Electronic Supplementary Information

Cobalt carbonyl-catalyzed carbonylation of functionalized aziridines to versatile β-lactam building blocks

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Contents

General methods

Commercially available reagents were purchased from common chemical suppliers and used without further purification. Melting points were measured using a Kofler bench, type WME Heizbank of Wagner & Munz. ^{1}H NMR spectra were recorded at 400 MHz (Bruker Avance III-400) in deuterated solvents with TMS as internal standard. ^{19}F NMR spectra were recorded at 376 MHz (Bruker Avance III-400), and ^{13}C NMR spectra were recorded at 100 MHz (Bruker Avance III-400). IR spectra were obtained from samples in neat form with an ATR (Attenuated Total Reflectance) accessory with a Perkin-Elmer Spectrum BX FT-IR or Shimadzu IRAFFINITY-1S WL spectrophotometer. Electron spray (ES) mass spectra were obtained with an Agilent 1100 Series MS (ES, 4000V) mass spectrometer. High resolution electron spray (ES-TOF) mass spectra were obtained with an Agilent Technologies 6210 Series Time-of Flight or Thermo Scientific MAT95XP-Trap.

Synthesis of 2-aryl-3-(hydroxymethyl)aziridines 3

2-Aryl-3-(hydroxymethyl)aziridines **3a-e** were prepared in three steps according to a literature procedure.[1]

***Cis*-1-*tert*-butyl-3-hydroxymethyl-2-(2-methoxyphenyl)aziridine 3a**: Spectral data were in accordance with those reported in the literature.[1]

***Cis*-1-*tert*-butyl-3-hydroxymethyl-2-(5-isopropyl-2-methoxyphenyl)aziridine 3b**: White solid. R_f = 0.12 (hexane/EtOAc 4/1). Mp 64°C. Yield 71%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (9H, s), 1.22 (6H, d, *J* = 6.9 Hz), 1.93 (1H, br s), 2.31 (1H, d x d x d, *J* = 6.7, 6.6, 5.4 Hz), 2.86 (1H, septet, *J* = 6.9 Hz), 2.94 (1H, d, *J* = 6.6 Hz), 3.13-3.18 (1H, m), 3.33-3.36 (1H, m), 3.84 (3H, s), 6.78 (1H, d, *J* = 8.4 Hz), 7.07 (1H, d x d, *J* = 8.4, 2.3 Hz), 7.30 (1H, d, *J* = 2.3 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 23.9, 24.5, 27.0, 33.3, 35.4, 38.8, 52.9, 55.5, 61.6, 109.9, 125.2, 125.7, 128.2, 141.1, 155.6. IR (ATR, cm^{-1}): ν_{OH} = 3447; ν_{max} = 2959, 1497, 1246, 1121, 1028, 808. MS (70 eV): m/z (%) 278 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{17}H_{28}NO_2^+$ 278.2115 $[M + H]^+$, found 278.2125.

***Cis*-2-(5-bromo-2-methoxyphenyl)-1-*tert*-butyl-3-(hydroxymethyl)aziridine 3c**: White solid. R_f = 0.10 (hexane/EtOAc 4/1). Mp 76°C. Yield 51%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (9H, s), 1.64 (1H, t, *J* = 5.9 Hz), 2.33 (1H, ~q, *J* = 5.9 Hz), 2.94 (1H, d, *J* = 5.9 Hz), 3.24 (2H, ~nonet, *J* = 5.9 Hz), 3.84 (3H, s), 6.71 (1H, d, *J* = 8.7 Hz), 7.31 (1H, d x d, *J* = 8.7, 2.5 Hz), 7.53 (1H, d, *J* = 2.5 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 26.9, 34.9, 39.2, 52.9, 55.7, 61.2, 111.6, 113.1, 128.7, 130.5, 132.4, 156.9. IR (ATR, cm^{-1}): ν_{OH} = 3401; ν_{max} = 2967, 1486, 1249, 1125, 1026, 805, 735. MS (70 eV): m/z (%) 314/316 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{14}H_{21}BrNO_2^+$ 314.0750 $[M + H]^+$, found 314.0747.

***Cis*-1-*tert*-butyl-2-(4-fluoro-2-methoxyphenyl)-3-(hydroxymethyl)aziridine 3d**: White solid. R_f = 0.10 (hexane/EtOAc 4/1). Mp 111°C. Yield 65%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (9H, s), 1.81 (1H, t, *J* = 6.1 Hz), 2.29 (1H, ~q, *J* = 6.1 Hz), 2.92 (1H, d, *J* = 6.1 Hz), 3.22 (2H, ~t, *J* = 6.1 Hz), 3.84 (3H, s), 6.57 (1H, d x d, *J* = 8.9, 2.4 Hz), 6.61 (1H, ~t x d, *J* = 8.9, 2.4 Hz), 7.38 (1H, ~t, *J* = 8.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -113.41-(-113.34) (m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 26.9, 34.9, 38.8, 52.9, 55.6, 61.0, 98.4 (d, *J* = 25.9 Hz), 106.7 (d, *J* = 21.0 Hz), 121.7 (d, *J* = 3.1 Hz), 130.5 (d, *J* = 10.0 Hz), 158.6 (d, *J* = 9.7 Hz), 162.7 (d, *J* = 244.5 Hz). IR (ATR, cm^{-1}): ν_{OH} = 3256; ν_{max} = 2864, 1504, 1277, 1146, 1053, 827, 754. MS (70 eV): m/z (%) 254 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{14}H_{21}FNO_2^+$ 254.1551 $[M + H]^+$, found 314.1561.

[1] M. D'hooghe, K. Mollet, S. Dekeukeleire and N. De Kimpe, *Org. Biomol. Chem.*, 2010, **8**, 607.

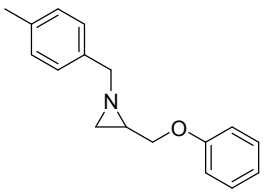
***Trans*-3-hydroxymethyl-1-isopropyl-2-phenylaziridine 3e**: Spectral data were in accordance with those reported in the literature.[1]

Synthesis of 2-(aryloxymethyl)aziridines 4

2-(Aryloxymethyl)aziridines **4a-e** were prepared according to a slightly modified literature procedure.[2] As a representative example, the synthesis of 1-(4-methylbenzyl)-2-(phenoxymethyl)aziridine **4b** is described here. 2-Bromomethyl-1-(4-methylbenzyl)aziridine **1b**[3] (7.20 g, 30 mmol, 1 equiv.) was added to a mixture of phenol (6.21 g, 66 mmol, 2.2 equiv.) and potassium carbonate (20.73 g, 150 mmol, 5 equiv.) dissolved in 200 mL of a solvent mixture containing DMF and acetone (1/1 on volumetric basis). After stirring for 16 hours at 50 °C, brine (200 mL) was added. The resulting mixture was extracted with Et_2O (3 x 200 mL), after which the combined organic phases were washed with brine (3 x 200 mL). Drying of the organic phase with $MgSO_4$, filtration of the drying agent and removal of the solvent *in vacuo* afforded 6.69 g (88% yield) 1-(4-methylbenzyl)-2-(phenoxymethyl)aziridine **4b** in high purity (>95% based on ^{1}H NMR in $CDCl_3$), which was used as such in the next reaction step.

1-Benzyl-2-(phenoxymethyl)aziridine 4a: Spectral data were in accordance with those reported in the literature.[4]

1-(4-Methylbenzyl)-2-(phenoxymethyl)aziridine 4b: White solid. R_f = 0.19 (hexane/EtOAc 4/1). Mp 51°C. Yield 88%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53 (1H, d, *J* = 6.4 Hz), 1.81 (1H, d, *J* = 3.4 Hz), 1.92-1.98 (1H, m), 2.33 (3H, s), 3.40 (1H, d, *J* = 13.3 Hz), 3.49 (1H, d, *J* = 13.3 Hz), 3.91 (1H, d x d, *J* = 10.4, 5.3 Hz), 3.95 (1H, d x d, *J* = 10.4, 6.2 Hz), 6.86-6.93 (3H, m), 7.12-7.14 (2H, m), 7.22-7.26 (4H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 21.2, 32.0, 37.9, 64.1, 70.2, 114.7, 120.8, 128.1, 129.1, 129.5, 135.9, 136.7, 158.8. IR (ATR, cm^{-1}): ν_{max} = 2920, 1495, 1346, 1240, 1034, 750. MS (70 eV): m/z (%) 254 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{17}H_{20}NO^+$ 254.1539 $[M + H]^+$, found 254.1542.



1-(2-Chlorobenzyl)-2-(phenoxymethyl)aziridine 4c: Spectral data were in accordance with those reported in the literature.[2]

1-(4-Chlorobenzyl)-2-(phenoxymethyl)aziridine 4d: Spectral data were in accordance with those reported in the literature.[5]

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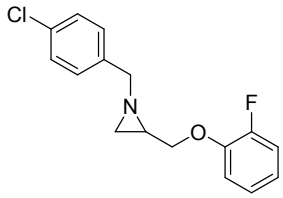
[2] M. D'hooghe, A. Waterinckx, T. Vanlangendonck and N. De Kimpe, *Tetrahedron*, 2006, **62**, 2295.

[3] N. De Kimpe, D. De Smaele and Z. Sakonyi, *J. Org. Chem.*, 1997, **62**, 2448.

[4] Y. Du, Y. Wu, A.-H. Liu and L.-N. He, *J. Org. Chem.*, 2008, **73**, 4709.

[5] M. D'hooghe, S. Catak, S. Stanković, M. Waroquier, Y. Kim, H.-J. Ha, V. Van Speybroeck and N. De Kimpe, *Eur. J. Org. Chem.*, 2010, 4920.

1-(4-Chlorobenzyl)-2-[(2-fluorophenoxy)methyl]aziridine 4e: Light-yellow liquid. R_f = 0.32 (hexane/EtOAc 3/2). Yield 94%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54 (1H, d, *J* = 6.5 Hz), 1.83 (1H, d, *J* = 3.3 Hz), 1.98-2.03 (1H, m), 3.39 (1H, d, *J* = 13.7 Hz), 3.46 (1H, d, *J* = 13.7 Hz), 3.90 (1H, d x d, *J* = 10.5, 6.9 Hz), 4.08 (1H, d x d, *J* = 10.5, 4.5 Hz), 6.84-7.07 (4H, m), 7.27 (2H, d, *J* = 8.5 Hz), 7.31 (2H, d, *J* = 8.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -134.25-(-134.19) (m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 31.7, 38.0, 63.4, 71.6, 115.3 (d, *J* = 1.3 Hz), 116.2 (d, *J* = 18.3 Hz), 121.4 (d, *J* = 6.8 Hz), 124.3 (d, *J* = 3.8 Hz), 128.5, 129.3, 132.8, 137.4, 146.7 (d, *J* = 10.5 Hz), 152.7 (d, *J* = 245.6 Hz). IR (ATR, cm^{-1}): ν_{max} = 2994, 1454, 1343, 1256, 1016, 741. MS (70 eV): m/z (%) 292/4 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{16}H_{16}ClFNO^+$ 292.0899 $[M + H]^+$, found 292.0903.



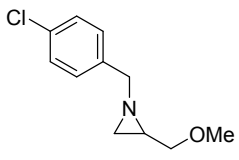
Synthesis of 2-(methoxymethyl)aziridines 6

2-(Methoxymethyl)aziridines **6a-c** were prepared according to a slightly modified literature procedure.[6] As a representative example, the synthesis of 1-(4-chlorobenzyl)-2-(methoxymethyl)aziridine **6c** is described here. 2-Bromomethyl-1-(4-chlorobenzyl)aziridine **1d**[3] (5.21 g, 20 mmol, 1 equiv.) was dissolved in a 4 M solution of sodium methoxide in methanol (15 mL, 60 mmol, 3 equiv.). After stirring for 3 hours at 50 °C, the reaction mixture was extracted with CH_2Cl_2 (3 x 15 mL). Drying of the organic phase with $MgSO_4$, filtration of the drying agent and removal of the solvent *in vacuo* afforded 4.15 g (98% yield) 1-(4-chlorobenzyl)-2-(methoxymethyl)aziridine **6c** in high purity (>95% based on ^{1}H NMR in $CDCl_3$), which was used as such in the next reaction step.

1-Benzyl-2-(methoxymethyl)aziridine 6a: Spectral data were in accordance with those reported in the literature.[7]

2-(Methoxymethyl)-1-(4-methylbenzyl)aziridine 6b: Spectral data were in accordance with those reported in the literature.[8]

1-(4-Chlorobenzyl)-2-(methoxymethyl)aziridine 6c: Light-yellow liquid. R_f = 0.20 (hexane/EtOAc 1/1). Yield 98%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (1H, d, *J* = 6.4 Hz), 1.73 (1H, d, *J* = 3.5 Hz), 1.75-1.81 (1H, m), 3.31 (1H, d x d, *J* = 10.6, 6.5 Hz), 3.336 (3H, s), 3.342 (1H, d, *J* = 13.6 Hz), 3.44 (1H, d x d, *J* = 10.6, 4.6 Hz), 3.52 (1H, d, *J* = 13.6 Hz), 7.29 (2H, d, *J* = 8.9 Hz), 7.31 (2H, d, *J* = 8.9 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 31.4, 38.5, 58.8, 63.6, 74.5, 128.5, 129.3, 132.8, 137.5. IR (ATR, cm^{-1}): ν_{max} = 2984, 1491, 1342, 1242, 1015,



[6] M. D'hooghe and N. De Kimpe, *Synlett*, 2004, 271.

[7] M. D'hooghe and N. De Kimpe, *Arkivoc*, 2008, 6.

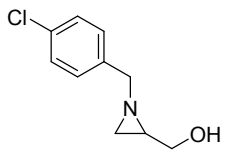
[8] S. Stanković, M. D'hooghe and N. De Kimpe, *Org. Biomol. Chem.*, 2010, **8**, 4266.

806. MS (70 eV): m/z (%) 212/4 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{11}H_{15}ClNO^+$ 212.0837 $[M + H]^+$, found 212.0843.

Synthesis of 1-(4-chlorobenzyl)-2-(hydroxymethyl)aziridine 13

2-Bromomethyl-1-(4-chlorobenzyl)aziridine **1d**[3] (1.04 g, 4 mmol, 1 equiv.) was added to a stirred solution of sodium acetate (0.49 g, 6 mmol, 1.5 equiv.) in DMSO (10 mL). After stirring for 16 hours at 100 °C, brine (10 mL) was added, after which the resulting mixture was extracted with Et_2O (3 x 10 mL). Next, the combined organic phases were washed with brine (3 x 10 mL), the organic phase was dried with $MgSO_4$, the drying agent was filtered off and the solvent was removed *in vacuo*. The resulting 2-(acetoxymethyl)aziridine was then dissolved in MeOH (10 mL) and stirred together with potassium carbonate (0.66 g, 4.8 mmol, 1.2 equiv.) for 1 hour at room temperature. Subsequently, the solvent was evaporated *in vacuo*, after which the residue was dissolved in Et_2O (10 mL) and washed with H_2O (10 mL). Drying of the organic phase with $MgSO_4$, filtration of the drying agent and removal of the solvent *in vacuo* afforded crude 1-(4-chlorobenzyl)-2-(hydroxymethyl)aziridine **13**, which was purified in 87% yield (0.69 g) by recrystallization from hexane/EtOAc (1/30).

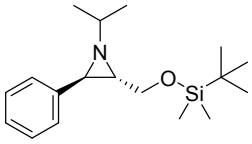
1-(4-Chlorobenzyl)-2-(hydroxymethyl)aziridine 13: White solid. Recrystallization from hexane/EtOAc (1/30). Mp 85°C. Yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (1H, d, *J* = 6.2 Hz), 1.80-1.85 (1H, m), 1.84 (1H, d, *J* = 3.5 Hz), 2.49 (1H, br s), 3.38 (1H, d x d, *J* = 11.8, 4.7 Hz), 3.43 (2H, s), 3.77 (1H, br d, *J* = 11.8 Hz), 7.28 (2H, d, *J* = 8.8 Hz), 7.31 (2H, d, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 31.2, 40.2, 62.5, 63.3, 128.6, 129.3, 133.0, 137.4. IR (ATR, cm^{-1}): ν_{OH} = 3110; ν_{max} = 2917, 1492, 1407, 1081, 1049, 1012, 807. MS (70 eV): m/z (%) 198/200 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{10}H_{13}ClNO^+$ 198.0680 $[M + H]^+$, found 198.0686.



Synthesis of *trans*-2-{[(*tert*-butyldimethylsilyl)oxy]methyl}-1-isopropyl-3-phenylaziridine 20

To an ice-cooled solution of *trans*-3-hydroxymethyl-1-isopropyl-2-phenylaziridine **3e** (0.96 g, 5 mmol, 1 equiv.) in anhydrous THF (20 mL), sodium hydride (0.18 g, 7.5 mmol, 1.5 equiv.) was added in small portions. The resulting mixture was stirred for 1 hour at room temperature, after which *tert*-butyldimethylsilyl chloride (0.90 g, 6 mmol, 1.2 equiv.) was added at 0 °C. After additional stirring for 15 hours at room temperature, Et_2O (50 mL) was added. The reaction mixture was washed with a 10% aqueous K_2CO_3 solution (50 mL) and brine (50 mL), after which the combined aqueous phases were extracted again with Et_2O (3 × 50 mL). Drying of the combined organic phases with $MgSO_4$, filtration of the drying agent and removal of the solvent *in vacuo* afforded crude *trans*-2-{[(*tert*-butyldimethylsilyl)oxy]methyl}-1-isopropyl-3-phenylaziridine **20**, which was purified in 63% yield (0.96 g) by column chromatography on silica gel (hexane/EtOAc 19/1).

***Trans*-2-{[(*tert*-butyldimethylsilyl)oxy]methyl}-1-isopropyl-3-phenylaziridine 20**:

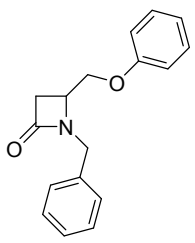


Obtained as a mixture of two invertomers (50/50) due to hindered *N*-inversion. Light-yellow liquid. R_f = 0.14 (hexane/EtOAc 19/1). Yield 63%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.08 (12H, s), 0.91 (18H, s), 0.74 (3H, d, *J* = 6.0 Hz), 1.11 (3H, d, *J* = 6.0 Hz), 1.14 (3H, d, *J* = 6.0 Hz), 1.25 (3H, d, *J* = 6.0 Hz), 1.92 (1H, septet, *J* = 6.0 Hz), 2.32-2.40 (2H, m), 2.35 (1H, d, *J* = 2.3 Hz), 2.54 (1H, septet, *J* = 6.0 Hz), 3.07 (1H, d, *J* = 2.8 Hz), 3.66 (1H, d x d, *J* = 10.6, 6.6 Hz), 3.74 (1H, d x d, *J* = 10.6, 5.1 Hz), 3.91 (1H, d x d, *J* = 11.6, 7.8 Hz), 4.04 (1H, d x d, *J* = 11.6, 2.8 Hz), 7.18-7.34 (10H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ -5.4, -5.3, -5.2, -3.5, 18.2, 18.3, 21.7, 22.5, 22.7, 23.2, 25.7, 25.9, 43.1, 43.2, 45.5, 48.6, 50.2, 51.7, 59.3, 66.2, 126.4, 126.7, 127.6, 127.9, 128.2, 130.3, 133.8, 140.6. IR (ATR, cm^{-1}): ν_{max} = 2957, 1462, 1253, 1088, 833, 774, 730, 697. MS (70 eV): m/z (%) 306 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{18}H_{32}NOSi^+$ 306.2248 $[M + H]^+$, found 306.2257.

Synthesis of β-lactams 5, 7, 9, 11, 18, 19, 21 and γ-lactone 16

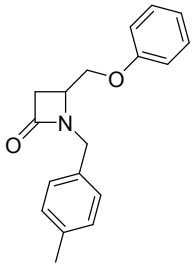
As a representative example for the cobalt carbonyl-catalyzed aziridine carbonylation, the synthesis of 1-benzyl-4-(phenoxymethyl)azetidin-2-one **5a** is described here. 1-Benzyl-2-(phenoxymethyl)aziridine **4a** (4.79 g, 20 mmol, 1 equiv.) was dissolved in dry anoxic 1,2-dimethoxyethane (20 mL) and placed in an argon-purged stainless steel autoclave (V = 75 mL, p_{max} = 100 bar) equipped with a stirring bar and copper heating jacket, together with 8 mol% $Co_2(CO)_8$ (0.55 g, 1.6 mmol, 0.08 equiv.). The autoclave was purged three times with carbon monoxide and then charged with 33 bar of carbon monoxide. After stirring the reaction for 92 hours at 50 °C, the autoclave was opened and Et_2O (20 mL) was added. The resulting mixture was left in contact with air for 4 hours to induce decomposition of the catalyst. A precipitate was formed and the reaction mixture was filtered through a small column packed with silica gel, using Et_2O as the eluent, affording 4.28 g (80% yield) 1-benzyl-4-(phenoxymethyl)azetidin-2-one **5a** in high purity (>95% based on ^{1}H NMR in $CDCl_3$).

1-Benzyl-4-(phenoxymethyl)azetidin-2-one 5a: Light-brown solid. Mp 102°C. Yield 80%.

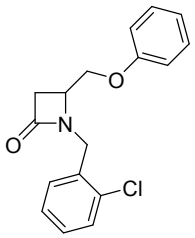


^{1}H NMR (400 MHz, $CDCl_3$): δ 2.85 (1H, d x d, *J* = 14.6, 1.8 Hz), 3.06 (1H, d x d, *J* = 14.6, 5.1 Hz), 3.85-3.89 (1H, m), 3.94 (1H, d x d, *J* = 9.8, 6.3 Hz), 4.04 (1H, d x d, *J* = 9.8, 3.5 Hz), 4.23 (1H, d, *J* = 15.0 Hz), 4.66 (1H, d, *J* = 15.0 Hz), 6.81-6.83 (2H, m), 6.95-6.99 (1H, m), 7.25-7.31 (7H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 39.5, 45.5, 49.7, 68.6, 114.4, 121.4, 127.7, 128.4, 128.8, 129.6, 136.0, 158.2, 166.7. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1740; ν_{max} = 2926, 1495, 1393, 1238, 1034, 754. MS (70 eV): m/z (%) 268 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{17}H_{18}NO_2^+$ 268.1332 $[M + H]^+$, found 268.1332.

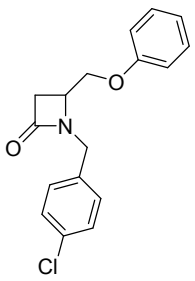
1-(4-Methylbenzyl)-4-(phenoxymethyl)azetidin-2-one 5b: Light-brown solid. Mp 114°C. Yield 81%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (3H, s), 2.85 (1H, d x d, *J* = 14.5, 1.7 Hz), 3.06 (1H, d x d, *J* = 14.5, 5.1 Hz), 3.84-3.88 (1H, m), 3.95 (1H, d x d, *J* = 9.9, 6.2 Hz), 4.04 (1H, d x d, *J* = 9.9, 3.6 Hz), 4.18 (1H, d, *J* = 15.0 Hz), 4.63 (1H, d, *J* = 15.0 Hz), 6.81-6.84 (2H, m), 6.96-6.99 (1H, m), 7.10-7.12 (2H, m), 7.19-7.21 (2H, m), 7.26-7.30 (2H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 21.1, 39.5, 45.2, 49.6, 68.5, 114.4, 121.3, 128.4, 129.4, 129.6, 132.9, 137.4, 158.2, 166.6. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1726; ν_{max} = 2922, 1462, 1236, 966, 746. MS (70 eV): m/z (%) 282 (M^+ + 1, 100).



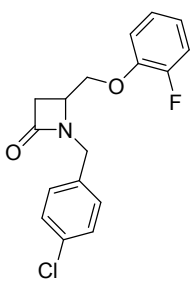
1-(2-Chlorobenzyl)-4-(phenoxymethyl)azetidin-2-one 5c: Light-brown solid. Mp 111°C. Yield 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.90 (1H, d x d, *J* = 14.5, 2.3 Hz), 3.10 (1H, d x d, *J* = 14.5, 5.2 Hz), 3.87-3.91 (1H, m), 3.97 (1H, d x d, *J* = 10.0, 5.6 Hz), 4.06 (1H, d x d, *J* = 10.0, 3.7 Hz), 4.44 (1H, d, *J* = 15.4 Hz), 4.71 (1H, d, *J* = 15.4 Hz), 6.80-6.82 (2H, m), 6.94-6.97 (1H, m), 7.16-7.228 (2H, m), 7.233-7.28 (2H, m), 7.32-7.35 (1H, m), 7.38-7.42 (1H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 39.7, 43.1, 50.4, 68.0, 114.4, 121.3, 127.1, 129.2, 129.5, 129.7, 130.6, 133.49, 133.51, 158.1, 166.8. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1744; ν_{max} = 2930, 1495, 1393, 1238, 907, 729. MS (70 eV): m/z (%) 302/4 (M^+ + 1, 100).



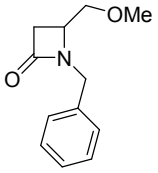
1-(4-Chlorobenzyl)-4-(phenoxymethyl)azetidin-2-one 5d: Light-brown solid. Mp 116°C. Yield 81%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.85 (1H, d x d, *J* = 14.6, 1.8 Hz), 3.08 (1H, d x d, *J* = 14.6, 5.1 Hz), 3.86-3.90 (1H, m), 3.95 (1H, d x d, *J* = 9.8, 6.8 Hz), 4.07 (1H, d x d, *J* = 9.8, 3.0 Hz), 4.23 (1H, d, *J* = 15.1 Hz), 4.66 (1H, d, *J* = 15.1 Hz), 6.80-6.82 (2H, m), 6.97-7.00 (1H, m), 7.23-7.31 (6H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 39.5, 44.9, 49.9, 68.7, 114.3, 121.5, 128.9, 129.6, 129.8, 133.6, 134.6, 158.0, 166.6. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1726; ν_{max} = 2922, 1462, 1236, 966, 746. MS (70 eV): m/z (%) 302/4 (M^+ + 1, 100).



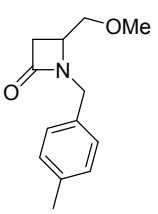
1-(4-Chlorobenzyl)-4-[(2-fluorophenoxy)methyl]azetidin-2-one 5e: Light-brown solid. Mp 94°C. Yield 76%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.80 (1H, d x d, *J* = 14.5, 1.9 Hz), 3.08 (1H, d x d, *J* = 14.5, 4.8 Hz), 3.88-3.93 (1H, m), 3.99 (1H, d x d, *J* = 9.6, 7.0 Hz), 4.17 (1H, d x d, *J* = 9.6, 3.1 Hz), 4.30 (1H, d, 14.9 Hz), 4.63 (1H, d, 14.9 Hz), 6.80-6.84 (1H, m), 6.92-6.97 (1H, m), 7.02-7.13 (2H, m), 7.26-7.31 (4H, m). ^{19}F NMR (376 MHz, $CDCl_3$): δ -133.86-(-133.80) (m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 39.3, 45.1, 49.6, 71.1, 114.9 (d, *J* = 1.3 Hz), 116.5 (d, *J* = 18.2 Hz), 122.1 (d, *J* = 6.8 Hz), 124.4 (d, *J* = 3.3 Hz), 128.9, 130.0, 133.6, 134.7, 146.1 (d, *J* = 10.8 Hz), 152.6 (d, *J* = 245.7 Hz), 166.3. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1728; ν_{max} = 2922, 1456, 1258, 964, 745. MS (70 eV): m/z (%) 320/2 (M^+ + 1, 100).



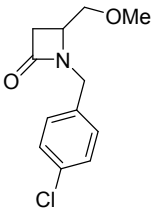
1-Benzyl-4-(methoxymethyl)azetidin-2-one 7a: Light-yellow liquid. R_f = 0.17 (hexane/EtOAc 1/1). Yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.69 (1H, d x d, *J* = 14.5, 2.2 Hz), 2.96 (1H, d x d, *J* = 14.5, 5.2 Hz), 3.24 (3H, s), 3.37 (1H, d x d, *J* = 10.1, 6.6 Hz), 3.46 (1H, d x d, *J* = 10.1, 3.7 Hz), 3.64-3.68 (1H, m), 4.25 (1H, d, *J* = 15.0 Hz), 4.56 (1H, d, *J* = 15.0 Hz), 7.26-7.35 (5H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 39.3, 45.4, 50.2, 59.0, 73.7, 127.5, 128.4, 128.6, 136.4, 166.9. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1740; ν_{max} = 2926, 1395, 1200, 1099, 712. MS (70 eV): m/z (%) 206 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{12}H_{16}NO_2^+$ 206.1176 $[M + H]^+$, found 206.1179.



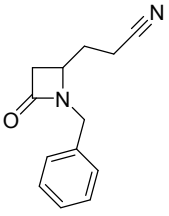
4-Methoxymethyl-1-(4-methylbenzyl)azetidin-2-one 7b: Light-yellow liquid. R_f = 0.15 (hexane/EtOAc 1/1). Yield 84%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (3H, s), 2.67 (1H, d x d, *J* = 14.4, 2.4 Hz), 2.94 (1H, d x d, *J* = 14.4, 5.2, Hz), 3.26 (3H, s), 3.38 (1H, d x d, *J* = 10.1, 6.4 Hz), 3.46 (1H, d x d, *J* = 10.1, 3.8 Hz), 3.62-3.66 (1H, m), 4.18 (1H, d, *J* = 14.9 Hz), 4.54 (1H, d, *J* = 14.9 Hz), 7.14 (2H, d, *J* = 8.1 Hz), 7.18 (2H, d, *J* = 8.1 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 21.1, 39.3, 45.1, 50.0, 59.0, 73.7, 128.4, 129.3, 133.3, 137.2, 166.8. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1740; ν_{max} = 2924, 1516, 1395, 1200, 1098, 729. MS (70 eV): m/z (%) 220 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{13}H_{18}NO_2^+$ 220.1332 $[M + H]^+$, found 220.1331.



1-(4-Chlorobenzyl)-4-(methoxymethyl)azetidin-2-one 7c: Light-yellow liquid. R_f = 0.13 (hexane/EtOAc 1/1). Yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67 (1H, d x d, *J* = 14.5, 2.3 Hz), 2.96 (1H, d x d, *J* = 14.5, 5.2 Hz), 3.25 (3H, s), 3.36 (1H, d x d, *J* = 10.1, 7.0 Hz), 3.48 (1H, d x d, *J* = 10.1, 3.4 Hz), 3.64-3.68 (1H, m), 4.26 (1H, d, *J* = 15.1 Hz), 4.49 (1H, d, *J* = 15.1 Hz), 7.24 (2H, d, *J* = 8.4 Hz), 7.31 (2H, d, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 39.3, 44.8, 50.4, 59.0, 74.0, 128.8, 129.8, 133.4, 135.1, 166.8 (C=O). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1740; ν_{max} = 2926, 1491, 1393, 1200, 1094, 733. MS (70 eV): m/z (%) 240/2 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{12}H_{15}ClNO_2^+$ 240.0786 $[M + H]^+$, found 240.0786.



1-Benzyl-4-(2-cyanoethyl)azetidin-2-one 9a: Yellow liquid. R_f = 0.12 (hexane/EtOAc 1/1). Yield 76%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68-1.77 (1H, m), 1.98 (1H, d x d x t, *J* = 14.2, 4.3, 7.1 Hz), 2.21 (1H, d x t, *J* = 17.1, 7.1 Hz), 2.26 (1H, d x t, *J* = 17.1, 7.4 Hz), 2.69 (1H, d x d, *J* = 14.7, 2.3 Hz), 3.13 (1H, d x d, *J* = 14.7, 5.0 Hz), 3.59-3.64 (1H, m), 4.29 (1H, d, *J* = 15.3 Hz), 4.49 (1H, d, *J* = 15.3 Hz), 7.25-7.39 (5H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 13.5, 28.6, 42.2, 45.2, 50.3, 118.4, 128.08, 128.14, 129.0, 135.7, 166.3. IR (ATR, cm^{-1}): ν_{CN} = 2247; $\nu_{C=O}$ = 1736; ν_{max} = 2922, 1396, 1263, 1119, 916. MS (70 eV): m/z (%) 215 (M^+ + 1, 37). HRMS (ESI) Calcd. for $C_{13}H_{15}N_2O^+$ 215.1179 $[M + H]^+$, found 215.1175.



4-(2-Cyanoethyl)-1-(4-methylbenzyl)azetidin-2-one 9b: Yellow liquid. R_f = 0.11 (hexane/EtOAc 1/1). Yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67-1.77 (1H, m), 1.98 (1H, d x d x t, *J* = 14.2, 4.3, 7.1 Hz), 2.21 (1H, d x t, *J* = 17.0, 7.1 Hz), 2.26 (1H, d x t, *J* = 17.0, 7.4 Hz), 2.35 (3H, s), 2.67 (1H, d x d, *J* = 14.7, 2.3 Hz), 3.12 (1H, d x d, *J* = 14.7, 5.0 Hz), 3.57-3.62 (1H, m), 4.24 (1H, d, *J* = 15.2 Hz), 4.45 (1H, d, *J* = 15.2 Hz), 7.14 (2H, d, *J* = 8.5 Hz), 7.17 (2H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 13.5, 21.1, 28.7, 42.1, 45.0, 50.2, 118.4, 128.1, 129.7, 132.6, 137.9, 166.2. IR (ATR, cm^{-1}): ν_{CN} = 2247; $\nu_{C=O}$ = 1736; ν_{max} = 2924, 1396, 1261, 1111, 910, 812, 727. MS (70 eV): m/z (%) 229 (M^+ + 1, 35).

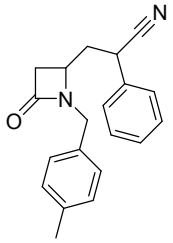
1-(4-Chlorobenzyl)-4-(2-cyanoethyl)azetidin-2-one 9c: Yellow liquid. R_f = 0.08 (hexane/EtOAc 1/1). Yield 88%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73 (1H, d x d x t, *J* = 14.2, 8.4, 7.1 Hz), 2.00 (1H, d x d x t, *J* = 14.2, 7.1, 4.3 Hz), 2.26 (1H, d x t, *J* = 17.1, 7.0 Hz), 2.31 (1H, d x t, *J* = 17.1, 7.4 Hz), 2.71 (1H, d x d, *J* = 14.8, 2.3 Hz), 3.15 (1H, d x d, *J* = 14.8, 5.0 Hz), 3.59-3.64 (1H, m), 4.26 (1H, d, *J* = 15.5 Hz), 4.46 (1H, d, *J* = 15.5 Hz), 7.21 (2H, d, *J* = 8.4 Hz), 7.34 (2H, d, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 13.6, 28.7, 42.4, 44.5, 50.4, 118.3, 129.2, 129.5, 134.0, 134.3, 166.2. IR (ATR, cm^{-1}): ν_{CN} = 2249; $\nu_{C=O}$ = 1736; ν_{max} = 2922, 1491, 1396, 1261, 1090, 908, 727. MS (70 eV): m/z (%) 249/51 (M^+ + 1, 73).

4-(2-Cyanoethyl)-1-(4-methoxybenzyl)azetidin-2-one 9d: Yellow liquid. R_f = 0.07 (hexane/EtOAc 1/1). Yield 86%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67-1.76 (1H, m), 1.98 (1H, d x d x t, *J* = 14.2, 4.3, 7.1 Hz), 2.22 (1H, d x t, *J* = 17.0, 7.1 Hz), 2.27 (1H, d x t, *J* = 17.0, 7.5 Hz), 2.67 (1H, d x d, *J* = 14.7, 2.3 Hz), 3.11 (1H, d x d, *J* = 14.7, 5.0 Hz), 3.57-3.62 (1H, m), 3.81 (3H, s), 4.23 (1H, d, *J* = 15.2 Hz), 4.42 (1H, d, *J* = 15.2 Hz), 6.88 (2H, d, *J* = 8.6 Hz), 7.18 (2H, d, *J* = 8.6 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 13.5, 28.7, 42.1, 44.6, 50.1, 55.3, 114.4, 118.4, 127.6, 129.5, 159.4, 166.2. IR (ATR, cm^{-1}): ν_{CN} = 2249; $\nu_{C=O}$ = 1736; ν_{max} = 2934, 1612, 1512, 1396, 1244, 1177, 1032, 908, 725. MS (70 eV): m/z (%) 245 (M^+ + 1, 33).

1-Benzyl-4-(2-cyano-2-phenylethyl)azetidin-2-one 11a: Obtained as an inseparable mixture of two diastereomers (54/46). Yellow liquid. R_f = 0.28 (hexane/EtOAc 1/1). Yield 98%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89 (1H, d x d x d, *J* = 13.8, 9.6, 6.7 Hz), 2.01 (1H, d x d x d, *J* = 14.0, 9.1, 7.5 Hz), 2.11 (1H, d x d x d, *J* = 14.0, 6.0, 5.5 Hz), 2.33 (1H, d x d x d, *J* = 13.8, 8.1, 3.6 Hz), 2.56 (1H, d x d, *J* = 14.8, 2.1 Hz), 2.58 (1H, d x d, *J* = 14.8, 2.2 Hz), 3.01 (1H, d x d, *J* = 14.8, 4.9 Hz), 3.08 (1H, d x d, *J* = 14.8, 5.0 Hz), 3.56 (1H, d x d, *J* = 9.1, 6.0 Hz), 3.58-3.63 (1H, m), 3.65-3.70 (1H, m), 3.68 (1H, d x d, *J* = 8.1, 6.7 Hz), 4.17 (1H, d, *J* = 15.3 Hz), 4.38 (1H, d, *J* = 15.5 Hz), 4.44 (1H, d, *J* = 15.5 Hz), 4.49 (1H, d, *J* = 15.3 Hz), 7.06-7.08 (2H, m), 7.17-7.23 (4H, m), 7.26-7.39 (14H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 34.1, 34.7, 38.6, 39.5, 42.8, 43.1, 44.9, 45.4, 49.2, 50.0, 119.7, 119.8, 126.9, 127.1, 128.0, 128.06, 128.14,

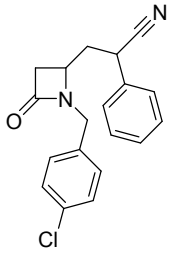
128.5, 128.6, 129.0, 129.1, 129.3, 129.4, 134.4, 134.5, 135.6, 136.2, 166.3, 166.7. IR (ATR, cm^{-1}): ν_{CN} = 2243; $\nu_{C=O}$ = 1738; ν_{max} = 2922, 1396, 1192, 1123, 908, 725. MS (70 eV): m/z (%) 291 (M^+ + 1, 23). HRMS (ESI) Calcd. for $C_{19}H_{19}N_2O^+$ 291.1492 $[M + H]^+$, found 291.1494.

4-(2-Cyano-2-phenylethyl)-1-(4-methylbenzyl)azetidin-2-one 11b: Obtained as an



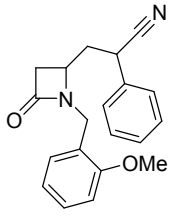
inseparable mixture of two diastereomers (55/45). Yellow liquid. R_f = 0.27 (hexane/EtOAc 1/1). Yield 81%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89 (1H, d x d x d, *J* = 13.8, 9.6, 6.5 Hz), 2.00 (1H, d x d x d, *J* = 14.0, 9.2, 7.5 Hz), 2.11 (1H, d x d x d, *J* = 14.0, 5.8, 5.8 Hz), 2.34 (1H, d x d x d, *J* = 13.8, 8.1, 3.6 Hz), 2.35 (3H, s), 2.36 (3H, s), 2.54 (1H, d x d, *J* = 14.7, 2.4 Hz), 2.57 (1H, d x d, *J* = 14.9, 2.3 Hz), 3.00 (1H, d x d, *J* = 14.7, 5.0 Hz), 3.07 (1H, d x d, *J* = 14.9, 5.2 Hz), 3.55 (1H, d x d, *J* = 9.2, 5.8 Hz), 3.56-3.61 (1H, m), 3.65-3.70 (1H, m), 3.67 (1H, d x d, *J* = 8.1, 6.5 Hz), 4.13 (1H, d, *J* = 15.2 Hz), 4.34 (1H, d, *J* = 15.4 Hz), 4.40 (1H, d, *J* = 15.4 Hz), 4.46 (1H, d, *J* = 15.2 Hz), 7.06-7.19 (12H, m), 7.30-7.39 (6H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 21.1, 34.1, 34.8, 38.6, 39.5, 42.8, 43.1, 44.6, 45.1, 49.1, 50.0, 119.7, 119.8, 126.9, 127.1, 128.0, 128.1, 128.5, 128.6, 129.3, 129.4, 129.68, 129.75, 132.4, 133.1, 134.4, 134.6, 137.8, 137.9, 166.2, 166.6. IR (ATR, cm^{-1}): ν_{CN} = 2241; $\nu_{C=O}$ = 1738; ν_{max} = 2920, 1395, 1113, 912, 727. MS (70 eV): m/z (%) 305 (M^+ + 1, 100).

1-(4-Chlorobenzyl)-4-(2-cyano-2-phenylethyl)azetidin-2-one 11c: Obtained as an



inseparable mixture of two diastereomers (54/46). Yellow liquid. R_f = 0.26 (hexane/EtOAc 1/1). Yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90 (1H, d x d x d, *J* = 13.8, 9.8, 6.2 Hz), 2.03 (1H, d x d x d, *J* = 13.9, 8.6, 8.4 Hz), 2.15 (1H, d x d x d, *J* = 13.9, 5.8, 5.5 Hz), 2.34 (1H, d x d x d, *J* = 13.8, 8.2, 3.4 Hz), 2.58 (2H, d x d, *J* = 14.8, 1.8 Hz), 3.04 (1H, d x d, *J* = 14.8, 5.0 Hz), 3.07 (1H, d x d, *J* = 14.8, 4.9 Hz), 3.59-3.68 (2H, m), 3.64 (1H, d x d, *J* = 8.6, 5.8 Hz), 3.72 (1H, d x d, *J* = 8.2, 6.2 Hz), 4.13 (1H, d, *J* = 15.4 Hz), 4.34 (1H, d, *J* = 15.6 Hz), 4.40 (1H, d, *J* = 15.6 Hz), 4.45 (1H, d, *J* = 15.4 Hz), 7.11-7.16 (4H, m), 7.20-7.22 (4H, m), 7.30-7.40 (10H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 34.2, 34.7, 38.6, 39.3, 43.0, 43.2, 44.2, 44.6, 49.3, 49.9, 119.6, 119.7, 126.9, 127.1, 128.66, 128.71, 129.2, 129.3, 129.39, 129.42, 129.45, 133.9, 134.0, 134.1, 134.25, 134.31, 134.7, 166.2, 166.6. IR (ATR, cm^{-1}): ν_{CN} = 2243; $\nu_{C=O}$ = 1740; ν_{max} = 2922, 1491, 1395, 1192, 1092, 908, 725. MS (70 eV): m/z (%) 325/7 (M^+ + 1, 36).

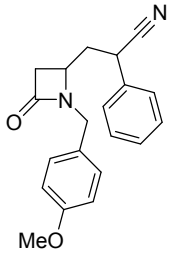
4-(2-Cyano-2-phenylethyl)-1-(2-methoxylbenzyl)azetidin-2-one 11d: Obtained as an



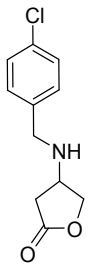
inseparable mixture of two diastereomers (55/45). Yellow liquid. R_f = 0.27 (hexane/EtOAc 1/1). Yield 89%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88 (1H, d x d x d, *J* = 13.7, 10.1, 6.0 Hz), 2.02 (1H, d x d x d, *J* = 13.8, 8.4, 8.4 Hz), 2.31 (1H, d x d x d, *J* = 13.8, 6.1, 4.8 Hz), 2.47 (1H, d x d, *J* = 14.7, 2.3 Hz), 2.51 (1H, d x d x d, *J* = 13.7, 8.9, 3.5 Hz), 2.54 (1H, d x d, *J* = 14.6, 2.1 Hz), 2.97 (1H, d x d, *J* = 14.7, 5.1 Hz), 2.98 (1H, d x d, *J* = 14.6, 5.0 Hz), 3.57-3.65 (2H, m), 3.70 (1H,

d x d, *J* = 8.9, 6.0 Hz), 3.73 (1H, d x d, *J* = 8.4, 6.1 Hz), 3.81 (3H, s), 3.84 (3H, s), 4.19 (1H, d, *J* = 14.8 Hz), 4.31 (1H, d, *J* = 15.3 Hz), 4.49 (1H, d, *J* = 14.8 Hz), 4.51 (1H, d, *J* = 15.3 Hz), 6.87-6.98 (4H, m), 7.16-7.40 (14H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 34.2, 34.6, 38.7, 39.2, 39.5, 39.7, 42.7, 42.9, 49.5, 49.8, 55.37, 55.39, 110.5, 110.6, 119.86, 119.92, 120.96, 121.01, 123.8, 124.0, 127.0, 127.1, 128.51, 128.54, 129.3, 129.4, 129.51, 129.54, 130.4, 130.5, 134.7, 134.8, 157.2, 157.3, 166.1, 166.5. IR (ATR, cm^{-1}): ν_{CN} = 2247; $\nu_{C=O}$ = 1738; ν_{max} = 2938, 1493, 1396, 1246, 1109, 1026, 907, 725. MS (70 eV): m/z (%) 321 (M^+ + 1, 38).

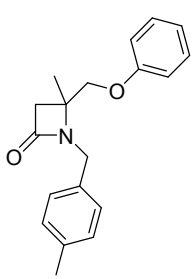
4-(2-Cyano-2-phenylethyl)-1-(4-methoxylbenzyl)azetidin-2-one 11e: Obtained as an inseparable mixture of two diastereomers (52/48). Yellow liquid. R_f = 0.22 (hexane/EtOAc 1/1). Yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89 (1H, d x d x d, *J* = 13.8, 9.7, 6.7 Hz), 2.00 (1H, d x d x d, *J* = 13.9, 9.0, 7.9 Hz), 2.12 (1H, d x d x d, *J* = 13.9, 5.7, 5.7 Hz), 2.34 (1H, d x d x d, *J* = 13.8, 8.2, 3.5 Hz), 2.54 (1H, d x d, *J* = 14.7, 2.1 Hz), 2.56 (1H, d x d, *J* = 14.8, 2.2 Hz), 3.00 (1H, d x d, *J* = 14.7, 5.0 Hz), 3.06 (1H, d x d, *J* = 14.8, 5.0 Hz), 3.56-3.61 (1H, m), 3.59 (1H, d x d, *J* = 9.0, 5.7 Hz), 3.63-3.68 (1H, m), 3.68 (1H, d x d, *J* = 8.2, 6.7 Hz), 3.808 (3H, s), 3.813 (3H, s), 4.11 (1H, d, *J* = 15.5 Hz), 4.35 (2H, s), 4.44 (1H, d, *J* = 15.5 Hz), 8.85-6.90 (4H, m), 7.10-7.20 (8H, m), 7.31-7.40 (6H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 34.1, 34.8, 38.6, 39.5, 42.8, 43.0, 44.3, 44.8, 49.0, 49.8, 55.3, 55.4, 114.4, 114.5, 119.7, 119.8, 126.9, 127.1, 127.5, 128.1, 128.5, 128.6, 129.3, 129.36, 129.39, 129.5, 134.4, 134.5, 159.35, 159.42, 166.2, 166.6. IR (ATR, cm^{-1}): ν_{CN} = 2241; $\nu_{C=O}$ = 1736; ν_{max} = 2914, 1512, 1244, 1175, 1107, 1030, 912, 820, 727. MS (70 eV): m/z (%) 321 (M^+ + 1, 26).



4-[(4-Chlorobenzyl)amino]dihydrofuran-2(3*H*)-one 16: Colorless liquid. R_f = 0.10 (hexane/EtOAc 1/1). Yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (1H, br s), 2.38 (1H, d x d, *J* = 17.5, 4.4 Hz), 2.71 (1H, d x d, *J* = 17.5, 7.1 Hz), 3.64-3.70 (1H, m), 3.74 (1H, d, *J* = 13.4 Hz), 3.79 (1H, d, *J* = 13.4 Hz), 4.11 (1H, d x d, *J* = 9.5, 3.9 Hz), 4.37 (1H, d x d, *J* = 9.5, 5.8 Hz), 7.25 (2H, d, *J* = 8.5 Hz), 7.31 (2H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 35.7, 50.9, 53.8, 73.3, 128.8, 129.4, 133.2, 137.7, 175.8. IR (ATR, cm^{-1}): ν_{NH} = 3319; $\nu_{C=O}$ = 1771; ν_{max} = 2922, 1408, 1171, 1088, 1013, 733. MS (70 eV): m/z (%) 226/8 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{11}H_{13}ClNO_2^+$ 226.0629 $[M + H]^+$, found 226.0629.



4-Methyl-1-(4-methylbenzyl)-4-(phenoxymethyl)azetidin-2-one 18a: Light-yellow liquid. R_f = 0.07 (hexane/EtOAc 4/1). Yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (3H, s), 2.26 (3H, s), 2.73 (1H, d, *J* = 14.3 Hz), 3.07 (1H, d, *J* = 14.3 Hz), 3.76 (1H, d, *J* = 9.8 Hz), 3.79 (1H, d, *J* = 9.8 Hz), 4.31 (1H, d, *J* = 15.2 Hz), 4.36 (1H, d, *J* = 15.2 Hz), 6.75-6.77 (2H, m), 6.93-6.96 (1H, m), 7.02-7.04 (2H, m), 7.18-7.20 (2H, m), 7.23-7.27 (2H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 20.5, 21.1, 43.8, 46.7, 57.8, 71.1, 114.4, 121.2, 128.4, 129.2, 129.4, 133.6, 137.2, 158.2, 166.2. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1736; ν_{max} = 2922,



1497, 1231, 1043, 908, 727. MS (70 eV): m/z (%) 296 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{19}H_{22}NO_2^+$ 296.1645 $[M + H]^+$, found 296.1646.

1-(4-Methoxybenzyl)-4-methyl-4-(phenoxymethyl)azetidin-2-one 18b: Light-yellow liquid. R_f = 0.06 (hexane/EtOAc 4/1). Yield 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (3H, s), 2.73 (1H, d, *J* = 14.3 Hz), 3.07 (1H, d, *J* = 14.3 Hz), 3.72 (3H, s, OCH_3), 3.75 (1H, d, *J* = 9.7 Hz), 3.79 (1H, d, *J* = 9.7 Hz), 4.29 (1H, d, *J* = 15.1 Hz), 4.36 (1H, d, *J* = 15.1 Hz), 6.74-6.78 (4H, m), 6.94-6.97 (1H, m), 7.21-7.28 (4H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 20.4, 43.4, 46.7, 55.2, 57.7, 71.1, 113.9, 114.4, 121.2, 128.7, 129.4, 129.7, 158.2, 159.0, 166.1. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1738; ν_{max} = 2931, 1512, 1385, 1231, 1173, 1032, 835, 753. MS (70 eV): m/z (%) 312 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{19}H_{22}NO_3^+$ 312.1594 $[M + H]^+$, found 312.1604.

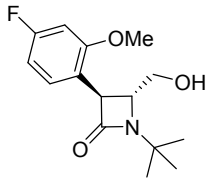
***Trans*-1-*tert*-butyl-4-hydroxymethyl-3-(2-methoxyphenyl)azetidin-2-one 19a**: Light-yellow solid. Mp 117°C. Yield 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (9H, s), 2.43 (1H, br s), 3.56-3.59 (1H, m), 3.81 (1H, d x d, *J* = 11.2, 6.6 Hz), 3.86 (3H, s), 3.99 (1H, d x d, *J* = 11.2, 3.2 Hz), 4.09 (1H, d, *J* = 2.2 Hz), 6.89 (1H, d, *J* = 7.7 Hz), 6.97 (1H, t x d, *J* = 7.7, 0.7 Hz), 7.28 (1H, t x d, *J* = 7.7, 1.5 Hz), 7.37 (1H, d x d, *J* = 7.7, 1.5 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 28.4, 52.0, 54.1, 55.5, 60.2, 64.4, 110.4, 121.3, 124.0, 128.3, 128.8, 156.7, 167.6. IR (ATR, cm^{-1}): ν_{OH} = 3316; $\nu_{C=O}$ = 1718; ν_{max} = 2970, 1494, 1365, 1246, 1026, 753. MS (70 eV): m/z (%) 264 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{15}H_{22}NO_3^+$ 264.1594 $[M + H]^+$, found 264.1591.

***Trans*-1-*tert*-butyl-4-hydroxymethyl-3-(5-isopropyl-2-methoxyphenyl)azetidin-2-one 19b**: Light-yellow solid. Mp 119°C. Yield 99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (3H, d, *J* = 6.8 Hz), 1.22 (3H, d, *J* = 6.8 Hz), 1.41 (9H, s, $C(CH_3)_3$); 2.48 (1H, br s), 2.86 (1H, septet, *J* = 6.8 Hz), 3.58-3.61 (1H, m), 3.80 (1H, d x d, *J* = 11.2, 6.6 Hz), 3.83 (3H, s), 3.98 (1H, d x d, *J* = 11.2, 3.1 Hz), 4.06 (1H, d, *J* = 1.7 Hz), 6.82 (1H, d, *J* = 8.4 Hz), 7.13 (1H, d x d, *J* = 8.4, 1.7 Hz), 7.21 (1H, d, *J* = 1.7 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 24.1, 24.2, 28.4, 33.3, 52.3, 54.1, 55.5, 60.1, 64.4, 110.4, 123.6, 126.1, 126.7, 141.7, 154.9, 167.8. IR (ATR, cm^{-1}): ν_{OH} = 3385; $\nu_{C=O}$ = 1713; ν_{max} = 2957, 1506, 1258, 1026, 818. MS (70 eV): m/z (%) 306 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{18}H_{28}NO_3^+$ 306.2064 $[M + H]^+$, found 306.2078.

***Trans*-3-(5-bromo-2-methoxyphenyl)-1-*tert*-butyl-4-(hydroxymethyl)azetidin-2-one 19c**: Light-yellow solid. Mp 136°C. Yield 96%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (9H, s), 2.30 (1H, br s), 3.58-3.61 (1H, m), 3.830 (3H, s), 3.834 (1H, d x d, *J* = 11.2, 6.1 Hz), 3.96 (1H, d x d, *J* = 11.2, 2.9 Hz), 4.05 (1H, d, *J* = 1.7 Hz), 6.75 (1H, d, *J* = 8.7 Hz), 7.37 (1H, d x d, *J* = 8.7, 2.1 Hz), 7.46 (1H, d, *J* = 2.1 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 28.4, 51.4, 54.2, 55.7, 59.9, 63.9, 112.1, 113.5, 126.2, 131.3, 131.4, 156.1, 166.9. IR (ATR, cm^{-1}): ν_{OH} = 3352; $\nu_{C=O}$ =

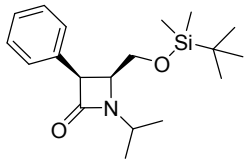
1709; ν_{max} = 2974, 1489, 1248, 1022, 750. MS (70 eV): m/z (%) 342/4 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{15}H_{21}BrNO_3^+$ 342.0699 $[M + H]^+$, found 342.0704.

***Trans*-1-*tert*-butyl-3-(4-fluoro-2-methoxyphenyl)-4-(hydroxymethyl)azetidin-2-one 19d**:



Light-yellow solid. Mp 131°C. Yield 99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (9H, s), 2.55 (1H, br s), 3.56-3.59 (1H, m), 3.820 (3H, s), 3.824 (1H, d x d, *J* = 11.3, 5.8 Hz), 3.91-3.96 (1H, m), 4.03 (1H, d, *J* = 2.0 Hz), 6.61 (1H, d x d, *J* = 8.4, 2.4 Hz), 6.64 (1H, ~t x d, *J* = 8.4, 2.4 Hz), 7.28 (1H, ~t, *J* = 8.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -111.91-(-111.84) (m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 28.3, 51.2, 54.1, 55.7, 60.1, 63.8, 99.1 (d, *J* = 26.3 Hz), 107.3 (d, *J* = 20.9 Hz), 119.8 (d, *J* = 3.4 Hz), 129.3 (d, *J* = 10.1 Hz), 158.1 (d, *J* = 10.0 Hz), 163.1 (d, *J* = 245.7 Hz), 167.7. IR (ATR, cm^{-1}): ν_{OH} = 3350; $\nu_{C=O}$ = 1711; ν_{max} = 2945, 1506, 1368, 1283, 1153, 1051, 810. MS (70 eV): m/z (%) 282 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{15}H_{21}FNO_3^+$ 282.1500 $[M + H]^+$, found 282.1507.

***Cis*-4-{[(*tert*-butyldimethylsilyl)oxy]methyl}-1-isopropyl-3-phenylazetidin-2-one 21**:



Light-yellow liquid. R_f = 0.25 (hexane/EtOAc 4/1). Yield 76%. ^{1}H NMR (400 MHz, $CDCl_3$): δ -0.17 (3H, s), -0.13 (3H, s), 0.81 (9H, s), 1.29 (3H, d, *J* = 6.7 Hz), 1.33 (3H, d, *J* = 6.7 Hz), 3.33 (1H, d x d, *J* = 10.9, 5.2 Hz), 3.40 (1H, d x d, *J* = 10.9, 6.9 Hz), 3.95 (1H, d x d x d, *J* = 6.9, 5.6, 5.2 Hz), 4.00 (1H, septet, *J* = 6.7 Hz), 4.43 (1H, d, *J* = 5.6 Hz), 7.22-7.33 (5H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ -5.8, 18.1, 19.9, 22.0, 25.8, 44.3, 55.8, 56.8, 63.6, 127.4, 128.5, 129.0, 133.0, 167.5. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1744; ν_{max} = 2930, 1391, 1254, 1082, 835, 731. MS (70 eV): m/z (%) 334 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{19}H_{32}NO_2Si^+$ 334.2197 $[M + H]^+$, found 334.2207.

Synthesis of β-lactams 12 and 30

As a representative example for the demethylation reaction, the synthesis of 4-hydroxymethyl-1-(4-methylbenzyl)azetidin-2-one **12a** is described here. To a solution of 4-methoxymethyl-1-(4-methylbenzyl)azetidin-2-one **7b** (0.44 g, 2 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (40 mL), boron tribromide (6 mL 1 M in CH_2Cl_2, 6 mmol, 3 equiv.) was added at -78 °C. The resulting mixture was allowed to warm to room temperature, stirred for 16 h, and re-cooled to -50 °C. The reaction was carefully quenched with H_2O and the solvent was evaporated *in vacuo*. Subsequently, a saturated aqueous NH_4Cl solution (10 mL) was added and the resulting mixture was extracted with EtOAc (3 x 15 mL). Drying of the combined organic phases with $MgSO_4$, filtration of the drying agent and removal of the solvent *in vacuo* afforded crude 4-hydroxymethyl-1-(4-methylbenzyl)azetidin-2-one **12a**, which was purified in 99% yield (0.41 g) by column chromatography on silica gel (EtOAc).

4-Hydroxymethyl-1-(4-methylbenzyl)azetidin-2-one 12a: Light-yellow liquid. R_f = 0.20 (EtOAc). Yield 99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (1H, br s), 2.34 (3H, s), 2.81 (1H, d x d, *J* = 14.4, 2.2 Hz), 2.94 (1H, d x d, *J* = 14.4, 4.9 Hz), 3.53-3.57 (1H, m), 3.62-3.69 (2H, m), 4.35 (1H, d, *J* = 15.0 Hz), 4.42 (1H, d, *J* = 15.0 Hz), 7.17 (2H, d, *J* = 8.1 Hz), 7.21 (2H, d, *J* = 8.1 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 21.2, 38.7, 45.2, 52.7, 62.5, 128.2, 129.7, 133.3, 137.8, 167.2. IR (ATR, cm^{-1}): ν_{OH} = 3362; $\nu_{C=O}$ = 1705; ν_{max} = 2916, 1404, 1248, 1103, 1053, 955, 808. MS (70 eV): m/z (%) 206 (M^+ + 1, 100).

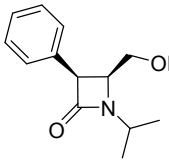
1-(4-Chlorobenzyl)-4-(hydroxymethyl)azetidin-2-one 12b: Colorless liquid. R_f = 0.16 (EtOAc). Yield 96%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93 (1H, br s), 2.79 (1H, d x d, *J* = 14.6, 1.9 Hz), 2.95 (1H, d x d, *J* = 14.6, 5.0 Hz), 3.59-3.66 (2H, m), 3.73-3.78 (1H, m), 4.29 (1H, d, *J* = 15.2 Hz), 4.50 (1H, d, *J* = 15.2 Hz), 7.25 (2H, d, *J* = 8.4 Hz), 7.32 (2H, d, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 38.8, 44.7, 52.4, 62.6, 129.1, 129.7, 133.7, 134.8, 167.3. IR (ATR, cm^{-1}): ν_{OH} = 3393; $\nu_{C=O}$ = 1721; ν_{max} = 2924, 1491, 1402, 1192, 1092, 955. MS (70 eV): m/z (%) 226/8 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{11}H_{13}ClNO_2^+$ 226.0629 $[M + H]^+$, found 226.0633.

***Trans*-1-*tert*-butyl-3-(2-hydroxyphenyl)-4-(tosyloxymethyl)azetidin-2-one 30**: White solid. Recrystallization from hexane/EtOAc (1/30). Mp 158°C. Yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (9H, s), 2.45 (3H, s), 4.03 (1H, d, *J* = 2.3 Hz), 4.11-4.14 (1H, m), 4.34 (1H, d x d, *J* = 10.9, 4.6 Hz), 4.39 (1H, d x d, *J* = 10.9, 4.4 Hz), 6.82 (1H, t, *J* = 7.4 Hz), 6.83 (1H, d, *J* = 7.4 Hz), 6.97 (1H, d, *J* = 7.4 Hz), 7.12 (1H, t x d, *J* = 7.4, 1.1 Hz), 7.35 (2H, d, *J* = 8.2 Hz), 7.80 (2H, d, *J* = 8.2 Hz), 8.10 (1H, s). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 21.7, 28.2, 52.1, 55.0, 55.1, 69.2, 117.5, 120.3, 120.4, 127.8, 128.0, 129.0, 130.1, 132.3, 145.6, 155.1, 168.5. IR (ATR, cm^{-1}): ν_{OH} = 3230; $\nu_{C=O}$ = 1719; ν_{max} = 2977, 1456, 1364, 1176, 913, 756. MS (70 eV): m/z (%) 404 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{21}H_{26}NO_5S^+$ 404.1526 $[M + H]^+$, found 404.1527.

Synthesis of *cis*-4-hydroxymethyl-1-isopropyl-3-phenylazetidin-2-one 22

To an ice-cooled solution of *cis*-4-{[(*tert*-butyldimethylsilyl)oxy]methyl}-1-isopropyl-3-phenylazetidin-2-one **21** (0.33 g, 1 mmol, 1 equiv.) in anhydrous THF (10 mL), tetrabutylammonium fluoride (2 mL 1 M in THF, 2 mmol, 2 equiv.) was added. The resulting mixture was stirred for 4 hour at room temperature, after which the solvent was evaporated *in vacuo*. Subsequently, a 2 M aqueous HCl solution (10 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 x 15 mL). Drying of the combined organic phases with $MgSO_4$, filtration of the drying agent and removal of the solvent *in vacuo* afforded crude *cis*-4-hydroxymethyl-1-isopropyl-3-phenylazetidin-2-one **22**, which was purified in 67% yield (0.15 g) by column chromatography on silica gel (hexane/EtOAc 1/1).

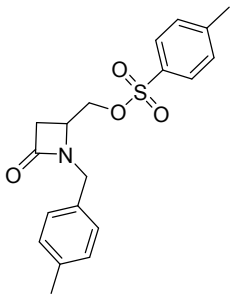
***Cis*-4-hydroxymethyl-1-isopropyl-3-phenylazetidin-2-one 22:** White solid. R_f = 0.14 (hexane/EtOAc 1/1). Mp 108°C. Yield 67%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (1H, t, *J* = 5.5 Hz), 1.28 (3H, d, *J* = 6.8 Hz), 1.32 (3H, d, *J* = 6.8 Hz), 3.45-3.50 (1H, m), 3.55-3.61 (1H, m), 3.96-4.06 (2H, m), 4.49 (1H, d, *J* = 5.6 Hz), 7.26-7.38 (5H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 20.0, 22.1, 44.2, 55.8, 56.0, 62.6, 127.9, 128.7, 128.9, 132.9, 167.1. IR (ATR, cm^{-1}): ν_{OH} = 3495; $\nu_{C=O}$ = 1705; ν_{max} = 2928, 1400, 1038, 733. MS (70 eV): m/z (%) 220 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{13}H_{18}NO_2^+$ 220.1332 $[M + H]^+$, found 220.1330.



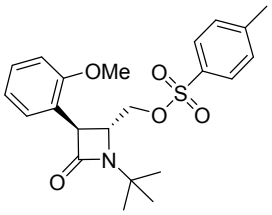
Synthesis of β-lactams 23 and 29

As a representative example for the tosylation reaction, the synthesis of 1-(4-methylbenzyl)-4-(tosyloxymethyl)azetidin-2-one **23** is described here. To an ice-cooled solution of 4-hydroxymethyl-1-(4-methylbenzyl)azetidin-2-one **12a** (0.21 g, 1 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (10 mL), 4-dimethylaminopyridine (0.02 g, 0.2 mmol, 0.2 equiv.), *p*-toluenesulfonyl chloride (0.38 g, 2 mmol, 2 equiv.) and triethylamine (0.20 g, 2 mmol, 2 equiv.) were added. After stirring for 7 hours at room temperature, brine (10 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 x 20 mL). Drying of the combined organic phases with $MgSO_4$, filtration of the drying agent and removal of the solvent *in vacuo* afforded crude 1-(4-methylbenzyl)-4-(tosyloxymethyl)azetidin-2-one **23**, which was purified in 93% yield (0.33 g) by column chromatography on silica gel (hexane/EtOAc 1/1).

1-(4-Methylbenzyl)-4-(tosyloxymethyl)azetidin-2-one 23: White solid. R_f = 0.17 (hexane/EtOAc 1/1). Mp 91°C. Yield 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (3H, s), 2.47 (3H, s), 2.66 (1H, d x d, *J* = 14.7, 2.2 Hz), 2.96 (1H, d x d, *J* = 14.7, 5.3 Hz), 3.63-3.67 (1H, m), 3.966 (1H, d x d, *J* = 10.7, 6.1 Hz), 3.972 (1H, d, *J* = 14.9 Hz), 4.09 (1H, d x d, *J* = 10.7, 3.9 Hz), 4.56 (1H, d, *J* = 14.9 Hz), 7.09 (2H, d, *J* = 8.1 Hz), 7.13 (2H, d, *J* = 8.1 Hz), 7.35 (2H, d, *J* = 8.2 Hz), 7.73 (2H, d, *J* = 8.2 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 21.2, 21.7, 39.4, 45.1, 48.6, 69.6, 127.9, 128.4, 129.5, 130.0, 132.28, 132.35, 137.6, 145.4, 165.8. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1738; ν_{max} = 2932, 1396, 1354, 1171, 964, 664. MS (70 eV): m/z (%) 360 (M^+ + 1, 100).



***Trans*-1-*tert*-butyl-3-(2-methoxyphenyl)-4-(tosyloxymethyl)azetidin-2-one 29**: White solid. R_f = 0.18 (hexane/EtOAc 3/1). Mp 113°C. Yield 97%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (9H, s), 2.46 (3H, s), 3.72-3.74 (1H, m), 3.73 (3H, s), 3.92 (1H, d, *J* = 2.5 Hz), 4.26 (1H, d x d, *J* = 10.7, 4.4 Hz), 4.41 (1H, d x d, *J* = 10.7, 3.4 Hz), 6.83 (1H, d, *J* = 7.7 Hz), 6.90 (1H, t x d, *J* = 7.7, 0.8 Hz), 7.25 (1H, t x d, *J* = 7.7, 1.6 Hz), 7.27 (1H, d x d, *J* = 7.7, 1.6 Hz), 7.36 (2H, d, *J* = 8.2 Hz), 7.81 (2H, d, *J* = 8.2 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 21.7, 28.3, 51.8, 54.2, 55.1, 56.6, 69.8, 110.3, 120.8, 123.2, 128.0, 128.8, 128.9, 130.0, 132.7, 145.2, 157.4, 166.9. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1739; ν_{max} = 2973, 1495, 1360,

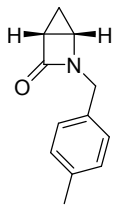


1175, 911, 814, 754. MS (70 eV): m/z (%) 418 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{22}H_{28}NO_5S^+$ 418.1683 $[M + H]^+$, found 418.1681.

Synthesis of c*is*-2-(4-methylbenzyl)-2-azabicyclo[2.1.0]pentan-3-one 24

To a solution of 1-(4-methylbenzyl)-4-(tosyloxymethyl)azetidin-2-one **23** (0.11 g, 0.3 mmol, 1 equiv.) in anhydrous THF (3 mL), lithium hexamethyldisilazide (0.6 mL 1 M in THF, 0.6 mmol, 2 equiv.) was added at -78 °C. After stirring for 30 minutes at -78 °C, the resulting mixture was allowed to warm to 0 °C and was additionally stirred for 30 minutes. Subsequently, a saturated aqueous NH_4Cl solution (5 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). Drying of the combined organic phases with $MgSO_4$, filtration of the drying agent and removal of the solvent *in vacuo* afforded 0.05 g (91% yield) c*is*-2-(4-methylbenzyl)-2-azabicyclo[2.1.0]pentan-3-one **24** in high purity (>90% based on ^1H NMR in $CDCl_3$).

C*is*-2-(4-methylbenzyl)-2-azabicyclo[2.1.0]pentan-3-one 24: Light-yellow liquid. R_f = 0.21 (hexane/EtOAc 3/1). Yield 91%. ^1H NMR (400 MHz, $CDCl_3$): δ 1.56 (1H, d x d x d, *J* = 5.8, 5.6, 2.9 Hz), 1.93 (1H, d x d x d, *J* = 5.6, 1.8, 1.0 Hz), 2.35 (3H, s), 2.46 (1H, d x d x d, *J* = 5.8, 4.0, 1.8 Hz), 3.65 (1H, d x d x d, *J* = 4.0, 2.9, 1.0 Hz), 3.96 (1H, d, *J* = 14.7 Hz), 4.26 (1H, d, *J* = 14.7 Hz), 7.15 (2H, d, *J* = 8.5 Hz), 7.18 (2H, d, *J* = 8.5 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 21.2, 24.0, 33.0, 34.7, 47.4, 128.3, 129.4, 133.7, 137.3, 172.1. MS (70 eV): m/z (%) 188 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{12}H_{14}NO^+$ 188.1070 $[M + H]^+$, found 188.1065.

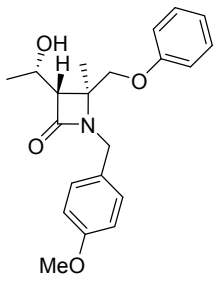


Synthesis of 3-(1-hydroxyethyl)-1-(4-methoxybenzyl)-4-methyl-4-(phenoxymethyl) azetidin-2-one 25

To a solution of 1-(4-methoxybenzyl)-4-methyl-4-(phenoxymethyl)azetidin-2-one **18b** (0.31 g, 1 mmol, 1 equiv.) in anhydrous THF (3 mL), lithium diisopropylamide (0.75 mL 2 M in THF/heptane/ethylbenzene, 1.5 mmol, 1.5 equiv.) was added at -78 °C. After stirring for 45 minutes at -78 °C, acetaldehyde (0.18 g, 4 mmol, 4 equiv.) was added and the resulting mixture was allowed to warm to room temperature over a period of 45 minutes. Subsequently, a saturated aqueous NH_4Cl solution (5 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). Drying of the combined organic phases with $MgSO_4$, filtration of the drying agent and removal of the solvent *in vacuo* afforded crude 3-(1-hydroxyethyl)-1-(4-methoxybenzyl)-4-methyl-4-(phenoxymethyl)azetidin-2-one **25**, which was purified in 81% yield (0.29 g) by preparative HPLC.

Obtained as a mixture of three diastereomers (56/30/14), which were separated by preparative HPLC in 81% combined yield. The relative configuration of the major diastereomer was established by single crystal X-ray analysis.

Diastereomer 1: (3*S,4*S**)-3-((*S**)-1-hydroxyethyl)-1-(4-methoxybenzyl)-4-methyl-4-(phenoxymethyl)azetidin-2-one**: White crystals. R_f = 0.18 (hexane/EtOAc 1/1). Mp 120°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (3H, d, *J* = 6.2 Hz), 1.35 (3H, s), 2.62 (1H, d, *J* = 3.4 Hz), 3.10 (1H, d, *J* = 7.7 Hz), 3.66 (1H, d, *J* = 9.7 Hz), 3.71 (1H, d, *J* = 9.7 Hz), 3.73 (3H, s), 4.14-4.21 (1H, m), 4.24 (1H, d, *J* = 15.2 Hz), 4.42 (1H, d, *J* = 15.2 Hz), 6.73-6.78 (4H, m), 6.94-6.97 (1H, m), 7.20-7.27 (4H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 16.0, 22.4, 42.9, 55.2, 60.8, 61.5, 64.9, 71.8, 114.0, 114.4, 121.3, 128.5, 129.5, 129.7, 158.1, 159.1, 168.2. IR (ATR, cm^{-1}): ν_{OH} = 3372; $\nu_{C=O}$ = 1721; ν_{max} = 2964, 1239, 1172, 1031, 831, 755. MS (70 eV): m/z (%) 356 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{21}H_{26}NO_4^+$ 356.1856 $[M + H]^+$, found 356.1868.



Diastereomer 2: Light-yellow liquid. R_f = 0.21 (hexane/EtOAc 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (3H, d, *J* = 6.2 Hz), 1.37 (3H, s), 2.52 (1H, d, *J* = 9.3 Hz), 2.95 (1H, d, *J* = 6.6 Hz), 3.76 (3H, s), 3.95 (1H, d, *J* = 9.7 Hz), 4.00 (1H, d, *J* = 9.7 Hz), 4.28-4.33 (1H, m), 4.32 (1H, d, *J* = 15.3 Hz), 4.38 (1H, d, *J* = 15.3 Hz), 6.75-6.81 (4H, m), 6.95-6.98 (1H, m), 7.20-7.28 (4H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 21.9, 22.9, 43.2, 55.3, 61.2, 64.3, 66.1, 69.5, 114.0, 114.3, 121.4, 128.7, 129.5, 129.7, 157.9, 159.1, 167.8. IR (ATR, cm^{-1}): ν_{OH} = 3434; $\nu_{C=O}$ = 1728; ν_{max} = 2970, 1512, 1242, 1033, 908, 728. MS (70 eV): m/z (%) 356 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{21}H_{26}NO_4^+$ 356.1856 $[M + H]^+$, found 356.1869.

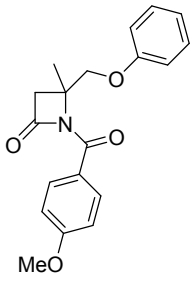
Diastereomer 3: Light-yellow liquid. R_f = 0.20 (hexane/EtOAc 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (3H, s), 1.46 (3H, d), 3.14 (1H, d), 3.72 (3H, s), 3.74 (1H, d, *J* = 9.6 Hz), 3.79 (1H, d, *J* = 9.6 Hz), 4.16-4.24 (1H, m), 4.26 (1H, d, *J* = 15.1 Hz), 4.37 (1H, d, *J* = 15.1 Hz), 6.73-6.77 (4H, m), 6.93-6.97 (1H, m), 7.20-7.27 (4H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 16.6, 22.7, 43.0, 55.2, 61.3, 62.6, 64.5, 71.7, 113.9, 114.4, 121.2, 128.7, 129.4, 129.7, 158.1, 159.0, 166.4. IR (ATR, cm^{-1}): ν_{OH} = 3425; $\nu_{C=O}$ = 1724; ν_{max} = 2931, 1513, 1241, 1034, 908, 727. MS (70 eV): m/z (%) 356 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{21}H_{26}NO_4^+$ 356.1856 $[M + H]^+$, found 356.1862.

Synthesis of 1-(4-methoxybenzoyl)-4-methyl-4-(phenoxymethyl)azetidin-2-one 26

To a solution of 1-(4-methoxybenzyl)-4-methyl-4-(phenoxymethyl)azetidin-2-one **18b** (0.31 g, 1 mmol, 1 equiv.) in CH_3CN/H_2O (2/1, 10 mL), potassium persulfate (0.92 g, 3.4 mmol, 3.4 equiv.) and potassium dihydrogen phosphate (0.93 g, 6.8 mmol, 6.8 equiv.) were added. After stirring for 4 hours at reflux, the solvent was evaporated *in vacuo* and the residue was dissolved in CH_2Cl_2 (10 mL). The resulting mixture was washed with H_2O (2 x 5 mL), a saturated aqueous $NaHCO_3$ solution (5 mL) and brine (5 mL), after which the combined aqueous phases were extracted again with CH_2Cl_2 (3 x 10 mL). Drying of the combined organic phases with $MgSO_4$, filtration of the drying agent and removal of the solvent *in vacuo* afforded crude 1-(4-methoxybenzoyl)-4-methyl-4-(phenoxymethyl)azetidin-2-one **26**, which

was purified in 70% yield (0.23 g) by column chromatography on silica gel (hexane/EtOAc 4/1).

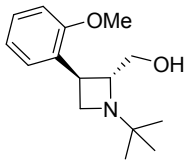
1-(4-Methoxybenzoyl)-4-methyl-4-(phenoxymethyl)azetidin-2-one 26: White crystals. R_f = 0.17 (hexane/EtOAc 4/1). Mp 78°C. Yield 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.79 (3H, s), 2.84 (1H, d, *J* = 15.8 Hz), 3.39 (1H, d, *J* = 15.8 Hz), 3.85 (3H, s), 4.17 (1H, d, *J* = 9.8 Hz), 4.63 (1H, d, *J* = 9.8 Hz), 6.90-6.97 (5H, m), 7.24-7.29 (2H, m), 7.88-7.92 (2H, m). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 20.8, 45.4, 55.4, 58.1, 69.0, 113.3, 114.8, 121.4, 124.7, 129.5, 131.9, 158.4, 163.4, 163.8, 166.3. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1785; ν_{max} = 2935, 1659, 1601, 1296, 1254, 1237, 1173, 1020, 759. MS (70 eV): m/z (%) 326 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{19}H_{20}NO_4^+$ 326.1387 $[M + H]^+$, found 326.1401.



Synthesis of *trans*-1-*tert*-butyl-2-hydroxymethyl-3-(2-methoxyphenyl)azetidine 27

To an ice-cooled solution of aluminum(III) chloride (0.40 g, 3 mmol, 3 equiv.) in anhydrous Et_2O (30 mL), lithium aluminum hydride (3 mL 1 M in Et_2O, 3 mmol, 3 equiv.) was added. The resulting mixture was stirred for 1 hour at room temperature, after which *trans*-1-*tert*-butyl-4-hydroxymethyl-3-(2-methoxyphenyl)azetidin-2-one **19a** (0.26 g, 1 mmol, 1 equiv.) was added. After 16 hours at reflux, water (30 mL) was added carefully to neutralise the residual hydride and the reaction mixture was extracted with Et_2O (6 x 30 mL). Drying of the combined organic phases with $MgSO_4$, filtration of the drying agent and removal of the solvent *in vacuo* afforded 0.23 g (93% yield) *trans*-1-*tert*-butyl-2-hydroxymethyl-3-(2-methoxyphenyl)azetidine **27** in high purity (>95% based on ^{1}H NMR in $CDCl_3$), which was used as such in the next reaction step.

***Trans*-1-*tert*-butyl-2-hydroxymethyl-3-(2-methoxyphenyl)azetidine 27**: Light-yellow liquid. Yield 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (9H, s), 3.84 (3H, s), 3.95 (1H, d x d, *J* = 9.3, 7.7 Hz), 4.02 (1H, d x d, *J* = 14.2, 4.2 Hz), 4.18 (1H, d x d, *J* = 14.2, 1.7 Hz), 4.30 (1H, d x d, *J* = 9.4, 9.3 Hz), 4.30-4.39 (1H, m), 4.53-4.56 (1H, m), 6.91 (1H, d, *J* = 7.7 Hz), 6.98 (1H, t x d, *J* = 7.7, 0.9 Hz), 7.12 (1H, t x d, *J* = 7.7, 1.6 Hz), 7.30 (1H, d x d, *J* = 7.7, 1.6 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 23.9, 29.4, 48.7, 55.2, 59.6, 60.7, 69.8, 110.7, 120.8, 124.8, 126.9, 129.1, 157.2. IR (ATR, cm^{-1}): ν_{OH} = 3292; ν_{max} = 2977, 2602, 1497, 1247, 1023, 758. MS (70 eV): m/z (%) 250 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{15}H_{24}NO_2^+$ 250.1802 $[M + H]^+$, found 250.1801.



Synthesis of *trans*-1-*tert*-butyl-3-chloro-4-(2-methoxyphenyl)pyrrolidine 28

To a solution of *trans*-1-*tert*-butyl-2-hydroxymethyl-3-(2-methoxyphenyl)azetidine **27** (0.12 g, 0.5 mmol, 1 equiv.) in CH_3CN (10 mL), triethylamine (0.15 g, 1.5 mmol, 3 equiv.) and *p*-toluenesulfonyl chloride (0.14 g, 0.75 mmol, 1.5 equiv.) were added. After stirring for 16

hours at 35 °C, brine (15 mL) was added and the resulting mixture was extracted with Et_2O (3 x 20 mL). Drying of the combined organic phases with $MgSO_4$, filtration of the drying agent and removal of the solvent *in vacuo* afforded crude *trans*-1-*tert*-butyl-3-chloro-4-(2-methoxyphenyl)pyrrolidine **28**, which was purified in 59% yield (0.08 g) by column chromatography on silica gel (hexane/EtOAc 4/1).

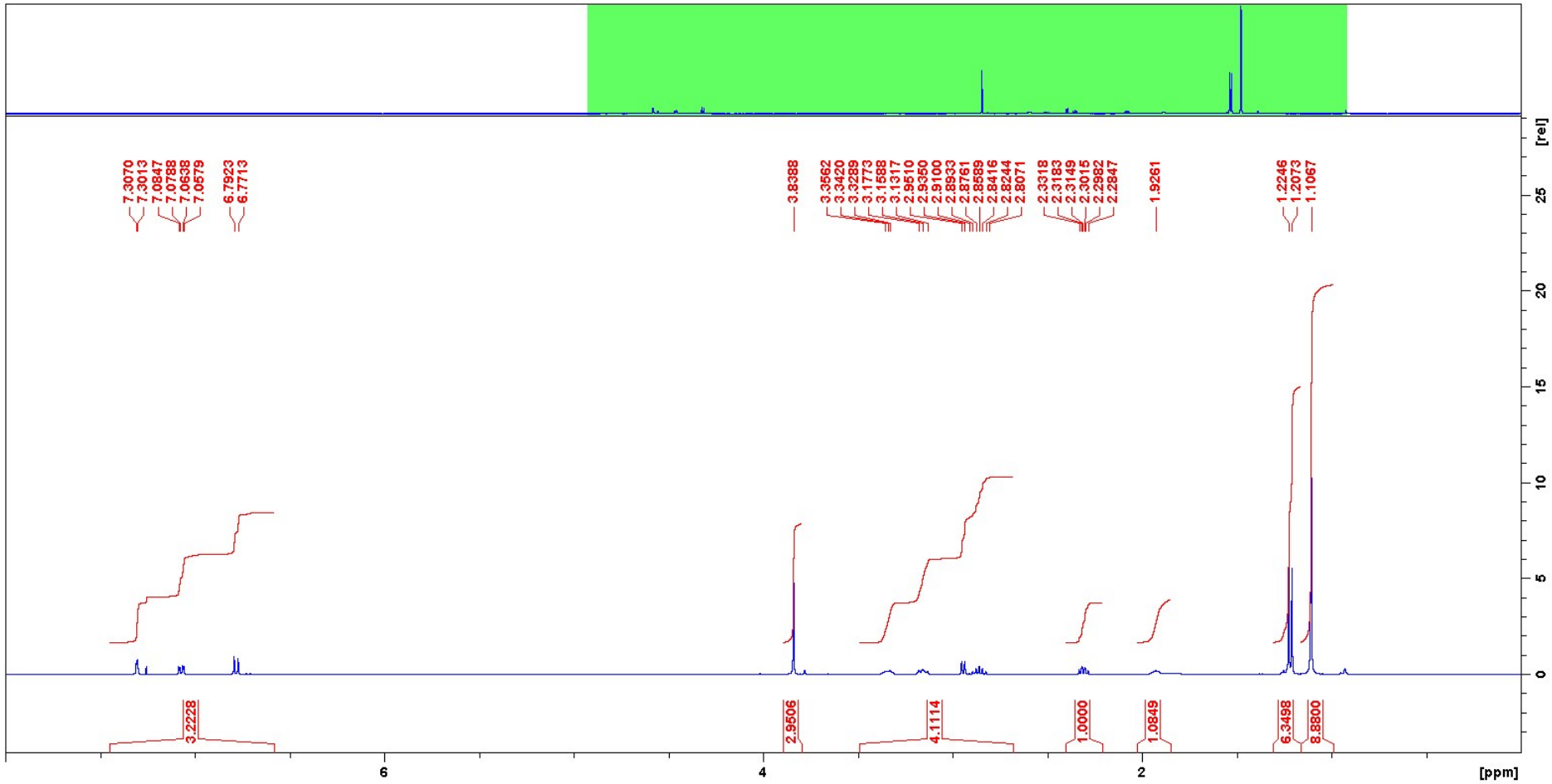
***Trans*-1-*tert*-butyl-3-chloro-4-(2-methoxyphenyl)pyrrolidine 28**: Light-yellow liquid. R_f = 0.17 (hexane/EtOAc 4/1). Yield 59%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (9H, s), 2.78 (1H, ~t, *J* = 8.4 Hz), 3.01 (1H, d x d, *J* = 10.0, 5.8 Hz), 3.26 (1H, ~t, *J* = 8.4 Hz), 3.38 (1H, d x d, *J* = 10.0, 7.0 Hz), 3.76 (1H, ~t x d, *J* = 8.4, 7.0 Hz), 3.83 (3H, s), 4.47 (1H, d x d x d, *J* = 7.0, 7.0, 5.8 Hz), 6.88 (1H, d, *J* = 7.7 Hz), 6.94 (1H, t x d, *J* = 7.7, 1.0 Hz), 7.23 (1H, t x d, *J* = 7.7, 1.7 Hz), 7.32 (1H, d x d, *J* = 7.7, 1.7 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 25.8, 48.6, 51.8, 52.6, 55.4, 55.7, 61.0, 110.7, 120.8, 128.0, 128.1, 128.8, 157.6. IR (ATR, cm^{-1}): ν_{max} = 2925, 1494, 1242, 1030, 751. MS (70 eV): m/z (%) 268/70 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{15}H_{23}ClNO^+$ 268.1463 $[M + H]^+$, found 268.1466.

Synthesis of *cis*-2-*tert*-butyl-2a,8b-dihydro-2*H*-chromeno[3,4-*b*]azet-1(3*H*)-one 31

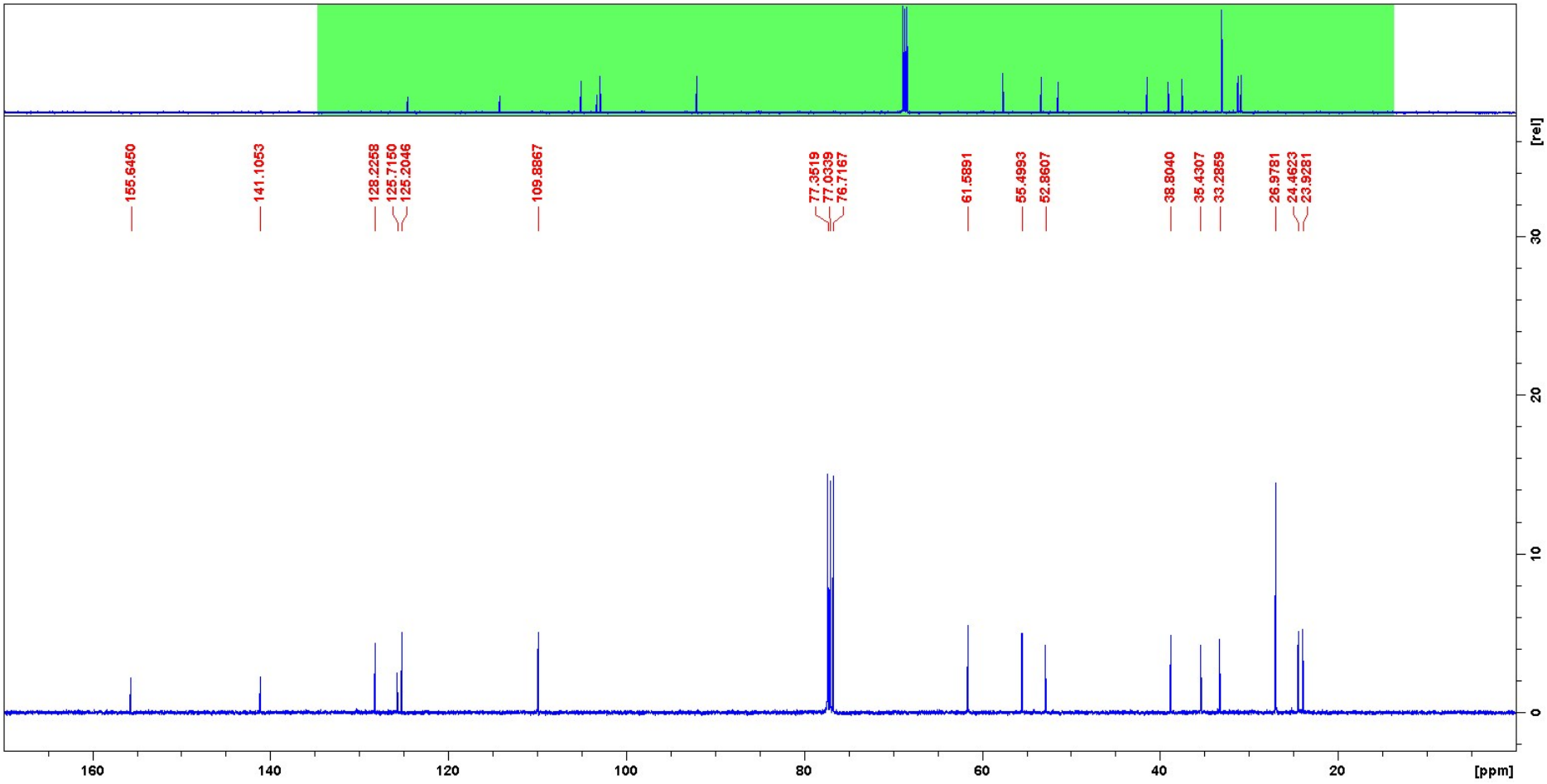
To a solution of *trans*-1-*tert*-butyl-3-(2-hydroxyphenyl)-4-(tosyloxymethyl)azetidin-2-one **30** (0.20 g, 0.5 mmol, 1 equiv.) in anhydrous THF (20 mL), diazabicycloundecene (0.15 g, 1 mmol, 2 equiv.) was added. After stirring for 3 hours at reflux, the solvent was evaporated *in vacuo*, after which the residue was dissolved in CH_2Cl_2 (20 mL) and washed with H_2O (10 mL) and a 3 M aqueous HCl solution (2 x 10 mL). Drying of the organic phases with $MgSO_4$, filtration of the drying agent and removal of the solvent *in vacuo* afforded 0.11 g (99% yield) *cis*-2-*tert*-butyl-2a,8b-dihydro-2*H*-chromeno[3,4-*b*]azet-1(3*H*)-one **31** in high purity (>95% based on ^{1}H NMR in $CDCl_3$).

***Cis*-2-*tert*-butyl-2a,8b-dihydro-2*H*-chromeno[3,4-*b*]azet-1(3*H*)-one 31**: White crystals. Mp 119°C. Yield 99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (9H, s), 3.71 (1H, d x d, *J* = 12.7, 1.8 Hz), 4.09 (1H, d, *J* = 5.5 Hz), 4.23 (1H, br d, *J* = 5.5 Hz), 4.47 (1H, d x d, *J* = 12.7, 0.8 Hz), 6.93 (1H, d, *J* = 7.7 Hz), 7.01 (1H, t x d, *J* = 7.7, 0.9 Hz), 7.18 (1H, t x d, *J* = 7.7, 1.6 Hz), 7.22 (1H, d x d, *J* = 7.7, 1.6 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 28.4, 48.3, 53.3, 54.2, 66.9, 117.5, 120.4, 122.8, 128.2, 129.6, 155.4, 164.8. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1731; ν_{max} = 2972, 1489, 1369, 1230, 998, 769. MS (70 eV): m/z (%) 232 (M^+ + 1, 100). HRMS (ESI) Calcd. for $C_{14}H_{18}NO_2^+$ 232.1332 $[M + H]^+$, found 232.1340.

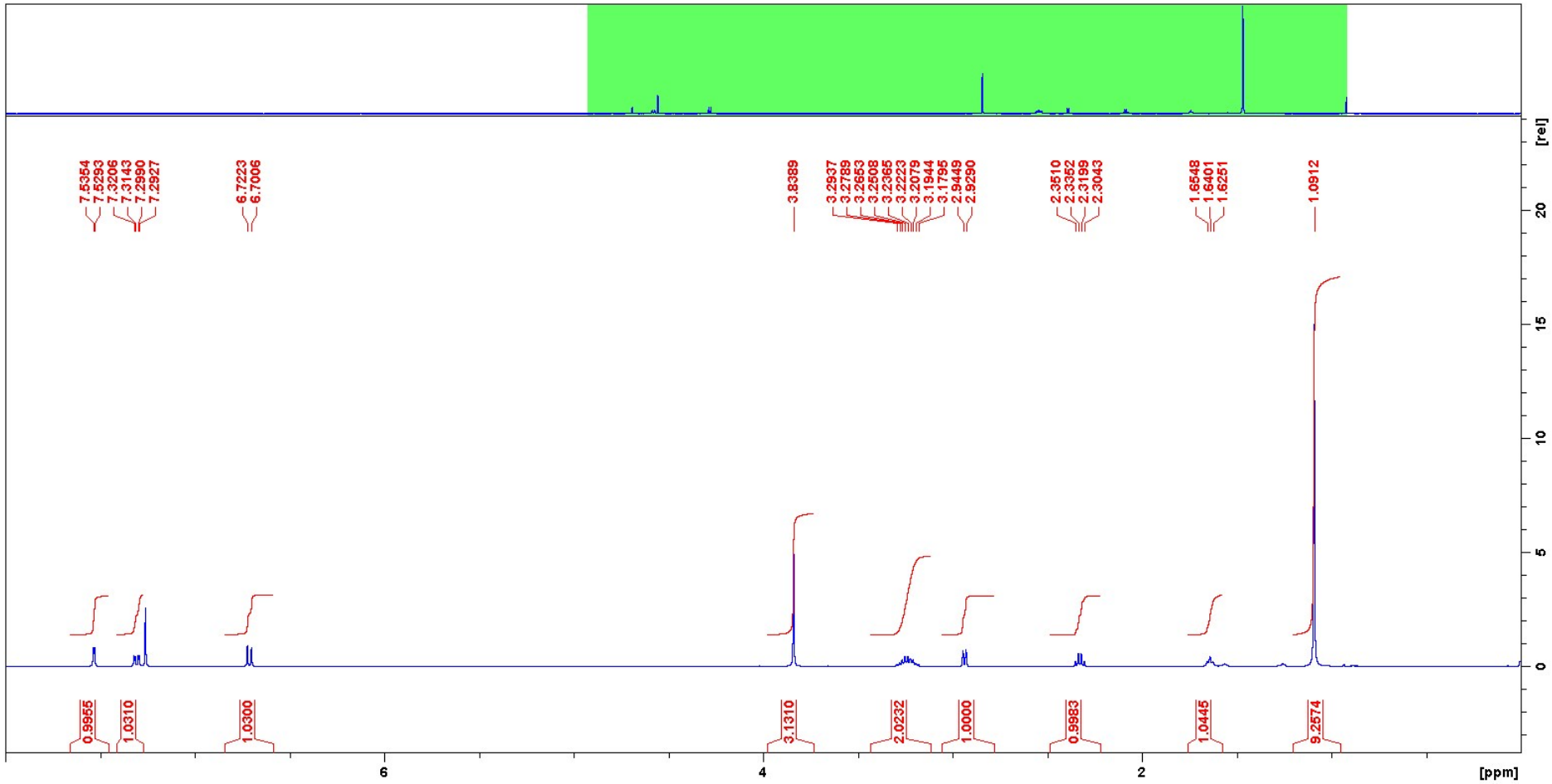
Compound **3b**: ^{1}H NMR



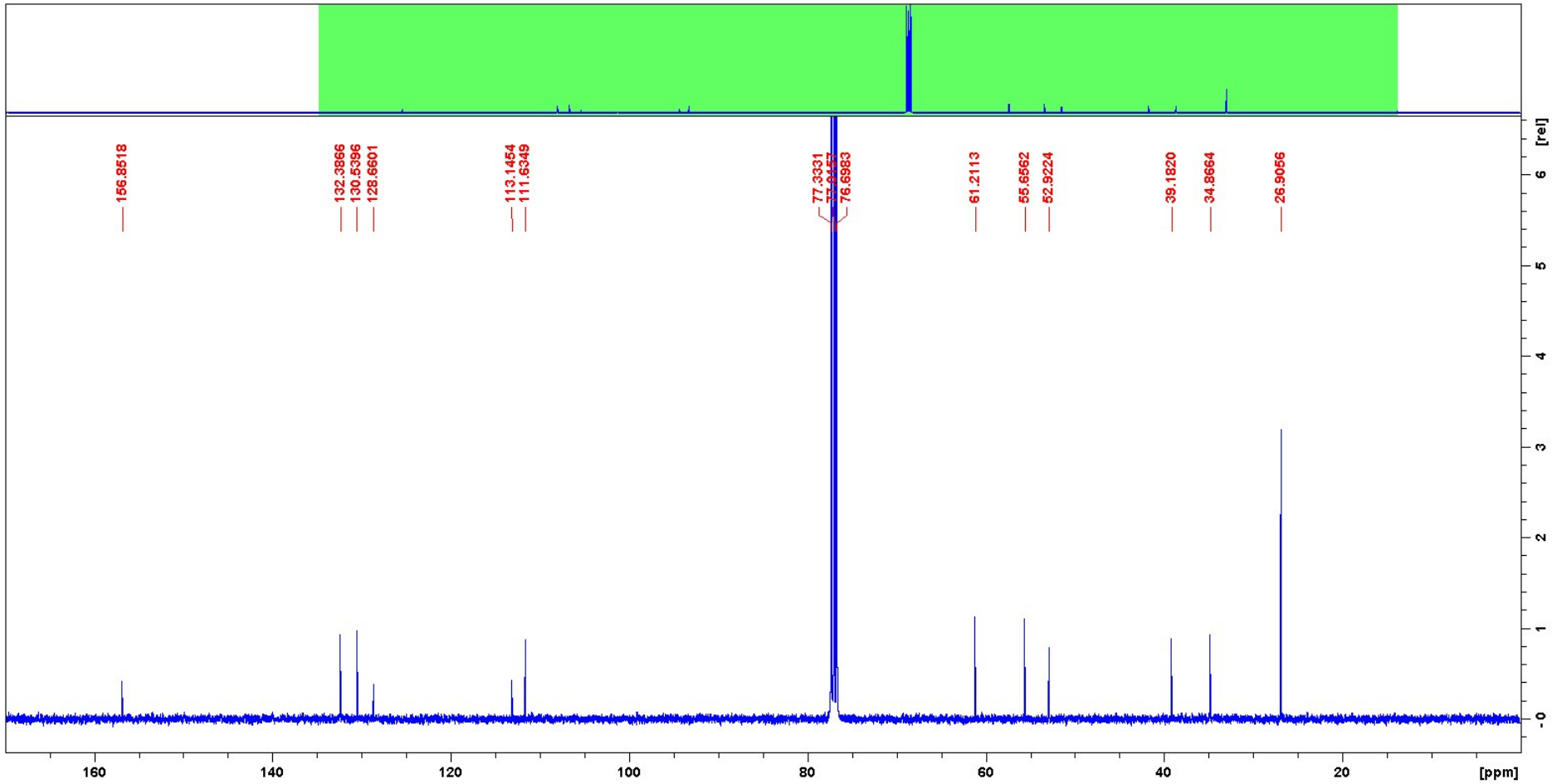
Compound **3b**: ^{13}C NMR



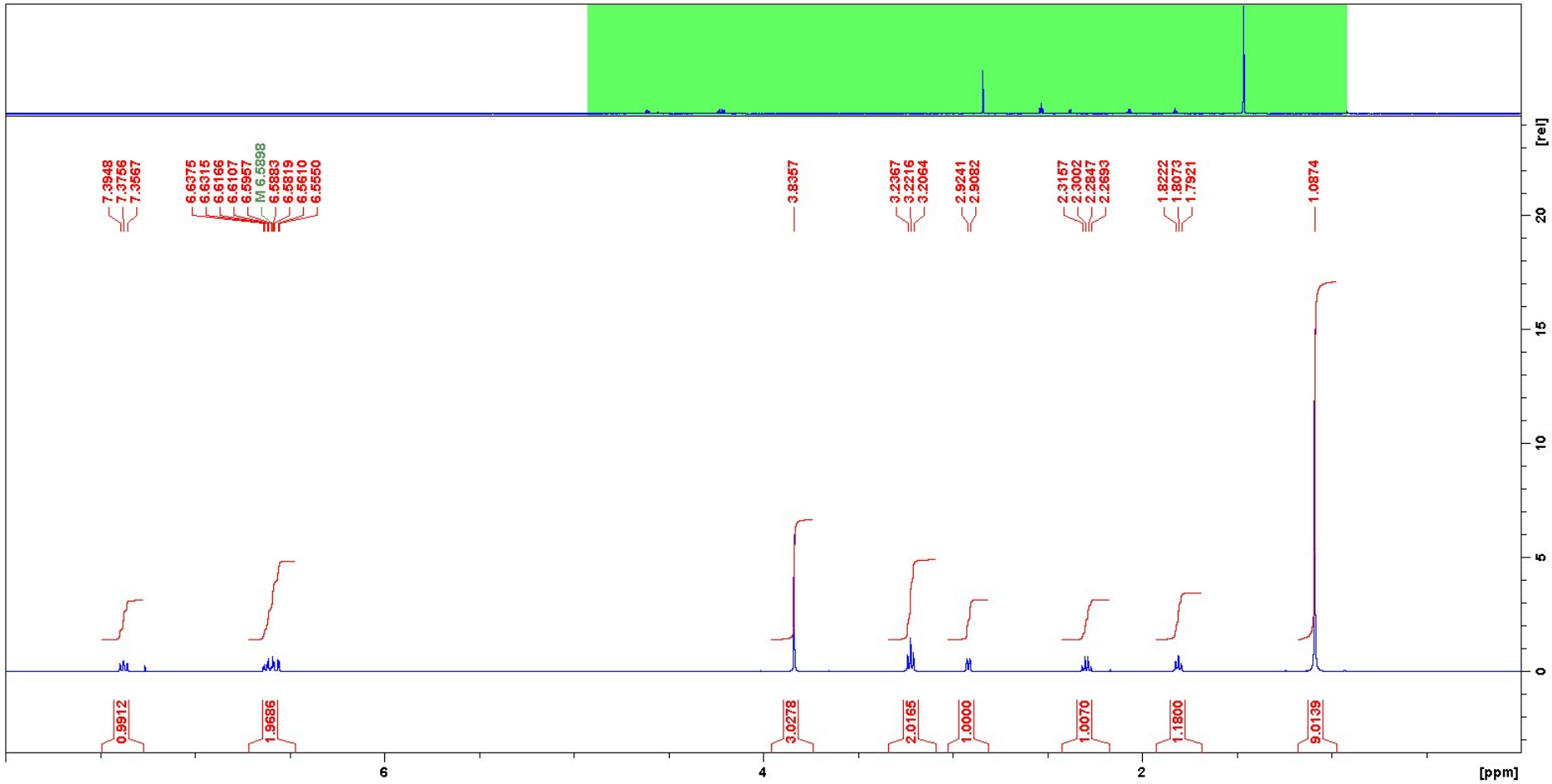
Compound **3c**: ^{1}H NMR



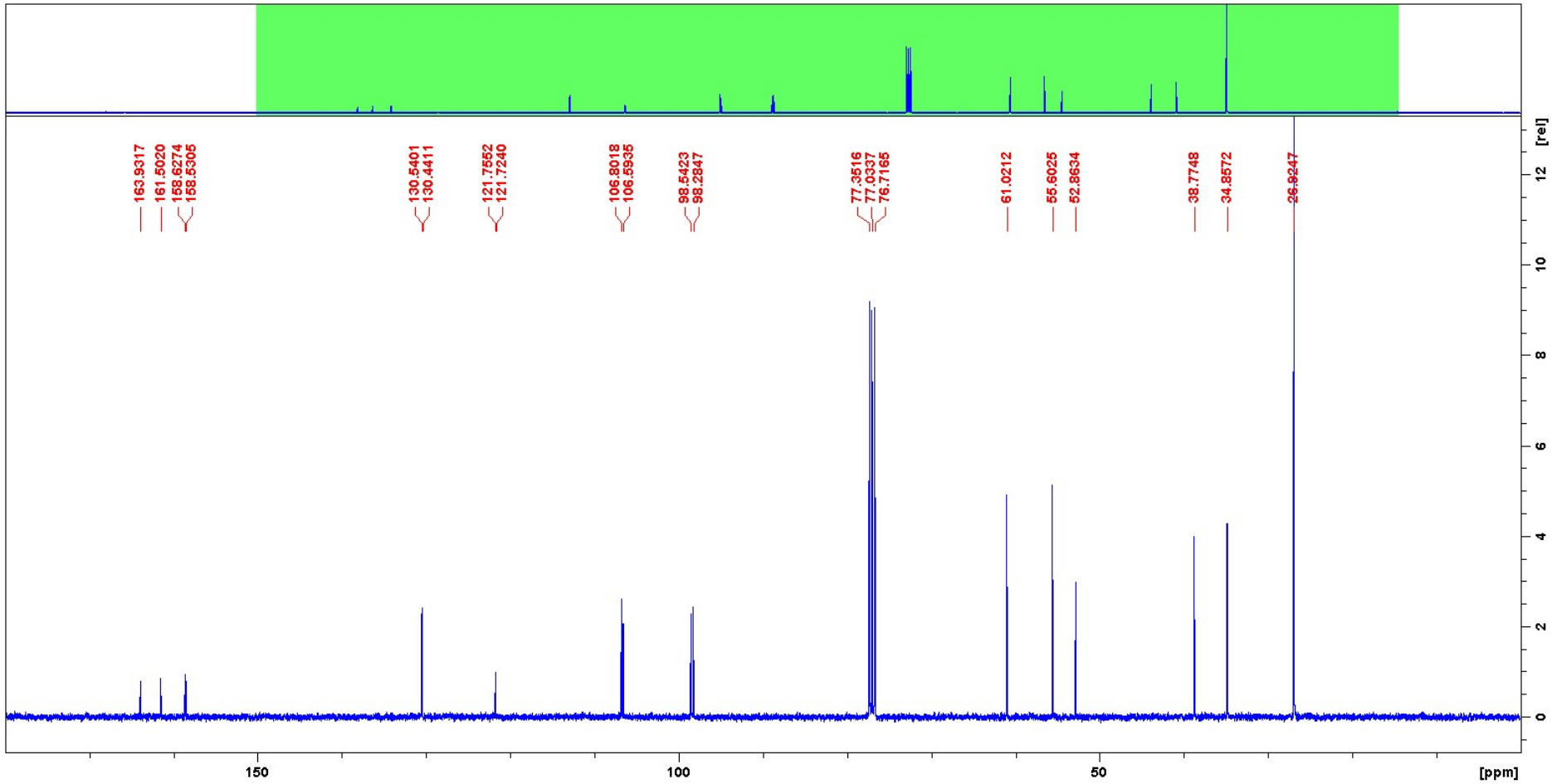
Compound **3c**: ^{13}C NMR



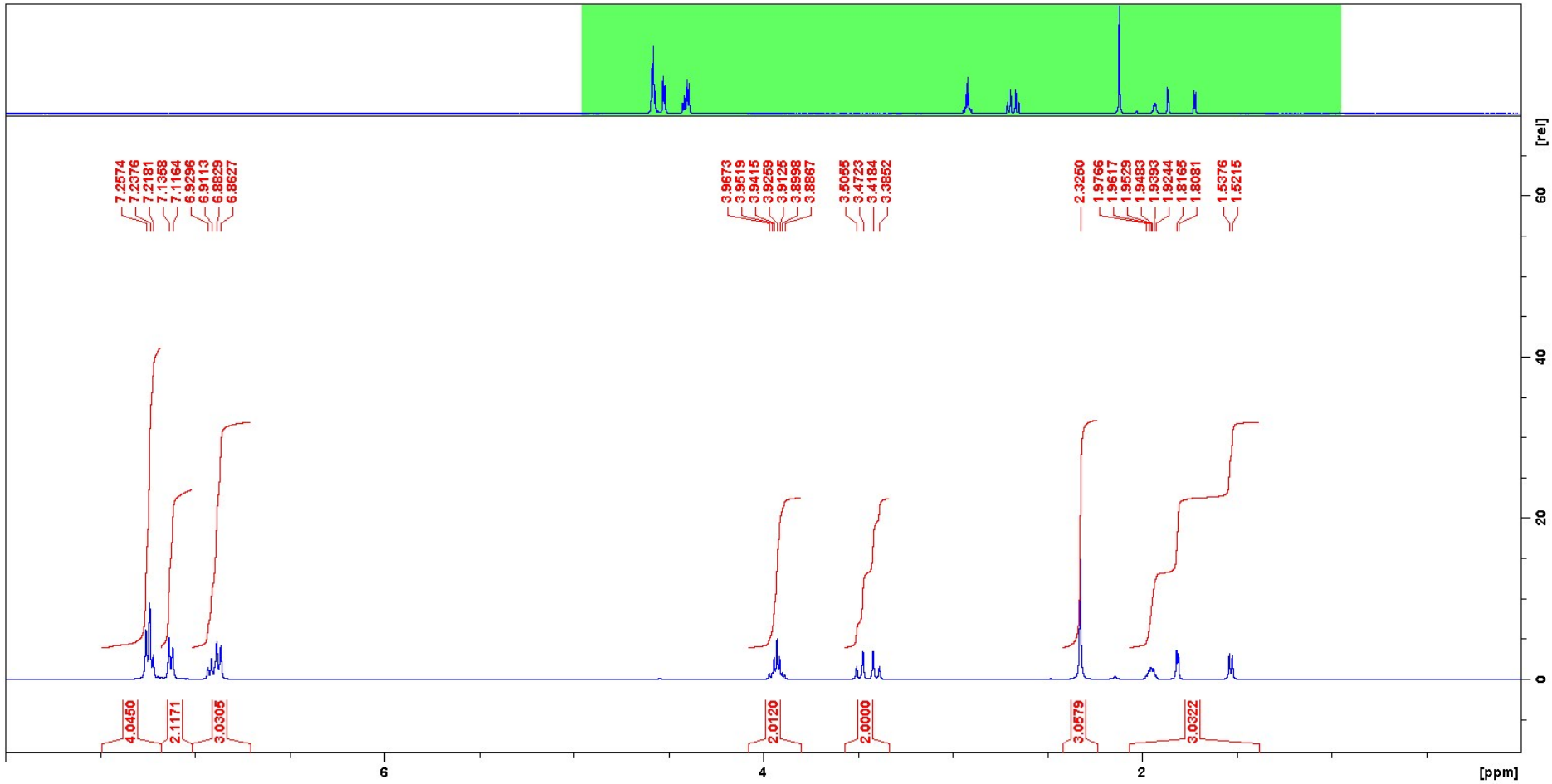
Compound **3d**: ^{1}H NMR



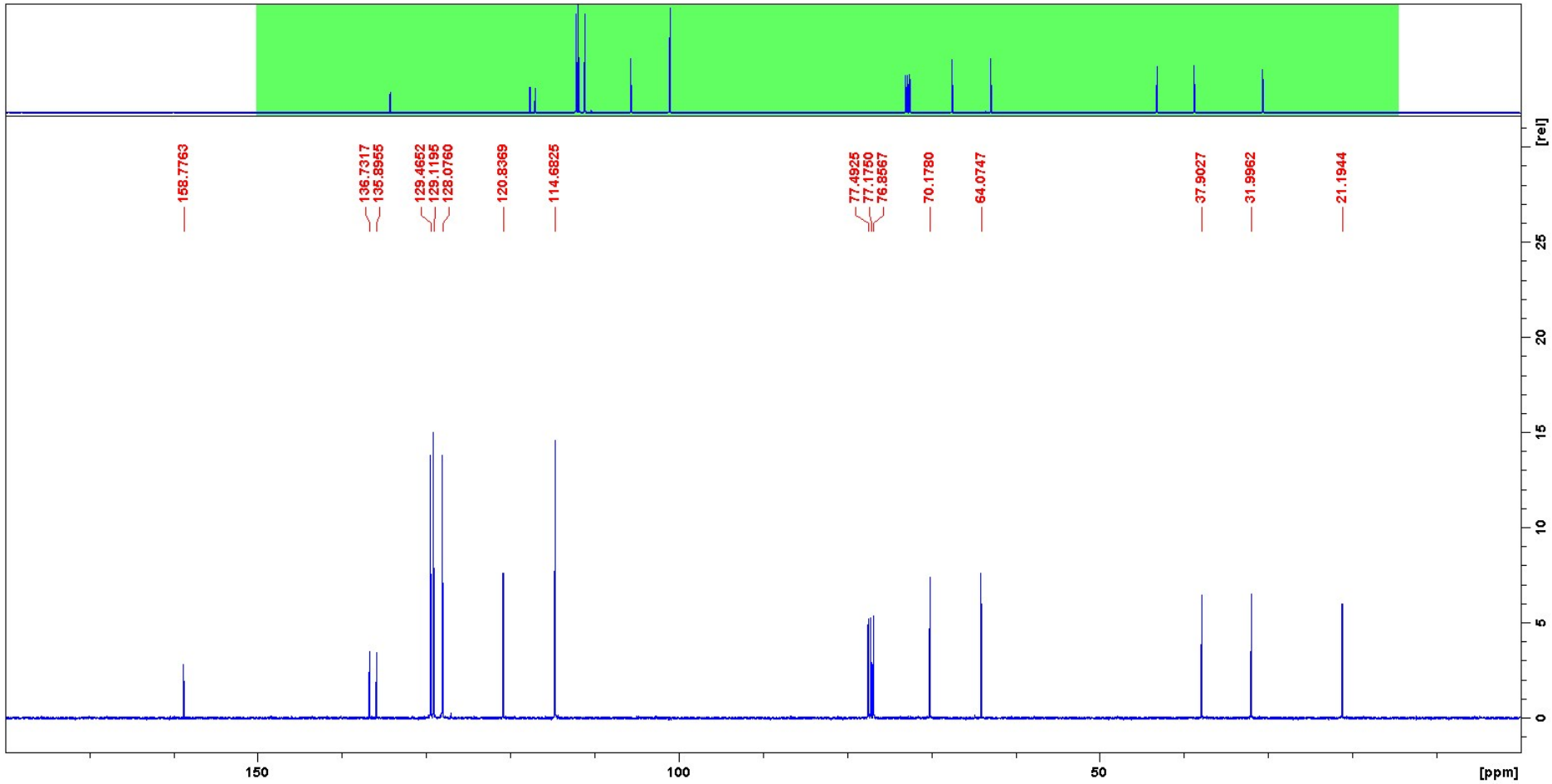
Compound **3d**: ^{13}C NMR



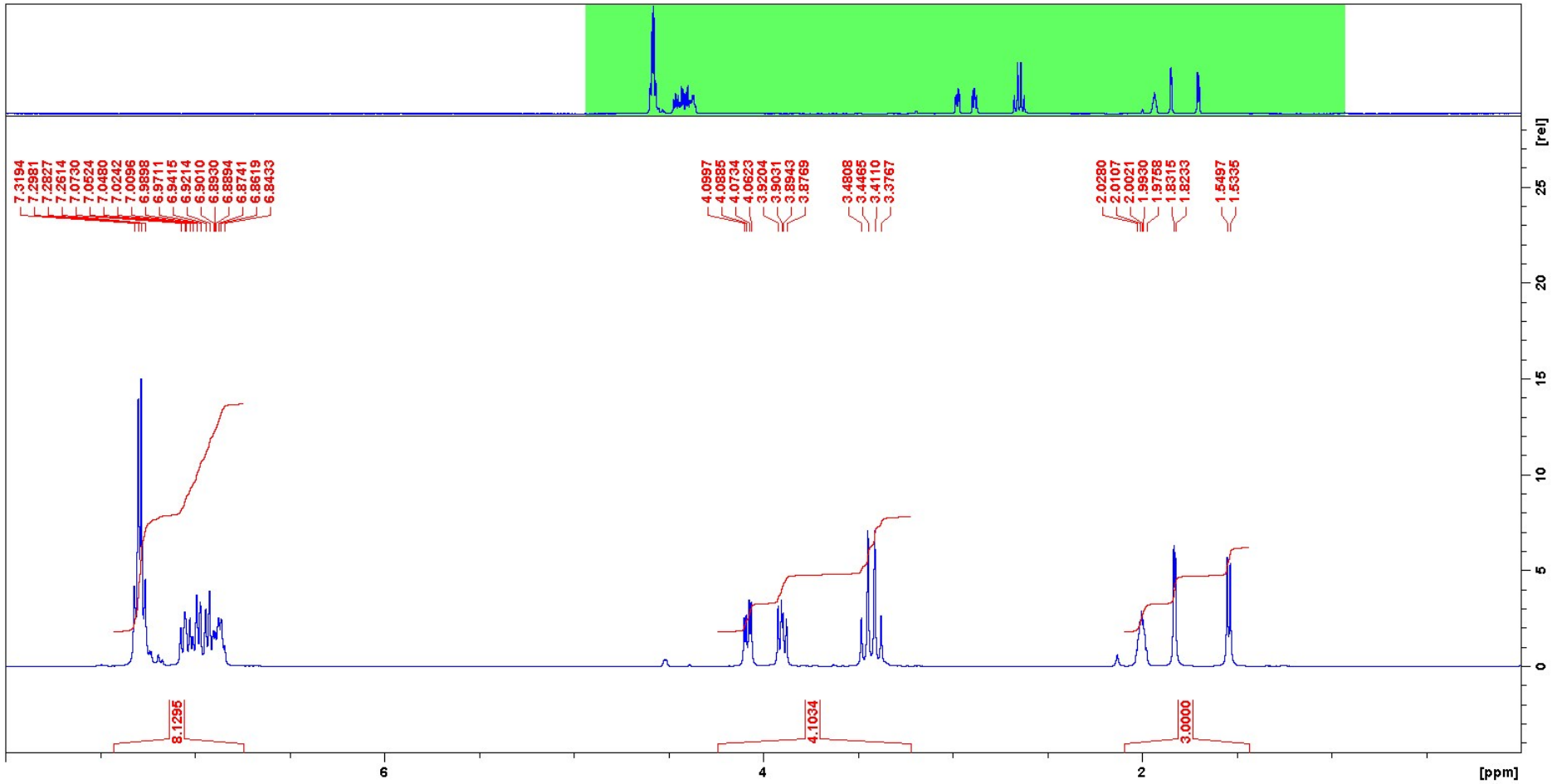
Compound **4b**: ^{1}H NMR



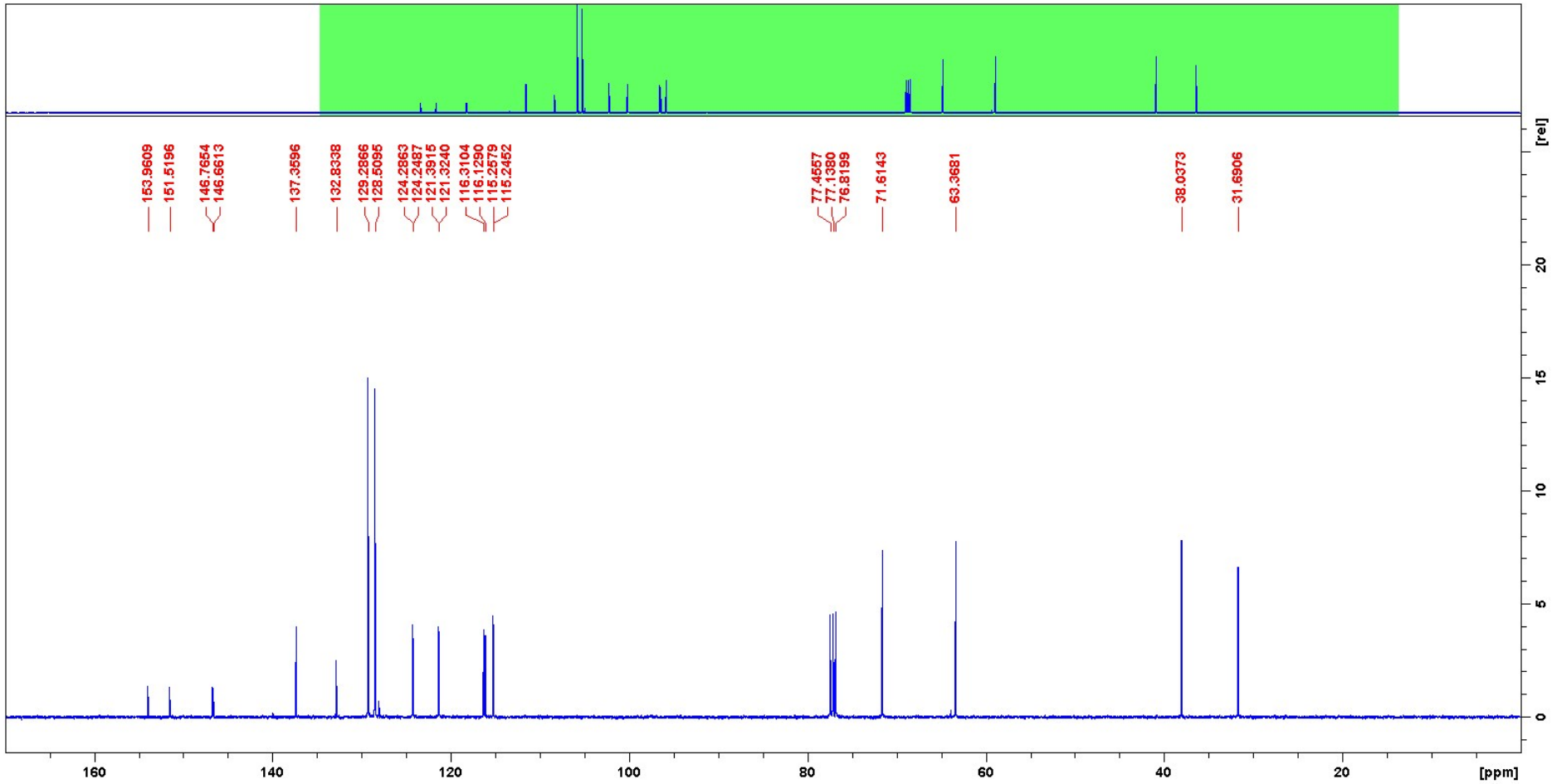
Compound **4b**: ^{13}C NMR



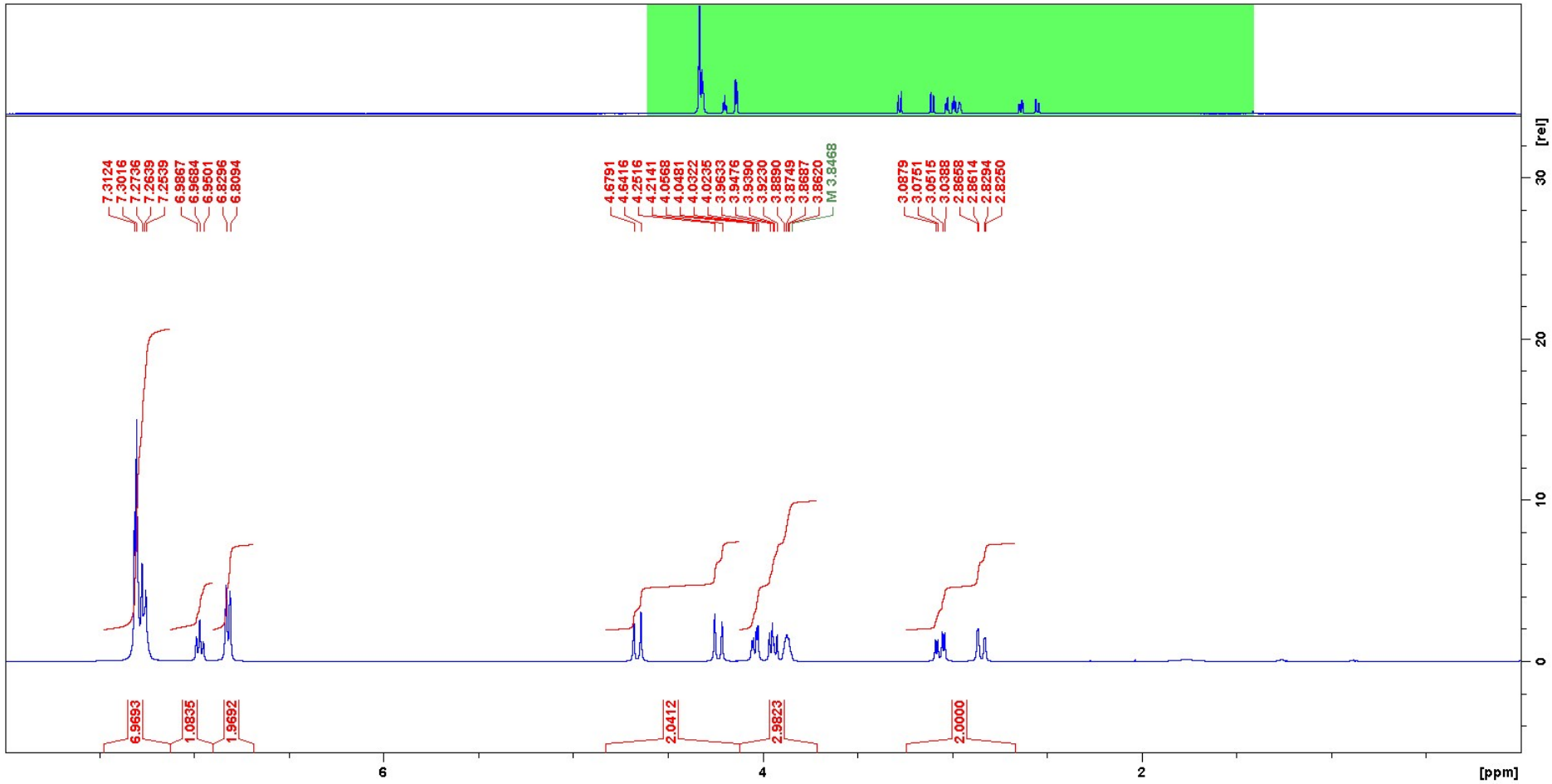
Compound **4e**: ^{1}H NMR



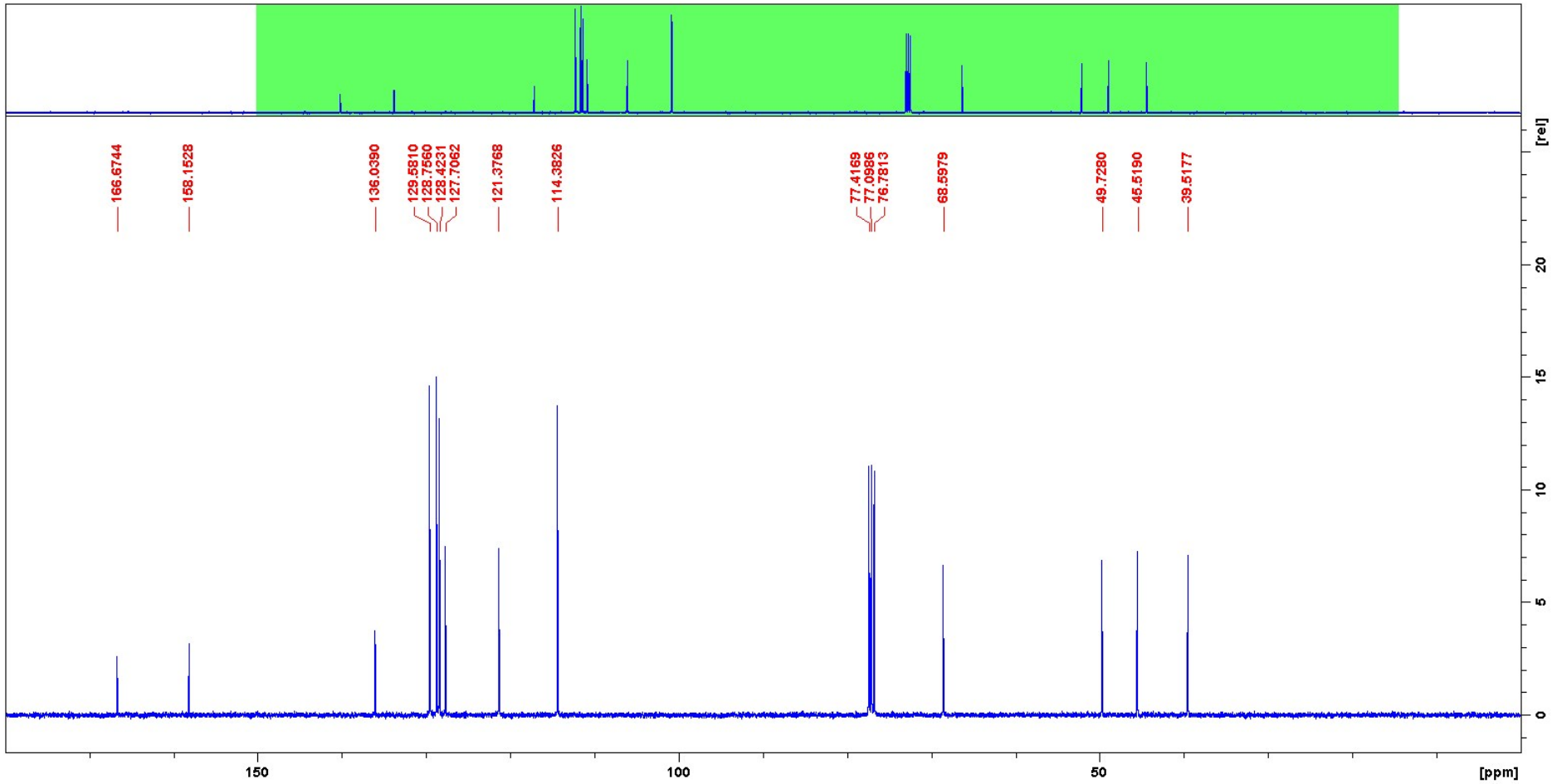
Compound **4e**: ^{13}C NMR



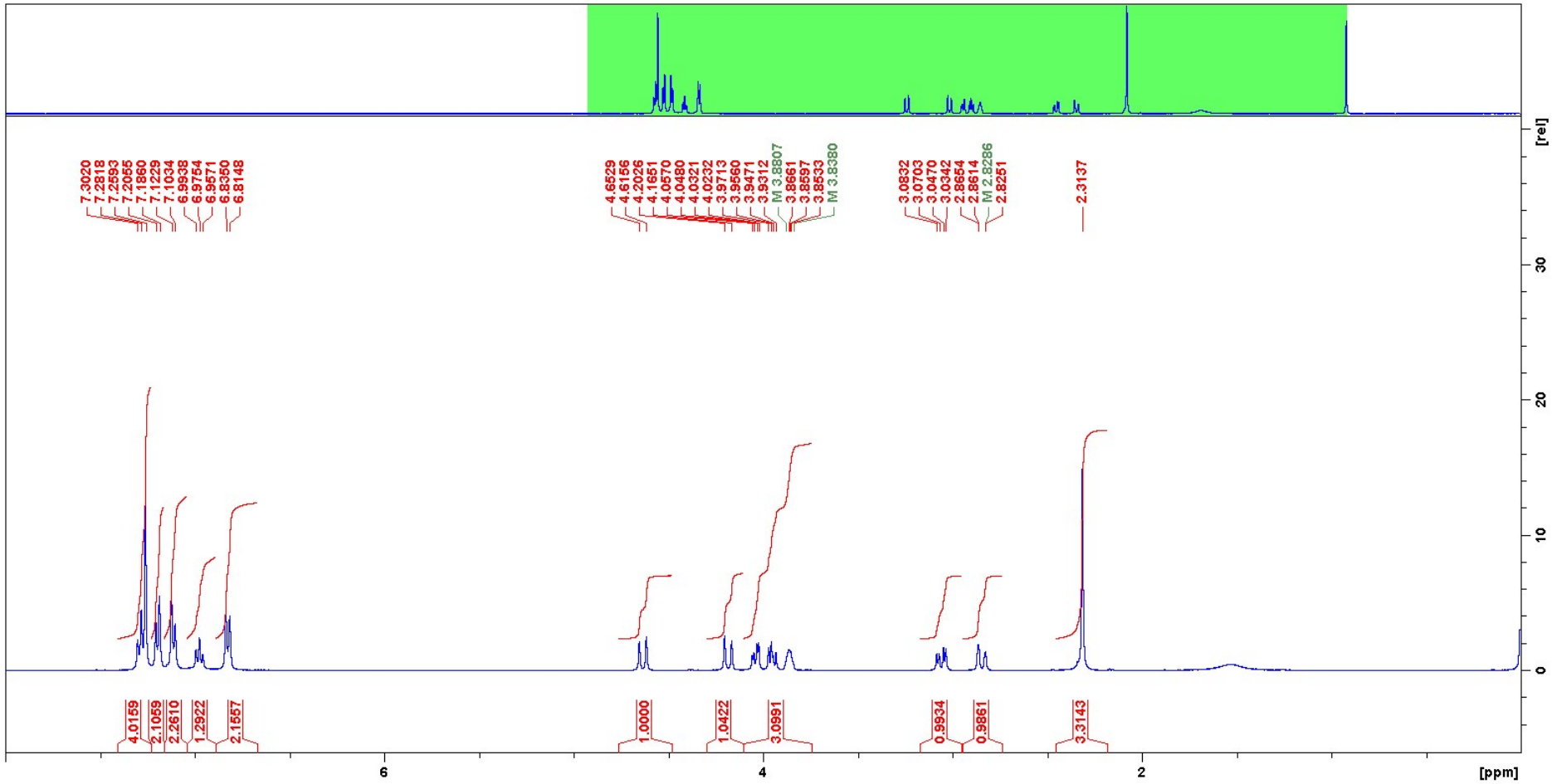
Compound **5a**: ^{1}H NMR



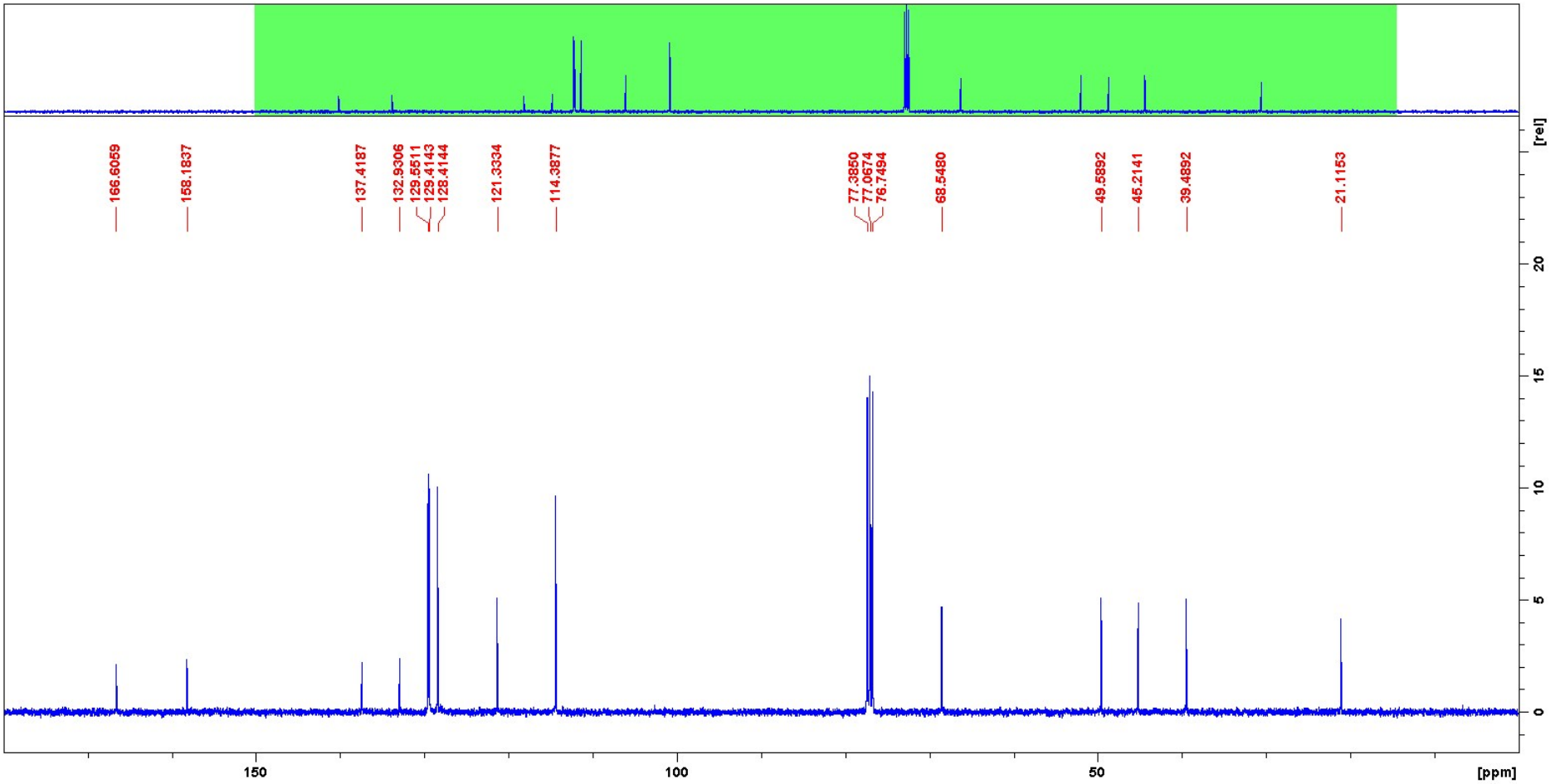
Compound **5a**: ^{13}C NMR



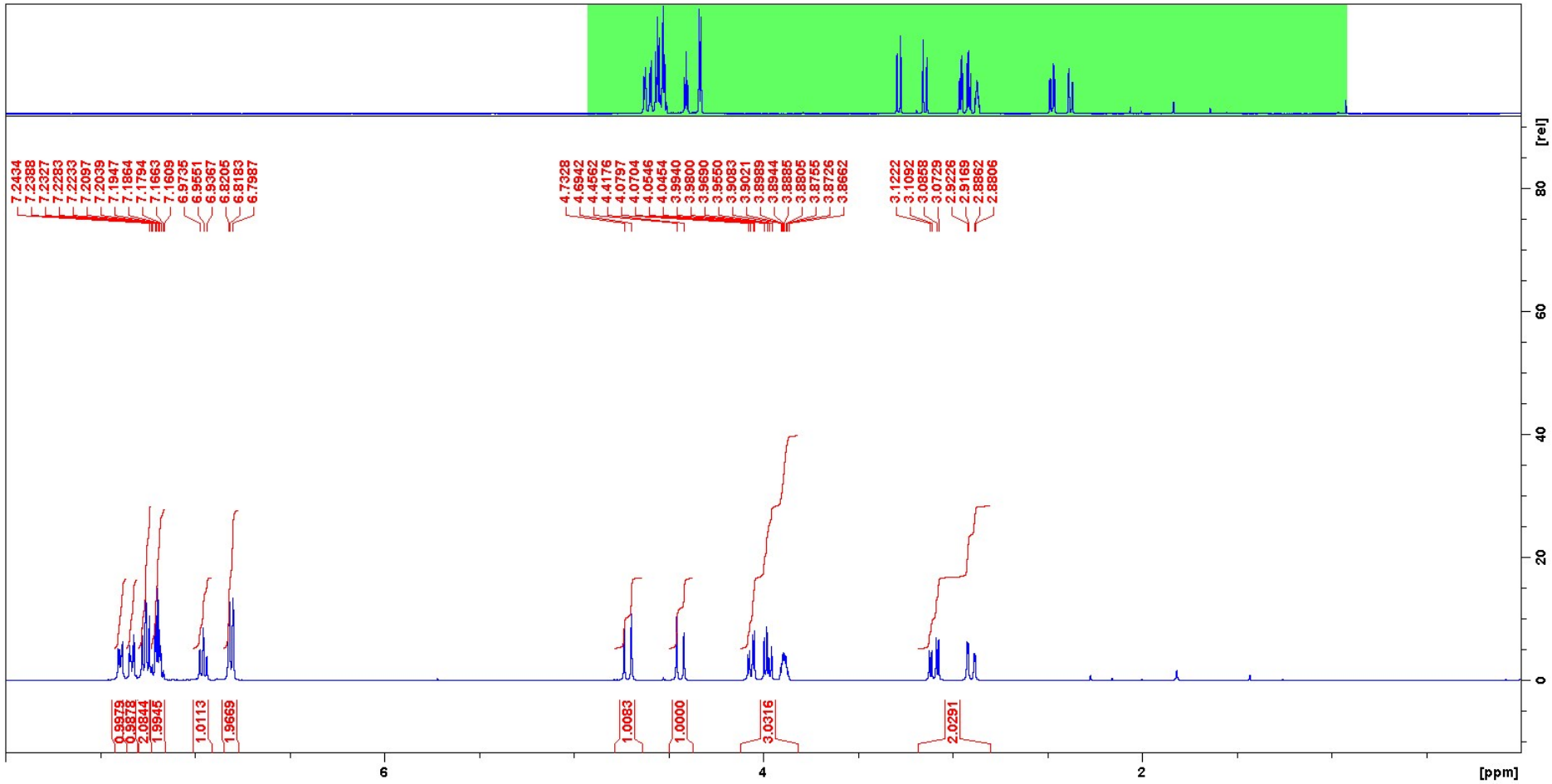
Compound **5b**: ^{1}H NMR



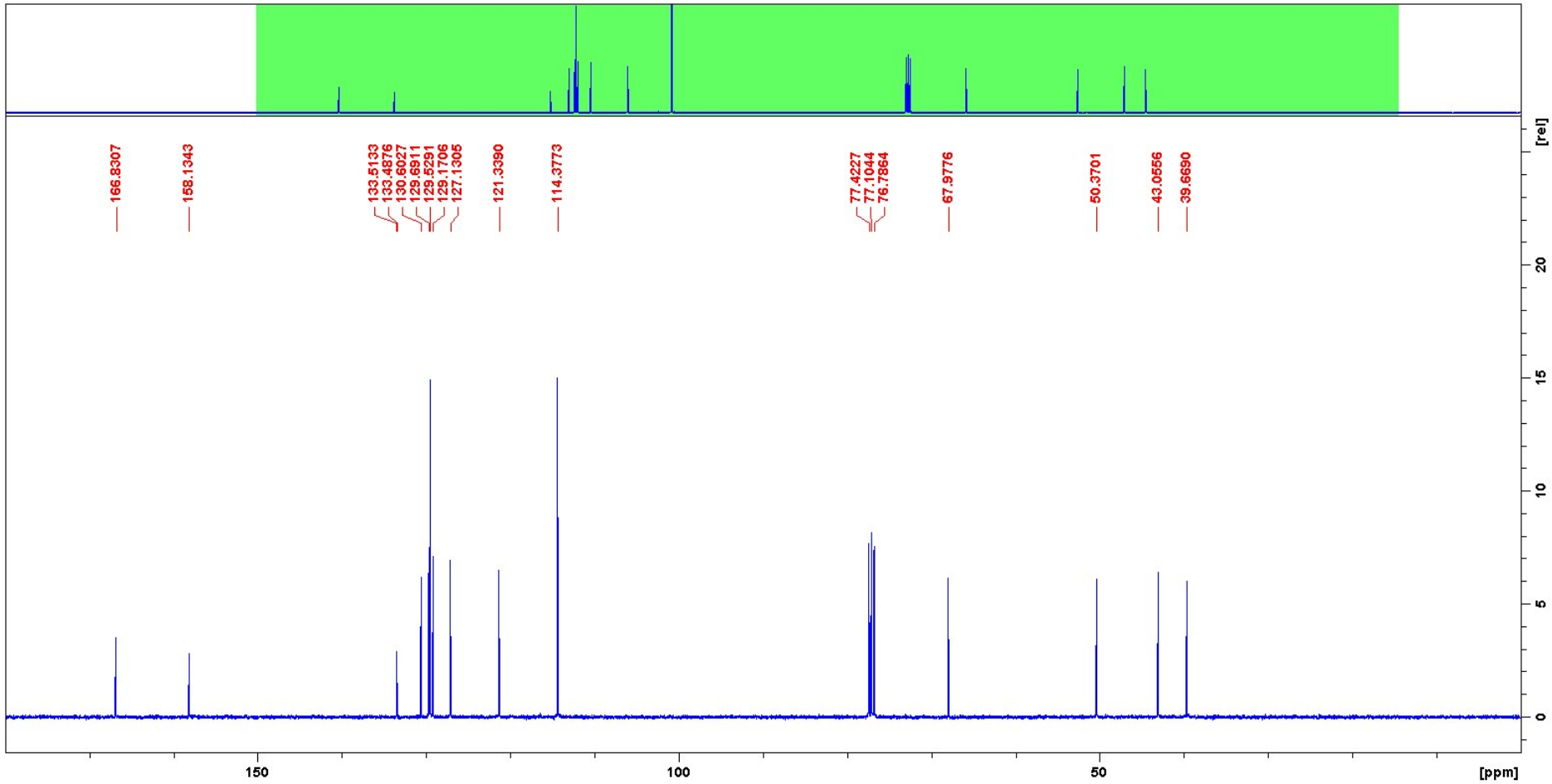
Compound **5b**: ^{13}C NMR



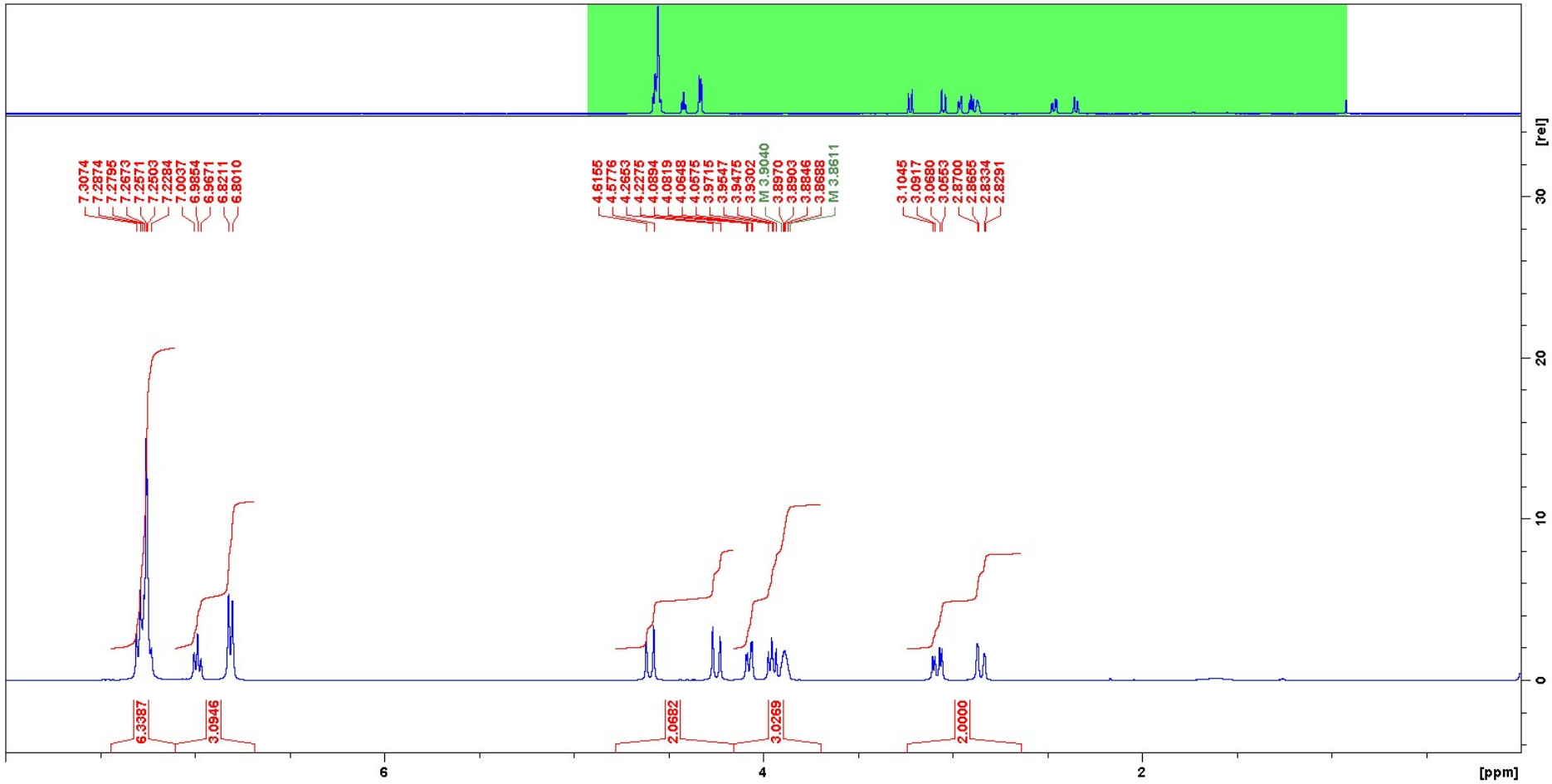
Compound **5c**: ^{1}H NMR



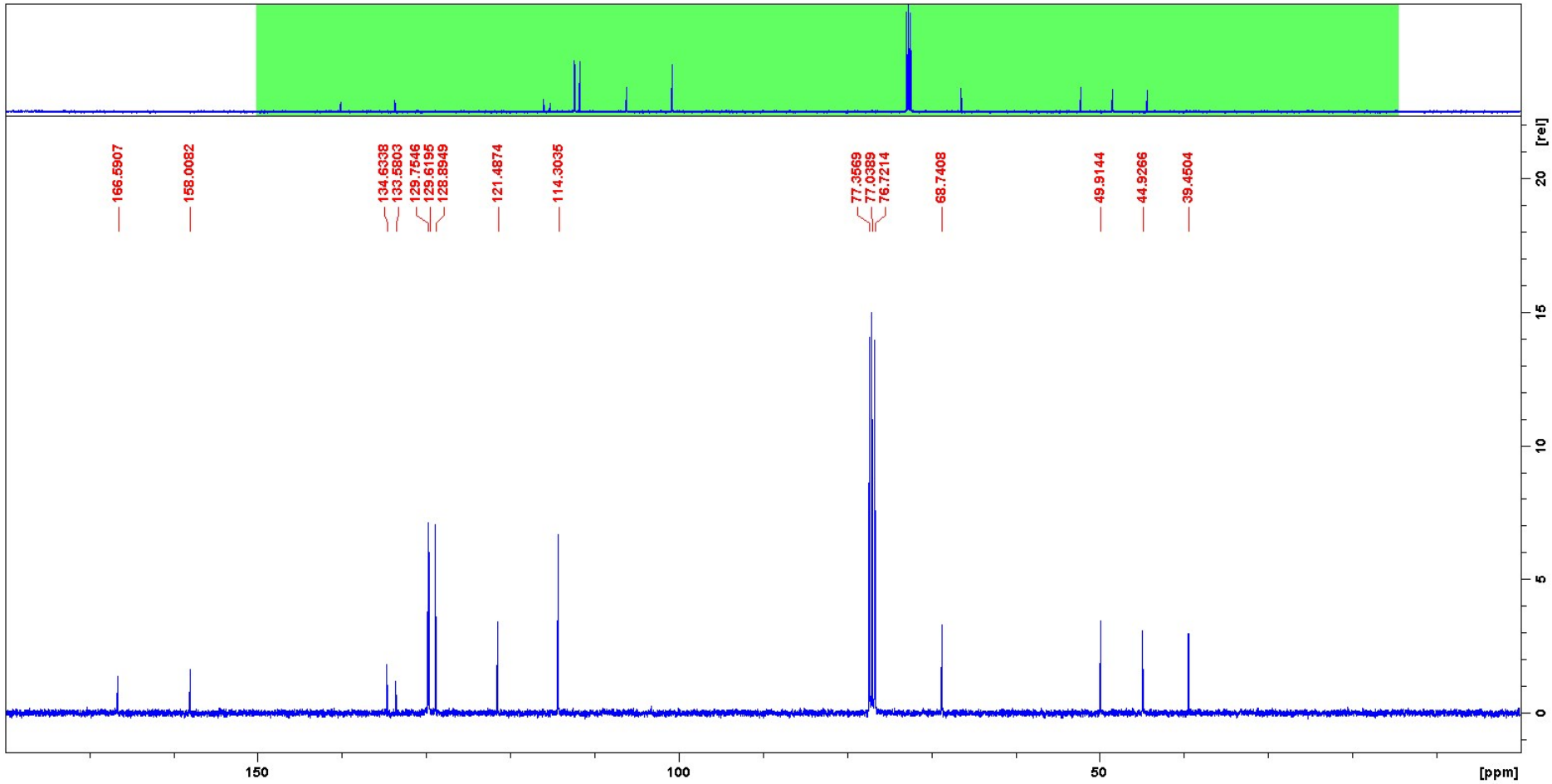
Compound **5c**: ^{13}C NMR



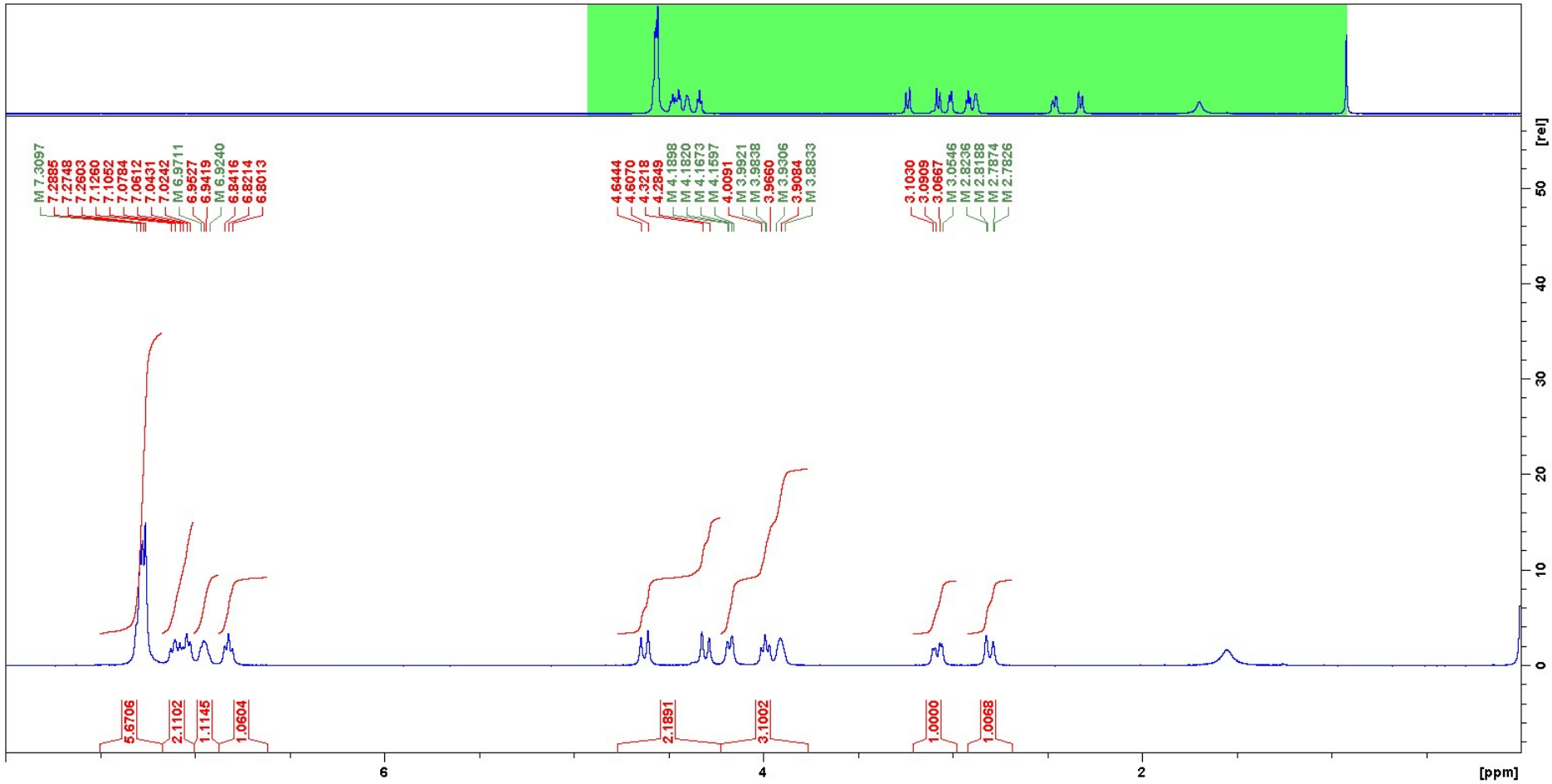
Compound **5d**: ^{1}H NMR



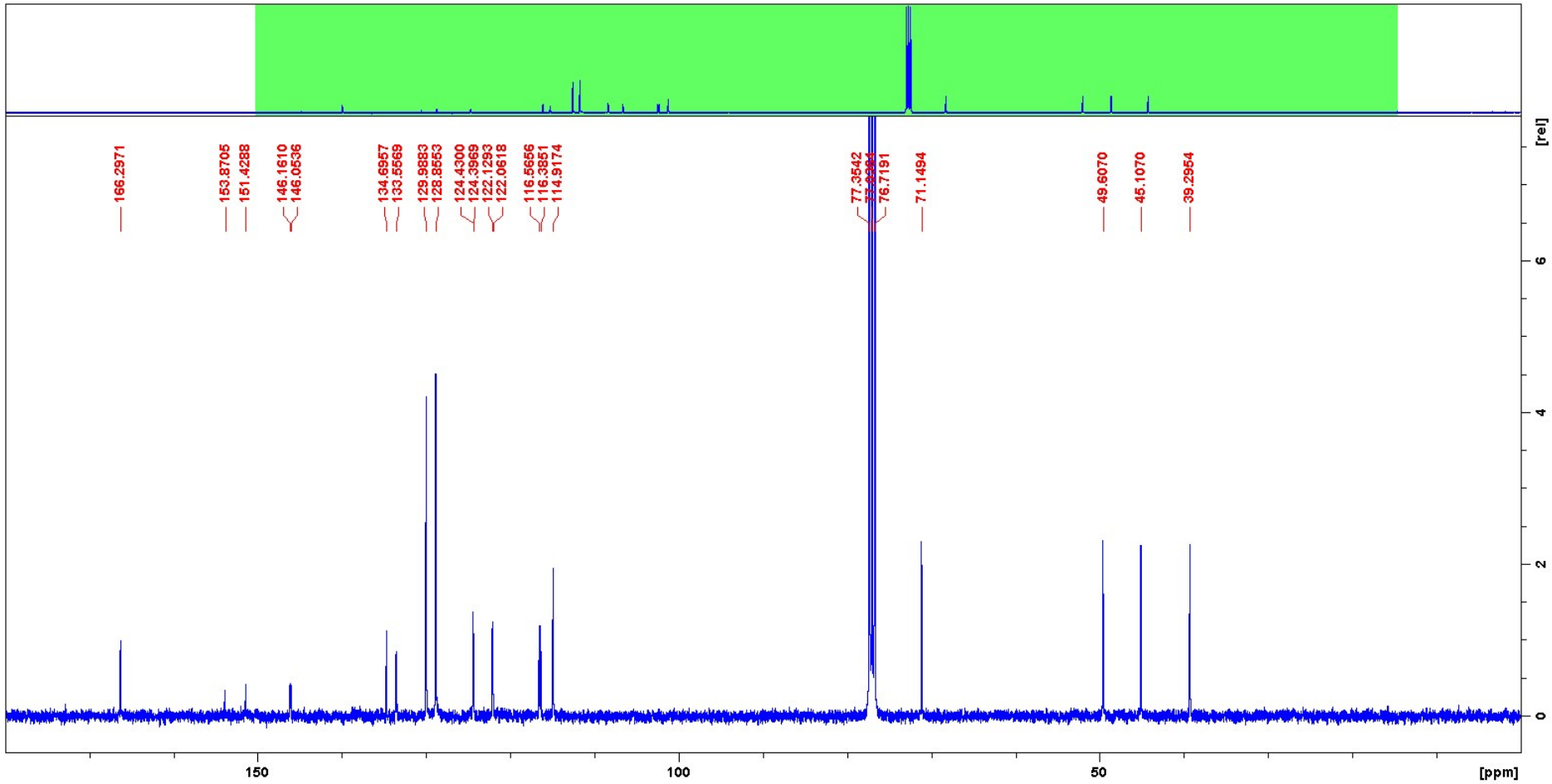
Compound **5d**: ^{13}C NMR



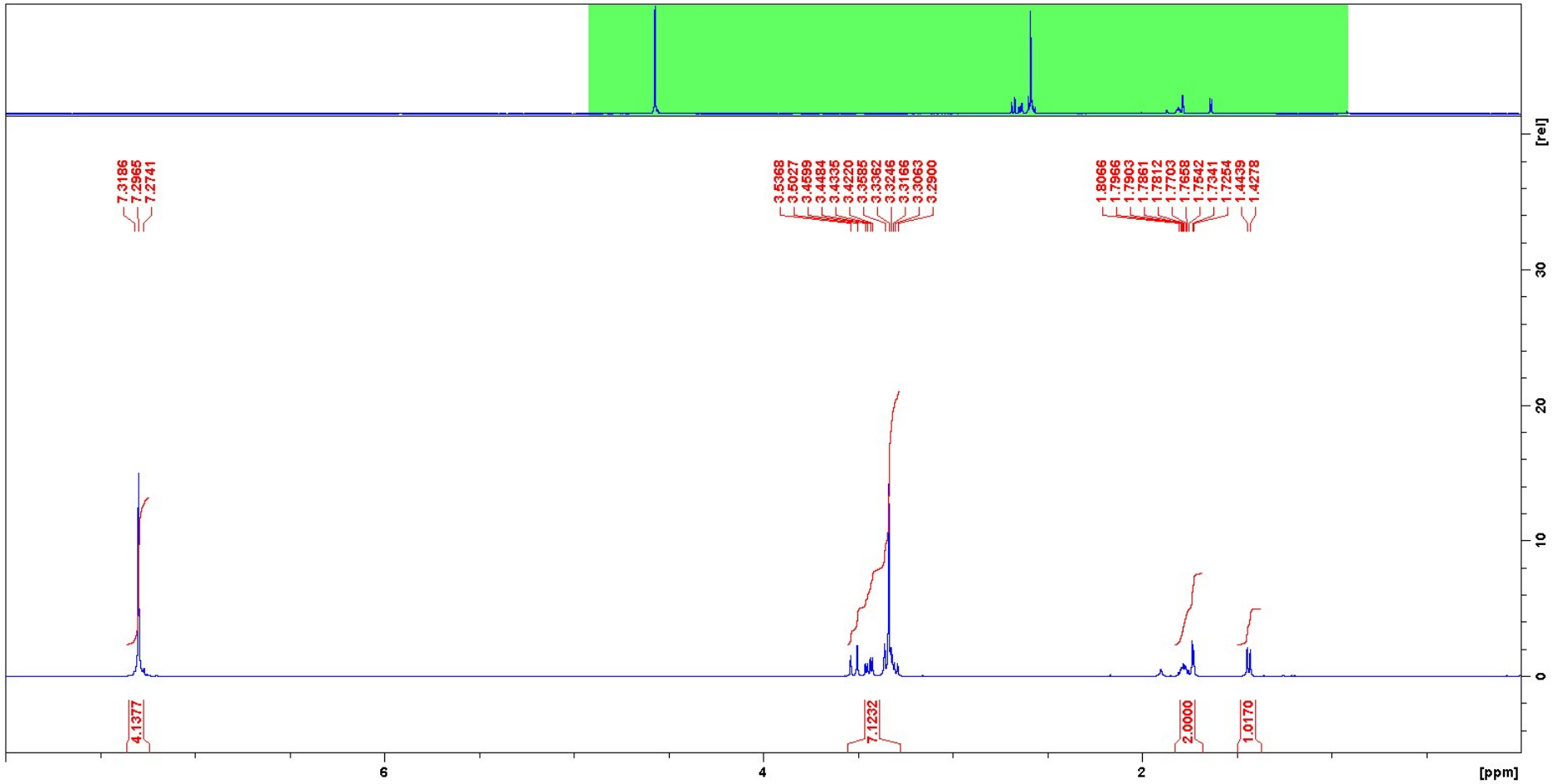
Compound **5e**: ^{1}H NMR



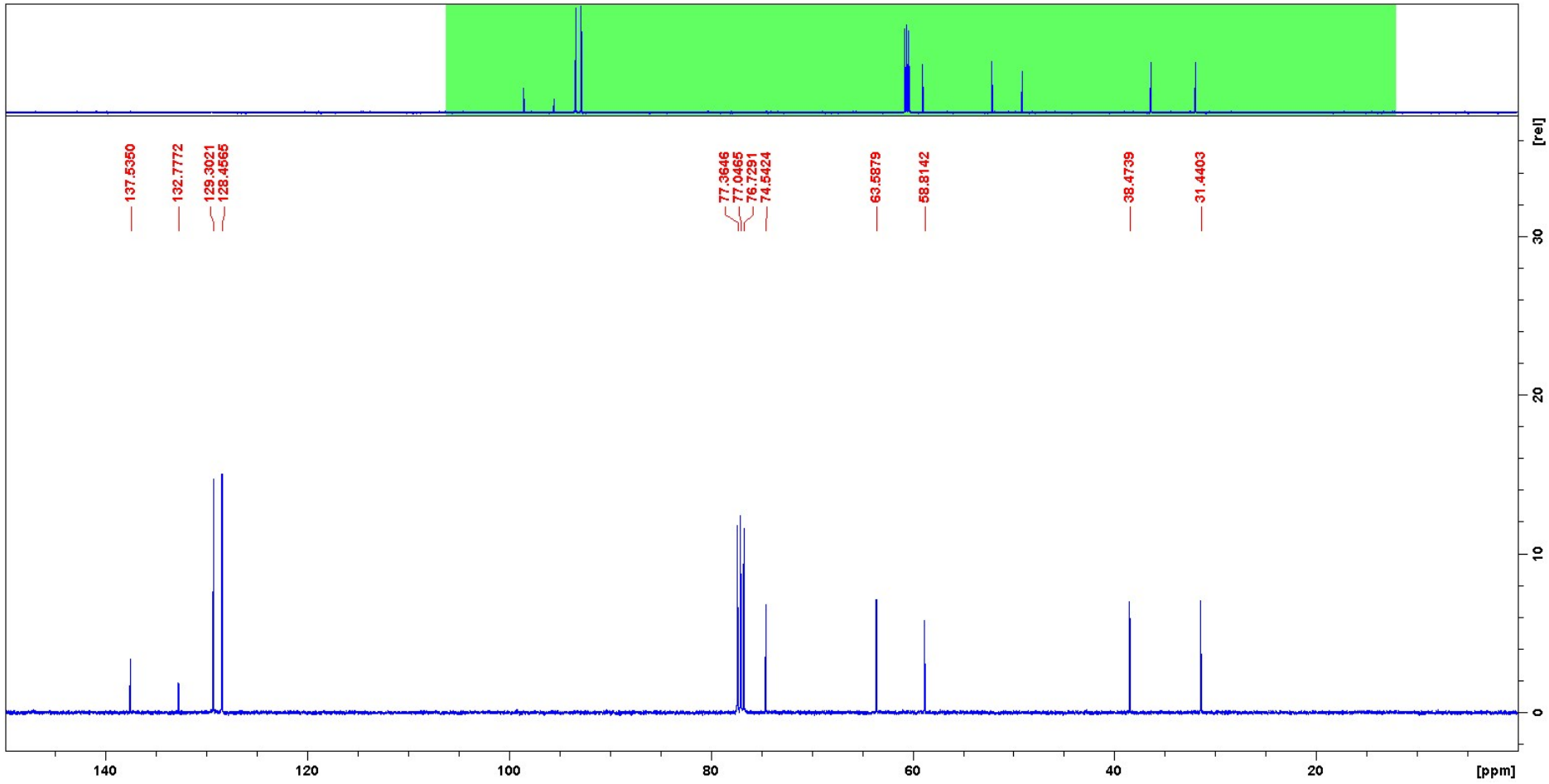
Compound **5e**: ^{13}C NMR



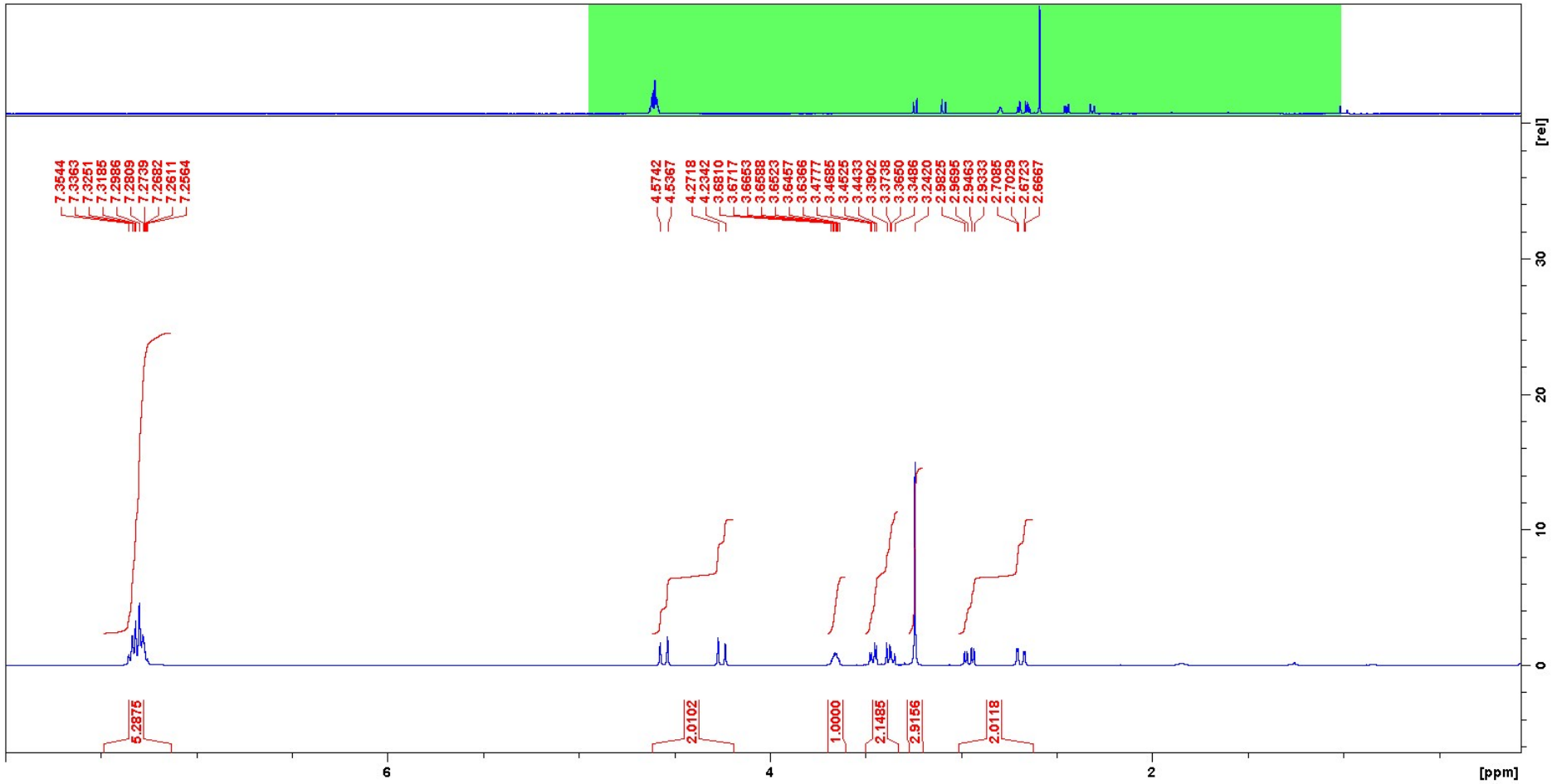
Compound **6c**: ^{1}H NMR



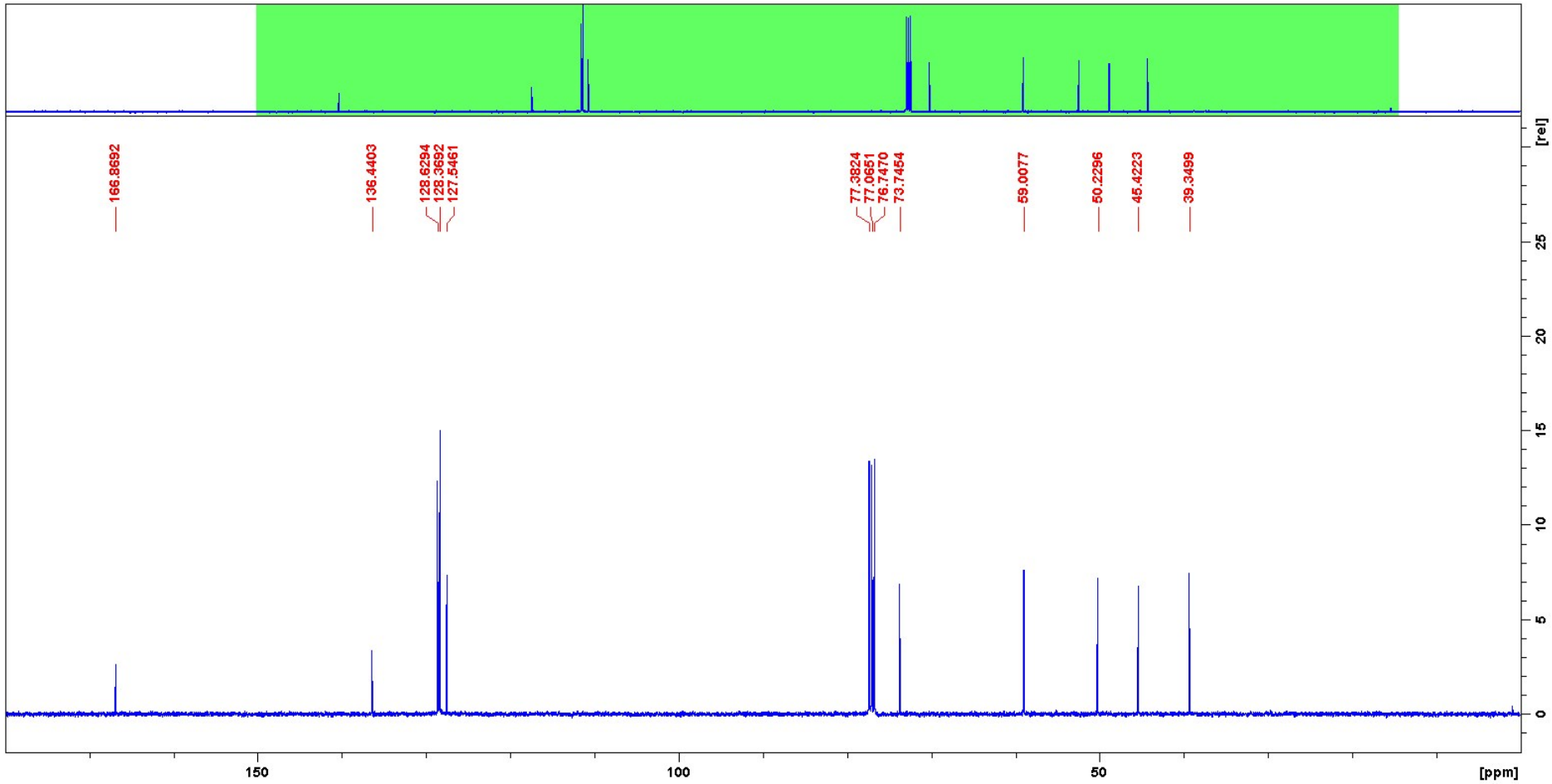
Compound **6c**: ^{13}C NMR



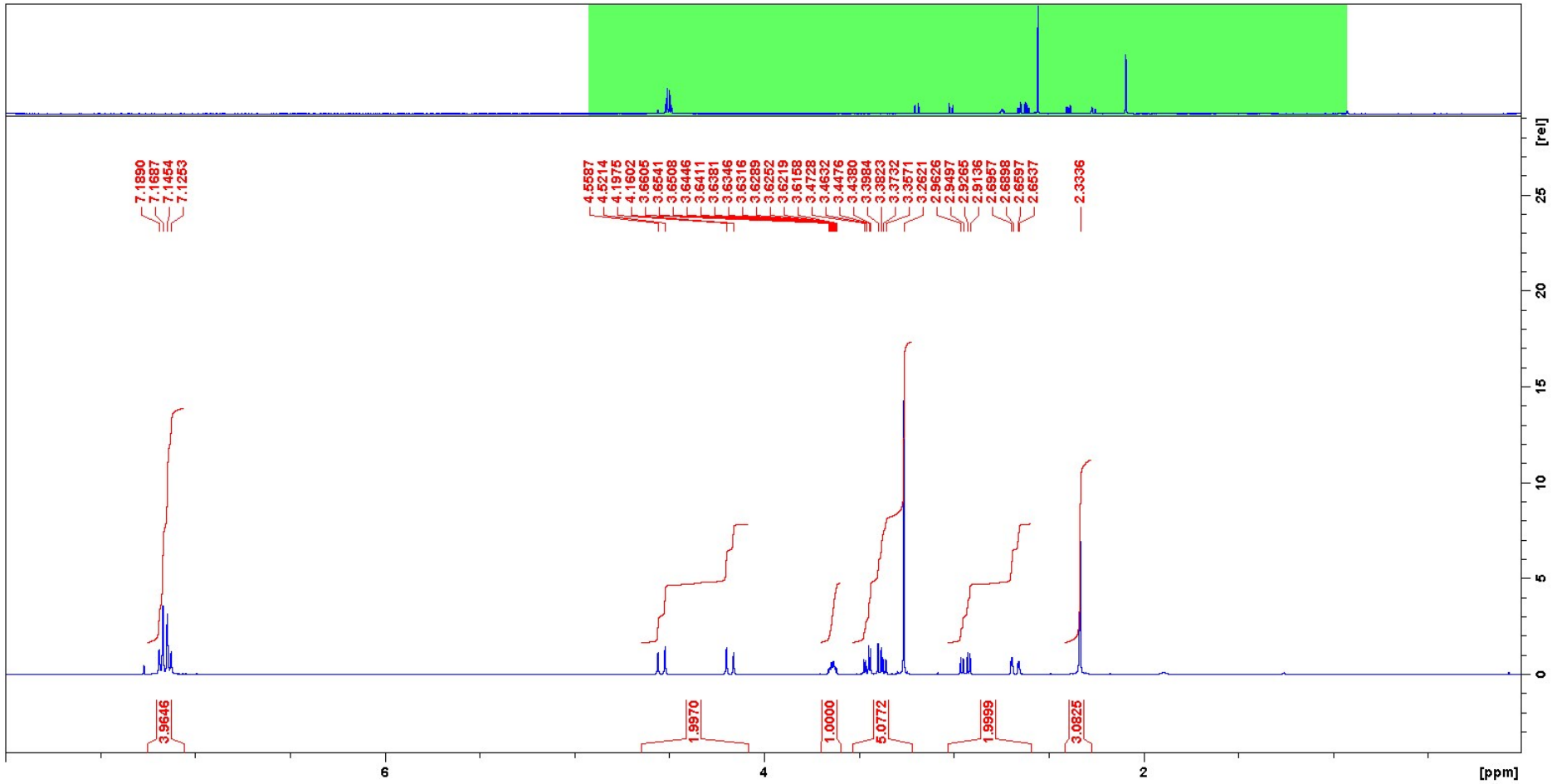
Compound **7a**: ^{1}H NMR



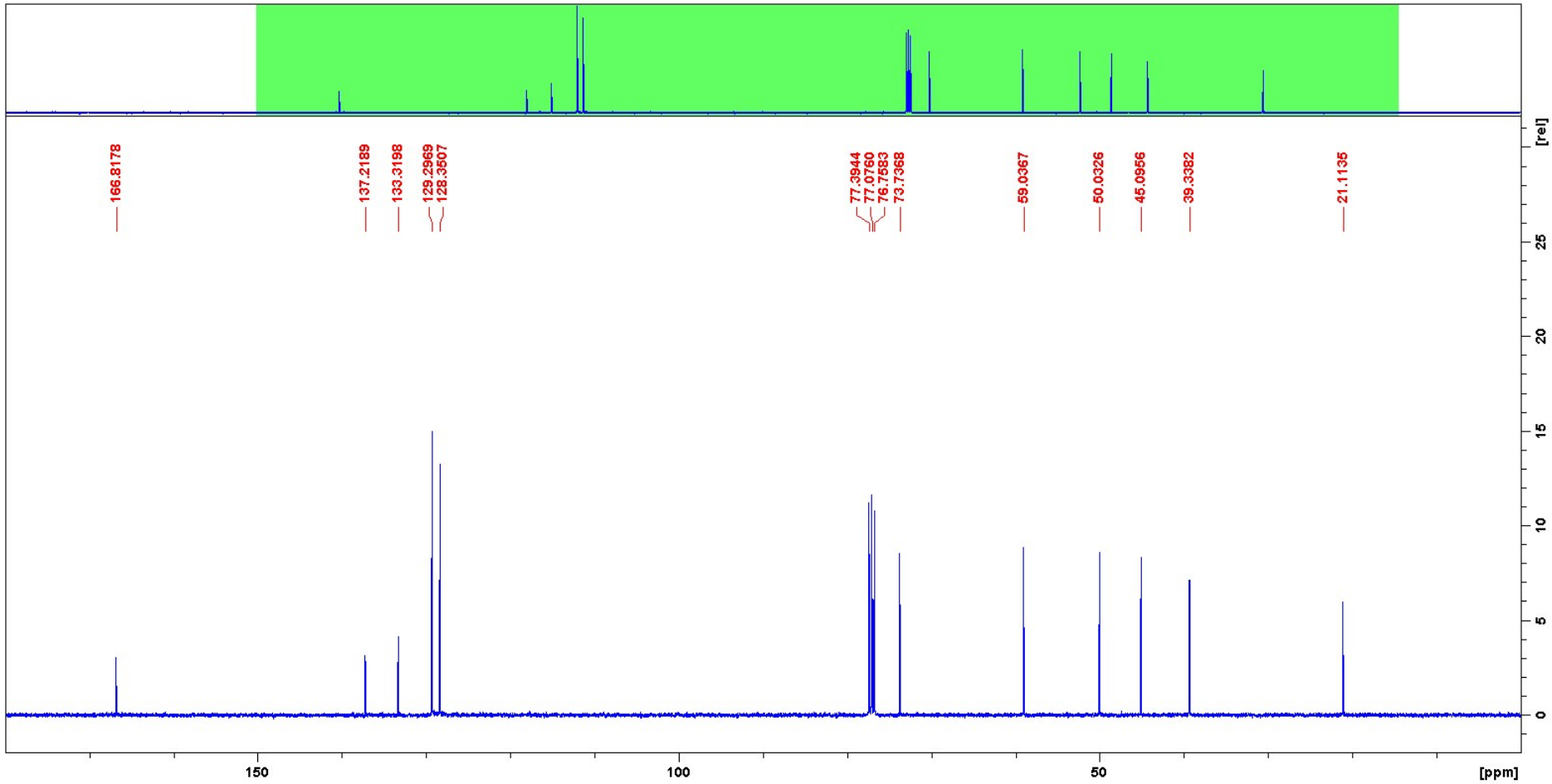
Compound **7a**: ^{13}C NMR



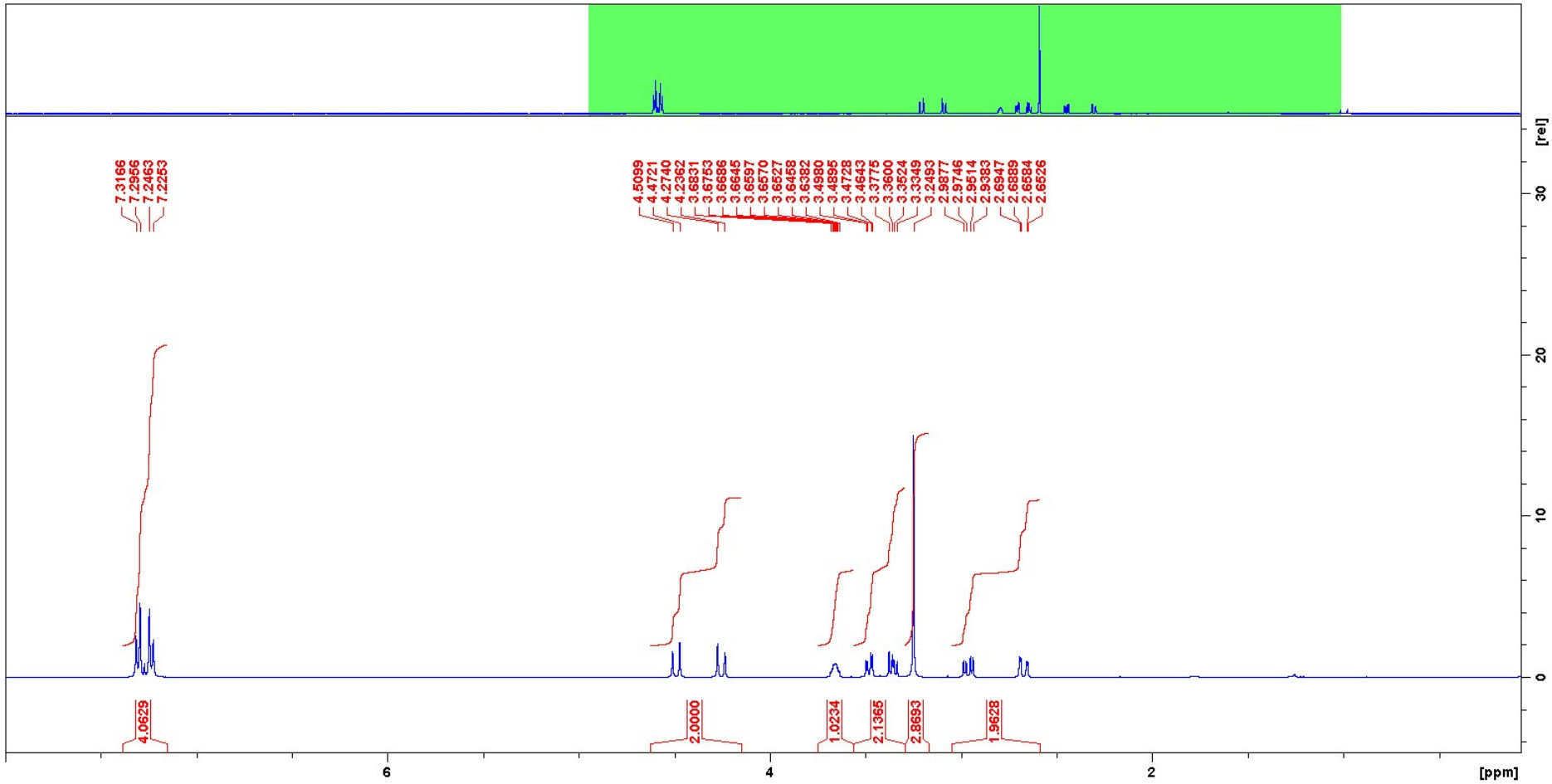
Compound **7b**: ^{1}H NMR



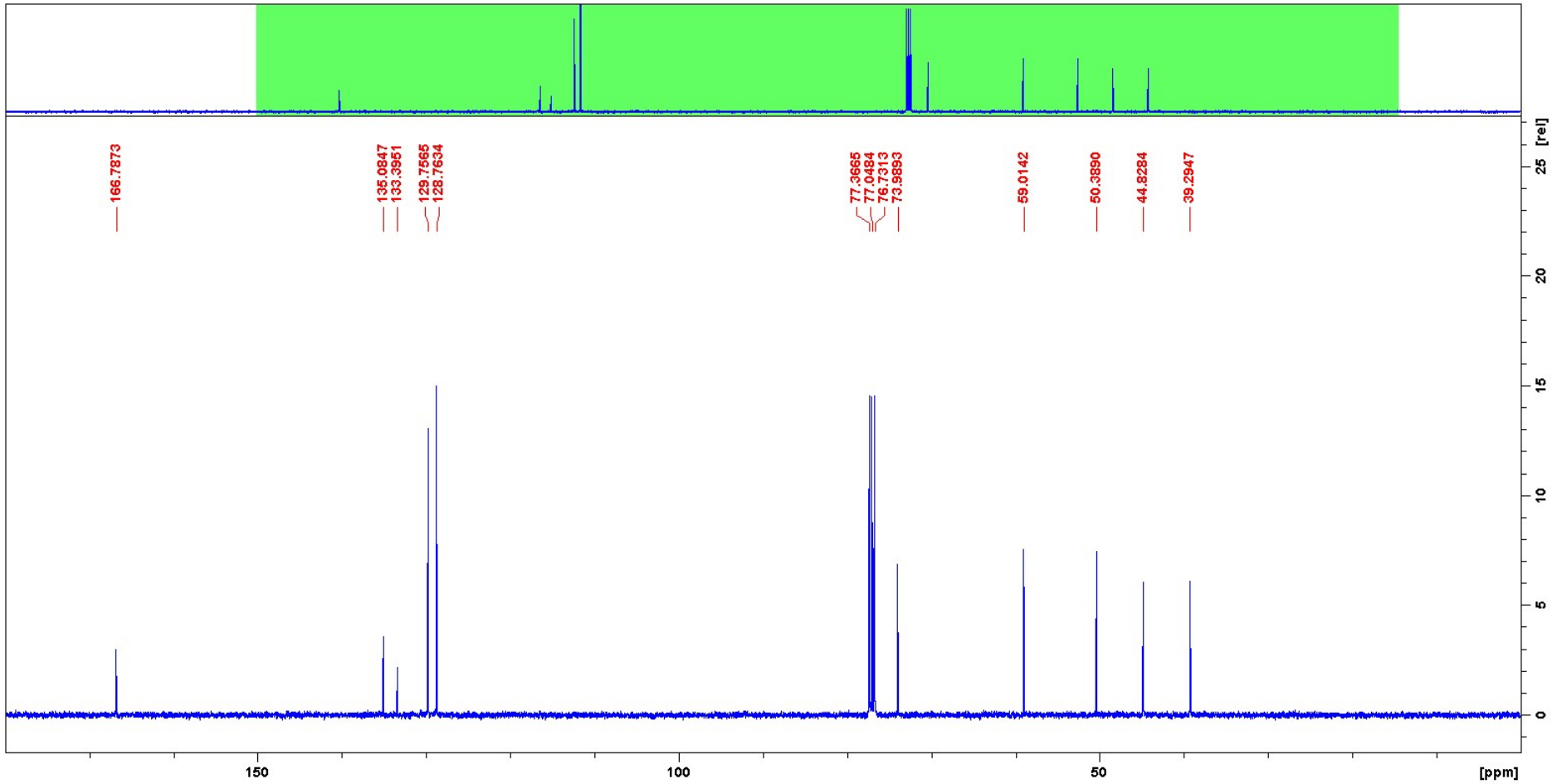
Compound **7b**: ^{13}C NMR



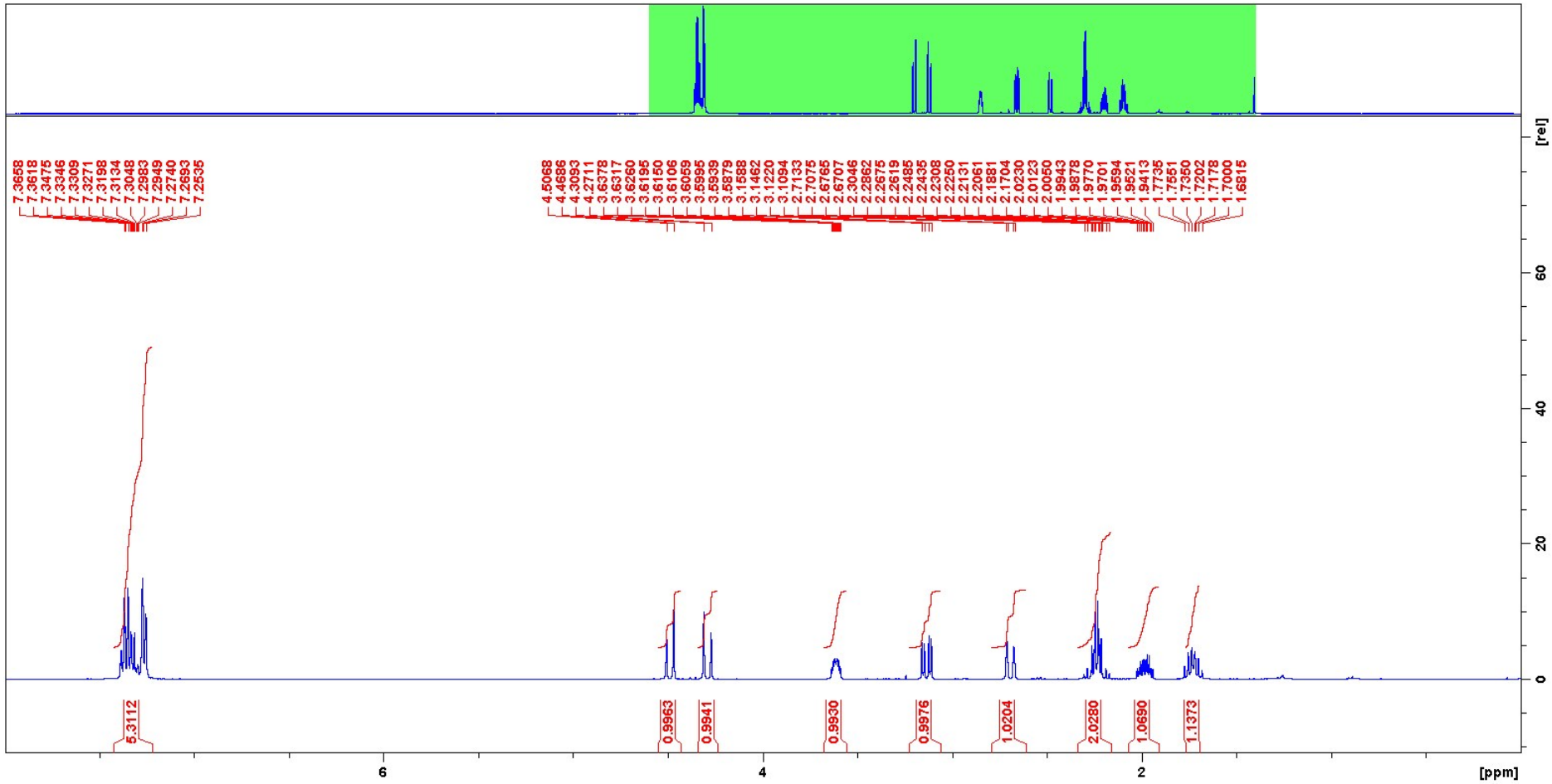
Compound **7c**: ^{1}H NMR



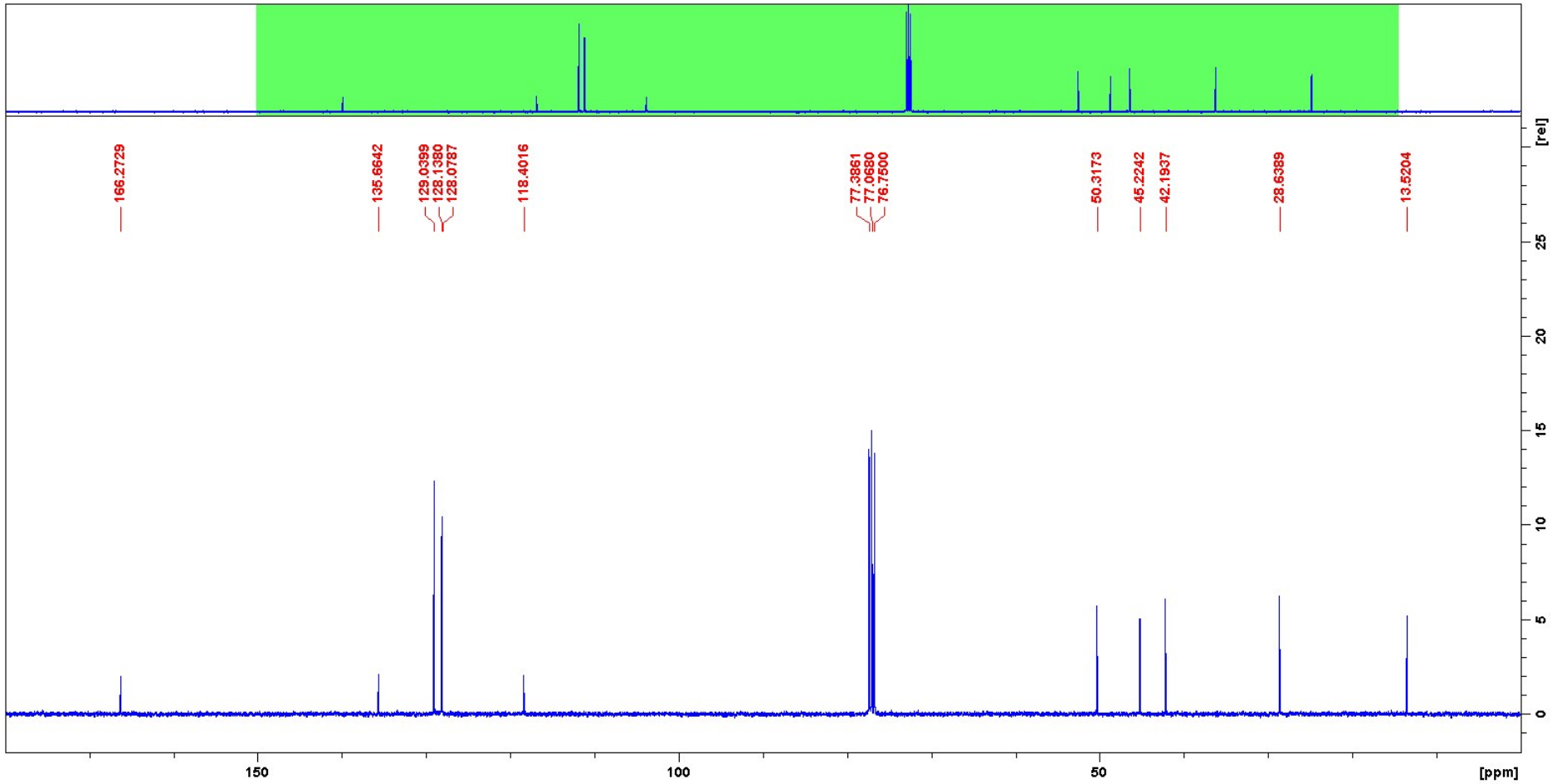
Compound **7c**: ^{13}C NMR



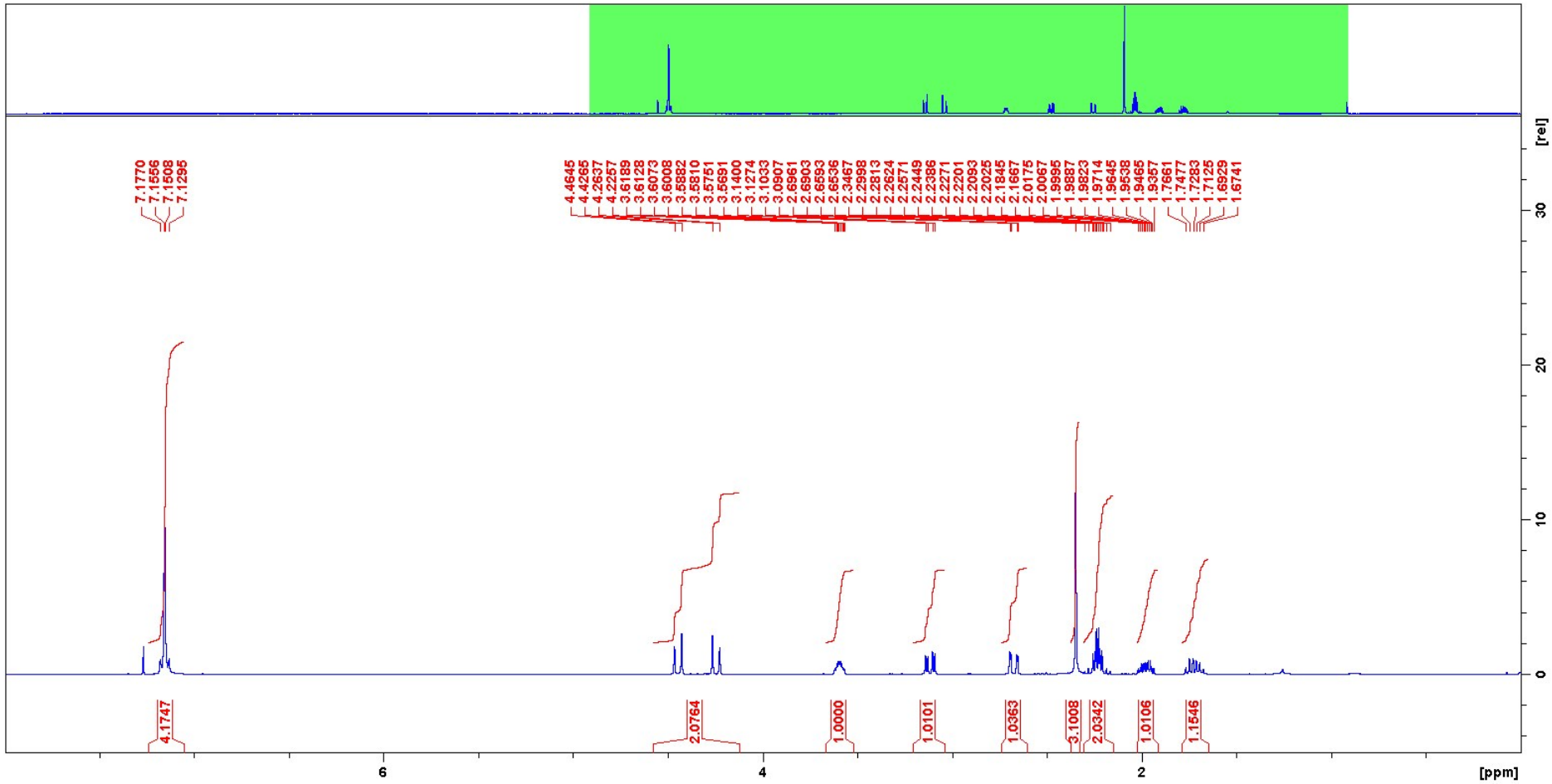
Compound **9a**: ^{1}H NMR



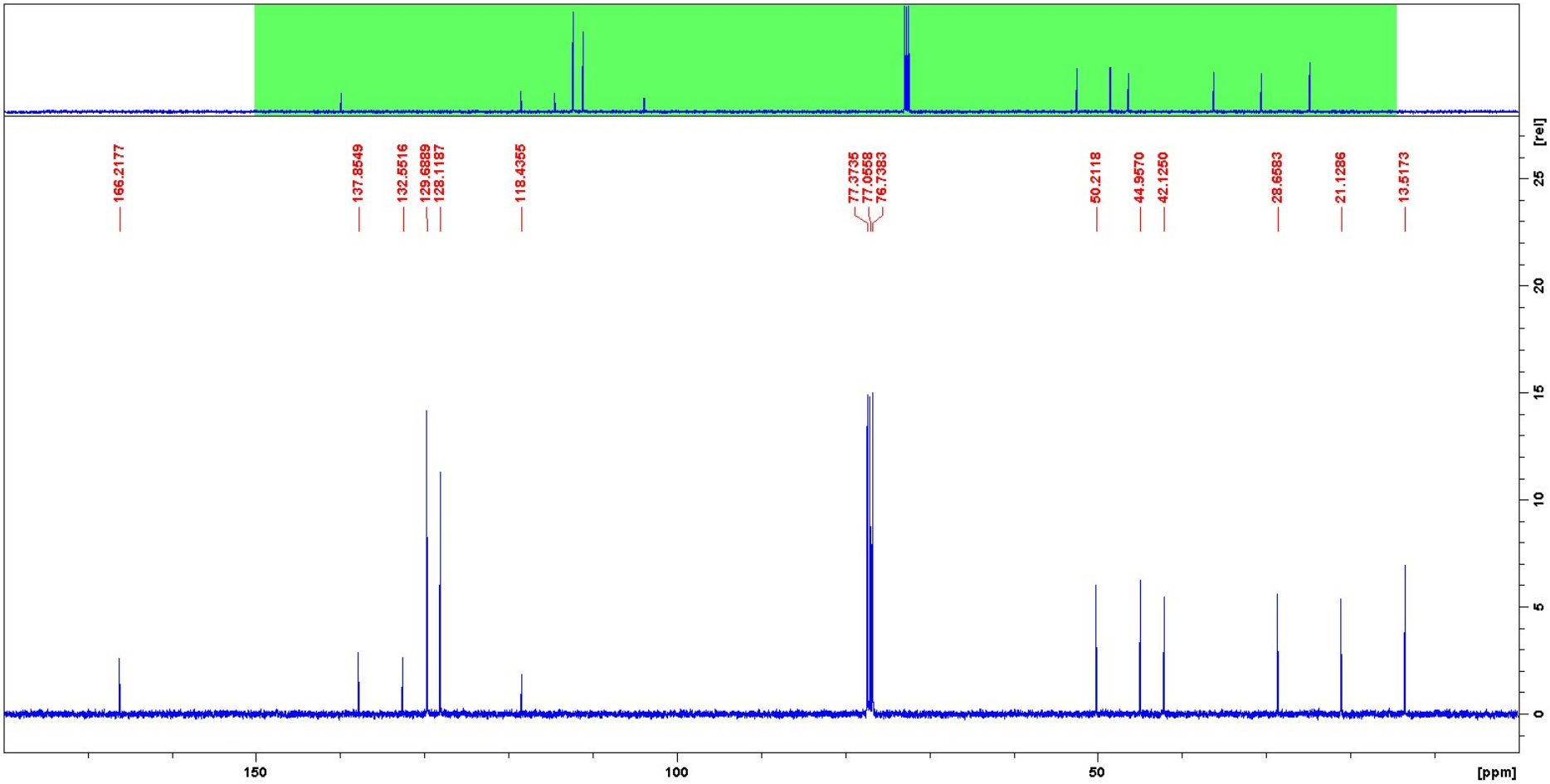
Compound **9a**: ^{13}C NMR



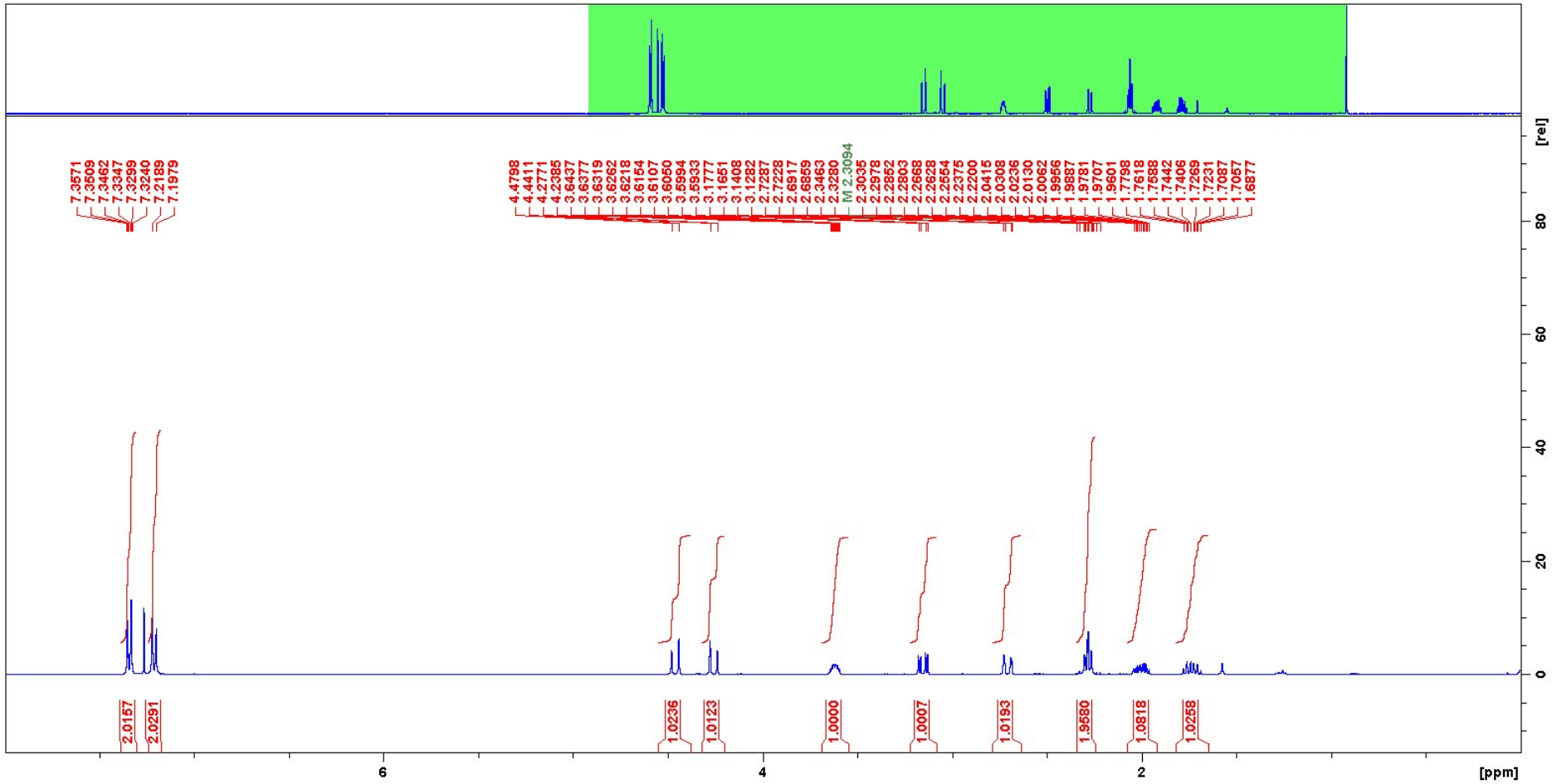
Compound **9b**: ^{1}H NMR



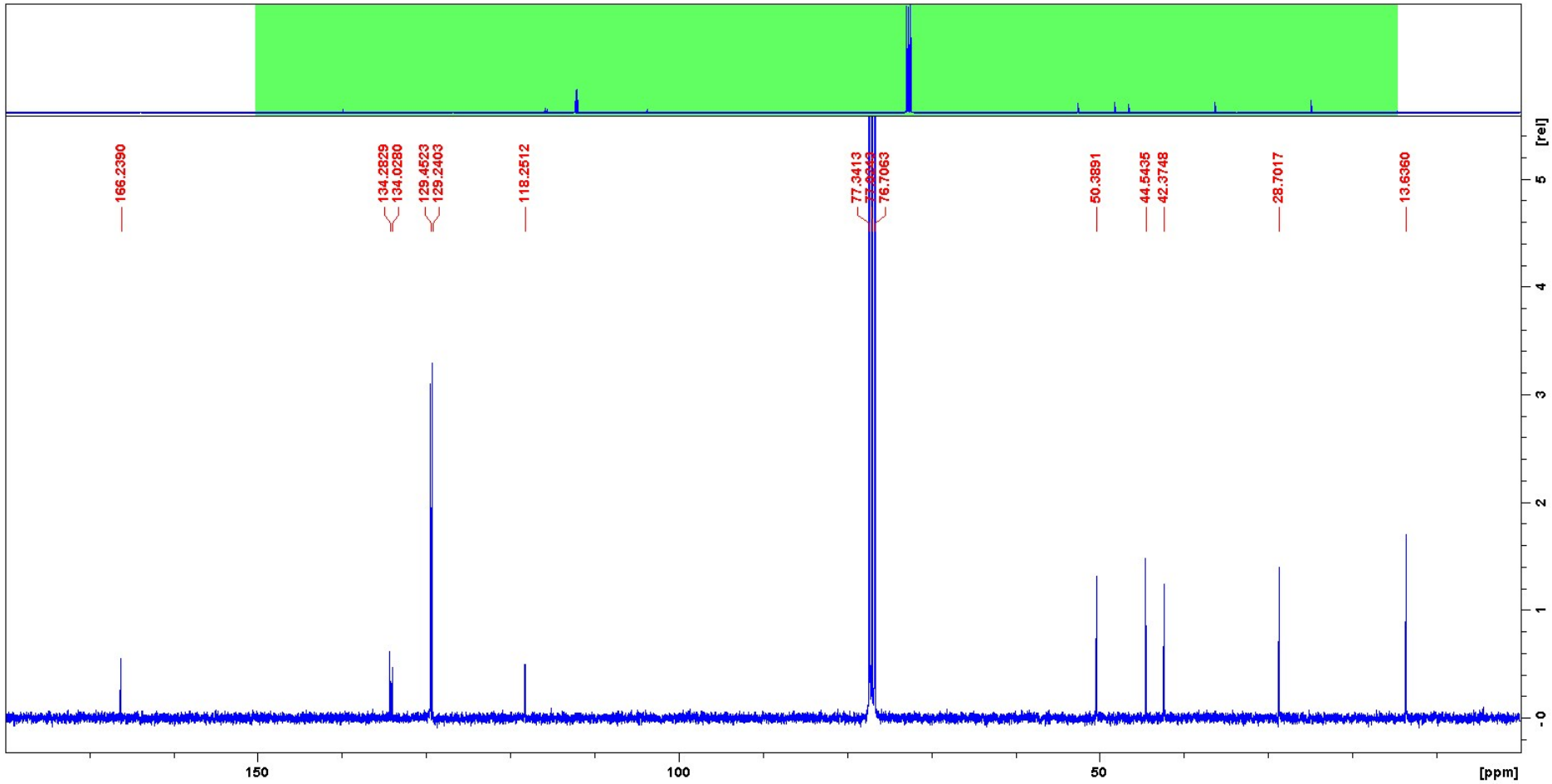
Compound **9b**: ^{13}C NMR



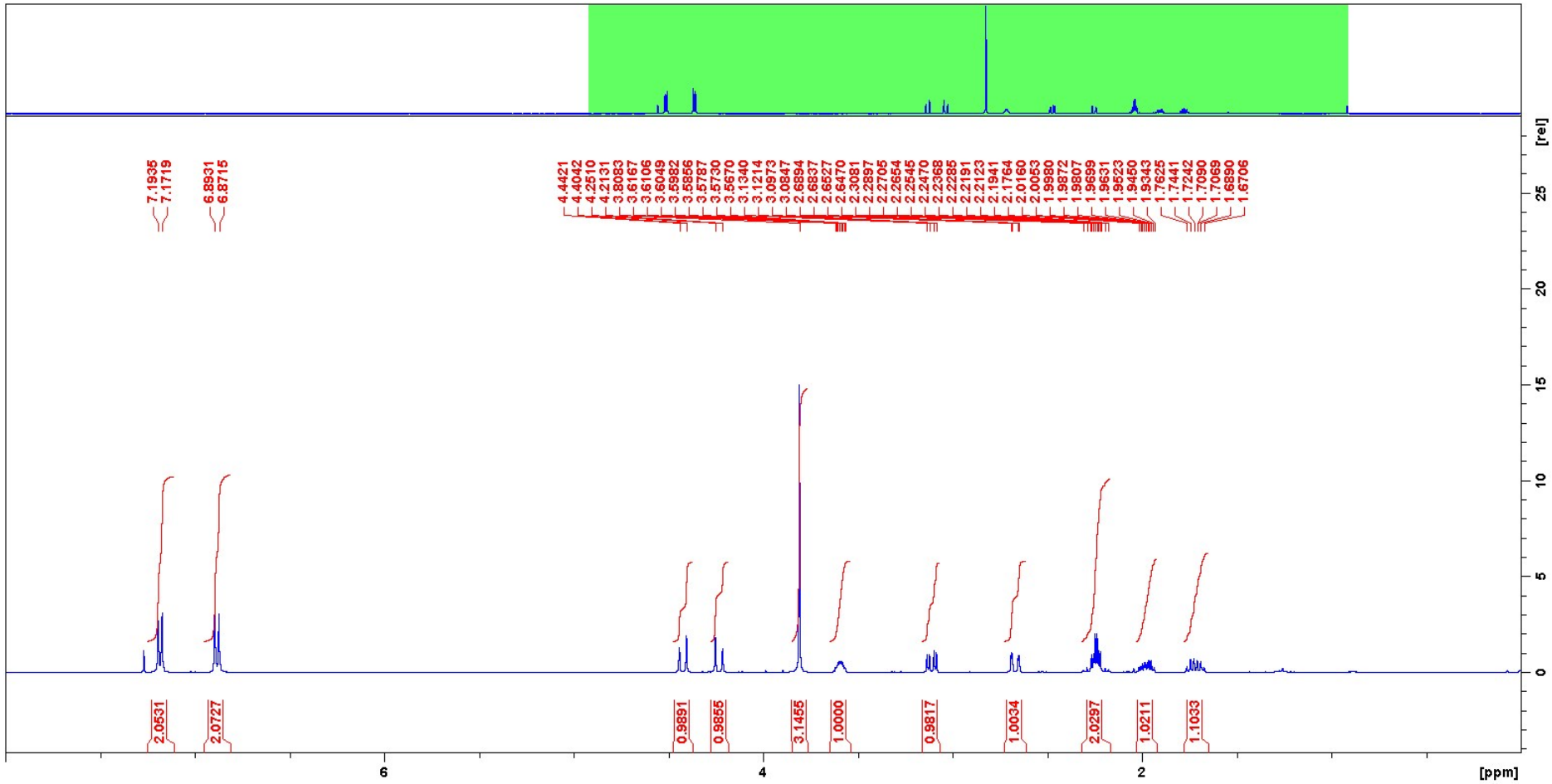
Compound **9c**: ^{1}H NMR



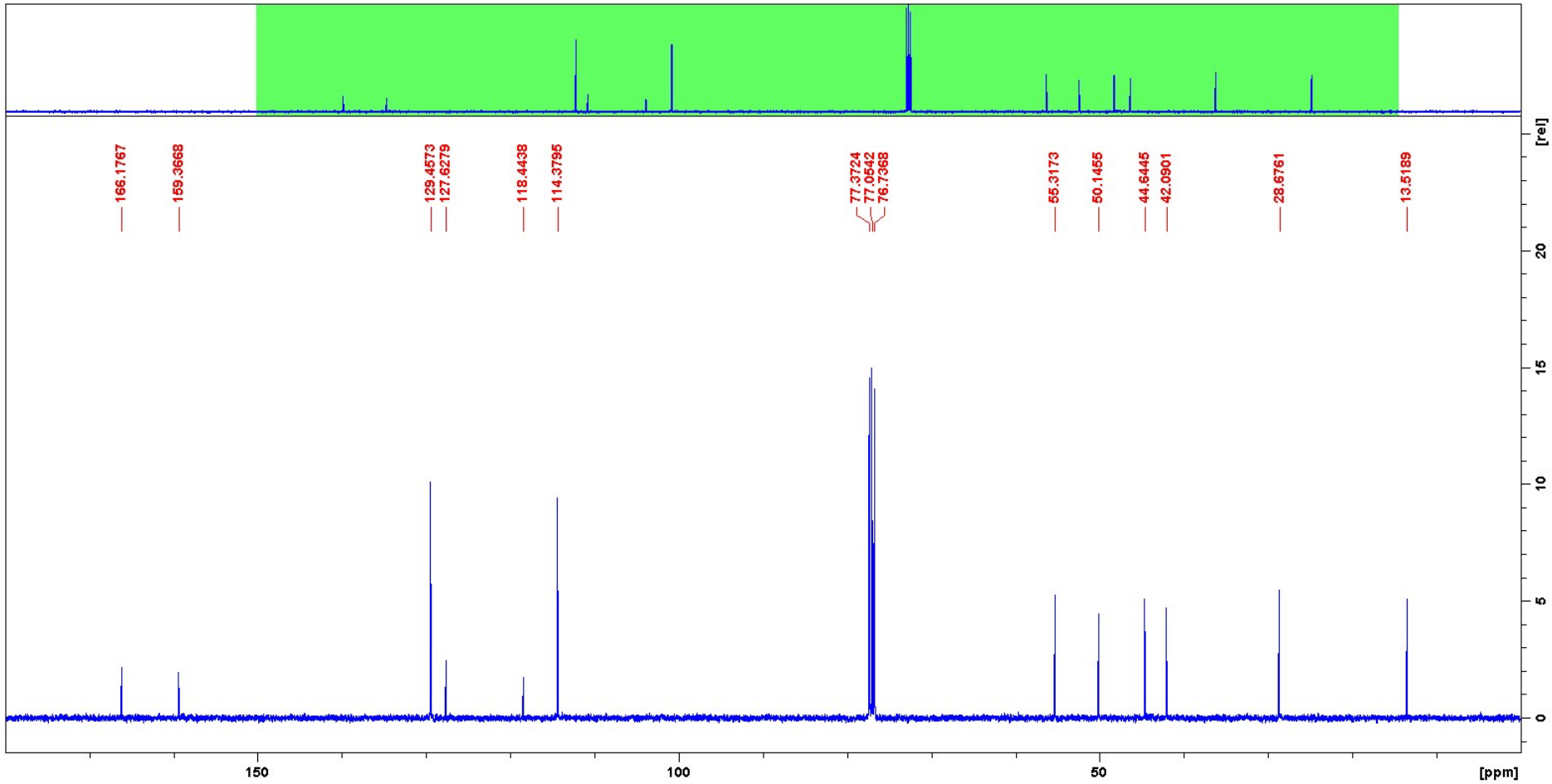
Compound **9c**: ^{13}C NMR



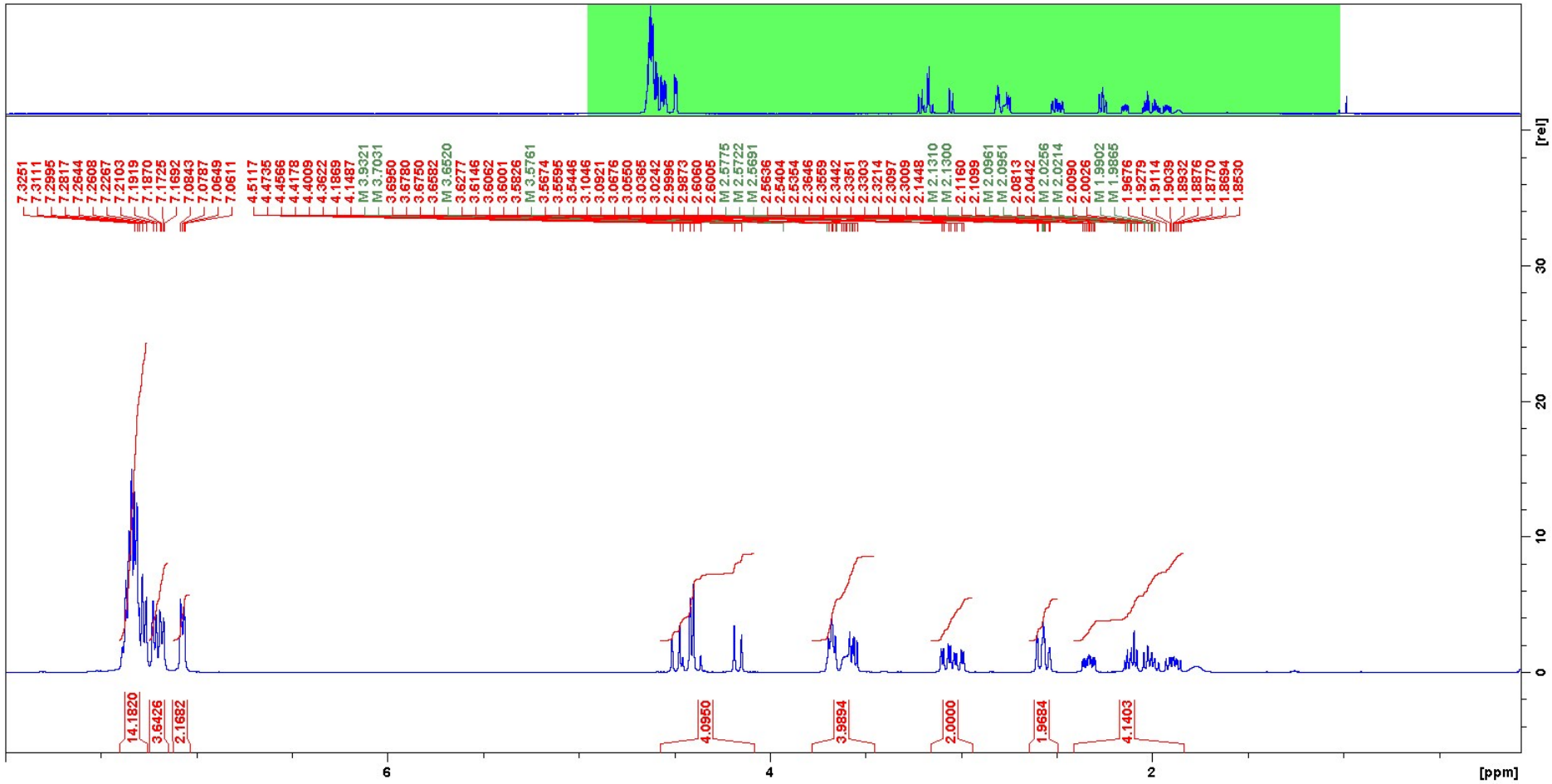
Compound **9d**: ^{1}H NMR



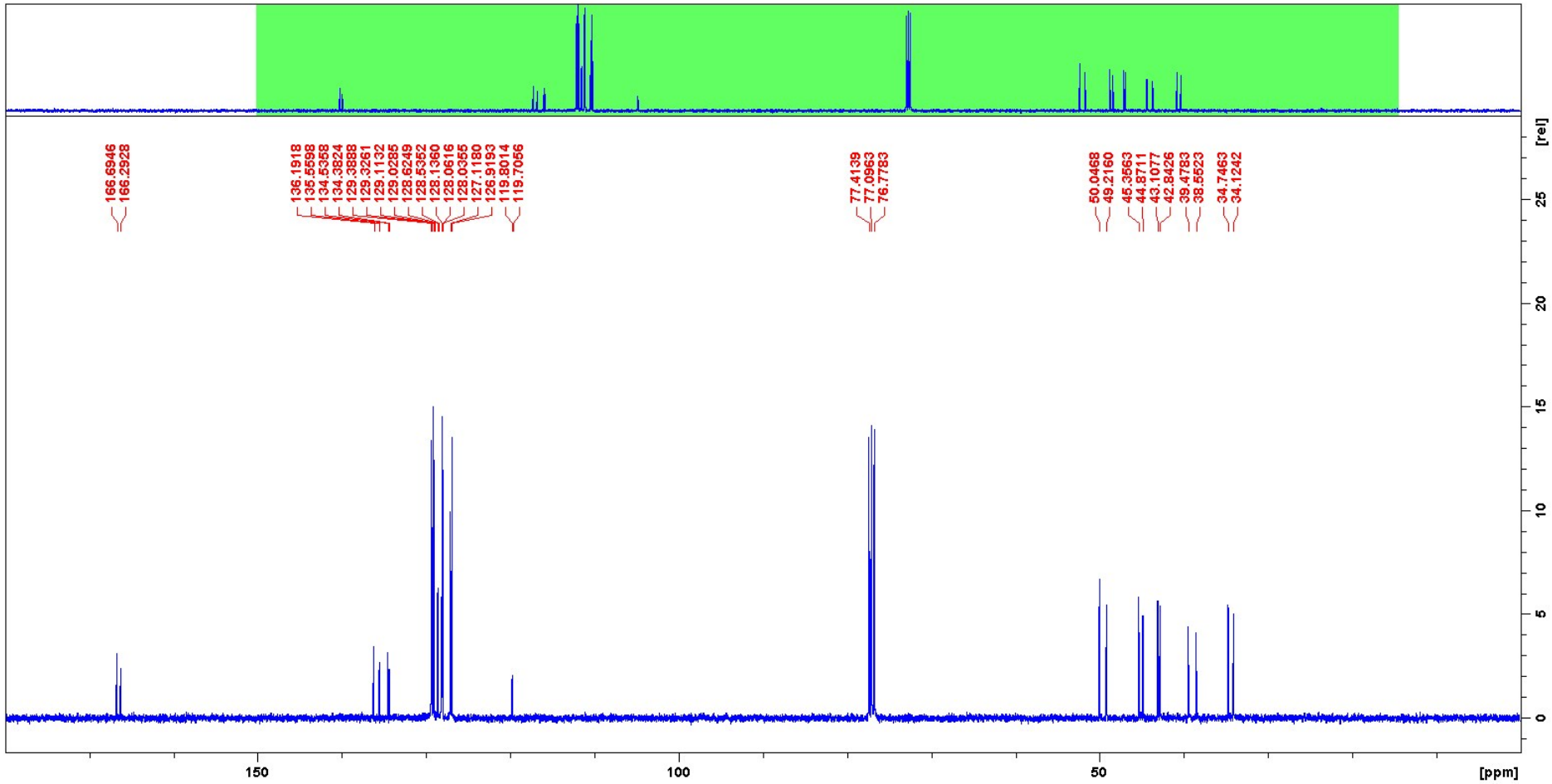
Compound **9d**: ^{13}C NMR



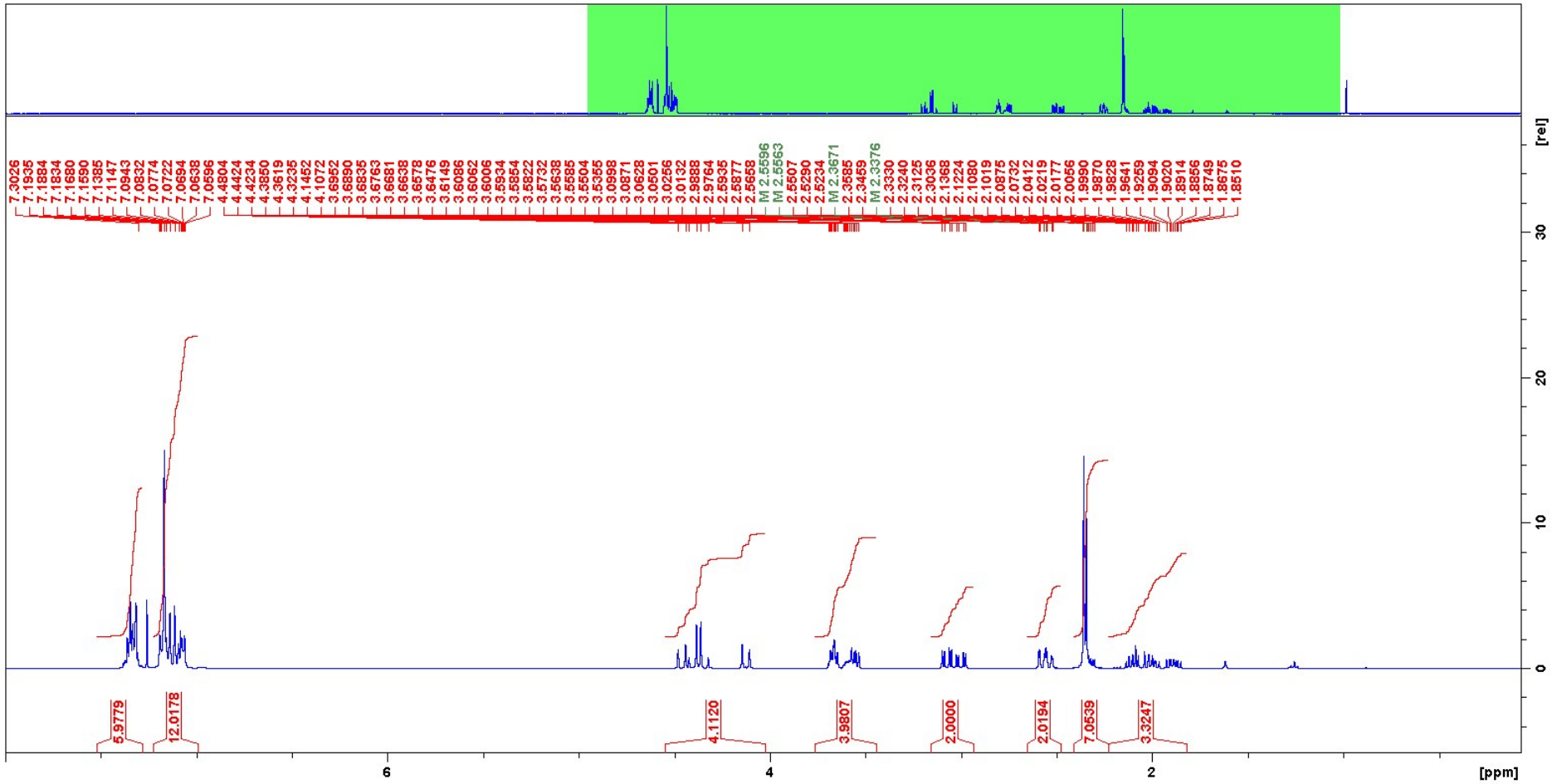
Compound **11a**: ^{1}H NMR



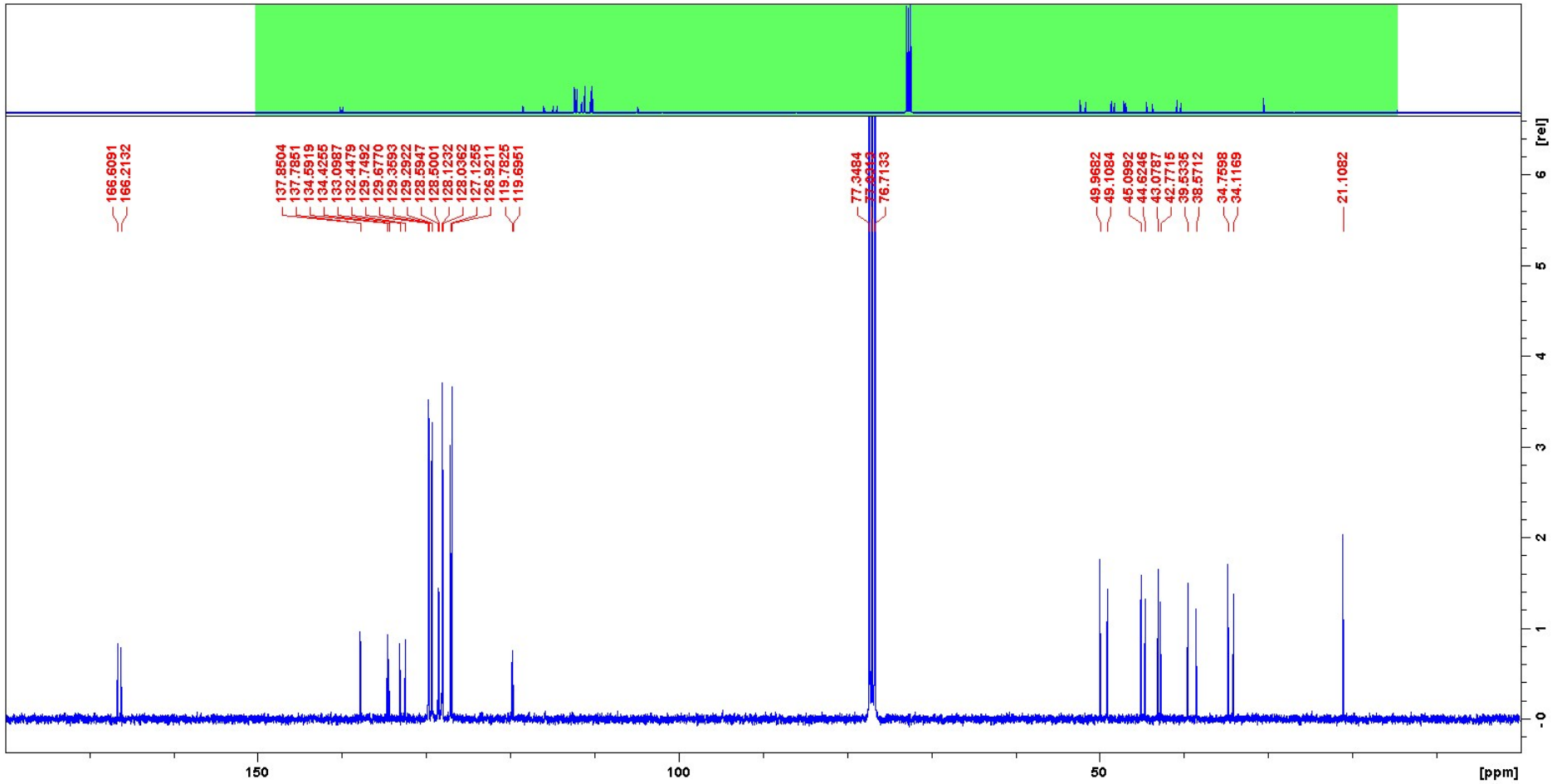
Compound **11a**: ^{13}C NMR



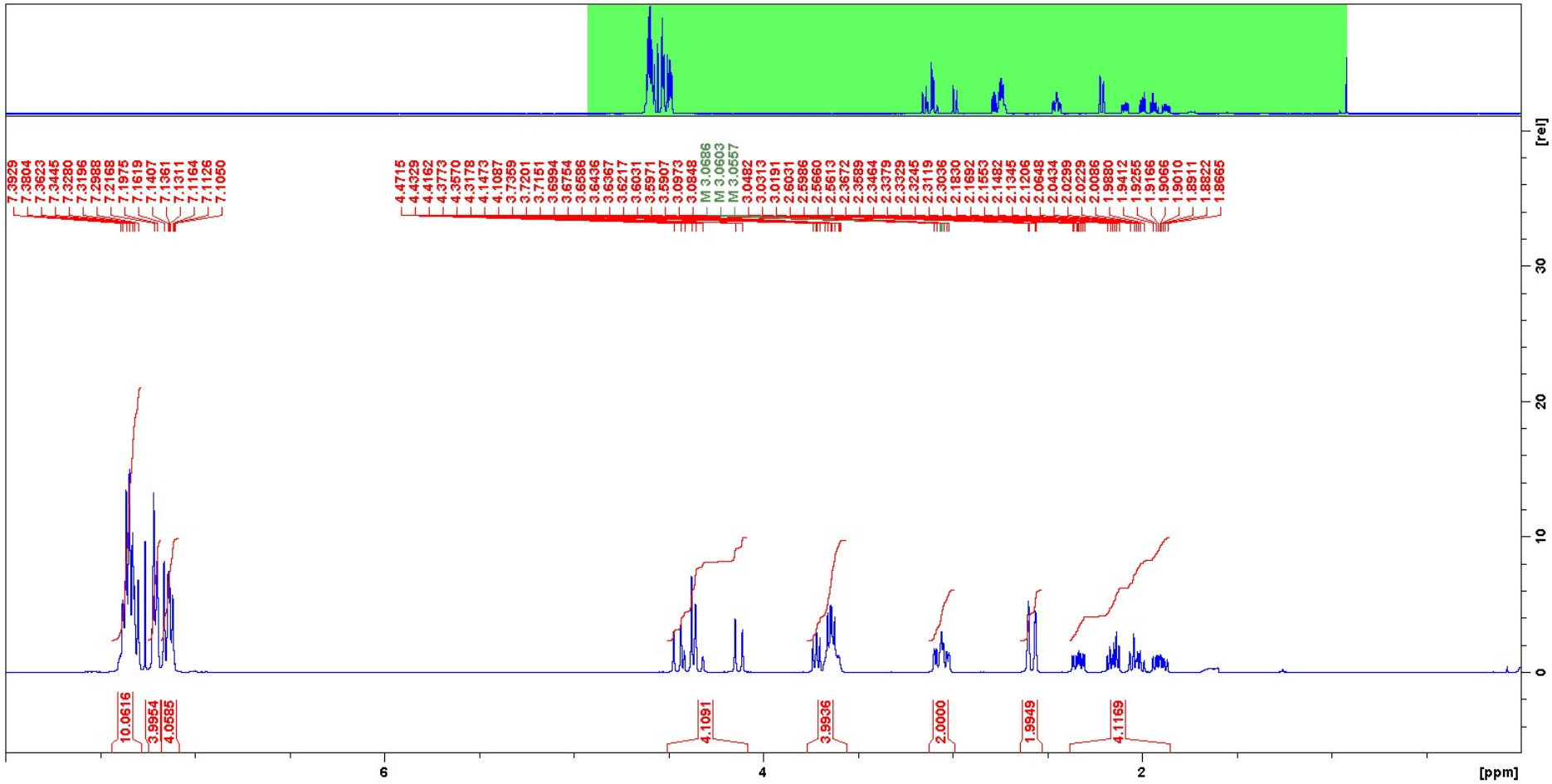
Compound **11b**: ^{1}H NMR



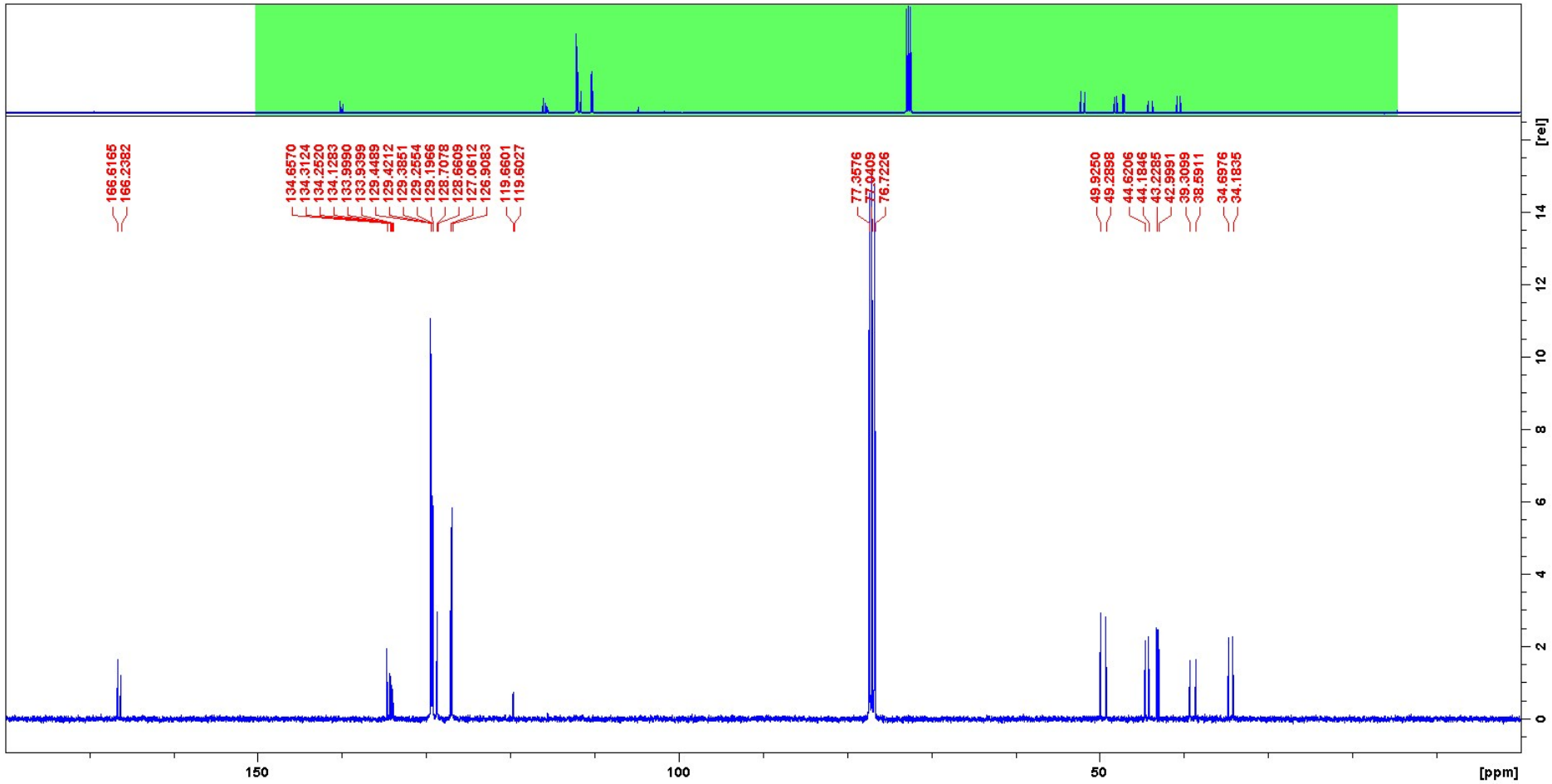
Compound **11b**: ^{13}C NMR



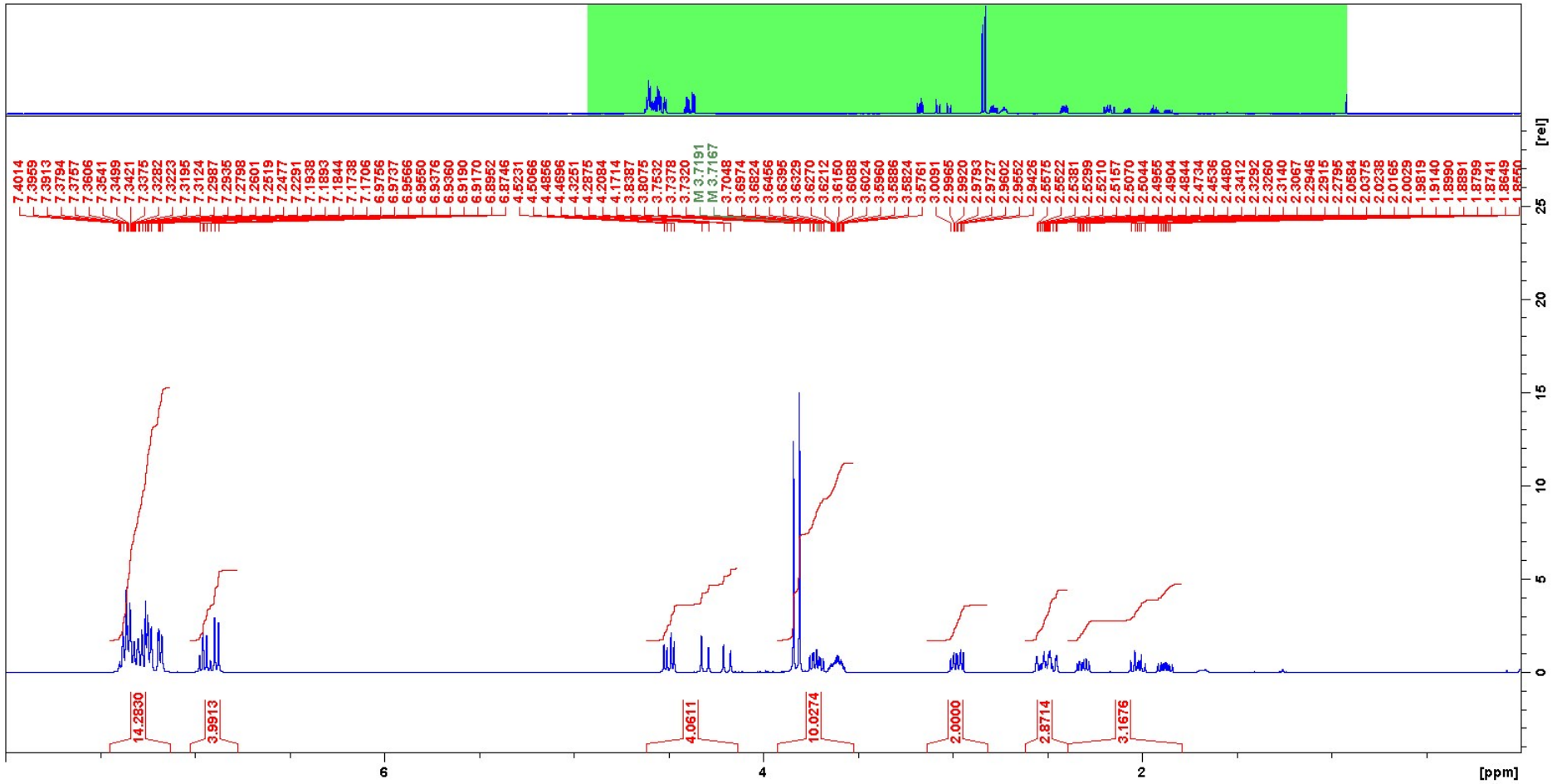
Compound **11c**: ^{1}H NMR



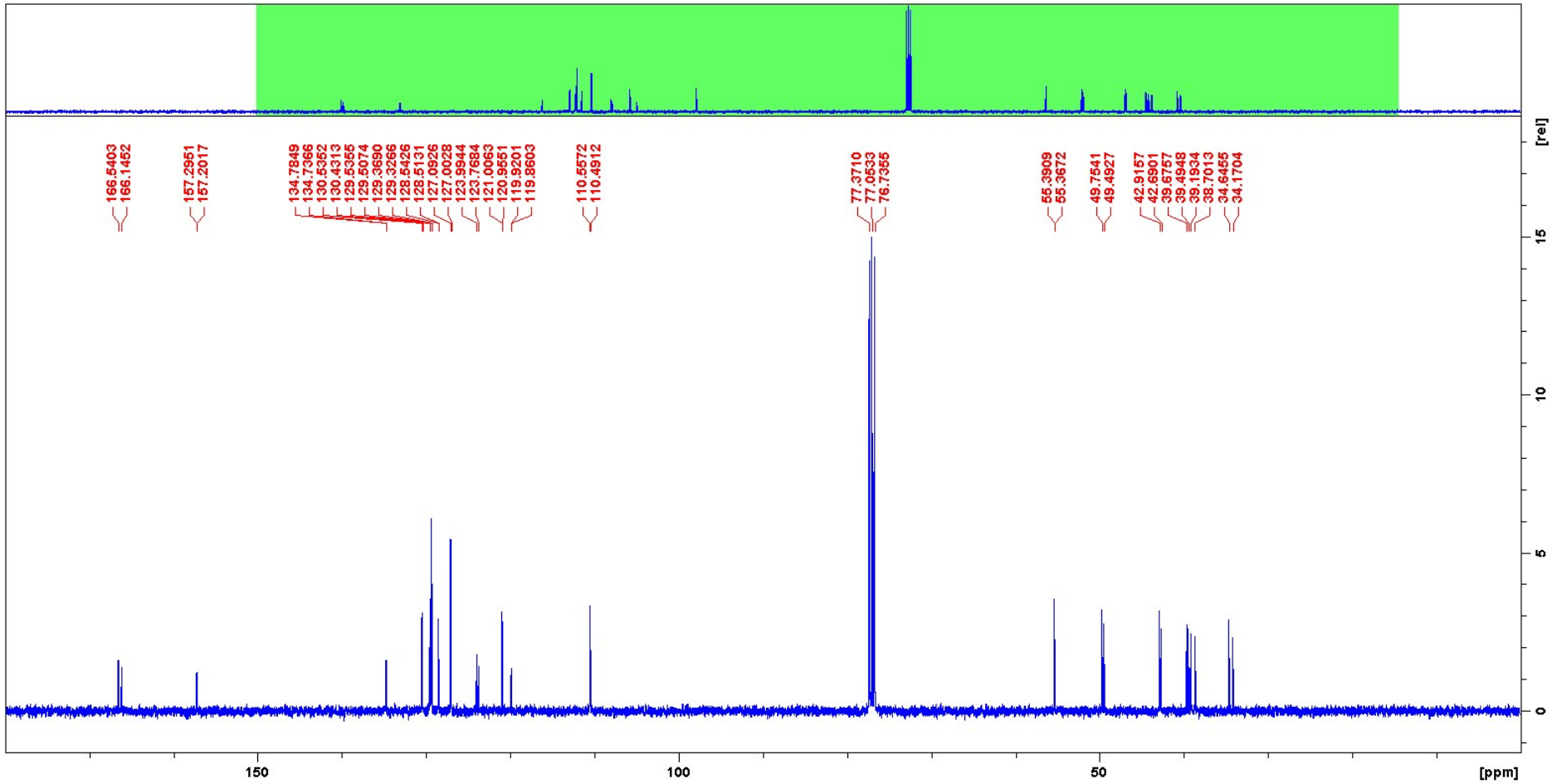
Compound **11c**: ^{13}C NMR



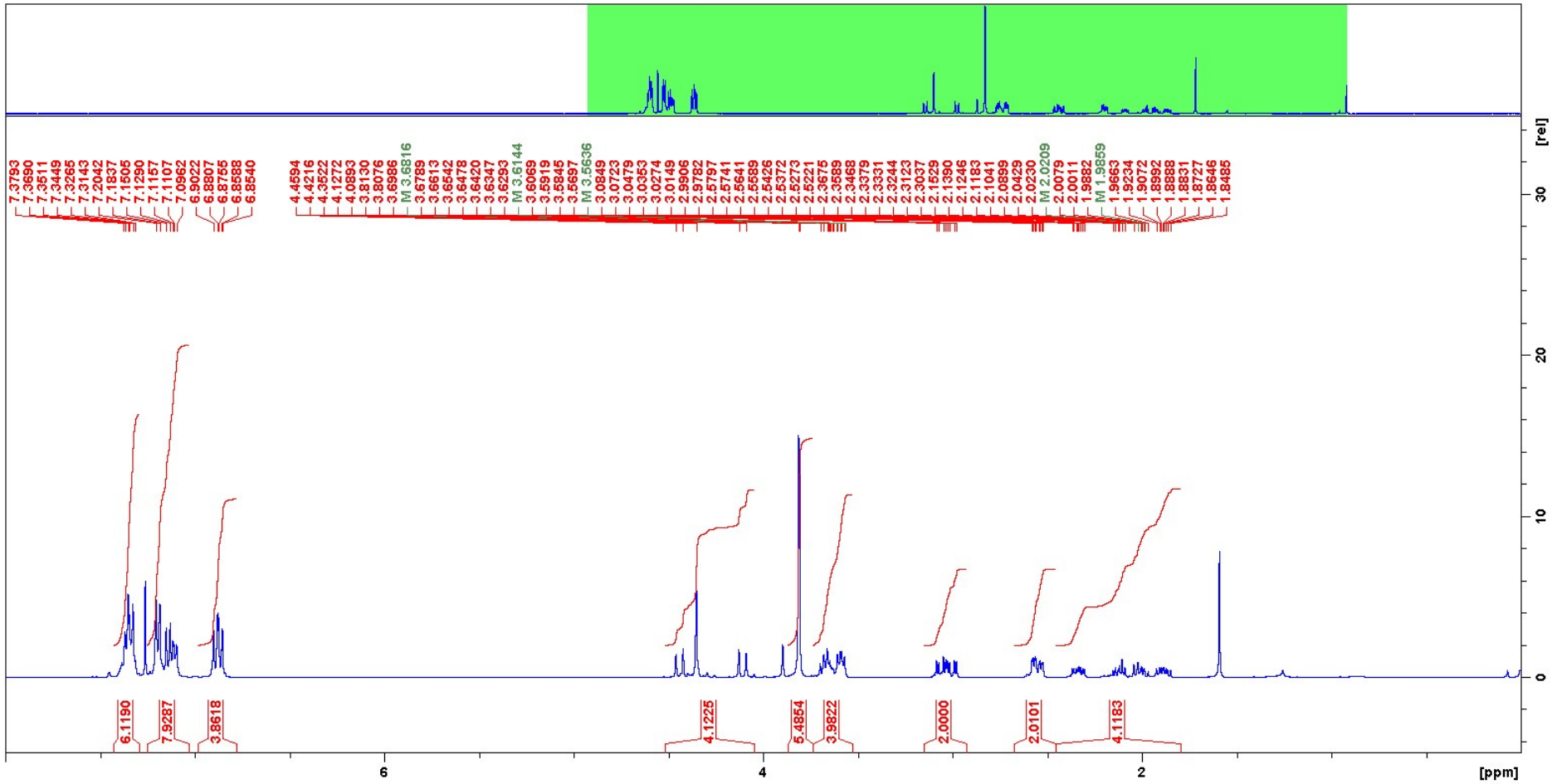
Compound **11d**: ^{1}H NMR



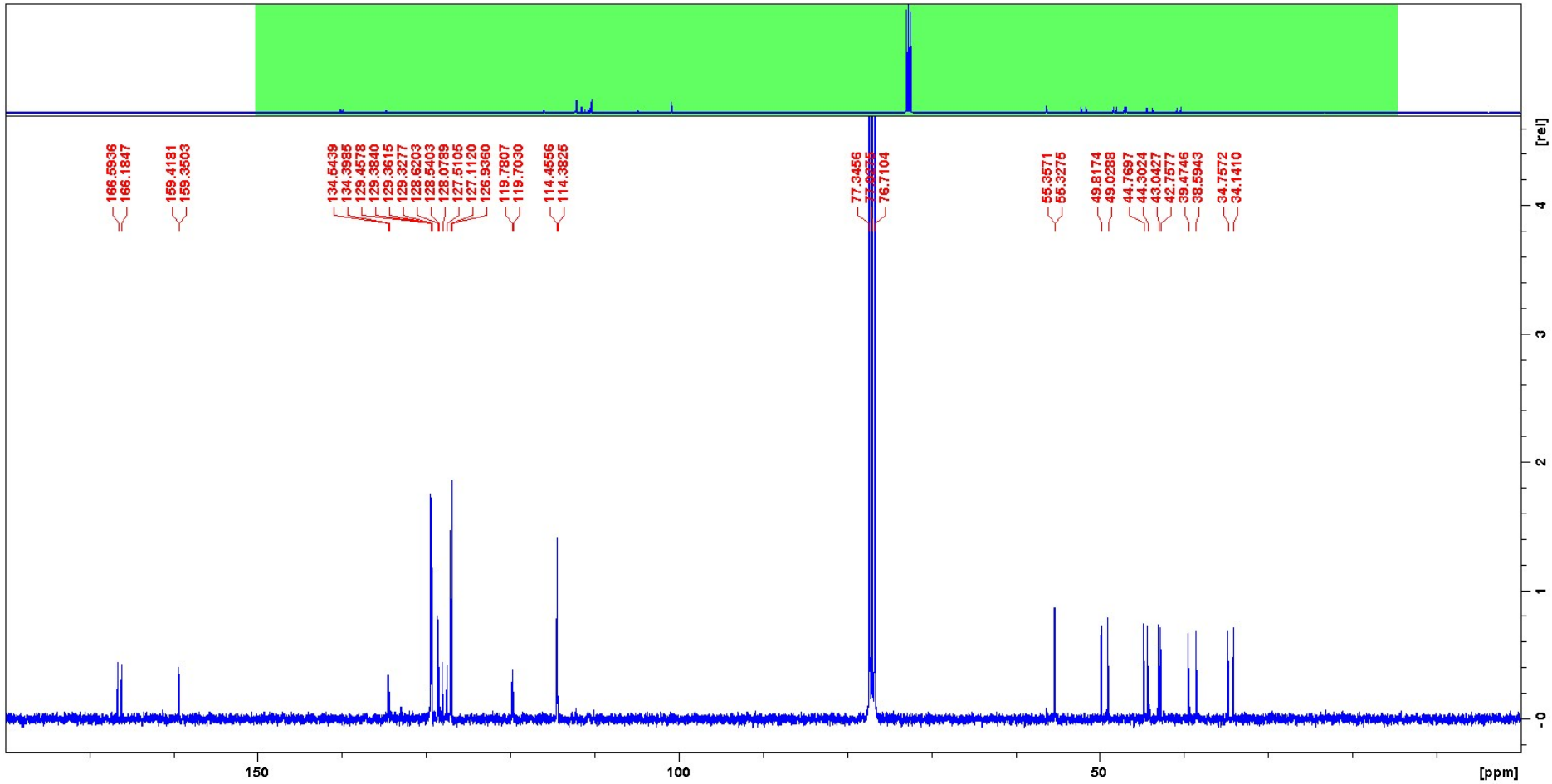
Compound **11d**: ^{13}C NMR



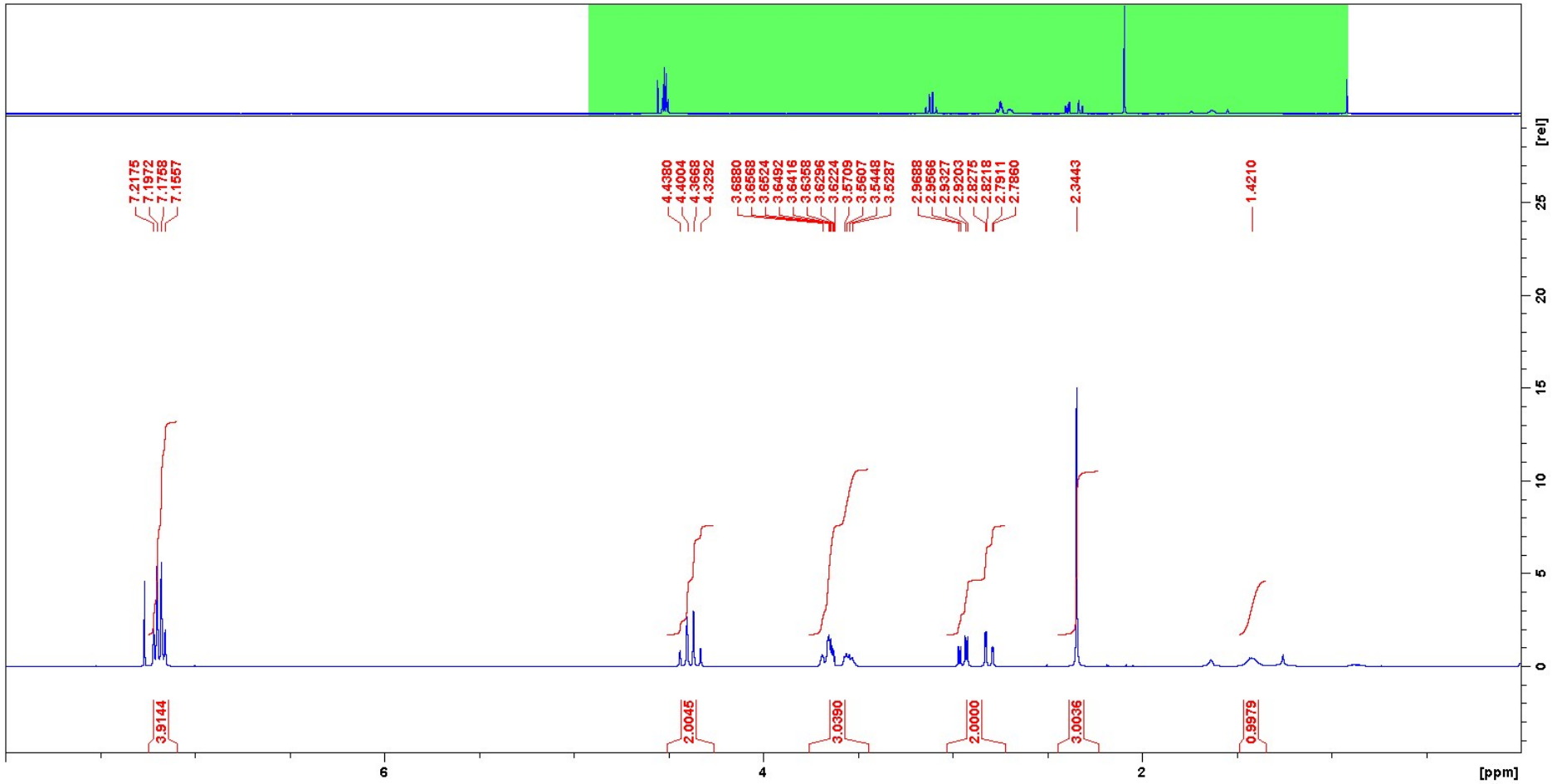
Compound **11e**: ^{1}H NMR



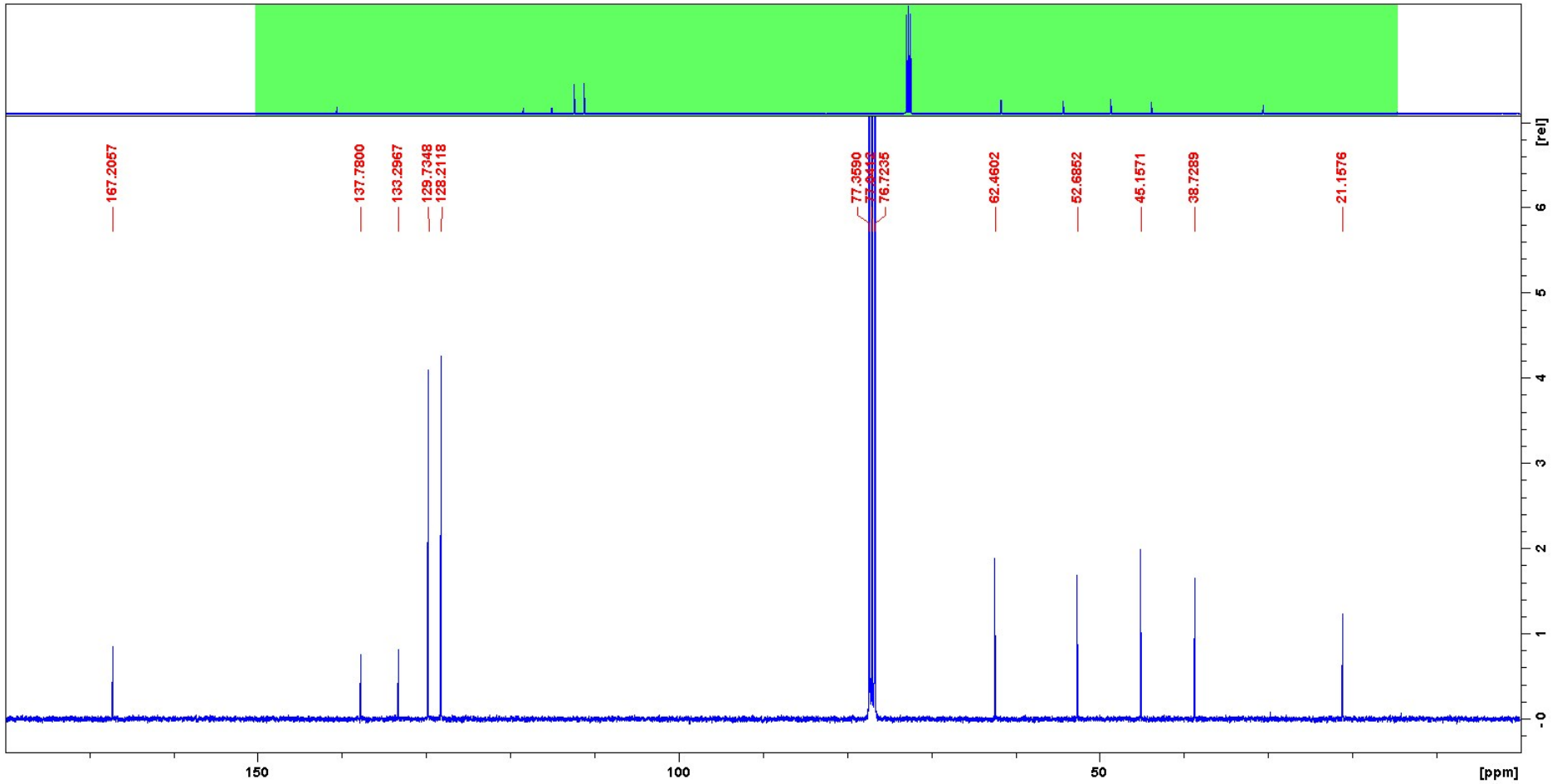
Compound **11e**: ^{13}C NMR



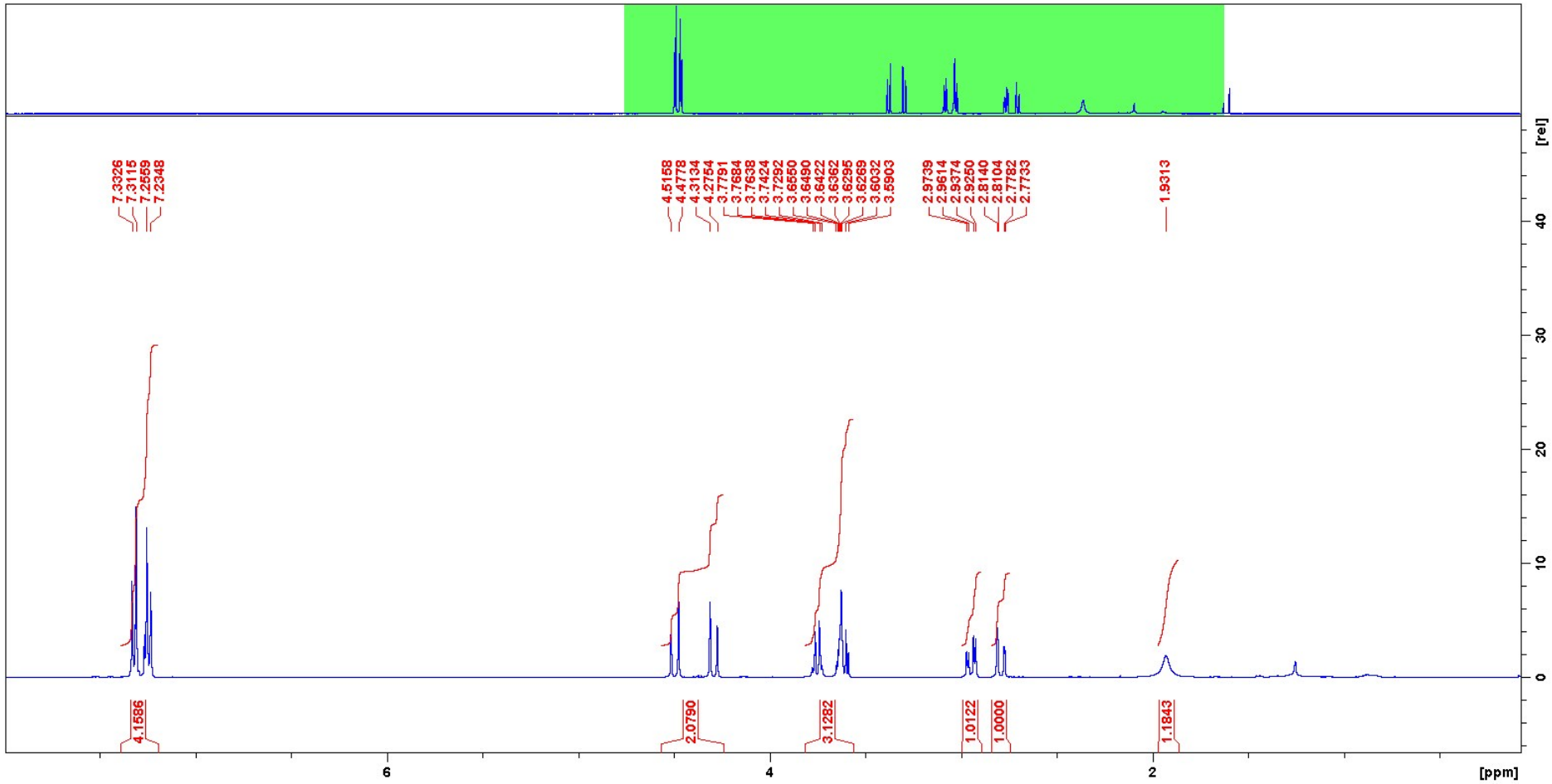
Compound **12a**: ^{1}H NMR



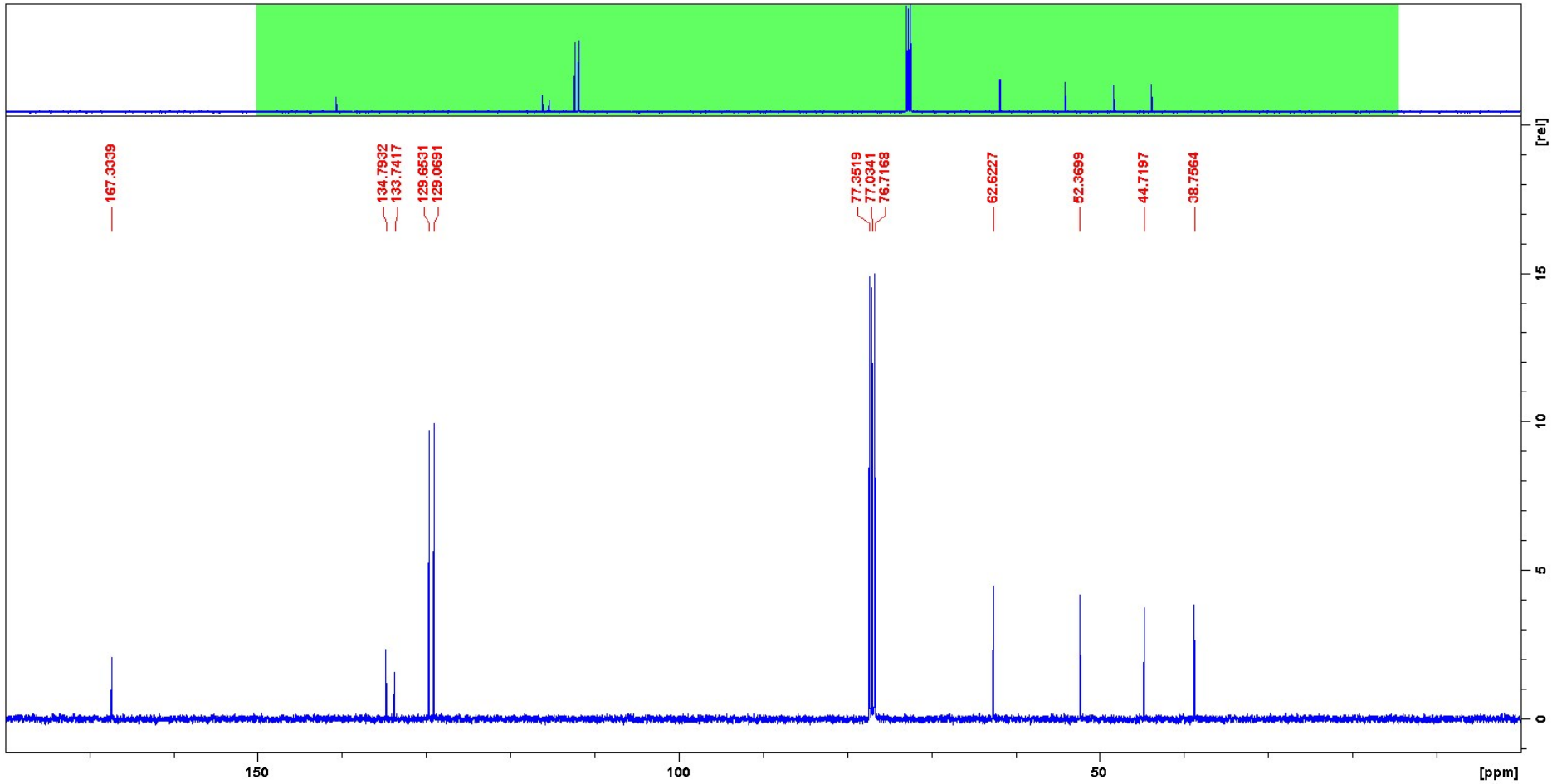
Compound **12a**: ^{13}C NMR



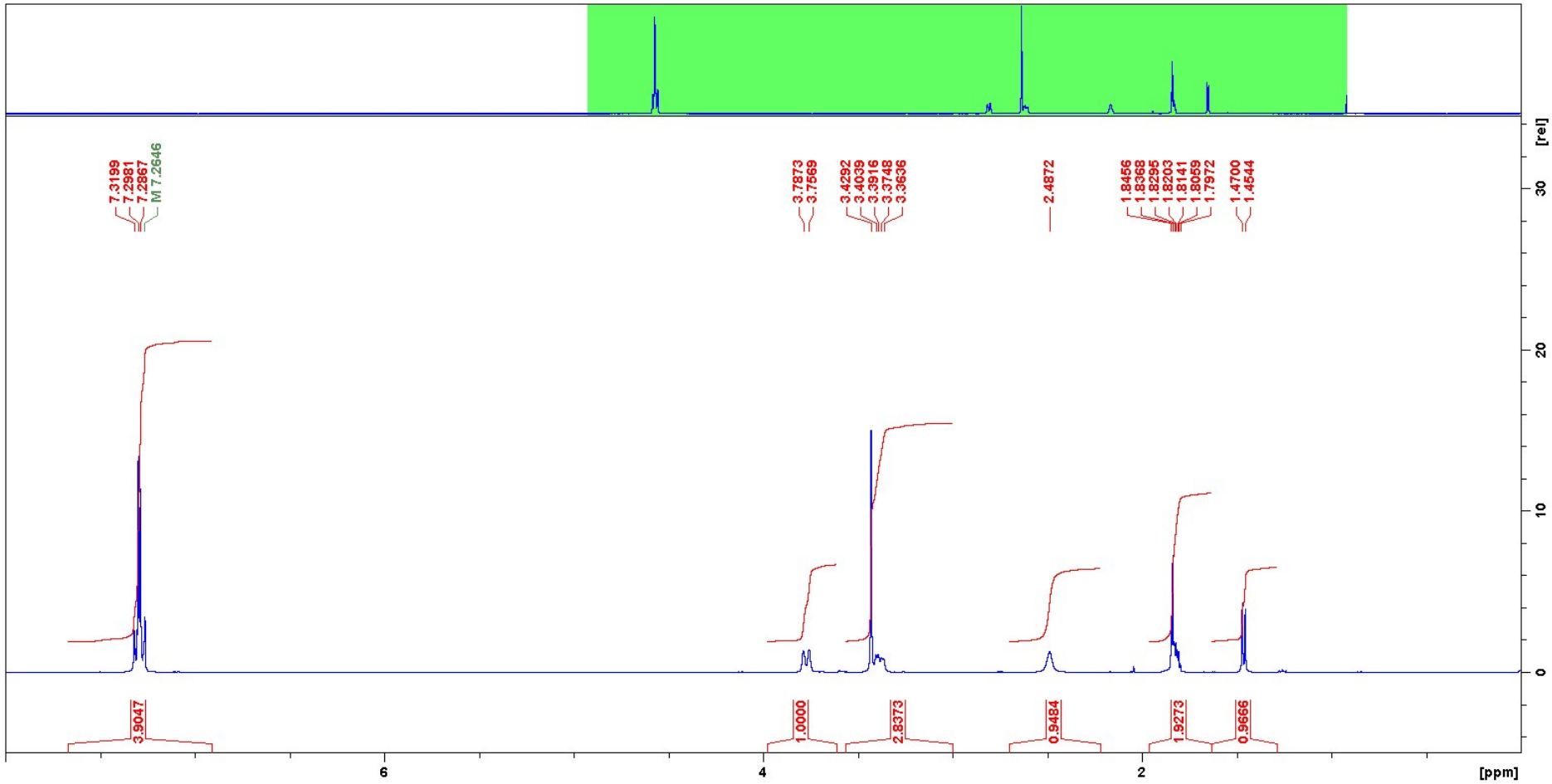
Compound **12b**: ^{1}H NMR



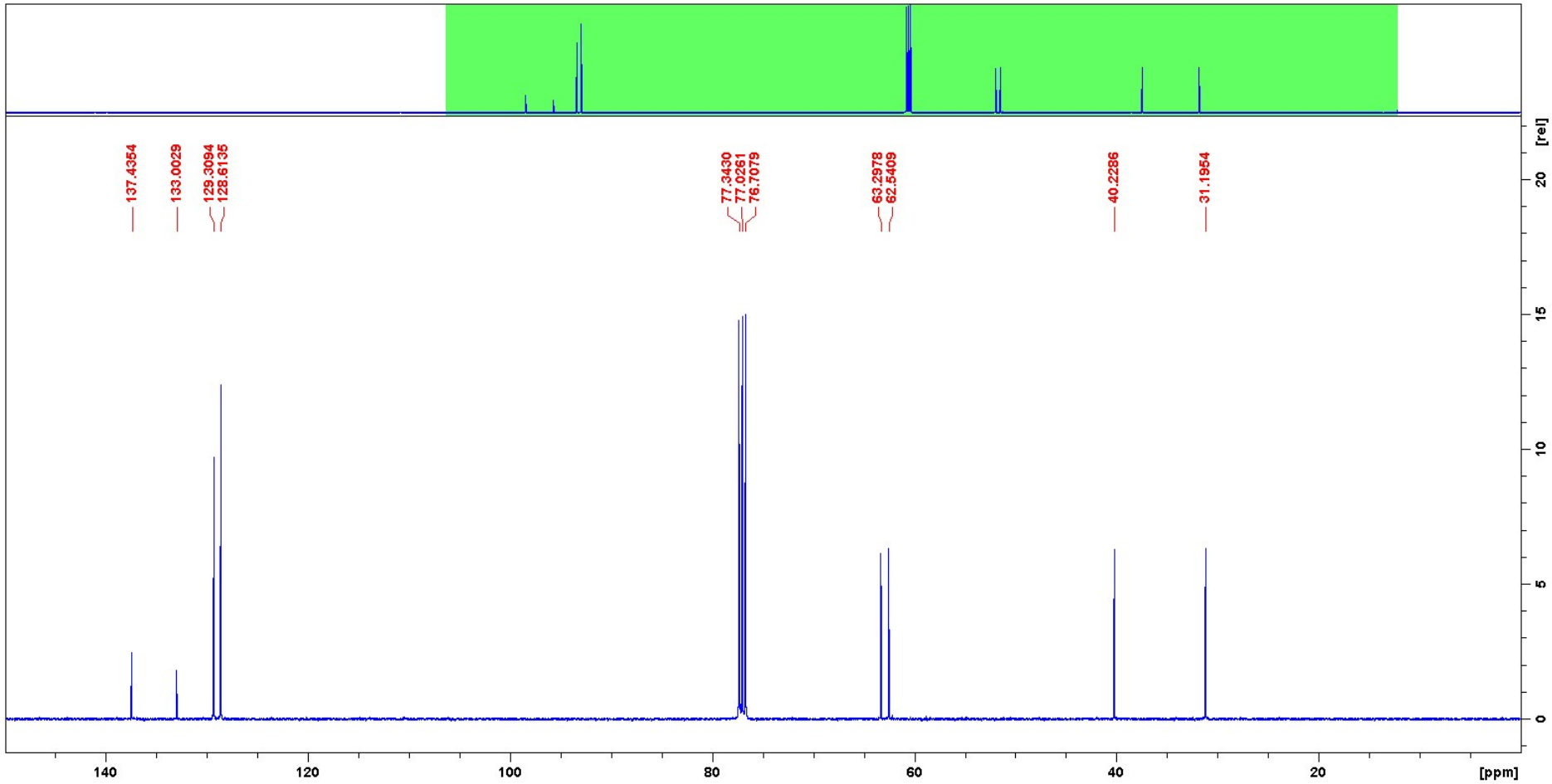
Compound **12b**: ^{13}C NMR



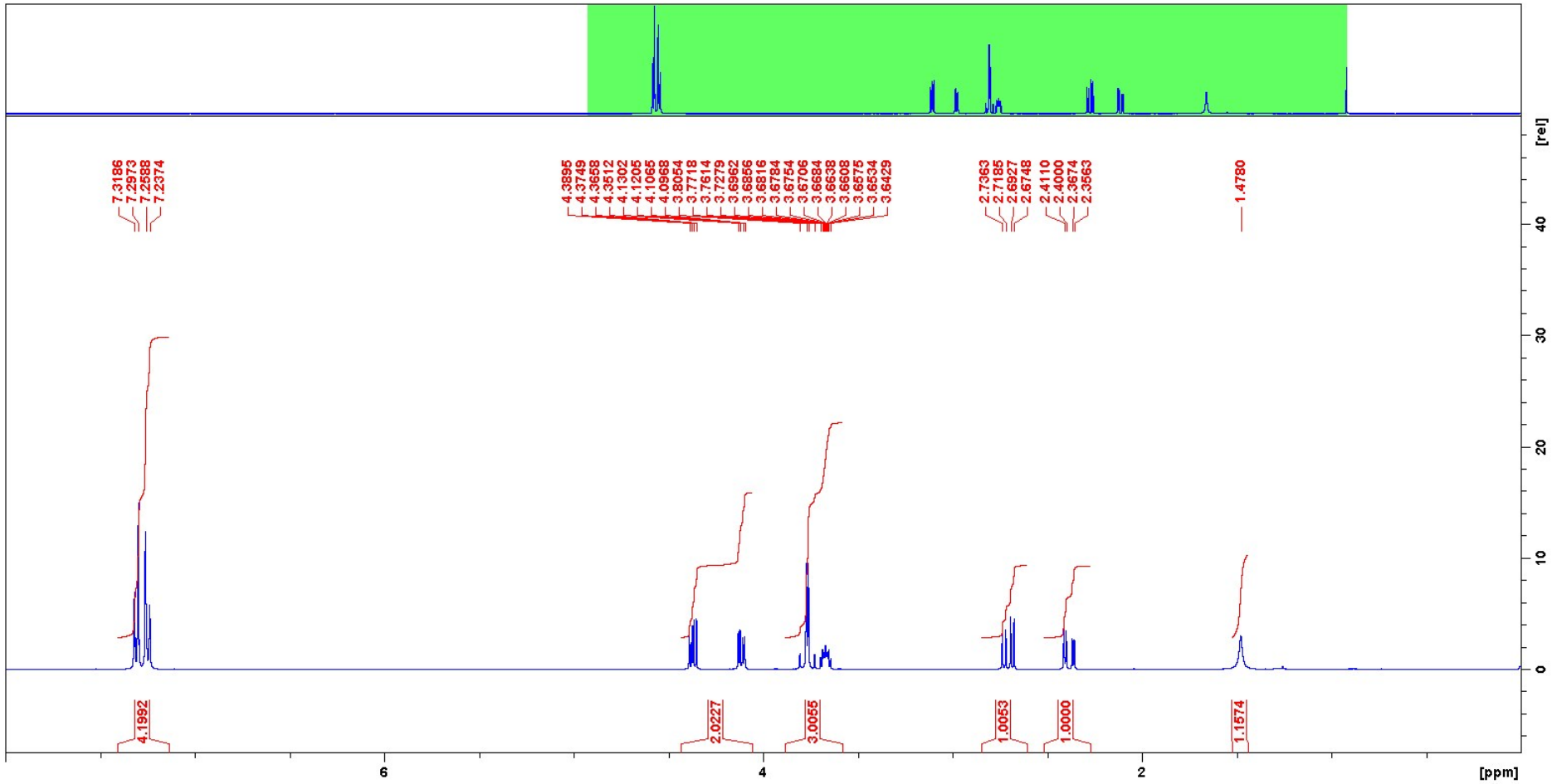
Compound **13**: ^{1}H NMR



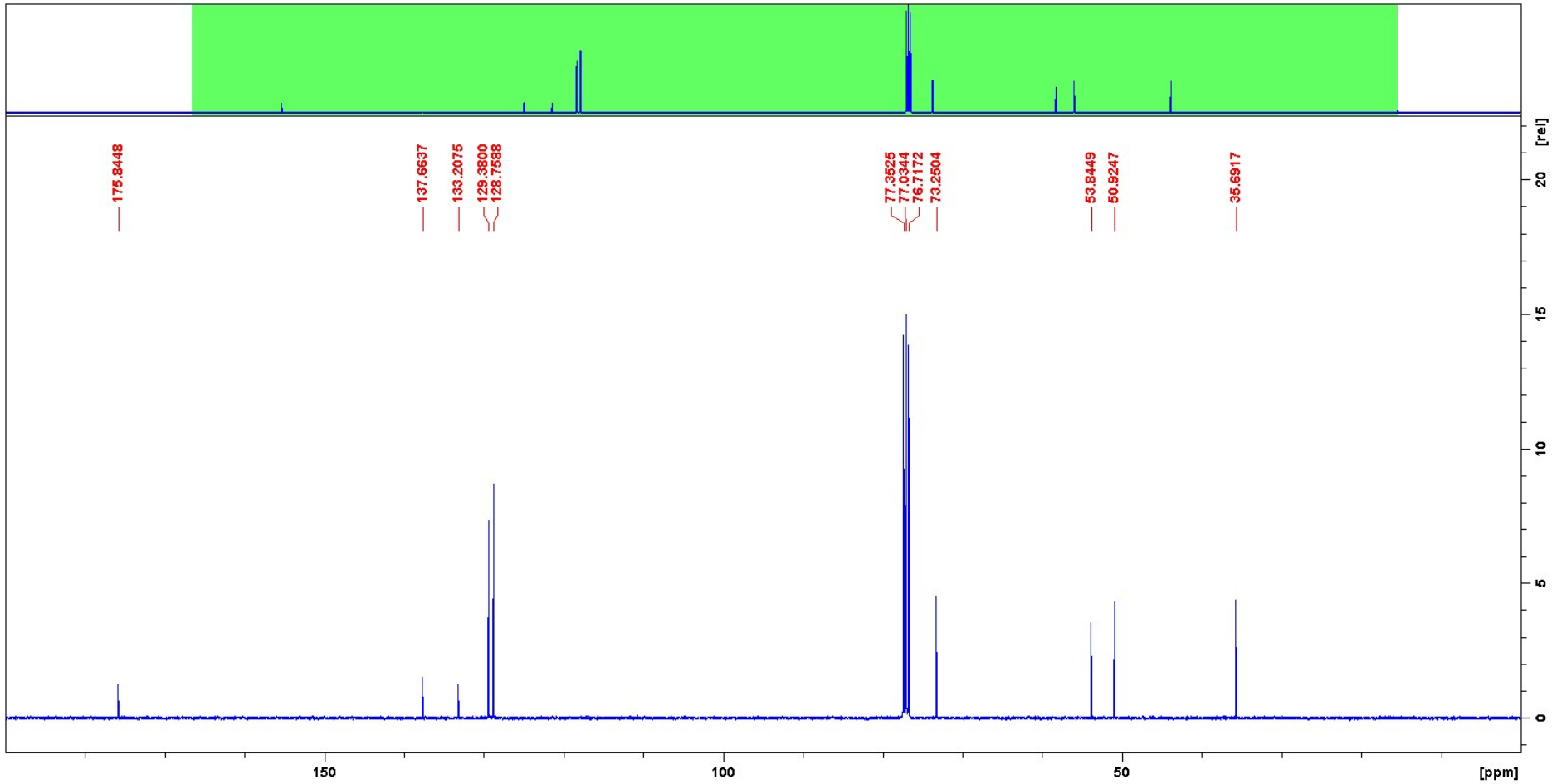
Compound **13**: ^{13}C NMR



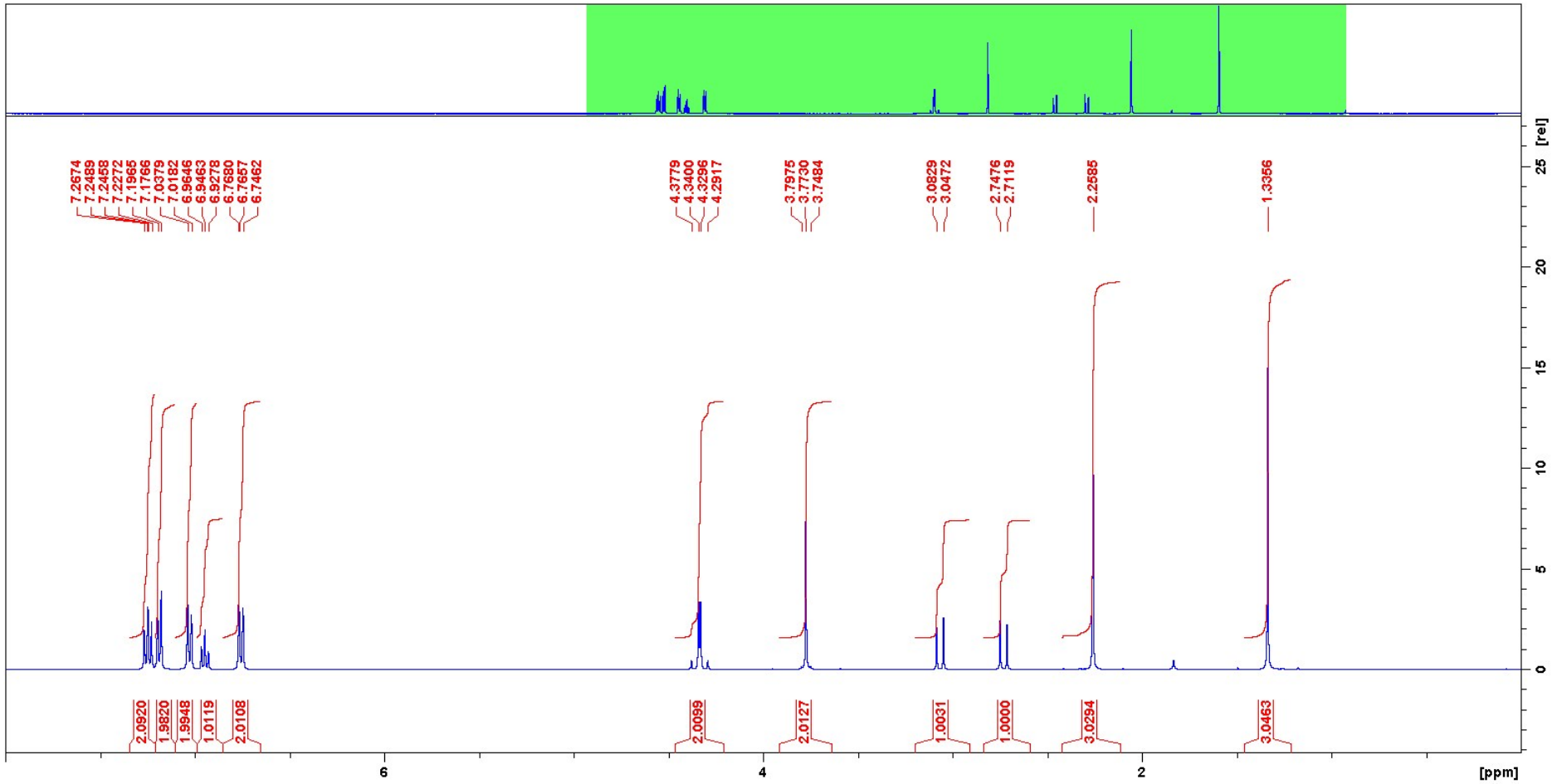
Compound **16**: ^{1}H NMR



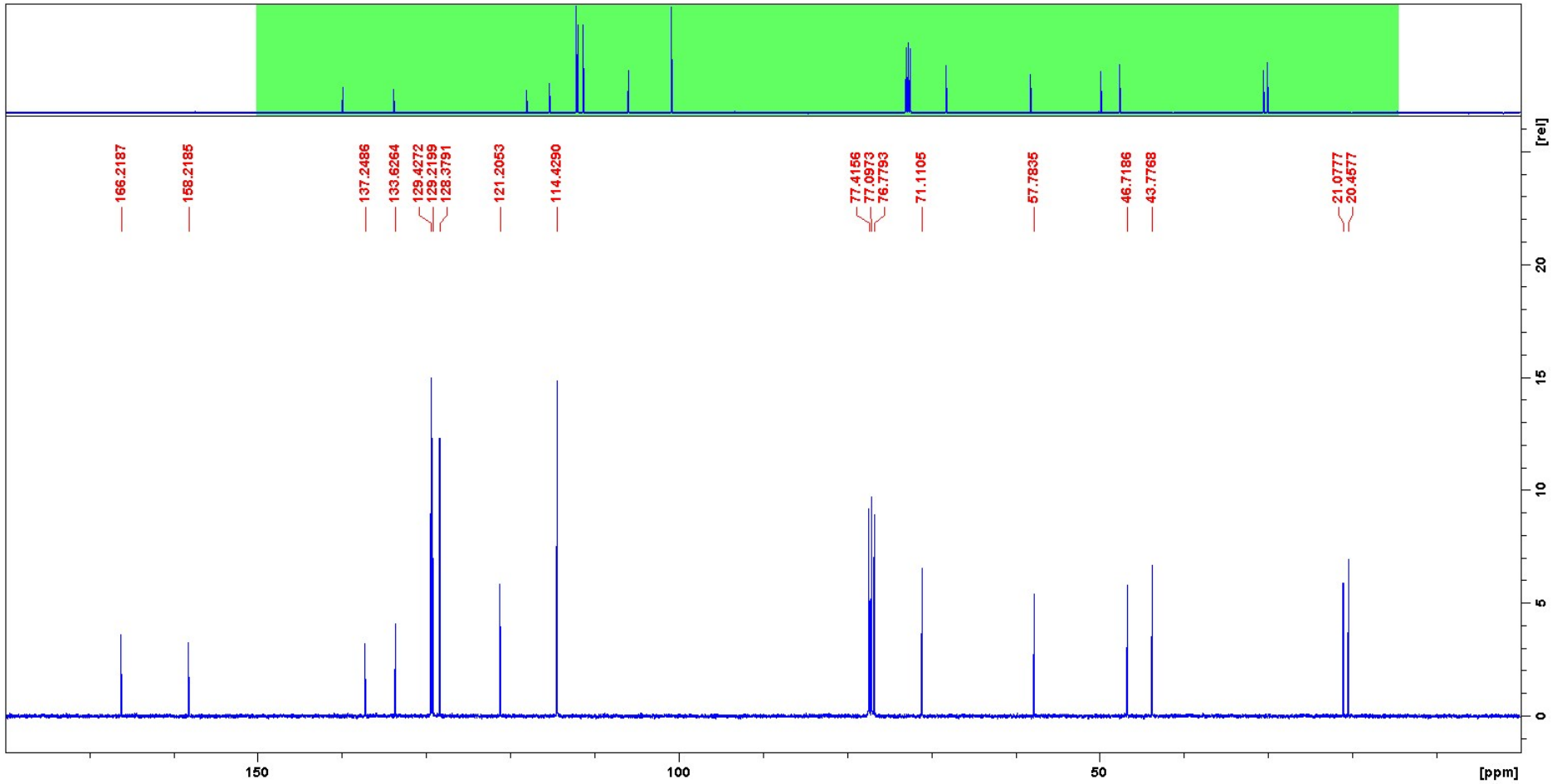
Compound **16**: ^{13}C NMR



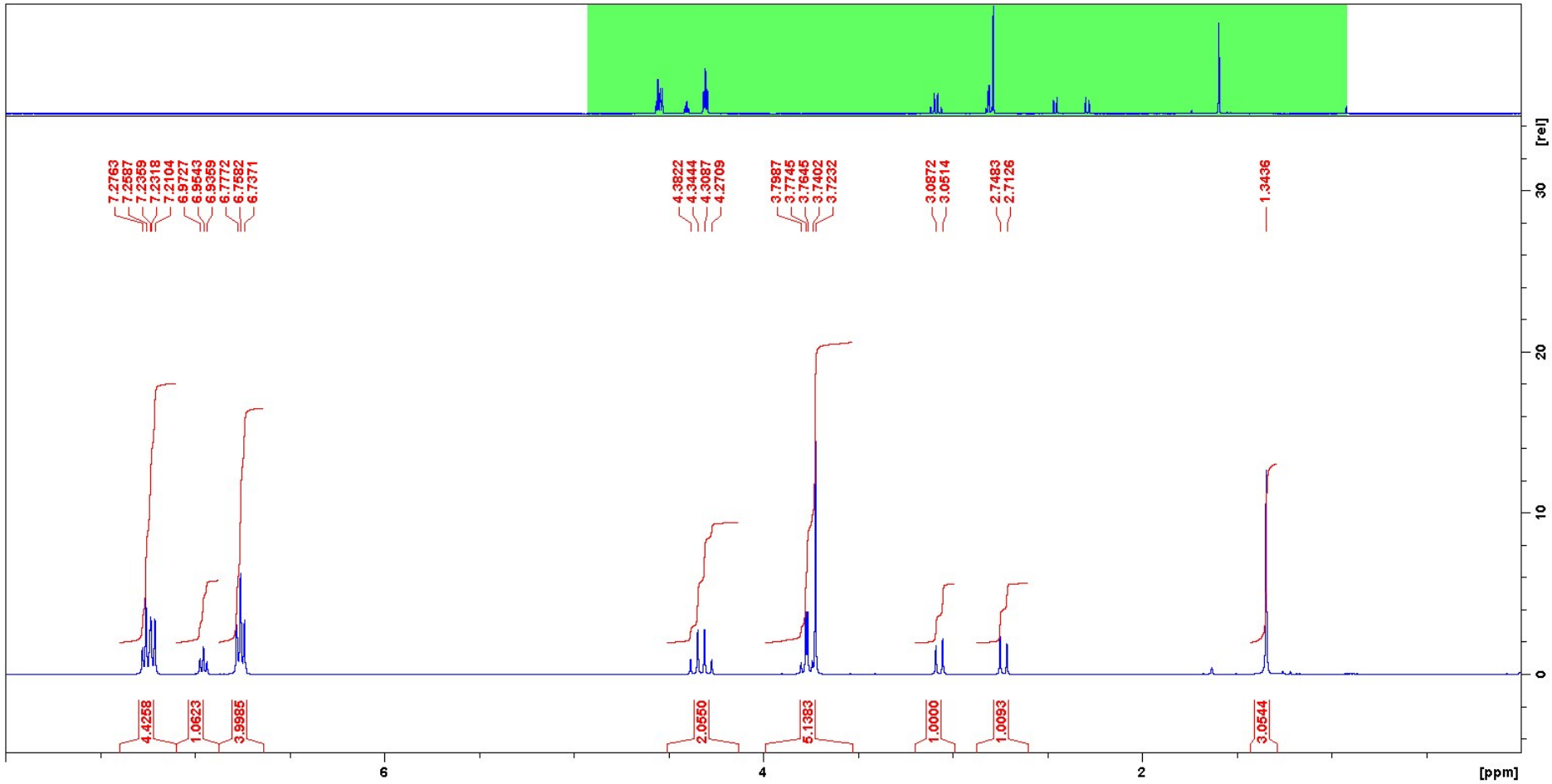
Compound **18a**: ^{1}H NMR



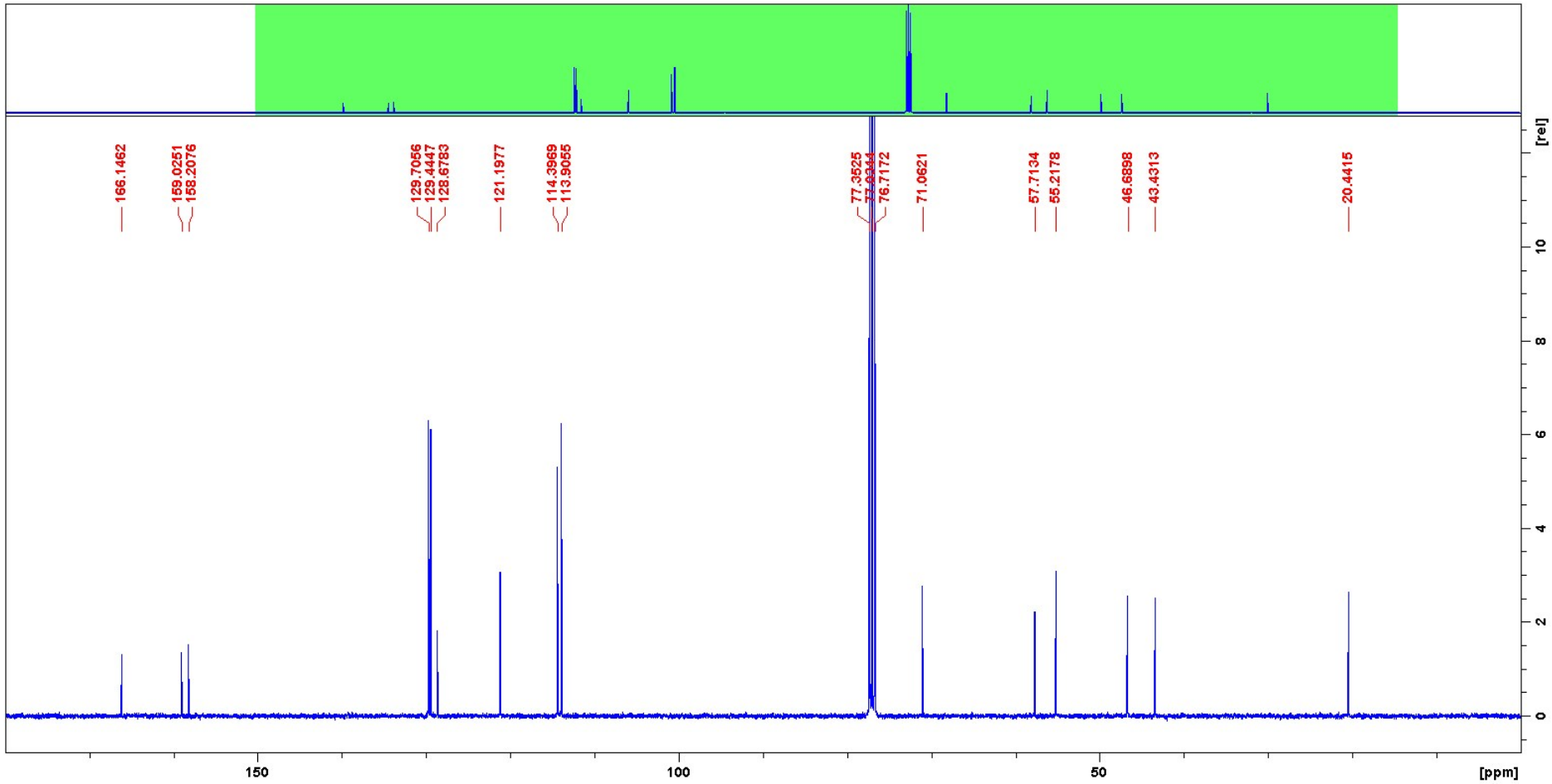
Compound **18a**: ^{13}C NMR



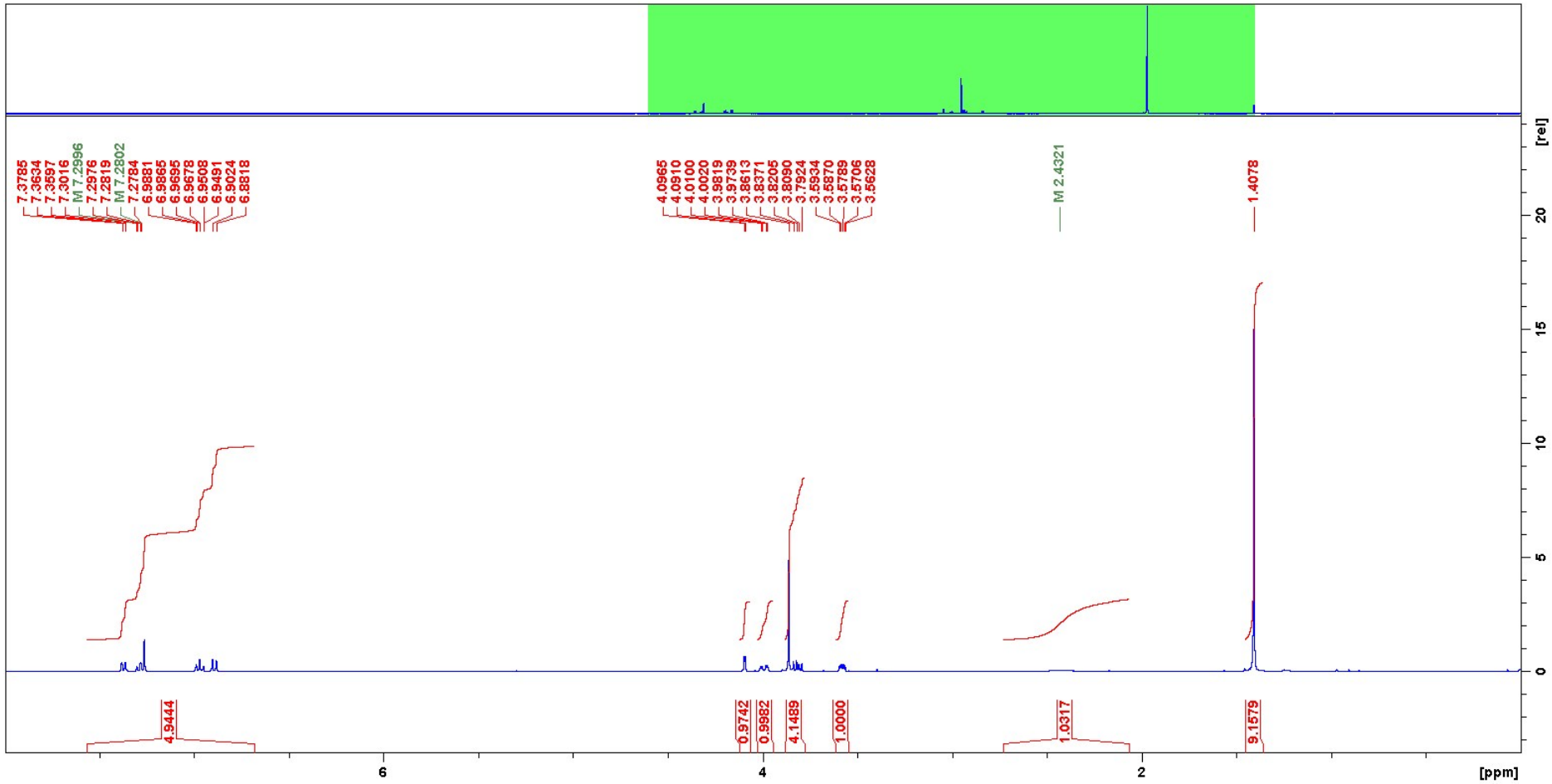
Compound **18b**: ^{1}H NMR



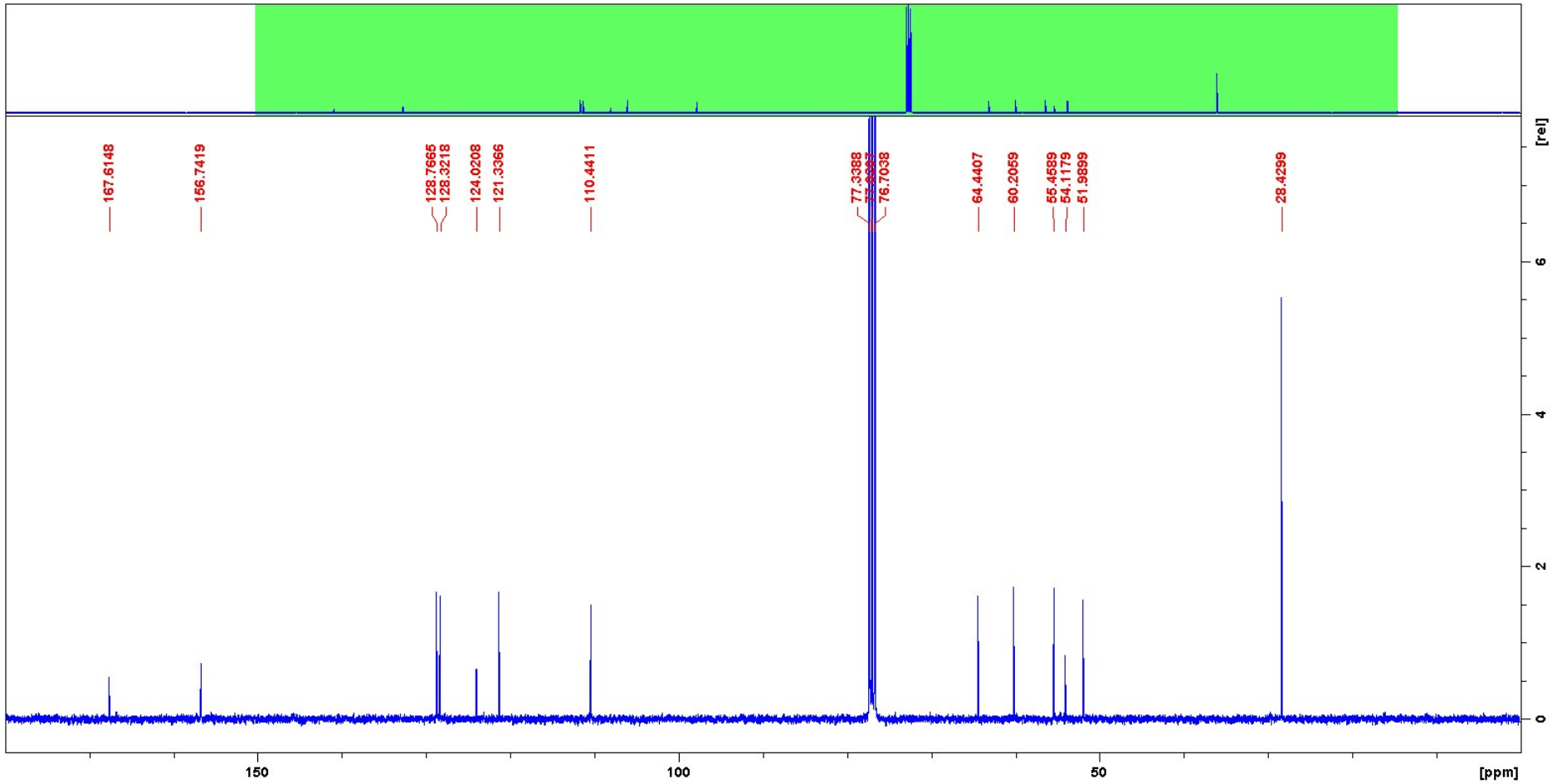
Compound **18b**: ^{13}C NMR



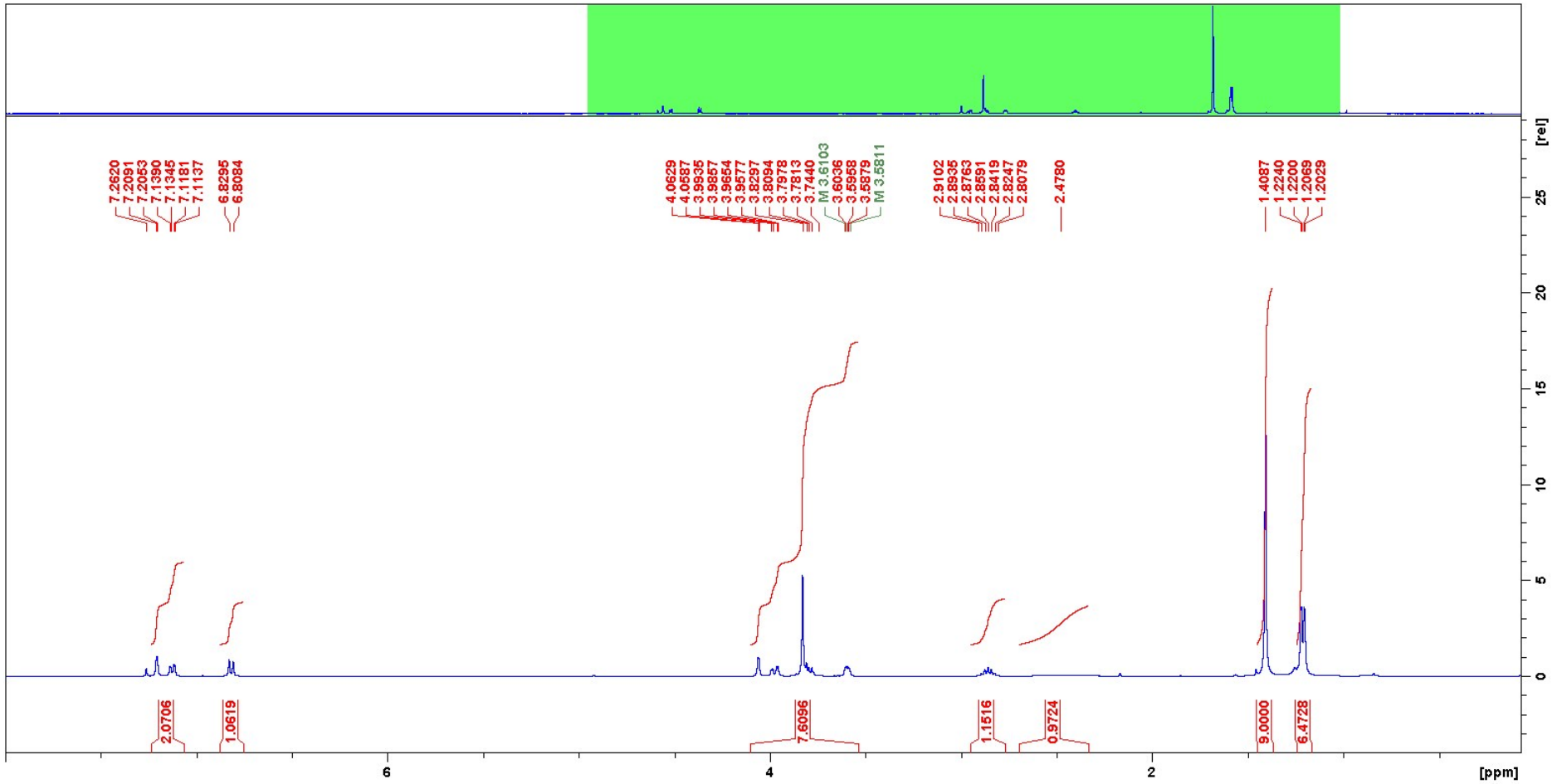
Compound **19a**: ^{1}H NMR



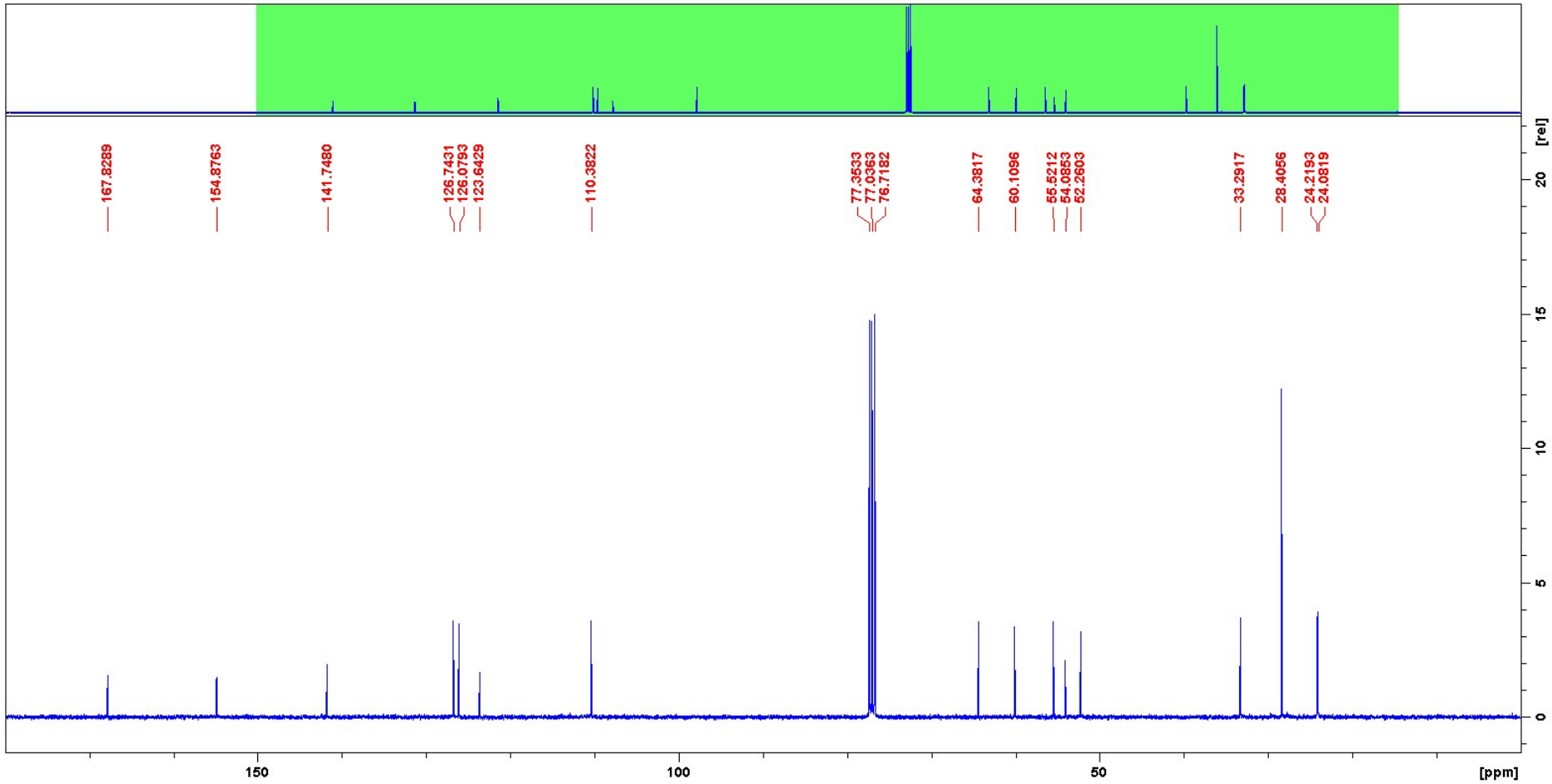
Compound **19a**: ^{13}C NMR



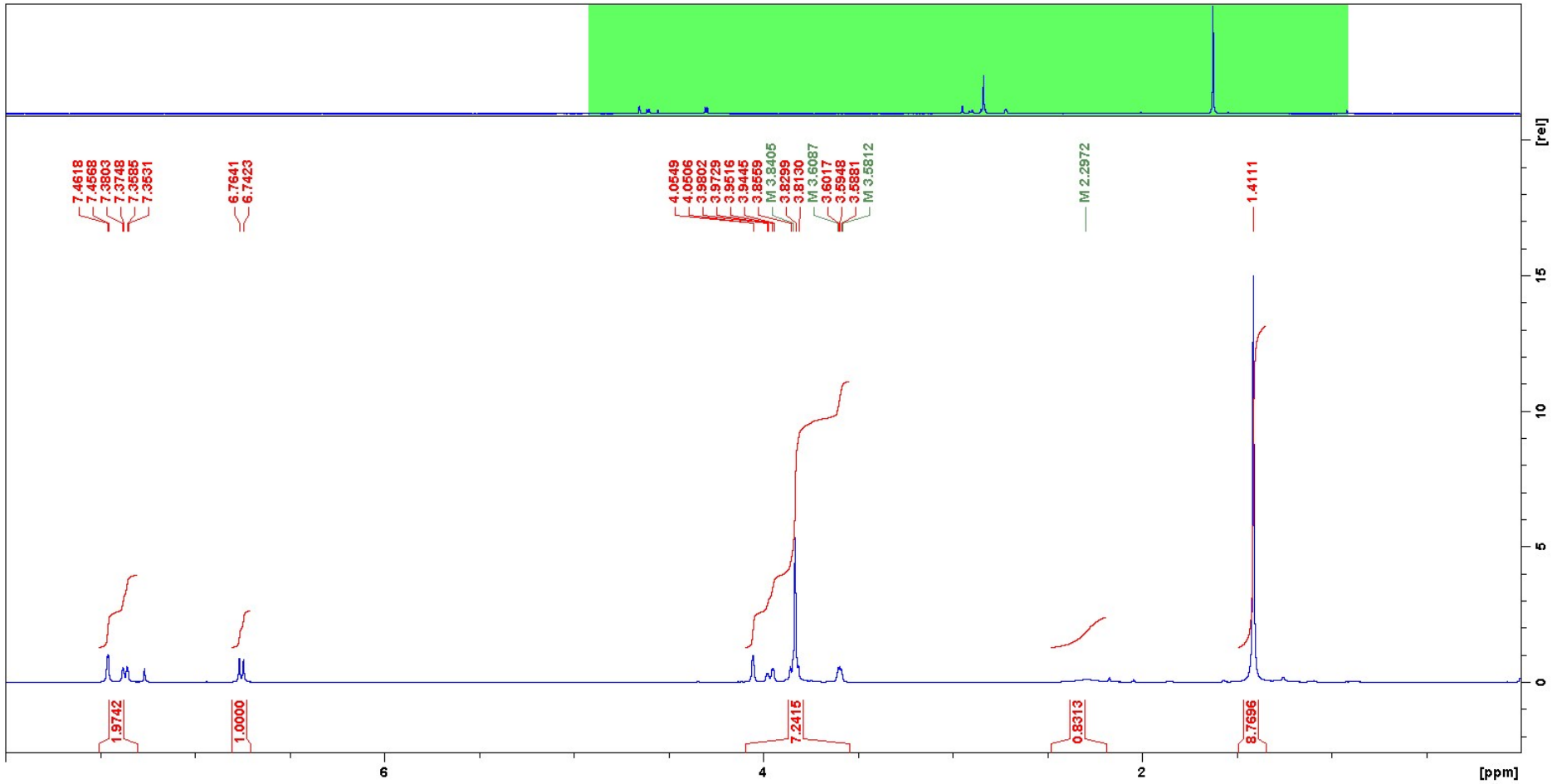
Compound **19b**: ^{1}H NMR



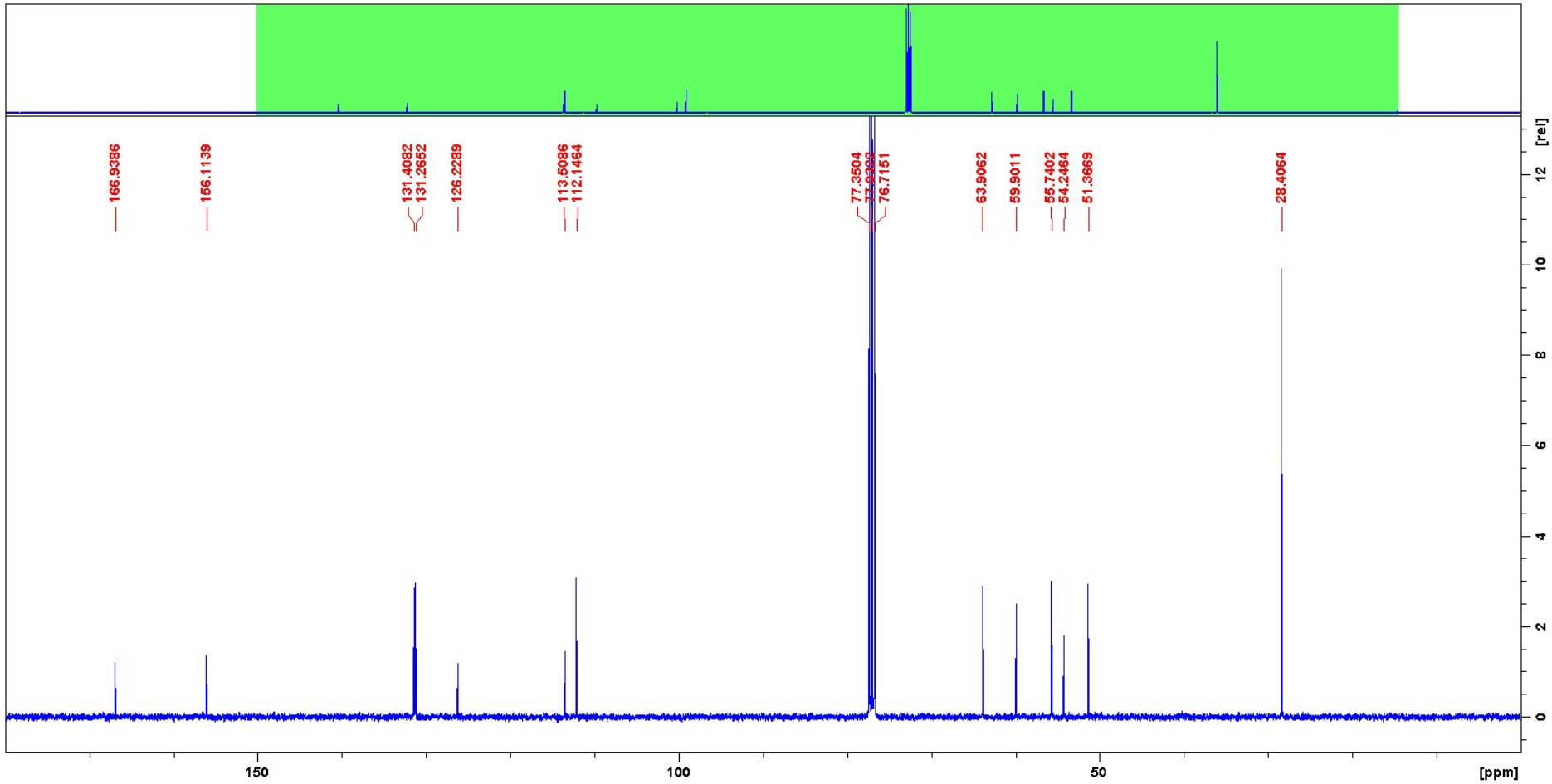
Compound **19b**: ^{13}C NMR



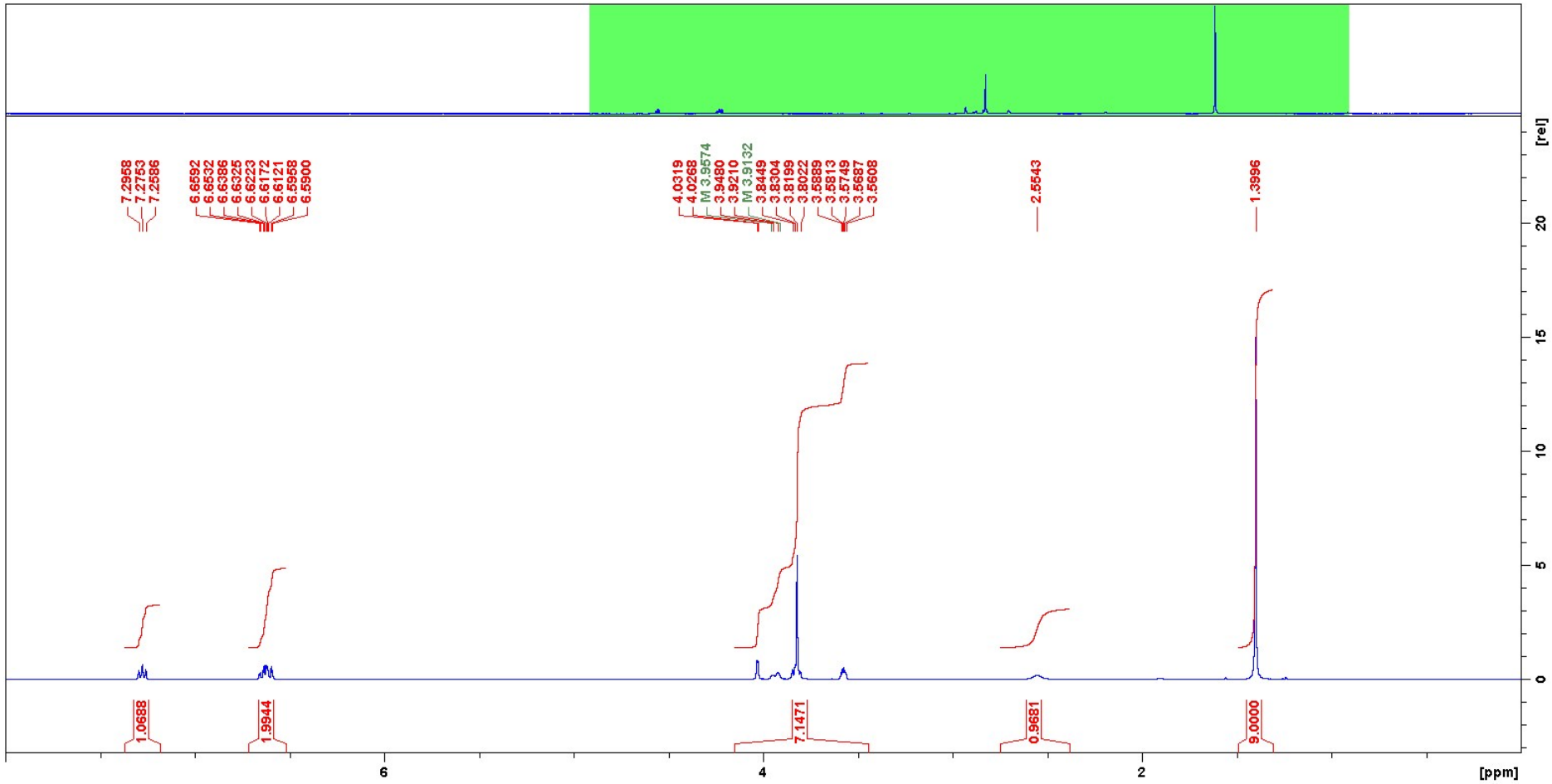
Compound **19c**: ^{1}H NMR



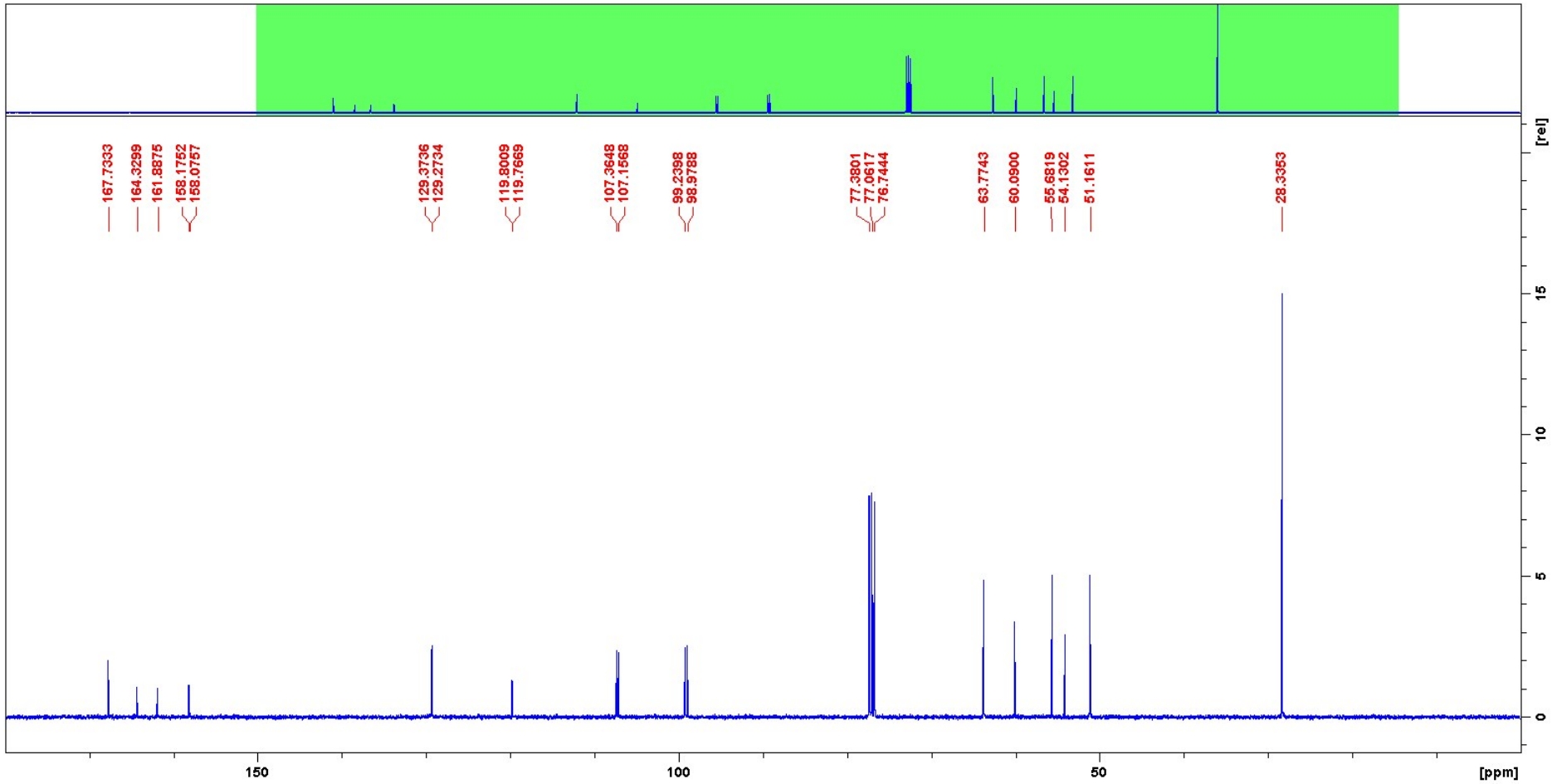
Compound **19c**: ^{13}C NMR



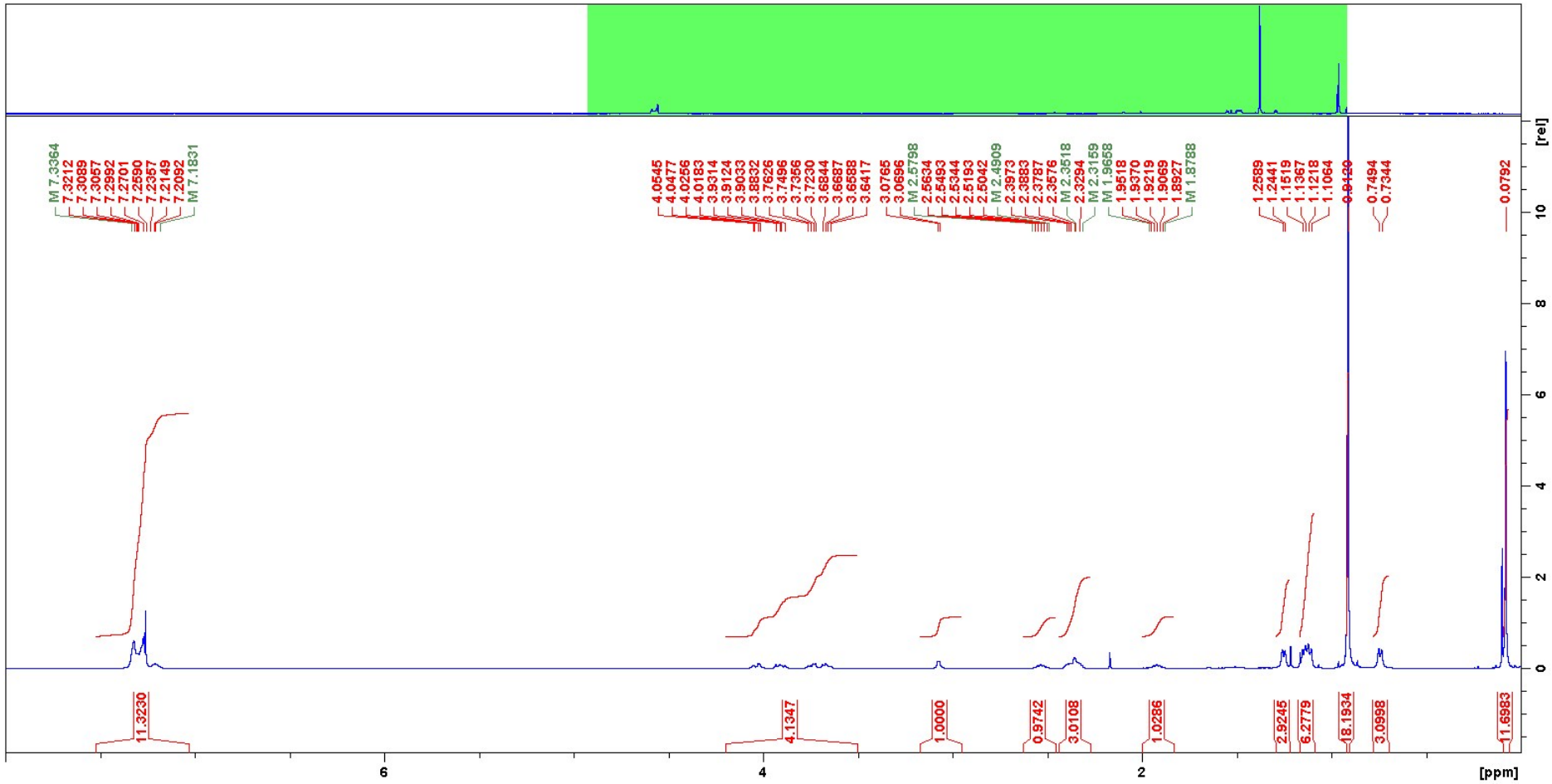
Compound **19d**: ^{1}H NMR



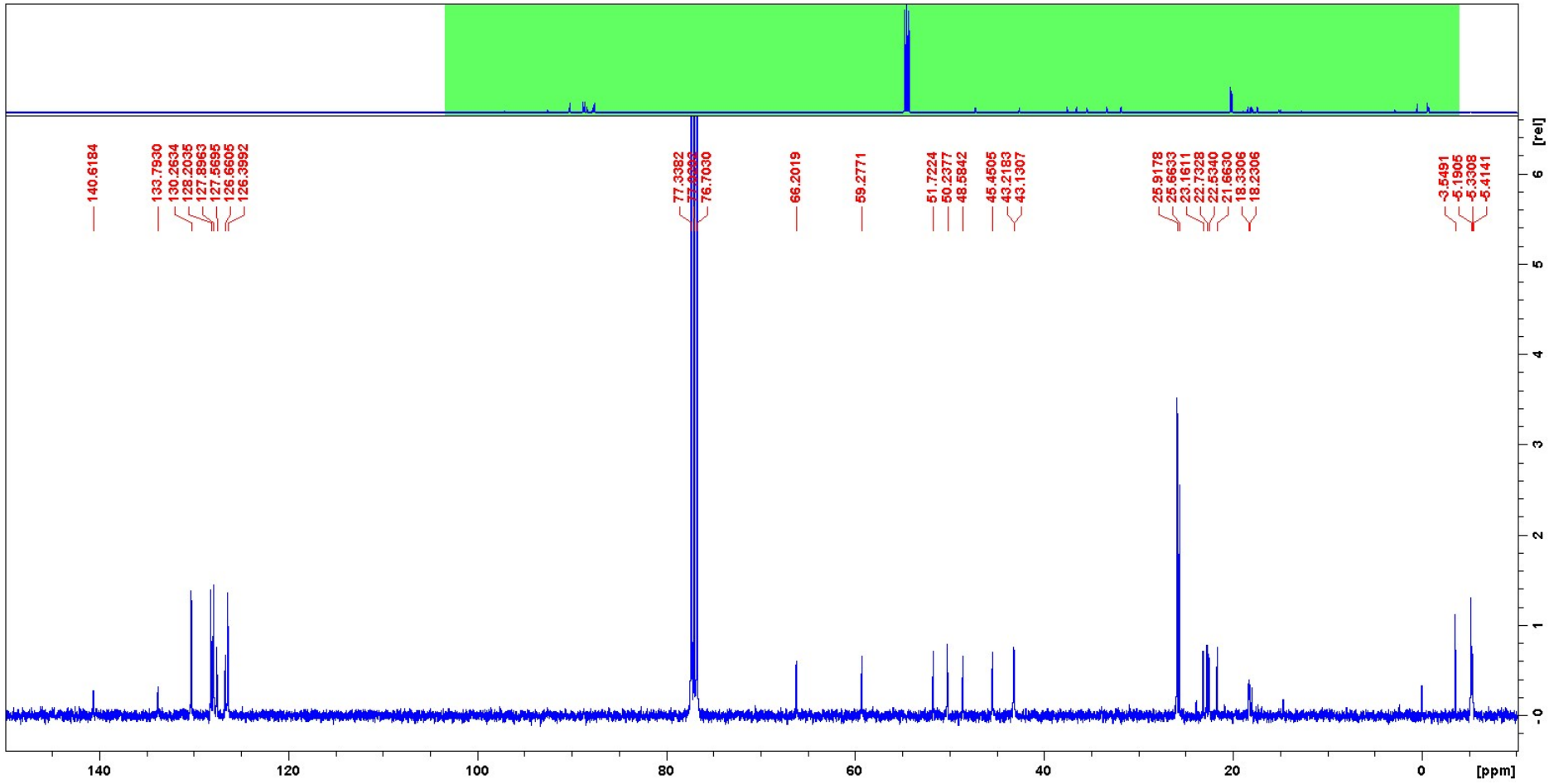
Compound **19d**: ^{13}C NMR



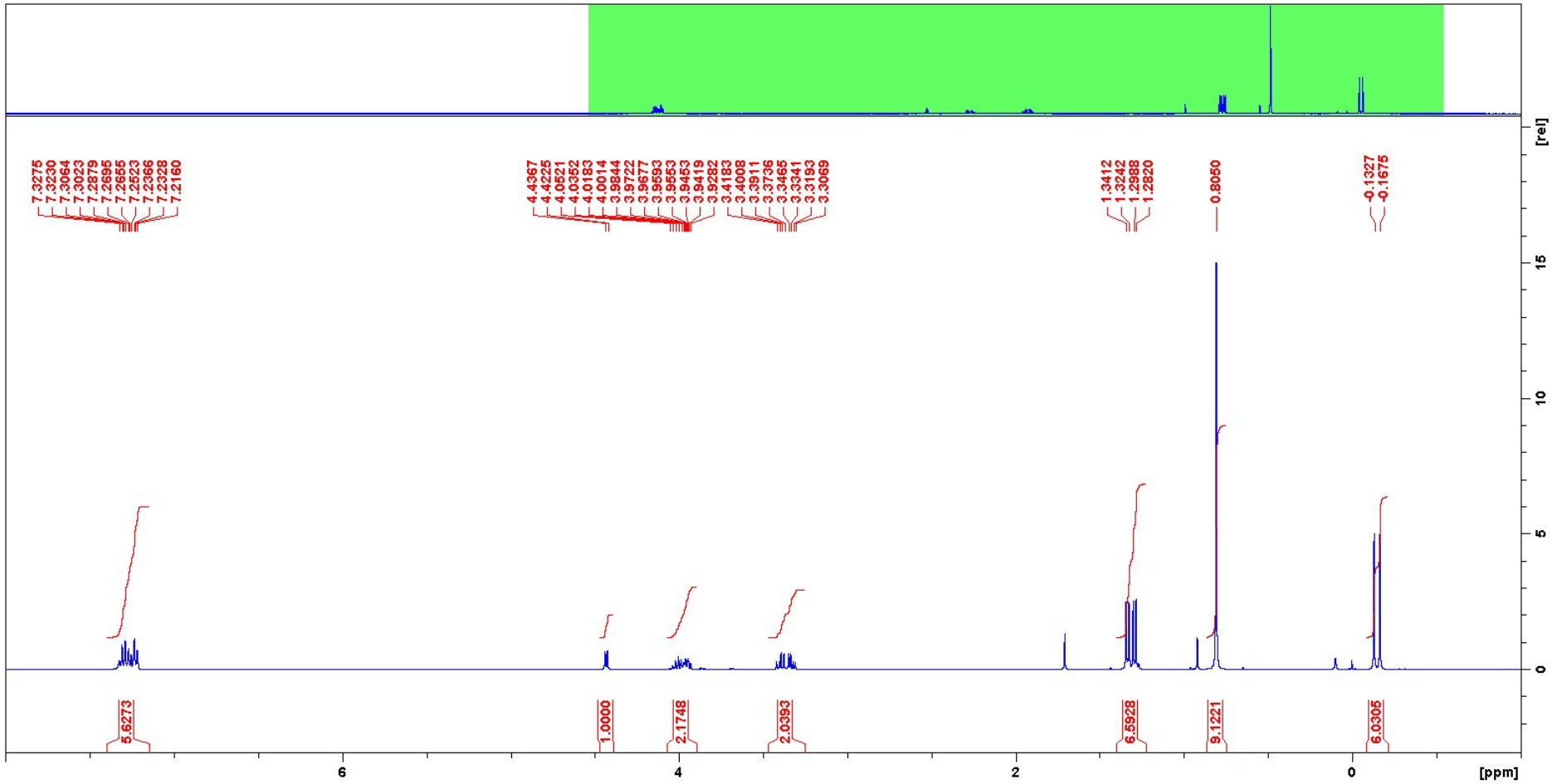
Compound **20**: ^{1}H NMR



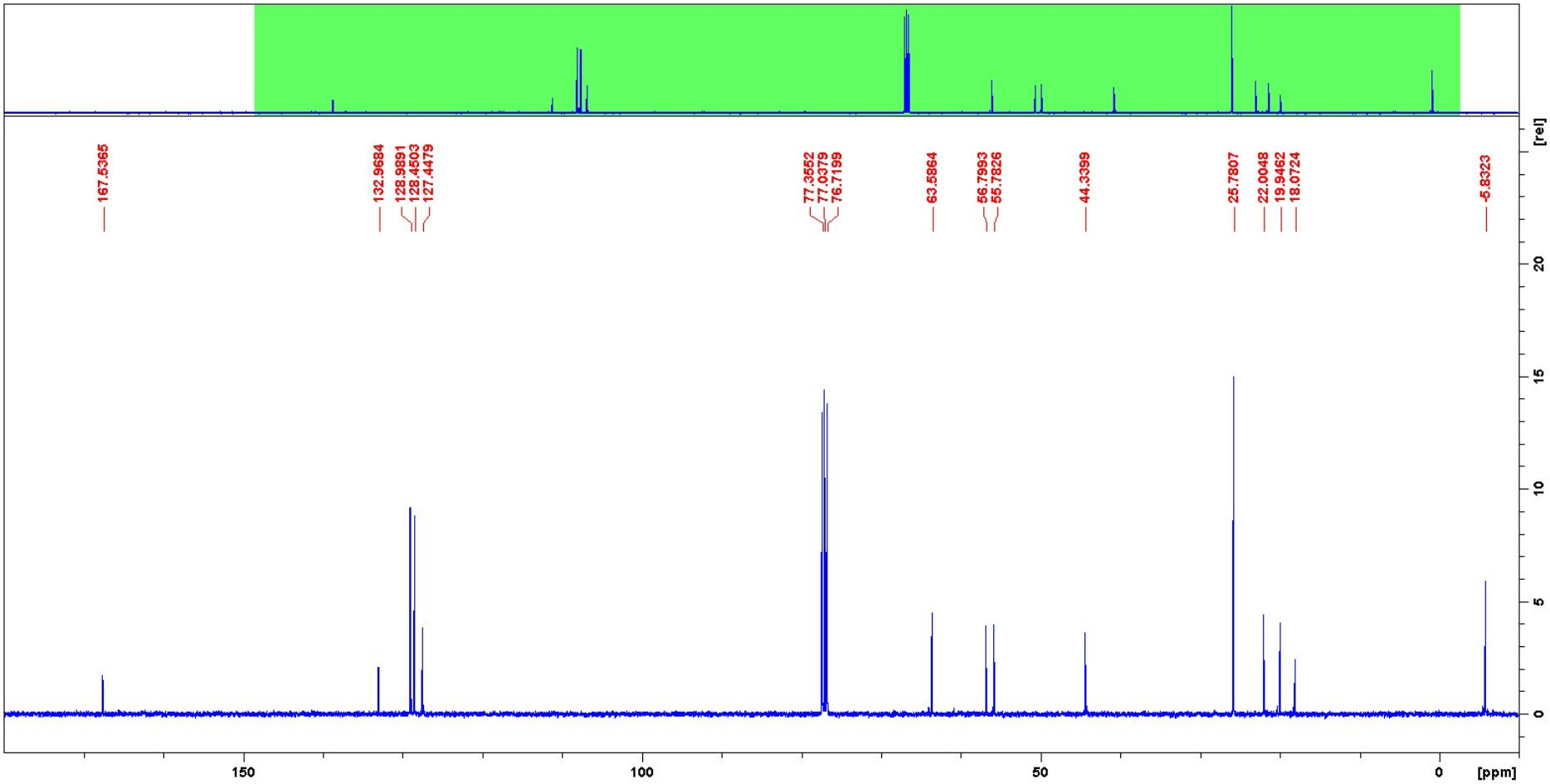
Compound **20**: ^{13}C NMR



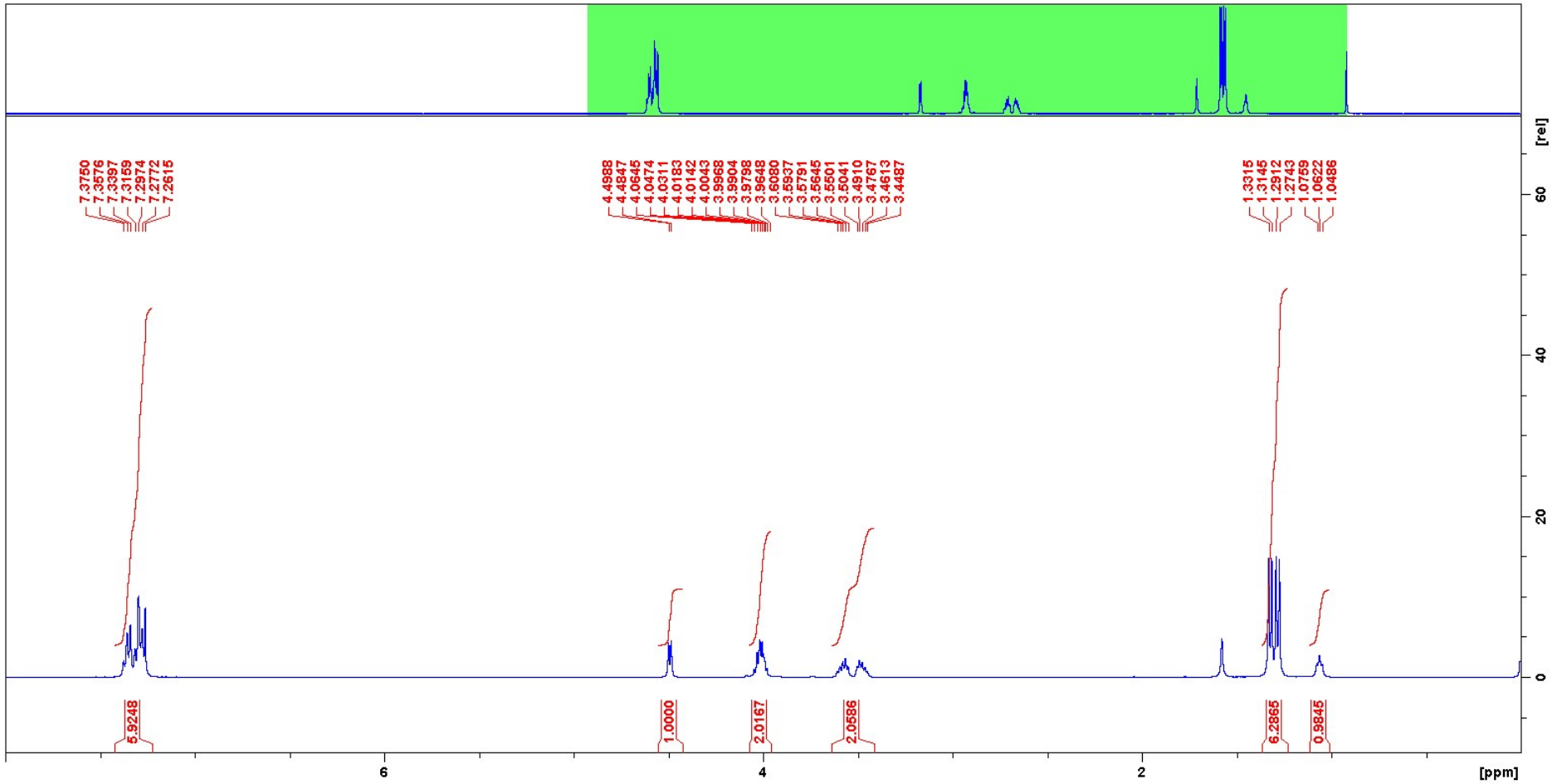
Compound **21**: ^{1}H NMR



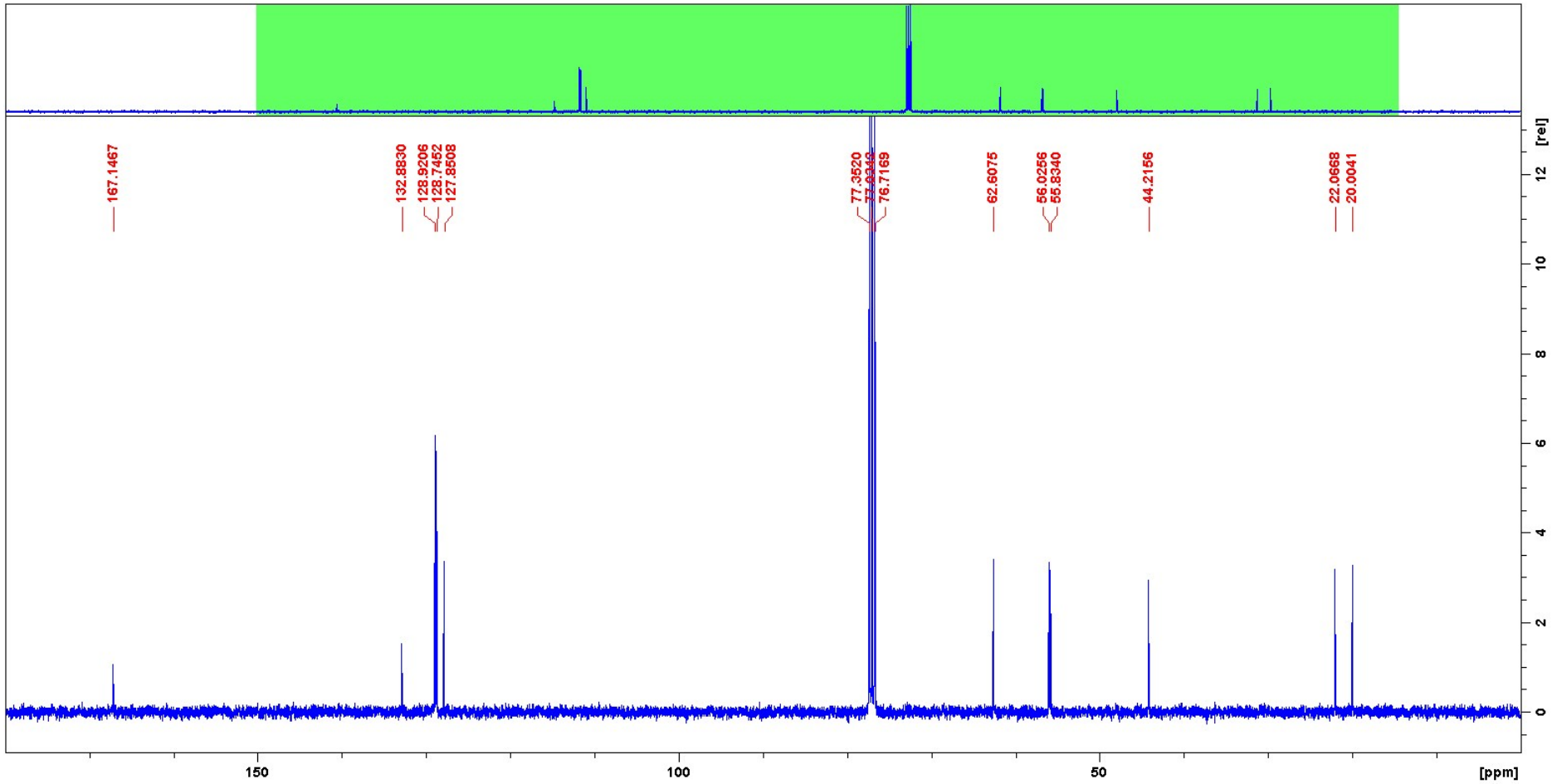
Compound **21**: ^{13}C NMR



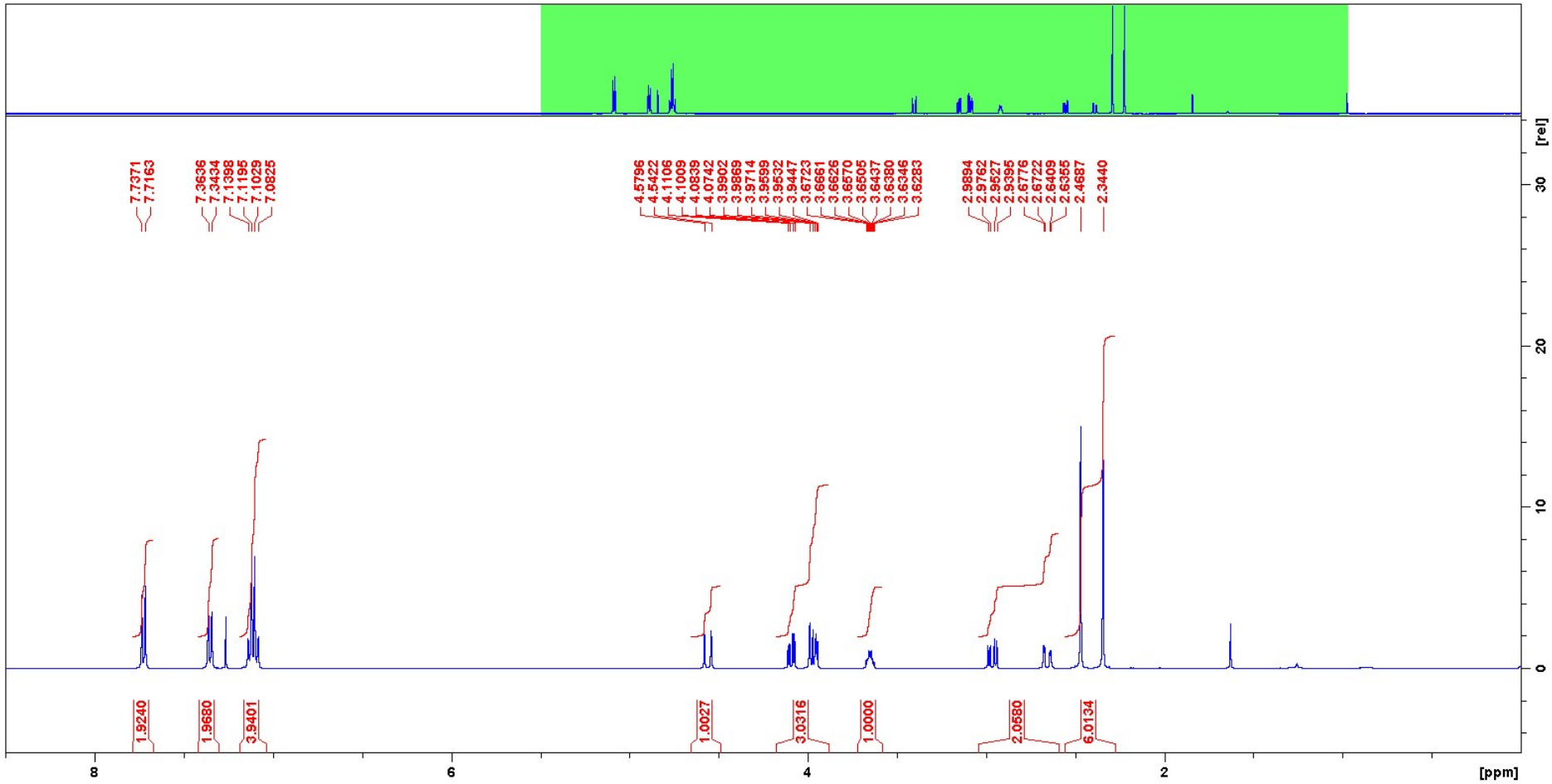
Compound **22**: ^{1}H NMR



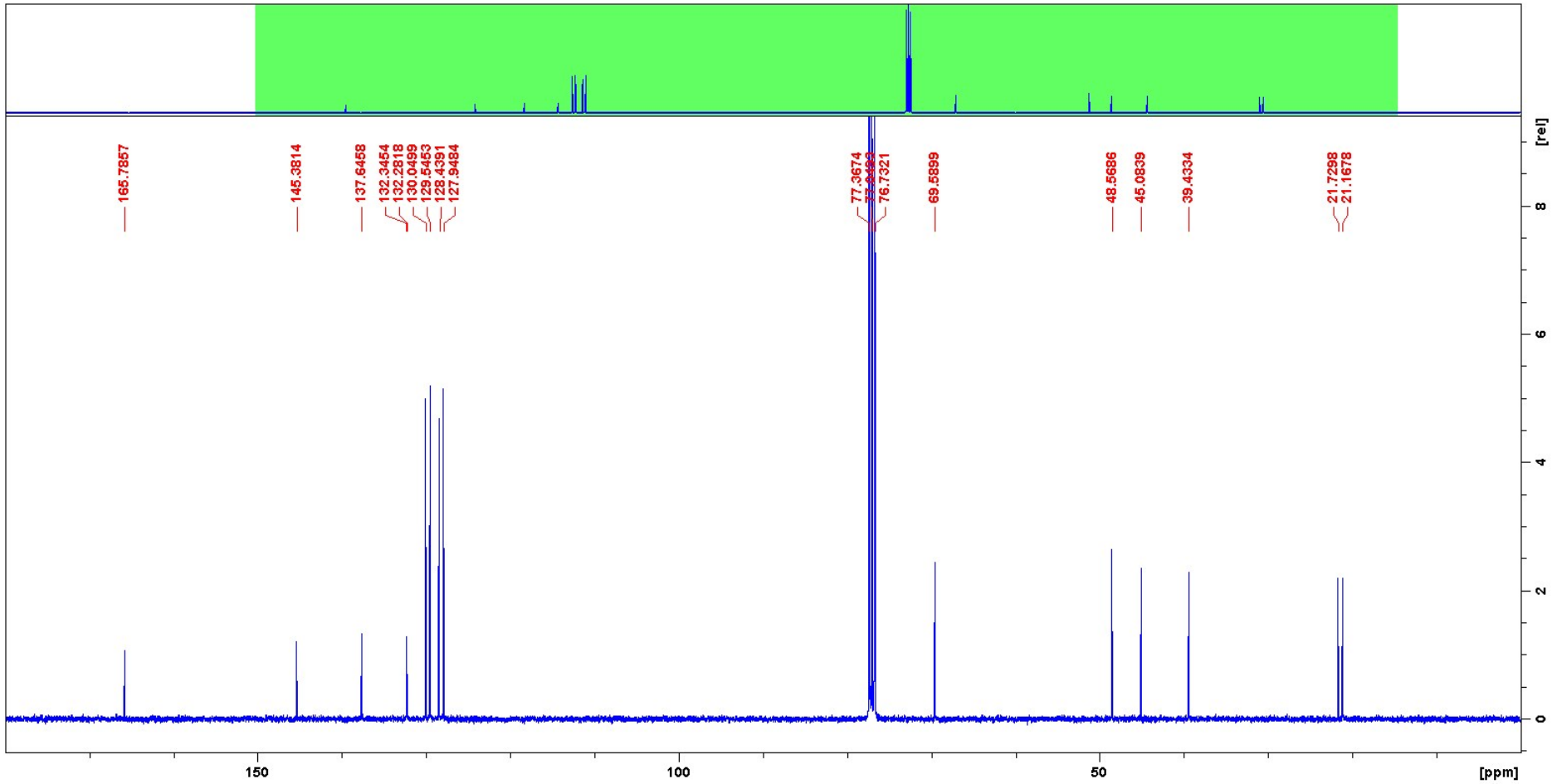
Compound **22**: ^{13}C NMR



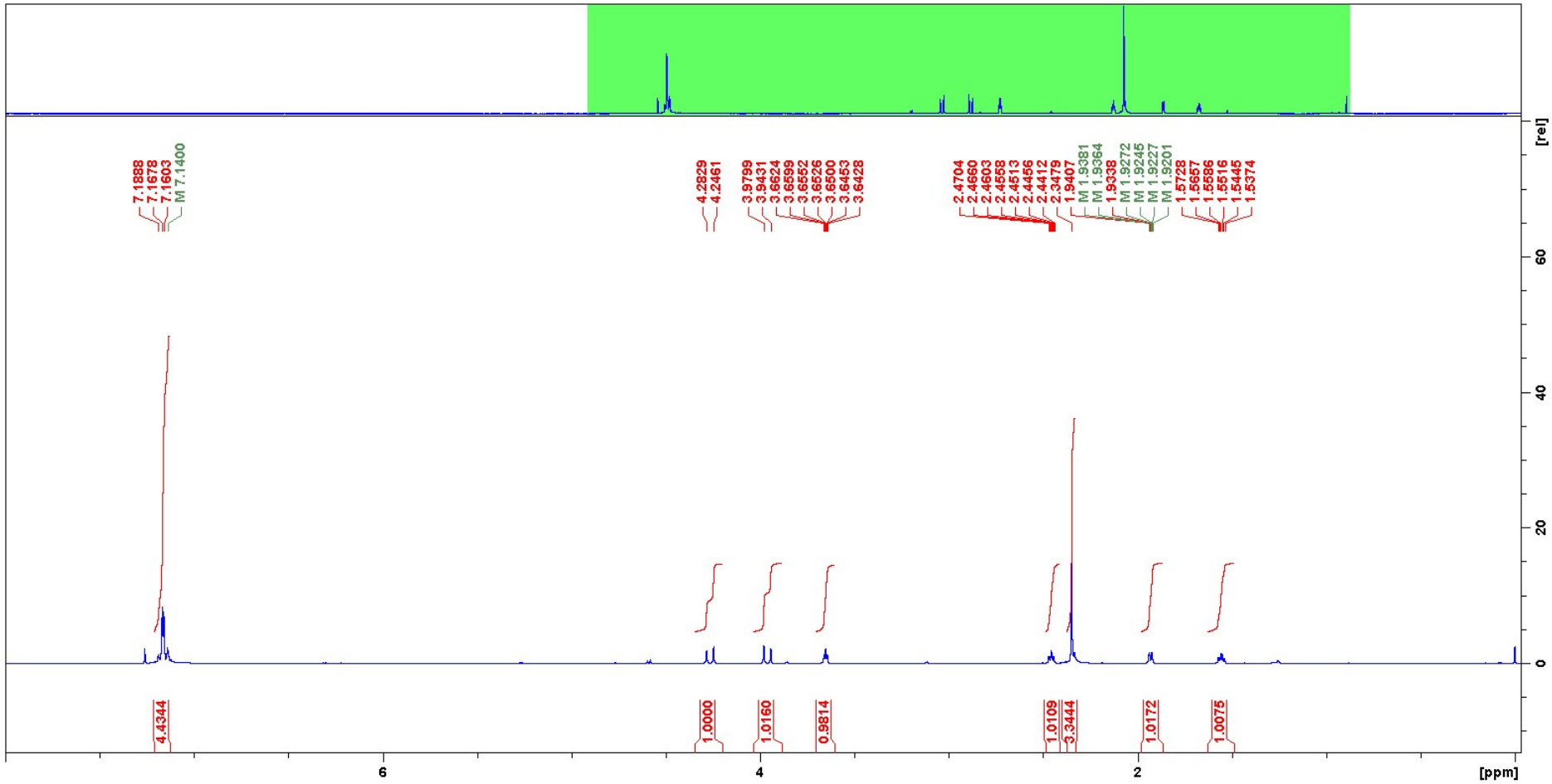
Compound **23**: ^{1}H NMR



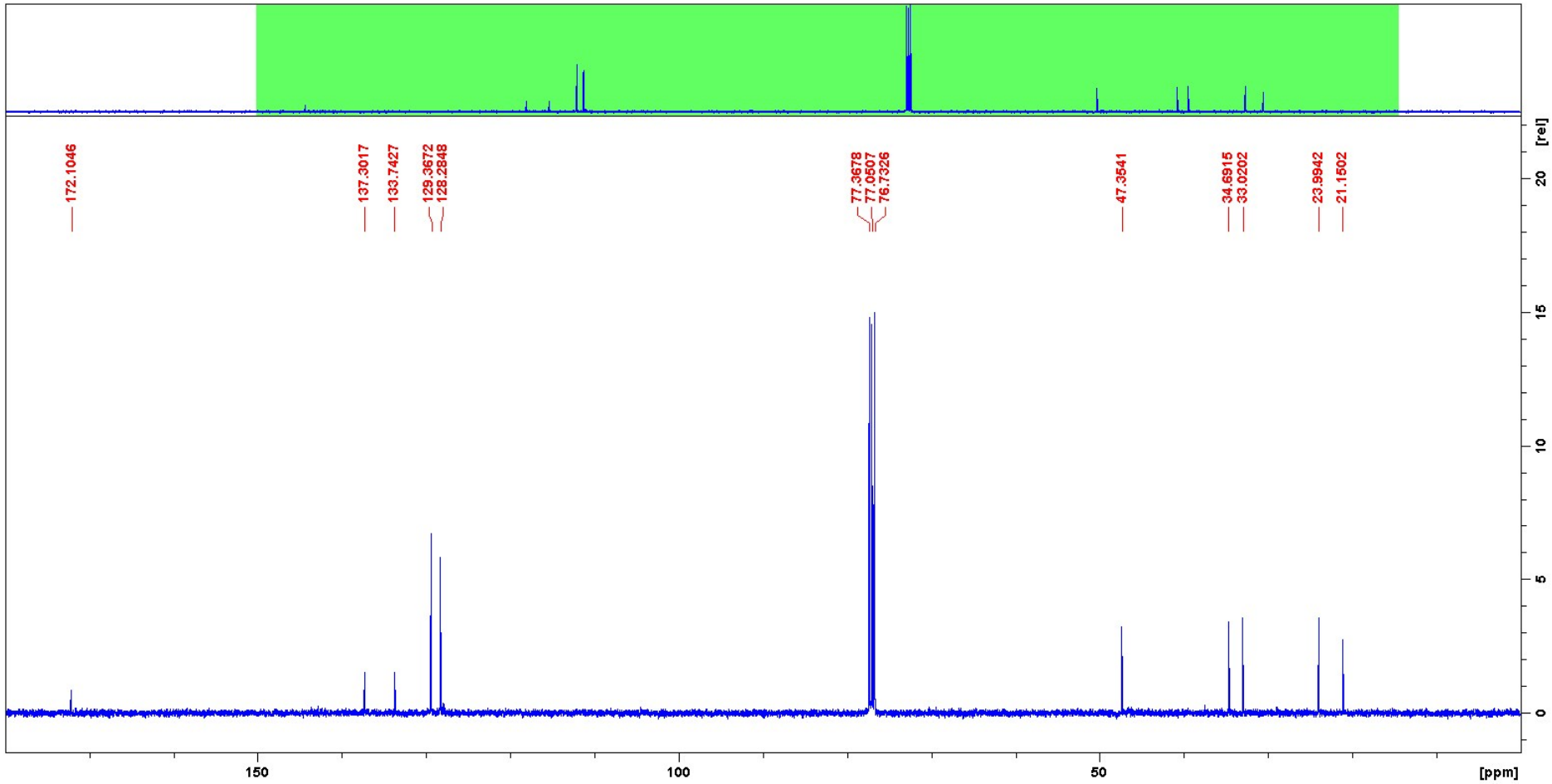
Compound **23**: ^{13}C NMR



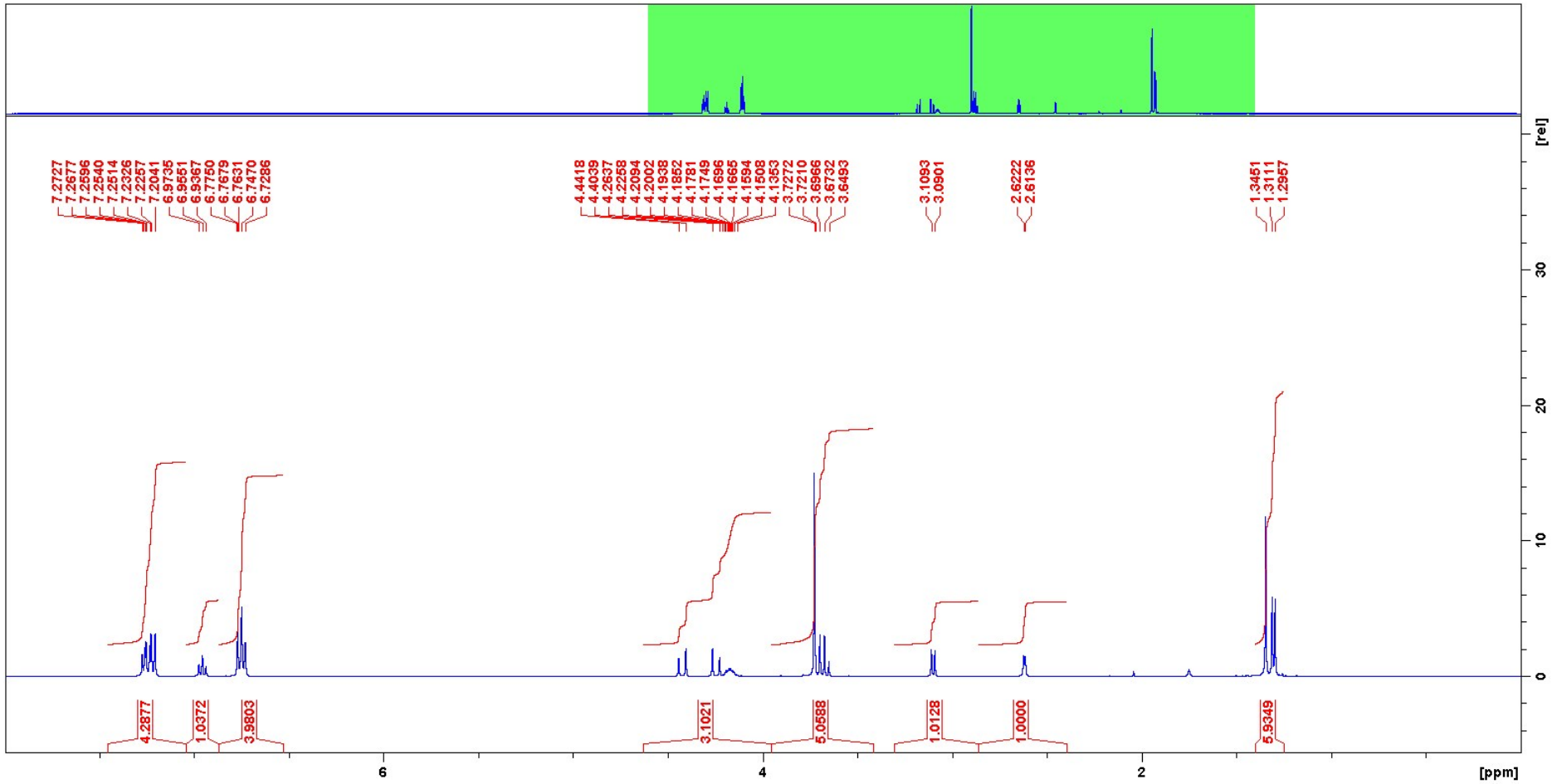
Compound **24**: ^{1}H NMR



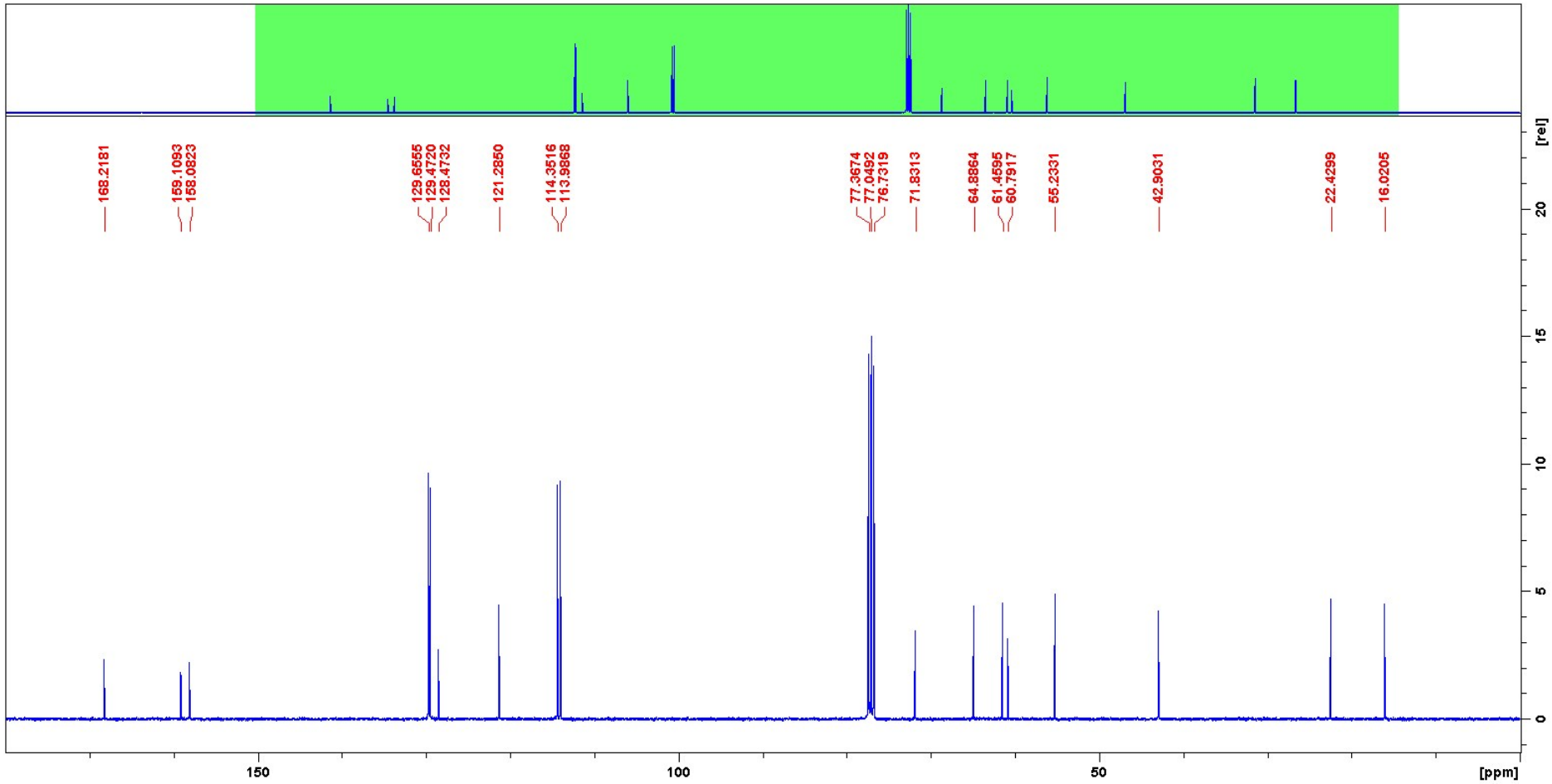
Compound **24**: ^{13}C NMR



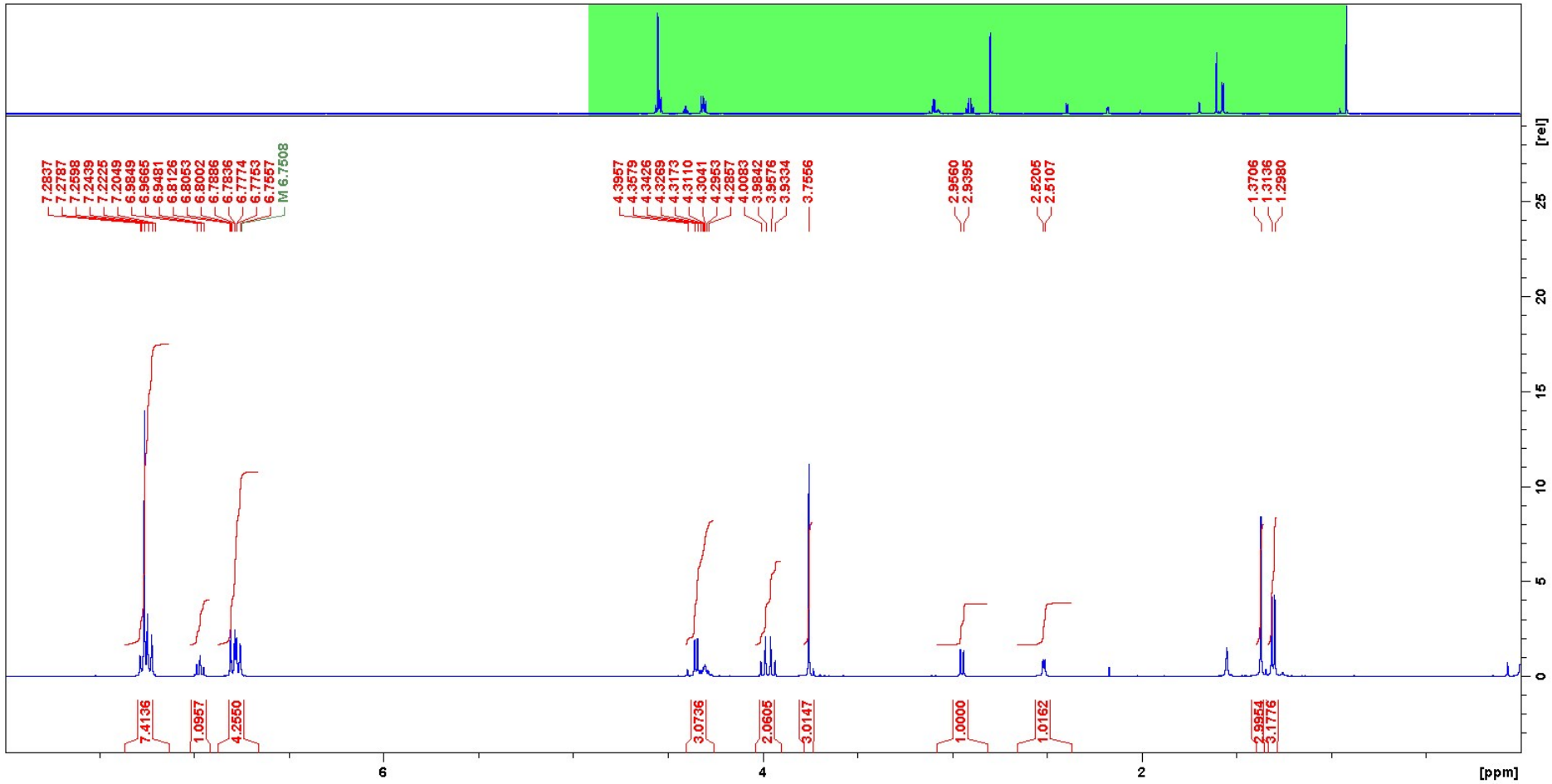
Compound **25_1**: ^{1}H NMR



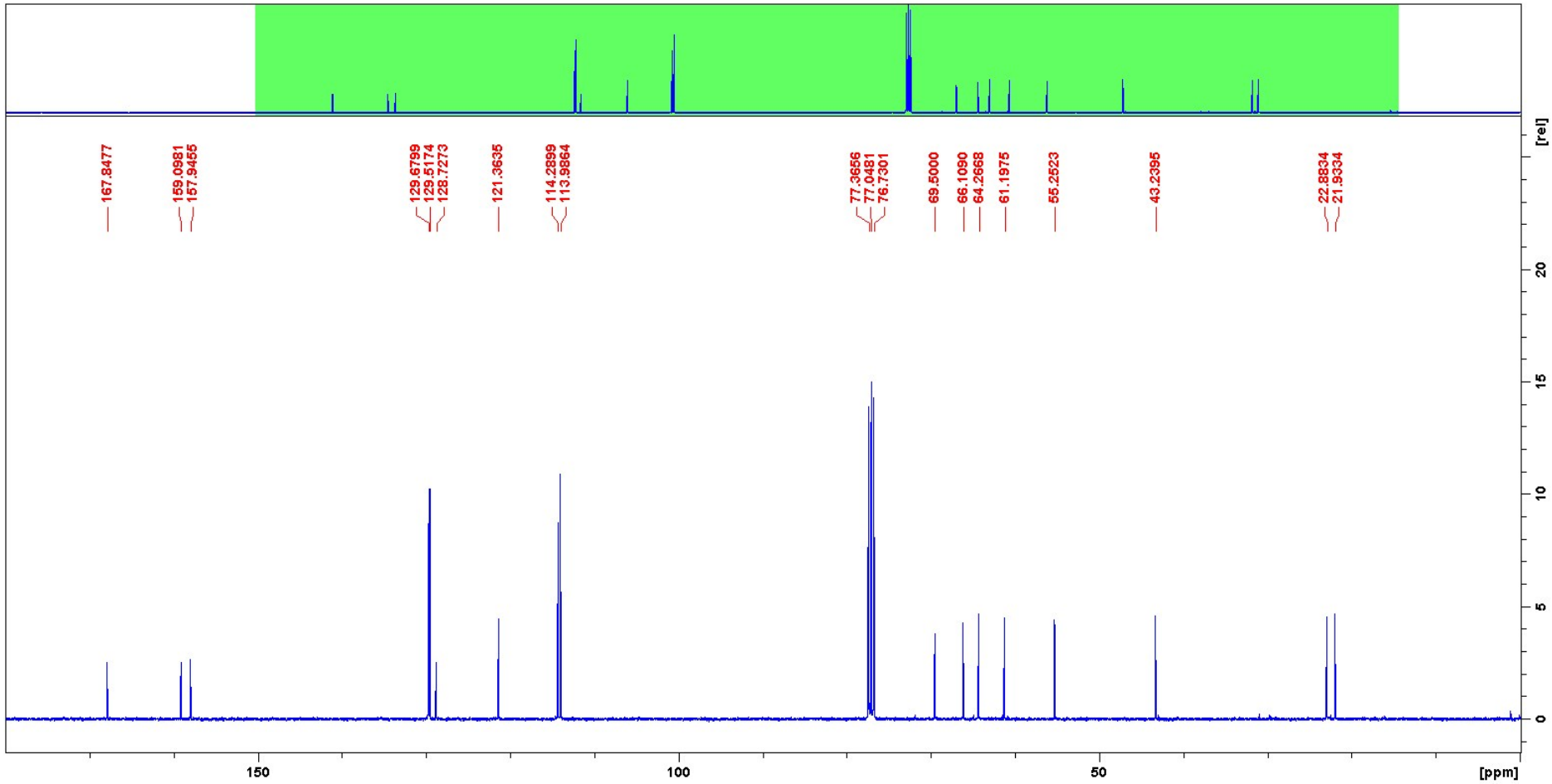
Compound **25_1**: ^{13}C NMR



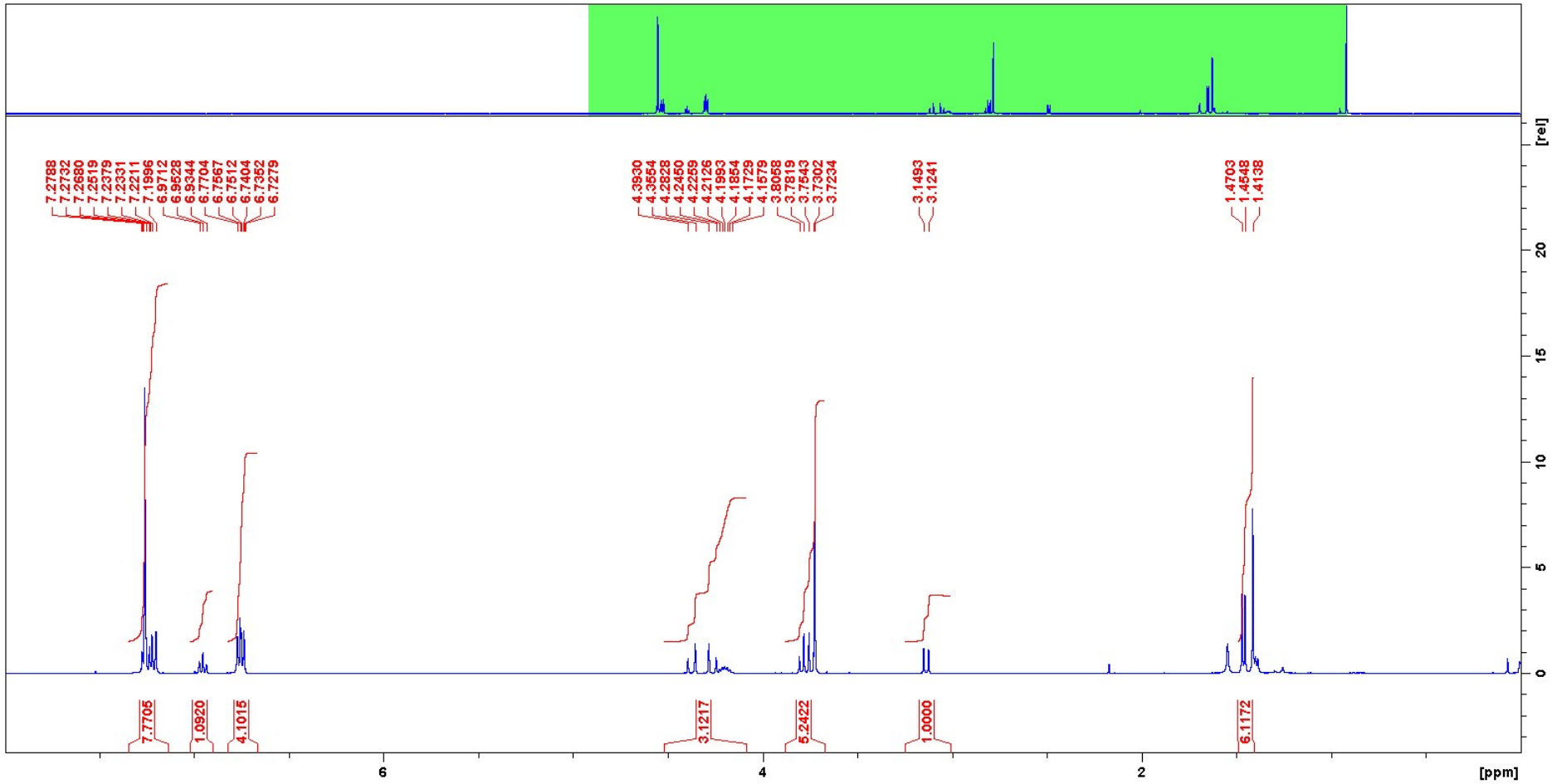
Compound **25_2**: ^{1}H NMR



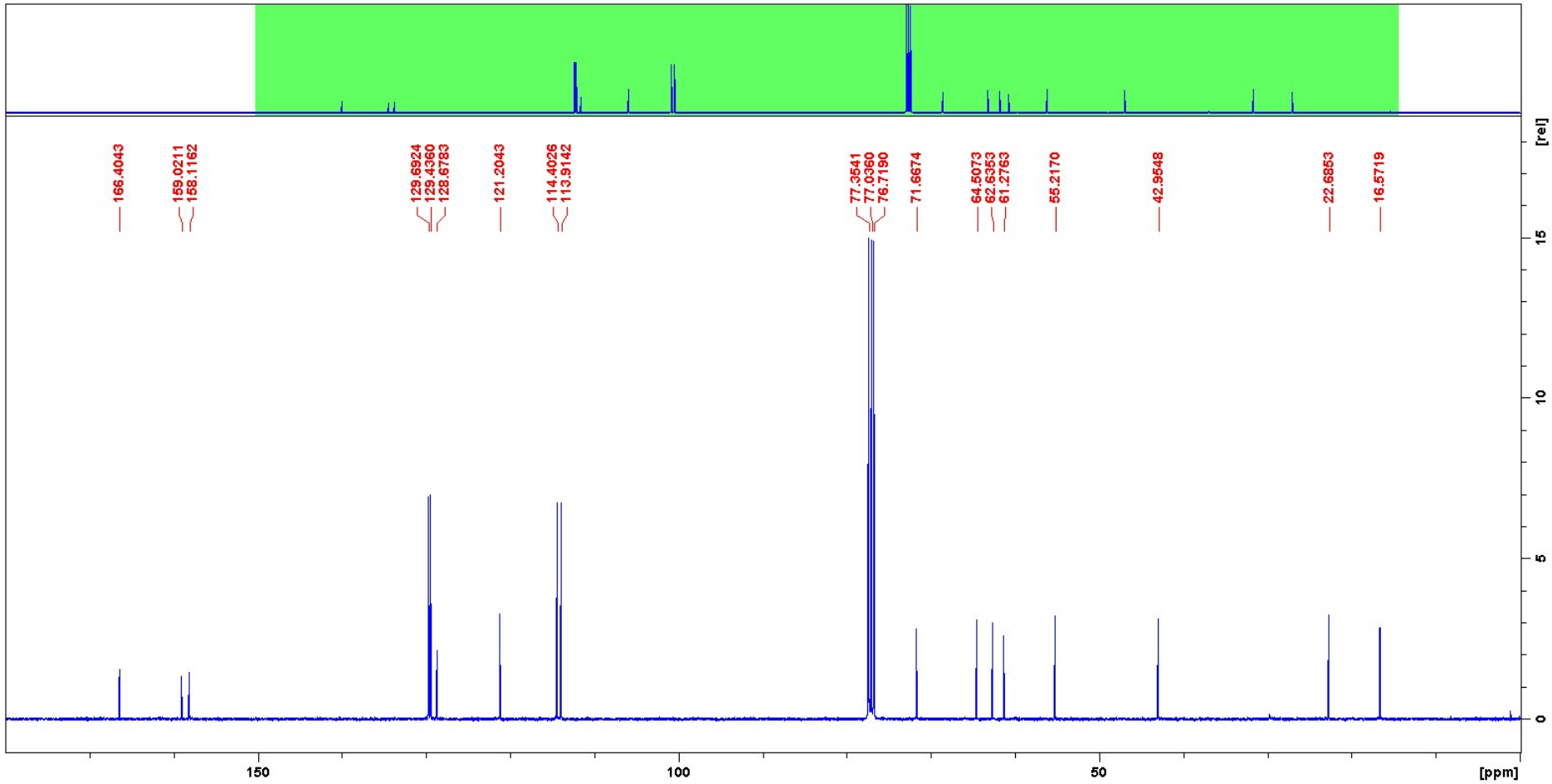
Compound **25_2**: ^{13}C NMR



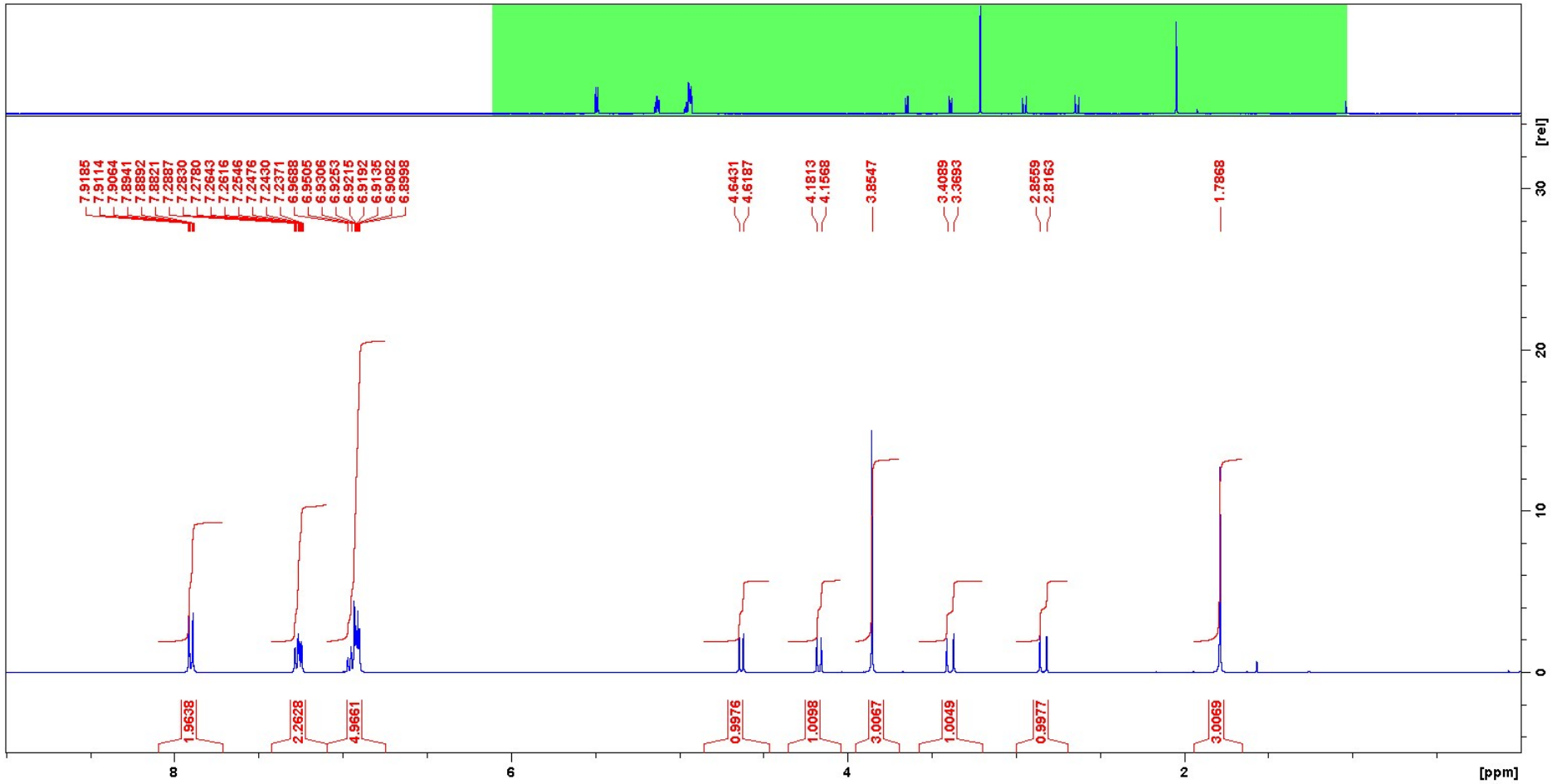
Compound **25_3**: ^{1}H NMR



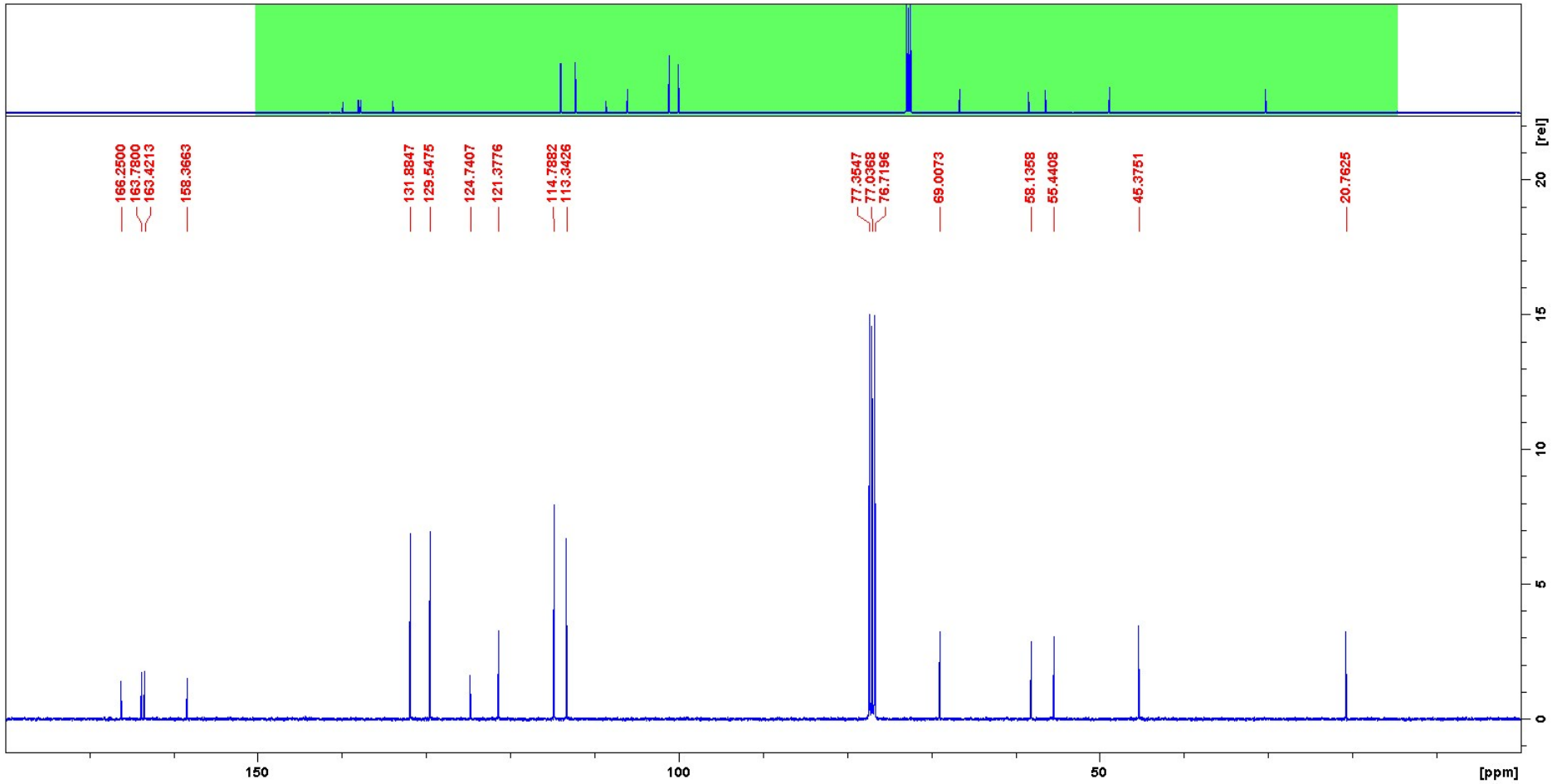
Compound **25_3**: ^{13}C NMR



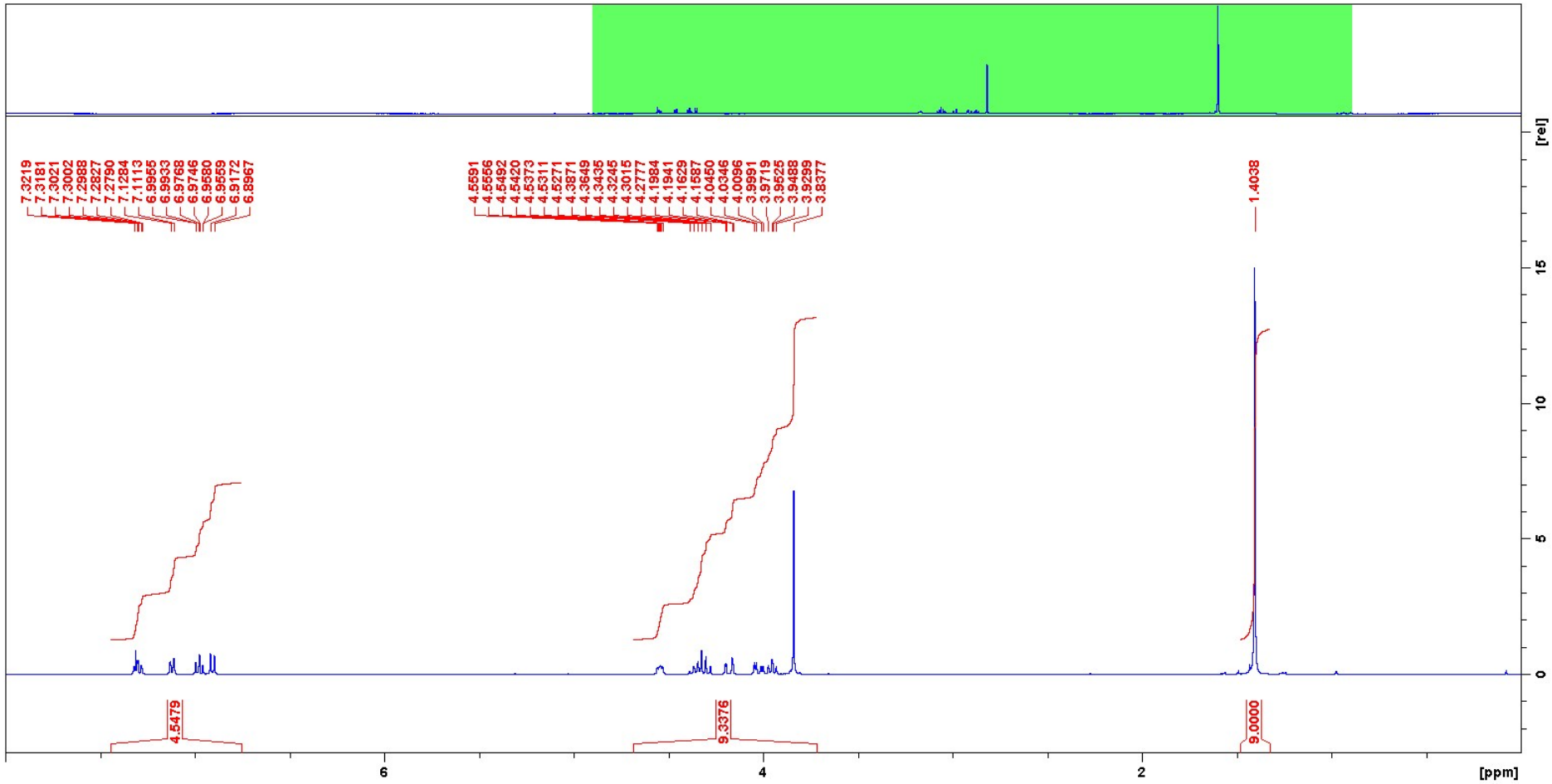
Compound **26**: ^{1}H NMR



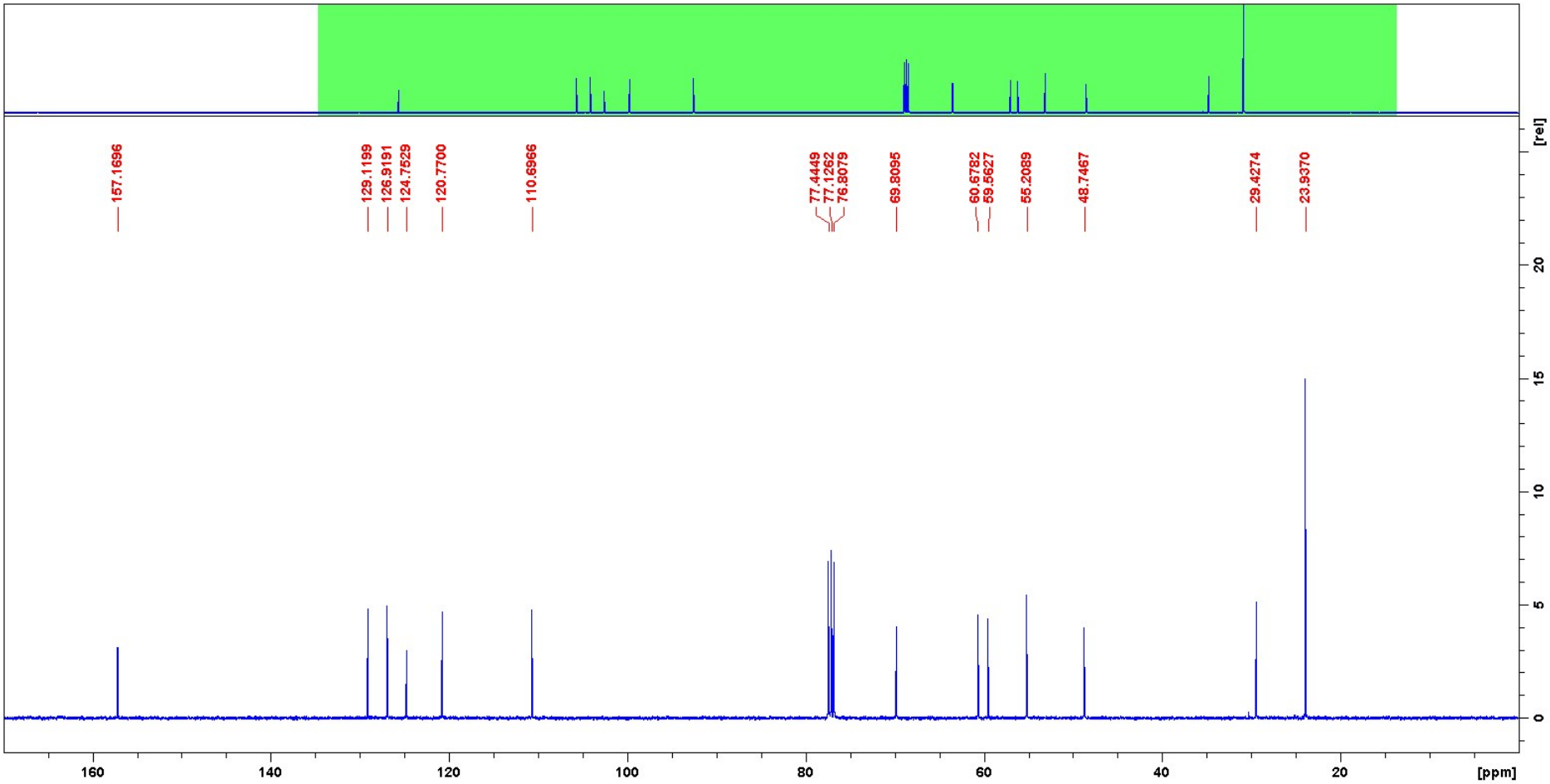
Compound **26**: ^{13}C NMR



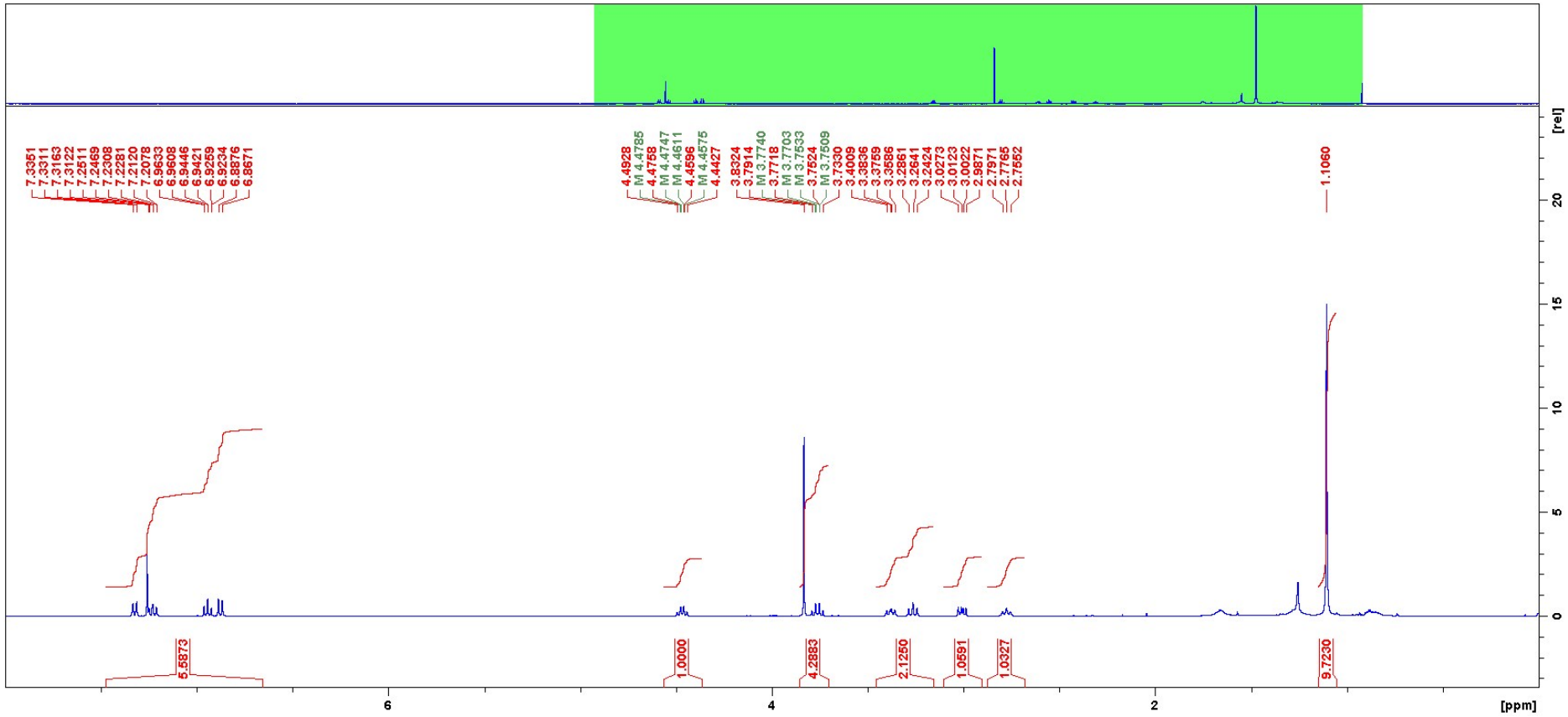
Compound **27**: ^{1}H NMR



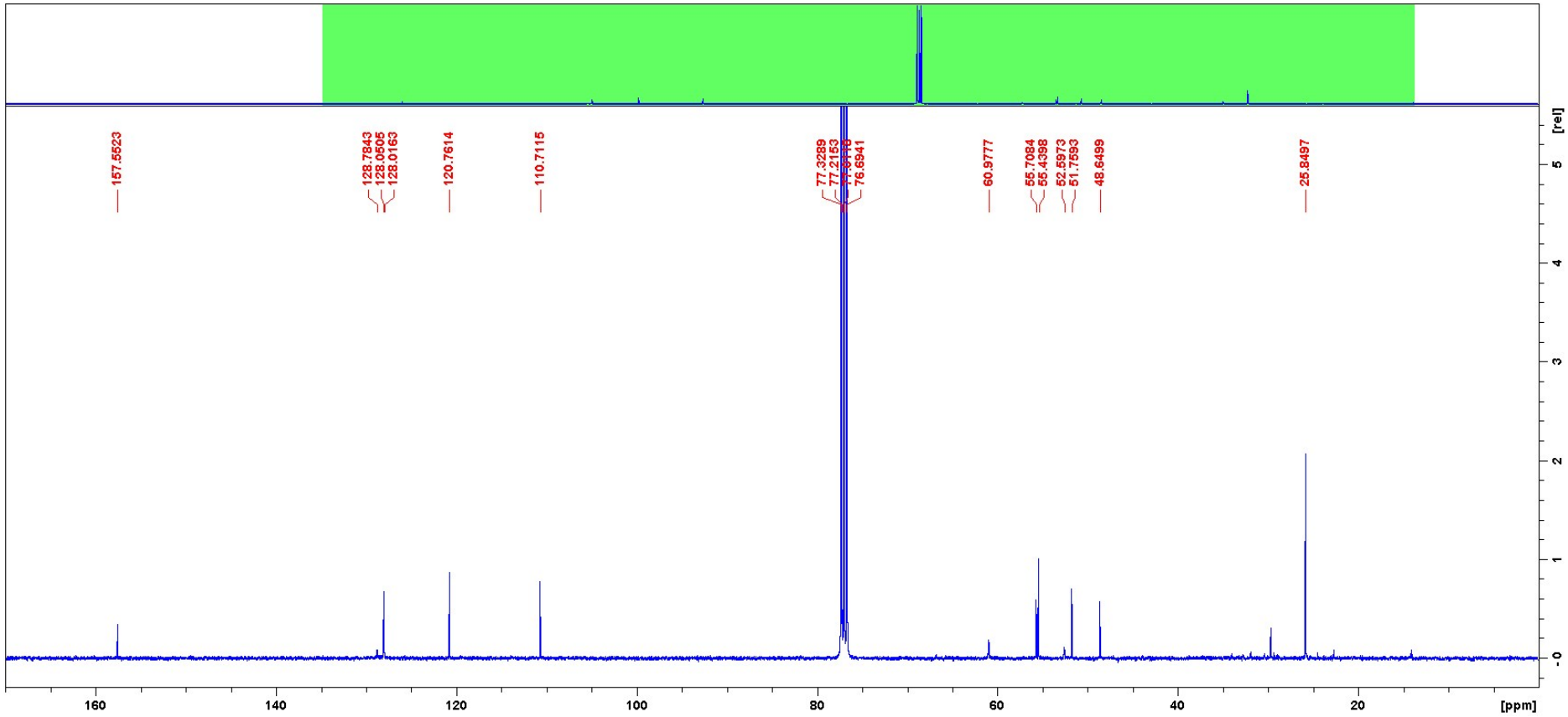
Compound **27**: ^{13}C NMR



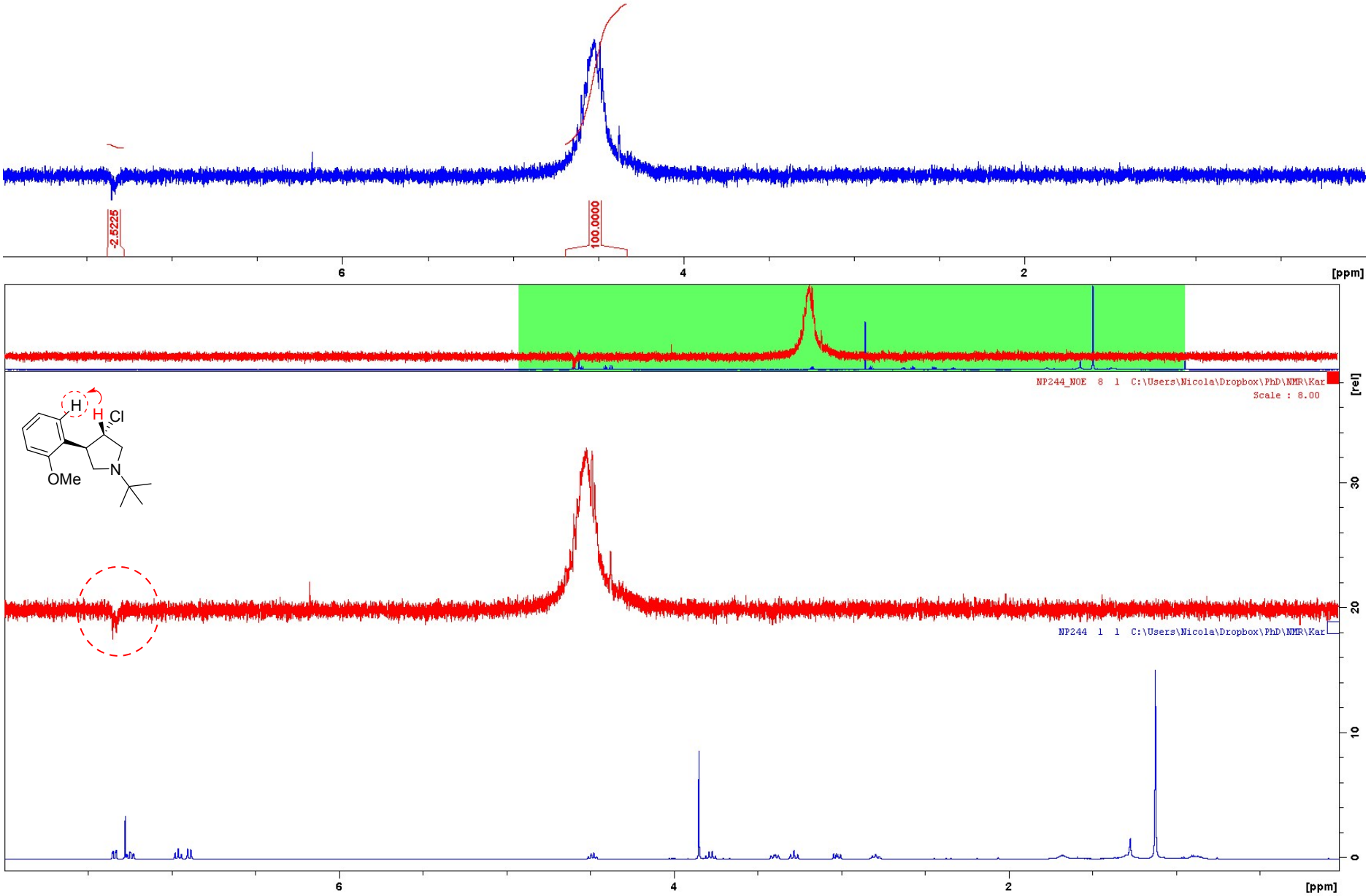
Compound **28**: ^{1}H NMR



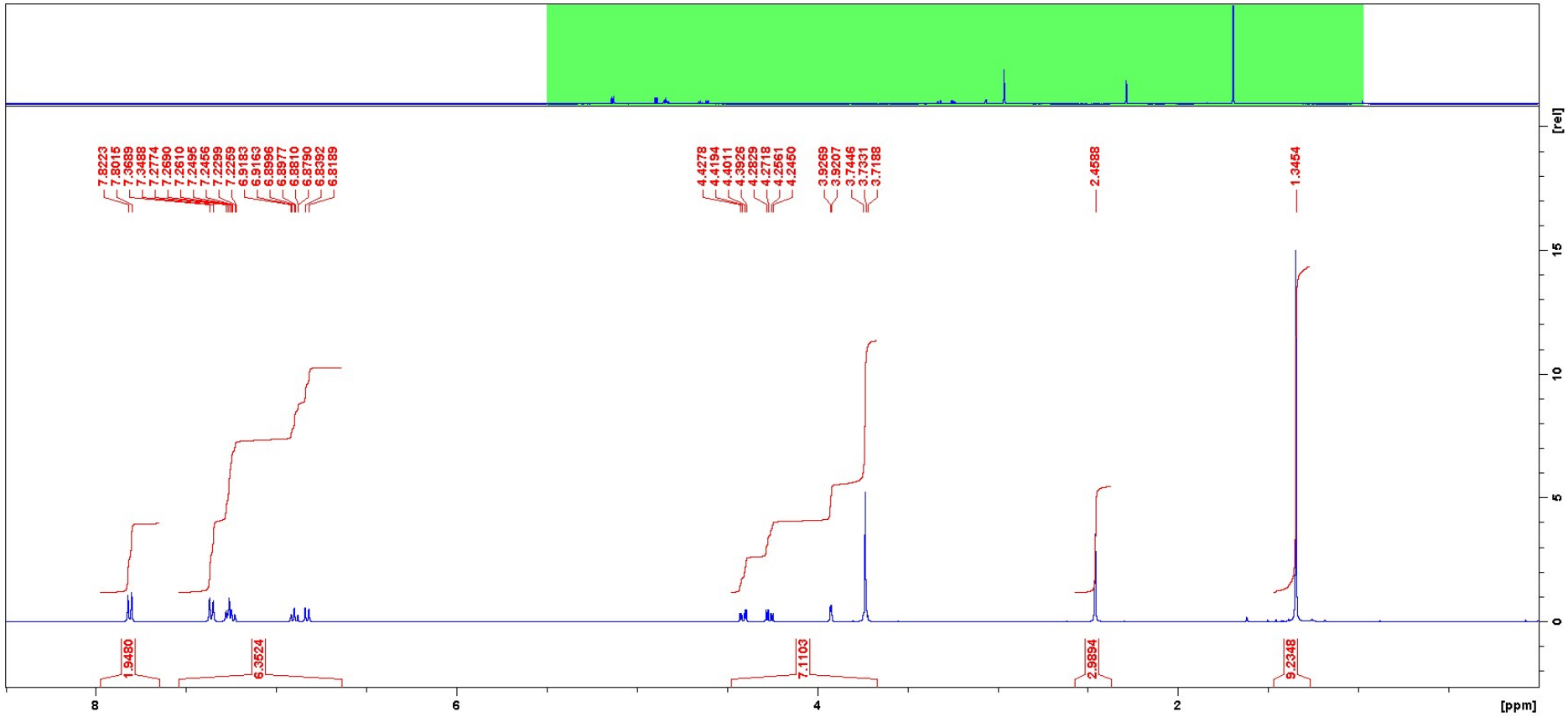
Compound **28**: ^{13}C NMR



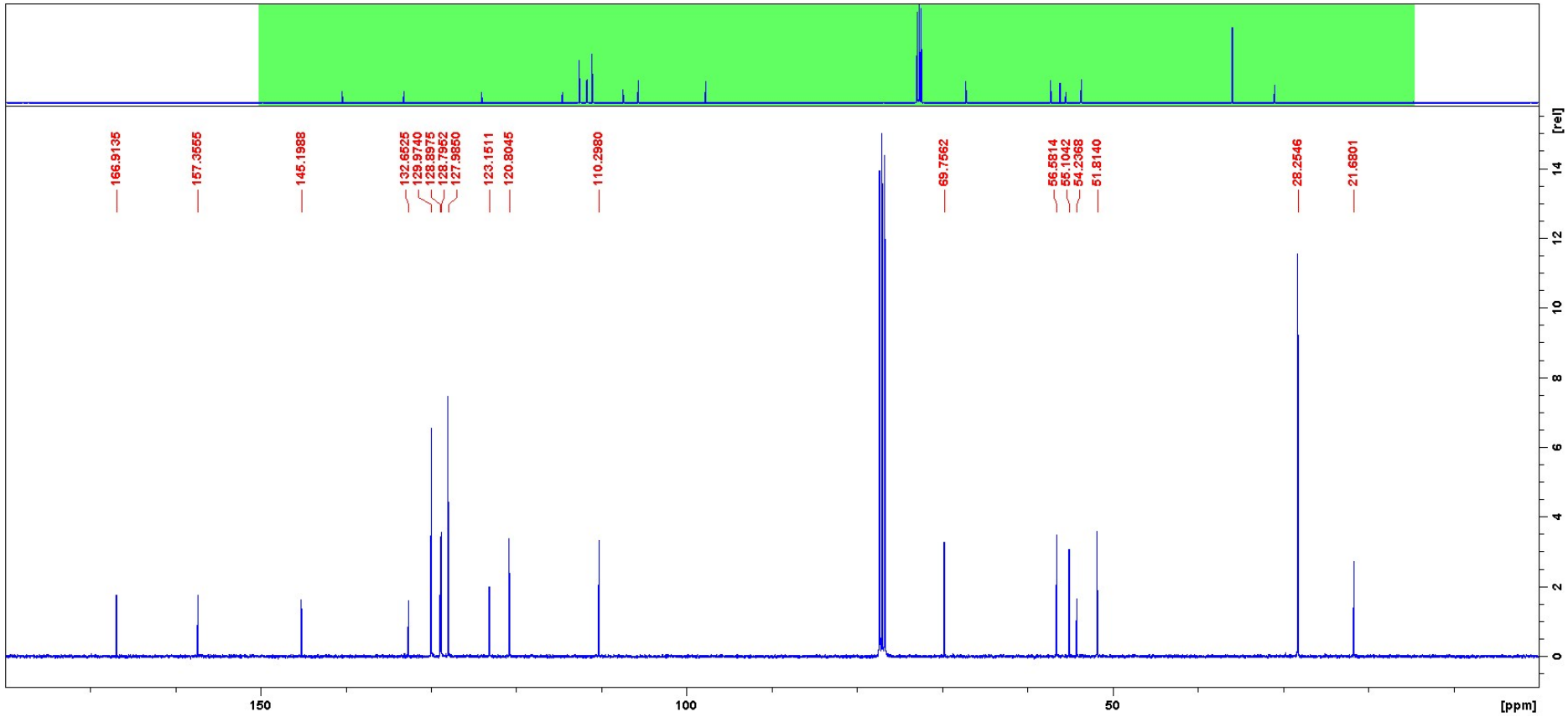
Compound **28**: *1D Selective Gradient NOESY*



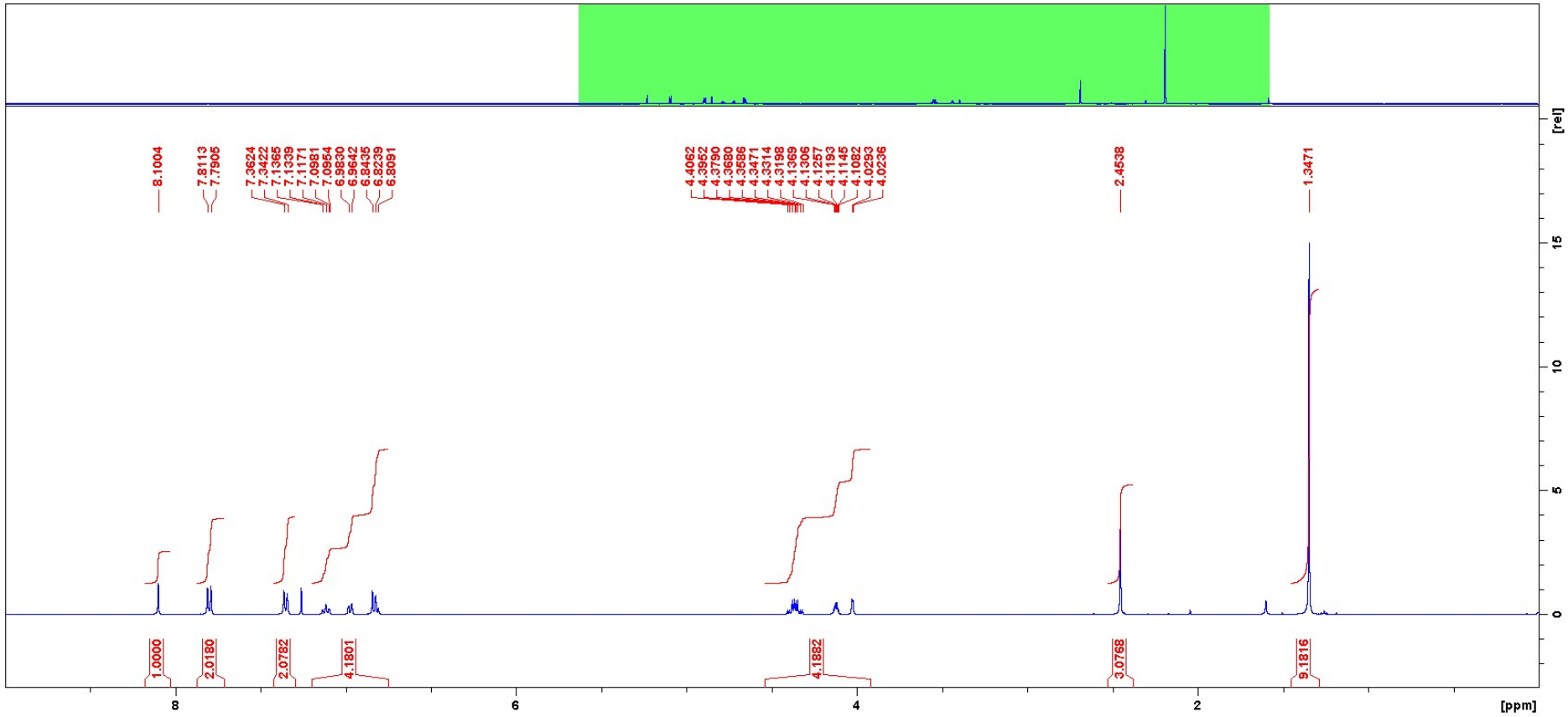
Compound **29**: ^{1}H NMR



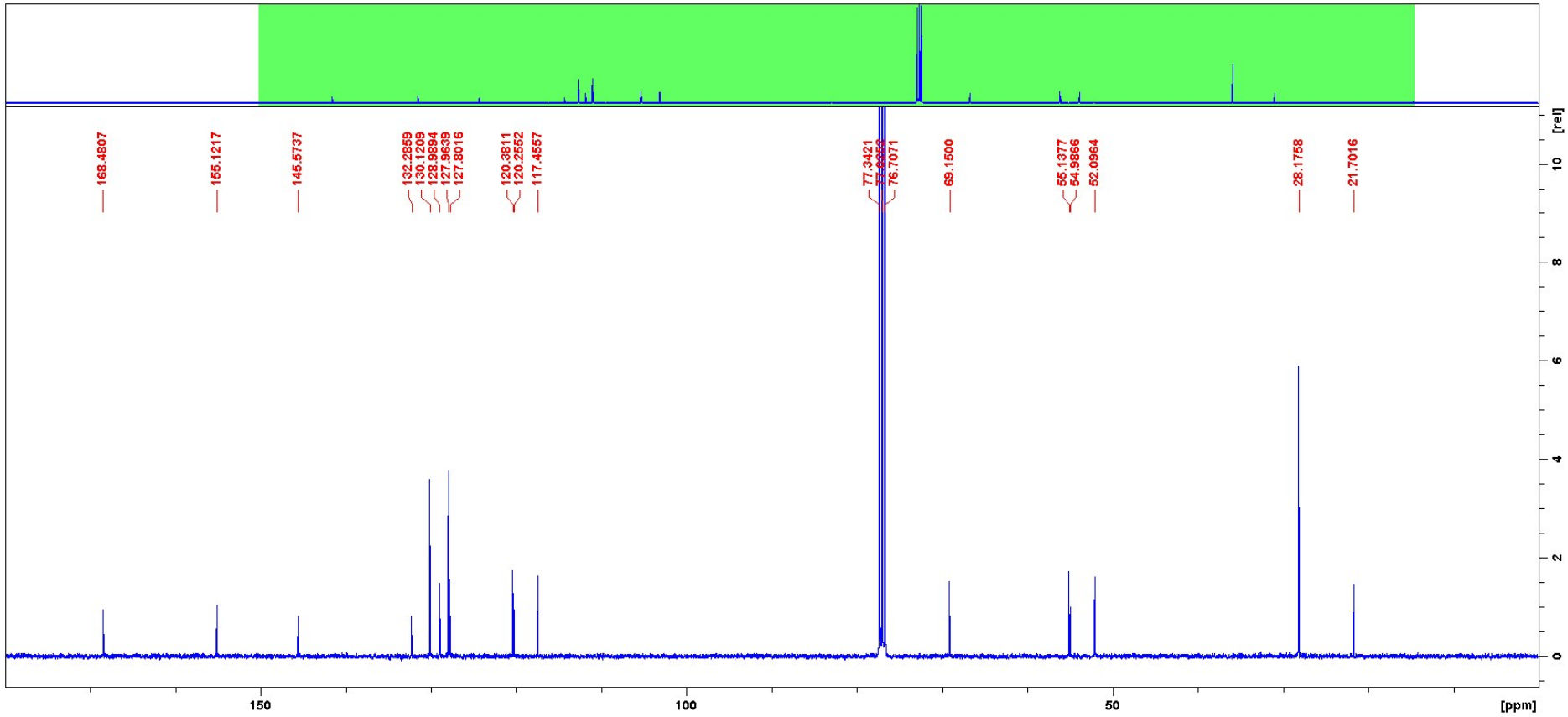
Compound **29**: ^{13}C NMR



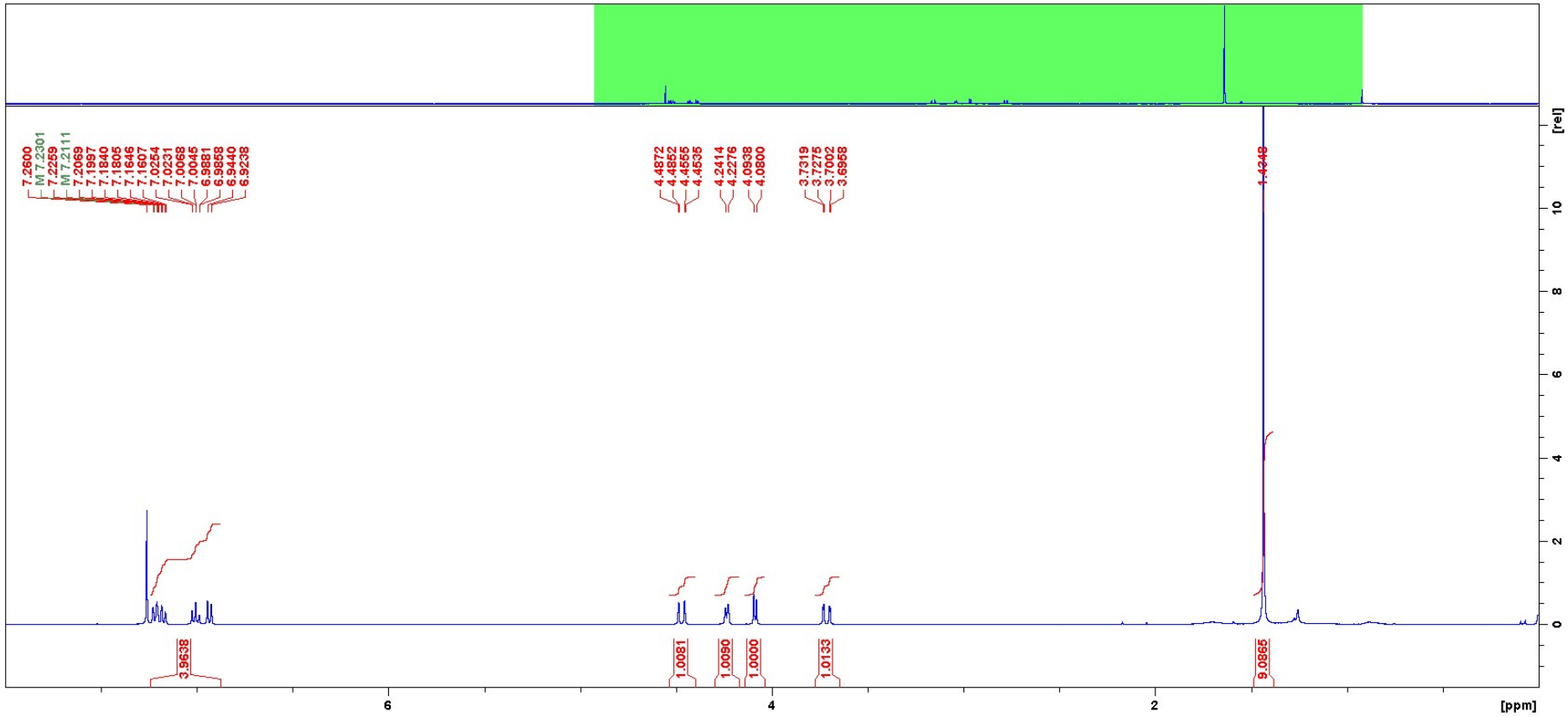
Compound **30**: ^{1}H NMR



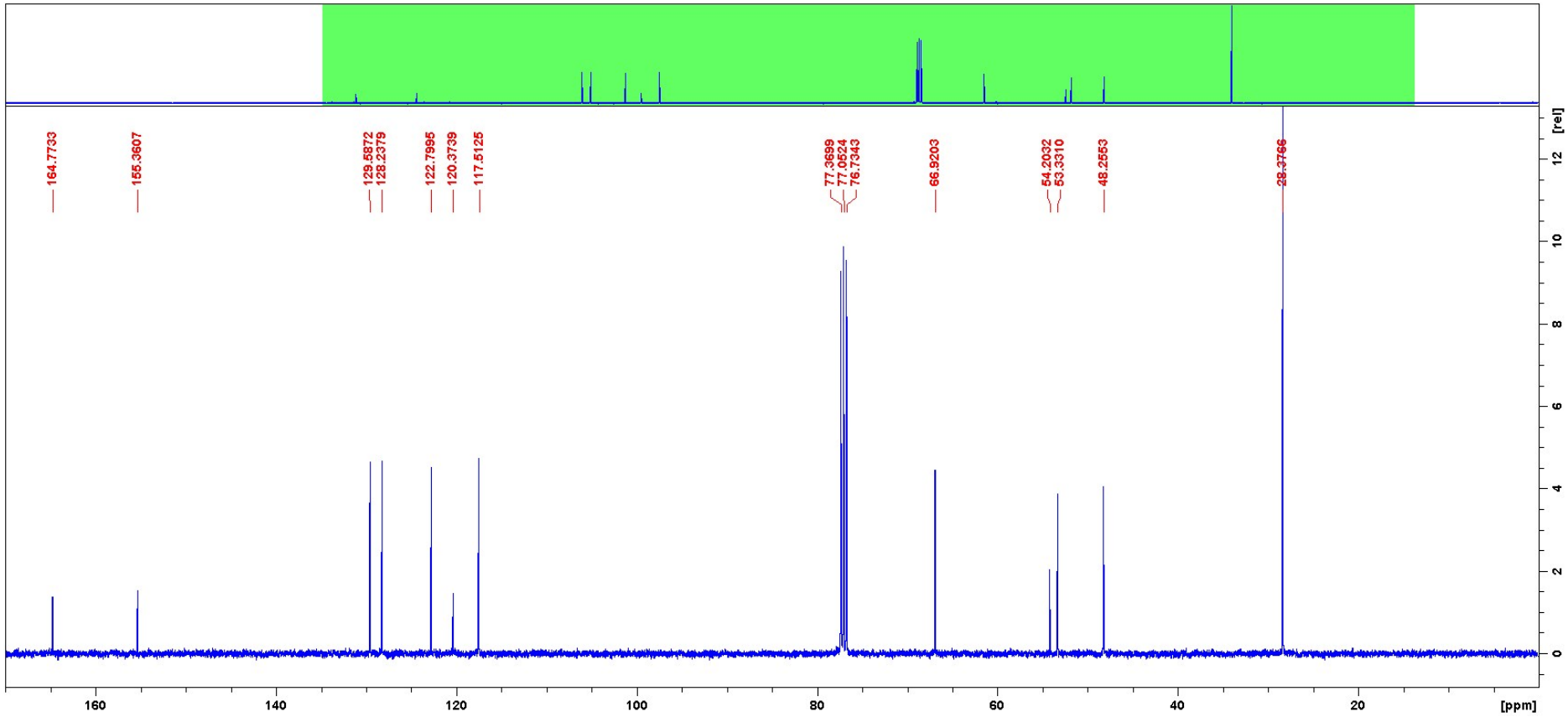
Compound **30**: ^{13}C NMR



Compound **31**: ^{1}H NMR



Compound **31**: ^{13}C NMR



Single crystal X-ray diffraction

For the structures of **25**, **26** and **31**, X-ray intensity data were collected at RT and 100 K, respectively, on an Agilent Supernova Dual Source (Cu at zero) diffractometer equipped with an Atlas CCD detector using ω scans and CuKα (λ = 1.54184 Å) radiation. The images were interpreted and integrated with the program CrysAlisPro.[9] Using Olex2,[10] the structures were solved by direct methods using the ShelXS structure solution program and refined by full-matrix least-squares on F^2 using the ShelXL program package.[11,12] Non-hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode and isotropic temperature factors fixed at 1.2 times U(eq) of the parent atoms (1.5 times for methyl and hydroxyl groups).

CCDC 1529989-1529991 contain the supplementary crystallographic data for this paper and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

Crystal data for compound ***25***. $C_{21}H_{25}NO_4$, M = 355.42, monoclinic, space group $P2_1/c$ (No. 14), a = 14.6008(4) Å, b = 8.3244(3) Å, c = 15.3345(5) Å, β = 99.473(3)°, V = 1838.38(10) Å^3, Z = 4, T = 100 K, ρ_{calc} = 1.284 g cm^{-3}, μ(Cu-Kα) = 0.717 mm^{-1}, F(000) = 760, 17634 reflections measured, 3696 unique (R_{int} = 0.0337) which were used in all calculations. The final $R1$ was 0.0393 ($I > 2\sigma(I)$) and $wR2$ was 0.1053 (all data). The asymmetric unit has chirality at C2(*S*), C3(*S*) and C4(*S*). Obviously, because of the centro-symmetric space group $P2_1/c$, also the inverse configuration is present in the crystal structure.

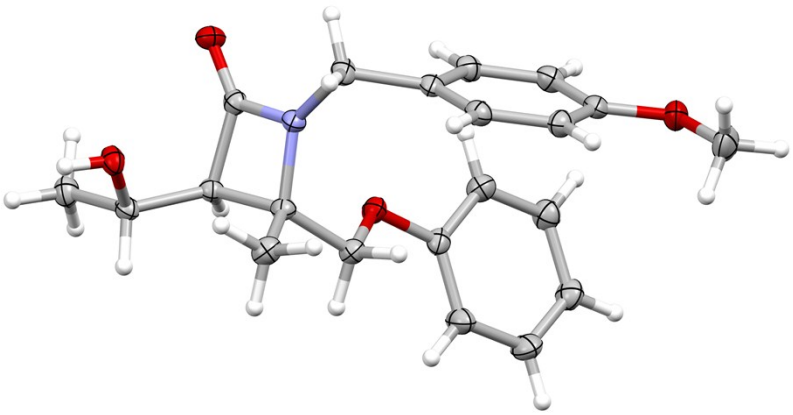


Figure S1 Asymmetric unit of the crystal structure of **25**, showing thermal displacement ellipsoids at the 50% probability level.

Crystal data for compound ***26***. $C_{19}H_{19}NO_4$, M = 325.35, triclinic, space group P-1 (No. 2), a =

[9] Rigaku Oxford Diffraction (2015). CrysAlis Pro; Rigaku Oxford Diffraction, Yarnton, England.

[10] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Cryst.*, 2009, **42**, 339.

[11] G. M. Sheldrick, *Acta Cryst.* 2008, **A64**, 112.

[12] G. M. Sheldrick, *Acta Cryst.* 2015, **C71**, 3.

7.6298(2) Å, b = 18.0069(7) Å, c = 18.6575(6) Å, α = 96.857(3)°, β = 98.399(3)°, γ = 100.637(3)°, V = 2129.09(9) Å^3, Z = 6, T = 100 K, ρ_{calc} = 1.316 g cm^{-3}, μ(Cu-Kα) = 0.757 mm^{-1}, F(000) = 1032, 36965 reflections measured, 9909 unique (R_{int} = 0.0588) which were used in all calculations. The final R1 was 0.0538 ($I > 2\sigma(I)$) and wR2 was 0.1610 (all data). The asymmetric unit contains three crystallographic independent molecules with the same chirality at C2(*S*), C21(*S*) and C40(*S*). Obviously, because of the centro-symmetric space group *P*-1, also the inverse configurations are present in the crystal structure.

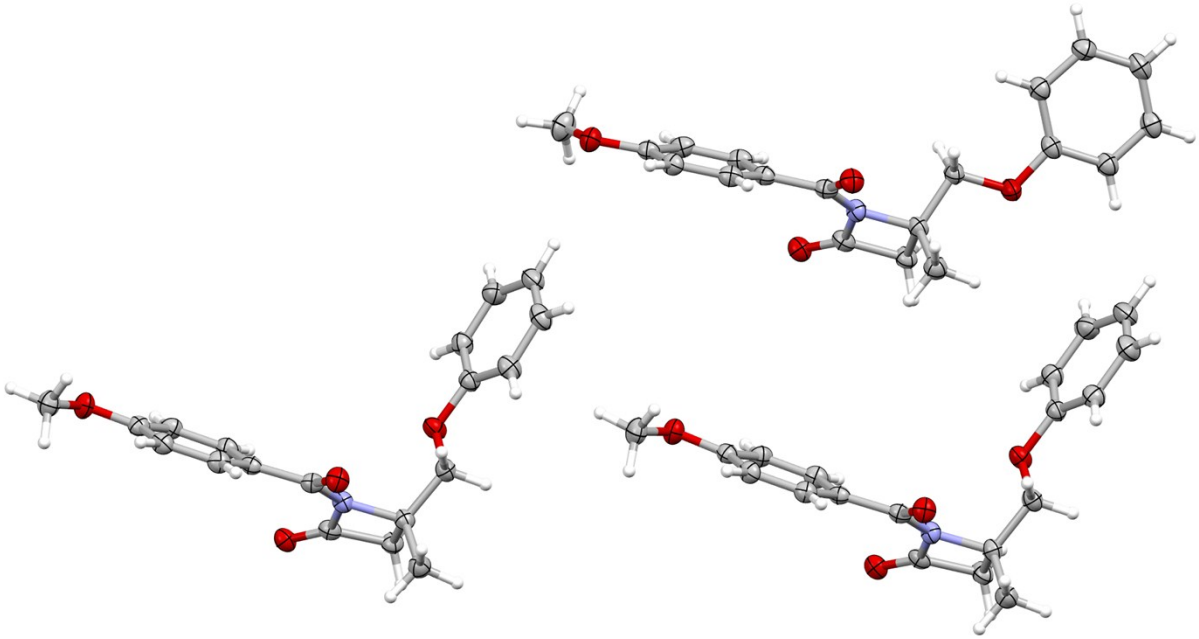


Figure S2 Asymmetric unit of the crystal structure of **26**, showing thermal displacement ellipsoids at the 50% probability level.

*Crystal data for compound **31***. $C_{14}H_{17}NO_2$, M = 231.29, triclinic, space group *P*-1 (No. 2), a = 8.9339(9) Å, b = 11.2293(11) Å, c = 13.7571(8) Å, α = 78.616(6)°, β = 88.105(7)°, γ = 69.424(9)°, V = 1265.7(2) Å^3, Z = 4, T = 100 K, ρ_{calc} = 1.214 g cm^{-3}, μ(Cu-Kα) = 0.648 mm^{-1}, F(000) = 496, 35490 reflections measured, 5062 unique (R_{int} = 0.1469) which were used in all calculations. The final R1 was 0.0831 ($I > 2\sigma(I)$) and wR2 was 0.1880 (all data). The asymmetric unit contains two crystallographic independent molecules with opposite chirality at C1(*S*), C3(*S*) and C15(*R*), C17(*R*), for the first and second molecule, respectively. Obviously, because of the centro-symmetric space group *P*-1, also the inverse configurations are present in the crystal structure.

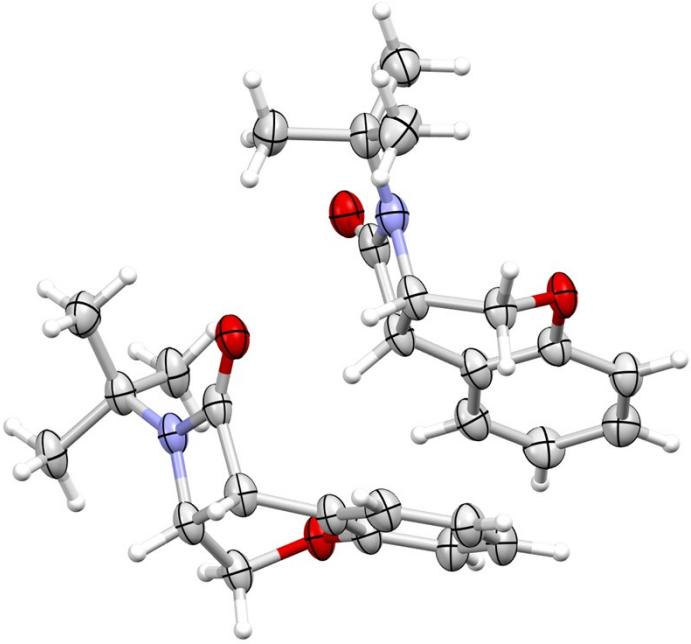


Figure S3 Asymmetric unit of the crystal structure of **31**, showing thermal displacement ellipsoids at the 50% probability level.