Supporting Information

Benzodioxole grafted Spirooxindole pyrrolidinyl derivatives: Synthesis, Characterization, Molecular docking and Anti-diabetic activity

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1. Experimental Section

General

The starting materials, solvents and reagents were acquired from commercial suppliers and utilized as such. Column chromatography was carried out by making use of silica gel – 60 (particle size 0.14 – 0.25 mm). Reaction progress was tracked by TLC using Merck silica gel 60 F_{254} plates and was visualized with aid of UV light. Melting points were determined on Veego (VMP-DS) melting point apparatus and were uncorrected. FT-IR spectra were measured using Shimadzu IR Tracer-100 spectrophotometer using potassium bromide pellets. ^{1}H and ^{13}C NMR spectra were collected on Bruker Avance III NMR spectrometer (500 and 125 MHz) using DMSO-d_6 as solvent. Chemical shifts are reported in parts per million (ppm) corresponding to tetramethylsilane (TMS), and coupling constants (*J*) are given in hertz (Hz). Data were reported in orders: chemical shift, multiplicity, integration, coupling constant. High-resolution mass spectra were obtained on an Agilent QTOF G6545 spectrometer, and acetonitrile was used to dissolve the samples. X-ray diffraction data were collected from Bruker AXS KAPPA APEX2 CCD diffractometer equipped with Mo kα radiation (k = 0.71073 Å).

General procedure for the synthesis of chalcones

A mixture of 3′,4′-(methylenedioxy)acetophenone (1 mmol) and substituted aryl aldehydes (1 mmol) was stirred in methanol (5 mL) in presence of 10% KOH (base) at room temperature for 3-4 h, and the reaction progress was examined by TLC. When the reaction was completed (TLC), the mixture was poured into ice-cold water and further, the precipitate was filtered and dried. Thus, the resulting solid was recrystallized with EtOH to obtain desired benzodioxole chalcones **1a-l**.

General procedure for the synthesis of compounds 5a-l

A mixture of benzodioxole chalcones **1a-l** (1 mmol), isatin **2** (1 mmol) and sarcosine **3** (1 mmol) was stirred in methanol (10 mL) under reflux in an oil bath for 1.5-2 h. Upon completion of the reaction monitored by TLC, the reaction mixture was concentrated under reduced pressure to acquire the crude product. Further, the crude was purified by column chromatography on silica gel using hexane/ethyl acetate (3:2 v/v), yielding desired products **5a-l**.

General procedure for the synthesis of compounds 6a-l

A mixture of benzodioxole chalcones **1a-l** (1 mmol), isatin **2** (1 mmol) and L-proline **4** (1 mmol) was stirred in methanol (10 mL) under reflux in an oil bath for 1.5-2 h. After completion of the reaction (TLC), the reaction mixture was concentrated under reduced pressure to acquire the crude product. Further, the crude was purified by column chromatography on silica gel using hexane/ethyl acetate (3:2 v/v), yielding desired products **6a-l**.

Single Crystal X-ray diffraction

The spirooxindole pyrrolizidine derivative **6i** was taken into a glass vial and dissolved in ethanol. The solvent was evaporated gradually through needle holes at room temperature and thus, the white crystal of **6i** was obtained. Bruker AXS KAPPA APEX2 CCD diffractometer, equipped with graphite monochromatic Mo Kα radiation (0.71075 Å) at 293(2) K was employed for data collection. SAINT program was used for the data reduction and cell refinement. The structure was solved using SHELXS. Final refinement was made by Full matrix least square techniques along with anisotropic thermal data for non-hydrogen atoms. Compound **6i (**CCDC 2143927) contains the crystallographic data are given in the supplementary information.

Biological methods (*In vitro*)

Inhibition of α–amylase and α–glucosidase

The inhibition of α-amylase (EC 3.2.1.1, type-VI B porcine pancreatic α-amylase) was evaluated using soluble starch (1%) as a substrate, and the inhibition of yeast α-glucosidase (EC 3.2.1.20, type-1 α-glucosidase) was evaluated using pNPG as a substrate, according to a modified method reported.[1] As a positive control, acarbose was used. The inhibitory activity of α-amylase and α-glucosidase was measured in percent inhibition and calculated using the formula below.

$$\text{Inhibition (\%)} = (A_{\text{control}} - A_{\text{sample}})/ A_{\text{control}} \times 100$$

The IC_{50} values were calculated using the curve that plotted the percent inhibition of each sample against its concentration. Each experiment was carried out in triplicate with suitable blanks. The IC_{50} was defined as the concentration required to inhibit 50% of α-glucosidase activity under the specified test conditions.

Inhibition of AGE (Advanced glycation end products) formation

HSA (human serum albumin) glycation

The albumin glycation was performed with HSA/fructose system according to the study with minor modifications.[2] In brief, 4 mL reaction mixture was prepared and incubated at 37^{o}C for 21 days under sterile conditions comprising of diverse concentrations of synthesized compounds/ aminoguanidine (positive control) dissolved in DMSO of 1 mL, 1 mL of phosphate buffer (100 mM, pH 7.4 with 0.02% sodium azide), 1 mL fructose (300 mM) and 1 mL of HSA (10 mg/mL). Earlier to incubation the reaction mixture was subjected for filtration through membrane filters (0.22 μm) under aseptic conditions. After that, the samples free of microbial contamination were dialyzed against phosphate buffer (100 mM, pH 7.4) and were stored frozen conditions at -800^{o}C till further analysis. The control (synthesized compounds replaced with DMSO, a carrier solvent) was also prepared and kept under the same conditions. Triplicates of each experiment/ incubation were carried out.

Analysis of AGE formation

Formation of AGE (fluorescent products) from experimental/test molecules including control (fluorescent intensities) through albumin glycation, were measured using a spectral scanning multimode reader (Thermo Scientific, Varioskan Flash) at emission and excitation wavelengths of 440 and 370 nm (slit = 10 nm), respectively. The fluorescence values for the test and control were blanked against HAS. The modified fluorescence values (F) for the test compounds (F_T) and control (F_c) were used to calculate the percent inhibition of AGE formation by the below formula:

$$\text{Inhibition (\%)} = (F_c - F_T)/ F_c \times 100$$

Biological methods (*In silico*)

Molecular docking simulations

To understand the interaction of the series **5** and **6** compounds with α-glucosidase, α-amylase, and human serum albumin at the molecular level, the molecular docking of the series **5** and **6** compounds was completed according to the previous study.[3] The homology-built model of α-glucosidase with 72% identical and 84% similar sequence with *Saccharomyces cerevisiae*

isomaltase (PDB ID: 3AXH) was used.[4] In the case of α-amylase (PDB ID: 1DHK) and human serum albumin (PDB ID: 1AO6), crystallographic x-ray structures were obtained from the RCSB PDB database. Both protein and ligand structures were prepared for docking simulation using the AutoDock Tools 1.5.6.[5] During the preparation, protein structures were cleaned by removing water and heteroatoms. They were stabilized by the addition of polar hydrogens and merging non-polar hydrogen atoms. Further, energy minimization was carried out by adding Kollmann united and Gasteiger charges. Before beginning with the virtual screening, the AD4 atom type was assigned to all the atoms of both the protein structures. In the case of ligand preparation, the 3D optimized structures of the chemical compounds were obtained using ChemSketch 1.2. Kollmann united and Gasteiger charges were added during the energy minimization of the ligands. For *in silico* α-glucosidase and α-amylase inhibition, acarbose was used as a control, whereas, in the case of human serum albumin, aminoguanidine was used. The binding site prediction was done using CASTp 3.0 online server.[6] Both protein and ligand structures were docked using AutoDock Vina 1.1.2[7] to perform the virtual screening based on the total number of hydrogen bonding and non-bonding interactions and binding affinity formed during docking simulation. Docking results were visualized using BIOVIA Discovery Studios Visualizer 2021.

Molecular dynamics simulation

Based on the results obtained from molecular docking simulations performed, compound **6i** and respective control (acarbose/ aminoguanidine) docked with their respective protein structures were subjected to molecular dynamics simulation. For this, GROMACS 2021.3,[8] a command-line interface biomolecular software package was employed according to the previous study.[4] The protein-ligand complexes were approximated by the CHARMM36 force field, and ligand topology was obtained using the SwissParam server.[9] Initially, hydrogens were added to the systems using the pdb2gmx module of the GROMACS. This, followed by 5000 steps of vacuum minimization using the steepest descent algorithm. The protein-ligand complex was placed in a cubic box with a distance of 10Å, which was incorporated with solvent, and neutralized with appropriate Na^+ and Cl^- ions to maintain the 0.15 M of salt concentration. All the protein-ligand complexes including α-glucosidase-**6i** (44291 residues), α-glucosidase-acarbose (44308 residues), α-amylase-**6i** (54062 residues), α-amylase-acarbose (54079 residues), human serum albumin-aminoguanidine (51090 residues), and human serum albumin-**6i** (51121 residues) were

energy minimized using the steepest descent and conjugate gradient methods. Further, the leapfrog integrator algorithm was used for the brief NPT and NVT ensembles (1000 ps with the dt of 2 fs). Using the same algorithm, the systems were subjected to simulation for 100 ns with the dt of 2 fs, after equilibrating at 310 K temperature and 1 bar pressure. The energies and coordinates of the system were saved at every 10 ps. Furthermore, the GROMACS simulation package of root-mean-square deviation (RMSD) radius of gyration (Rg), root-mean square-fluctuation (RMSF) and solvent accessible surface area (SASA) was used to perform trajectory analysis. Using the XMGRACE software,[10] the findings from the trajectory analysis were shown as graphs.

Binding free energy calculations

Another application of molecular dynamics simulations and thermodynamics is to analyze the extent of ligand binding with protein is the calculation of a protein-ligand complex's binding free energy. In this study, Molecular Mechanics/ Poisson-Boltzmann Surface Area (MM-PBSA) approach the g_mmpbsa tool, which utilizes GROMACS trajectories as input, was employed to determine binding free energy for each ligand-protein combination.[11] The binding free energy is determined in the g_mmpbsa programme using three components namely, polar and apolar solvation energies and molecular mechanical energy. The molecular dynamics trajectories of the last 50 ns (both acarbose and aminoguanidine) and dt 1000 frames were used to calculate the binding free energy. The binding free energy is calculated using equation (I), whereas the free energy of each complex component is computed using equation (II). Further, the average potential energy in a vacuum is evaluated using equation (III), where E_{bonded} indicates angle, torsion angle and bond length, and $E_{non\text{-}bonded}$ represents electrostatic and van der Waals energies. The energy required to translocate the solute from vacuum to the solvent was calculated by using the equation (IV). The letters G_{polar} and $G_{non\text{-}polar}$, respectively, denote electrostatic and non-electrostatic support for the solvation free energy.

$$\Delta G_{binding} = G_{complex} - (G_{protein} + G_{ligand}) \text{ ---------- (I)}$$

$$G = (E_{MM})\text{-}TS + (G_{sol}) \text{ ---------- (II)}$$

$$E_{MM} = E_{bonded} + E_{non\text{-}bonded} \text{ ---------- (III)}$$

$G_{sol} = Gpolar + G_{non\text{-}polar}$ ---------- (IV)

Statistical analysis

All of the experiments were done in triplicate, and the findings were given as Mean ± SE. The IC_{50} values were calculated using Graph Pad PRISM software (version 4.03). ANOVA (one-way analysis of variance) and Duncan's Multiple Range Test with SPSS Software were used to compare the control and test groups statistically (version 21.0, Chicago, USA). If the 'p' values were 0.05 or less, the results were judged statistically significant.

Spectral characterization data of compounds 5a-l

(3*R*,3′*S*,4′*R*)-3′-(benzo[*d*][1,3]dioxole-5-carbonyl)-1′-methyl-4′-phenylspiro[indoline-3,2′-pyrrolidin]-2-one (5a)

Off-white solid. Yield: 80%. Mp. 155.157 °C. IR:ν_{max} (KBr, cm^{-1}) 3143 (NH), 2936 (O-CH_2-O), 1711 (C=O), 1675 (C=O). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ_H: 2.07 (N-CH_3) (s, 3H), 3.40 (H-5) (d, 2H, *J* = 6.5 Hz), 4.32-4.35 (H-3 & H-4) (m, 2H), 6.02 (O-CH_2-O) (d, 2H, *J* = 3.0 Hz), 6.56 (d, 1H, *J* = 7.5 Hz, -Ar-H), 6.80 (d, 1H, *J* = 8.0 Hz, -Ar-H), 6.84-6.86 (m, 2H, -Ar-H), 6.95 (d, 1H, *J* = 7.5 Hz, -Ar-H), 7.01-7.05 (m, 2H, -Ar-H), 7.22 (t, 1H, *J* = 7.3 Hz, -Ar-H), 7.32 (t, 2H, *J* = 7.5 Hz, -Ar-H), 7.40 (d, 2H, *J* = 7.0 Hz, -Ar-H), 10.59 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-*d*$_6$) δ_C: 34.95 (N-CH_3), 44.71 (C-4), 60.17 (C-5), 61.70 (C-3), 73.23 (C-2), 102.47 (O-CH_2-O), 106.92, 108.12, 109.59, 122.14, 124.16, 126.60, 127.17, 127.31, 128.11, 129.06, 129.48, 131.94, 141.80, 142.52, 148.02, 151.83, 179.52 (C=O), 195.24 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{26}H_{23}N_2O_4$ 427.1658; found 427.1658.

(3*R*,3′*S*,4′*R*)-3′-(benzo[*d*][1,3]dioxole-5-carbonyl)-4′-(4-fluorophenyl)-1′-methylspiro[indoline-3,2′-pyrrolidin]-2-one (5b)

Light beige solid. Yield: 94%. Mp. 192-194 °C. IR:ν_{max} (KBr, cm^{-1}) 3334 (NH), 2970 (O-CH_2-O), 1718 (C=O), 1690 (C=O). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ_H: 2.06 (N-CH_3) (s, 3H), 3.39 (H-5) (d, 2H, *J* = 3.0 Hz), 4.31 (H-3) (d, 1H, *J* = 9.0 Hz), 4.34-4.35 (H-4) (m, 1H), 6.01 (O-CH_2-O) (d, 1H, *J* = 3.5 Hz), 6.56 (d, 2H, *J* = 7.5 Hz, -Ar-H), 6.79 (d, 1H, *J* = 8.0 Hz, -Ar-H), 6.83-6.86 (m, 2H, -Ar-H), 6.93 (d, 1H, *J* = 7.0 Hz, -Ar-H), 7.01-7.05 (m, 2H, -Ar-H), 7.15 (t, 2H, *J* = 8.8 Hz, -Ar-H), 7.43-7.45 (m, 2H, -Ar-H), 10.58 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-*d*$_6$) δ_C: 34.91 (N-CH_3), 43.93 (C-4), 60.21 (C-5), 61.85 (C-3), 73.21 (C-2), 102.46 (O-CH_2-O), 106.96, 108.10, 109.61, 115.79 (d, J_{CF} = 80.0 Hz), 122.15, 124.19, 126.54, 127.23, 129.51, 129.95 (d, J_{CF} = 30.0 Hz), 131.91, 137.94, 137.92, 142.51, 147.99, 151.84, 160.56, 162.49, 179.48 (C=O), 195.21 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{26}H_{22}FN_2O_4$ 445.1564; found 445.1565.

(3*R*,3′*S*,4′*R*)-3′-(benzo[*d*][1,3]dioxole-5-carbonyl)-4′-(4-chlorophenyl)-1′-methylspiro[indoline-3,2′-pyrrolidin]-2-one (5c)

Pale yellow solid. Yield: 91%. Mp. 196-198 °C. IR:ν_{max} (KBr, cm^{-1}) 3248 (NH), 2916 (O-CH_2-O), 1720 (C=O), 1659 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 2.06 (N-CH_3) (s, 3H), 3.39 (H-5) (d, 2H, *J* = 8.0 Hz), 4.31 (H-3) (d, 1H, *J* = 9.5 Hz), 4.33-4.35 (H-4) (m, 1H), 6.02 (O-CH_2-O) (d, 2H, *J* = 4.0 Hz), 6.55 (d, 1H, *J* = 7.5 Hz, -Ar-H), 6.80 (d, 1H, *J* = 8.0 Hz, -Ar-H), 6.83-6.86 (m, 2H, -Ar-H), 6.93 (d, 1H, *J* = 7.5 Hz, -Ar-H), 7.01-7.04 (m, 2H, -Ar-H), 7.38 (d, 2H, *J* = 8.5 Hz, -Ar-H), 7.43 (d, 2H, *J* = 8.5 Hz, -Ar-H), 10.59 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 34.92 (N-CH_3), 44.03 (C-4), 60.02 (C-5), 61.73 (C-3), 73.19 (C-2), 102.47 (O-CH_2-O), 106.97, 108.10, 109.63, 122.15, 24.22, 126.53, 127.16, 129.02, 129.54, 130.04, 131.79, 131.85, 140.84, 142.52, 147.99, 151.85, 179.40 (C=O), 195.13 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{26}H_{22}ClN_2O_4$ 461.1268; found 461.1267.

(3*R*,3′*S*,4′*R*)-3′-(benzo[*d*][1,3]dioxole-5-carbonyl)-4′-(4-bromophenyl)-1′-methylspiro[indoline-3,2′-pyrrolidin]-2-one (**5d**)

White solid. Yield: 89%. Mp. 212-214 °C. IR:ν_{max} (KBr, cm^{-1}) 3257 (NH), 2825 (O-CH_2-O), 1726 (C=O), 1673 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 2.05 (N-CH_3) (s, 3H), 3.38 (H-5) (d, 2H, *J* = 7.5 Hz), 4.30 (H-3) (d, 1H, *J* = 7.0 Hz), 4.31-4.33 (H-4) (m, 1H), 6.0 (O-CH_2-O) (d, 2H, *J* = 3.5 Hz), 6.55 (d, 1H, *J* = 7.5 Hz, -Ar-H), 6.79 (d, 1H, *J* = 8.0 Hz, -Ar-H), 6.83-6.85 (m, 2H, -Ar-H), 6.93 (d, 1H, *J* = 7.0 Hz, -Ar-H), 7.00-7.04 (m, 2H, -Ar-H), 7.37 (d, 2H, *J* = 8.0 Hz, -Ar-H), 7.51 (d, 2H, *J* = 8.5 Hz, -Ar-H), 10.57 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 34.91 (N-CH_3), 44.09 (C-4), 59.96 (C-5), 61.71 (C-3), 73.21 (73.21), 102.47 (O-CH_2-O), 106.98, 108.10, 109.63, 120.26, 122.15, 124.22, 126.53, 127.15, 129.53, 130.42, 131.86, 131.94, 141.27, 142.51, 147.99, 151.85, 179.39 (C=O), 195.13 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{26}H_{22}BrN_2O_4$ 505.0763; found 505.0757.

(3*R*,3′*S*,4′*R*)-3′-(benzo[*d*][1,3]dioxole-5-carbonyl)-1′-methyl-4′-(*p*-tolyl)spiro[indoline-3,2′-pyrrolidin]-2-one (**5e**)

Off-white solid. Yield: 87%. Mp. 202-204 °C. IR:ν_{max} (KBr, cm^{-1}) 3361 (NH), 2943 (O-CH_2-O), 1710 (C=O), 1699 (C=O). 1H NMR (500 MHz, DMSO-d_6) δ_H: 2.06 (CH_3) (s, 3H), 2.24 (N-CH_3) (s, 3H), 3.36 (H-5) (d, 1H, *J* = 7.0 Hz), 3.40 (H-5) (t, 1H, *J* = 9.0 Hz), 4.28 (H-3) (d, 1H, *J* = 9.5 Hz), 4.30-4.34 (H-4) (m, 1H), 6.01 (O-CH_2-O) (d, 2H, *J* = 2.5 Hz), 6.56 (d, 1H, *J* = 7.5 Hz, -Ar-H), 6.80 (d, 1H, *J* = 8.0 Hz, -Ar-H), 6.83-6.86 (m, 2H, -Ar-H), 6.95 (d, 1H, *J* = 7.0 Hz, -Ar-H),

7.01-7.04 (m, 2H, -Ar-H), 6.95 (d, 1H, *J* = 7.0 Hz, -Ar-H), 7.01-7.04 (m, 2H, -Ar-H), 7.12 (d, 2H, *J* = 8.0 Hz, -Ar-H), 7.28 (d, 2H, *J* = 8.0 Hz, -Ar-H), 10.55 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 21.04 (CH_3), 34.95 (N-CH_3), 44.42 (C-4), 60.19 (C-5), 61.83 (C-3), 73.24 (C-2), 102.46 (O-CH_2-O), 106.90, 108.11, 109.56, 122.11, 124.11, 126.63, 127.37, 127.96, 129.44, 129.60, 132.02, 136.21, 138.70, 142.51, 148.02, 151.81, 179.55 (C=O), 195.27 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{27}H_{25}N_2O_4$ 441.1814; found 441.1821.

(3*R*,3′*S*,4′*R*)-3′-(benzo[*d*][1,3]dioxole-5-carbonyl)-4′-(4-methoxyphenyl)-1′-methylspiro[indoline-3,2′-pyrrolidin]-2-one (5f)

Beige solid. Yield: 83%. Mp. 130-106 °C. IR:ν_{max} (KBr, cm^{-1}) 3205 (NH), 2963 (O-CH_2-O), 1713 (C=O). 1676 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 3.06 (N-CH_3) (s, 3H), 3.40 (H-5) (d, 2H, *J* = 8.0 Hz), 3.70 (O-CH_3) (s, 3H), 4.27-4.31 (H-3 & H-4) (m, 2H), 6.01 (O-CH_2-O) (d, 2H, *J* = 2.5 Hz), 6.56 (d, 1H, *J* = 7.5 Hz, -Ar-H), 6.80 (d, 1H, *J* = 8.5 Hz, -Ar-H), 6.83-6.85 (m, 2H, -Ar-H), 6.88 (d, 2H, *J* = 8.5 Hz, -Ar-H), 6.94 (d, 1H, *J* = 7.0 Hz, -Ar-H), 7.00-7.04 (m, 2H, -Ar-H), 7.31 (d, 2H, *J* = 8.5 Hz, -Ar-H), 10.56 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 34.95 (N-CH_3), 44.05 (C-4), 55.47 (O-CH_3), 60.25 (C-5), 61.95 (C-3), 73.22 (C-2), 102.46 (O-CH_2-O), 106.90, 108.11, 109.56, 114.48, 122.11, 124.12, 126.61, 127.39, 129.07, 129.44, 132.02, 133.56, 142.51, 148.02, 151.81, 158.53, 179.58 (C=O), 195.32 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{27}H_{25}N_2O_5$ 457.1763; found 457.1763.

(3*R*,3′*S*,4′*R*)-3′-(benzo[*d*][1,3]dioxole-5-carbonyl)-4′-(4-ethylphenyl)-1′-methylspiro[indoline-3,2′-pyrrolidin]-2-one (5g)

Pale yellow solid. Yield: 85%. Mp. 199-202 °C. IR:ν_{max} (KBr, cm^{-1}) 3258 (NH), 2977 (O-CH_2-O), 1712 (C=O), 1684 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.13 (CH_3) (t, 3H, *J* = 7.8 Hz), 2.06 (N-CH_3) (s, 3H), 2.54 (H-5) (d, 2H, *J* = 7.5 Hz), 3.40 (H-3 & H-4) (t, 2H, *J* = 8.3 Hz), 4.29-4.34 (CH_2) (m 2H), 6.01 (O-CH_2-O) (d, 2H, *J* = 2.5 Hz), 6.55 (d, 1H, *J* = 8.0 Hz, -Ar-H), 6.80 (d, 1H, *J* = 8.5 Hz, -Ar-H), 6.83-6.86 (m, 1H, -Ar-H), 6.94 (d, 1H, *J* = 7.5 Hz, -Ar-H), 7.01-7.05 (m, 2H, -Ar-H), 7.15 (d, 2H, *J* = 8.0 Hz, -Ar-H), 7.30 (d, 2H, *J* = 8.0 Hz, -Ar-H), 10.56 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 16.03 (CH_3), 28.21 (CH_2), 34.95 (N-CH_3), 44.41 (C-4), 60.18 (C-5), 61.77 (C-3), 73.21 (C-2), 102.46 (O-CH_2-O), 106.91, 108.11, 109.57, 122.12, 124.14, 126.61, 127.37, 128.02, 128.42, 129.45, 131.97, 138.93, 142.50, 142.60, 148.02,

151.82, 179.56 (C=O), 195.27 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{28}H_{27}N_2O_4$ 455.1971; found 455.1985.

(3*R*,3′*S*,4′*R*)-3′-(benzo[*d*][1,3]dioxole-5-carbonyl)-1′-methyl-4′-(4-(methylthio)phenyl)spiro[indoline-3,2′-pyrrolidin]-2-one (5h)

Yellow solid. Yield: 82%. Mp. 102-104 °C. IR:ν_{max} (KBr, cm^{-1}) 3267 (NH), 2976 (O-CH_2-O), 1709 (C=O), 1672 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 2.06 (N-CH_3) (s, 3H), 2.43 (S-CH_3) (s, 3H), 3.38-3.41 (H-5) (m, 2H), 4.29-4.31 (H-3 & H-4) (m, 2H), 6.01 (O-CH_2-O) (d, 2H, *J* = 3.0 Hz), 6.55 (d, 1H, *J* = 7.5 Hz, -Ar-H), 6.80 (d, 1H, *J* = 8.0 Hz, -Ar-H), 6.83-6.86 (m, 2H, -Ar-H), 6.94 (d, 1H, *J* = 7.0 Hz, -Ar-H), 7.01-7.04 (m, 2H, -Ar-H), 7.22 (d, 2H, *J* = 8.5 Hz, -Ar-H), 7.34 (d, 2H, *J* = 8.0 Hz, -Ar-H), 10.57 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 15.32 (S-CH_3), 34.94 (N-CH_3), 44.26 (C-4), 60.04 (C-5), 61.78 (C-3), 73.21 (C-2), 102.47 (O-CH_2-O), 106.92, 108.12, 109.59, 122.14, 124.16, 126.59, 126.86, 127.28, 128.73, 129.49, 131.93, 136.74, 138.44, 142.50, 148.01, 151.83, 179.49 (C=O), 195.22 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{27}H_{25}N_2O_4S$ 473.1535; found 473.1534.

(3*R*,3′*S*,4′*R*)-3′-(benzo[*d*][1,3]dioxole-5-carbonyl)-4′-(3-fluorophenyl)-1′-methylspiro[indoline-3,2′-pyrrolidin]-2-one (5i)

Pale yellow solid. Yield: 90%. Mp. 164-166 °C. IR:ν_{max} (KBr, cm^{-1}) 3186 (NH), 2969 (O-CH_2-O), 1714 (C=O), 1672 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 2.05 (N-CH_3) (s, 3H), 3.40 (H-5) (d, 2H, *J* = 7.5 Hz), 4.33-4.38 (H-3 & H-4) (m, 2H), 6.01 (O-CH_2-O) (d, 2H, *J* = 3.5 Hz, -Ar-H), 6.56 (d, 1H, *J* = 8.0 Hz, -Ar-H), 6.79 (d, 1H, *J* = 8.5 Hz, -Ar-H), 6.82-6.85 (m, 2H, -Ar-H), 6.93 (d, 1H, *J* = 7.0 Hz, -Ar-H), 7.01-7.06 (m, 3H, -Ar-H), 7.23-7.25 (m, 2H, -Ar-H), 7.34-7.37 (m, 1H, -Ar-H), 10.59 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 34.90 (N-CH_3), 44.29 (C-4), 60.01 (C-5), 61.56 (C-3), 73.21 (C-2), 102.46 (O-CH_2-O), 107.01, 108.10, 109.64, 114.03 (d, J_{CF} = 20.0 Hz), 114.90, 122.14, 124.27, 126.52, 127.10, 129.54, 130.96 (d, J_{CF} = 7.5 Hz), 131.84, 142.53, 144.94, 147.98, 151.84, 161.78, 163.71, 179.39 (C=O), 195.16 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{26}H_{22}FN_2O_4$ 445.1564; found 445.1563.

(3*R*,3′*S*,4′*R*)-3′-(benzo[*d*][1,3]dioxole-5-carbonyl)-4′-(3-chlorophenyl)-1′-methylspiro[indoline-3,2′-pyrrolidin]-2-one (**5j**)

Off-white solid. Yield: 89%. Mp. 168-171 °C. IR:ν_{max} (KBr, cm^{-1}) 3240 (NH), 2919 (O-CH_2-O), 1722 (C=O), 1689 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 2.06 (N-CH_3) (s, 3H), 3.40 (H-5) (d, 2H, J = 7.5 Hz), 4.33 (H-3) (d, 1H, J = 9.5 Hz), 4.35-4.37 (H-4) (m, 1H), 6.02 (O-CH_2-O) (d, 2H, J = 4.0 Hz), 6.56 (d, 1H, J = 7.5 Hz, -Ar-H), 6.79 (d, 1H, J = 8.0 Hz, -Ar-H), 6.83-6.85 (m, 2H, -Ar-H), 6.93 (d, 1H, J = 7.5 Hz, -Ar-H), 7.01-7.06 (m, 2H, -Ar-H), 7.28-7.30 (m, 1H, -Ar-H), 7.34-7.39 (m, 2H, -Ar-H), 7.47 (s, 1H, -Ar-H), 10.60 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 34.90 (N-CH_3), 44.24 (C-4), 59.99 (C-5), 61.64 (C-3), 73.21 (C-2), 102.46 (O-CH_2-O), 107.02, 108.09, 109.66, 122.15, 124.29, 126.49, 126.92, 127.08, 127.24, 128.08, 129.55, 130.94, 131.82, 133.65, 142.53, 144.54, 147.98, 151.85, 179.36 (C=O), 195.12 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{26}H_{22}ClN_2O_4$ 461.1268; found 461.1265.

(3*R*,3′*S*,4′*R*)-3′-(benzo[*d*][1,3]dioxole-5-carbonyl)-4′-(3-bromophenyl)-1′-methylspiro[indoline-3,2′-pyrrolidin]-2-one (**5k**)

Light yellow solid. Yield: 85%. Mp. 186-188 °C. IR:ν_{max} (KBr, cm^{-1}) 3244 (NH), 2973 (O-CH_2-O), 1716 (C=O), 1683 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 2.05 (N-CH_3) (s, 3H), 3.39 (H-5) (d, 2H, J = 7.5 Hz), 4.32 (H-3) (d, 1H, J = 9.0 Hz), 4.34-4.36 (m, 1H), 6.02 (O-CH_2-O) (d, 2H. J = 4.0 Hz), 6.56 (d, 1H, J = 7.5 Hz, -Ar-H), 6.79 (d, 1H, J = 8.5 Hz, -Ar-H), 6.82-6.85 (m, 2H, -Ar-H), 6.92 (d, 1H, J = 7.0 Hz, -Ar-H), 7.00-7.05 (m, 2H, -Ar-H), 7.29 (t, 1H, J = 7.8 Hz, -Ar-H), 7.42-7.43 (m, 2H, -Ar-H), 7.60 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 34.90 (N-CH_3), 44.22 (C-4), 60.00 (C-5), 61.67 (C-3), 73.22 (C-2), 102.46 (O-CH_2-O), 107.01, 108.10, 109.66, 122.15, 122.32, 124.39, 126.49, 127.08, 127.30, 129.56, 130.16, 130.96, 131.27, 131.82, 142.53, 144.82, 147.98, 151.85, 179.35 (C=O), 195.11 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{26}H_{22}BrN_2O_4$ 505.0763; found 505.0761.

(3*R*,3′*S*,4′*R*)-3′-(benzo[*d*][1,3]dioxole-5-carbonyl)-4′-(2,4-dichlorophenyl)-1′-methylspiro[indoline-3,2′-pyrrolidin]-2-one (**5l**)

Yellow solid. Yield: 79%. Mp. 201-203 °C. IR:ν_{max} (KBr, cm^{-1}) 3238 (NH), 2967 (O-CH_2-O), 1714 (C=O), 1682 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 2.03 (N-CH_3) (s, 3H), 3.22 (H-5) (t, 1H, J = 8.8 Hz), 3.41 (H-5) (t, 1H, J = 7.8 Hz), 4.49 (H-3) (d, 1H, J = 8.5 Hz), 4.78-4.83 (H-4) (m, 1H), 6.02 (O-CH_2-O) (d, 2H, J = 3.5 Hz), 6.57 (d, 1H, J = 7.5 Hz, -Ar-H), 6.79 (d, 1H, J = 8.5 Hz, -Ar-H), 6.83-6.86 (m, 2H, -Ar-H), 6.94 (d, 1H, J = 7.0 Hz, -Ar-H), 7.04-7.08 (m, 2H, -

Ar-H), 7.47 (dd, 1H, *J* = 2.0 & 8.5 Hz, -Ar-H), 7.56 (d, 1H, *J* = 2.0 Hz, -Ar-H), 7.86 (d, 1H, *J* = 8.5 Hz, -Ar-H), 10.60 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 34.86 (N-CH_3), 44.57 (C-4), 59.93 (C-5), 60.55 (C-3), 73.15 (C-2), 102.44 (O-CH_2-O), 107.13, 108.07, 109.74, 122.12, 124.32, 126.63, 126.68, 128.41, 129.14, 129.59, 130.66, 131.77, 132.43, 134.68, 138.66, 142.52, 147.93, 151.80, 179.17 (C=O), 194.80 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{26}H_{21}Cl_2N_2O_4$ 495.0878; found 495.0876.

Spectral characterization data of compounds 6a-l

(1′*R*,2′*S*,3*R*)-2′-(benzo[*d*][1,3]dioxole-5-carbonyl)-1′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**6a**)

White solid. Yield: 81%. Mp. 198-200 ^{o}C. IR:ν_{max} (KBr, cm^{-1}) 3197 (NH), 2961 (O-CH_2-O), 1717 (C=O), 1653 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.70-1.74 (H-6) (m, 2H), 1.85-1.89 (H-7) (m, 2H), 2.33-2.37 (H-8) (m, 1H), 2.59 (H-8) (dd, 1H, *J* = 7.3 & 16.3 Hz), 3.86 (H-4) (t, 1H, *J* = 10.5 Hz), 3.90-3.94 (H-5) (m, 1H), 4.77 (H-3) (d, 1H, *J* = 11.0 Hz), 6.04 (O-CH_2-O) (d, 2H, *J* = 3.5 Hz), 6.59 (d, 1H, *J* = 7.5 Hz, -Ar-H), 6.83-6.84 (m, 2H, -Ar-H), 6.93 (t, 1H, *J* = 7.5 Hz, -Ar-H), 7.09-7.12 (m, 2H, -Ar-H), 7.21 (dd, 2H, *J* = 7.8 & 15.8 Hz, -Ar-H), 7.31 (t, 2H, *J* = 7.5 Hz, -Ar-H), 7.44 (d, 2H, *J* = 7.0 Hz, -Ar-H), 10.30 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 27.18 (C-7), 30.04 (C-6), 48.03 (C-4), 52.96 (C-8), 63.06 (C-3), 71.88 (C-5), 73.09 (C-2), 102.48 (O-CH_2-O), 107.27, 108.20, 110.04, 121.52, 124.55, 125.34, 127.14, 127.92, 128.17, 129.08, 129.67, 131.92, 140.54, 142.41, 147.99, 151.92, 180.02 (C=O), 194.81 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{28}H_{25}N_2O_4$ 453.1814; found 453.1821.

(1′*R*,2′*S*,3*R*)-2′-(benzo[*d*][1,3]dioxole-5-carbonyl)-1′-(4-fluorophenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (6b)

Beige solid. Yield: 95%. Mp. 156-158 ^{o}C. IR:ν_{max} (KBr, cm^{-1}) 3168 (NH), 2956 (O-CH_2-O), 1726 (C=O), 1669 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.70-1.72 (H-6) (m, 2H), 1.84-1.89 (H-7) (m, 2H), 2.32-2.36 (H-8) (m, 1H), 2.57 (H-8) (d, 1H, *J* = 9.0 Hz), 3.85-3.94 (H-4 & H-5) (m, 2H), 4.73 (H-3) (d, 1H, *J* = 11.0 Hz), 6.04 (O-CH_2-O) (d, 2H, *J* = 2.5 Hz), 6.59 (d, 1H, *J* = 8.0 Hz, -Ar-H), 6.83 (d, 2H, *J* = 8.5 Hz, -Ar-H), 6.92 (t, 1H, *J* = 7.5 Hz, -Ar-H), 7.10-7.12 (m, 2H, -Ar-H), 7.14 (d, 2H, *J* = 9.0 Hz, -Ar-H), 7.23 (d, 1H, *J* = 7.5 Hz, -Ar-H), 7.49 (dd, 2H, *J* = 5.8 & 8.3 Hz, -Ar-H), 10.33 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 27.14 (C-7), 29.87 (C-6), 48.01 (C-4), 52.09 (C-8), 63.14 (C-3), 71.78 (C-5), 73.02 (C-2), 102.46 (O-CH2-O), 107.28, 108.16, 110.02, 115.77 (d, J_{CF} = 21.25 Hz), 121.49, 124.56, 125.23, 127.85, 129.68, 129.99 (d, J_{CF} = 7.5 Hz), 131.83, 136.59, 142.37, 147.93, 151.90, 160.59, 162.51, 179.91 (C=O), 194.78 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{28}H_{24}FN_2O_4$ 471.1720; found 471.1722.

(1′*R*,2′*S*,3*R*)-2′-(benzo[*d*][1,3]dioxole-5-carbonyl)-1′-(4-chlorophenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**6c**)

Light yellow solid. Yield: 93%. Mp. 121-123 °C. IR:ν_{max} (KBr, cm^{-1}) 3220 (NH), 2968 (O-CH_2-O), 1721 (C=O), 1652 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.70-1.73 (H-6) (m, 2H), 1.84-1.89 (H-7) (m, 2H), 2.33-2.36 (H-8) (m, 1H), 2.58 (H-8) (dd, 1H, *J* = 7.5 & 16.0 Hz), 3.86 (H-4) (d, 1H, *J* = 10.0 Hz), 3.89-3.91 (H-5) (m, 1H), 4.74 (H-3) (d, 1H, *J* = 10.5 Hz), 6.04 (O-CH_2-O) (d, 2H, *J* = 2.5 Hz), 6.59 (d, 1H, *J* = 7.5 Hz, -Ar-H), 6.82-6.84 (m, 2H, -Ar-H), 6.92 (t, 1H, *J* = 7.5 Hz, -Ar-H), 7.09-7.12 (m, 2H, -Ar-H), 7.22 (d, 1H, *J* = 7.0 Hz, -Ar-H), 7.36 (d, 2H, *J* = 8.5 Hz, -Ar-H), 7.48 (d, 2H, *J* = 8.5 Hz, -Ar-H), 10.30 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 27.11 (C-7), 29.81 (C-6), 48.00 (C-4), 52.21 (C-8), 63.11 (C-3), 71.69 (C-5), 73.00 (C-2), 102.45 (O-CH_2-O), 107.30, 108.15, 110.03, 121.49, 124.56, 125.20, 127.83, 128.99, 129.70, 130.07, 131.78, 131.81, 139.50, 142.39, 147.93, 151.90, 179.86 (C=O), 194.76 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{28}H_{24}ClN_2O_4$ 487.1425; found 487.1431.

(1′*R*,2′*S*,3*R*)-2′-(benzo[*d*][1,3]dioxole-5-carbonyl)-1′-(4-bromophenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (6d)

Brown solid. Yield: 90%. Mp. 107-109 °C. IR:ν_{max} (KBr, cm^{-1}) 3205 (NH), 2955 (O-CH_2-O), 1715 (C=O), 1668 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.68-1.76 (H-6) (m, 2H), 1.83-1.89 (H-7) (m, 2H), 2.32-2.36 (H-8) (m, 1H), 2.57 (H-8) (dd, 1H, *J* = 7.5 & 16.0 Hz), 3.83-3.92 (H-4 & H-5) (m, 2H), 4.74 (H-3) (d, 1H, *J* = 11.0 Hz), 6.04 (O-CH_2-O) (d, 2H, *J* = 2.5 Hz), 6.59 (d, 1H, *J* = 8.0 Hz, -Ar-H), 6.82-6.84 (m, 2H, -Ar-H), 6.92 (t, 1H, *J* = 7.3 Hz, -Ar-H), 7.09-7.12 (m, 2H, -Ar-H), 7.22 (d, 1H, *J* = 7.5 Hz, -Ar-H), 7.42 (d, 2H, *J* = 8.5 Hz, -Ar-H), 7.50 (d, 2H, *J* = 8.5 Hz, -Ar-H), 10.31 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 27.12 (C-7), 29.82 (C-6), 48.02 (C-4), 52.27 (C-8), 63.04 (C-3), 71.68 (C-5), 73.02 (C-2), 102.46 (O-CH_2-O), 107.29, 108.16, 110.04, 120.26, 121.51, 124.58, 125.17, 127.83, 129.71, 130.48, 131.78, 131.91, 139.92, 142.36, 147.92, 151.91, 179.87 (C=O), 194.75 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{28}H_{24}BrN_2O_4$ 531.0919; found 531.0924.

(1′*R*,2′*S*,3*R*)-2′-(benzo[*d*][1,3]dioxole-5-carbonyl)-1′-(*p*-tolyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (6e)

Beige solid. Yield: 86%. Mp. 127-129 °C. IR:ν_{max} (KBr, cm^{-1}) 3248 (NH), 2957 (O-CH_2-O), 1717 (C=O), 1665 (C=O). ^{1}H NMR (DMSO-d_6) δ_H: 1.74-1.77 (H-6) (m, 2H), 1.87-1.93 (H-7) (m, 2H), 2.27 (CH_3) (s, 3H), 2.36-2.40 (H-8) (m, 1H), 2.62 (H-8) (dd, 1H, *J* = 7.5 & 16.0 Hz),

3.86 (H-4) (t, 1H, *J* = 10.5 Hz), 3.92-3.96 (H-5) (m, 1H), 4.78 (H-3) (d, 1H, *J* = 11.5 Hz), 6.08 (O-CH_2-O) (d, 2H, *J* = 2.0 Hz), 6.63 (d, 1H, *J* = 7.5 Hz, -Ar-H), 6.88 (t, 2H, *J* = 1.5 Hz, -Ar-H), 6.96 (t, 1H, *J* = 7.3 Hz, -Ar-H), 7.15 (d, 4H, *J* = 8.0 Hz, -Ar-H), 7.26 (d, 1H, *J* = 7.5 Hz, -Ar-H), 7.35 (d, 2H, *J* = 8.0 Hz, -Ar-H), 10.34 (NH) (brs, 1H). ^{13}C NMR (DMSO-d_6) δ_C: 21.03 (CH_3), 27.15 (C-7), 30.00 (C-6), 48.01 (C-4), 52.65 (C-8), 63.03 (C-3), 71.81 (C-5), 73.05 (C-2), 102.45 (O-CH_2-O), 107.22, 108.17, 110.00, 121.47, 124.50, 125.34, 127.91, 127.98, 129.62, 131.93, 136.22, 137.39, 142.37, 147.97, 151.87, 180.02 (C=O), 194.76 (C=O). HR-S (ESI) m/z: $[M+H]^+$ calcd. for $C_{29}H_{27}N_2O_4$ 467.1971; found 467.1973.

(1′*R*,2′*S*,3*R*)-2′-(benzo[*d*][1,3]dioxole-5-carbonyl)-1′-(4-methoxyphenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (6f)

White solid. Yield: 82%. Mp. 113-115 ^oC. IR:ν_{max} (KBr, cm^{-1}) 3236 (NH), 2952 (O-CH_2-O), 1715 (C=O), 1667 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.71-1.73 (H-6) (m, 2H), 1.82-1.89 (H-7) (m, 2H), 2.32-2.36 (H-8) (m, 1H), 2.57 (H-8) (dd, 1H, *J* = 8.5 & 15.0 Hz), 3.70 (O-CH_3) (s, 3H), 3.80 (H-4) (t, 1H, *J* = 10.5 Hz), 3.87-3.91 (H-5) (m, 1H), 4.71 (H-3) (d, 1H, *J* = 11.0 Hz), 6.04 (O-CH_2-O) (d, 2H, *J* = 2.0 Hz), 6.59 (d, 1H, *J* = 7.5 Hz, -Ar-H), 6.84 (d, 2H, *J* = 8.0 Hz, -Ar-H), 6.87 (d, 2H, *J* = 9.0 Hz, -Ar-H), 6.92 (t, 1H. *J* = 7.5 Hz, -Ar-H), 7.09-7.12 (m, 2H, -Ar-H), 7.22 (d, 1H, *J* = 7.5 Hz, -Ar-H), 7.34 (d, 2H, *J* = 8.5 Hz, -Ar-H), 10.30 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 27.17 (C-7), 30.00 (C-6), 48.02 (C-4), 52.24 (C-8), 55.43 (O-CH_3), 63.09 (C-3), 71.78 (C-5), 73.06 (C-2), 102.46 (O-CH_2-O), 107.22, 108.18, 109.99, 114.48, 121.47, 124.52, 125.33, 127.91, 129.09, 129.61, 131.91, 132.22, 142.33, 147.97, 151.88, 158.53, 180.01 (C=O), 194.76 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{29}H_{27}N_2O_5$ 483.1920; found 483.1917.

(1′*R*,2′*S*,3*R*)-2′-benzo[*d*][1,3]dioxole-5-carbonyl)-1′-(4-ethylphenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (6g)

White solid. Yield: 84%. Mp. 168- 170 ^oC. IR:ν_{max} (KBr, cm^{-1}) 3237 (NH), 2971 (O-CH_2-O), 1732 (C=O), 1664 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.71-1.72 (H-6) (m, 2H), 1.84-1.88 (H-7) (m, 2H), 2.33-2.36 (H-8) (m, 1H), 2.43 (CH_3) (s, 3H), 2.55-2.60 (CH_2) (m, 2H), 3.43-3.48 (H-8) (m, 1H), 3.82 (H-4) (t, 1H, *J* = 10.5 Hz), 3.88-3.92 (H-5) (m, 1H), 4.73 (H-3) (d, 1H, *J* = 11.5 Hz), 6.04 (O-CH_2-O) (d, 2H, *J* = 3.0 Hz), 6.59 (d, 1H, *J* = 7.5 Hz, -Ar-H), 6.84 (d, 2H, *J*

= 8.0 Hz, -Ar-H), 6.92 (t, 1H, *J* = 7.5 Hz, -Ar-H), 7.09-7.12 (m, 2H, -Ar-H), 7.20-7.23 (m, 3H, -Ar-H), 7.38 (d, 2H, *J* = 8.5 Hz, -Ar-H), 10.30 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 15.27 (CH_3), 19.02 (CH_2), 27.14 (C-7), 29.93 (C-6), 48.01 (C-4), 52.47 (C-8), 63.05 (C-3), 71.70 (C-5), 73.04 (C-2), 102.46 (O-CH_2-O), 107.25, 108.17, 110.01, 121.49, 124.53, 125.28, 126.84, 127.88, 128.77, 129.65, 131.88, 136.70, 137.14, 142.37, 147.96, 151.89, 179.95 (C=O), 194.75 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{30}H_{29}N_2O_4$ 481.2127; found 481.2617.

(1′*R*,2′*S*,3*R*)-2′-(benzo[*d*][1,3]dioxole-5-carbonyl)-1′-(4-(methylthio)phenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (6h)

White solid. Yield: 80%. Mp. 111-113 ^{o}C. IR:ν_{max} (KBr, cm^{-1}) 3234 (NH), 2938 (O-CH_2-O), 1733 (C=O), 1663 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.70-1.73 (H-6) (m, 2H), 1.84-1.89 (H-7) (m, 2H), 2.32-2.36 (H-8) (m, 1H), 2.43 (S-CH_3) (s, 1H), 2.57 (H-8) (dd, 1H, *J* = 8.3 & 15.3 Hz), 3.82 (H-4) (t, 1H, *J* = 10.5 Hz), 3.87-3.92 (H-5) (m, 1H), 4.73 (H-3) (d, 1H, *J* = 11.0 Hz), 6.04 (O-CH_2-O) (d, 2H, *J* = 2.0 Hz), 6.59 (d, 1H, *J* = 7.5 Hz, -Ar-H), 6.83-6.84 (m, 2H, -Ar-H), 6.92 (t, 1H, *J* = 7.5 Hz, -Ar-H), 7.09-7.12 (m, 2H, -Ar-H), 7.21 (t, 3H, *J* = 7.8 Hz, -Ar-H), 7.38 (d, 2H, *J* = 8.0 Hz, -Ar-H), 10.31 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 15.24 (S-CH_3), 27.15 (C-7), 29.94 (C-6), 48.02 (C-4), 52.47 (C-8), 63.02 (C-3), 71.71 (C-5), 73.07 (C-2), 102.46 (O-CH_2-O), 107.24, 108.18, 110.03, 121.51, 124.55, 125.56, 126.80, 127.88, 128.78, 129.66, 131.85, 136.70, 137.10, 142.33, 147.96, 151.90, 179.98 (C=O), 194.74 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{29}H_{27}N_2O_4S$ 499.1692; found 499.1689.

(1′*R*,2′*S*,3*R*)-2′-(benzo[*d*][1,3]dioxole-5-carbonyl)-1′-(3-fluorophenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (6i)

White solid. Yield: 92%. Mp. 129-132 ^{o}C. IR:ν_{max} (KBr, cm^{-1}) 3183 (NH), 2957 (O-CH_2-O), 1720 (C=O), 1667 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.71-1.76 (H-6) (m, 2H), 1.85-1.89 (H-7) (m, 2H), 2.34-2.36 (H-8) (m, 1H), 2.57-2.59 (H-8) (m, 1H), 3.89 (H-4) (d, 1H, *J* = 10.0 Hz), 3.92-3.94 (H-5) (m, 1H), 4.77 (H-3) (d, 1H, *J* = 11.0 Hz), 6.04 (O-CH_2-O) (d, 2H, *J* = 2.5 Hz), 6.59 (d, 1H, *J* = 8.0 Hz, -Ar-H), 6.82-6.86 (m, 2H, -Ar-H), 6.92 (t, 1H, *J* = 7.5 Hz, -Ar-H), 7.01-7.05 (m, 1H, -Ar-H), 7.09-7.12 (m, 2H, -Ar-H), 7.22 (d, 1H, *J* = 7.5 Hz, -Ar-H), 7.30 (d, 2H, *J* = 7.5 Hz, -Ar-H), 7.35 (dd, 1H, *J* = 7.8 & 14.3 Hz, -Ar-H), 10.30 (NH) (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 27.08 (C-7), 29.79 (C-6), 48.01 (C-4), 52.52 (C-8), 62.99 (C-3),

71.64 (C-5), 73.03 (C-2), 102.44 (O-CH_2-O), 107.35, 108.15, 110.02, 114.20 (d, J_{CF} = 20.0 Hz), 115.06 (d, J_{CF} = 21.3 Hz), 121.48, 124.21, 124.61, 125.20, 127.82, 129.70, 130.91 (d, J_{CF} = 8.8 Hz), 131.81, 142.41, 143.55 (d, J_{CF} = 7.5 Hz), 147.92, 151.89, 161.78, 163.72, 179.82 (C=O), 194.82 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{28}H_{24}FN_2O_4$ 471.1720; found 471.1721.

(1′*R*,2′*S*,3*R*)-2′-(benzo[*d*][1,3]dioxole-5-carbonyl)-1′-(3-chlorophenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**6j**)

Pale yellow solid. Yield: 90%. Mp. 212-214 °C. IR:ν_{max} (KBr, cm^{-1}) 3087 (NH), 2955 (O-CH_2-O), 1719 (C=O), 1684 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.71-1.76 (H-6) (m, 2H), 1.84-1.89 (H-7) (m, 2H), 2.33-2.37 (H-8) (m, 1H), 2.55-2.58 (H-8) (m, 1H), 3.88 (H-4) (d, 1H, *J* = 10.0 Hz), 3.91-3.93 (H-5) (m, 1H), 4.76 (H-3) (d, 1H, *J* = 10.5 Hz), 6.04 (O-CH_2-O) (d, 2H, *J* = 3.0 Hz), 6.59 (d, 1H, *J* = 7.5 Hz, -Ar-H), 6.81-6.86 (m, 2H, -Ar-H), 6.92 (t, 1H, *J* = 7.5 Hz, -Ar-H), 7.09-7.12 (m, 1H, -Ar-H), 7.23 (d, 1H, *J* = 7.5 Hz, -Ar-H), 7.26-7.28 (m, 1H, -Ar-H), 7.35 (t, 1H, *J* = 8.0 Hz, -Ar-H), 7.44 (d, 1H, *J* = 7.5 Hz, -Ar-H), 7.53 (s, 1H, -Ar-H), 10.31 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 27.07 (C-7), 29.73 (C-6), 48.02 (C-4), 52.42 (C-8), 63.08 (C-3), 71.66 (C-5), 73.02 (C-2), 102.44 (O-CH_2-O), 107.36, 108.14, 110.03, 121.49, 124.61, 125.18, 126.75, 127.20, 127.81, 128.38, 129.71, 130.90, 131.78, 133.63, 142.40, 143.16, 147.91, 151.89, 179.82 (C=O), 194.81 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{28}H_{24}ClN_2O_4$ 487.1425; found 487.1428.

(1′*R*,2′*S*,3*R*)-2′-(benzo[*d*][1,3]dioxole-5-carbonyl)-1′-(3-bromophenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**6k**)

Pale yellow solid. Yield: 88%. Mp. 205-207 °C. IR:ν_{max} (KBr, cm^{-1}) 3291 (NH), 2956 (O-CH_2-O), 1722 (C=O), 1684 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.69-1.75 (H-6) (m, 2H), 1.84-1.88 (H-7) (m, 2H), 2.33-2.37 (H-8) (m, 1H), 2.55-2.59 (H-8) (m, 1H), 3.87 (H-4) (d, 1H, *J* = 10.0 Hz), 3.90-3.93 (H-5) (m, 1H), 4.75 (H-3) (d, 1H, *J* = 10.5 Hz), 6.04 (O-CH_2-O) (d, 2H, *J* = 2.5 Hz), 6.58 (d, 1H, *J* = 7.5 Hz, -Ar-H), 6.82-6.85 (m, 2H, -Ar-H), 6.92 (t, 1H, *J* = 7.5 Hz, -Ar-H), 7.09-7.12 (m, 2H, -Ar-H), 7.23 (d, 1H, *J* = 7.5 Hz, -Ar-H), 7.28 (t, 1H, *J* = 7.8 Hz, -Ar-H), 7.41 (d, 1H, *J* = 8.0 Hz, -Ar-H), 7.49 (d, 1H, *J* = 7.5 Hz, Ar-H), 7.67 (s, 1H, -Ar-H), 10.30 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 27.06 (C-7), 29.72 (C-6), 48.02 (C-4), 52.38 (C-8), 63.11 (C-3), 71.69 (C-5), 73.02 (C-2), 102.44 (O-CH_2-O), 107.36, 108.14, 110.02,

121.49, 122.31, 124.61, 125.18, 127.10, 127.81, 129.71, 130.11, 131.22, 131.29, 131.78, 142.40, 143.45, 147.91, 151.89, 179.82 (C=O), 194.81 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{28}H_{24}BrN_2O_4$ 531.0919; found 531.0920.

(1′*R*,2′*S*,3*R*)-2′-(benzo[*d*][1,3]dioxole-5-carbonyl)-1′-(2,4-dichlorophenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (6l)

Brown solid. Yield: 77%. Mp. 156-158 ^oC. IR:ν_{max} (KBr, cm^{-1}) 3199 (NH), 2955 (O-CH_2-O), 1715 (C=O), 1670 (C=O). ^1H NMR (500 MHz, DMSO-d_6) δ_H: 1.70-1.78 (H-6) (m, 1H), 1.84-1.88 (H-7) (m, 1H), 2.34-2.40 (H-8) (m, 1H), 2.59 (H-8) (dd, 1H, *J* = 7.5 & 9.0 Hz), 3.84-3.88 (H-4) (m, 1H), 4.44 (H-5) (t, 1H, *J* = 10.8 Hz), 4.91 (H-3) (d, 1H, *J* = 11.5 Hz), 6.04 (O-CH_2-O) (d, 2H, *J* = 2.0 Hz), 6.60 (d, 1H, *J* = 8.0 Hz, -Ar-H), 6.82-6.86 (m, 2H, -Ar-H), 6.94 (t, 1H, *J* = 7.3 Hz, -Ar-H), 7.09-7.12 (m, 2H, -Ar-H), 7.15 (d, 1H, *J* = 7.5 Hz, -Ar-H), 7.40 (dd, 1H, *J* = 2.0 & 8.5 Hz, -Ar-H), 7.59 (d, 1H, *J* = 2.0 Hz, -Ar-H), 7.79 (d, 1H, *J* = 9.0 Hz, -Ar-H), 10.35 (NH) (brs, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 26.98 (C-7), 29.68 (C-6), 47.90 (C-4), 47.94 (C-8), 62.88 (C-3), 72.15 (C-5), 73.05 (C-2), 102.46 (O-CH_2-O), 107.39, 108.14, 110.19, 121.68, 124.63, 125.02, 127.37, 128.35, 129.36, 129.85, 130.39, 131.64, 132.29, 135.10, 136.87, 142.45, 147.87, 151.90, 179.61 (C=O), 194.71 (C=O). HR-MS (ESI) m/z: $[M+H]^+$ calcd. for $C_{28}H_{23}Cl_2N_2O_4$ 521.1035; found 521.1034.

Table 1. Crystal data and structure refinement details of compound **6i**.

CCDC	2143927
Chemical formula	$C_{28}H_{23}FN_2O_4$
Formula weight	470.48
Temperature	293(2) K
Wavelength	0.71075 Å
Crystal system	Triclinic
Space group	P - 1
Unit cell dimensions	a = 9.9780 (11) Å b = 10.7417 (12) Å c = 12.4901 (14) Å α = 104.108 (7)° β = 91.854 (7)° γ = 117.657 (8)°
Volume, V	1133.4(2) $Å^3$
Z	2
Density (calculated)	1.379 Mg/m^3
Absorption coefficient (μ)	0.098 mm^{-1}
F_{000}	492
Crystal size	0.200 x 0.200 x 0.200 mm^3
Theta range for data collection	3.029 to 27.484°
Index ranges	$-12 \leq h \leq 12$, $-13 \leq k \leq 13$, $-16 \leq l \leq 16$
Reflections collected	11826
Independent reflections	5167 [R(int) = 0.0406]
Completeness to theta = 25.242°	99.6%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5167 / 0 / 316
Goodness-of-fit on F^2	1.037
Final R indices [I > 2sigma(I)]	R1 = 0.0520, wR2 = 0.1387
R indices (all data)	R1 = 0.0618, wR2 = 0.1498
Largest diff. peak and hole	1.231 and -0.467 $e.Å^{-3}$

Table 2. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x10^3$) for compound **6i**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(1)	3285(1)	5337(1)	83(1)	24(1)
O(2)	2120(1)	5577(1)	3953(1)	29(1)
F(1)	-1811(2)	7987(2)	2216(1)	59(1)
N(2)	289(1)	3105(1)	419(1)	18(1)
O(3)	7348(2)	10304(2)	5266(1)	38(1)
O(4)	7919(2)	11270(2)	3773(1)	44(1)
N(1)	4102(2)	4130(2)	989(1)	24(1)
C(18)	2113(2)	3060(2)	1907(1)	20(1)
C(12)	1687(2)	3911(2)	1273(1)	17(1)
C(9)	1413(2)	5136(2)	2013(1)	17(1)
C(23)	-1009(2)	5166(2)	2625(1)	18(1)
C(10)	-288(2)	4257(2)	2098(1)	17(1)
C(16)	3109(2)	4562(2)	696(1)	19(1)
C(8)	2471(2)	6008(2)	3137(1)	19(1)
C(4)	3906(2)	7403(2)	3231(1)	20(1)
C(28)	-1662(2)	4951(2)	3580(1)	22(1)
C(11)	-956(2)	3364(2)	864(1)	19(1)
C(17)	3542(2)	3235(2)	1696(1)	23(1)
C(3)	4890(2)	8127(2)	4276(2)	23(1)
C(24)	-1054(2)	6209(2)	2165(2)	25(1)
C(2)	6202(2)	9408(2)	4354(2)	26(1)
C(19)	1372(2)	2204(2)	2592(2)	25(1)
C(15)	-333(2)	1516(2)	-87(2)	26(1)
C(7)	6555(2)	9989(2)	3464(2)	30(1)
C(5)	4272(2)	7997(2)	2344(2)	29(1)
C(22)	4258(2)	2592(2)	2136(2)	30(1)
C(20)	2064(2)	1528(2)	3035(2)	30(1)
C(13)	-2369(2)	1836(2)	636(2)	28(1)
C(27)	-2363(2)	5753(2)	4062(2)	30(1)
C(26)	-2427(2)	6776(2)	3604(2)	35(1)
C(21)	3485(2)	1723(2)	2806(2)	32(1)
C(25)	-1756(2)	6979(2)	2671(2)	33(1)
C(6)	5611(2)	9313(2)	2448(2)	38(1)
C(1)	8510(2)	11404(2)	4876(2)	43(1)
C(14)	-1733(2)	773(2)	445(2)	40(1)

Table 3. Anisotropic displacement parameters ($Å^2 x\ 10^3$) of compound **6i**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	22(1)	31(1)	25(1)	14(1)	11(1)	15(1)
O(2)	29(1)	34(1)	20(1)	12(1)	5(1)	10(1)
F(1)	89(1)	70(1)	75(1)	47(1)	42(1)	69(1)
N(2)	18(1)	20(1)	18(1)	5(1)	5(1)	11(1)
O(3)	28(1)	30(1)	43(1)	4(1)	-10(1)	7(1)
O(4)	30(1)	28(1)	55(1)	10(1)	2(1)	1(1)
N(1)	18(1)	37(1)	29(1)	17(1)	11(1)	18(1)
C(18)	22(1)	23(1)	19(1)	7(1)	5(1)	14(1)
C(12)	19(1)	21(1)	18(1)	9(1)	7(1)	12(1)
C(9)	18(1)	19(1)	17(1)	8(1)	7(1)	11(1)
C(23)	16(1)	21(1)	20(1)	6(1)	4(1)	11(1)
C(10)	18(1)	19(1)	19(1)	9(1)	6(1)	11(1)
C(16)	18(1)	23(1)	19(1)	5(1)	5(1)	12(1)
C(8)	20(1)	23(1)	19(1)	7(1)	5(1)	13(1)
C(4)	19(1)	21(1)	24(1)	6(1)	4(1)	12(1)
C(28)	23(1)	26(1)	22(1)	10(1)	9(1)	13(1)
C(11)	18(1)	22(1)	21(1)	8(1)	6(1)	12(1)
C(17)	24(1)	29(1)	21(1)	8(1)	6(1)	17(1)
C(3)	23(1)	26(1)	24(1)	7(1)	3(1)	15(1)
C(24)	28(1)	30(1)	26(1)	11(1)	10(1)	19(1)
C(2)	21(1)	23(1)	31(1)	1(1)	-1(1)	14(1)
C(19)	28(1)	30(1)	27(1)	14(1)	10(1)	18(1)
C(15)	29(1)	21(1)	27(1)	1(1)	4(1)	14(1)
C(7)	23(1)	20(1)	41(1)	7(1)	7(1)	7(1)
C(5)	28(1)	26(1)	25(1)	8(1)	3(1)	7(1)
C(22)	28(1)	43(1)	30(1)	12(1)	6(1)	26(1)
C(20)	40(1)	34(1)	26(1)	16(1)	10(1)	24(1)
C(13)	20(1)	25(1)	32(1)	5(1)	5(1)	7(1)
C(27)	29(1)	37(1)	28(1)	9(1)	15(1)	19(1)
C(26)	36(1)	41(1)	43(1)	10(1)	16(1)	31(1)
C(21)	41(1)	41(1)	28(1)	13(1)	2(1)	30(1)
C(25)	39(1)	37(1)	42(1)	18(1)	13(1)	30(1)
C(6)	38(1)	31(1)	34(1)	15(1)	8(1)	6(1)
C(1)	25(1)	33(1)	52(1)	-1(1)	-1(1)	6(1)
C(14)	37(1)	29(1)	47(1)	7(1)	6(1)	14(1)

Table 4. Bond lengths [Å] of compound **6i**.

Atoms	Length (Å)	Atoms	Length (Å)
O(1)-C(16)	1.2229(19)	C(17)-C(22)	1.381(2)
O(2)-C(8)	1.2159(19)	C(3)-C(2)	1.368(2)
F(1)-C(25)	1.360(2)	C(3)-H(3)	0.9300
N(2)-C(15)	1.471(2)	C(24)-C(25)	1.374(2)
N(2)-C(12)	1.472(2)	C(24)-H(24)	0.9300
N(2)-C(11)	1.4896(19)	C(2)-C(7)	1.381(3)
O(3)-C(2)	1.374(2)	C(19)-C(20)	1.395(2)
O(3)-C(1)	1.422(3)	C(19)-H(19)	0.9300
O(4)-C(7)	1.365(2)	C(15)-C(14)	1.520(3)
O(4)-C(1)	1.428(3)	C(15)-H(15A)	0.9700
N(1)-C(16)	1.348(2)	C(15)-H(15B)	0.9700
N(1)-C(17)	1.402(2)	C(7)-C(6)	1.366(3)
N(1)-H(1)	0.8600	C(5)-C(6)	1.396(3)
C(18)-C(19)	1.385(2)	C(5)-H(5)	0.9300
C(18)-C(17)	1.392(2)	C(22)-C(21)	1.387(3)
C(18)-C(12)	1.527(2)	C(22)-H(22)	0.9300
C(12)-C(16)	1.553(2)	C(20)-C(21)	1.384(3)
C(12)-C(9)	1.556(2)	C(20)-H(20)	0.9300
C(9)-C(8)	1.519(2)	C(13)-C(14)	1.521(3)
C(9)-C(10)	1.534(2)	C(13)-H(13A)	0.9700
C(9)-H(9)	0.9800	C(13)-H(13B)	0.9700
C(23)-C(28)	1.395(2)	C(27)-C(26)	1.382(3)
C(23)-C(24)	1.395(2)	C(27)-H(27)	0.9300
C(23)-C(10)	1.509(2)	C(26)-C(25)	1.376(3)
C(10)-C(11)	1.535(2)	C(26)-H(26)	0.9300
C(10)-H(10)	0.9800	C(21)-H(21)	0.9300
C(8)-C(4)	1.491(2)	C(6)-H(6)	0.9300
C(4)-C(5)	1.386(2)	C(1)-H(1A)	0.9700
C(4)-C(3)	1.410(2)	C(1)-H(1B)	0.9700
C(28)-C(27)	1.388(2)	C(14)-H(14A)	0.9700
C(28)-H(28)	0.9300	C(14)-H(14B)	0.9700
C(11)-C(13)	1.536(2)	C(17)-C(22)	1.381(2)
C(11)-H(11)	0.9800		

Table 5. Bond Angles (°) of compound **6i**.

Atoms	Angles (°)	Atoms	Angles (°)
C(15)-N(2)-C(12)	118.53(13)	C(3)-C(2)-O(3)	128.15(17)
C(15)-N(2)-C(11)	108.62(12)	C(3)-C(2)-C(7)	122.34(17)
C(12)-N(2)-C(11)	110.07(12)	O(3)-C(2)-C(7)	109.51(15)
C(2)-O(3)-C(1)	105.63(16)	C(18)-C(19)-C(20)	119.31(16)
C(7)-O(4)-C(1)	105.46(16)	C(18)-C(19)-H(19)	120.3
C(16)-N(1)-C(17)	111.74(13)	C(20)-C(19)-H(19)	120.3
C(16)-N(1)-H(1)	124.1	N(2)-C(15)-C(14)	105.84(14)
C(17)-N(1)-H(1)	124.1	N(2)-C(15)-H(15A)	110.6
C(19)-C(18)-C(17)	118.60(15)	C(14)-C(15)-H(15A)	110.6
C(19)-C(18)-C(12)	133.14(14)	N(2)-C(15)-H(15B)	110.6
C(17)-C(18)-C(12)	108.25(13)	C(14)-C(15)-H(15B)	110.6
N(2)-C(12)-C(18)	118.95(13)	H(15A)-C(15)-H(15B)	108.7
N(2)-C(12)-C(16)	109.05(12)	O(4)-C(7)-C(6)	127.99(18)
C(18)-C(12)-C(16)	101.31(12)	O(4)-C(7)-C(2)	110.17(17)
N(2)-C(12)-C(9)	100.81(11)	C(6)-C(7)-C(2)	121.84(16)
C(18)-C(12)-C(9)	115.38(13)	C(4)-C(5)-C(6)	121.78(17)
C(16)-C(12)-C(9)	111.54(12)	C(4)-C(5)-H(5)	119.1
C(8)-C(9)-C(10)	114.16(12)	C(6)-C(5)-H(5)	119.1
C(8)-C(9)-C(12)	115.92(12)	C(17)-C(22)-C(21)	117.21(16)
C(10)-C(9)-C(12)	101.25(12)	C(17)-C(22)-H(22)	121.4
C(8)-C(9)-H(9)	108.4	C(21)-C(22)-H(22)	121.4
C(10)-C(9)-H(9)	108.4	C(21)-C(20)-C(19)	120.59(17)
C(12)-C(9)-H(9)	108.4	C(21)-C(20)-H(20)	119.7
C(28)-C(23)-C(24)	119.25(14)	C(19)-C(20)-H(20)	119.7
C(28)-C(23)-C(10)	119.69(14)	C(14)-C(13)-C(11)	104.96(14)
C(24)-C(23)-C(10)	121.05(14)	C(14)-C(13)-H(13A)	110.8
C(23)-C(10)-C(9)	115.24(13)	C(11)-C(13)-H(13A)	110.8
C(23)-C(10)-C(11)	115.32(13)	C(14)-C(13)-H(13B)	110.8
C(9)-C(10)-C(11)	100.14(12)	C(11)-C(13)-H(13B)	110.8
C(23)-C(10)-H(10)	108.6	H(13A)-C(13)-H(13B)	108.8
C(9)-C(10)-H(10)	108.6	C(26)-C(27)-C(28)	120.58(16)
C(11)-C(10)-H(10)	108.6	C(26)-C(27)-H(27)	119.7
O(1)-C(16)-N(1)	126.29(14)	C(28)-C(27)-H(27)	119.7
O(1)-C(16)-C(12)	125.19(14)	C(25)-C(26)-C(27)	117.68(16)
N(1)-C(16)-C(12)	108.51(13)	C(25)-C(26)-H(26)	121.2
O(2)-C(8)-C(4)	120.86(15)	C(27)-C(26)-H(26)	121.2
O(2)-C(8)-C(9)	119.66(14)	C(20)-C(21)-C(22)	121.12(16)

C(4)-C(8)-C(9)	119.46(13)	C(20)-C(21)-H(21)	119.4
C(5)-C(4)-C(3)	120.37(15)	C(22)-C(21)-H(21)	119.4
C(5)-C(4)-C(8)	122.42(15)	F(1)-C(25)-C(24)	118.22(17)
C(3)-C(4)-C(8)	117.21(14)	F(1)-C(25)-C(26)	118.06(16)
C(27)-C(28)-C(23)	120.54(16)	C(24)-C(25)-C(26)	123.72(17)
C(27)-C(28)-H(28)	119.7	C(7)-C(6)-C(5)	116.89(18)
C(23)-C(28)-H(28)	119.7	C(7)-C(6)-H(6)	121.6
N(2)-C(11)-C(10)	104.62(12)	C(5)-C(6)-H(6)	121.6
N(2)-C(11)-C(13)	105.93(12)	O(3)-C(1)-O(4)	108.34(15)
C(10)-C(11)-C(13)	116.67(13)	O(3)-C(1)-H(1A)	110.0
N(2)-C(11)-H(11)	109.8	O(4)-C(1)-H(1A)	110.0
C(10)-C(11)-H(11)	109.8	O(3)-C(1)-H(1B)	110.0
C(13)-C(11)-H(11)	109.8	O(4)-C(1)-H(1B)	110.0
C(22)-C(17)-C(18)	123.15(16)	H(1A)-C(1)-H(1B)	108.4
C(22)-C(17)-N(1)	126.67(15)	C(15)-C(14)-C(13)	103.16(15)
C(18)-C(17)-N(1)	110.18(14)	C(15)-C(14)-H(14A)	111.1
C(2)-C(3)-C(4)	116.78(16)	C(13)-C(14)-H(14A)	111.1
C(2)-C(3)-H(3)	121.6	C(15)-C(14)-H(14B)	111.1
C(4)-C(3)-H(3)	121.6	C(13)-C(14)-H(14B)	111.1
C(25)-C(24)-C(23)	118.23(16)	H(14A)-C(14)-H(14B)	109.1
C(25)-C(24)-H(24)	120.9		
C(23)-C(24)-H(24)	120.9		

Table 6. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$) of compound **6i**.

Atom	x	y	z	U(eq)
H(1)	4974	4374	768	29
H(9)	1517	5824	1588	20
H(10)	-393	3579	2532	20
H(28)	-1627	4265	3897	27
H(11)	-1180	3944	465	23
H(3)	4658	7752	4883	28
H(24)	-621	6377	1531	30
H(19)	423	2082	2755	30
H(15A)	423	1226	68	31
H(15B)	-621	1251	-892	31
H(5)	3607	7504	1661	35
H(22)	5219	2736	1988	35
H(20)	1566	942	3488	35
H(13A)	-2904	1776	1272	33
H(13B)	-3074	1622	-20	33
H(27)	-2793	5600	4699	36
H(26)	-2906	7308	3916	42
H(21)	3928	1262	3107	38
H(6)	5850	9712	1853	45
H(1A)	9412	11279	4865	52
H(1B)	8801	12372	5371	52
H(14A)	-1445	652	1146	47
H(14B)	-2475	-180	-54	47

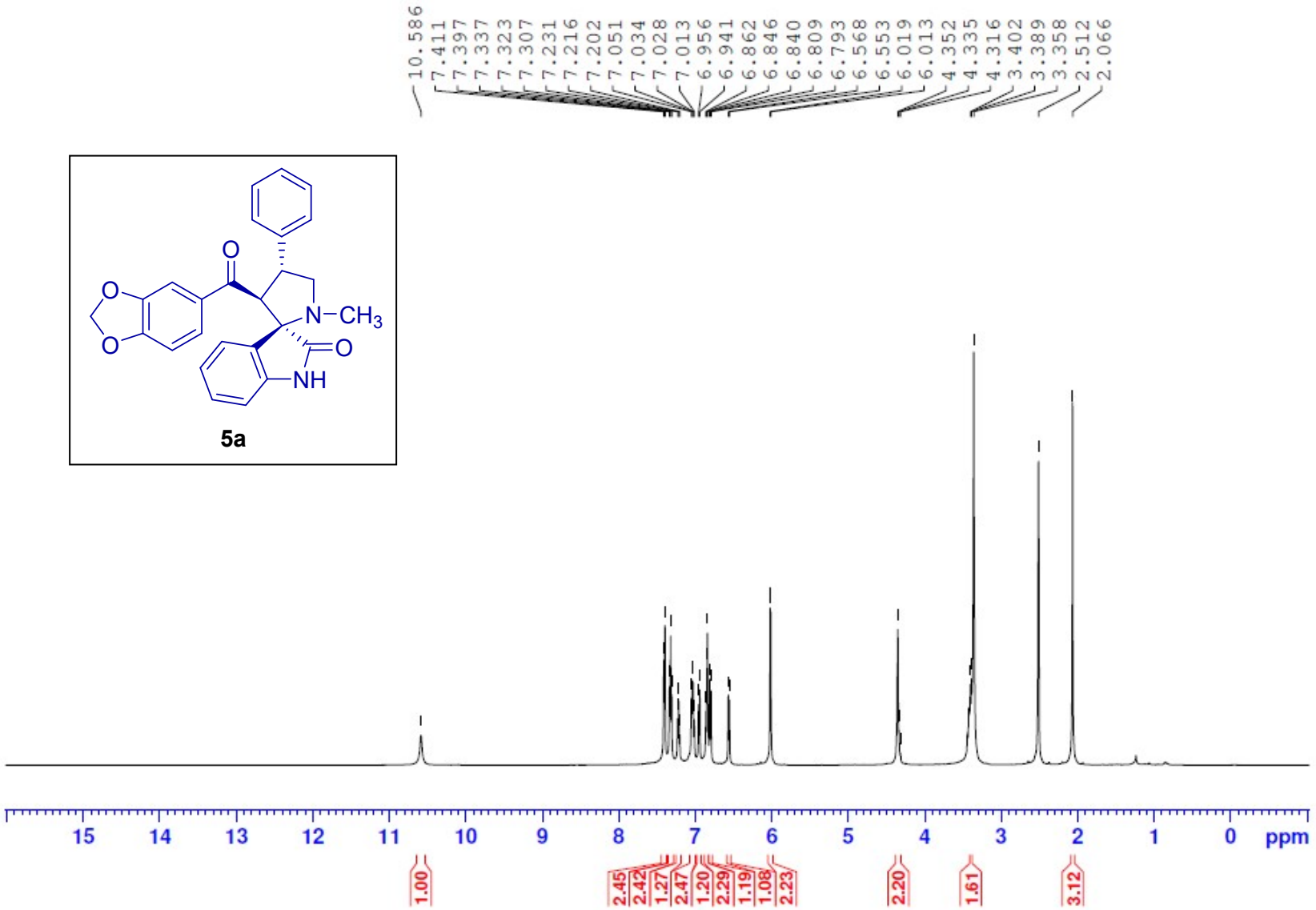


Fig 1. ^{1}H NMR spectrum of compound **5a**.

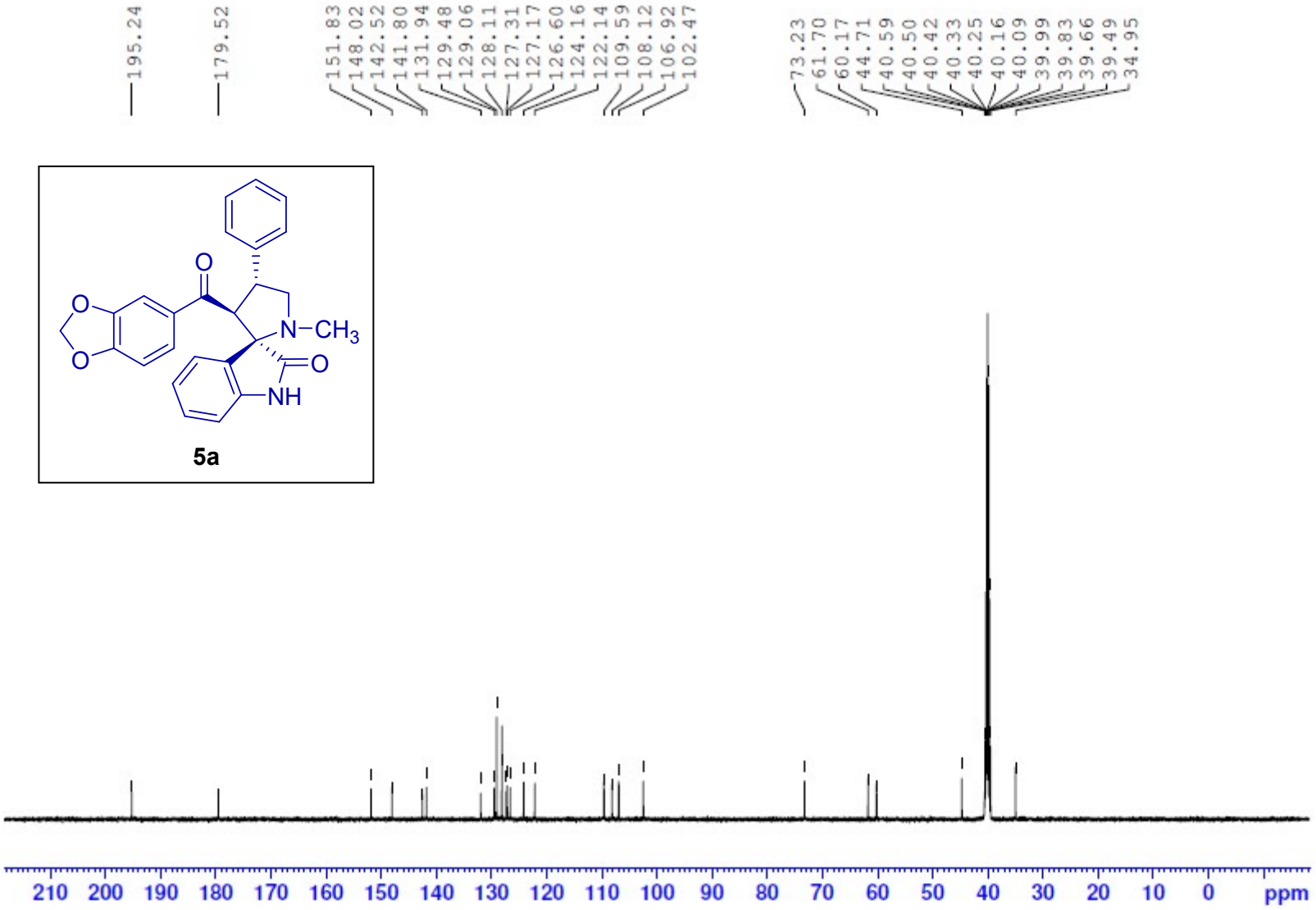


Fig 2. ^{13}C NMR spectrum of compound **5a**.

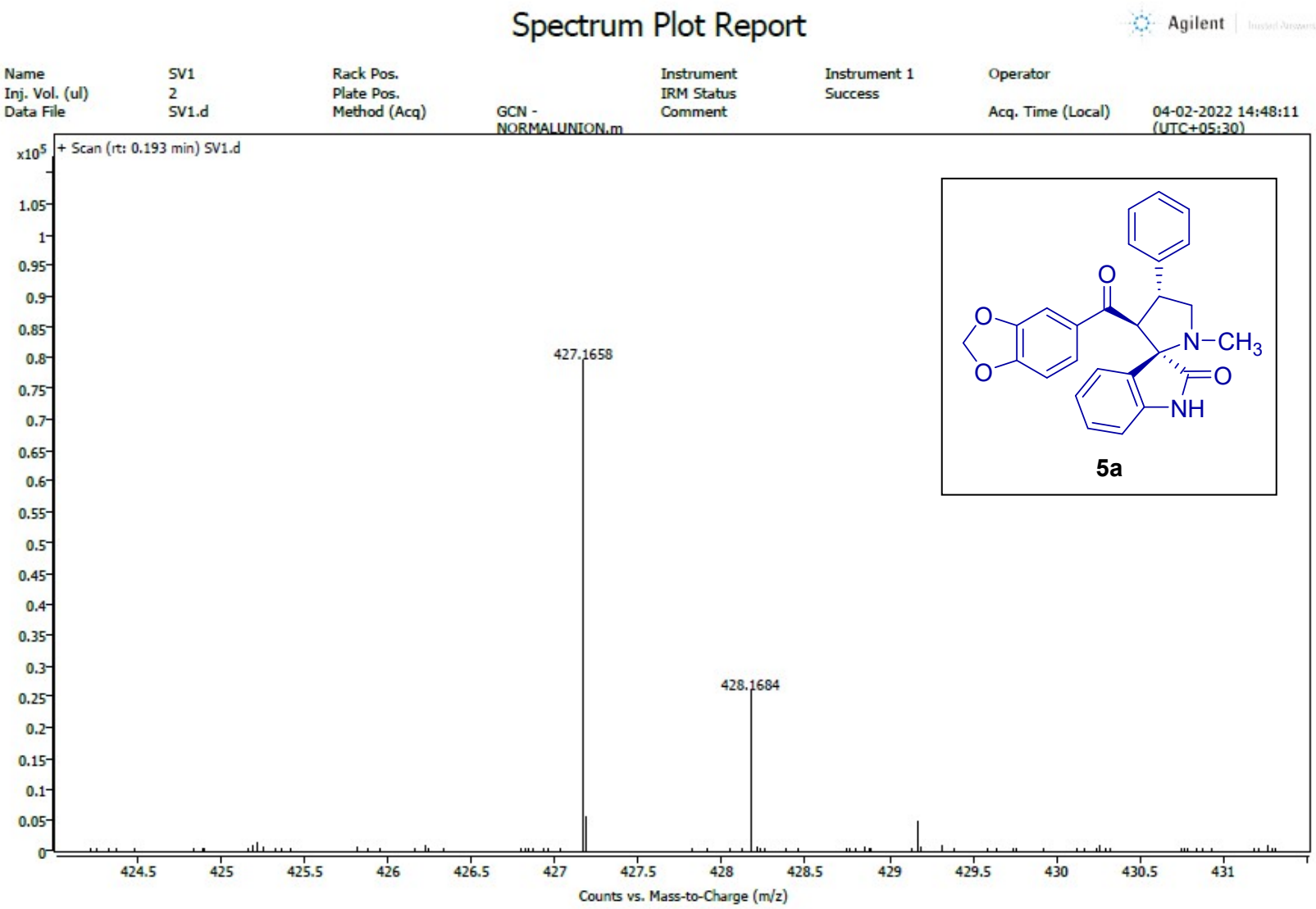


Fig 3. HR-MS spectrum of compound **5a**.

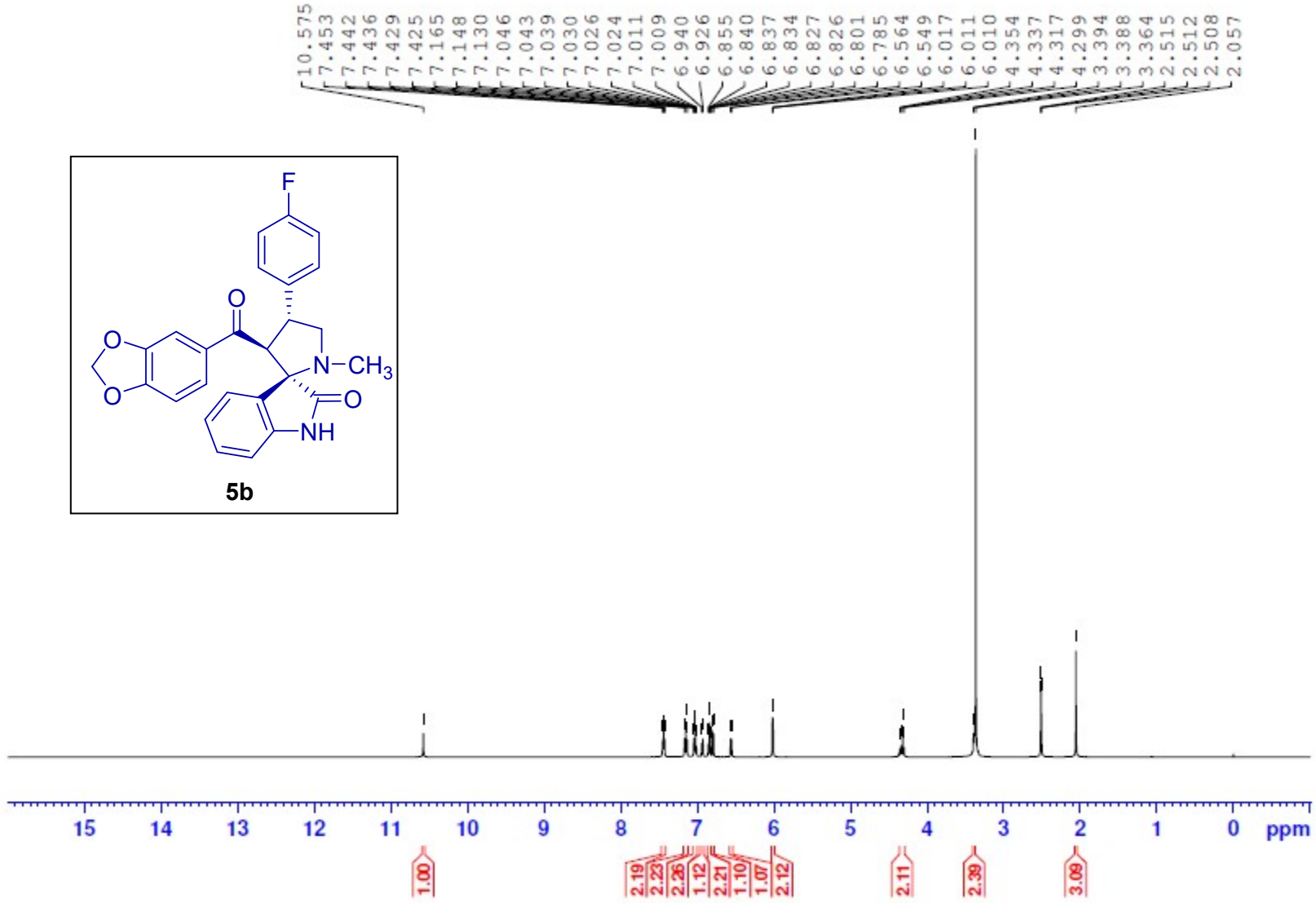


Fig 4. [1]H NMR spectrum of compound **5b**.

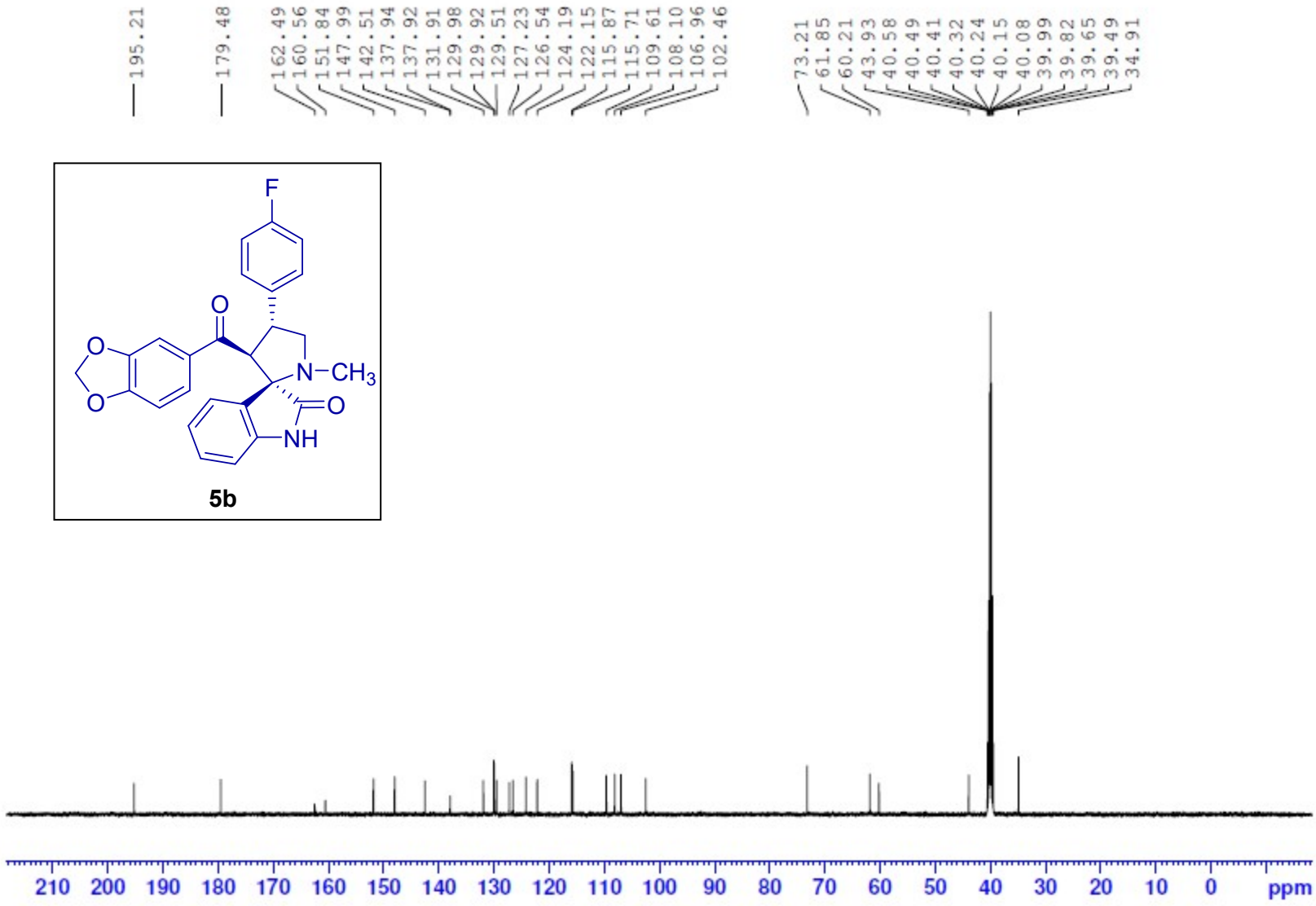


Fig 5. ^{13}C NMR spectrum of compound **5b**.

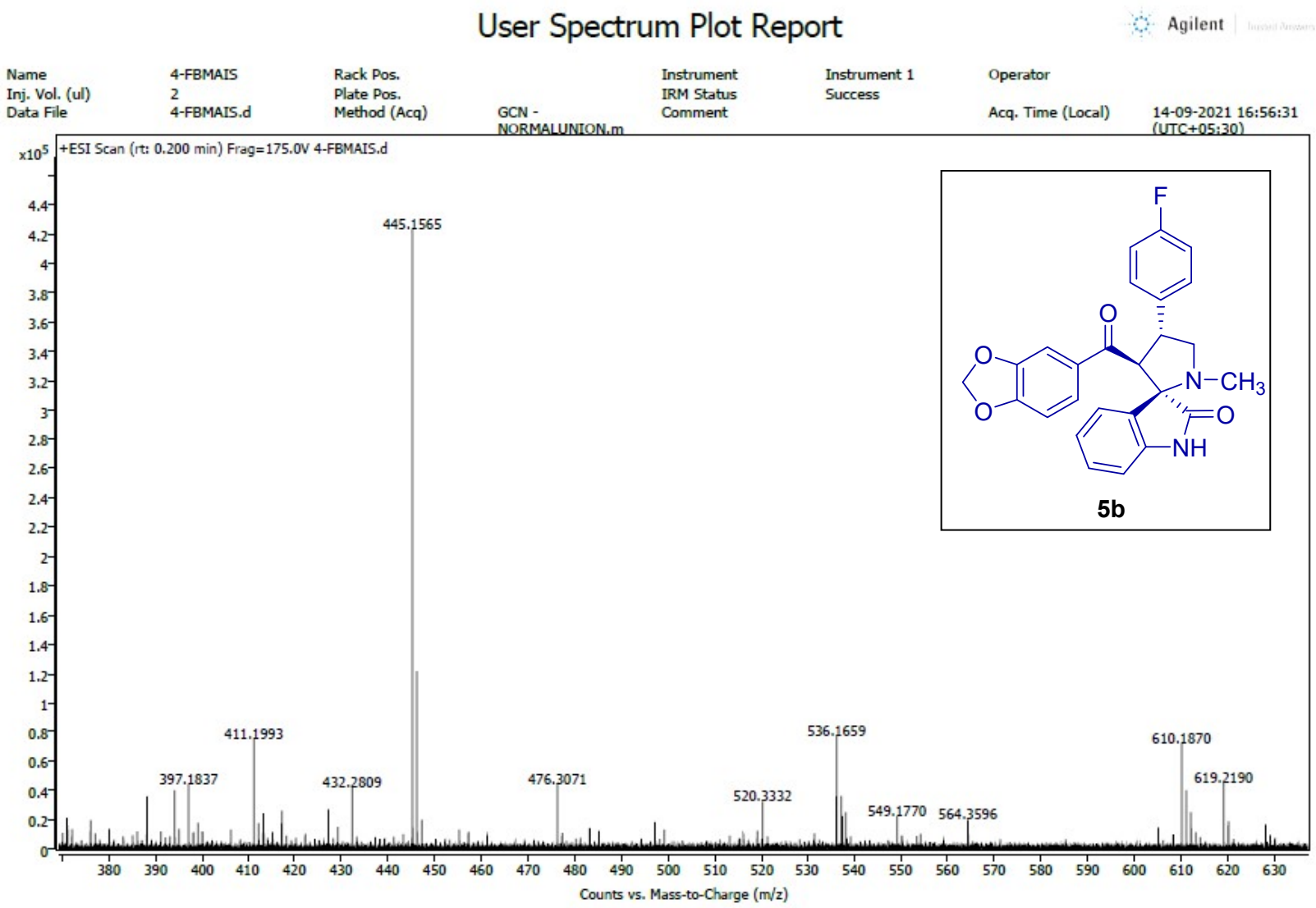


Fig 6. HR-MS spectrum of compound **5b**.

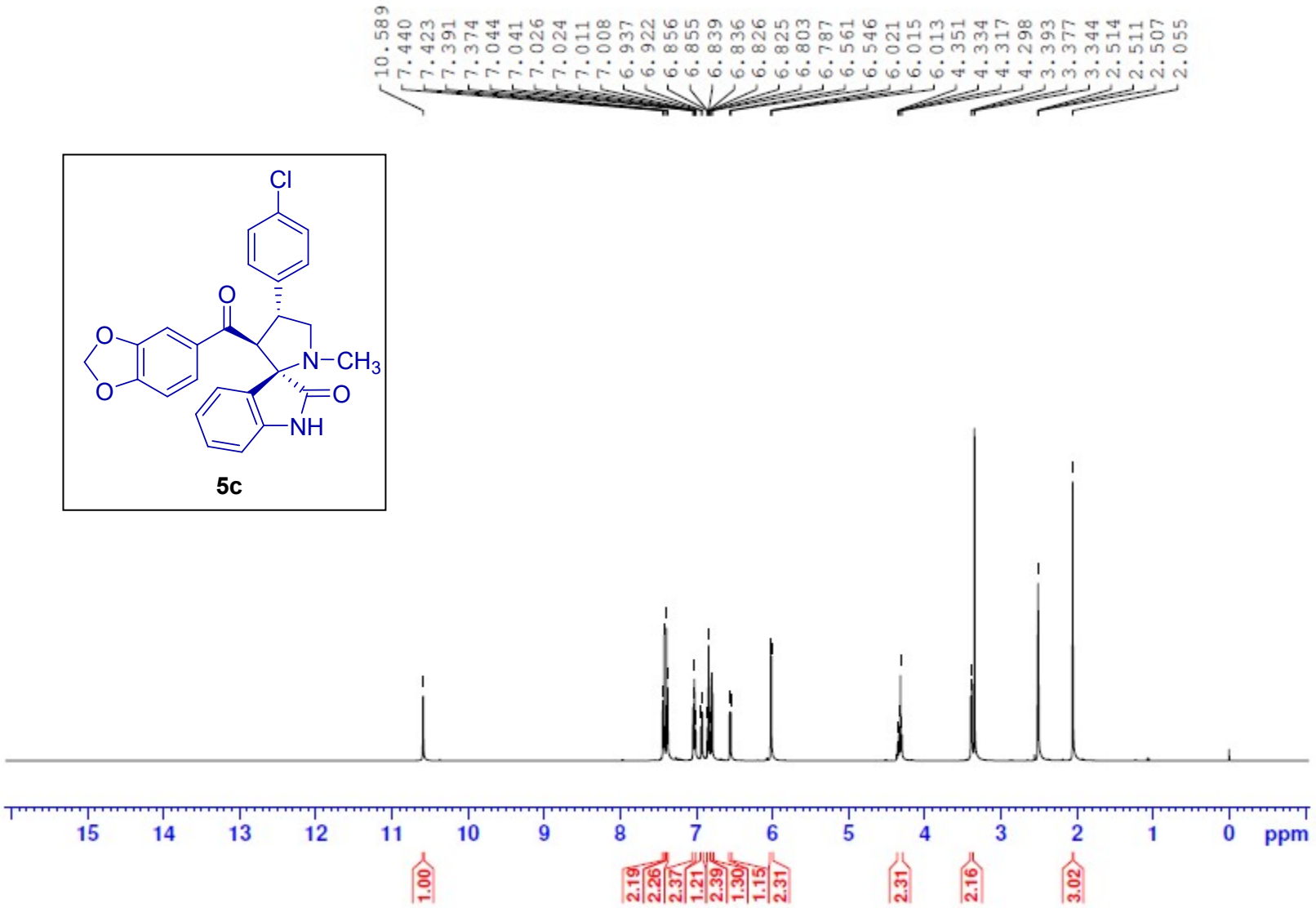


Fig 7. ^{1}H NMR spectrum of compound **5c**.

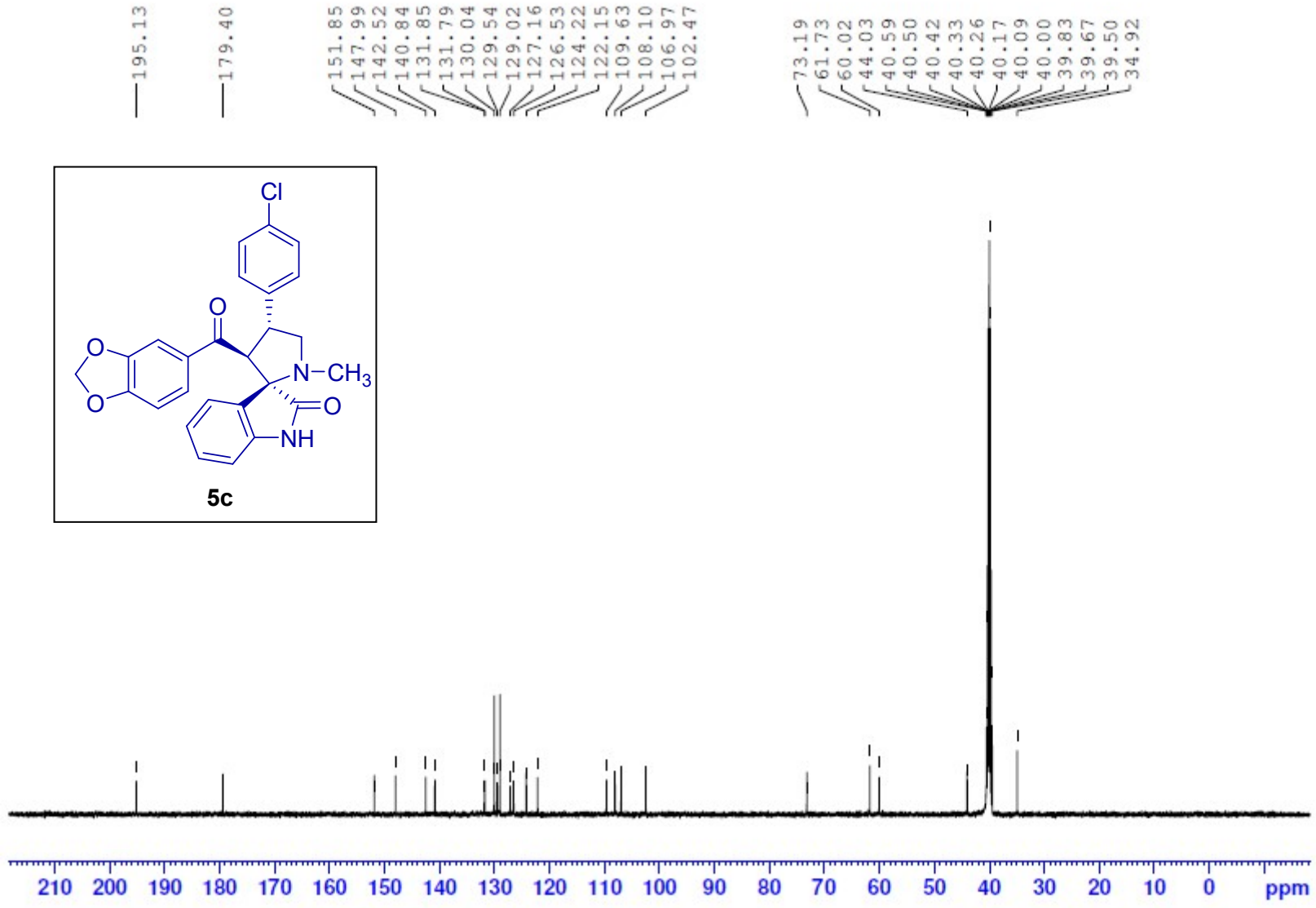


Fig 8. ^{13}C NMR spectrum of compound **5c**.

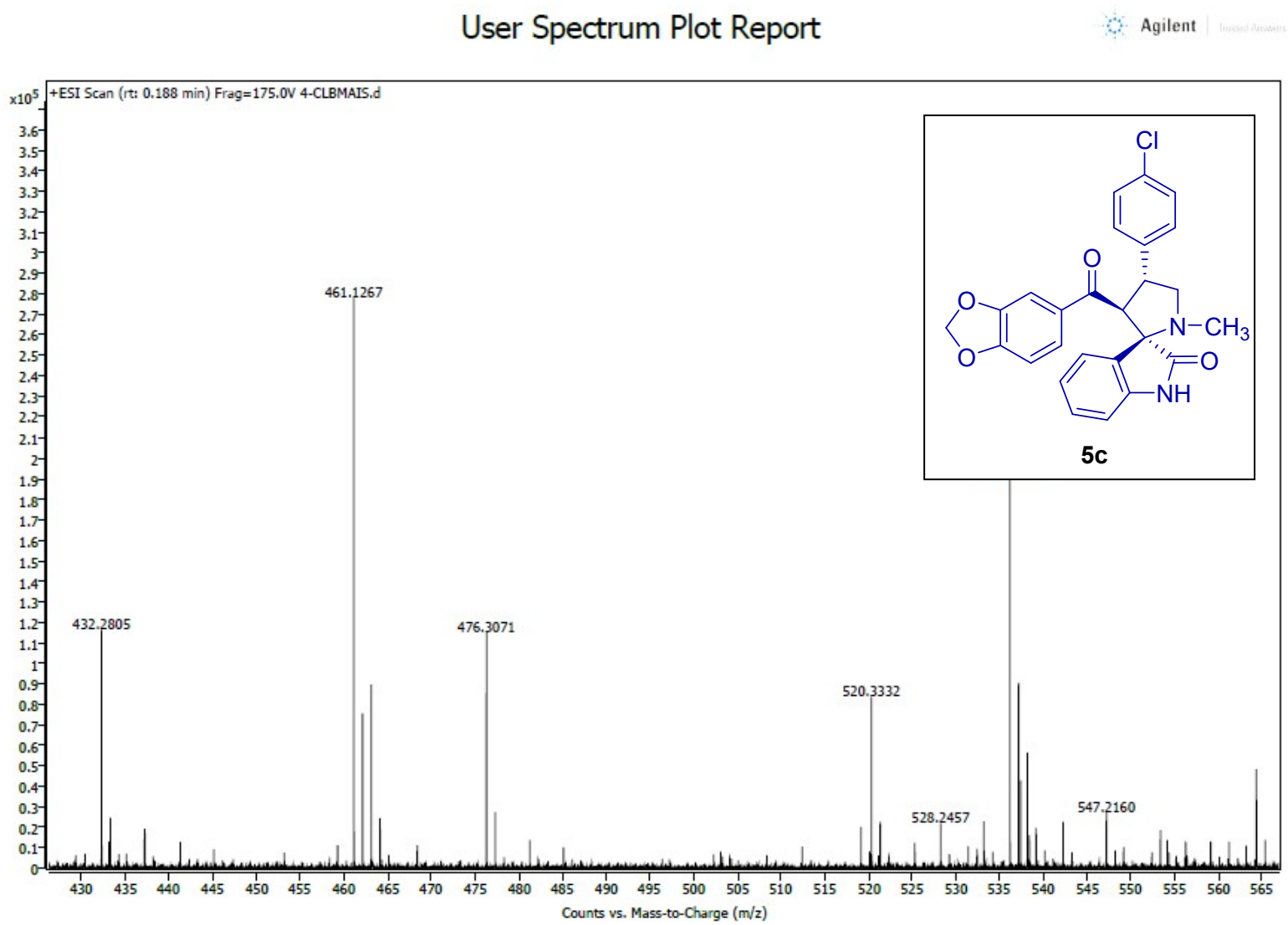


Fig 9. HR-MS spectrum of compound **5c**.

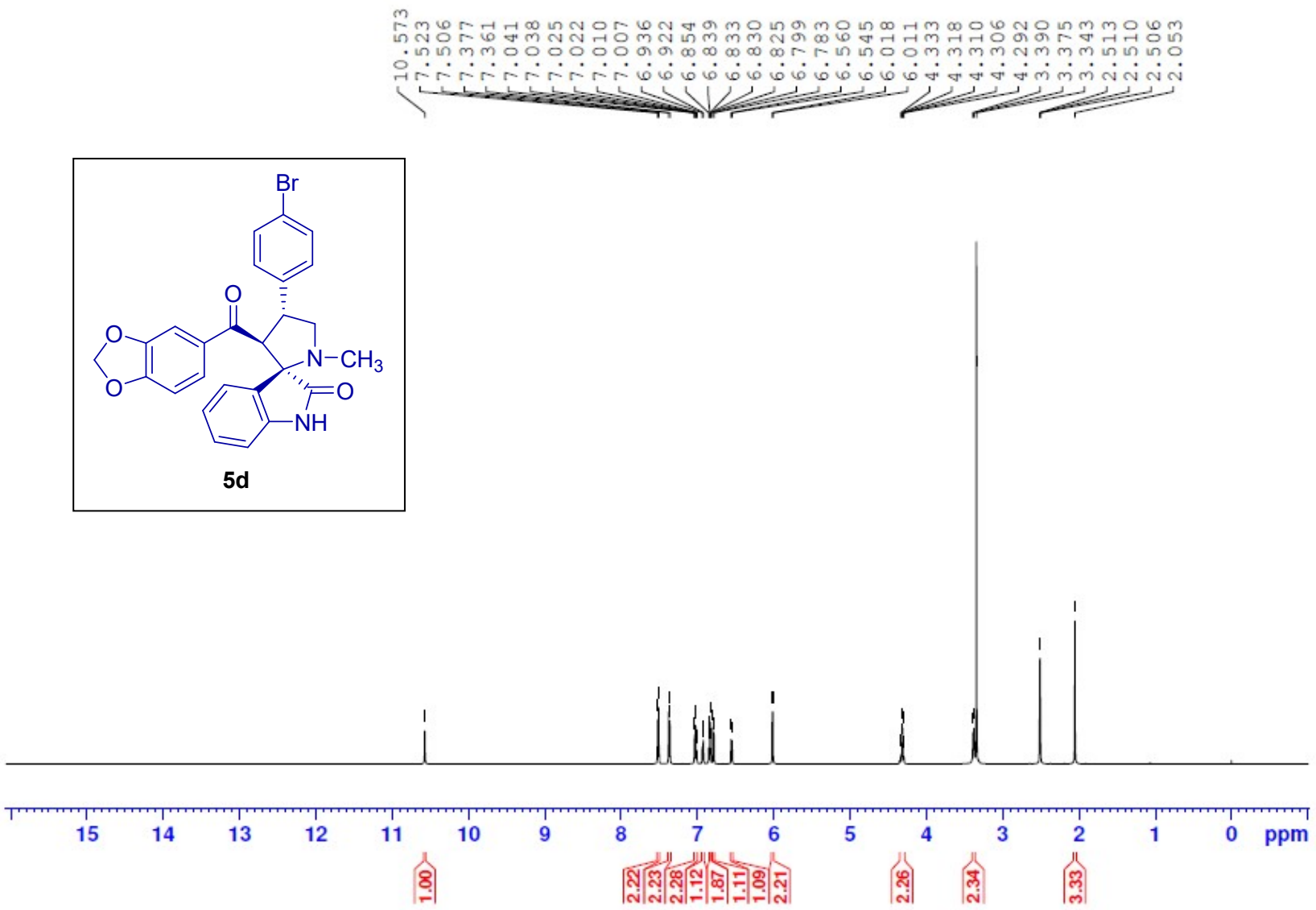


Fig 10. ^{1}H NMR spectrum of compound **5d**.

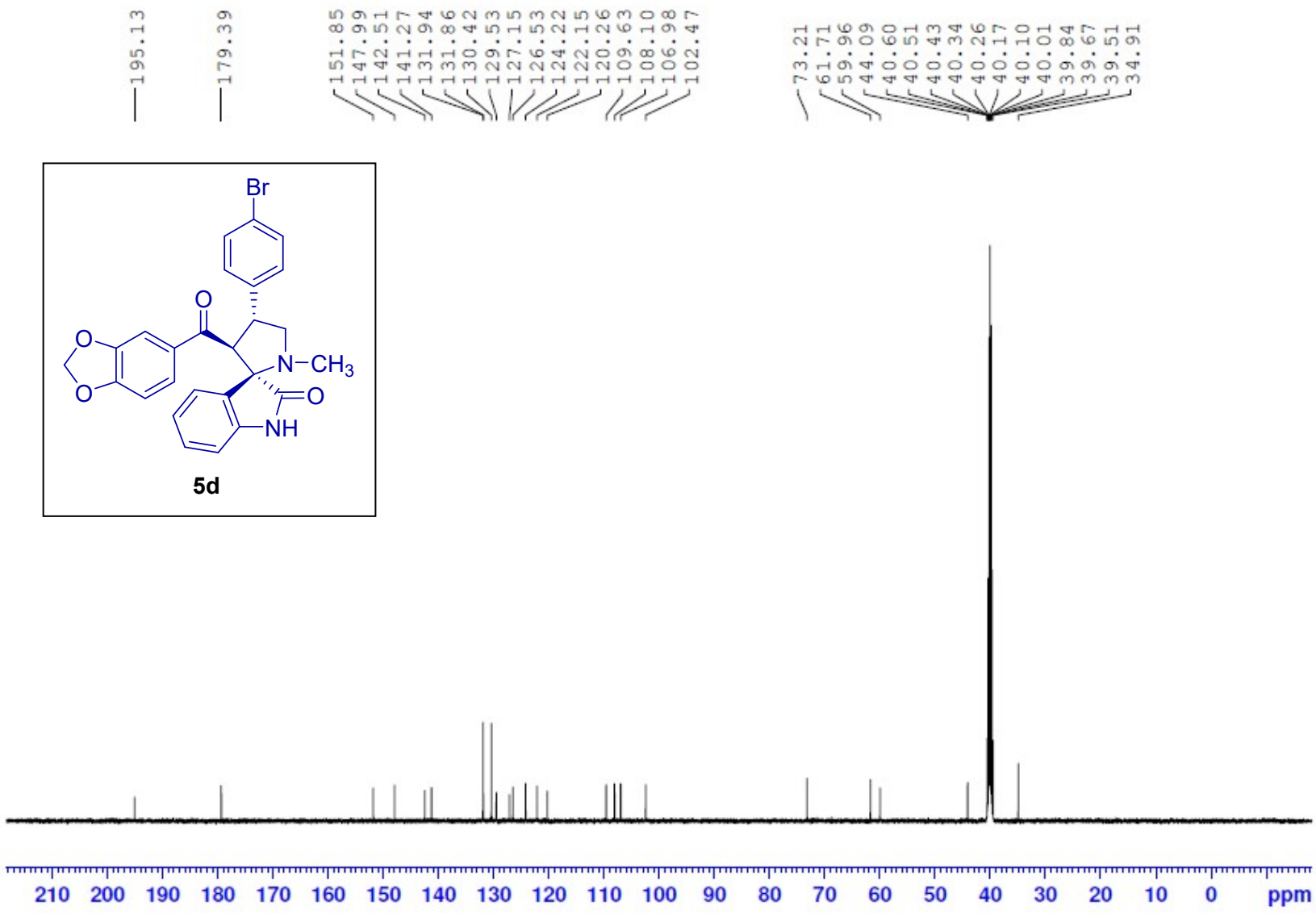


Fig 11. ^{13}C NMR spectrum of compound **5d**.

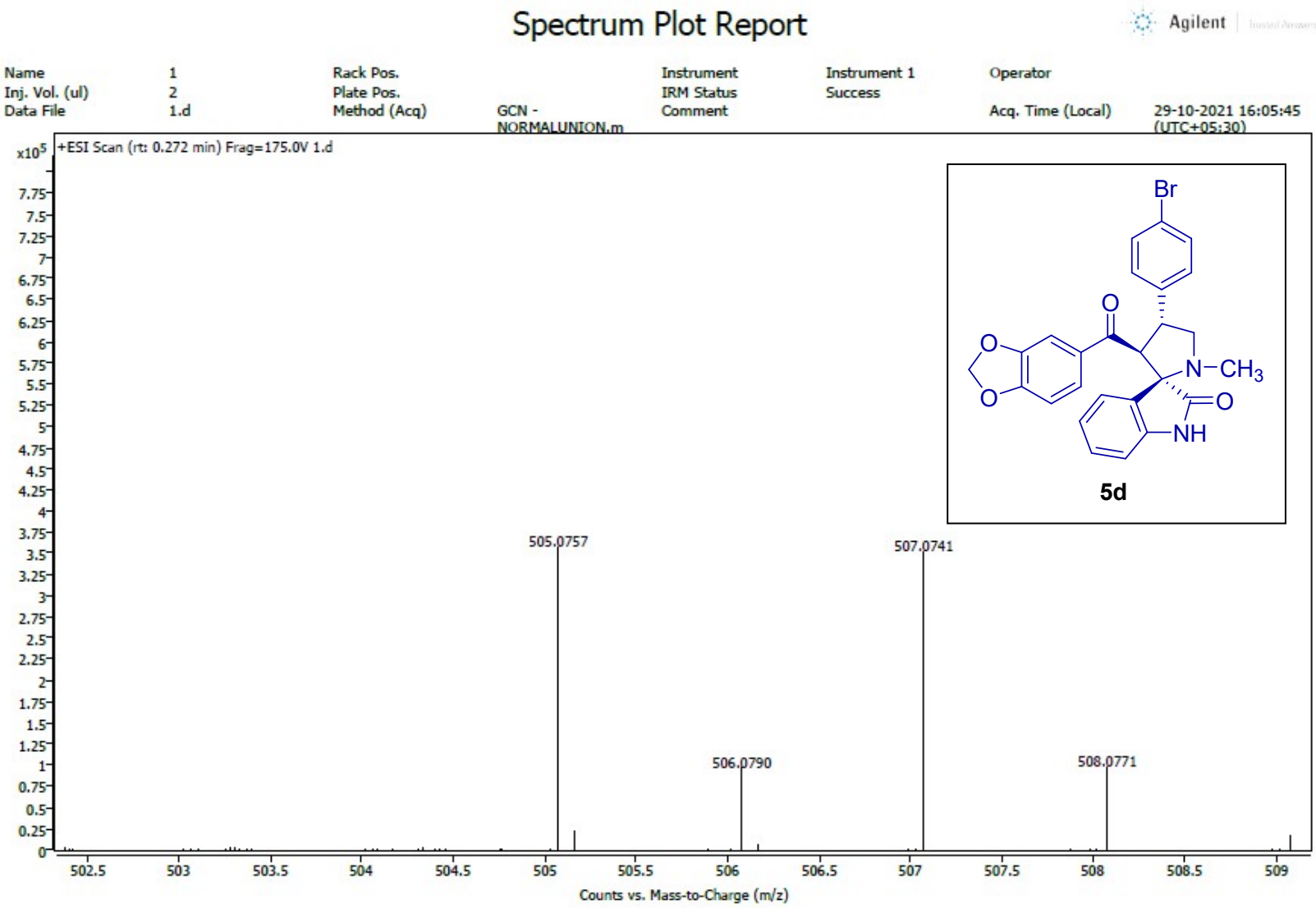


Fig 12. HR-MS spectrum of compound **5d**.

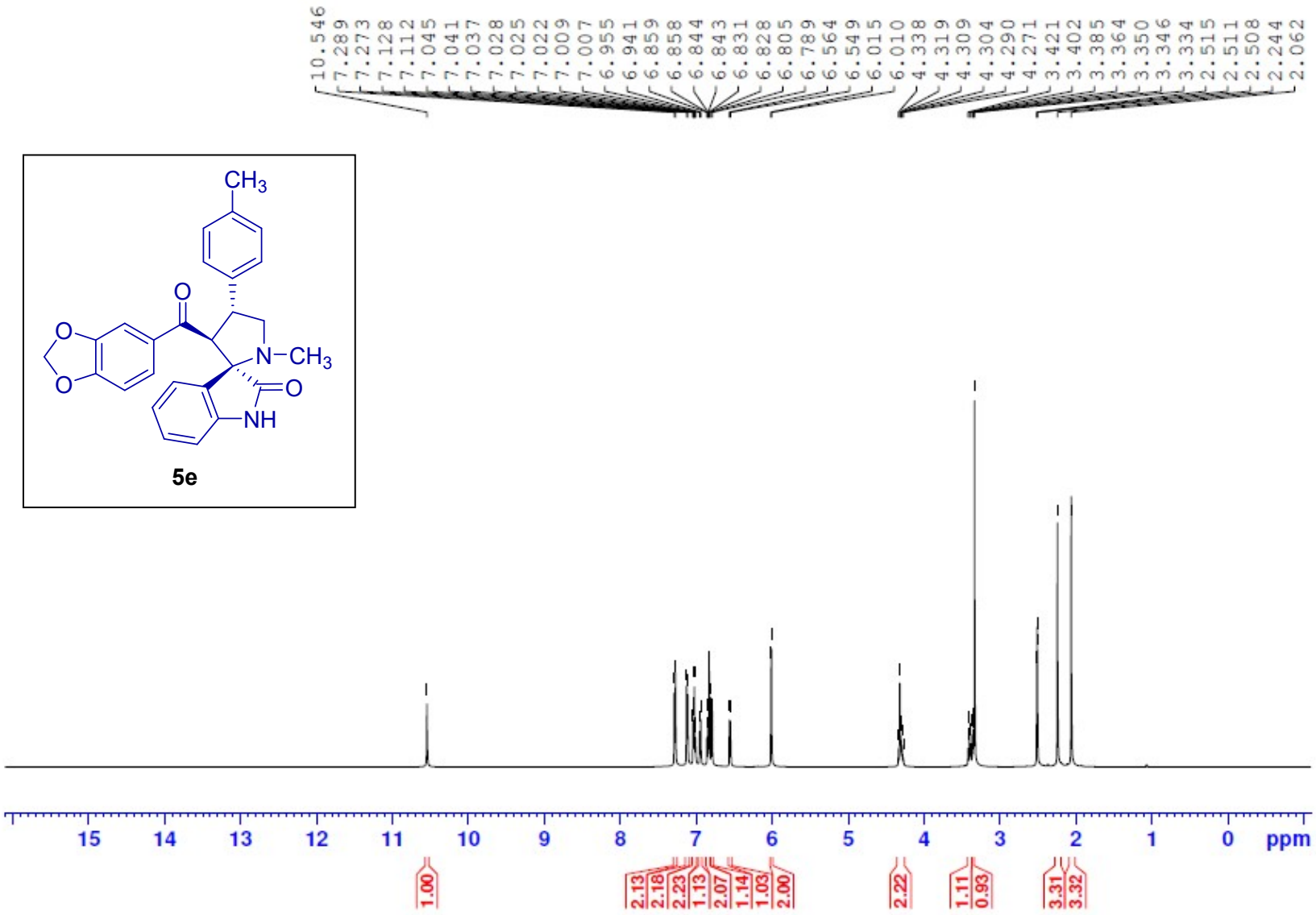


Fig 13. [1]H NMR spectrum of compound **5e**.

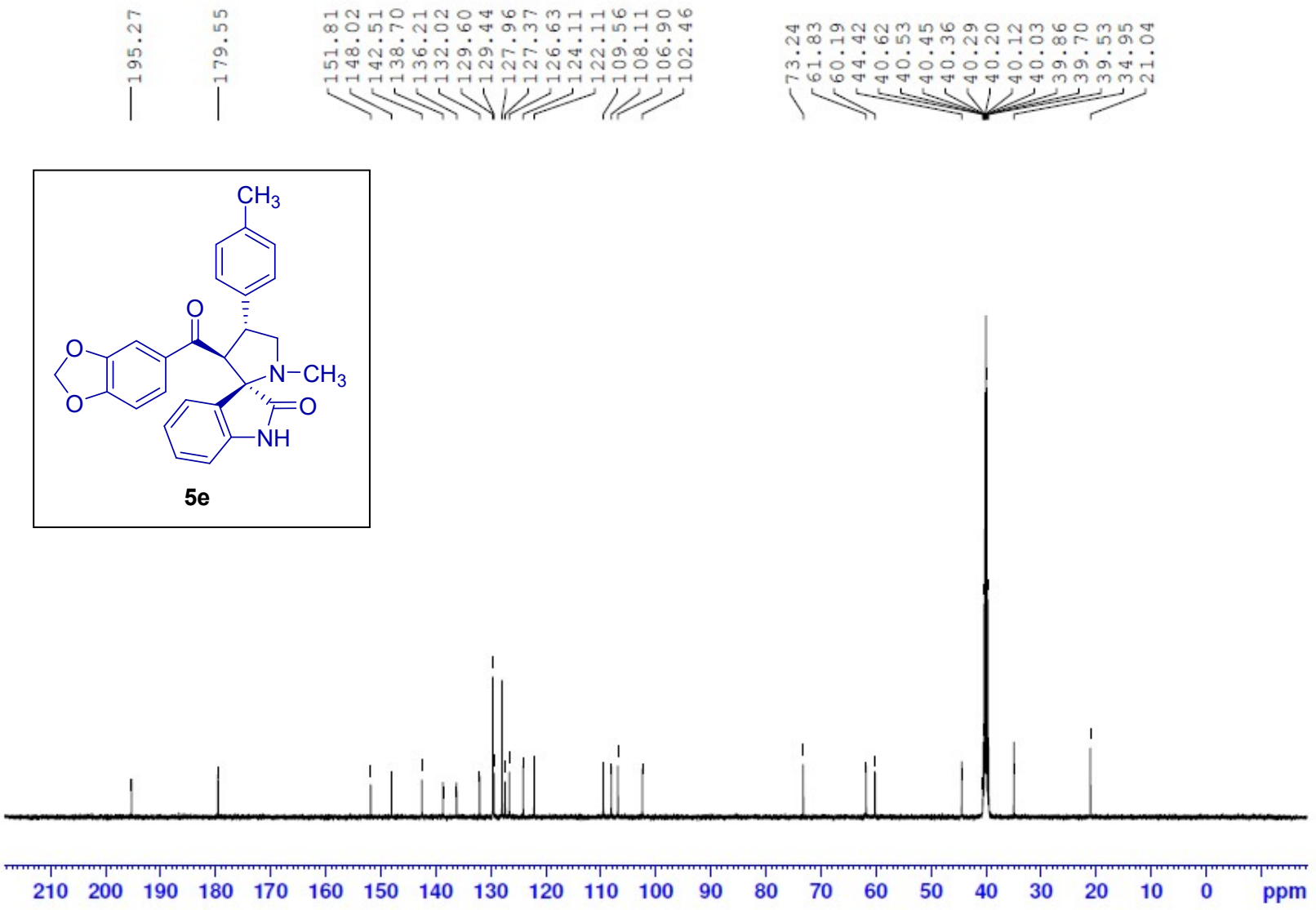


Fig 14. ^{13}C NMR spectrum of compound **5e**.

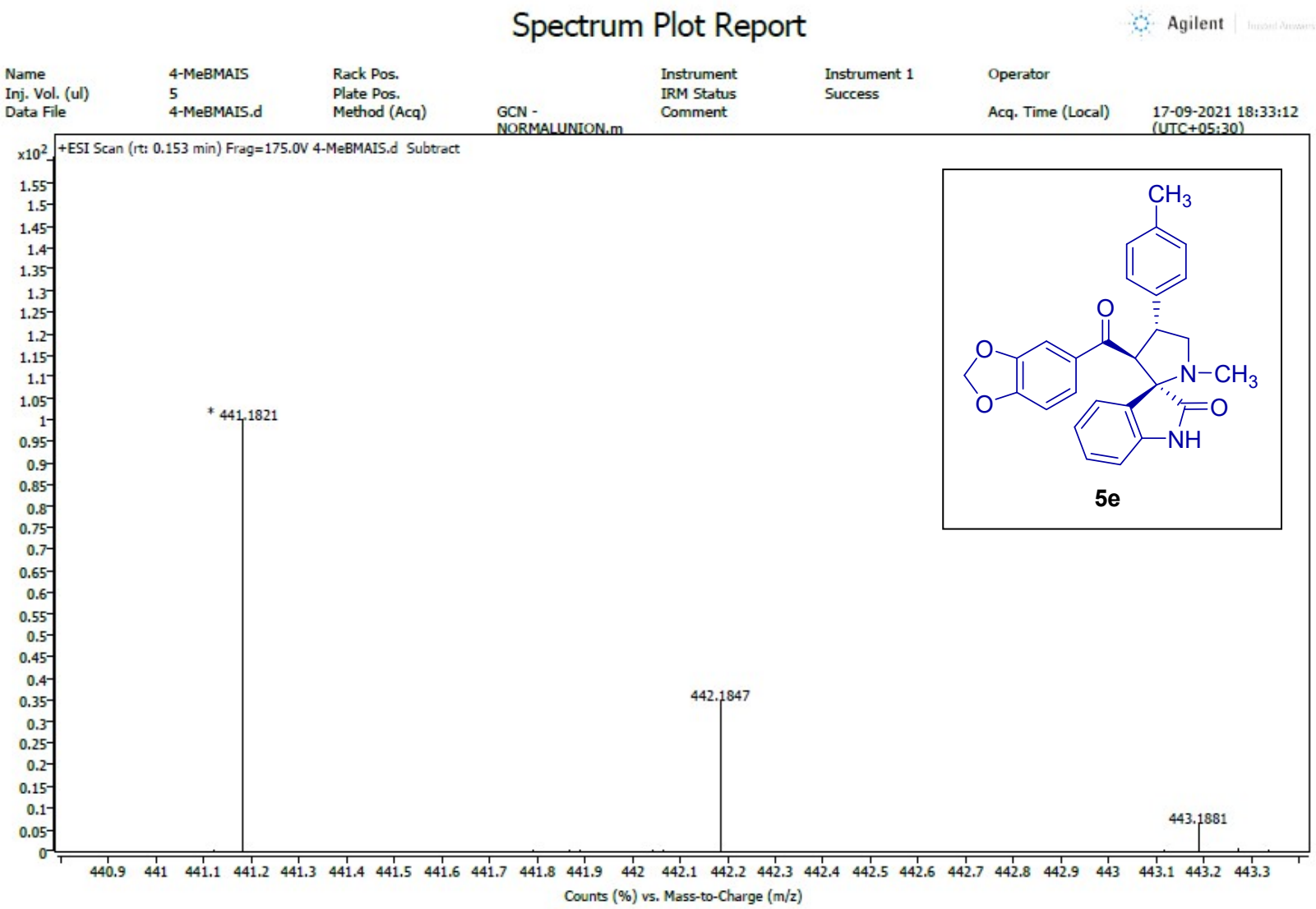


Fig 15. HR-MS spectrum of compound **5e**.

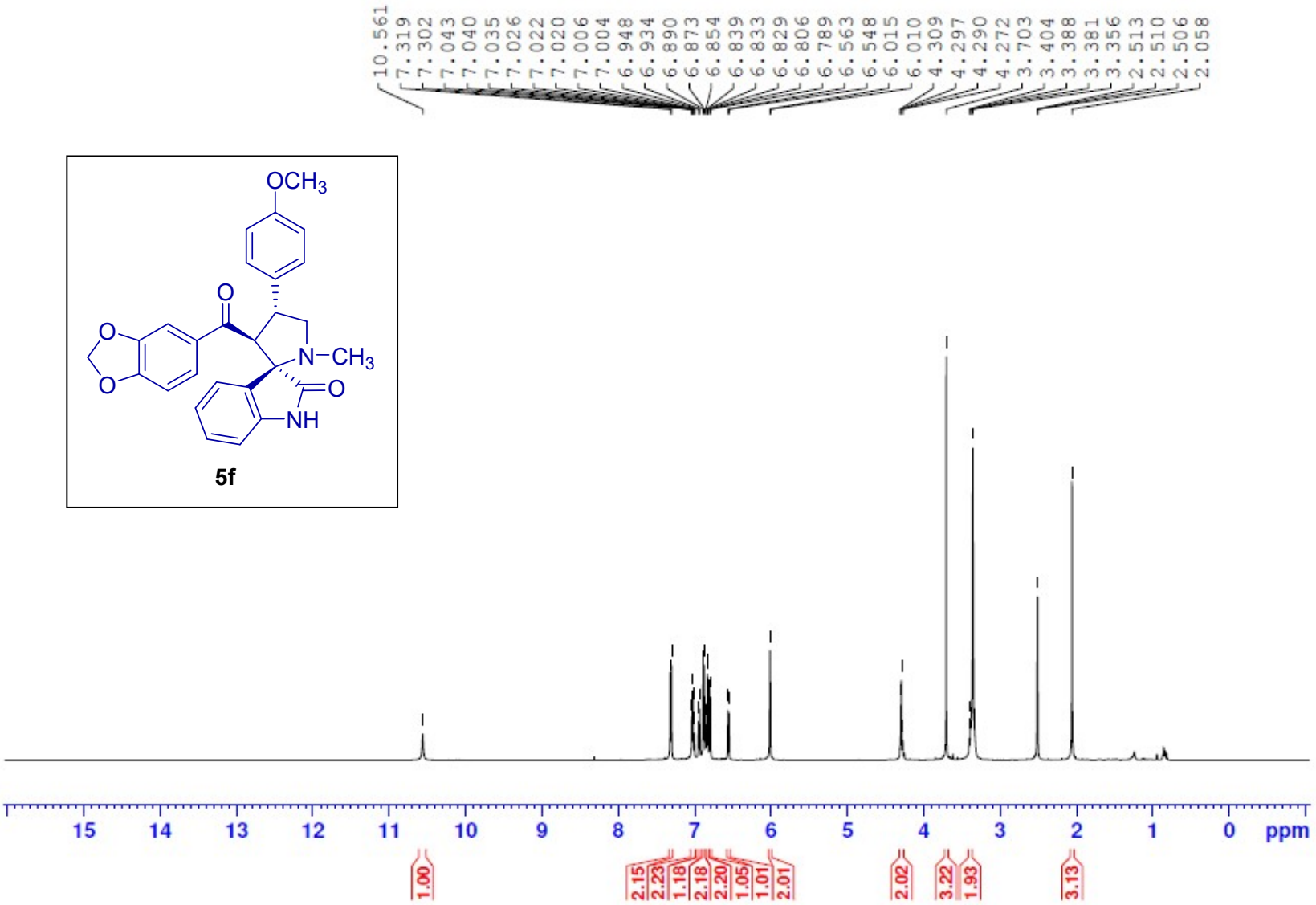


Fig 16. ^{1}H NMR spectrum of compound **5f**.

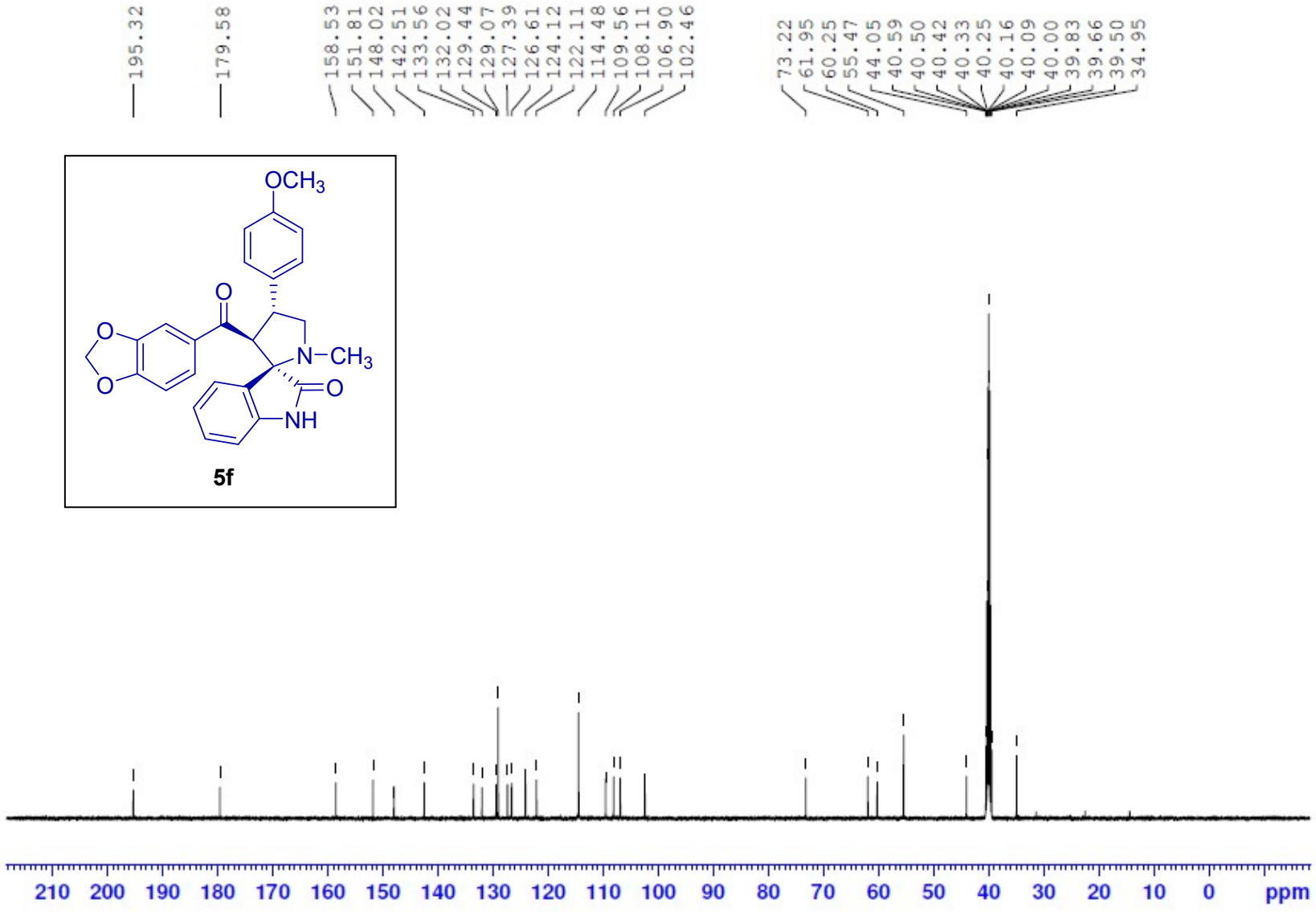


Fig 17. ^{13}C NMR spectrum of compound **5f**.

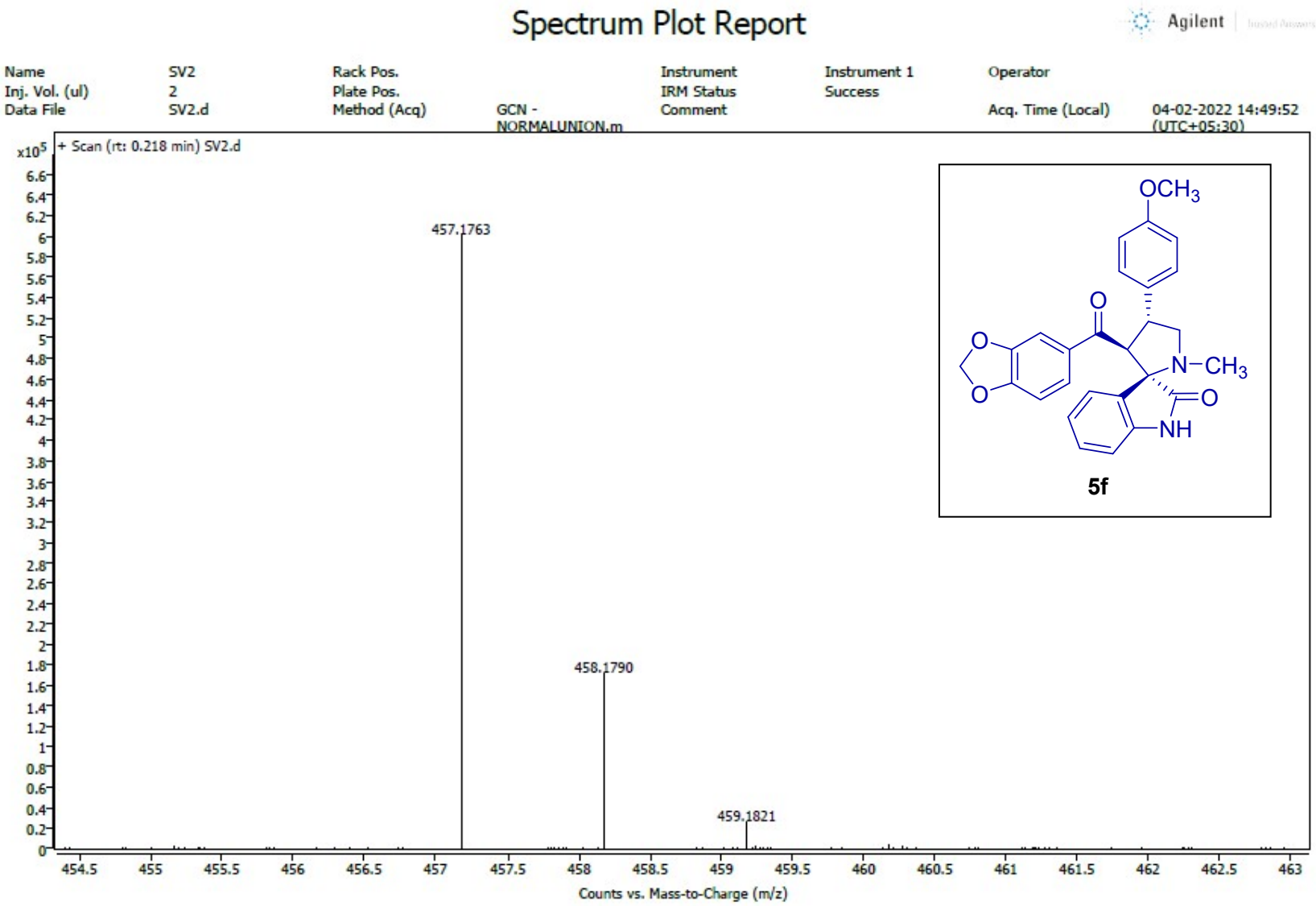


Fig 18. HR-MS spectrum of compound **5f**.

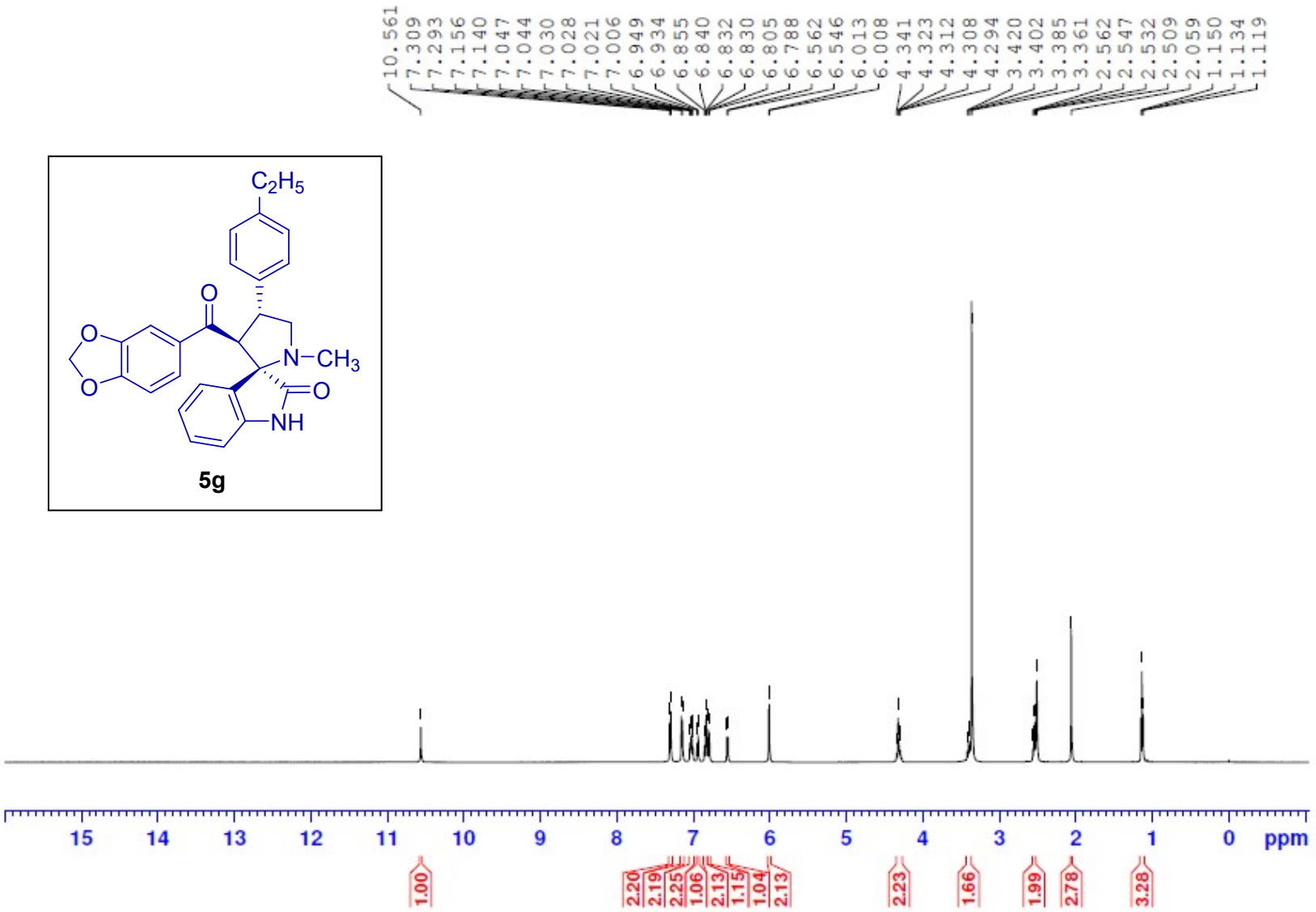


Fig 19. ^{1}H NMR spectrum of compound **5g**.

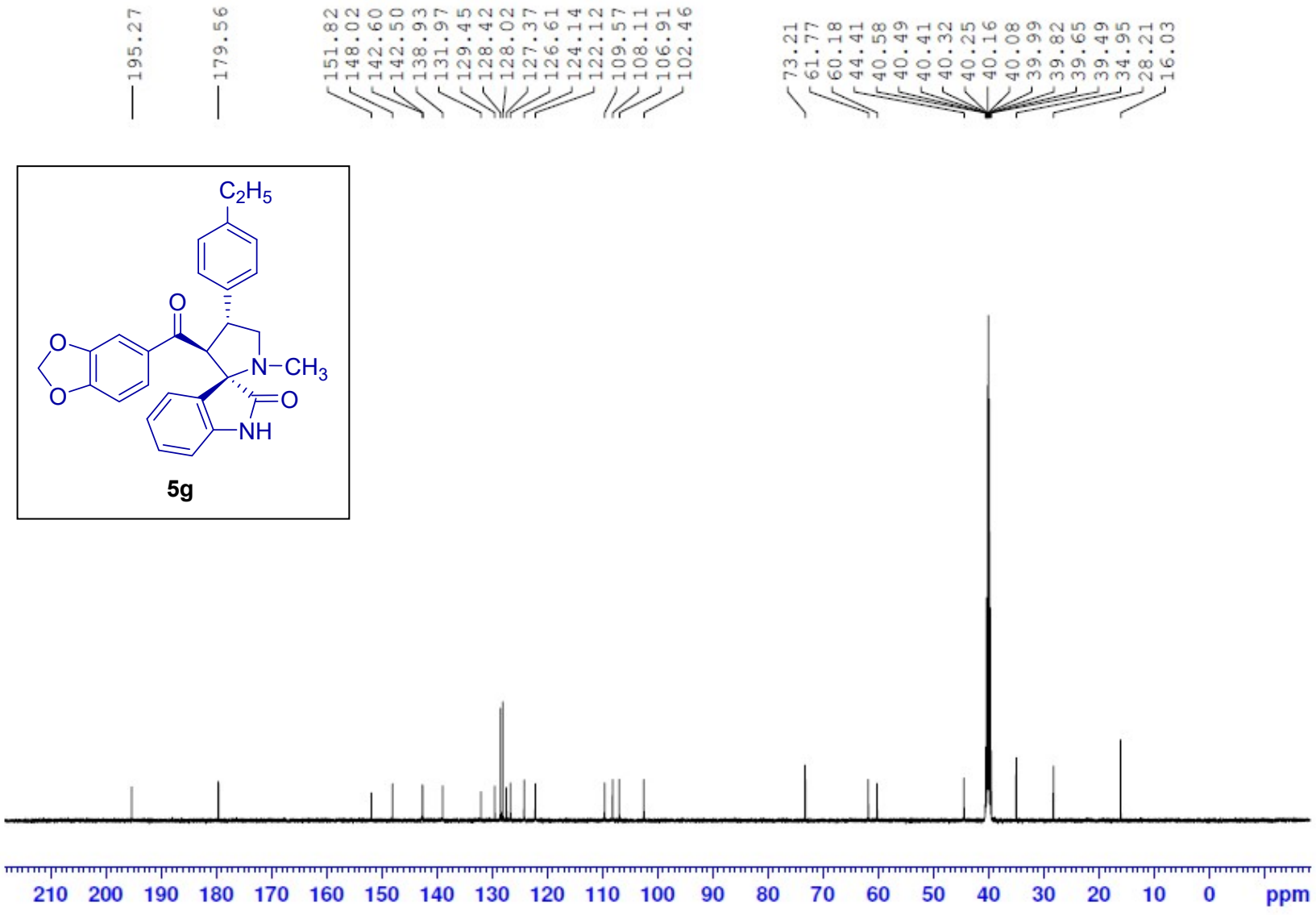


Fig 20. ^{13}C NMR spectrum of compound **5g**.

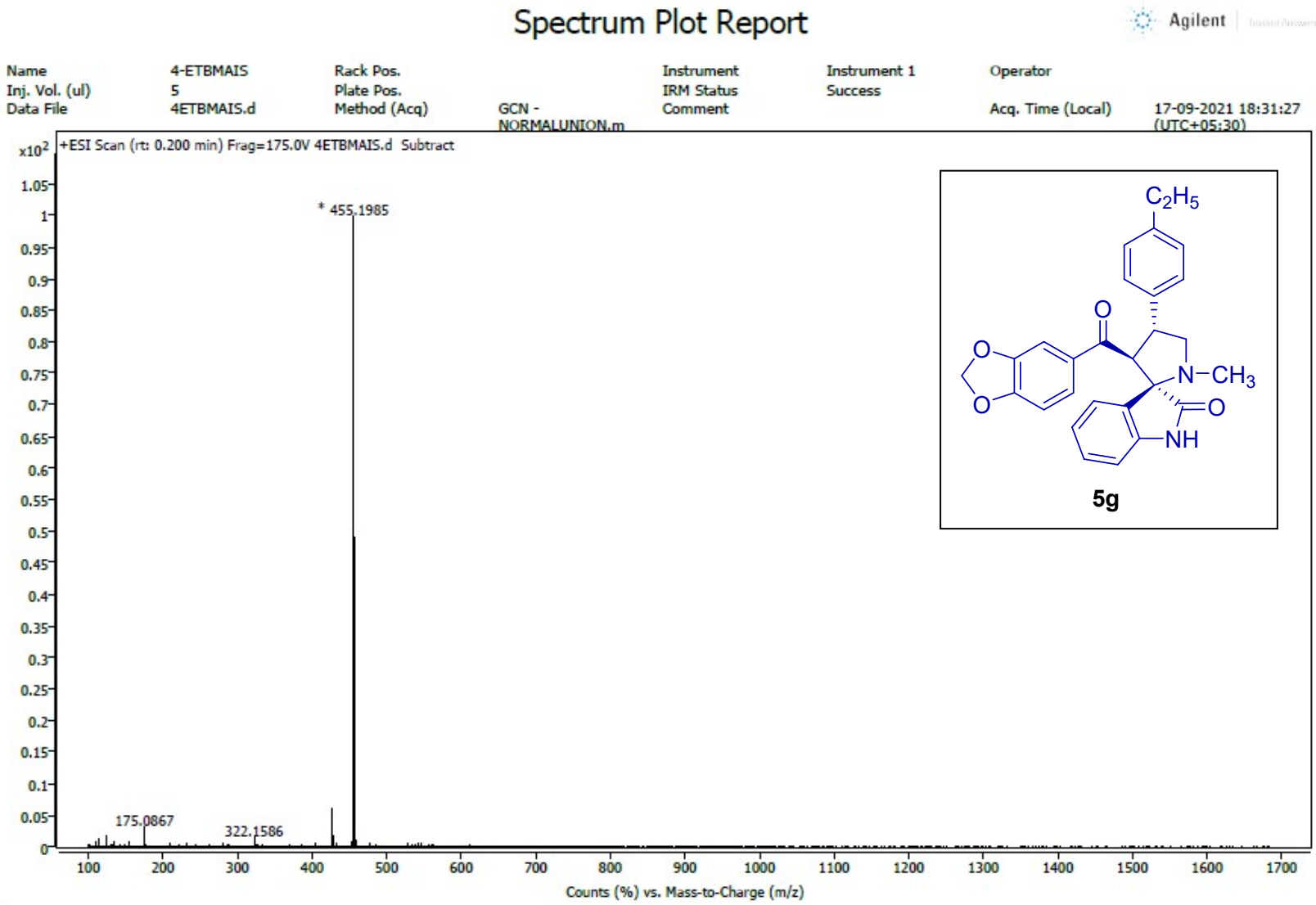
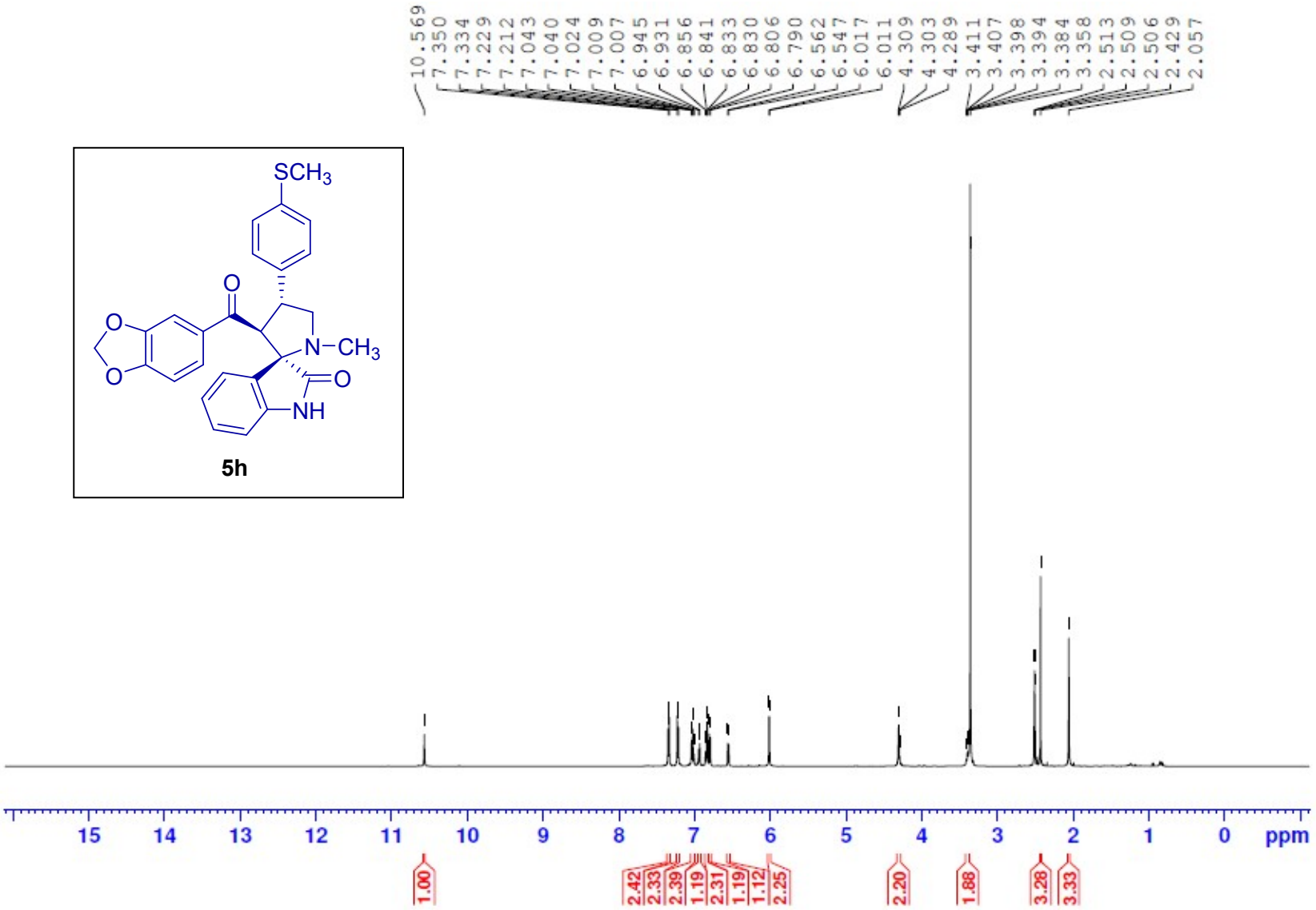


Fig 21. HR-MS spectrum of compound **5g**.



. **Fig 22.** [1]H NMR spectrum of compound **5h**.

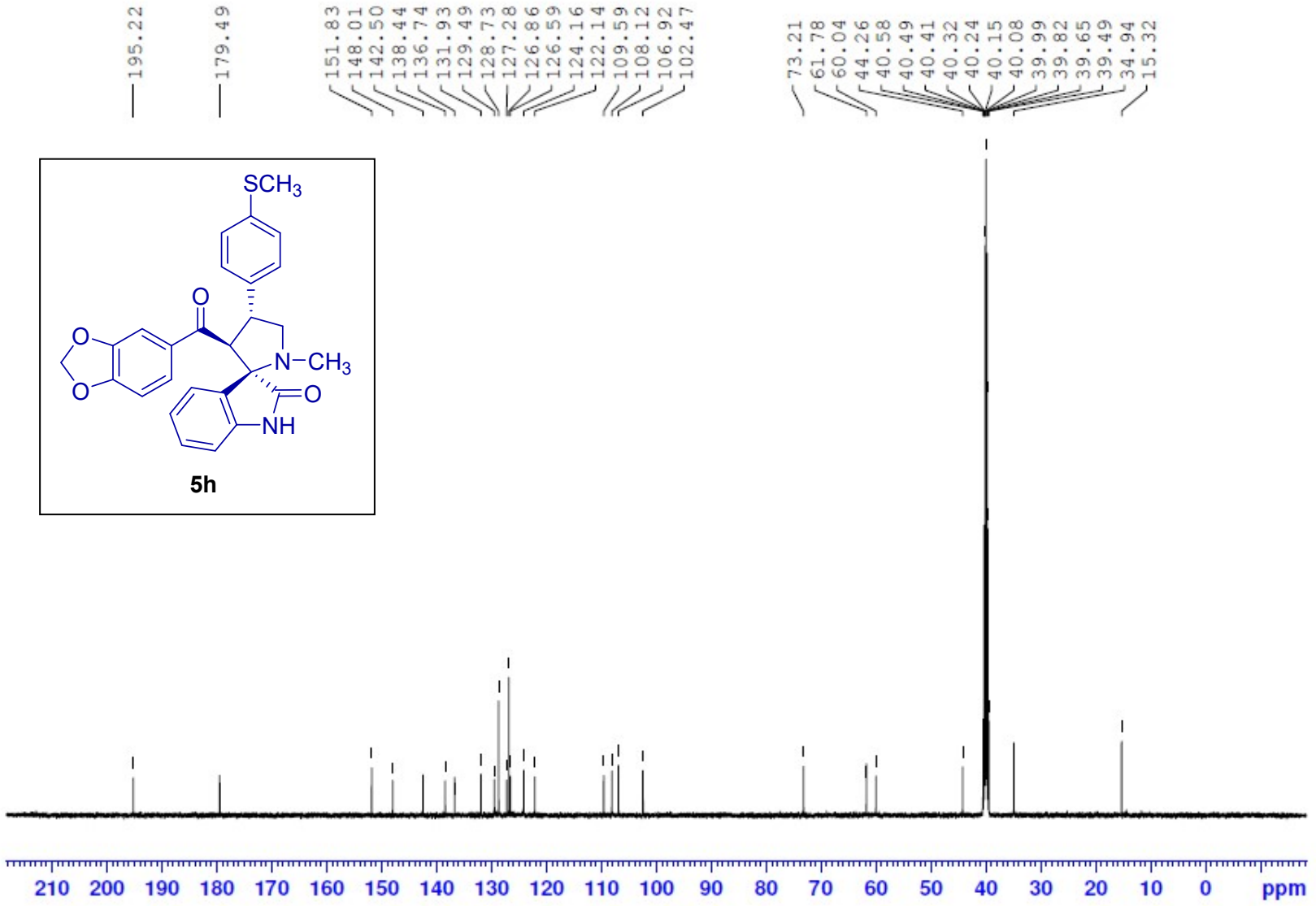


Fig 23. ^{13}C NMR spectrum of compound **5h**.

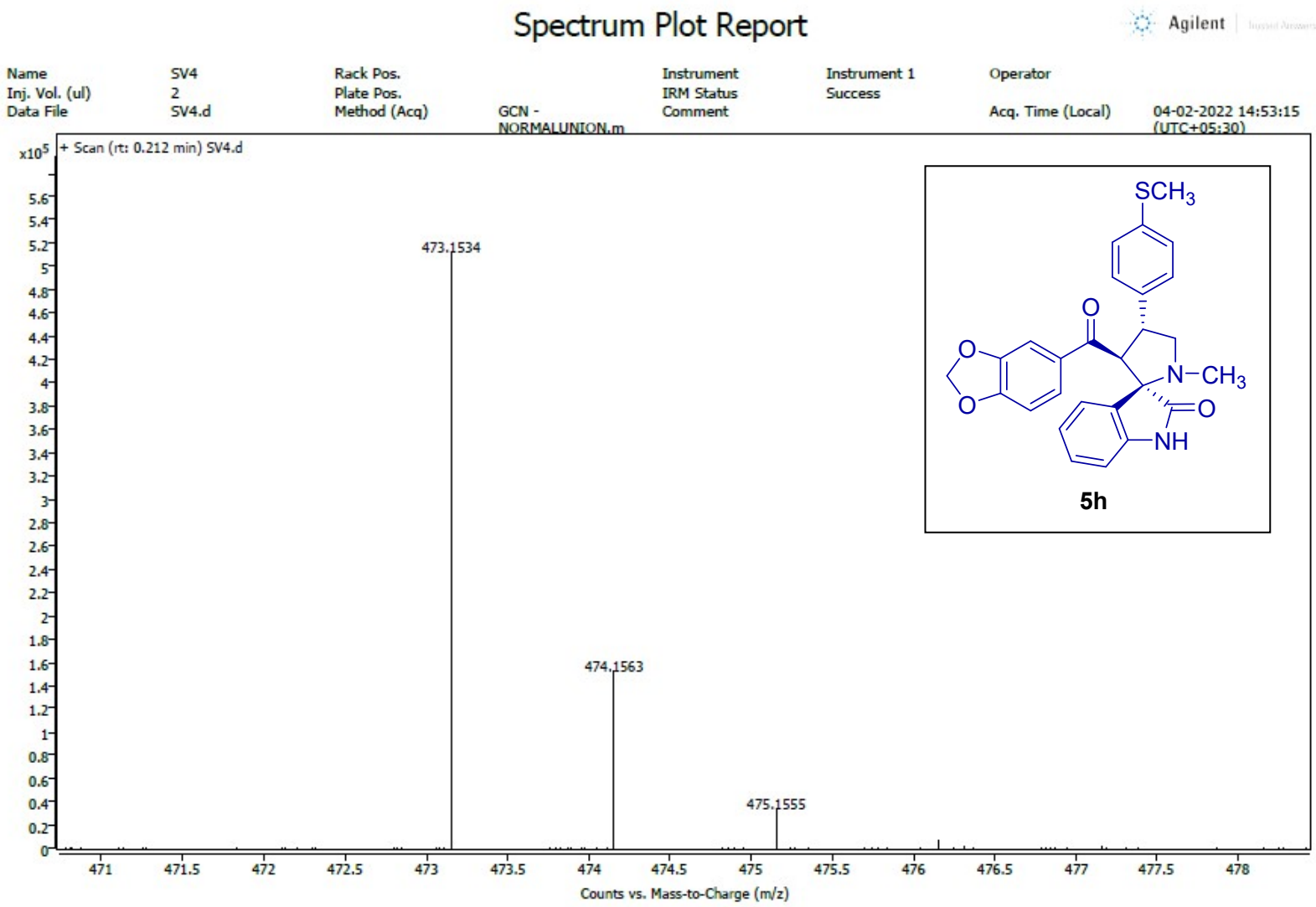


Fig 24. HR-MS spectrum of compound **5h**.

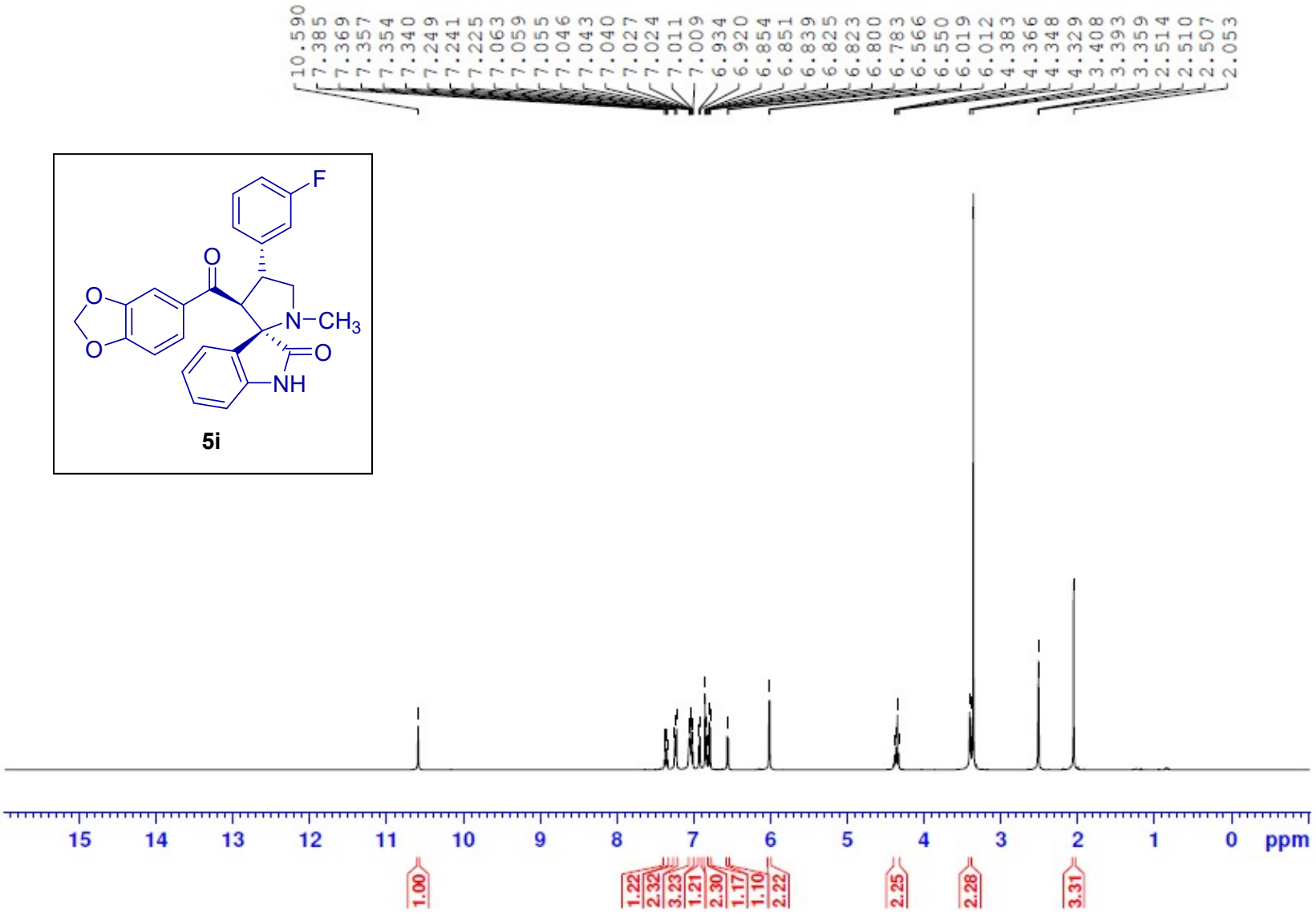


Fig 25. ^{1}H NMR spectrum of compound **5i**.

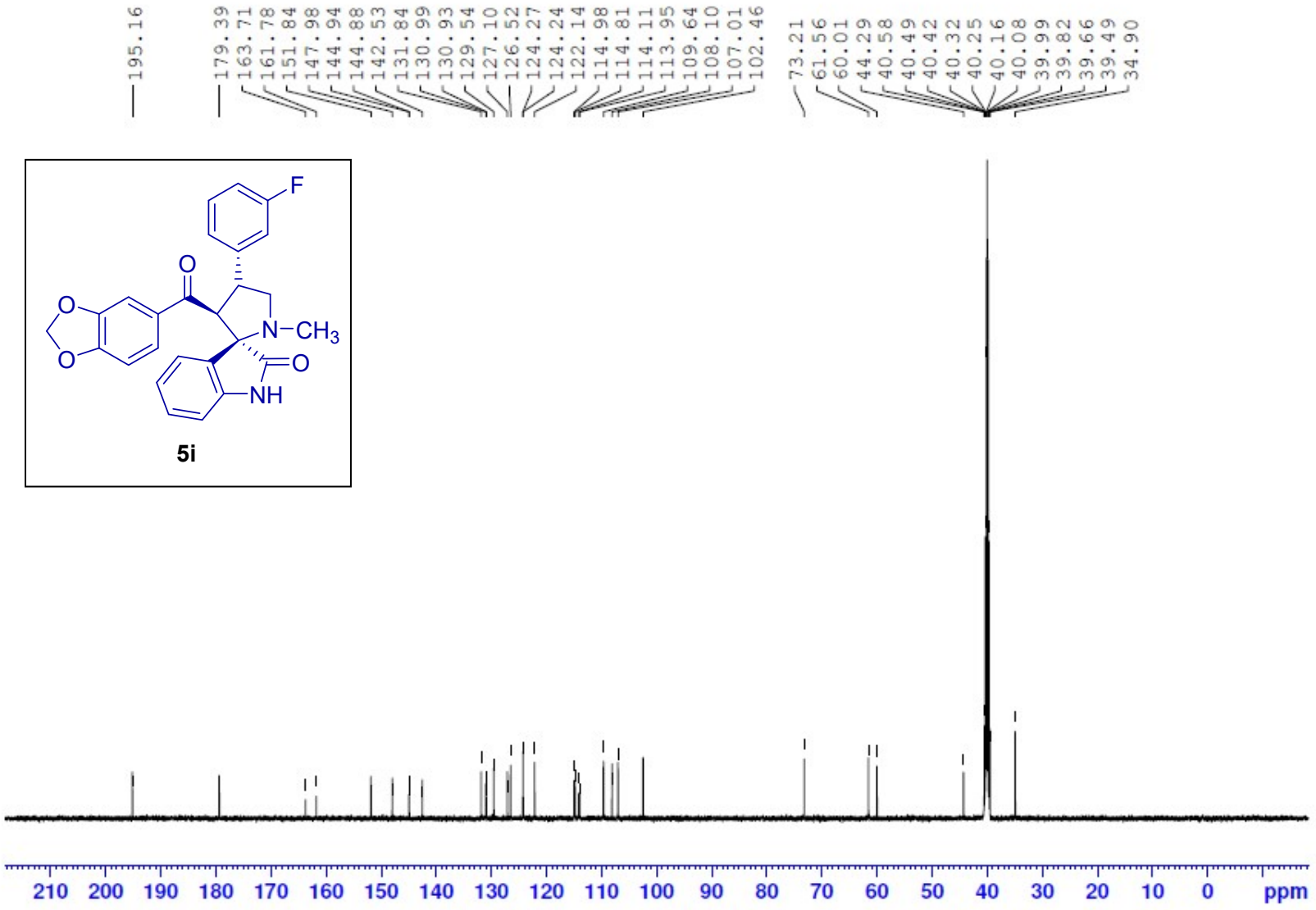


Fig 26. ^{13}C NMR spectrum of compound **5i**.

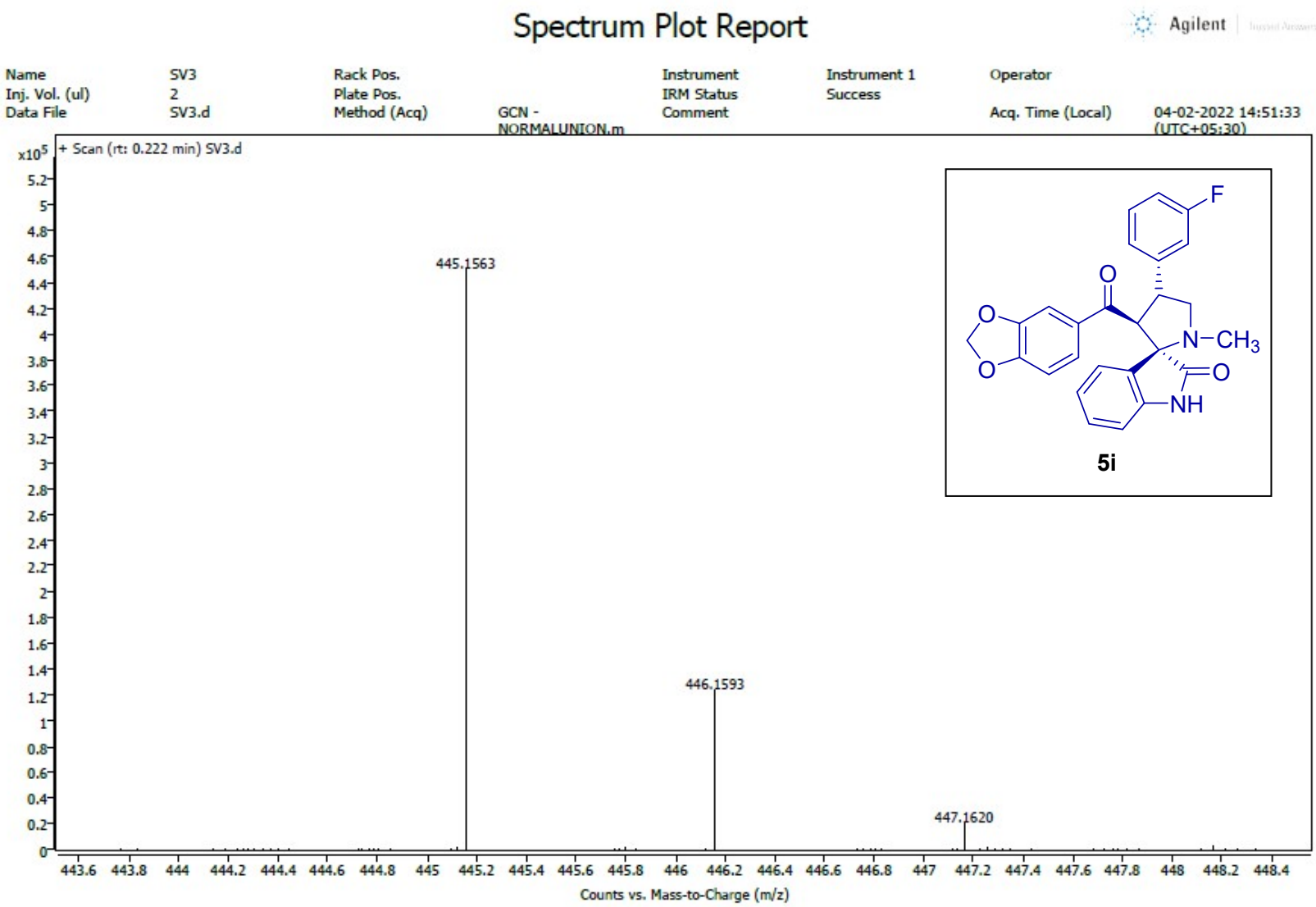


Fig 27. HR-MS spectrum of compound **5i**.

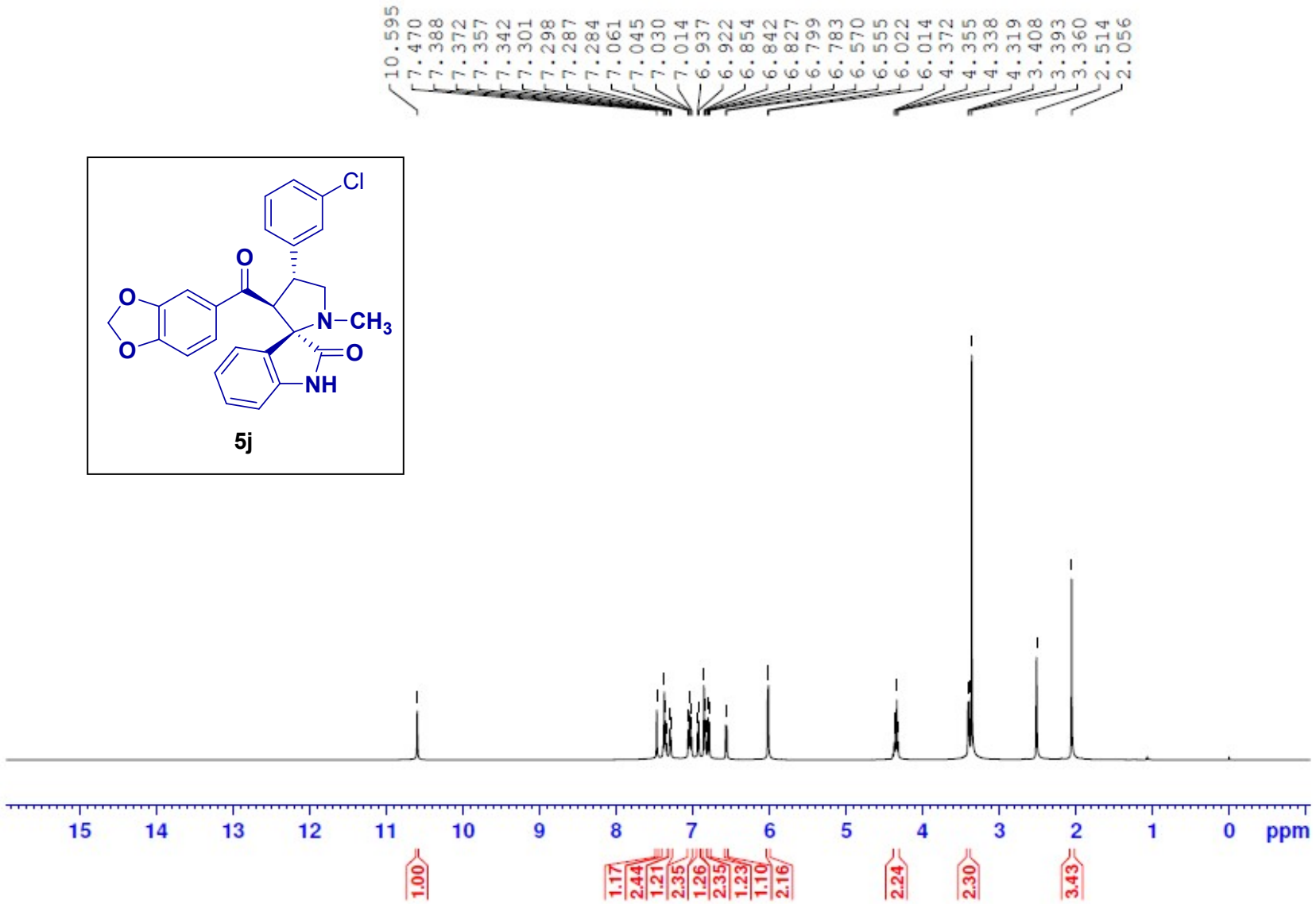


Fig 28. ^{1}H NMR spectrum of compound **5j**.

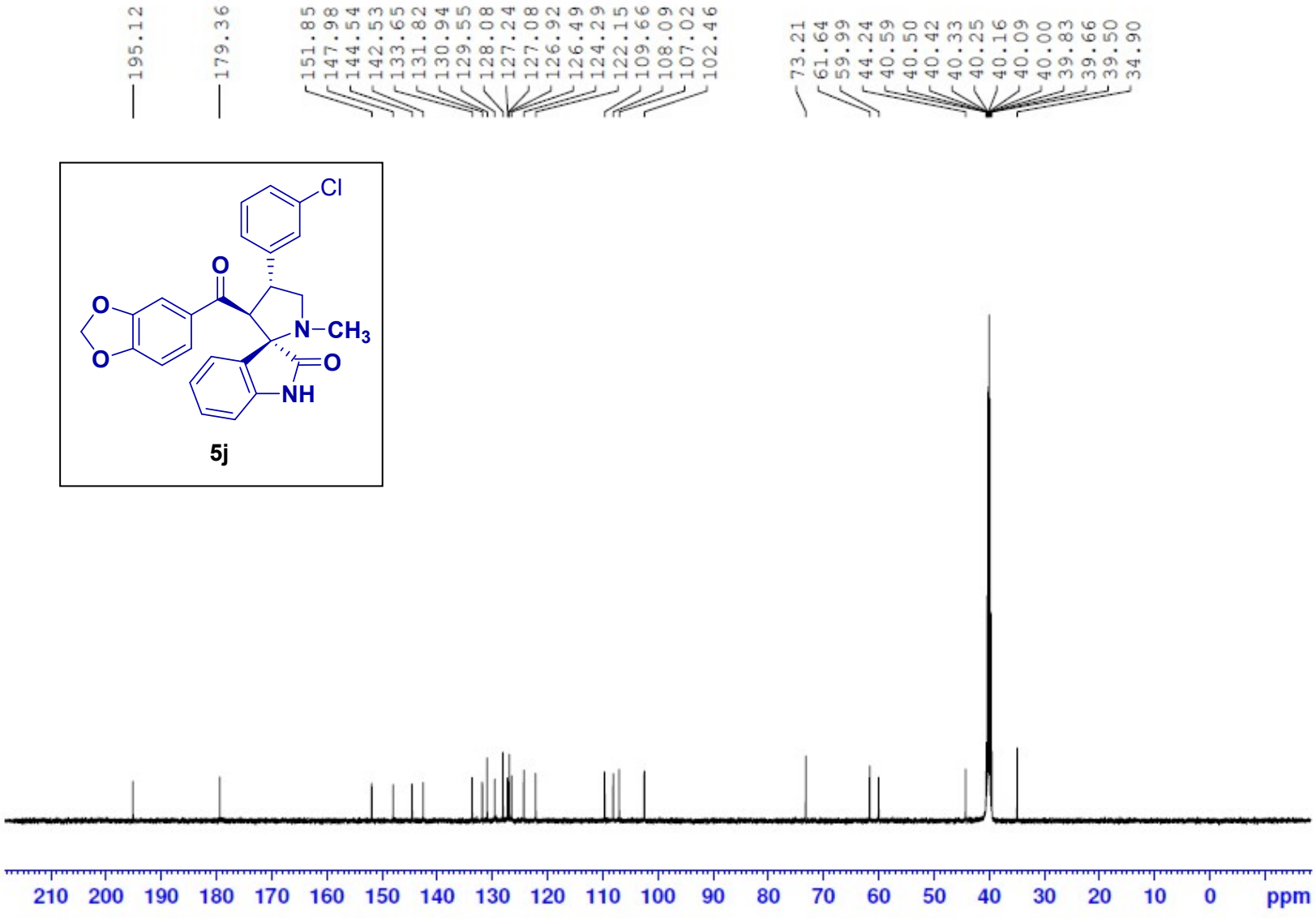


Fig 29. ^{13}C NMR spectrum of compound **5j**.

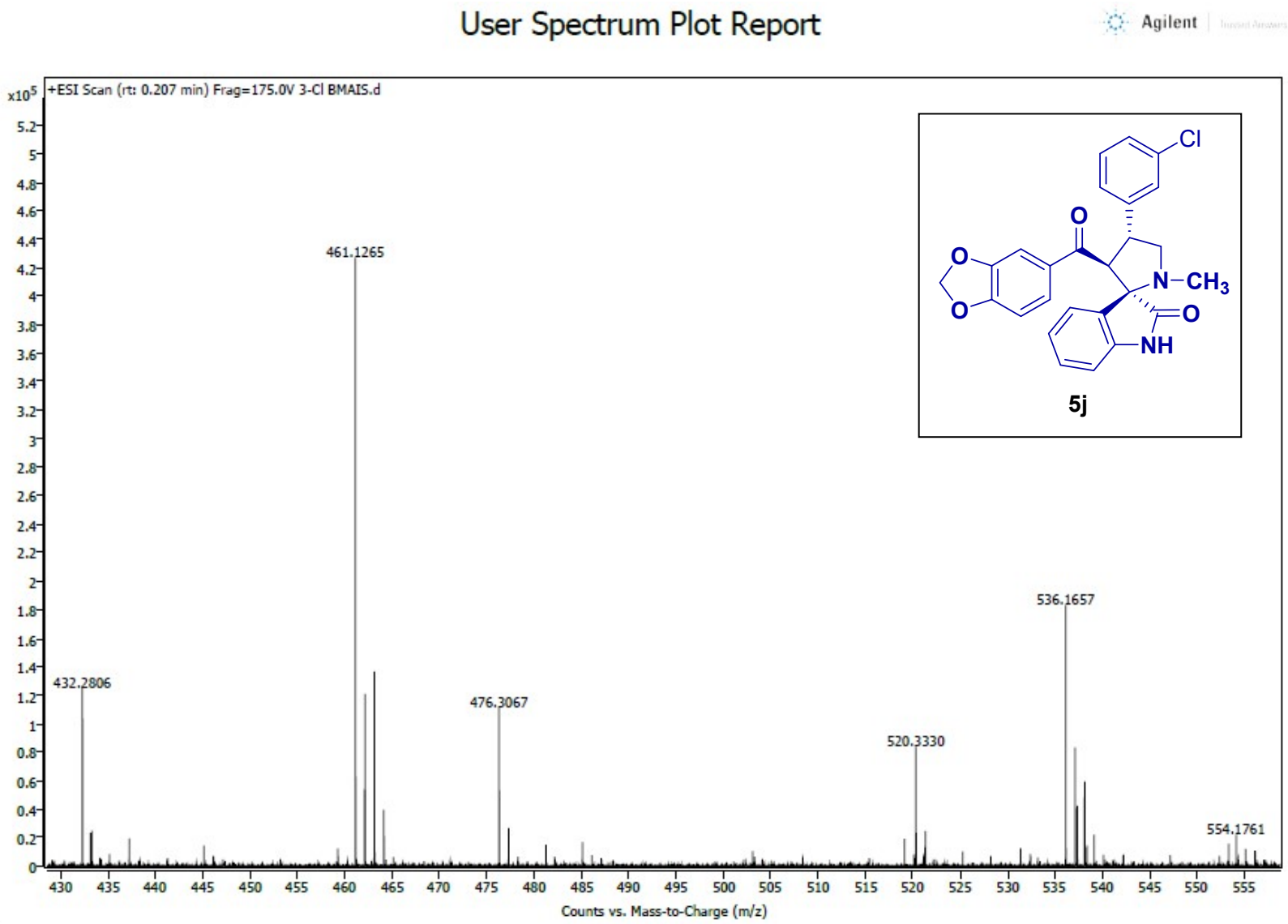


Fig 30. HR-MS spectrum of compound **5j**.

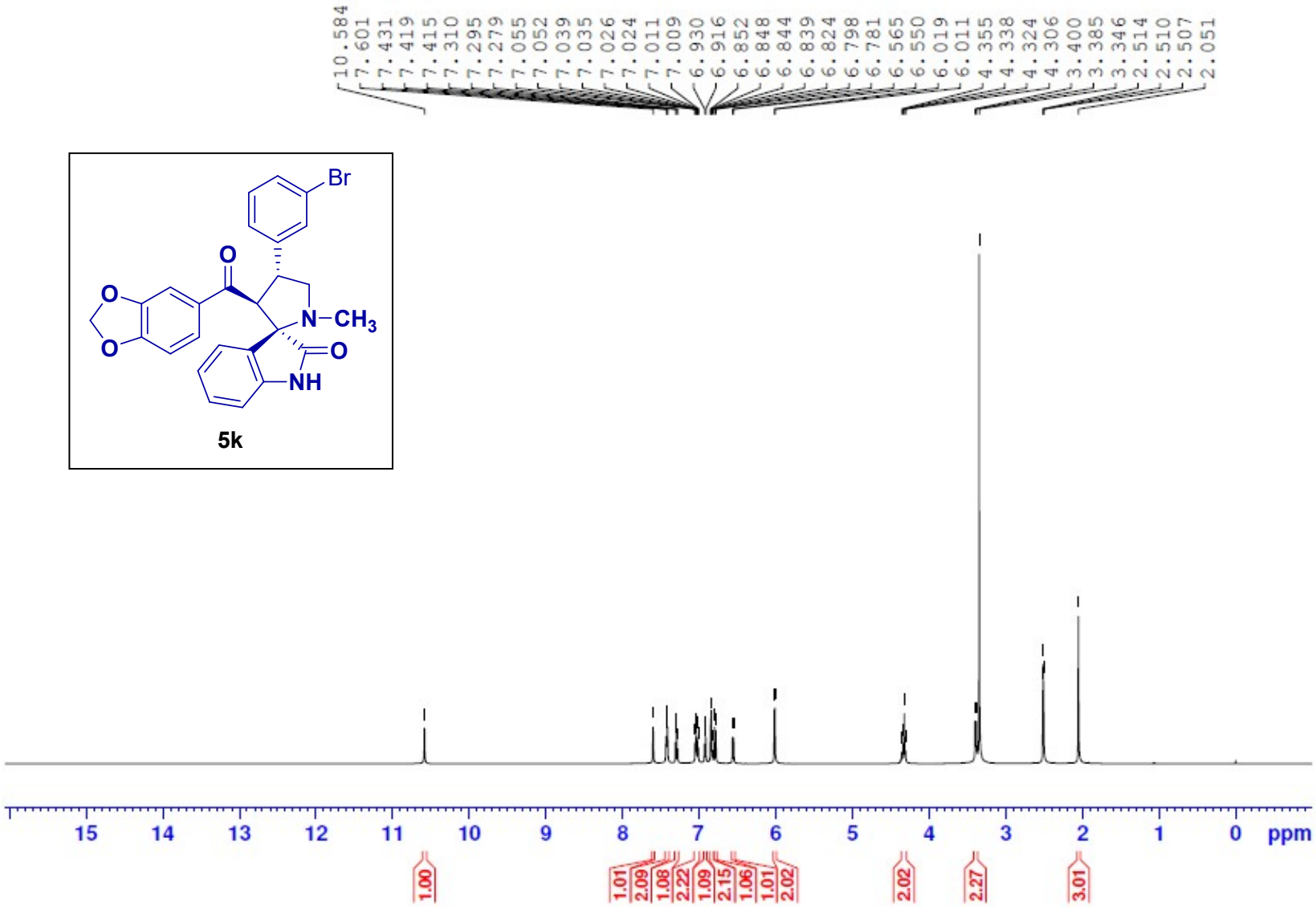


Fig 31. ^{1}H NMR spectrum of compound **5k**.

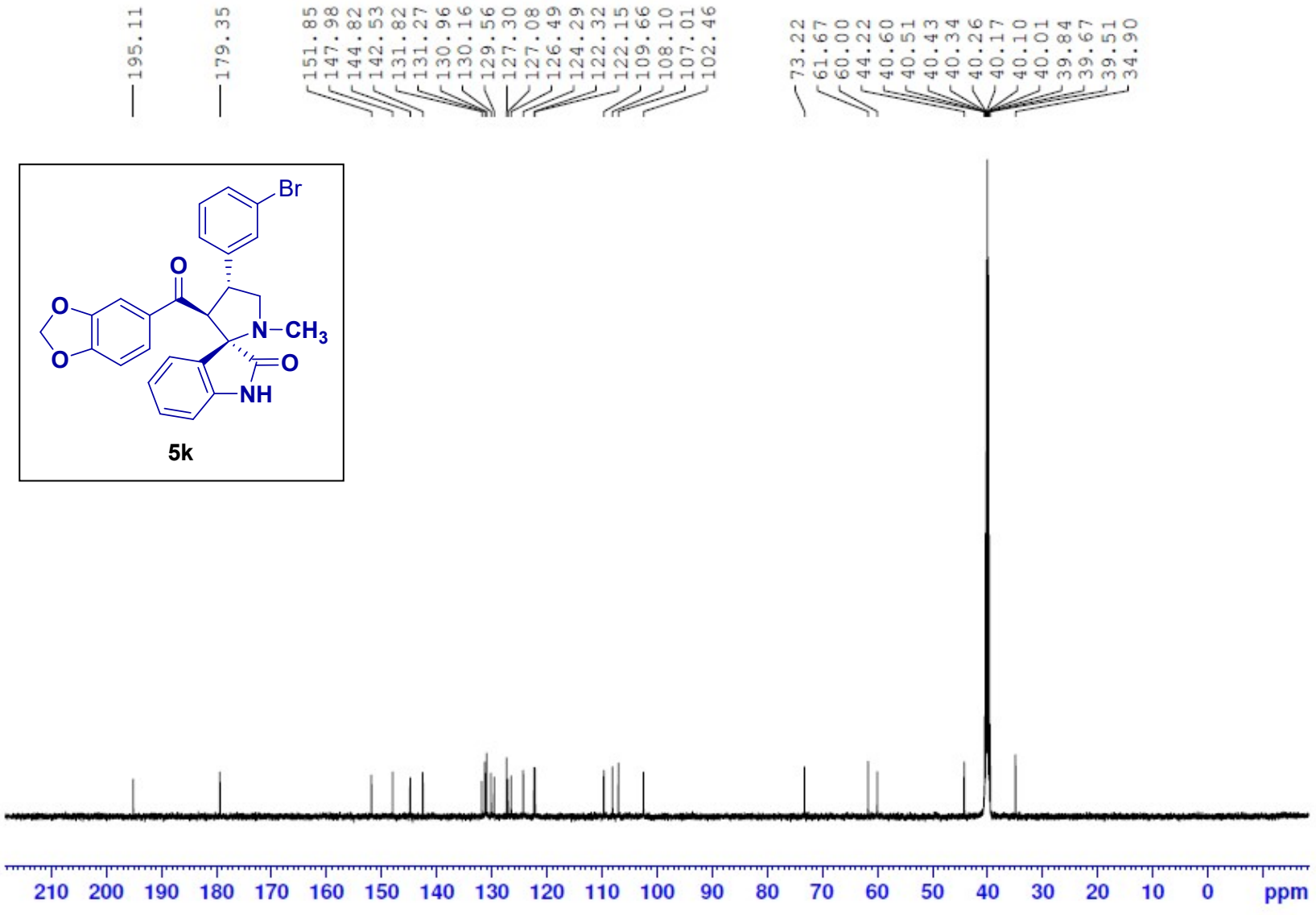


Fig 32. ^{13}C NMR spectrum of compound **5k**.

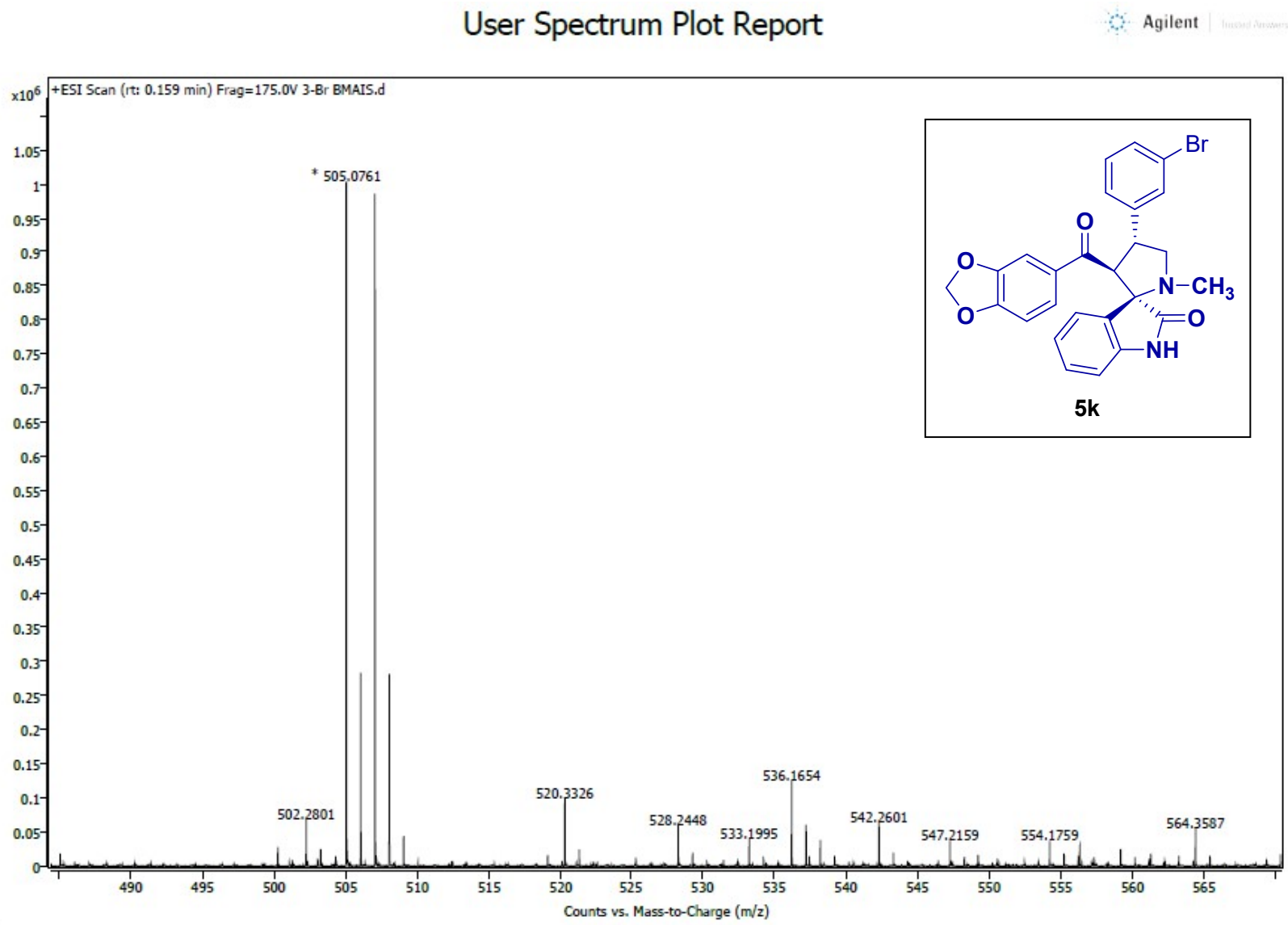


Fig 33. HR-MS spectrum of compound **5k**.

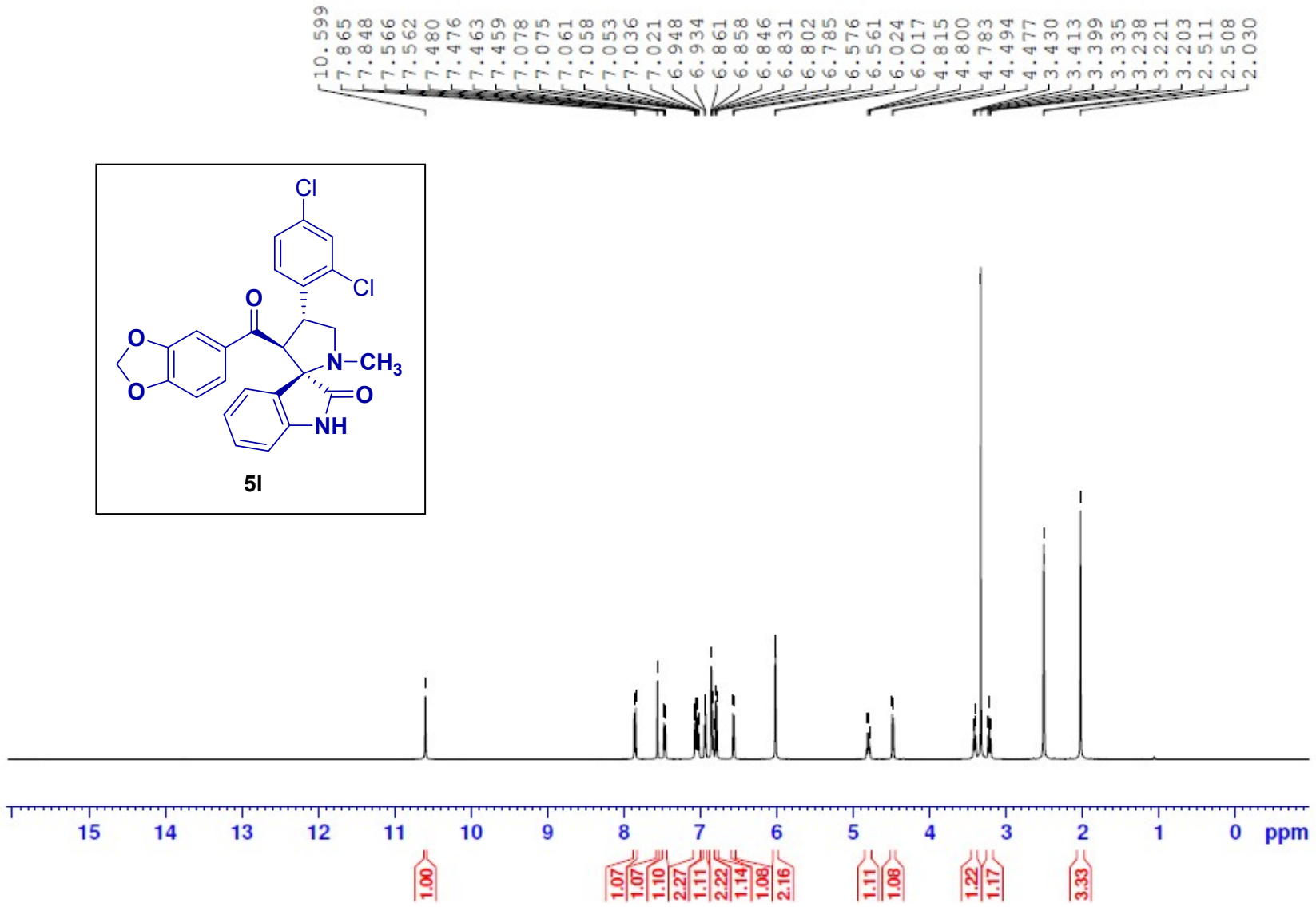


Fig 34. ^{1}H NMR spectrum of compound **5l**.

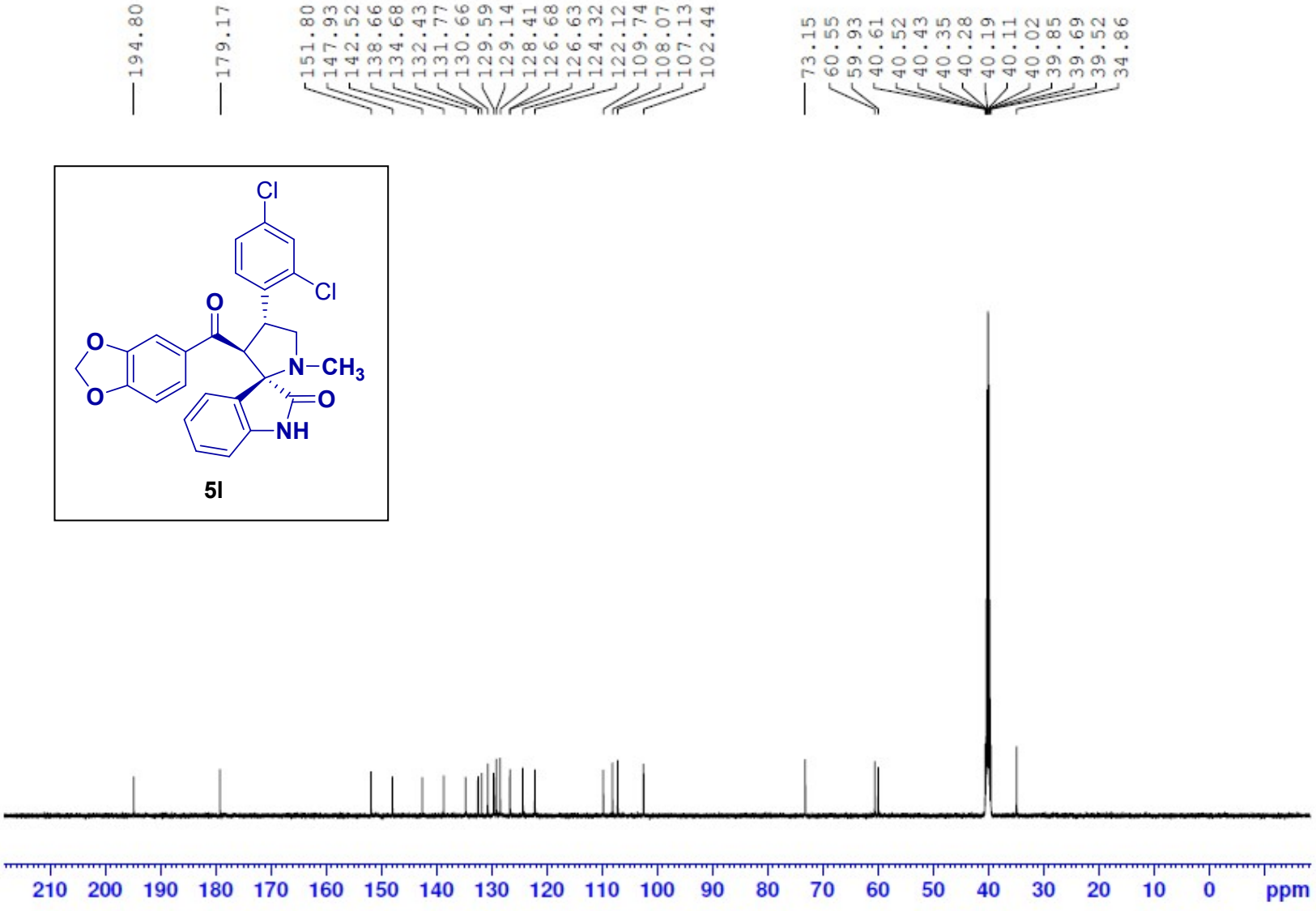


Fig 35. ^{13}C NMR spectrum of compound **5l**.

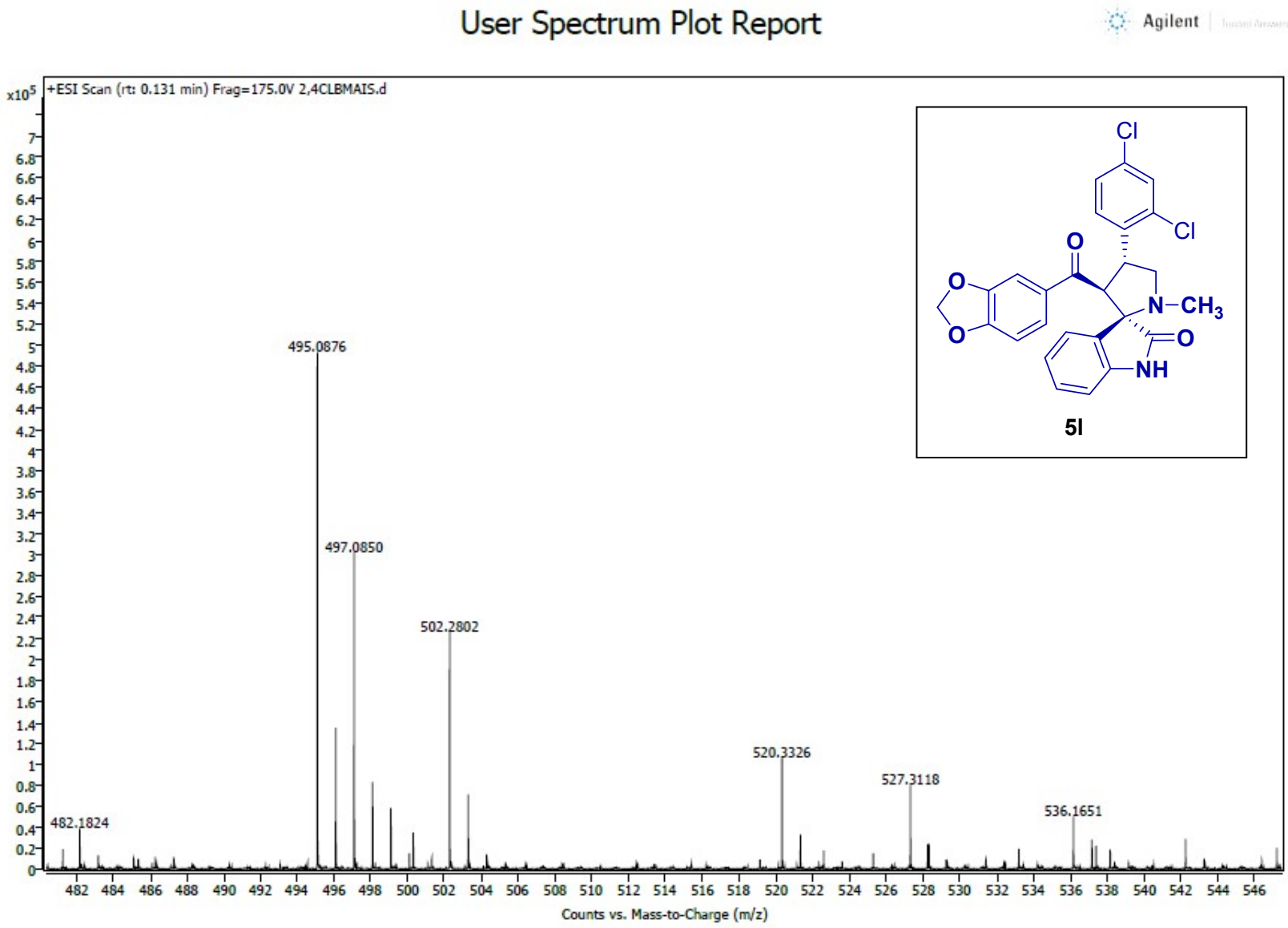


Fig 36. HR-MS spectrum of compound **5l**.

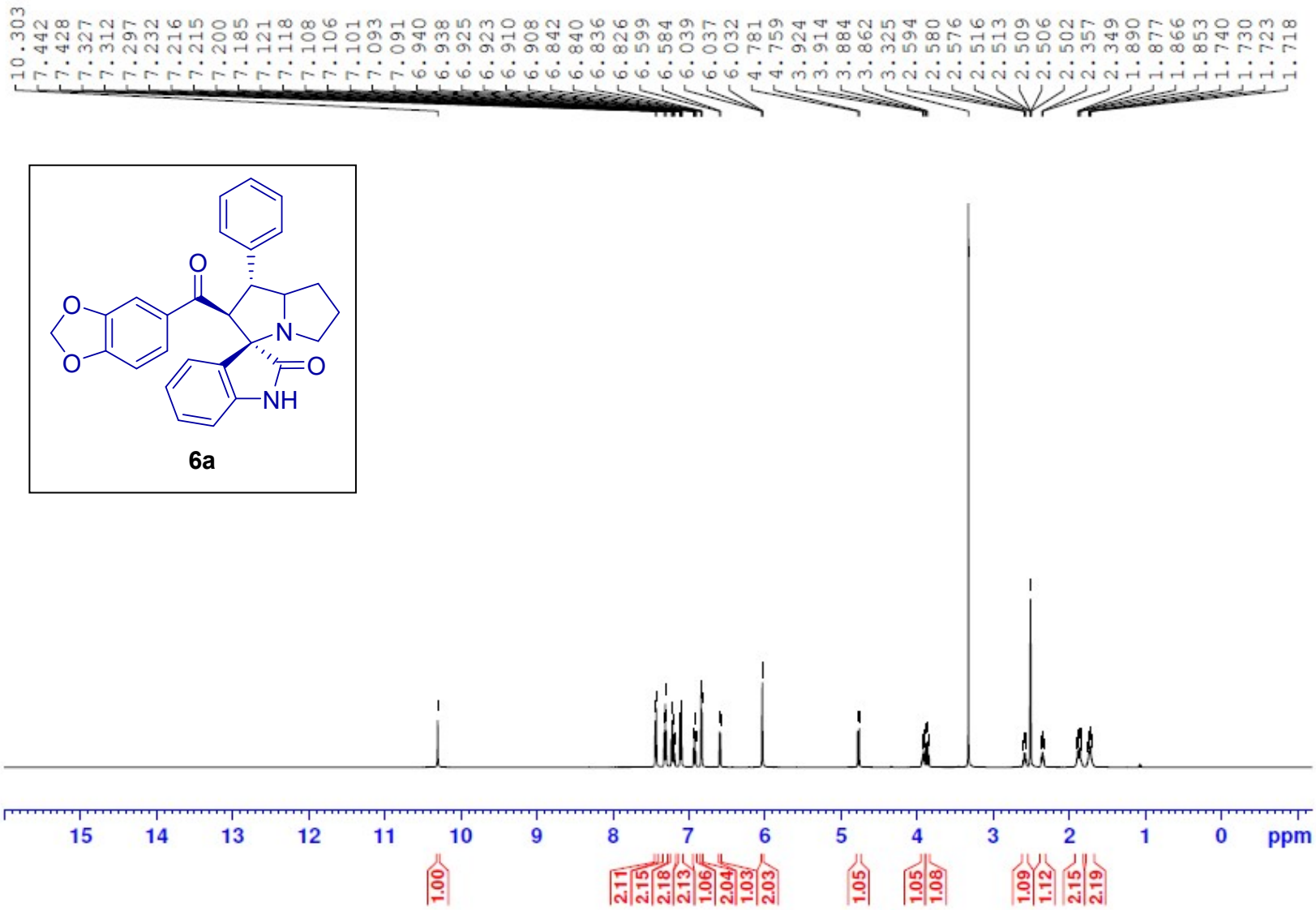


Fig 37. ^{1}H NMR spectrum of compound **6a**.

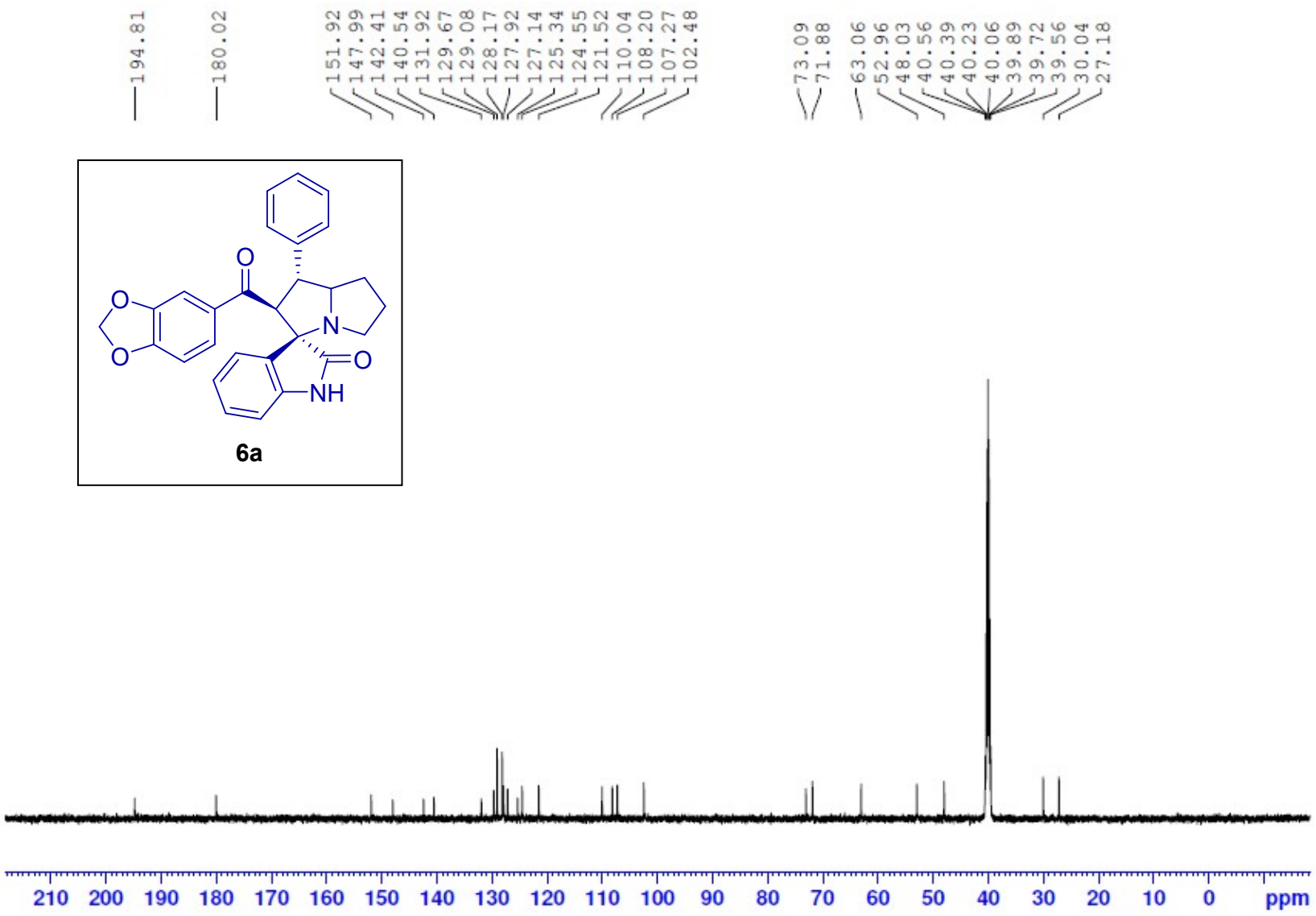


Fig 38. ^{13}C NMR spectrum of compound **6a**.

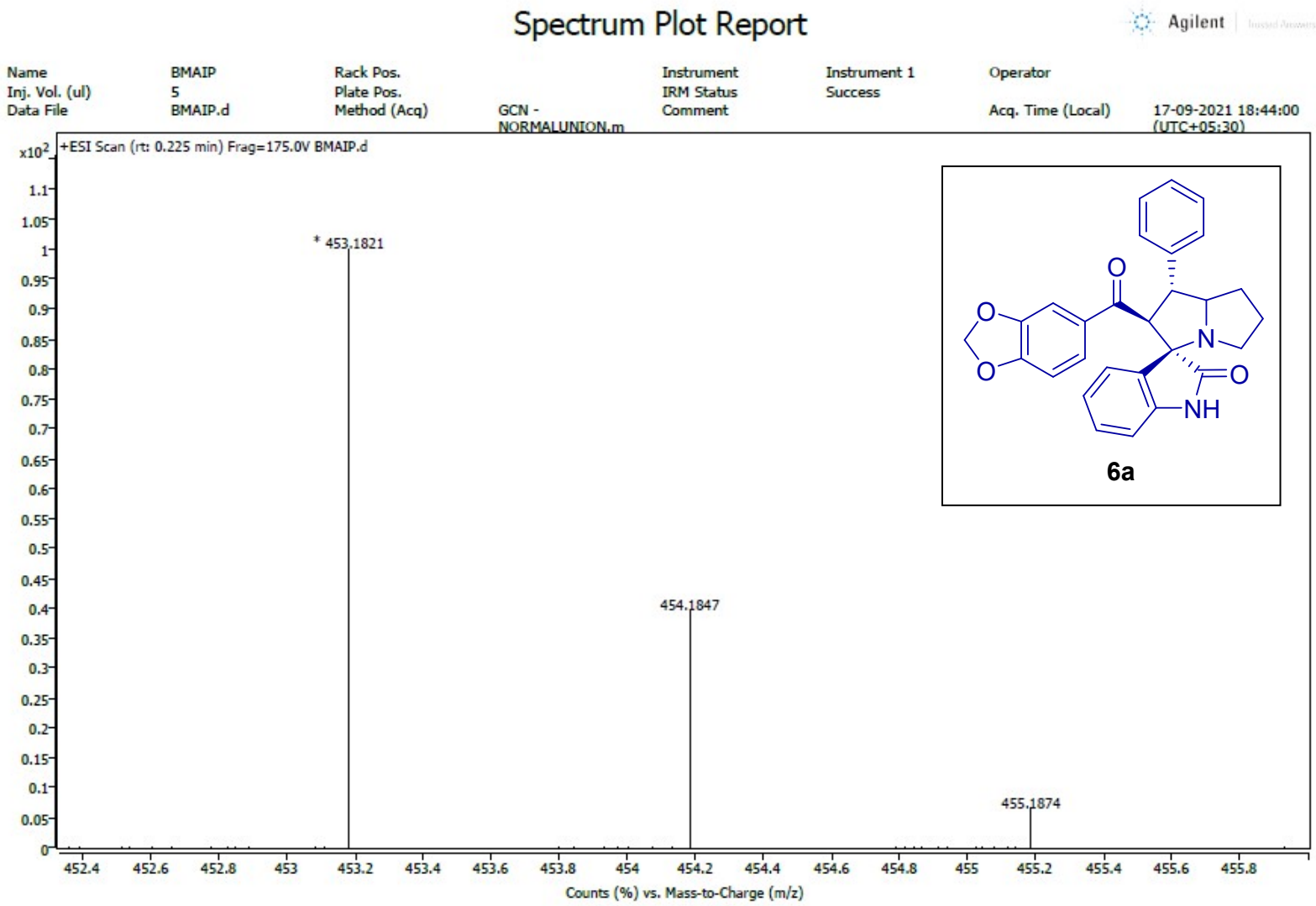


Fig 39. HR-MS spectrum of compound **6a**.

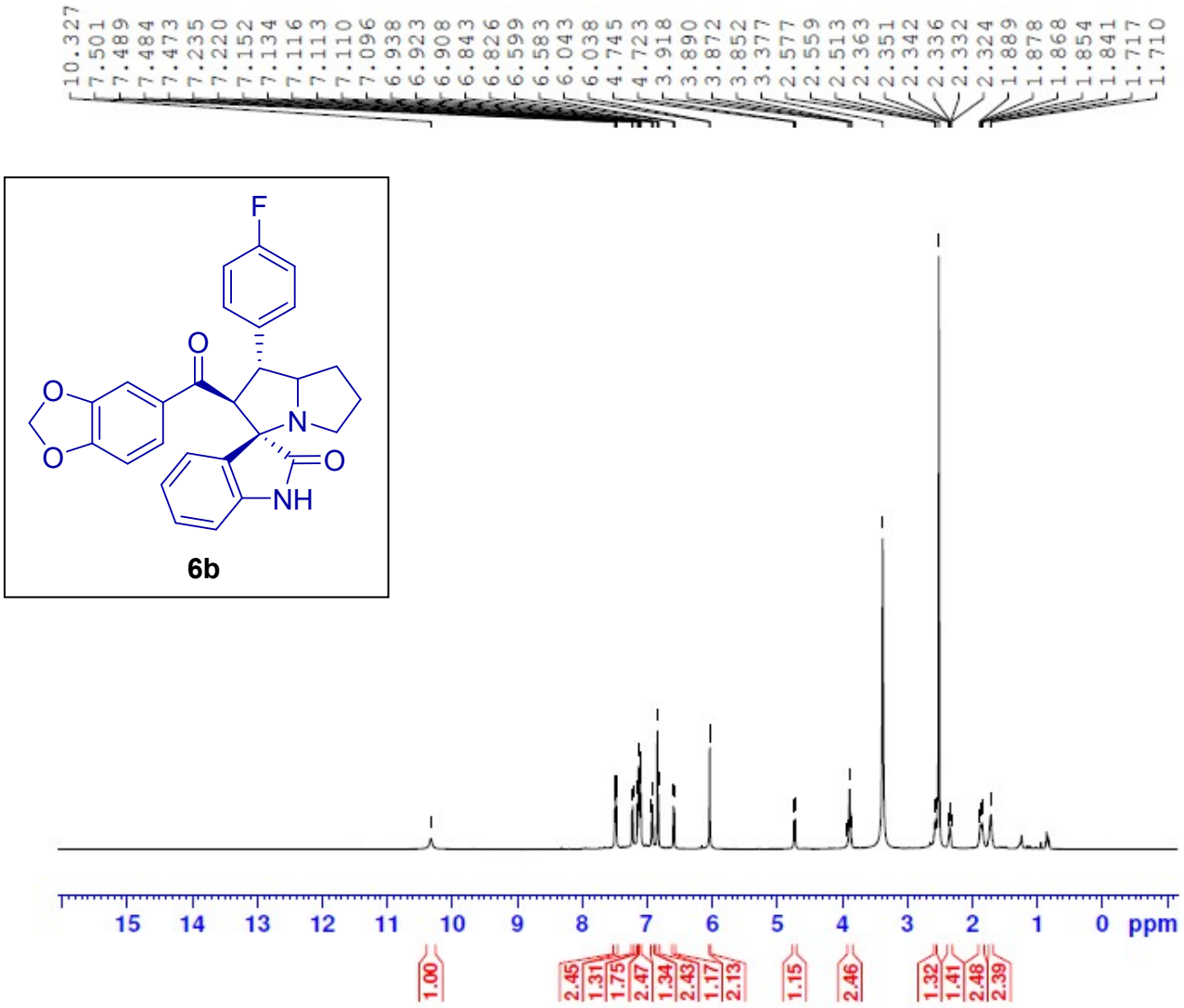


Fig 40. ^{1}H NMR spectrum of compound **6b**.

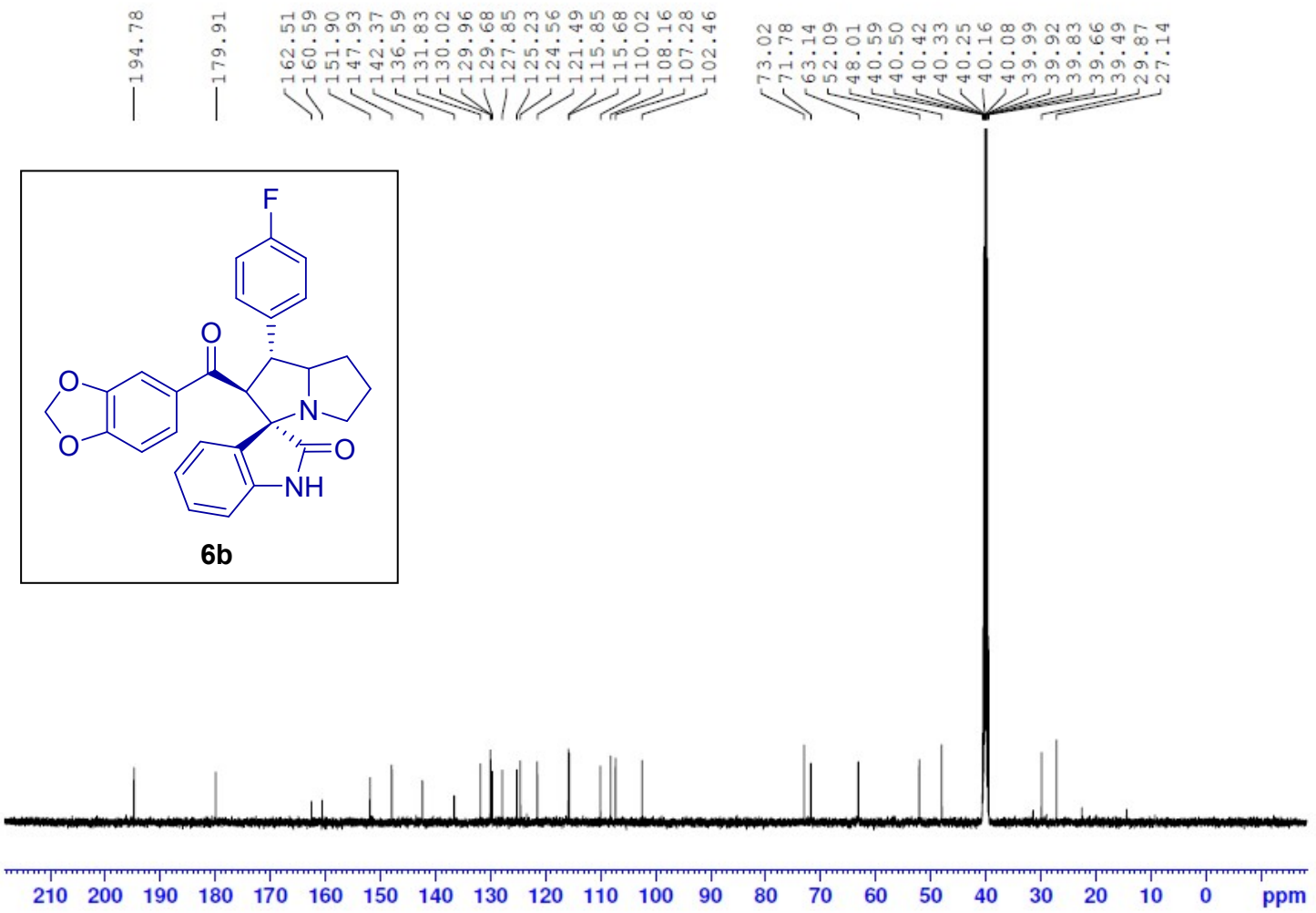


Fig 41. ^{13}C NMR spectrum of compound **6b**.

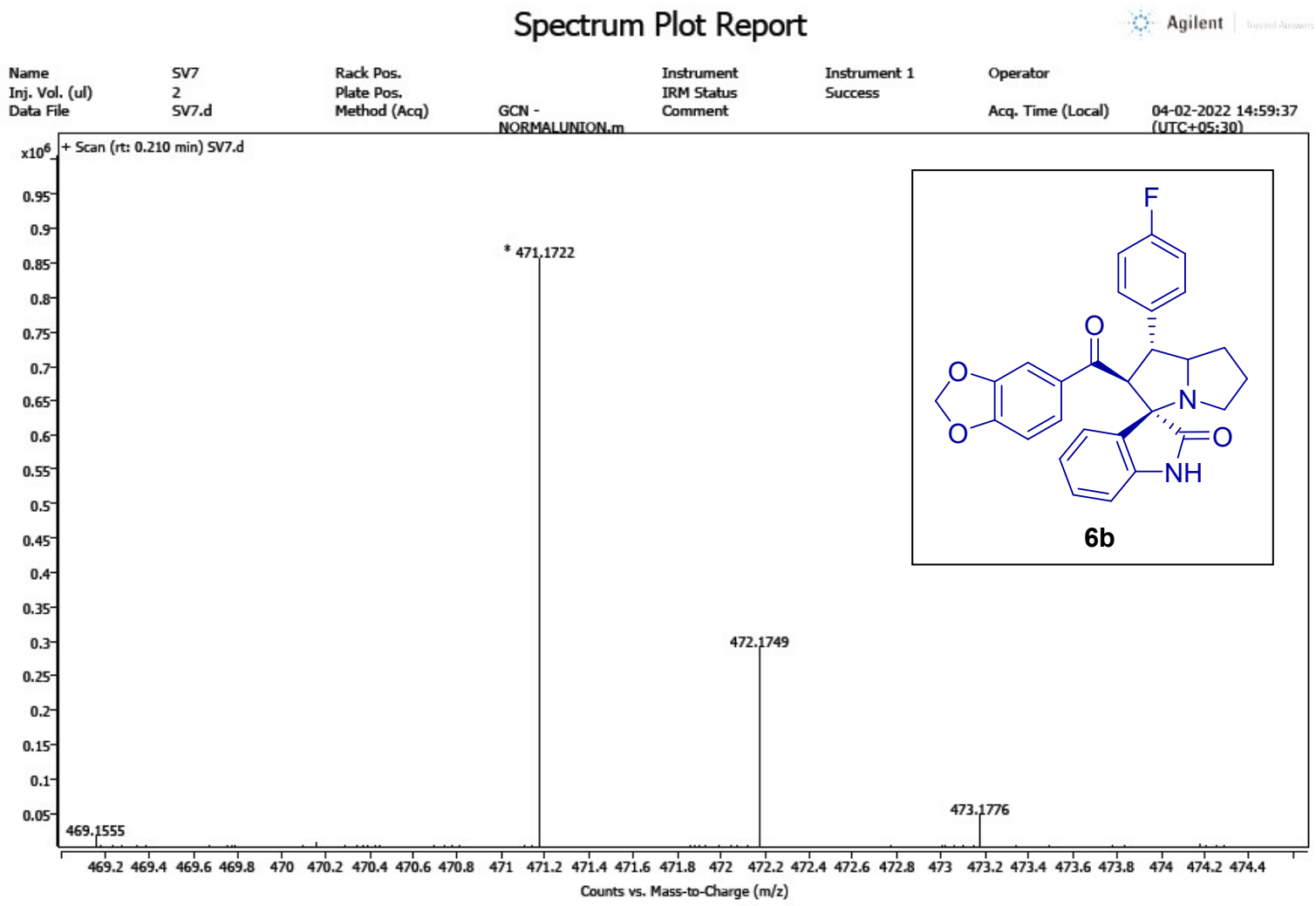


Fig 42. HR-MS spectrum of compound **6b**.

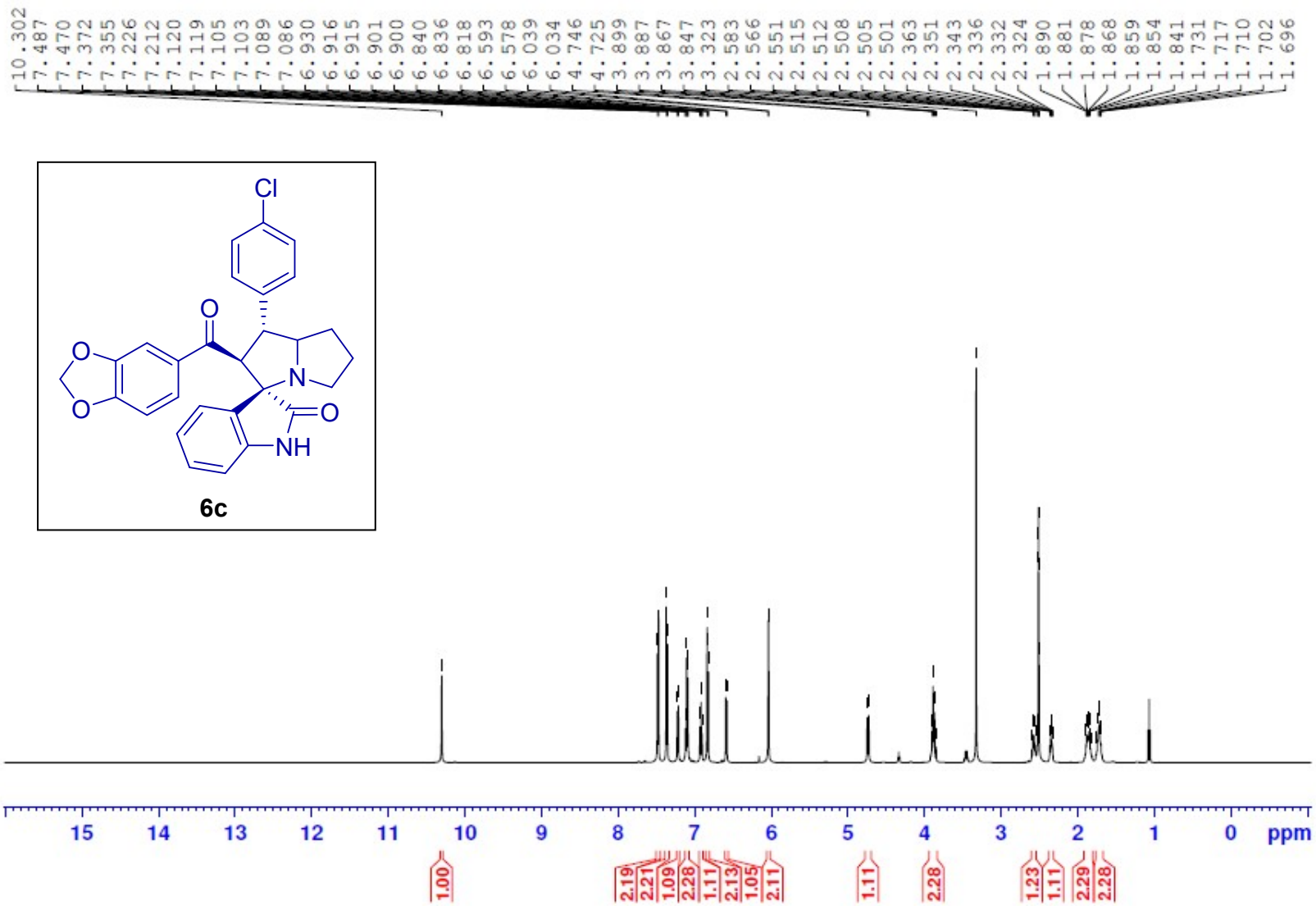


Fig 43. ^{1}H NMR spectrum of compound **6c**.

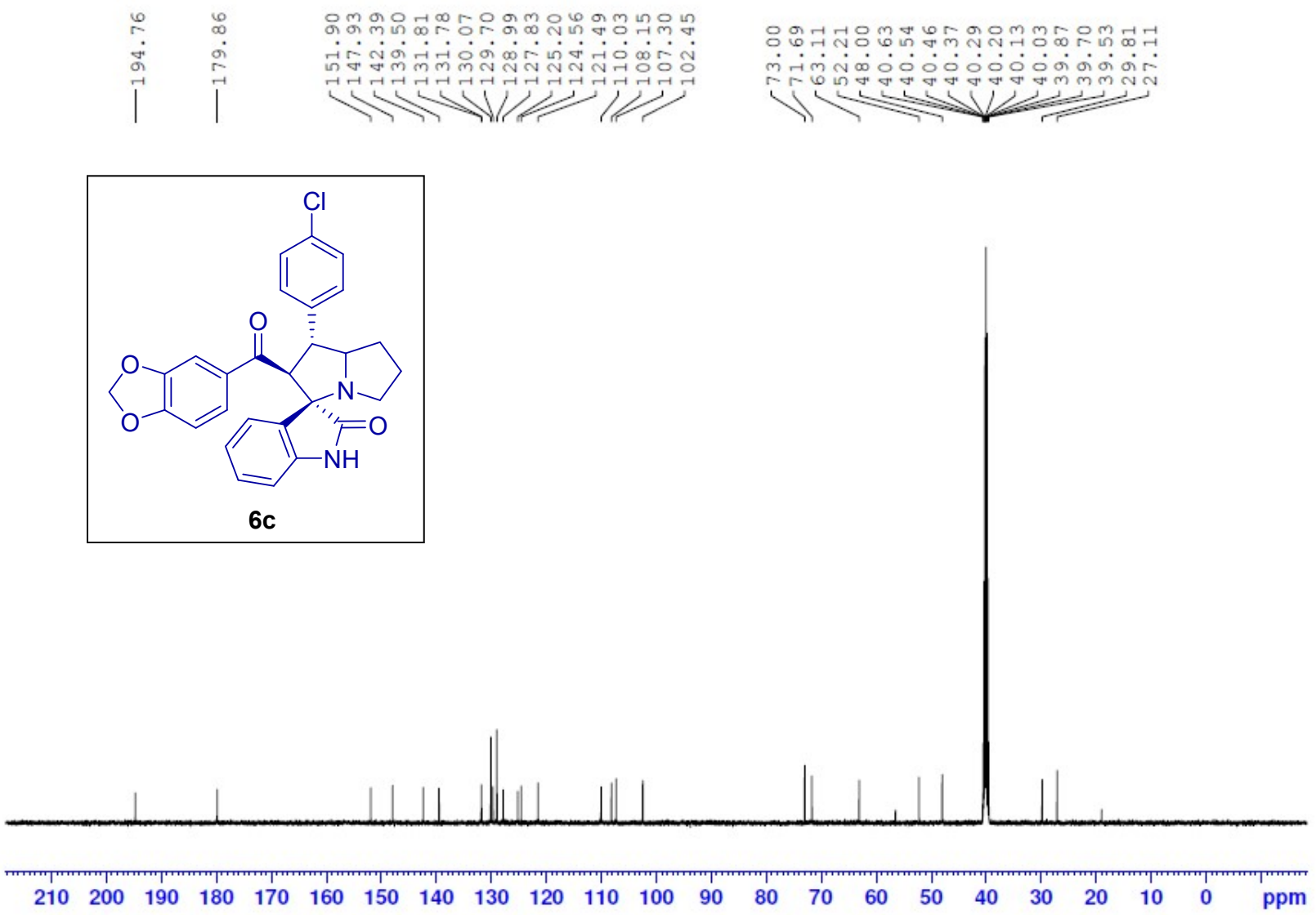


Fig 44. ^{13}C NMR spectrum of compound **6c**.

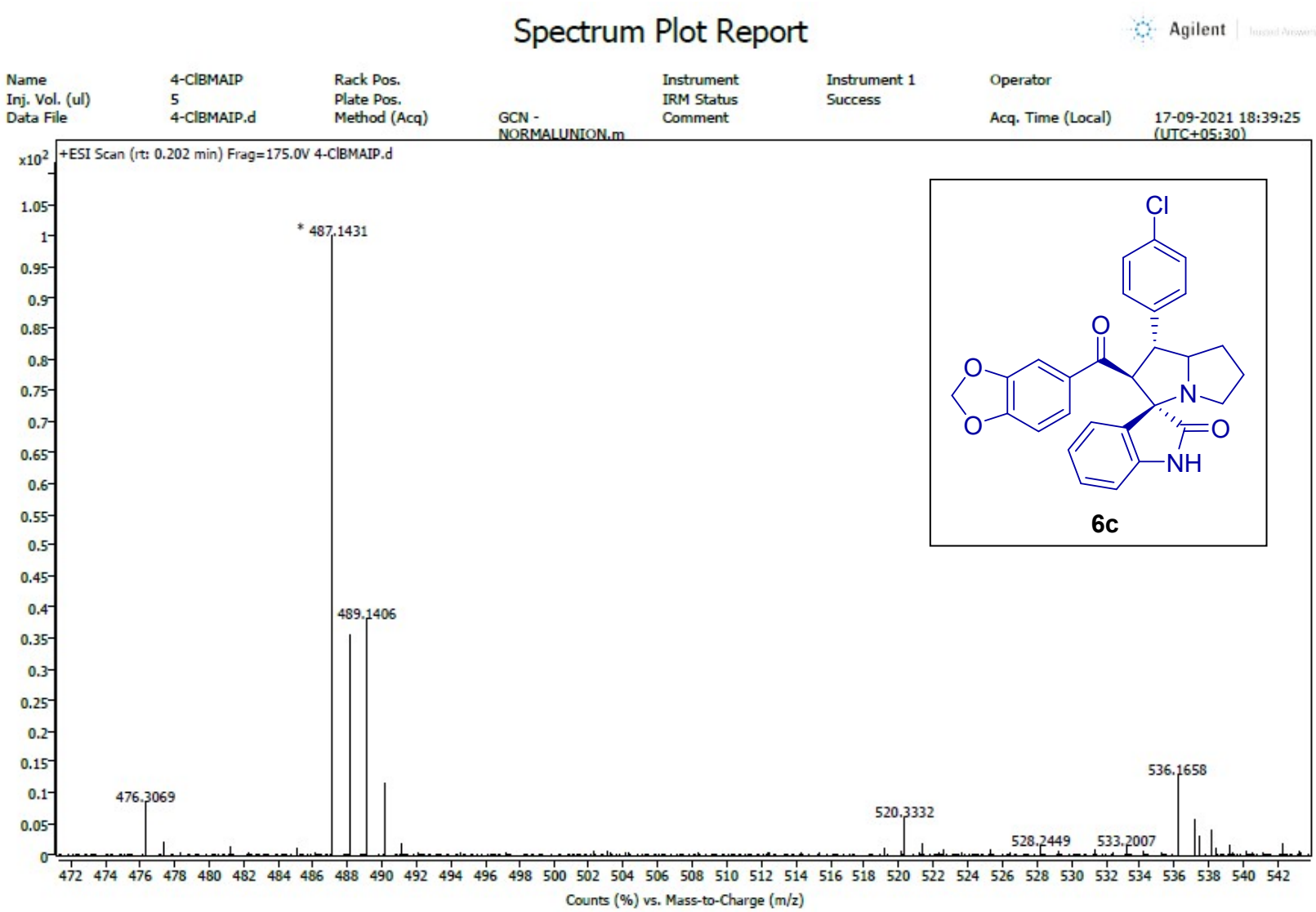


Fig 45. HR-MS spectrum of compound **6c**.

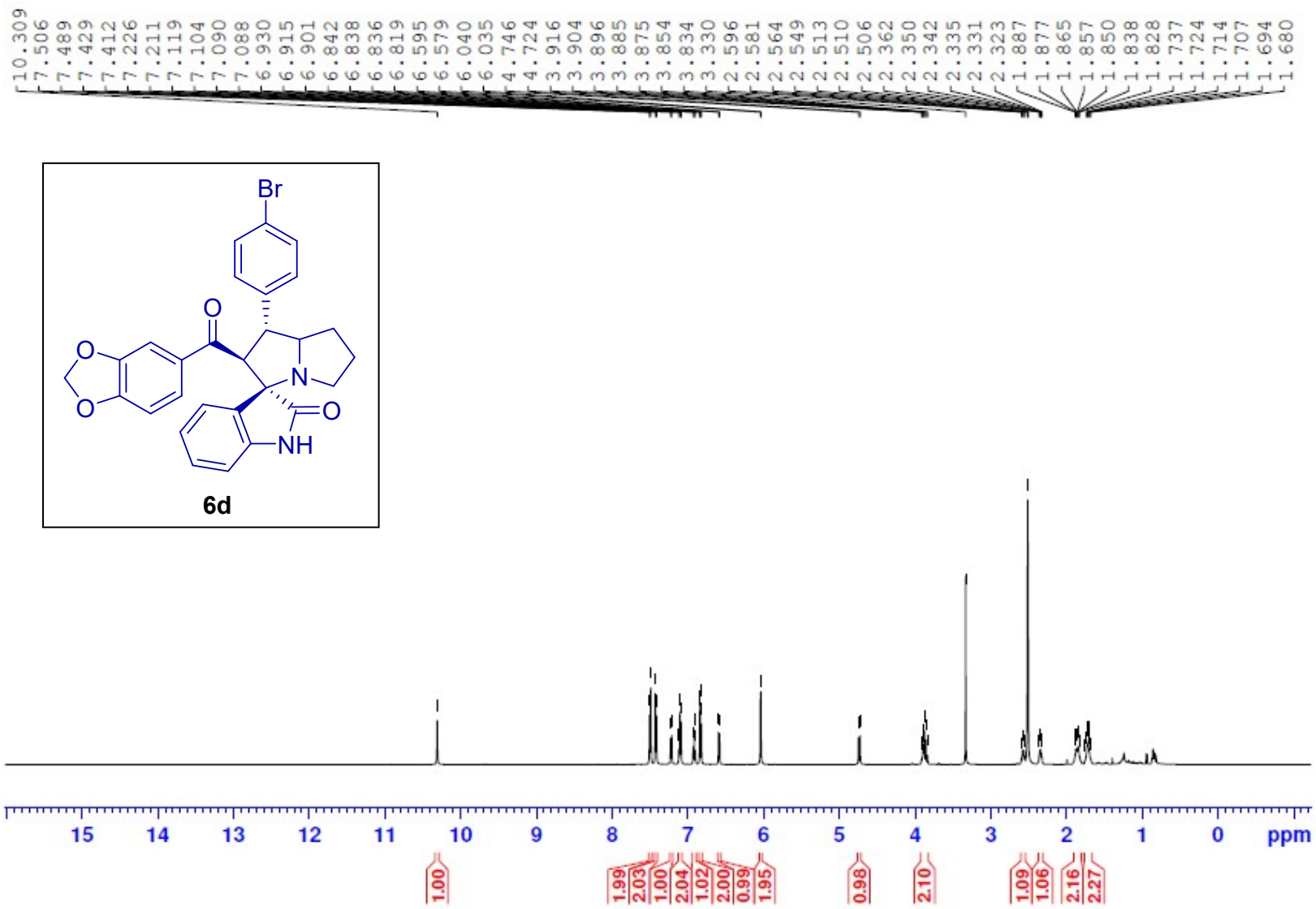


Fig 46. ^{1}H NMR spectrum of compound **6d**.

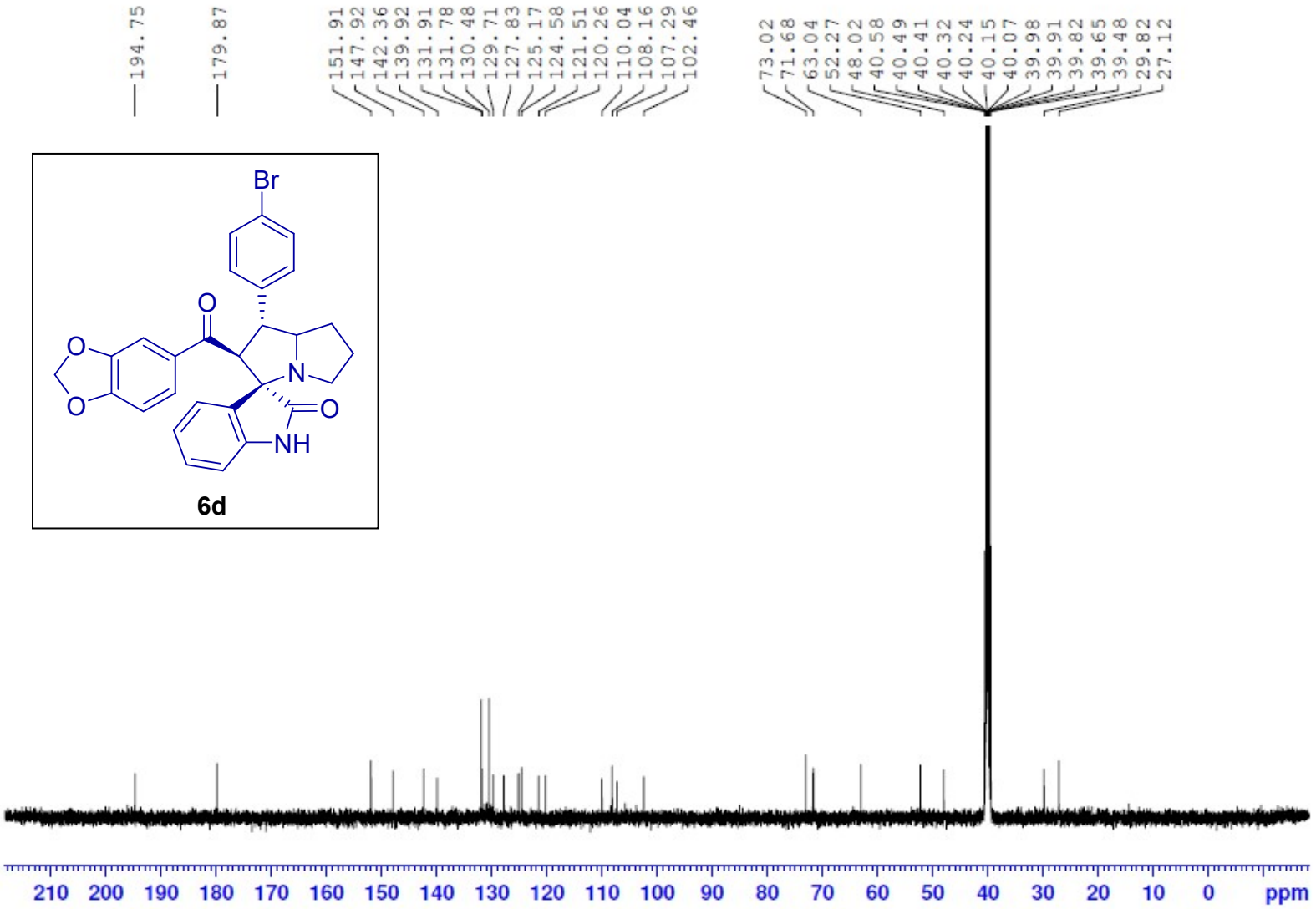


Fig 47. ^{13}C NMR spectrum of compound **6d**.

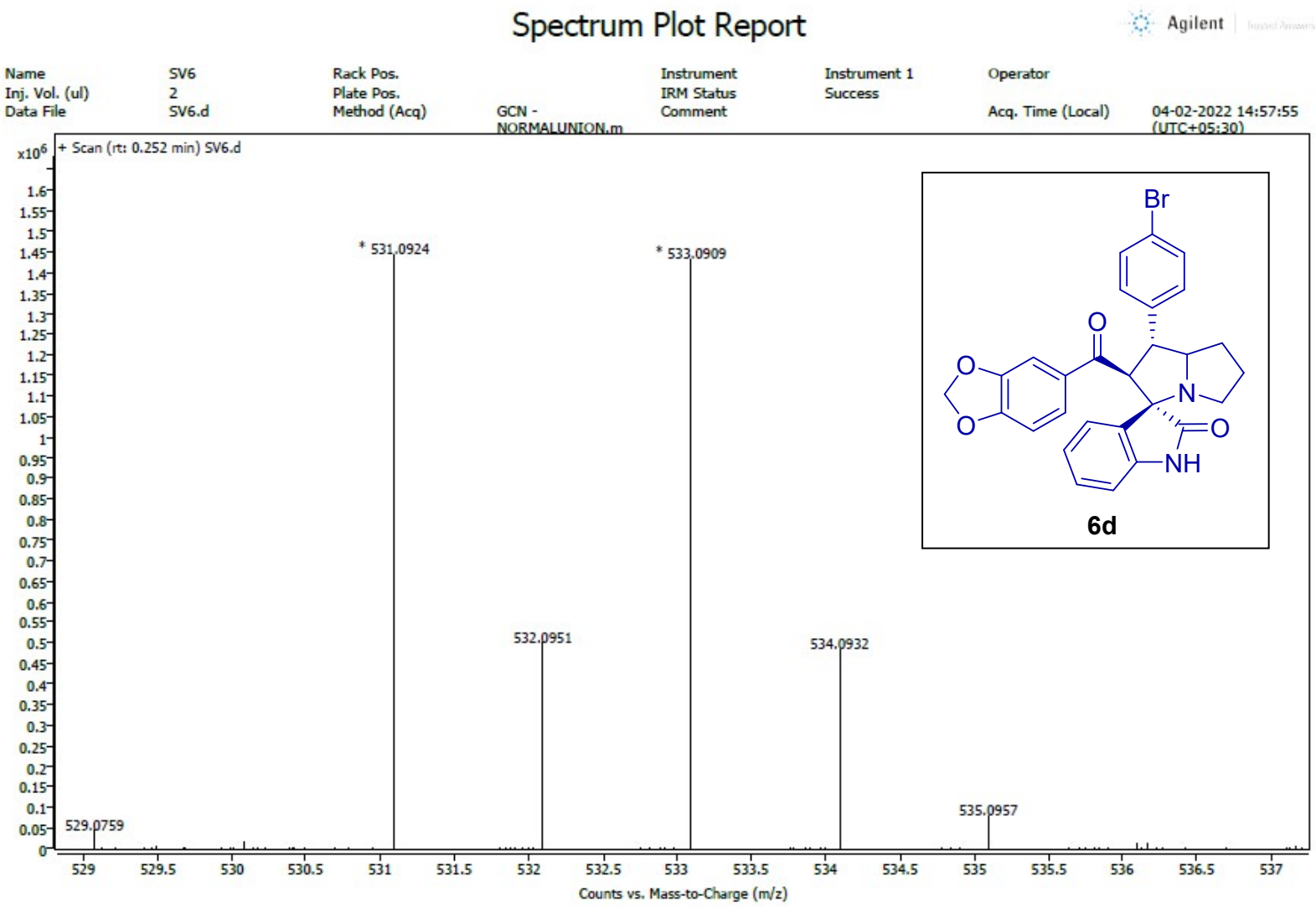


Fig 48. HR-MS spectrum of compound **6d**.

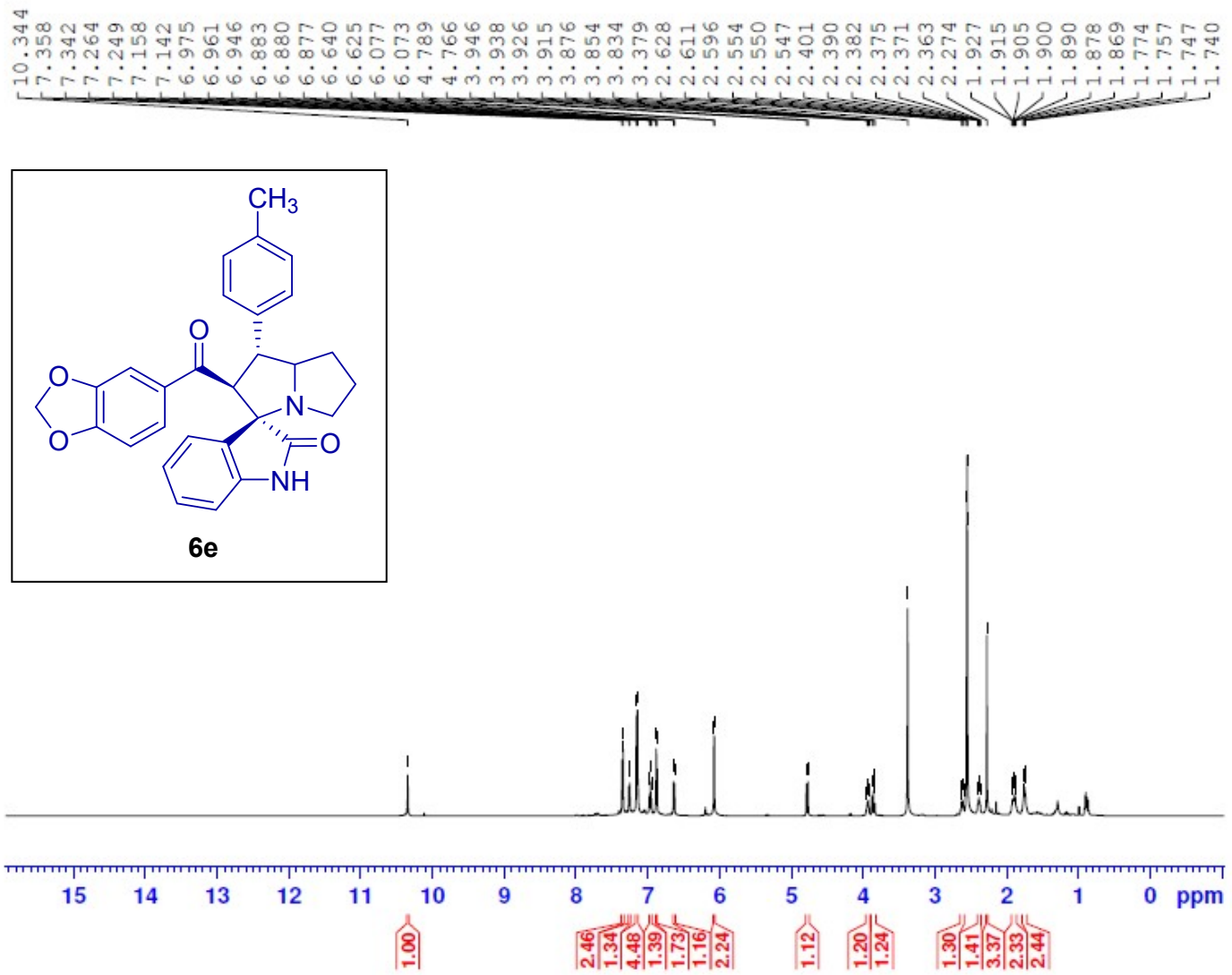


Fig 49. ^{1}H NMR spectrum of compound **6e**.

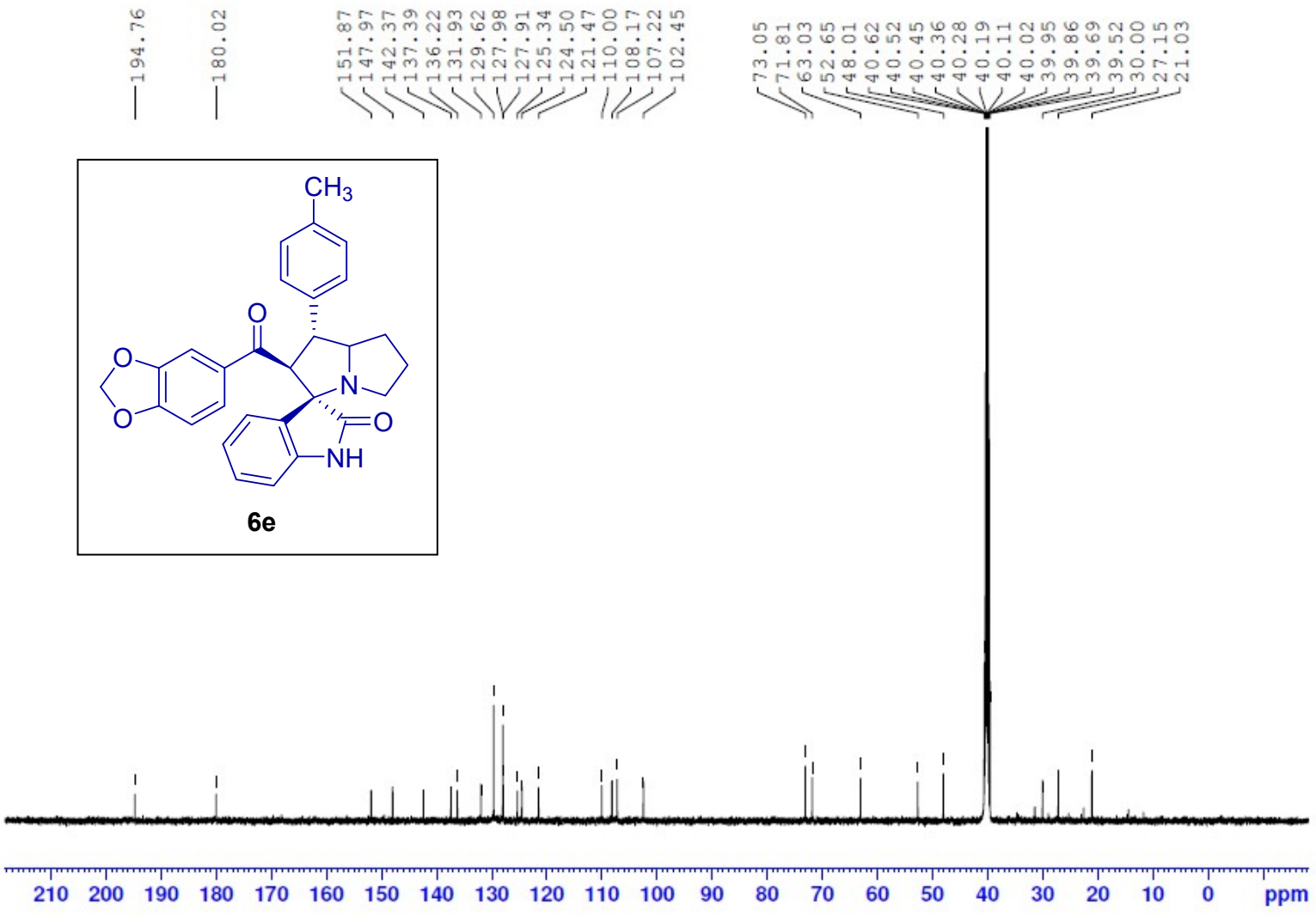


Fig 50. ^{13}C NMR spectrum of compound **6e**.

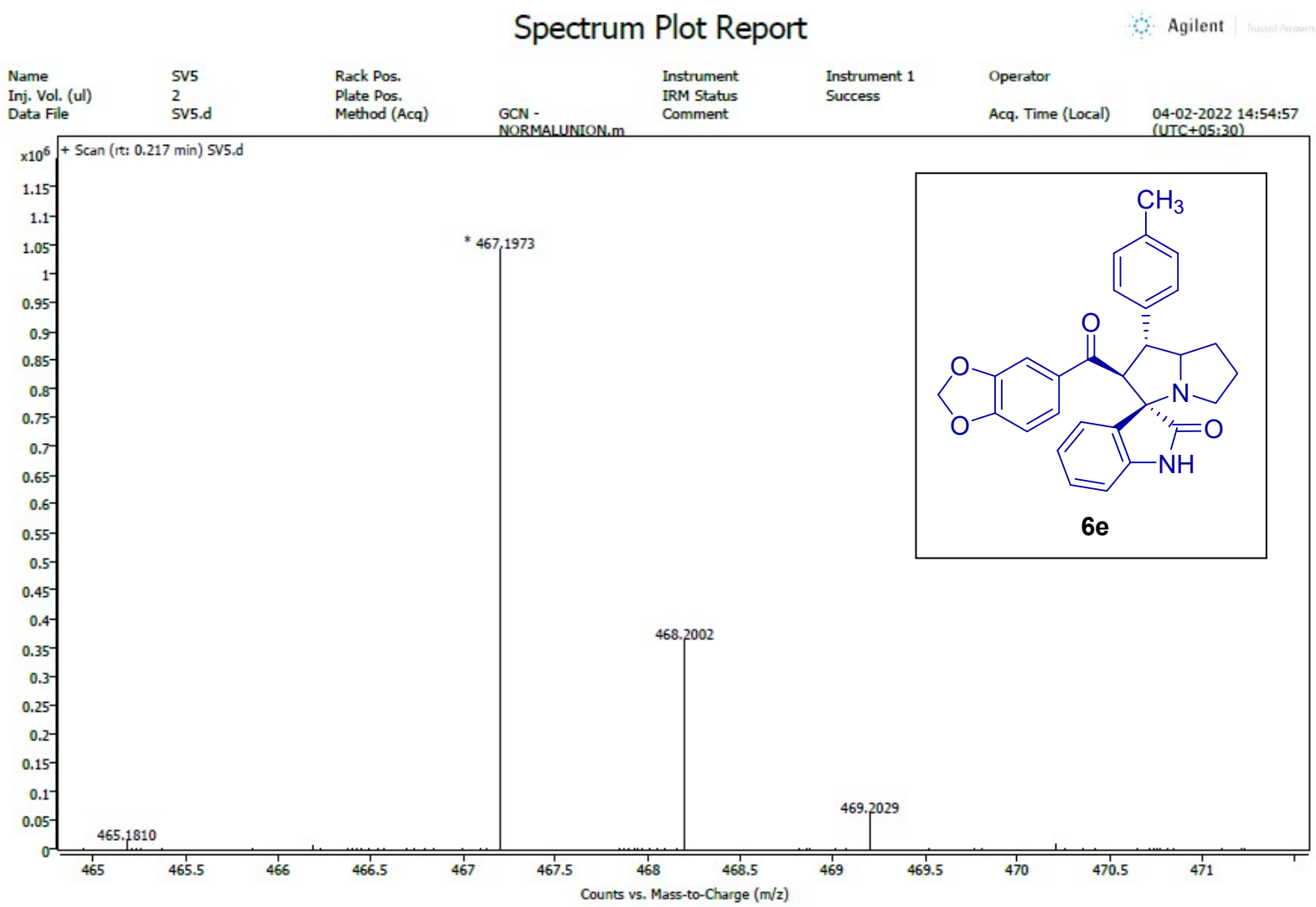


Fig 51. HR-MS spectrum of compound **6e**.

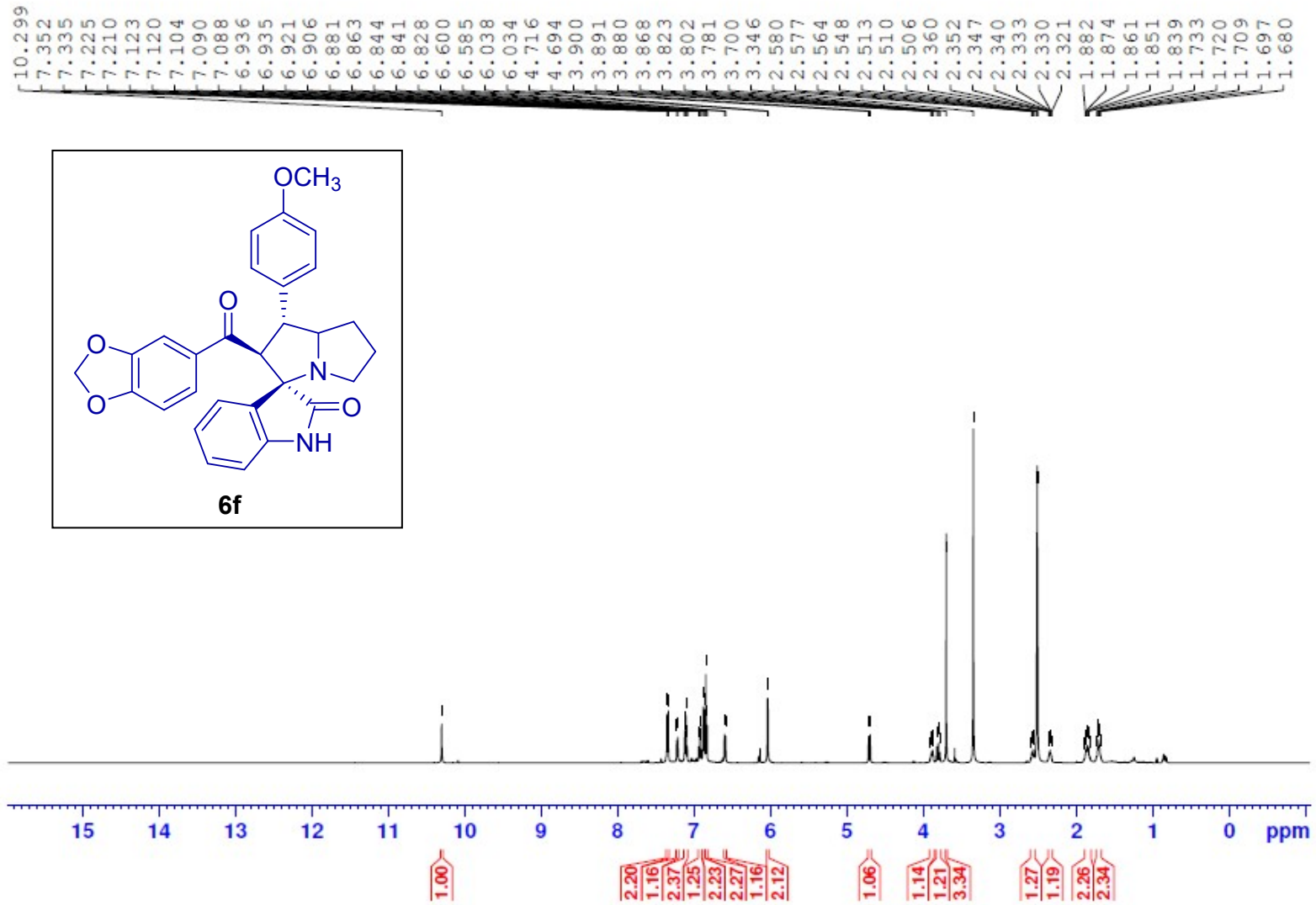


Fig 52. [1]H NMR spectrum of compound **6f**.

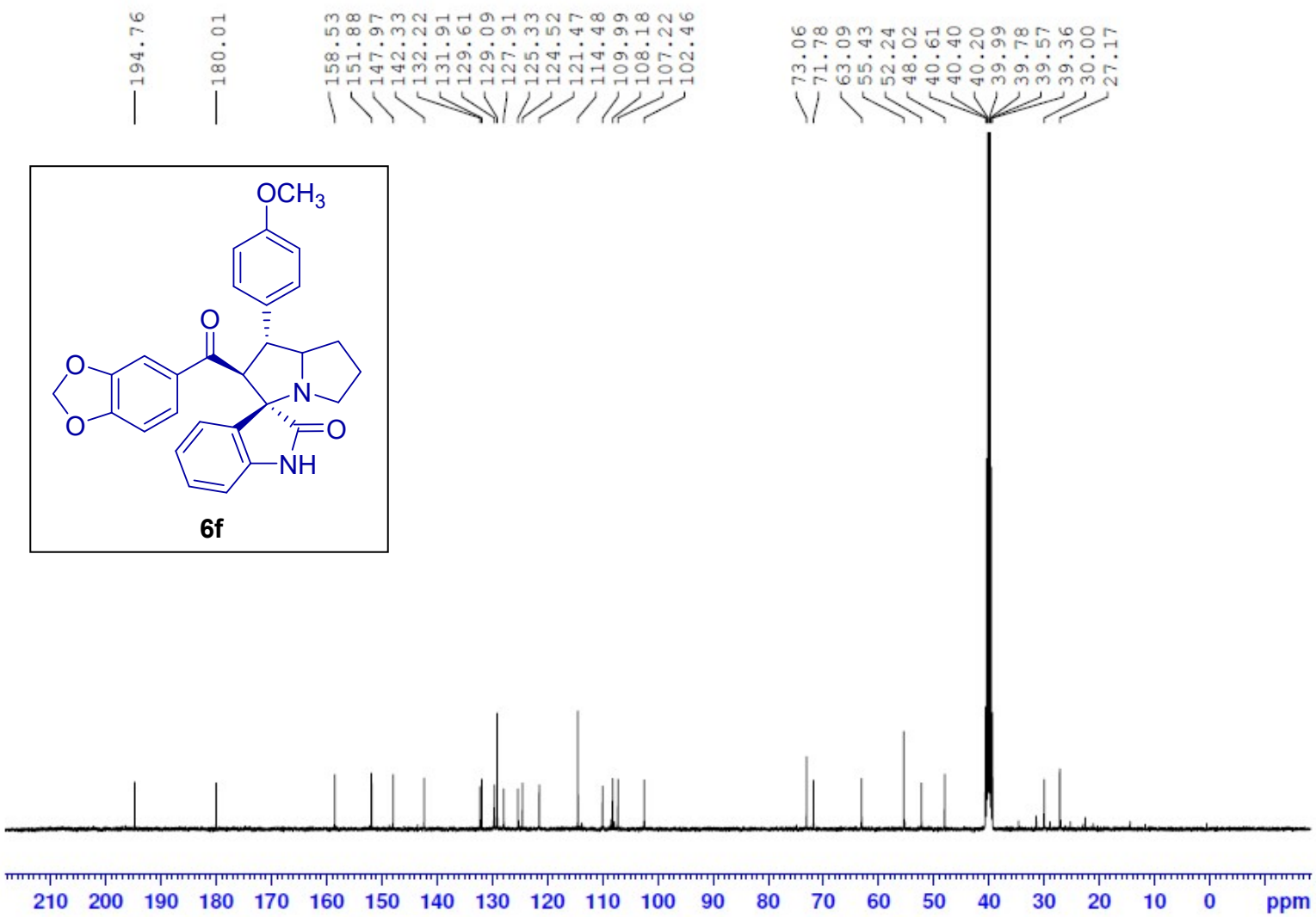


Fig 53. ^{13}C NMR spectrum of compound **6f**.

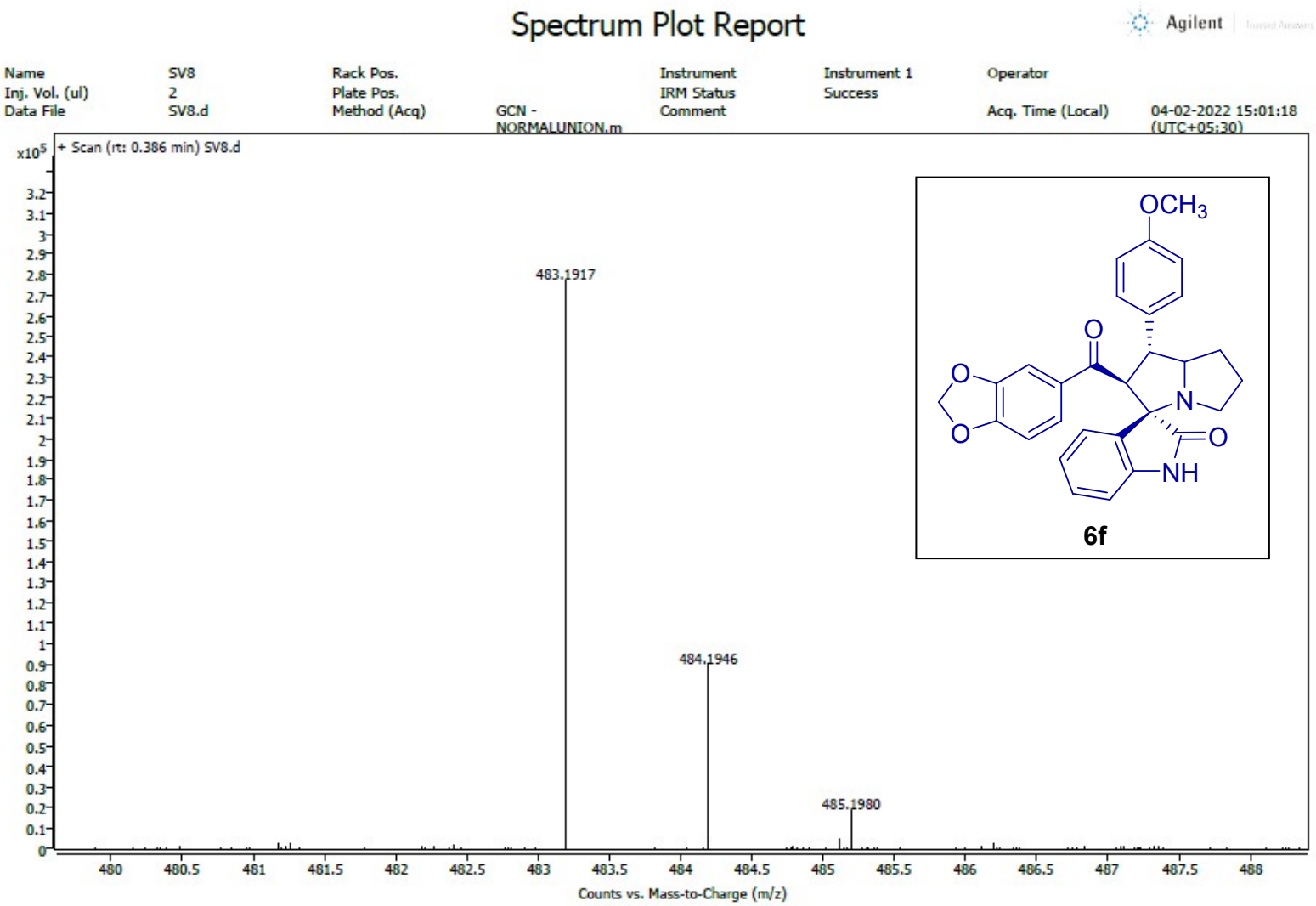


Fig 54. HR-MS spectrum of compound **6f**.

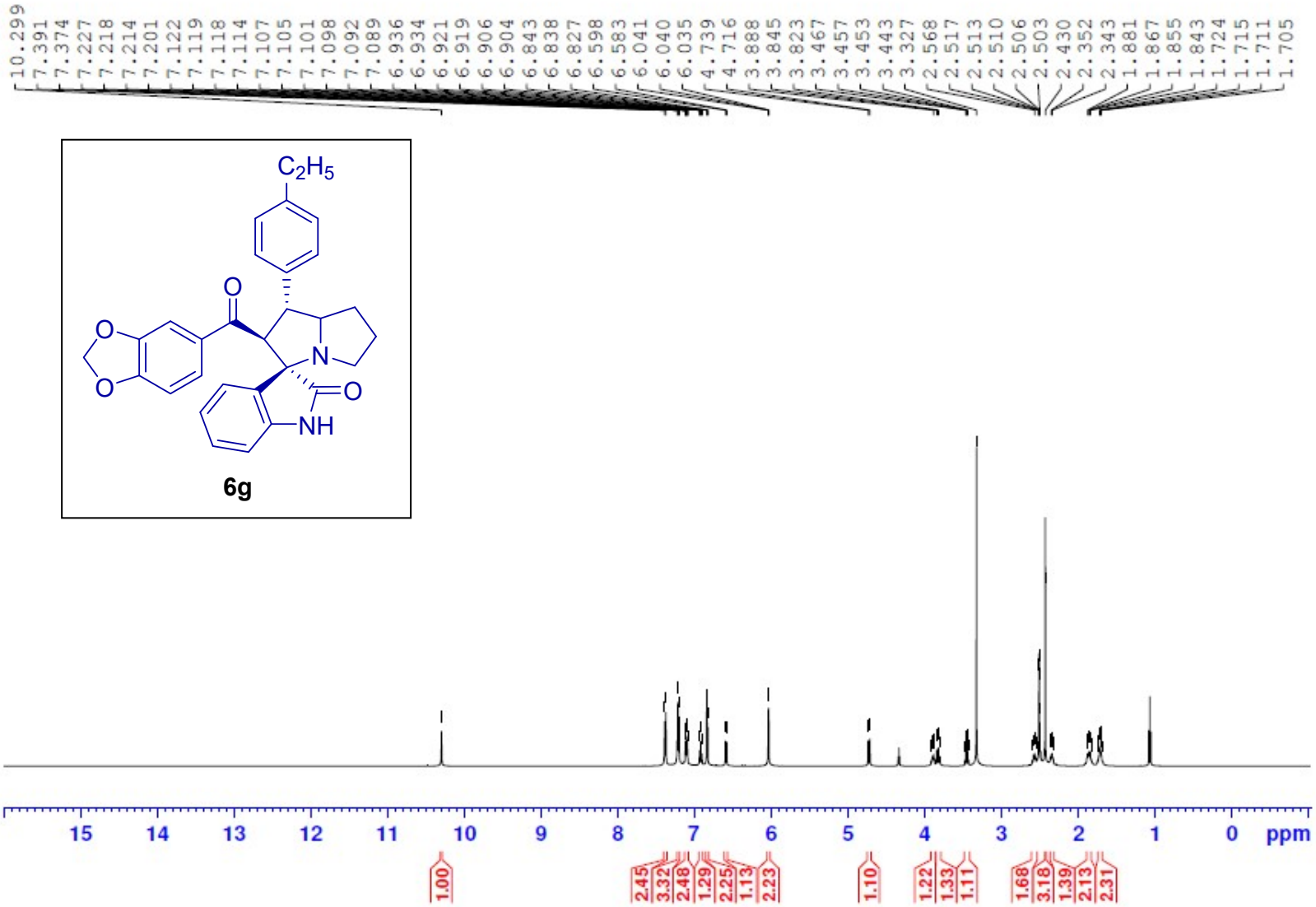


Fig 55. ^{1}H NMR spectrum of compound **6g**.

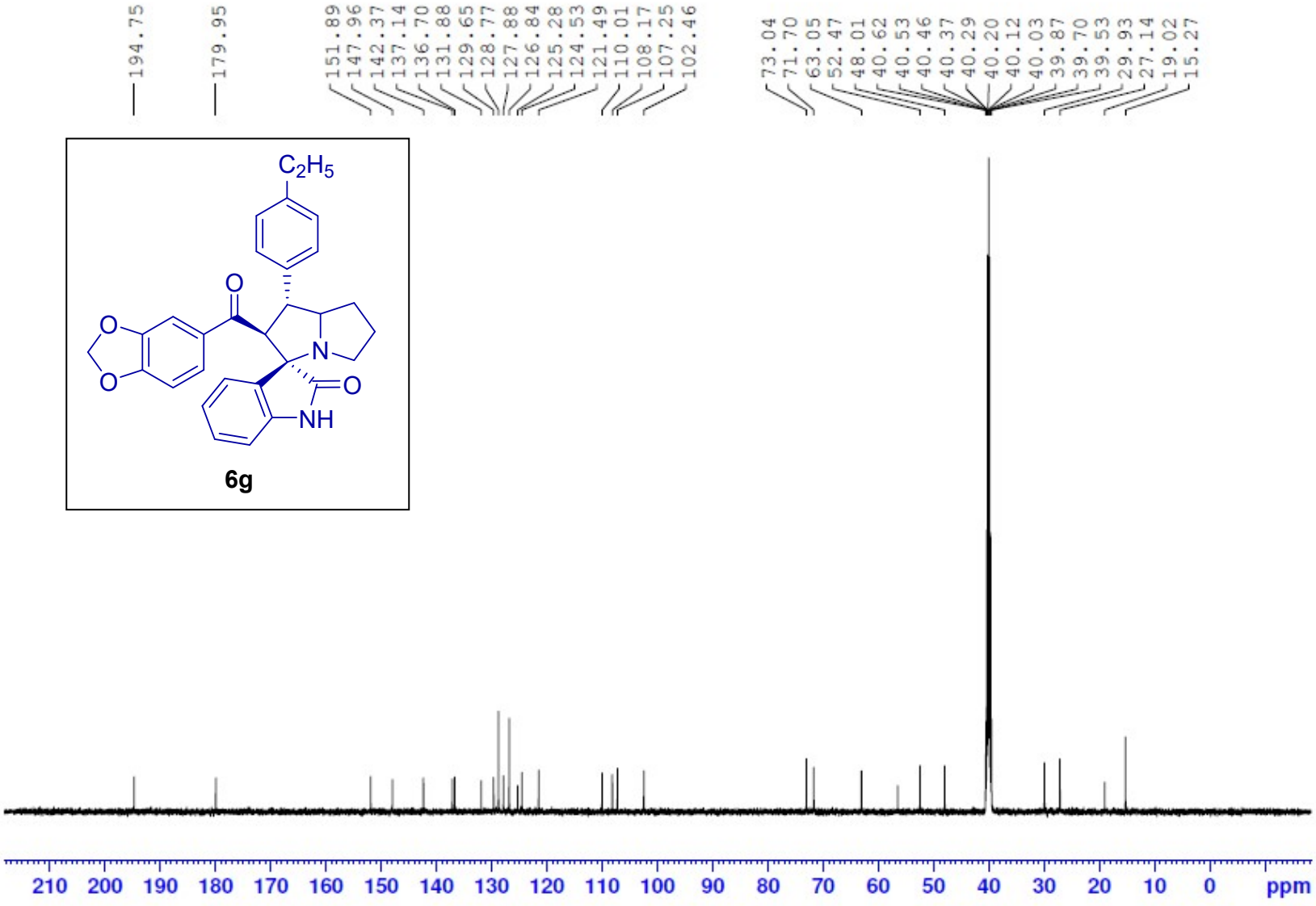


Fig 56. ^{13}C NMR spectrum of compound **6g**.

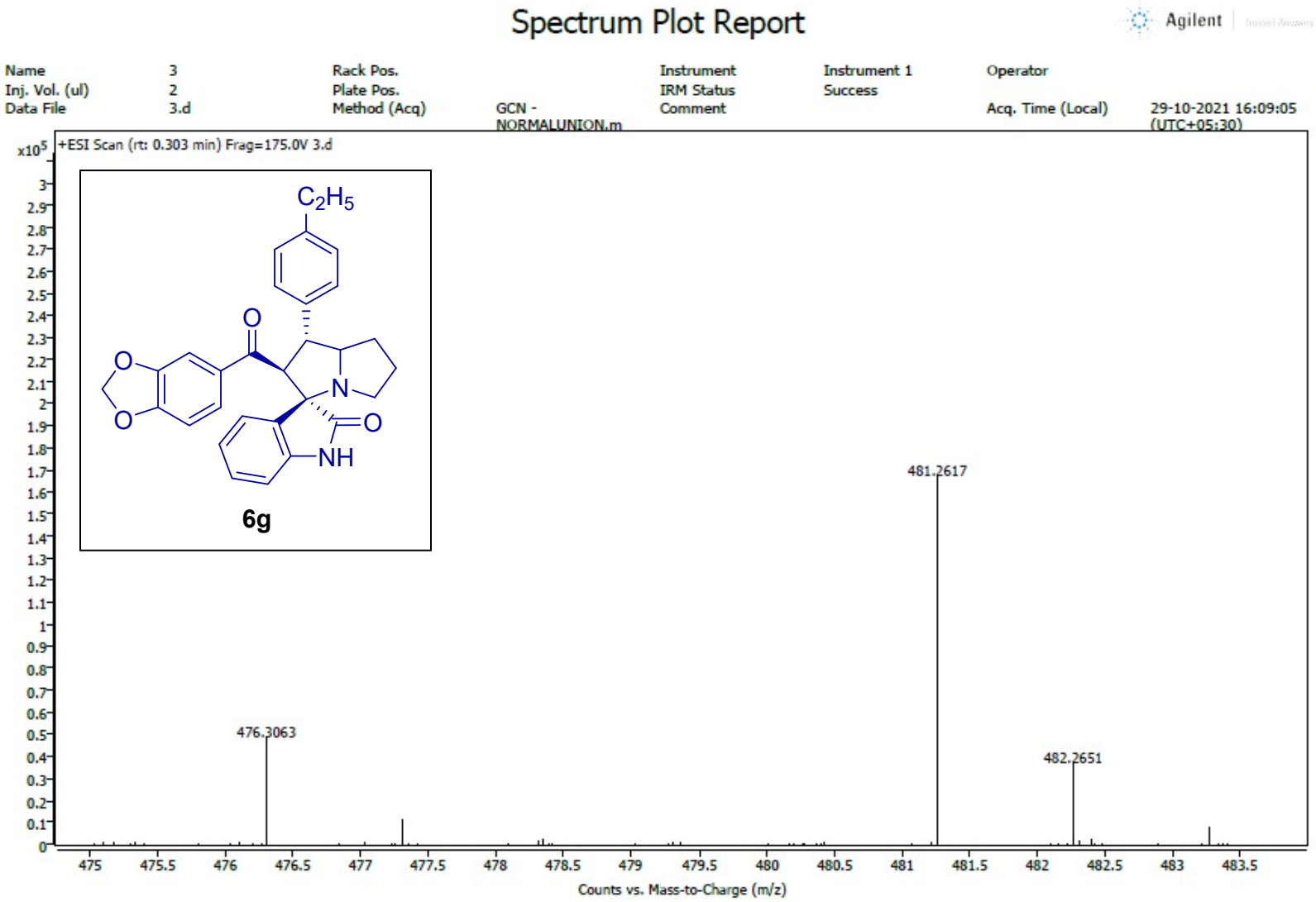


Fig 57. HR-MS spectrum of compound **6g**.

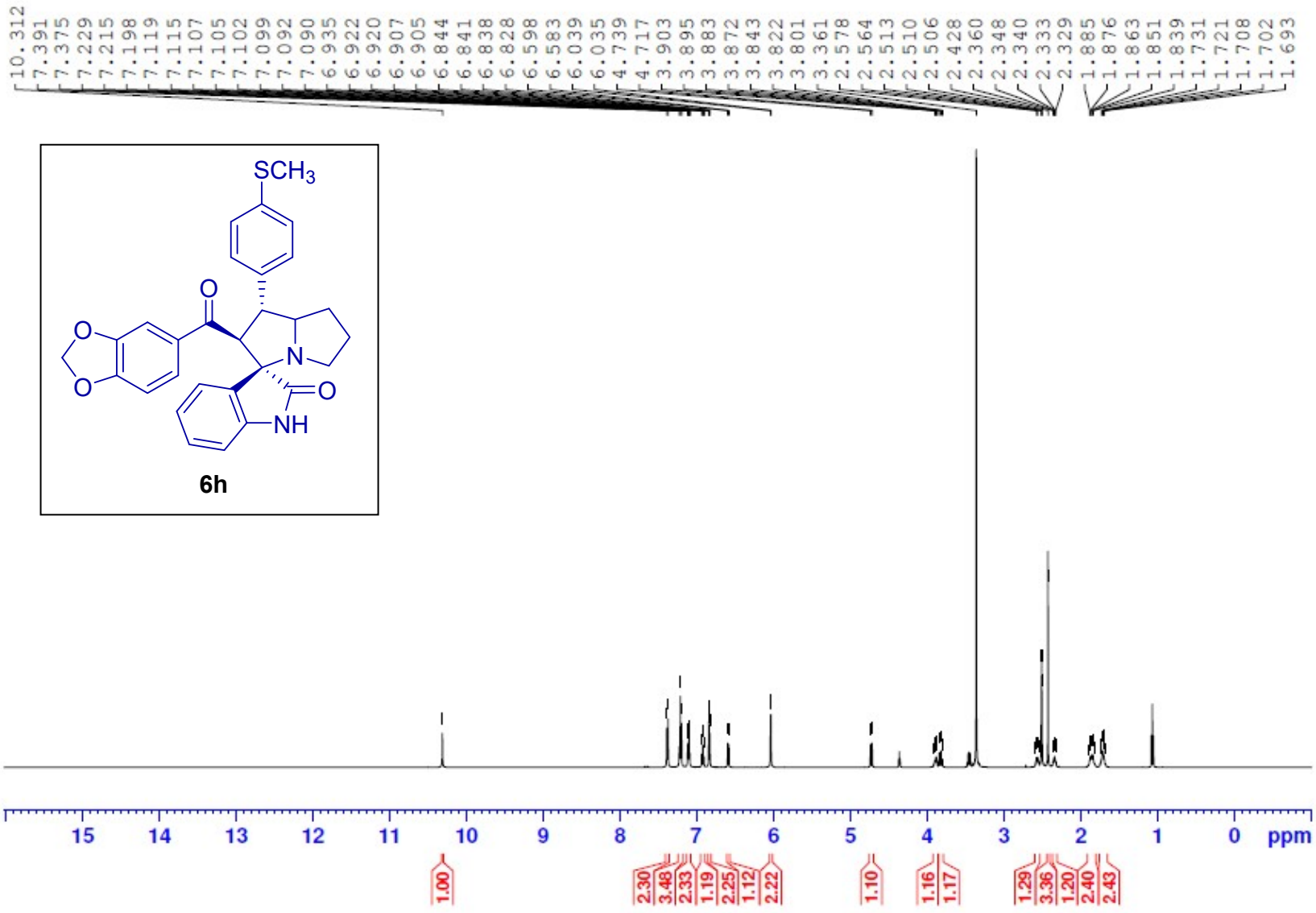


Fig 58. ^{1}H NMR spectrum of compound **6h**.

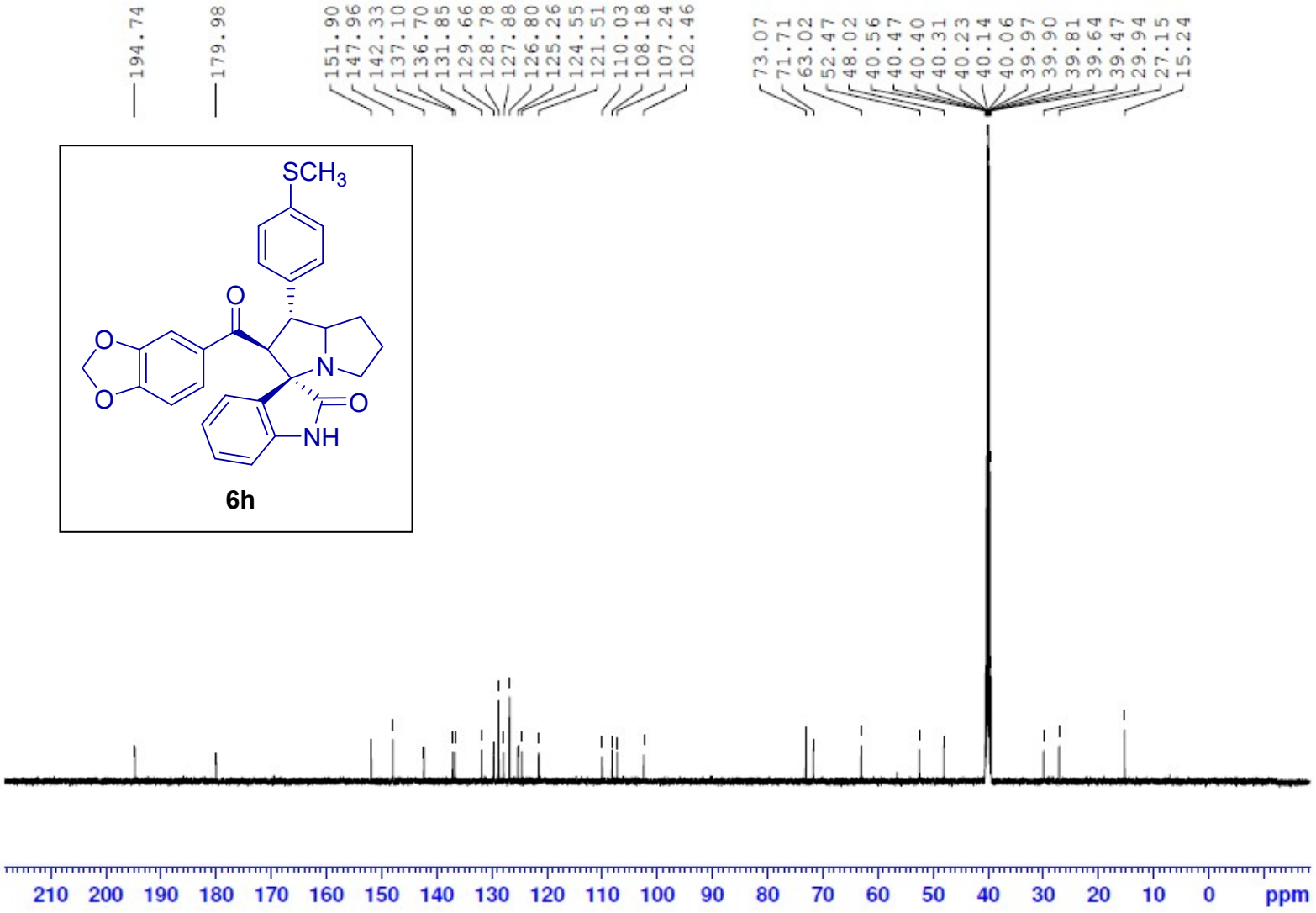


Fig 59. ^{13}C NMR spectrum of compound **6h**.

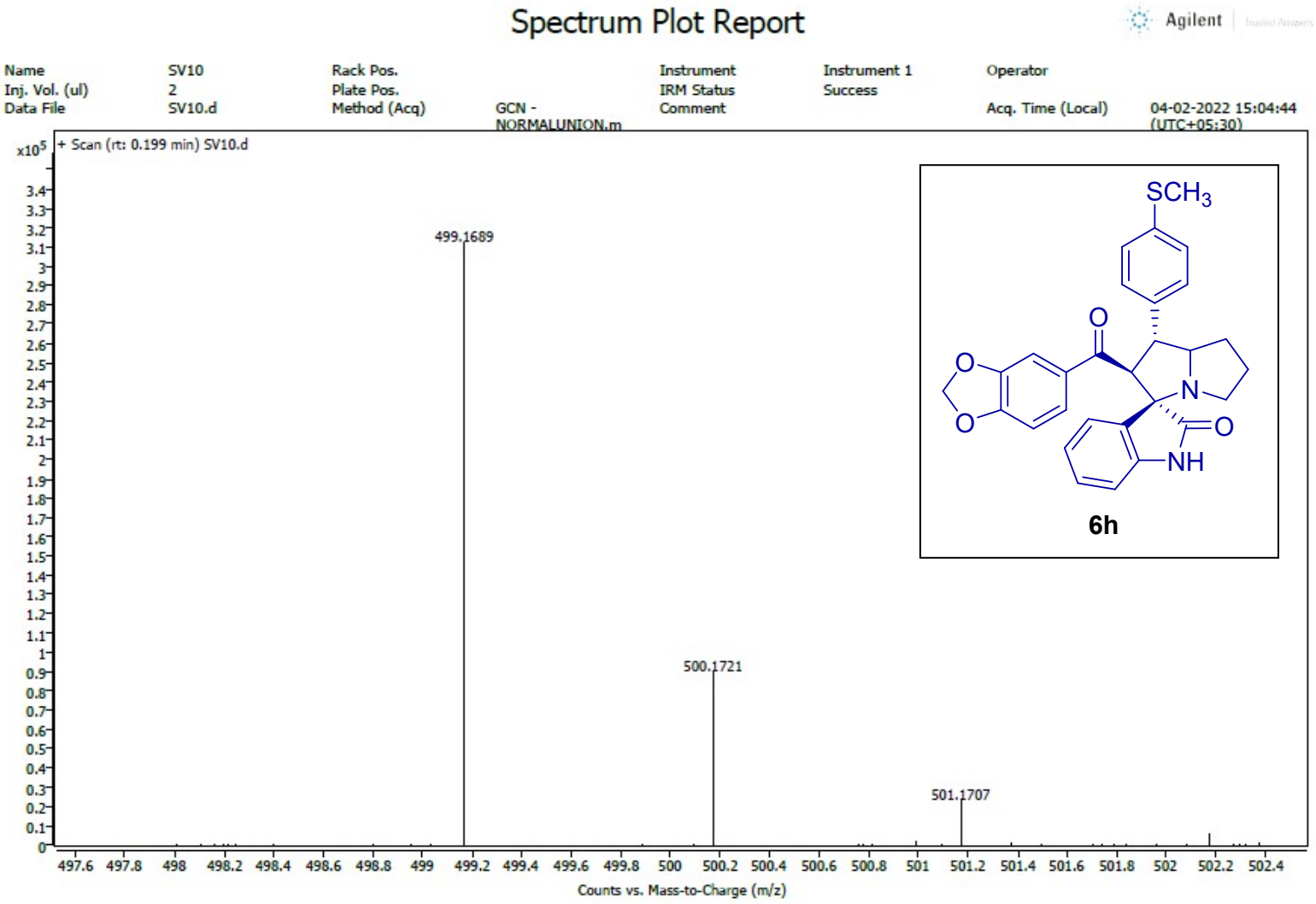


Fig 60. HR-MS spectrum of compound **6h**.

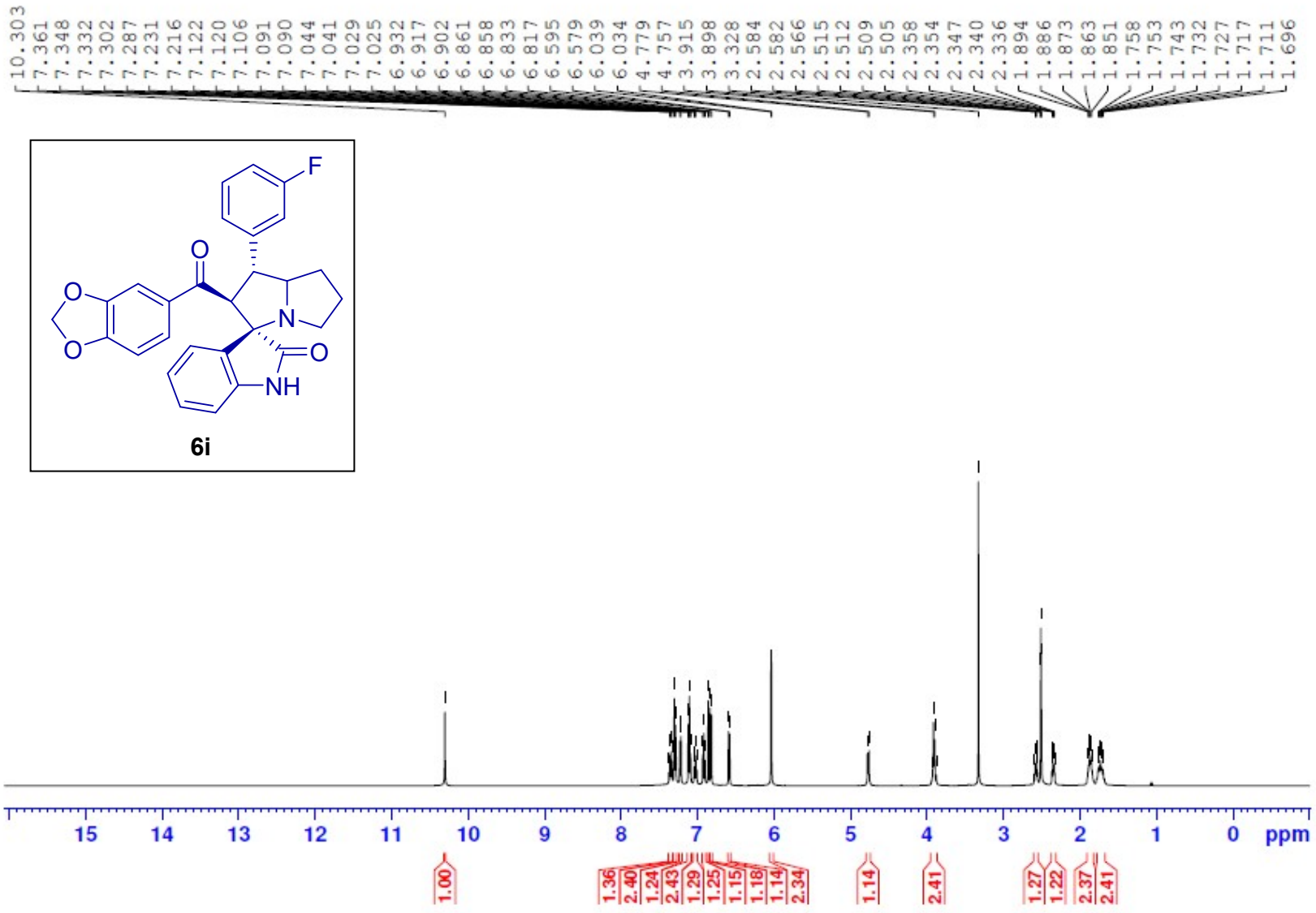


Fig 61. ^{1}H NMR spectrum of compound **6i**.

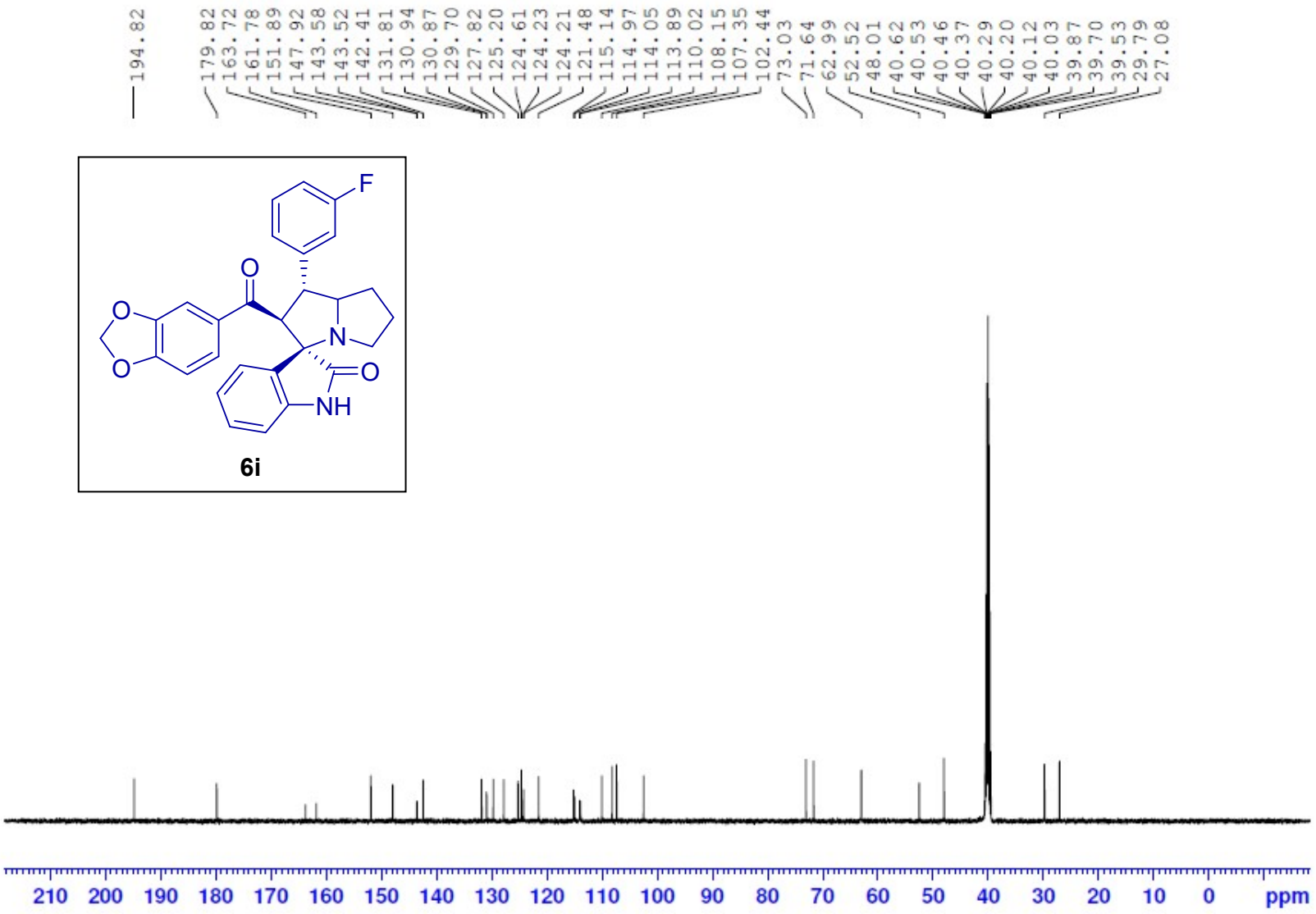


Fig 62. ^{13}C NMR spectrum of compound **6i**.

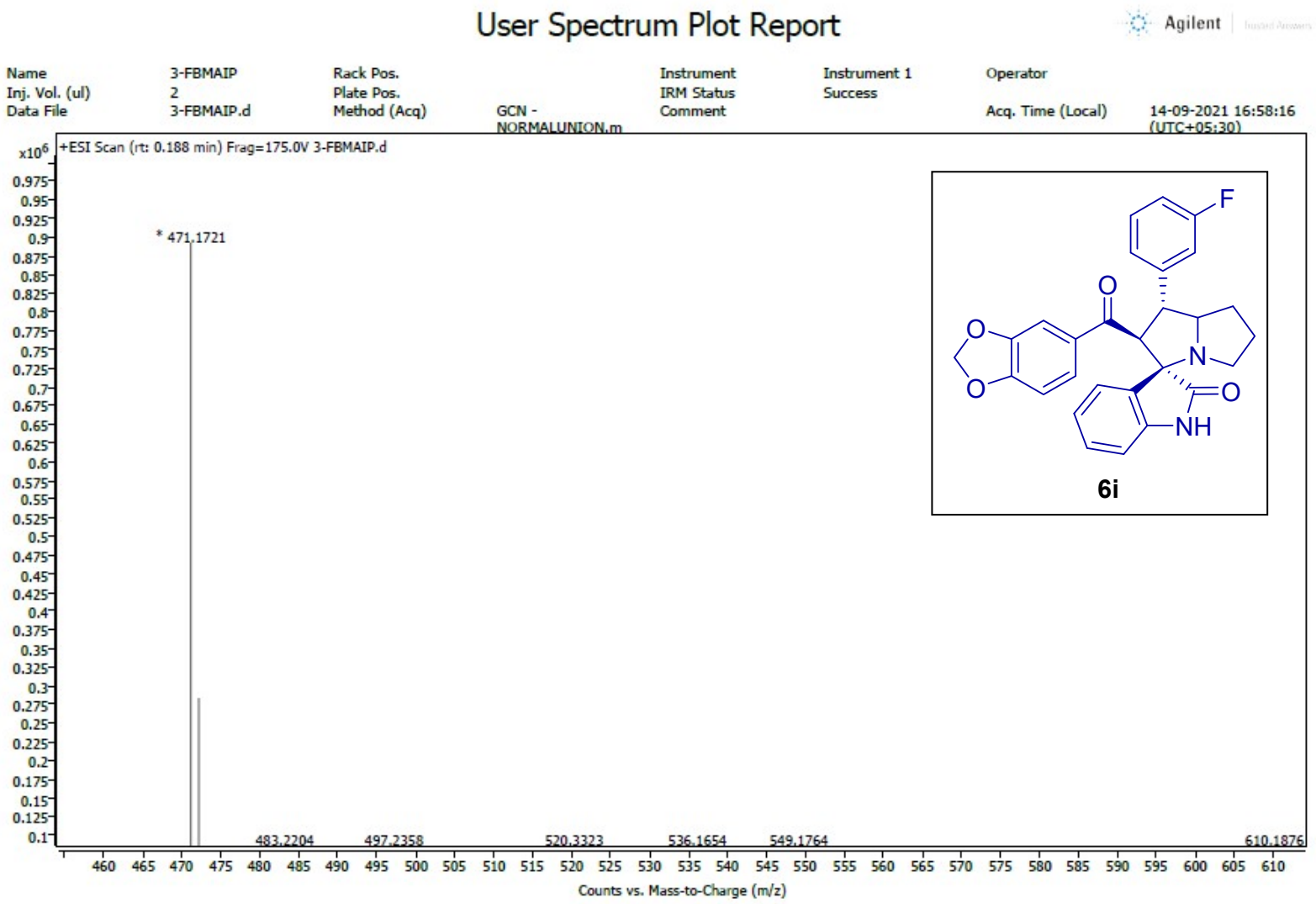


Fig 63. HR-MS spectrum of compound **6i**.

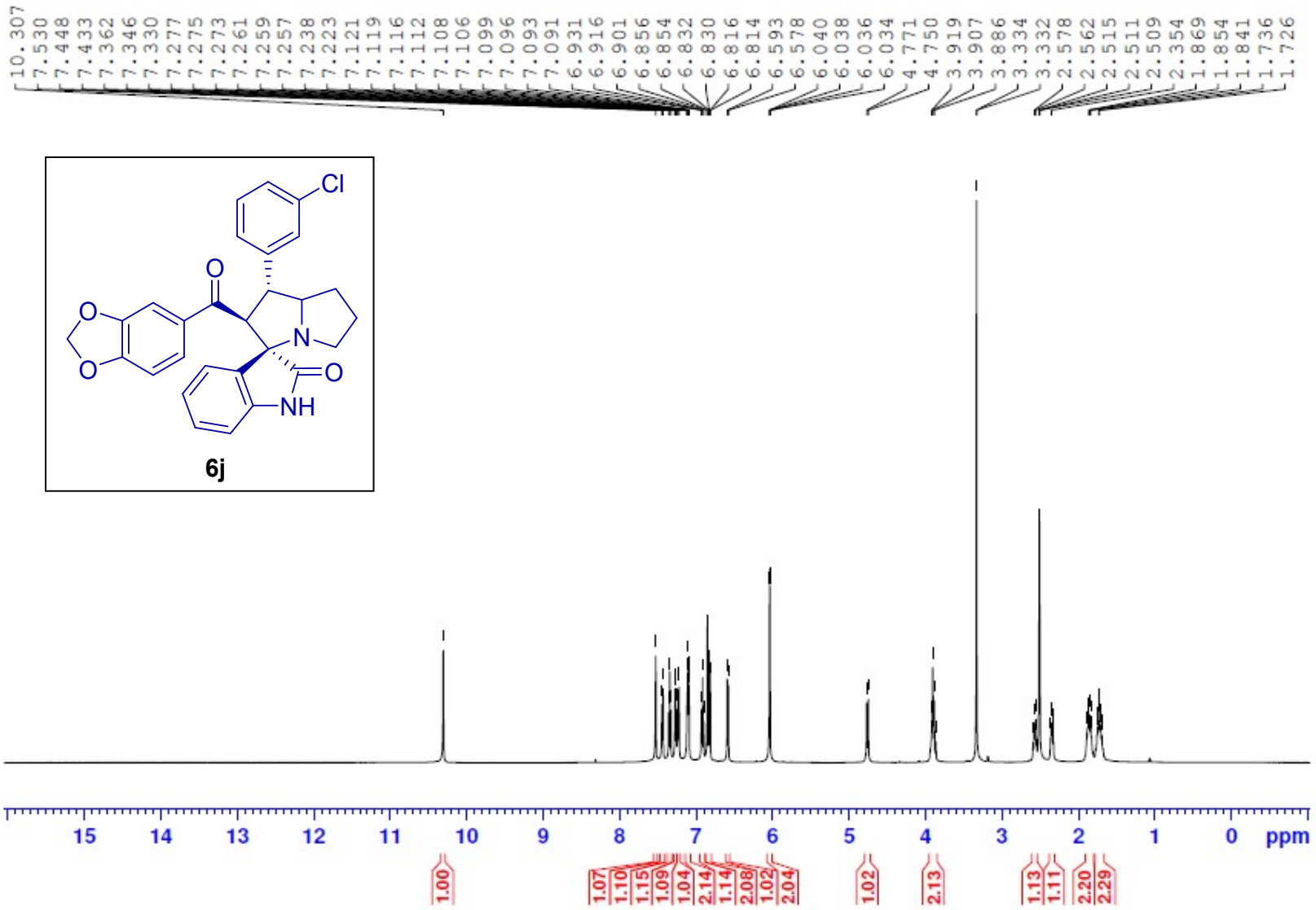


Fig 64. ^{1}H NMR spectrum of compound **6j**.

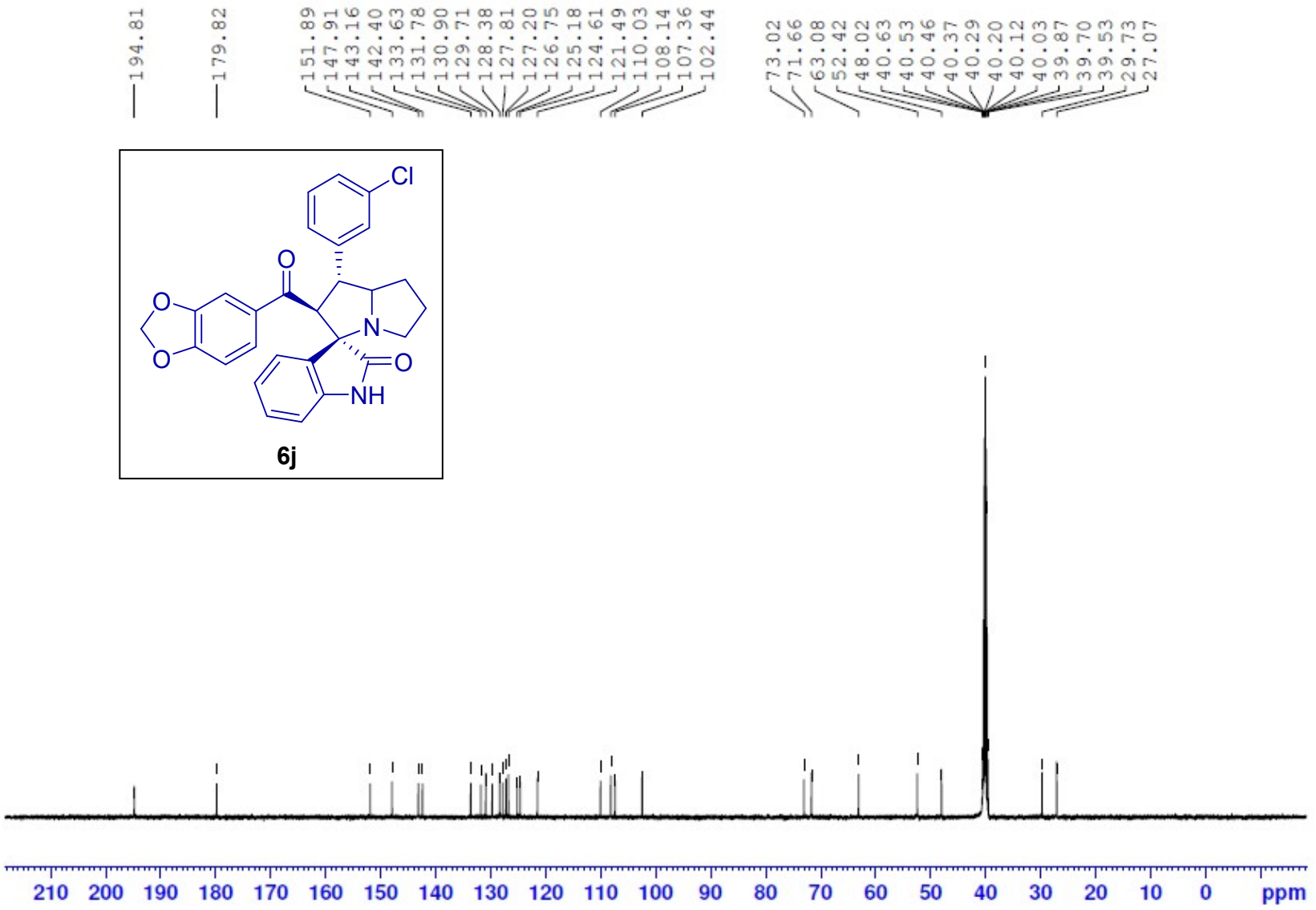


Fig 65. ^{13}C NMR spectrum of compound **6j**.

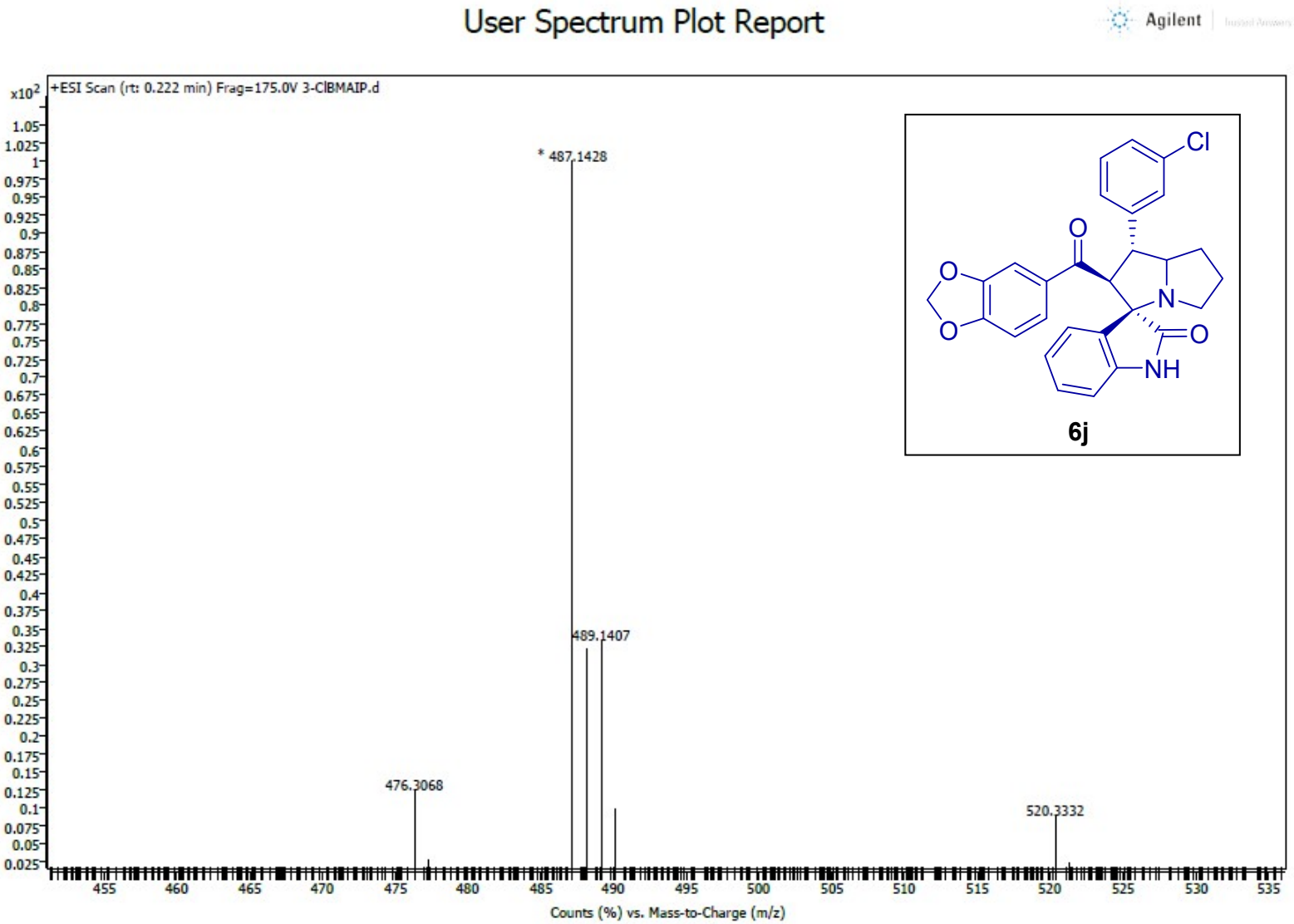


Fig 66. HR-MS spectrum of compound **6j**.

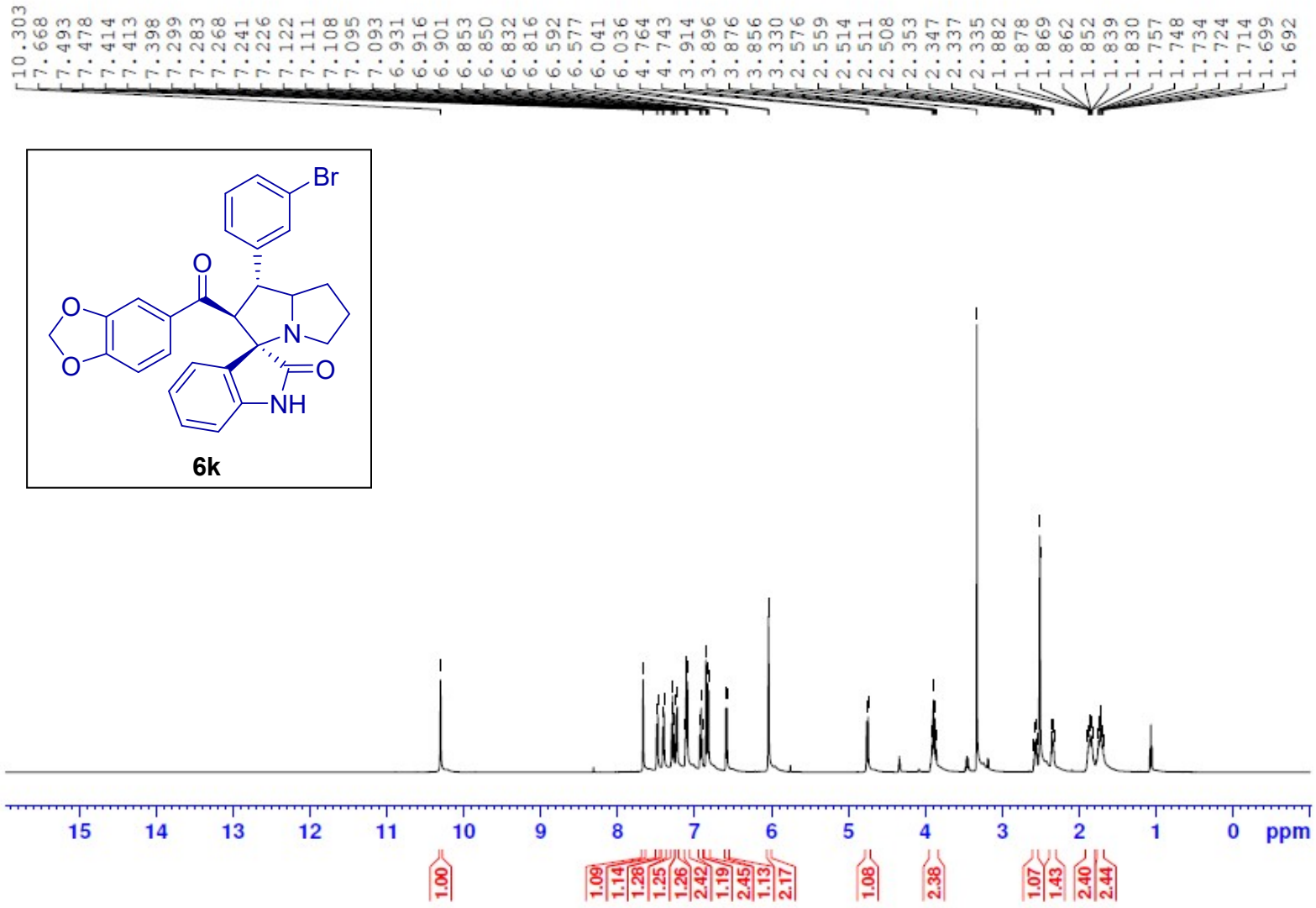


Fig 67. ^{1}H NMR spectrum of compound **6k**.

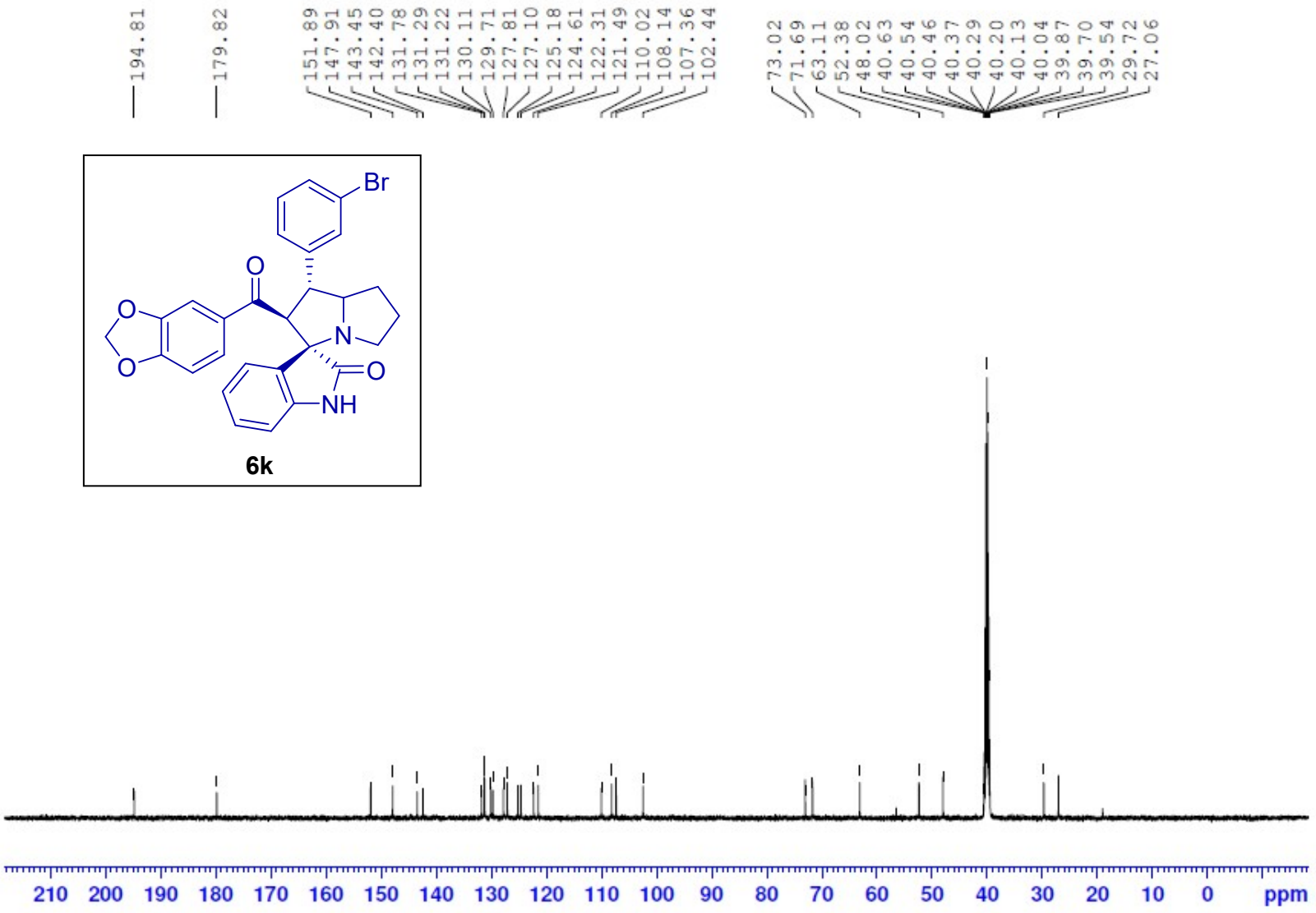


Fig 68. ^{13}C NMR spectrum of compound **6k**.

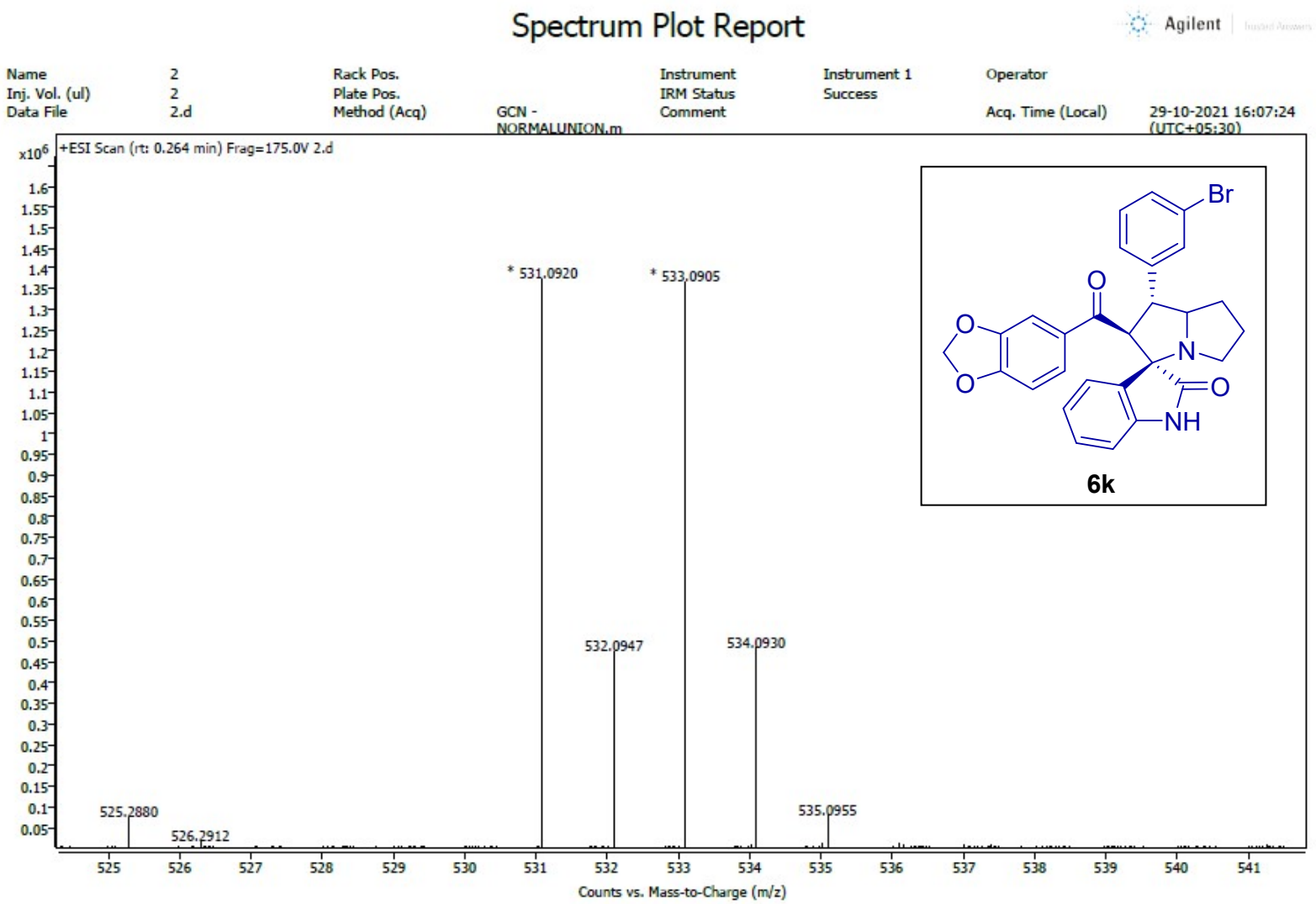


Fig 69. HR-MS spectrum of compound **6k**.

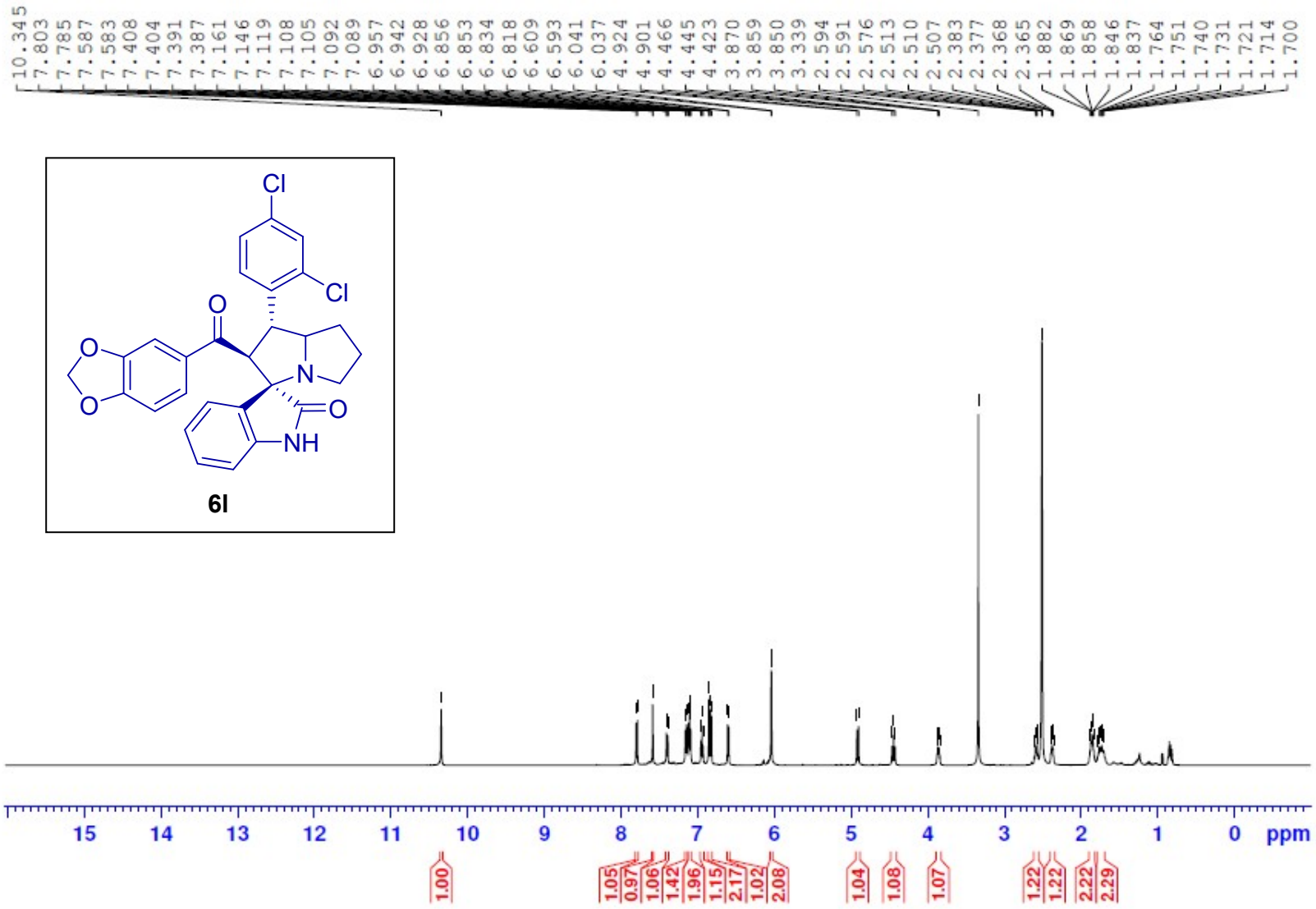


Fig 70. ^{1}H NMR spectrum of compound **6l**.

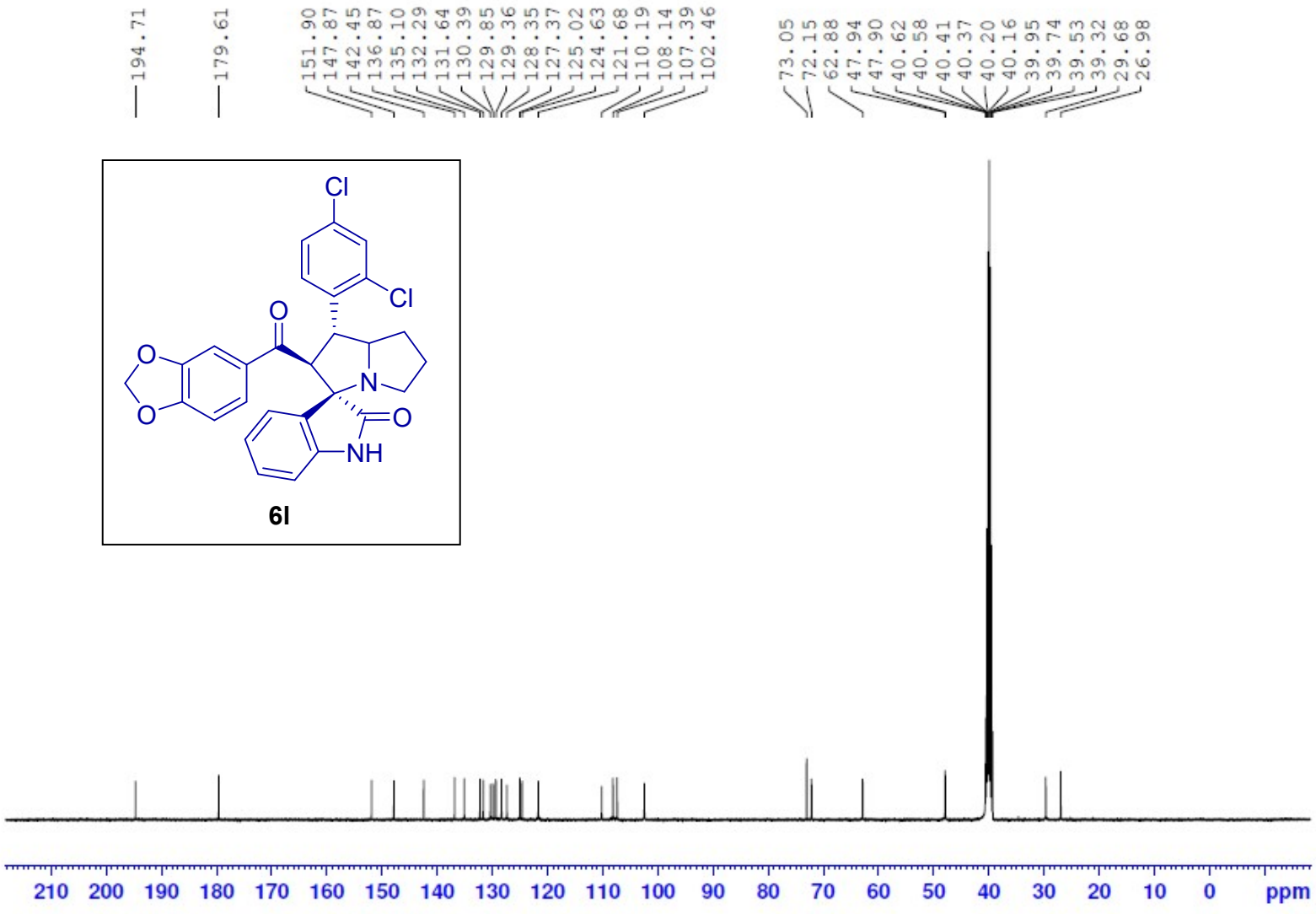


Fig 71. ^{13}C NMR spectrum of compound **6l**.

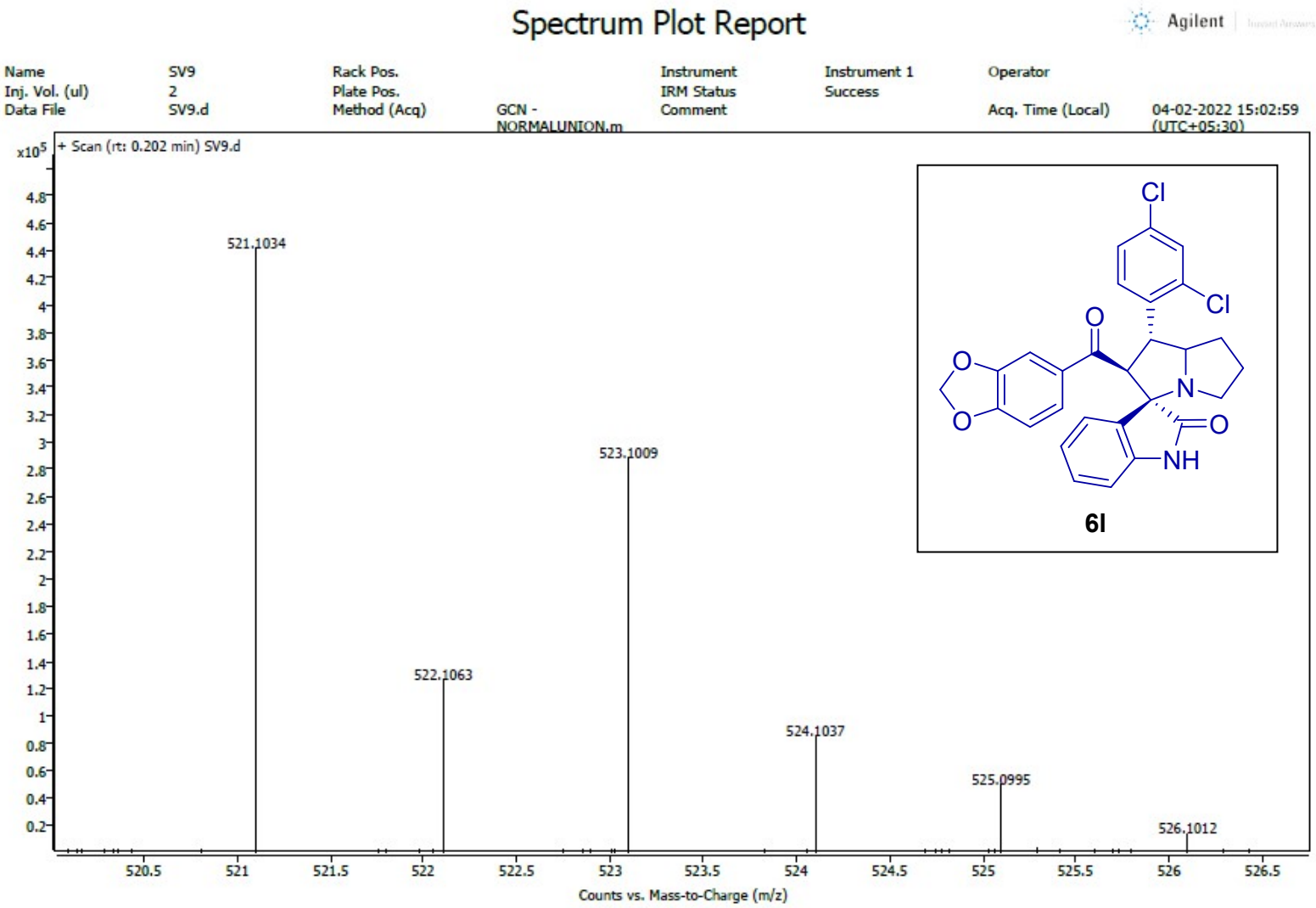


Fig 72. HR-MS spectrum of compound **6l**.

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