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A Facile Synthesis of 1,4-benzodiazepine-2,5-diones and Quinazolinones from Amino Acids as Anti-Tubercular Agents

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3. Experimental Section:

3.1. Materials and methods:

All reactions were carried out using round-bottomed flask, unless otherwise stated. All reagents were obtained from commercial suppliers and used without further purification. The starting material, isatoic anhydride procured from Avra chemicals, L-amino acid methyl ester hydrochlorides from Sigma-Aldrich and H_2PtCl_6 from Rankem. The reactions were monitored by TLC and were visualized under UV lamp (254 nm and 365 nm). Melting points were determined on a Superfit melting point apparatus (India) and were uncorrected. FT-IR was performed using Perkin Elmer Spectrum Two. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Agilent Technologies (USA) using DMSO or $CDCl_3$ as a solvent and tetramethyl silane as an internal standard. The following abbreviations are used for the multiplicities: s: singlet; d: doublet; t: triplet; m: multiplet, br: broad and coupling constants (*J*) are reported in Hertz (Hz). LC mass spectra were recorded on Waters synapp G-2 using Masslynx 4.1 software with capillary voltage of 2.5-3.5 kV and APCI mode of ionization.

3.2. General Procedure for Synthesis of Intermediates 3a-m:

L-amino acid methyl ester hydrochlorides **2** (0.002 mol, 1.0 equiv.) were dissolved in minimum amount of water (4 mL), to this added Na_2CO_3 (0.43g, 0.004 mol, 2.0 equiv.). The resulted neutralized solution of amino acid was added drop wise to well-stirred solution of isatoic anhydride **1** (0.45g, 0.0028 mol, 1.4 equiv.) in ACN (8 mL) at room temperature. The resulting mixture was stirred until the completion (2-3 hour) of the reaction (monitored by TLC). The reaction mixture was evaporated under reduced pressure; the remaining residual mass was quenched with saturated K_2CO_3 solution (20 mL) to remove unreacted isatoic anhydride. The obtained aqueous layer was extracted with EtOAc (2 × 20 mL) and washed with 5% Na_2CO_3 (2 x 20 mL) and with brine (1 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain the residual product with almost >95 % purity.

3.3. General Procedure for Synthesis of 1,4-Benzodiazepine-2,5-diones (4a-j):

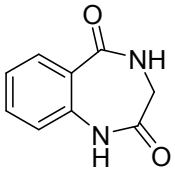
To a solution of intermediate **3** (0.001 mol, 1.0 equiv.) in THF (3 mL), H_2PtCl_6 (0.06g, 15 mol %) was added. The resulting mixture was heated to reflux with constant

stirring until the completion (30-40 min) of the reaction (monitored by TLC). The reaction mixture was quenched with saturated Na_2CO_3 solution (10 mL) and extracted with chloroform (2 × 15 mL). The organic layer was washed with 1N NaOH (1 × 10 mL), 1N HCl (1 × 10 mL), water (1 × 10 mL) and finally with brine (1 × 10 mL). The obtained organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude products. The crude products were purified by either column chromatography (Eluent: EtOAc:Hexane :: 1:2) or recrystallization with MTBE whichever is permissible.

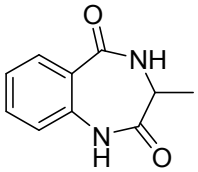
3.4. General Procedure for Synthesis of Quinazolinones (5c & 5e):

To a solution of intermediate **3** (0.001 mol, 1.0 equiv.) in DMF (3 mL), dry/moist H_2PtCl_6 (0.06g, 15 mol %) was added. The resulting mixture was heated to reflux with constant stirring until the completion (30-40 min) of the reaction (monitored by TLC). The reaction mixture was quenched with saturated Na_2CO_3 solution (10 mL) and extracted with $CHCl_3$ (2 × 15 mL). The organic layer was washed with 1N HCl (1 × 10 mL), water (1 × 10 mL) and finally with brine (1 × 10 mL). The obtained organic layer was treated with 1N NaOH the product went to aqueous layer, later by acidification, the product was isolated and extracted to organic layer dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, to obtain the residual products with almost >95 % purity. The obtained product seems astonishing, yielding six membered quinazolinone derivative.

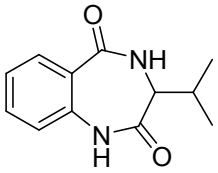
Characterization Data



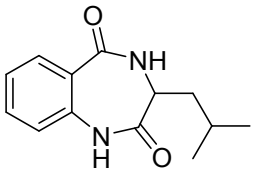
Compound 4a: 3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione
Colourless solid; Yield = 62.5% (110 mg); M.P. = 321-324 °C;
IR (thin film): 2820, 1698, 1597 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.32 (s, 1H, -NH), 8.50 (t, 1H, -NH, J = 5.6 Hz), 7.73 (dd, 1H, Ar-H, J = 1.2 & 6.8 Hz), 7.50-7.46 (m, 1H, Ar-H), 7.19 (t, 1H, Ar-H, J = 6.8 Hz), 7.08 (d, 1H, Ar-H, J = 8 Hz), 3.56 (d, 2H, $-CH_2$, J = 6 Hz);
^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 168.5, 137.6, 132.7, 131.2, 126.0, 124.3, 121.3, 44.9;
LCMS (APCI): m/z calcd. For $C_9H_8N_2O_2$: 176.0586; found: 176.9819 $(M+1)^+$



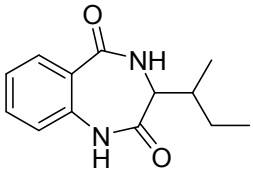
Compound 4b: 3-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione
Light creamy solid; Yield = 63.1% (121 mg); M.P. = 328-330 °C;
IR (thin film): 3015, 1708, 1611 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.32 (s, 1H, -NH), 8.37 (d, 1H, -NH, J = 4.8 Hz), 7.71 (d, 1H, Ar-H, J = 8 Hz), 7.47 (m, 1H, Ar-H), 7.18 (t, 1H, Ar-H, J = 7.6 Hz), 7.06 (d, 1H, Ar-H, J = 8 Hz), 3.79-3.76 (m, 1H, $-^{\alpha}CH$), 1.20 (d, 3H, $-CH_3$, J = 6.8 Hz);
^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 168.1, 137.2, 132.6, 130.6, 130.8, 126.7, 124.3, 121.3, 47.7, 14.2;
LCMS (APCI): m/z calcd. For $C_{10}H_{10}N_2O_2$: 190.0742; found: 191.0731 $(M+1)^+$



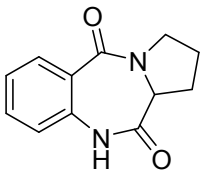
Compound 4c: 3-isopropyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione
Off-white solid; Yield = 63.6% (144 mg); M.P. = 250-253 °C;
IR (thin film): 2960, 1699, 1563 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.36 (s, 1H, -NH), 8.55 (d, 1H, -NH, J = 6 Hz), 7.73 (dd, 1H, Ar-H, J = 2.2 & 8.8 Hz), 7.50-7.49 (m, 1H, Ar-H), 7.22 (t, 1H, Ar-H, J = 9.6 Hz), 7.09 (d, 1H, , Ar-H, J = 10.8 Hz), 3.24-3.19 (m, 1H, $-^{\alpha}CH$), 1.9 (br, 1H, $-^{\beta}CH$), 0.94-0.87 (m, 6H, $-(CH_3)_2$);
^{13}C NMR (100 MHz, DMSO): δ 169.8, 166.6, 137.0, 132.0, 130.9, 126.2, 123.9, 120.7, 52.2, 38.7, 35.7;
LCMS (APCI): m/z calcd. For $C_{12}H_{14}N_2O_2$: 218.1055; found: 219.0239 $(M+1)^+$



Compound 4d: 3-isobutyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione
Off-white solid; Yield = 59% (135 mg); M.P. = 242-243 °C;
IR (thin film): 2907, 1701, 1598, 1320 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.34 (s, 1H, -NH), 8.41 (d, 1H, -NH, J = 6 Hz), 7.70 (dd, 1H, Ar-H, J = 1.2 & 6.8 Hz), 7.49-7.45 (m, 1H, Ar-H), 7.18 (t, 1H, Ar-H, J = 7.6 Hz), 7.06 (d, 1H, , Ar-H, J = 8.4 Hz), 3.58-3.53 (m, 1H, -$^{\alpha}$CH, J = 6.4 Hz), 1.69-1.66 (m, 1H, -$^{\gamma}$CH), 1.54-1.50 (m, 2H, -$^{\beta}CH_2$), 0.82 (d, 3H, -CH_3, J = 6.4 Hz), 0.74 (d, 3H, -CH_3, J = 6.8 Hz)
^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 169.0, 137.0, 132.3, 131.6, 128.4, 126.9, 124.4, 53.7, 41.3, 24.4, 22.5;
LCMS (APCI): m/z calcd. For $C_{13}H_{16}N_2O_2$: 232.1212; found: 233.1427 $(M+1)^+$

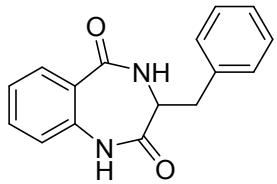


Compound 4e: 3-(sec-butyl)-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione
Colourless solid; Yield = 59.9% (139 mg); M.P. = 245-248 °C;
IR (thin film): 3211, 1711, 1552, 1525 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.34 (s, 1H, -NH), 8.41 (d, 1H, -NH, J = 6 Hz), 7.70 (dd, 1H, Ar-H, J = 1.2 & 6.8 Hz), 7.49-7.45 (m, 1H, Ar-H), 7.18 (t, 1H, Ar-H, J = 7.6 Hz), 7.06 (d, 1H, , Ar-H, J = 8.4 Hz), 3.58-3.53 (m, 1H, -$^{\alpha}$CH, J = 6.4 Hz), 1.69-1.66 (m, 1H, -$^{\beta}$CH), 1.54-1.50 (m, 2H, -$^{\gamma}CH_2$), 0.82 (d, 3H, -CH_3, J = 6.4 Hz), 0.74 (d, 3H, -CH_3, J = 6.8 Hz);
^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 168.7, 136.4, 132.4, 130.4, 126.4, 124.9, 120.8, 39.3, 27.1, 16.4, 10.9;
LCMS (APCI): m/z calcd. For $C_{13}H_{16}N_2O_2$: 232.1212; found: 233.0291 $(M+1)^+$

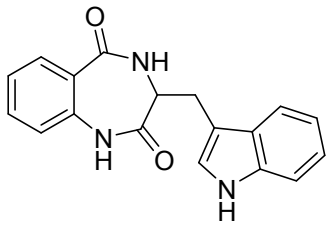


Compound 4f: 1,2,3,11a-tetrahydro-5H-benzo[e]pyrrolo[1,2-a][1,4]diazepine-5,11(10H)-dione
creamy solid; Yield = 70.3% (152 mg); M.P. = 321-324 °C;
IR (thin film): 2914, 1713, 1622, 1369 cm^{-1}
^{1}H NMR (400 MHz, DMSO): δ 10.45 (s, 1H, -NH), 7.76 (dd, 1H, Ar-H, J = 1.6 & 6 Hz), 7.50-7.46 (m, 1H, Ar-H), 7.21-7.18 (m, 1H, Ar-H), 7.11 (d, 1H, Ar-H, J = 7.6 Hz), 4.08 (t, 1H, -$^{\alpha}$CH), 3.59-3.54 (m, 1H, -$^{\delta}CH_2$), 3.46-3.40 (m, 1H, -$^{\delta}CH_2$), 1.96-1.77 (m, 4H, -$^{\beta\&\gamma}CH_2$);

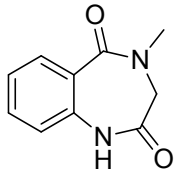
^{13}C NMR (100 MHz, DMSO): δ 171.2, 165.0, 136.8, 132.5, 130.7, 127.0, 124.2, 121.7, 56.6, 47.3, 26.2, 23.5;
LCMS (APCI): m/z calcd. For $C_{12}H_{12}N_2O_2$: 216.0899, found: 217.0070 $(M+1)^+$



Compound 4g: 3-benzyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione
Off-white solid; Yield = 63.5% (169 mg); M.P. = 280-281 °C;
IR (thin film): 3340, 1695, 1596, 1050 cm^{-1}
^{1}H NMR (400 MHz, DMSO): δ 10.40 (s, 1H, -NH), 8.50 (d, 1H, -NH, J = 6.4 Hz), 7.48 (t, 1H, Ar-H, J = 7.2 Hz), 7.30-7.07 (m, 8H, Ar-H), 3.90-3.85 (m, 1H, -$^{\alpha}$CH), 3.14-3.09 (m, 1H, -CH_2), 2.87-2.81 (m, 1H, -CH_2);
^{13}C NMR (100 MHz, DMSO): δ 171.7, 168.1, 138.4, 137.2, 132.7, 130.8, 129.8, 128.6, 126.8, 124.4, 121.4, 54.3, 33.7
LCMS (APCI): m/z calcd. For $C_{16}H_{14}N_2O_2$: 266.1055, found: 267.0137 $(M+1)^+$

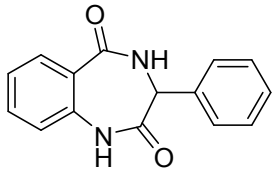


Compound 4h: 3-((1H-indol-3-yl)methyl)-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione
Light brownish solid; Yield = 77.8% (239 mg); M.P. = 251-253 °C;
IR (thin film): 3105, 1756, 1699, 1640, 1365 cm^{-1}
^{1}H NMR (400 MHz, DMSO): δ 10.85 (s, 1H, indole-NH), 10.42 (s, 1H, -NH), 8.45 (d, 1H, -NH, J = 4.4 Hz), 7.63 (d, 1H, Ar-H, J = 6.8 Hz), 7.47-7.46 (m, 2H, Ar-H), 7.30 (d, 1H, indole-Ar-H, J = 7.6 Hz), 7.22 (s, 1H, indole-Ar-H), 7.15 (t, 1H, Ar-H, J = 6.8, 7.2 Hz), 7.09 (d, 1H, indole-Ar-H, J = 7.6 Hz), 7.01 (t, 1H, indole-Ar-H, J = 6.4 Hz), 6.88 (t, 1H, indole-Ar-H, J = 6.8 Hz), 3.87 (m, 1H, $^{\alpha}$CH), 3.23-3.20 (m, 1H, -$^{\beta}CH_2$), 3.01-3.95 (m, 1H, -$^{\beta}CH_2$);
^{13}C NMR (100 MHz, DMSO): δ 171.9, 168.0, 137.2, 136.5, 132.7, 130.8, 127.4, 124.7, 124.3, 121.4, 118.8, 118.6, 111.8, 110.1, 53.3, 24.0;
LCMS (APCI): m/z calcd. For $C_{18}H_{15}N_3O_2$: 305.1164, found: 306.0160 $(M^+ + 1)$

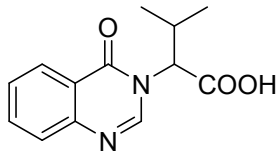


2k

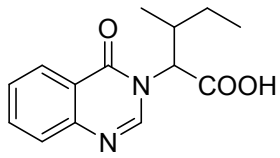
Compound 4i: 4-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione
Colourless solid; Yield = 66.8% (127mg); M.P. = 188-192 °C;
IR (thin film): 2842, 1685, 1596, 1050cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.50 (s, 1H, -NH), 7.72 (dd, 1H, Ar-H, J = 1.2 & 6.8 Hz), 7.49-7.45 (m, 1H, Ar-H), 7.19 (t, 1H, Ar-H, J = 7.6 Hz), 7.09 (d, 1H, Ar-H, J = 8 Hz), 3.81 (s, 2H, -CH_2), 3.09 (s, 3H, *N*-CH_3);
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 167.0, 137.4, 132.4, 131.3, 126.6, 124.3, 121.2, 52.6, 36.3;
LCMS (APCI): m/z calcd. For $C_{10}H_{10}N_2O_2$: 190.0742; found: 190.9944 (M^++1)



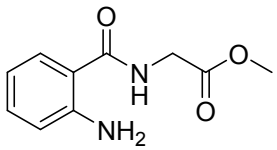
Compound 4j: 3-phenyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione
Colourless solid; Yield = 63.5% (160 mg); M.P. = 289-291°C;
IR (thin film): 3076, 1693, 1595, 1505, 1298 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (s, 1H, -NH), 7.96 (d, 1H, -NH, J = 7.6 Hz), 7.47 (t, 1H, Ar-H, J = 7.6 Hz), 7.34 (broad, 5H, Ar-H); 7.25 (t, 1H, Ar-H, J = 7.2 Hz), 7.06 (d, 1H, Ar-H, J = 3.6 Hz), 6.99 (d, 1H, Ar-H, J = 8 Hz), 4.99 (d, 1H, -$^{\alpha}$CH, J = 3.2 Hz);
^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 168.6, 135.5, 133.2, 131.4, 128.9, 128.8, 127.7, 125.3, 120.7, 58.0, 29.6;
LCMS (APCI): m/z calcd. for $C_{15}H_{12}N_2O_2$: 252.0899; found: 253.0992 $(M+1)^+$



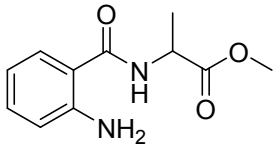
Compound 5c: 3-methyl-2-(4-oxoquinazolin-3(4H)-yl)butanoic acid
Colourless solid; Yield = 72% (178 mg); M.P. = 218-220 °C;
IR (thin film): 3075, 1682, 1596, 1506, 1263 cm^{-1}
^{1}H NMR (400 MHz, DMSO): δ 13.1 (br, 1H, -COOH), 8.39 (s, 1H, =CH), 8.13 (dd, 1H, Ar-H, J = 1.2 & 6.8 Hz), 7.86-7.82 (m, 1H, Ar-H), 7.68 (d, 1H, Ar-H, J = 8 Hz), 7.55 (t, 1H, Ar-H, J = 8 Hz), 4.94 (d, 1H, -$^{\alpha}$CH, J = 9.6 Hz), 2.64-2.58 (m, 1H, -$^{\beta}CH_2$), 1.11 (d, 3H, -CH_3, J = 6.4 Hz), 0.74 (d, 3H, -CH_3, J = 6.4 Hz);
^{13}C NMR (100 MHz, DMSO): δ 171.0, 160.5, 147.8, 147.4, 135.2, 127.8, 126.8, 121.5, 63.1, 28.8, 20.8, 19.5;
LCMS (API): m/z calcd. For $C_{12}H_{12}N_2O_2$: 246.1004, found: 247.0138 $(M+1)^+$



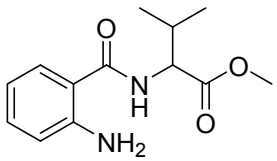
Compound 5e: 3-methyl-2-(4-oxoquinazolin-3(4H)-yl)pentanoic acid
Off-white solid; Yield = 78% (203 mg); M.P. = 203-205 °C;
IR (thin film): 3297, 1706, 1686, 1615, 1552 cm^{-1}
^{1}H NMR (400 MHz, DMSO): δ 13.1 (br, 1H, -COOH), 8.47 (s, 1H, =CH), 8.14 (d, 1H, Ar-H, J = 7.6 Hz), 7.84 (t, 1H, Ar-H J = 7.6 Hz), 7.69 (d, 1H, Ar-H, J = 8.4 Hz), 7.55 (t, 1H, Ar-H, J = 7.6 Hz), 5.05 (d, 1H, -$^{\alpha}$CH, J = 9.6 Hz), 1.21 (m, 1H, -$^{\beta}$CH), 1.07 (d, 3H, -CH_3, J = 6.4 Hz), 1.10-0.94 (m, 2H, -CH_2), 0.76 (t, 3H, -CH_3, J = 7.2 Hz);
^{13}C NMR (100 MHz, DMSO): δ 171.2, 160.5, 147.7, 147.2, 135.2, 127.8, 127.7, 126.8, 121.4, 61.4, 34.8, 25.3, 16.7, 10.7;
LCMS (API): m/z calcd. For $C_{14}H_{16}N_2O_3$: 260.1161, found: 261.0240 $(M+1)^+$



Compound 3a: methyl (2-aminobenzoyl)glycinate
Creamy solid; Yield = 58.8% (241 mg); M.P. = 114-116 °C;
IR (thin film): 2943, 1697, 1647, 1543 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, 1H, Ar-H, J = 7.6 Hz), 7.20 (t, 1H, Ar-H, J = 7.6 Hz), 6.67-6.63 (m, 2H, Ar-H), 6.67-6.63 (m, 1H, -NH), 5.50 (broad, 2H, -NH_2); 4.18 (d, 2H, -CH_2, J = 5.2 Hz), 3.78 (s, 3H, -OCH_3);
^{3}C NMR (100 MHz, $CDCl_3$): δ 170.1, 167.8, 142.2, 133.9, 126.3, 118.6, 117.8, 116.1, 50.8, 42.1;
LCMS (APCI): m/z calcd. for $C_{10}H_{12}N_2O_3$: 208.0848; found: 209.0011 $(M+1)^+$



Compound 3b: methyl (2-aminobenzoyl)alaninate
Light yellowish solid; Yield = 58.4% (257 mg); M.P. = 101-104 °C;
IR (thin film): 3076, 1693, 1595, 1505 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, 1H, Ar-H, J = 7.2 Hz), 7.24 (t, 1H, Ar-H, J = 7.8 Hz), 6.66-6.57 (m, 2H, Ar-H), 6.66-6.57 (m, 1H, -NH), 5.53 (broad, 2H, -NH_2); 4.26 (m, 1H, -$^{\alpha}$CH), 3.76 (s, 3H, -OCH_3), 1.01 (d, 3H, -CH_3, J = 6.2 Hz)
^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 168.9, 141.5, 133.4, 129.2, 121.1, 118.1, 117.9, 52.7, 50.2, 18.9;
LCMS (APCI): m/z calcd. for $C_{11}H_{14}N_2O_3$: 222.1004; found: 222.9917 $(M^+ + 1)$



Compound 3c: methyl (2-aminobenzoyl)valinate

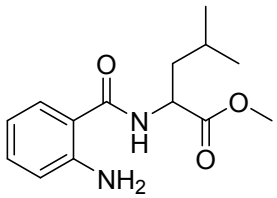
Off-white solid; Yield = 56.1% (230mg); M.P. = 96-98 °C;

IR (thin film): 2896, 1688, 1605, 1514, 1227 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, 1H, Ar-H, J = 7.2 Hz), 7.22-6.81 (m, 3H, Ar-H), 7.22-6.81 (m, 1H, -NH), 5.48 (broad, 2H, $-NH_2$); 4.57-4.49 (m, 1H, $-^{\alpha}CH$), 3.76 (s, 3H, $-OCH_3$), 1.69-1.63 (m, 1H, $-^{\beta}CH$), 0.98-0.87 (m, 6H, $-(CH_3)_2$);

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 168.4, 148.9, 133.7, 126.4, 121.2, 120.1, 119.0, 54.3, 50.4, 36.7, 16.5, 16.4;

LCMS (APCI): m/z calcd. for $C_{13}H_{18}N_2O_3$: 250.1317; found: 251.0417 $(M+1)^+$



Compound 3d: methyl (2-aminobenzoyl)leucinate

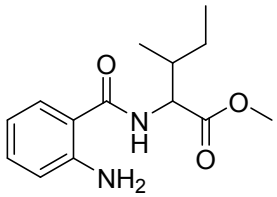
Light creamy solid; Yield = 63.2 % (335mg); M.P. = 98-101 °C;

IR (thin film): 2974, 1679, 1595, 1543, 1359 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, 1H, Ar-H, J = 7.6 Hz), 7.24 (t, 1H, Ar-H, J = 7.6 Hz), 6.76-6.68 (m, 2H, Ar-H), 6.76-6.68 (m, 1H, -NH), 5.57 (broad, 2H, $-NH_2$); 4.29-4.26 (m, 1H, $-^{\alpha}CH$), 3.78 (s, 3H, $-OCH_3$), 1.70-1.68 (m, 2H, $-^{\beta}CH_2$) 1.51-1.49 (m, 1H, $-^{\gamma}CH$), 0.93 (d, 3H, $-CH_3$, J = 6.8 Hz), 0.82 (d, 3H, $-CH_3$, J = 6.8 Hz);

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 168.2, 142.5, 132.0, 128.7, 128.1, 120.5, 119.4, 53.7, 50.4, 41.0, 26.5, 19.9, 19.8;

LCMS (APCI): m/z calcd. for $C_{14}H_{20}N_2O_3$: 264.1474; found: 265.1349 $(M+1)^+$



Compound 3e: methyl 2-(2-aminobenzamido)-3-methylpentanoate

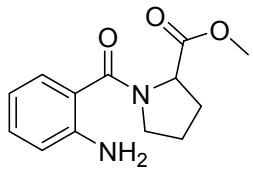
Light rosy solid; Yield = 64.5% (342 mg); M.P. = 91-92 °C;

IR (thin film): 2987, 1697, 1505, 1227 cm^{-1}

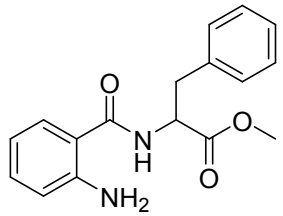
^{1}H NMR (400 MHz, $CDCl_3$):): δ 7.40 (d, 1H, Ar-H, J = 7.6 Hz), 7.25 (t, 1H, Ar-H, J = 7.6 Hz), 6.81-6.66 (m, 2H, Ar-H), 6.81-6.66 (m, 1H, -NH), 5.44 (broad, 2H, $-NH_2$); 4.36-4.31 (m, 1H, $-^{\alpha}CH$), 3.80 (s, 3H, $-OCH_3$), 1.57-1.54 (m, 1H, $-^{\beta}CH$), 1.52-1.48 (m, 2H, $-^{\gamma}CH_2$), 0.92 (d, 3H, $-CH_3$, J = 6.8Hz), 0.84 (d, 3H, $-CH_3$, J = 6.8 Hz);

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 168.7, 140.0, 133.2, 128.4, 121.2, 120.4, 120.1, 54.7, 43.4, 38.4, 33.4, 26.1, 19.7;

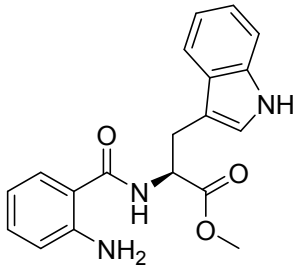
LCMS (APCI): m/z calcd. for $C_{14}H_{20}N_2O_3$: 264.1474; found: 265.1295$(M+1)^+$



Compound 3f: methyl (2-aminobenzoyl)prolinate
Colourless floppy solid; Yield = 66% (330 mg); M.P. = 116-118 °C;
IR (thin film): 3075, 2832, 1761, 1694, 1593, 1507, 1228 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, 1H, Ar-H, J = 6.8 Hz), 7.17 (t, 1H, Ar-H, J = 6.8 Hz), 6.81-6.76 (m, 2H, Ar-H), 6.81-6.76 (m, 1H, -NH), 5.47 (broad, 2H, $-NH_2$); 4.50-4.46 (m, 1H, $-^{\alpha}CH$), 3.69 (s, 3H, $-OCH_3$), 3.47-3.43 (m, 1H, $-^{\delta}CH_2$), 2.01-1.81 (m, 4H, $-^{\beta\&\gamma}CH_2$);
^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 167.4, 140.1, 136.4, 130.5, 124.5, 118.6, 118.1, 55.1, 49.2, 36.4, 24.8, 20.7;
LCMS (APCI): m/z calcd. for $C_{13}H_{16}N_2O_3$: 248.1161; found: 249.1007 $(M+1)^+$

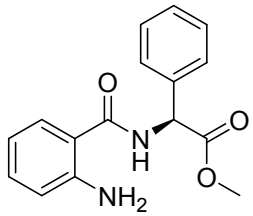


Compound 3g: methyl (2-aminobenzoyl)phenylalaninate
Light sandy brown solid; Yield = 68.1% (409 mg); M.P. = 120-121 °C;
IR (thin film): 3348, 2847, 1541, 1264 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, 1H, Ar-H, J = 7.6 Hz), 7.24 (t, 1H, Ar-H, J = 7.6 Hz), 6.80-6.63 (m, 7H, Ar-H), 6.70-6.63 (m, 1H, -NH), 5.50 (broad, 2H, $-NH_2$); 4.81-4.78 (m, 1H, $-^{\alpha}CH$), 3.81 (s, 3H, $-CH_3$), 2.88-2.74 (m, 2H, $-CH_2$);
^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 169.4, 141.7, 137.5, 133.6, 126.9, 126.4, 124.1, 123.9, 122.2, 122.0, 58.1, 53.4, 34.8;
LCMS (APCI): m/z calcd. for $C_{17}H_{18}N_2O_3$: 298.1317; found: 299.0332 $(M+1)^+$

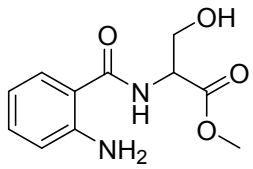


Compound 3h: methyl (2-aminobenzoyl)tryptophanate
Light brownish solid; Yield = 66.5% (446 mg); M.P. = 118-119 °C;
IR (thin film): 3456, 2949, 1532, 1057 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.69 (s, 1H, indole-NH), 7.66 (d, 1H, Ar-H, J = 7.0 Hz), 7.57-7.53 (m, 2H, Ar-H), 7.46-6.89 (m, 6H, Ar-H), 7.46-6.89 (m, 1H, -NH), 5.61 (broad, 2H, $-NH_2$), 4.62 (m, 1H, $^{\alpha}CH$), 3.58 (s, 3H, $-OCH_3$), 3.09-2.97 (m, 2H, $-^{\beta}CH_2$);

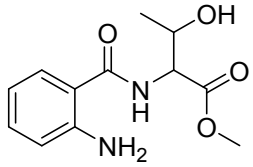
^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 168.7, 142.6, 136.7, 133.4, 132.9, 131.7, 129.8, 124.7, 122.8, 121.1, 119.1, 112.1, 110.6, 60.2, 51.0, 23.7;
LCMS (APCI): m/z calcd. for $C_{19}H_{19}N_3O_3$: 337.1426; found: 338.0373 $(M+1)^+$



Compound 3j: methyl (S)-2-(2-aminobenzamido)-2-phenylacetate
Colourless solid; Yield = 56.5% (327 mg); M.P. = 116-118 °C;
IR (thin film): 3447, 2973, 1572, 1066 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (t, 1H, Ar-H, J = 6.8 Hz), 7.24-6.82 (m, 8H, Ar-H), 5.68 (broad, 2H, $-NH_2$), 5.01 (d, 1H, $-^{\alpha}CH$, J = 4.1 Hz), 3.77 (s, 3H, $-OCH_3$);
^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 167.9, 141.7, 134.5, 132.7, 129.4, 128.9, 128.8, 126.11, 118.8, 118.2, 117.6, 116.4, 61.2, 51.9;
LCMS (APCI): m/z calcd. for $C_{16}H_{16}N_2O_3$: 284.1161; found: 285.0210 $(M+1)^+$



Compound 3k: methyl (2-aminobenzoyl)serinate
Creamy solid; Yield = 61.3% (292mg); M.P. = 133-134 °C;
IR (thin film): 3447, 2973, 1572, 1066 cm^{-1}
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, 1H, Ar-H, J = 7.2 Hz), 7.23 (t, 1H, Ar-H, J = 7.0 Hz), 6.71-6.59 (m, 2H, Ar-H), 6.71-6.63 (m, 1H, -NH), 5.47 (broad, 2H, $-NH_2$); 4.63-4.59 (m, 1H, $-^{\alpha}CH$), 3.80 (s, 3H, $-OCH_3$), 2.01 (d, 2H, $-^{\beta}CH_2$, J = 6.8 Hz);
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 168.3, 148.7, 133.7, 130.1, 128.3, 118.7, 116.8, 60.4, 56.7, 50.1;
LCMS (APCI): m/z calcd. for: $C_{11}H_{14}N_2O_4$: 238.0954; found: 238.9813 $(M+1)^+$



Compound 3l: methyl 2-(2-aminobenzamido)-3-hydroxybutanoate

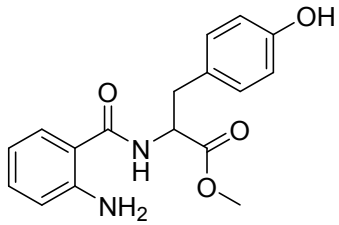
Creamy solid; Yield = 59.7% (301 mg); M.P. = 127-128 °C;

IR (thin film): 3447, 2973, 1572, 1066 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, 1H, Ar-H, J = 7.0 Hz), 7.21 (t, 1H, Ar-H, J = 7.0 Hz), 6.81-6.56 (m, 2H, Ar-H), 6.81-6.67 (m, 1H, -NH), 5.51 (broad, 2H, $-NH_2$); 4.63-4.59 (m, 1H, -$^{\alpha}$CH), 3.76 (s, 3H, $-OCH_3$), 2.32 (m, 1H, -$^{\beta}$CH), 1.21 (d, 3H, $-CH_3$, J = 6.2 Hz);

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 168.4, 140.1, 133.7, 126.1, 121.5, 118.3, 118.0, 57.4, 51.3, 44.3, 20.8;

LCMS (APCI): m/z calcd. for $C_{12}H_{16}N_2O_4$: 252.1110; found: 253.0058 $(M+1)^+$



Compound 3m: methyl (2-aminobenzoyl)tyrosinate

Light buff solid; Yield = 59% (371 mg); M.P. = 132-134 °C;

IR (thin film): 3447, 2973, 1572, 1066 cm^{-1}

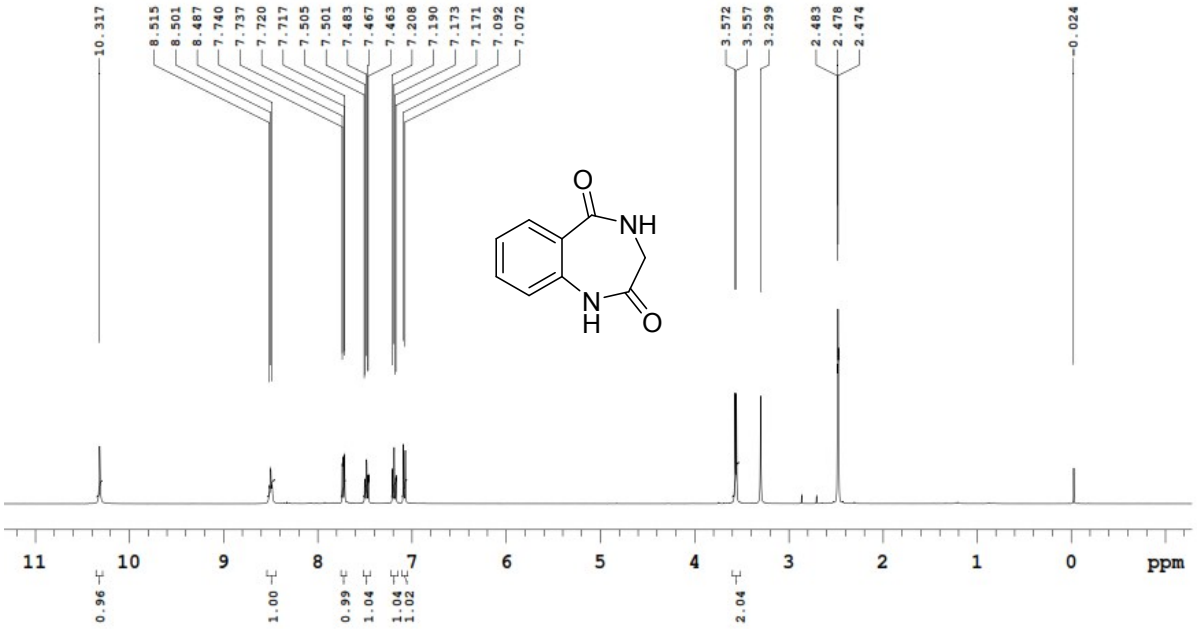
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, 1H, Ar-H, J = 6.2 Hz), 7.30 (t, 1H, Ar-H, J = 6.2 Hz), 7.23 (dd, 2H, Ar-H, J = 1.6 & 6.0 Hz), 7.01-6.76 (m, 4H, Ar-H), 7.01-6.76 (m, 1H, -NH), 5.66 (broad, 2H, $-NH_2$); 4.52-4.49 (m, 1H, -$^{\alpha}$CH), 3.77 (s, 3H, $-OCH_3$), 2.69-2.53 (m, 2H, $-CH_2$);

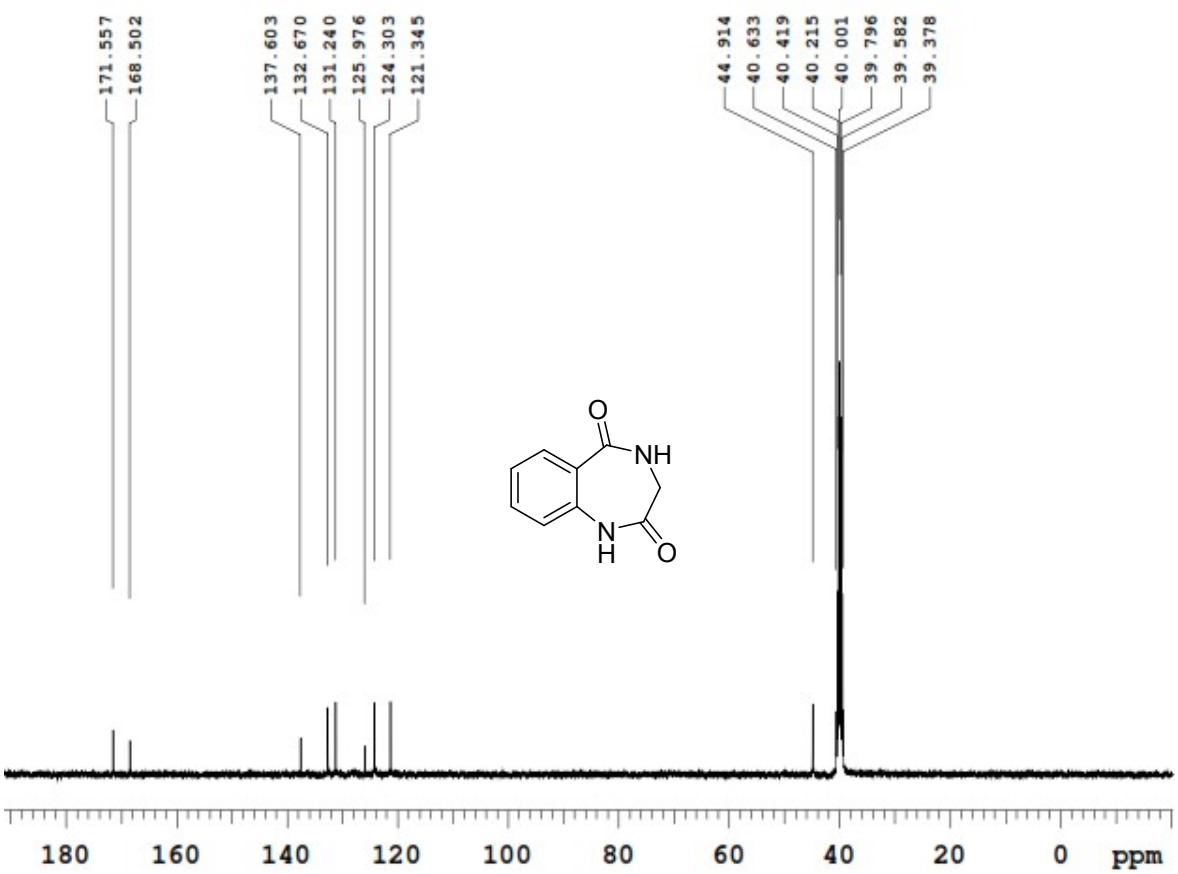
^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 168.4, 151.1, 148.6, 131.2, 131.0, 130.2, 130.0, 128.4, 118.8, 118.4, 116.8, 115.6, 115.1, 56.4, 51.4, 28.4;

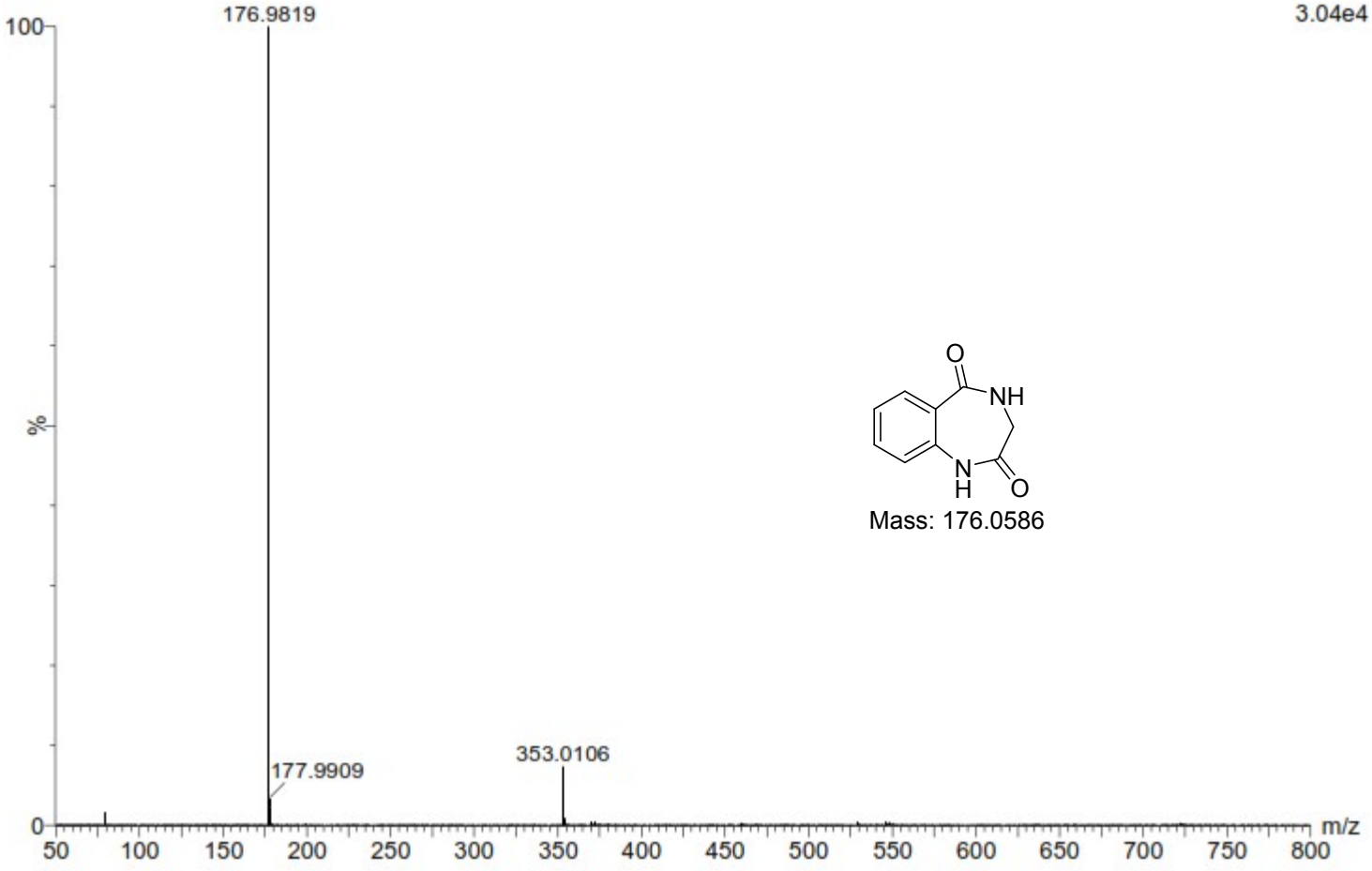
LCMS (APCI): m/z calcd. for $C_{17}H_{18}N_2O_4$: 314.1267; found: 315.0268 $(M+1)^+$

Spectra for Compounds

^{1}H NMR, ^{13}C NMR and Mass Spectra for Compound **4a**

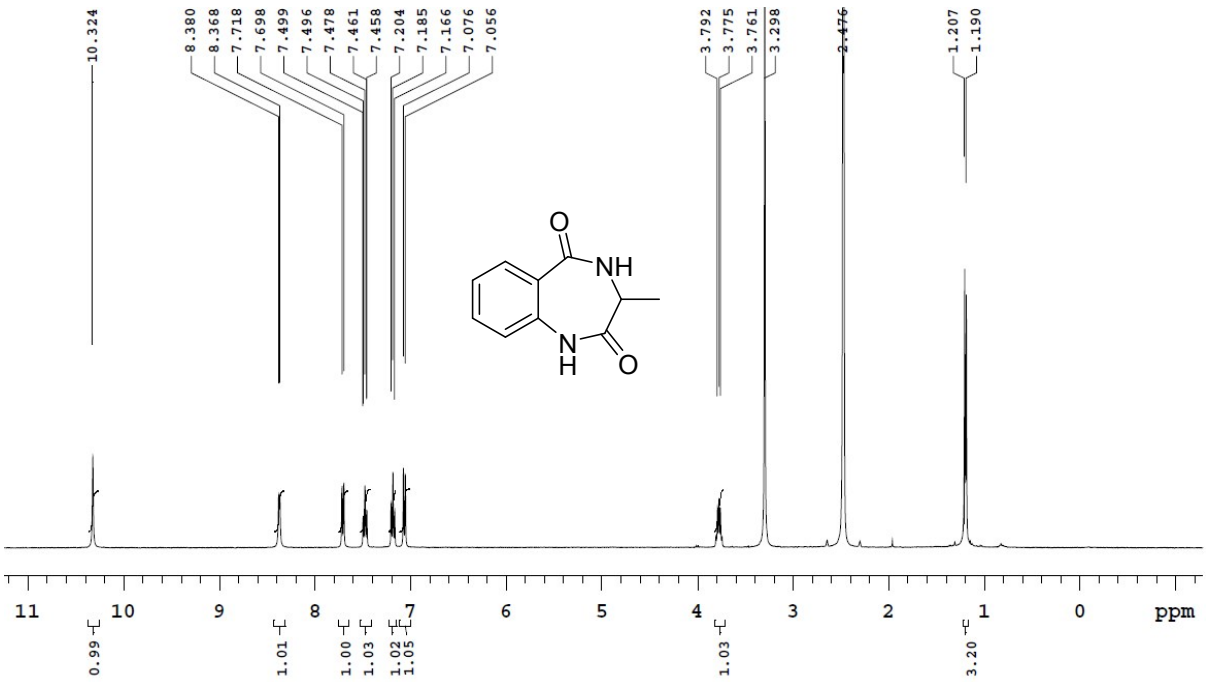


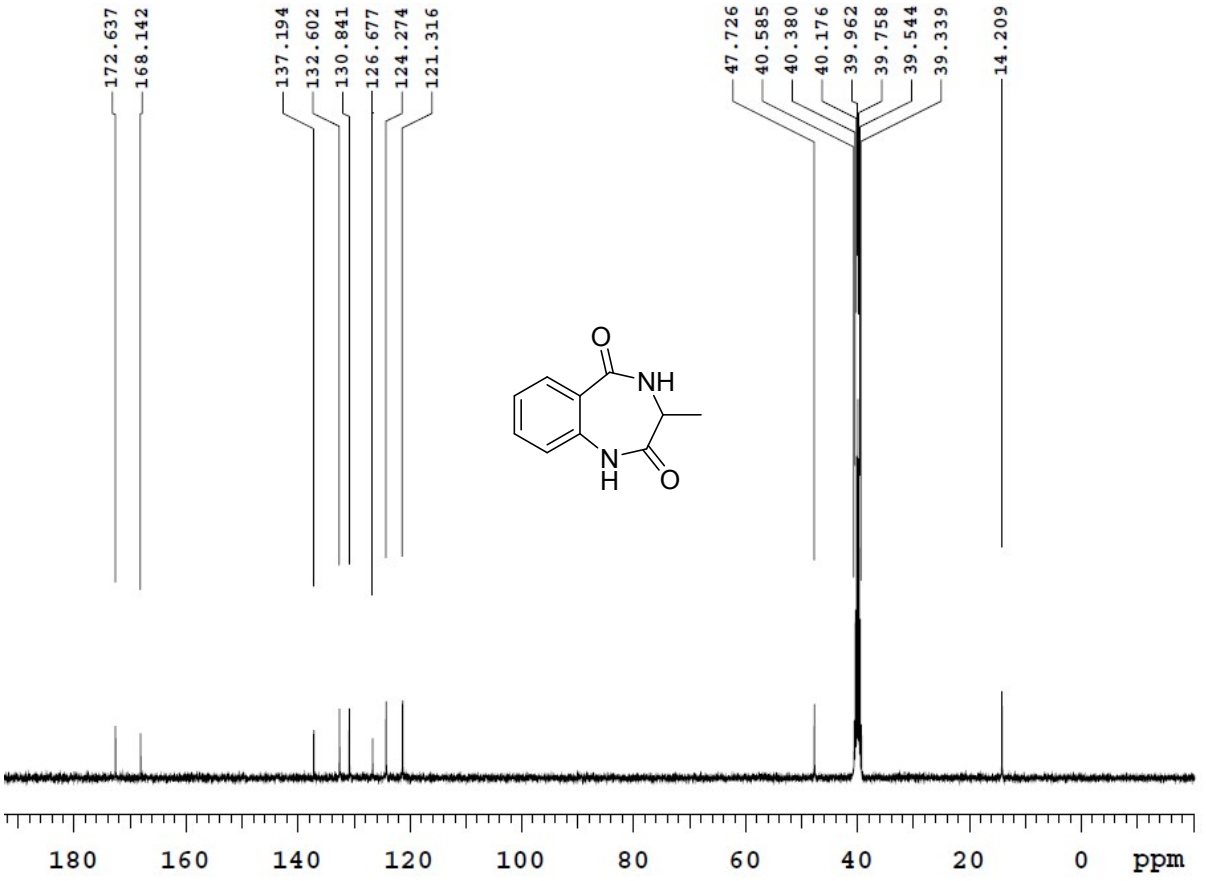


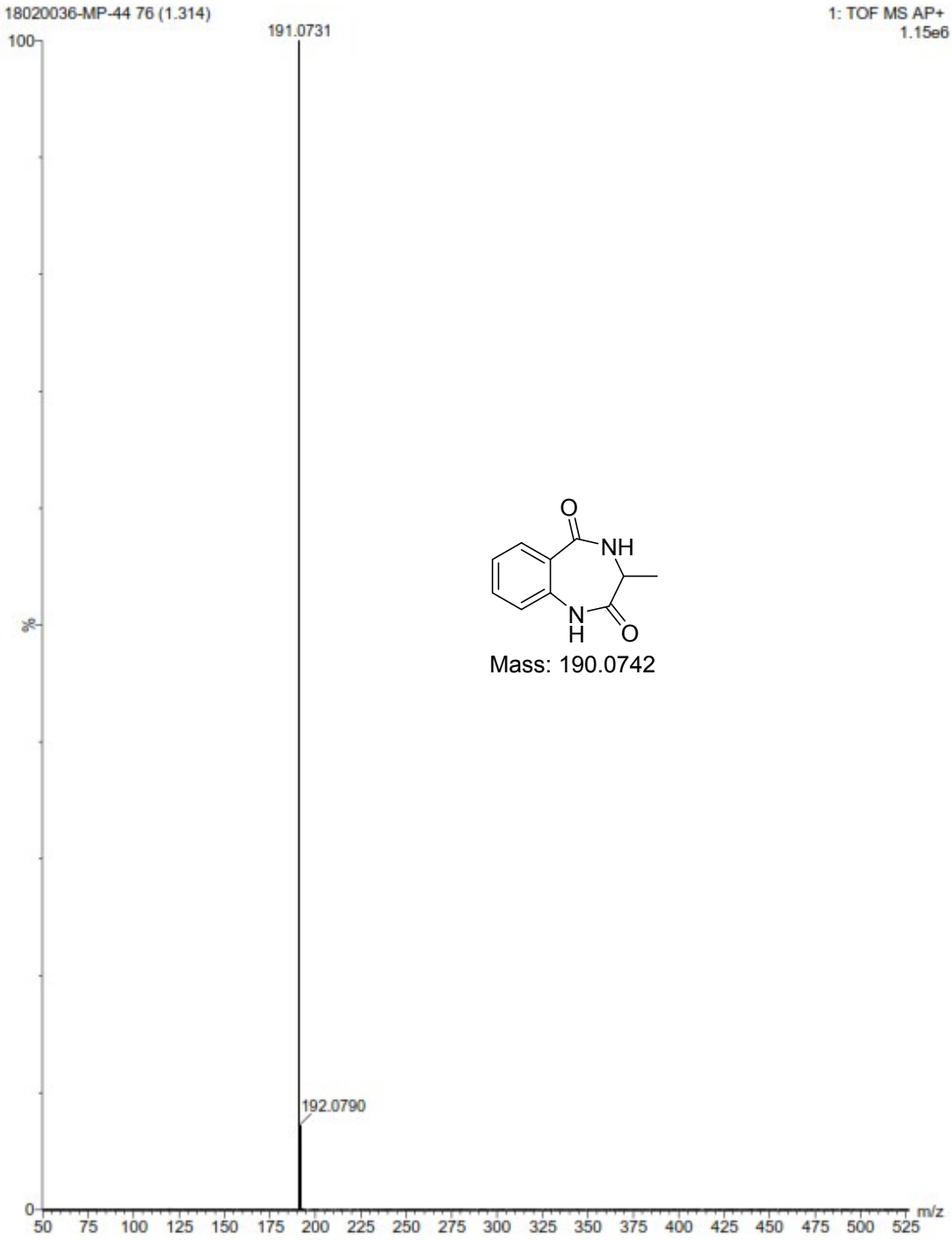


Mass: 176.0586

^{1}H NMR, ^{13}C NMR and Mass Spectra for Compound **4b**

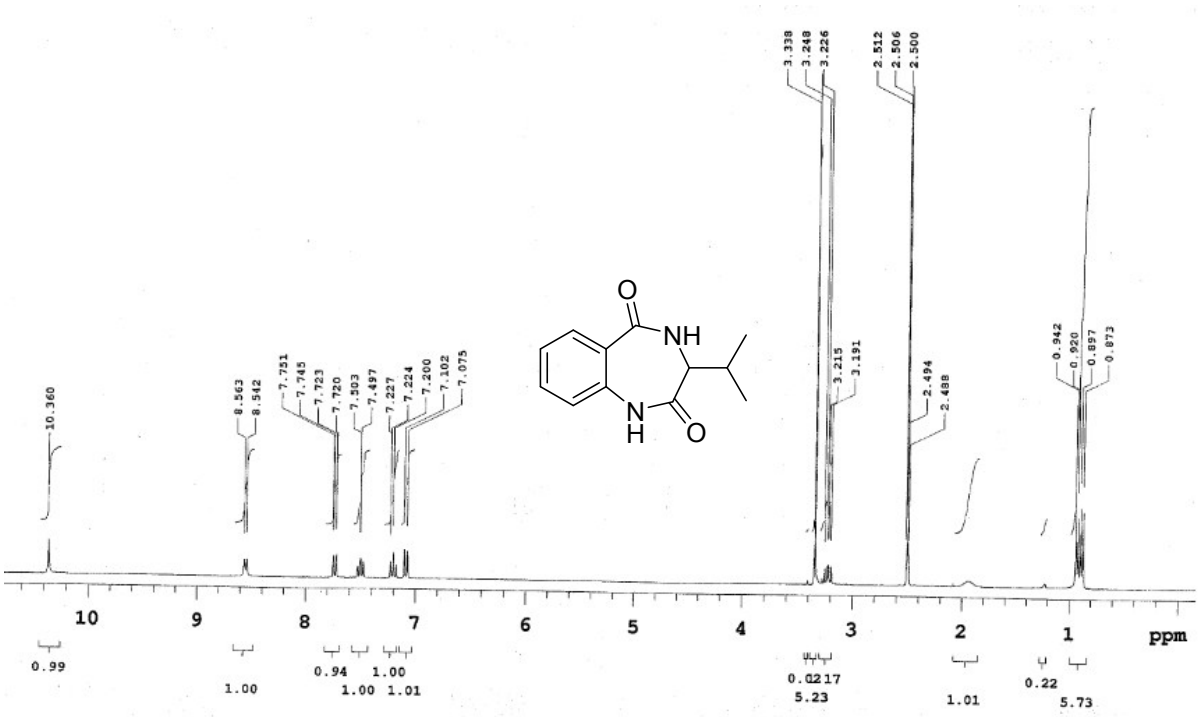


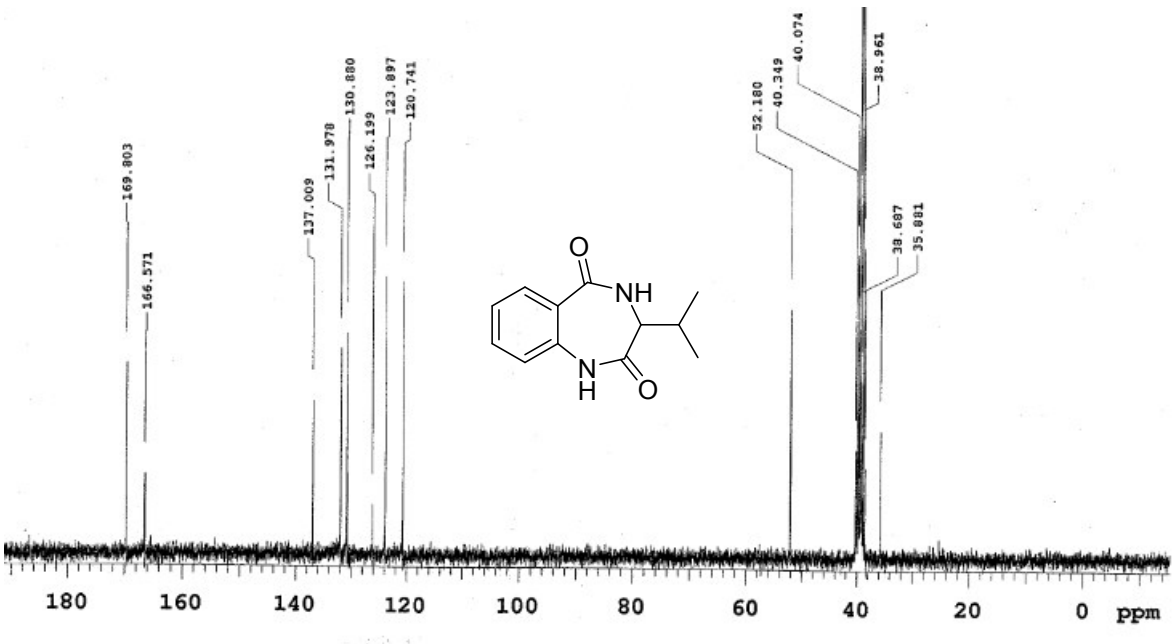


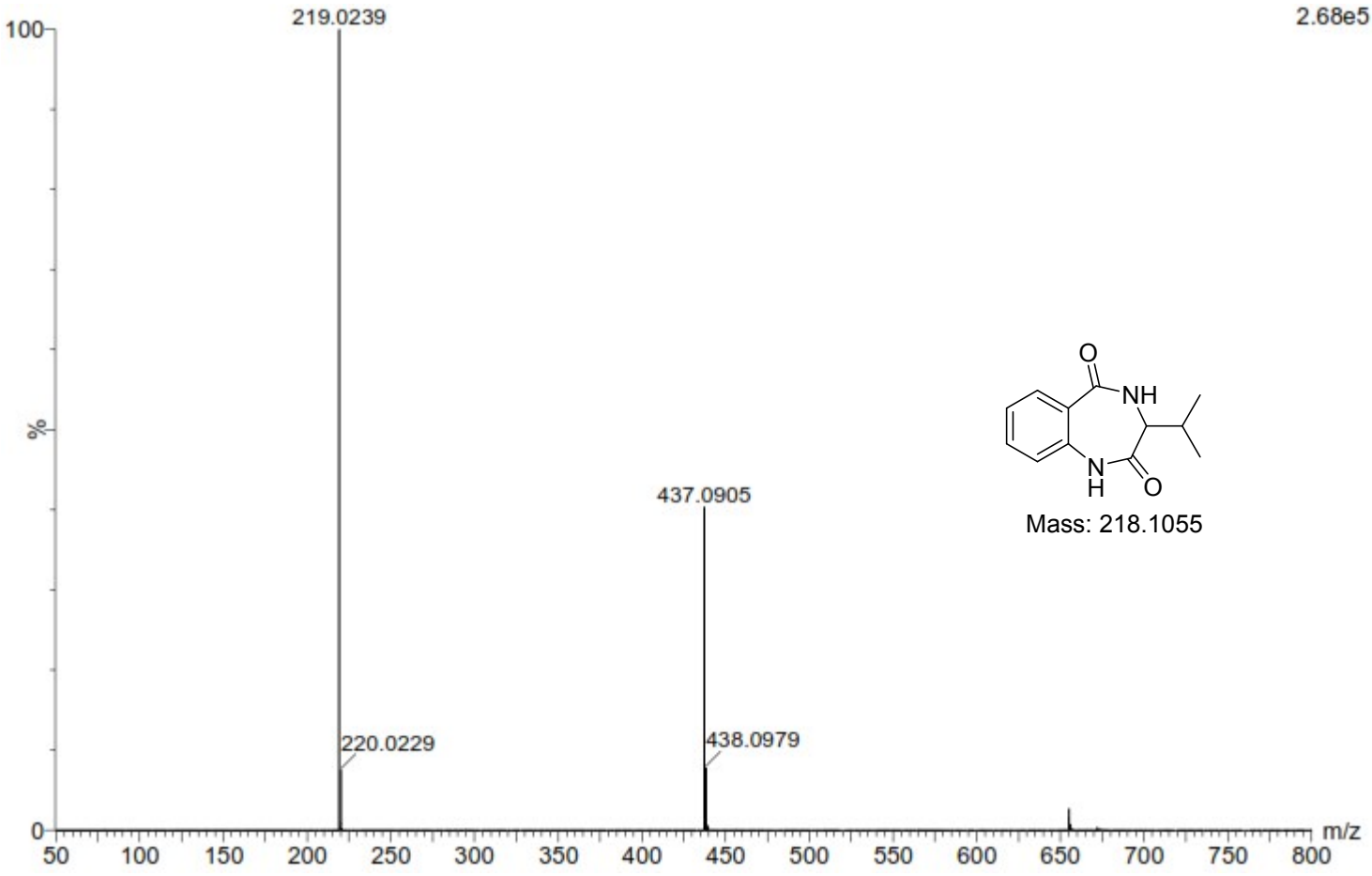


Mass: 190.0742

^{1}H NMR,^{13}C NMR and Mass Spectra for Compound **4c**

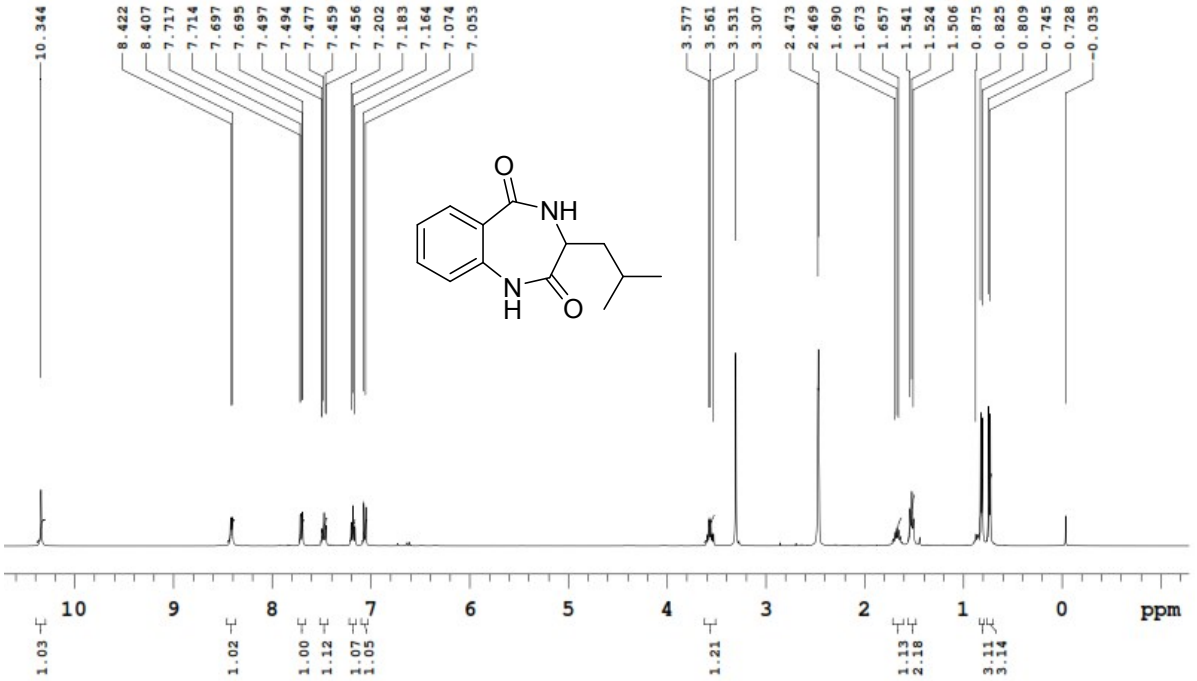


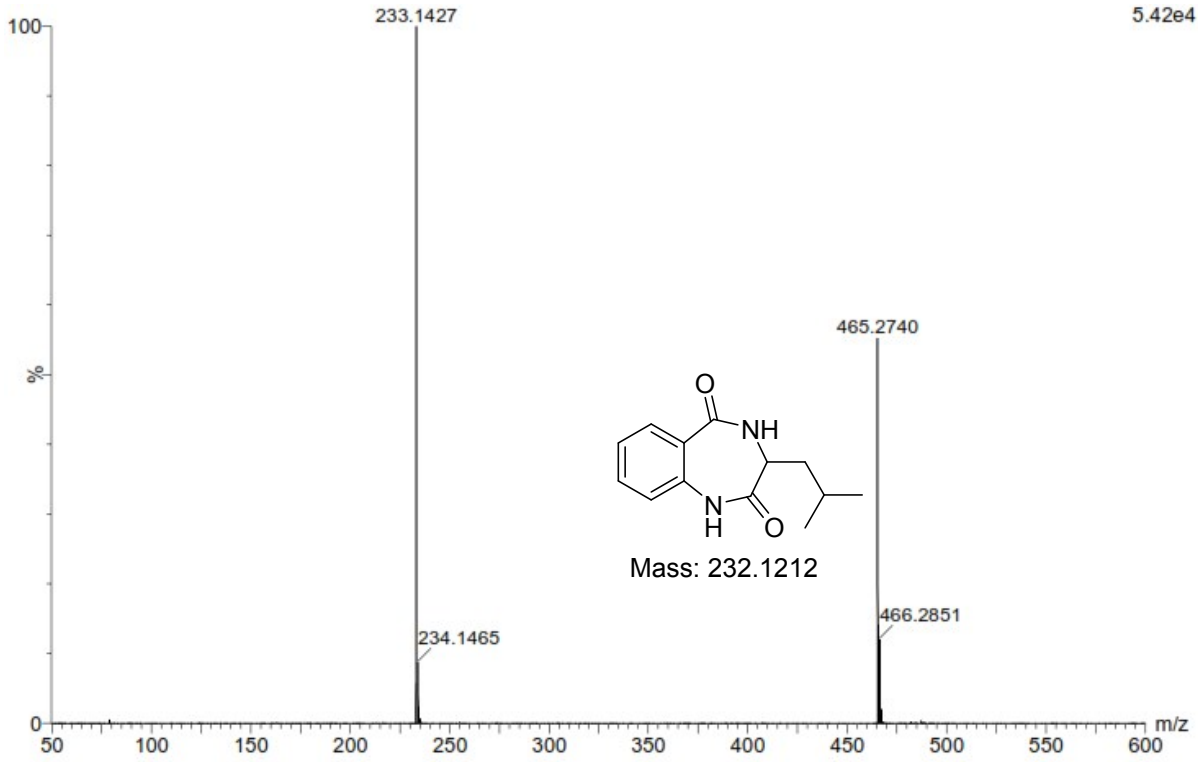




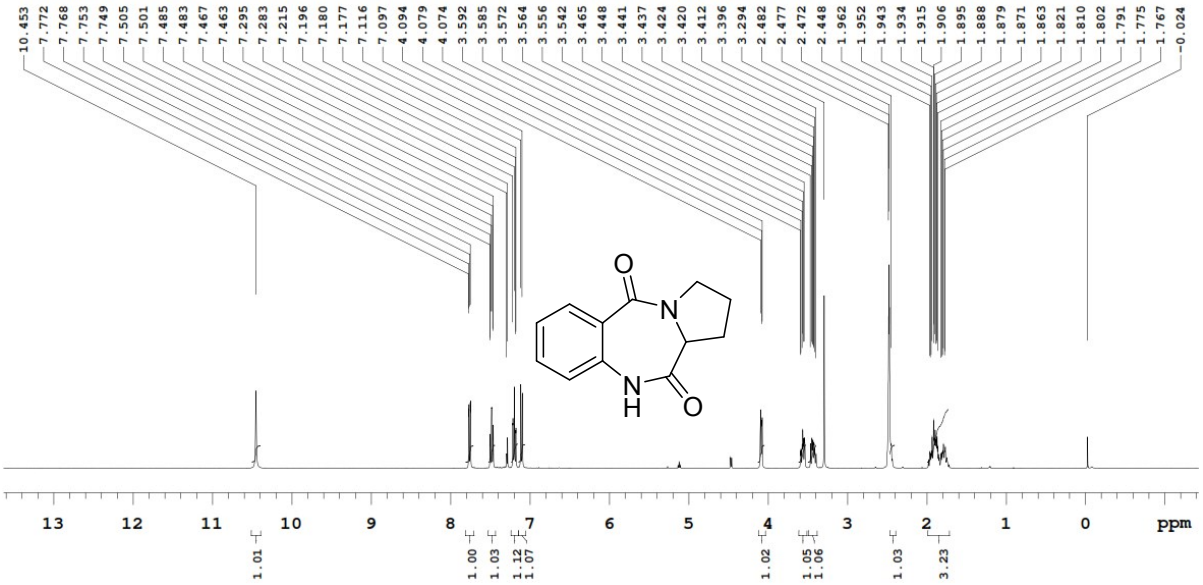
Mass: 218.1055

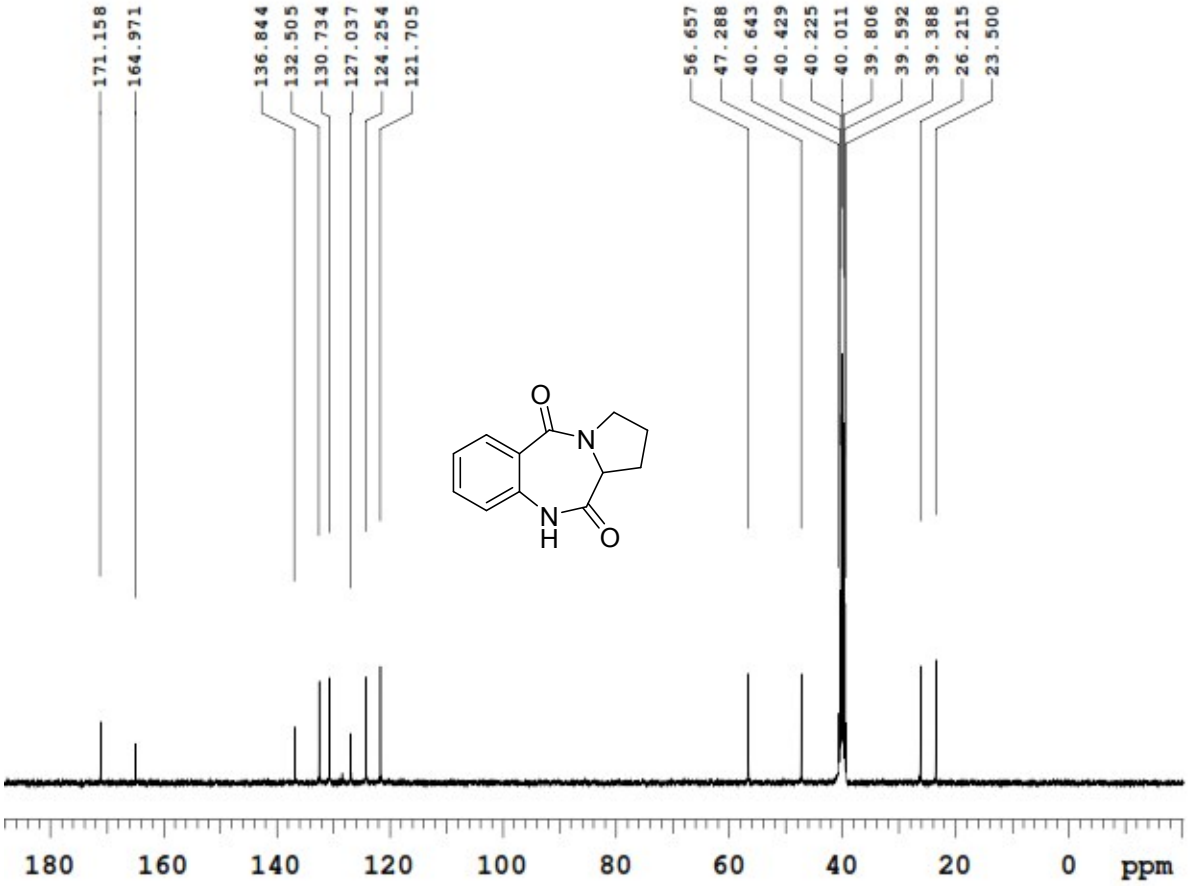
[1]H NMR and Mass Spectra for Compound **4d**

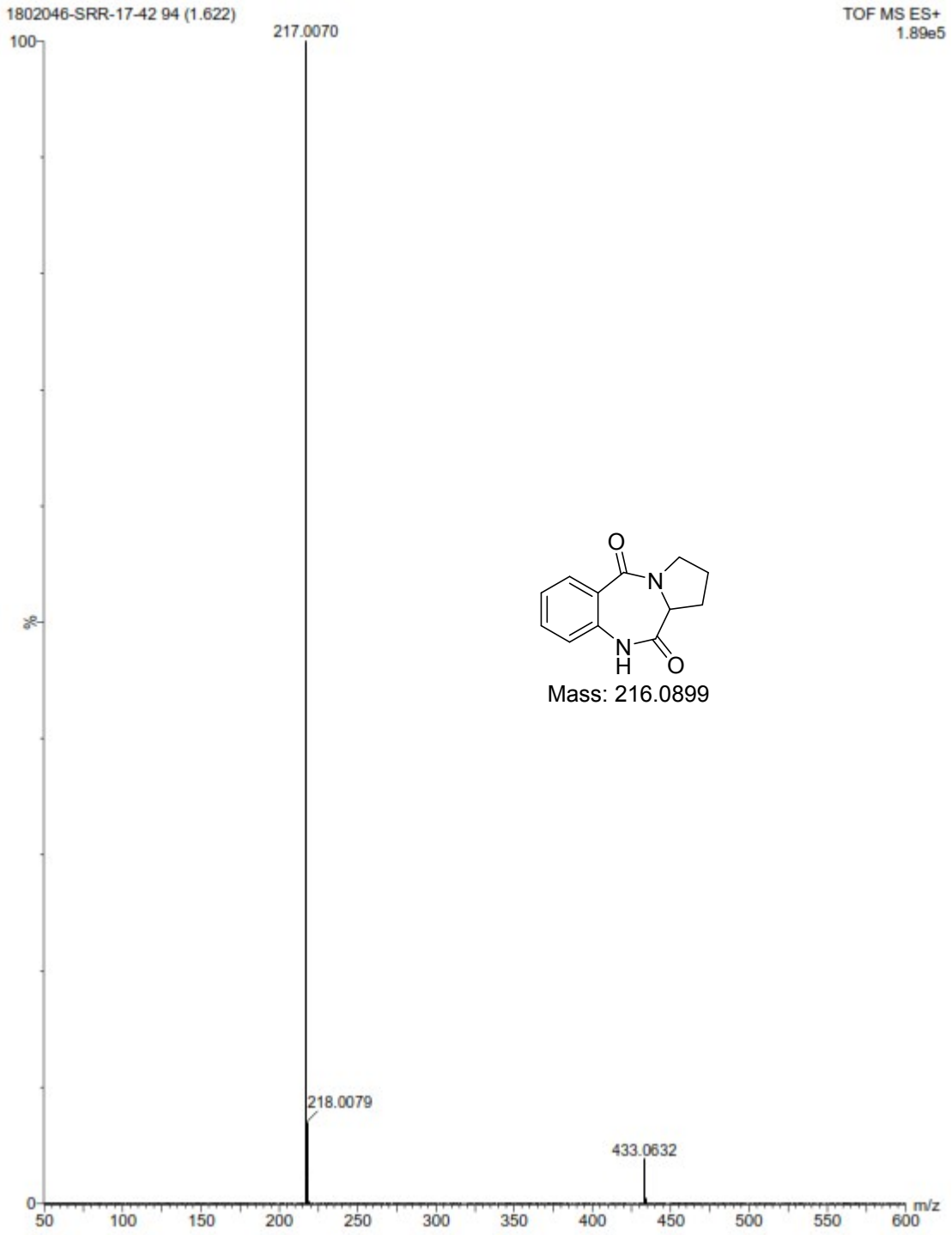




^{1}H NMR, ^{13}C NMR and Mass Spectra for Compound **4f**

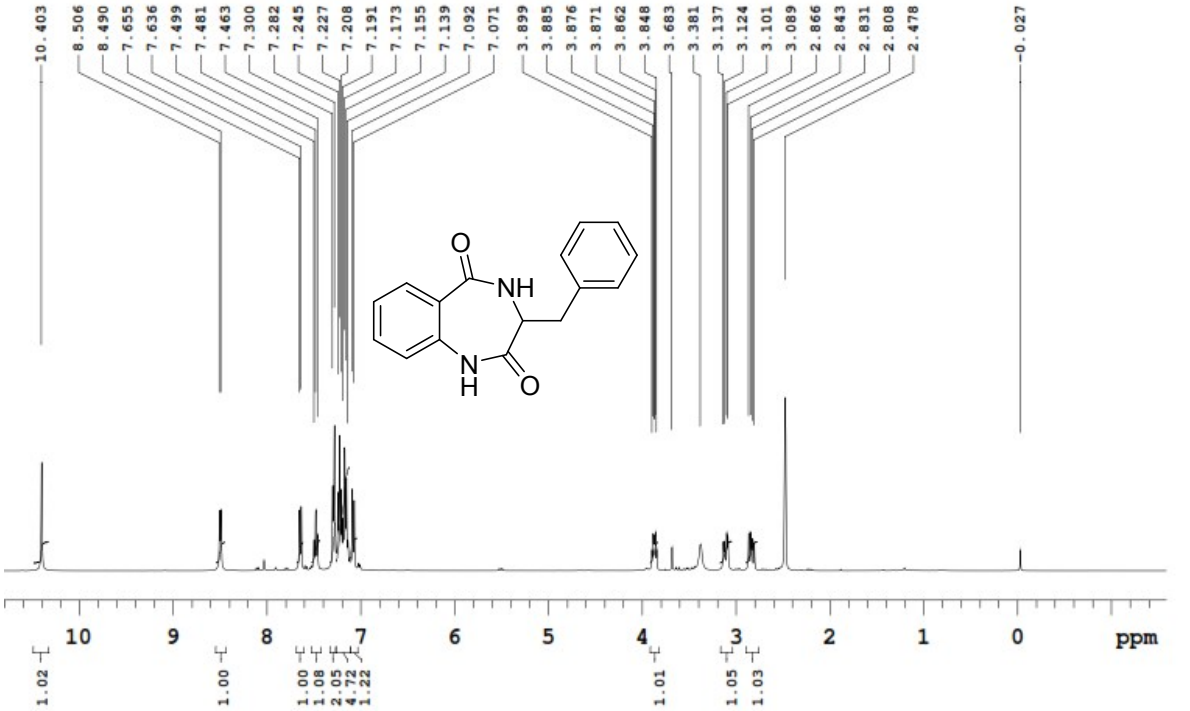


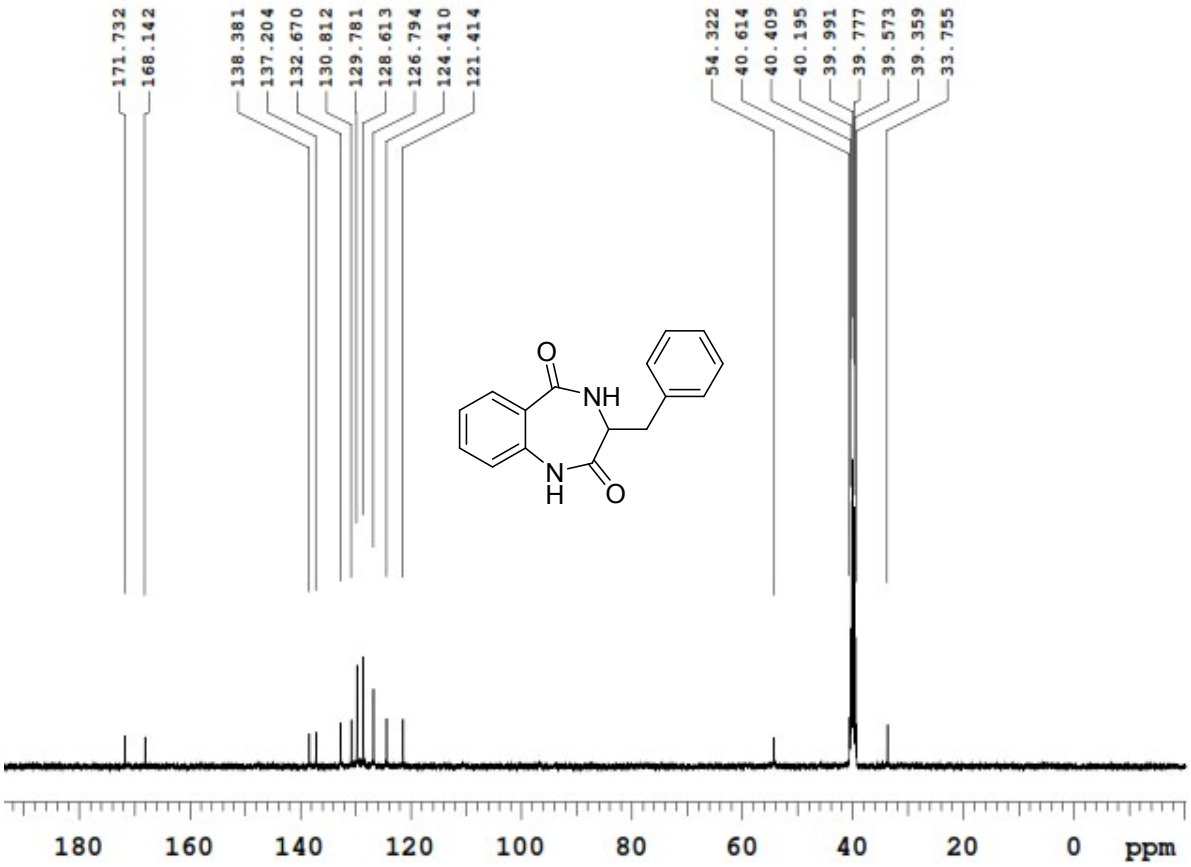


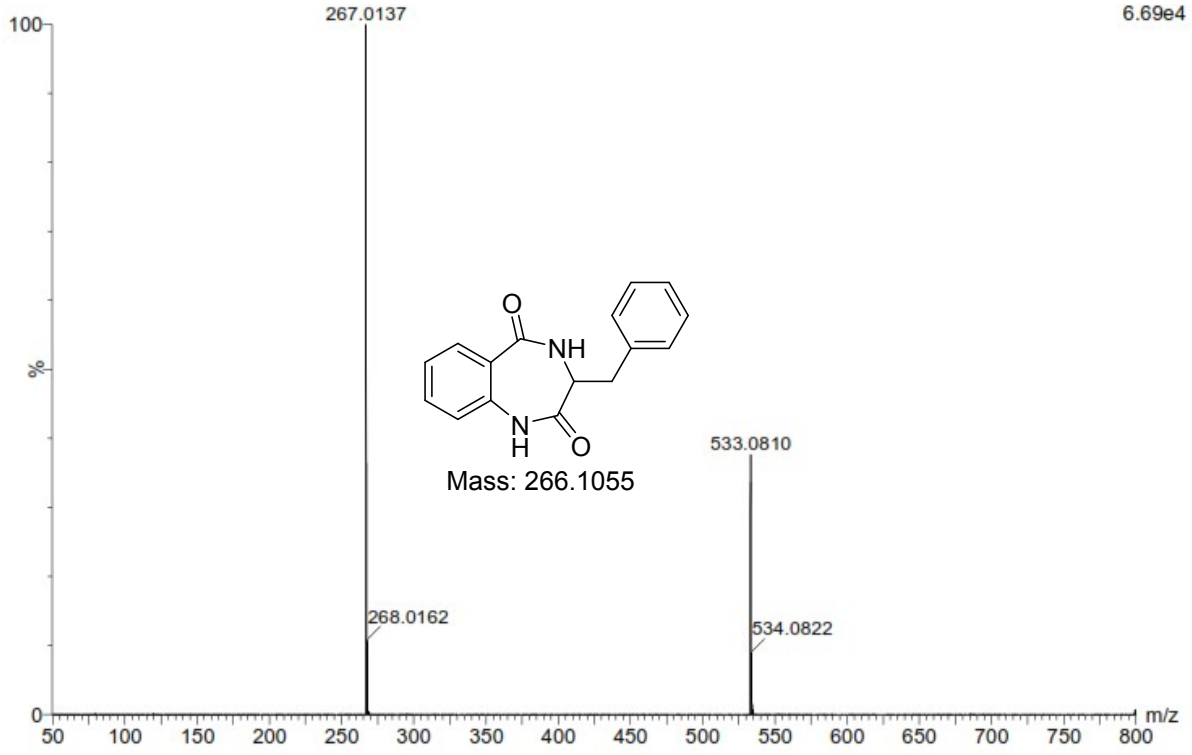


Mass: 216.0899

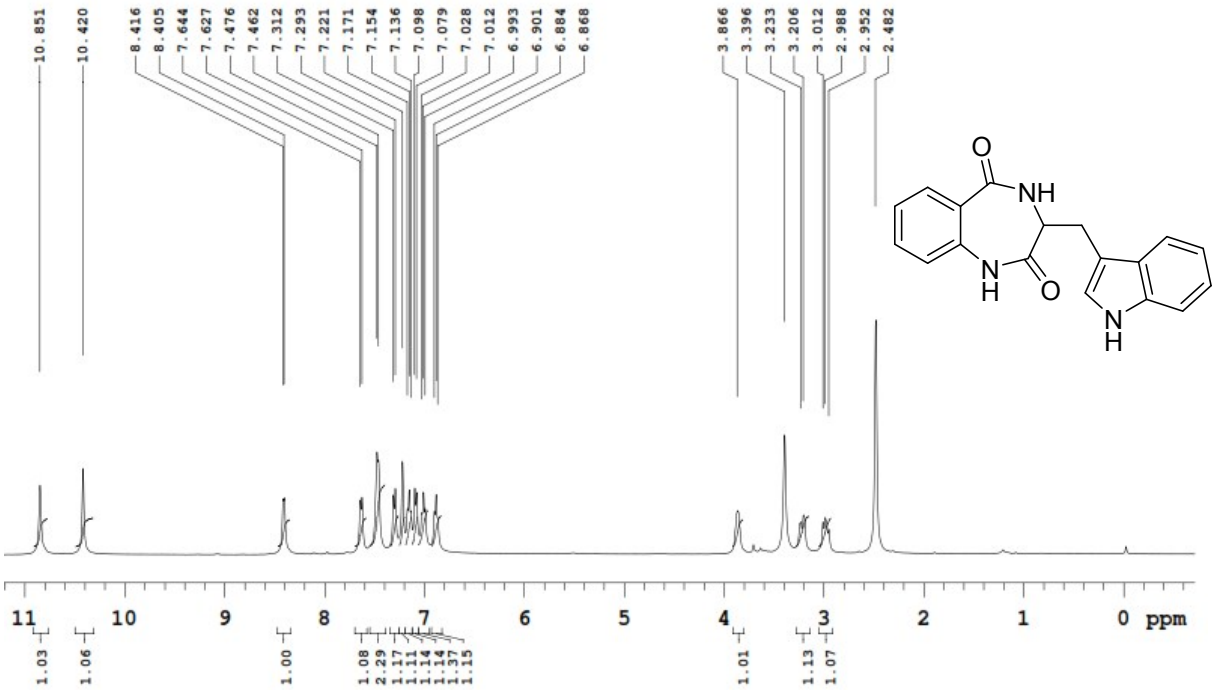
^{1}H NMR, ^{13}C NMR and Mass Spectra for Compound **4g**

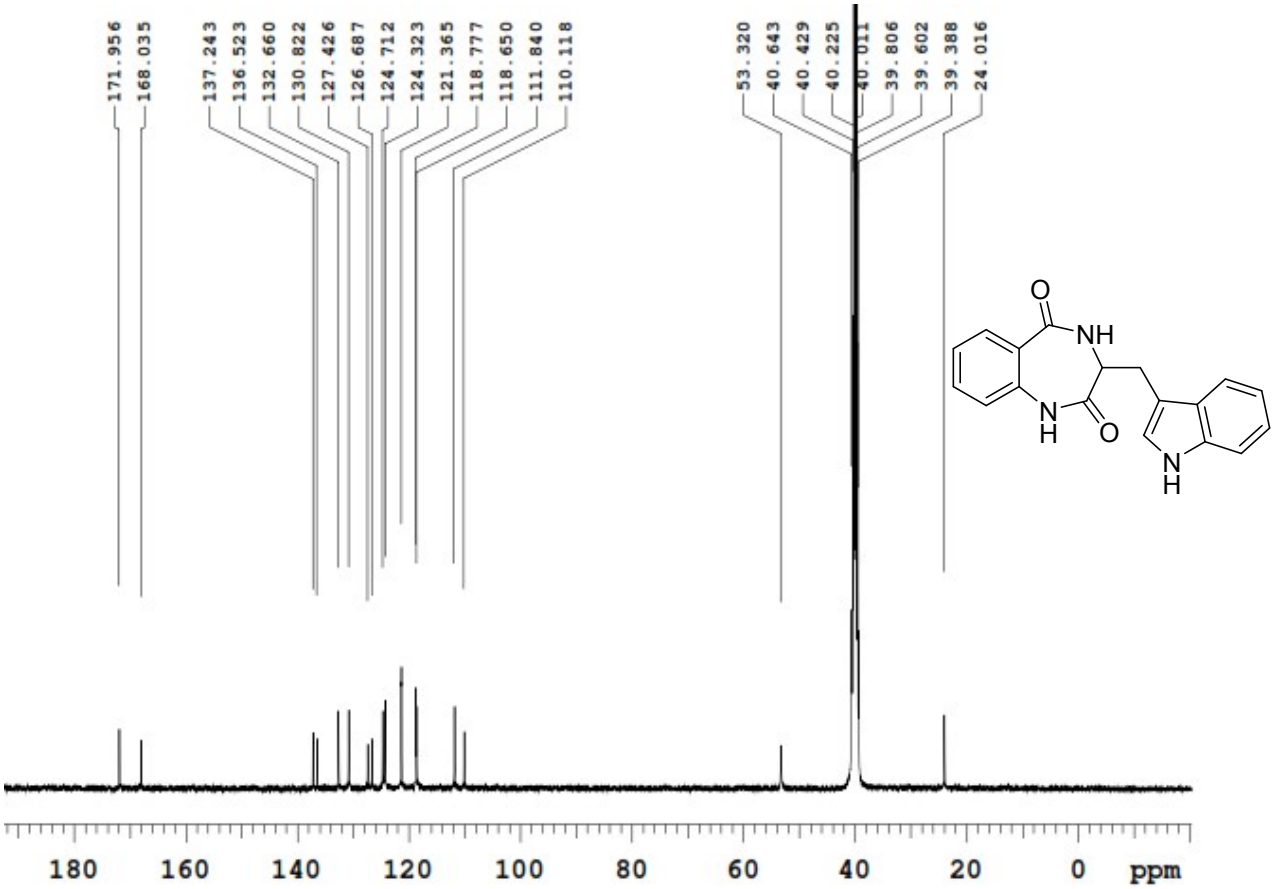


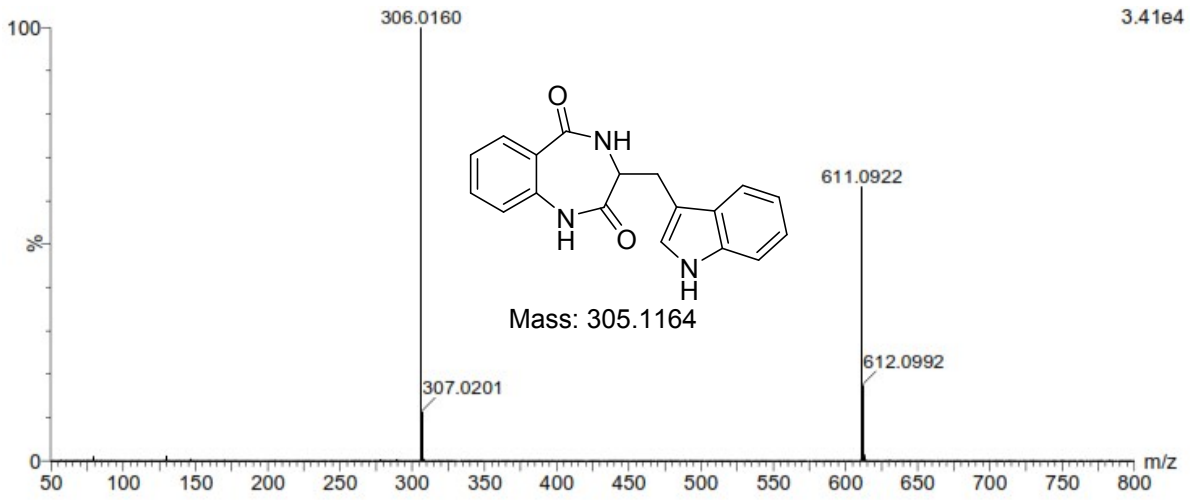



267.0137
6.69e4
100
%
O
NH
N
H
O
Mass: 266.1055
533.0810
268.0162
534.0822
0
50 100 150 200 250 300 350 400 450 500 550 600 650 700 750 800
m/z

^{1}H NMR, ^{13}C NMR and Mass Spectra for Compound **4h**

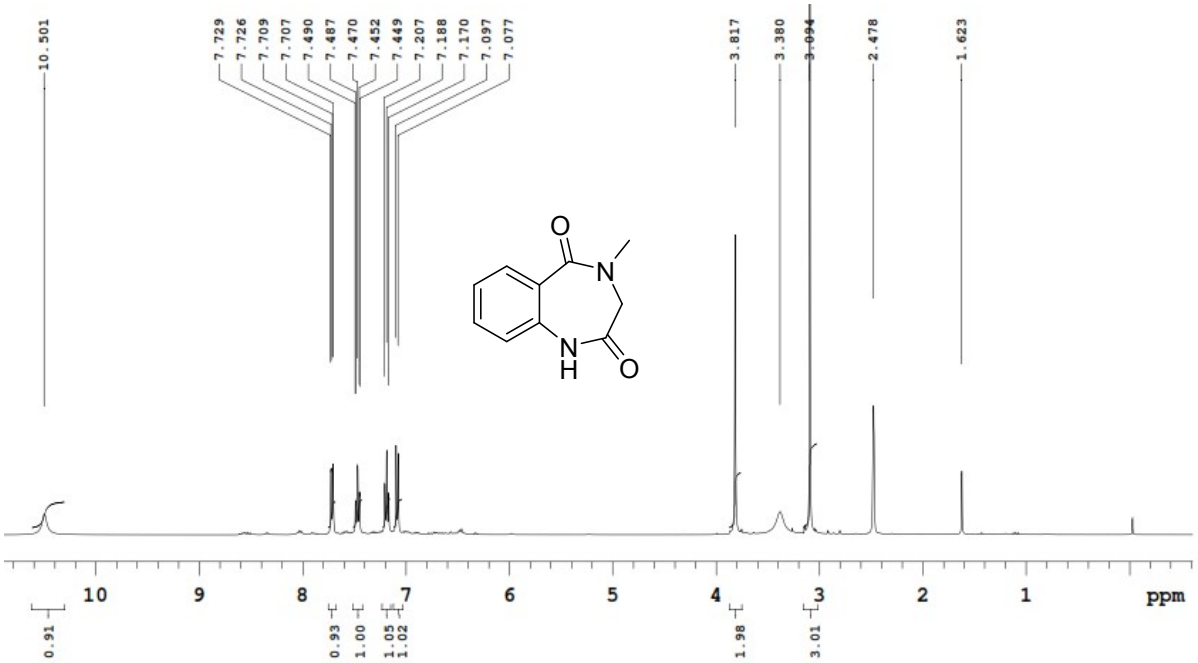


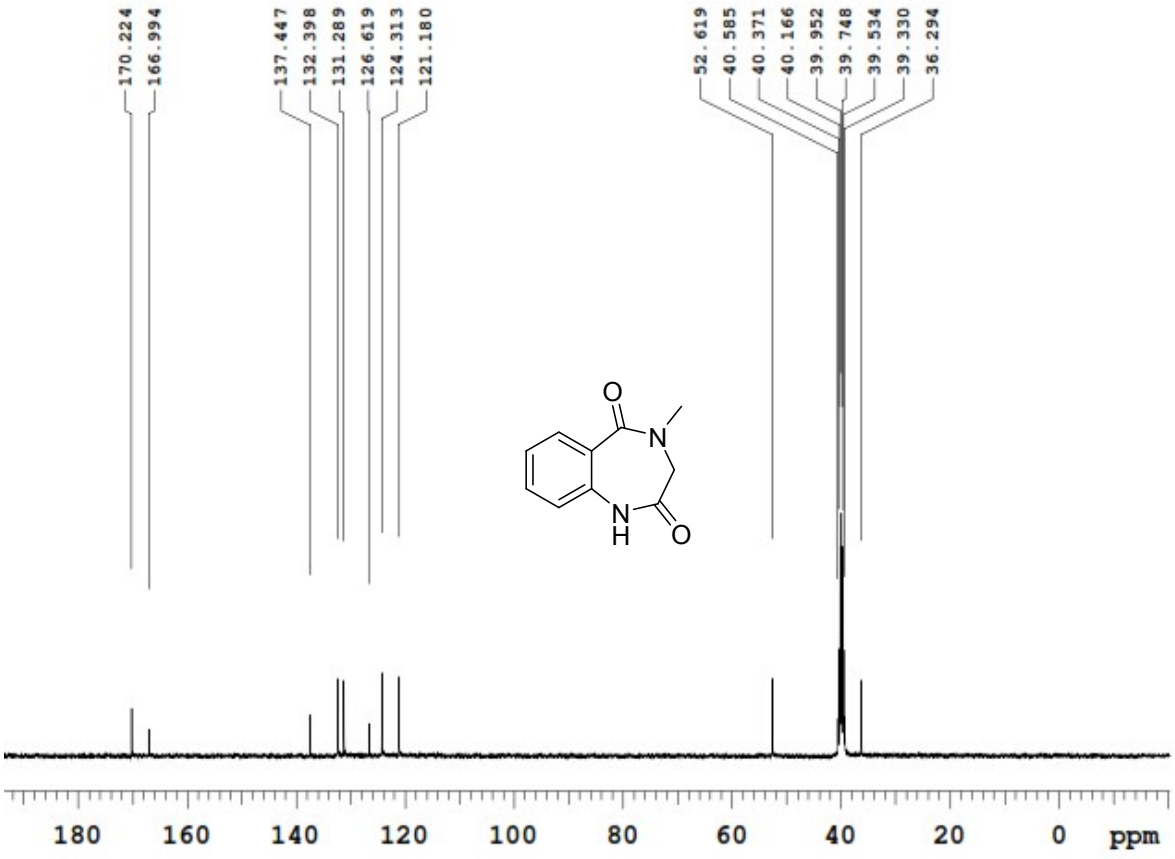


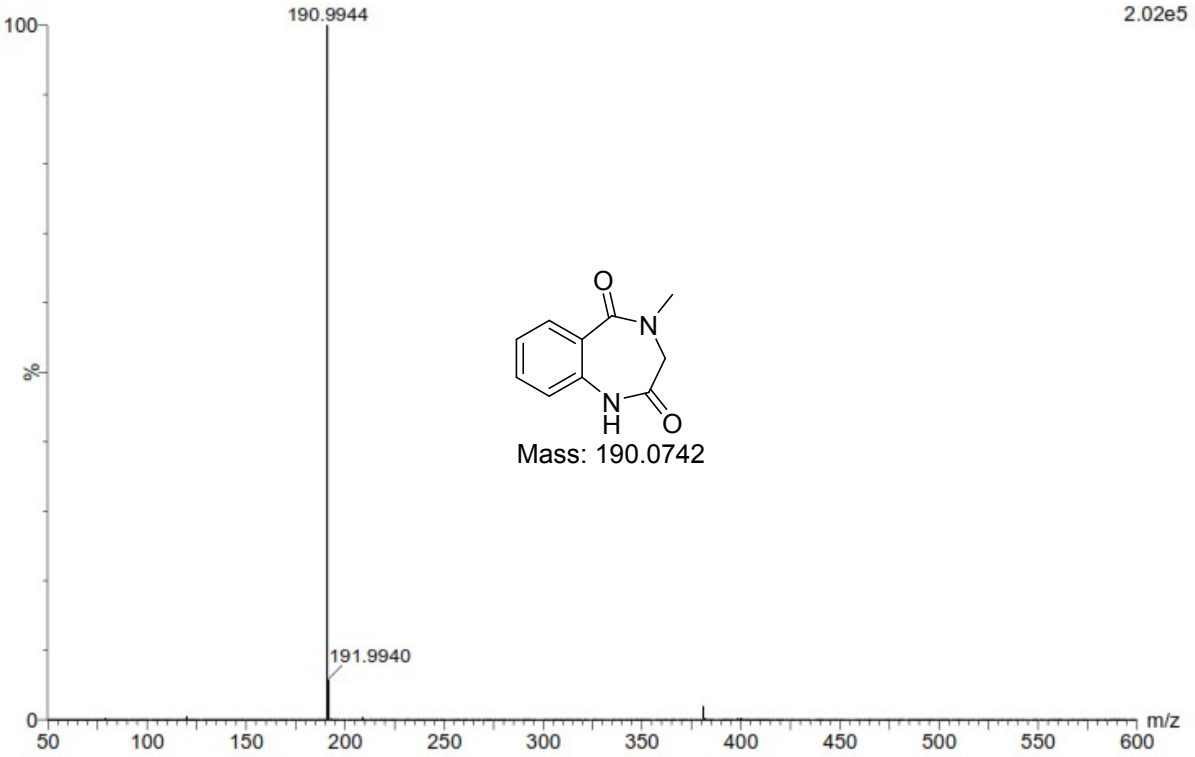


Mass: 305.1164

^{1}H NMR, ^{13}C NMR and Mass Spectra for Compound **4i**

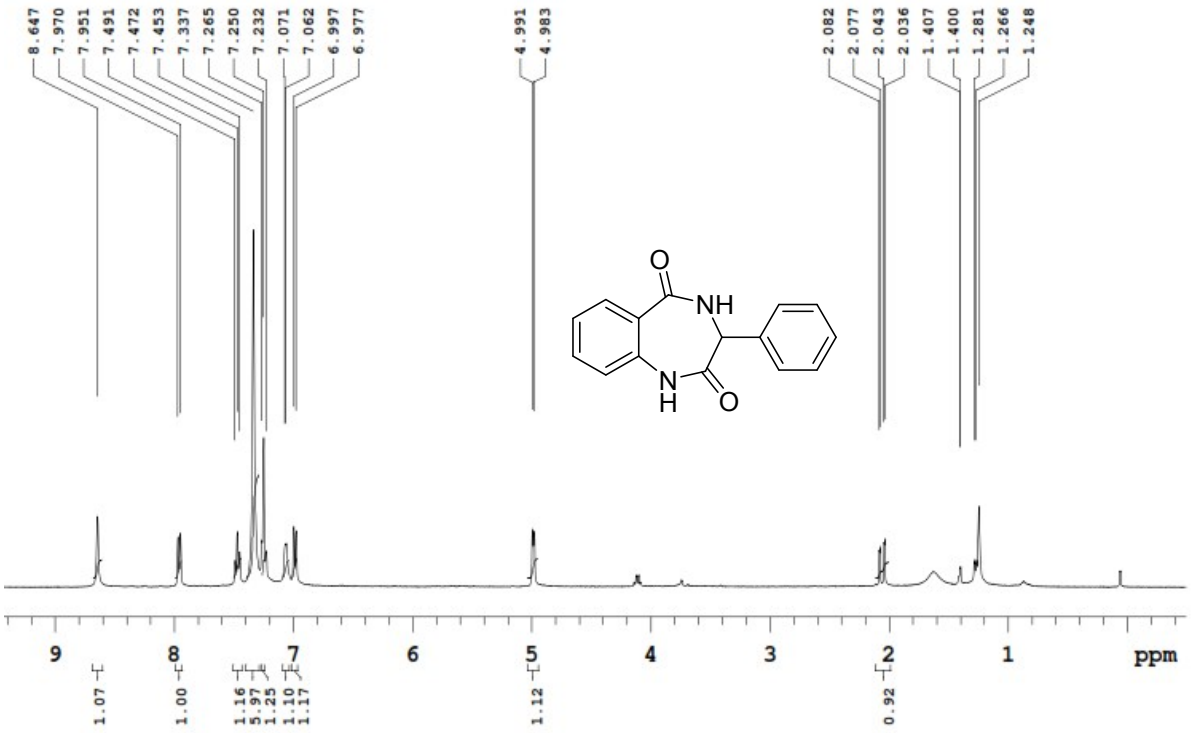


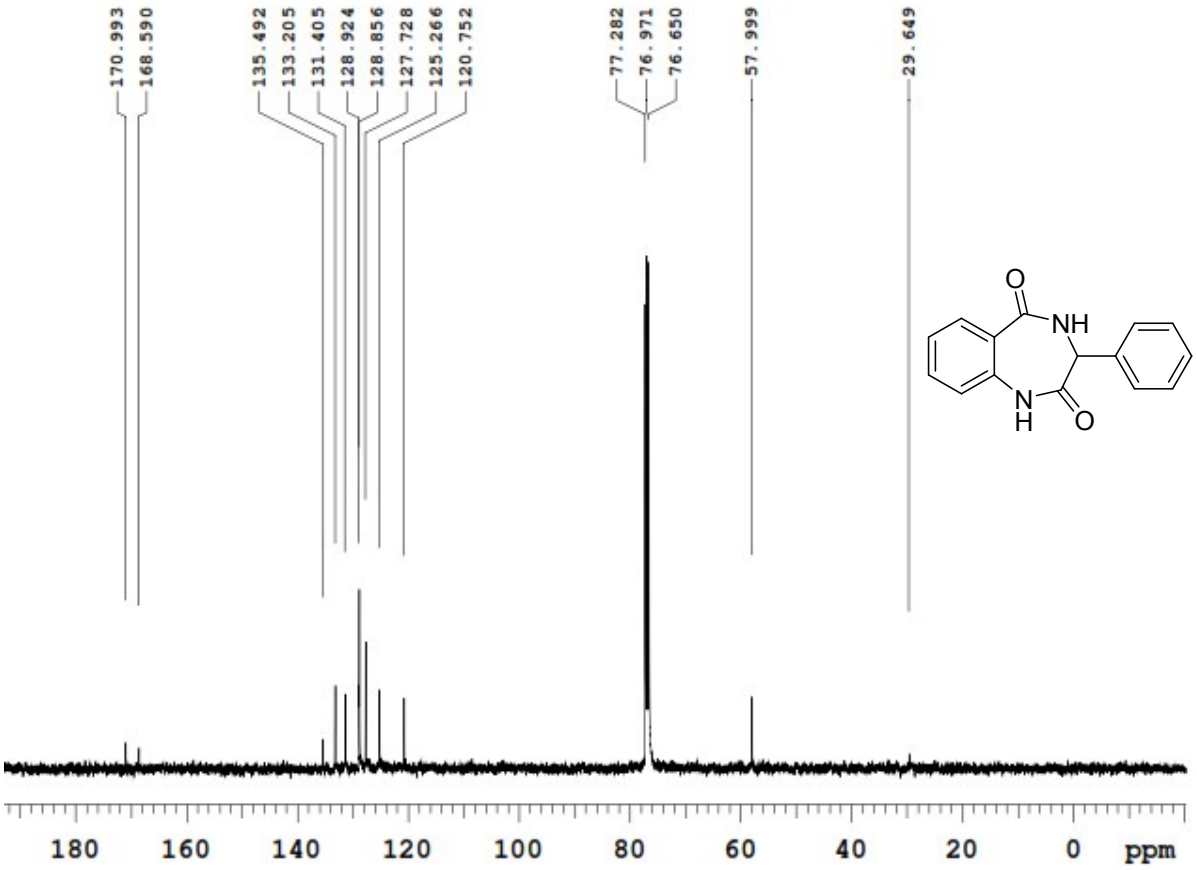


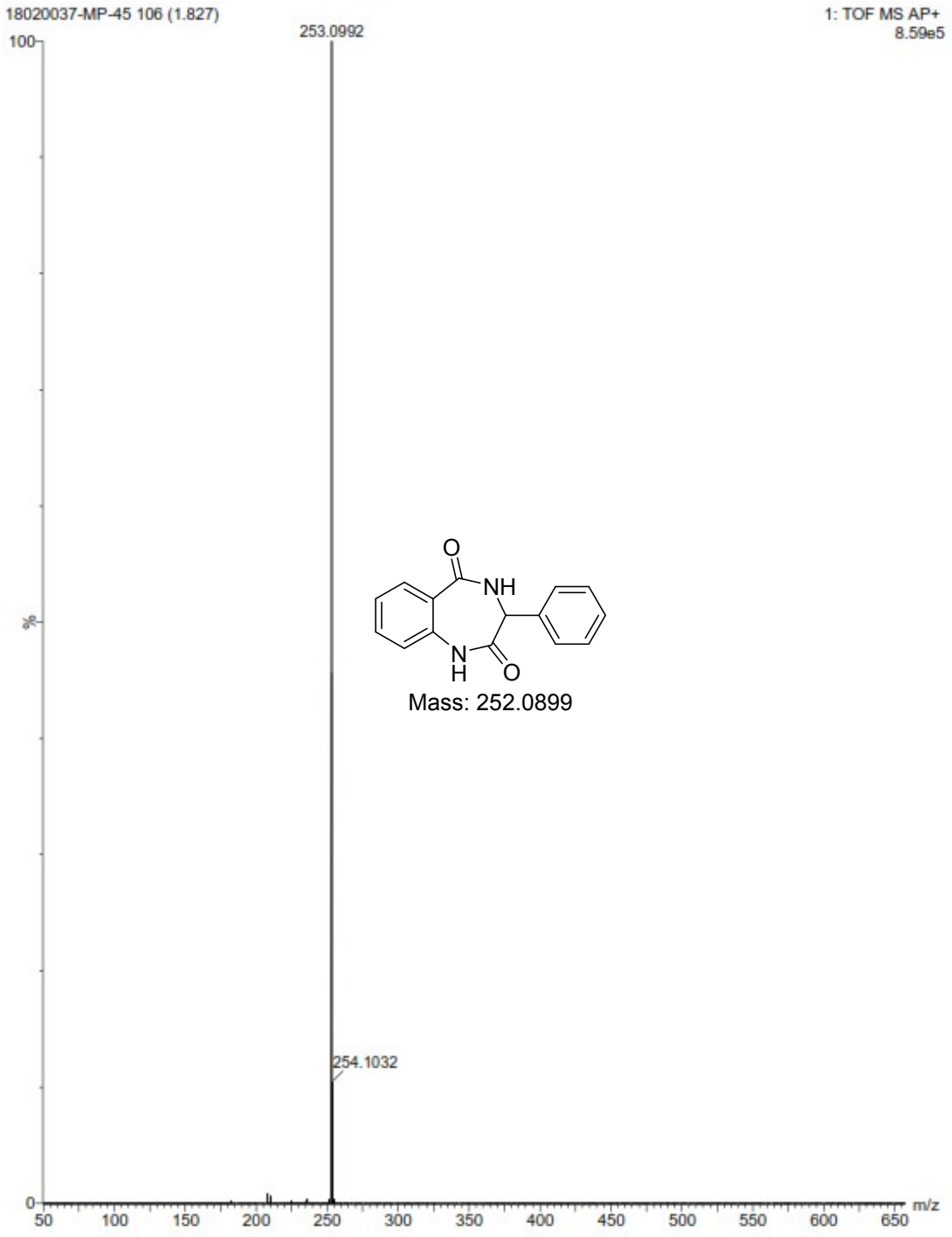


Mass: 190.0742

^{1}H NMR, ^{13}C NMR and Mass Spectra for Compound **4j**

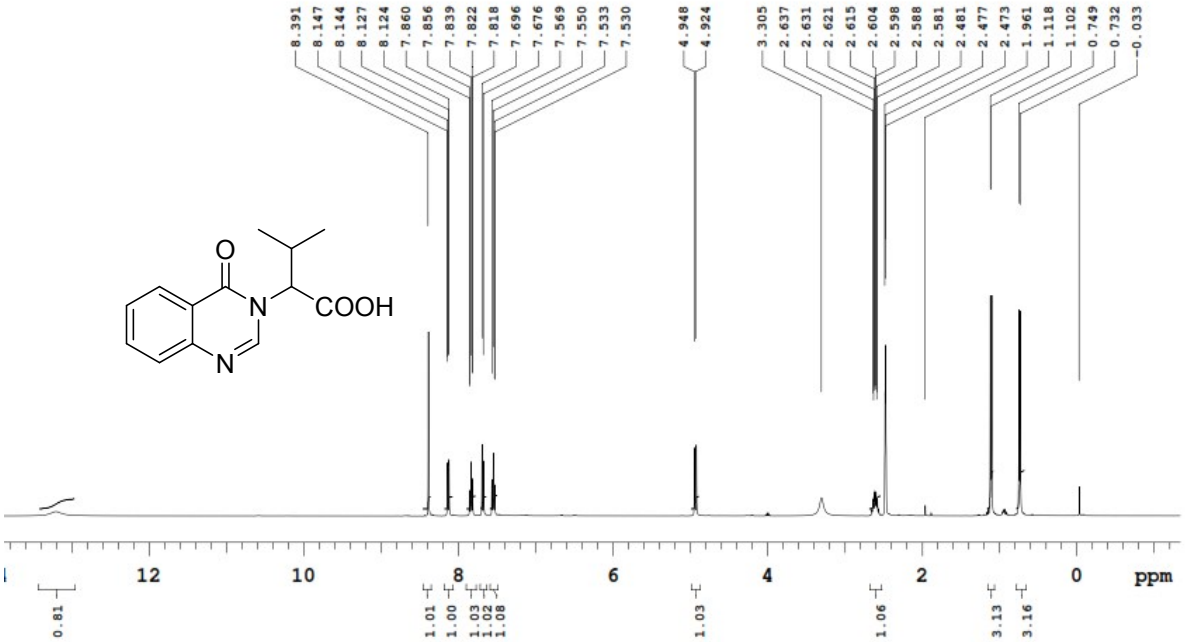


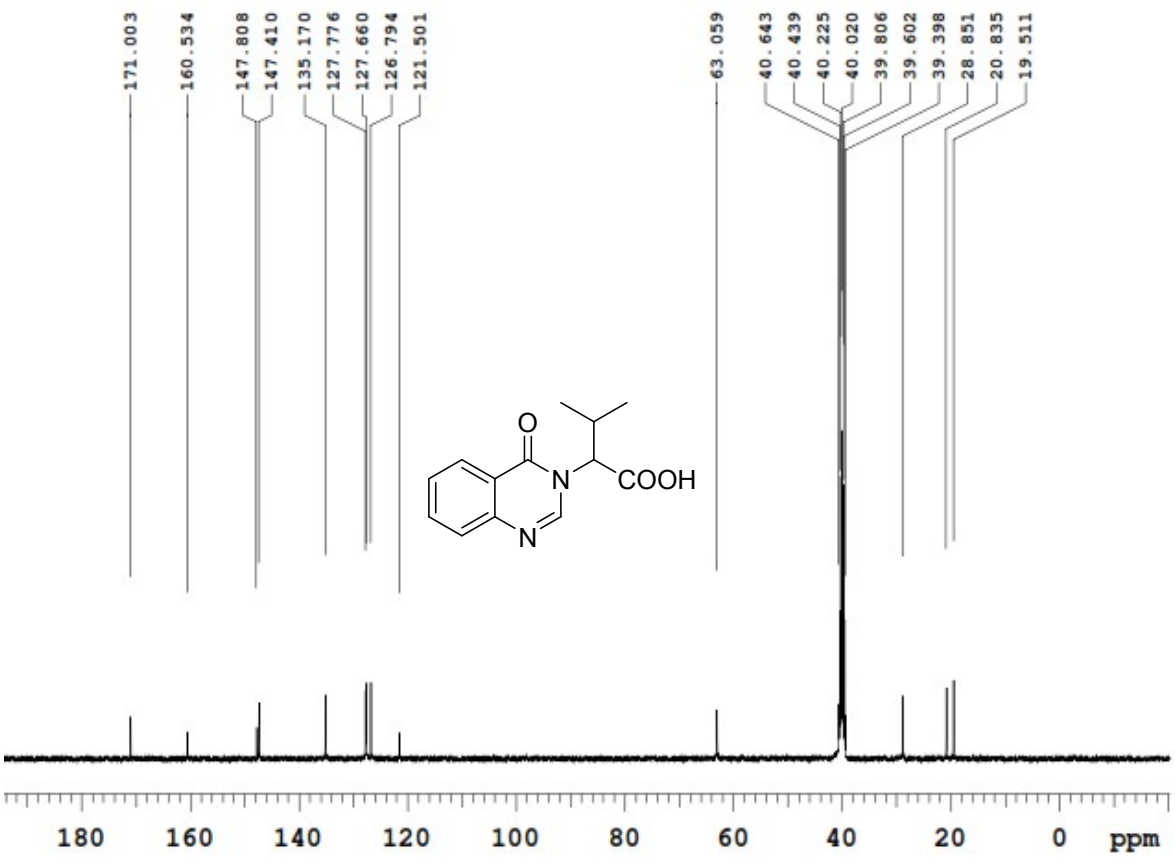


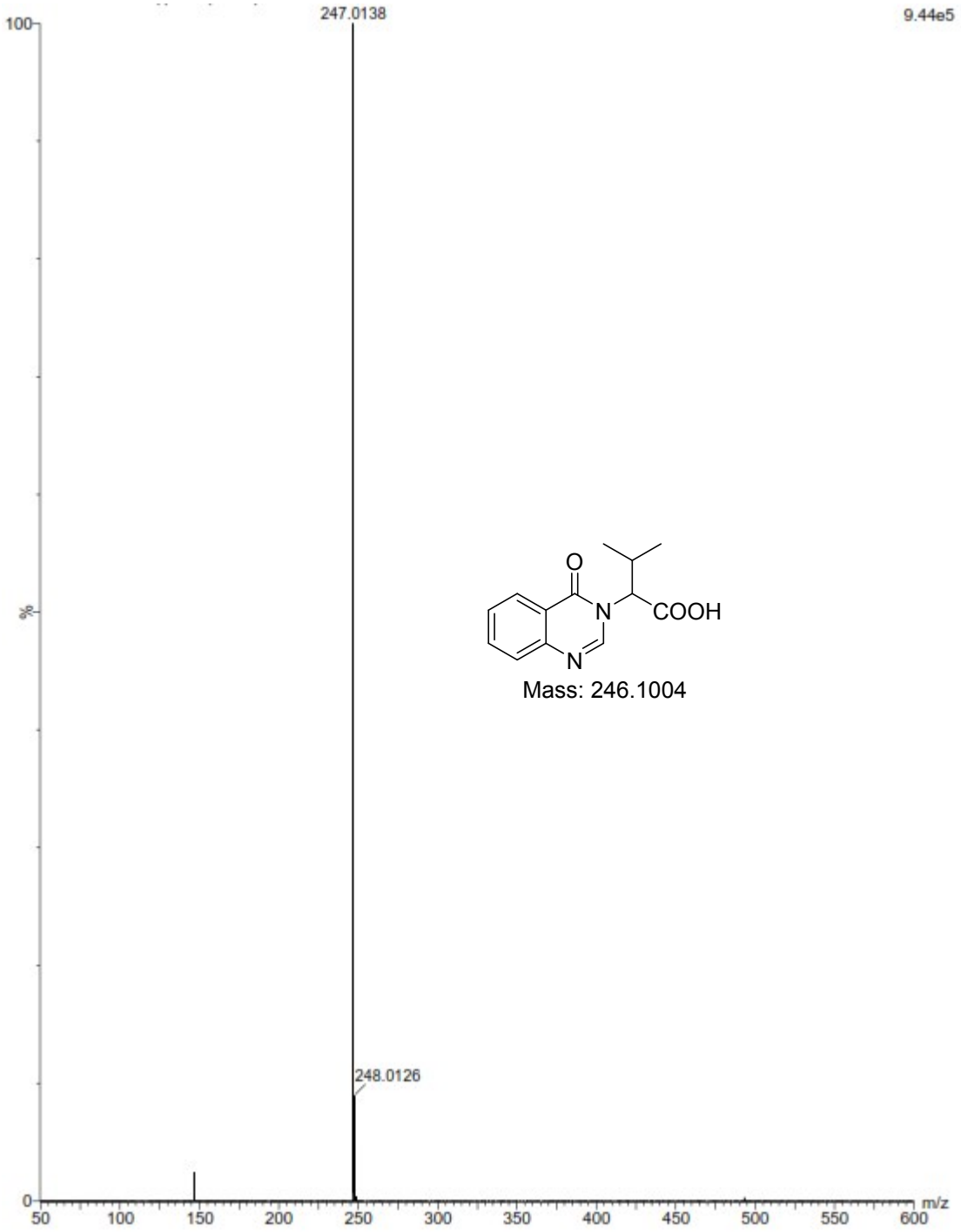


Mass: 252.0899

^{1}H NMR, ^{13}C NMR and Mass Spectra for Compound **5c**

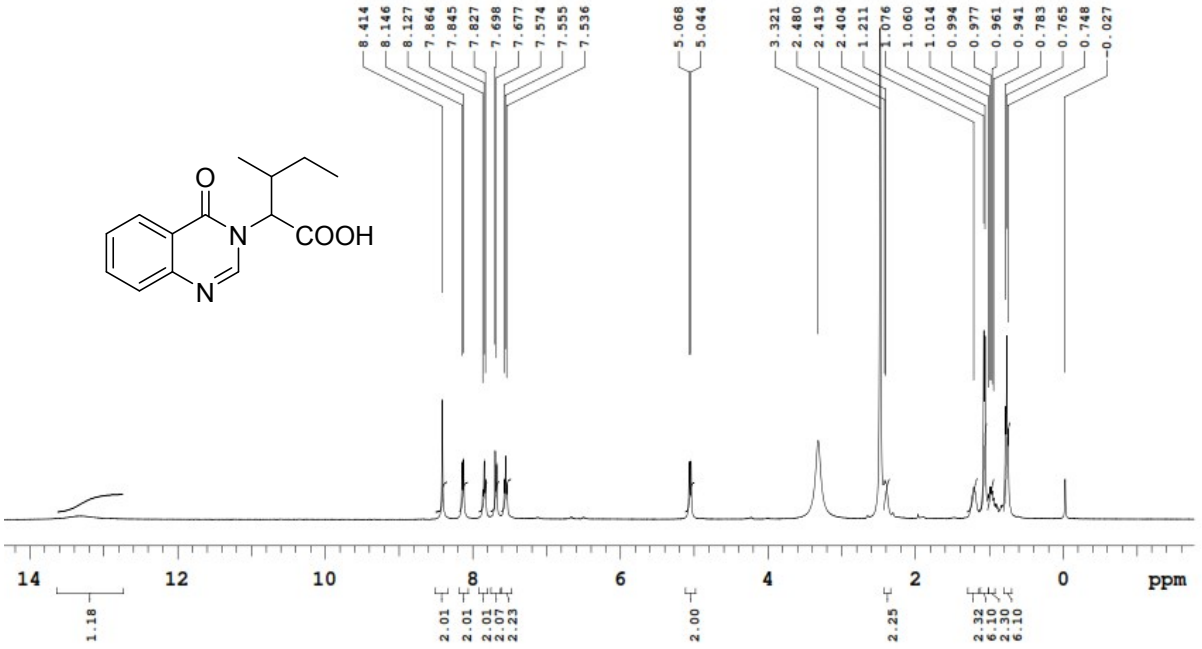


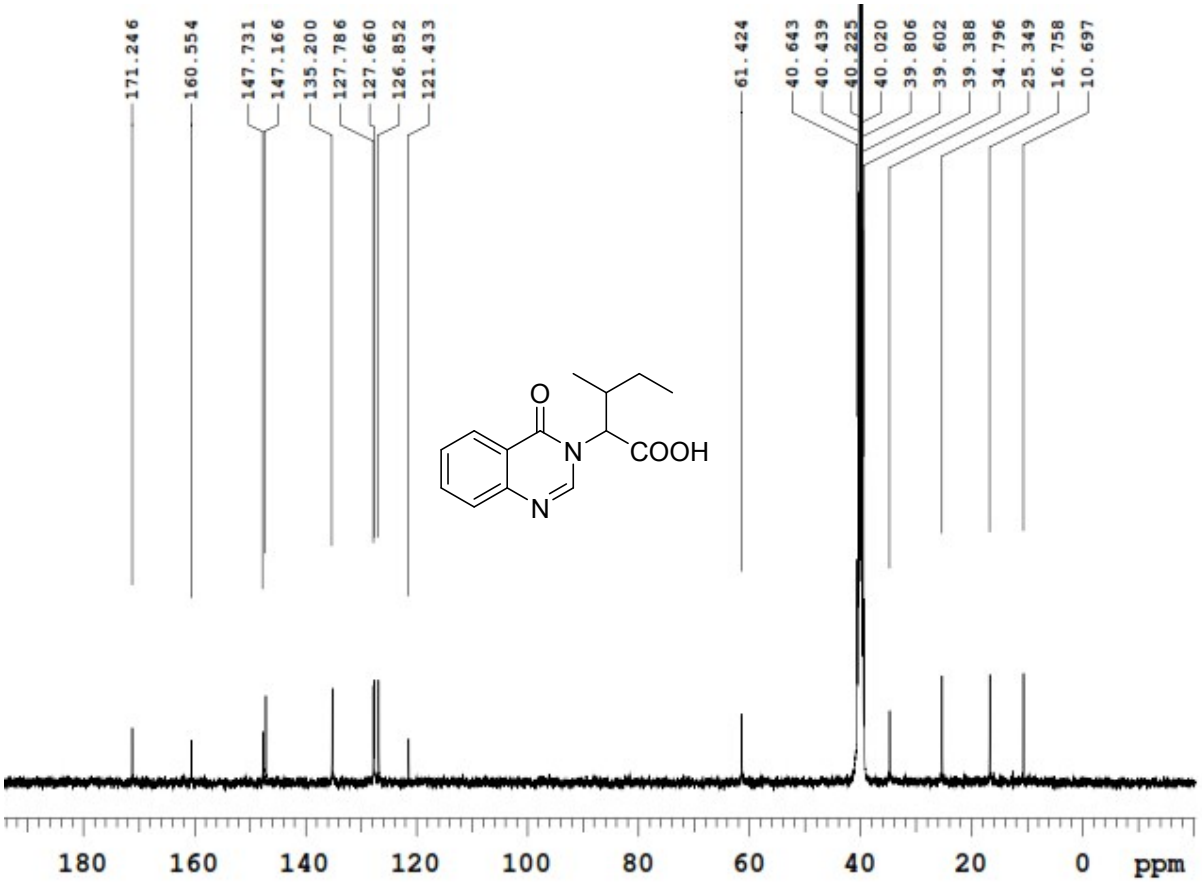


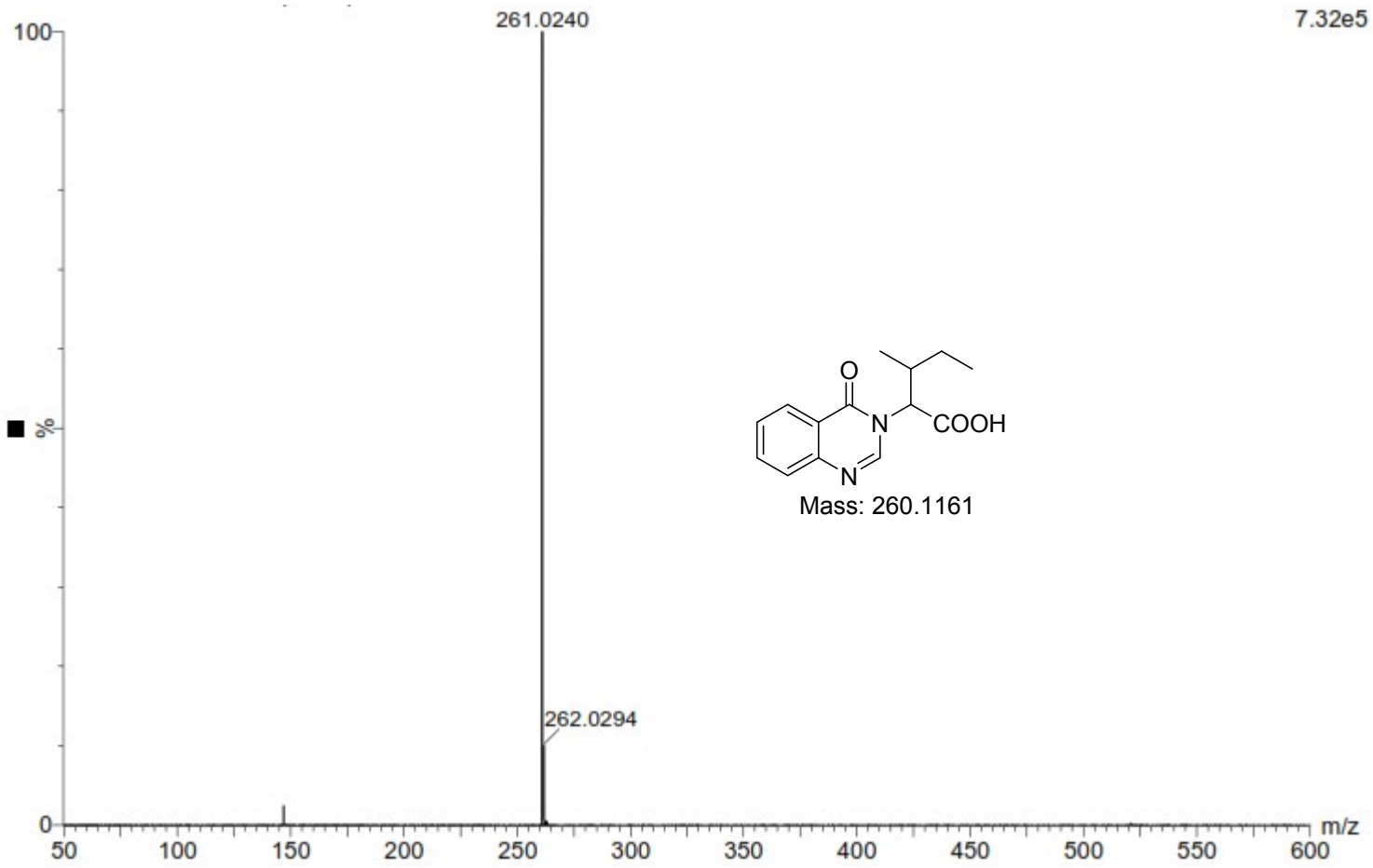


Mass: 246.1004

^{1}H NMR, ^{13}C NMR and Mass Spectra for Compound **5e**

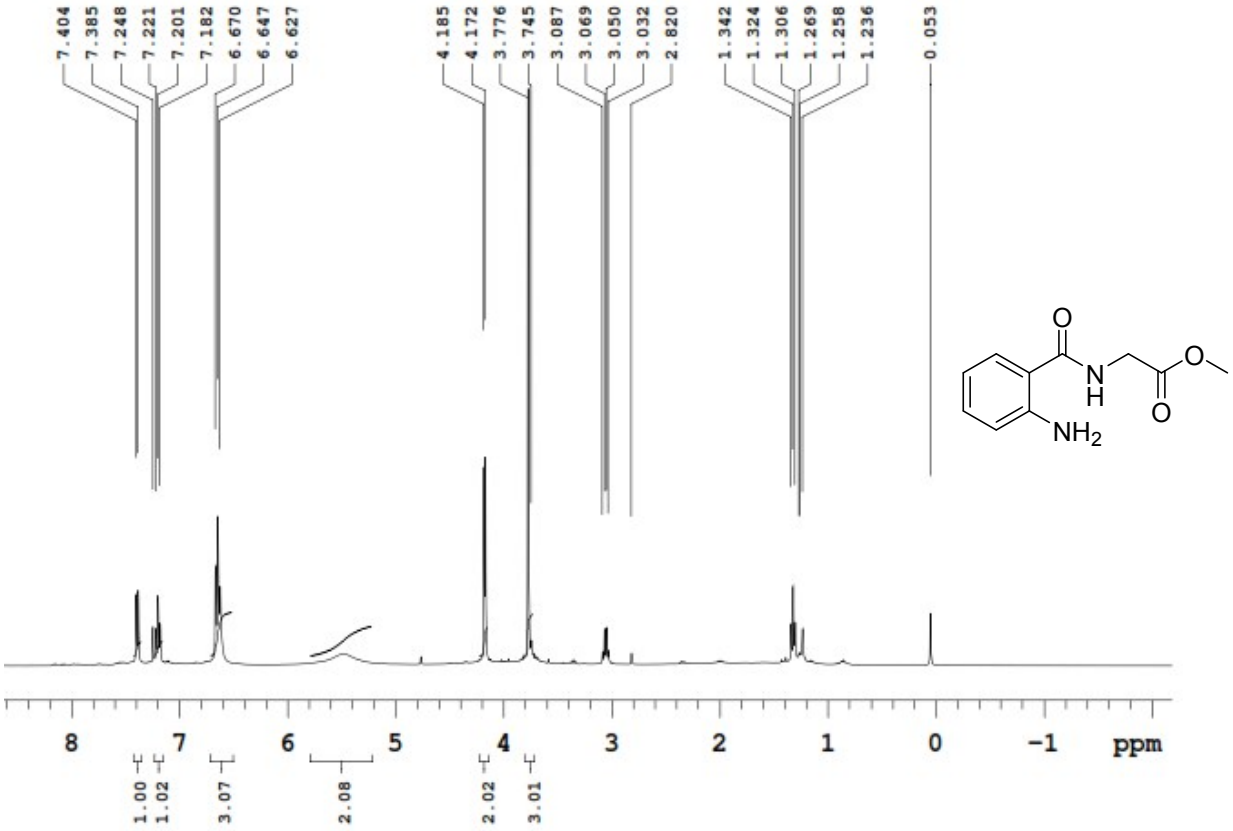


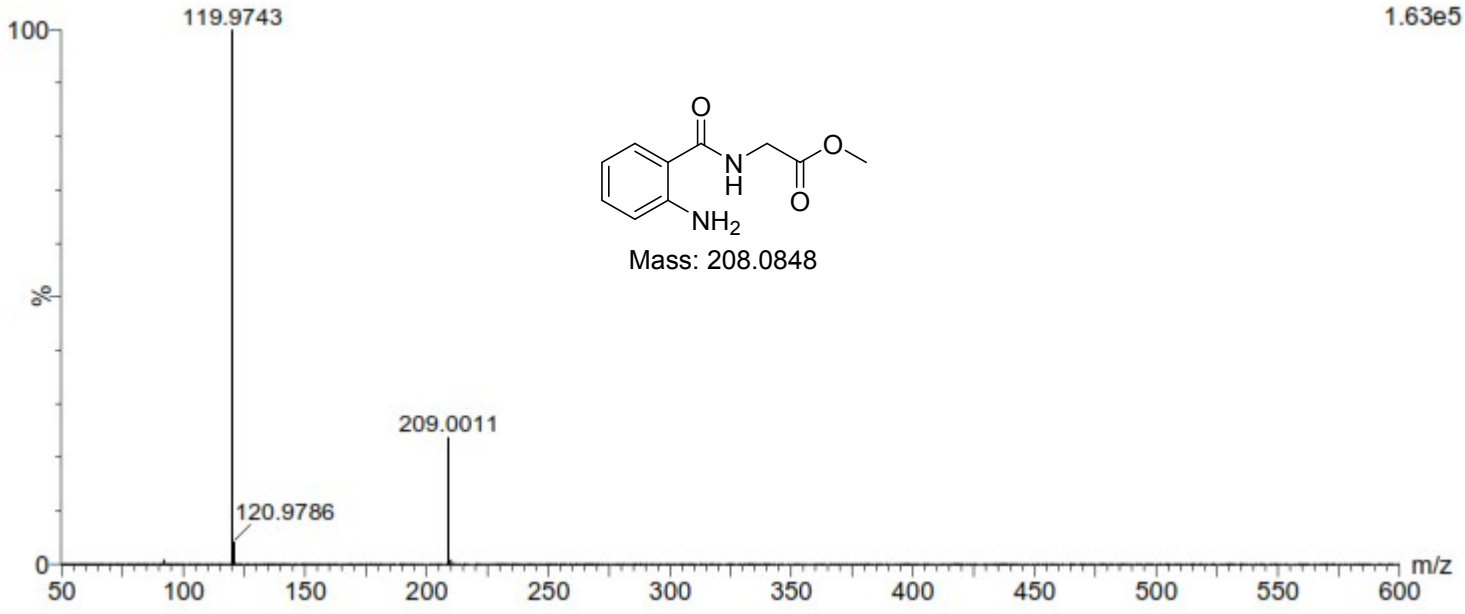




Mass: 260.1161

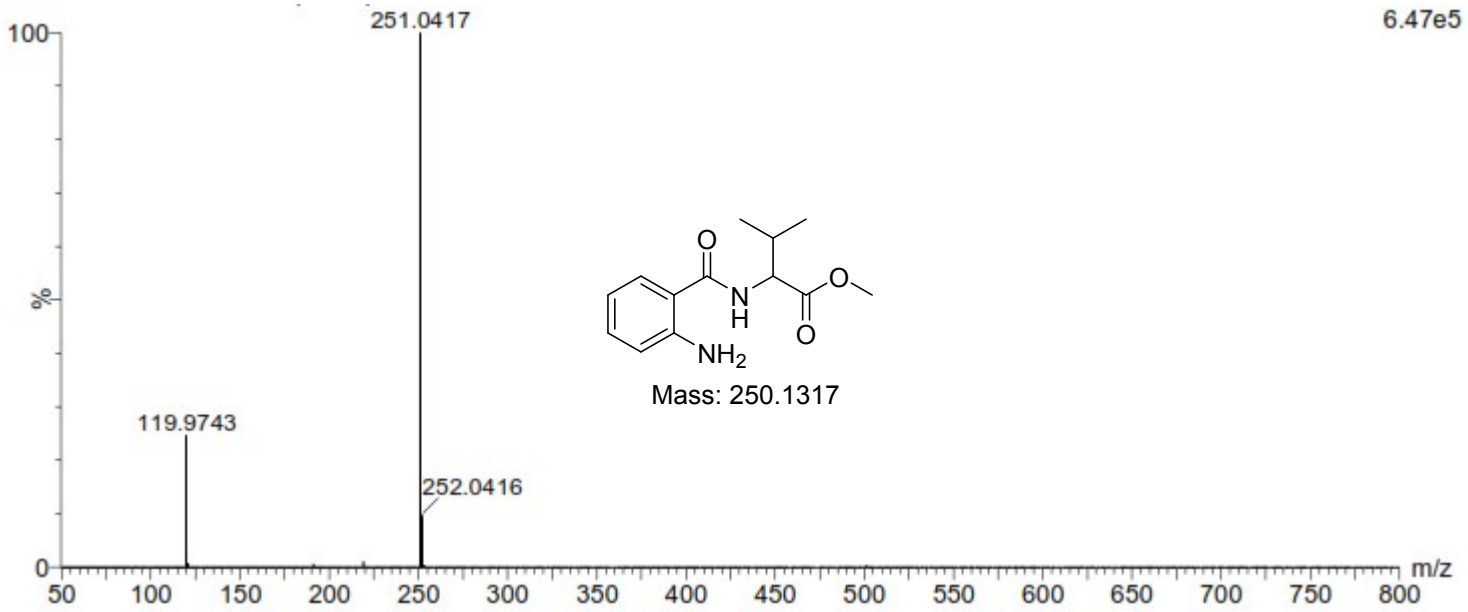
[1]H NMR and Mass Spectra for Compound **3a**



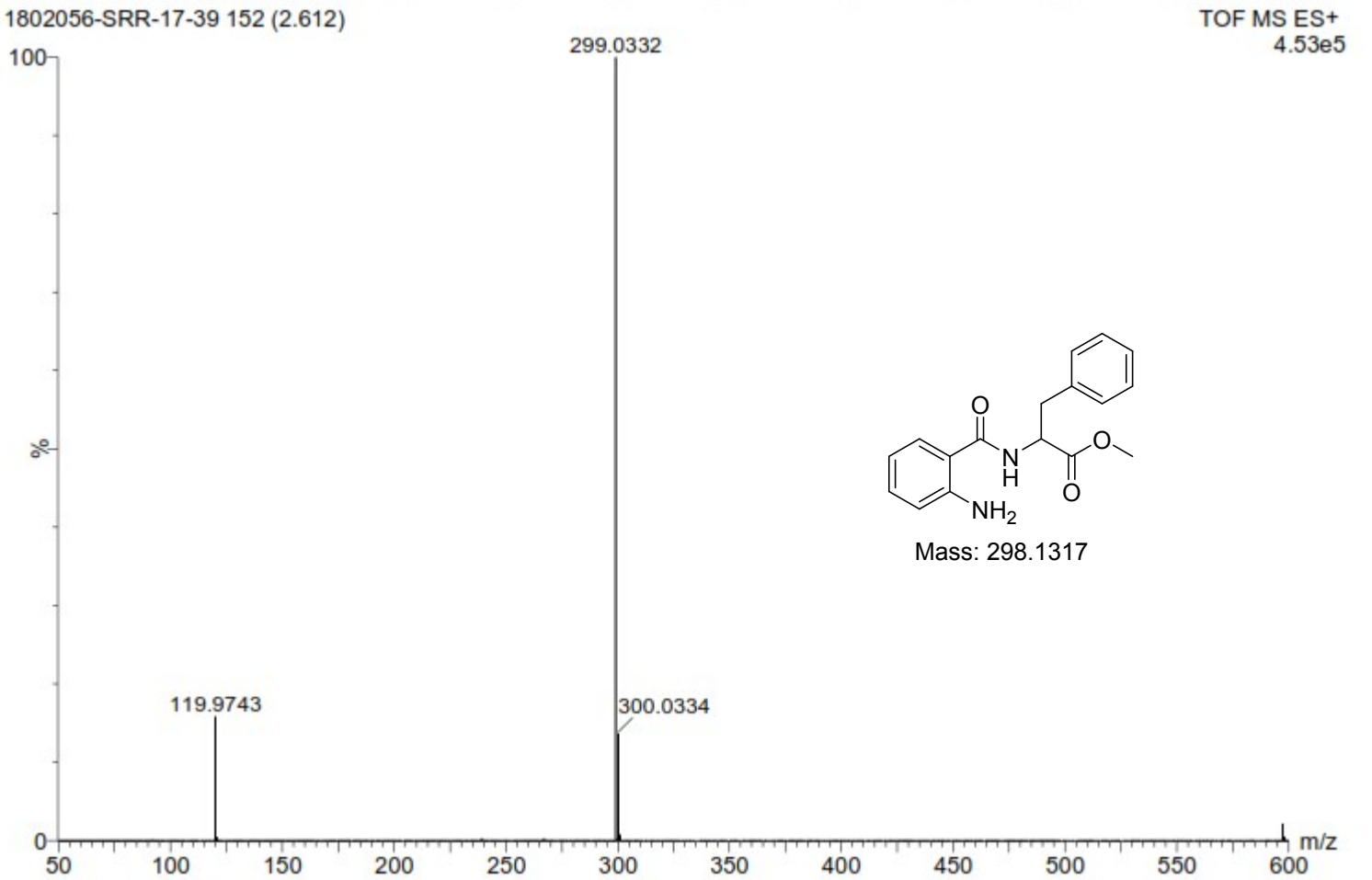


Mass: 208.0848

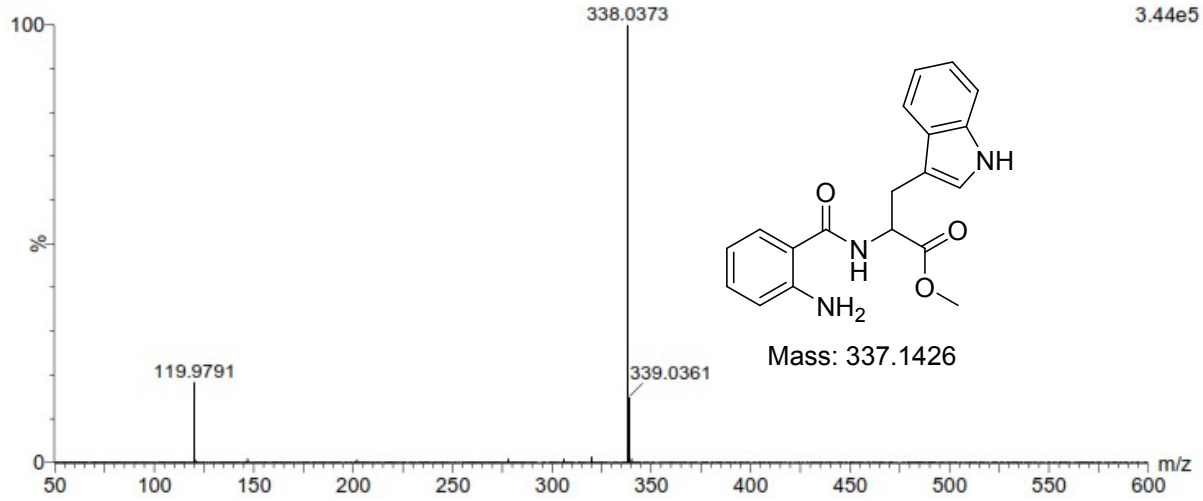
Mass Spectrum for Compound **3c**



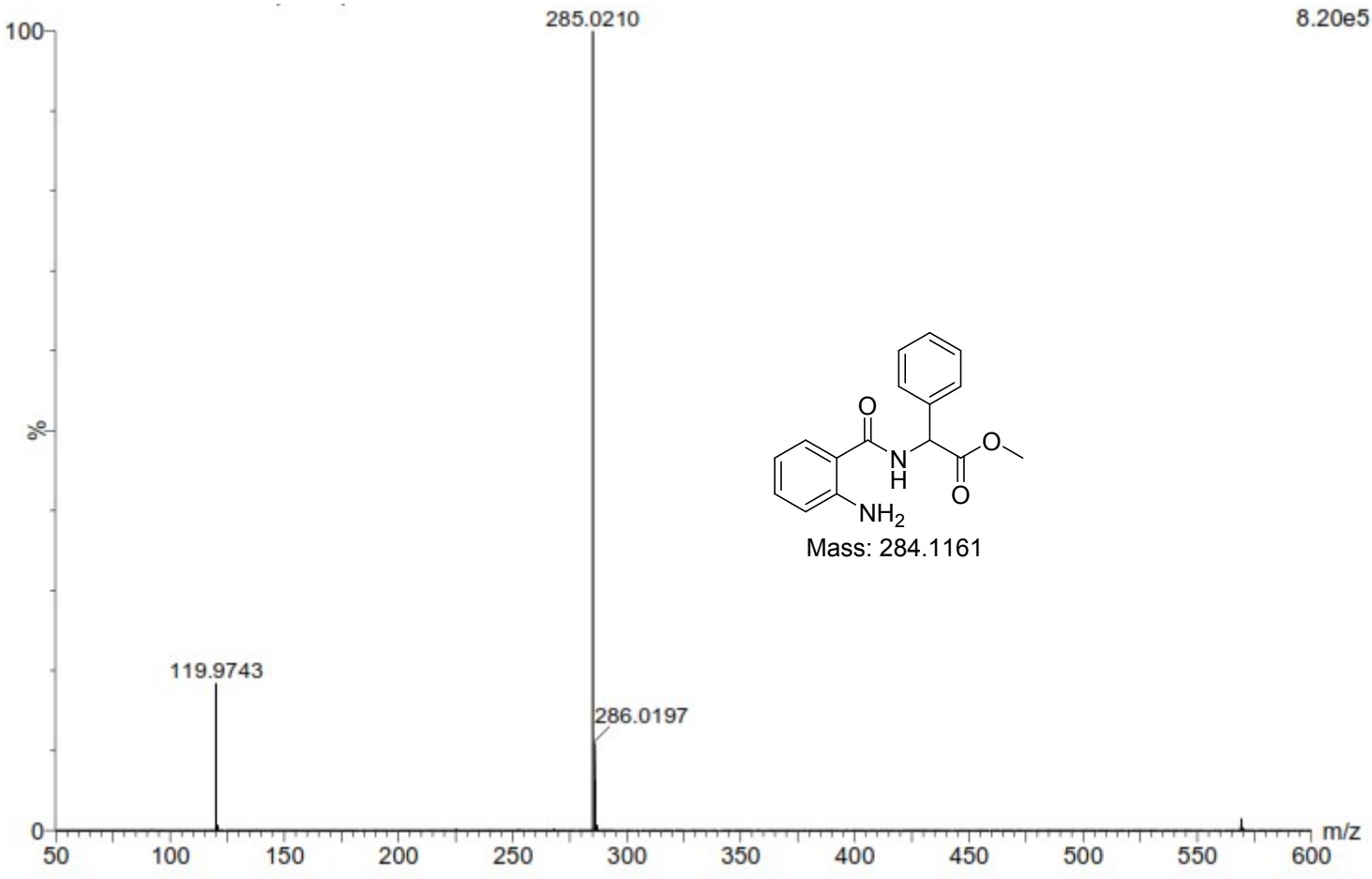
Mass Spectrum for Compound **3g**



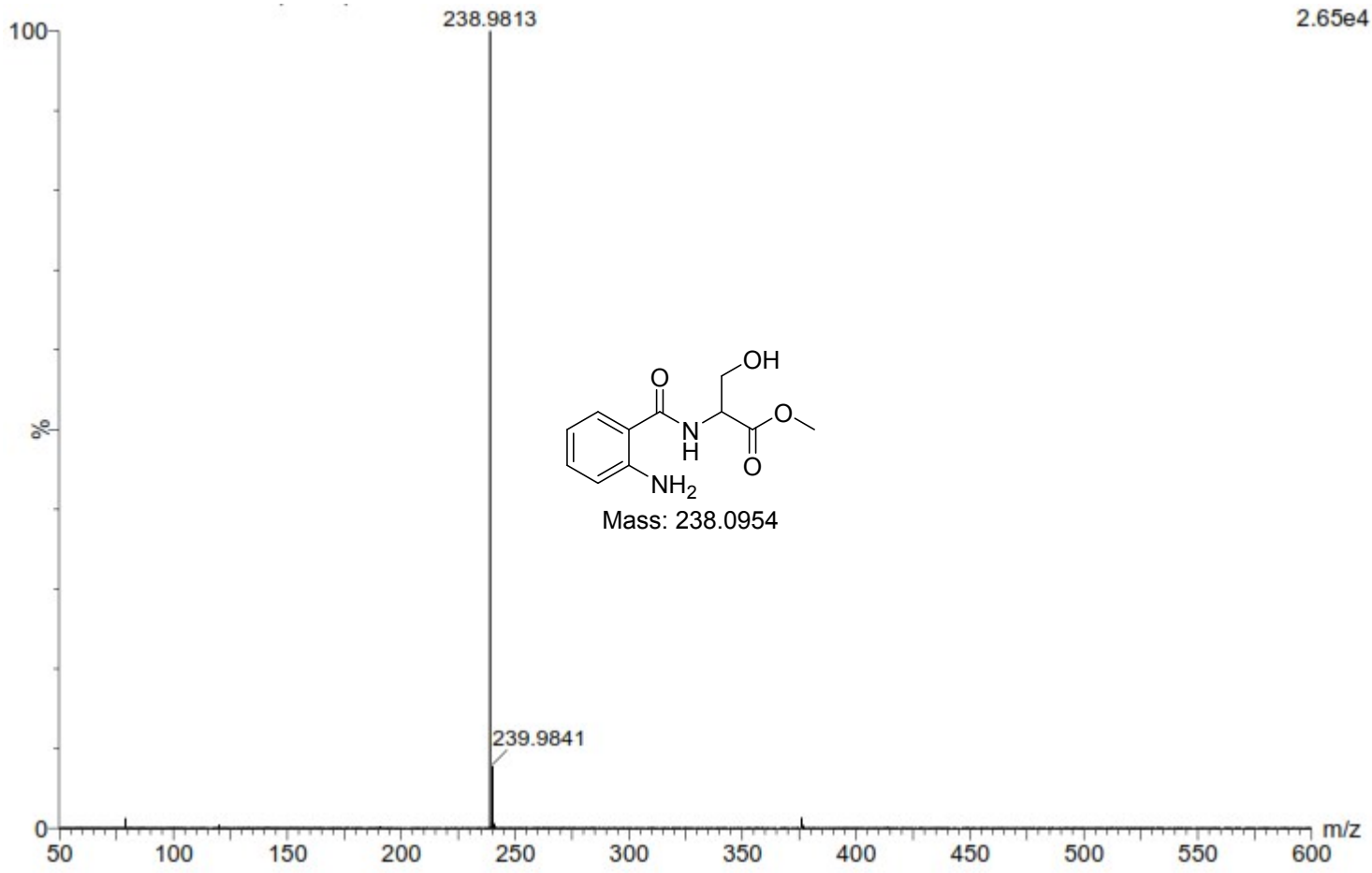
Mass Spectrum for Compound **3h**



Mass Spectrum for Compound **3j**

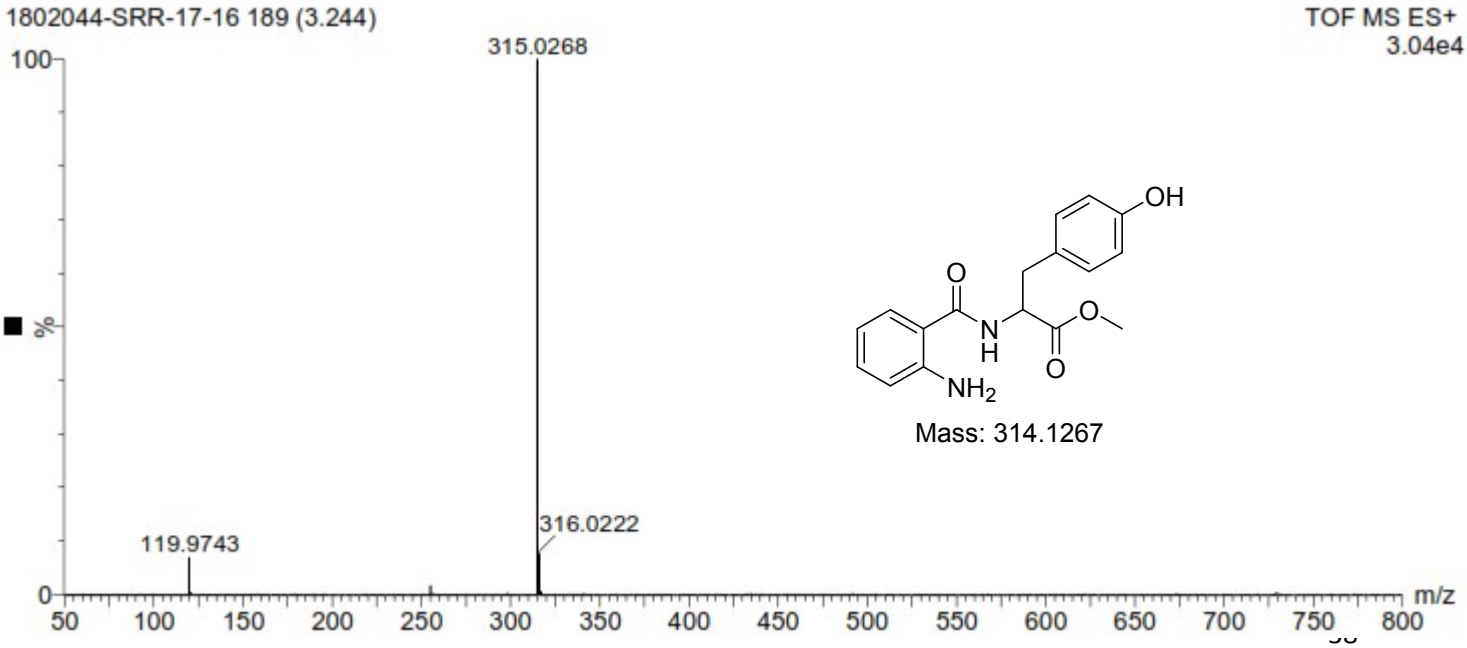


Mass Spectrum for Compound **3k**



Mass: 238.0954

Mass Spectrum for Compound **3m**



Mass: 314.1267