Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Synthesis of 3,5-disubstituted isoxazoles by domino reductive Nef reaction/cyclization of β-nitroenones

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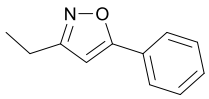
1. Experimental Section

General Remarks. ^{1}H NMR analyses were recorded at 400 MHz on a Varian Mercury Plus 400. ^{13}C NMR analyses were recorded at 100 MHz. IR spectra were recorded with a Perkin Elmer FTIR spectrometer Spectrum Two UATR. Microanalyses were performed with a CHNS-O analyzer Model EA 1108 from Fisons Instruments. GS-MS analyses were obtained on a Hewlett-Packard GC/MS 6890 N that works with the EI technique (70 eV). Flow chemical reactions were performed by means of FlowLab™ system of Uniqsis. Microwave irradiations were performed by means of a Biotage® Initiator. Compounds **1a-n** were prepared starting from alkyl- and arylglyoxals and nitro compounds by following reported procedures.[1]

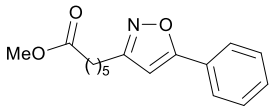
Batch general procedure. A solution of the appropriate β-nitroenone **1a-n** (1 mmol) and tin(II) chloride dihydrate (2 mmol) in ethyl acetate (13 mL) was irradiated, by means of a Biotage® Initiator microwave oven, at 90°C for 2 hours. Then, the solution was transferred into a separatory funnel, treated with a 0.5 N aqueous solution of HCl (30 mL), extracted by fresh EtOAc (3 x 30 mL), and the collected organic phase was dried using anhydrous Na_2SO_4. Finally, after the filtration of the sodium sulphate and the evaporation of the solvent under reduced pressure, the crude reaction product **2a-n** was purified by flash column chromatography (Hexane:EtOAc = 95:5).

Flow general procedure. The appropriate β-nitroenone **1a-c** (1 mmol) was taken up in ethyl acetate (6.5 mL) and filled into reservoir A, and tin(II) chloride dihydrate (2 mmol) was taken up in ethyl acetate (6.5 mL) and filled into reservoir B. The two solutions were simultaneously pumped with a flow rate of 0.042 mL/min for each pump into a T-connector before passing through a 10 mL PTFE coil reactor heated at 90°C (residence time 2 hours), and the outflow was dropped into a flask containing 30 mL of a stirring 0.5 N aqueous solution of HCl. The two layers were separated, the aqueous one was extracted with fresh EtOAc (3 x 30 mL), and the collected organic phase was dried using anhydrous Na_2SO_4. Finally, after the filtration of the sodium sulphate and the evaporation of the solvent under reduced pressure, the crude reaction product **2a-c** was purified by flash column chromatography (Hexane:EtOAc = 95:5).

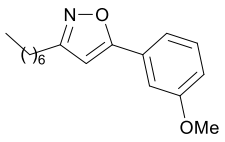
2. Characterization of Compound 2a-n.



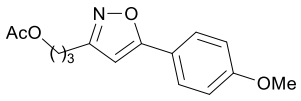
3-Ethyl-5-phenylisoxazole **2a**. Yellow oil. IR (cm^{-1}, neat): 1615, 1575, 1450, 1420, 947, 762, 689. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.79-7.72 (m, 2H), 7.50-7.36 (m, 3H), 6.38 (s, 1H), 2.74 (q, 2H, *J* = 7.6 Hz), 1.32 (t, 3H, *J* = 7.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.7, 165.9, 130.1, 129.0, 127.8, 125.9, 99.0, 19.8, 12.8. GC-MS (EI, 70 eV): m/z: 173 ([M^+], 98), 131 (12), 105 (100), 77 (56), 68 (18), 51 (17). Anal. Calcd. For $C_{11}H_{11}NO$ (173.21): C, 76.28; H, 6.40; N, 8.09. Found: C, 76.32; H, 6.37; N, 8.12.



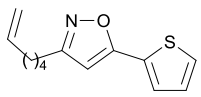
Methyl 6-(5-phenylisoxazol-3-yl)hexanoate **2b**. White solid, m.p. = 30-34°C. IR (cm^{-1}, neat): 2940, 1722, 614, 1593, 1575, 1453, 1431, 1203, 1175, 767, 691. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.75 (dd, 2H, *J* = 8.0, 1.6 Hz), 7.48-7.38 (m, 3H), 6.37 (s, 1H), 3.66 (s, 3H), 2.71 (t, 2H, *J* = 7.6 Hz), 2.32 (t, 2H, *J* = 7.5 Hz), 1.79-1.63 (m, 4H), 1.48-1.37 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 174.2, 169.7, 164.5, 130.1, 129.0, 127.8, 125.9, 99.2, 51.6, 34.0, 28.8, 28.1, 26.1, 24.7. GC-MS (EI, 70 eV): m/z: 273 ([M^+], 7), 272 (9), 242 (17), 200 (18), 172 (42), 159 (100), 131 (14), 105 (34), 77 (23). Anal. Calcd. For $C_{16}H_{19}NO_3$ (273.33): C, 70.31; H, 7.01; N, 5.12. Found: C, 70.28; H, 7.03; N, 5.10.



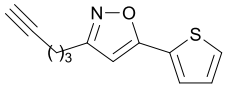
3-Heptyl-5-(3-methoxyphenyl)isoxazole **2c**. Yellow oil. IR (cm^{-1}, neat): 2926, 1601, 1576, 1466, 1436, 1228, 1041, 779, 685. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.38-7.27 (m, 3H), 6.95 (dt, 1H, *J* = 6.7, 2.6 Hz), 6.36 (s, 1H), 3.85 (s, 3H), 2.72-2.66 (m, 2H), 1.76-1.63 (m, 2H), 1.45-1.20 (m, 8H), 0.88 (t, 3H, *J* = 6.9 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.4, 164.9, 160.0, 129.0, 128.8, 118.3, 116.0, 110.9, 99.5, 55.5, 31.8, 29.3, 29.1, 28.5, 26.2, 22.7, 14.2. GC-MS (EI, 70 eV): m/z: 273 ([M^+], 18), 230 (19), 202 (64), 189 (100), 161 (14), 135 (23), 107 (12), 77 (10), 41 (10). Anal. Calcd. For $C_{17}H_{23}NO_2$ (273.38): C, 74.69; H, 8.48; N, 5.12. Found: C, 74.73; H, 8.51; N, 5.10.



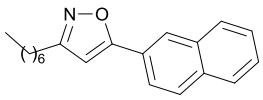
3-(5-(4-Methoxyphenyl)isoxazol-3-yl)propyl acetate **2d**. pale pink solid, m.p. = 85-87°C. IR (cm^{-1}, neat): 1735, 1618, 1514, 1472, 1234, 1175, 1019, 836, 827, 608, 523, 408. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, 2H, *J* = 8.9 Hz), 6.95 (d, 2H, *J* = 8.9 Hz), 6.25 (s, 1H), 4.15 (t, 1H, *J* = 6.4 Hz), 3.84 (s, 3H), 2.81-2.73 (m, 2H), 2.11-1.98 (m, 2H), 2.05 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.1, 169.8, 163.5, 161.0, 127.3, 120.3, 114.3, 97.7, 63.5, 55.4, 27.3, 22.9, 20.9. GC-MS (EI, 70 eV): m/z: 275 ([M^+], 21), 232 (12), 189 (100), 161 (11), 135 (47), 77 (10), 43 (16). Anal. Calcd. For $C_{15}H_{17}NO_4$ (275.30): C, 65.44; H, 6.22; N, 5.09. Found: C, 65.48; H, 6.25; N, 5.07.



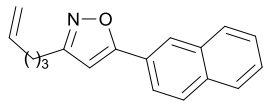
3-(Hex-5-en-1-yl)-5-(thiophen-2-yl)isoxazole **2e**. Orange oil. IR (cm^{-1}, neat): 2927, 1638, 1603, 1423, 907, 850, 703. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.47 (dd, 1H, *J* = 3.7, 1.2 Hz), 7.41 (dd, 1H, *J* = 5.0, 1.2 Hz), 7.10 (dd, 1H, *J* = 5.0, 3.7 Hz), 6.23 (s, 1H), 5.86-5.73 (m, 1H), 5.05-4.91 (m, 2H), 2.69 (t, 2H, *J* = 7.6 Hz), 2.15-2.05 (m, 2H), 1.76-1.64 (m, 2H), 1.54-1.43 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 164.7, 164.6, 138.6, 129.7, 128.1, 127.8, 126.8, 114.9, 99.0, 33.5, 28.5, 27.8, 26.0. GC-MS (EI, 70 eV): m/z: 234 ([M+1$^+$], 4), 233 ([M^+], 26), 232 (24), 204 (14), 178 (49), 165 (100), 122 (37), 111 (93), 41 (28), 39 (29). Anal. Calcd. For $C_{13}H_{15}NOS$ (233.33): C, 66.92; H, 6.48; N, 6.00; S, 13.74. Found: C, 66.96; H, 6.51; N, 5.98; S, 13.71.



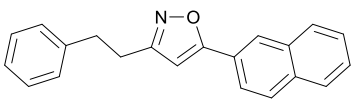
3-(Pent-4-yn-1-yl)-5-(thiophen-2-yl)isoxazole **2f**. Yellow oil. IR (cm^{-1}, neat): 2115, 1600, 1424, 850, 794, 705. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.48 (dd, 1H, *J* = 3.7, 1.2 Hz), 7.43 (dd, 1H, *J* = 5.0, 1.2 Hz), 7.11 (dd, 1H, *J* = 5.0, 3.7 Hz), 6.27 (s, 1H), 2.85-2.80 (m, 2H), 2.31 (dt, 2H, *J* = 7.0, 2.7 Hz), 2.01 (t, 1H, *J* = 2.7 Hz), 1.98-1.89 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 164.9, 163.8, 129.6, 128.2, 127.9, 127.0, 99.1, 83.5, 69.4, 27.1, 25.1, 18.1. GC-MS (EI, 70 eV): m/z: 218 ([M+1$^+$], 4), 217 ([M^+], 20), 216 (19), 188 (31), 165 (93), 136 (19), 111 (100), 39 (44). Anal. Calcd. For $C_{12}H_{11}NOS$ (217.29): C, 66.33; H, 5.10; N, 6.45; S, 14.75. Found: C, 66.29; H, 5.08; N, 6.48; S, 14.72.



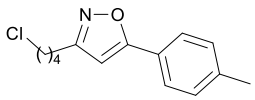
3-Heptyl-5-(naphthalen-2-yl)isoxazole **2g**. White solid, m.p. = 53-55°C. IR (cm^{-1}, neat): 2919, 1614, 1587, 1567, 1461, 1422, 860, 827, 797, 746, 725, 475. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.28 (s, 1H), 7.95-7.75 (m, 4H), 7.57-7.47 (m, 2H), 6.48 (s, 1H), 2.73 (t, 2H, *J* = 7.7 Hz), 1.80-1.67 (m, 2H), 1.48-1.22 (m, 8H), 0.90 (t, 3H, *J* = 6.7 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.5, 164.9, 133.8, 133.1, 128.8, 128.6, 127.8, 127.2, 126.9, 125.4, 124.9, 123.0, 99.5, 31.7, 29.2, 29.0, 28.4, 26.2, 22.7, 14.1. GC-MS (EI, 70 eV): m/z: 293 ([M^+], 24), 250 (15), 222 (55), 209 (100), 181 (18), 155 (27), 127 (35). Anal. Calcd. For $C_{20}H_{23}NO$ (293.41): C, 81.87; H, 7.90; N, 4.77. Found: C, 81.91; H, 7.93; N, 4.80.



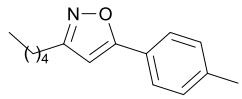
5-(Naphthalen-2-yl)-3-(pent-4-en-1-yl)isoxazole **2h**. Yellow waxy solid. IR (cm^{-1}, neat): 2929, 1636, 1600, 1425, 855, 825, 799, 745, 723, 479. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.29 (s, 1H), 7.95-7.77 (m, 4H), 7.57-7.50 (m, 2H), 6.49 (s, 1H), 5.92-5.78 (m, 1H), 5.12-4.99 (m, 2H), 2.76 (t, 2H, *J* = 7.7 Hz), 2.24-2.13 (m, 2H), 1.92-1.80 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.6, 164.5, 137.8, 133.8, 133.1, 128.8, 128.6, 127.8, 127.2, 126.9. 125.4, 124.9, 123.0, 115.4, 99.5, 33.2, 27.5, 25.6. GC-MS (EI, 70 eV): m/z: 263 ([M^+], 44), 209 (100), 181 (31), 155 (33), 127 (57), 108 (12). Anal. Calcd. For $C_{18}H_{17}NO$ (263.34): C, 82.10; H, 6.51; N, 5.32. Found: C, 82.06; H, 6.48; N, 5.30.



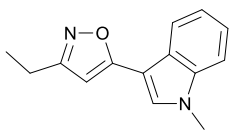
5-(Naphthalen-2-yl)-3-phenethylisoxazole **2i**. Pale yellow solid, m.p. = 84-89°C. IR (cm^{-1}, neat): 1602, 1422, 853, 821, 797, 741, 722, 477. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.28 (s, 1H), 7.96-7.83 (m, 3H), 7.79 (dd, 1H, *J* = 8.6, 1.6 Hz), 7.57-7.51 (m, 2H), 7.37-7.21 (m, 5H), 6.42 (s, 1H), 3.08 (s, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.6, 164.0, 140.7, 133.8, 133.1, 128.8, 128.7, 128.6, 128.4, 127.9, 127.2, 126.9, 126.4, 125.5, 124.8, 123.0, 99.7, 34.5, 28.1. GC-MS (EI, 70 eV): m/z: 299 ([M^+], 100), 270 (16), 195 (25), 155 (71), 144 (47), 127 (62), 91 (41). Anal. Calcd. For $C_{21}H_{17}NO$ (299.37): C, 84.25; H, 5.72; N, 4.68. Found: C, 84.22; H, 5.69; N, 4.70.



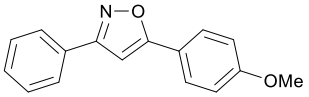
3-(4-Chlorobutyl)-5-(p-tolyl)isoxazole **2j**. White solid, m.p. = 62-64°C. IR (cm^{-1}, neat): 2946, 1616, 1600, 1514, 1462, 1424, 1328, 829, 789, 771, 506. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.65 (d, 2H, *J* = 8.1 Hz), 7.25 (d, 2H, *J* = 8.0 Hz), 6.33 (S, 1H), 3.58 (t, 2H, *J* = 5.9 Hz), 2.74 (t, 2H, *J* = 7.0 Hz), 2.39 (s, 3H), 1.92-1.82 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 170.0, 163.9, 140.3, 129.6, 125.7, 124.8, 98.4, 44.6, 31.8, 25.4, 25.3, 21.5. GC-MS (EI, 70 eV): m/z: 249 ([M^+], 10), 214 (100), 186 (54), 119 (40), 91 (27), 65 (9). Anal. Calcd. For $C_{14}H_{16}ClNO$ (249.74): C, 67.33; H, 6.46; N, 5.61. Found: C, 67.36; H, 6.43; N, 5.59.



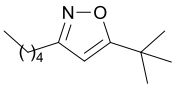
3-Pentyl-5-(p-tolyl)isoxazole **2k**. IR (cm^{-1}, neat): 2928, 1621, 1602, 1515, 1465, 1427, 820, 789, 504. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.65 (d, 2H, *J* = 8.1 Hz), 7.25 (d, 2H, *J* = 8.0 Hz), 6.32 (s, 1H), 2.69 (t, 2H, *J* = 7.7 Hz), 2.39 (s, 3H), 1.77-1.58 (m, 2H), 1.45-1.29 (m, 4H), 0.91 (t, 3H, *J* = 6.7 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.7, 164.7, 140.2, 129.6, 125.7, 125.0, 98.5, 31.4, 28.1, 26.1, 22.4, 21.4, 13.9. GC-MS (EI, 70 eV): m/z: 229 ([M^+], 9), 228 (15), 200 (11), 186 (42), 173 (100), 145 (14), 119 (42), 91 (28). Anal. Calcd. For $C_{15}H_{19}NO$ (229.32): C, 78.56; H, 8.35; N, 6.11. Found: C, 78.60; H, 8.32; N, 6.09.



3-Ethyl-5-(1-methyl-1H-indol-3-yl)isoxazole **2l**. White solid, m.p. = 63-65°C. IR (cm^{-1}, neat): 1624, 1609, 1357, 1344, 1092, 760, 750, 731, 420. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.94 (d, 1H, *J* = 6.9 Hz), 7.56 (s, 1H), 7.40-7.24 (m, 3H), 6.28 (s, 1H), 3.84 (s, 3H), 2.77 (q, 2H, *J* = 7.6 Hz), 1.35 (t, 3H, *J* = 7.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.1, 165.5, 137.1, 128.5, 124.8, 122.7, 121.0, 120.1, 109.9, 104.2, 96.6, 33.2, 19.7, 12.8. GC-MS (EI, 70 eV): m/z: 227 ([M+1$^+$], 16), 226 ([M^+], 100), 169 (12), 158 (62), 156 (18). Anal. Calcd. For $C_{14}H_{14}N_2O$ (226.28): C, 74.31; H, 6.24; N, 12.38. Found: C, 74.28; H, 6.22; N, 12.40.



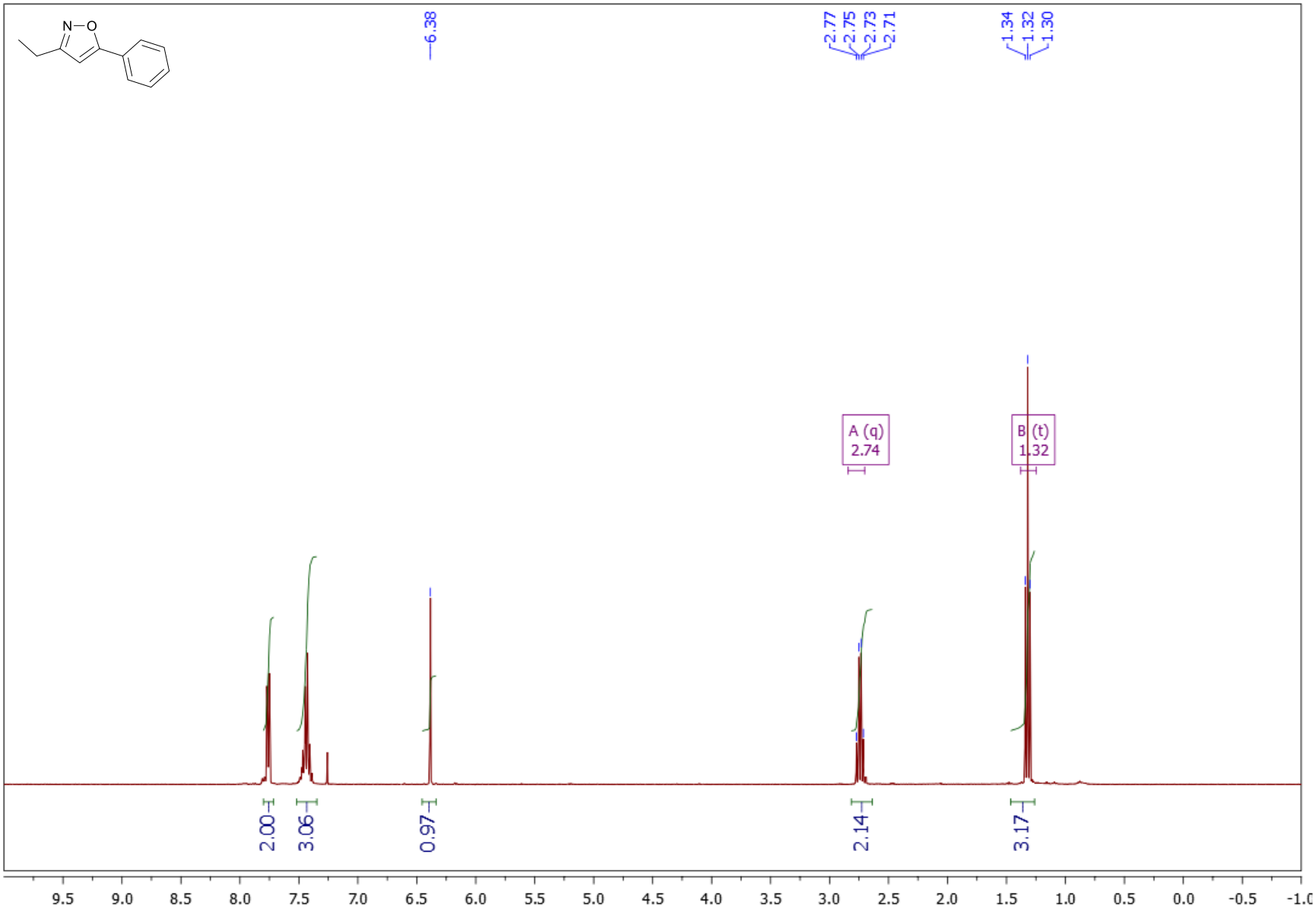
5-(4-Methoxyphenyl)-3-phenylisoxazole **2m**. White solid, m.p. = 102-104°C. IR (cm^{-1}, neat): 1614, 1598, 1501, 1464, 1399, 1260, 1248, 1177, 1033, 840, 800, 768, 690. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.88-7.84 (m, 2H), 7.78 (d, 2H, *J* = 8.9 Hz), 7.51-7.41 (m, 3H), 7.00 (d, 2H, *J* = 8.9 Hz), 6.71 (s, 1H), 3.86 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 170.4, 162.9, 161.1, 129.9, 129.3, 128.9, 127.4, 126.8, 120.3, 114.4, 96.1, 55.4. GC-MS (EI, 70 eV): m/z: 252 ([M+1$^+$], 14), 251 ([M$^+$], 81), 135 (100), 77 (24). Anal. Calcd. For $C_{16}H_{13}NO_2$ (251.28): C, 76.48; H, 5.21; N, 5.57. Found: C, 76.51; H, 5.19; N, 5.59.



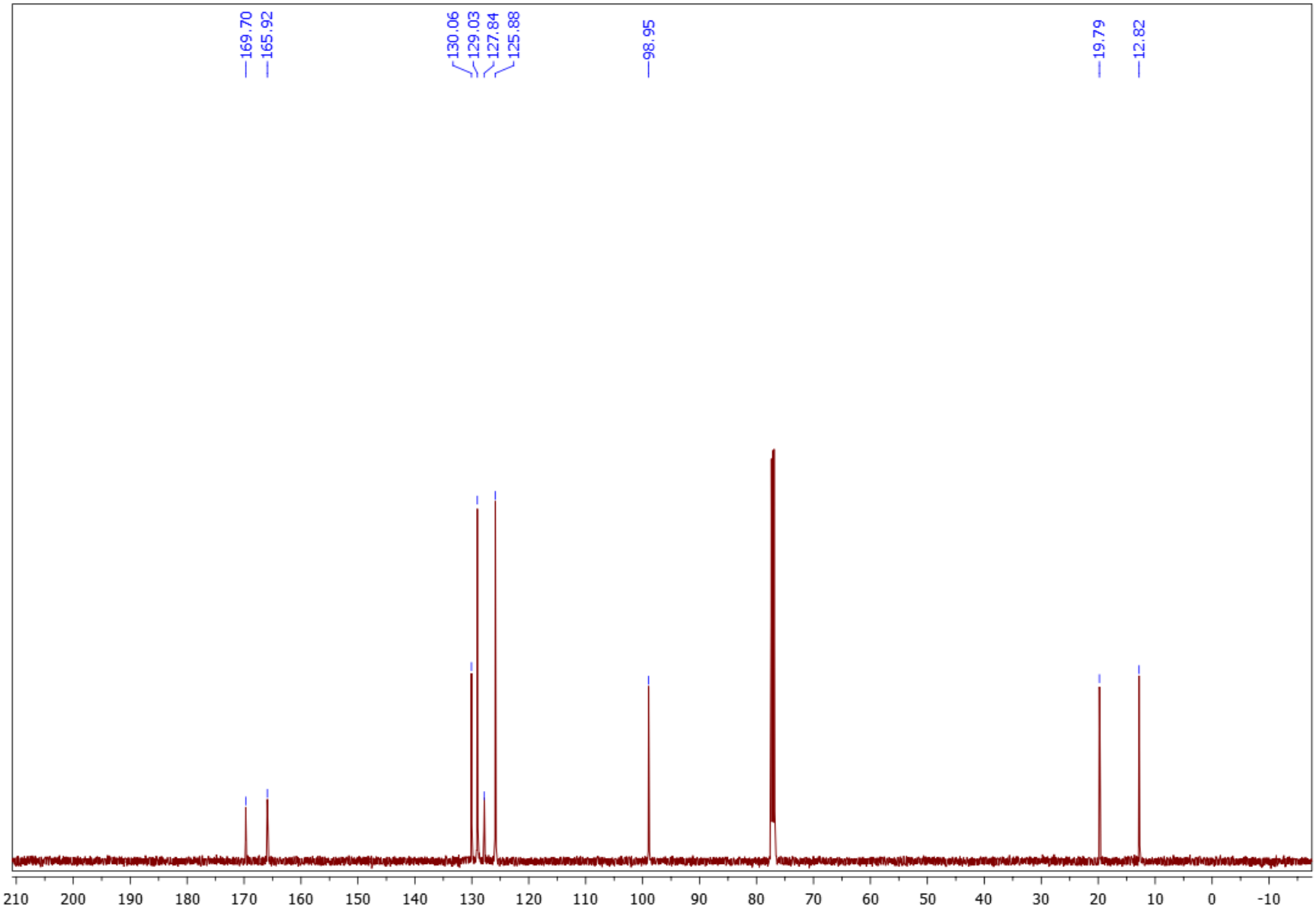
5-(*tert*-Butyl)-3-pentylisoxazole **2n**. pale yellow oil. IR (cm^{-1}, neat): 2935, 1614, 1598, 1501, 1464, 1399. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.75 (s, 1H), 2.62-2.56 (m, 2H), 1.70-1.57 (m, 2H), 1.39-1.24 (m, 4H), 1.31 (s, 9H), 0.89 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 180.8, 163.8, 97.8, 32.6, 31.5, 29.9, 28.0, 26.1, 22.3, 13.9. GC-MS (EI, 70 eV): m/z: 195 ([M$^+$], 5), 166 (11), 152 (55), 139 (100), 82 (16), 57 (15), 40 (20). Anal. Calcd. For $C_{12}H_{21}NO$ (195.31): C, 73.80; H, 10.84; N, 7.17. Found: C, 73.77; H, 10.87; N, 7.15.

3. Copy of NMR spectra of Compounds 2a-m.

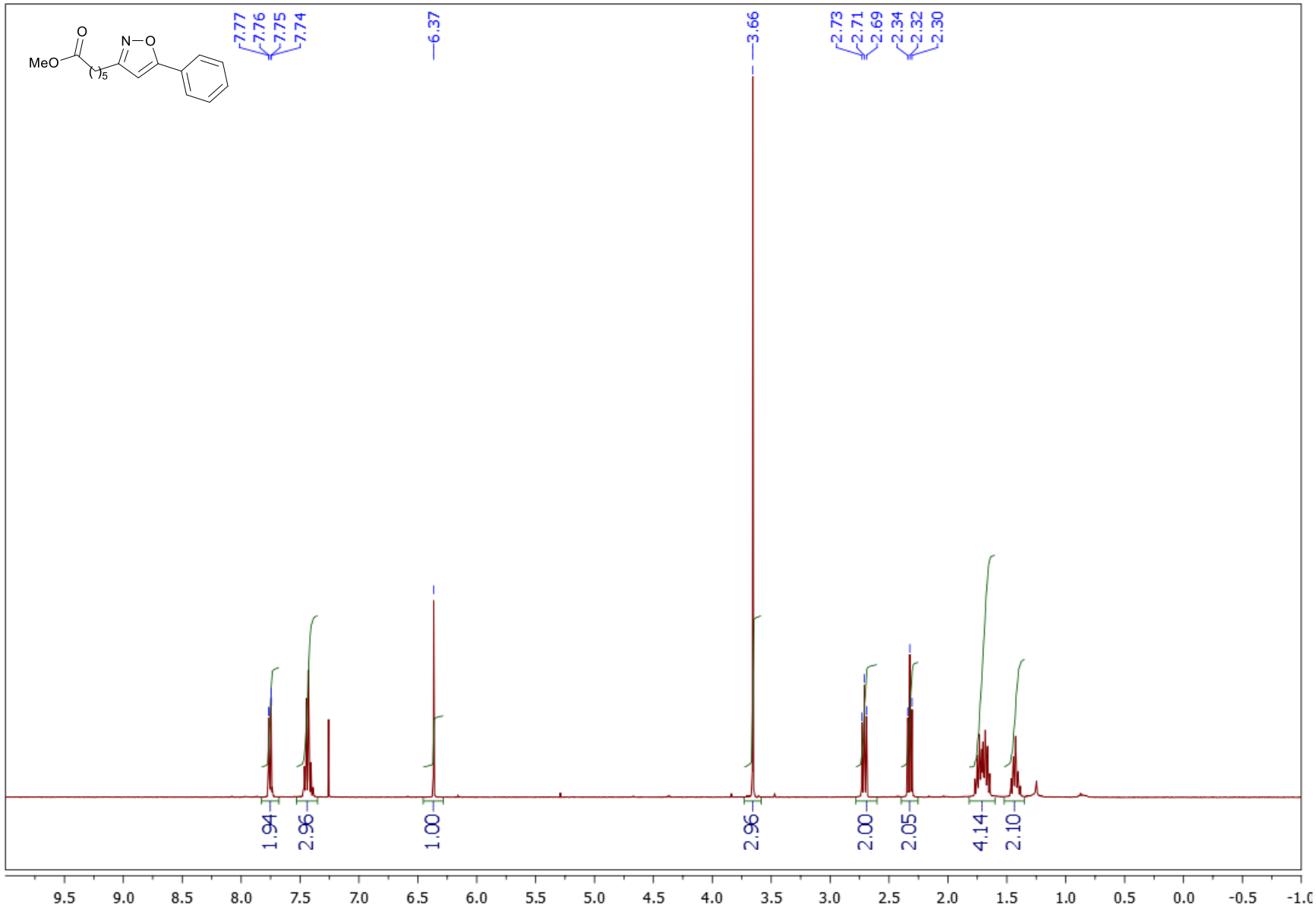
^{1}H-NMR (400 MHz, $CDCl_3$) of compounds **2a**.



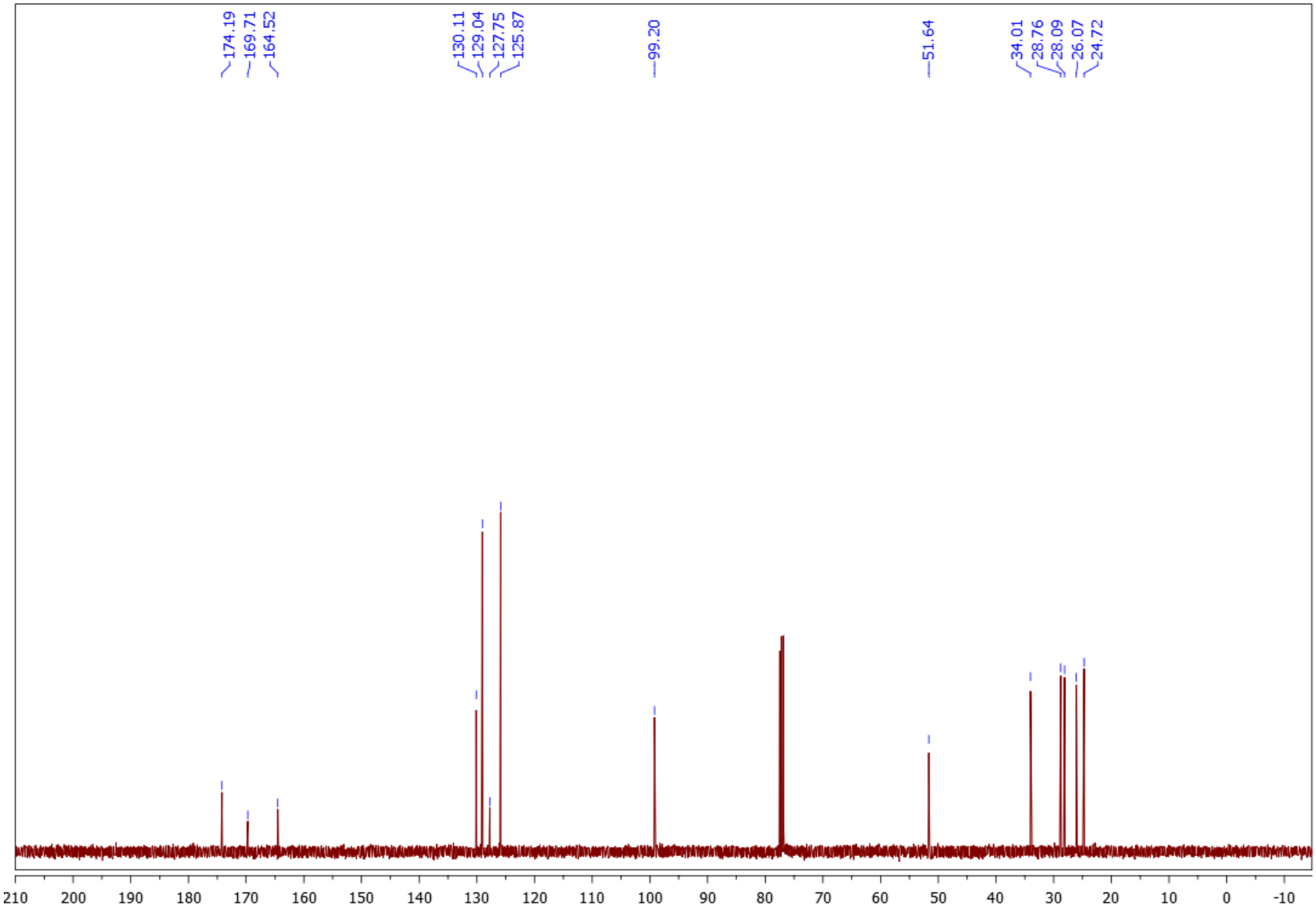
^{13}C-NMR (100 MHz, $CDCl_3$) of compounds **2a**.



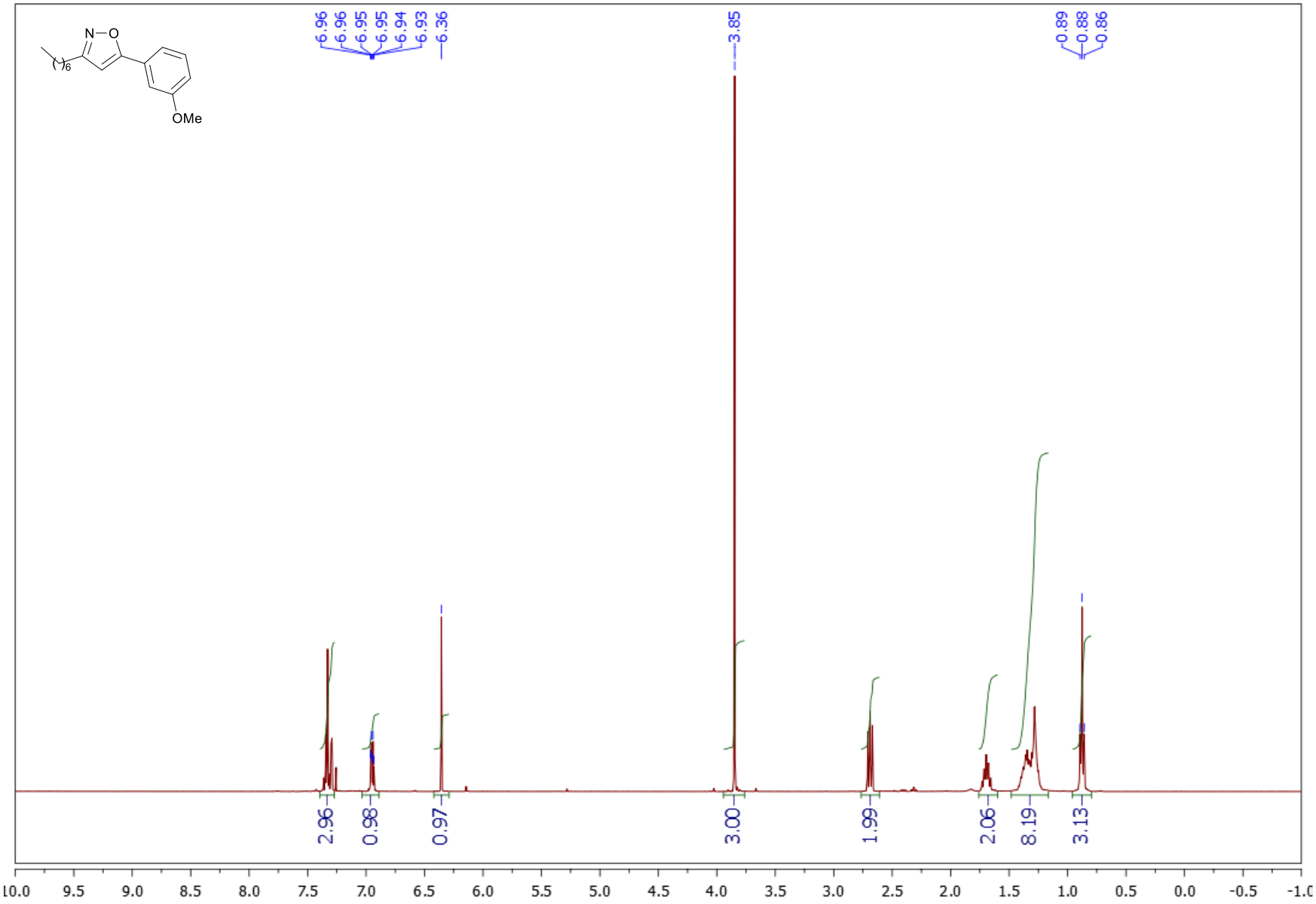
^{1}H-NMR (400 MHz, $CDCl_3$) of compounds **2b**.



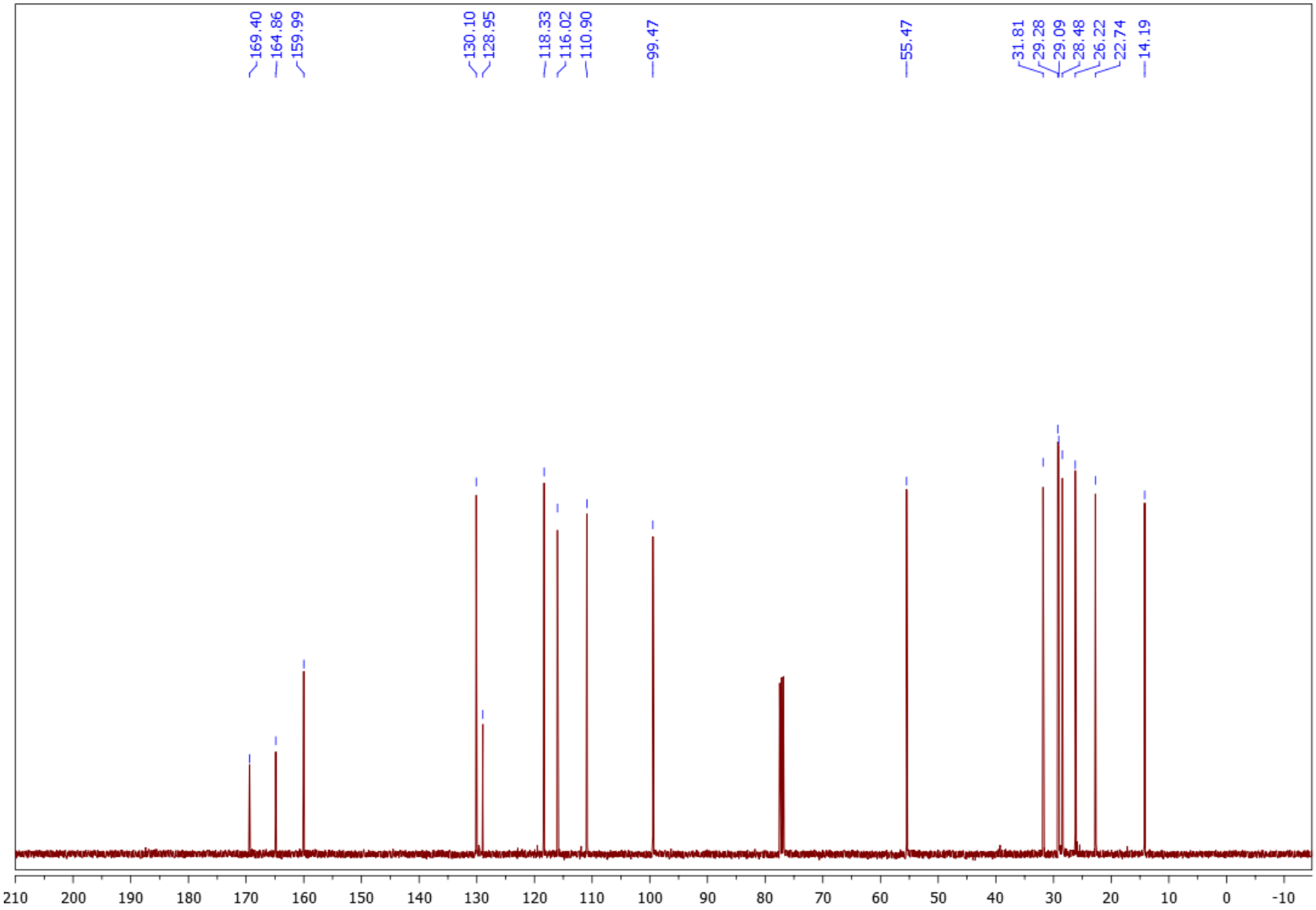
^{13}C-NMR (100 MHz, $CDCl_3$) of compounds **2b**.



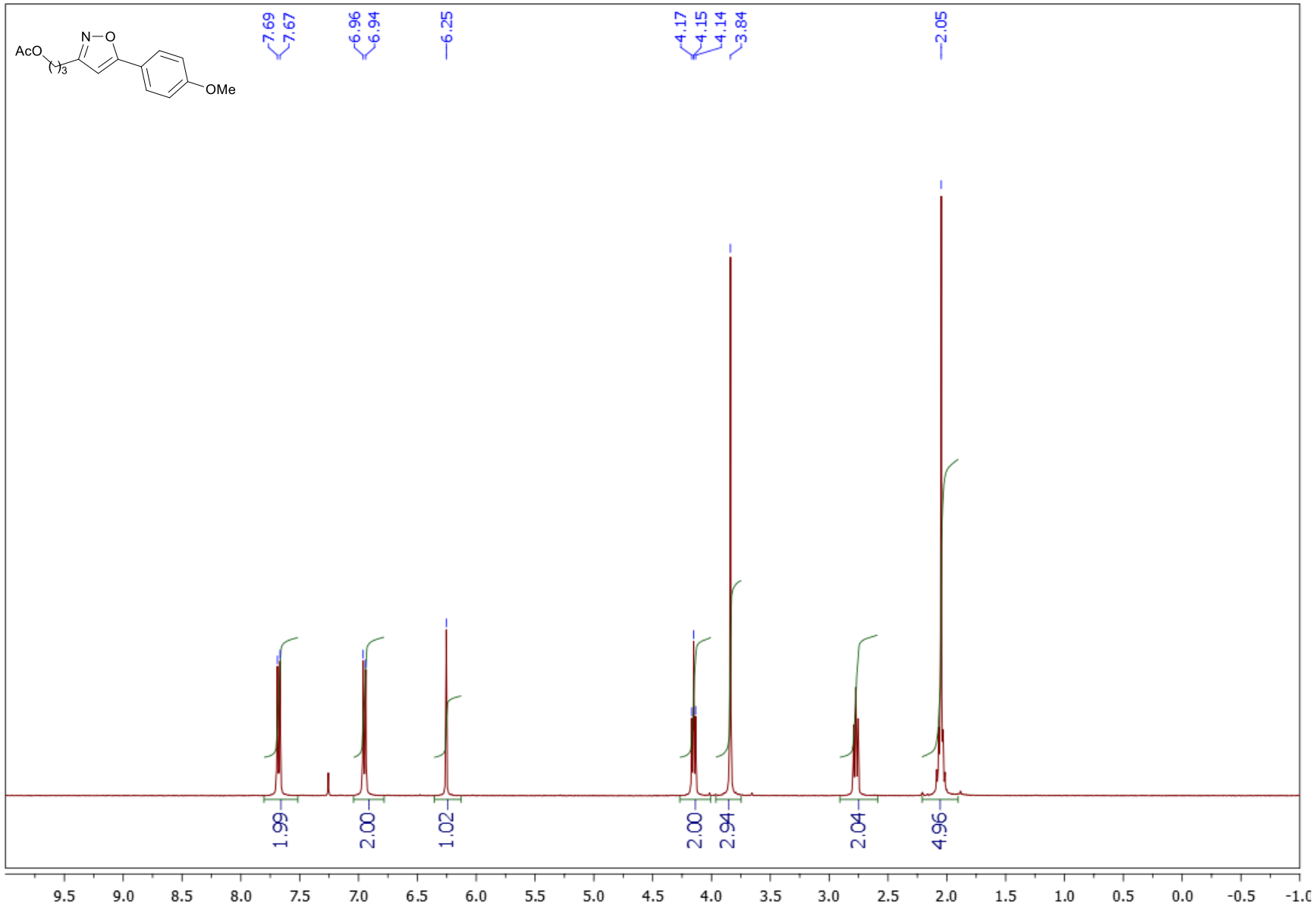
^{1}H-NMR (400 MHz, $CDCl_3$) of compounds **2c**.



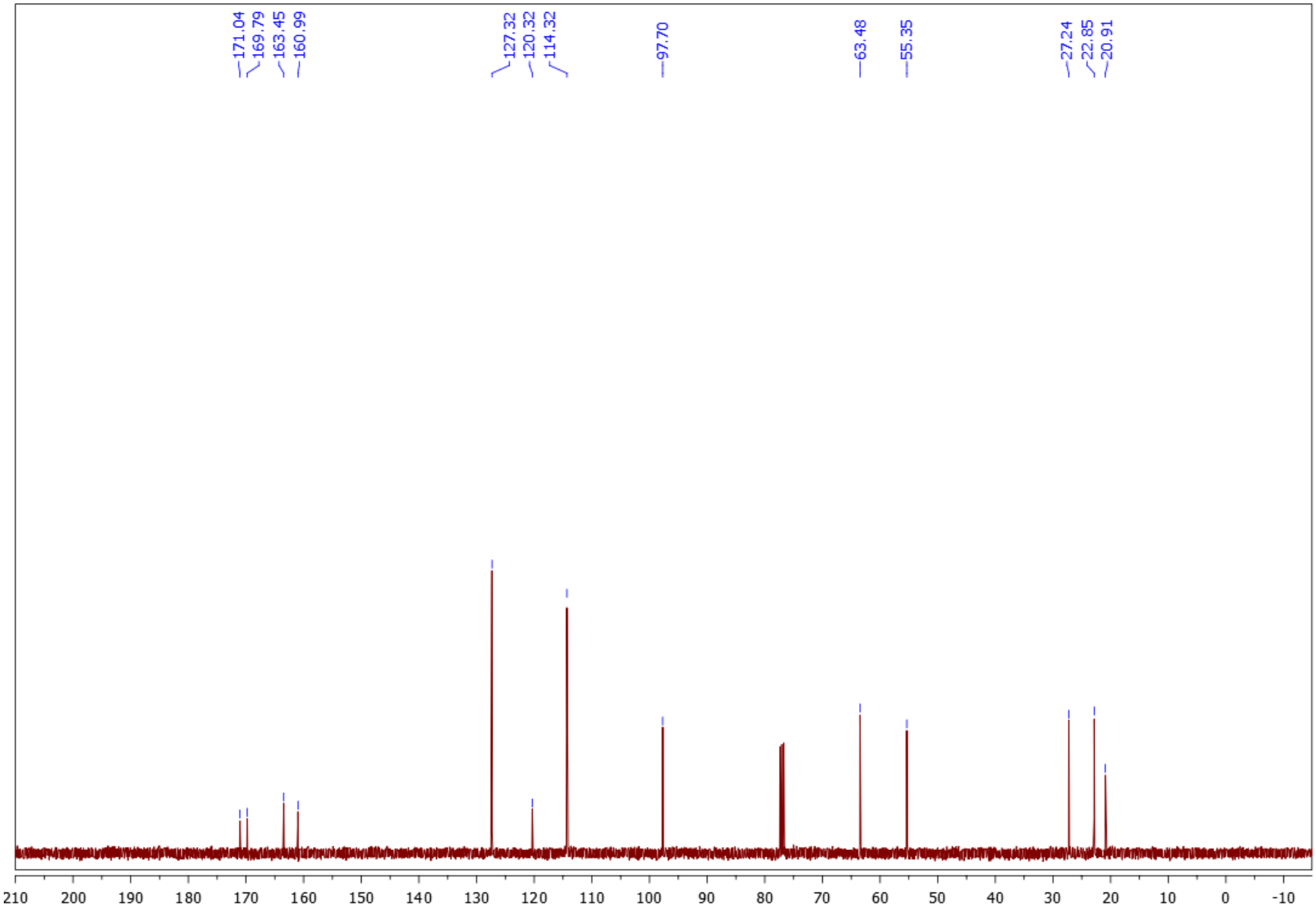
^{13}C-NMR (100 MHz, $CDCl_3$) of compounds **2c**.



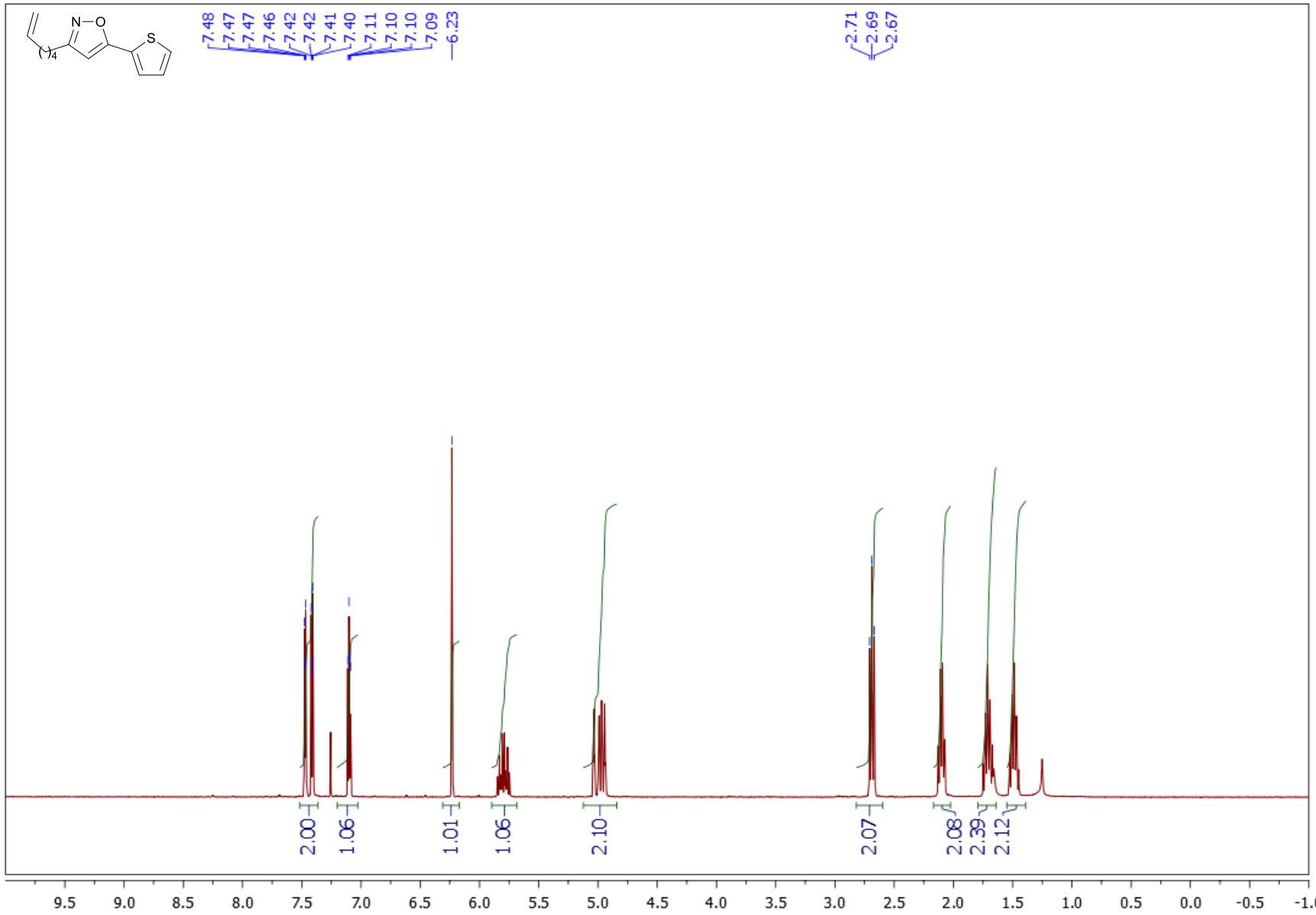
^{1}H-NMR (400 MHz, $CDCl_3$) of compounds **2d**.



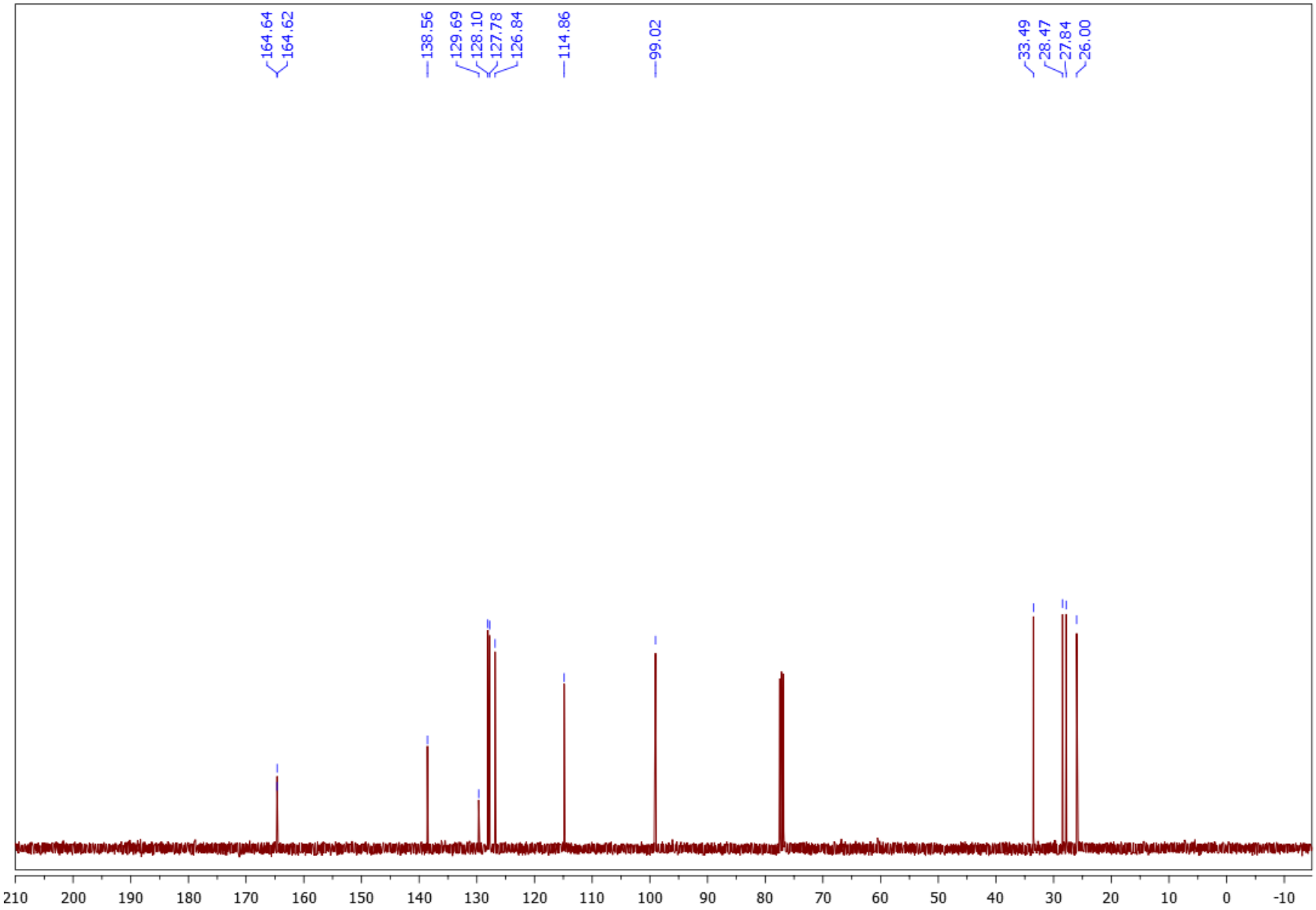
^{13}C-NMR (100 MHz, $CDCl_3$) of compounds **2d**.



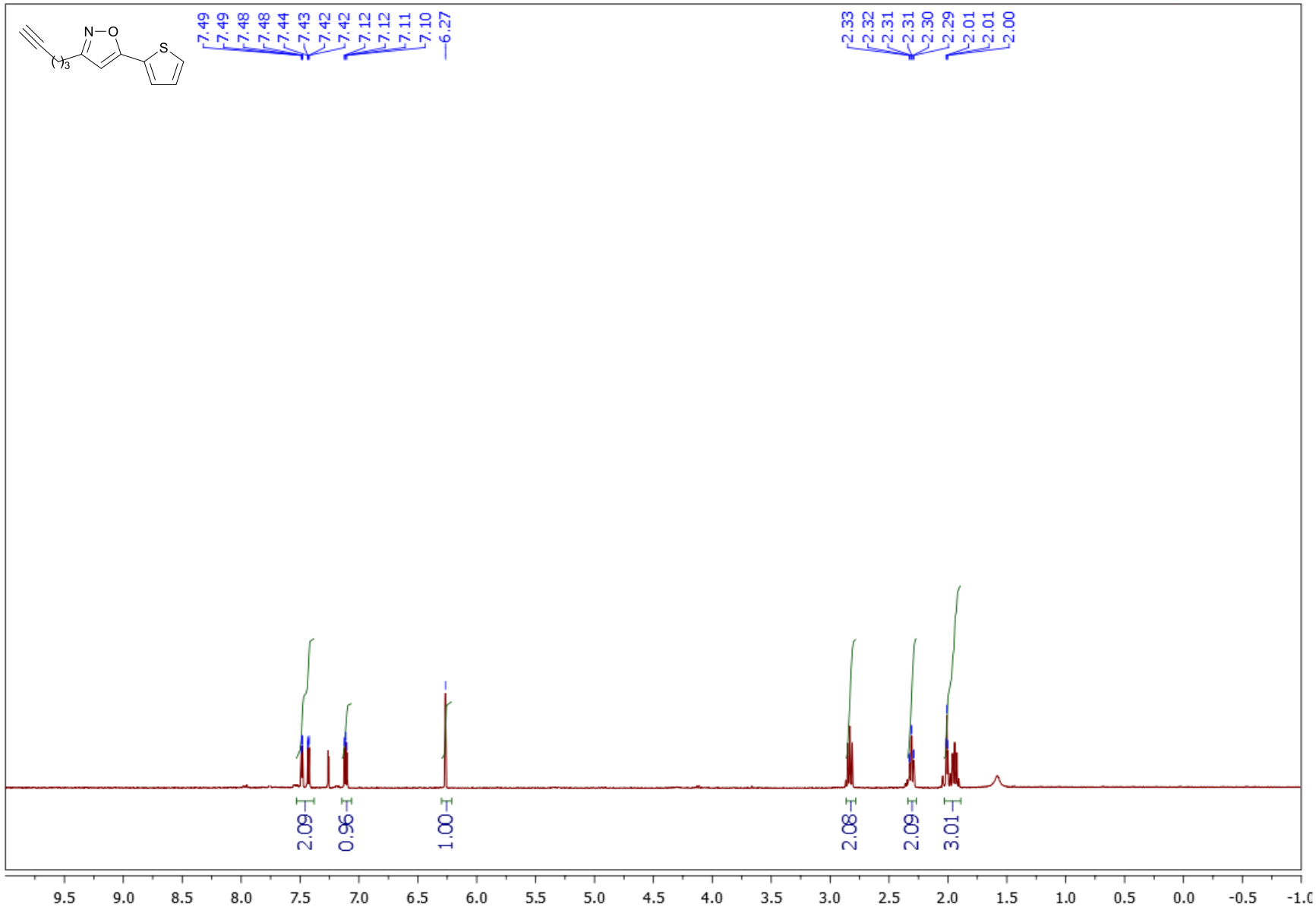
^{1}H-NMR (400 MHz, $CDCl_3$) of compounds **2e**.



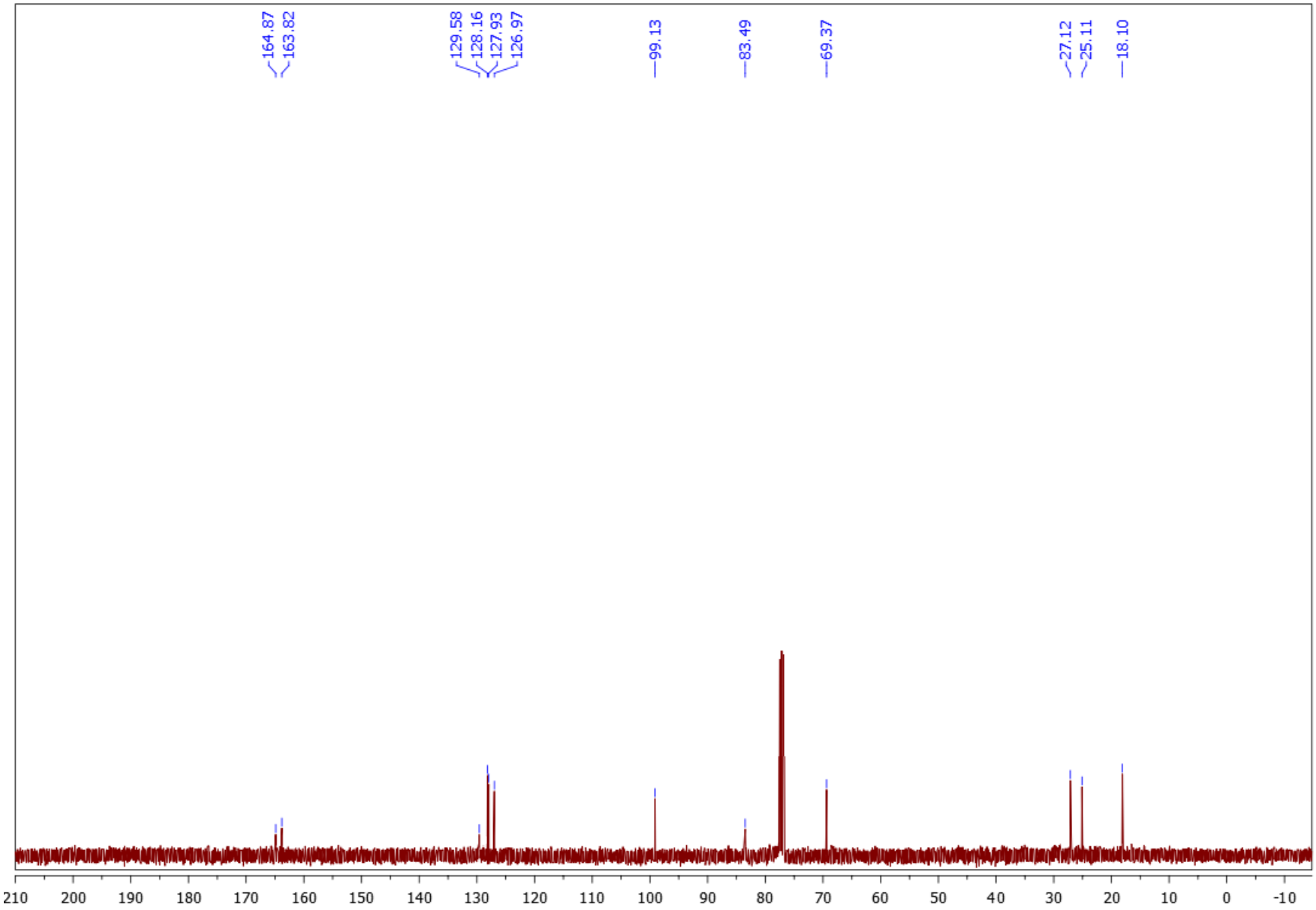
^{13}C-NMR (100 MHz, $CDCl_3$) of compounds **2e**.



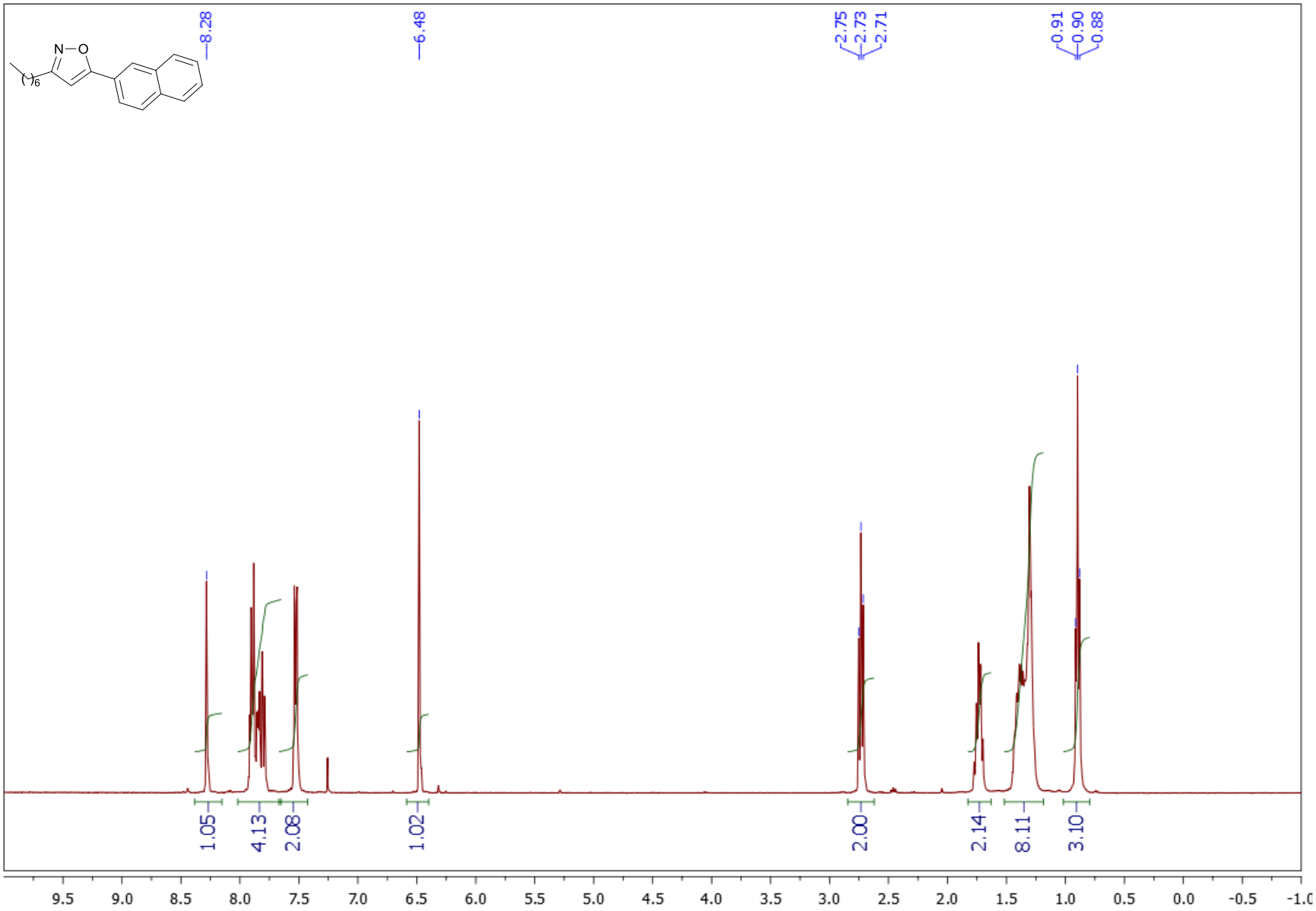
^{1}H-NMR (400 MHz, $CDCl_3$) of compounds **2f**.



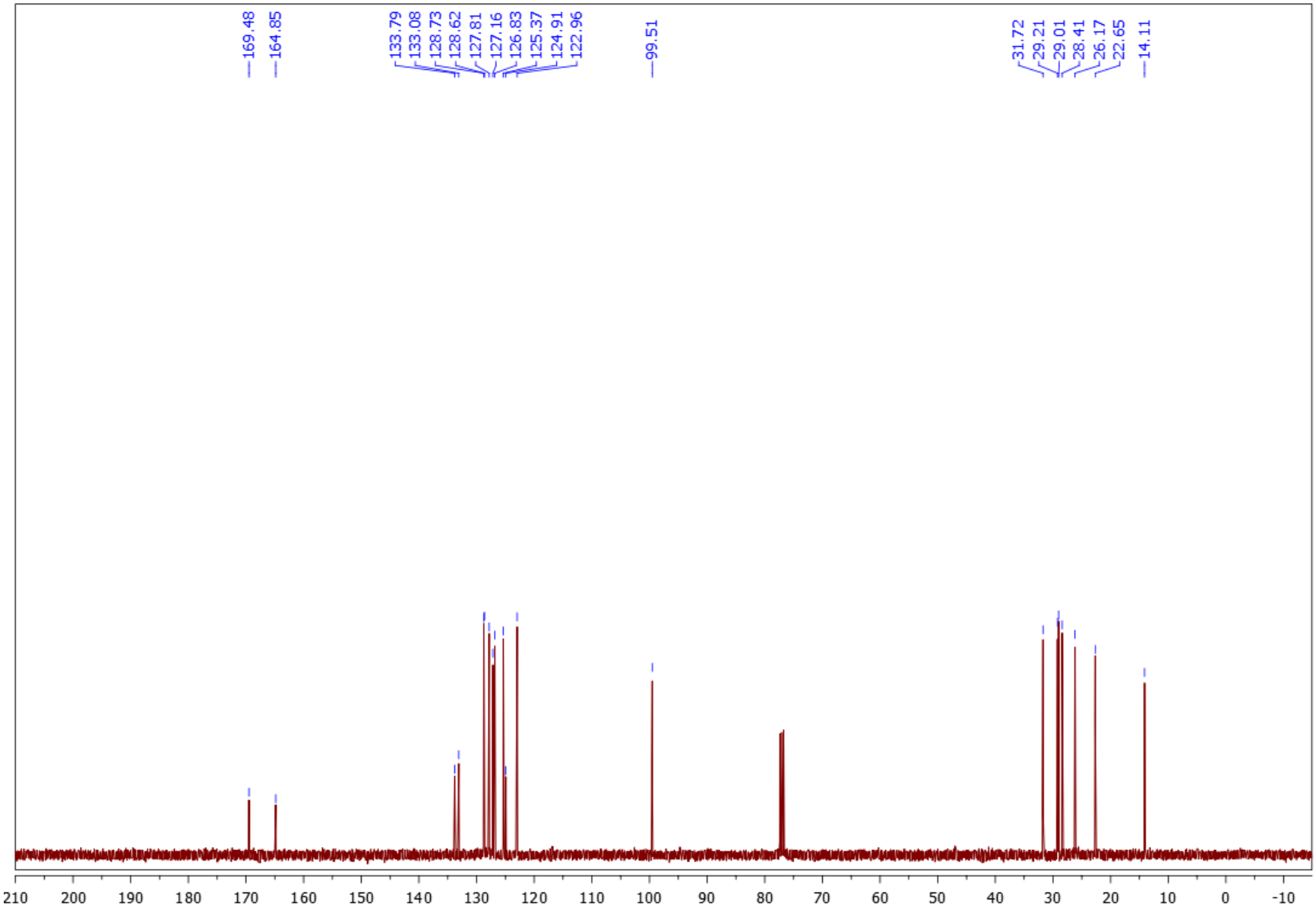
^{13}C-NMR (100 MHz, $CDCl_3$) of compounds **2f**.



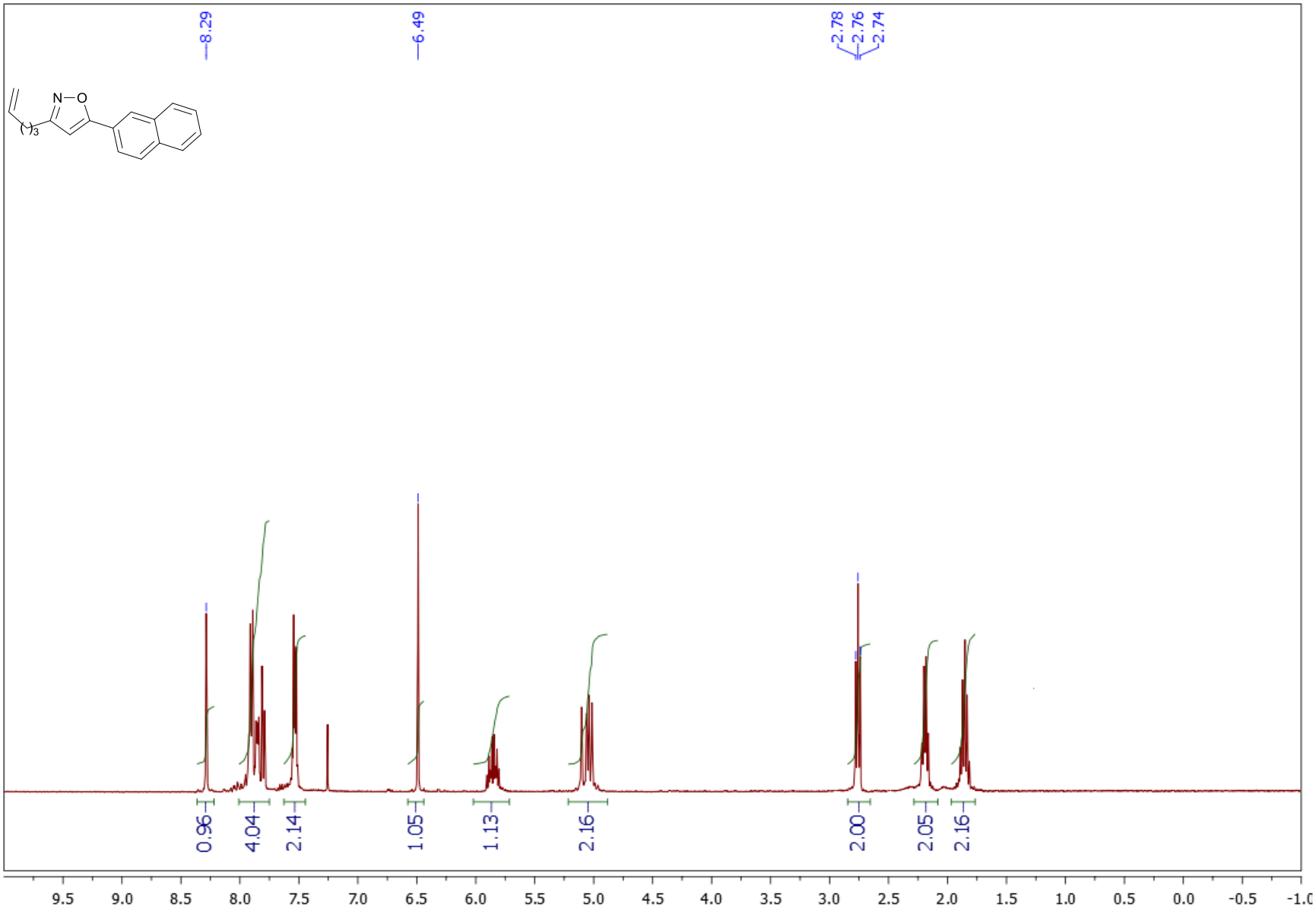
^{1}H-NMR (400 MHz, $CDCl_3$) of compounds **2g**.



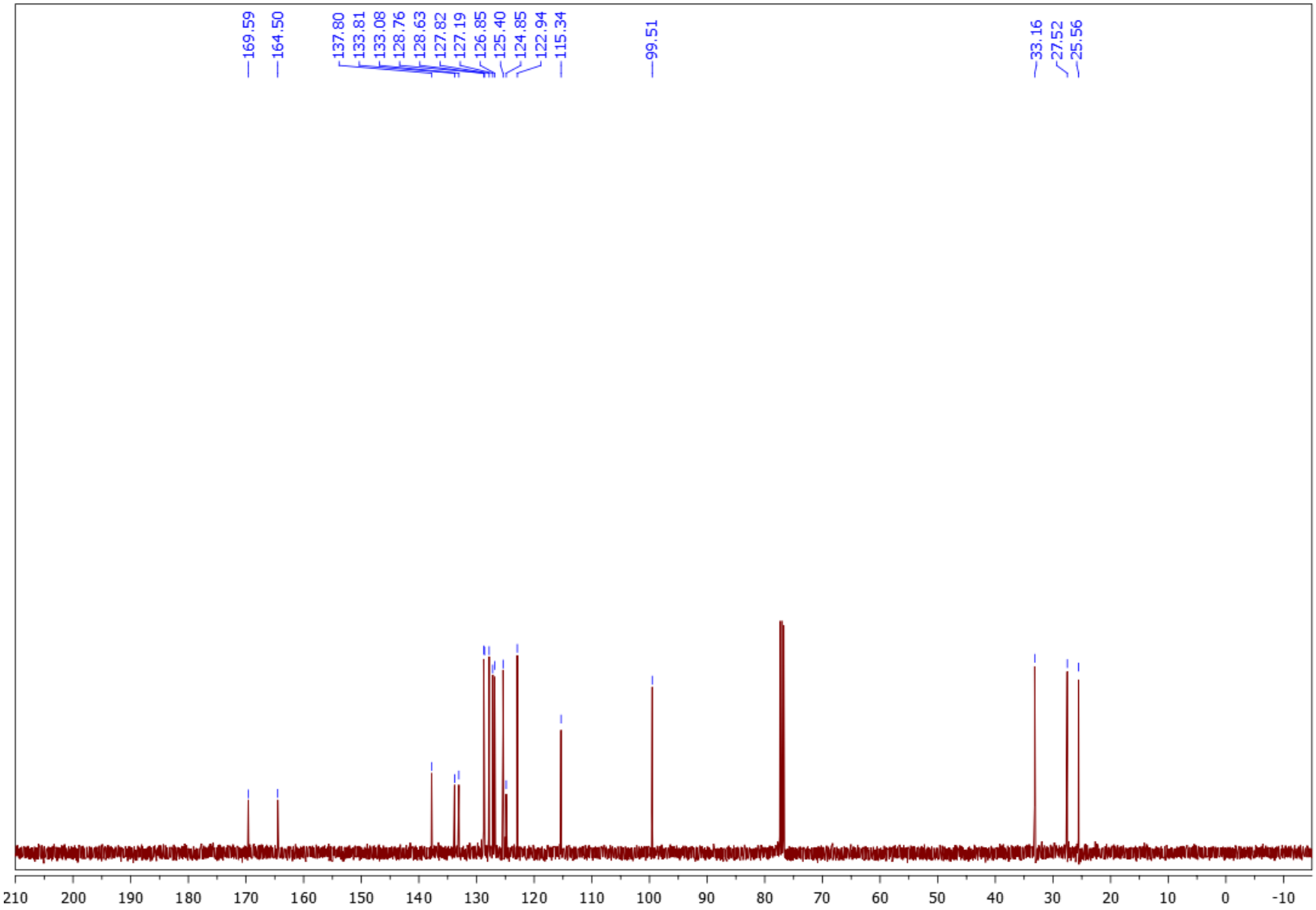
^{13}C-NMR (100 MHz, $CDCl_3$) of compounds **2g**.



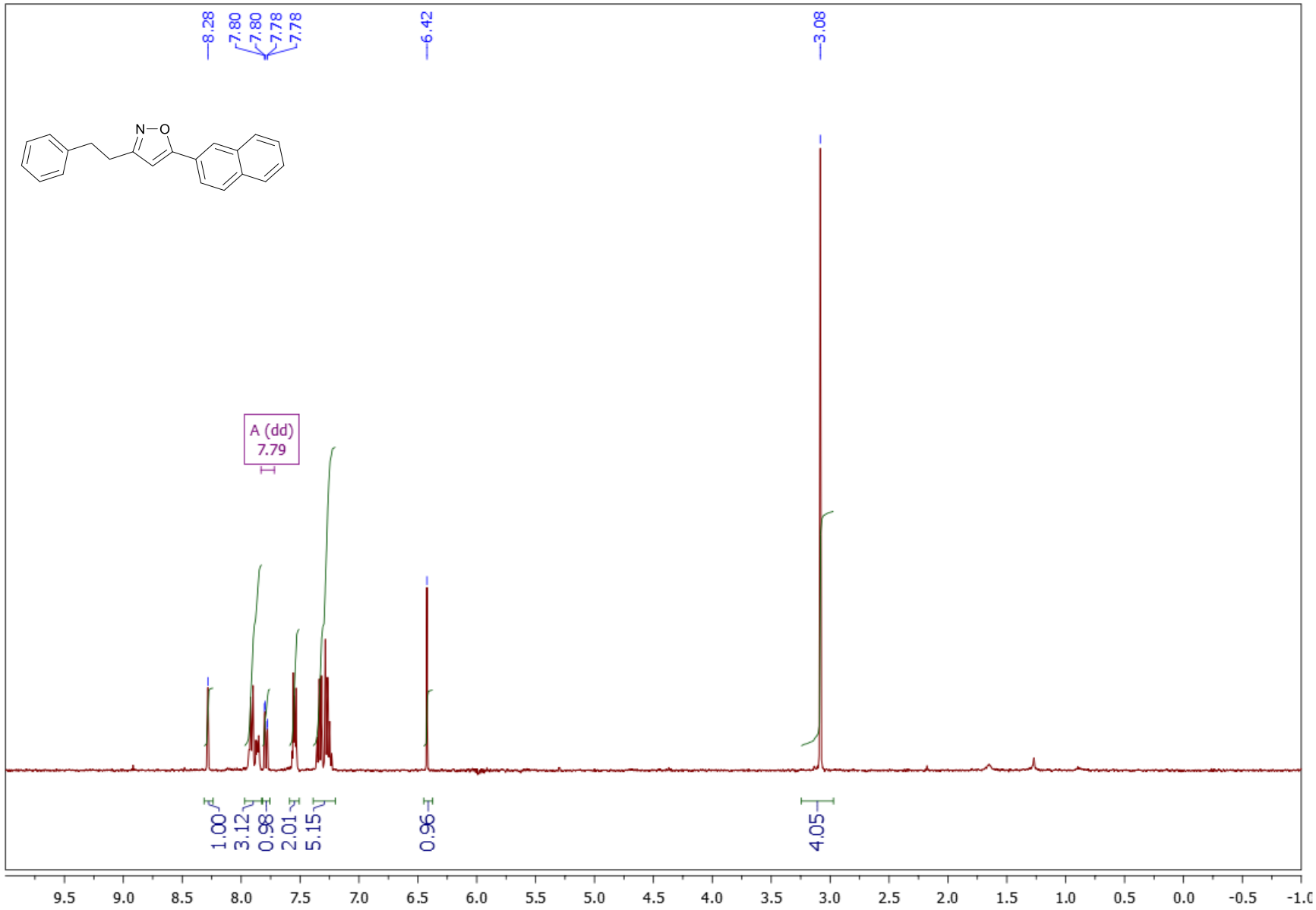
^{1}H-NMR (400 MHz, $CDCl_3$) of compounds **2h**.



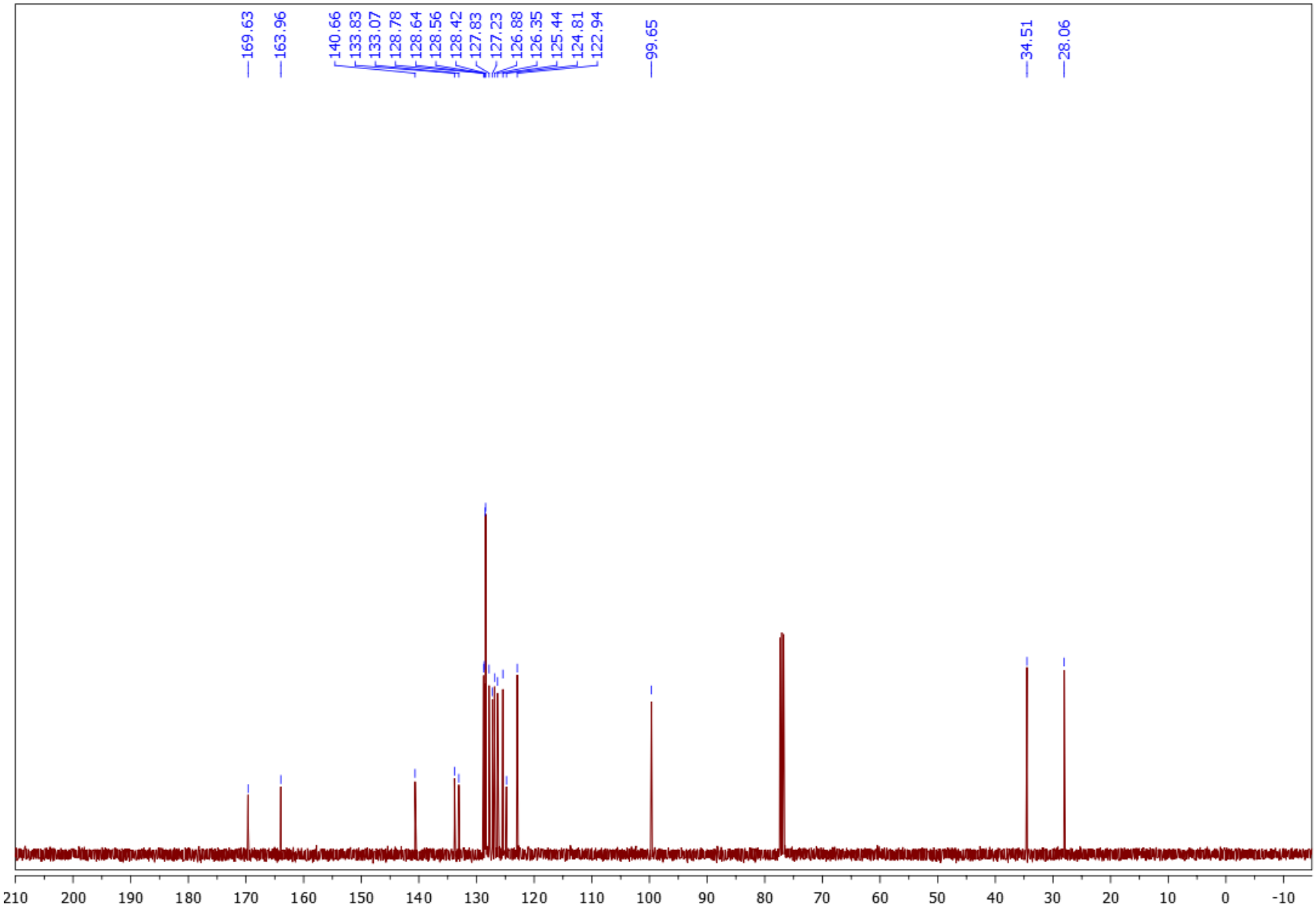
^{13}C-NMR (100 MHz, $CDCl_3$) of compounds **2h**.



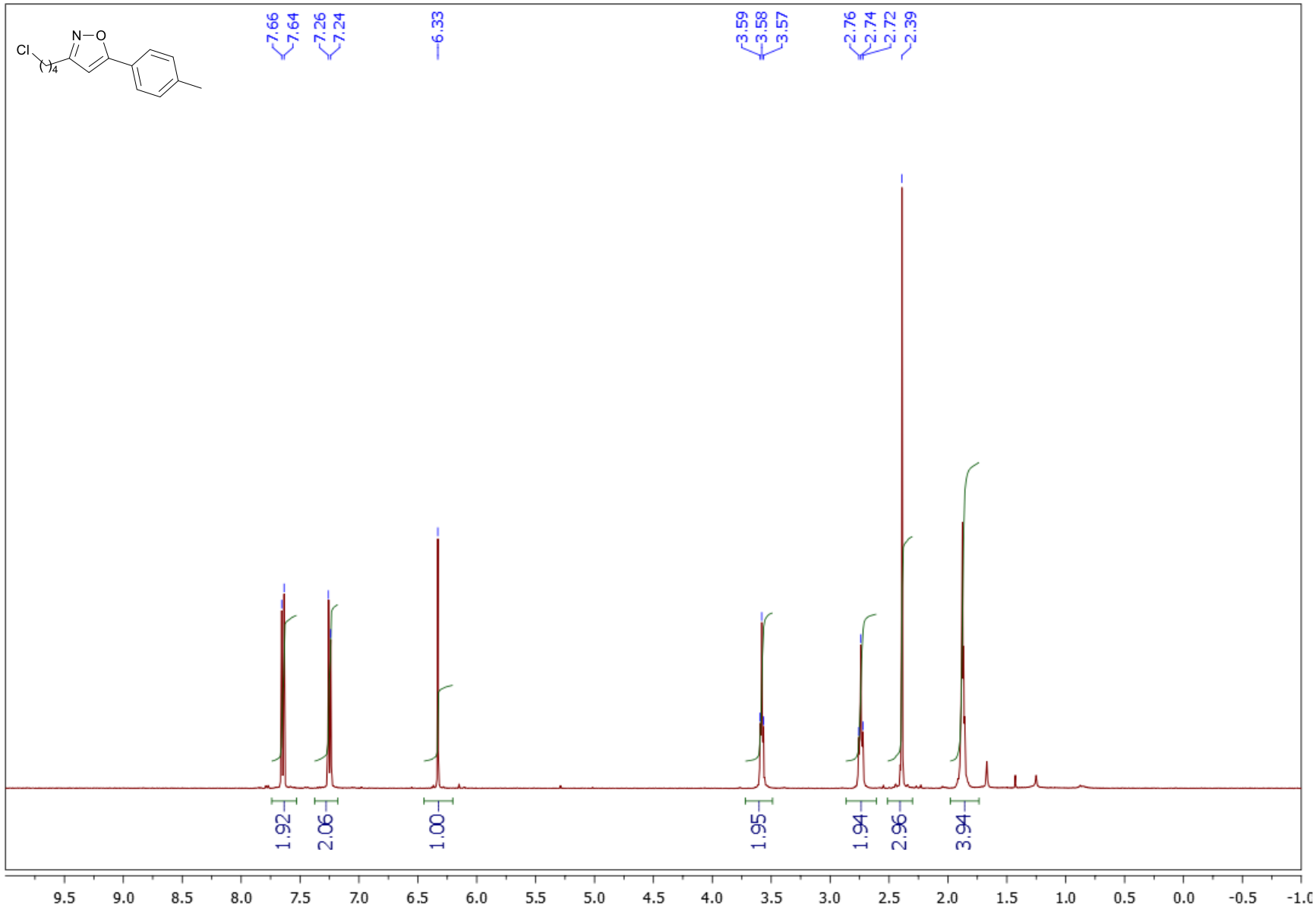
^{1}H-NMR (400 MHz, $CDCl_3$) of compounds **2i**.



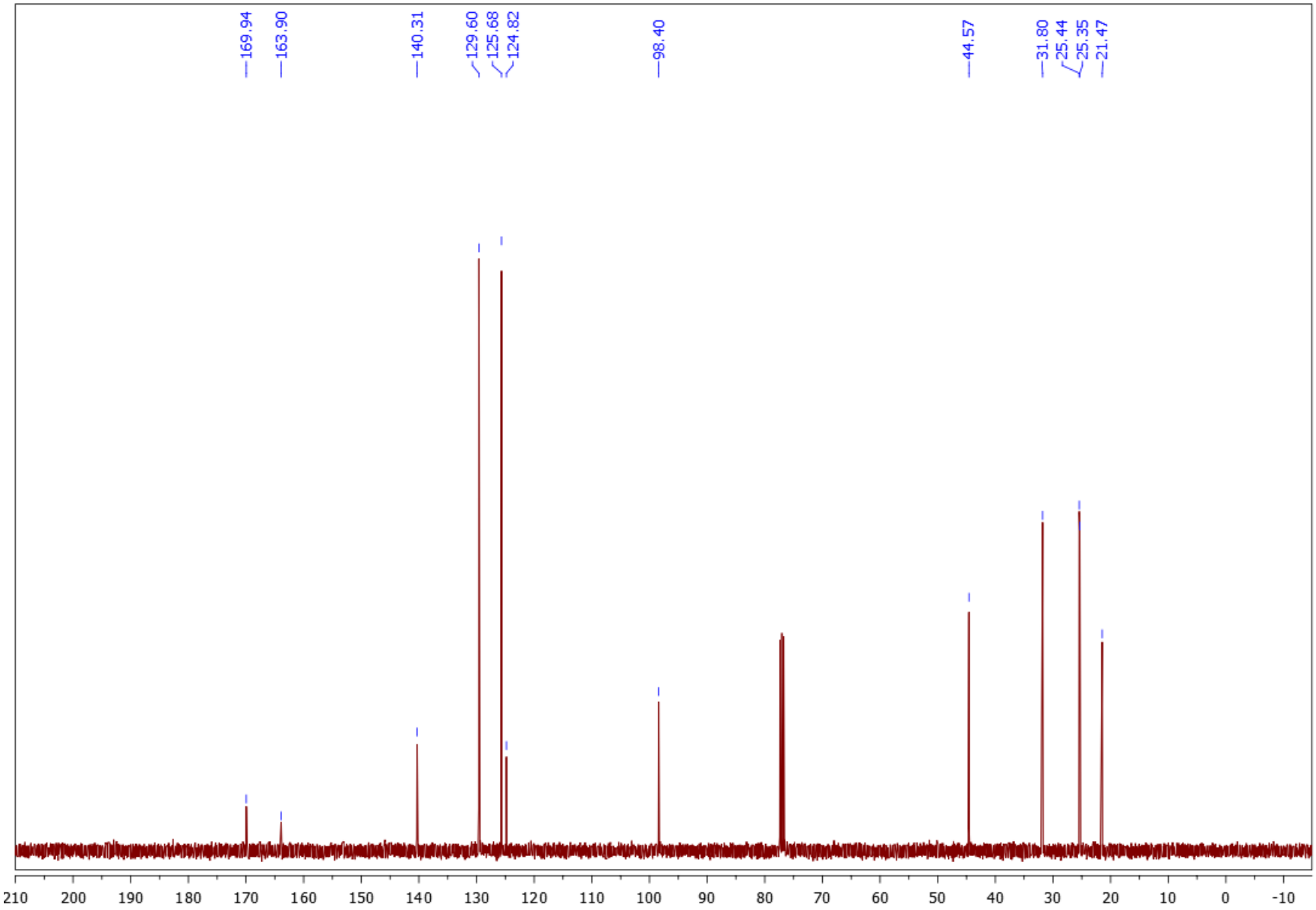
^{13}C-NMR (100 MHz, $CDCl_3$) of compounds **2i**.



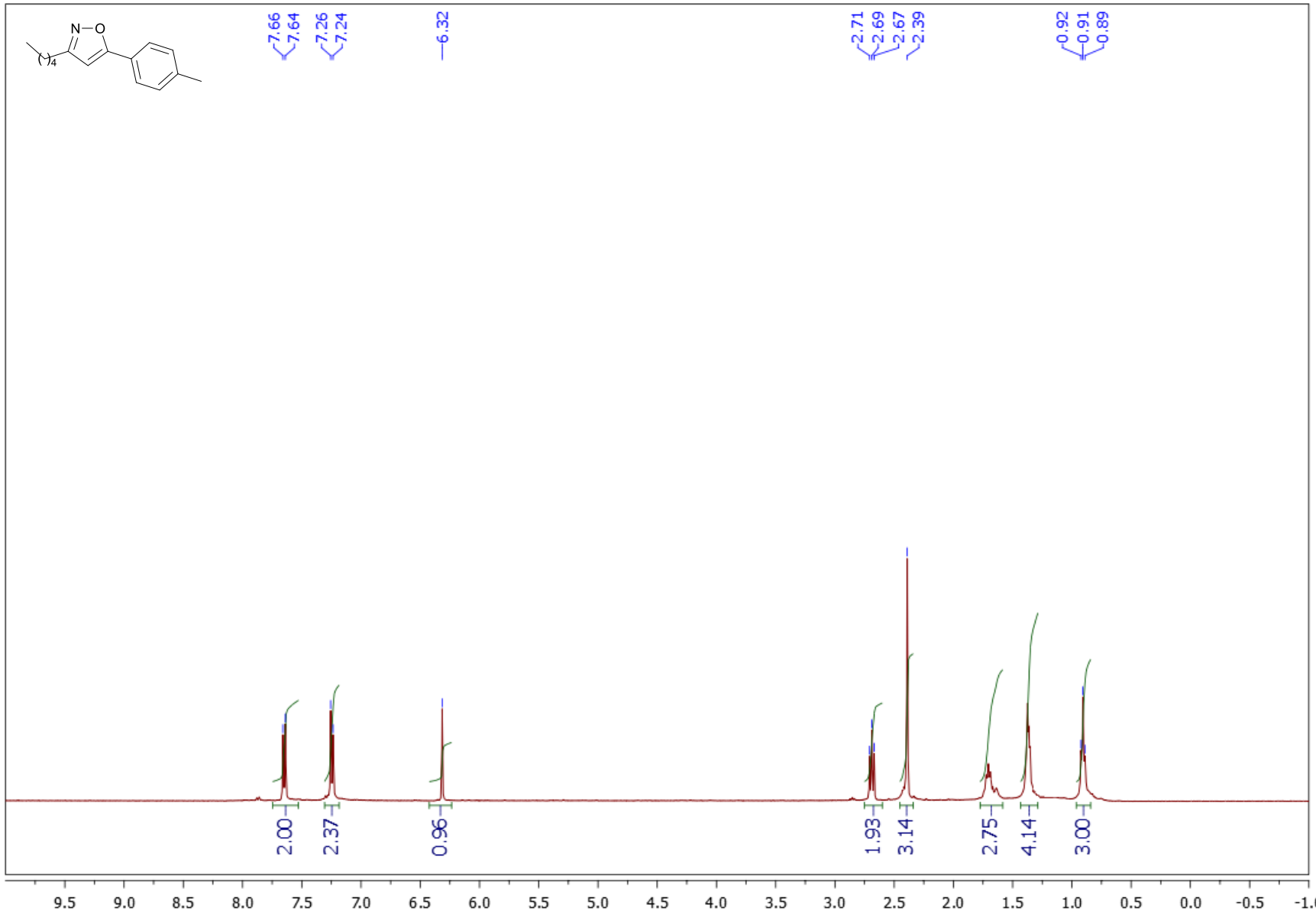
^{1}H-NMR (400 MHz, $CDCl_3$) of compounds **2j**.



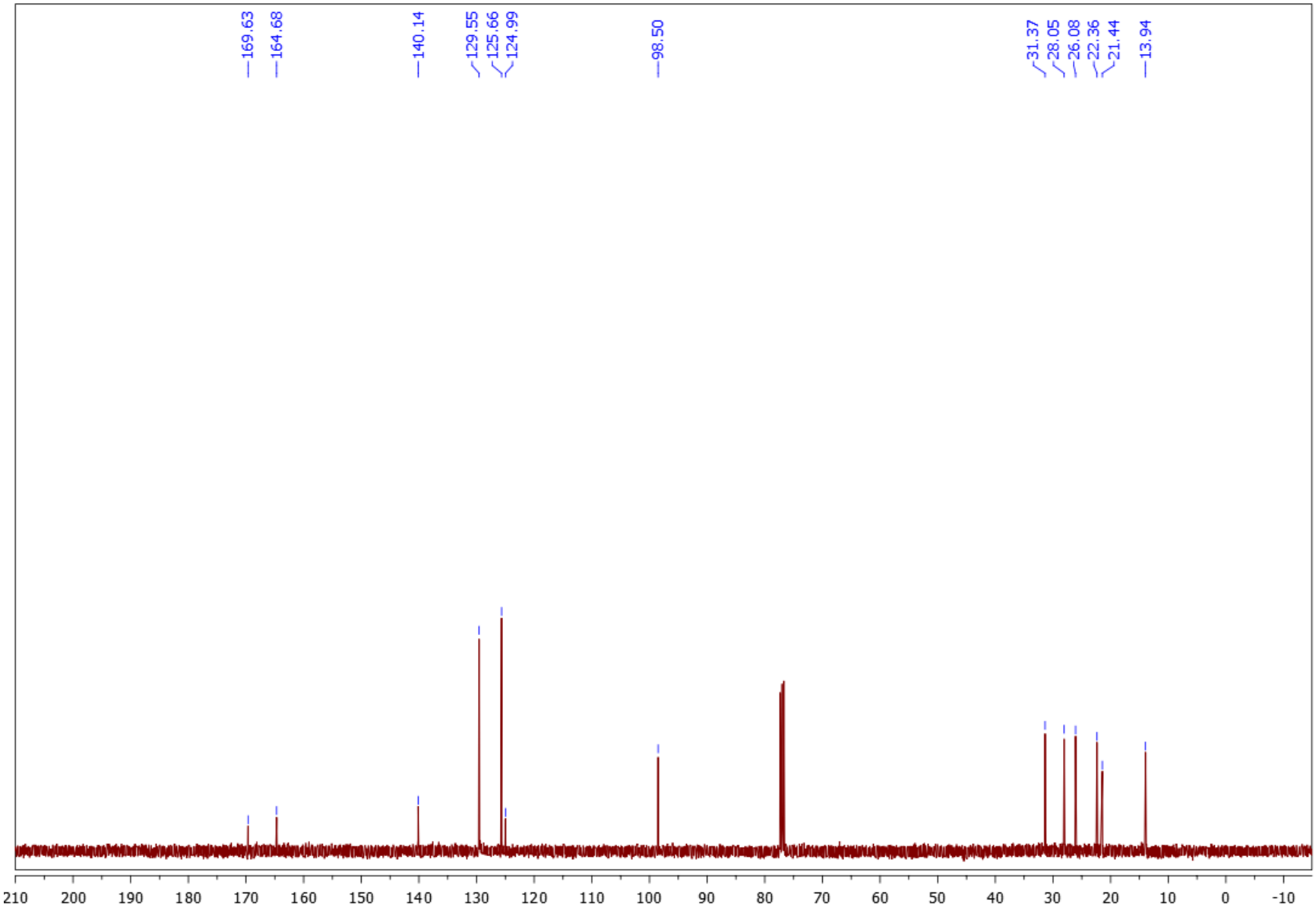
^{13}C-NMR (100 MHz, $CDCl_3$) of compounds **2j**.



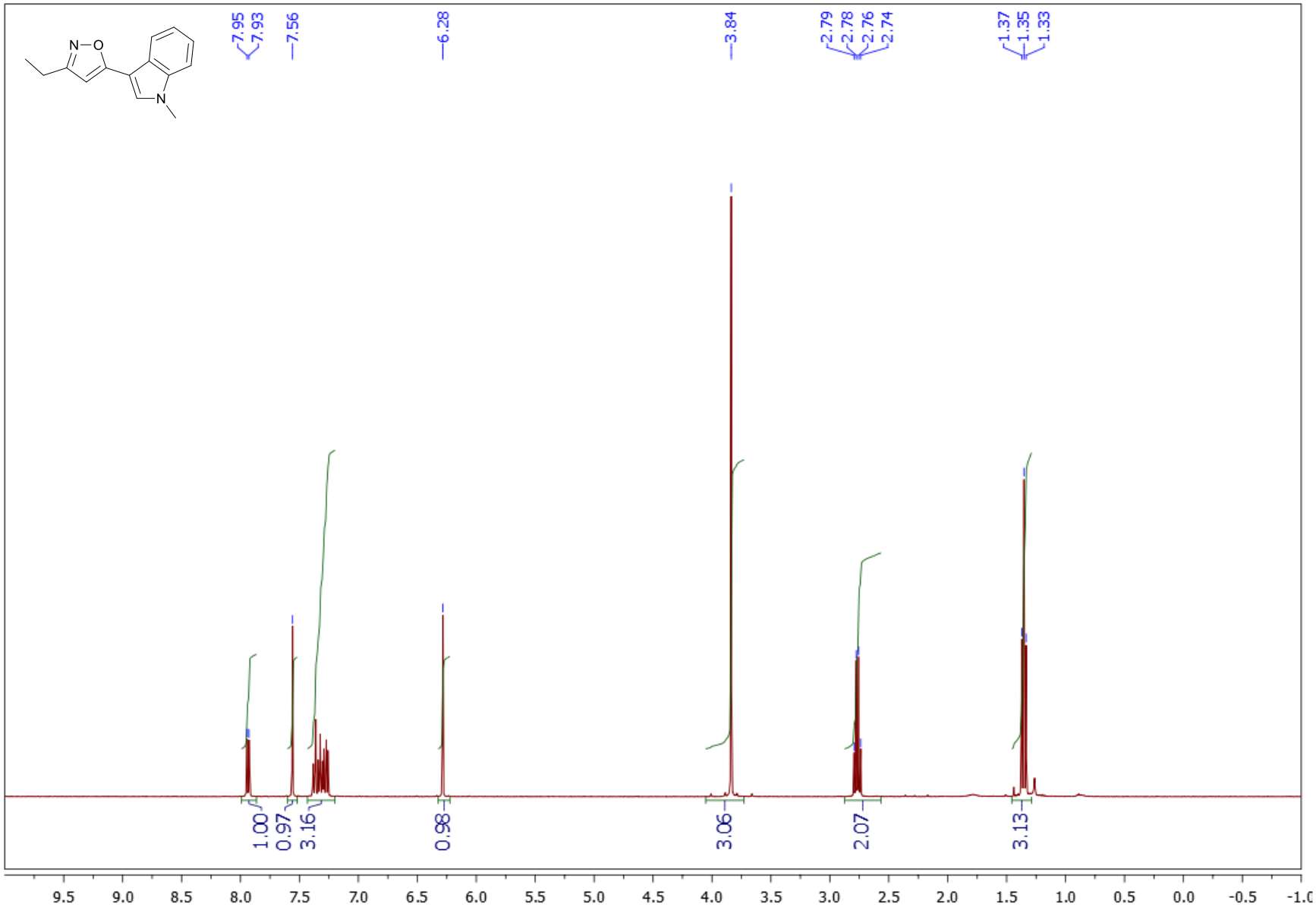
^{1}H-NMR (400 MHz, $CDCl_3$) of compounds **2k**.



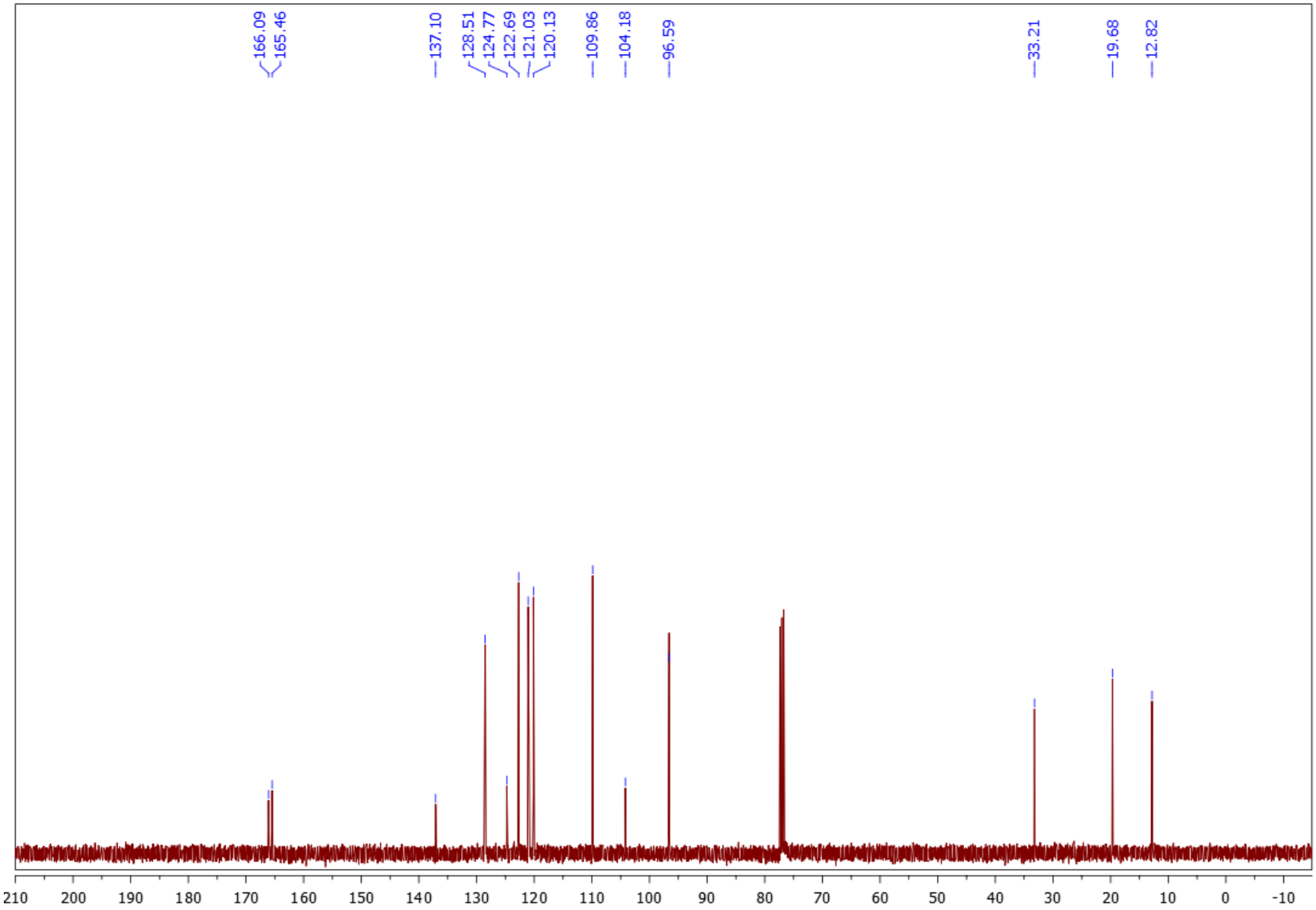
^{13}C-NMR (100 MHz, $CDCl_3$) of compounds **2k**.



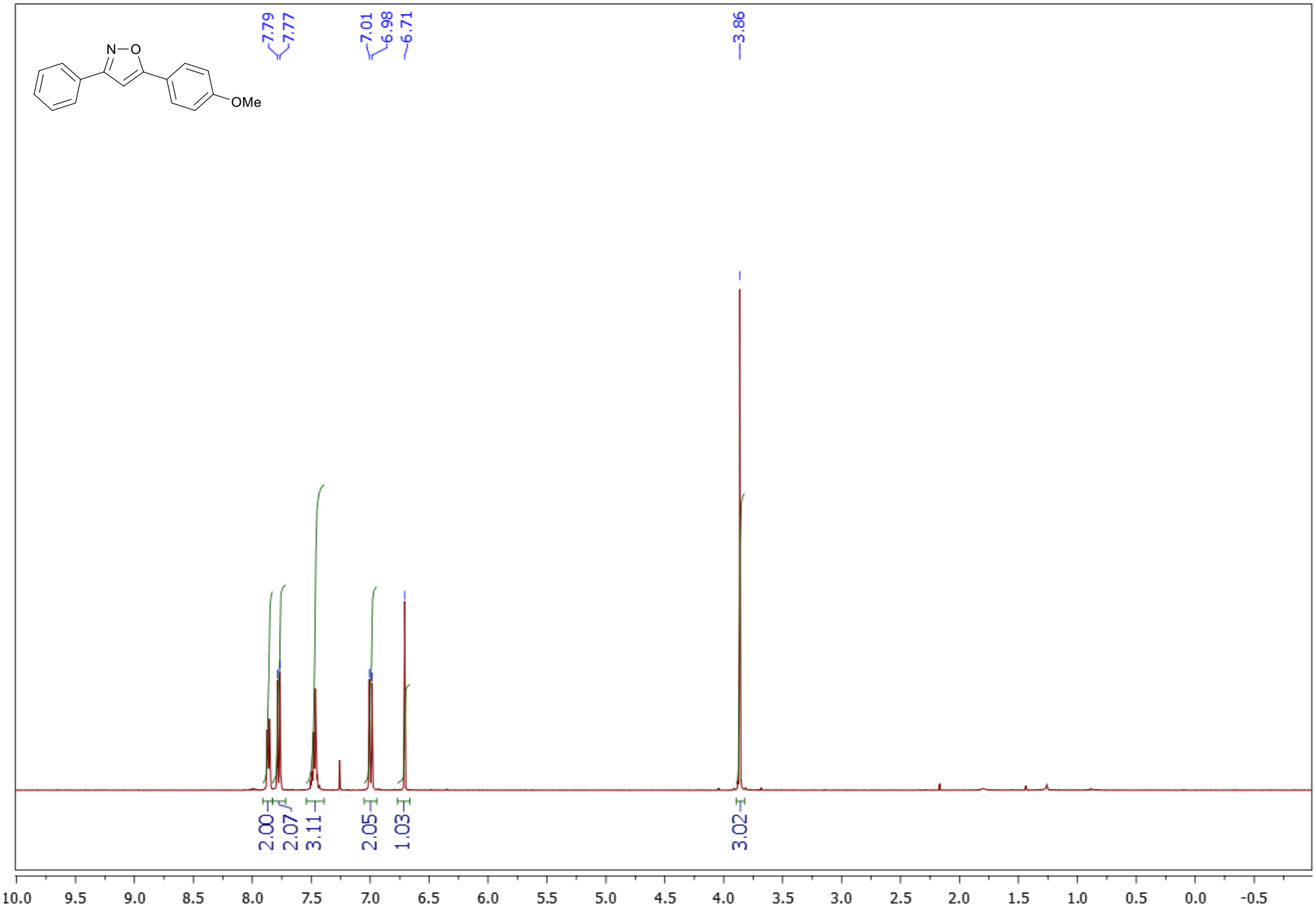
^{1}H-NMR (400 MHz, $CDCl_3$) of compounds **2k**.



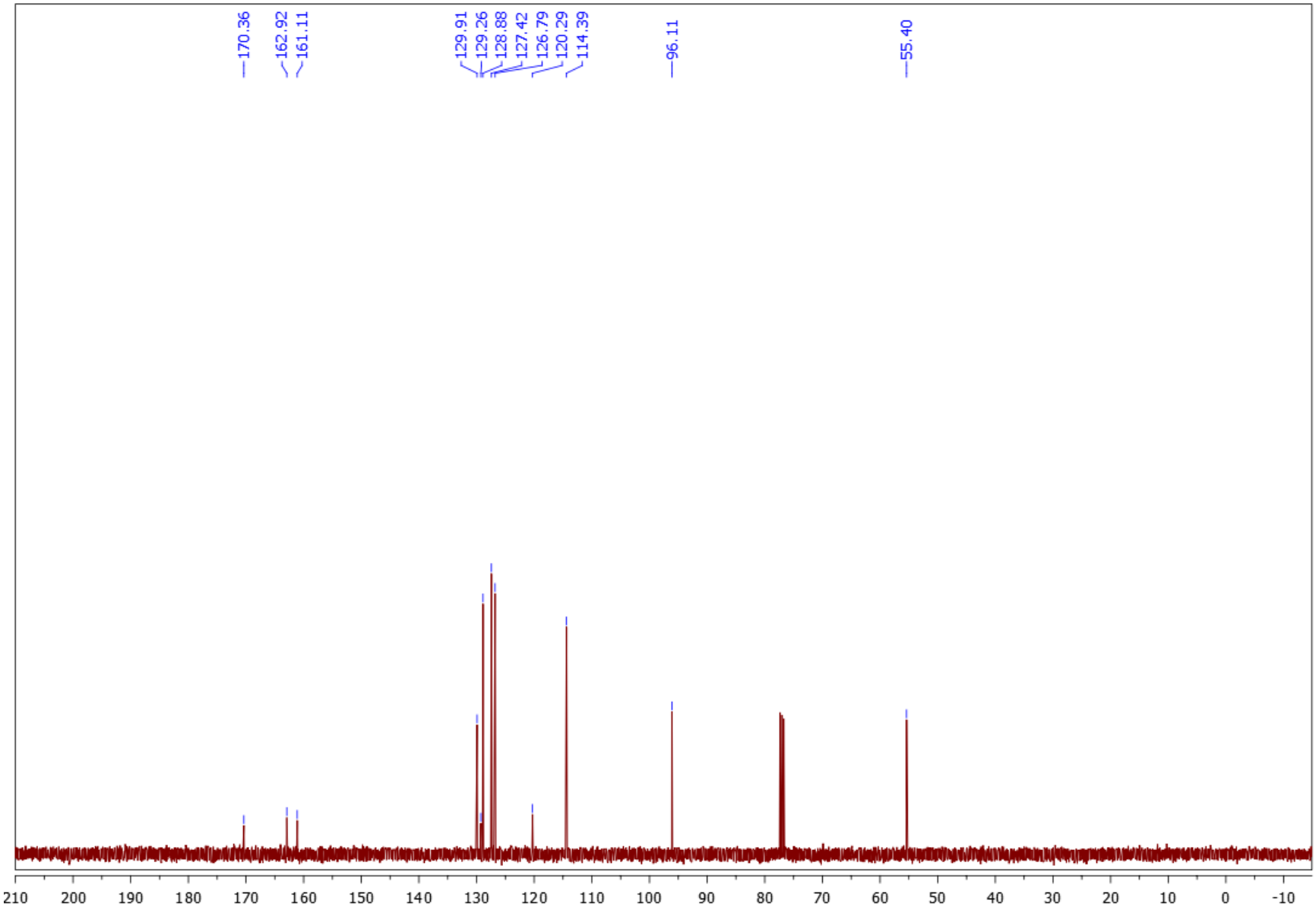
^{13}C-NMR (100 MHz, $CDCl_3$) of compounds **2l**.



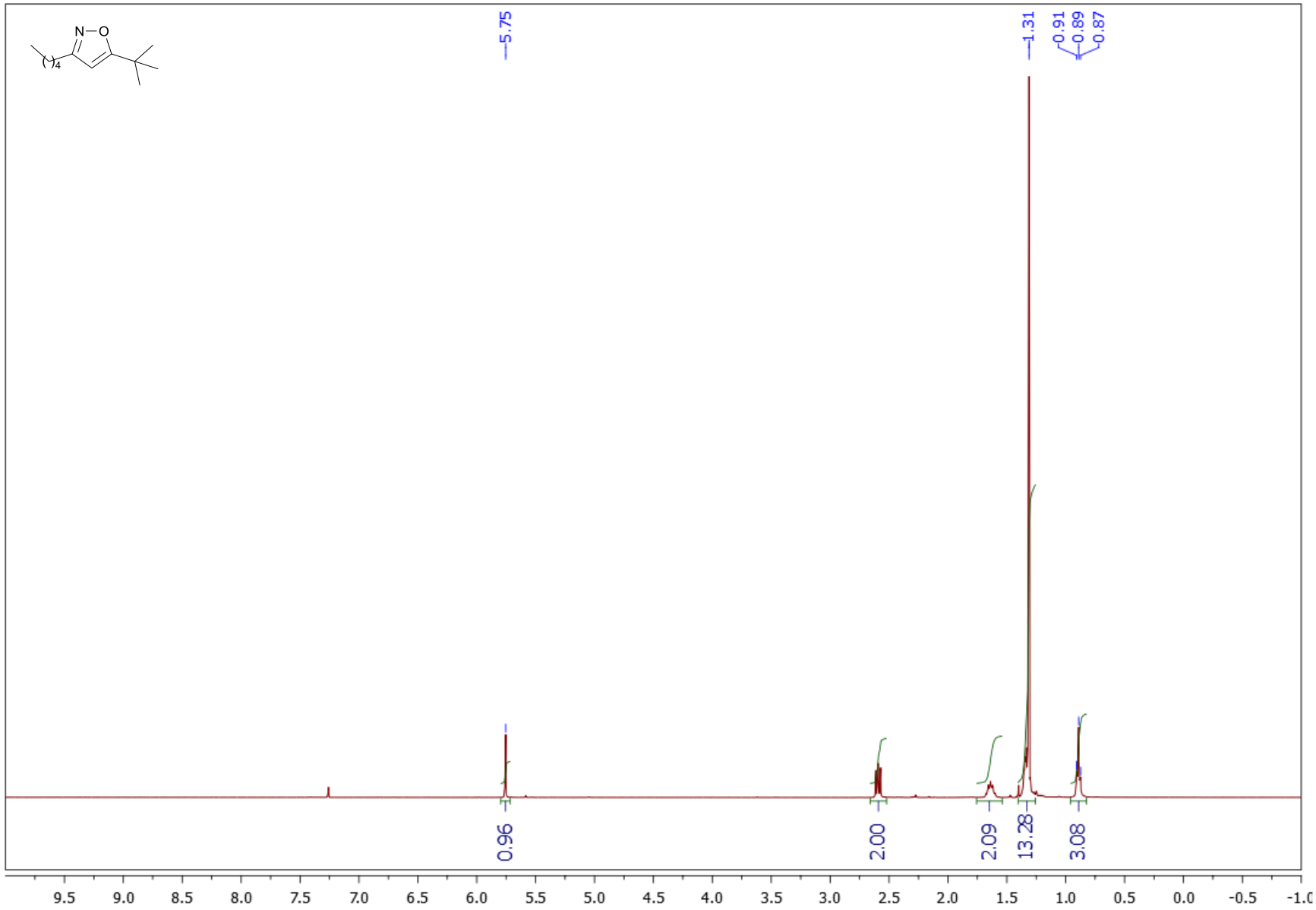
^{1}H-NMR (400 MHz, $CDCl_3$) of compounds **2m**.



^{13}C-NMR (100 MHz, $CDCl_3$) of compounds **2m**.



^{1}H-NMR (400 MHz, $CDCl_3$) of compounds **2n**.



^{13}C-NMR (100 MHz, $CDCl_3$) of compounds **2n**.