Supplementary Information File

Synthesis of New Hybrid Derivatives from Metronidazole and Eugenol Analogues as Trypanocidal Agents

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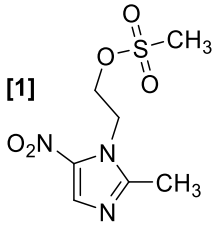
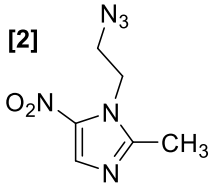
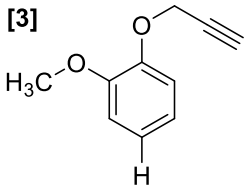
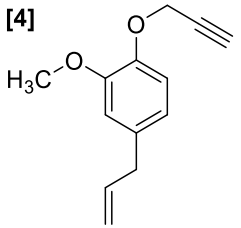
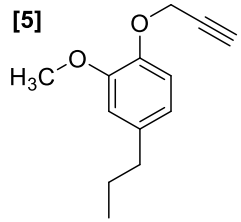
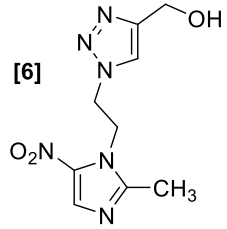
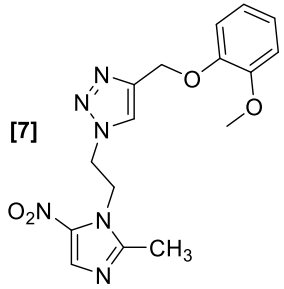
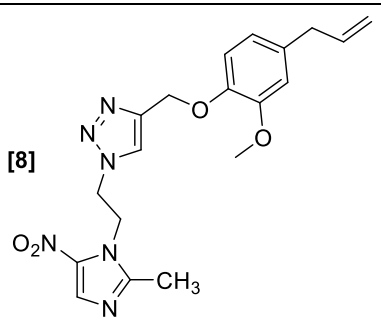
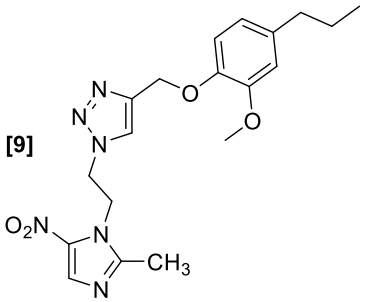
Fourier Transform InfraRed Spectroscopy (FTIR) was performed on a Shimadzu® Affinity-1 spectrometer using a zinc selenide attenuated total reflectance (ATR) sampling accessory supplied by Pike Technologies® (USA). Readings were taken at room temperature, 32 scans per analysis, resolution of 4.0cm^{-1}, range from 4000-600cm^{-1}.
Nuclear Magnetic Resonance Spectroscopy (NMR) was performed on a Bruker® 300 spectrometer. All ^{1}H experiments (including the 2D HSQC & HMQC experiments) were recorded at 300 MHz and ^{13}C experiments were recorded at 75 MHz. Samples were dissolved into $CDCl_3$ as a solvent apart from compounds **[1]**, **[2]** and **[6]** which, due to their low solubility in $CDCl_3$ required the use of DMSO-d_6. Chemical shifts were recorded in parts per million (ppm) based on the corresponding solvent. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet.
Liquid Chromatography–Mass Spectrometry (LC-MS) analysis was performed on a Waters Acquity UPLC H-Class system; comprising a quaternary solvent manager attached to a triple-quadrupole (Acquity TQD) mass spectrometer. The samples were prepared in acetonitrile, and the mobile phase was acetonitrile spiked with 0.1% formic acid. The flow rate and injection volume were 0.4 mL / min and 10.0 µL, respectively. Electrospray ionisation (ESI) with positive ionisation mode was found to be suitable and optimised as follows: cone voltage between 3 and 40V, capillary at 3KV and extractor 3V, source block temperature 120 °C, desolvation line 500 °C, nitrogen was used as the nebulising gas at 1000 litres/hour. The output signals were monitored and processed using Empower 3 software.

Contents

1. Structures and Chemical Data for Compounds [1]-[9]

[1] 	[2] 	[3] 	[4] 	[5] 
Chemical Formula: $C_7H_{11}N_3O_5S$ **Exact Mass:** 249.04 **Molecular Weight:** 249.24 **Predicted m/z**: 249.04 (100.0%), 250.05 (7.6%), 251.04 (4.5%), 250.04 (1.1%), 251.05 (1.0%) **Calculated Elemental Analysis**: C:33.73, H:4.45, N:16.86, O:32.10, S:12.86	**Chemical Formula**: $C_6H_8N_6O_2$ **Exact Mass**: 196.07 **Molecular Weight**: 196.17 **Predicted m/z**: 196.07 (100.0%), 197.07 (6.5%), 197.07 (1.1%), 197.07 (1.1%) **Calculated Elemental Analysis**: C:36.74, H:4.11, N:42.84, O:16.31	**Chemical Formula**: $C_{10}H_{10}O_2$ **Exact Mass**: 162.07 **Molecular Weight**: 162.19 **Predicted m/z**: 162.07 (100.0%), 163.07 (10.8%) **Calculated Elemental Analysis**: C:74.06, H:6.22, O:19.73	**Chemical Formula**: $C_{14}H_{16}O_2$ **Exact Mass**: 216.12 **Molecular Weight**: 216.28 **Predicted m/z**: 216.12 (100.0%), 217.12 (15.1%), 218.12 (1.1%) **Calculated Elemental Analysis**: C:77.75, H:7.46, O:14.79	**Chemical Formula**: $C_{14}H_{18}O_2$ **Exact Mass**: 218.13 **Molecular Weight**: 218.30 **Predicted m/z**: 218.13 (100.0%), 219.13 (15.1%), 220.14 (1.1%) **Calculated Elemental Analysis**: C:77.03, H:8.31, O:14.66

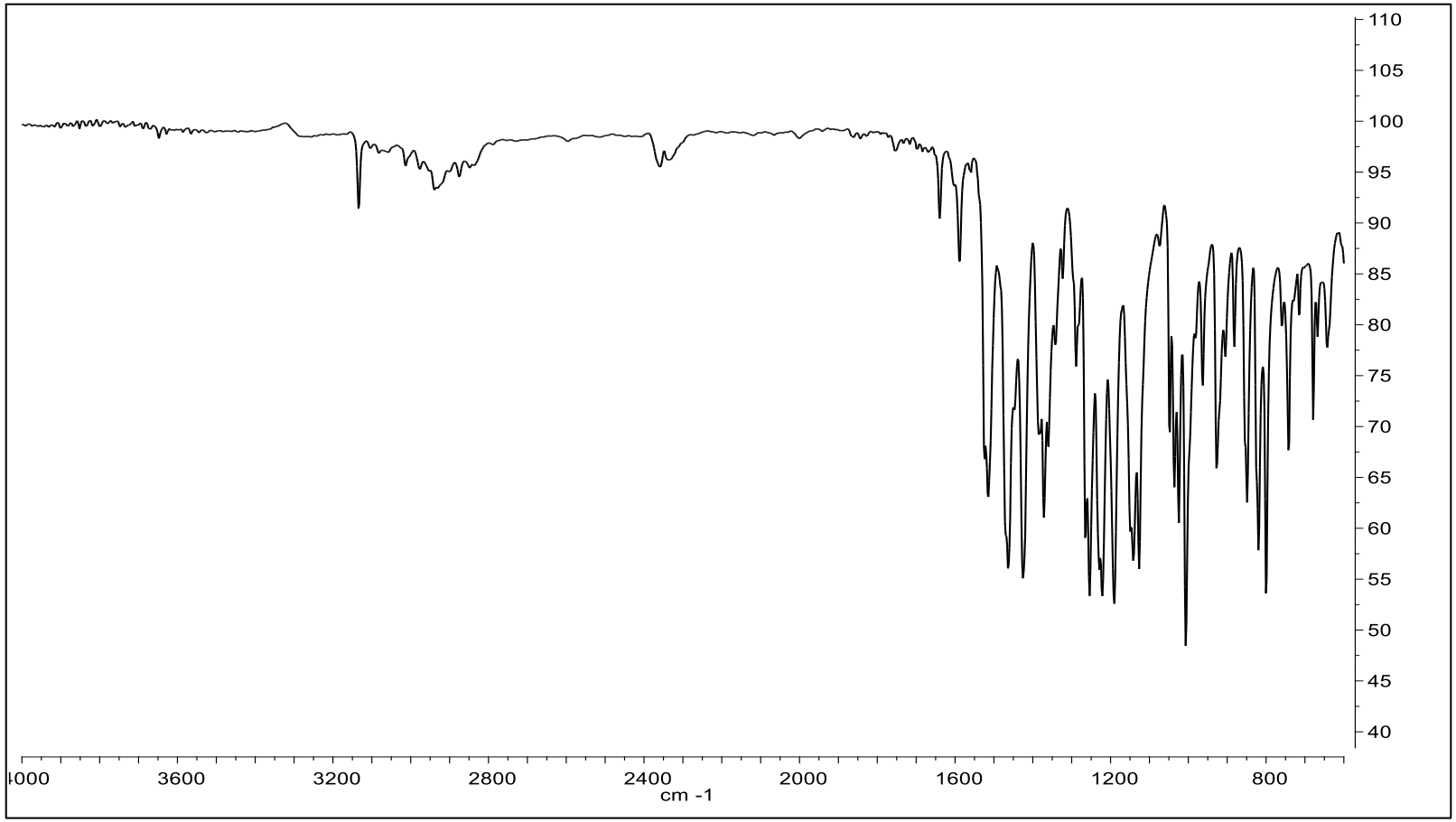
[6] 	[7] 	[8] 	[9] 
Chemical Formula: $C_9H_{12}N_6O_3$ **Exact Mass**: 252.10 **Molecular Weight**: 252.23 **Predicted m/z**: 252.10 (100.0%), 253.10 (9.7%), 253.09 (2.2%) **Calculated Elemental Analysis**: C:42.86, H:4.80, N:33.32, O:19.03	**Chemical Formula**: $C_{16}H_{18}N_6O_4$ **Exact Mass**: 358.14 **Molecular Weight**: 358.36 **Predicted m/z**: 358.14 (100.0%), 359.14 (17.3%), 359.14 (2.2%), 360.15 (1.4%) **Calculated Elemental Analysis**: C:53.63, H:5.06, N:23.45, O:17.86	**Chemical Formula**: $C_{19}H_{22}N_6O_4$ **Exact Mass:** 398.17 **Molecular Weight**: 398.42 **Predicted m/z**: 398.17 (100.0%), 399.17 (20.5%), 399.17 (2.2%), 400.18 (2.0%) **Calculated Elemental Analysis**: C:57.28, H:5.57, N:21.09, O:16.06	**Chemical Formula**: $C_{19}H_{24}N_6O_4$ **Exact Mass**: 400.19 **Molecular Weight**: 400.44 **Predicted m/z**: 400.19 (100.0%), 401.19 (20.5%), 401.18 (2.2%), 402.19 (2.0%) **Calculated Elemental Analysis**: C:56.99, H:6.04, N:20.99, O:15.98

Note: the data presented in this table was calculated using the Analysis tool within the ChemBioDraw® Program, by CambridgeSoft Corp.

2. Compound [1] = [2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl methanesulfonate]

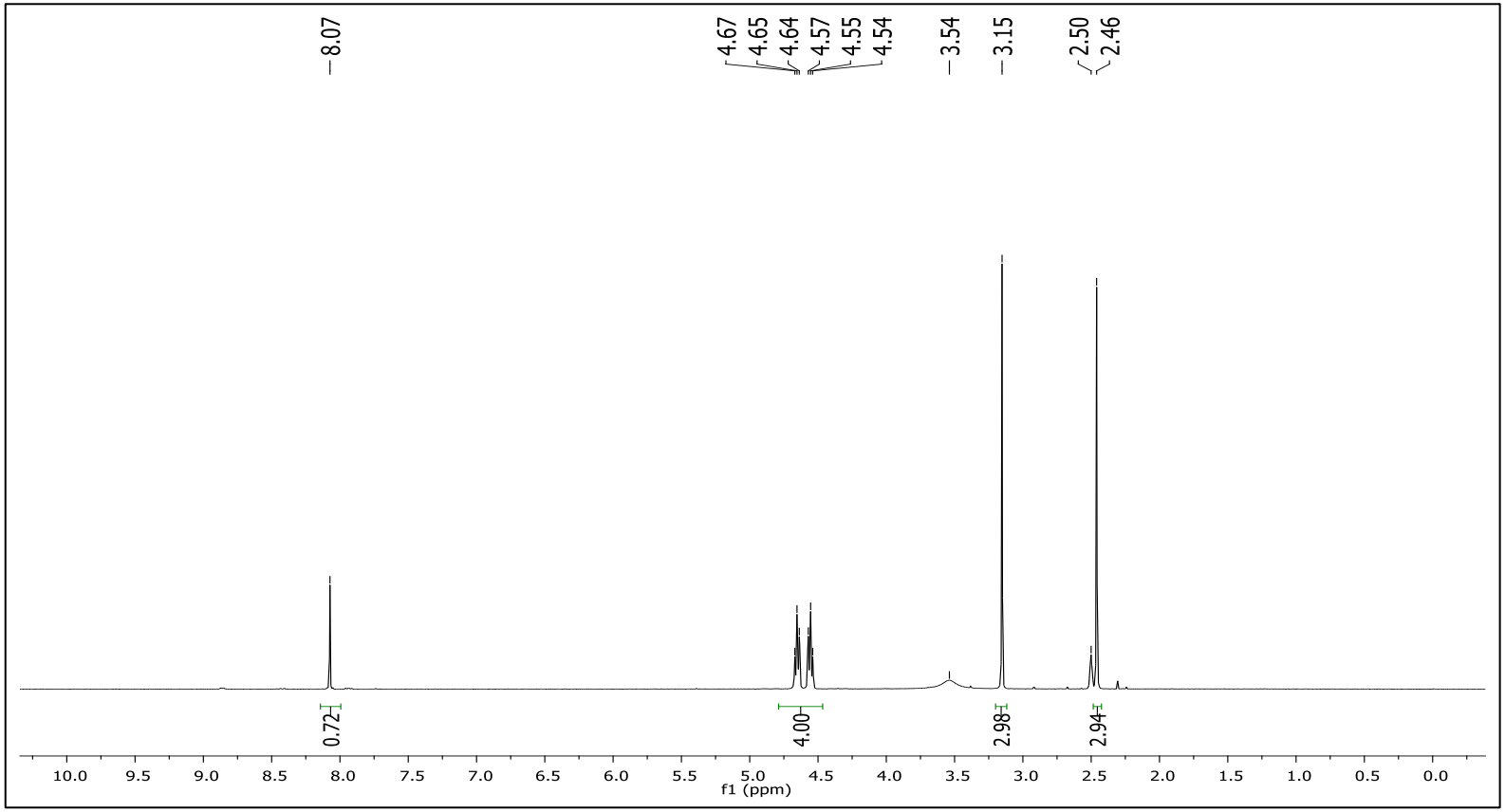
*2.1. FTIR (ATR) Spectrum of Compound **[1]***

Assigned bands (cm^{-1}): 3058 (C4-H), 2805 (C6,7,8-H), 1351 (S=O), 1118 (S=O), 1285 (N=O), 1108 (N=O), 1055 (C-O).



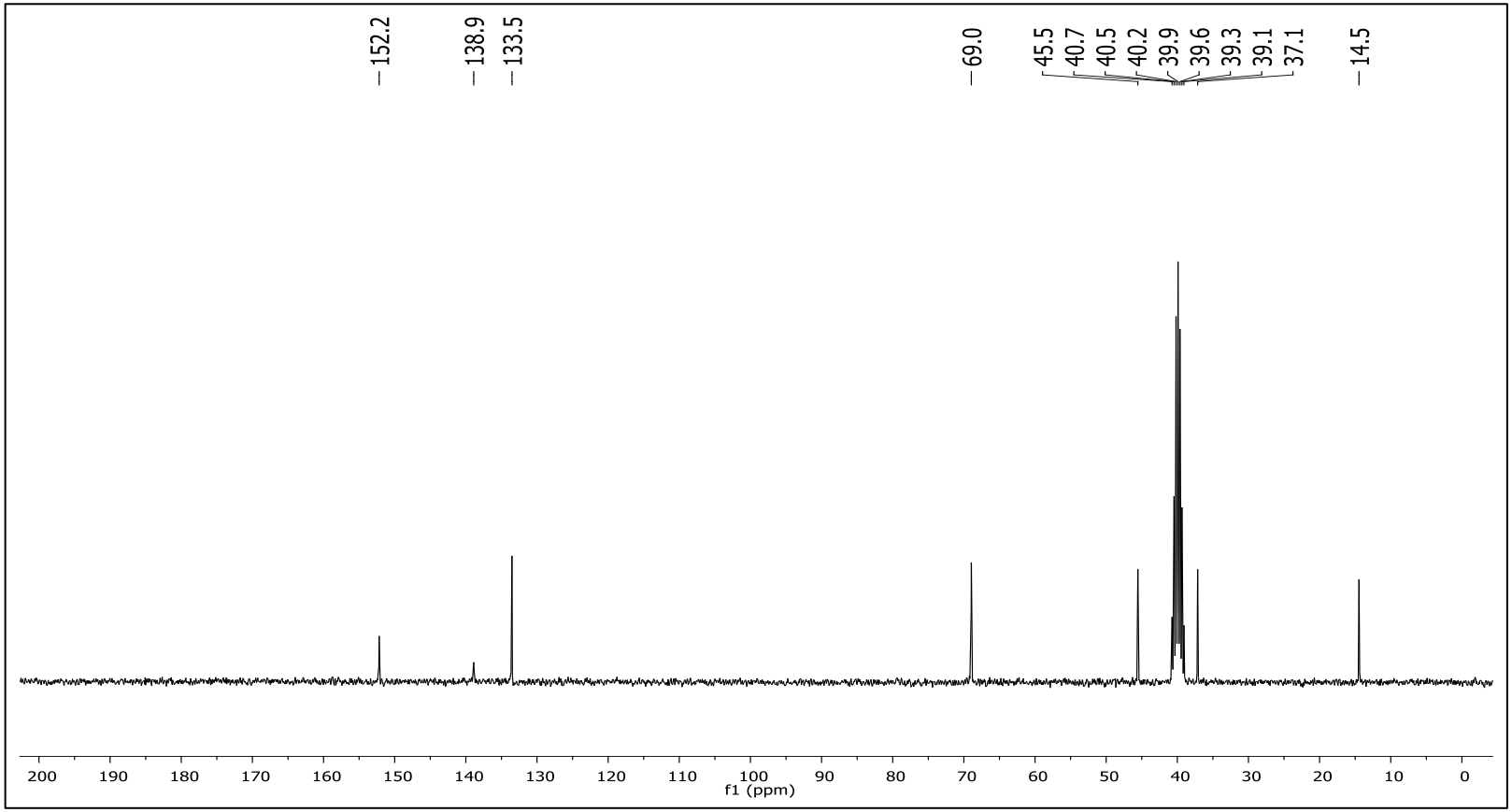
2.2. *^{1}H NMR Spectrum [300 MHz, DMSO-d_6 (ppm)] of Compound* ***[1]***

Assigned signals (ppm): 8.07 [s, 1H, H4], 4.65 [t, ^{3}J = 6.3 Hz, 2H, H8], 4.55 [t, ^{3}J = 6.3 Hz, 2H, H7], 3.15 [s, 3H, -$SO_2C\underline{H}_3$], 2.46 [s, 3H, H6].



2.3. *^{13}C NMR Spectrum [75 MHz, DMSO-d_6 (ppm)] of Compound* ***[1]***

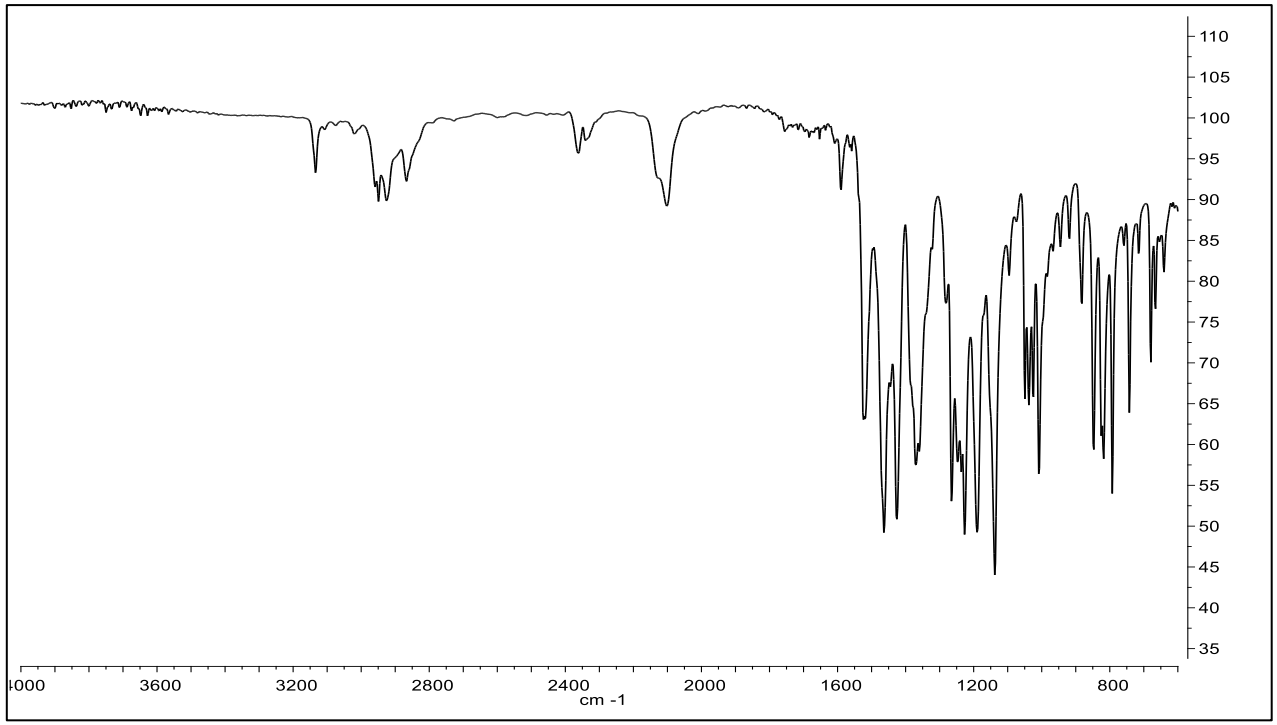
Assigned signals (ppm): 152.18 [C1], 138.89 [C5], 133.51 [C4], 68.95 [C8], 45.54 [C7], 37.14 [$-SO_2CH_3$], 13.46 [C6].



3. Compound [2] = [1-(2-azidoethyl)-2-methyl-5-nitro-1H-imidazole]

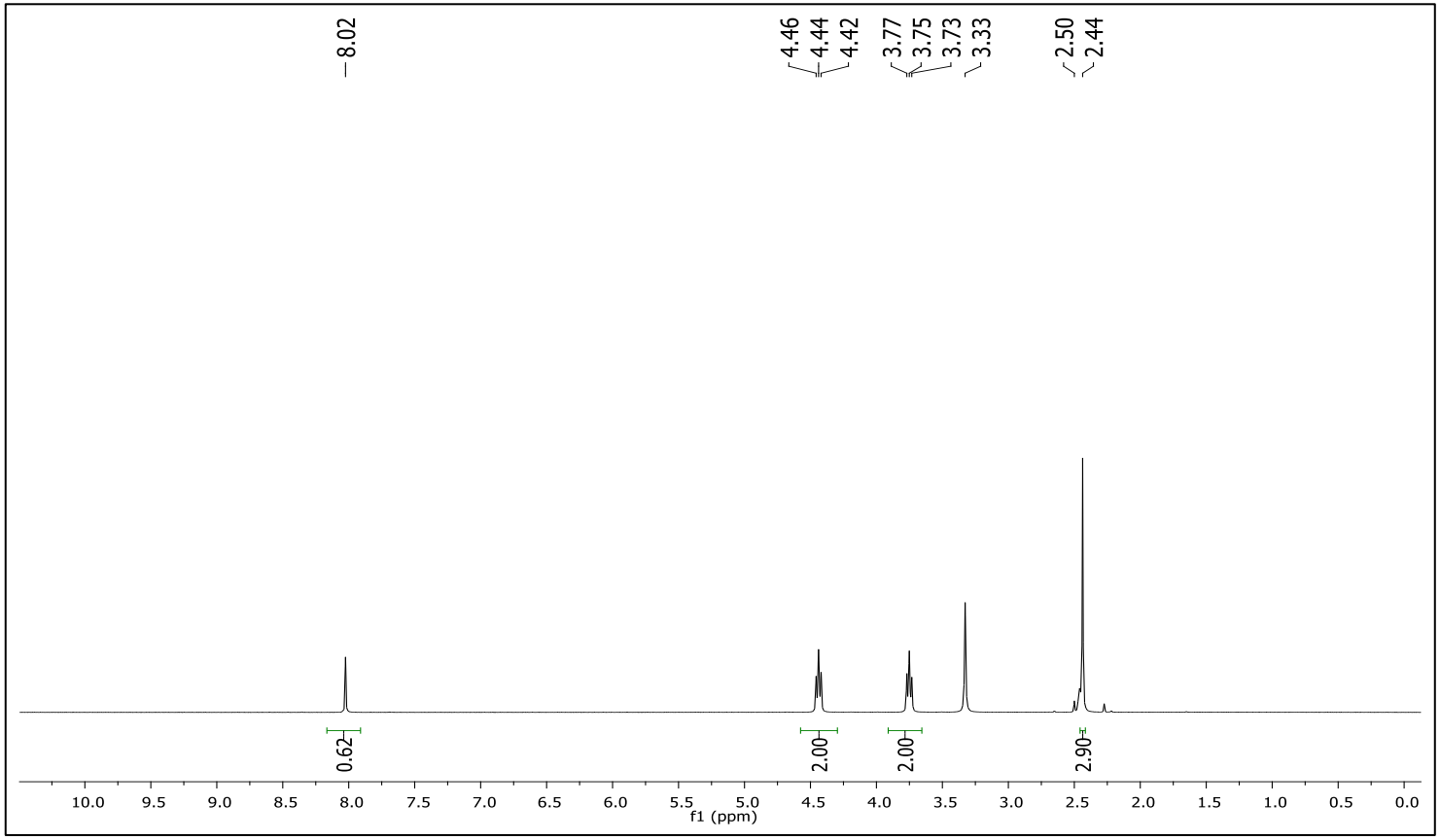
*3.1. FTIR (ATR) Spectrum of Compound **[2]***

Assigned bands (cm^{-1}): 3055 (C4-H), 2811 (C6,7,8-H), 2108 (N=N=N), 1285 (N=O), 1108 (N=O), 1051 (C-O).



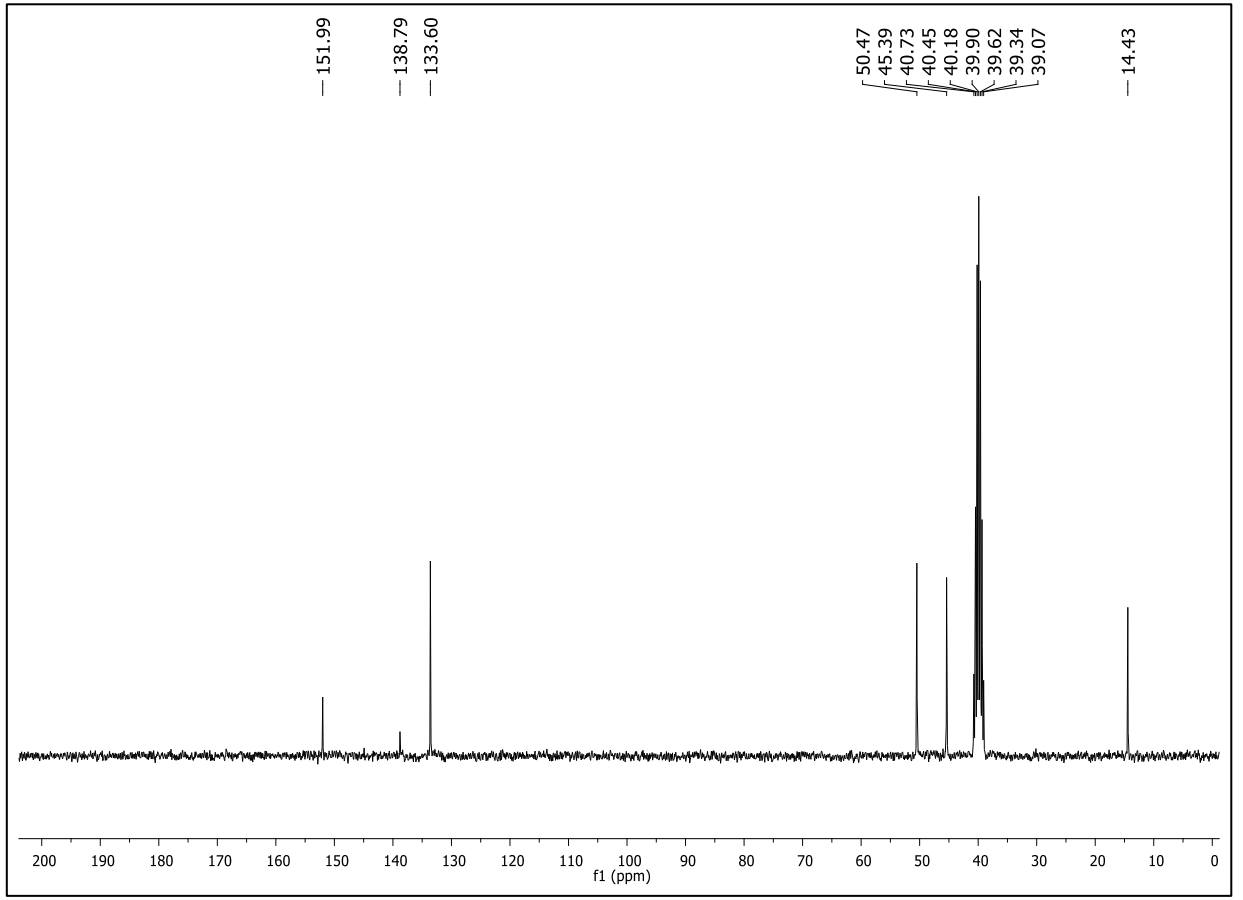
*3.2. ^{1}H NMR Spectrum [300 MHz, DMSO-d_6 (ppm)] of Compound **[2]***

Assigned signals (ppm): 8.02 [s, 1H, H4], 4.44 [t, ^{3}J = 6.4 Hz, 2H, H8], 3.73 [t, ^{3}J = 6.4 Hz 2H, H7], 2.44 [s, 3H, H6].



3.3. *^{13}C NMR Spectrum [75 MHz, DMSO-d_6 (ppm)] of Compound* ***[2]***

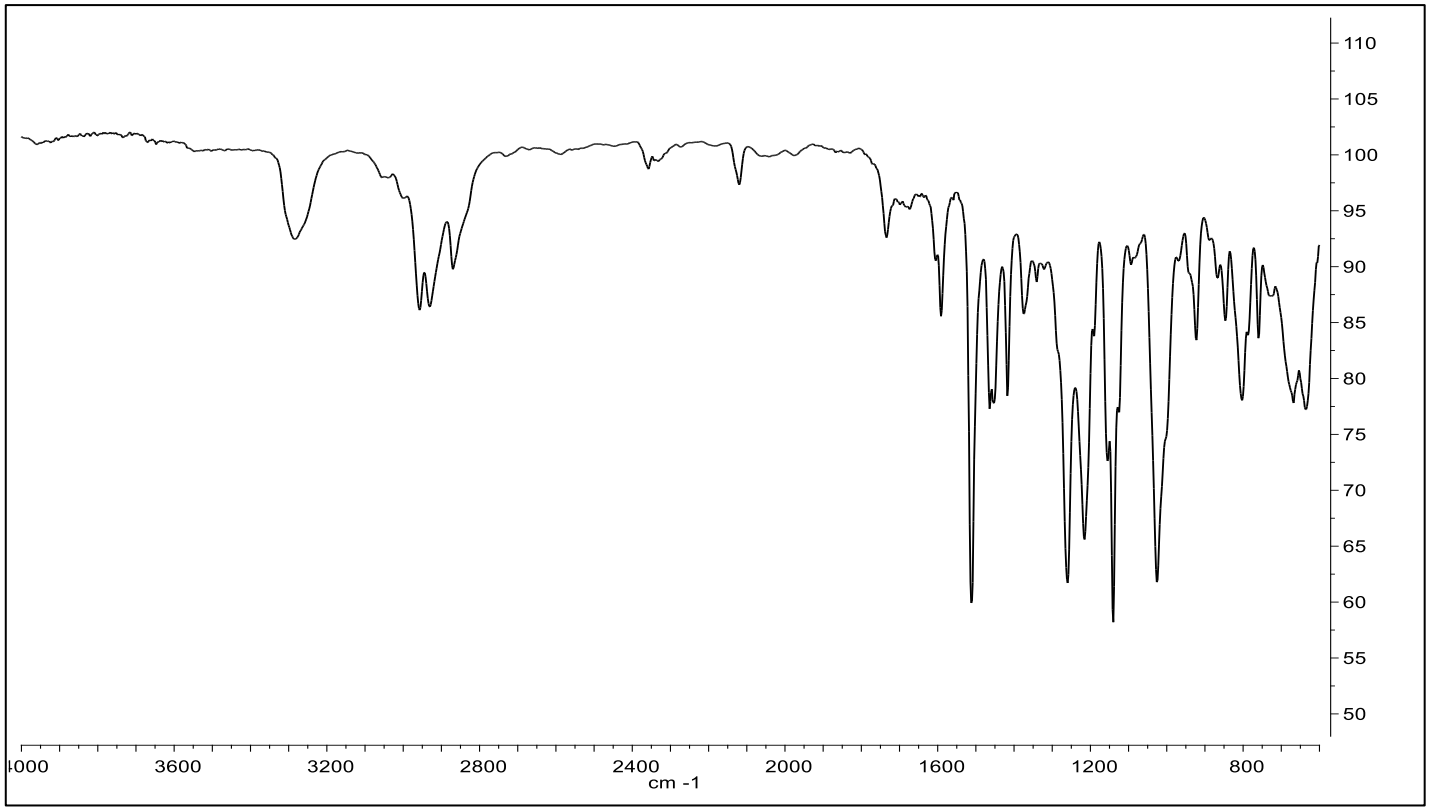
Assigned signals (ppm): 151.99 [C2], 138.79 [C5], 133.60 [C4], 50.47 [C8], 45.39 [C7], 14.43 [C6].



4. Compound [3] = [4-allyl-2-methoxy-1-(prop-2-yn-1-yloxy)benzene]

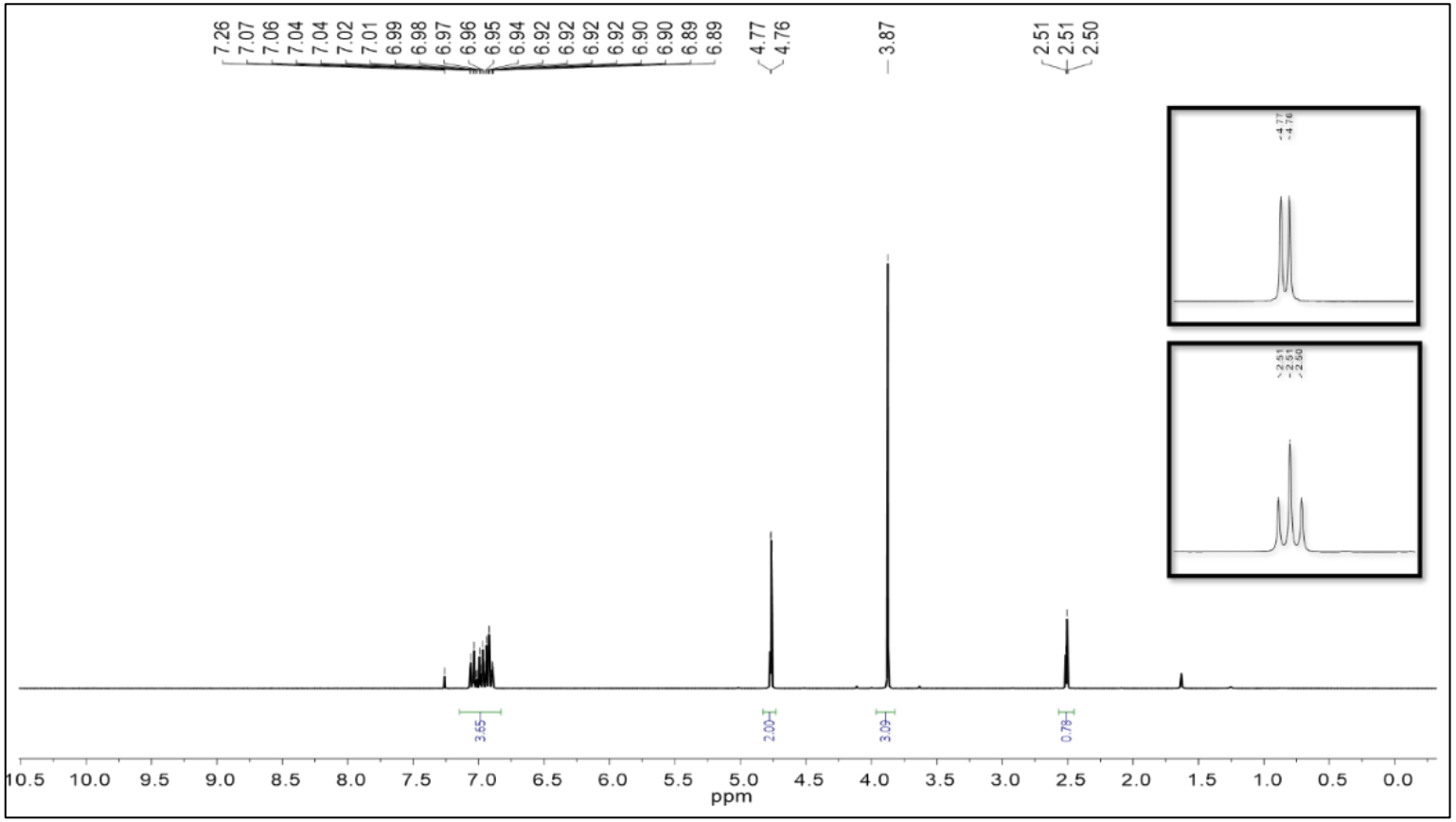
*4.1. FTIR (ATR) Spectrum of Compound **[3]***

Assigned bands (cm^{-1}): 3311 (C10-H), 3010 (CAr-H), 2105 (C≡C), 1504 (C=C), 1035 (C-O).



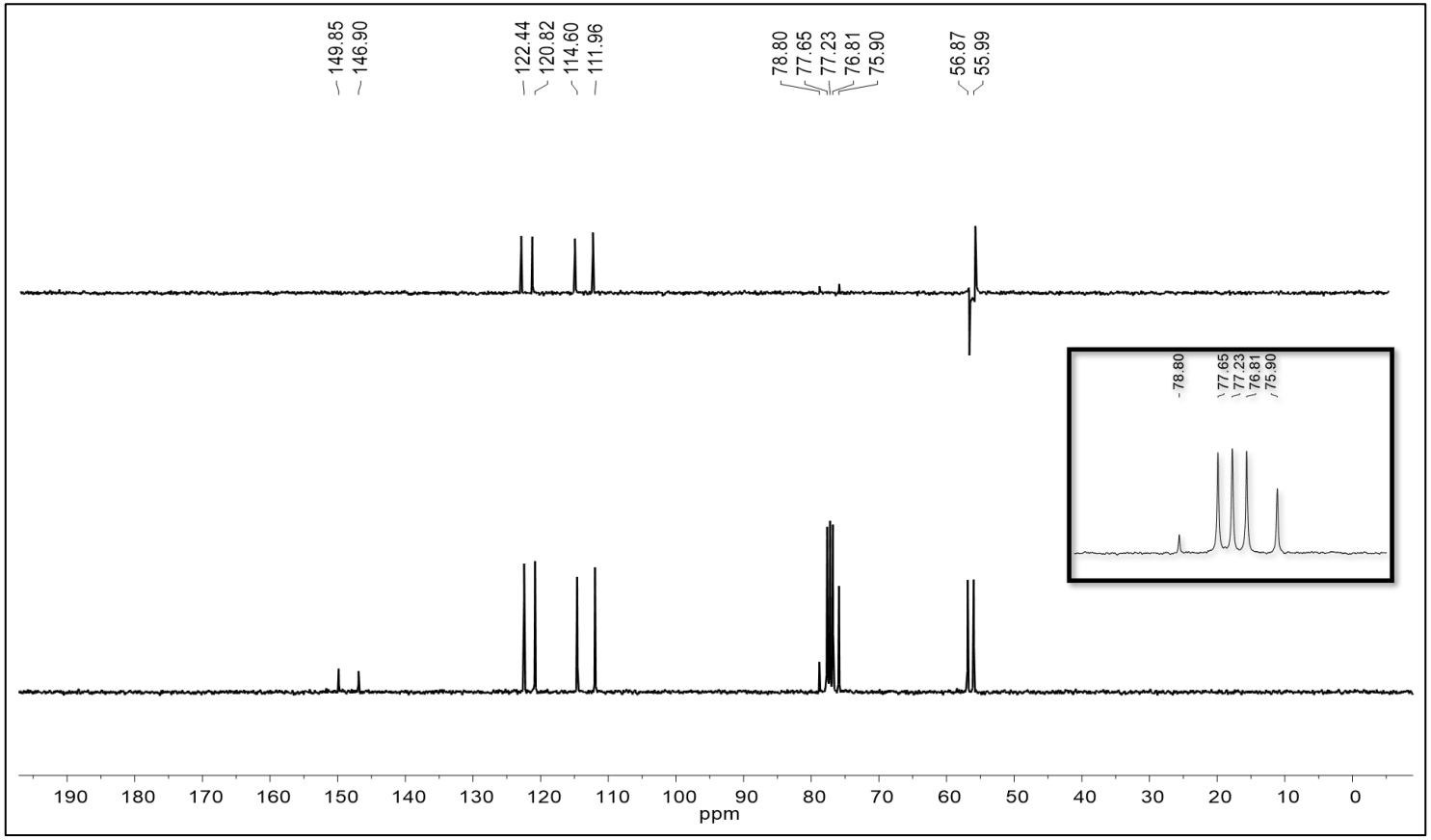
4.2. *^{1}H NMR Spectrum [300 MHz, $CDCl_3$ (ppm)] of Compound* ***[3]***

Assigned signals (ppm): 6.95 [m, 4H, H3'-6'], 4.77 [s, 2H, H8'], 3.87 [s, 3H, H7'], 2.51 [s, 1H, H10].



4.3. *^{13}C NMR Spectrum [75 MHz, $CDCl_3$ (ppm)] of Compound* ***[3]***

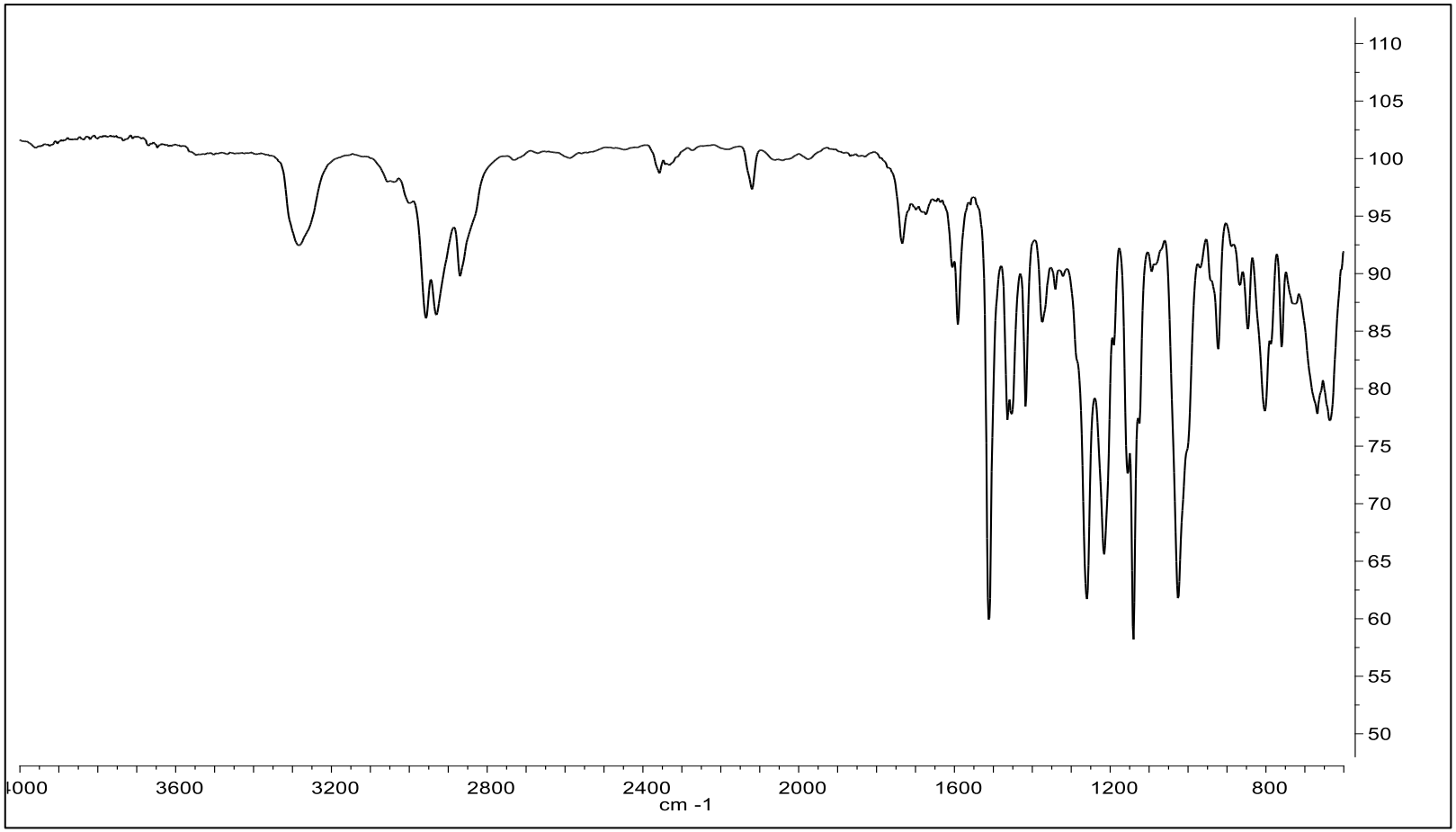
Assigned signals (ppm): 149.7 [C1'], 146.7 [C2'], 122.3 [C4'], 120.7 [C5'], 114.4 [C6'], 111.8 [C3'], 78.5 [C9], 75.7 [C10], 56.6 [C8'], 55.8 [C7'].



5. Compound [4] = [2-methoxy-1-(prop-2-yn-1-yloxy)-4-propylbenzene]

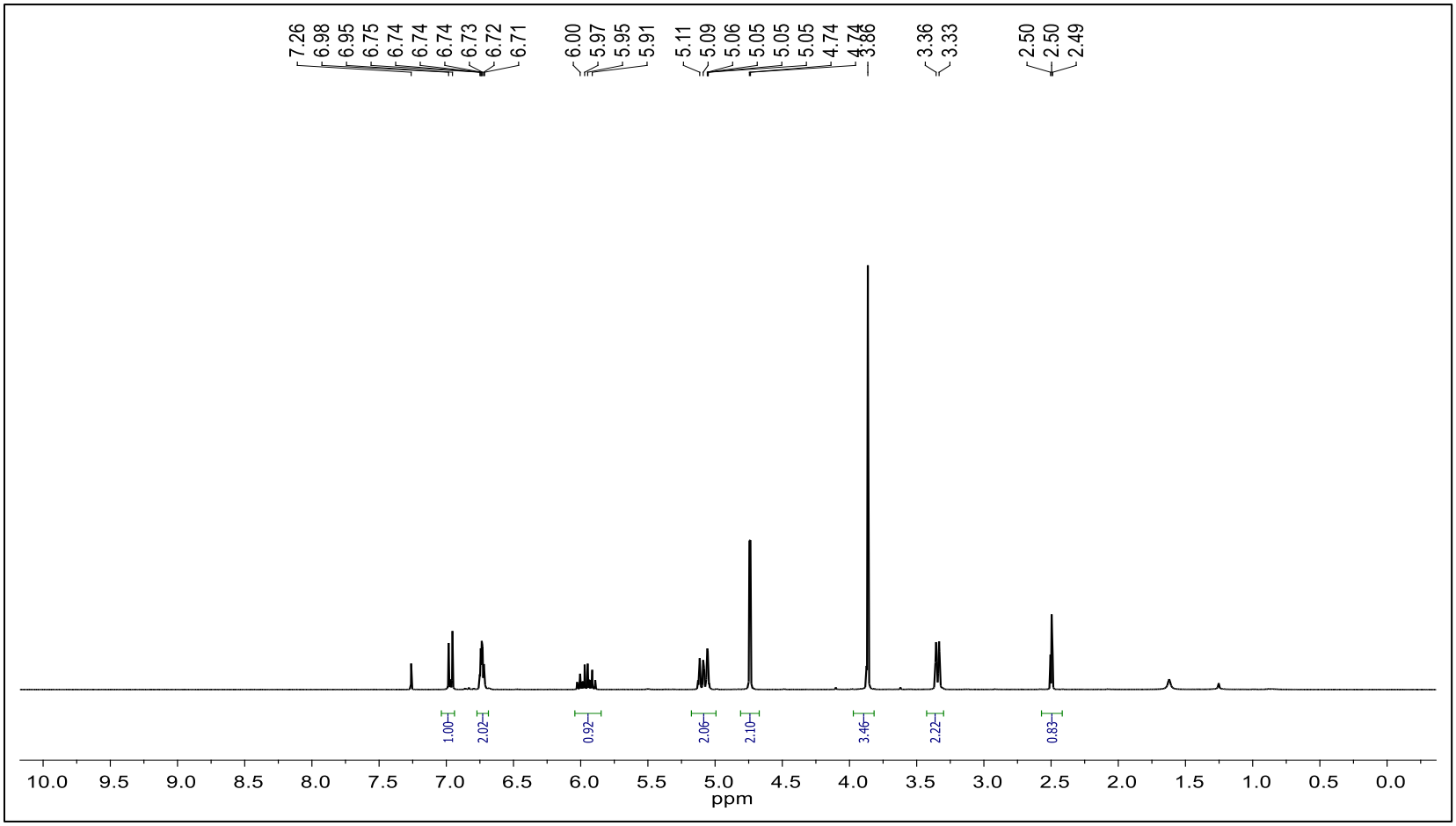
*5.1. FTIR (ATR) Spectrum of Compound **[4]***

Assigned bands (cm^{-1}): 3308 (C10-H), 3005 (CAr-H), 2111 (C≡C), 1511 (C=C), 1045 (C-O).



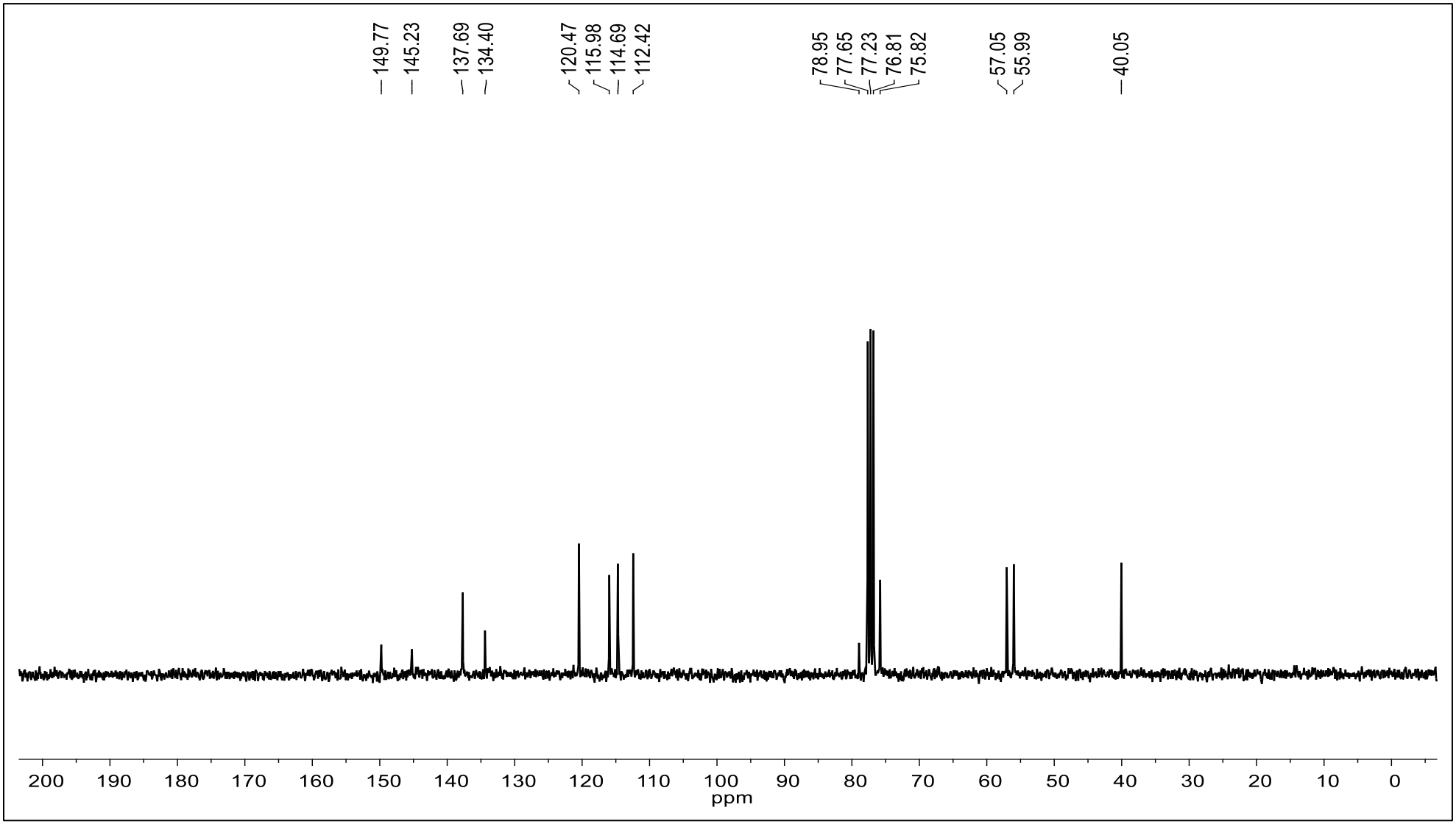
5.2. ^{1}H NMR Spectrum [300 MHz, $CDCl_3$ (ppm)] of Compound ***[4]***

Assigned signals (ppm): 6.93 [d, ^{3}J = 8,1 Hz, 1H, H6'], 6.72 [m, 2H, H3', H5'], 4.72 [s, 2H, H8'], 4.11 [s, 1H, H10], 3.65 [s, 3H, H7'], 2.51 [t, ^{3}J = 7.6 Hz, 2H, Ar-C<u>H</u>$_2$], 1.61 [s, ^{3}J = 7.6 Hz, 2H, -C<u>H</u>$_2$], 0.93 [t, ^{3}J = 7.6 Hz, 3H, -C<u>H</u>$_3$].



5.3. *^{13}C NMR Spectrum [75 MHz, $CDCl_3$ (ppm)] of Compound* ***[4]***

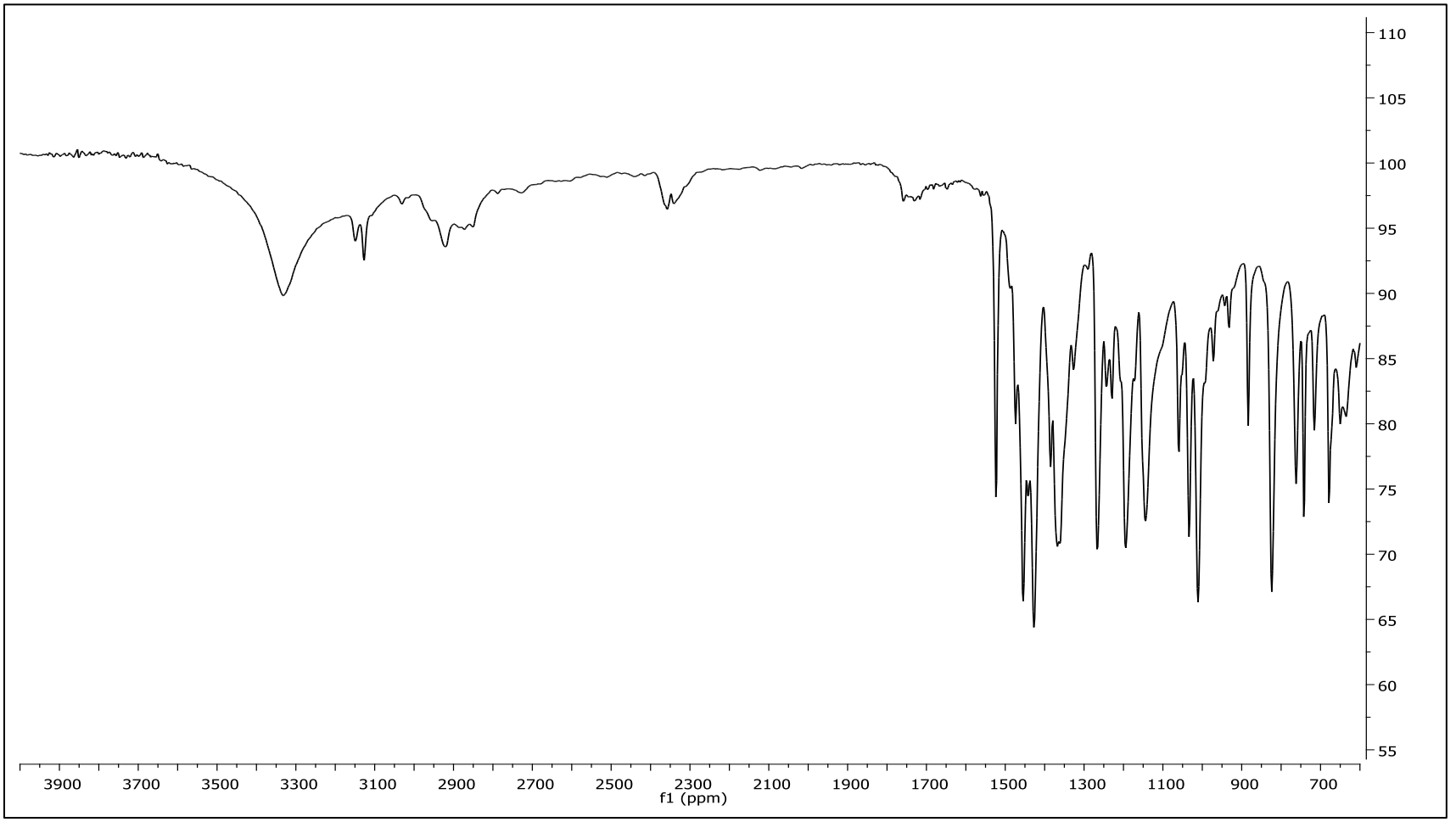
Assigned signals (ppm): 149.9 [C2'], 149.4 [C1'], 136.9 [C4'], 120.1 [C5'], 114.5 [C6'], 112.2 [C3'], 78.9 [C9], 75.5 [C10], 56.9 [C8'], 55.8 [C7'], 37.7 [Ar-$\underline{C}H_2$], 29.7 [$\underline{C}H_2$'], 14,2 [$\underline{C}H_3$].



Compound [5] = [1-methoxy-2-(prop-2-yn-1-yloxy)benzene]

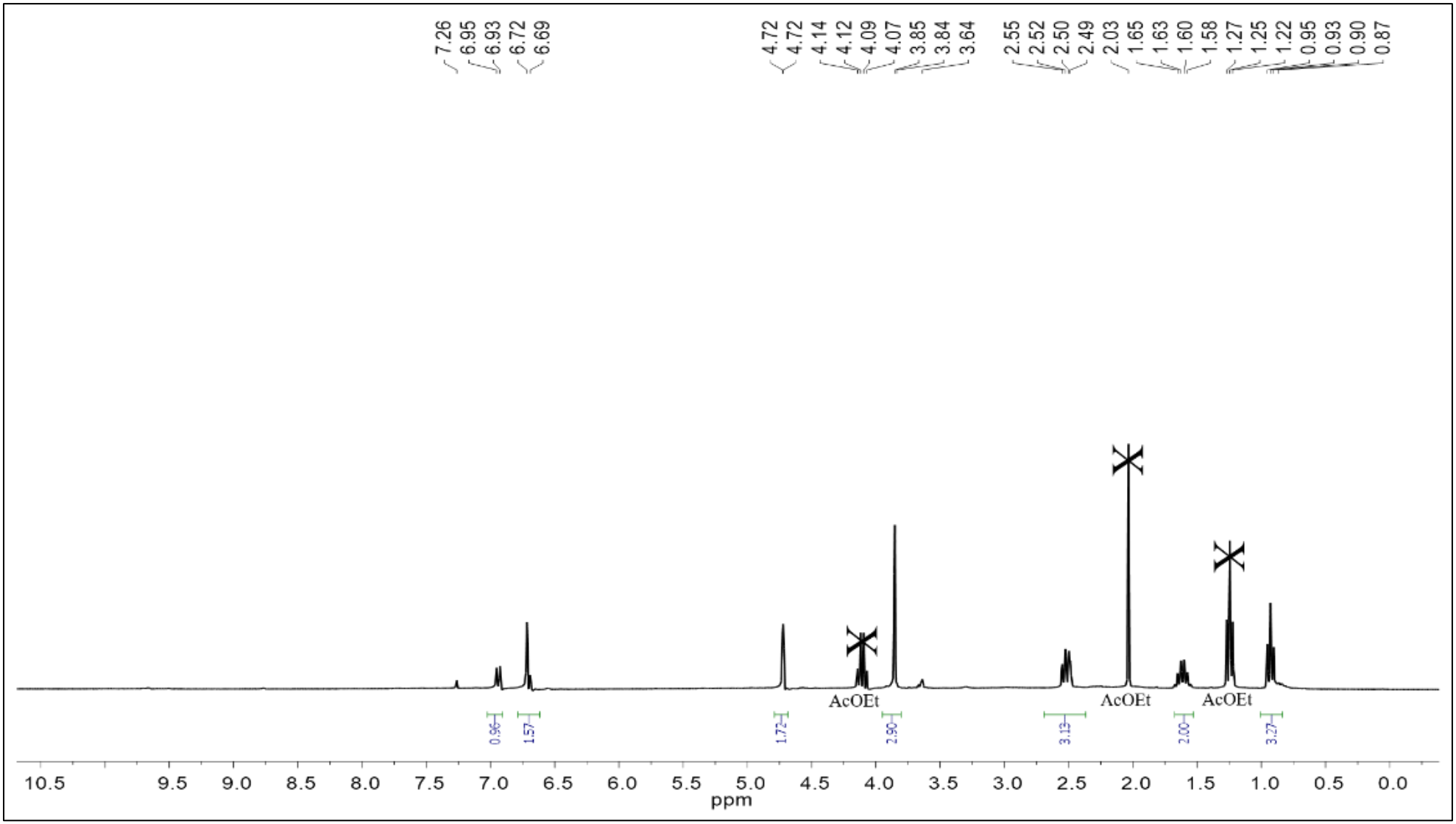
*5.4. FTIR (ATR) Spectrum of Compound **[5]***

Assigned bands (cm^{-1}): 3299 (C10-H), 3007 (CAr-H), 2115 (C≡C), 1499 (C=C), 1045 (C-O).



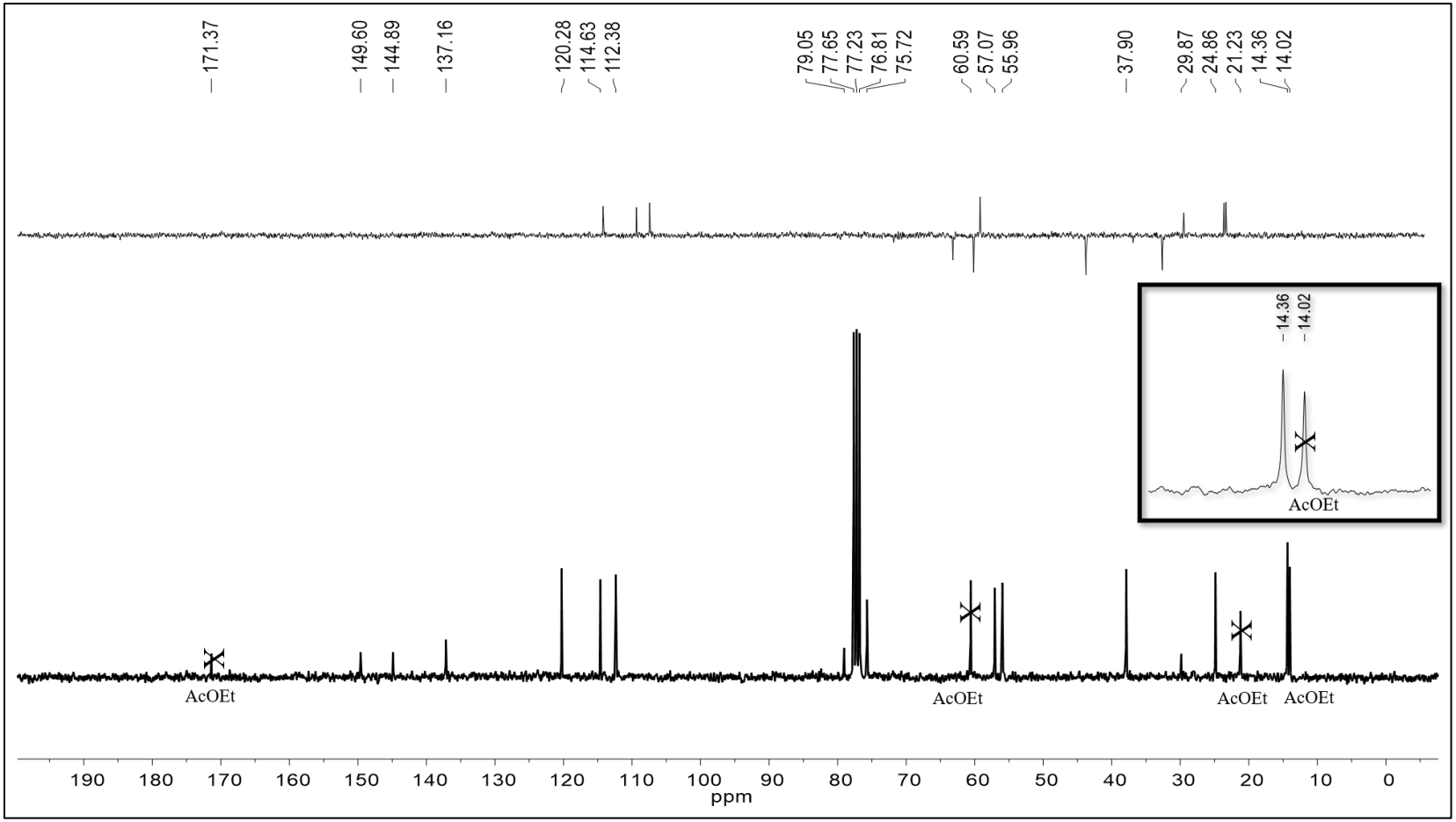
5.5. *^{1}H NMR Spectrum [300 MHz, $CDCl_3$ (ppm)] of Compound* ***[5]***

Assigned signals (ppm): 6.97 [d, ^{3}J = 8.6 Hz, 1H, H6'], 6.74 [m, 2H, H3', H5'], 5.96 [m, 1H, C<u>H</u>=CH_2], 5.08 [m, 2H, CH=C<u>H_2</u>], 4.74 [d, ^{3}J = 2.4 Hz, 2H, H8'], 3.86 [s, 3H, H7'], 3.34 [d, ^{3}J = 6.8 Hz, 2H, Ar-C<u>H_2</u>'], 2.49 [t, ^{3}J = 2.4 Hz, 2H, H10].



5.6. *^{13}C NMR Spectrum [75 MHz, $CDCl_3$ (ppm)] of Compound* ***[5]***

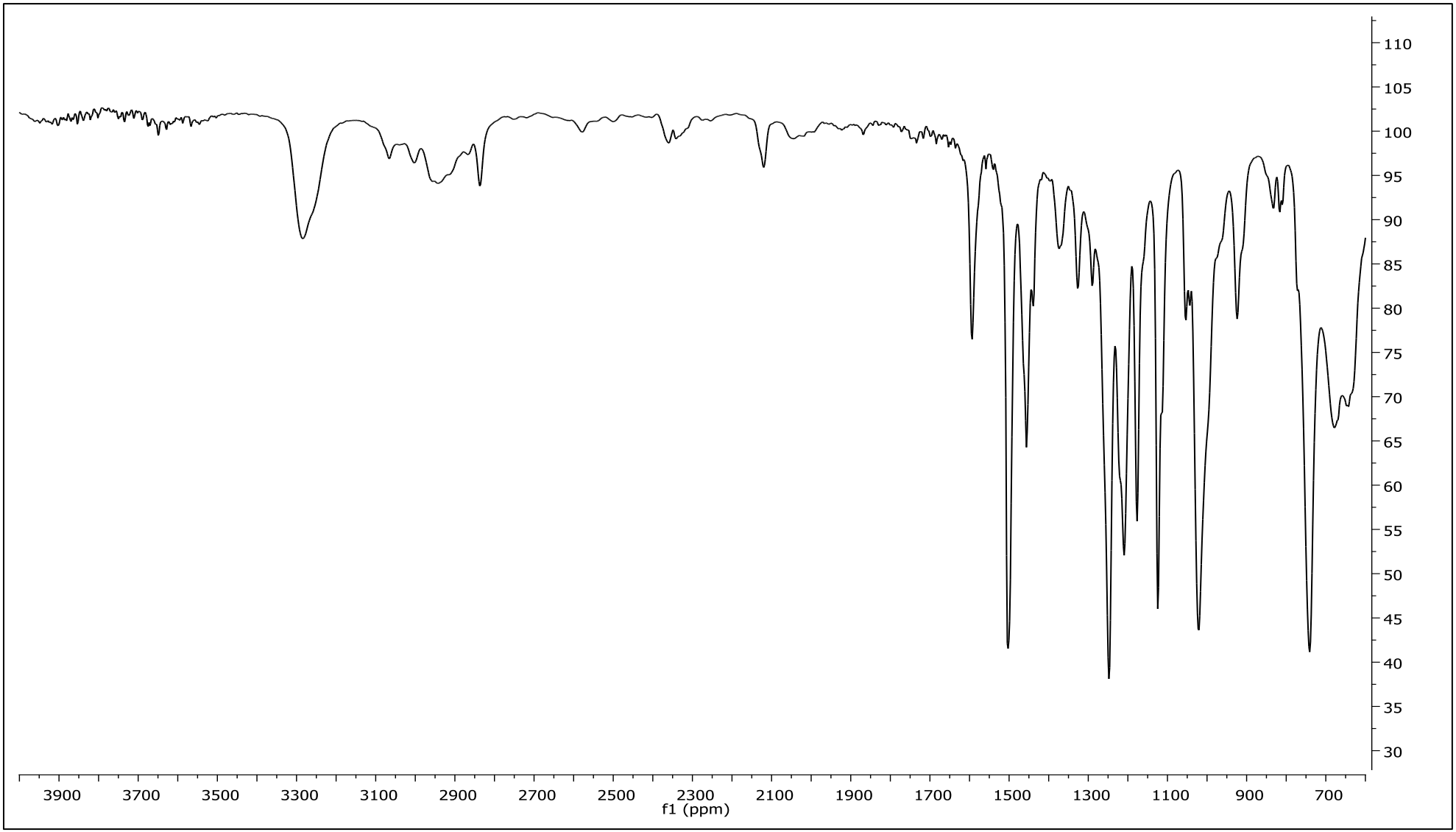
Assigned signals (ppm): 149.6 [C2'], 145.1 [C1'], 137.5 [$\underline{C}H=CH_2$], 133.2 [C4'], 120.3 [C5'], 115.8 [$CH=\underline{C}H_2$],114.5 [C6'], 112.3 [C3'], 78.8 [C9], 75.7 [C10], 56.9 [C8'], 55.8 [C7'], 39.9 [Ar-$\underline{C}H_2$].



6. Compound [6] = [(1-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methanol]

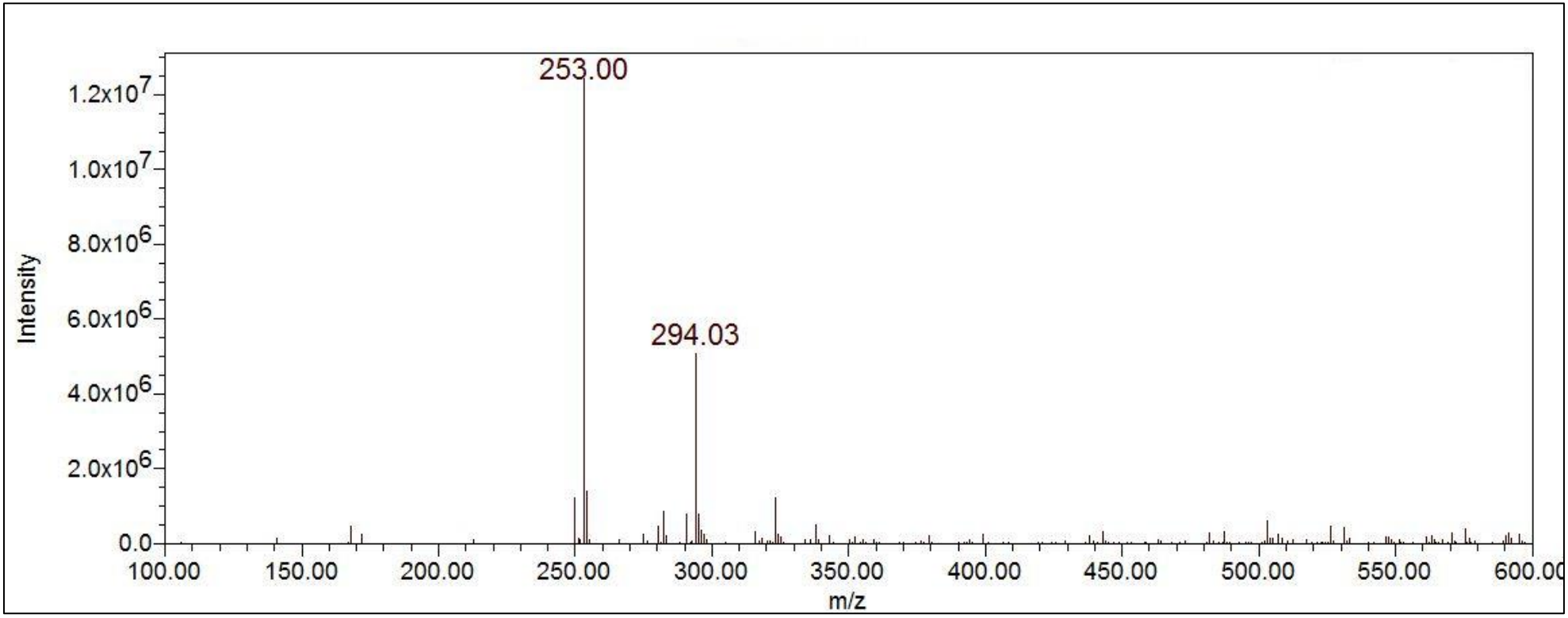
*6.1. FTIR (ATR) Spectrum of Compound **[6]***

Assigned bands (cm^{-1}): 3059 (C10-H), 3015 (CAr-H), 1504 (C=C), 1284 (N=O), 1118 (N=O), 1051 (C-O).



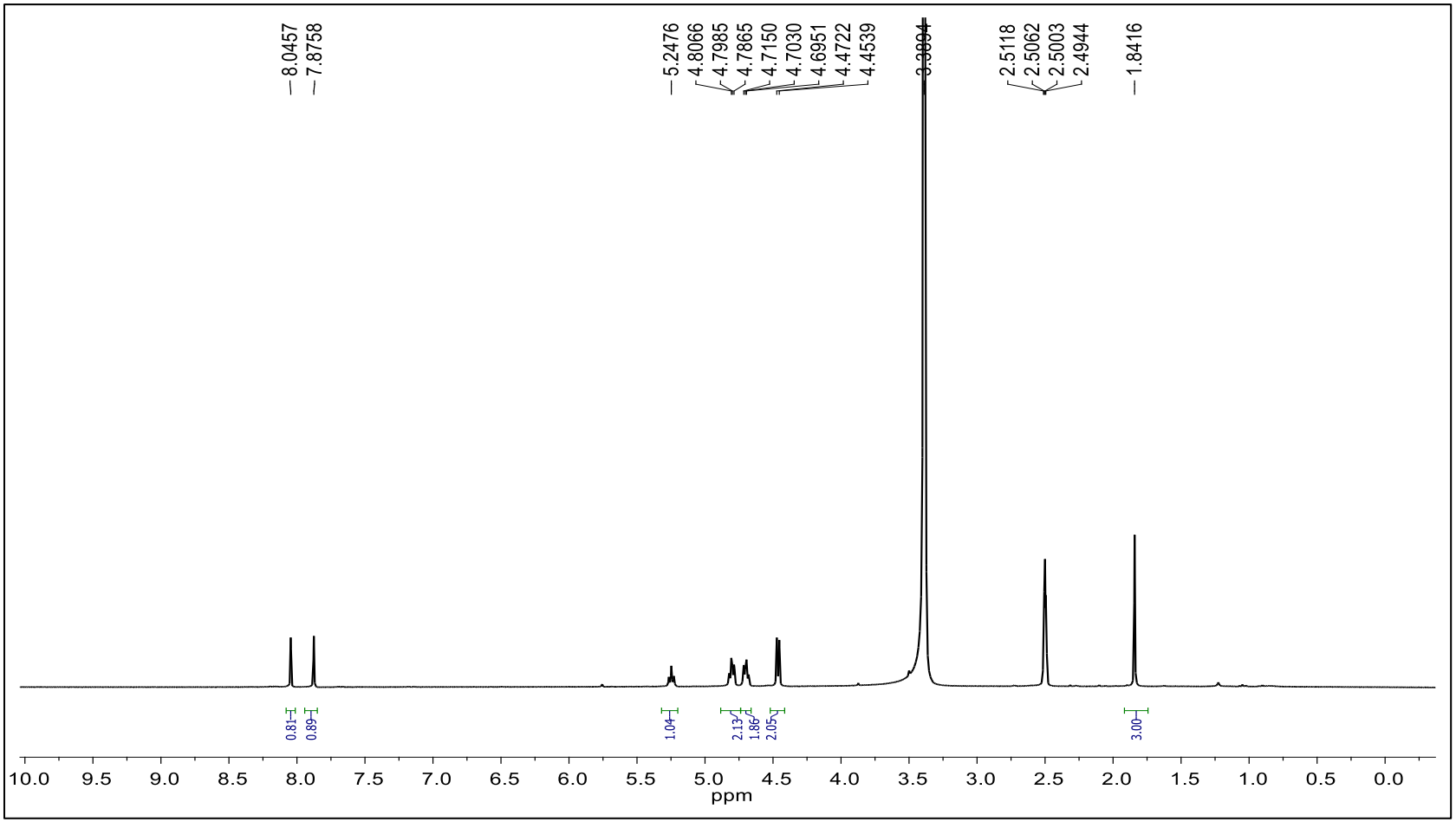
6.2. LCMS (ESI) Spectrum of Compound ***[6]***

LC-MS (ESI) m/z calculated for $C_9H_{12}N_6O_3$ = 252.10, m/z + H^+ = 253.0. Found 253.00.



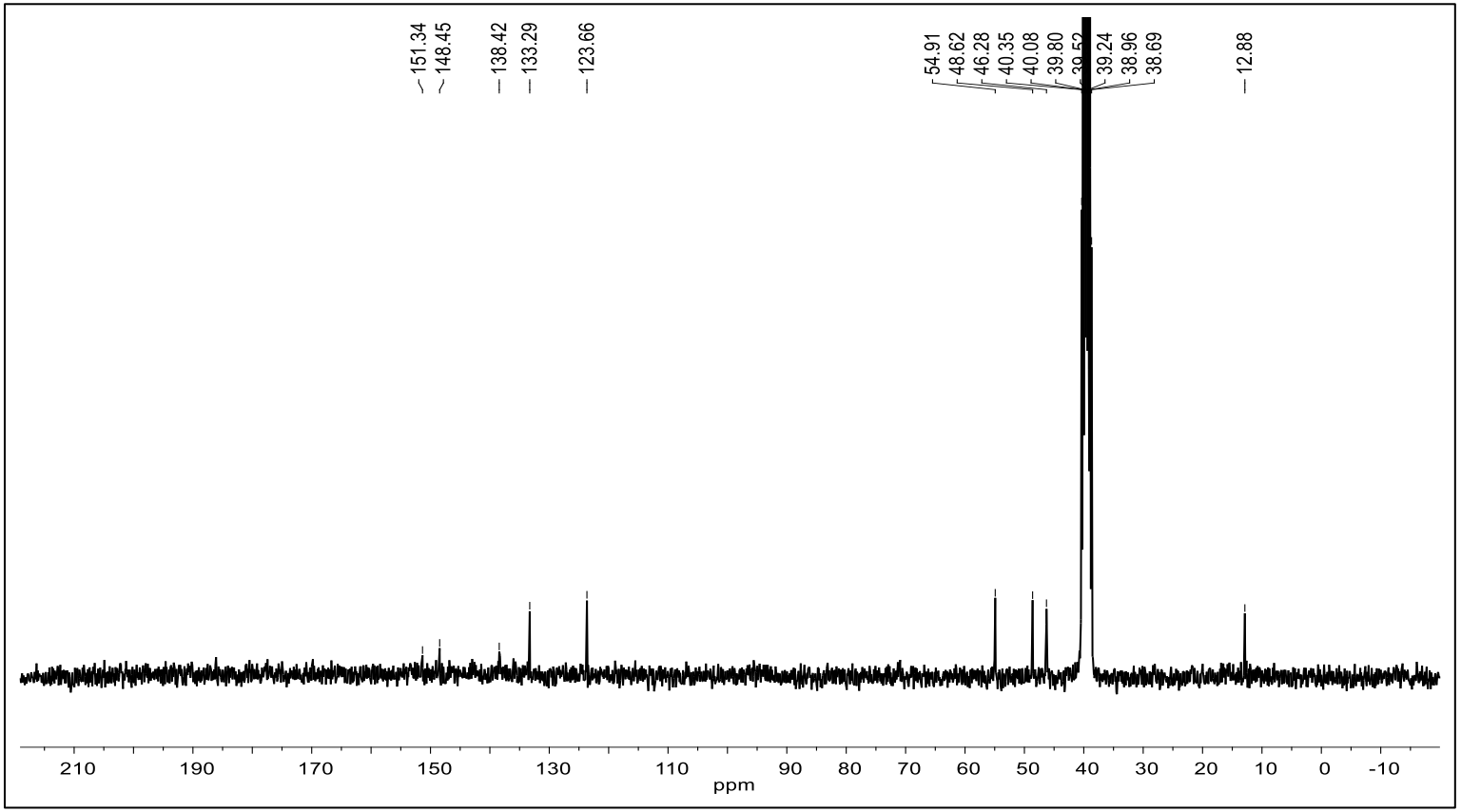
6.3. *^{1}H NMR Spectrum [300 MHz, DMSO-d_6 (ppm)] of Compound* ***[6]***

Assigned signals (ppm): 8.04 [s, 1H, H4], 7.87 [s, 1H, H10'], 5.25 [t, ^{3}J = 5.7 Hz, 1H, OH], 4.79 [t, ^{3}J = 5.7 Hz, 2H, H8], 4.68 [t, ^{3}J = 5.7 Hz, 2H, H7], 4.47 [d, ^{3}J = 5.7 Hz, 2H, H11], 1.83 [s, 3H, H6].



6.4. *^{13}C NMR Spectrum [75 MHz, DMSO-d_6 (ppm)] of Compound* ***{6]***

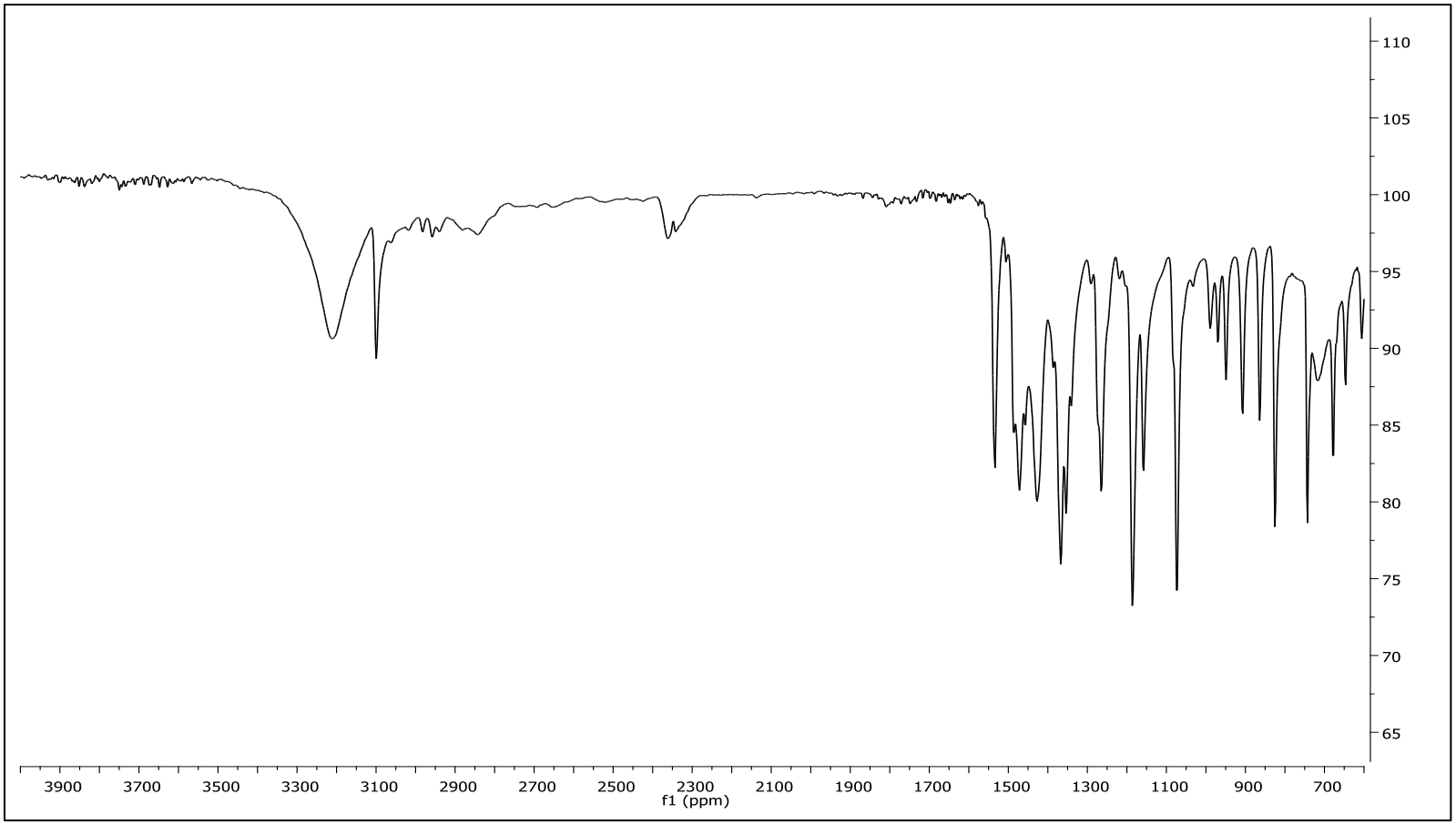
Assigned signals (ppm): 151.8 [C2], 149.9 [C9'], 138.9 [C5], 133.7 [C4], 124.1 [C10'], 53.3 [C8], 49.0 [C8'], 46.7 [C7], 13.3 [C6]



7. Compound [7] = [4-((2-methoxyphenoxy)methyl)-1-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)-1H-1,2,3-triazole]

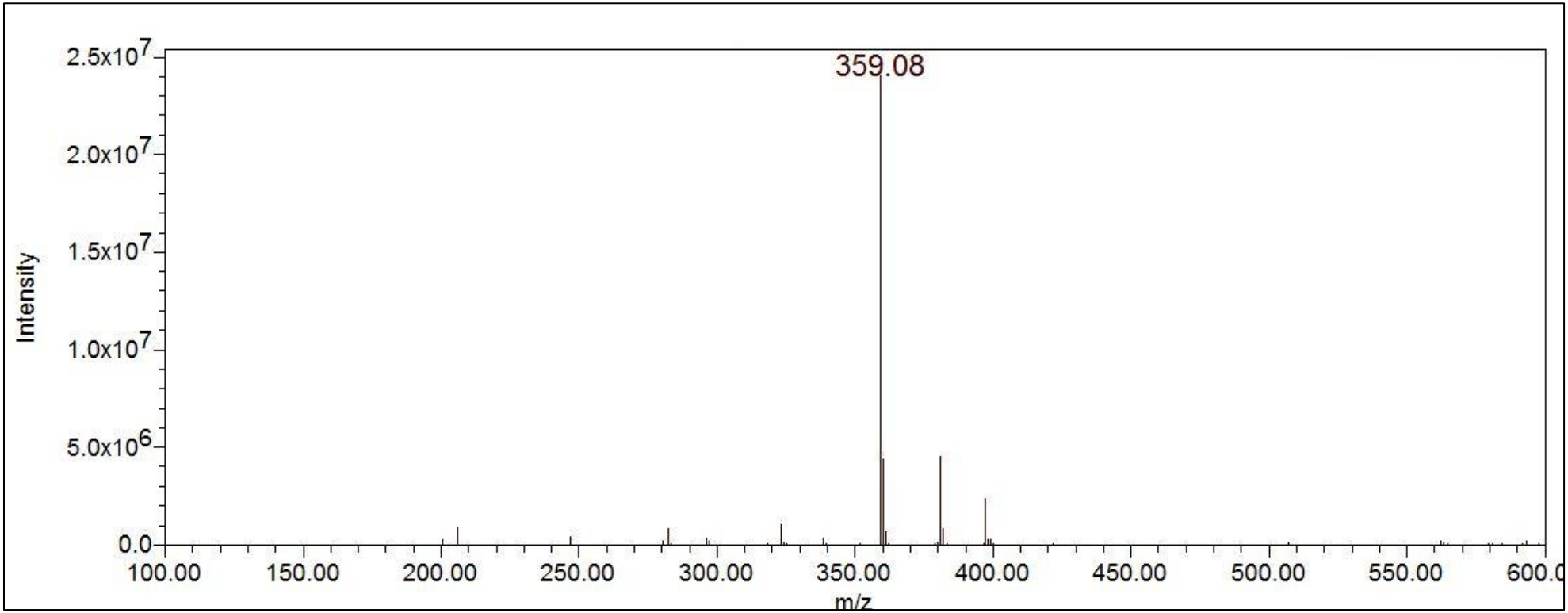
*7.1. FTIR (ATR) Spectrum of Compound **[7]***

Assigned bands (cm^{-1}): 3055 (C10-H), 3011 (CAr-H), 1507 (C=C), 1294 (N=O), 1201 (N=O), 1032 (C-O).



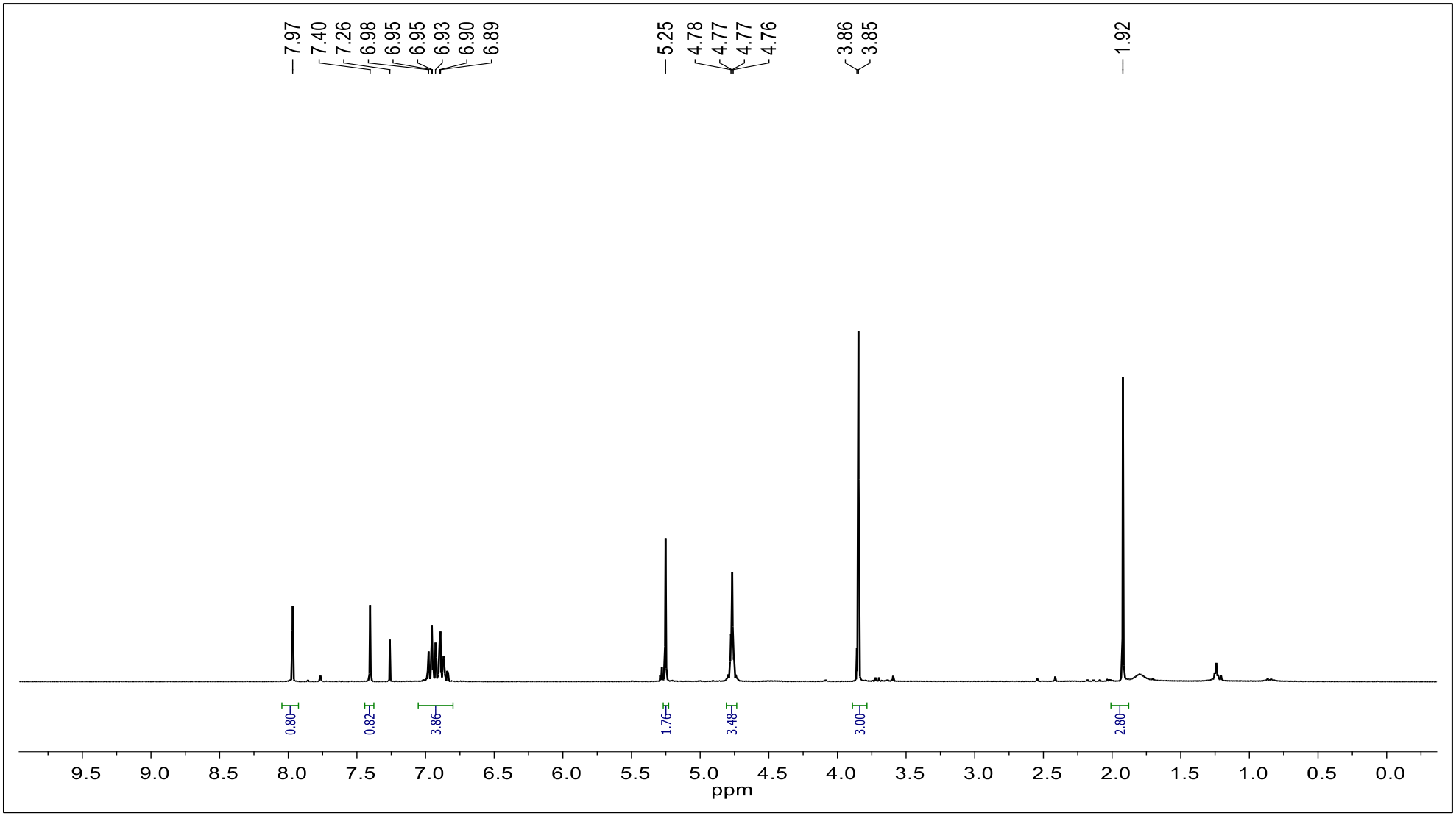
*7.2. LCMS (ESI) Spectrum of Compound **[7]***

LC-MS (ESI) m/z calculated for $C_{16}H_{18}N_6O_4$ = 358.14, m/z + H^+ = 359.14. Found 359.08.

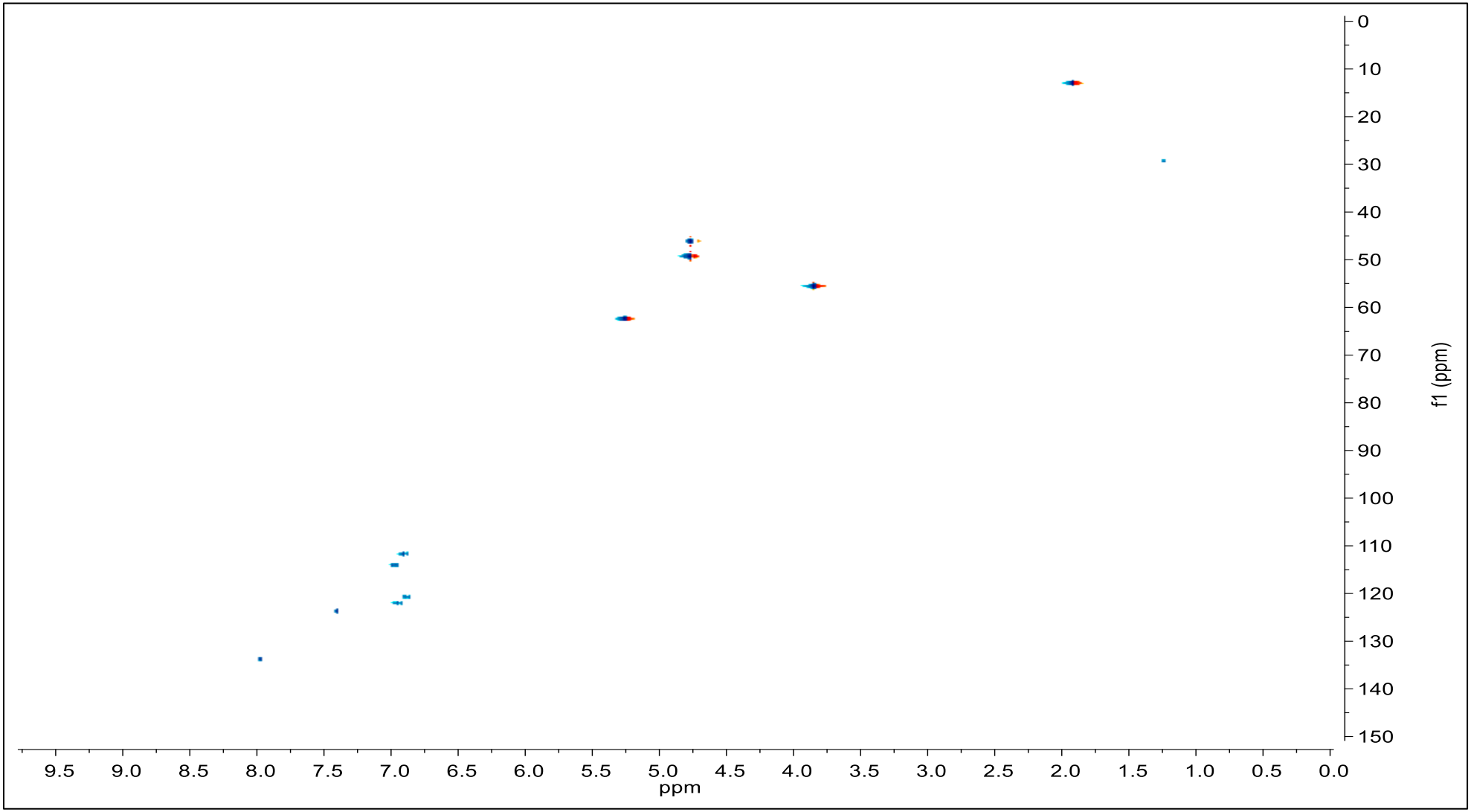


7.3. *^{1}H NMR Spectrum [300 MHz, $CDCl_3$ (ppm)] of Compound* ***[7]***

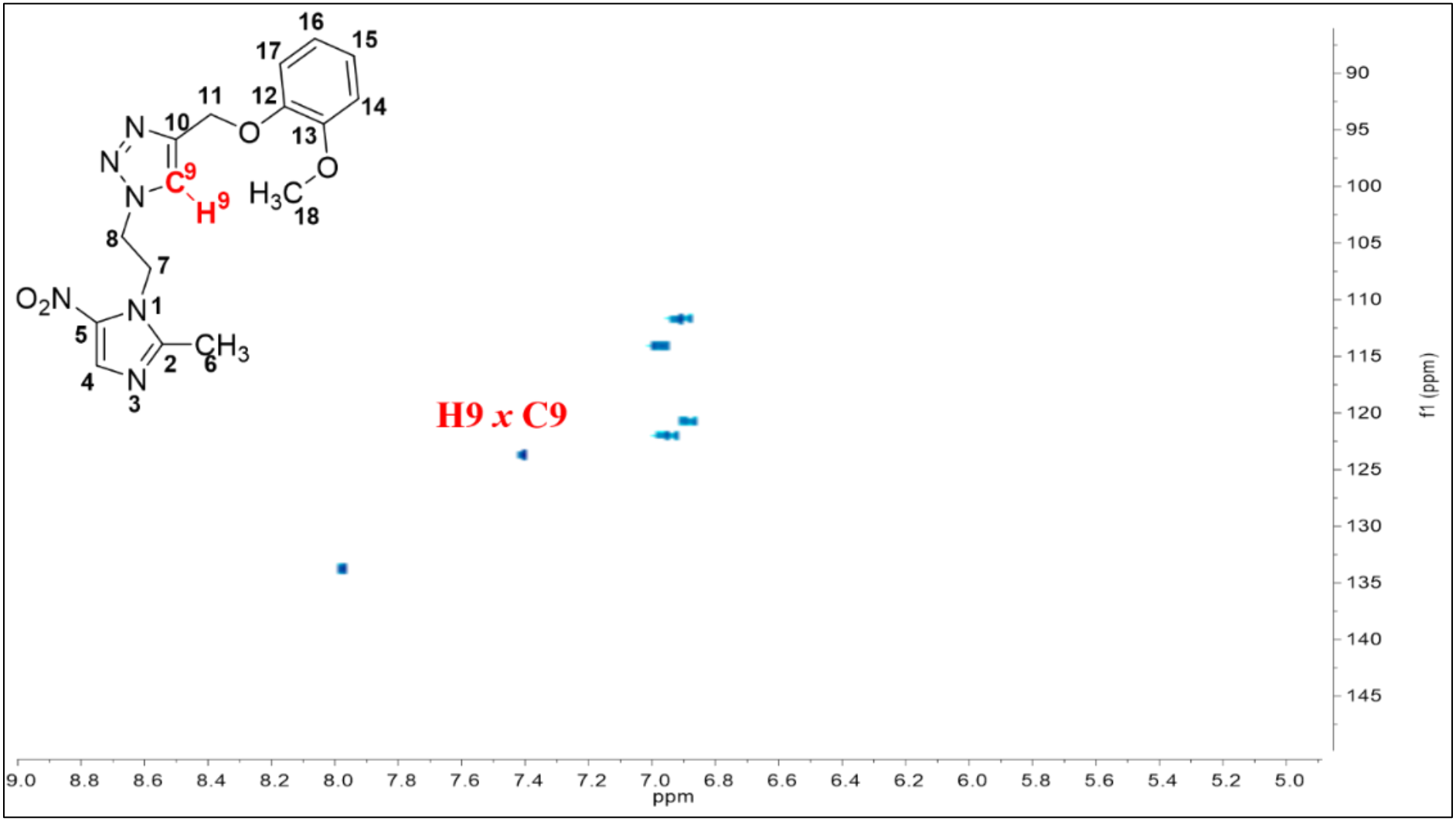
Assigned signals (ppm): 7.97 [s, 1H, H4], 7.40 [s, 1H, H10'], 6.91 [m, 4H, H3'-H6'], 5.25 [s, 2H, H8'], 4.77 [s, 4H, H7, H8], 3.85 [s, 3H, H7'], 1.92 [s, 3H, H6].



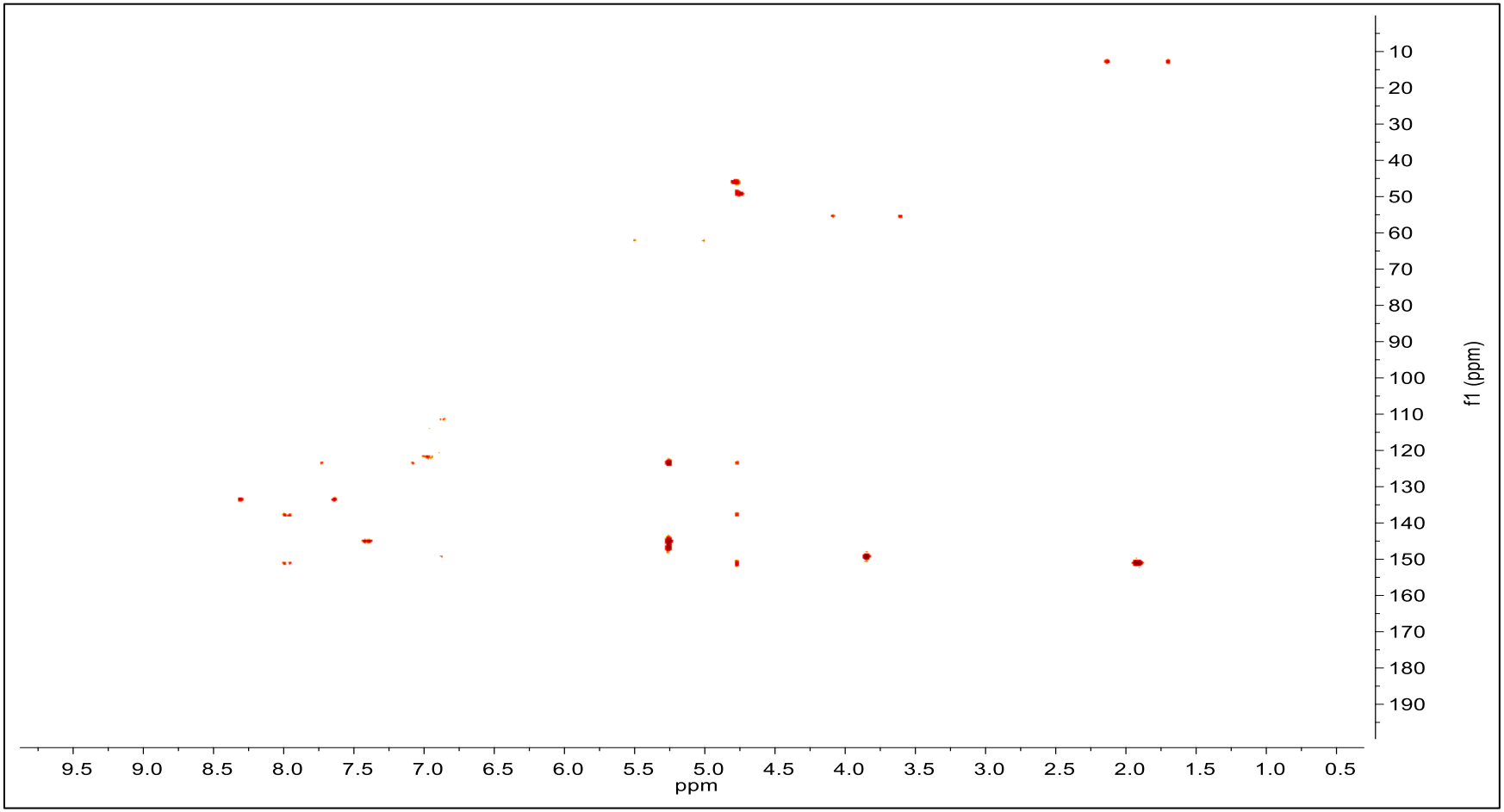
7.4. *^{1}H NMR 2D HSQC Spectrum [300 MHz, $CDCl_3$ (ppm)] (complete) of Compound* ***[7]***



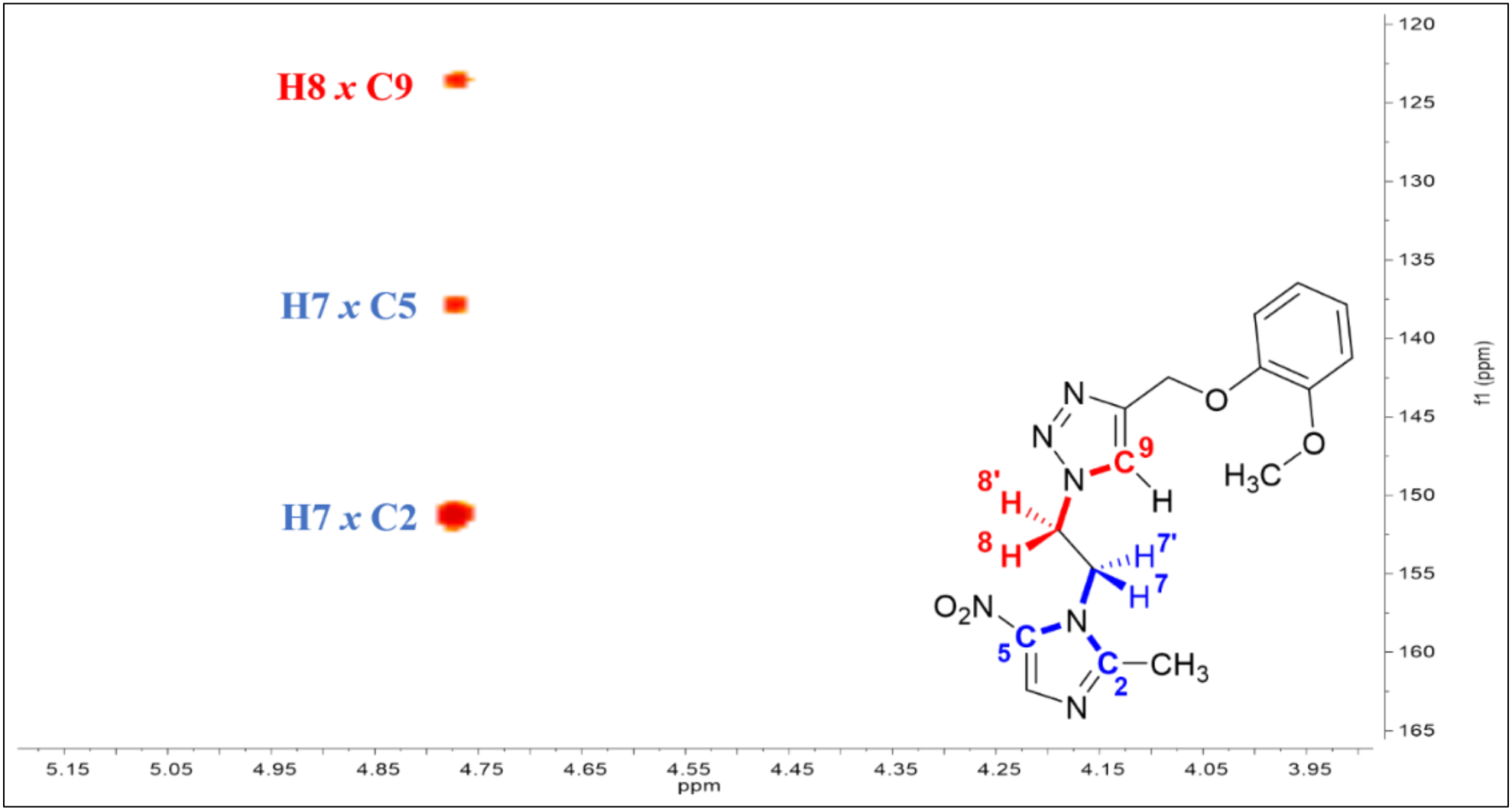
7.5. *^{1}H NMR 2D HSQC Spectrum [300 MHz, $CDCl_3$ (ppm)] (expanded) of Compound* ***[7]***



7.6. ^{1}H NMR 2D HMQC Spectrum [300 MHz, $CDCl_3$ (ppm)] (complete) of Compound ***[7]***

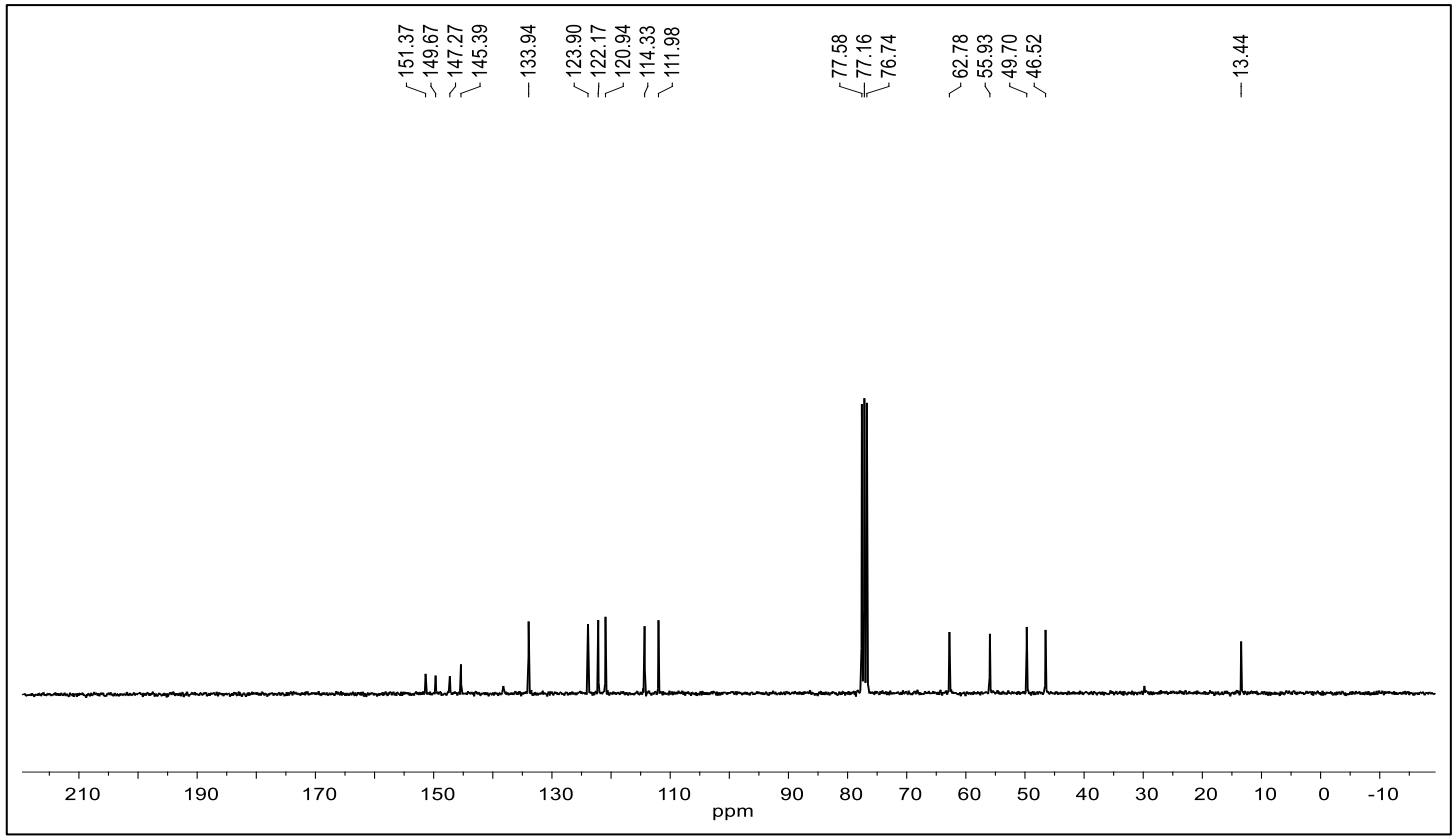


7.7. *^{1}H NMR 2D HMQC Spectrum [300 MHz, $CDCl_3$ (ppm)] (expanded) of Compound* ***[7]***



7.8. *^{13}C NMR Spectrum [75 MHz, $CDCl_3$ (ppm)] of Compound* ***[7]***

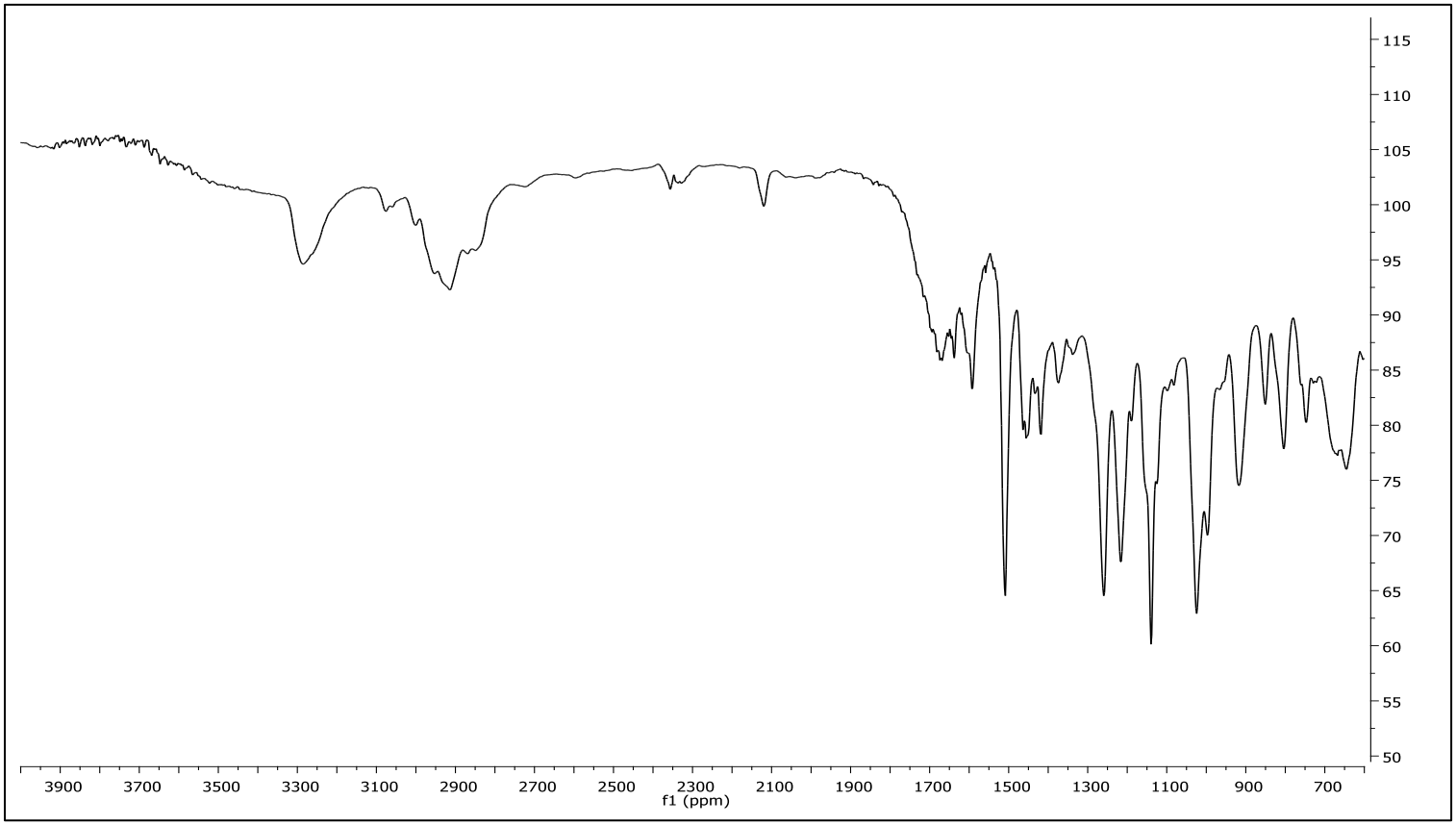
Assigned signals (ppm): 151.3 [C2], 149.6 [C9'], 147.2 [C1'], 145.3 [C2'], 138.1 [C5], 133.8 [C4], 123.8 [C10'], 122.1 [C5'], 120.1 [C6'], 114.1 [C4'], 111.9 [C3'], 62.7 [C8'], 55.9 [C7'], 49.6 [C8], 46.4 [C7], 13.3 [C6].



8. Compound [8] = [4-((4-allyl-2-methoxyphenoxy)methyl)-1-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)-1H-1,2,3-triazole]

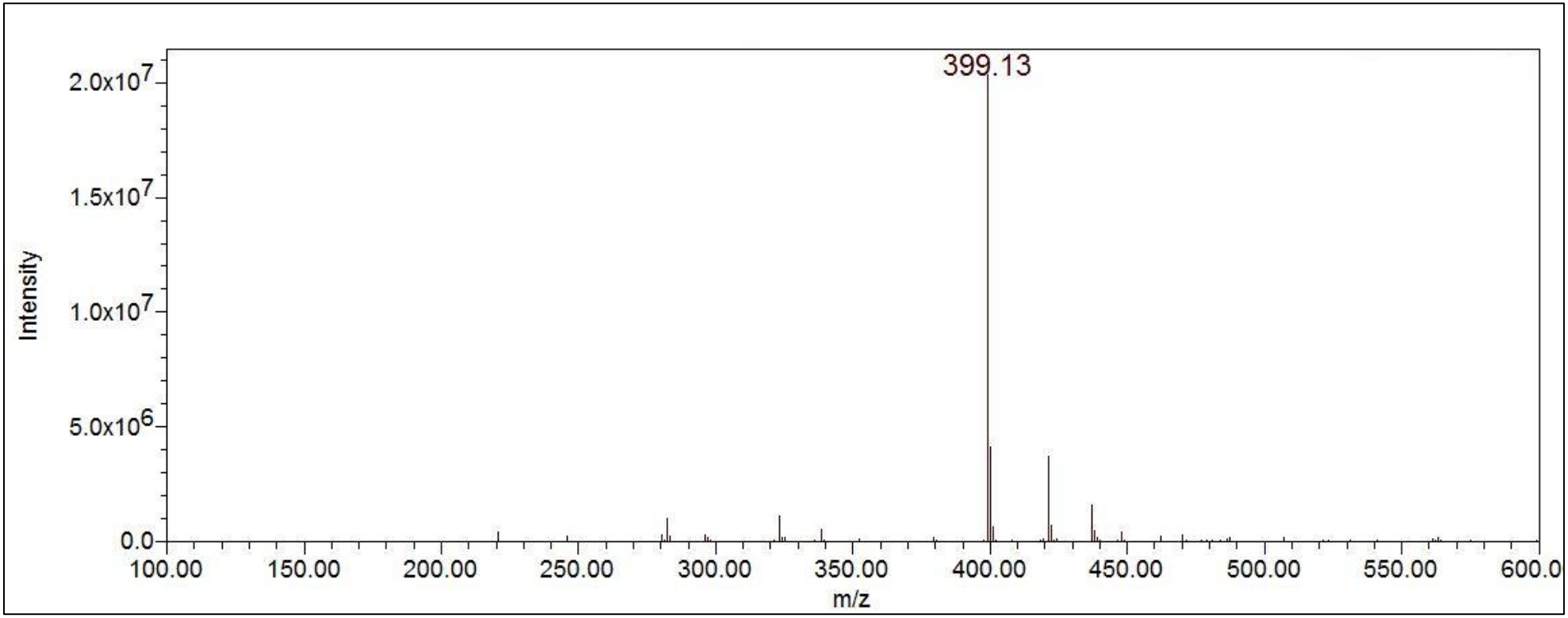
*8.1. FTIR (ATR) Spectrum of Compound **[8]***

Assigned signals (cm^{-1}): 3033 (C10-H), 3014 (CAr-H), 1518 (C=C), 1255 (N=O), 1237 (N=O), 1035 (C-O).



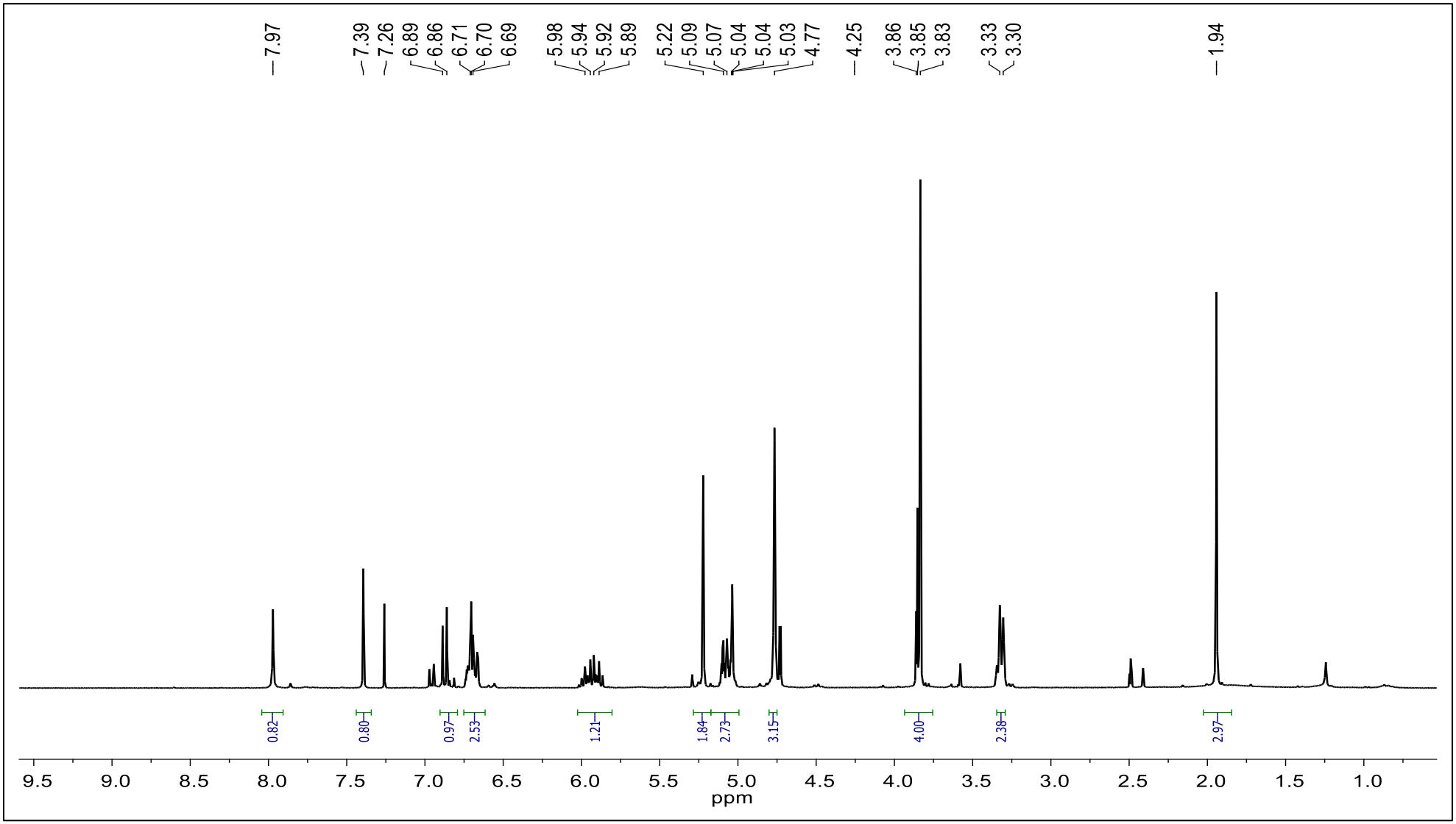
8.2. LCMS (ESI) Spectrum of Compound ***[8]***

LC-MS (ESI) m/z calculated for $C_{19}H_{22}N_6O_4$ = 398.17, m/z + H^+ = 399.17. Found 399.13.



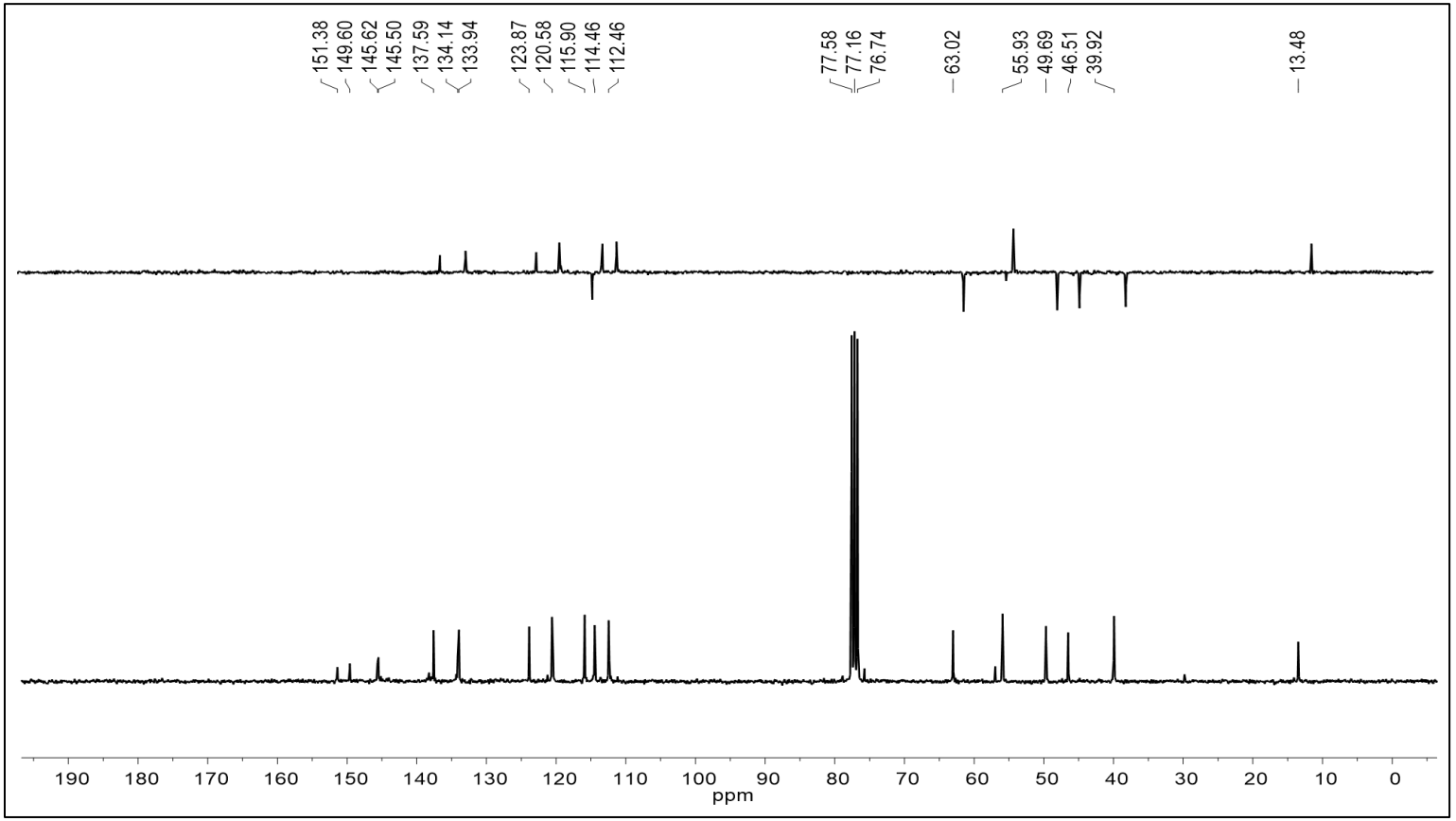
8.3. *^{1}H NMR Spectrum [300 MHz, $CDCl_3$ (ppm)] of Compound* ***[8]***

Assigned signals (ppm): 7.97 [s, 1H, H4], 7.40 [s, 1H, H10'], 6.87 [d, ^{3}J = 7.8 Hz, 1H, H6'], 6.72 [m, H3', H5'], 5.92 [m, 1H, C<u>H</u>=CH_2], 5.22 [s, 2H, H8'], 5.07 [m, 2H, C=C<u>H_2</u>], 4.76 [m, 4H, H7, H8], 3.85 [s, 3H, H7'], 3.31 [d, ^{3}J = 8.0 Hz, 2H, Ar-C<u>H_2</u>], 1.94, [s, 3H, H6].



8.4. *^{13}C NMR Spectrum [75 MHz, $CDCl_3$ (ppm)] of Compound* ***[8]***

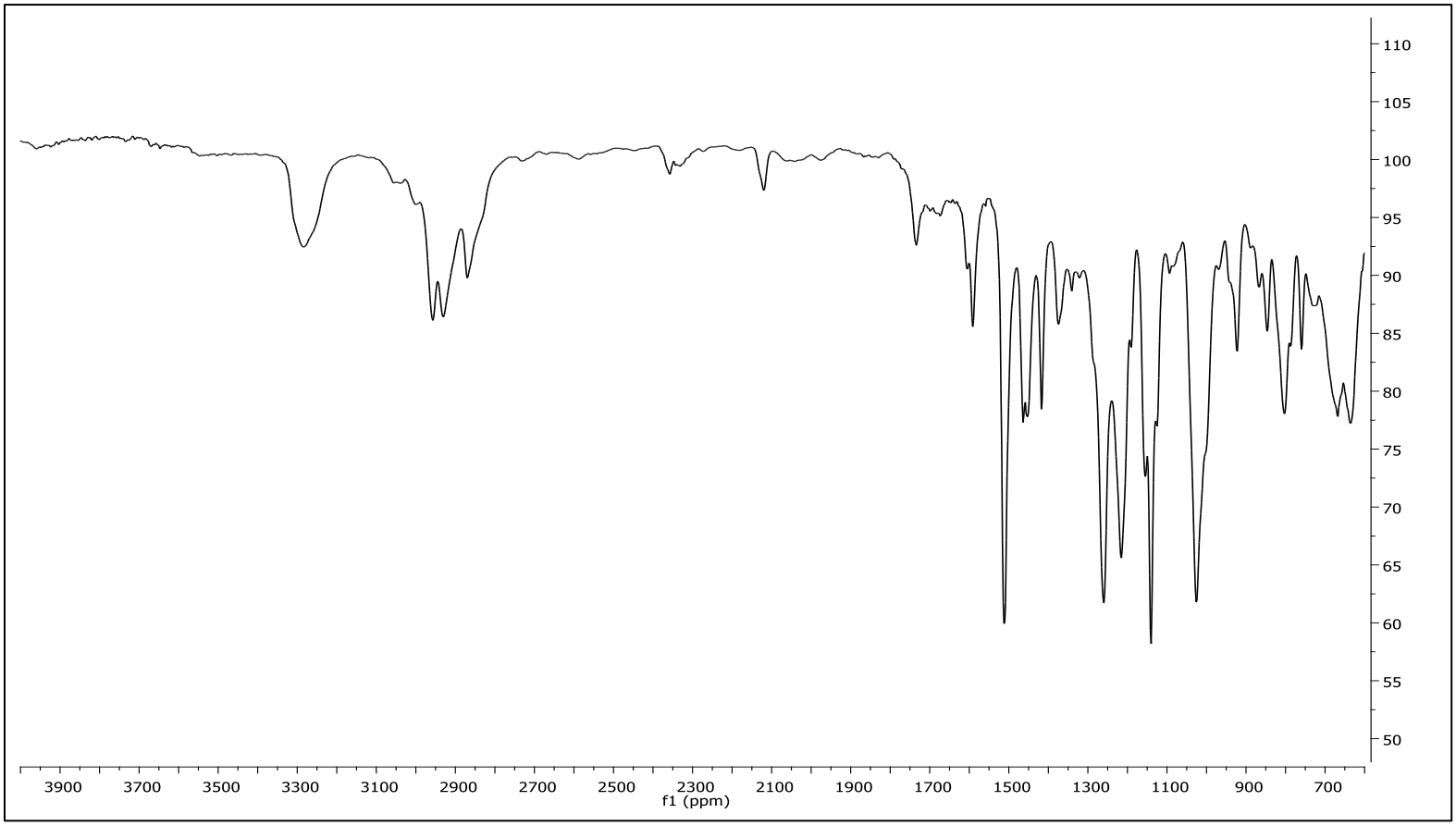
Assigned signals (ppm): 151.3 [C2], 149.5 [C9'], 145.5 [C2'], 145.41 [C1'], 137.5 [C5], 134.4 [C4'], 133.8 [C4], 133.5 [C $\underline{C}H=CH_2$], 123.8 [C10'], 120.5 [C5'], 115.8 [$CH=\underline{C}H_2$]], 114.5 [C6'], 112.4 [C3'], 62.9 [C8'], 55.8 [C7'], 49.6 [C8], 46.4 [C7], 39.8 [Ar-$\underline{C}H_2$], 13.4 [C6].



9. Compound [9] = [4-((2-methoxy-4-propylphenoxy)methyl)-1-(2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl)-1H-1,2,3-triazole]

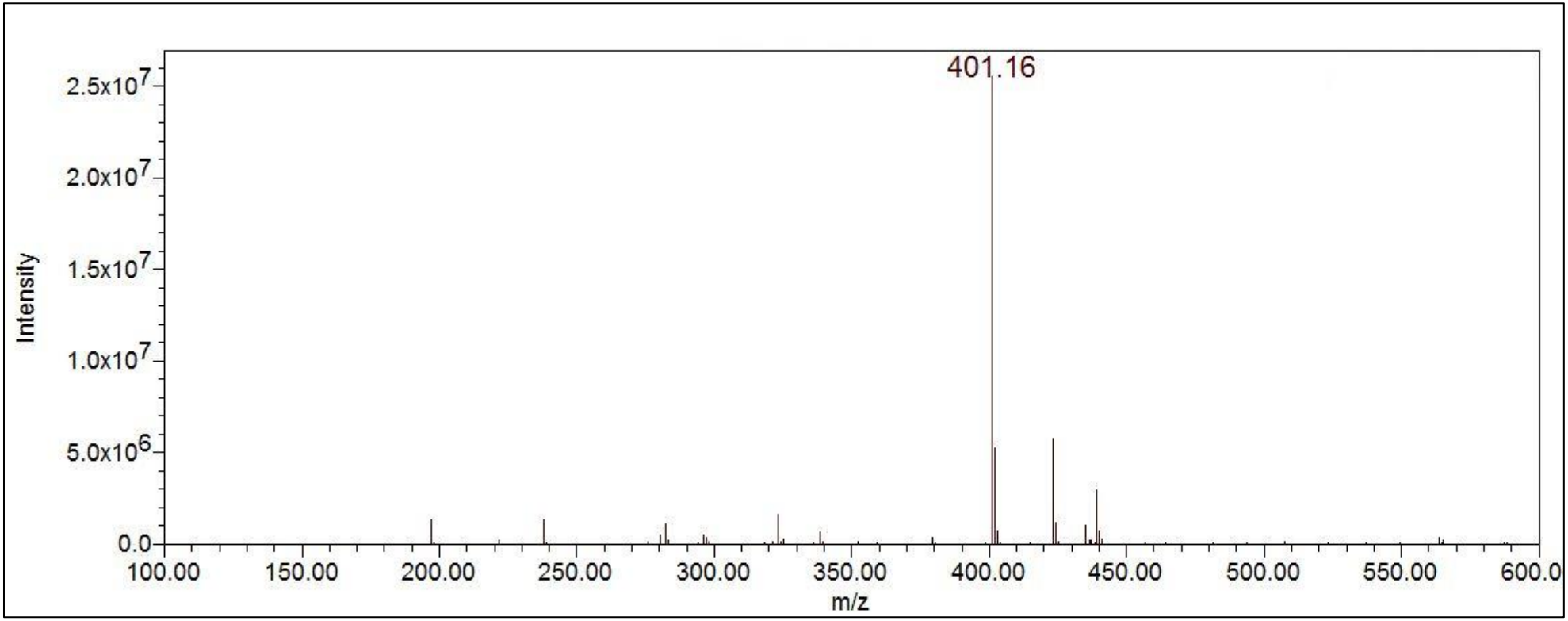
*9.1. FTIR (ATR) Spectrum of Compound **[9]***

Assigned bands (cm^{-1}): 3049 (C10-H), 3010 (CAr-H), 1508 (C=C), 1285 (N=O), 1215 (N=O), 1033 (C-O).



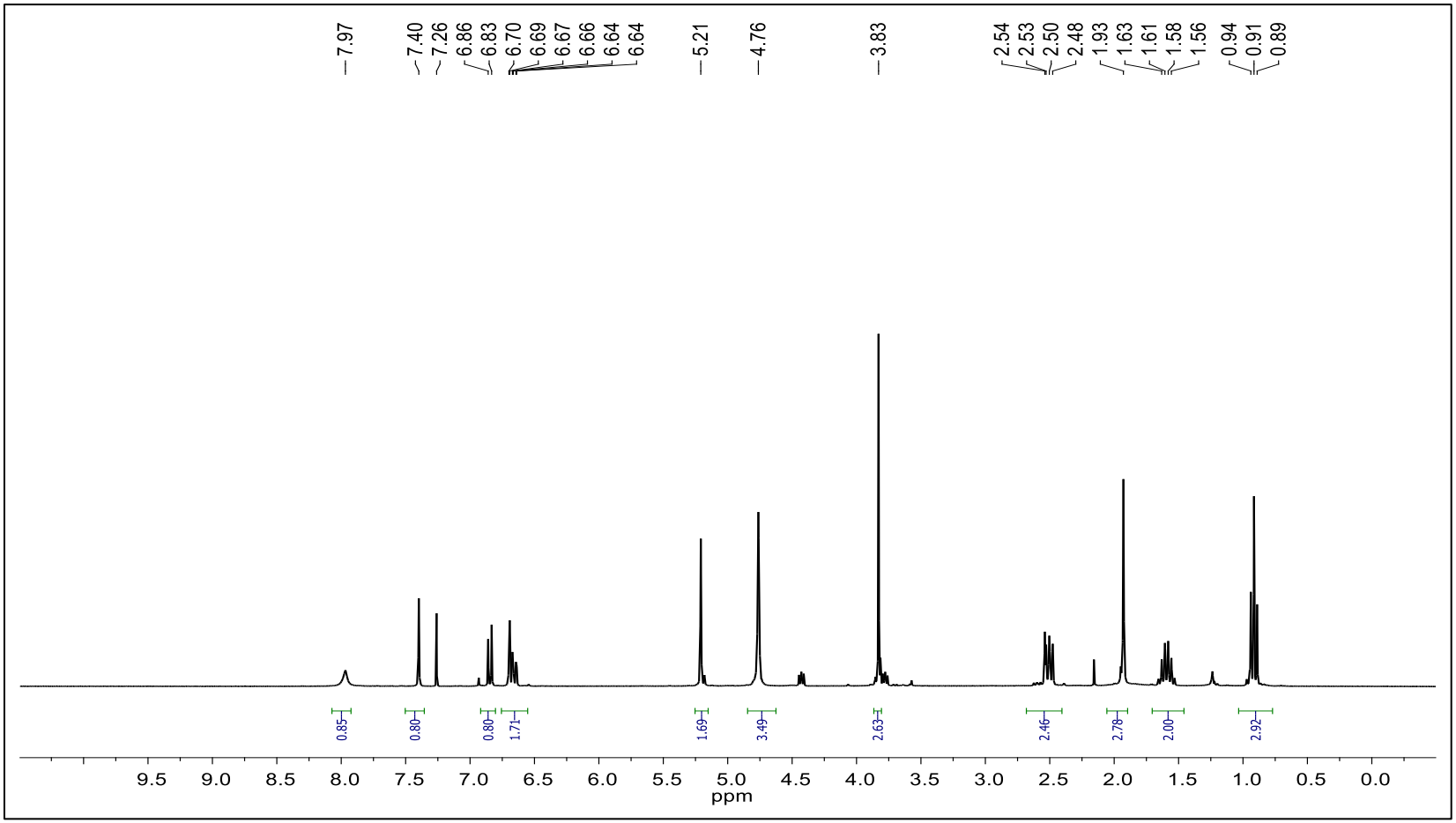
*9.2. LCMS (ESI) Spectrum of Compound **[9]***

LC-MS (ESI) m/z calculated for $C_{19}H_{24}N_6O_4$ = 400.19, m/z + H^+ = 401.19. Found 401.16.



9.3. *^{1}H NMR Spectrum [300 MHz, $CDCl_3$ (ppm)] of Compound* ***[9]***

Assigned signals (ppm): 7.97 [s, 1H, H4], 7.39 [s, 1H, H10'], 6.84 [d, ^{3}J = 8.1 Hz, 1H, H6'], 6.67 [m, H3', H5'], 5.21 [s, 2H, H8'], 4.75 [s, 4H, H7, H8], 3.81 [s, 3H, H7'], 2.50 [t, ^{3}J = 7.9 Hz, 2H, Ar-C<u>H</u>$_2$], 1.95, [s, 3H, H6], 1.60 [s, ^{3}J = 7.3 Hz, 2H, -C<u>H</u>$_2$], 0.94 [t, ^{3}J = 7.3 Hz, 3H, -C<u>H</u>$_3$].



9.4. *^{13}C NMR Spectrum [75 MHz, $CDCl_3$ (ppm)] of Compound* ***[9]***

Assigned signals (ppm): 149.3 [C2], 145.5 [C9'], 145.2 [C2'], 136.8 [C1'], 133.9 [C5], 133.6 [C4'], 133.5 [C4], 123.8 [C10'], 120.3 [C5'], 114.3 [C6'], 112.3 [C3'], 62.9 [C8'], 55.8 [C7'], 49.6 [C8], 46.4 [C7], 37.7 [Ar-$\underline{C}H_2$], 24.7 [$\underline{C}H_2$], 13.8 [$\underline{C}H_3$], 13.4 [C6].