One-pot synthesis of azepine spiro[4.6]-γ-lactams by a Hantzsch-type reaction

Electronic Supporting Information

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Table of Contents

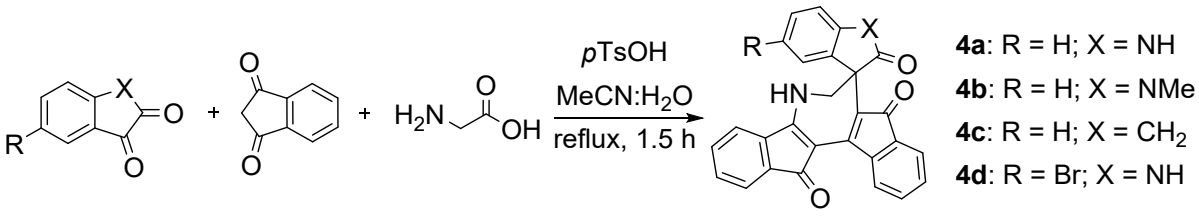
S1: Experimental Procedures

S1.1 General considerations

All chemicals and solvents were at minimum analytical reagent grade. ^{1}H- and ^{13}C-NMR experiments were performed on a Bruker Avance III 500 MHz or 800 MHz spectrometer in DMSO-*d*^{6} at 300 K. Chemical shifts were reported in parts per million and referenced to the solvent residual peak for DMSO-*d6*, taken as δ 2.50 ppm and δ 39.52 ppm for ^{1}H-NMR and ^{13}C-NMR, respectively. Post-processing of the resulting spectra was done using Bruker Topspin 4.4.1 software. High-resolution mass spectra (HRMS) were obtained on a MaXis UHR ESI QTOF spectrometer. Real-time mass detection was performed using a Waters RADIAN ASAP single quadrupole mass detector coupled with an atmospheric pressure solids analysis probe. Samples were applied directly to a glass capillary, without chromatographic separation. MassLynx software was used to analyse the data. Fourier transform infrared spectroscopy (FTIR) was performed with a Perkin Elmer Spectrum 2 FTIR with a diamond anvil cell. Samples were scanned four times with a resolution of 4 cm^{-1} across a 4500–450 cm^{-1} range. Spectral data was analysed on Perkin Elmer Spectrum IR software.

S1.2 Synthesis and Characterisation

General procedure for spiro[4.6]-γ-lactams 4a-d: A solution of 1,3-indandione (1 mmol), chosen isatin variant (0.5 mmol), and *p*-TSA (0.15 mmol) dissolved in acetonitrile (8 mL) was combined with glycine (0.5 mmol) in water (4 mL) and refluxed with stirring for 90 minutes. The reaction mixture was then cooled to room temperature, and water (10 mL) added to precipitate a red solid. The crude product was purified one of two ways: **4a** was filtered and washed with dichloromethane, then recrystallised from acetone and *n*-hexane (1:1) to yield a red crystalline product. **4b-d** were subjected to column chromatography using dichloromethane as eluent, with a gradient addition of acetone after the initial fractions had been obtained. Fractions containing the product were combined and dried under reduced pressure.



5,6-dihydrospiro[diindeno[1,2-b:1',2'-d]azepine-7,3'-indoline]-2',8,13-trione (4a): Yield 30%; FTIR (cm^{-1}): 3347, 3218, 1701, 1686, 1655; ESI-HRMS (+ve): m/z= 439.1048 (100%, [M+Na]$^{+}$) ($C_{27}H_{16}N_2NaO_3$), calculated m/z= 439.1059; ^{1}H-NMR (500 MHz, DMSO-*d6*, 300 K): δ_H 3.49 (d, 1H, J= 13.25 Hz), 3.87 (d, 1H, J= 13.45 Hz), 6.76 (d, 1H, J= 7.30 Hz), 6.85 (td, 1H, J= 7.52 Hz & 0.83 Hz), 6.92 (d, 1H, J= 7.70 Hz), 7.19 (m, 2H, J= 2.75 Hz), 7.25 (t, 1H, J= 3.82 Hz), 7.42 (td, 1H, J= 7.56 Hz & 1.37 Hz), 7.64 (m, 3H, J= 2.55 Hz), 7.88 (m, 1H, J= 2.58 Hz), 8.23 (d, 1H, J= 7.55 Hz), 10.35 (s, 1H, NH), 10.77 (s, 1H, NH); ^{13}C-NMR (125 MHz, DMSO-*d6*, 300 K): δ_C 50.65, 101.27, 109.58, 120.10, 120.45, 121.36, 121.74, 124.35, 127.02, 128.34, 128.62, 132.36, 132.54, 132.69, 135.49, 136.69, 142.10, 142.70, 153.08, 166.88, 175.84, 188.57, 190.65.

1'-methyl-5,6-dihydrospiro[diindeno[1,2-b:1',2'-d]azepine-7,3'-indoline]-2',8,13-trione (4b): Following the general procedure, compound **4b** was obtained by substituting isatin for 1-methylisatin. Yield 42%; FTIR (cm^{-1}): 3247, 3092, 3054, 1716, 1690, 1673; ESI-HRMS (+ve): m/z= 431.1390 (100%, [M+H]$^{+}$) ($C_{28}H_{19}N_2O_3$), calculated m/z= 431.1396; ^{1}H-NMR (500 MHz, DMSO-*d6*, 300 K): δ_H 3.28 (s, 3H), 3.50 (dd, 1H, J= 6.75 & 13.40 Hz), 3.91 (dd, 1H, J= 2.30 & 13.40 Hz), 6.82 (d, 1H, J= 7.15 Hz), 6.93 (t, 1H, J= 7.40 Hz), 7.12 (d, 1H, J= 7.85 Hz), 7.18 (d,

1H, J= 6.70 Hz), 7.26 (t, 1H, J= 7.25 Hz), 7.30 (t, 1H, J= 7.72 Hz), 7.43 (td, 1H, J= 0.98 & 7.60 Hz), 7.65 (m, 3H, J= 2.71 Hz), 7.91 (m, 1H, J= 2.57 Hz), 8.25 (d, 1H, J= 7.60 Hz), 10.36 (NH); ^{13}C-NMR (125 MHz, DMSO-*d6*, 300 K): δ_C 26.81, 31.17, 50.79, 101.76, 109.07, 120.63, 120.92, 121.87, 122.87, 124.51, 127.50, 127.58, 128.93, 129.15, 132.28, 132.74, 132.90, 133.07, 133.20, 135.91, 137.15, 143.13, 144.02, 153.43, 167.48, 174.70, 189.09, 191.05.

5,6-dihydrospiro[diindeno[1,2-b:1',2'-d]azepine-7,1'-indene]-2',8,13(3'H)-trione (4c): Following the general procedure, compound **4c** was obtained by substituting isatin for 1,2-indandione. Yield 32%; FTIR (cm^{-1}): 3072, 1705, 1581; ESI-HRMS (+ve): m/z= 416.1281 (100%, $[M+H]^+$) ($C_{28}H_{18}NO_3$), calculated m/z= 416.1287; ^{1}H-NMR (500 MHz, DMSO-d*6*, 300K): δ_H 3.20 (s, 2H), 3.49 (m, 1H, J= 5.93 Hz), 3.69 (d, 1H, J= 5.28 Hz), 7.15 (d, 1H, J= 6.34 Hz), 7.23 (t, 1H, J= 6.97 Hz), 7.59 (m, 6H, J= 5.67 Hz), 7.70 (t, 1H, J= 4.95 Hz), 7.78 (d, 1H, J= 7.54 Hz), 7.91 (d, 1H, J= 7.20 Hz), 8.11 (d, 1H, J= 7.50 Hz), 10.34 (NH); Suitable ^{13}C-NMR data could not be obtained†.

5'-bromo-5,6-dihydrospiro[diindeno[1,2-b:1',2'-d]azepine-7,3'-indoline]-2',8,13-trione (4d): Following the general procedure, compound **4d** was obtained by substituting isatin for 5-bromoisatin. Yield 27%; FTIR (cm^{-1}): 3283, 3061, 1697, 1666, 1644; ESI-HRMS (+ve): m/z= 495.0339 (100%, $[M+H]^+$) ($C_{27}H_{16}BrN_2O_3$), calculated m/z= 495.0344; ^{1}H-NMR (400 MHz, DMSO-*d6*, 300 K): δ_H 3.56 (d, 1H, J= 13.32 Hz), 3.84 (d, 1H, J= 13.32 Hz), 6.87 (d, 1H, J=1.95 Hz), 6.91 (d, 1H, J= 8.29 Hz), 7.21 (d, 1H, J= 6.44 Hz), 7.26 (t, 1H, J= 7.27 Hz), 7.42 (m, 2H, J= 3.52 Hz), 7.65 (m, 3H, J= 2.40 Hz), 7.90 (d, 1H, J= 6.19 Hz), 8.30 (d, 1H, J= 7.60 Hz), 10.36 (NH), 10.92 (NH); ^{13}C-NMR (125 MHz, DMSO-*d6*, 300 K): δ_C 29.61, 50.31, 101.44, 111.65, 113.08, 120.15, 120.58, 121.49, 125.99, 126.81, 127.23, 128.79, 131.12, 132.23, 132.50, 132.71, 132.86, 135.04, 135.32, 136.59, 141.47, 142.66, 153.29, 167.47, 175.42, 188.72, 190.73.

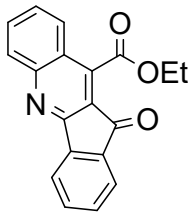
†The product from reaction with 1,2-indandione, **4c**, was obtained as a red oil. While assignment by ^{1}H-NMR spectroscopy and HRMS data was achieved, a suitable ^{13}C-NMR spectrum could not be obtained. This may be due to both carbonyl groups of 1,2-indandione being reactive towards **2**, unlike for isatin, wherein the amide group inactivates that ketone. This appears to promote formation of intractable mixtures that resisted complete separation. Similarly, crystallographic investigations (*vide infra*) showed the isatin moiety to be important for crystallising these materials owing to the prevalence of hydrogen-bonding interactions these groups promote in the solid-state.

S1.3 Other isolates from the reaction mixture

2,2'(2-oxoindoline-3,3-diyl)bis(1H-indene-1,3(2H)-dione) (6): *Method 1:* Isolated as a second crop of crystals obtained from the mother liquor after isolation of **4a**. Yield: 25% as grey single crystals. Characterization data matched that reported in the literature‡. *Method 2*: Orange powder **6"** was dissolved in ethyl acetate and then washed three times with a 5% aqueous HCl solution. The organic fraction was then collected, dried ($MgSO_4$) and concentrated to dryness giving **6**, which could be further purified by recrystallisation. Characterization data matched that reported in the literature‡.

[TEA·CH_2OH][**6**-H] (**6"**): Isolated as an orange powder after filtration of a stirred solution of **4a** in DCM containing 1-2 drops of triethylamine after 12 hours; ESI-HRMS (-ve): m/z= 420.0872 (100%, $[M-H]^-$) ($C_{26}H_{14}NO_5^-$), calculated m/z= 420.0872; ^{1}H-NMR (400 MHz, DMSO-d6, 300 K): δH 1.23 (t, 9H, J= 7.25 Hz), 3.34 (q, 2H, J= 7.30 Hz), 5.29 (s, 2H), 5.77 (s, OH), 6.59 (d, 1H, J= 8.01 Hz), 6.73 (t, 1H, J= 7.11 Hz), 6.96 (t, 1H, J= 8.13 Hz), 7.30 (m, 5H, J= 9.62 Hz), 7.47 (m, 4H, J= 3.43 Hz), 9.87 (s, NH).

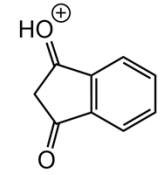
Ethyl 11-oxo-11H-indeno[1,2-b]quinoline-10-carboxylate (8): Isolated as yellow crystals from the general procedure after **6**. Yield: 3%; m.p.: 163.9–164.4 °C; FTIR (cm^{-1}): 1715, 1619, 1606; ESI-HRMS (+ve): m/z= 304.0963 (100%, $[M+H]^+$) ($C_{19}H_{14}NO_3$), calculated m/z = 304.0974; ^{1}H-NMR (500 MHz, DMSO-d^6, 300 K): δ_H 1.41 (t, 3H, J= 7.12 Hz), 4.58 (q, 2H, J= 7.11 Hz), 7.66 (td, 1H, J= 11.19 Hz & 0.93 Hz), 7.72 (m, 1H, J= 2.74 Hz), 7.83 (m, 2H, J= 1.90 Hz), 7.88 (m, 1H, J= 1.92 Hz), 7.94 (m, 1H, J= 2.79 Hz), 8.07 (m, 1H, J= 2.07 Hz), 8.17 (m, 1H, J= 1.88 Hz); ^{13}C-NMR (125 MHz, DMSO-d^6, 300 K): δ_C 13.96, 62.46, 121.65, 121.88, 122.83, 124.23, 126.99, 128.68, 129.99, 132.57, 133.11, 136.21, 136.47, 136.59, 142.93, 149.87, 160.84, 164.64, 188.58.



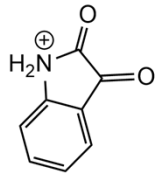
‡ R. Ghahremanzadeh, F. Fereshtehnejad, P. Mirzaei, A. Bazgir, *Ultrason. Sonochem.*, 2010, **18**, 415.

S2. RADIAN ASAP Mass spectrometry data

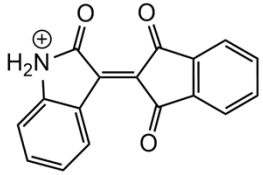
S2.1 Summary of major m/z fragments assigned in this study:



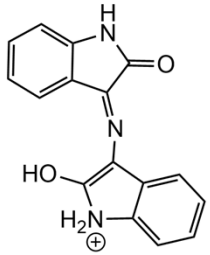
Chemical Formula: $C_9H_7O_2^+$
m/z: 147.0 (100.0%), 148.0 (9.8%)



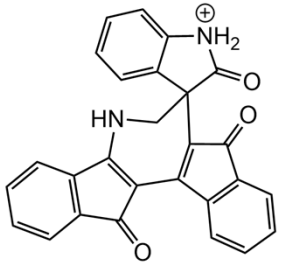
Chemical Formula: $C_8H_6NO_2^+$
m/z: 148.0 (100.0%), 149.0 (9.2%)



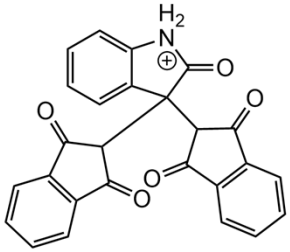
Chemical Formula: $C_{17}H_{10}NO_3^+$
m/z: 276.1 (100.0%), 277.1 (19.0%)



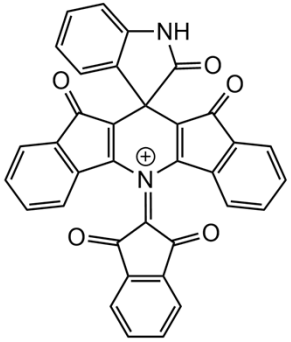
Chemical Formula: $C_{16}H_{12}N_3O_2^+$
m/z: 278.1 (100.0%), 279.1 (18.6%),



Chemical Formula: $C_{27}H_{17}N_2O_3^+$
m/z: 417.1 (100.0%), 418.1 (30.3%), 419.1 (5.0%)

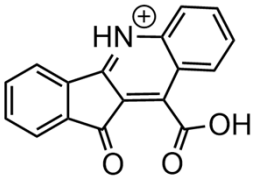


Chemical Formula: $C_{26}H_{16}NO_5^+$
m/z: 422.1 (100.0%), 423.1 (28.9%)

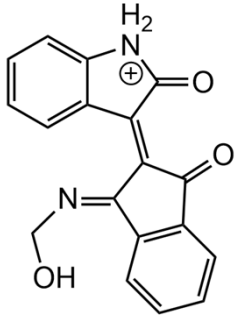


Chemical Formula: $C_{35}H_{17}N_2O_5^+$
m/z: 545.1 (100.0%), 546.1 (39.0%), 547.1 (8.4%), 548.1 (1.3%)

Other species of relevance:



Chemical Formula: $C_{17}H_{10}NO_3^+$
m/z: 276.1 (100.0%), 277.1 (19.0%)



Chemical Formula: $C_{18}H_{13}N_2O_3^+$
m/z: 305.1 (100.0%), 306.1 (20.5%)

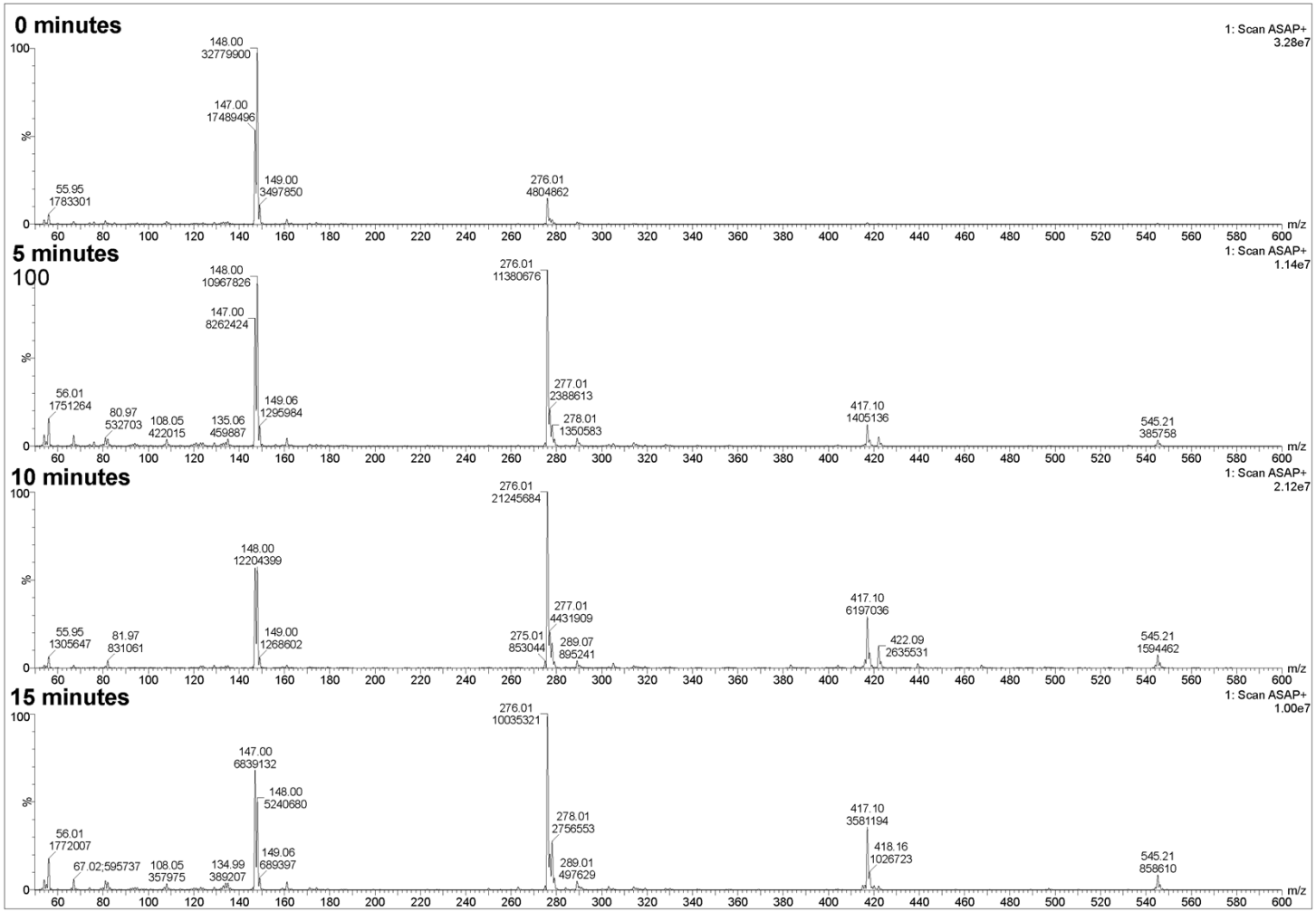


Figure S2.1: Real-time mass spectrum (positive ionisation) of the reaction progress between isatin, 1,3-indandione, and glycine from 0 minutes to 15 minutes.

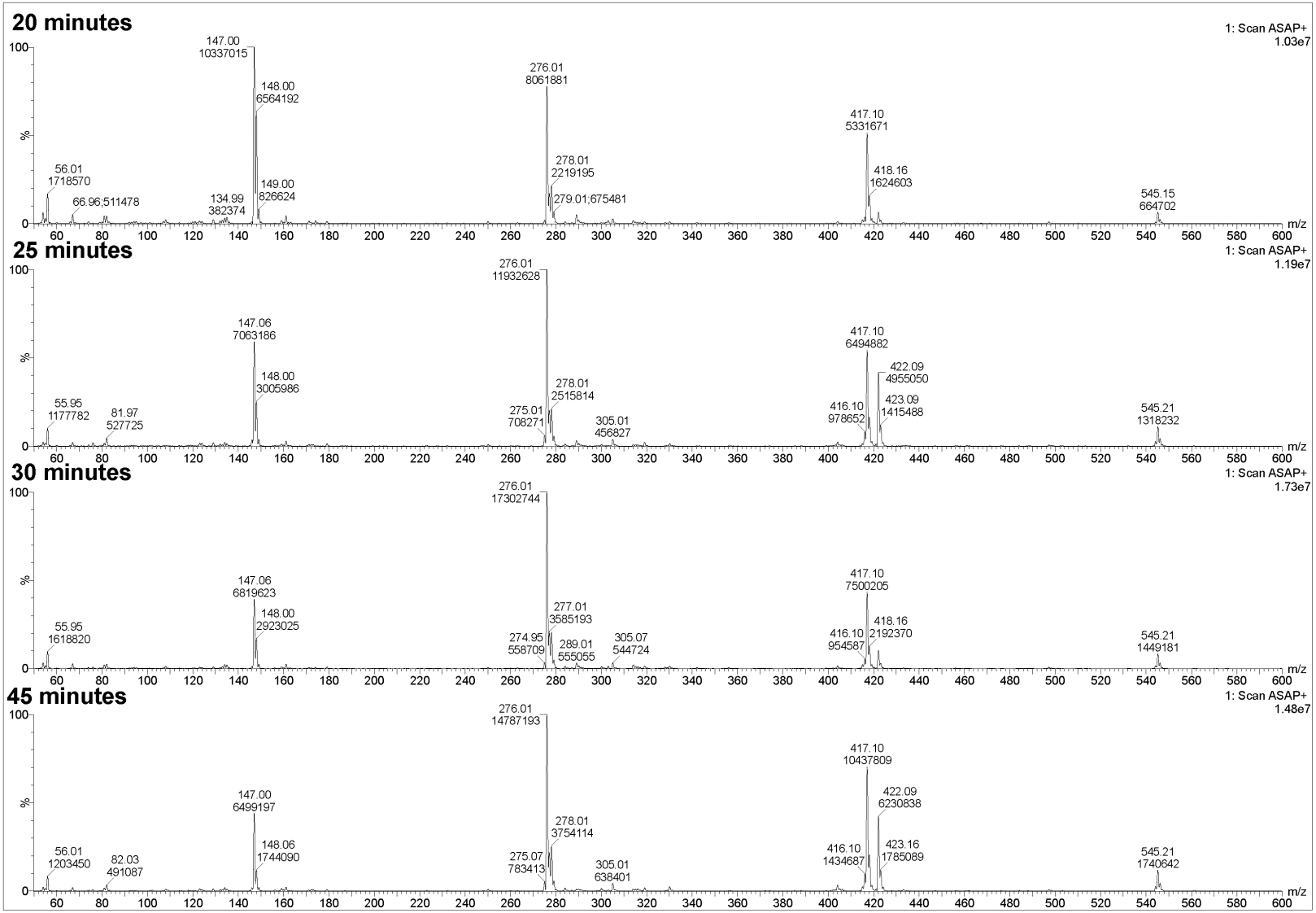


Figure S2.2: Real-time mass spectrum (positive ionisation) of the reaction progress between isatin, 1,3-indandione, and glycine from 20 minutes to 45 minutes.

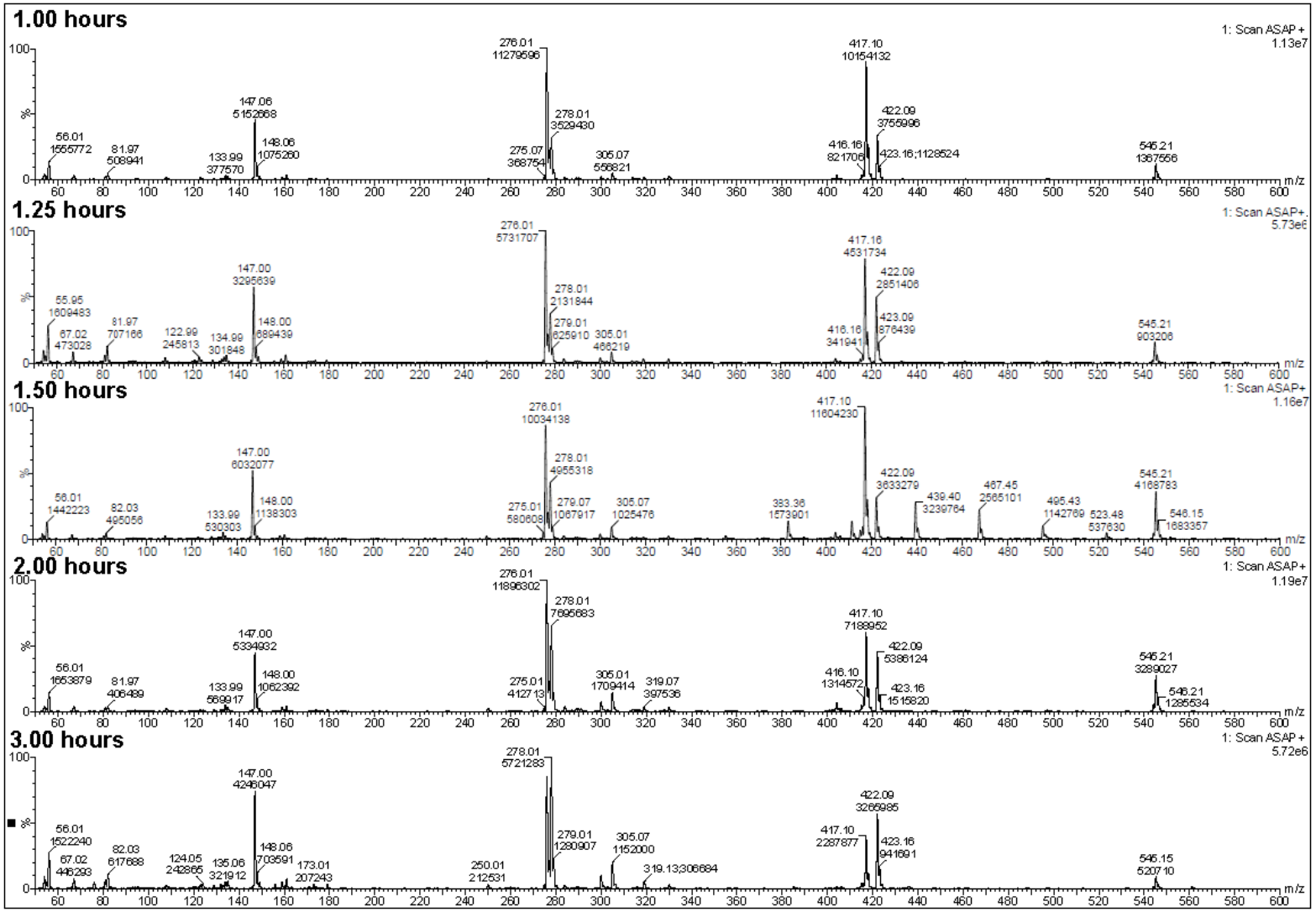


Figure S2.3: Real-time mass spectrum (positive ionisation) of the reaction progress between isatin, 1,3-indandione, and glycine from 1 hour to 3 hours.

S3. NMR spectroscopy data

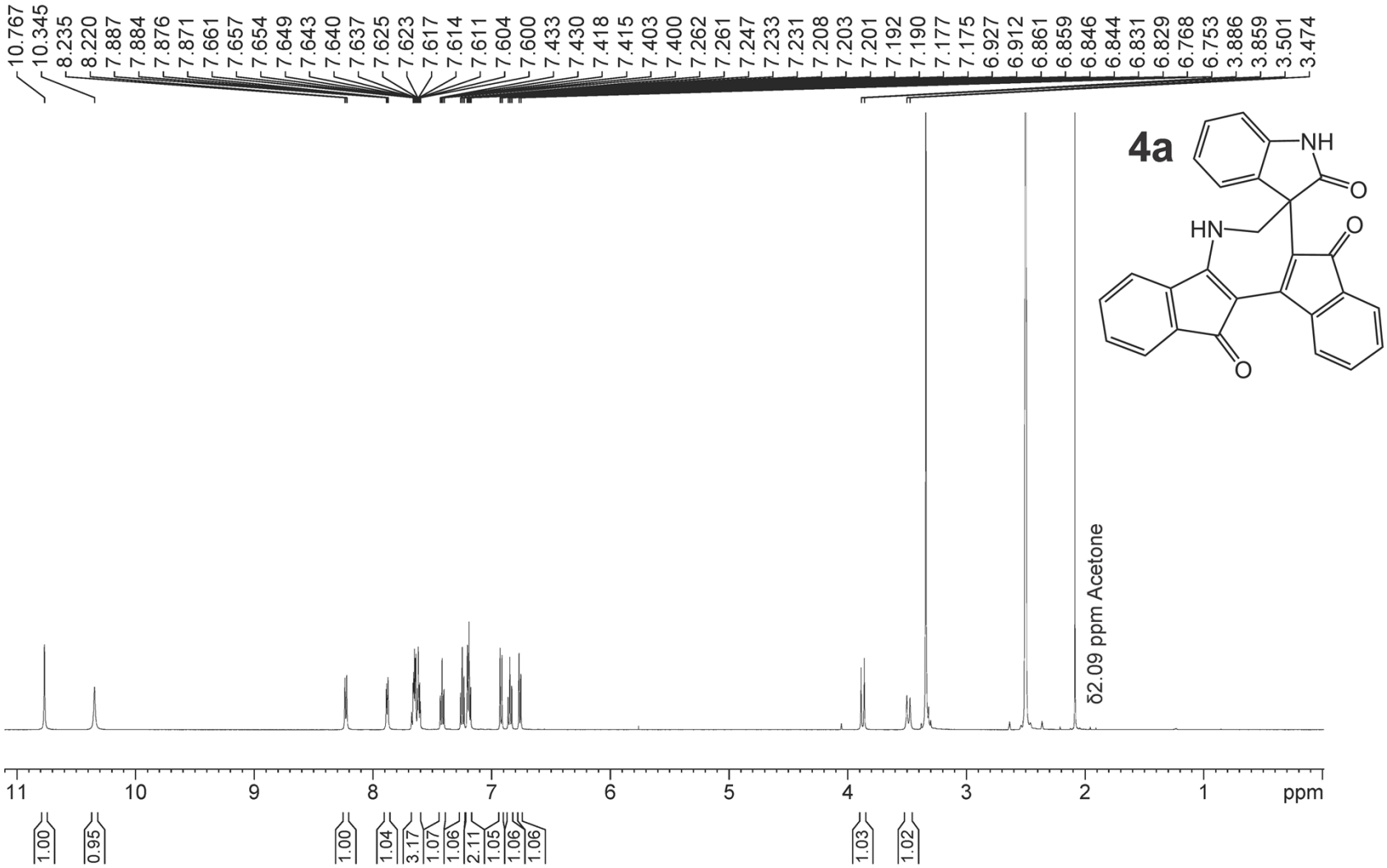


Figure S3.1: ^{1}H-NMR spectrum of compound **4a**.

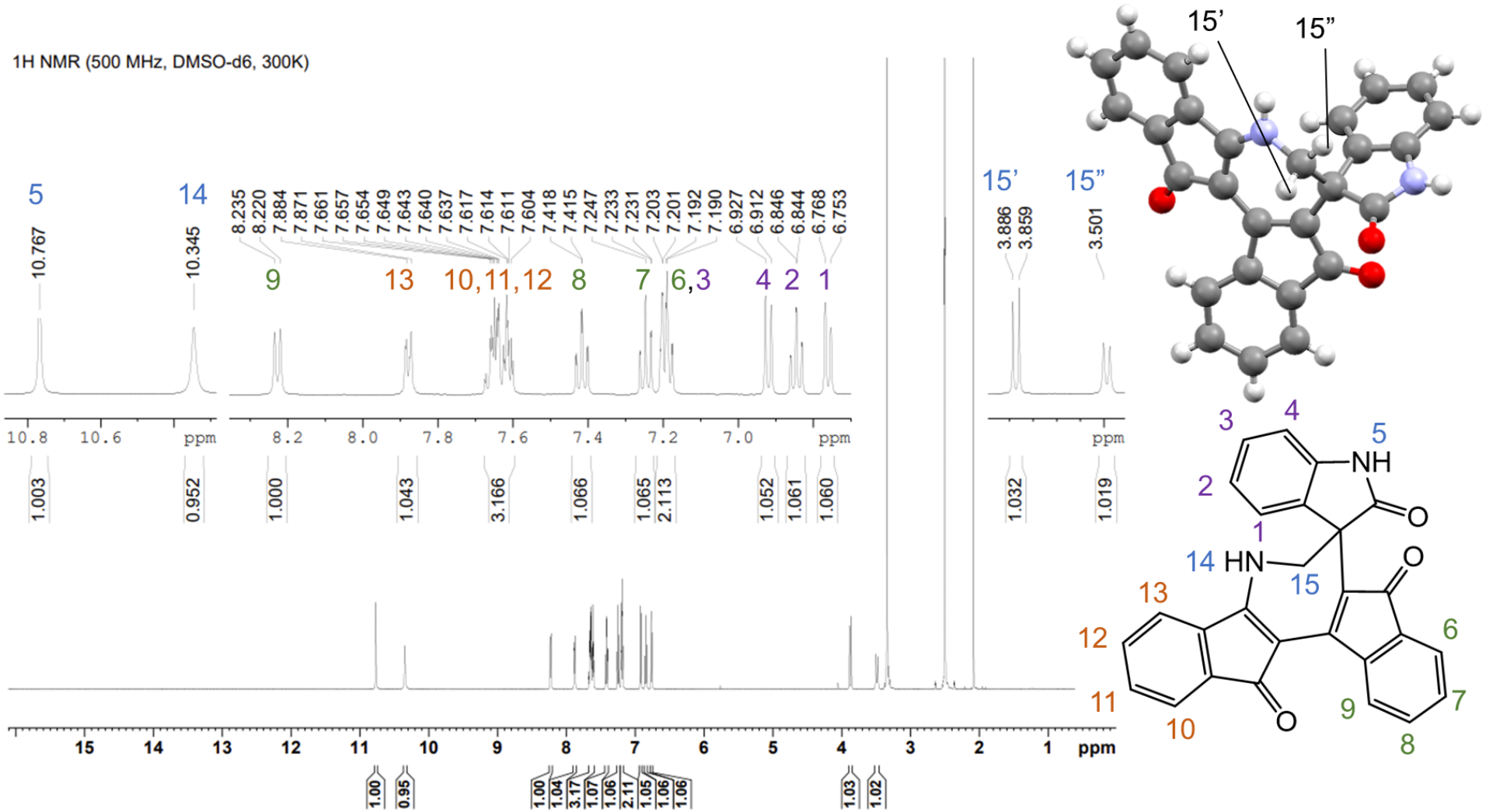


Figure S3.2: [1]H-NMR assignment of compound **4a**.

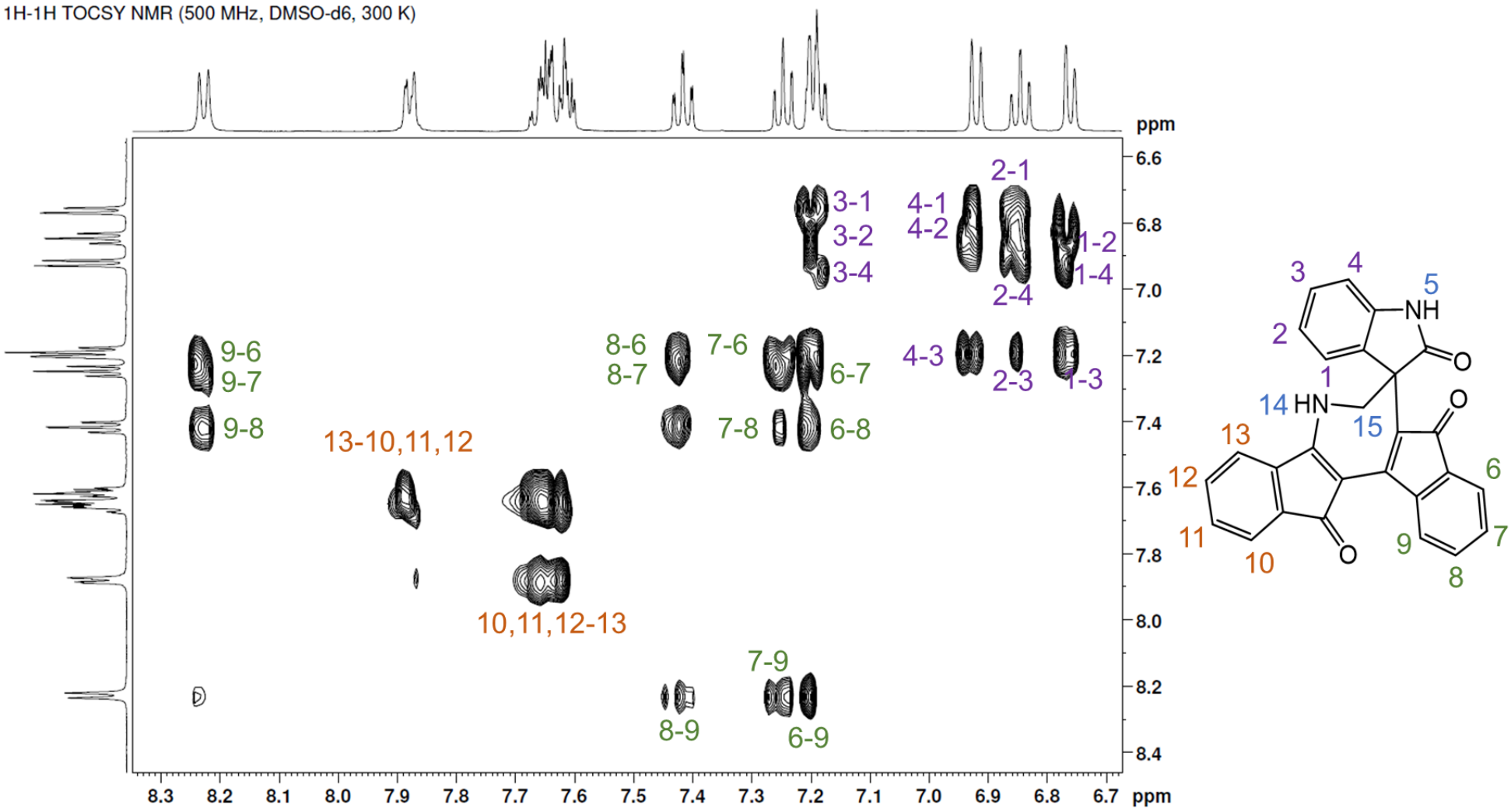


Figure S3.3: ^{1}H-^{1}H TOCSY NMR experiment of compound **4a** with a labelled chemical structure and spin systems illustrated.

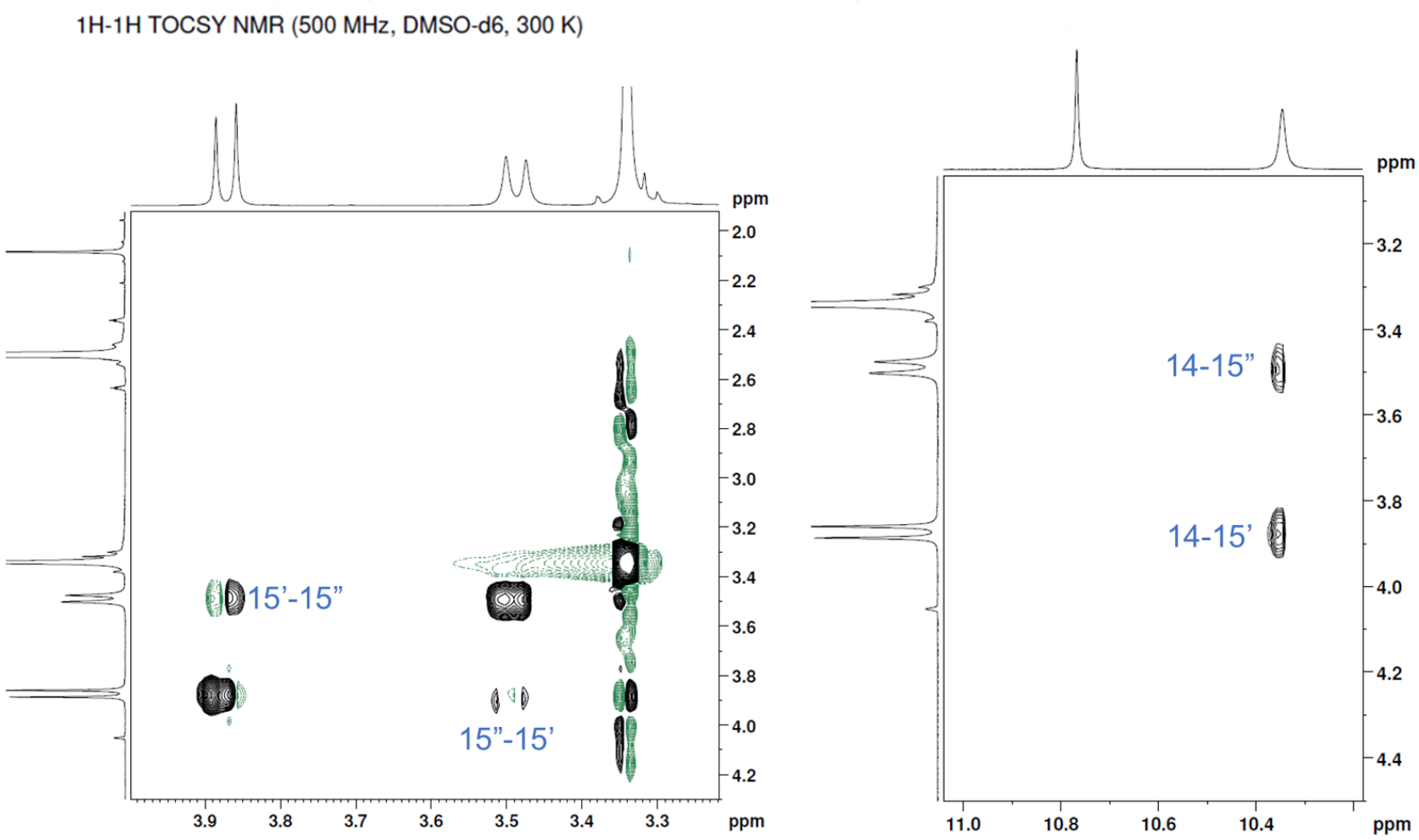


Figure S3.4: ^{1}H-^{1}H TOCSY NMR spectrum of compound **4a**.

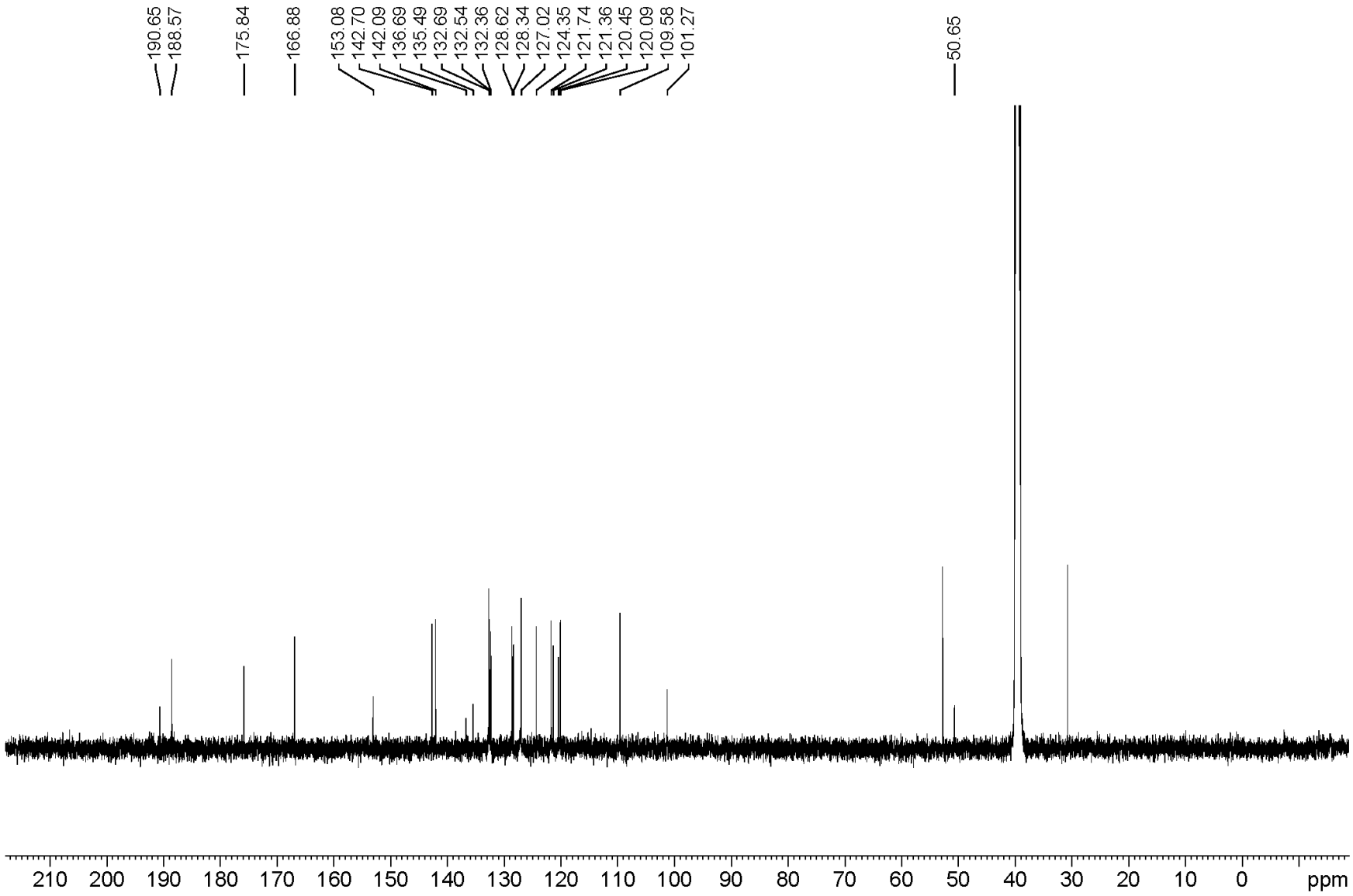


Figure S3.5: ^{13}C NMR spectrum of compound **4a**.

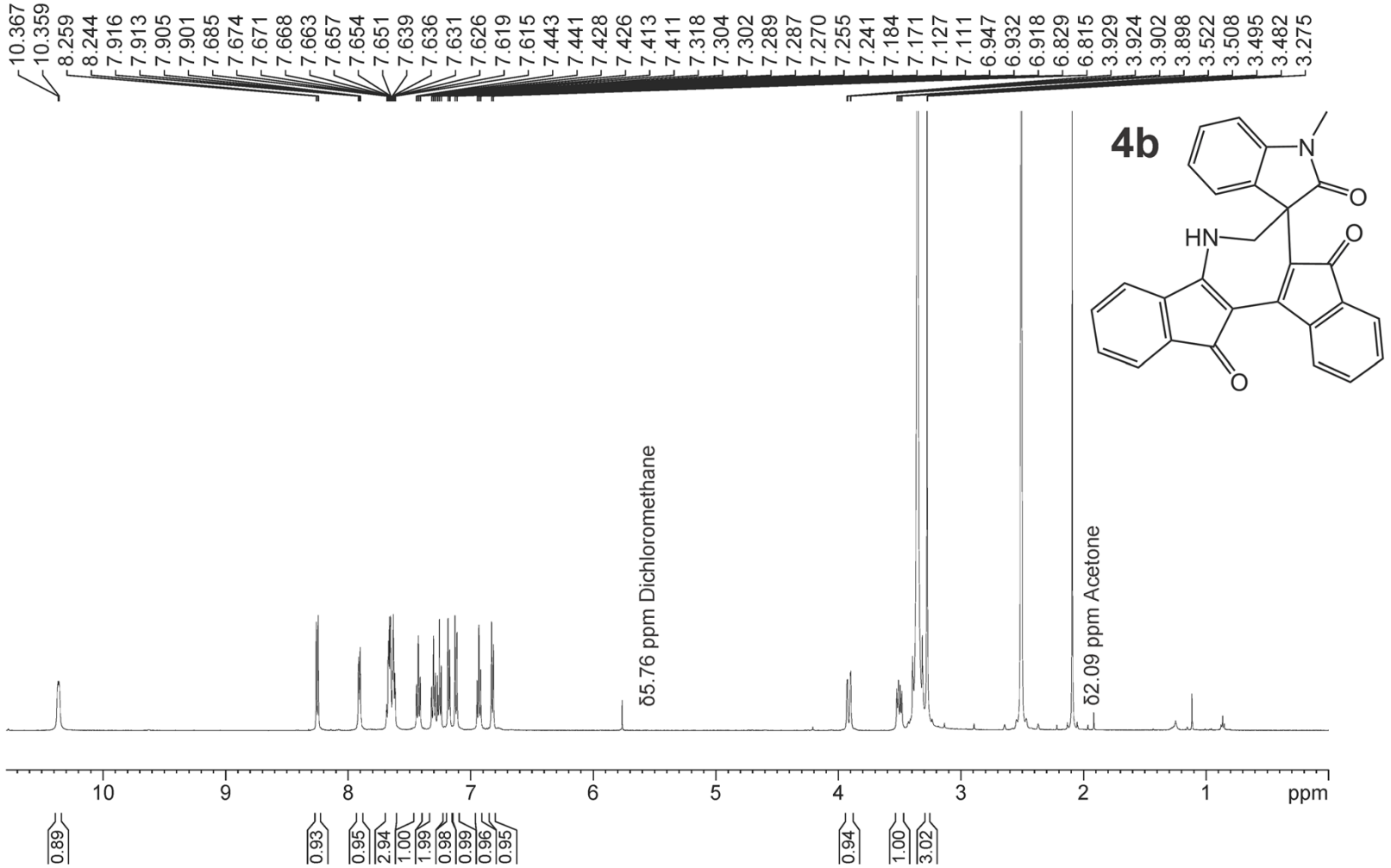


Figure S3.6: [1]H-NMR spectrum of compound **4b**.

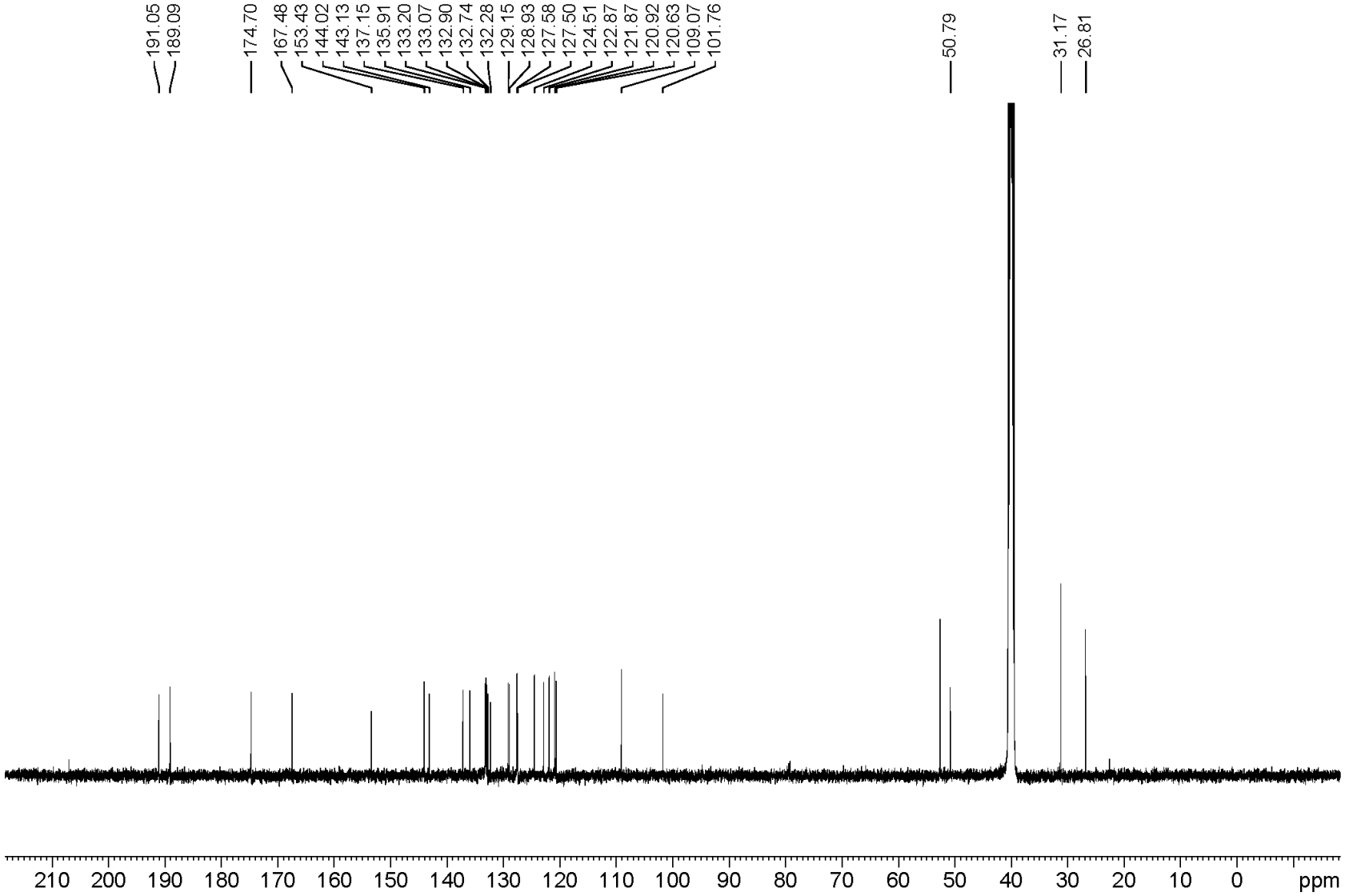


Figure S3.7: ^{13}C NMR spectrum of compound **4b**.

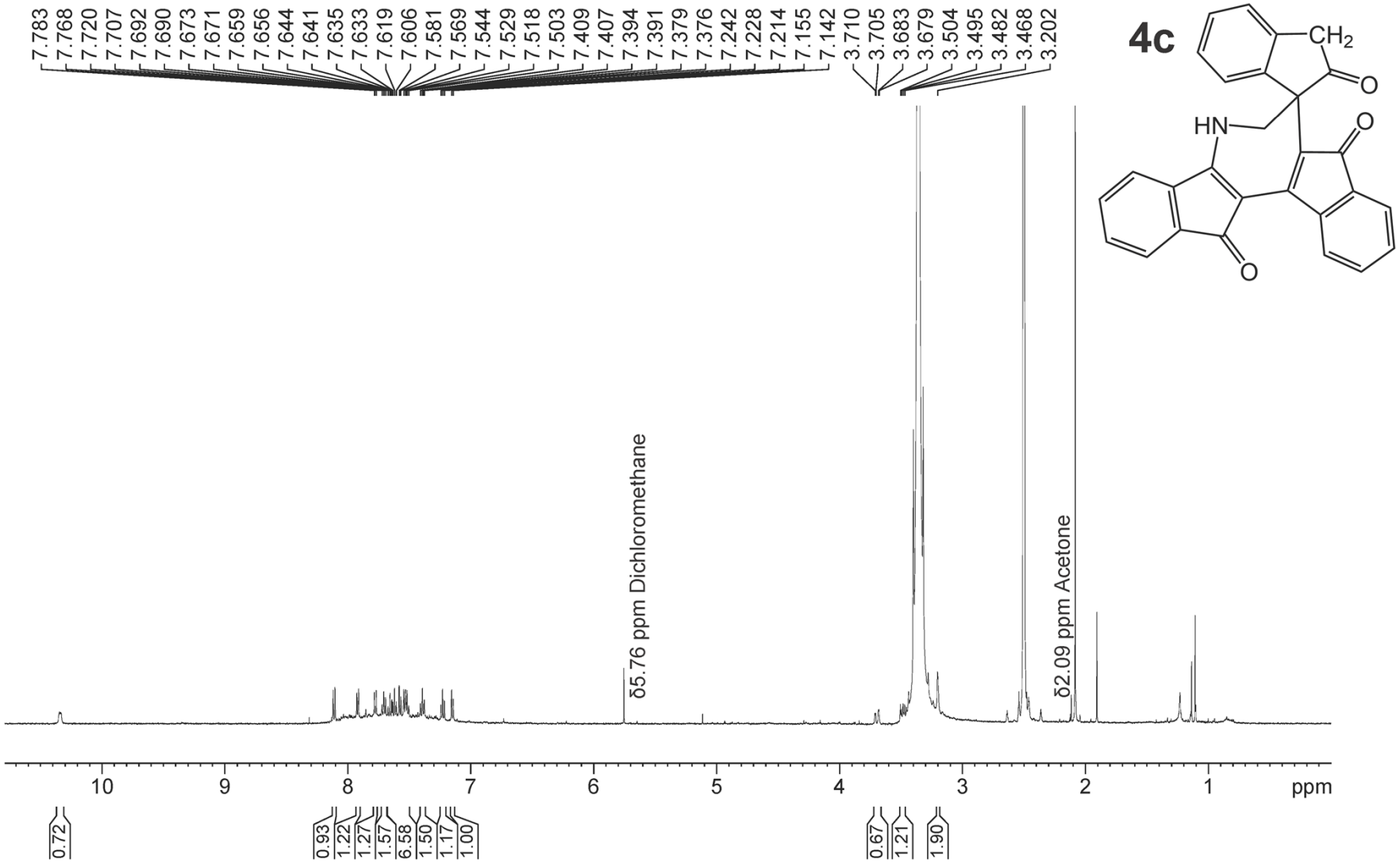


Figure S3.8: [1]H-NMR spectrum of compound **4c**.

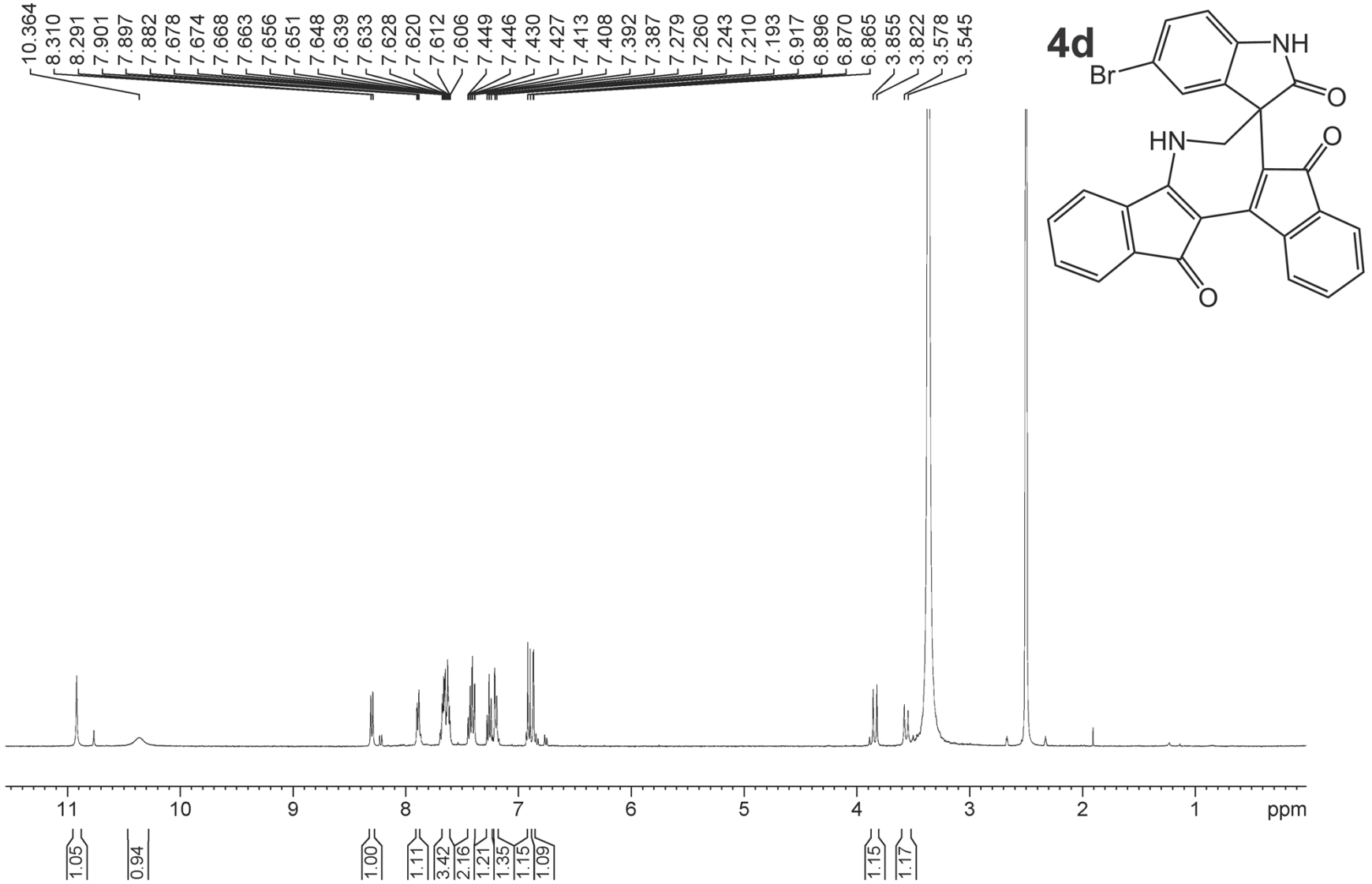


Figure S3.9: ^{1}H-NMR spectrum of compound **4d**.

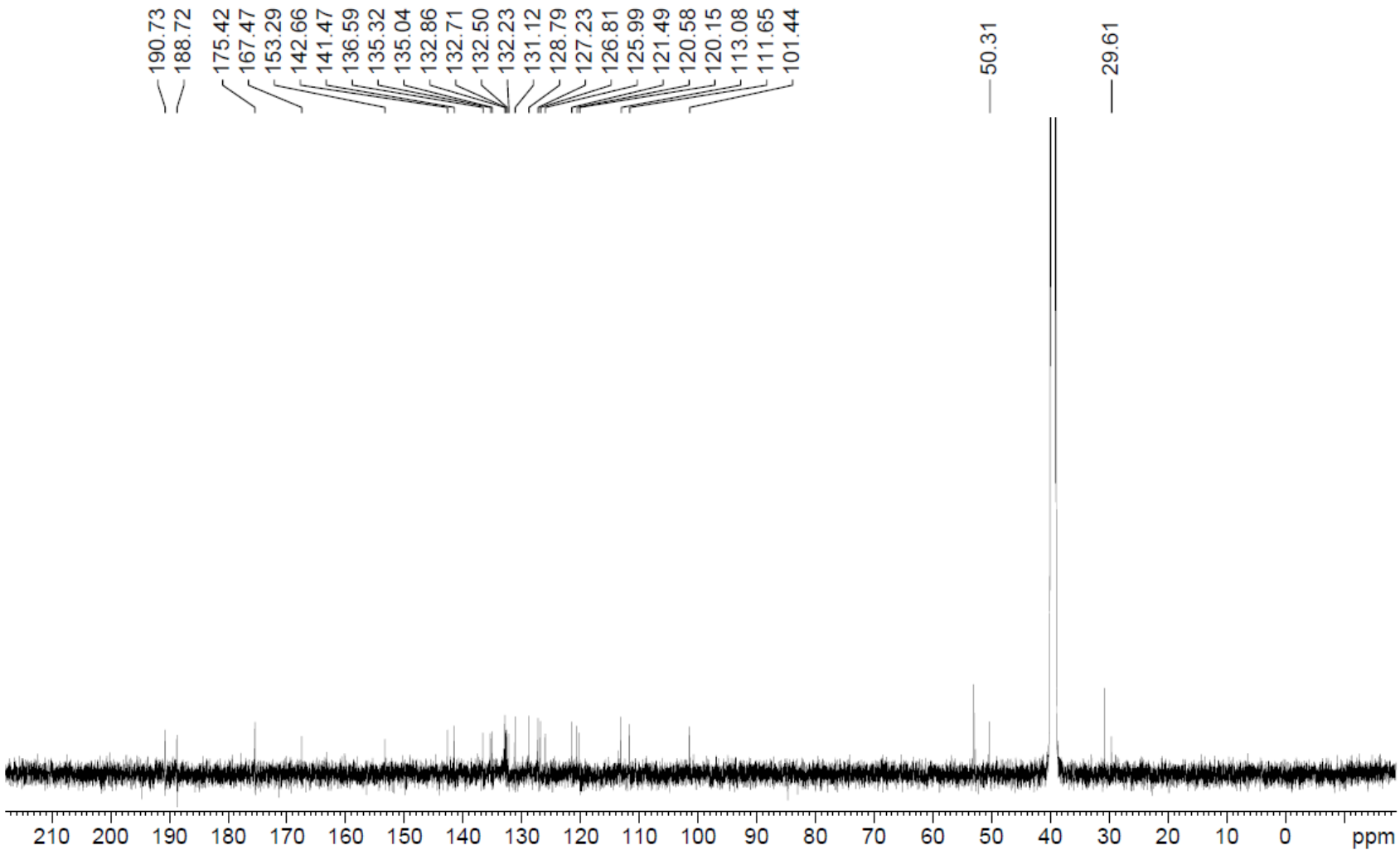


Figure S3.10: ^{13}C NMR spectrum of compound **4d**.

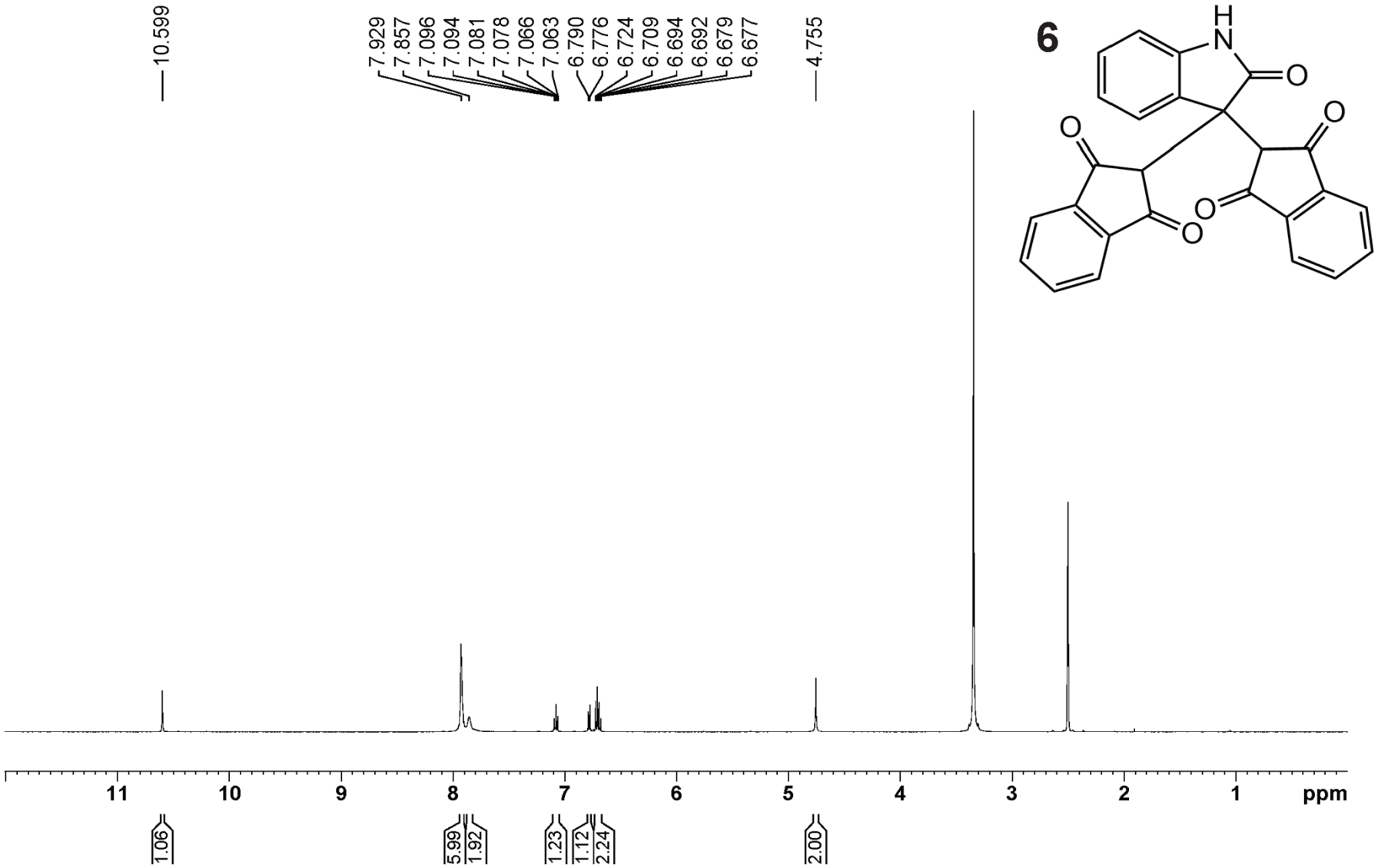


Figure S3.11: ^{1}H-NMR spectrum of compound **6**.

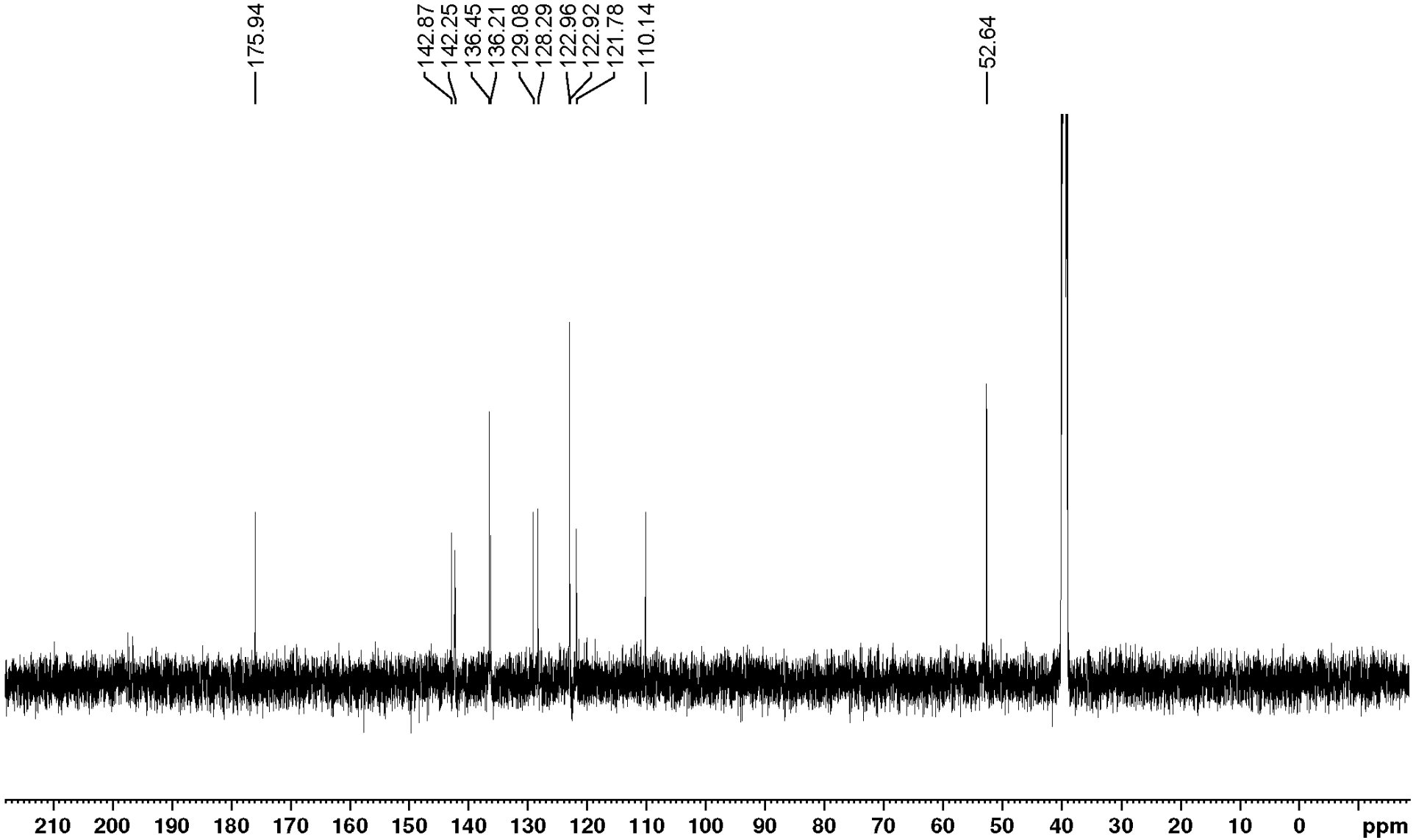


Figure S3.12: ^{13}C-NMR spectrum of compound **6**.

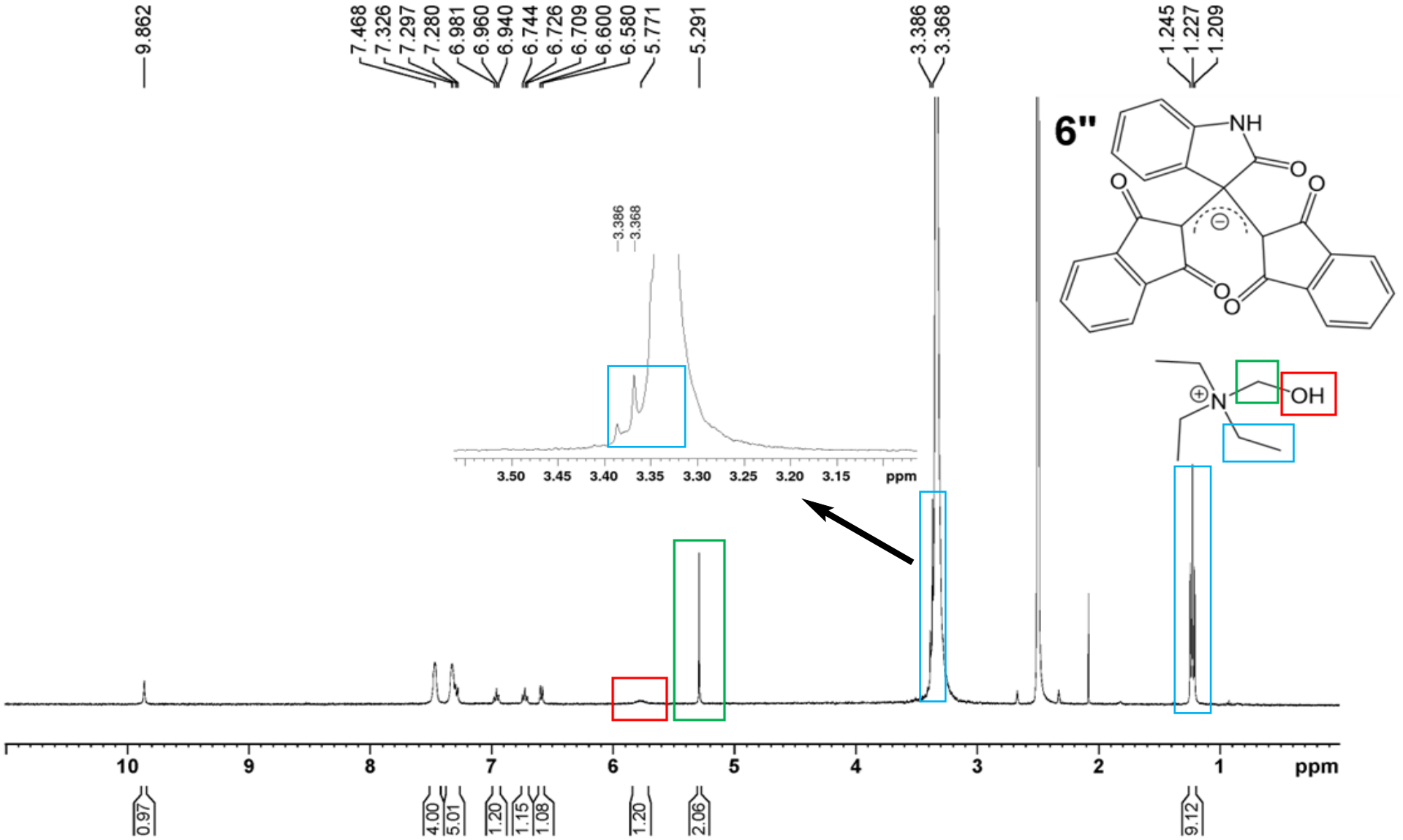


Figure S3.13: ^{1}H-NMR spectrum of compound **6''**. Note the 6H quartet of the three NEt arms is partially obscured by the water peak.

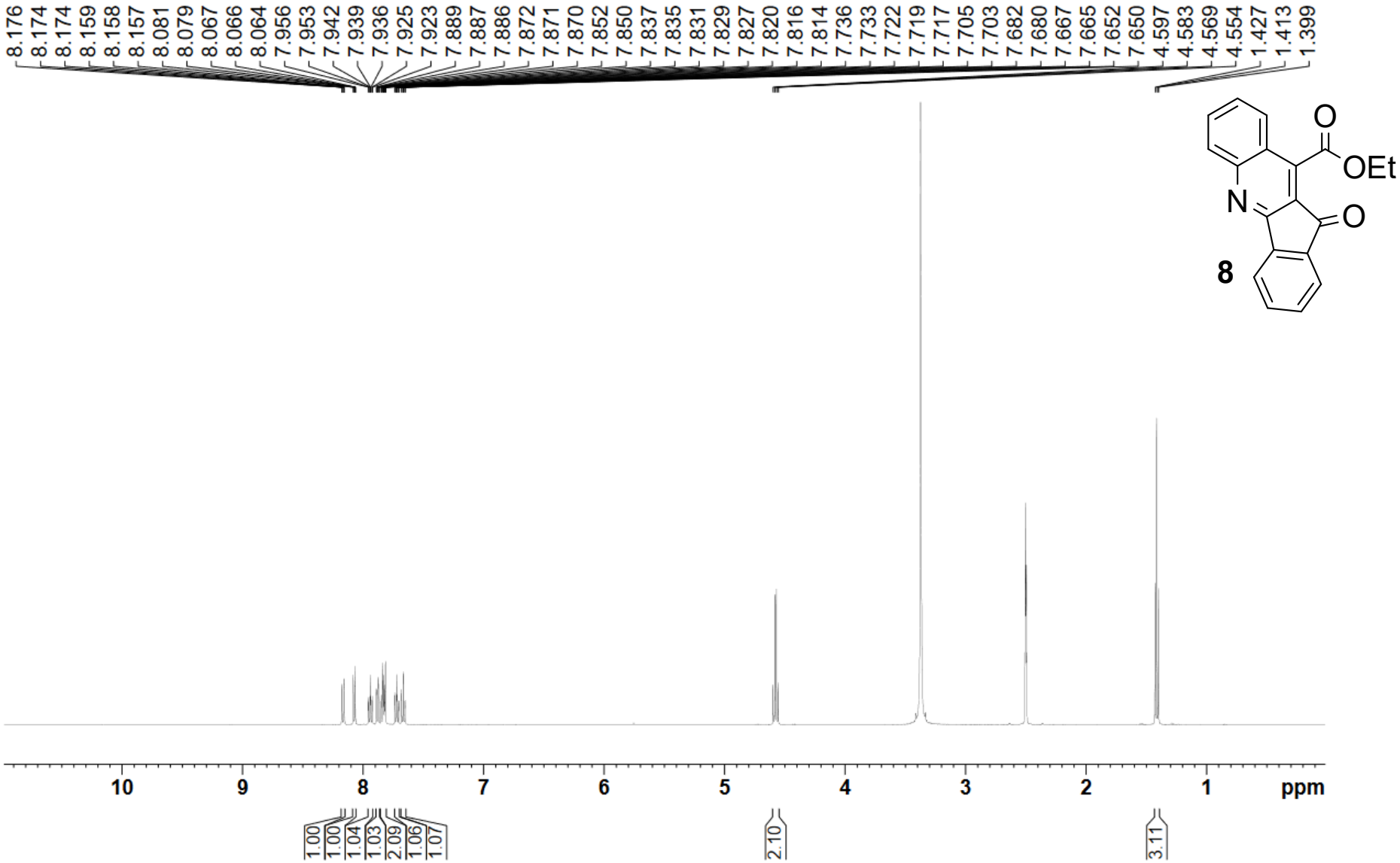


Figure S3.14: ^{1}H-NMR spectrum of compound **8**.

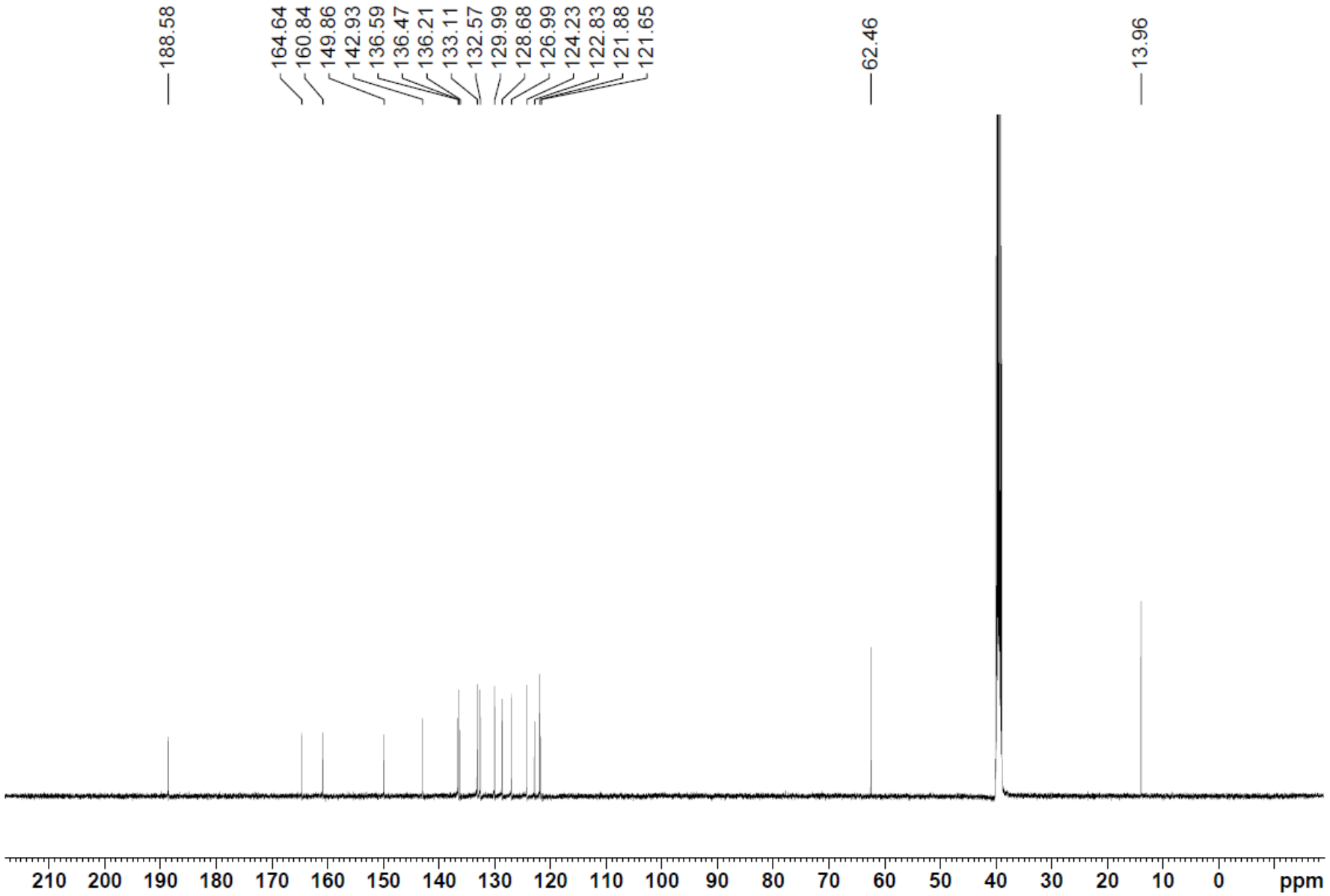


Figure S3.15: ^{13}C NMR spectrum of compound **8**.

S4. Single-Crystal X-Ray Diffraction Data

S4.1. Preparing single crystals for analysis

The chosen final product was suspended in a small amount of DCM and loaded onto a makeshift celite filter-aid column. After washing the solid with additional DCM, the retained solid was collected in a glass vial by passing 10 mL of acetone through the column. Approximately 10 mL of *n*-hexane was added to the solution, and the vial was covered with pierced parafilm and left to evaporate overnight at room temperature, resulting in the formation of red prismatic crystals. The vial was capped to prevent further evaporation of solvent until the crystals could be analysed by single-crystal X-ray crystallography.

S4.2. X-ray Crystallography

Single crystal diffraction data were collected using either a Rigaku XtaLAB Synergy Dualflex, Oxford Gemini Ultra or Bruker D8 Venture. The instruments employed confocal mirror monochromated micro-focus Mo-Kα radiation (0.71073 Å), graphite monochromated Mo-Kα (0.71073 Å) or micro-focus confocal mirror monochromated Cu-Kα radiation (1.54178 Å) . Data integration and reduction were undertaken with either CrysAlisPro[1] or APEX-5[2] and subsequent computations were carried out using the OLEX-2[3] graphical user interface. Multi-scan absorption corrections were applied using Before structures were solved using SHELXT[4] intrinsic phasing methods and refined using SHELXL[5] Typically, non-hydrogen atoms with occupancies greater than 0.5 were refined anisotropically. Carbon-bound hydrogen atoms were included in idealised positions and refined using a riding model. Disorder was modelled using standard crystallographic methods including constraints, restraints, and rigid bodies where necessary. In several instances solvents of crystallisation were exceptionally disordered solvent masking was employed.[6] The CCDC numbers for this study are 2390183-2390189.

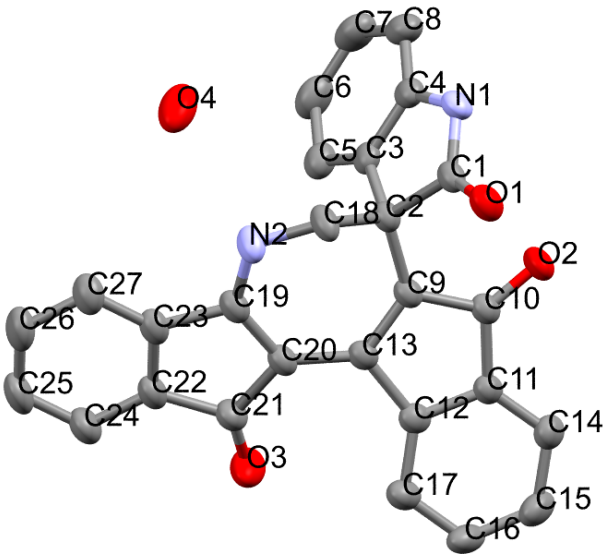


Figure S4.1: 3D (50% ellipsoids) X-ray single-crystal structure of 5,6-dihydrospiro[diindeno[1,2-b:1',2'-d]azepine-7,3'-indoline]-2',8,13-trione. Hydrogen atoms have been omitted for clarity.

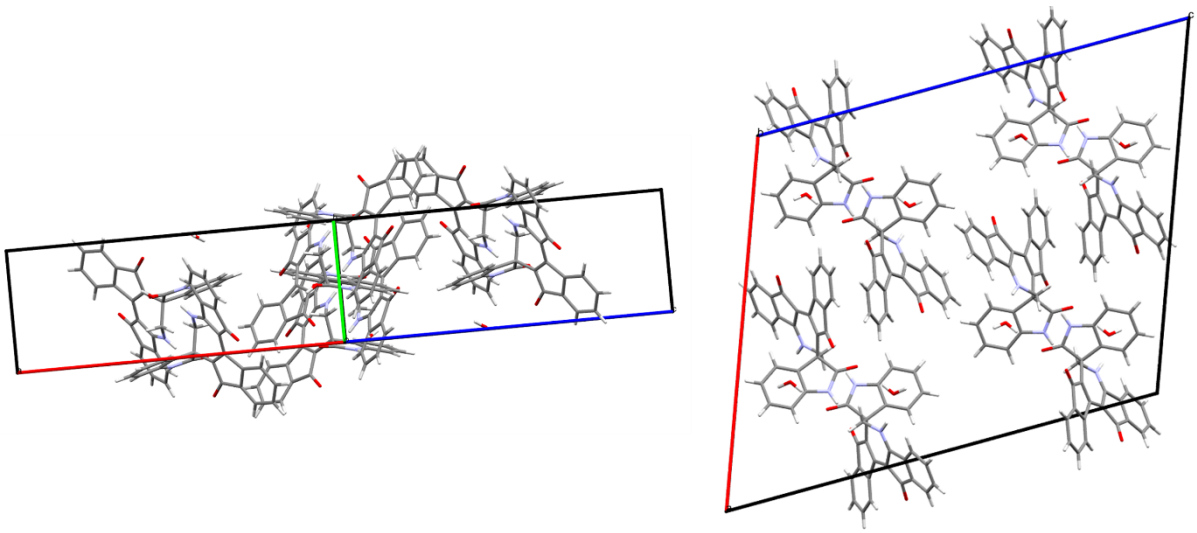


Figure S4.2: Crystal packing of 5,6-dihydrospiro[diindeno[1,2-b:1',2'-d]azepine-7,3'-indoline]-2',8,13-trione *a* and *c* axes (left) and viewing down b axis (right).

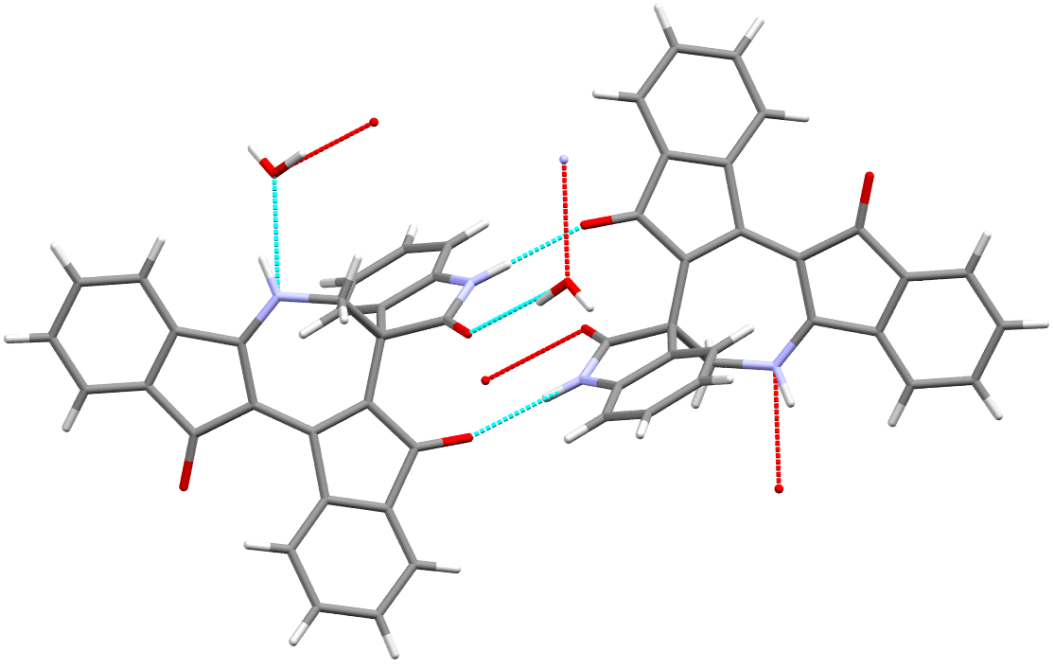


Figure S4.3: Hydrogen bonding of 5,6-dihydrospiro[diindeno[1,2-b:1',2'-d]azepine-7,3'-indoline]-2',8,13-trione (dashed lines).

4.3. References

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