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Experimental section

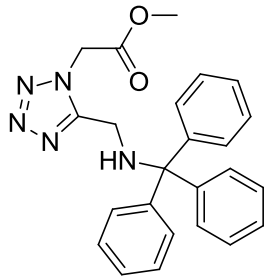
General methods

Nuclear magnetic resonance spectra (NMR) were recorded on a Bruker Avance 500 spectrometer (^{1}H NMR (500 MHz), ^{13}C NMR (126 MHz)). Chemical shifts for ^{1}H NMR were reported as δ values and coupling constants were in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, d = doublet, t = triplet, dd = double doublet, m = multiplet, bs = broad singlet. Chemical shifts for ^{13}C NMR reported in ppm relative to the solvent peak. Thin layer chromatography was performed on Fluka precoated silica gel plates (0.20 mm thick, particle size 25 µm). Flash chromatography was performed on a Teledyne ISCO Combiflash Rf, using RediSep Rf Normal-phase Silica Flash Columns (Silica Gel 60 Å, 230 - 400 mesh). Reagents were available from commercial suppliers and used without any purification unless otherwise noted. All isocyanides were made in house by either performing the Hoffman or Ugi procedure. Other reagents were purchased from Sigma Aldrich, ABCR, Acros and AK Scientific and were used without further purification. All microwave irradiation reactions were carried out in a Biotage Initiator™ Microwave Synthesizer. Electrospray ionization mass spectra (ESI-MS) were recorded on a Waters Investigator Semi-prep 15 SFC-MS instrument.

Synthetic procedure A

Aldehyde (1 mmol), tritylamine (1 mmol) were mixed in methanol (1 mL) and subjected to microwave irradiation for 15 minutes. Subsequently isocyanide (1mmol) and azidotrimethylsilane (1 mmol) were added and the mixture was stirred at room temperature for 18h. The solvent was evaporated under reduced pressure and the residue was purified using flash chromatography to obtain the desired product.

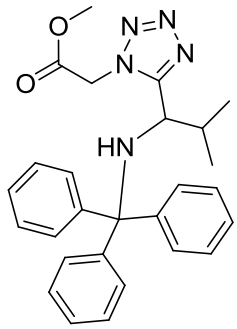
Methyl 2-(5-((tritylamino)methyl)-1H-tetrazol-1-yl)acetate (7a):



The product was obtained using procedure **A**. Yield: 82%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.8 Hz, 6H), 7.30 (d, *J* = 7.8 Hz, 6H), 7.22 (m, 3H), 5.15 (s, 2H), 3.77 (d, *J* =7.4 Hz, 2H), 3.74 (s, 3H), 2.57 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 154.4, 144.3, 128.4, 128.1, 127.8, 127.1, 126.9, 71.1, 53.1, 48.0, 37.2. MS (ESI) m/z calculated for $C_{24}H_{23}N_5O_2$: $[M]^+$: 413.18; found $[M-H]^+$: 412.24.

Methyl 2-(5-(2-methyl-1-(tritylamino)propyl)-1H-tetrazol-1-yl)acetate (7b):

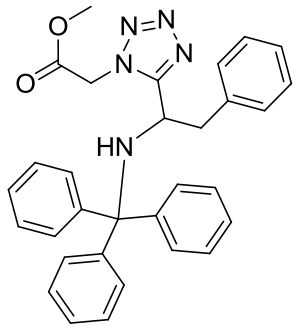


The product was obtained using procedure **A**. Yield: 68%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.7 Hz, 6H), 7.19 (t, *J* = 7.7 Hz, 6H), 7.14 (t, *J* = 7.1 Hz, 3H), 4.78 (d, *J* = 17.6 Hz, 1H), 4.22 (d, *J* = 17.6 Hz, 1H), 3.81 (dd, *J* = 7.7, 5.3 Hz, 1H), 3.69 (s, 3H), 2.98 (d, *J* = 7.7 Hz, 1H), 2.33 – 2.23 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.73 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 156.3, 144.9, 128.4, 127.8, 127.1, 126.7, 71.3, 53.3, 52.8, 47.7, 34.6, 19.1, 17.3.

MS (ESI) m/z calculated for $C_{27}H_{29}N_5O_2$: $[M]^+$: 455.23; found $[M\text{-}H]^+$: 454.34.

Methyl 2-(5-(2-phenyl-1-(tritylamino)ethyl)-1H-tetrazol-1-yl)acetate (7c):

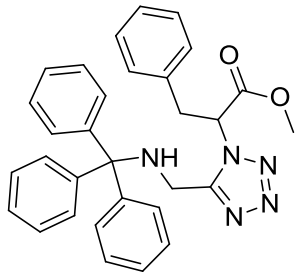


The product was obtained using procedure **A**. Yield: 74%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 4H), 7.25 – 7.20 (m, 6H), 7.17 – 7.12 (m, 8H), 7.02 – 6.99 (m, 2H), 4.65 (d, *J* = 17.5 Hz, 1H), 4.22 – 4.14 (m, 1H), 4.05 (d, *J* = 17.5 Hz, 1H), 3.66 (s, 3H), 3.05 (d, *J* = 7.0 Hz, 1H), 2.99 (d, *J* = 7.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.5, 157.9, 144.7, 136.2, 129.7, 128.8, 128.5, 128.0, 127.9, 127.8, 127.2, 126.8, 126.5, 71.4, 52.9, 50.9, 47.4, 43.6.

MS (ESI) m/z calculated for $C_{31}H_{29}N_5O_2$: $[M]^+$: 503.23; found $[M\text{-}H]^+$: 502.25.

Methyl 3-phenyl-2-(5-((tritylamino)methyl)-1H-tetrazol-1-yl)propanoate (7d):



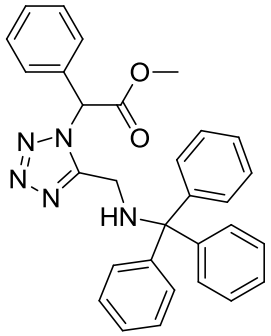
The product was obtained using procedure **A**. Yield: 85%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.0 Hz, 6H), 7.29 (t, *J* = 8.0 Hz, 6H), 7.26 – 7.22 (m, 3H), 7.14 – 7.10 (m, 3H), 6.88 – 6.83 (m, 2H), 5.36 (dd, *J* = 9.5, 6.5 Hz, 1H), 3.76 (s, 3H), 3.64 – 3.59 (m, 2H), 3.45 (dd, *J* = 14.0, 6.5 Hz, 1H), 3.26 (dd, *J* = 14.0, 8.4 Hz, 1H), 2.15 (t, *J* = 7.2 Hz,

1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.4, 154.4, 144.2, 135.0, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.4, 127.1, 126.9, 70.9, 61.7, 53.3, 36.8, 36.5.

MS (ESI) m/z calculated for $C_{31}H_{29}N_5O_2$: $[M]^+$: 503.23; found $[M-H]^+$: 502.25.

Methyl 2-phenyl-2-(5-((tritylamino)methyl)-1H-tetrazol-1-yl)acetate (7e):

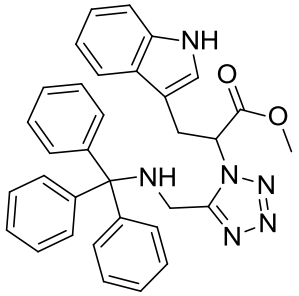


The product was obtained using procedure **A**. Yield: 71%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.1 Hz, 6H), 7.38 – 7.27 (m, 9H), 7.24 (dd, *J* = 12.8, 5.4 Hz, 4H), 7.18 (d, *J* = 7.3 Hz, 2H), 6.50 (s, 1H), 3.78 (s, 3H), 3.66 (dd, *J* = 14.4, 6.2 Hz, 1H), 3.49 (dd, *J* = 14.4, 8.1 Hz, 1H), 2.55 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 154.1, 144.4, 131.5, 129.7, 129.1, 128.7, 128.5, 128.4, 128.1, 126.8, 71.0, 63.9, 53.4, 37.4.

MS (ESI) m/z calculated for $C_{30}H_{27}N_5O_2$: $[M]^+$: 489.22; found $[M-H]^+$: 488.27.

Methyl 3-(1H-indol-3-yl)-2-(5-((tritylamino)methyl)-1H-tetrazol-1-yl)propanoate (7f):



The product was obtained using procedure **A**. Yield: 78%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (bs, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.24 – 7.08 (m, 18H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.48 (d, *J* = 2.1 Hz, 1H), 5.39 (dd, *J* = 11.3, 3.9 Hz, 1H), 3.81 (dd, *J* = 15.0, 3.8 Hz, 1H), 3.76 (s, 3H), 3.70 (dd, *J* = 15.0, 11.4 Hz, 1H), 3.12 – 3.03 (m, 2H). ^{13}C NMR (126

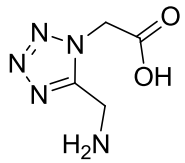
MHz, $CDCl_3$) δ 167.6, 154.8, 144.3, 135.9, 128.3, 128.2, 128.1, 128.0, 126.7, 126.0, 123.5, 122.3, 119.9, 117.4, 111.6, 108.5, 70.9, 60.7, 53.3, 36.5, 27.4.

MS (ESI) m/z calculated for $C_{33}H_{30}N_6O_2$: $[M]^+$: 542.24; found $[M-H]^+$: 541.32.

Synthetic procedure B

The Ugi tetrazole (1.0 mmol) was added to 6N HCl solution (5mL) and heated for 18h at 80^{o}C. The precipitate was filtrated off and the filtrate was evaporated under reduced pressure to give the corresponding tetrazole aminoacid. Which was neutralized to pH 7with dilute aq. NH_3 and the water was evaporated to dryness.

2-(5-(aminomethyl)-1H-tetrazol-1-yl)acetic acid (8a):

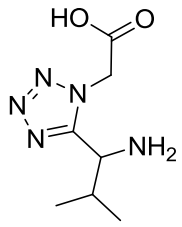


The product was obtained using procedure **B**. Yield: 82 %

^{1}H NMR (500 MHz, MeOD) δ 5.47 (s, 2H), 4.55 (s, 2H) ppm. ^{13}C NMR (126 MHz, MeOD) δ 168.9, 152.4, 49.6, 34.2.

MS (ESI) m/z calculated for $C_4H_7N_5O_2$:$[M]^+$: 157.13; found $[M-H]^+$: 156.

2-(5-(1-amino-2-methylpropyl)-1H-tetrazol-1-yl)acetic acid (8b):

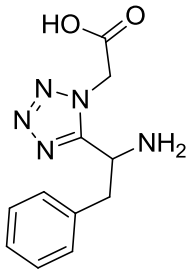


The product was obtained using procedure **B**. Yield: 95 %

^{1}H NMR (500 MHz, MeOD) δ 5.57 (d, *J* = 18.0 Hz, 1H), 5.44 (d, *J* = 18.0 Hz, 1H), 4.72 (d, *J* = 7.6 Hz, 1H), 2.51 – 2.42 (m, 1H), 1.12 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 168.9, 154.6, 51.0, 49.7, 33.0, 18.9, 18.5.

MS (ESI) m/z calculated for $C_7H_{13}N_5O_2$: $[M]^+$: 199.11; found $[M-H]^+$: 198.

2-(5-(1-amino-2-phenylethyl)-1H-tetrazol-1-yl)acetic acid (8c):

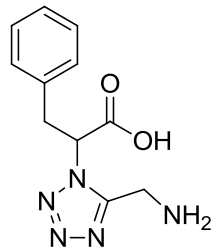


The product was obtained using procedure **B**. Yield: 76 %

^{1}H NMR (500 MHz, MeOD) δ 7.36-7.31 (m, 3H), 7.18-7.12 (m, 2H), 5.20 (d, *J* = 18.0 Hz, 1H), 5.13 (t, *J* = 7.8 Hz, 1H), 4.61 (d, *J* = 18.0 Hz, 1H), 3.78 (s, 2H), 3.46 (dd, *J* = 13.5, 6.8 Hz, 1H), 3.36-3.28 (m, 1H). ^{13}C NMR (126 MHz, MeOD) δ 168.6, 154.5, 134.8, 130.7, 130.2, 129.2, 49.0, 47.5, 40.0.

MS (ESI) m/z calculated for $C_{11}H_{13}N_5O_2$: $[M]^+$: 247.11; found $[M-H]^+$: 246.

2-(5-(aminomethyl)-1H-tetrazol-1-yl)-3-phenylpropanoic acid (8d):

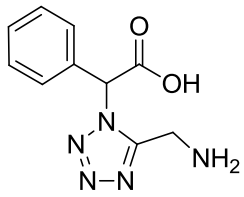


The product was obtained using procedure **B**. Yield: 85 %.

^{1}H NMR (500 MHz, MeOD) δ 7.28-7.19 (m, 3H), 7.13 (d, *J* = 8.0 Hz, 2H), 5.82 (dd, *J* = 11.0, 4.4 Hz, 1H), 4.33 (d, *J* = 16.3 Hz, 1H), 3.91 (d, *J* = 16.3 Hz, 1H), 3.78 (dd, *J* = 14.4, 4.4 Hz, 1H), 3.56 (dd, *J* = 14.4, 11.1 Hz, 1H). ^{13}C NMR (126 MHz, MeOD) δ 169.1, 151.7, 136.4, 129.9, 129.7, 128.3, 63.5, 37.5, 34.8.

MS (ESI) m/z calculated for $C_{11}H_{13}N_5O_2$: $[M]^+$: 247.11; found $[M-H]^+$: 246.

2-(5-(aminomethyl)-1H-tetrazol-1-yl)-2-phenylacetic acid (8e):

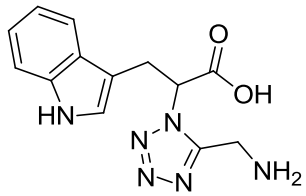


The product was obtained using procedure **B**. Yield: 78%.

^{1}H NMR (500 MHz, MeOD) δ 7.53 – 7.48 (m, 5H), 6.93 (s, 1H), 4.54 (d, *J* = 16.3 Hz, 1H), 4.05 (d, *J* = 16.3 Hz, 1H). ^{13}C NMR (126 MHz, MeOD) δ 177.6, 160.3, 142.1, 139.4, 138.8, 138.2, 72.6, 41.7.

MS (ESI) m/z calculated for $C_{10}H_{11}N_5O_2$: $[M]^+$: 233.09; found $[M+H]^+$: 234.

2-(5-(aminomethyl)-1H-tetrazol-1-yl)-3-(1H-indol-3-yl)propanoic acid (8f):



The product was obtained using procedure **B**. Yield: 70 %

^{1}H NMR (500 MHz, MeOD) δ 7.45 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.89 (s, 1H), 5.85 (dd, *J* = 10.5, 4.4 Hz, 1H), 4.07 (d, *J* = 16.2 Hz, 1H), 3.87 (dd, *J* = 15.1, 4.4 Hz, 1H), 3.73 (dd, *J* = 15.1, 10.5 Hz, 1H), 3.54 (d, *J* = 16.2 Hz, 1H) ppm. ^{13}C NMR (126 MHz, MeOD) δ 169.9, 151.9, 137.7, 127.7, 125.0, 122.9, 120.4, 118.5, 112.7, 109.1, 63.2, 34.0, 28.3.

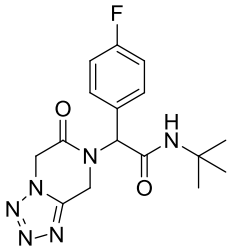
MS (ESI) m/z calculated for $C_{13}H_{14}N_6O_2$: $[M]^+$: 286.12; found $[M-H]^+$: 285.

Synthetic procedure C

The mixture of tetrazole aminoacid (1 mmol), aldehyde (1 mmol) and isocyanide (1mmol) in 2,2,2-Trifluoroethanol (TFE) (1mL) was subjected to microwave irradiation for 30 minutes at 120 ^{o}C. The solvent was evaporated under reduced pressure and the residue was purified using flash chromatography to obtain the desired product.

In all the cases, the spectral data are given for the major diastereomer

N-(tert-butyl)-2-(4-fluorophenyl)-2-(6-oxo-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8H)-yl)acetamide (11a):

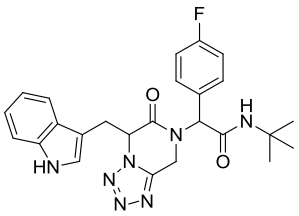


The product was obtained using procedure **C**. Yield: 45%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.35 (m, 2H), 7.18 – 7.10 (m, 2H), 6.22 (s, 1H), 5.96 (s, 1H), 5.27 (d, *J* = 17.0 Hz, 1H), 5.15 (s, 2H), 4.28 (d, *J* = 17.0 Hz, 1H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.5, 163.1 (*J* = 250.7 Hz), 161.4, 147.2, 131.6 (*J* = 8.4 Hz), 128.4 (*J* = 3.4 Hz), 116.6 (*J* = 21.7 Hz), 59.8, 52.2, 47.8, 39.5, 28.5.

MS (ESI) m/z calculated for $C_{16}H_{19}FN_6O_2$: $[M]^+$: 346.16; found $[M-H]^+$: 345.16.

2-(5-((1H-indol-3-yl)methyl)-6-oxo-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8H)-yl)-N-(tert-butyl)-2-(4-fluorophenyl)acetamide (11n):

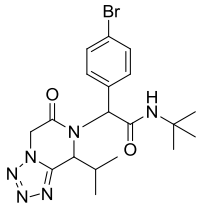


The product was obtained using procedure **C**. Yield: 20%.

^{1}H NMR (500 MHz, MeOD) δ 7.42 (d, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.91 (t, *J* = 8.5 Hz, 2H), 6.39 – 6.35 (m, 2H), 6.19 (s, 1H), 5.83 (s, 1H), 5.78 – 5.74 (m, 1H), 4.60 (s, 1H), 4.51 (dd, *J* = 16.8, 1.2 Hz, 1H), 3.99 (dd, *J* = 14.9, 3.0 Hz, 1H), 3.65 (dd, *J* = 14.9, 4.0 Hz, 1H), 2.72 (dd, *J* = 16.8, 1.2 Hz, 1H), 1.32 (s, 9H). ^{13}C NMR (126 MHz, MeOD) δ 170.5, 164.1 (*J* = 247.8 Hz), 149.6, 132.6 (*J* = 8.5 Hz), 128.5, 124.9, 123.0, 120.7, 119.1, 116.7 (*J* = 21.9 Hz), 112.8, 107.3, 61.7, 61.3, 52.5, 40.9, 30.5, 28.7.

MS (ESI) m/z calculated for $C_{25}H_{26}FN_7O_2$: $[M]^+$: 475.21; found $[M\text{-}H]^+$: 474.25.

2-(4-bromophenyl)-N-(tert-butyl)-2-(8-isopropyl-6-oxo-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8H)-yl)acetamide (11b):

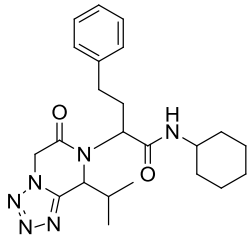


The product was obtained using procedure **C**. Yield: 53%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 5.81 (s, 1H), 5.56 (s, 1H), 5.24 (d, *J* = 17.9 Hz, 1H), 5.10 (d, *J* = 17.9 Hz, 1H), 4.46 (d, *J* = 3.0 Hz, 1H), 2.71 – 2.60 (m, 1H), 1.36 (s, 9H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.63 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 162.5, 148.7, 132.7, 131.7, 131.2, 124.2, 64.9, 57.1, 52.0, 48.4, 33.1, 28.4, 18.4, 15.1.

MS (ESI) m/z calculated for $C_{19}H_{25}BrN_6O_2$: $[M]^+$: 448.12; found $[M\text{-}H]^+$: 447.14.

N-cyclohexyl-2-(8-isopropyl-6-oxo-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8H)-yl)-4-phenylbutanamide (11c):

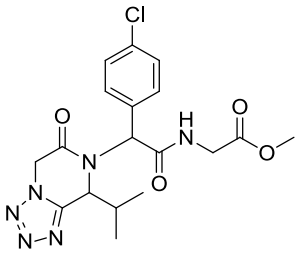


The product was obtained using procedure **C**. Yield: 33%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.5 Hz, 2H), 7.16 – 7.07 (m, 3H), 6.85 (d, *J* = 8.0 Hz, 1H), 5.15 (d, *J* = 18.1 Hz, 1H), 5.04 (d, *J* = 3.4 Hz, 1H), 4.99 (d, *J* = 18.1 Hz, 1H), 4.87 (t, *J* = 7.2 Hz, 1H), 3.82 – 3.73 (m, 1H), 2.75 – 2.66 (m, 1H), 2.65 – 2.56 (m, 1H), 2.56 – 2.46 (m, 2H), 2.05 – 1.96 (m, 1H), 1.96 – 1.89 (m, 1H), 1.87 – 1.80 (m, 1H), 1.77 – 1.56 (m, 3H), 1.44 – 1.31 (m, 2H), 1.30 – 1.12 (m, 3H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.52 (d, *J* = 7.0, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 163.7, 148.0, 139.7, 128.4, 128.1, 126.3, 57.0, 55.6, 48.2, 32.6, 32.4, 32.0, 28.3, 25.3, 24.5, 18.7, 15.1.

MS (ESI) m/z calculated for $C_{23}H_{32}N_6O_2$: $[M]^+$: 424.26; found $[M-H]^+$: 423.26.

Methyl 2-(2-(4-chlorophenyl)-2-(8-isopropyl-6-oxo-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8H)-yl)acetamido)acetate (11d):

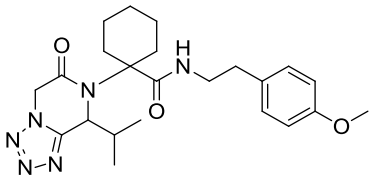


The product was obtained using procedure **C**. Yield: 58%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 6.56 (t, *J* = 5.2 Hz, 1H), 5.67 (s, 1H), 5.25 (d, *J* = 17.8 Hz, 1H), 5.10-5.07 (m, 1H), 5.04 (d, *J* = 17.8 Hz, 1H), 4.01 (d, *J* = 5.4 Hz, 2H), 3.71 (s, 3H), 1.99 – 1.90 (m, 1H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.60 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 168.0, 162.8, 148.5, 136.0, 131.5, 131.0, 129.7, 64.1, 59.0, 52.4, 48.5, 41.4, 33.3, 18.6, 15.0.

MS (ESI) m/z calculated for $C_{18}H_{21}ClN_6O_4$: $[M]^+$: 420.13; found $[M-H]^+$: 419.14.

1-(8-isopropyl-6-oxo-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8H)-yl)-N-(4 methoxyphenethyl)cyclohexanecarboxamide (11e):

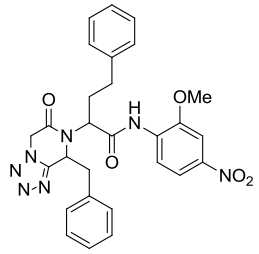


The product was obtained using procedure **C**. Yield: 32%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (m, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 2H), 5.21 (s, 1H), 5.11 (d, *J* = 18.0 Hz, 1H), 4.87 (d, *J* = 18.0 Hz, 1H), 3.78 (s, 3H), 3.58 – 3.42 (m, 2H), 2.77 (t, *J* = 6.8 Hz, 2H), 2.62 – 2.53 (m, 1H), 2.52 – 2.44 (m, 1H), 2.39 – 2.30 (m, 1H), 2.17 – 2.09 (m, 1H), 1.92 – 1.79 (m, 2H), 1.56 – 1.33 (m, 5H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.53 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 163.9, 158.1, 148.8, 130.8, 129.6, 113.8, 67.4, 55.6, 55.1, 48.7, 41.0, 34.4, 33.8, 32.9, 32.0, 25.0, 22.5, 22.2, 18.7, 14.8.

MS (ESI) m/z calculated for $C_{23}H_{32}N_6O_3$: $[M]^+$: 440.25; found $[M-H]^+$: 439.33.

2-(8-benzyl-6-oxo-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8H)-yl)-N-(2-methoxy-4-nitrophenyl)-4-phenylbutanamide (11f):

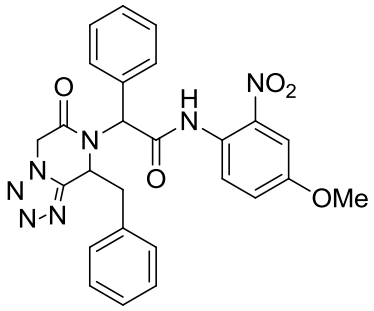


The product was obtained using procedure **C**. Yield: 72%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.62 (s, 1H), 8.70 (d, *J* = 9.0 Hz, 1H), 7.98 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.85 (d, *J* = 2.4 Hz, 1H), 7.25 – 7.04 (m, 6H), 6.96 – 6.88 (m, 2H), 6.43 (d, *J* = 7.3 Hz, 1H), 6.33 (d, *J* = 7.3 Hz, 1H), 5.66 (t, *J* = 3.4 Hz, 1H), 5.10 (t, *J* = 7.0 Hz, 1H), 4.65 (d, *J* = 17.7 Hz, 1H), 4.08 (s, 3H), 3.41 (dd, *J* = 14.4, 4.0 Hz, 1H), 3.16 (dd, *J* = 14.2, 4.0 Hz, 1H), 2.99 (d, *J* = 17.7 Hz, 1H), 2.81 – 2.74 (m, 1H), 2.73 – 2.67 (m, 1H), 2.66 – 2.58 (m, 1H), 2.26 – 2.17 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 164.5, 150.0, 148.1, 143.9, 139.2, 133.0, 132.3, 129.7, 128.8, 128.7, 128.1, 127.8, 126.6, 119.0, 117.6, 105.5, 58.0, 56.7, 50.6, 47.4, 40.0, 32.3, 28.7.

MS (ESI) m/z calculated for $C_{28}H_{27}N_7O_5$: $[M]^+$: 541.20; found $[M-H]^+$: 540.23.

2-(8-benzyl-6-oxo-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8H)-yl)-N-(4-methoxy-2-nitrophenyl)-3-phenylpropanamide (11g):

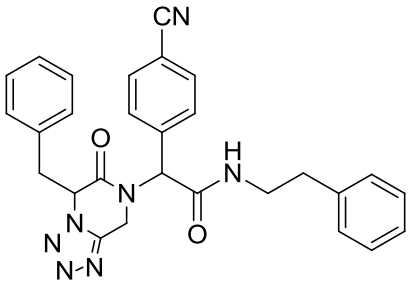


The product was obtained using procedure **C**. Yield: 36%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.23 (s, 1H), 8.58 (d, *J* = 9.3 Hz, 1H), 7.71 (dd, *J* = 6.4, 2.8 Hz, 2H), 7.66 – 7.59 (m, 4H), 7.33 – 7.27 (m, 1H), 7.25 – 7.17 (m, 3H), 6.66 (d, *J* = 7.4 Hz, 2H), 6.23 (s, 1H), 5.66 (t, *J* = 3.5 Hz, 1H), 4.77 (d, *J* = 17.4 Hz, 1H), 3.85 (s, 3H), 3.04 (d, *J* = 17.4 Hz, 1H), 2.87 (dd, *J* = 14.0, 3.5 Hz, 1H), 2.50 (dd, *J* = 14.0, 3.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 163.5, 155.5, 150.3, 137.2, 131.6, 130.8, 130.4, 130.2, 130.0, 129.0, 128.2, 127.5, 123.6, 123.2, 108.8, 64.7, 55.9, 52.7, 47.7, 40.4.

MS (ESI) m/z calculated for $C_{26}H_{23}N_7O_5$: $[M]^+$: 513.18; found $[M-H]^+$: 512.33.

2-(5-benzyl-6-oxo-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8H)-yl)-2-(4-cyanophenyl)-N-phenethylacetamide (11i):

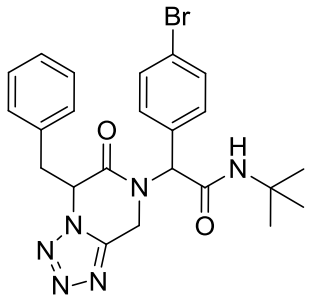


The product was obtained using procedure **C**. Yield: 33%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.08 (m, 8H), 7.02 – 6.95 (m, 2H), 6.50 (d, *J* = 7.2 Hz, 2H), 6.21 (s, 1H), 6.04 (t, *J* = 5.8 Hz, 1H), 5.56 (t, *J* = 3.7 Hz, 1H), 4.82 (dd, *J* = 17.0 Hz, 1.0, 1H), 3.86 (d, *J* = 17.0 Hz, 1H), 3.79 – 3.50 (m, 4H), 2.80 (td, *J* = 6.8, 2.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 163.6, 147.2, 138.0, 137.1, 132.6, 132.5, 129.6, 129.0, 128.9, 128.6, 128.4, 128.0, 126.5, 117.7, 112.8, 60.0, 58.8, 40.3, 38.9, 38.8, 35.0.

MS (ESI) m/z calculated for $C_{28}H_{25}N_7O_2$: $[M]^+$: 491.21; found $[M+H]^+$: 492.28.

2-(5-benzyl-6-oxo-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8H)-yl)-2-(4-bromophenyl)-N-(tert-butyl)acetamide (11j):

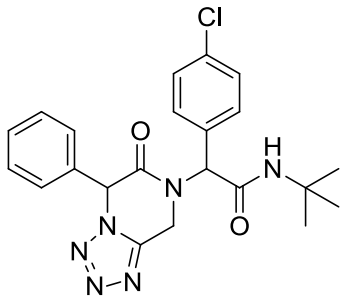


The product was obtained using procedure **C**. Yield: 40%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.26 – 7.23 (m, 1H), 7.19 – 7.11 (m, 2H), 7.02 – 6.94 (m, 2H), 6.54 (d, *J* = 7.7 Hz, 2H), 6.04 (s, 1H), 5.68 – 5.56 (m, 1H), 5.41 (s, 1H), 4.93 (d, *J* = 16.6 Hz, 1H), 3.68 (dd, *J* = 14.0, 3.1 Hz, 1H), 3.60 (dd, *J* = 14.0, 4.4 Hz, 1H), 3.02 (d, *J* = 16.6, 1H), 1.33 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 164.6, 147.8, 132.4, 132.2, 131.0, 130.7, 129.0, 128.9, 128.6, 127.9, 123.6, 60.3, 60.0, 52.0, 39.1, 38.3, 28.5.

MS (ESI) m/z calculated for $C_{23}H_{25}BrN_6O_2$: $[M]^+$: 496.12; found $[M-H]^+$: 495.23.

N-(tert-butyl)-2-(4-chlorophenyl)-2-(6-oxo-5-phenyl-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8H)-yl)acetamide (11m):

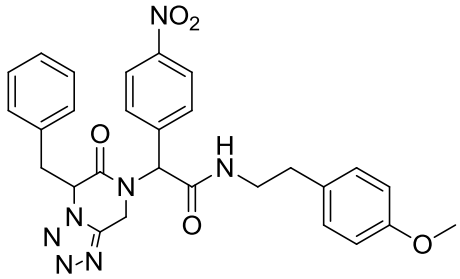


The product was obtained using procedure **C**. Yield: 42%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 4H), 7.36 – 7.29 (m, 3H), 7.04 (d, *J* = 7.3 Hz, 2H), 6.28 (s, 1H), 6.23 (s, 1H), 5.96 (bs, 1H), 5.31 (dd, *J* = 17.3, 1.0 Hz, 1H), 4.26 (dd, *J* = 17.3, 1.0 Hz, 1H), 1.30 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 163.6, 147.2, 135.7, 134.0, 131.0, 130.9, 130.7, 129.7, 129.4, 126.7, 62.9, 60.4, 52.1, 39.1, 28.3.

MS (ESI) m/z calculated for $C_{22}H_{23}ClN_6O_2$: $[M]^+$: 438.16; found $[M-H]^+$: 437.17.

2-(5-benzyl-6-oxo-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8H)-yl)-N-(4-methoxyphenethyl)-2-(4-nitrophenyl)acetamide (11h):

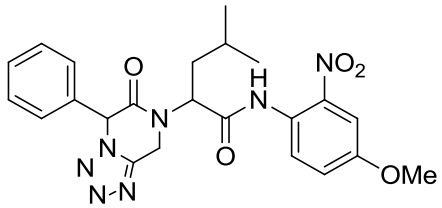


The product was obtained using procedure **C**. Yield: 37%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.6 Hz, 2H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.06 – 6.99 (m, 6H), 6.76 (d, *J* = 8.6 Hz, 2H), 6.53 (d, *J* = 7.1 Hz, 2H), 6.22 (s, 1H), 5.93 (t, *J* = 5.7 Hz, 1H), 5.59 (t, *J* = 3.7 Hz, 1H), 4.87 (dd, *J* = 16.7, 1.2 Hz, 1H), 3.76 (s, 3H), 3.70 – 3.63 (m, 2H), 3.63 – 3.50 (m, 2H), 3.11 (dd, *J* = 16.7, 1.2 Hz, 1H), 2.81 – 2.68 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 163.8, 158.4, 148.1, 147.2, 138.9, 132.8, 130.2, 129.6, 129.2, 128.8, 128.0, 124.0, 114.0, 60.1, 58.7, 55.2, 40.6, 39.1, 38.9, 34.3.

MS (ESI) m/z calculated for $C_{28}H_{27}N_7O_5$: $[M]^+$: 541.21; found $[M-H]^+$: 540.16.

N-(4-methoxy-2-nitrophenyl)-4-methyl-2-(6-oxo-5-phenyl-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8H)-yl)pentanamide (11k):

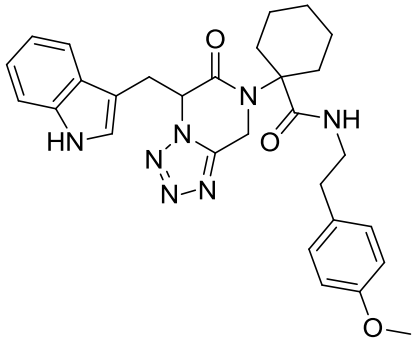


The product was obtained using procedure **C**. Yield: 44%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.48 (d, *J* = 9.3 Hz, 1H), 7.57 (d, *J* = 2.8 Hz, 1H), 7.39 (dd, *J* = 7.4, 2.8 Hz, 2H), 7.34 – 7.30 (m, 1H), 7.22 – 7.17 (m, 2H), 7.16 – 7.12 (m, 1H), 6.50 (s, 1H), 5.48 – 5.40 (m, 1H), 5.19 (d, *J* = 17.2 Hz, 1H), 4.89 (d, *J* = 17.2 Hz, 1H), 3.83 (s, 3H), 2.00 – 1.88 (m, 2H), 1.56 – 1.42 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 164.0, 155.6, 146.9, 137.6, 133.5, 129.7, 129.4, 126.4, 124.0, 122.9, 108.8, 63.0, 55.9, 38.6, 36.0, 25.1, 22.9, 21.5.

MS (ESI) m/z calculated for $C_{23}H_{25}N_7O_5$:$[M]^+$: 479.19; found $[M-H]^+$: 478.17.

1-(5-((1H-indol-3-yl)methyl)-6-oxo-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8H)-yl)-N-(4-methoxyphenethyl)cyclohexanecarboxamide (11o):

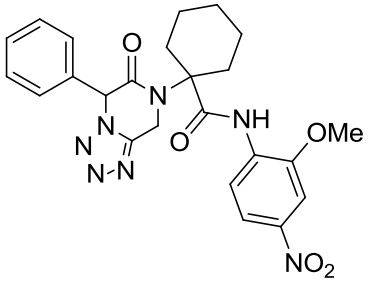


The product was obtained using procedure **C**. Yield: 49%.

^{1}H NMR (500 MHz, DMSO) δ 7.59 (bs, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.98 (t, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.85 – 6.79 (m, 2H), 6.58 (s, 1H), 5.48 (s, 1H), 4.73 (d, *J* = 16.3 Hz, 1H), 3.84 (d, *J* = 16.3 Hz, 1H), 3.70 (s, 3H), 3.69 – 3.64 (m, 1H), 3.54 – 3.48 (m, 2H), 3.15 – 3.05 (m, *J* = 10.8 Hz, 2H), 3.00 – 2.94 (m, 1H), 2.84 – 2.79 (m, 1H), 2.21 – 2.15 (m, 1H), 1.88 – 1.79 (m, 1H), 1.71 – 1.66 (m, 2H), 1.43 – 1.34 (m, 2H), 1.32 – 1.23 (m, 1H), 1.12 – 1.01 (m, 2H), 0.95 – 0.87 (m, 1H). ^{13}C NMR (126 MHz, DMSO) δ 172.2, 163.6, 157.6, 148.7, 135.8, 131.7, 129.7, 129.6, 126.8, 121.1, 113.7, 113.6, 111.3, 106.1, 79.3, 64.9, 59.8, 55.0, 34.4, 32.6, 32.1, 29.4, 28.4, 24.7, 22.0.

MS (ESI) m/z calculated for $C_{29}H_{33}N_7O_3$: $[M]^+$: 527.27; found $[M-H]^+$: 526.33.

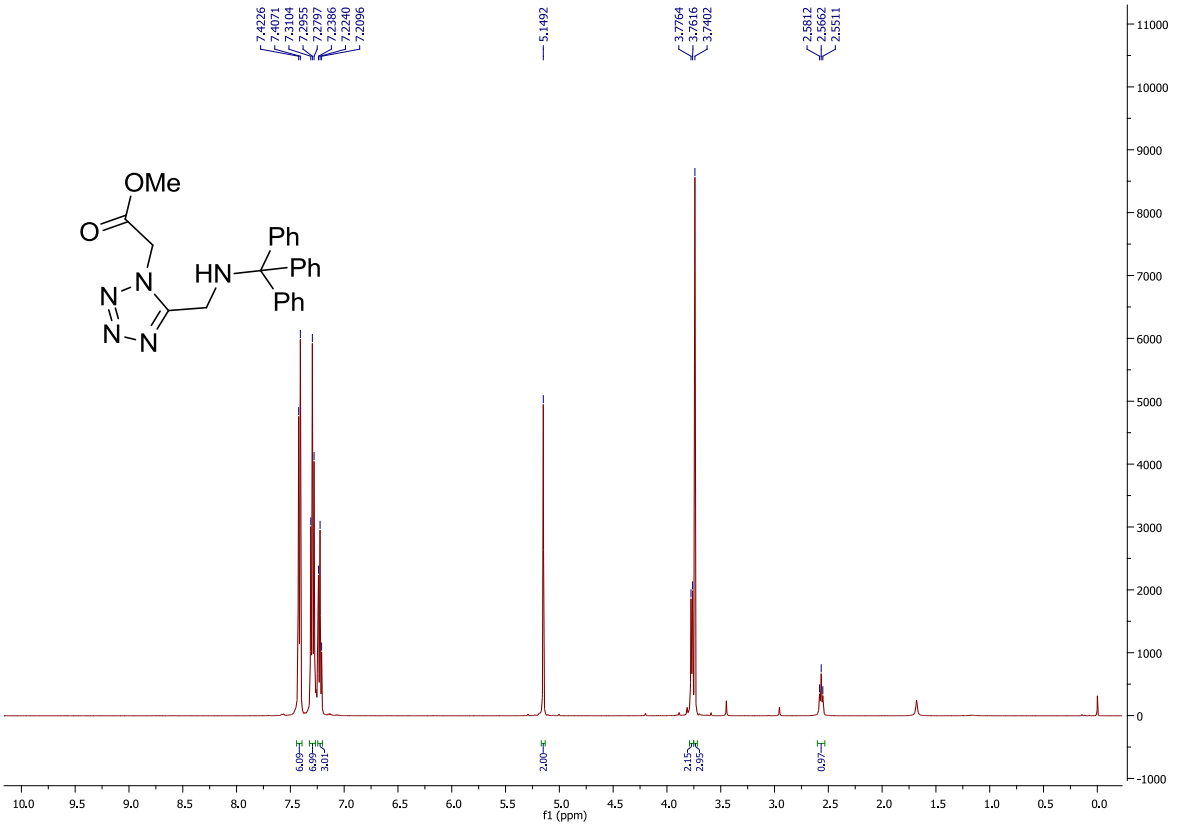
N-(2-methoxy-4-nitrophenyl)-1-(6-oxo-5-phenyl-5,6-dihydrotetrazolo[1,5-a]pyrazin-7(8H)-yl)cyclohexanecarboxamide (11l):



The product was obtained using procedure **C**. Yield: 71%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.50 (d, *J* = 9.0 Hz, 1H), 7.90 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.72 (d, *J* = 2.4 Hz, 1H), 7.33 – 7.33 (m, 3H), 7.14 (dd, *J* = 7.6, 1.8 Hz, 2H), 6.23 (s, 1H), 5.31 (d, *J* = 16.5 Hz, 1H), 5.10 (d, *J* = 16.5 Hz, 1H), 3.94 (s, 3H), 2.38 – 2.17 (m, 2H), 1.89 – 1.45 (m, 6H), 1.34 – 1.23 (m, 1H), 0.90 – 0.82 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 165.5, 147.7, 143.4, 133.6, 133.2, 129.8, 129.5, 126.7, 118.4, 117.7, 105.2, 67.4, 63.5, 56.5, 39.6, 32.3, 31.8, 25.0, 22.6, 22.4.

MS (ESI) m/z calculated for $C_{24}H_{25}N_7O_5$: $[M]^+$: 491.19; found $[M-H]^+$: 490.23.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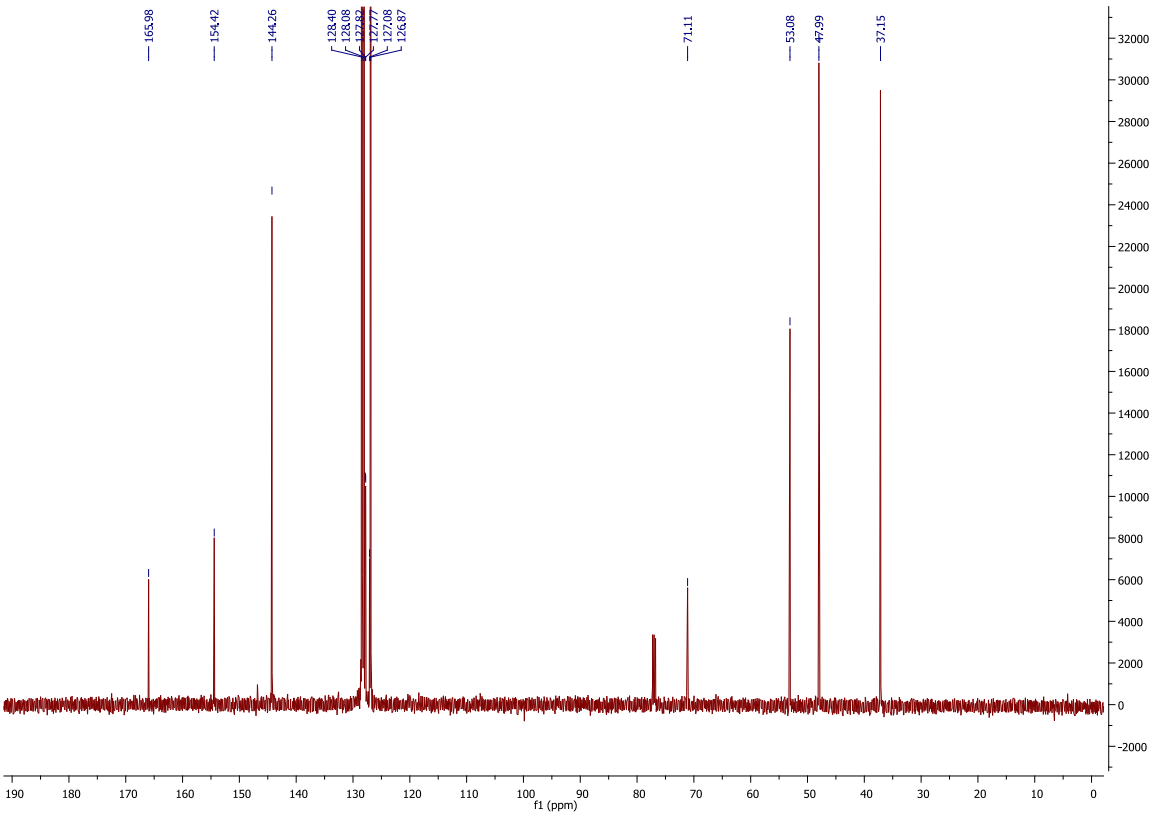
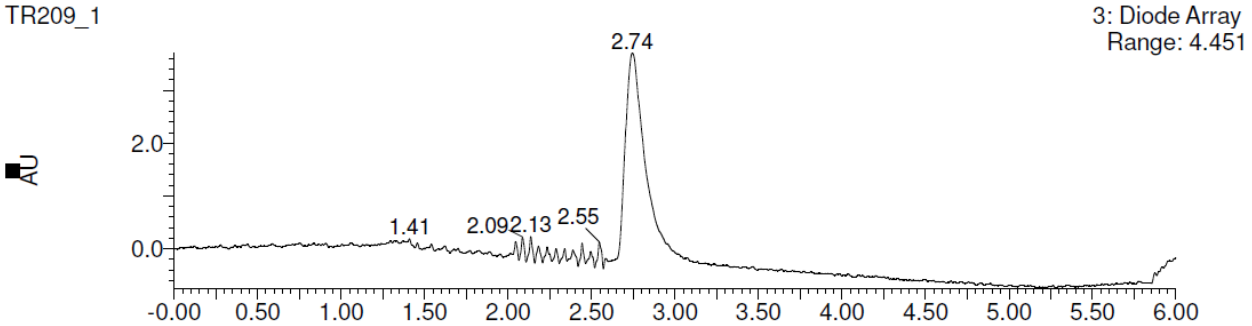
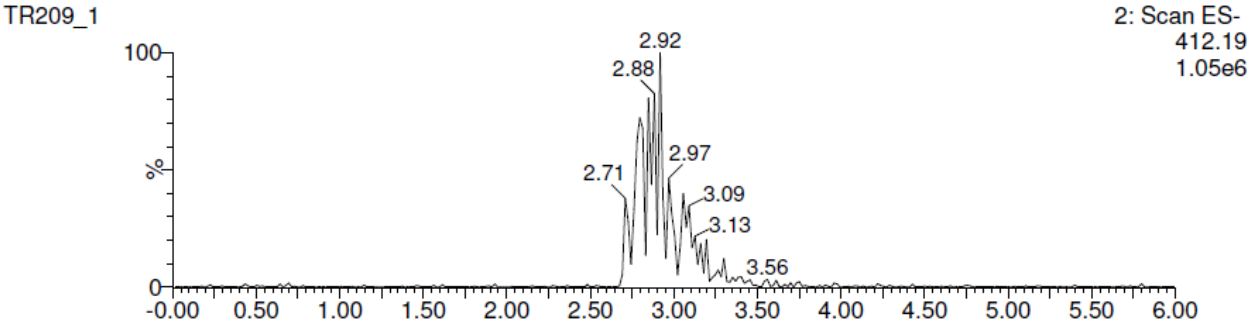
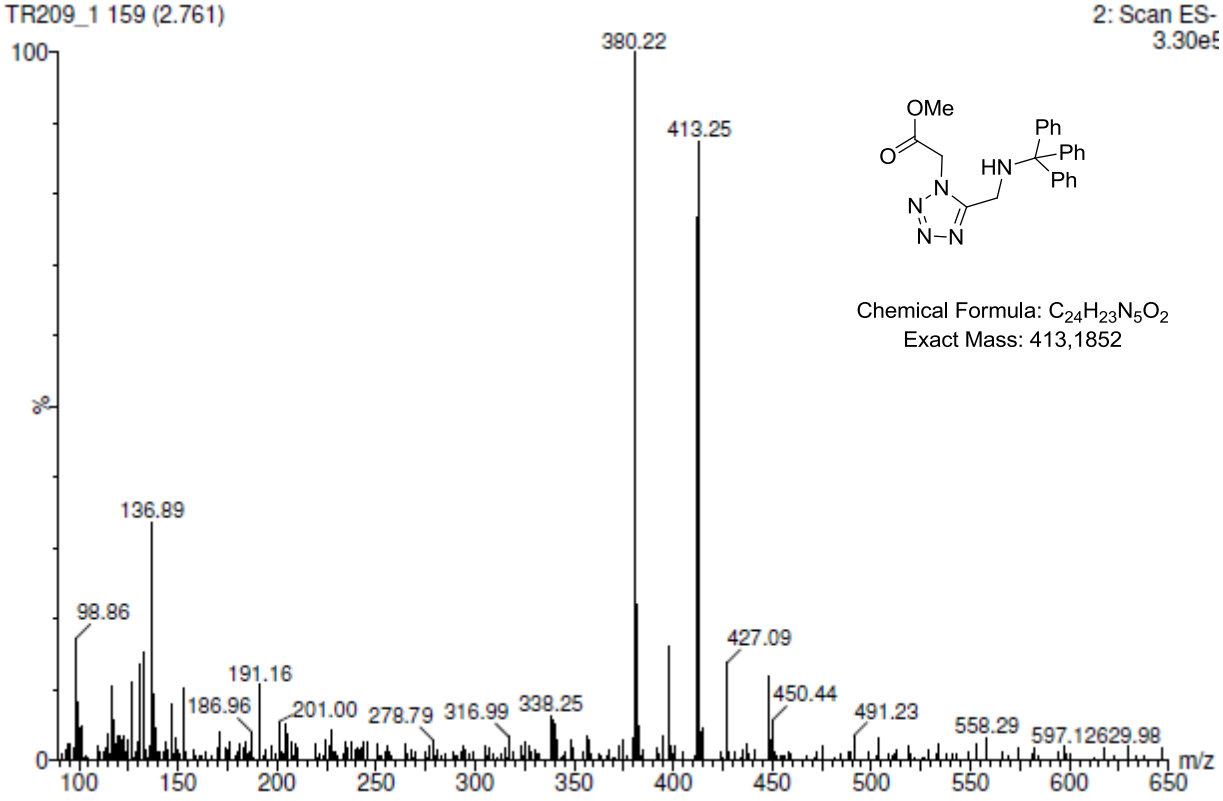
7.4071
7.3104
7.2955
7.2797
7.2386
7.2240
7.2096
5.1492
3.7764
3.7616
3.7402
2.5812
2.5662
2.5511
OMe
O
N
N
N
N
HN
Ph
Ph
Ph
6.09
6.99
3.01
2.00
2.15
2.95
0.97
f1 (ppm)


165.98
154.42
144.26
128.40
128.08
127.82
127.77
127.08
126.87
71.11
53.08
47.99
37.15
f1 (ppm)

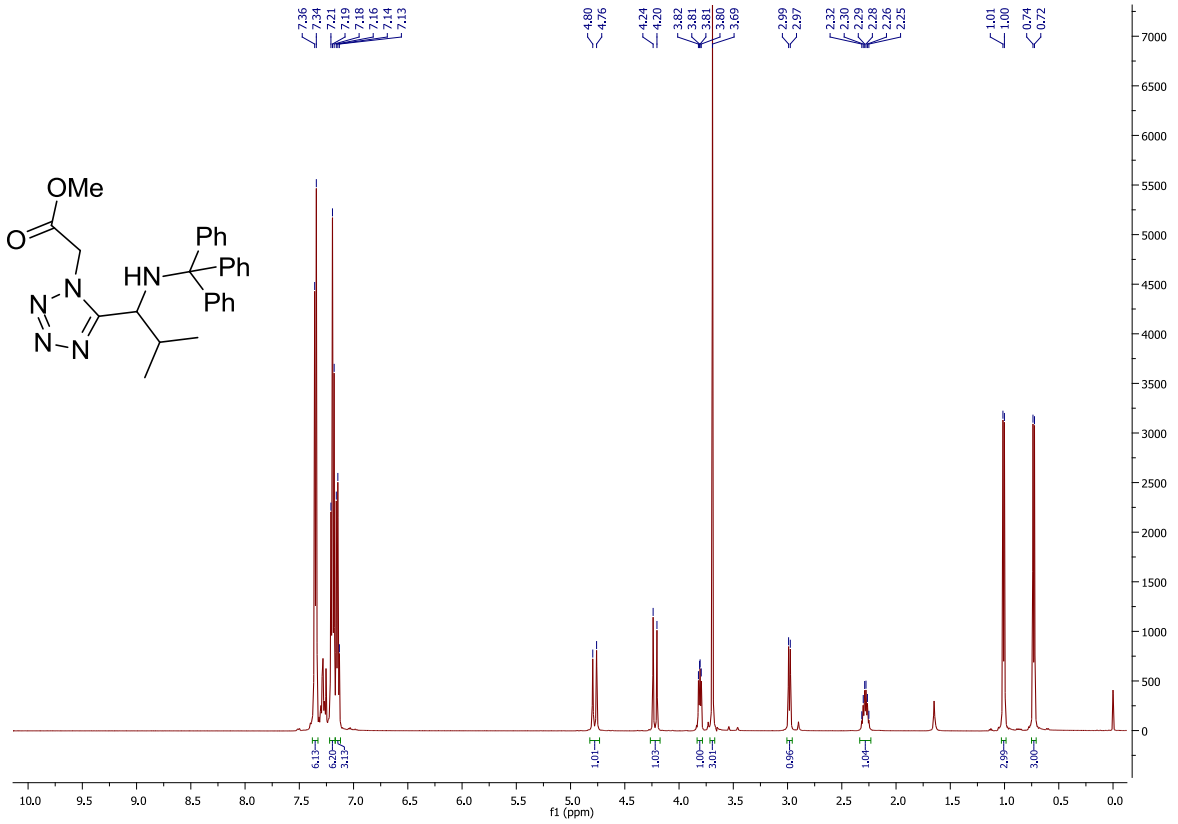
TR209_1_Silica_4.6X250_MeOH_5-30%_6

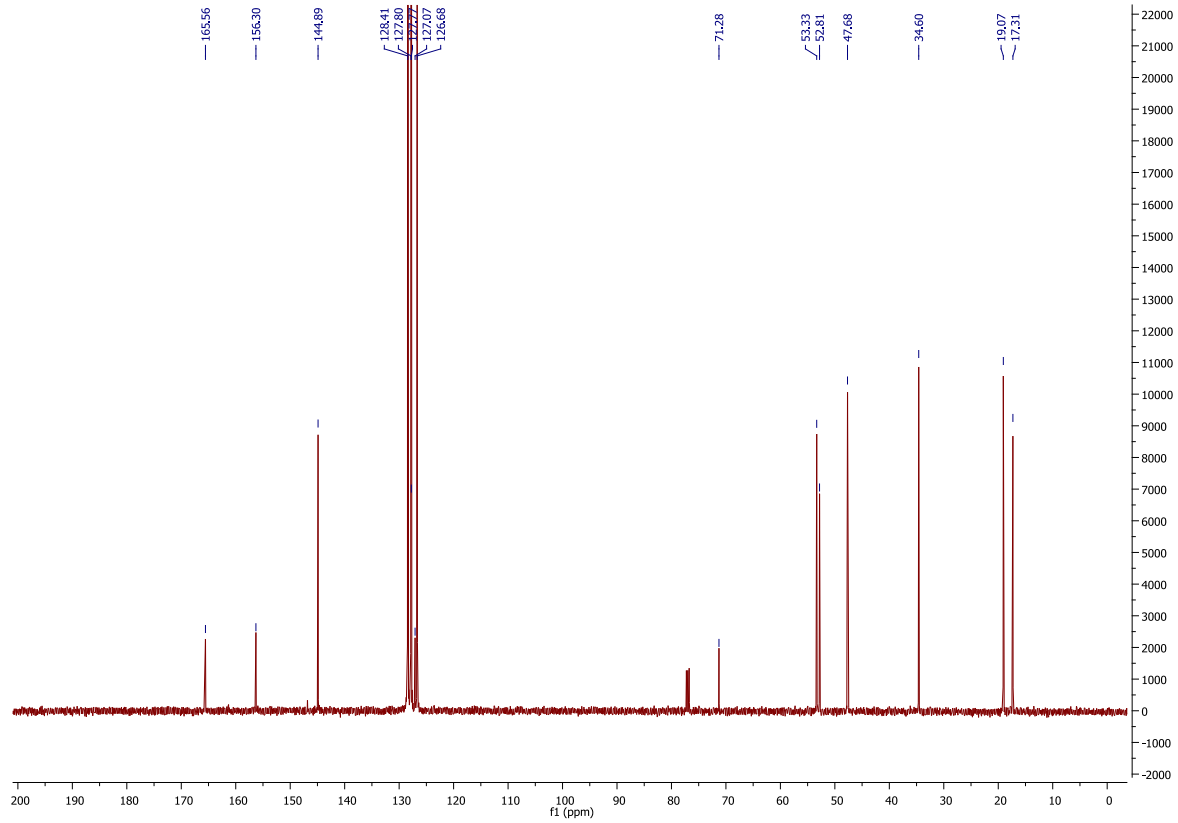


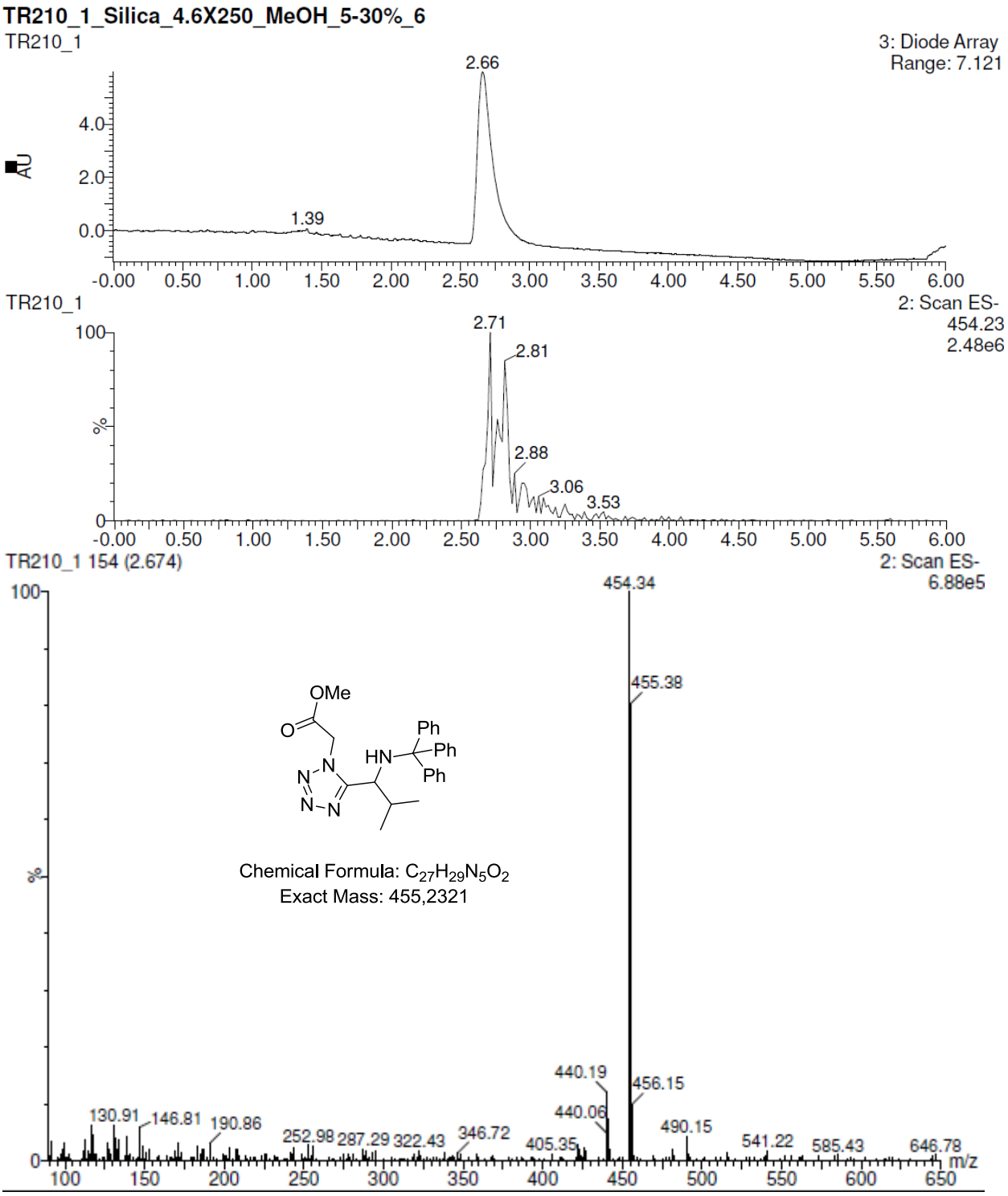


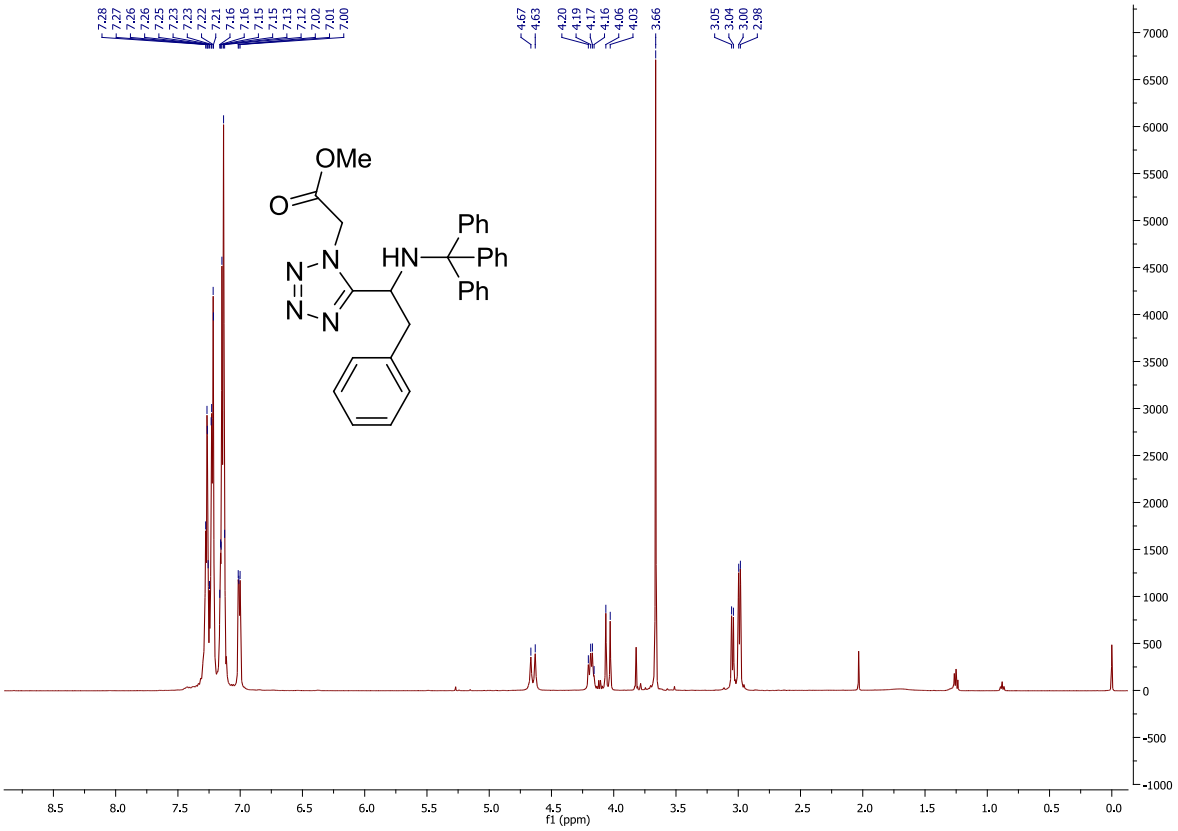


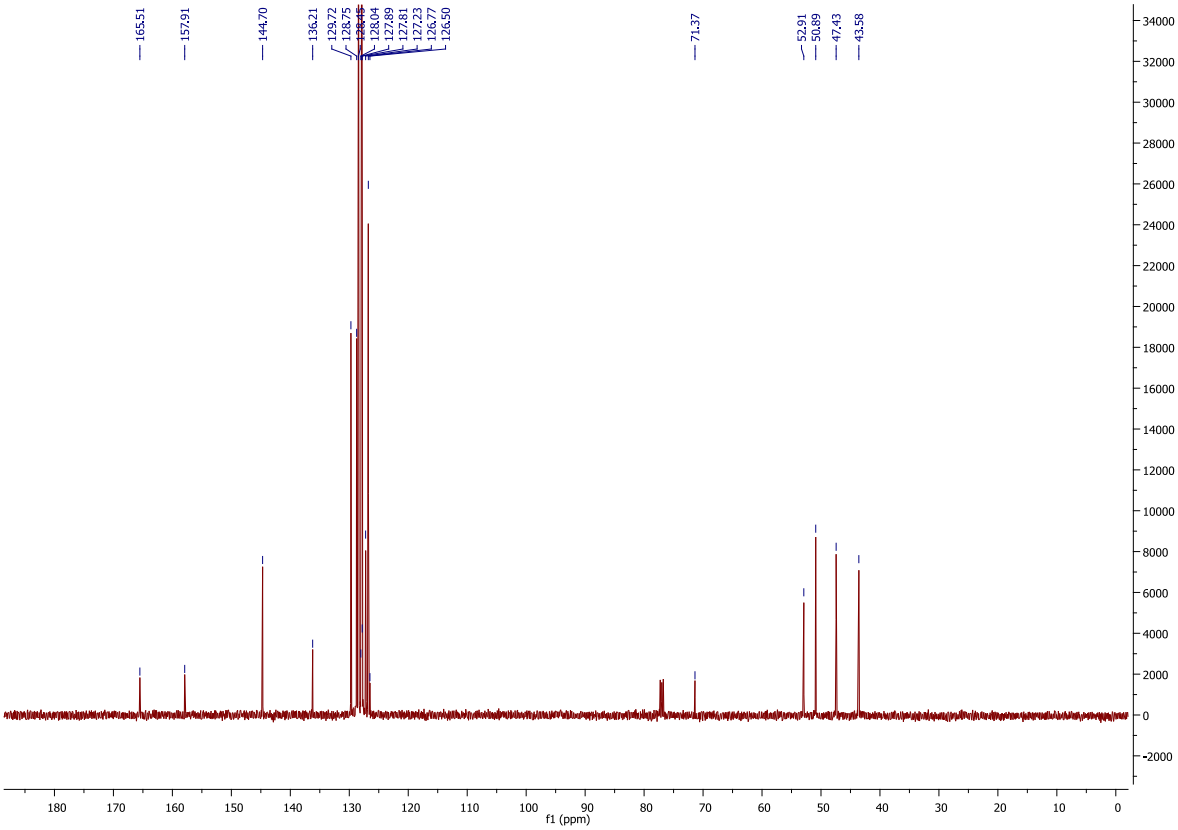
Chemical Formula: $C_{24}H_{23}N_5O_2$
Exact Mass: 413,1852


OMe
O
Ph
HN
Ph
Ph
N
N
N
N
7.36
7.34
7.21
7.19
7.18
7.16
7.14
7.13
4.80
4.76
4.24
4.20
3.82
3.81
3.81
3.80
3.69
2.99
2.97
2.32
2.30
2.29
2.28
2.26
2.25
1.01
1.00
0.74
0.72
6.13
6.25
3.13
1.01
1.03
1.00
3.01
0.96
1.04
2.99
3.00
f1 (ppm)

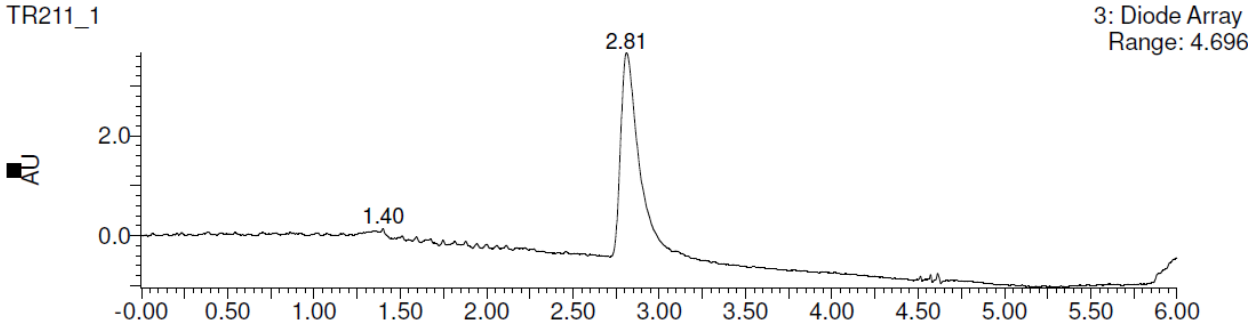

165.56
156.30
144.89
128.41
127.80
127.27
127.07
126.68
71.28
53.33
52.81
47.68
34.60
19.07
17.31
f1 (ppm)

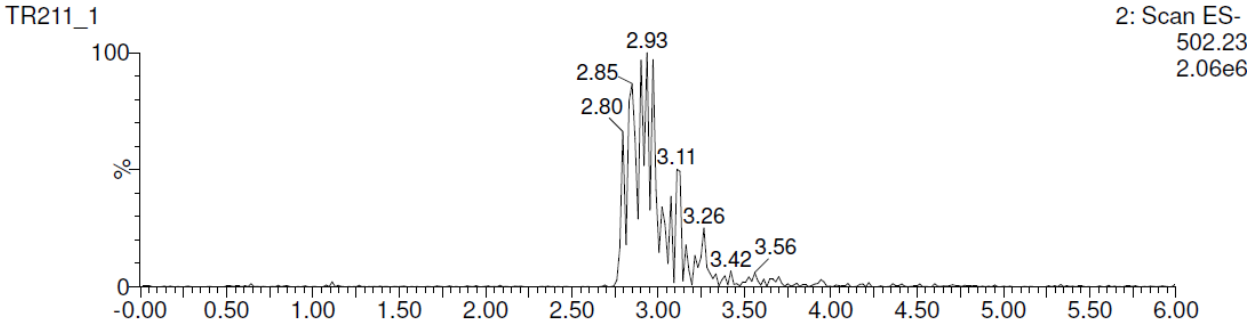

TR210_1_Silica_4.6X250_MeOH_5-30%_6
TR210_1
3: Diode Array
Range: 7.121
2.66
1.39
AU
TR210_1
2: Scan ES-
454.23
2.48e6
2.71
2.81
2.88
3.06
3.53
%
TR210_1 154 (2.674)
2: Scan ES-
6.88e5
454.34
455.38
OMe
O
Ph
HN
Ph
Ph
N
N
N
N
Chemical Formula: C27H29N5O2
Exact Mass: 455,2321
440.19
456.15
440.06
130.91
146.81
190.86
252.98
287.29
322.43
346.72
405.35
490.15
541.22
585.43
646.78
m/z

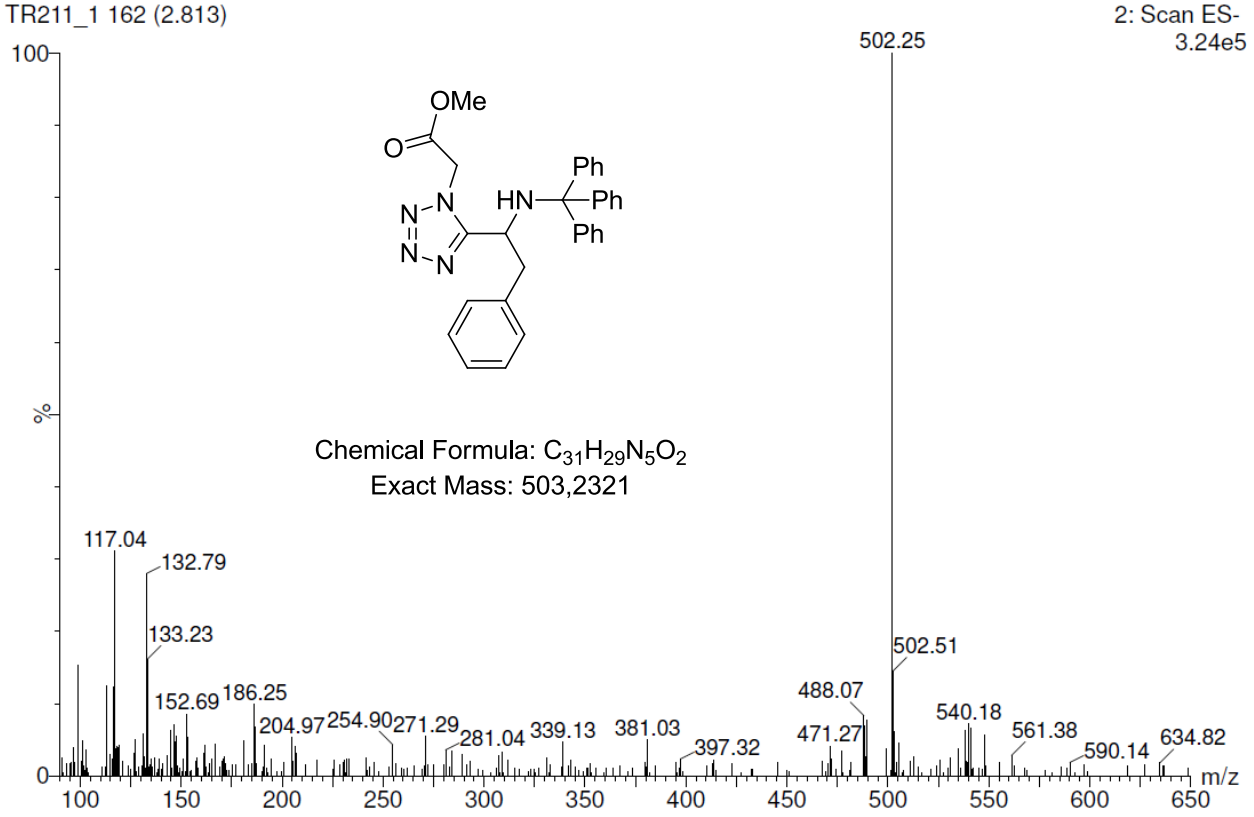

7.28
7.27
7.26
7.26
7.25
7.23
7.23
7.22
7.21
7.16
7.16
7.15
7.15
7.13
7.12
7.02
7.01
7.00
4.67
4.63
4.20
4.19
4.17
4.16
4.06
4.03
3.66
3.05
3.04
3.00
2.98
OMe
O
N
N
N
N
HN
Ph
Ph
Ph
f1 (ppm)


165.51
157.91
144.70
136.21
129.72
128.75
128.04
127.89
127.81
127.23
126.77
126.50
71.37
52.91
50.89
47.43
43.58
f1 (ppm)

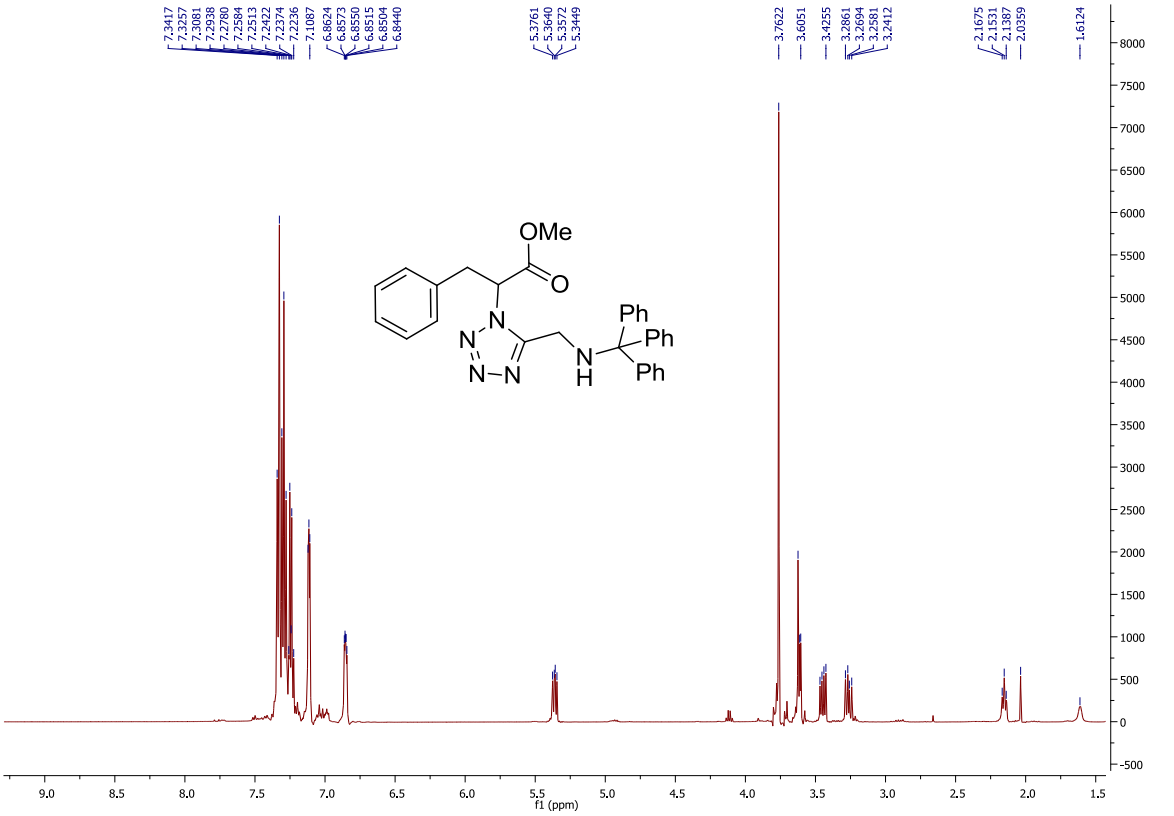
TR211_1_Silica_4.6X250_MeOH_5-30%_6

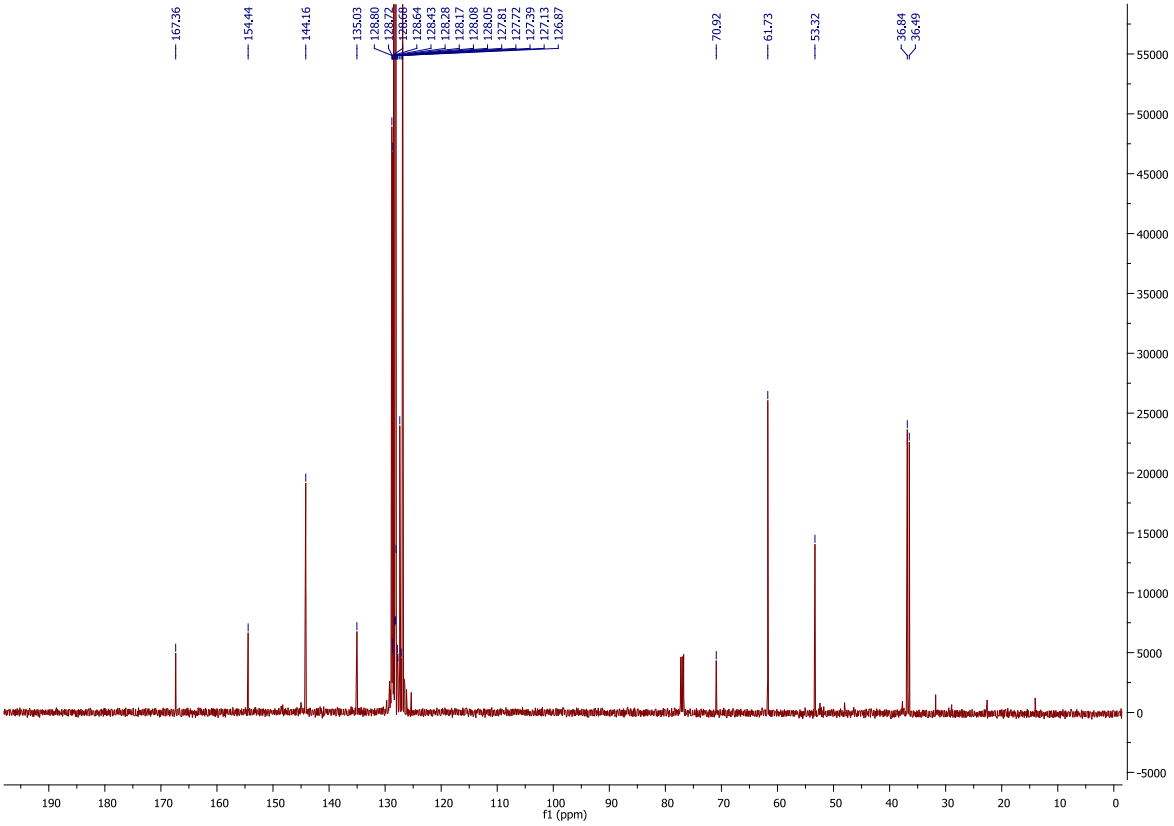




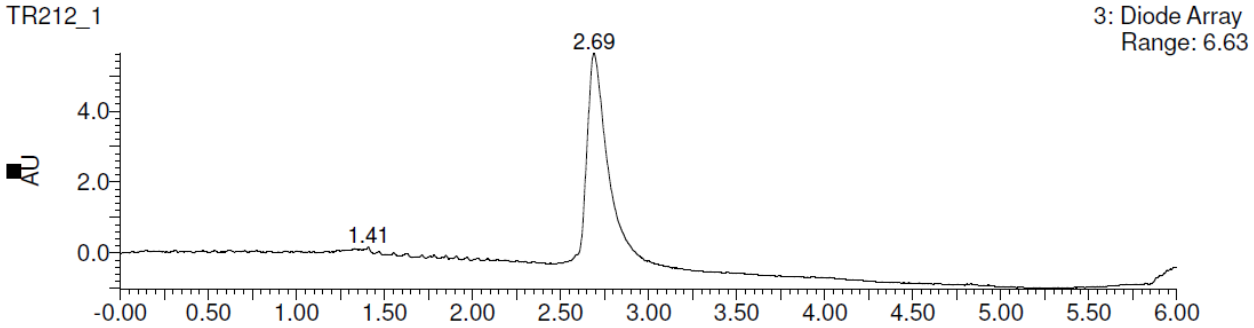


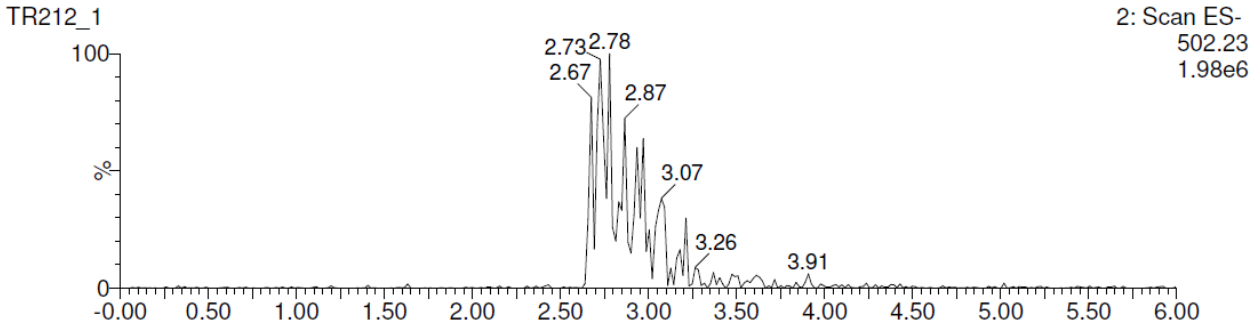
Chemical Formula: $C_{31}H_{29}N_5O_2$
Exact Mass: 503,2321

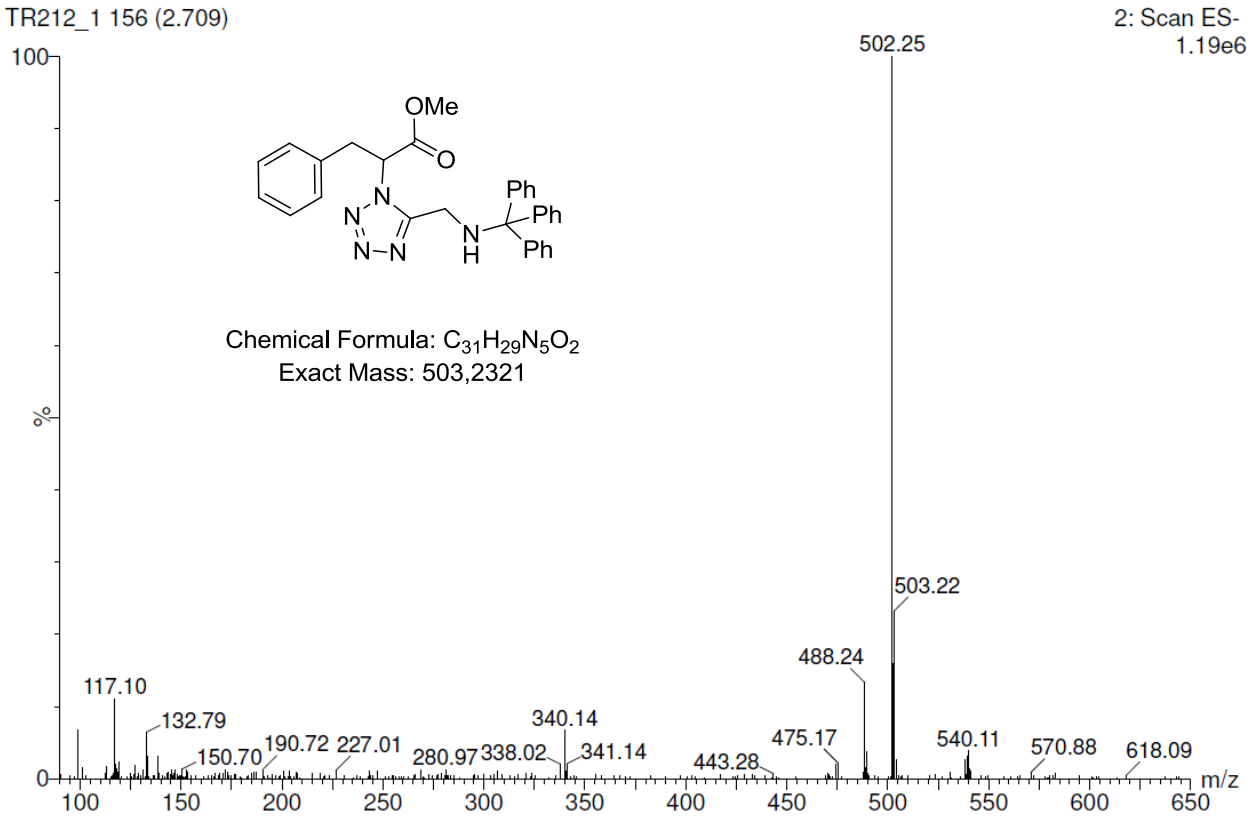

7.3417
7.3257
7.3081
7.2938
7.2780
7.2584
7.2513
7.2422
7.2374
7.2236
7.1087
6.8624
6.8573
6.8550
6.8515
6.8504
6.8440
5.3761
5.3640
5.3572
5.3449
3.7622
3.6051
3.4255
3.2861
3.2694
3.2581
3.2412
2.1675
2.1531
2.1387
2.0359
1.6124
OMe
O
N
N
N
N
H
Ph
Ph
Ph
f1 (ppm)


167.36
154.44
144.16
135.03
128.80
128.72
128.64
128.43
128.28
128.17
128.08
128.05
127.81
127.72
127.39
127.13
126.87
70.92
61.73
53.32
36.84
36.49
f1 (ppm)

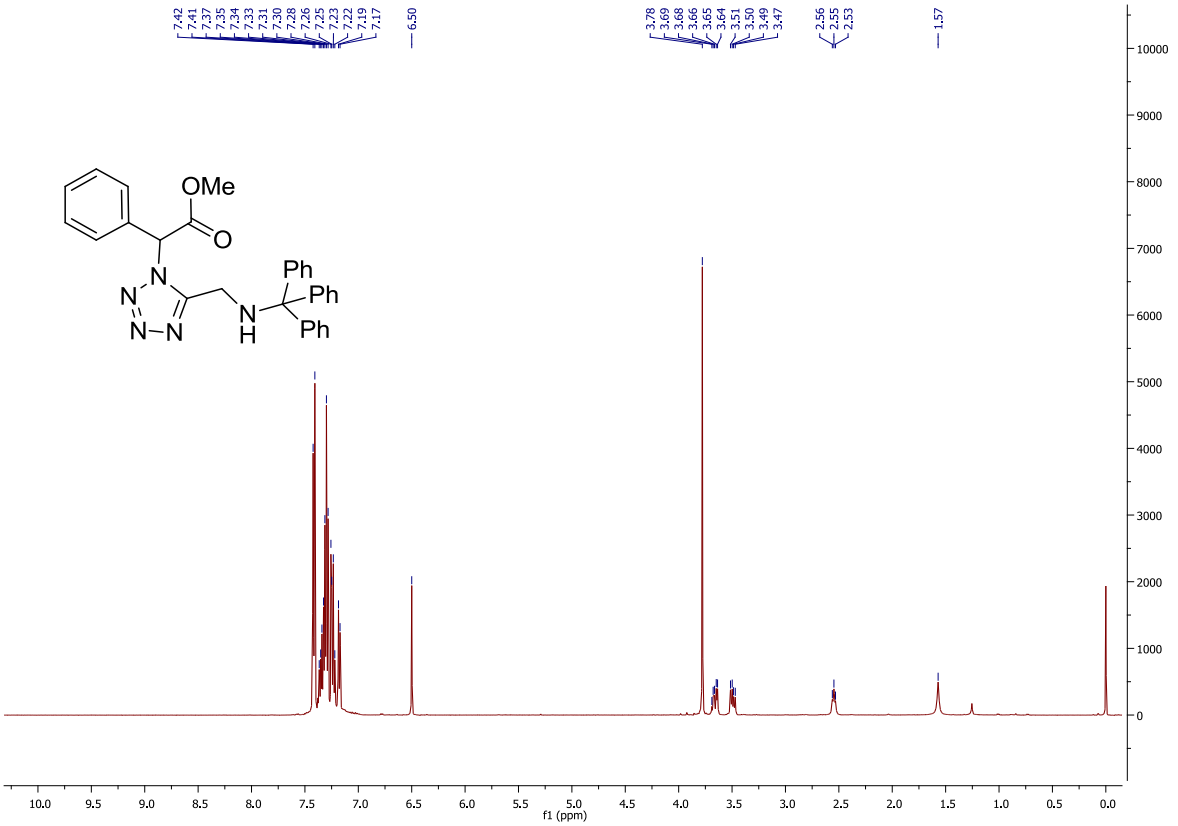
TR212_1_Silica_4.6X250_MeOH_5-30%_6

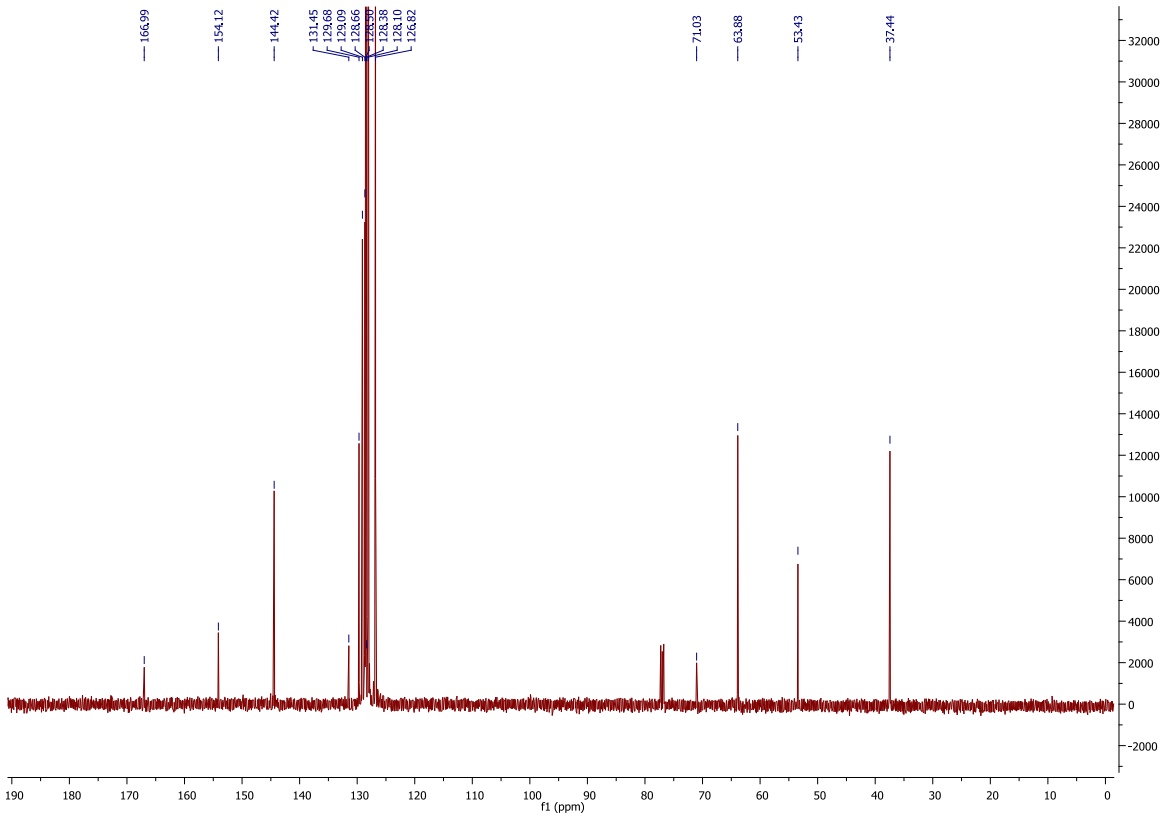




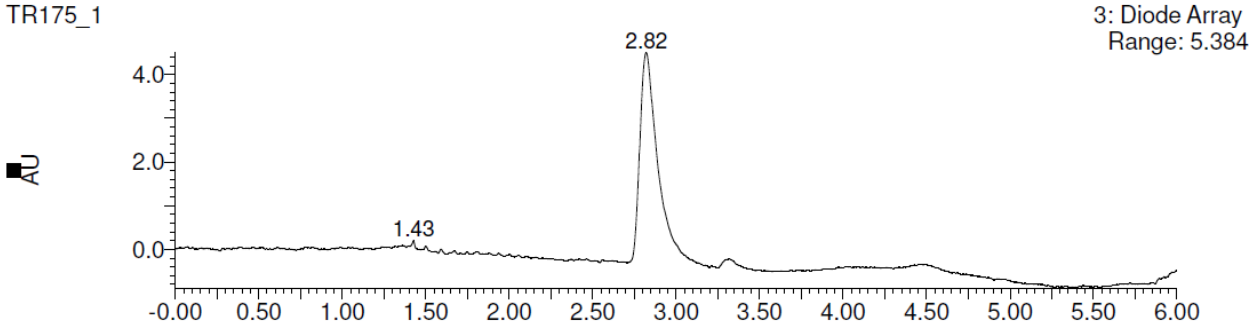


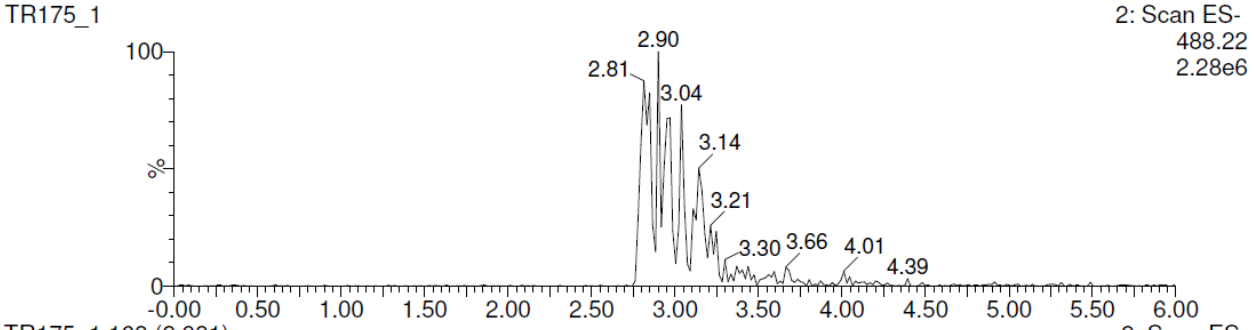
Chemical Formula: $C_{31}H_{29}N_5O_2$
Exact Mass: 503,2321

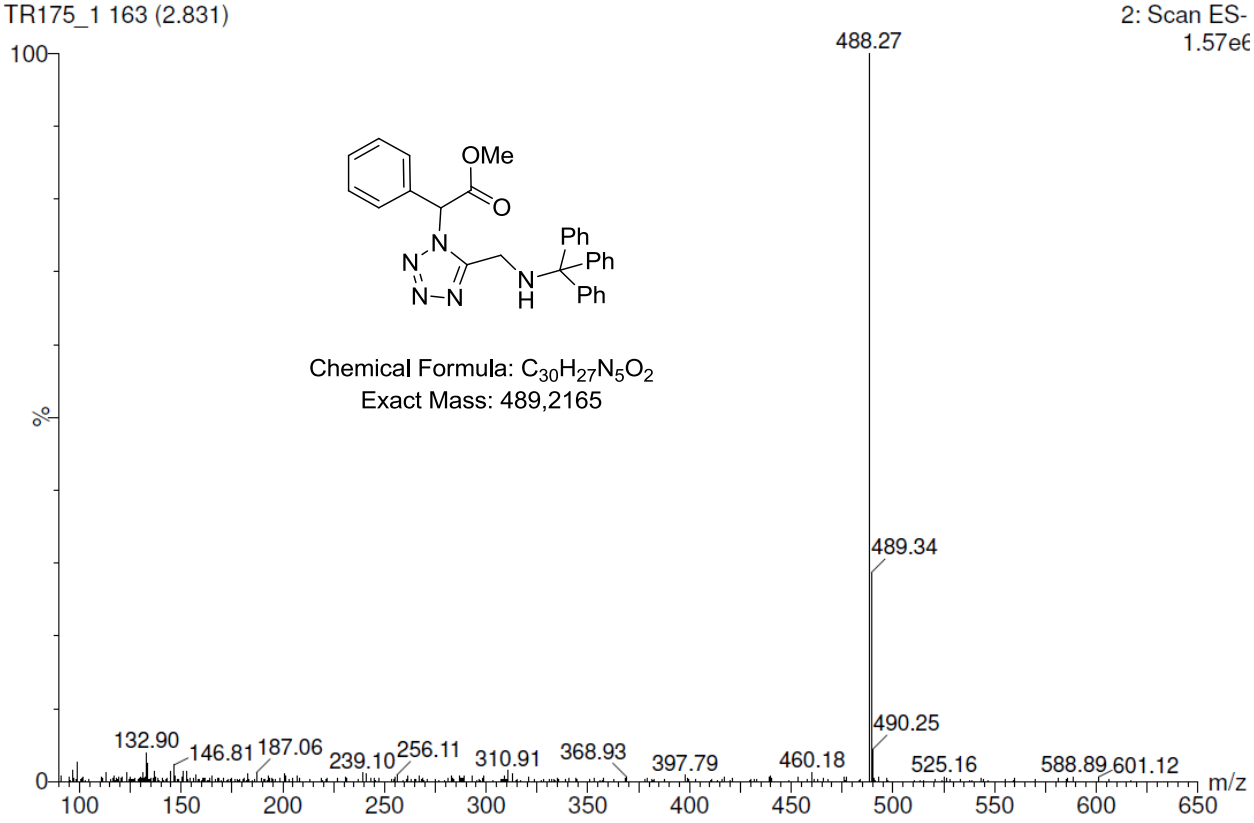

7.42
7.41
7.37
7.35
7.34
7.33
7.31
7.30
7.28
7.26
7.25
7.23
7.22
7.19
7.17
6.50
3.78
3.69
3.68
3.66
3.65
3.64
3.51
3.50
3.49
3.47
2.56
2.55
2.53
1.57
OMe
O
N
N
N
N
H
Ph
Ph
Ph
f1 (ppm)

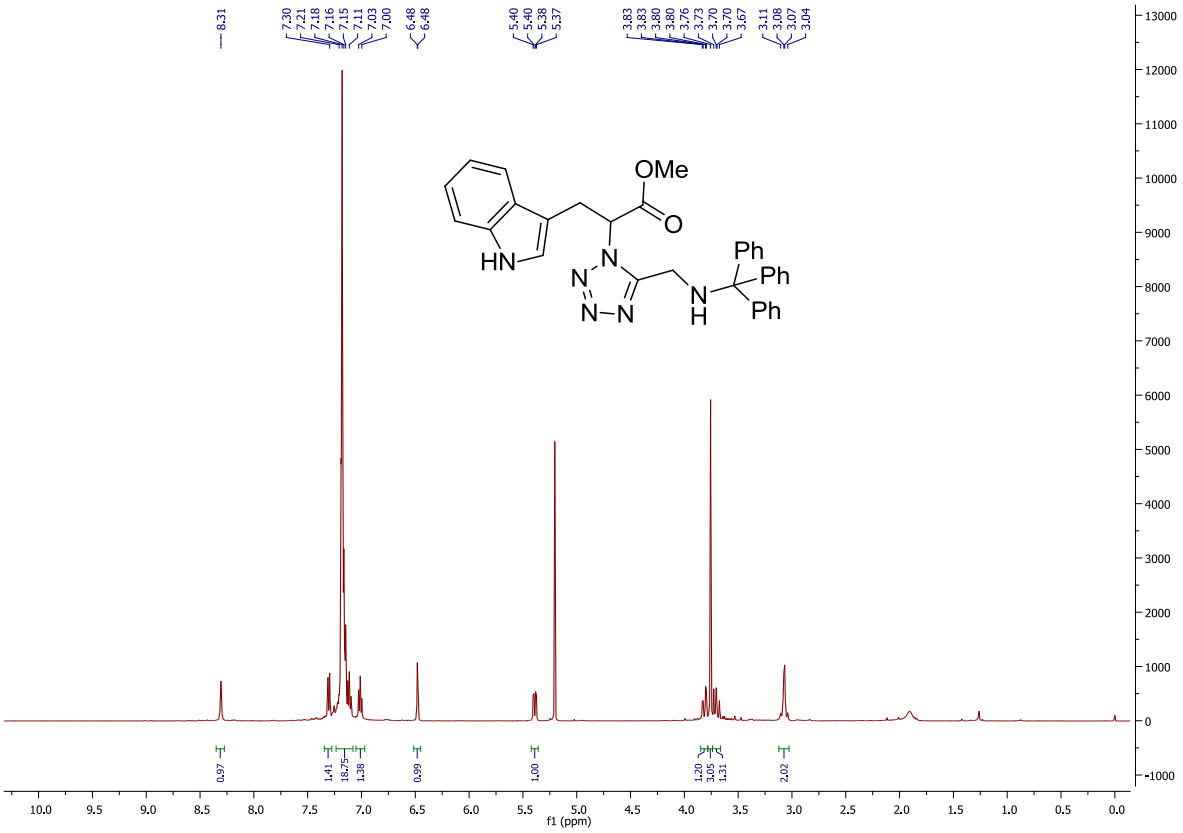

166.99
154.12
144.42
131.45
129.68
129.09
128.66
128.38
128.10
126.82
71.03
63.88
53.43
37.44
f1 (ppm)

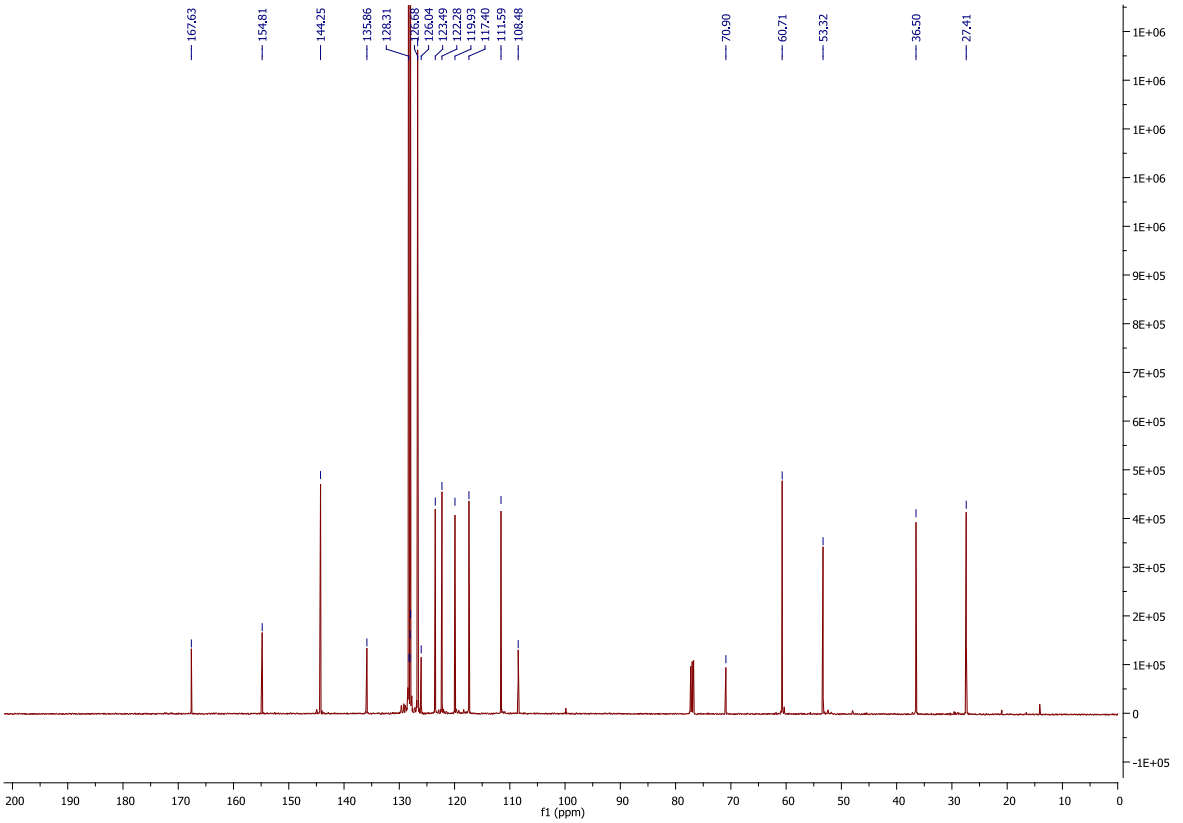
TR175_1_Silica_4.6X250_MeOH_5-30%_6



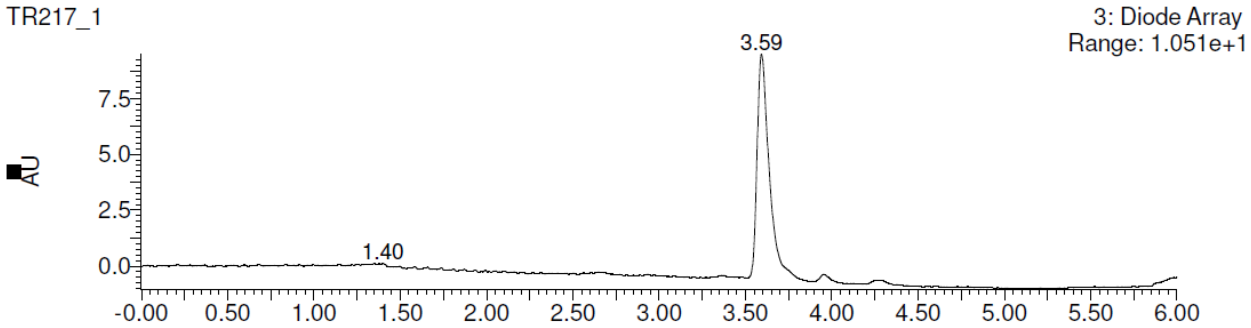


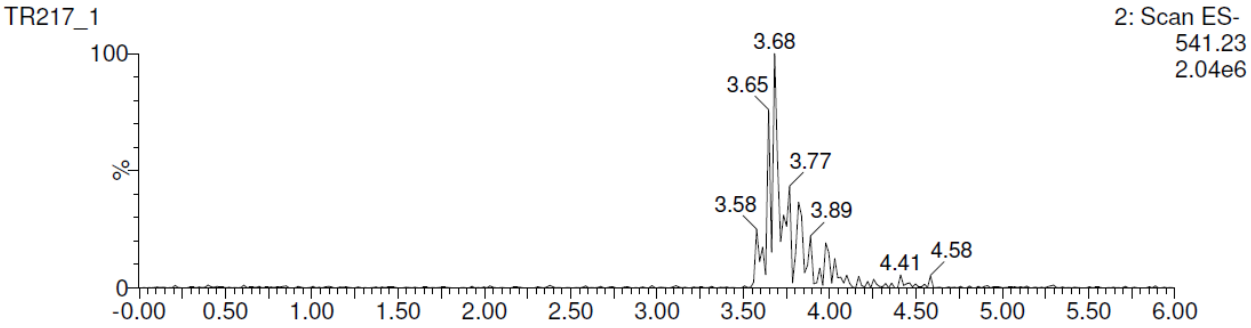


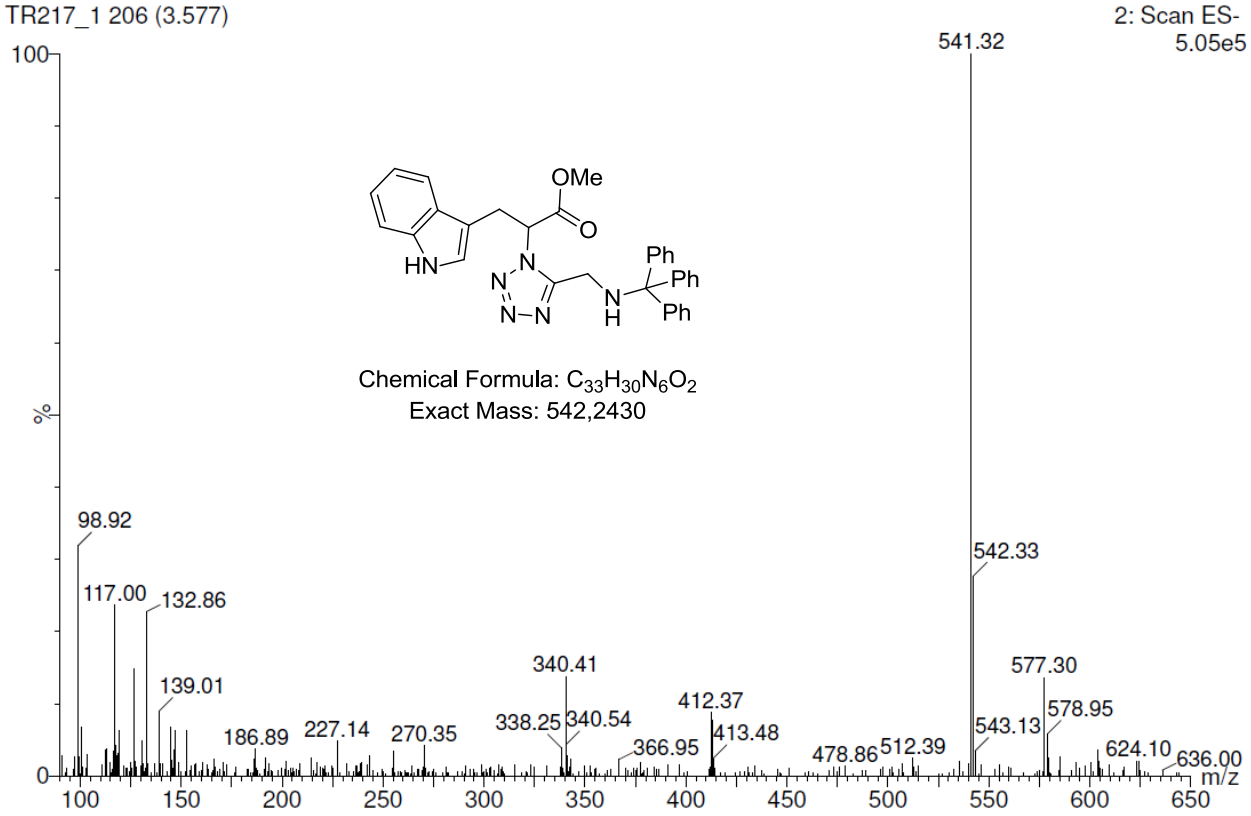

8.31
7.30
7.21
7.18
7.16
7.15
7.11
7.03
7.00
6.48
6.48
5.40
5.40
5.38
5.37
3.83
3.83
3.80
3.80
3.76
3.73
3.70
3.70
3.67
3.11
3.08
3.07
3.04
OMe
O
HN
N
N
N
N
H
Ph
Ph
Ph
0.97
1.41
18.75
1.38
0.99
1.00
1.20
3.05
1.31
2.02
f1 (ppm)


167.63
154.81
144.25
135.86
128.31
126.68
126.04
123.49
122.28
119.93
117.40
111.59
108.48
70.90
60.71
53.32
36.50
27.41
f1 (ppm)

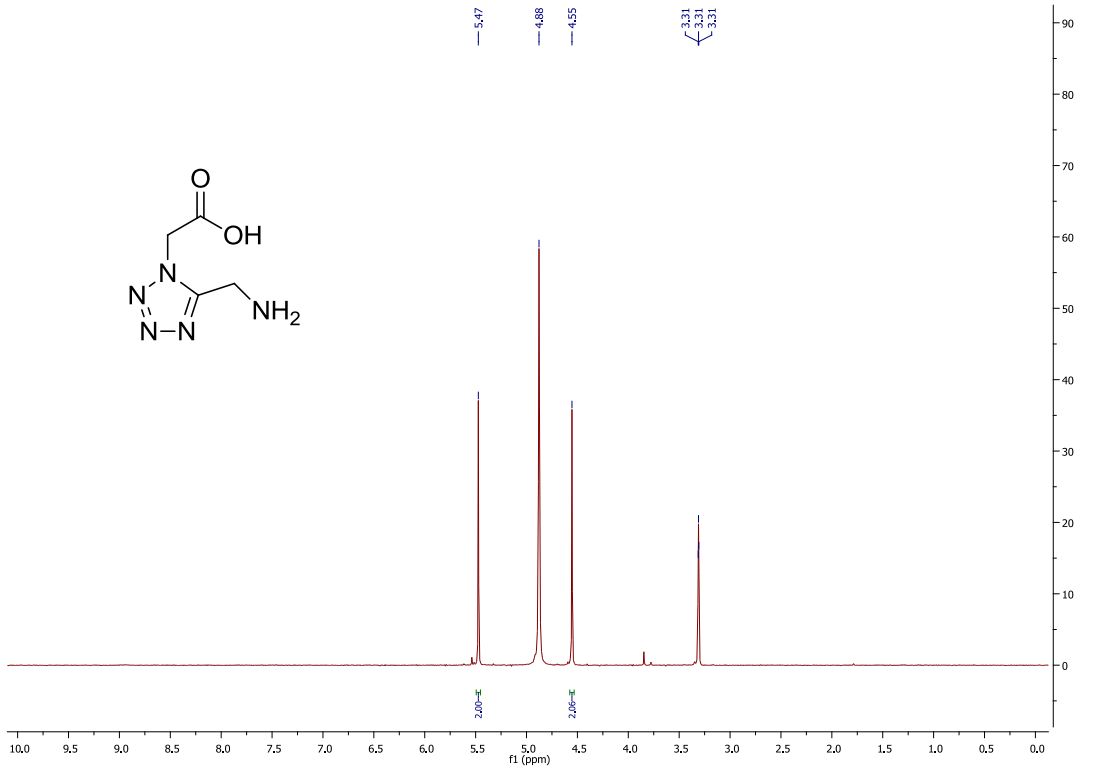
TR217_1_Silica_4.6X250_MeOH_5-30%_6

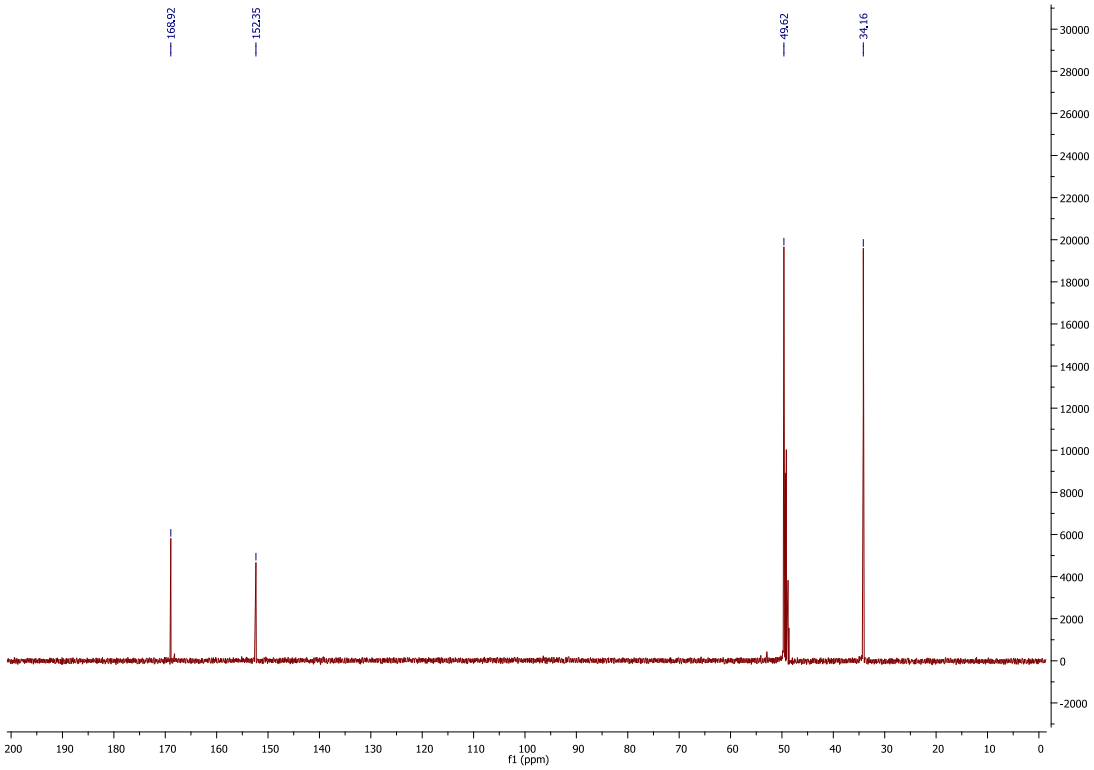


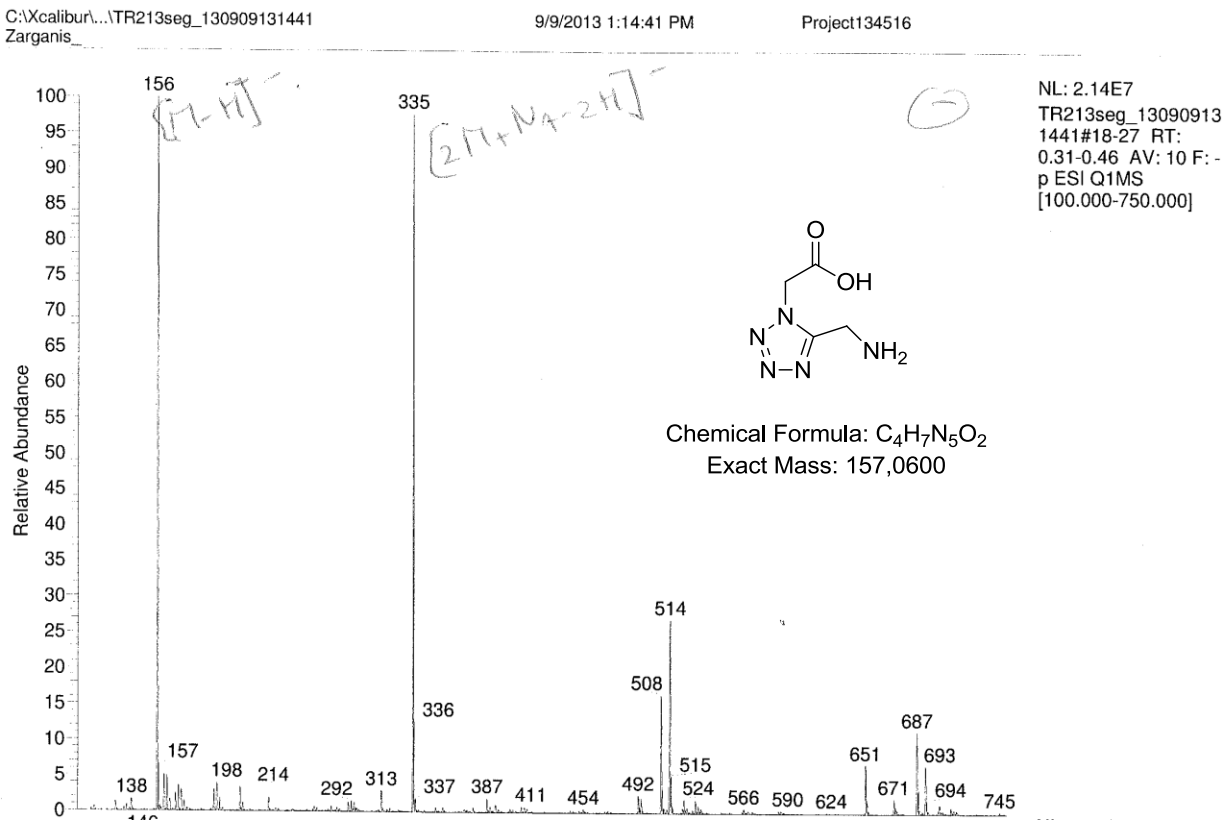


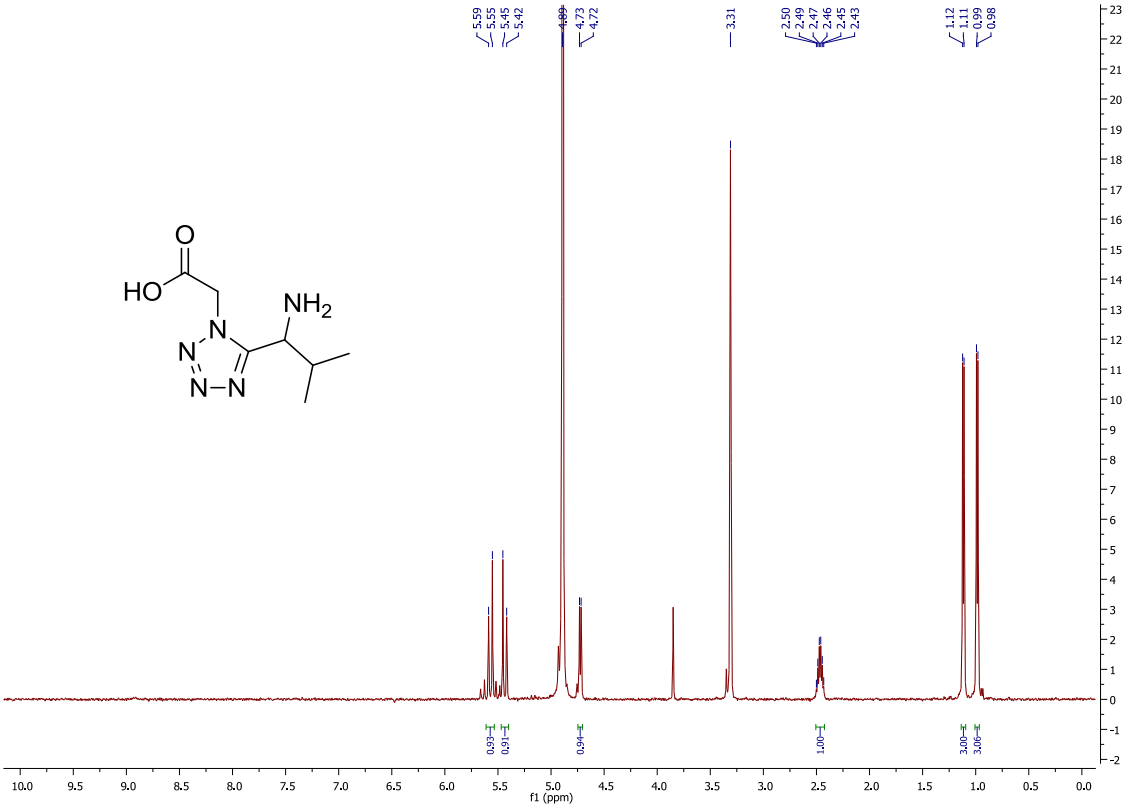


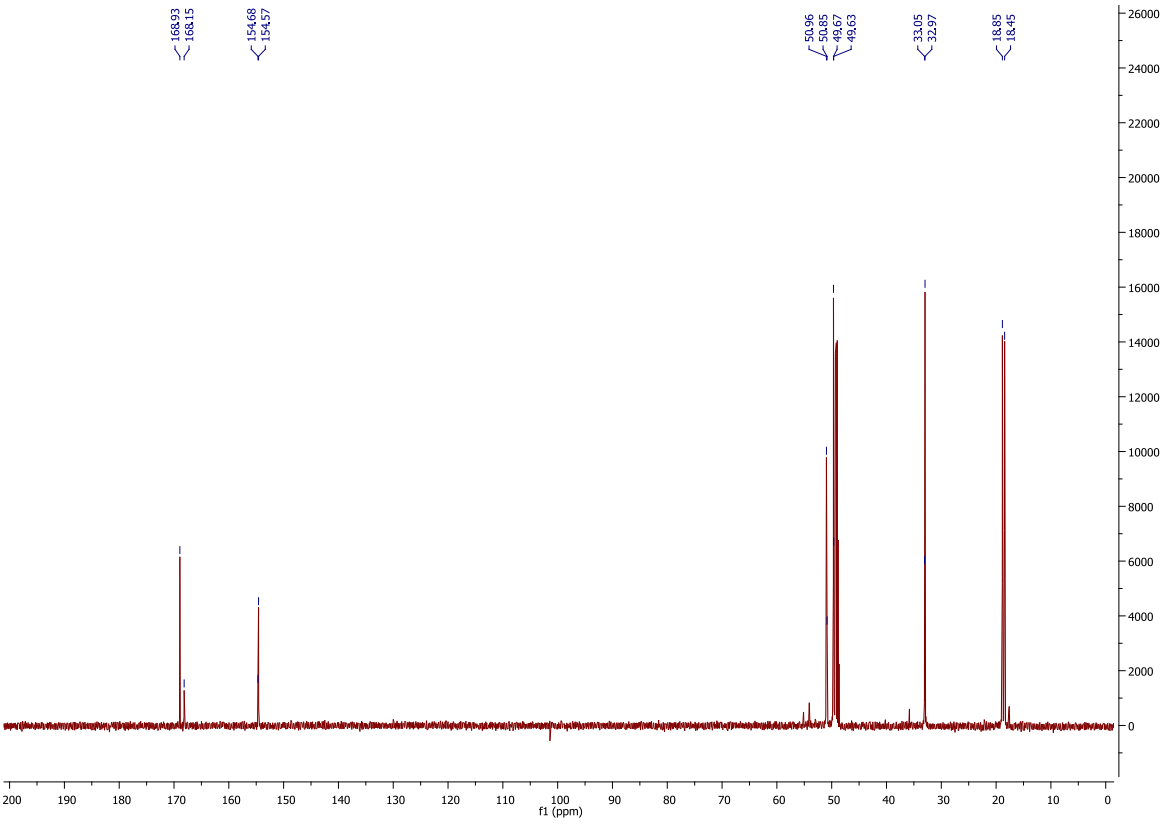
Chemical Formula: $C_{33}H_{30}N_6O_2$
Exact Mass: 542,2430


5.47
4.88
4.55
3.31
3.31
3.31
2.00
2.06
f1 (ppm)

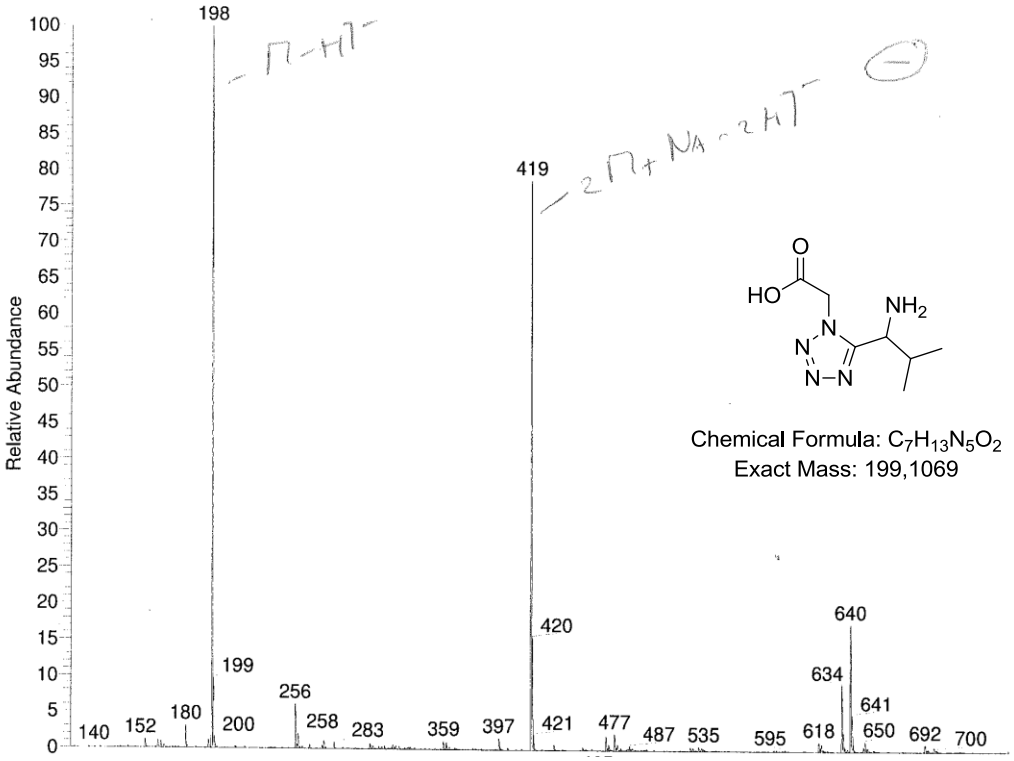

168.92
152.35
49.62
34.16
f1 (ppm)

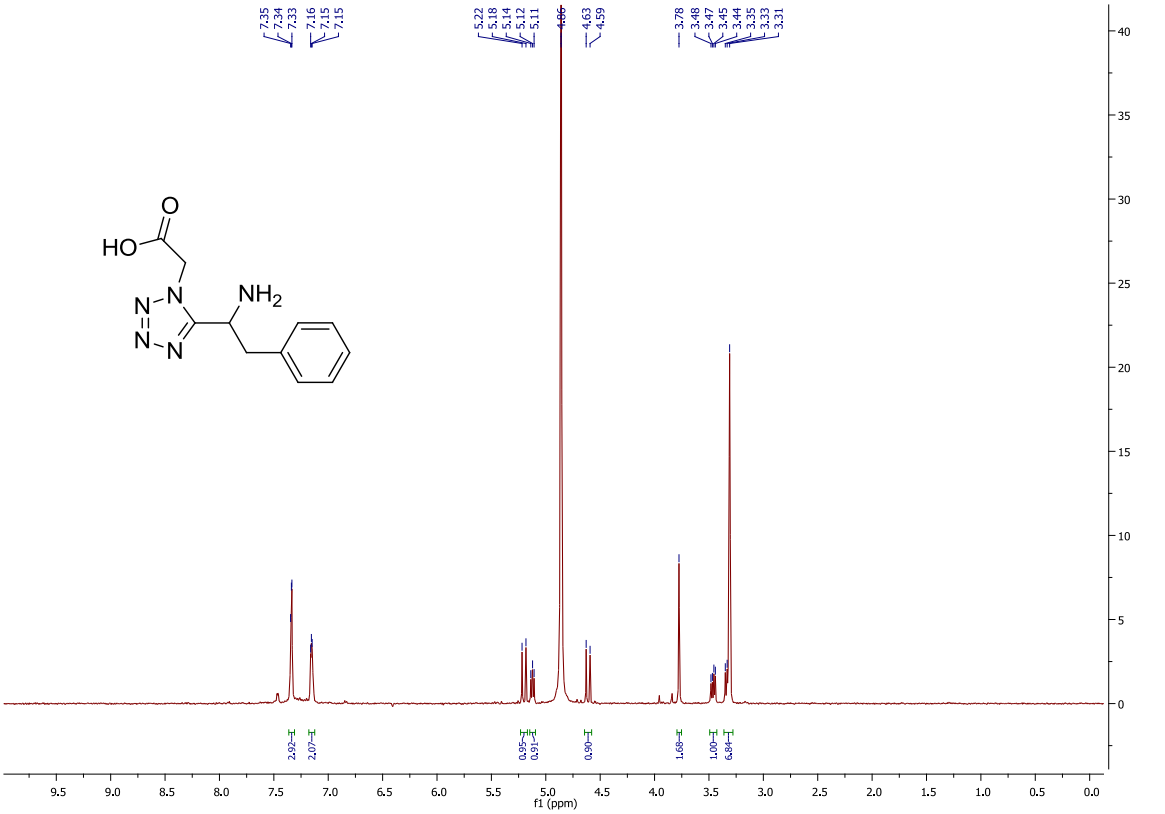

C:\Xcalibur\...\TR213seg_130909131441
Zarganis_
9/9/2013 1:14:41 PM
Project134516
NL: 2.14E7
TR213seg_13090913
1441#18-27 RT:
0.31-0.46 AV: 10 F: -
p ESI Q1MS
[100.000-750.000]
Relative Abundance
156
335
514
508
336
687
693
651
157
198
214
292
313
515
138
337
387
411
454
492
524
566
590
624
671
694
745
OH
N
NH2
Chemical Formula: C4H7N5O2
Exact Mass: 157,0600

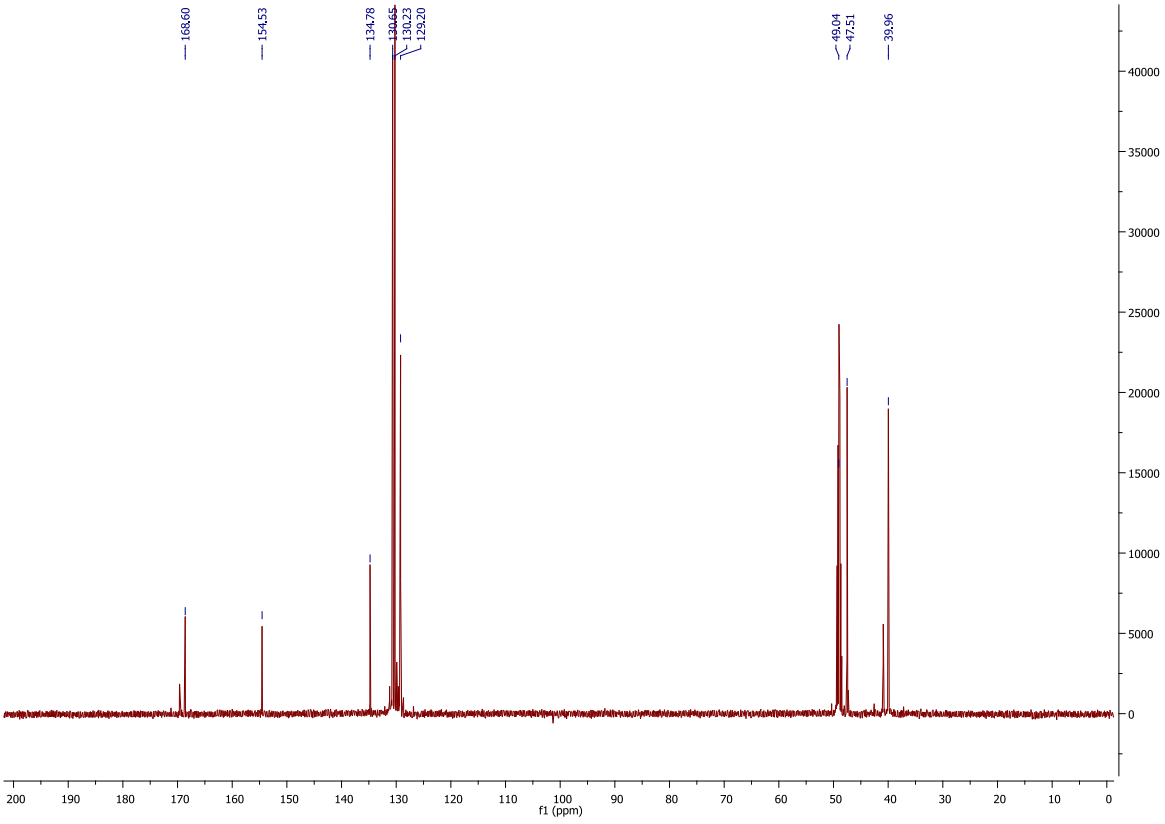

5.59
5.55
5.45
5.42
4.73
4.72
3.31
2.50
2.49
2.47
2.46
2.45
2.43
1.12
1.11
0.99
0.98
O
HO
NH2
N
N
N
N
0.93
0.91
0.94
1.00
3.00
3.00
f1 (ppm)

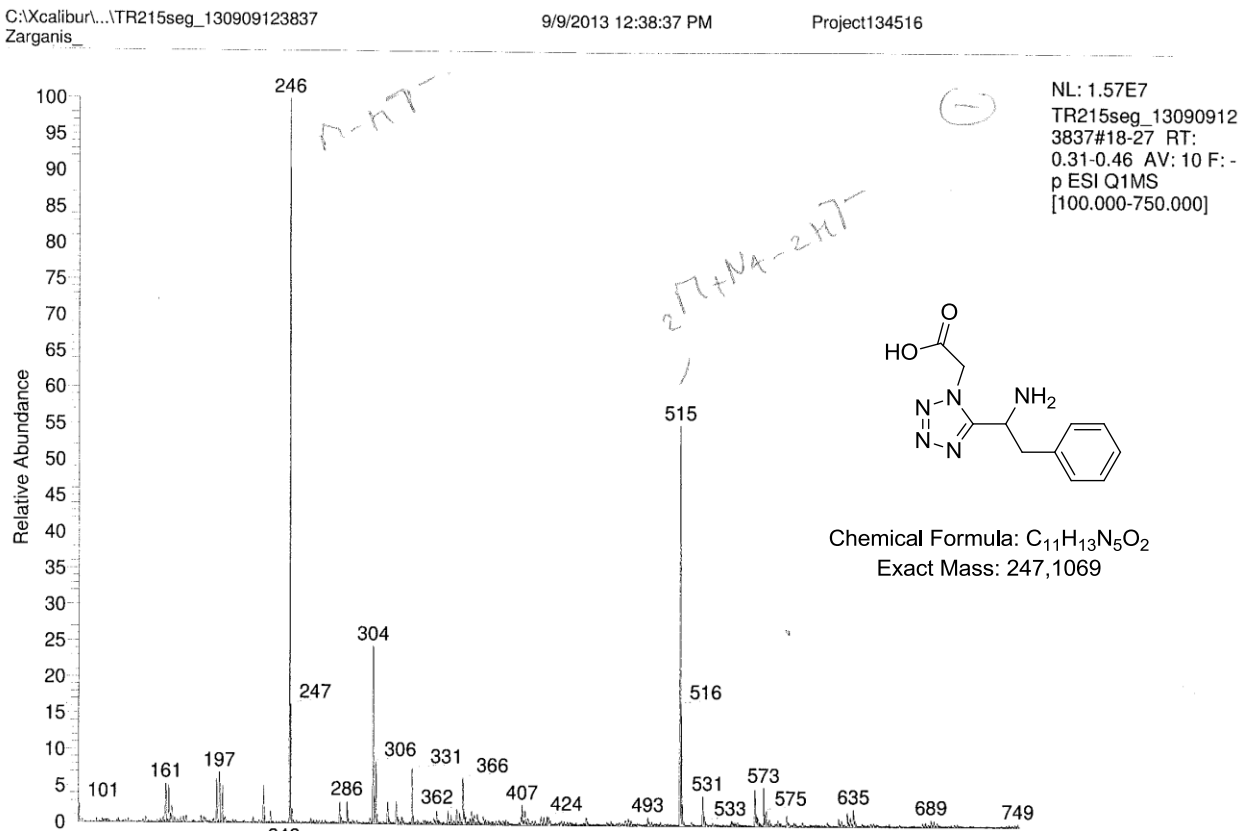

168.93
168.15
154.68
154.57
50.96
50.85
49.67
49.63
33.05
32.97
18.85
18.45
f1 (ppm)

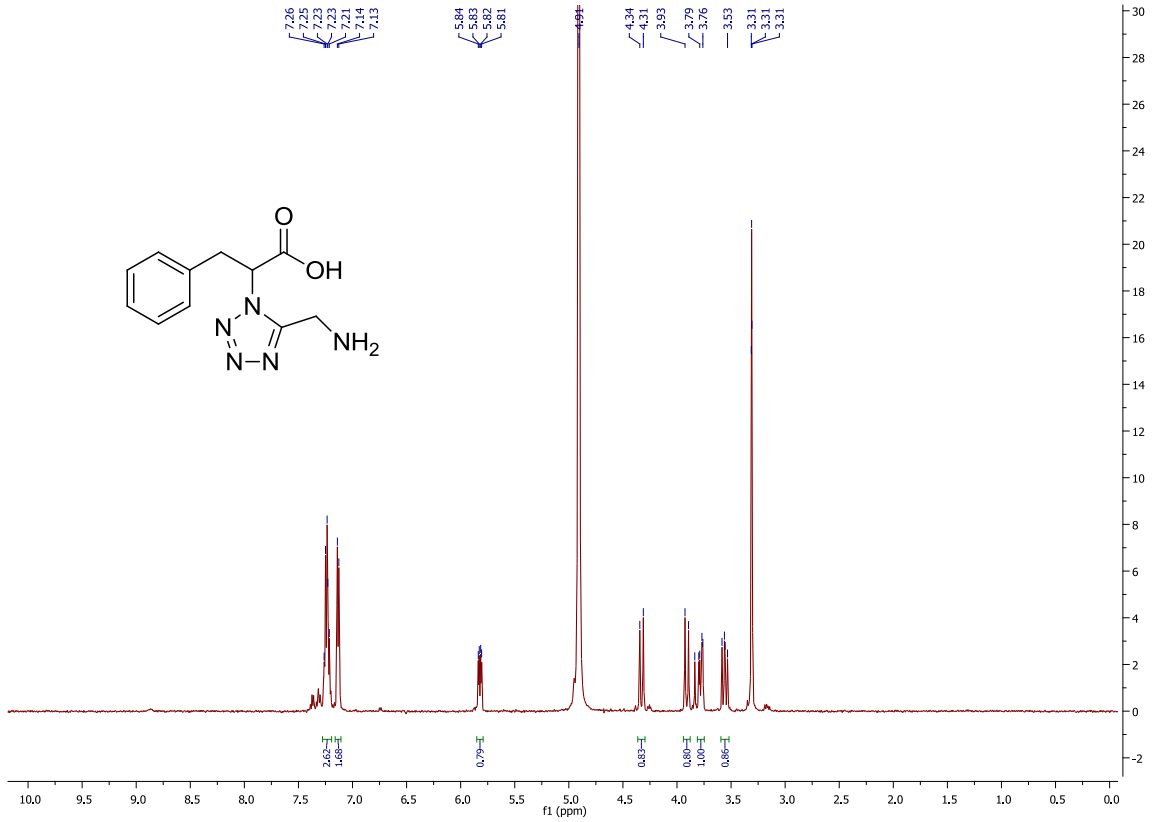
C:\Xcalibur\...\TR214seg_130909124017 9/9/2013 12:40:17 PM Project134516
Zarganis_

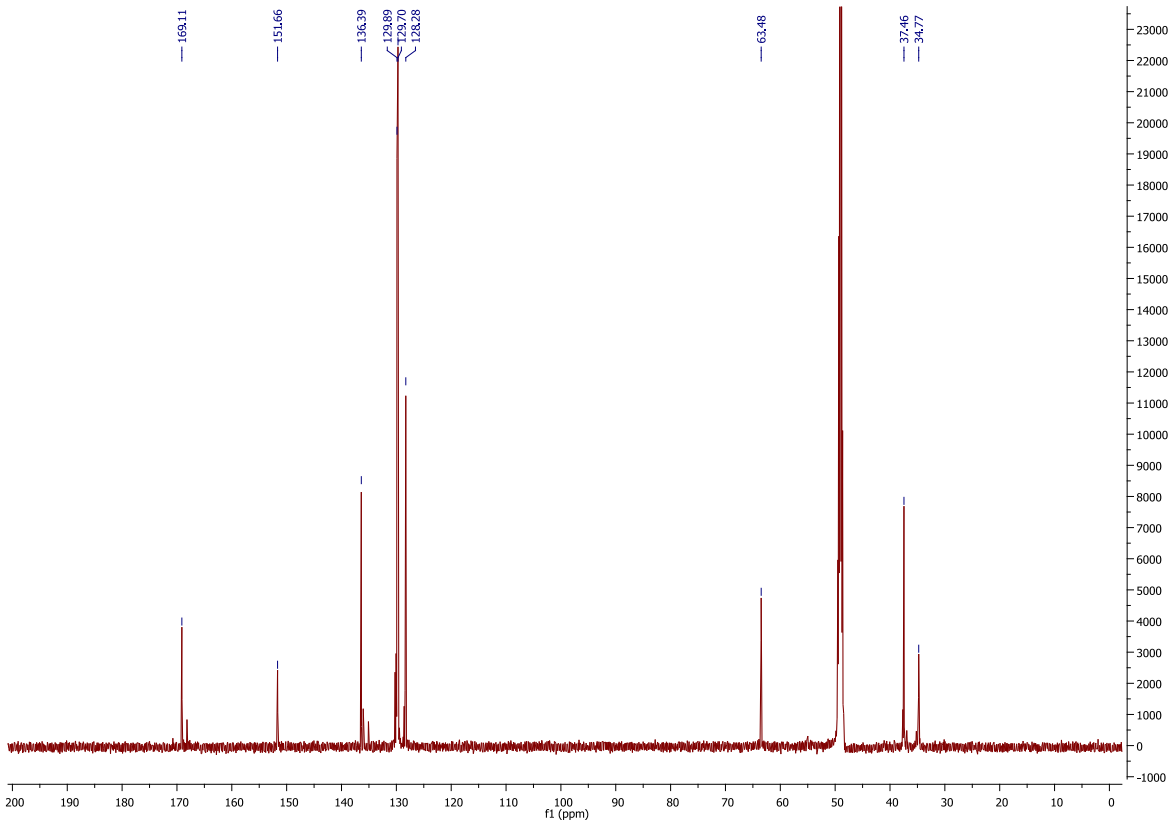


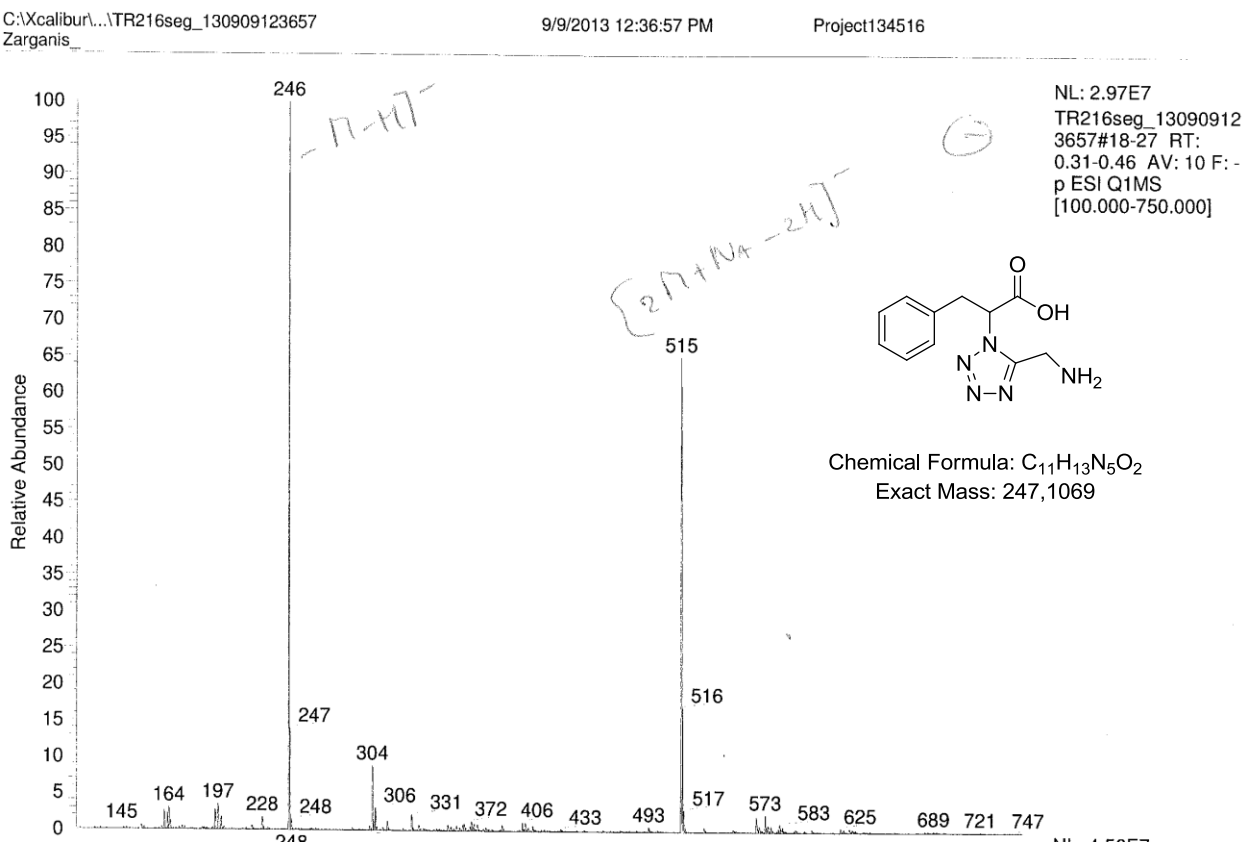

7.35
7.34
7.33
7.16
7.15
7.15
5.22
5.18
5.14
5.12
5.11
4.86
4.63
4.59
3.78
3.48
3.47
3.45
3.44
3.35
3.33
3.31
O
HO
N
N
N
N
NH2
2.92
2.07
0.95
0.91
0.90
1.68
1.00
6.84
f1 (ppm)

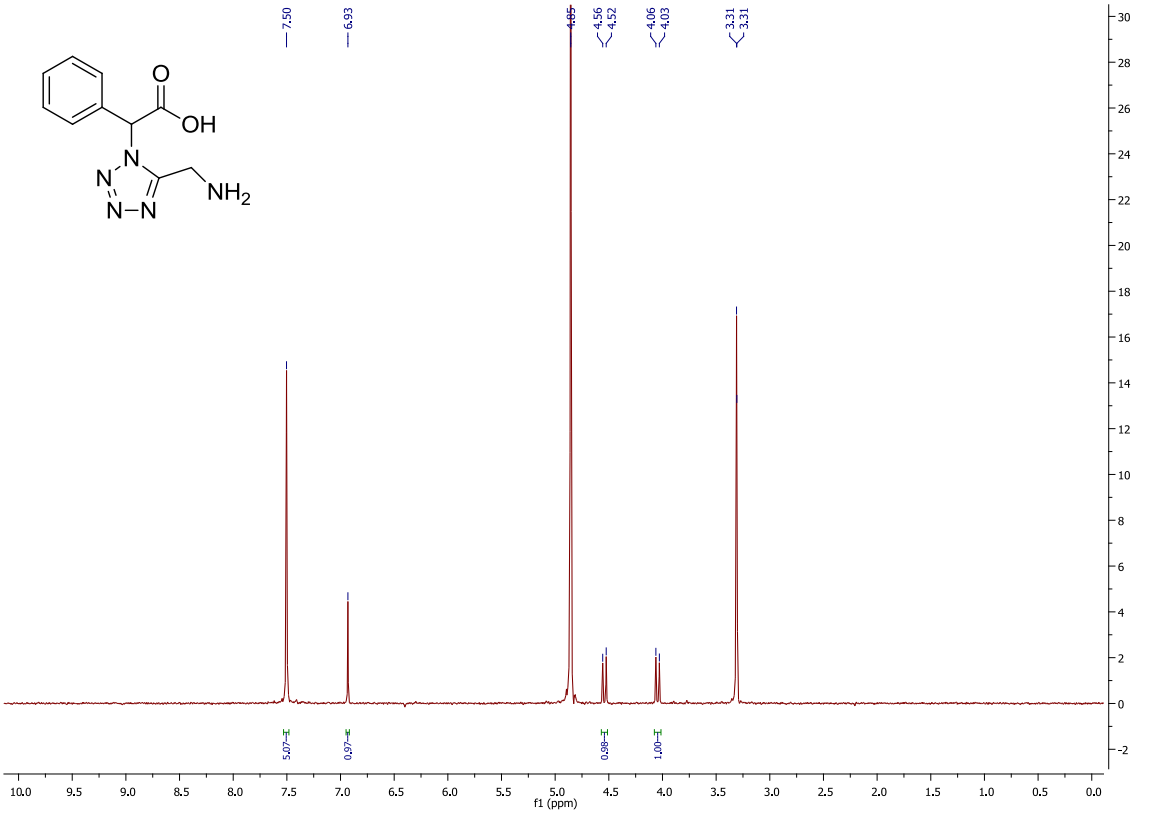

168.60
154.53
134.78
130.65
130.23
129.20
49.04
47.51
39.96
f1 (ppm)

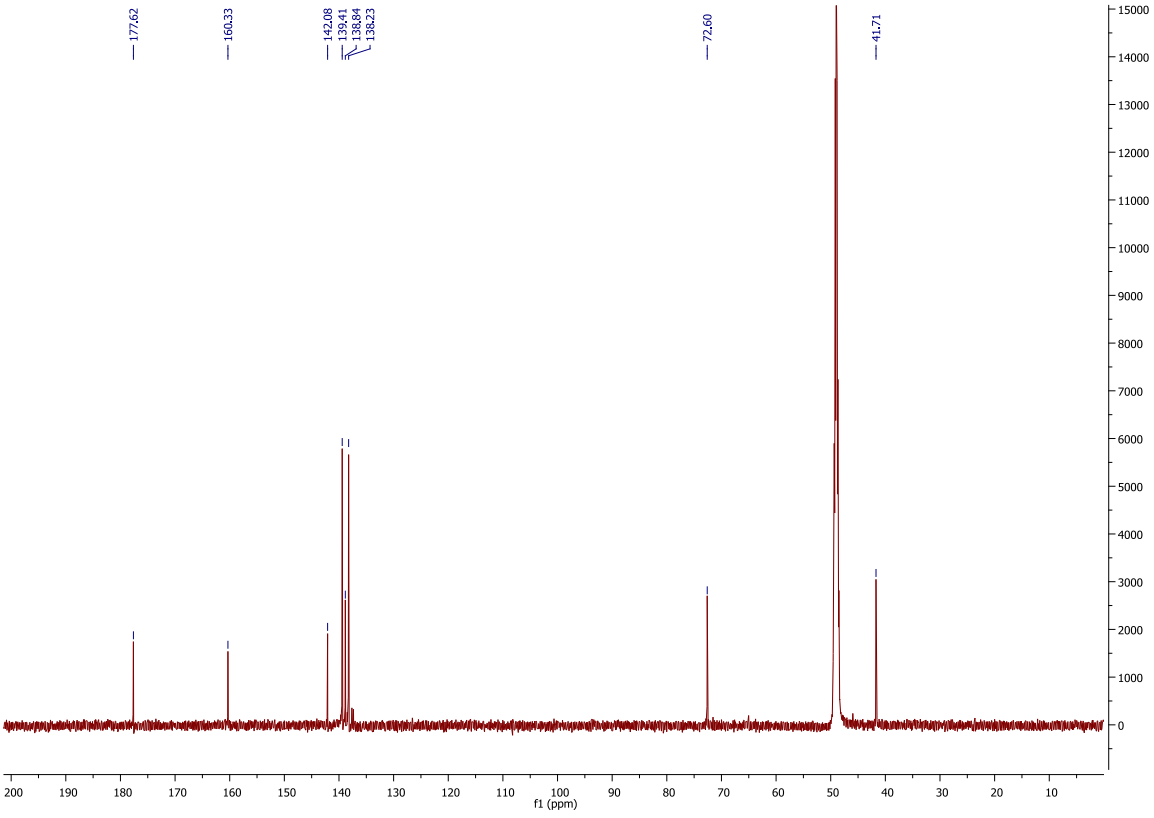

C:\Xcalibur\...\TR215seg_130909123837
Zarganis_
9/9/2013 12:38:37 PM
Project134516
NL: 1.57E7
TR215seg_13090912
3837#18-27 RT:
0.31-0.46 AV: 10 F: -
p ESI Q1MS
[100.000-750.000]
Relative Abundance
246
515
304
247
516
306
331
366
161
197
101
286
362
407
424
493
531
533
573
575
635
689
749
HO
O
N
N
N
NH2
Chemical Formula: C11H13N5O2
Exact Mass: 247,1069

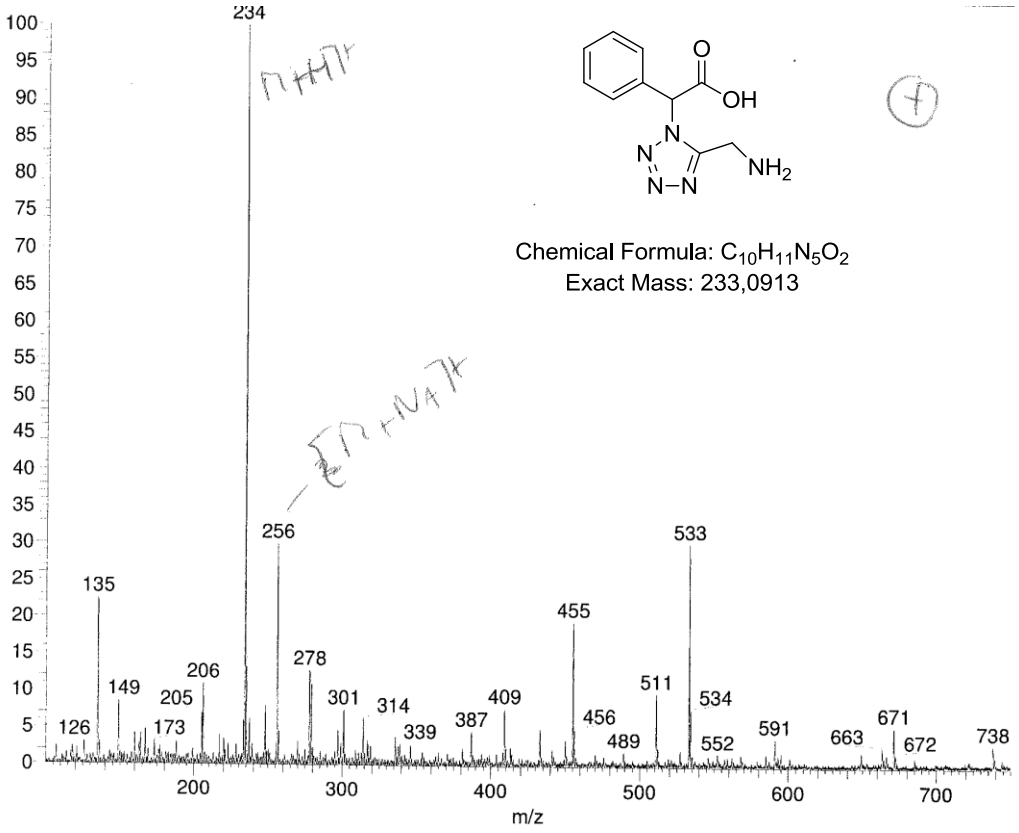

7.26
7.25
7.23
7.23
7.21
7.14
7.13
5.84
5.83
5.82
5.81
4.34
4.31
3.93
3.79
3.76
3.53
3.31
3.31
3.31
O
OH
N
N
N–N
NH2
2.62
1.68
0.79
0.83
0.80
1.00
0.86
f1 (ppm)

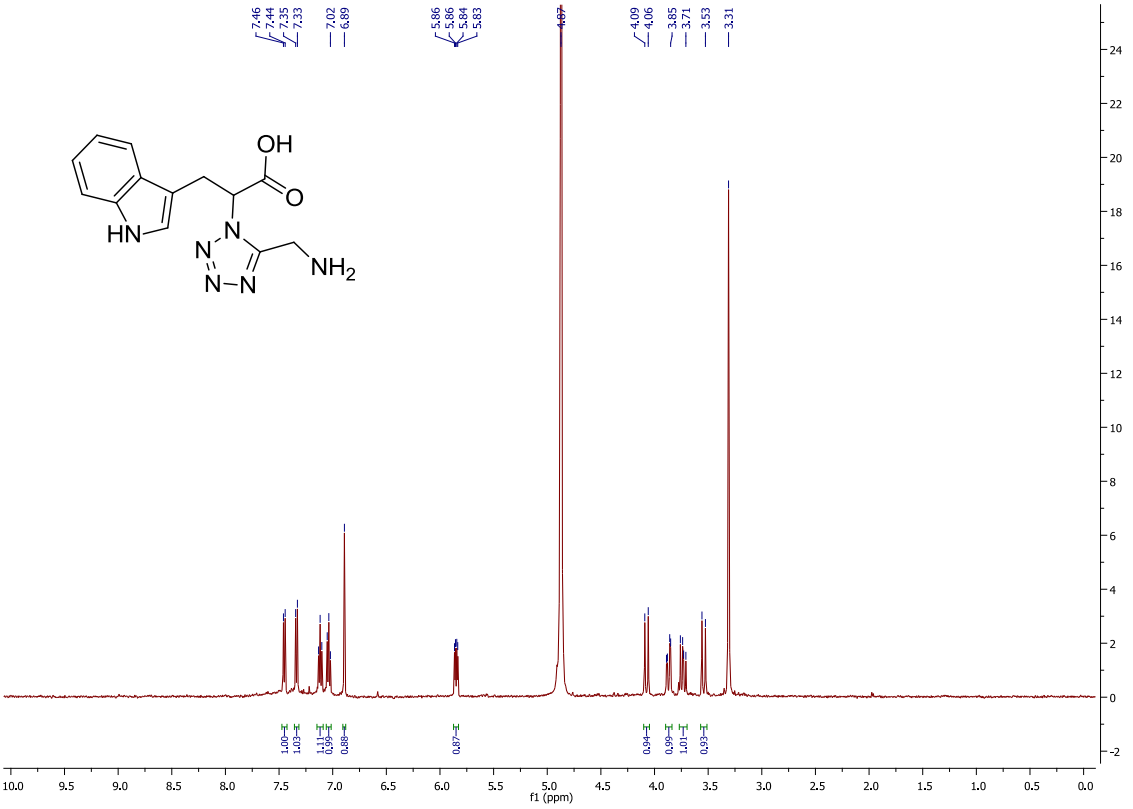

169.11
151.66
136.39
129.89
129.70
128.28
63.48
37.46
34.77
f1 (ppm)

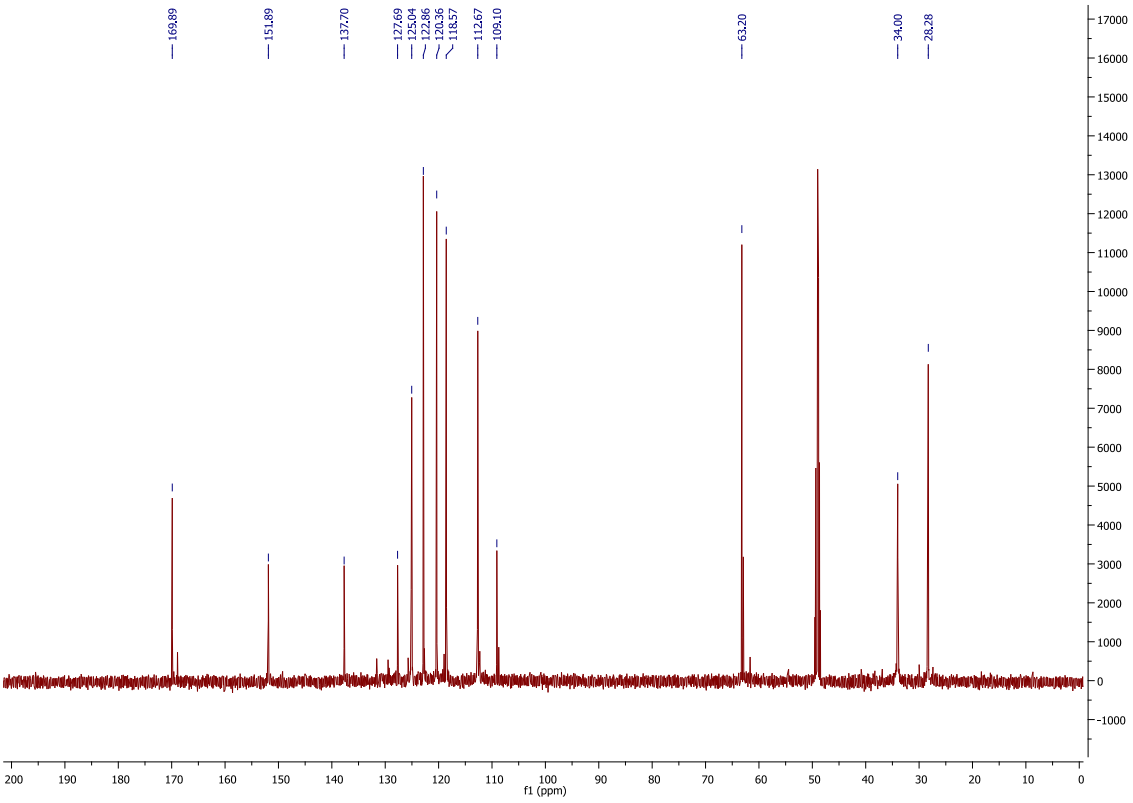

C:\Xcalibur\...\TR216seg_130909123657
Zarganis_
9/9/2013 12:36:57 PM
Project134516
NL: 2.97E7
TR216seg_13090912
3657#18-27 RT:
0.31-0.46 AV: 10 F: -
p ESI Q1MS
[100.000-750.000]
Relative Abundance
246
515
247
304
516
145
164
197
228
248
306
331
372
406
433
493
517
573
583
625
689
721
747
Chemical Formula: C11H13N5O2
Exact Mass: 247,1069

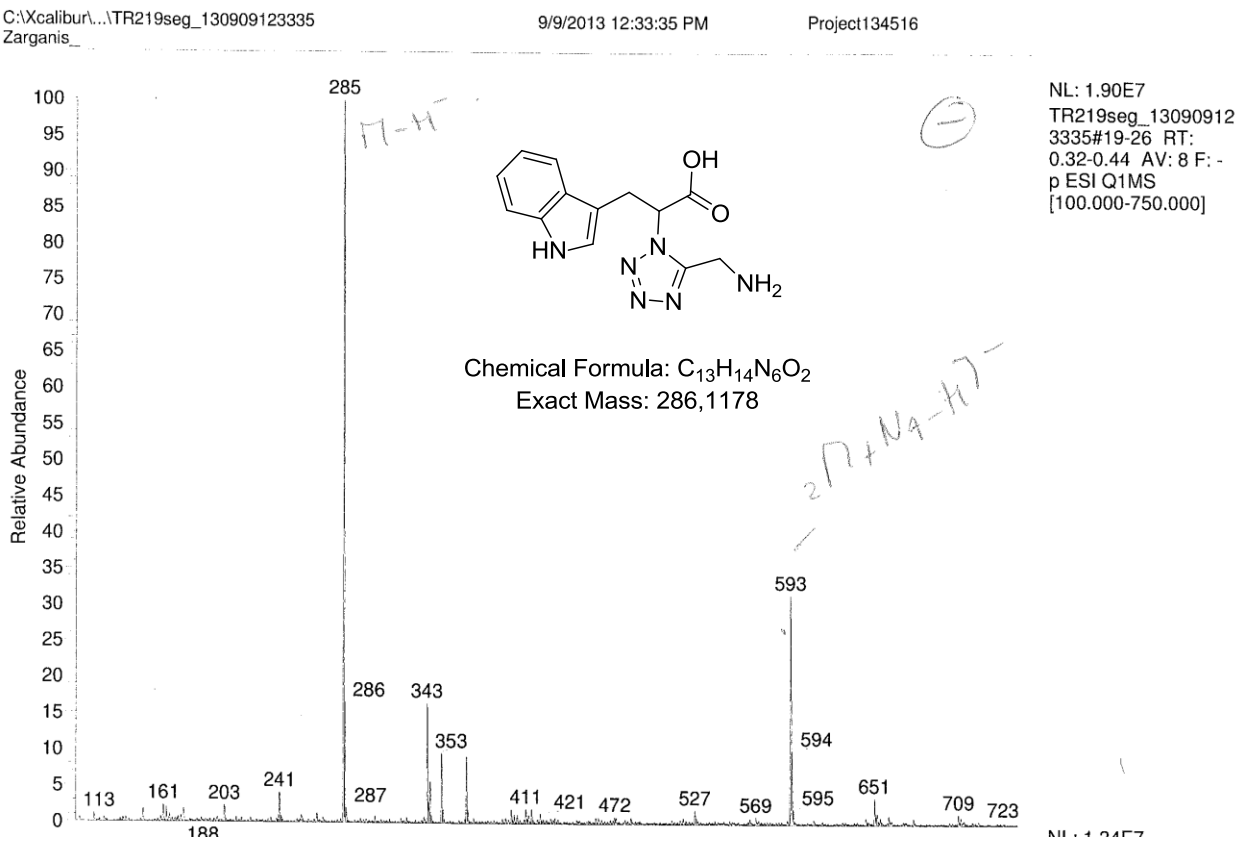

7.50
6.93
4.85
4.56
4.52
4.06
4.03
3.31
3.31
5.07
0.97
0.98
1.00
f1 (ppm)

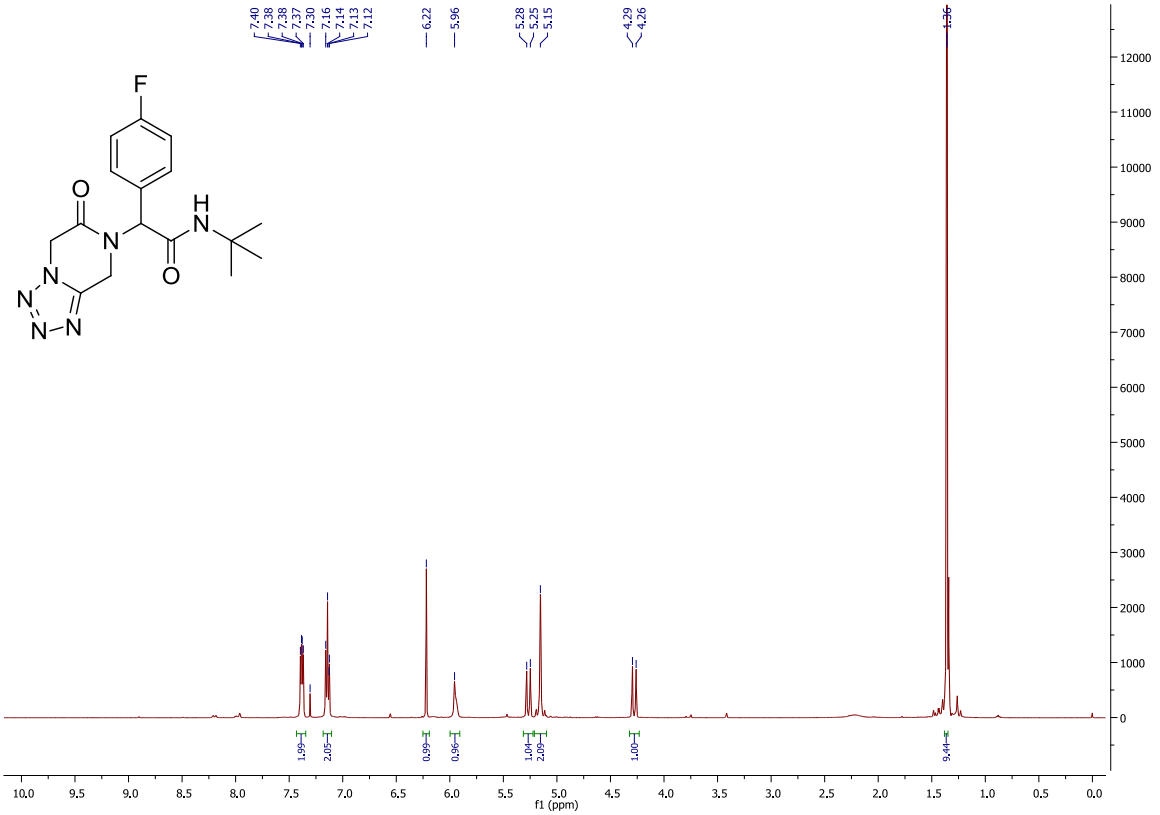

177.62
160.33
142.08
139.41
138.84
138.23
72.60
41.71
f1 (ppm)

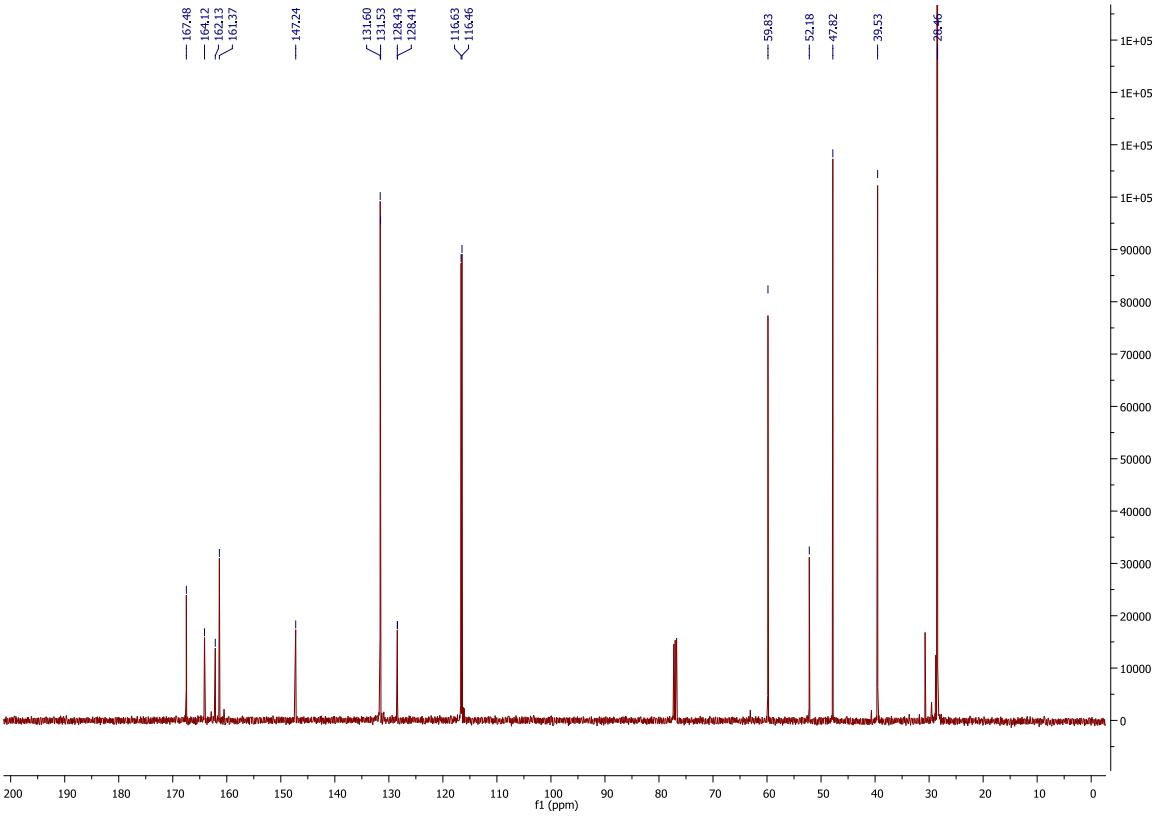

NL: 2.52E7
TR218seg_13090912
3517#12-17 RT:
0.20-0.28 AV: 6 F: +
p ESI Q1MS
[100.000-750.000]
Chemical Formula: $C_{10}H_{11}N_5O_2$
Exact Mass: 233,0913
234
256
533
455
135
278
206
149
205
301
314
409
511
534
126
173
339
387
456
489
552
591
663
671
672
738
m/z


7.46
7.44
7.35
7.33
7.02
6.89
5.86
5.86
5.84
5.83
4.87
4.09
4.06
3.85
3.71
3.53
3.31
OH
O
HN
N
N
N–N
NH2
1.00
1.03
1.11
0.99
0.88
0.87
0.94
0.99
1.01
0.93
f1 (ppm)

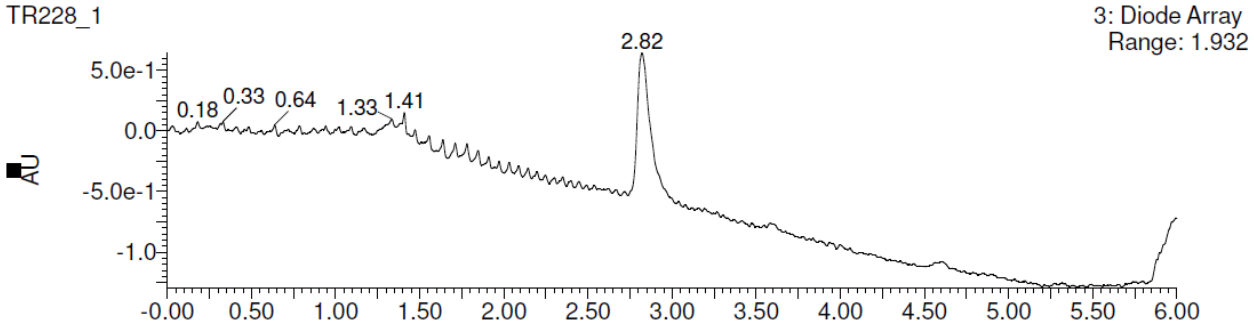

169.89
151.89
137.70
127.69
125.04
122.86
120.36
118.57
112.67
109.10
63.20
34.00
28.28
f1 (ppm)

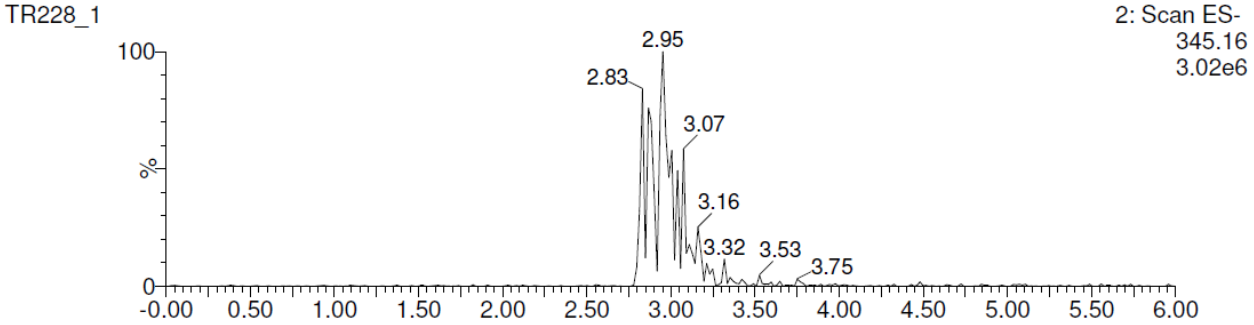

C:\Xcalibur\...\TR219seg_130909123335
Zarganis_
9/9/2013 12:33:35 PM
Project134516
NL: 1.90E7
TR219seg_13090912
3335#19-26 RT:
0.32-0.44 AV: 8 F: -
p ESI Q1MS
[100.000-750.000]
Relative Abundance
285
286
343
353
593
594
113
161
203
241
287
411
421
472
527
569
595
651
709
723
OH
O
HN
N
N
N
N
NH2
Chemical Formula: C13H14N6O2
Exact Mass: 286,1178

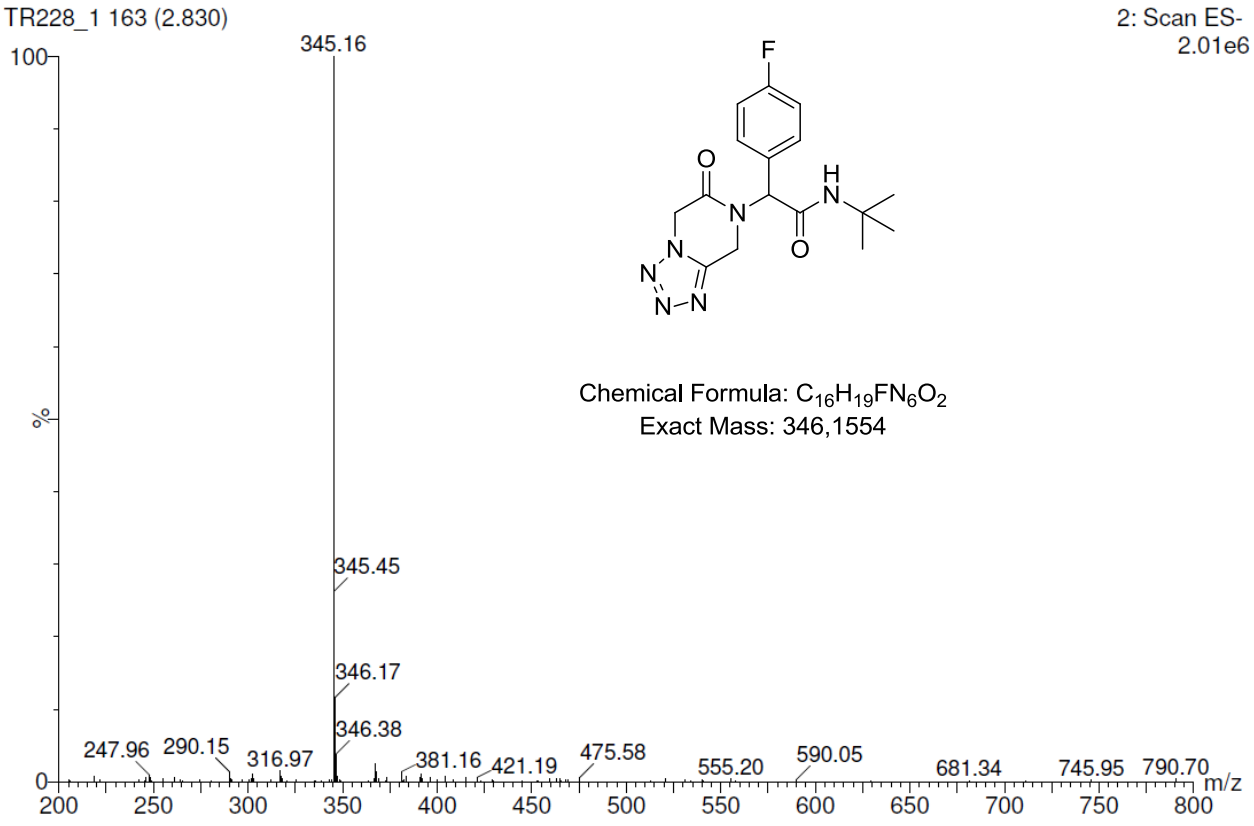

7.40
7.38
7.38
7.37
7.30
7.16
7.14
7.13
7.12
6.22
5.96
5.28
5.25
5.15
4.29
4.26
1.36
F
O
H
N
N
O
N
N
N
1.99
2.05
0.99
0.96
1.04
2.09
1.00
9.44
f1 (ppm)


167.48
164.12
162.13
161.37
147.24
131.60
131.53
128.43
128.41
116.63
116.46
59.83
52.18
47.82
39.53
28.46
f1 (ppm)

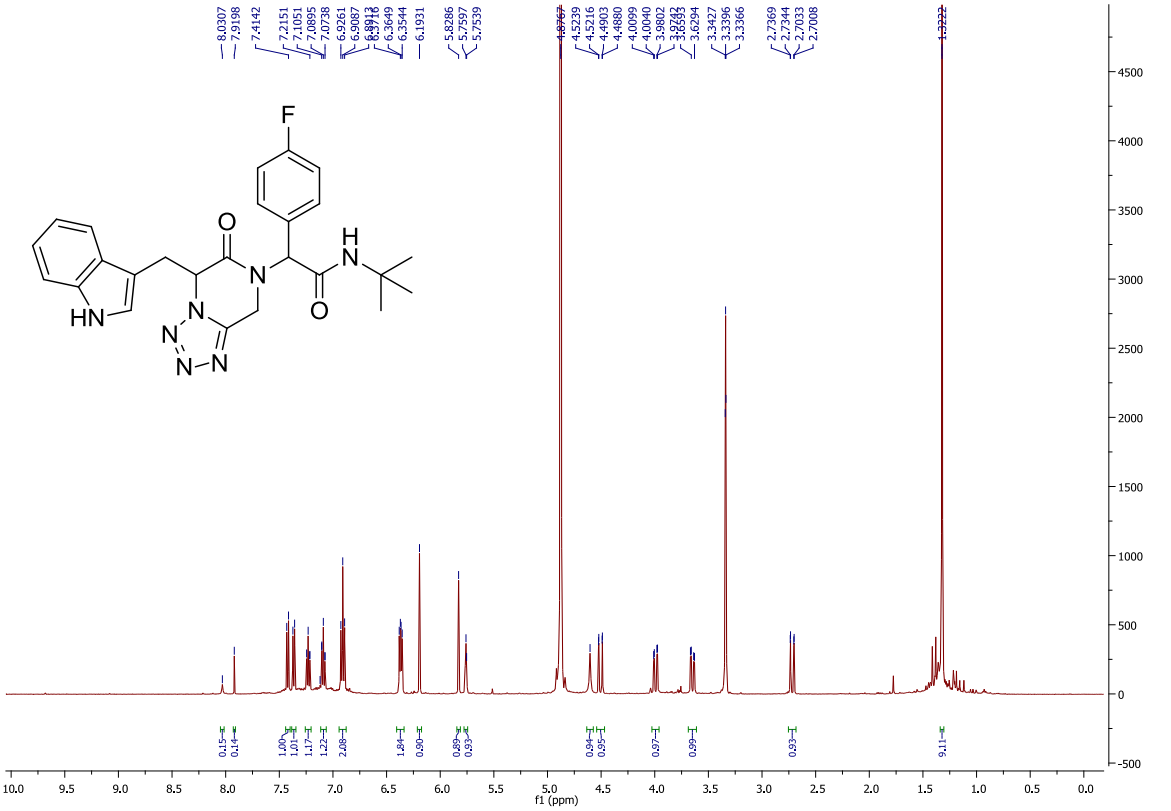
TR228_1_Silica_4.6X250_MeOH_5-30%_6

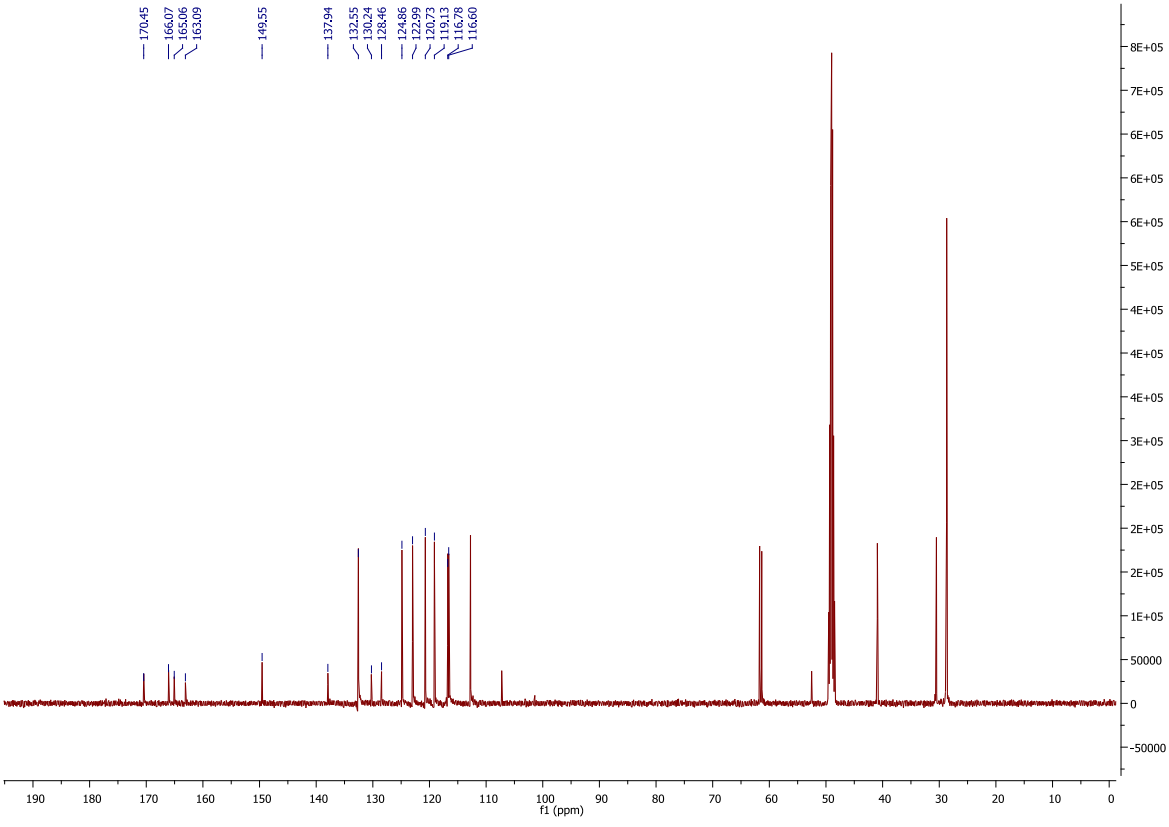




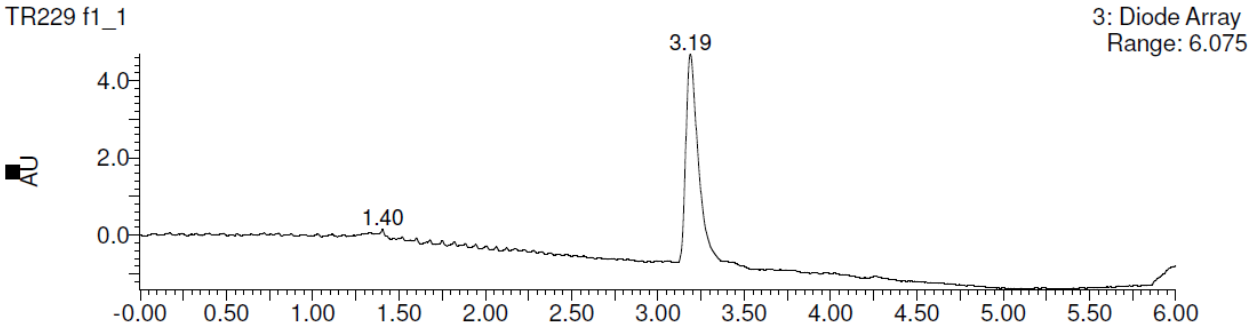


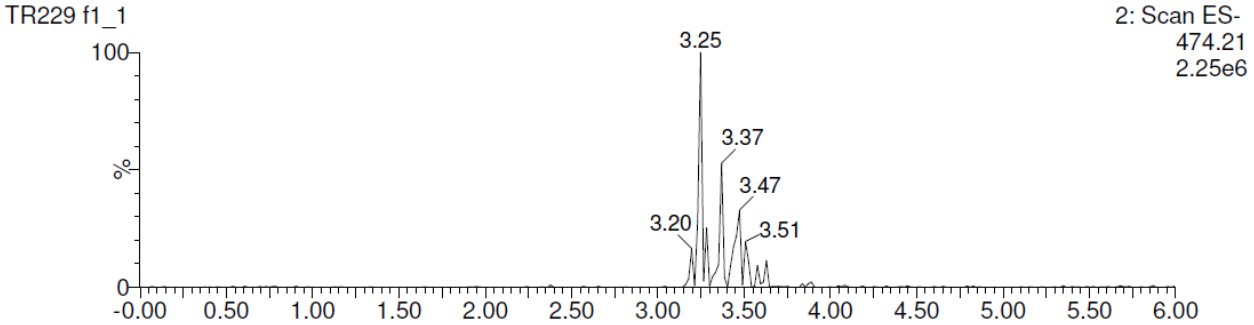
Chemical Formula: $C_{16}H_{19}FN_6O_2$
Exact Mass: 346,1554

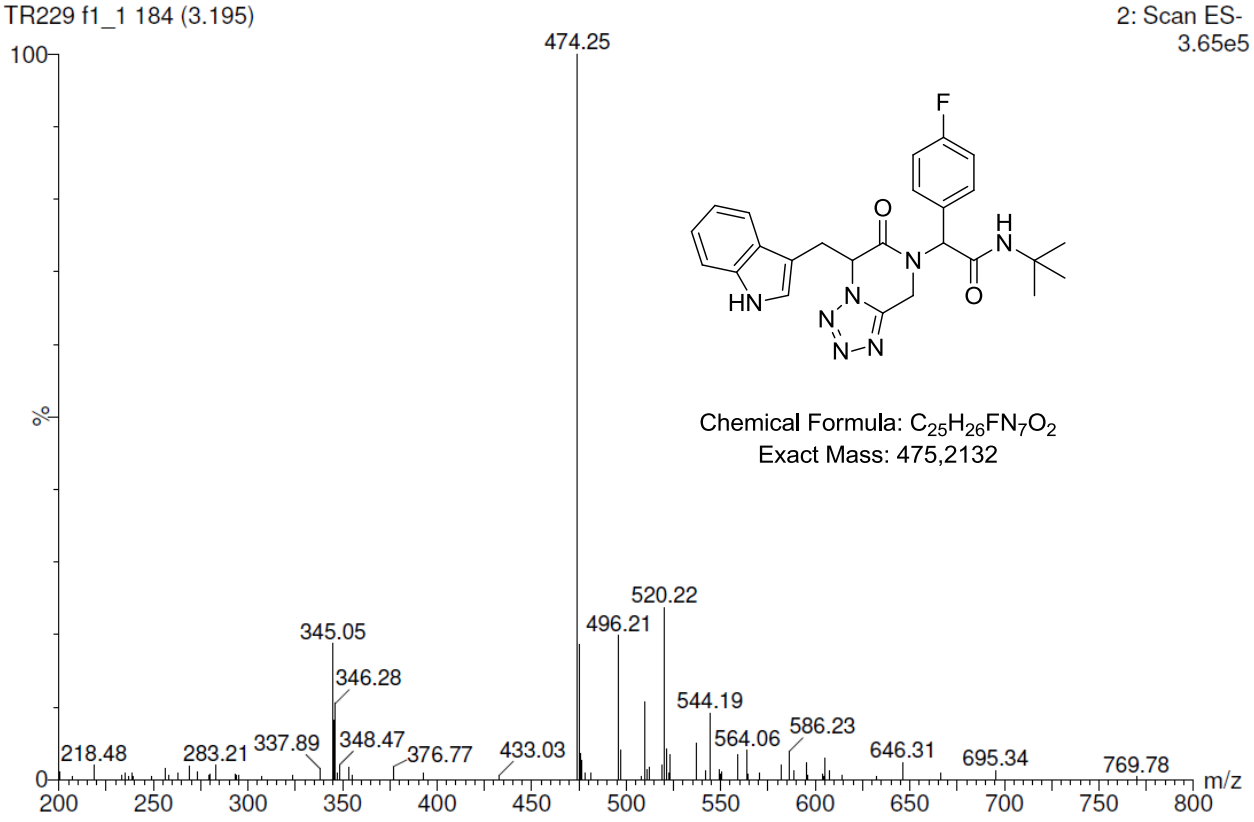

8.0307
7.9198
7.4142
7.2151
7.1051
7.0895
7.0738
6.9261
6.9087
6.8913
6.8716
6.3649
6.3544
6.1931
5.8286
5.7597
5.7539
4.5239
4.5216
4.4903
4.4880
4.0099
4.0040
3.9802
3.6294
3.3427
3.3396
3.3366
2.7369
2.7344
2.7033
2.7008
1.3222
F
O
H
N
HN
N
N
N
N
O
f1 (ppm)


170.45
166.07
165.06
163.09
149.55
137.94
132.55
130.24
128.46
124.86
122.99
120.73
119.13
116.78
116.60
f1 (ppm)

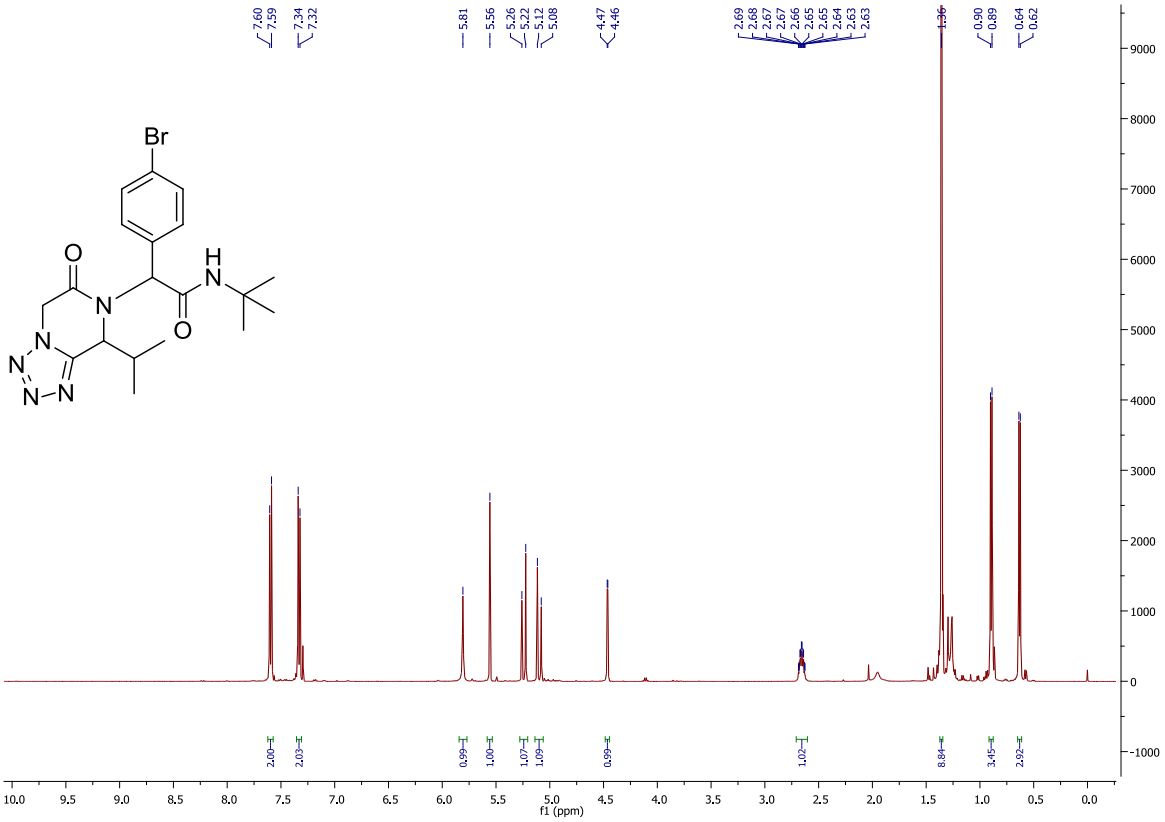
TR229 f1_1_Silica_4.6X250_MeOH_5-30%_6

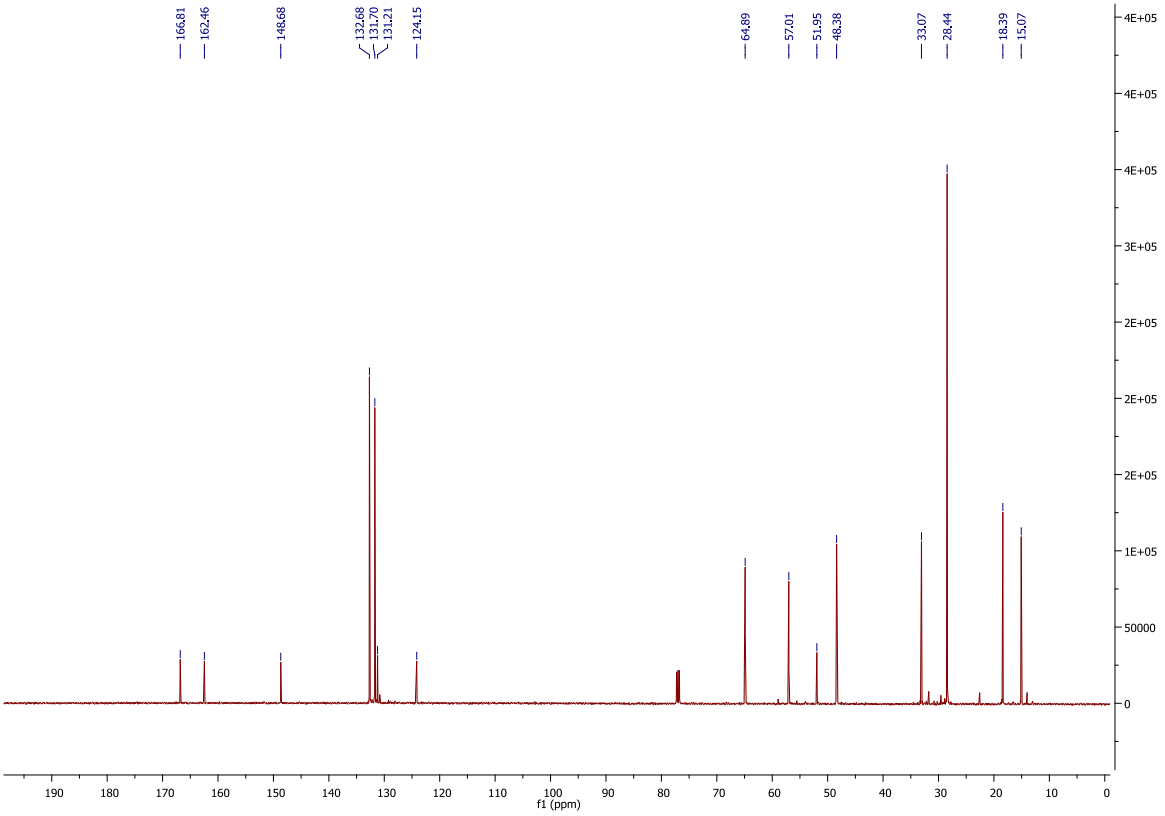




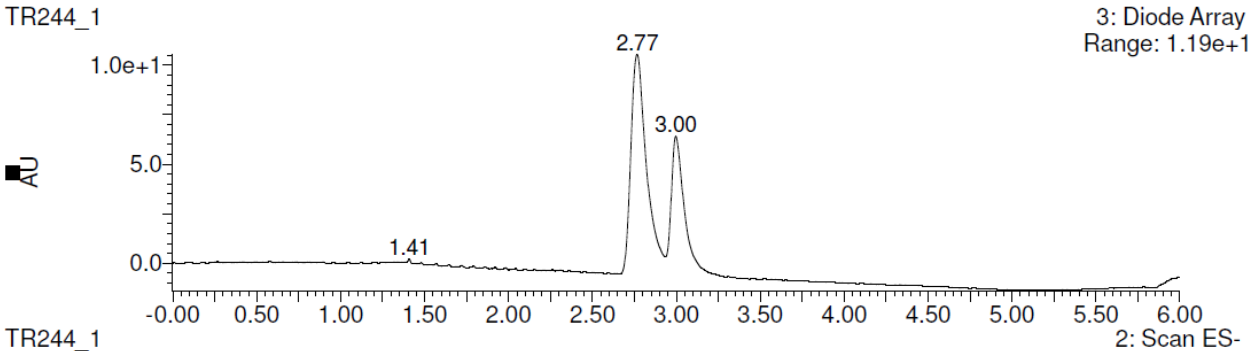


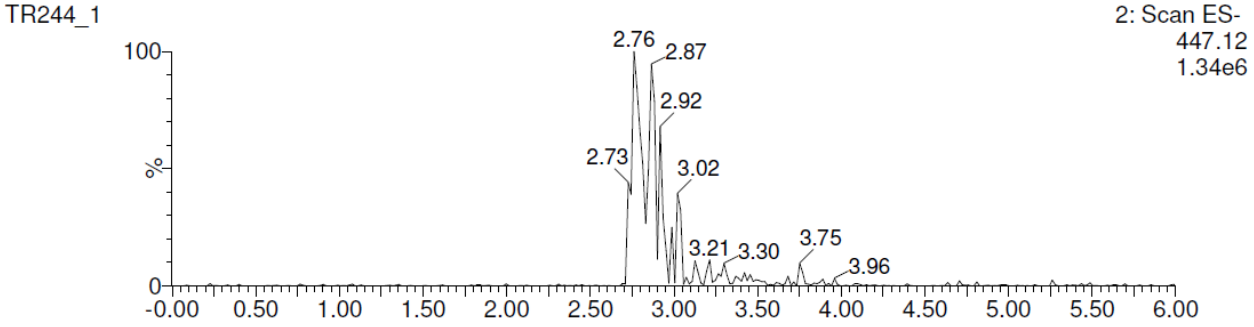
Chemical Formula: $C_{25}H_{26}FN_7O_2$
Exact Mass: 475,2132

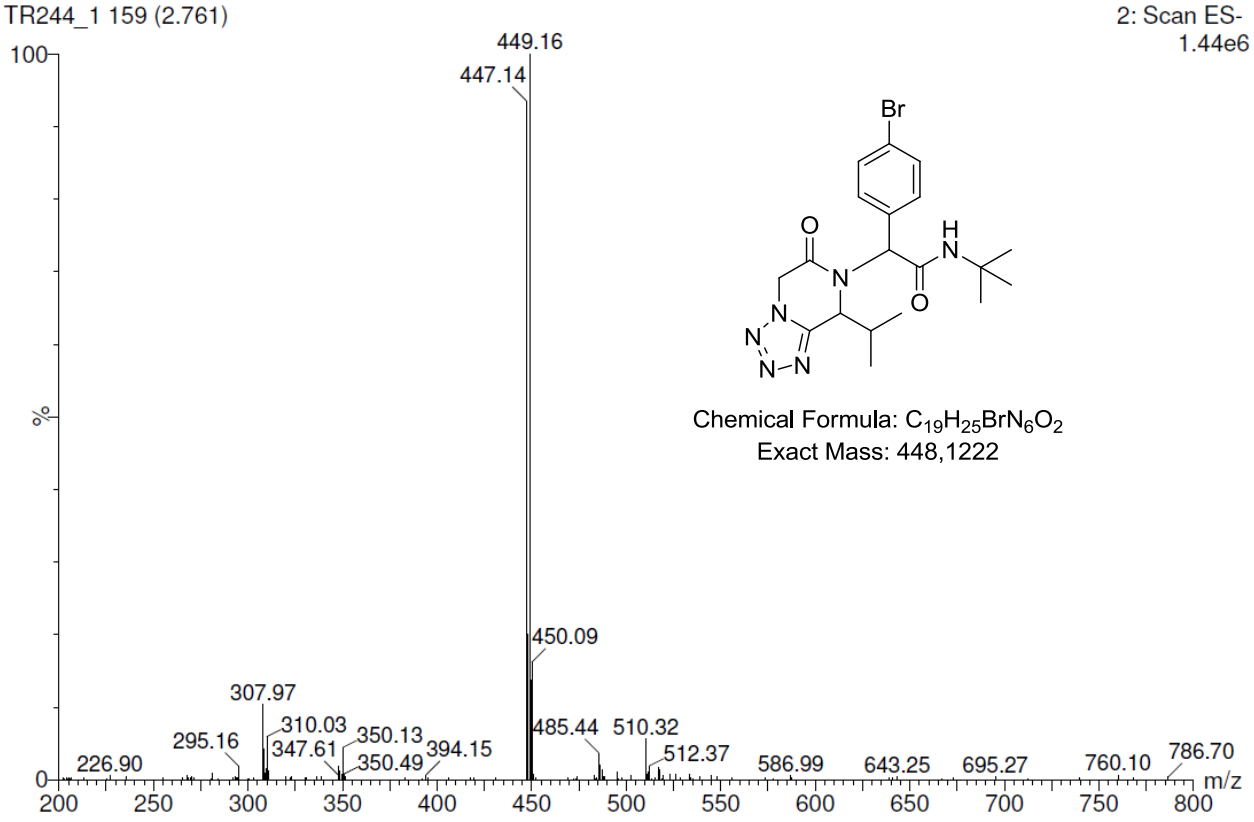

7.60
7.59
7.34
7.32
5.81
5.56
5.26
5.22
5.12
5.08
4.47
4.46
2.69
2.68
2.67
2.67
2.66
2.65
2.65
2.64
2.63
2.63
1.36
0.90
0.89
0.64
0.62
Br
O
H
N
O
N
N
N
N
2.00
2.03
0.99
1.00
1.07
1.09
0.99
1.02
8.84
3.45
2.92
f1 (ppm)


166.81
162.46
148.68
132.68
131.70
131.21
124.15
64.89
57.01
51.95
48.38
33.07
28.44
18.39
15.07
f1 (ppm)

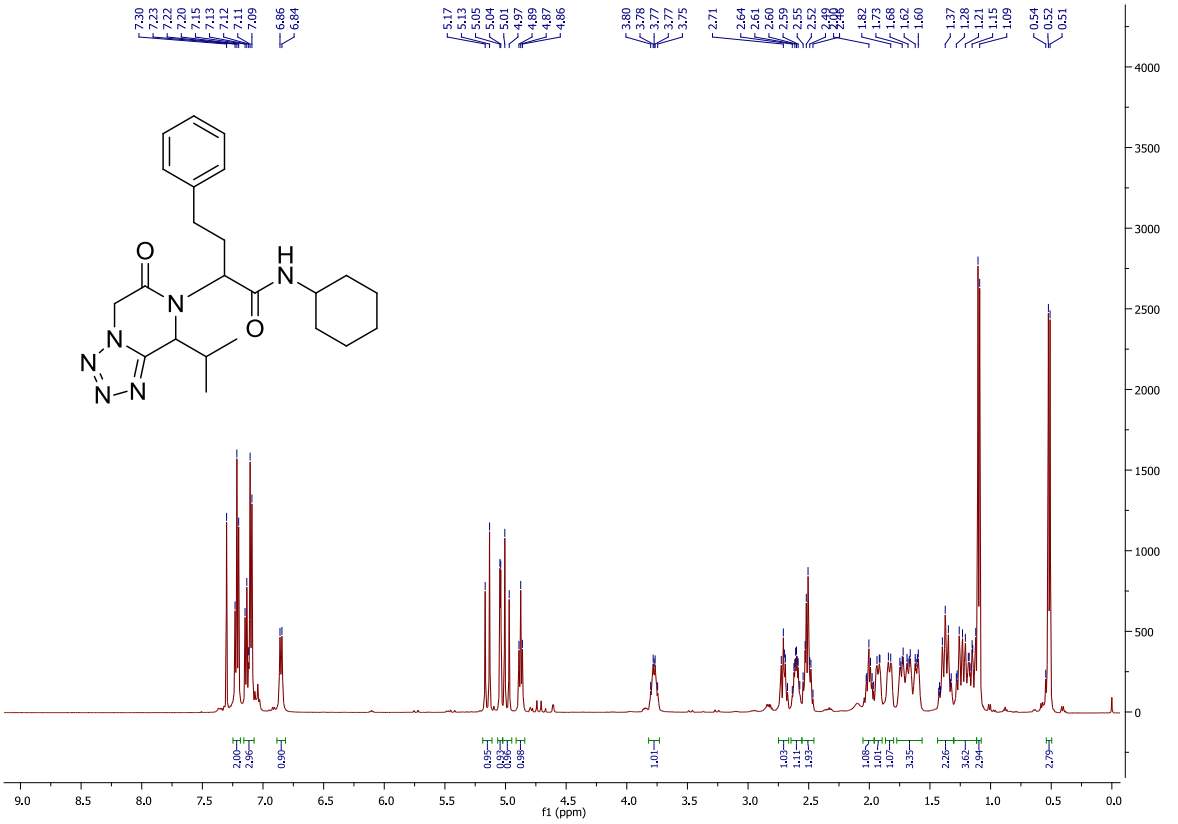
TR244_1_Silica_4.6X250_MeOH_5-30%_6

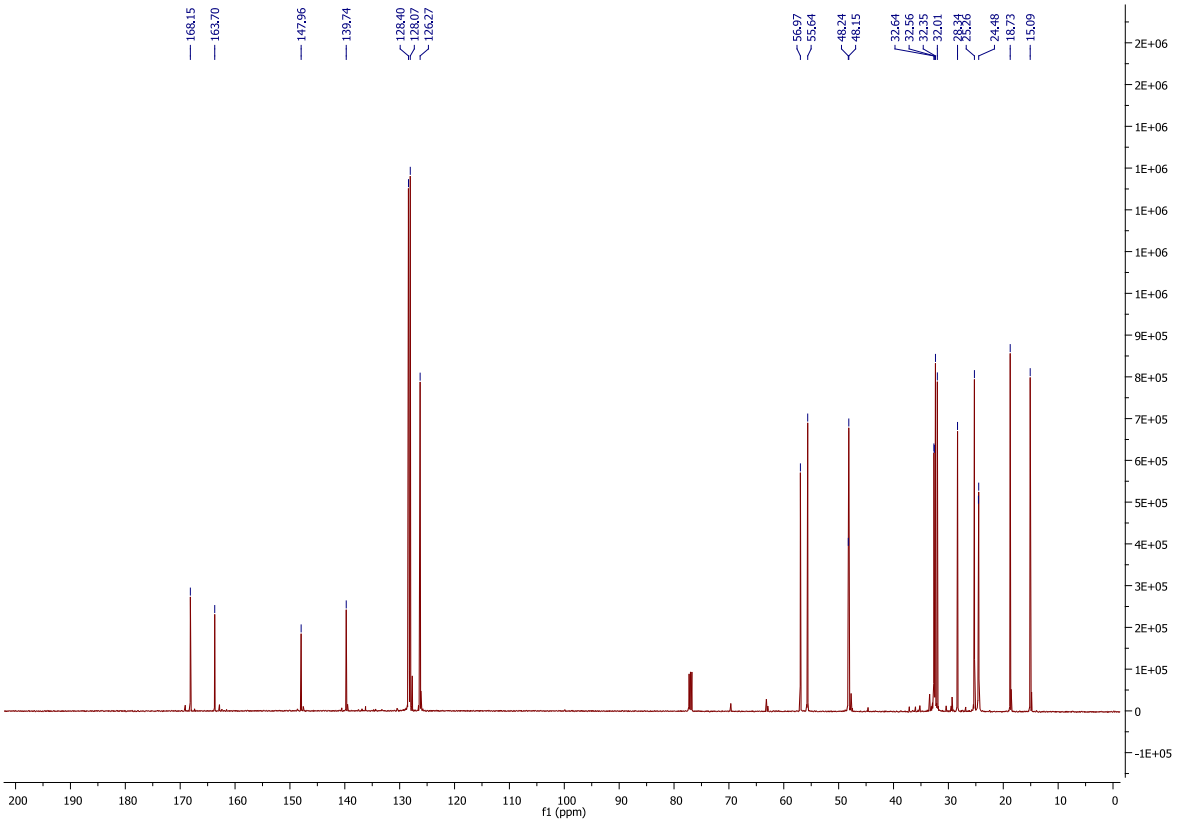




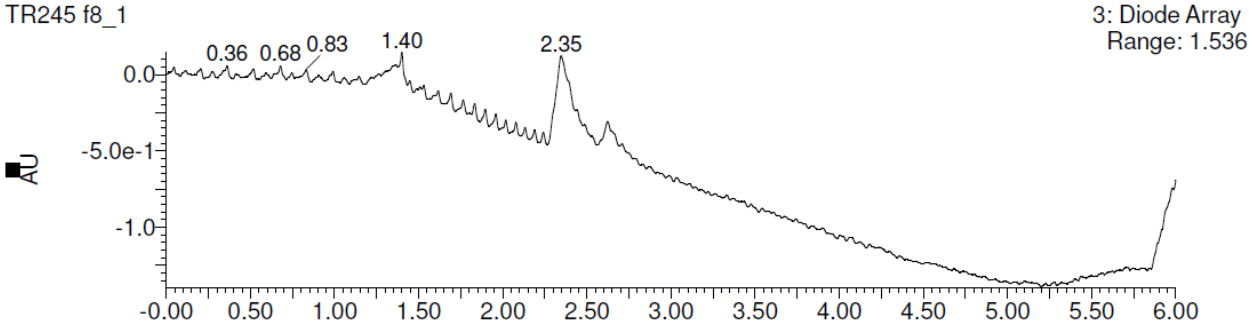


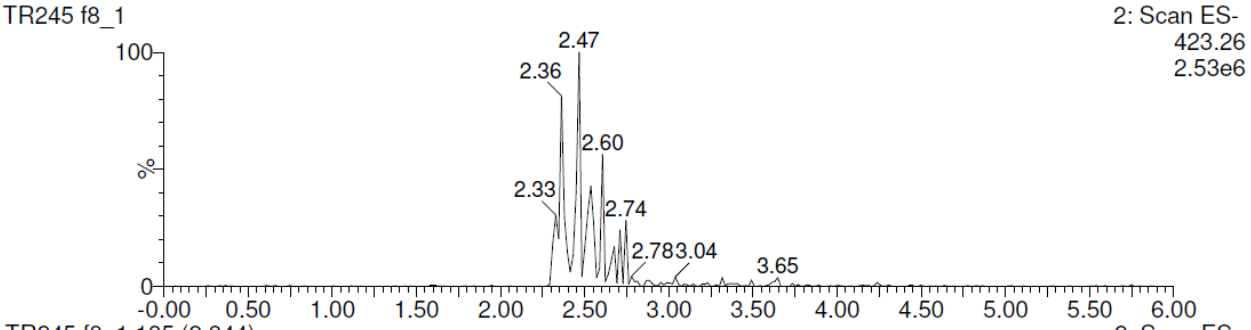
Chemical Formula: $C_{19}H_{25}BrN_6O_2$
Exact Mass: 448,1222

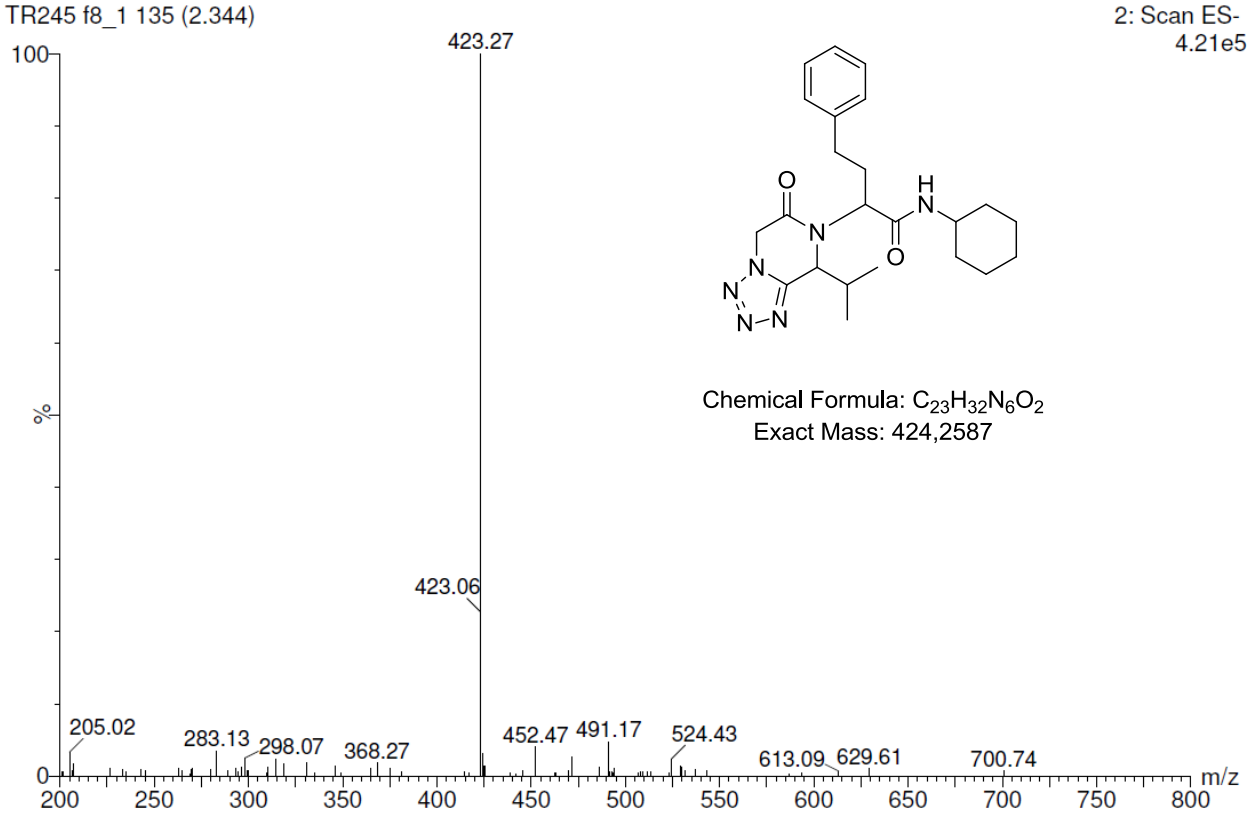

7.30
7.23
7.22
7.20
7.15
7.13
7.12
7.11
7.09
6.86
6.84
5.17
5.13
5.05
5.04
5.01
4.97
4.89
4.87
4.86
3.80
3.78
3.77
3.77
3.75
2.71
2.64
2.61
2.60
2.59
2.55
2.52
1.82
1.73
1.68
1.62
1.60
1.37
1.28
1.21
1.15
1.09
0.54
0.52
0.51
O
N
H
N
O
N
N
N
N
2.00
2.96
0.90
0.95
1.01
1.03
1.11
1.97
1.08
1.07
3.35
2.26
3.62
2.94
2.79
f1 (ppm)


168.15
163.70
147.96
139.74
128.40
128.07
126.27
56.97
55.64
48.24
48.15
32.64
32.56
32.35
32.01
28.34
25.26
24.48
18.73
15.09
f1 (ppm)

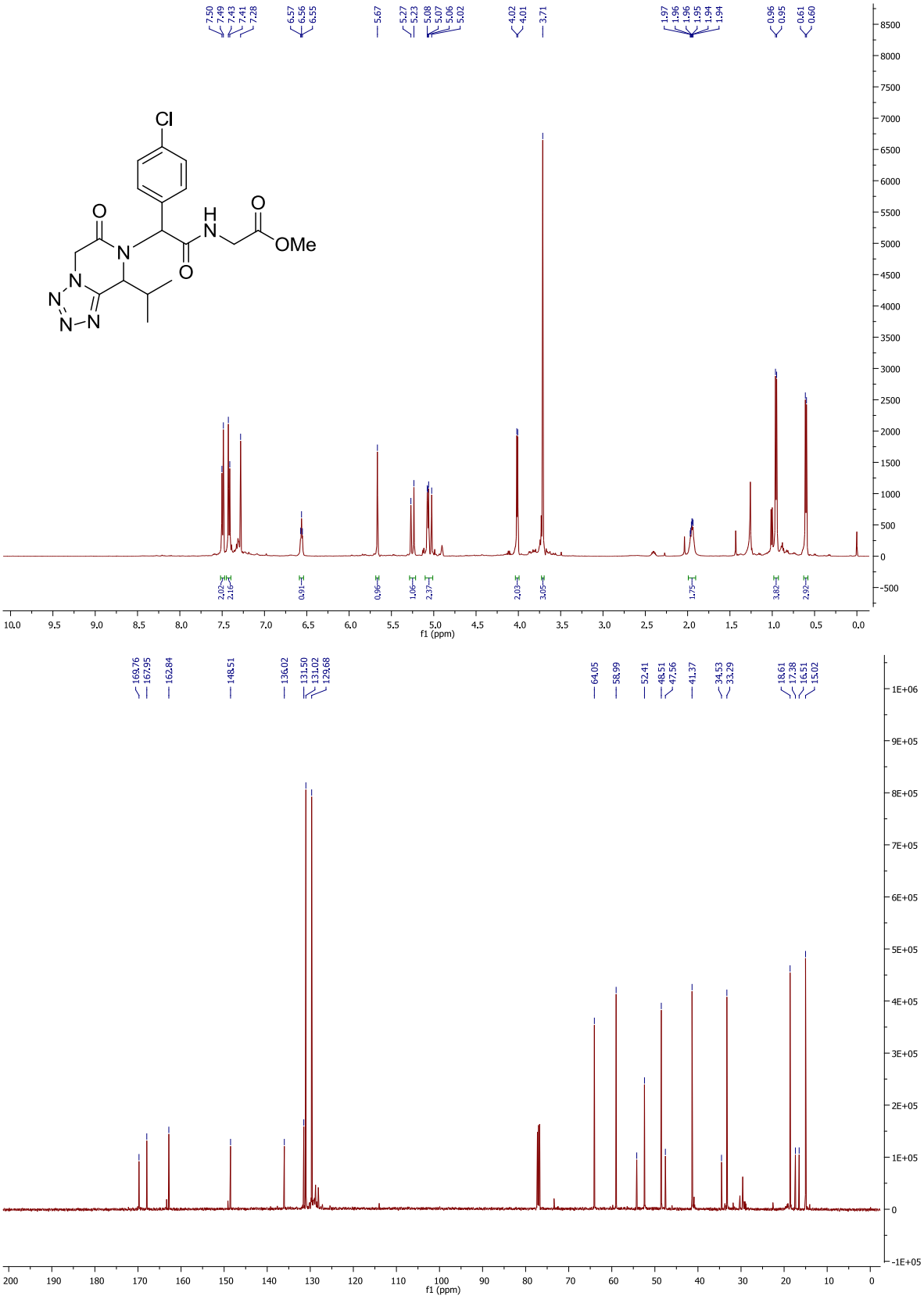
TR245 f8_1_Silica_4.6X250_MeOH_5-30%_6



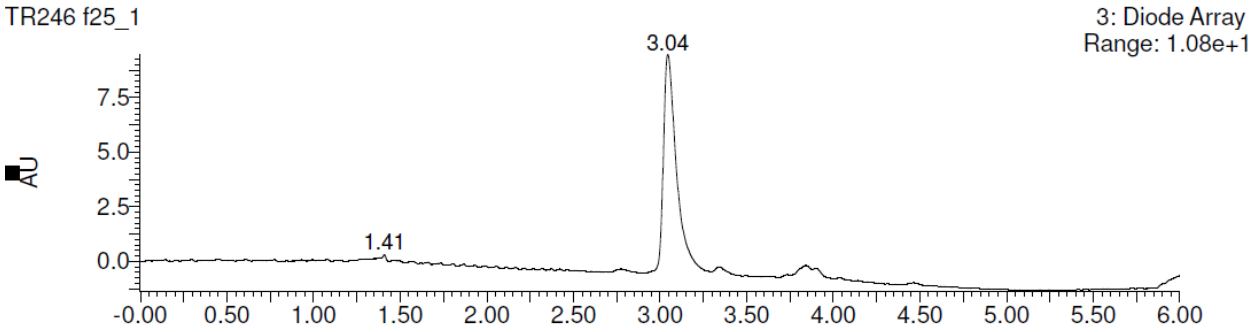


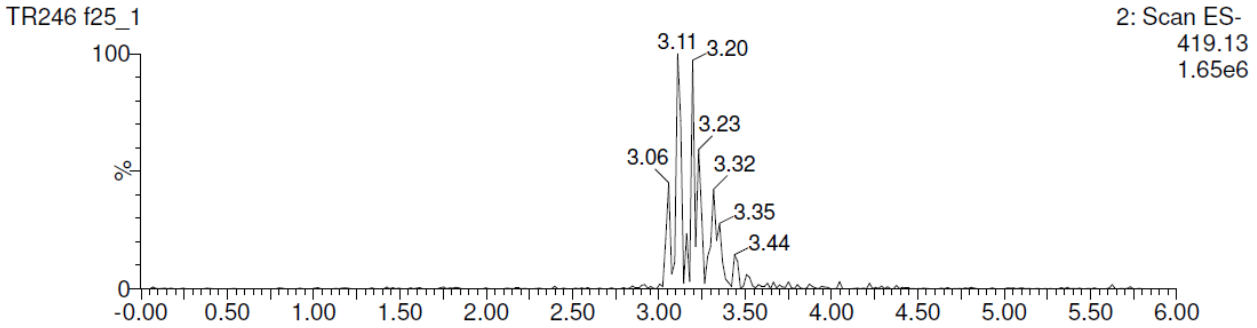


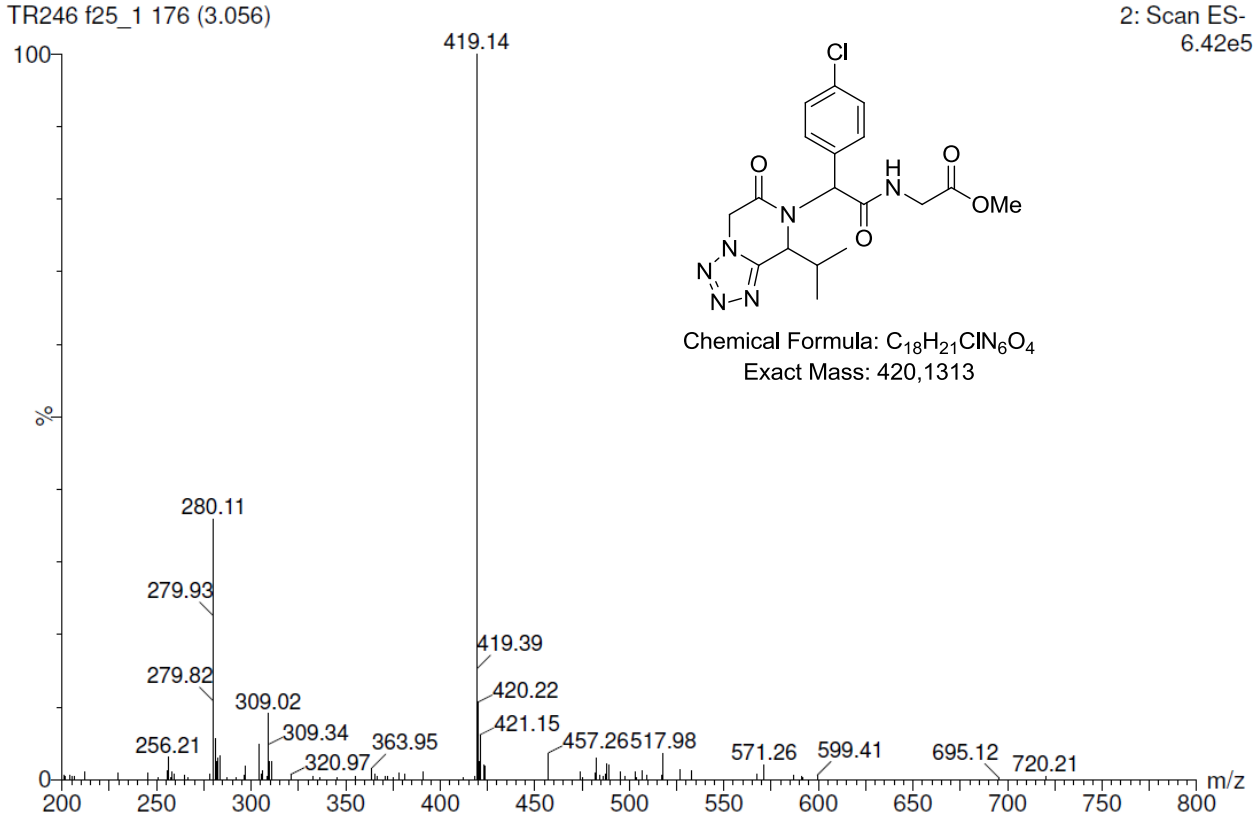
Chemical Formula: $C_{23}H_{32}N_6O_2$
Exact Mass: 424,2587


Cl
O
N
N
N
N
O
H
N
O
OMe
7.50
7.49
7.43
7.41
7.28
6.57
6.56
6.55
5.67
5.27
5.23
5.08
5.07
5.06
5.02
4.02
4.01
3.71
1.97
1.96
1.96
1.95
1.94
1.94
0.96
0.95
0.61
0.60
f1 (ppm)
169.76
167.95
162.84
148.51
136.02
131.50
131.02
129.68
64.05
58.99
52.41
48.51
47.56
41.37
34.53
33.29
18.61
17.38
16.51
15.02
f1 (ppm)

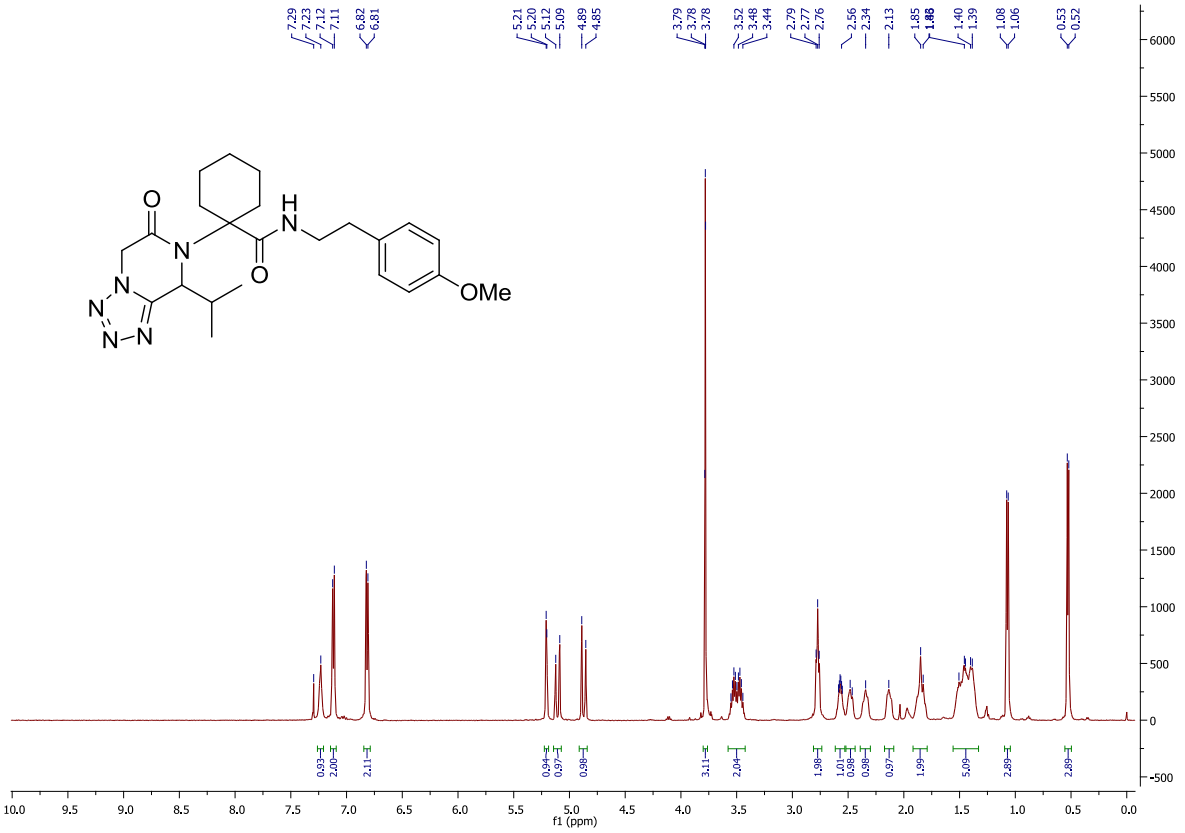
TR246 f25_1_Silica_4.6X250_MeOH_5-30%_6

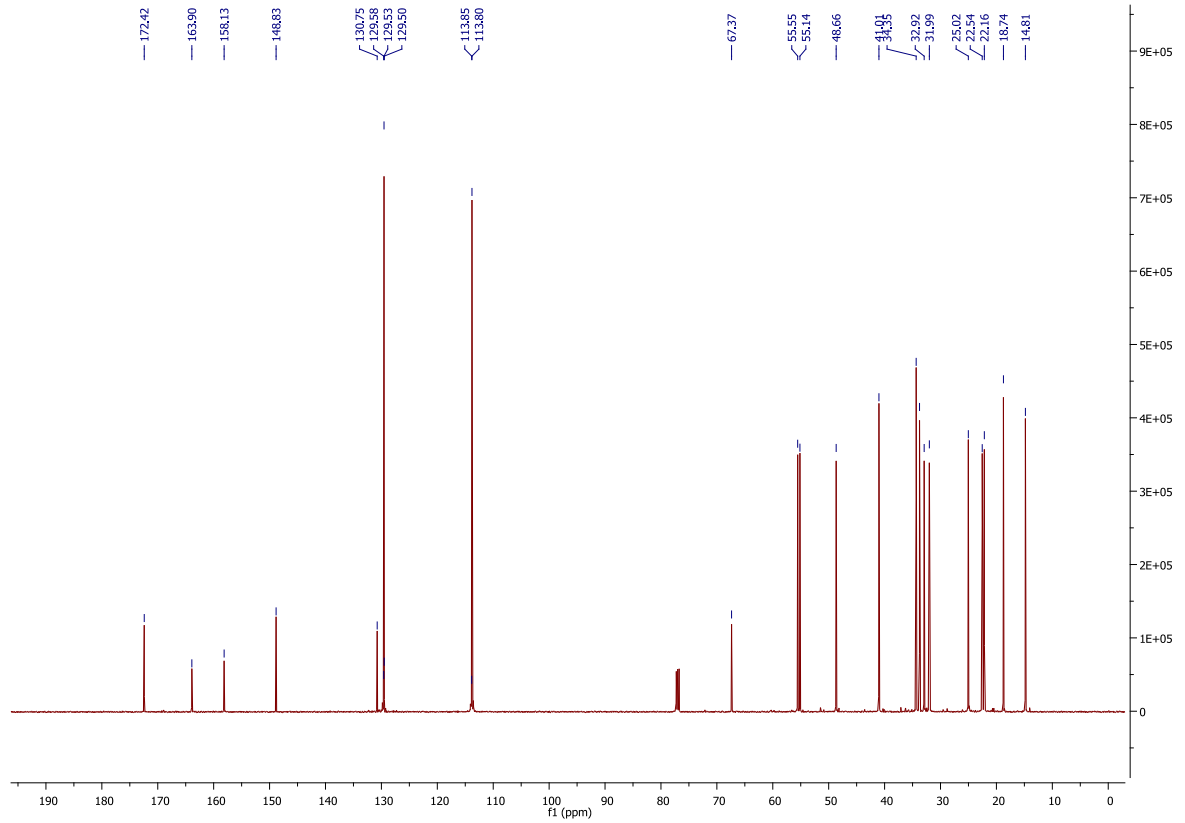




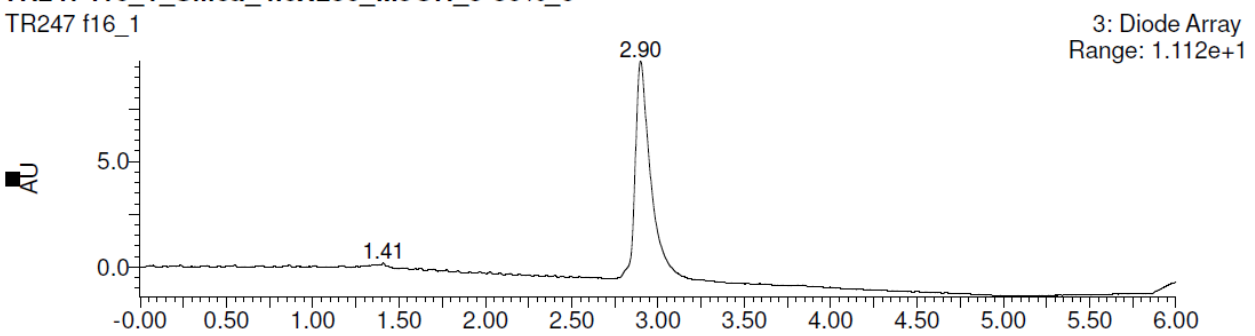


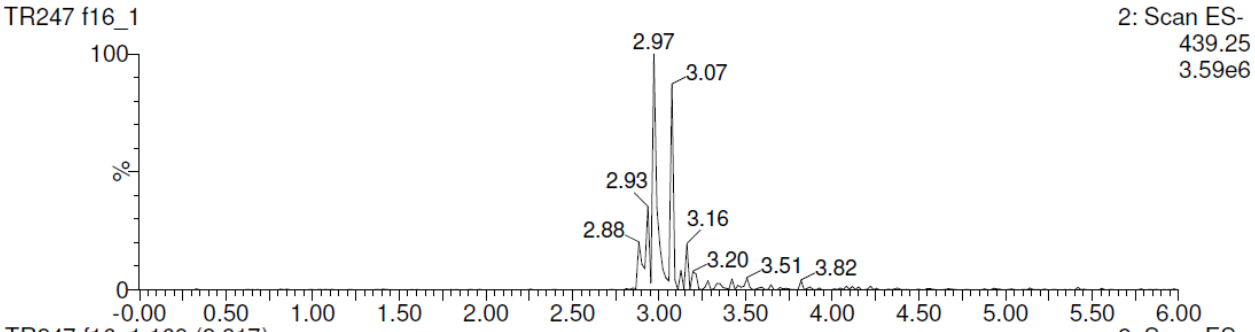
Chemical Formula: $C_{18}H_{21}ClN_6O_4$
Exact Mass: 420,1313

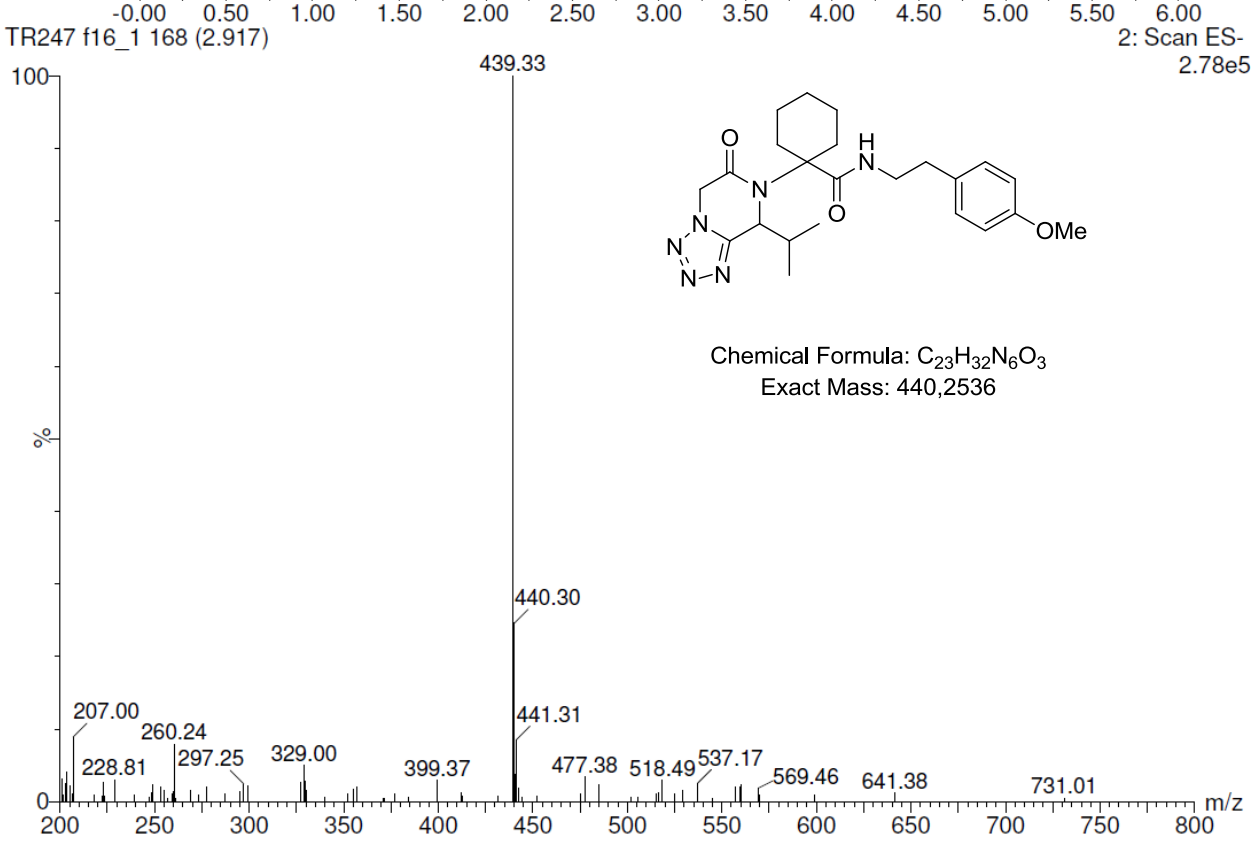

7.29
7.23
7.12
7.11
6.82
6.81
5.21
5.20
5.12
5.09
4.89
4.85
3.79
3.78
3.78
3.52
3.48
3.44
2.79
2.77
2.76
2.56
2.34
2.13
1.85
1.40
1.39
1.08
1.06
0.53
0.52
O
N
H
N
O
N
N
N
N
OMe
0.93
2.00
2.11
0.94
0.97
0.98
3.11
2.04
1.98
1.01
0.98
0.98
0.97
1.99
5.09
2.89
2.89
f1 (ppm)


172.42
163.90
158.13
148.83
130.75
129.58
129.53
129.50
113.85
113.80
67.37
55.55
55.14
48.66
41.01
34.55
32.92
31.99
25.02
22.54
22.16
18.74
14.81
f1 (ppm)

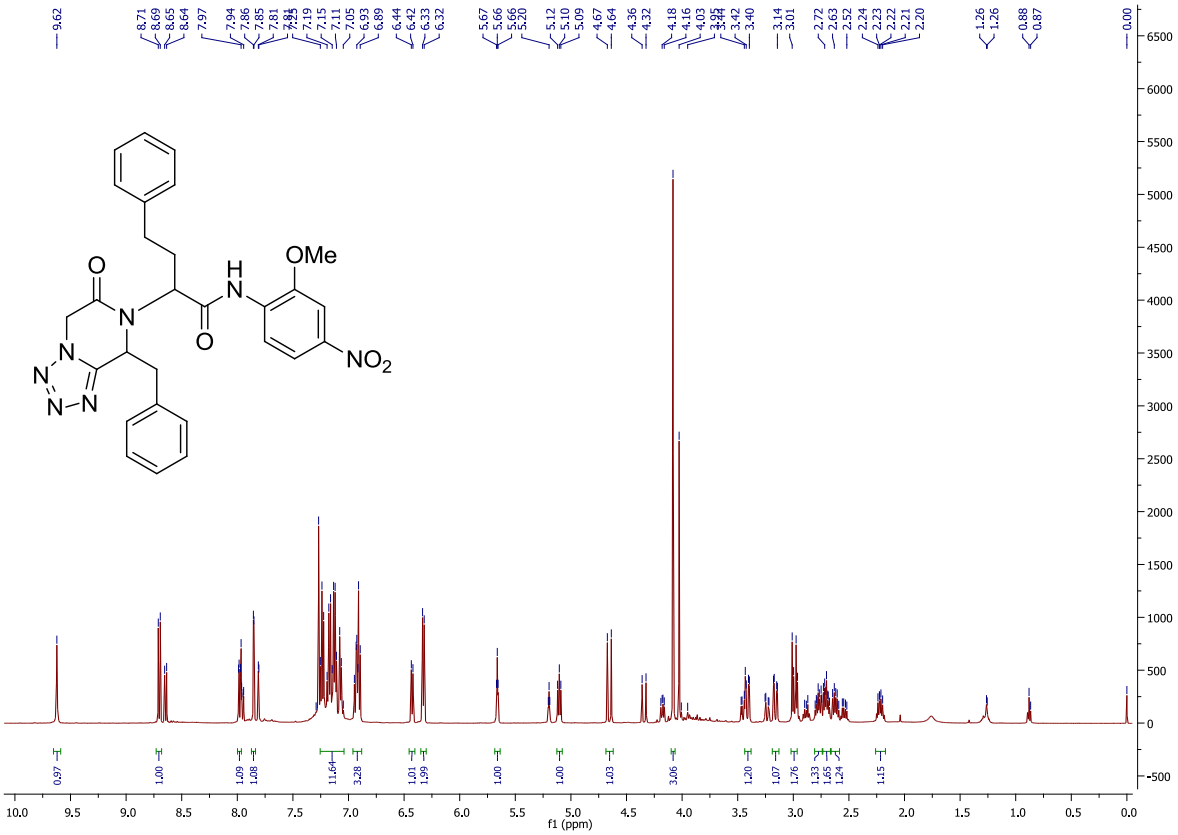
TR247 f16_1_Silica_4.6X250_MeOH_5-30%_6

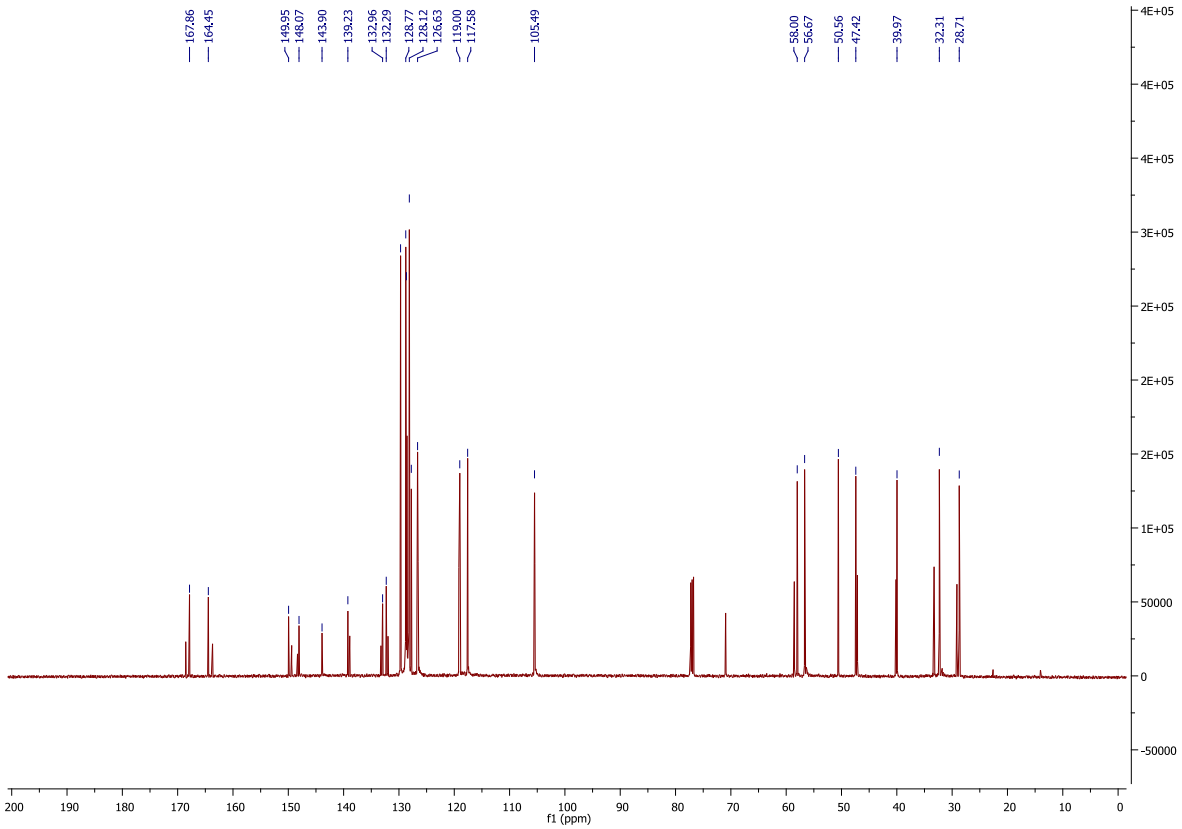




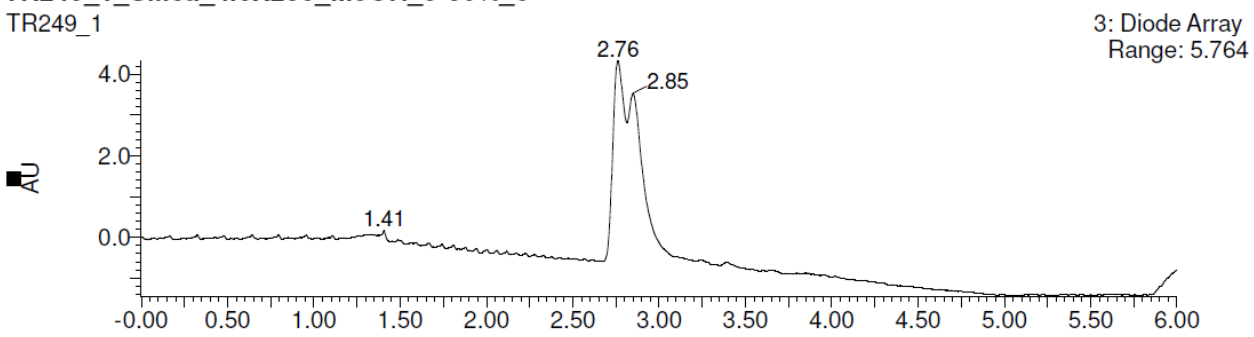


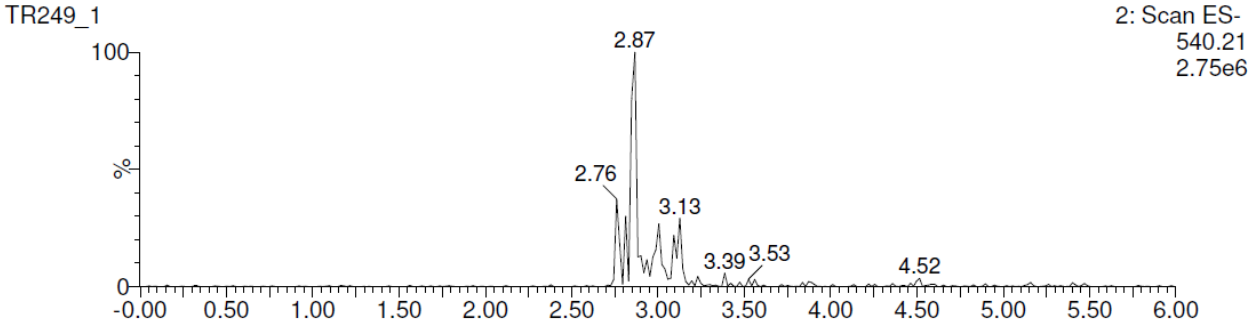
Chemical Formula: $C_{23}H_{32}N_6O_3$
Exact Mass: 440,2536

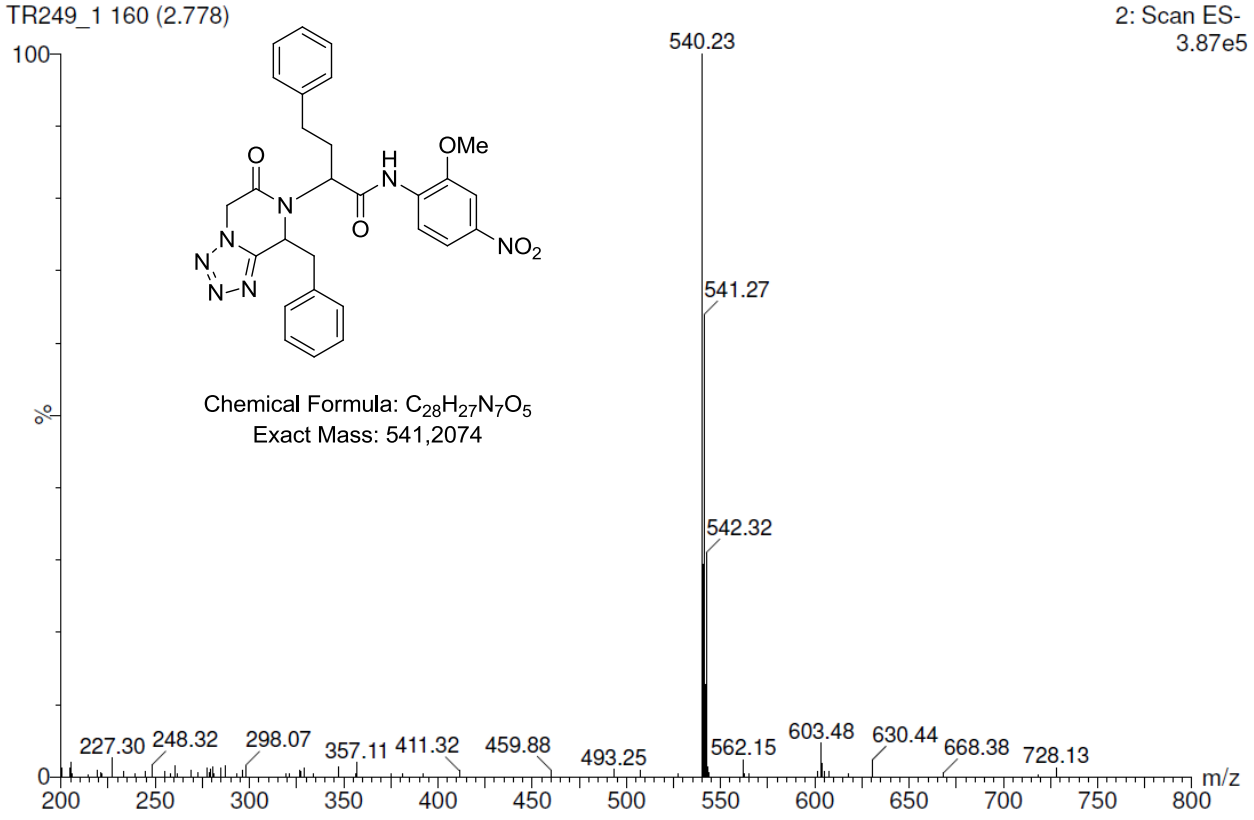

9.62
8.71
8.69
8.65
8.64
7.97
7.94
7.86
7.85
7.81
7.19
7.15
7.11
7.05
6.93
6.89
6.44
6.42
6.33
6.32
5.67
5.66
5.66
5.20
5.12
5.10
5.09
4.67
4.64
4.36
4.32
4.18
4.16
4.03
3.42
3.40
3.14
3.01
2.72
2.63
2.52
2.24
2.23
2.22
2.21
2.20
1.26
1.26
0.88
0.87
0.00
O
N
N
N
N
O
H
N
OMe
NO2
0.97
1.00
1.09
1.08
11.64
3.28
1.01
1.99
1.00
1.00
1.03
3.06
1.20
1.07
1.76
1.33
1.65
1.24
1.15
f1 (ppm)

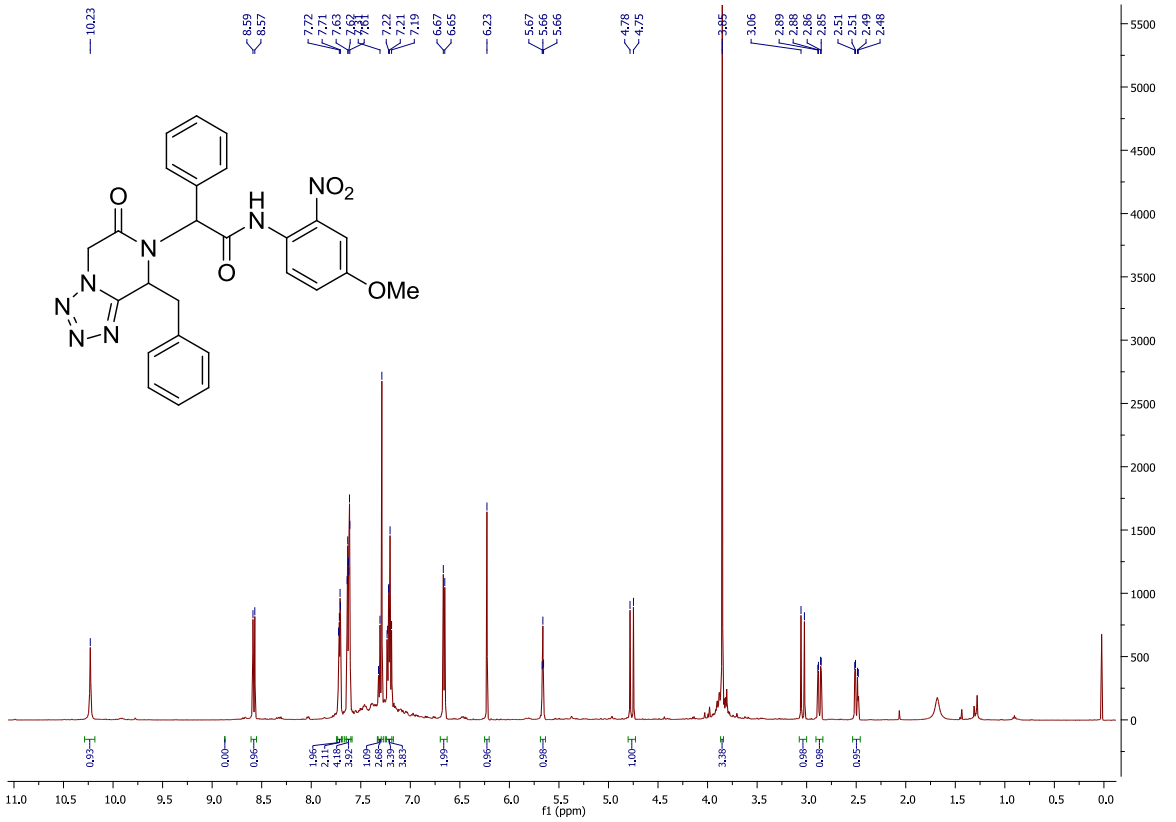

167.86
164.45
149.95
148.07
143.90
139.23
132.96
132.29
128.77
128.12
126.63
119.00
117.58
105.49
58.00
56.67
50.56
47.42
39.97
32.31
28.71
f1 (ppm)

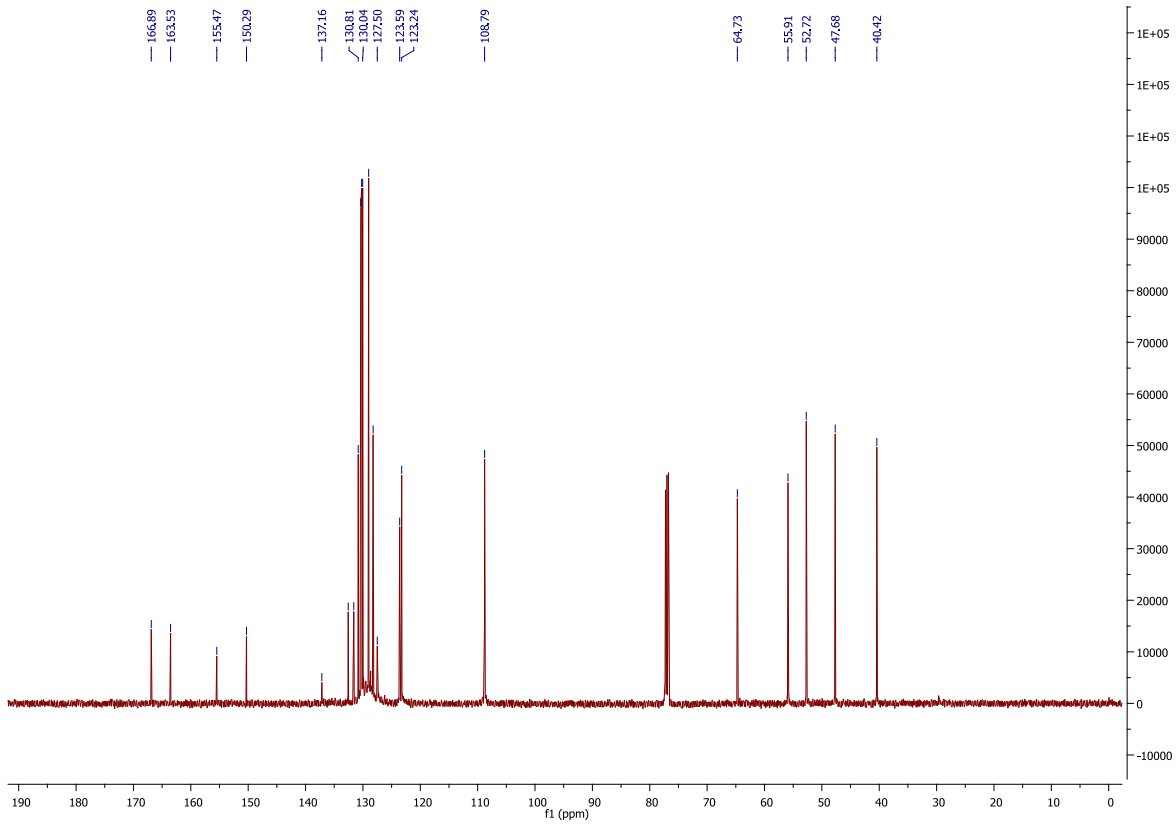
TR249_1_Silica_4.6X250_MeOH_5-30%_6



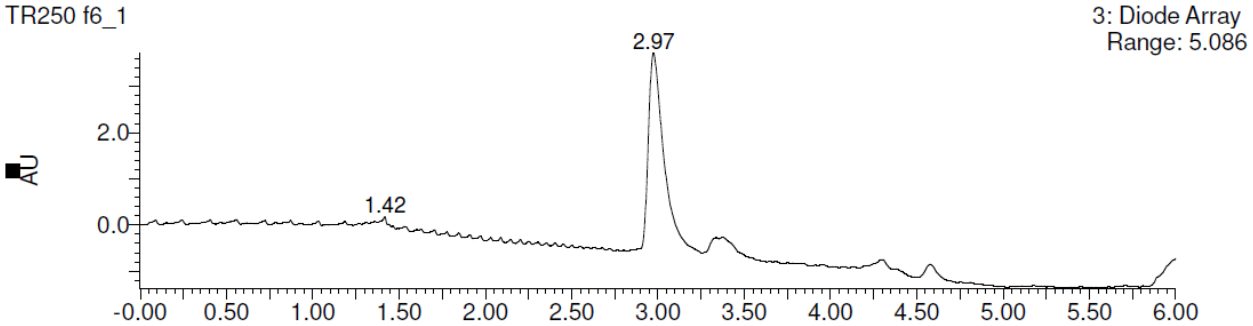


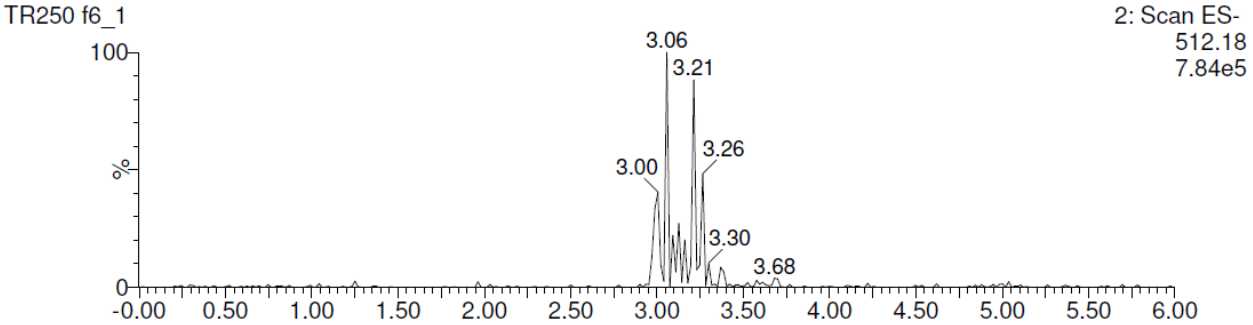


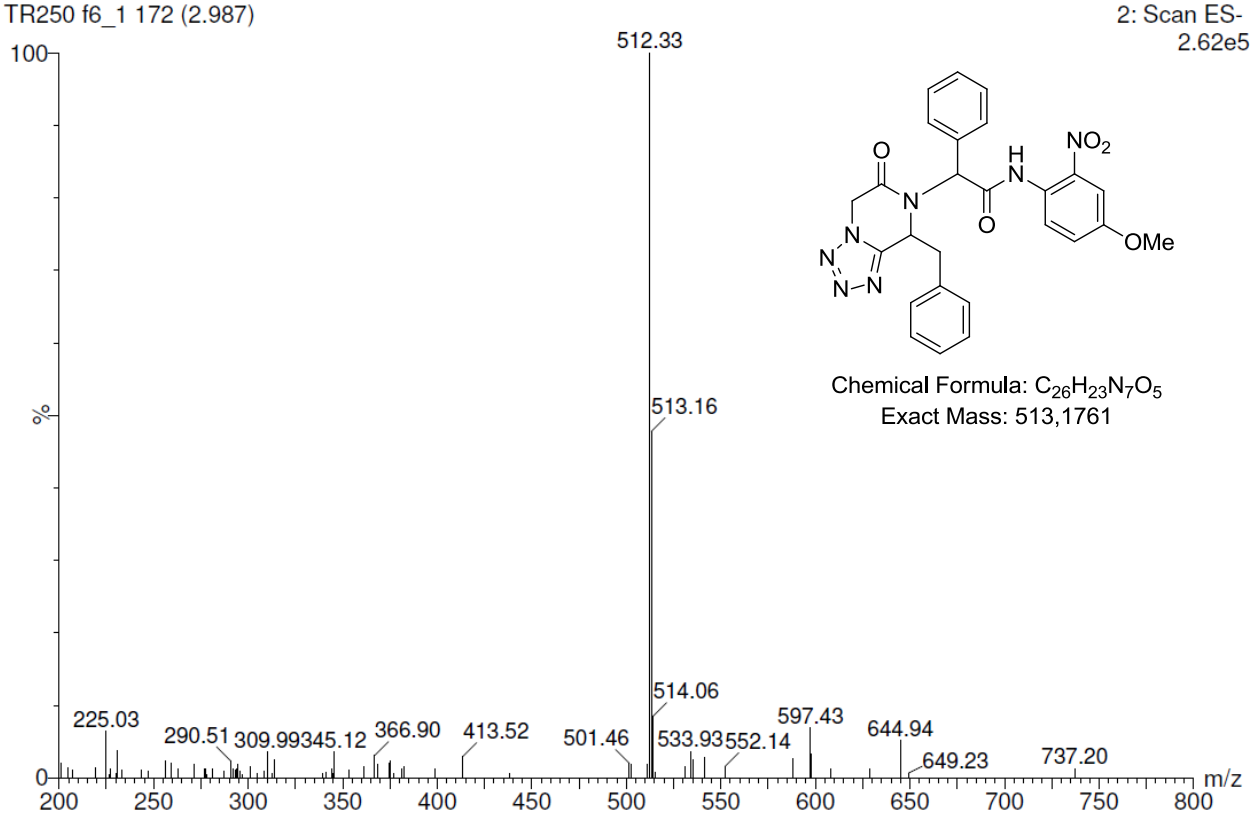

10.23
8.59
8.57
7.72
7.71
7.63
7.61
7.22
7.21
7.19
6.67
6.65
6.23
5.67
5.66
5.66
4.78
4.75
3.85
3.06
2.89
2.88
2.86
2.85
2.51
2.51
2.49
2.48
O
N
N
N
N
O
H
N
NO2
OMe
f1 (ppm)


166.89
163.53
155.47
150.29
137.16
130.81
130.04
127.50
123.59
123.24
108.79
64.73
55.91
52.72
47.68
40.42
f1 (ppm)

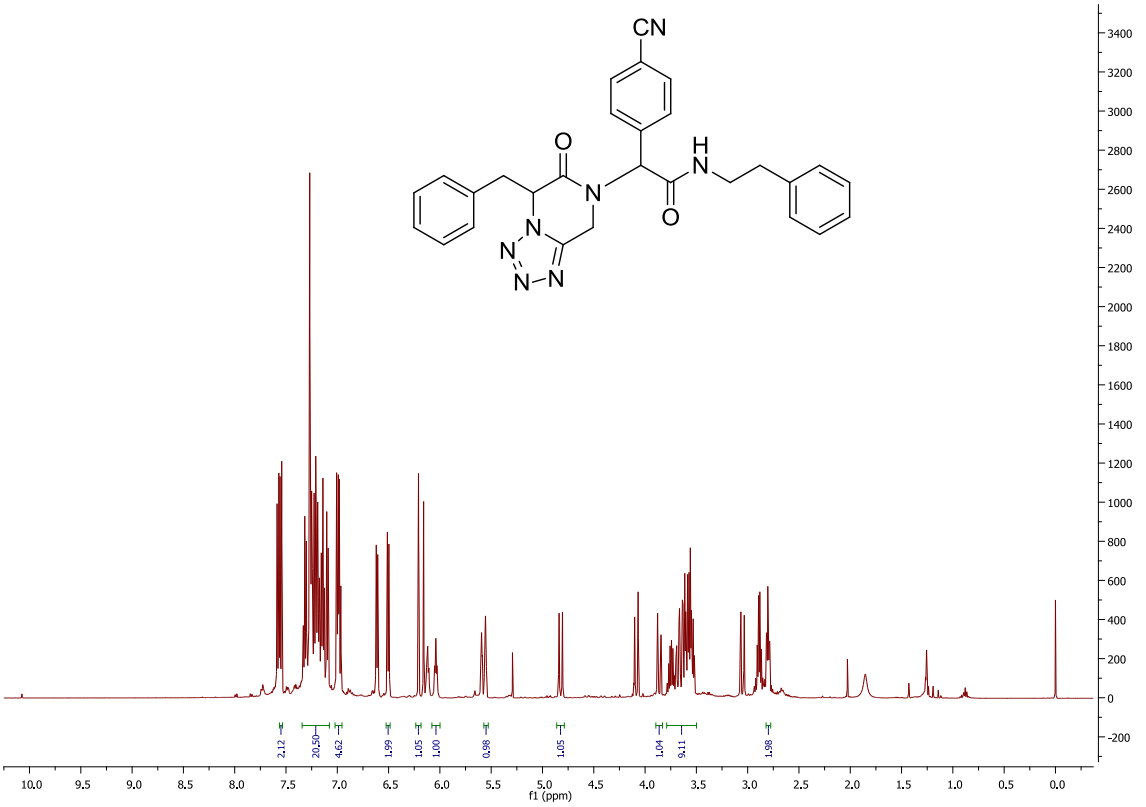
TR250 f6_1_Silica_4.6X250_MeOH_5-30%_6

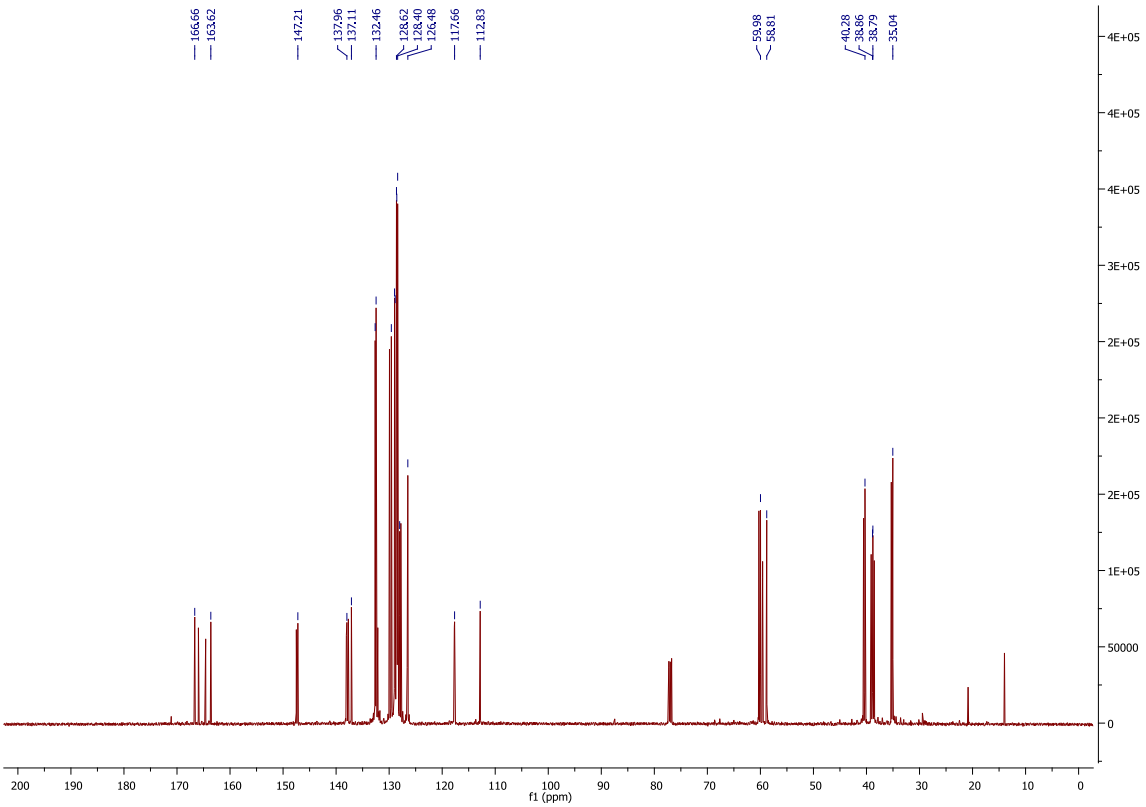


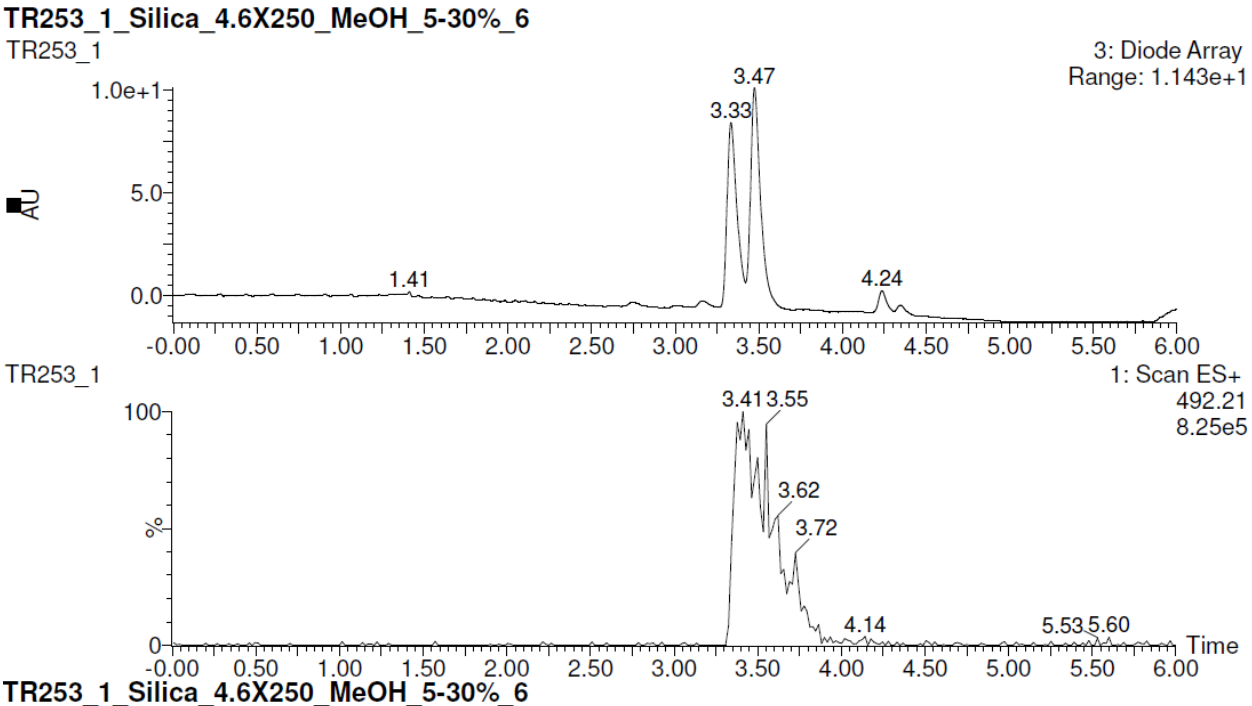


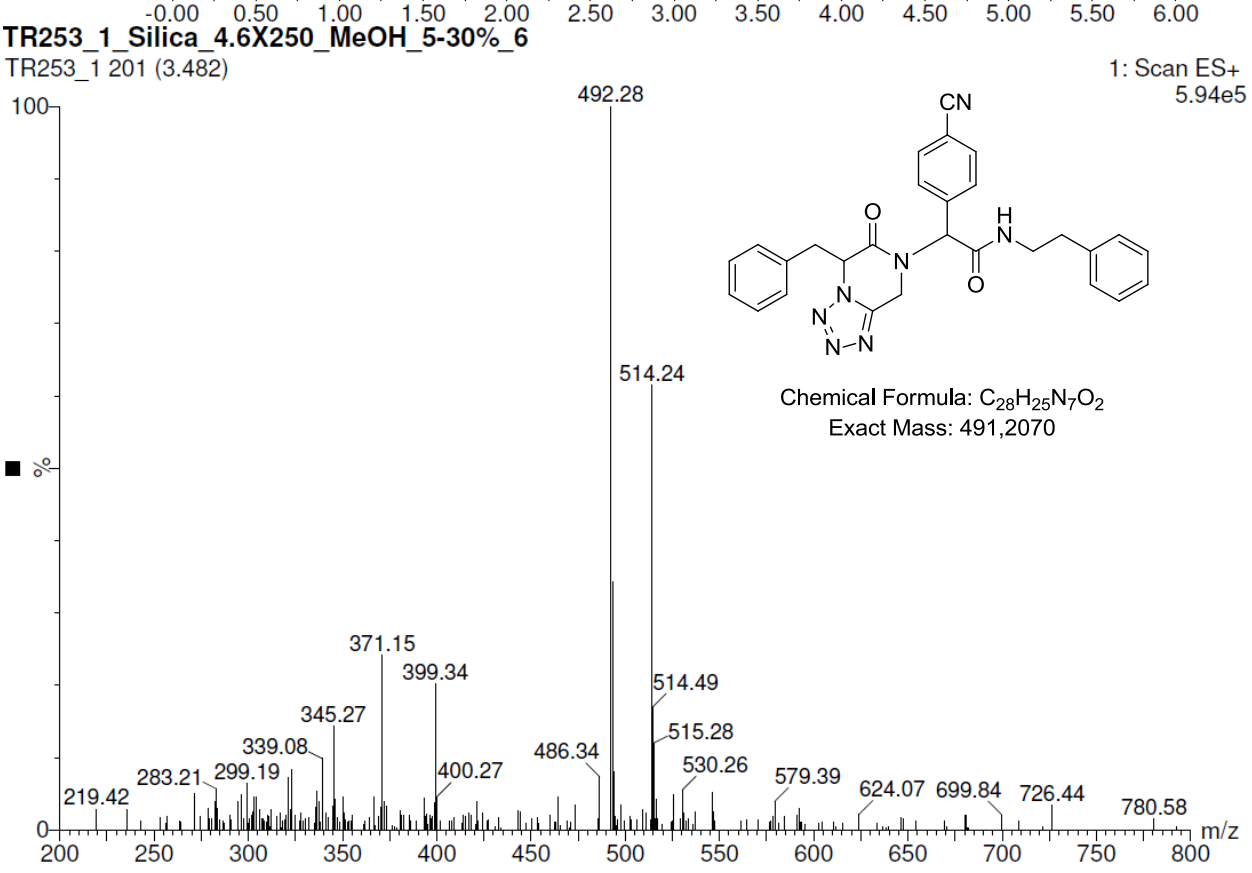


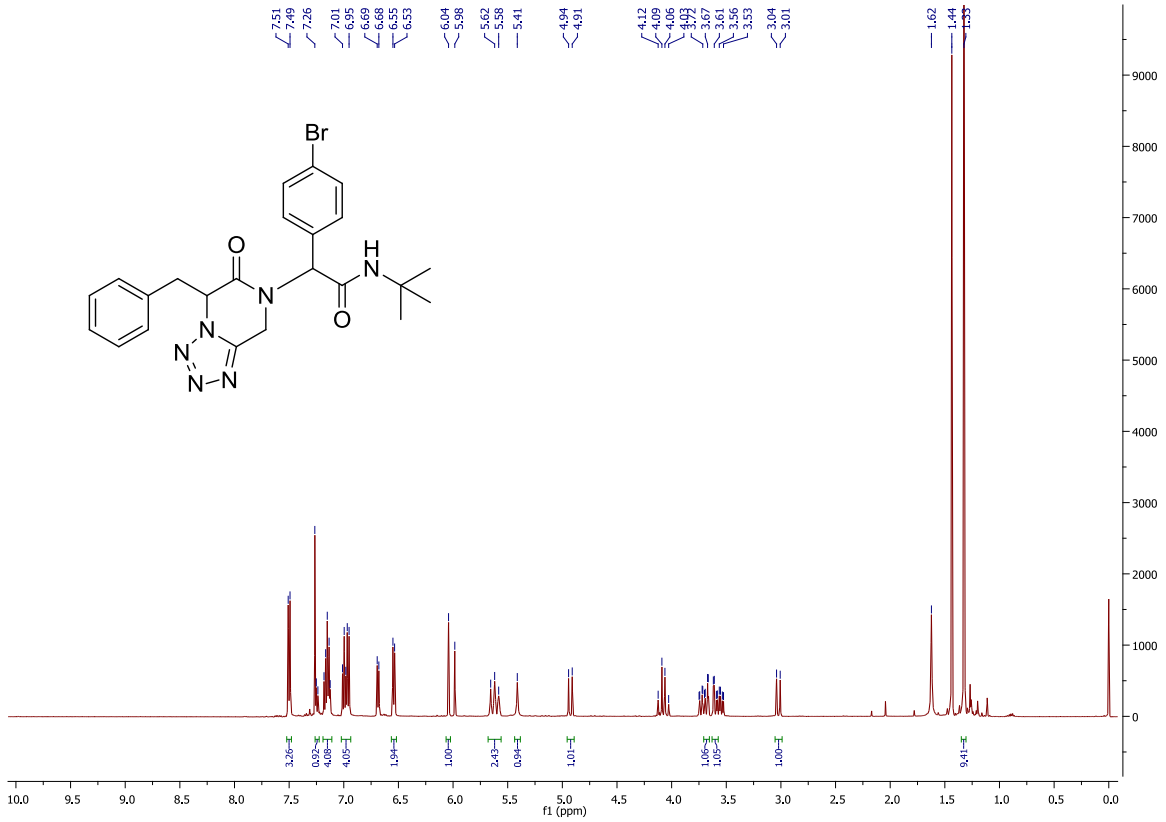
Chemical Formula: $C_{26}H_{23}N_7O_5$
Exact Mass: 513,1761

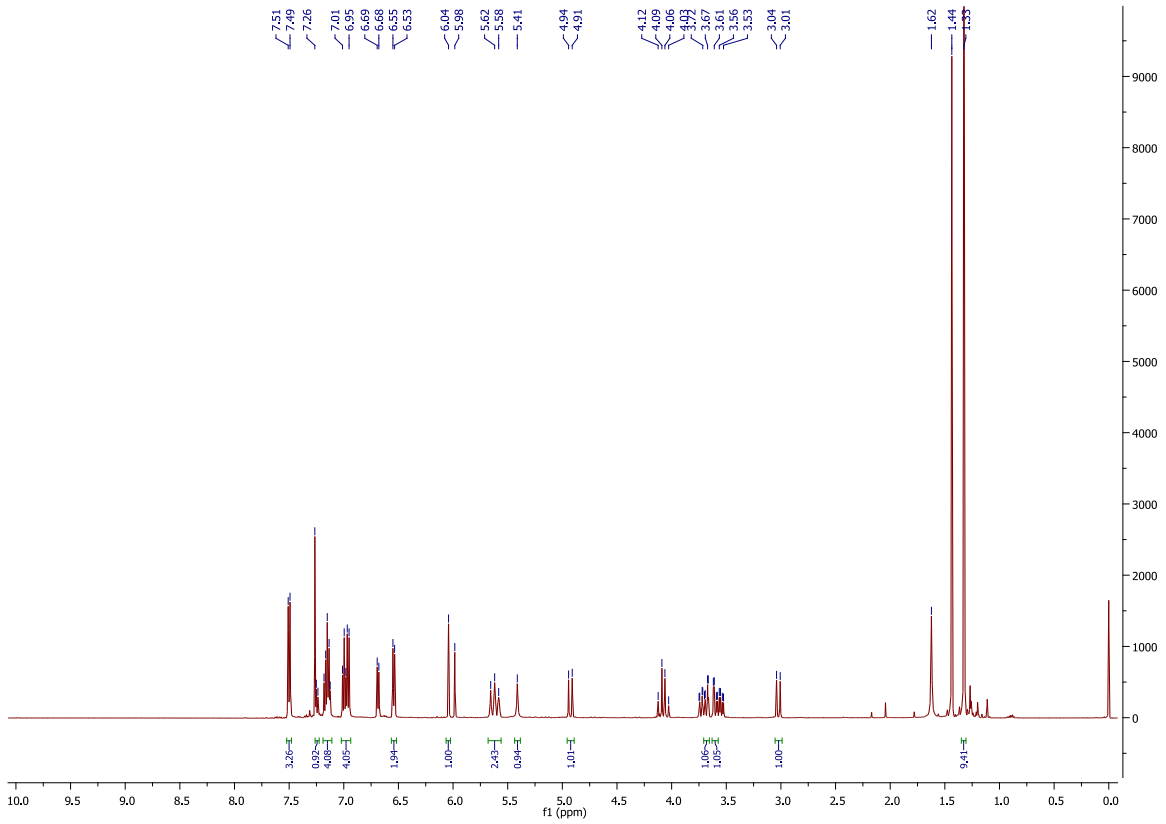

CN
O
N
H
N
O
N
N
N
2.12
20.50
4.62
1.99
1.05
1.00
0.98
1.05
1.04
9.11
1.98
f1 (ppm)

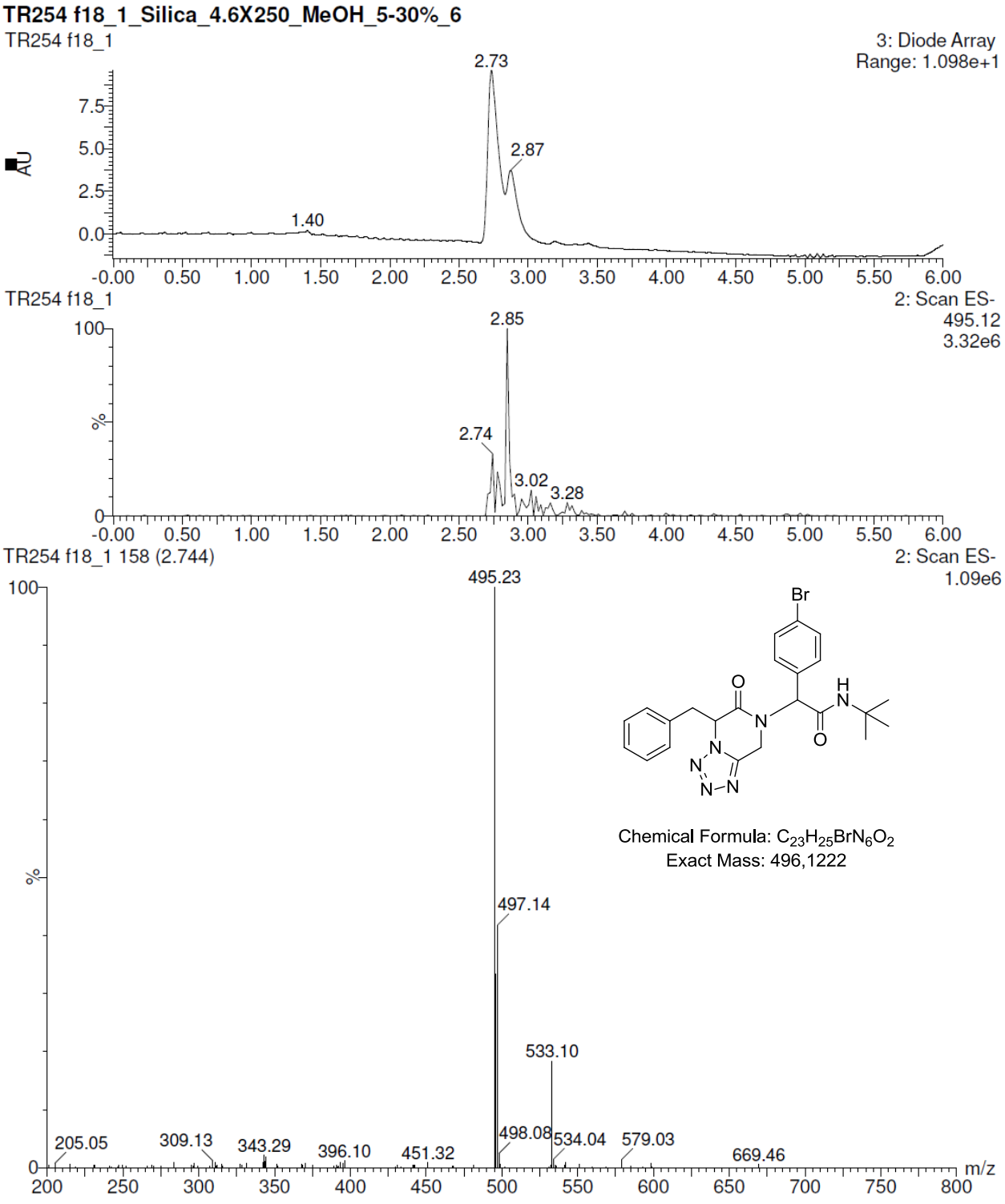

166.66
163.62
147.21
137.96
137.11
132.46
128.62
128.40
126.48
117.66
112.83
59.98
58.81
40.28
38.86
38.79
35.04
f1 (ppm)

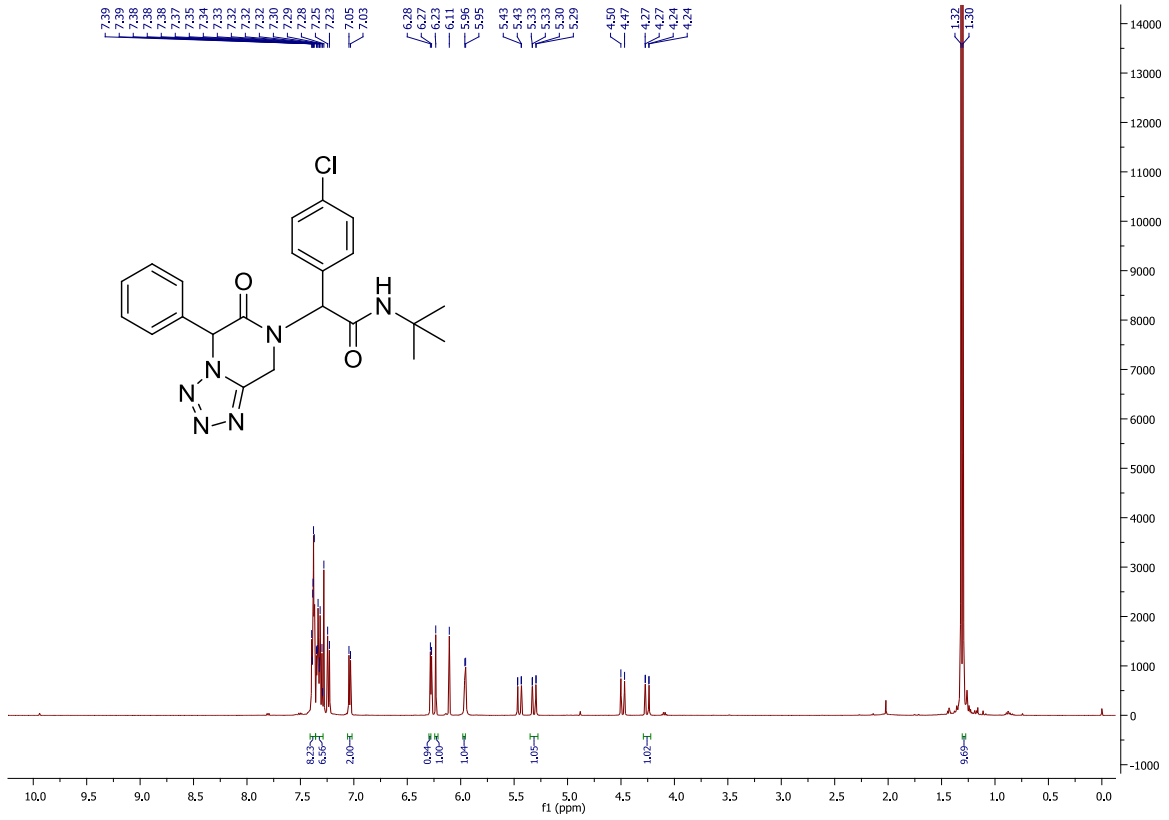

TR253_1_Silica_4.6X250_MeOH_5-30%_6
TR253_1
3: Diode Array
Range: 1.143e+1
1.0e+1
5.0
0.0
AU
3.47
3.33
1.41
4.24
-0.00 0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00
TR253_1
1: Scan ES+
492.21
8.25e5
100
%
0
3.41 3.55
3.62
3.72
4.14
5.53 5.60
Time
-0.00 0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00

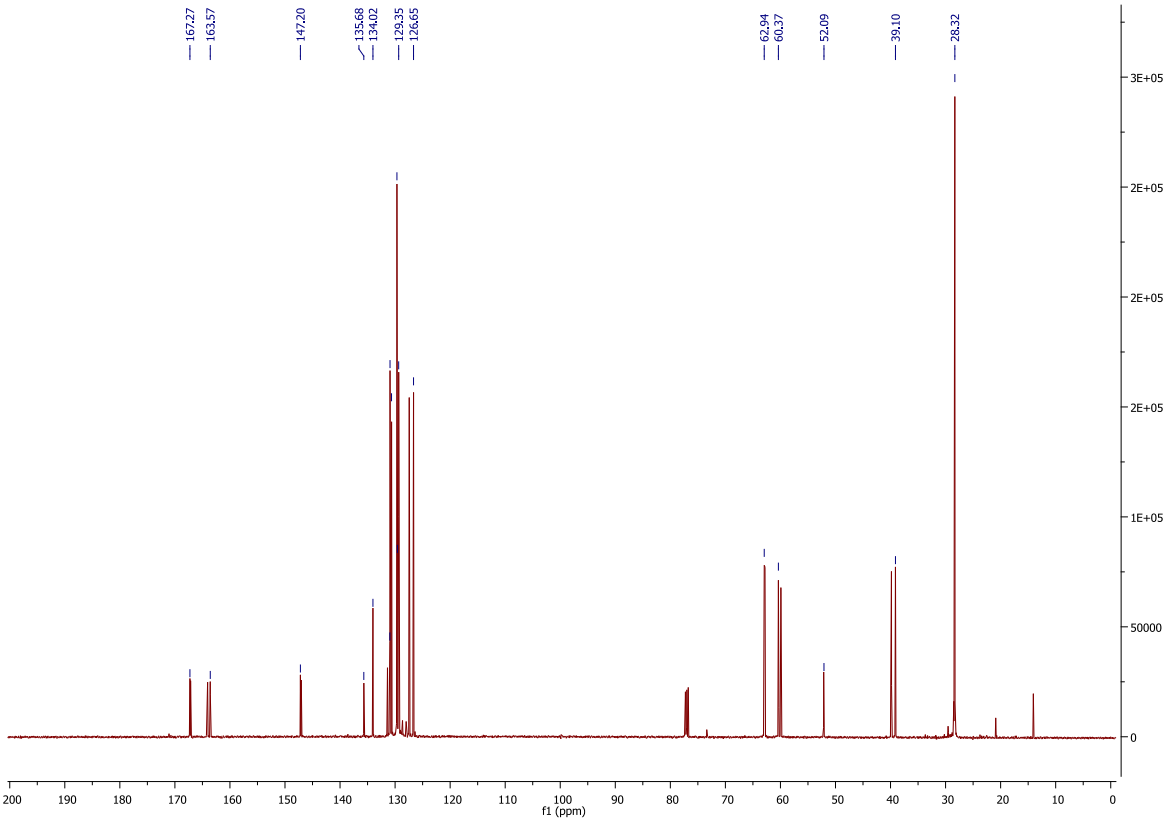

TR253_1_Silica_4.6X250_MeOH_5-30%_6
TR253_1 201 (3.482)
1: Scan ES+
5.94e5
100
%
0
492.28
514.24
371.15
399.34
514.49
345.27
515.28
339.08
486.34
530.26
283.21
299.19
400.27
579.39
624.07
699.84
726.44
780.58
219.42
200 250 300 350 400 450 500 550 600 650 700 750 800
m/z
CN
O
H
N
N
N
N
N
O
Chemical Formula: C28H25N7O2
Exact Mass: 491,2070


Br
O
N
H
N
O
N
N
N
N
7.51
7.49
7.26
7.01
6.95
6.69
6.68
6.55
6.53
6.04
5.98
5.62
5.58
5.41
4.94
4.91
4.12
4.09
4.06
4.03
3.72
3.67
3.61
3.56
3.53
3.04
3.01
1.62
1.44
1.35
3.26
0.92
4.08
4.05
1.94
1.00
2.43
0.94
1.01
1.06
1.05
1.00
9.41
f1 (ppm)

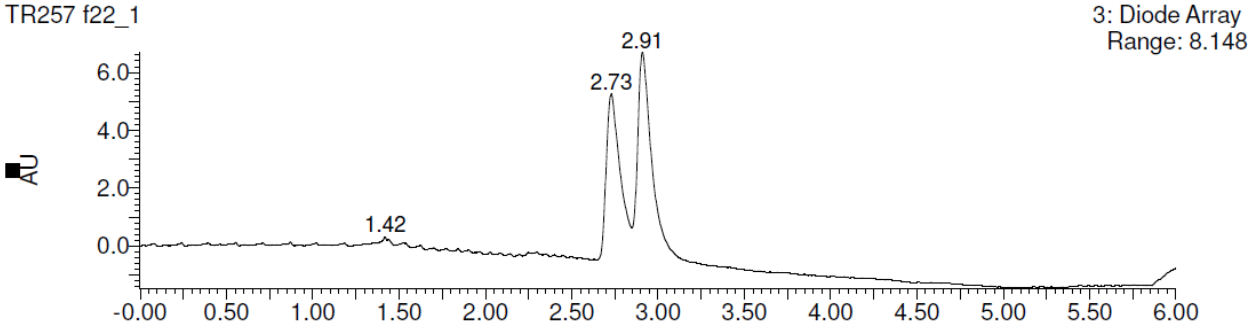

7.51
7.49
7.26
7.01
6.95
6.69
6.68
6.55
6.53
6.04
5.98
5.62
5.58
5.41
4.94
4.91
4.12
4.09
4.06
4.03
3.72
3.67
3.61
3.56
3.53
3.04
3.01
1.62
1.44
1.35
3.26
0.92
4.08
4.05
1.94
1.00
2.43
0.94
1.01
1.06
1.05
1.00
9.41
f1 (ppm)

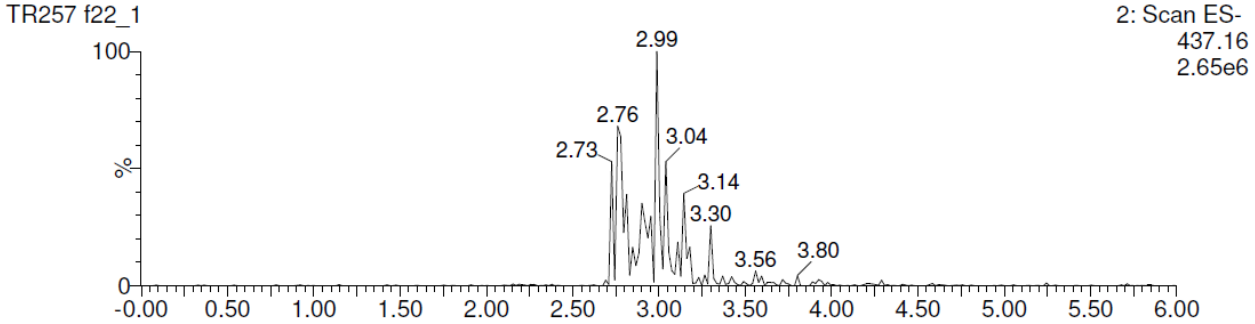

TR254 f18_1_Silica_4.6X250_MeOH_5-30%_6
TR254 f18_1
3: Diode Array
Range: 1.098e+1
2.73
2.87
1.40
AU
TR254 f18_1
2: Scan ES-
495.12
3.32e6
2.85
2.74
3.02
3.28
%
TR254 f18_1 158 (2.744)
2: Scan ES-
1.09e6
495.23
497.14
533.10
205.05
309.13
343.29
396.10
451.32
498.08
534.04
579.03
669.46
m/z
Br
O
H
N
Chemical Formula: C23H25BrN6O2
Exact Mass: 496,1222

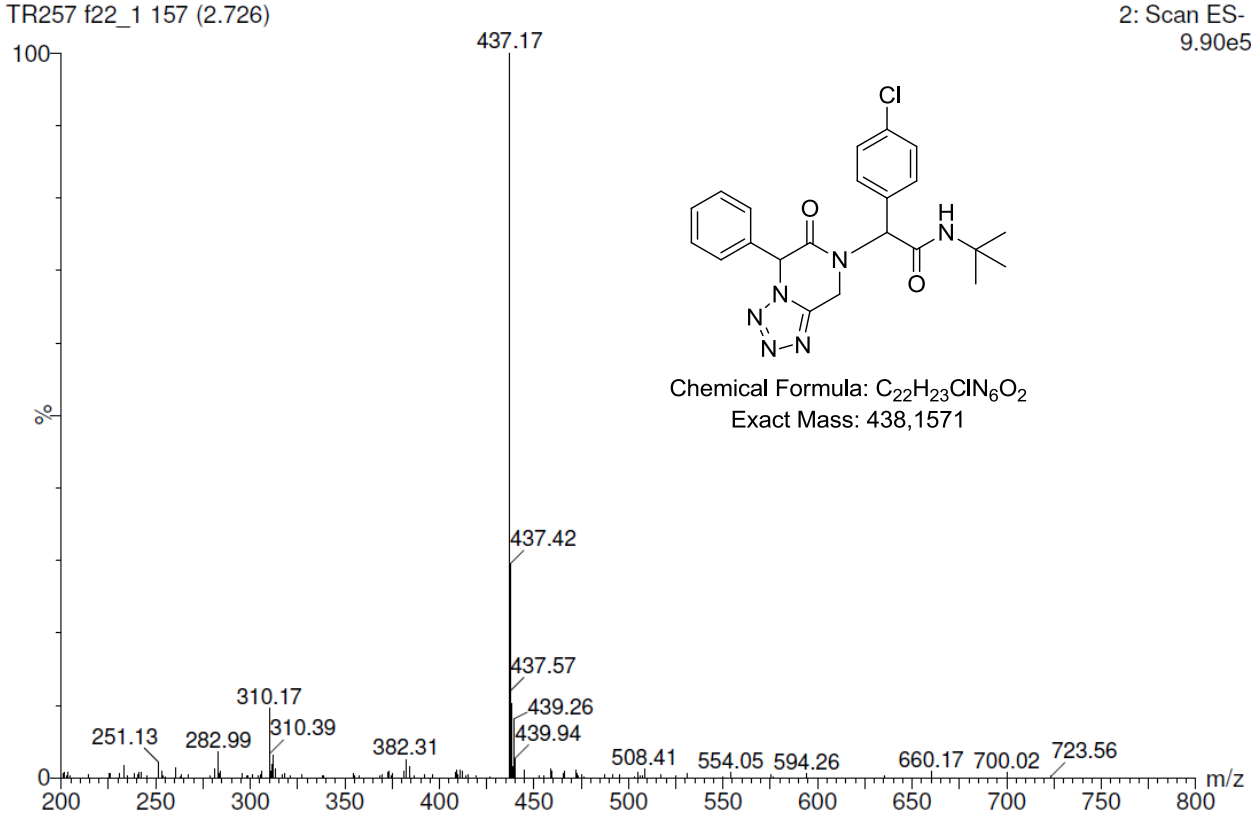

7.39
7.39
7.38
7.38
7.38
7.37
7.35
7.34
7.33
7.32
7.32
7.32
7.30
7.29
7.28
7.25
7.23
7.05
7.03
6.28
6.27
6.23
6.11
5.96
5.95
5.43
5.43
5.33
5.33
5.30
5.29
4.50
4.47
4.27
4.27
4.24
4.24
1.32
1.30
Cl
O
N
H
N
O
N
N
N
8.23
6.86
2.00
0.94
1.00
1.04
1.05
1.02
9.69
f1 (ppm)


167.27
163.57
147.20
135.68
134.02
129.35
126.65
62.94
60.37
52.09
39.10
28.32
f1 (ppm)

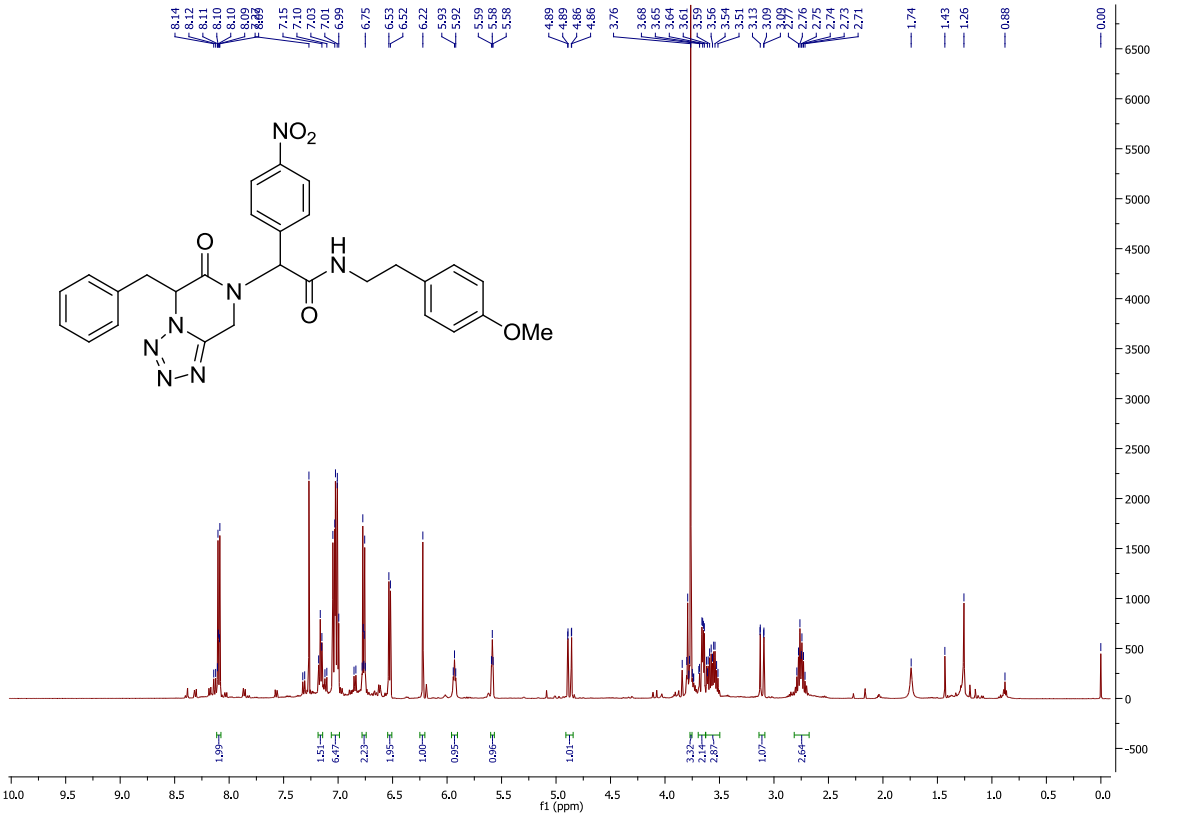
TR257 f22_1_Silica_4.6X250_MeOH_5-30%_6

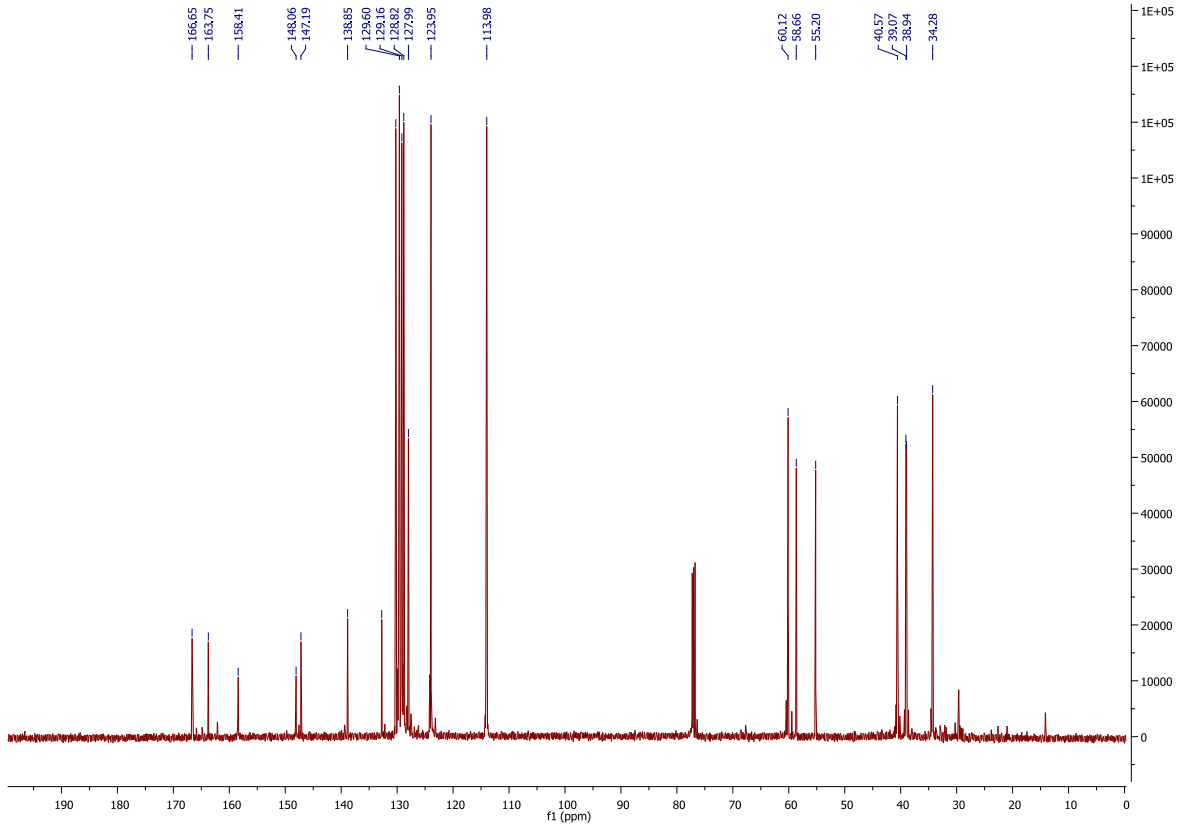




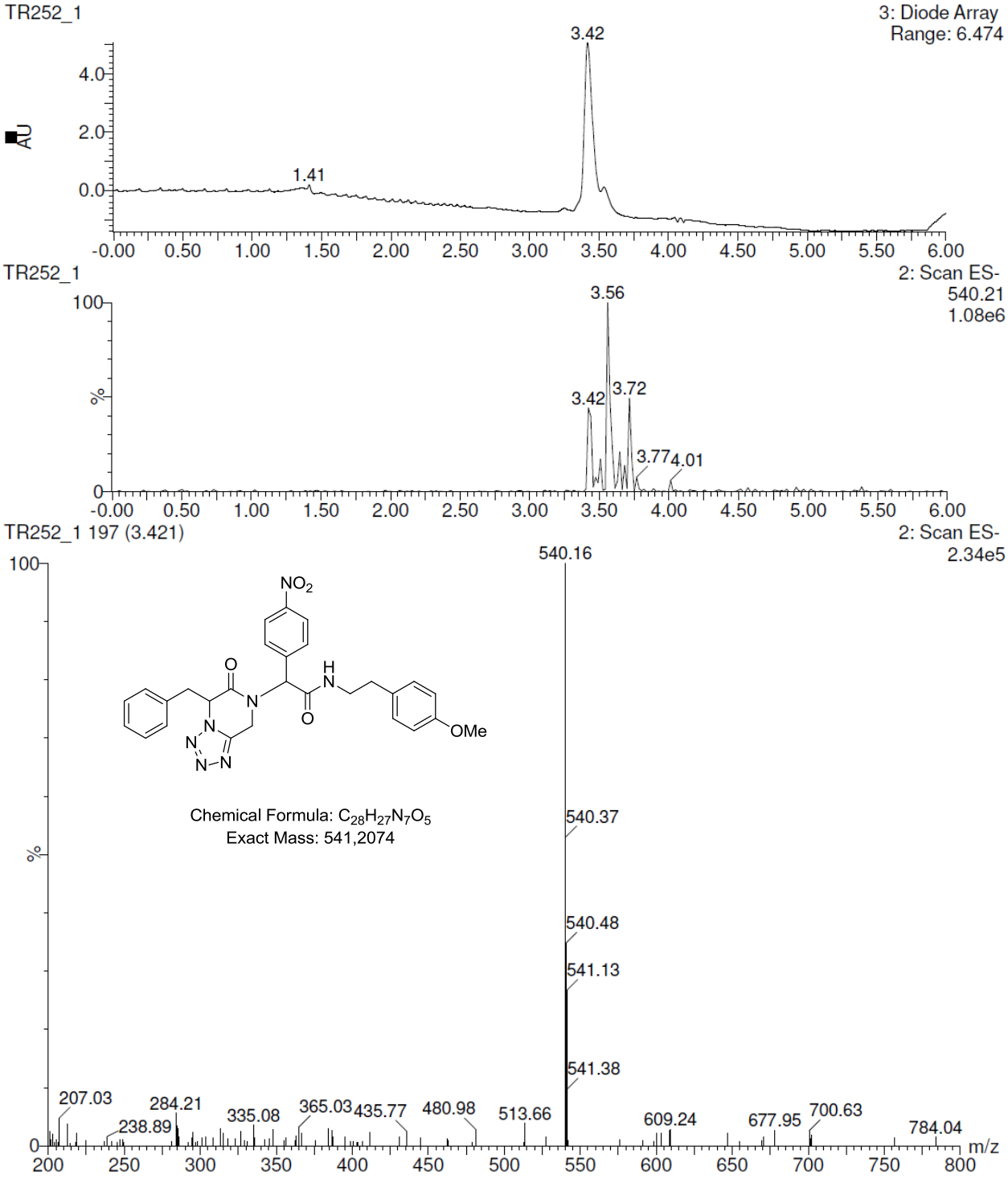


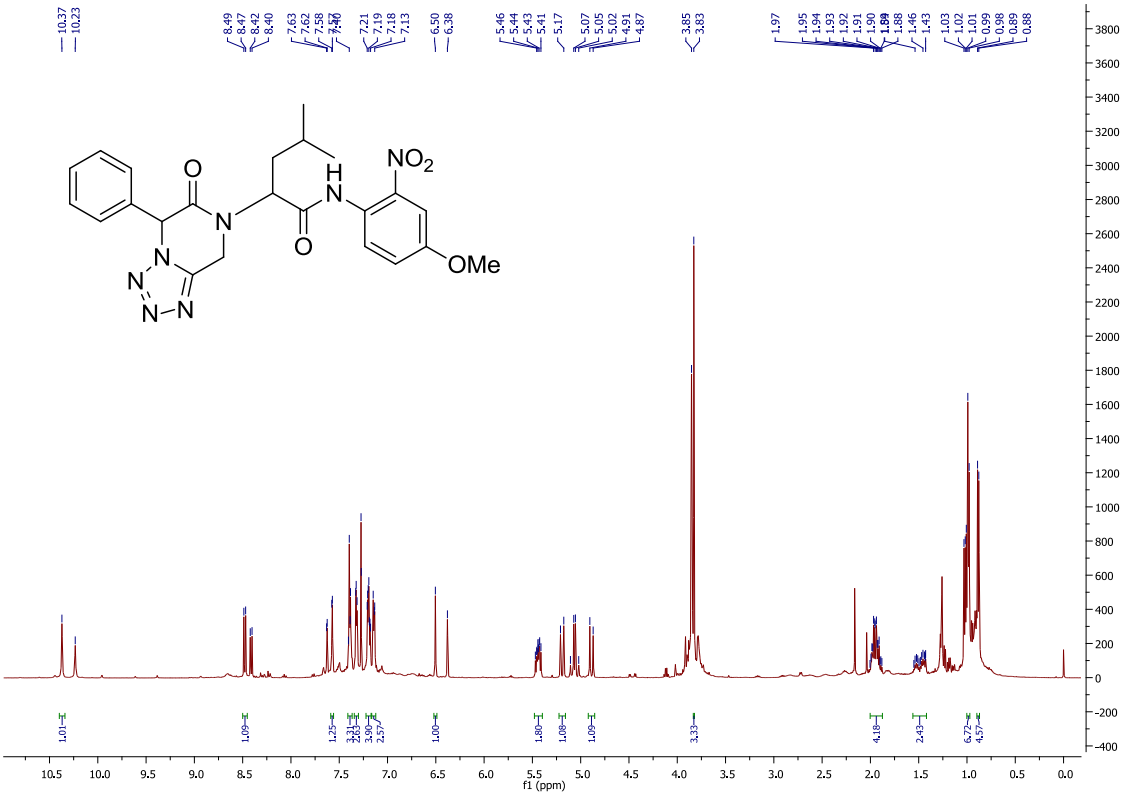
Chemical Formula: $C_{22}H_{23}ClN_6O_2$
Exact Mass: 438,1571

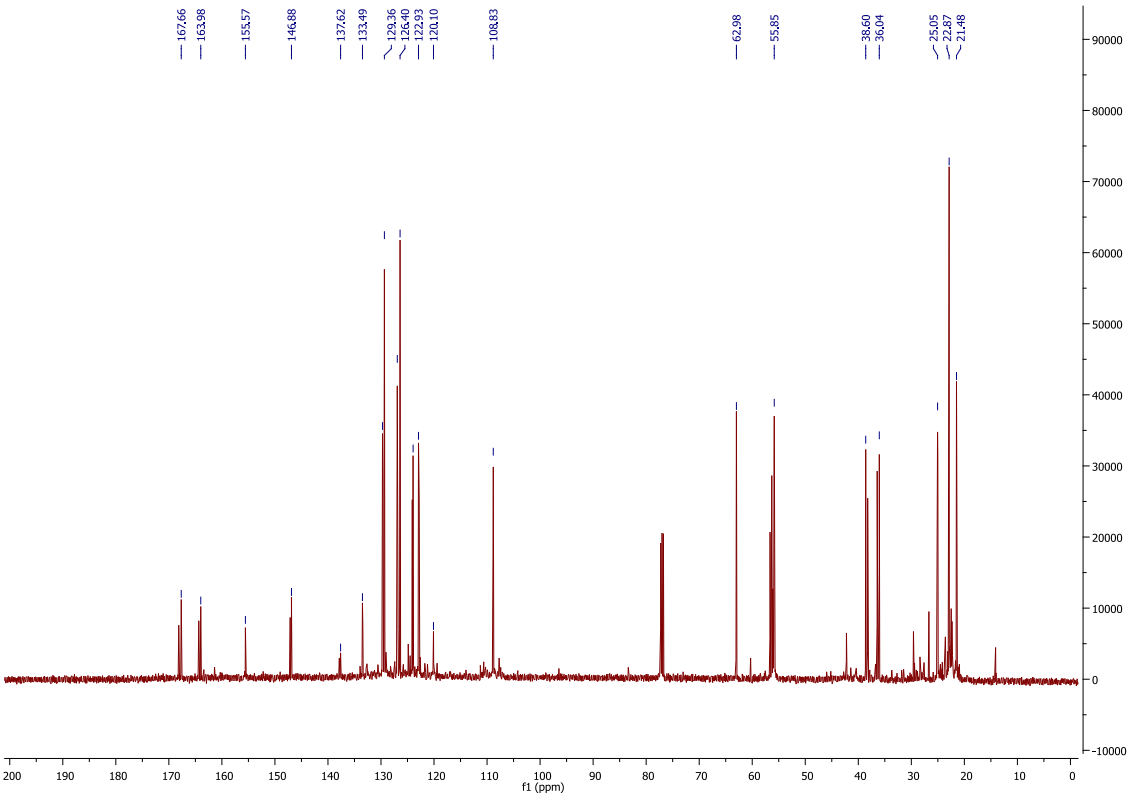

NO2
O
N
H
N
O
N
N
N
N
OMe
f1 (ppm)


f1 (ppm)

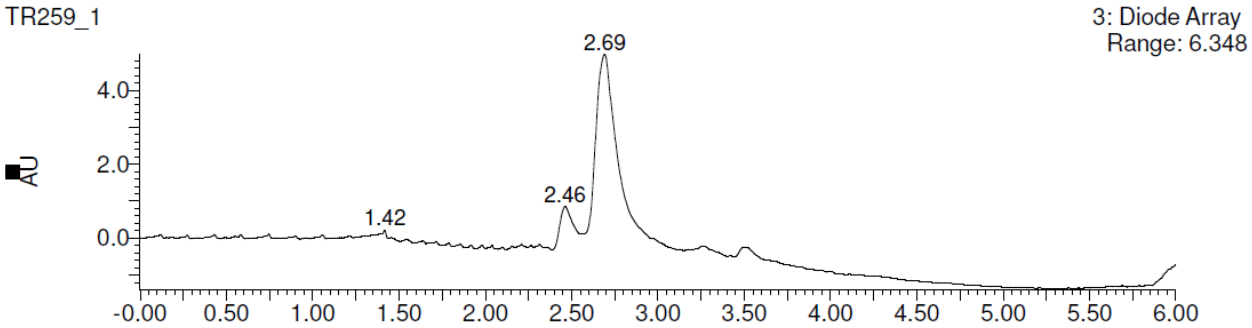
TR252_1_Silica_4.6X250_MeOH_5-30%_6

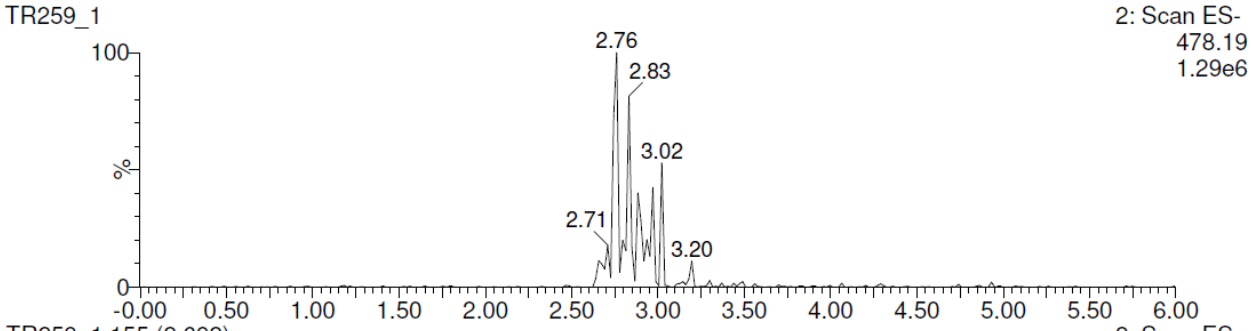


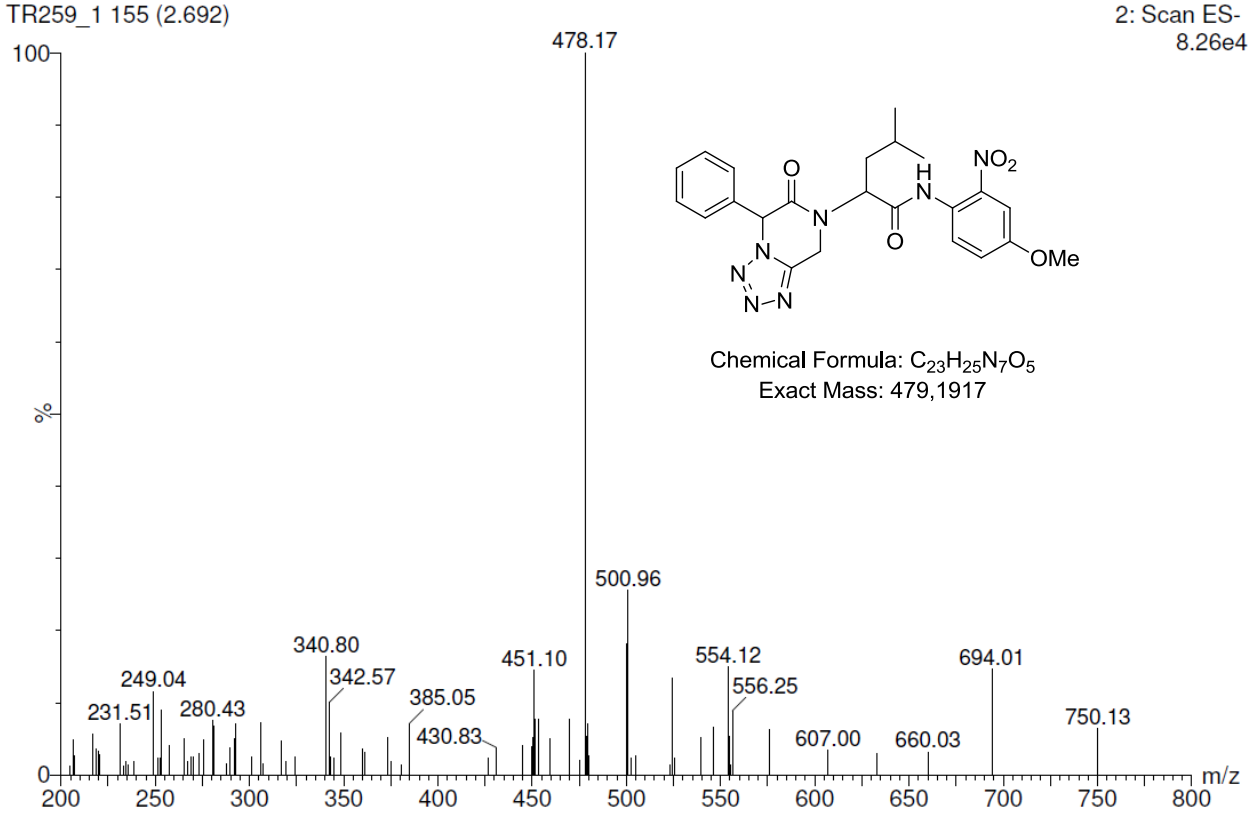

10.37
10.23
8.49
8.47
8.42
8.40
7.63
7.62
7.58
7.56
7.40
7.21
7.19
7.18
7.13
6.50
6.38
5.46
5.44
5.43
5.41
5.17
5.07
5.05
5.02
4.91
4.87
3.85
3.83
1.97
1.95
1.94
1.93
1.92
1.91
1.90
1.88
1.46
1.43
1.03
1.02
1.01
0.99
0.98
0.89
0.88
O
N
H
N
O
NO2
OMe
N
N
N
N
1.01
1.09
1.25
2.13
3.90
2.57
1.00
1.80
1.08
1.09
3.33
4.18
2.43
6.72
4.57
f1 (ppm)


167.66
163.98
155.57
146.88
137.62
133.49
129.36
126.40
122.93
120.10
108.83
62.98
55.85
38.60
36.04
25.05
22.87
21.48
f1 (ppm)

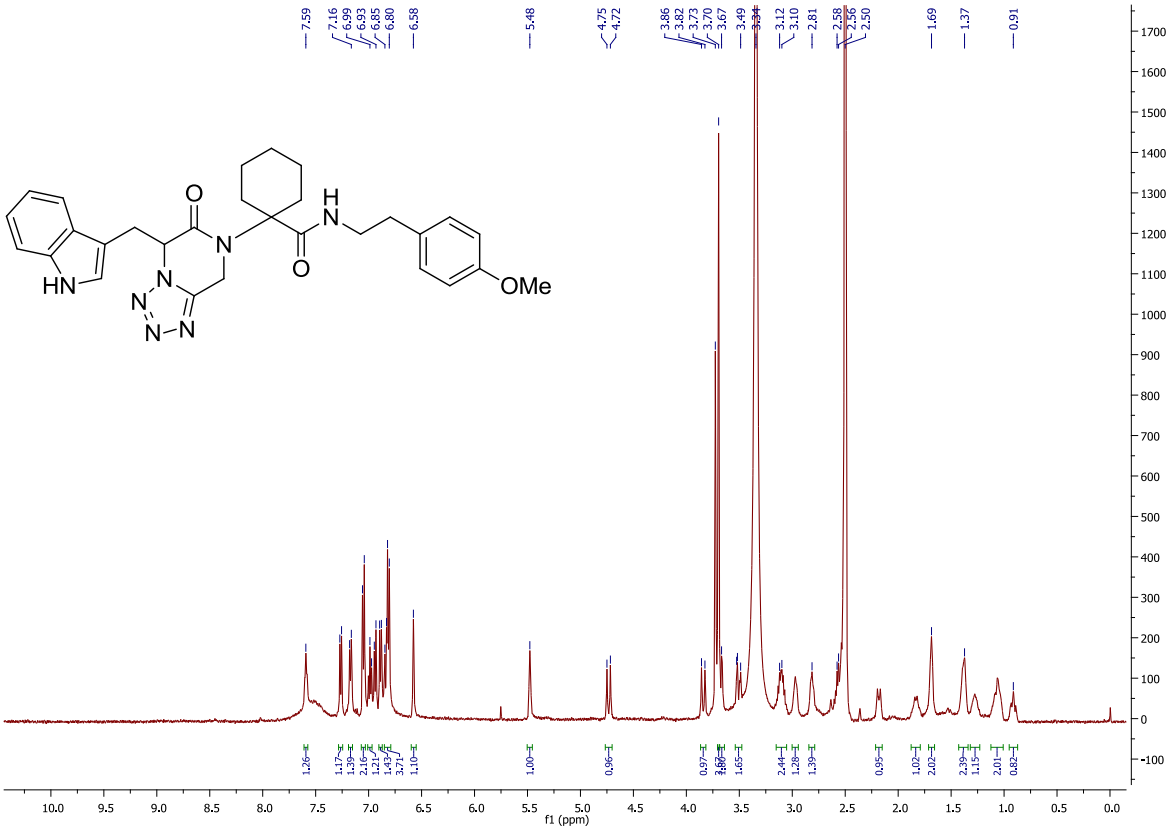
TR259_1_Silica_4.6X250_MeOH_5-30%_6

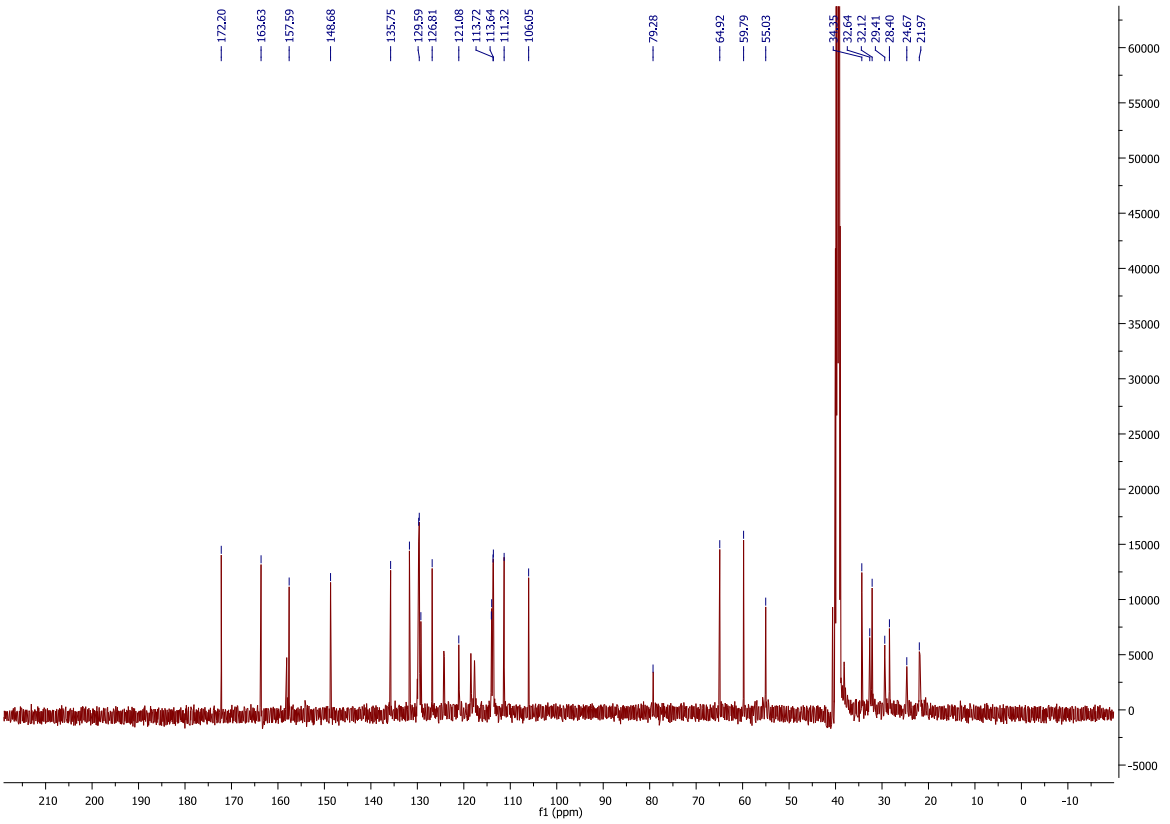




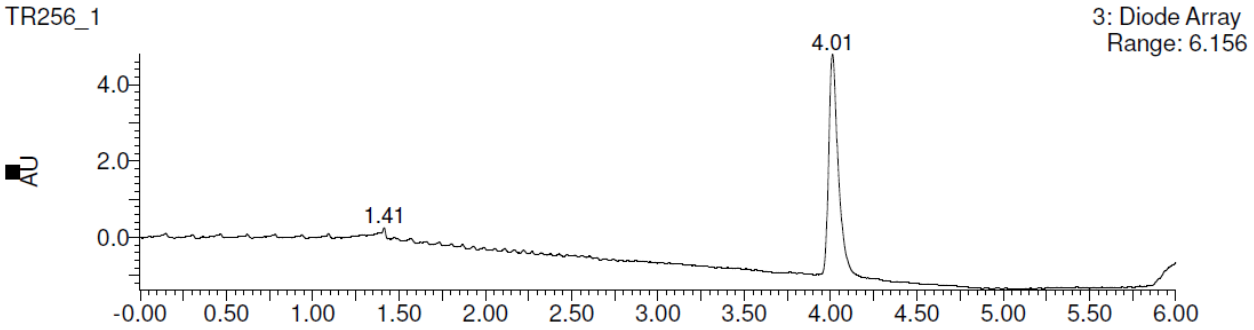


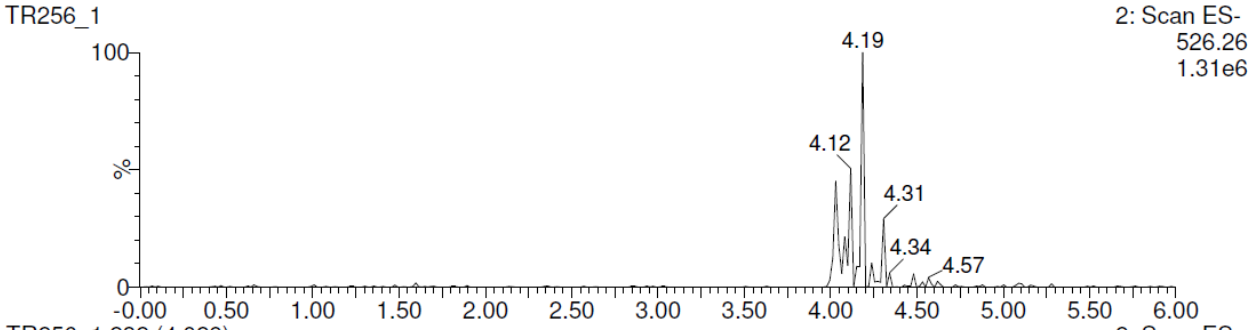
Chemical Formula: $C_{23}H_{25}N_7O_5$
Exact Mass: 479,1917

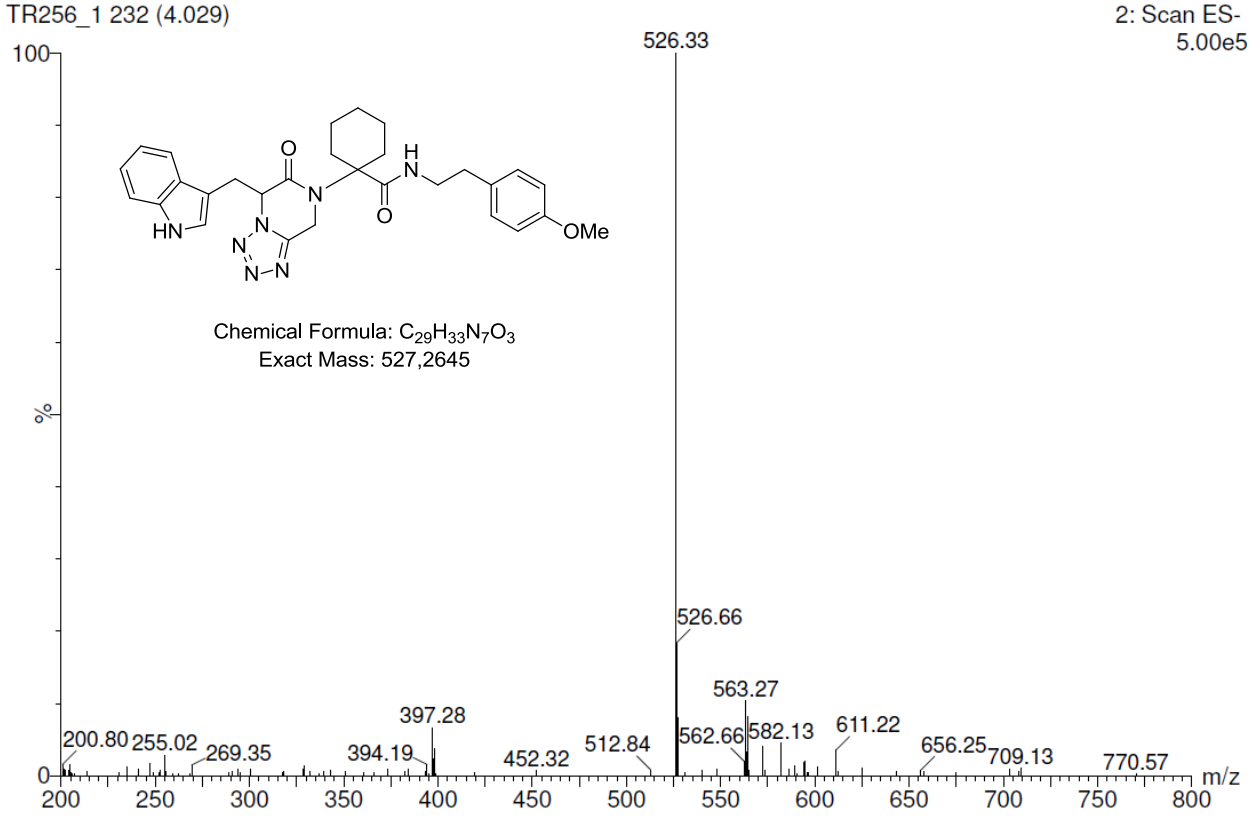

7.59
7.16
6.99
6.93
6.85
6.80
6.58
5.48
4.75
4.72
3.86
3.82
3.73
3.70
3.67
3.49
3.34
3.12
3.10
2.81
2.58
2.56
2.50
1.69
1.37
0.91
HN
O
N
N
N
N
H
N
O
OMe
f1 (ppm)

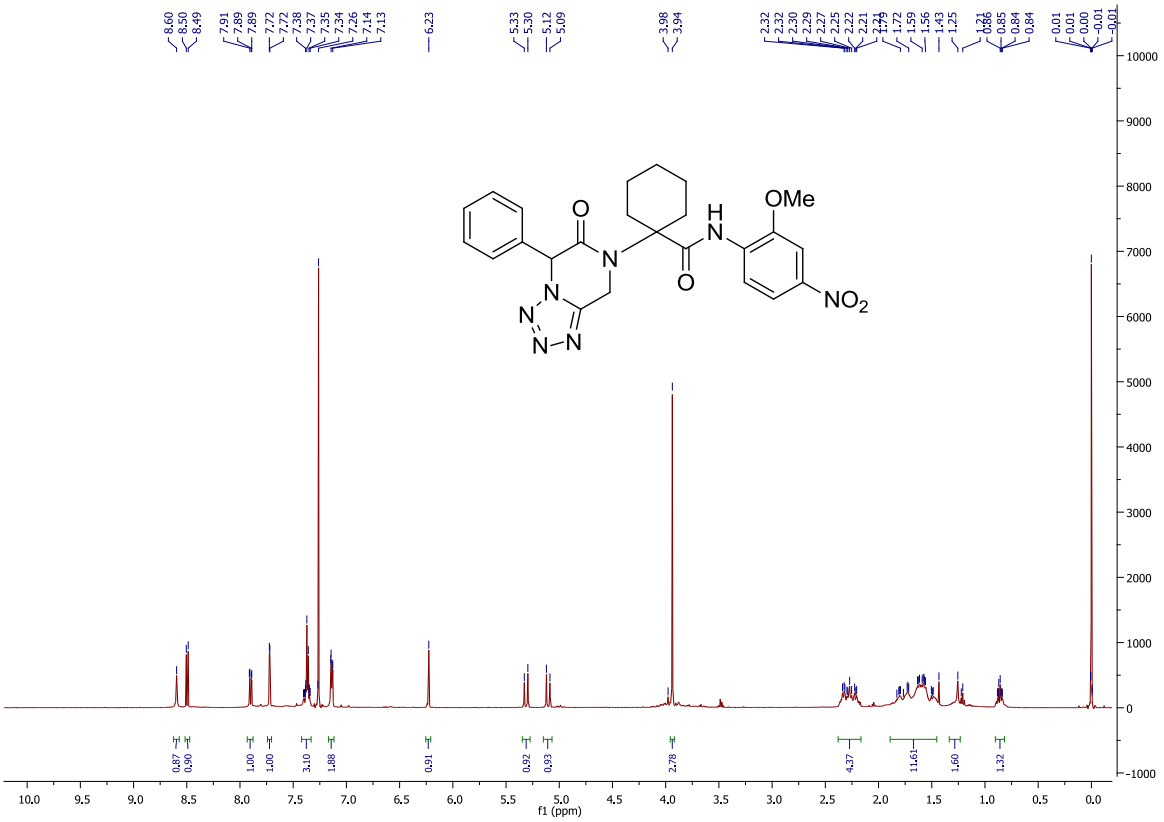

172.20
163.63
157.59
148.68
135.75
129.59
126.81
121.08
113.72
113.64
111.32
106.05
79.28
64.92
59.79
55.03
34.35
32.64
32.12
29.41
28.40
24.67
21.97
f1 (ppm)

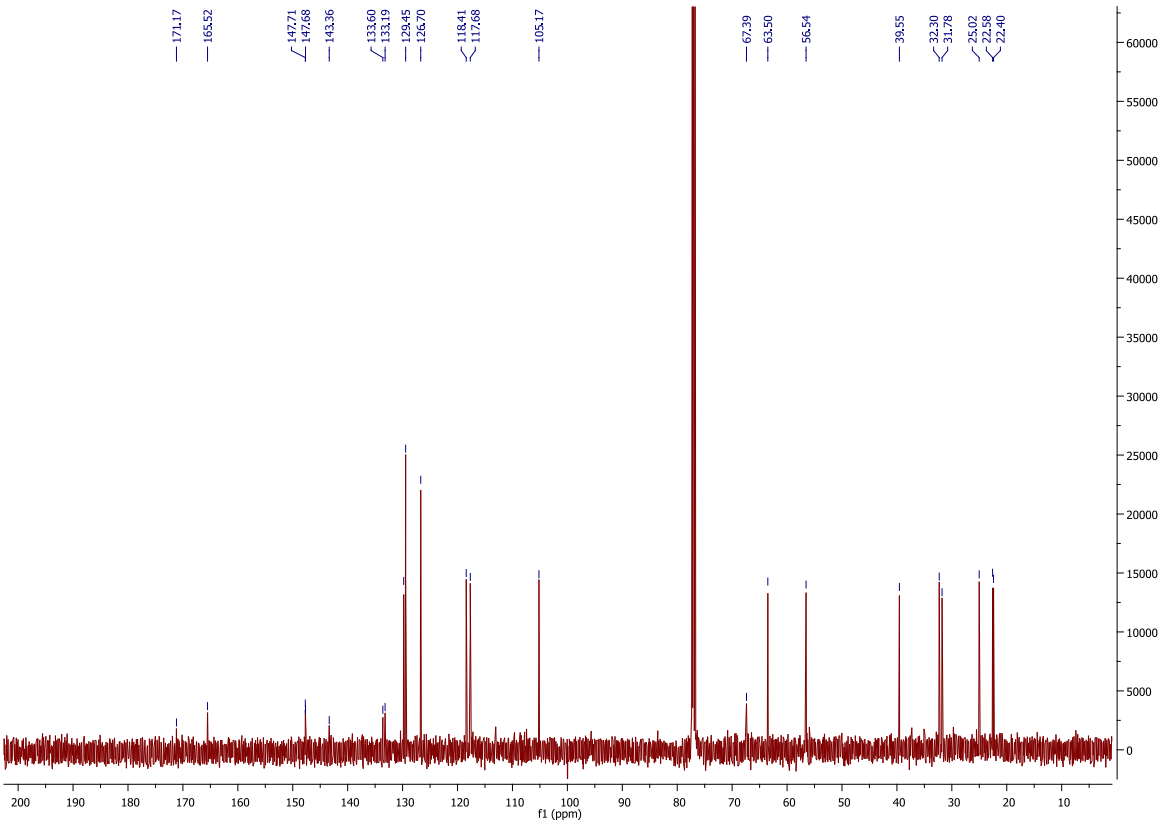
TR256_1_Silica_4.6X250_MeOH_5-30%_6

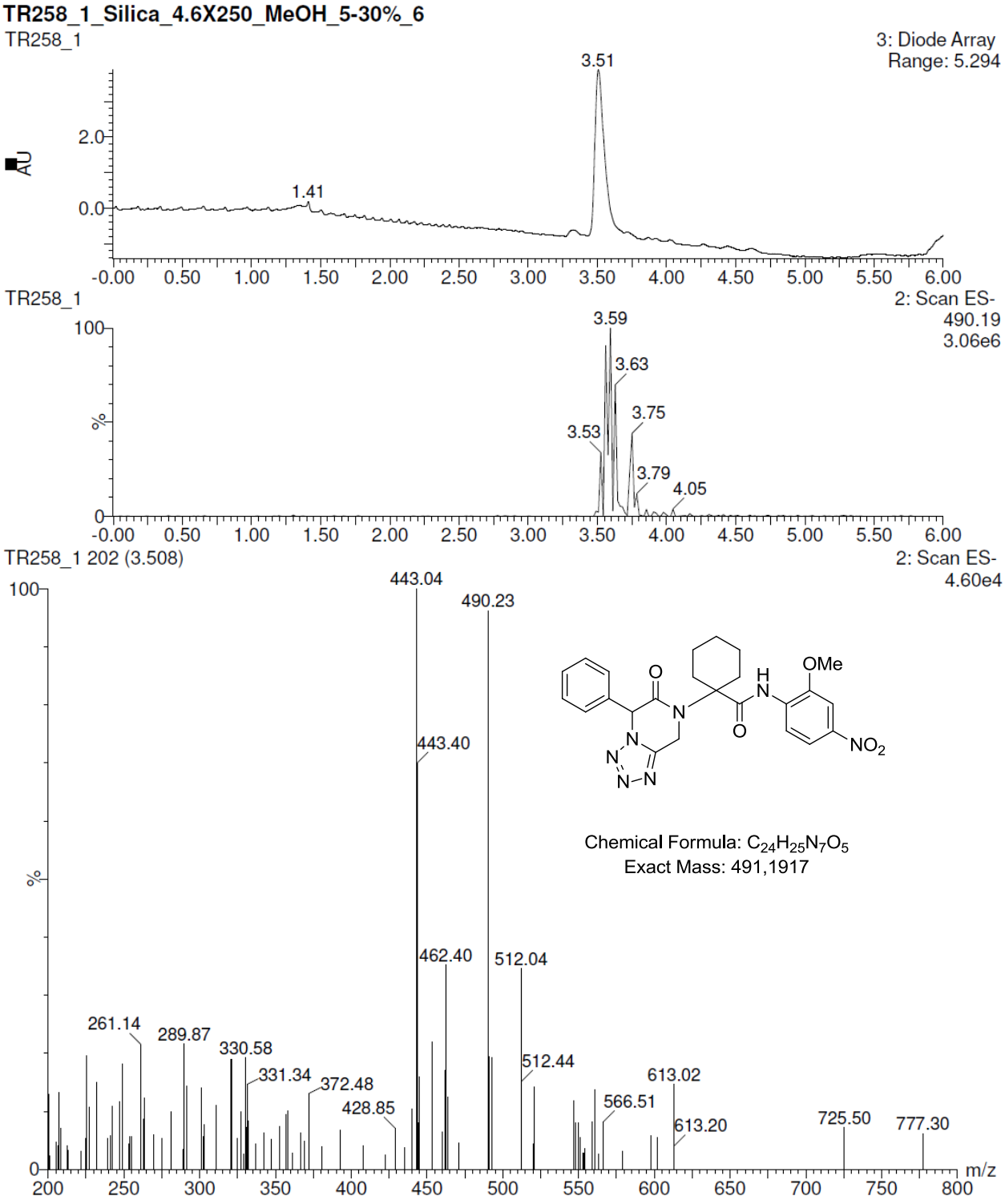







8.60
8.50
8.49
7.91
7.89
7.89
7.89
7.72
7.72
7.38
7.37
7.35
7.34
7.26
7.14
7.13
6.23
5.33
5.30
5.12
5.09
3.98
3.94
2.32
2.32
2.30
2.29
2.27
2.25
2.22
2.21
1.72
1.59
1.56
1.43
1.25
0.86
0.85
0.84
0.84
0.01
0.01
0.00
-0.01
-0.01
O
N
N
N
N
H
N
O
OMe
NO2
0.87
0.90
1.00
1.00
3.10
1.88
0.91
0.92
0.93
2.78
4.37
11.61
1.60
1.32
f1 (ppm)


171.17
165.52
147.71
147.68
143.36
133.60
133.19
129.45
126.70
118.41
117.68
105.17
67.39
63.50
56.54
39.55
32.30
31.78
25.02
22.58
22.40
f1 (ppm)


TR258_1_Silica_4.6X250_MeOH_5-30%_6
TR258_1
3: Diode Array
Range: 5.294
3.51
1.41
AU
2.0
0.0
-0.00 0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00
TR258_1
2: Scan ES-
490.19
3.06e6
100
%
0
3.59
3.63
3.75
3.53
3.79
4.05
-0.00 0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00
TR258_1 202 (3.508)
2: Scan ES-
4.60e4
100
%
0
443.04
490.23
443.40
462.40
512.04
512.44
261.14
289.87
330.58
331.34
372.48
428.85
566.51
613.02
613.20
725.50
777.30
200 250 300 350 400 450 500 550 600 650 700 750 800
m/z
O
N
H
N
OMe
O
N
N
N
N
NO2
Chemical Formula: C24H25N7O5
Exact Mass: 491,1917

Computational Library

A virtual library of 100,000 randomly generated compounds were made for each library using previously described methods (Koes, D. et al. *PLoS One* **2012**, *7*, e32839.). 1000 compounds of each reaction were randomly selected and physiochemical properties relating to drug likeness were analyzed via ChemAxon's Instant JChem Software (Instant JChem 5.9.2, 2012, ChemAxon http://www.chemaxon.com). Principal moment of inertia was calculated using Schrodinger's Maestro V 9.3(**Suite 2012**: Maestro, version 9.3, Schrödinger, LLC, New York, NY, 2012.)

PCA Data:

Importance of components:

	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8	PC9	PC10
Standard deviation	3.774	2.7358	1.69848	1.43924	1.27598	1.0874	1.00623	0.99	0.89896	0.81885
Proportion of Variance	0.407	0.2139	0.08242	0.05918	0.04652	0.03378	0.02893	0.028	0.02309	0.01916
Cumulative Proportion	0.407	0.6208	0.70323	0.76241	0.80893	0.84271	0.87164	0.8996	0.92273	0.94189

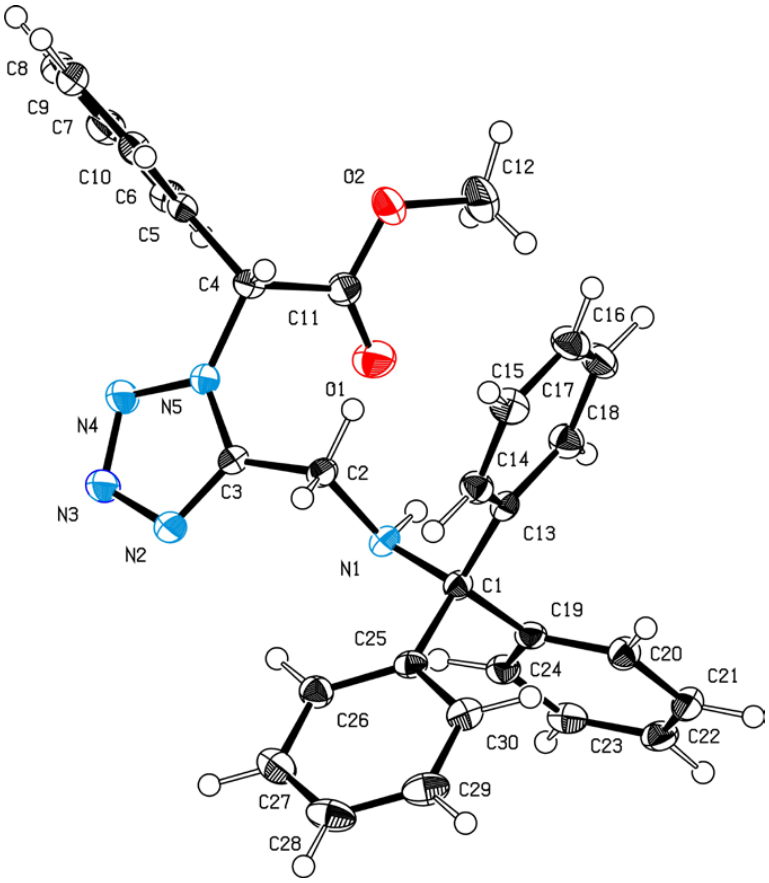
Rotation:

	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8	PC9	PC10
Mass	0.258705	0.014708	-0.077005	0.023445	-0.034303	0.020495	-0.007753	0.001122	0.004544	-0.015128
donorcount	0.152854	-0.222774	0.026563	0.173554	0.088181	-0.066643	-0.069352	0.069098	0.080295	0.435077
donsitecount	0.144728	-0.231833	0.037370	0.168639	0.087503	-0.054775	-0.071318	0.069175	0.071336	0.484416
acceptorcount	0.220940	-0.089600	0.143997	0.103002	-0.024664	0.027887	-0.024726	0.040056	0.000874	-0.371341
accsitecount	0.209907	-0.134012	0.092947	0.109912	0.006882	-0.032200	-0.037850	0.037888	0.037465	-0.472966
logP	0.046896	0.273409	-0.331467	-0.036007	-0.083508	0.054038	0.007544	0.007227	0.015290	0.014617
pH0	0.021696	0.244639	-0.319969	-0.019325	-0.111630	0.033178	-0.042704	0.005074	0.061362	-0.252434
pH7	0.011278	0.288340	-0.294525	-0.064074	-0.082554	0.047474	0.013492	0.016485	0.003620	0.053433
pH14	-0.026198	0.262314	-0.243063	-0.161756	-0.112661	0.135859	-0.047475	0.043304	-0.076876	0.224523
PSA	0.220095	-0.146863	0.110381	0.133655	-0.024219	0.031618	-0.042116	0.047809	0.014107	-0.142322
Atomcount	0.250847	-0.033297	-0.128809	-0.058870	-0.037514	0.045378	-0.027288	0.014084	-0.009316	0.103476
AliphaticAtomCount	0.202419	-0.192790	-0.133416	-0.176500	-0.049634	0.052915	-0.037071	0.034388	-0.017106	0.007181
AromaticAtomCount	0.163352	0.250225	0.050071	0.240062	0.027820	-0.052066	-0.033462	0.041264	0.031952	-0.019939
BondCount	0.253622	-0.017187	-0.115512	-0.061356	-0.028391	0.034839	-0.023869	0.012468	-0.006580	0.101253
AliphaticBond Count	0.222586	-0.151350	-0.114543	-0.185382	-0.031864	0.027118	-0.030067	0.031687	-0.009455	-0.001171
AromaticBond Count	0.160495	0.253328	0.058645	0.244296	0.031566	-0.048922	-0.033617	0.042700	0.030155	-0.002148
RotatableBond Count	0.211434	-0.125220	-0.133187	0.065362	-0.194420	0.158503	-0.041647	0.008710	-0.042614	0.049979
RingCount	0.205950	0.202513	0.099602	-0.073924	0.102245	-0.116749	-0.029500	0.013145	0.031956	0.037975
AliphaticRingCount	0.130283	-0.040139	0.042061	-0.527364	0.172060	-0.199537	0.009889	0.040129	0.036707	0.028700
AromaticRingCount	0.158033	0.257058	0.089085	0.233677	0.013572	-0.013642	-0.027937	0.039359	0.014556	0.026313
HeteroRingCount	0.160335	0.126946	0.332753	-0.123855	-0.010302	0.156726	-0.118133	0.098985	-0.152745	0.042251
HeteroaliphaticRing Count	0.157307	-0.067008	0.072142	-0.359287	0.175691	-0.189145	-0.142307	0.179238	-0.027425	-0.105514
HeteroaromaticRingCount	0.084376	0.193998	0.343983	0.092701	-0.128791	0.310169	-0.0446343	0.002438	-0.161678	0.119820
RingAtomCount	0.215114	0.187560	0.040753	-0.017348	0.149256	-0.131513	-0.028691	0.015648	0.052886	0.034913
RingBondCount	0.212434	0.194588	0.056875	-0.030471	0.145560	-0.128706	-0.026341	0.012754	0.049970	0.030609

ChainAtomCount	0.187737	-0.192686	-0.165671	0.066447	-0.214460	0.169376	-0.044828	0.016533	-0.050094	-0.056006
ChainBondCount	0.212262	-0.157556	-0.156116	0.062970	-0.185363	0.139208	-0.034746	0.010183	-0.040253	-0.041406
SmallestRingSize	-0.042525	-0.093518	-0.255180	0.235165	0.443817	0.013961	-0.121878	0.093220	-0.355634	-0.047239
LargestRingSize	0.037893	0.019578	-0.074393	-0.041934	0.532188	0.429119	-0.065082	0.077368	-0.440503	-0.044982
RingCountofSize4	0.015133	-0.001250	0.026083	-0.218592	-0.146152	-0.095385	-0.565537	0.649941	-0.322431	-0.007838
RingCountofSize5	0.092818	0.161856	0.319175	-0.206161	-0.156799	0.229359	-0.093989	0.137379	-0.114021	0.081719
RingCountofSize6	0.192218	0.142342	-0.099602	0.098052	0.226325	-0.343501	-0.044012	0.010367	0.075410	-0.009788
RingCountofSize7	-0.008600	0.018298	-0.009621	-0.118770	0.274441	0.387261	-0.308256	0.549630	0.566695	-0.035844
RingCountofSize8	0.006500	-0.020502	-0.000605	-0.043791	0.179761	0.346878	0.697536	0.415271	0.382244	-0.022576
VDWVol	0.257403	-0.008683	-0.118251	-0.016344	-0.036393	0.033506	-0.019511	0.008745	-0.003306	0.052294

Single Crystal X-Ray Structure Determination of Compounds

Structure determination of compound **1e**



Structure determination of compound **5n**