Supporting Information

for

An Isoquinoline Scaffold as a Novel Class of Allosteric HIV-1 Integrase Inhibitors

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Table of Contents

Biological Methods

Recombinant protein expression and purification: His and Flag tagged Integrase (IN) and LEDGF/p75 were expressed in *Escherichia coli BL21 (DE3) strain and purified as described previously.*[1–4]

LEDGF dependent and independent integration assays: Previously developed homogenous time resolved fluorescence (HTRF) technique was used to determine the IC_{50} values of compounds. [5–7]

IN-LEDGF binding inhibition assay: The activity of the compounds to inhibit IN-LEDGF binding was determined by the HTRF based assay as reported previously.[3,8]

IN multimerization assay: Hyper-multimerization of His and Flag tagged INs in the presence of ALLINIs was determined by previously developed HTRF based assay.[3,9]

IN-RNA binding inhibition assay: The inhibitory activities of the compounds to interfere with IN-RNA binding were analyzed by Alpha screen based assay.[10] Briefly, different concentrations of ALLINIs were incubated with 100 nM His_6 tagged IN in buffer containing 100 mM NaCl, 1 mM $MgCl_2$, 1 mM DTT, 1mg/mL BSA, 25 mM Tris (pH 7.4) at 4°C for 2 hours. This mixture was then added to the nickel acceptor beads while biotinylated-TAR RNA was added to the streptavidin donor beads. Followed by 2-hour incubation at 4°C, the RNA mixture was added to the IN-drug mixture and the reading was taken after 1 hour incubation at 4°C by PerkinElmer Life Sciences Enspire multimode plate reader. The IC_{50} values were calculated by OriginLab software.

Antiviral activities: The antiviral activities (EC_{50}s) of the compounds with pNL4-3 WT and A128T replication competent viruses were determined in full replication cycle as mentioned previously.[11]

HIV-1 IN CCD (F185H) Expression, Purification, Crystallization, and X-ray Crystallography: The HIV-1 IN CCD (residues 50–212) containing the F185H mutation was expressed and purified as described.[12] The protein was concentrated to 8 mg/ml and crystallized using hanging-drop vapor diffusion method with a crystallization buffer consisting of 100 mM sodium cacodylate pH 6.5, 100 mM ammonium sulfate, 10% (w/v) PEG 8000, and 5 mM DTT. Crystallization drops were prepared using an equal volume of protein and well solution. Crystallization trays were prepared on ice at room temperature and then transferred to 4 °C for storage. Crystals formed within one week and continued to grow thereafter in size. Crystal data were collected on a Rigaku Micromax-007 at 100 K. Data were integrated and scaled using HKL3000[13] and Scalepack.[14] Phaser[15] in the PHENIX suite[16] was used to run molecular replacement using Protein Data Bank code 4O55 as a search model.[12] Phenix.refine[17] was used for data refinement, and manual refinement was done in Coot.[18] The coordinates are deposited in the Protein Data Bank under accession codes 6EB1 and 6EB2. The data and refinement statistics are given in Table X.

X-Ray Crystallography

	6b PDB: 6EB1	**6l PDB: 6EB2**
Data Collection		
Wavelength (Å)	1.541	1.541
Space group	P 31 2 1	P 31 2 1
Unit cell	72.34, 72.34, 66.62, 90, 90, 120	72.10 72.10 66.43
Resolution (Å)	50.00 – 2.10	45.49 – 2.49
R-meas	0.123 (0.608)	0.120 (0.567)
I/sigma(I)	14.2 (1.5)	15.1 (2.9)
Completeness (%)	99.5 (99.0)	97.1 (99.4)
Redundancy	3.8 (3.5)	4.2 (4.0)
Refinement		
Resolution (Å)	45.64 – 2.20	45.50 – 2.49
Number of reflections	17287	12806
Rwork/Rfree	0.204/0.241	0.203/0.248
Number of Atoms		
Protein	1060	1034
Ligand	35	41
Water	50	22
Wilson B-factor (Å^2)	24.43	35.73
R.m.s deviations		
Bond lengths (Å)	0.009	0.014
Bond angles (°)	1.030	1.362
Ramachandran		
Favored (%)	98.45	96.83
Ouliers (%)	0	0

Statistics for highest resolution shells shown in parentheses.

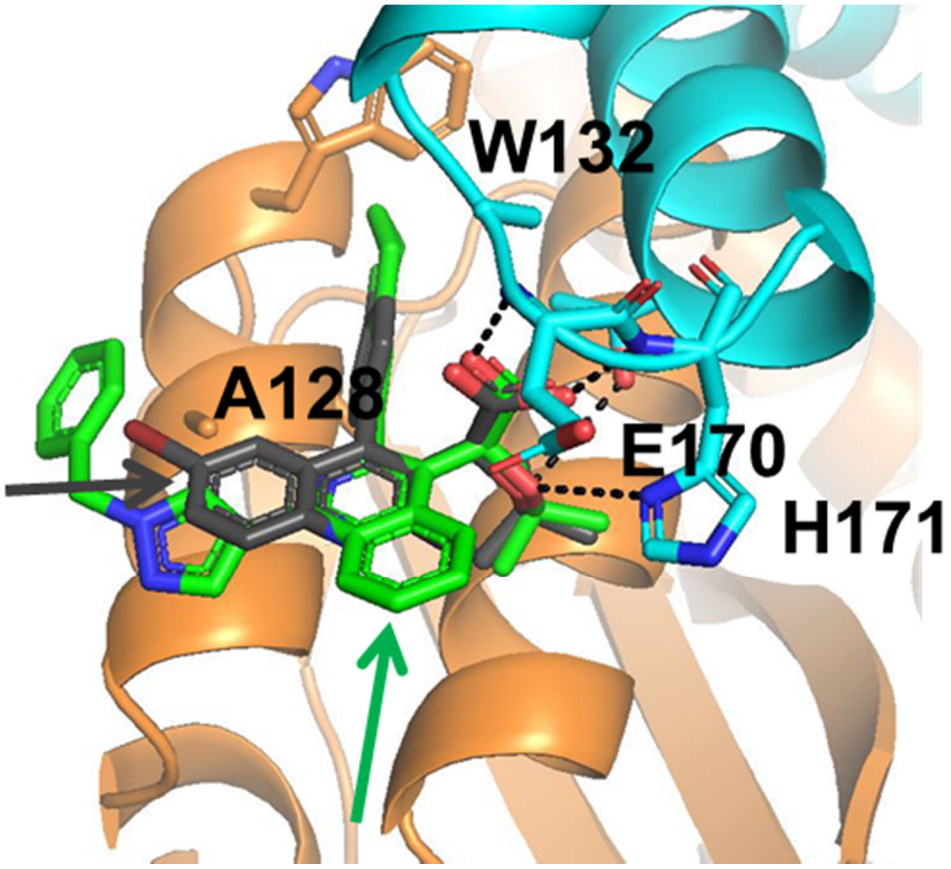
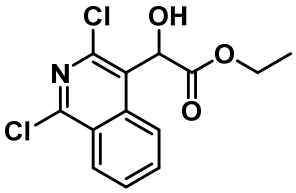


Figure S1. Superimposition of crystal structures of **6l** (green) and **BIB-II** (gray) bound to the CCD dimer. Green and gray arrows point to isoquinoline and quinoline rings in **6l** and **BIB-II**, respectively. Hydrogen bonding interactions are indicated by dashed lines.

Synthetic Materials and Methods

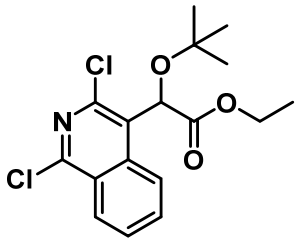
All reactions were performed at room temperature unless otherwise stated. Commercially available chemicals were used as purchased. Ice/water was used as the temperature bath to achieve 0 °C. Ice/NaCl was used to achieve -15 °C. Dry THF and DCM were obtained from an Innovative Technology PureSolv system. NMR spectra were recorded at 300 K using Bruker AV 300 MHz, AVIII 400 MHz, or Ascend 700 MHz NMR. ^{1}H NMR chemical shifts are reported in parts per million (ppm) and are referenced to the solvent residual signals: $CDCl_3$ (δ = 7.26), DMSO-d_6 (δ = 2.50), Acetone-d_6 (δ = 2.05) and CD_3OD (δ = 3.31). ^{13}C-NMR chemical shifts are reported in ppm and are referenced to the solvent residual signals: $CDCl_3$ (δ = 77.16), DMSO-d_6 (δ = 39.52), Acetone-d_6 (δ = 29.84) and CD_3OD (δ = 49.00). Spin multiplicities are described as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet) and m (multiplet) and coupling constant (*J*) values are reported in hertz (Hz). Electrospray ionization mass spectra (ESI-MS) were recorded on a Thermo LTQ Orbitrap mass spectrometer. Thin layer chromatography was performed on Sorbtech UV254 aluminum backed plates. The compounds were visualized by UV light at 254 nm. Flash column chromatography was carried out using Sorbtech 40-63 µm silica gel with solvents as described. Analytical High Performance Liquid Chromatography was performed using a Shimadzu LC-20AT equipped with an SPD-20AV Detector and either (1) ACE Excel 3 C18-PFP column (dimensions 150 x 4.6 mm id) (compounds **6a**, **6d**, **6f**, **6h**, **6i**, **6j**, **6k**, **6l**, **9**) or (2) Phenomenex LUNA 5 µm C18 column (dimensions 150 x 4.60 mm) (compound **6c**). The flow rate was 1 ml/min and the detecting wavelength was 254 nm. There were three separate gradients used with solvent A: H_2O (0.1 % Formic acid) and solvent B: MeOH (0.1% Formic Acid). Gradient 1 (compounds **6a**, **6h**): 0-3 min 5% B, 3-13 min 5-95% B, 13-18 min 95% B, 18.01-20 min 5% B. Gradient 2 (compounds **6d**, **6i**, **6j**, **6k**, **6f**, **6l**, **9**): 0-3 min 5% B, 3-18 min 5-95% B, 18-21 min 95% B, 21.01-23 min 5% B. Gradient 3 (compound **6c**): 0-3 min 5% B, 3-16 min 5-95% B, 16-21 min 95% B, 21.01-23 min 5% B. Purity was assessed by HPLC. Compounds **6a**, **6c**, **6d**, **6f**, **6h**, **6i**, **6j**, **6k**, **6l**, and **9** were ≥ 90%.

Experimental Procedures

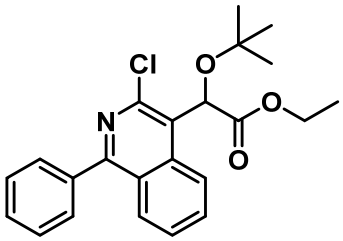


Ethyl 2-(1,3-dichloroisoquinolin-4-yl)-2-hydroxyacetate (2). 1,3-Dichloroisoquinoline **1** (500 mg, 2.52 mmol) was iodinated following the procedure reported by Yang et al.[19] Following initial purification by column chromatography, the resulting mixture of 1,3-Dichloroisoquinoline and 1,3-dichloro-4-iodoisoquinoline was carried on without further purification. Acylation was performed following a similar procedure reported by Fandrick et al.[20] To a mixture of 1,3-dichloro-4-iodoisoquinoline and 1,3-dichloroisoquinoline (2.52 mmol) and copper (I) bromide dimethyl sulfide complex (25 mg, 0.13 mmol) in anhydrous THF (3.5 mL) at -15 °C was added *i*-PrMgCl (2M in THF, 1.32 mL, 2.65 mmol) dropwise over several minutes. The resulting mixture was then added dropwise to a solution of ethyl chlorooxoacetate (310 µL, 2.77 mmol) in anhydrous THF (1.1 mL) at -15 °C. After stirring for 30 min at -10 °C to -15 °C, the mixture was then warmed to 0 °C and ethanol (1.13 mL) and sodium borohydride (87 mg, 2.29 mmol)

were added sequentially. The mixture was stirred for 10 min. at 0 °C and water (10 mL) was added dropwise over several minutes at 0 °C. The mixture was then extracted with ethyl acetate (3x), the organic layers were combined and dried over sodium sulfate, and concentrated in vacuo. Flash chromatography (silica gel, 20% ethyl acetate in hexanes) afforded compound **2** (322 mg, 42 % over 3 steps) as a white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* = 8.6 Hz, 1H), 7.78 (ddd, *J* = 8.5, 7.0, 1.2 Hz, 1H), 7.69 (ddd, *J* = 8.1, 7.0, 0.9 Hz, 1H), 6.10 (d, *J* = 2.7 Hz, 1H), 4.29 – 4.21 (m, 1H), 4.21 – 4.13 (m, 1H), 3.70 (d, *J* = 2.7 Hz, 1H), 1.11 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 173.3, 151.6, 144.1, 137.6, 132.6, 128.7, 127.4, 126.5, 125.1, 124.1, 69.5, 63.0, 14.1. HRMS (ESI/ion trap) m/z: $[M+Na]^+$ Calcd for $C_{13}H_{11}Cl_2NO_3Na$ 322.00082; found 322.00206.

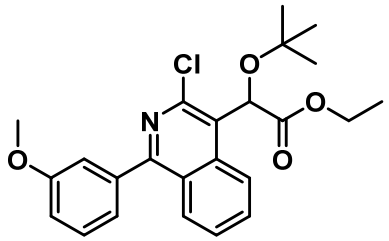


Ethyl 2-(tert-butoxy)-2-(1,3-dichloroisoquinolin-4-yl)acetate (3). To a solution of ethyl 2-(1,3-dichloroisoquinolin-4-yl)-2-hydroxyacetate **2** (557 mg, 1.86 mmol) in *tert*-butyl acetate (37 mL) at 0 °C was added perchloric acid (70% aq., 4.33 mL). The reaction mixture was stirred for 2 hours at 0 °C and quenched by pouring into a solution of saturated aqueous sodium carbonate. The aqueous layer was extracted with ethyl acetate (3x), the organic layers were combined and dried over sodium sulfate, and concentrated in vacuo. Flash chromatography (silica gel, 20% ethyl acetate in hexanes) afforded compound **3** (504 mg, 76%) as a white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 8.6 Hz, 1H), 8.30 (d, *J* = 8.5 Hz, 1H), 7.76 (ddd, *J* = 8.5, 7.0, 1.3 Hz, 1H), 7.66 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 5.95 (s, 1H), 4.18 – 3.99 (m, 2H), 1.24 (s, 9H), 1.08 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 171.5, 150.9, 142.4, 137.9, 132.0, 128.6, 127.7, 126.8, 126.7, 126.7, 76.9, 71.3, 61.7, 28.1, 14.1. HRMS (ESI/ion trap) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{19}Cl_2NO_3Na$ 378.06342; Found 378.06401.

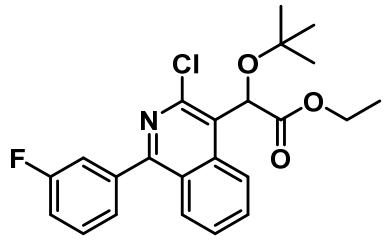


Ethyl 2-(tert-butoxy)-2-(3-chloro-1-phenylisoquinolin-4-yl)acetate (4a). A mixture of ethyl 2-(tert-butoxy)-2-(1,3-dichloroisoquinolin-4-yl)acetate (**3**) (292 mg, 0.82 mmol), phenyl boronic acid (200 mg, 1.64 mmol), and sodium carbonate (520 mg, 4.91 mmol) in toluene (4.1 mL), ethanol (2 mL) and water (1.6 mL) was degassed with argon for 5 min. Palladium tetrakis(triphenylphosphine) (189 mg, 0.16 mmol) was added and the reaction mixture was heated to 90 °C for 7 hours. The mixture was filtered through celite and concentrated in vacuo. Flash chromatography (silica gel, 6% ethyl acetate in hexanes) afforded

compound **4a** (299 mg, 92%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, *J* = 8.7 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.76 – 7.64 (m, 3H), 7.59 – 7.46 (m, 4H), 6.07 (s, 1H), 4.27 – 3.99 (m, 2H), 1.30 (s, 9H), 1.13 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 161.4, 144.3, 138.3, 137.4, 130.8, 130.3, 129.2, 128.5, 128.1, 127.2, 126.6, 126.4, 126.2, 76.7, 71.6, 61.6, 28.2, 14.1. HRMS (ESI/ion trap) m/z: $[M+Na]^+$ Calcd for $C_{23}H_{24}ClNO_3Na$ 420.13369; Found 420.13363.

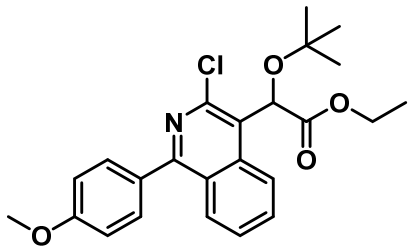


Ethyl 2-(tert-butoxy)-2-(3-chloro-1-(3-methoxyphenyl)isoquinolin-4-yl)acetate (4b). A mixture of ethyl 2-(tert-butoxy)-2-(1,3-dichloroisoquinolin-4-yl)acetate (**3**) (100 mg, 0.28 mmol), 3-methoxyphenylboronic acid (64 mg, 0.42 mmol), and sodium carbonate (119 mg, 1.12 mmol) in toluene (1.4 mL), ethanol (0.7 mL) and water (0.6 mL) was degassed with argon for 5 min. Palladium tetrakis(triphenylphosphine) (65 mg, 0.06 mmol) was added and the reaction mixture was heated to 90 °C for 5 hours. The mixture was filtered through celite and concentrated in vacuo. Flash chromatography (silica gel, gradient 12-15% ethyl acetate in hexanes) afforded compound **4b** (91 mg, 76%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, *J* = 8.6 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.70 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 1H), 7.56 – 7.47 (m, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.30 – 7.21 (m, 2H), 7.05 (ddd, *J* = 8.3, 2.4, 0.9 Hz, 1H), 6.07 (s, 1H), 4.25 – 4.02 (m, 2H), 3.87 (s, 3H), 1.29 (s, 9H), 1.13 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 161.2, 159.8, 144.3, 139.6, 137.4, 130.8, 129.5, 128.1, 127.2, 126.7, 126.4, 126.4, 122.8, 115.5, 115.3, 76.7, 71.7, 61.6, 55.6, 28.2, 14.2. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{24}H_{27}ClNO_4$ 428.16231; Found 428.16142.

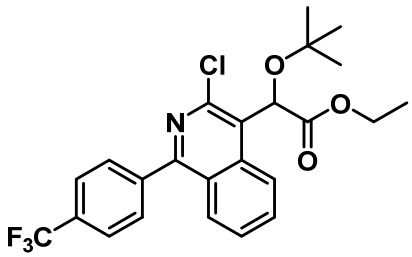


Ethyl 2-(tert-butoxy)-2-(3-chloro-1-(3-fluorophenyl)isoquinolin-4-yl)acetate (4c). A mixture of ethyl 2-(tert-butoxy)-2-(1,3-dichloroisoquinolin-4-yl)acetate **(3**) (111 mg, 0.31 mmol), 3-fluorobenzeneboronic acid (87 mg, 0.62 mmol), and sodium carbonate (198 mg, 1.87 mmol) in toluene (1.6 mL), ethanol (0.8 mL) and water (0.6 mL) was degassed with argon for 5 min. Palladium tetrakis(triphenylphosphine) (72 mg, 0.06 mmol) was added and the reaction mixture was heated to 90 °C for 7 hours. The mixture was filtered through celite and concentrated in vacuo. Flash chromatography (silica gel, 5% ethyl acetate in hexanes) afforded compound **4c** (94 mg, 73%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 – 8.58 (m, 1H), 8.04 (ddd, *J* = 8.5, 1.2, 0.7 Hz, 1H), 7.71 (ddd, *J* = 8.7, 6.8, 1.3 Hz, 1H), 7.56 – 7.38 (m, 4H), 7.24 – 7.15 (m, 1H), 6.07 (s, *J* = 2.7 Hz, 1H), 4.18 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.08 (dq, *J* = 10.8, 7.1 Hz, 1H), 1.29 (s, 9H), 1.12 (t, *J*

= 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 162.8 (d, *J* = 247.0 Hz), 159.7 (d, *J* = 2.3 Hz), 144.2, 140.3 (d, *J* = 7.6 Hz), 137.4, 130.9, 130.1 (d, *J* = 8.2 Hz), 127.6, 127.5, 126.8, 126.5, 126.4, 126.0 (d, *J* = 3.0 Hz), 117.3 (d, *J* = 22.5 Hz), 116.2 (d, *J* = 21.1 Hz), 76.7, 71.6, 61.5, 28.1, 14.1. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{23}H_{24}ClFNO_3$ 416.14233; Found 416.14158.

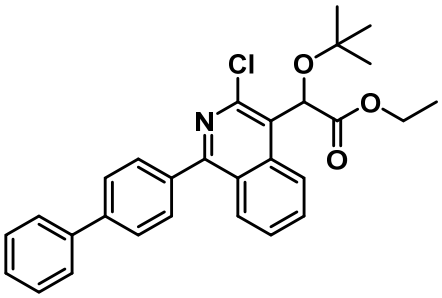


Ethyl 2-(tert-butoxy)-2-(3-chloro-1-(4-methoxyphenyl)isoquinolin-4-yl)acetate (4d). A mixture of ethyl 2-(tert-butoxy)-2-(1,3-dichloroisoquinolin-4-yl)acetate (**3**) (100 mg, 0.28 mmol), 4-methoxyphenylboronic acid (64 mg, 0.42 mmol), and sodium carbonate (179 mg, 1.69 mmol) in toluene (1.4 mL), ethanol (0.7 mL) and water (0.6 mL) was degassed with argon for 5 min. Palladium tetrakis(triphenylphosphine) (65 mg, 0.06 mmol) was added and the reaction mixture was heated to 90 ^{o}C for 6 hours. The mixture was filtered through celite and concentrated in vacuo. Flash chromatography (silica gel, 8% ethyl acetate in hexanes) afforded compound **4d** (96 mg, 80%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 8.7 Hz, 1H), 8.15 – 8.07 (m, 1H), 7.73 – 7.62 (m, 3H), 7.50 (ddd, *J* = 8.3, 6.8, 1.1 Hz, 1H), 7.09 – 7.01 (m, 2H), 6.06 (s, *J* = 2.7 Hz, 1H), 4.17 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.08 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.88 (s, 3H), 1.29 (s, 9H), 1.12 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 161.0, 160.6, 144.3, 137.5, 131.8, 130.8, 130.6, 128.1, 127.1, 126.6, 126.4, 125.7, 114.0, 76.6, 71.6, 61.5, 55.5, 28.2, 14.1. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{24}H_{27}ClNO_4$ 428.16231; Found 428.16139.

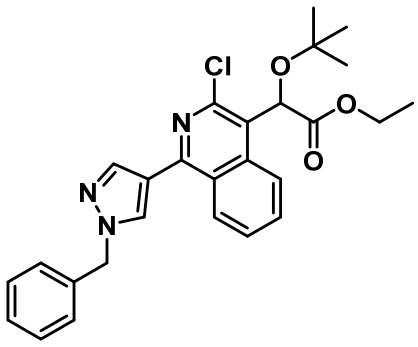


Ethyl 2-(tert-butoxy)-2-(3-chloro-1-(4-(trifluoromethyl)phenyl)isoquinolin-4-yl)acetate (4e). A mixture of ethyl 2-(tert-butoxy)-2-(1,3-dichloroisoquinolin-4-yl)acetate (**3**) (100 mg, 0.28 mmol), 4-trifluoromethylphenylboronic acid (80 mg, 0.42 mmol), and sodium carbonate (179 mg, 1.69 mmol) in toluene (1.4 mL), ethanol (0.7 mL) and water (0.6 mL) was degassed with argon for 5 min. Palladium tetrakis(triphenylphosphine) (65 mg, 0.06 mmol) was added and the reaction mixture was heated to 90 ^{o}C for 6 hours. The mixture was filtered through celite and concentrated in vacuo. Flash chromatography (silica gel, 5% ethyl acetate in hexanes) afforded compound **4e** (111 mg, 85%) as a clear colorless foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 – 8.60 (m, 1H), 7.98 (ddd, *J* = 8.5, 1.2, 0.7 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.77 – 7.70 (m, 1H), 7.54 (ddd, *J* = 8.4, 6.8, 1.1 Hz, 1H), 6.08 (s, *J* = 2.8 Hz, 1H), 4.19 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.09 (dq, *J* = 10.8, 7.1 Hz, 1H), 1.30 (s, 9H), 1.14 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100

MHz, $CDCl_3$) δ 171.9, 159.7, 144.3, 141.8, 137.5, 131.3 (q, *J* = 32.6 Hz), 131.0, 130.6, 127.7, 127.4, 127.1, 126.7, 126.4, 125.5 (q, *J* = 3.7 Hz), 124.2 (q, *J* = 271.8 Hz), 76.8, 71.6, 61.6, 28.2, 14.1. HRMS (ESI/ion trap) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{23}ClF_3NO_3Na$ 488.12108; Found 488.12015.

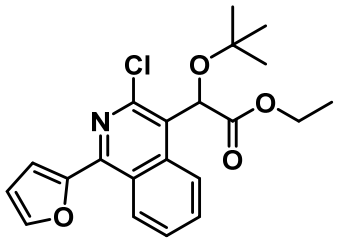


Ethyl 2-(1-([1,1'-biphenyl]-4-yl)-3-chloroisoquinolin-4-yl)-2-(tert-butoxy)acetate (4f). A mixture of ethyl 2-(tert-butoxy)-2-(1,3-dichloroisoquinolin-4-yl)acetate (**3**) (127 mg, 0.36 mmol), 4-biphenylboronic acid pinacol ester (149 mg, 0.53 mmol), and sodium carbonate (226 mg, 2.13 mmol) in toluene (1.8 mL), ethanol (0.9 mL) and water (0.7 mL) was degassed with argon for 5 min. Palladium tetrakis(triphenylphosphine) (82 mg, 0.07 mmol) was added and the reaction mixture was heated to 90 ^oC for 6 hours. The mixture was filtered through celite and concentrated in vacuo. Flash chromatography (silica gel, 5% ethyl acetate in hexanes) afforded compound **4f** (134 mg, 80%) as a white powder. ^1H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, *J* = 8.6 Hz, 1H), 8.18 (d, *J* = 8.2 Hz, 1H), 7.86 – 7.66 (m, 7H), 7.59 – 7.45 (m, 3H), 7.44 – 6.88 (m, 1H), 6.13 (s, 1H), 4.27 – 4.16 (m, 1H), 4.16 – 4.05 (m, 1H), 1.33 (s, 9H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 160.9, 144.3, 142.06, 142.05, 140.6, 137.4, 137.1, 130.7, 129.0, 128.0, 127.7, 127.25, 127.21, 127.18, 126.5, 126.4, 126.2, 76.6, 71.6, 61.5, 28.1, 14.1. HRMS (ESI/ion trap) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{28}ClNO_3Na$ 496.16499; Found 496.16570.

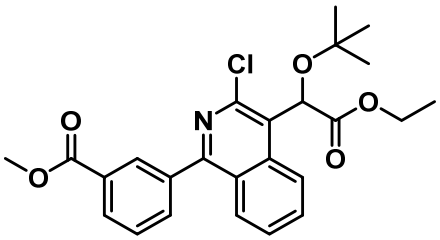


Ethyl 2-(1-(1-benzyl-1H-pyrazol-4-yl)-3-chloroisoquinolin-4-yl)-2-(tert-butoxy)acetate (4g). A mixture of ethyl 2-(tert-butoxy)-2-(1,3-dichloroisoquinolin-4-yl)acetate (**3**) (100 mg, 0.28 mmol), 1-benzylpyrazole-4-boronic acid pinacol ester (120 mg, 0.42 mmol), and sodium carbonate (119 mg, 1.12 mmol) in toluene (1.4 mL), ethanol (0.7 mL) and water (0.6 mL) was degassed with argon for 5 min. Palladium tetrakis(triphenylphosphine) (65 mg, 0.06 mmol) was added and the reaction mixture was heated to 90 ^oC for 5 hours. The mixture was filtered through celite and concentrated in vacuo. Flash chromatography (silica gel, 15% ethyl acetate in hexanes) afforded compound **4g** (105 mg, 78%) as a white foam. ^1H NMR

(300 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.7 Hz, 1H), 8.33 (d, *J* = 8.4 Hz, 1H), 8.07 (s, 1H), 7.99 (s, 1H), 7.73 – 7.65 (m, 1H), 7.55 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.41 – 7.28 (m, 5H), 6.01 (s, 1H), 5.40 (s, 2H), 4.19 – 4.09 (m, 1H), 4.09 – 3.98 (m, 1H), 1.26 (s, 9H), 1.08 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 153.5, 144.3, 140.4, 137.4, 135.9, 131.0, 130.7, 129.0, 128.4, 128.1, 127.4, 127.0, 126.5, 126.2, 125.4, 121.2, 76.6, 71.6, 61.5, 56.5, 28.1, 14.1. HRMS (ESI/ion trap) m/z: $[M+Na]^+$ Calcd for $C_{27}H_{28}ClN_3O_3Na$ 500.17114; Found 500.17216.

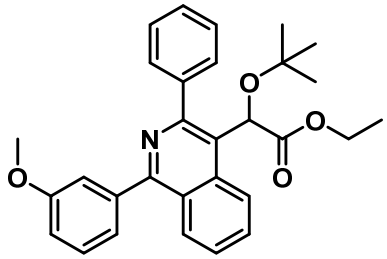


Ethyl 2-(tert-butoxy)-2-(3-chloro-1-(furan-2-yl)isoquinolin-4-yl)acetate (4h). A mixture of ethyl 2-(tert-butoxy)-2-(1,3-dichloroisoquinolin-4-yl)acetate (**3**) (160 mg, 0.45 mmol), furan-2-boronic acid (75 mg, 0.67 mmol), and sodium carbonate (190 mg, 1.80 mmol) in toluene (2.3 mL), ethanol (1.1 mL) and water (0.9 mL) was degassed with argon for 5 min. Palladium tetrakis(triphenylphosphine) (104 mg, 0.09 mmol) was added and the reaction mixture was heated to 90 °C for 2 hours. The mixture was filtered through celite and concentrated in vacuo. Flash chromatography (silica gel, 5% ethyl acetate in hexanes) afforded compound **4h** (114 mg, 65%) as a tan powder. ^1H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 8.6 Hz, 1H), 8.53 (d, *J* = 8.6 Hz, 1H), 7.81 – 7.63 (m, 2H), 7.65 – 7.52 (m, 1H), 7.26 (d, *J* = 3.2 Hz, 1H), 6.60 (d, *J* = 1.0 Hz, 1H), 6.02 (s, *J* = 12.6 Hz, 1H), 4.22 – 3.96 (m, 2H), 1.25 (s, 9H), 1.06 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 152.8, 149.0, 144.6, 144.3, 137.7, 130.7, 127.6, 127.1, 126.31, 126.31, 125.1, 114.4, 112.1, 76.6, 71.5, 61.4, 28.1, 14.0. HRMS (ESI/ion trap) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{22}ClNO_4Na$ 410.11296; Found 410.11335.

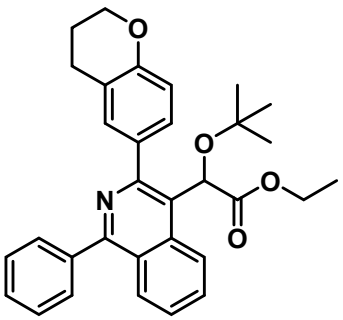


Methyl 3-(4-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-3-chloroisoquinolin-1-yl)benzoate (4i). A mixture of ethyl 2-(tert-butoxy)-2-(1,3-dichloroisoquinolin-4-yl)acetate (**3**) (125 mg, 0.35 mmol), (3-(methoxycarbonyl)phenyl)boronic acid (95 mg, 0.53 mmol) (prepared by Fischer esterification of the boronic acid), and sodium carbonate (149 mg, 1.41 mmol) in toluene (1.8 mL), ethanol (0.9 mL) and water (0.7 mL) was degassed with argon for 5 min. Palladium tetrakis(triphenylphosphine) (81 mg, 0.07 mmol) was added and the reaction mixture was heated to 90 °C for 2 hours. The mixture was filtered through celite and concentrated in vacuo. Flash chromatography (silica gel, 10% ethyl acetate in hexanes) afforded compound **4i** (147 mg, 92%) as a clear colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 8.7 Hz, 1H),

8.36 (s, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.70 (t, *J* = 7.7 Hz, 1H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 6.05 (s, 1H), 4.22 – 4.11 (m, 1H), 4.11 – 4.01 (m, 1H), 3.90 (s, 3H), 1.27 (s, 9H), 1.10 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 166.6, 160.0, 144.2, 138.5, 137.4, 134.5, 131.3, 130.8, 130.5, 130.2, 128.7, 127.51, 127.49, 126.7, 126.5, 126.4, 76.7, 71.5, 61.5, 52.3, 28.1, 14.1. HRMS (ESI/ion trap) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{26}ClNO_5Na$ 478.13917; Found 478.14014.

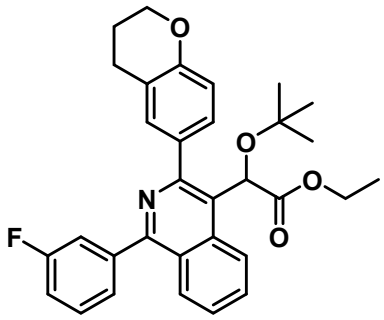


Ethyl 2-(tert-butoxy)-2-(1-(3-methoxyphenyl)-3-phenylisoquinolin-4-yl)acetate (5a). A mixture of ethyl 2-(tert-butoxy)-2-(3-chloro-1-(3-methoxyphenyl)isoquinolin-4-yl)acetate (**4b**) (32 mg, 0.07 mmol), phenyl boronic acid (14 mg, 0.11 mmol), sodium carbonate (48 mg, 0.45 mmol), and bis(tri-tert-butylphosphine)palladium(0) (8 mg, 0.01 mmol) in dimethylacetamide (0.8 mL) and water (0.2 mL) was degassed with argon for 5 min. The reaction mixture was heated to 130 °C for 14 hours and then cooled to room temperature. The mixture was filtered through celite and concentrated in vacuo. The residue was diluted with ethyl acetate and washed with water (2x). The organic layer was dried over sodium sulfate and concentrated in vacuo. Flash chromatography (silica gel, 10% ethyl acetate in hexanes) afforded compound **5a** (16 mg, 46%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 8.6 Hz, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.79 – 7.73 (m, 2H), 7.70 (ddd, *J* = 8.5, 6.8, 1.3 Hz, 1H), 7.54 – 7.38 (m, 5H), 7.32 – 7.25 (m, 2H), 7.01 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 5.69 (s, 1H), 4.29 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.19 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.86 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.96 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 160.3, 159.7, 151.3, 141.2, 141.0, 135.9, 130.3, 130.1, 129.4, 128.3, 128.2, 128.0, 126.83, 126.79, 126.6, 126.1, 122.9, 115.7, 114.6, 76.2, 71.3, 61.6, 55.5, 28.0, 14.3. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{30}H_{32}NO_4$ 470.23258; Found 470.23222.

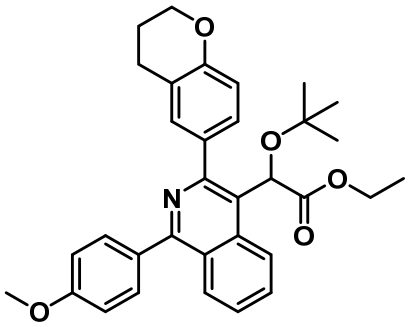


Ethyl 2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-phenylisoquinolin-4-yl)acetate (5b). A mixture of ethyl 2-(tert-butoxy)-2-(3-chloro-1-phenylisoquinolin-4-yl)acetate (**4a**) (95 mg, 0.24 mmol), 2-(chroman-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane(94 mg, 0.36 mmol), sodium carbonate (152 mg, 1.44 mmol), and bis(tri-tert-butylphosphine)palladium(0) (25 mg, 0.05 mmol) in dimethylacetamide (2.4 mL) and water

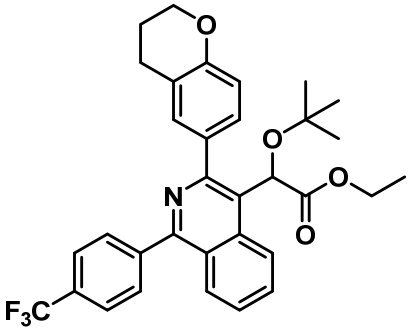
(0.5 mL) was degassed with argon for 5 min. The reaction mixture was heated to 130 °C for 16 hours and then cooled to room temperature. The mixture was filtered through celite and concentrated in vacuo. The residue was diluted with ethyl acetate and washed with water (2x). The organic layer was dried over sodium sulfate and concentrated in vacuo. Flash chromatography (silica gel, gradient 3% ethyl acetate and 20% dichloromethane in hexanes to 5% ethyl acetate and 20% dichloromethane in hexanes) afforded compound **5b** (17 mg, 14%) as a yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 8.6 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.77 – 7.63 (m, 3H), 7.55 – 7.42 (m, 6H), 6.88 (d, *J* = 8.3 Hz, 1H), 5.74 (s, 1H), 4.38 – 4.08 (m, 4H), 2.95 – 2.74 (m, 2H), 2.13 – 1.96 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.99 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 160.3, 155.0, 151.4, 139.9, 136.0, 132.9, 131.8, 130.4, 130.0, 129.1, 128.6, 128.3, 127.9, 126.7, 126.6, 126.4, 125.7, 122.1, 116.4, 76.2, 71.3, 66.8, 61.5, 28.1, 25.1, 22.5, 14.3. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{32}H_{34}NO_4$ 496.24824; Found 496.24694.



Ethyl 2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-(3-fluorophenyl)isoquinolin-4-yl)acetate (5c). A mixture of ethyl 2-(tert-butoxy)-2-(3-chloro-1-(3-fluorophenyl)isoquinolin-4-yl)acetate (**4c**) (42 mg, 0.10 mmol), 2-(chroman-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane(52 mg, 0.20 mmol), sodium carbonate (64 mg, 0.60 mmol), and bis(tri-tert-butylphosphine)palladium(0) (20 mg, 0.04 mmol) in dimethylacetamide (1.0 mL) and water (0.2 mL) was degassed with argon for 5 min. The reaction mixture was heated to 130 °C for 18 hours and then cooled to room temperature. The mixture was filtered through celite and concentrated in vacuo. The residue was diluted with ethyl acetate and washed with water (2x). The organic layer was dried over sodium sulfate and concentrated in vacuo. Flash chromatography (silica gel, 5-10% ethyl acetate in hexanes) afforded compound **5c** (38 mg, 73%) as a yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.6 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.69 (t, *J* = 7.7 Hz, 1H), 7.56 – 7.40 (m, 6H), 7.22 – 7.12 (m, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 5.73 (s, 1H), 4.41 – 4.09 (m, 4H), 2.99 – 2.73 (m, 2H), 2.16 – 1.97 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.99 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 162.8 (d, *J* = 246.3 Hz), 158.8 (d, *J* = 2.2 Hz), 155.1, 151.4, 142.0 (d, *J* = 7.5 Hz), 136.1, 132.7, 131.8, 130.1, 129.8 (d, *J* = 8.2 Hz), 129.1, 127.5, 126.9, 126.8, 126.23, 126.20, 126.1 (d, *J* = 2.9 Hz), 122.1, 117.4 (d, *J* = 22.2 Hz) 116.5, 115.5 (d, *J* = 21.1 Hz), 76.3, 71.3, 66.8, 61.5, 28.1, 25.1, 22.5, 14.3. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{32}H_{33}FNO_4$ 514.23881; Found 514.23773.

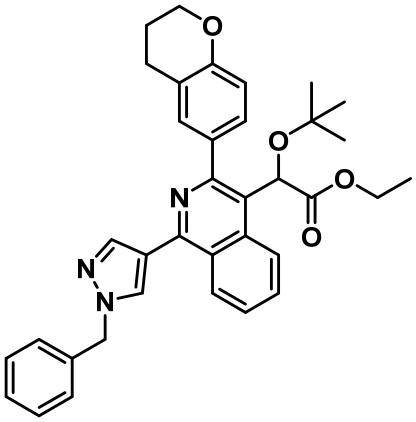


Ethyl 2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-(4-methoxyphenyl)isoquinolin-4-yl)acetate (5d). A mixture of ethyl 2-(tert-butoxy)-2-(3-chloro-1-(4-methoxyphenyl)isoquinolin-4-yl)acetate (**4d**) (45 mg, 0.11 mmol), 2-(chroman-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane(55 mg, 0.21 mmol), sodium carbonate (70 mg, 0.66 mmol), and palladium tetrakis(triphenylphosphine) (51 mg, 0.04 mmol) in dimethylacetamide (1.1 mL) and water (0.2 mL) was degassed with argon for 5 min. The reaction mixture was heated to 130 °C for 15 hours and then cooled to room temperature. The mixture was filtered through celite and concentrated in vacuo. The residue was diluted with ethyl acetate and washed with water (2x). The organic layer was dried over sodium sulfate and concentrated in vacuo. Flash chromatography (silica gel, 15% ethyl acetate in hexanes) afforded compound **5d** (27 mg, 49%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, *J* = 8.6 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.75 – 7.61 (m, 3H), 7.55 – 7.41 (m, 3H), 7.03 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 1H), 5.73 (s, 1H), 4.37 – 4.08 (m, 4H), 3.88 (s, 3H), 2.96 – 2.73 (m, 2H), 2.13 – 1.98 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.99 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 160.1, 159.9, 155.0, 151.4, 136.1, 133.1, 132.5, 131.84, 131.77, 129.8, 129.2, 128.0, 126.7, 126.44, 126.41, 125.3, 122.0, 116.4, 113.8, 76.2, 71.4, 66.8, 61.4, 55.5, 28.1, 25.1, 22.3, 14.3. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{33}H_{36}NO_5$ 526.25880; Found 526.25992.

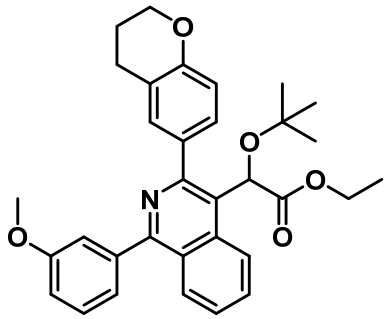


Ethyl 2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-(4-(trifluoromethyl)phenyl)isoquinolin-4-yl)acetate (5e). A mixture of ethyl 2-(tert-butoxy)-2-(3-chloro-1-(4-(trifluoromethyl)phenyl)isoquinolin-4-yl)acetate (**4e**) (48 mg, 0.10 mmol), 2-(chroman-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane(54 mg, 0.21 mmol), sodium carbonate (66 mg, 0.62 mmol), and palladium tetrakis(triphenylphosphine) (48 mg, 0.04 mmol) in dimethylacetamide (1.0 mL) and water (0.2 mL) was degassed with argon for 5 min. The reaction mixture was heated to 130 °C for 20 hours and then cooled to room temperature. The mixture was filtered through celite and concentrated in vacuo. The residue was diluted with ethyl acetate and washed with

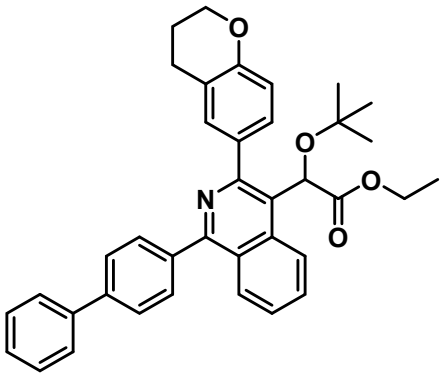
water (2x). The organic layer was dried over sodium sulfate and concentrated in vacuo. Flash chromatography (silica gel, gradient 5-7% ethyl acetate in hexanes) afforded compound **5e** (20 mg, 34%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, *J* = 8.6 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.57 – 7.41 (m, 3H), 6.89 (d, *J* = 8.3 Hz, 1H), 5.74 (s, 1H), 4.39 – 4.09 (m, 4H), 2.97 – 2.72 (m, 2H), 2.16 – 1.97 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 158.7, 155.2, 151.5, 143.5, 136.1, 132.6, 131.8, 130.9, 130.7, 130.5, 130.2, 130.0, 129.1, 127.3, 127.0, 126.5, 126.2, 125.4, 125.3, 122.6, 122.2, 120.4, 116.5, 76.3, 71.4, 66.8, 61.5, 28.1, 25.1, 22.5, 14.3. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{33}H_{33}F_3NO_4$ 564.23562; Found 564.23540.



Ethyl 2-(1-(1-benzyl-1H-pyrazol-4-yl)-3-(chroman-6-yl)isoquinolin-4-yl)-2-(tert-butoxy)acetate (5f). Ethyl 2-(1-(1-benzyl-1H-pyrazol-4-yl)-3-chloroisoquinolin-4-yl)-2-(tert-butoxy)acetate (**4g**) (81 mg, 0.17 mmol), 2-(chroman-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane(66 mg, 0.25 mmol), sodium carbonate (107 mg, 1.01 mmol), and bis(tri-tert-butylphosphine)palladium(0) (17 mg, 0.03 mmol) in dimethylacetamide (1.7 mL) and water (0.3 mL) was degassed with argon for 5 min. The reaction mixture was heated to 130 ^{o}C for 15 hours and then cooled to room temperature. The mixture was filtered through celite and concentrated in vacuo. The residue was diluted with ethyl acetate and washed with water (2x). The organic layer was dried over sodium sulfate and concentrated in vacuo. Flash chromatography was performed twice (silica gel, 20% ethyl acetate and 20% chloroform in hexanes; 3% ethanol, 3% acetonitrile, and 10% ethyl acetate in hexanes) to afford compound **5f** (22 mg, 23%) as a yellow foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.6 Hz, 1H), 8.33 (d, *J* = 8.4 Hz, 1H), 8.07 (s, 1H), 7.96 (s, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.50 – 7.41 (m, 2H), 7.42 – 7.30 (m, 5H), 6.88 (d, *J* = 8.1 Hz, 1H), 5.67 (s, 1H), 5.39 (s, 2H), 4.35 – 4.06 (m, 4H), 2.97 – 2.74 (m, 2H), 2.14 – 1.99 (m, 2H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.96 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 155.1, 152.5, 151.5, 140.6, 136.3, 136.1, 132.9, 131.7, 130.8, 129.9, 129.1, 129.0, 128.3, 128.2, 126.9, 126.8, 126.2, 125.2, 122.5, 122.0, 116.4, 76.1, 71.3, 66.8, 61.4, 56.5, 28.1, 25.1, 22.5, 14.3. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{36}H_{38}N_3O_4$ 576.28568; Found 576.28612.

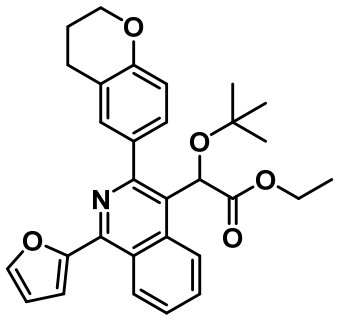


Ethyl 2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-(3-methoxyphenyl)isoquinolin-4-yl)acetate (5g). A mixture of ethyl 2-(tert-butoxy)-2-(3-chloro-1-(3-methoxyphenyl)isoquinolin-4-yl)acetate (**4b**) (78 mg, 0.18 mmol), 2-(chroman-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (71 mg, 0.27 mmol), sodium carbonate (115 mg, 1.06 mmol), and bis(tri-tert-butylphosphine)palladium(0) (19 mg, 0.04 mmol) in dimethylacetamide (1.8 mL) and water (0.4 mL) was degassed with argon for 5 min. The reaction mixture was heated to 130 °C for 14 hours and then cooled to room temperature. The mixture was filtered through celite and concentrated in vacuo. The residue was diluted with ethyl acetate and washed with water (2x). The organic layer was dried over sodium sulfate and concentrated in vacuo. Flash chromatography (silica gel, 12% ethyl acetate in hexanes) afforded compound **5g** (61 mg, 64%) as a yellow foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.75 – 7.63 (m, 1H), 7.55 – 7.36 (m, 4H), 7.28 (d, *J* = 9.0 Hz, 2H), 7.01 (dd, *J* = 8.1, 2.5 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 5.75 (s, 1H), 4.38 – 4.08 (m, 4H), 3.85 (s, 3H), 2.97 – 2.73 (m, 2H), 2.13 – 1.98 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 160.1, 159.6, 155.0, 151.3, 141.2, 136.0, 132.9, 131.8, 129.9, 129.2, 129.1, 127.9, 126.7, 126.5, 126.4, 125.8, 122.8, 122.0, 116.3, 115.7, 114.5, 76.2, 71.4, 66.7, 61.4, 55.5, 28.0, 25.1, 22.5, 14.3. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{33}H_{36}NO_5$ 526.25880; Found 526.25981.

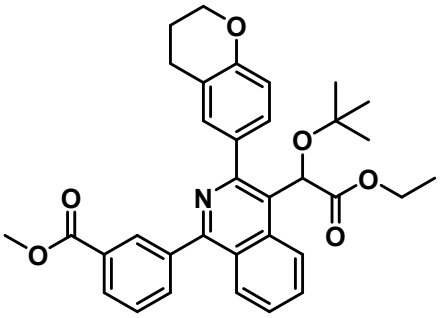


Ethyl 2-(1-([1,1'-biphenyl]-4-yl)-3-(chroman-6-yl)isoquinolin-4-yl)-2-(tert-butoxy)acetate (5h). A mixture of ethyl 2-(1-([1,1'-biphenyl]-4-yl)-3-chloroisoquinolin-4-yl)-2-(tert-butoxy)acetate (**4f**) (70 mg, 0.15 mmol), 2-(chroman-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (58 mg, 0.22 mmol), sodium carbonate (94 mg, 0.89 mmol), and bis(tri-tert-butylphosphine)palladium(0) (15 mg, 0.03 mmol) in dimethylacetamide (1.5 mL) and water (0.3 mL) was degassed with argon for 5 min. The reaction mixture was heated to 130 °C for 14 hours and then cooled to room temperature. The mixture was filtered through celite and concentrated in vacuo. The residue was diluted with ethyl acetate and washed with

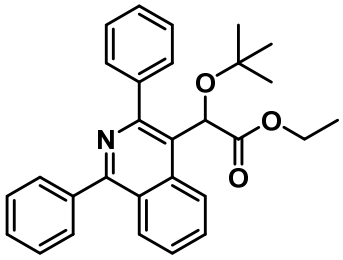
water (2x). The organic layer was dried over sodium sulfate and concentrated in vacuo. Flash chromatography (silica gel, 10% ethyl acetate in hexanes) afforded compound **5h** (38 mg, 45%) as a yellow powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, *J* = 8.6 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.86 – 7.79 (m, 2H), 7.77 – 7.65 (m, 5H), 7.56 – 7.44 (m, 5H), 7.43 – 7.34 (m, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 5.76 (s, 1H), 4.38 – 4.09 (m, 4H), 2.97 – 2.76 (m, 2H), 2.12 – 2.01 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 159.9, 155.1, 151.5, 141.5, 141.0, 138.9, 136.1, 133.0, 131.9, 130.9, 130.0, 129.2, 129.0, 127.9, 127.6, 127.3, 127.1, 126.8, 126.6, 126.4, 125.8, 122.1, 116.4, 76.2, 71.4, 66.8, 61.5, 28.1, 25.1, 22.5, 14.3. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{38}H_{38}NO_4$ 572.27954; Found 572.28001.



Ethyl 2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-(furan-2-yl)isoquinolin-4-yl)acetate (5i). A mixture of ethyl 2-(tert-butoxy)-2-(3-chloro-1-(furan-2-yl)isoquinolin-4-yl)acetate (**4h**) (106 mg, 0.27 mmol), 2-(chroman-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (107 mg, 0.41 mmol), sodium carbonate (174 mg, 1.64 mmol), and bis(tri-tert-butylphosphine)palladium(0) (28 mg, 0.06 mmol) in dimethylacetamide (2.7 mL) and water (0.5 mL) was degassed with argon for 5 min. The reaction mixture was heated to 130 ^{o}C for 16 hours and then cooled to room temperature. The mixture was filtered through celite and concentrated in vacuo. The residue was diluted with ethyl acetate and washed with water (2x). The organic layer was dried over sodium sulfate and concentrated in vacuo. Flash chromatography was performed twice (silica gel, 8% ethyl acetate in hexanes; 15% ethyl acetate in hexanes) to afford compound **5i** (37 mg, 28%) as an orange foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (d, *J* = 8.3 Hz, 1H), 8.48 (d, *J* = 8.2 Hz, 1H), 7.75 – 7.63 (m, 2H), 7.58 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.53 – 7.43 (m, 2H), 7.19 (d, *J* = 3.4 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.60 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.70 (s, 1H), 4.35 – 4.21 (m, 3H), 4.14 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.98 – 2.75 (m, 2H), 2.13 – 2.01 (m, 2H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.96 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 155.1, 154.0, 151.4, 148.6, 143.8, 136.4, 132.7, 131.8, 129.9, 129.2, 127.0, 126.9, 126.7, 126.2, 125.2, 122.0, 116.4, 113.1, 111.7, 76.2, 71.3, 66.7, 61.4, 28.1, 25.1, 22.5, 14.2. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{30}H_{32}NO_5$ 486.22750; Found 486.22788.

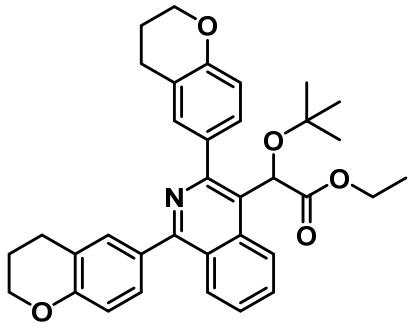


Methyl 3-(4-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-3-(chroman-6-yl)isoquinolin-1-yl)benzoate (5j). A mixture of methyl 3-(4-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-3-chloroisoquinolin-1-yl)benzoate (**4i**) (98 mg, 0.22 mmol), 2-(chroman-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (84 mg, 0.32 mmol), sodium carbonate (137 mg, 1.29 mmol), and bis(tri-tert-butylphosphine)palladium(0) (22 mg, 0.04 mmol) in dimethylacetamide (2.1 mL) and water (0.4 mL) was degassed with argon for 5 min. The reaction mixture was heated to 130 °C for 15 hours and then cooled to room temperature. The mixture was filtered through celite and concentrated in vacuo. The residue was diluted with ethyl acetate and washed with water (2x). The organic layer was dried over sodium sulfate and concentrated in vacuo. Flash chromatography (silica gel, 3% acetone and 10% ethyl acetate in hexanes) afforded compound **5j** (65 mg, 55%) as a yellow foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, *J* = 8.6 Hz, 1H), 8.39 (s, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.75 – 7.65 (m, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.54 – 7.43 (m, 3H), 6.89 (d, *J* = 8.3 Hz, 1H), 5.74 (s, 1H), 4.36 – 4.10 (m, 4H), 3.92 (s, 3H), 2.96 – 2.74 (m, 2H), 2.12 – 1.98 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.00 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 167.0, 159.1, 155.1, 151.4, 140.2, 136.0, 134.8, 132.7, 131.7, 131.4, 130.3, 130.0, 129.7, 129.1, 128.5, 127.4, 126.8, 126.3, 126.2, 122.1, 116.4, 76.2, 71.3, 66.7, 61.5, 52.3, 28.0, 25.1, 22.5, 14.3. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{34}H_{36}NO_6$ 554.25371; Found 554.25418.

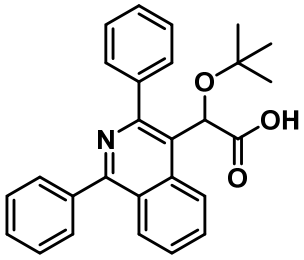


Ethyl 2-(tert-butoxy)-2-(1,3-diphenylisoquinolin-4-yl)acetate (5k). A mixture of ethyl 2-(tert-butoxy)-2-(1,3-dichloroisoquinolin-4-yl)acetate (**3**) (70 mg, 0.20 mmol), phenyl boronic acid (72 mg, 0.59 mmol), sodium carbonate (125 mg, 1.18 mmol), and bis(tri-tert-butylphosphine)palladium(0) (20 mg, 0.04 mmol) in dimethylacetamide (2.0 mL) and water (0.4 mL) was degassed with argon for 5 min. The reaction mixture was heated to 130 °C for 14 hours and then cooled to room temperature. The mixture was filtered through celite and concentrated in vacuo. The residue was diluted with ethyl acetate and washed with water (2x). The organic layer was dried over sodium sulfate and concentrated in vacuo. Flash chromatography (silica gel, 10% ethyl acetate in hexanes) afforded compound **5k** (69 mg, 92%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 8.5 Hz, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.82 – 7.67 (m, 5H), 7.57 – 7.39 (m, 7H), 5.70 (s, 1H), 4.37 – 4.12 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.96 (s, 9H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ 173.8, 160.5, 151.4, 141.0, 139.8, 135.9, 130.3, 130.3, 130.1, 128.6, 128.4, 128.3, 128.2, 128.0, 126.83, 126.76, 126.6, 125.9, 76.2, 71.2, 61.6, 28.0, 14.2. HRMS (ESI/ion trap) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{29}NO_3Na$ 440.22202; Found 440.22118.

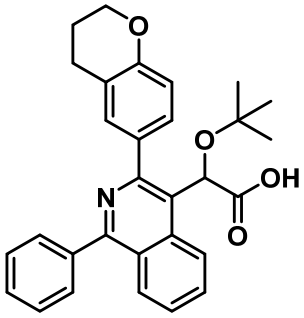


Ethyl 2-(tert-butoxy)-2-(1,3-di(chroman-6-yl)isoquinolin-4-yl)acetate (5l). A mixture of ethyl 2-(tert-butoxy)-2-(1,3-dichloroisoquinolin-4-yl)acetate (**3**) (50 mg, 0.14 mmol), 2-(chroman-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (80 mg, 0.31 mmol), sodium carbonate (89 mg, 0.84 mmol), and bis(tri-tert-butylphosphine)palladium(0) (14 mg, 0.03 mmol) in dimethylacetamide (1.4 mL) and water (0.3 mL) was degassed with argon for 5 min. The reaction mixture was heated to 130 °C for 14 hours and then cooled to room temperature. The mixture was filtered through celite and concentrated in vacuo. The residue was diluted with ethyl acetate and washed with water (2x). The organic layer was dried over sodium sulfate and concentrated in vacuo. Flash chromatography (silica gel, gradient 12-15% ethyl acetate in hexanes) afforded compound **5l** (49 mg, 63%) as an off-white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, *J* = 8.6 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.73 – 7.62 (m, 1H), 7.54 – 7.41 (m, 5H), 6.96 – 6.85 (m, 2H), 5.71 (s, 1H), 4.37 – 4.07 (m, 6H), 2.96 – 2.74 (m, 4H), 2.13 – 1.98 (m, 4H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.99 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 160.1, 155.6, 155.0, 151.3, 136.2, 133.1, 131.92, 131.89, 131.8, 129.8, 129.5, 129.2, 128.1, 126.6, 126.39, 126.36, 125.2, 122.3, 122.0, 116.4, 116.3, 76.1, 71.4, 66.8, 66.7, 61.4, 28.1, 25.1, 22.53, 22.50, 14.3. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{35}H_{38}NO_5$ 552.27445; Found 552.27494.

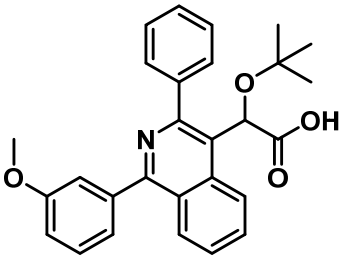


2-(tert-butoxy)-2-(1,3-diphenylisoquinolin-4-yl)acetic acid (6a). To a solution of ethyl 2-(tert-butoxy)-2-(1,3-diphenylisoquinolin-4-yl)acetate (**5k**) (26 mg, 0.06 mmol) in 1:1 tetrahydrofuran to methanol (0.7 mL) was added sodium hydroxide (3M aqueous, 0.1 mL, 0.34 mmol). The reaction mixture was stirred overnight at room temperature and concentrated in vacuo. The residue was diluted with water and acetic acid was added to adjust to pH 4. The precipitated product was collected and washed with water. Flash chromatography (silica gel, 1% acetic acid and 30% ethyl acetate in hexanes) and trituration with hexanes

afforded compound **6a** (15 mg, 62%) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.07 (m, 2H), 7.82 (d, *J* = 6.7 Hz, 2H), 7.78 – 7.66 (m, 3H), 7.59 – 7.39 (m, 7H), 5.83 (s, 1H), 0.94 (s, *J* = 7.3 Hz, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 161.3, 152.7, 140.3, 139.5, 135.4, 130.6, 130.41, 130.39, 128.8, 128.61, 128.57, 128.5, 128.4, 127.0, 126.6, 125.2, 124.2, 78.2, 71.2, 28.1. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{27}H_{26}NO_3$ 412.19072; Found 412.19012.

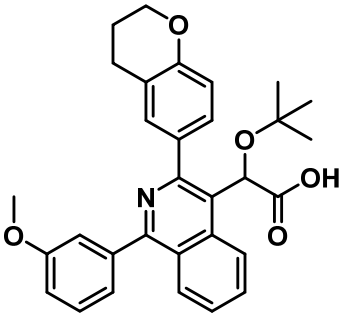


2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-phenylisoquinolin-4-yl)acetic acid (6b). To a solution of ethyl 2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-phenylisoquinolin-4-yl)acetate (**5b**) (14 mg, 0.03 mmol) in 1:1 tetrahydrofuran to methanol (0.3 mL) was added sodium hydroxide (3M aqueous, 48 µL, 0.15 mmol). The reaction mixture was stirred overnight at room temperature. The reaction was monitored by TLC and more sodium hydroxide was added if necessary. The mixture was concentrated in vacuo, and the residue was diluted with water and acetic acid was added to adjust to pH 4. The precipitated product was collected and washed with water to afford compound **6b** (10 mg, 76%) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.03 (m, 2H), 7.78 – 7.62 (m, 3H), 7.61 – 7.43 (m, 6H), 6.88 (d, *J* = 8.3 Hz, 1H), 5.89 (s, 1H), 4.24 (t, *J* = 5.1 Hz, 2H), 2.95 – 2.73 (m, 2H), 2.11 – 1.96 (m, 2H), 0.96 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 161.0, 155.4, 152.6, 139.6, 135.5, 132.3, 131.9, 130.4, 129.4, 128.8, 128.5, 128.4, 127.5, 126.7, 126.3, 125.1, 123.9, 122.4, 116.7, 78.2, 71.4, 66.8, 28.2, 25.1, 22.5. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{30}H_{30}NO_4$ 468.21693; Found 468.21584.

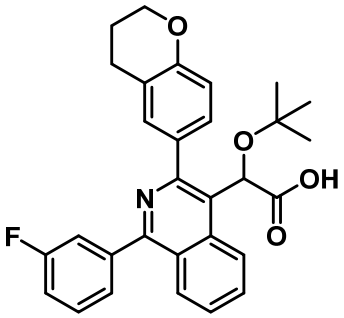


2-(tert-butoxy)-2-(1-(3-methoxyphenyl)-3-phenylisoquinolin-4-yl)acetic acid (6c). To a solution of ethyl 2-(tert-butoxy)-2-(1-(3-methoxyphenyl)-3-phenylisoquinolin-4-yl)acetate (**5a**) (13 mg, 0.03 mmol) in 1:1 tetrahydrofuran to methanol (0.3 mL) was added sodium hydroxide (3M aqueous, 46 µL, 0.14 mmol). The reaction mixture was stirred overnight at room temperature. The reaction was monitored by TLC and more sodium hydroxide was added if necessary. The mixture was concentrated in vacuo, and the residue was diluted with water and acetic acid was added to adjust to pH 4. The precipitated product was collected and washed with water to afford compound **6c** (8 mg, 69%) as a white powder. ^{1}H NMR (300

MHz, $CDCl_3$) δ 8.15 (t, *J* = 7.8 Hz, 2H), 7.82 (d, *J* = 6.6 Hz, 2H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.60 – 7.36 (m, 5H), 7.28 (d, *J* = 11.2 Hz, 2H), 7.02 (dd, *J* = 7.9, 2.4 Hz, 1H), 5.84 (s, 1H), 3.86 (s, 3H), 0.94 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 161.1, 159.7, 152.6, 140.8, 140.3, 135.4, 130.6, 130.4, 129.4, 128.6, 128.6, 128.5, 127.0, 126.6, 125.2, 124.3, 122.9, 115.7, 114.8, 78.2, 71.2, 55.6, 28.1. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{28}H_{28}NO_4$ 442.20128; Found 442.20052.

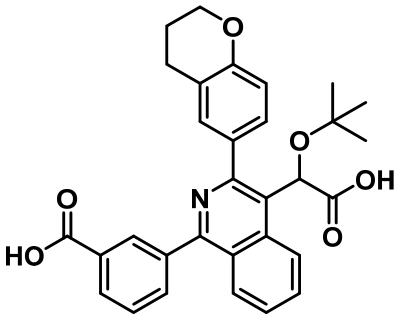


2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-(3-methoxyphenyl)isoquinolin-4-yl)acetic acid (6d). To a solution of ethyl 2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-(3-methoxyphenyl)isoquinolin-4-yl)acetate (**5a**) (55 mg, 0.10 mmol) in 1:1 tetrahydrofuran to methanol (1.0 mL) was added sodium hydroxide (3M aqueous, 174 µL, 0.52 mmol). The reaction mixture was stirred overnight at room temperature. The reaction was monitored by TLC and more sodium hydroxide was added if necessary. The mixture was concentrated in vacuo, and the residue was diluted with water and acetic acid was added to adjust to pH 4. The precipitated product was collected and washed with water to afford compound **6d** (42 mg, 81%) as an off-white powder. ^{1}H NMR (300 MHz, acetone-d_6) δ 8.60 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.74 – 7.56 (m, 3H), 7.55 – 7.40 (m, 2H), 7.31 – 7.22 (m, 2H), 7.11 – 7.03 (m, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 5.82 (s, 1H), 4.20 (t, *J* = 5.1 Hz, 2H), 3.85 (s, 3H), 2.93 – 2.71 (m, 2H), 2.04 – 1.97 (m, 2H), 0.91 (s, 9H). ^{13}C NMR (75 MHz, acetone-d_6) δ 177.1, 160.5, 159.9, 155.9, 151.6, 142.2, 137.1, 133.8, 133.0, 130.19, 130.17, 129.9, 128.04, 127.95, 127.88, 127.2, 126.7, 123.4, 122.7, 116.7, 116.5, 114.9, 76.3, 72.1, 67.2, 55.7, 28.3, 25.60, 23.10. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{31}H_{32}NO_5$ 498.22750; Found 498.22513.

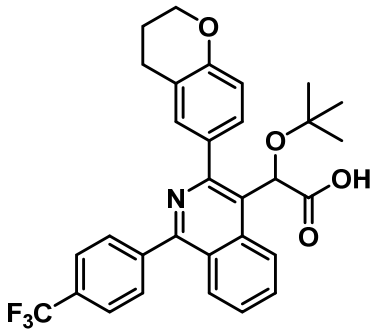


2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-(3-fluorophenyl)isoquinolin-4-yl)acetic acid (6e). To a solution of ethyl 2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-(3-fluorophenyl)isoquinolin-4-yl)acetate (**5c**) (25 mg, 0.05 mmol) in 1:1 tetrahydrofuran to methanol (0.5 mL) was added sodium hydroxide (3M aqueous, 80 µL, 0.24 mmol). The reaction mixture was stirred overnight at room temperature. The reaction was

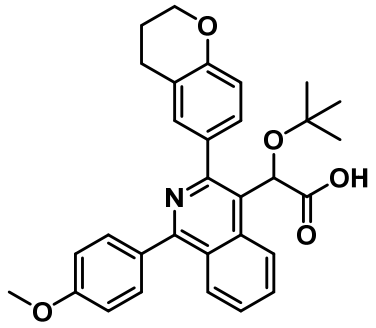
monitored by TLC and more sodium hydroxide was added if necessary. The mixture was concentrated in vacuo, and the residue was diluted with water and acetic acid was added to adjust to pH 4. The precipitated product was collected and washed with water to afford compound **6e** (11 mg, 47%) as an off-white powder. ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (d, *J* = 8.6 Hz, 1H), 7.97 – 7.87 (m, 1H), 7.74 – 7.63 (m, 3H), 7.60 – 7.49 (m, 2H), 7.48 – 7.42 (m, 1H), 7.38 (ddd, *J* = 9.6, 2.5, 1.5 Hz, 1H), 7.31 – 7.21 (m, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 5.65 (s, 1H), 4.29 – 4.19 (m, 2H), 2.99 – 2.76 (m, 2H), 2.11 – 1.98 (m, 2H), 0.90 (s, 9H). ^{13}C NMR (100 MHz, MeOD) δ 179.9, 164.0 (d, *J* = 245.3 Hz), 159.3 (d, *J* = 2.2 Hz), 156.4, 151.5, 143.0 (d, *J* = 7.5 Hz), 137.8, 133.8, 133.4, 131.9, 131.1 (d, *J* = 8.3 Hz), 130.8, 130.7, 129.0, 128.0, 127.8, 127.5, 127.1 (d, *J* = 2.9 Hz) 123.1, 117.9 (d, *J* = 22.4 Hz), 117.0, 116.4 (d, *J* = 21.3 Hz), 76.2, 73.5, 67.7, 28.5, 26.0, 23.6. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{30}H_{29}FNO_4$ 486.20751; Found 486.20875.



3-(4-(tert-butoxy(carboxy)methyl)-3-(chroman-6-yl)isoquinolin-1-yl)benzoic acid (6f). To a solution of methyl 3-(4-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-3-(chroman-6-yl)isoquinolin-1-yl)benzoate (**5j**) (51 mg, 0.09 mmol) in 1:1 tetrahydrofuran to methanol (0.9 mL) was added sodium hydroxide (3M aqueous, 154 µL, 0.46 mmol). The reaction mixture was stirred overnight at room temperature. The reaction was monitored by TLC and more sodium hydroxide was added if necessary. The mixture was concentrated in vacuo, and the residue was diluted with water and acetic acid was added to adjust to pH 4. The precipitated product was collected and washed with water to afford compound **6f** (30 mg, 64%) as an off-white powder. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.54 (d, *J* = 8.6 Hz, 1H), 8.41 (s, 1H), 8.20 (d, *J* = 7.8 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 7.7 Hz, 1H), 7.80 – 7.68 (m, 2H), 7.67 – 7.56 (m, 3H), 6.87 (d, *J* = 8.3 Hz, 1H), 5.88 (s, 1H), 4.23 (t, *J* = 5.2 Hz, 2H), 2.94 – 2.77 (m, 2H), 2.11 – 1.99 (m, 2H), 0.96 (s, 9H). ^{13}C NMR (100 MHz, acetone-d_6) δ 175.2, 167.7, 159.5, 156.1, 152.2, 141.0, 137.0, 135.4, 133.4, 132.8, 132.2, 131.8, 130.7, 130.5, 130.0, 129.3, 128.0, 127.8, 127.5, 127.2, 126.6, 123.0, 116.9, 76.8, 71.6, 67.2, 28.2, 25.6, 23.1. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{31}H_{30}NO_6$ 512.20676; Found 512.20715.

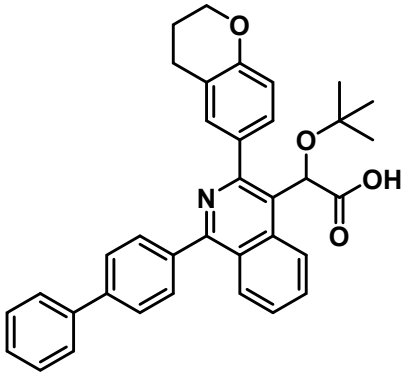


2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-(4-(trifluoromethyl)phenyl)isoquinolin-4-yl)acetic acid (6g). To a solution of ethyl 2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-(4-(trifluoromethyl)phenyl)isoquinolin-4-yl)acetate (**5e**) (12 mg, 0.02 mmol) in 1:1 tetrahydrofuran to methanol (0.2 mL) was added sodium hydroxide (3M aqueous, 36 µL, 0.11 mmol). The reaction mixture was stirred overnight at room temperature. The reaction was monitored by TLC and more sodium hydroxide was added if necessary. The mixture was concentrated in vacuo, and the residue was diluted with water and acetic acid was added to adjust to pH 4. The precipitated product was collected and washed with water to afford compound **6g** (8 mg, 70%) as a white powder. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.64 (d, *J* = 8.6 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 2H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.79 – 7.61 (m, 4H), 6.90 (d, *J* = 8.3 Hz, 1H), 5.89 (s, 1H), 4.27 (t, *J* = 5.2 Hz, 2H), 2.97 – 2.80 (m, 2H), 2.13 – 2.02 (m, 2H), 0.98 (s, 9H). ^{13}C NMR (75 MHz, acetone-d_6) δ 175.8, 158.7, 156.1, 152.1, 144.79, 144.77, 144.75, 144.73, 137.1, 133.5, 132.9, 131.8, 131.0, 130.6, 130.5, 130.1, 128.2, 127.9, 127.8, 127.7, 127.1, 126.6, 126.04, 125.99, 125.9, 125.9, 125.2, 123.7, 122.9, 116.8, 76.6, 71.9, 67.3, 28.2, 25.6, 23.1. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{31}H_{29}F_3NO_4$ 536.20432; Found 536.20620.

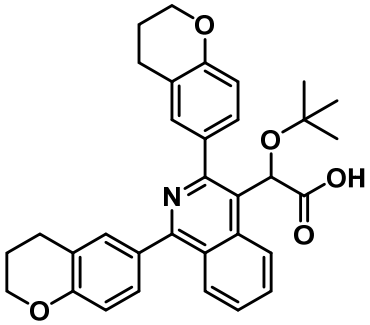


2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-(4-methoxyphenyl)isoquinolin-4-yl)acetic acid (6h). To a solution of ethyl 2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-(4-methoxyphenyl)isoquinolin-4-yl)acetate (**5d**) (20 mg, 0.04 mmol) in 1:1 tetrahydrofuran to methanol (0.4 mL) was added sodium hydroxide (3M aqueous, 63 µL, 0.19 mmol). The reaction mixture was stirred overnight at room temperature. The reaction was monitored by TLC and more sodium hydroxide was added if necessary. The mixture was concentrated in vacuo, and the residue was diluted with water and acetic acid was added to adjust to pH 4. The precipitated product was collected and washed with water to afford compound **6h** (15 mg, 80%) as a yellow powder. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.51 (d, *J* = 8.5 Hz, 1H), 8.14 (d, *J* = 8.3 Hz, 1H), 7.70 (d, *J* = 8.7 Hz, 3H), 7.65 – 7.54 (m, 3H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 1H), 5.85 (s, 1H), 4.23 (t, *J* = 5.2 Hz, 2H), 3.90 (s, 3H), 2.94 – 2.76 (m, 2H), 2.10 – 1.98 (m, 2H), 0.95 (s, *J* = 7.4 Hz, 9H). ^{13}C NMR (100

MHz, acetone-d_6) δ 175.5, 161.2, 160.2, 156.1, 152.1, 137.2, 133.8, 133.2, 132.9, 132.6, 130.4, 130.1, 128.4, 127.5, 127.4, 126.8, 126.5, 122.9, 116.9, 114.5, 76.7, 71.8, 67.3, 55.8, 28.3, 25.7, 23.2. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{31}H_{32}NO_5$ 498.22750; Found 498.22872.

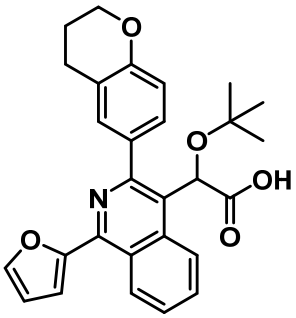


2-(1-([1,1'-biphenyl]-4-yl)-3-(chroman-6-yl)isoquinolin-4-yl)-2-(tert-butoxy)acetic acid (6i). To a solution of ethyl 2-(1-([1,1'-biphenyl]-4-yl)-3-(chroman-6-yl)isoquinolin-4-yl)-2-(tert-butoxy)acetate (**5h**) (33 mg, 0.06 mmol) in 1:1 tetrahydrofuran to methanol (0.6 mL) was added sodium hydroxide (3M aqueous, 96 µL, 0.29 mmol). The reaction mixture was stirred overnight at room temperature. The reaction was monitored by TLC and more sodium hydroxide was added if necessary. The mixture was concentrated in vacuo, and the residue was diluted with water and acetic acid was added to adjust to pH 4. The precipitated product was collected and washed with water to afford compound **6i** (24 mg, 76%) as an off-white powder. ^{1}H NMR (300 MHz, acetone-d_6) δ 8.56 (d, *J* = 8.7 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.84 (s, 4H), 7.82 – 7.68 (m, 3H), 7.68 – 7.56 (m, 3H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 5.89 (s, 1H), 4.23 (t, *J* = 5.1 Hz, 2H), 2.96 – 2.75 (m, 2H), 2.11 – 1.98 (m, 2H), 0.97 (s, 9H). ^{13}C NMR (100 MHz, acetone-d_6) δ 175.4, 160.0, 156.0, 152.1, 142.0, 141.3, 139.8, 137.0, 133.6, 132.9, 131.7, 130.5, 130.0, 129.8, 128.5, 128.2, 127.9, 127.52, 127.51, 127.5, 126.9, 126.7, 122.9, 116.9, 76.7, 71.7, 67.2, 28.2, 25.6, 23.1. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{36}H_{34}NO_4$ 544.24824; Found 544.24576.

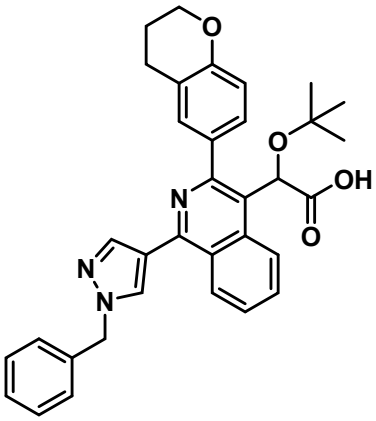


2-(tert-butoxy)-2-(1,3-di(chroman-6-yl)isoquinolin-4-yl)acetic acid (6j). To a solution of ethyl 2-(tert-butoxy)-2-(1,3-di(chroman-6-yl)isoquinolin-4-yl)acetate (**5l**) (43 mg, 0.08 mmol) in 1:1 tetrahydrofuran to methanol (0.8 mL) was added sodium hydroxide (3M aqueous, 130 µL, 0.39 mmol). The reaction mixture

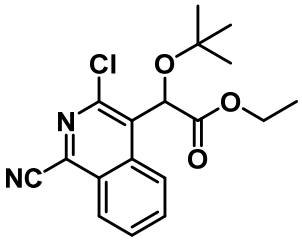
was stirred overnight at room temperature. The reaction was monitored by TLC and more sodium hydroxide was added if necessary. The mixture was concentrated in vacuo, and the residue was diluted with water and acetic acid was added to adjust to pH 4. The precipitated product was collected and washed with water to afford compound **6j** (33 mg, 81%) as a yellow powder. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.52 (d, *J* = 8.5 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.68 – 7.57 (m, 3H), 7.57 – 7.51 (m, 1H), 7.47 – 7.40 (m, 2H), 6.86 (dd, *J* = 11.1, 8.3 Hz, 2H), 5.82 (s, 1H), 4.28 – 4.17 (m, 4H), 2.92 – 2.76 (m, 4H), 2.10 – 1.97 (m, 4H), 0.92 (s, 9H). ^{13}C NMR (75 MHz, acetone-d_6) δ 176.2, 160.2, 156.5, 155.9, 151.9, 137.1, 133.9, 132.9, 132.8, 132.6, 130.2, 130.08, 130.06, 128.4, 127.6, 127.1, 126.68, 126.67, 123.1, 122.8, 116.9, 116.7, 76.5, 71.9, 67.3, 67.2, 28.2, 25.6, 25.5, 23.12, 23.06. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{33}H_{34}NO_5$ 524.24315; Found 524.24465.



2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-(furan-2-yl)isoquinolin-4-yl)acetic acid (6k). To a solution of ethyl 2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-(furan-2-yl)isoquinolin-4-yl)acetate (**5i**) (31 mg, 0.06 mmol) in 1:1 tetrahydrofuran to methanol (0.6 mL) was added sodium hydroxide (3M aqueous, 106 µL, 0.32 mmol). The reaction mixture was stirred overnight at room temperature. The reaction was monitored by TLC and more sodium hydroxide was added if necessary. The mixture was concentrated in vacuo, and the residue was diluted with water and acetic acid was added to adjust to pH 4. The precipitated product was collected and washed with water to afford compound **6k** (23 mg, 79%) as a yellow powder. ^{1}H NMR (300 MHz, acetone-d_6) δ 8.81 (dd, *J* = 6.8, 2.7 Hz, 1H), 8.54 (dd, *J* = 6.9, 2.5 Hz, 1H), 7.87 (s, 1H), 7.73 – 7.59 (m, 4H), 7.23 (d, *J* = 3.4 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.69 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.81 (s, 1H), 4.23 (t, *J* = 5.1 Hz, 2H), 2.97 – 2.74 (m, 2H), 2.11 – 1.98 (m, 2H), 0.91 (s, 9H). ^{13}C NMR (100 MHz, acetone-d_6) δ 176.1, 156.0, 155.5, 152.1, 148.6, 145.0, 137.4, 133.6, 132.8, 130.4, 130.0, 127.8, 127.7, 127.4, 125.6, 122.8, 116.8, 113.6, 112.6, 76.5, 71.9, 67.2, 28.2, 25.6, 23.1. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{28}H_{28}NO_5$ 458.19620; Found 458.19701.



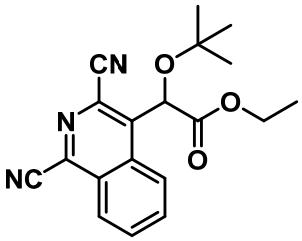
2-(1-(1-benzyl-1H-pyrazol-4-yl)-3-(chroman-6-yl)isoquinolin-4-yl)-2-(tert-butoxy)acetic acid (6l). To a solution of ethyl 2-(1-(1-benzyl-1H-pyrazol-4-yl)-3-(chroman-6-yl)isoquinolin-4-yl)-2-(tert-butoxy)acetate (**5f**) (15 mg, 0.03 mmol) in 1:1 tetrahydrofuran to methanol (0.3 mL) was added sodium hydroxide (3M aqueous, 43 µL, 0.13 mmol). The reaction mixture was stirred overnight at room temperature. The reaction was monitored by TLC and more sodium hydroxide was added if necessary. The mixture was concentrated in vacuo, and the residue was diluted with water and acetic acid was added to adjust to pH 4. The aqueous layer was extracted with ethyl acetate (3x) and the combined organic layers were dried over sodium sulfate and concentrated in vacuo to afford compound **6l** (13 mg, 91%) as yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, *J* = 11.0 Hz, 1H), 8.38 (t, *J* = 8.1 Hz, 2H), 8.03 (s, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.49 – 7.40 (m, 2H), 7.41 – 7.27 (m, 5H), 6.87 (d, *J* = 8.5 Hz, 1H), 5.59 (s, 1H), 5.45 (s, *J* = 15.4 Hz, 2H), 4.20 (t, *J* = 4.9 Hz, 2H), 2.90 – 2.71 (m, 2H), 2.04 – 1.89 (m, 2H), 0.86 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.6, 154.5, 151.5, 150.5, 140.0, 137.3, 135.4, 132.2, 131.6, 131.4, 129.8, 128.58, 128.55, 127.8, 127.7, 127.0, 126.5, 126.2, 124.9, 124.8, 121.9, 121.0, 115.8, 75.2, 70.2, 66.1, 55.0, 27.6, 24.4, 21.8. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{34}H_{34}N_3O_4$ 548.25438; Found 548.25192.



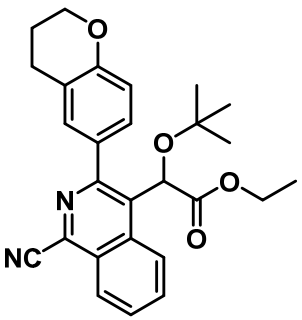
Ethyl 2-(tert-butoxy)-2-(3-chloro-1-cyanoisoquinolin-4-yl)acetate (S1). A mixture of ethyl 2-(tert-butoxy)-2-(1,3-dichloroisoquinolin-4-yl)acetate (**3**) (400 mg, 1.12 mmol), tris(dibenzylideneacetone)dipalladium(0) (21 mg, 0.02 mmol), 1,1′-bis(diphenylphosphino)ferrocene (16 mg, 0.03 mmol), zinc powder (9 mg, 0.13 mmol), and zinc cyanide (106 mg, 0.90 mmol) in dimethylacetamide (2.8 mL) was degassed with argon for 5 min. The reaction mixture was heated to 80 ^{o}C for 2 hours. The mixture was filtered through celite with ethyl acetate and washed with brine (2x). The organic layer was dried with sodium sulfate and concentrated in vacuo. Flash chromatography (silica gel, 5% ethyl acetate in hexanes) afforded compound **S1** (357 mg, 92%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (dd, *J* = 7.6, 1.1 Hz, 1H), 8.32 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.89 – 7.73 (m, 2H), 6.02 (s, 1H), 4.24 – 3.97 (m, 2H), 1.24 (s, 9H), 1.09 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 144.7, 136.8, 134.2,

132.7, 132.4, 130.0, 129.2, 126.9, 125.7, 114.9, 77.3, 71.5, 61.9, 28.1, 14.1. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{18}H_{20}ClN_2O_3$ 347.11570; Found 347.11596.

Note: Employing 0.6 equivalents of zinc (II) cyanide at 130 °C resulted in appreciable formation (9% yield) of the undesired C1,C3-bis-nitrile byproduct **S2** (see below) in addition to a 65% yield of **S1**. Lowering the reaction temperature to 80 °C in analogy to the coupling of the aromatic substituents to form **4a**-**i** greatly reduced the formation of this byproduct. Coupled with a slight increase in the amount of zinc (II) cyanide used in the reaction (0.8 equivalents), the yield of the desired nitrile could be increased to 92% in this step.

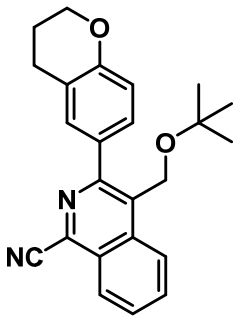


Ethyl 2-(tert-butoxy)-2-(1,3-dicyanoisoquinolin-4-yl)acetate (S2). A mixture of ethyl 2-(tert-butoxy)-2-(1,3-dichloroisoquinolin-4-yl)acetate (**3**) (300 mg, 0.84 mmol), tris(dibenzylideneacetone)dipalladium(0) (15 mg, 0.02 mmol), 1,1'-bis(diphenylphosphino)ferrocene (19 mg, 0.03 mmol), zinc powder (6.5 mg, 0.1 mmol), and zinc cyanide (59 mg, 0.50 mmol) in dimethylacetamide (2.1 mL) was degassed with argon for 5 min. The reaction mixture was heated to 130 °C for 2 hours. The mixture was filtered through celite with ethyl acetate and washed with brine (2x). The organic layer was dried with sodium sulfate and concentrated in vacuo. Flash chromatography (silica gel, 15% ethyl acetate in hexanes) afforded compound **S2** (25 mg, 9%) as a white crystalline powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 – 8.72 (m, 1H), 8.47 – 8.39 (m, 1H), 8.02 – 7.92 (m, 2H), 5.91 (s, 1H), 4.17 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.05 (dq, *J* = 10.8, 7.1 Hz, 1H), 1.29 (s, 9H), 1.10 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 140.1, 136.5, 134.2, 133.3, 132.6, 130.2, 127.9, 126.8, 126.2, 115.7, 114.5, 78.1, 71.9, 62.4, 28.0, 14.0. HRMS (ESI/ion trap) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{19}N_3O_3Na$ 360.13186; Found 360.13373.

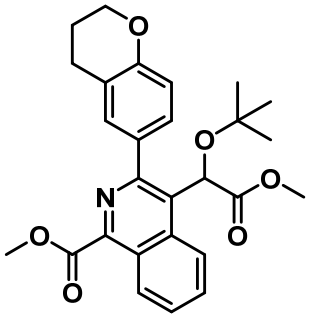


Ethyl 2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-cyanoisoquinolin-4-yl)acetate (7). A mixture of ethyl 2-(tert-butoxy)-2-(3-chloro-1-cyanoisoquinolin-4-yl)acetate (**S1**) (250 mg, 0.72 mmol), 2-(chroman-6-yl)-4,4,5,5-

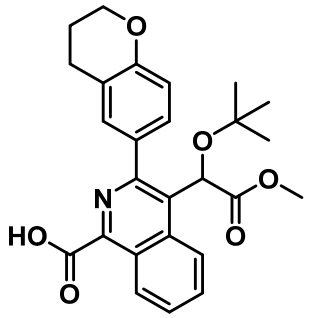
tetramethyl-1,3,2-dioxaborolane (281 mg, 1.08 mmol), sodium bicarbonate (303 mg, 3.60 mmol), and bis(tri-tert-butylphosphine)palladium(0) (74 mg, 0.14 mmol) in dimethylacetamide (7.2 mL) was degassed with argon for 5 min. The reaction mixture was heated to 130 °C for 14 hours and then cooled to room temperature. The mixture was filtered through celite and concentrated in vacuo. The residue was diluted with ethyl acetate and washed with water (2x). The organic layer was dried over sodium sulfate and concentrated in vacuo. Flash chromatography (silica gel, 10% ethyl acetate in hexanes) and trituration with hexanes afforded compound **7** (150 mg, 47%) as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 – 8.52 (m, 1H), 8.39 – 8.32 (m, 1H), 7.83 – 7.71 (m, 2H), 7.47 – 7.37 (m, 2H), 6.91 (d, *J* = 8.2 Hz, 1H), 5.71 (s, 1H), 4.33 – 4.22 (m, 3H), 4.21 – 4.09 (m, 1H), 2.97 – 2.76 (m, 2H), 2.14 – 2.00 (m, 2H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.95 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 155.7, 152.8, 135.6, 134.4, 131.7, 131.6, 131.3, 130.8, 129.1, 128.9, 128.7, 127.3, 125.6, 122.6, 116.8, 116.0, 76.7, 71.0, 66.9, 61.9, 28.0, 25.1, 22.4, 14.2. HRMS (ESI/ion trap) m/z: $[M+Na]^+$ Calcd for $C_{27}H_{28}N_2O_4Na$ 467.19413; Found 467.19459.



4-(tert-butoxymethyl)-3-(chroman-6-yl)isoquinoline-1-carbonitrile (S3). A mixture of ethyl 2-(tert-butoxy)-2-(3-chloro-1-cyanoisoquinolin-4-yl)acetate (**7**) (201.6 mg, 0.58 mmol), 2-(chroman-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (227 mg, 0.87 mmol), sodium carbonate (370 mg, 3.49 mmol), and bis(tri-tert-butylphosphine)palladium(0) (59 mg, 0.12 mmol) in dimethylacetamide (5.8 mL) and H_2O (1.2 mL) was degassed with argon for 5 min. The reaction mixture was heated to 130 °C for 16 hours and then cooled to room temperature. The mixture was filtered through celite and concentrated in vacuo. The residue was diluted with ethyl acetate and washed with water (2x). The organic layer was dried over sodium sulfate and concentrated in vacuo. Flash chromatography (silica gel, 5% ethyl acetate in hexanes) afforded compound **S3** (38.2 mg, 18%) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 8.0 Hz, 1H), 8.27 (d, J = 8.6 Hz, 1H), 7.86 (t, J = 7.2 Hz, 1H), 7.74 (t, J = 7.5 Hz, 1H), 7.60 – 7.49 (m, 2H), 6.90 (d, J = 8.2 Hz, 1H), 4.79 (s, 2H), 4.25 (t, J = 5.1 Hz, 2H), 2.88 (t, J = 6.4 Hz, 2H), 2.11 – 2.02 (m, 2H), 1.40 (s, J = 5.0 Hz, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 154.2, 137.3, 134.2, 131.9, 131.6, 130.8, 129.2, 128.8, 128.2, 128.1, 125.6, 124.9, 122.2, 116.5, 116.1, 74.9, 66.8, 59.0, 27.8, 25.1, 22.4. HRMS (ESI/ion trap) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{24}N_2O_2Na$ 395.17300; Found 395.17314.

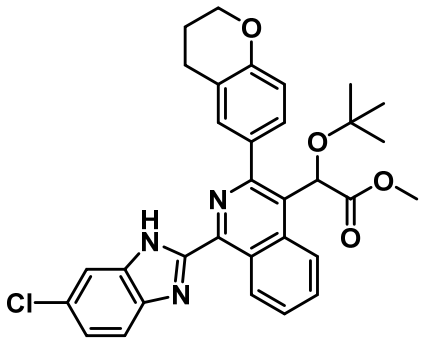


Methyl 4-(1-(tert-butoxy)-2-methoxy-2-oxoethyl)-3-(chroman-6-yl)isoquinoline-1-carboxylate (S4). A mixture of ethyl 2-(tert-butoxy)-2-(3-(chroman-6-yl)-1-cyanoisoquinolin-4-yl)acetate (**7**) (142 mg, 0.32 mmol), sodium hydroxide (10N aqueous, 0.3 mL), ethanol (3.2 mL), and tetrahydrofuran (0.3 mL) was heated to reflux for 15 hours. The reaction mixture was cooled to room temperature, the ethanol and tetrahydrofuran was removed under reduced pressure, and water was added to dilute the mixture. Concentrated hydrochloric acid was added dropwise to adjust to pH 2-4. The mixture was extracted with ethyl acetate (3x) and the combined organic layers were dried over sodium sulfate and concentrated in vacuo to afford the crude diacid (134 mg, 96%) as a yellow powder. The Diacid (126 mg, 0.29 mmol) was dissolved in methanol (0.5 mL) and ether (4.8 mL) and treated with (trimethylsilyl)diazomethane (2M in hexanes, 0.7 mL, 1.39 mmol) dropwise and stirred at room temperature for 10 min. The reaction mixture was concentrated under reduced pressure. Flash chromatography (silica gel, 20% ethyl acetate in hexanes) afforded compound **S4** (102 mg, 76%) as a yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 8.6 Hz, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 7.77 – 7.66 (m, 1H), 7.67 – 7.58 (m, 1H), 7.46 – 7.35 (m, 2H), 6.88 (d, *J* = 8.2 Hz, 1H), 5.74 (s, 1H), 4.24 (t, *J* = 5.1 Hz, 2H), 4.05 (s, 3H), 3.72 (s, 3H), 2.96 – 2.75 (m, 2H), 2.11 – 1.98 (m, 2H), 0.93 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 166.9, 155.4, 151.0, 149.4, 136.2, 131.9, 131.8, 130.7, 129.7, 129.0, 127.9, 126.6, 126.3, 125.7, 122.5, 116.6, 76.5, 71.1, 66.8, 53.1, 52.7, 28.0, 25.1, 22.5. HRMS (ESI/ion trap) m/z: $[M+Na]^+$ Calcd for $C_{27}H_{29}NO_6Na$ 486.18871; Found 486.18873.

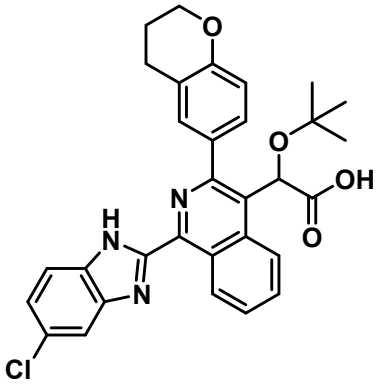


4-(1-(tert-butoxy)-2-methoxy-2-oxoethyl)-3-(chroman-6-yl)isoquinoline-1-carboxylic acid (8). Methyl 4-(1-(tert-butoxy)-2-methoxy-2-oxoethyl)-3-(chroman-6-yl)isoquinoline-1-carboxylate (**S4**) (50 mg, 0.11 mmol) was dissolved in tetrahydrofuran (1.1 mL) and methanol (0.5 mL) and sodium hydroxide (1M aqueous, 0.15 mL, 0.15 mmol) was added dropwise. The reaction mixture was stirred for 1 hour at room temperature, and then acidified with 1M hydrochloric acid. The mixture was further diluted with brine, extracted with ethyl acetate (3x), and the combined organic layers were dried over sodium sulfate and concentrated in vacuo to afford compound **10** (48 mg, 99%) as a yellow powder. ^{1}H NMR (300 MHz, $CDCl_3$)

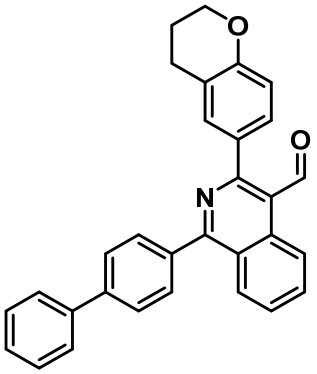
δ 10.25 (s, 1H), 9.60 (d, *J* = 7.8 Hz, 1H), 8.49 (d, *J* = 8.0 Hz, 1H), 7.85 – 7.67 (m, 2H), 7.48 – 7.34 (m, 2H), 6.92 (d, *J* = 8.3 Hz, 1H), 5.76 (s, 1H), 4.35 – 4.22 (m, 2H), 3.75 (s, 3H), 3.01 – 2.76 (m, 2H), 2.17 – 2.03 (m, 2H), 0.94 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 164.1, 155.8, 148.8, 143.1, 137.4, 133.1, 131.59, 131.55, 130.4, 129.2, 128.8, 127.6, 126.6, 126.5, 122.6, 116.9, 76.8, 70.8, 66.8, 52.8, 28.0, 25.1, 22.3. HRMS (ESI/ion trap) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{27}NO_6Na$ 472.17306; Found 472.17362.



Methyl 2-(tert-butoxy)-2-(1-(6-chloro-1H-benzo[d]imidazol-2-yl)-3-(chroman-6-yl)isoquinolin-4-yl)acetate (S5). To a solution of 4-(1-(tert-butoxy)-2-methoxy-2-oxoethyl)-3-(chroman-6-yl)isoquinoline-1-carboxylic acid (**8**) (47 mg, 0.10 mmol) in dimethylformamide (0.3 mL) was added 4-chloro-o-phenylenediamine (15 mg, 0.10 mmol), triethylamine (44 µL, 0.31 mmol), and HATU (48 mg, 0.13 mmol). The reaction mixture was stirred at room temperature for 40 min and water was added. The mixture was extracted with ethyl acetate (3x) and the combined organic layers were dried over sodium sulfate and concentrated in vacuo. The resulting residue was dissolved in glacial acetic acid (1.0 mL) and heated to 70 ^{o}C for 40 min. The solution was concentrated in vacuo, diluted with ethyl acetate, and washed with saturated aqueous sodium bicarbonate and brine. The organic layer was dried over sodium sulfate and concentrated in vacuo. Flash chromatography (silica gel, 15% ethyl acetate in hexanes) afforded compound **S5** (26 mg, 45%) as a yellow foam. ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.15 – 10.07 (m, 1H), 8.52 – 8.47 (m, 1H), 7.83 – 7.57 (m, 4H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.41 (d, *J* = 1.8 Hz, 1H), 7.30 (dd, *J* = 8.6, 1.9 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 5.71 (s, 1H), 4.29 (t, *J* = 5.2 Hz, 2H), 3.75 (s, 3H), 2.93 – 2.86 (m, 1H), 2.86 – 2.79 (m, 1H), 2.15 – 2.04 (m, 2H), 0.97 (s, 9H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 173.8, 155.6, 145.2, 136.8, 133.1, 131.7, 131.3, 129.3, 129.0, 128.63, 128.60, 126.5, 126.3, 124.4, 122.4, 116.8, 76.6, 71.1, 66.9, 52.8, 28.1, 25.1, 22.4. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{32}H_{31}ClN_3O_4$ 556.19976; Found 556.20014.



2-(tert-butoxy)-2-(1-(5-chloro-1H-benzo[d]imidazol-2-yl)-3-(chroman-6-yl)isoquinolin-4-yl)acetic acid (9). To a solution of methyl 2-(tert-butoxy)-2-(1-(6-chloro-1H-benzo[d]imidazol-2-yl)-3-(chroman-6-yl)isoquinolin-4-yl)acetate (**S5**) (24 mg, 0.04 mmol) in tetrahydrofuran (0.2 mL) and methanol (0.4 mL) was added sodium hydroxide (2M aqueous, 360 µL, 0.72 mmol). The reaction mixture was stirred overnight at room temperature. The mixture was acidified with 1M hydrochloric acid, diluted with brine, and extracted with ethyl acetate (3x). The combined organic layers were dried over sodium sulfate, concentrated in vacuo, and triturated with hexanes to afford compound **9** (20 mg, 85%) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.20 – 8.11 (m, 1H), 7.84 – 7.57 (m, 4H), 7.56 – 7.46 (m, 2H), 7.30 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 5.82 (s, 1H), 4.27 (t, *J* = 5.2 Hz, 2H), 2.93 – 2.75 (m, 2H), 2.14 – 2.00 (m, 2H), 0.95 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 155.6, 151.8, 146.2, 136.1, 131.7, 131.4, 131.3, 129.1, 128.9, 128.5, 127.3, 126.2, 125.1, 124.4, 122.5, 116.9, 78.2, 71.1, 66.9, 28.2, 25.0, 22.3. HRMS (ESI/ion trap) m/z: $[M+H]^+$ Calcd for $C_{31}H_{29}ClN_3O_4$ 542.18411; Found 542.18316.



Thermal degradation of 6i to 1-([1,1'-biphenyl]-4-yl)-3-(chroman-6-yl)isoquinoline-4-carbaldehyde (10). A solution of 2-(1-([1,1'-biphenyl]-4-yl)-3-(chroman-6-yl)isoquinolin-4-yl)-2-(tert-butoxy)acetic acid (**6i**) (5 mg, 0.009 mmol) in DMSO-d_6 (0.75 mL) was placed in an NMR tube and heated to 60 °C for 17 h. The mixture was then heated to 100 °C for 17 d. The progress of the reaction was monitored by NMR analysis, and upon completion, the solution was diluted with 5 mL of hexane:ethyl acetate (2:8), washed 2x with 5 mL H_2O, and concentrated in vacuo. Flash chromatography (silica gel, 7% ethyl acetate in hexanes) afforded compound **10** (1.6 mg, 39%) as a yellow foamy solid. ^{1}H NMR (700 MHz, DMSO) δ 10.12 (s, 1H), 9.21 (d, *J* = 8.6 Hz, 1H), 8.20 (d, *J* = 8.3 Hz, 1H), 8.00 (ddd, *J* = 8.4, 6.9, 1.2 Hz, 1H), 7.93 – 7.90 (m, 2H), 7.89 – 7.86 (m, 2H), 7.82 – 7.80 (m, 2H), 7.76 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.56 – 7.53 (m, 2H), 7.49 (d, *J* = 2.1

Hz, 1H), 7.46 – 7.41 (m, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 4.26 – 4.22 (m, 2H), 2.86 (t, *J* = 6.4 Hz, 2H), 2.01 – 1.96 (m, 2H). ^{13}C NMR (176 MHz, DMSO) δ 193.6, 163.2, 158.1, 156.2, 141.2, 139.5, 137.6, 134.0, 133.1, 132.9, 130.9, 130.8, 129.5, 129.1, 128.0, 127.9, 127.8, 126.9, 126.8, 124.3, 124.2, 122.6, 120.1, 116.3, 66.4, 24.3, 21.6. HRMS (ESI/ion trap) m/z: $[M+Na]^+$ Calcd for $C_{31}H_{23}NO_2Na$ 464.16210; Found 464.16182.

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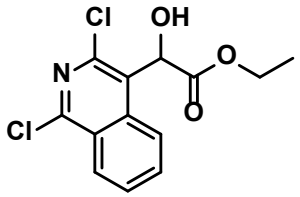
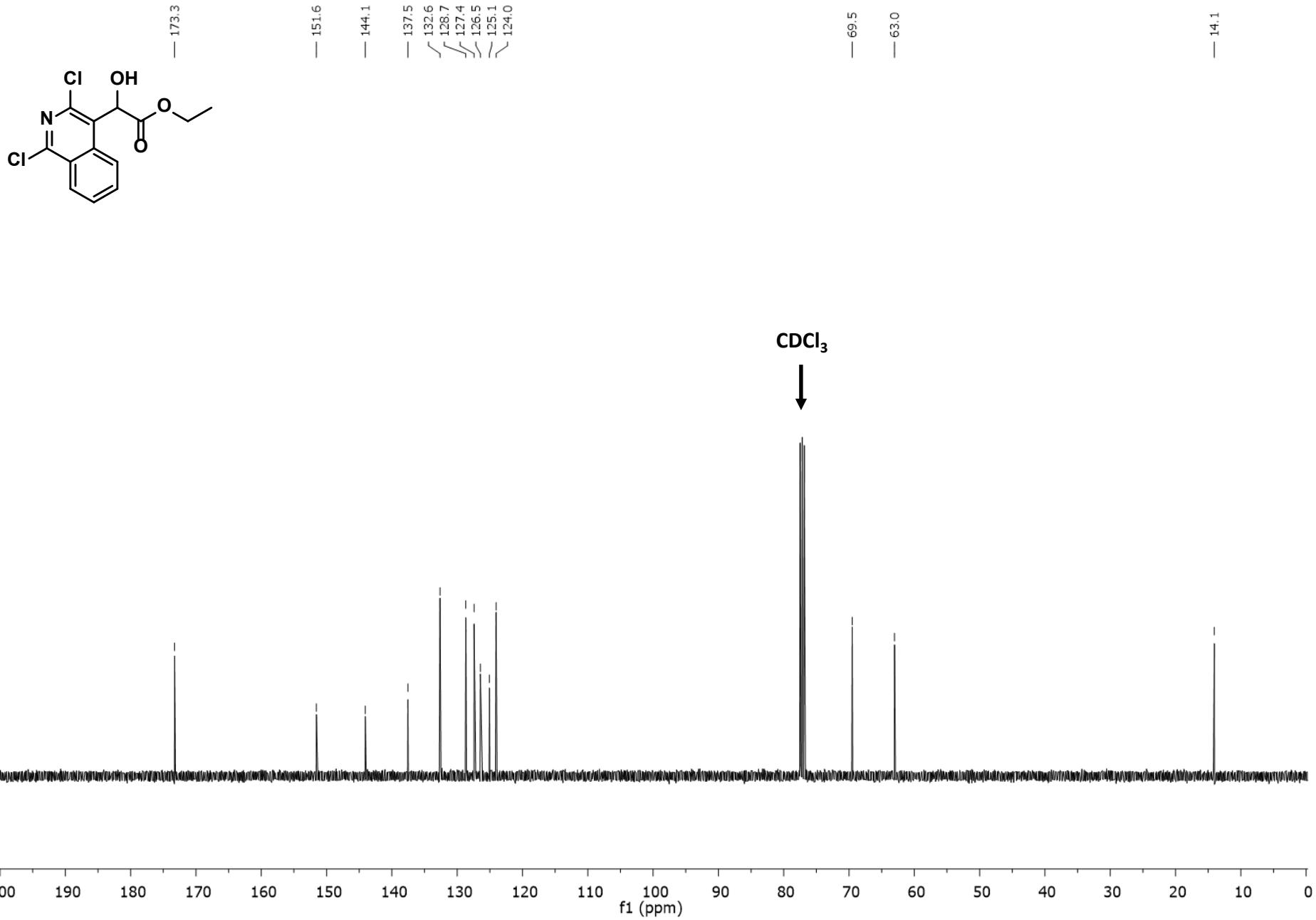
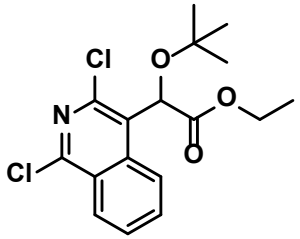
^{1}H NMR Spectrum of Compound **2** (400 MHz, $CDCl_3$)



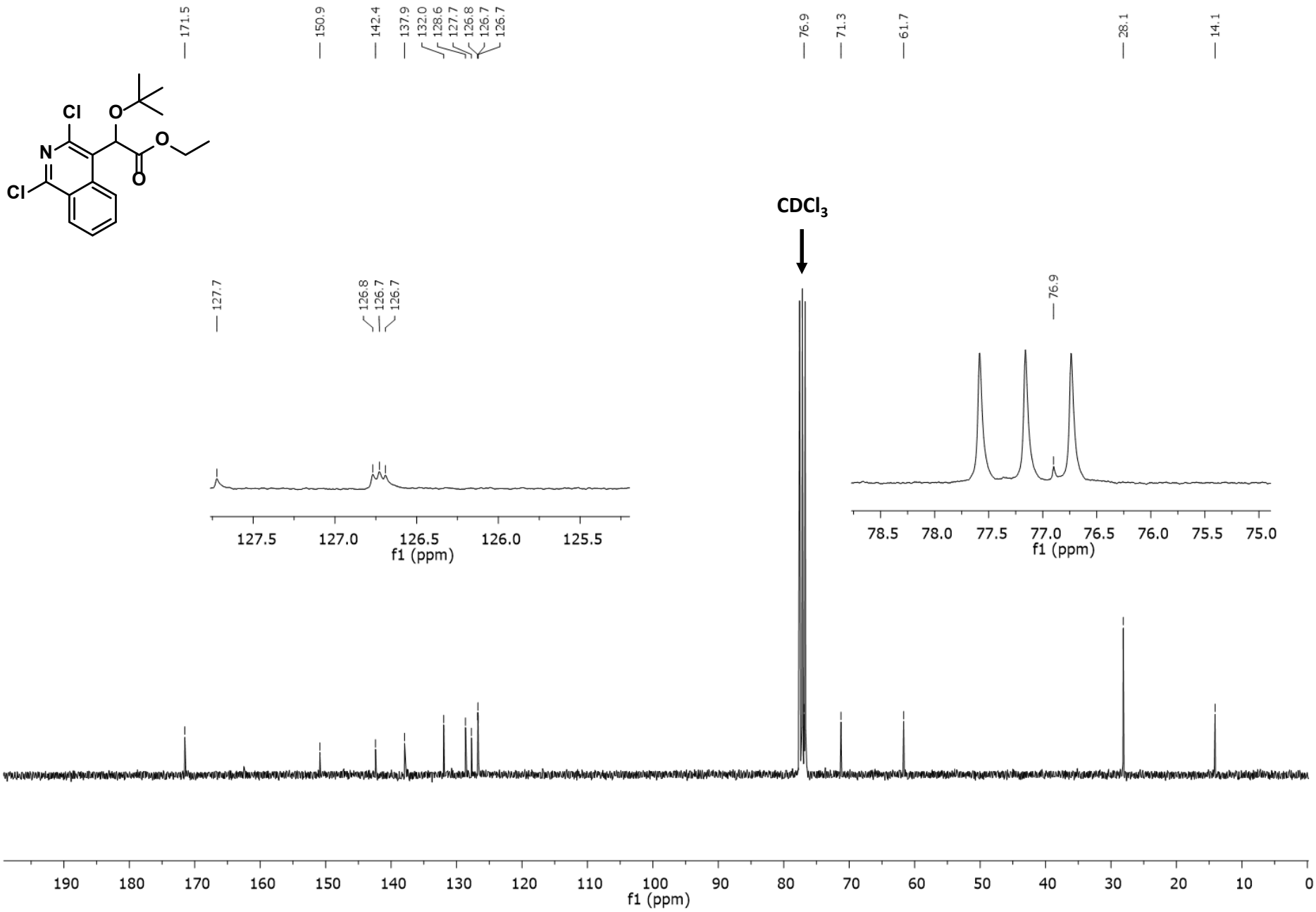
^{13}C NMR Spectrum of Compound **2** (100 MHz, $CDCl_3$)



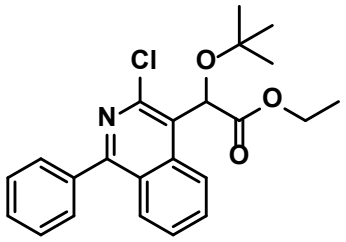
^{1}H NMR Spectrum of Compound **3** (400 MHz, $CDCl_3$)



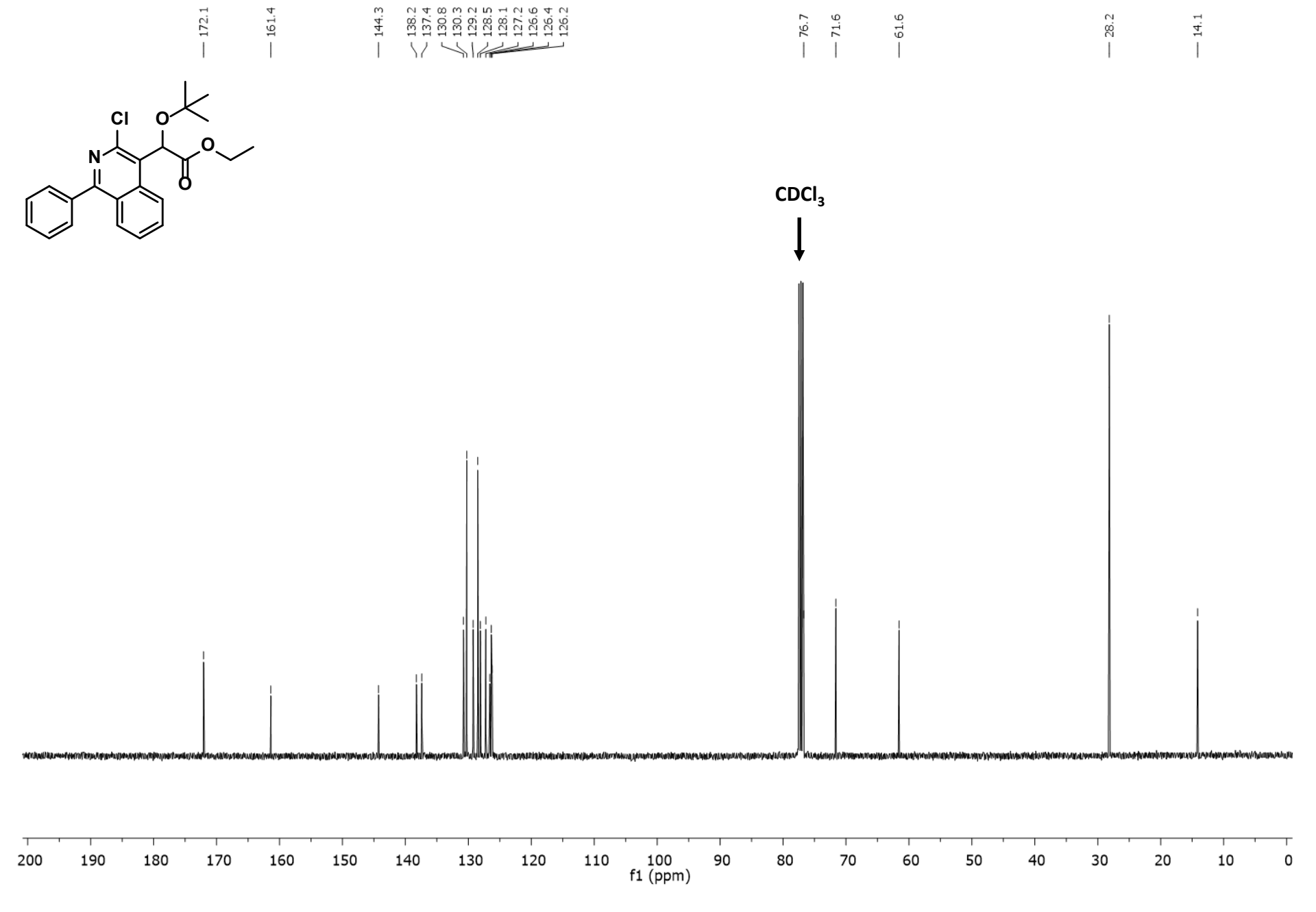
^{13}C NMR Spectrum of Compound **3** (75 MHz, $CDCl_3$)



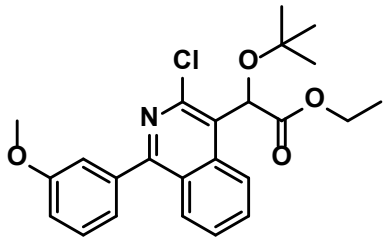
^{1}H NMR Spectrum of Compound **4a** (300 MHz, $CDCl_3$)



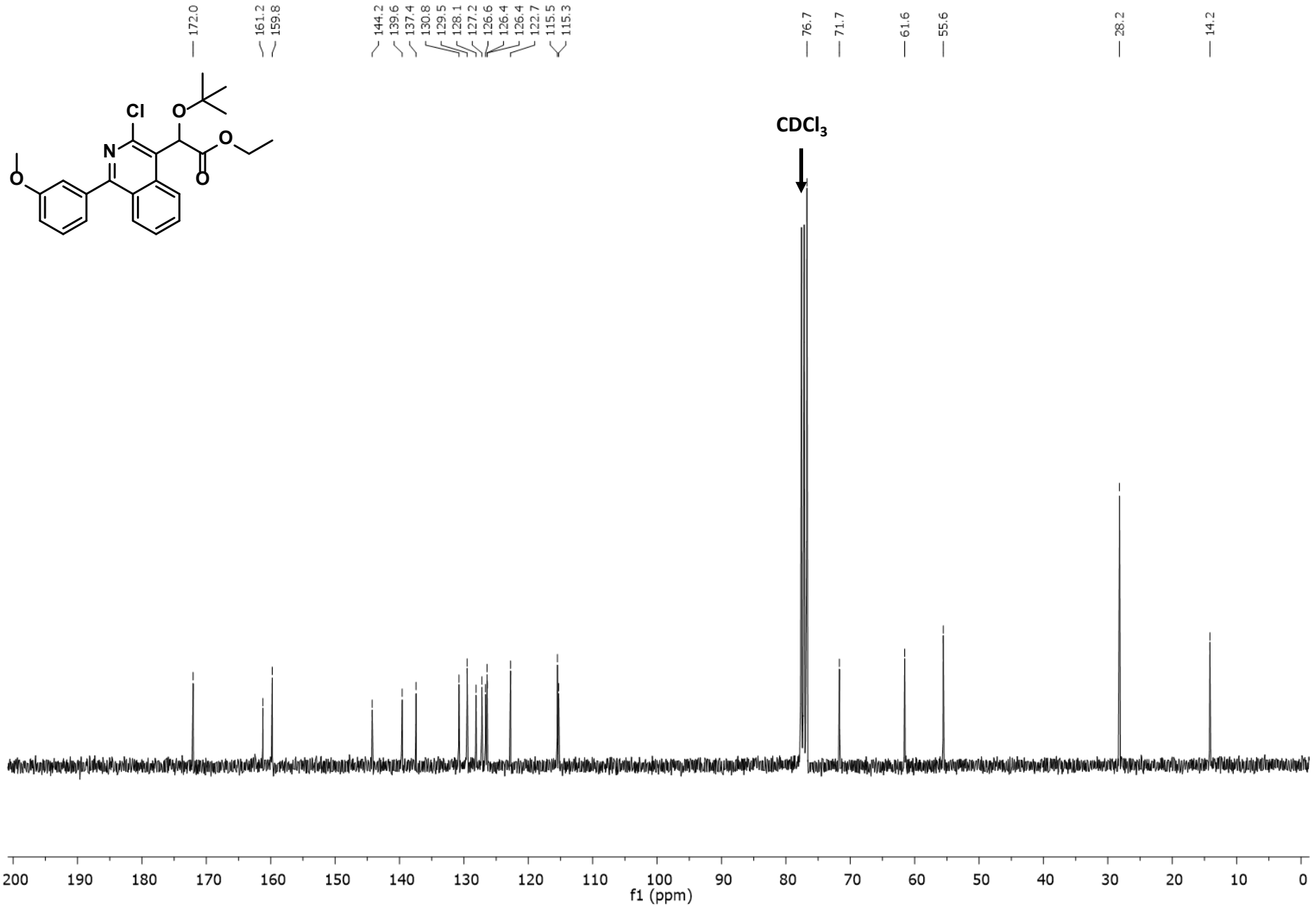
^{13}C NMR Spectrum of Compound **4a** (100 MHz, $CDCl_3$)



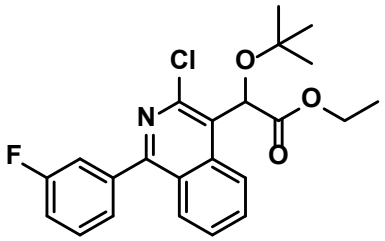
^{1}H NMR Spectrum of Compound **4b** (300 MHz, $CDCl_3$)



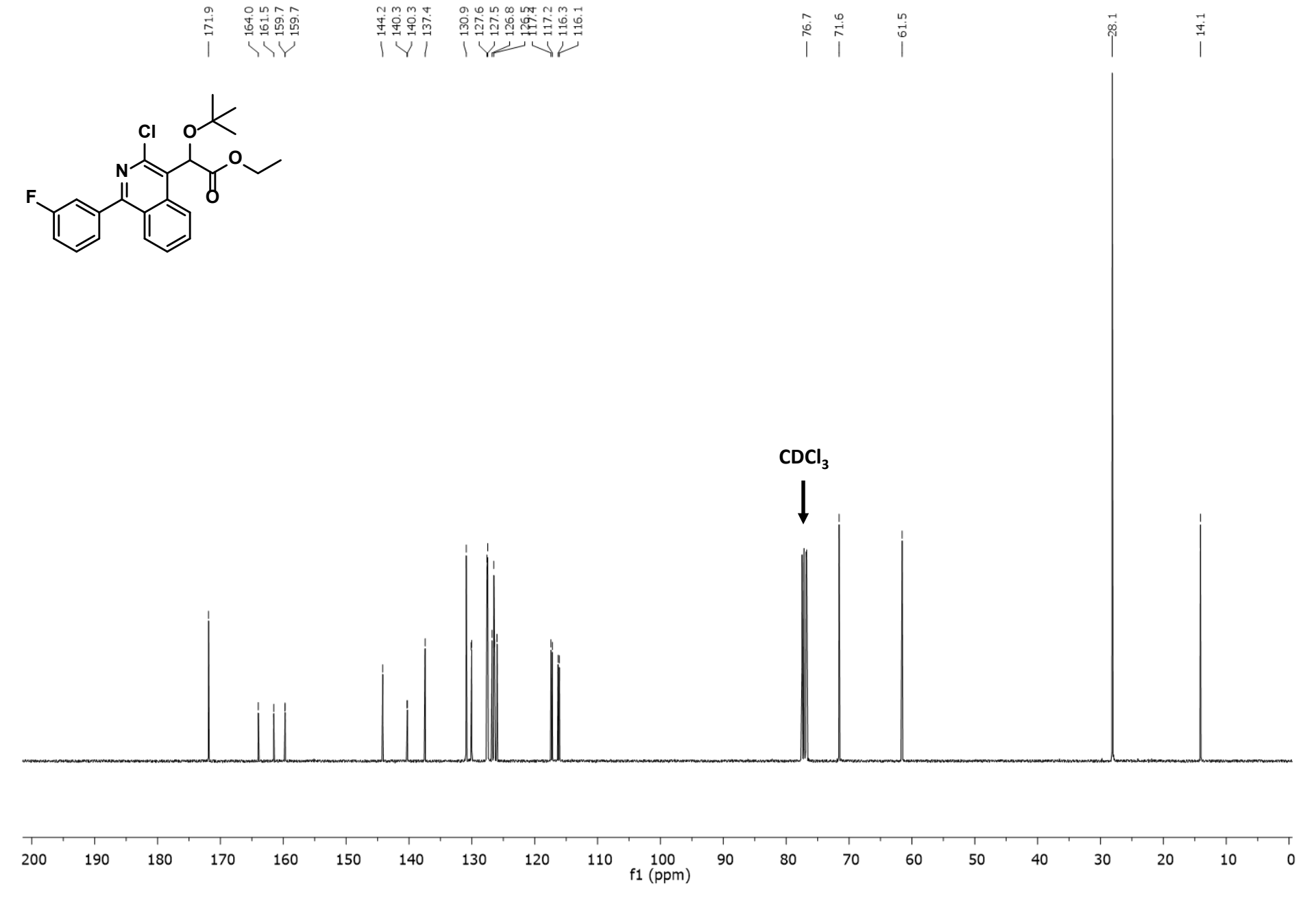
^{13}C NMR Spectrum of Compound **4b** (75 MHz, $CDCl_3$)



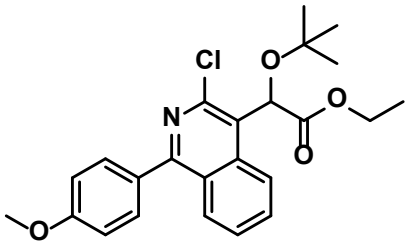
^{1}H NMR Spectrum of Compound **4c** (400 MHz, $CDCl_3$)



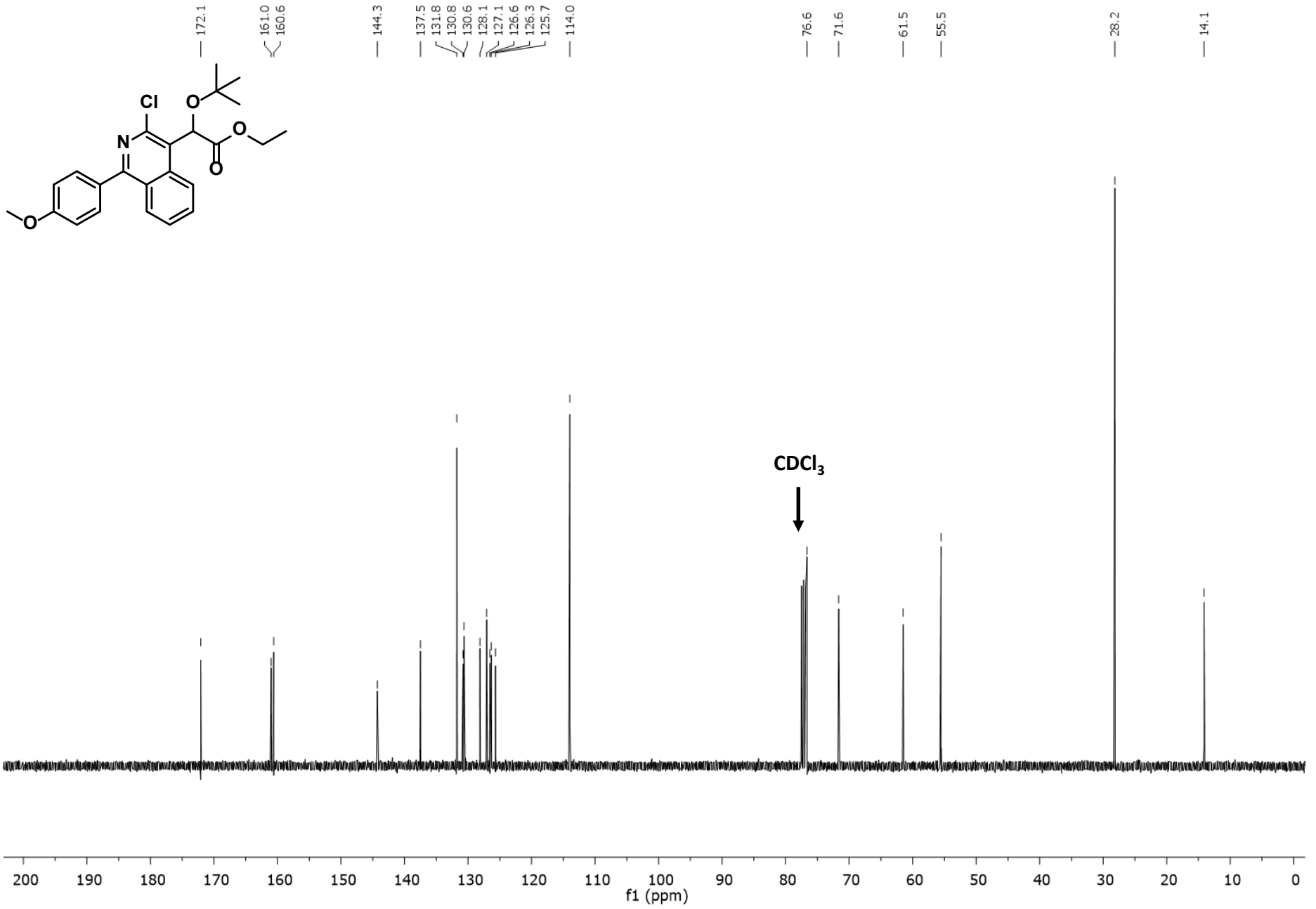
^{13}C NMR Spectrum of Compound **4c** (100 MHz, $CDCl_3$)



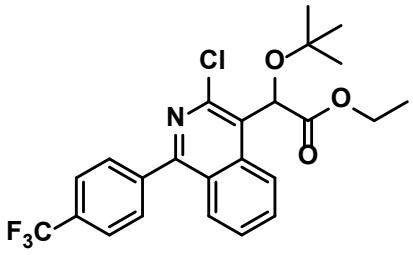
^{1}H NMR Spectrum of Compound **4d** (400 MHz, $CDCl_3$)



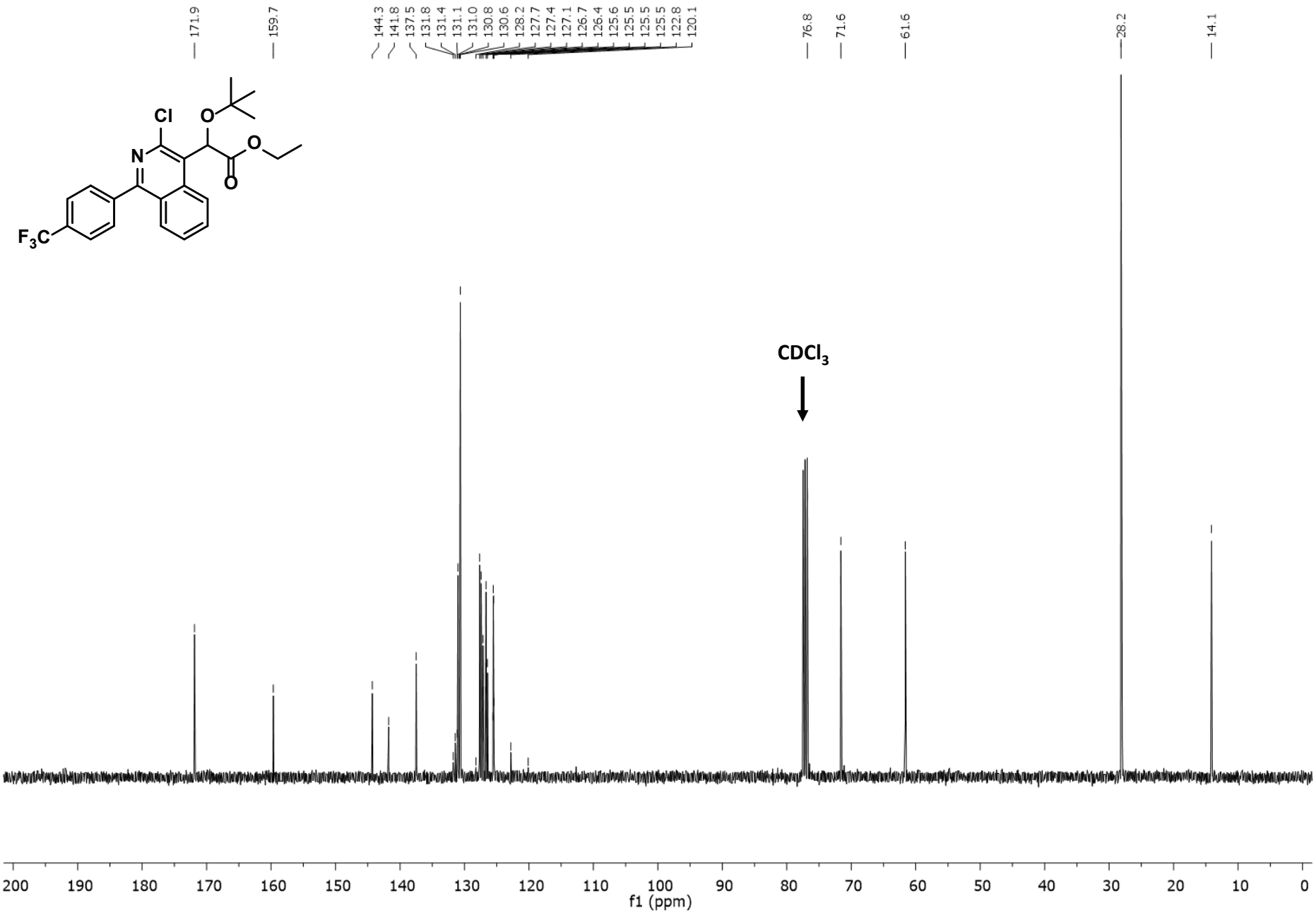
^{13}C NMR Spectrum of Compound **4d** (100 MHz, $CDCl_3$)



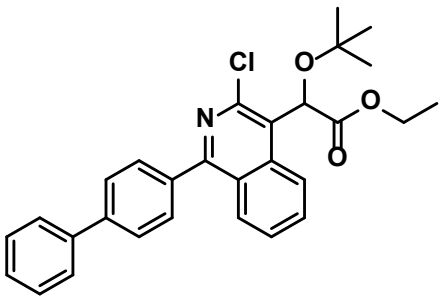
[1]H NMR Spectrum of Compound **4e** (400 MHz, $CDCl_3$)



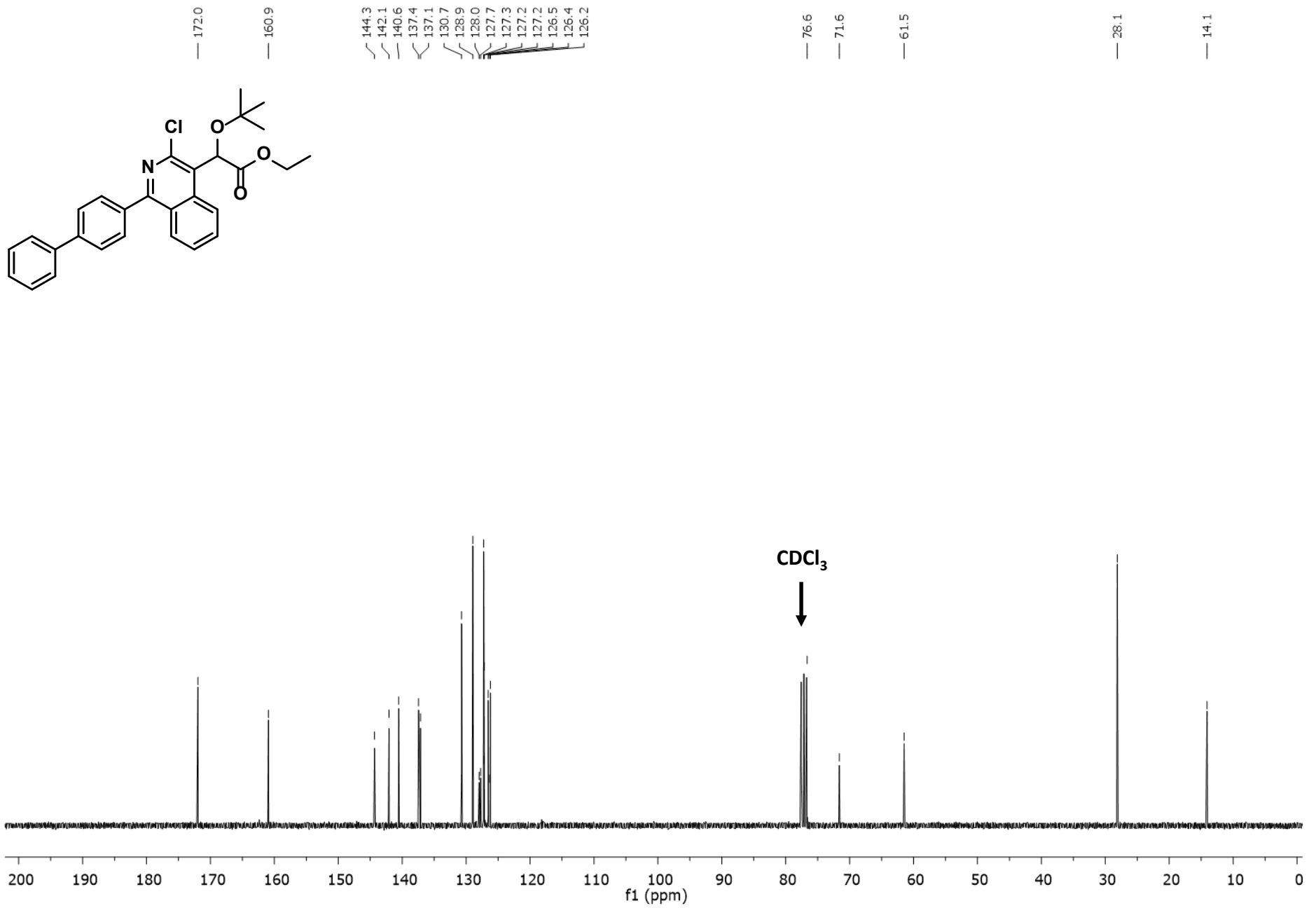
^{13}C NMR Spectrum of Compound **4e** (100 MHz, $CDCl_3$)



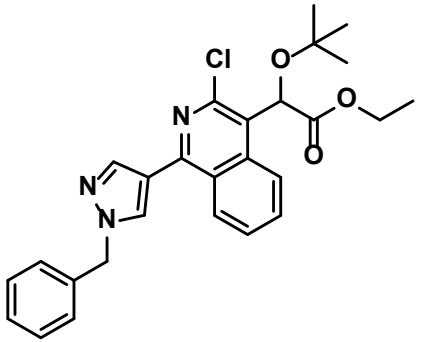
^{1}H NMR Spectrum of Compound **4f** (300 MHz, $CDCl_3$)



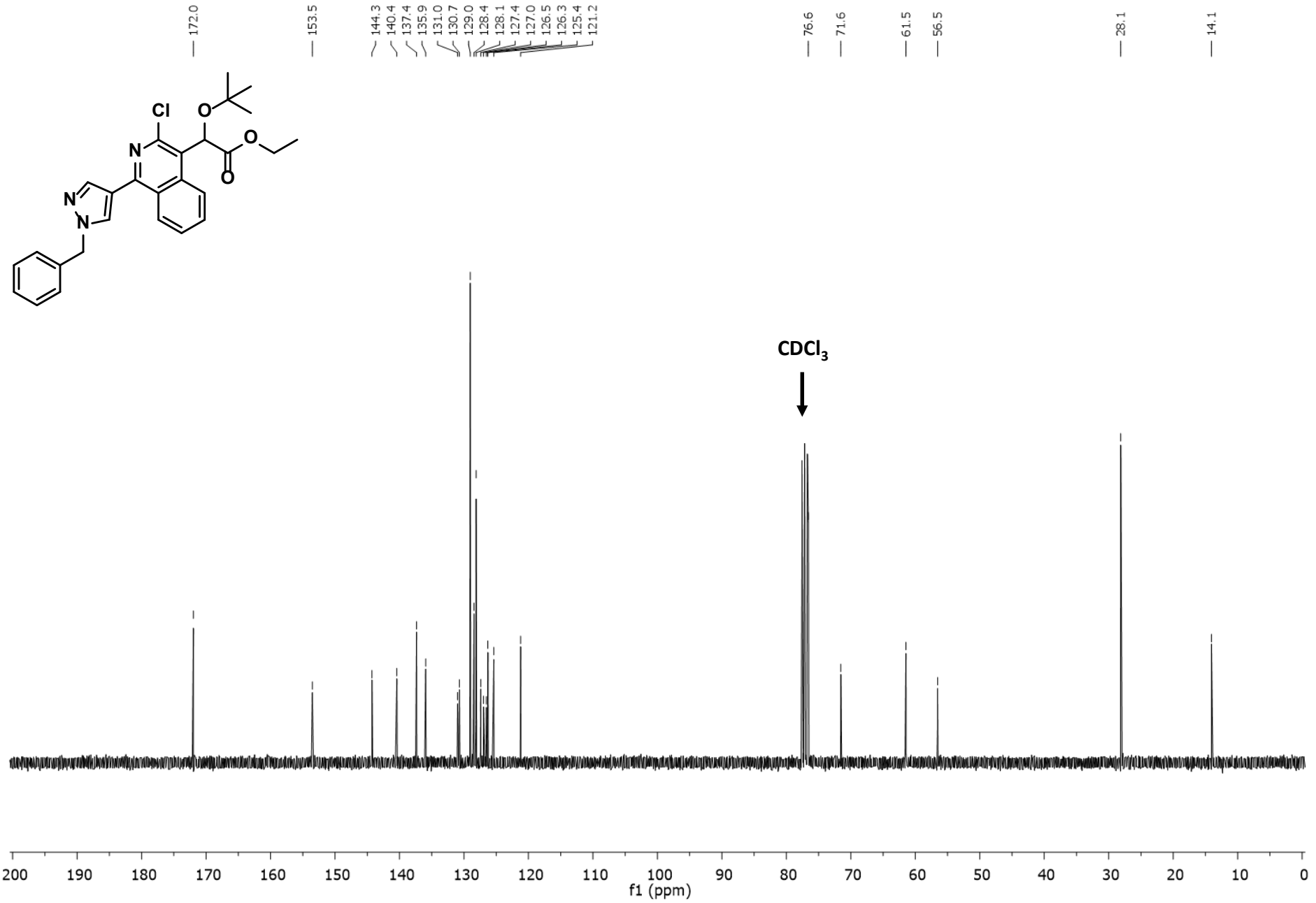
^{13}C NMR Spectrum of Compound **4f** (75 MHz, $CDCl_3$)



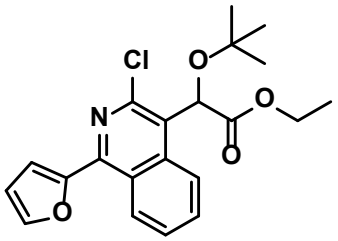
[1]H NMR Spectrum of Compound **4g** (300 MHz, $CDCl_3$)



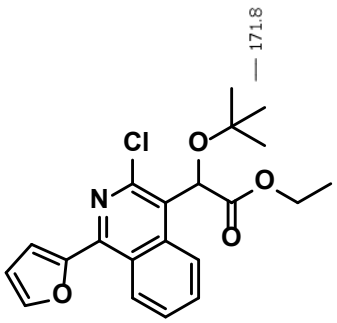
^{13}C NMR Spectrum of Compound **4g** (75 MHz, $CDCl_3$)



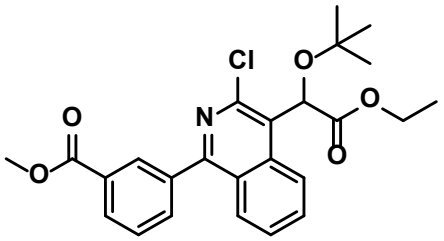
[1]H NMR Spectrum of Compound **4h** (400 MHz, $CDCl_3$)



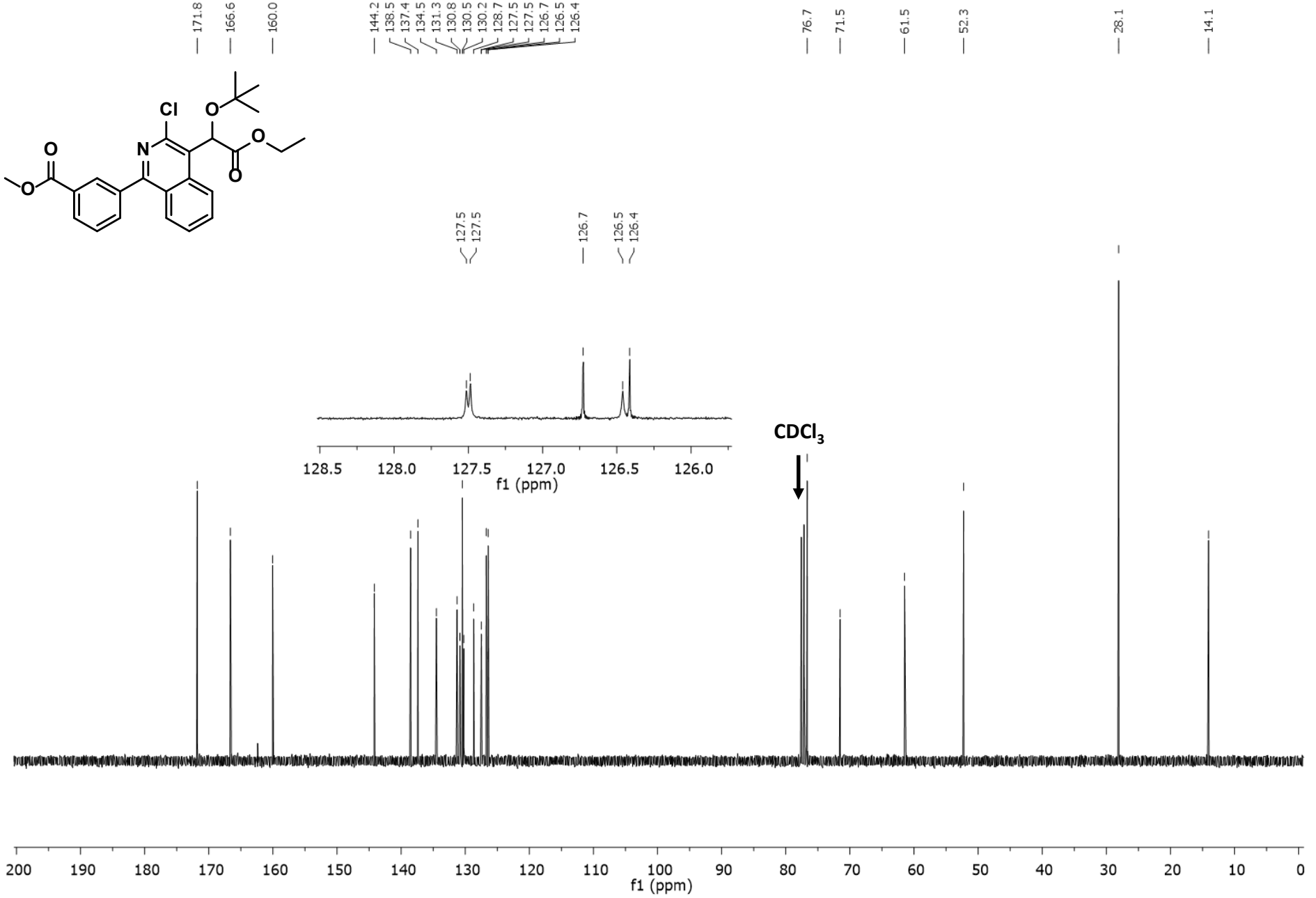
^{13}C NMR Spectrum of Compound **4h** (75 MHz, $CDCl_3$)



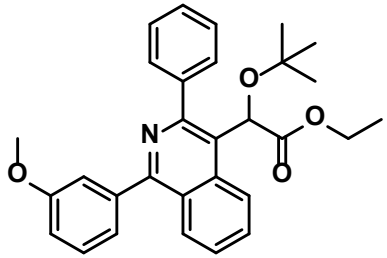
^{1}H NMR Spectrum of Compound **4i** (400 MHz, $CDCl_3$)



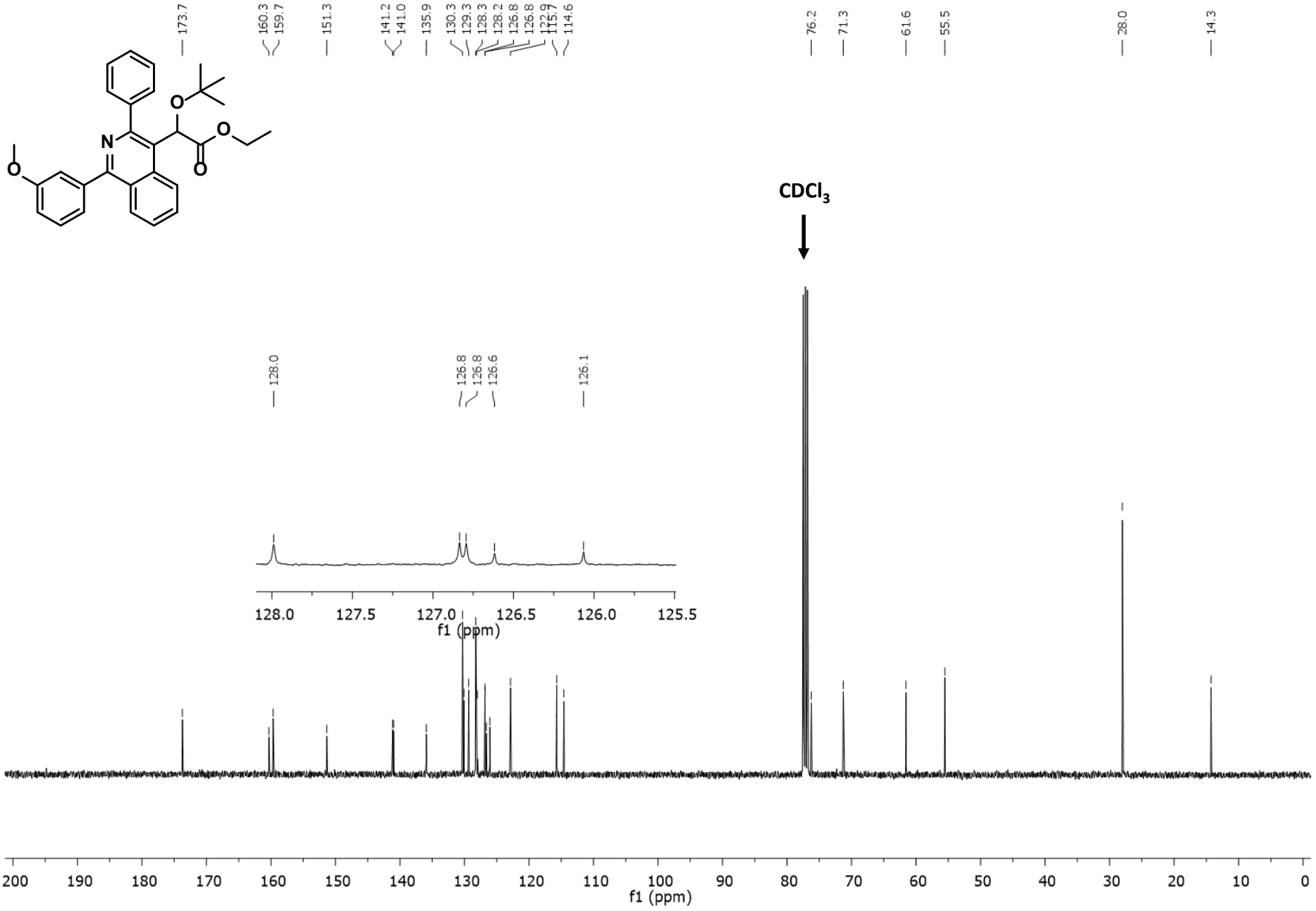
^{13}C NMR Spectrum of Compound **4i** (75 MHz, $CDCl_3$)



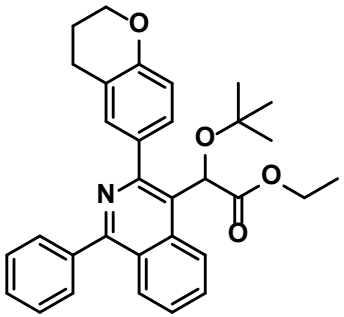
^{1}H NMR Spectrum of Compound **5a** (400 MHz, $CDCl_3$)



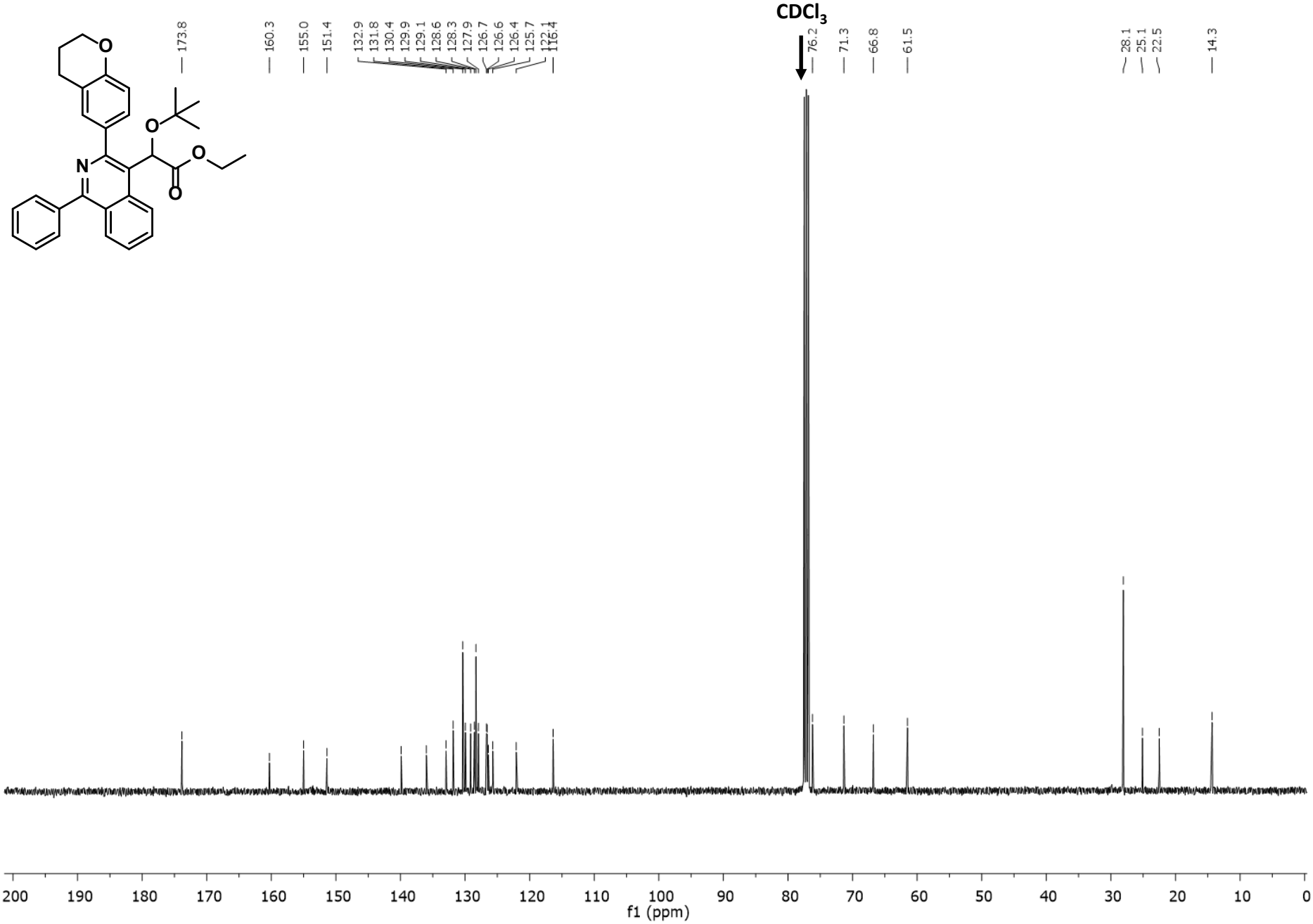
^{13}C NMR Spectrum of Compound **5a** (100 MHz, $CDCl_3$)



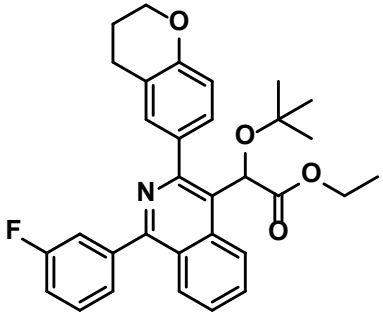
[1]H NMR Spectrum of Compound **5b** (400 MHz, $CDCl_3$)



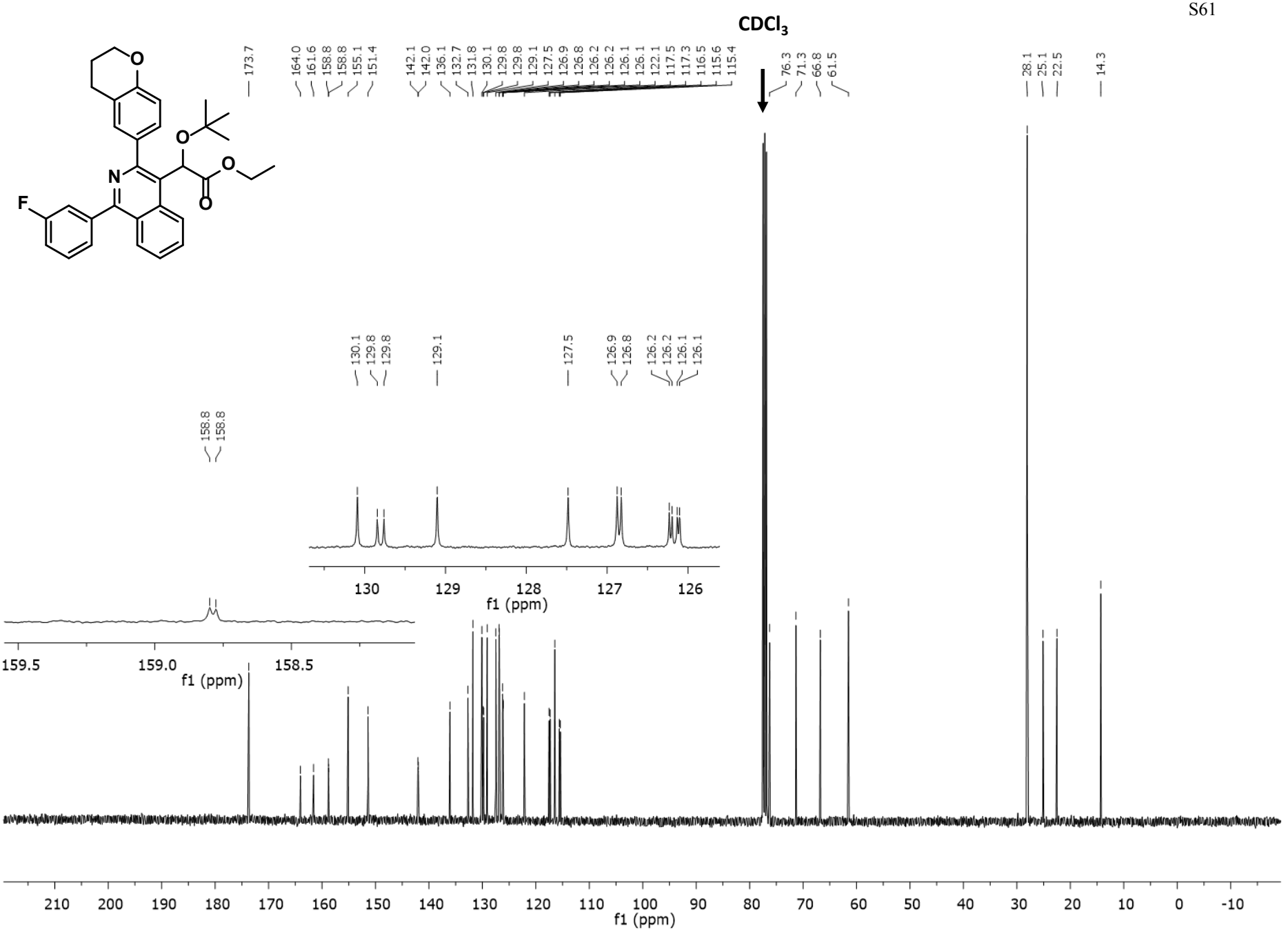
^{13}C NMR Spectrum of Compound **5b** (100 MHz, $CDCl_3$)



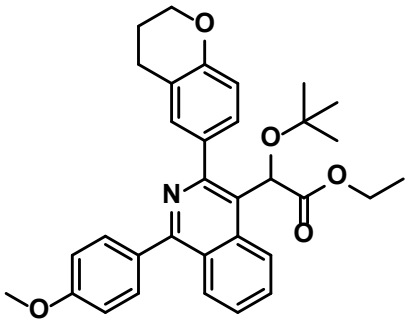
^{1}H NMR Spectrum of Compound **5c** (400 MHz, $CDCl_3$)



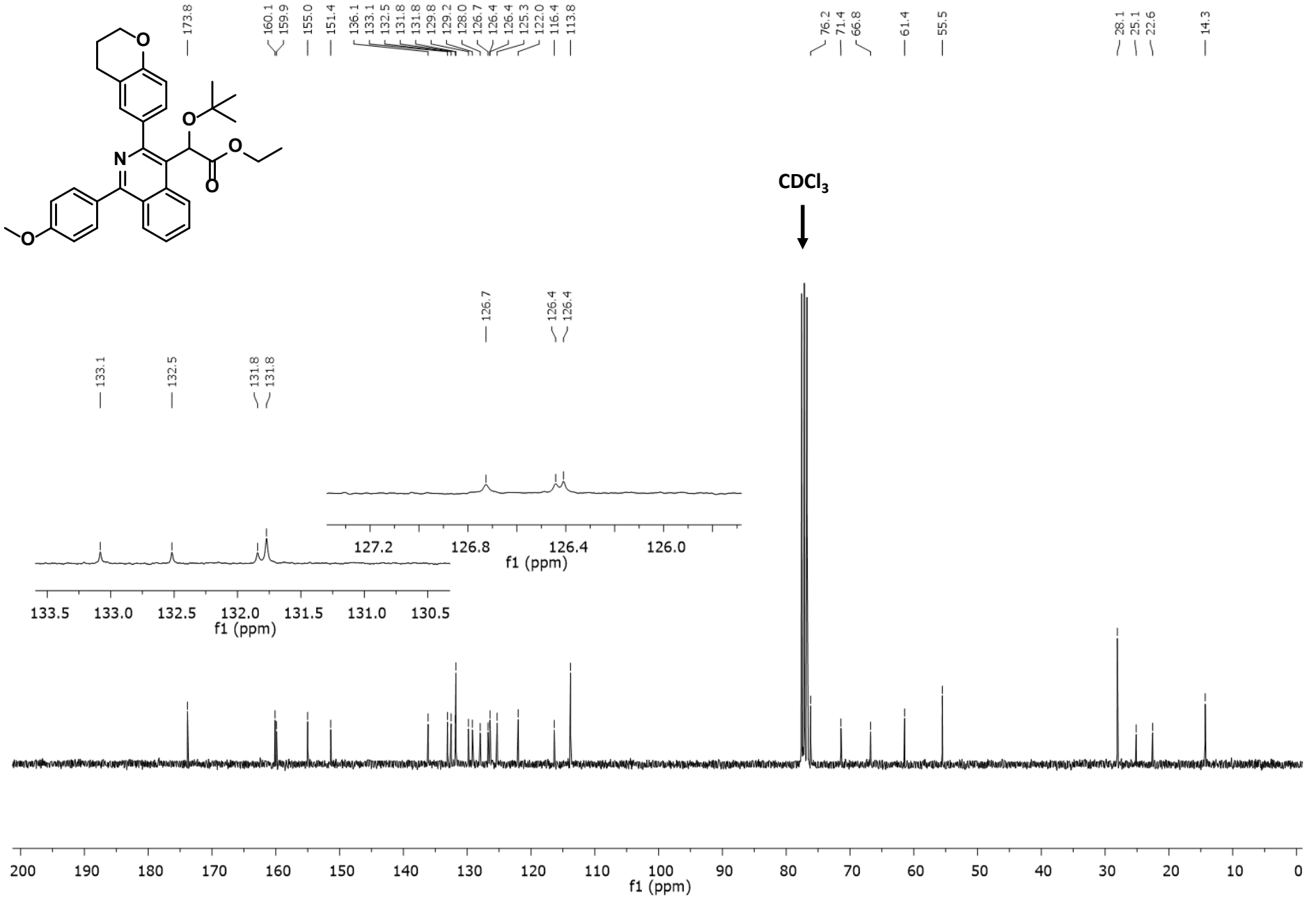
^{13}C NMR Spectrum of Compound **5c** (100 MHz, $CDCl_3$)



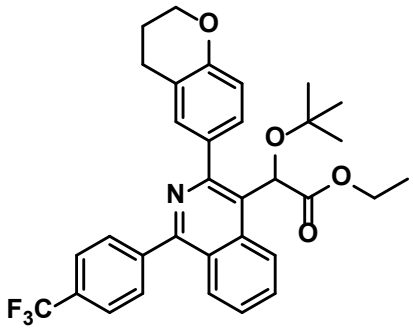
^{1}H NMR Spectrum of Compound **5d** (300 MHz, $CDCl_3$)



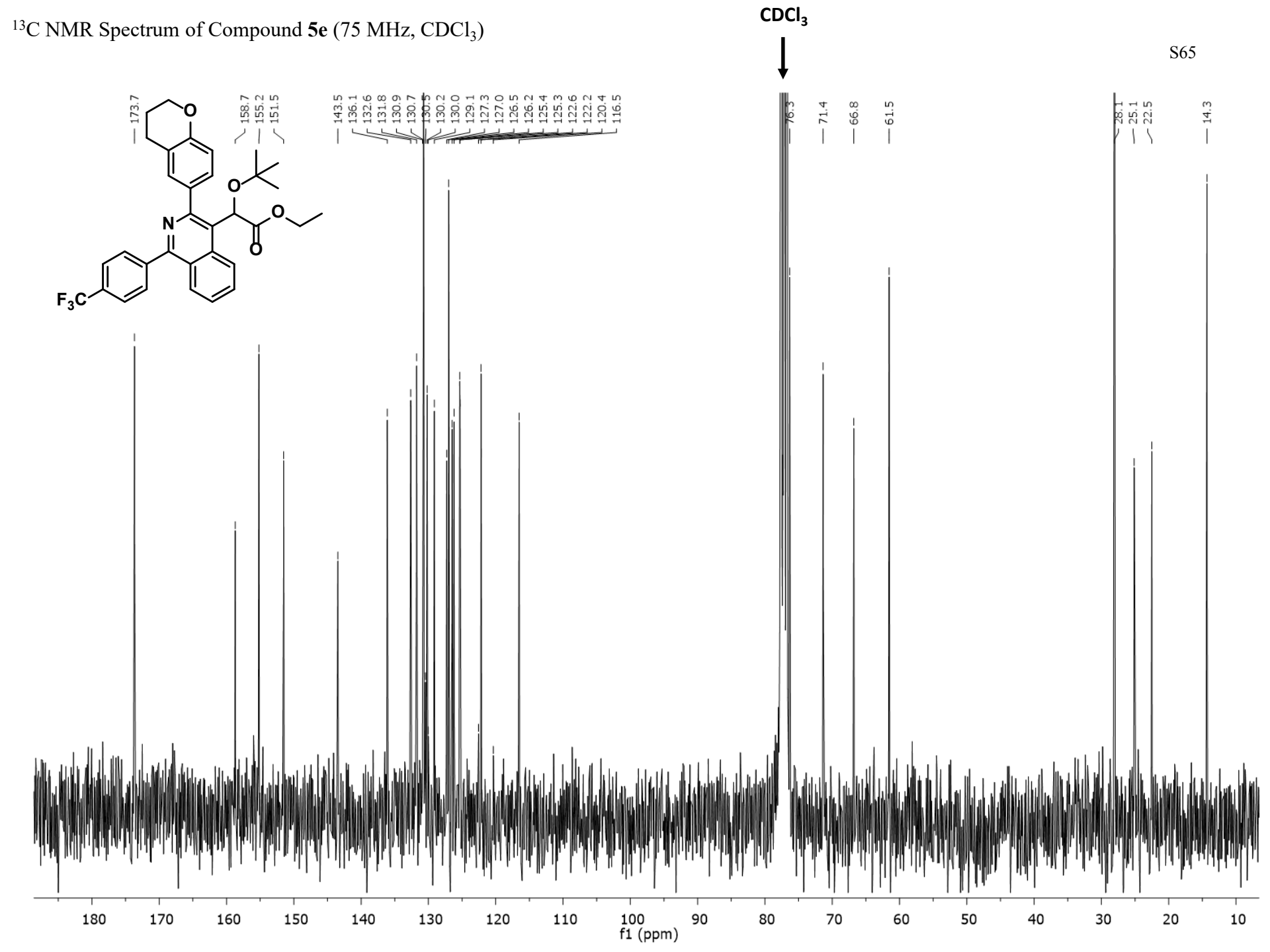
^{13}C NMR Spectrum of Compound **5d** (75 MHz, $CDCl_3$)



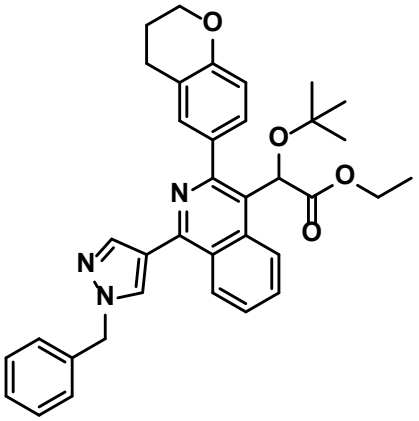
^{1}H NMR Spectrum of Compound **5e** (300 MHz, $CDCl_3$)

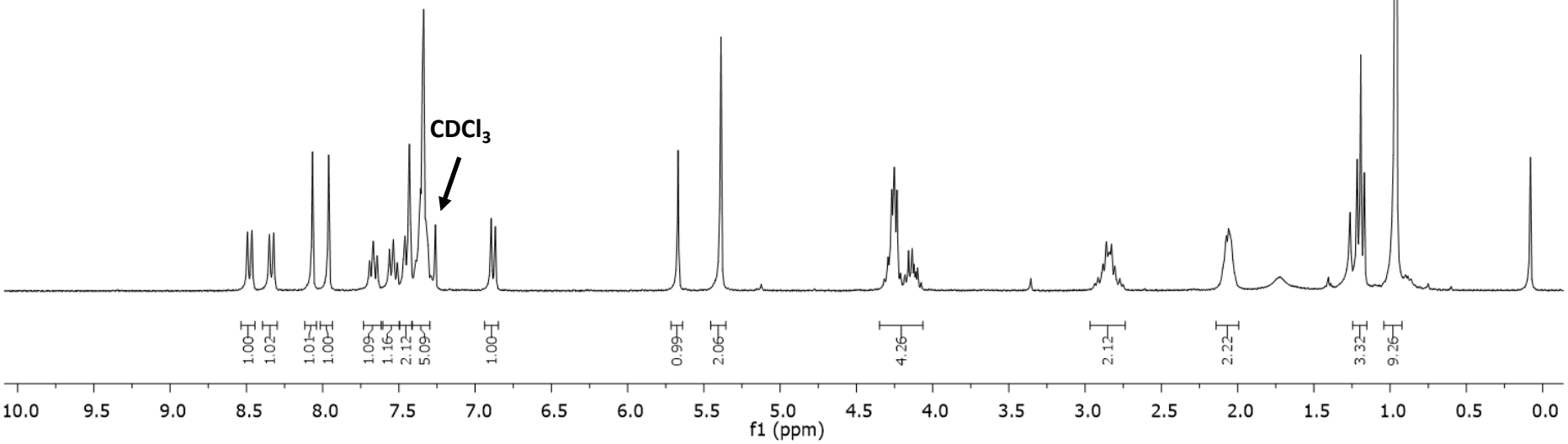


^{13}C NMR Spectrum of Compound **5e** (75 MHz, $CDCl_3$)

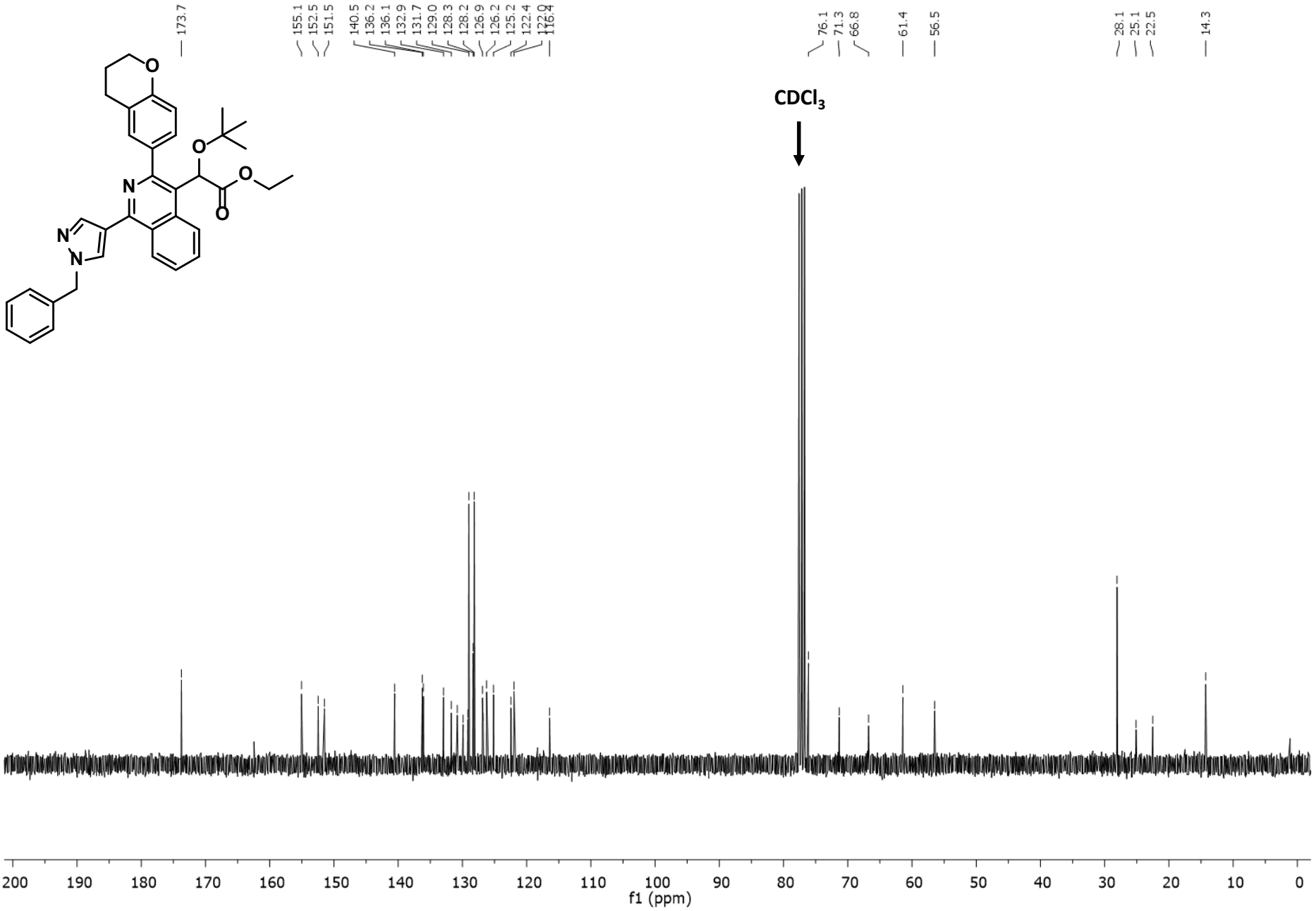


^{1}H NMR Spectrum of Compound **5f** (300 MHz, $CDCl_3$)

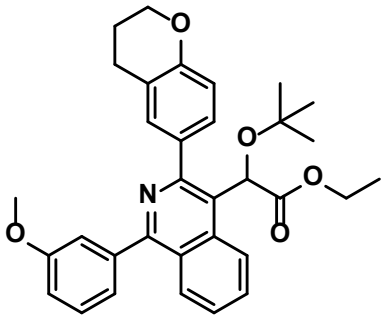




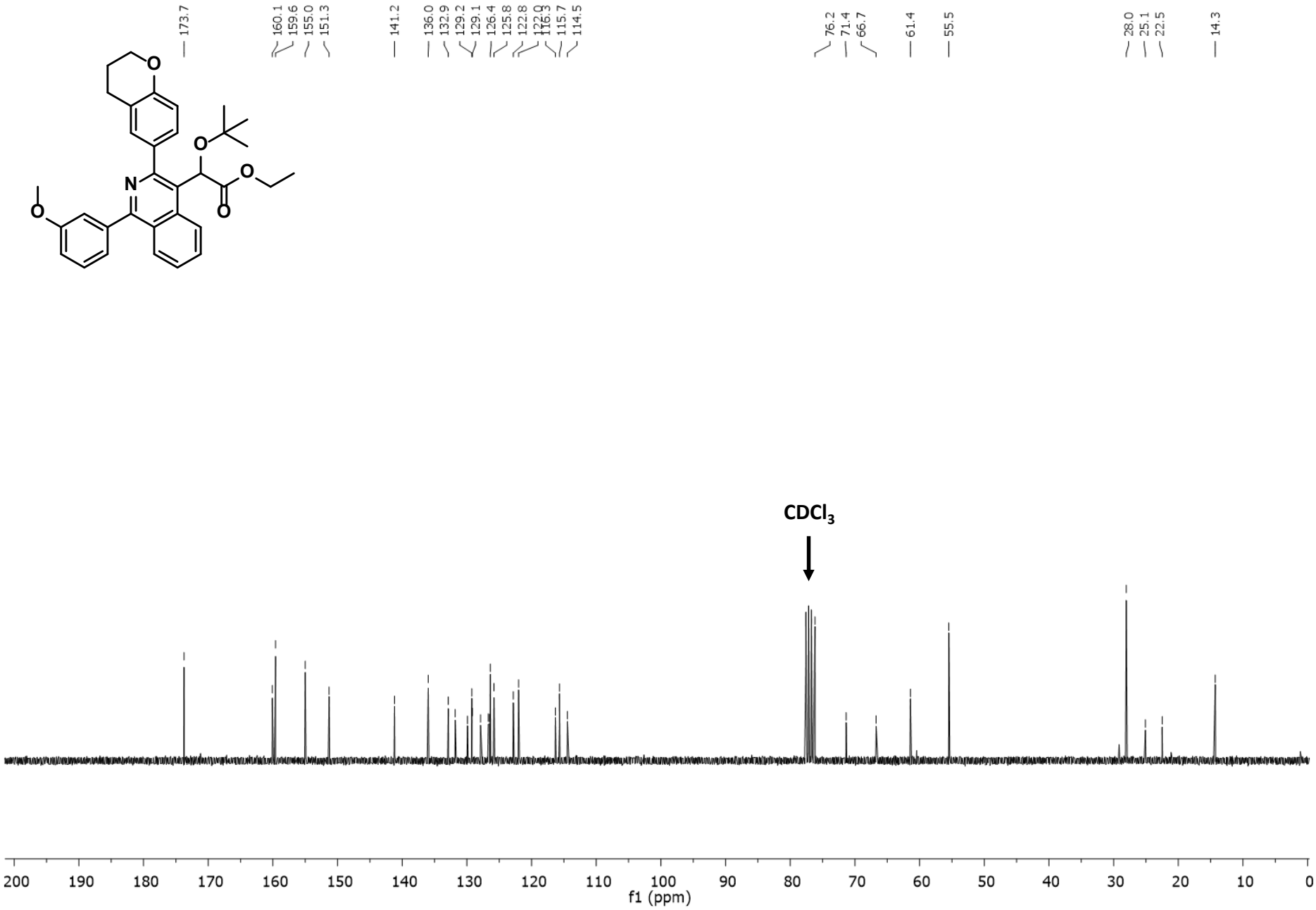
^{13}C NMR Spectrum of Compound **5f** (75 MHz, $CDCl_3$)



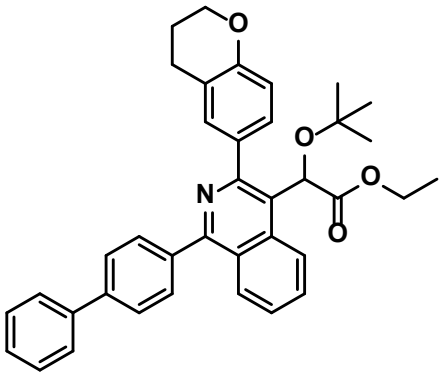
^{1}H NMR Spectrum of Compound **5g** (300 MHz, $CDCl_3$)



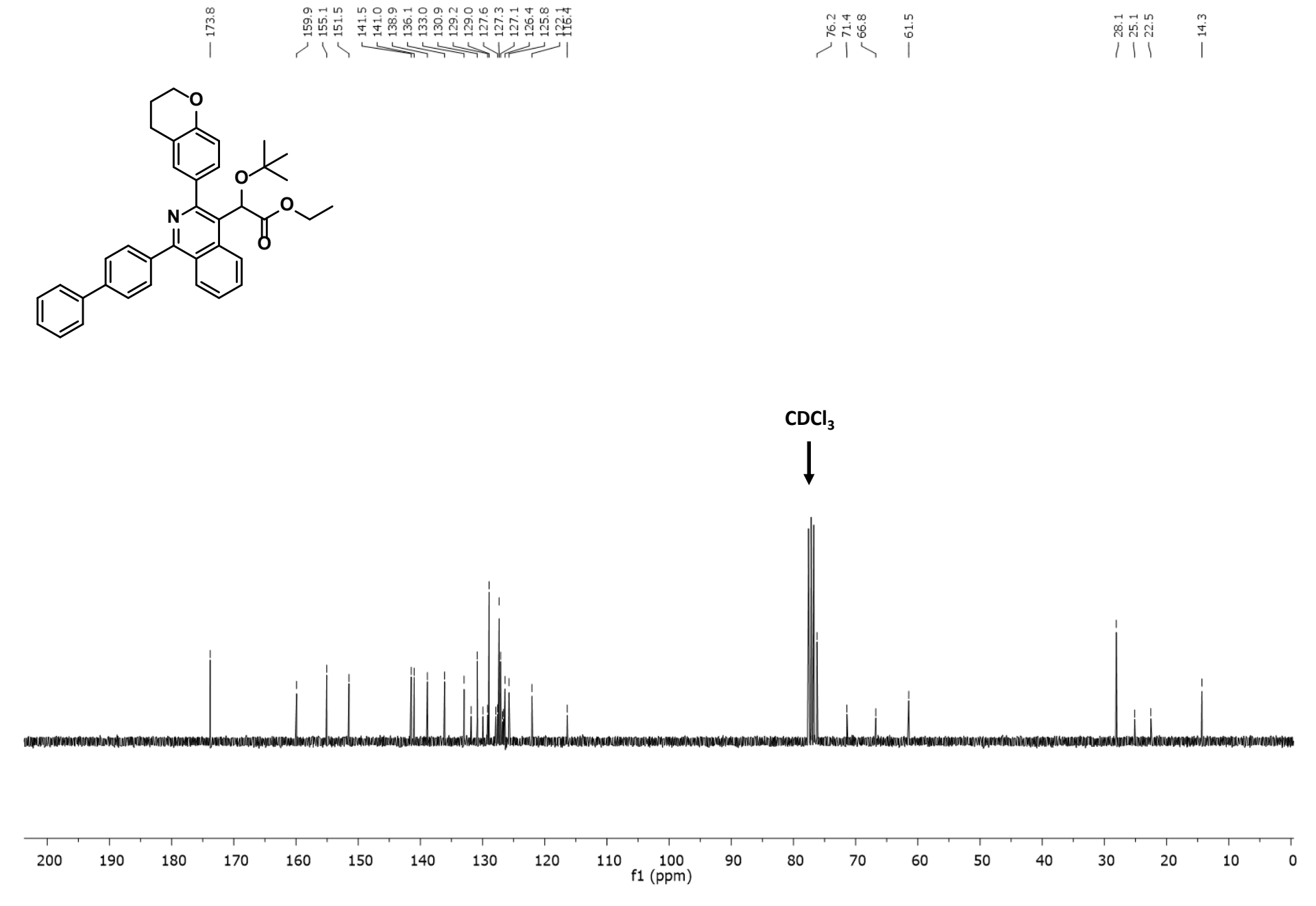
^{13}C NMR Spectrum of Compound **5g** (75 MHz, $CDCl_3$)



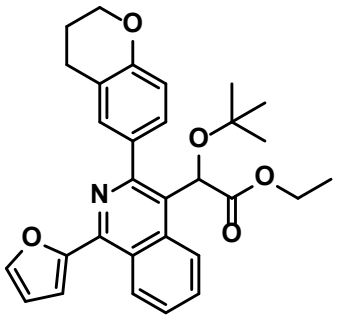
[1]H NMR Spectrum of Compound **5h** (300 MHz, $CDCl_3$)



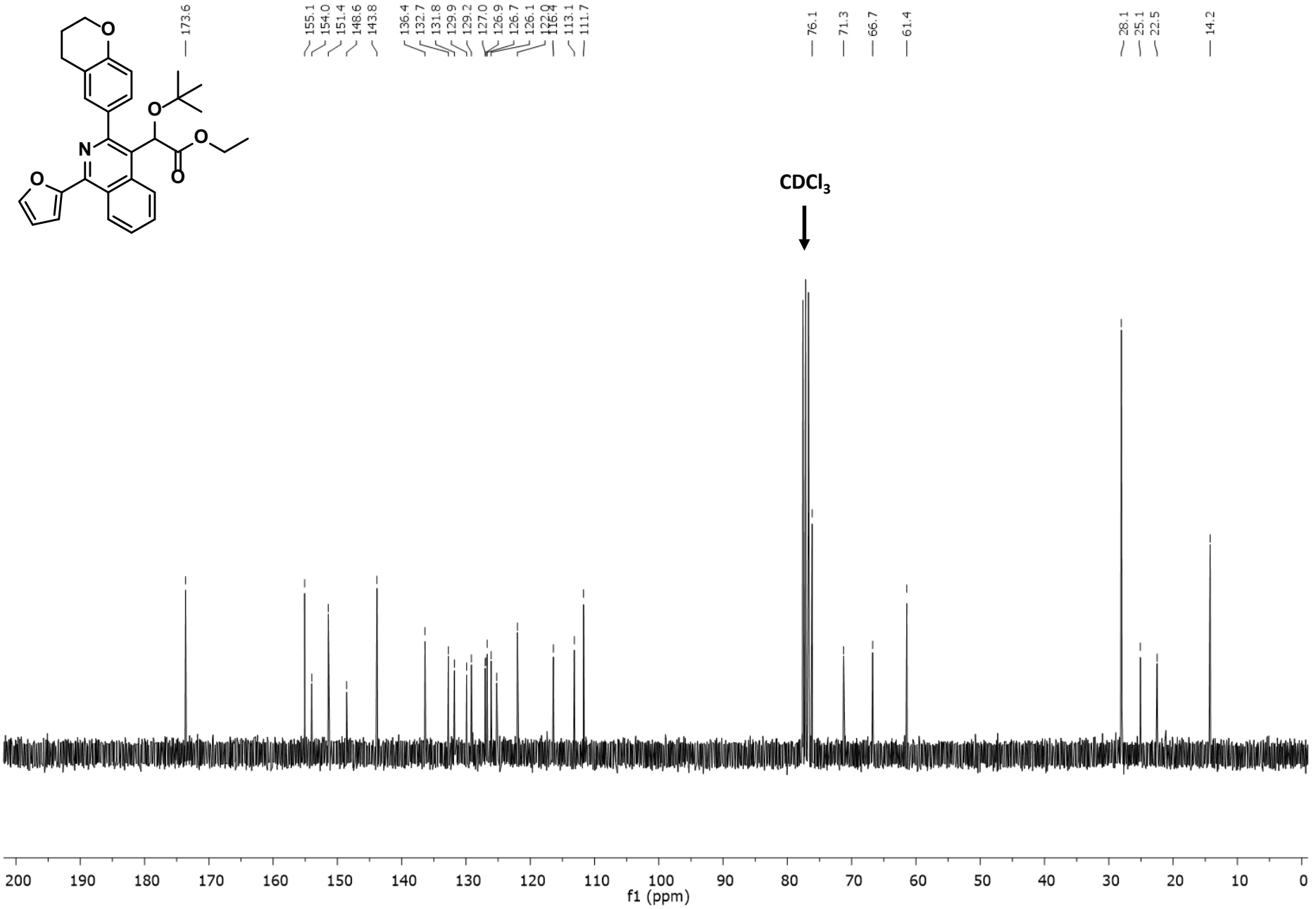
^{13}C NMR Spectrum of Compound **5h** (75 MHz, $CDCl_3$)



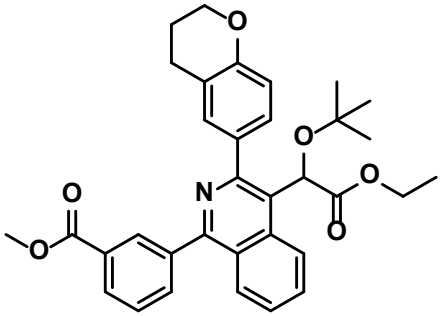
^{1}H NMR Spectrum of Compound **5i** (300 MHz, $CDCl_3$)

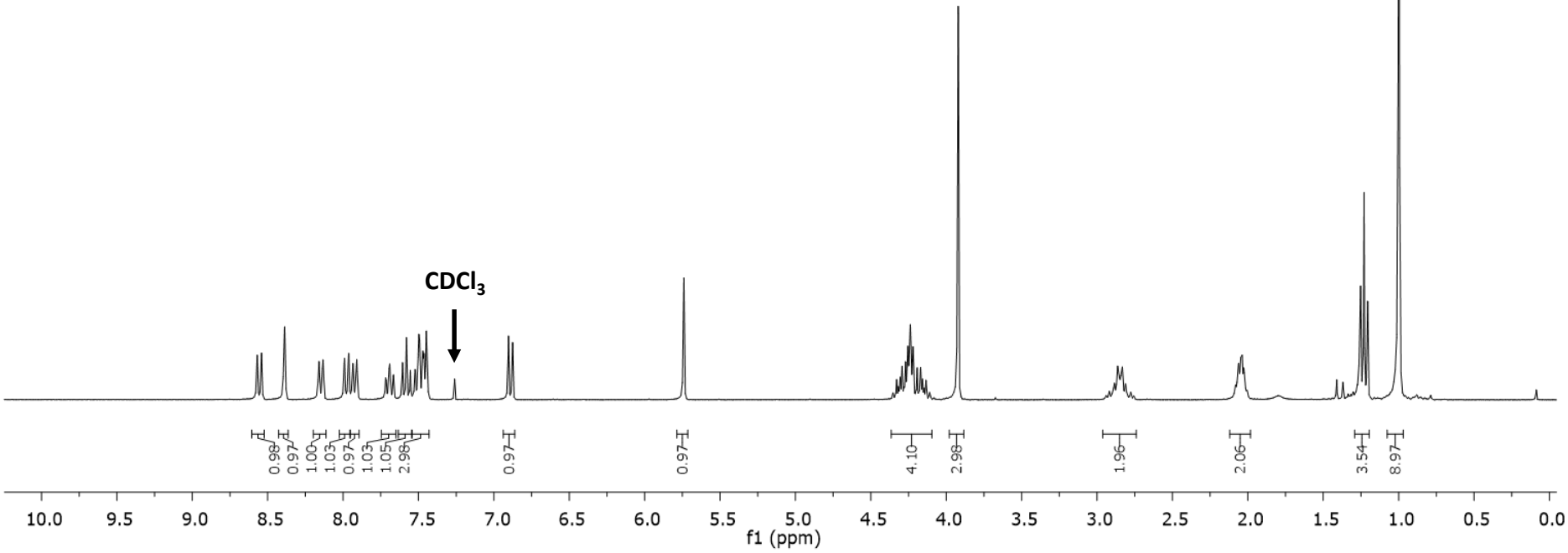


^{13}C NMR Spectrum of Compound **5i** (75 MHz, $CDCl_3$)

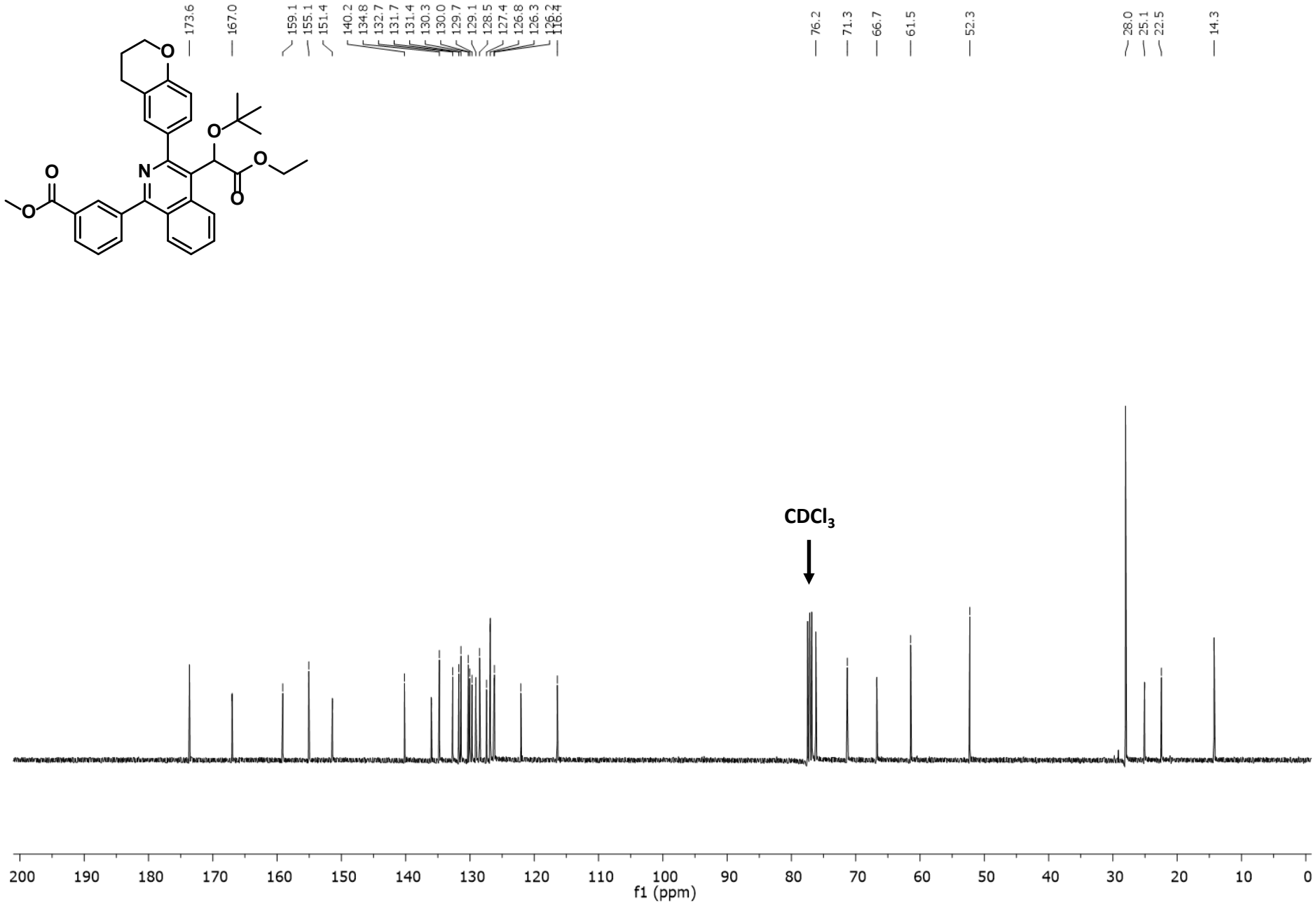


^{1}H NMR Spectrum of Compound **5j** (300 MHz, $CDCl_3$)

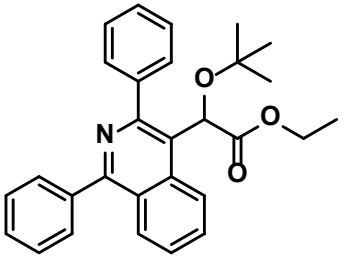


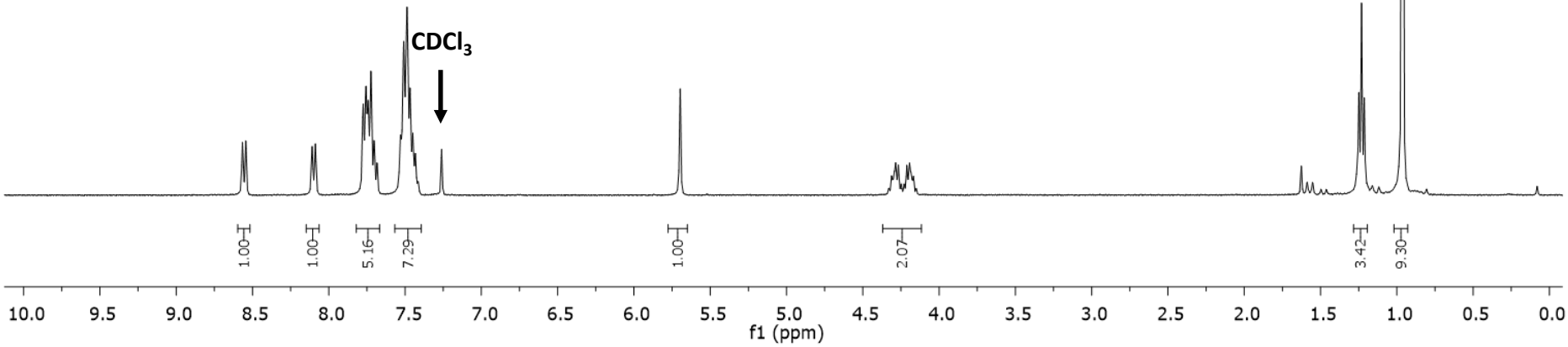


^{13}C NMR Spectrum of Compound **5j** (100 MHz, $CDCl_3$)

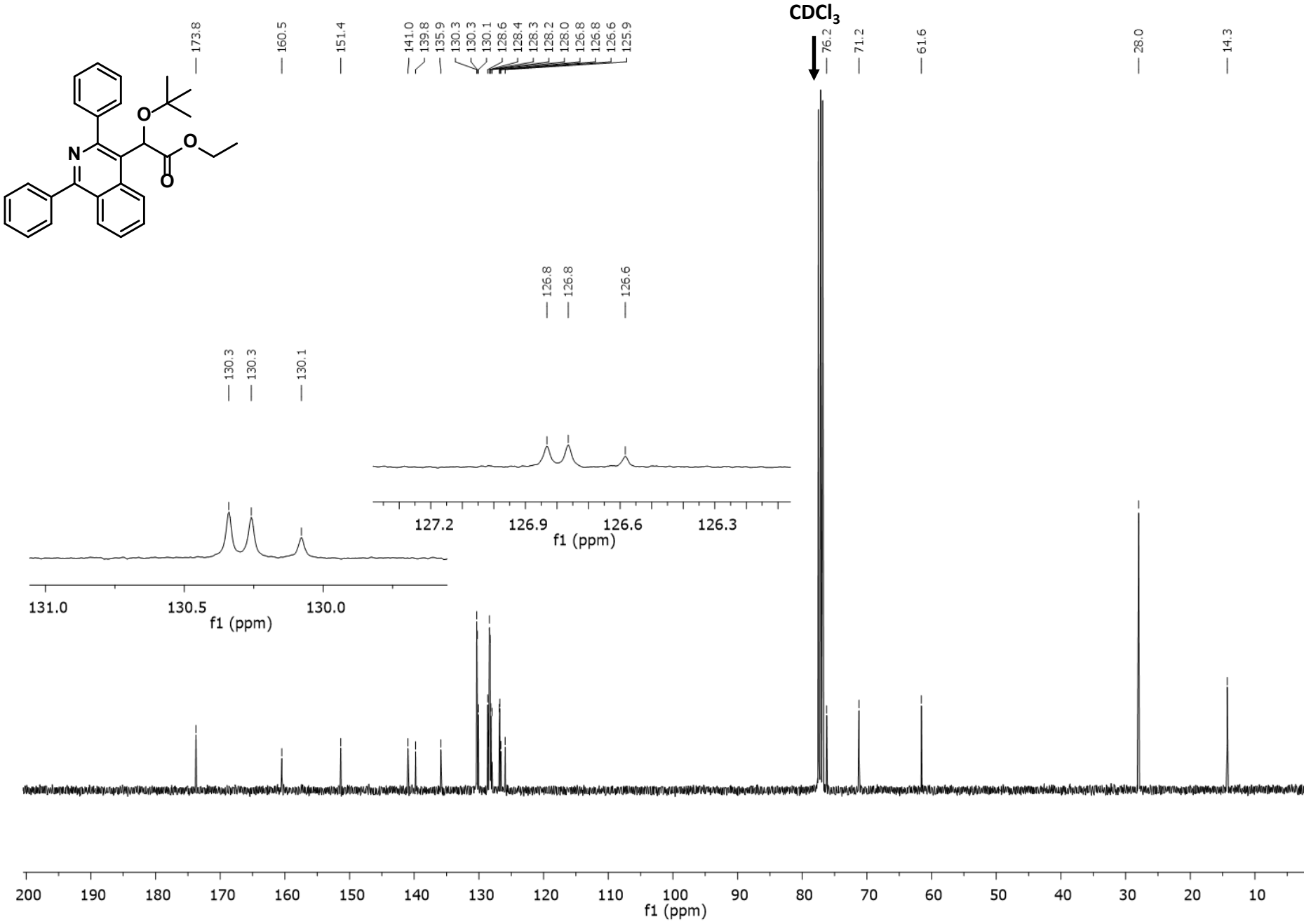


[1]H NMR Spectrum of Compound **5k** (400 MHz, $CDCl_3$)

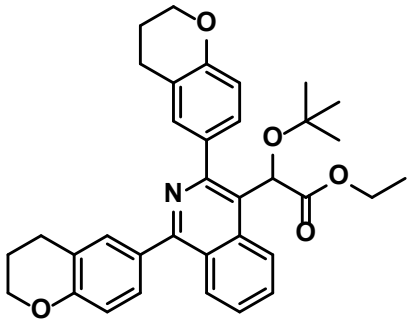




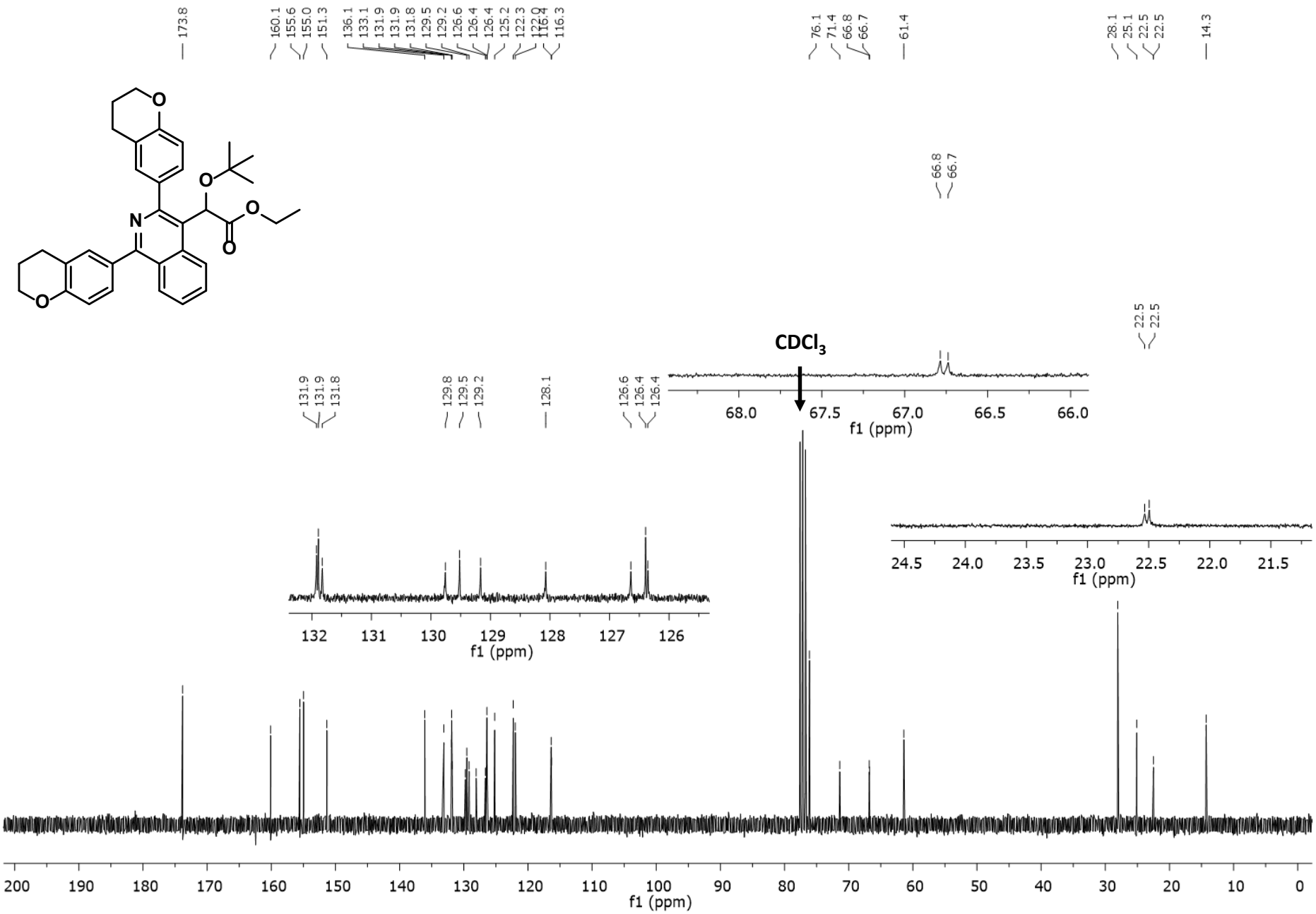
^{13}C NMR Spectrum of Compound **5k** (100 MHz, $CDCl_3$)



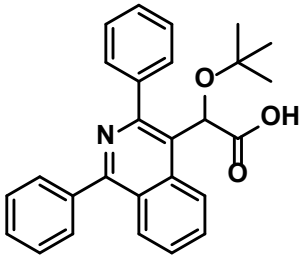
^{1}H NMR Spectrum of Compound **5l** (300 MHz, $CDCl_3$)



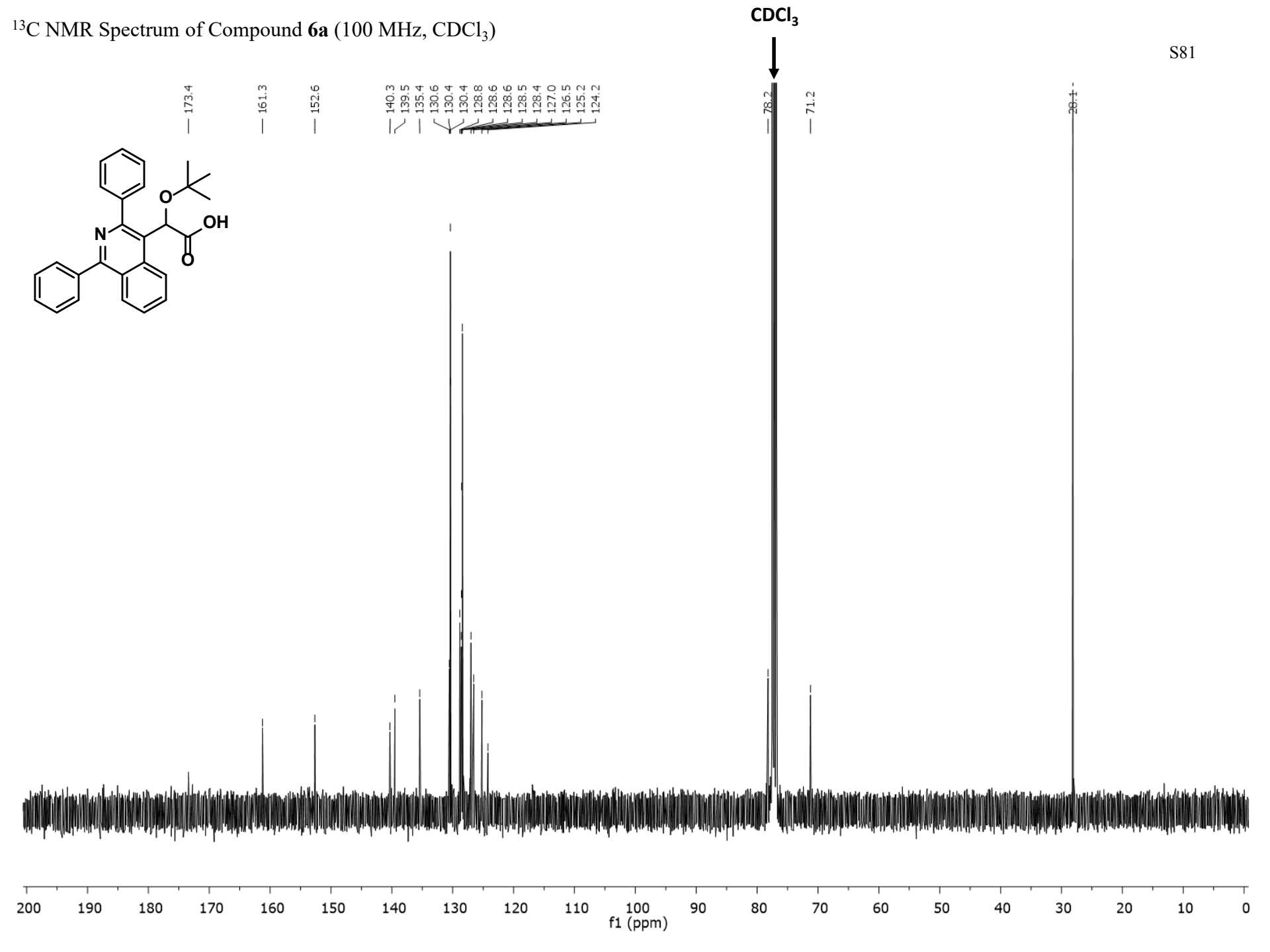
^{13}C NMR Spectrum of Compound **5l** (75 MHz, $CDCl_3$)



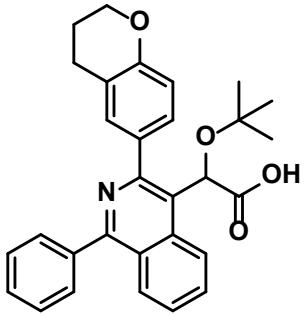
^{1}H NMR Spectrum of Compound **6a** (400 MHz, $CDCl_3$)



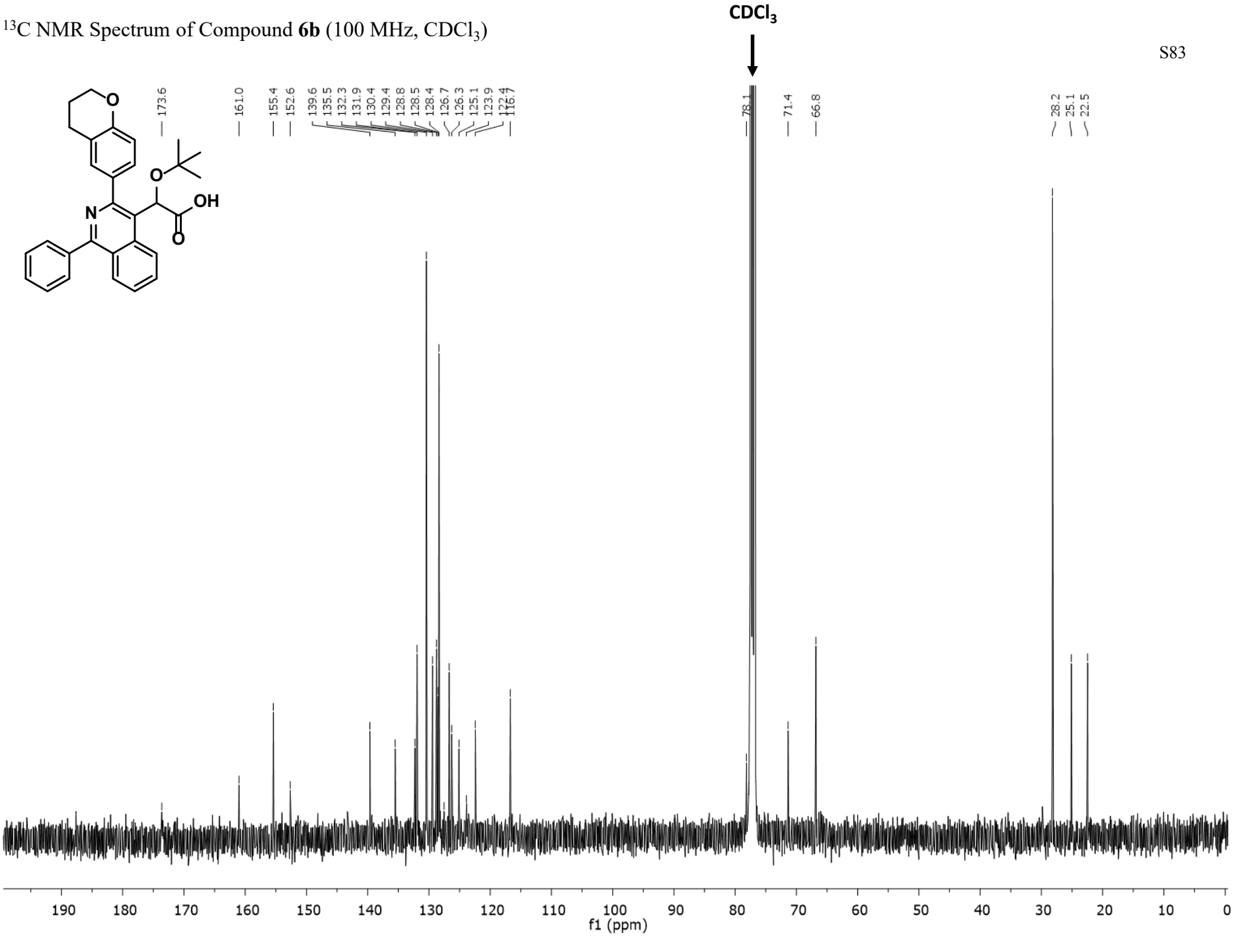
^{13}C NMR Spectrum of Compound **6a** (100 MHz, $CDCl_3$)



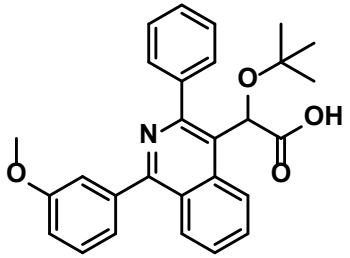
^{1}H NMR Spectrum of Compound **6b** (400 MHz, $CDCl_3$)



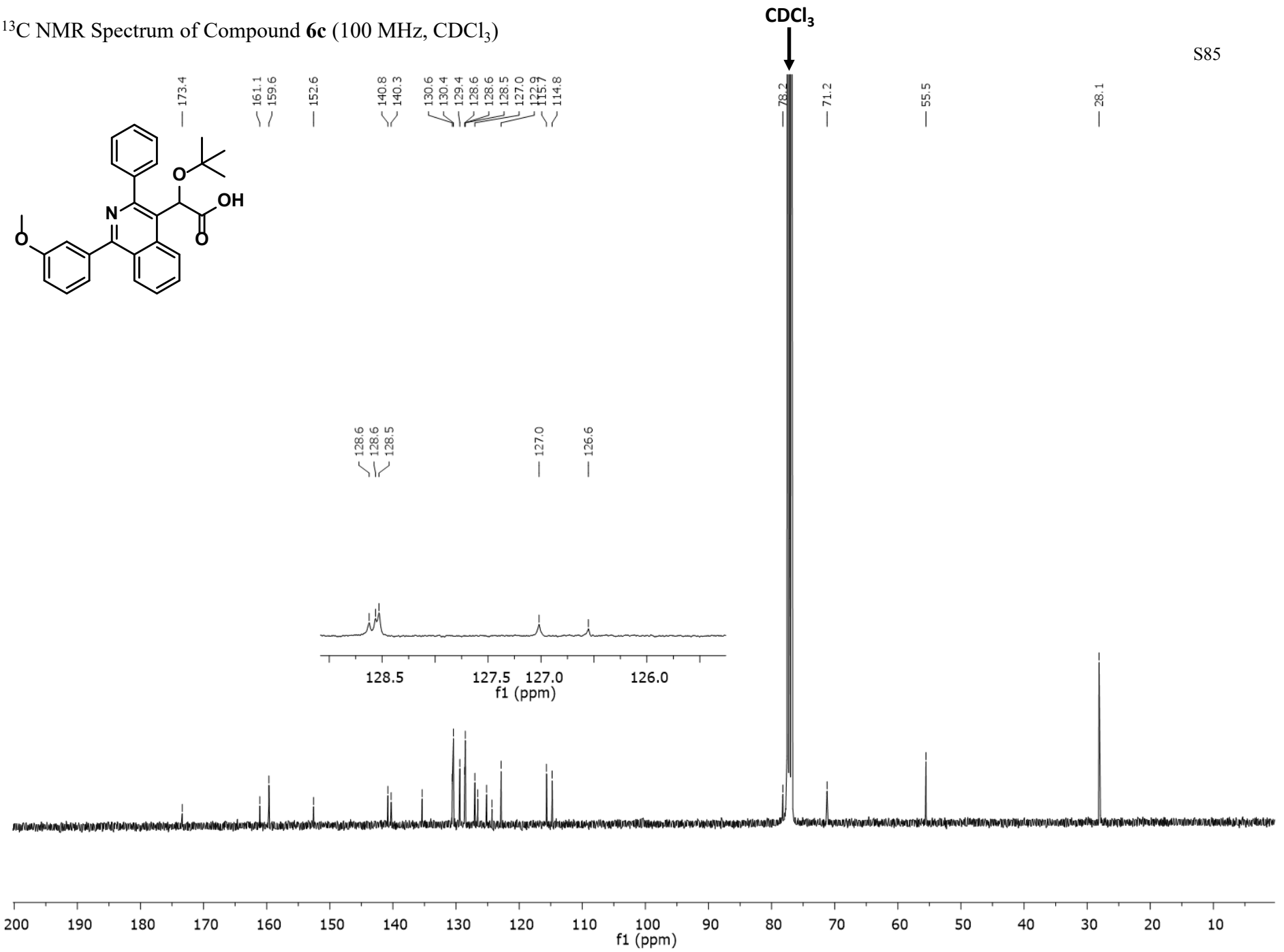
^{13}C NMR Spectrum of Compound **6b** (100 MHz, $CDCl_3$)



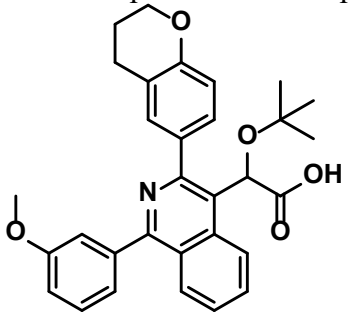
^{1}H NMR Spectrum of Compound **6c** (300 MHz, $CDCl_3$)



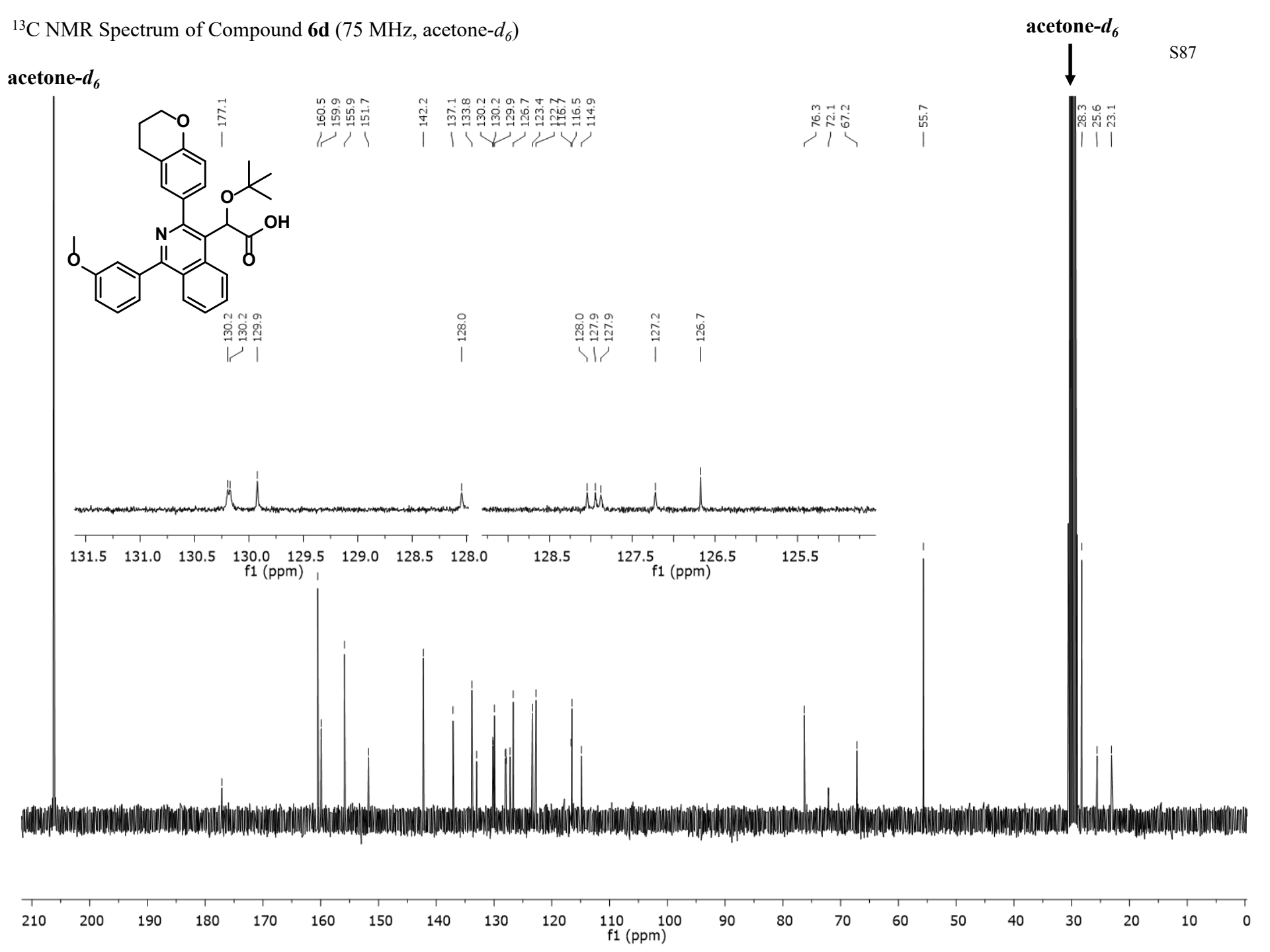
^{13}C NMR Spectrum of Compound **6c** (100 MHz, $CDCl_3$)



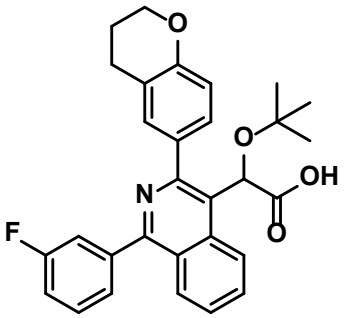
[1]H NMR Spectrum of Compound **6d** (300 MHz, acetone-d_6)



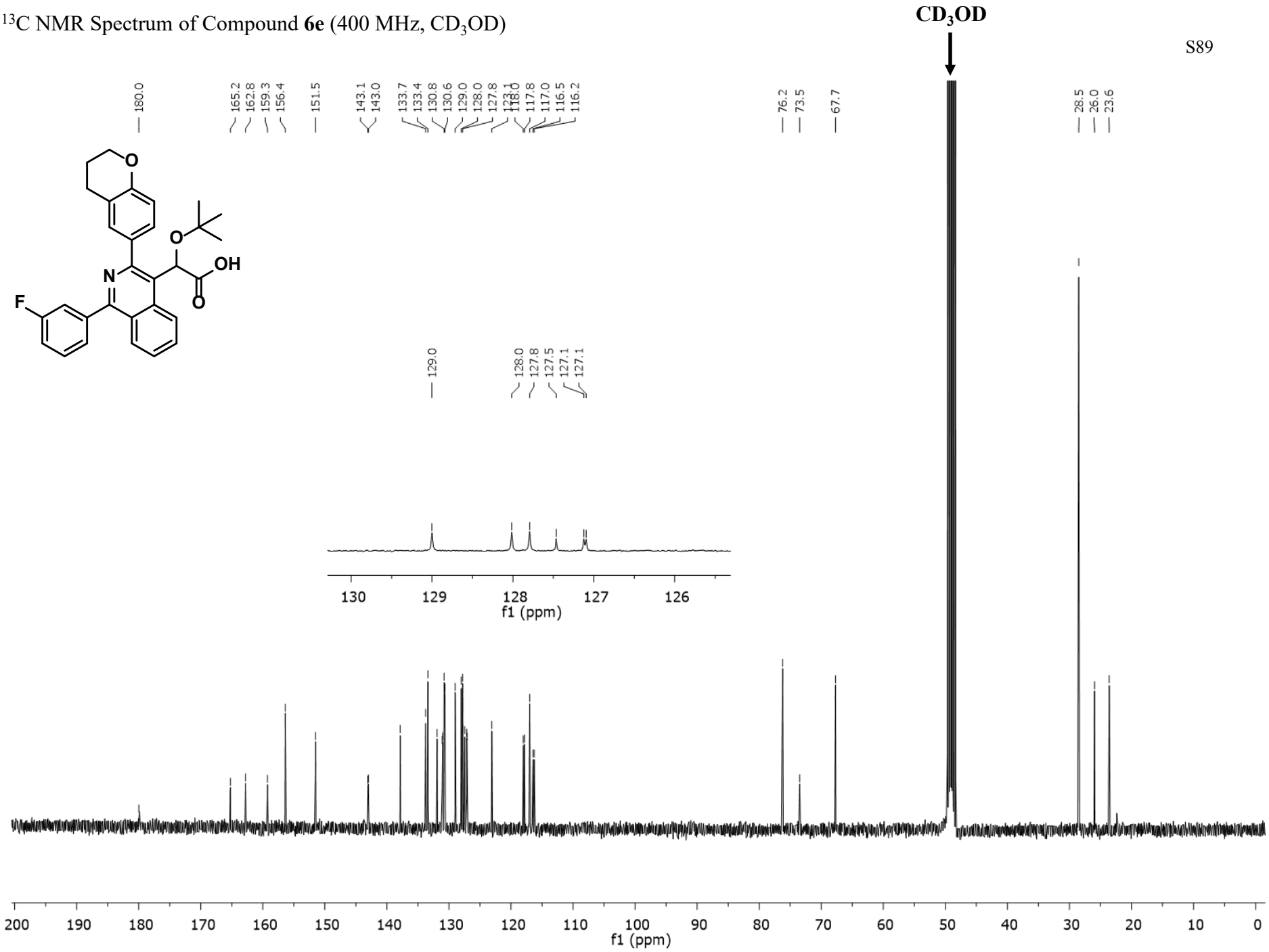
^{13}C NMR Spectrum of Compound **6d** (75 MHz, acetone-d_6)



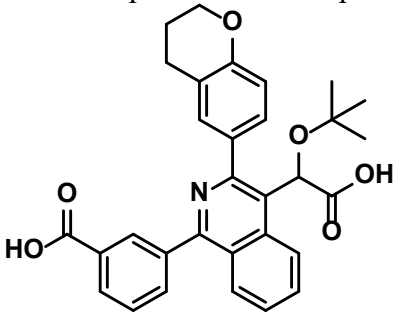
^{1}H NMR Spectrum of Compound **6e** (400 MHz, CD_3OD)



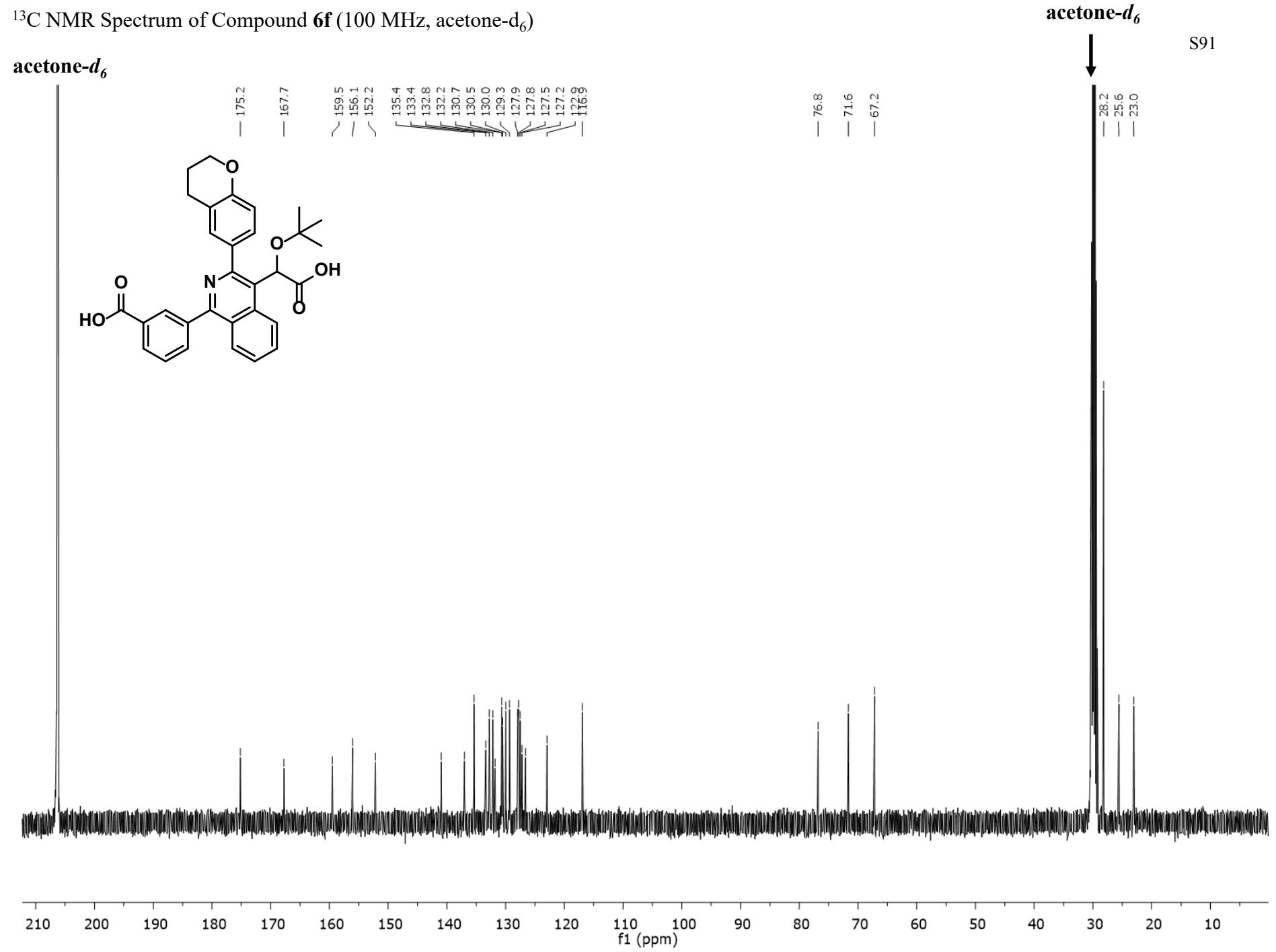
^{13}C NMR Spectrum of Compound **6e** (400 MHz, CD_3OD)



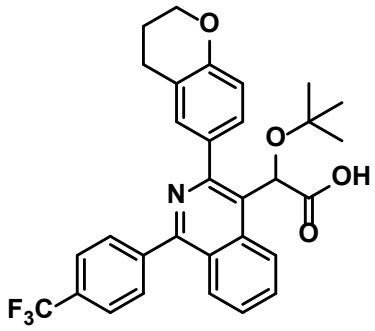
[1]H NMR Spectrum of Compound **6f** (400 MHz, acetone-d_6)



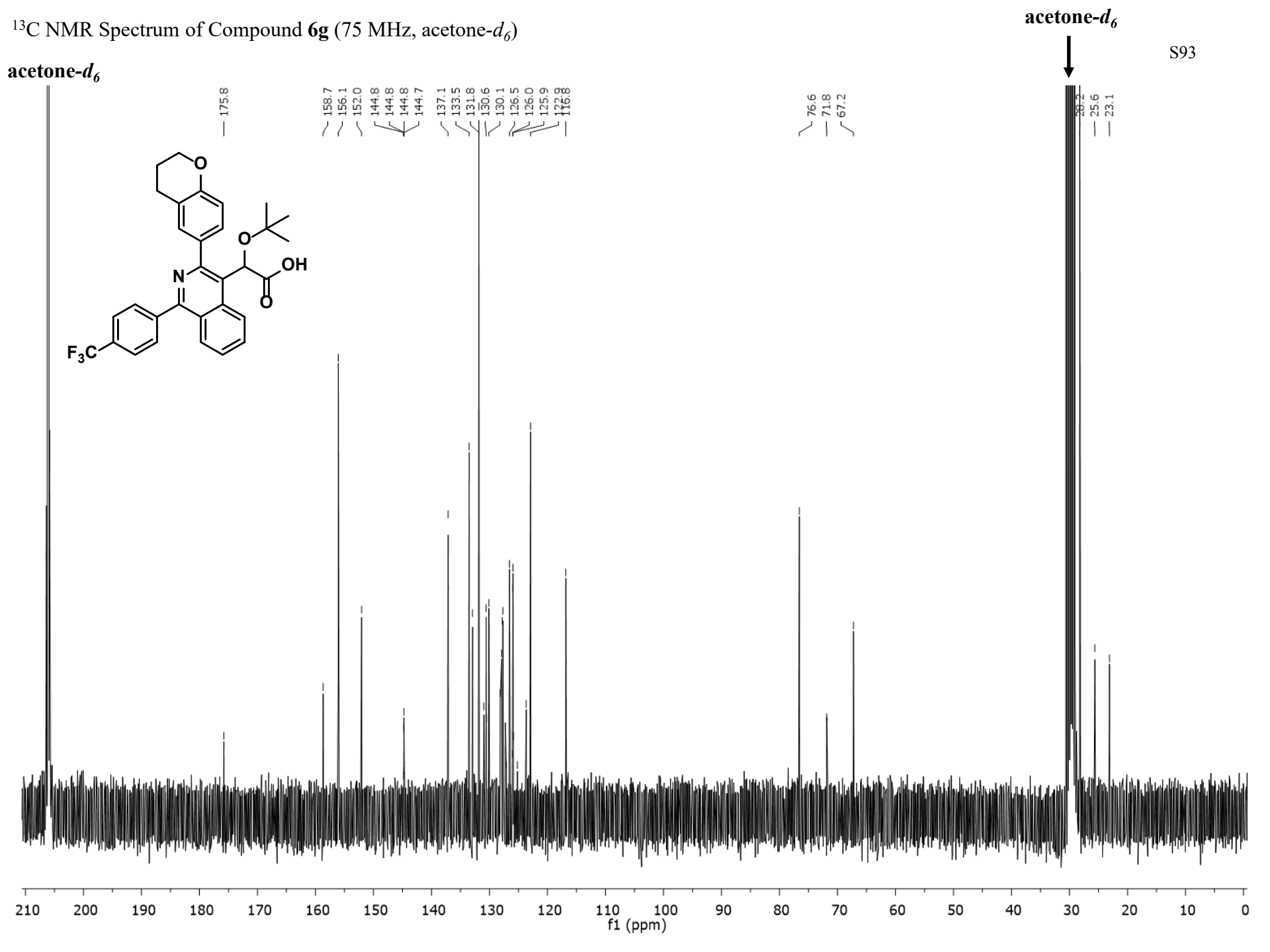
^{13}C NMR Spectrum of Compound **6f** (100 MHz, acetone-d_6)



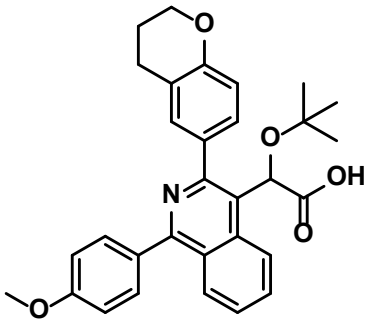
[1]H NMR Spectrum of Compound **6g** (400 MHz, acetone-d_6)



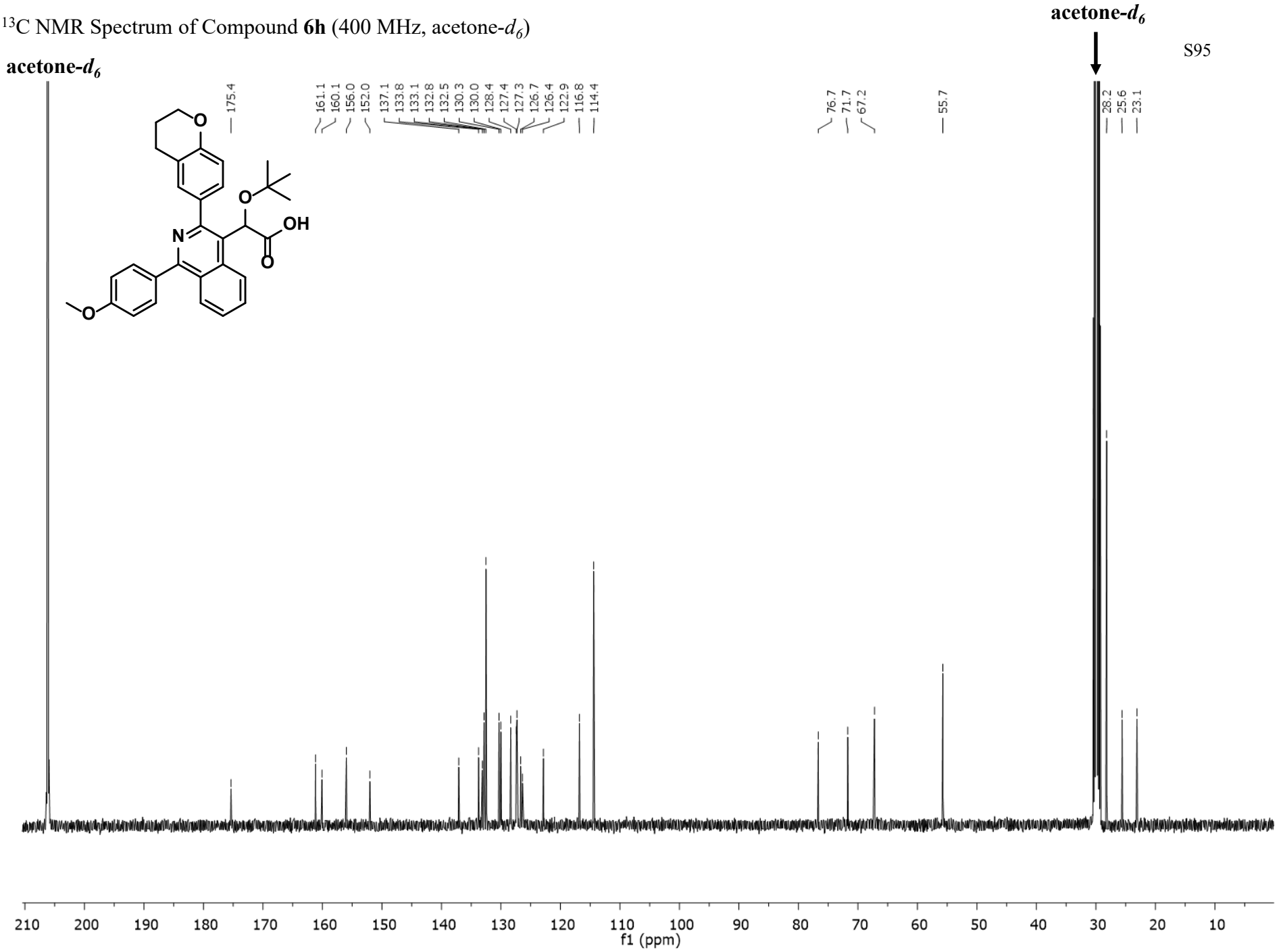
^{13}C NMR Spectrum of Compound **6g** (75 MHz, acetone-d_6)



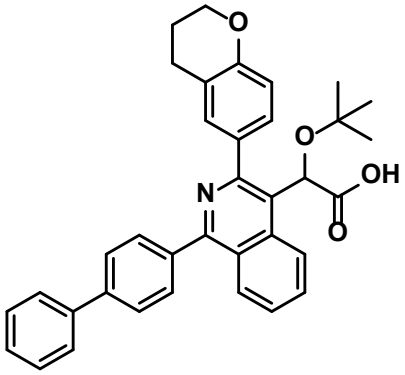
[1]H NMR Spectrum of Compound **6h** (400 MHz, acetone-d_6)



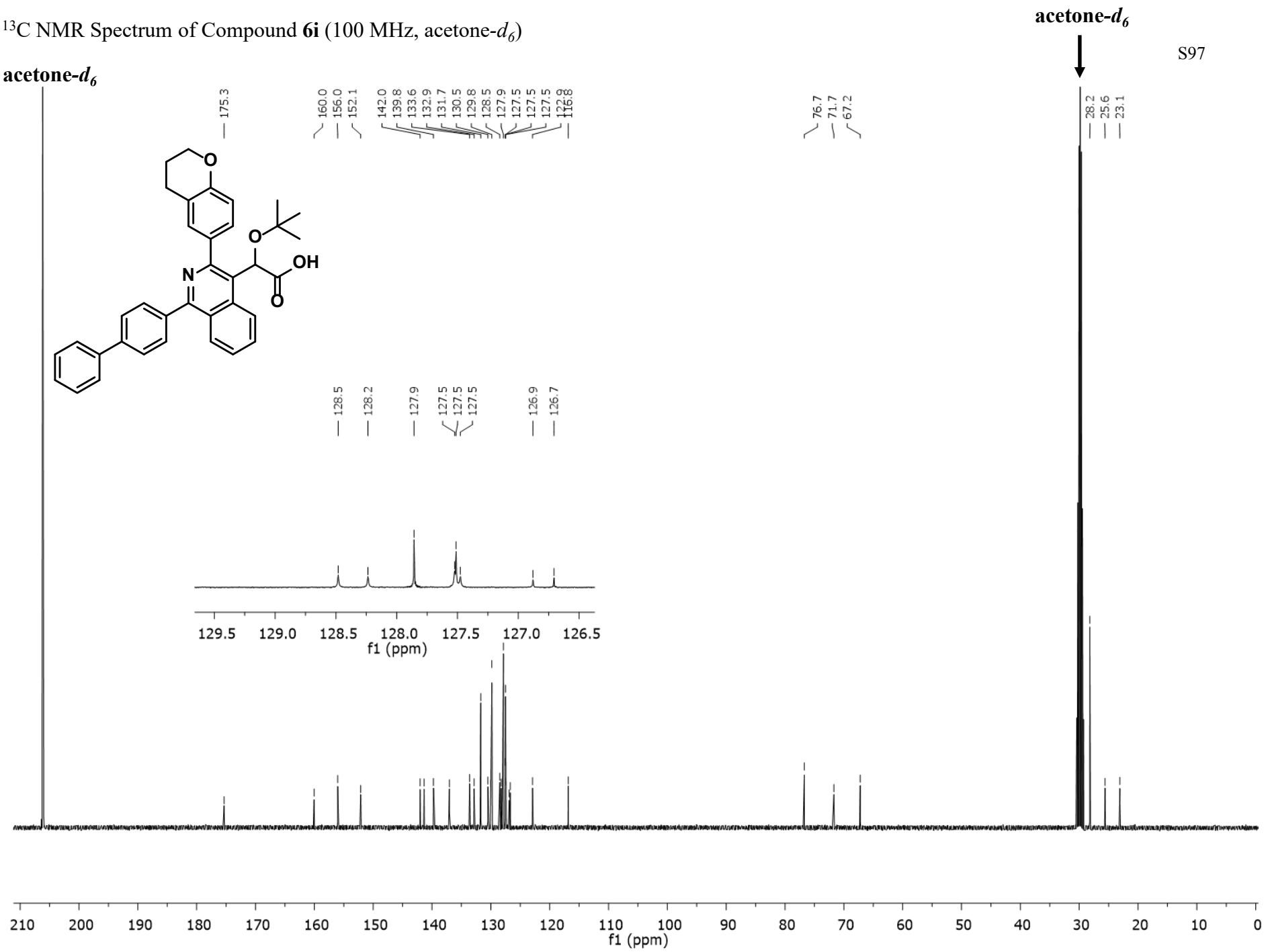
^{13}C NMR Spectrum of Compound **6h** (400 MHz, acetone-d_6)



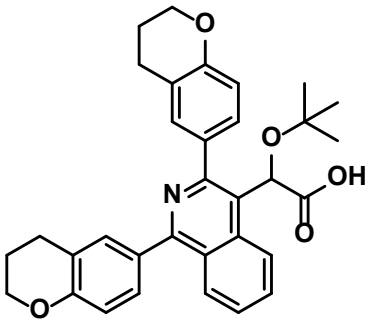
^{1}H NMR Spectrum of Compound **6i** (300 MHz, acetone-d_6)



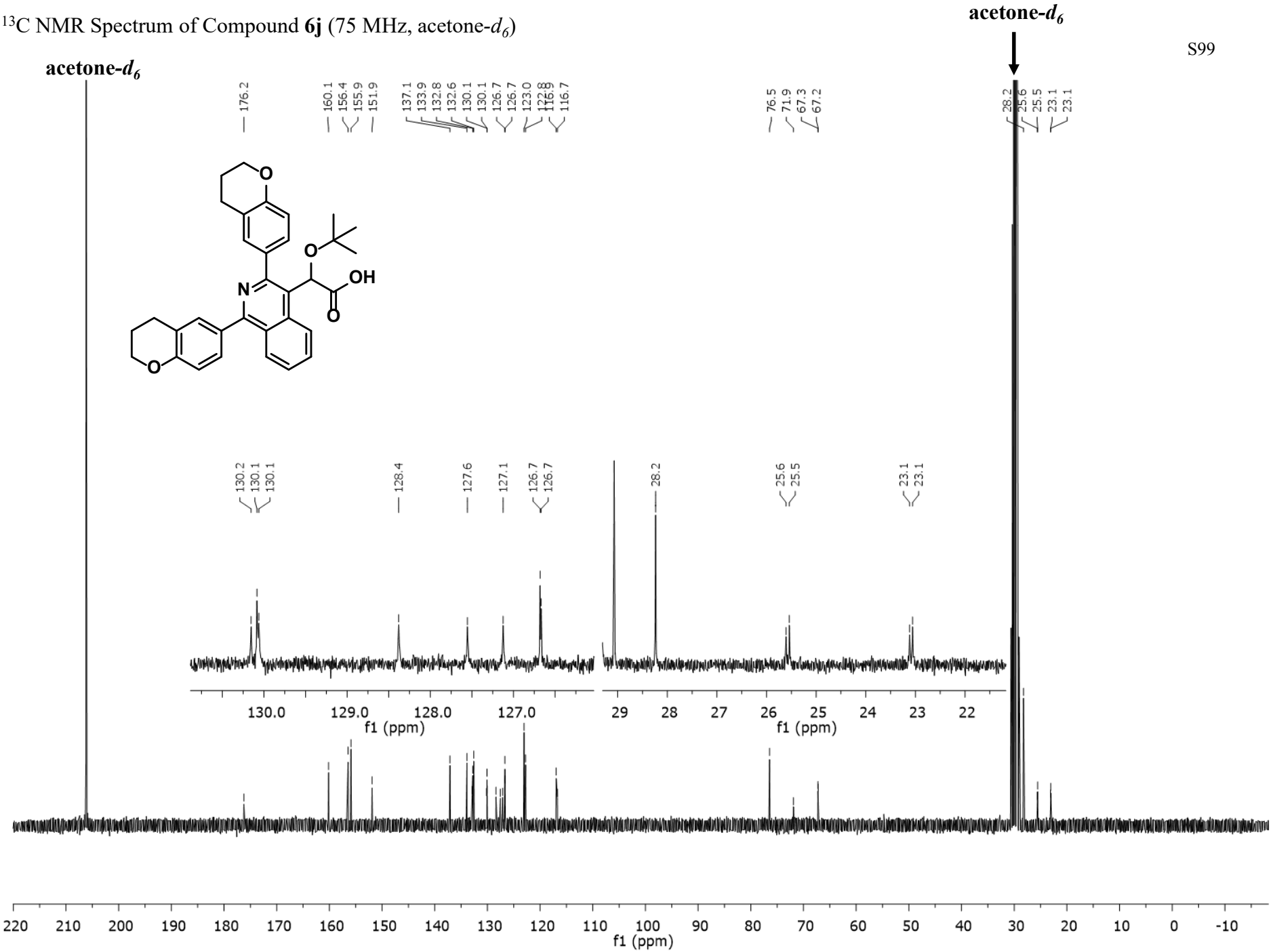
^{13}C NMR Spectrum of Compound **6i** (100 MHz, acetone-d_6)



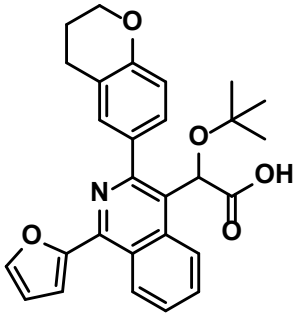
[1]H NMR Spectrum of Compound **6j** (400 MHz, acetone-d_6)



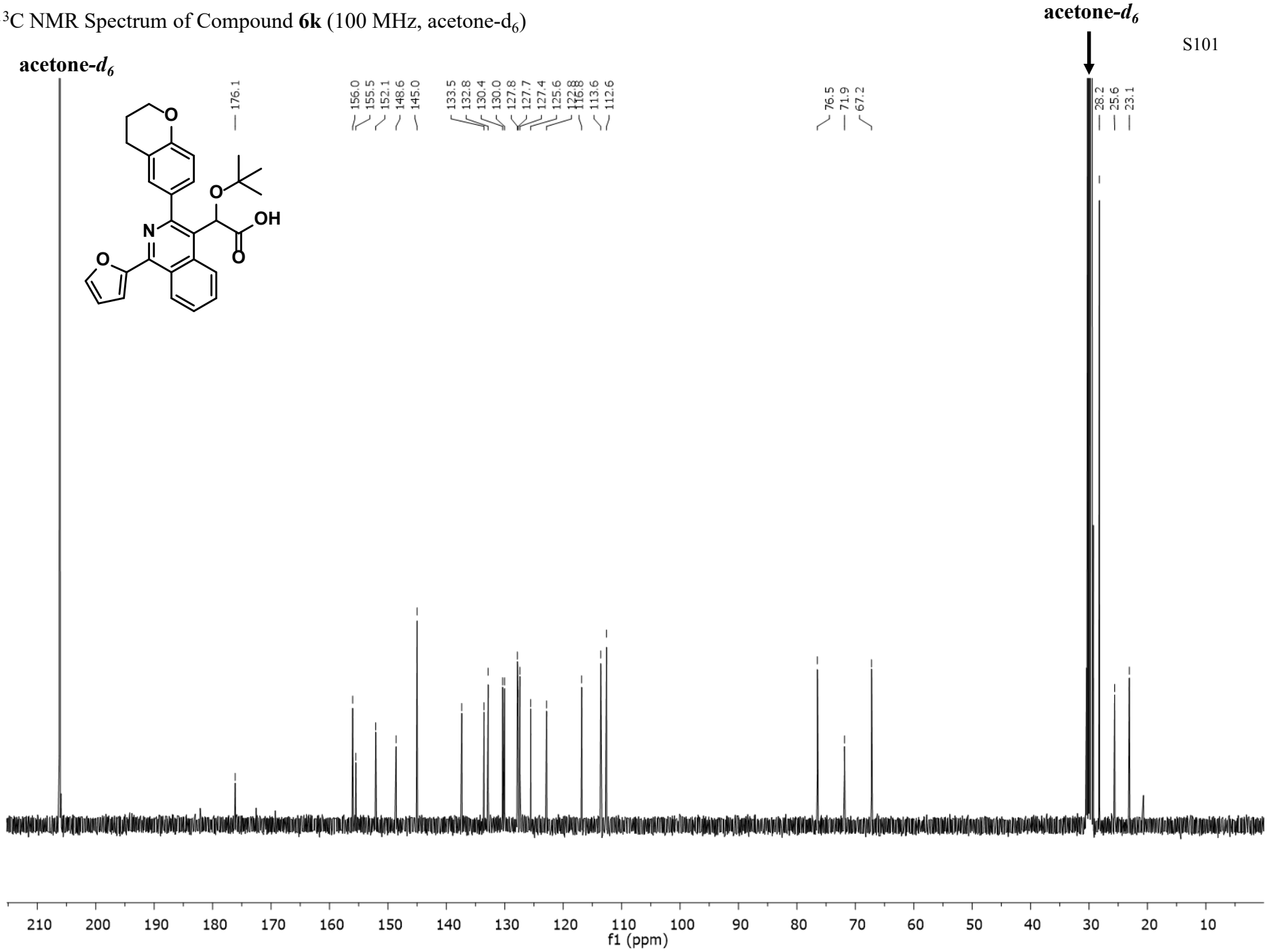
^{13}C NMR Spectrum of Compound **6j** (75 MHz, acetone-d_6)



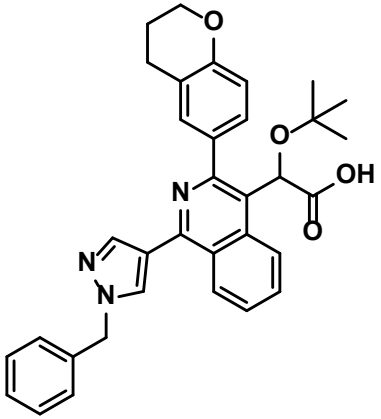
^{1}H NMR Spectrum of Compound **6k** (300 MHz, acetone-d_6)



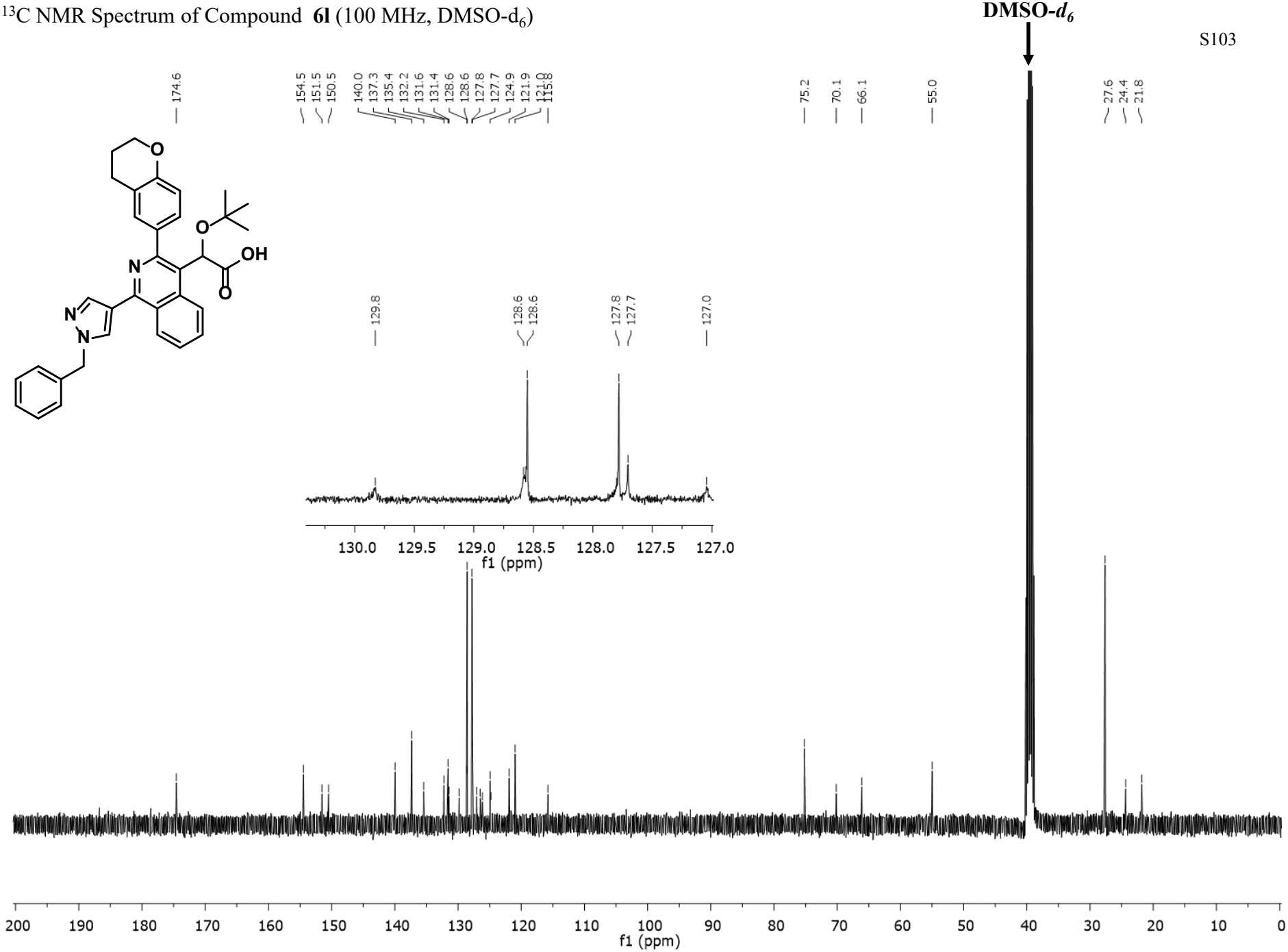
^{13}C NMR Spectrum of Compound **6k** (100 MHz, acetone-d_6)



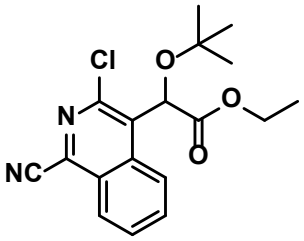
^{1}H NMR Spectrum of Compound **6l** (400 MHz, DMSO-d_6)



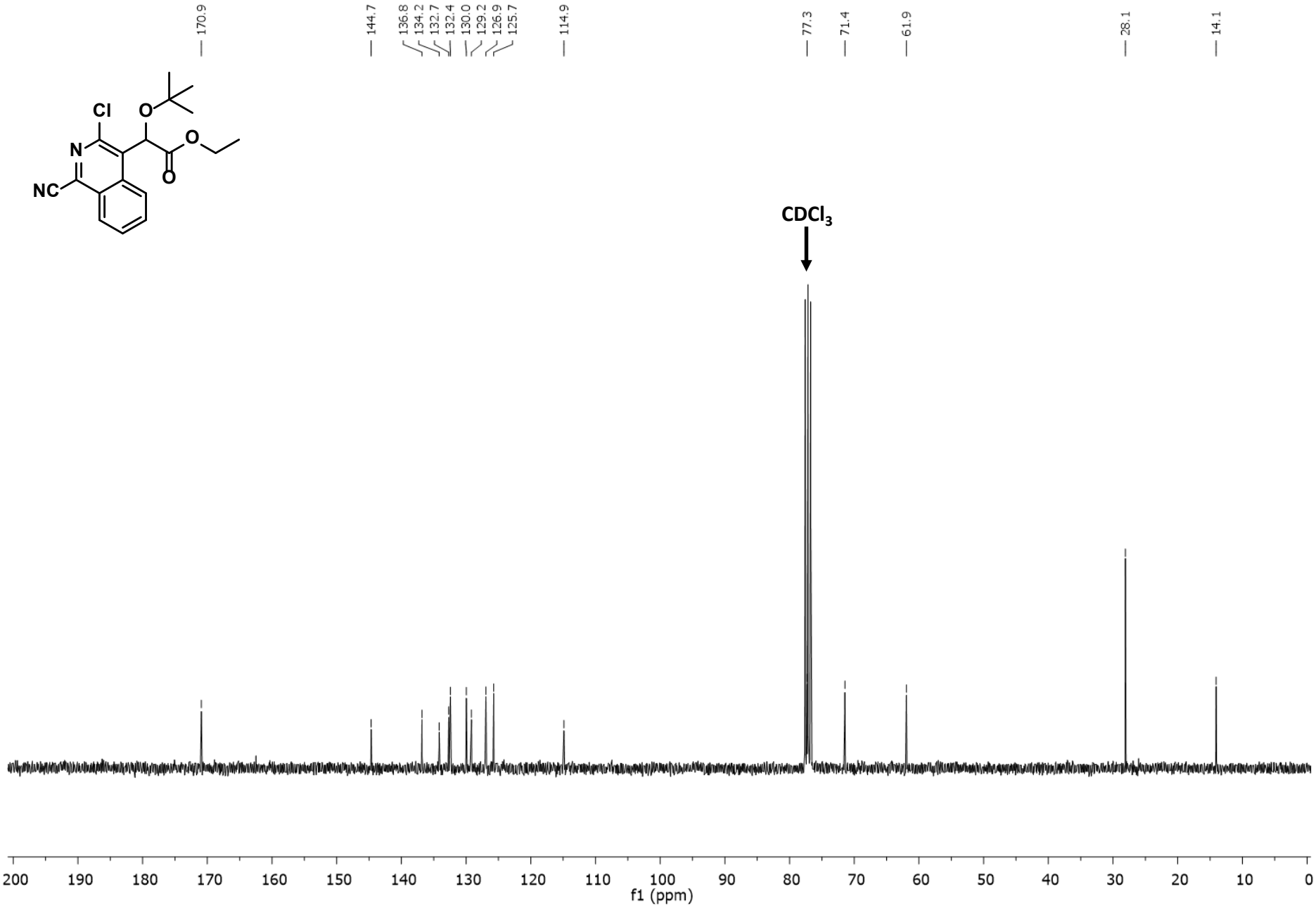
^{13}C NMR Spectrum of Compound **6l** (100 MHz, DMSO-d_6)



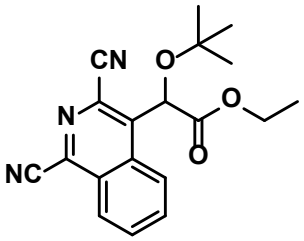
^{1}H NMR Spectrum of Compound **S1** (300 MHz, $CDCl_3$)



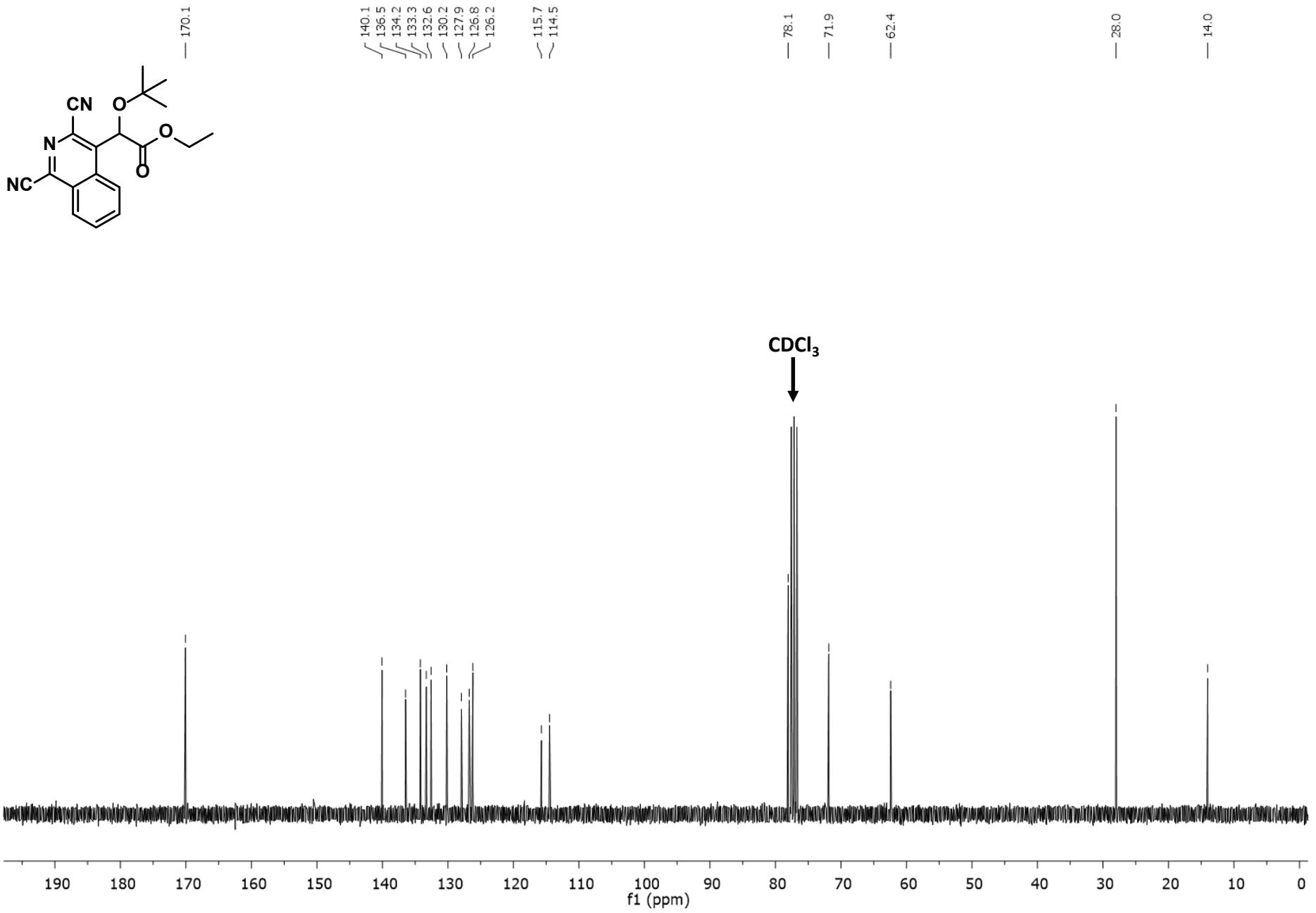
^{13}C NMR Spectrum of Compound **S1** (75 MHz, $CDCl_3$)



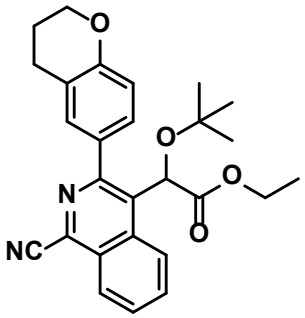
^{1}H NMR Spectrum of Compound **S2** (300 MHz, $CDCl_3$)



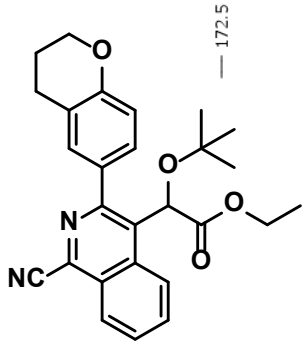
^{13}C NMR Spectrum of Compound **S2** (75 MHz, $CDCl_3$)



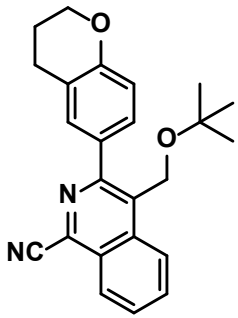
^{1}H NMR Spectrum of Compound **7** (300 MHz, $CDCl_3$)



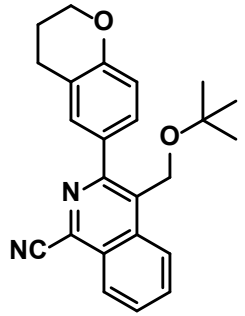
^{13}C NMR Spectrum of Compound **7** (100 MHz, $CDCl_3$)



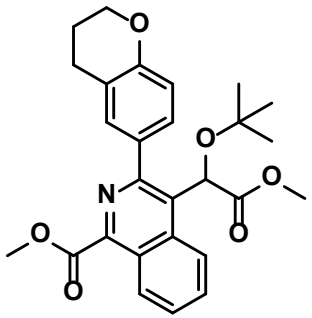
^{1}H NMR Spectrum of Compound **S3** (400 MHz, $CDCl_3$)



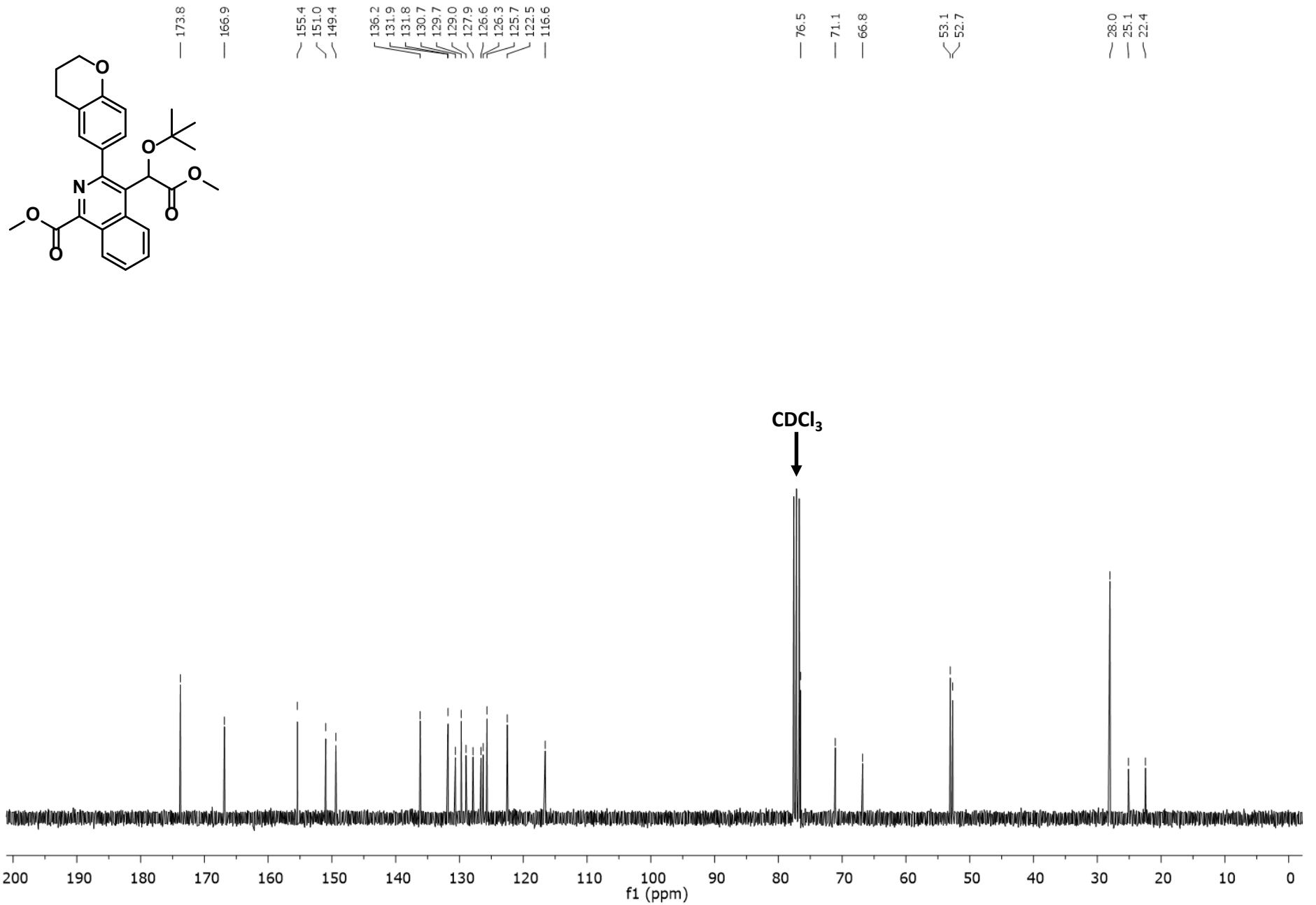
^{13}C NMR Spectrum of Compound **S3** (100 MHz, $CDCl_3$)



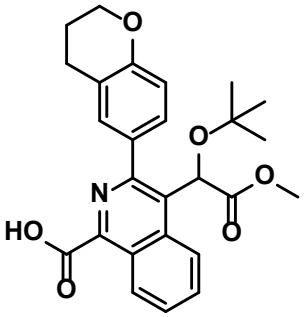
^{1}H NMR Spectrum of Compound **S4** (400 MHz, $CDCl_3$)



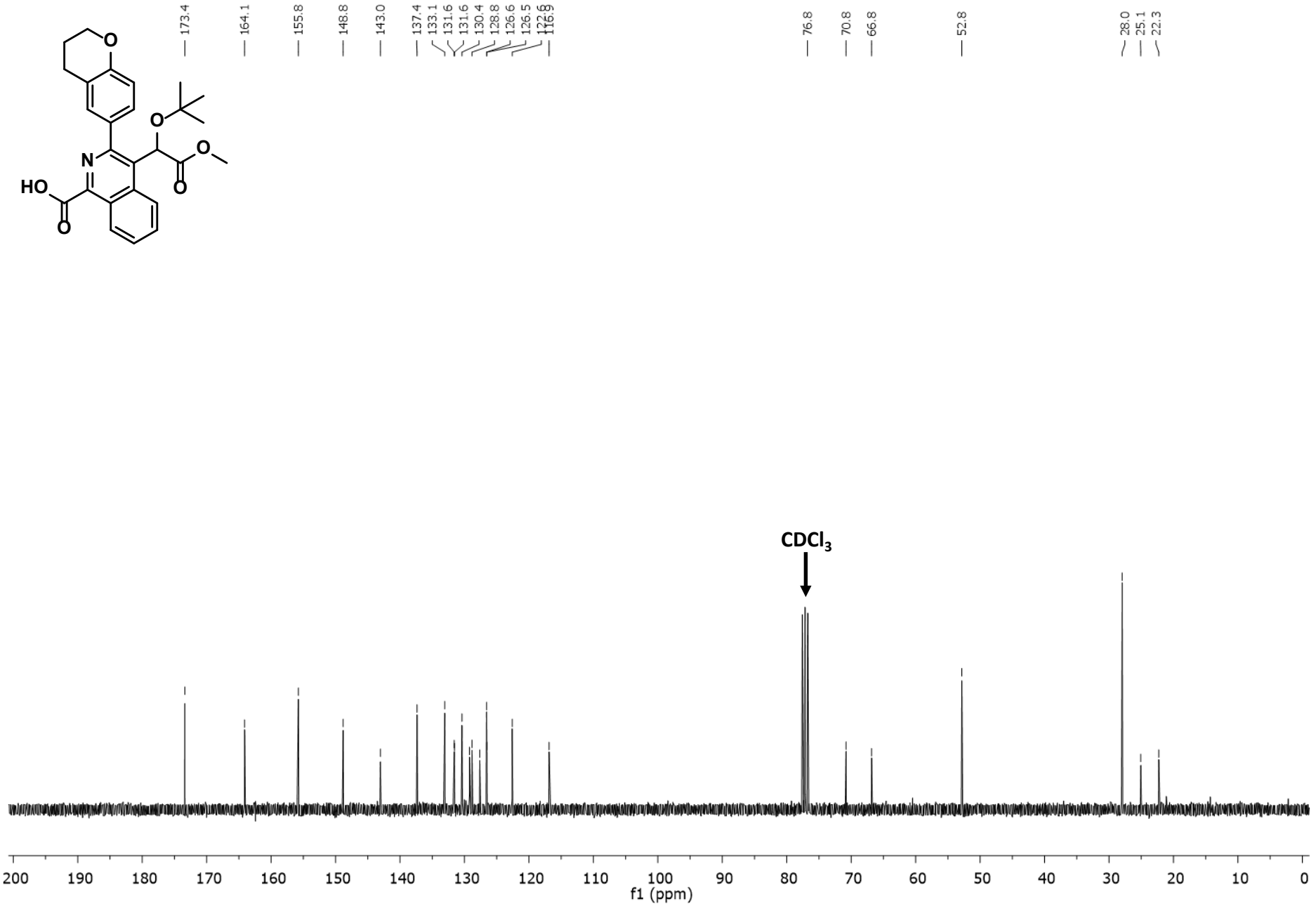
^{13}C NMR Spectrum of Compound **S4** (75 MHz, $CDCl_3$)



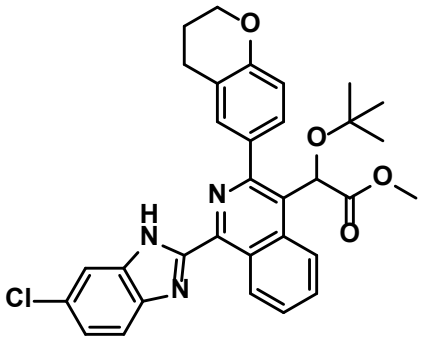
^{1}H NMR Spectrum of Compound **8** (300 MHz, $CDCl_3$)



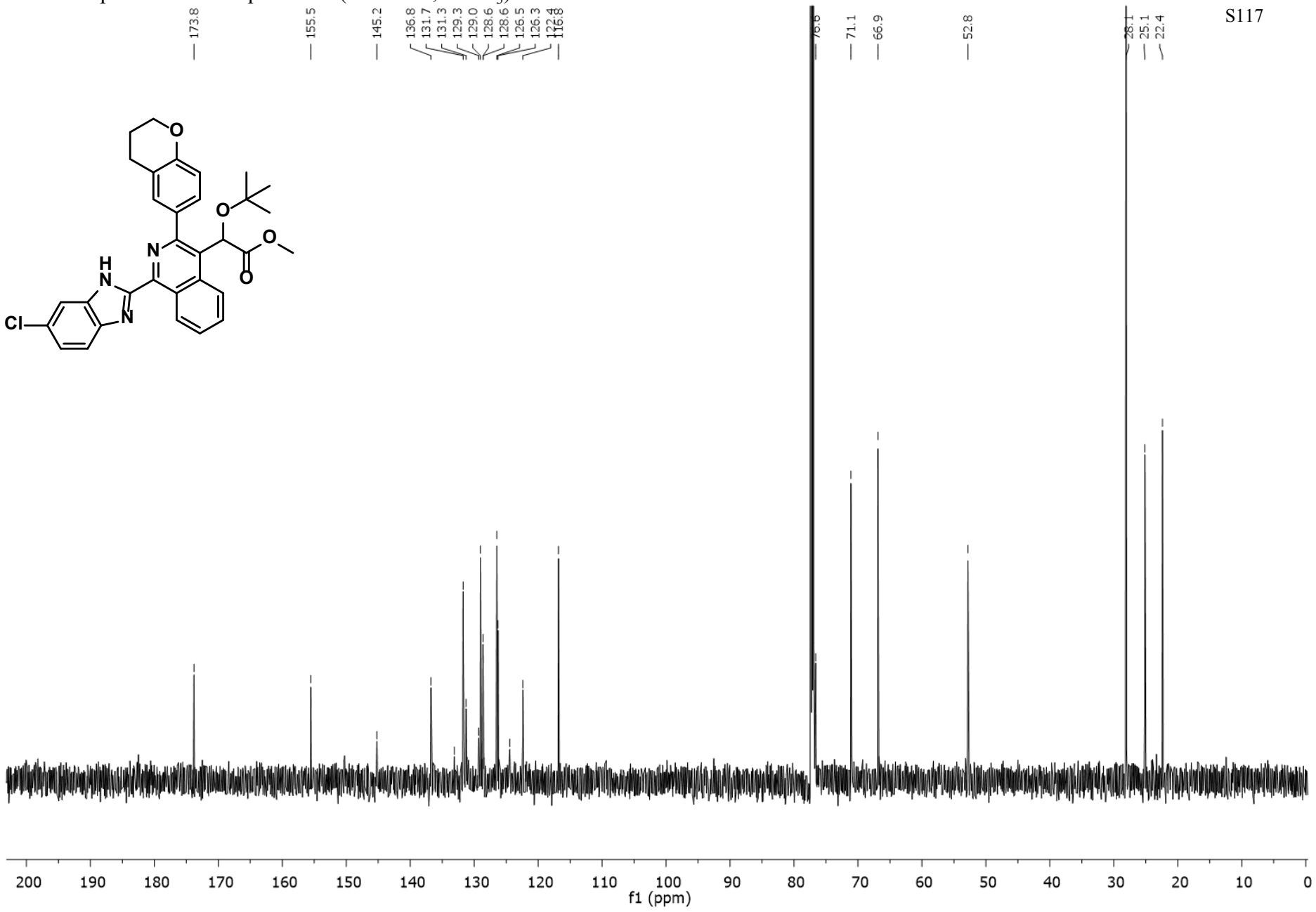
^{13}C NMR Spectrum of Compound **8** (75 MHz, $CDCl_3$)



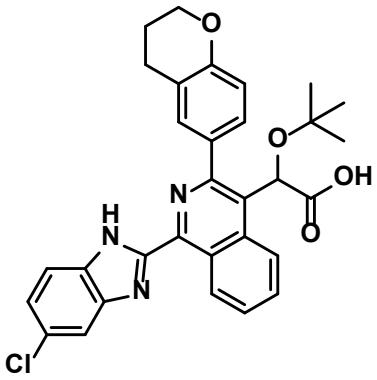
^{1}H NMR Spectrum of Compound **S5** (700 MHz, $CDCl_3$)

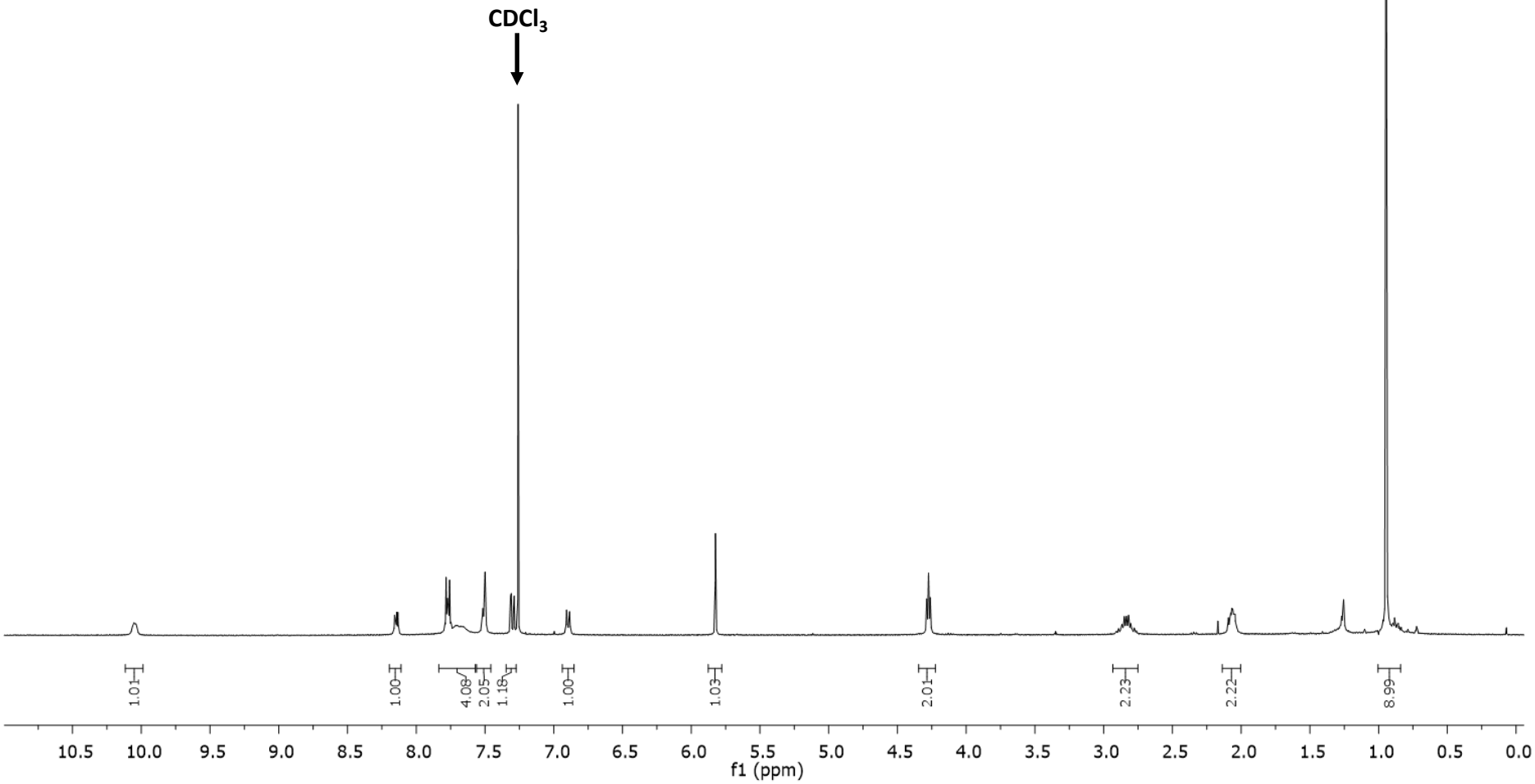


^{13}C NMR Spectrum of Compound **S5** (175 MHz, $CDCl_3$)

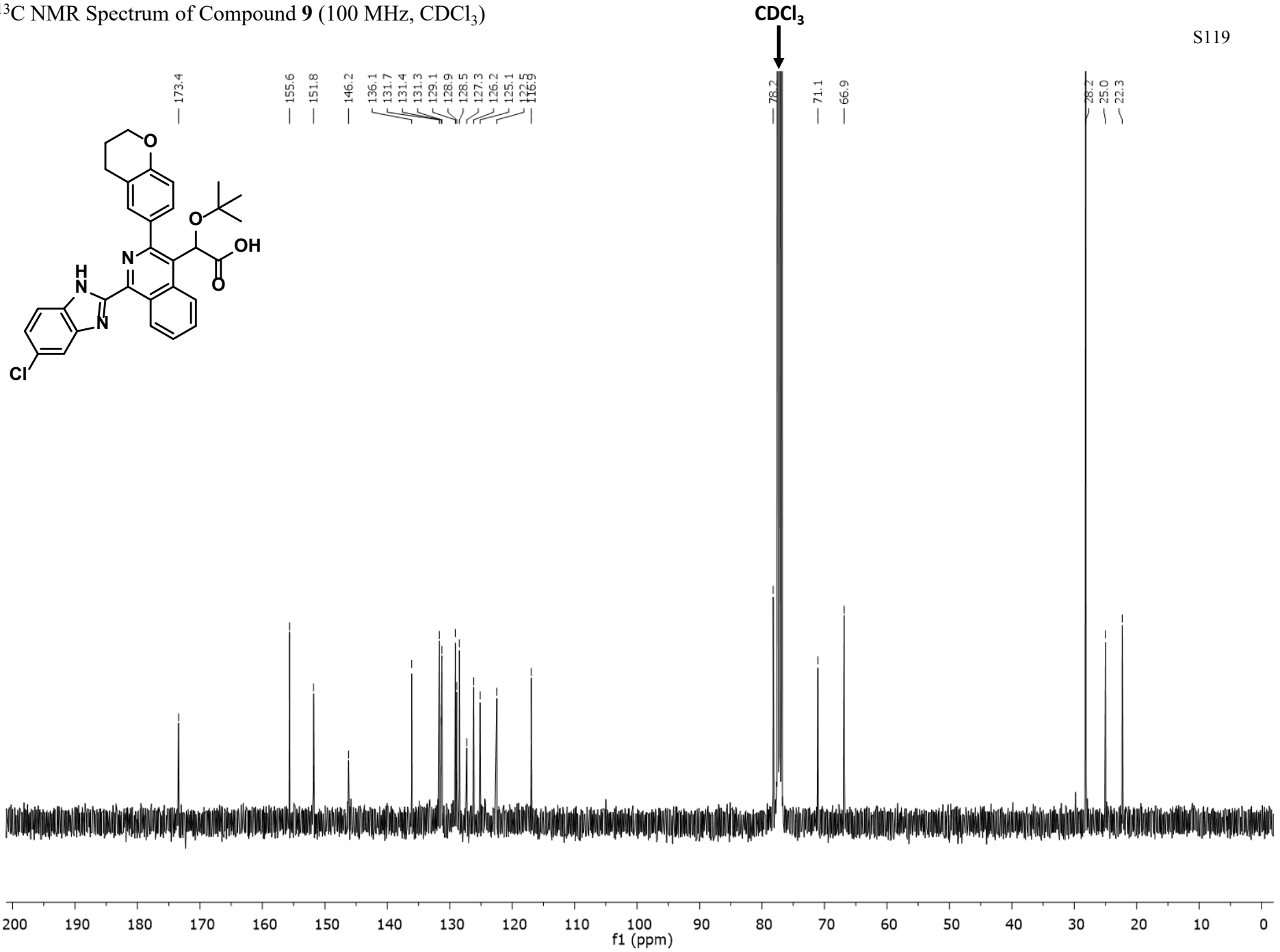


^{1}H NMR Spectrum of Compound **9** (400 MHz, $CDCl_3$)

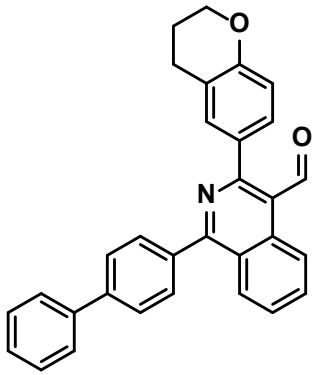




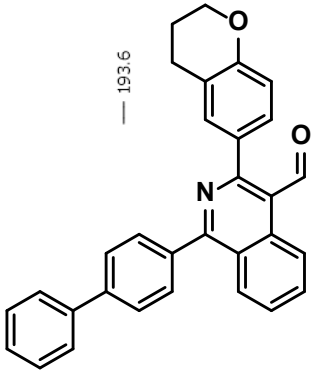
^{13}C NMR Spectrum of Compound **9** (100 MHz, $CDCl_3$)



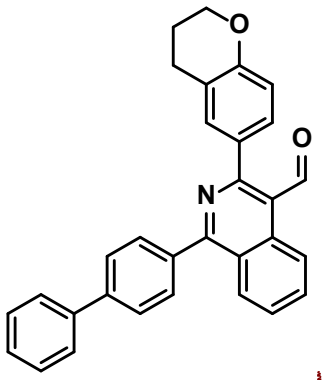
[1]H NMR Spectrum of Compound **10** (700 MHz, DMSO-d_6)

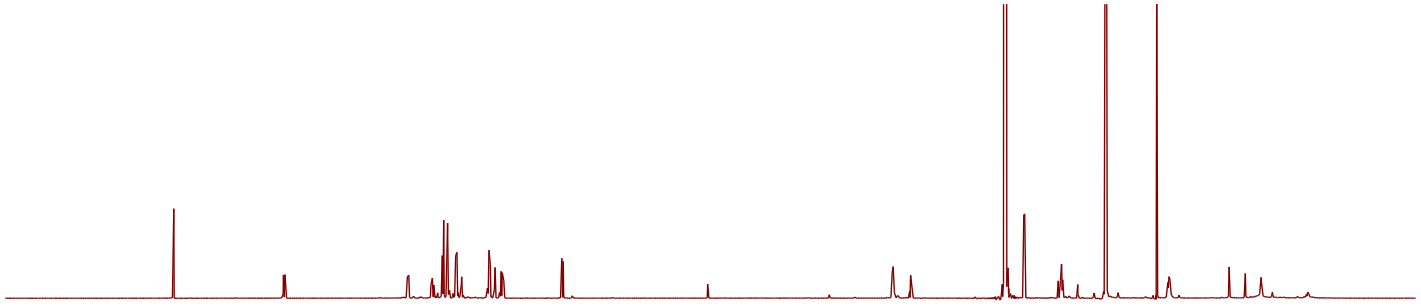


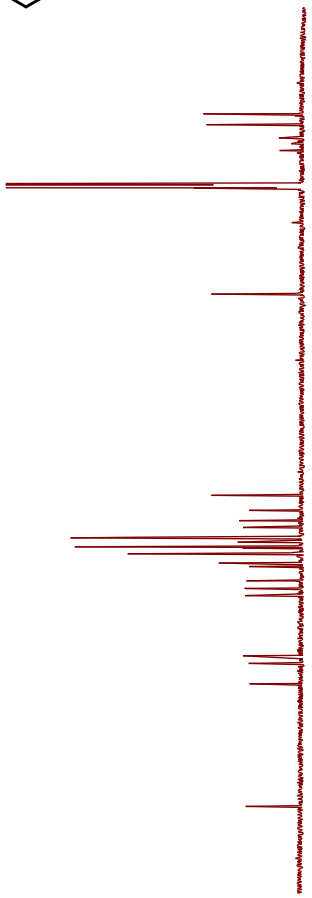
^{13}C NMR Spectrum of Compound **10** (175 MHz, DMSO-d_6)

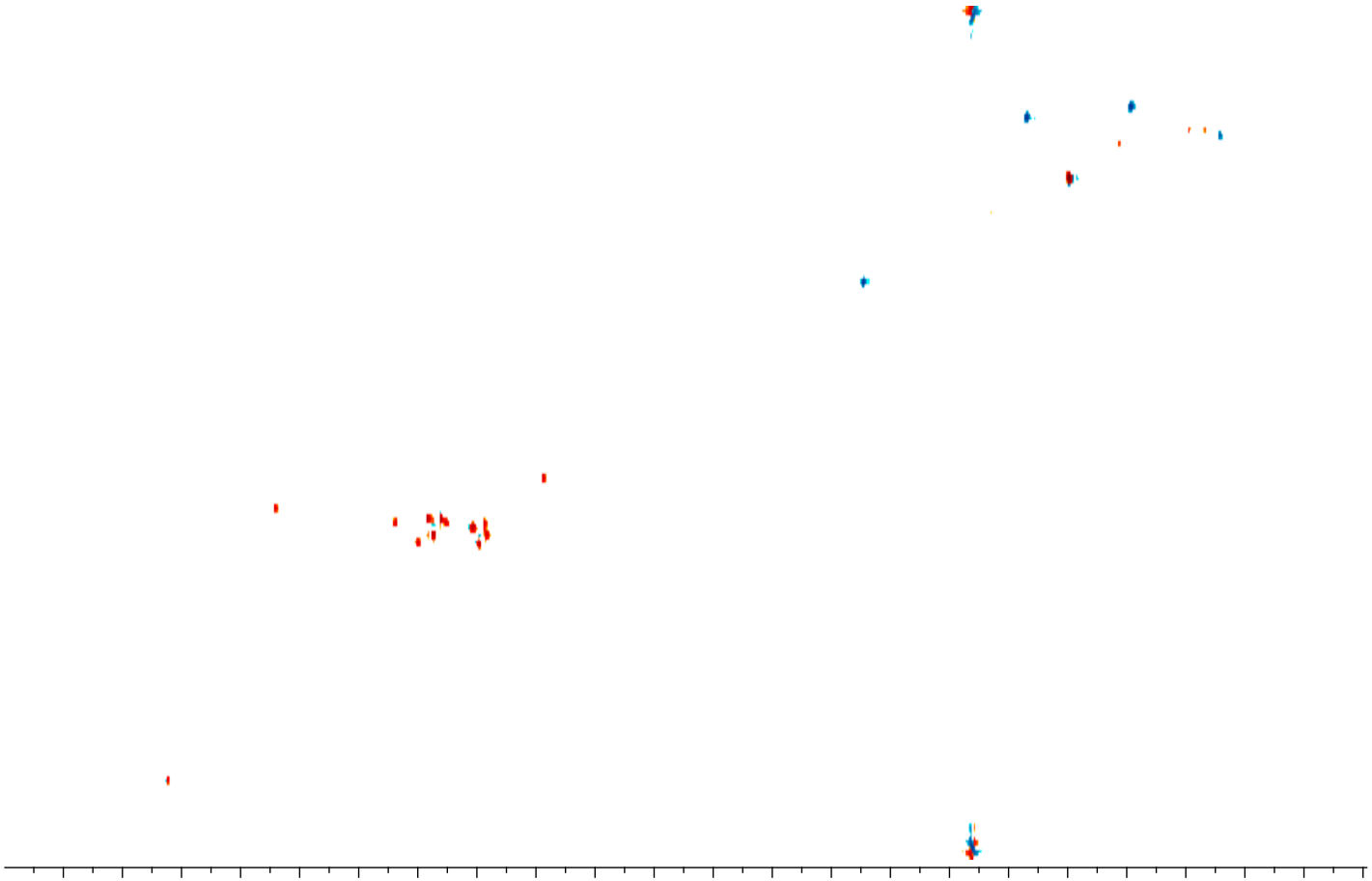


HSQC ^{1}H-^{13}C NMR Spectrum of Compound **10** (700 MHz, DMSO-d_6)

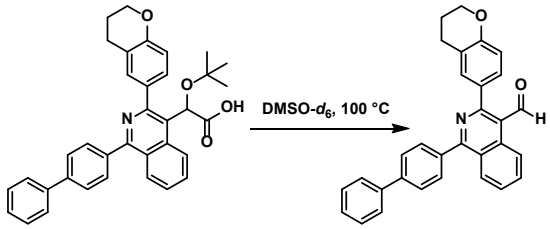








Thermal Degradation of Compound **6i** ^{1}H NMR (400 MHz DMSO-*d*6)



17 d
100 °C

10 d
100 °C

6 d
100 °C

17h
60 °C

0h

10.36 1.00

3.26 1.00

1.64 1.00

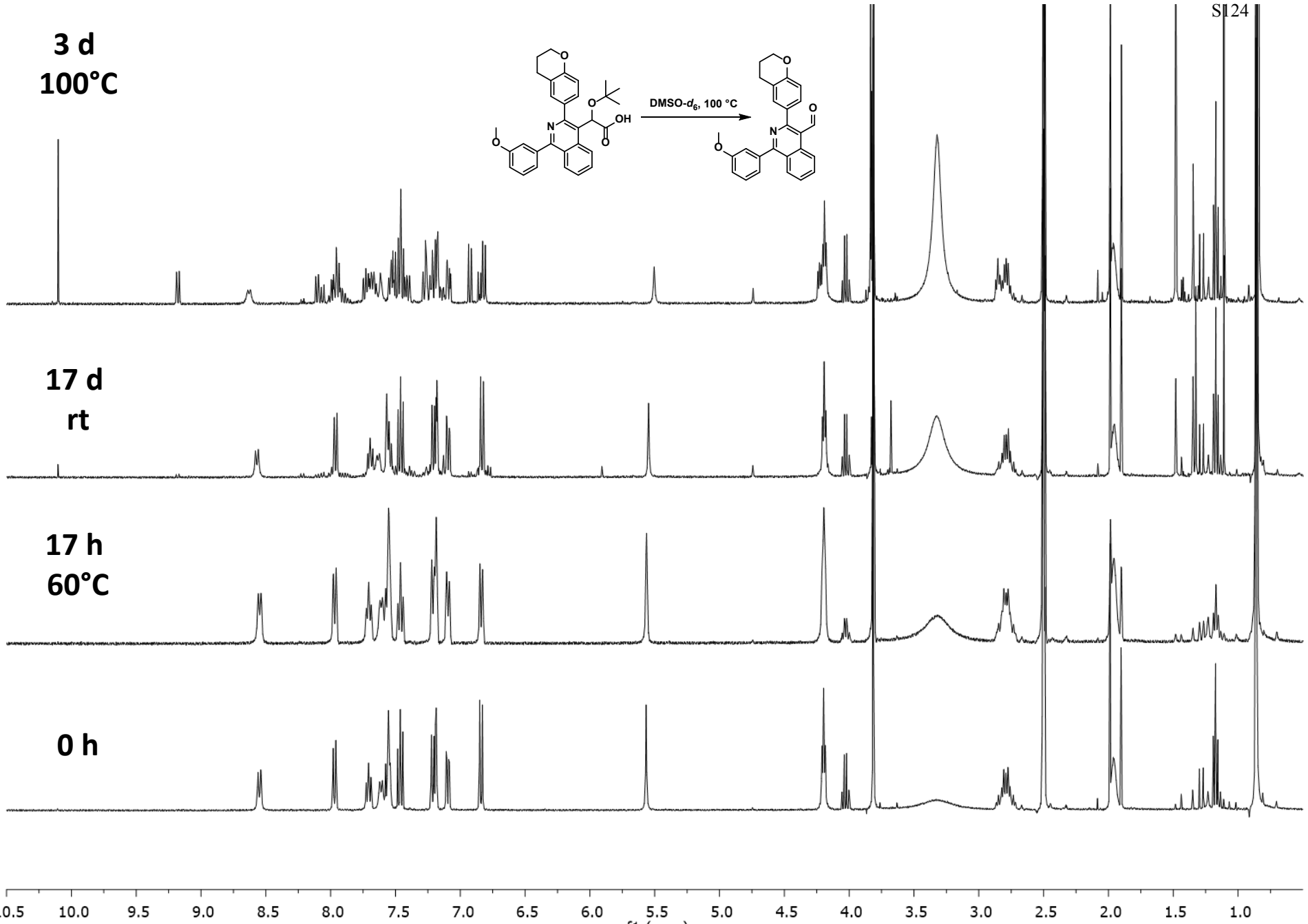
0.06 1.00

0.03 1.00

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0

f1 (ppm)

Thermal Degradation of Compound **6d** ^{1}H NMR (400 MHz DMSO-*d*6)



Thermal Degradation of Compound **6e** ^{1}H NMR (400 MHz DMSO-*d*6)