Electrochemical Oxidation-Cyclocondensation of Chitin-Derived 3-Acetamido-5-acetylfuran (3A5AF) for the Synthesis of 3-Acetyl-4-Acetamidopyrrolin-2-ones

Supporting Information

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General experimental information

Unless otherwise noted, all reactions were performed under an atmosphere of dry nitrogen in oven-dried (100 °C) glassware. Commercially available starting materials were purchased from AK Scientific and/or Merck and were used as received unless otherwise noted. All the solvents used were dried by passage through a column of activated alumina under nitrogen using an LC Technology solvent purification system. Thin-layer chromatography (TLC) was performed using F254 0.2 mm silica plates, followed by visualisation with UV irradiation at 254 nm, and staining with ethanolic vanillin or potassium permanganate solution. Flash column chromatography was performed using 40−60 μm silica gel. Melting points were recorded on an electrothermal melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with an FT-IR spectrometer using a diamond ATR sampling accessory. Absorption maxima are expressed in wavenumbers (cm^{-1}). NMR spectra were recorded at ambient temperature in $CDCl_3$/TMS, CD_3OD or DMSO-d_6 solutions using a spectrometer operating at 400 MHz for ^1H nuclei and 100 MHz for ^{13}C nuclei. All chemical shifts are reported in ppm on the δ scale and were measured relative to the residual $CDCl_3$ (δ7.26) peak, the residual CD_3OD (δ3.31) peak, or the residual DMSO-d_6 (δ 2.50) peak. The ^{13}C NMR values were referenced to the residual chloroform (δ 77.1 ppm) or DMSO (δ 39.5 ppm) peaks. Coupling constants, *J*, are reported in Hertz [Hz] where applicable. Multiplicities are reported as "s" (singlet), "d" (doublet), "t" (triplet), "q" (quartet), "p" (quintet), "sxt" (sextet), "m" (multiplet), "br" (broad or combination thereof). Where distinguishable from those due to a major isomer/diastereomer or rotamer, resonances due to the minor isomer, diastereomer and rotamer are denoted by an asterisk (*). Assignments are made with the aid of COSY, NOESY, HMBC and edited HSQC experiments. High-resolution mass spectra were recorded on a microTOF QII (electrospray ionisation, ESI) or Thermo Orbitrap Exploris 120 mass spectrometer, with electrospray ionisation using a capillary voltage of 4500 V for positive mode and 3200 V for

negative mode. Optical rotations were measured using a Rudolph Research Analytical Autopol® IV Automatic Polarimeter at $\lambda = 598$ using 100 mm polarimeter cells at the recorded temperature and solvent and are given in 10^{-1} deg cm^2 g^{-1}. X-ray diffraction measurements of single crystals were performed on a Rigaku Oxford Diffraction XtaLAB-Synergy-S single-crystal diffractometer with a PILATUS 200K hybrid pixel array detector using Cu Kα radiation (λ = 1.54184 Å). The data were processed with the SHELX2018-3 and Olex2 software packages.[1–3] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were inserted at calculated positions or located directly and refined with a riding model or without restrictions. Mercury 2020.3.1[4] was used to visualize the molecular structure. Crystal growth for X-ray crystallographic analysis purposes was achieved using slow evaporation or slow vapour diffusion. Bulk electrolysis experiments were conducted using an ElectraSyn 2.0, fitted with the appropriate electrodes in an undivided cell. Cyclic voltammetry experiments were carried out in a CH instruments CH660 potentiostat, with a three-electrode cell configuration, all experiments were carried out in triplicate.

Anodic oxidation of 3A5AF – optimisation study

With no precautions to exclude air or moisture, the ElectraSyn vial (5 mL) with a stirrer bar was charged with NH_4Br (1 mg, 5 mol%) and a solution of 3A5AF (38 mg, 0.23 mmol) in MeOH (3 mL). The ElectraSyn vial cap equipped with an anode and cathode was inserted into the mixture (**Figure S1**). The reaction mixture was electrolysed with stirring at a constant current (7 – 100 mA) until 2 F/mol had been consumed. Upon completion, the ElectraSyn vial cap was removed, the electrodes were rinsed with MeOH, and the resulting solution was concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with EtOAc.

Figure S1. IKA ElectraSyn 2.0 and a 5 mL ElectraSyn undivided vial (left) fitted with an ElectraSyn glassy carbon anode (GC) and nickel foam cathode (4 x 0.8 x 0.2 cm; 3.4 cm^2 area exposed to the electrolyte; right) were used unless otherwise stated. Electrodes (right) used in the initial screening, from left to right: boron-doped diamond (BDD), RVC, graphite, glassy carbon (GC), nickel foam, nickel, stainless steel, platinum-plated on ceramic.

Divided cell experiment

With no precautions to exclude air or moisture, the anodic chamber of an H-type cell (**Figure S2**) was charged with **3A5AF** (38 mg, 0.23 mmol, 1 equiv.), NH_4Br (1 mg, 5 mol%) and MeOH (3 mL), and the cathodic chamber was charged with NH_4Br (1 mg, 5 mol%) and MeOH (3 mL). The anodic chamber was equipped with a glassy carbon electrode and the cathodic chamber was equipped with a nickel foam electrode, and the reaction mixture was electrolysed under a constant current of 25 mA until 2.0 F/mol had been consumed. Each chamber was collected separately. The crude material present in the anodic chamber was purified by flash chromatography on silica gel eluting with EtOAc. To give **1** as a viscous yellow oil (26 mg, 0.11 mmol, 50%). HRMS (ESI, $[M + Na]^+$) found 252.0842; $[C_{10}H_{15}NO_5 + Na]^+$ requires 252.0842; υ_{max}/cm^{-1} (ATR): 3292, 2940, 2838, 1727, 1692, 1667, 1540, 1442, 1375, 1248, 1088, 1009, 936, 813, 755, 659, 610; ^1H NMR (400 MHz, CD_3Cl) δ 7.31 (br s, 1 H, NH), 6.14 (s, 0.3 H, CH)*, 6.12 (s, 0.6 H, CH)*, 5.77 (s, 0.6 H, Me)*, 5.47 (s, 0.9 H, Me)*, 3.53 (s, 3 H, Me)*, 3.41 (s, 2 H, Me)*, 3.29 (s, 3 H, Me)*, 3.24 (s, 2 H, Me)*, 2.27 (s, 2 H, Me)*, 2.25 (s, 3 H, Me)*, 2.13 (s, 2 H, Me)*, 2.12 (s, 3 H, Me)**;*** ^{13}C NMR (100 MHz, CD_3Cl) δ 203.3 (C)*, 202.9 (C)*, 168.91 (C)*, 168.86 (C)*, 137.2 (C)*, 136.9 (C)*, 113.7 (C)*, 112.8 (C)*, 107.8 (CH)*, 106.7 (CH)*, 105.7 (CH)*, 104.9 (CH)*, 56.3 (Me)*, 54.6 (Me)*, 50.6 (Me)*, 50.3 (Me)*, 25.1 (2 x Me)*, 24.8 (Me)*, 23.9 (Me), *Diastereomers.

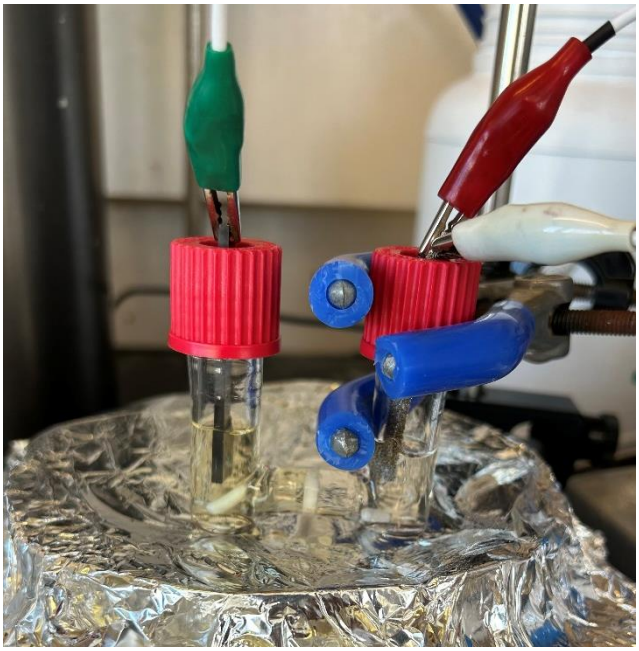


Figure S2. Divided cell (H-type), equipped with an IKA glassy carbon anode and an IKA nickel foam cathode.

Cyclic voltammetry experiments

Anodic scan: Electrochemical behaviour of 3A5AF and NH_4Br using a three-electrode cell

Cyclic voltammetry experiments were conducted with a CH660 potentiostat with a three-electrode cell (**Figure S3**). The redox behaviour of the reaction mixture [3A5AF (blue line), NH_4Br (red dashed line)] was studied in MeOH containing $LiClO_4$ (0.1 M) as the supporting electrolyte at room temperature (**Figure S4**). The electrochemical cell was made up of a BASi platinum wire auxiliary electrode (7.5 cm), a BASi glassy carbon working electrode (⌀ 3.0 mm) and a BASi Ag/AgCl (3 M NaCl) reference electrode. The substrate concentration was 1 mM, and the potential was scanned from -0.25 V to 2.0 V with a scan rate of 0.1 Vs^{-1}. All experiments were done in triplicate.

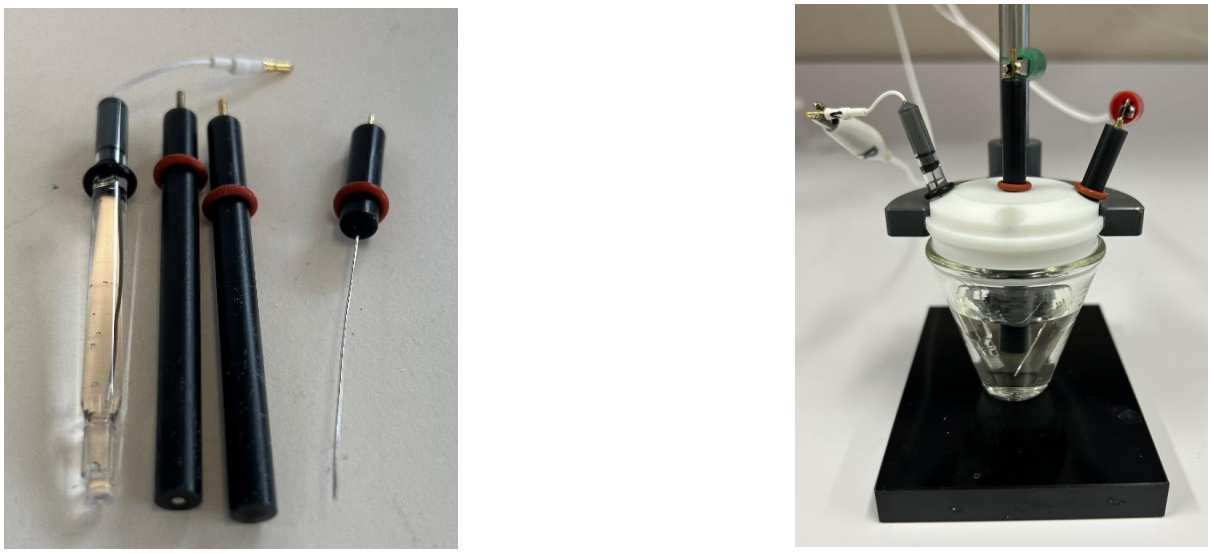


Figure S3. Electrodes used for cyclic voltammetry; from left to right, BASi Ag/AgCl (3 M NaCl) reference electrode, BASi platinum electrode, BASi glassy carbon electrode (⌀ 3.0 mm) and a BASi platinum wire auxiliary electrode (7.5 cm). A three-electrode cell made up of a BASi Ag/AgCl (3 M NaCl) reference electrode, a BASi glassy carbon working electrode (⌀ 3.0 mm) or BASi platinum working electrode and a BASi platinum wire auxiliary electrode (7.5 cm).

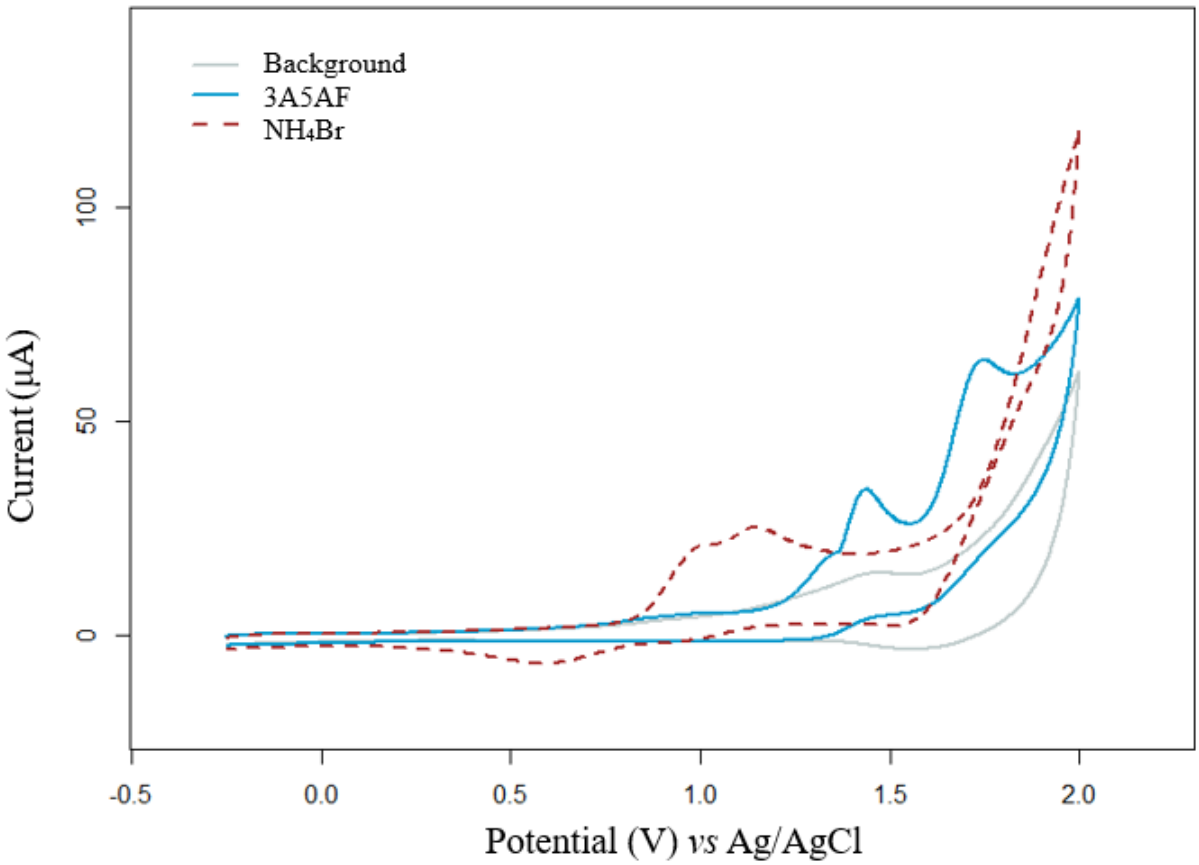


Figure S4. Cyclic voltammogram (-0.25 to 2.0 V *vs* Ag/AgCl) of 3A5AF and NH_4Br in MeOH with $LiClO_4$ (0.1 M).

Cathodic scan: Electrochemical behaviour of **3A5AF** and NH_4Br using a three-electrode cell

Cyclic voltammetry experiments were conducted with a CH660 potentiostat, with a three-electrode cell (**Figure S3**). The redox behaviour of the reaction mixture [3A5AF (blue line), NH_4Br (red dashed line)] was studied in MeOH containing LiClO4 (0.1 M) as the supporting electrolyte at room temperature (**Figure S5**). The electrochemical cell was made up of a BASi platinum wire auxiliary electrode (7.5 cm), a BASi platinum working electrode (⌀ 1.6 mm) and a BASi Ag/AgCl (3 M NaCl) reference electrode. The substrate concentration was 1 mM, and the potential was scanned from 0 V to -1.5 V with a scan rate of 0.1 Vs^{-1}. All experiments were done in triplicate.

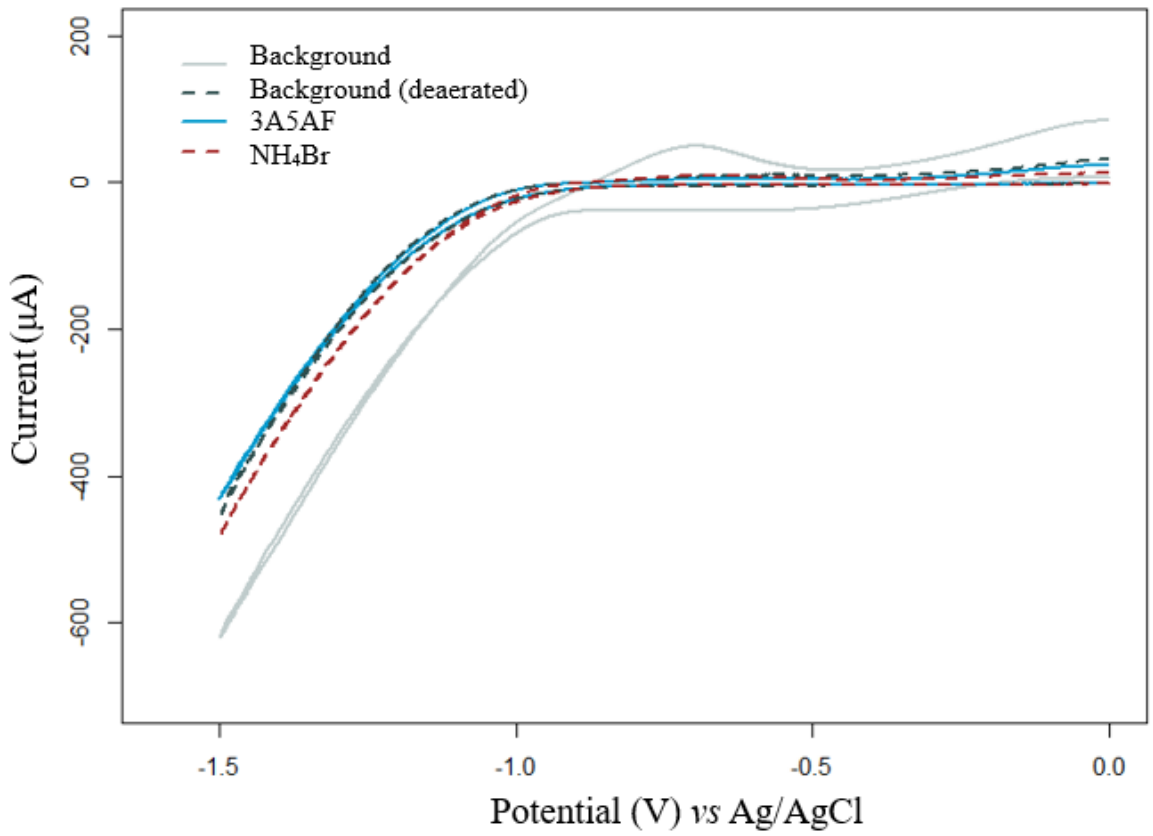
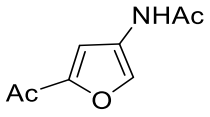


Figure S5. Cyclic voltammogram (0 to -1.5 V *vs* Ag/AgCl) of 3A5AF and NH_4Br in MeOH with $LiClO_4$ (0.1 M).

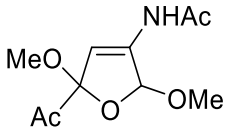
Experimental procedures

3-Acetylamido-5-acetylfuran (3A5AF)



Synthesised by modification of a reported procedure.[5] A mixture of *N*-acetylglucosamine (5 g, 23 mmol) and [BMim]Cl (37.5 g, 0.21 mol) was heated to 100 °C, and once the IL had melted, $B(OH)_3$ (2.84 g, 46 mmol) was added and the solution was stirred at 180 °C for 1 h. The reaction mixture was then diluted with cold water (100 mL), extracted with EtOAc (10 x 100 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude was dissolved in MeOH (20 mL) and the solution was decolourised with activated carbon, filtered and concentrated under reduced pressure. The crude was recrystallised from hot water-MeOH (5:1) to give the *title compound* (1.15 g, 6.9 mmol, 30%) as a pale-yellow crystalline solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (s, 1 H, ArH), 7.20 (d, *J* 1.0, 1 H, ArH), 2.45 (s, 3 H, Me), 2.11 (s, 3 H, Me), 1 x NH not observed. NMR spectroscopic data is in agreement with previous reports.[6]

***N*-(5-Acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (1)**



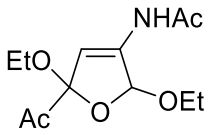
With no precautions to exclude air or moisture, a beaker (50 mL) with a stirrer bar was charged with NH_4Br (17.5 mg, 5 mol%) and a solution of 3A5AF (600 mg, 3.59 mmol) in MeOH (30 mL). The ElectraSyn vial cap equipped with an anode (glassy carbon) and cathode (nickel foam) was inserted into the mixture (**Figure S6**). The reaction mixture was electrolysed with stirring at a constant current of 25 mA until 2 F/mol had been consumed. Upon completion, the ElectraSyn vial cap was removed, the electrodes were rinsed with MeOH, and the resulting

solution was concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (EtOAc) to give *title compound* as a viscous yellow oil (716.5 mg, 3.12 mmol, 87%). HRMS (ESI, $[M + Na]^+$) found 252.0842; $[C_{10}H_{15}NO_5 + Na]^+$ requires 252.0842; υ_{max}/cm^{-1} (ATR): 3292, 2940, 2838, 1727, 1692, 1667, 1540, 1442, 1375, 1248, 1088, 1009, 936, 813, 755, 659, 610; ^1H NMR (400 MHz, CD_3Cl) δ 7.31 (br s, 1 H, NH), 6.14 (s, 0.3 H, CH)*, 6.12 (s, 0.6 H, CH)*, 5.77 (s, 0.6 H, Me)*, 5.47 (s, 0.9 H, Me)*, 3.53 (s, 3 H, Me)*, 3.41 (s, 2 H, Me)*, 3.29 (s, 3 H, Me)*, 3.24 (s, 2 H, Me)*, 2.27 (s, 2 H, Me)*, 2.25 (s, 3 H, Me)*, 2.13 (s, 2 H, Me)*, 2.12 (s, 3 H, Me)**;*** ^{13}C NMR (100 MHz, CD_3Cl) δ 203.3 (C)*, 202.9 (C)*, 168.91 (C)*, 168.86 (C)*, 137.2 (C)*, 136.9 (C)*, 113.7 (C)*, 112.8 (C)*, 107.8 (CH)*, 106.7 (CH)*, 105.7 (CH)*, 104.9 (CH)*, 56.3 (Me)*, 54.6 (Me)*, 50.6 (Me)*, 50.3 (Me)*, 25.1 (2 x Me)*, 24.8 (Me)*, 23.9 (Me).

*Diastereomers.

Figure S6. IKA ElectraSyn 2.0 and a 50 mL beaker (left) fitted with an ElectraSyn glassy carbon anode (GC) and nickel foam cathode (4 x 0.8 x 0.2 cm; 3.4 cm^2 area exposed to the electrolyte; right) were used unless otherwise stated.

***N*-(5-Acetyl-2,5-diethoxy-2,5-dihydrofuran-3-yl)acetamide (3)**



With no precautions to exclude air or moisture, the ElectraSyn vial (5 mL) with a stirrer bar was charged with NH_4Br (1 mg, 5 mol%) and a solution of 3A5AF (38 mg, 0.23 mmol) in EtOH (3 mL). The ElectraSyn vial cap equipped with an anode (glassy carbon) and a cathode (nickel foam) was inserted into the mixture (**Figure S1**). The reaction mixture was electrolysed with stirring at a constant current (25 mA) until 2 F/mol had been consumed. Upon completion, the ElectraSyn vial cap was removed, the electrodes were rinsed with EtOH, and the resulting solution was concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with EtOAc to give the *title compound* as a viscous yellow oil (40.6 mg, 0.18 mmol, 69%). HRMS (ESI, $[M+Na]^+$) found 280.1152; $[C_{12}H_{19}NO_5 + Na]^+$ requires 280.1155; υ_{max}/cm^{-1} (ATR): 3293, 2979, 1692, 1665, 1531, 1372, 1239, 1107, 1004, 932, 878, 592; ^1H NMR (400 MHz, CD_3Cl) δ 7.21 (br s, 1 H, NH)*, 7.17 (br s, 0.7 H, NH)*, 6.17 (s, 0.9, CH)*, 6.15 (s, 0.5, CH)*, 5.80 (d, *J* 1.0, 1 H, CH)*, 5.55-5.53 (m, 0.6 H, CH)*, 3.93-3.85 (m, 0.7 H, CH)*, 3.80-3.71 (m, 1 H, CH)*, 3.70-3.64 (m, 0.8 H, CH)*, 3.56-3.45 (m, 2 H, CH)*, 3.44-3.38 (m, 1 H, CH)*, 2.27 (s, 3 H, Me)*, 2.26 (s, 2 H, Me)*, 2.12 (s, 3 H, Me)*, 2.11 (s, 2 H, Me)*, 1.29-1.25 (m, 2 H, Me)*, 1.25-1.21 (m, 3 H, Me)*, 1.21-1.17 (m, 6 H, 2 x Me)*; ^{13}C NMR (100 MHz, CD_3Cl) δ 203.7 (C)*, 203.4 (C)*, 169.04 (C)*, 168.99 (C)*, 137.2 (C)*, 137.0 (C)*, 113.3 (C)*, 112.5 (C)*, 107.7 (CH)*, 107.0 (CH)*, 104.9 (CH)*, 103.9 (CH)*, 65.0 (CH_2)*, 63.6 (CH_2)*, 58.9 (CH_2)*, 58.7 (CH_2)*, 25.0 (Me)*, 24.8 (Me)*, 23.92 (Me)*, 23.89 (Me)*, 15.4 (Me)*, 15.3 (3 x Me)*

*Diastereomers.

General Procedure. Synthesis of 3-acetyl-4-acetamidopyrrolin-2-ones

With no precautions to exclude air, a solution of *N*-(2,5-dimethoxy-5-methyltetrahydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and the stated primary amine (0.135 mmol, 1 equiv.) in EtOAc-water (1:1, 1 mL) was added glacial acetic acid (100 µL) and the reaction mixture was vigorously stirred at 25 °C for the time stated. The reaction mixture was concentrated *in vacuo*, and the crude material was purified by flash column chromatography on silica gel using the eluent stated to give the desired 3-acetyl-4-acetamidopyrrolin-2-one.

When amine hydrochloride salts were used, the salt (0.135 mmol, 1 equiv.) was taken up in water (0.5 mL) and solid $NaHCO_3$ (11.3 mg, 0.135 mmol, 1 equiv.) was added. To this solution was added a solution of **1** (62 mg, 0.27 mmol, 2 equiv.) in EtOAc (0.5 mL) and glacial acetic acid (100 µL) and the reaction was conducted as described above.

***N*-(4-Acetyl-1-(2-(5-methoxyindol-3-yl)ethyl)-5-oxo-2,5-dihydropyrrol-3-yl)acetamide (10)**

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and 5-methoxytryptamine (25.7 mg, 0.135 mmol, 1 equiv.) were stirred for 24 h. Flash column chromatography eluting with (acetone-light petroleum; 2:3) gave the *title compound* as a pale-yellow solid (24.0 mg, 0.068 mmol, 50%); mp 164.5-166.0 °C; HRMS (ESI, $[M + Na]^+$) found 378.1424; $[C_{19}H_{21}N_3O_4 + Na]^+$ requires 378.1424; υ_{max}/ cm^{-1} (ATR): 3356, 2919, 1717, 1664, 1638, 1588, 1487, 1437, 1426, 1360, 1321, 1281, 1215, 1185, 1123, 1094, 1055, 1025, 997, 921, 831, 806, 777; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 11.31 (br s, 1 H, NH), 10.64 (br s, 1 H, NH), 7.22 (d, *J* 8.8, 1 H, ArH), 7.12 (d, *J* 2.3, 1 H, ArH), 7.03 (d, *J* 2.4, 1 H, ArH), 6.71 (dd, *J* 8.7, 2.4, 1 H, ArH), 4.54 (s, 2 H, CH_2), 3.75 (s, 3 H, Me), 3.63 (t, *J* 7.4, 2 H, CH_2), 2.90 (t, *J* 7.4, 2 H, CH_2), 2.47 (s, 3 H, Me), 2.23 (s, 3 H, Me). ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 196.9 (C), 169.8 (C), 166.7 (C), 161.2 (C), 153.0

(C), 131.4 (C), 127.5 (C), 123.4 (CH), 112.0 (CH), 111.11 (C), 111.09 (CH), 107.9 (C), 100.1 (CH), 55.3 (Me), 50.5 (CH_2), 41.7 (CH_2), 28.4 (Me), 24.2 (Me), 23.9 (CH_2).

***N*-(4-Acetyl-1-benzyl-5-oxo-2,5-dihydropyrrol-3-yl)acetamide (11)**

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and benzylamine (14.5 mg, 0.135 mmol, 1 equiv.) were stirred for 24 h. Flash column chromatography eluting with (EtOAc-light petroleum; 3:2) gave the *title compound* as a pale-yellow oil (24 mg, 0.088 mmol, 65%). HRMS (ESI, [M + H]$^+$) found 273.1234; [$C_{15}H_{16}N_2O_3$ + H]$^+$ requires 273.1234; ν_{max}/cm^{-1} (ATR): 3238, 2921, 1679, 1644, 1579, 1496, 1425, 1358, 1269, 1220, 1180, 1078, 993; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.60 (br s, 1 H, NH), 7.35-7.24 (m, 5 H, 5 x ArH), 4.63 (s, 2 H, CH_2), 4.46 (s, 2 H, CH_2), 2.64 (s, 3 H, Me), 2.23 (s, 3 H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0 (C), 169.5 (C), 167.6 (C), 161.2 (C), 136.9 (C), 129.0 (2 x CH), 128.2 (2 x CH), 127.9 (CH), 108.9 (C), 50.3 (CH_2), 45.7 (CH_2), 29.0 (Me), 24.6 (Me).

***N*-(4-Acetyl-1-butyl-5-oxo-2,5-dihydropyrrol-3-yl)acetamide (12)**

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and *n*-butylamine (9.9 mg, 0.135 mmol, 1 equiv.) were stirred for 28 h. Flash column chromatography eluting with (EtOAc-light petroleum; 3:2) gave the *title compound* as a pale-yellow oil (20.4 mg, 0.087 mmol, 63%). HRMS (ESI, [M + H]$^+$) found 239.1389; [$C_{12}H_{18}N_2O_3$ + H]$^+$ requires 239.1390; ν_{max}/cm^{-1} (ATR): 3228, 2962, 2932, 2873, 1713, 1681, 1640, 1584, 1427, 1357, 1324, 1268, 1222, 1170, 1098, 1038, 991, 957, 780; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.58 (br s, 1 H, NH), 4.54 (s, 2 H, CH_2), 3.44 (t, *J* 7.3, 2 H, CH_2), 2.60 (s, 3 H, Me), 2.26 (s, 3 H, Me), 1.56 (p, *J* 7.4, 2 H, CH_2), 1.33 (sxt., *J* 7.4, 2 H, CH_2), 0.93 (t, *J* 7.2, 3 H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) 199.1 (C), 169.6 (C), 167.5 (C), 160.8 (C), 109.3 (C), 50.7 (CH_2), 41.6 (CH_2), 30.5 (CH_2), 29.0 (Me), 24.6 (Me), 20.2 (CH_2), 13.9 (Me).

N-(4-Acetyl-1-allyl-5-oxo-2,5-dihydropyrrol-3-yl)acetamide (13)

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and allylamine (7.7 mg, 0.135 mmol, 1 equiv.) were stirred for 26 h. Flash column chromatography eluting with (EtOAc-light petroleum; 3:2) to afford the *title compound* as a pale-yellow oil (13 mg, 0.058 mmol, 43%). HRMS (ESI, $[M + Na]^+$) found 245.0896; $[C_{11}H_{14}N_2O_3 + Na]^+$ requires 245.0897; ν_{max}/cm^{-1} (ATR): 3237, 2922, 1720, 1683, 1645, 1582, 1430, 1360, 1270, 1219, 1187, 1168, 993, 956, 932, 768, 727; ^1H NMR (400 MHz, $CDCl_3$) δ 11.60 (br s, 1 H, NH), 5.83-5.70 (m, 1 H, CH), 5.23-5.20 (m, 1 H, ½ CH_2), 5.20-5.16 (m, 1 H, ½ CH_2), 4.53 (s, 2 H, CH_2), 4.05 (d, *J* 6.0, 2 H, CH_2), 2.60 (s, 3 H, Me), 2.25 (s, 3 H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0 (C), 169.5 (C), 167.4 (C), 161.2 (C), 132.8 (CH), 118.3 (CH_2), 109.1 (C), 50.4 (CH_2), 44.4 (CH_2), 28.9 (Me), 24.6 (Me).

***N*-(4-Acetyl-5-oxo-1-(prop-2-yn-1-yl)-2,5-dihydropyrrol-3-yl)acetamide (14)**

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and propargyl amine (7.4 mg, 0.135 mmol, 1 equiv.) were stirred for 30 h. Flash column chromatography eluting with (EtOAc-light petroleum; 3:2) gave the *title compound* as a pale-yellow solid (15.8 mg, 0.072 mmol, 53%). mp 99.5-102.2 °C; HRMS (ESI, $[M + Na]^+$) found 243.0742; $[C_{11}H_{12}N_2O_3 + Na]^+$ requires 243.0740; υ_{max}/ cm^{-1} (ATR): 3286, 3246, 2918, 1720, 1679, 1641, 1570, 1450, 1426, 1361, 1309, 1271, 1220, 1185, 1153, 996, 957, 904; ^1H NMR (400 MHz, $CDCl_3$) δ 11.63 (br s, 1 H, NH), 4.68 (s, 2 H, CH_2), 4.27 (d, *J* 2.5, 2 H, CH_2), 2.59 (s, 3 H, Me), 2.28 (s, 3 H, Me), 2.26 (t, *J* 3.5, 1 H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8 (C), 169.5 (C), 167.2 (C), 161.5 (C), 108.6 (C), 77.9 (C), 72.9 (CH), 50.0 (CH_2), 31.2 (CH_2), 29.0 (Me), 24.7 (Me).

_N_-(4-Acetyl-1-isopropyl-5-oxo-2,5-dihydropyrrol-3-yl)acetamide (15)

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and isopropyl amine (8 mg, 0.135 mmol, 1 equiv.) were stirred for 30 h. Flash column chromatography eluting with (EtOAc-light petroleum; 1:1) gave the *title compound* as a pale-yellow solid (14.4 mg, 0.064 mmol, 48%). mp 125.9-128.5 °C; HRMS (ESI, $[M + Na]^+$) found 247.1051; $[C_{11}H_{16}N_2O_3 + Na]^+$ requires 247.1053; υ_{max}/ cm^{-1} (ATR): 2971, 2930, 1720, 1670, 1643, 1593, 1453, 1421, 1357, 1272, 1239, 1186, 1218, 1185, 1141, 1127, 1023, 989, 959, 825, 788; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.60 (br s, 1 H, NH), 4.51 (s, 2 H, CH_2), 4.50 (m, 1 H, CH), 2.60 (s, 3 H, Me), 2.26 (s, 3 H, Me), 1.21 (d, *J* 6.8, 6 H, 2 x Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2 (C), 169.6 (C), 166.9 (C), 161.0 (C), 109.6 (C), 46.3 (CH_2), 42.3 (CH), 29.0 (Me), 24.7 (Me), 20.8 (2 x Me).

Methyl 2-(4-acetamido-3-acetyl-2-oxo-2,5-dihydropyrrol-1-yl)acetate (16)

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and glycine methyl ester (12 mg, 0.135 mmol, 1 equiv.) were stirred for 30 h. Flash column chromatography eluting with (EtOAc-light petroleum; 1:1) gave the *title compound* as a pale-yellow solid (11 mg, 0.043 mmol, 32%). mp 137.7-139.4 °C; HRMS (ESI, $[M + H]^+$) found 255.0976; $[C_{11}H_{14}N_2O_5 + H]^+$ requires 255.0975; υ_{max}/ cm^{-1} (ATR): 3222, 2925, 1745, 1716, 1680, 1650, 1582, 1428, 1361, 1329, 1254, 1228, 1158, 1000, 935, 783, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.63 (br s, 1 H, NH), 4.69 (s, 2 H, CH_2), 4.23 (s, 2 H, CH_2), 3.75 (s, 3 H, Me), 2.59 (s, 3 H, Me), 2.27 (s, 3 H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7 (C), 169.6 (C), 169.5 (C), 168.1 (C), 161.8 (C), 108.5 (C), 52.5 (Me), 51.2 (CH_2), 42.9 (CH_2), 28.9 (Me), 24.6 (Me).

***N*-(4-Acetyl-1-(2-nitroethyl)-5-oxo-2,5-dihydropyrrol-3-yl)acetamide (17)**

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and 2-nitroethanamine (12 mg, 0.135 mmol, 1 equiv.) were stirred for 24 h. Flash column chromatography eluting with (EtOAc-light petroleum; 1:1) gave the *title compound* as a pale-yellow solid (18.9 mg, 0.074 mmol, 55%). mp 109.0-111.0 °C; HRMS (ESI, $[M + Na]^+$) found 278.0746; $[C_{10}H_{13}N_3O_5 + Na]^+$ requires 278.0747; υ_{max}/ cm^{-1} (ATR): 3194, 2917, 1722, 1681, 1640, 1567, 1584, 1548, 1356, 1272, 1223, 1184, 1160, 1010, 949, 904, 855, 766; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.59 (br s, 1 H, NH), 4.70-4.63 (m, 4 H, 2 x CH_2), 4.02 (t, *J* 5.5, 2 H, CH_2), 2.57 (s, 3 H, Me), 2.27 (s, 3 H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5 (C), 169.5 (C), 168.2 (C), 161.7 (C), 108.5 (C), 73.5 (CH_2), 51.9 (CH_2), 40.1 (CH_2), 28.9 (Me), 24.6 (Me).

***N*-(4-Acetyl-5-oxo-1-phenethyl-2,5-dihydropyrrol-3-yl)acetamide (18)**

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and phenylethylamine (16.4 mg, 0.135 mmol, 1 equiv.) were stirred for 24 h. Flash column chromatography in silica gel (EtOAc-light petroleum; 3:2) gave the *title compound* as a pale-yellow solid (20.1 mg, 0.070 mmol, 52%). mp 135.0-137.5 °C; HRMS (ESI, $[M + H]^+$) found 287.1389; $[C_{16}H_{18}N_2O_3 + H]^+$ requires 287.1390; υ_{max}/ cm^{-1} (ATR): 3245, 2926, 2859, 1714, 1682, 1640, 1590, 1454, 1423, 1436, 1404, 1361, 1327, 1276, 1214, 1182, 1133, 1026, 1002, 955, 942, 913, 771, 755, 705; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.55 (br s, 1 H, NH), 7.32-7.28 (m, 2 H, 2 x ArH), 7.28-7.19 (m, 3 H, 3 x ArH), 4.44 (s, 2 H, CH_2), 3.69 (t, *J* 7.5, 2 H, CH_2), 2.90 (t, *J* 7.5, 2 H, CH_2), 2.60 (s, 3 H, Me), 2.24 (s, 3 H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9 (C), 169.5 (C), 167.5 (C), 160.9 (C), 138.5 (C), 128.8 (4 x CH), 126.7 (CH), 109.2 (C), 51.1 (CH_2), 43.5 (CH_2), 34.8 (CH_2), 28.9 (Me), 24.6 (Me).

***N*-(4-Acetyl-1-(3,4-dihydroxyphenethyl)-5-oxo-2,5-dihydropyrrol-3-yl)acetamide (19)**

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and dopamine (20.7 mg, 0.135 mmol, 1 equiv.) were stirred for 25 h. Flash column chromatography eluting with (DCM-MeOH; 9:1) gave the *title compound* as a colourless solid (14 mg, 0.044 mmol, 33%). mp 212.0-214.0 °C; HRMS (ESI, $[M + Na]^+$) found 341.1106; $[C_{16}H_{18}N_2O_5 + Na]^+$ requires 341.1108; υ_{max}/ cm^{-1} (ATR): 3417, 3238, 1717, 1656, 1643, 1586, 1516, 1434, 1360, 1274, 1225, 1178, 1111, 999, 956, 875, 820, 772; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 11.30 (br s, 1 H, NH), 8.75 (br s, 1 H, OH), 8.65 (br s, 1 H, OH), 6.62 (d, *J* 7.9, 1 H, ArH), 6.59 (d, *J* 2.0, 1 H, ArH), 6.45 (dd, *J* 7.9, 2.0, 1 H, ArH), 4.49 (s, 2 H, CH_2), 3.49 (t, *J* 7.4, 2 H, CH_2), 2.62 (t, *J* 7.4, 2 H, CH_2), 2.46 (s, 3 H, Me), 2.23 (s, 3 H, Me). ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 196.8 (C), 169.9 (C), 166.6 (C), 161.2 (C), 145.1 (C), 143.6 (C), 129.7 (C), 119.2 (CH), 116.0 (CH), 115.6 (CH), 107.9 (C), 50.6 (CH_2), 42.9 (CH_2), 33.4 (CH_2), 28.4 (Me), 24.3 (Me).

***N*-(4-Acetyl-1-(2-(benzylthio)ethyl)-5-oxo-2,5-dihydropyrrol-3-yl)acetamide (20)**

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and 2-(benzylthio)ethan-1-amine[7] (22.6 mg, 0.135 mmol, 1 equiv.) were stirred for 23 h. Flash column chromatography eluting with (EtOAc-light petroleum; 3:2) gave the *title compound* as a pungent pale-yellow solid (23.3 mg, 0.070 mmol, 52%). mp 164.5-166.0 °C; HRMS (ESI, $[M + Na]^+$) found 355.1086; $[C_{17}H_{20}N_2O_3S + Na]^+$ requires 355.1087; υ_{max}/ cm^{-1} (ATR): 3215, 2917, 1717, 1681, 1645, 1582, 1494, 1424, 1347, 1323, 1264, 1228, 1194, 1149, 1071, 1021, 993, 949, 912, 887, 797, 774, 760, 704, 625; ^1H NMR (400 MHz, $CDCl_3$) δ 11.56 (br s, 1 H, NH), 7.34-7.27 (br s, 4 H, 4 x ArH), 7.25-7.19 (m, 1 H, ArH), 4.55 (s, 2 H, CH_2), 3.74 (s, 2 H, CH_2), 3.55 (t, *J* 6.7, 2 H, CH_2), 2.62 (t, *J* 6.8, 2 H, CH_2), 2.58 (s, 3 H, Me), 2.25 (s, 3 H, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9 (C), 169.5 (C), 167.6 (C), 161.1 (C), 138.1 (C), 129.0 (2 x CH), 128.7 (2 x

CH), 127.2 (CH), 109.0 (C), 51.2 (CH_2), 40.8 (CH_2), 36.1 (CH_2), 30.0 (CH_2), 28.9 (Me), 24.6 (Me).

***N*-(4-Acetyl-1-(furan-2-ylmethyl)-5-oxo-2,5-dihydropyrrol-3-yl)acetamide (21)**

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and furfuryl amine (13.1 mg, 0.135 mmol, 1 equiv.) were stirred for 24 h. Flash column chromatography eluting with (EtOAc-light petroleum; 3:2) gave the *title compound* as a yellow solid (21.1 mg, 0.080 mmol, 60%). mp 102.7-106.0 °C; HRMS (ESI, $[M + H]^+$) found 263.1026; $[C_{13}H_{14}N_2O_4 + H]^+$ requires 263.1026; υ_{max}/ cm^{-1} (ATR) 3235, 2919, 1716, 1672, 1635, 1558, 1432, 1421, 1366, 1350, 1322, 1265, 1224, 1178, 1152, 1068, 1026, 993, 926, 884, 834, 804, 754, 727, 704; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.59 (br s, 1 H, NH), 7.34 (dd, *J* 1.8, 0.8, 1 H, ArH), 6.30 (dd, *J* 3.2, 1.9, 1 H, ArH), 6.27-6.24 (m, 1 H, ArH), 4.60 (s, 2 H, CH_2), 4.56 (s, 2 H, CH_2), 2.60 (s, 3 H, Me), 2.23 (s, 3 H, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9 (C), 169.5 (C), 167.3 (C), 161.3 (C), 150.2 (C), 142.8 (CH), 110.5 (CH), 108.8 (C), 108.6 (CH), 50.6 (CH_2), 38.3 (CH_2), 28.9 (Me), 24.6 (Me).

***N*-(4-Acetyl-1-(4-methoxyphenyl)-5-oxo-2,5-dihydropyrrol-3-yl)acetamide (22)**

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and *p*-anisidine (16.6 mg, 0.135 mmol, 1 equiv.) were stirred for 24 h. Flash column chromatography eluting with (acetone-light petroleum; 1:4) gave the *title compound* as a pale-yellow oil (13.8 mg, 0.048 mmol, 35%). HRMS (ESI, $[M + H]^+$) found 289.1183; $[C_{15}H_{16}N_2O_4 + H]^+$ requires 289.1183; υ_{max}/ cm^{-1} (ATR) 3239, 2920, 2849, 1716, 1683, 1646, 1592, 1511, 1428, 1417, 1408, 1360, 1373, 1299, 1241, 1208, 1181, 1168, 1024, 999, 950, 901, 832, 797, 771, 754, 735, 624; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.66 (br s, 1 H, NH), 7.60-7.55 (m, 2 H, 2 x ArH), 6.96-6.90 (m, 2 H, 2 x ArH), 4.97 (s, 2 H, CH_2), 3.81 (s, 3 H, Me), 2.65 (s, 3 H, Me), 2.30 (s, 3 H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1

(C), 169.7 (C), 166.3 (C), 160.3 (C), 156.8 (C), 131.0 (C), 121.7 (2 x CH), 114.5 (2 x CH), 109.6 (C), 55.6 (C), 51.5 (C), 29.2 (C), 24.7 (C).

_N_-(4-Acetyl-1-(3-nitrophenyl)-5-oxo-2,5-dihydropyrrol-3-yl)acetamide (23)

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and *m*-nitroaniline (18.6 mg, 0.135 mmol, 1 equiv.) were stirred for 24 h. Flash column chromatography eluting with (light petroleum-EtOAc; 6.5:3.5) gave the *title compound* as a pale-yellow solid (17.1 mg, 0.056 mmol, 42%) mp 179.0-181.5 °C; HRMS (ESI, $[M - H]^-$) found 302.0781; $[C_{14}H_{13}N_3O_5 - H]^-$ requires 302.0782; υ_{max}/ cm^{-1} (ATR) 2920, 1696, 1639, 1589, 1523, 1482, 1449, 1423, 1344, 1297, 1276, 1254, 1184, 1085, 1062, 991, 956, 907, 892, 787, 738, 693, 641; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.70 (br s, 1 H, NH), 8.63 (t, *J* 2.2, 1 H, ArH), 8.09 (ddd, *J* 8.3, 2.3, 0.7, 1 H, ArH), 7.99-7.93 (m, 1 H, ArH), 7.54 (t, *J* 8.3, 1 H, ArH), 5.05 (s, 2 H, CH_2), 2.63 (s, 3 H, Me), 2.33 (s, 3 H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6 (C), 169.8 (C), 166.7 (C), 160.5 (C), 148.9 (C), 139.8 (C), 130.1 (CH), 124.2 (CH), 118.6 (CH), 113.4 (CH), 109.1 (C), 50.6 (CH_2), 29.3 (Me), 24.7 (Me).

_N_-(4-Acetyl-1-(4-nitrophenyl)-5-oxo-2,5-dihydropyrrol-3-yl)acetamide (24)

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and *p*-nitroaniline (18.6 mg, 0.135 mmol, 1 equiv.) were stirred for 24 h. Flash column chromatography eluting with (light petroleum-EtOAc; 6.5:3.5) gave the *title compound* as a colourless solid (15.9 mg, 0.052 mmol, 39%). mp 198.0-200.0 °C (darkens) 228.5-230.5 °C (melts); HRMS (ESI, $[M - H]^-$) found 302.0783; $[C_{14}H_{13}N_3O_5 - H]^-$ requires 302.0782; υ_{max}/ cm^{-1} (ATR) 3225, 2929, 1714, 1689, 1647, 1571, 1504, 1425, 1403, 1357, 1338, 1251, 1182, 1120, 1020, 992, 950, 897, 854, 827, 802, 752, 736, 689, 621; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.73 (br s, 1 H, NH), 8.26 (d, *J* 9.3, 2 H, 2 x ArH),

7.95 (d, *J* 9.3, 2 H, 2 x ArH), 5.05 (s, 2 H, CH_2), 2.65 (s, 3 H, Me), 2.34 (s, 3 H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6 (C), 169.8 (C), 166.8 (C), 160.6 (C), 144.4 (C), 143.3 (C), 125.3 (2 x CH), 117.9 (2 x CH), 109.2 (C), 50.6 (CH_2), 29.4 (Me), 24.8 (Me).

***N*-(4-Acetyl-5-oxo-1-(pyridin-3-yl)-2,5-dihydropyrrol-3-yl)acetamide (25)**

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and 3-aminopyridine (12.7 mg, 0.135 mmol, 1 equiv.) were stirred for 24 h. Flash column chromatography eluting with (EtOAc) gave the *title compound* as a pale-yellow solid (15.0 mg, 0.058 mmol, 43%). mp 197.5-200.0 °C; HRMS (ESI, $[M + H]^+$) found 260.1029; $[C_{13}H_{13}N_3O_3 + H]^+$ requires 260.1030; υ_{max}/ cm^{-1} (ATR): 3209, 2924, 1719, 1693, 1651, 1583, 1489, 1436, 1422, 1364, 1262, 1179, 1164, 1075, 1014, 958, 899, 803; ^1H NMR (400 MHz, $CDCl_3$) 11.71 (br s, 1 H, NH), 8.89 (d, *J* 2.6, 1 H, ArH), 8.40 (dd, *J* 4.7, 1.4, 1 H, ArH), 8.23 (ddd, *J* 8.5, 2.7, 1.5, 1 H, ArH), 7.34-7.32 (m, 1 H, ArH), 5.04 (s, 2 H, CH_2), 2.65 (s, 3 H, Me), 2.33 (s, 3 H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7 (C), 169.7 (C), 166.7 (C), 160.7 (C), 145.4 (CH), 140.3 (CH), 135.6 (C), 126.4 (CH), 123.8 (CH), 109.2 (C), 50.2 (CH_2), 29.3 (Me), 24.7 (Me).

Methyl 3-(4-acetamido-3-acetyl-2-oxo-2,5-dihydropyrrol-1-yl)thiophene-2-carboxylate (26)

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and methyl 3-aminothiophene-2-carboxylate (21.2 mg, 0.135 mmol, 1 equiv.) were stirred for 24 h. Flash column chromatography eluting with (EtOAc-light petroleum; 3:2) gave the *title compound* as a colourless solid (19 mg, 0.059 mmol, 44%). mp 189.8-191.2 °C; HRMS (ESI, $[M + H]^+$) found 323.0695; $[C_{14}H_{14}N_2O_5S + H]^+$ requires 323.0696; υ_{max}/ cm^{-1} (ATR): 3216, 2933, 1714, 1694, 1642, 1584, 1540, 1421, 1357, 1292, 1249, 1182, 1156, 1124, 1074, 994, 956, 775, 759; ^1H NMR (400 MHz, $CDCl_3$) δ 11.71 (br s, 1 H, NH), 7.52 (d, *J* 5.2, 1 H, ArH), 7.22 (d, *J* 5.2, 1 H, ArH), 5.12 (s, 2 H, CH_2),

3.84 (s, 3 H, Me), 2.62 (s, 3 H, Me), 2.29 (s, 3 H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7 (C), 169.4 (C), 167.1 (C), 162.4 (C), 161.2 (C), 140.6 (C), 130.2 (CH), 127.6 (CH), 123.5 (C), 108.3 (C), 52.3 (CH_2), 52.2 (Me), 29.0 (Me), 24.6 (Me).

(2*S*,3*R*,4*R*,5*S*,6*R*)-3-(4-Acetamido-3-acetyl-2-oxo-2,5-dihydropyrrol-1-yl)-6 (acetoxymethyl)tetrahydropyran-2,4,5-triyl triacetate (27)

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and 1,3,4,6-tetra-*O*-acetyl-beta-D-glucosamine (46.9 mg, 0.135 mmol, 1 equiv.) were stirred for 24 h. Flash column chromatography eluting with (EtOAc-light petroleum; 3:2) gave the *title compound* as a yellow solid (45 mg, 0.088 mmol, 65%). $[\alpha]_D^{20.5}$ + 76.0 (*c* 0.1, MeOH); mp 78.5-80.0 °C; HRMS (ESI, $[M + Na]^+$) found 535.1532; $[C_{22}H_{28}N_2O_{12} + Na]^+$ requires 535.1534; υ_{max}/ cm^{-1} (ATR): 2635, 1744, 1691, 1648, 1582, 1457, 1424, 1363, 1275, 1213, 1275, 1213, 1071, 1034, 958, 908, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.58 (br s, 1 H, NH), 6.04 (d, *J* 8.9, 1 H, CH), 5.46 (t, *J* 9.8, 1 H, CH), 5.18 (t, *J* 9.6, 1 H, CH), 4.72 (d, *J* 20.7, 1 H, ½ CH_2), 4.49 (d, *J* 20.7, 1 H, ½ CH_2), 4.41-4.33 (m, 1 H, CH), 4.30 (dd, *J* 12.5, 4.7, 1 H, ½ CH_2), 4.12 (dd, *J* 12.5, 2.1, 1 H, ½ CH_2), 3.86 (dq, *J* 10.1, 2.3, 1 H, CH), 2.55 (s, 3 H, Me), 2.25 (s, 3 H, Me), 2.09 (s, 3 H, Me), 2.06 (s, 3 H, Me), 2.02 (s, 3 H, Me), 1.95 (s, 3 H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5 (C), 170.7 (C), 170.3 (C), 169.4 (2 x C), 169.1 (C), 168.1 (C), 161.8 (C), 107.9 (C), 90.7 (CH), 72.9 (CH), 70.7 (CH), 68.3 (CH), 61.7 (CH_2), 55.0 (CH), 48.6 (CH_2), 29.0 (Me), 24.6 (Me), 21.0 (Me), 20.8 (Me), 20.7 (2 x Me).

***N*-(4-Acetyl-1-(bicyclo[1.1.1]pentan-1-yl)-5-oxo-2,5-dihydropyrrol-3-yl)acetamide (28)**

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and bicyclo[1.1.1]pentan-1-amine (11.2 mg, 0.135 mmol, 1 equiv.) were stirred for 30 h. Flash column chromatography eluting with (EtOAc-light petroleum; 3:2) gave the *title compound* as a pale-yellow solid (23.2 mg, 0.093

mmol, 69%). mp 135.7-138.5 °C; HRMS (ESI, $[M + H]^+$) found 249.1232; $[C_{13}H_{16}N_2O_3 + H]^+$ requires 249.1234; υ_{max}/ cm^{-1} (ATR): 3228, 2982, 2913, 2876, 1725, 1687, 1641, 1586, 1450, 1423, 1389, 1357, 1308, 1258, 1231, 1181, 1128, 1001, 948, 892, 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.56 (br s, 1 H, NH), 4.50 (s, 2 H, CH_2), 2.55 (s, 3 H, Me), 2.49 (s, 1 H, CH), 2.24 (s, 3 H, Me), 2.18 (s, 6 H, 3 x CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0 (C), 169.5 (C), 167.6 (C), 160.6 (C), 109.4 (C), 52.6 (3 x CH_2), 50.1 (C), 49.2 (CH_2), 28.9 (Me), 24.9 (Me), 24.6 (CH).

Methyl 4-(4-acetamido-3-acetyl-2-oxo-2,5-dihydropyrrol-1-yl)bicyclo[2.2.2]octane-1-carboxylate (29)

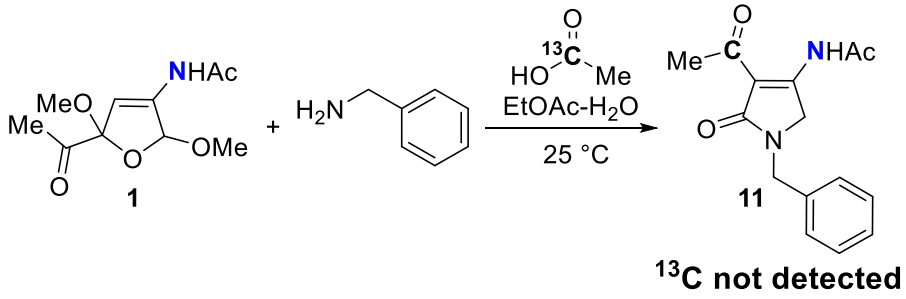
According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and methyl 4-aminobicyclo[2.2.2]octane-1-carboxylate (24.7 mg, 0.135 mmol, 1 equiv.) were stirred for 30 h. Flash column chromatography eluting with (EtoAc-light petroleum; 3:2) gave the *title compound* as a pale-yellow solid (16 mg, 0.046 mmol, 34%). mp 149.5-151.0 °C (darkens) 205.0-206.5 °C (melts); HRMS (ESI, $[M + H]^+$) found 349.1758; $[C_{18}H_{24}N_2O_5 + H]^+$ requires 349.1758; υ_{max}/ cm^{-1} (ATR): 3284, 2953, 2924, 1776, 1718, 1672, 1642, 1590, 1506, 1456, 1362, 1345, 1273, 1256, 1221, 1211, 1175, 1150, 1072, 1000, 959, 854, 795, 756, 628; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.50 (br s, 1 H, NH), 4.56 (s, 2 H, CH_2), 3.63 (s, 3 H, Me), 2.54 (s, 3 H, Me), 2.23 (s, 3 H, Me), 2.14-2.07 (m, 6 H, 3 x CH_2), 1.95-1.88 (m, 6 H, 3 x CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2 (C), 177.7 (C), 169.5 (C), 168.1 (C), 160.3 (C), 110.4 (C), 54.5 (C), 51.9 (Me), 48.7 (CH_2), 38.2 (C), 29.1 (Me), 28.68 (3 x CH_2), 28.67 (3 x CH_2), 24.6 (Me).

(1*R*,2*S*)-2-((4-Acetamido-3-acetyl-2-oxo-2,5-dihydropyrrol-1-yl)methyl)-*N*,*N*-diethyl-1-phenylcyclopropane-1-carboxamide (30)

According to the general procedure, *N*-(5-acetyl-2,5-dimethoxy-2,5-dihydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and milnacipran (33.3 mg, 0.135 mmol, 1 equiv.)

were stirred for 25 h. Flash column chromatography eluting with (EtOAc-light petroleum; 3:2) gave the *title compound* as a viscous yellow oil (38 mg, 0.092 mmol, 68%). $[\alpha]_D^{21.8}$ + 4.0 (*c* 0.1, MeOH); HRMS (ESI, $[M + H]^+$) found 412.2229; $[C_{23}H_{29}N_3O_4 + H]^+$ requires 412.2231; υ_{max}/ cm^{-1} (ATR): 3242, 2975, 2935, 2241, 1721, 1680, 1628, 1582, 1497, 1427, 1361, 1271, 1219, 1190, 1170, 1141, 993, 919, 763, 729, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.60 (s, 1 H, NH), 7.33-7.26 (m, 2 H, 2 x ArH), 7.25-7.18 (m, 3 H, 3 x ArH), 4.84 (d, *J* 21.8, 1 H, ½ CH_2), 4.63 (d, *J* 21.8, 1 H, ½ CH_2), 4.14 (dd, *J* 14.2, 4.3, 1 H, ½ CH_2), 3.57 (sxt, *J* 7.1, 1 H, ½ CH_2), 3.49 (sxt, *J* 6.8, 1 H, ½ CH_2), 3.25 (sxt, *J* 6.2, 1 H, ½ CH_2), 3.16 (sxt, *J* 6.4, 1 H, ½ CH_2), 2.92 (dd, *J* 14.3, 9.7, 1 H, ½ CH_2), 2.61 (s, 3 H, Me), 2.27 (s, 3H, Me), 1.95-1.85 (m, 1 H, CH), 1.62 (dd, *J* 6.3, 5.1, 1 H, ½ CH_2), 1.18 (dd, *J* 8.5, 5.0, 1 H, ½ CH_2), 1.13 (t, *J* 7.1, 3 H, Me), 0.62 (t, *J* 7.1, 3 H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9 (C), 169.4 (2 x C), 167.6 (C), 161.4 (C), 140.4 (C), 128.9 (2 x CH), 126.8 (CH), 126.2 (2 x CH), 109.1 (C), 51.1 (CH_2), 42.8 (CH_2), 41.8 (CH_2), 39.6 (CH_2), 34.1 (C), 28.9 (Me), 24.6 (Me), 23.8 (CH), 20.8 (CH_2), 12.7 (Me), 12.6 (Me).

Labelling experiment



With no precautions to exclude air, a solution of *N*-(2,5-dimethoxy-5-methyltetrahydrofuran-3-yl)acetamide (**1**, 62 mg, 0.27 mmol, 2 equiv.) and the benzylamine (14.5 mg, 0.135 mmol, 1 equiv.) in EtOAc-water (1:1, 1 mL) was added acetic acid-1-^{13}C (100 µL) and the reaction mixture was vigorously stirred at 25 °C for 24 h. The reaction mixture was concentrated *in vacuo*, and the crude material was purified by flash column chromatography on silica gel (EtOAc-light petroleum; 3:2) to give *N*-(4-acetyl-1-benzyl-5-oxo-2,5-dihydropyrrol-3-yl)acetamide **11** as a pale-yellow oil (20 mg, 0.073 mmol, 54%). HRMS (ESI, $[M + H]^+$) found 273.1234; $[C_{15}H_{16}N_2O_3 + H]^+$ requires 273.1234.

$[C_{14}{}^{13}CH_{16}N_2O_3 + H]^+$ requires 274.1267. Not detected **(see Figure S7)**

^{13}C NMR spectrum shows no sign of isotopic enrichment (**Figures S8**)

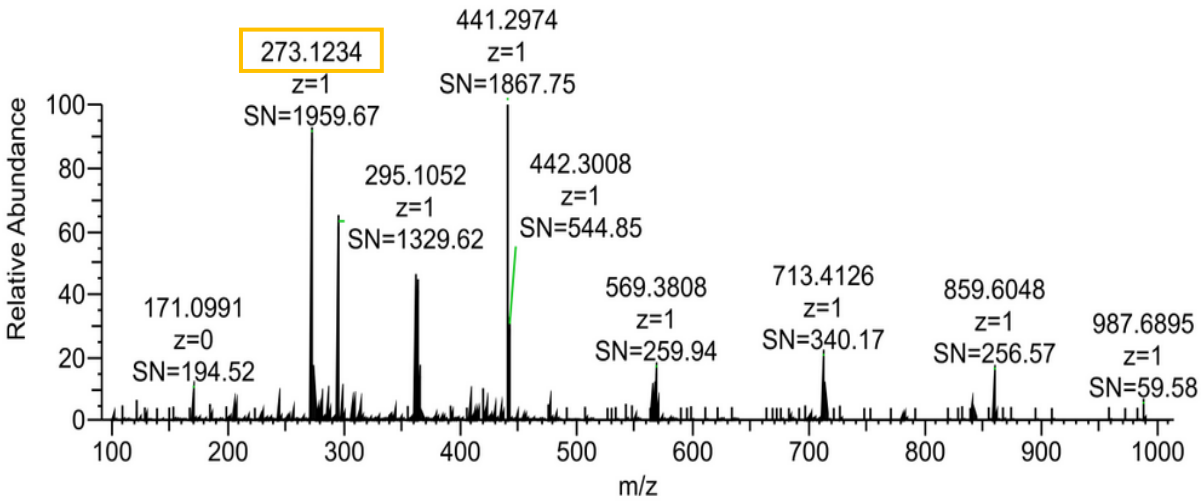


Figure S7. HRMS spectrum of the product of the ^{13}C labelled acetic acid experiment; showing $[M + H]^+$ *m/z* = 273.1234 corresponding to the unlabelled product

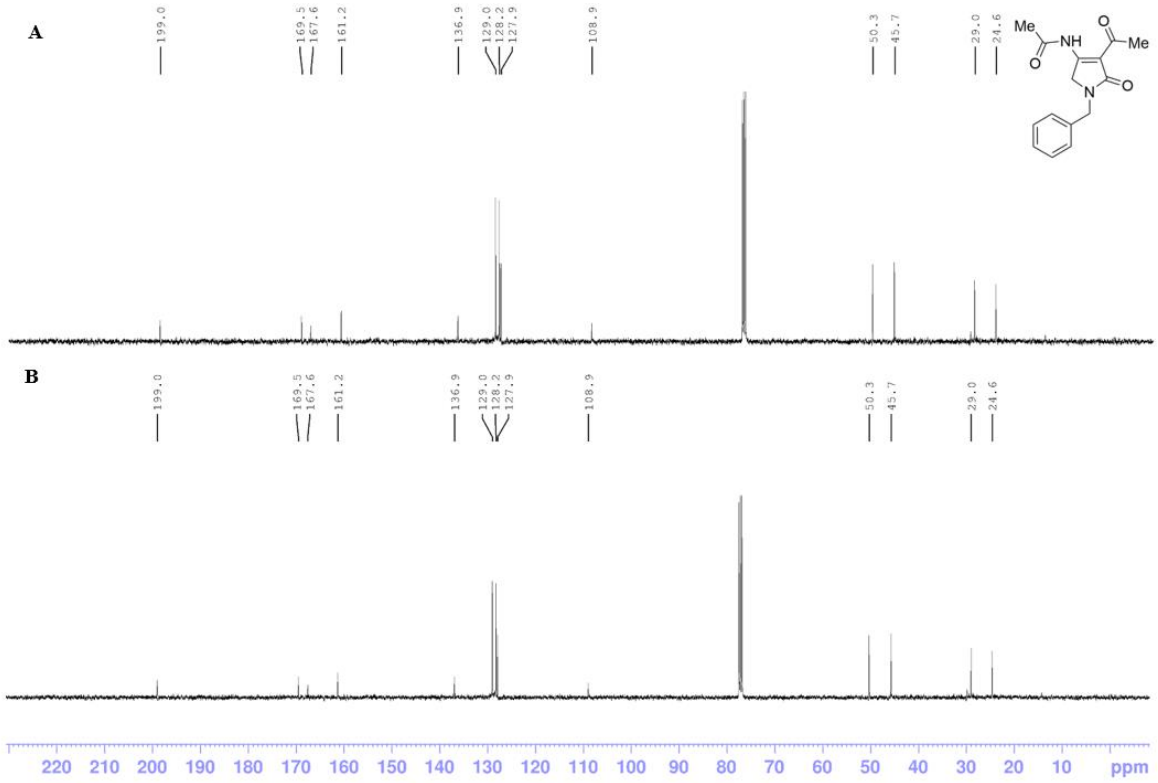
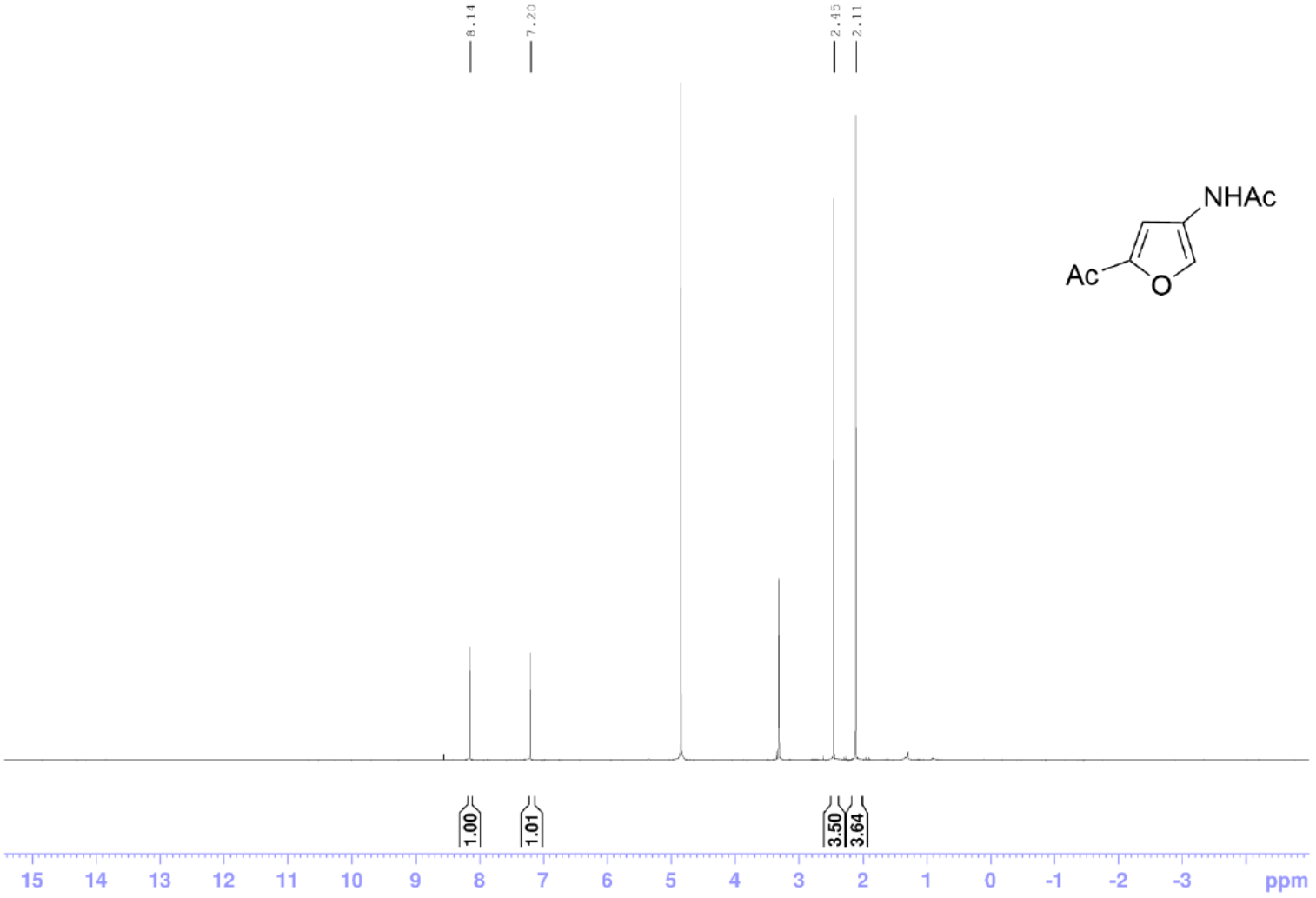
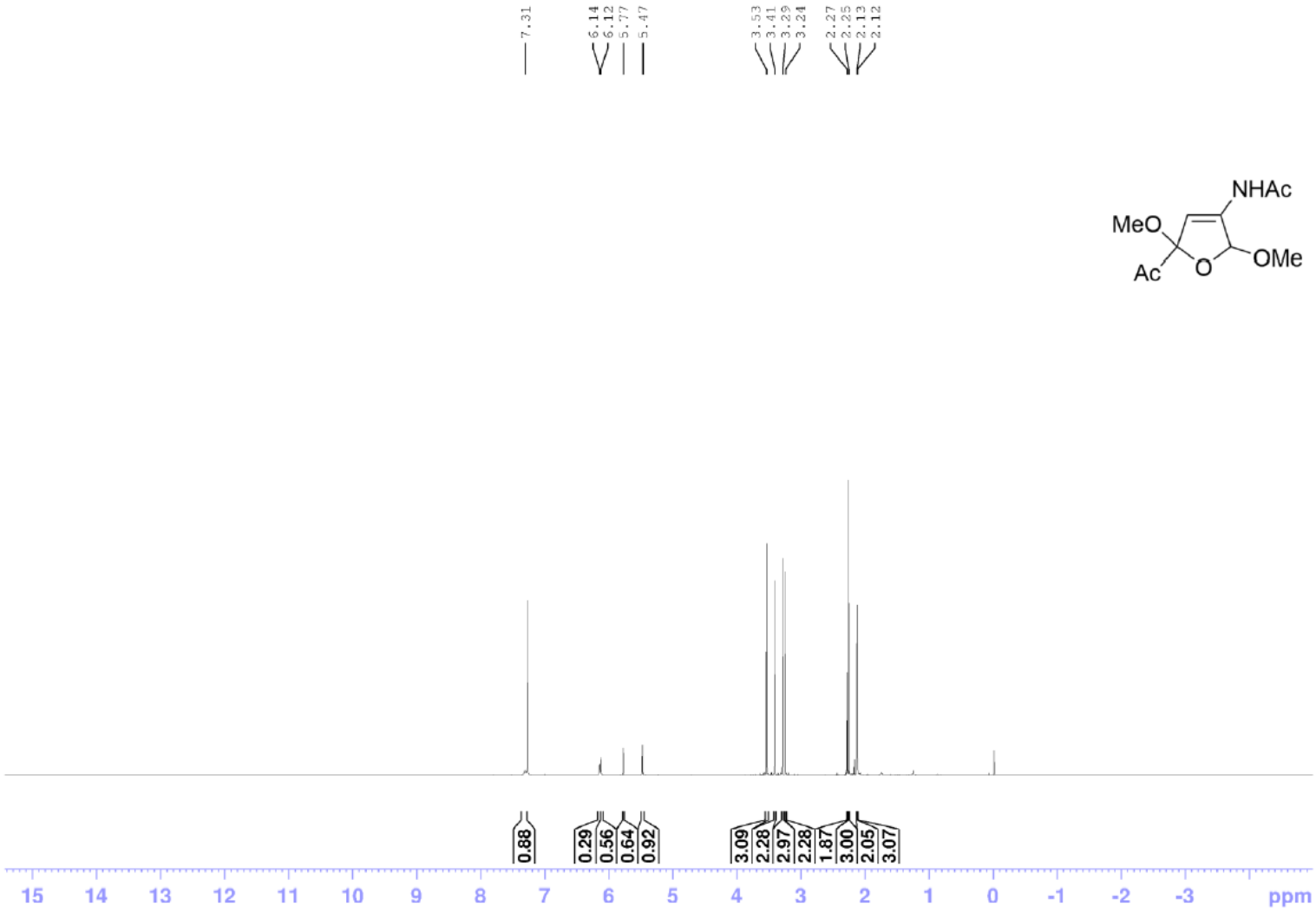


Figure S8. (**A**) ^{13}C NMR spectrum of **11** synthesised using **unlabelled** acetic acid; (**B**) ^{13}C NMR spectrum of **11** synthesised using **labelled** acetic acid.

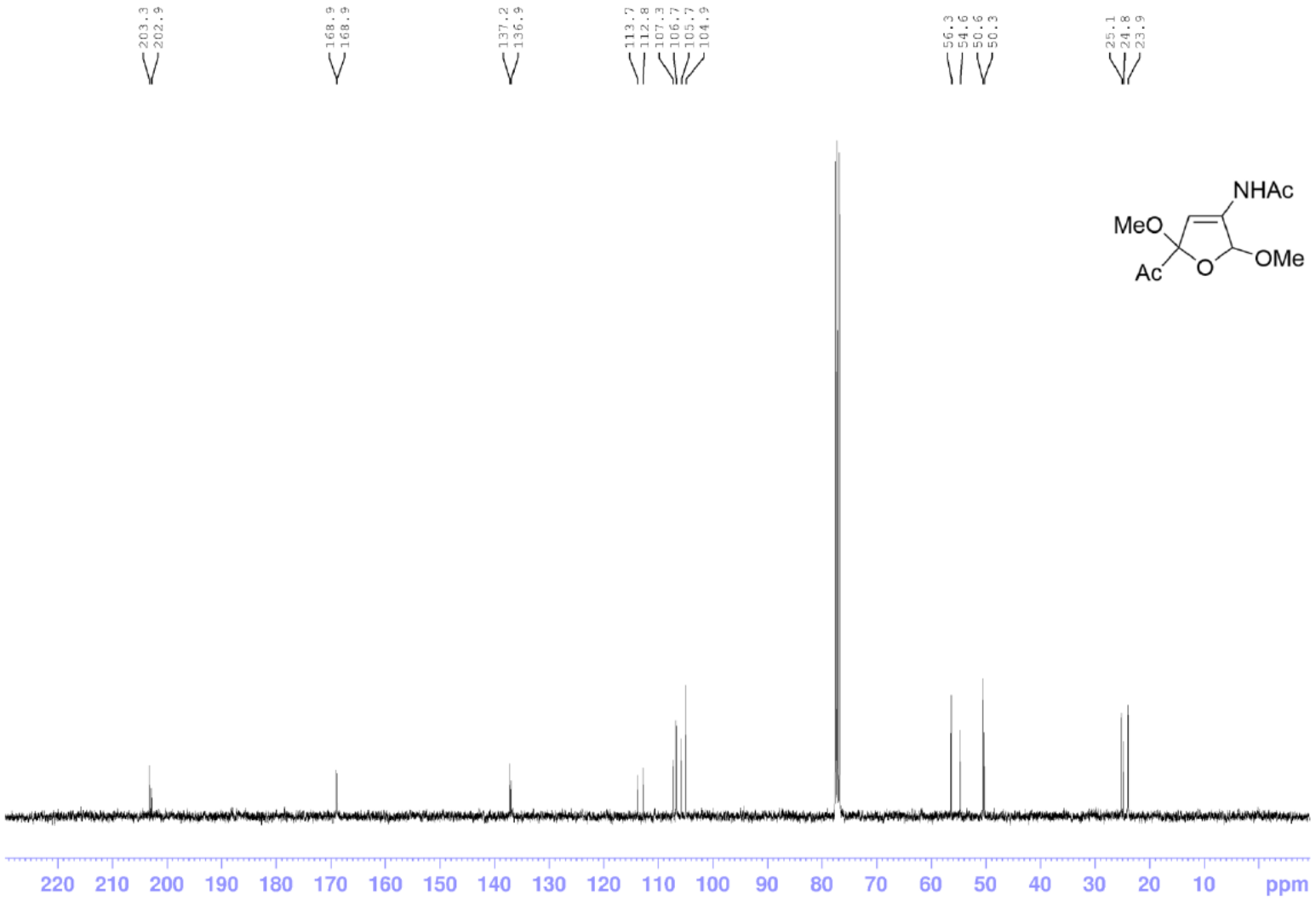
^{1}H NMR spectrum of **3A5AF** (400 MHz, CD_3OD)



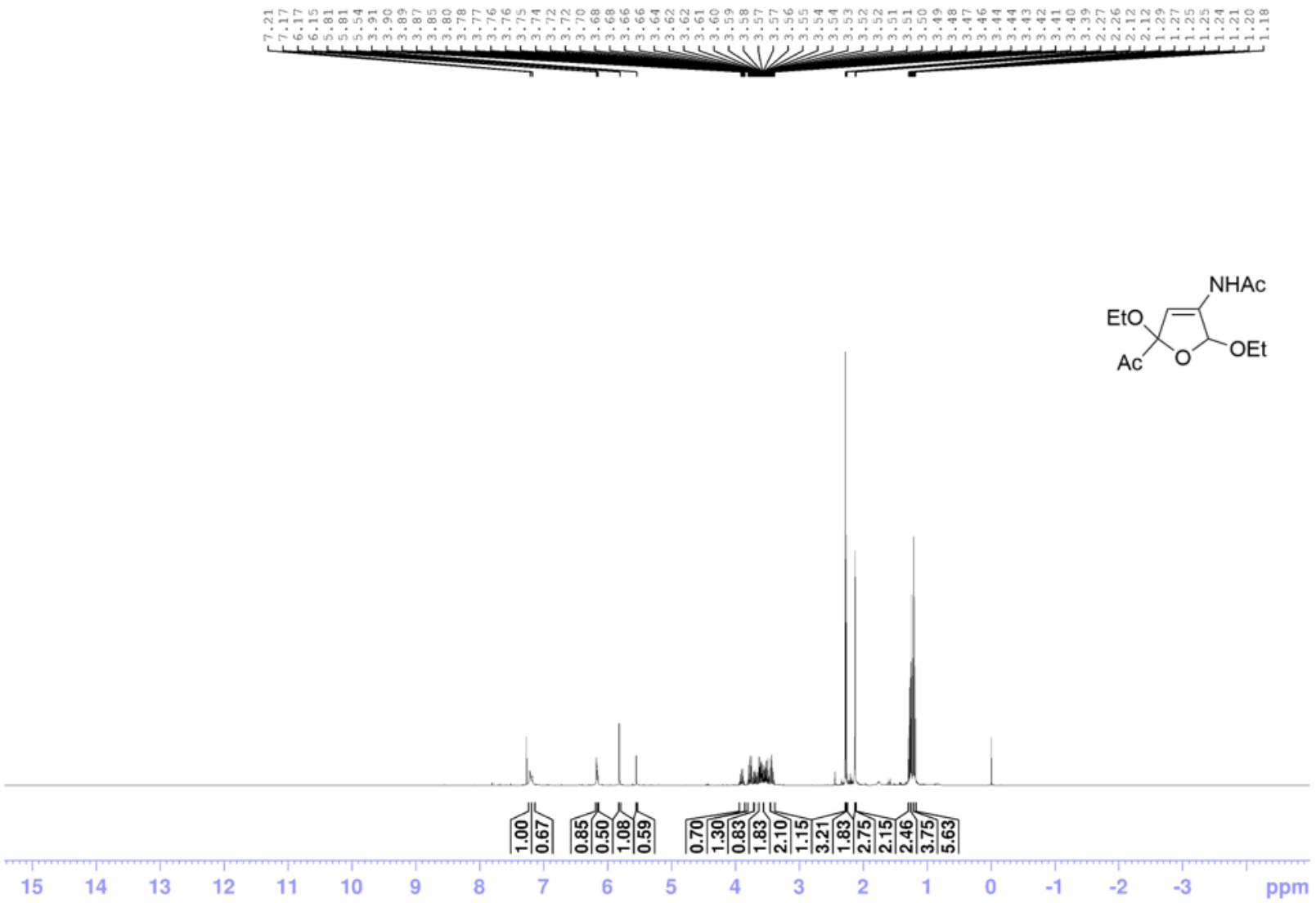
^{1}H NMR spectrum of **1** (400 MHz, $CDCl_3$)



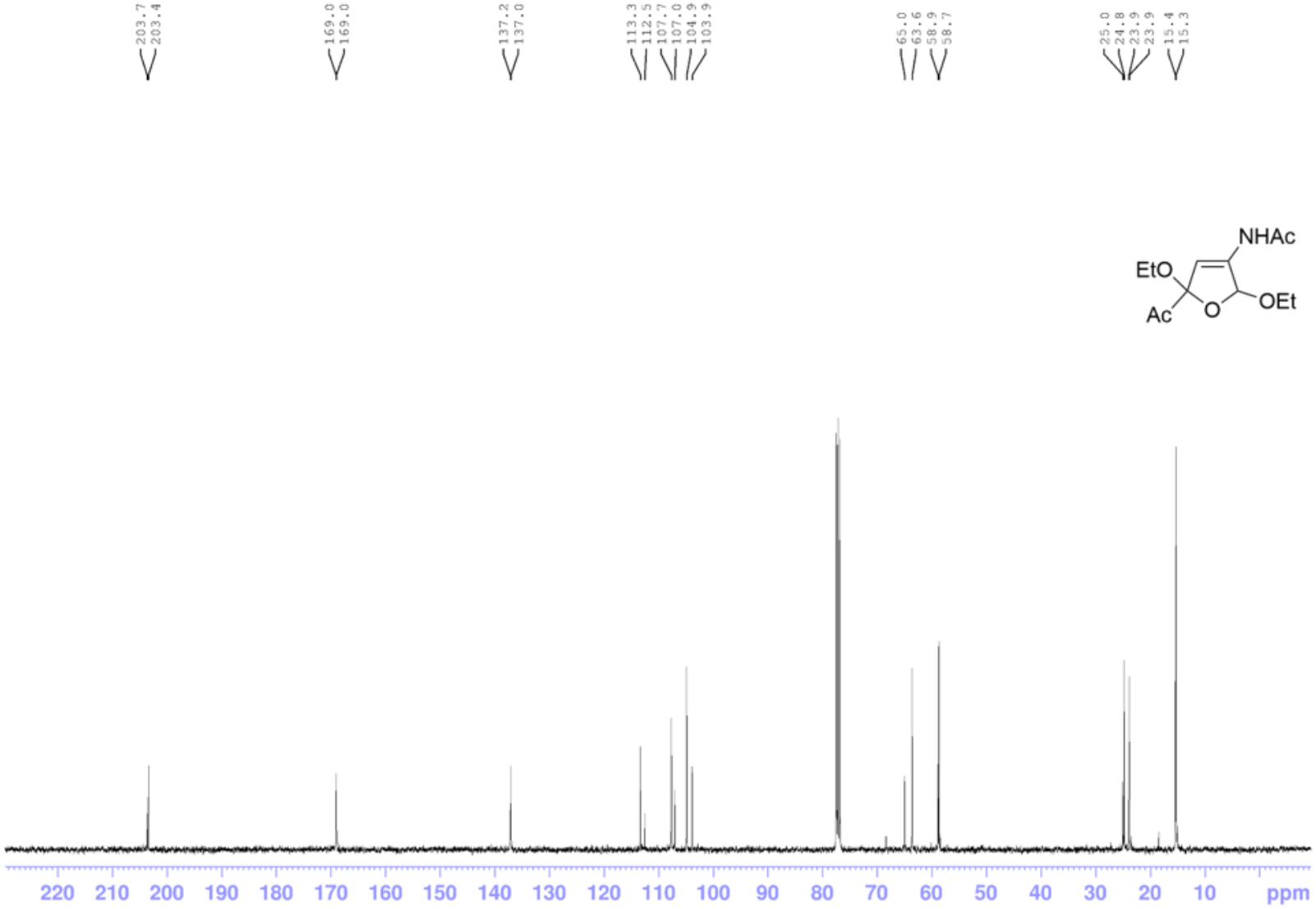
^{13}C NMR spectrum of **1** (100 MHz, $CDCl_3$)



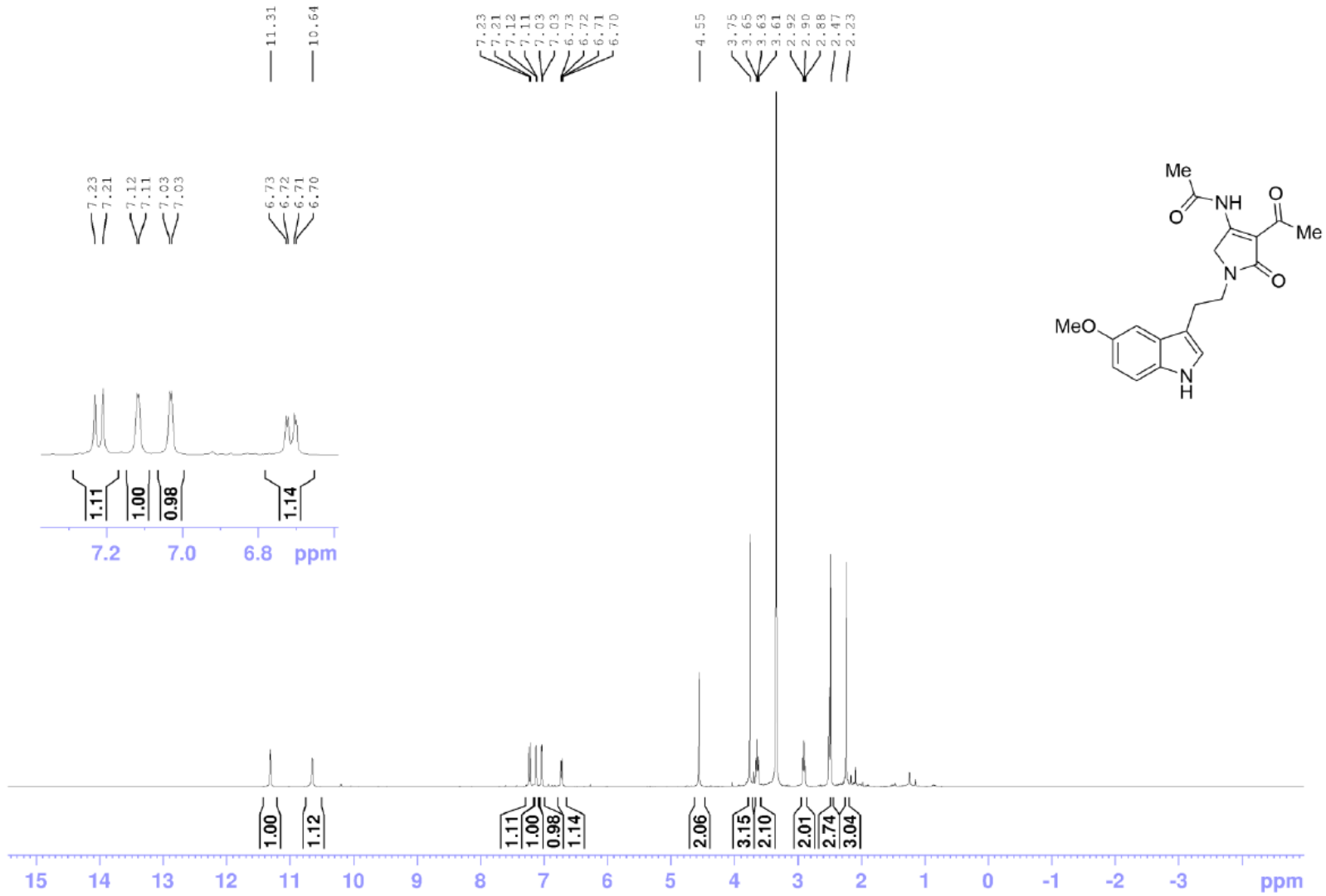
^{1}H NMR spectrum of **3** (400 MHz, $CDCl_3$)



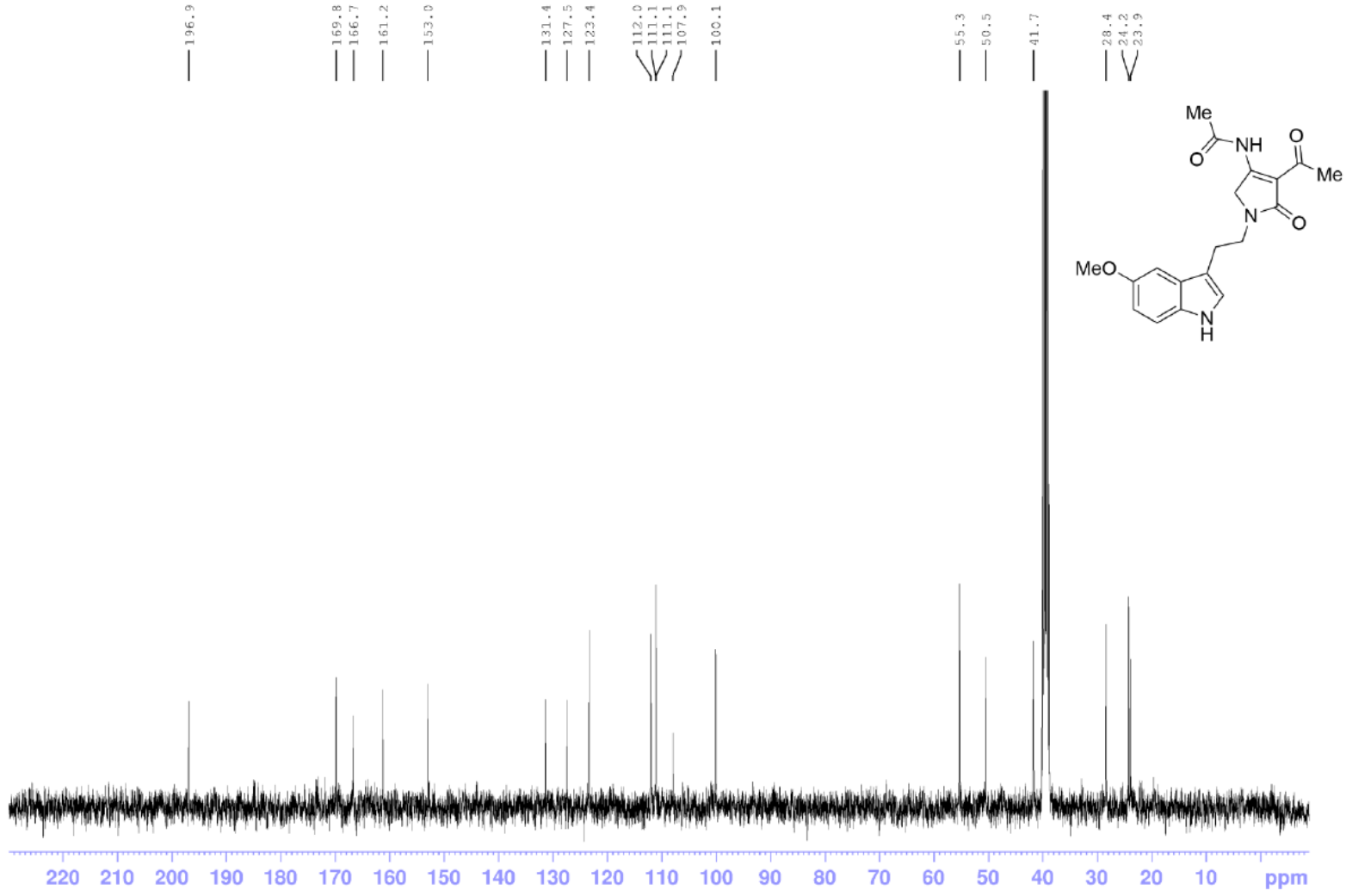
^{13}C NMR spectrum of **3** (100 MHz, $CDCl_3$)



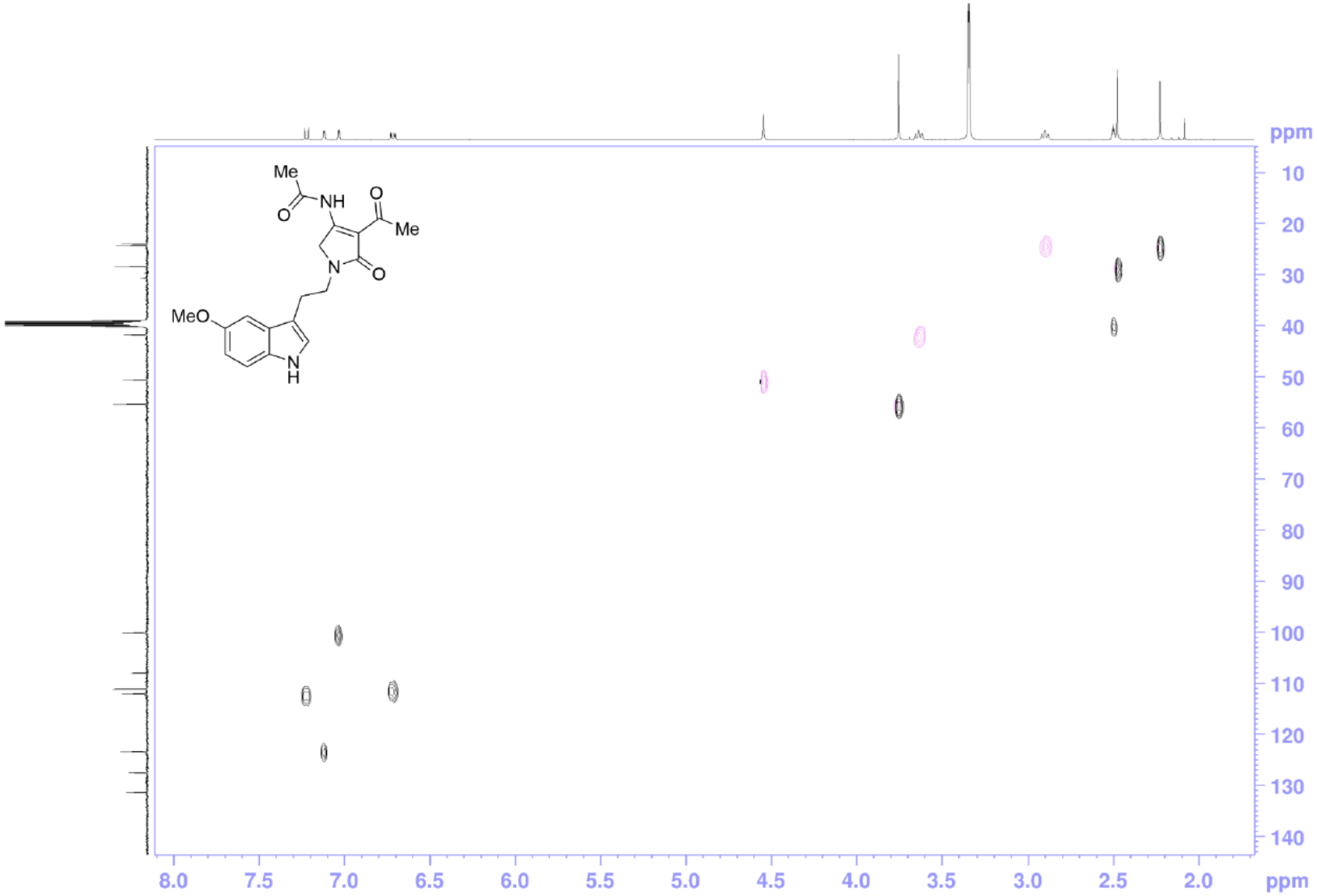
^{1}H NMR spectrum of **10** (400 MHz, $(CD_3)_2SO$)



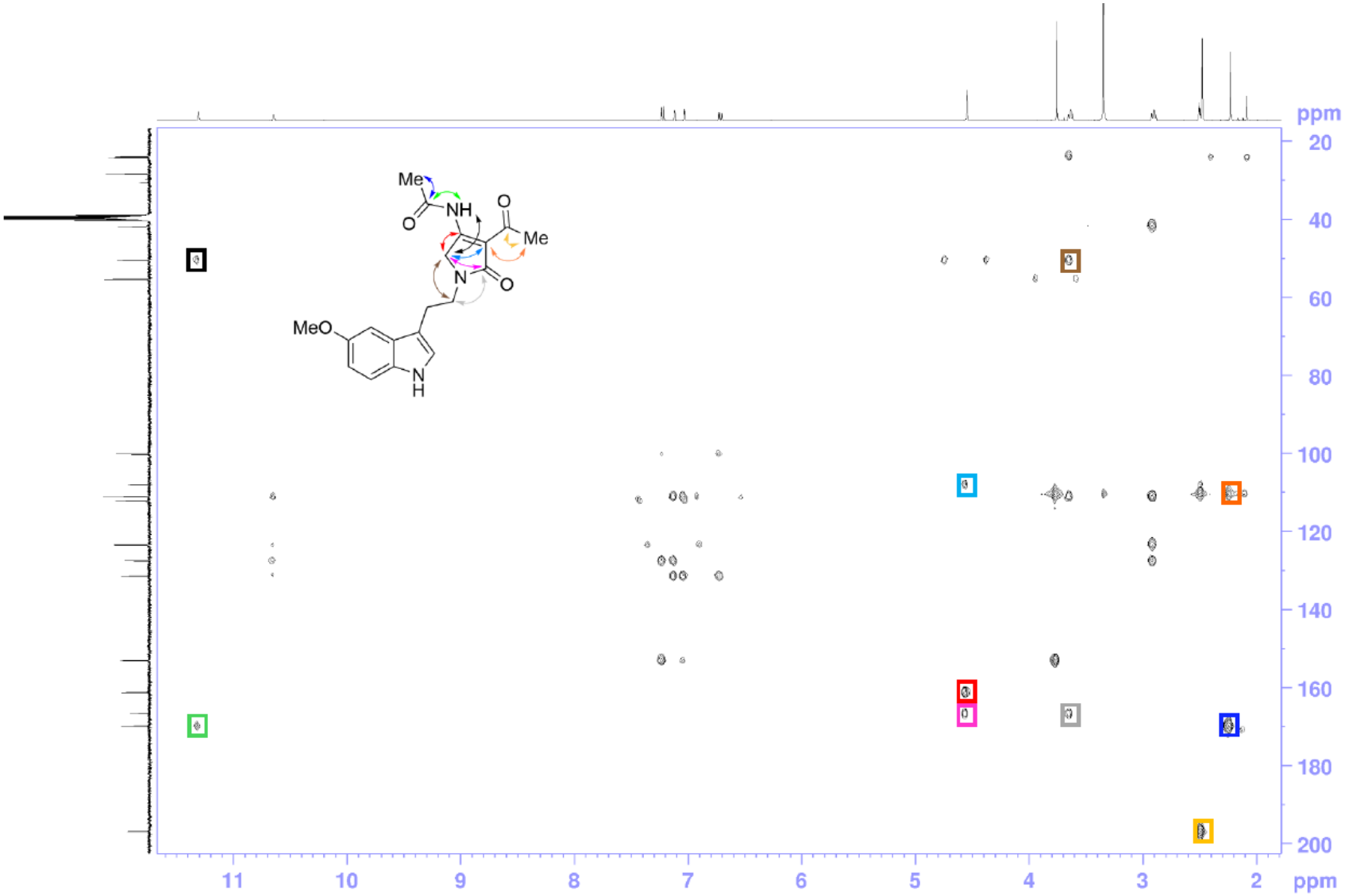
^{13}C NMR spectrum of **10** (100 MHz, $(CD_3)_2SO$)



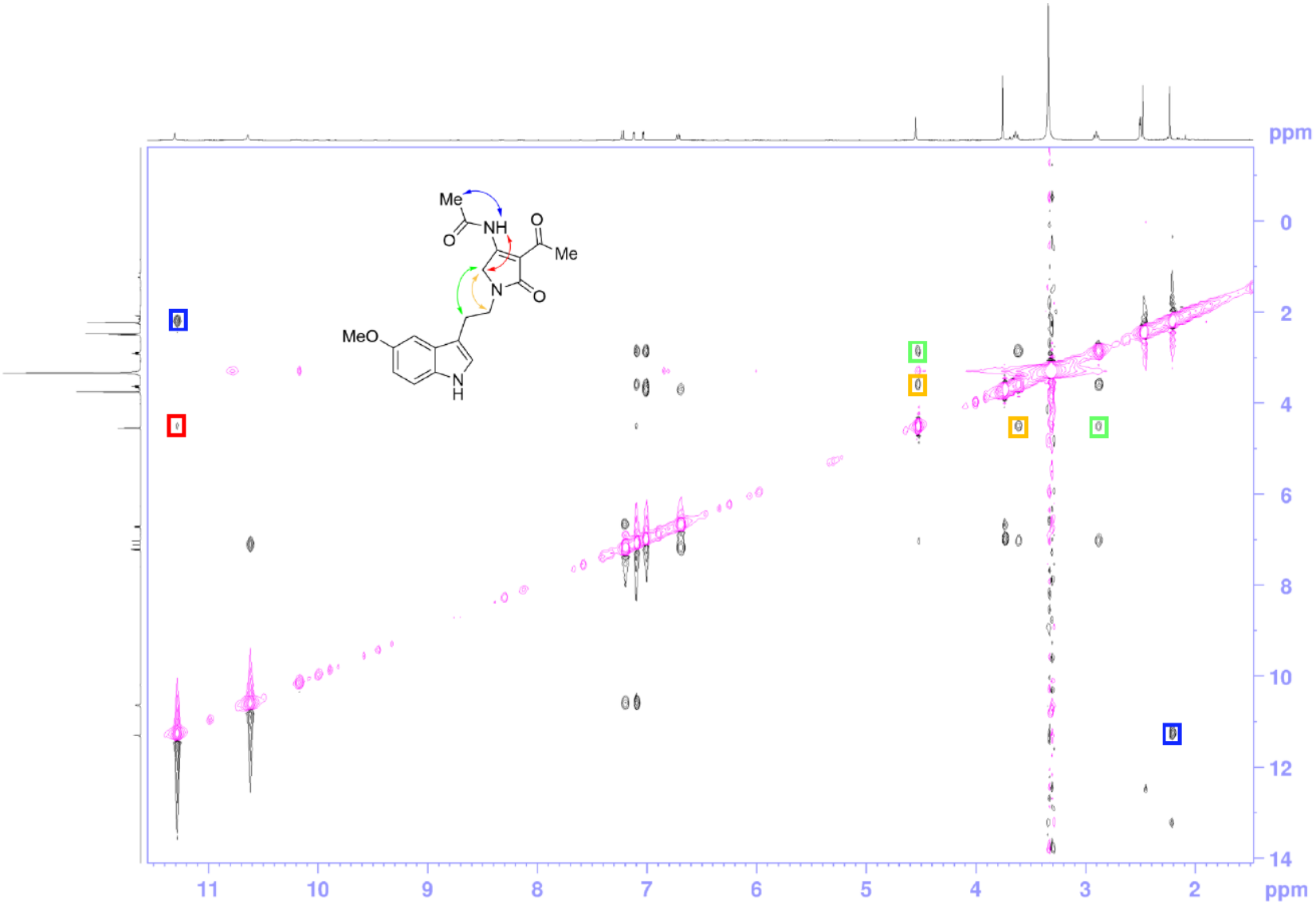
Edited HSQC spectrum of **10** ($(CD_3)_2SO$)



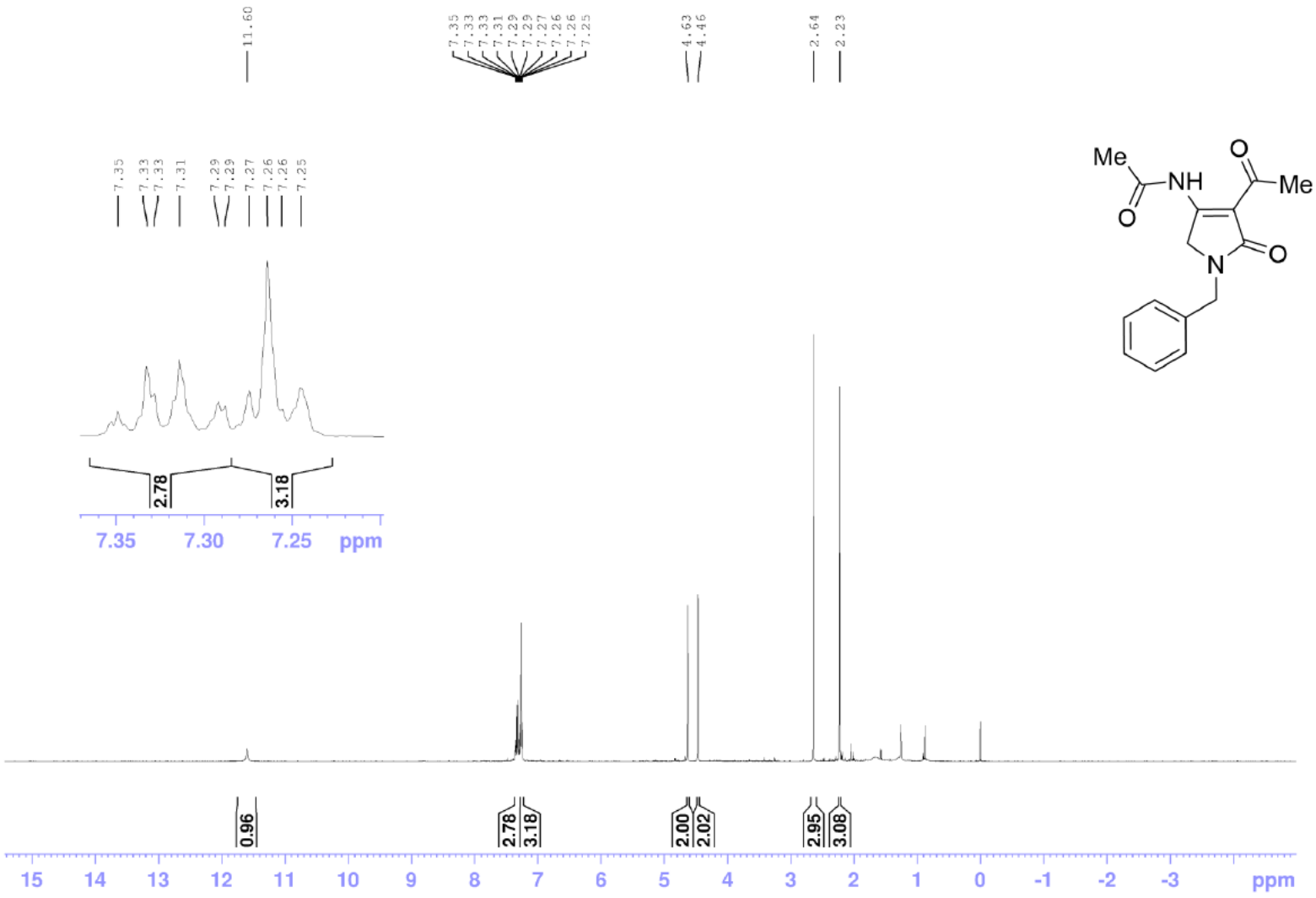
HMBC spectrum of **10** ($(CD_3)_2SO$)



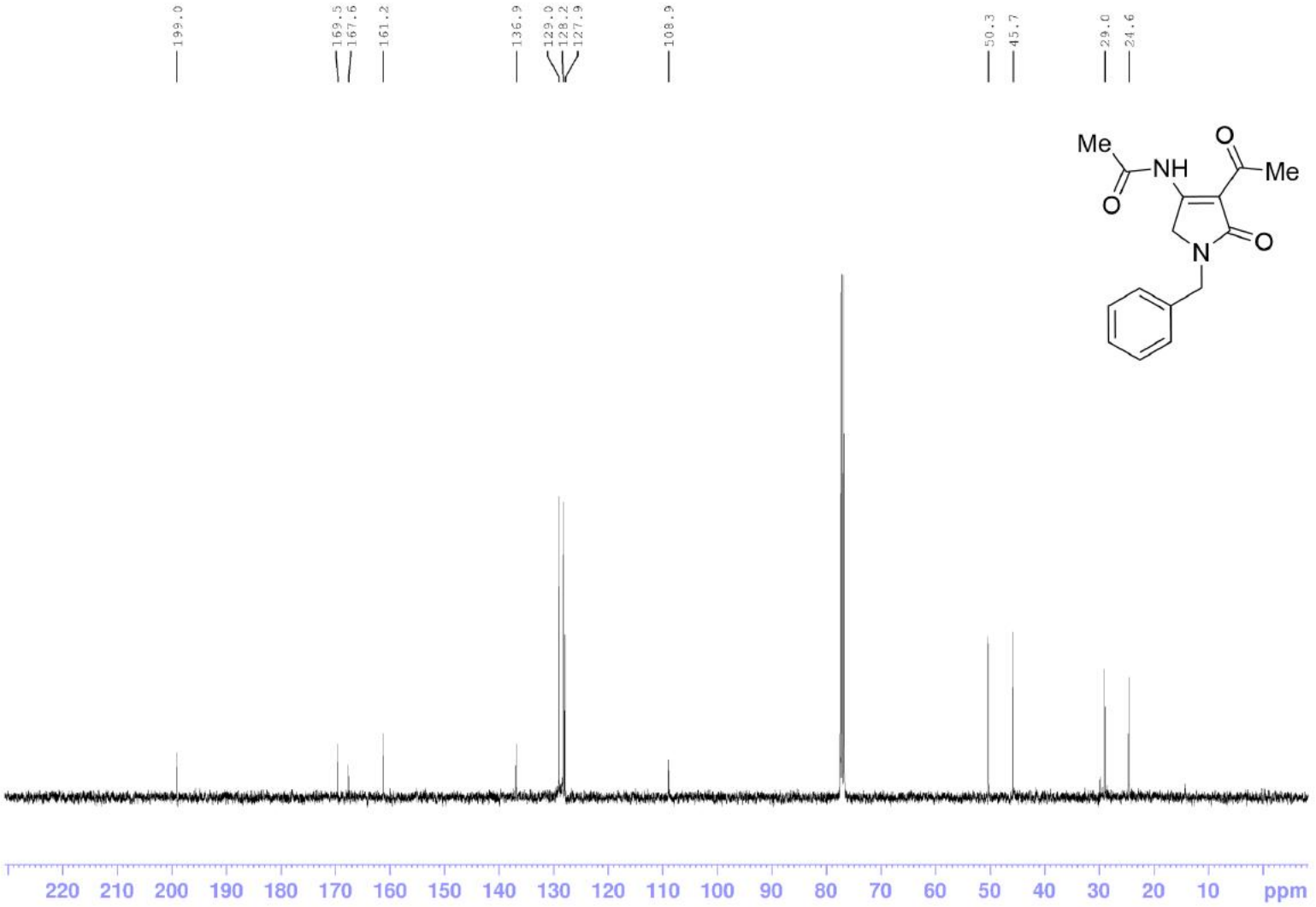
NOESY spectrum of **10** ($(CD_3)_2SO$)



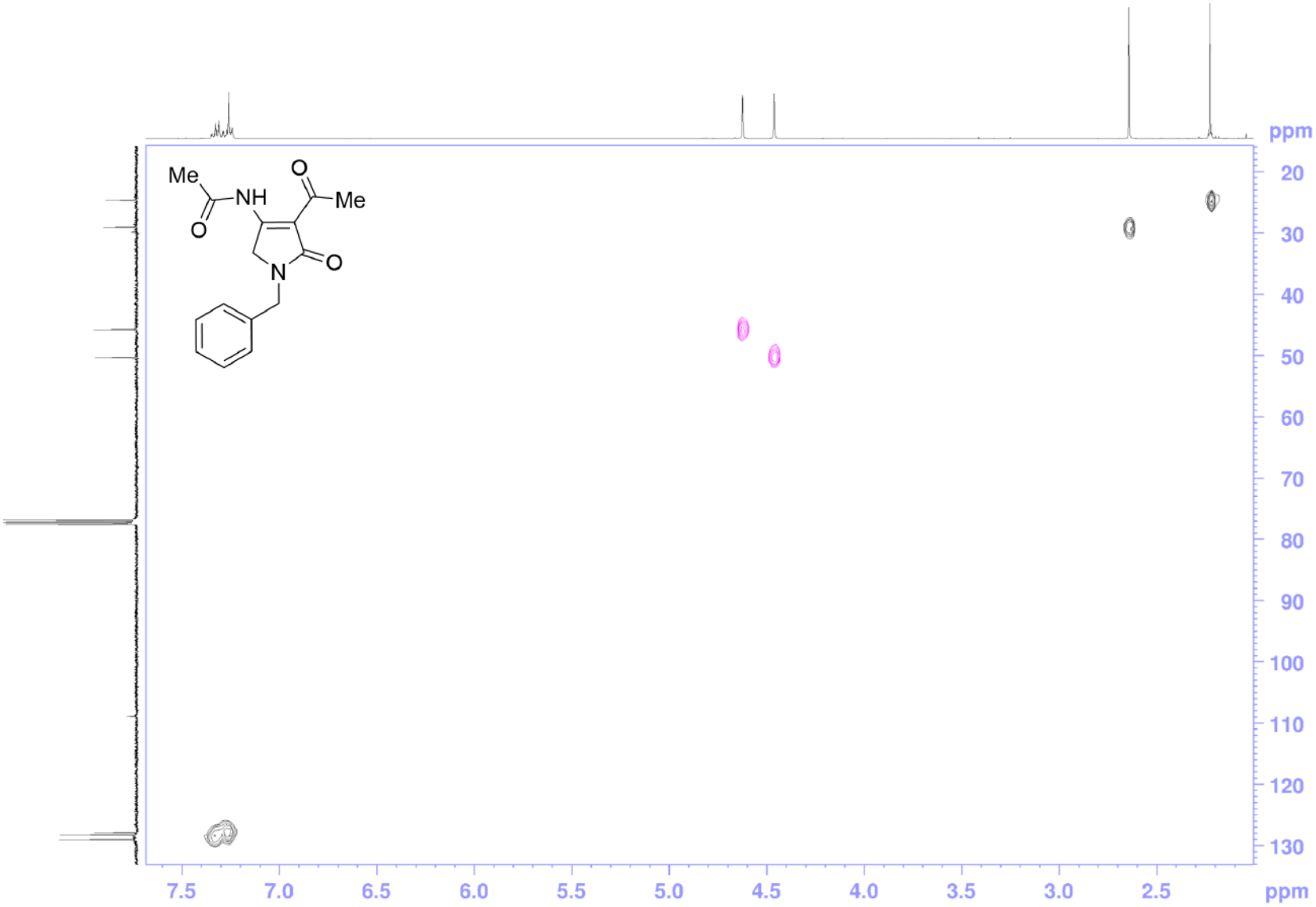
^{1}H NMR spectrum of **11** (400 MHz, $CDCl_3$)



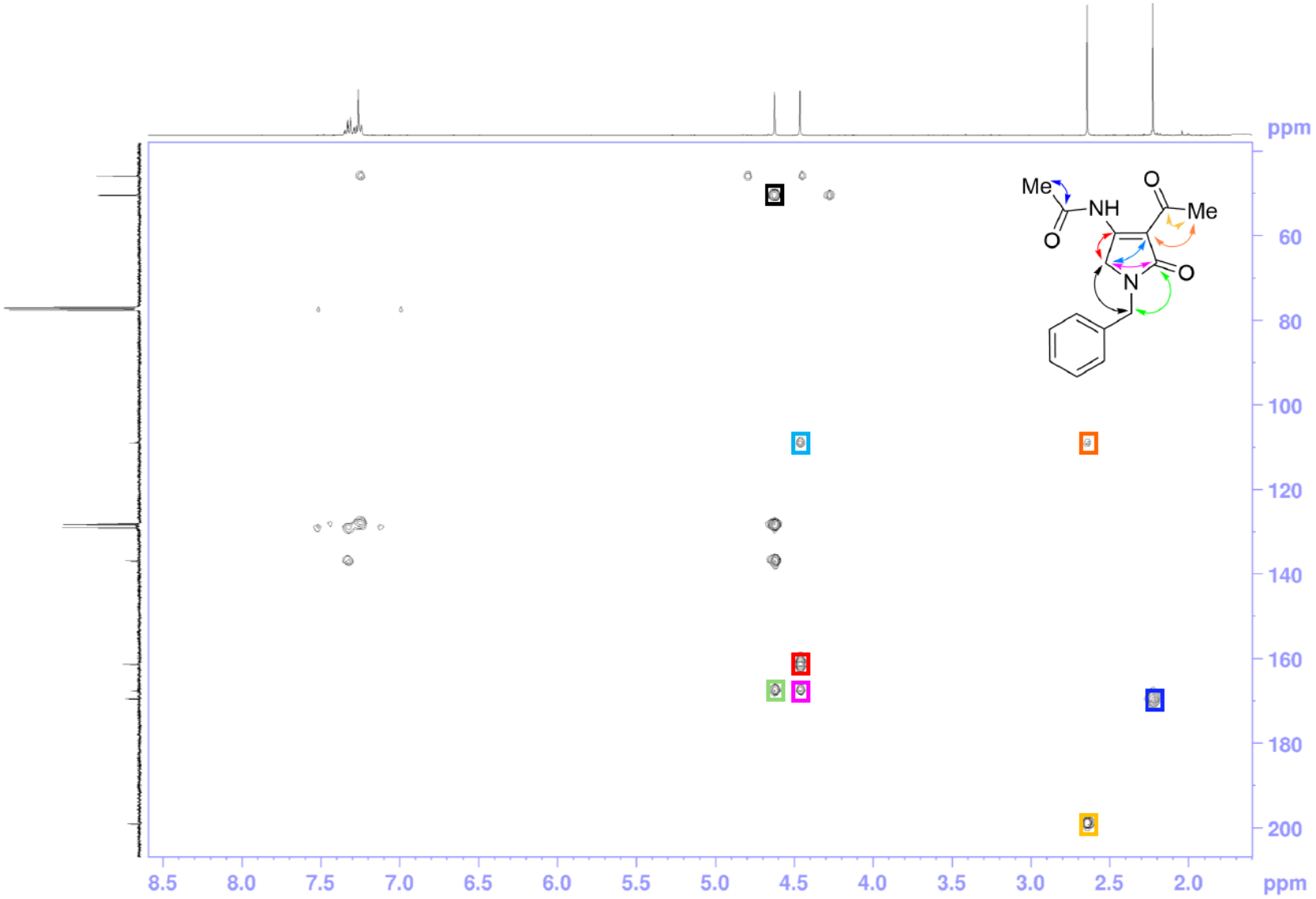
^{13}C NMR spectrum of **11** (100 MHz, $CDCl_3$)



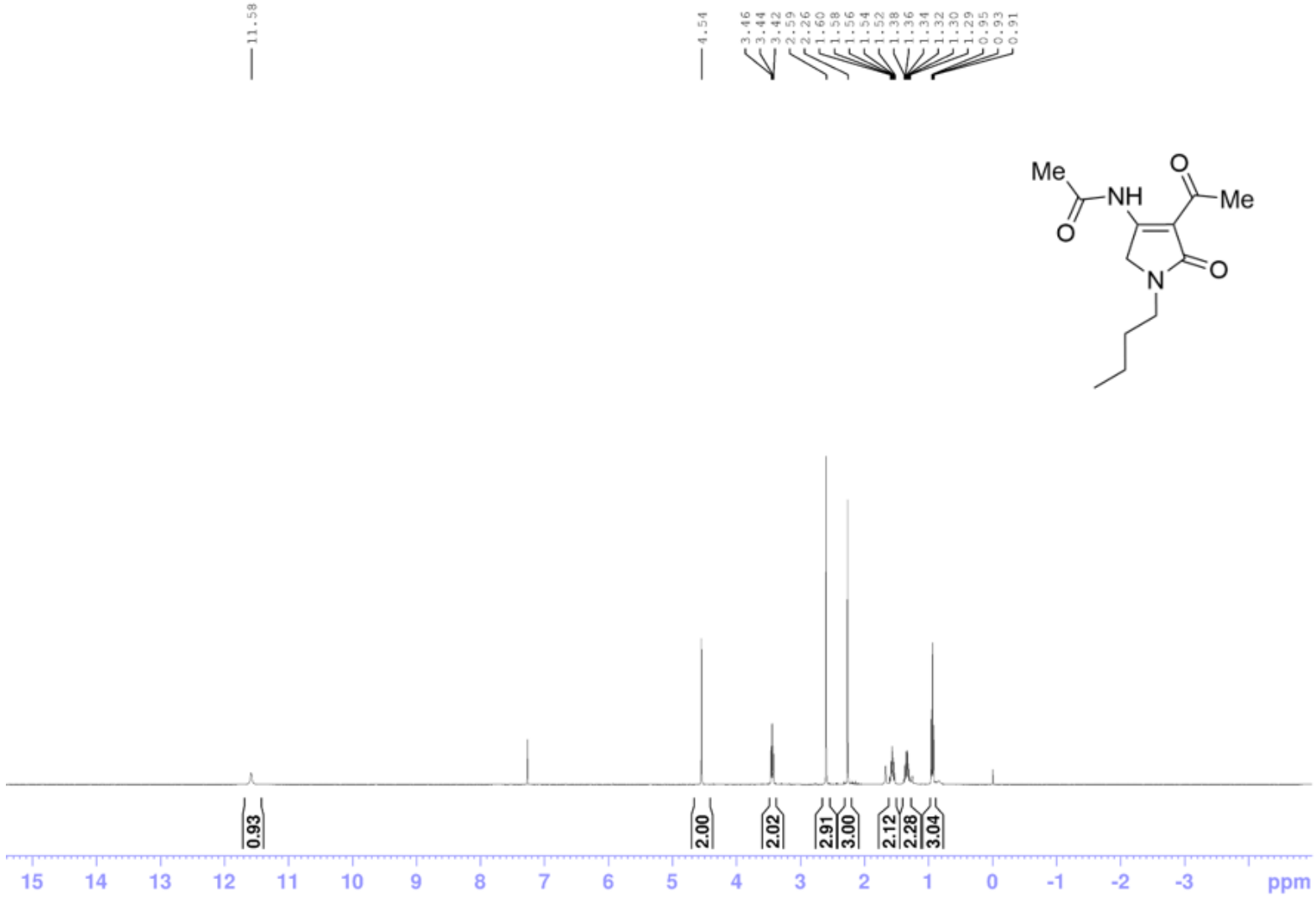
Edited HSQC spectrum of **11** ($CDCl_3$)



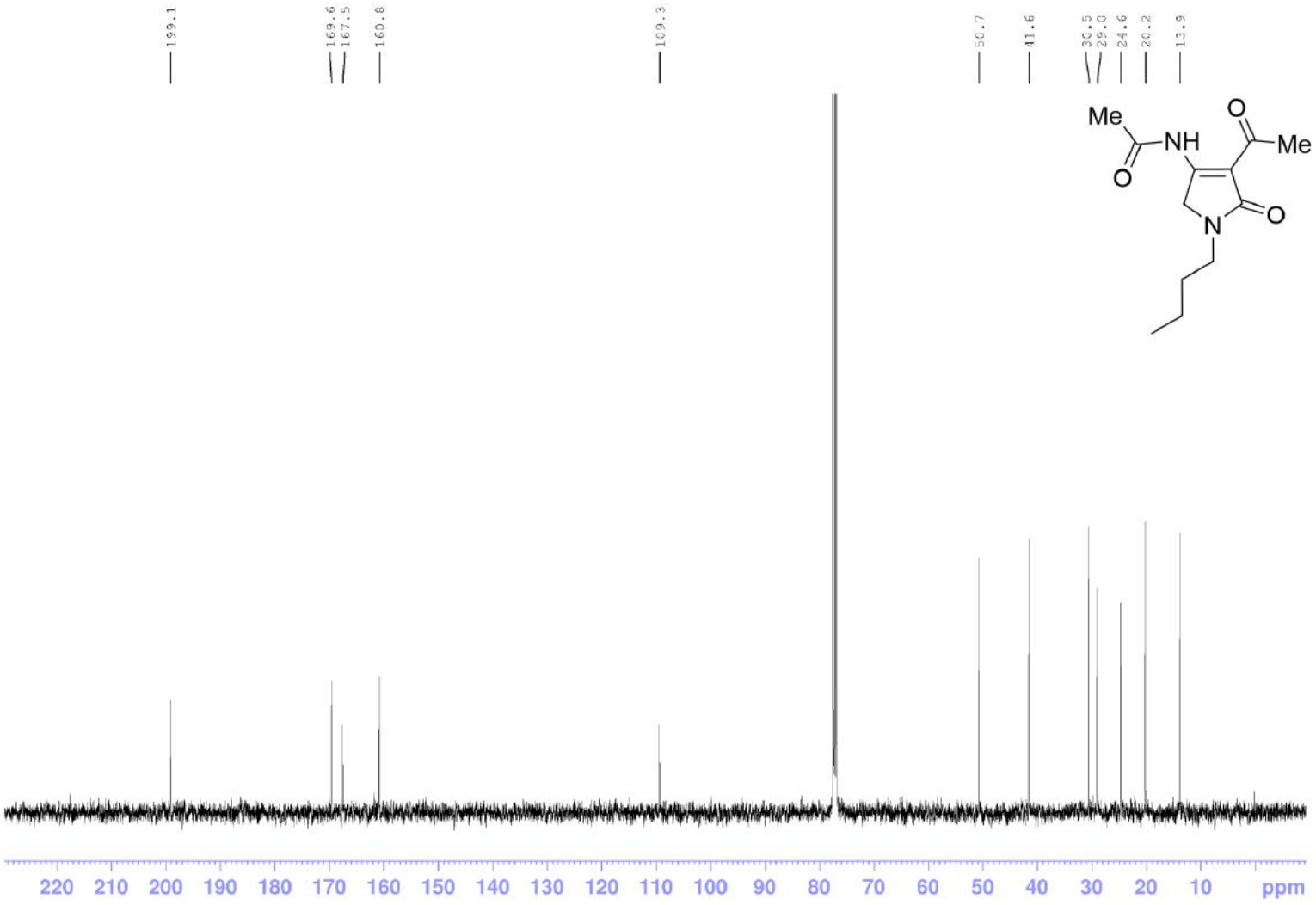
HMBC spectrum of **11** ($CDCl_3$)



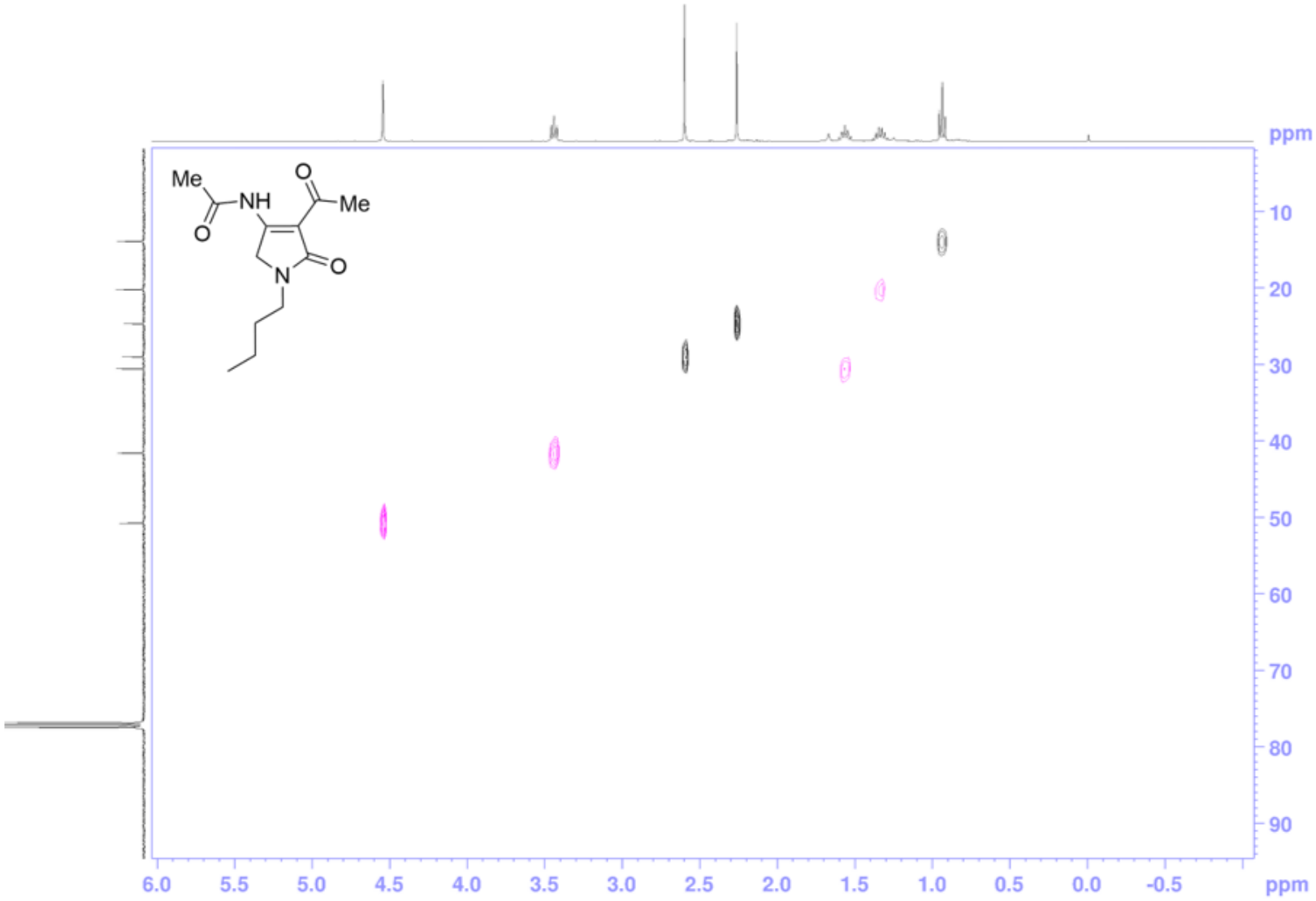
^{1}H NMR spectrum of **12** (400 MHz, $CDCl_3$)



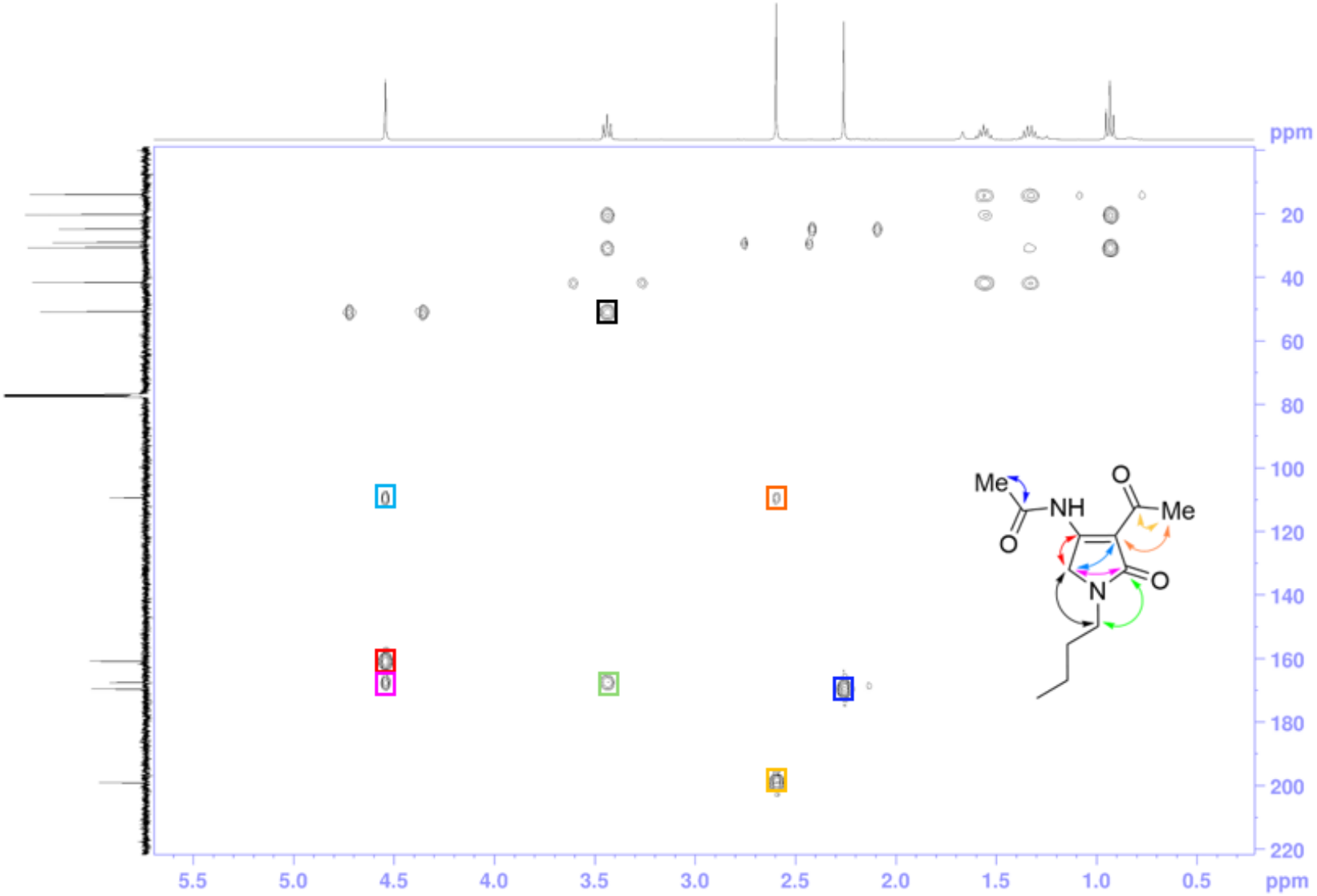
^{13}C NMR spectrum of **12** (100 MHz, $CDCl_3$)



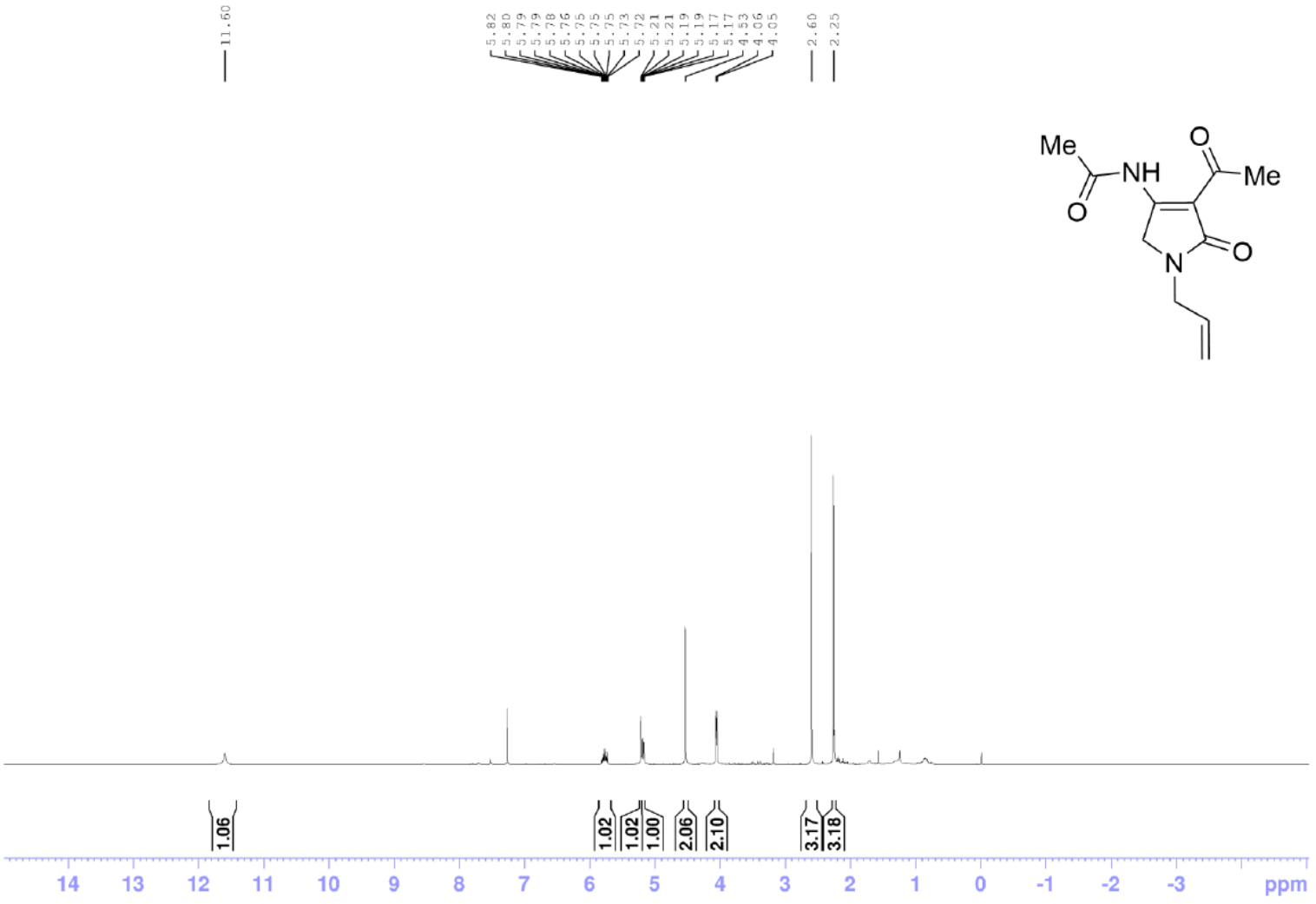
Edited HSQC spectrum of **12** ($CDCl_3$)



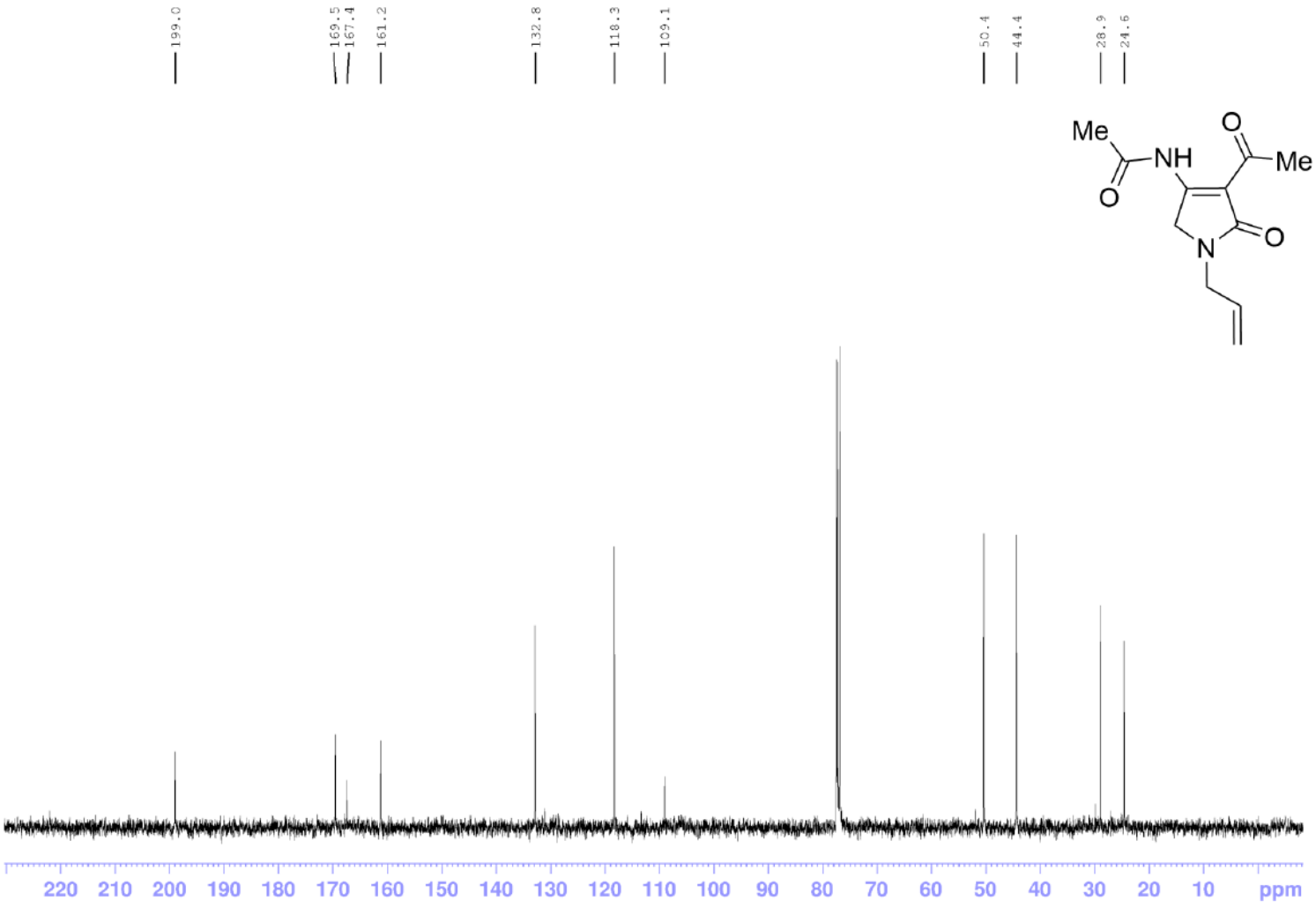
HMBC spectrum of **12** ($CDCl_3$)



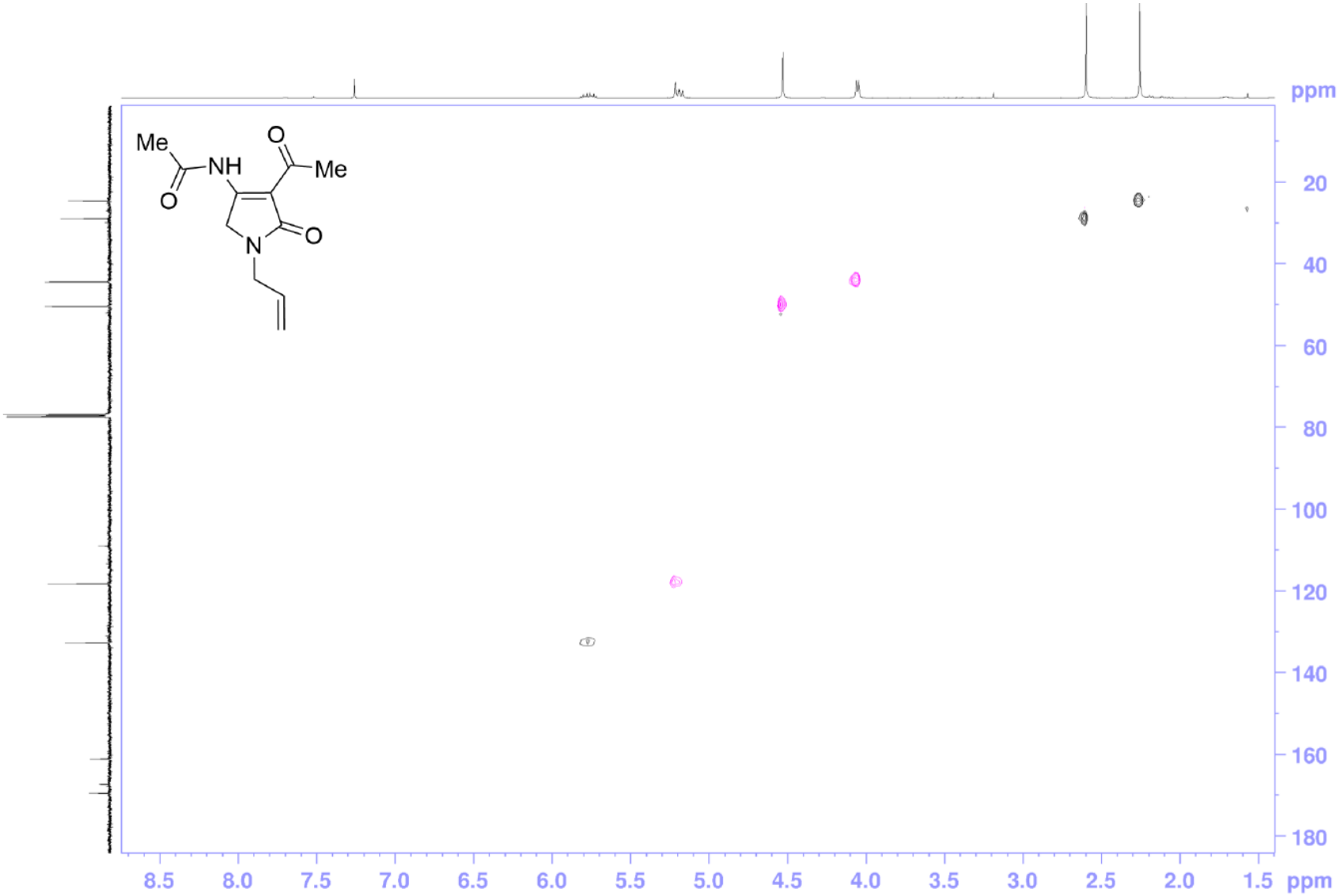
^{1}H NMR spectrum of **13** (400 MHz, $CDCl_3$)



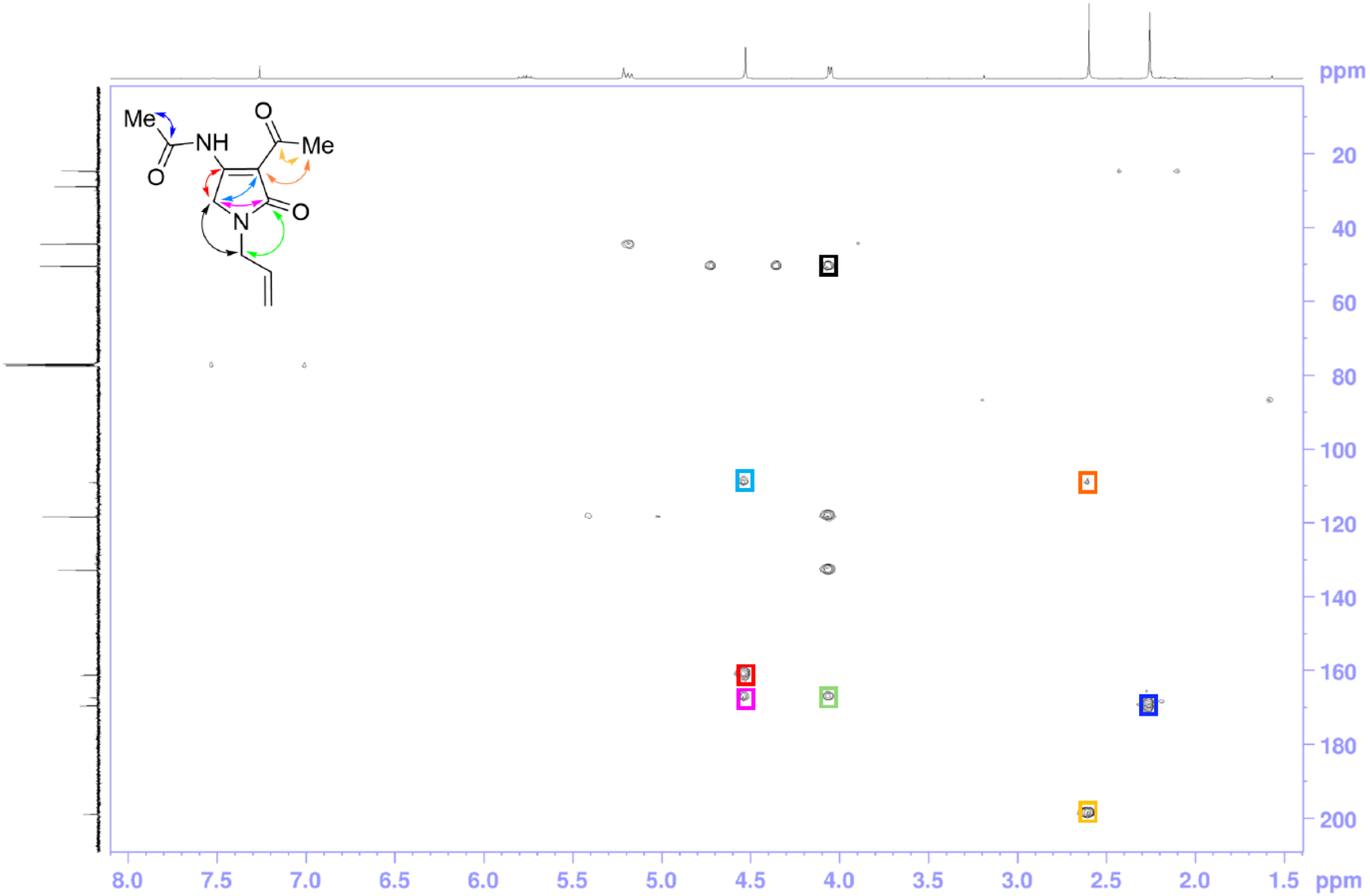
^{13}C NMR spectrum of **13** (100 MHz, $CDCl_3$)



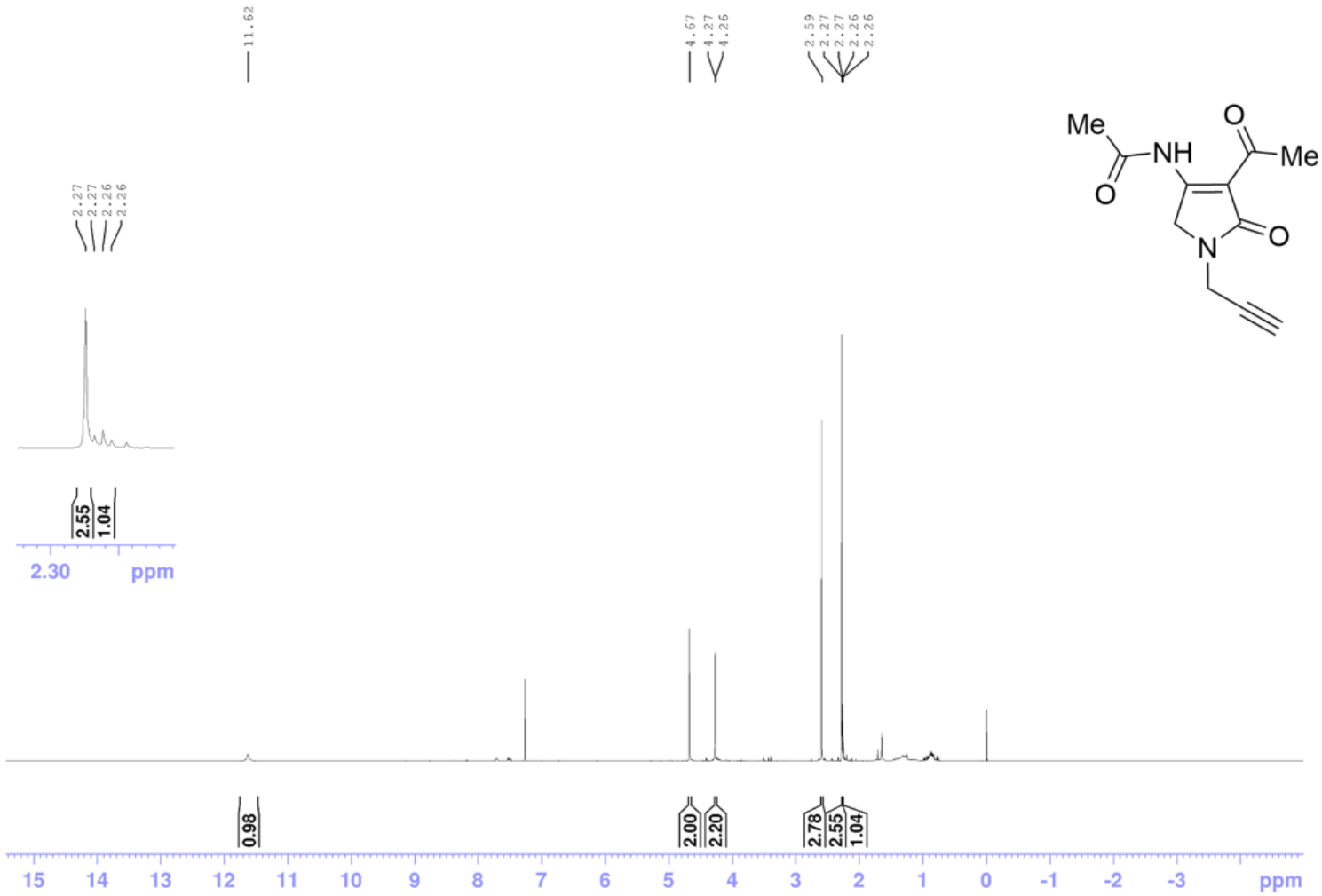
Edited HSQC spectrum of **13** ($CDCl_3$)



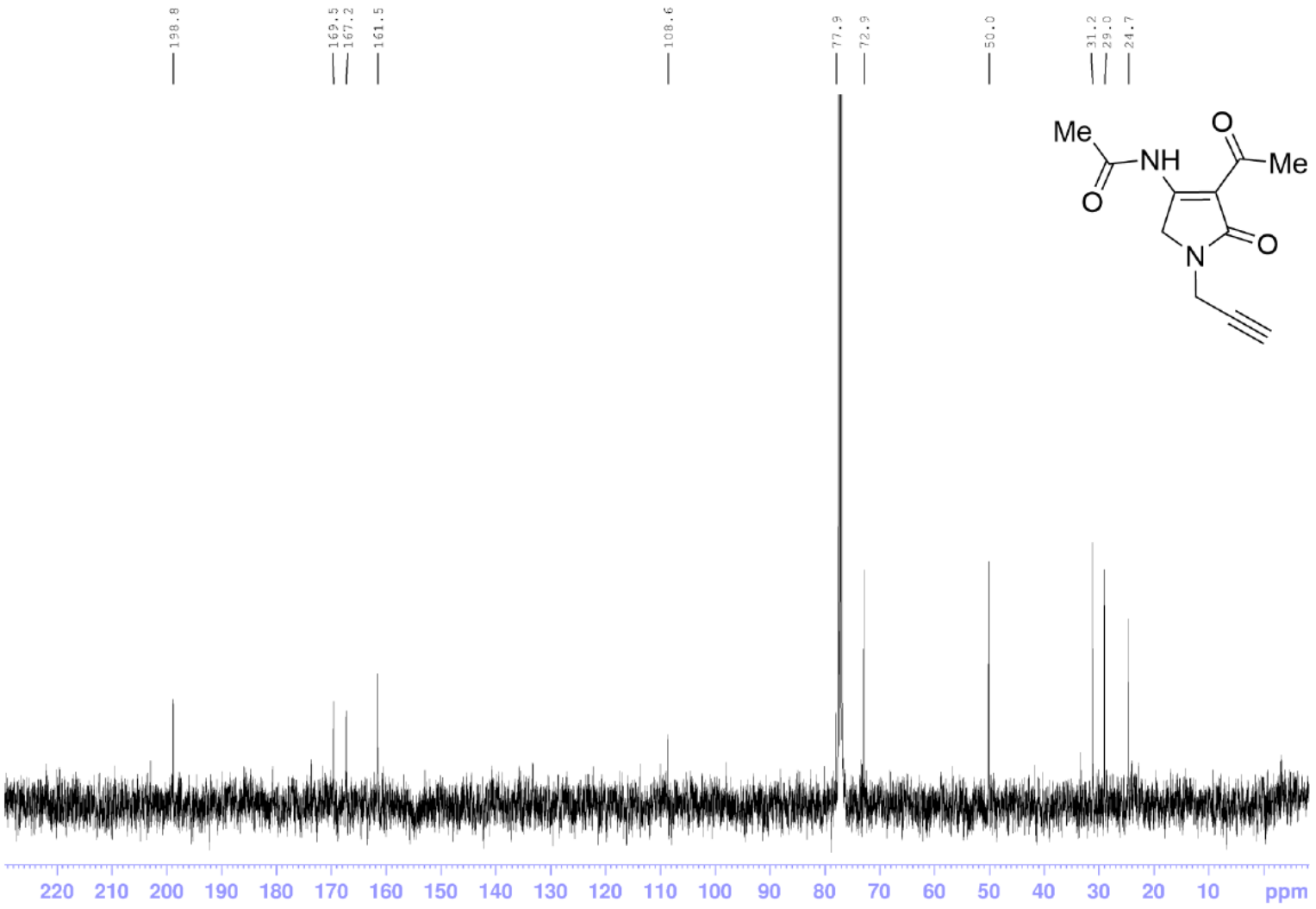
HMBC spectrum of **13** ($CDCl_3$)



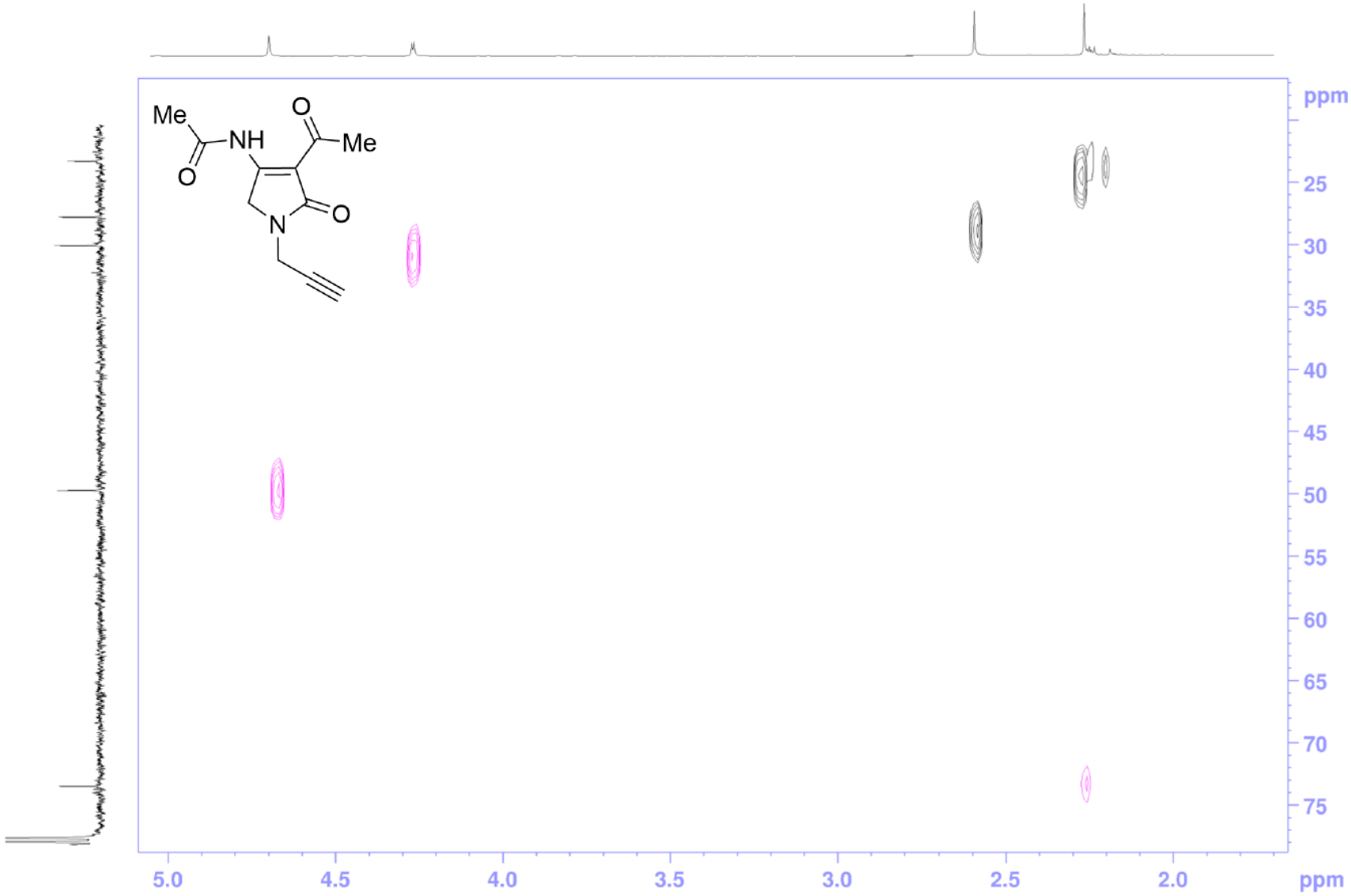
^{1}H NMR spectrum of **14** (400 MHz, $CDCl_3$)



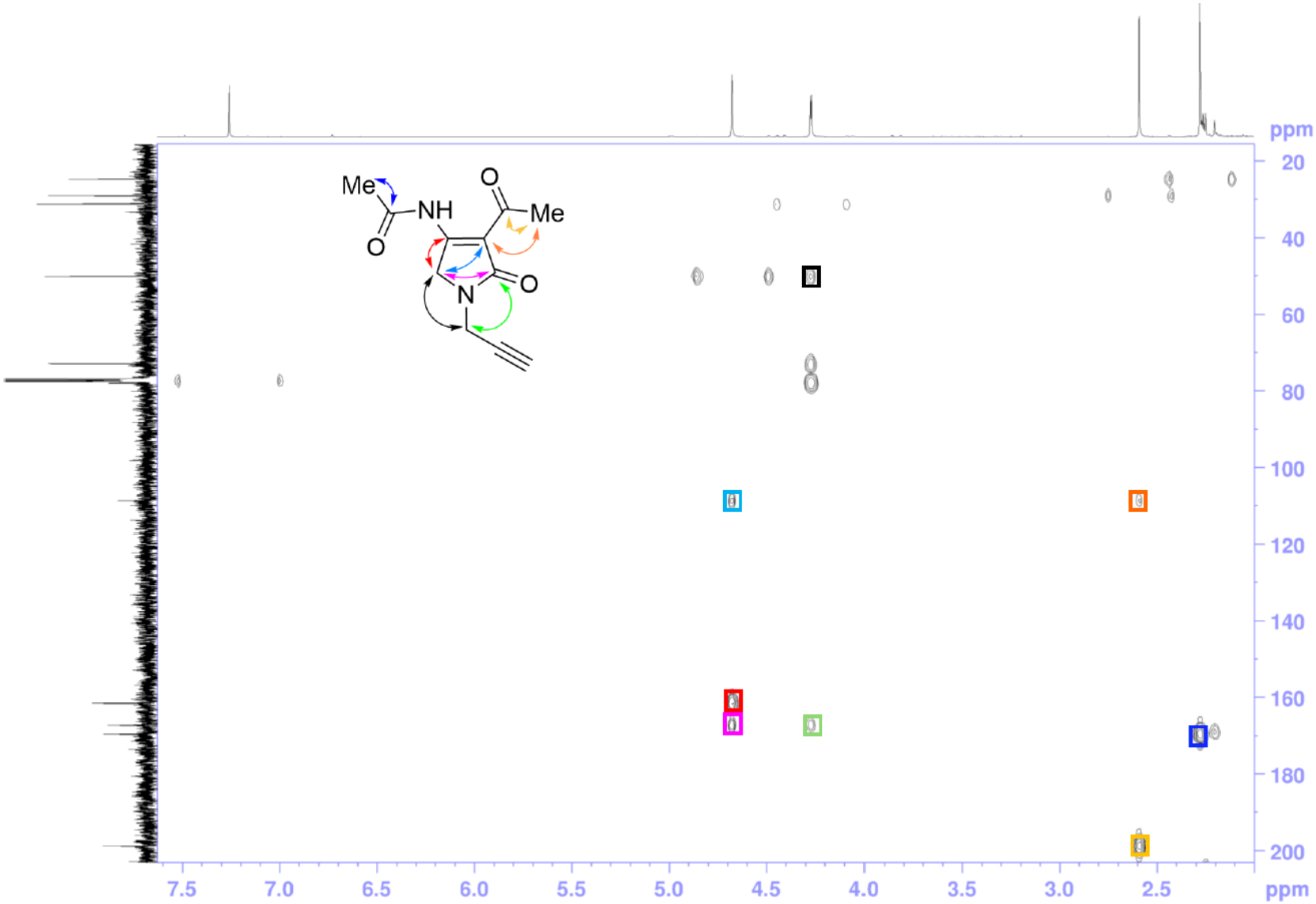
^{13}C NMR spectrum of **14** (100 MHz, $CDCl_3$)



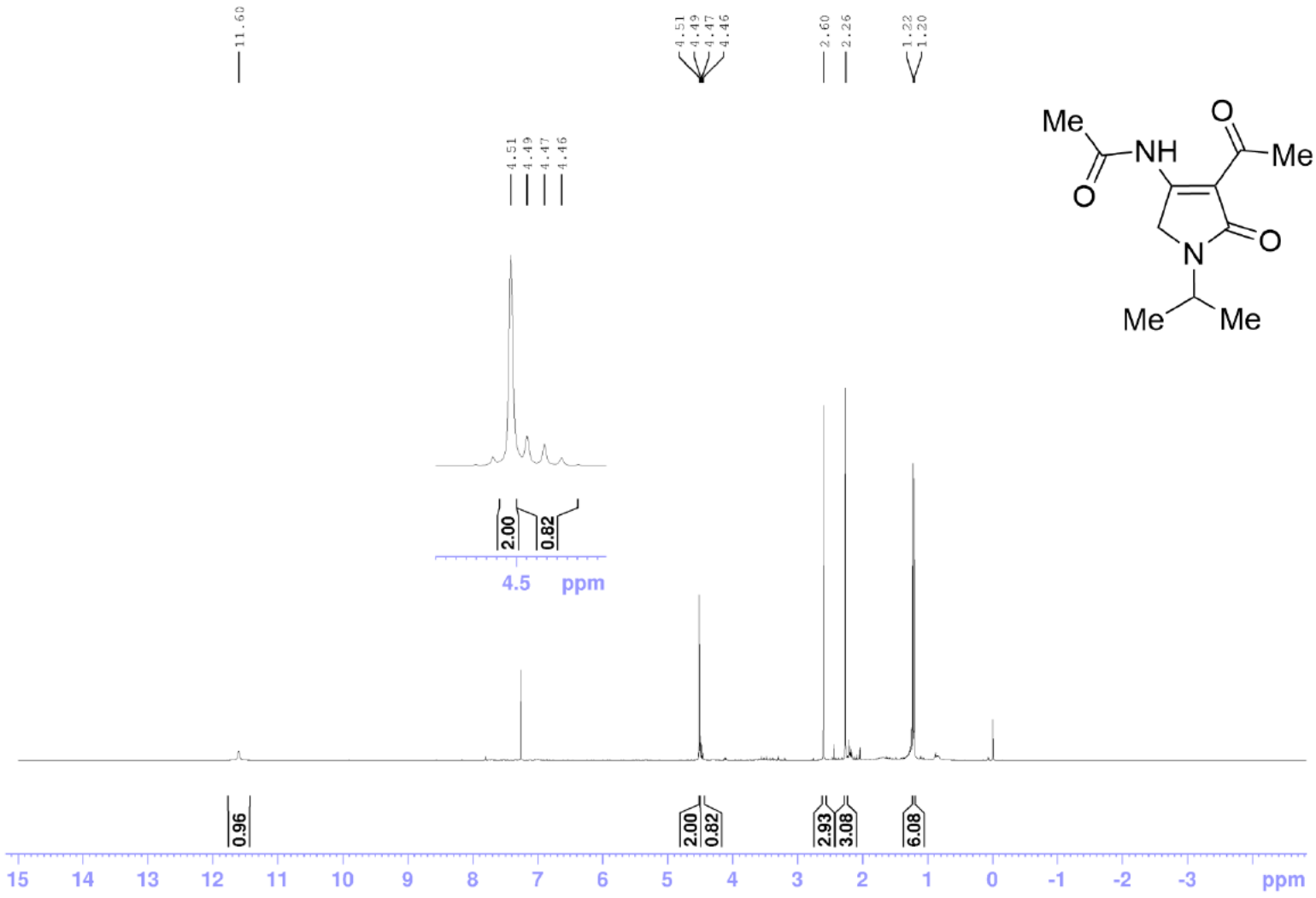
Edited HSQC spectrum of **14** ($CDCl_3$)



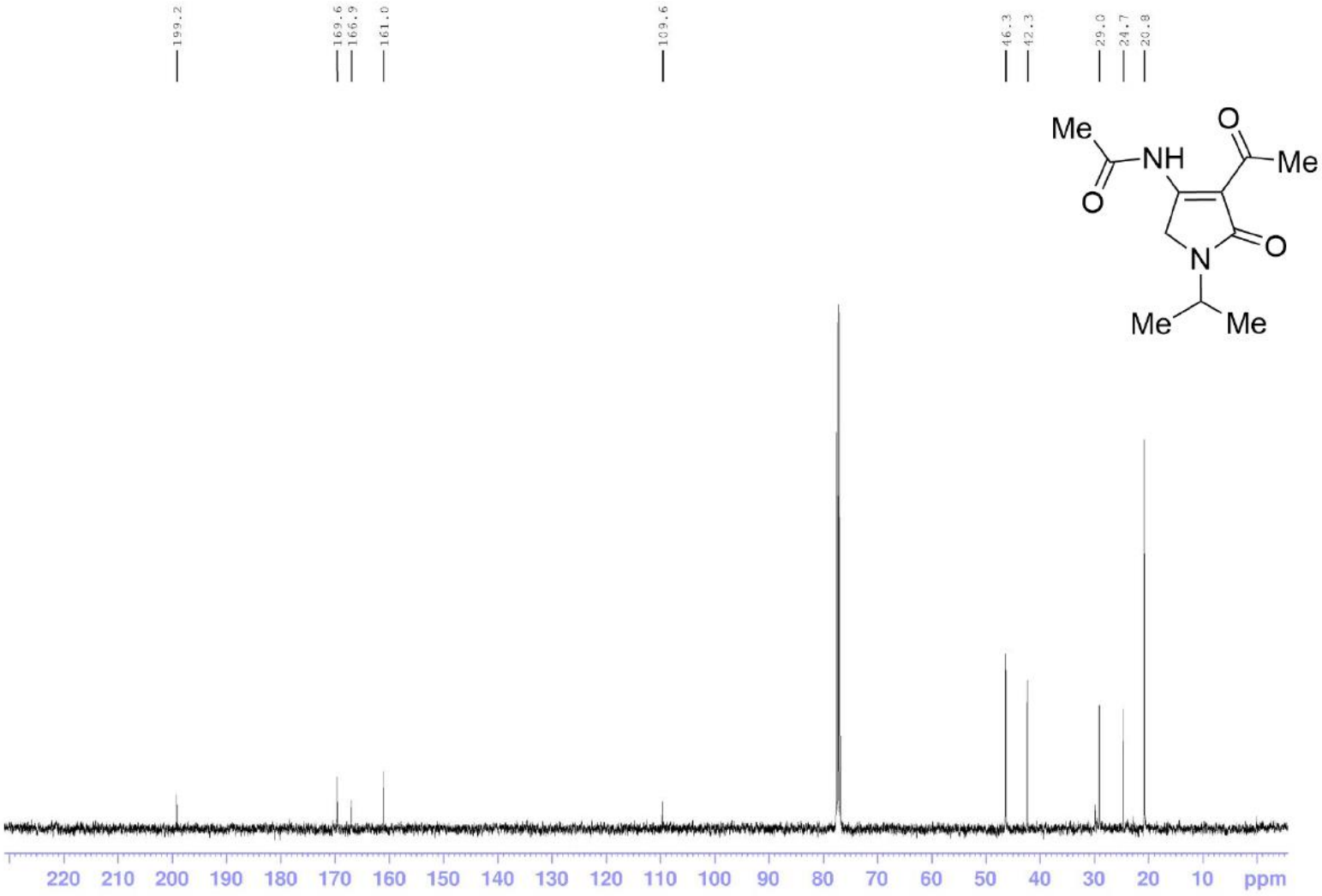
HMBC spectrum of **14** ($CDCl_3$)



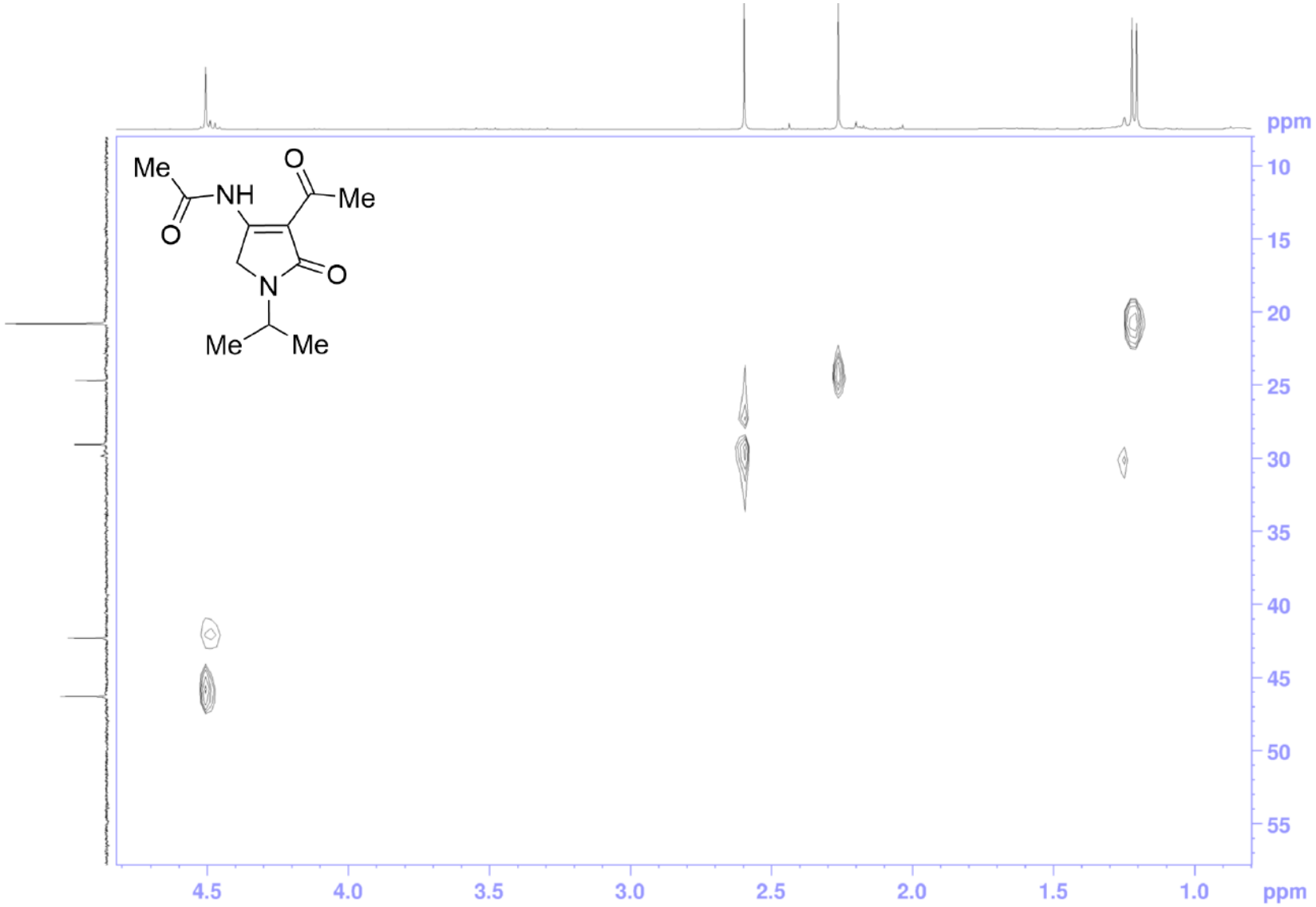
^{1}H NMR spectrum of **15** (400 MHz, $CDCl_3$)



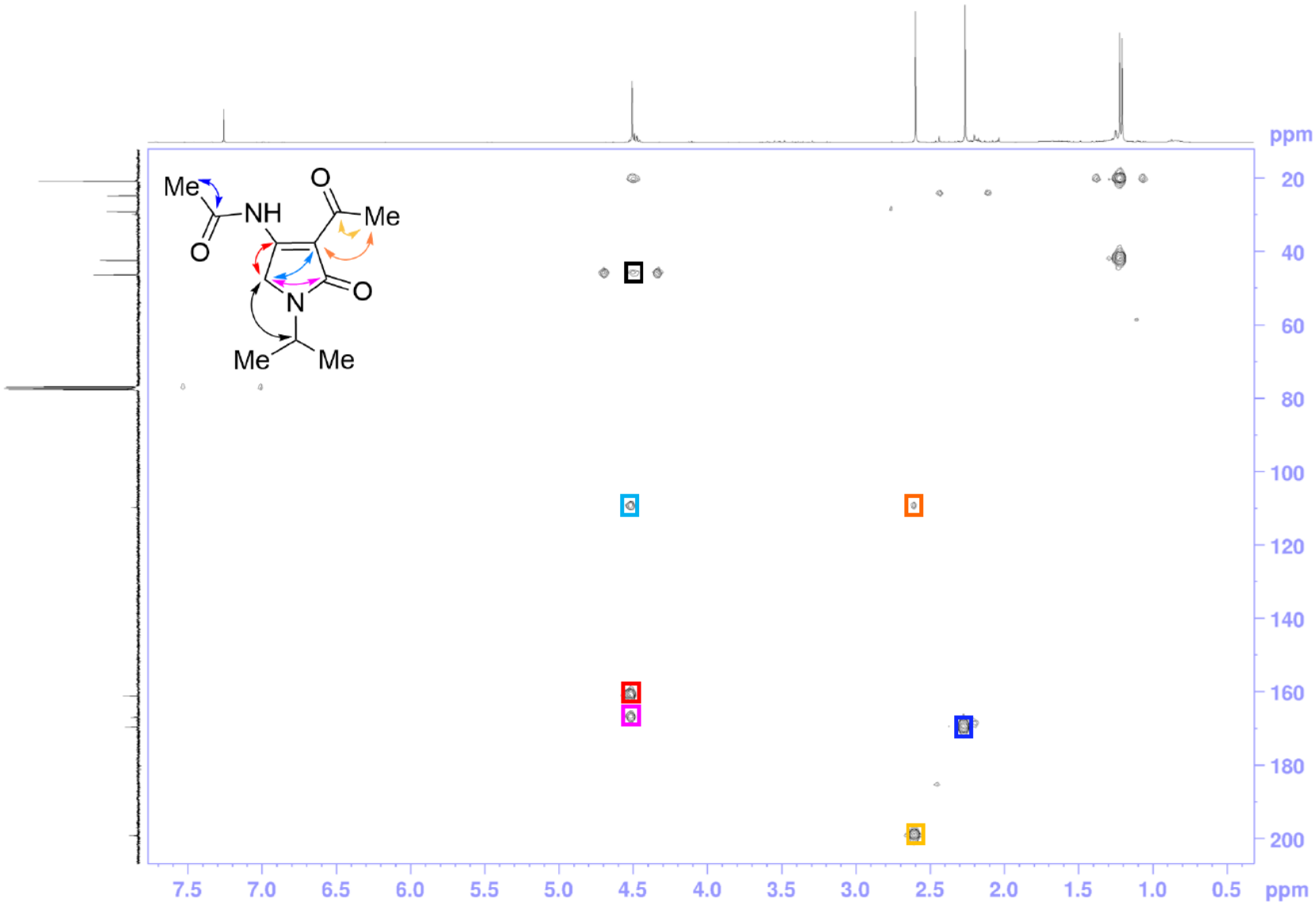
^{13}C NMR spectrum of **15** (100 MHz, $CDCl_3$)



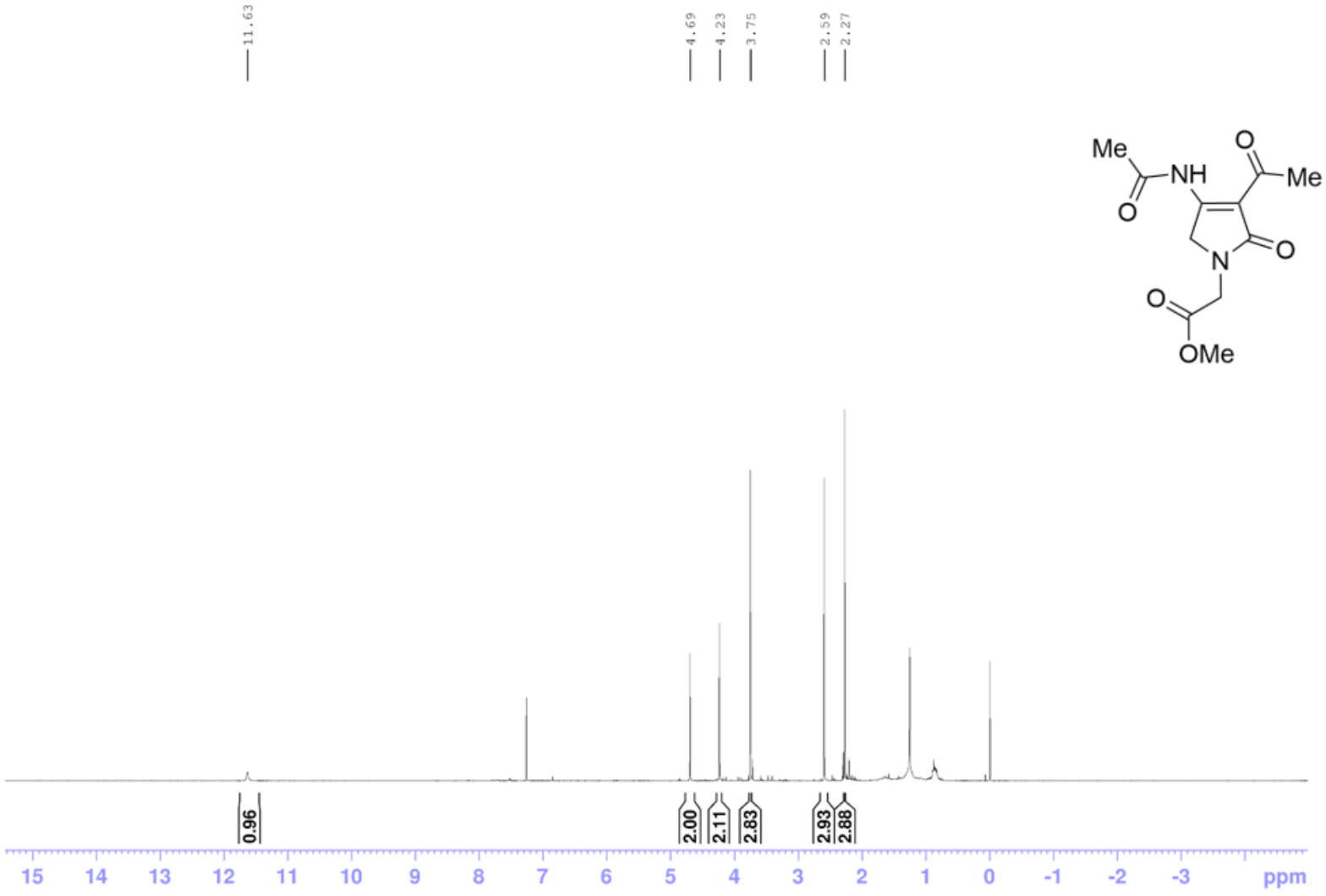
HSQC spectrum of **15** ($CDCl_3$)



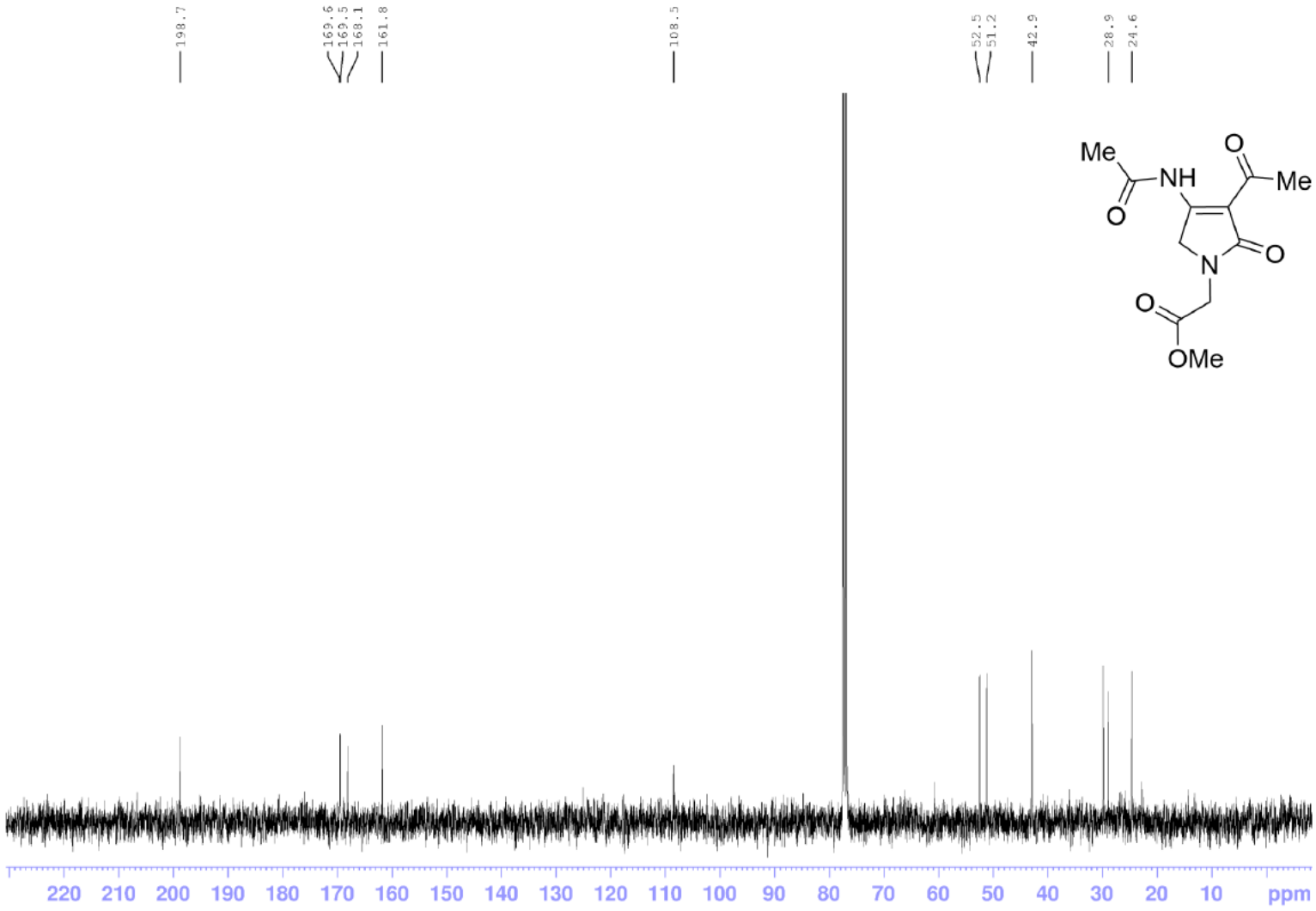
HMBC spectrum of **15** ($CDCl_3$)



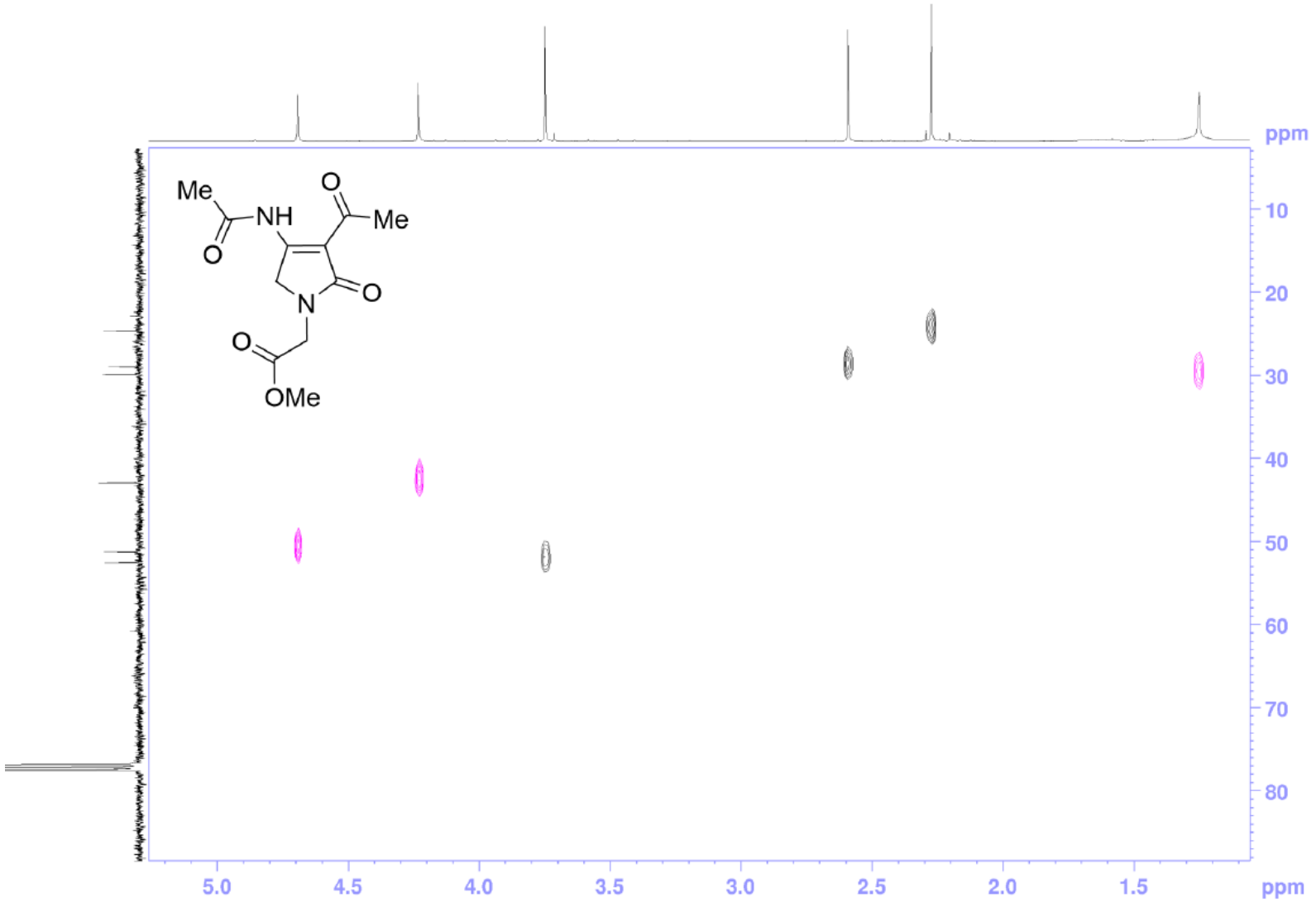
^{1}H NMR spectrum of **16** (400 MHz, $CDCl_3$)



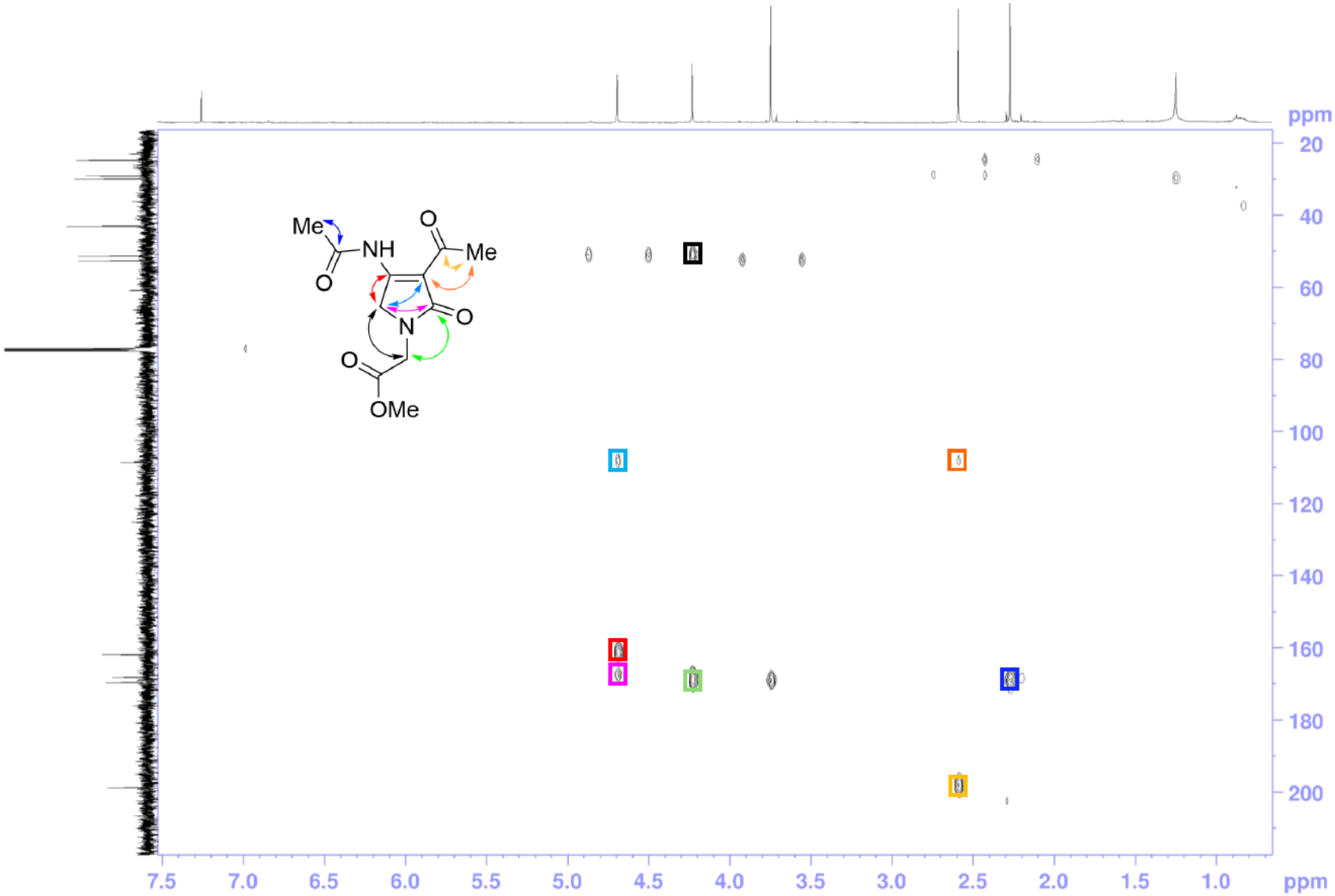
^{13}C NMR spectrum of **16** (100 MHz, $CDCl_3$)



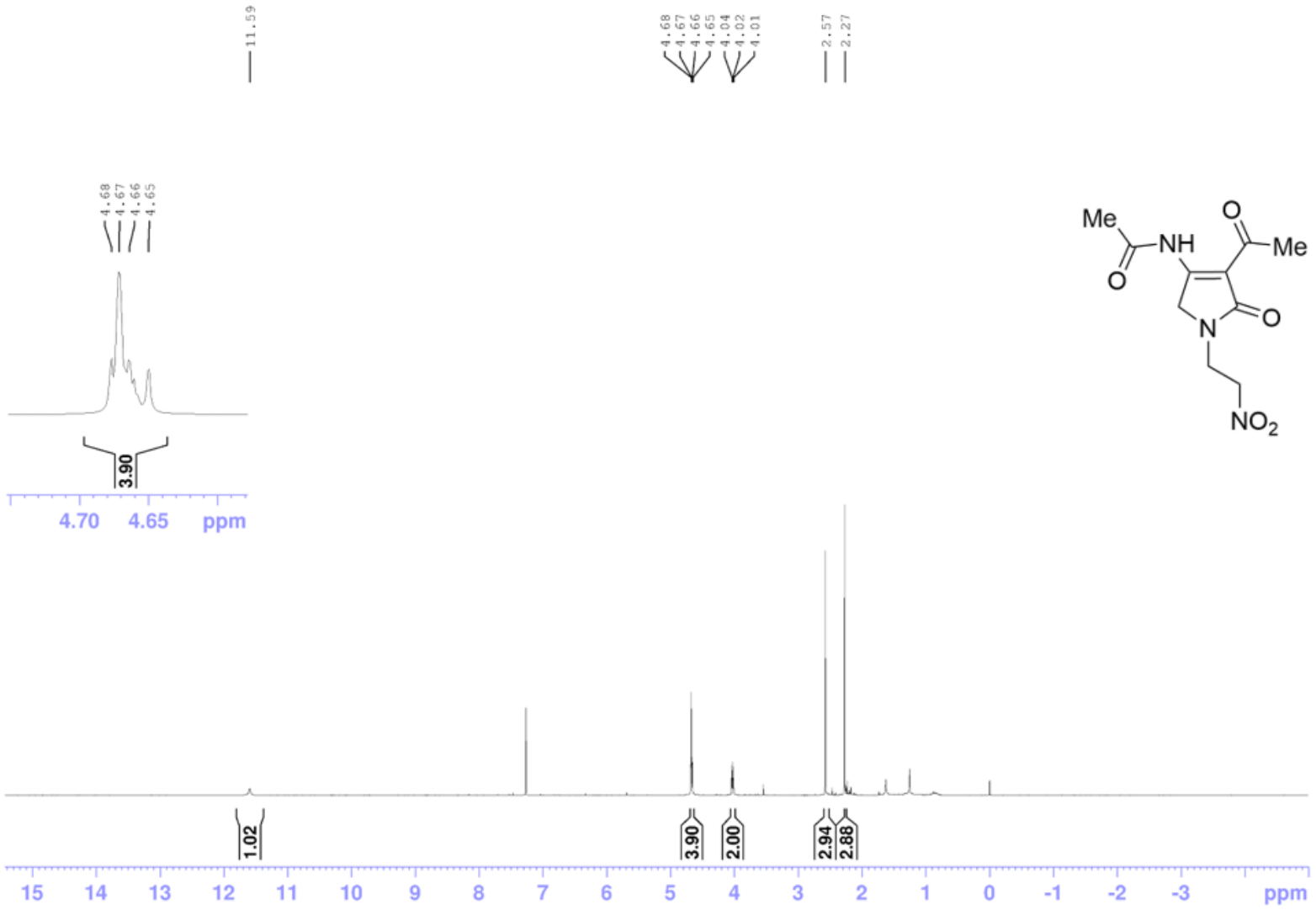
Edited HSQC spectrum of **16** ($CDCl_3$)



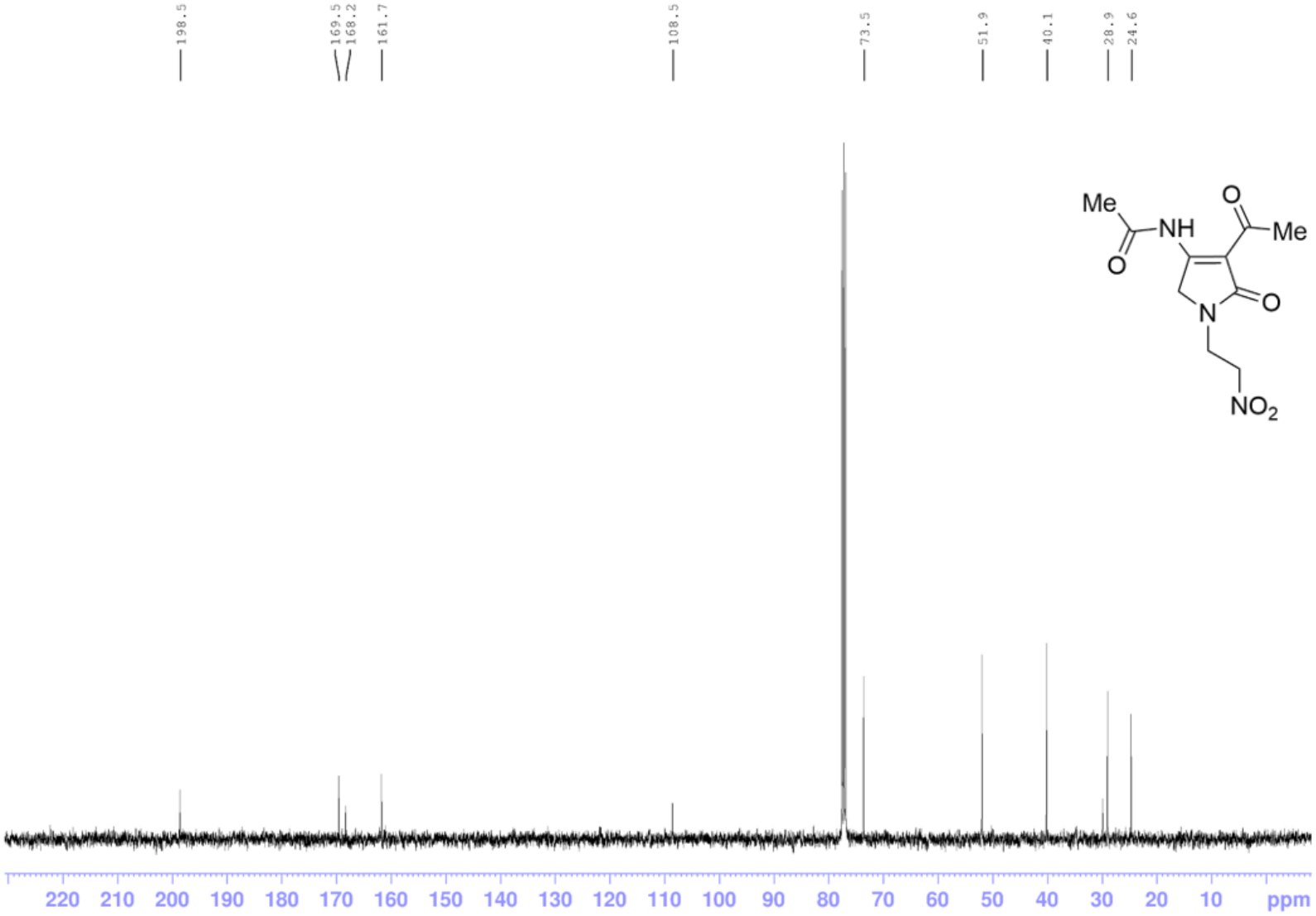
HMBC spectrum of **16** ($CDCl_3$)



^{1}H NMR spectrum of **17** (400 MHz, $CDCl_3$)

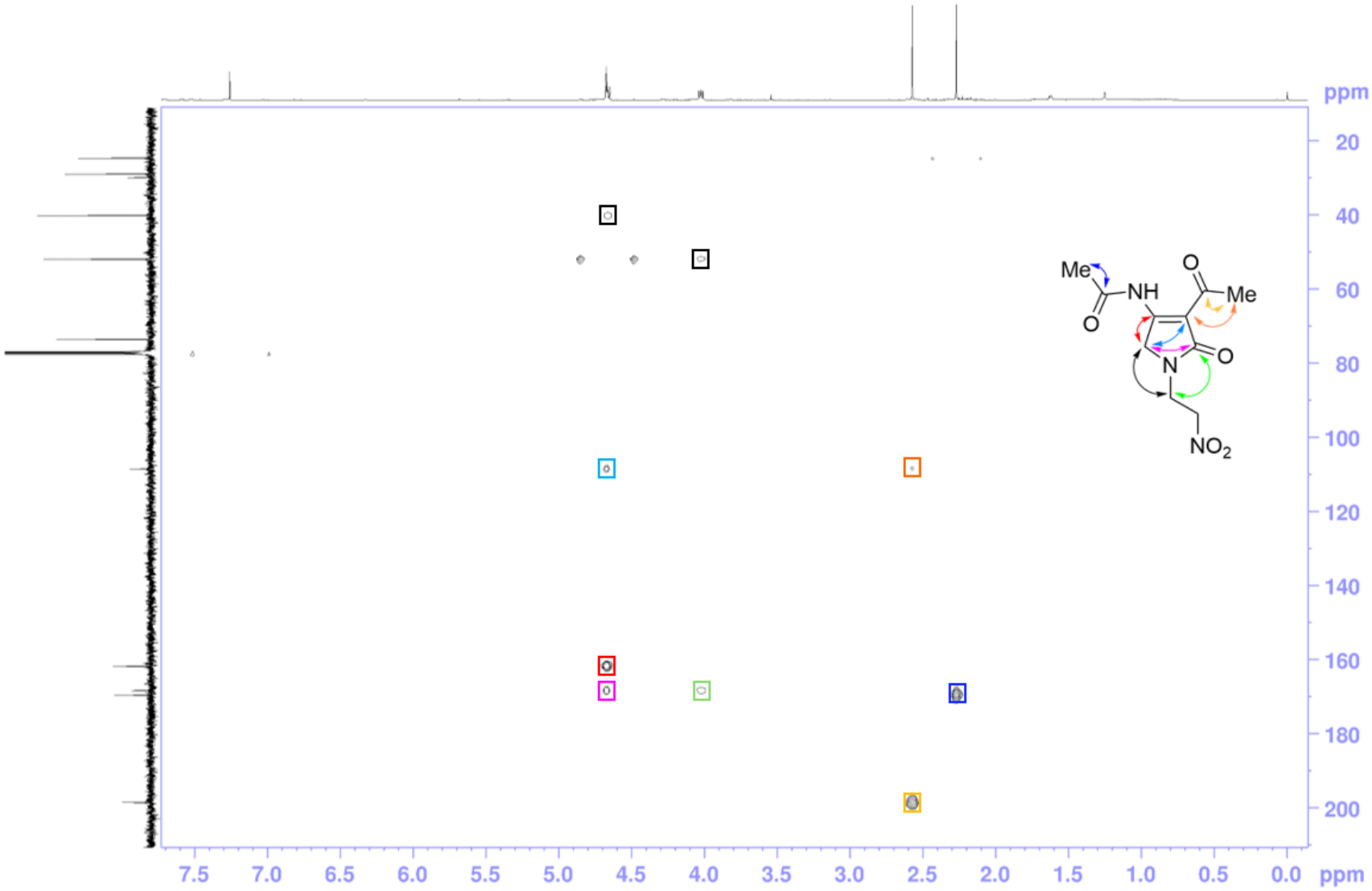


^{13}C NMR spectrum of **17** (100 MHz, $CDCl_3$)

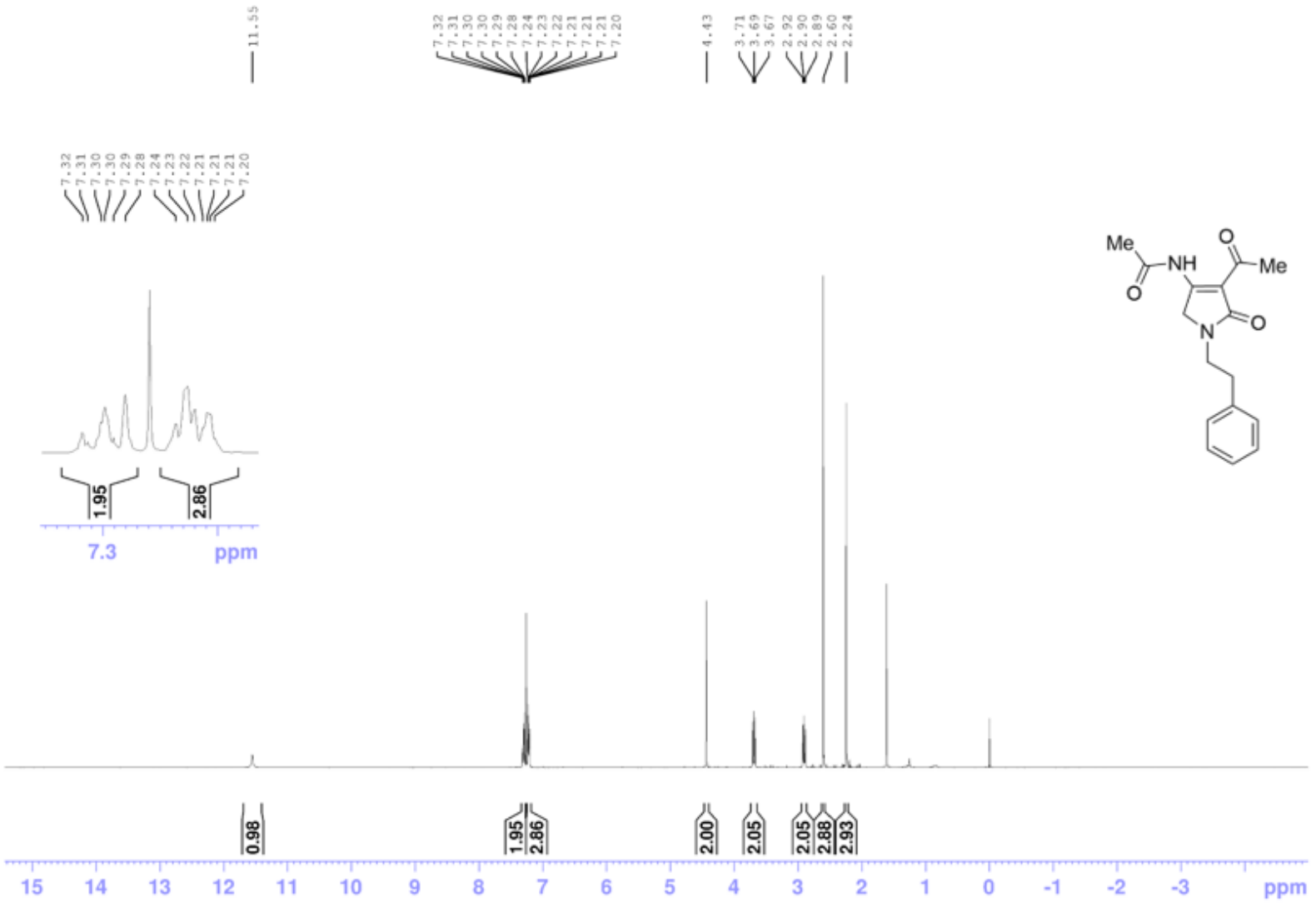


Edited HSQC spectrum of **17** ($CDCl_3$)

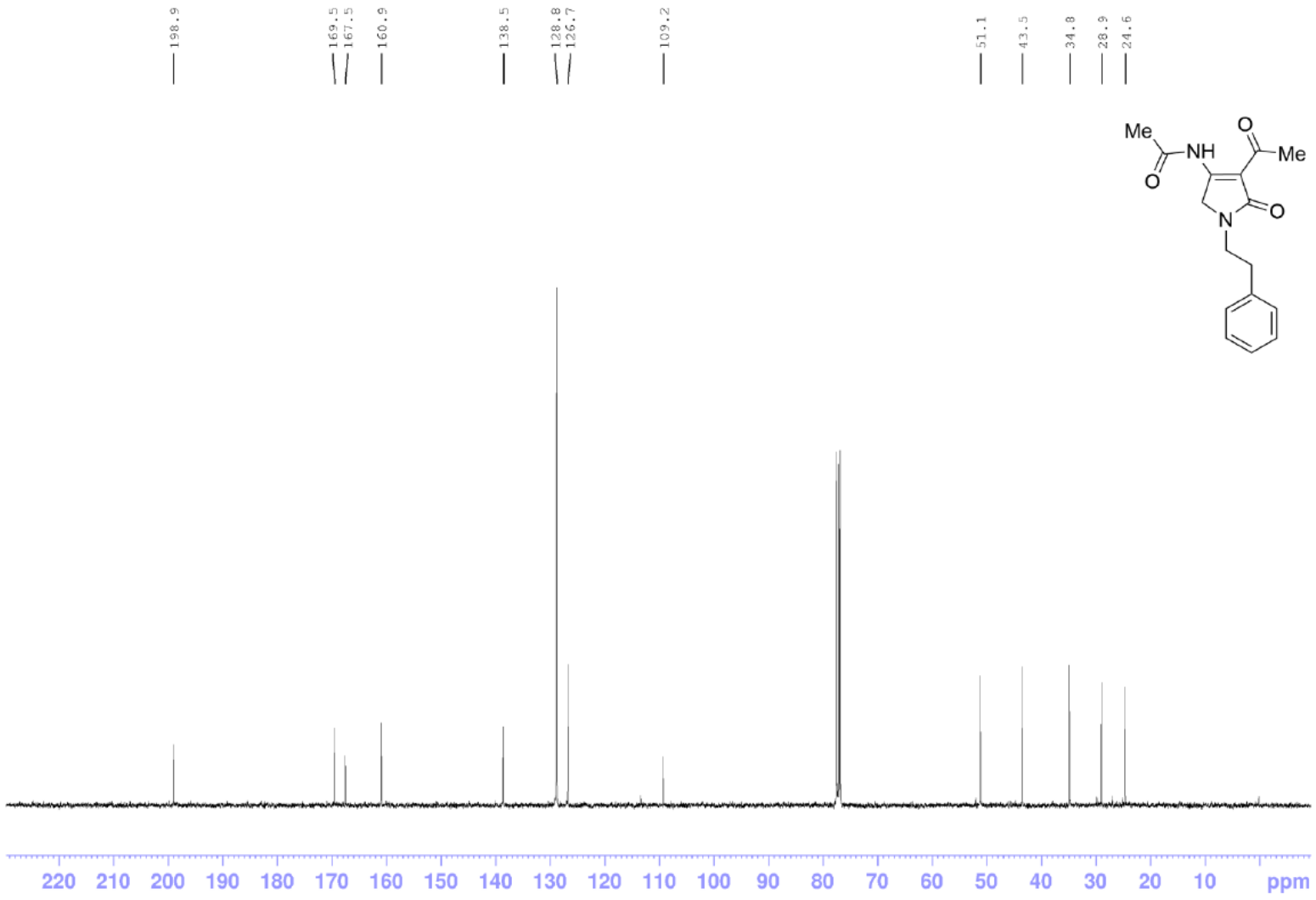
HMBC spectrum of **17** ($CDCl_3$)



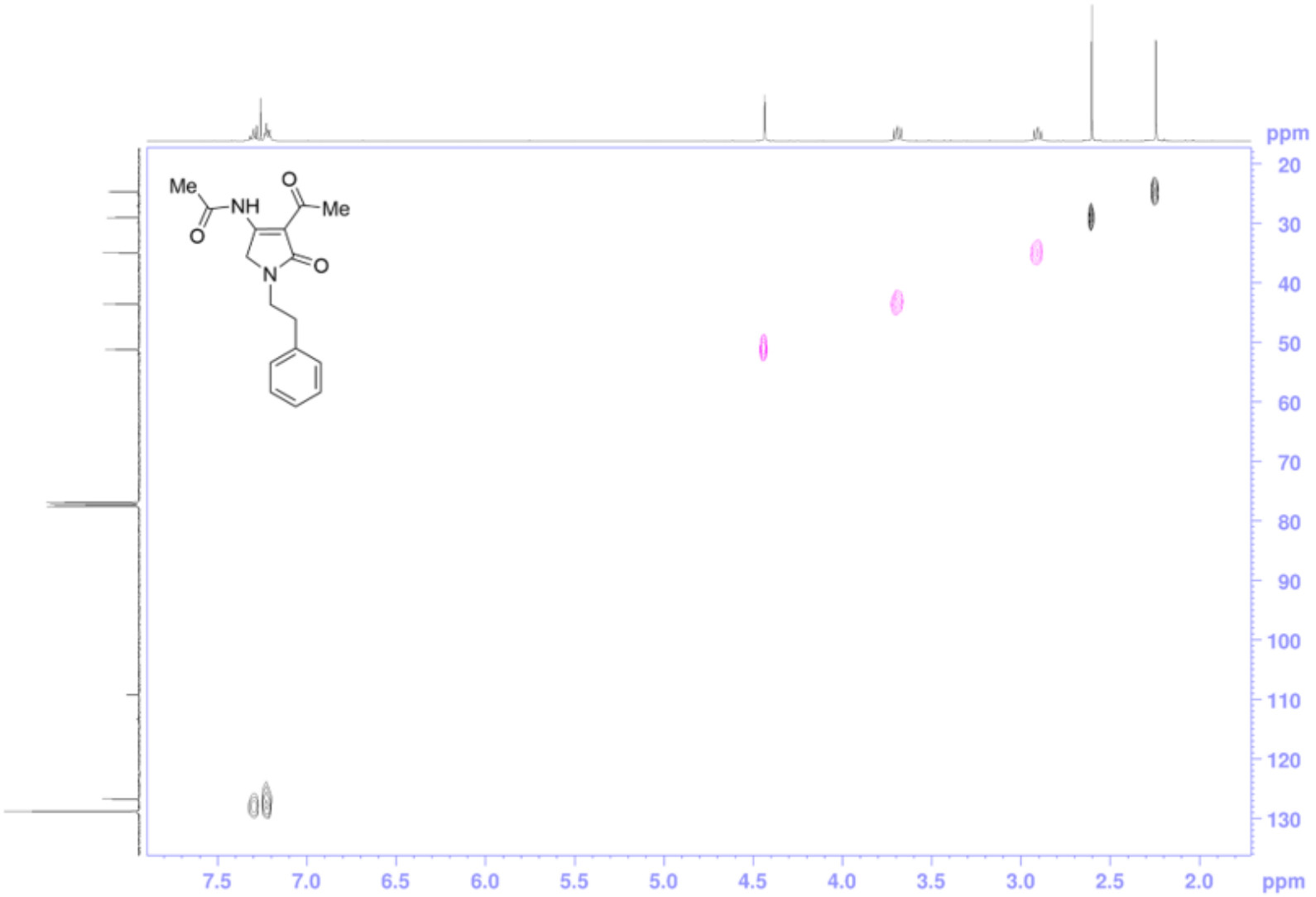
^{1}H NMR spectrum of **18** (400 MHz, $CDCl_3$)



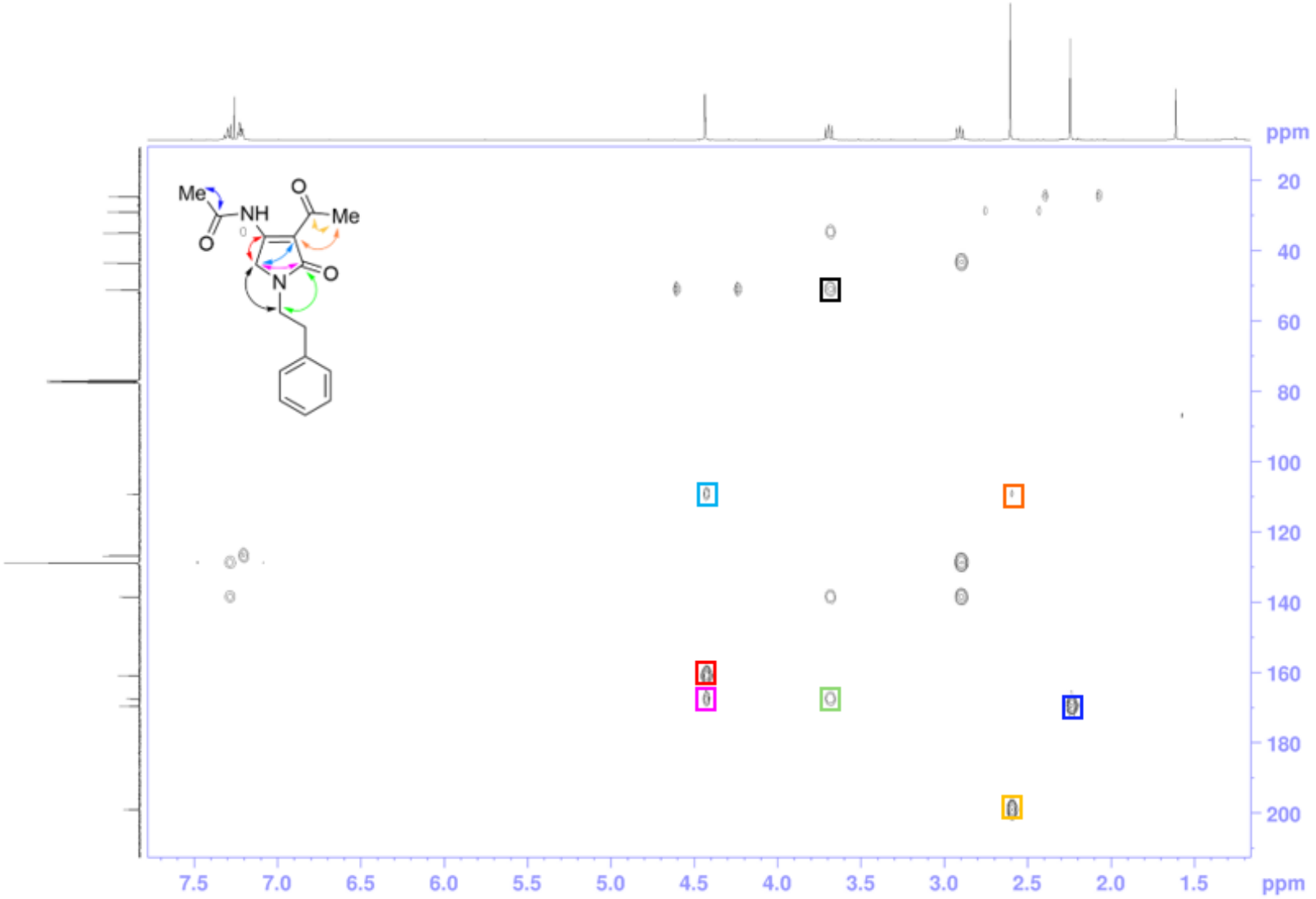
^{13}C NMR spectrum of **18** (100 MHz, $CDCl_3$)



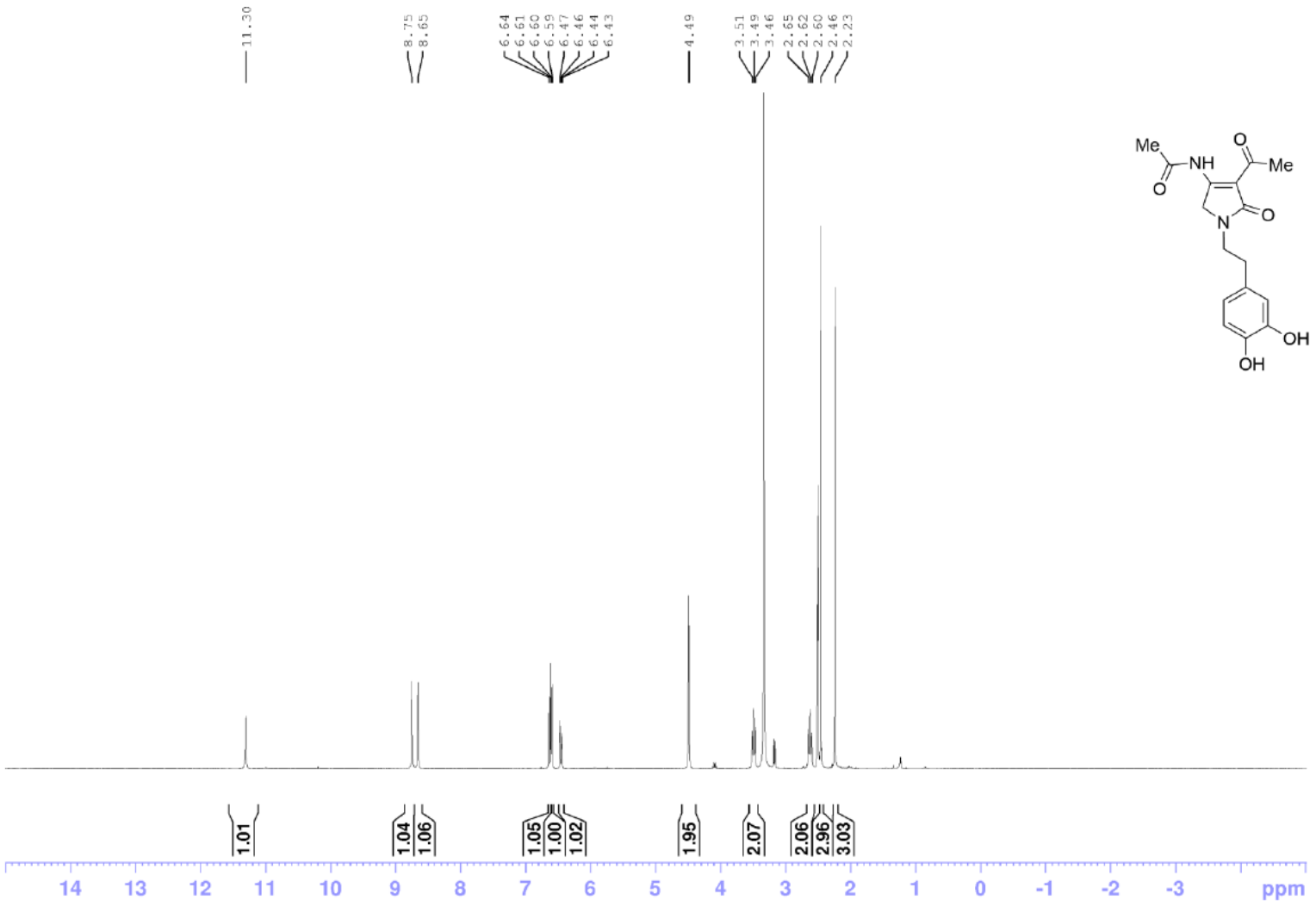
Edited HSQC spectrum of **18** ($CDCl_3$)



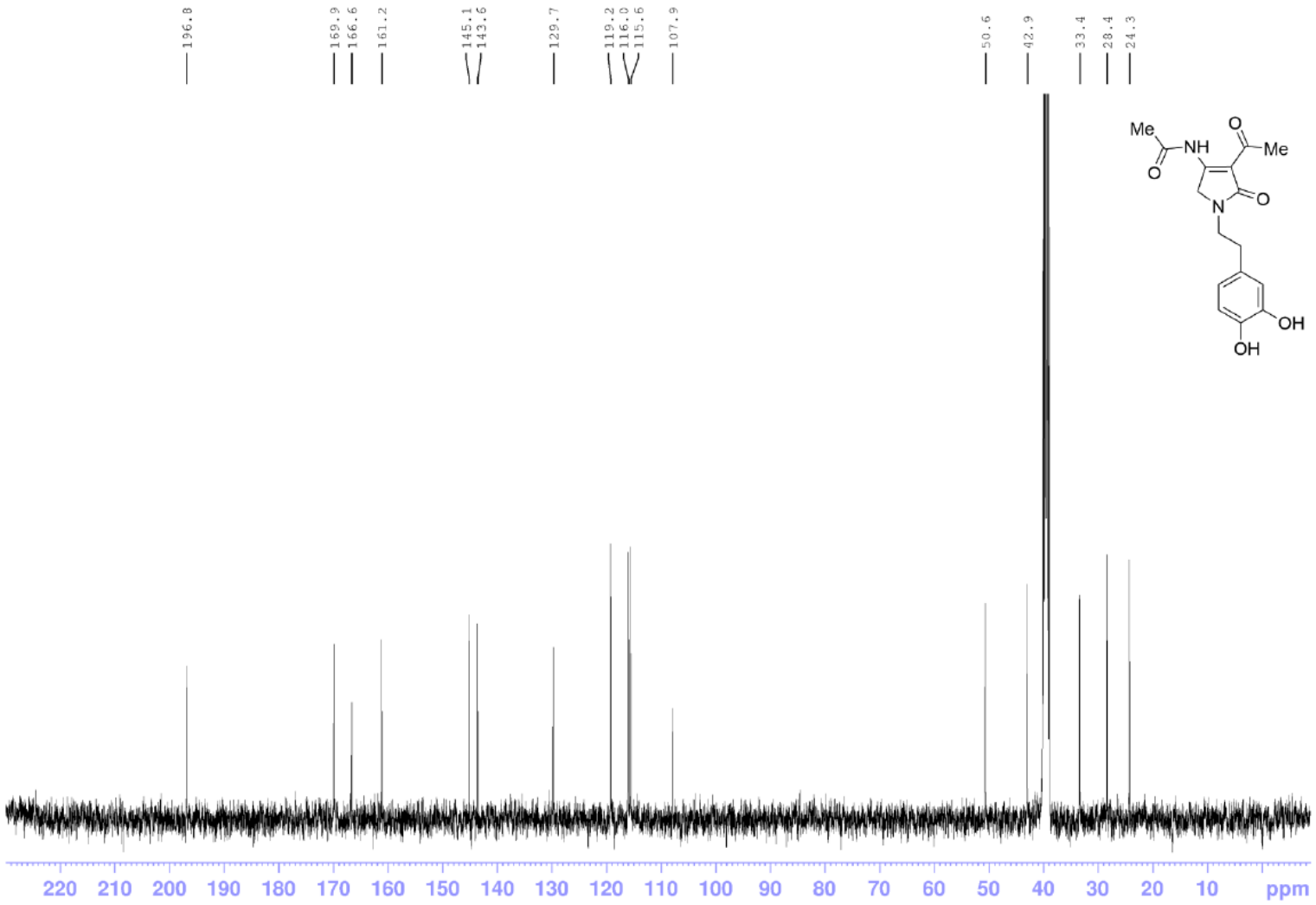
HMBC spectrum of **18** ($CDCl_3$)



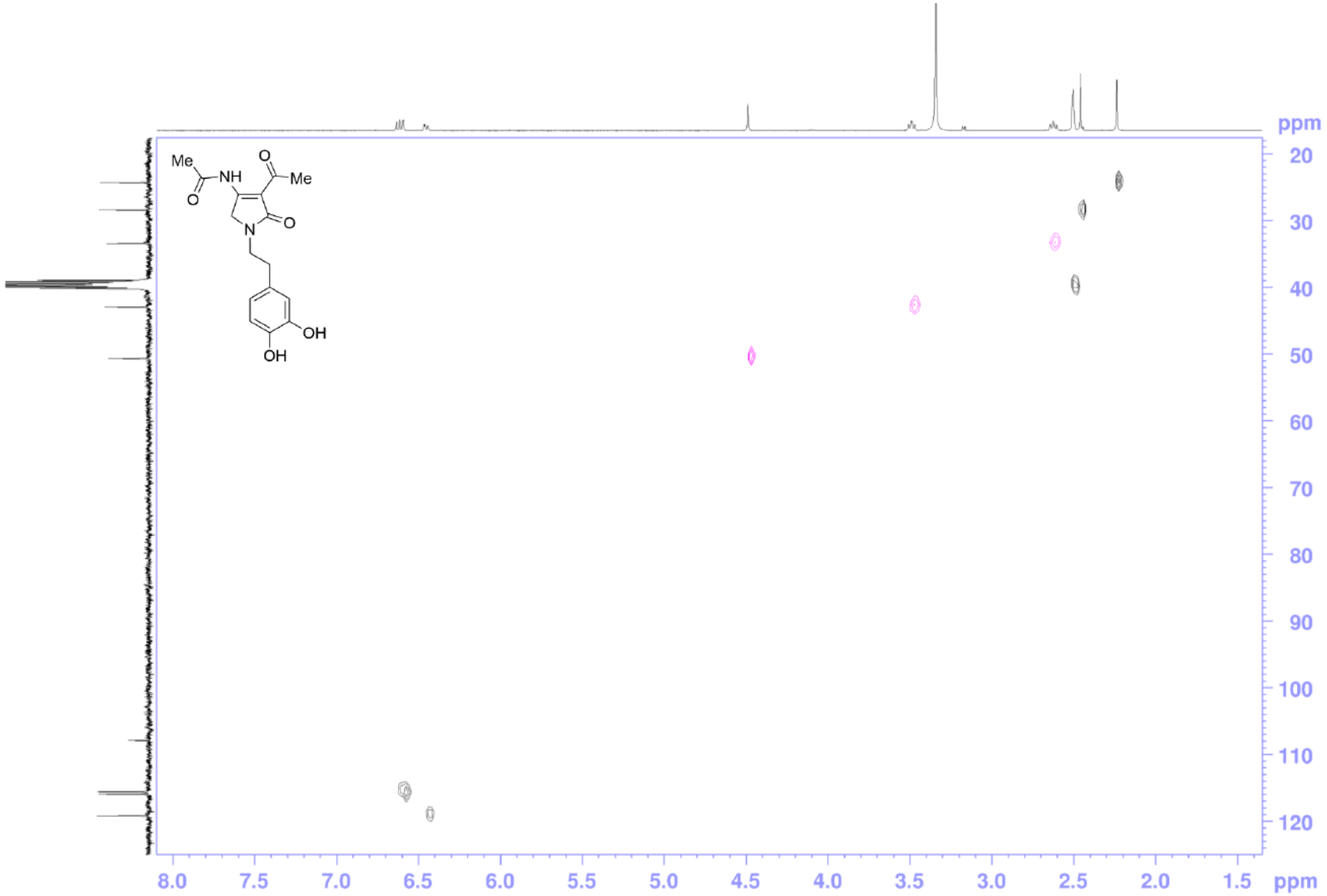
^{1}H NMR spectrum of **19** (400 MHz, $(CD_3)_2SO$)



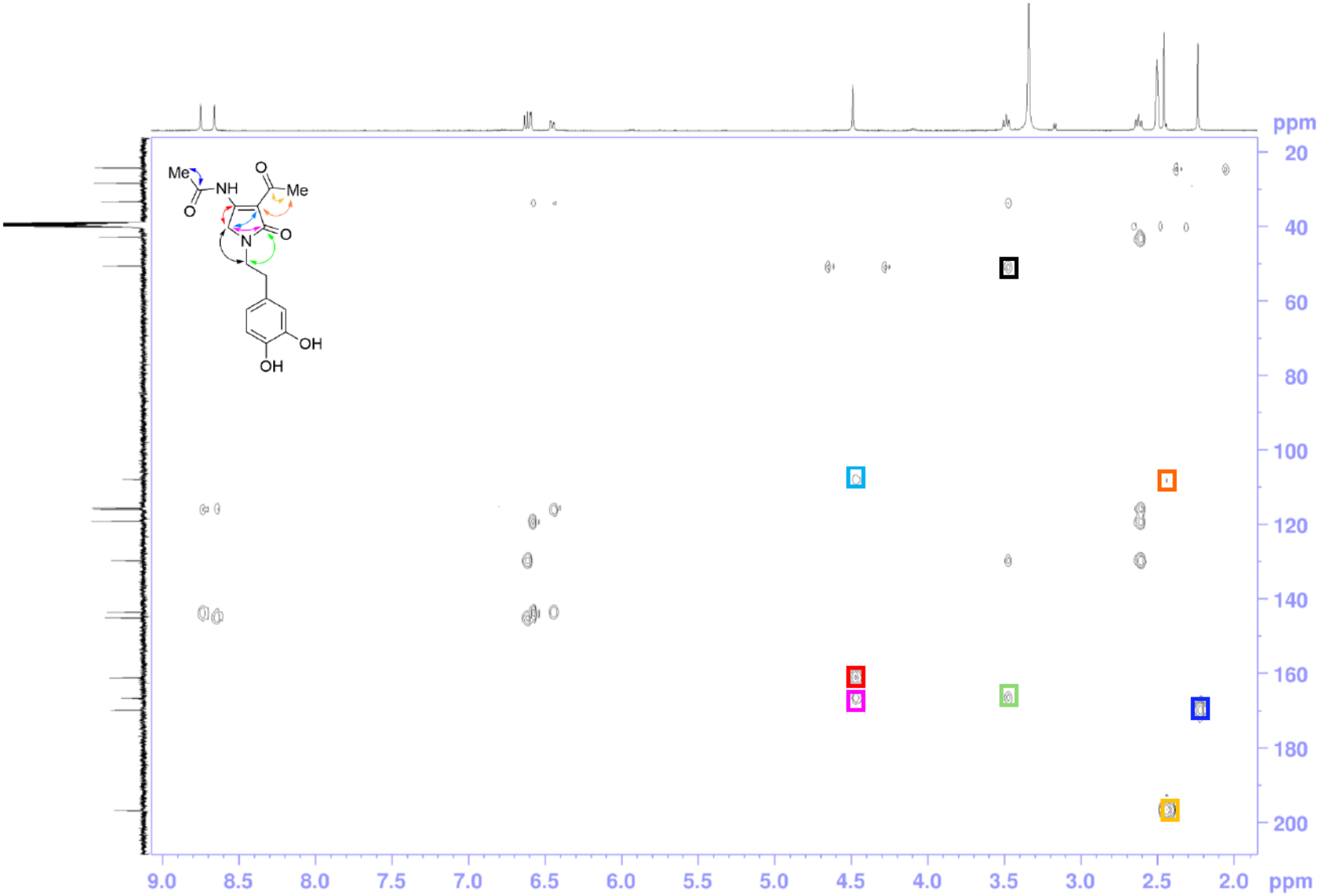
^{13}C NMR spectrum of **19** (100 MHz, $(CD_3)_2SO$)



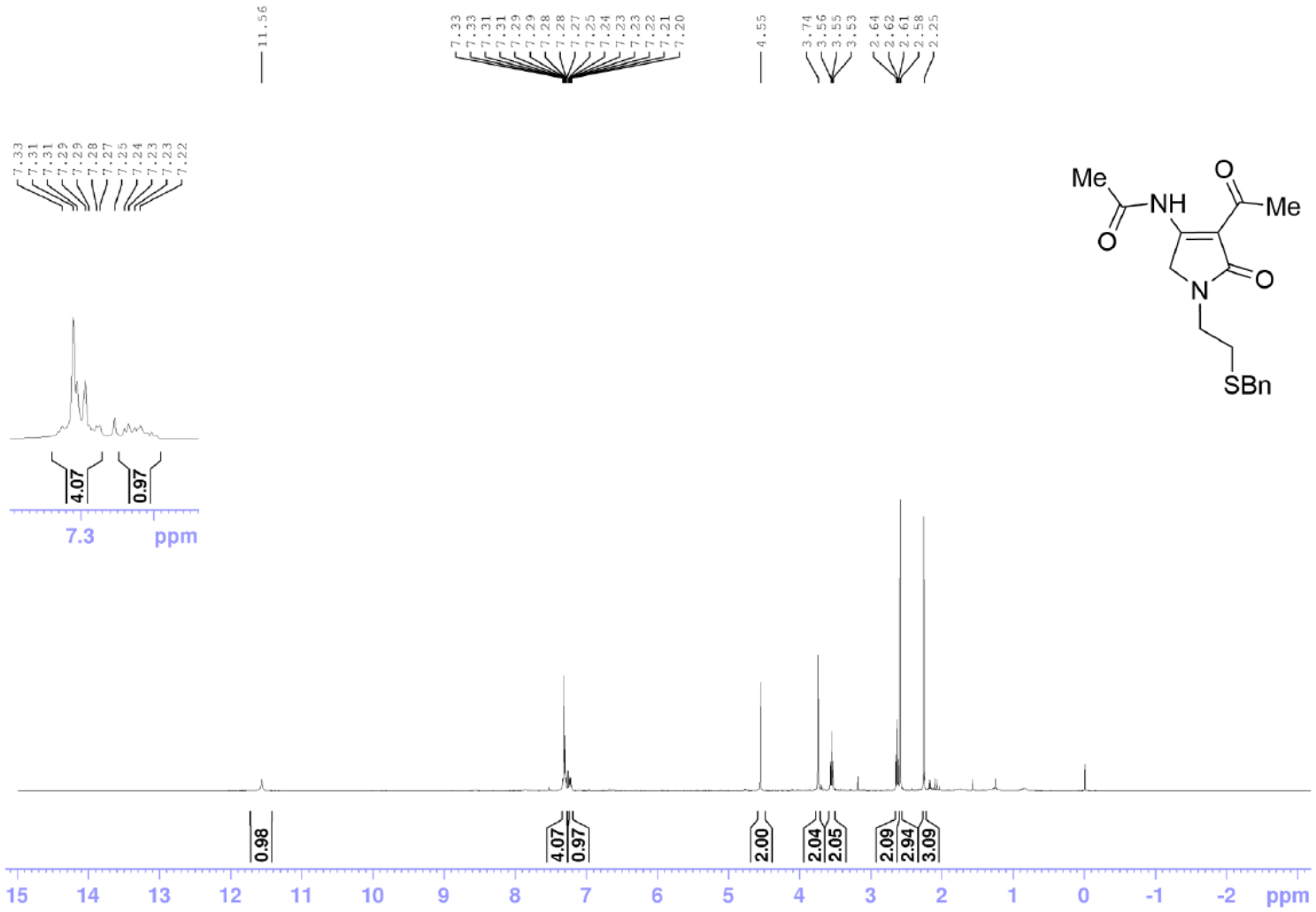
Edited HSQC spectrum of **19** ($(CD_3)_2SO$)



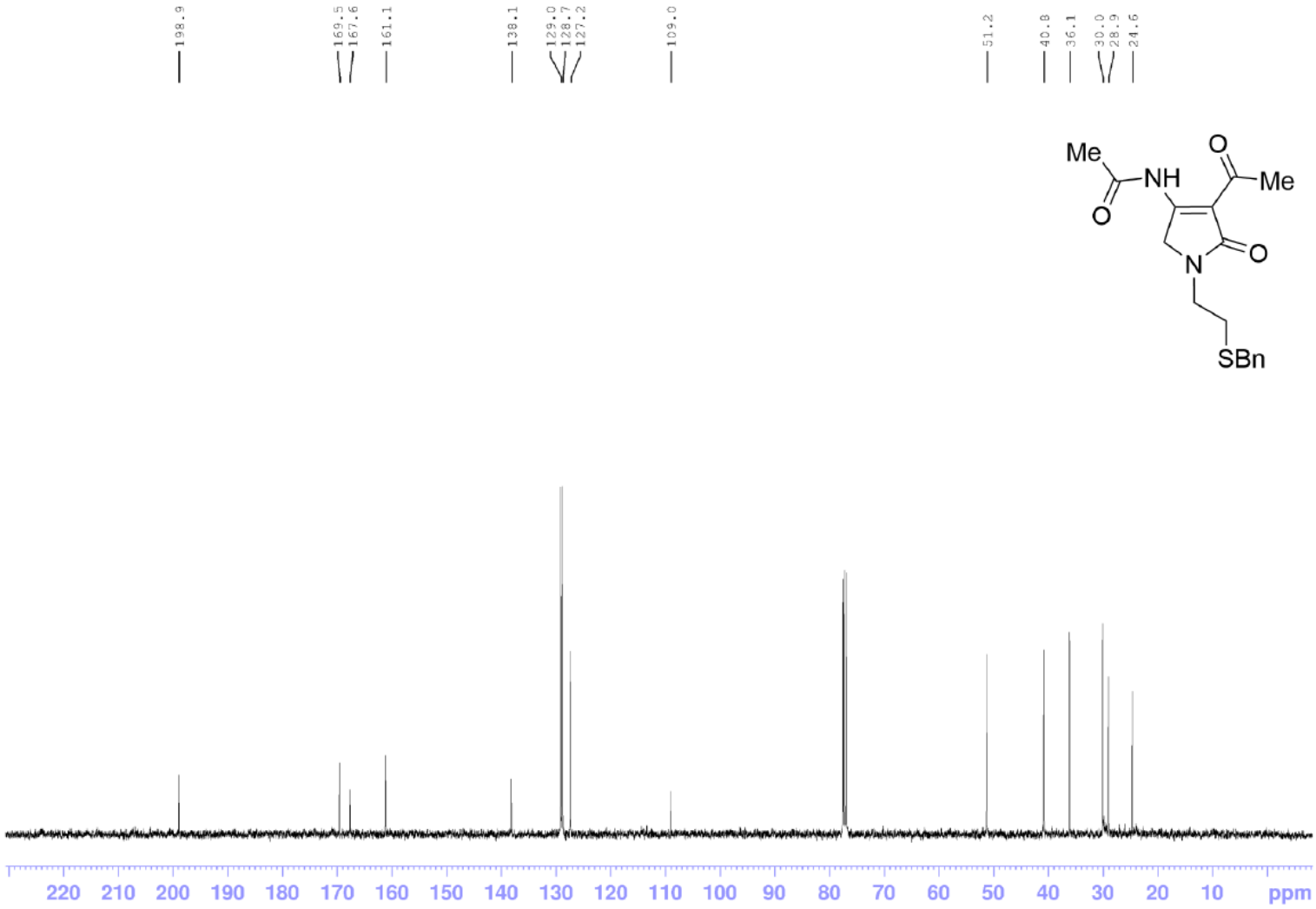
HMBC spectrum of **19** ($(CD_3)_2SO$)



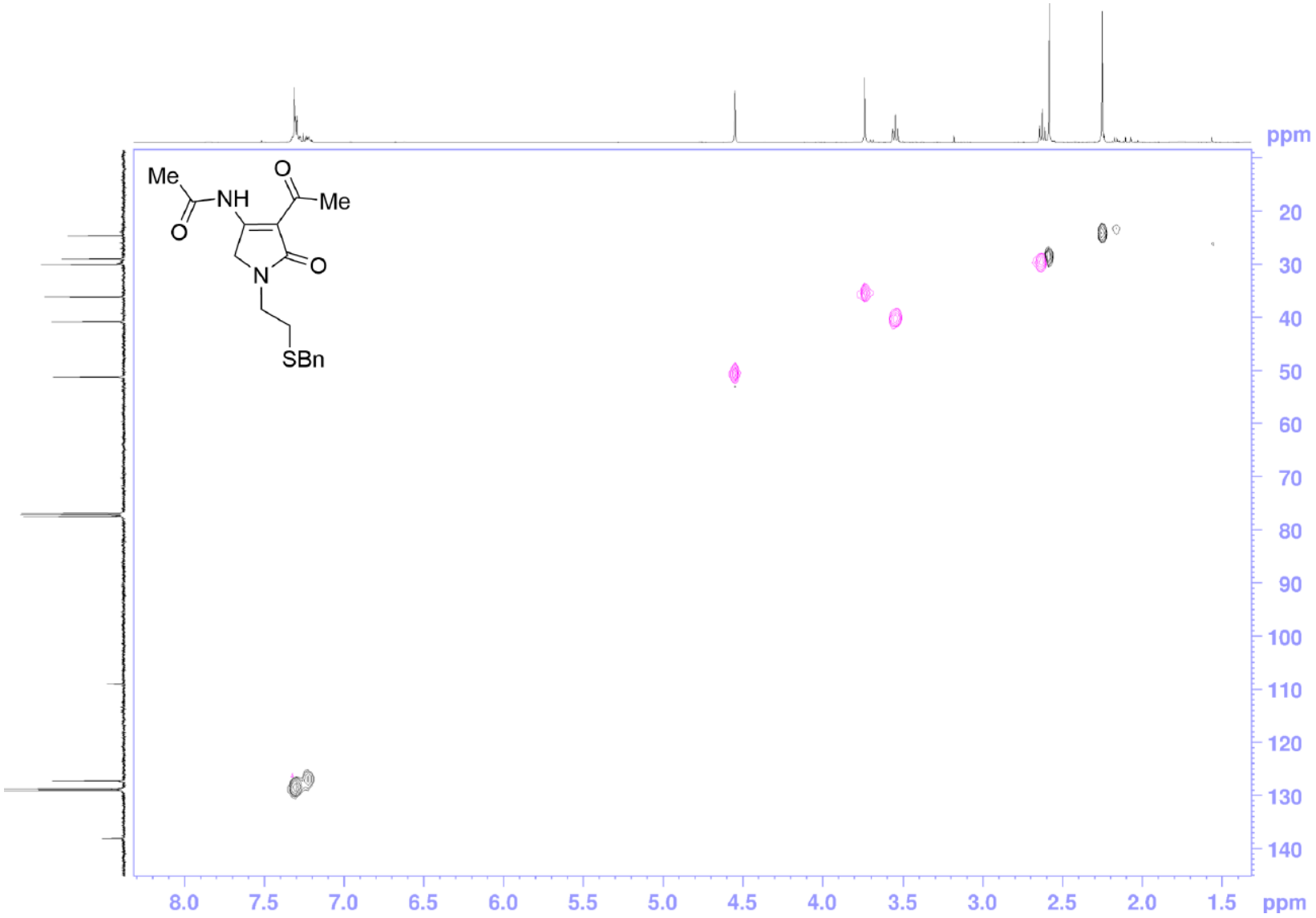
^{1}H NMR spectrum of **20** (400 MHz, $CDCl_3$)



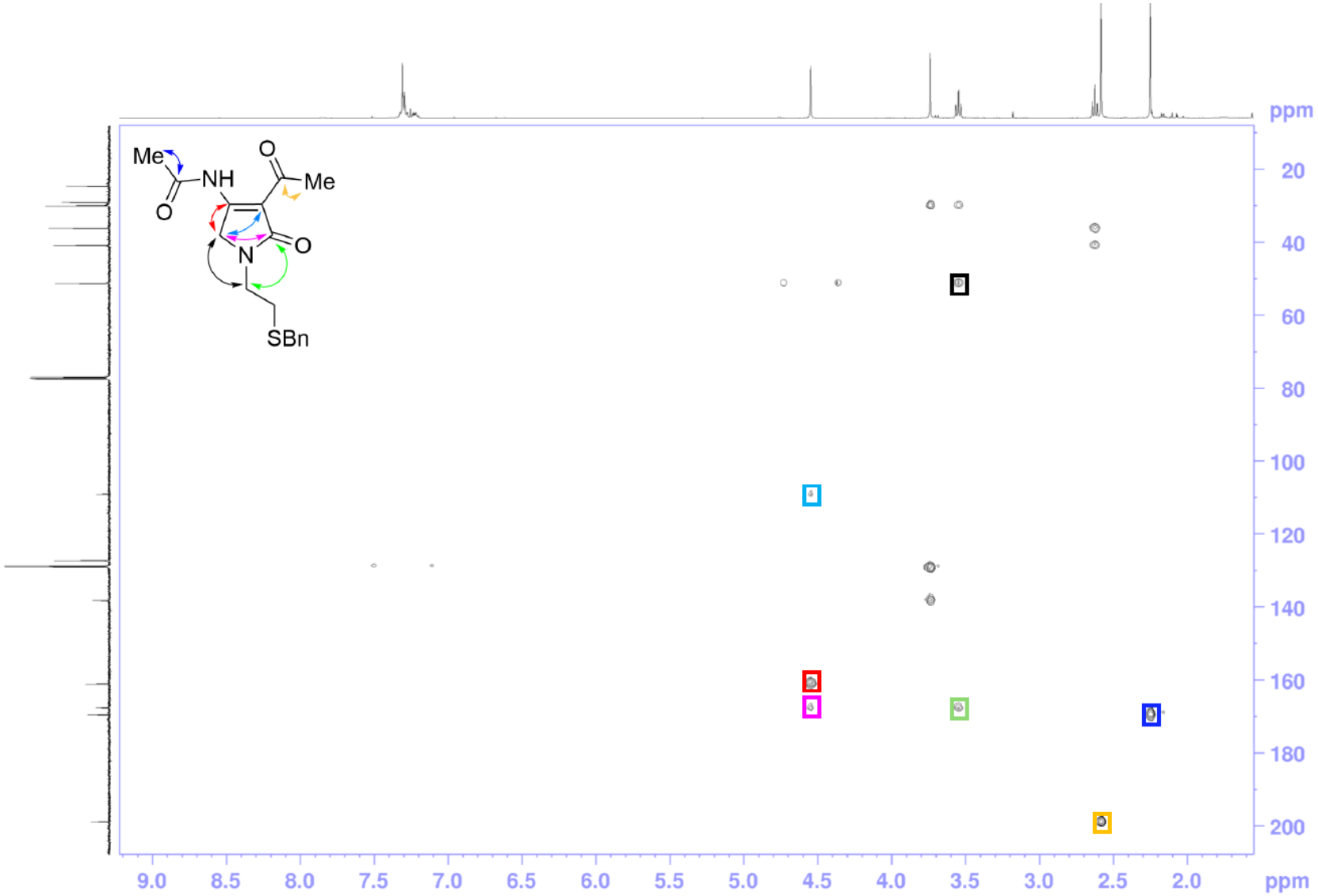
^{13}C NMR spectrum of **20** (100 MHz, $CDCl_3$)



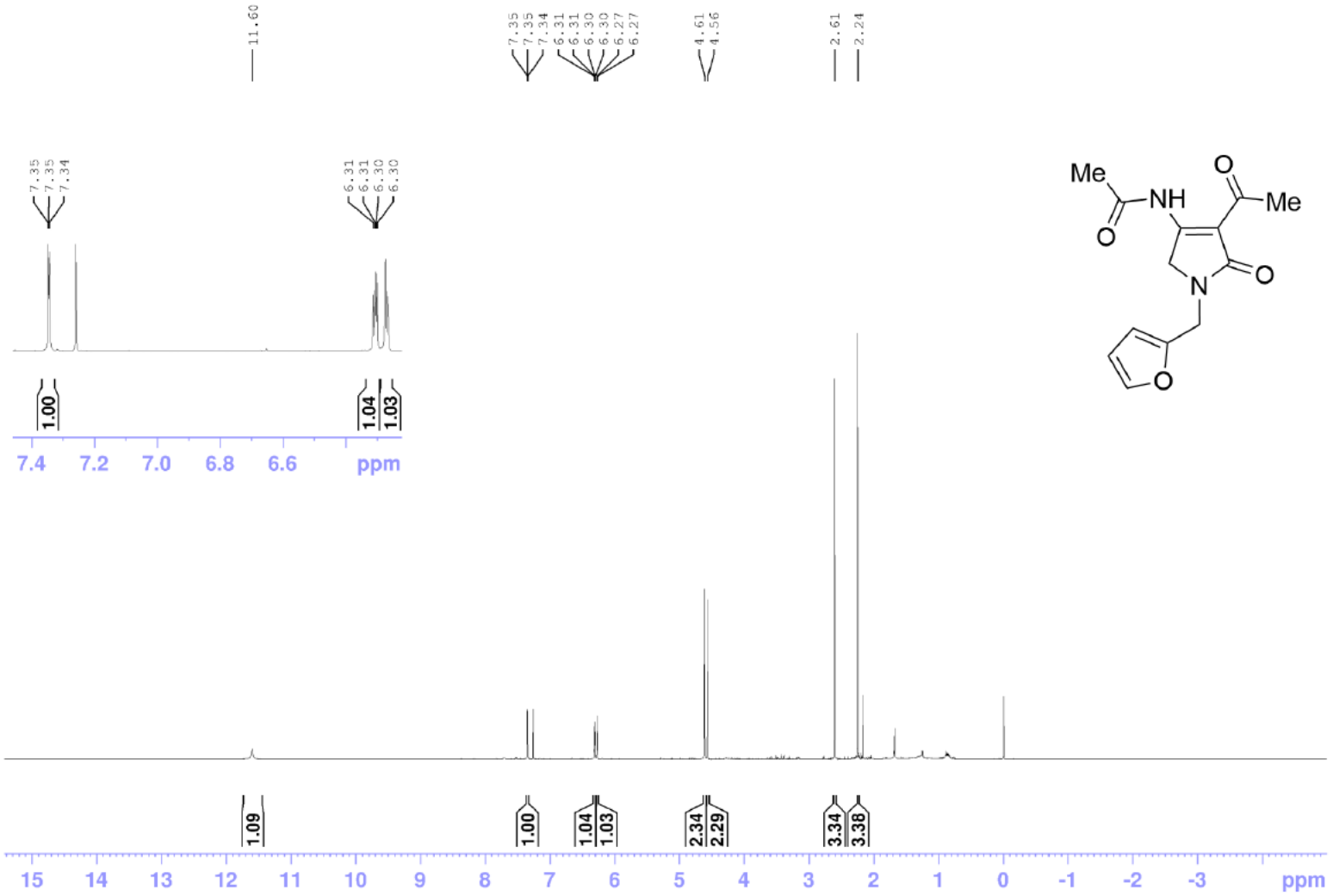
Edited HSQC spectrum of **20** ($CDCl_3$)



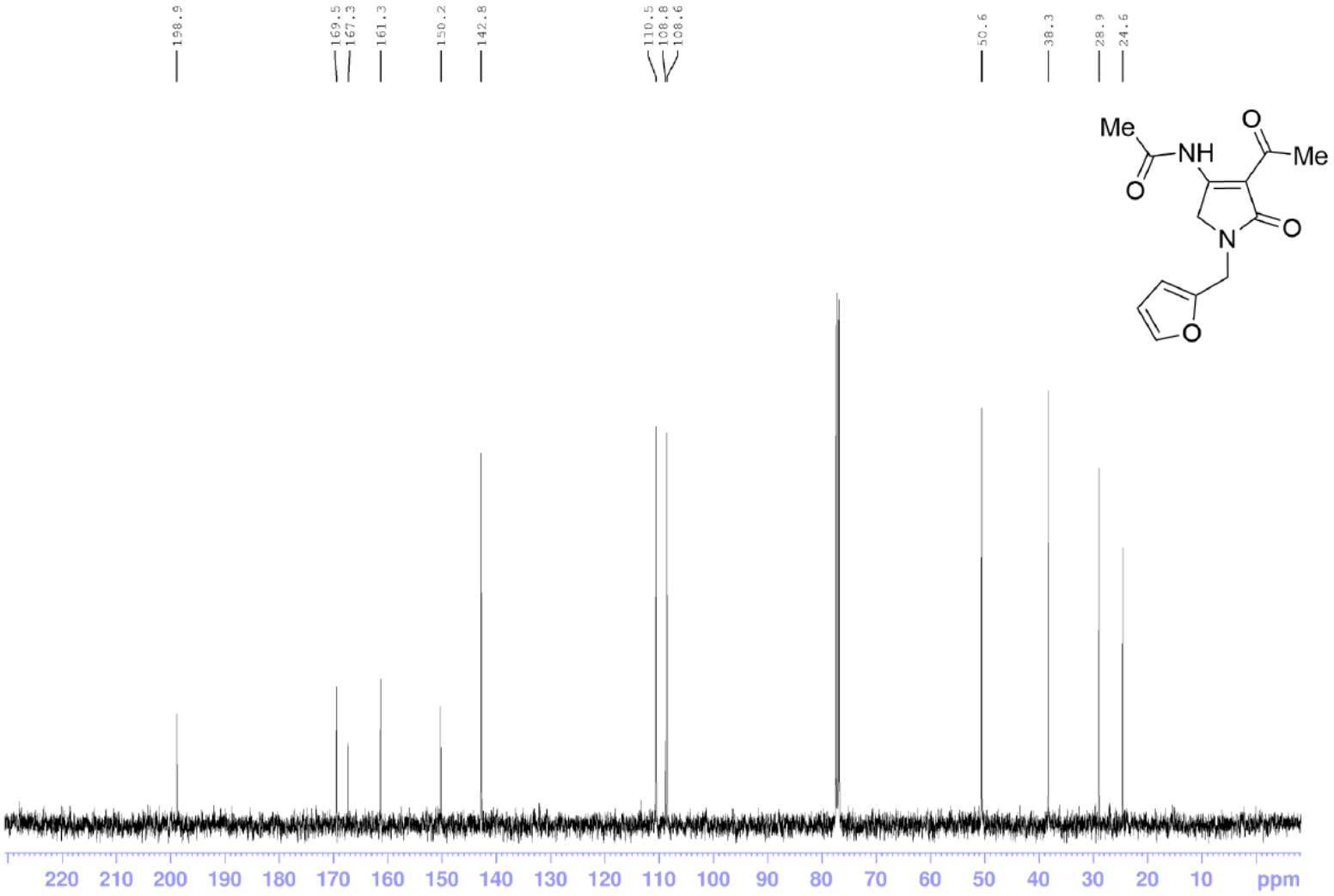
HMBC spectrum of **20** ($CDCl_3$)



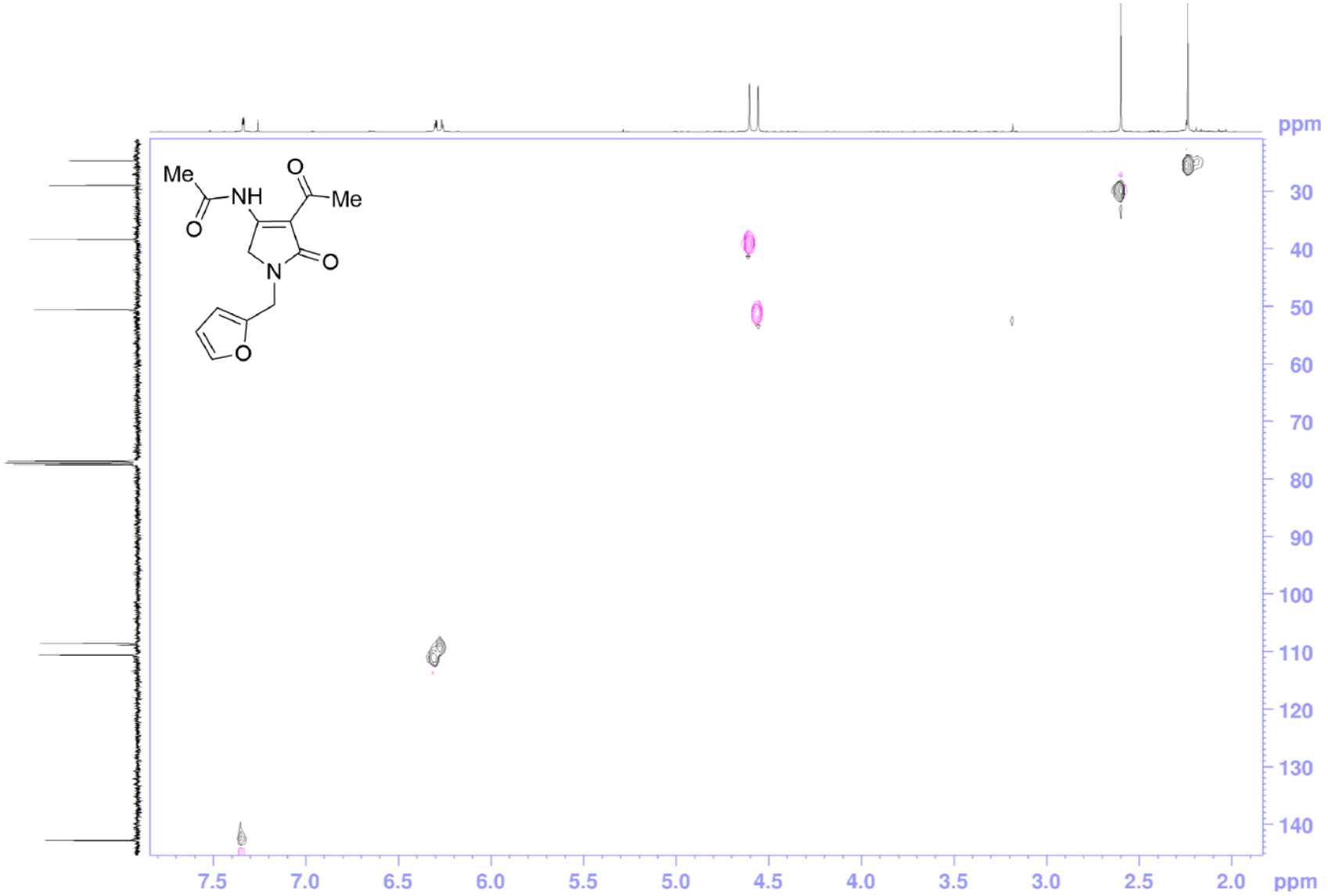
^{1}H NMR spectrum of **21** (400 MHz, $CDCl_3$)



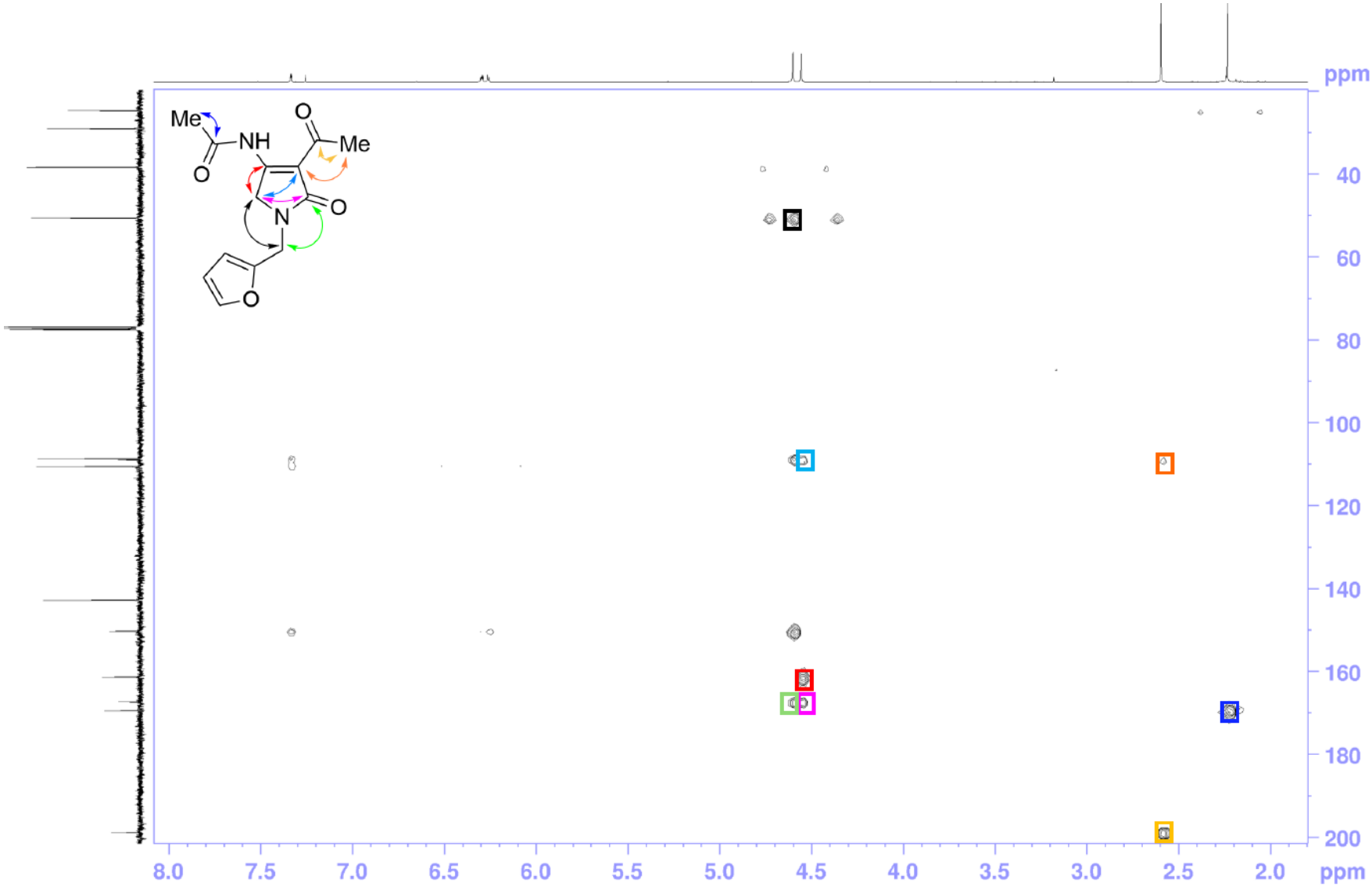
^{13}C NMR spectrum of **21** (100 MHz, $CDCl_3$)



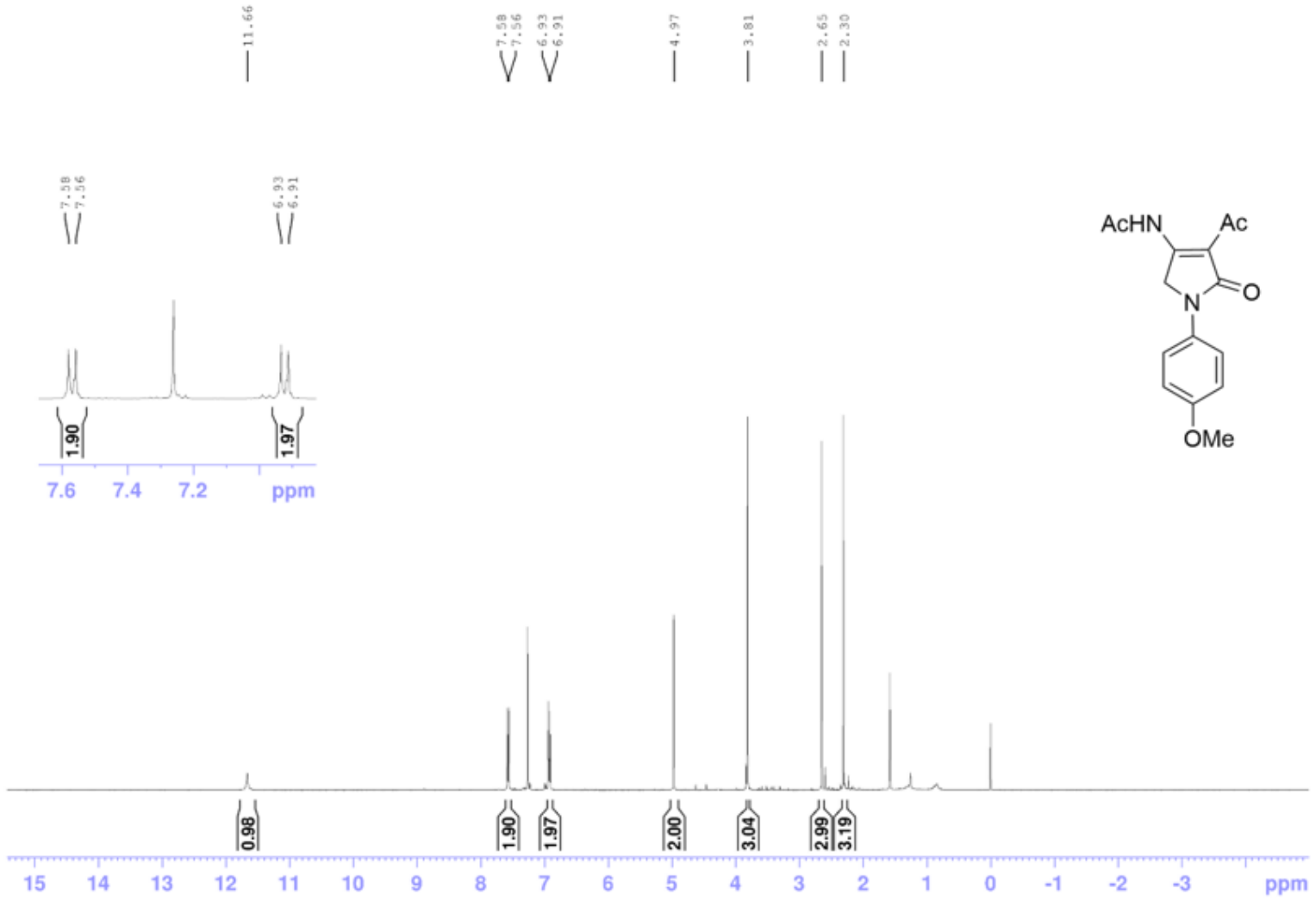
Edited HSQC spectrum of **21** ($CDCl_3$)



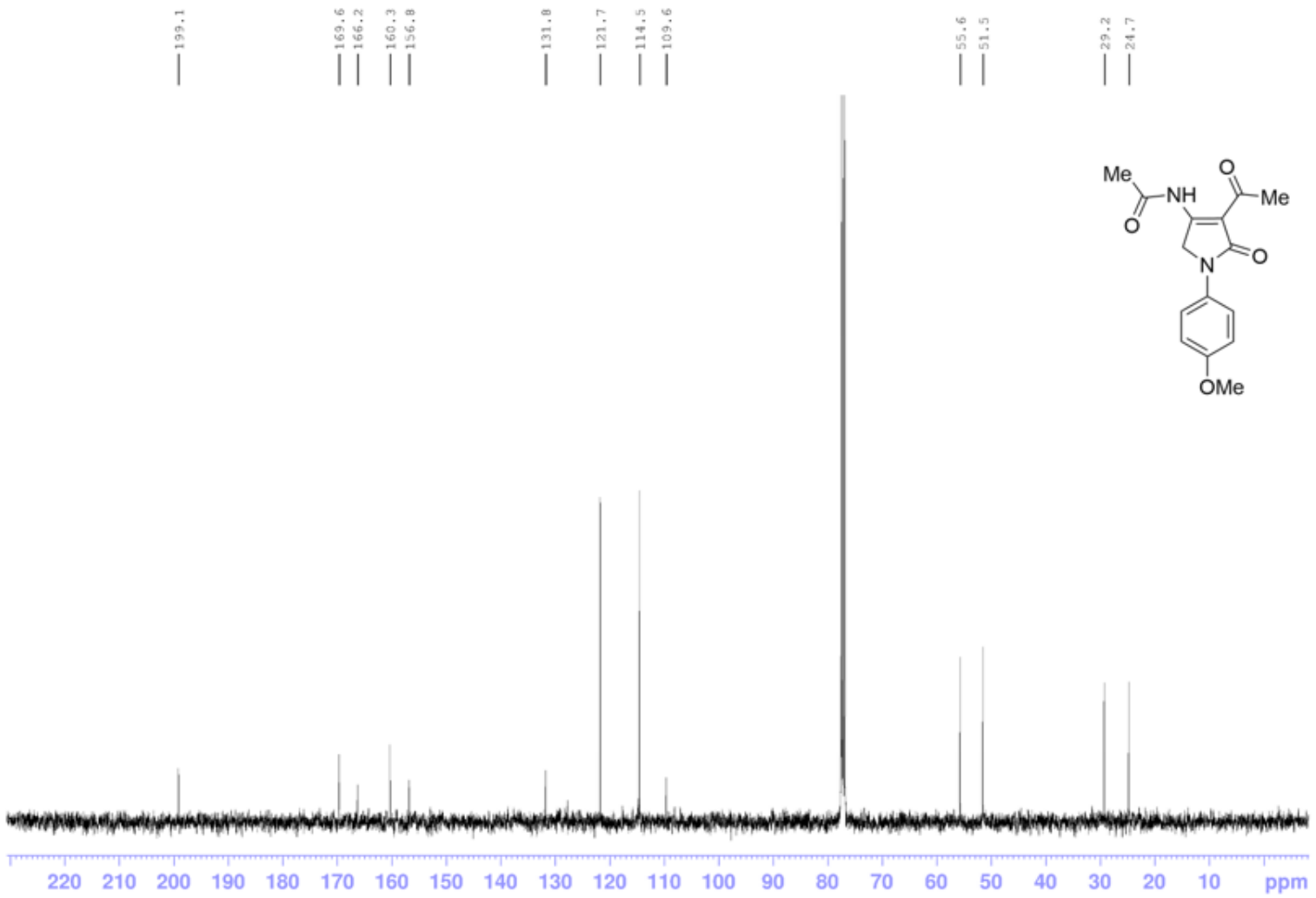
HMBC spectrum of **21** ($CDCl_3$)



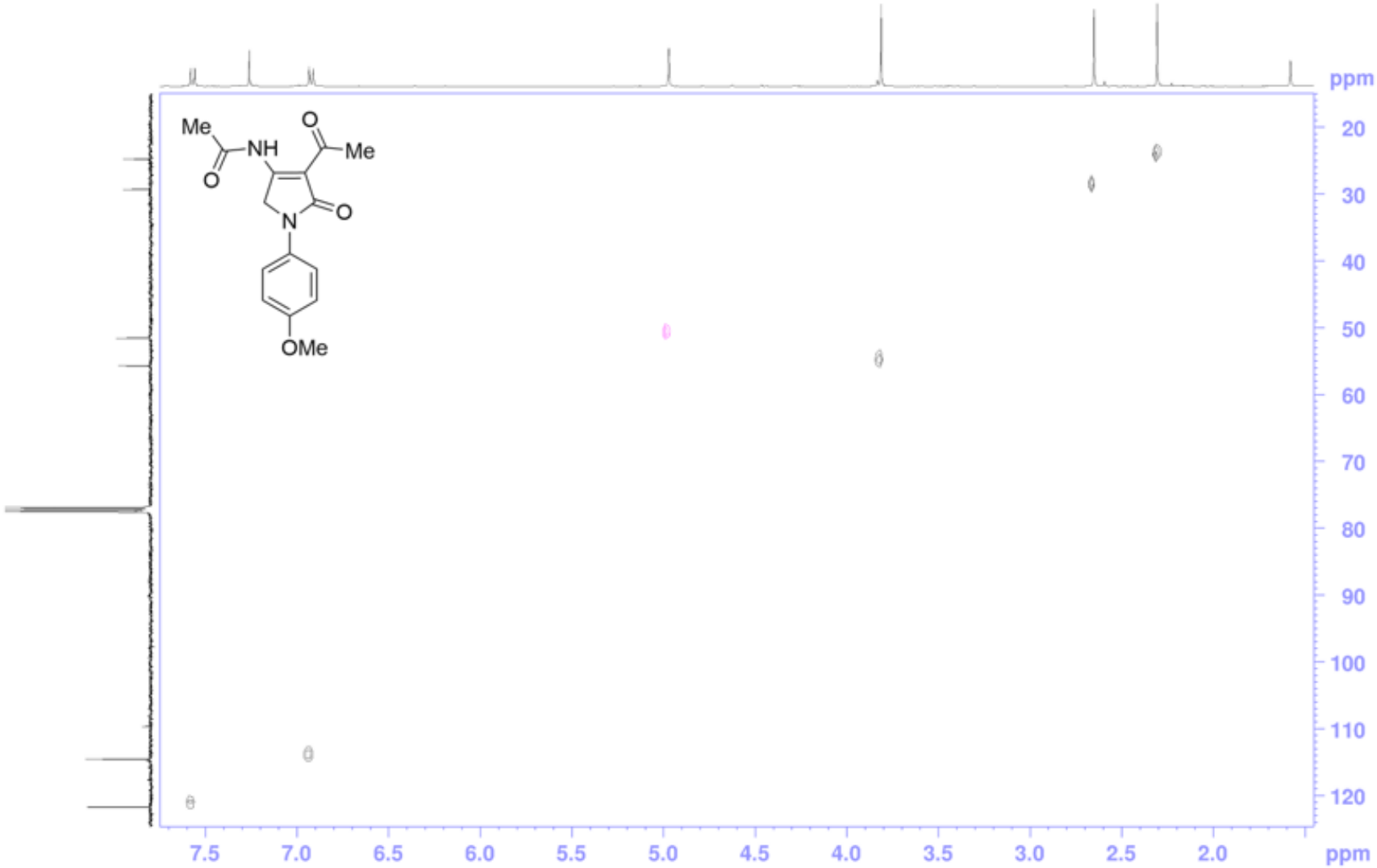
^{1}H NMR spectrum of **22** (400 MHz, $CDCl_3$)



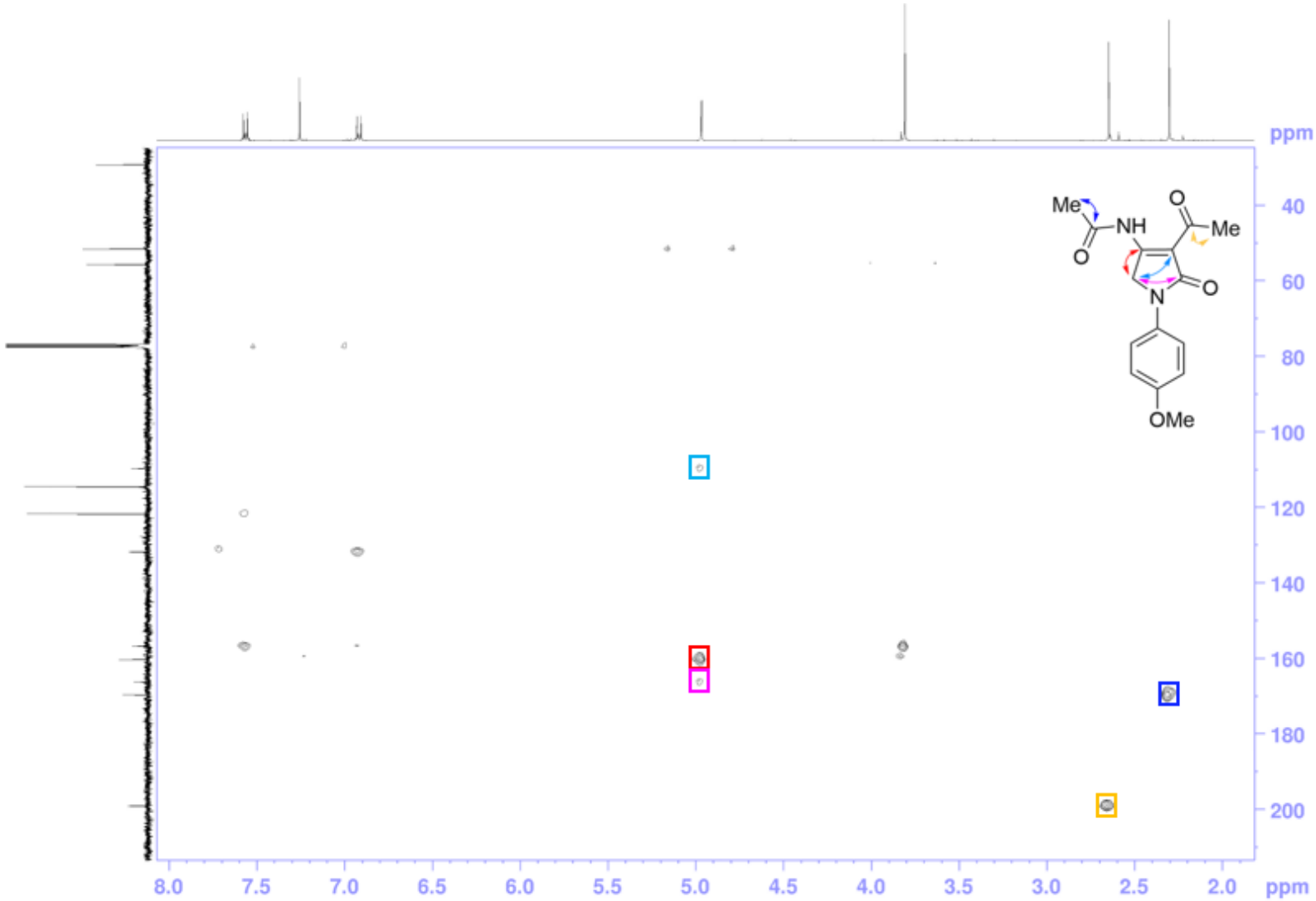
^{13}C NMR spectrum of **22** (100 MHz, $CDCl_3$)



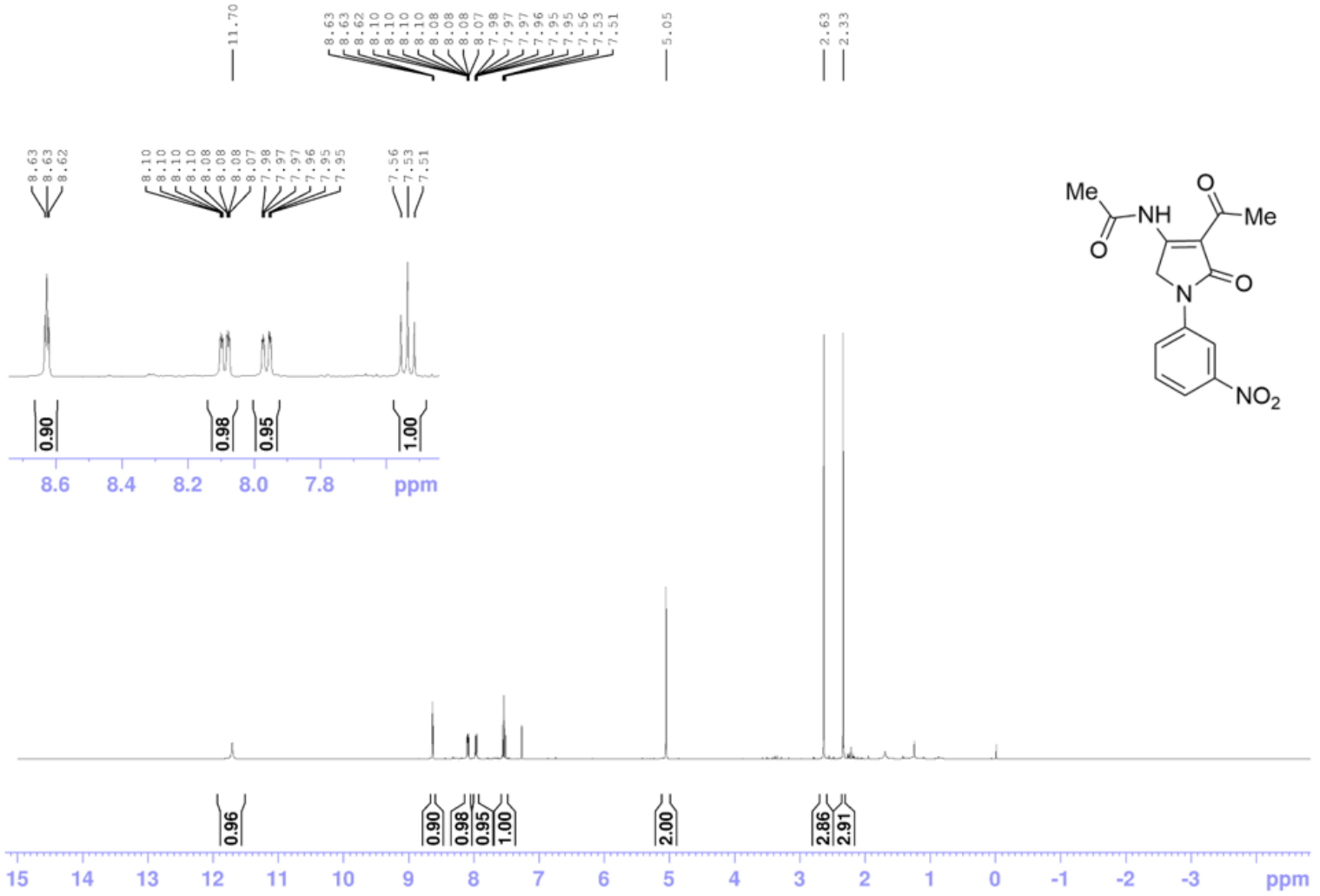
Edited HSQC spectrum of **22** ($CDCl_3$)



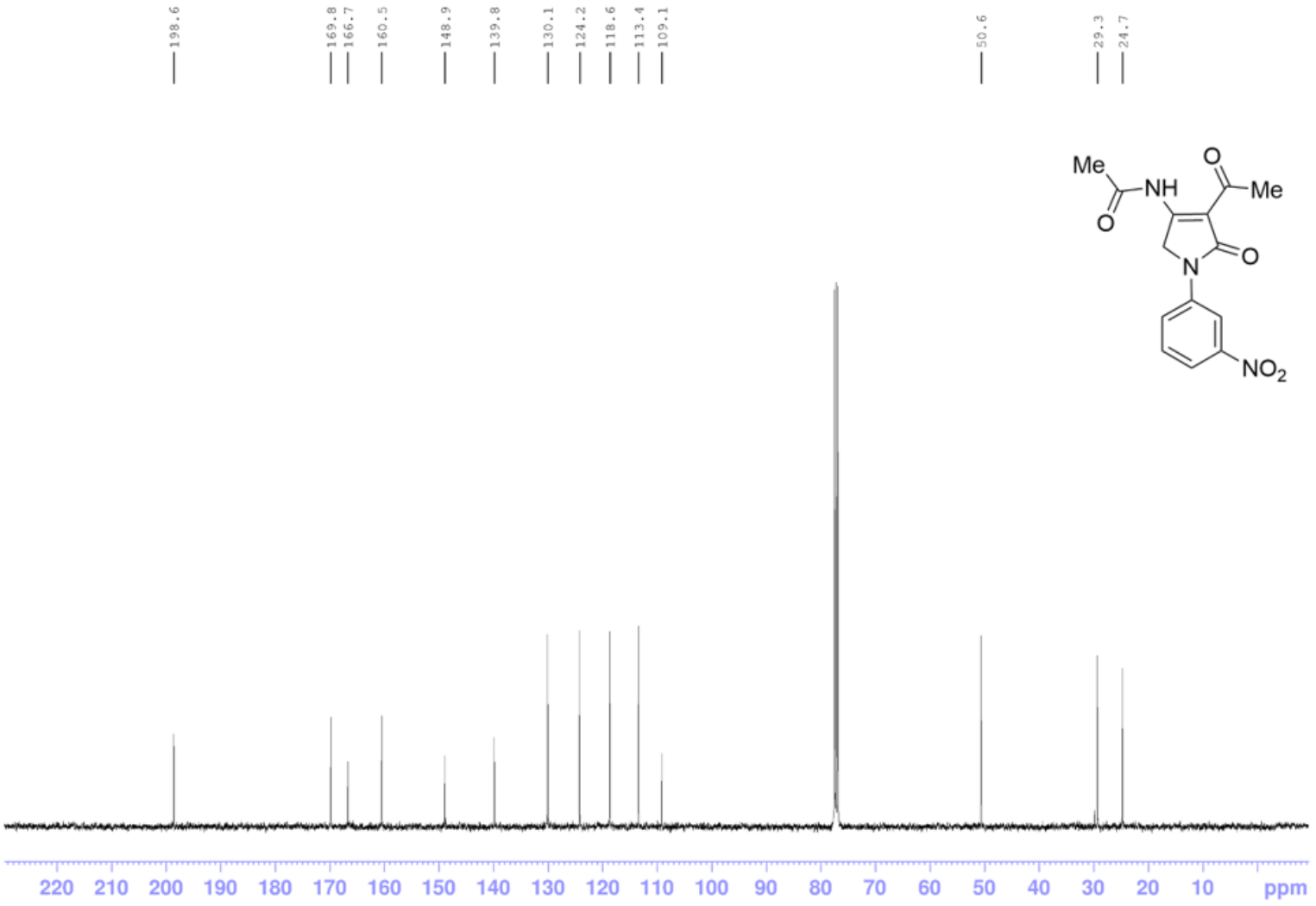
HMBC spectrum of **22** ($CDCl_3$)



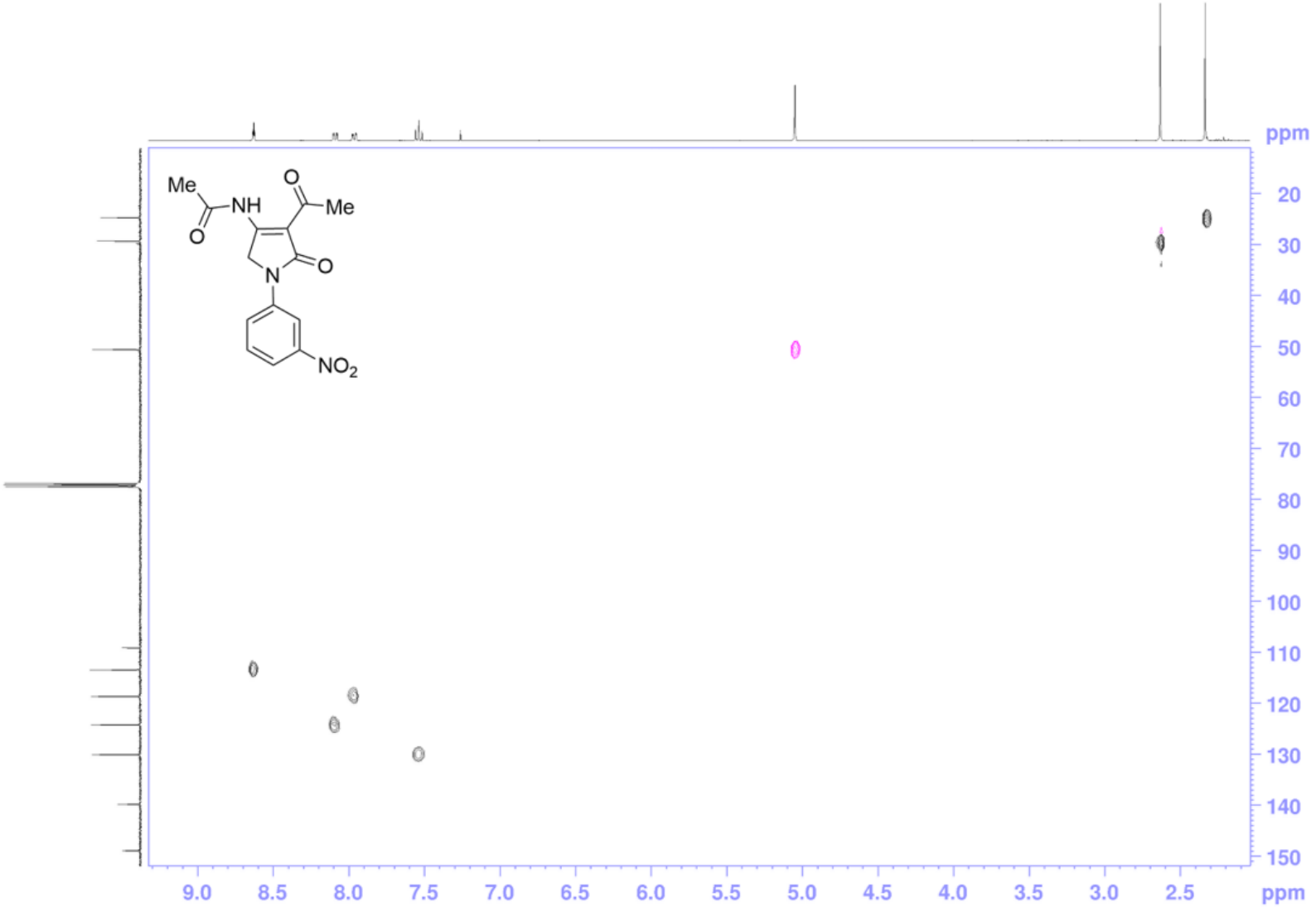
^{1}H NMR spectrum of **23** (400 MHz, $CDCl_3$)



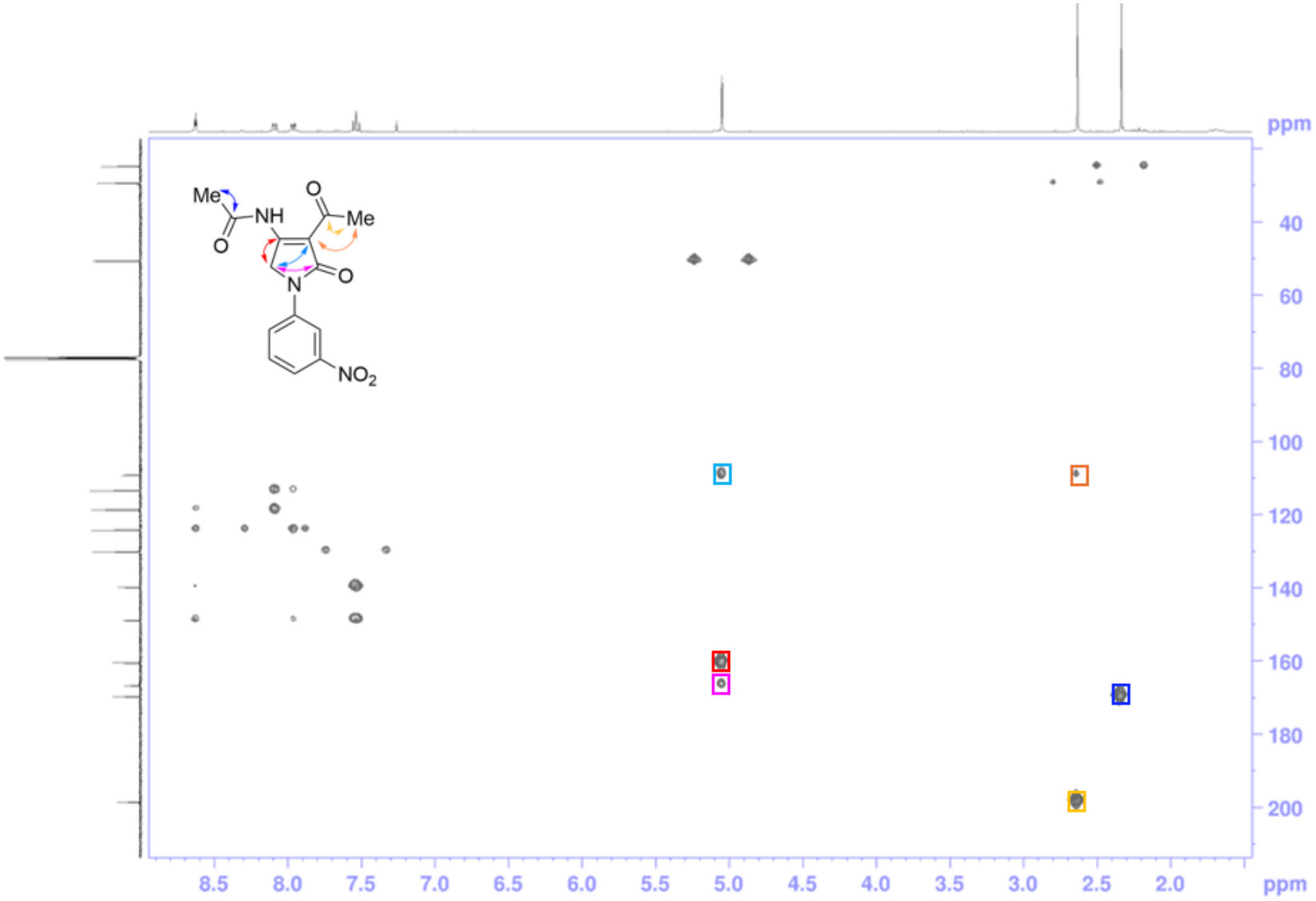
^{13}C NMR spectrum of **23** (100 MHz, $CDCl_3$)



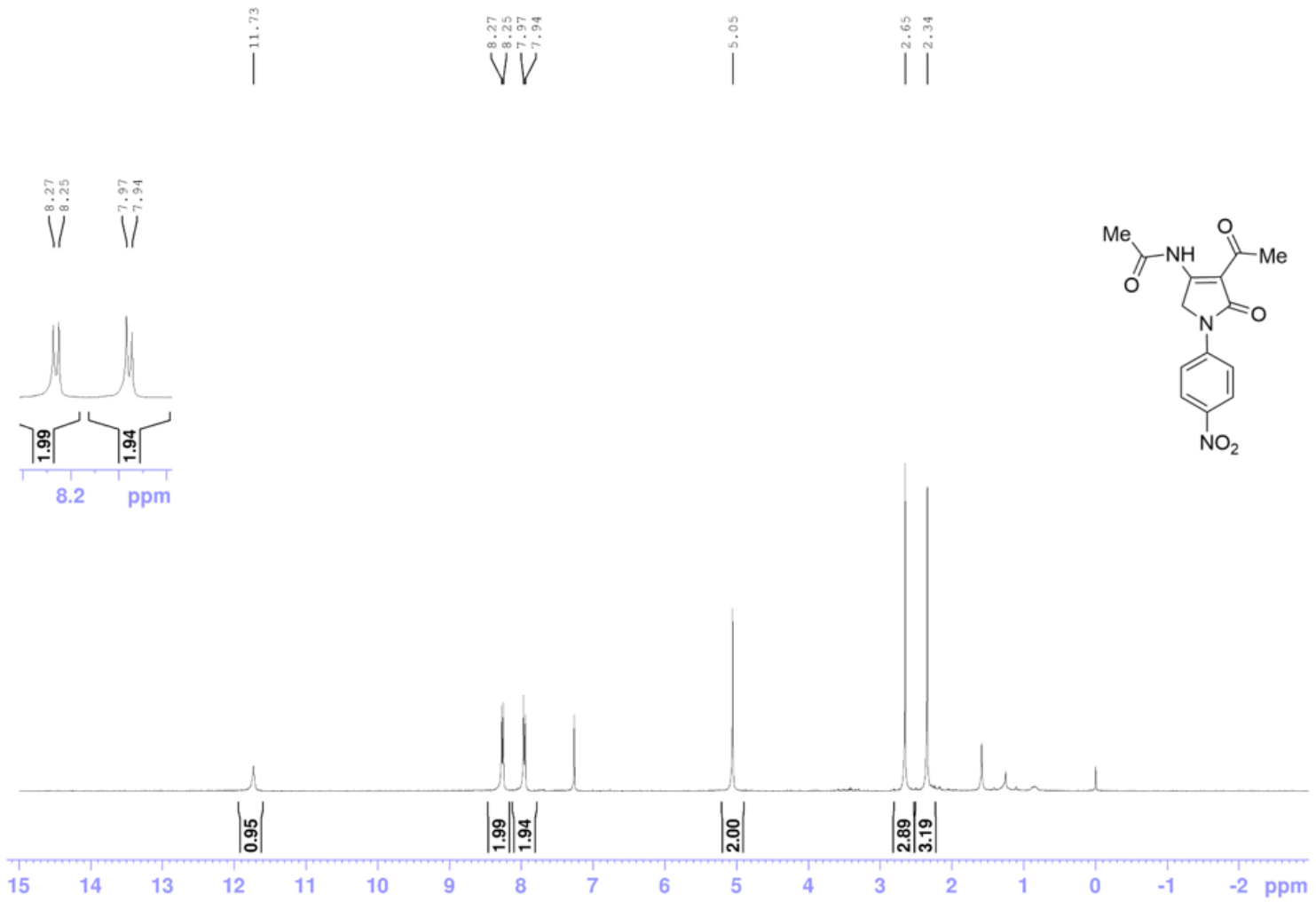
Edited HSQC spectrum of **23** ($CDCl_3$)



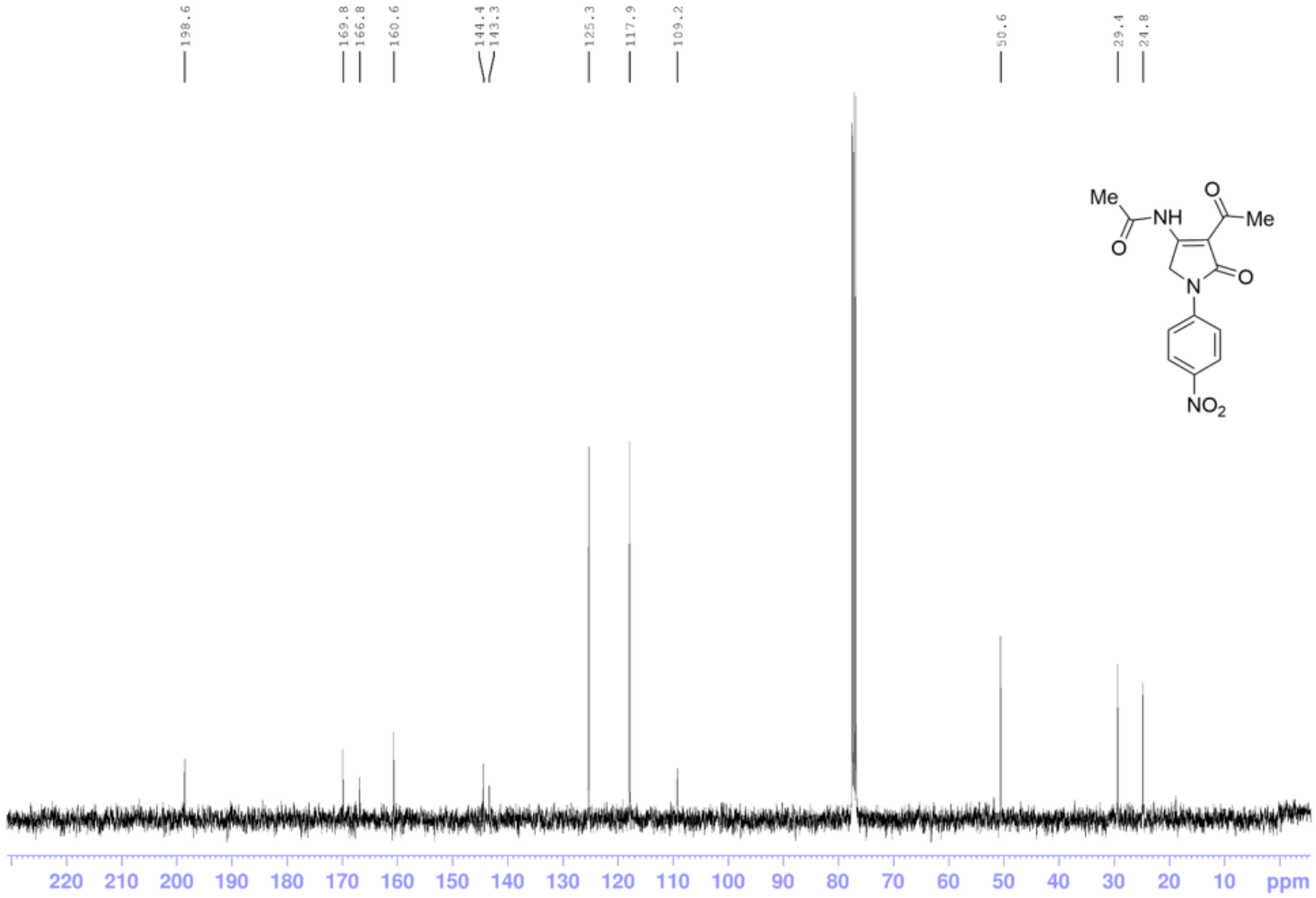
HMBC spectrum of **23** ($CDCl_3$)



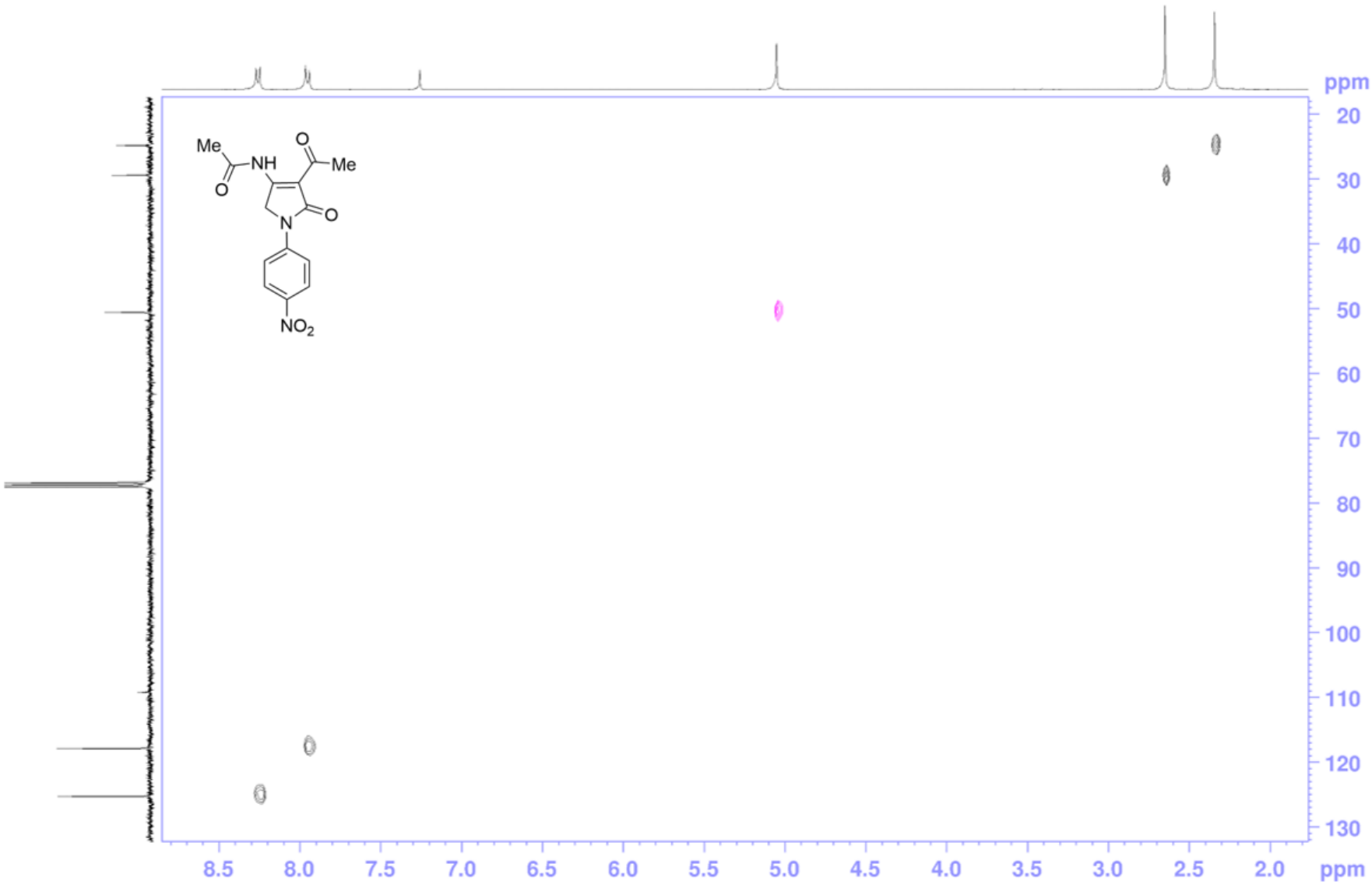
^{1}H NMR spectrum of **24** (400 MHz, $CDCl_3$)



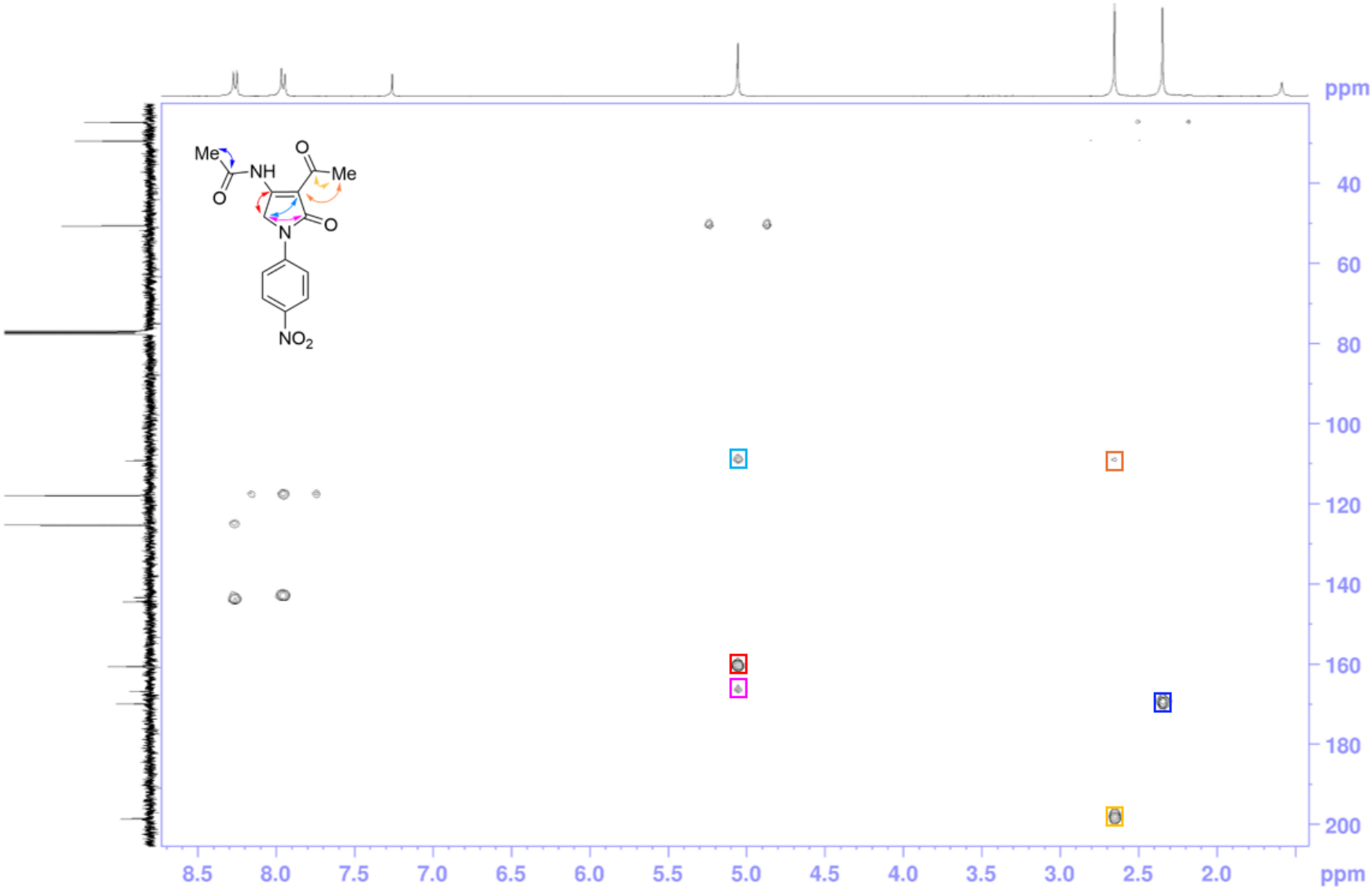
^{13}C NMR spectrum of **24** (100 MHz, $CDCl_3$)



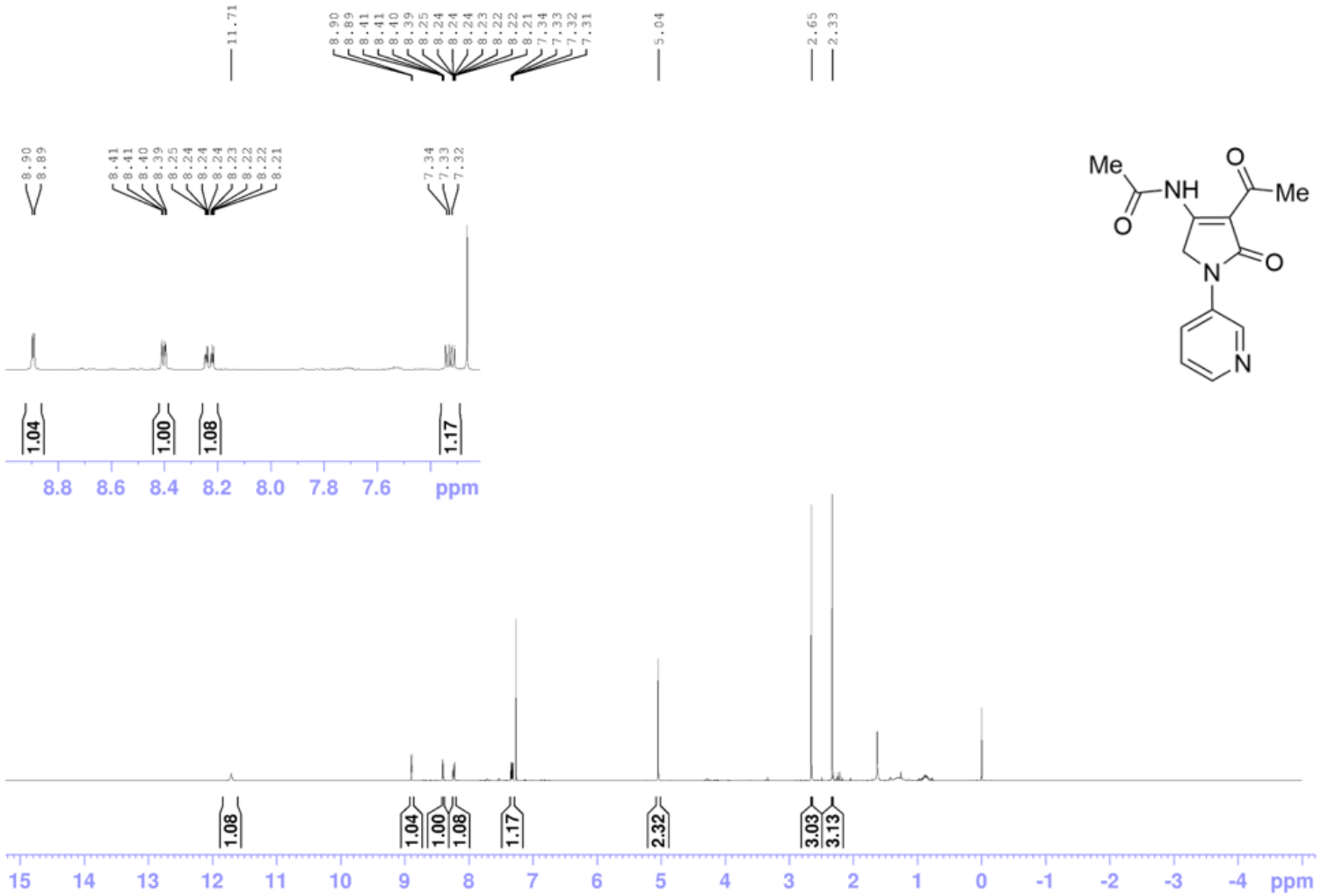
Edited HSQC spectrum of **24** ($CDCl_3$)



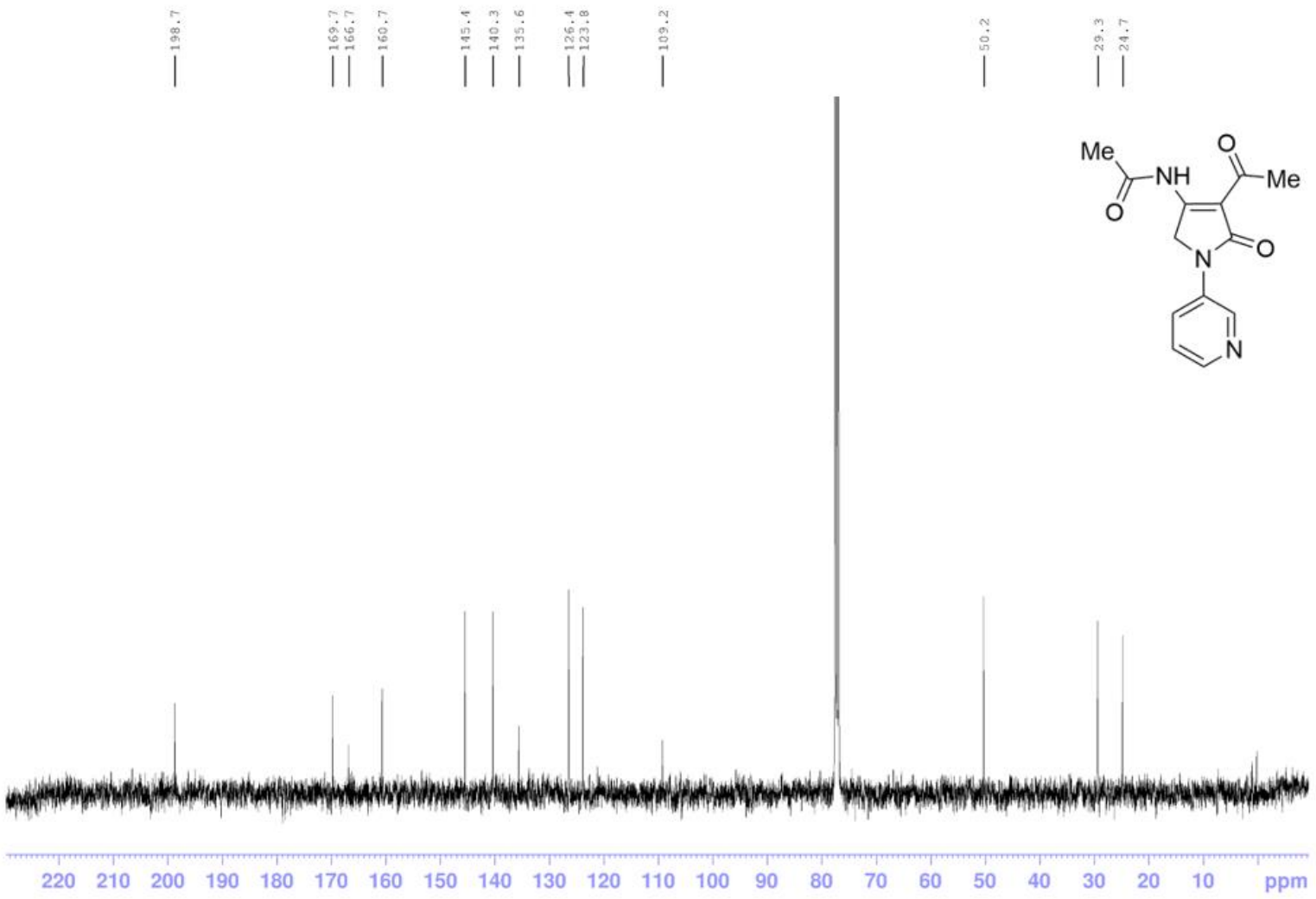
HMBC spectrum of **24** ($CDCl_3$)



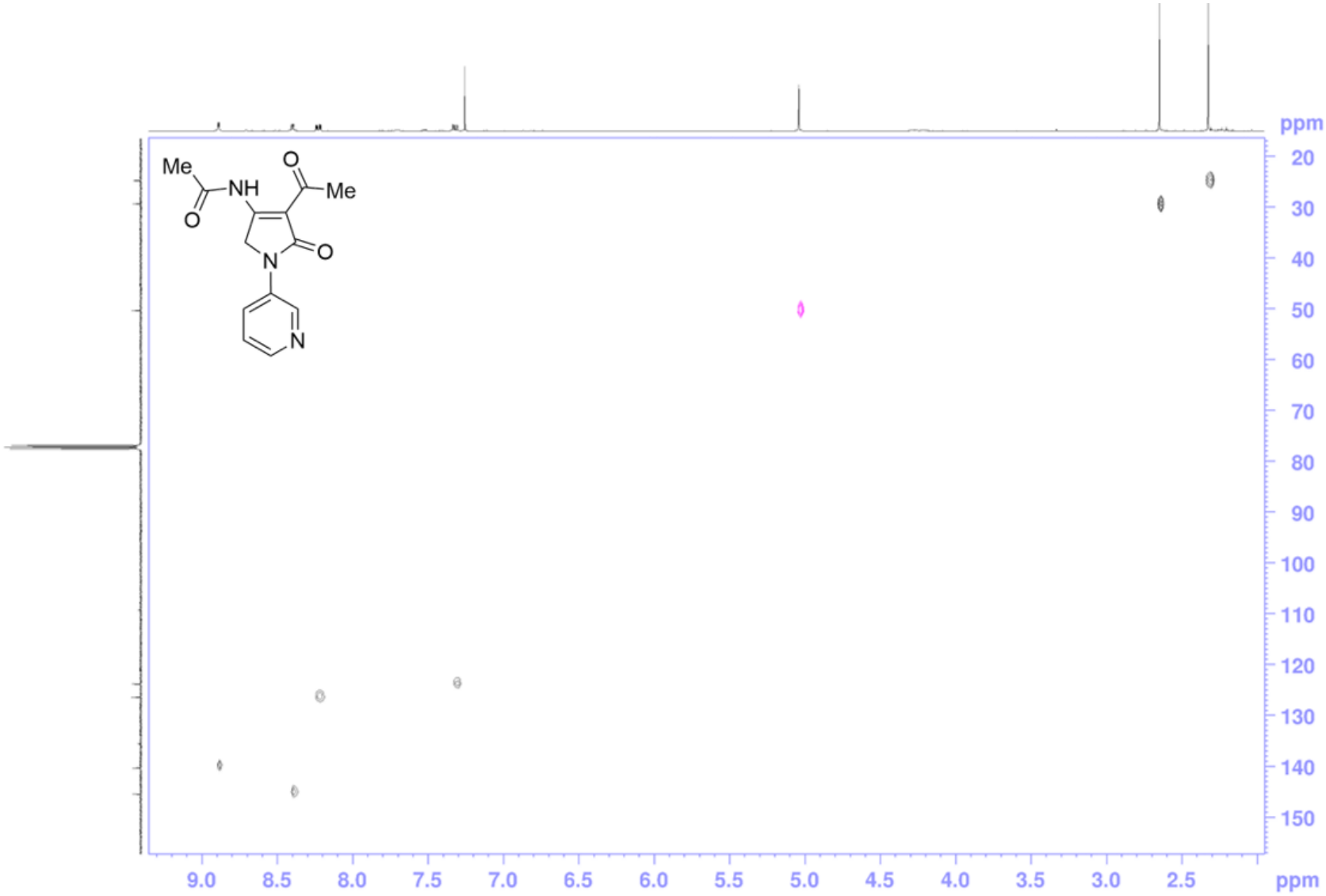
^{1}H NMR spectrum of **25** (400 MHz, $CDCl_3$)



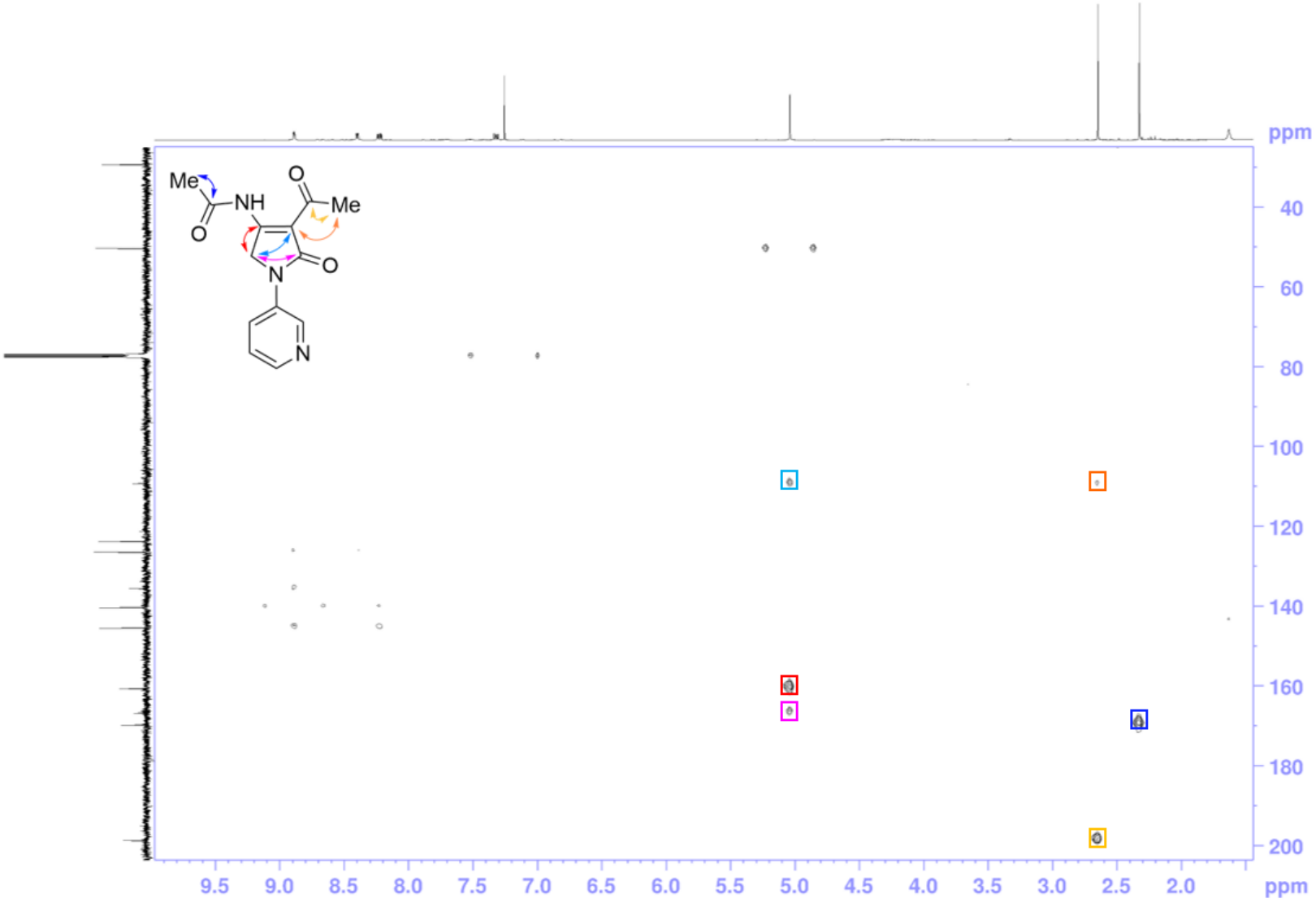
^{13}C NMR spectrum of **25** (100 MHz, $CDCl_3$)



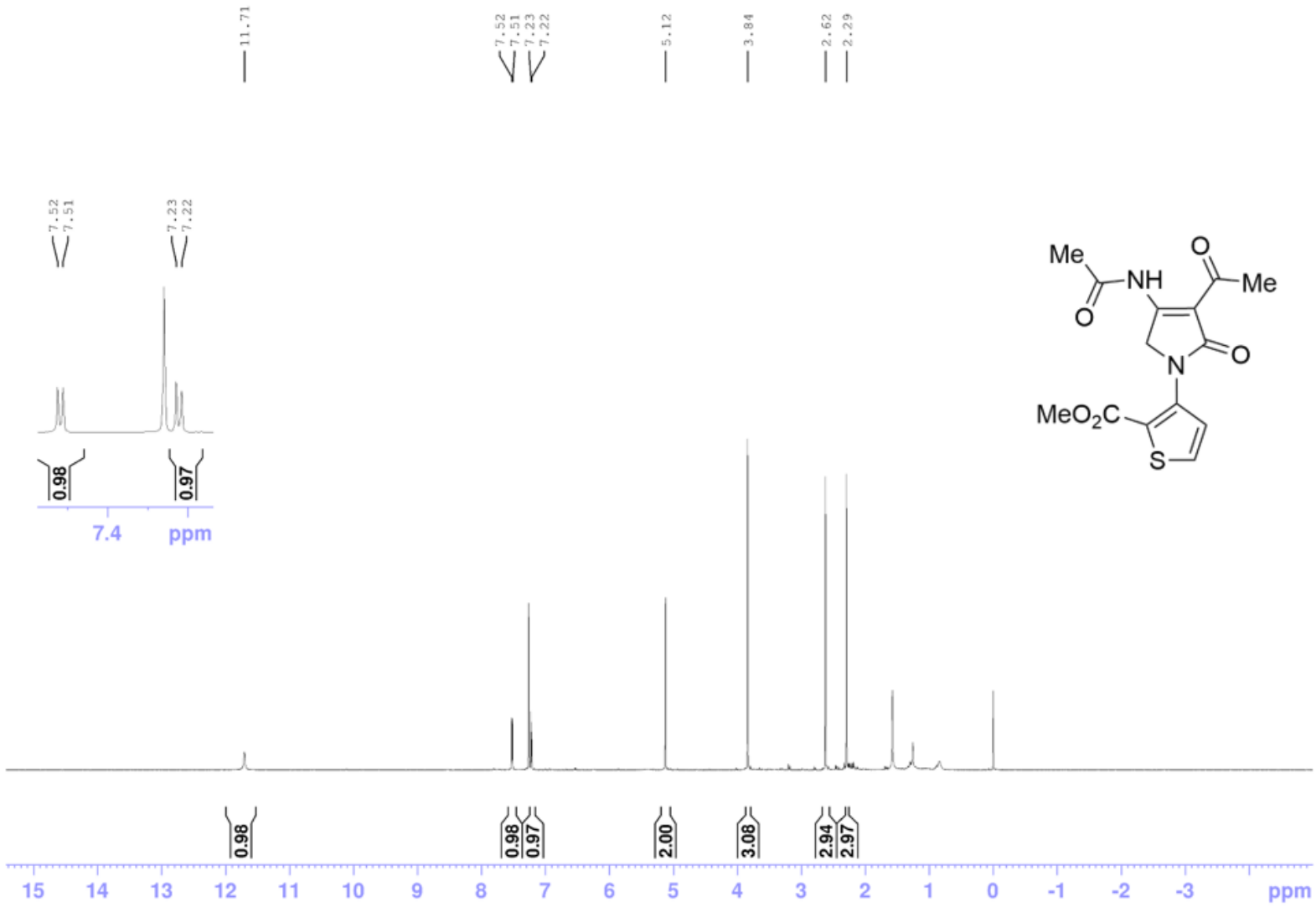
Edited HSQC spectrum of **25** ($CDCl_3$)



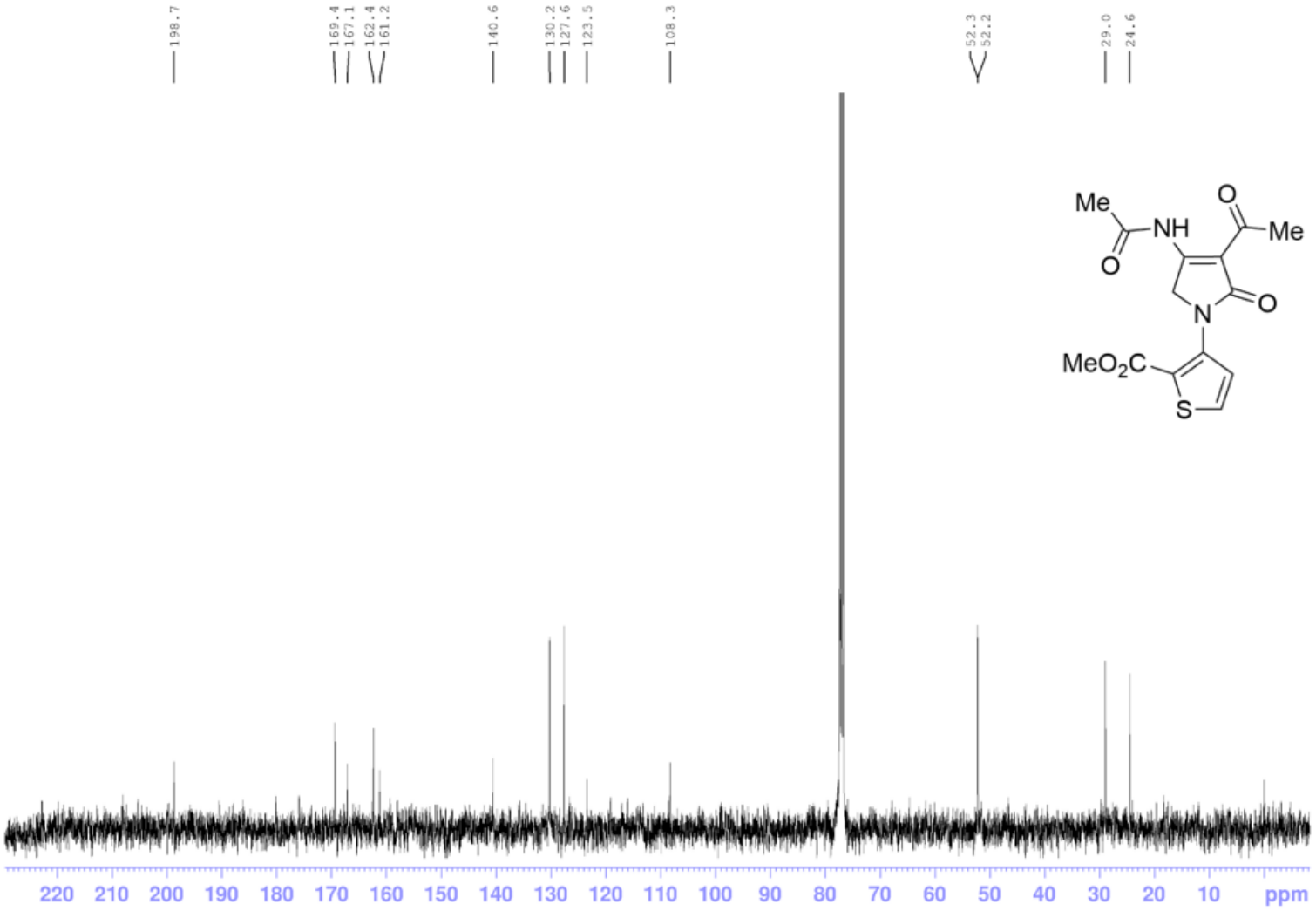
HMBC spectrum of **25** ($CDCl_3$)



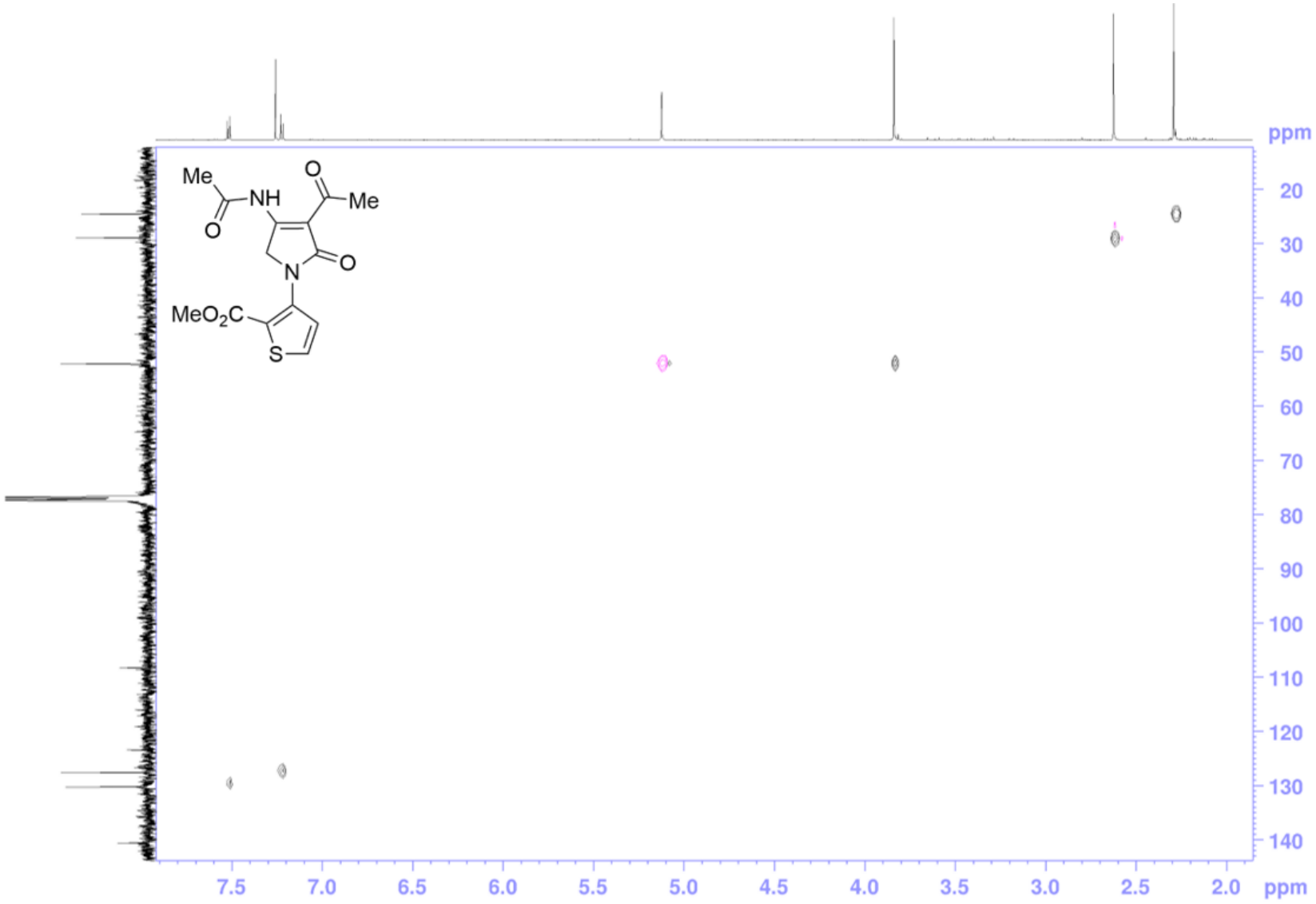
^{1}H NMR spectrum of **26** (400 MHz, $CDCl_3$)



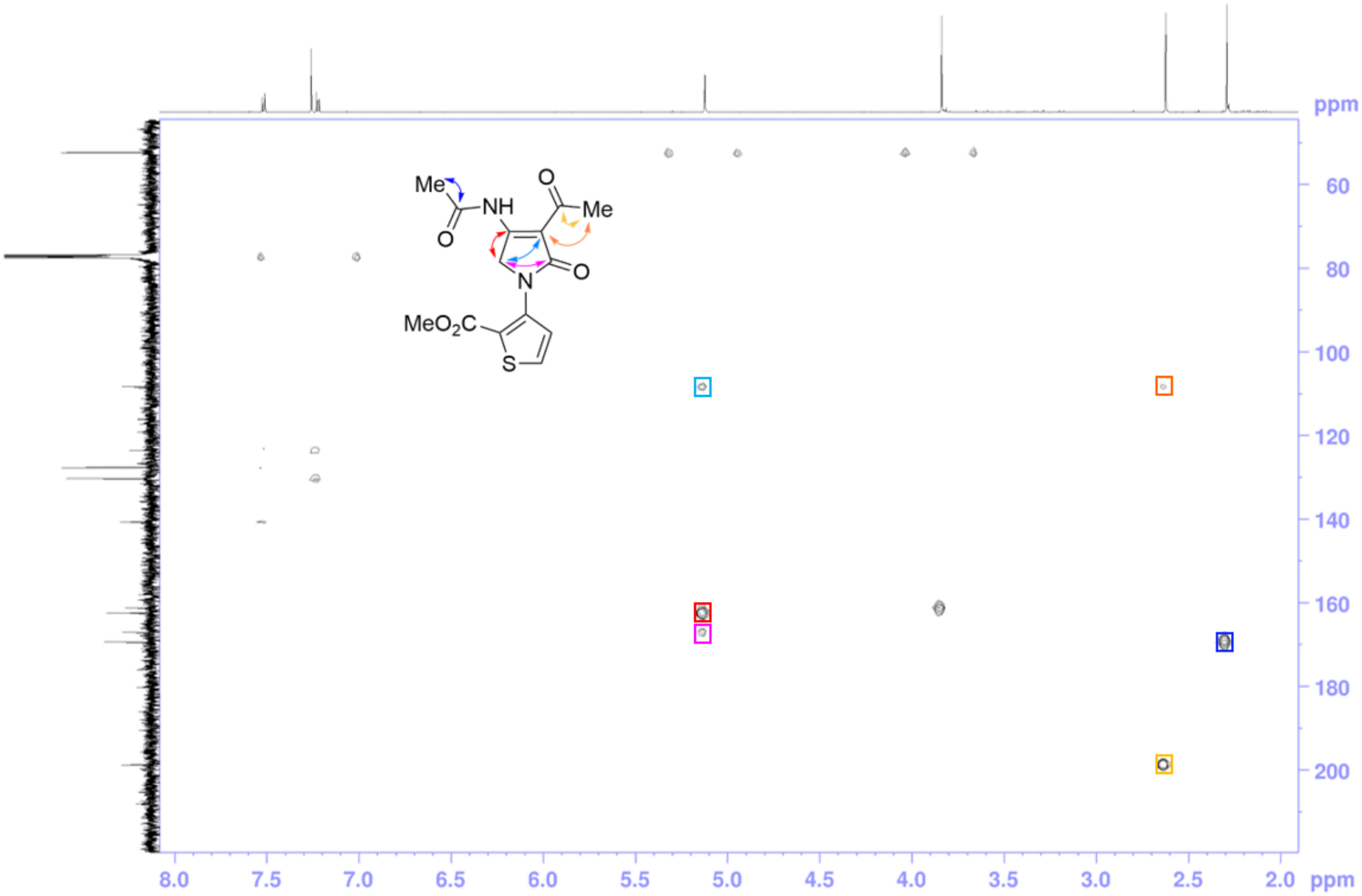
^{13}C NMR spectrum of **26** (100 MHz, $CDCl_3$)



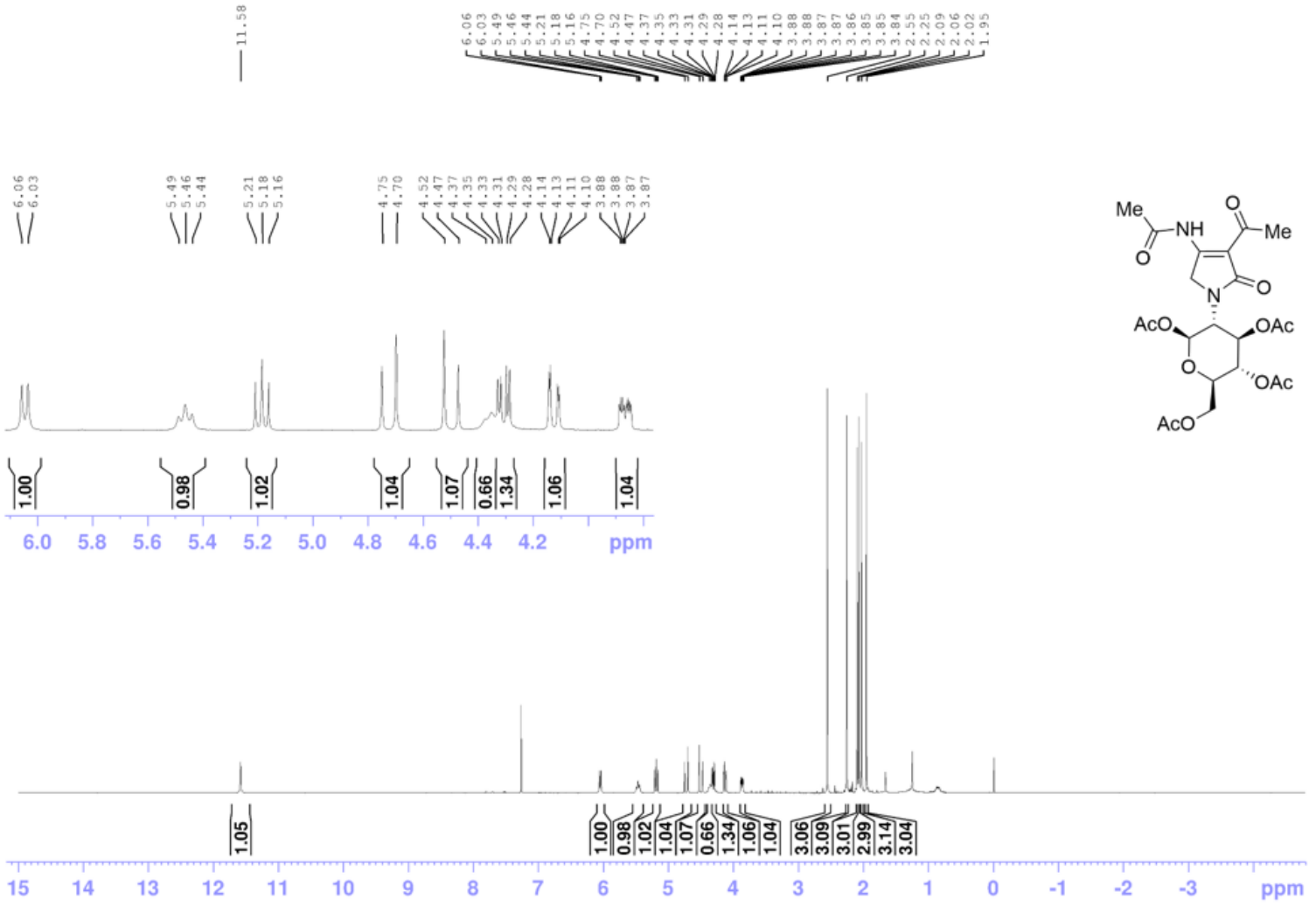
Edited HSQC spectrum of **26** ($CDCl_3$)



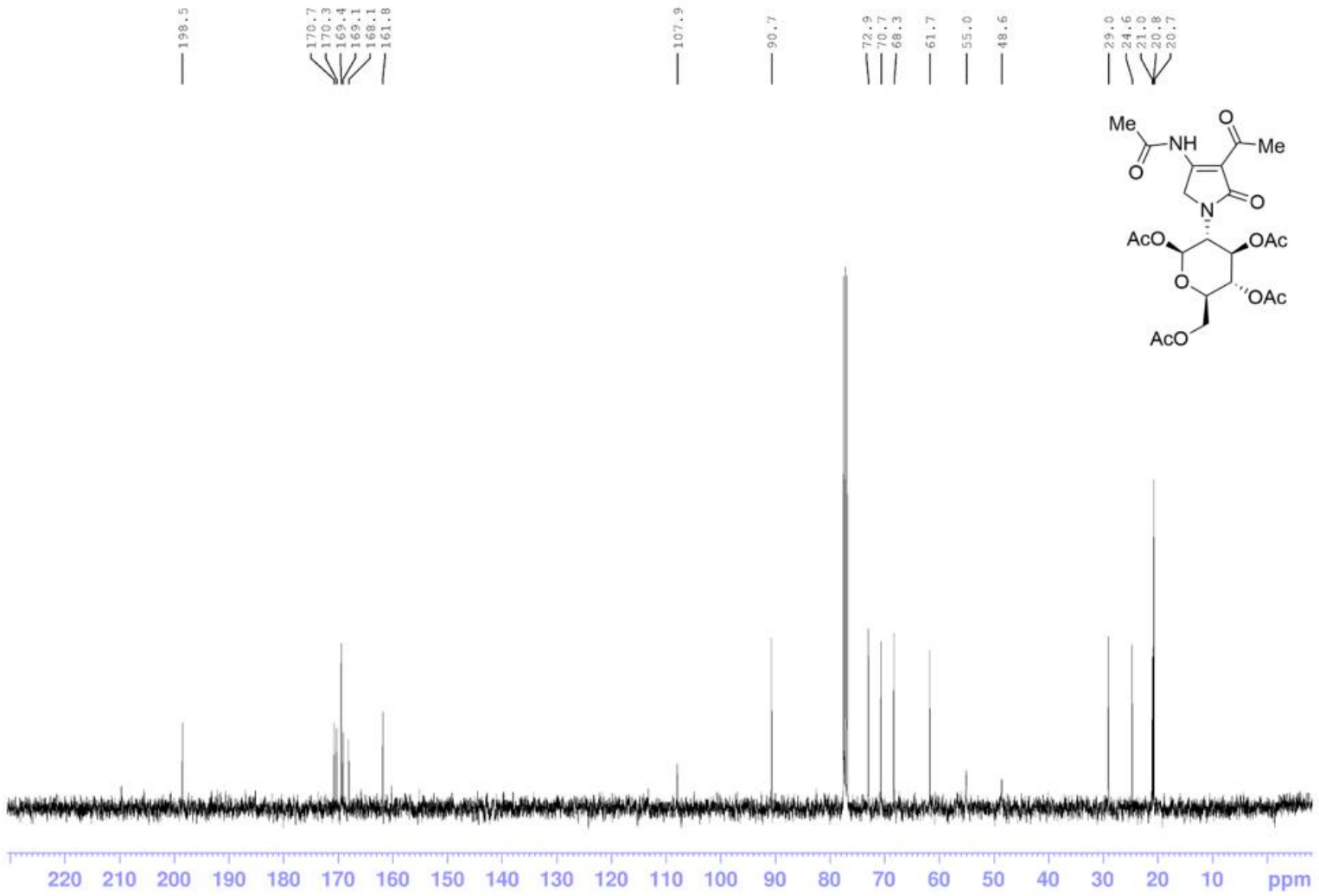
HMBC spectrum of **26** ($CDCl_3$)



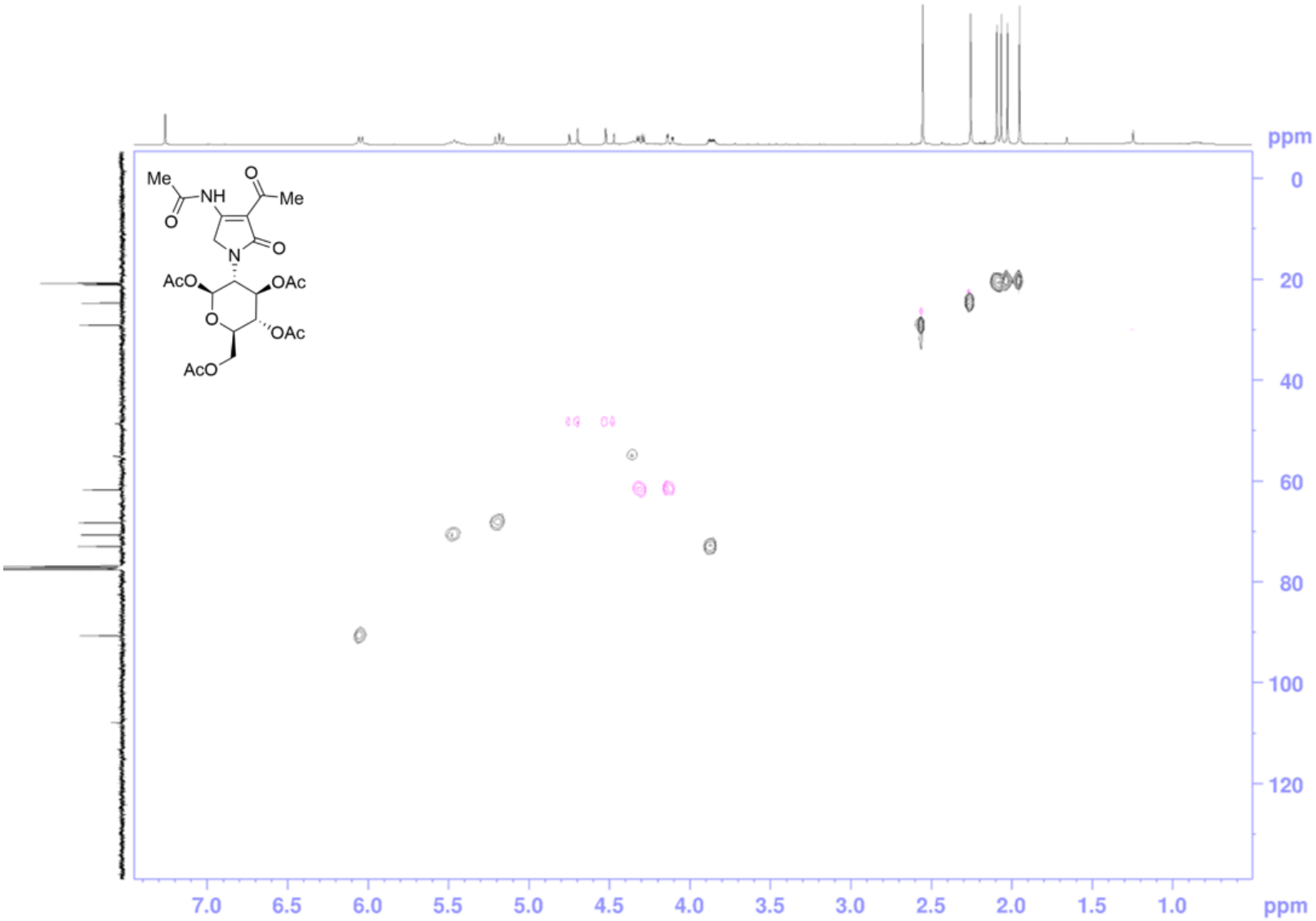
^{1}H NMR spectrum of **27** (400 MHz, $CDCl_3$)



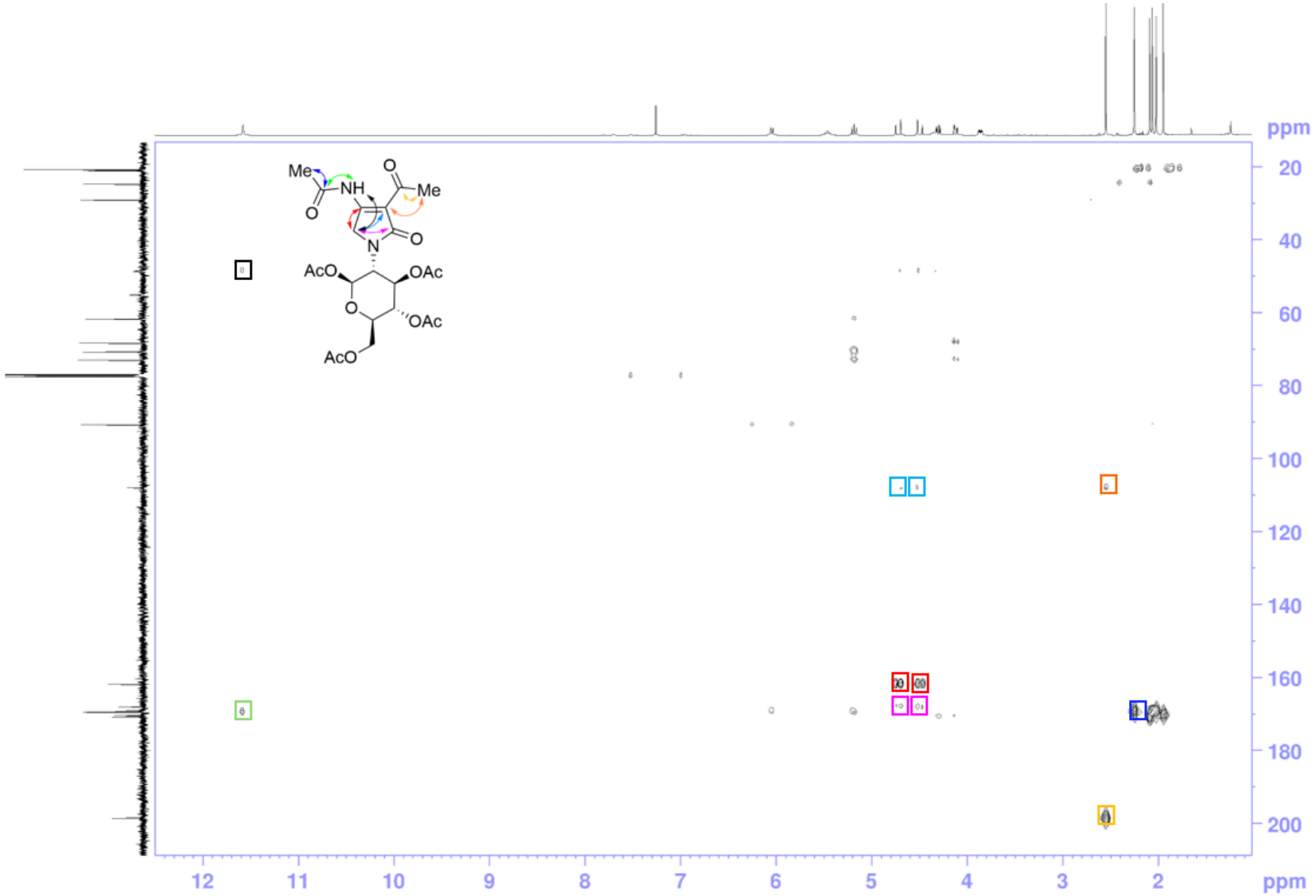
^{13}C NMR spectrum of **27** (100 MHz, $CDCl_3$)



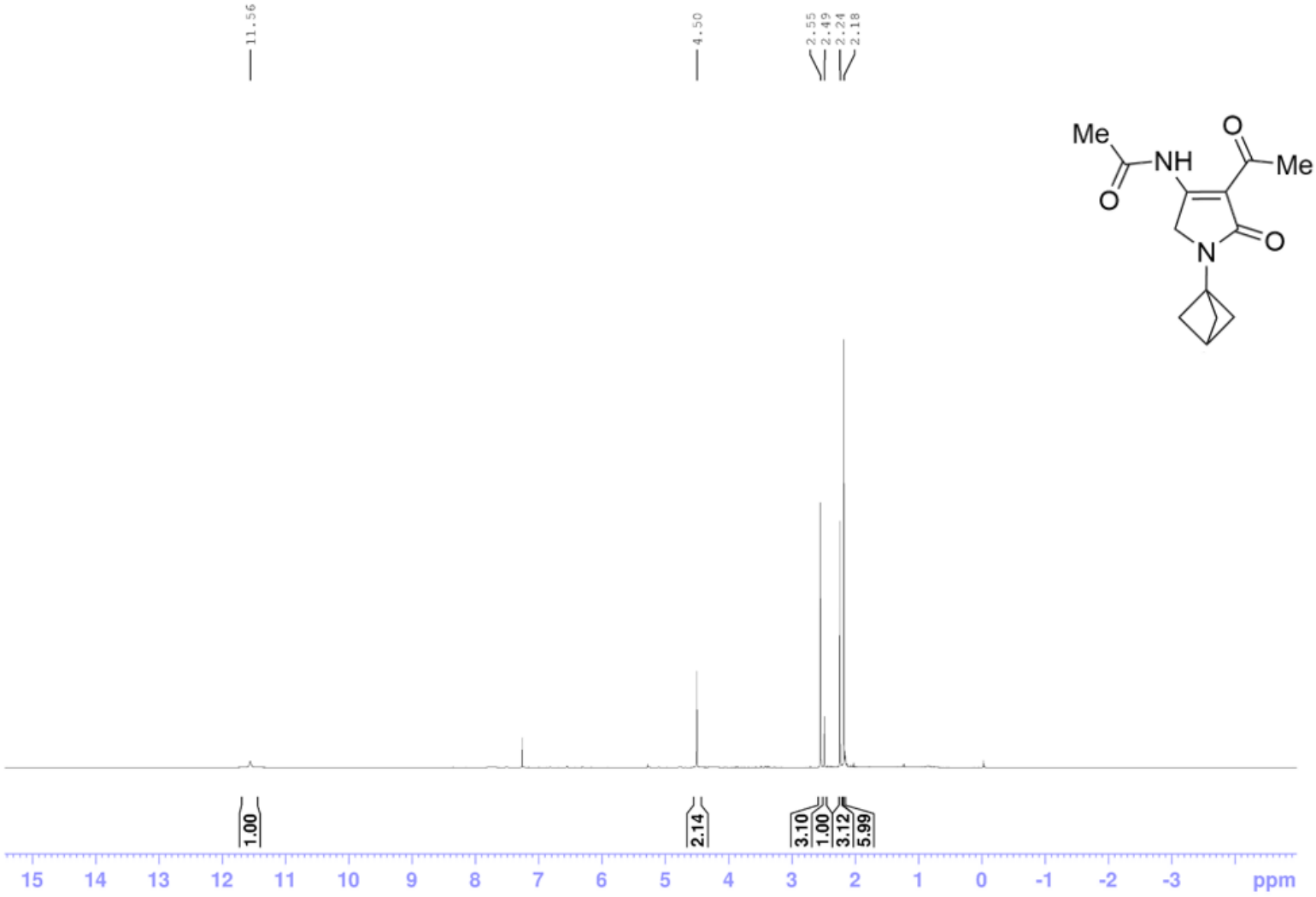
Edited HSQC spectrum of **27** ($CDCl_3$)



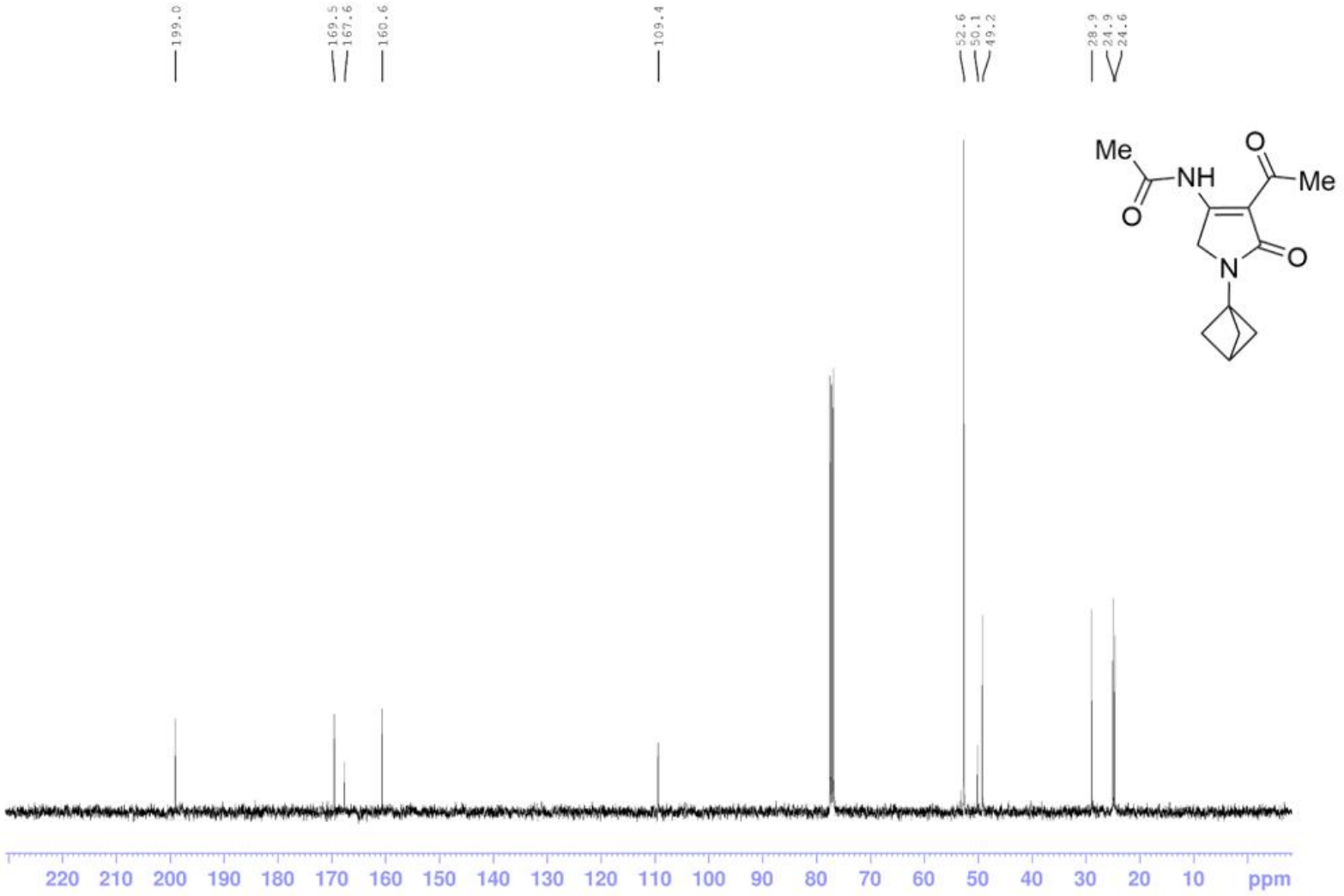
HMBC spectrum of **27** ($CDCl_3$)



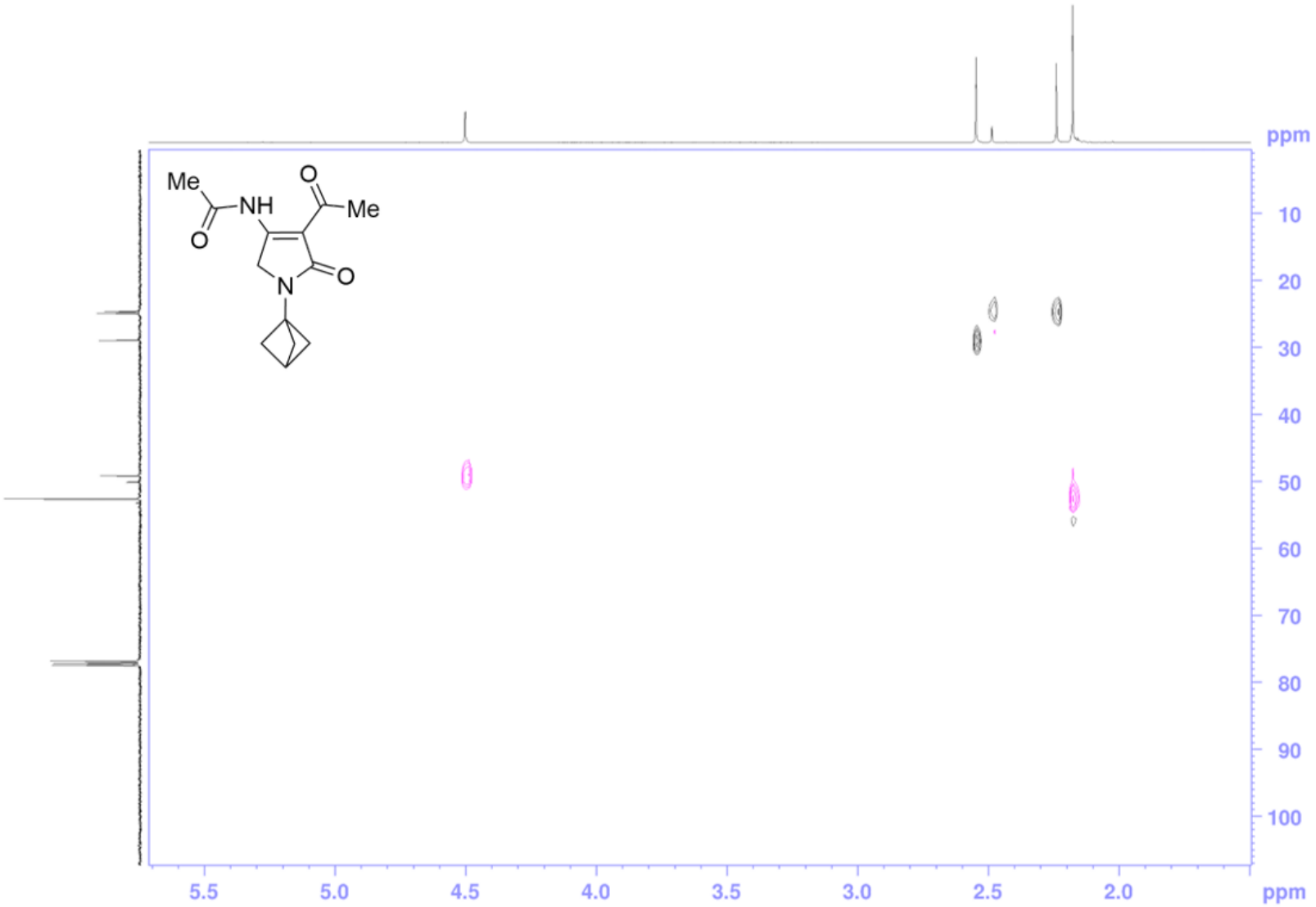
^{1}H NMR spectrum of **28** (400 MHz, $CDCl_3$)



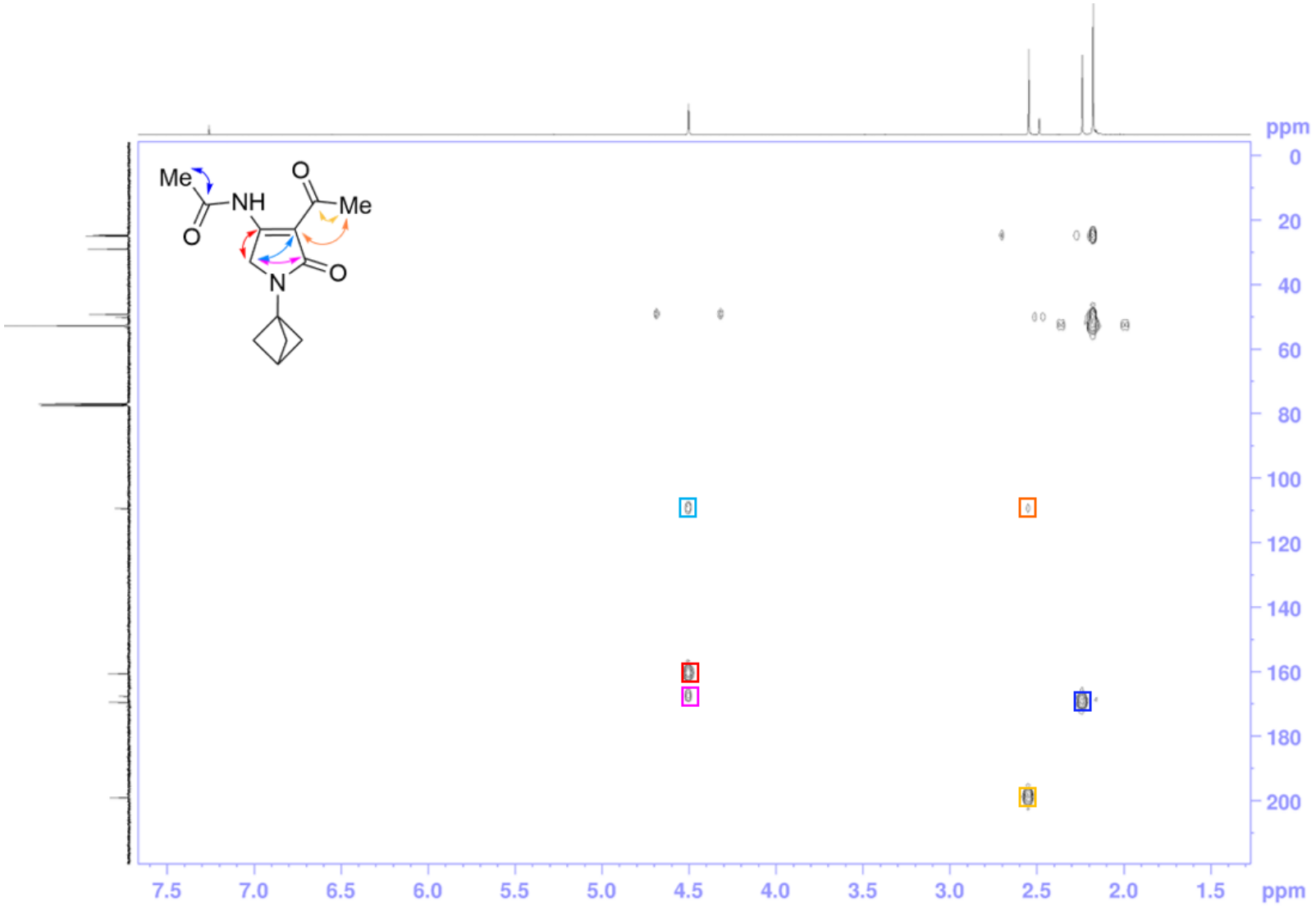
^{13}C NMR spectrum of **28** (100 MHz, $CDCl_3$)



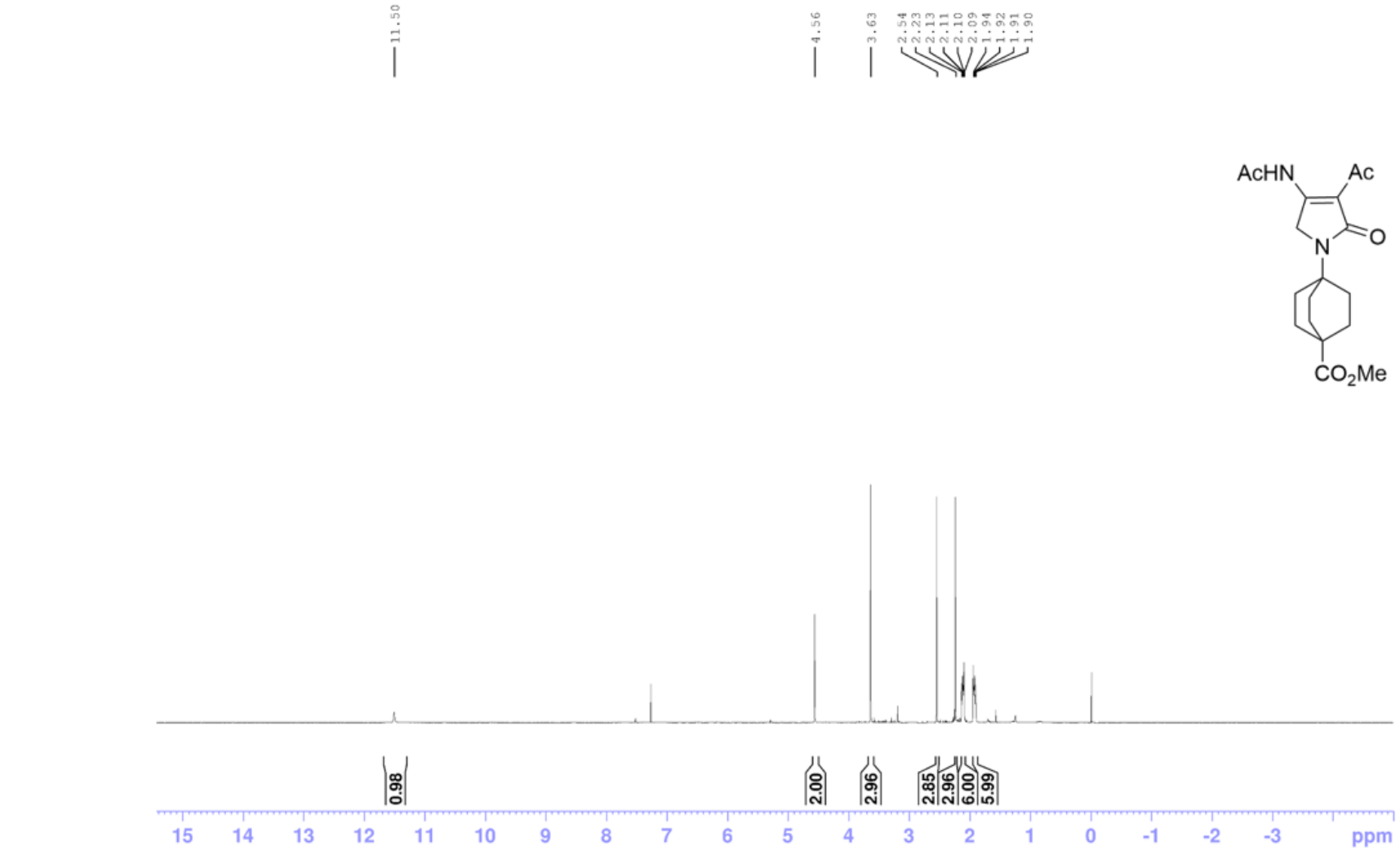
Edited HSQC spectrum of **28** ($CDCl_3$)



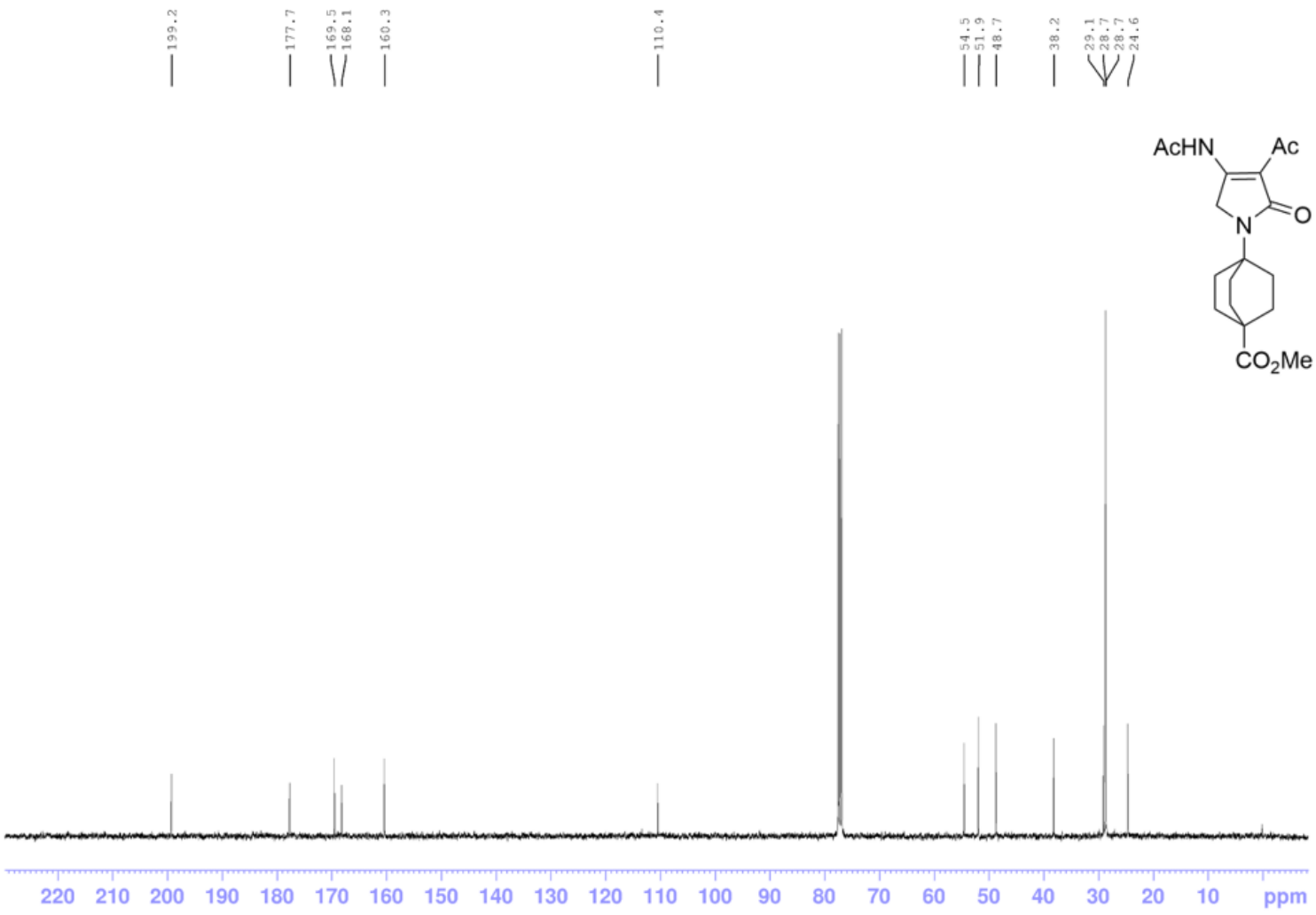
HMBC spectrum of **28** ($CDCl_3$)



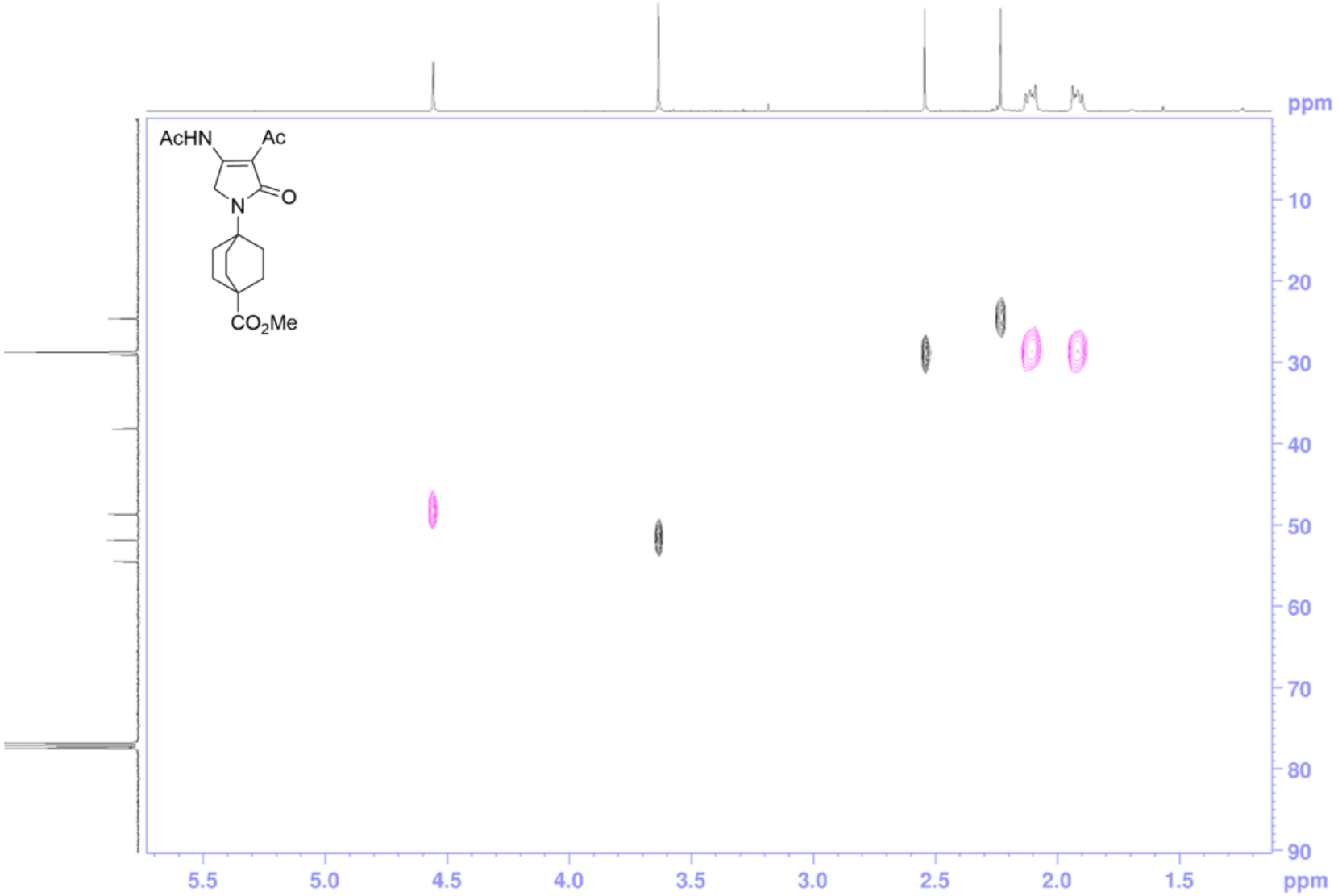
^{1}H NMR spectrum of **29** (400 MHz, $CDCl_3$)



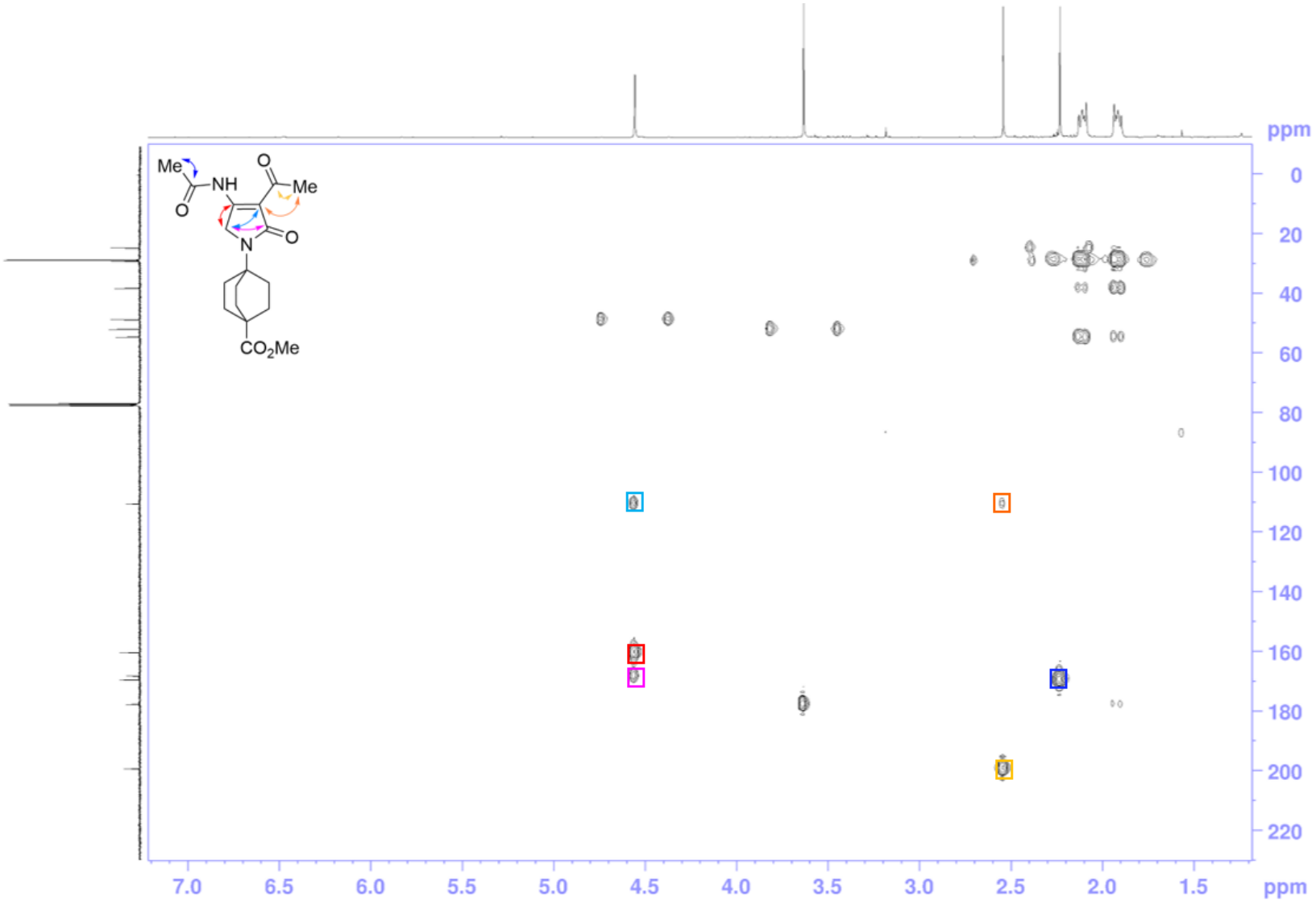
^{13}C NMR spectrum of **29** (100 MHz, $CDCl_3$)



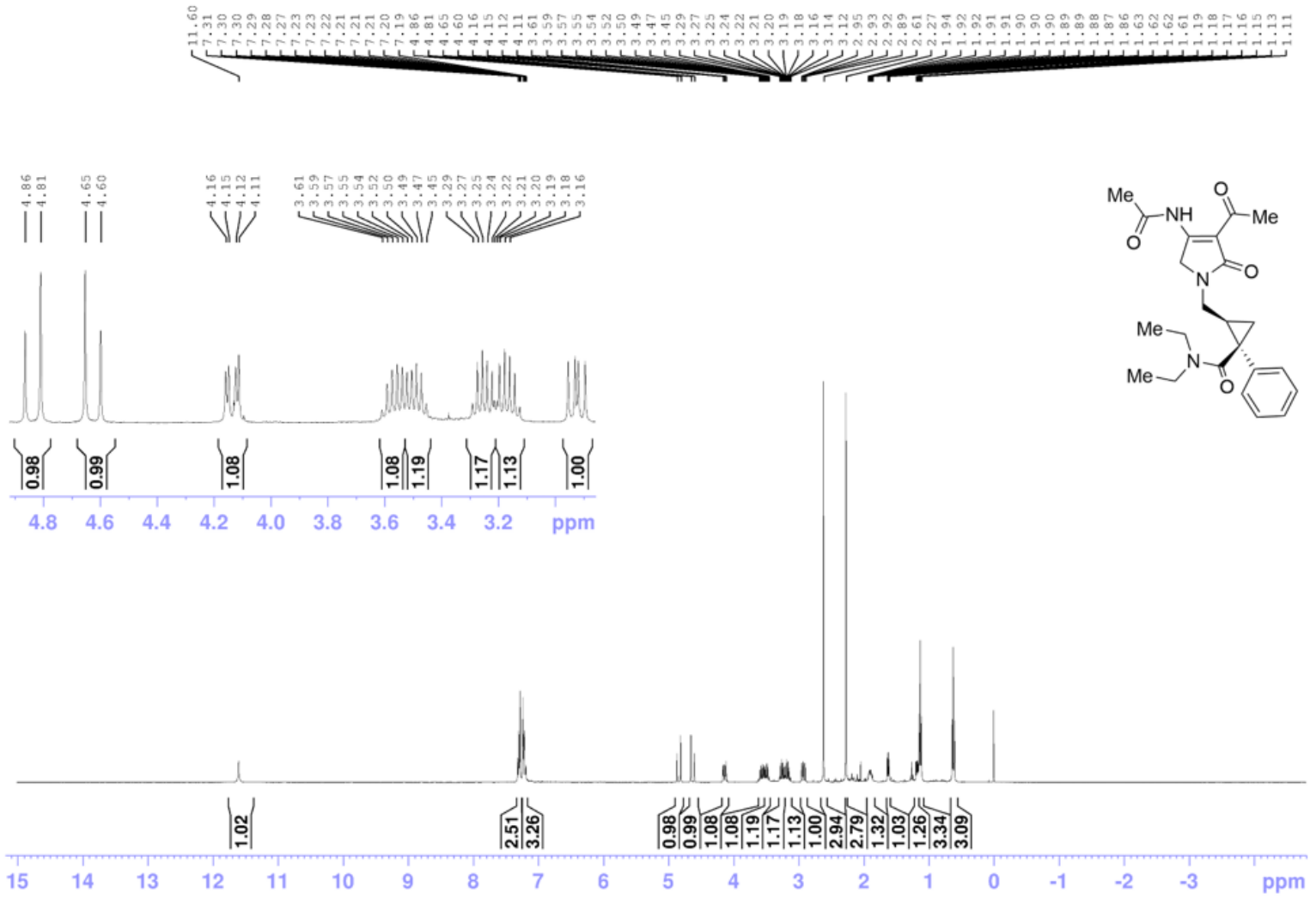
Edited HSQC spectrum of **290** ($CDCl_3$)



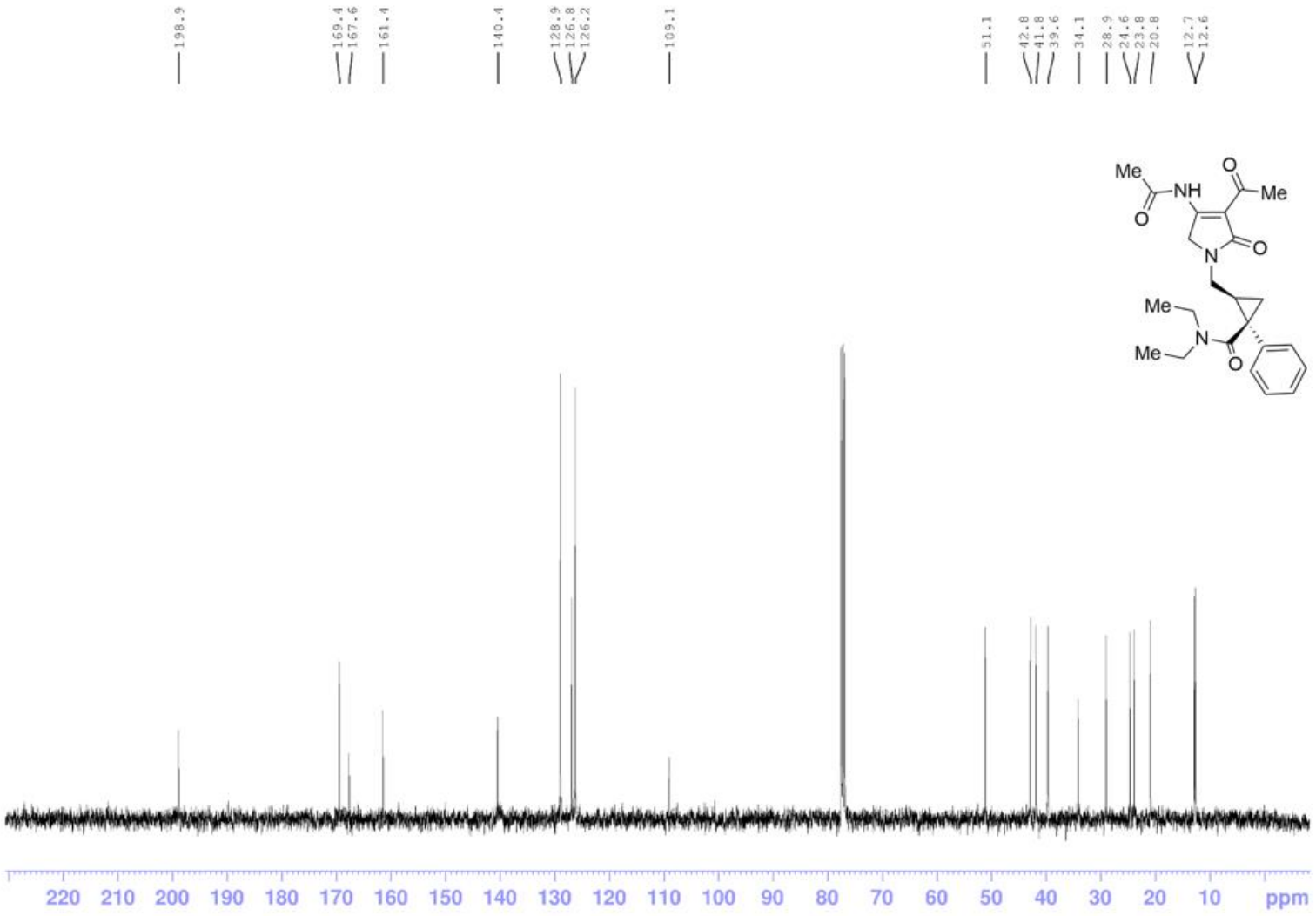
HMBC spectrum of **29** ($CDCl_3$)



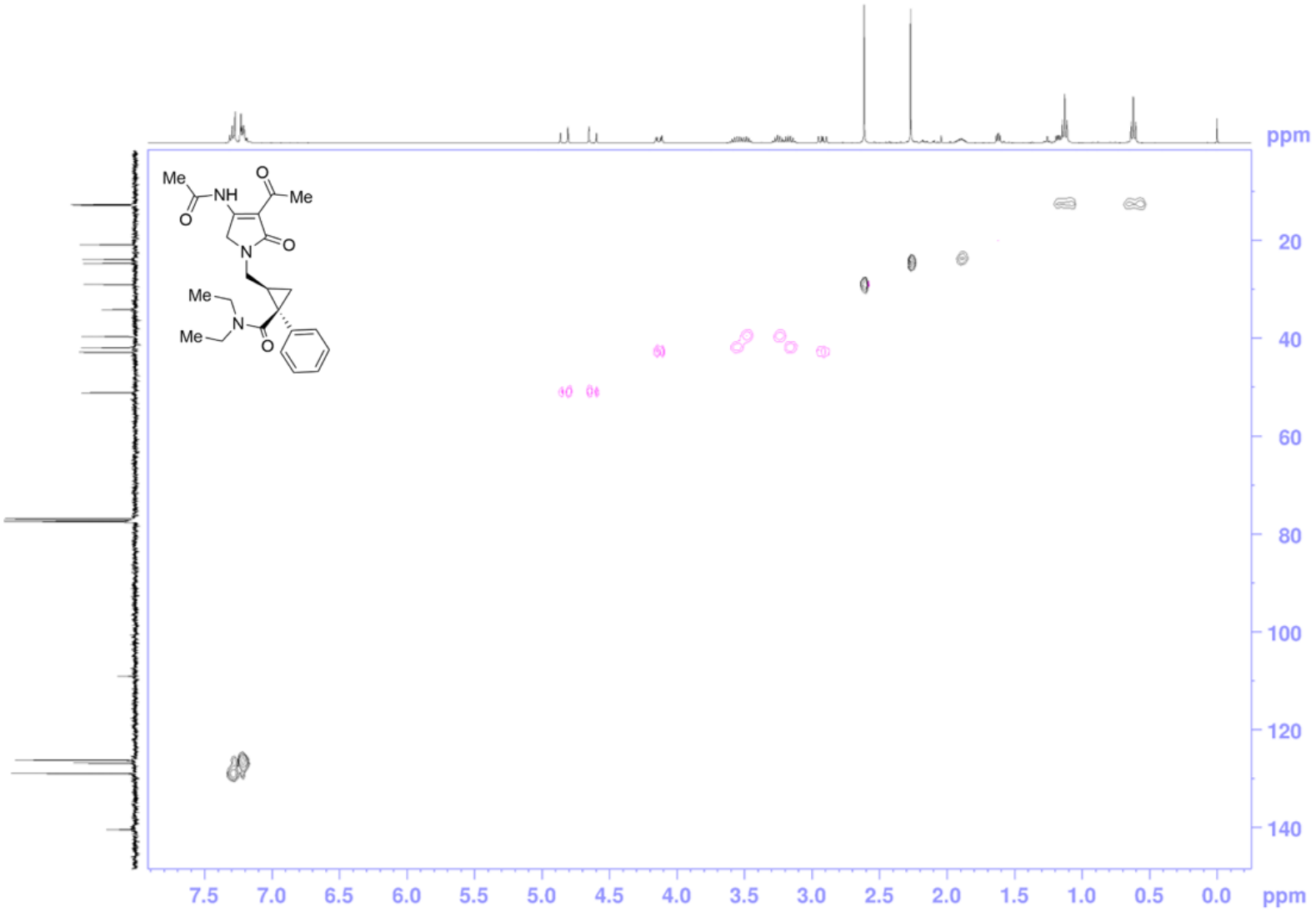
^{1}H NMR spectrum of **30** (400 MHz, $CDCl_3$)



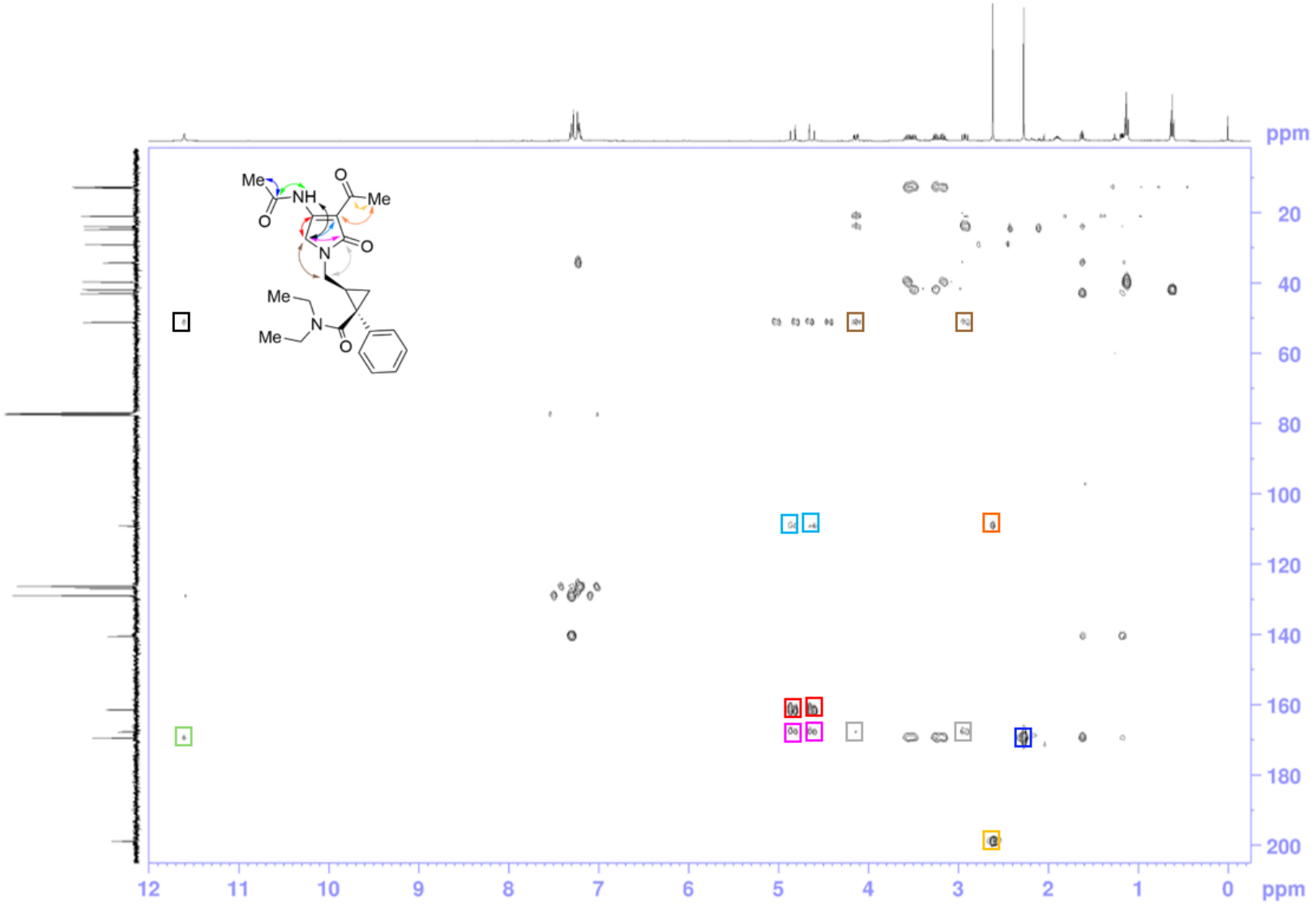
^{13}C NMR spectrum of **30** (100 MHz, $CDCl_3$)



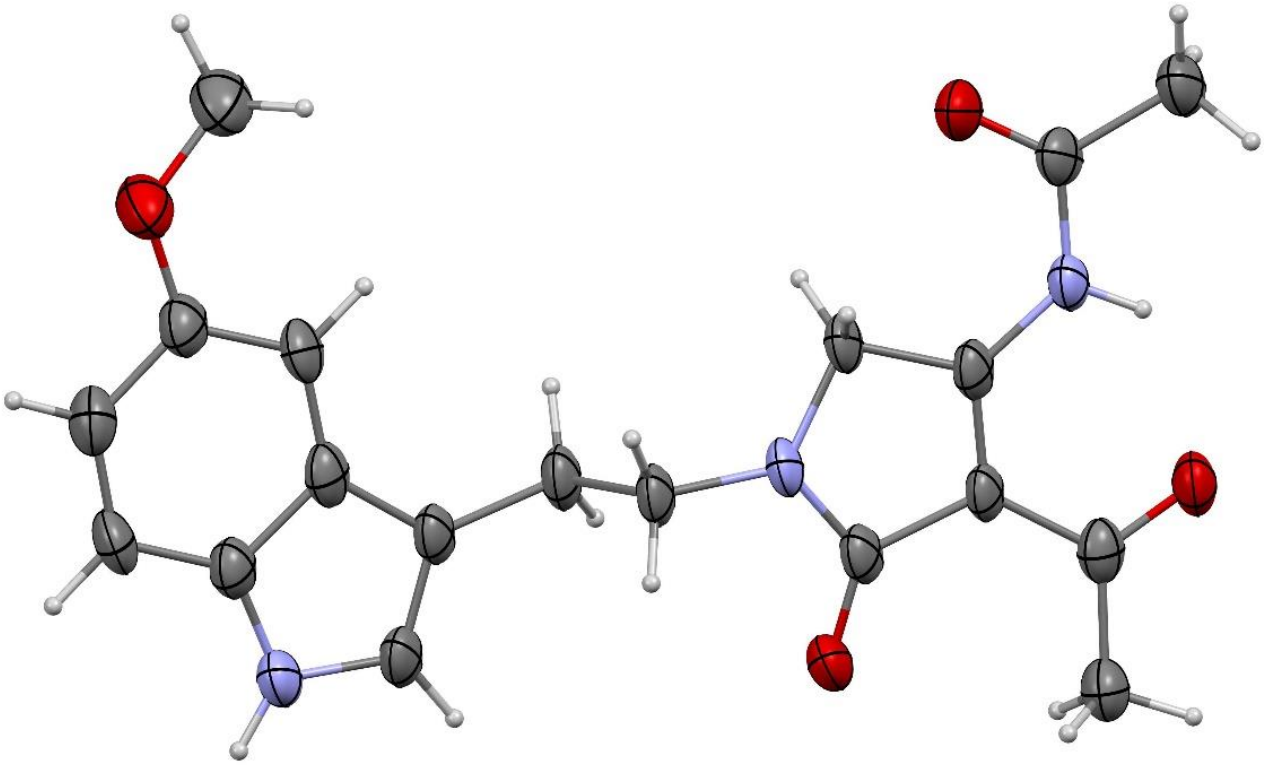
HSQC spectrum of **30** ($CDCl_3$)



HSQC spectrum of **30** ($CDCl_3$)



Crystallographic data for **10**



Molecular structure of 3-acetyl-4-acetamidopyrrolin-2-one **10** (CCDC 2401057). Atomic displacement parameters are drawn at the 50 % probability level

Table S1 Crystal data and structure refinement for **10**

CCDC number	2401057
Identification code	JA_92.11_1
Empirical formula	$C_{19}H_{21}N_3O_4$
Formula weight	355.39
Temperature/K	120.0(4)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	9.5658(8)
b/Å	8.2756(5)
c/Å	22.671(2)
α/°	90
β/°	99.436(9)
γ/°	90
Volume/Å^3	1770.4(3)
Z	4
ρ_{calc}g/cm^3	1.333
μ/mm^{-1}	0.781
F(000)	752.0
Crystal size/mm^3	0.12 × 0.08 × 0.05
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	11.234 to 130.176
Index ranges	$-11 \leq h \leq 11$, $-8 \leq k \leq 9$, $-26 \leq l \leq 26$
Reflections collected	10105
Independent reflections	2943 [R_{int} = 0.0539, R_{sigma} = 0.0412]
Data/restraints/parameters	2943/0/238
Goodness-of-fit on F^2	1.200
Final R indexes [I>=2σ (I)]	R_1 = 0.0823, wR_2 = 0.1888
Final R indexes [all data]	R_1 = 0.1029, wR_2 = 0.1980
Largest diff. peak/hole / e Å^{-3}	0.26/-0.28

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