Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.
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Biocatalytic stereoselective synthesis of pyrrolidine-2,3-diones containing all-carbon quaternary stereocenters

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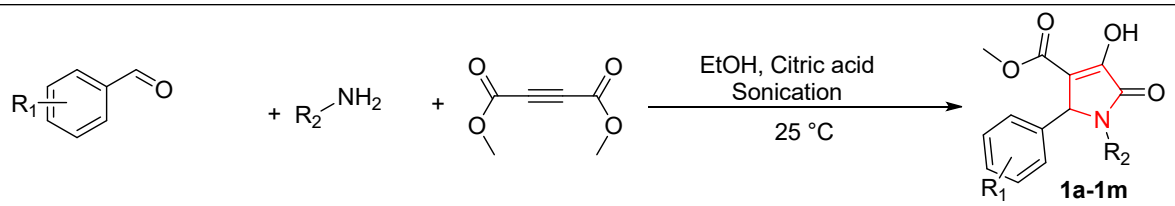
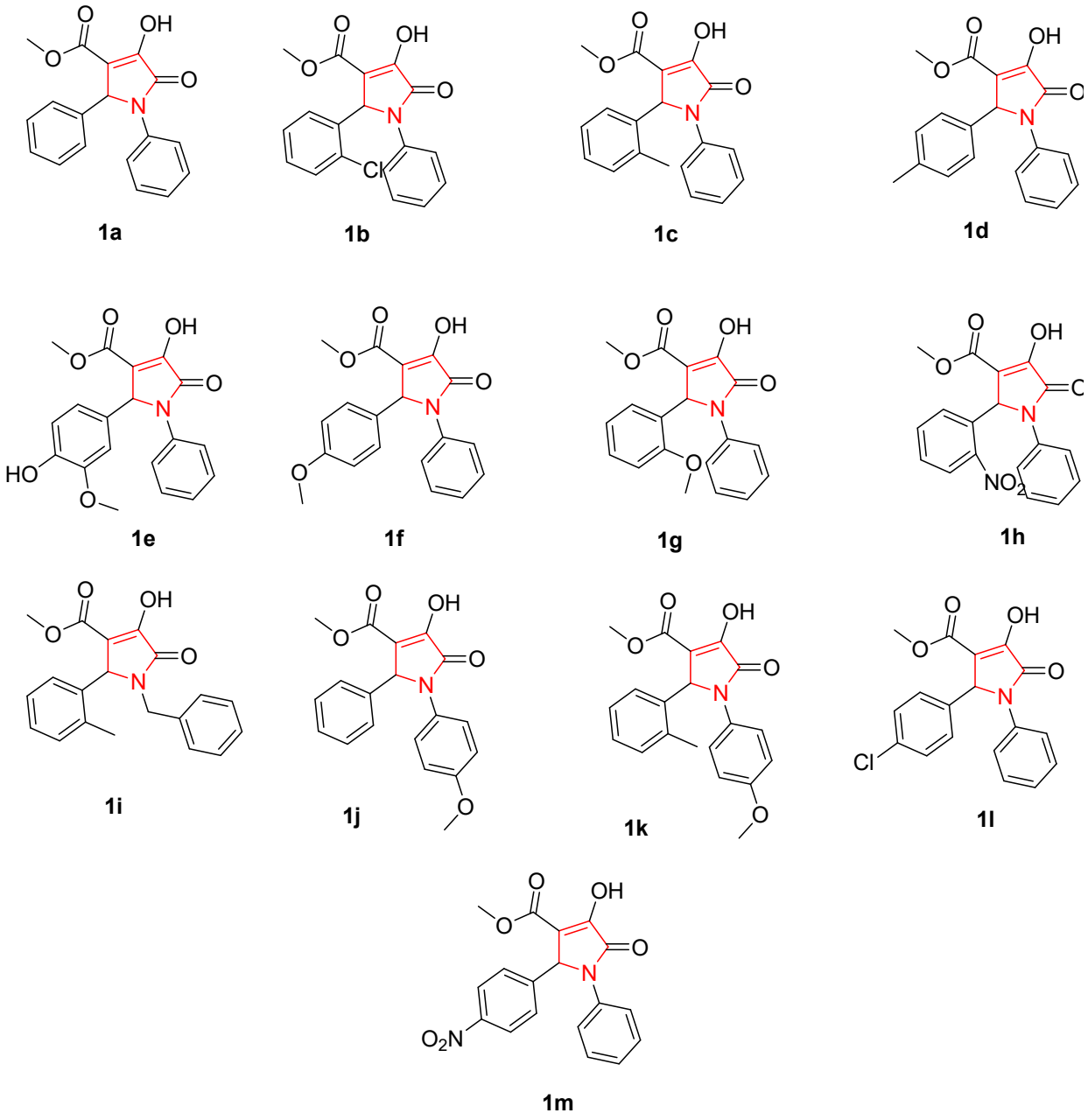
General Remarks:

All reagents are commercially available and used without further purification. Solvents used for extraction and purification were distilled before use. *Myceliophthora thermophila* laccase (Novozym 51003) was a generous gift from Novozymes (Copenhagen, Denmark) and Laccase from *Trametes versicolor* Purchased from Sigma. Reactions were monitored by thin-layer chromatography (TLC) using silica gel 60 F_{254}. All organic synthesis products were purified by preparative thin-layer chromatography (TLC), (CAMAG ® instrument, in-house prepared 20 × 20 cm silica plates) and characterized by NMR spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded at 300 (75) MHz on a Bruker Avance spectrometer using DMSO-*d6* and $CDCl_3$ as solvents. The chemical shifts were referenced to the solvent signals at δH/C 2.49/39.50 ppm (DMSO-*d6*) and δH/C 7.26/77 ppm ($CDCl_3$) relative to TMS. Melting points were determined with a Thermo Scientific 9100 melting point apparatus and are uncorrected. Mass spectra were recorded with an Agilent Technologies (HP) 5973 mass spectrometer.

Synthesis of 3-hydroxy-1,5-dihydro-2H-pyrrol-2-ones (1a-1m): Pyrrolidinones **1a-1m** were prepared according to literature[1]: A mixture of dimethyl acetylenedicarboxylate (DMAD) (1 mmol) and different amines (1 mmol) in ethanol (2 mL) was stirred at room temperature (25 °C) for 5 min. After that, benzaldehyde derivatives (1 mmol) and citric acid (200 mg) were added to the reaction mixture which was sonicated for 1.5 h. After the reaction was completed, the resulting precipitate was filtered and washed with cold ethanol. Selected pyrrolidinones (**1a, 1f, 1g, 1h**) were characterized by ^{1}H and ^{13}C NMR spectroscopy to confirm their structure and purity.

Table S1. Pyrrolidinones **1a-1m**



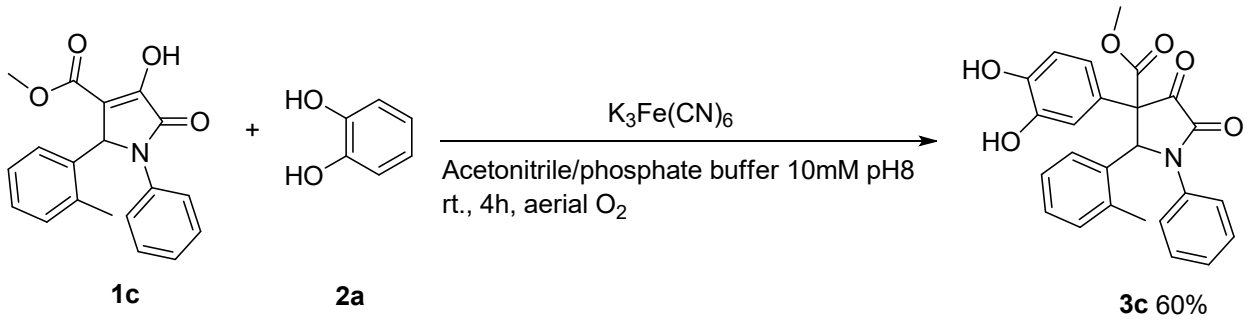


Synthesis of 4-phenyl-pyrrolidine-2,3-diones (3a-3o): A 100 mL round bottom flask with a magnetic stirrer bar was charged with a solution of 3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-one 1 (0.1 mmol) and catechol 2 (0.15 mmol) in acetonitrile (8 mL). Phosphate buffer (10 mM, pH 8.0, 16 mL) and *Myceliophthora thermophila* laccase (Novozyme 51003) (1 mL) (1000 U) was added, and the mixture was stirred under air. The reaction was monitored with TLC until 1 was completely

consumed (4.5 h). Then the reaction mixture was diluted with EtOAc, the layers were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried with anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The reaction mixture was purified by preparative TLC (eluting with *n*-hexane:ethyl acetate, 5:1-2:1), provided target compound 3.

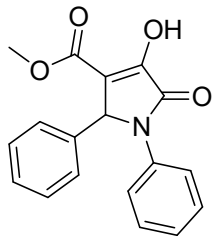
Synthesis of 3c [methyl 3-(3,4-dihydroxyphenyl)-4,5-dioxo-1,2-diphenylpyrrolidine-3-carboxylate] by $K_3Fe(CN)_6$

A 100 mL round bottom flask with a magnetic stirrer bar was charged with a solution of methyl 4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **1c** (1 mmol) and catechol **2a** (1.5 mmol) in acetonitrile (8 mL). $K_3Fe(CN)_6$ (2 mmol) was dissolved in phosphate buffer (10 mM, pH 8.0, 16 mL) and added dropwise to the mixture under air. The reaction progress was detected with TLC until methyl 4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1H-pyrrole-3-carboxylate was completely consumed. Then the reaction mixture was diluted with EtOAc, the layers were separated, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried with anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The reaction mixture was purified by preparative TLC (eluting with *n*-hexane:ethyl acetate, 5:1-2:1), provided target compound **3c**.

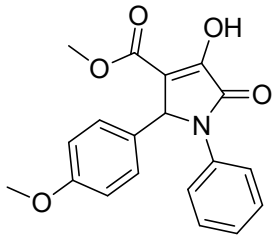


1c **2a** **3c** 60%

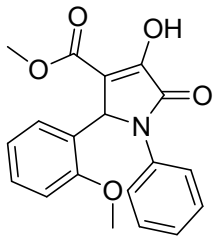
Characterization data



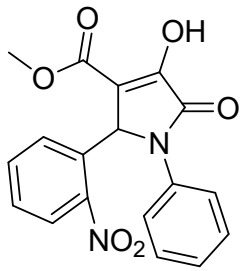
Methyl 4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (1a)[2, 3], Solid (white), melting point: 181-183 ℃, isolated yield (94%), ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.66 (s, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.39 – 7.05 (m, 8H), 6.08 (s, 1H), 3.58 (s, 3H).^{13}C NMR (75 MHz, DMSO-d_6) δ 171.8, 164.4, 162.9, 153.0, 136.9, 136.7, 129.1, 128.7, 128.4, 128.1, 125.8, 122.9, 112.4, 61.0, 51.6.



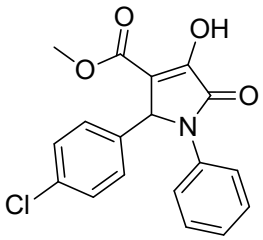
Methyl 4-hydroxy-2-(4-methoxyphenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (1f)[4], Solid (white), melting point: 188-190 ℃, isolated yield (91%),^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.14 (s, 1H), 7.21 (m, 3H), 7.11 (m, 3H), 6.94 (m, 1H), 6.85 – 6.74 (m, 2H), 5.99 (d, 1H), 3.73 (d, 6H).^{13}C NMR (75 MHz, Chloroform-*d*) δ 165.1, 163.2, 157.8, 156.4, 136.9, 132.9, 130.7, 129.0, 128.2, 126.6, 125.1, 124.7, 114.3, 113.2, 57.7, 55.3, 52.0.



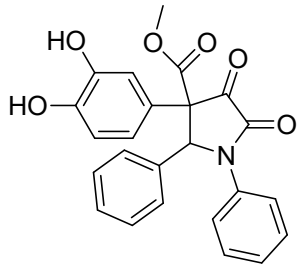
Methyl 4-hydroxy-2-(2-methoxyphenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (1g)[5], Solid (white), melting point: 170-172 ℃, isolated yield (82%),^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 8.0 Hz, 2H), 7.26 (t, *J* = 7.9 Hz, 2H), 7.22 – 7.14 (m, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.82 (t, *J* = 7.8 Hz, 2H), 6.31 (s, 1H), 3.88 (s, 3H), 3.72 (s, 3H).^{13}C NMR (75 MHz, Chloroform-*d*) δ 165.2, 163.4, 157.8, 156.1, 136.2, 129.7, 129.2, 128.8, 125.7, 122.7, 122.0, 120.9, 114.0, 111.4, 77.5, 77.1, 76.6, 55.9, 52.0.



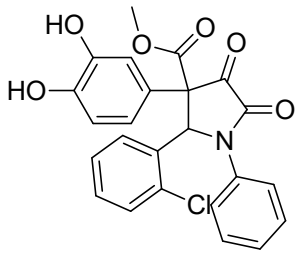
Methyl 4-hydroxy-2-(2-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (1h), solid Melting point: 192-194 ℃, ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.88 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 2H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.34 (q, *J* = 9.2, 8.5 Hz, 3H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.86 (s, 1H), 3.54 (s, 3H).^{13}C NMR (75 MHz, DMSO-d_6) δ 164.86, 162.74, 153.91, 150.60, 136.69, 134.20, 131.50, 129.76, 129.44, 127.78, 126.09, 125.22, 122.41, 111.77, 54.93, 51.78. Anal. Calcd for $C_{18}H_{14}N_2O_6$: C 61.02, H 3.98, N 7.91; Found: C 61.17, H 4.12, N 7.81.



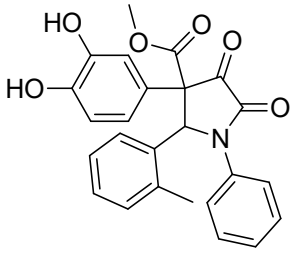
Methyl 2-(4-chlorophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (1l)[4], solid Melting point: 165-167 ℃, ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.95 (s, 1H), 7.58 (d, *J* = 7.9 Hz, 2H), 7.41 – 7.20 (m, 6H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.13 (s, 1H), 3.60 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.34, 162.89, 153.28, 136.50, 136.16, 132.90, 130.10, 129.20, 128.77, 125.94, 122.97, 111.93, 60.24, 51.63.



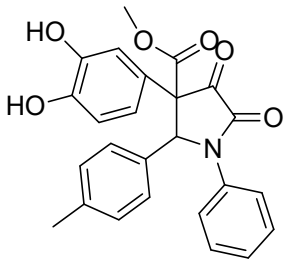
Methyl 3-(3,4-dihydroxyphenyl)-4,5-dioxo-1,2-diphenylpyrrolidine-3-carboxylate (3a), Solid (yellow), Melting point: 115-117 ℃, isolated yield (53%, 22 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.37 (s, 1H), 7.84 (d, J = 8.1 Hz, 2H), 7.41 (t, J = 7.7 Hz, 2H), 7.28 (m, 6H), 6.85 (m, 3H), 6.53 (s, 1H), 3.13 (s, 3H).^{13}C NMR (75 MHz, DMSO-d_6) δ 191.5, 167.7, 157.5, 146.7, 146.3, 136.9, 135.7, 129.6, 129.4, 129.1, 128.1, 127.4, 123.5, 122.1, 118.6, 116.4, 115.2, 64.6, 64.1, 52.5. MS (EI, 70 eV): m/z = 417 [M^+], Anal. Calcd for $C_{24}H_{19}NO_6$: C 69.06, H 4.59, N 3.36; Found: C 69.62, H 4.41, N 3.21.



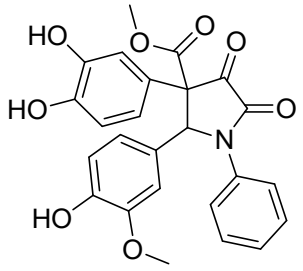
Methyl 2-(2-chlorophenyl)-3-(3,4-dihydroxyphenyl)-4,5-dioxo-1-phenylpyrrolidine-3-carboxylate (3b), Solid (yellow), Melting point: 186-188 ℃, isolated yield (51%, 23 mg), ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.31 (s, 2H), 7.86 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 8.0 Hz, 2H), 7.52 – 7.40 (m, 2H), 7.32 (m, 3H), 7.24 – 7.14 (m, 1H), 6.92 (s, 1H), 6.84 (s, 2H), 6.67 (s, 1H), 3.15 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 191.0, 167.2, 157.1, 146.9, 146.7, 136.6, 134.2, 132.9, 131.3, 130.3, 130.0, 128.4, 128.0, 123.6, 122.2, 122.0, 118.0, 116.8, 64.0, 61.9, 52.6. MS (EI, 70 eV): m/z = 451 [M^+], Anal. Calcd for $C_{24}H_{19}NO_6$: C 63.79; H 4.02; N, 3.10, Found: C 63.77, H 4.12, N 3.15.



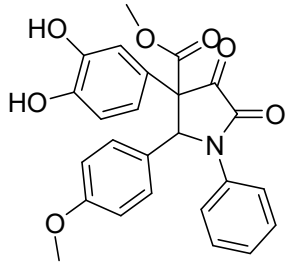
Methyl 3-(3,4-dihydroxyphenyl)-4,5-dioxo-1-phenyl-2-(o-tolyl)pyrrolidine-3-carboxylate (3c), Solid (yellow), Melting point: 123-125 ℃, isolated yield (81%, 35 mg), ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.38 (s, 2H), 7.73 (d, J = 7.8 Hz, 2H), 7.43 (t, J = 7.8 Hz, 2H), 7.27 (t, J = 7.3 Hz, 1H), 7.22 – 7.11 (m, 3H), 6.92 (m, 2H), 6.89 – 6.80 (m, 2H), 6.43 (s, 1H), 3.07 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 191.7, 167.7, 157.3, 146.8, 146.5, 137.5, 136.9, 133.6, 131.2, 129.8, 129.2, 127.7, 126.9, 126.2, 124.0, 122.4, 118.0, 116.6, 114.8, 64.3, 61.6, 52.5, 19.7. MS (EI, 70 eV): m/z = 431 [M^+], Anal. Calcd for $C_{24}H_{19}NO_6$: C 69.60; H 4.91; N 3.25; Found: C 69.63, H 4.82, N 3.33.



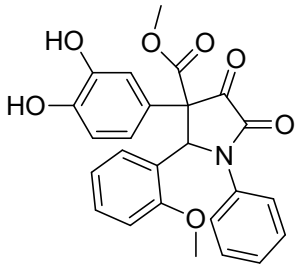
Methyl 3-(3,4-dihydroxyphenyl)-4,5-dioxo-1-phenyl-2-(p-tolyl)pyrrolidine-3-carboxylate (3d), Solid (yellow), Melting point: 119-121 ℃, isolated yield (63%, 26 mg), ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.34 (s, 2H), 7.83 (d, J = 8.1 Hz, 2H), 7.41 (t, J = 7.8 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 7.16 (d, J = 9.6 Hz, 4H), 6.84 (d, J = 9.2 Hz, 3H), 6.47 (s, 1H), 3.16 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 191.6, 167.8, 146.7, 146.3, 137.0, 133.0, 129.6, 127.4, 126.9, 123.6, 122.0, 116.4, 115.2, 64.8, 63.2, 52.4, 24.1. MS (EI, 70 eV): m/z = 431 [M^+], Anal. Calcd for $C_{24}H_{19}NO_6$: C 69.60; H 4.91; N 3.25; Found: C 69.62, H 4.83, N 3.31.



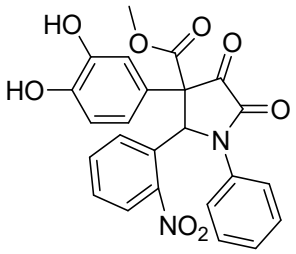
Methyl 3-(3,4-dihydroxyphenyl)-2-(4-hydroxy-3-methoxyphenyl)-4,5-dioxo-1-phenylpyrrolidine-3-carboxylate (3e), Solid (yellow), Melting point: 133-135 ℃, isolated yield (87%, 40 mg), ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.27 (s, 3H), 7.82 (d, J = 8.1 Hz, 2H), 7.42 (t, J = 7.8 Hz, 2H), 7.26 (t, J = 7.4 Hz, 1H), 6.94 – 6.77 (m, 4H), 6.69 (d, J = 8.2 Hz, 1H), 6.57 (d, J = 8.3 Hz, 1H), 6.37 (s, 1H), 3.69 (s, 3H), 3.23 (s, 3H).^{13}C NMR (75 MHz, DMSO-d_6) δ 191.7, 167.6, 157.4, 147.8, 147.4, 146.6, 146.3, 137.1, 129.6, 127.3, 126.2, 123.7, 122.1, 118.5, 116.4, 116.0, 115.1, 64.7, 64.1, 56.1, 52.6. MS (EI, 70 eV): m/z = 463 [M^+], Anal. Calcd for $C_{24}H_{19}NO_6$: C 64.79; H 4.57; N 3.02; Found: C 64.72, H 4.51, N 3.01.



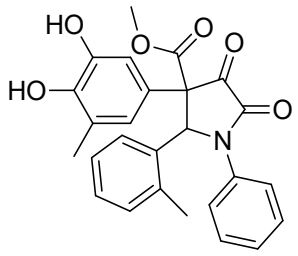
Methyl 3-(3,4-dihydroxyphenyl)-2-(4-methoxyphenyl)-4,5-dioxo-1-phenylpyrrolidine-3-carboxylate (3f), Solid (yellow), Melting point: 152-154 ℃, isolated yield (72%, 31 mg), ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.28 (d, 2H), 7.85 (d, J = 8.1 Hz, 2H), 7.41 (t, J = 7.7 Hz, 2H), 7.23 (m, 3H), 6.94 – 6.81 (m, 5H), 6.48 (s, 1H), 3.68 (s, 3H), 3.20 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 191.6, 167.7, 159.9, 157.4, 146.7, 146.4, 137.0, 129.6, 127.3, 123.6, 122.1, 116.5, 114.4, 67.7, 63.8, 55.5, 52.6. MS (EI, 70 eV): m/z = 447 [M^+], Anal. Calcd for $C_{24}H_{19}NO_6$: C 67.11; H 4.73; N 3.13; Found: C 67.23, H 4.83, N 3.23.



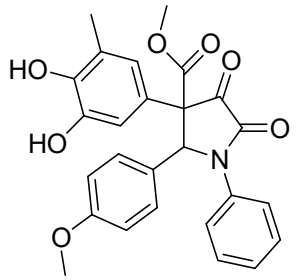
Methyl 3-(3,4-dihydroxyphenyl)-2-(2-methoxyphenyl)-4,5-dioxo-1-phenylpyrrolidine-3-carboxylate (3g), Solid (yellow), Melting point: 161-163 ℃, isolated yield (67%, 29 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.34 (s, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 7.5 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 7.24 (dt, J = 14.8, 7.5 Hz, 2H), 6.92 (dd, J = 18.3, 7.8 Hz, 2H), 6.82 (d, J = 6.2 Hz, 3H), 6.22 (s, 1H), 3.56 (s, 2H), 3.11 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 187.8, 167.5, 158.6, 157.9, 146.6, 146.5, 137.3, 133.3, 131.1, 129.5, 126.9, 124.4, 123.0, 122.1, 120.8, 117.8, 116.6, 114.4, 112.5, 64.9, 61.1, 55.1, 52.1. MS (EI, 70 eV): m/z = 447 [M^+], Anal. Calcd for $C_{24}H_{19}NO_6$: C 67.11; H 4.73; N 3.13; Found: C 67.22 H 4.81, N 3.21.



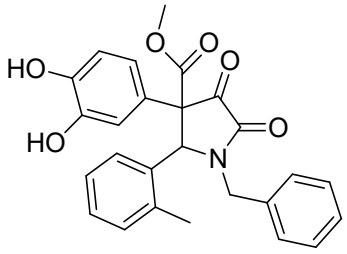
Methyl 3-(3,4-dihydroxyphenyl)-2-(2-nitrophenyl)-4,5-dioxo-1-phenylpyrrolidine-3-carboxylate (3h), Solid (brown), Melting point: 179-181 ℃, isolated yield (47%, 21 mg), ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.45 (s, 2H), 8.09 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.1 Hz, 2H), 7.72 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.8 Hz, 3H), 7.30 (t, J = 7.4 Hz, 1H), 7.24 (s, 1H), 6.84 (d, J = 8.5 Hz, 2H), 6.75 (dd, J = 8.4, 2.5 Hz, 1H), 3.17 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 190.6, 167.2, 157.4, 149.4, 146.9, 146.6, 136.5, 135.0, 131.2, 130.1, 130.0, 128.6, 128.0, 126.3, 123.4, 122.2, 118.0, 116.9, 114.3, 64.6, 59.8, 53.0. MS (EI, 70 eV): m/z = 462 [M^+], Anal. Calcd for $C_{24}H_{19}NO_6$: C 62.34; H 3.92; N 6.06; Found: C 62.52, H 3.71, N 6.11.



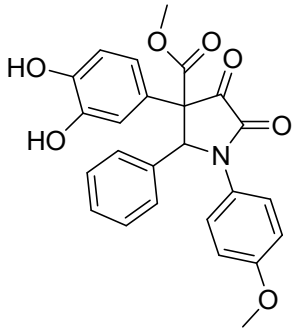
Methyl 3-(3,4-dihydroxy-5-methylphenyl)-4,5-dioxo-1-phenyl-2-(o-tolyl)pyrrolidine-3-carboxylate (3i), Solid (yellow), Melting point: 165-167 ℃, isolated yield (91%, 40 mg), ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.19 (s, 2H), 7.72 (d, J = 8.0 Hz, 2H), 7.43 (t, J = 7.7 Hz, 2H), 7.33 – 7.22 (m, 1H), 7.17 (d, J = 5.0 Hz, 3H), 6.93 (d, J = 7.0 Hz, 1H), 6.80 (s, 1H), 6.75 (s, 1H), 6.41 (s, 1H), 3.07 (s, 3H), 2.38 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 191.6, 167.7, 157.4, 146.0, 144.8, 137.6, 136.9, 133.7, 131.2, 129.8, 129.2, 127.7, 126.9, 126.2, 125.9, 123.1, 122.4, 119.7, 112.0, 64.2, 61.7, 52.5, 19.8, 16.8. MS (EI, 70 eV): m/z = 445 [M^+], Anal. Calcd for $C_{24}H_{19}NO_6$: C 70.10; H 5.20; N 3.14; Found: C 70.12, H 5.26, N 3.44.



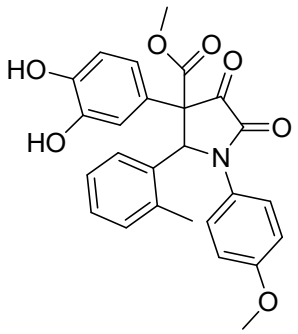
Methyl 3-(3,4-dihydroxy-5-methylphenyl)-2-(4-methoxyphenyl)-4,5-dioxo-1-phenylpyrrolidine-3-carboxylate (3j), Solid (yellow), Melting point: 143-145 ℃, isolated yield (42%, 19 mg), ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.59 (s, 1H), 8.67 (s, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.46 – 7.34 (m, 2H), 7.18 (m, 4H), 6.97 – 6.82 (m, 2H), 6.76 (d, J = 5.5 Hz, 2H), 6.46 (s, 1H), 3.68 (s, 3H), 3.18 (s, 2H), 2.12 (s, 3H).^{13}C NMR (75 MHz, DMSO-d_6) δ 191.5, 167.7, 159.8, 157.5, 145.7, 144.6, 137.0, 129.6, 127.3, 127.0, 125.7, 124.1, 122.8, 122.2, 114.4, 112.4, 64.6, 63.7, 55.5, 52.5, 16.8. MS (EI, 70 eV): m/z = 461 [M^+], Anal. Calcd for $C_{24}H_{19}NO_6$: C 67.67; H 5.02; N 3.04; Found: C 67.62, H 5.11, N 3.56.



Methyl 1-benzyl-3-(3,4-dihydroxyphenyl)-4,5-dioxo-2-(o-tolyl)pyrrolidine-3-carboxylate (3k), Solid (yellow), isolated yield (74%, 32 mg), Melting point: 196-198 ℃, ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.52 – 7.32 (m, 3H), 7.27 (m, 3H), 7.12 (d, J = 7.5 Hz, 2H), 6.96 – 6.78 (m, 1H), 6.55 (d, J = 6.6 Hz, 2H), 6.18 (d, J = 8.4 Hz, 1H), 5.44 (s, 1H), 5.18 (d, J = 14.4 Hz, 1H), 3.86 (d, J = 14.3 Hz, 1H), 3.00 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 192.5, 167.7, 158.2, 146.5, 137.8, 134.2, 132.6, 131.2, 129.5, 129.4, 129.0, 126.9, 126.2, 124.2, 116.8, 116.0, 115.0, 63.9, 59.8, 52.4, 46.9, 19.3. MS (EI, 70 eV): m/z = 445 [M^+], Anal. Calcd for $C_{24}H_{19}NO_6$: C 70.10; H 5.20; N 3.14; Found: C 69.93, H 5.21, N 3.31.



Methyl 3-(3,4-dihydroxyphenyl)-1-(4-methoxyphenyl)-4,5-dioxo-2-phenylpyrrolidine-3-carboxylate (3l), Solid (yellow), Melting point:141-143 ℃, isolated yield (75%, 33 mg), ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.34 (s, 2H), 7.76 (d, J = 8.9 Hz, 2H), 7.30 (d, J = 7.5 Hz, 5H), 7.00 – 6.92 (m, 2H), 6.87 (q, J = 7.5, 5.8 Hz, 3H), 6.46 (s, 1H), 3.72 (s, 3H), 3.12 (s, 3H).^{13}C NMR (75 MHz, DMSO-d_6) δ 191.6, 167.7, 158.2, 157.2, 146.7, 146.4, 135.8, 129.9, 129.4, 129.0,128.2, 123.8, 118.5, 116.4, 115.2, 114.7, 64.5, 60.2, 55.7, 52.5. MS (EI, 70 eV): m/z = 447 [M^+], Anal. Calcd for $C_{24}H_{19}NO_6$: C 67.11; H 4.73; N 3.13; Found: C 67.32, H 4.21, N 3.51.



Methyl 3-(3,4-dihydroxyphenyl)-1-(4-methoxyphenyl)-4,5-dioxo-2-(o-tolyl)pyrrolidine-3-carboxylate (3m), Solid (yellow), Melting point: 151-153 ℃, isolated yield (94%. 43 mg), ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.41 (s, 2H), 7.66 (d, J = 8.7 Hz, 2H), 7.19 (s, 3H), 6.92 (m, 6H), 6.38 (s, 1H), 3.74 (s, 3H), 3.08 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 191.8, 167.8, 158.3, 157.1, 146.9, 146.7, 137.6, 133.7, 131.2, 129.7, 129.1, 126.8, 126.2, 124.0, 117.9, 116.6, 114.8, 114.7, 64.2, 61.9, 55.7, 52.4, 19.7. MS (EI, 70 eV): m/z = 461 [M^+], Anal. Calcd for $C_{24}H_{19}NO_6$: C 67.67; H 5.02; N 3.04; Found: C 67.62, H 5.01, N 3.11.

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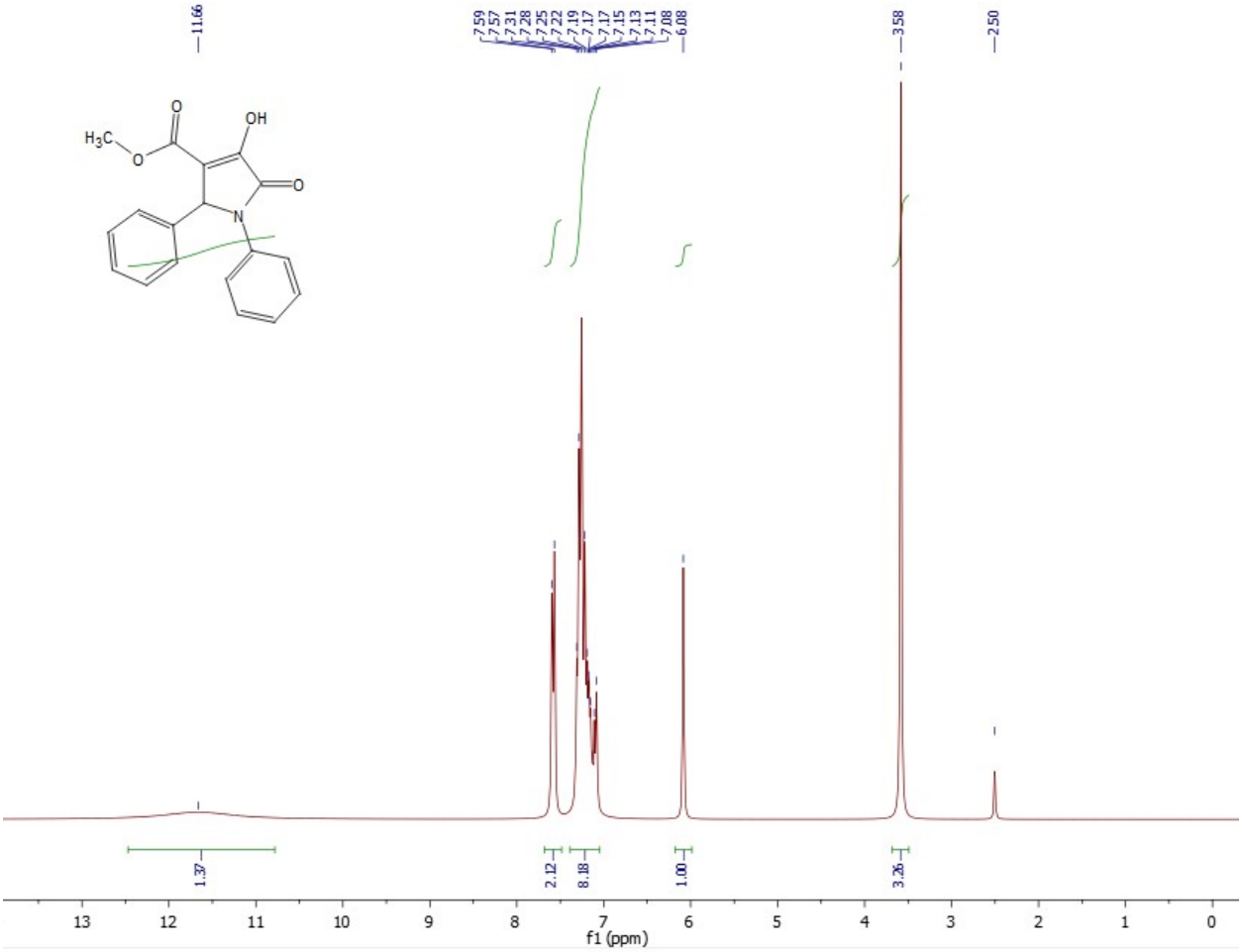
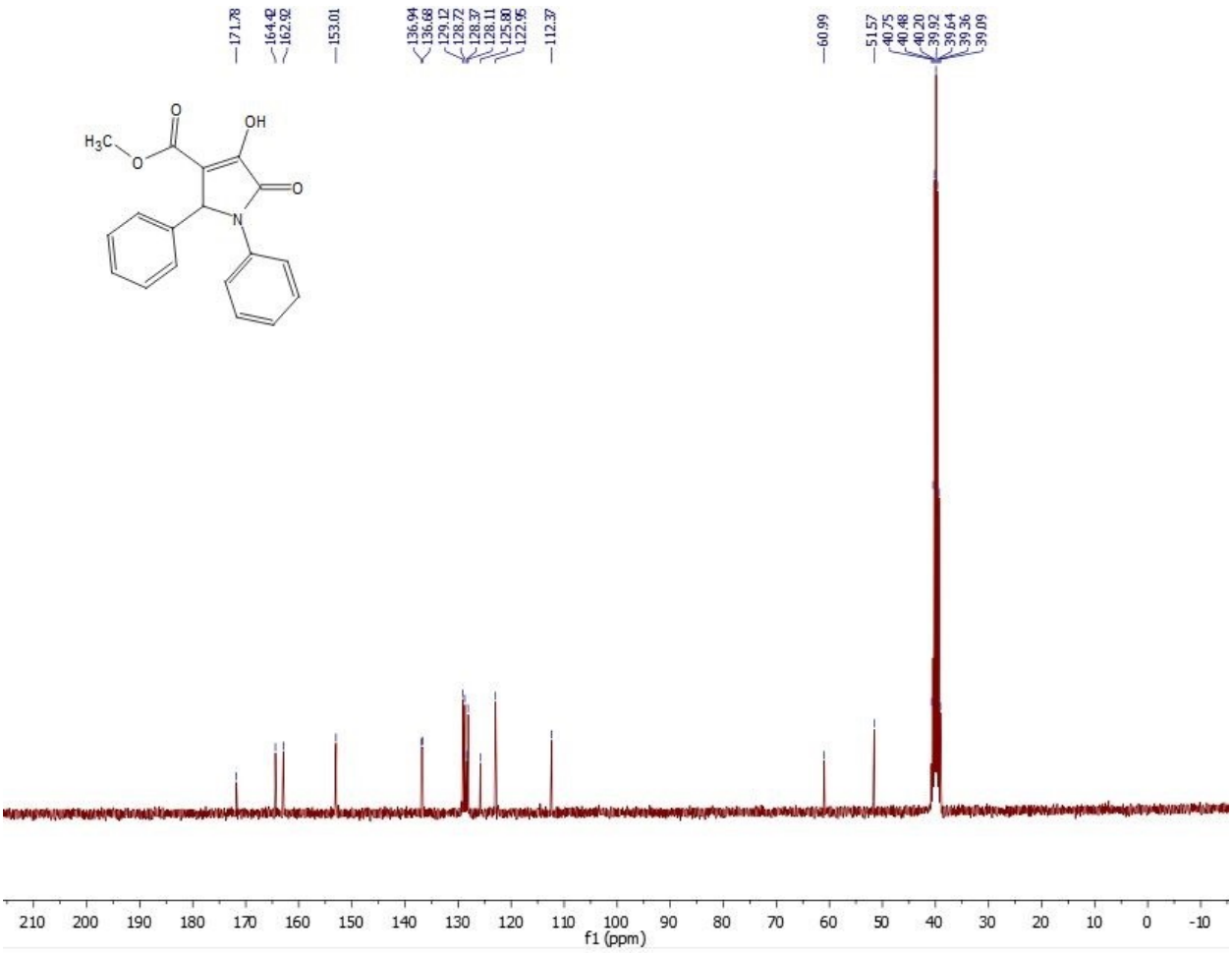
1. H. Ahankar, A. Ramazani, K. Ślepokura, T. Lis and S. W. Joo, *Green Chem.,* 2016, **18**, 3582-3593.
2. R. Sarkar and C. Mukhopadhyay, *Tetrahedron Lett.*, 2013, **54**, 3706-3711.
3. J. Sun, Q. Wu, E. Y. Xia and C. G. Yan, *Eur. J. Org. Chem.*, 2011.
4. A. Dutta, M. A. Rohman, R. Nongrum, A. Thongni, S. Mitra and R. Nongkhlaw, *New J. Chem.*, 2021, **45**, 8136-8148.
5. A. Moshtaghi Zonouz, I. Eskandari and B. Notash, *Synth. Commun.,* 2015, **45**, 2115-2121.

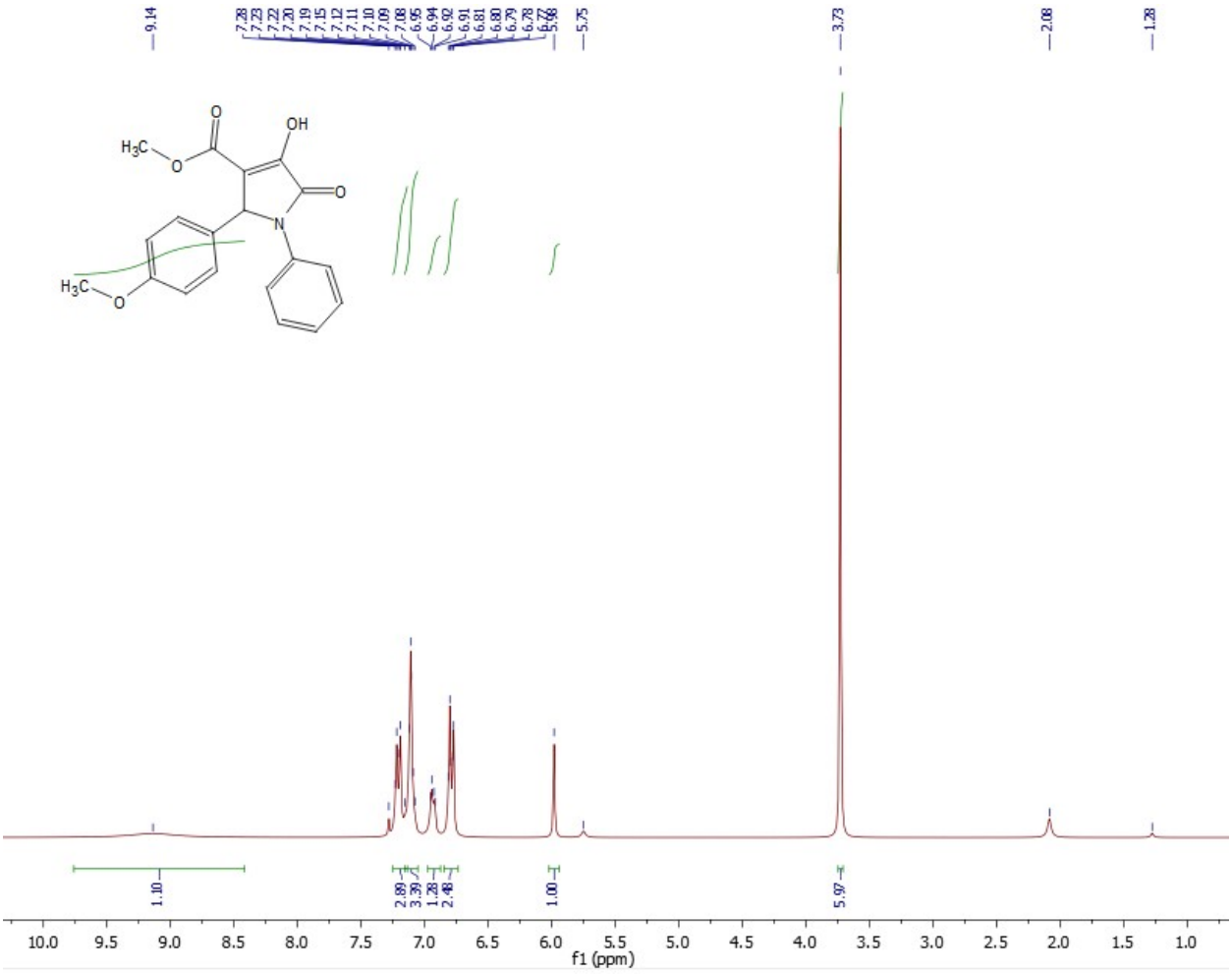
^{1}H NMR, ^{13}C NMR and mass spectra



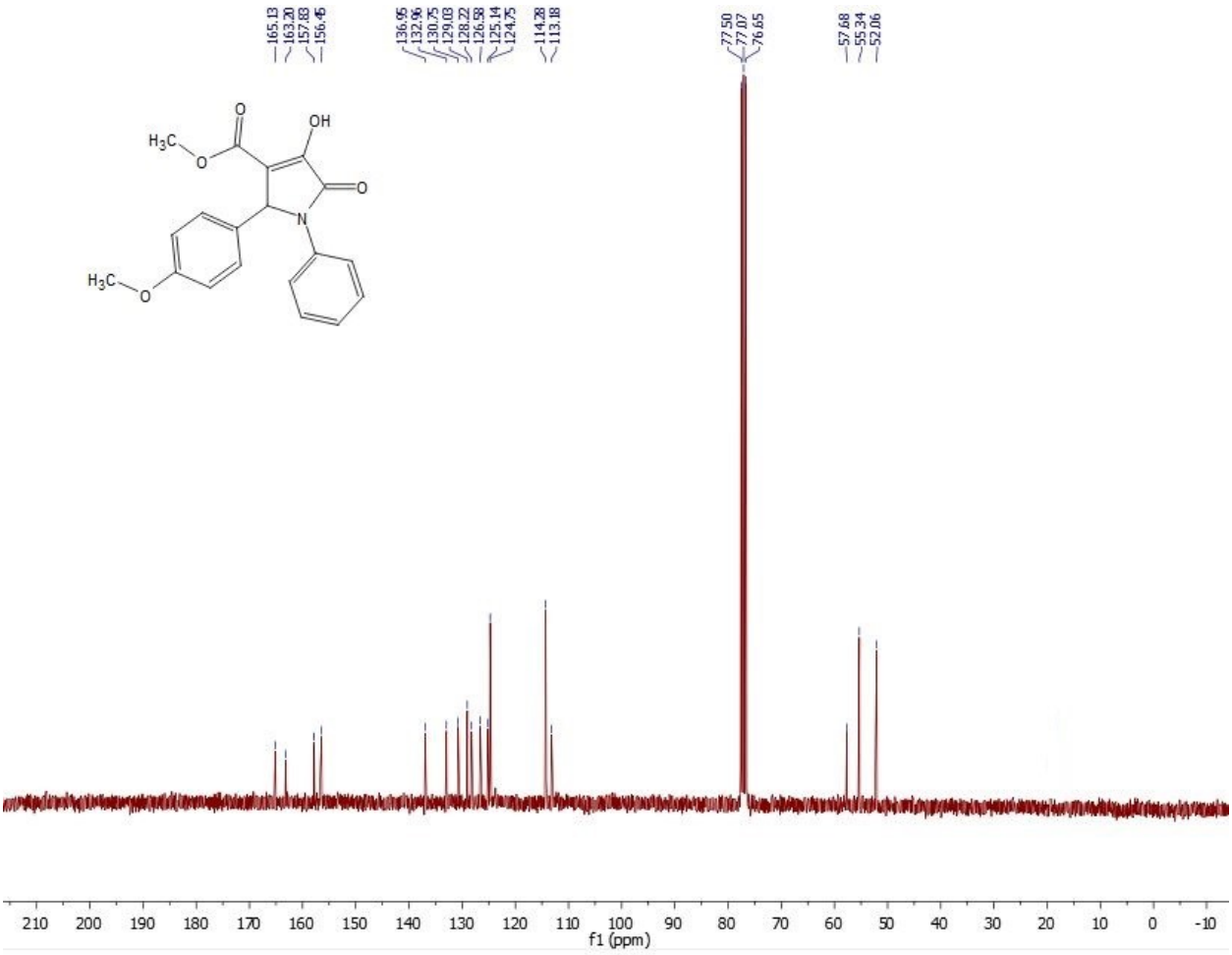
^{1}H NMR (300 MHz, DMSO-d_6) of compound **1a**



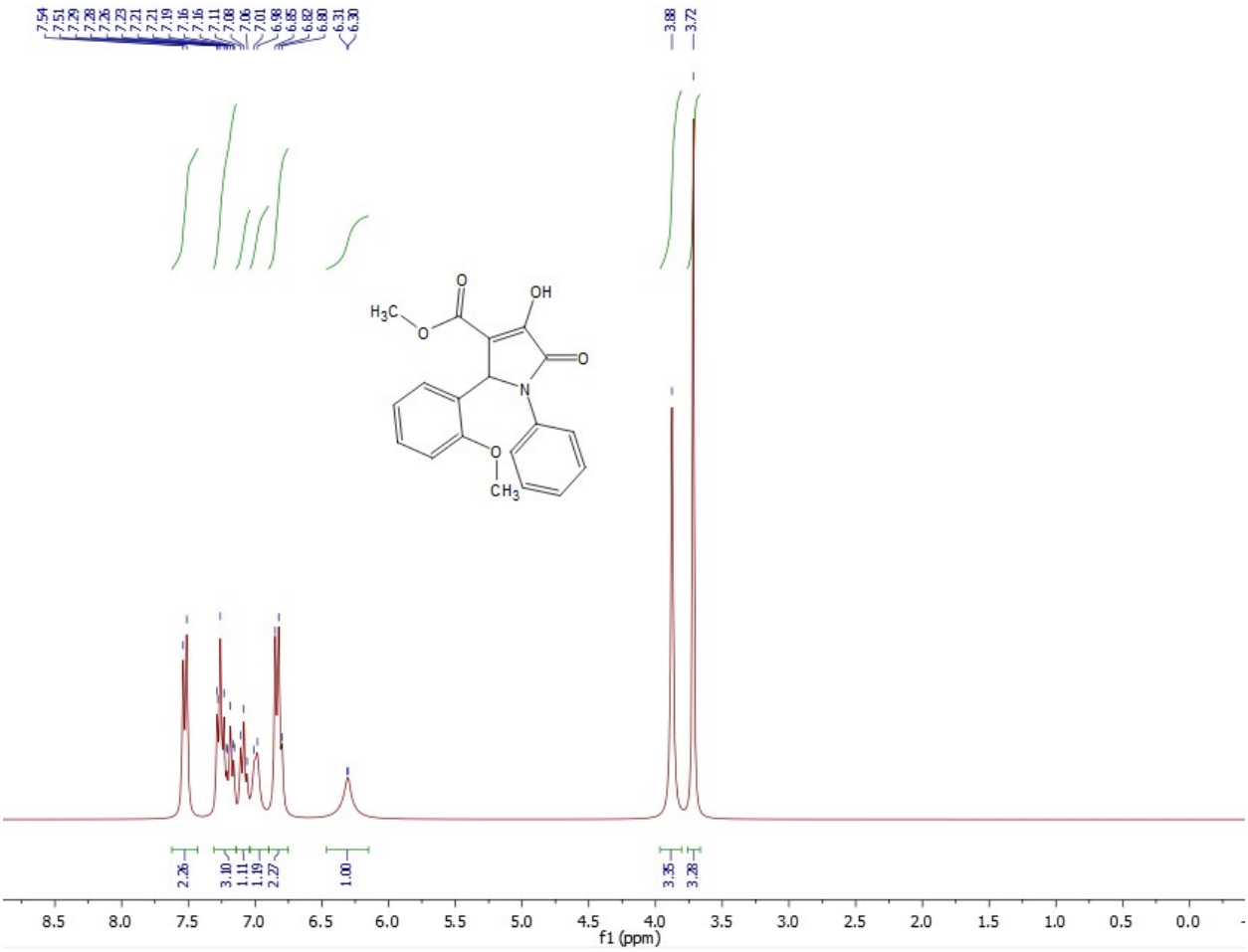
^{13}CNMR (75 MHz, DMSO-d_6) of compound **1a**



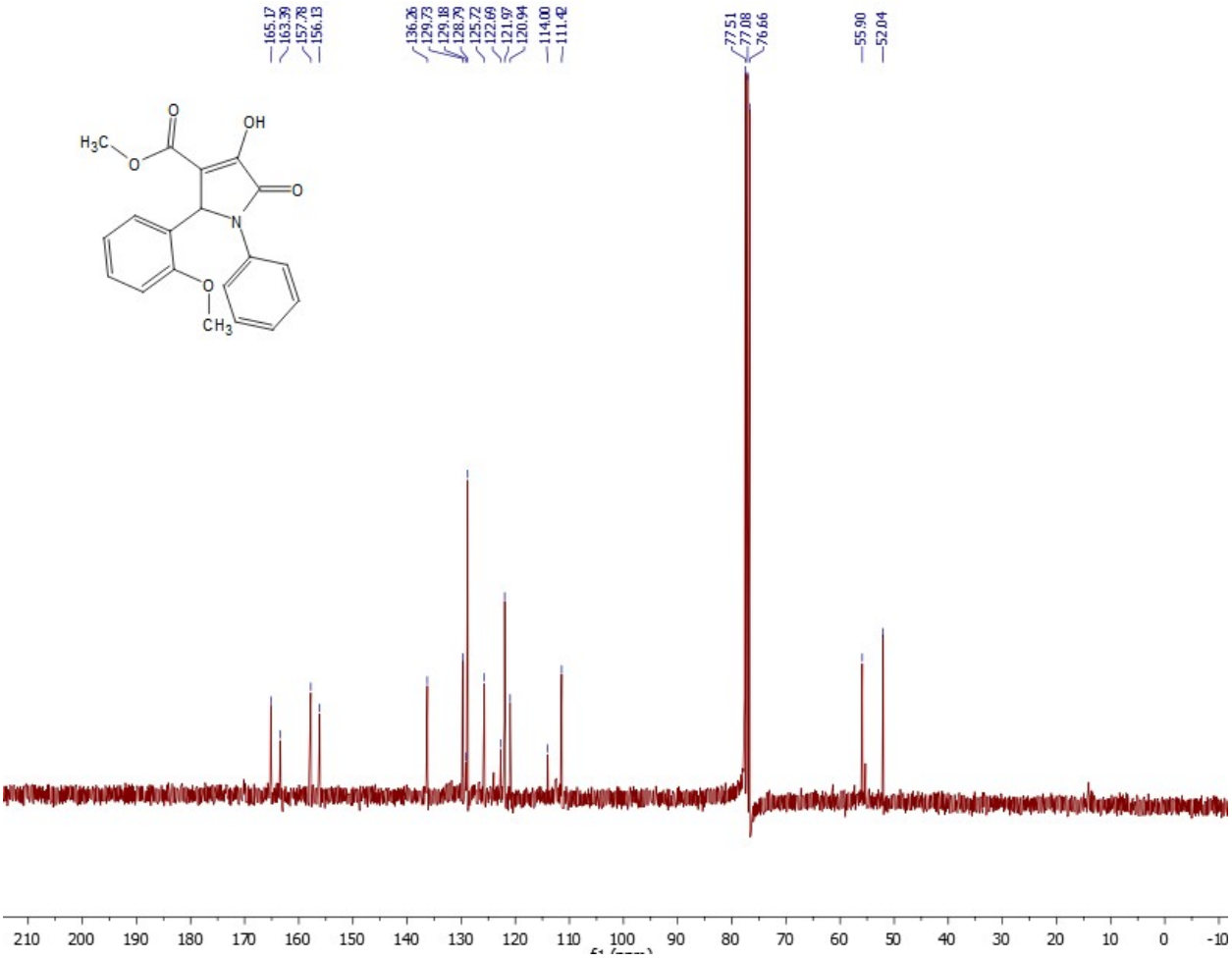
[1]HNMR (300 MHz, Chloroform-*d*) of compound **1f**



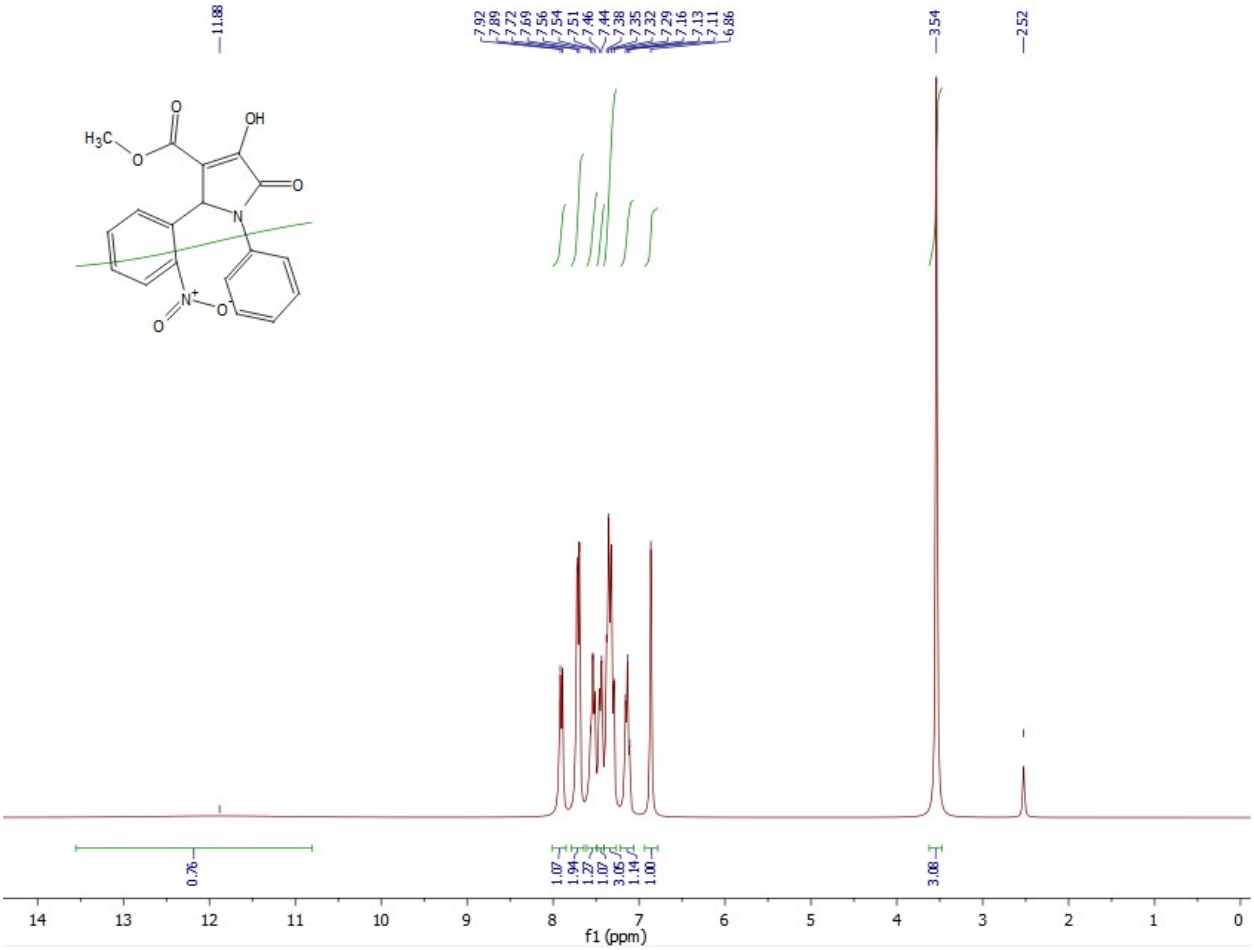
^{13}CNMR (75 MHz, Chloroform-*d*) of compound **1f**



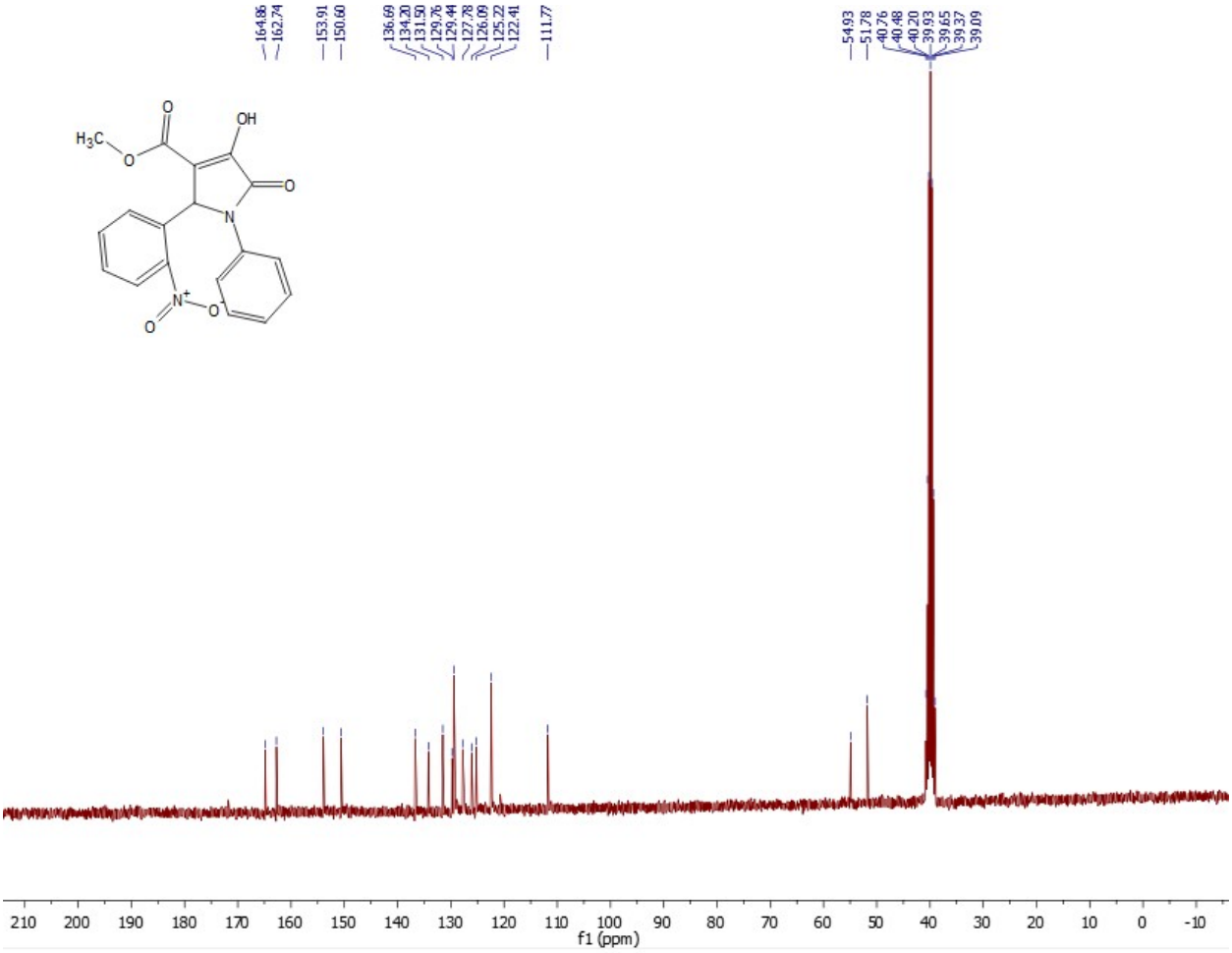
^{1}H NMR (300 MHz, Chloroform-*d*) of compound **1g**



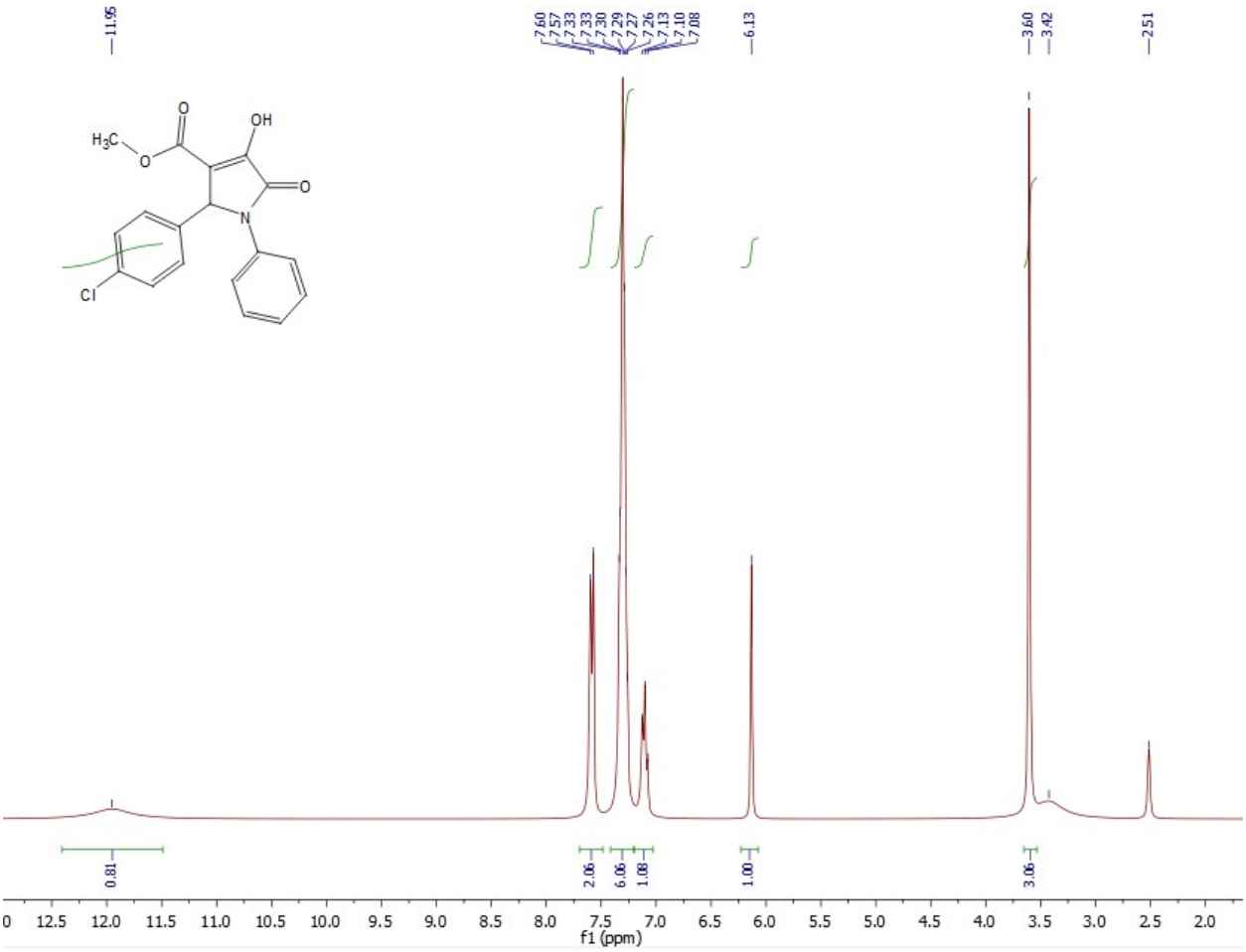
^{13}CNMR (75 MHz, Chloroform-*d*) of compound **1g**



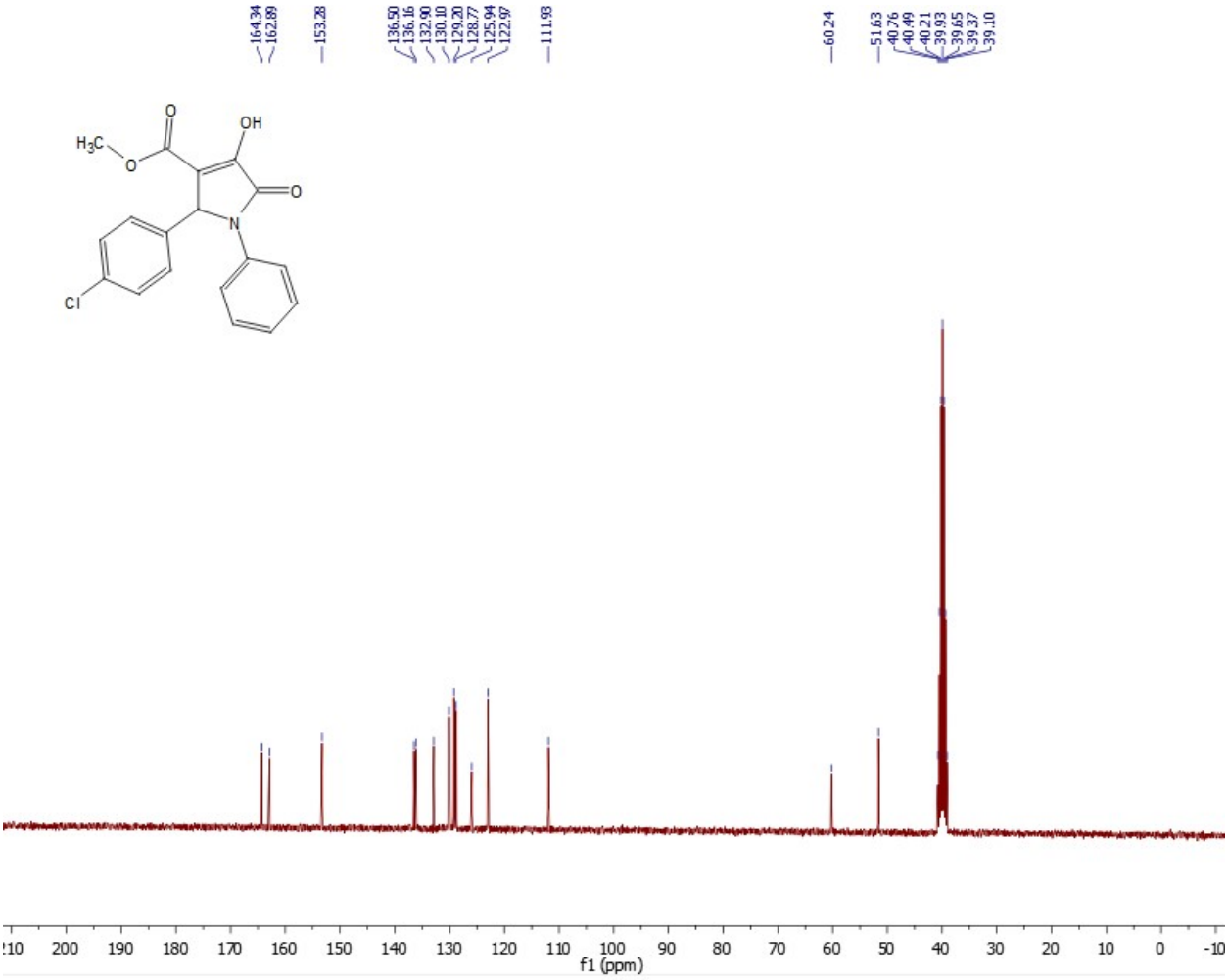
^{1}HNMR (300 MHz, DMSO-d_6) of compound **1h**



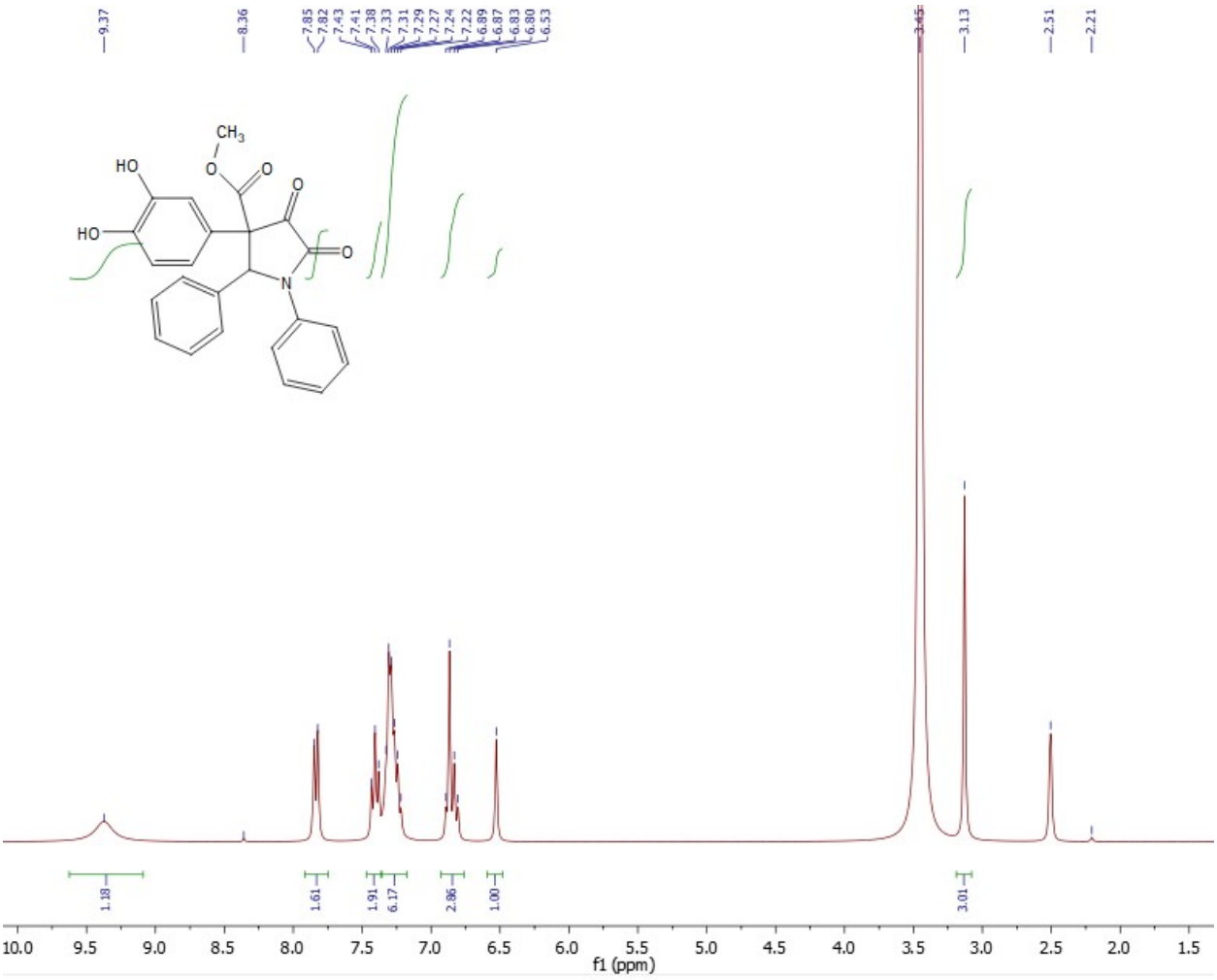
^{13}CNMR (75 MHz, DMSO-d_6) of compound **1h**



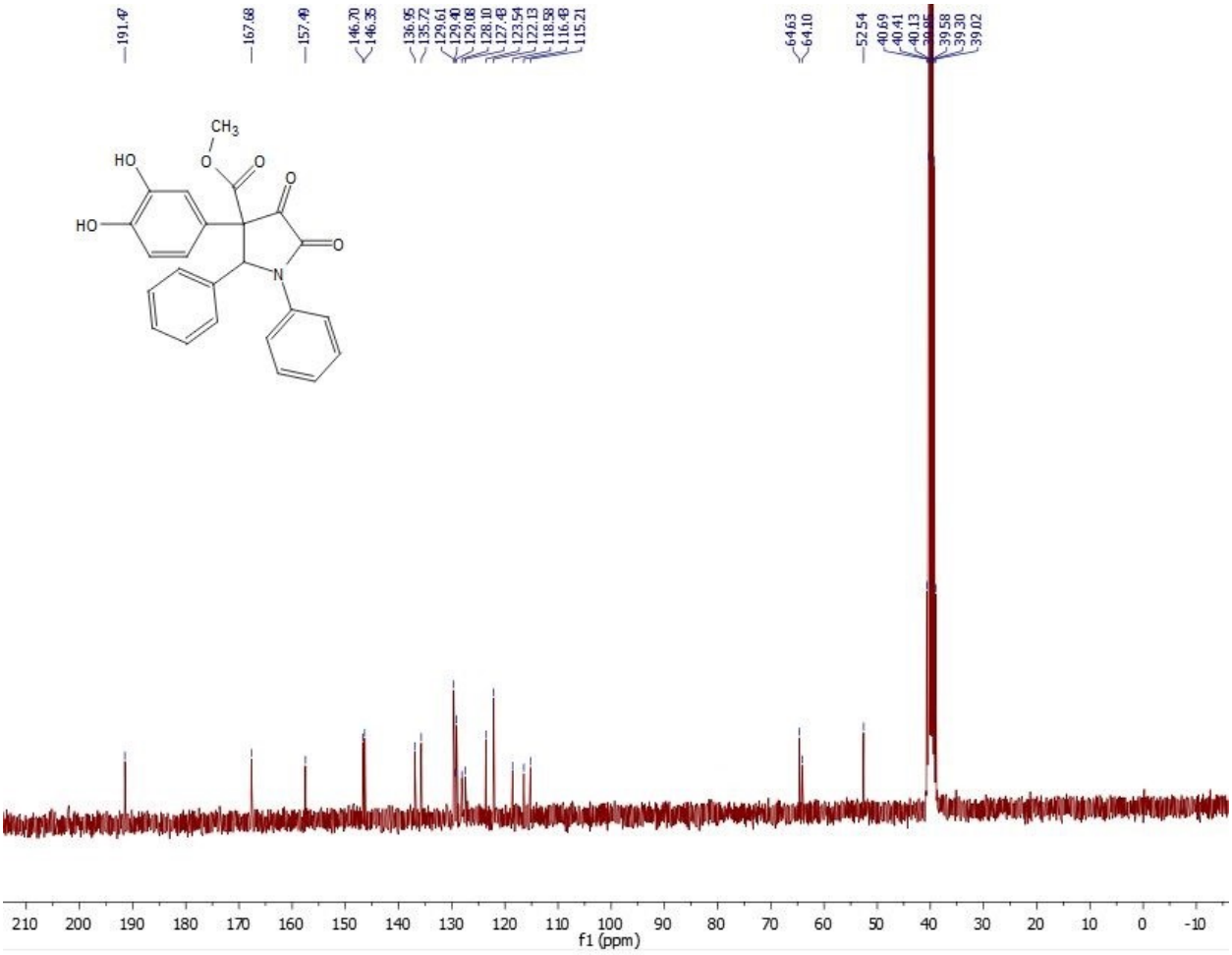
^{1}HNMR (300 MHz, DMSO-d_6) of compound **1l**



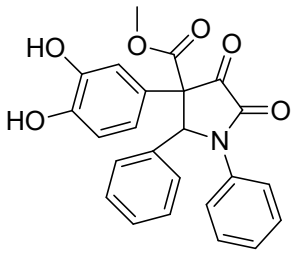
^{13}CNMR (75 MHz, DMSO-d_6) of compound **1l**

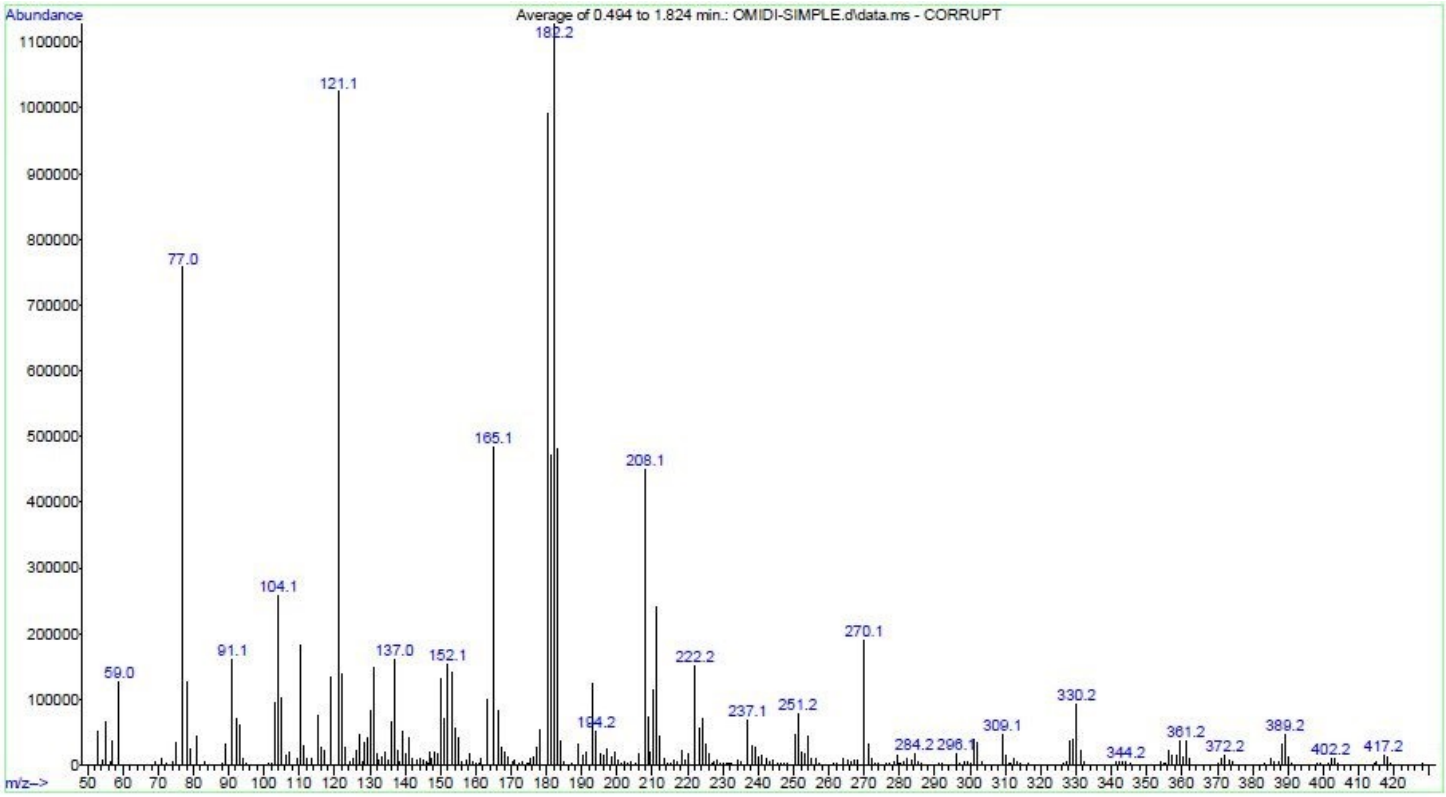


^{1}HNMR (300 MHz, DMSO-d_6) of compound **3a**



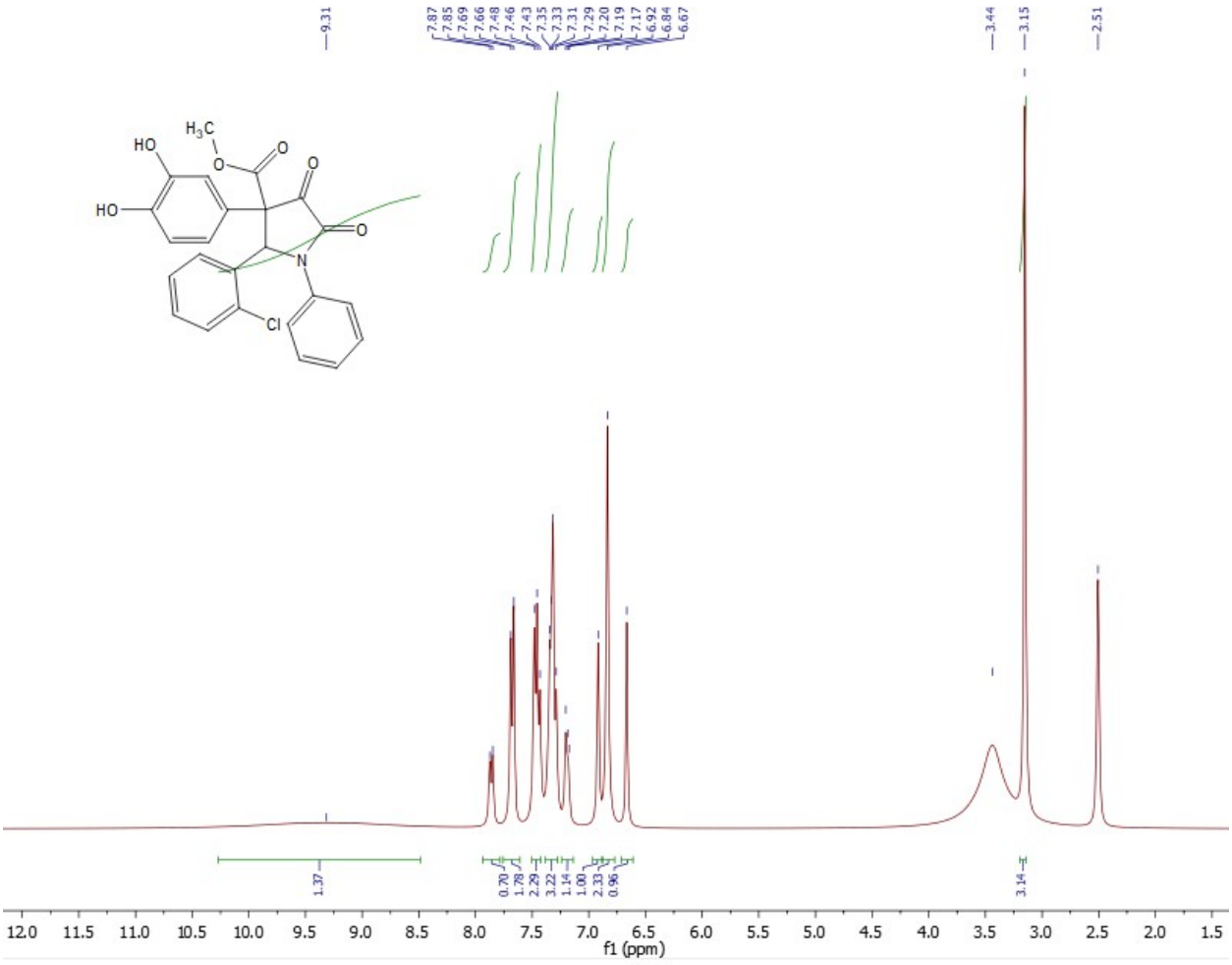
^{13}CNMR (75 MHz, DMSO-d_6) of compound **3a**



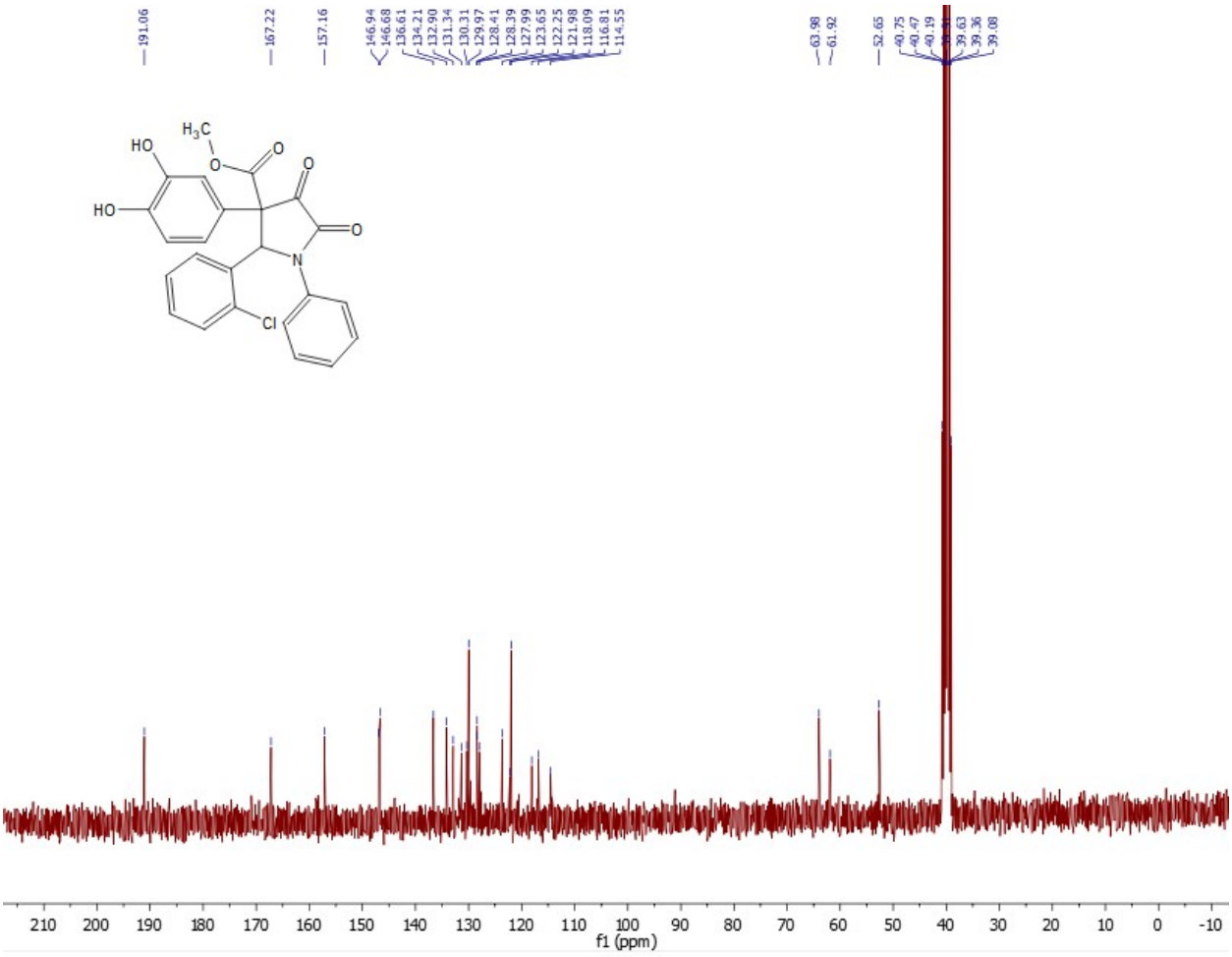


Mass spectra of compound **3a**

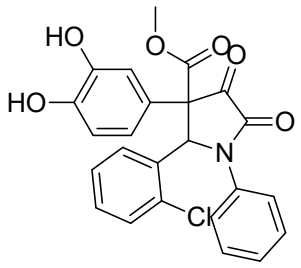
MW: 417



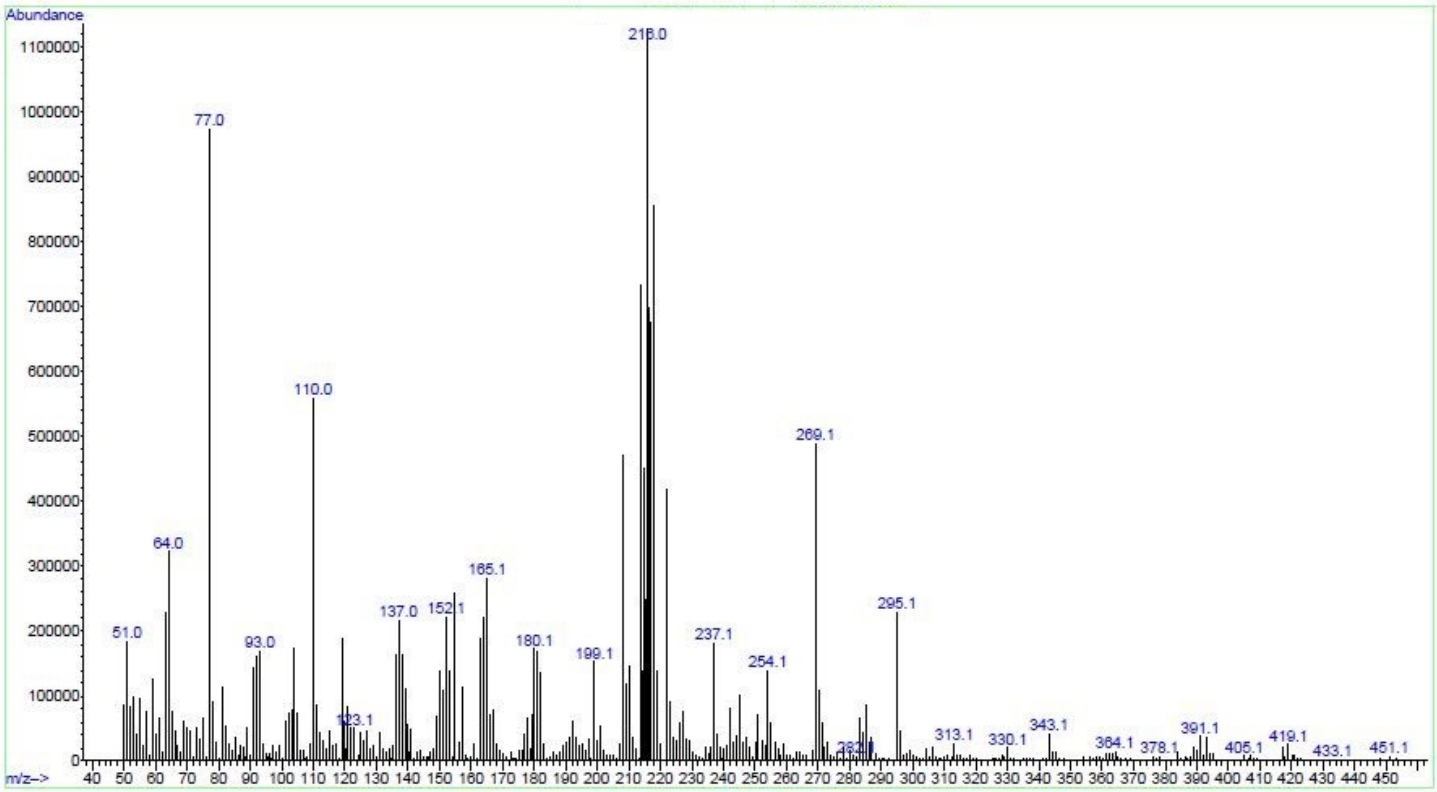
^{1}HNMR (300 MHz, DMSO-d_6) of compound **3b**



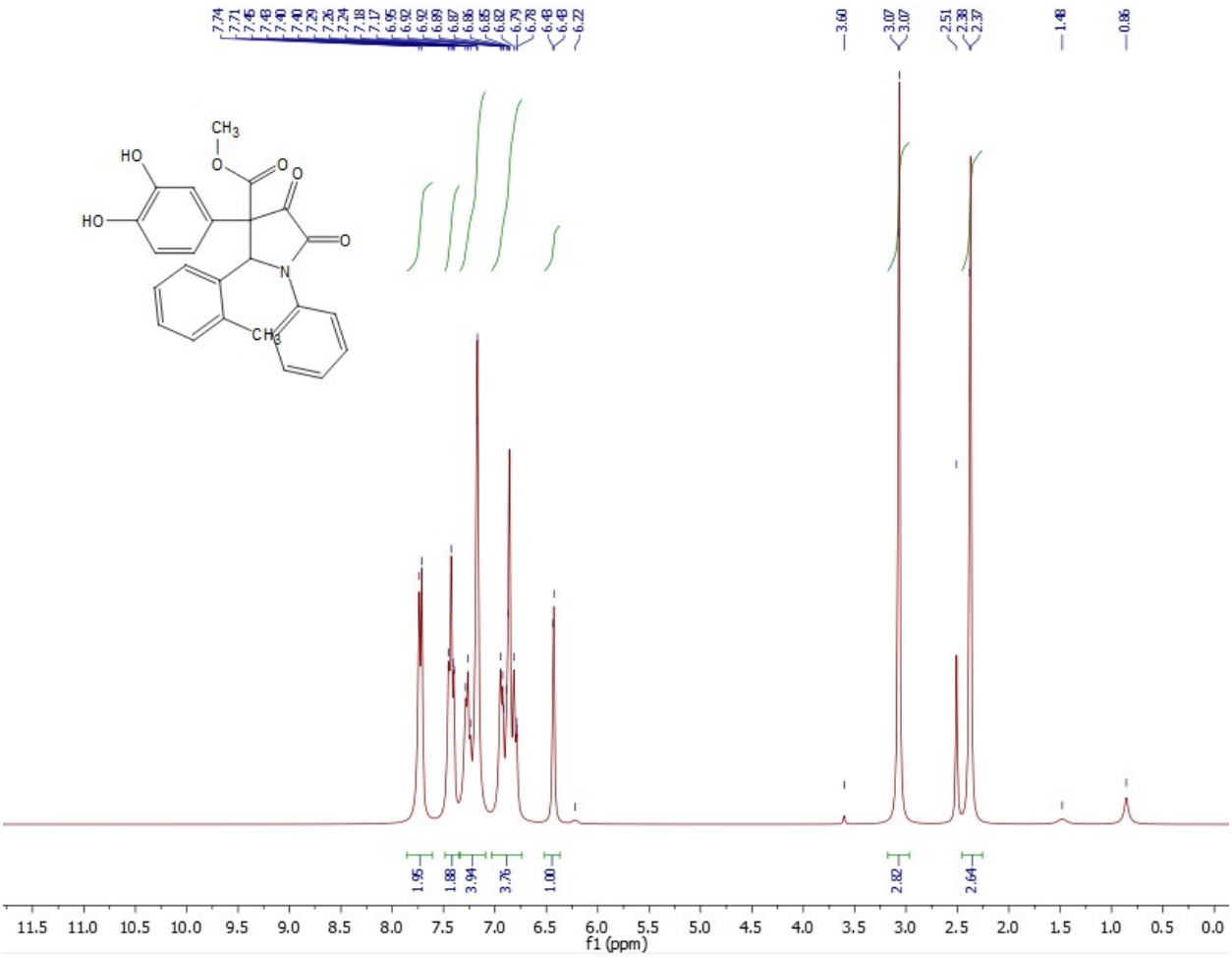
^{13}CNMR (75 MHz, DMSO-d_6) of compound **3b**



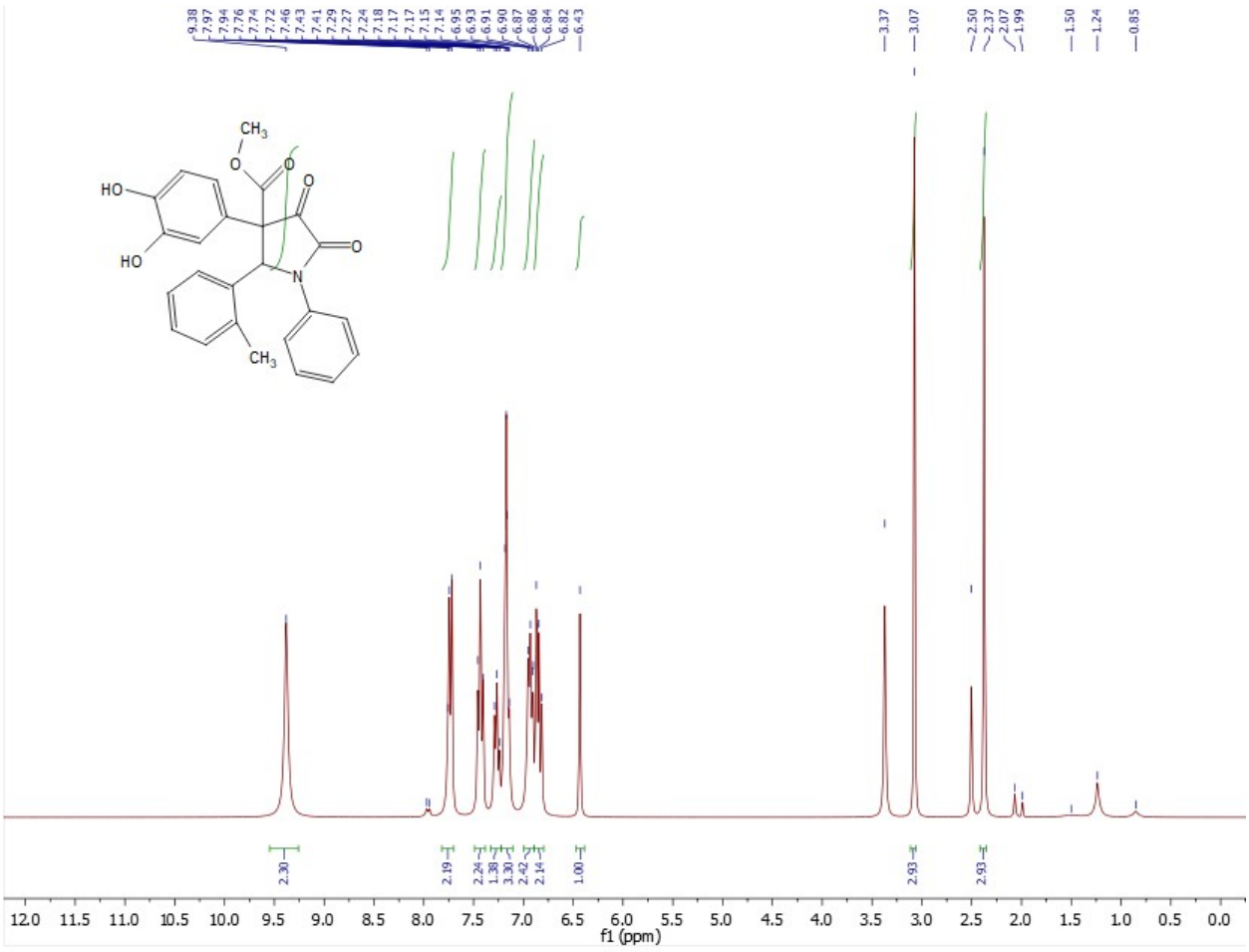
MW: 451



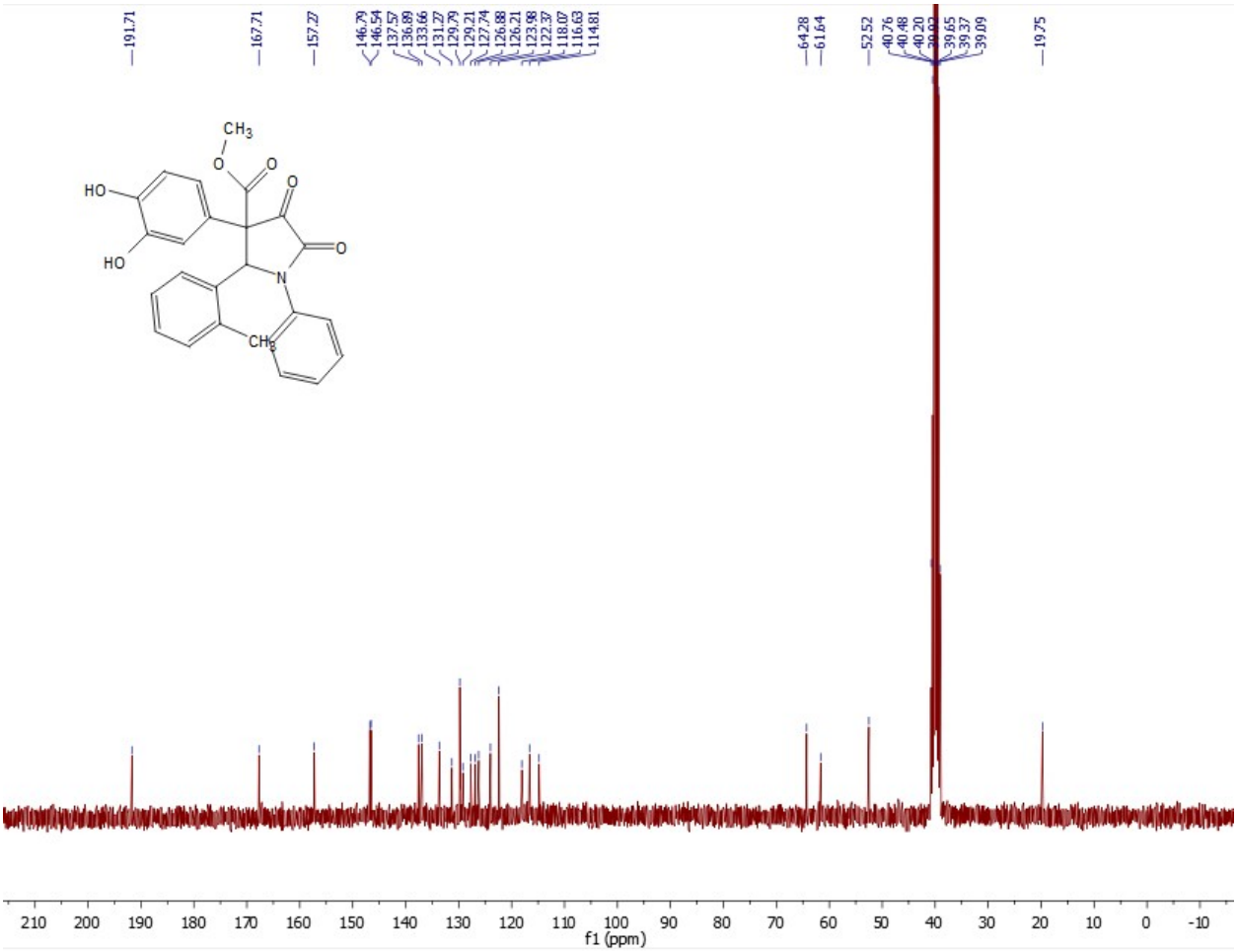
Mass spectra of compound **3b**



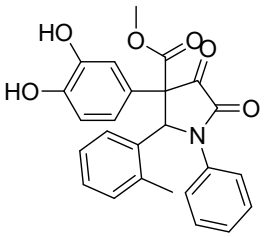
^{1}HNMR (300 MHz, DMSO-d_6) of compound **3c** with $K_3Fe(CN)_6$



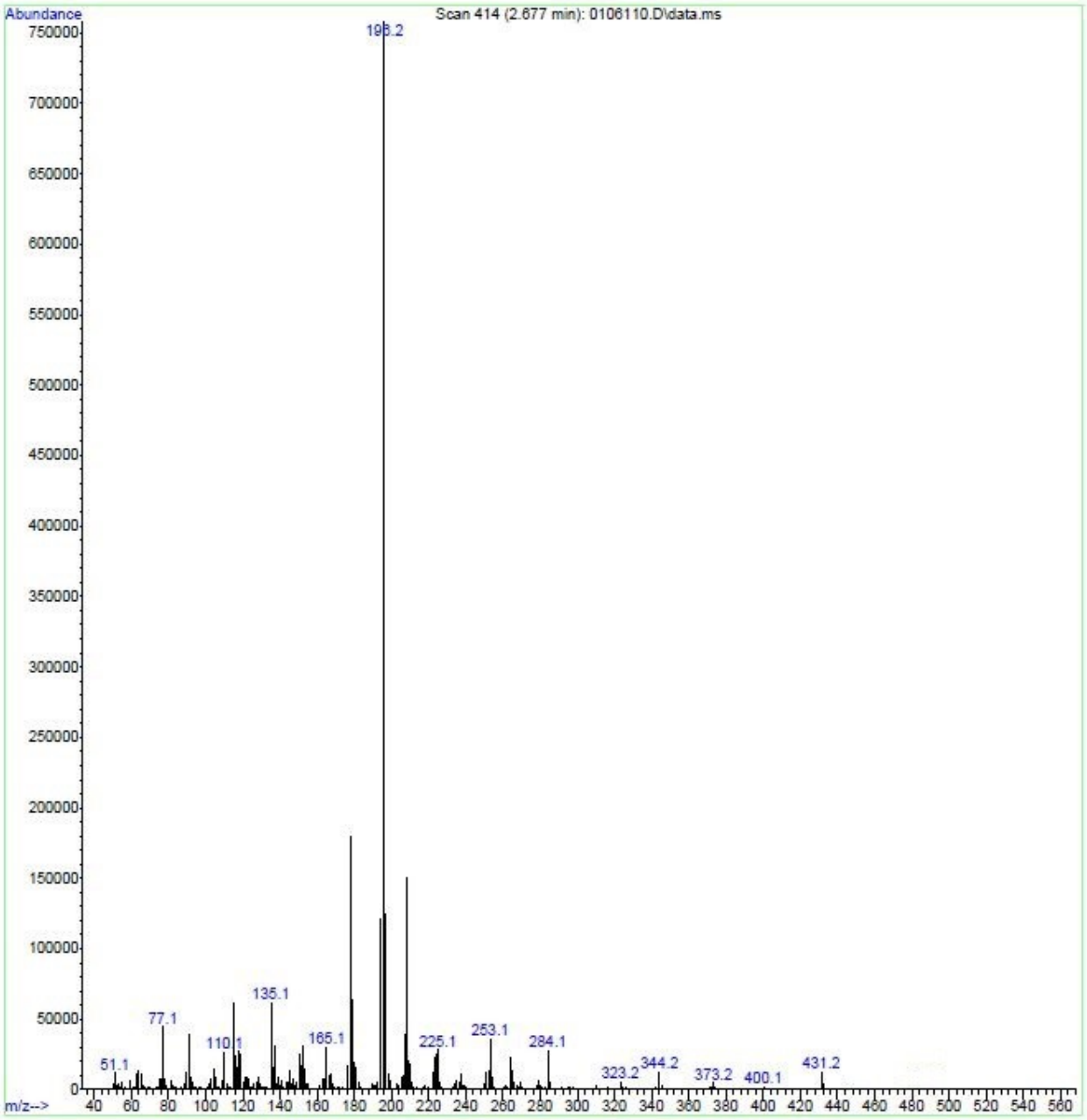
^{1}HNMR (300 MHz, DMSO-d_6) of compound **3c**



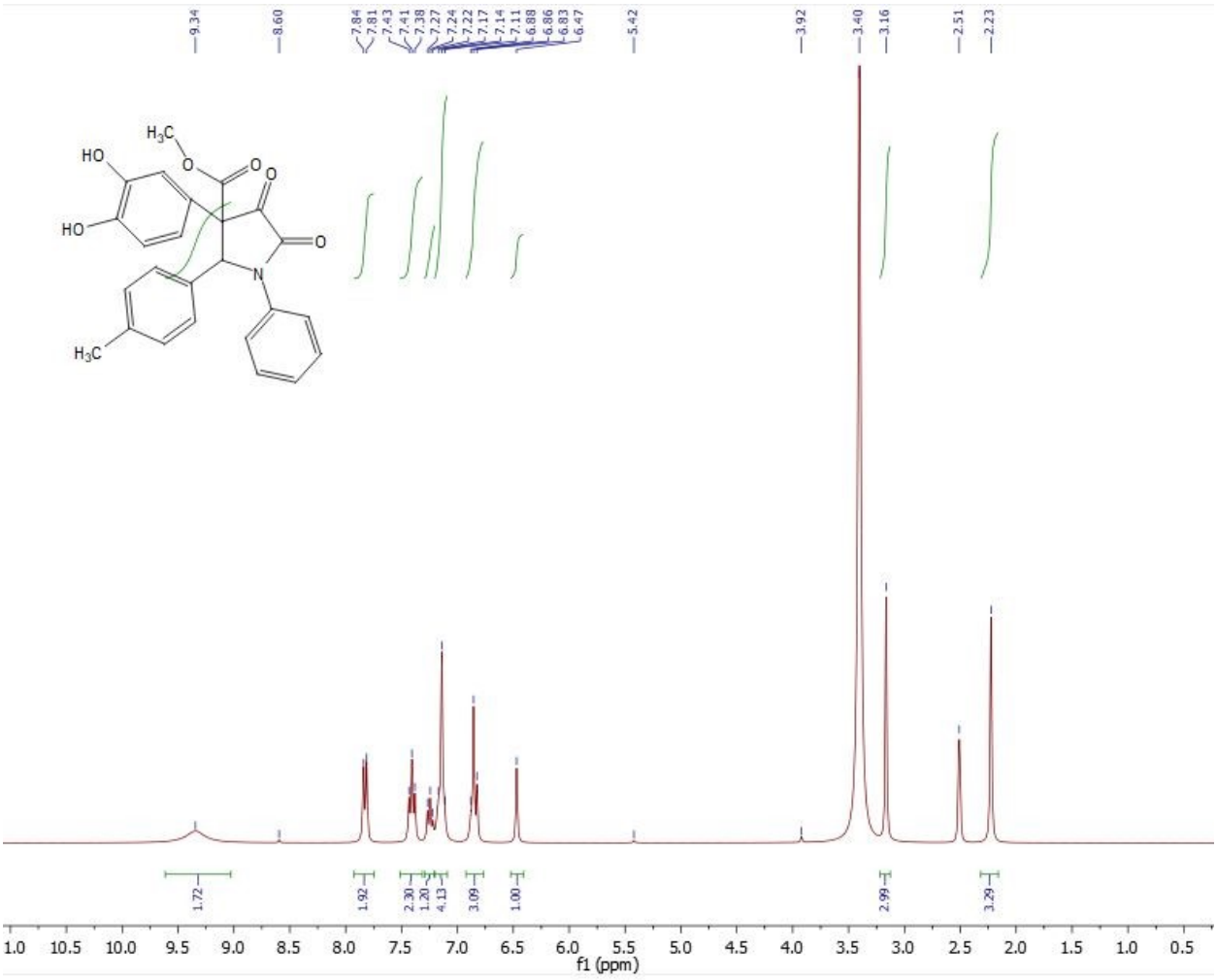
^{13}CNMR (75 MHz, DMSO-d_6) of compound **3c**



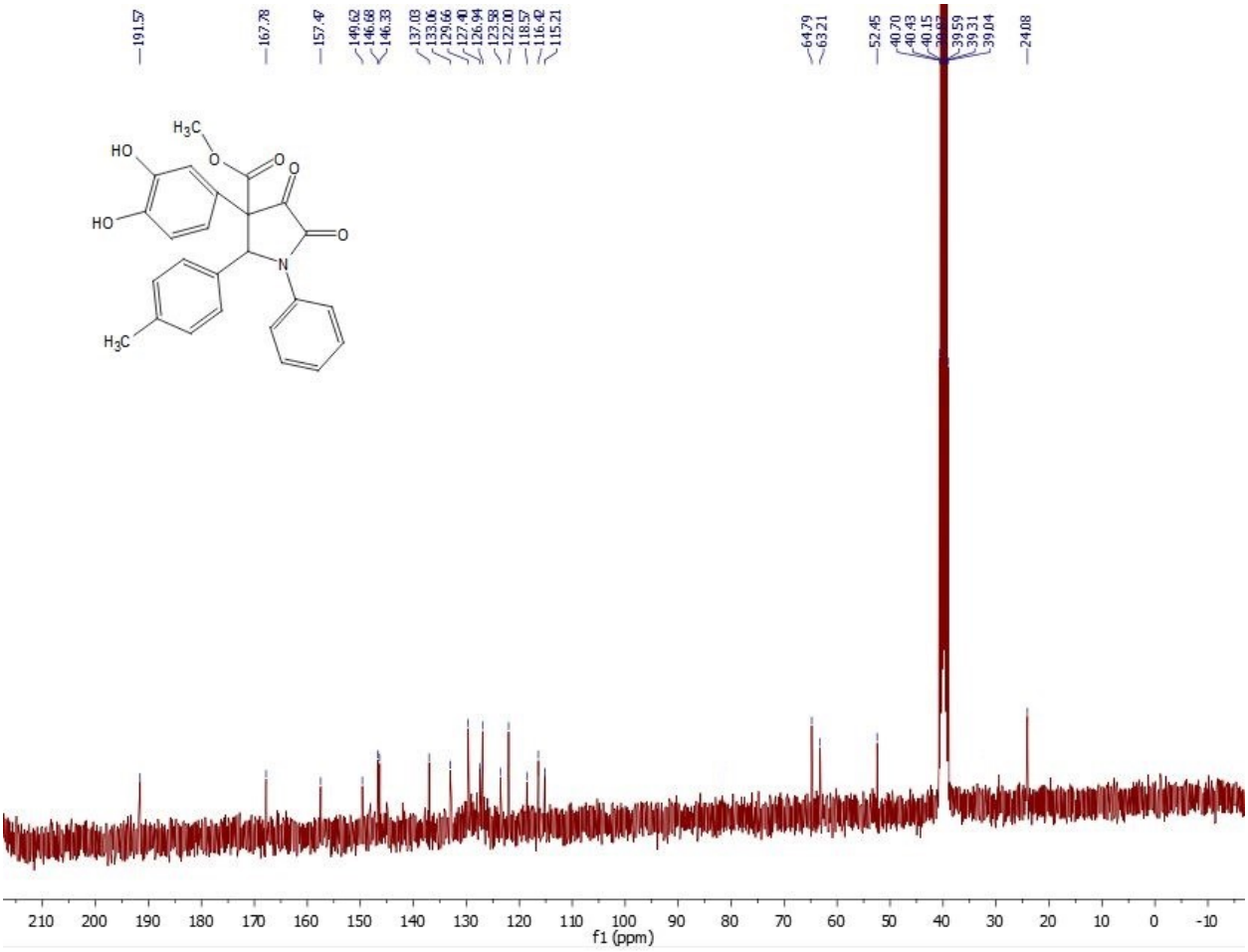
MW: 431



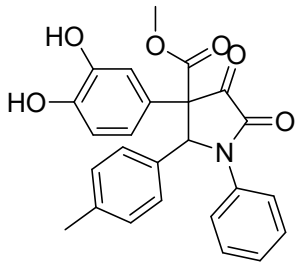
Mass spectra of compound **3c**



^{1}HNMR (300 MHz, DMSO-d_6) of compound **3d**



^{13}CNMR (75 MHz, DMSO-d_6) of compound **3d**



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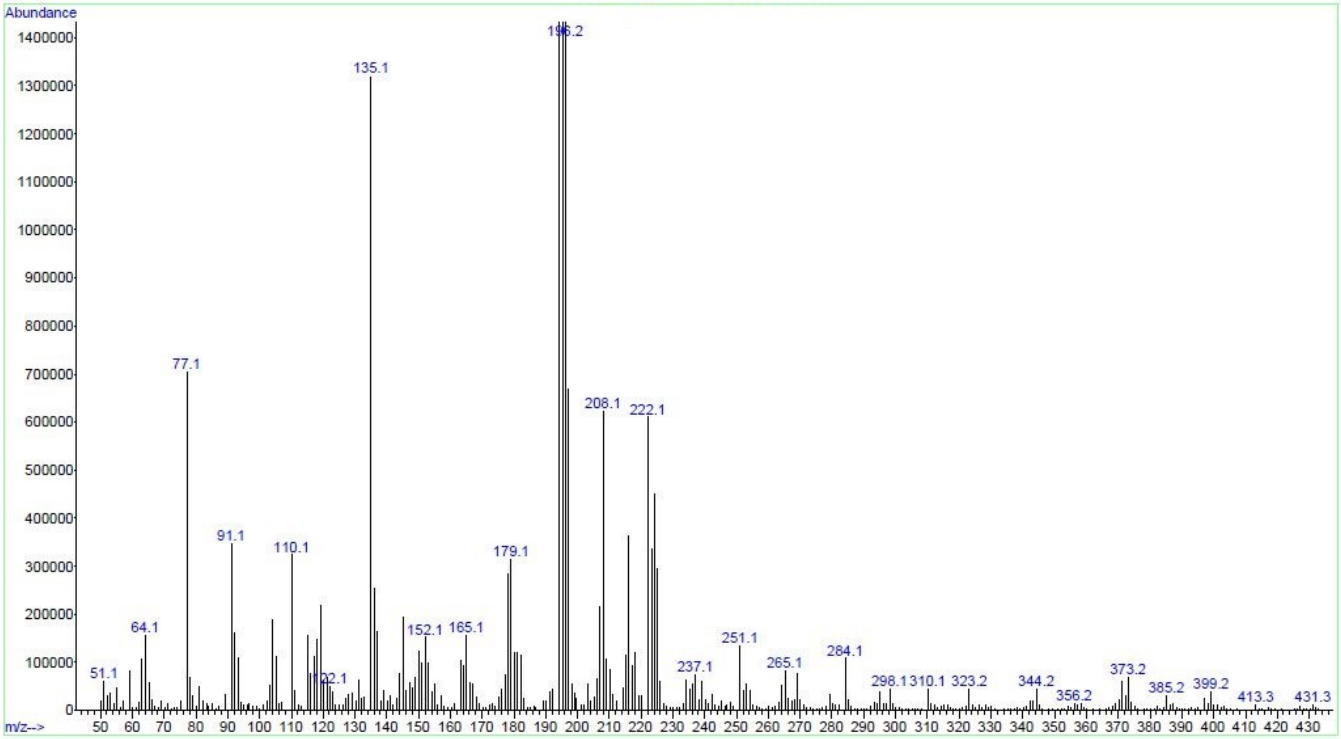
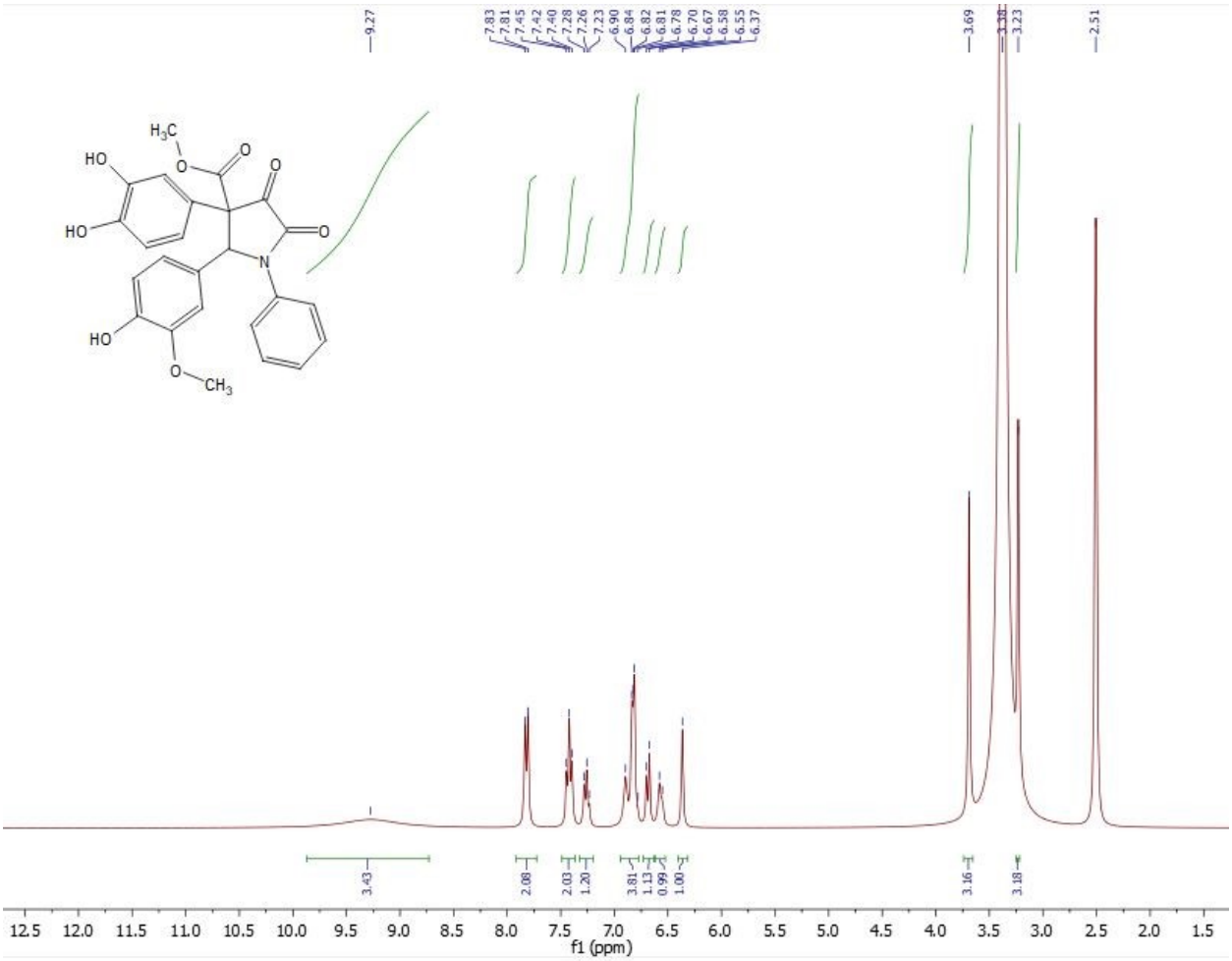
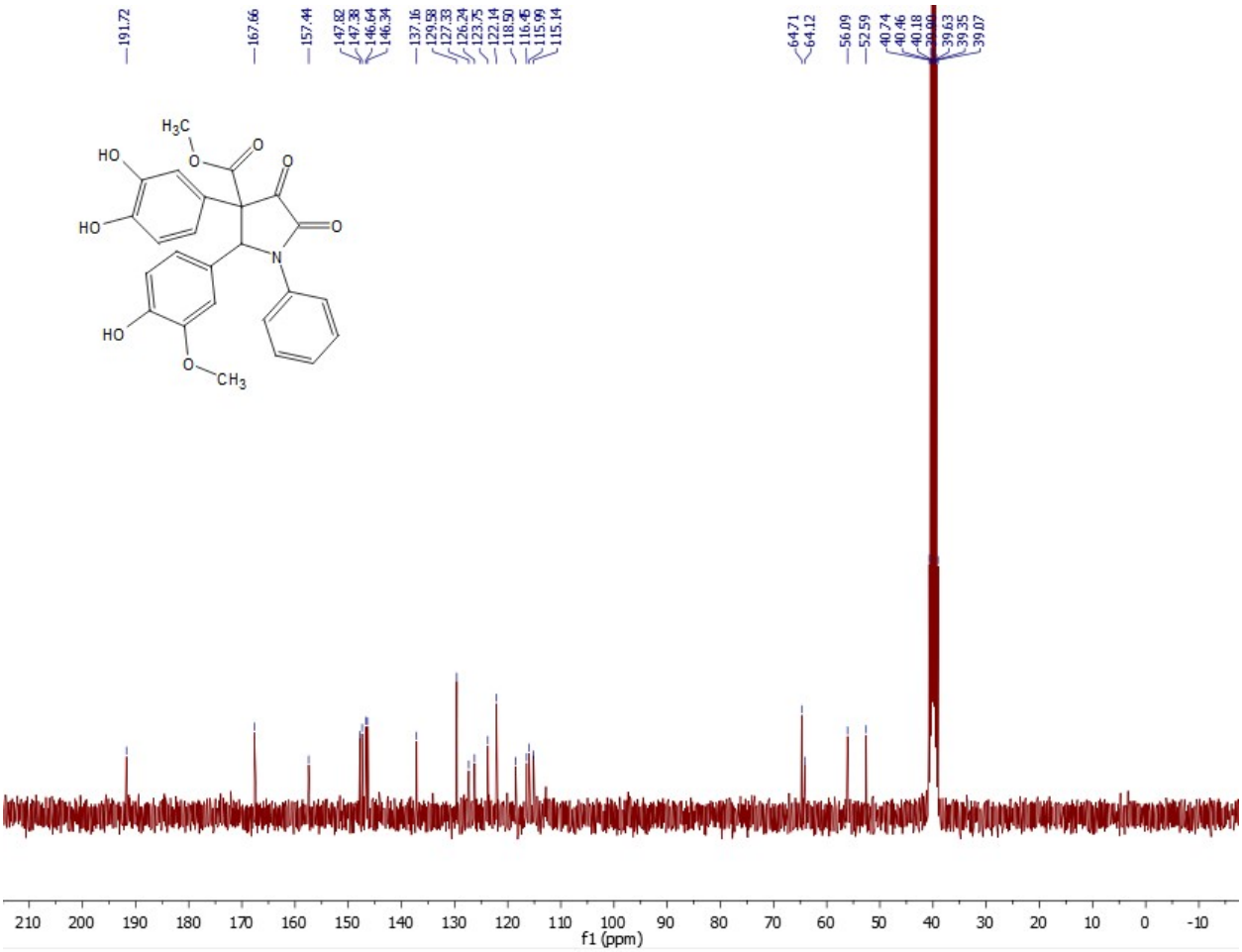


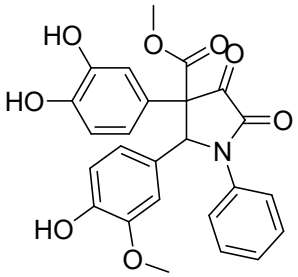
Mass spectra of compound **3d**



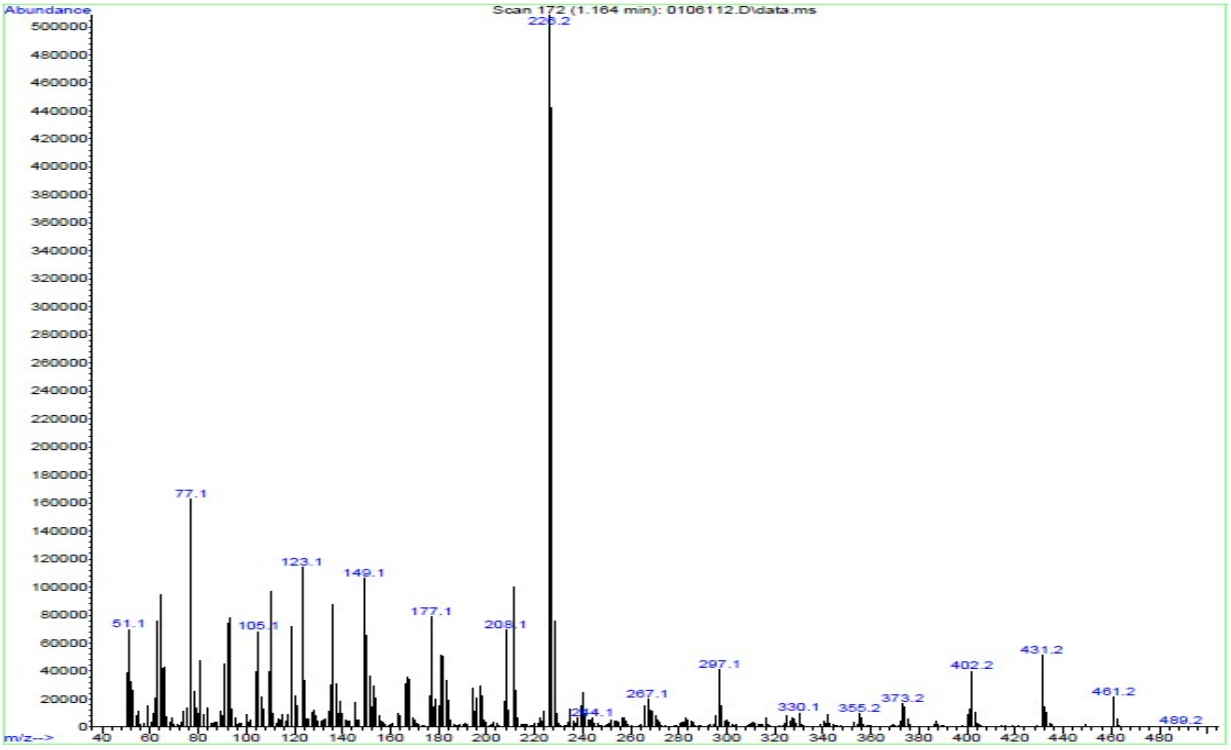
[1]HNMR (300 MHz, DMSO-d_6) of compound **3e**



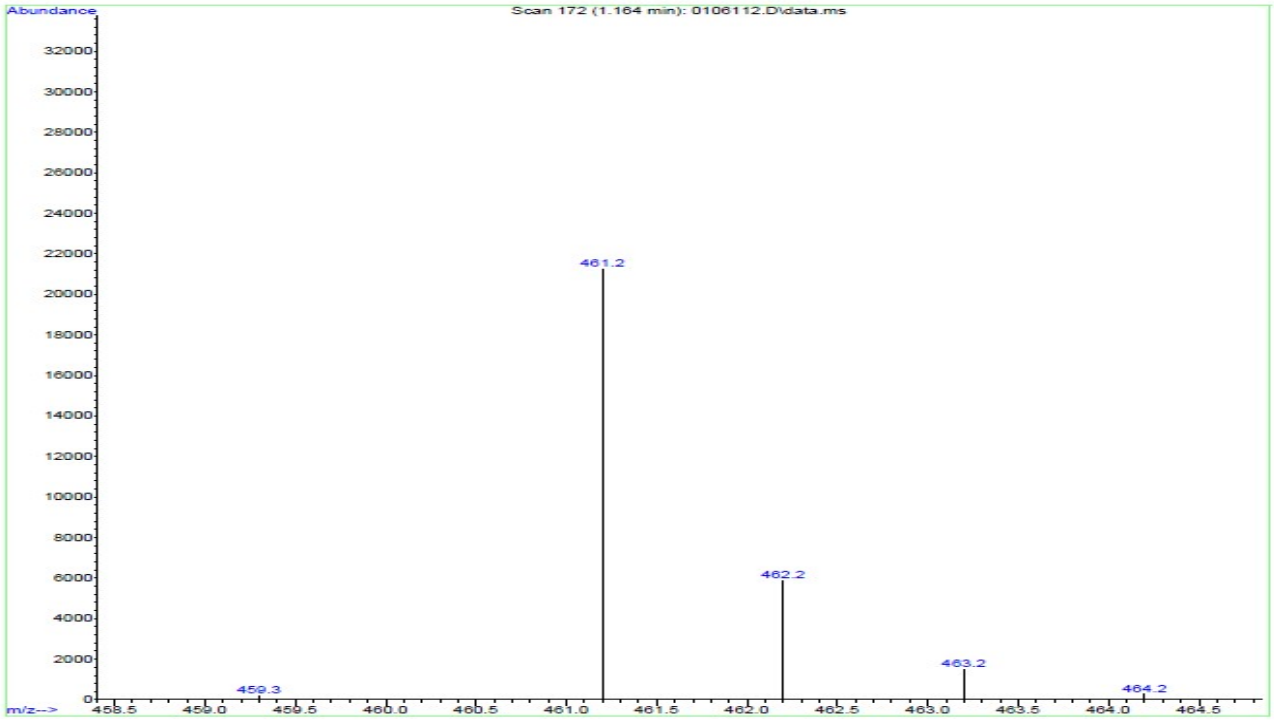
^{13}CNMR (75 MHz, DMSO-d_6) of compound **3e**



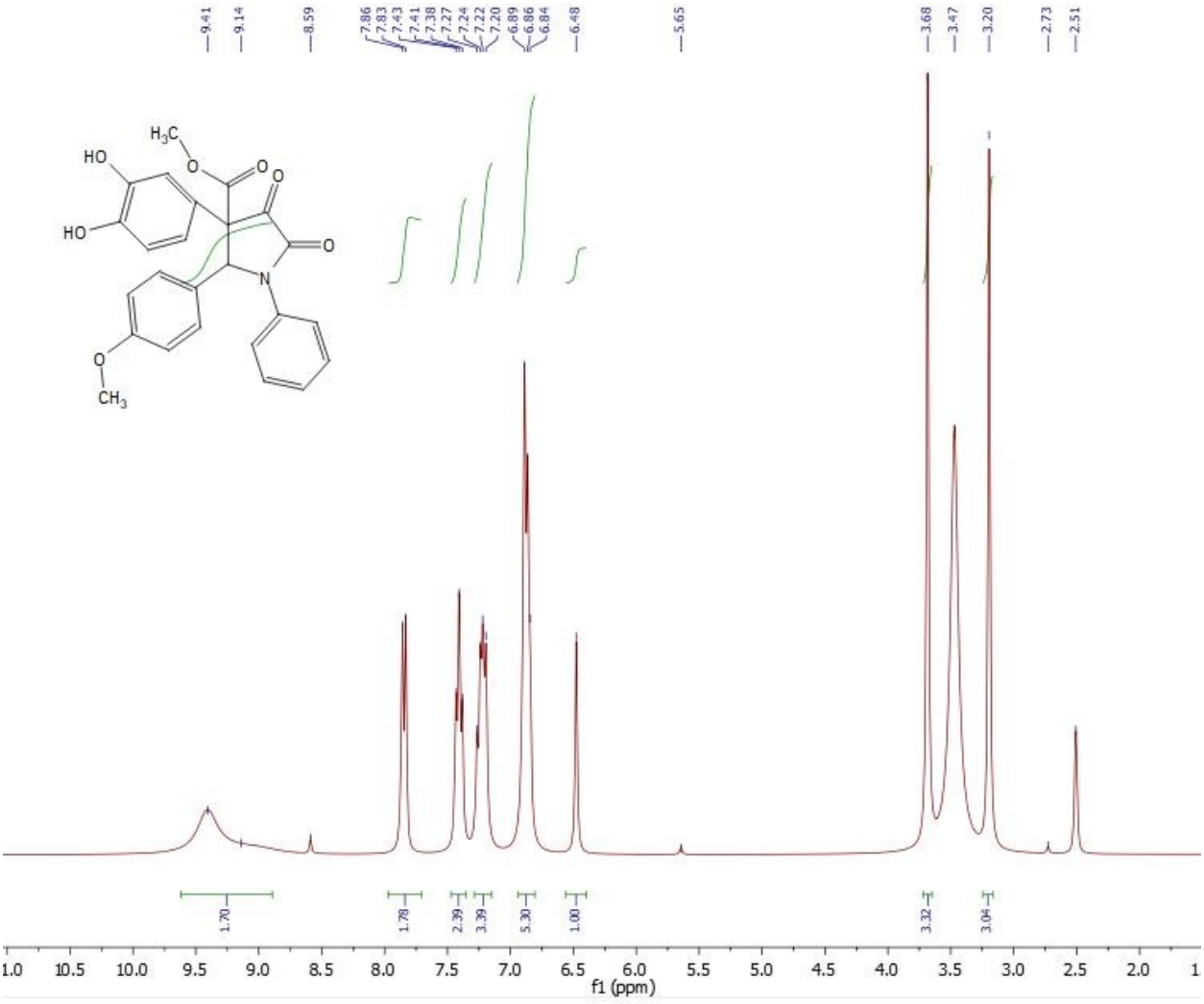
MW: 463



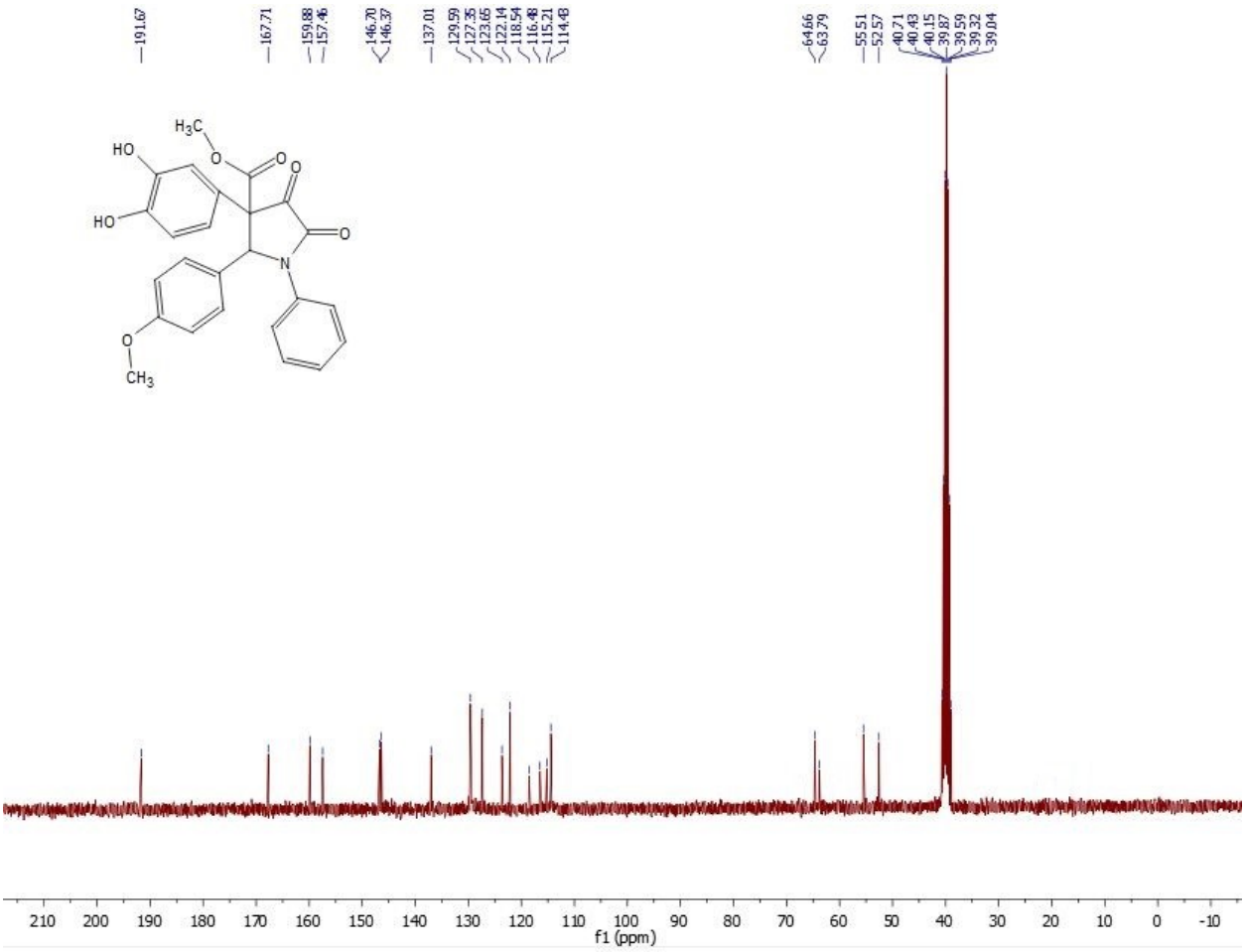
Mass spectra of compound **3e**



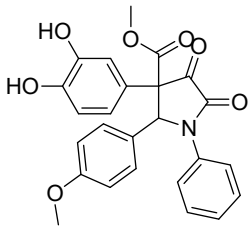
Mass spectra of compound **3e**



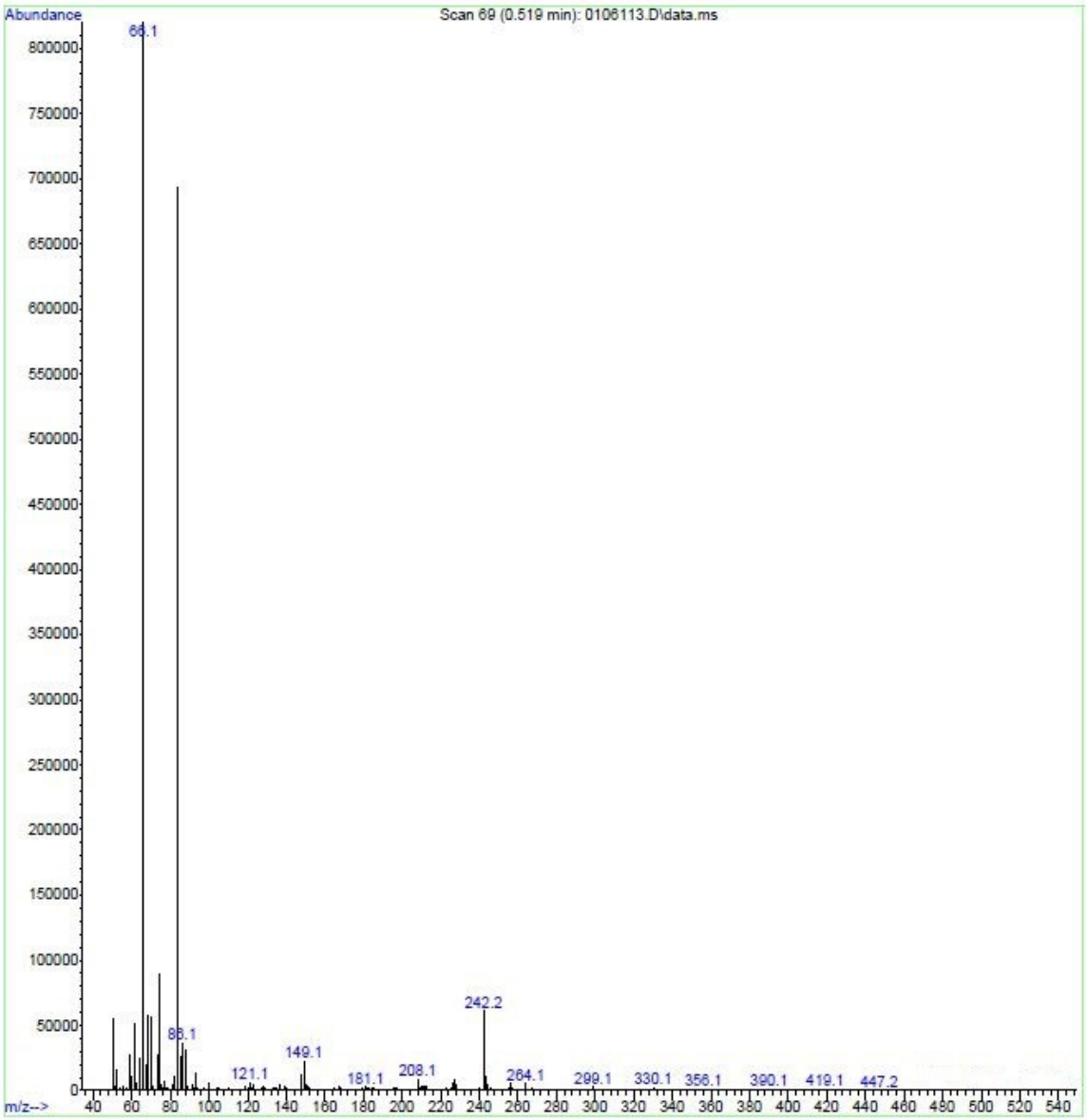
^{1}HNMR (300 MHz, DMSO-d_6) of compound **3f**



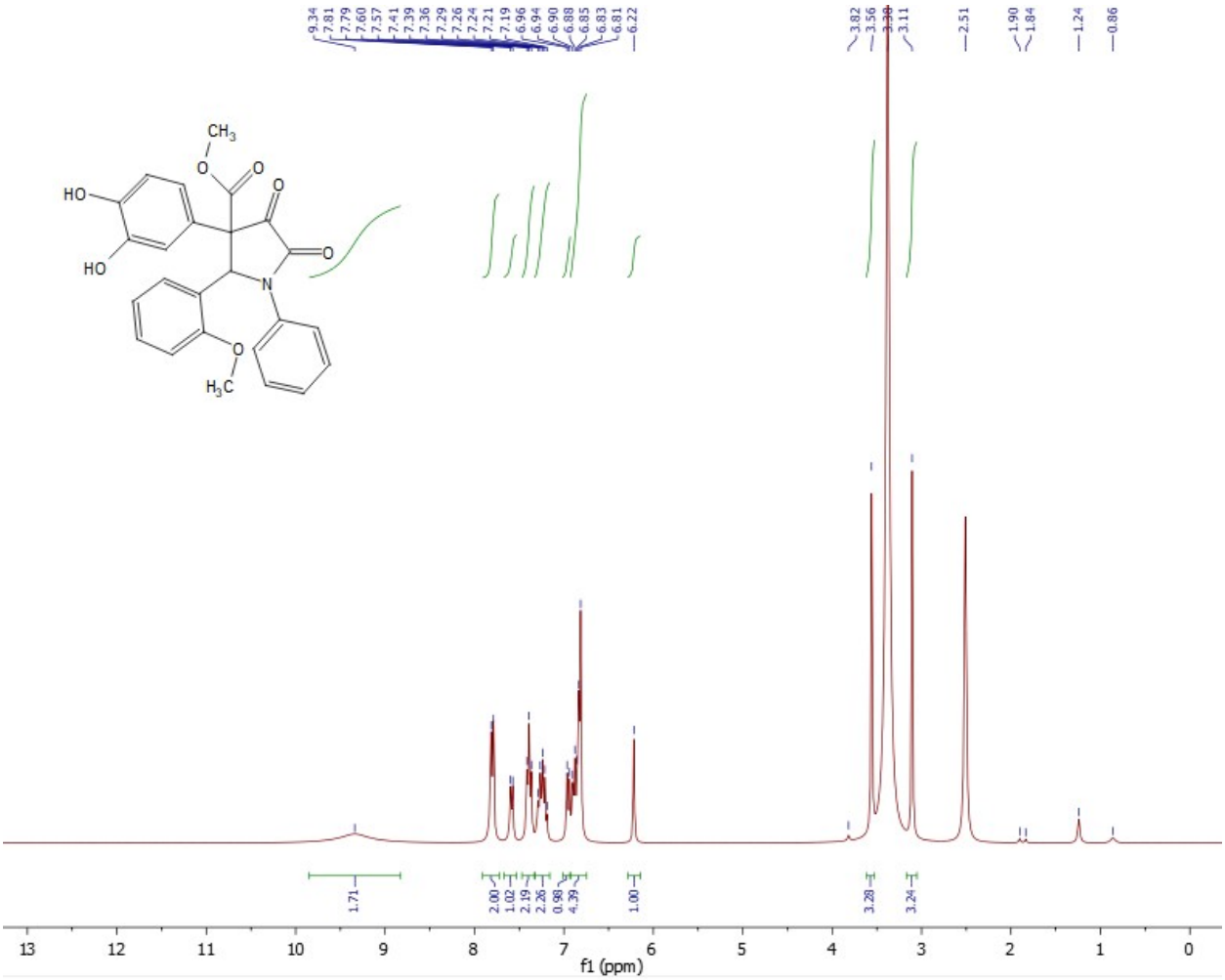
^{13}CNMR (75 MHz, DMSO-d_6) of compound **3f**



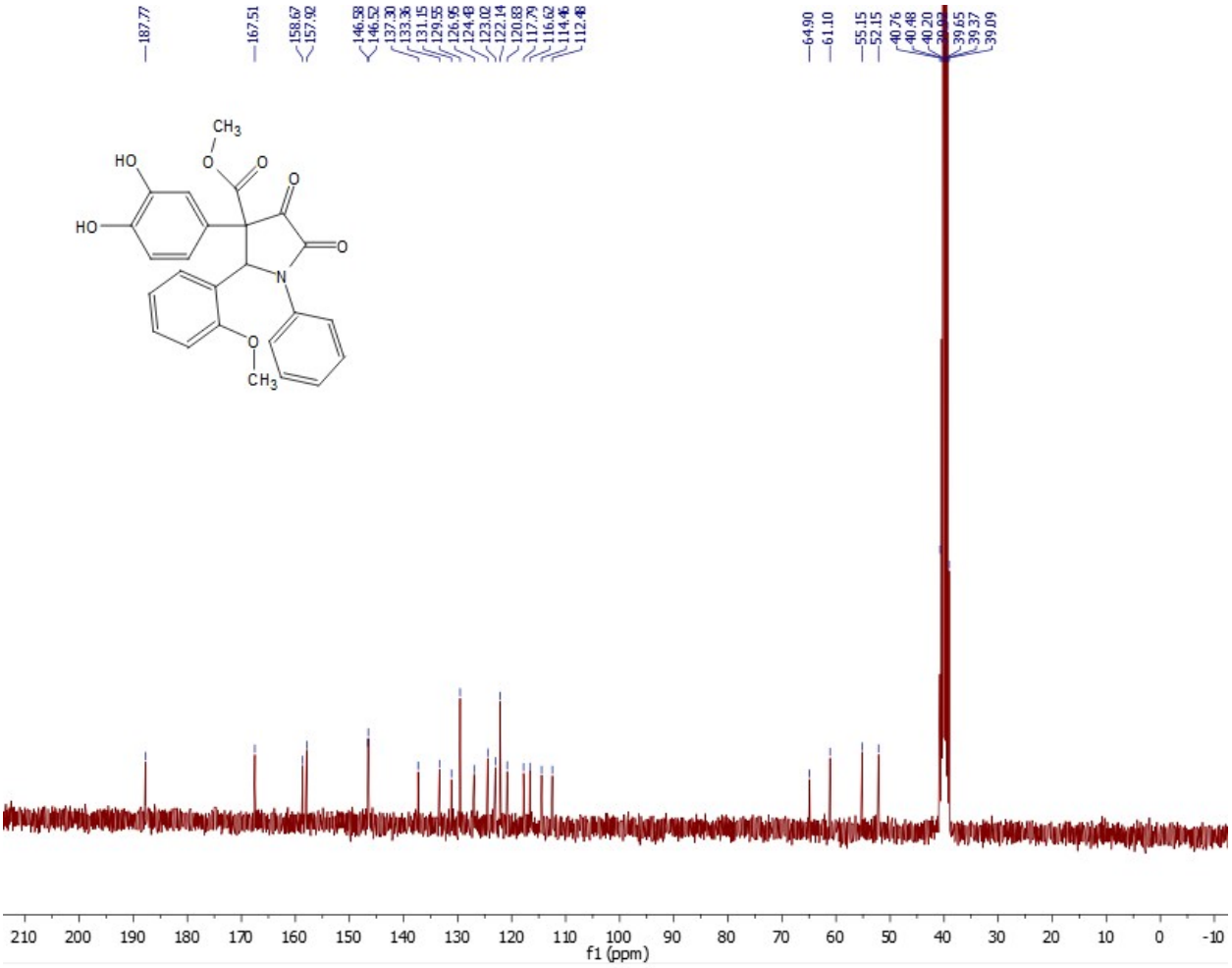
MW: 447



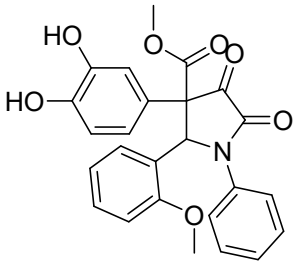
Mass spectra of compound **3f**

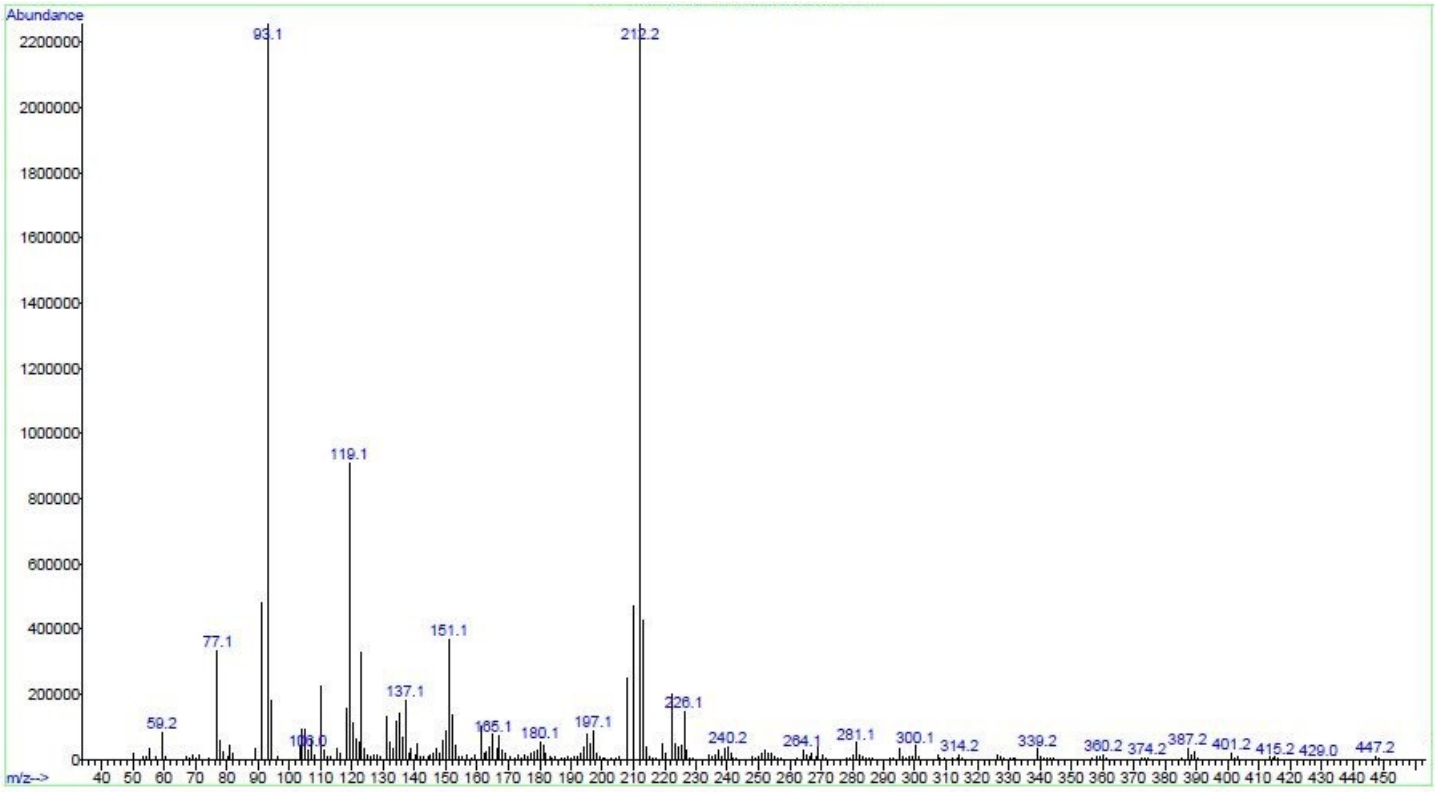


^{1}HNMR (300 MHz, DMSO-d_6) of compound **3g**



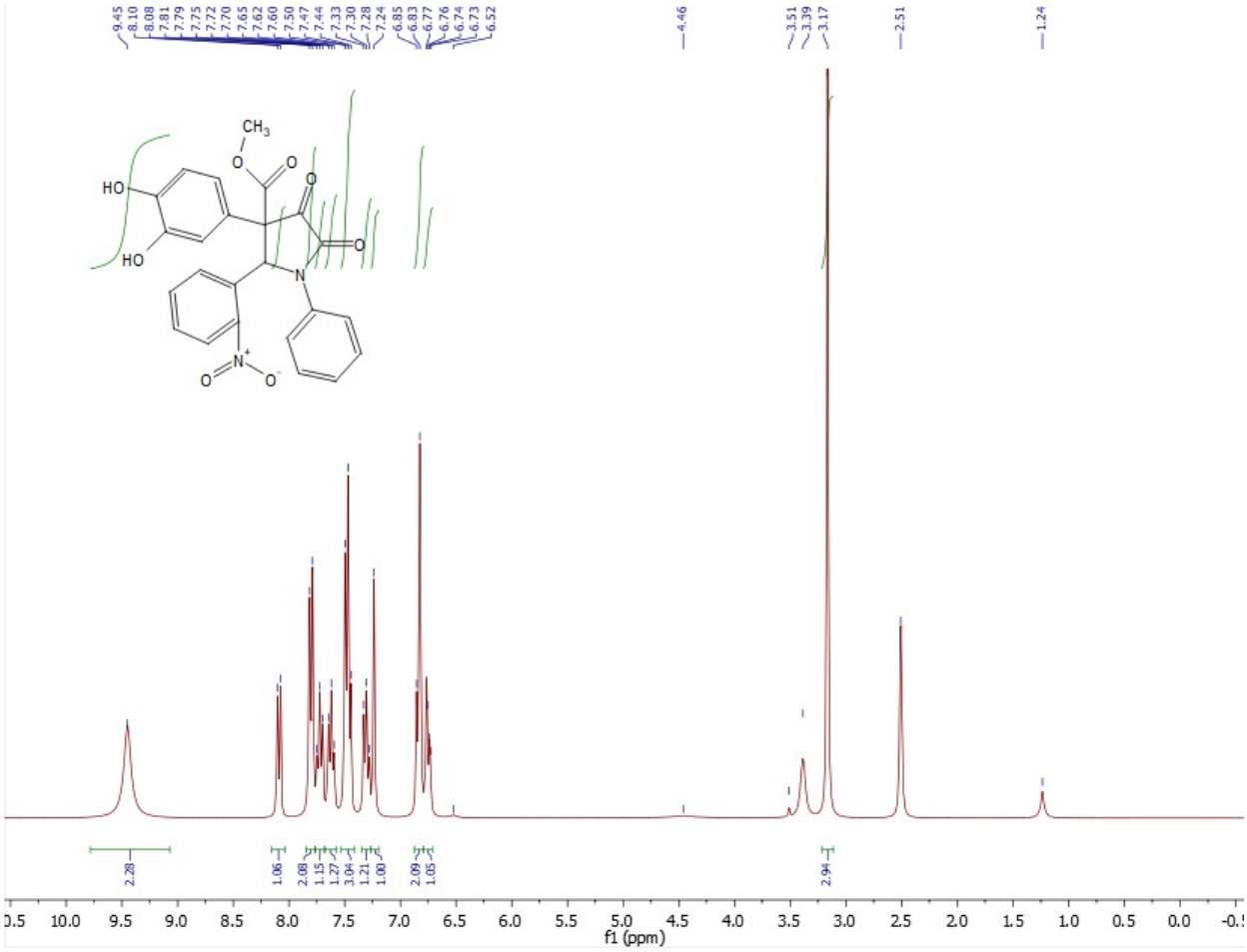
^{13}CNMR (75 MHz, DMSO-d_6) of compound **3g**



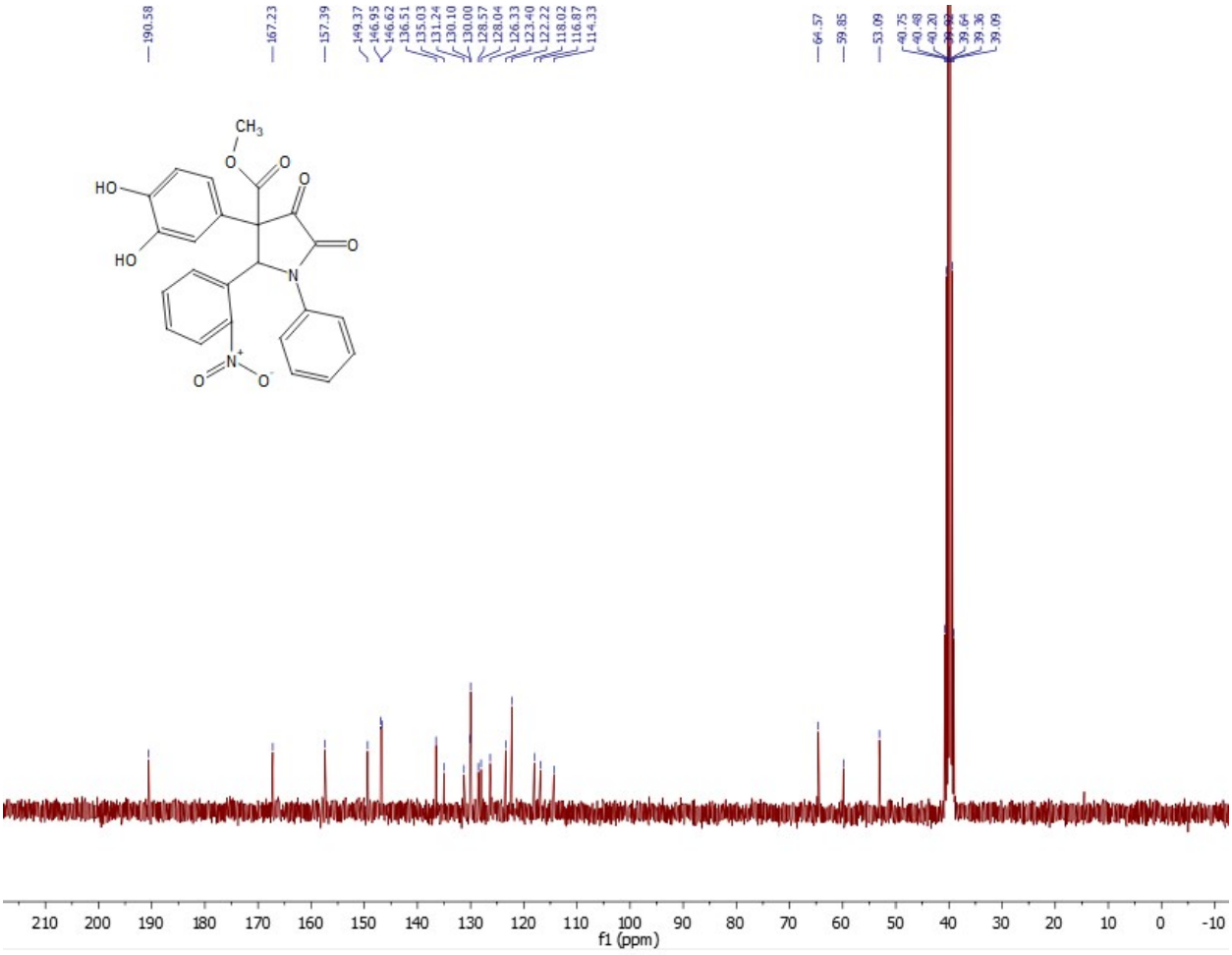


Mass spectra of compound **3g**

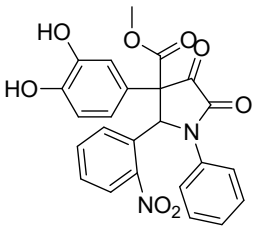
MW: 447



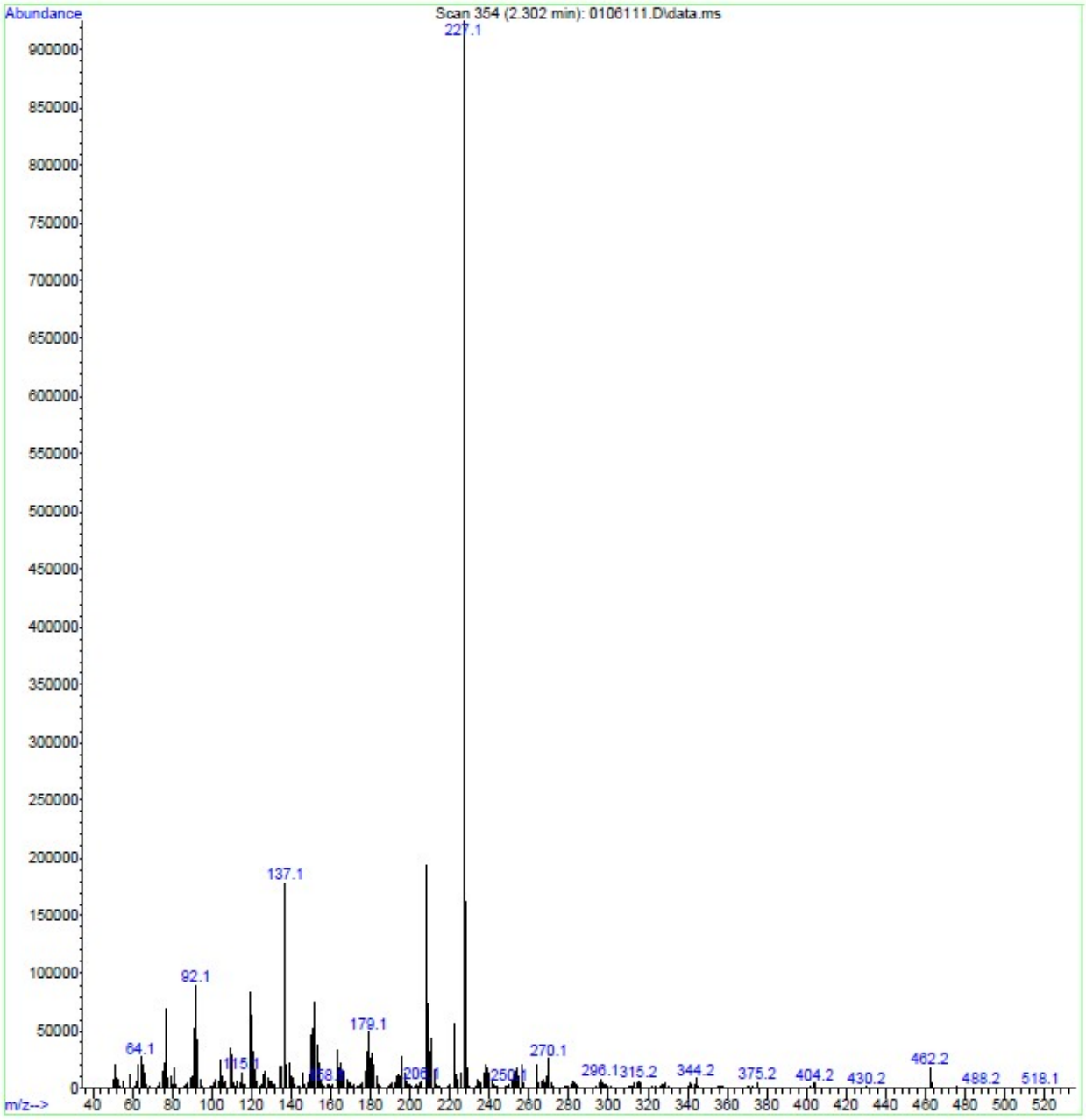
[1]HNMR (300 MHz, DMSO-d_6) of compound **3h**



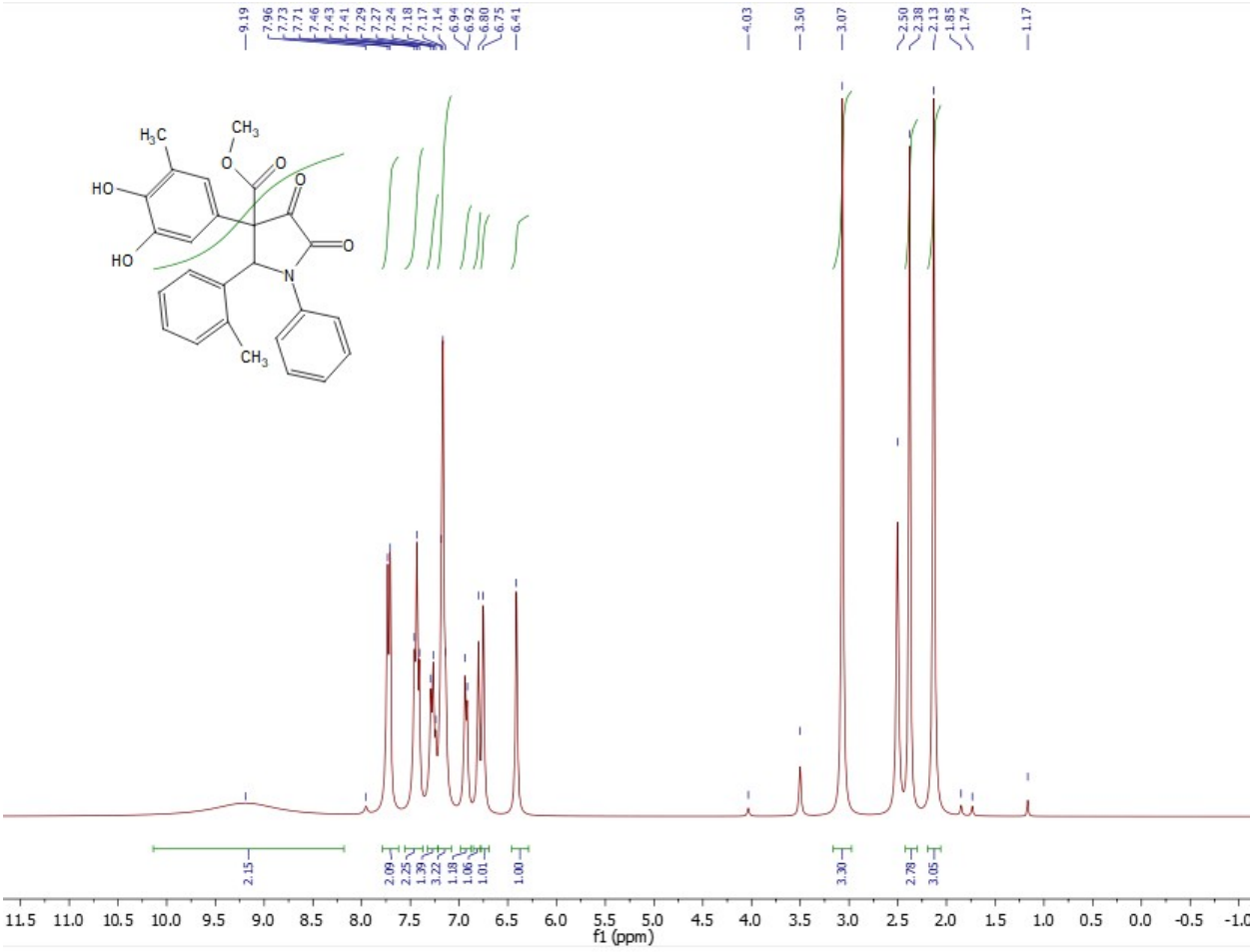
^{13}CNMR (75 MHz, DMSO-d_6) of compound **3h**



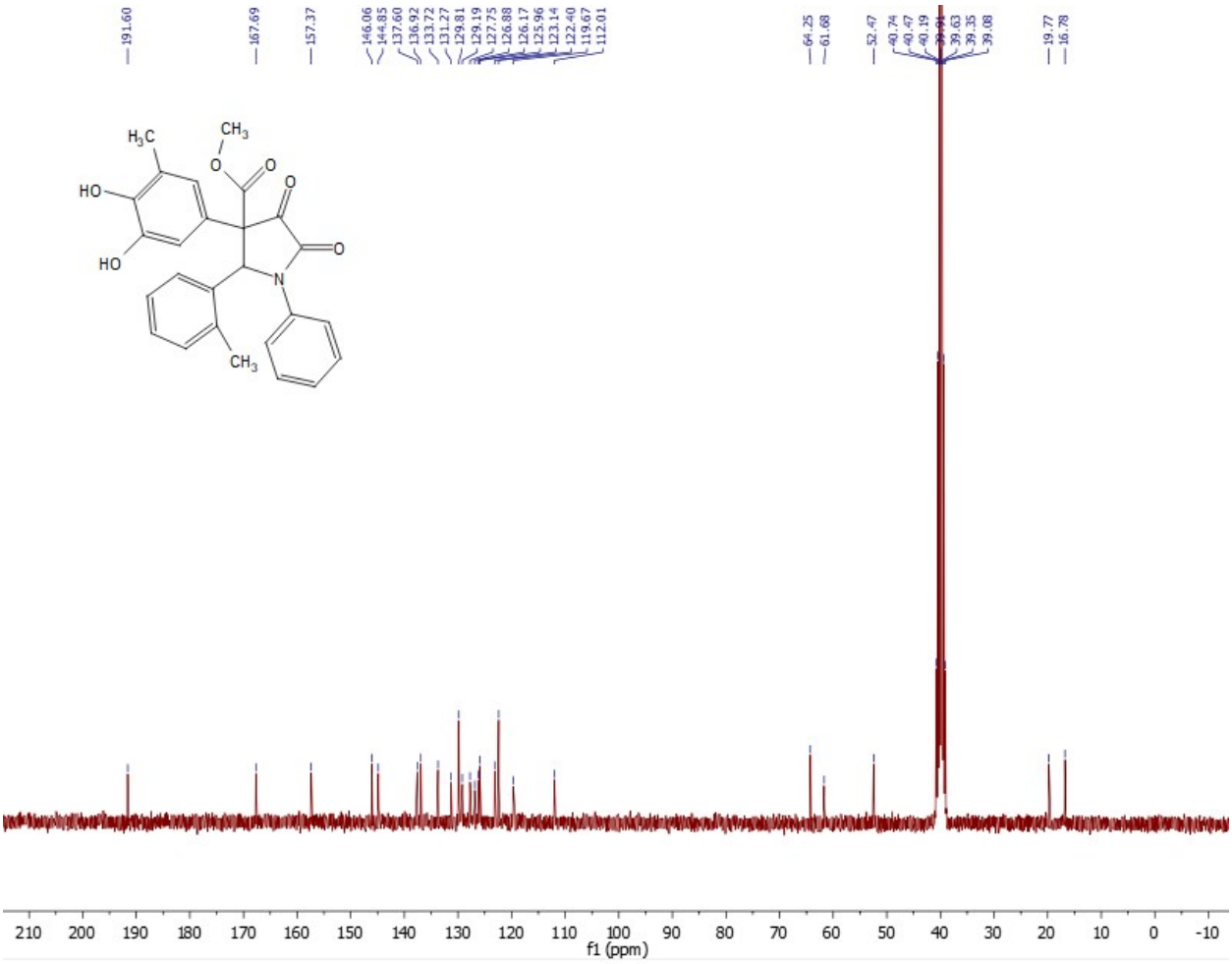
MW: 462



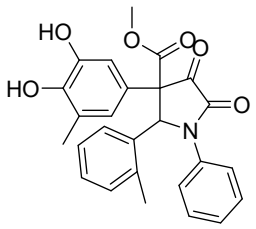
Mass spectra of compound **3h**



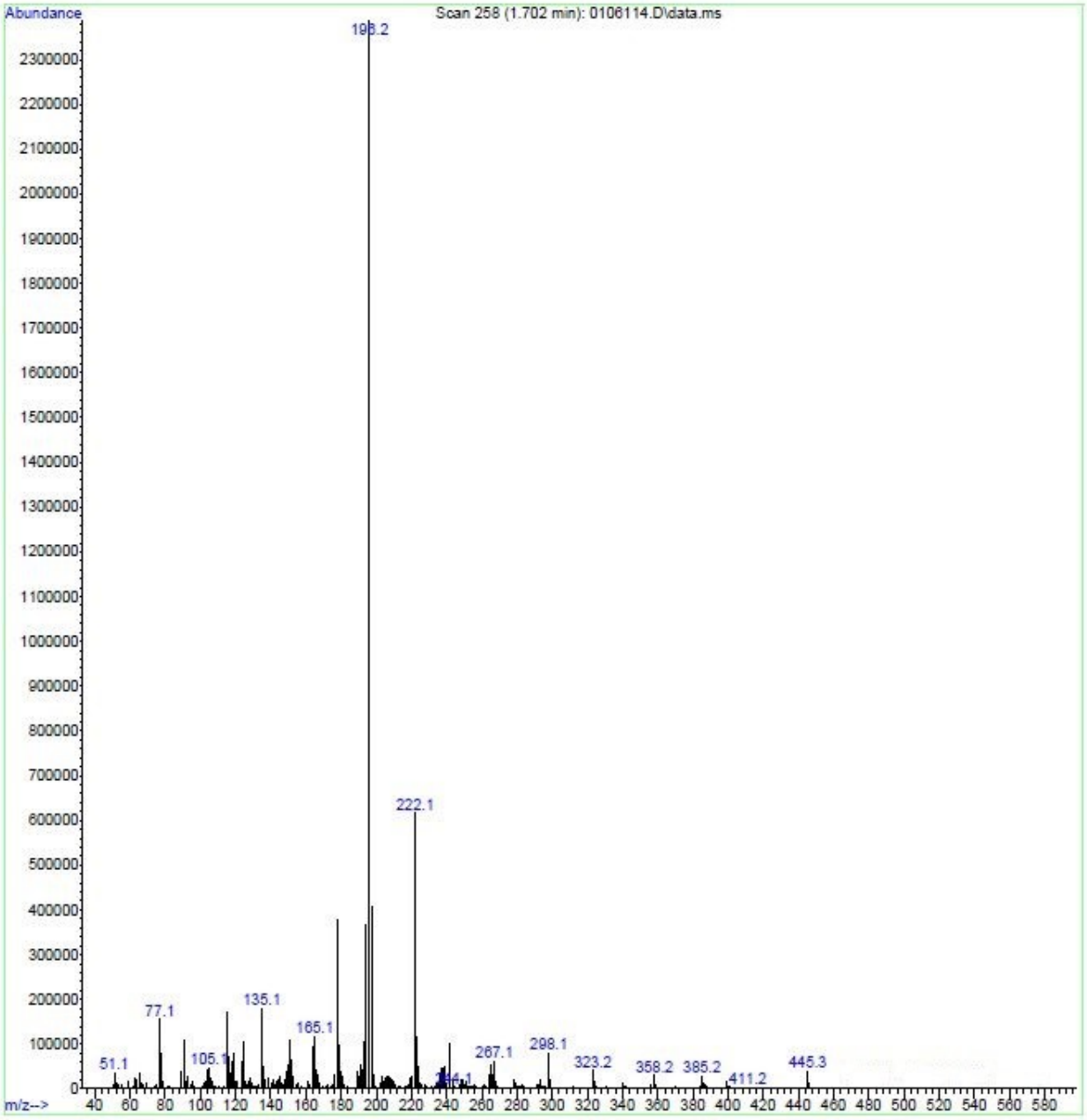
^{1}HNMR (300 MHz, DMSO-d_6) of compound **3i**



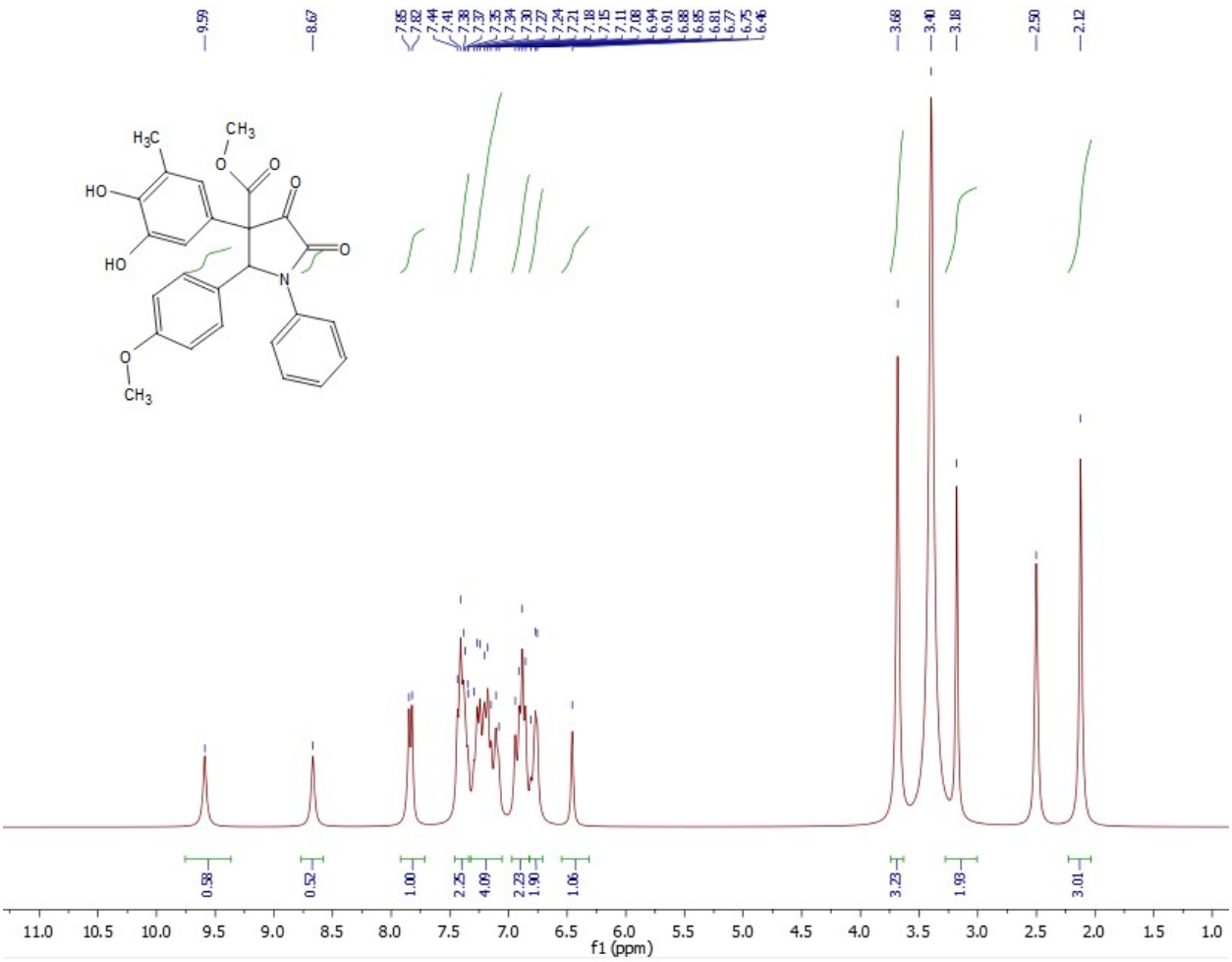
^{13}CNMR (75 MHz, DMSO-d_6) of compound **3i**



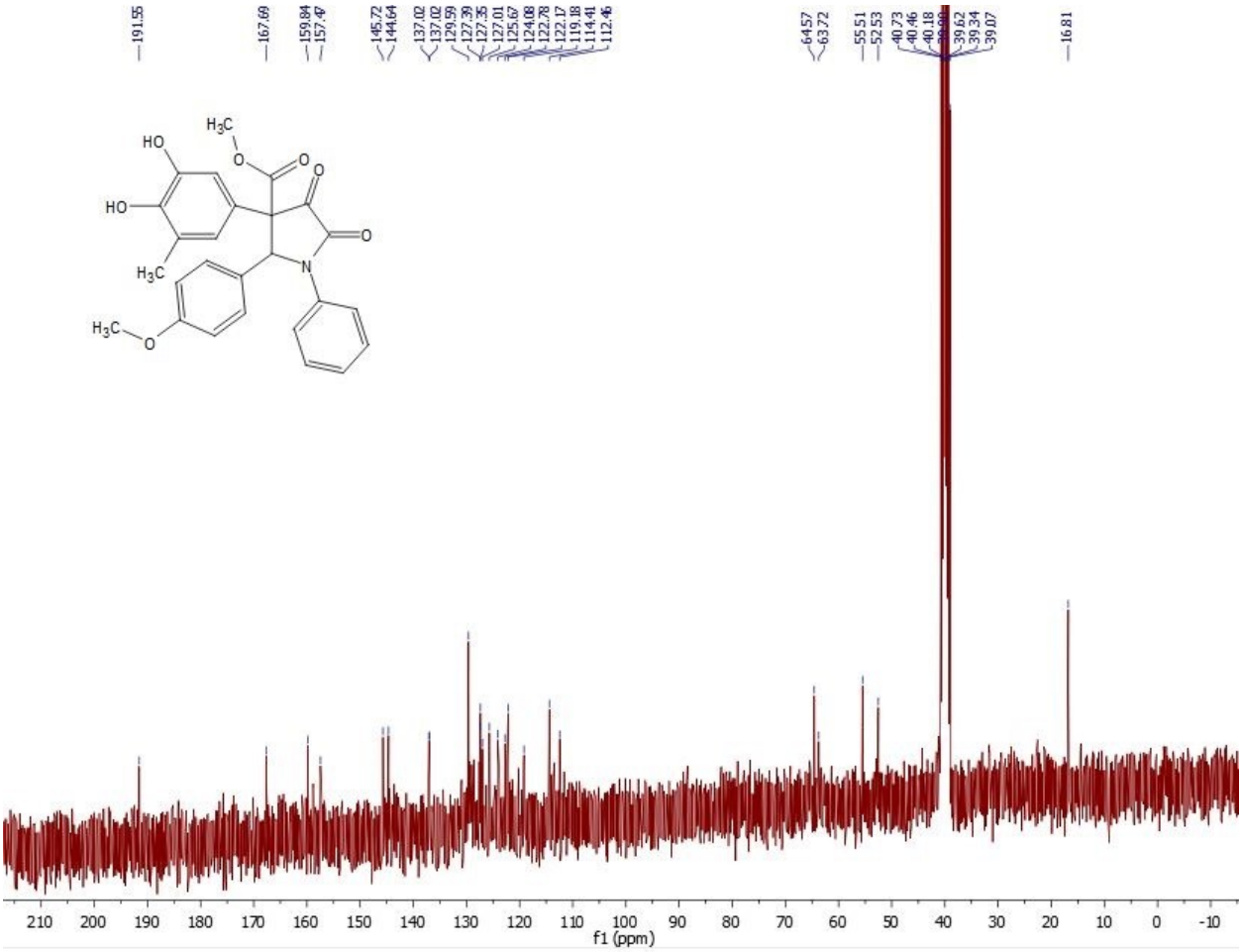
MW: 445



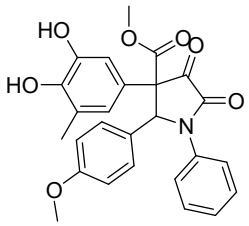
Mass spectra of compound **3i**



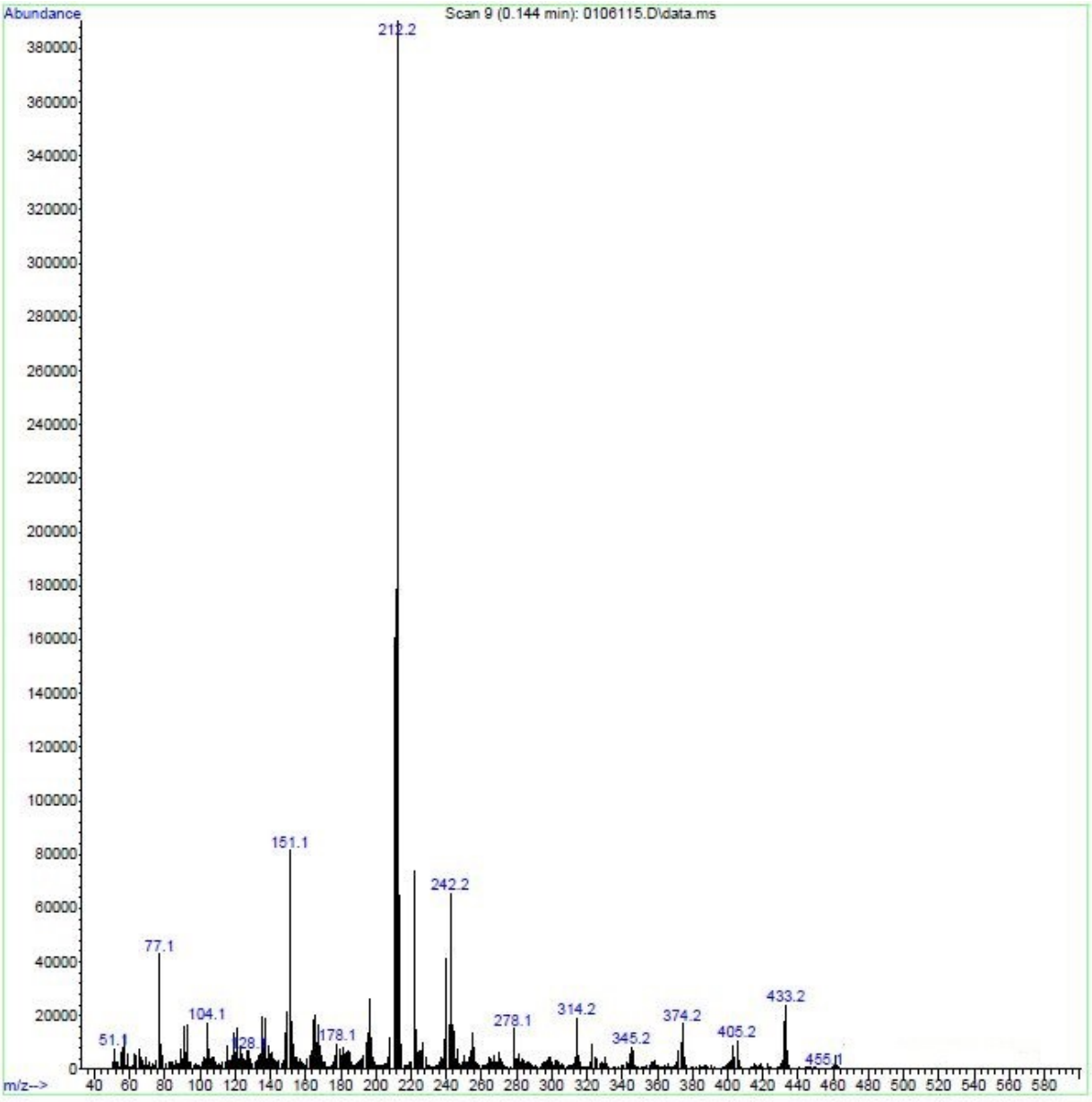
^{1}HNMR (300 MHz, DMSO-d_6) of compound **3j**



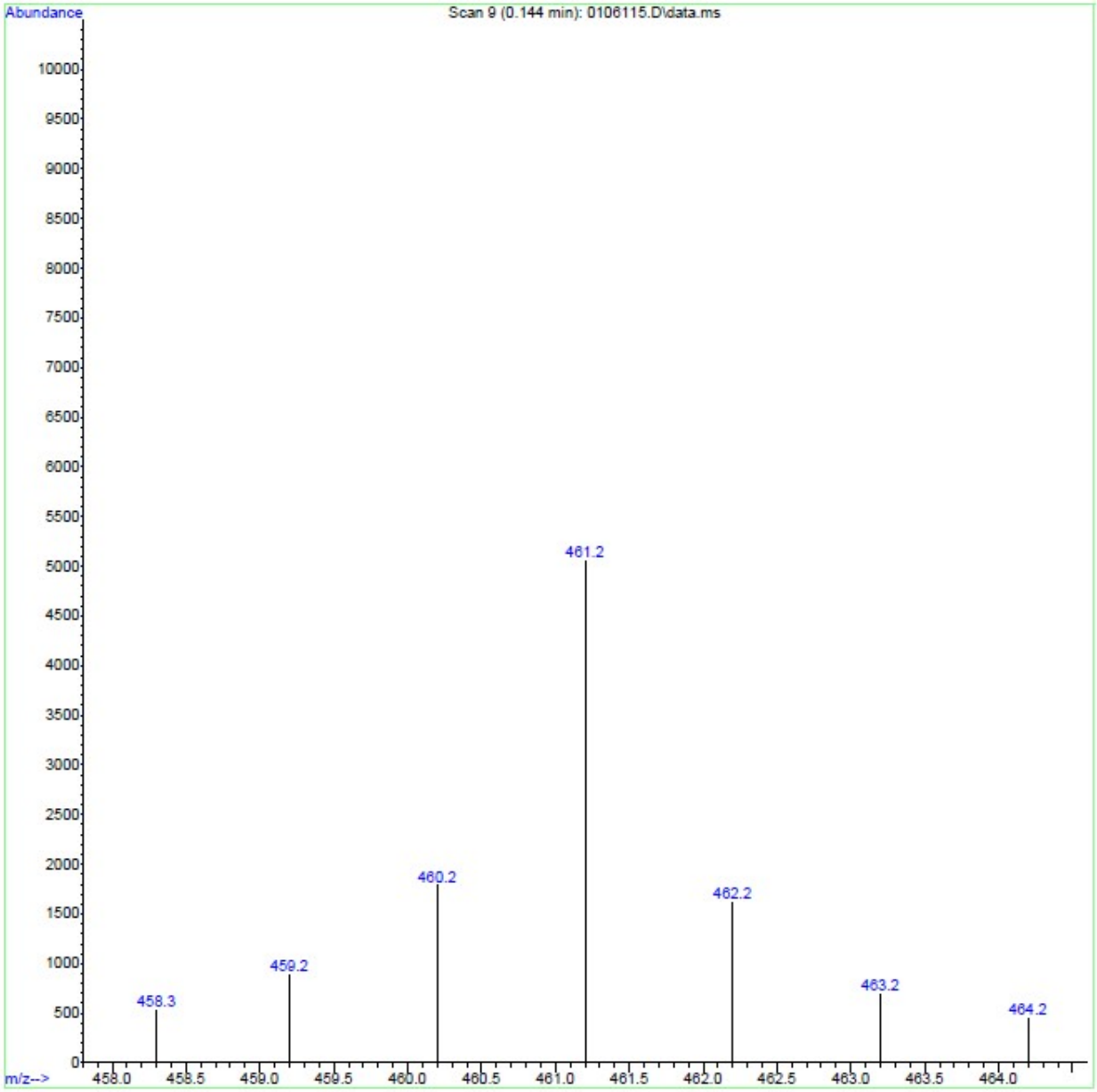
^{13}CNMR (75 MHz, DMSO-d_6) of compound **3j**



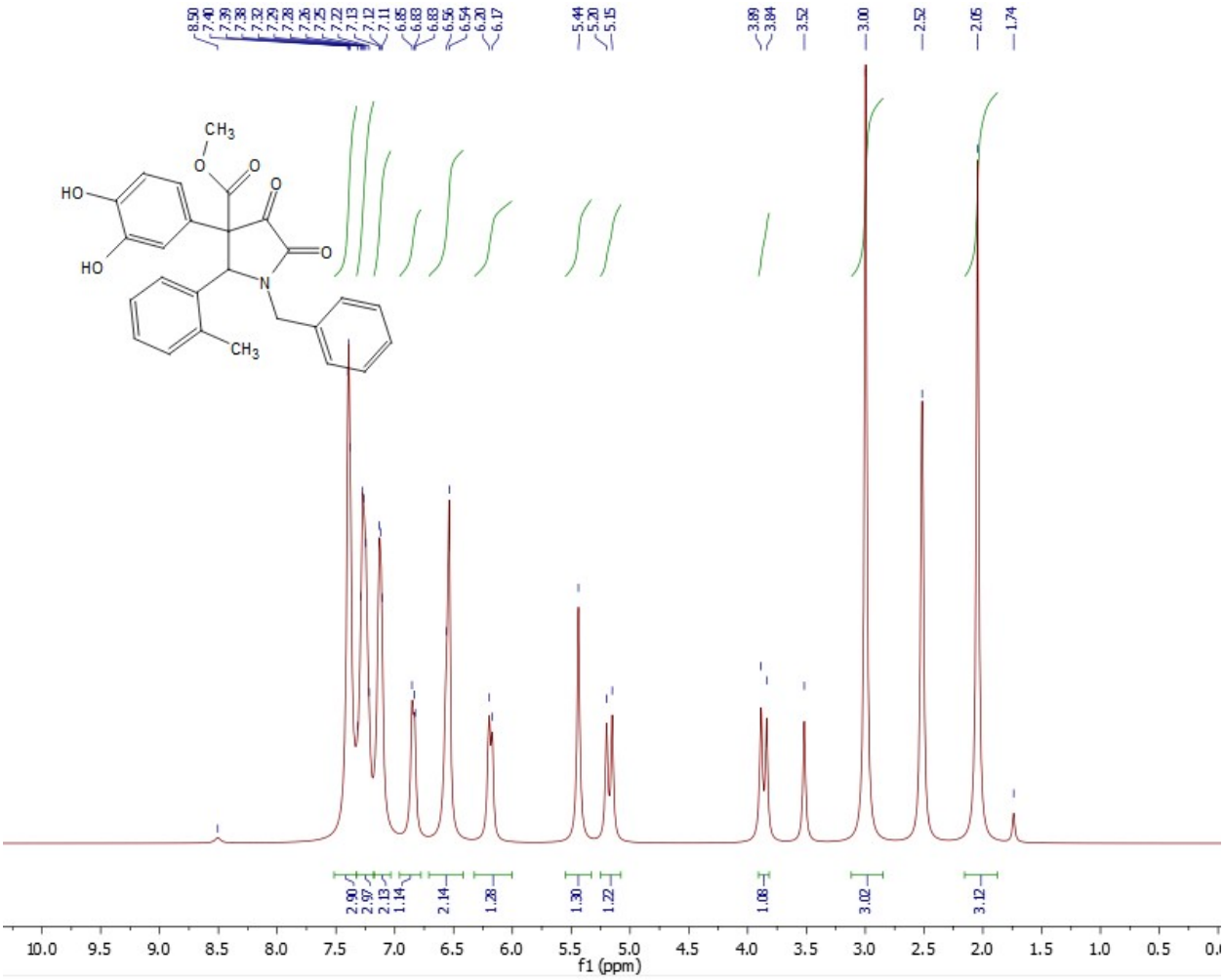
MW: 461



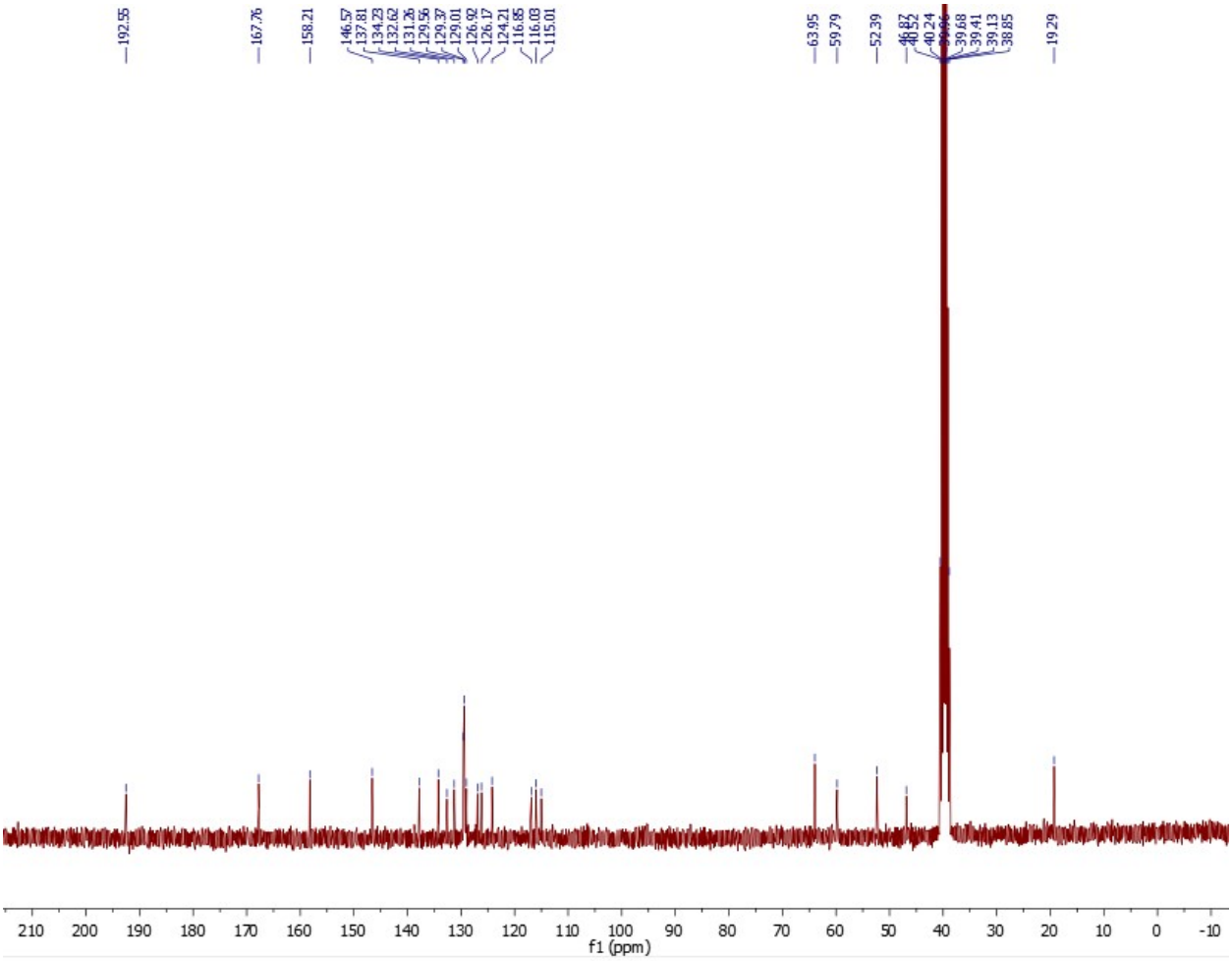
Mass spectra of compound **3j**



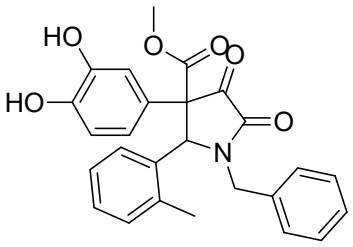
Mass spectra of compound **3j**



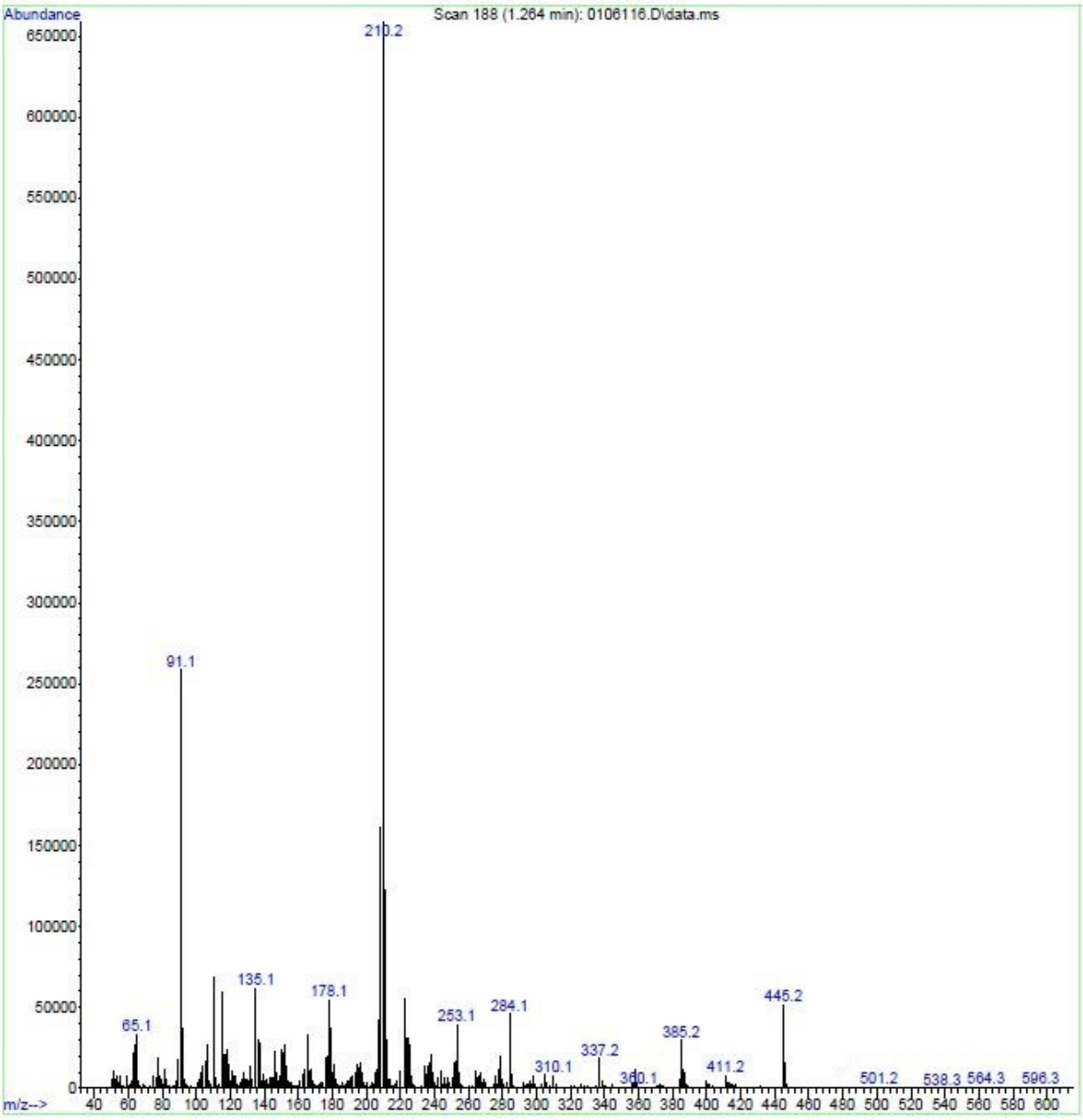
^{1}HNMR (300 MHz, DMSO-d_6) of compound **3k**



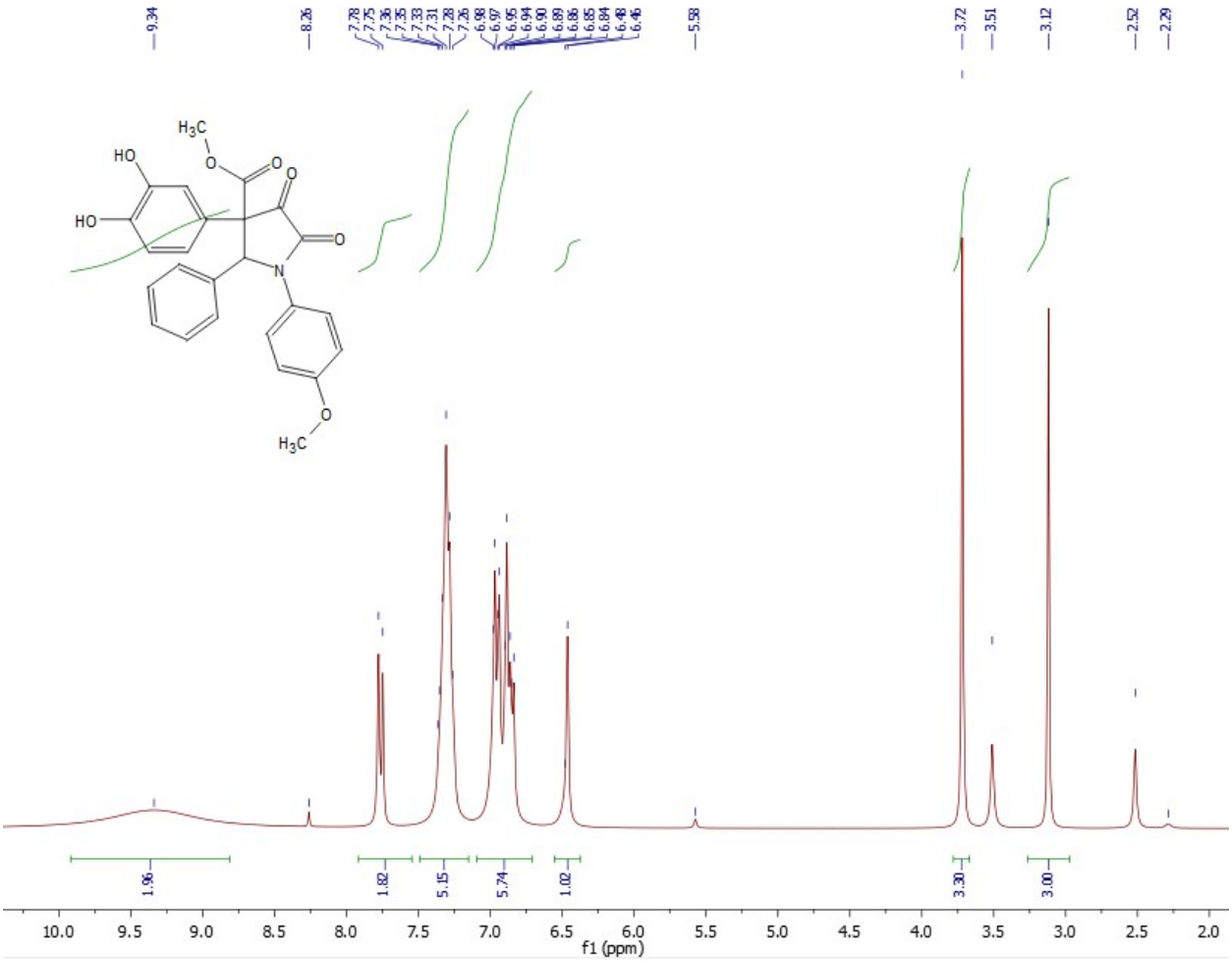
^{13}CNMR (75 MHz, DMSO-d_6) of compound **3k**



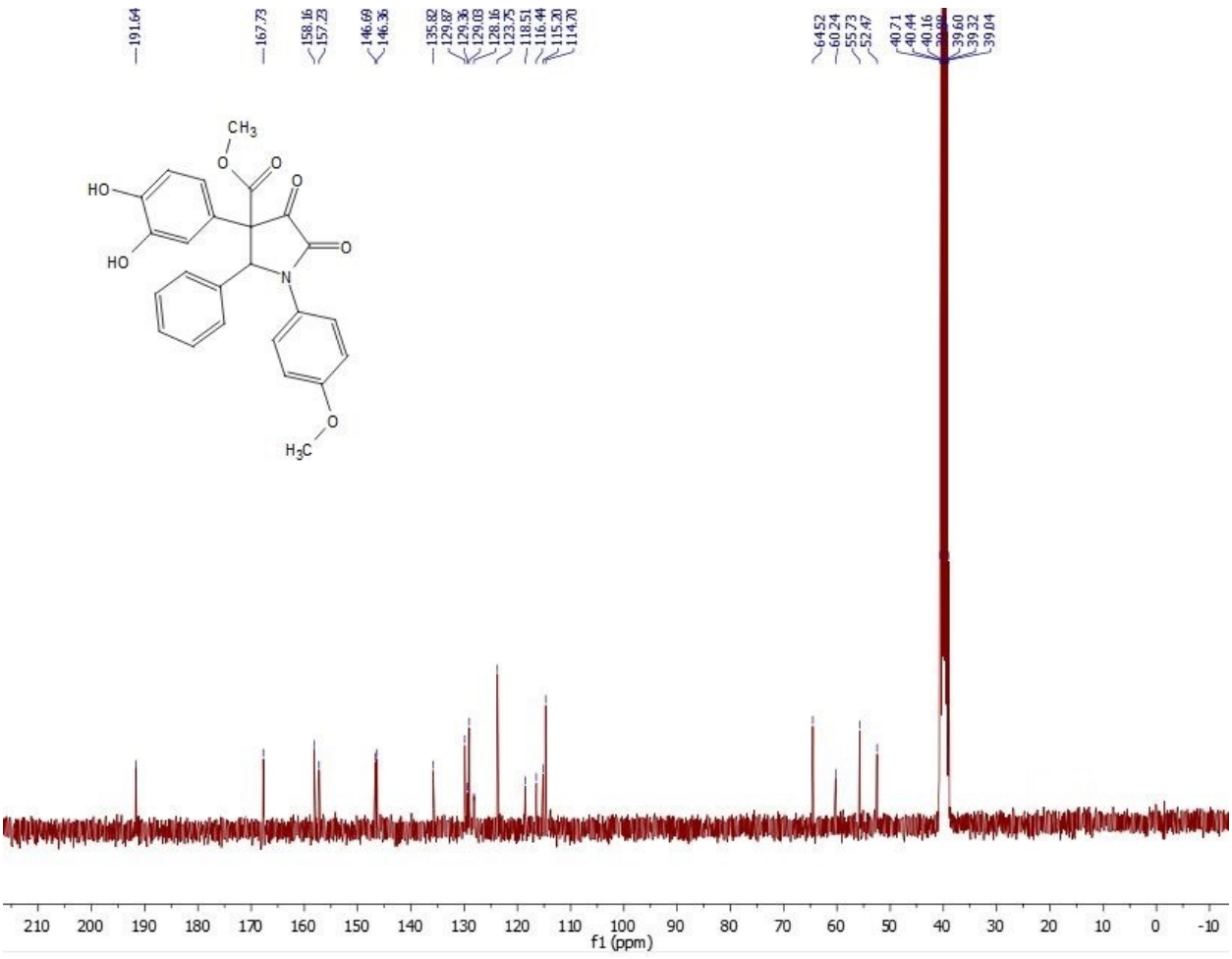
MW: 445



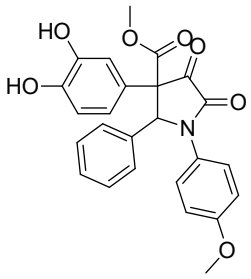
Mass spectra of compound **3k**



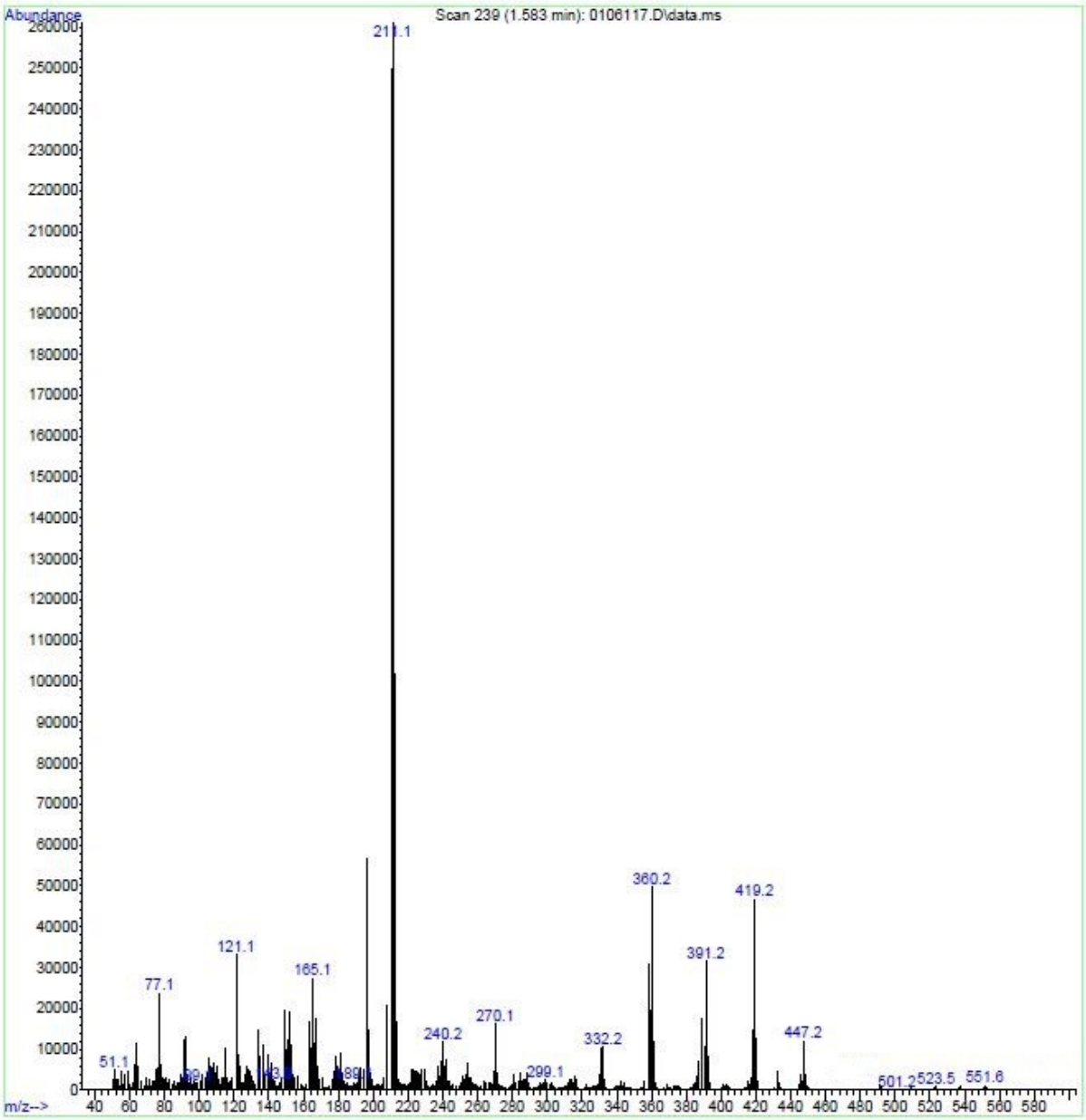
[1]HNMR (300 MHz, DMSO-d_6) of compound **3l**



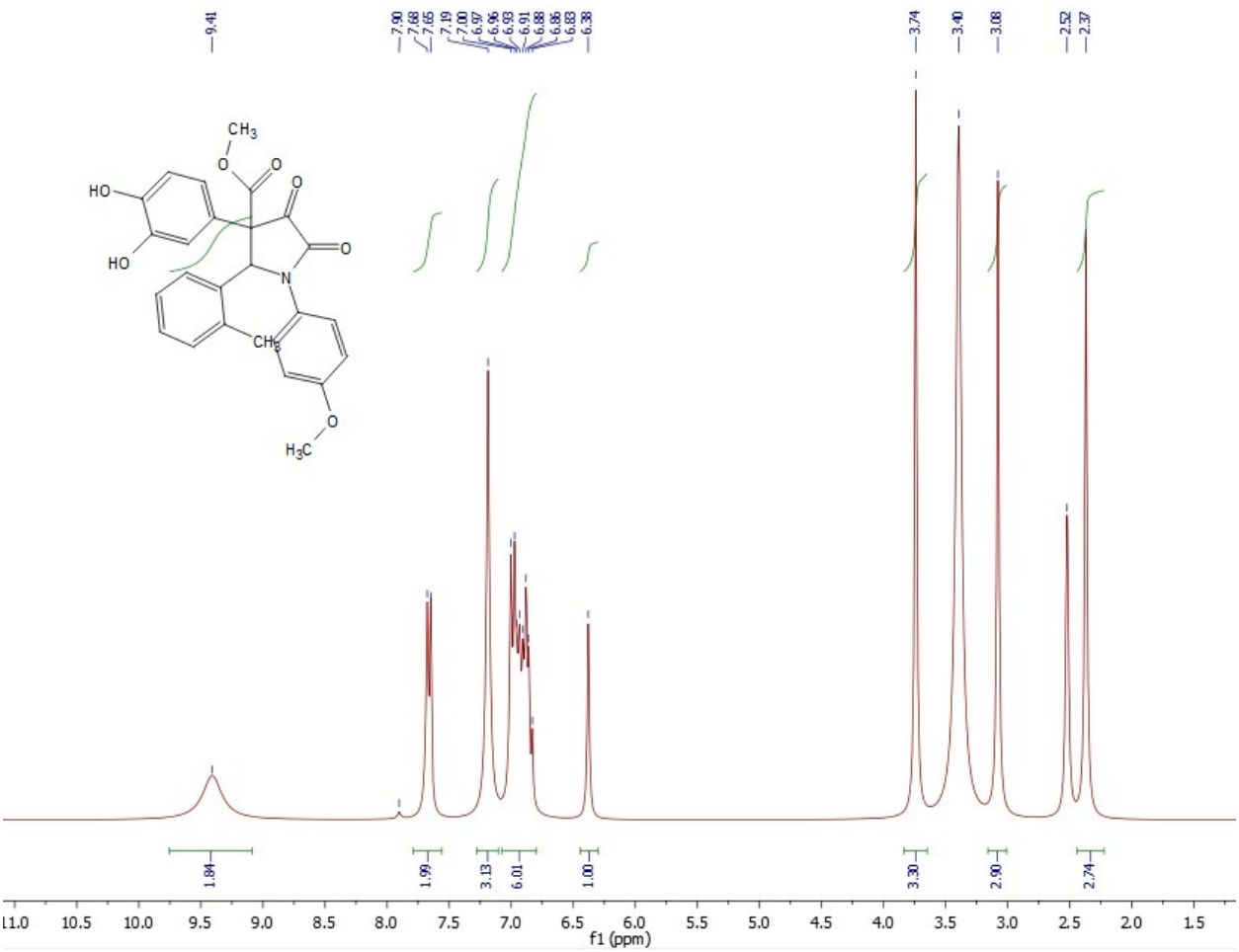
^{13}CNMR (75 MHz, DMSO-d_6) of compound **3l**



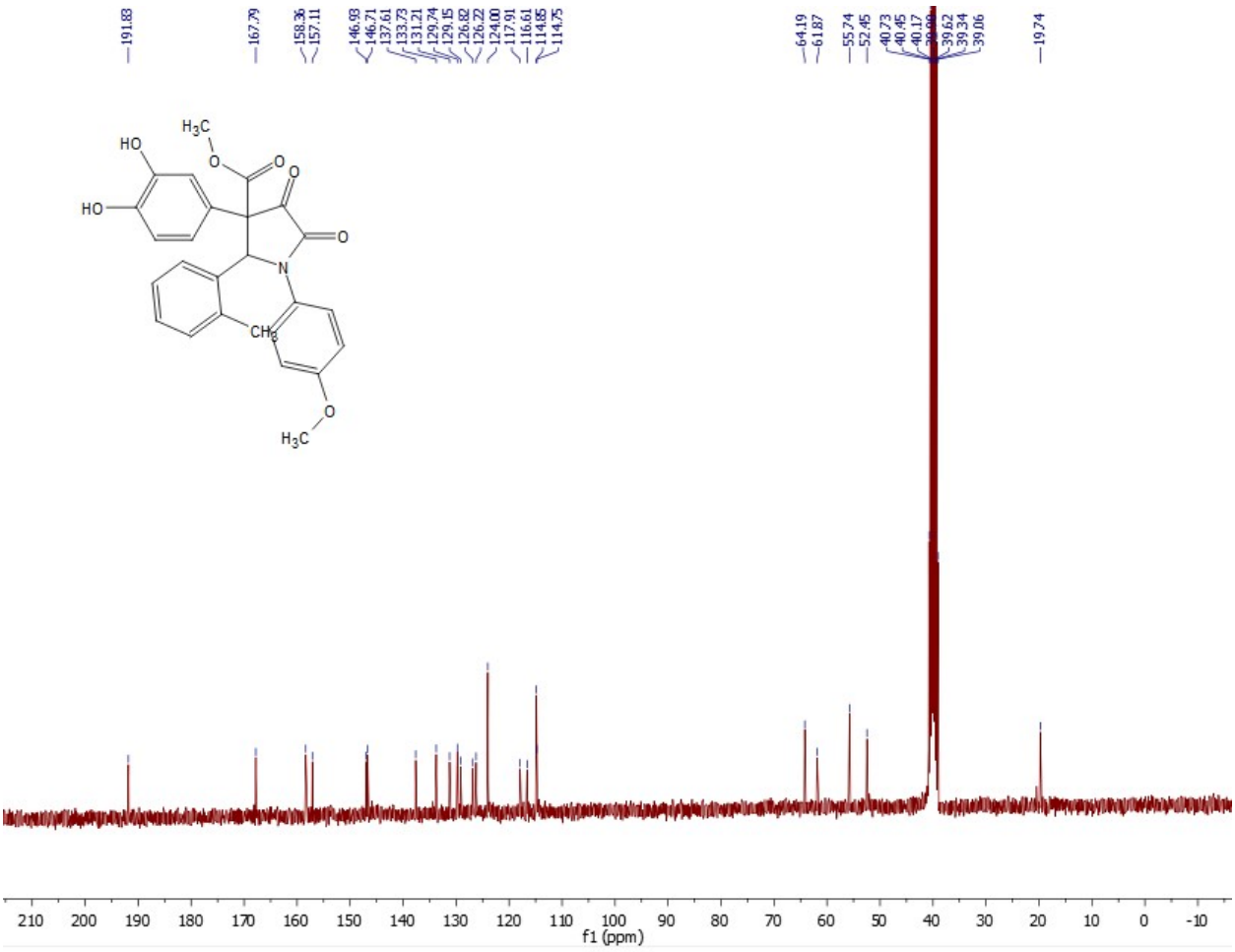
MW: 447



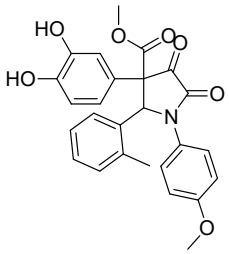
Mass spectra of compound **3l**



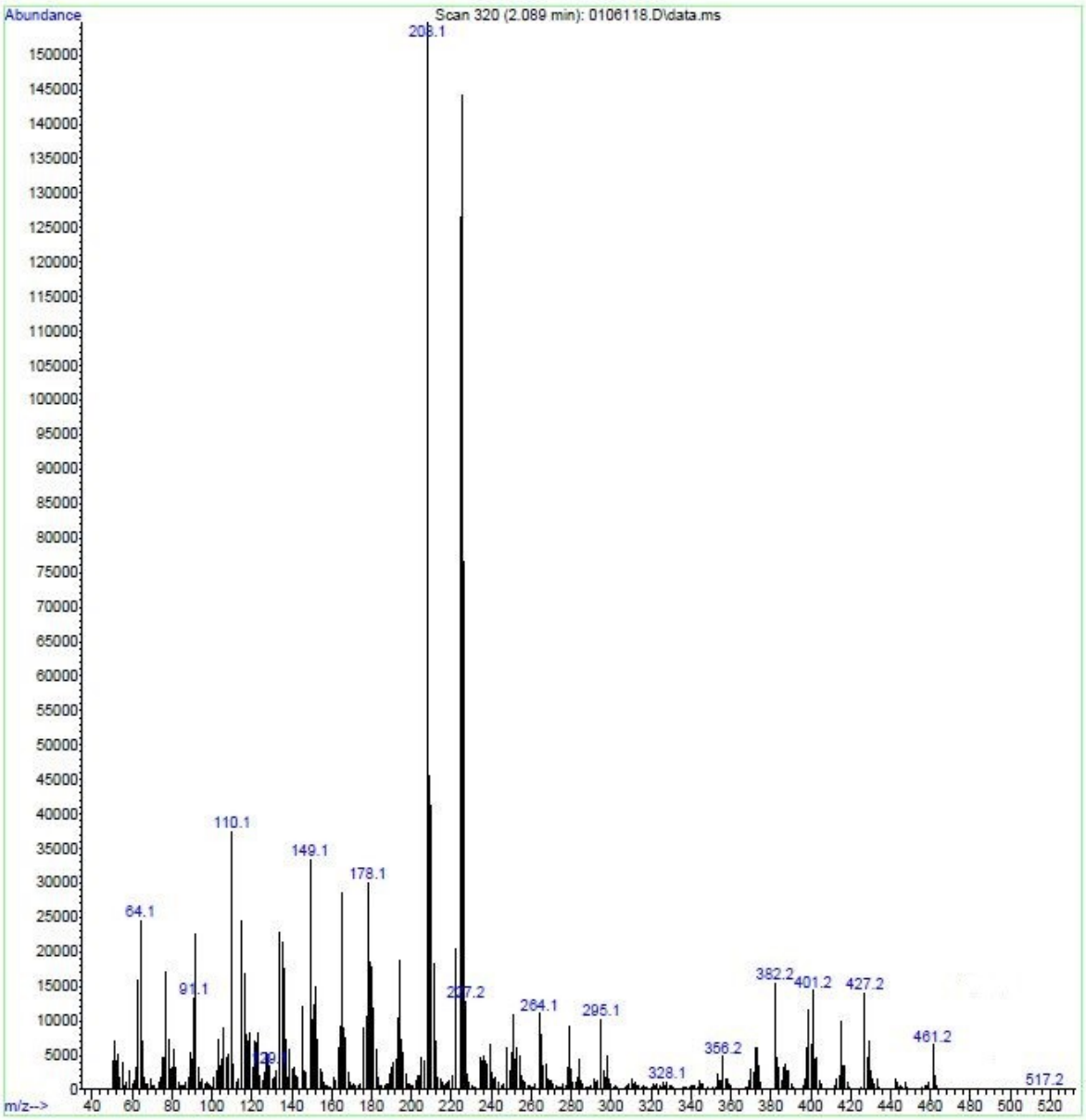
^{1}HNMR (300 MHz, DMSO-d_6) of compound **3m**



^{13}CNMR (75 MHz, DMSO-d_6) of compound **3m**



MW: 461



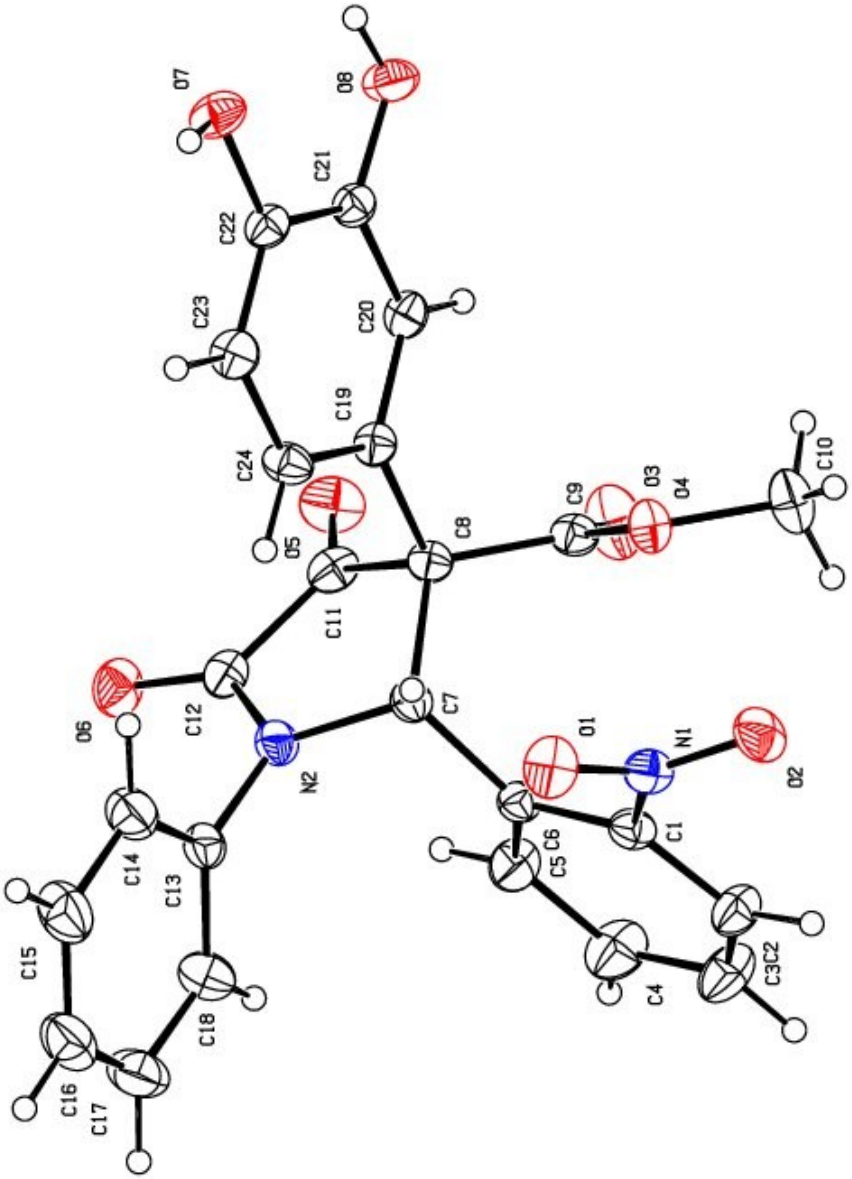
Mass spectra of compound **3m**

Crystallographic data (X-Ray)

The X-ray diffraction measurements were made with a STOE IPDS-2T diffractometer with graphite-monochromated MoKa radiation. Cell constants and an orientation matrix for data collection were obtained by least-squares refinement of diffraction data from 5628 unique reflection for **3h**. Data were collected at a temperature of 298(2) K to a maximum 2θ value of 58.48 and in a series of ω scans in 1º oscillations and integrated using the Stoe X-AREA[1] software package. The data were corrected for Lorentz and Polarizing effects. The structure was solved by using SHELXS. The Data reduction and structure refinement was carried out with SHELXL using the X-STEP32 crystallographic software package.[2] Complete crystallographic data for compound an **3h** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 2213845. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The single crystal of compound **3h** was prepared from its solution in EtOAc by slow evaporation of the solvent.

1. X-AREA:Program for the Acquisition and Analysis of Data, version 1.30, *Darmstadt, Germany*, **2005**.

2. *X-STEP32 Version 1.07b*, *Crystallographic Package*; Stoe & Cie GmbH: Darmstadt, Germany, **2000**.



ORTEP diagram of **3h**. Thermal ellipsoids are at 30% probability level. (CCDC No. 2213845)

Table S2. Crystal data and structure refinement for **3h**

Empirical formula	$C_{24}H_{18}N_2O_8$
Formula weight	462.40
Temperature	298 K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, C_2/c
Unit cell dimensions	a=29.297(6) Å alpha=90 deg. b=8.3200(17) Å beta=115.25(3) deg. c=18.920(4) Å gamma=90 deg.
Volume	4171.1(18) $Å^3$
Z, Calculated density	8, 1.473 Mg/m^3
Absorption coefficient	0.112 mm^{-1}
F(000)	1920.0
Crystal size	0.4 x 0.3 x 0.3 mm
Theta range for data collection	2.22 to 29.24 deg.
Limiting indices	-32<=h<=40, -11<=k<=11, -25<=l<=22
Reflections collected / unique	22356 / 5628 [R(int) = 0.1263]
Completeness to theta = 29.24	99.1 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5628 / 0 / 314
Goodness-of-fit on F^2	1.025
Final R indices [I>2sigma(I)]	*R1* = 0.0647, *wR2* = 0.1332
R indices (all data)	*R1* = 0.1129, *wR2* = 0.1501
Largest diff. peak and hole	0.302 and -0.265 e. $Å^{-3}$