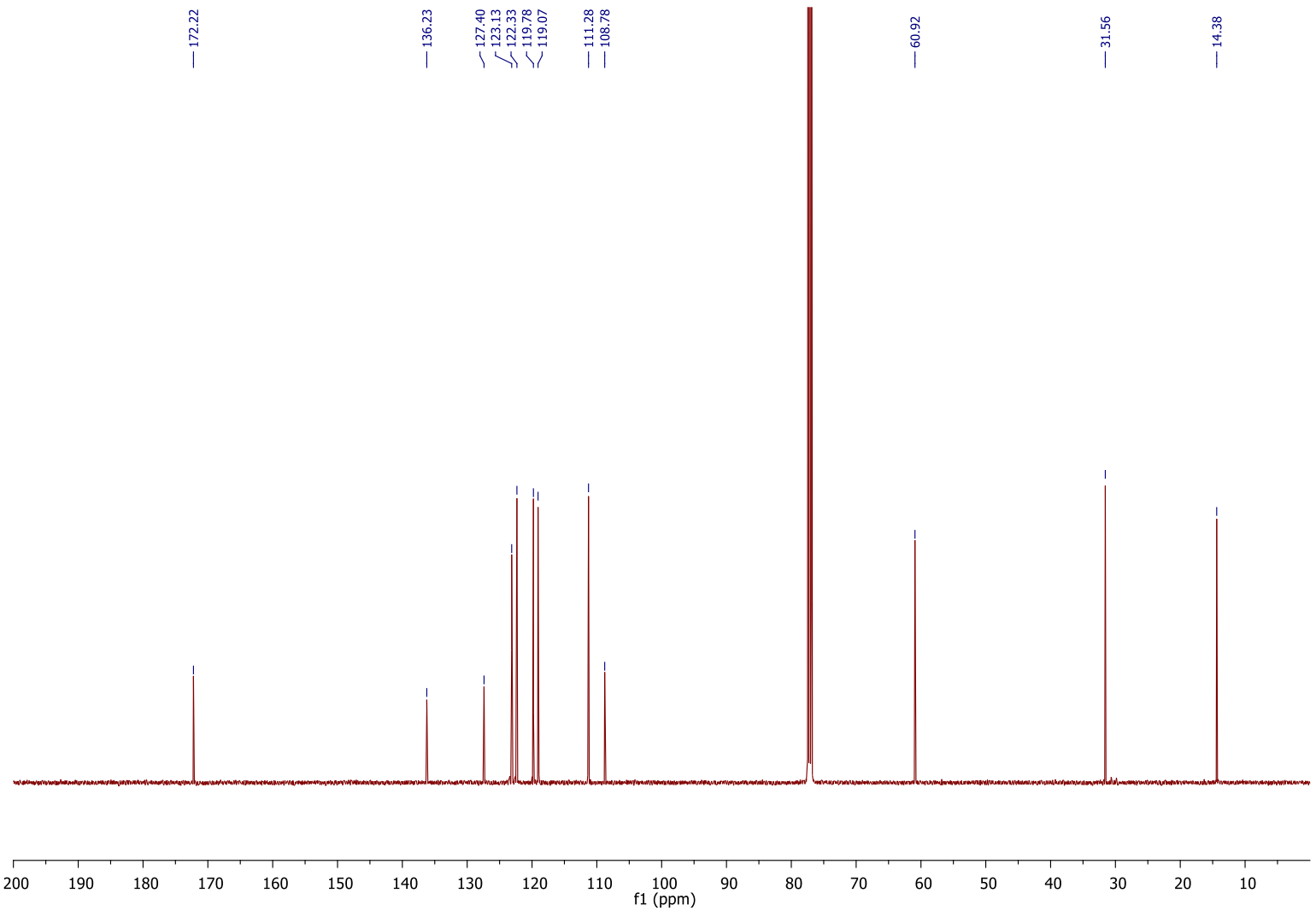
500 MHz ^{1}H spectrum in $CDCl_3$
Compound **SI2**



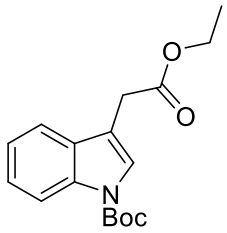


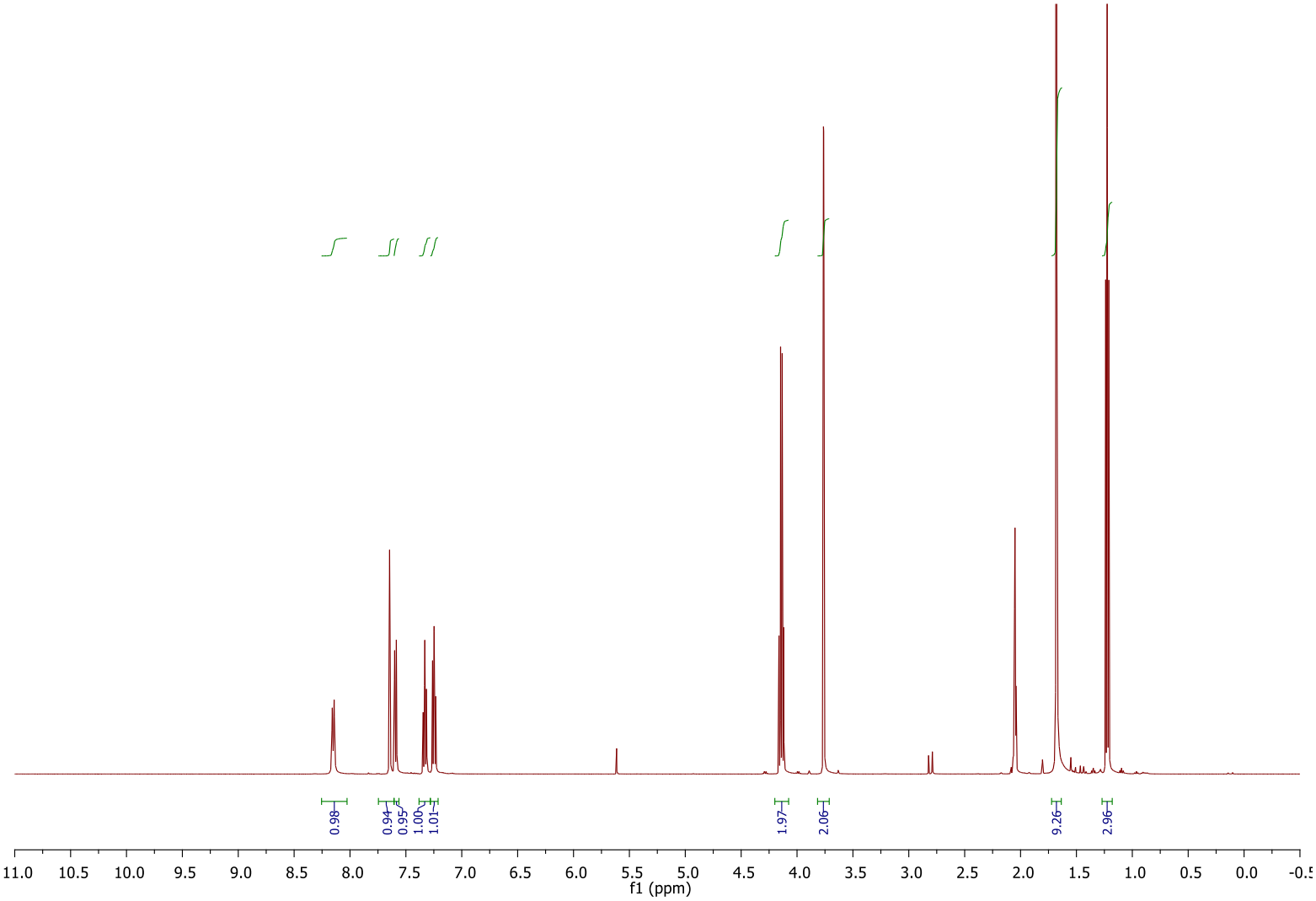
126 MHz ^{13}C spectrum in $CDCl_3$
Compound **SI2**



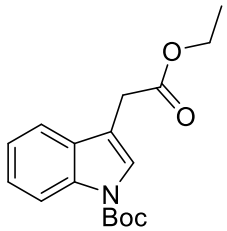


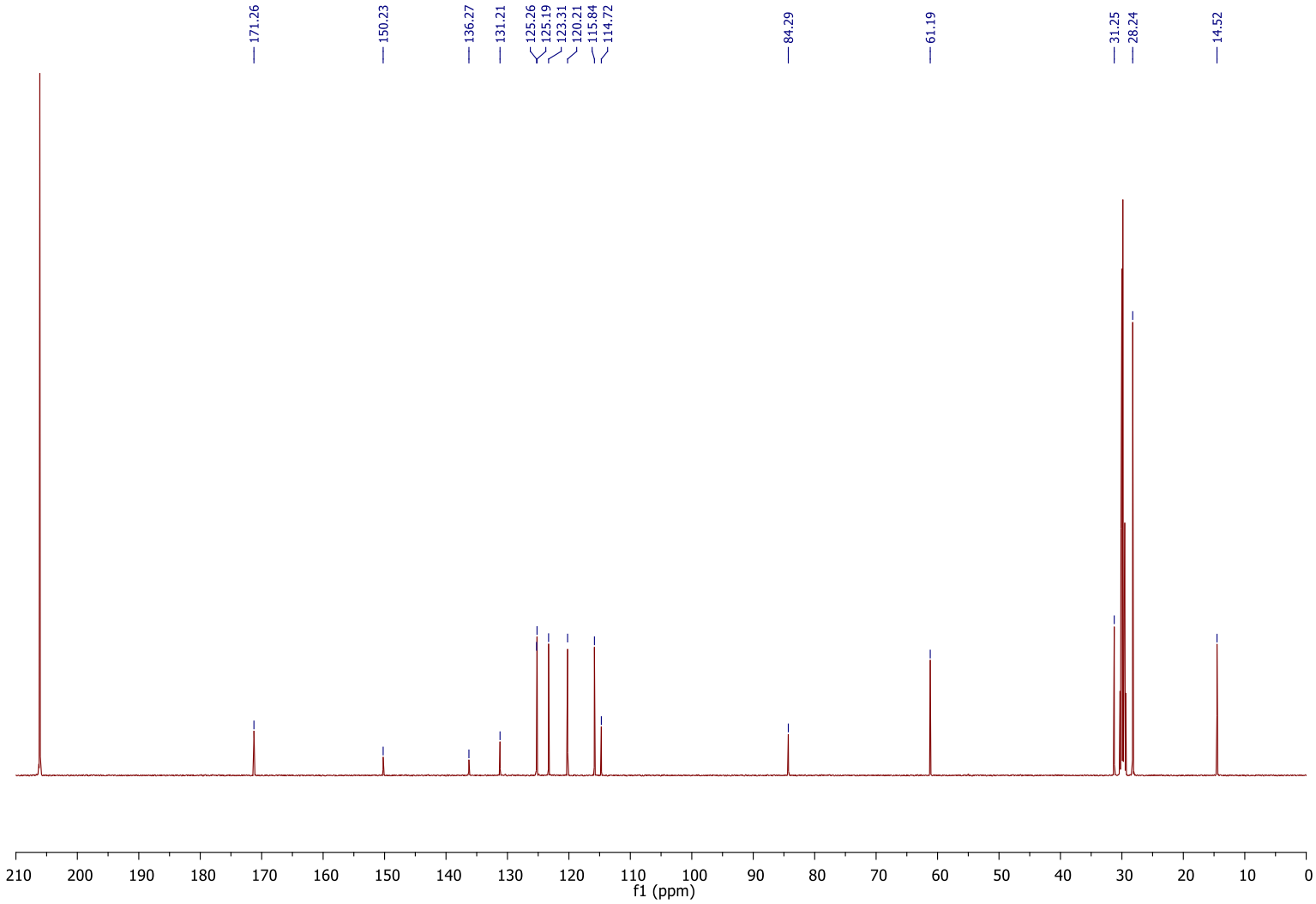
500 MHz ^{1}H spectrum in $CDCl_3$
Compound **SI3**



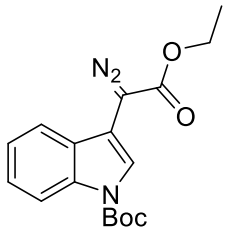


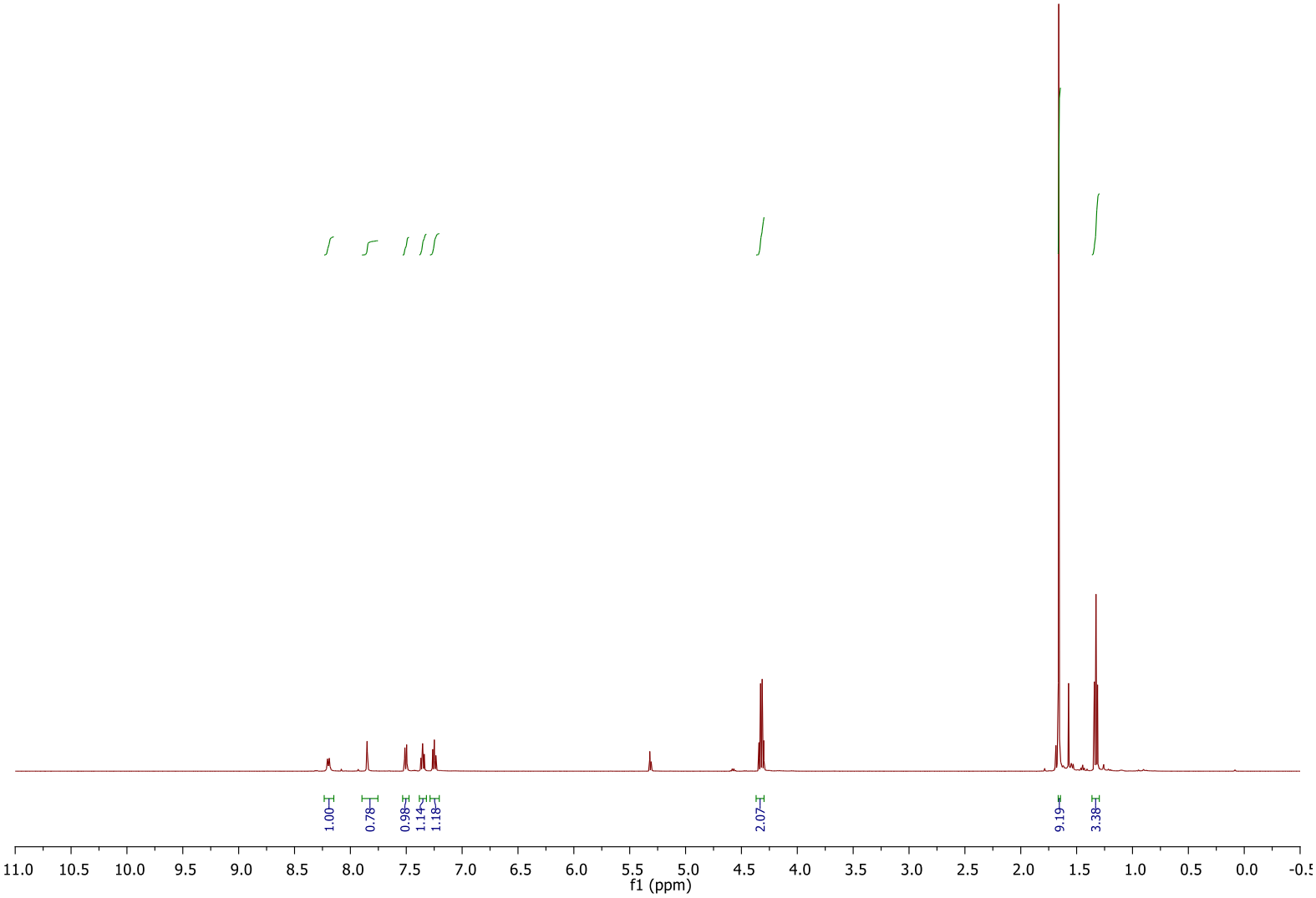
126 MHz ^{13}C spectrum in $CDCl_3$
Compound **SI3**



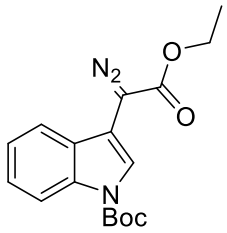


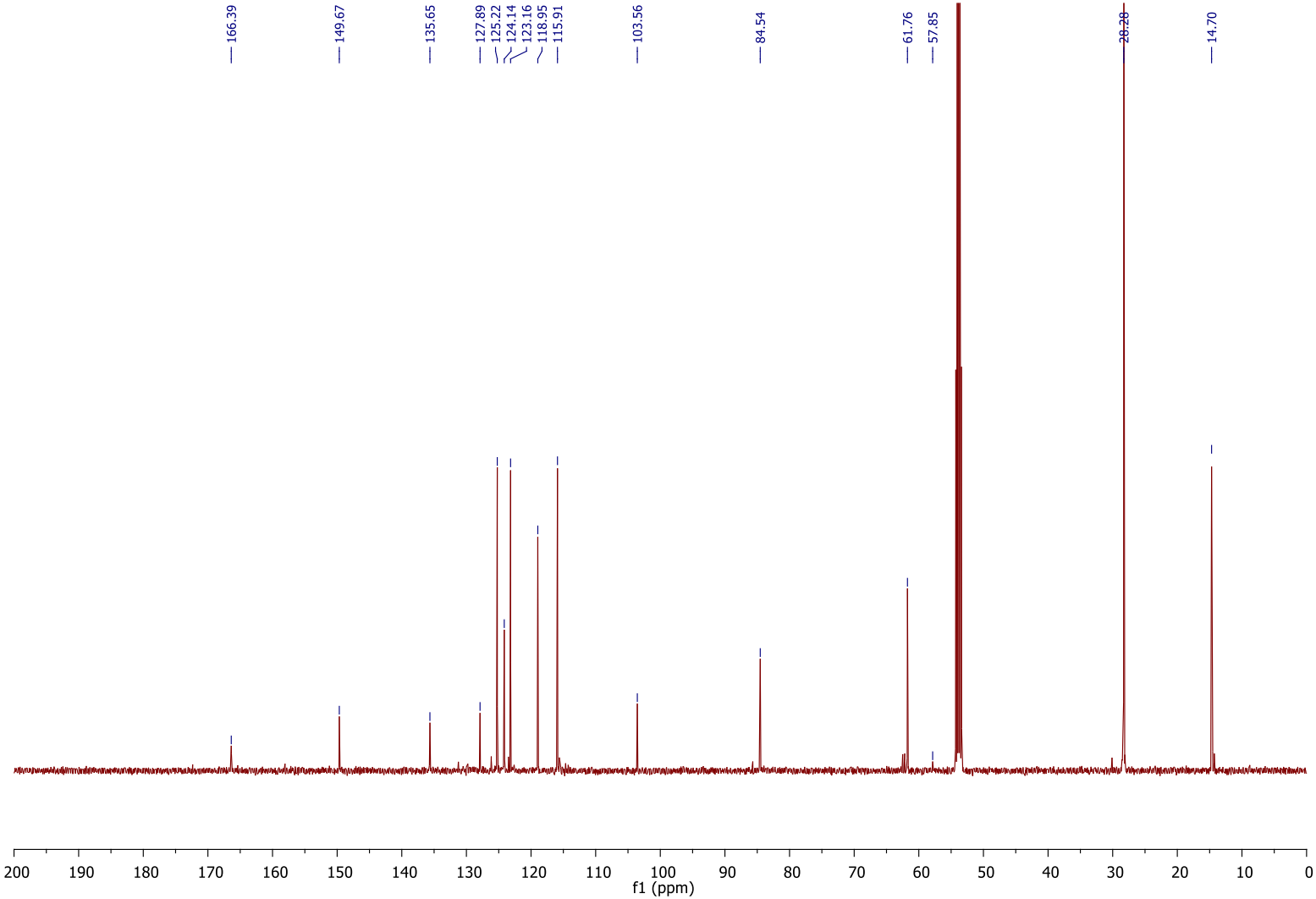
500 MHz ^{1}H spectrum in $CDCl_3$
Compound **S4**



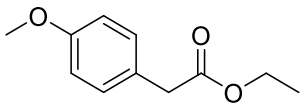


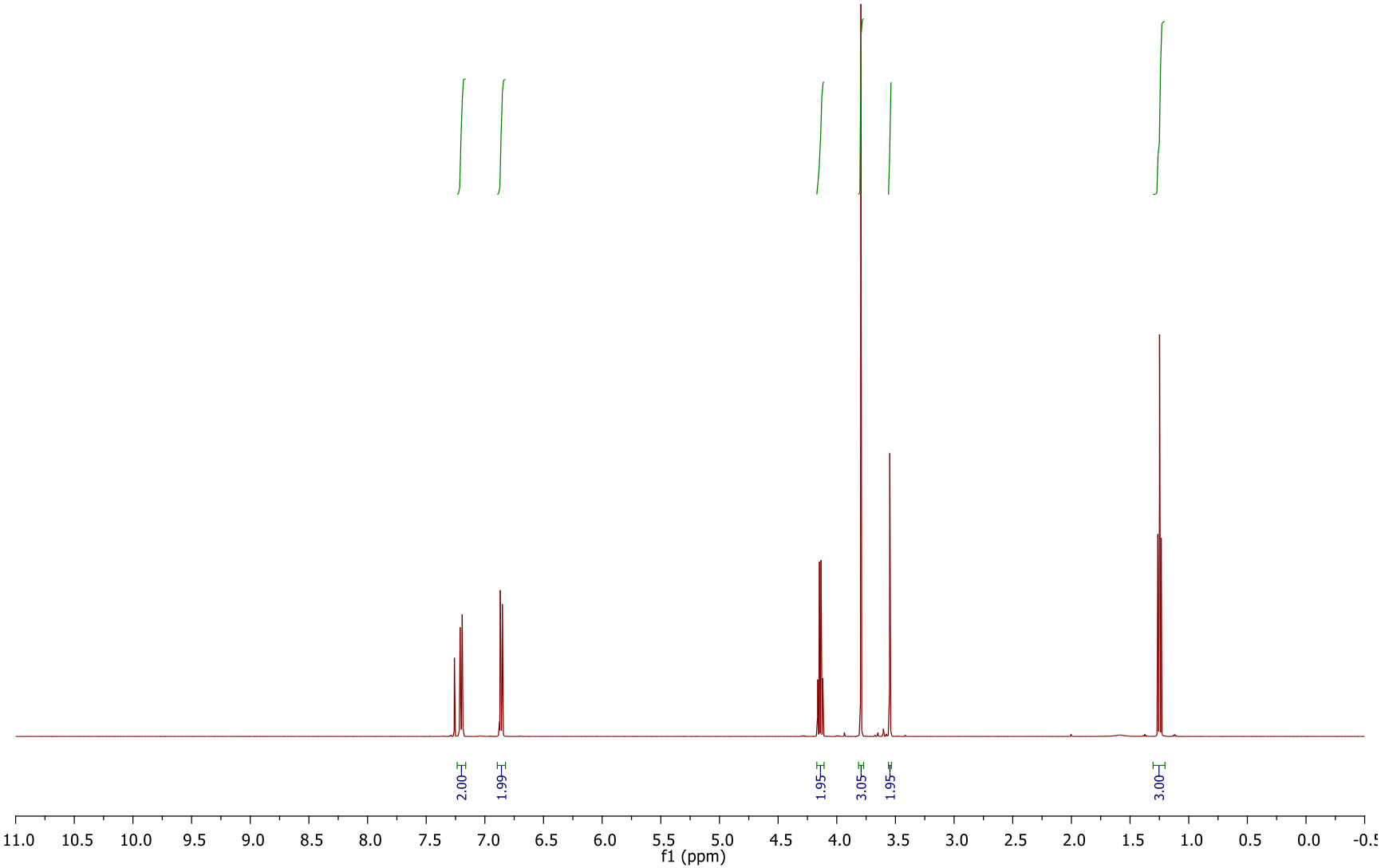
126 MHz ^{13}C spectrum in $CDCl_3$
Compound **S4**



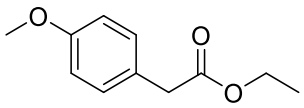


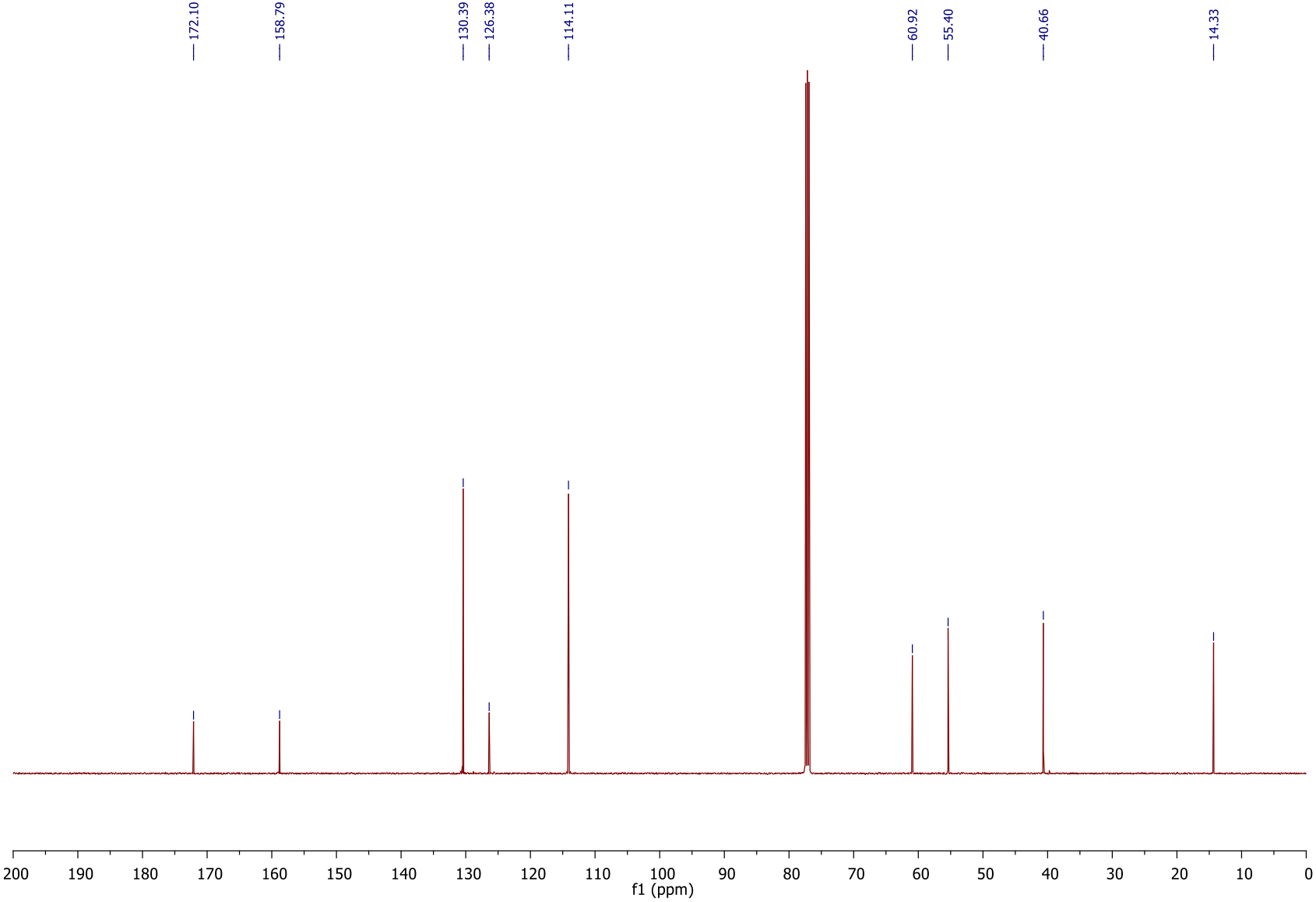
500 MHz ^{1}H spectrum in $CDCl_3$
Compound **SI4**





126 MHz ^{13}C spectrum in $CDCl_3$
Compound **SI4**





500 MHz ^{1}H spectrum in $CDCl_3$
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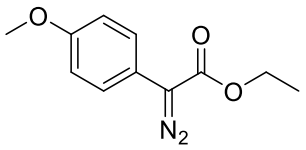
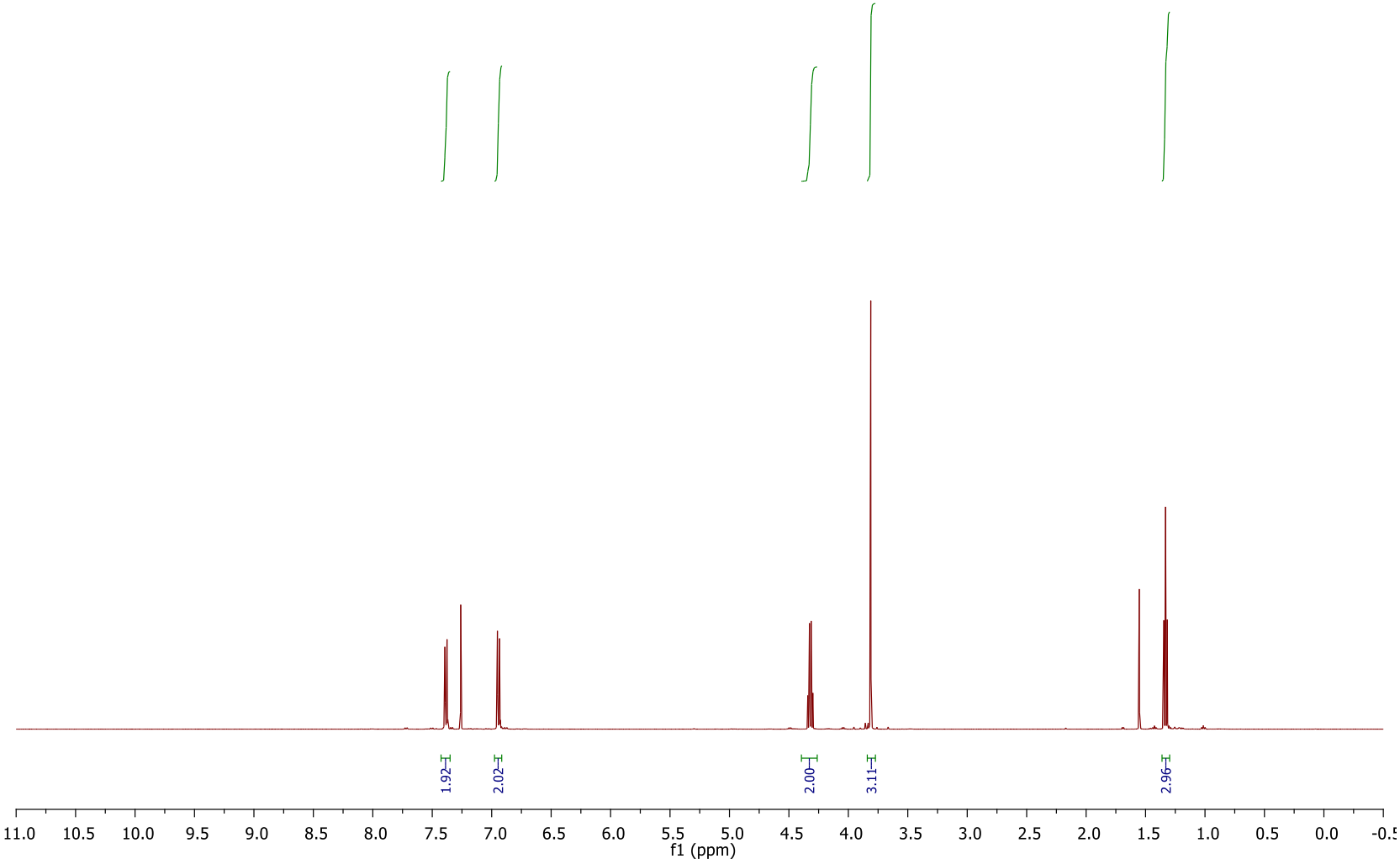
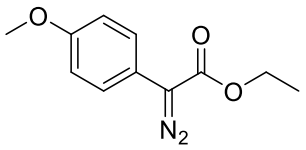
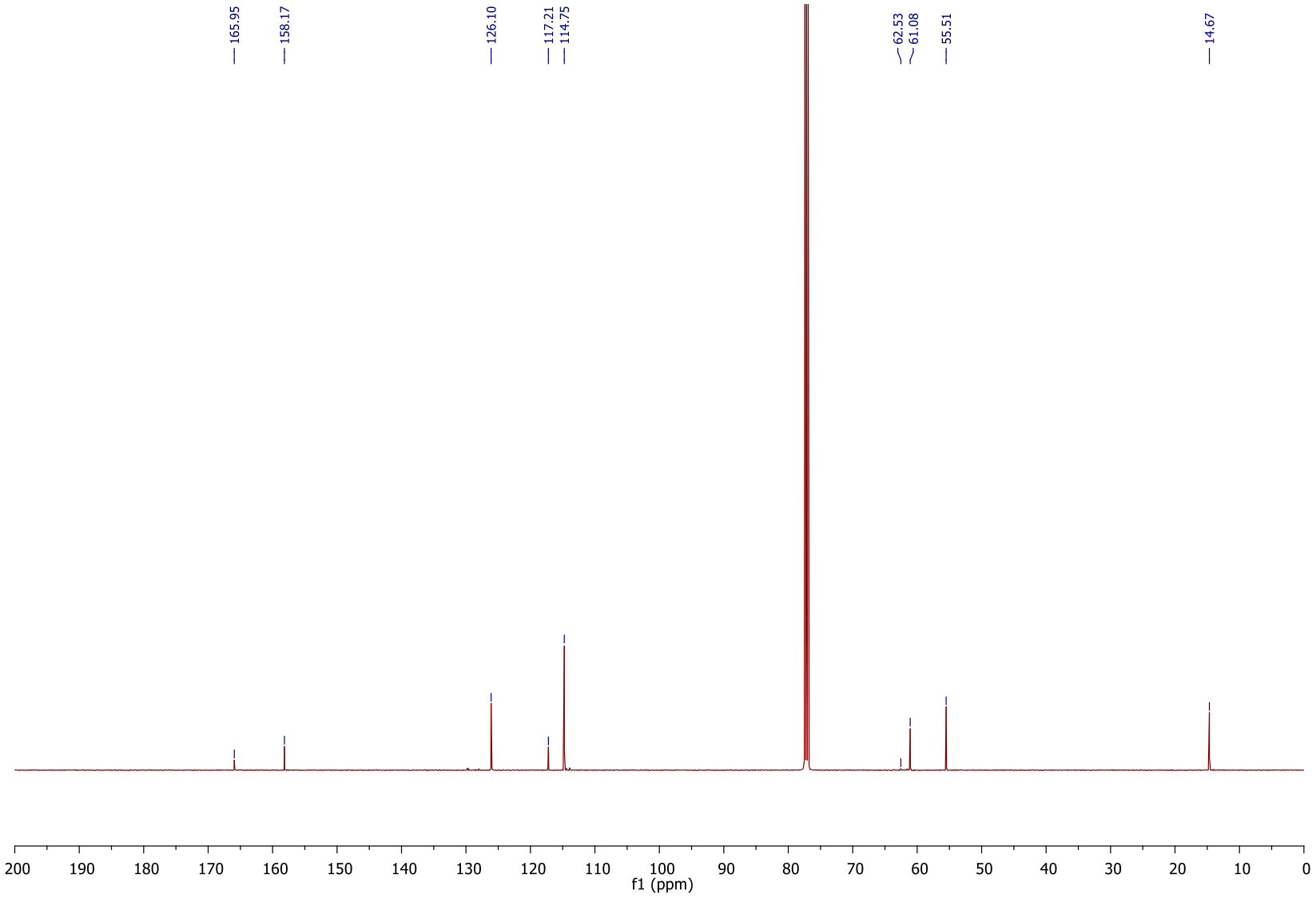




126 MHz ^{13}C spectrum in $CDCl_3$
Compound **S5**





500 MHz ^{1}H spectrum in $CDCl_3$
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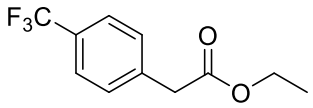

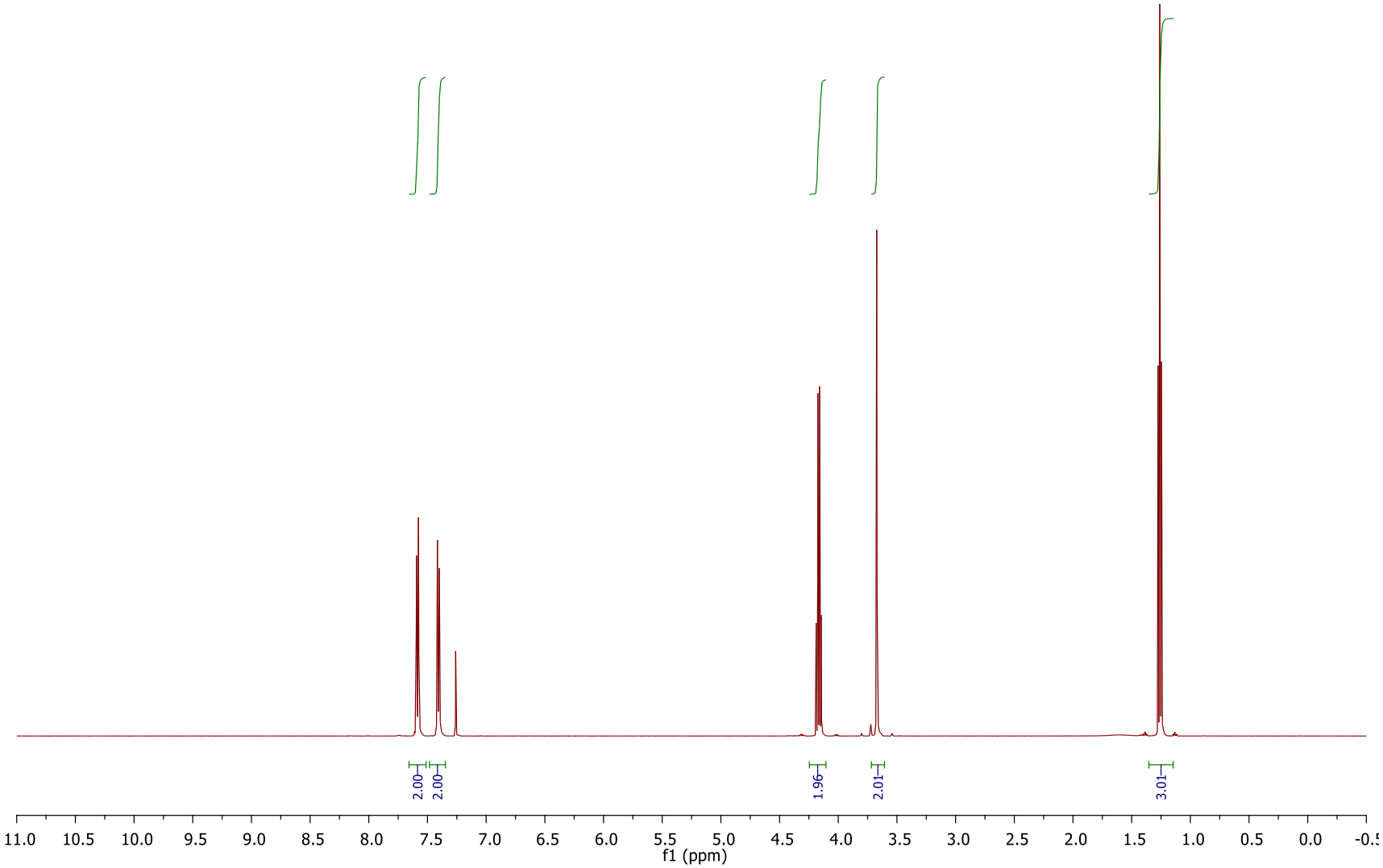

126 MHz ^{13}C spectrum in $CDCl_3$
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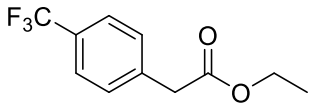

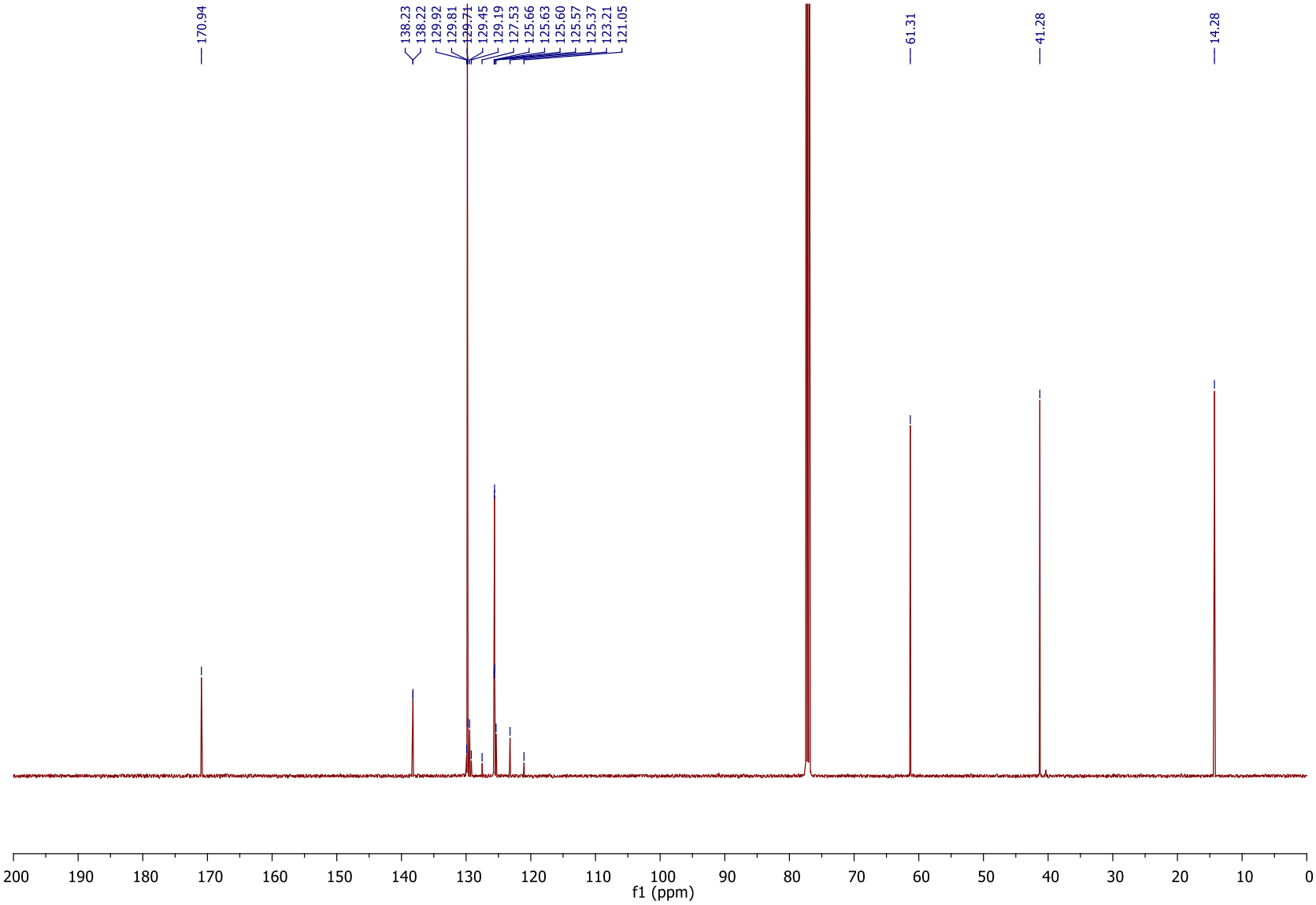

376 MHz ^{19F} spectrum in $CDCl_3$
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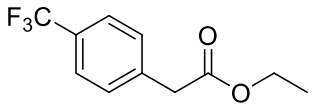

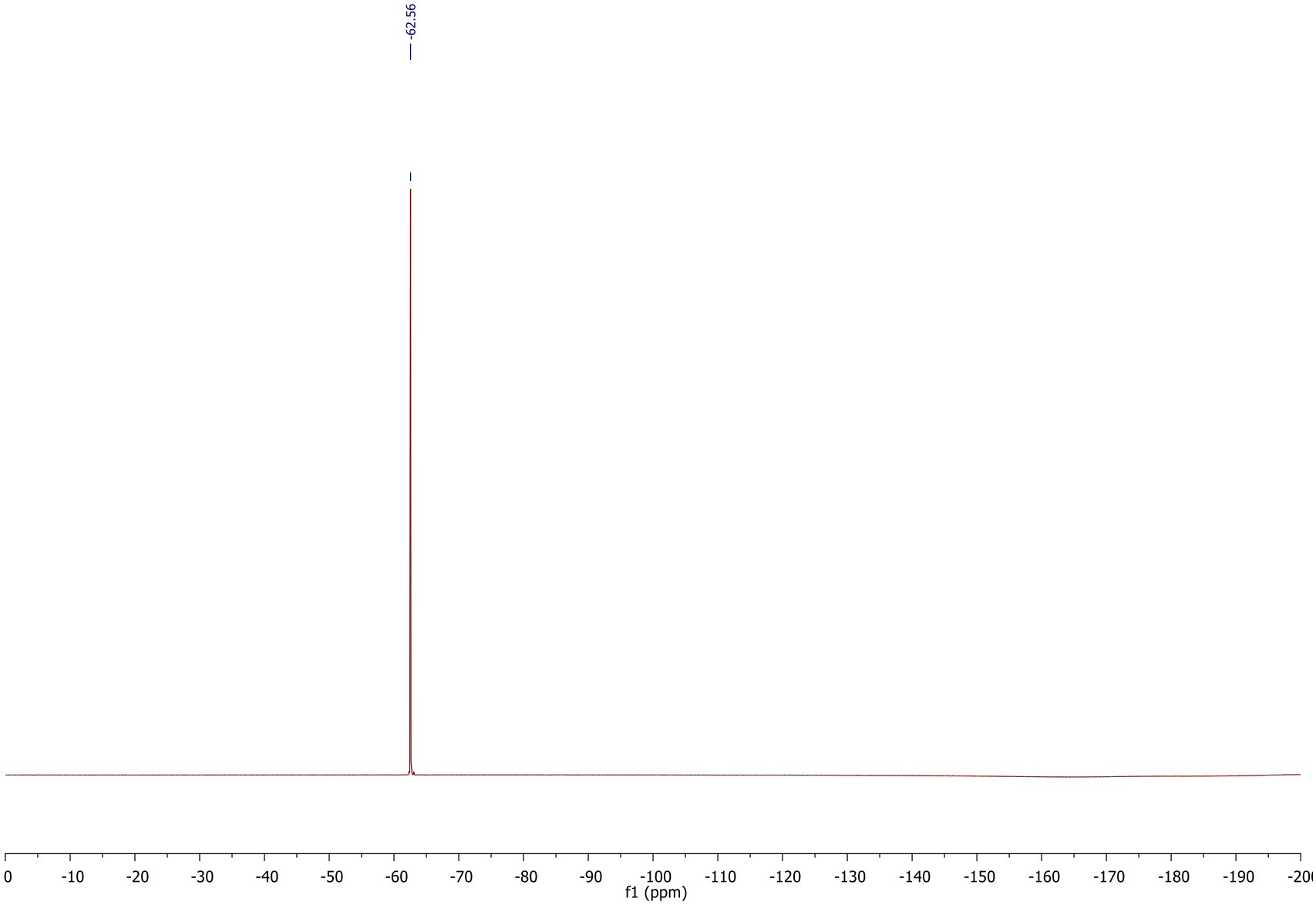

500 MHz ^{1}H spectrum in $CDCl_3$
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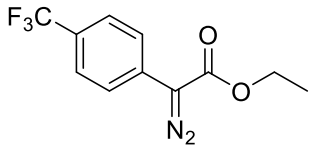
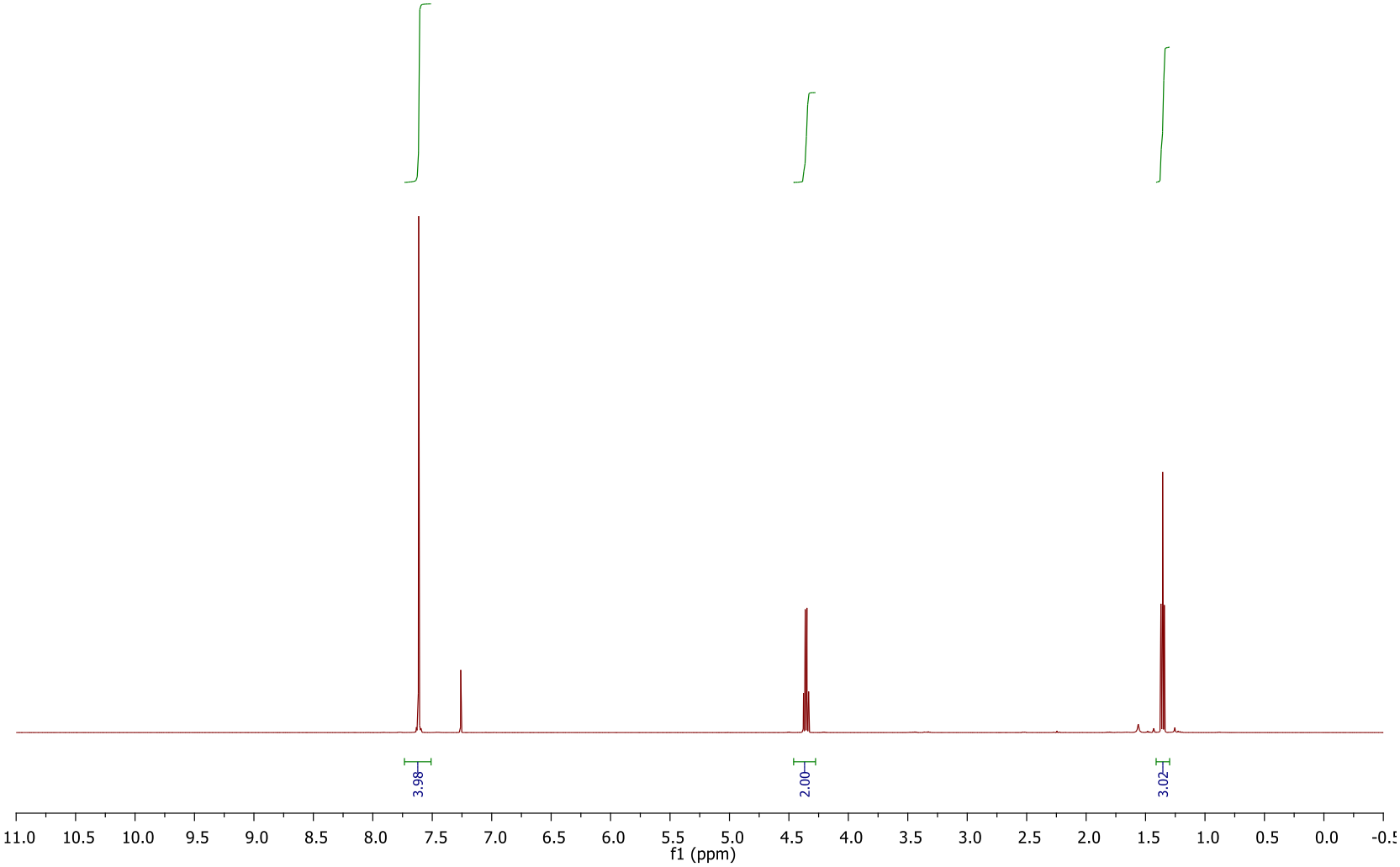
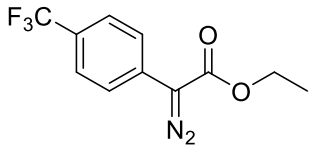
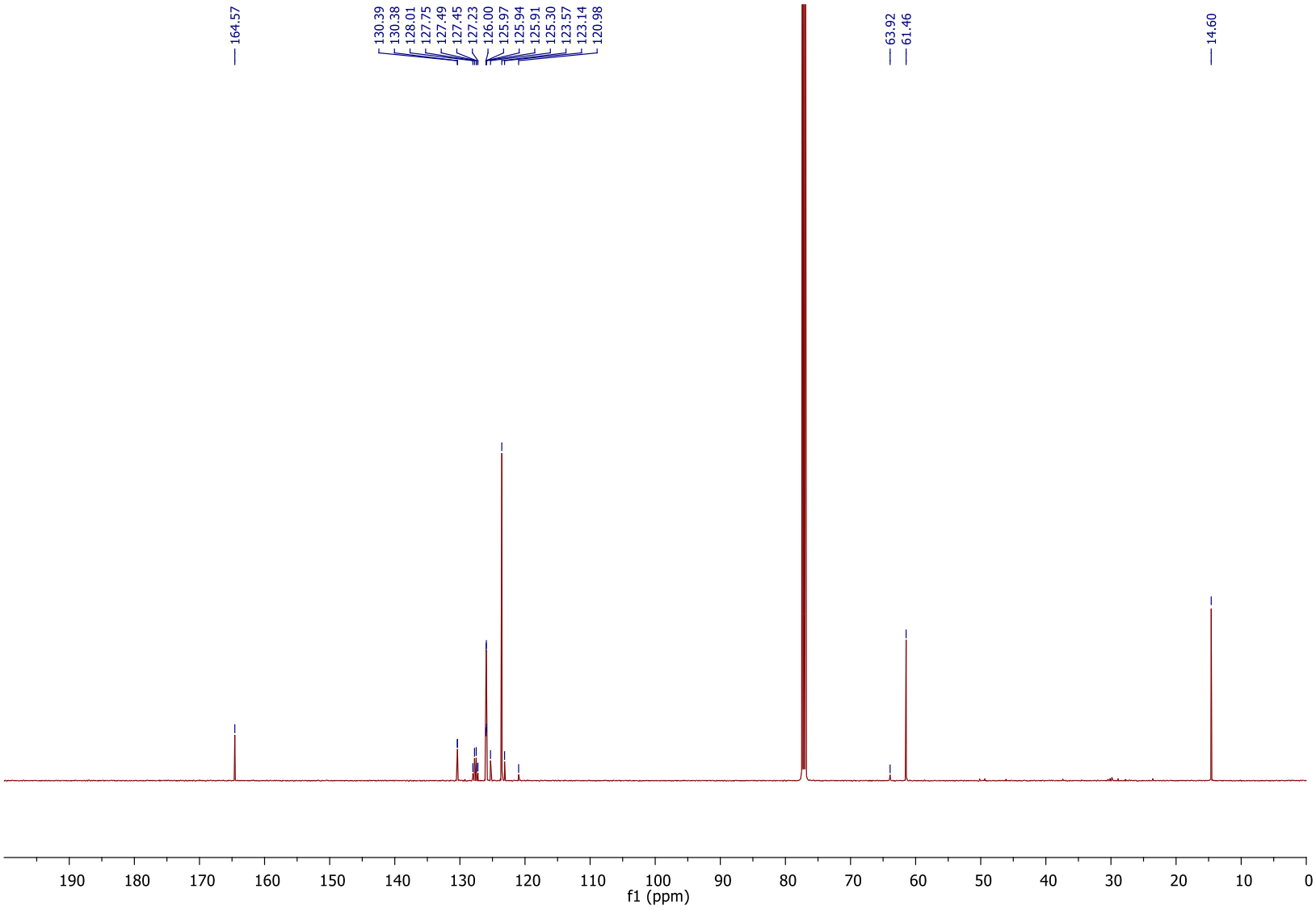


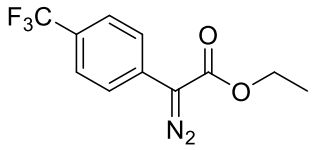


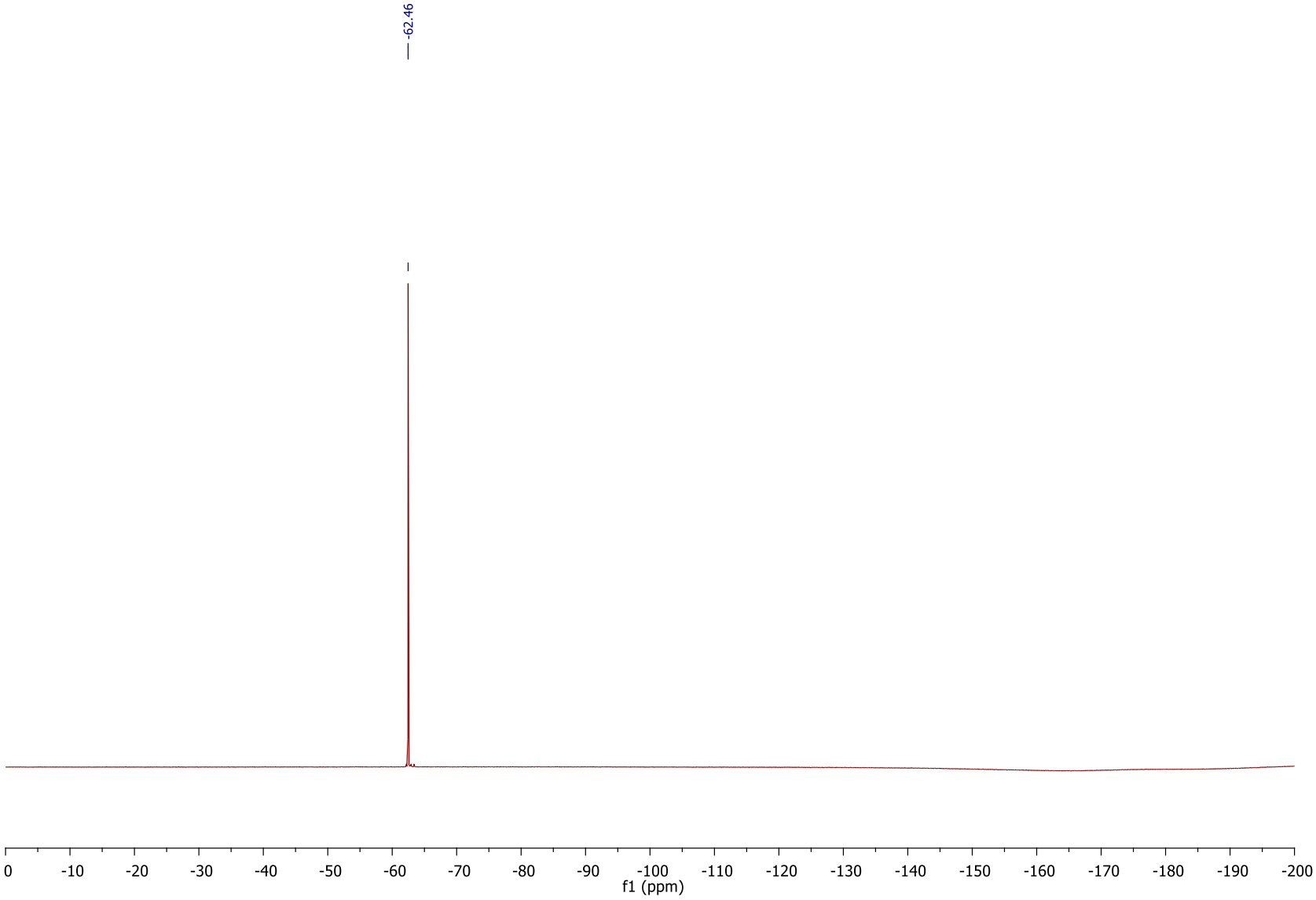
126 MHz ^{13}C spectrum in $CDCl_3$
Compound **S6**



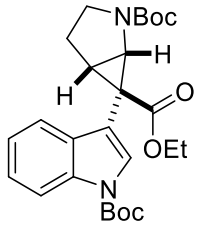


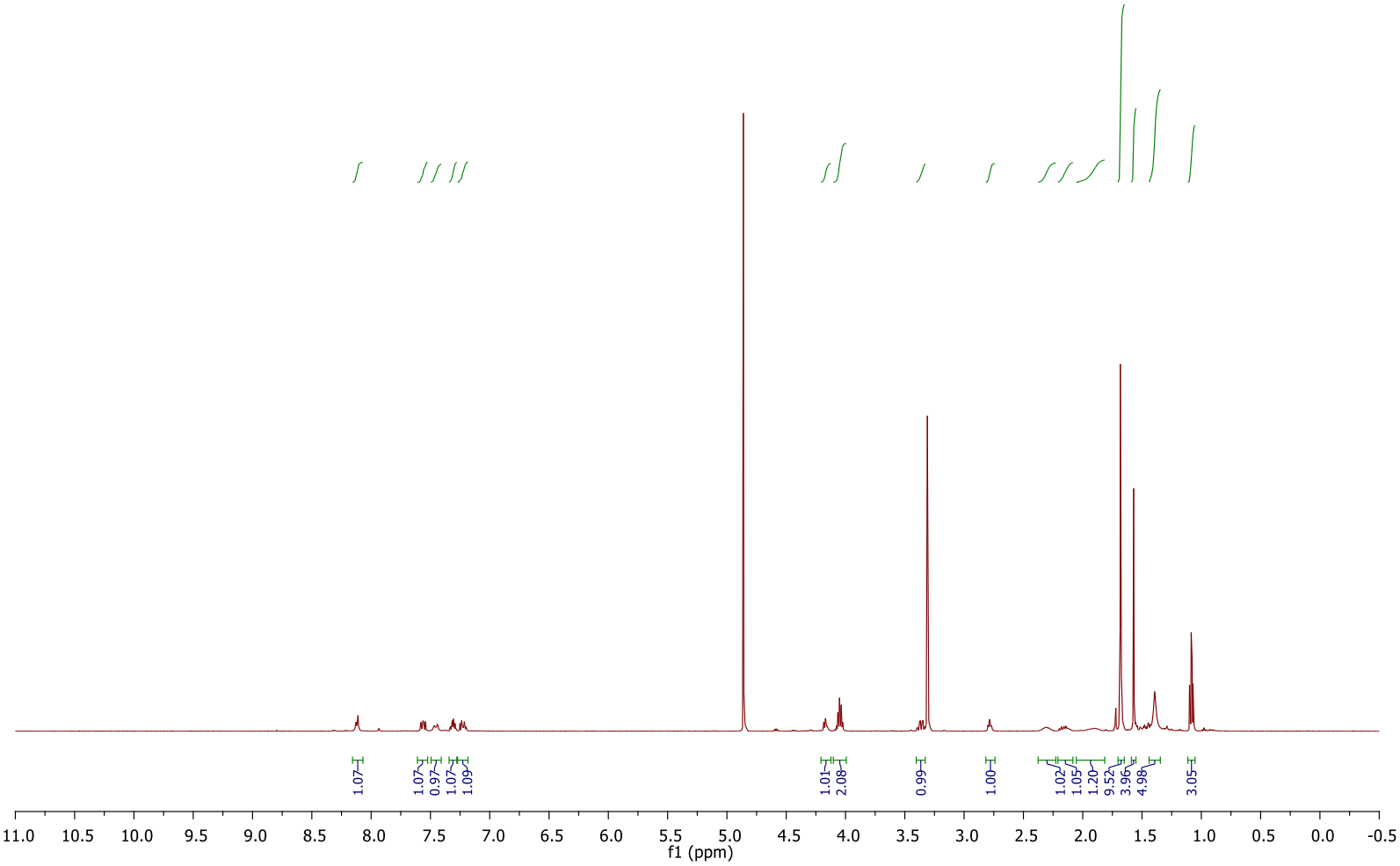
376 MHz ^{19}F spectrum in $CDCl_3$
Compound **S6**



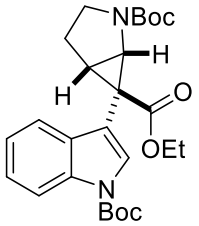


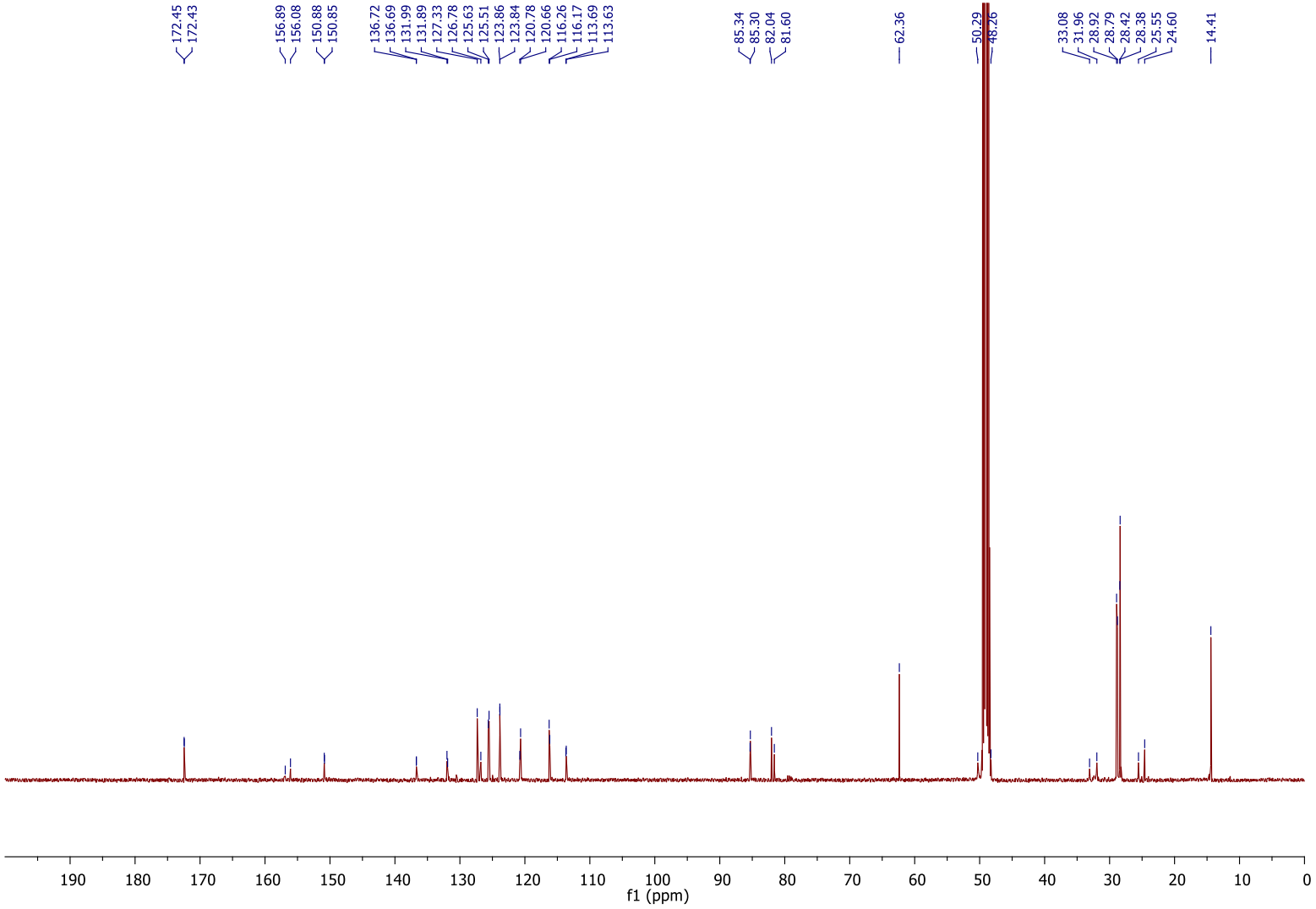
500 MHz ^{1}H spectrum in $CDCl_3$
Compound 1



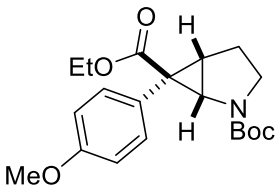


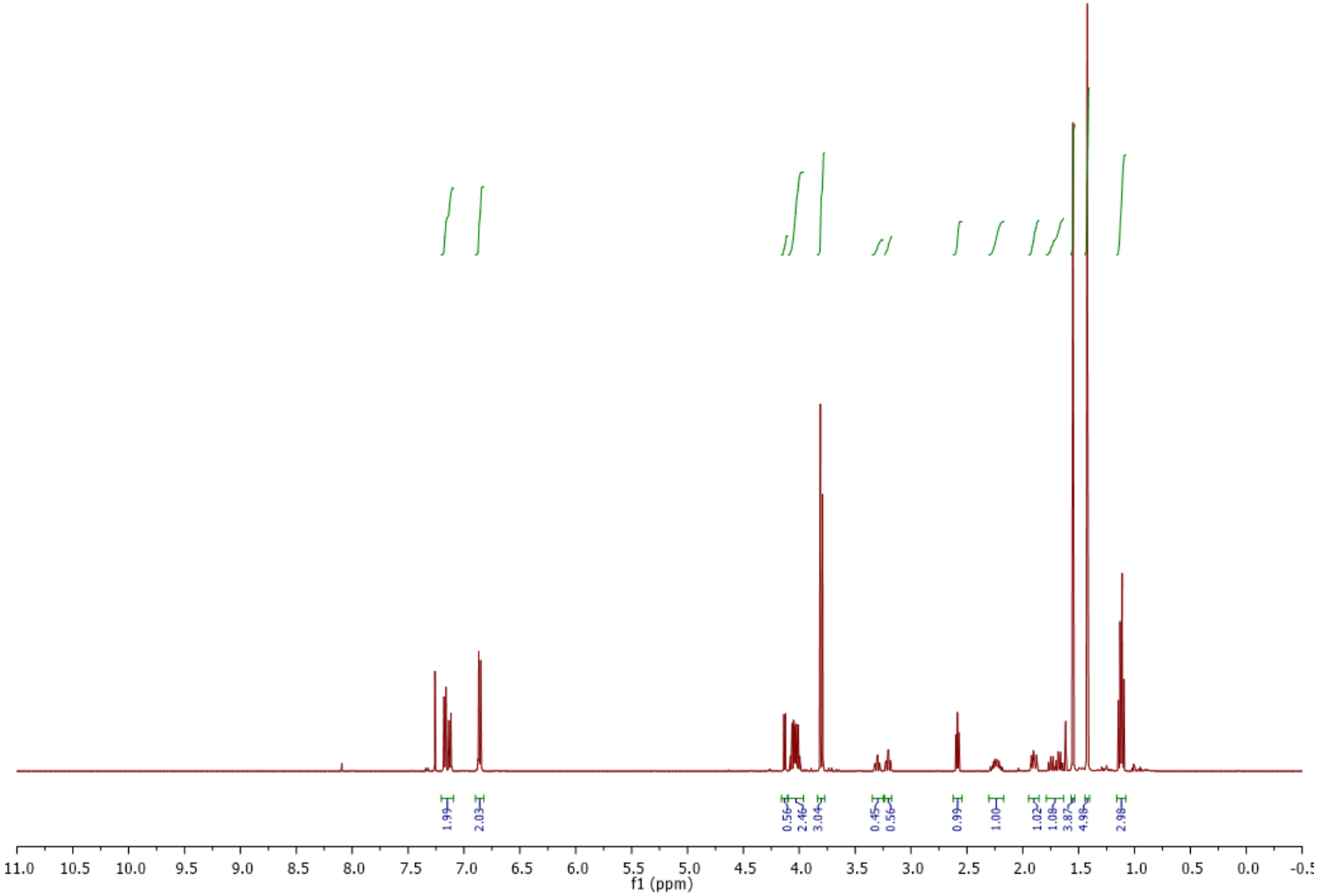
126 MHz ^{13}C spectrum in $CDCl_3$
Compound 1



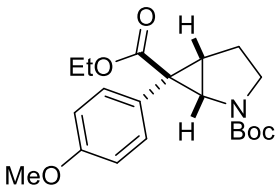


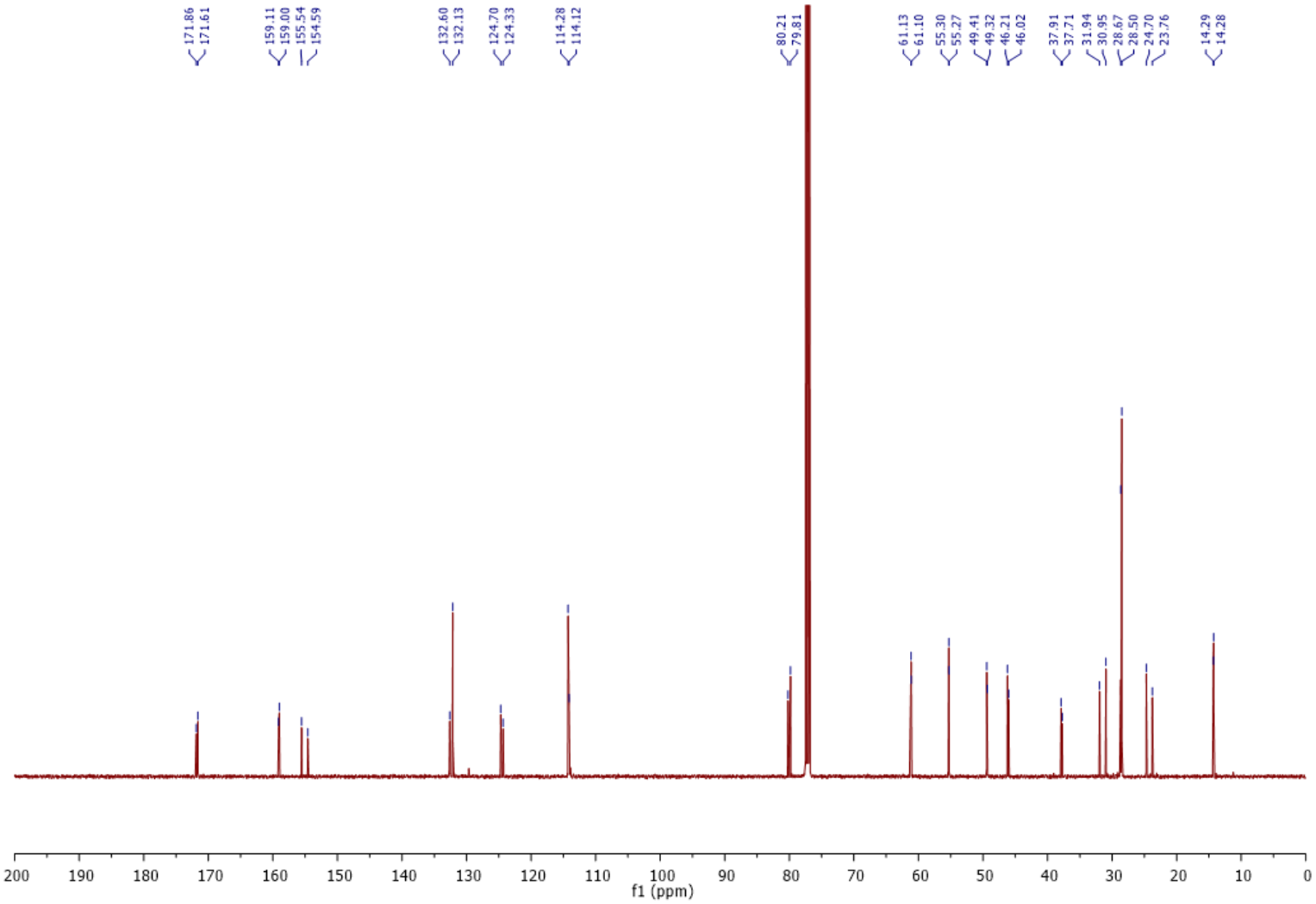
500 MHz ^{1}H spectrum in $CDCl_3$
Compound 2



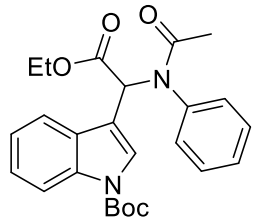


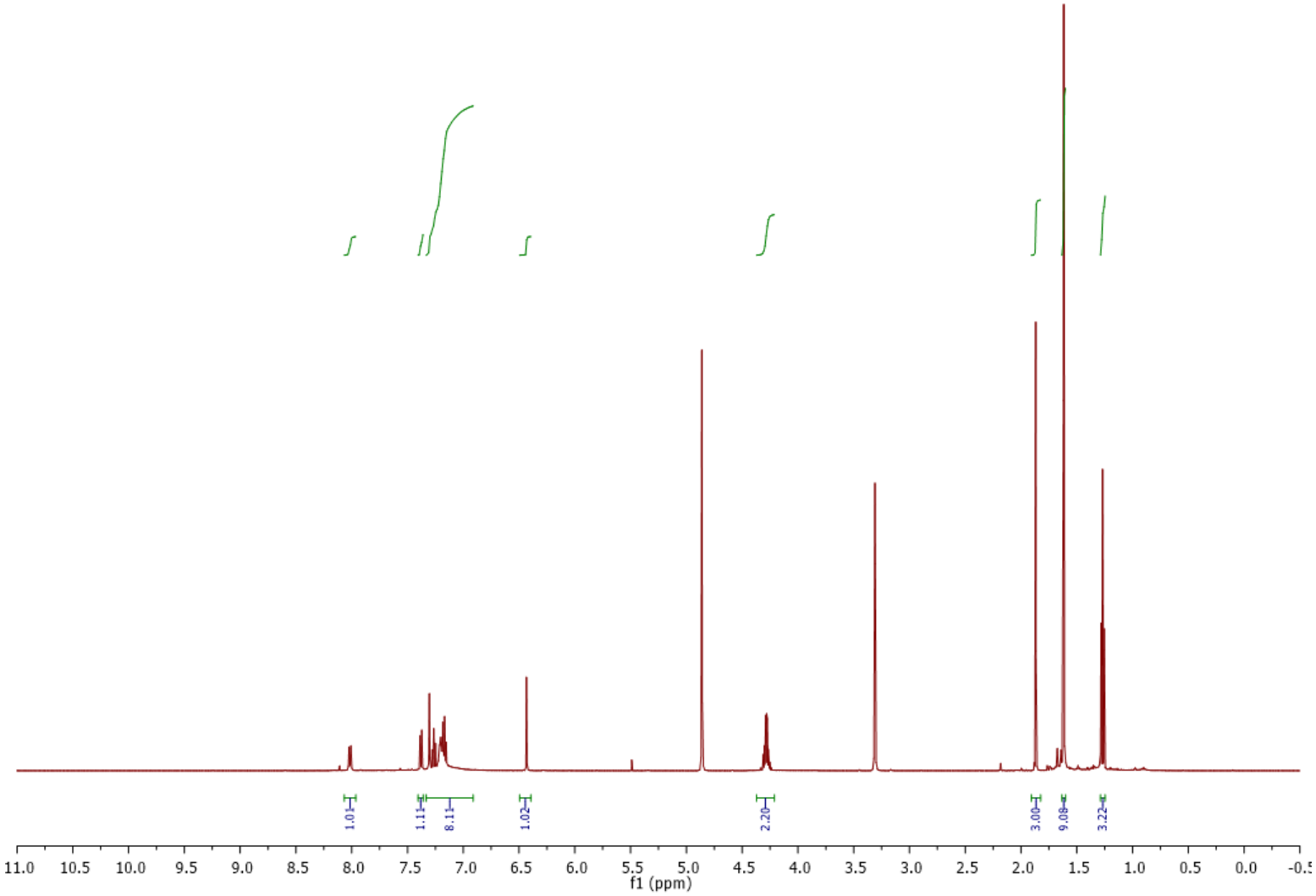
126 MHz ^{13}C spectrum in $CDCl_3$
Compound 2



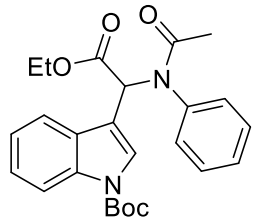


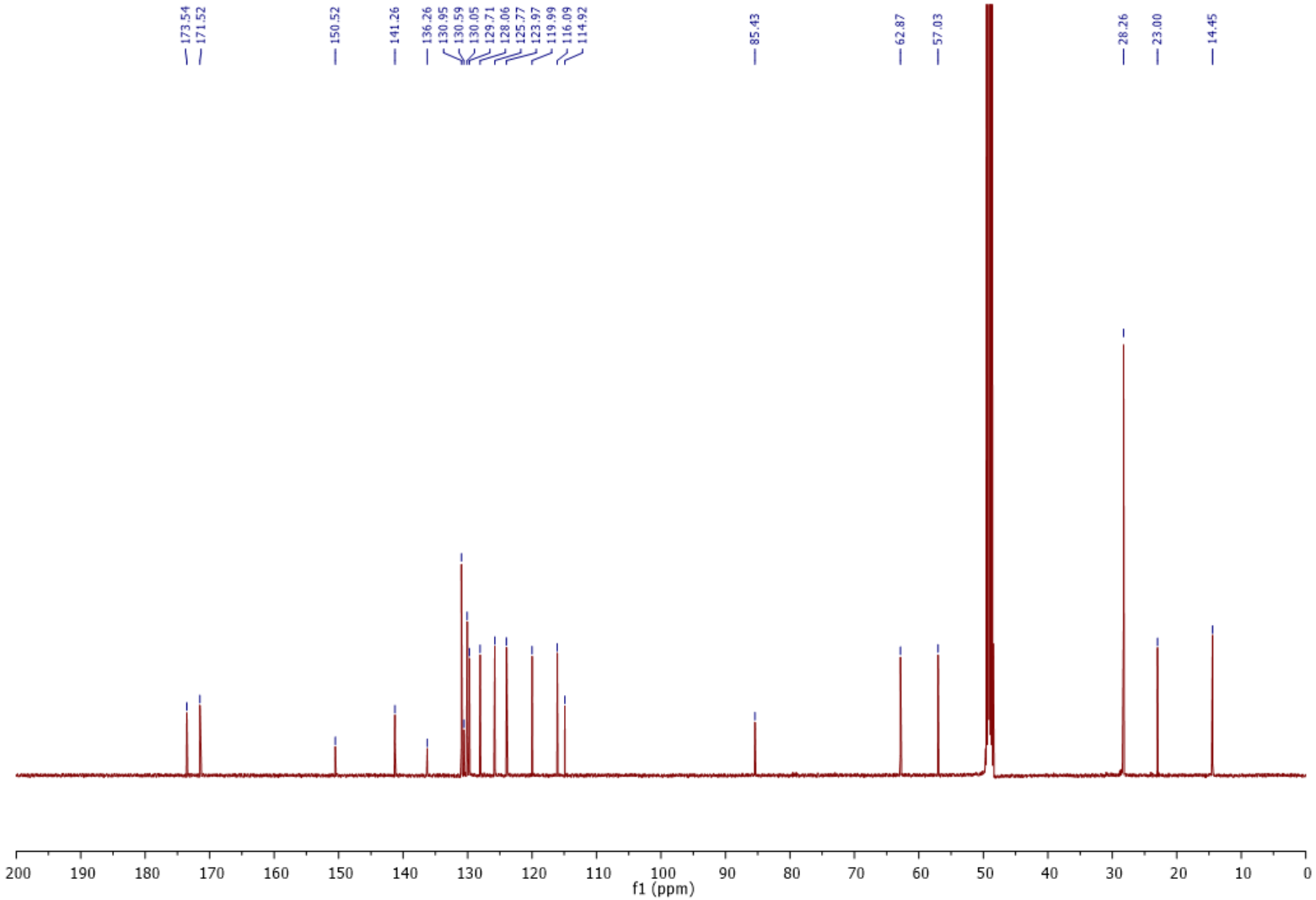
500 MHz ^{1}H spectrum in $CDCl_3$
Compound 3



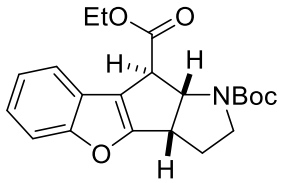


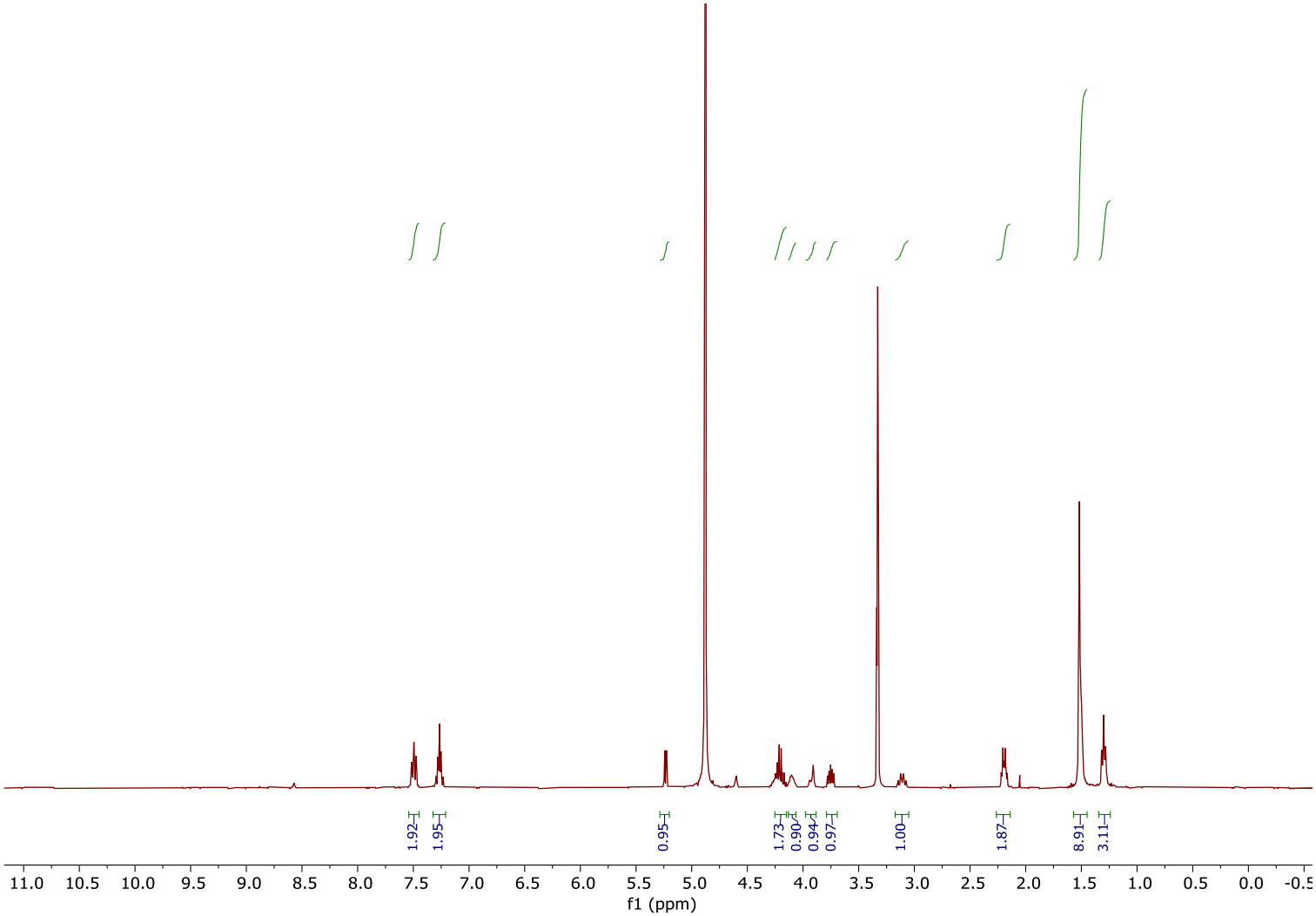
126 MHz ^{13}C spectrum in $CDCl_3$
Compound 3



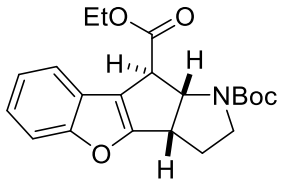


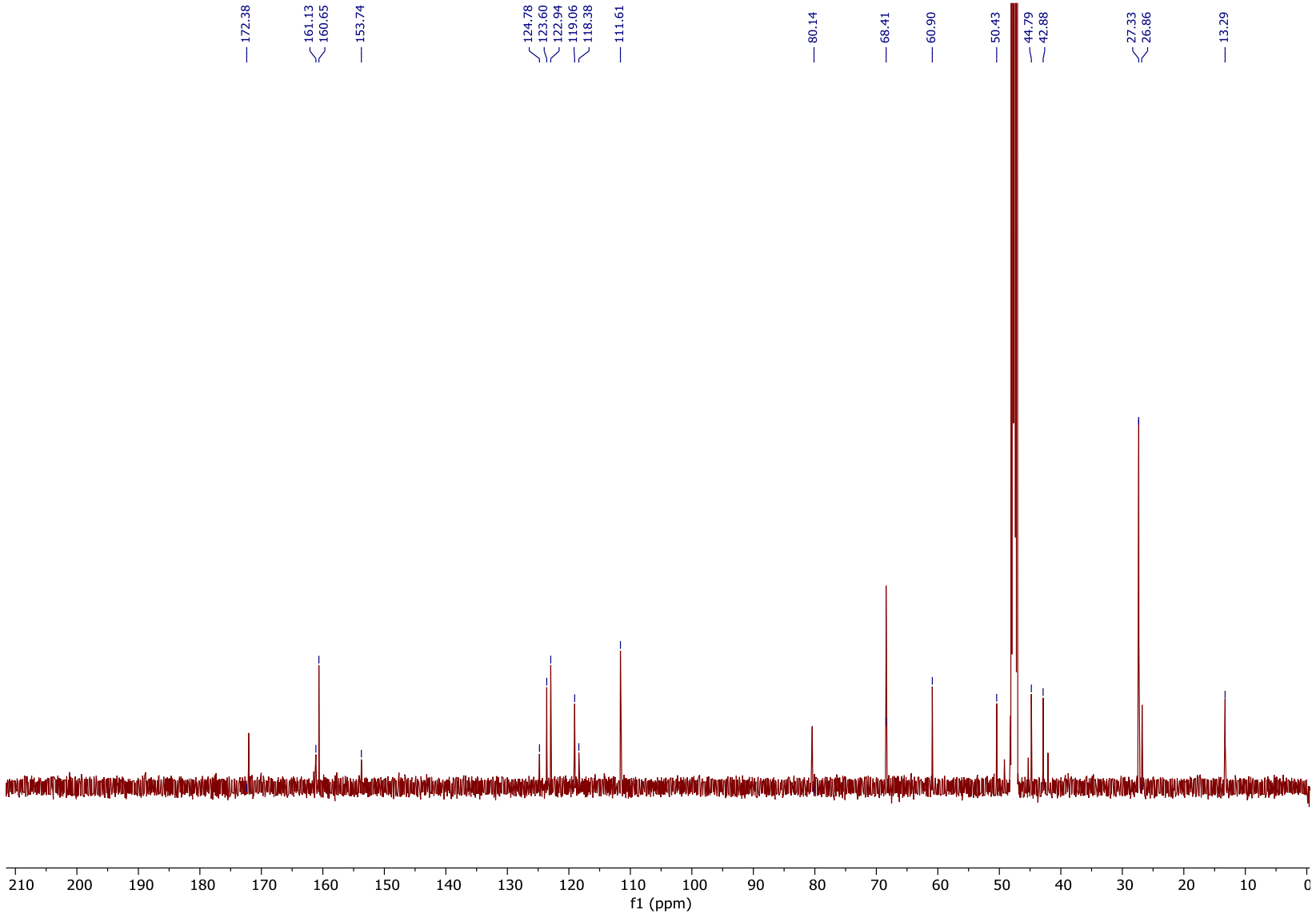
400 MHz ^{1}H spectrum in spectrum in CD_3OD
Compound **4a**



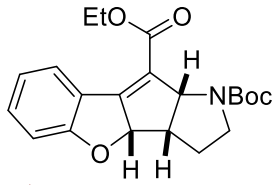


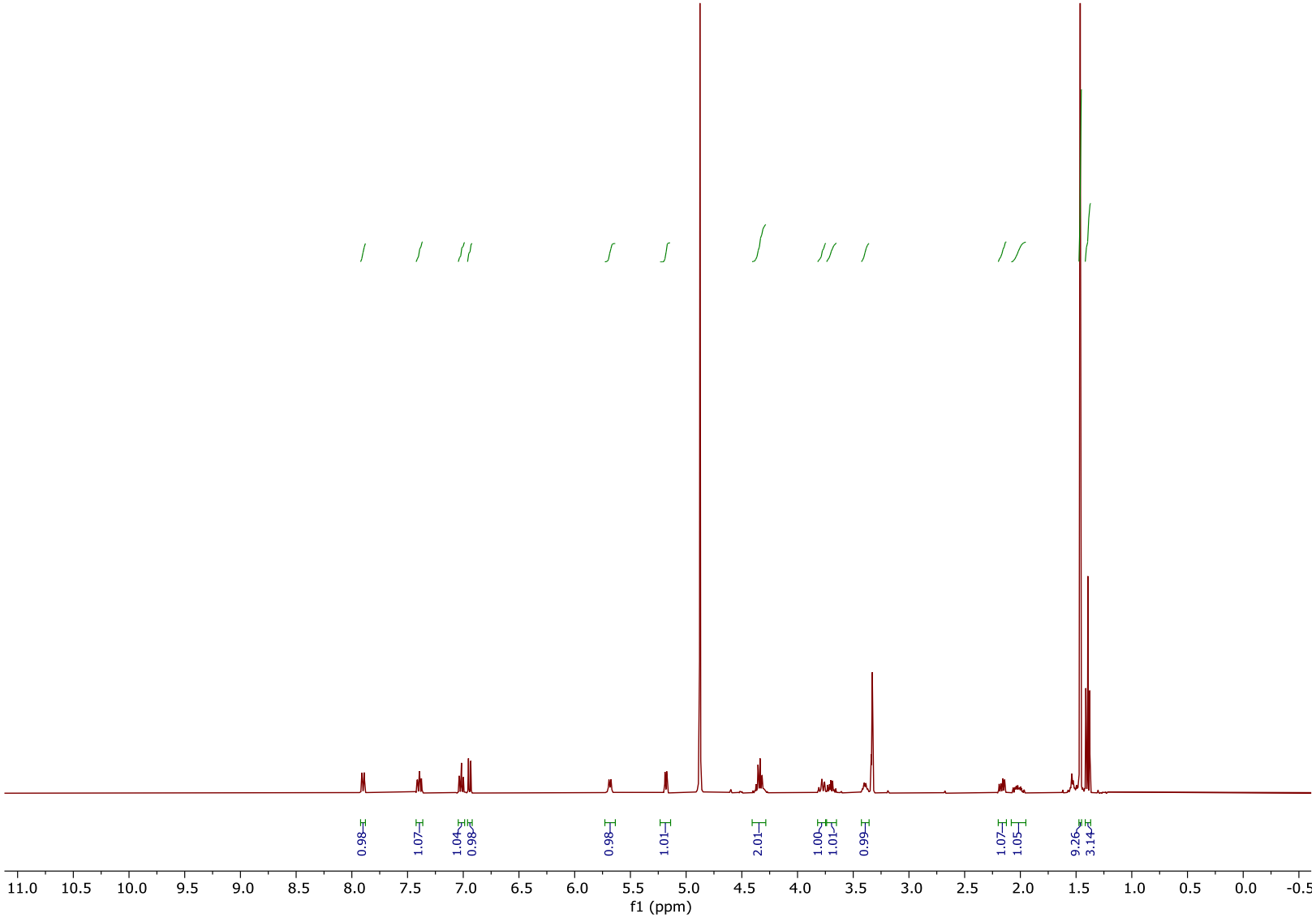
126 MHz ^{13}C spectrum in spectrum in CD_3OD
Compound **4a**



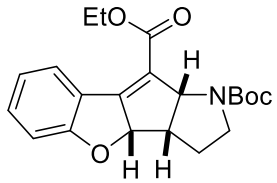


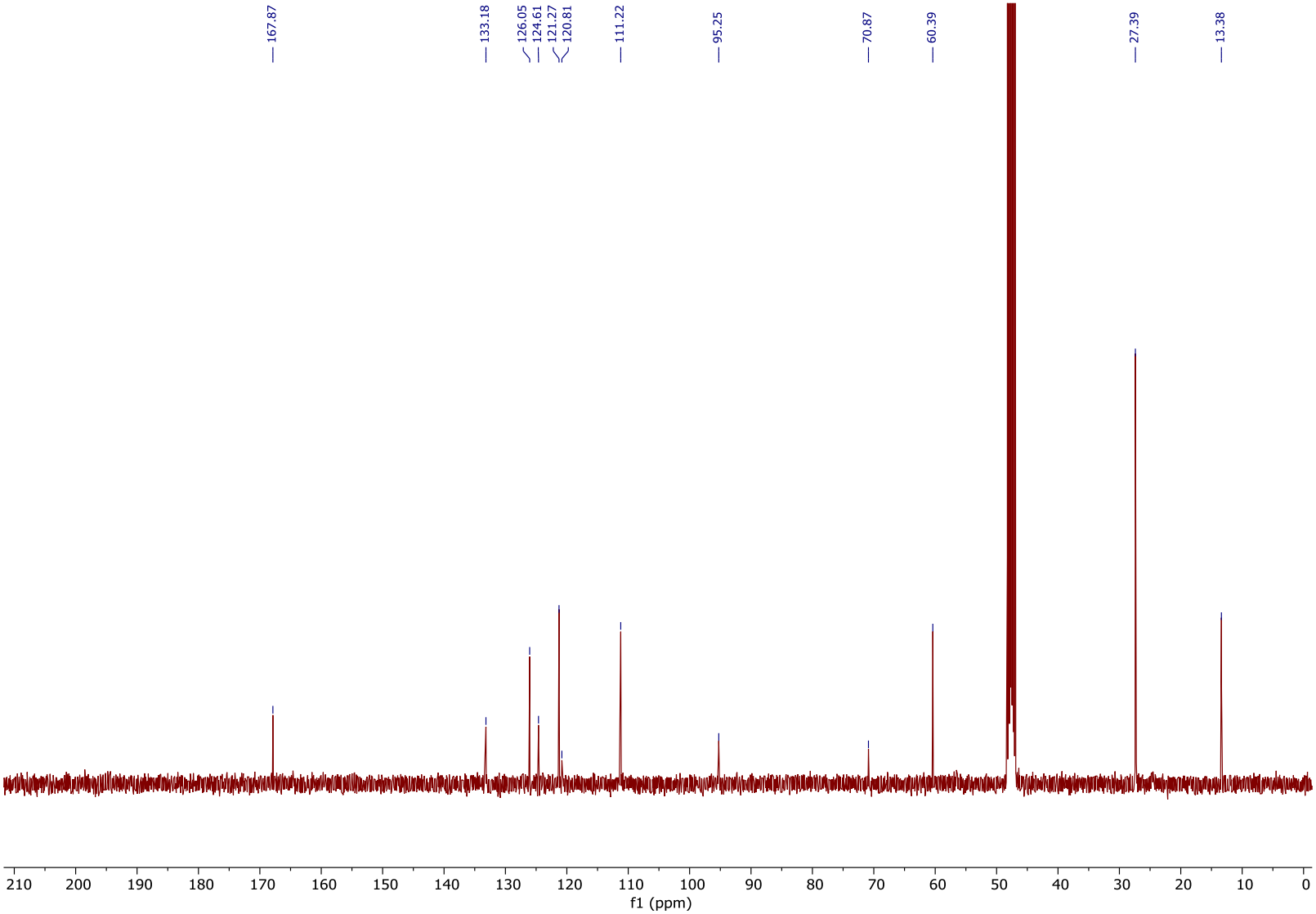
400 MHz ^{1}H spectrum in spectrum in CD_3OD
Compound **4b**



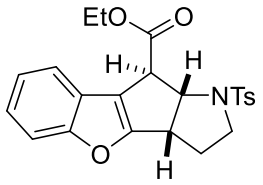


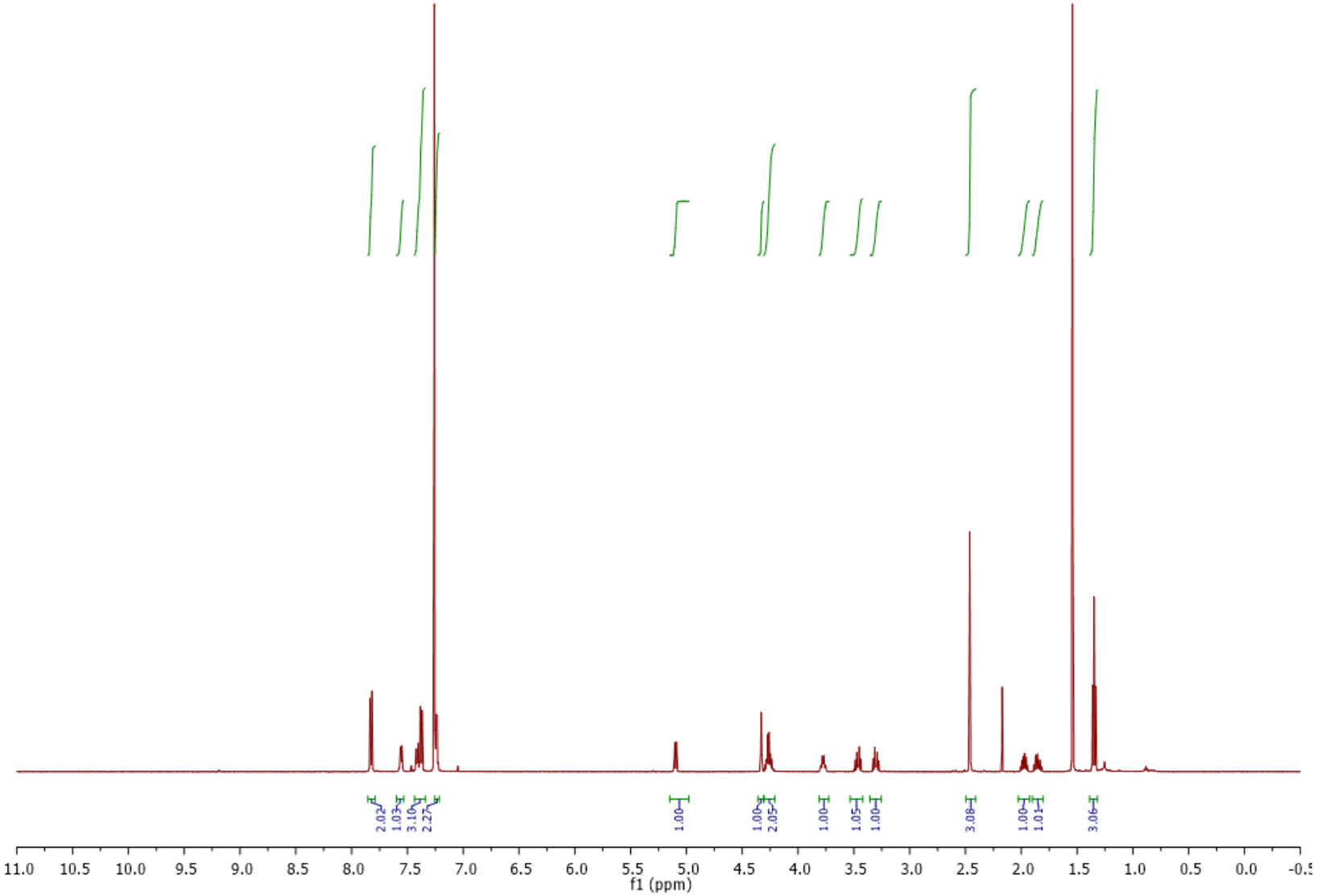
126 MHz ^{13}C spectrum in CD_3OD
Compound **4b**



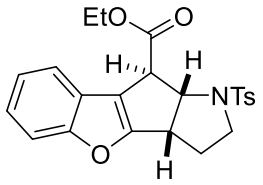


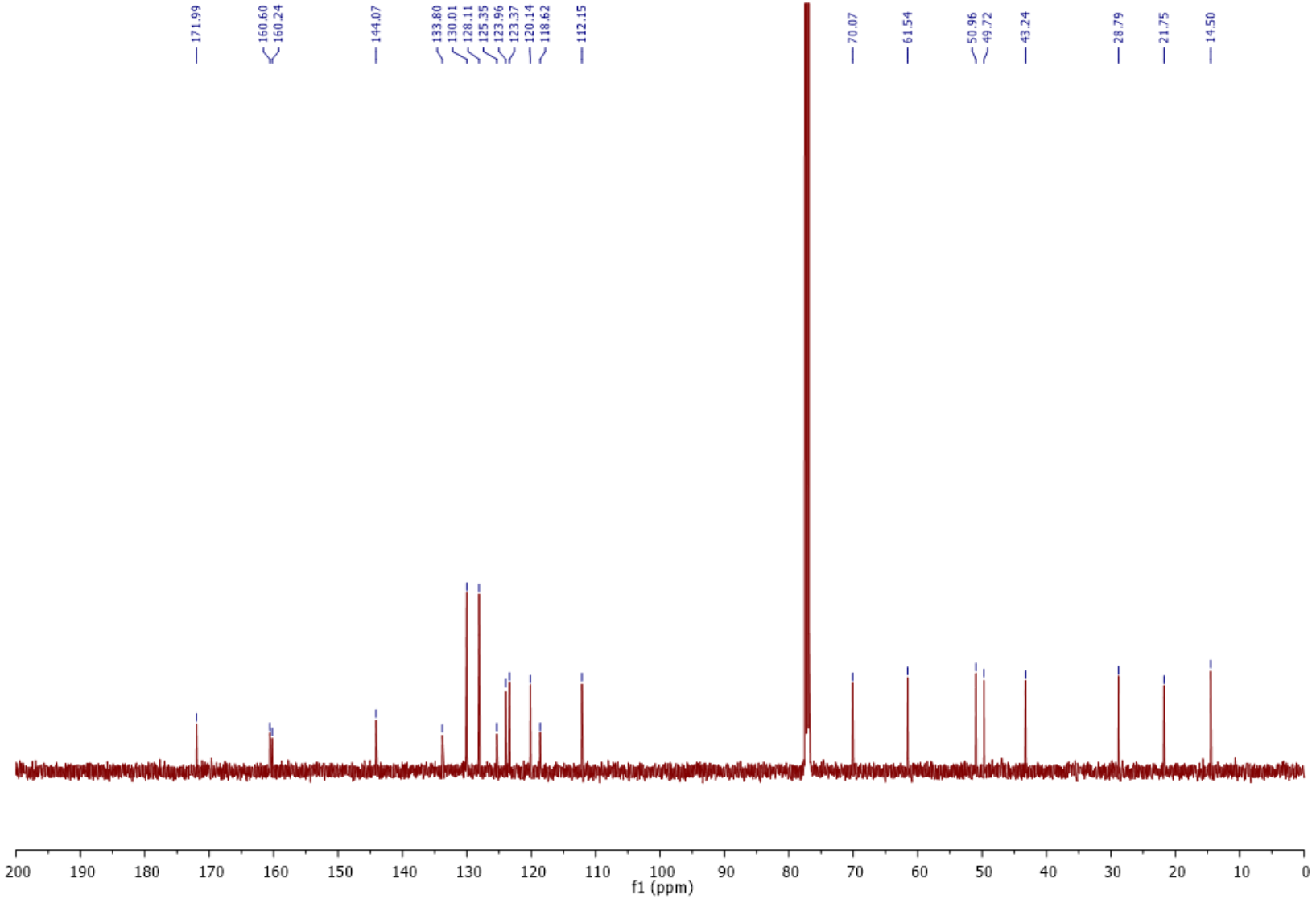
500 MHz ^{1}H spectrum in $CDCl_3$
Compound **SI6a**



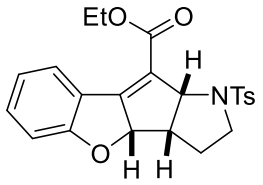


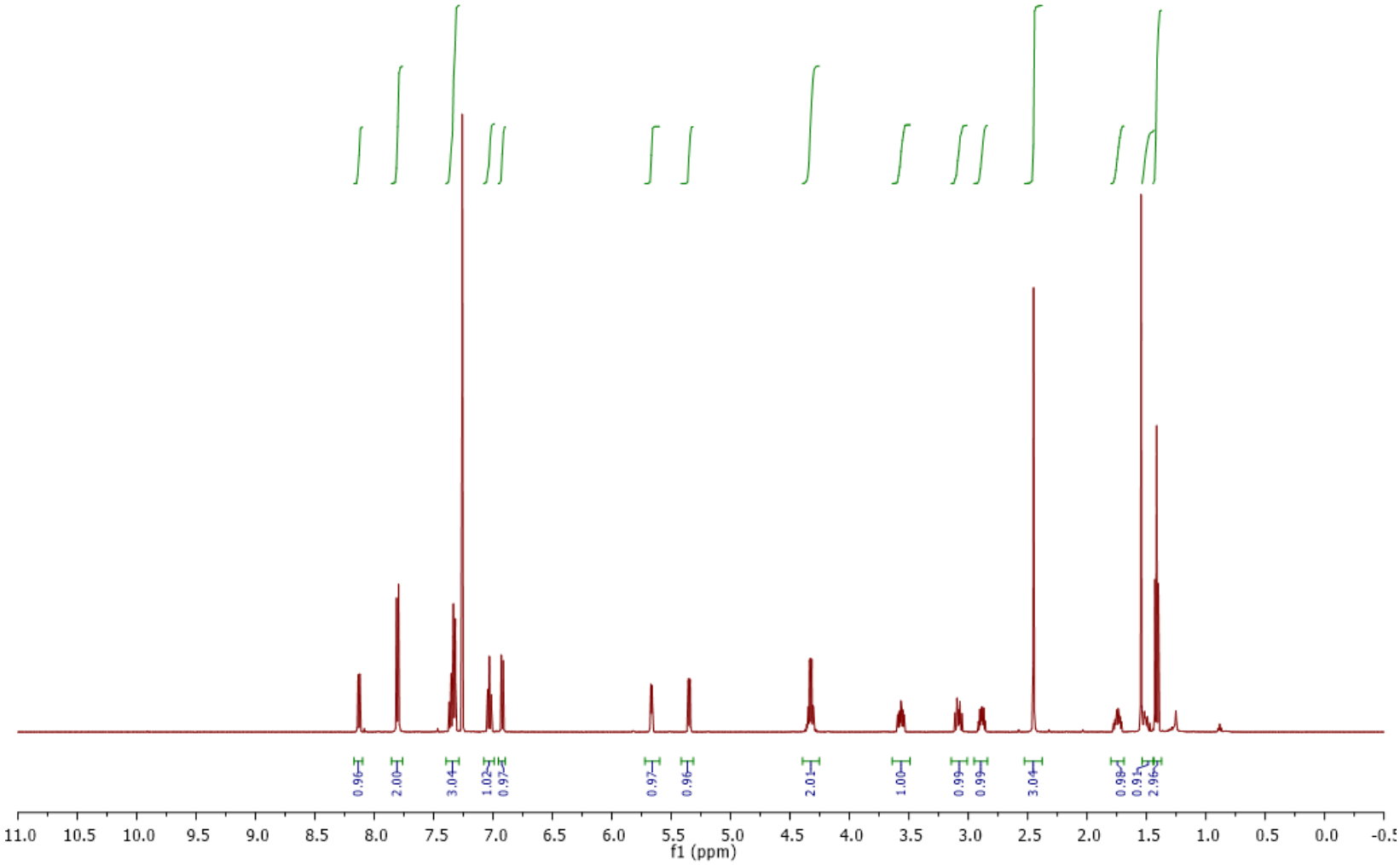
126 MHz ^{13}C spectrum in $CDCl_3$
Compound **SI6a**



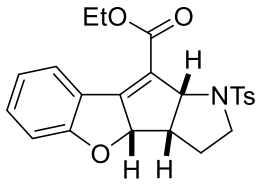


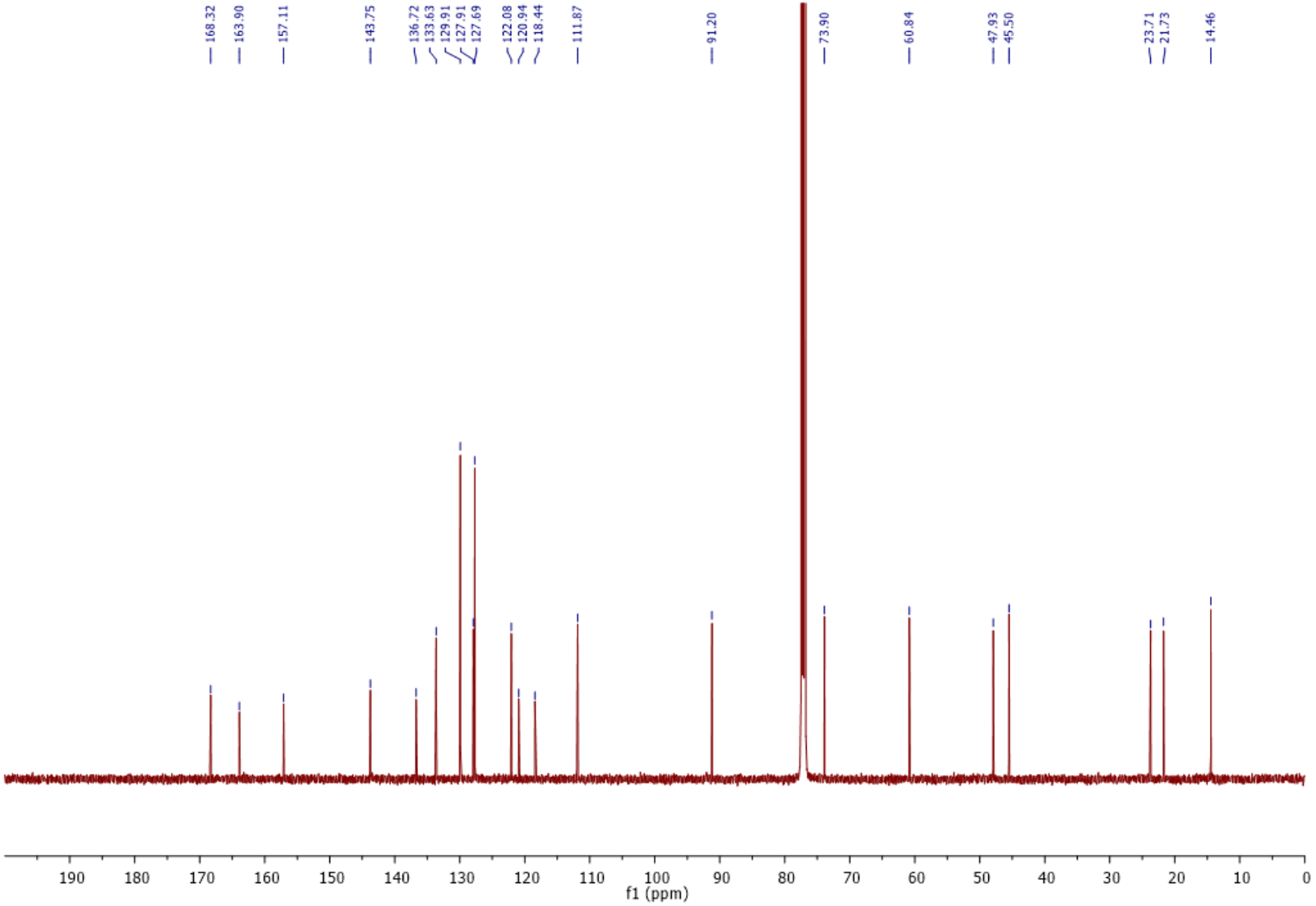
500 MHz ^{1}H spectrum in $CDCl_3$
Compound **SI6b**



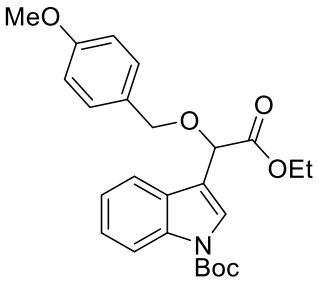


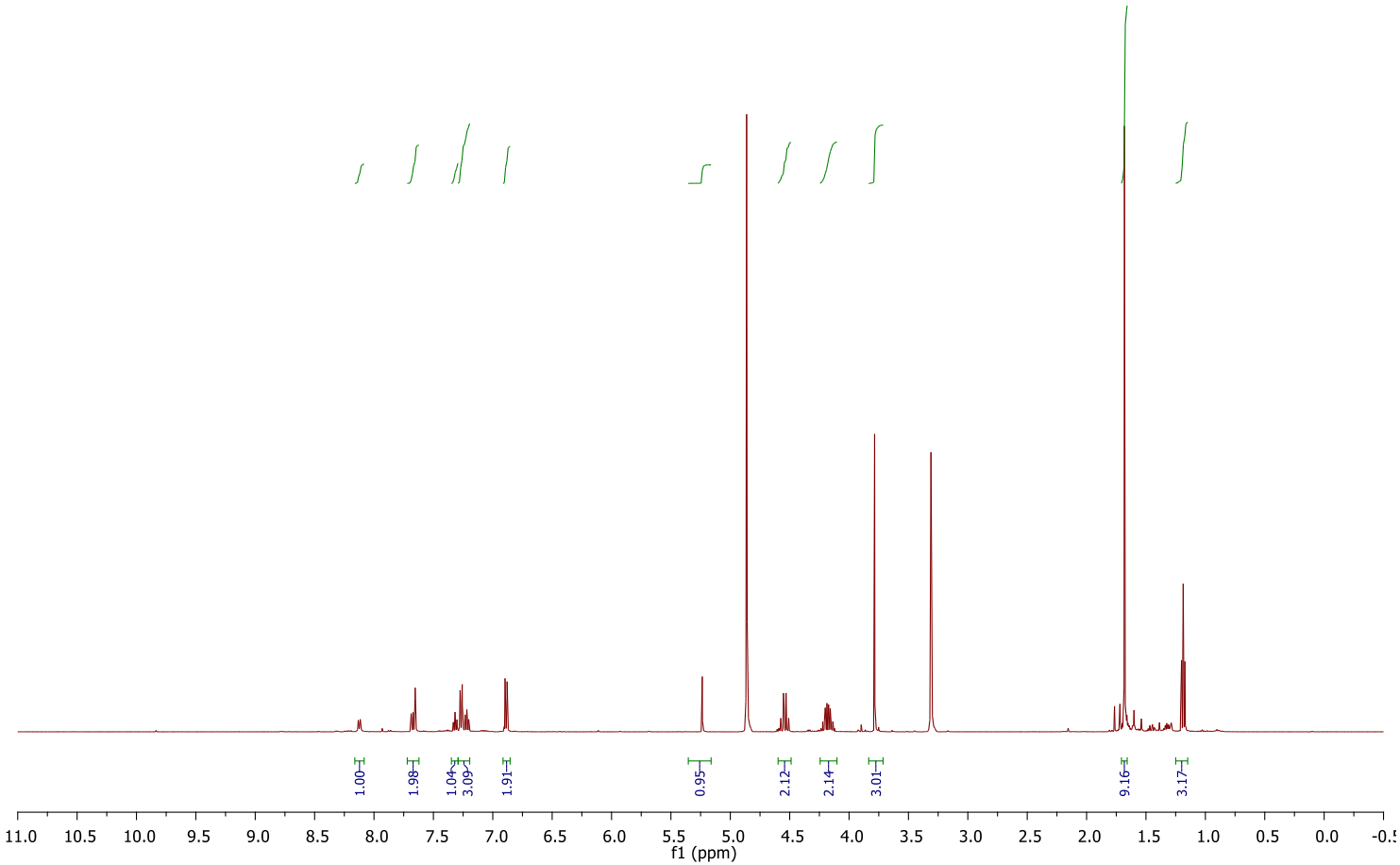
126 MHz ^{13}C spectrum in $CDCl_3$
Compound **SI6b**



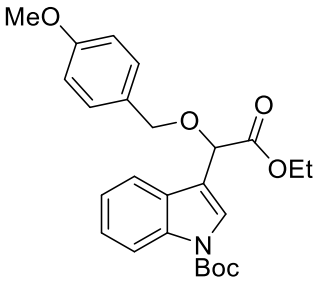


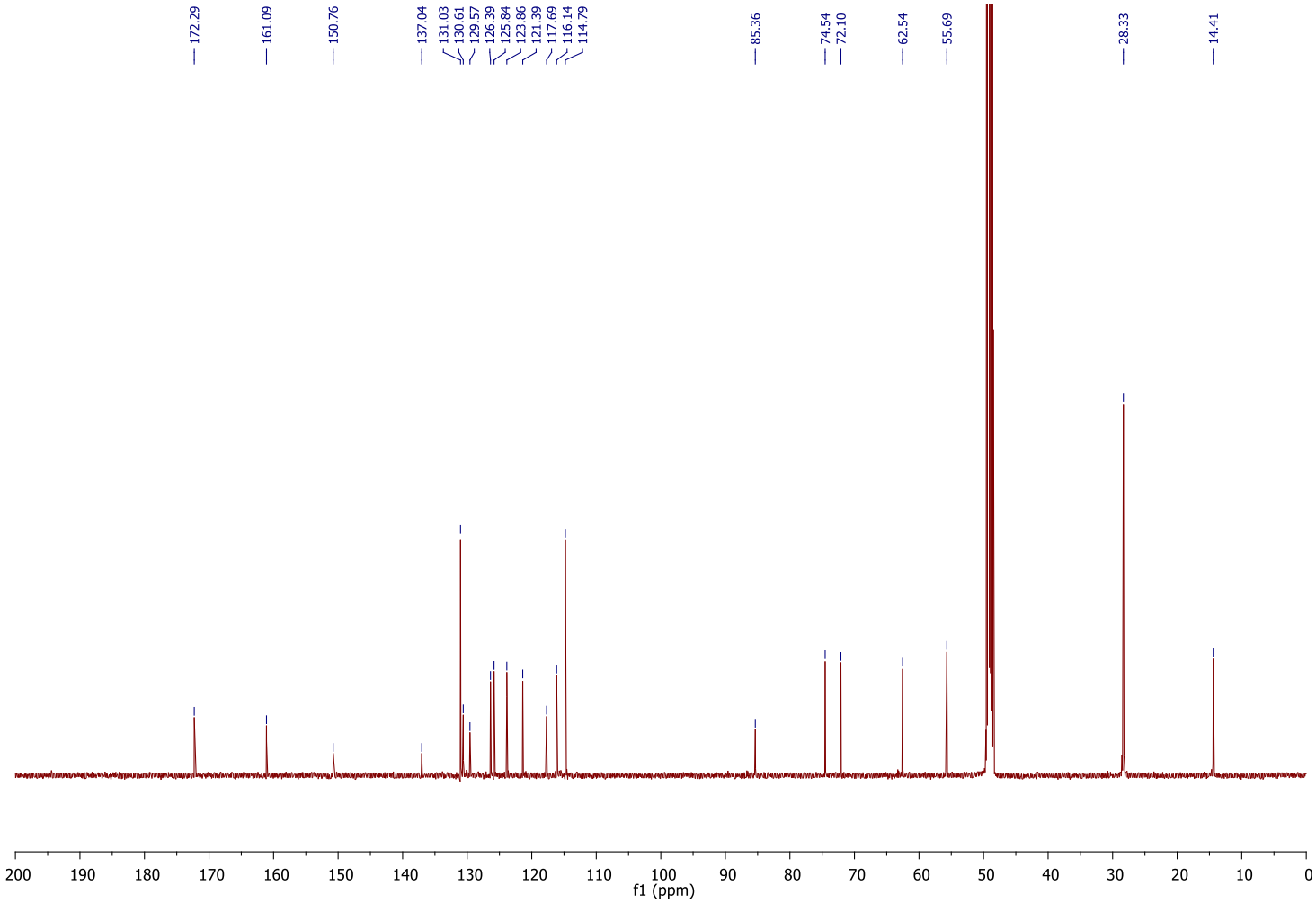
500 MHz ^{1}H spectrum in $CDCl_3$
Compound **5**



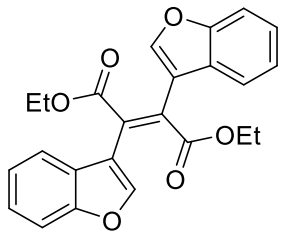


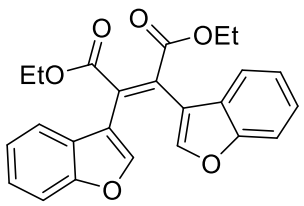
126 MHz ^{13}C spectrum in $CDCl_3$
Compound **5**

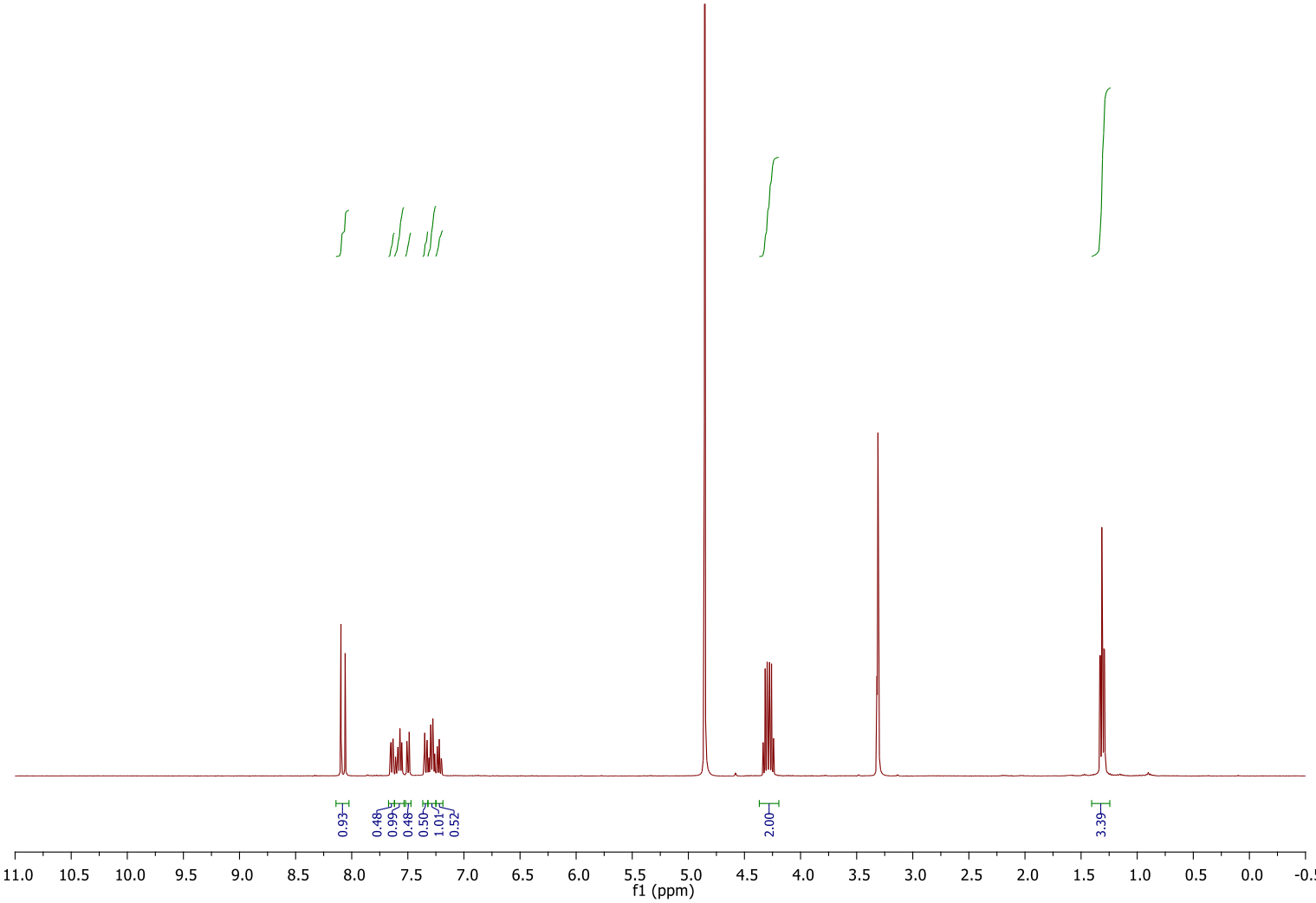




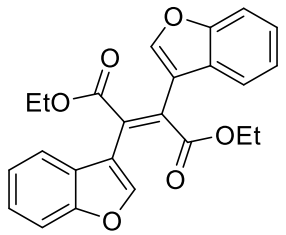
500 MHz ^{1}H spectrum in $CDCl_3$
Compound **6**

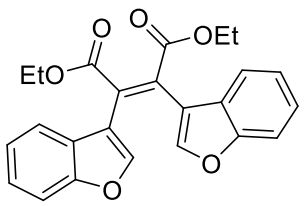


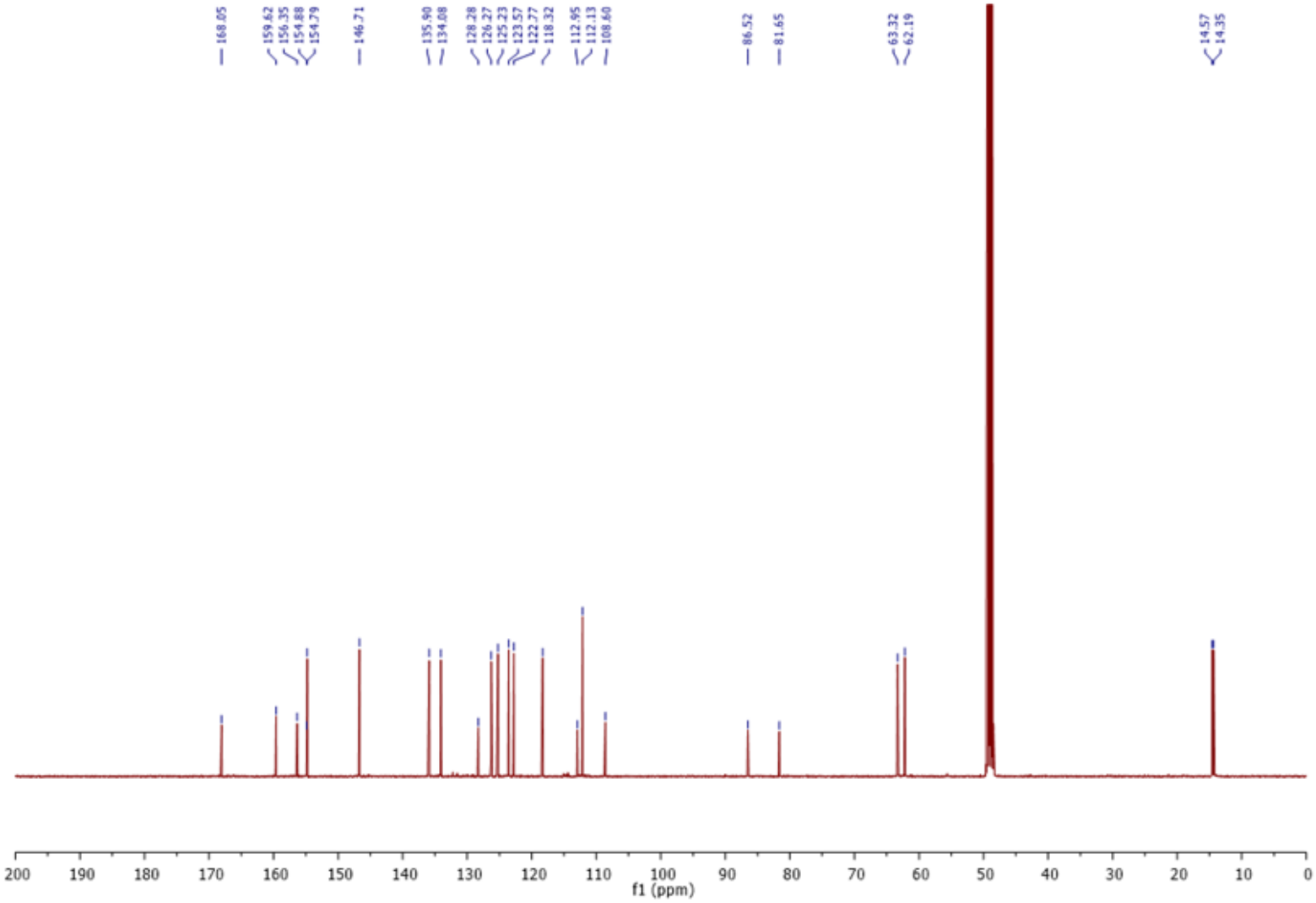




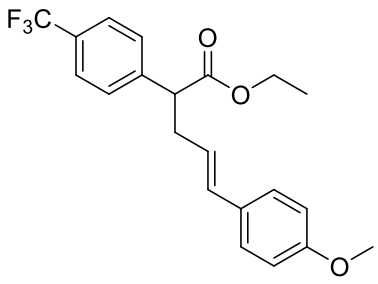
126 MHz ^{13}C spectrum in $CDCl_3$
Compound **6**

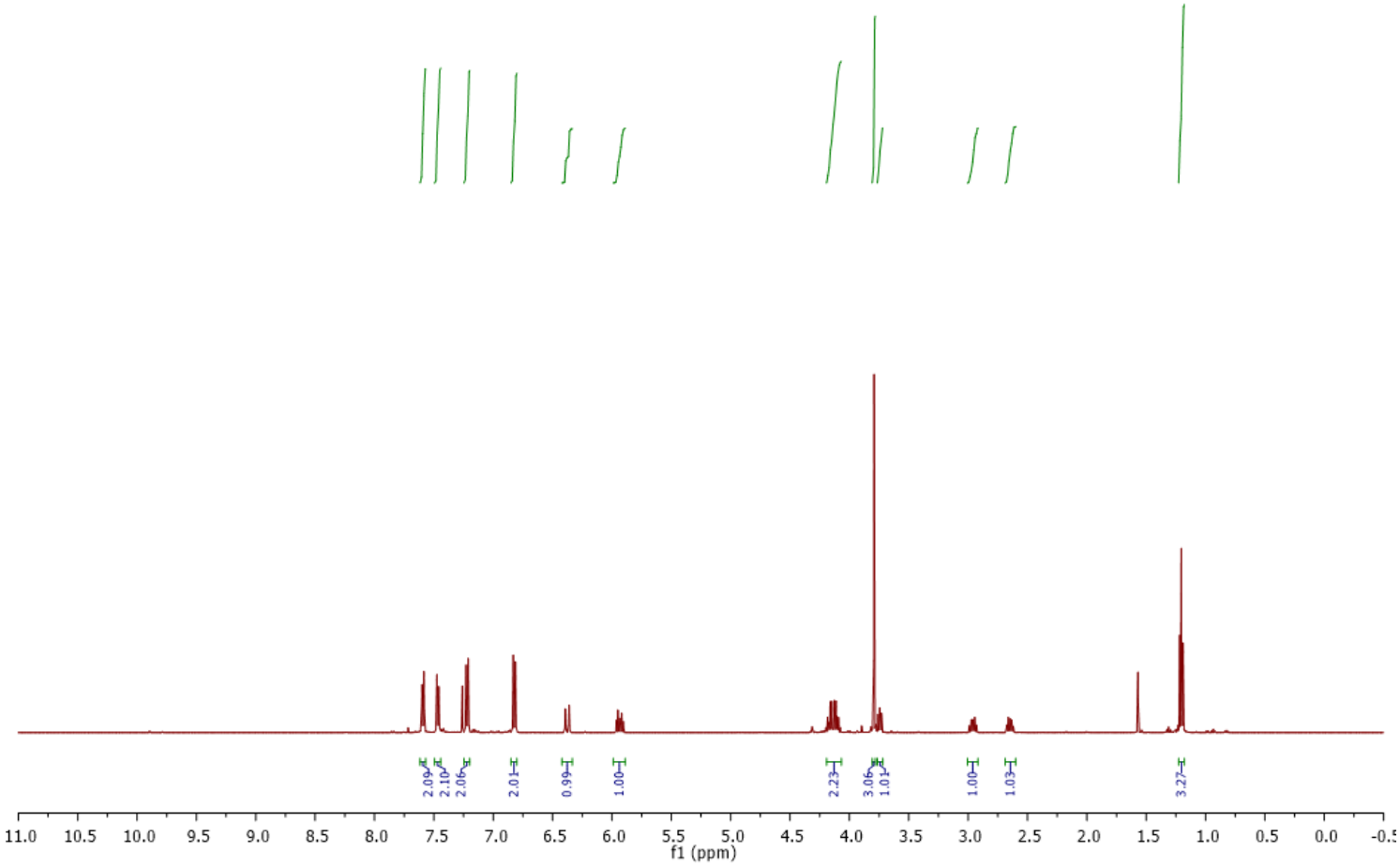




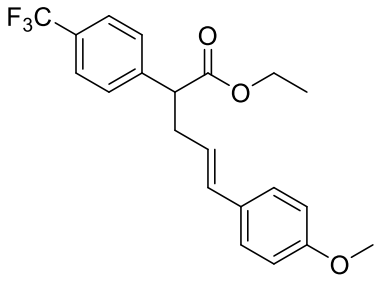


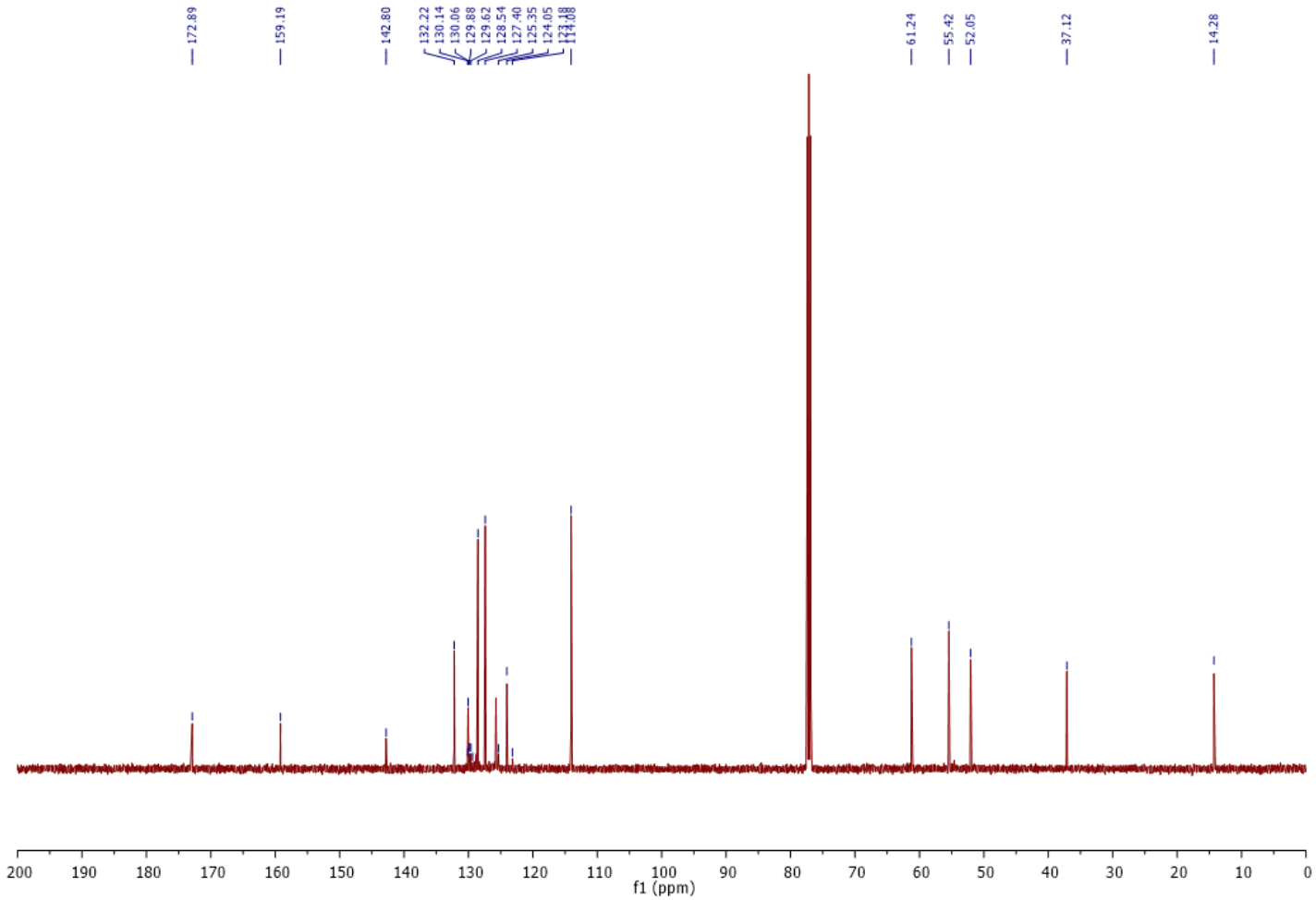
500 MHz ^{1}H spectrum in $CDCl_3$
Compound **7**



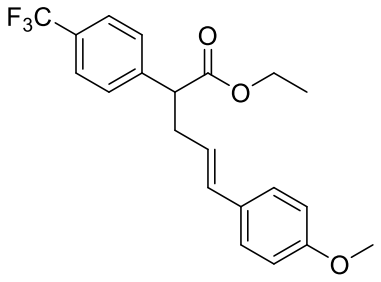


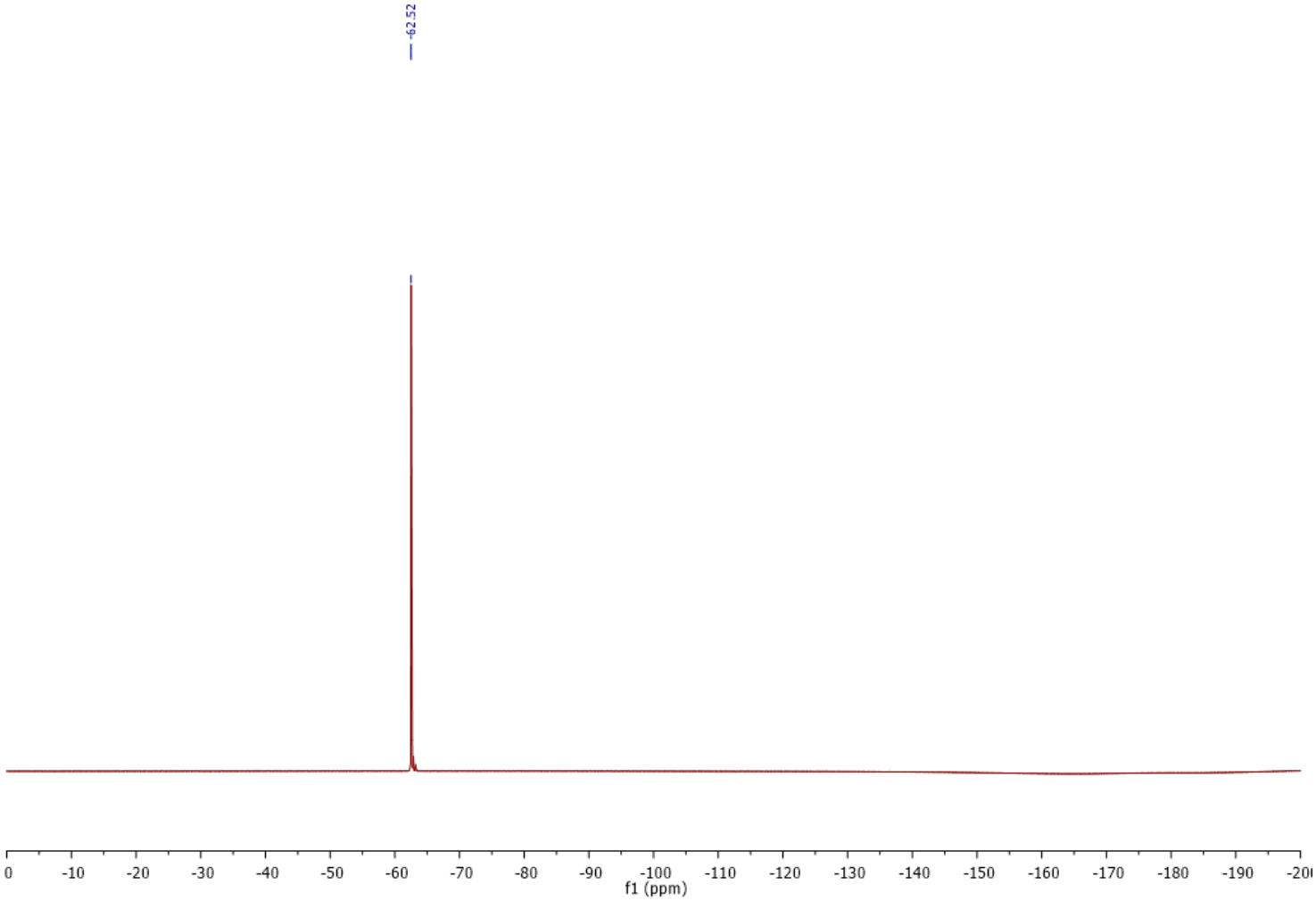
126 MHz ^{13}C spectrum in $CDCl_3$
Compound **7**



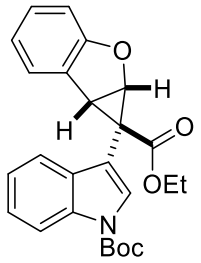


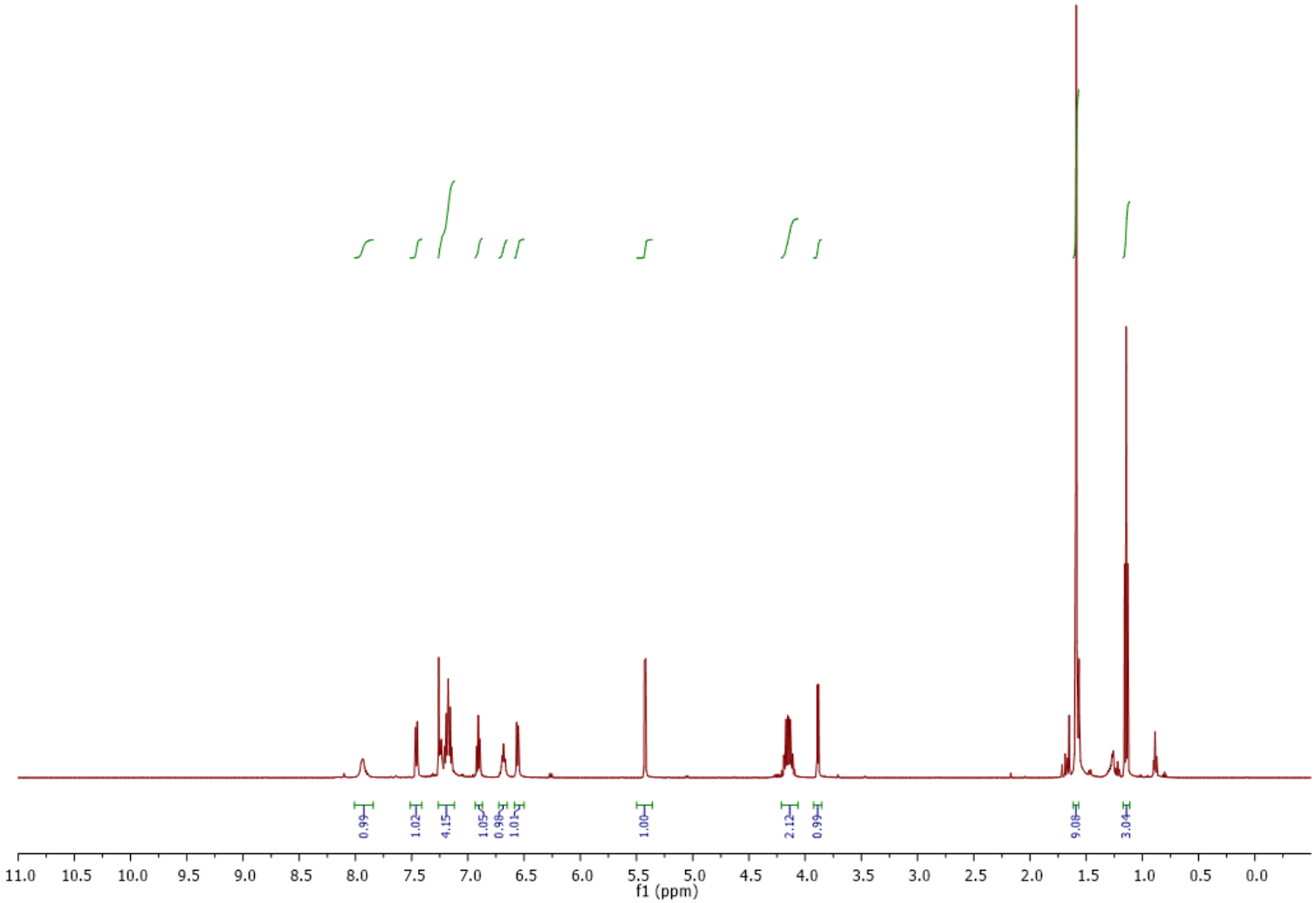
376 MHz ^{1}H spectrum in $CDCl_3$
Compound **7**





500 MHz ^{1}H spectrum in $CDCl_3$
Compound **8**





126 MHz ^{13}C spectrum in $CDCl_3$
Compound **8**