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A facile synthesis of 2-ethynylpyrroles by Bu^tOK-assisted room temperature deprotection of 2-(acylethynyl)pyrroles

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Contents

1. Materials and Methods

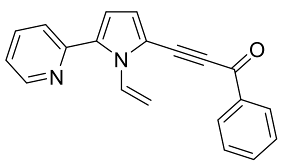
1.1. General Information

IR spectra were obtained on a “Bruker IFS-25” spectrometer (KBr pellets or films in 400-4000 cm^{-1} region). ^{1}H (400.13 MHz), ^{13}C (100.6 MHz) NMR spectra were recorded on a “Bruker Avance 400” instrument in $CDCl_3$. The assignment of signals in the ^{1}H NMR spectra was made using COSY and NOESY experiments. Resonance signals of carbon atoms were assigned based on ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC experiments. The ^{1}H chemical shifts (δ) were referenced to the residual solvent protons (7.26 ppm, $CDCl_3$), the ^{13}C chemical shifts were expressed with respect to the deuterated solvent (77.1 ppm). Coupling constants in hertz (Hz) were measured from one-dimensional spectra and multiplicities were abbreviated as following: br (broad), s (singlet), d (doublet), t (triplet), m (multiplet). The chemical shifts were recorded in ppm. The (C, H, N) microanalyses were performed on a Flash EA 1112 CHNS-O/MAS (CHN Analyzer) instrument. Fluorine content was determined on a SPECOL 11 (Carl Zeiss Jena, Germany) spectrophotometer. Chlorine content was determined by using the titrimetric method. Melting points (uncorrected) were determined with SMP50 Stuart Automatic melting point (Stuart Scientific).

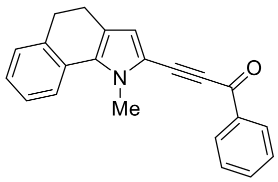
1.2. Synthetic procedures

All acylethynylpyrroles **1a-i** were synthesized by previously described procedure.[S1]

1.2.1. Synthesis of 2-acylethynylpyrroles 1



1-Phenyl-3-[5-(pyridin-2-yl)-1-vinyl-1*H*-pyrrol-2-yl]prop-2-yn-1-one (1c) was obtained accordingly[S1] from 5-(pyridin-2-yl)-1-vinyl-1*H*-pyrrole (170 mg, 1 mmol) and 1-benzoyl-2-bromoacetylene (209 mg, 1 mmol) in the solid Al_2O_3 (3.79 g) for 24 h at room temperature. Yield: 176 mg (59%), yellow oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.68-8.66 (m, 1H, H-3, pyridine), 8.20-8.18 (m, 2H, H*o*, Ph), 7.76-7.72 (m, 1H, H*p*, Ph), 7.62-7.58 (m, 2H, H-4, pyridine, H_x), 7.53-7.49 (m, 3H, H-6, pyridine, H*m*, Ph), 7.24-7.21 (m, 1H, H-5, pyridine), 7.02 (d, J = 3.9 Hz, 1H, H-3, pyrrole), 6.66 (d, J = 3.9 Hz, 1H, H-4, pyrrole), 5.71 (d, J = 15.9 Hz, 1H, H_a), 5.33 (d, J = 8.9 Hz, 1H, H_b); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 177.5, 150.8, 149.5, 137.3, 137.2, 136.7, 133.9, 132.3, 129.5 (2C), 128.7 (2C), 123.4, 123.3, 122.2, 114.7, 112.6, 109.6, 95.2, 87.9; IR (KBr) 2172, 1628, 1584, 1431, 1338, 1313, 1259, 1229, 1173, 1034, 1001, 769 cm^{-1}; Anal. Calcd for $C_{20}H_{14}N_2O$: C, 80.52; H, 4.73; N, 9.39%. Found: C, 80.24; H, 4.51; N, 9.18%.

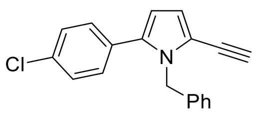


3-(1-Methyl-4,5-dihydro-1*H*-benzo[*g*]indol-2-yl)-1-phenylprop-2-yn-1-one (1e) was obtained accordingly[S1] from 1-methyl-4,5-dihydro-1*H*-benzo[*g*]indole (183 mg, 1 mmol) and 1-benzoyl-2-bromoacetylene (209 mg, 1 mmol) in the solid Al_2O_3 (3.92 g) for 2 h at room temperature. Yield: 233 mg (75%), yellow crystals, mp 130-131 °C; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.20-8.19 (m, 2H, H*o*, Ph), 7.64-7.58 (m, 2H, H-6, H*p*, Ph), 7.54-7.50 (m, 2H, H*m*, Ph), 7.32-7-30 (m, 2H, H-7,9), 7.22-7.18 (m, 1H, H-8), 6.76 (s, 1H, H-3), 4.09 (s, 3H, NMe), 2.89 (t, J = 7.3 Hz, 2H, CH_2), 2.69 (t, J = 7.3 Hz, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 177.2, 138.2, 137.4, 134.7, 133.6, 129.2 (2C), 129.0, 128.7 (3C), 127.0, 126.9, 123.6, 122.1, 118.6, 114.3, 97.3, 89.2, 34.9, 31.0, 22.2; IR (KBr) 2155, 1624, 1575, 1512, 1467, 1445, 1376, 1311, 1261, 1243, 1169, 1031, 1013, 903, 762, 730, 697 cm^{-1}; Anal. Calcd for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.50%. Found: C, 84.51; H, 5.31; N, 4.26%.

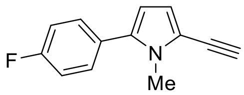
1.2.2. Synthesis of 2-ethynylpyrroles 2a-f. General procedure

2-(Acylethynyl)pyrrole **1a-i** (1 mmol) was dissolved in dry THF (4 mL), and then Bu^{t}OK (224 mg, 2 mmol) was added in portions under nitrogen. The reaction mixture was stirred at room temperature for 1 hour, while in the meantime it turned into an orange suspension. Then the mixture was diluted with cold (0-5 °C) water (30 mL) and extracted with cold (0-5 °C) *n*-hexane (3×10 mL). The combined organic extracts were washed with water (3×5 mL) and dried over Na_2SO_4. The residue, after removing the solvent, was purified by flash chromatography (dried SiO_2, *n*-hexane) to afford 2-ethynylpyrroles **2a-i**.

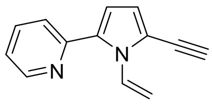
Spectral characteristics of **2g-i** are in accord with those previously published.[S2]



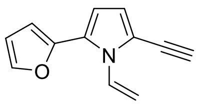
1-Benzyl-2-(4-chlorophenyl)-5-ethynyl-1*H*-pyrrole (2a). Yield: 268 mg (92%), colorless oil; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.28-7.23 (m, 5H, Ph), 7.17-7.15 (m 2H, Ph), 6.95-6.93 (m, 2H, Ph), 6.63 (d, 1H, J = 3.8 Hz, H-4, pyrrole), 6.21 (d, 1H, J = 3.8 Hz, H-3, pyrrole), 5.25 (s, 2H, CH_2), 3.30 (s, 1H, ≡CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.4, 135.5, 133.7, 131.2, 130.2 (2C), 128.7 (2C), 128.7 (2C), 127.3, 126.2 (2C), 116.5, 116.2, 109.6, 82.1, 76.1, 49.0; IR (KBr) 3295, 2924, 2852, 2102, 1539, 1496, 1452, 1416, 1387, 1358, 1321, 1181, 1095, 1015, 833, 768, 727, 694, 573, 510 cm^{-1}; Anal. Calcd for $C_{19}H_{14}ClN$: C, 78.21; H, 4.84; Cl, 12.15; N, 4.80%. Found: C, 78.02; H, 4.60; Cl, 12.41; N, 5.04%.



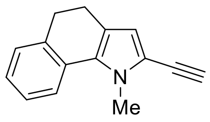
2-Ethynyl-5-(4-fluorophenyl)-1-methyl-1*H*-pyrrole (2b). Yield: 175 mg (88%), colorless oil; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.37-7.33 (m, 2H, 4-F-C_6H_4), 7.13-7.08 (m, 2H, 4-F-C_6H_4), 6.54 (d, 1H, J = 3.8 Hz, H-4, pyrrole), 6.12 (d, 1H, J = 3.8 Hz, H-3, pyrrole), 3.65 (s, 3H, NMe), 3.43 (s, 1H, ≡CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 162.4 (d, J_{CF} = 247.5 Hz, C-4, 4-FC_6H_4), 135.6, 130.6 (d, J_{CF} = 8.5 Hz, C-2,6, 4-FC_6H_4), 129.1 (d, J_{CF} = 3.0 Hz, C-1, 4-FC_6H_4), 116.2, 115.6 (d, J_{CF} = 20.4 Hz, C-3,5, 4-FC_6H_4), 115.5, 108.6, 82.0, 76.4, 33.1; IR (KBr) 3298, 2102, 1601, 1546, 1507, 1462, 1386, 1325, 1225, 1158, 1096, 839, 815, 769, 676, 576, 513 cm^{-1}; Anal. Calcd for $C_{13}H_{10}FN$: C, 78.37; H, 5.06; F, 9.54; N, 7.03%. Found: C, 78.09; H, 5.36; F, 9.35; N, 7.18%.



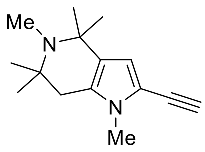
2-(5-Ethynyl-1-vinyl-1*H*-pyrrol-2-yl)pyridine (2c). Yield: 175 mg (90%), colorless oil; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.63-8.61 (m, 1H, H-3, pyridine), 7.70-7.66 (m, 1H, H-4, pyridine), 7.52-7.50 (m, 1H, H-6, pyridine), 7.38 (dd, J = 15.9, 8.9 Hz, 1H, H_x), 7.17-7.14 (m, 1H, H-5, pyridine), 6.64 (d, J = 3.9 Hz, 1H, H-4, pyrrole), 6.52 (d, J = 3.9 Hz, 1H, H-3, pyrrole), 5.62 (d, J = 15.9 Hz, 1H, H_a), 5.10 (d, J = 8.9 Hz, 1H, H_b), 3.43 (s, 1H, ≡CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 151.5, 149.3, 136.5, 134.3, 132.1, 123.1, 121.6, 118.7, 116.4, 111.8, 107.6, 82.9, 76.7; IR (KBr) 3289, 2920, 2850, 2102, 1641, 1586, 1563, 1538, 1483, 1454, 1433, 1398, 1334, 1297, 1230, 1197, 1152, 1091, 1055, 1011, 991, 958, 889, 769, 683 cm^{-1}; Anal. Calcd for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42%. Found: C, 80.71; H, 5.03; N, 14.68%.



2-Ethynyl-5-(furan-2-yl)-1-vinyl-1*H*-pyrrole (2d). Yield: 165 mg (90%), colorless oil; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.45-7.44 (m, 1H, H-5, furan), 6.99 (dd, J = 15.8, 8.8 Hz, 1H, H_x), 6.61 (d, J = 3.8 Hz, 1H, H-4, pyrrole), 6.45-6.42 (m, 2H, H-3,4, furan), 6.38 (d, J = 3.8 Hz, 1H, H-3, pyrrole), 5.62 (d, J = 15.8 Hz, 1H, H_a), 5.15 (d, J = 8.8 Hz, 1H, H_b), 3.42 (s, 1H, ≡CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 146.4, 142.2, 130.9, 126.2, 118.5, 115.0, 111.3, 109.7, 108.7, 108.2, 82.7, 76.4; IR (KBr) 3289, 3121, 2920, 2851, 2361, 2342, 2103, 1644, 1542, 1504, 1454, 1420, 1402, 1372, 1296, 1217, 1159, 1008, 964, 885, 776, 738, 671 cm^{-1}; Anal. Calcd for $C_{12}H_9NO$: C, 78.67; H, 4.95; N, 7.65; O, 8.73%. Found: C, 78.41; H, 5.18; N, 7.91%.



2-Ethynyl-1-methyl-4,5-dihydro-1*H*-benzo[*g*]indole (2e). Yield: 174 mg (84%), colorless oil; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.52-7.50 (m, 1H, H-6), 7.26-7.22 (m, 2H, H-7,9), 7.14-7.09 (m, 1H, H-8), 6.38 (s, 1H, H-3), 3.95 (s, 3H, NMe), 3.48 (s, 1H, ≡CH), 2.85 (t, *J* = 7.3 Hz, 2H, CH_2), 2.63 (t, *J* = 7.3 Hz, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 137.3, 130.6, 129.6, 128.8, 126.7, 125.7, 121.9, 121.1, 116.1, 113.5, 82.6, 76.7, 34.5, 31.2, 22.3; IR (KBr) 3287, 2932, 2841, 2097, 1600, 1507, 1464, 1433, 1375, 1305, 1106, 806, 759, 734, 689 cm^{-1}; Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76%. Found: C, 86.69; H, 6.11; N, 6.51%.



2-Ethynyl-1,4,4,5,6,6-hexamethyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-c]pyridine (2f). Yield: 209 mg (91%), colorless oil; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 6.29 (s, 1H, H-3, pyrrole), 3.49 (s, 3H, 1-NMe), 3.38 (s, 1H, ≡CH), 2.45 (s, 2H, CH_2-7), 2.35 (s, 3H, 5-NMe), 1.29 (s, 6H, 2Me-4), 1.13 (s, 6H, 2Me-6); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 127.4, 125.5, 113.0, 111.7, 81.2, 76.9, 55.4, 54.3, 38.2, 30.8, 29.1, 28.8 (2C), 25.6 (2C). IR (KBr) 3309, 2986, 2929, 2098, 1589, 1462, 1384, 1360, 1266, 1246, 1176, 1135, 1078, 948, 794, 695 cm^{-1}; Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16%. Found: C, 77.95; H, 9.87; N, 12.01%.

1.3. Computational details

The Gibbs free energies, G, for each of the products and reactants, were obtained as sums of the total energy and the thermochemical correction (including all temperature-dependent contributions to G for T = 298.15 K) calculated using the B2PLYP[S3] and B3LYP[S4,S5] functionals, respectively, in combination with the 6-311G** basis set.[S6] The molecular geometries were optimized at the B3LYP/6-311G** level of theory and the solvent (THF) was treated at the level of the C-PCM model.[S7,S8] This computational scheme (referred to as B2PLYP/6-311G**//B3LYP/6-311G** + C-PCM) proved to be very useful in our previous studies (see, *e.g.*, Ref. S9 where also further details justifying its use could be found). All computations were performed using the Gaussian-09 suite of programs.[S10]

2. References

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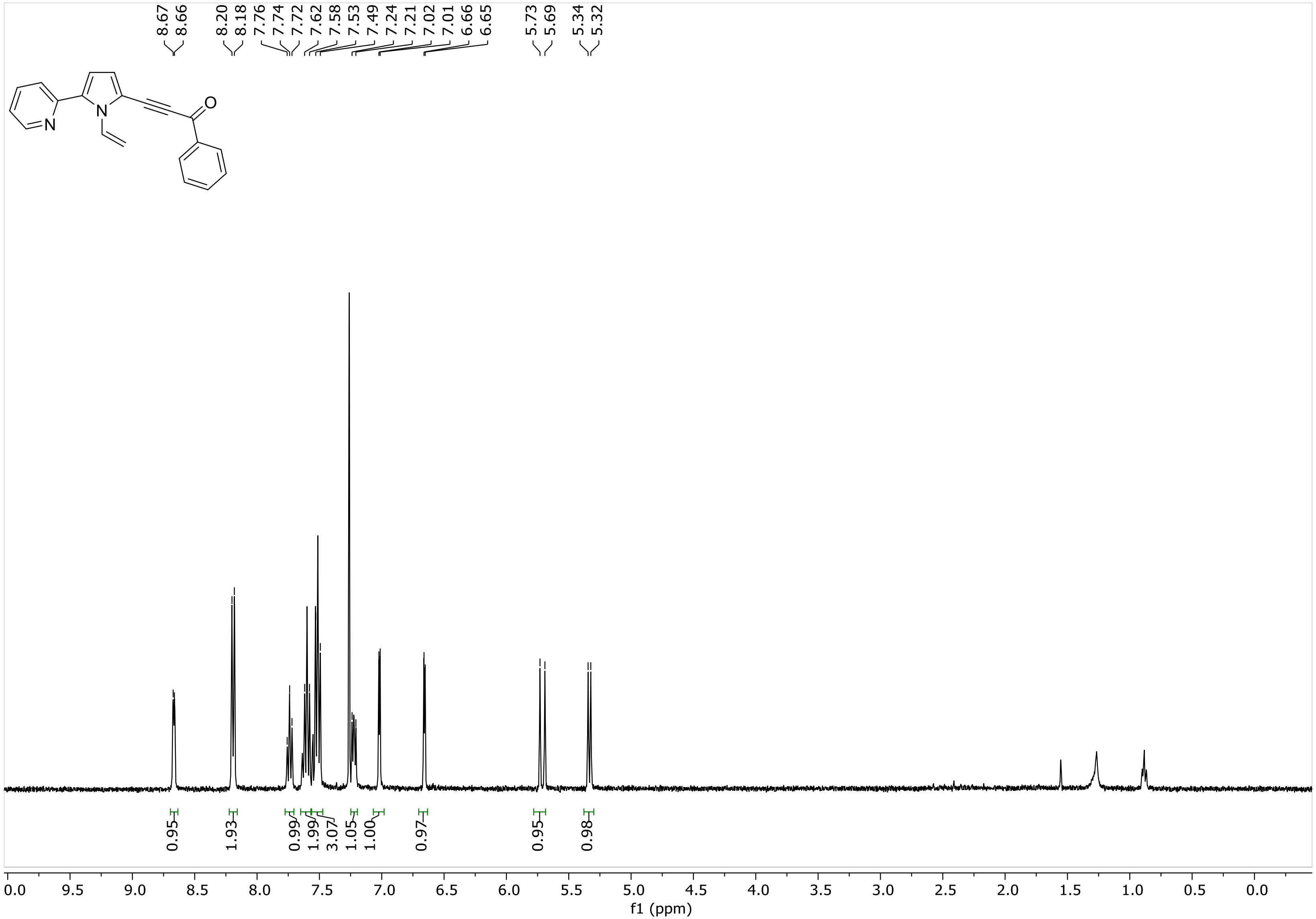
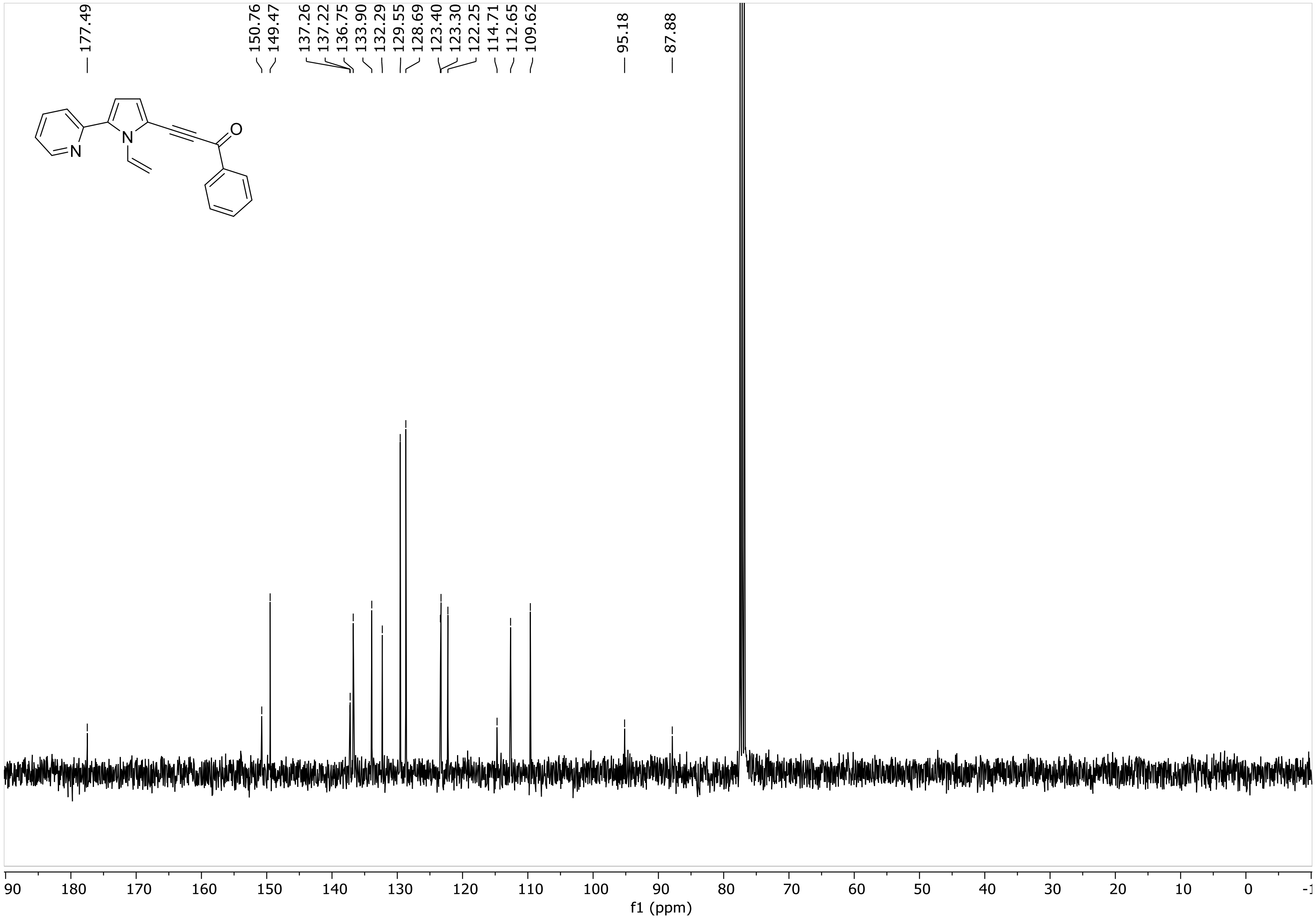
NMR Spectra of synthesized compounds

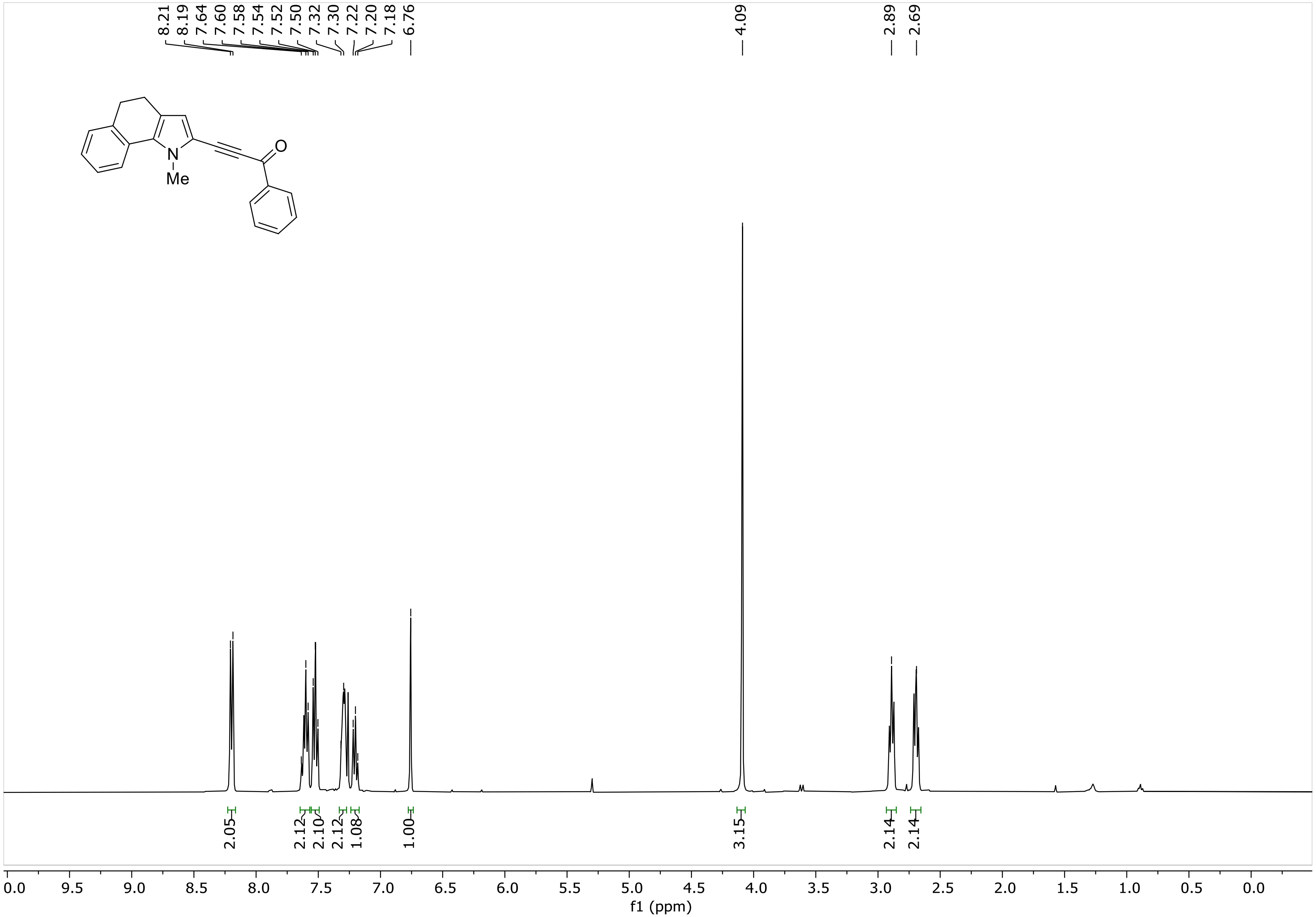
^{1}H NMR spectrum of 1-phenyl-3-[5-(pyridin-2-yl)-1-vinyl-1*H*-pyrrol-2-yl]prop-2-yn-1-one (**1c**) in $CDCl_3$



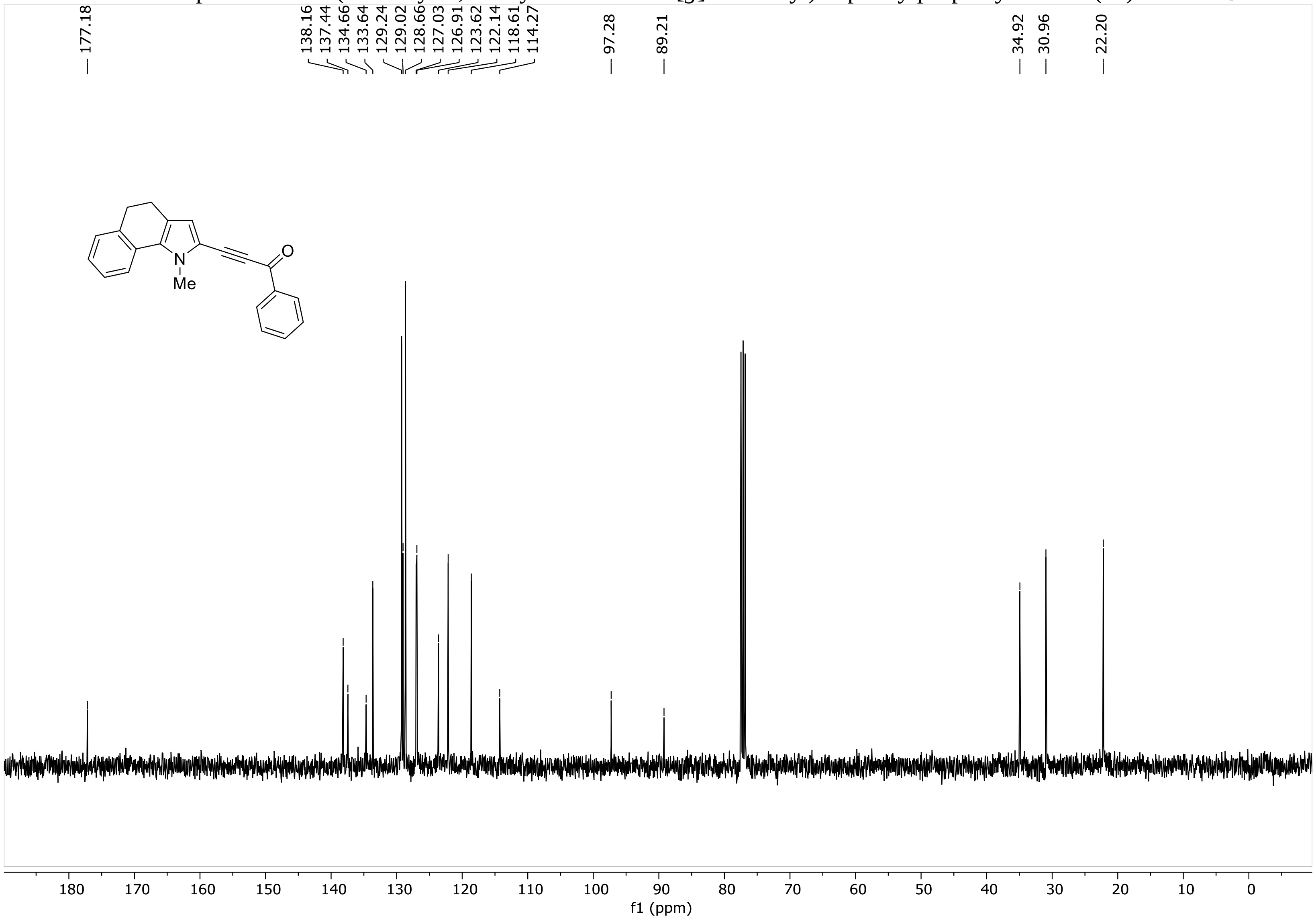
^{13}C NMR spectrum of 1-phenyl-3-[5-(pyridin-2-yl)-1-vinyl-1*H*-pyrrol-2-yl]prop-2-yn-1-one (**1c**) in $CDCl_3$



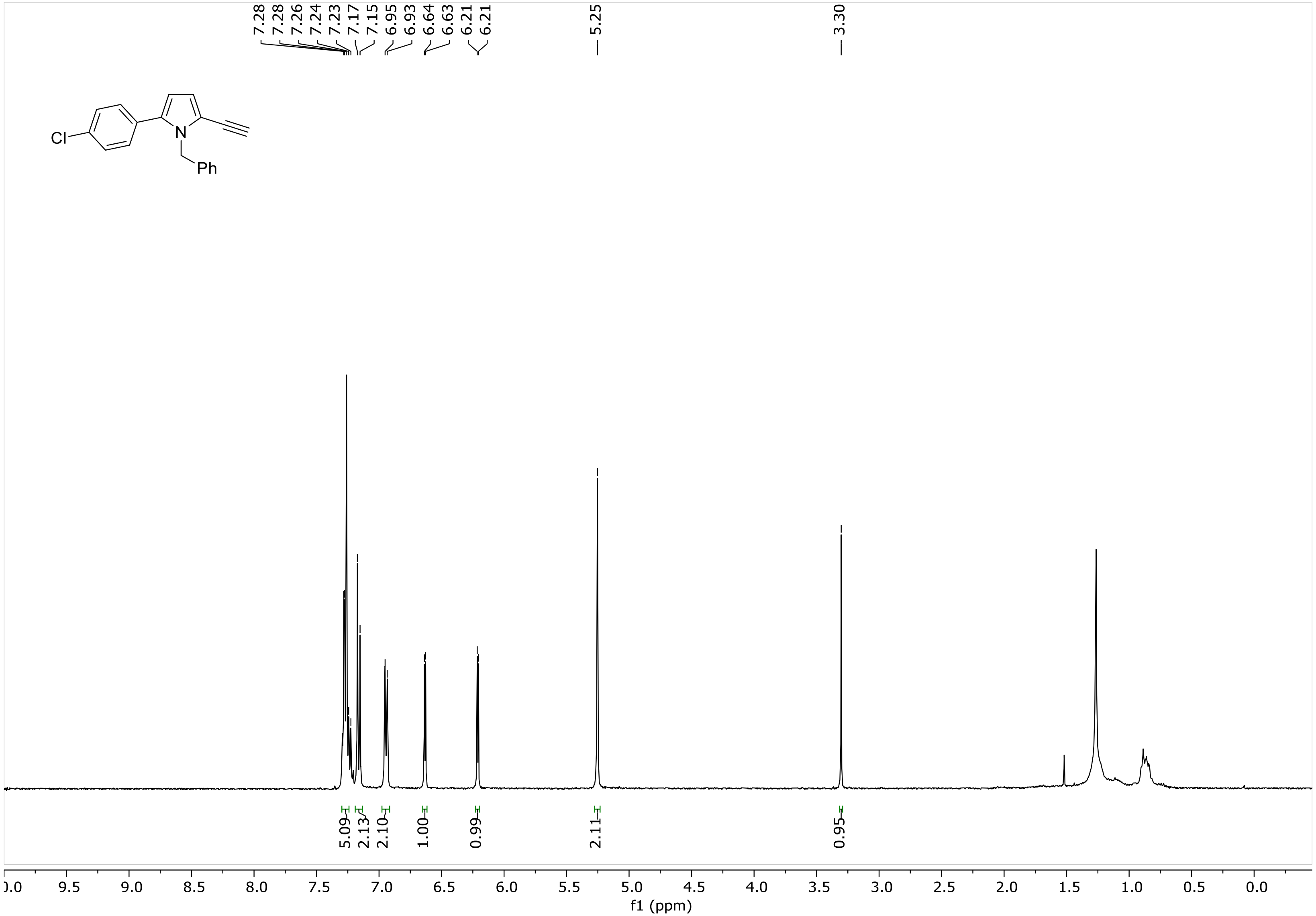
[1]H NMR spectrum of 3-(1-methyl-4,5-dihydro-1*H*-benzo[*g*]indol-2-yl)-1-phenylprop-2-yn-1-one (**1e**) in $CDCl_3$



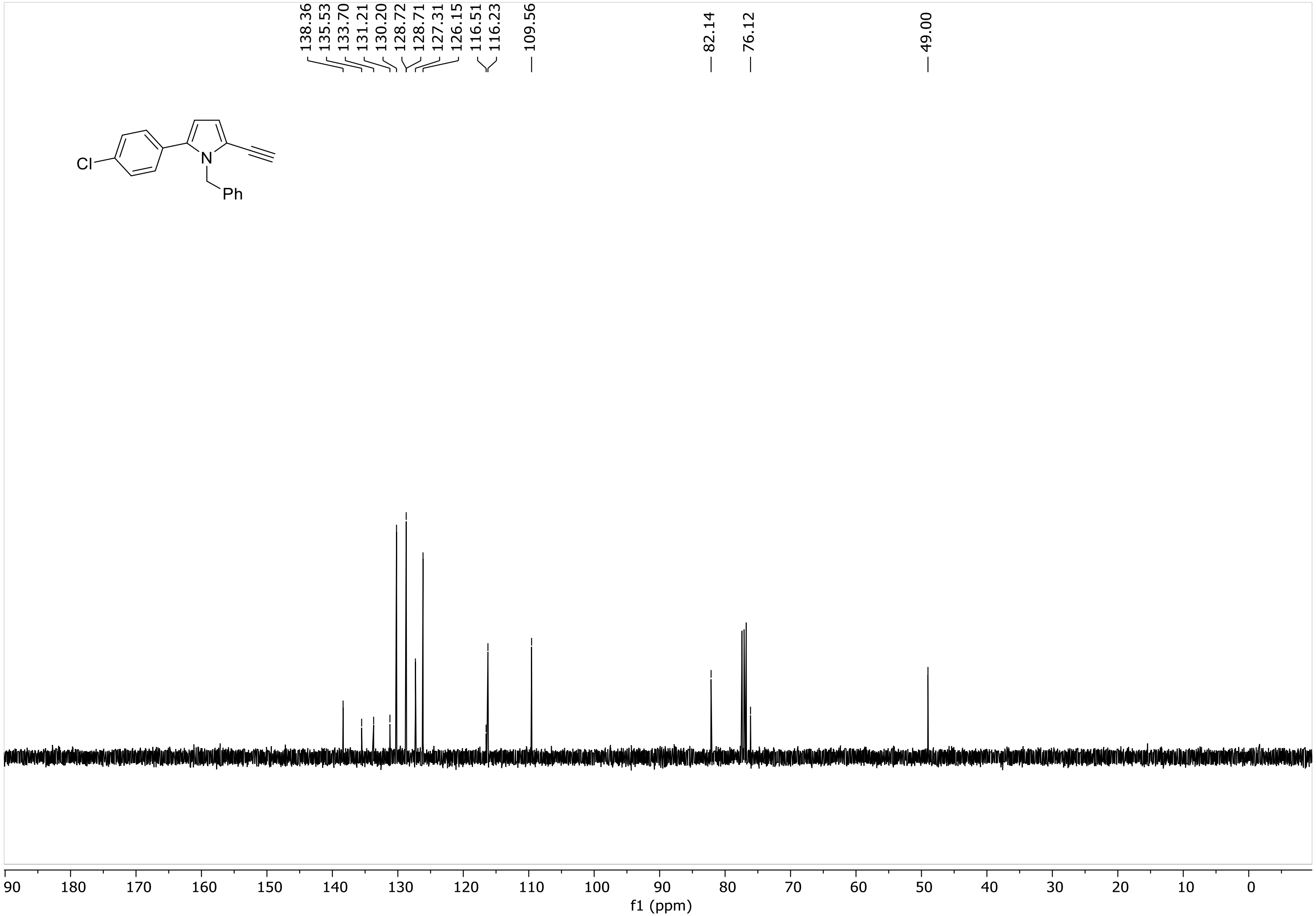
^{13}C NMR spectrum of 3-(1-methyl-4,5-dihydro-1*H*-benzo[*g*]indol-2-yl)-1-phenylprop-2-yn-1-one (**1e**) in $CDCl_3$



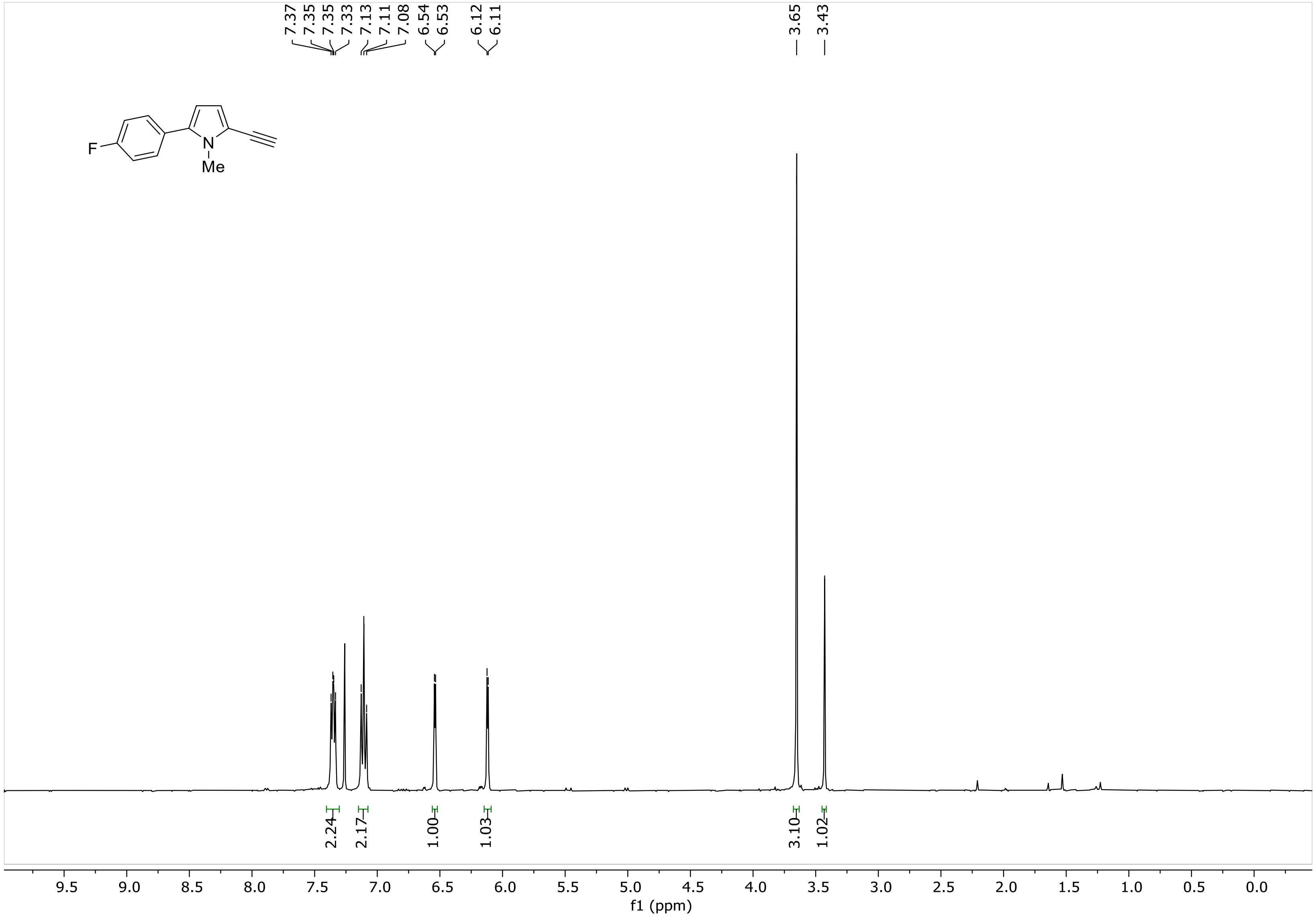
^{1}H NMR spectrum of 1-benzyl-2-(4-chlorophenyl)-5-ethynyl-1*H*-pyrrole **(2a)** in $CDCl_3$



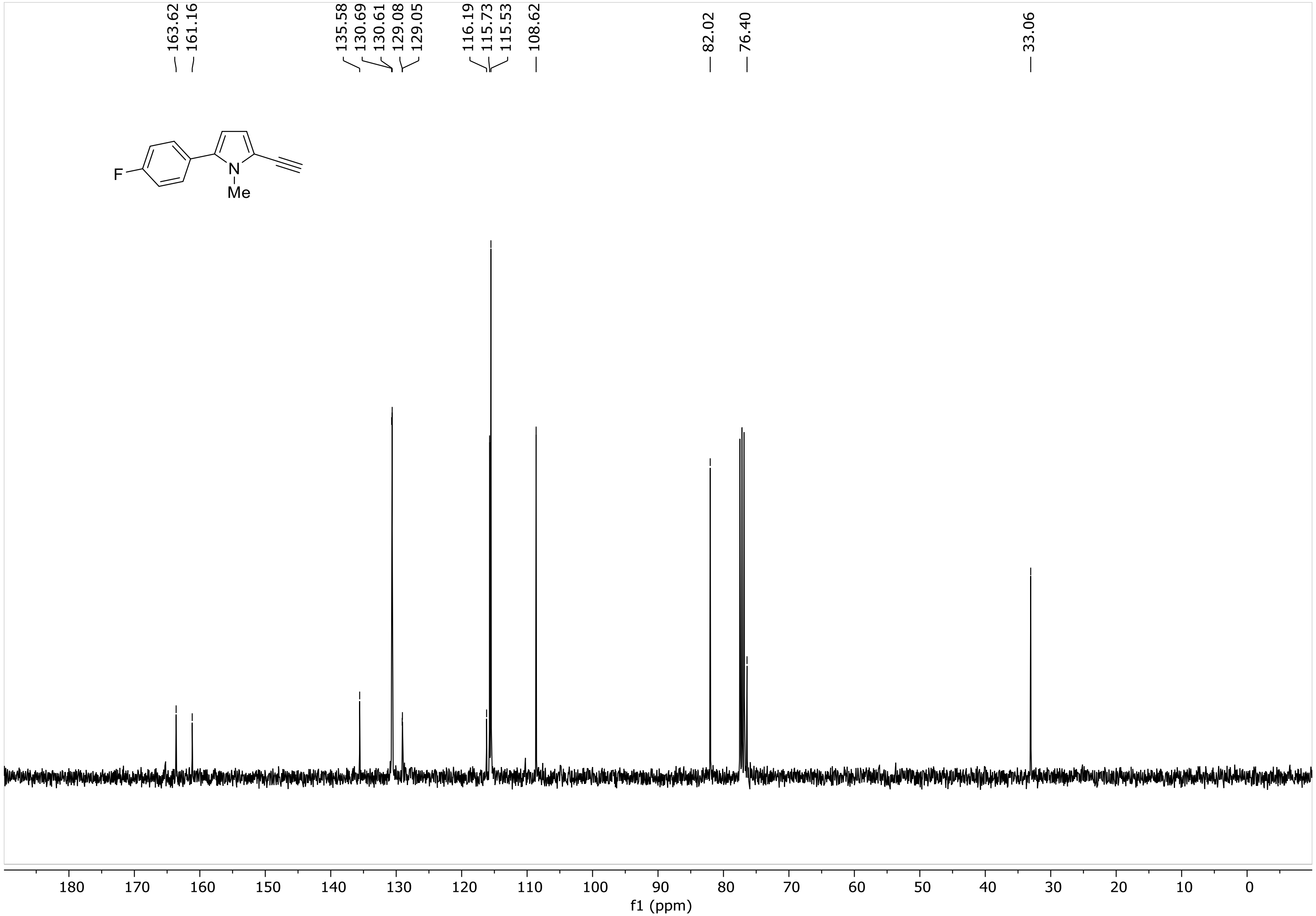
^{13}C NMR spectrum of 1-benzyl-2-(4-chlorophenyl)-5-ethynyl-1*H*-pyrrole **(2a)** in $CDCl_3$



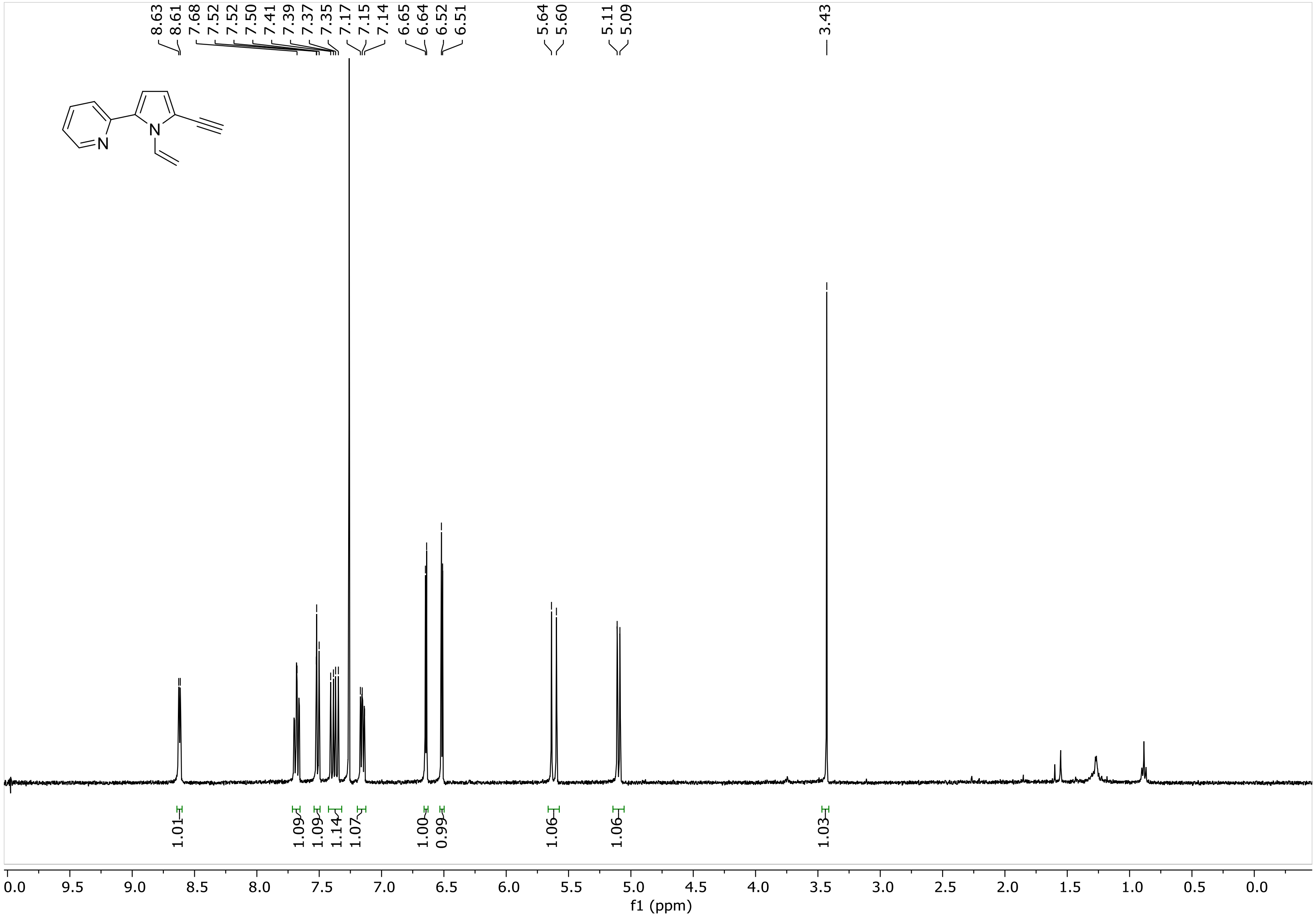
[1]H NMR spectrum of 2-ethynyl-5-(4-fluorophenyl)-1-methyl-1*H*-pyrrole **(2b)** in $CDCl_3$



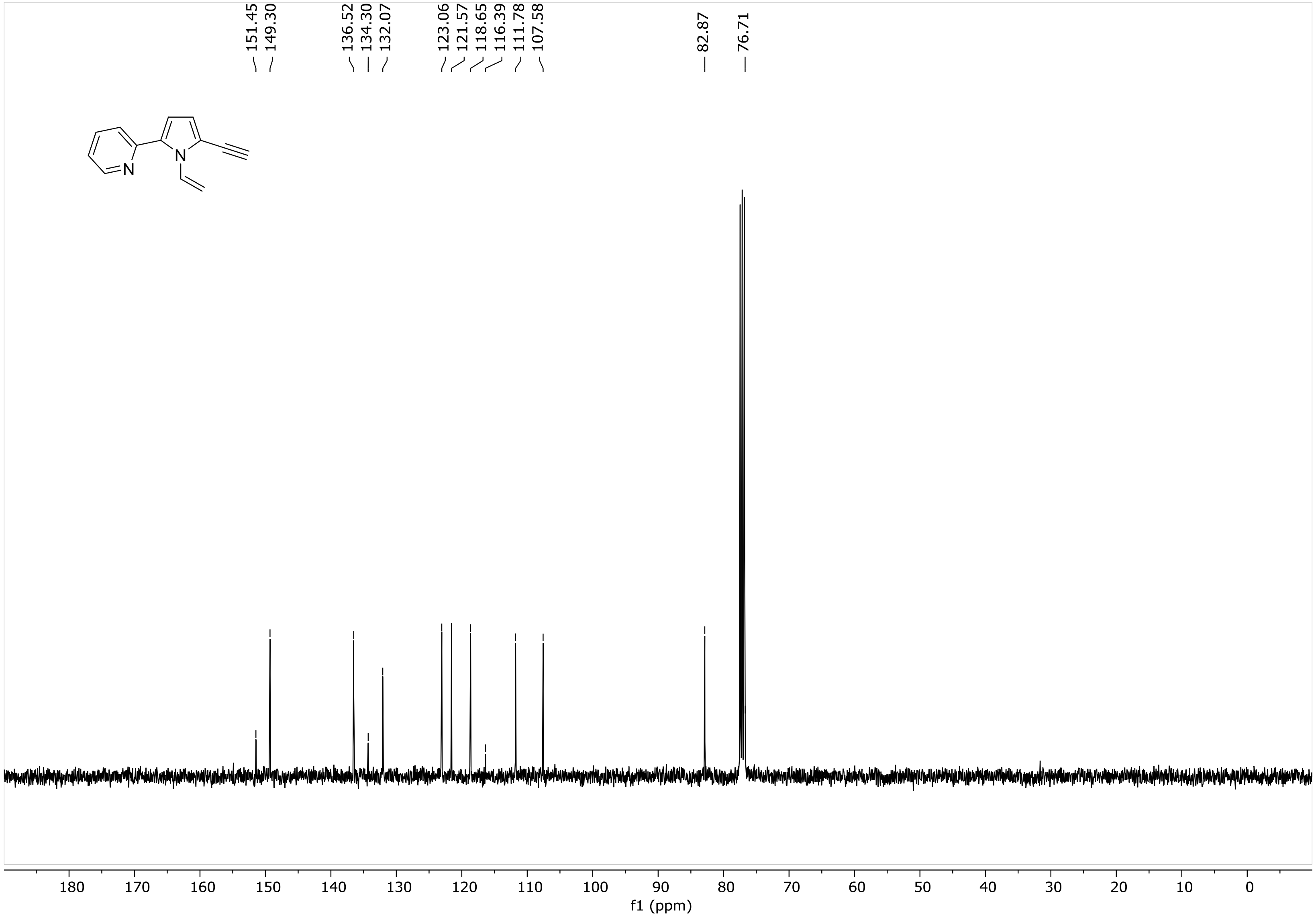
^{13}C NMR spectrum of 2-ethynyl-5-(4-fluorophenyl)-1-methyl-1*H*-pyrrole **(2b)** in $CDCl_3$



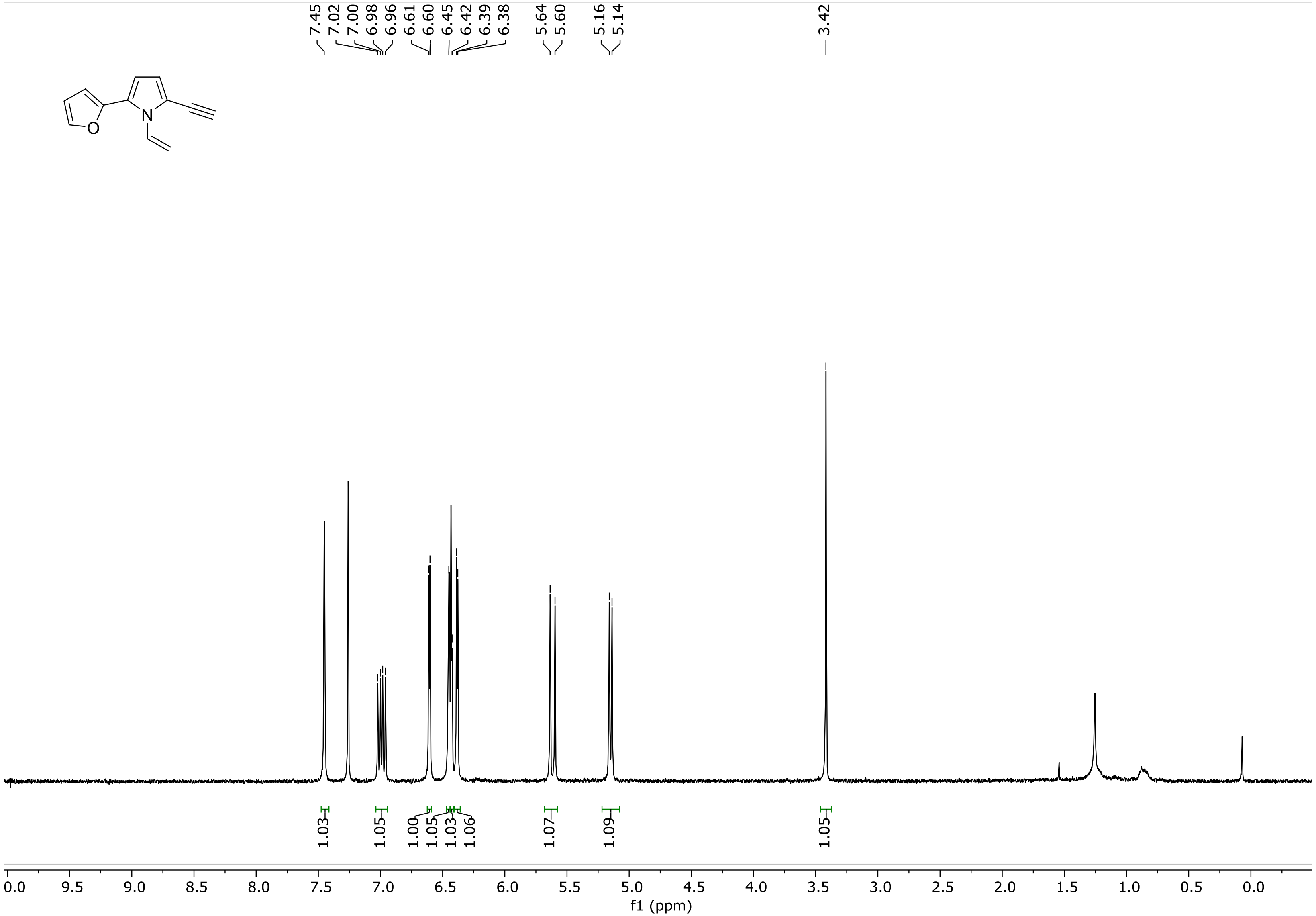
^1H NMR spectrum of 2-(5-ethynyl-1-vinyl-1*H*-pyrrol-2-yl)pyridine **(2c)** in $CDCl_3$



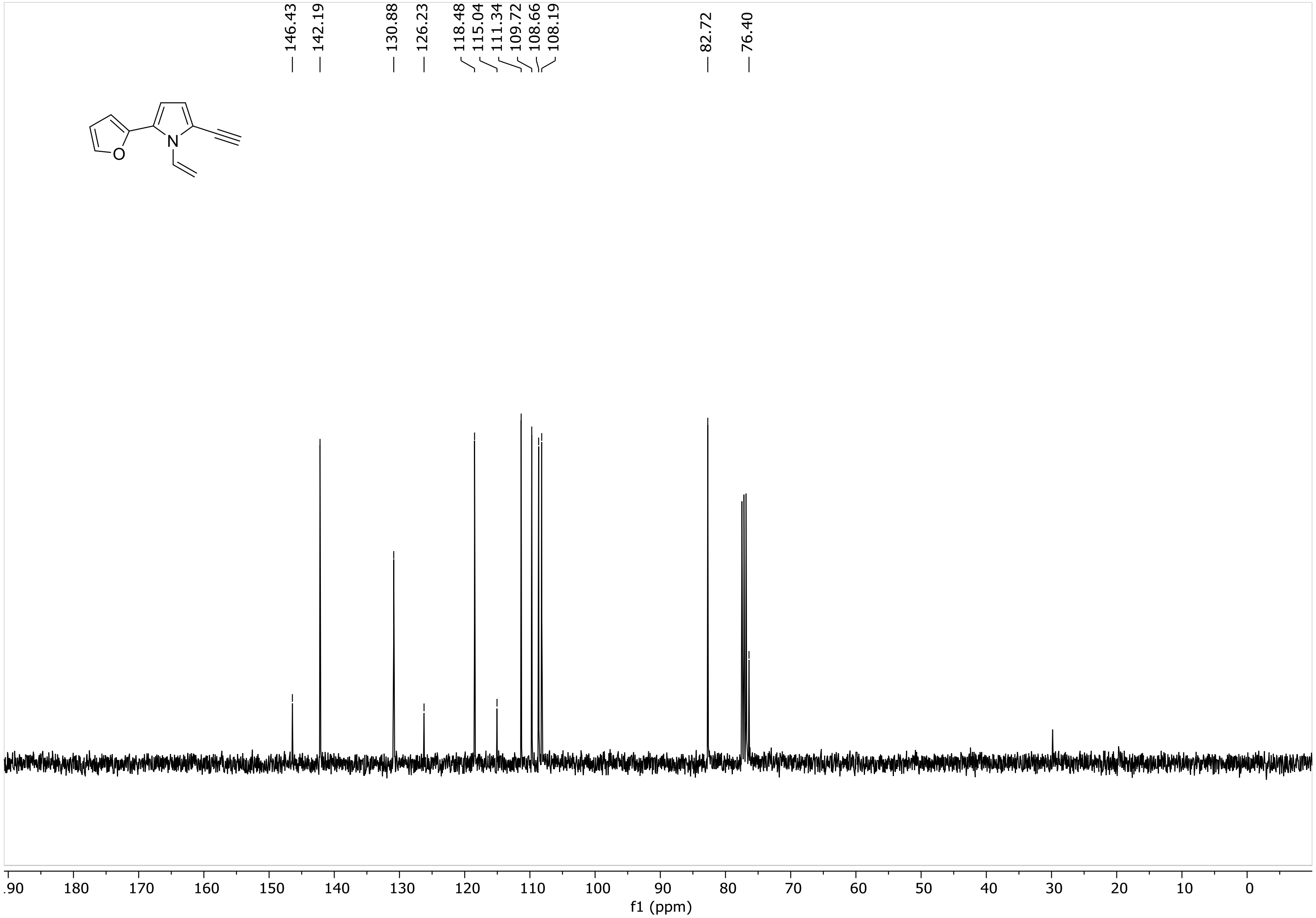
^{13}C NMR spectrum of 2-(5-ethynyl-1-vinyl-1*H*-pyrrol-2-yl)pyridine **(2c)** in $CDCl_3$



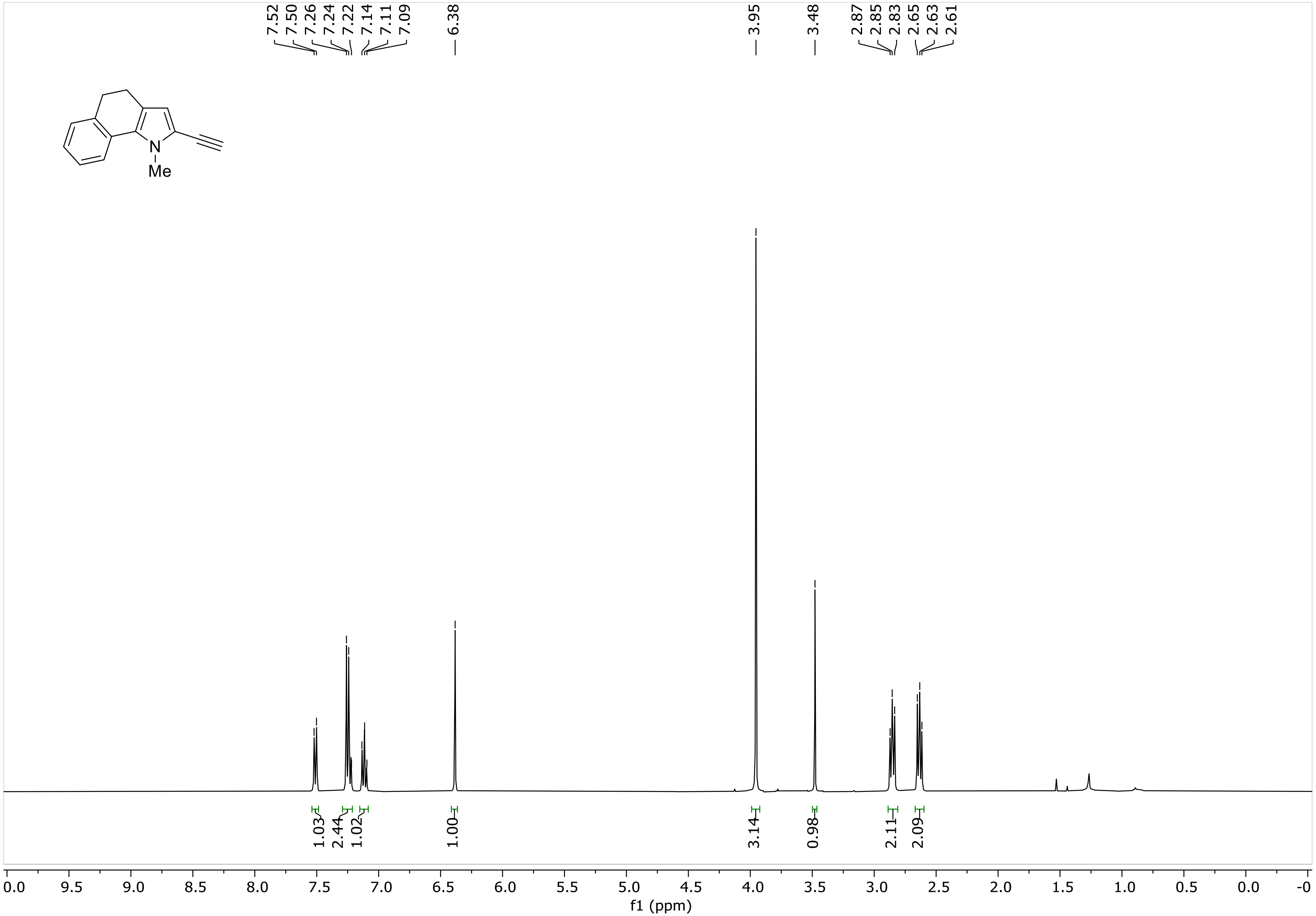
[1]H NMR spectrum of 2-ethynyl-5-(furan-2-yl)-1-vinyl-1*H*-pyrrole **(2d)** in $CDCl_3$



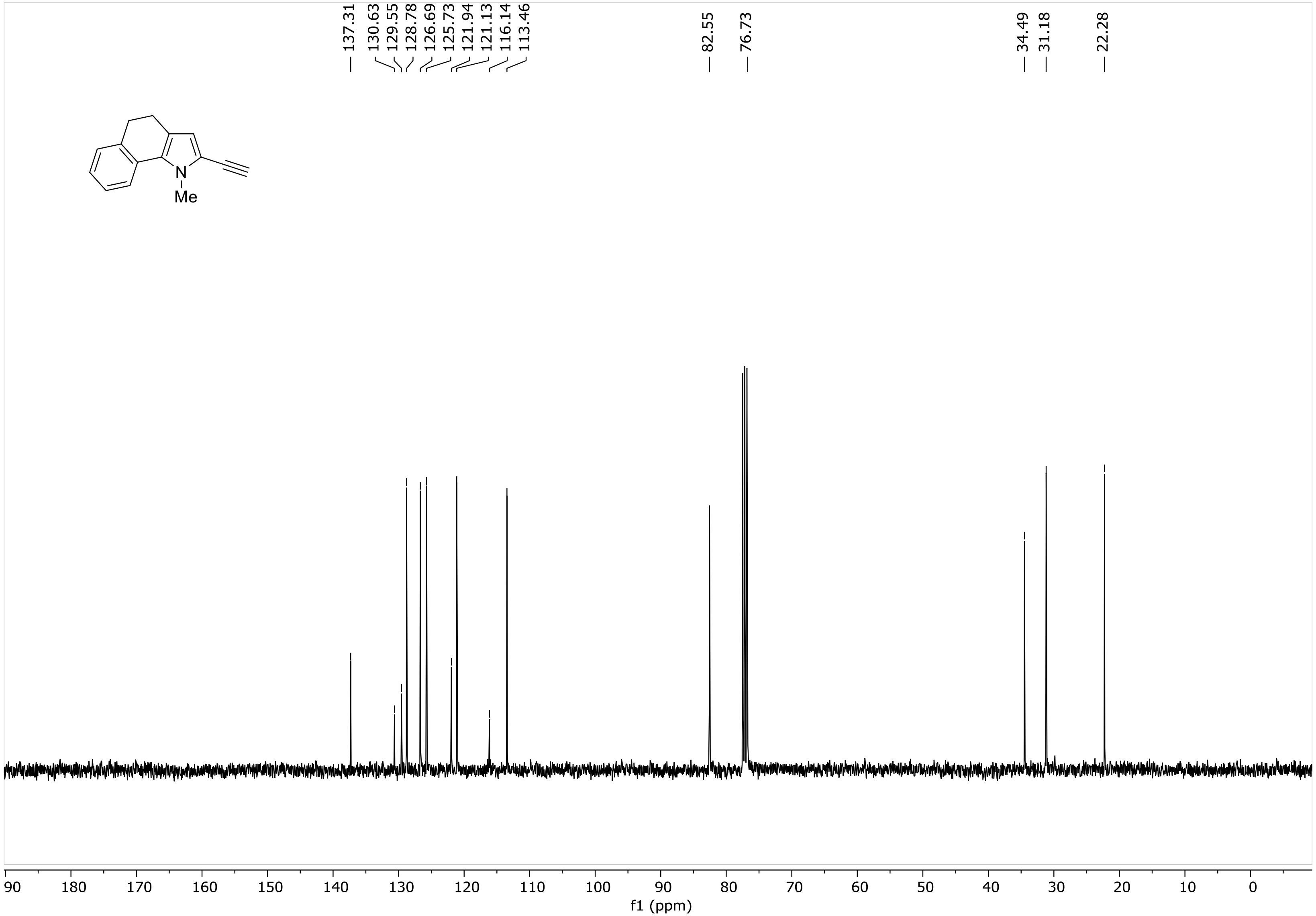
^{13}C NMR spectrum of 2-ethynyl-5-(furan-2-yl)-1-vinyl-1*H*-pyrrole **(2d)** in $CDCl_3$



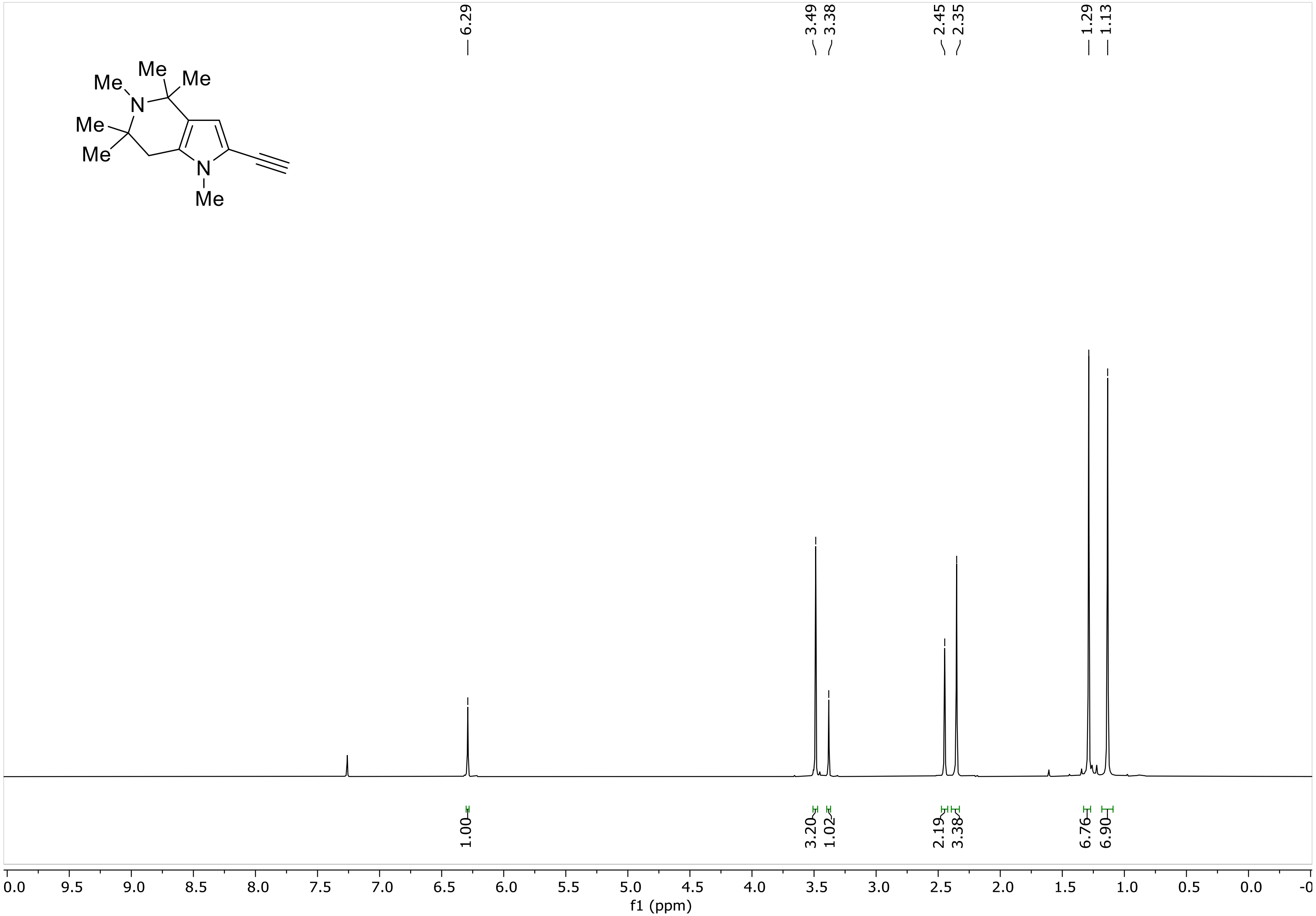
^{1}H NMR spectrum of 2-ethynyl-1-methyl-4,5-dihydro-1*H*-benzo[*g*]indole **(2e)** in $CDCl_3$



^{13}C NMR spectrum of 2-ethynyl-1-methyl-4,5-dihydro-1*H*-benzo[*g*]indole **(2e)** in $CDCl_3$



[1]H NMR spectrum of 2-ethynyl-1,4,4,5,6,6-hexamethyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-c]pyridine **(2f)** in $CDCl_3$



[13]C NMR spectrum of 2-ethynyl-1,4,4,5,6,6-hexamethyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[3,2-c]pyridine **(2f)** in $CDCl_3$