

SUPPLEMENTARY MATERIALS

1,2,3-Triazole hybrids containing isatins and phenolic moieties: regioselective synthesis and molecular docking studies

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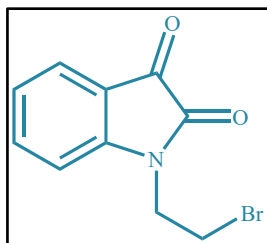
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General procedure for synthesis of 1-(2-bromoethyl)isatins 6-9:

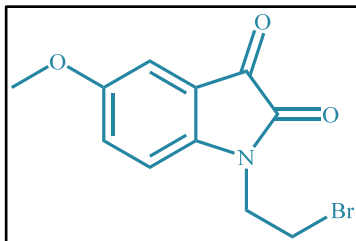
In 250 ml three-necked round-bottomed flask, equipped with bubble condenser and magnetic stir bar, opportune isatin **1-4** (3.40×10^{-2} mol) was dissolved in *dry* DMF (30 ml) and anhydrous K_2CO_3 (7.05 g, 5.1×10^{-2} mol) was added. The resulting suspension was stirred at room temperature for 20 min before the addition of freshly distilled 1,2-dibromoethane **5** (29.5 ml, 63.85 g, 3.40×10^{-1} mol). The reaction mixture was heated to 40 °C with constant stirring for about 5 h. After the completion of reaction, water (20 ml) was added and crude was extracted with ethyl acetate (3 x 30 ml). The combined organic layers were washed with brine solution, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. Purification of reaction crude by flash chromatography by using hexane:ethyl acetate (8:2 v/v) furnished the desired 1-(2-bromoethyl)isatin **6-9** in good yields.

1-(2-Bromoethyl)isatin (6)



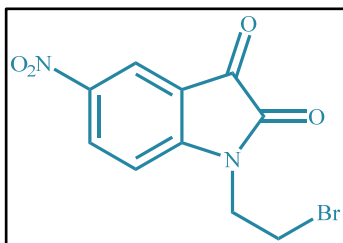
1H NMR (DMSO- d_6 , 300 MHz): δ (ppm) 3.72 (t, $J=6.73$ Hz, 2H, CH_2), 4.12 (t, $J=6.73$ Hz, 2H, CH_2), 7.15 (t, $J=7.55$ Hz, 1H, Ar), 7.30 (d, $J=7.98$ Hz, 1H, Ar), 7.57 (d, $J=7.45$ Hz, 1H, Ar), 7.68 (t, $J=7.51$ Hz, 1H, Ar). ^{13}C NMR (DMSO- d_6 , 125 MHz): δ (ppm) 30.08, 42.12, 112.02, 118.32, 124.36, 125.53, 139.24, 151.13, 159.06, 183.91. ESI(+)-MS: m/z $[M+H]^+$ calcd for $[C_{10}H_9BrNO_2]^+$, 253.9811, found 253.9798.

1-(2-Bromoethyl)-5-methyisatin (7)



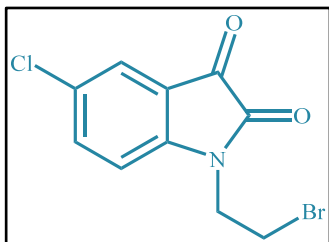
1H NMR (DMSO- d_6 , 300 MHz): δ (ppm) 3.70 (t, $J=6.48$ Hz, 2H, CH_2), 3.77 (s, 3H, CH_3), 4.09 (t, $J=6.48$ Hz, 2H, CH_2), 7.12-7.17 (m, 1H, Ar), 7.22-7.27 (m, 2H, Ar). ^{13}C NMR (DMSO- d_6 , 125 MHz): δ (ppm) 30.24, 42.19, 56.92, 110.24, 113.20, 118.88, 125.12, 145.02, 156.83, 159.19, 184.24. ESI(+)-MS: m/z $[M+H]^+$ calcd for $[C_{11}H_{11}BrNO_3]^+$, 283.9917, found 284.0002.

1-(2-Bromoethyl)-5-nitroisatin (8)



1H NMR (DMSO- d_6 , 300 MHz): δ (ppm) 3.76 (t, $J=6.12$ Hz, 2H, CH_2), 4.16 (t, $J=6.12$ Hz, 2H, CH_2), 7.46 (d, $J=8.80$ Hz, 1H, Ar), 8.24 (d, $J=2.35$ Hz, 1H, Ar), 8.37 (dd, $J=8.78$ Hz, 2.47 Hz, 1H, Ar). ^{13}C NMR (DMSO- d_6 , 125 MHz): δ (ppm) 30.29, 42.26, 101.26, 111.62, 121.23, 126.14, 129.40, 144.33, 149.90, 173.99. ESI(+)-MS: m/z $[M+H]^+$ calcd for $[C_{10}H_8BrN_2O_4]^+$, 298.9662, found 298.9657.

1-(2-Bromoethyl)-5-chloroisatin (9)

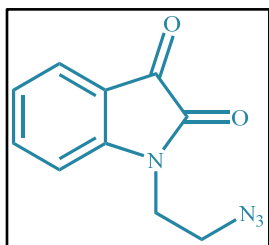


^1H NMR (DMSO- d_6 , 300 MHz): δ (ppm) 3.69 (t, $J=6.58$ Hz, 2H, CH_2), 4.11 (t, $J=6.58$ Hz, 2H, CH_2), 7.36 (d, $J=8.51$ Hz, 1H, Ar), 7.64 (d, $J=2.21$ Hz, 1H, Ar), 7.73 (dd, $J=8.54$ Hz, 2.25 Hz, 1H, Ar). ^{13}C NMR (DMSO- d_6 , 125 MHz): δ (ppm) 29.96, 42.30, 113.86, 119.78, 125.05, 128.63, 138.09, 149.74, 158.89, 182.87.

General procedure for synthesis of 1-(2-azidoethyl)isatins 10-13:

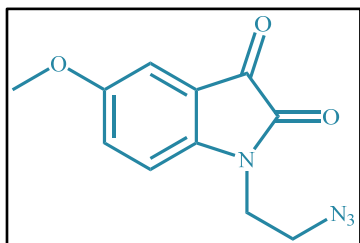
In 250 ml three-necked round-bottomed flask, equipped with bubble condenser and magnetic stir bar, opportune 1-(2-bromoethyl)isatin **6-9** (2.58×10^{-2} mol) in *dry* DMF (30 ml) was dissolved and NaN₃ (3.87×10^{-2} mol) was added. The reaction mixture was heated at 60 °C for 3 h under stirring and was monitored by TLC. Upon completion, water was added (50 ml) and the reaction mixture was extracted with ethyl acetate (3 x 30 ml). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography using hexane:ethyl acetate (8:2 v/v) to furnish the desired 1-(2-azidoethyl)isatin **10-13** in good yields.

1-(2-azidoethyl)isatin (10)



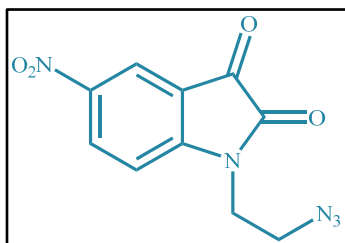
¹H-NMR (DMSO-*d*₆, 300 MHz): δ (ppm) 3.63 (t, *J*=5.68 Hz, 2H, CH₂), 3.89 (t, *J*=5.68 Hz, 2H, CH₂), 7.15 (t, *J*=7.54 Hz, 1H, Ar), 7.28 (d, *J*=7.95 Hz, 1H, Ar), 7.56 (d, *J*=7.54 Hz, 1H, Ar), 7.68 (t, *J*=7.74 Hz, 1H, Ar). ¹³C-NMR (DMSO-*d*₆, 125 MHz): δ (ppm) 39.93, 48.93, 111.91, 118.36, 124.30, 125.48, 139.22, 151.37, 159.25, 183.98. ESI(+)-MS: *m/z* [M+H]⁺ calcd for [C₁₀H₉N₄O₂]⁺, 217.0720, found 217.0720.

1-(2-azidoethyl)-5-methylisatin (11)



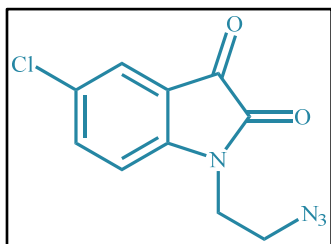
¹H NMR (DMSO-*d*₆, 300 MHz): δ (ppm) 3.61 (t, *J*=5.83 Hz, 2H, CH₂), 3.77 (s, 3H, CH₃), 3.86 (t, *J*=5.83 Hz, 2H, CH₂), 7.12-7.16 (m, 1H, Ar), 7.18-7.31 (m, 2H, Ar). ¹³C NMR (DMSO-*d*₆, 125 MHz): δ (ppm) 40.00, 49.00, 56.89, 110.18, 113.09, 118.89, 125.11, 145.22, 156.80, 159.35, 184.29. ESI(+)-MS: *m/z* [M+H]⁺ calcd for [C₁₁H₁₁N₄O₃]⁺, 247.0826, found 247.0824.

1-(2-azidoethyl)-5-nitroisatin (12)



¹H NMR (DMSO-*d*₆, 300 MHz): δ (ppm) 3.63 (t, *J*=5.55 Hz, 2H, CH₂), 3.93 (t, *J*=5.55 Hz, 2H, CH₂), 7.45 (d, *J*= 8.81 Hz, 1H, Ar), 8.24 (d, *J*= 2.42 Hz, 1H, Ar), 8.39 (dd, *J*=8.76 Hz, 2.36 Hz, 1H, Ar). ¹³C NMR (DMSO-*d*₆, 125 MHz): δ (ppm) 48.92, 67.15, 101.26, 111.46, 121.21, 126.17, 129.48, 144.31, 150.05, 174.08. ESI(+)-MS: *m/z* [M+H]⁺ calcd for [C₁₀H₈N₅O₄]⁺, 262.0571, found 262.0620.

1-(2-Azidoethyl)-5-chloroisatin (13)

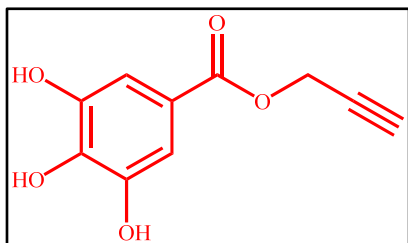


^1H NMR (DMSO- d_6 , 300 MHz): δ (ppm) 3.61 (t, $J=5.74$ Hz, 2H, CH_2), 3.88 (t, $J=5.74$ Hz, 2H, CH_2), 7.33 (d, $J=8.48$ Hz, 1H, Ar), 7.62 (d, $J=2.24$ Hz, 1H, Ar), 7.73 (dd, $J=8.50$ Hz, 2.26 Hz, 1H, Ar). ^{13}C NMR (DMSO- d_6 , 125 MHz): δ (ppm) 40.10, 49.07, 113.77, 119.81, 125.00, 128.57, 138.10, 150.02, 159.07, 182.97. ESI(+)-MS: m/z $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{10}\text{H}_8\text{ClN}_4\text{O}_2]^+$, 251.0330, found 251.0378.

General procedure for synthesis of propargyl esters 20-22:

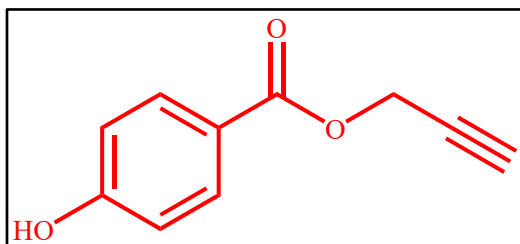
In 250 ml three-necked round-bottomed flask, equipped with bubble condenser and magnetic stir bar, opportune carboxylic acid **14-16** (5.88×10^{-2} mol) was placed and freshly distilled thionyl chloride was added (30 ml, 4.11×10^{-1} mol). The reaction was conducted at reflux for 6h and subsequently the thionyl chloride in excess was removed under vacuum. The oily residue corresponding to acyl chloride **17-19**, was cooled by using an ice bath and then, propargyl alcohol (41 ml, 7.06×10^{-1} mol) was added dropwise for 30 min. The mixture was stirred at room temperature for 2h and then was concentrated in vacuo. Purification of crude product by flash chromatography using CHCl_3 :MeOH (9:1 v/v) furnished the desired propargyl ester derivatives **20-22** in good yields.

Propargyl 3,4,5-trihydroxybenzoate (20)



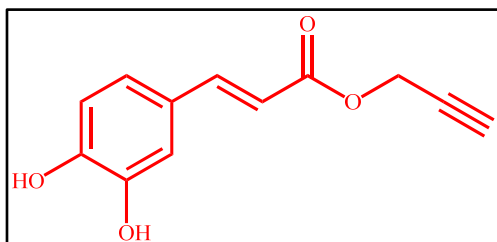
^1H NMR (DMSO- d_6 , 300 MHz): δ (ppm) 3.57 (t, $J=2.43$ Hz, 1H, CH), 4.84 (d, $J=2.43$ Hz, 2H, CH_2), 6.95 (s, 2H, Ar), 9.27 (bs, 3H, OH). ^{13}C NMR (DMSO- d_6 , 125 MHz): δ (ppm) 52.88, 78.58, 79.82, 109.66, 119.56, 139.87, 146.69, 166.07. ESI(+)-MS: m/z $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{10}\text{H}_9\text{O}_5]^+$, 209.0444, found 209.0453.

Propargyl 4-hydroxybenzoate (21)



^1H NMR (DMSO- d_6 , 300 MHz): δ (ppm) 3.58 (t, $J=2.42$ Hz, 1H, CH), 4.88 (d, $J=2.42$ Hz, 2H, CH_2), 6.81-6.90 (m, 2H, Ar), 7.78-7.87 (m, 2H, Ar), 10.46 (bs, 1H, OH). ^{13}C NMR (DMSO- d_6 , 125 MHz): δ (ppm) 52.86, 78.58, 79.71, 116.47, 120.52, 132.62, 163.31, 165.77. ESI(+)-MS: m/z $[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{10}\text{H}_9\text{O}_3]^+$, 177.0546, found 177.0546.

Propargyl (*E*)-3-(3,4-dihydroxyphenyl)acrylate (22)



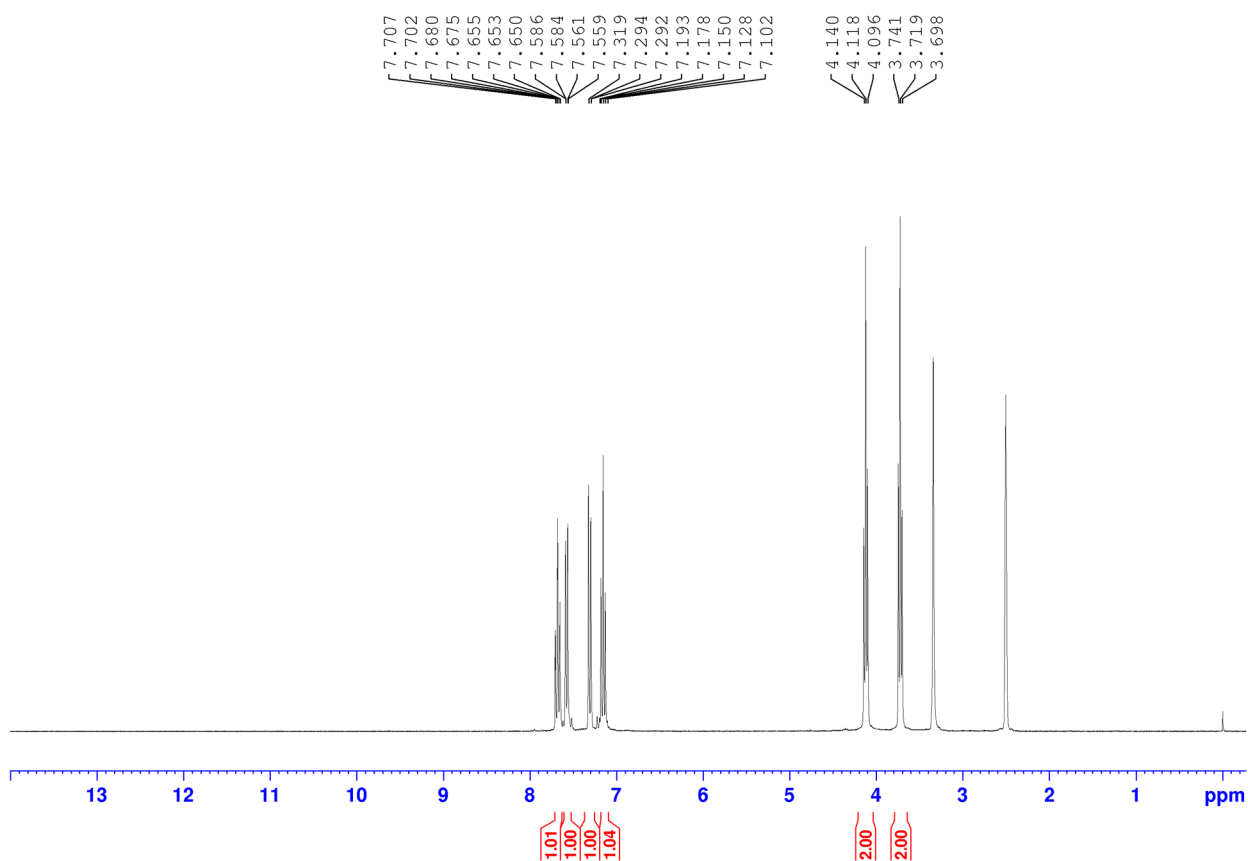
^1H NMR (DMSO- d_6 , 300 MHz): δ (ppm) 3.55 (t, $J=2.41$ Hz, 1H, $\text{C}\equiv\text{C}-\text{H}$), 4.79 (d, $J=2.42$ Hz, 2H, $\text{C}\equiv\text{C}-\text{CH}_2$), 6.31 (d, $J=15.91$ Hz, 1H, $\text{O}=\text{C}-\text{C}-\text{H}$), 6.77 (d, $J=8.10$ Hz, 1H, Ar), 6.99-7.11 (m, 2H, Ar), 7.53 (d, $J=15.91$ Hz, 1H, $\text{OC}-\text{C}=\text{C}-\text{H}$), 9.46 (bs, 2H, OH). ^{13}C NMR (DMSO- d_6 , 125 MHz): δ (ppm) 52.65, 78.57, 79.94, 114.14, 115.92, 116.96, 123.00, 126.54, 146.76, 147.35, 149.85, 167.03. ESI(+)-MS: m/z

$[\text{M}+\text{H}]^+$ calcd for $[\text{C}_{12}\text{H}_{11}\text{O}_4]^+$, 219.0652, found 219.0650.

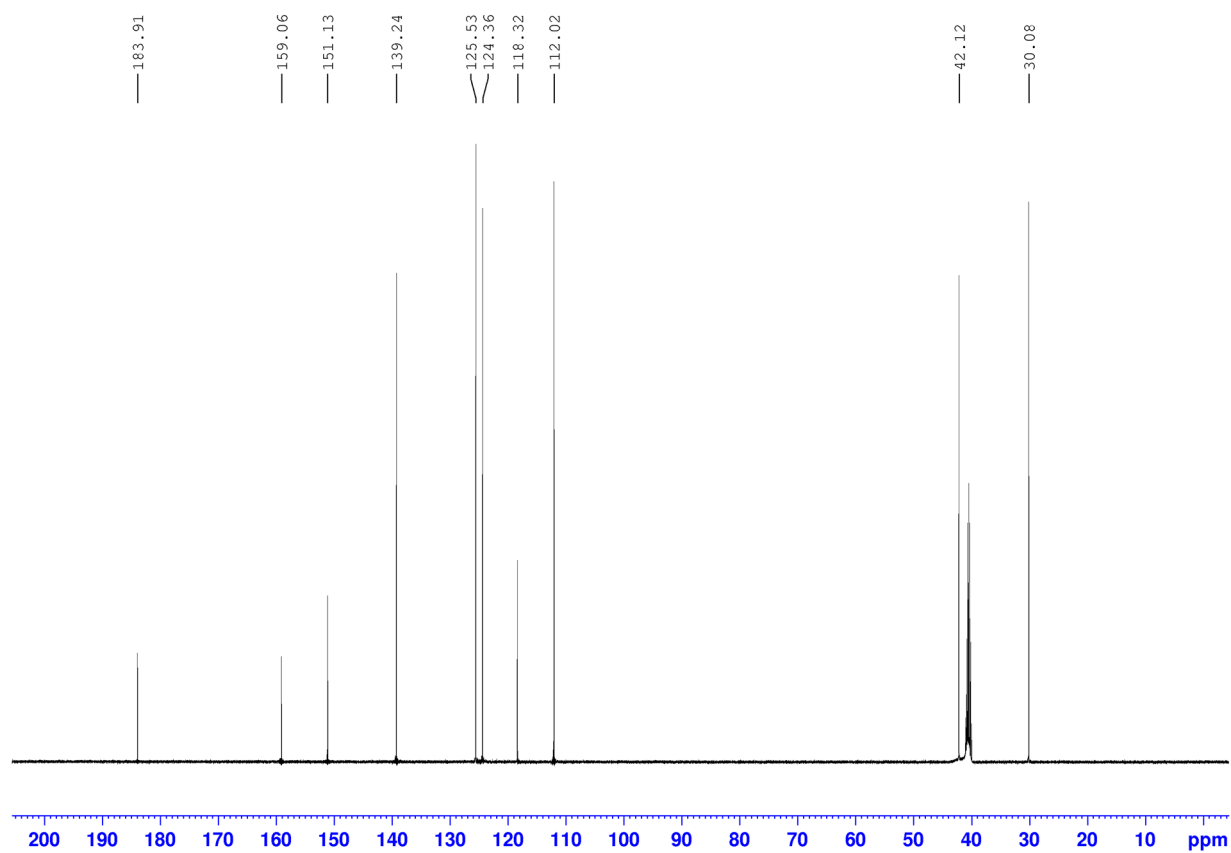
Characterization spectra of 1-(2-bromoethyl) isatins 6-9.

1-(2-Bromoethyl)isatin (6)

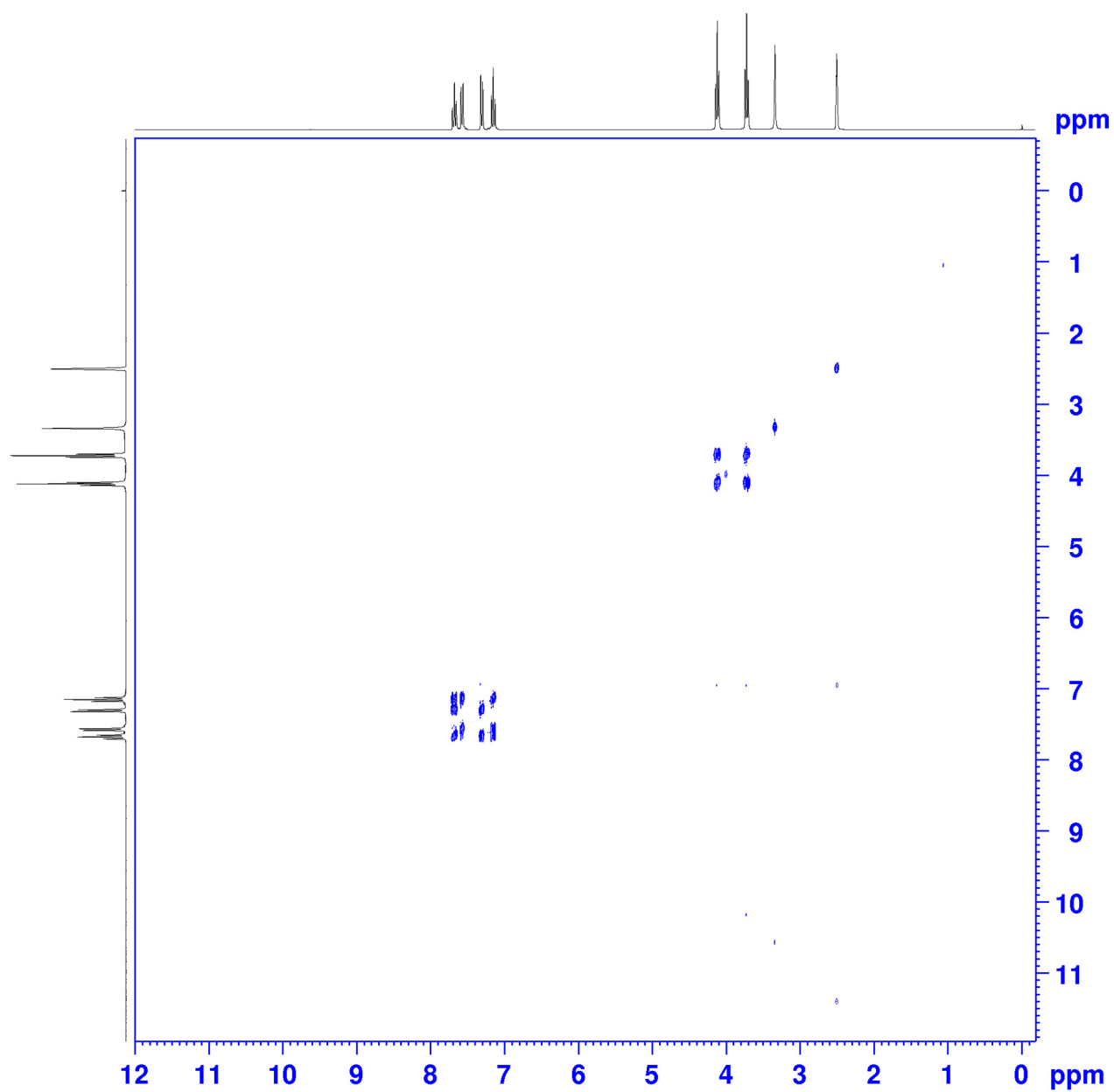
^1H NMR (300 MHz)



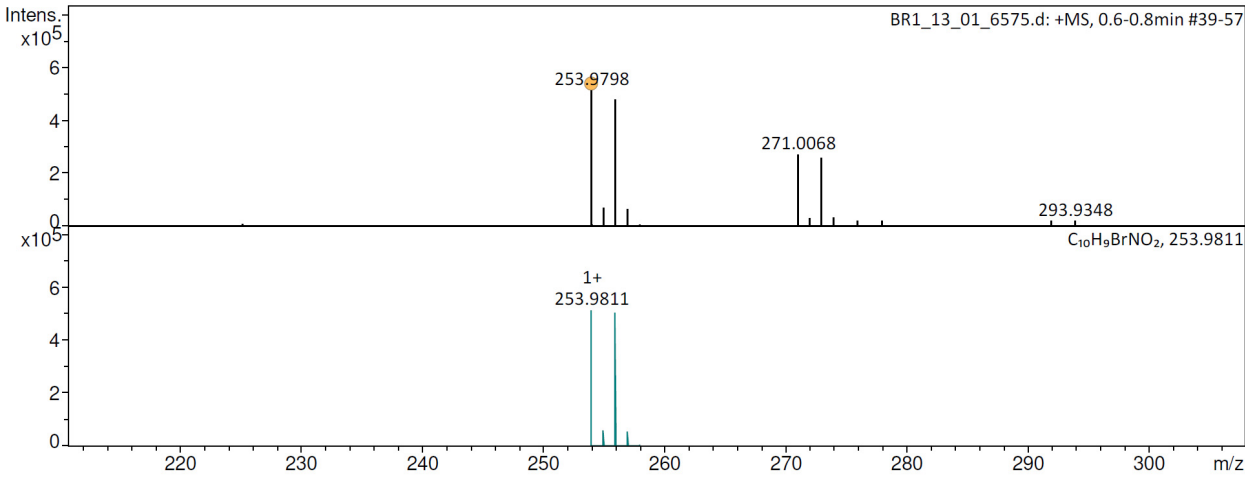
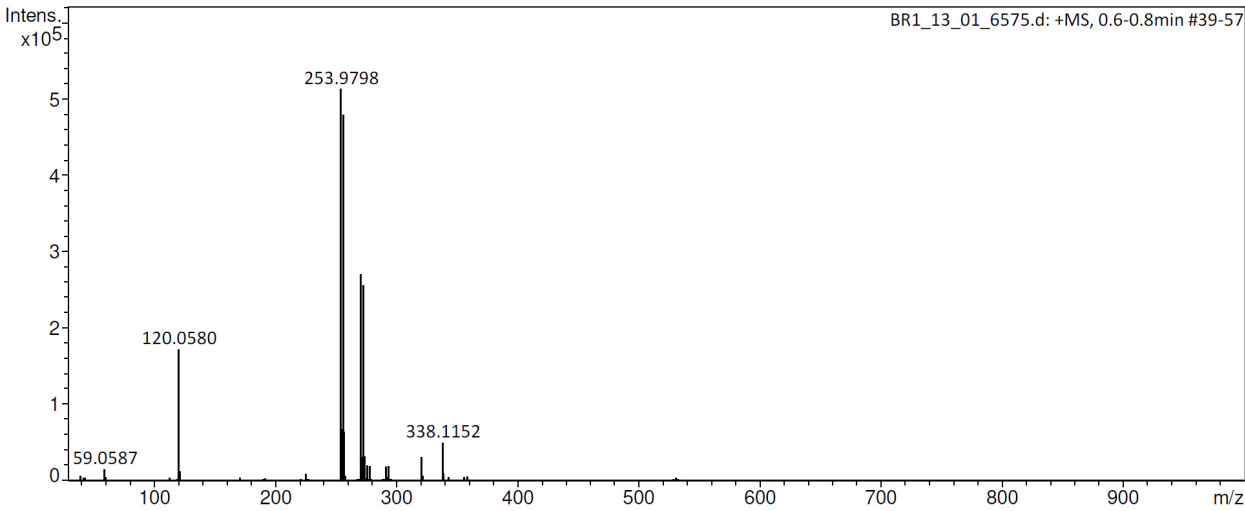
^{13}C NMR (500 MHz)



COSY NMR (300 MHz)

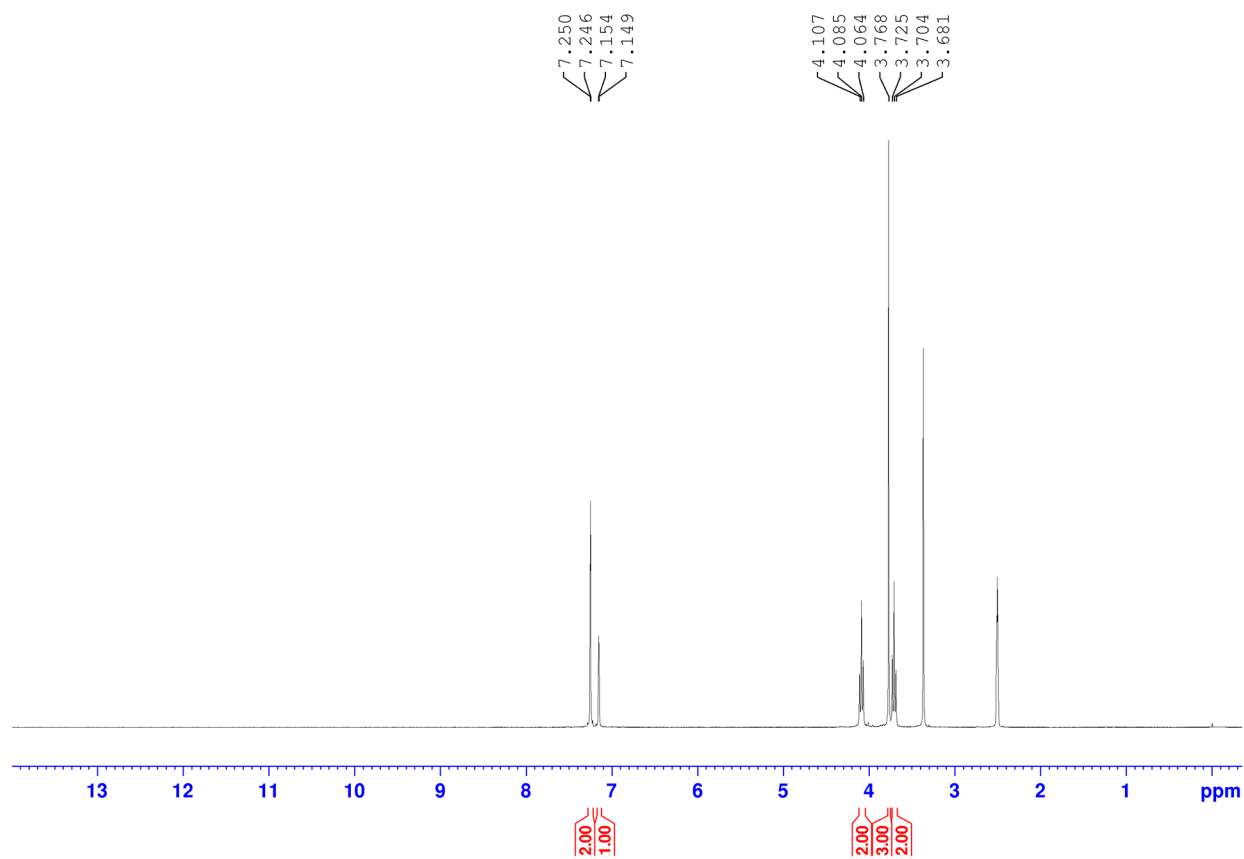


HRMS

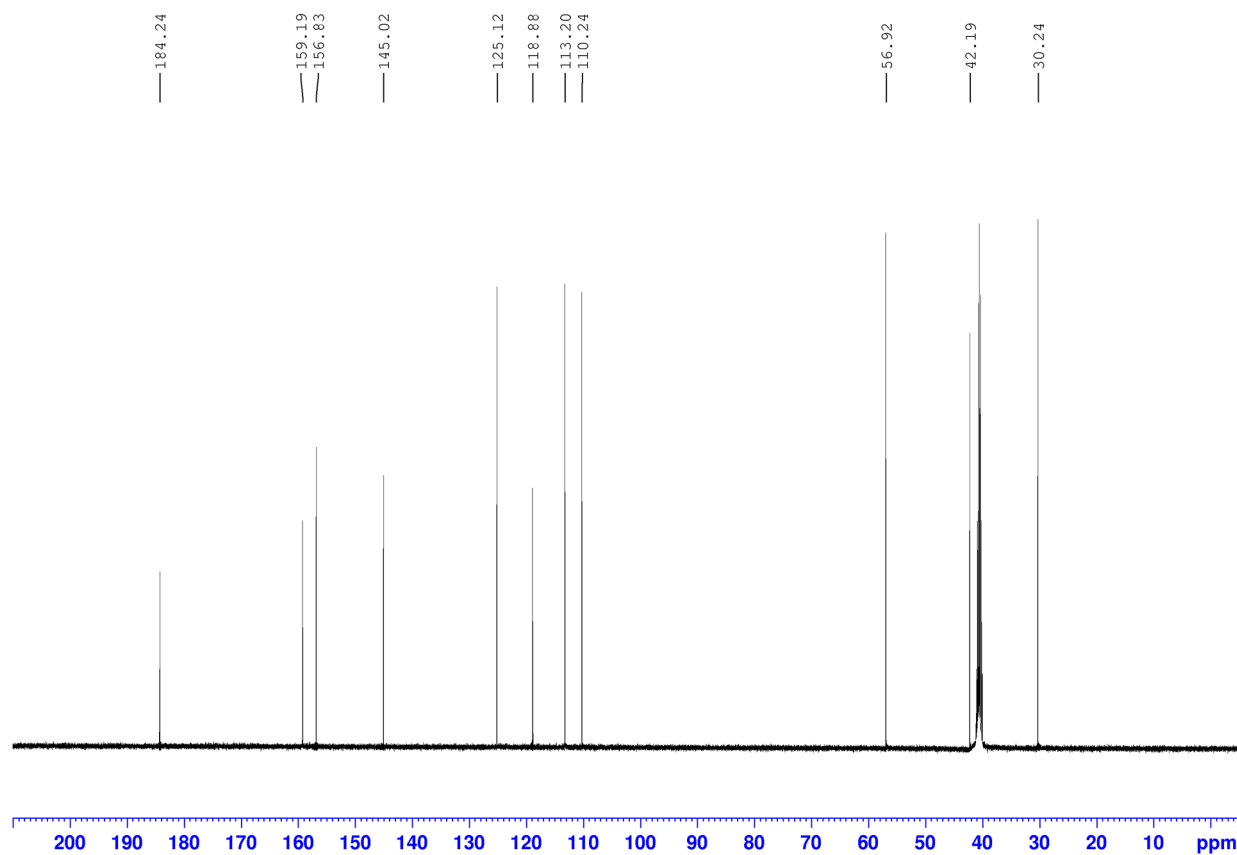


1-(2-Bromoethyl)-5-methylisatin (7)

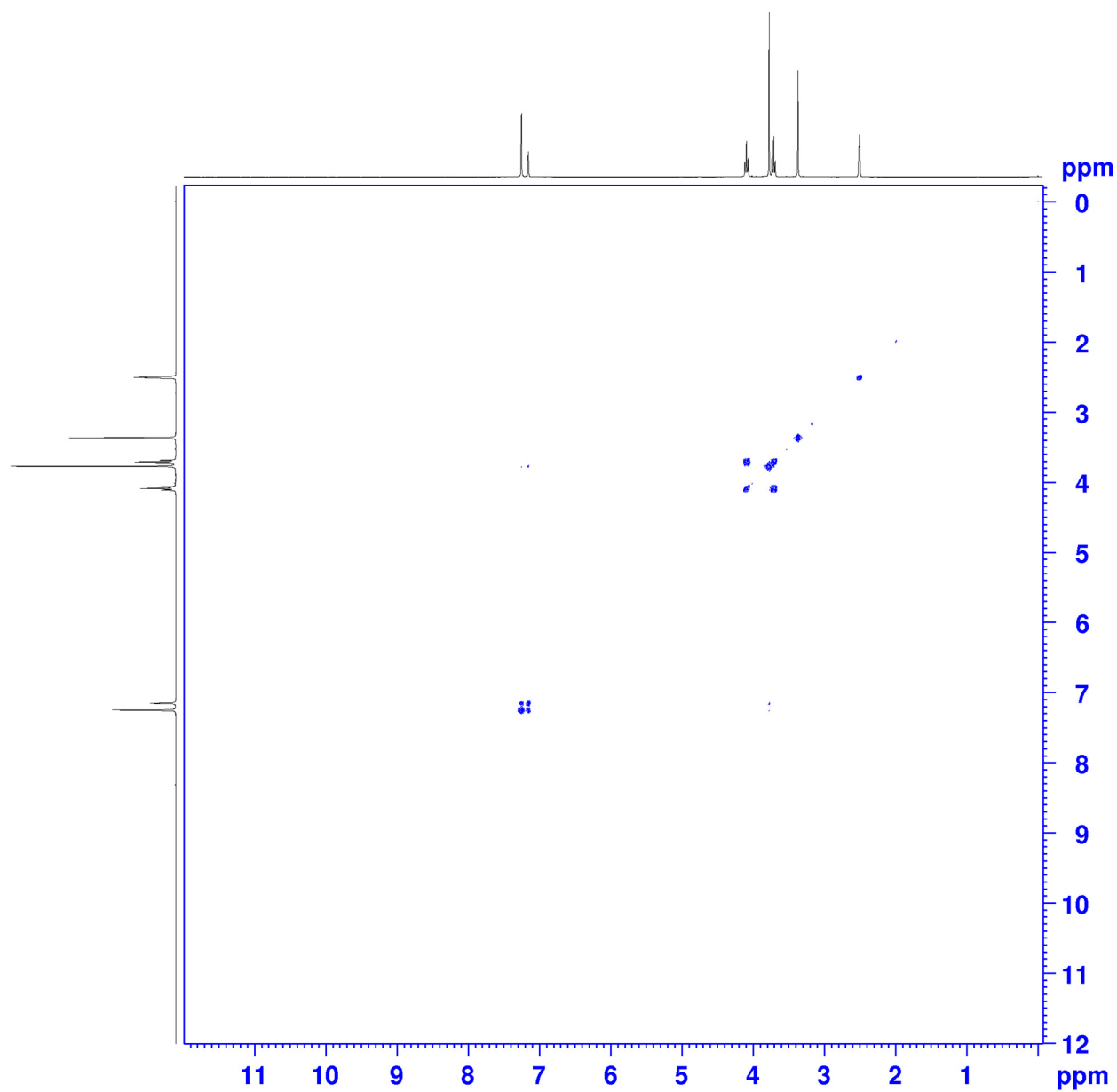
^1H NMR (300 MHz)



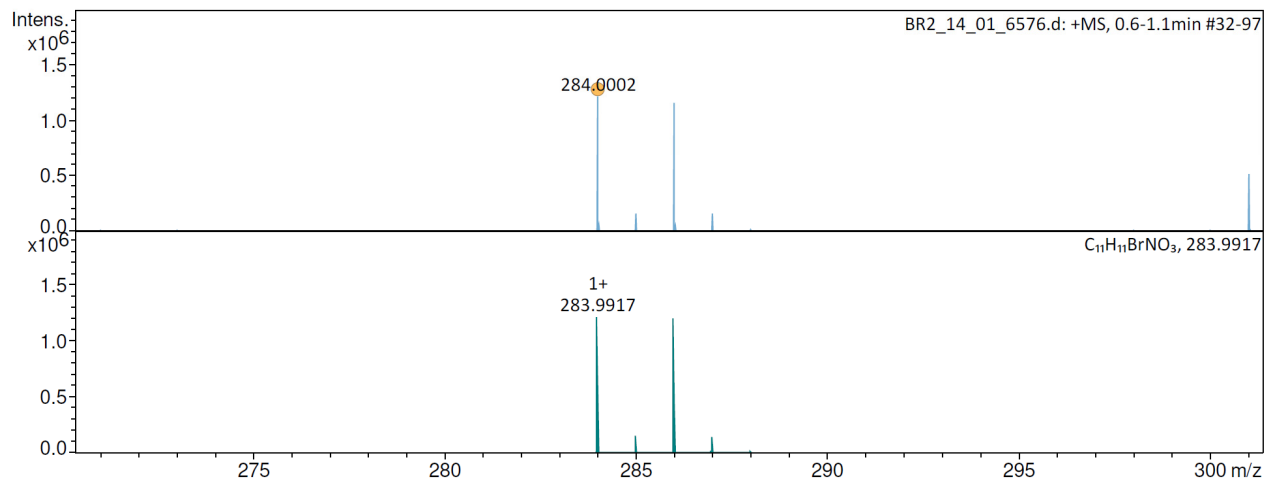
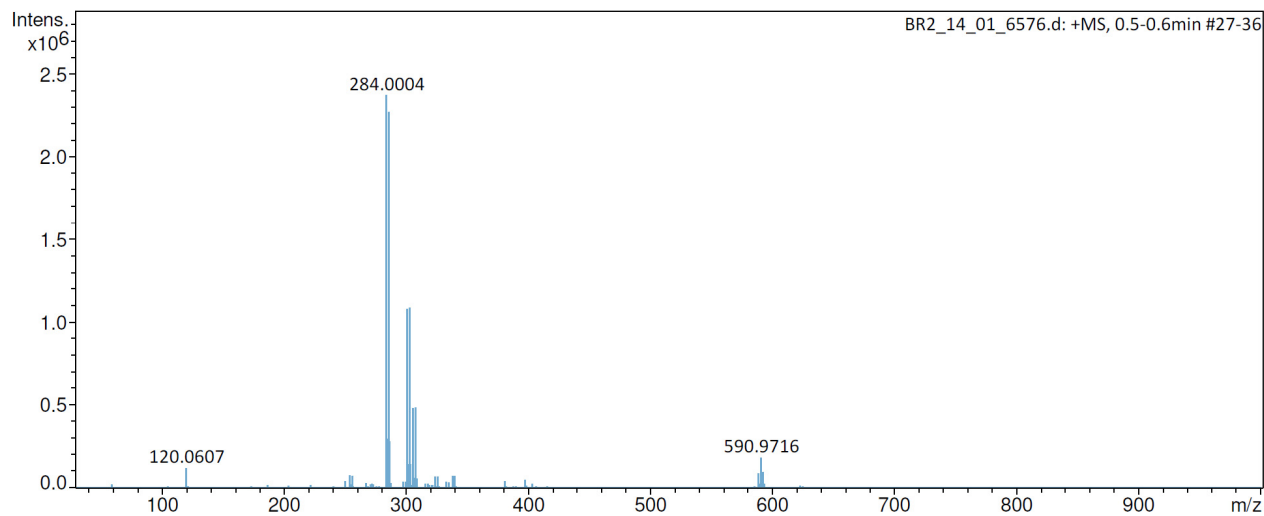
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COSY NMR (300 MHz)

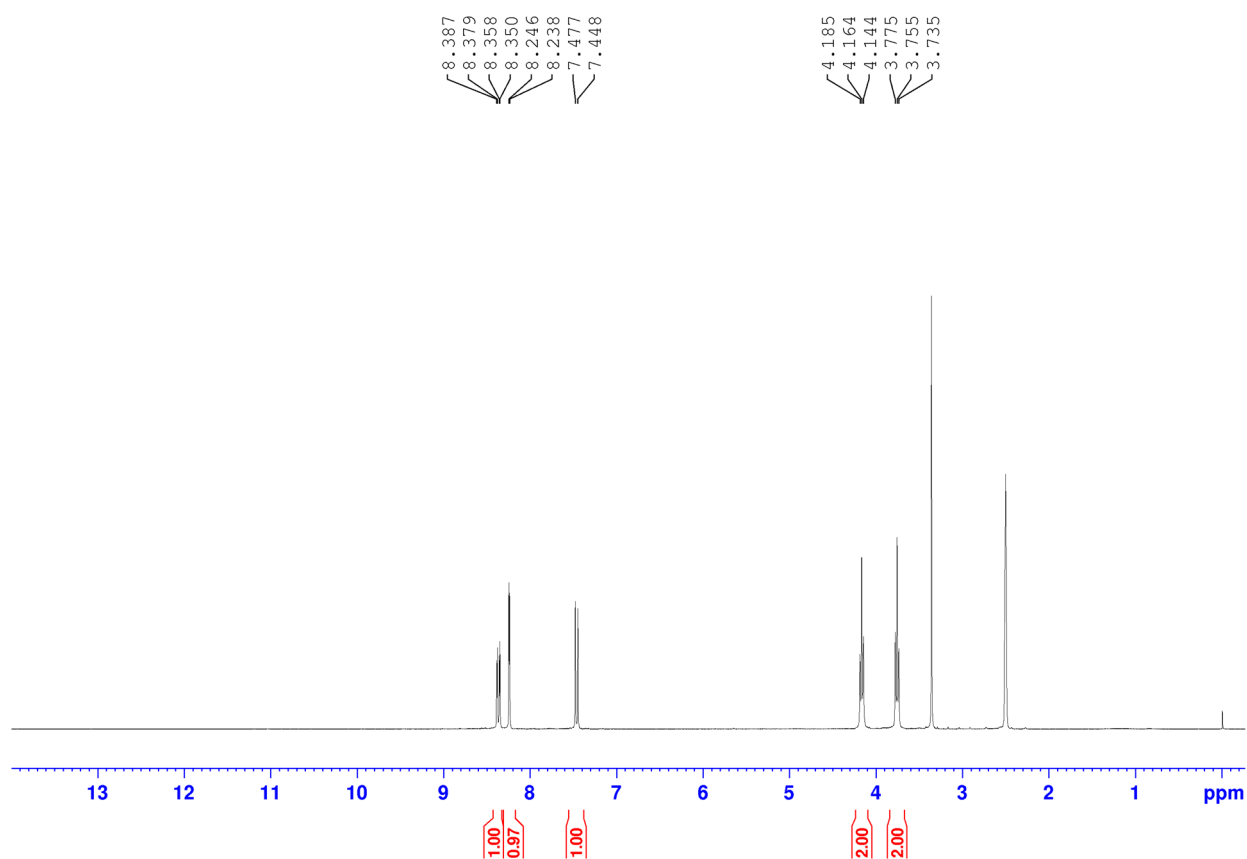


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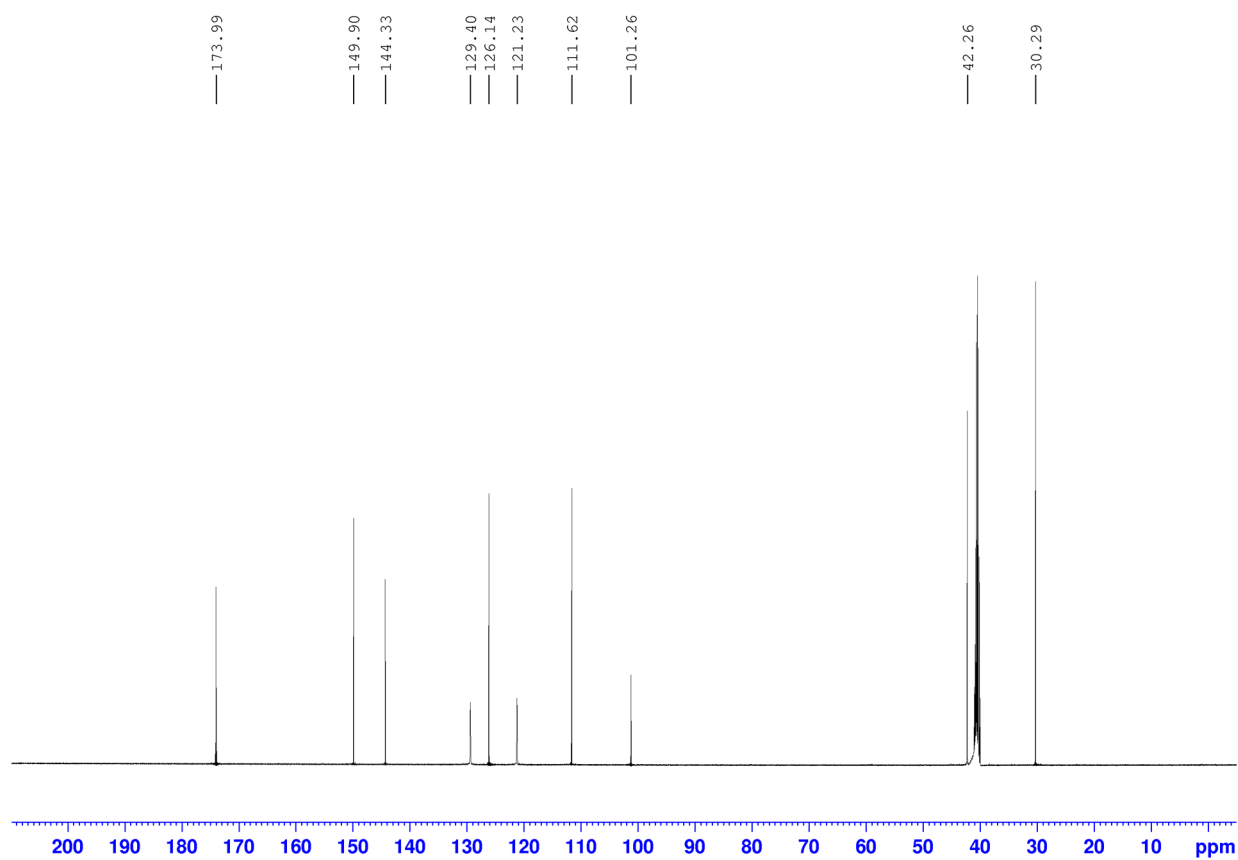


1-(2-Bromoethyl)-5-nitroisatin (8)

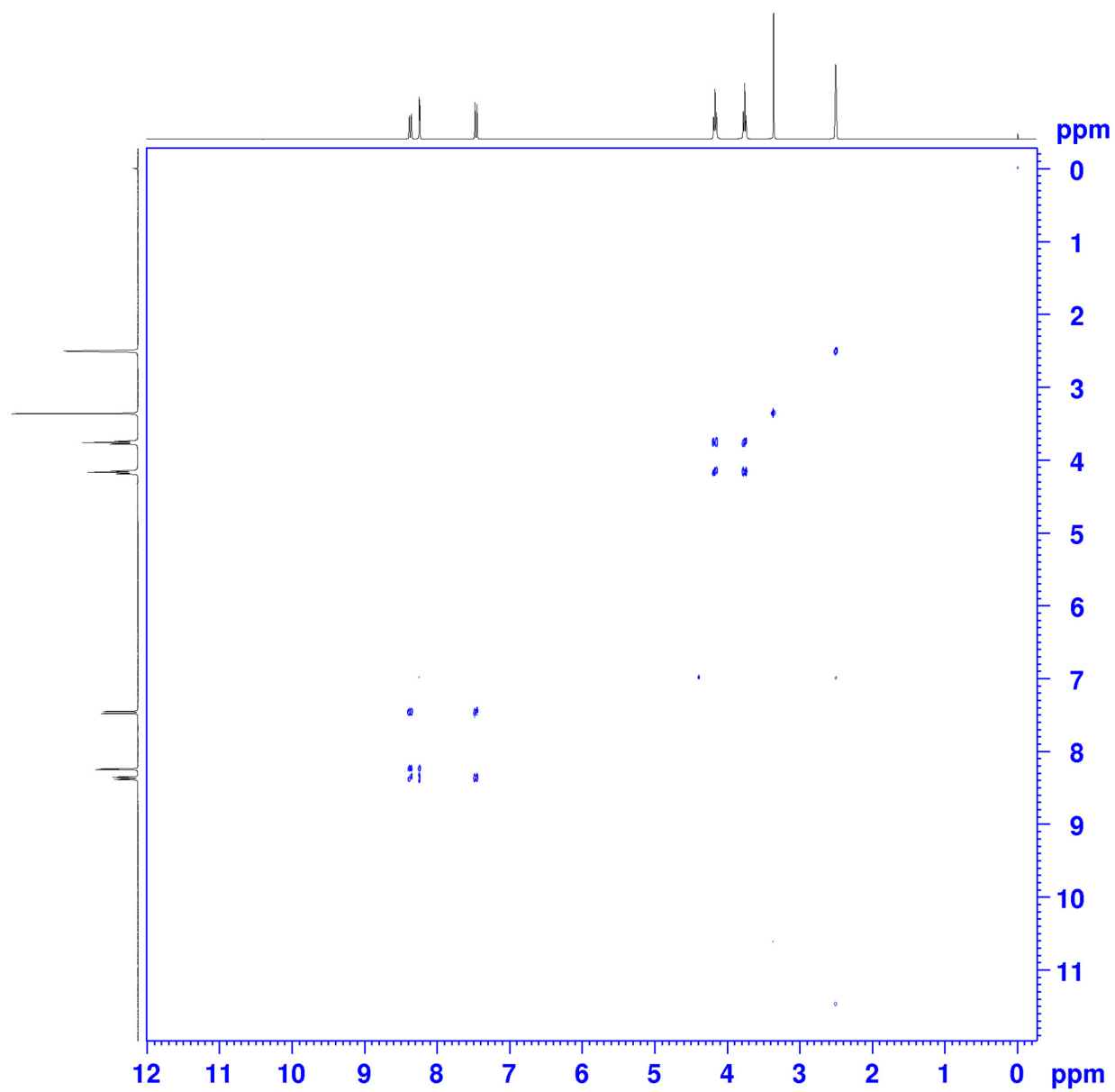
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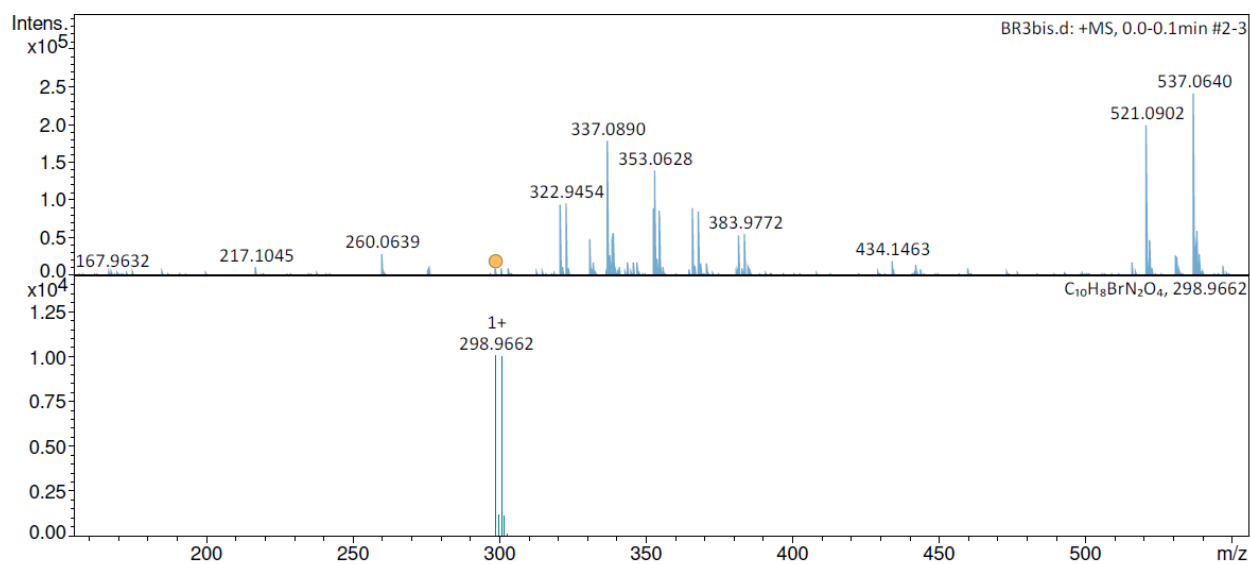
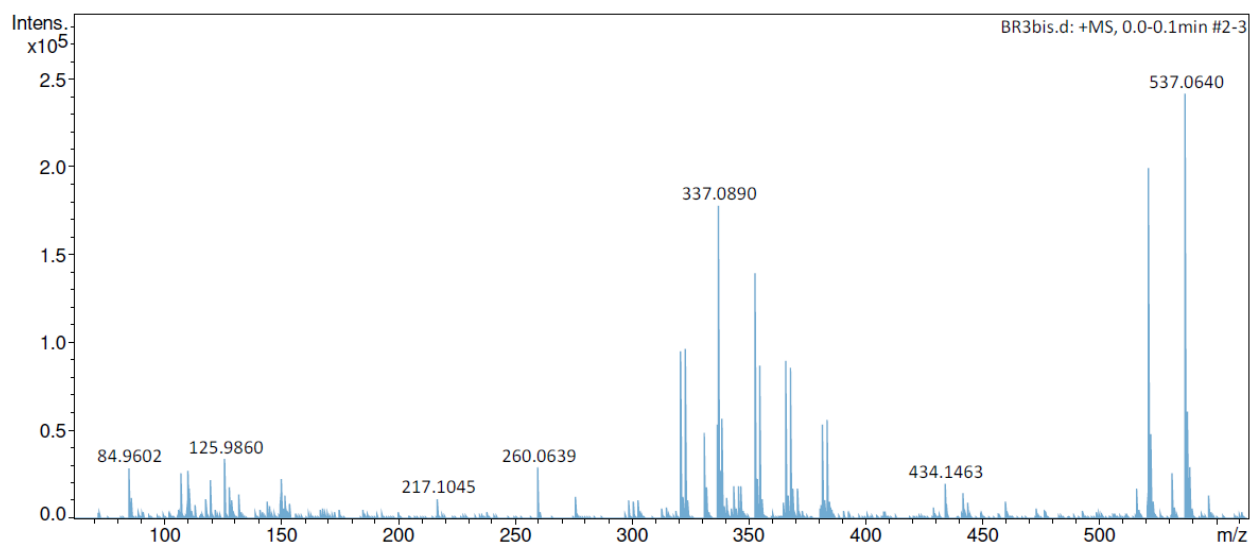
^{13}C NMR (125 MHz)



COSY NMR (300 MHz)

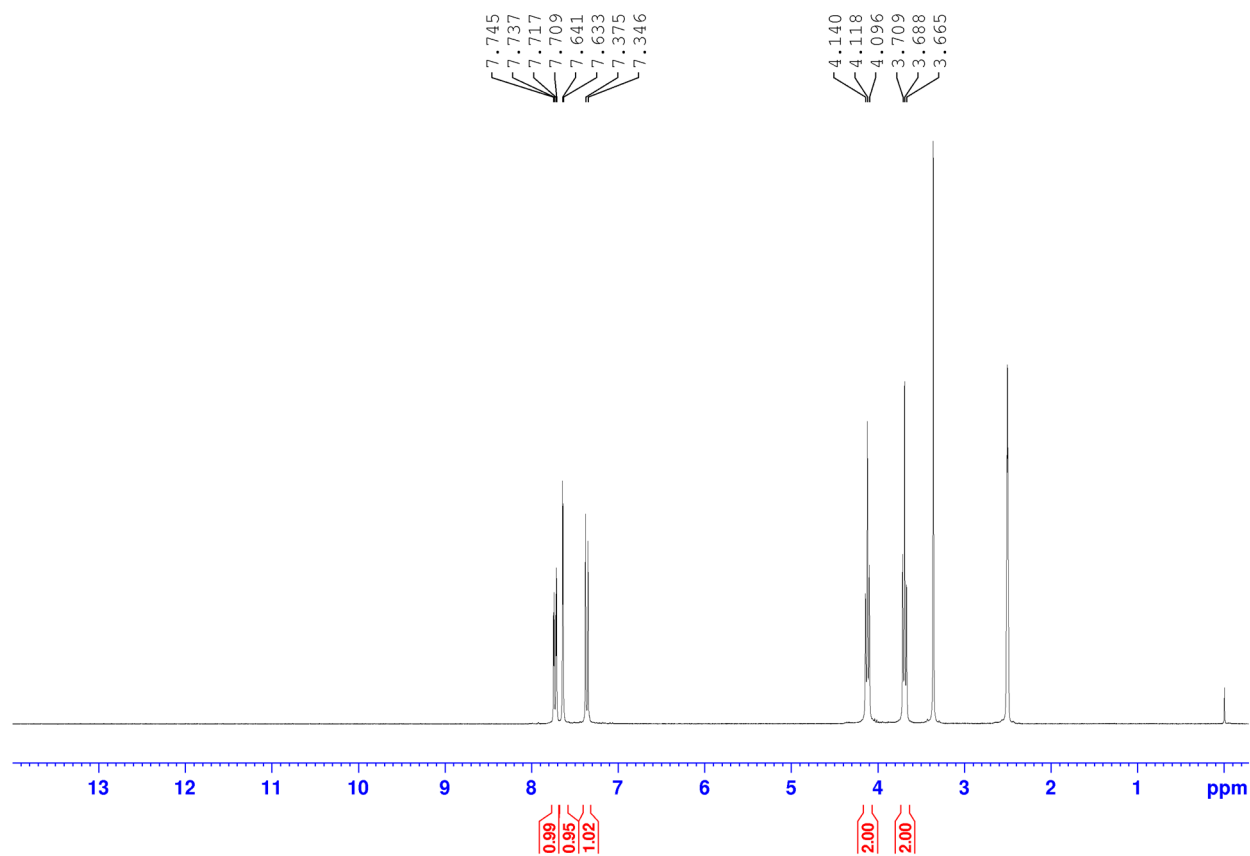


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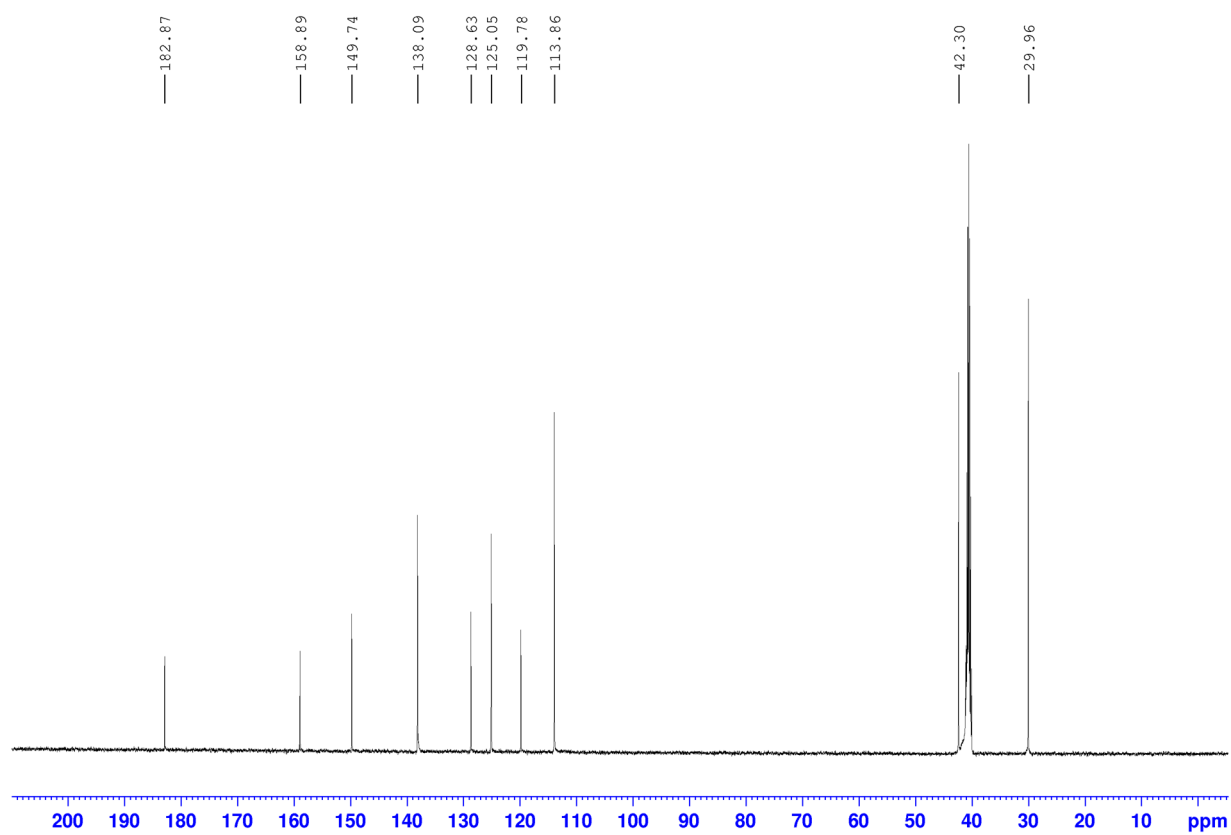


1-(2-Bromoethyl)-5-chloroisatin (9)

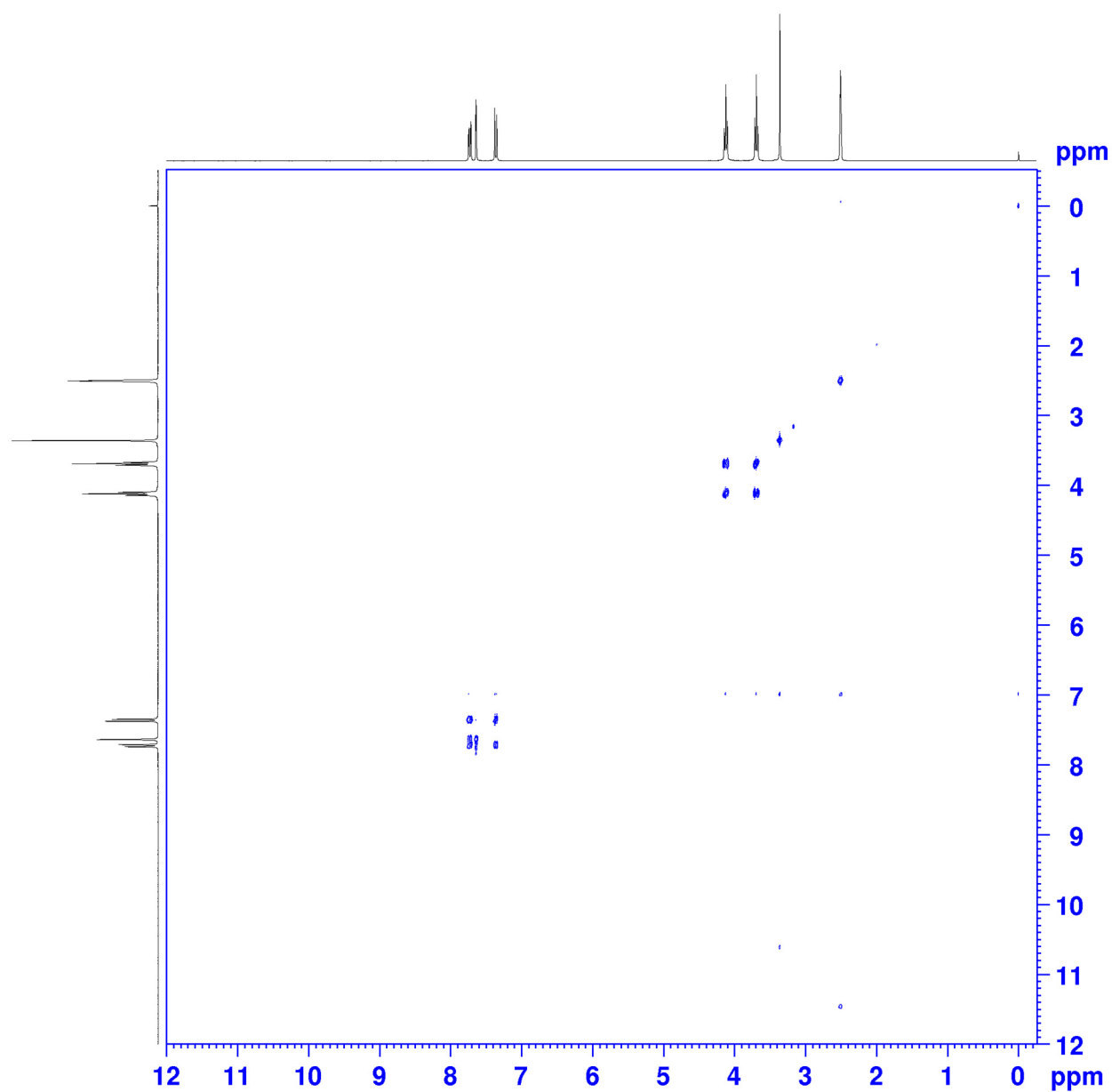
^1H NMR (300 MHz)



^{13}C NMR (500 MHz)



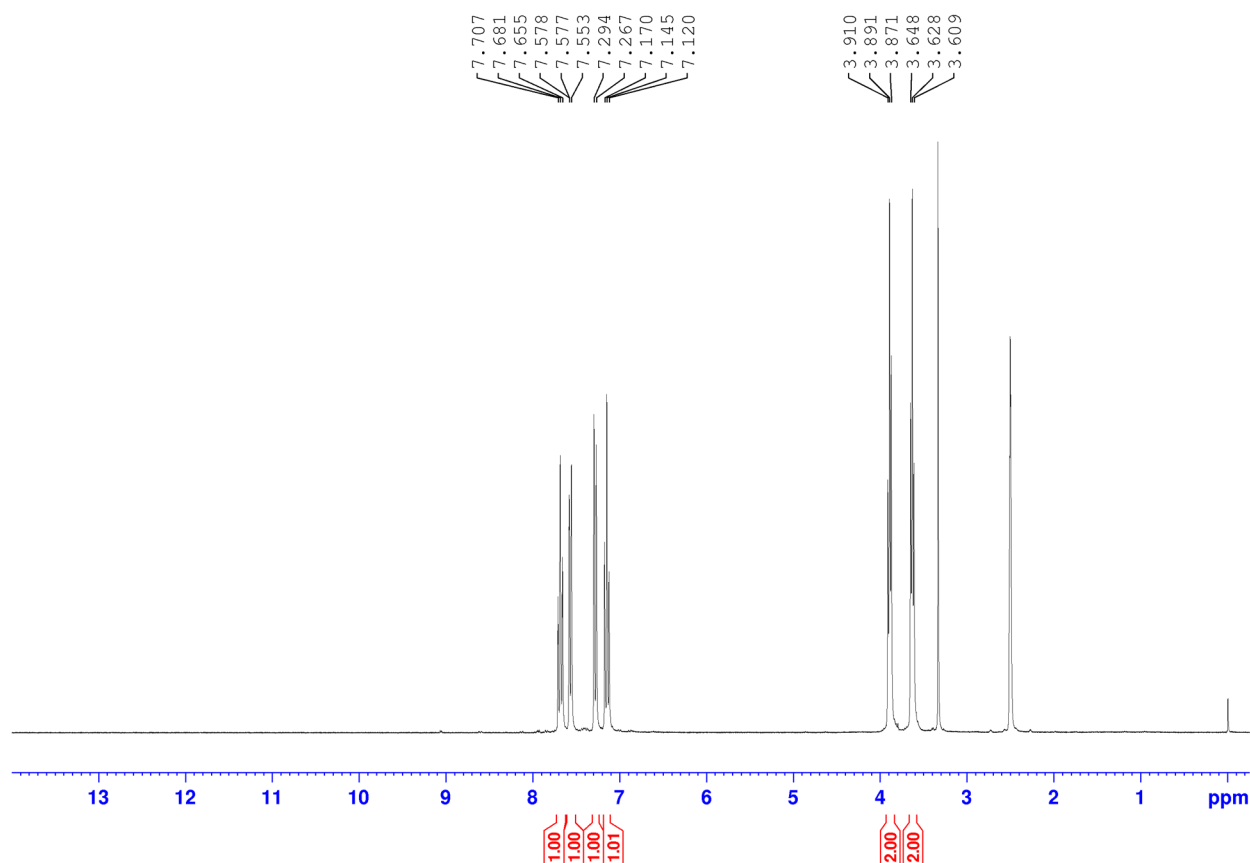
COSY NMR (300 MHz)



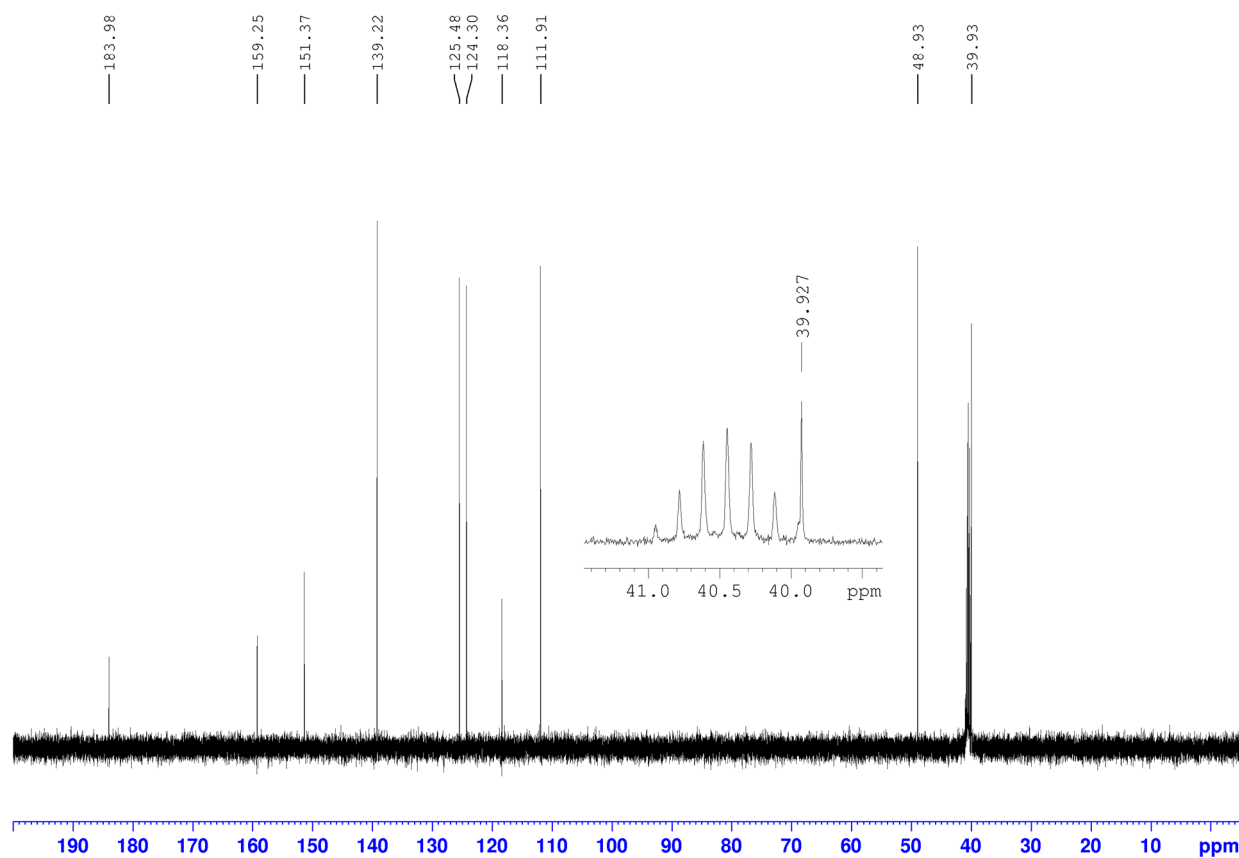
Characterization spectra of 1-(2-azidoethyl) isatins 10-13.

1-(2-azidoethyl)isatin (10)

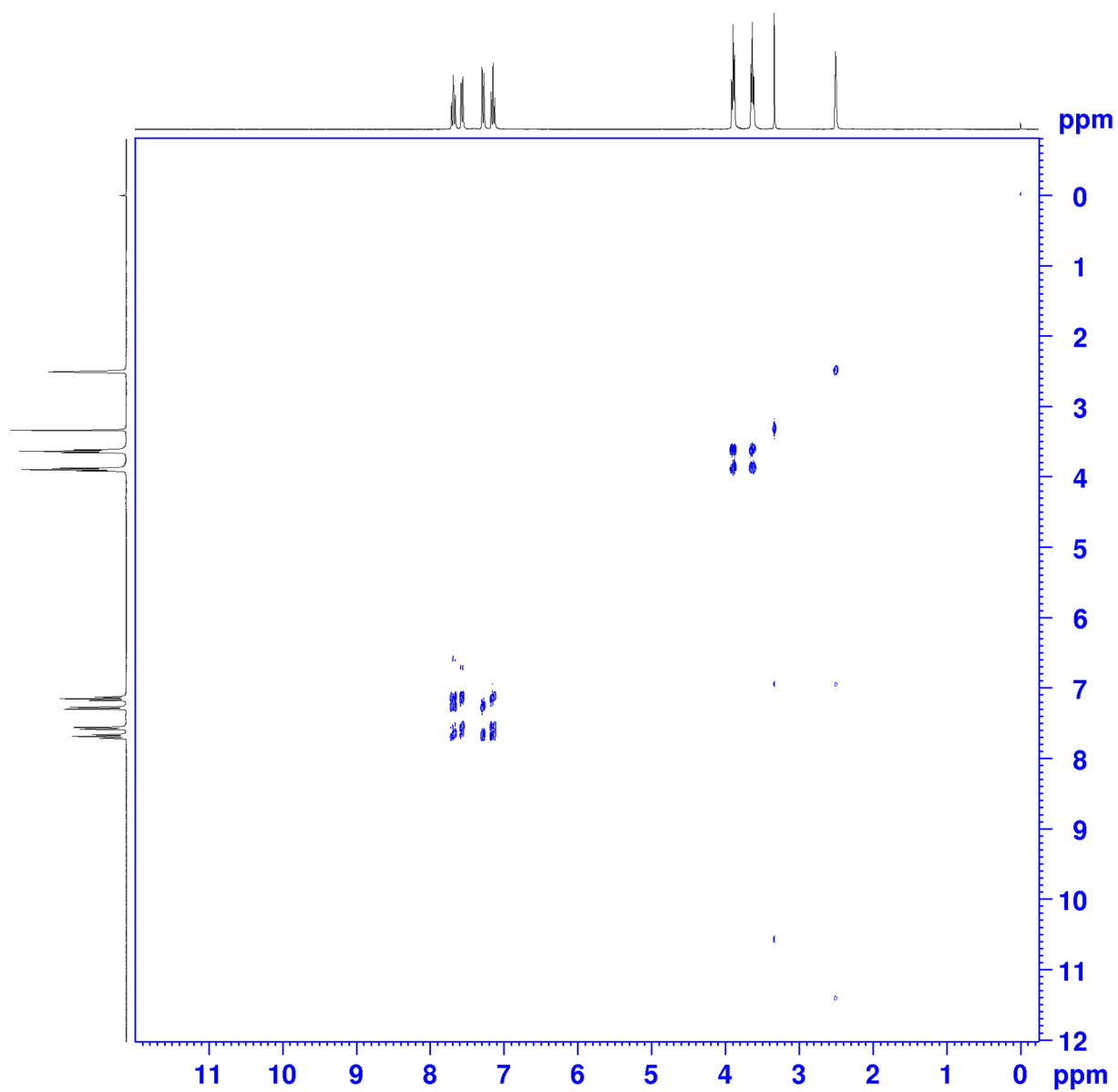
^1H NMR (300 MHz)



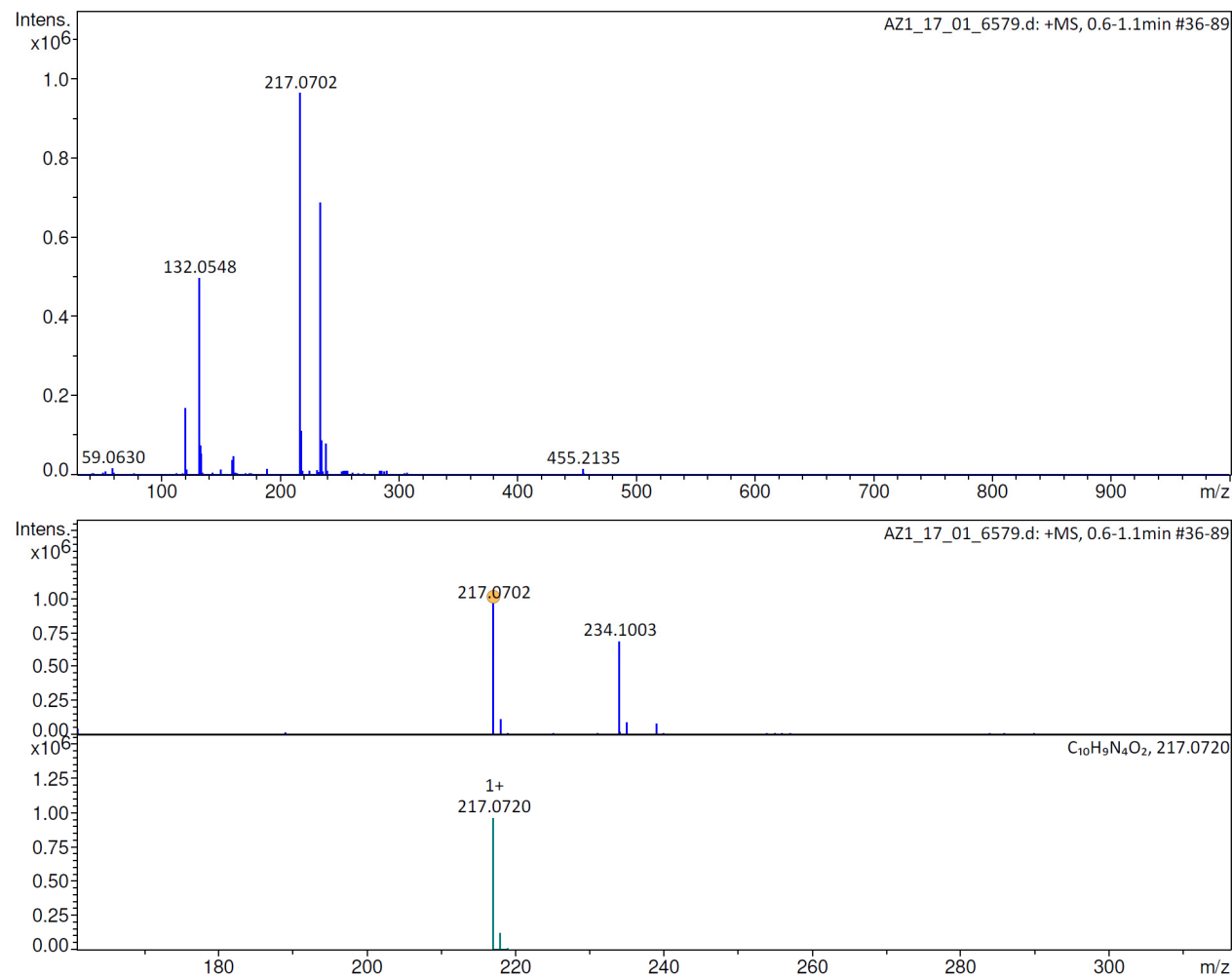
^{13}C NMR (125 MHz)



COSY NMR (300 MHz)

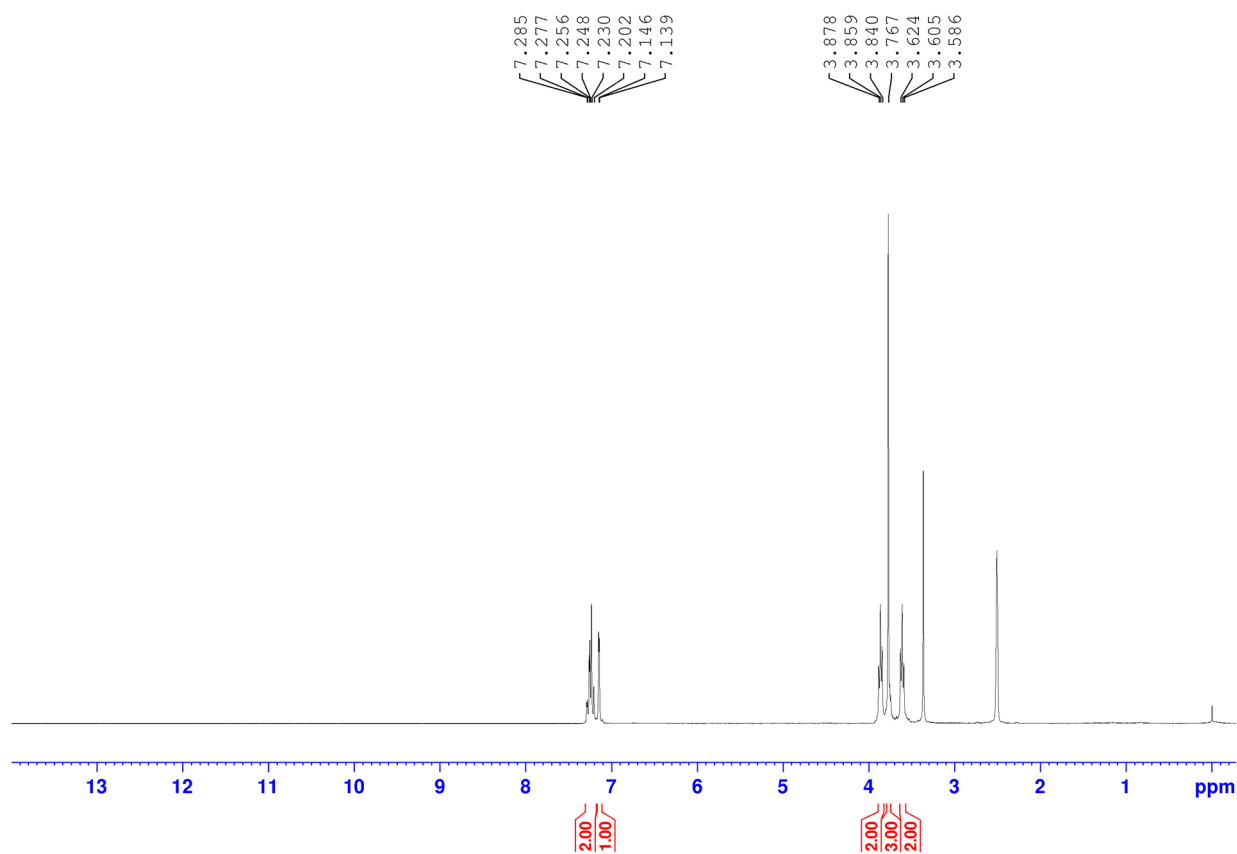


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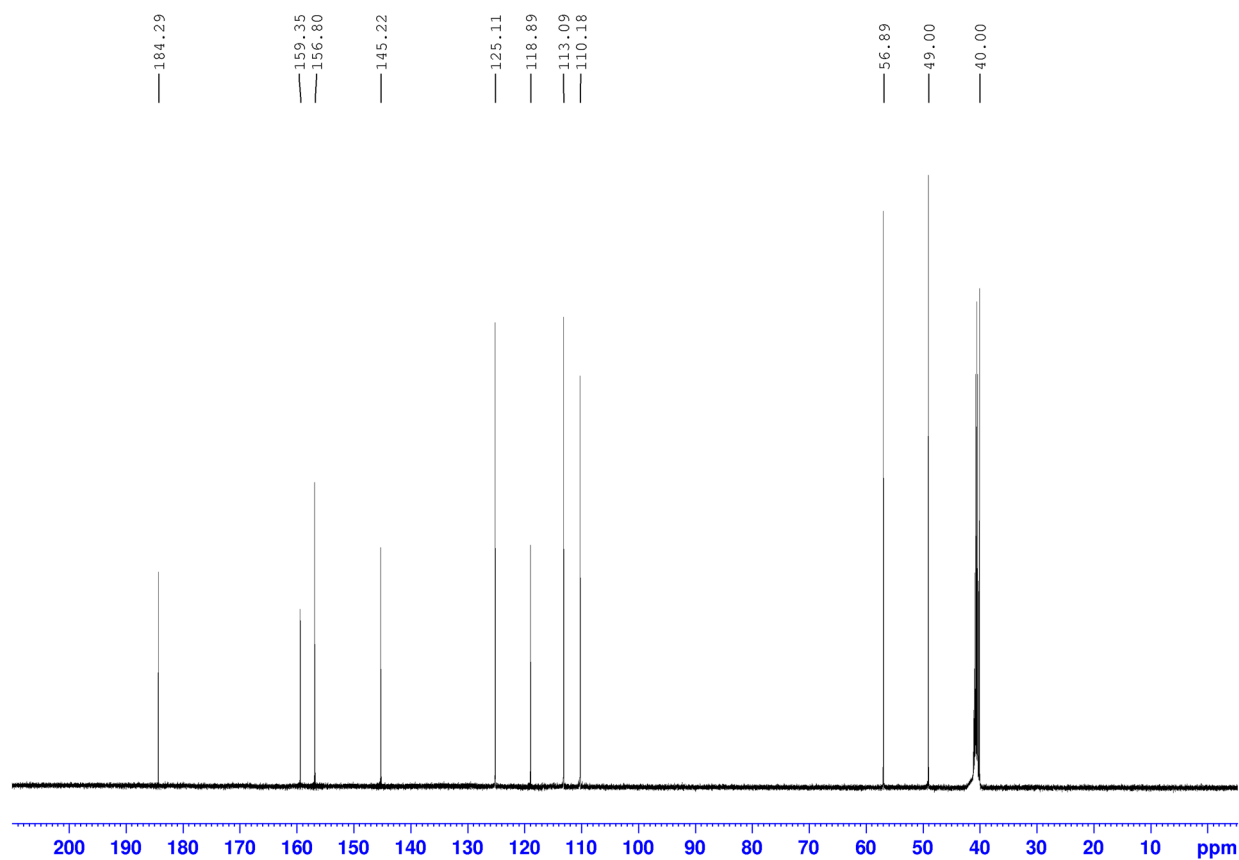


1-(2-azidoethyl)-5-methylisatin (11)

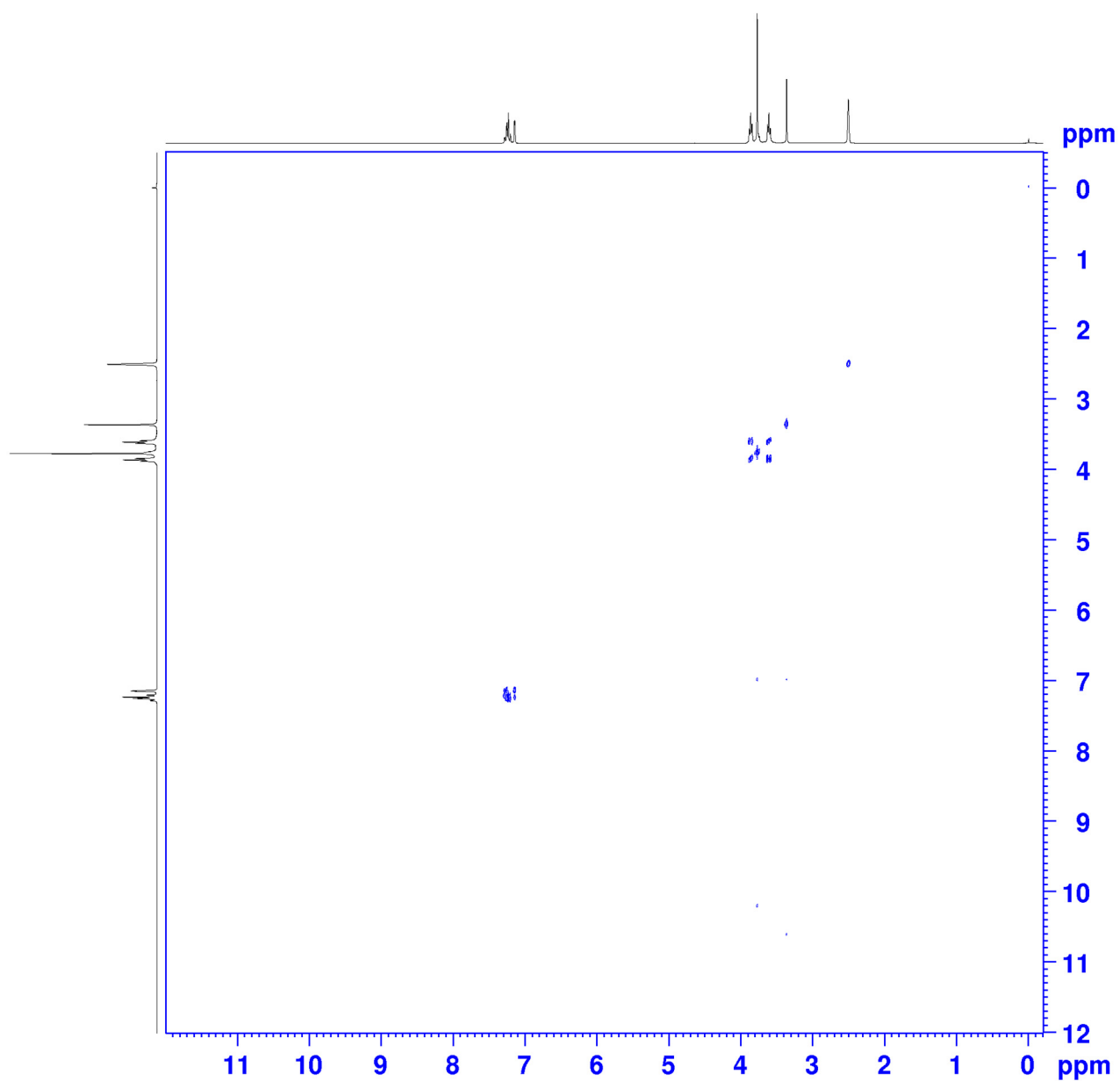
^1H NMR (300 MHz)



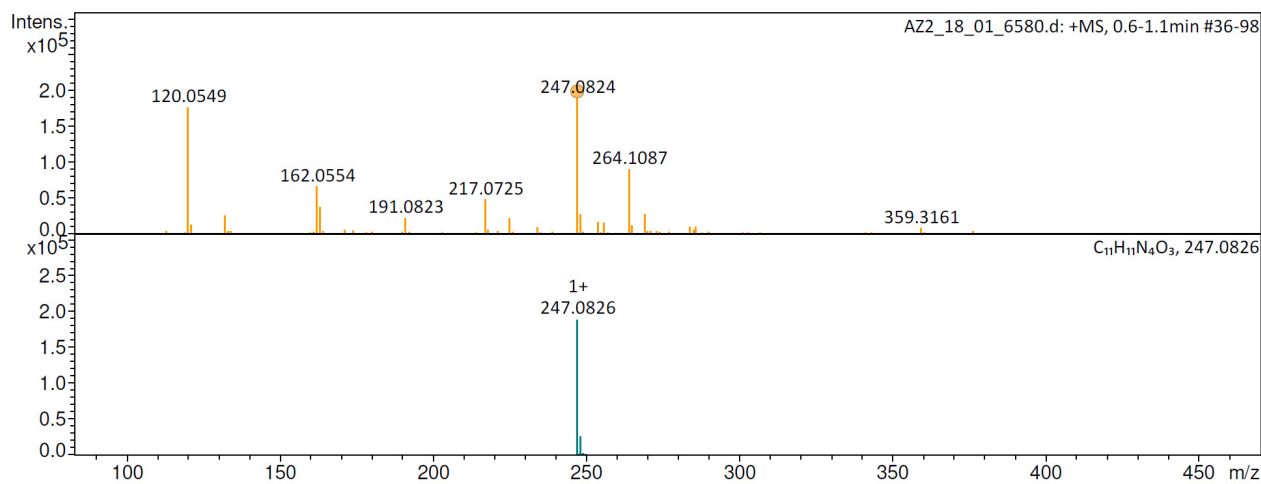
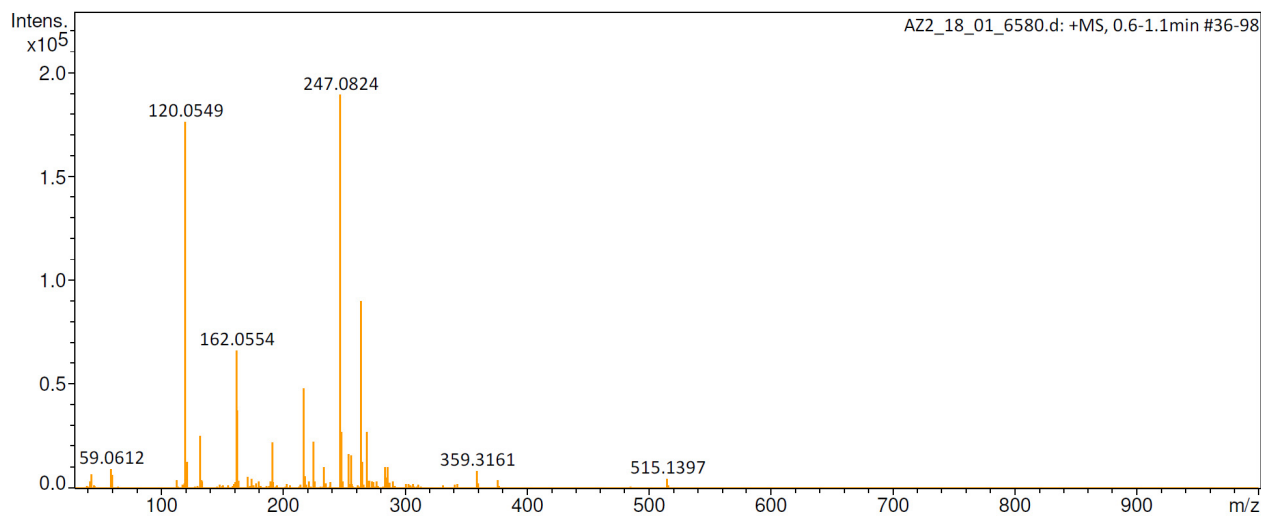
^{13}C NMR (125 MHz)



COSY NMR (300 MHz)

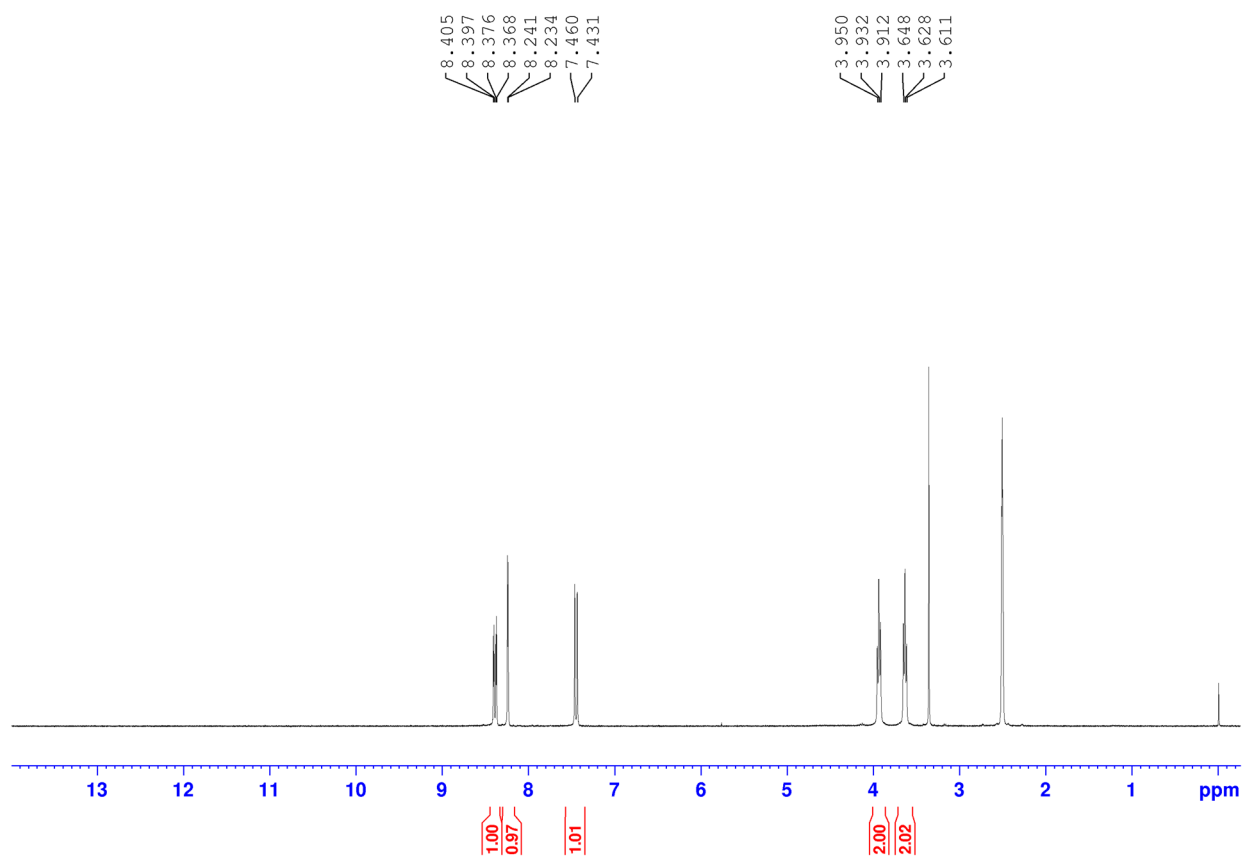


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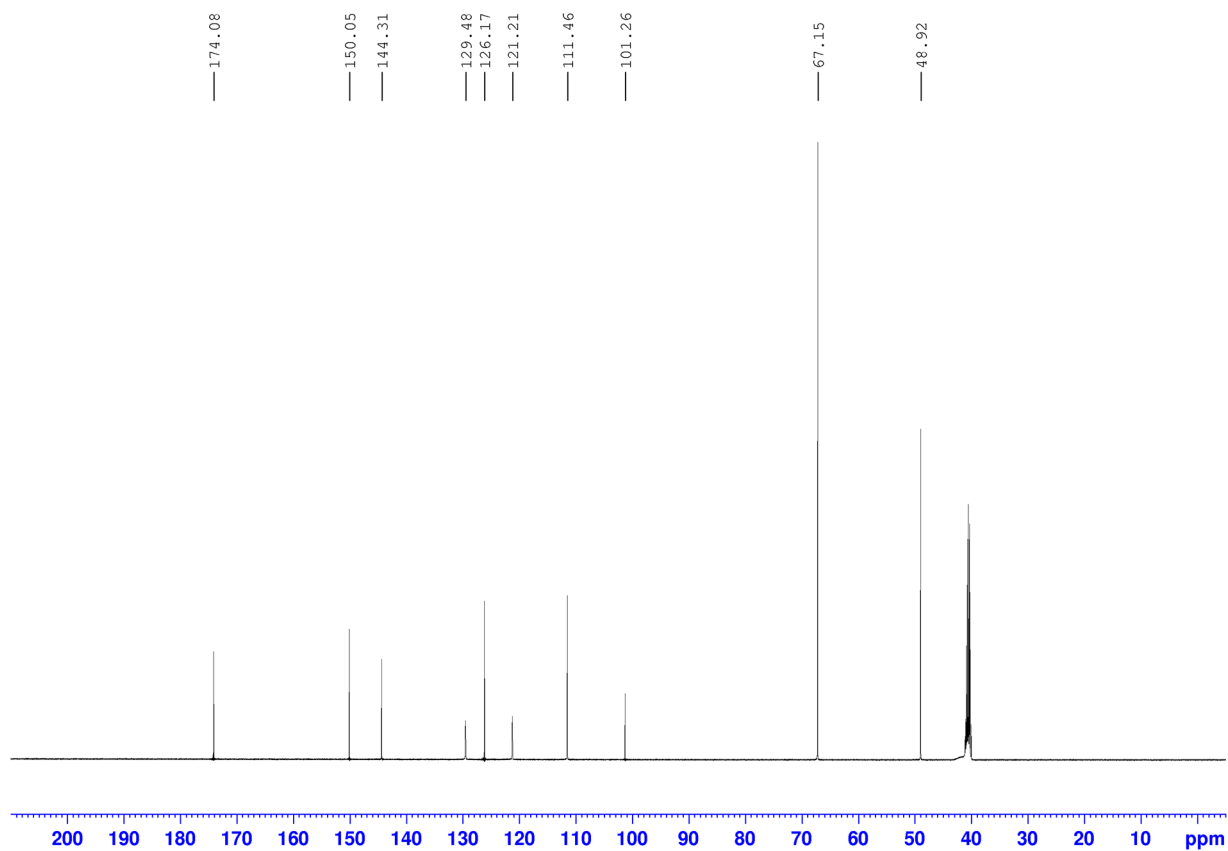


1-(2-azidoethyl)-5-nitroisatin (12)

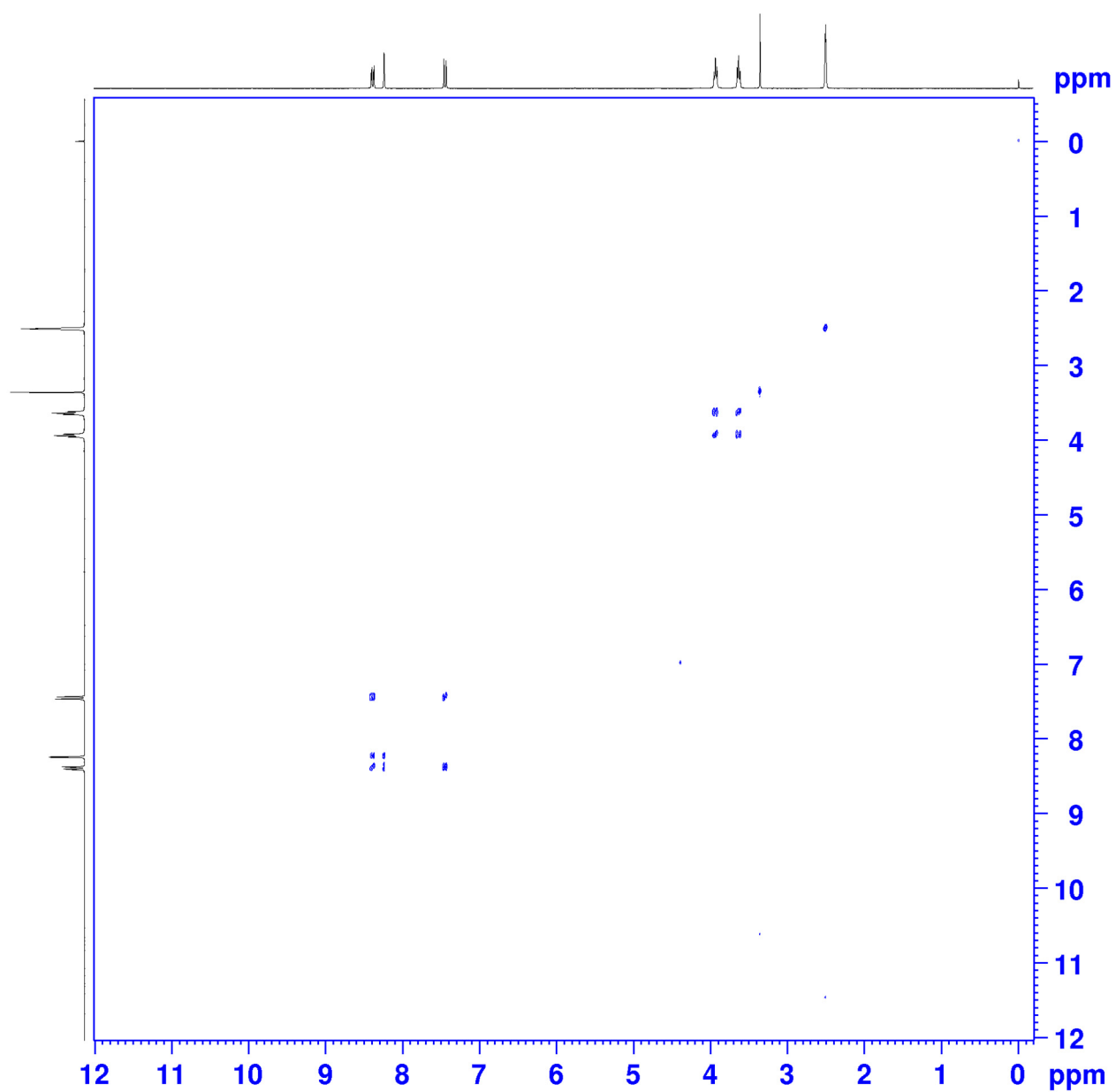
¹H NMR (300 MHz)



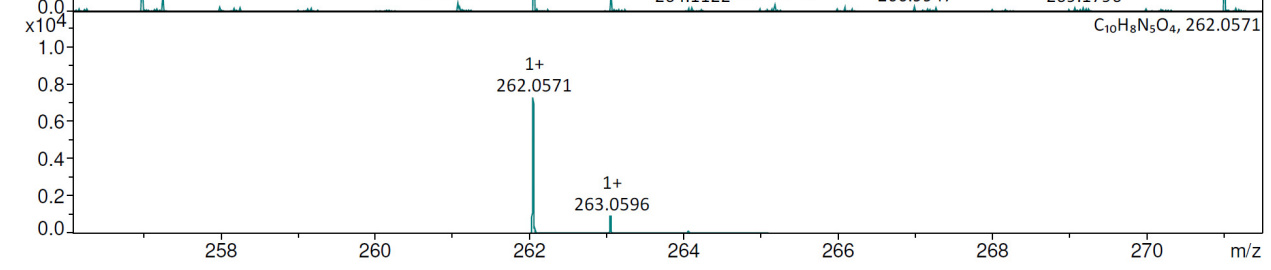
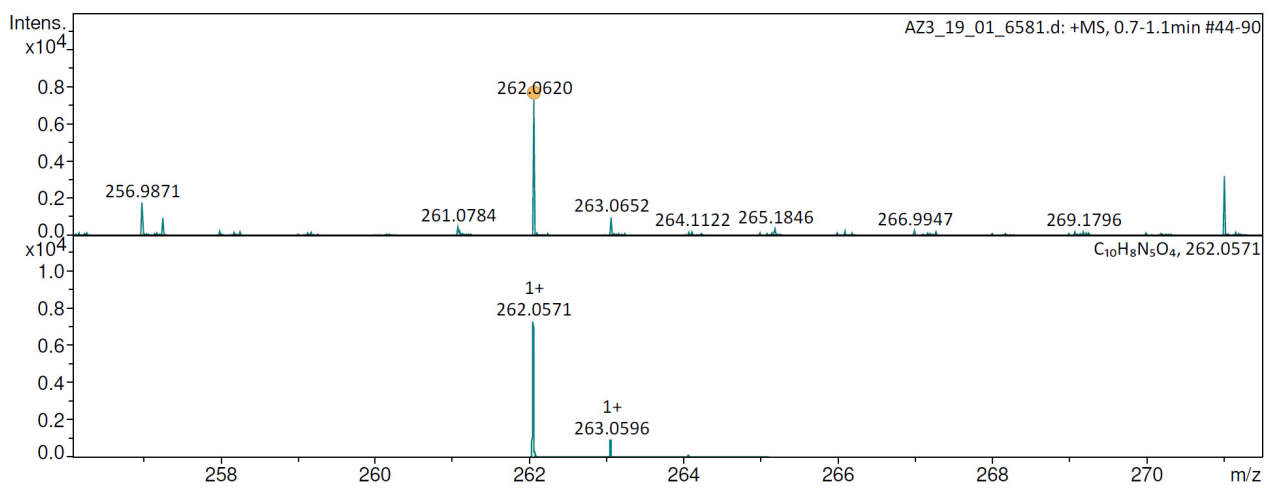
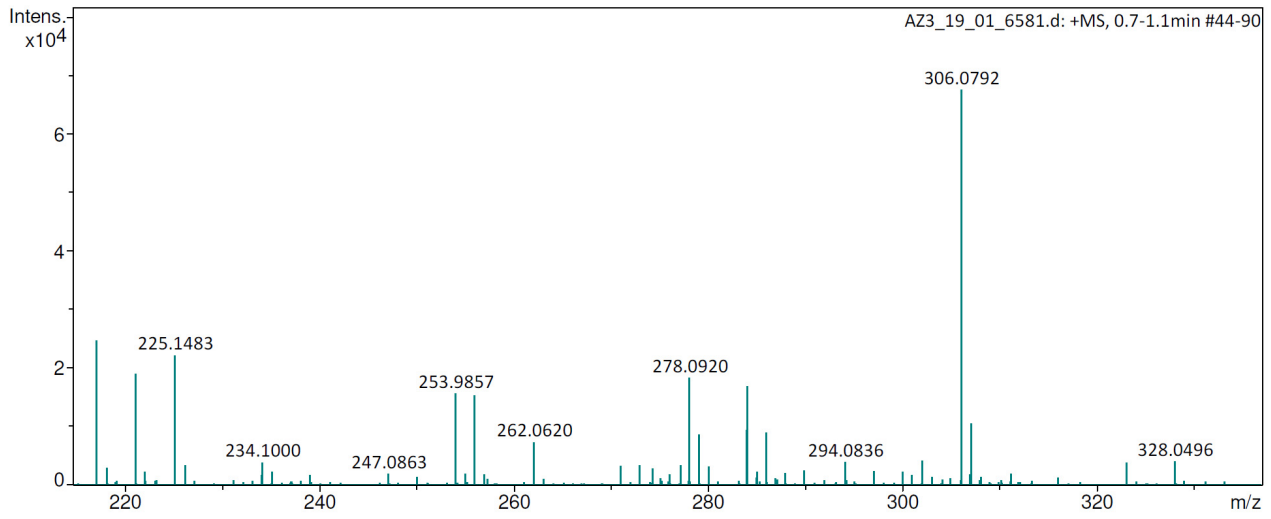
^{13}C NMR (125 MHz)



COSY NMR (300 MHz)

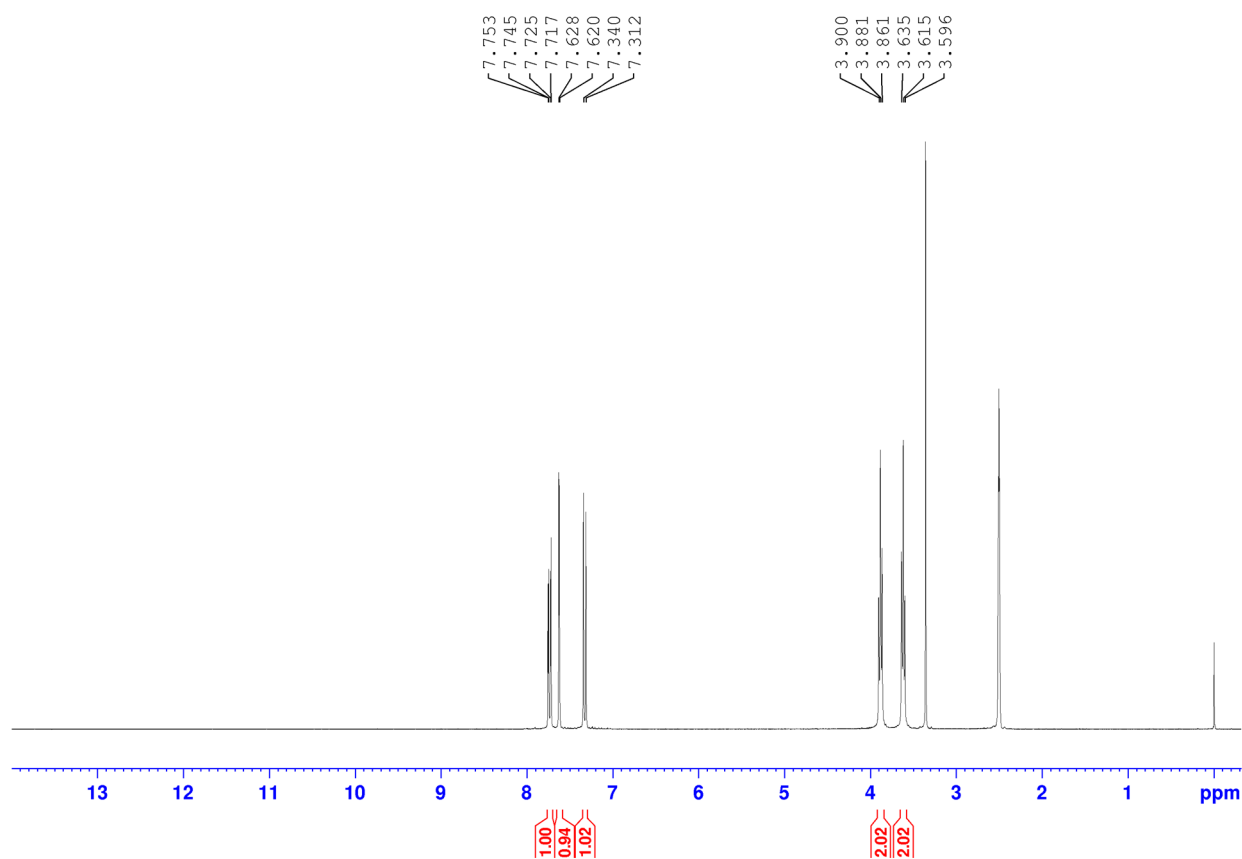


HRMS

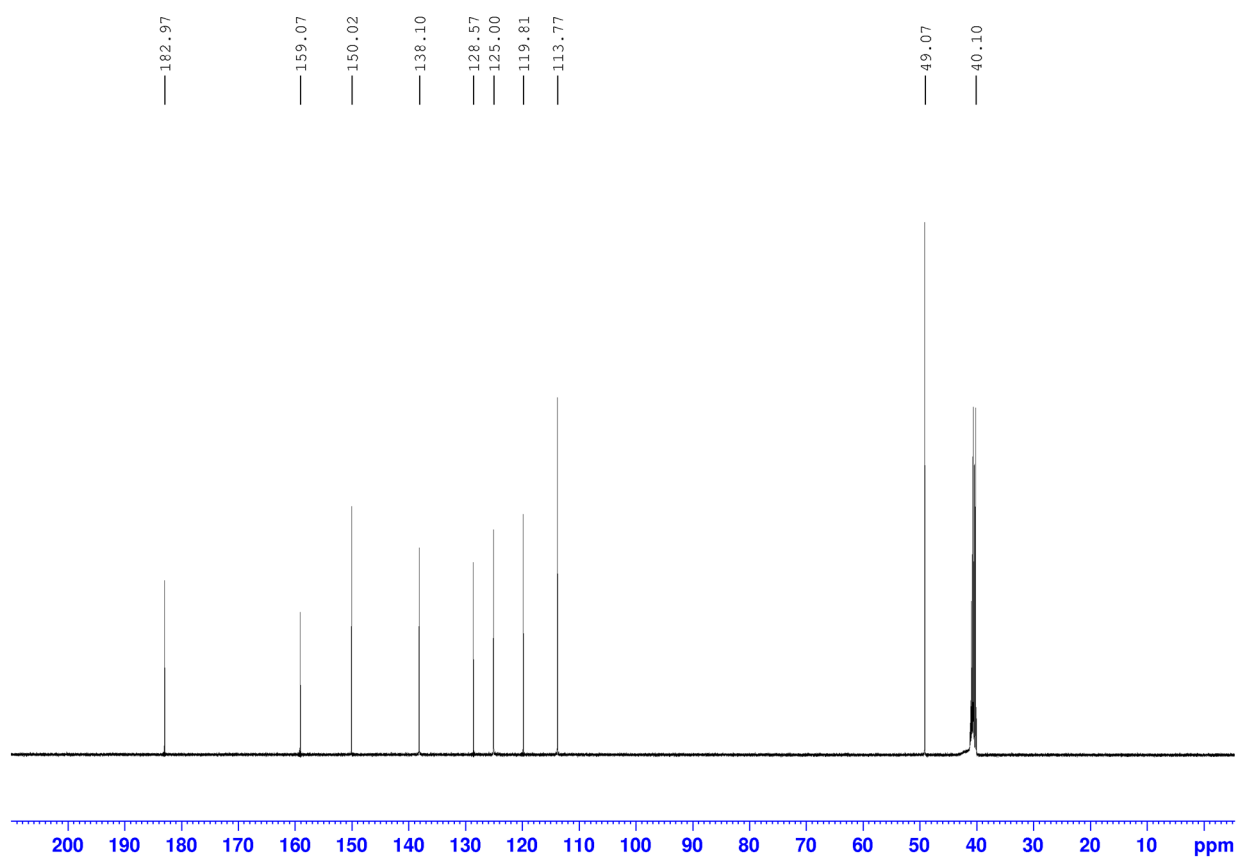


1-(2-Azidoethyl)-5-chloroisatin (13)

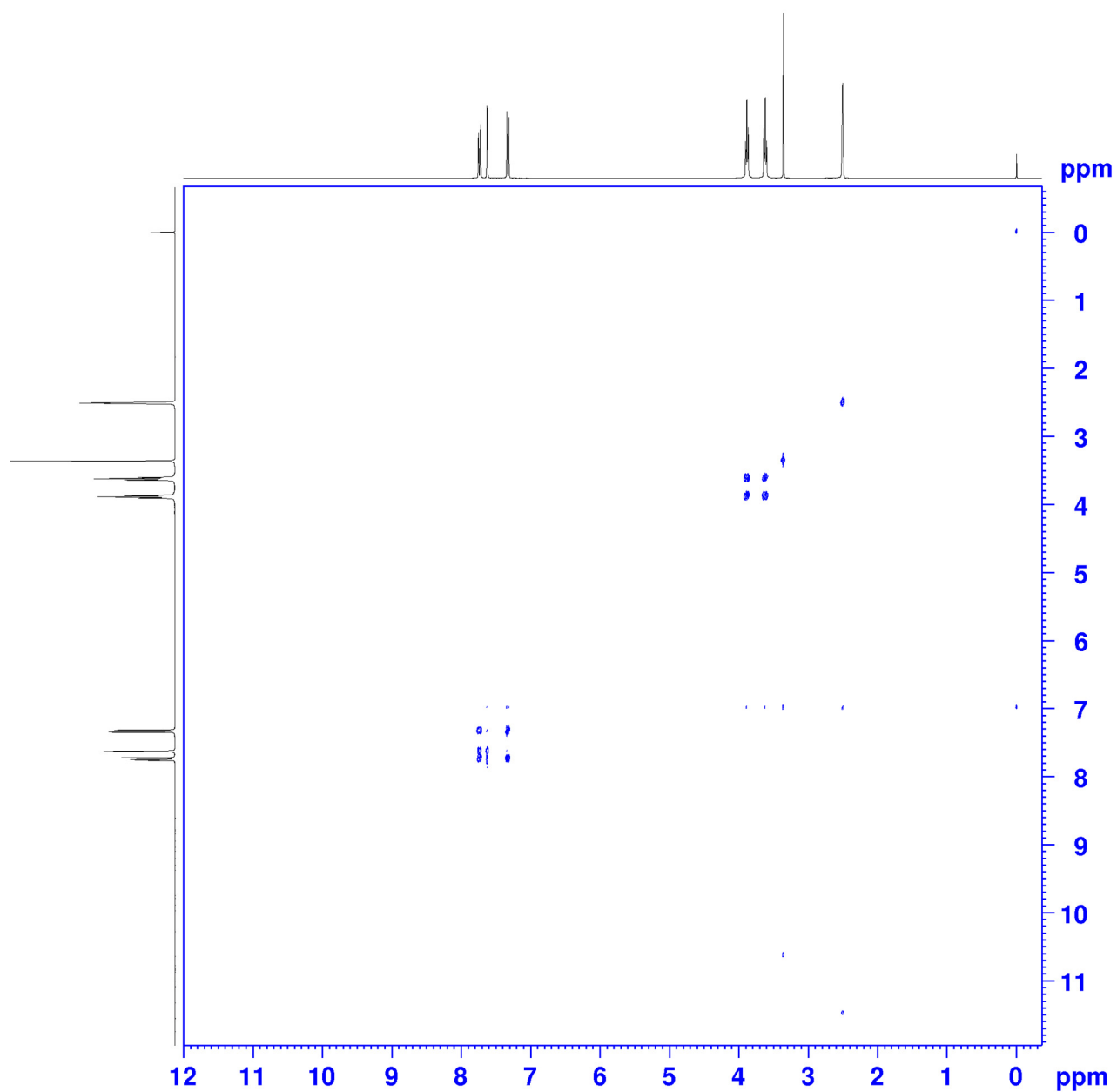
^1H NMR (300 MHz)



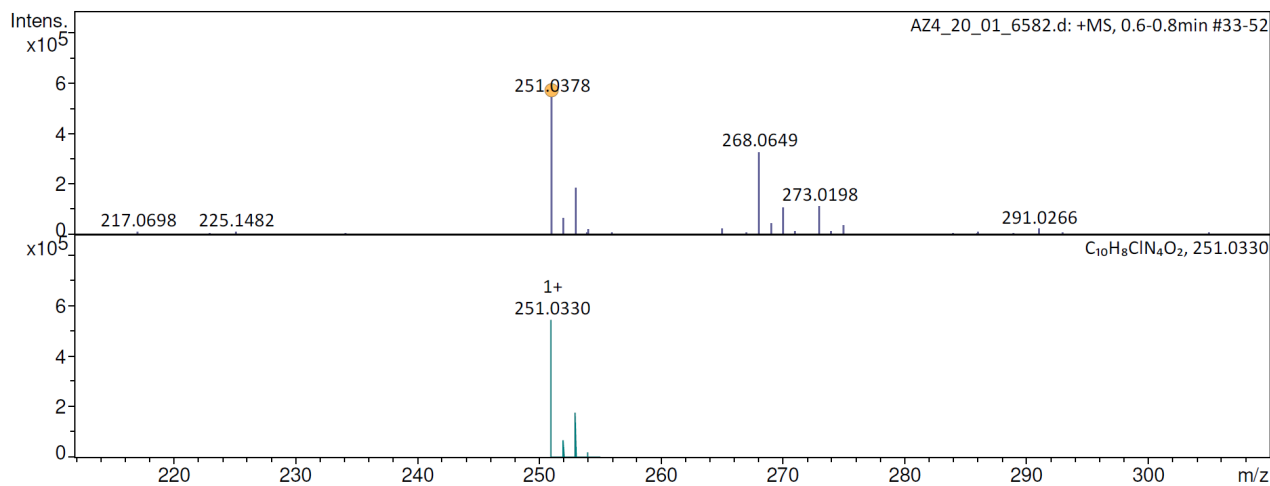
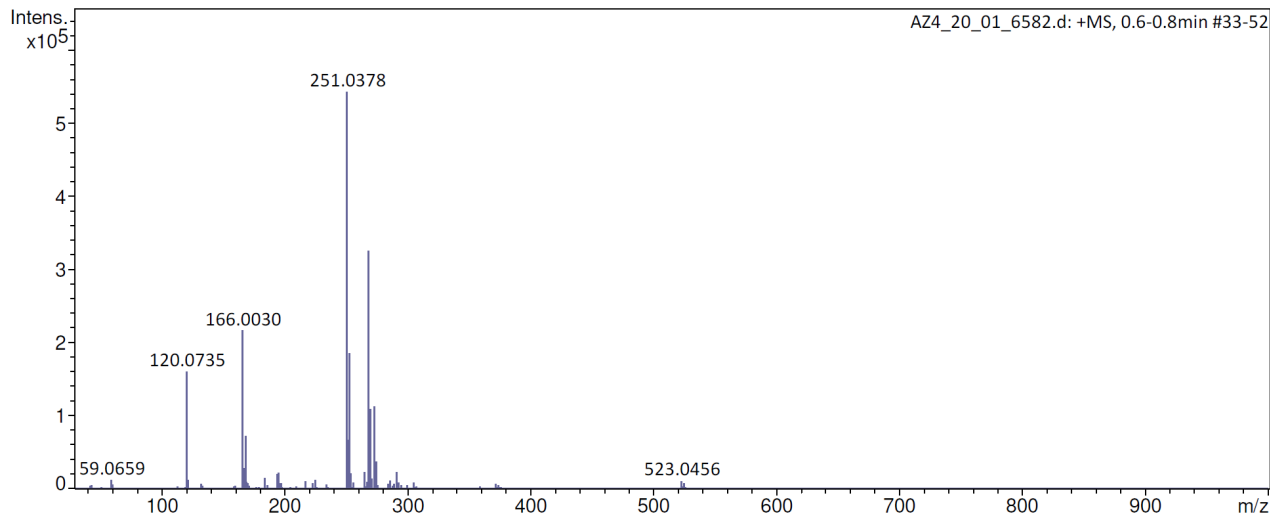
^{13}C NMR (125 MHz)



COSY NMR (300 MHz)



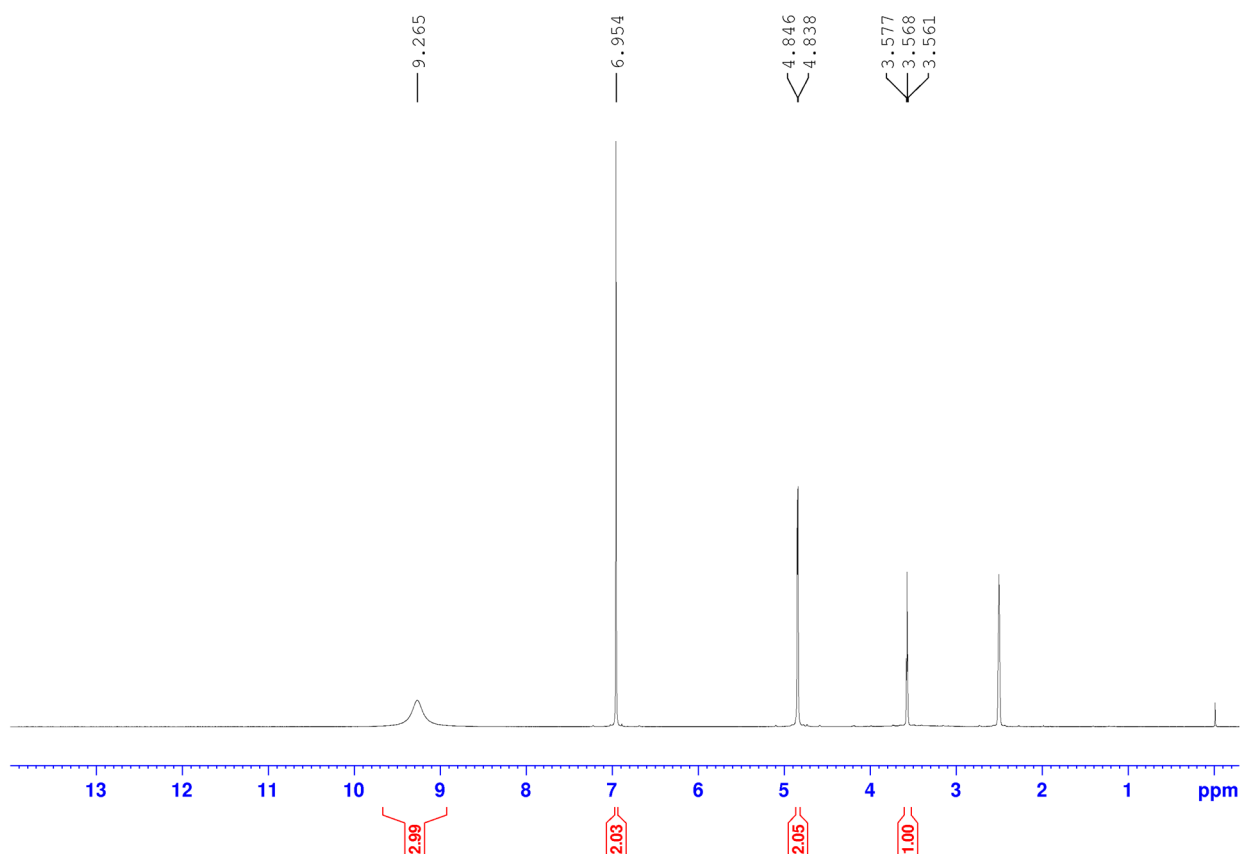
HRMS



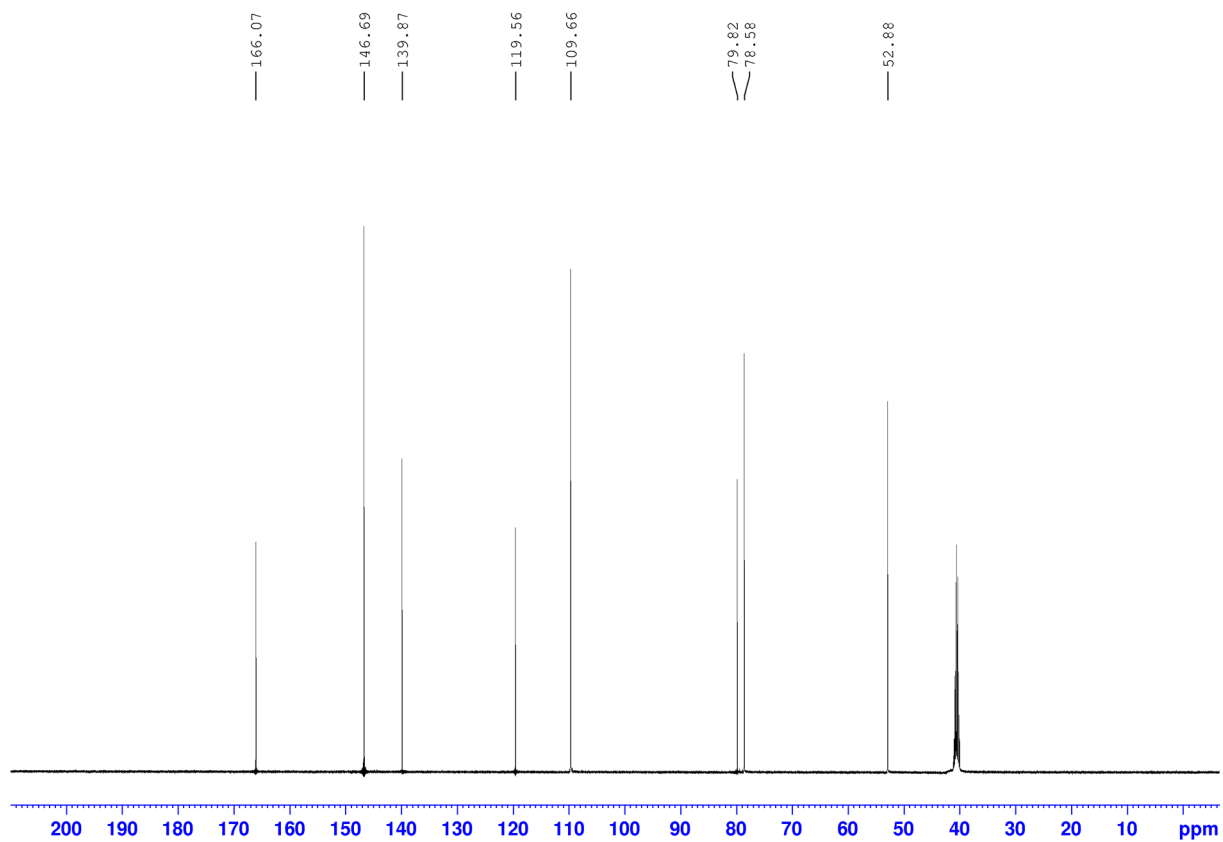
Characterization spectra of propargyl esters 20-22.

Propargyl 3,4,5-trihydroxybenzoate (20)

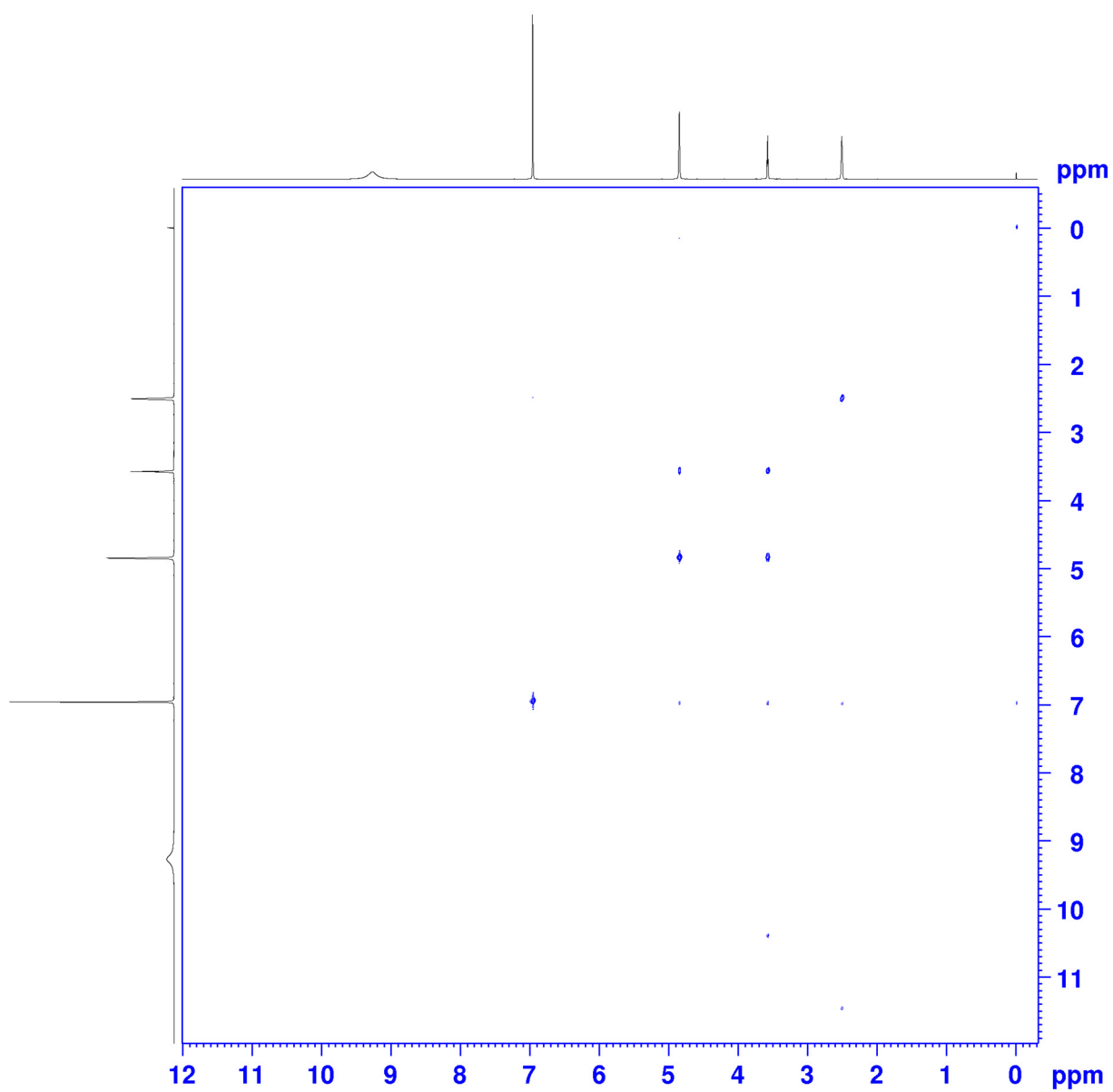
^1H NMR (300 MHz)



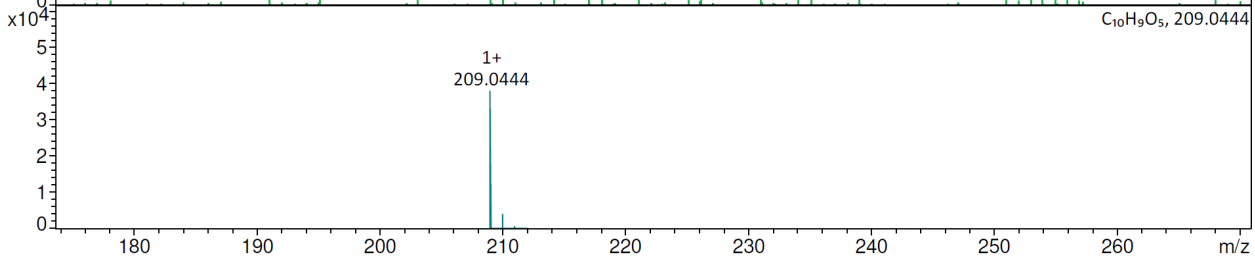
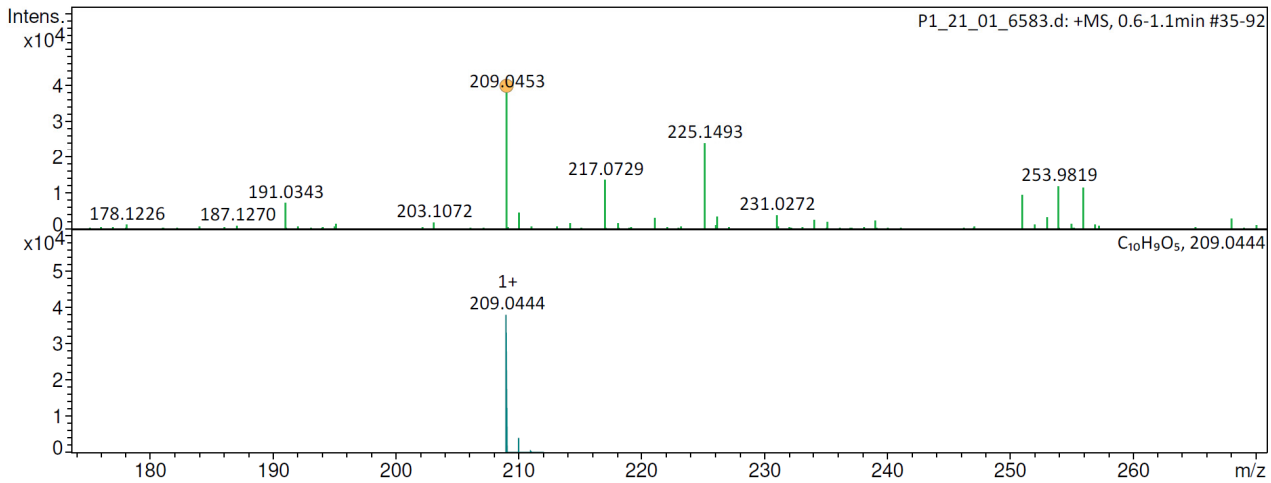
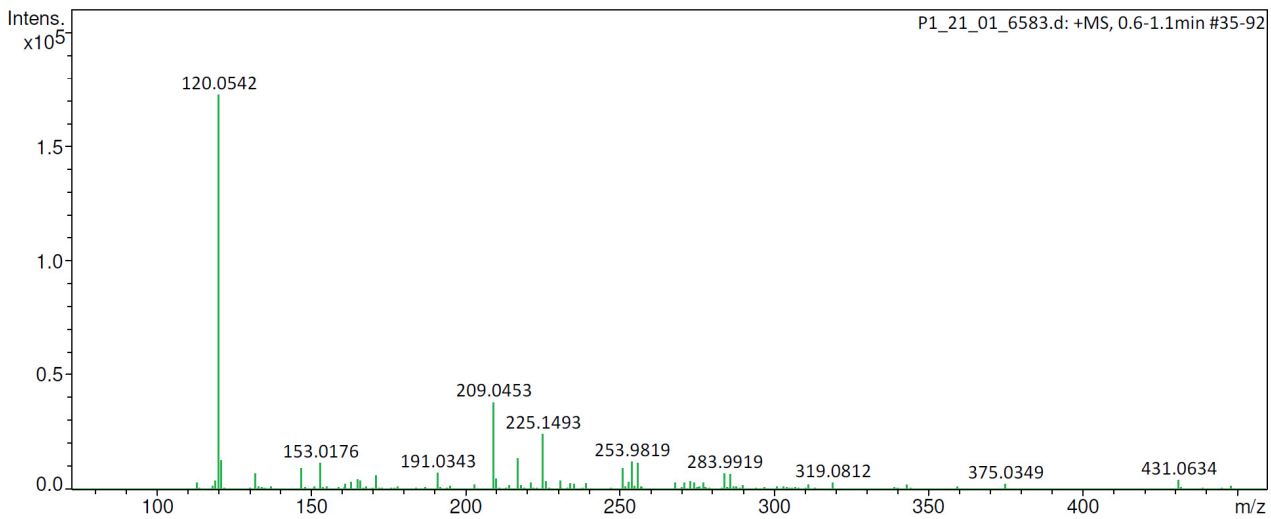
^{13}C NMR (125 MHz)



COSY NMR (300 MHz)

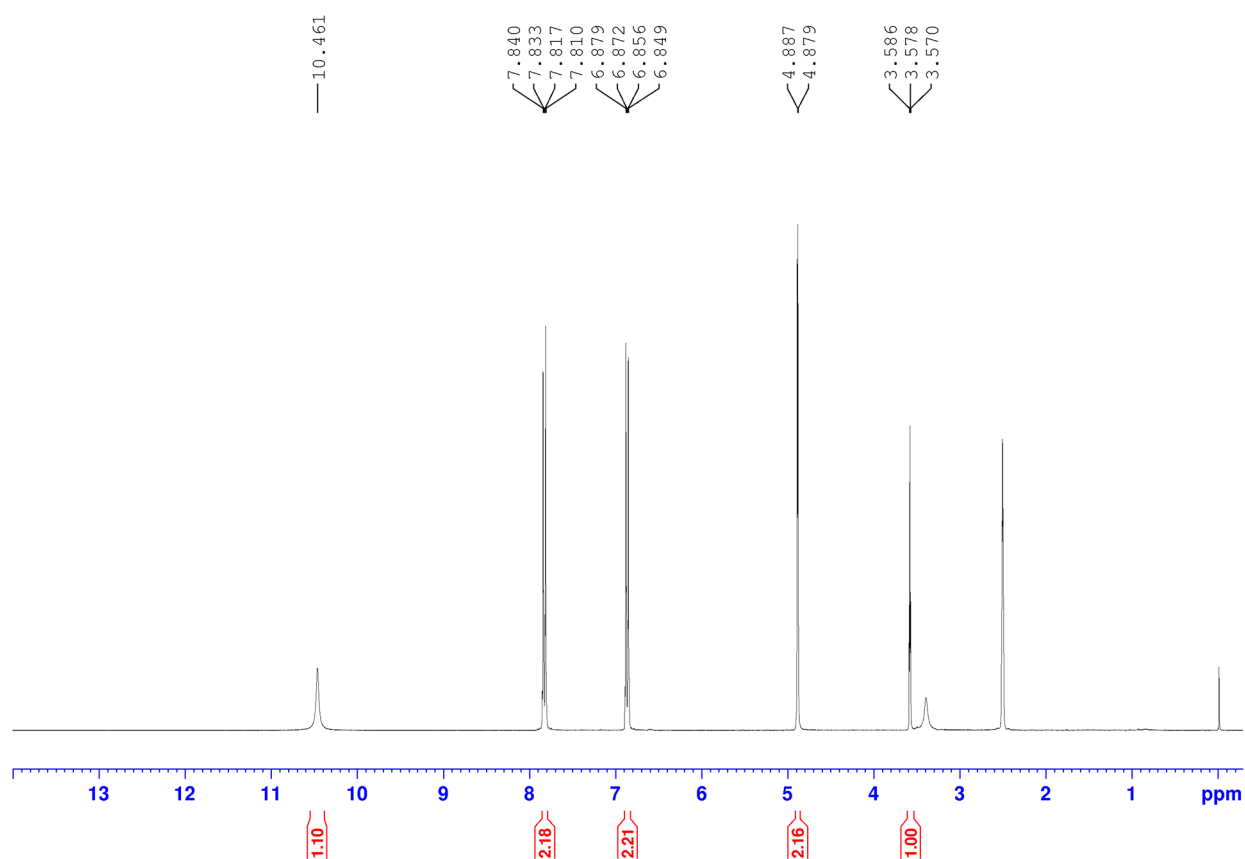


HRMS

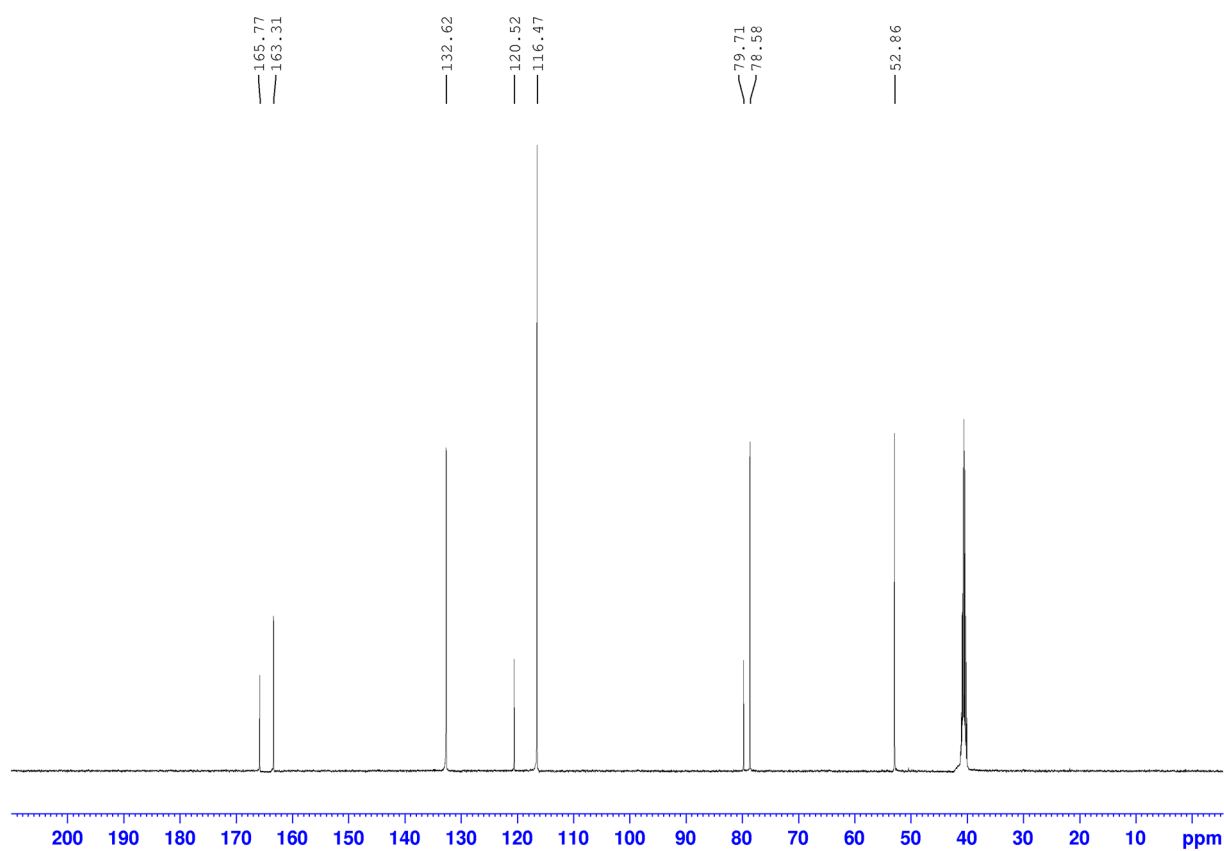


Propargyl 4-hydroxybenzoate (21)

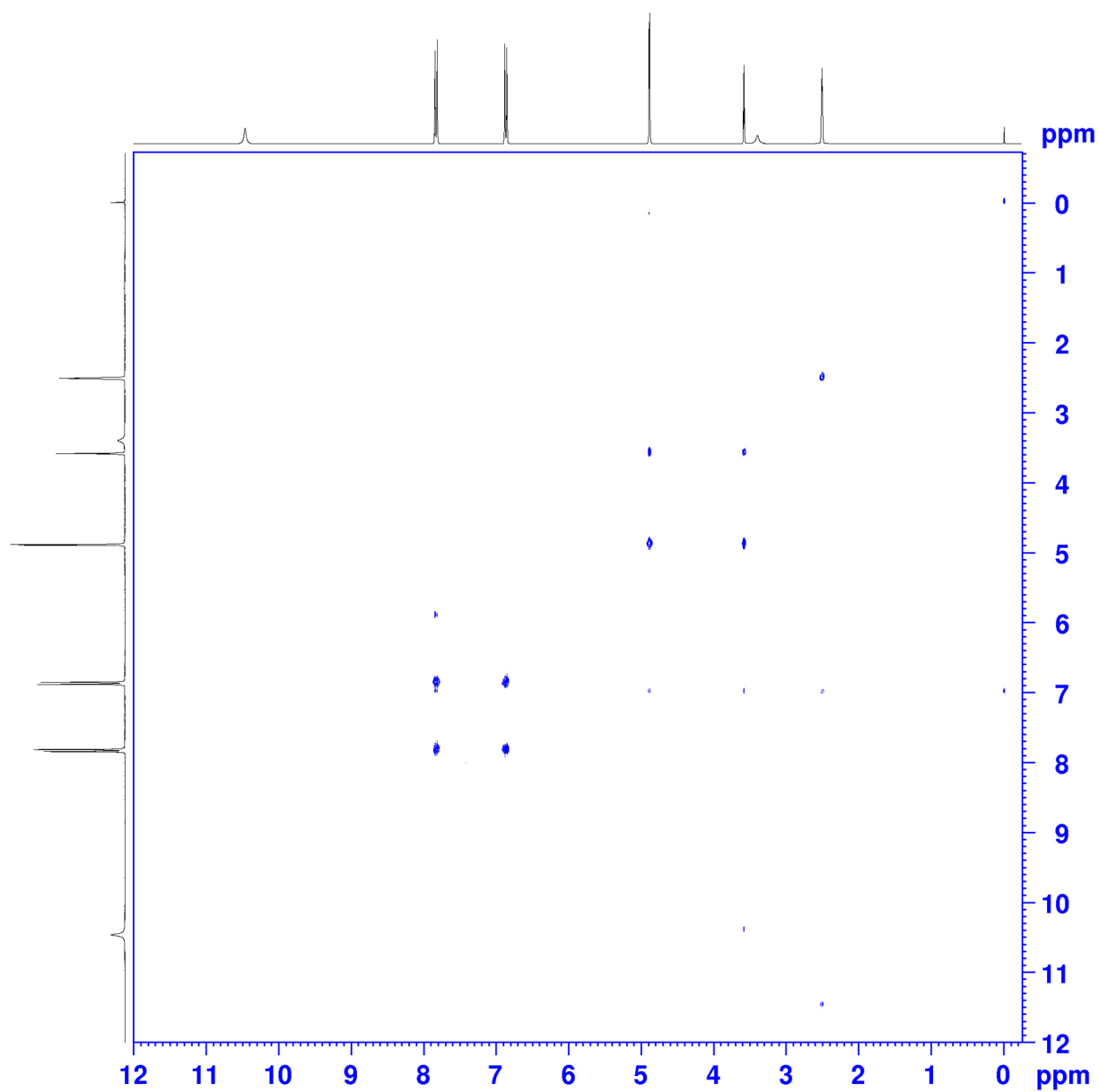
^1H NMR (300 MHz)



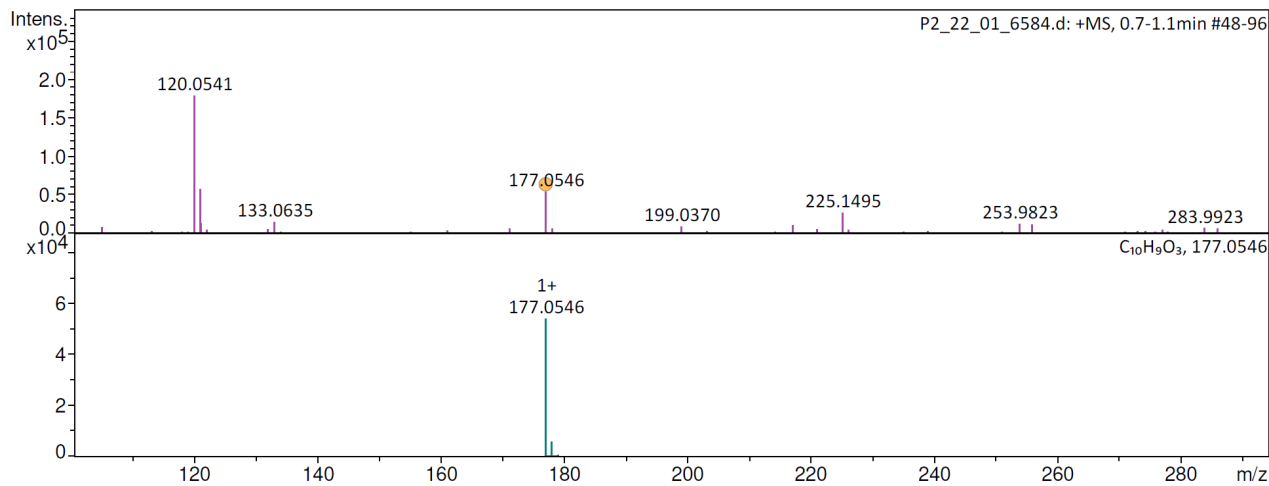
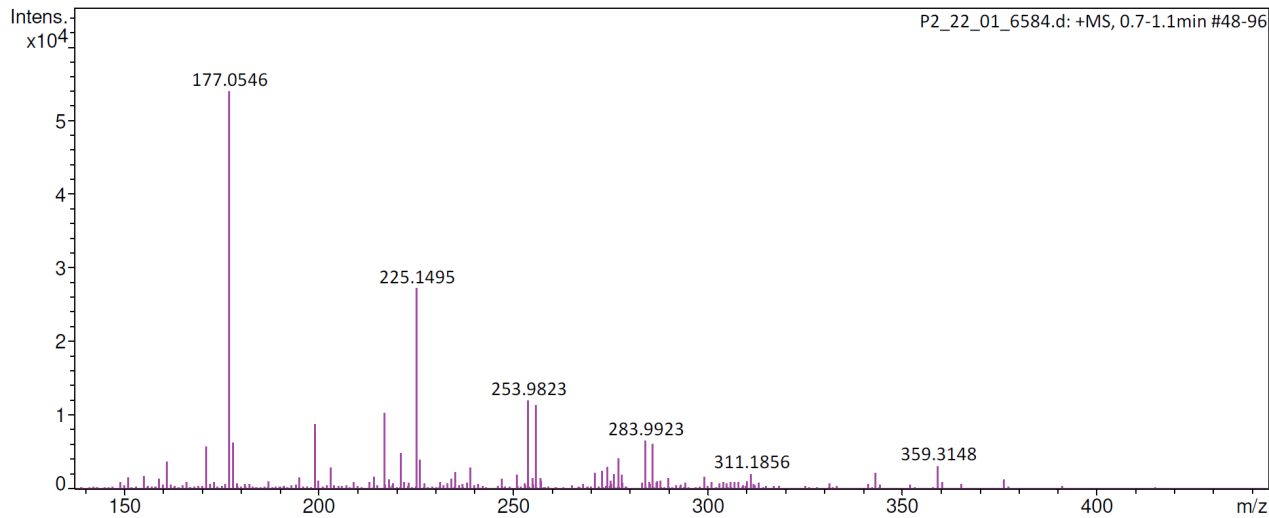
^{13}C NMR (125 MHz)



COSY NMR (300 MHz)

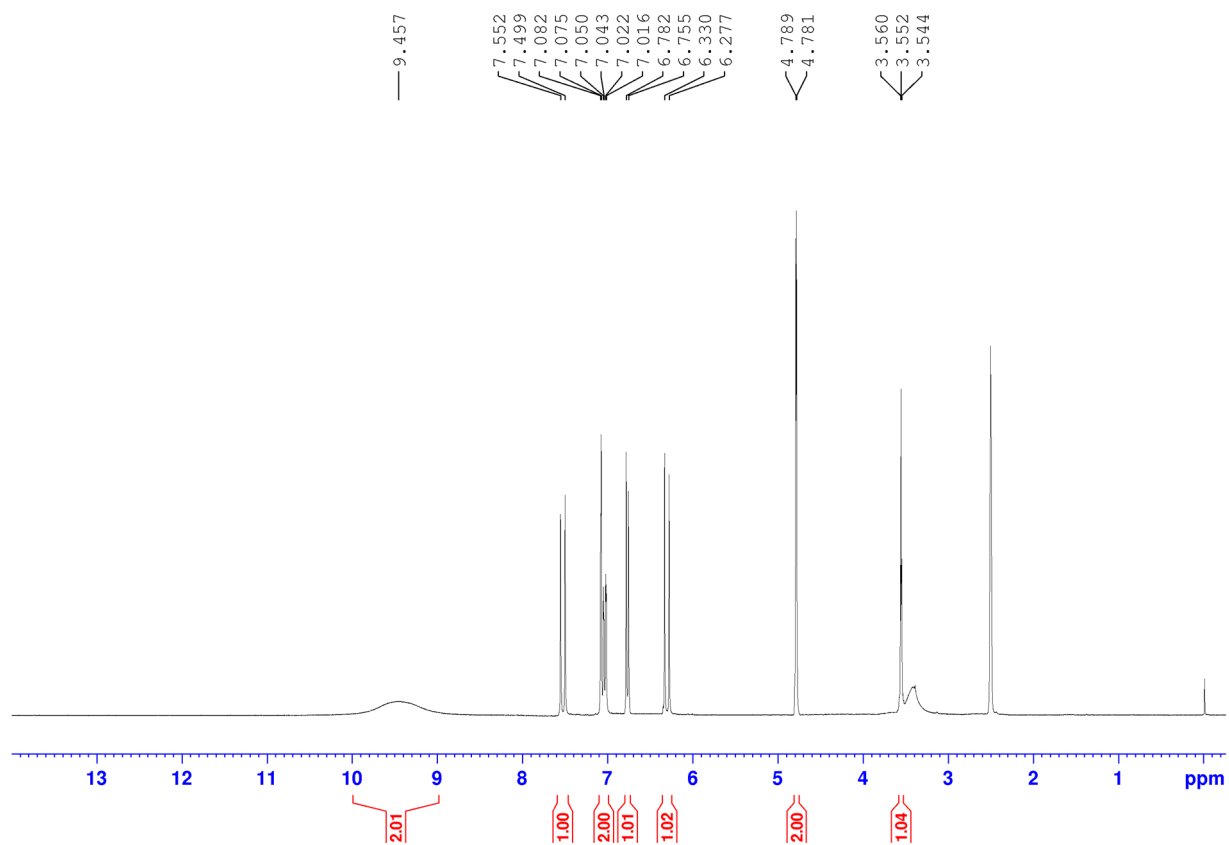


HRMS

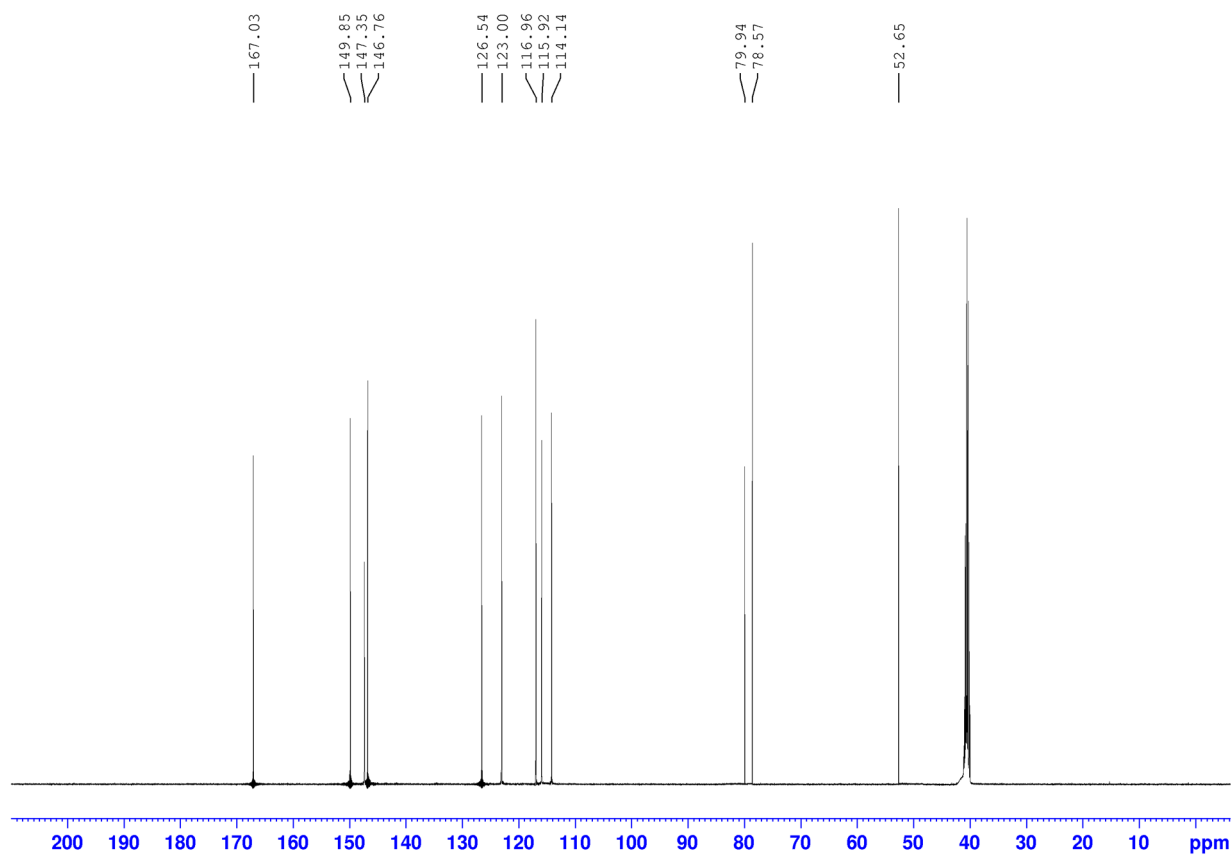


Propargyl (*E*)-3-(3,4-dihydroxyphenyl)acrylate (22)

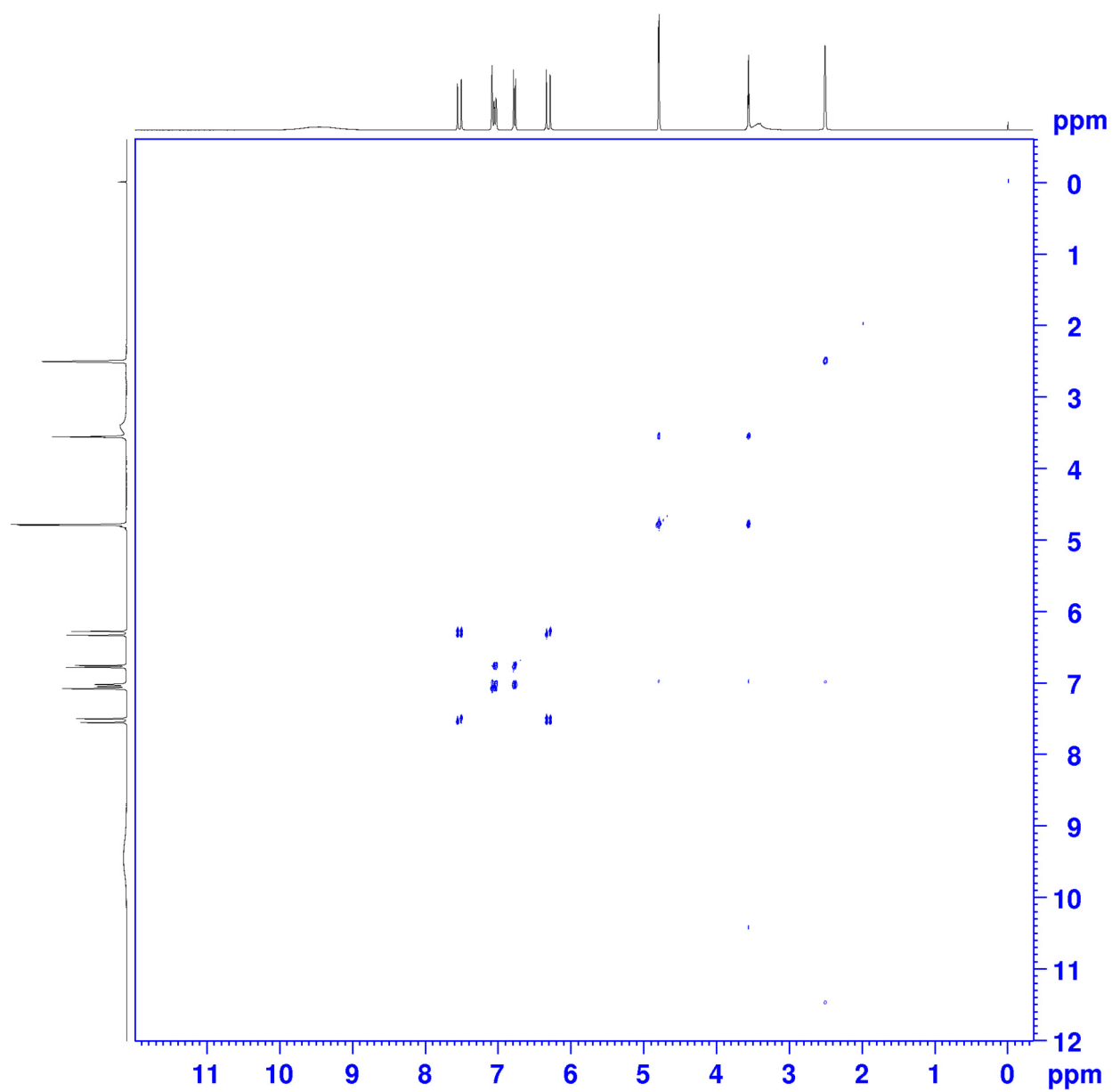
^1H NMR (300 MHz)



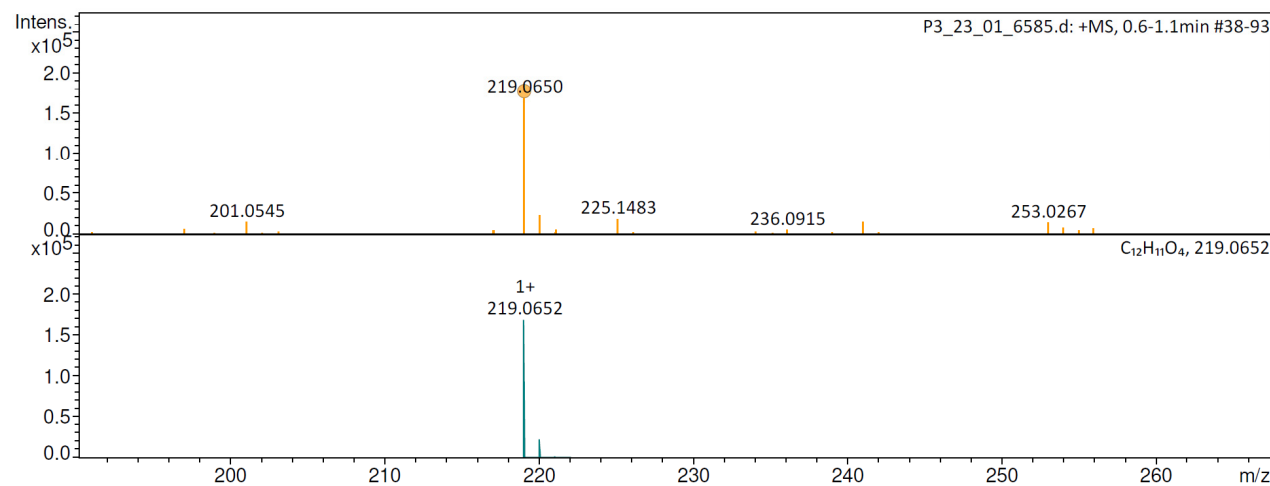
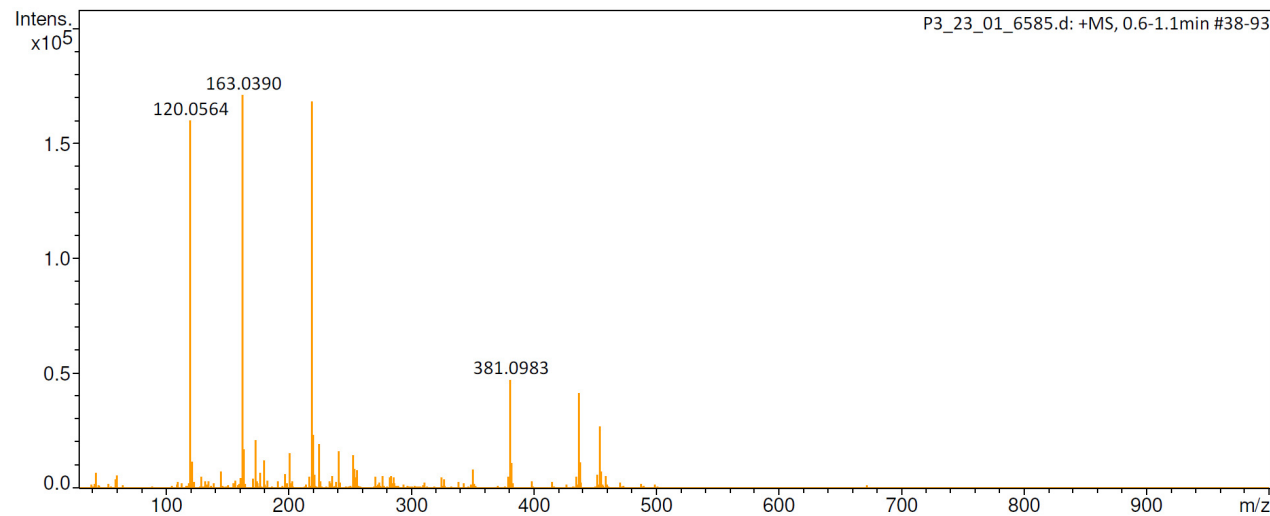
^{13}C NMR (125 MHz)



COSY NMR (300 MHz)

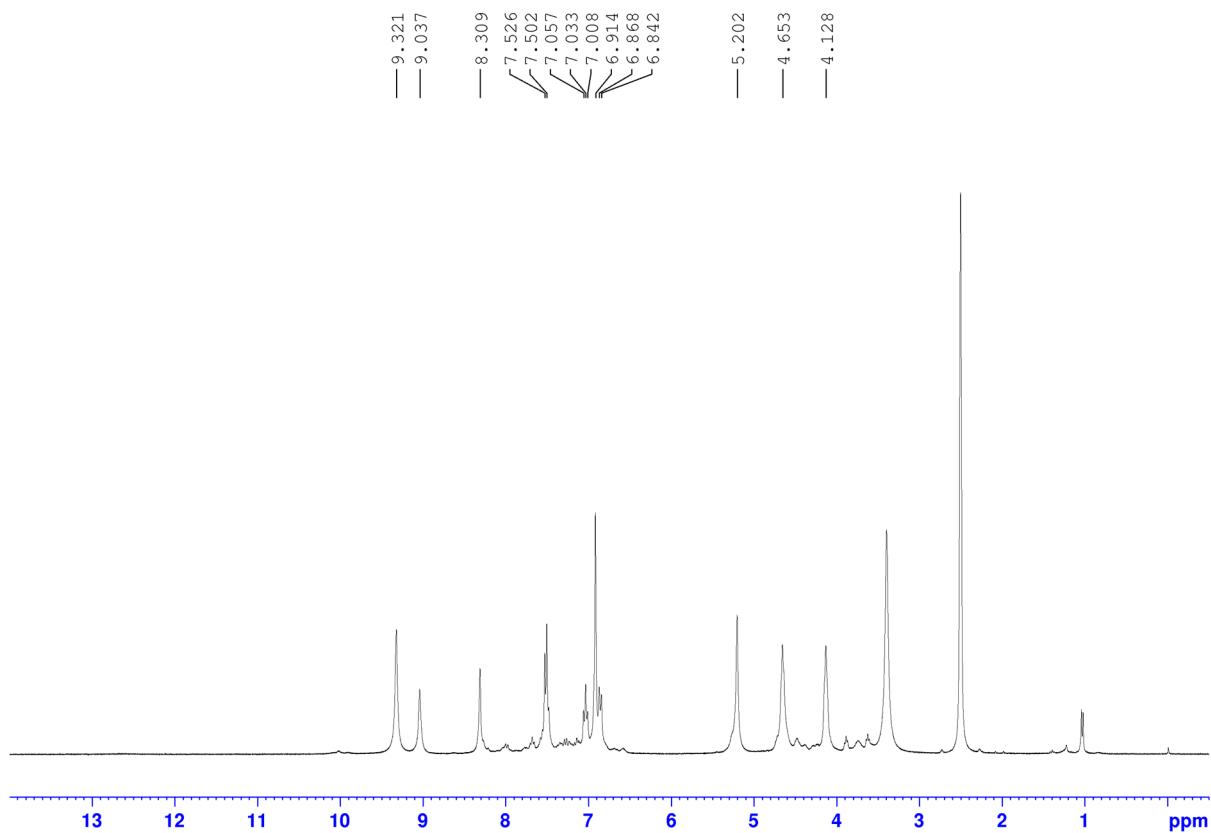


HRMS

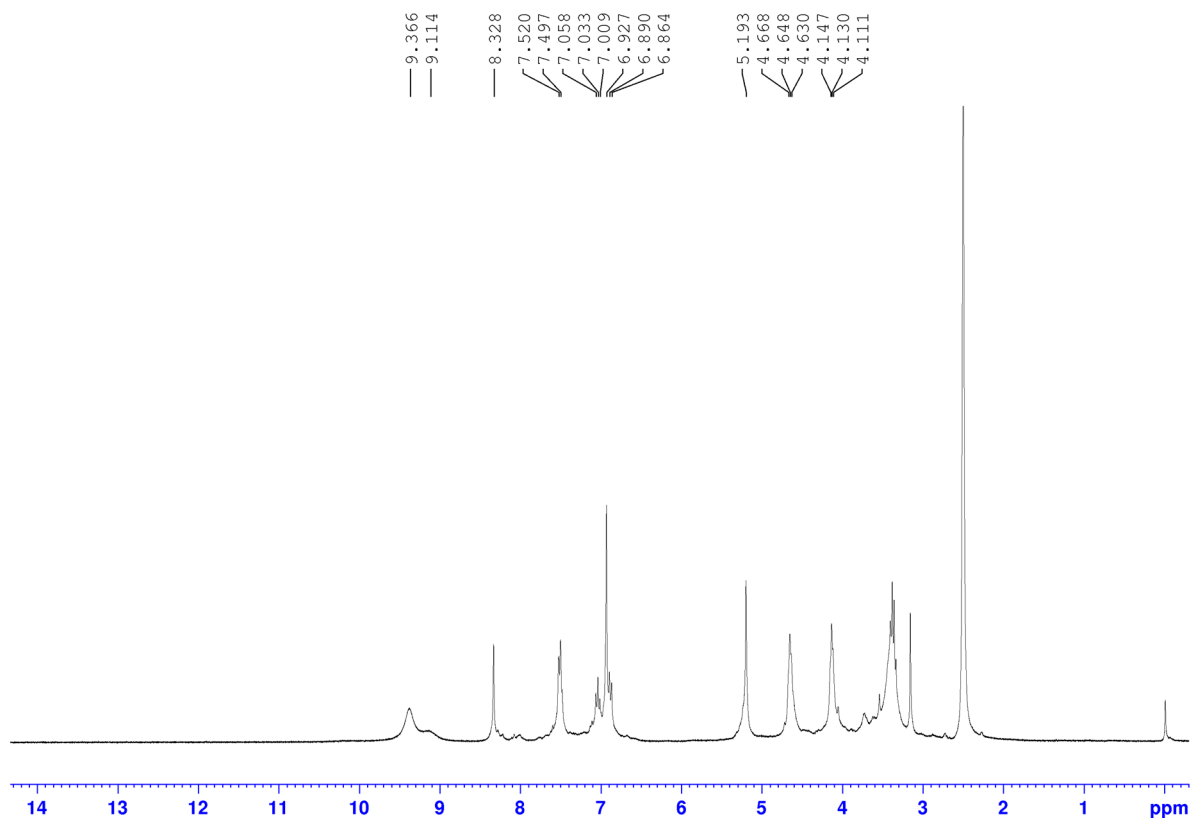


¹H NMR (300 MHz) spectra of crude of the model reaction for synthesis of 23

- Optimized reaction conditions



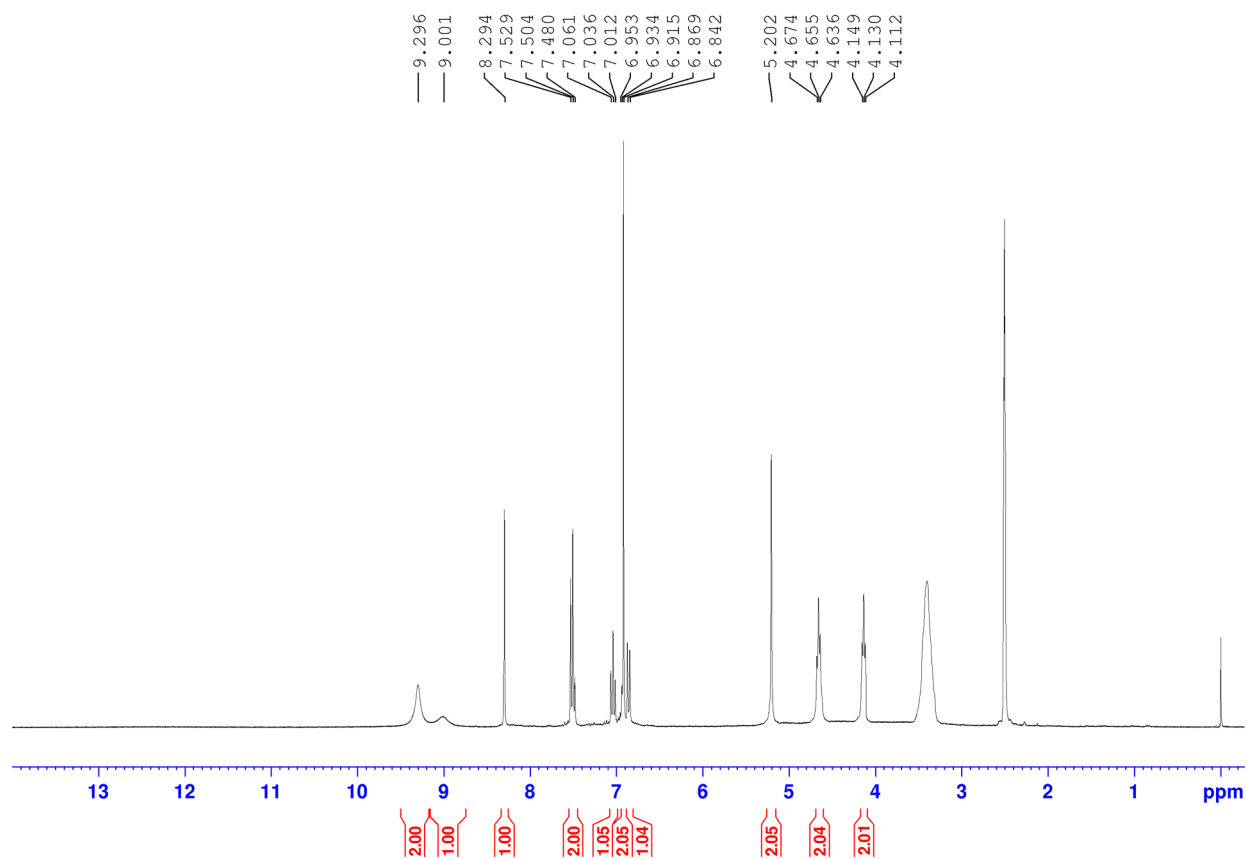
- Gram-Scale reaction



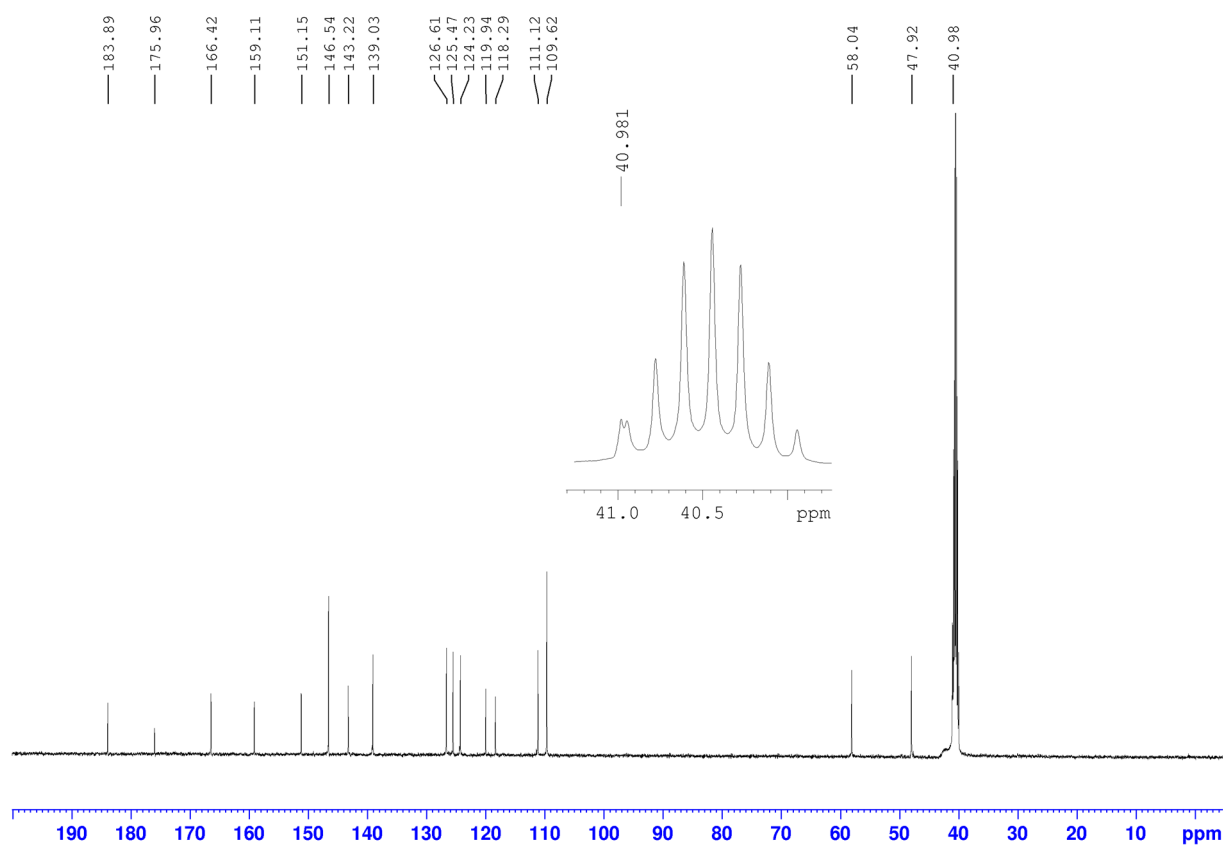
Characterization spectra of hybrid molecules 23-34

(1-(2-(isatin-1-yl)ethyl)-1,2,3-triazol-4-yl)methyl 3,4,5-trihydroxybenzoate (23)

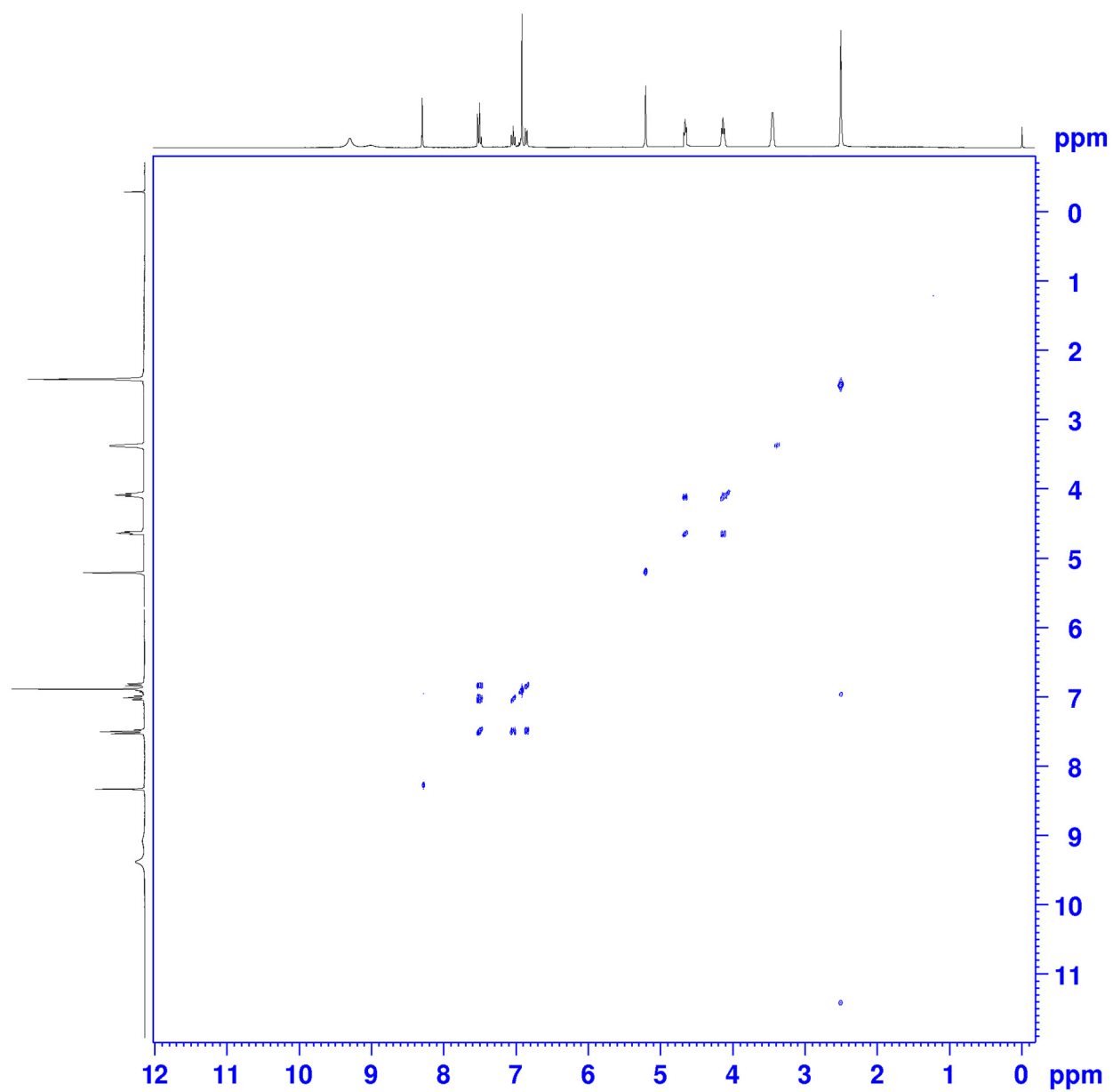
^1H NMR (300 MHz)



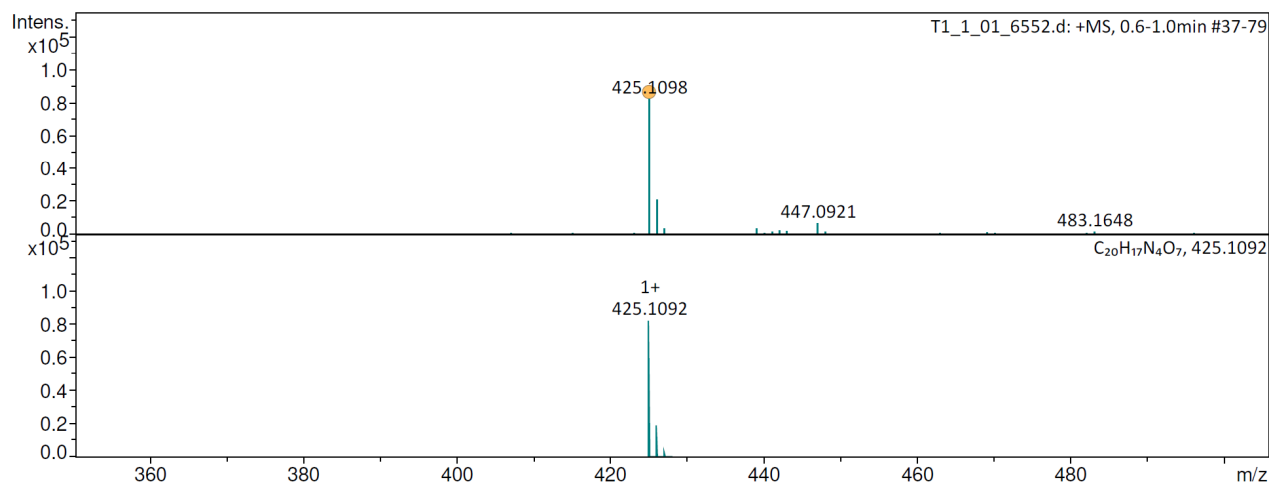
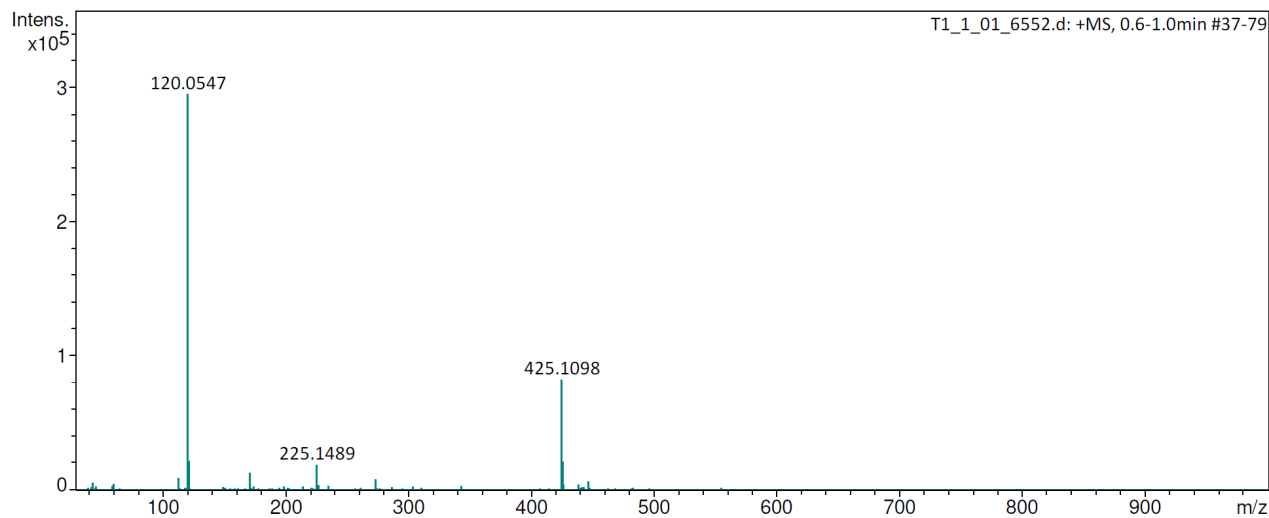
^{13}C NMR (125 MHz)



COSY NMR (300 MHz)

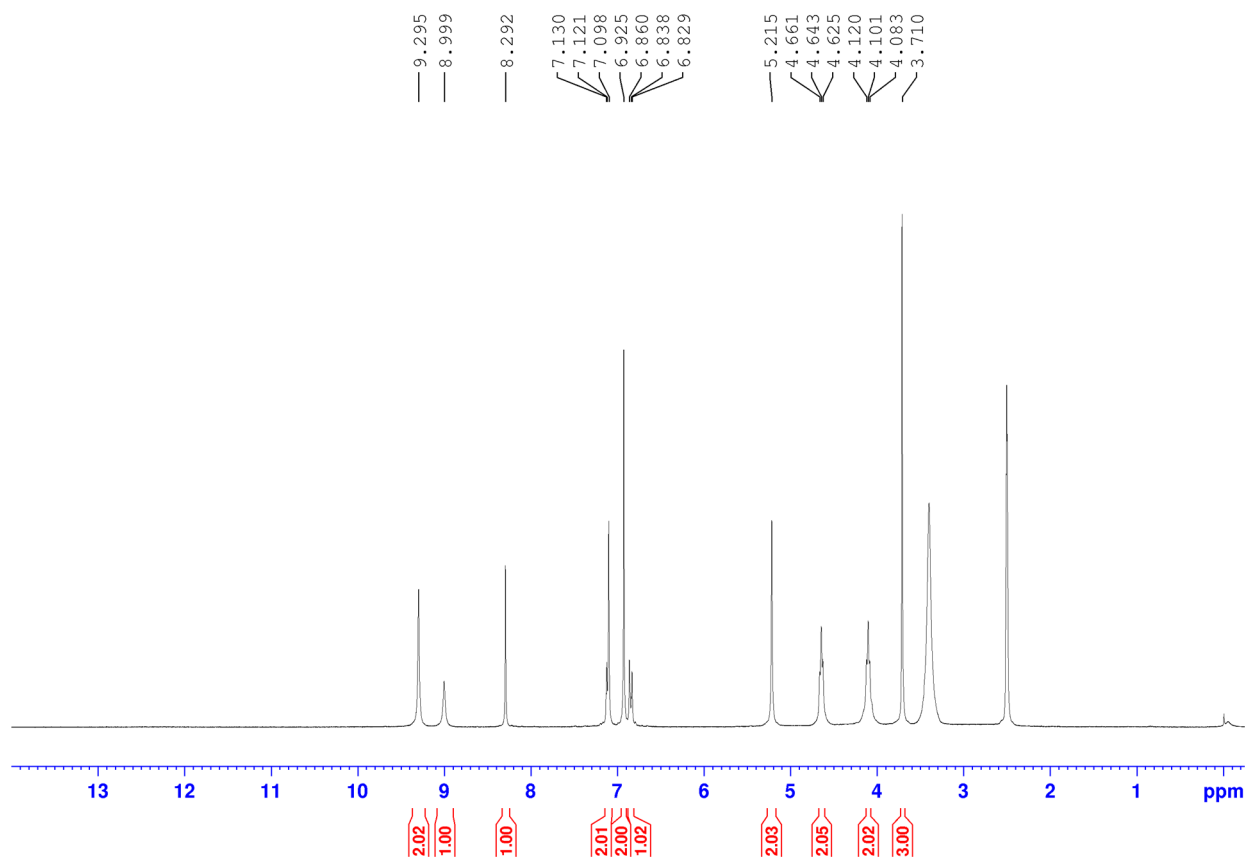


HRMS

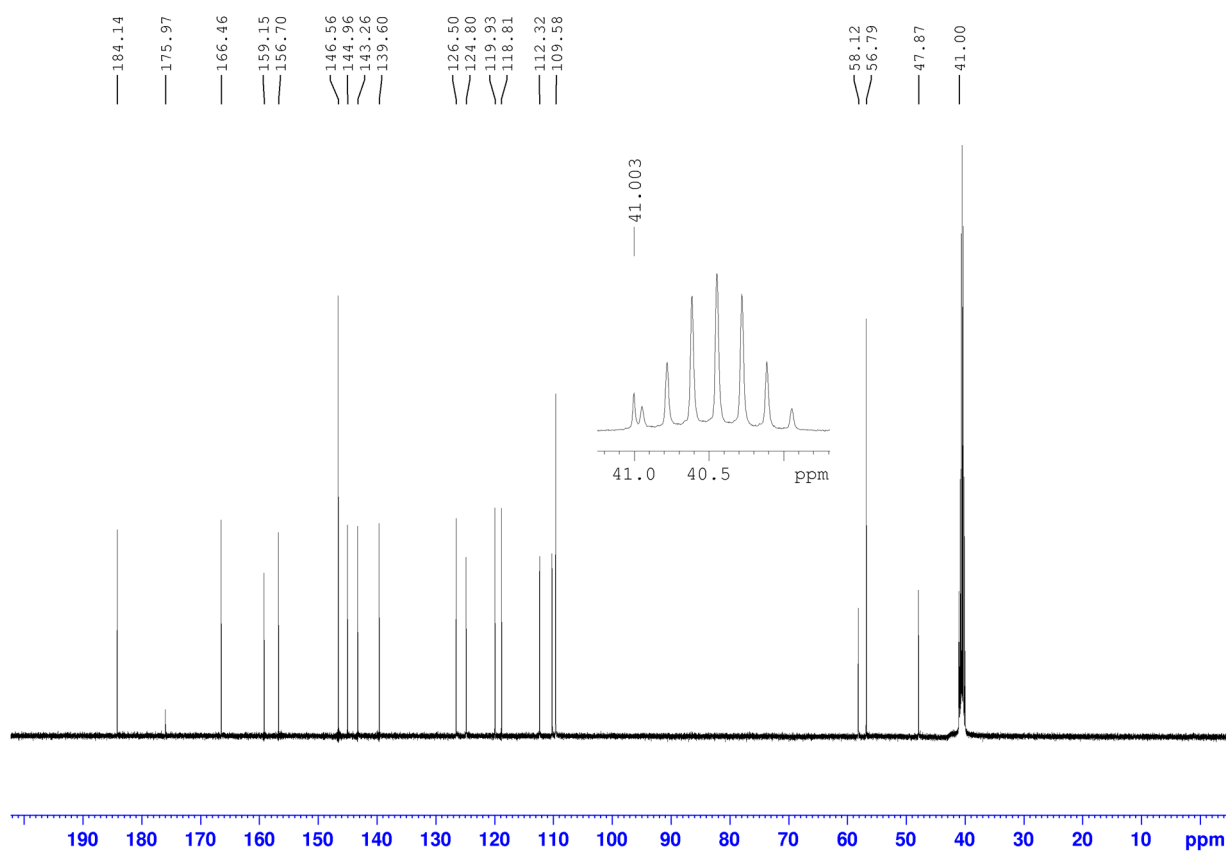


(1-(2-(5-methoxy-isatin-1-yl)ethyl)-1,2,3-triazol-4-yl)methyl 3,4,5-trihydroxybenzoate (24)

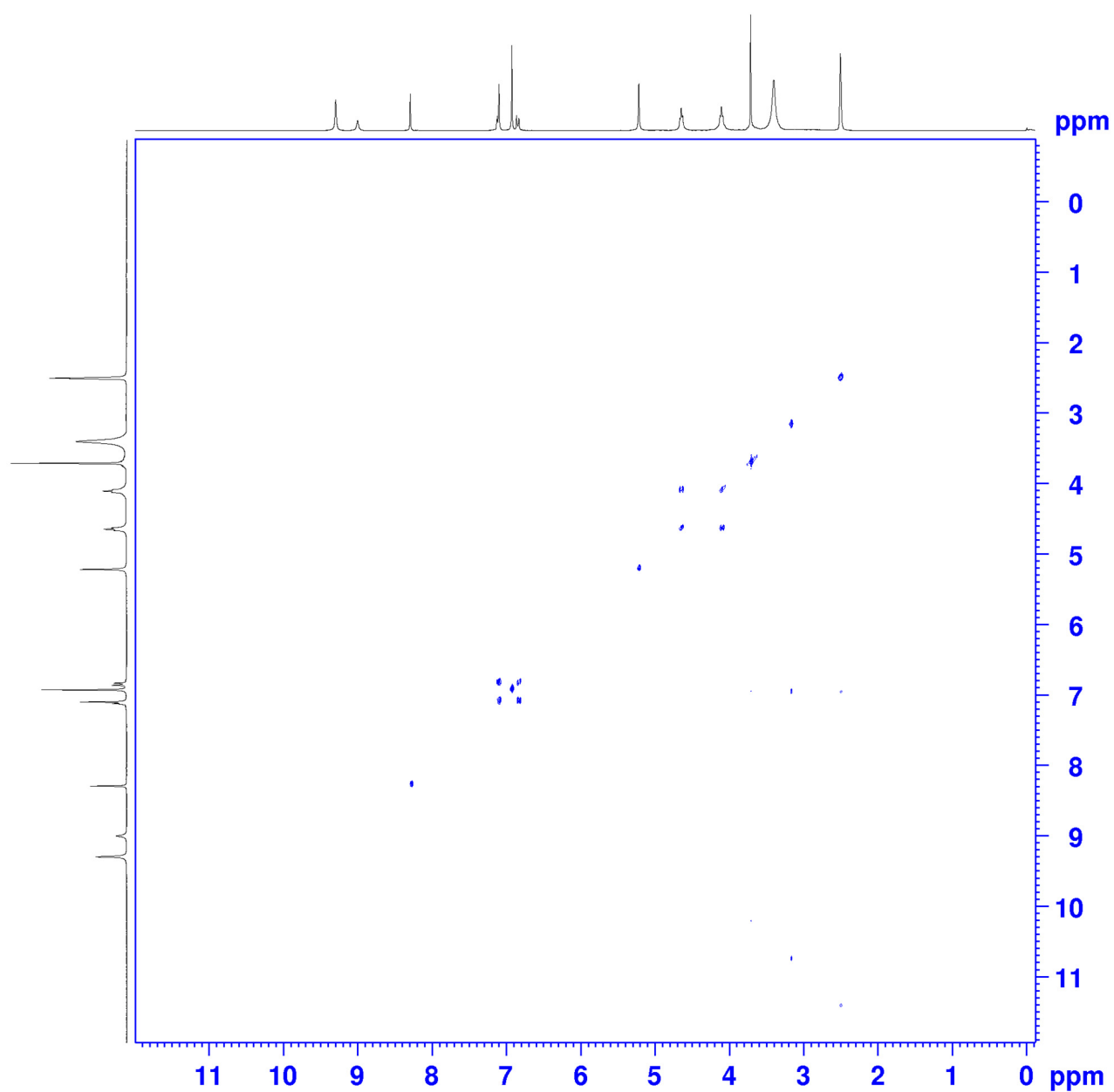
¹H NMR (300 MHz)



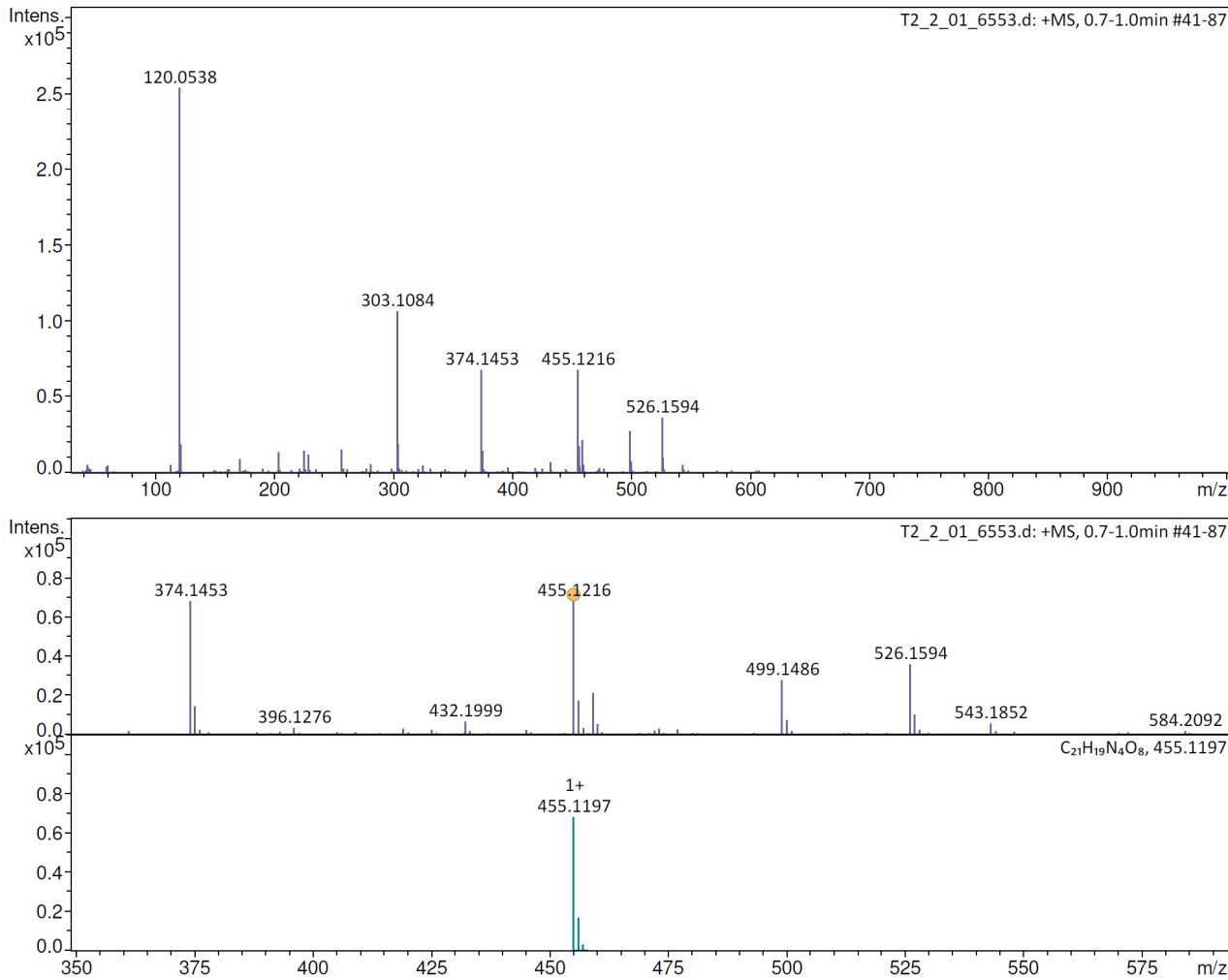
^{13}C NMR (125 MHz)



COSY NMR (300 MHz)

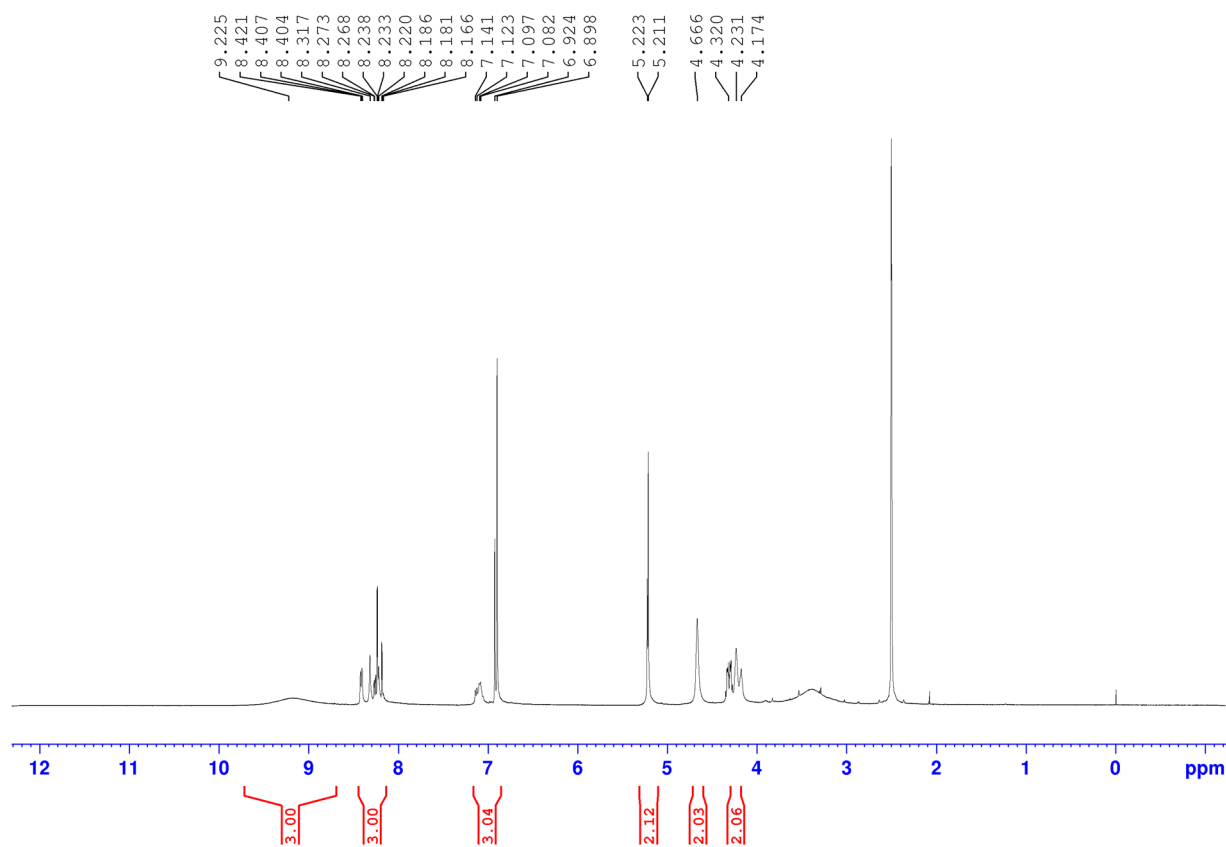


HRMS

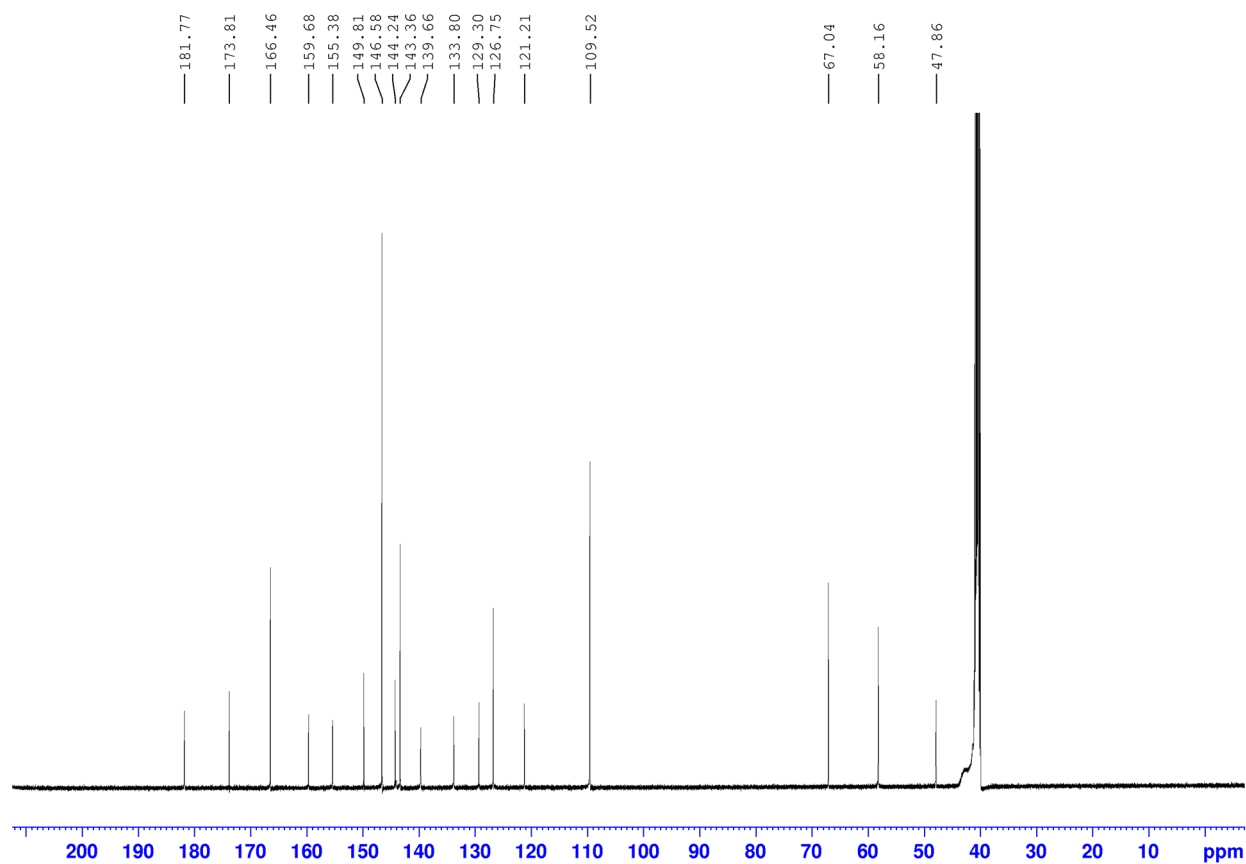


(1-(2-(5-nitro-isatin-1-yl)ethyl)-1,2,3-triazol-4-yl)methyl 3,4,5-trihydroxybenzoate (25)

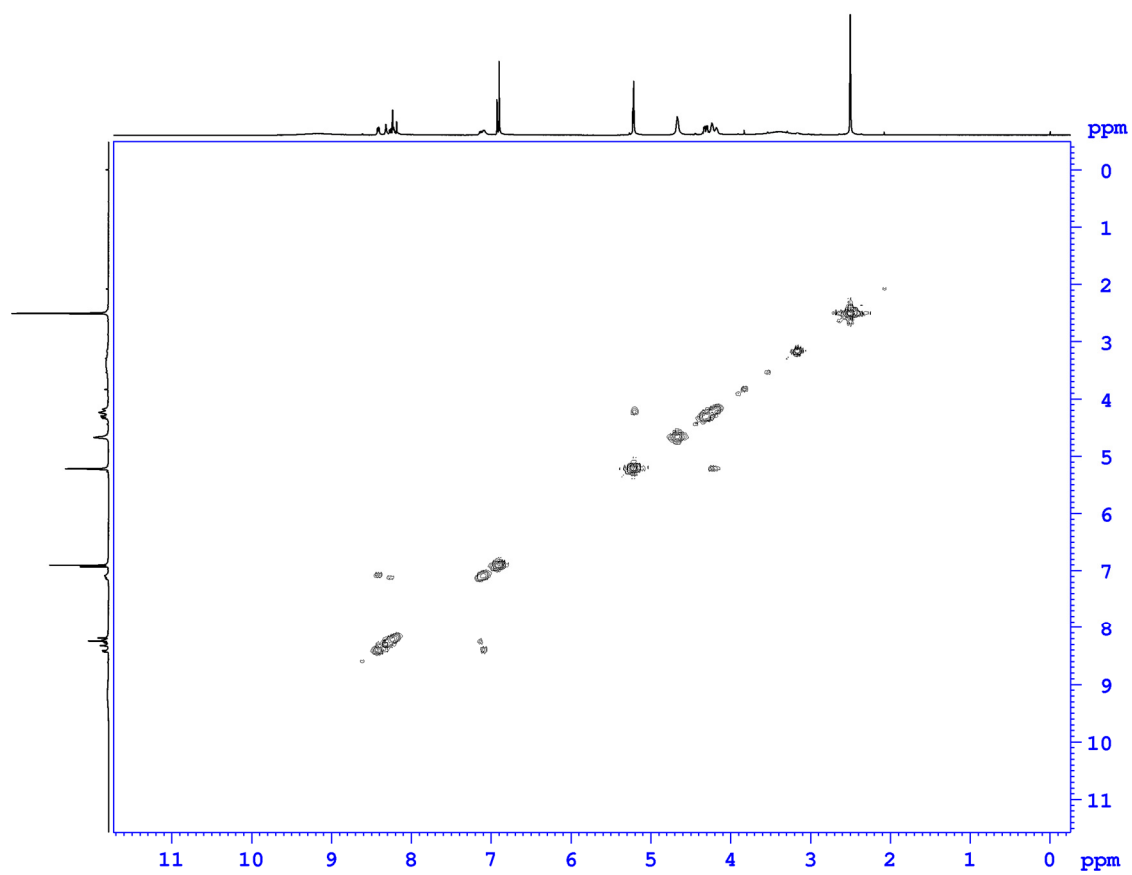
¹H NMR (300 MHz)



^{13}C NMR (125 MHz)

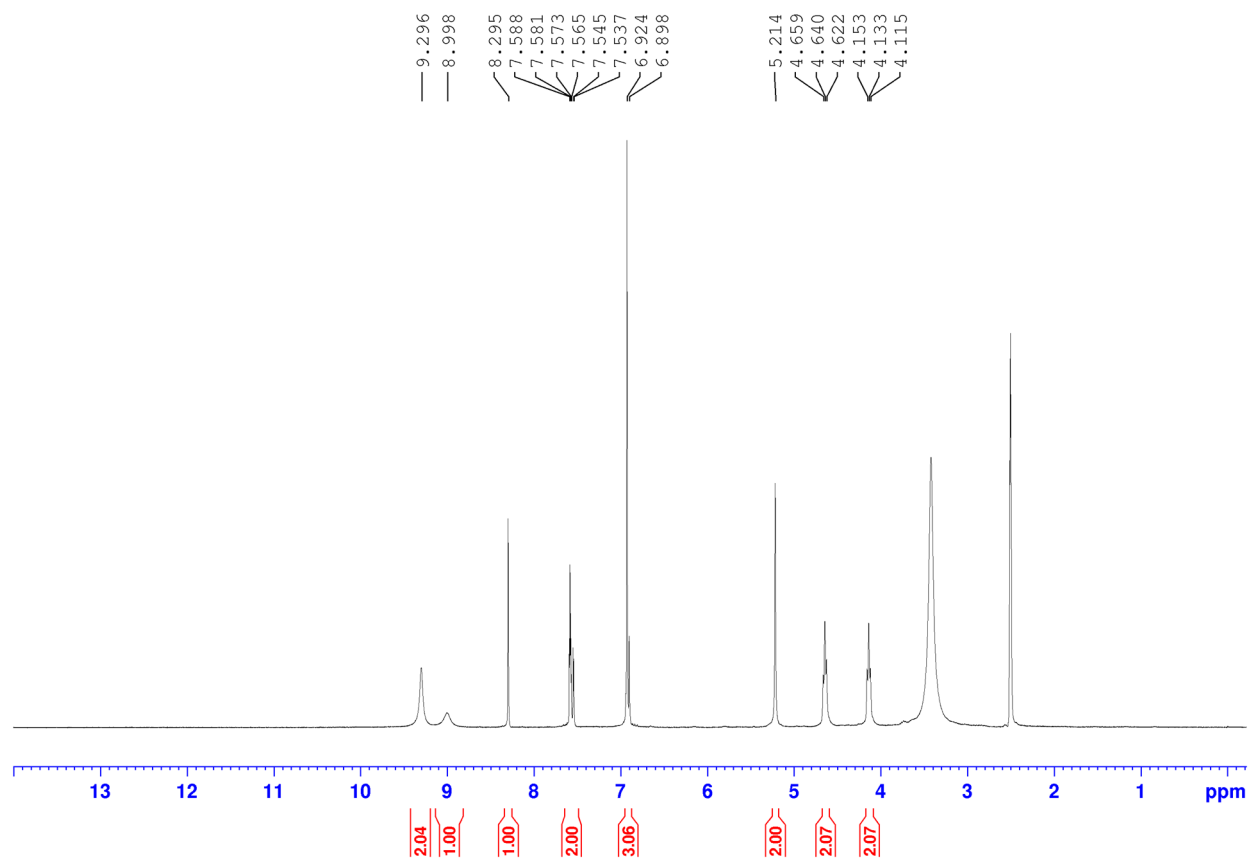


COSY NMR (300 MHz)

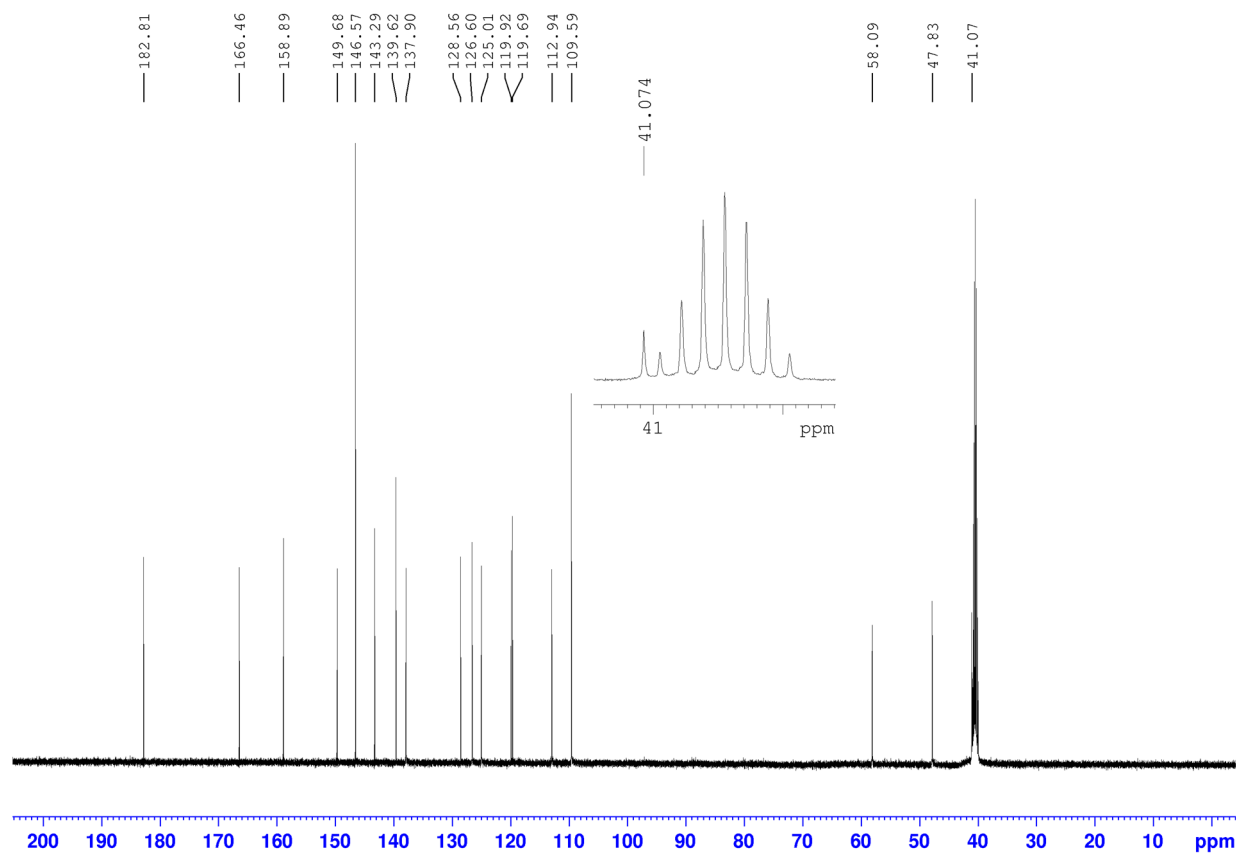


(1-(2-(5-chloro-isatin-1-yl)ethyl)-1,2,3-triazol-4-yl)methyl 3,4,5-trihydroxybenzoate (26)

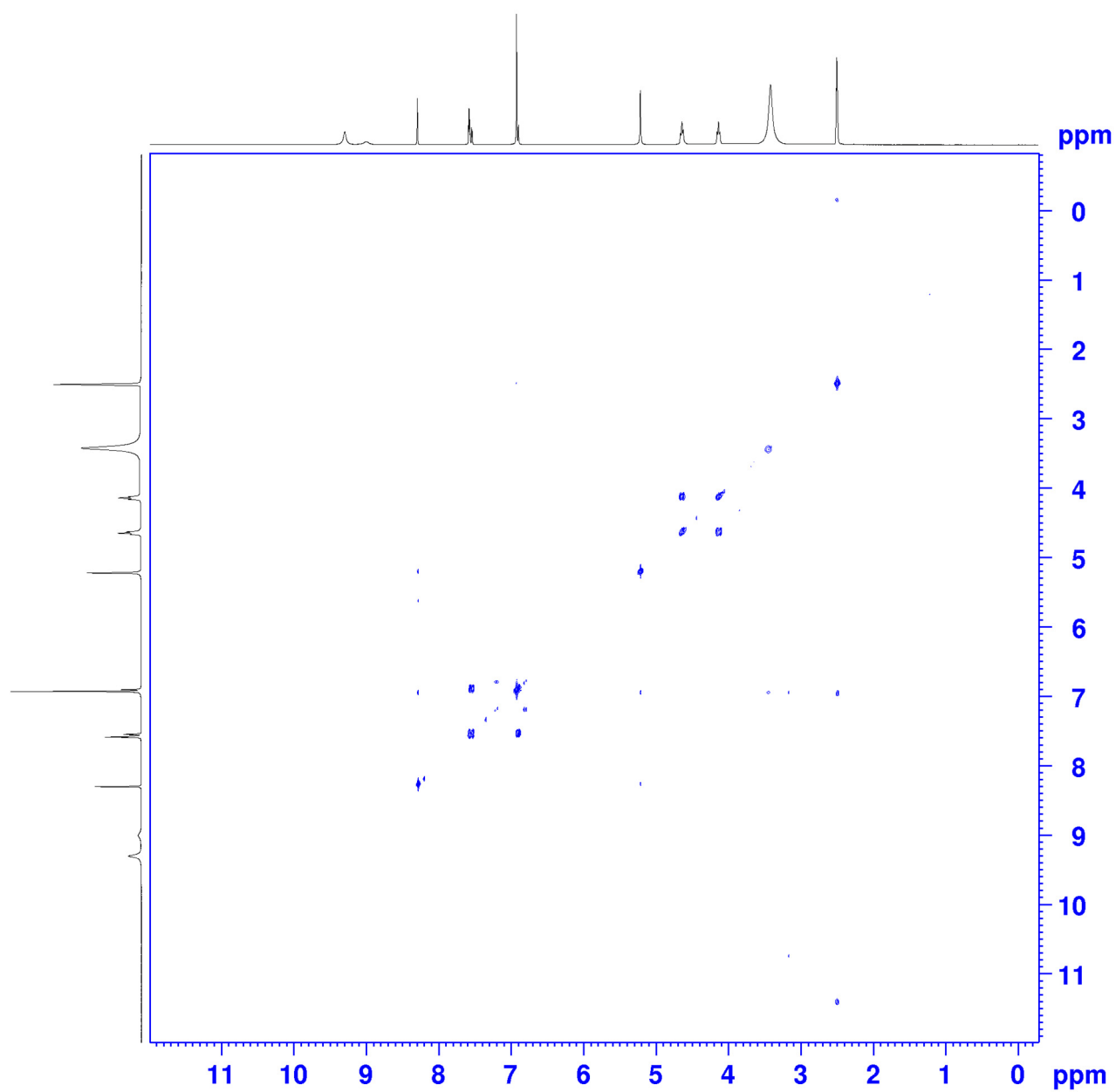
¹H NMR (300 MHz)



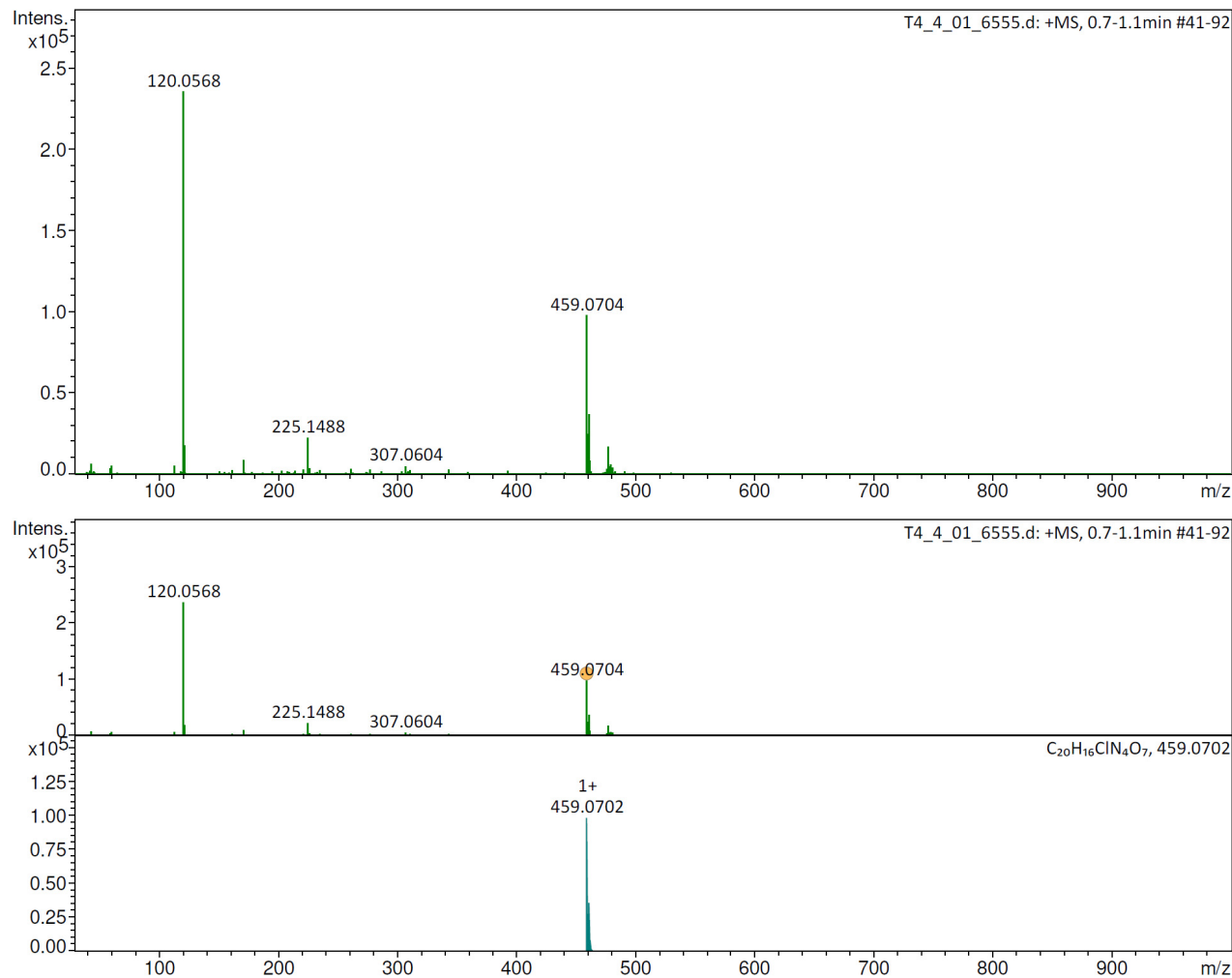
^{13}C NMR (125 MHz)



COSY NMR (300 MHz)

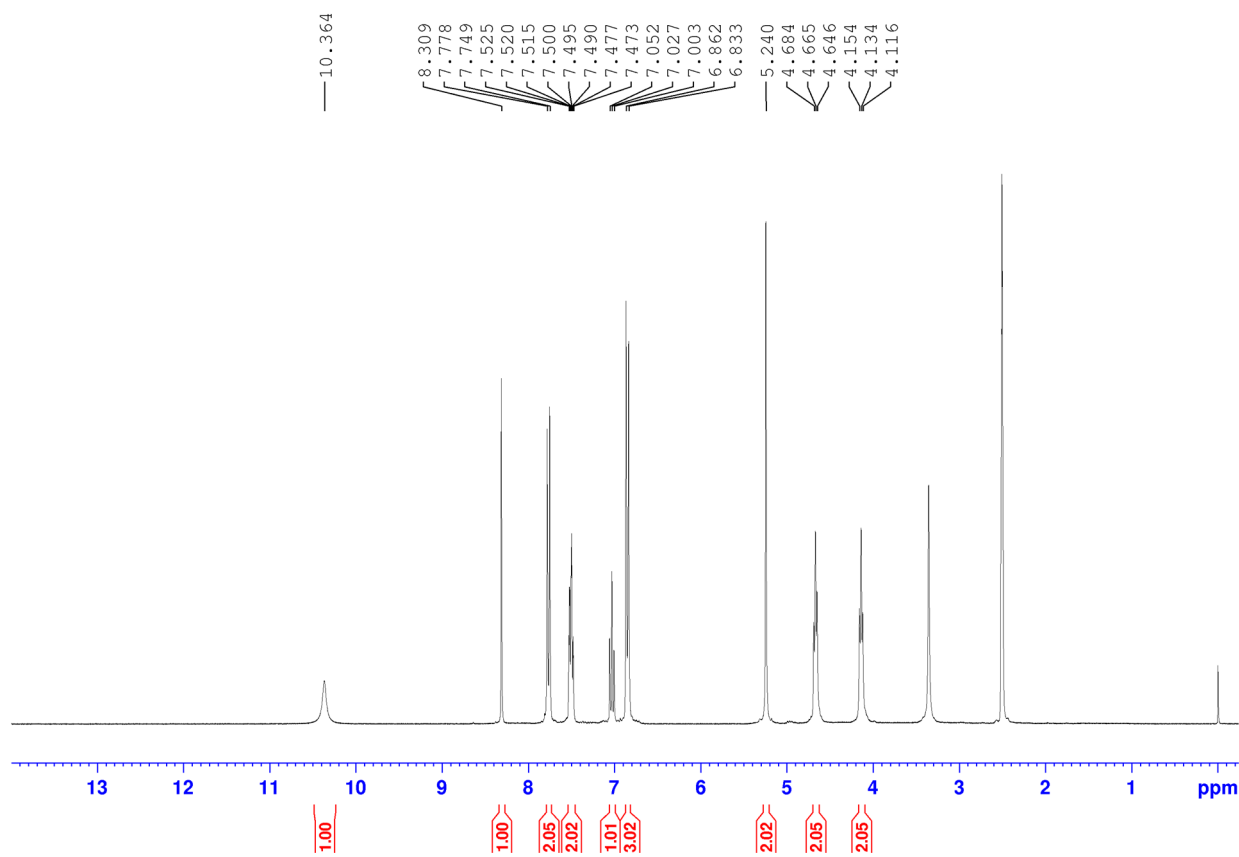


HRMS

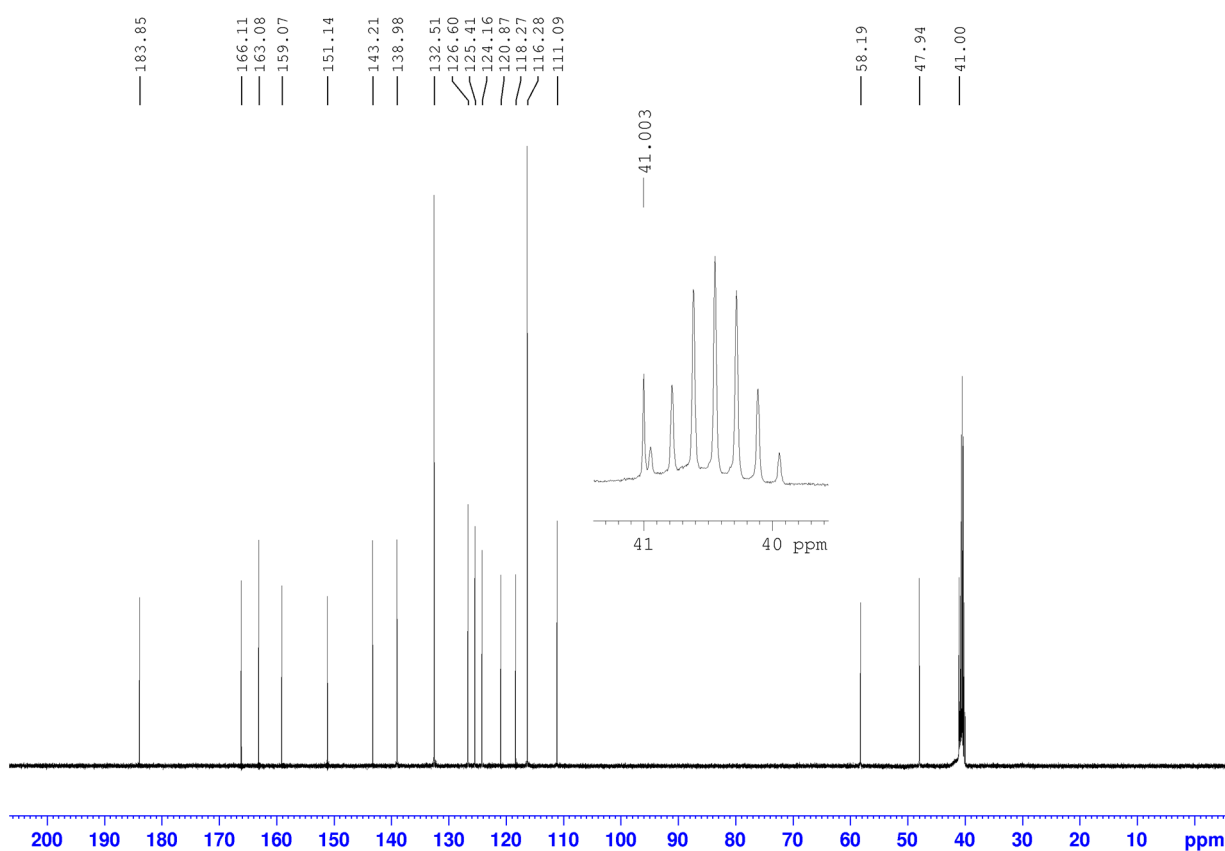


(1-(2-(isatin-1-yl)ethyl)-1,2,3-triazol-4-yl)methyl 4-hydroxybenzoate (27)

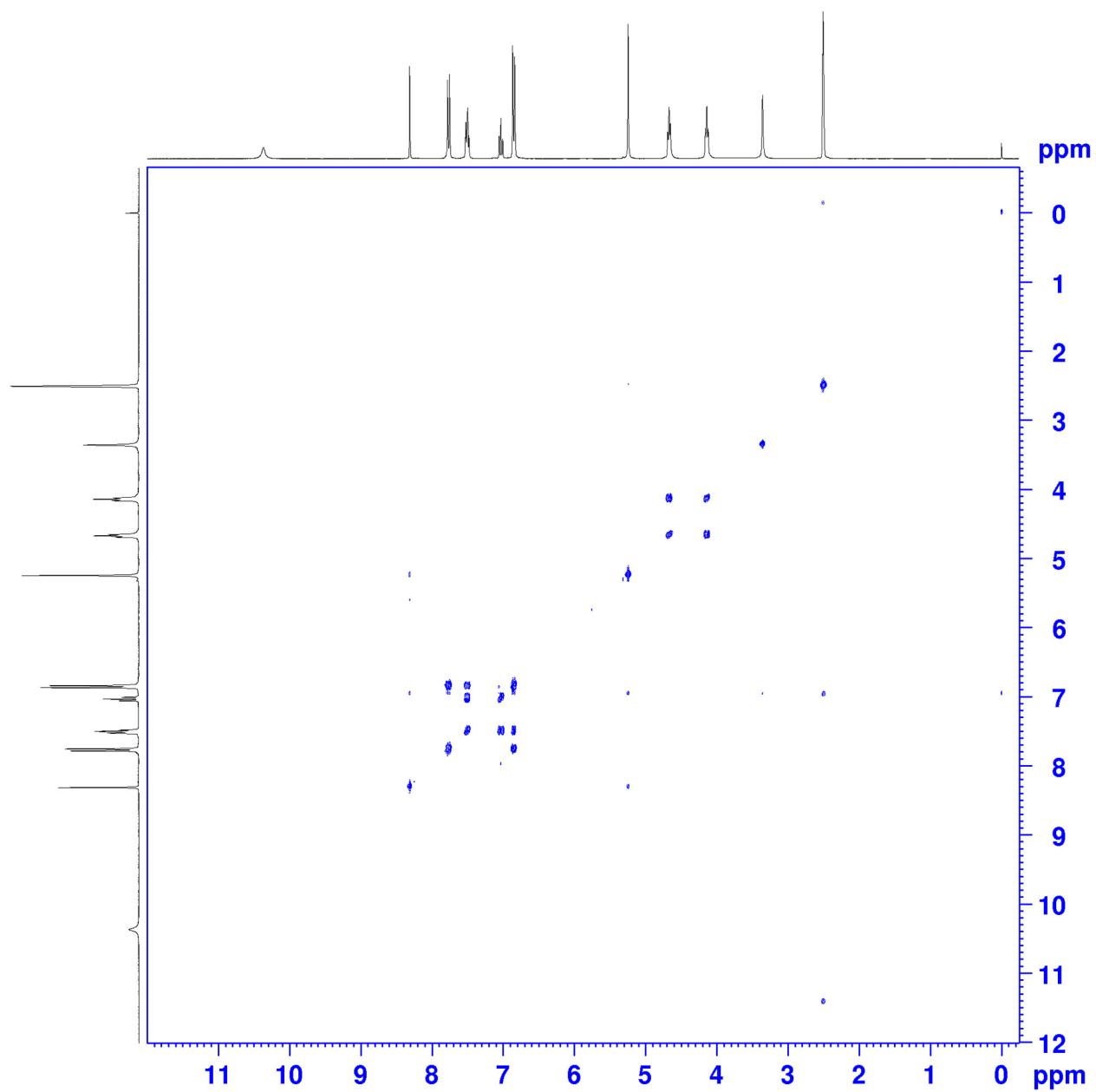
¹H NMR (300 MHz)



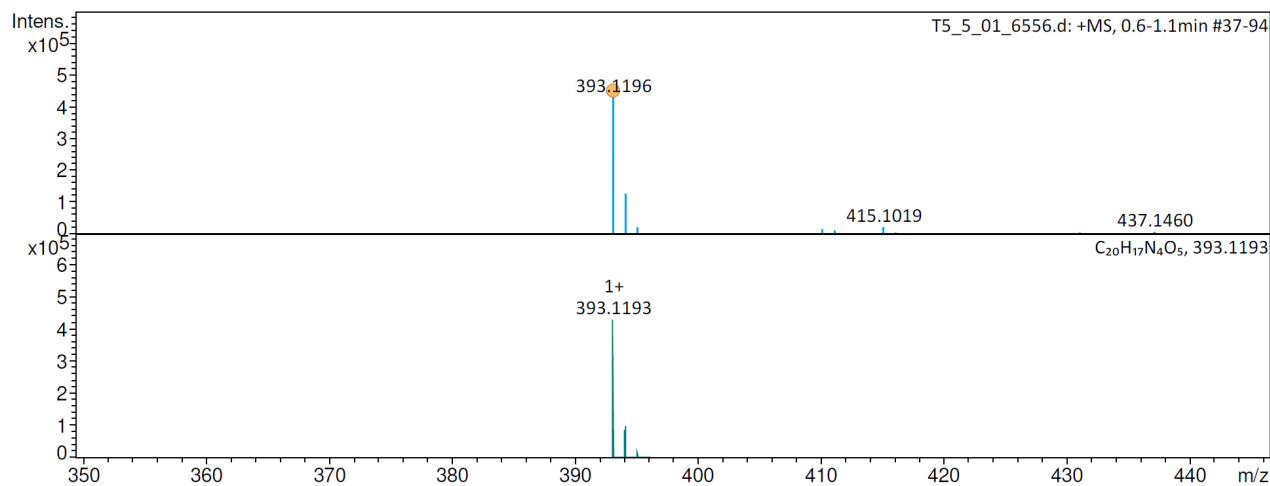
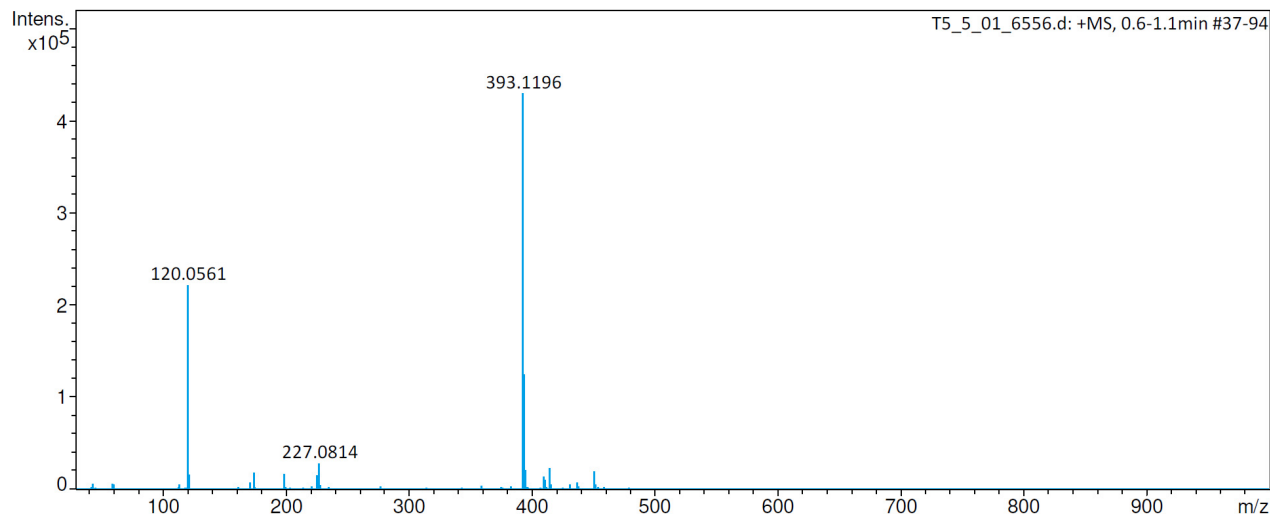
^{13}C NMR (125 MHz)



COSY NMR (300 MHz)

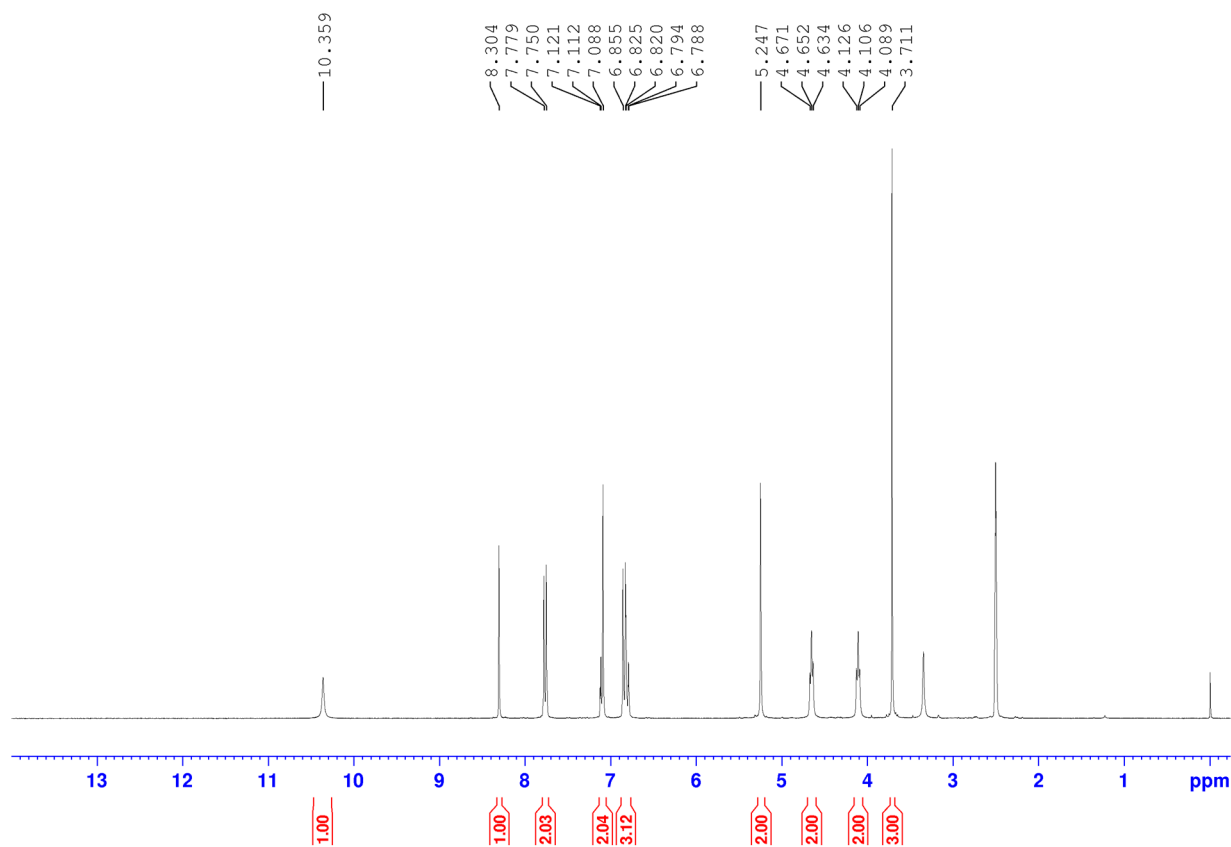


HRMS

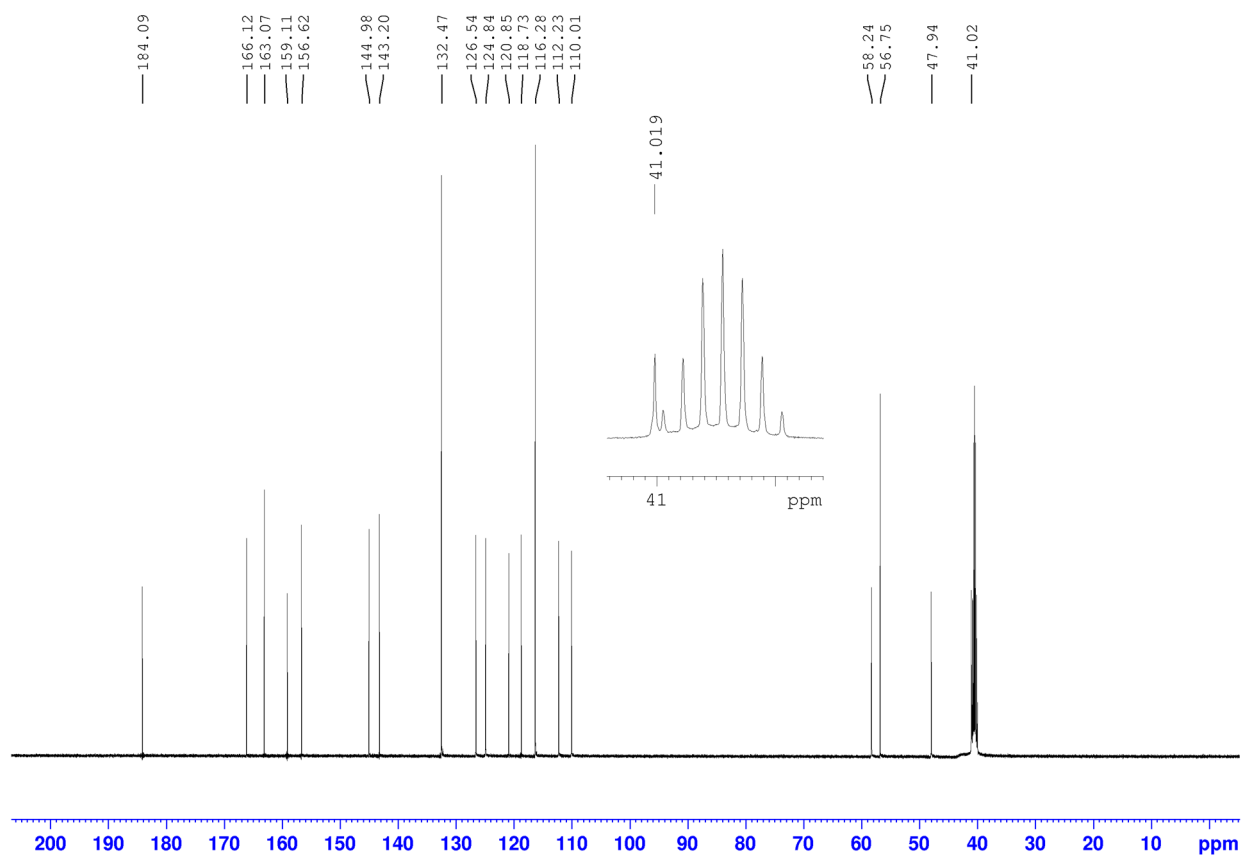


(1-(2-(5-methoxy-isatin-1-yl)ethyl)-1,2,3-triazol-4-yl)methyl 4-hydroxybenzoate (28)

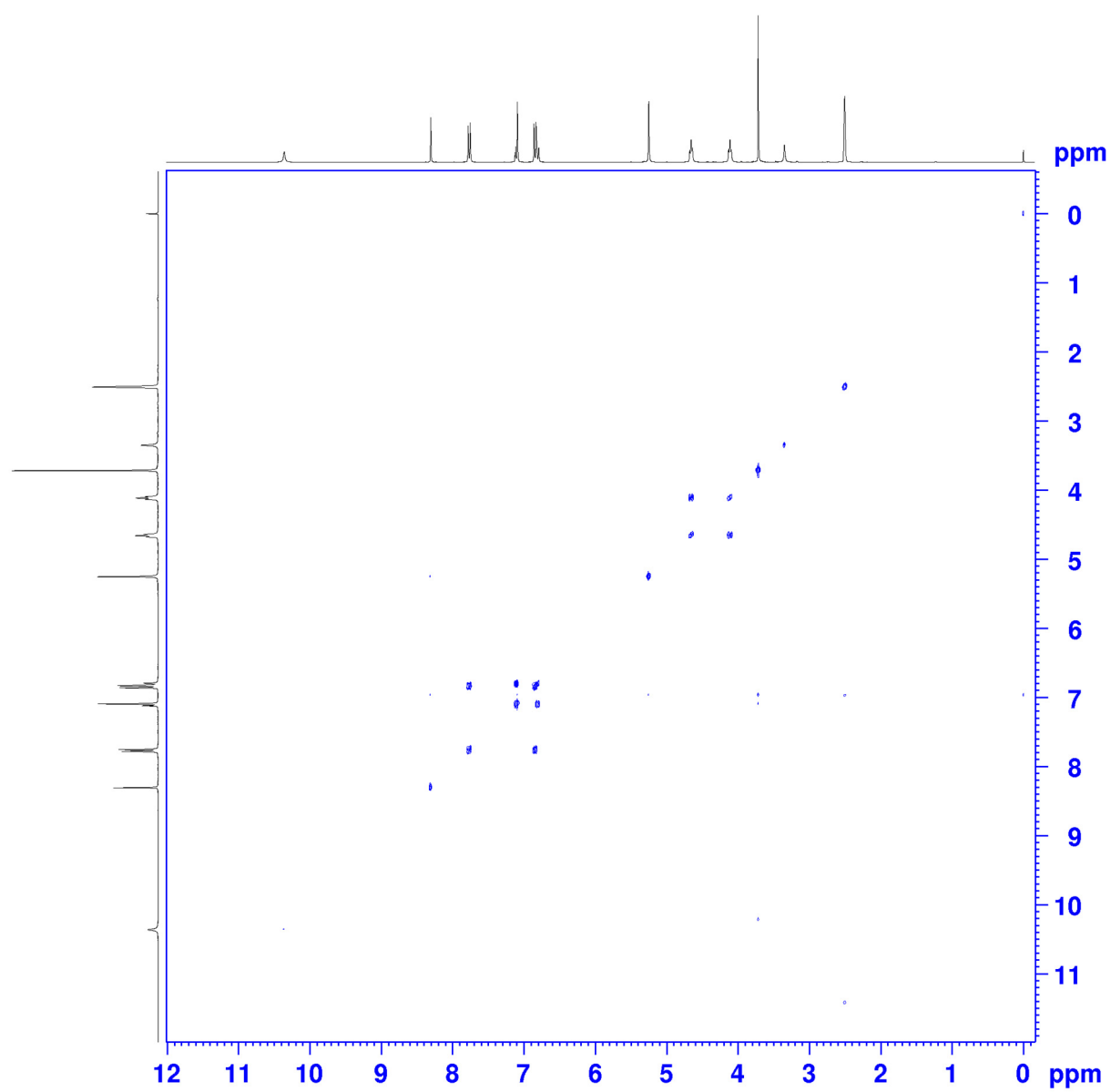
¹H NMR (300 MHz)



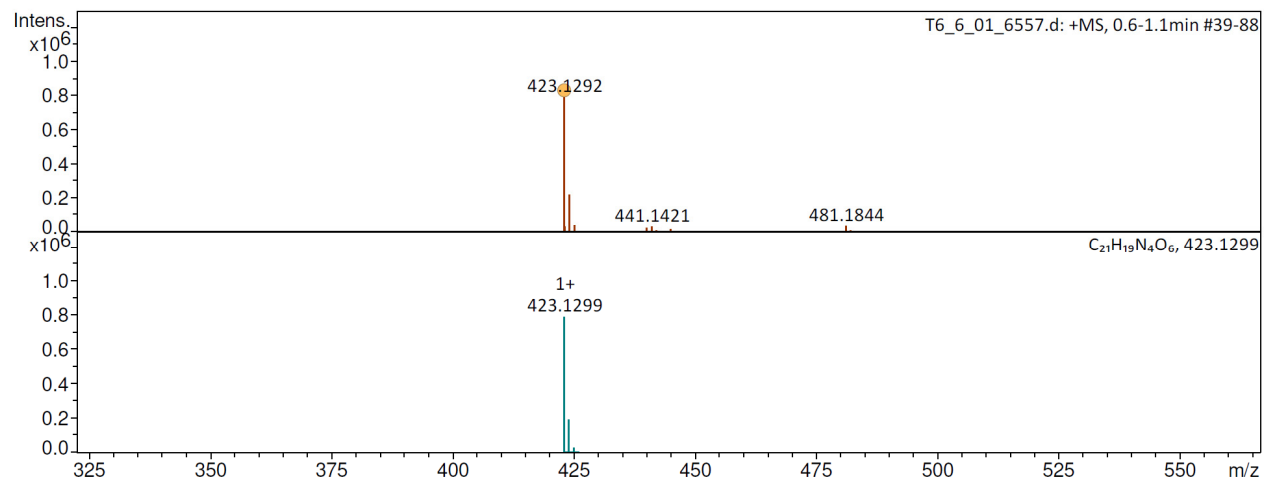
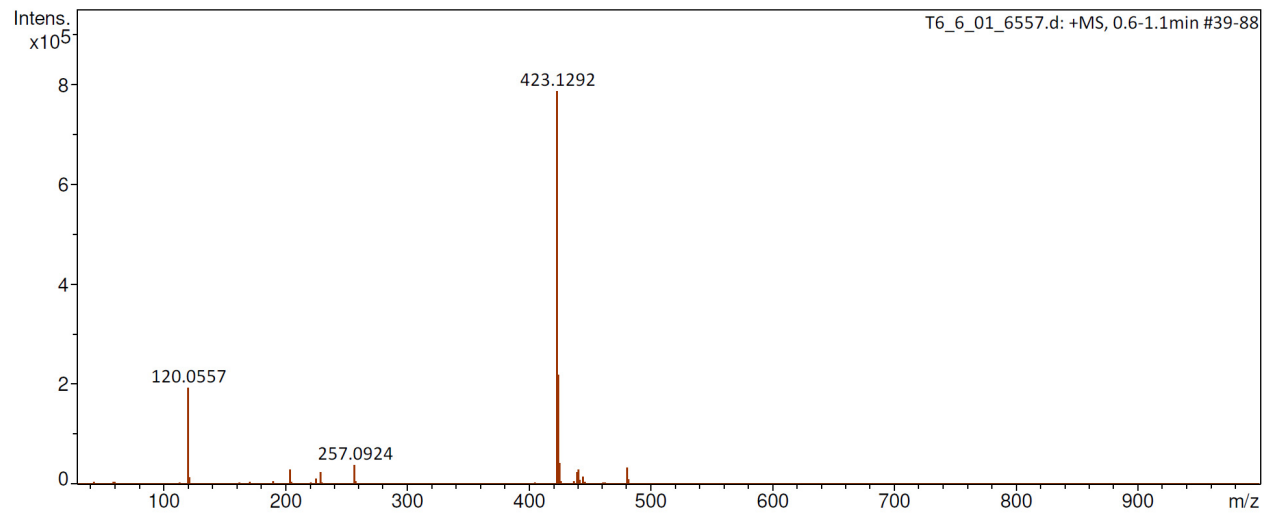
^{13}C NMR (125 MHz)



COSY NMR (300 MHz)

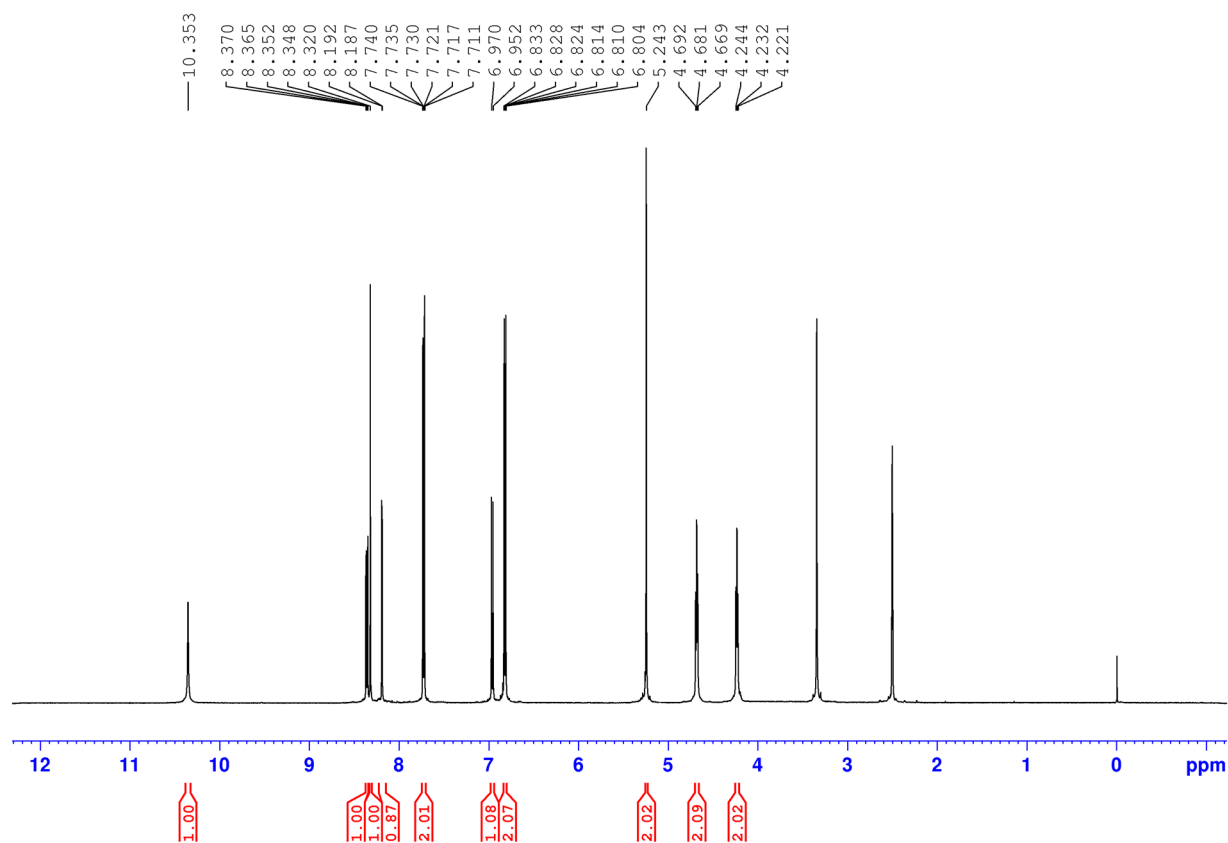


HRMS

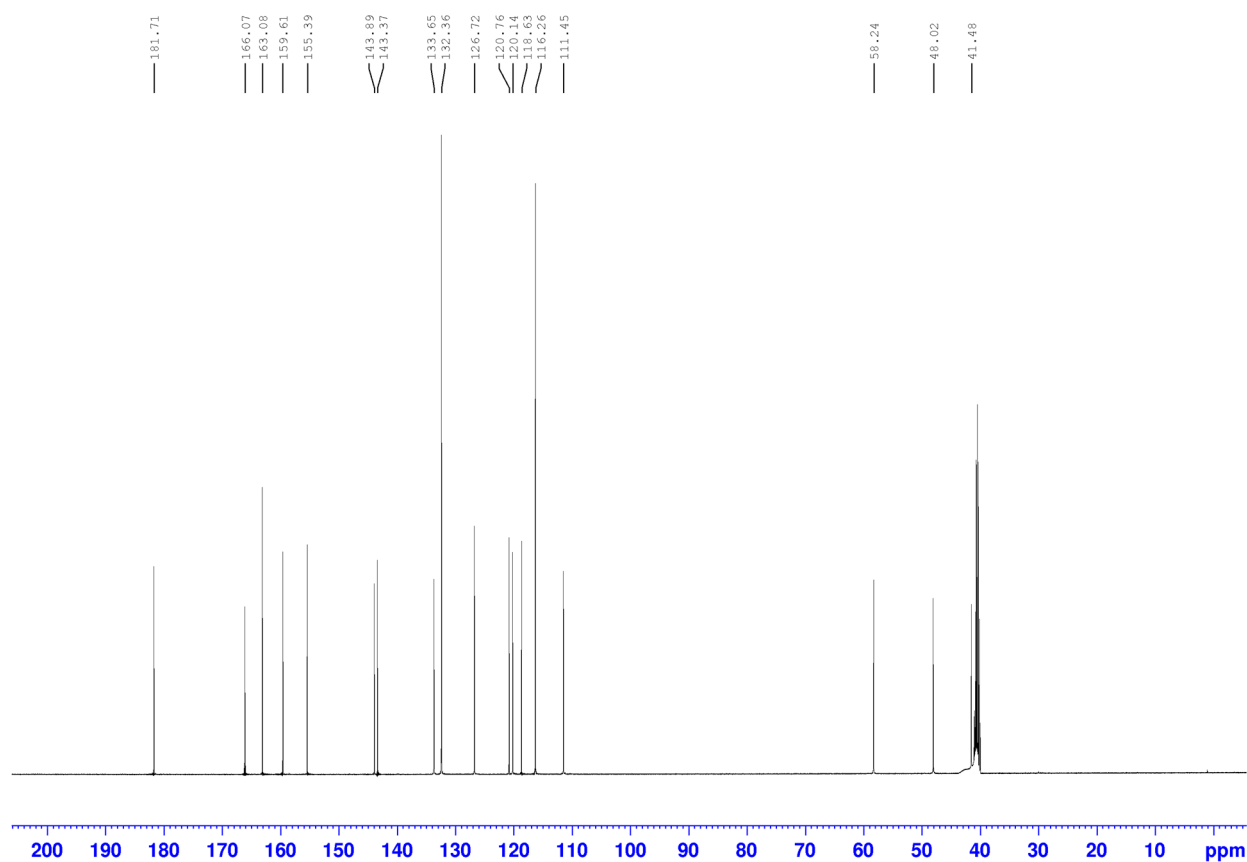


(1-(2-(5-nitro-isatin-1-yl)ethyl)-1,2,3-triazol-4-yl)methyl 4-hydroxybenzoate (29)

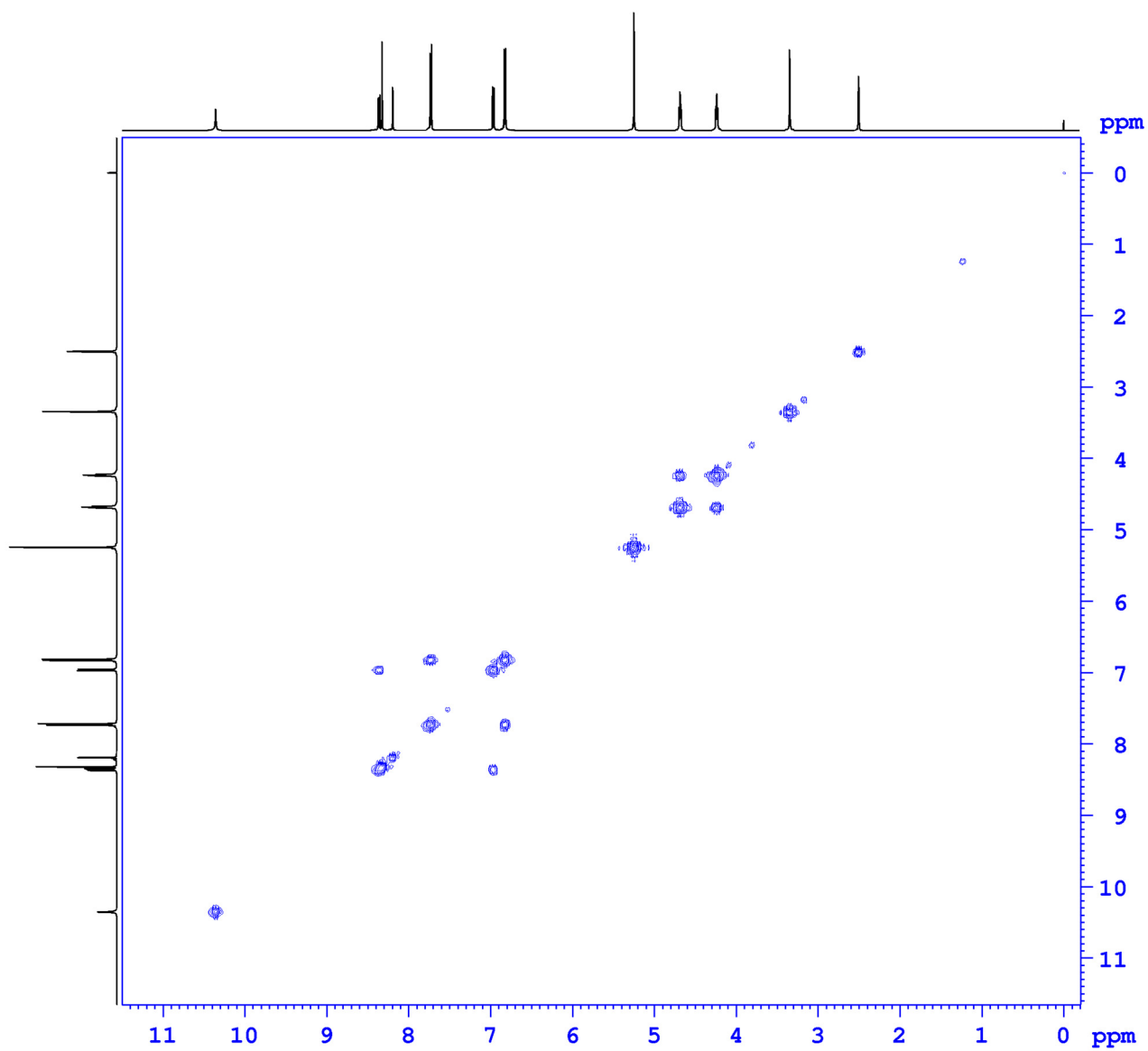
¹H NMR (500 MHz)



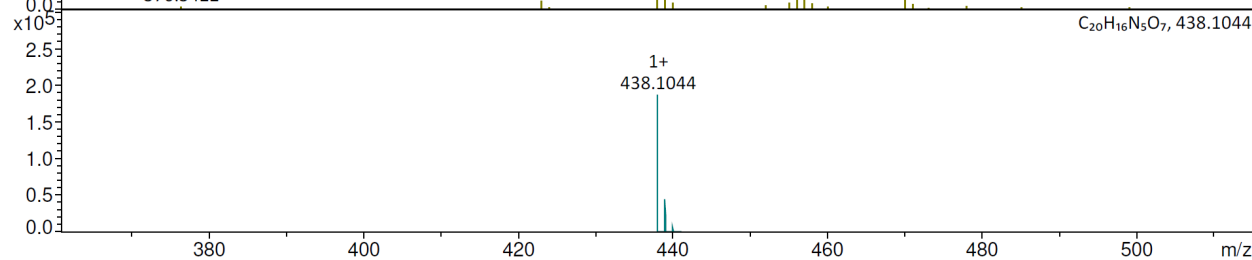
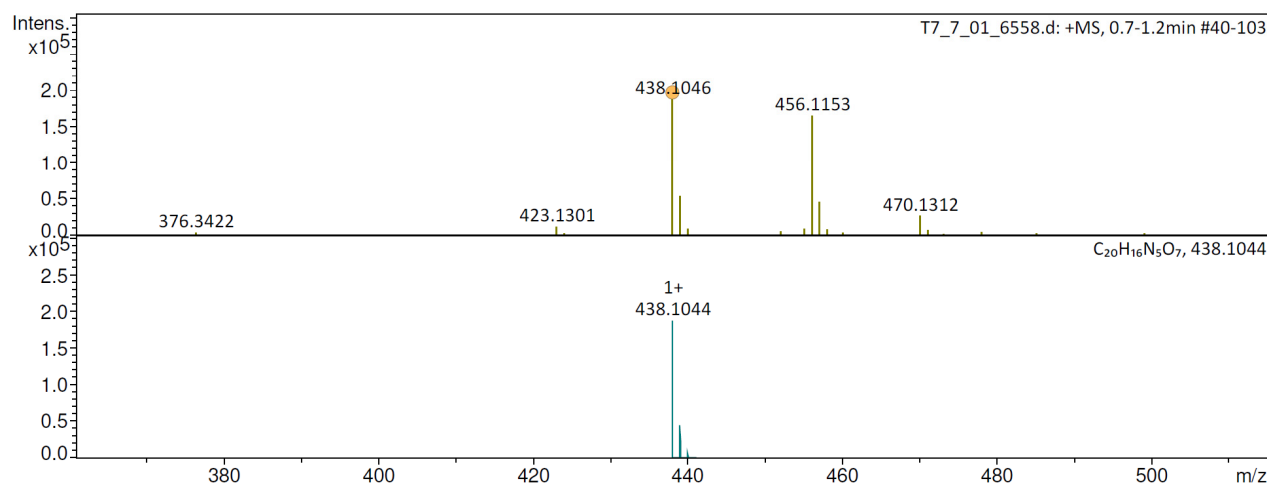
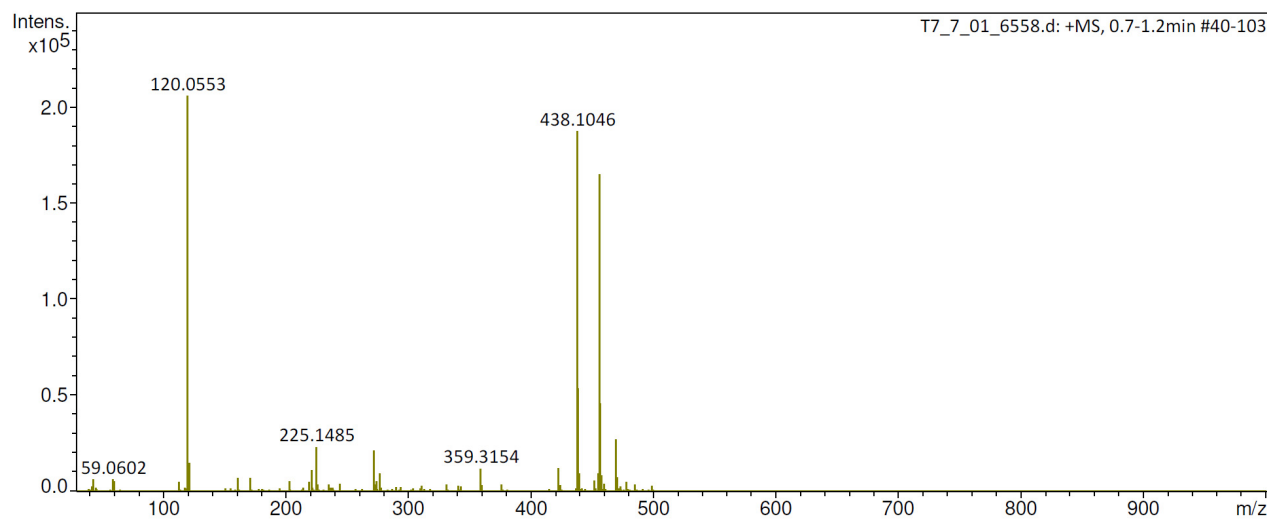
¹³C NMR (125 MHz)



COSY NMR (500 MHz)

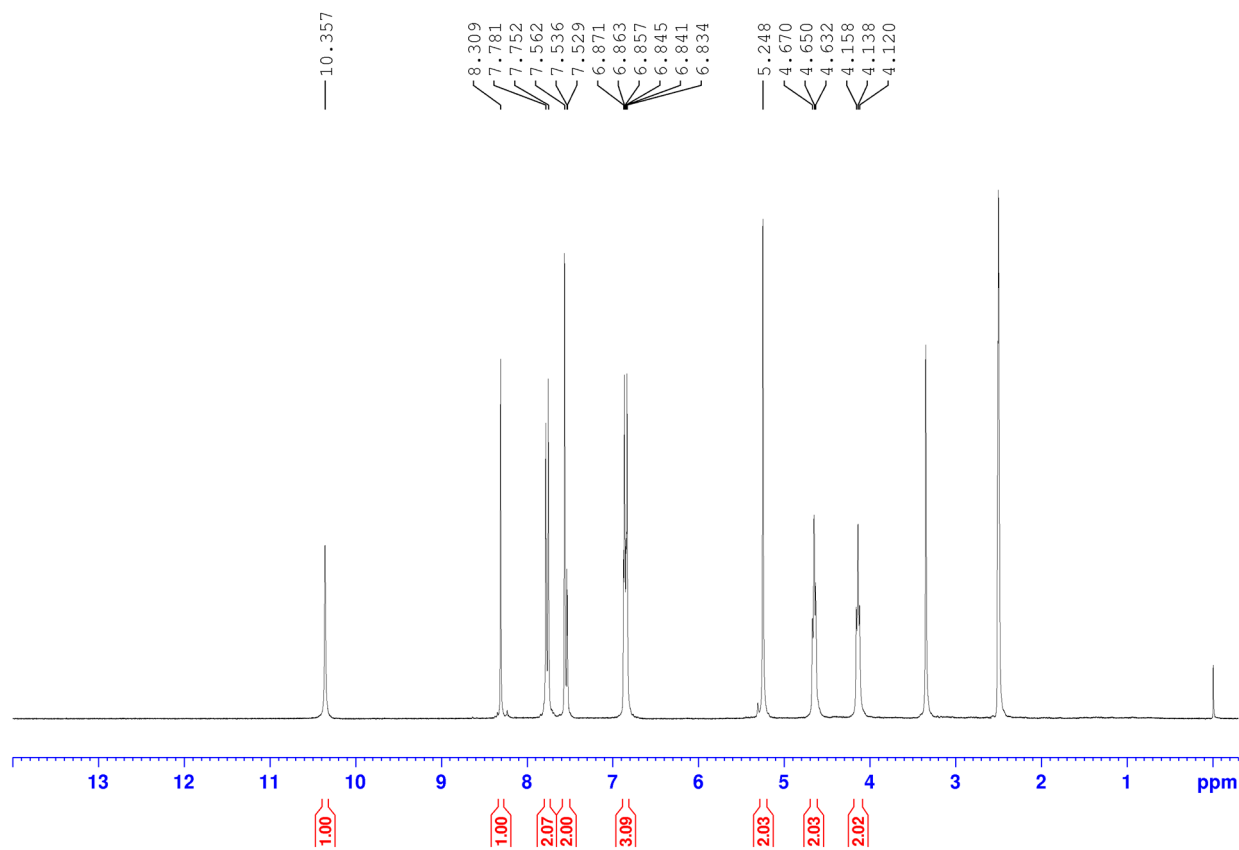


HRMS

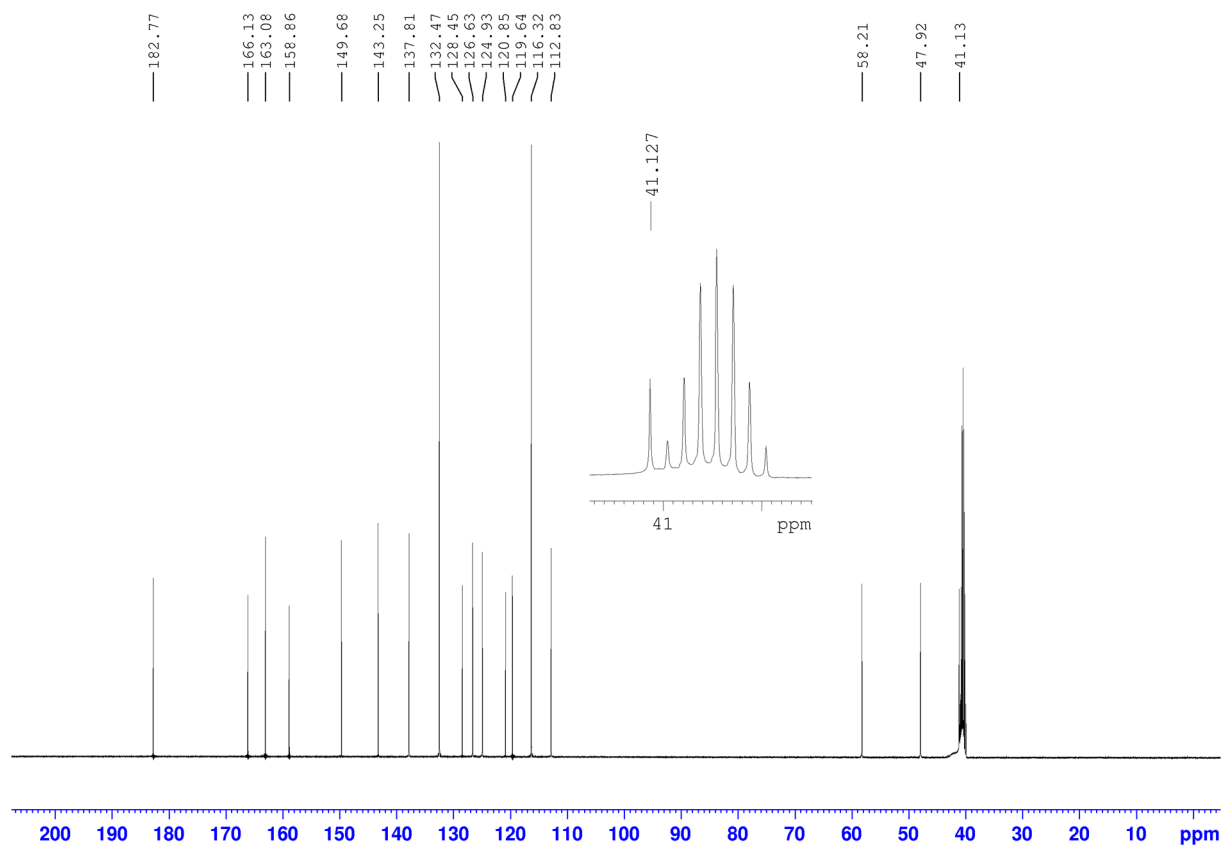


(1-(2-(5-chloro-isatin-1-yl)ethyl)-1,2,3-triazol-4-yl)methyl 4-hydroxybenzoate (30)

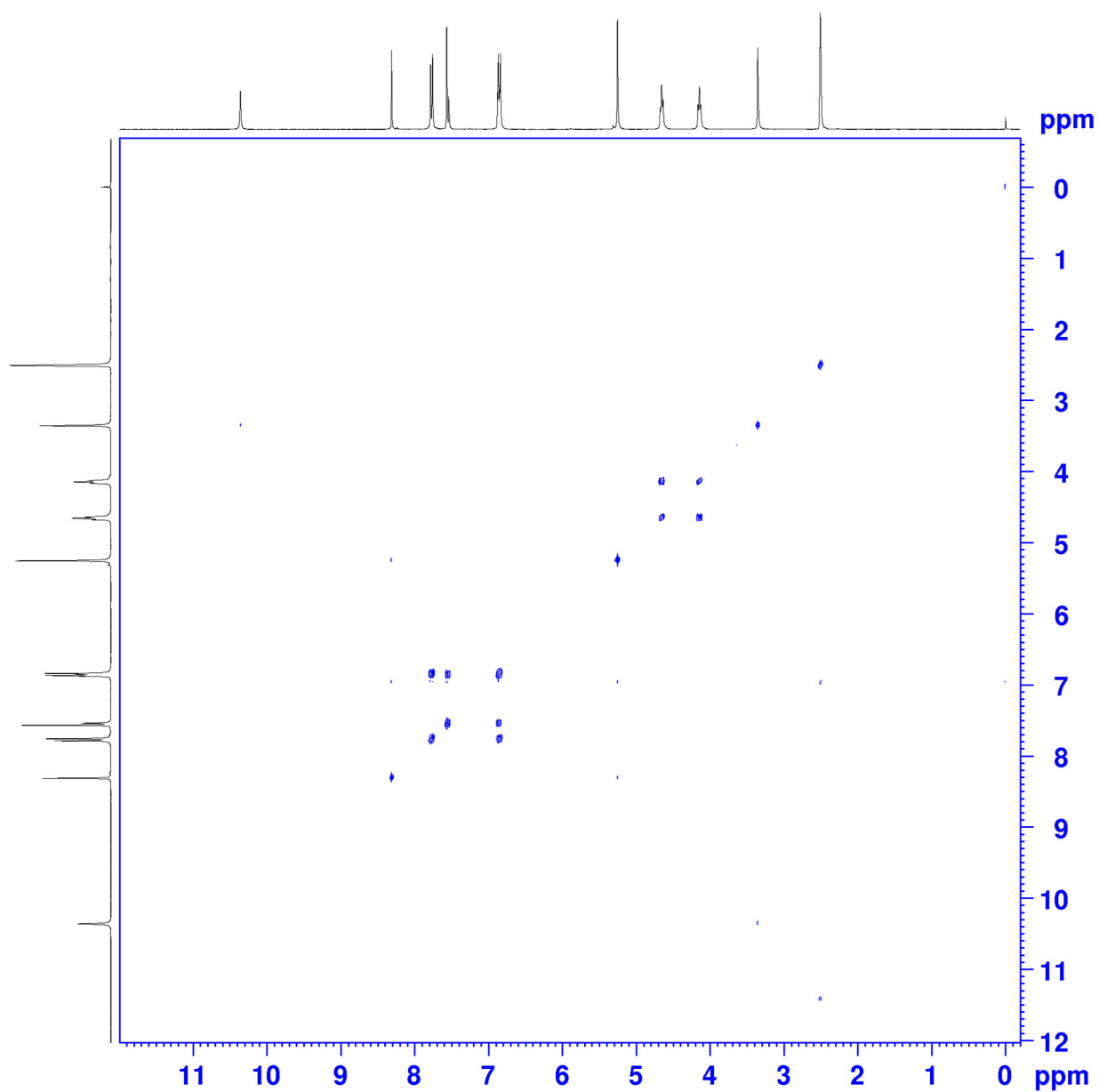
¹H NMR (300 MHz)



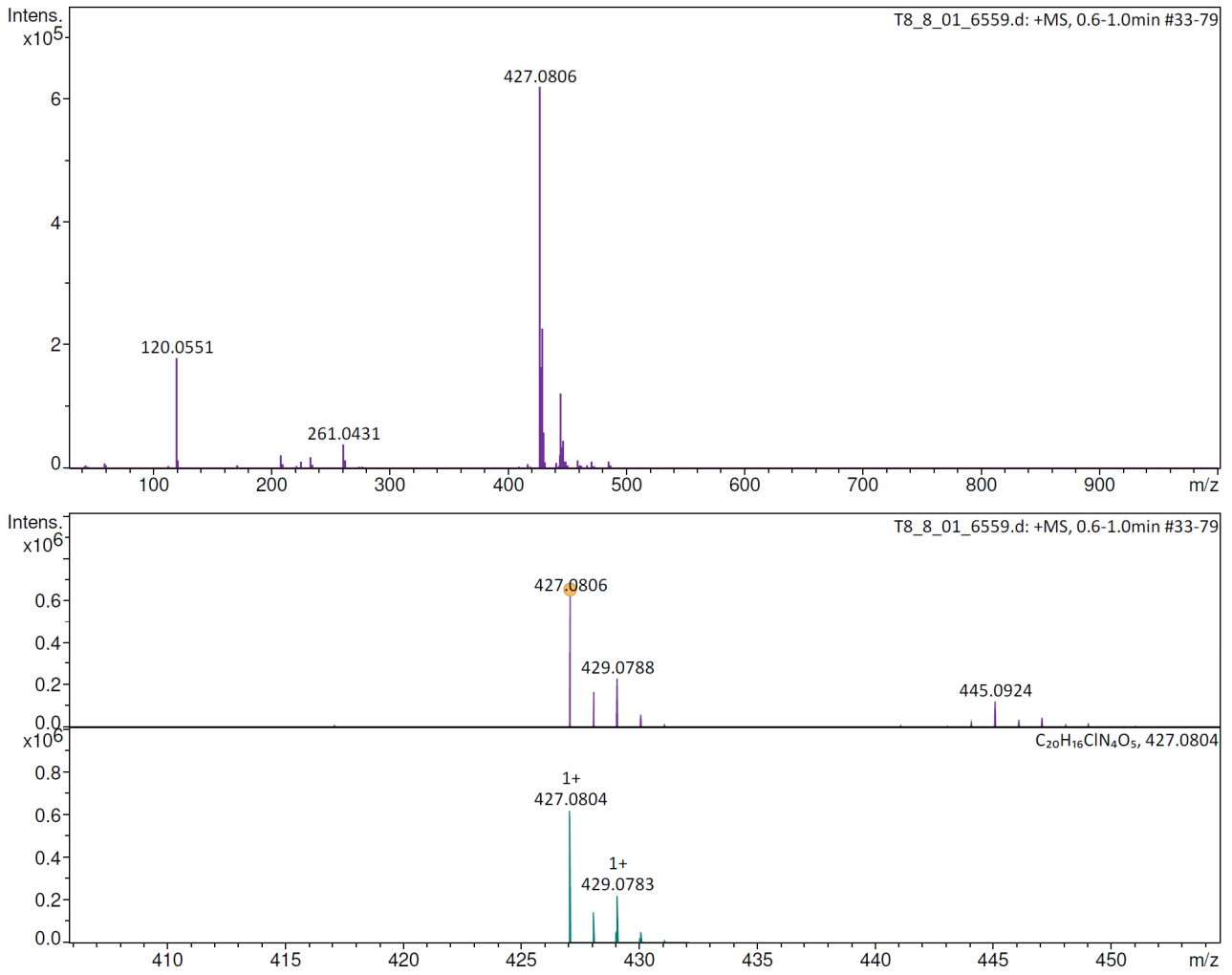
^{13}C NMR (125 MHz)



COSY NMR (300 MHz)

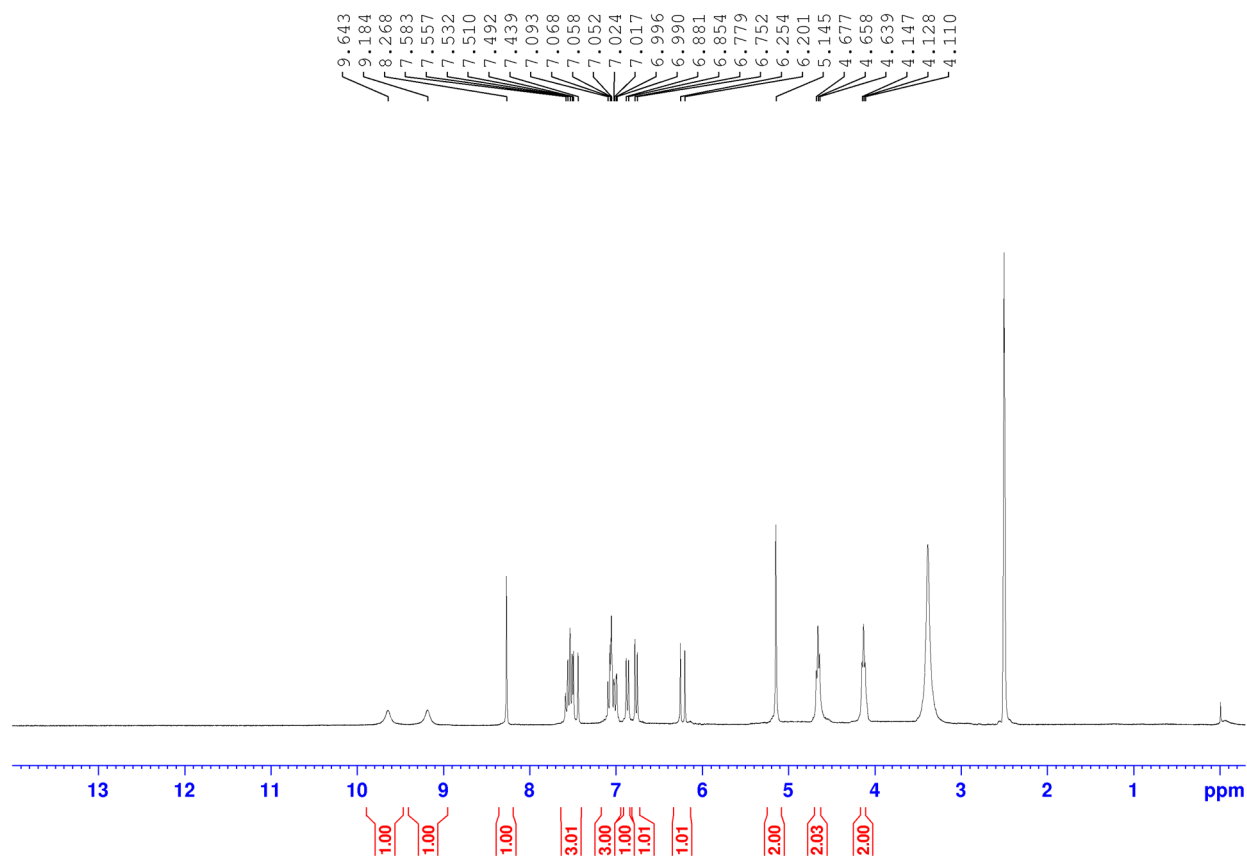


HRMS

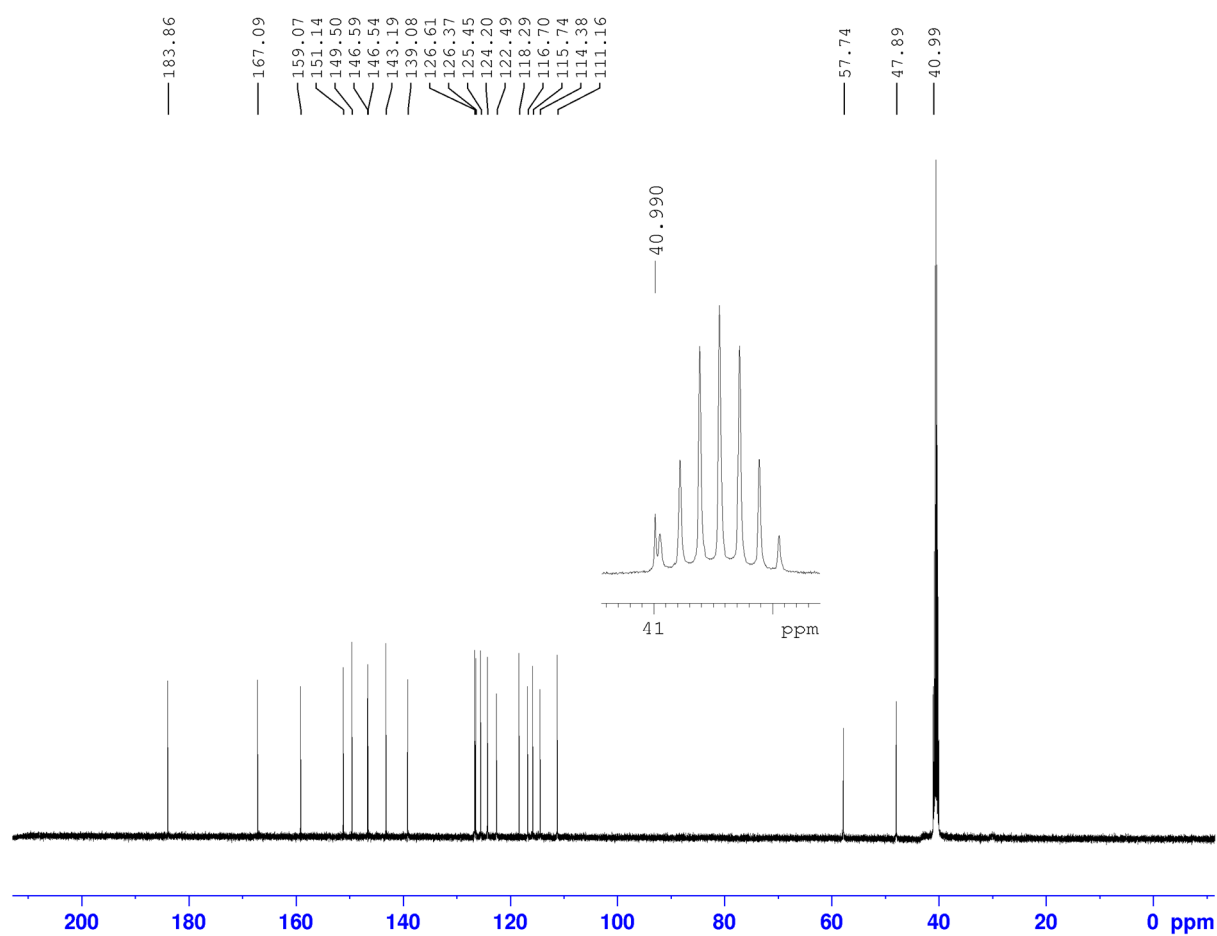


(1-(2-(isatin-1-yl)ethyl)-1,2,3-triazol-4-yl)methyl (E)-3-(3,4-dihydroxyphenyl)acrylate (31)

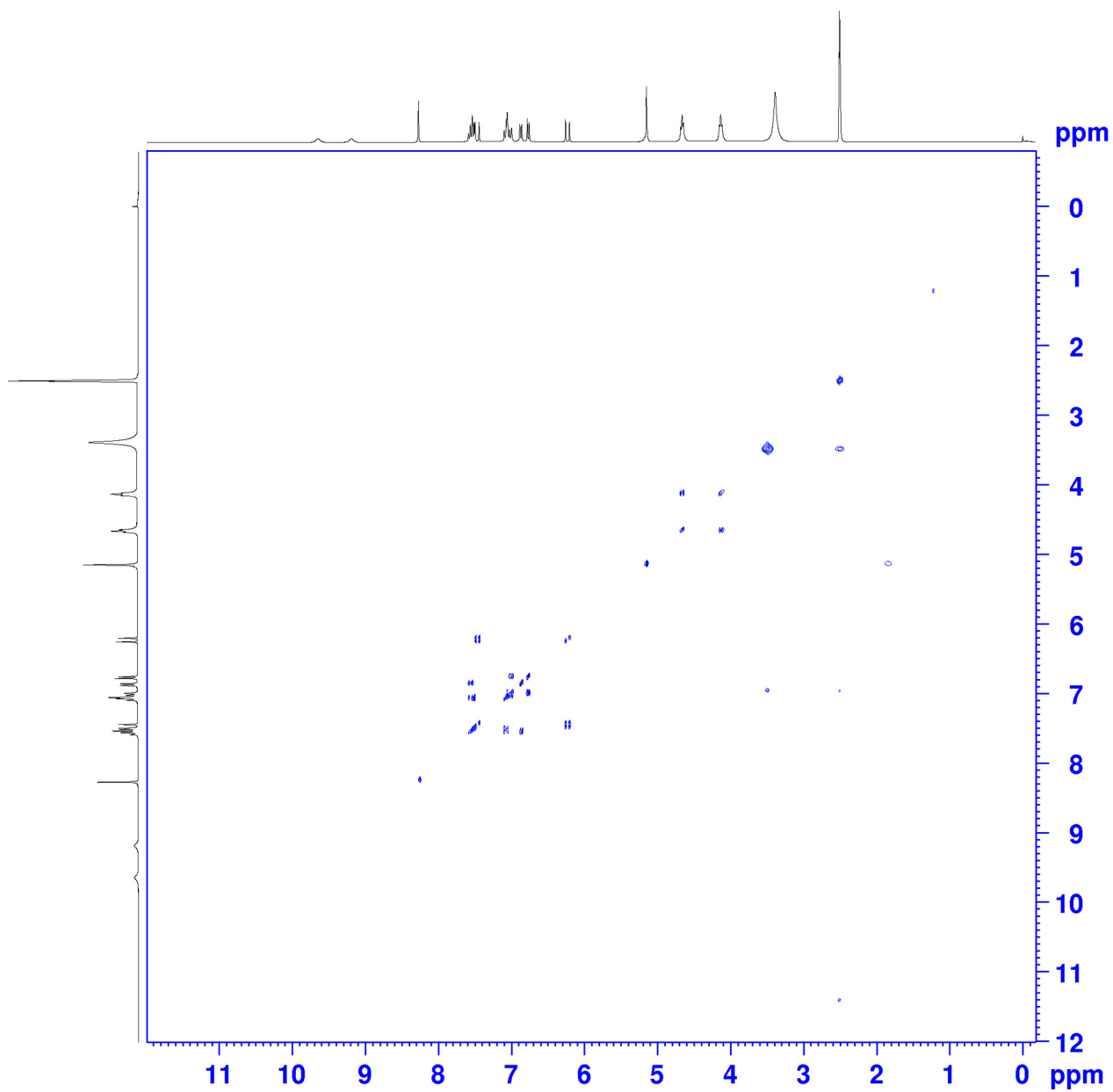
¹H NMR (300 MHz)



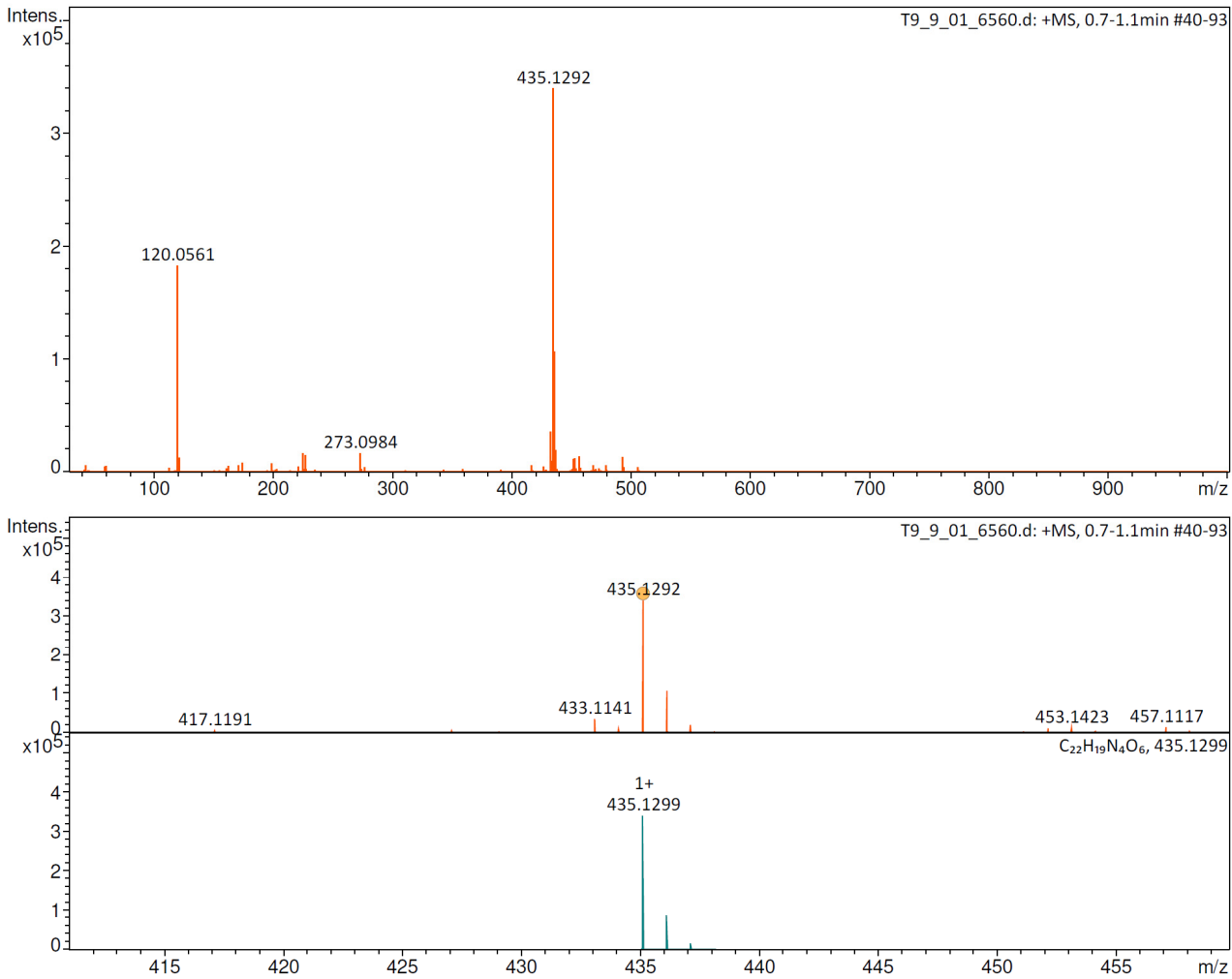
^{13}C NMR (125 MHz)



COSY NMR (300 MHz)

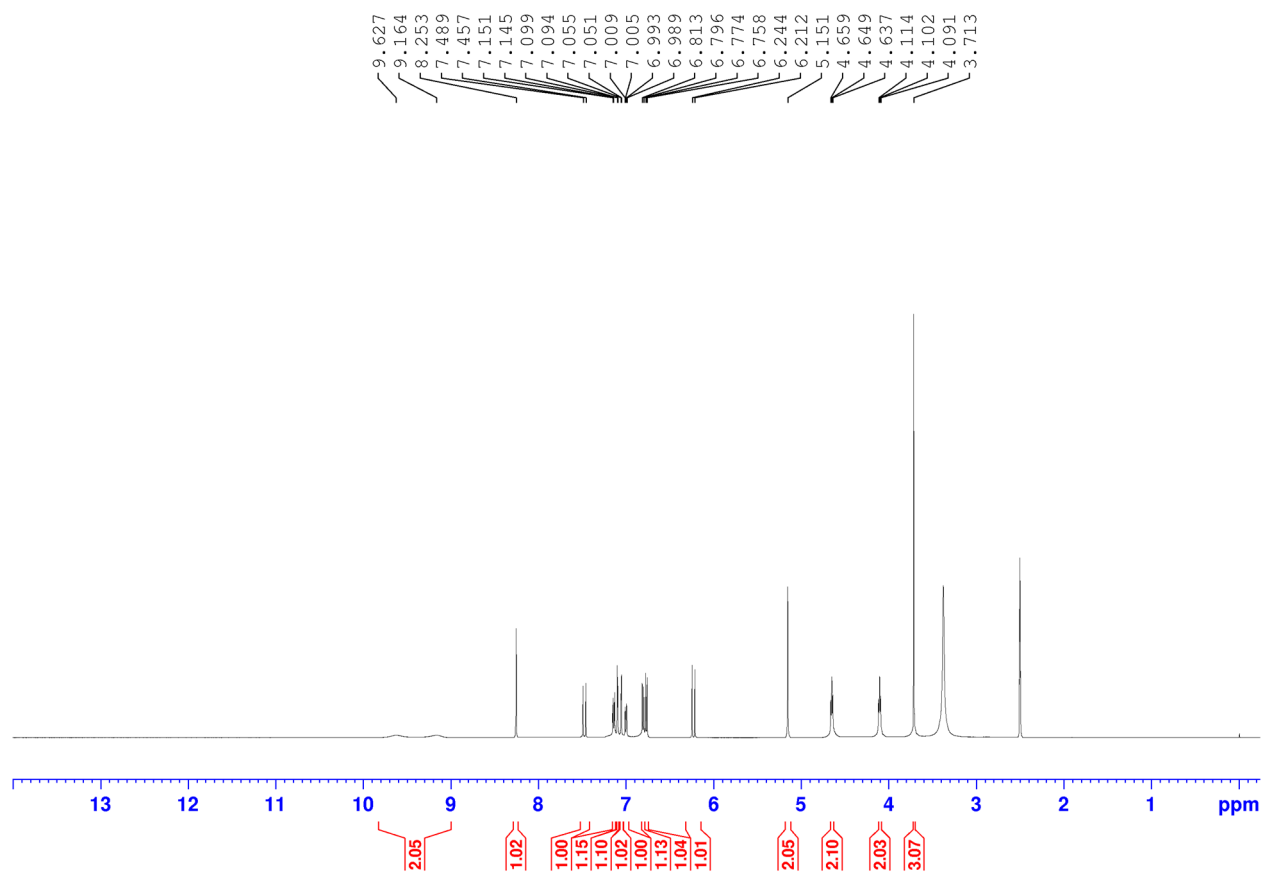


HRMS

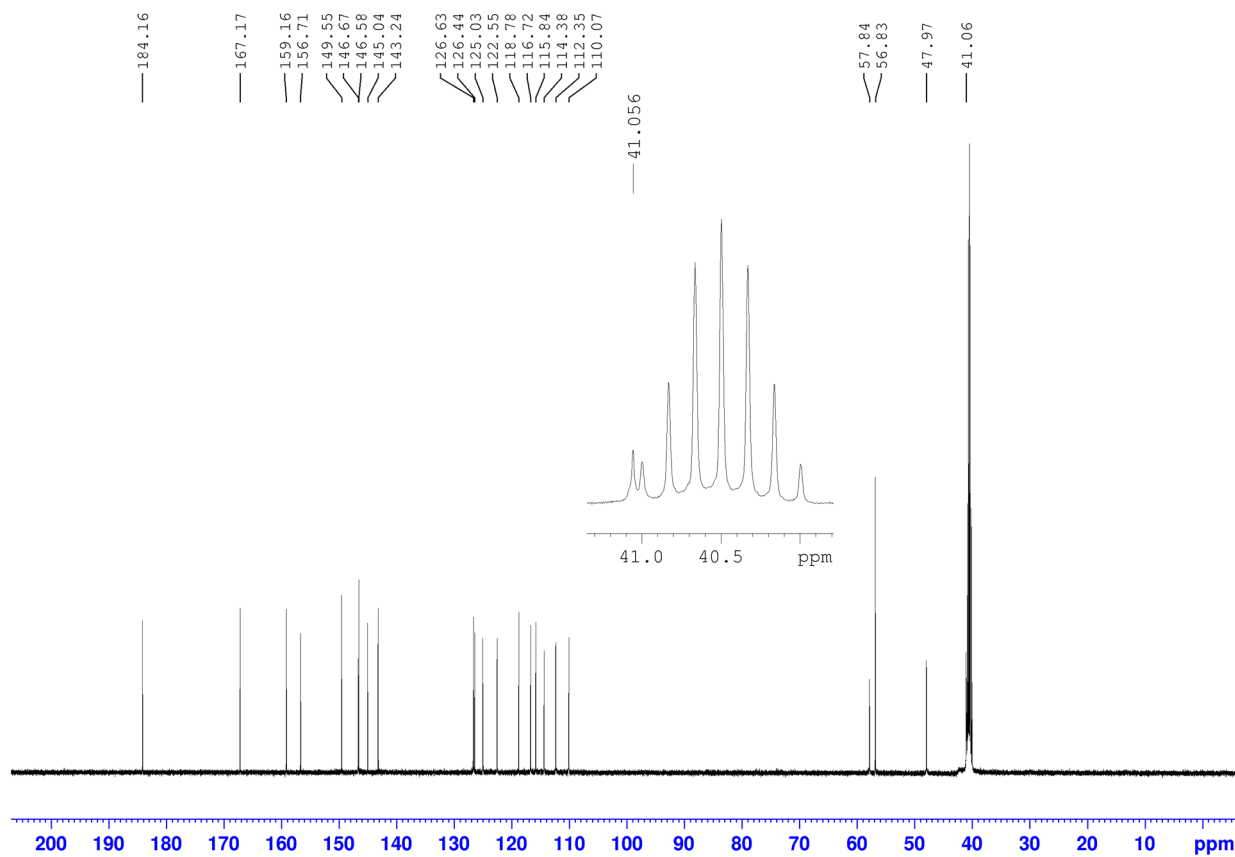


(1-(2-(5-methoxyisatin-1-yl)ethyl)-1,2,3-triazol-4-yl)methyl (E)-3-(3,4-dihydroxyphenyl)acrylate (32)

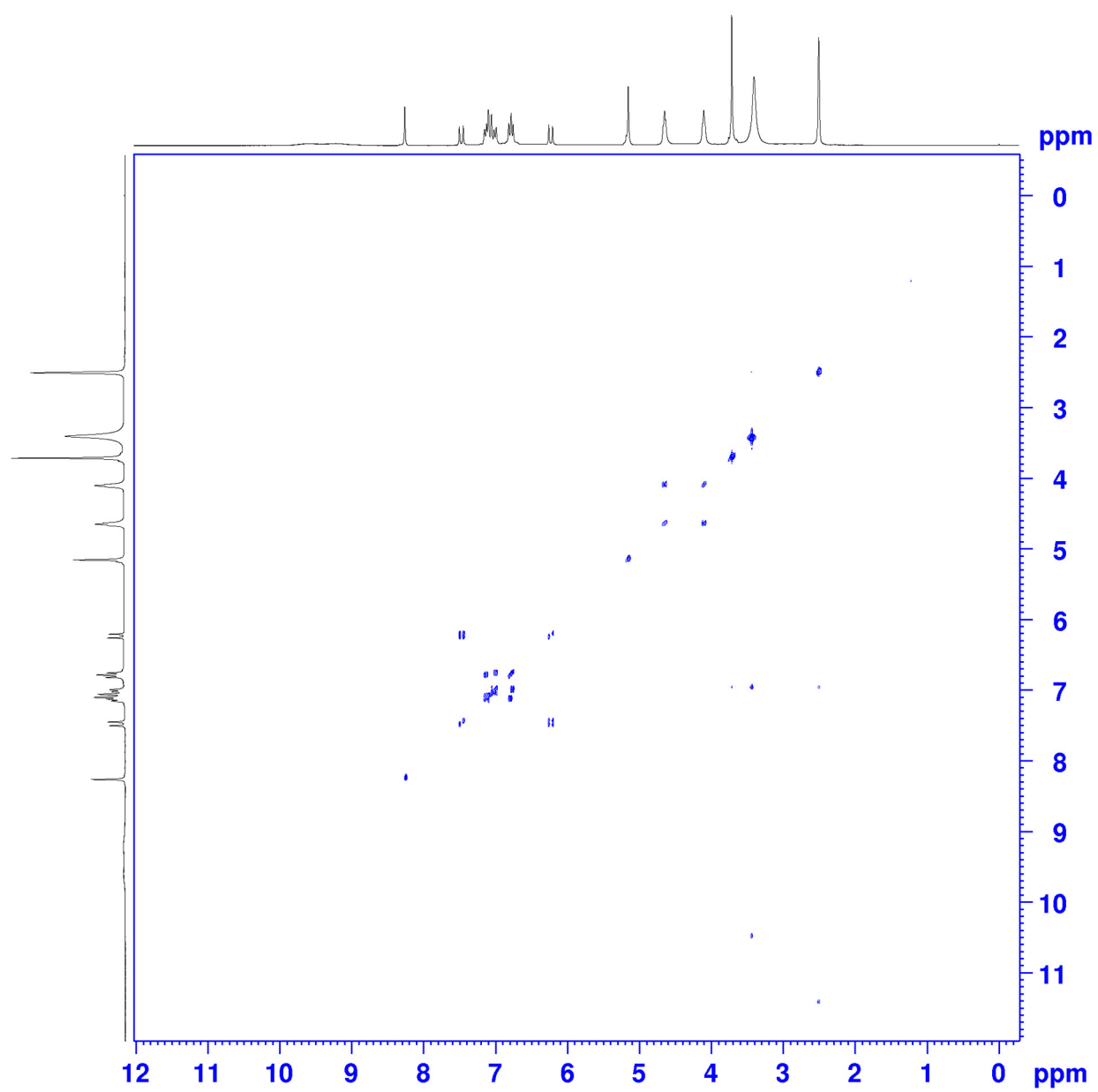
¹H NMR (500 MHz)



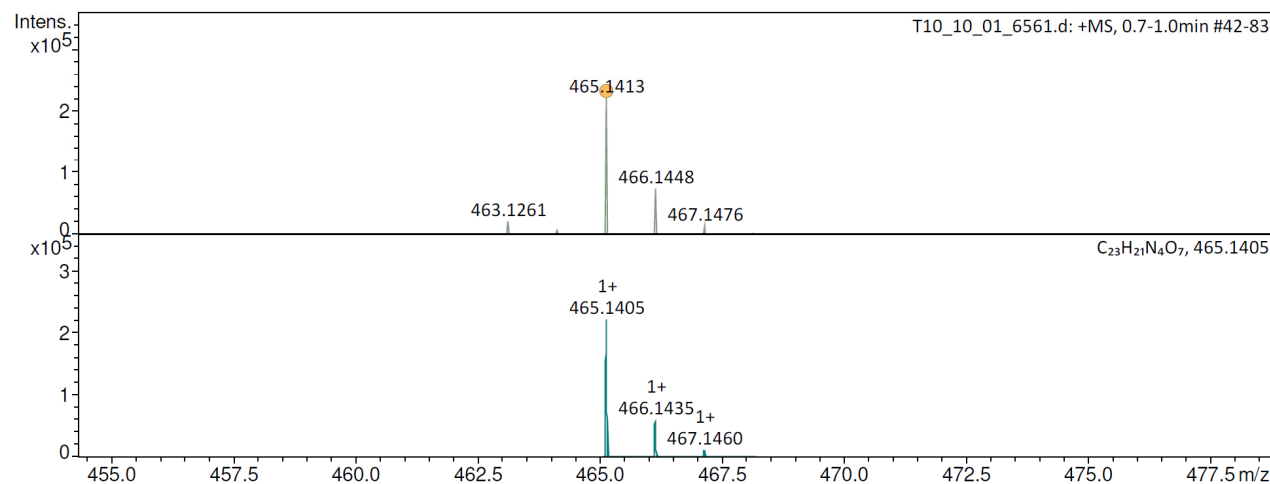
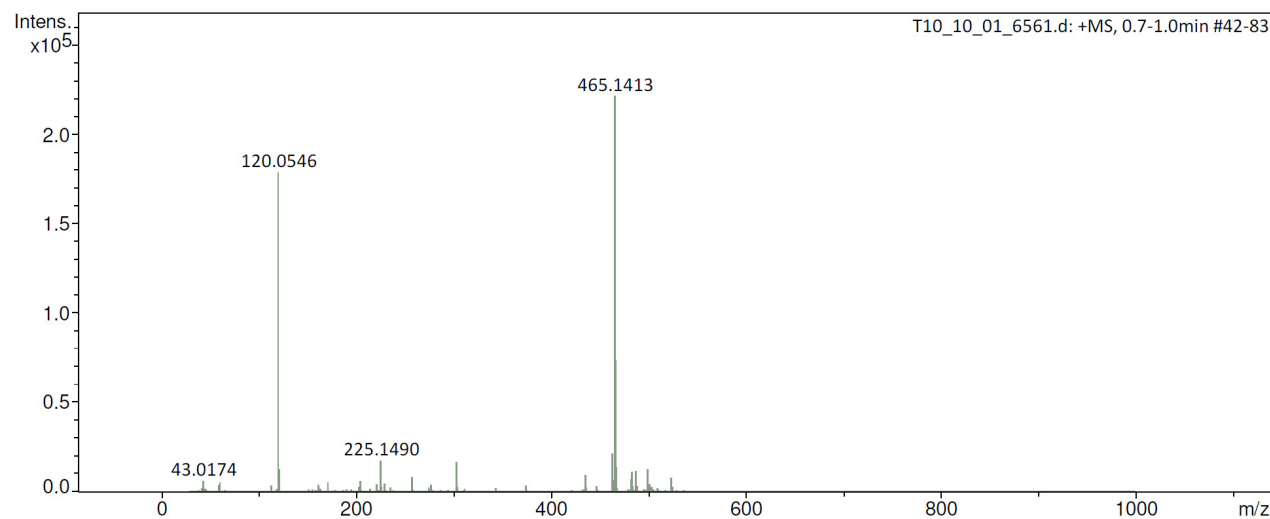
^{13}C NMR (125 MHz)



COSY NMR (300 MHz)

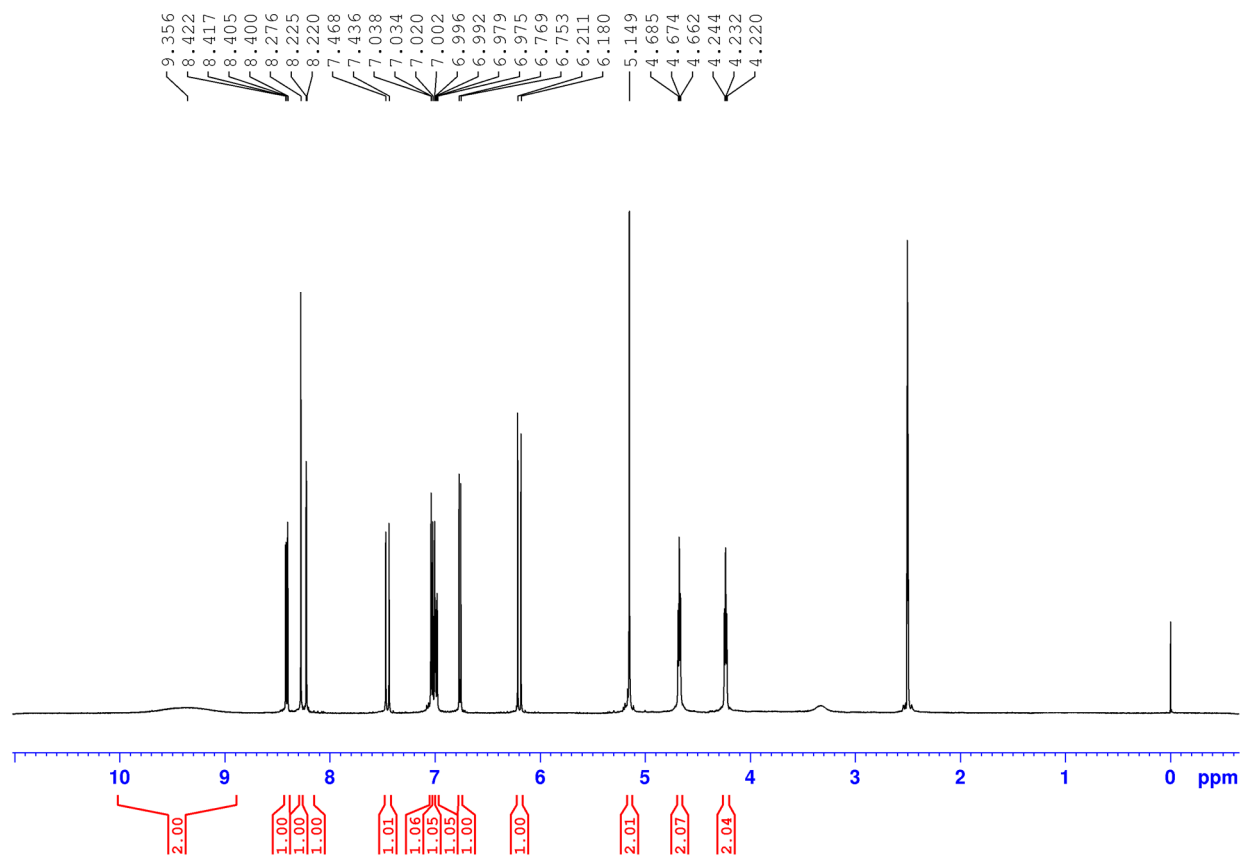


HRMS

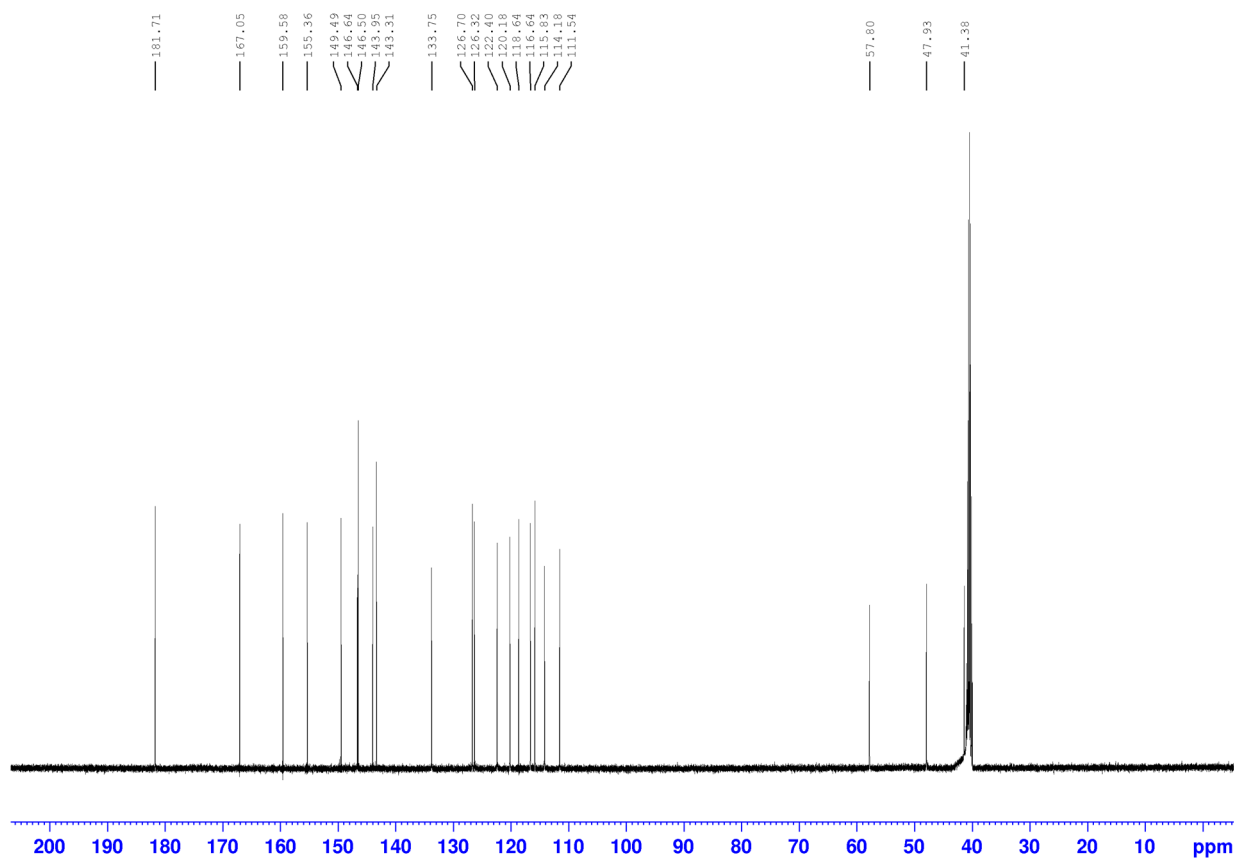


(1-(2-(5-nitro-isatin-1-yl)ethyl)-1,2,3-triazol-4-yl)methyl (E)-3-(3,4-dihydroxyphenyl)acrylate (33)

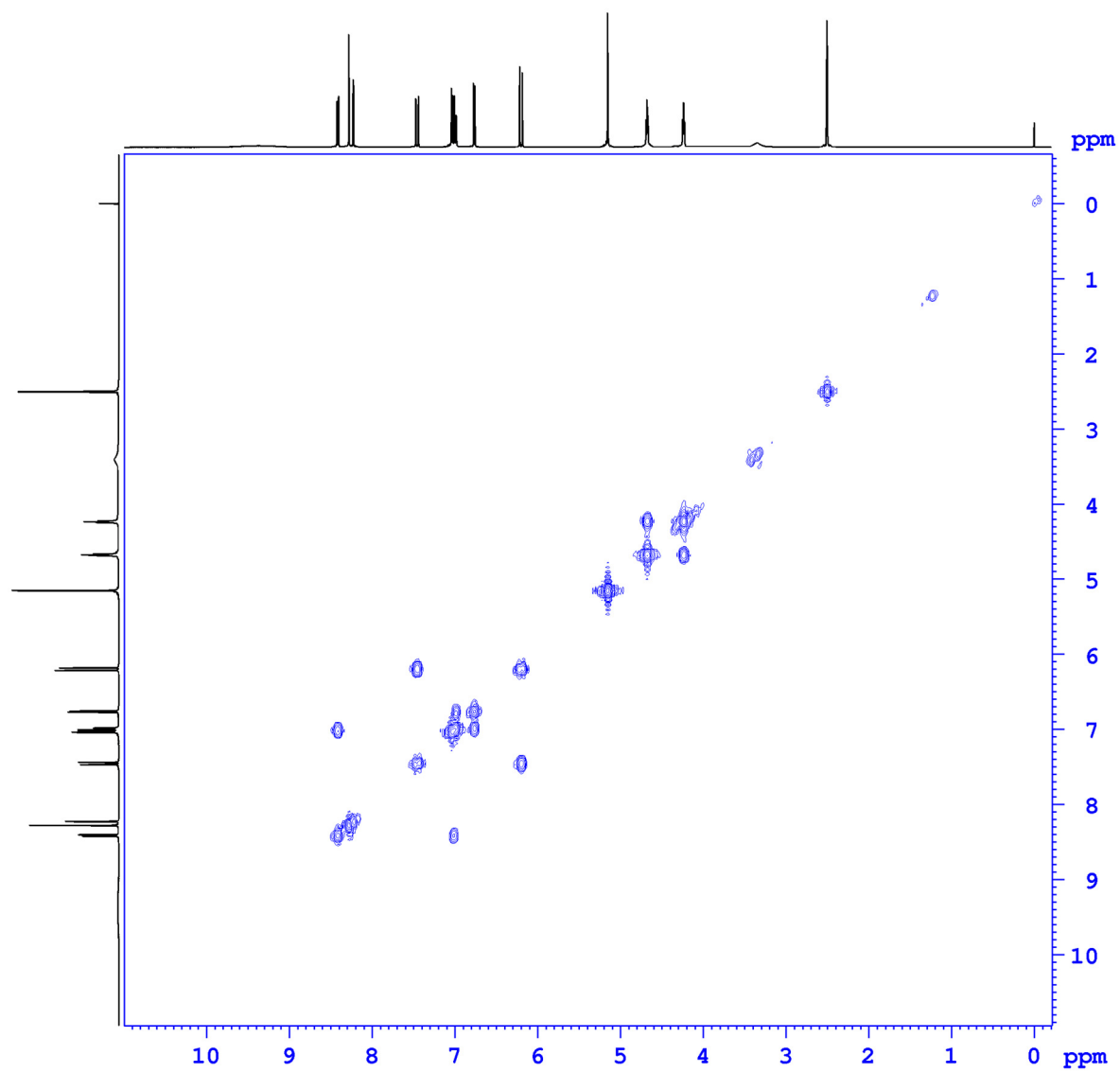
¹H NMR (500 MHz)



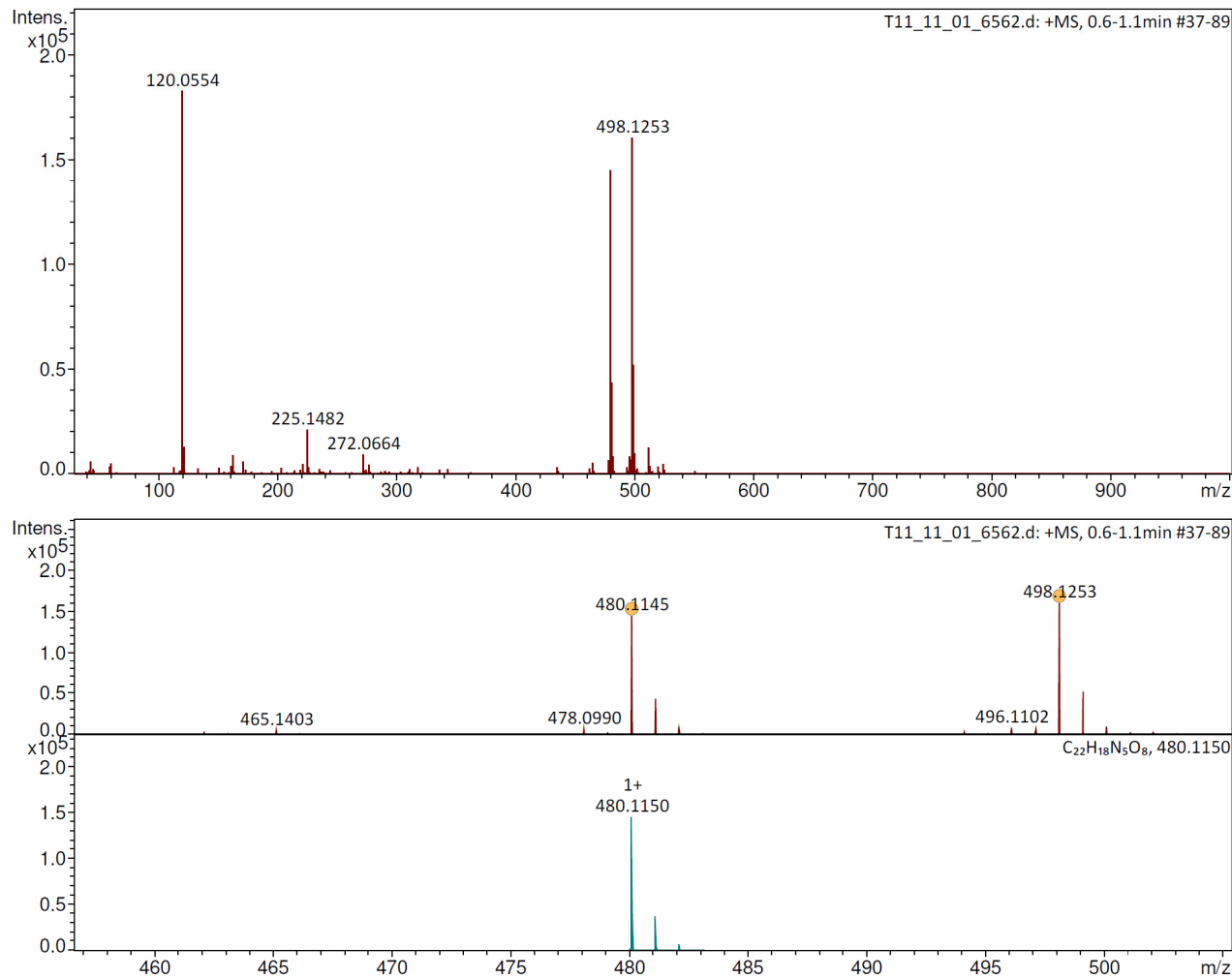
^{13}C NMR (125 MHz)



COSY NMR (500 MHz)

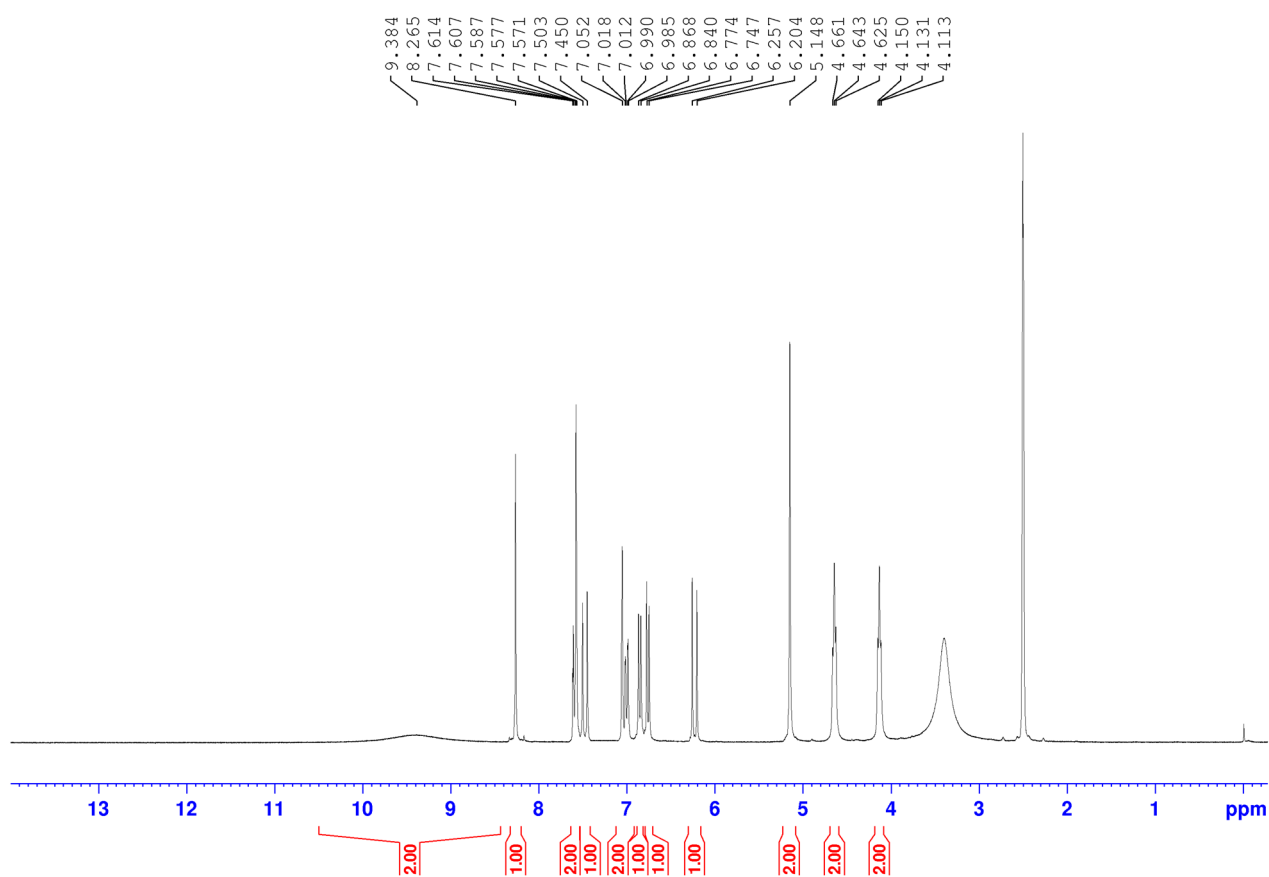


HRMS

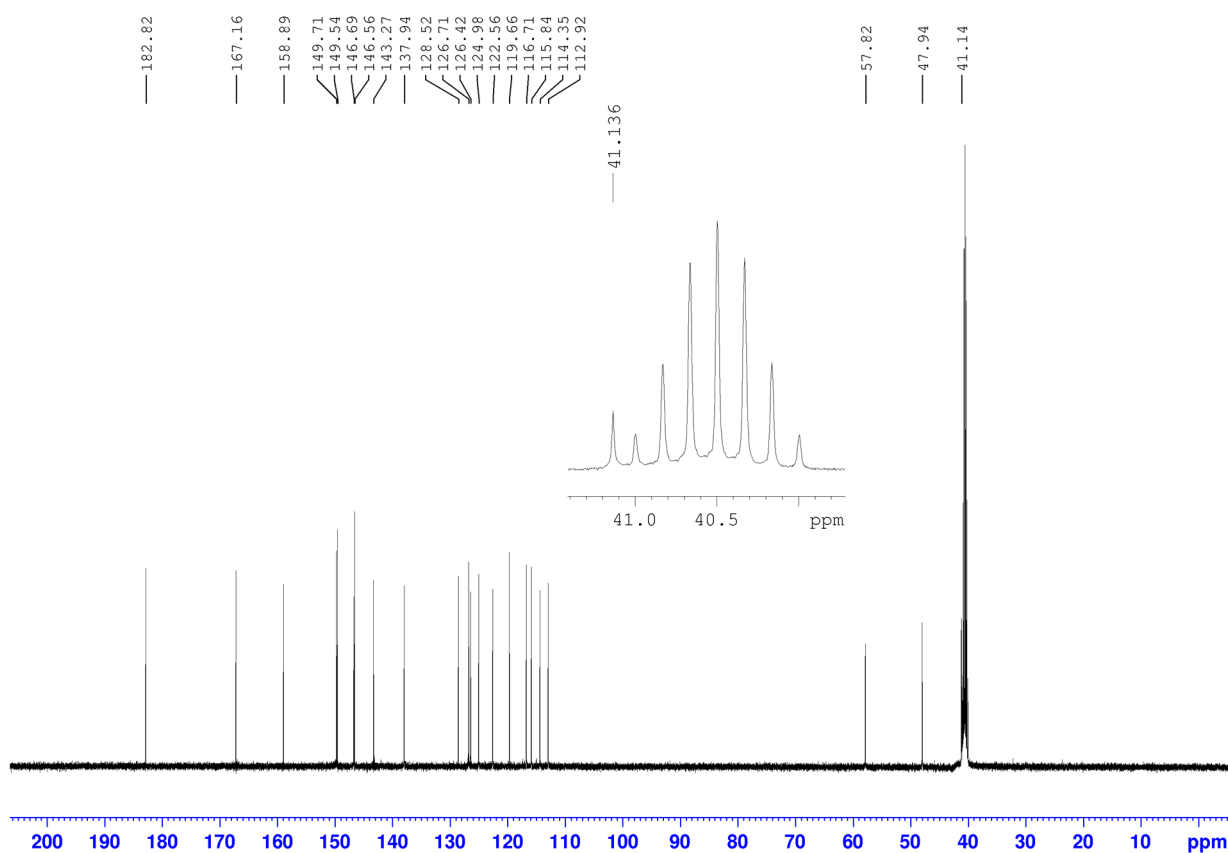


(1-(2-(5-chloro-isatin-1-yl)ethyl)-1,2,3-triazol-4-yl)methyl (E)-3-(3,4-dihydroxyphenyl)acrylate (34)

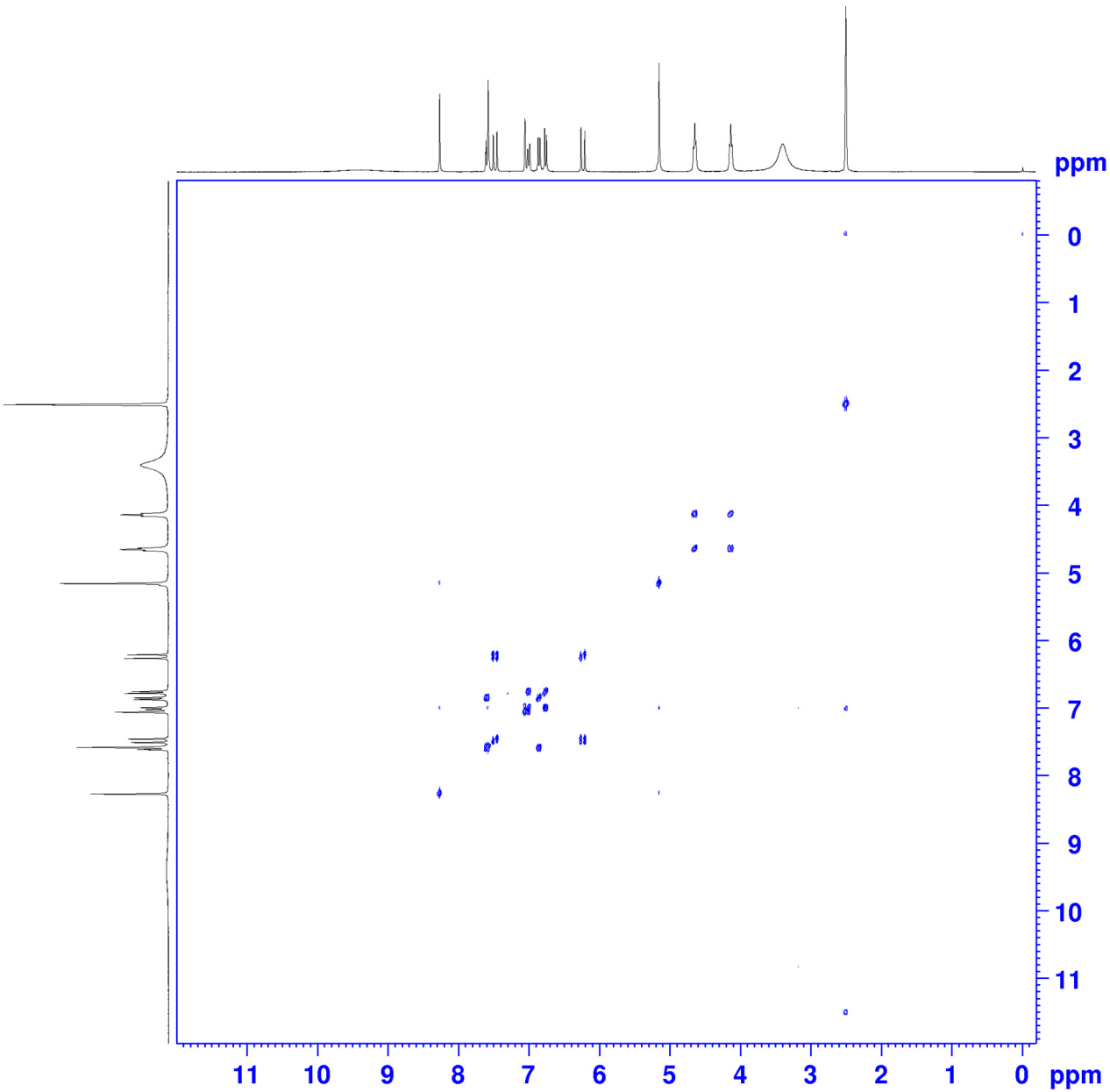
¹H NMR (300 MHz)



^{13}C NMR (125 MHz)



COSY NMR (300 MHz)



HRMS

