

Supporting Information for

Total Synthesis of (-)-Tetrazomine. Determination of the Stereochemistry of Tetrazomine and the Synthesis and Biological Activity of Tetrazomine Analogs

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Experimental Section

General. ¹H-NMR and ¹³C-NMR were obtained on either a Varian Gemini (300MHz) or Varian (400MHz) spectrometer. The high resolution polyacrylamide gel was visualized using a Molecular Dynamics Storm 840 phosphoimager.

1-[1-Azido-1-(2-phenyl methoxy)ethyl]-2-methoxy-benzene (6). To a solution of epoxide **5** (22.0 g, 147 mmol) in 1:1 acetone/H₂O (400 mL) was added sodium azide (14.3 g, 221 mmol, 1.5 eq.) and this solution was heated to reflux for 3 h. The acetone was removed via rotary evaporation the aqueous layer was extracted with CH₂Cl₂. The organic phase was dried over MgSO₄ and concentrated to afford a clear oil. This oil was taken up in THF (100 mL) and added via cannula to a suspension of NaH (6.68 g, 153 mmol, 1.05 eq, 55% dispersion in oil) in THF (100 mL) and this solution was allowed to stir at rt for 15 min. To this solution, benzyl bromide (22.6 mL, 190 mmol, 1.3 eq.) was added dropwise and potassium iodide (100mg) was added in one portion and stirred for 2 h. The solution was poured onto ice and extracted with ethyl acetate. The organic layer was washed with brine, dried over MgSO₄, and concentrated. The crude oil was purified by flash chromatography (10% EtOAc/hex) to afford 13.18 g of **6** (94%) as a light yellow oil. ¹H-NMR (300 MHz) (CDCl₃ vs TMS) δ 3.68 (1H, dd, *J* = 9.9, 8.4 Hz); 3.78 (1H, dd, *J* = 9.9, 3.6 Hz); 3.89 (3H, s); 4.66 (1H, 1/2 ABq, *J* = 12.0 Hz); 4.70 (1H, 1/2 ABq, *J* = 12.0 Hz); 5.29 (1H, dd, *J* = 8.7, 3.6 Hz); 6.94 (1H, d, *J* = 7.8 Hz); 7.03 (1H, t, *J* = 6.9 Hz); 7.31-7.42 (7H, m). ¹³C-NMR (75 MHz) (CDCl₃) δ 55.35, 59.51, 72.84, 73.12, 110.43, 120.43, 124.75, 127.17, 127.53, 128.12, 128.30, 129.24, 137.83, 156.26. IR (NaCl, neat) 2937, 2860, 2359, 2097, 1602, 1028 cm⁻¹. HRMS (FAB) calc. for C₁₆H₁₈N₃O₂ (MH⁺) 284.1399; found 284.1398.

1-[1-Amino-1-(2-phenylmethoxy)methyl]-2-methoxy-benzene (7): To an argon degassed solution of **6** (11.78 g, 41.6 mmol) in EtOH (140 mL) was added 5% Pd on carbon (4.42 g, 2.08 mmol, 0.05 eq.). Hydrogen was bubbled through the mixture for 10 min and a hydrogen balloon was attached. The solution was stirred for 3 h at rt. The mixture was purged with argon and the solution was filtered through Celite. The crude oil was purified via flash chromatography (gradient 4 – 6% MeOH/CH₂Cl₂) to afford 9.30 g of **7** (87%) as a clear oil. ¹H-NMR (300 MHz) (CDCl₃ vs TMS) δ 1.87 (2H, s, broad, D₂O exch.); 3.53 (1H, t, *J* = 9.3 Hz); 3.76 (1H, dd, *J* = 9.3, 3.9 Hz); 3.86 (3H, s); 4.63 (3H, m); 6.91 (1H, d, *J* = 8.1Hz); 7.02 (1H, t, *J* = 7.4Hz); 7.26-7.40 (6H, m);

7.49 (1H, dd, $J = 7.4, 1.5$ Hz). ^{13}C -NMR (75 MHz) (CDCl_3) δ 49.81, 55.10, 72.92, 74.85, 110.20, 120.54, 127.20, 127.43, 127.58, 127.98, 128.24, 103.45, 138.38, 156.74. IR (NaCl, neat) 3378, 2857, 2360, 1600, 1049, 1028 cm^{-1} . HRMS (FAB) calc. for $\text{C}_{16}\text{H}_{20}\text{NO}_2$ (MH^+) 258.1494; found 258.1496.

1-[1-Amino-1-(2-phenylmethoxy)methyl]-2-methoxy-3-nitro-benzene (8): A solution of **7** (16.02 g, 62.4 mmol) in CH_2Cl_2 (250 mL) was cooled to -20°C . Potassium nitrate (6.62 g, 65.5 mmol, 1.05 eq.) was added followed by the slow addition of TFAA (44 mL, 312 mmol, 5 eq.). This solution was stirred at -20°C for 48 h. Saturated NaHCO_3 was added slowly to adjust to pH 7. The aqueous layer was extracted with CH_2Cl_2 (3x) and the combined organic layers were dried over MgSO_4 and concentrated. The crude oil was purified via a short column (25% EtOAc/hex). The semi crude product was dissolved in 1:1 THF/EtOH (200 mL) and 2 M LiOH (100 mL) was added. This solution was allowed to stir for 14 h. Acetic acid was slowly added until the pH was 7-8. The solvent was reduced to approx 1/2 original volume via rotary evaporation and the product was partitioned in EtOAc/ H_2O . The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated. Purification via flash chromatography (2.5% MeOH/ CH_2Cl_2) afforded 10.5 g of **8** (56%) as a yellow oil. ^1H -NMR (300 MHz) (CDCl_3 vs TMS) δ 1.78 (2H, s, broad); 3.49 (1H, dd, $J = 8.7, 7.8$ Hz); 3.70 (1H, dd, $J = 8.7, 3.9$ Hz); 3.91 (3H, s); 4.60 (2H, s); 4.68 (1H, dd, $J = 7.9, 3.9$ Hz); 7.25 (1H, t, $J = 8.1$ Hz); 7.33-7.42 (5H, m); 7.77 (1H, dd, $J = 8.1, 1.5$ Hz); 7.83 (1H, dd, $J = 8.1, 1.5$ Hz). ^{13}C -NMR (75 MHz) (CDCl_3) δ 48.75, 62.82, 73.03, 74.67, 123.74, 124.04, 127.44, 127.53, 128.19, 132.42, 137.69, 138.76, 143.38, 150.84. IR (NaCl, neat) 3378, 3312, 2916, 1528, 1355, 1089, 1027 cm^{-1} . HRMS (FAB) calc. for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_4$ (MH^+) 303.1345; found 303.1349.

N-(2,2-diethoxyethyl)-2-methoxy-3-nitro- α -[(phenylmethoxy)methyl]-benzenemethanamine (9). To a solution of **8** (6.00 g, 19.8 mmol) in acetonitrile (50 mL) was added bromoacetaldehyde diethyl acetal (15.0 mL, 99.3 mmol, 5 eq.) and potassium carbonate (10.9g, 79.2 mmol, 4 eq.). The solution was heated to reflux for 5 days. The solvent was removed *in vacuo* and the crude mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated. The crude product was purified via flash chromatography (25% EtOAc/hex) to afford 6.11 g **9** (74%) as a yellow oil. ^1H -NMR (300 MHz) (CDCl_3 vs TMS) δ 1.22 (3H, t, $J = 6.9$ Hz); 1.26 (3H, t, $J = 6.9$ Hz); 2.27 (1H, s, broad, D_2O exch.); 2.55 (1H, dd, $J = 11.7, 4.8$ Hz); 2.67 (1H, dd, $J = 11.7, 6.0$ Hz); 3.47 (1H, dd, $J = 9.6, 8.7$ Hz); 3.56 (2H, m); 3.64-3.77 (3H, m); 3.90 (3H, s); 4.44 (1H, dd, $J = 8.4, 4.2$ Hz); 4.58 (2H, s); 4.62 (1H, dd, $J = 6.3, 4.8$ Hz); 7.25 (1H, t, $J = 7.8$ Hz); 7.35 (5H, m); 7.77 (1H, dd, $J = 7.8, 1.2$ Hz); 7.87 (1H, dd, $J = 7.8, 1.2$ Hz). ^{13}C -NMR (75 MHz) (CDCl_3) δ 15.39, 49.89, 55.60, 62.18, 62.23, 63.07, 73.12, 73.76, 101.91, 124.02, 124.32, 127.54, 127.65, 128.31, 133.20, 137.06, 137.83, 143.72, 151.79. IR (NaCl, neat) 3340, 2975, 2688, 1602, 1530, 1356, 1064 cm^{-1} . HRMS (FAB) calc. for $\text{C}_{22}\text{H}_{31}\text{N}_2\text{O}_6$ (MH^+) 419.2182; found 419.2184.

{[[2-Benzyloxy-1-(2-methoxy-3-nitro-phenyl)-ethyl]-(2,2-diethoxyethyl)-carbamoyl]-methyl}-methyl-carbamic acid 9H-fluoren-9-ylmethyl ester (10). To a solution of N-Fmoc-sarcosine (6.70g, 21.4 mmol, 1.25 eq.) in CH_2Cl_2 (100 mL) was added oxalyl chloride (2.0 mL, 23.0 mmol, 1.35 eq.) and DMF (159 μL , 2.1 mmol, 0.12 eq.) and was stirred at rt for 1 h. Hexanes (100 mL) were added and the solution was filtered through a cotton plug and concentrated. A solution of amine **9** (7.15 g, 17.1 mmol), pyridine (4.15 mL, 51.3 mmol, 3.0 eq.) and DMAP (209 mg, 1.71 mmol, 0.10 eq.) in CH_2Cl_2 (100 mL) at 0°C was added to the acid chloride and the solution was allowed to stir at 0°C for 45 min. Dilute HCl(aq.) was added and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with sat NaHCO_3 and water. The organic layer was dried over MgSO_4 and concentrated. The

crude product was purified via flash chromatography (30-40% EtOAc/hex) to afford 10.0 g **10** (82%) as a light yellow foam. ¹H-NMR (300 MHz) (d₆-DMSO, 120°C) δ 1.02 (3H, t, *J* = 7.2 Hz); 1.09 (3H, t, *J* = 6.9 Hz); 2.82 (3H, s); 2.87 (1H, s); 3.37-3.60 (6H, m); 3.82 (3H, s); 4.05 (2H, ddd, *J* = 10.2, 6.9, 6.9 Hz); 4.21-4.34 (5H, m); 4.54 (2H, s); 5.62 (1H, m); 7.24-7.32 (8H, m); 7.40 (2H, t, *J* = 7.5 Hz); 7.63 (2H, dd, *J* = 7.5, 2.7 Hz); 7.84 (4H, m). ¹³C-NMR (75 MHz) (d₆-DMSO, 120°C) δ 14.23, 14.28, 34.45, 46.51, 47.57, 50.08, 53.14, 61.71, 61.91, 62.11, 66.32, 68.56, 71.94, 100.42, 119.17, 123.12, 123.90, 124.25, 126.28, 126.70, 126.77, 126.81, 127.42, 133.24, 137.51, 140.21, 143.39, 150.82, 155.45, 168.81. IR (NaCl, neat) 2959, 1735, 1716, 1697, 1153, 1079 cm⁻¹. HRMS (FAB) calc. for C₄₀H₄₆N₃O₉ (MH⁺) 712.3234; found 712.3233.

1,2-dihydro-8-methoxy-2-[(methylamino)acetyl]-1-[(phenylmethoxy)methyl]-7-isoquinoliny)-(9H-fluoren-9-ylmethoxycarbonyl)-carbamic acid methyl ester. (11): To an argon degassed solution of **10** (6.45 g, 9.07 mmol) in 1:1 THF/EtOH (140 mL) in a pressure vessel was added PtO₂ (102 mg, 0.45 mmol, 0.05 eq.) and the vessel was sealed and pressurized with 80 psi H₂. The solution was stirred at rt for 16 h. The vessel was depressurized and the solution was purged with Ar. The catalyst was removed by filtering through celite and the solution was concentrated. The crude product was dissolved in dioxane (75 mL) to this solution was added 6N HCl (4.48 mL, 26.9 mmol, 3 eq.) and the solution was stirred in a oil bath at 90°C for 15 min. The solution was allowed to cool to room temp. Excess sat. NaHCO₃ was added and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated. The crude product was redissolved in CH₂Cl₂ (50 mL) and cooled to 4°C. Methyl chlorofomate (2.07 mL, 26.9 mmol, 3 eq.) was added followed by pyridine (724 μL, 9.0 mmol, 1 eq.) and this solution was stirred at 4°C for 18 hr. Saturated NaHCO₃ was added and the mixture was extracted with CH₂Cl₂ (3x). The combined organic layers were dried over MgSO₄ and concentrated. The crude product was purified via flash chromatography (45% EtOAc/hex) to afford 5.22 g **11** (89%) as a light yellow foam. ¹H-NMR (300 MHz) (d₆-DMSO, 120°C) δ 2.83 (3H, s); 3.38 (1H, dd, *J* = 10.2, 3.4 Hz); 3.58 (1H, dd, *J* = 10.5, 8.7 Hz); 3.71 (3H, s); 3.78 (3H, s); 4.29 (5H, m); 4.37 (1H, 1/2 ABq *J* = 12.3 Hz); 4.48 (1H, 1/2 ABq, 12.3 Hz); 6.03 (1H, d, *J* = 7.5 Hz); 6.87 (1H, s, broad); 6.94 (1H, d, *J* = 7.5 Hz); 7.20-7.38 (10 H, m); 7.58 (3H, m); 7.80 (2H, dd, *J* = 7.7, 2.9 Hz); 8.23 (1H, s, broad). ¹³C-NMR (d₆-DMSO, 120°C) δ 34.50, 46.42, 49.69, 51.07, 60.32, 66.32, 68.84, 71.79, 109.54, 119.15, 119.76, 122.20, 122.33, 122.58, 124.10, 126.24, 126.58, 126.70, 126.80, 127.35, 127.51, 129.68, 137.55, 140.17, 143.31, 147.26, 153.80, 155.31, 166.25 Note: one carbon resonance not observed. HRMS (FAB) calcd for C₃₈H₃₈N₃O₇ (MH⁺) 648.2710; found 648.2698.

1,2-dihydro-8-methoxy-2-[(methylamino)acetyl]-1-[(phenylmethoxy)methyl]-7-isoquinoliny)-carbamic acid methyl ester. (12): To a solution of **11** (5.06 g, 7.80 mmol) in acetonitrile (50 mL) was added pyrrolidine (5 mL) and this was allowed to stir at rt for 1 h. The solution was concentrated and the crude product was purified via flash chromatography (3-7.5 % MeOH/CH₂Cl₂) to afford 3.12 g **12** (94%) as a white foam. ¹H-NMR (300 MHz) (d₆-DMSO, 120°C) δ 2.37 (3H, s); 3.00 (1H, s, broad, D₂O exchangeable); 3.39 (1H, dd, *J* = 10.5, 4.5 Hz); 3.61 (3H, m); 3.68 (3H, s); 3.71 (3H, s); 4.44 (1H, 1/2 ABq, *J* = 12.0 Hz); 4.51 (1H, ABq, *J* = 12.0 Hz); 5.99 (1H, d, *J* = 7.8 Hz); 6.05 (1H, s, broad); 6.89 (1H, d, *J* = 8.1 Hz); 6.98 (1H, d, *J* = 7.2 Hz); 7.24-7.35 (5H, m); 7.54 (1H, d, *J* = 8.1 Hz); 8.22 (1H, s). ¹³C-NMR (75 MHz) (d₆-DMSO, 120°C) δ 35.11, 51.04, 51.82, 60.33, 68.85, 71.74, 108.96, 119.44, 119.58, 122.23, 122.50, 122.94, 126.09, 126.56, 126.62, 127.36, 127.70, 129.49, 147.30, 153.79 (Note: one carbon resonance not observed) IR (NaCl, neat) 3421, 3328, 2945, 2860, 1729, 1671, 1628, 1526, 1229, 1088 cm⁻¹. HRMS (FAB) calc. for C₂₃H₂₈N₃O₅ (MH⁺) 426.2029; found 426.2025.

[2-[8-methoxy-7-[(methoxycarbonyl)amino]-1-[(phenylmethoxy)methyl]2(1H)-isoquinolinyl]-2-oxoethyl]methyl-carbamic acid 9H-fuoren-9-ylmethyl ester. (13): To a solution of **12** (1.50 g, 3.53 mmol) in THF (40 mL) was added iodoacetonitrile (281 μ L, 3.88 mmol, 1.1 eq.) and diisopropylethyl amine (675 μ L, 3.88 mmol, 1.1 eq.). This solution was stirred at rt for 18 h. The solution was diluted with EtOAc and washed with sat. NaHCO_3 and brine then dried over MgSO_4 and concentrated. The crude product was purified via flash chromatography (50-60 % EtOAc/hex) to afford 1.64 g **13** (99%) as a white foam. $^1\text{H-NMR}$ (300MHz) (d_6 -DMSO, 120°C) δ 2.40 (3H, s); 3.40 (2H, m); 3.59 (1H, t, $J = 10.2$ Hz); 3.71 (3H, s); 3.74 (3H, s); 3.82 (3H, s); 4.45 (1H, 1/2 ABq, $J = 12.0$ Hz); 4.52 (1H, 1/2 ABq, $J = 12.0$ Hz); 6.00 (1H, d, $J = 7.5$ Hz); 6.12 (1H, s, broad); 6.91 (1H, d, $J = 8.4$ Hz); 7.01 (1H, d, $J = 7.5$ Hz); 7.25-7.25 (5H, m); 7.56 (1H, d, $J = 8.4$ Hz); 8.22 (1H, s). $^{13}\text{C-NMR}$ (75 MHz) (d_6 -DMSO, 120°C) δ 40.92, 43.68, 51.06, 56.71, 60.35, 68.77, 71.77, 109.24, 114.86, 119.69, 122.22, 122.50, 122.91, 126.63, 126.68, 127.40, 127.55, 129.60, 129.94, 137.57, 147.25, 153.79, 166.76. IR (NaCl, neat) 2925, 1733, 1669, 1524, 1093, 1047 cm^{-1} . HRMS (FAB) calc. for $\text{C}_{25}\text{H}_{29}\text{N}_4\text{O}_5$ (MH^+) 465.2138; found 265.2127.

[1,3,4,6-tetrahydro-7-methoxy-2-methyl-4-oxo-6[(phenylmethoxy)methyl]-2-Hpyrazino[1,2-b]isoquinolin-8-yl]carbamic acid methyl ester (14): To a solution of **13** (2.65 g, 5.71 mmol) in dichloroethane (220 mL) was added trifluoroacetic anhydride (806 μ L, 5.71 mmol, 1.0 eq.), trifluoroacetic acid (660 μ L, 8.57 mmol, 1.5 eq.), and Silver(I)trifluoroacetate (1.32 g, 5.71 mmol, 1.05 eq.) The mixture was heated to reflux for 45min. The mixture was cooled to rt. Excess sat. NaHCO_3 was added and the mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over MgSO_4 , filtered and concentrated. The crude product was purified via flash chromatography (3% MeOH/ CH_2Cl_2) to afford 2.32 g **14** (93%) as a yellow foam. $^1\text{H-NMR}$ (300 MHz) (CDCl_3 vs TMS) δ 2.42 (3H, s); 3.38 (2H, m); 3.50 (2H, m); 3.63 (2H, dd, $J = 10.5, 8.4$ Hz); 3.83 (3H, s); 3.85 (3H, s); 4.45, (1H, 1/2 ABq, $J = 12.3\text{Hz}$), 4.67 (1H, 1/2 ABq, $J = 12.3\text{Hz}$); 5.70 (1H, s); 6.35 (1H, dd, $J = 8.1, 3.4$ Hz); 6.86 (1H, d, $J = 8.4$ Hz); 7.07(1H, s); 7.30(5H, m), 7.98 (1H, d, $J = 8.1\text{Hz}$). $^{13}\text{C-NMR}$ (75 MHz) (CDCl_3) δ 44.16, 46.77, 52.34, 55.60, 59.58, 61.45, 69.83, 72.59, 105.68, 118.67, 120.98, 121.62, 127.01, 127.30, 127.44, 128.10, 129.96, 130.91, 138.02, 144.77, 153.01, 165.81. IR(NaCl, neat) 3420, 3318, 2926, 2854, 1731, 1682, 1645, 1526, 1234, 1204, 1096 cm^{-1} . HRMS (FAB) calcd for $\text{C}_{24}\text{H}_{28}\text{N}_3\text{O}_5$ 438.2029; found 438.2024.

(5 α ,8 α ,10 α , 11 α)-5,7,8,9,10,11--hexahydro-5-(benzyloxymethyl)-3-amino(carbamic acid methyl ester)-4-methoxy-13-methyl-7-oxo, 8,11-Iminoazepino[1,2-b]isoquinoline-10-carboxylic acid tert-butyl ester (17).

(5 β ,8 α ,10 α , 11 α) 5,7,8,9,10,11--hexahydro-5-(benzyloxymethyl)-3-amino(carbamic acid methyl ester)-4-methoxy-13-methyl-7-oxo, 8,11-Iminoazepino[1,2-b]isoquinoline-10-carboxylic acid tert-butyl ester (18). To a solution of **14** (2.31 g, 5.3 mmol) in CHCl_3 (75 mL) was added NBS (943 mg, 5.3 mmol, 1.0 eq.) and the solution was heated to reflux for 45 min (a dark green color formed). The solution was cooled to 0°C and t-butyl acrylate (15.5 mL, 106 mmol, 20 eq.) was added followed by the dropwise addition (over 10 min.) of a solution of Et_3N (5.9 mL, 42 mmol, 8 eq.) in CH_2Cl_2 (20 mL) (The solution turned dark blue). This solution was stirred at rt for 3h. The solvent was then removed under reduced pressure. The crude material was taken up in CH_2Cl_2 and washed with sat. NaHCO_3 . The organic layer was dried over MgSO_4 and the solvent was removed. The crude product was purified via flash chromatography (50-60% EtOAc/hex) to afford 1.04 g **17** (35%) as a white foam and recovered 211 mg **14** (9%). The minor diastereomer had to be repurified via flash chromatography (gradient 1-1.5% MeOH/ CH_2Cl_2) to afford 200 mg **18** (7%).

17: ¹H-NMR (300 MHz) (CDCl₃ vs. TMS) δ 1.51 (9H, s); 2.21 (1H, dd, *J* = 13.2, 9.9 Hz); 2.55 (3H, s); 2.60 (1H, m); 2.83 (1H, dd, *J* = 9.9, 5.1 Hz); 3.52 (1H, dd, *J* = 10.8, 4.2 Hz); 3.65 (1H, dd, *J* = 10.8, 7.5 Hz); 3.78 (1H, m); 3.80 (6H, s); 4.19 (1H, s); 4.42 (1H, 1/2 ABq, *J* = 12.0 Hz); 4.58 (1H, 1/2 ABq, *J* = 12.0 Hz); 5.69 (1H, s); 6.28 (1H, dd, *J* = 7.2, 4.2 Hz); 6.86 (1H, d, *J* = 8.4 Hz); 7.07 (1H, s); 7.21-7.33 (5H, m); 7.98 (1H, d, *J* = 8.4 Hz). ¹³C-NMR (75 MHz) (CDCl₃) δ 28.05, 32.48, 34.92, 47.48, 51.26, 52.39, 61.41, 64.76, 65.92, 70.40, 72.39, 81.16, 103.48, 118.83, 120.64, 121.34, 127.21, 127.25, 127.67, 128.05, 129.80, 135.34, 137.83, 144.93, 153.63, 170.50, 171.98. HRMS (FAB) calcd. for C₃₁H₃₈N₃O₇ (M+H) 564.2710, found 564.2693.

18: ¹H-NMR (300 MHz) (CDCl₃ vs. TMS) δ 1.52 (9H, s); 2.33 (1H, dd, *J* = 12.9, 9.9 Hz); 2.48 (3H, s); 2.54 (1H, m); 3.09 (1H, dd, *J* = 9.9, 6.3 Hz); 3.44 (1H, dd, *J* = 10.5, 3.9 Hz); 3.62 (1H, dd, *J* = 10.5, 8.4 Hz); 3.68 (1H, d, *J* = 6.6 Hz); 3.84 (3H, s); 3.87 (3H, s); 3.98 (1H, s); 4.42 (1H, 1/2 ABq, *J* = 11.7 Hz); 4.65 (1H, 1/2 ABq, *J* = 11.7 Hz); 5.72 (1H, s); 6.26 (1H, dd, *J* = 8.4, 3.6 Hz); 6.88 (1H, d, *J* = 8.4 Hz); 7.06 (1H, s); 7.31 (5H, m); 7.98 (1H, d, *J* = 8.4 Hz). ¹³C-NMR (75 MHz) (CDCl₃) δ 28.07, 34.55, 35.91, 45.86, 48.21, 52.46, 61.58, 65.31, 67.13, 70.31, 73.00, 81.20, 105.24, 118.91, 121.53, 121.97, 126.57, 127.67, 127.96, 128.31, 130.20, 133.75, 137.77, 144.78, 153.75, 169.10, 172.42. IR (NaCl, neat) 2949, 1724, 1687, 1525, 1230, 1205, 1096 cm⁻¹. HRMS (FAB) calcd. for C₃₁H₃₈N₃O₇ (M+H) 564.2710, found 564.2699.

(5α,8α,10α,11α,11a)-5,7,8,9,10,11,11a,12-octahydro-5-(hydroxymethyl)-3-amino(carbamic acid methyl ester)-4-methoxy-13-methyl-7-oxo 8,11-Iminoazepino[1,2-b]isoquinoline-10-carboxylic acid *tert*-butyl ester (19). To an argon degassed solution of **17** (930 mg, 1.65 mmol) in absolute EtOH (40 mL) in a pressure vessel, Raney Nickel (W-2, Aldrich) (4 mL) was added and the vessel was pressurized to 100 psi with H₂. This mixture was stirred for 24 h. The pressure was released and the mixture was degassed with Ar. The catalyst was removed by filtering through celite. The solvent was removed *in vacuo* and the crude product was purified via flash chromatography (5% MeOH/CH₂Cl₂) to afford 710 mg **19** (90%) as a white foam. ¹H-NMR (300 MHz) (CDCl₃ vs TMS) δ 1.46 (9H, s); 2.12 (1H, dd, *J* = 13.2, 9.6 Hz); 2.51 (3H, s); 2.53 (1H, m); 2.83 (2H, m); 3.04 (1H, dd, *J* = 9.0, 6.6 Hz); 3.15 (1H, s, broad, D₂O exchangeable); 3.60 (2H, m); 3.72 (1H, m); 3.77 (6H, s); 3.90 (1H, dd, *J* = 7.8, 3.7 Hz); 4.40 (1H, m); 5.77 (1H, dd, *J* = 6.9, 3.3 Hz); 6.91 (1H, d, *J* = 8.4 Hz); 7.07 (1H, s); 7.90 (1H, d, *J* = 8.4 Hz). ¹³C-NMR (75 MHz) (CDCl₃) δ 27.79, 29.03, 31.90, 36.72, 42.07, 49.28, 49.55, 52.16, 60.67, 63.83, 66.06, 66.17, 80.91, 118.85, 124.52, 125.63, 127.90, 129.36, 145.18, 153.70, 171.21, 172.86. IR (NaCl, neat) 3431, 2948, 1727, 1648, 1066 cm⁻¹. HRMS (FAB) calcd. for C₂₄H₃₄N₃O₇ (MH⁺) 476.2397; found 476.2388.

(5α,8α,10α,11α,11a)-5,7,8,9,10,11,11a,12-octahydro-5-formyl-3-amino(carbamic acid methyl ester)-4-methoxy-13-methyl-7-oxo, 8,11-Iminoazepino[1,2-b]isoquinoline-10-carboxylic acid *tert*-butyl ester (20). To a solution of DMSO (424 μL, 5.98 mmol, 4 eq.) in CH₂Cl₂ (35 mL) at -78°C was added oxalyl chloride (260 μL, 2.98 mmol, 2 eq.). The solution was stirred at -78°C for 10 min. To this solution **19** (710 mg, 1.49 mmol, 1 eq.) in 20 mL CH₂Cl₂ cooled to -78°C was added via a cannula. The resulting solution was stirred at -78°C for 1 h. Triethylamine (2.07 mL, 14.9 mmol, 10 eq.) was added slowly and the solution was allowed to warm to rt. The solvent was removed *in vacuo* and the crude material was partitioned between NaHCO₃ (aq) and CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂ (3x). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified by flash chromatography (70% EtOAc/hexanes) to afford 694 mg **20** (98%) as a white foam. ¹H-NMR (300 MHz) (CDCl₃ vs TMS) δ 1.48 (9H, s); 2.18 (1H, dd, *J* = 13.2, 9.9 Hz); 2.57 (1H, m); 2.71 (3H, s); 2.74 (1H, m); 2.87 (1H, m); 3.13 (1H, dd, *J* = 9.0, 6.3 Hz); 3.65 (2H, m); 3.81 (3H, s); 3.85 (3H, s); 4.12 (1H, m); 6.15 (1H, s); 6.98 (1H, d, *J* = 8.4 Hz); 7.10 (1H, s); 8.00 (1H, d, *J* = 8.4 Hz); 9.67 (1H, s). ¹³C-NMR (75 MHz) (CDCl₃) δ 27.93, 29.28, 32.93, 36.10, 42.52, 50.85,

52.39, 57.48, 60.17, 65.35, 65.58, 81.04, 119.77, 120.20, 125.32, 127.73, 129.84, 145.20, 153.58, 172.01, 172.85, 194.57. IR (NaCl, neat) 2932, 1737, 1703, 1472, 1031 cm^{-1} . HRMS (FAB) calcd. for $\text{C}_{24}\text{H}_{32}\text{N}_3\text{O}_7$ (MH^+) 474.2240; found 474.2241.

(5 α ,8 β ,10 β ,11 β ,11a β)-5,7,8,9,10,11,11a,12-octahydro-5-formyl-3-amino(carbamic acid methyl ester)-4-methoxy-13-methyl-7-oxo, 8,11-Iminoazepino[1,2-b]isoquinoline-10-carboxylic acid *tert*-butyl ester (21). To a solution of **20** (290 mg, 0.613 mmol) in THF (20 mL) was added DBU (84 μL , 0.613 mmol, 1 eq.) and the solution was allowed to stir at room temperature for 24 h. Sat. NaHCO_3 was added and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified via flash chromatography (gradient 80/20/0 - 90/10/0 - 94/0/4 EtOAc/hexanes/MeOH) to afford 160 mg **21** (55%) as a white foam along with starting aldehyde 109 mg **20** (38%). ^1H -NMR (300 MHz) (CDCl_3 vs TMS) δ 1.49 (9H, s); 2.40 (1H, dd, J = 12.9, 9.9 Hz); 2.47 (3H, s); 2.64 (2H, m); 2.74 (1H, m); 3.39 (1H, t, J = 8.1 Hz); 3.66 (3H, m); 3.81 (3H, s); 3.83 (3H, s); 5.99 (1H, s); 6.98 (1H, d, J = 8.4 Hz); 7.09 (1H, s); 7.99 (1H, d, J = 8.4 Hz); 9.46 (1H, s). ^{13}C -NMR (75 MHz) (CDCl_3) δ 27.97, 31.35, 33.43, 37.93, 42.25, 52.47, 55.60, 58.30, 61.06, 66.66, 66.72, 81.00, 119.65, 120.06, 124.49, 130.36, 131.53, 145.96, 153.72, 170.30, 173.22, 192.70. IR (NaCl, neat) 2977, 2948, 1729, 1659, 1525, 1078 cm^{-1} . HRMS (FAB) calcd. for $\text{C}_{24}\text{H}_{32}\text{N}_3\text{O}_7$ (MH^+) 474.2240; found 474.2237.

(5 α ,8 β ,10 β ,11 β ,11a β)-5,7,8,9,10,11,11a,12-octahydro-5-(hydroxymethyl)-3-amino(carbamic acid methyl ester)-4-methoxy-13-methyl-7-oxo, 8,11-Iminoazepino[1,2-b]isoquinoline-10-carboxylic acid, *tert*-butyl ester (22). To a solution of **21** (174 mg, 0.368 mmol) in absolute EtOH (15 mL) at 0°C was added sodium borohydride (56mg, 1.47mmol, 4 eq.). This mixture was stirred at 0°C for 1 h. Aqueous 1 M HCl was added slowly until there was no more H_2 evolution. Excess sat. NaHCO_3 was added and the ethanol was removed by rotary evaporation. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated. The crude product was purified via flash chromatography (5% MeOH/ CH_2Cl_2) to afford 156 mg **22** (89%) as a white solid. TLC ^1H -NMR (300 MHz) (CDCl_3 vs TMS) δ 1.44 (9H, s); 2.25 (1H, dd, J = 12.9, 9.3 Hz); 2.37 (3H, s); 2.55 (2H, m); 2.87 (1H, t, J = 12.9 Hz); 3.12 (1H, dd, J = 9.0, 6.9 Hz); 3.20 (1H, t, J = 5.7 Hz); 3.50 (3H, m, 1 H is D_2O exchangeable); 3.70 (3H, s); 3.73 (3H, s); 3.79 (2H, m); 5.45 (1H, dd, J = 5.1, 3.6 Hz); 6.88 (1H, d, J = 7.8 Hz); 7.15 (1H, s); 7.84 (1H, d, J = 7.8 Hz). ^{13}C -NMR (75 MHz) (CDCl_3) δ 27.92, 31.63, 33.64, 37.93, 42.20, 52.08, 52.31, 56.68, 61.10, 66.90, 67.39, 67.45, 81.00, 118.77, 123.68, 126.39, 130.14, 131.65, 145.57, 153.79, 172.27, 173.05. IR (NaCl, neat) 3388, 2977, 2948, 1725, 1638, 1527, 1064 cm^{-1} . HRMS (FAB) calcd. for $\text{C}_{24}\text{H}_{34}\text{N}_3\text{O}_7$ (MH^+) 476.2397; found 476.2400.

(5 α ,8 β ,10 β ,11 β ,11a β)-5,7,8,9,10,11,11a,12-octahydro-5-(hydroxymethyl)-3-amino(carbamic acid methyl ester)-7-cyano--10-(hydroxy methyl)-4-methoxy-13-methyl-8,11-Iminoazepino[1,2-b]isoquinoline (23). To a solution of lithium aluminum hydride (1M soln. in hexanes) (160 μL , 0.16mmol, 8 eq.) in THF (750 μL) at 0°C , ethyl acetate (7.8 μL , 0.08 mmol, 4 eq.) was added. This solution was allowed to stir at 0°C for 2 hours. To this solution, a solution of **22** (9.5 mg, 0.020 mmol) in THF (1 mL) was added dropwise. This solution was allowed to stir at 0°C for 45 min. Acetic acid (34 μL , 0.60 mmol, 30 eq.) was added slowly followed by an aqueous solution of KCN (4.5 M, 27 μL , 6 eq.). The resulting solution was stirred at room temperature for 16 hours. Excess sat. NaHCO_3 was added and the solution was extracted with 1:1 EtOAc/THF (3 x 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 . The solvent was removed *in vacuo* and the crude material was purified by flash chromatography (2.5-5% MeOH/ CH_2Cl_2) to yield 5.7mg **23** (69%) as an oil. ^1H -NMR (400 MHz) (CDCl_3) δ 1.93 (3H, m); 2.19 (1H, s, broad); 2.46 (1H, dd, J = 11.1, 1.8 Hz); 2.51-2.56 (2H, m);

2.63 (3H, s); 3.01 (1H, s); 3.13 (1H, d, $J = 8.7$ Hz); 3.50-3.54 (2H, m); 3.60 (1H, dd, $J = 7.5, 5.4$ Hz); 3.66-3.73 (2H, m); 3.78 (3H, s); 3.79 (3H, s); 3.93 (1H, d, $J = 1.8$ Hz); 4.17 (1H, dd, $J = 3.3, 3.3$ Hz); 6.87 (1H, d, $J = 6.3$ Hz); 7.01 (1H, s); 7.87 (1H, s, broad). ^{13}C -NMR (100 MHz) (CDCl_3) δ 31.40, 32.63, 39.91, 41.00, 52.63, 55.23, 57.02, 58.11, 61.24, 63.09, 61.20, 67.33, 67.70, 118.63, 118.75, 124.46, 126.91, 130.08, 131.68, 145.57, 154.18. IR (NaCl, neat) 3418, 2979, 2248, 1724, 1048. HRMS (FAB) calcd. for $\text{C}_{21}\text{H}_{29}\text{N}_4\text{O}_5$ (MH^+) 417.2138; found 417.2135.

(5 α ,8 β ,10 β ,11 β ,11a β)-10-(triisopropylsilyloxymethyl) 5,7,8,9,10,11, 11a,12-octahydro-5-(triisopropylsilyloxymethyl)-3-amino(carbamic acid methyl ester)-7-cyano-4-methoxy-13-methyl-8,11-Iminoazepino[1,2-b]isoquinoline (24). Aminonitrile **23** (28 mg, 0.67 mmol), triisopropylsilyl chloride (58 μL , 0.269 mmol, 4 eq.), imidazole (37 mg, 0.536 mmol, 8 eq.), and Et_3N (93 μL , 0.67 mmol, 1.0 eq.) were dissolved in a minimum amount of DMF (ca. 500 μL). This solution was allowed to stir for 18 hours. The solution was partitioned in water and Et_2O . The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (2.5 % $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to yield 45 mg **24** (92%) as a clear oil. TLC (5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) $R_f = 0.44$ (UV and PMA). ^1H -NMR (300 MHz) (CDCl_3) δ 0.95-1.20 (42H, m); 1.71 (1H, ddd, $J = 12, 6, 6$ Hz); 2.03 (1H, m); 2.40 (1H, m); 2.57 (3H, s); 2.61 (2H, m); 2.95 (3H, m); 3.36 (1H, m); 3.43 (1H, dd, $J = 9.0, 9.0$ Hz); 3.60 (1H, dd, $J = 9.6, 9.6$ Hz); 3.72 (1H, m); 3.78 (3H, s); 3.80 (3H, s); 4.15 (1H, dd, $J = 8.4, 2.1$ Hz); 4.33 (1H, d, $J = 2.1$ Hz); 6.85 (1H, d, $J = 8.0$ Hz); 7.02 (1H, s); 7.88 (1H, dd, $J = 8.0$ Hz). ^{13}C -NMR (75 MHz) (CDCl_3) δ 11.79, 11.94, 17.94, 18.04, 29.77, 32.64, 41.19, 42.07, 52.32, 57.22, 58.76, 59.09, 60.95, 63.42, 67.29, 67.49, 70.94, 117.76, 119.40, 124.03, 126.44, 129.68, 132.06, 145.28, 153.92. IR (NaCl, neat) 2939, 2865, 1727, 1498, 1461, 1095, 1064 cm^{-1} . HRMS (FAB) calcd. For $\text{C}_{39}\text{H}_{69}\text{N}_4\text{O}_5\text{Si}_2$ (MH^+) 729.4807; found 729.4805.

(5 α ,8 β ,10 β ,11 β ,11a β)-10-(triisopropylsilyloxymethyl) 5,7,8,9,10,11, 11a,12-octahydro-5-(triisopropylsilyloxymethyl)-3-amino-7-cyano-4-methoxy-13-methyl-8,11-Iminoazepino[1,2-b]isoquinoline (25). To a solution of **24** (12 mg, 0.17 mmol) in EtOH (2 mL) was added 2M LiOH (200 μL) and the solution was heated to reflux for 5.5 h. The solvent was removed *in vacuo* and the crude product was partitioned between CH_2Cl_2 and water. The pH was adjusted to 7 with dilute HCl and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 and the solvent was removed. The crude product was purified via flash chromatography (2.5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to afford 7 mg **25** (63%) as a clear oil. ^1H -NMR (300 MHz) (CDCl_3) δ 1.11 (42H, m); 1.61 (1H, s); 1.76 (1H, dd, $J = 12.0, 5.7$ Hz); 2.08 (1H, dd, $J = 12.3, 9.0$ Hz); 2.37 (1H, dd, $J = 14.4, 2.4$ Hz); 2.61 (3H, s); 2.64 (1H, m); 3.07 (2H, m); 3.40 (1H, d, $J = 6.3$ Hz); 3.47 (1H, t, $J = 9.3$ Hz); 3.71 (4H, m); 3.84 (3H, s); 3.92 (1H, dd, $J = 9.3, 2.4$ Hz); 4.20 (1H, dd, $J = 9.0, 2.4$ Hz); 4.41 (1H, d, $J = 2.4$ Hz); 6.63 (1H, d, $J = 8.1$ Hz); 6.71 (1H, d, $J = 8.1$ Hz). ^{13}C -NMR (75 MHz) (CDCl_3) δ 12.04, 12.17, 18.20, 18.26, 30.03, 32.64, 41.33, 42.33, 57.49, 59.00, 59.34, 59.56, 63.69, 67.59, 67.79, 71.52, 115.06, 119.79, 123.96, 127.06, 127.41, 138.14, 144.20. IR (NaCl, neat) 3437, 3368, 2942, 2865, 1734, 1498, 1461, 1097, 1064 cm^{-1} . HRMS (FAB) calcd. For $\text{C}_{37}\text{H}_{67}\text{N}_4\text{O}_3\text{Si}_2$ (MH^+) 671.4752; found 671.4769.

(2S,3R)- 3-tert-butoxy-1-(9H-fluoren-9-ylmethyl)ester-2-piperidinecarboxylic acid allyl ester [(+)-27]. To a slurry of (-)-**26** (145 mg, 0.36 mmol) and Amberlyst 15 (120 mg) in hexanes (8 mL) in an open tube was bubbled isobutene for 10 min. The tube was sealed and the mixture stirred for 48 h. The mixture was filtered through Celite and the filtrate was washed with hexanes. The solvent was removed *in vacuo* and the crude oil was purified via flash chromatography (10% EtOAc/hex) to afford 142 mg (+)-**27** (86%) as a clear oil. ^1H -NMR (300 MHz) (d_6 -DMSO, 120°C) δ 1.17 (9H, s); 1.45 (1H, m); 1.67 (3H, m); 3.01 (1H, s, broad); 3.21 (1H, ddd, $J = 12.6, 3.3, 3.3$ Hz); 3.71 (2H, m); 4.25 (1H, t, $J = 6.3$ Hz); 4.44 (2H, d, $J = 6.0$ Hz);

4.55 (2H, m); 4.73 (1H, d, $J = 6.6$ Hz); 5.19 (1H, m); 5.90 (1H, m); 7.32 (2H, t, $J = 7.5$ Hz); 7.41 (2H, t, $J = 7.5$ Hz); 7.62 (2H, dd, $J = 7.5, 3.3$ Hz); 7.84 (2H, d, $J = 7.5$ Hz). ^{13}C -NMR (d_6 -DMSO, 120°C) δ 21.80, 27.17, 27.31, 46.47, 57.72, 63.69, 66.24, 66.37, 73.26, 116.71, 119.22, 124.02, 126.21, 126.24, 126.82, 131.85, 140.27, 143.24, 154.23, 168.75. IR (NaCl, neat) 2972, 1734, 1701, 1265, 1210, 1049 cm^{-1} . HRMS (FAB) calc. for $\text{C}_{28}\text{H}_{34}\text{NO}_5$ (MH^+) 464.2437; found 464.2437. $[\alpha]_D^{20} = +5.5$ ($c=0.55$ CHCl_3).

(2S,3R)- 3-tert-butoxy-1-(9H-fluoren-9-ylmethyl)ester-2-piperidinecarboxylic acid [(+)-28].

To a solution of (+)-**27** (142 mg, 0.32 mmol) and palladium tetrakis triphenyl phosphine (29 mg, 0.025 mmol, 0.08 eq.) in CH_2Cl_2 (8 mL) was added hydroxymethanesulfinic acid sodium salt (53 mg, 0.35 mmol, 1.1 eq.) in MeOH (4 mL) and the solution was stirred for 3 h. Hydrochloric acid (1 M) was added to adjust to pH 2 and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine and dried over MgSO_4 and concentrated. The crude product was purified via flash chromatography (gradient 1-2.5% MeOH/ CH_2Cl_2) to afford 123 mg (+)-**28** (95%) as a white foam. ^1H -NMR (300 MHz) (d_6 -DMSO, 120°C) δ 1.21 (9H, s); 1.44 (1H, m); 1.66 (3H, m); 3.17 (1H, ddd, $J = 12.3, 3.3, 3.3$ Hz); 3.72 (2H, m); 4.26 (1H, t, $J = 6.3$ Hz); 4.42 (2H, d, $J = 5.7$ Hz); 4.68 (1H, d, $J = 6.3$ Hz); 7.32 (2H, t, $J = 7.5$ Hz); 7.41 (2H, t, $J = 7.5$ Hz); 7.63 (2H, d, $J = 7.5$ Hz); 7.84 (2H, t, $J = 7.5$ Hz); 11.6 (1H, s, broad). ^{13}C -NMR (d_6 -DMSO, 120°C) δ 21.98, 27.22, 27.57, 46.48, 57.7, 66.29, 66.61, 73.69, 98.84, 119.22, 124.15, 126.26, 126.85, 140.25, 143.27, 154.35, 169.82. IR (NaCl, neat) 3066, 2971, 1768, 1701, 1420, 1150, 1059 cm^{-1} . HRMS (FAB) calc. for $\text{C}_{25}\text{H}_{30}\text{NO}_5$ (MH^+) 424.2124; found 424.2121. $[\alpha]_D^{20} = +19.1$ ($c=0.23$ CHCl_3).

(5S,7R,8S,10R,11R,11aS)-5,7,8,9,10,11,11a,12-octahydro-5-(triisopropylsilyloxymethyl)-3-amino [(2'S,3'R)-piperidine-2'-carboxy-3'-tert-butyloxy]-7-cyano-4-methoxy--10-(triisopropylsilyloxymethyl)-13-methyl-8,11-Iminoazepino[1,2-b]isoquinoline [(+)-30] and (5R,7S,8R,10S,11S,11aR)-5,7,8,9,10,11,11a,12-octahydro-5-(triisopropylsilyloxymethyl)-3-amino [(2'S,3'R)-piperidine-2'-carboxy-3'-tert-butyloxy]-7-cyano--10-(triisopropylsilyloxymethyl)-4-methoxy-13-methyl-8,11-Iminoazepino[1,2-b]isoquinoline [(-)-31]. To a solution of (+)-**28** (44 mg, 1.04 mmol, 1.8 eq) in CH_2Cl_2 (4 mL) was added oxalyl chloride (10 μL , 0.116 mmol, 2.0 eq) and DMF (0.8 μL , 0.01 mmol, 0.18 eq) and the resultant solution was stirred at rt for 1 h. Hexanes (4 mL) were added and the solution was filtered through a cotton plug and the solvent removed *in vacuo*. A solution of aniline **25** (39 mg, 0.058 mmol, 1 eq) and DMAP (7.1 mg, 0.058 mmol, 1 eq) in CH_2Cl_2 (1 mL) was added to the acid chloride and the solution was stirred at rt for 24 h. The solution was diluted with CH_2Cl_2 and washed with $\text{NaHCO}_3(\text{aq})$. The organic layer was dried over Na_2SO_4 and the solvent was removed. The crude product was redissolved in CH_2Cl_2 (4 mL) and DBU (10 μL , 0.075 mmol, 1.3 eq) was added and the solution was stirred at rt for 15 h. The solution was washed with NaHCO_3 and dried over Na_2SO_4 . The solvent was removed and the crude product was purified via flash chromatography (gradient 2.5-4.0% MeOH/ CH_2Cl_2) to afford 17 mg (+)-**30** (36%) and 17 mg (-)-**31** (36%).

(+)-**30**: ^1H -NMR (400 MHz) (CDCl_3) δ 1.07 (42H, m); 1.25 (3H, s); 1.28 (6H, s); 1.63 (2H, m); 1.71 (3H, m); 1.80 (1H, m); 2.01 (1H, d, $J = 8.0$ Hz); 2.04 (1H, d, $J = 9.2$ Hz); 2.42 (1H, d, $J = 12.8$ Hz); 2.57 (3H, s); 2.62 (1H, m); 2.74 (2H, m); 3.04 (2H, m); 3.37 (1H, d, broad, $J = 6.4$ Hz); 3.43 (1H, t, $J = 8.8$ Hz); 3.57 (1H, d, $J = 4.0$ Hz); 3.61 (1H, t, $J = 9.6$ Hz); 3.73 (1H, dd, $J = 9.6, 5.8$ Hz); 3.80 (3H, s); 3.86 (1H, dd, $J = 9.2, 1.5$ Hz); 4.16 (2H, m); 4.37 (1H, d, $J = 2.8$ Hz); 6.85 (1H, d, $J = 8.0$ Hz); 8.30 (1H, d, $J = 8.0$ Hz); 10.06 (1H, s, broad). ^{13}C -NMR (100 MHz) (CDCl_3) δ 11.78, 11.95, 17.98, 18.05, 23.96, 28.17, 29.75, 31.24, 32.68, 41.25, 42.12, 42.69, 57.28, 58.81, 59.20, 61.10, 62.24, 63.49, 67.35, 67.54, 68.64, 71.15, 75.67, 119.13, 119.39, 123.81, 126.41,

130.36, 132.42, 146.08, 170.24. IR (NaCl, neat) 2928, 2864, 1733, 1652, 1559, 1049 cm^{-1} . HRMS (FAB) calcd. For $\text{C}_{47}\text{H}_{84}\text{N}_5\text{O}_5\text{Si}_2$ (MH^+) 854.6011; found 854.6006. $[\alpha]_{\text{D}}^{25} = +26.7$ ($c = 0.08$ CHCl_3).

(-)-**31**: ^1H -NMR (400 MHz) (CDCl_3) δ 1.02-1.13 (42H, m); 1.26 (9H, s); 1.58-1.80 (7H, m); 2.03 (1H, dd, $J = 10.0, 9.2$ Hz); 2.42 (1H, dd, $J = 15.2, 2.0$ Hz); 2.57 (3H, s); 2.62 (2H, m); 2.84 (1H, m); 3.03 (2H, m); 3.36 (1H, d, broad, $J = 7.6$ Hz); 3.44 (1H, t, $J = 8.8$ Hz); 3.61 (2H, t, $J = 9.6$ Hz); 3.72 (1H, dd, $J = 9.2, 6.9$ Hz); 3.80 (3H, s); 3.85 (1H, dd, $J = 9.2, 2.4$ Hz); 4.17 (1H, dd, $J = 6.4, 2.0$ Hz); 4.28 (1H, m); 4.35 (1H, d, $J = 2.8$ Hz); 6.85 (1H, d, $J = 8.8$ Hz); 8.06 (1H, d, $J = 8.8$ Hz); 9.51 (1H, s, broad). ^{13}C -NMR (100 MHz) (CDCl_3) δ 11.80, 11.95, 17.98, 18.05, 22.92, 28.52, 29.68, 29.82, 31.33, 32.75, 41.13, 42.09, 57.10, 58.73, 59.10, 60.73, 63.43, 67.26, 67.31, 67.52, 71.08, 74.69, 74.88, 119.45, 120.29, 123.78, 126.45, 129.57, 132.94, 146.69, 169.97. IR (NaCl, neat) 2928, 2865, 1733, 1653, 1457, 1047 cm^{-1} . HRMS (FAB) calcd. For $\text{C}_{47}\text{H}_{84}\text{N}_5\text{O}_5\text{Si}_2$ (MH^+) 854.6011; found 854.6003. $[\alpha]_{\text{D}}^{25} = -8.2$ ($c = 0.11$ CHCl_3).

(5S,7R,8S,10R,11R,11aS)-5,7,8,9,10,11,11a,12-octahydro-5-(triisopropylsilyloxymethyl)-3-amino [(2'S,3'R)-piperidine-2'-carboxy-3'-hydroxy]-7-cyano--10-(triisopropylsilyloxymethyl)-4-methoxy-13-methyl-8,11-Iminoazepino[1,2-b]isoquinoline

[(+)-32]. To a mixture of (+)-30 (9 mg, 0.011 mmol) and 1,3-dimethoxybenzene (50 μL) at 0°C was added TFA (1 mL) and this solution was stirred at 4°C for 26h. The solvent was removed *in vacuo* and the crude product was partitioned in CH_2Cl_2 and NaHCO_3 . The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 and the solvent was removed. The crude product was purified via flash chromatography (gradient 1-2.5-5.0 % $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to afford 4.5 mg (+)-32 (53%) as a clear oil. ^1H -NMR (400 MHz) (CDCl_3) δ 1.02-1.10 (42H, m); 1.58 (2H, m); 1.71 (2H, m); 1.83 (2H, m); 1.91 (1H, m); 2.03 (1H, dd, $J = 13.2, 8.8$ Hz); 2.41 (1H, d, $J = 12.4$ Hz); 2.57 (3H, s); 2.63 (2H, m); 2.83 (1H, m); 3.04 (2H, m); 3.36 (1H, m); 3.43 (1H, t, $J = 8.8$ Hz); 3.60 (2H, t, $J = 10.0$ Hz); 3.71 (1H, d, $J = 7.2$ Hz); 3.73 (1H, d, $J = 8.8$ Hz); 3.82 (3H, s); 3.83 (1H, d, $J = 4.4$ Hz); 4.16 (1H, d, $J = 6.0$ Hz); 4.32 (1H, d, $J = 2.0$ Hz); 4.36 (1H, m); 6.85 (1H, d, $J = 8.0$ Hz); 8.12 (1H, d, $J = 8.0$ Hz); 9.39 (1H, s, broad). ^{13}C -NMR (100 MHz) (CDCl_3) δ 11.83, 11.96, 17.99, 18.07, 22.13, 29.79, 30.72, 32.84, 41.21, 42.09, 45.38, 57.25, 58.73, 59.10, 61.14, 62.64, 63.46, 65.84, 67.31, 67.52, 70.74, 119.34, 119.45, 123.92, 126.64, 129.29, 133.44, 146.17, 170.30. IR (NaCl, neat) 3220, 3066, 2944, 1716, 1528, 1167, 1044 cm^{-1} . HRMS (FAB) calcd. For $\text{C}_{43}\text{H}_{76}\text{N}_5\text{O}_5\text{Si}_2$ (MH^+) 798.5385; found 798.5373. $[\alpha]_{\text{D}}^{25} = +31.0$ ($c = 0.33$ CHCl_3).

2a'-cyanotetrazominol (33): To a solution of **32** (6.2 mg, 0.0078 mmol) in MeCN (1 mL) was added 5% HF(aq.)/MeCN (150 μL) and the solution was stirred for 4 h. Excess sat. NaHCO_3 was added and the mixture was lyophilized. The crude product was taken up in dd H_2O and filtered through a Nalgene syringe filter (0.2 μm , nylon). The solution was then purified using a HP-20 column at 4°C (100:0-10:90 $\text{H}_2\text{O}:\text{MeOH}$). The MeOH was removed from the organic fractions by rotary evaporation and the remaining water was removed by lyophilization to afford 3 mg **33** (79%) as a white solid. TLC (9:90:1 $\text{MeOH}/\text{CH}_2\text{Cl}_2/\text{conc. NH}_4\text{OH}$) $R_f = 0.31$ (UV and PMA). ^1H -NMR (400 MHz) (D_2O) δ 1.52 (1H, m); 1.81 (2H, m); 1.96 (2H, m); 2.05 (1H, dd, $J = 14.0, 8.4$ Hz); 2.44 (3H, s); 2.60-2.75 (4H, m); 2.88 (1H, d, $J = 10.4$ Hz); 3.07 (1H, s); 3.11 (1H, d, $J = 14.0$ Hz); 3.59-3.70 (6H, m); 3.78 (3H, s); 4.17 (1H, t, $J = 1.2$ Hz); 4.26 (1H, d, $J = 1.2$ Hz); 4.33 (1H, s, broad); 7.05 (1H, d, $J = 8.4$ Hz); 7.50 (1H, d, $J = 7.5$ Hz). ^{13}C -NMR (125 MHz) (D_2O vs. $\text{d}_4\text{-MeOH}$) δ 20.15, 30.82, 31.19, 33.25, 42.28, 45.12, 48.63, 58.93, 58.99, 59.04, 62.30, 63.07, 64.74, 66.49, 67.05, 67.20, 68.75, 120.29, 125.24, 125.41, 128.35, 128.59, 137.75, 150.70, 172.49. HRMS (FAB) calcd. for $\text{C}_{25}\text{H}_{36}\text{N}_5\text{O}_5$ (MH^+) 486.2716; found 486.2722. IR (KBr) 3430, 2933, 1738, 1731, 1574, 1384, 1136 cm^{-1} .

Tetrazomine (1). To a solution of **33** (1.5 mg, 0.003 mmol) in 4:1 MeOH/ddH₂O (500 μ L) was added TFA (1.2 μ L, 0.015 mmol, 5 eq.) followed by silver trifluoroacetate (2.1 mg, 0.009 mmol, 3 eq). This solution was allowed to stir at rt for 4 h. Excess Dowex (Cl⁻) ion exchange resin was added and the mixture was stirred for 15 min. The mixture was filtered through a cotton plug and the resin was washed with ddH₂O. The filtrate was then lyophilized to afford crude tetrazomine that was purified *via* HPLC (Waters Resolve C₁₈, isocratic 90/10/0.1 H₂O/MeOH/TFA) to afford 1.0 mg tetrazomine•2HCl (61%). ¹H-NMR (400 MHz) (D₂O) δ 1.84 (1H, d, *J* = 12.4 Hz); 1.93 (1H, t, *J* = 9.6 Hz); 2.09 (3H, m); 2.42 (1H, dd, *J* = 14.8, 10.4 Hz); 2.75 (2H, m); 2.99 (3H, s); 3.04 (1H, m); 3.15 (1H, ddd, *J* = 12.4, 12.4, 2.8 Hz); 3.52 (1H, s, broad); 3.55 (1H, s, broad); 3.69 (1H, m); 3.75 (2H, m); 3.82 (3H, s); 3.83 (1H, m); 3.90 (1H, s); 3.99 (1H, m); 4.34 (1H, d, *J* = 1.6 Hz); 4.50 (1H, t, *J* = 4 Hz); 4.73 (1H, s, broad); 5.01 (1H, d, *J* = 2.8 Hz); 7.10 (1H, d, *J* = 8.8 Hz); 7.51 (1H, d, *J* = 8.8 Hz). HRMS (FAB) calcd. For C₂₄H₃₅N₄O₅ (MH⁺) 459.2607; found 459.2612. $[\alpha]_D^{25}$ = -57 (c = 0.04 MeOH); $[\alpha]_D^{25}$ (natural tetrazomine) = -59 (c = 0.1 MeOH) Lit. $[\alpha]_D^{25}$ = -62 (c = 1.0, MeOH). The synthetic material was identical to the natural product²¹ by ¹H nmr, ¹³C nmr, IR and mobility on TLC.

(5S,7R,8S,10R,11R,11aS)-8,11-5,7,8,9,10,11,11a,12-octahydro-5-(triisopropylsilyloxymethyl)-3-amino [(2'S,3'R)-piperidine-2'-carboxy-3'-hydroxy]-7-cyano-4-methoxy-13-methyl-10-(triisopropylsilyloxymethyl)Iminoazepino[1,2-b]isoquinoline [(+)-34**].** To a mixture of **31** (8 mg, 0.0094 mmol) and 1,3-dimethoxybenzene (50 μ L) at 0°C was added TFA (1 mL) and this solution was stirred at 4°C for 26 h. The solvent was removed *in vacuo* and the crude product was partitioned in CH₂Cl₂ and NaHCO₃. The aqueous layer was extracted with CH₂Cl₂ (3x). The combined organic layers were dried over Na₂SO₄ and the solvent was removed. The crude product was purified via flash chromatography (gradient 1-2.5-5.0 % MeOH/CH₂Cl₂) to afford 4 mg **34** (54%) as a clear oil. ¹H-NMR (400 MHz) (CDCl₃) δ 0.85 (3H, m); 1.07 (35H, m); 1.25 (4H, m); 1.56 (4H, m); 1.70 (2H, m); 1.85 (2H, m); 2.03 (1H, dd, *J* = 14.0, 8.4 Hz); 2.42 (1H, d, *J* = 14.0 Hz); 2.57 (3H, s); 2.63 (2H, m); 2.79 (1H, m); 3.02 (2H, m); 3.38 (1H, m); 3.43 (1H, t, *J* = 8.4 Hz); 3.60 (2H, t, *J* = 8.8 Hz); 3.73 (2H, m); 3.82 (3H, s); 4.17 (1H, dd, *J* = 7.6, 0.8 Hz); 4.29 (1H, m); 4.33 (1H, d, *J* = 1.2 Hz); 6.86 (1H, d, *J* = 8.0 Hz); 8.14 (1H, d, *J* = 8.0 Hz); 9.38 (1H, s, broad). ¹³C-NMR (100 MHz) (CDCl₃) δ 11.81, 11.95, 17.98, 18.05, 29.68, 29.72, 30.45, 32.83, 41.24, 42.09, 45.01, 57.28, 58.72, 59.11, 61.22, 63.48, 65.95, 67.32, 67.51, 68.00, 70.76, 119.20, 119.54, 123.93, 126.67, 129.22, 146.13, 151.61, 161.80. IR (NaCl, neat) 3220, 3066, 2944, 1716, 1528, 1167, 1044 cm⁻¹. HRMS (FAB) calcd. for C₄₃H₇₆N₅O₅Si₂ (MH⁺) 798.5385; found 798.5375. $[\alpha]_D^{25}$ = -21.9 (c = 0.29 CHCl₃).

2',3'-*epi-ent* cyanotetrazominol (35): To a solution of **34** (3.5 mg, 0.0044 mmol) in MeCN (500 μ L) was added 5% HF(aq.)/MeCN (100 μ L) and the solution was stirred for 3 h. Excess sat. NaHCO₃ was added and the mixture was lyophilized. The crude product was taken up in dd H₂O and filtered through a Nalgene syringe filter (0.2 μ m, nylon). The solution was then purified using a HP-20 column (100:0-10:90 H₂O:MeOH). The MeOH was removed from the organic fractions by rotary evaporation and the remaining water was removed by lyophilization to afford 1.5 mg **35** (70%) as a white solid. TLC (9:90:1 MeOH/CH₂Cl₂/conc. NH₄OH) R_f = 0.25 (UV and PMA). ¹H-NMR (300 MHz) (D₂O) δ 1.49 (2H, m); 1.78-2.07 (5H, m); 2.42 (3H, s); 2.57-2.75 (4H, m); 2.86 (1H, d, *J* = 11.1 Hz); 3.04 (1H, s); 3.09 (1H, d, *J* = 14.1 Hz); 3.59-3.71 (4H, m); 3.75 (3H, s); 4.14 (1H, t, *J* = 3.0 Hz); 4.23 (1H, d, *J* = 1.2 Hz); 4.29 (1H, m); 7.03 (1H, d, *J* = 8.1 Hz); 7.42 (1H, d, *J* = 8.1 Hz). ¹³C-NMR (125 MHz) (D₂O vs. d₄-MeOH) δ 20.0, 30.8, 31.1, 33.2, 41.9, 42.3, 48.61, 60.0, 62.3, 63.1, 64.7, 66.7, 67.0, 67.2, 67.8, 68.7, 69.0, 119.8, 125.2, 125.7, 126.8, 128.1, 137.9, 174.0. HRMS (FAB) calcd. for C₂₅H₃₆N₅O₅ (MH⁺) 486.2716; found 486.2739. $[\alpha]_D^{25}$ = -22.0 (c = 0.09 MeOH). IR (KBr) 3428, 2934, 1667, 1537, 1455, 1134 cm⁻¹.

ent-2',3'-Tetrazomine (36): To a solution of **35** (1mg, 0.0021 mmol) in 4:1 MeOH/H₂O (250 μ L) was added TFA (1 μ L, 0.011 mmol, 5 eq) followed by silver trifluoroacetate (1.4 mg, 0.0062 mmol, 3 eq.). The mixture was stirred at room temperature for 4 h. Excess Dowex (Cl⁻) was added and the mixture was stirred at rt for 15 min. The mixture was filtered through a cotton plug followed by filtration through a nylon (0.2 μ m) syringe filter. The product was then lyophilized to afford 1 mg (90%) **36** as a white foam. ¹H-NMR (500 MHz) (D₂O) δ 1.75 (1H, d, J = 13.0 Hz); 1.95 (1H, m); 2.01 (3H, m); 2.35 (1H, m) 2.63-2.74 (2H, m); 2.91 (3H, s); 3.08 (1H, dd, J = 3.5, 14 Hz); 3.45 (2H, m); 3.59 (1H, d, J = 5Hz); 3.61 (1H, d, J = 4.5 Hz); 3.65-3.68 (3H, m); 3.72 (3H, s); 3.75 (1H, m); 3.92 (1H, m); 4.27 (1H, s); 4.42 (1H, t, J = 3.5 Hz); 4.61 (1H, s); 4.94 (1H, d, J = 2.5 Hz); 7.02 (1H, d, J = 8.0 Hz); 7.35 (1H, d, J = 8.0 Hz) HRMS (FAB) calcd. For C₂₄H₃₅N₄O₅ (MH⁺) 459.2607; found 459.2621

(5S,7R,8S,10R,11R,11aS)-5,7,8,9,10,11,11a,12-octahydro-5-(triisopropylsilyloxymethyl)-3-amino (2'S-piperidine-2'-carboxy-)-7-cyano--10-(triisopropylsilyloxymethyl) 8,11-Iminoazepino[1,2-b]isoquinoline-4-methoxy-13-methyl- (38).

(5R,7S,8R,10S,11S,11aR)-5,7,8,9,10,11,11a,12-octahydro-5-(triisopropylsilyloxymethyl)-3-amino-(2'S-piperidine-2'-carboxy)-7-cyano--10-(triisopropylsilyloxymethyl)-4-methoxy-13-methyl-8,11-Iminoazepino[1,2-b]isoquinoline (40). To a solution of Fmoc-pipecolic acid (10 mg, 0.029 mmol, 1.5 eq.) in CH₂Cl₂ (1 mL) was added oxalyl chloride (3 μ L, 0.033 mmol, 1.7 eq.) followed by DMF (0.25 μ L, 0.0029 mmol, 0.15 eq). This solution was stirred at rt for 1 h. Hexanes (1 mL) was added and the solution was filtered through a cotton plug and the solvent was removed. Aniline **25** (13 mg, 0.0194 mmol, 1 eq) was dissolved in a minimum amount of CH₂Cl₂ and added to the acid chloride with DMAP (2.4 mg, 0.0194 mmol, 1 eq). This solution was stirred at rt for 18 h. The solution was diluted with CH₂Cl₂ and washed with NaHCO₃, dried over Na₂SO₄, and the solvent was removed. The crude product was purified by preparative TLC (20% EtOAc/hex) to afford 6 mg of each diastereomer. Each diastereomer was separately dissolved in CH₂Cl₂ (1 mL) and DBU (0.7 μ L, 0.0050 mmol, 1 eq) was added and the solution was stirred at rt for 1 h. The solvent was removed and the crude product was purified via column chromatography (1-5% MeOH/CH₂Cl₂; extracted with THF) to afford 3.8 mg **38** (30%) as a clear oil and 3.5 mg **40** (28%) as a clear oil.

38: ¹H-NMR (400 MHz) (CDCl₃) δ 1.04 (42H, m); 1.48-1.71 (5H, m); 1.80 (1H, m); 2.03 (2H, m); 2.38 (1H, d, J = 14.4 Hz); 2.54 (3H, s); 2.59 (2H, m); 2.87 (1H, t, J = 6.4 Hz); 3.01 (2H, m); 3.24 (1H, d, J = 8.0 Hz); 3.38 (1H, d, J = 4.0 Hz); 3.43 (1H, d, J = 12.0 Hz); 3.58 (1H, t, J = 9.6 Hz); 3.67 (1H, m); 3.73 (1H, d, J = 10.0 Hz); 3.79 (1H, s, broad); 3.82 (3H, s); 4.14 (1H, d, J = 8.8 Hz); 4.30 (1H, s); 6.81 (1H, d, J = 8.8 Hz); 8.06 (1H, d, J = 8.8 Hz); 8.99 (1H, s, broad). ¹³C-NMR (100 MHz) (CDCl₃) δ 11.83, 11.96, 17.99, 18.07, 23.09, 28.89, 29.70, 29.78, 32.84, 41.24, 42.11, 45.01, 57.27, 58.72, 59.11, 59.81, 61.33, 63.49, 67.32, 67.52, 70.82, 119.42, 119.74, 123.90, 126.59, 129.34, 133.43, 146.39, 159.36. HRMS (FAB) calcd. for C₄₃H₇₆N₅O₄Si₂ (MH⁺) 782.5436; found 782.5399. $[\alpha]_D^{25}$ = -31.9 (c = 0.32, CHCl₃).

40: ¹H-NMR (400 MHz) (CDCl₃) δ 1.06 (42H, m); 1.25 (2H, s); 1.58-1.85 (7H, m); 2.03 (1H, dd, J = 12.4, 9.2 Hz); 2.36 (1H, d, J = 9.2 Hz); 2.41 (1H, d, J = 15.2 Hz); 2.57 (3H, s); 2.63 (2H, m); 3.02 (3H, m); 3.38 (1H, s, broad); 3.43 (1H, t, J = 8.8 Hz); 3.60 (1H, t, J = 9.2 Hz); 3.72 (1H, dd, J = 9.2, 6.8 Hz); 3.81 (3H, s); 3.84 (1H, m); 4.17 (1H, dd, J = 6.4, 1.2 Hz); 4.33 (1H, d, J = 1.2 Hz); 6.83 (1H, d, J = 8.4 Hz); 8.03 (1H, d, J = 8.4 Hz); 8.85 (1H, s, broad). ¹³C-NMR (100 MHz) (CDCl₃) δ 11.81, 11.95, 17.99, 18.05, 22.65, 28.10, 29.60, 29.76, 32.84, 41.25, 42.09, 44.64, 57.30, 58.68, 59.14, 59.22, 61.16, 63.48, 67.31, 67.51, 70.85, 119.43, 120.38, 123.87, 124.29, 126.64, 133.92, 146.72, 159.16. HRMS (FAB) calcd. for C₄₃H₇₆N₅O₄Si₂ (MH⁺) 782.5436; found 782.5443. $[\alpha]_D^{25}$ = +14.4 (c = 0.29 CHCl₃).

3-deoxy-2'-cyantetrazominol (39): To a solution of **38** (4 mg, 0.0051 mmol) in MeCN (500 μ L) was added 5% HF/MeCN (100 μ L). This solution was stirred at rt for 4 h. Excess sat NaHCO₃ was added and the solution was lyophilized. The crude product was taken up in ddH₂O and filtered through a cotton plug followed by a syringe filter (nylon 2 μ M). The product was purified using a HP20 column at 4°C (1:0 to 10:90 H₂O:MeOH) and the solvent was removed by rotary evaporation followed by lyophilization to afford 1.8 mg (75%) **39** as a white foam. ¹H-NMR (300 MHz) (D₂O) δ 1.49 (2H, m); 1.78-2.07 (5H, m); 2.42 (3H, s); 2.57-2.75 (4H, m); 2.86 (1H, d, J = 11.1 Hz); 3.04 (1H, s); 3.09 (1H, d, J = 14.1 Hz); 3.59-3.71 (4H, m); 3.75 (3H, s); 4.14 (1H, t, J = 3.0 Hz); 4.23 (1H, d, J = 1.2 Hz); 4.29 (1H, m); 7.03 (1H, d, J = 8.1 Hz); 7.42 (1H, d, J = 8.1 Hz). ¹³C-NMR (125 MHz) (D₂O vs. d₄-MeOH) δ 24.08, 24.95, 30.07, 30.80, 33.28, 41.84, 42.28, 45.75, 58.91, 58.98, 59.26, 60.32, 62.23, 64.72, 66.43, 67.18, 68.73, 120.27, 125.26, 128.05, 128.69, 135.50, 138.31, 151.38, 153.38. HRMS (FAB) calcd. for C₂₅H₃₆N₅O₄ (MH⁺) 470.2756; found 470.2767. $[\alpha]_D^{25}$ = -17.4 (c = 0.17 MeOH). IR (KBr) 3550, 2942, 1698, 1537, 1454, 1043 cm⁻¹.

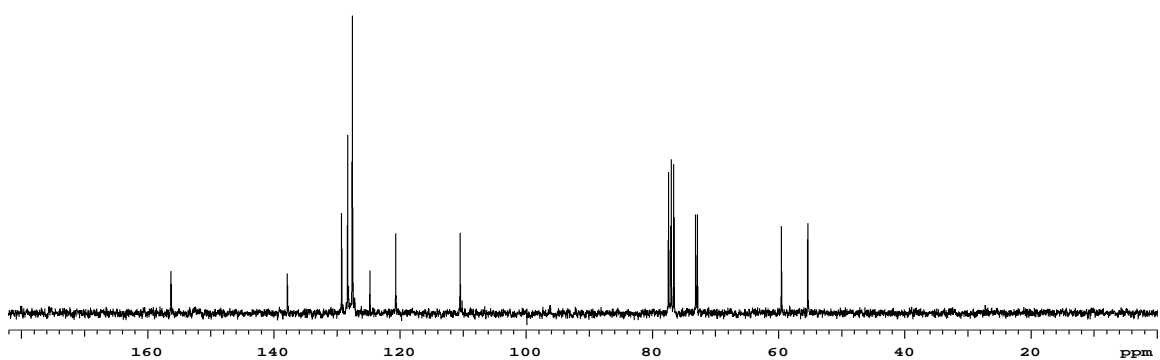
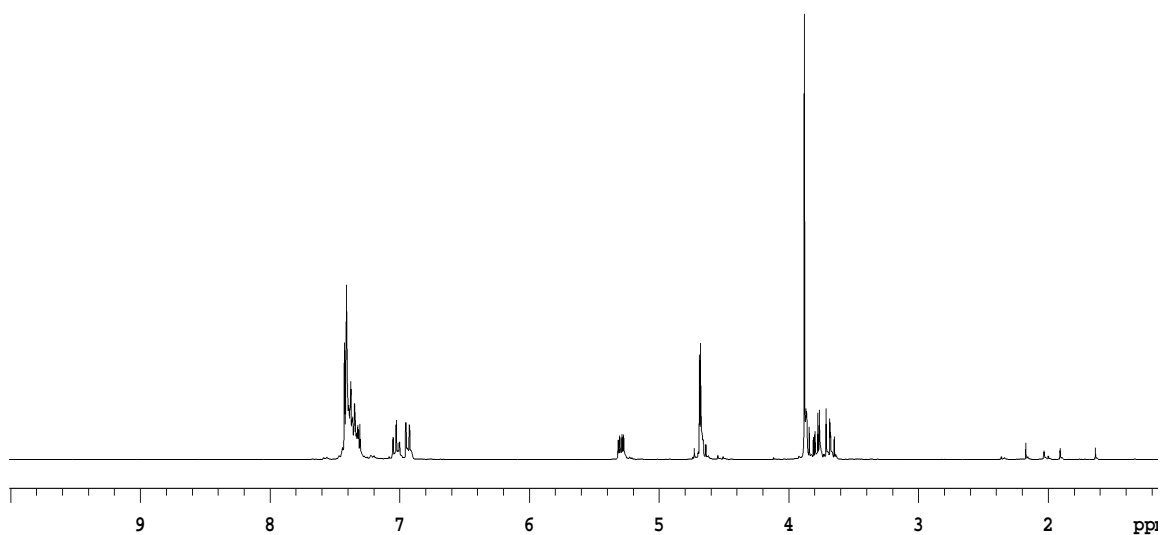
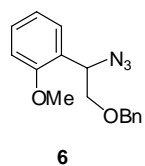
3-deoxy-2-*epi-ent*-2'-cyantetrazominol (41): To a solution of **40** (4 mg, 0.0051 mmol) in MeCN (500 μ L) was added 5% HF/MeCN (100 μ L). This solution was stirred at rt for 4 h. Excess sat NaHCO₃ was added and the solution was lyophilized. The crude product was taken up in ddH₂O and filtered through a cotton plug followed by a syringe filter (nylon 2 μ M). The product was desalted using a HP20 column (1:0 to 10:90 H₂O:MeOH) and the solvent was removed by rotary evaporation followed by lyophilization to afford 1.8 mg (75%) **41** as a white foam. ¹H-NMR (300 MHz) (D₂O) δ 1.67 (2H, m); 1.88-2.04 (4H, m); 2.36 (1H, m); 2.42 (3H, s); 2.63 (3H, m); 2.87 (1H, d, J = 10.2 Hz); 3.05 (2H, s, broad); 3.49 (1H, d, J = 10.5 Hz); 3.55 (4H, m); 3.73 (3H, s); 4.06-4.16 (2H, m); 4.24 (1H, d, J = 1.2 Hz); 7.04 (1H, d, J = 7.8 Hz); 7.38 (1H, d, J = 7.8 Hz). ¹³C-NMR (125 MHz) (D₂O vs. d₄-MeOH) δ 24.13, 25.04, 30.20, 30.81, 33.30, 41.86, 42.29, 45.72, 58.95, 59.04, 60.29, 60.39, 62.32, 64.74, 66.49, 67.19, 68.75, 120.26, 125.36, 126.54, 128.06, 128.76, 138.53, 151.67, 154.00. HRMS (FAB) calcd. for C₂₅H₃₆N₅O₄ (MH⁺) 470.2767; found 470.2765. IR (KBr) 3407, 2939, 1687, 1538, 1460, 1030 cm⁻¹. $[\alpha]_D^{25}$ = +17.0 (c = 0.1 MeOH).

3-Deoxy-tetrazomine (42): To a solution of **39** (0.7 mg, 0.0015 mmol) in 4:1 MeOH/H₂O (250 μ L) was added TFA (0.6 μ L, 0.0075 mmol, 5 eq) followed by AgOCOCF₃ (1mg, 0.0045 mmol, 3 eq) and the solution was allowed to stir at rt for 4 h. Excess Dowex (Cl⁻) in ddH₂O (1 mL) was added and the slurry was stirred for 15 min. The reaction mixture was filtered through a cotton plug followed by filtration through a syringe filter (Gelman GHP 0.45 μ M). The solvent was removed via lyophilization to afford pure 0.6 mg **42**•2HCl (78%) as a white foam. ¹H-NMR (400 MHz) (D₂O) 1.72 (2H, m); 1.85-2.09 (3H, m); 2.41 (2H, m); 2.68-2.80 (2H, m); 2.96 (3H, s); 3.02 (1H, m); 3.13 (1H, m); 3.52 (2H, m); 3.67 (2H, m); 3.77 (3H, s); 3.97 (1H, d, J = 3.2 Hz, broad); 4.16 (1H, dd, J = 12.0, 3.2 Hz); 4.47 (1H, t, J = 3.2 Hz); 4.99 (1H, d, J = 3.2 Hz); 7.08 (1H, d, J = 8.0 Hz); 7.39 (1H, d, J = 8.0 Hz). ¹³C-NMR (125 MHz) (D₂O vs. d₄-MeOH) δ 21.6, 21.7, 31.1, 37.1, 40.6, 44.1, 49.3, 54.5, 57.4, 58.1, 59.3, 61.4, 63.9, 65.9, 69.7, 70.3, 81.6, 124.4, 125.5, 126.1, 127.3, 169.3. HRMS (FAB) calcd. for C₂₄H₃₅N₄O₄ (MH⁺) 443.2658; found 443.2667. $[\alpha]_D^{25}$ = +36.0 (c = 0.033 MeOH).

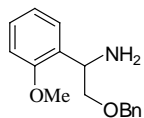
***ent*,2-*epi*-3-Deoxy-tetrazomine (43).** To a solution of **41** (0.7 mg, 0.0015 mmol) in 4:1 MeOH/H₂O (250 μ L) was added TFA (0.6 μ L, 0.0075 mmol, 5 eq) followed by AgOCOCF₃ (1mg, 0.0045 mmol, 3 eq) and the solution was allowed to stir at rt for 4 h. Excess Dowex (Cl⁻) in ddH₂O (1 mL) was added and the slurry was stirred for 15 min. The reaction mixture was filtered through a cotton plug followed by filtration through a syringe filter (Gelman GHP 0.45 μ M). The solvent was removed via lyophilization to afford pure 0.6 mg **43**•2HCl (75%) as a

white foam. ^1H -NMR (400 MHz) (D_2O) 1.71 (2H, m); 1.85-2.10 (3H, m); 2.39 (2H, m); 2.74 (2H, m); 2.96 (3H, s); 3.02 (1H, m); 3.12 (1H, m); 3.52 (2H, t, $J = 13.6$ Hz); 3.66 (2H, m); 3.76 (3H, s); 3.78 (1H, m); 3.87 (1H, s); 4.16 (1H, dd, $J = 12.0, 3.6$ Hz); 4.64 (1H, t, $J = 3.6$ Hz); 4.99 (1H, d, $J = 3.2$ Hz); 7.07 (1H, d, $J = 8.0$ Hz); 7.30 (1H, d, $J = 8.0$ Hz). ^{13}C -NMR (100 MHz) (D_2O vs. d_4MeOH) δ 21.6, 21.8, 26.5, 27.6, 31.2, 37.1, 40.7, 44.2, 54.1, 54.6, 58.2, 61.6, 63.9, 66.0, 69.7, 70.3, 73.4, 124.6, 125.9, 126.2, 126.9, 128.8, 136.5, 169.5. HRMS (FAB) calcd. for $\text{C}_{24}\text{H}_{35}\text{N}_4\text{O}_4$ (MH^+) 443.2658; found 443.2667. $[\alpha]_{\text{D}}^{25} = -27.0$ ($c = 0.033$ MeOH).

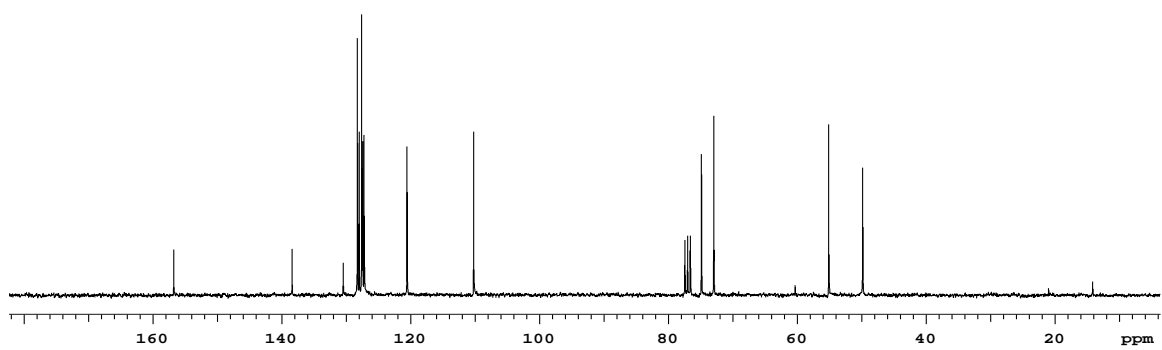
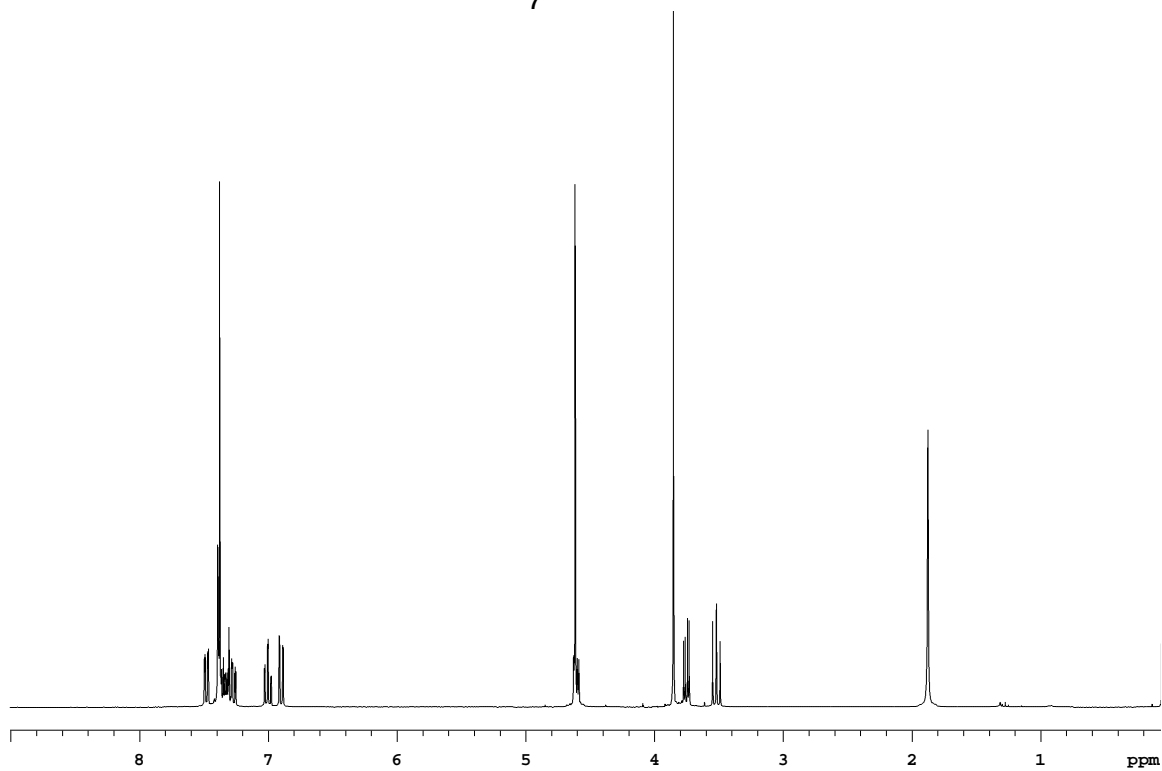
NMR Spectra of Selected Compounds



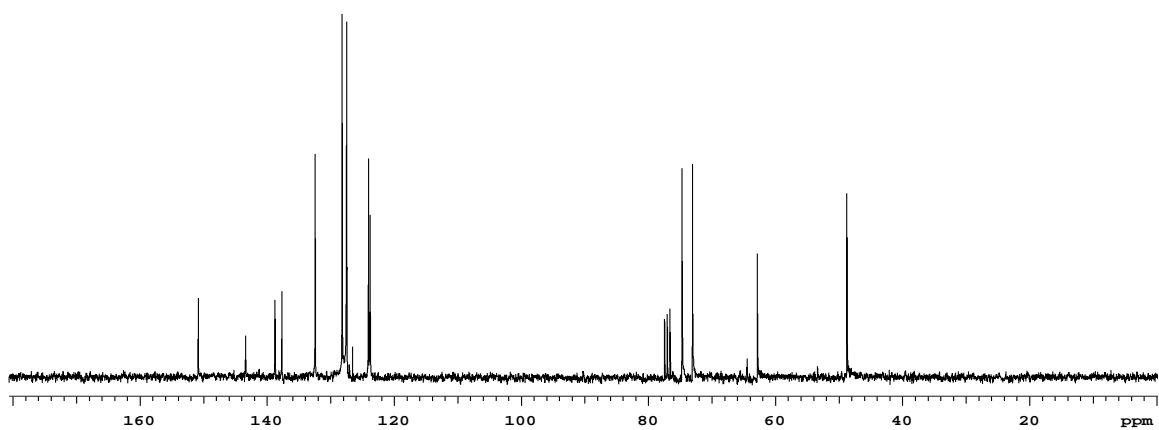
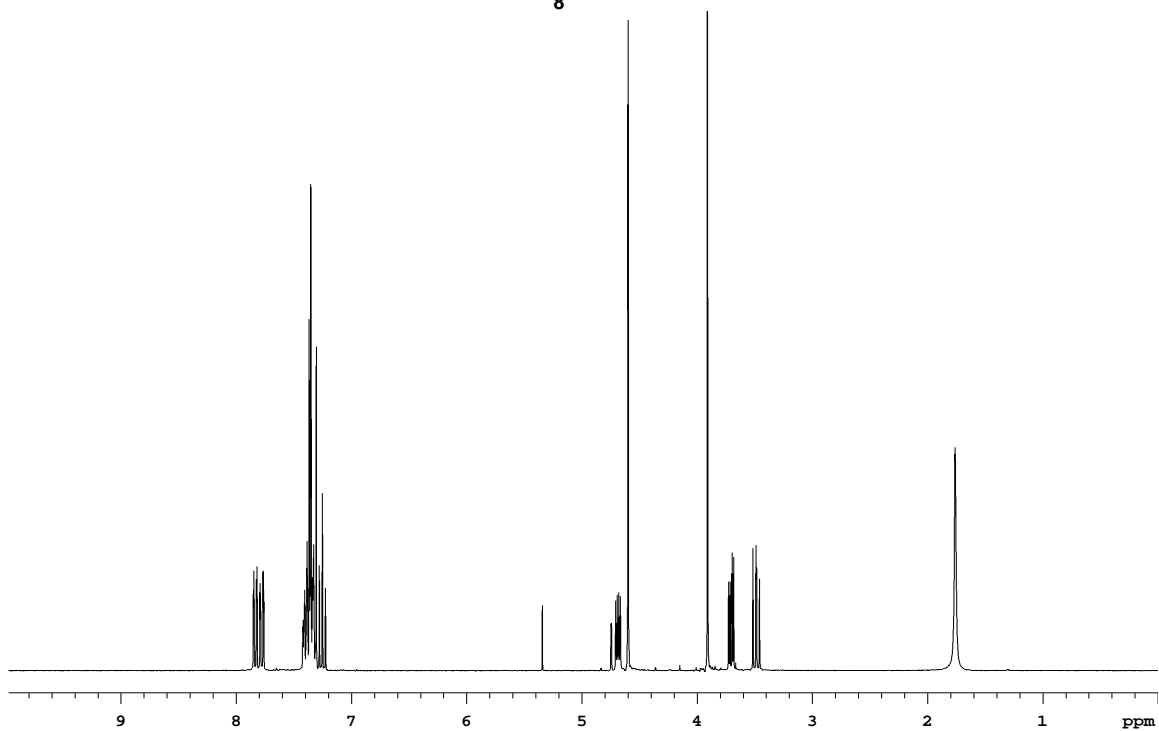
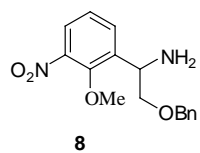
Compound **6**: ^1H -NMR (300 MHz) and ^{13}C -NMR (75 MHz) in CDCl_3



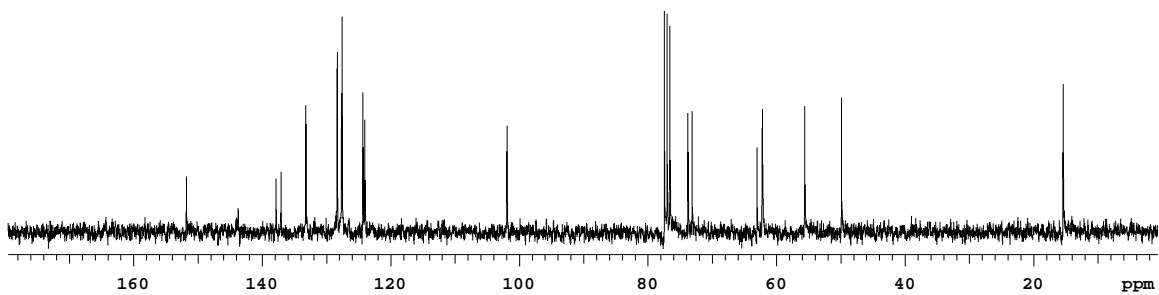
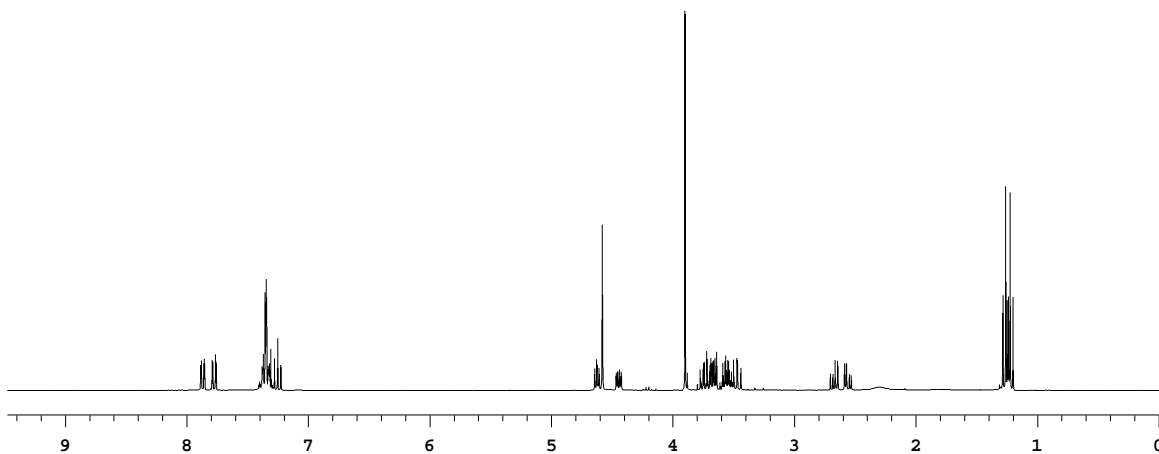
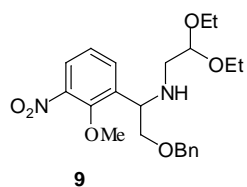
7



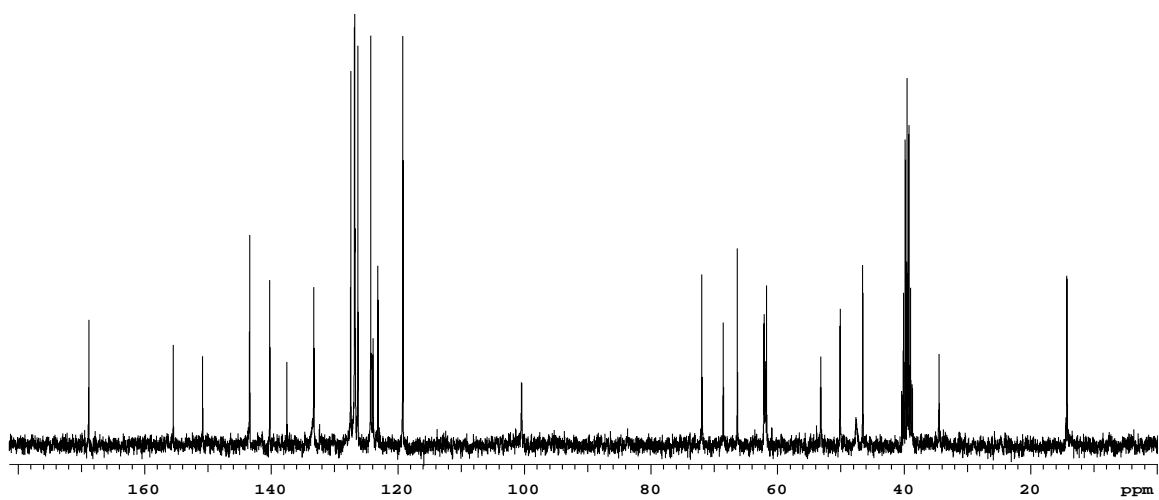
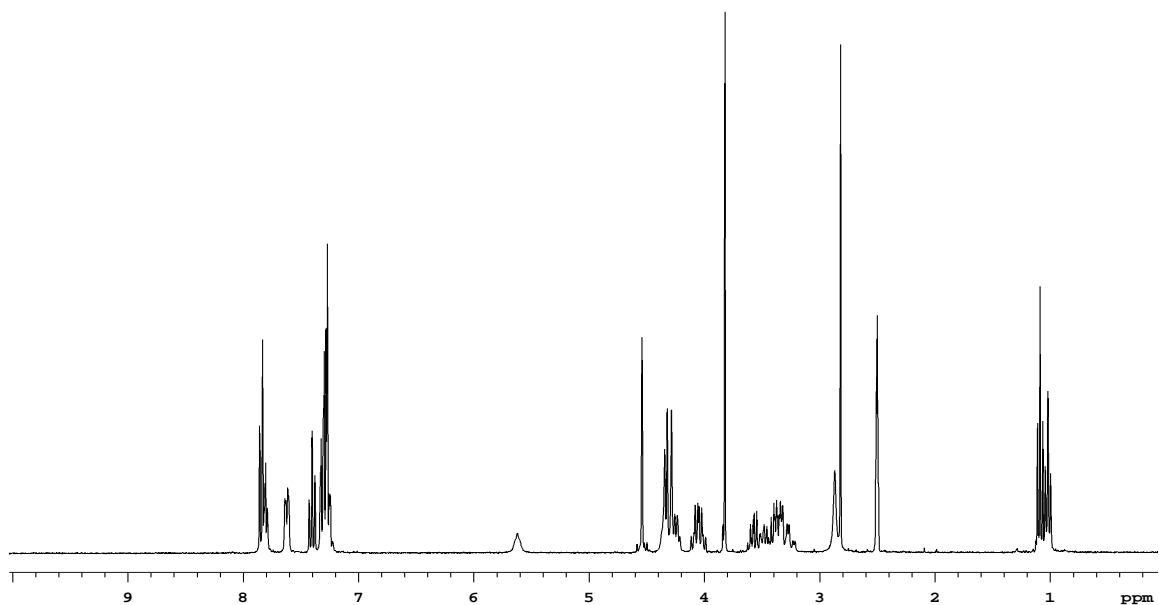
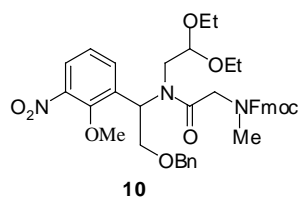
Compound 7: ¹H-NMR (300 MHz) and ¹³C-NMR (75 MHz) in CDCl₃



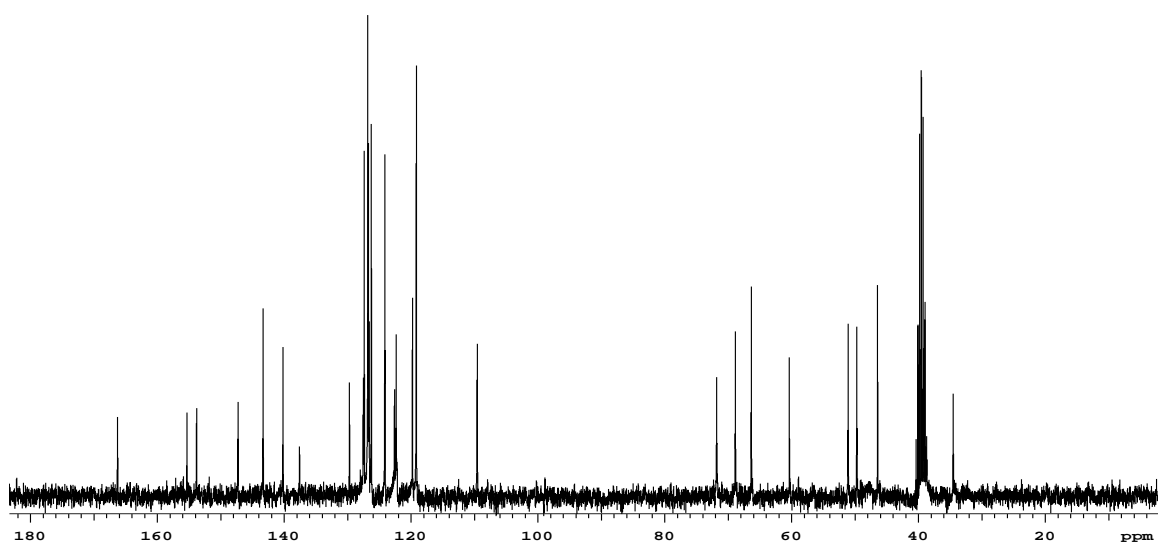
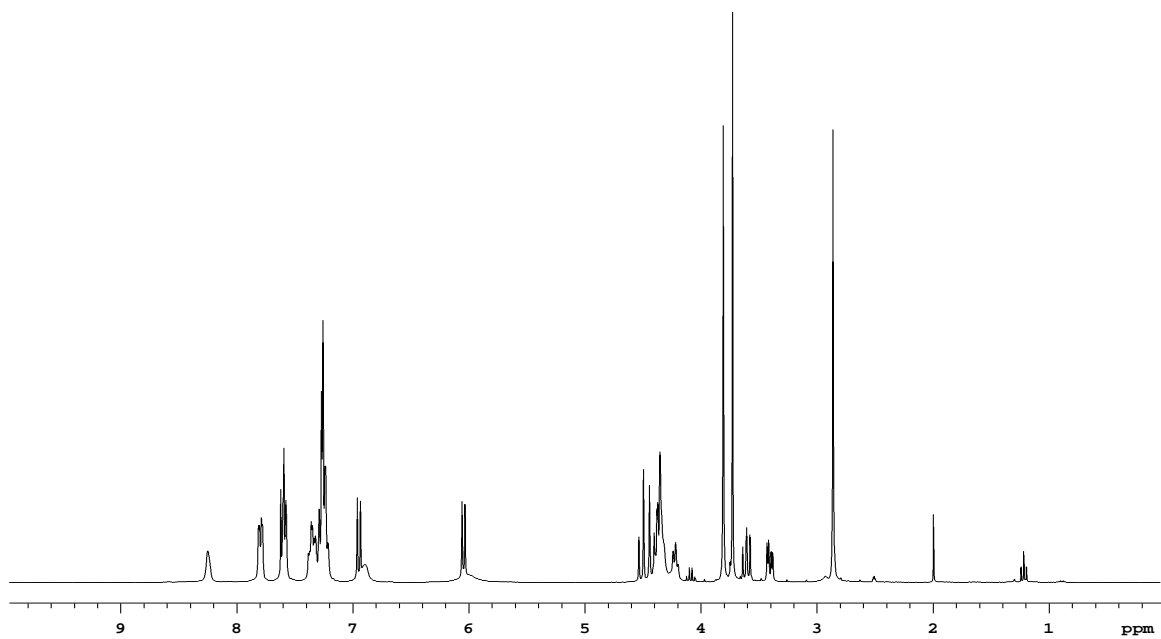
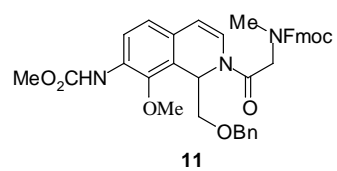
Compound **8**: ¹H-NMR (300 MHz) and ¹³C-NMR (75 MHz) in CDCl₃



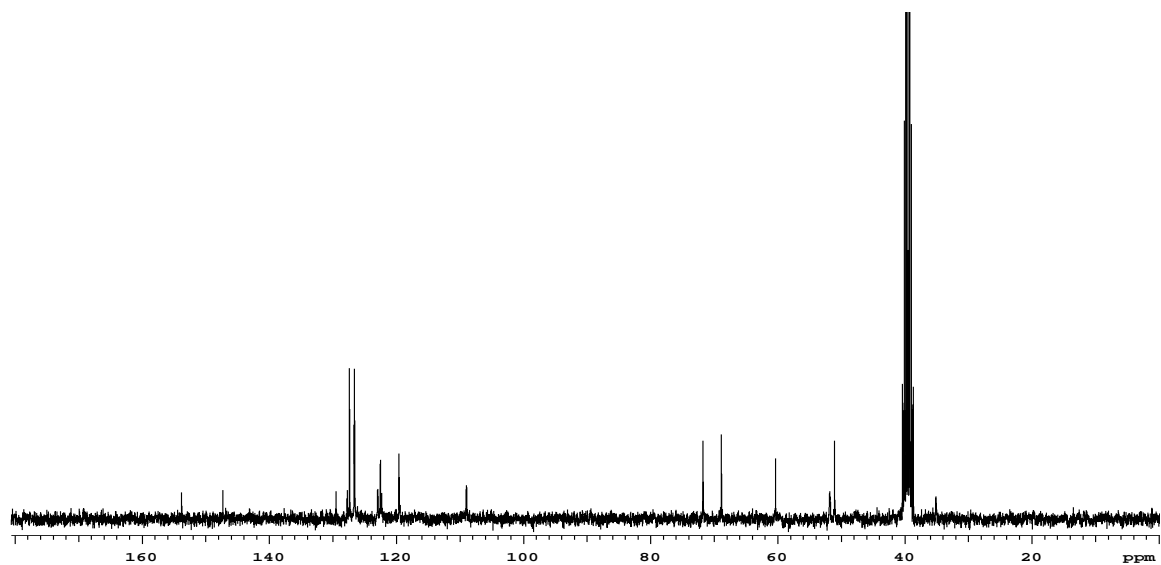
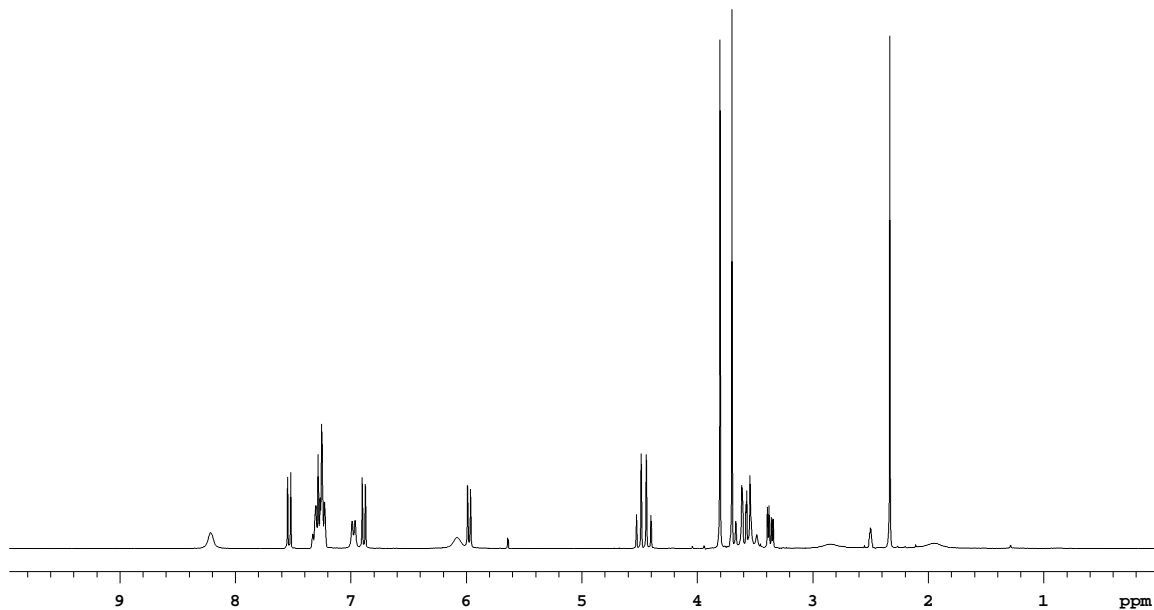
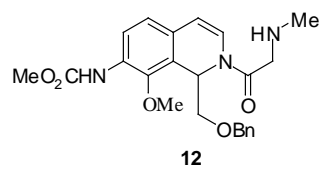
Compound **9**: ¹H-NMR (300 MHz) and ¹³C-NMR (75 MHz) in CDCl₃



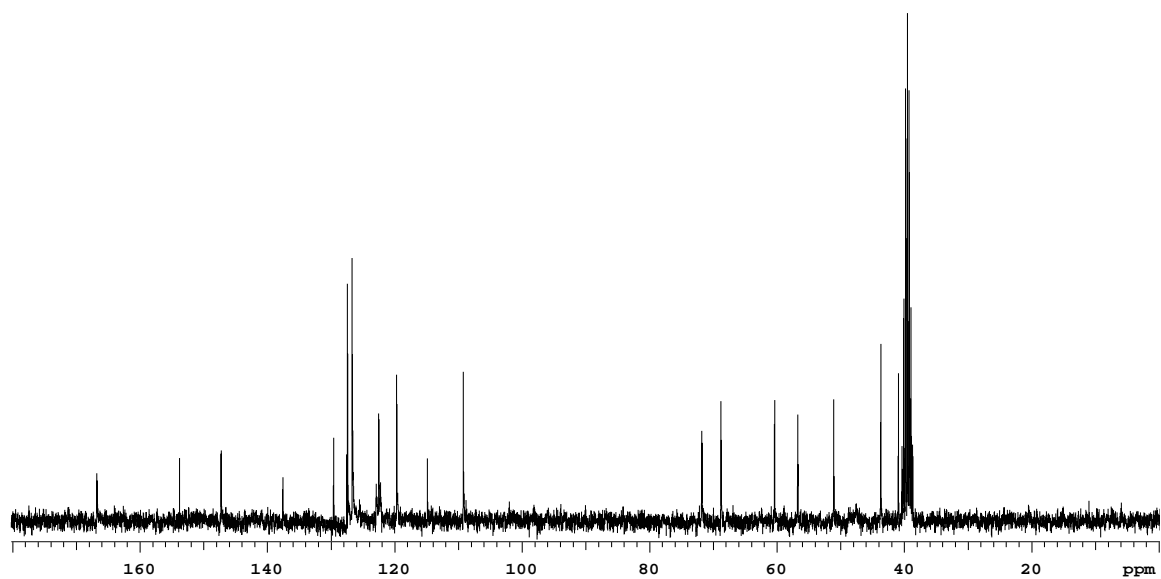
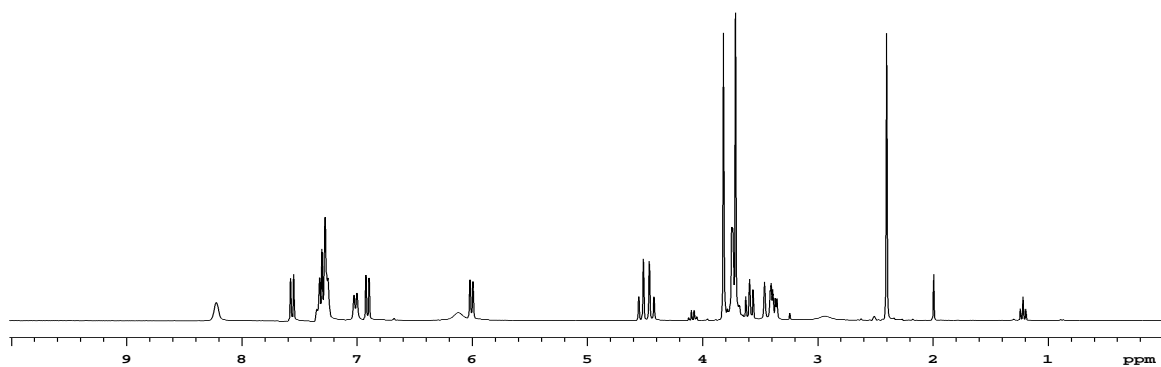
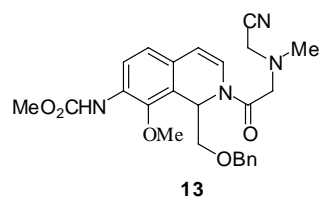
Compound **10**: ^1H -NMR (300 MHz) and ^{13}C -NMR (75 MHz) in d_6 -DMSO at 120°C



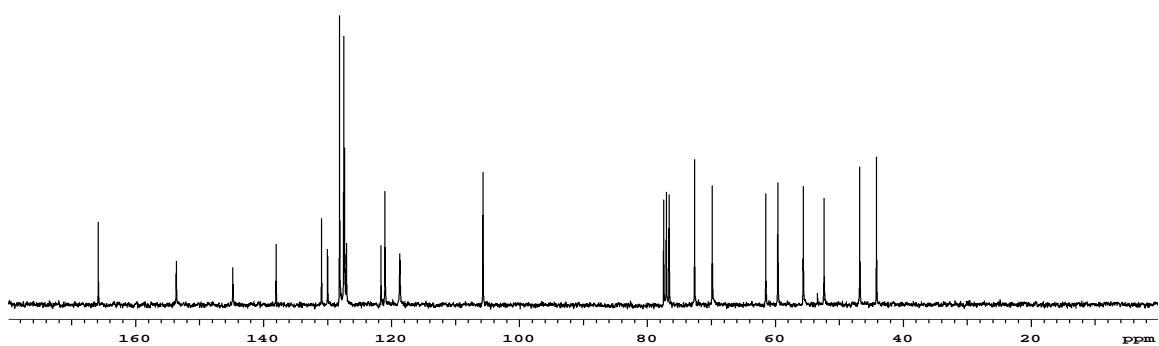
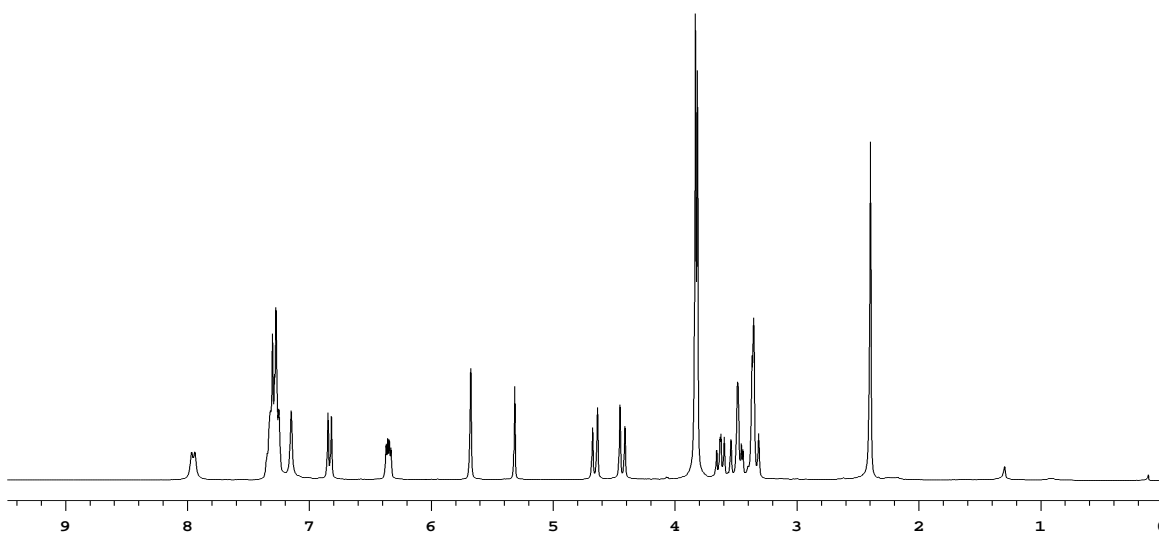
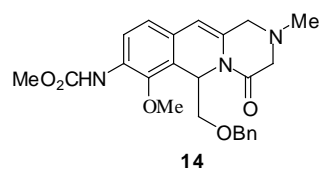
Compound **11**: ¹H-NMR (300 MHz) and ¹³C-NMR (75 MHz) in d₆-DMSO at 120°C



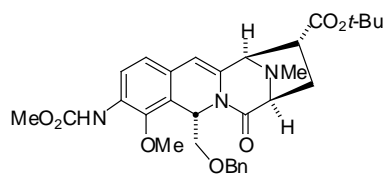
Compound **12**: ¹H-NMR (300 MHz) and ¹³C-NMR (75 MHz) in d₆-DMSO at 120°C



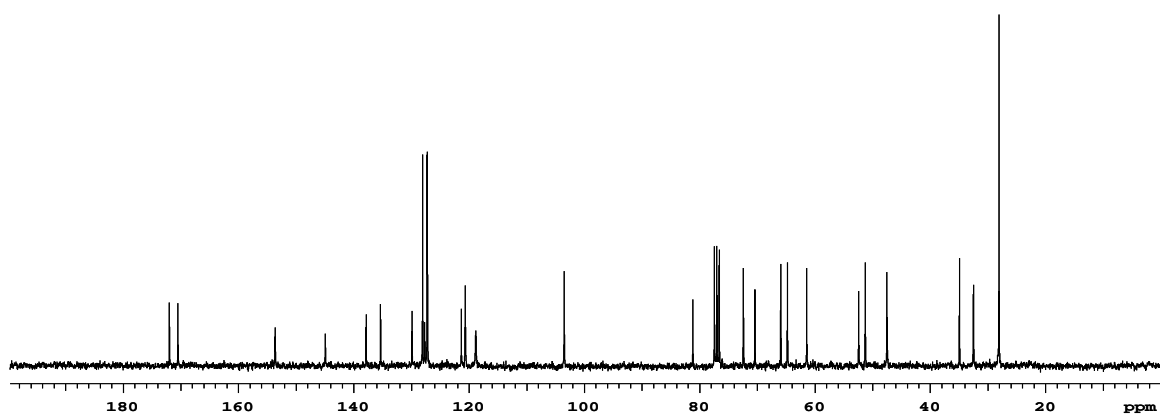
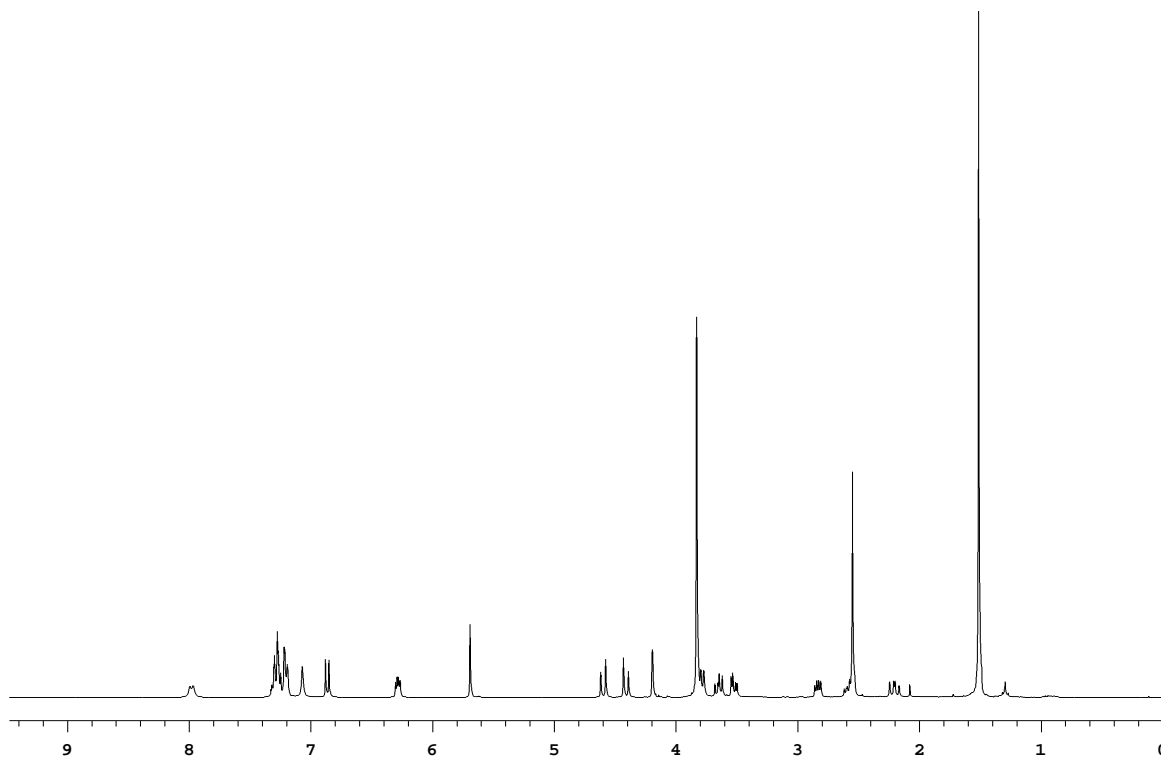
Compound **13**: ¹H-NMR (300 MHz) and ¹³C-NMR (75 MHz) in d₆-DMSO at 120°C



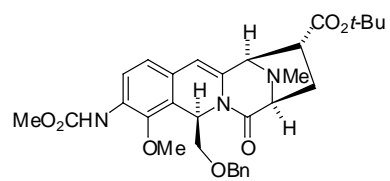
Compound **14**: ^1H -NMR (300 MHz) and ^{13}C -NMR (75 MHz) in CDCl_3



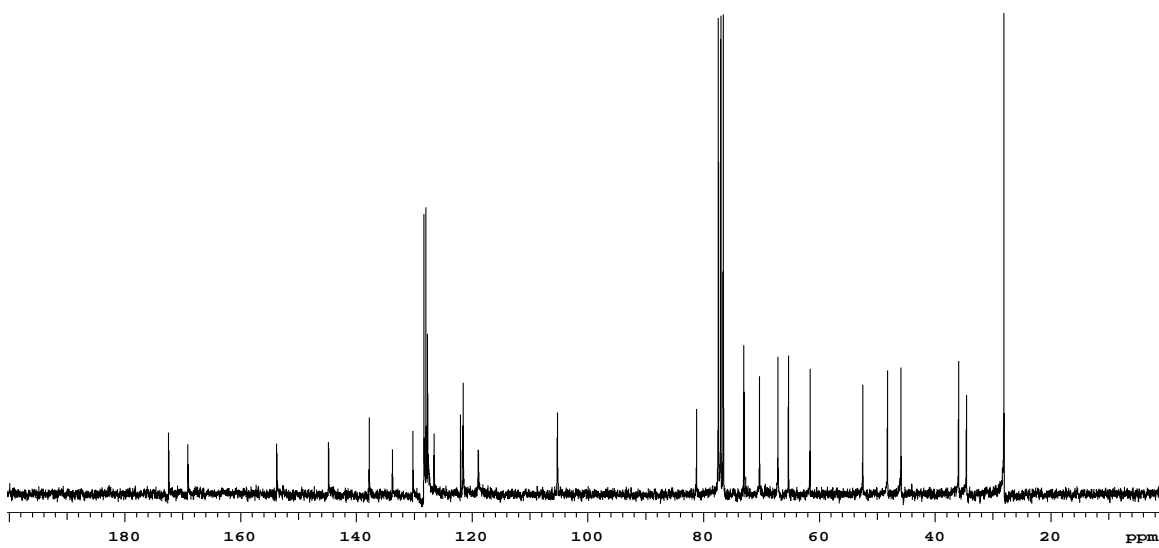
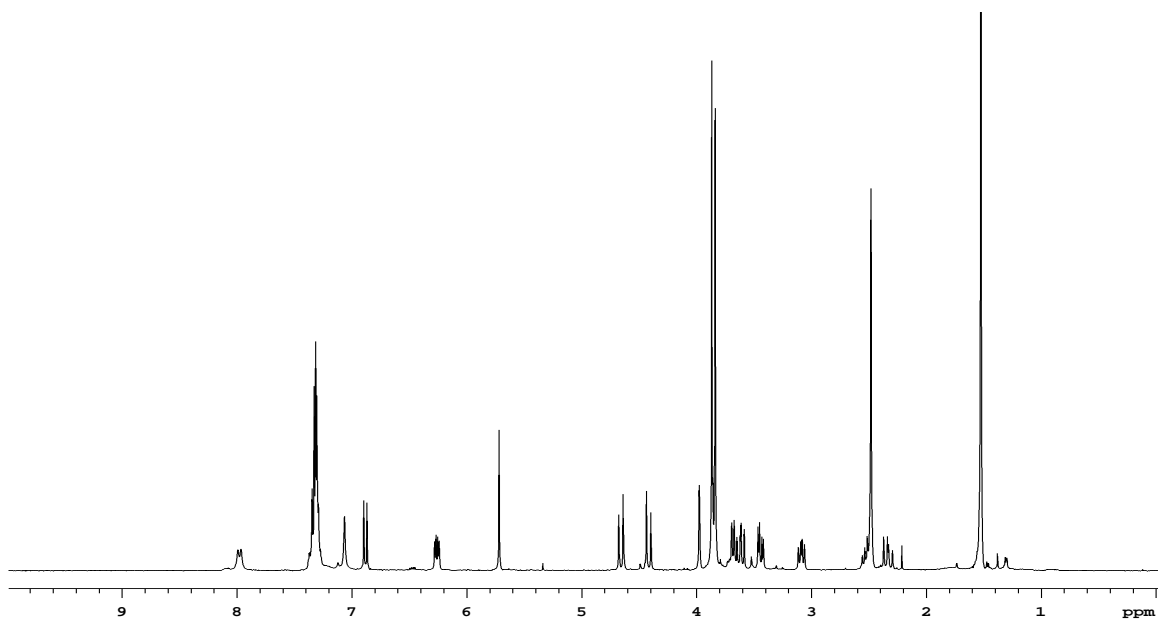
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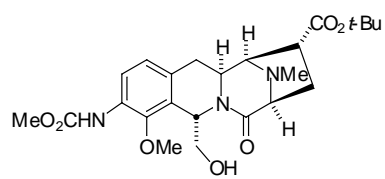
Compound **17**: ^1H -NMR (300 MHz) and ^{13}C -NMR (75 MHz) in CDCl_3



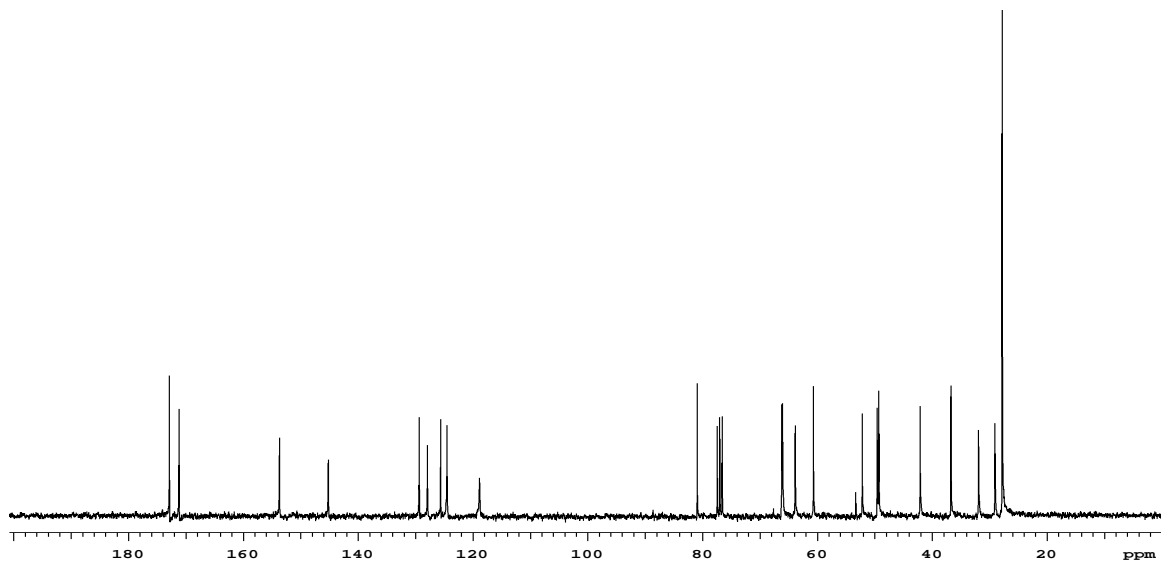
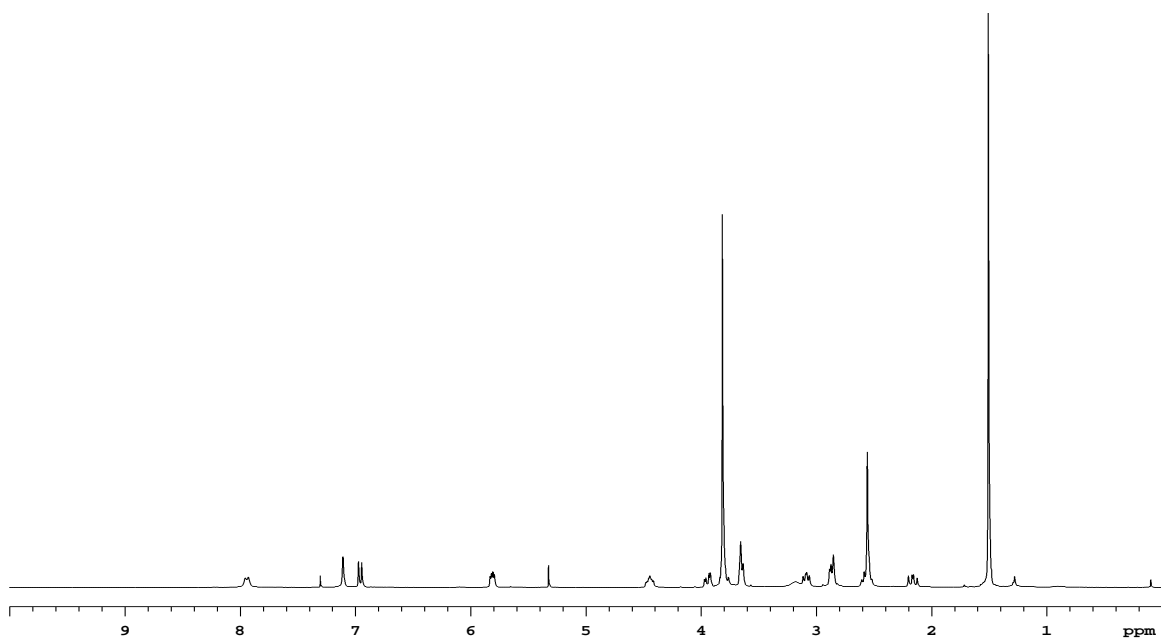
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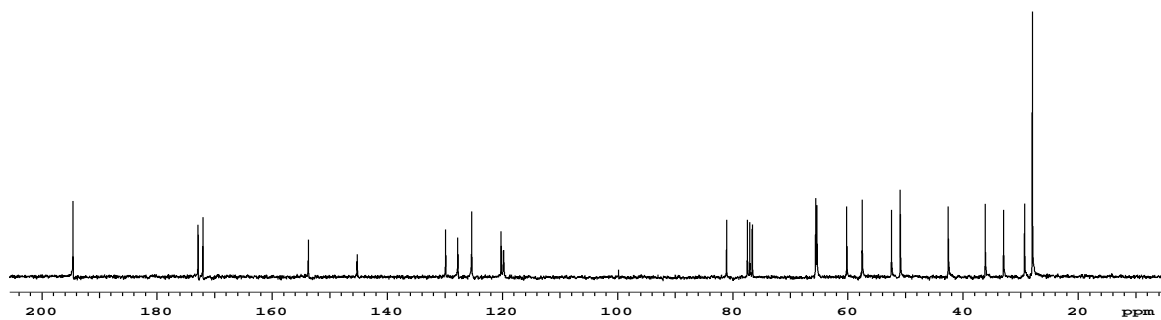
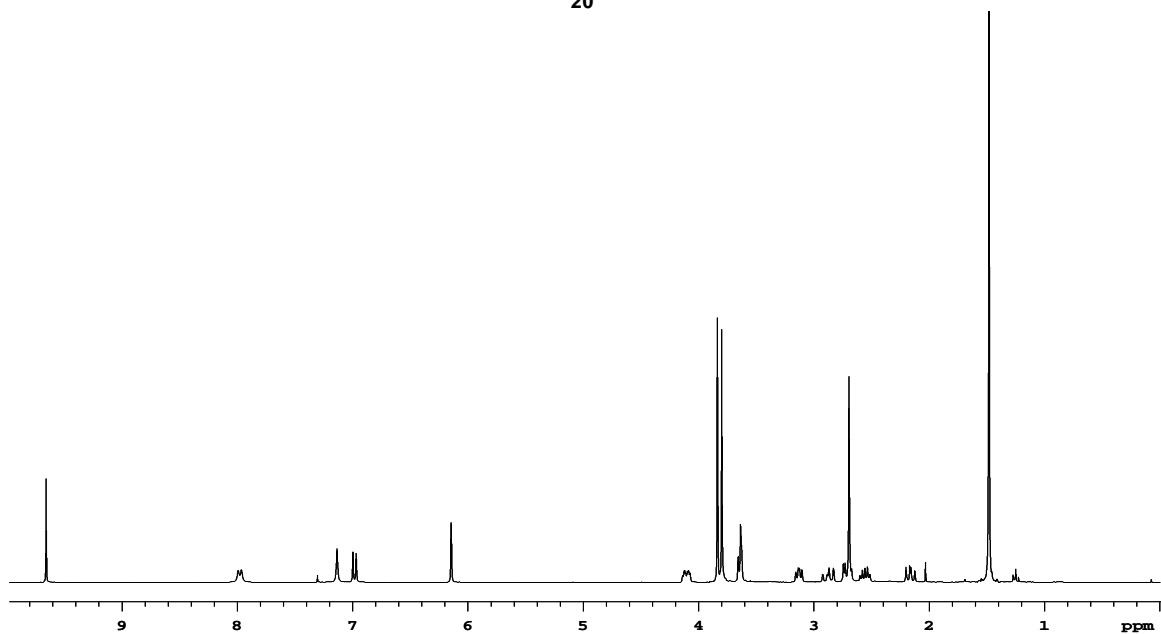
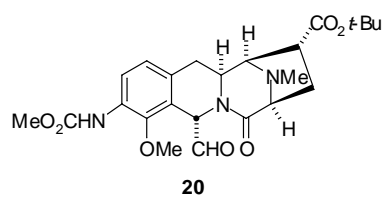
Compound **18**: ^1H -NMR (300 MHz) and ^{13}C -NMR (75 MHz) in CDCl_3



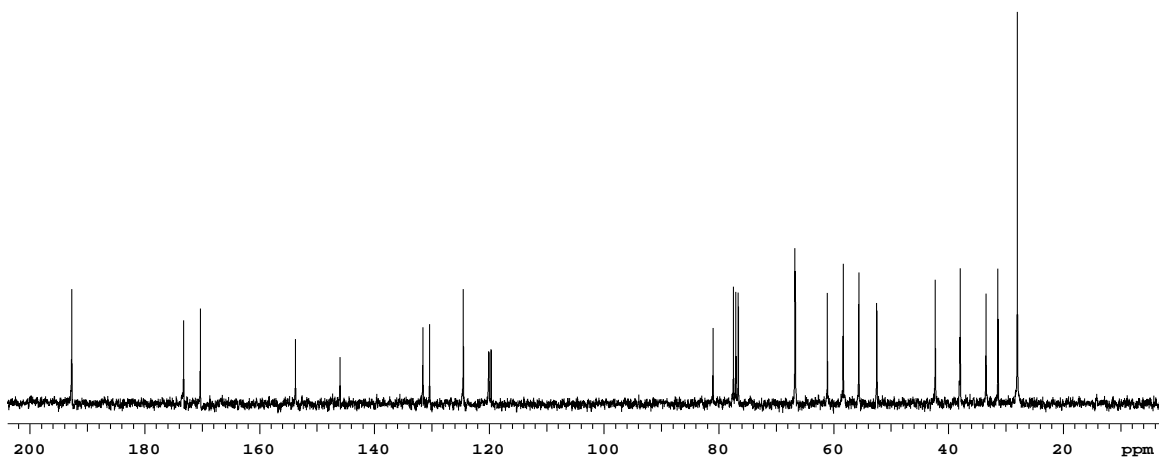
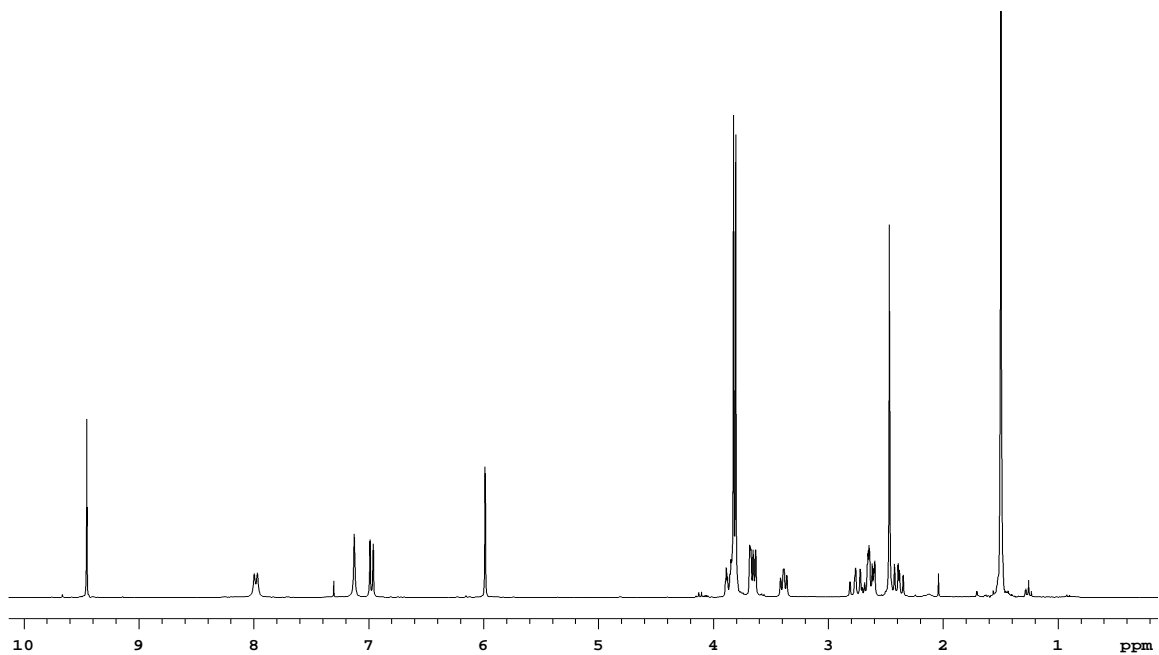
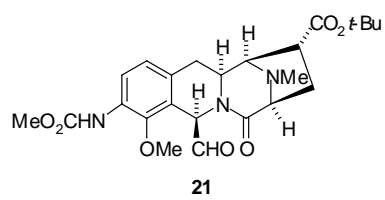
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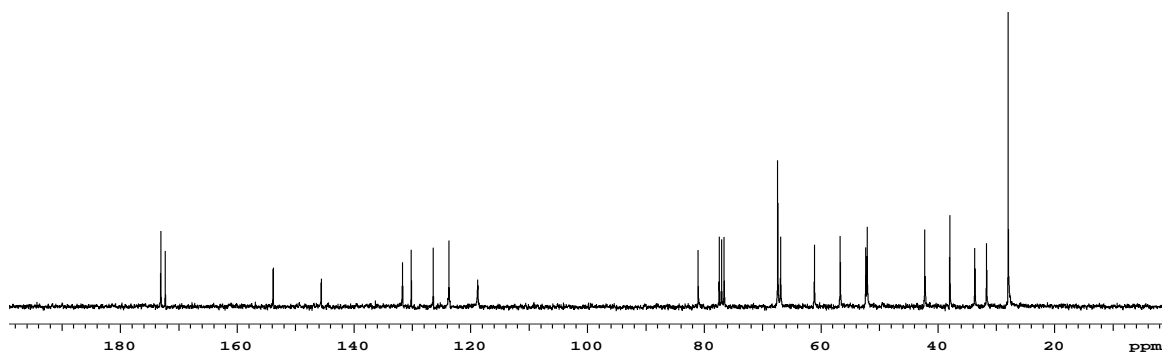
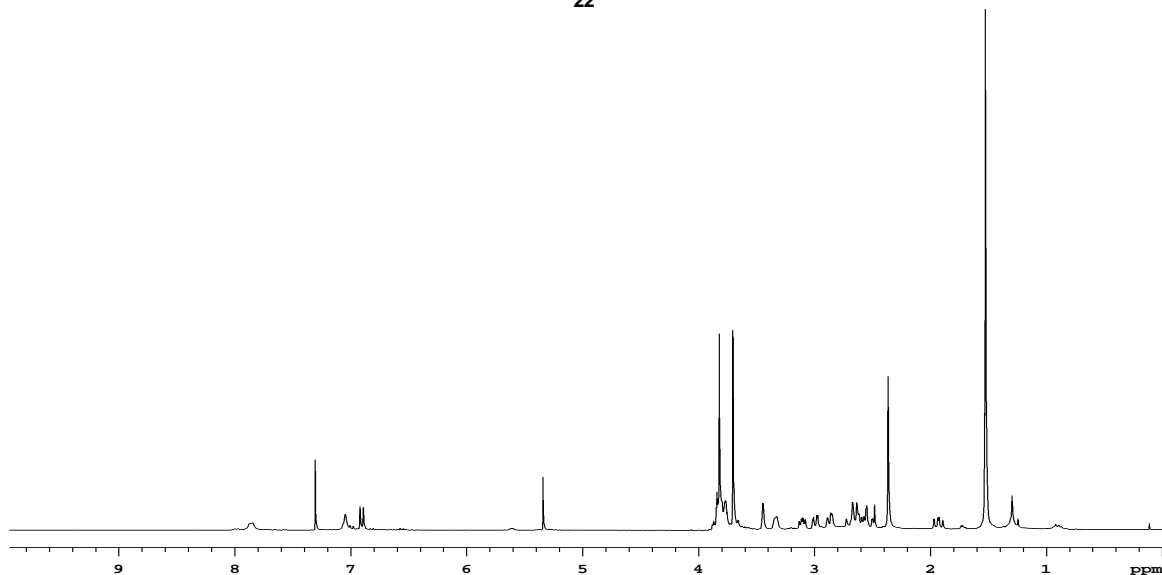
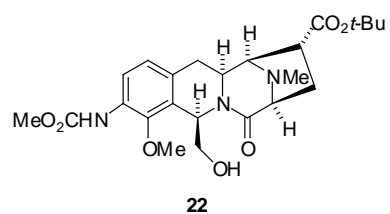
Compound **19**: ^1H -NMR (300 MHz) and ^{13}C -NMR (75 MHz) in CDCl_3



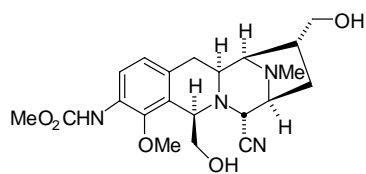
Compound **20**: ^1H -NMR (300 MHz) and ^{13}C -NMR (75 MHz) in CDCl_3



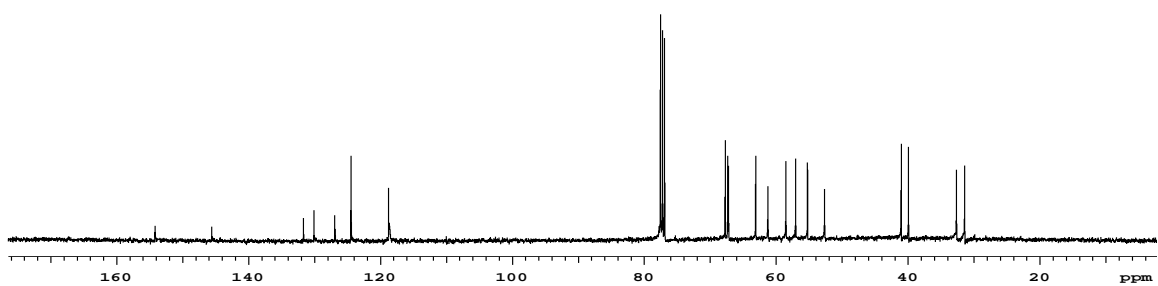
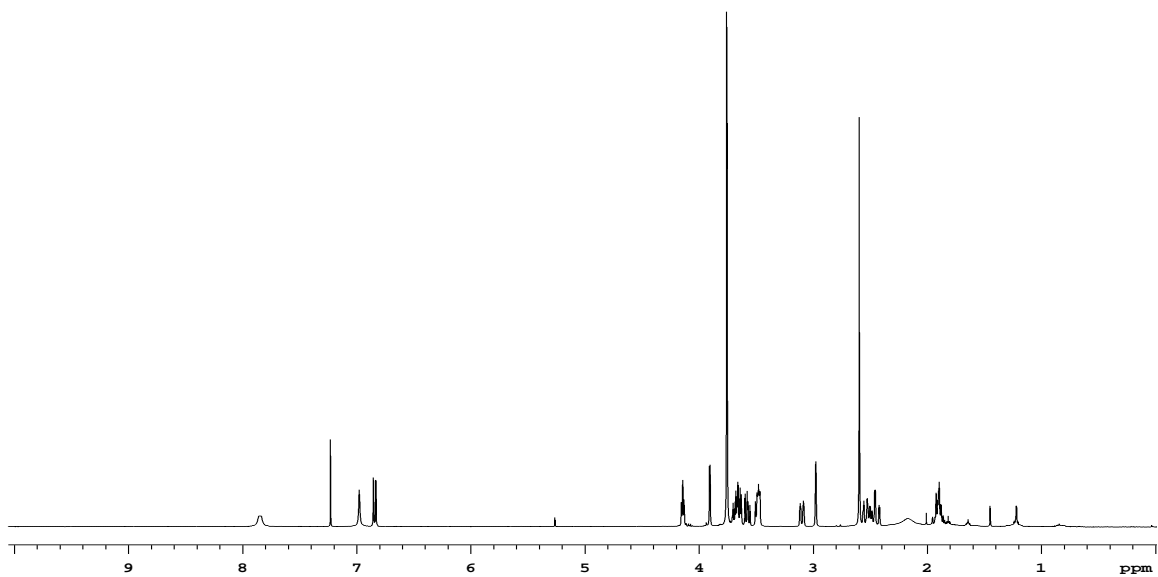
Compound **21**: ^1H -NMR (300 MHz) and ^{13}C -NMR (75 MHz) in CDCl_3



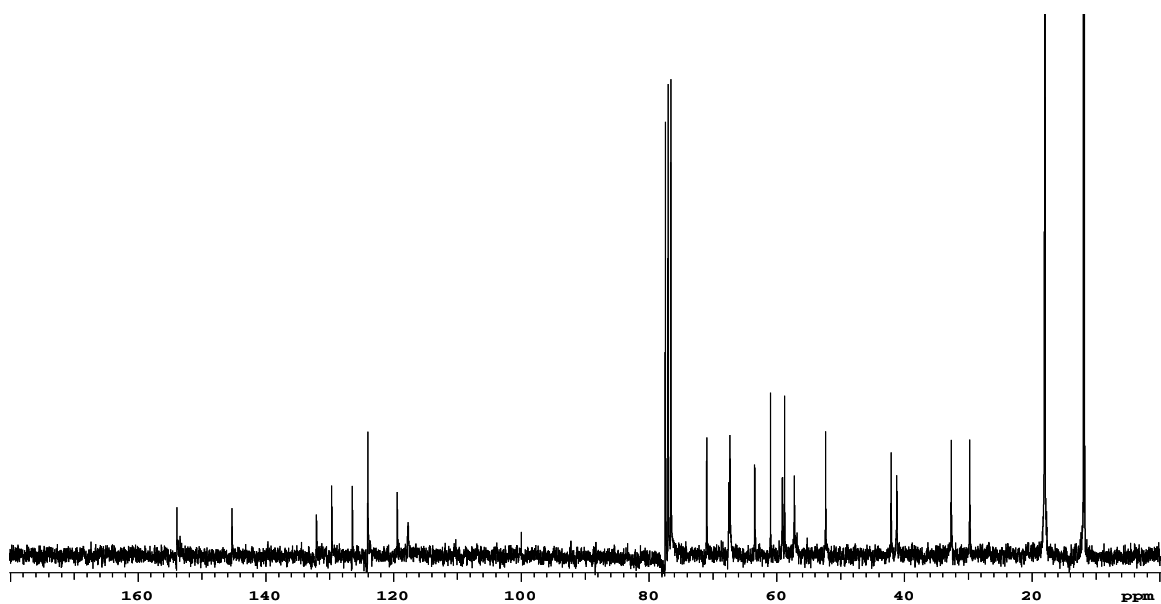
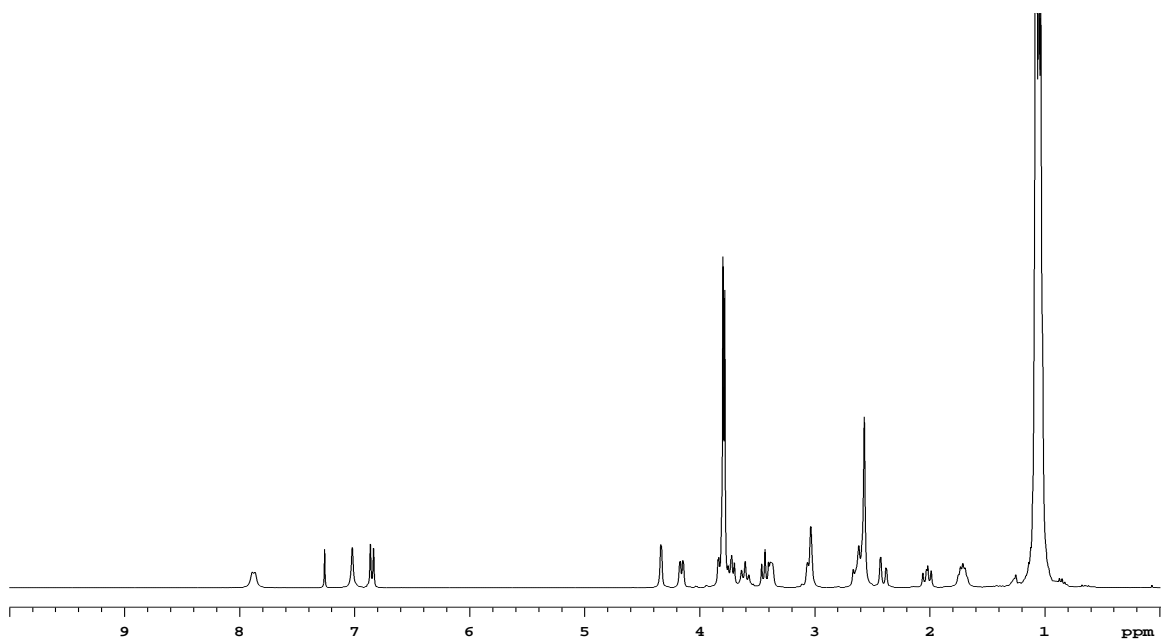
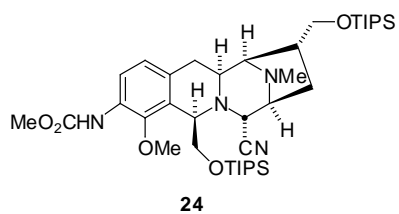
Compound **22**: ^1H -NMR (300 MHz) and ^{13}C -NMR (75 MHz) in CDCl_3



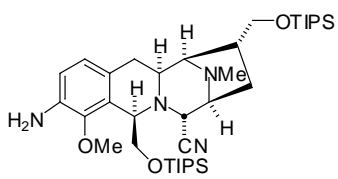
23



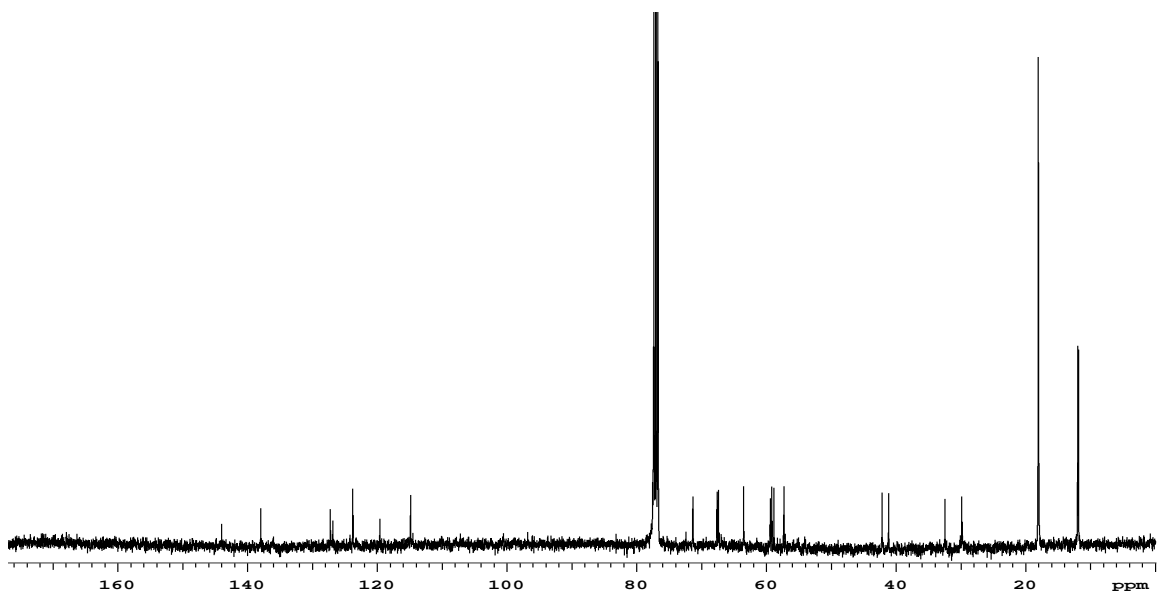
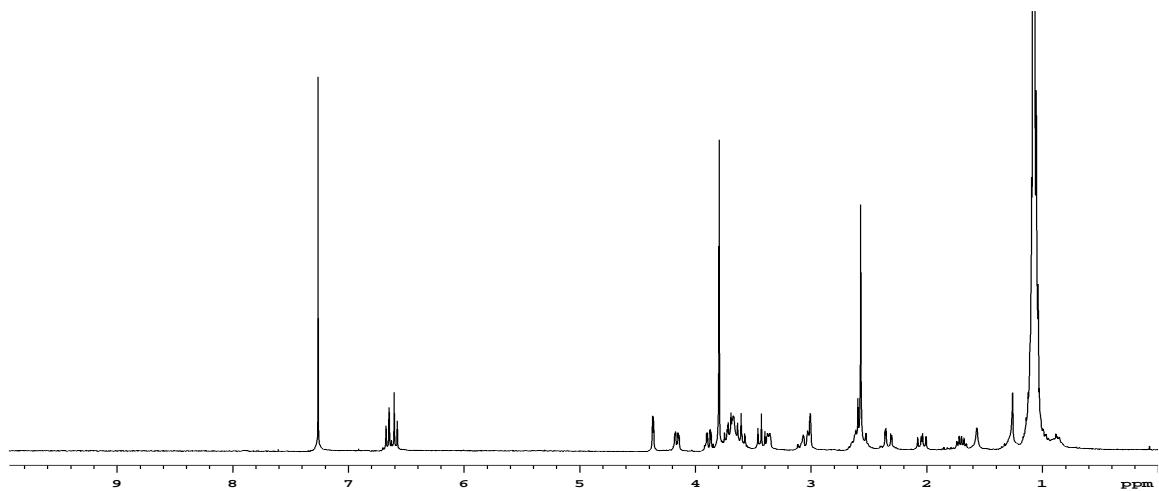
Compound **23**: ^1H -NMR (400 MHz) and ^{13}C -NMR (100 MHz) in CDCl_3



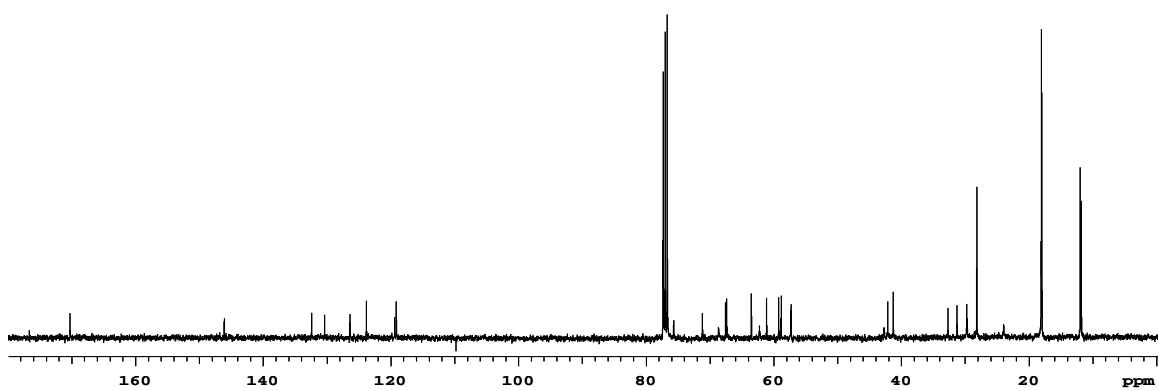
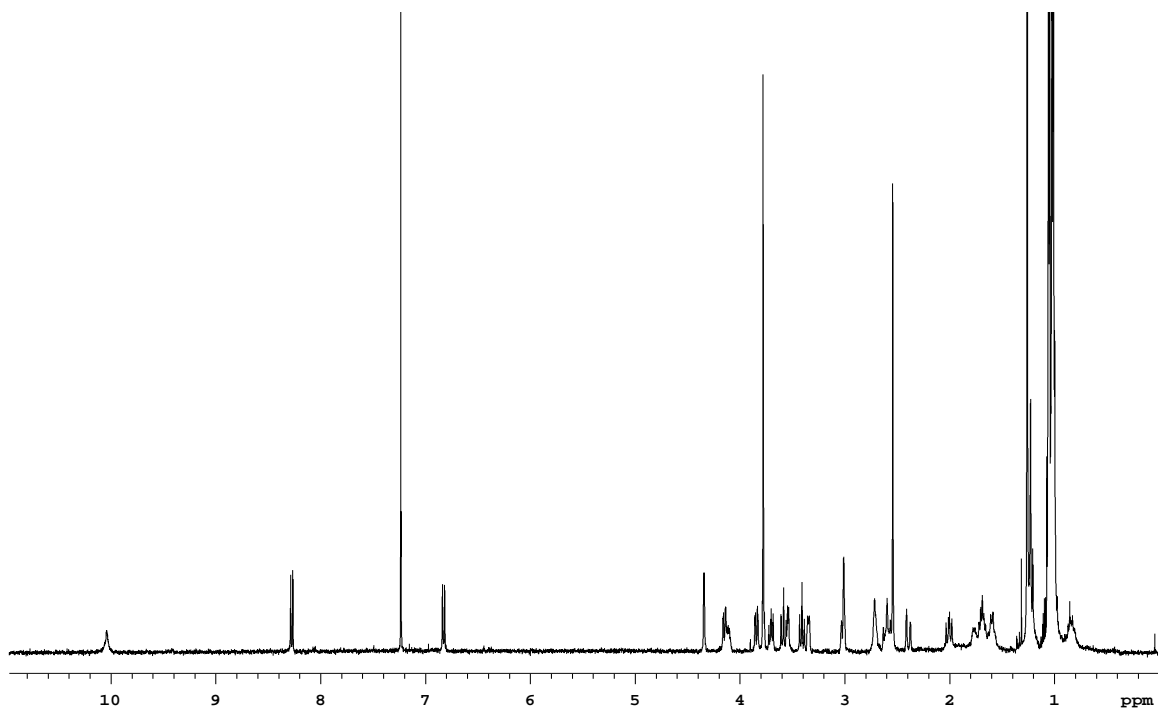
Compound **24**: ^1H -NMR (300 MHz) and ^{13}C -NMR (75 MHz) in CDCl_3



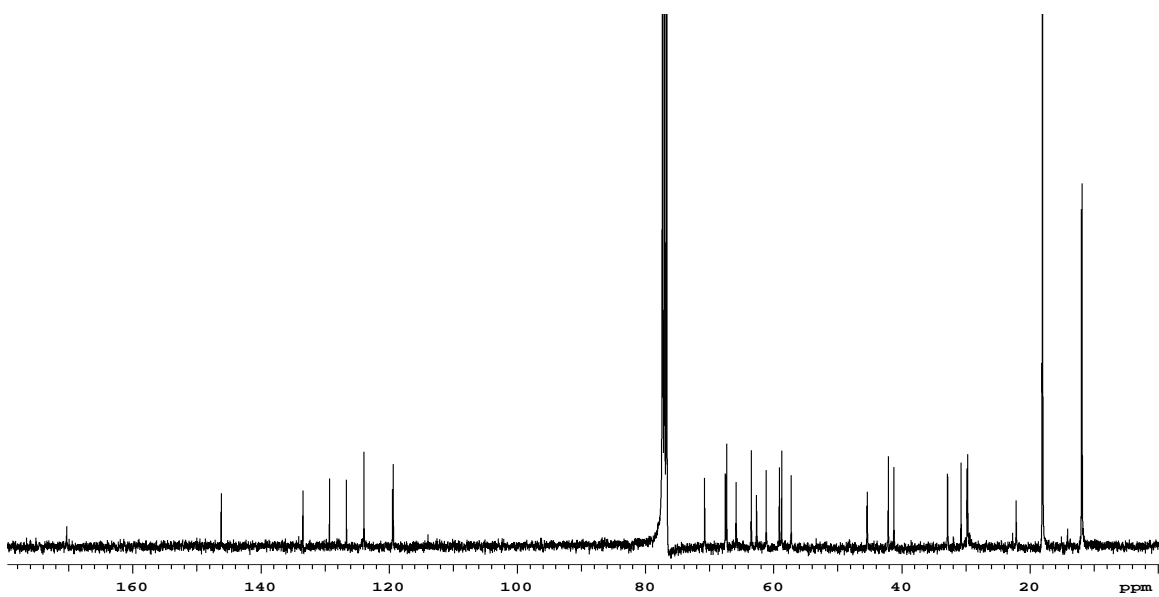
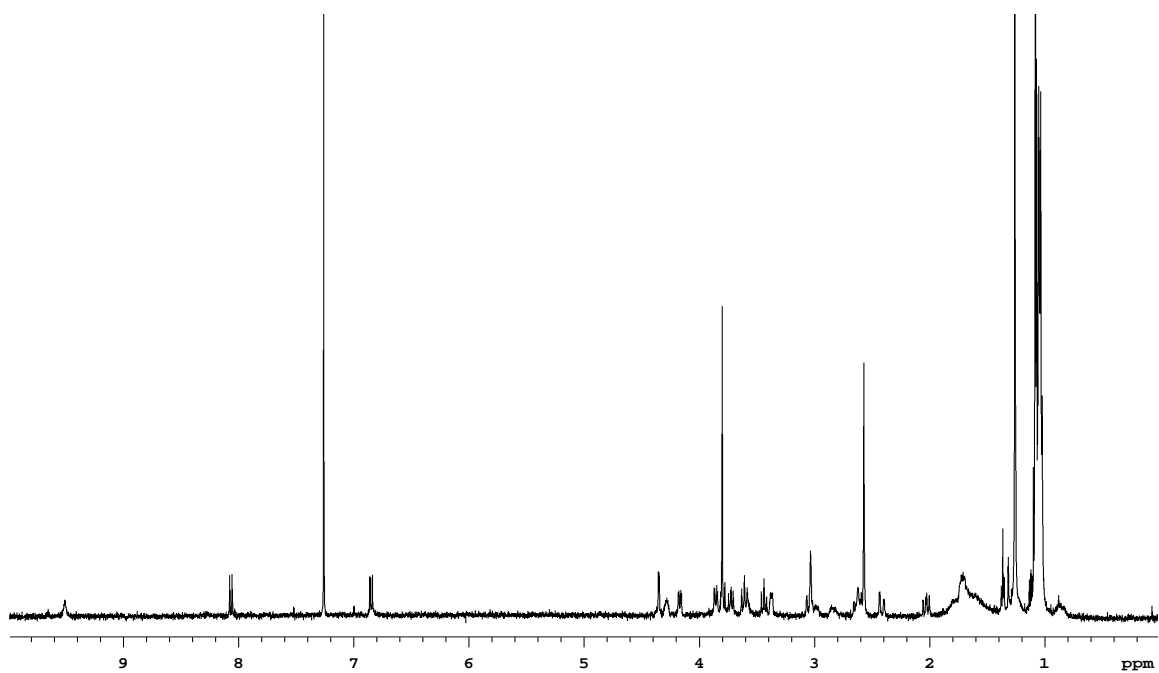
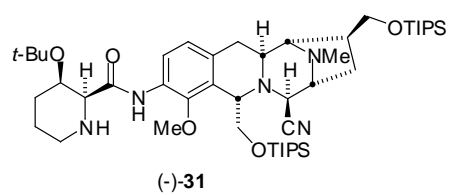
25



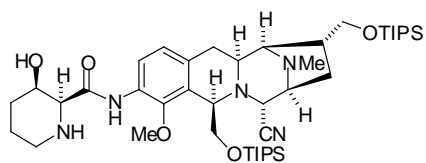
Compound **25**: ^1H -NMR (300 MHz) and ^{13}C -NMR (100 MHz) in CDCl_3



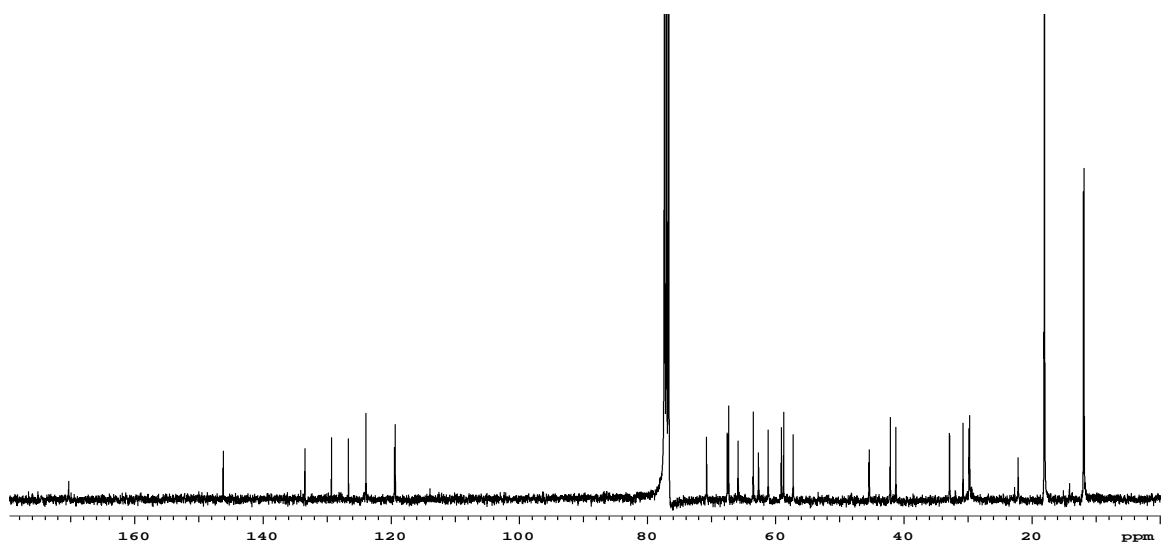
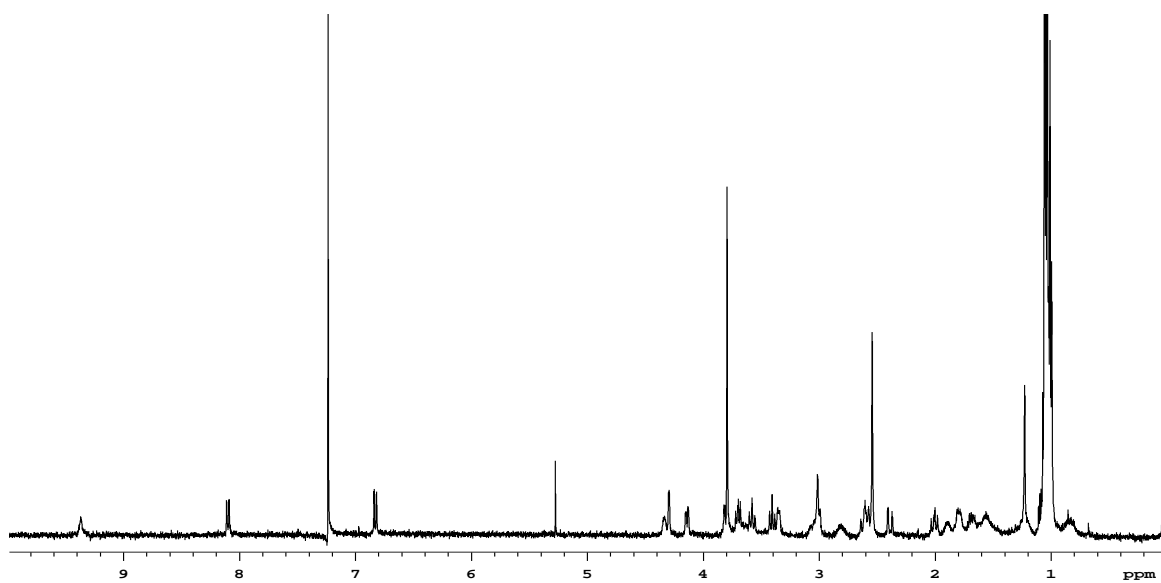
Compound **30**: ^1H -NMR (400 MHz) and ^{13}C -NMR (100 MHz) in CDCl_3



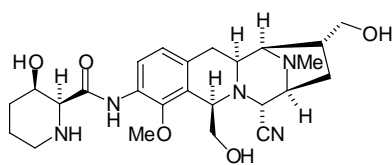
Compound **31**: ¹H-NMR (400 MHz) and ¹³C-NMR (100 MHz) in CDCl₃



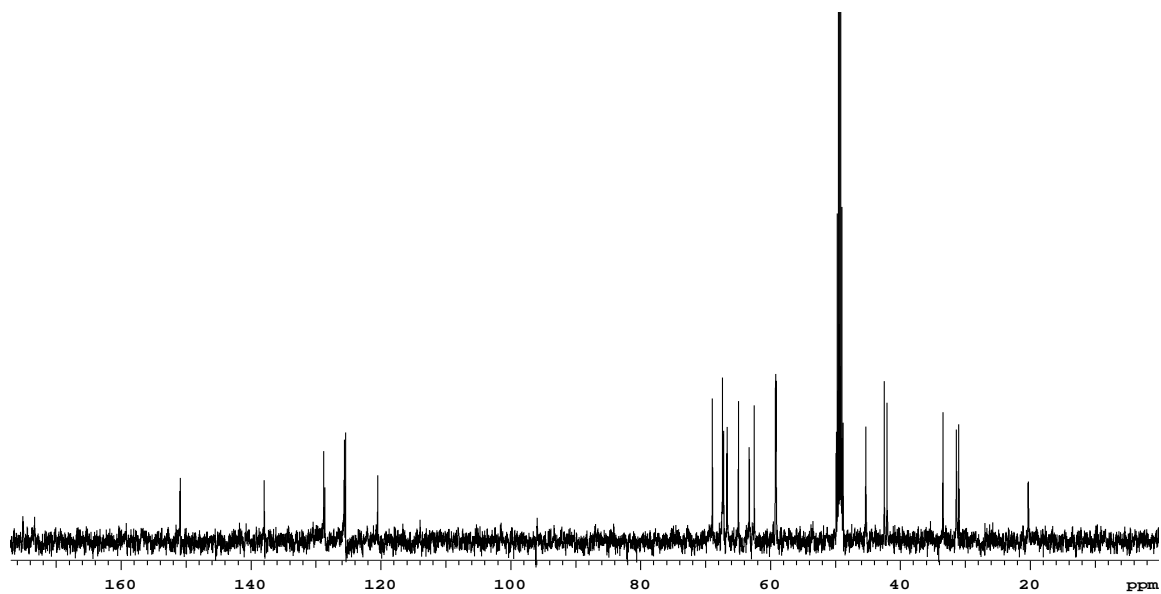
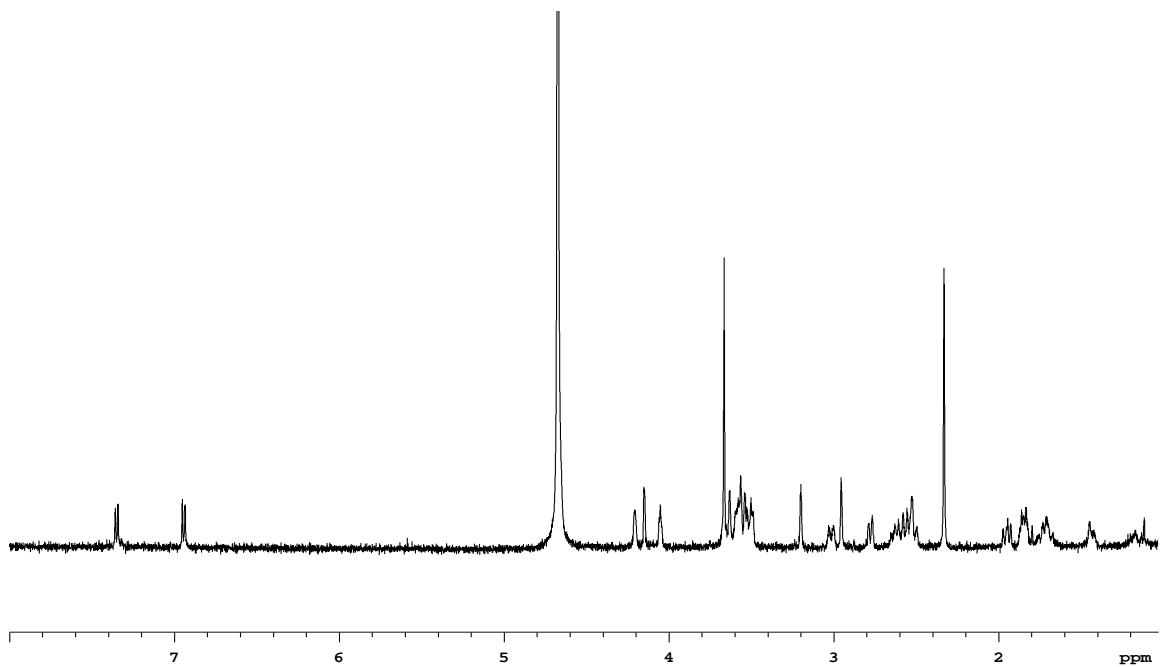
(+)-32



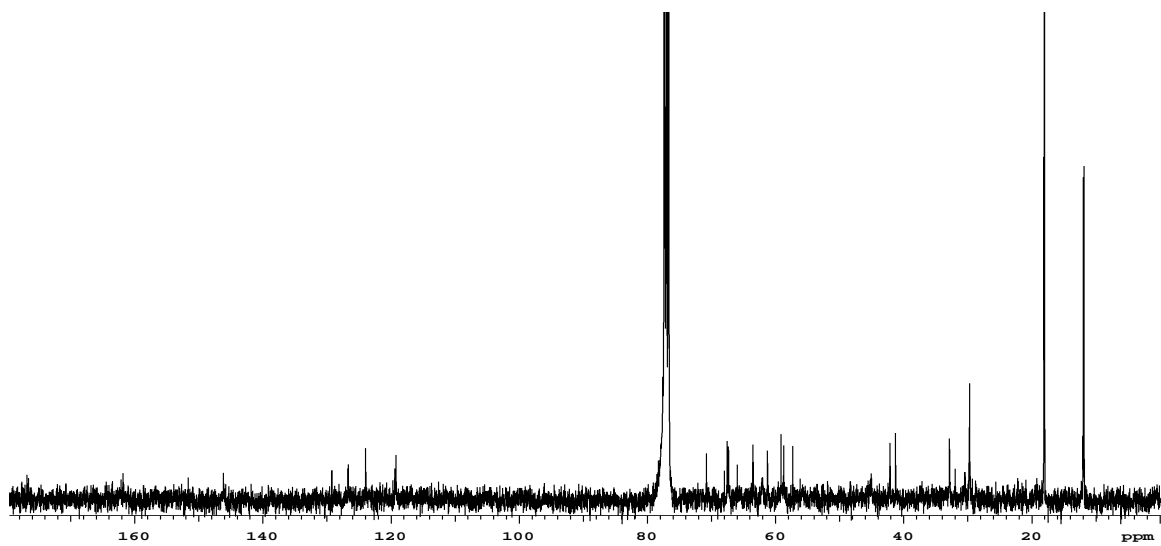
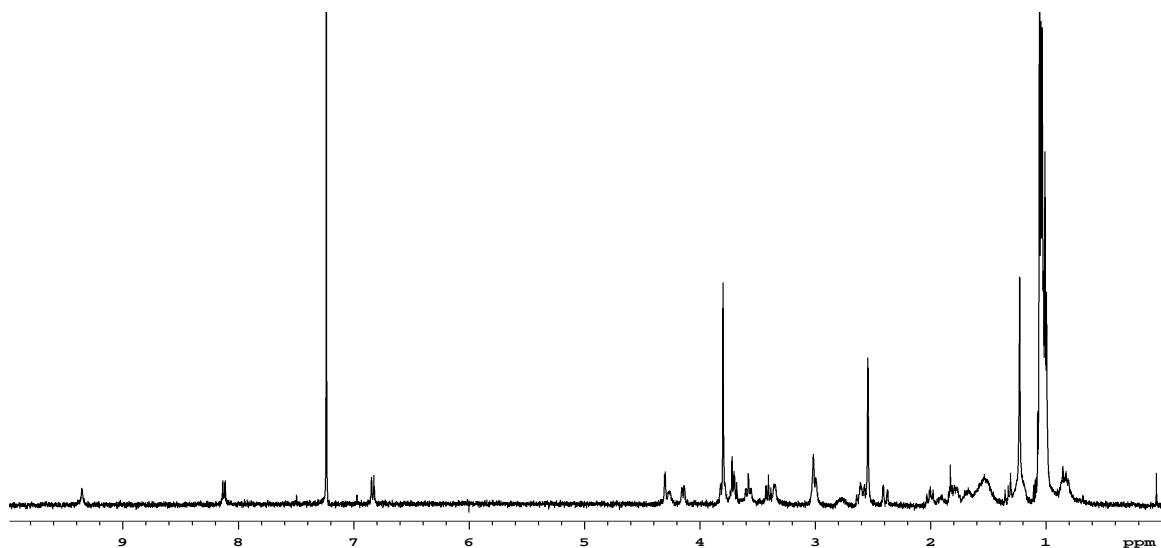
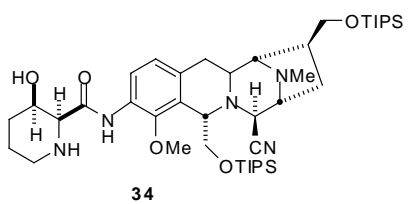
Compound **32**: ^1H -NMR (400 MHz) and ^{13}C -NMR (100 MHz) in CDCl_3



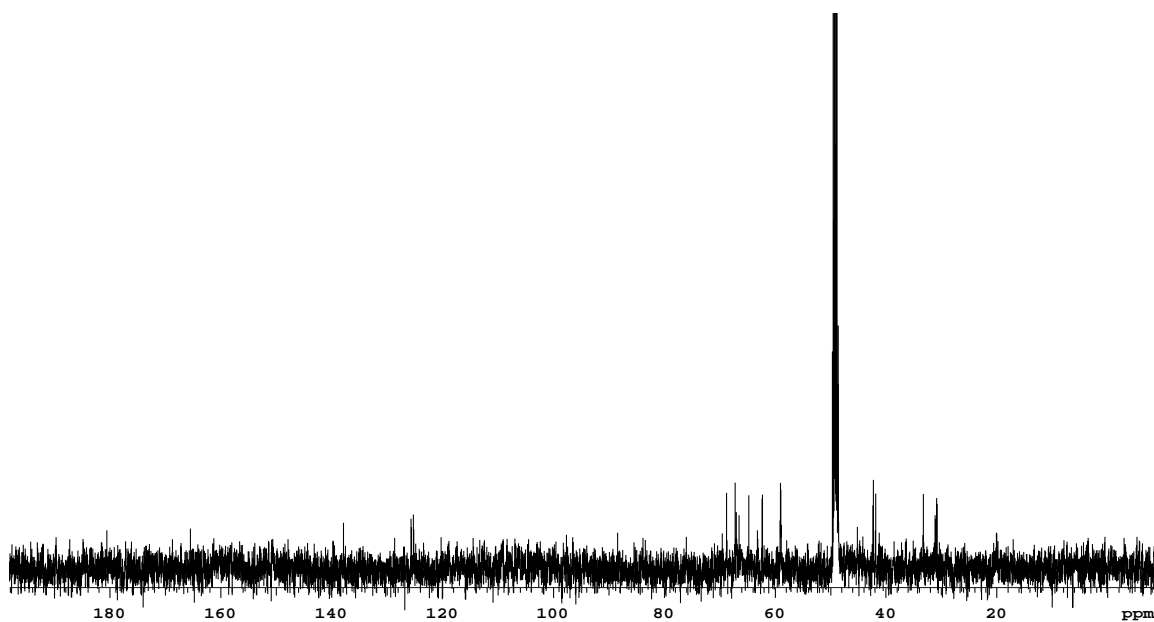
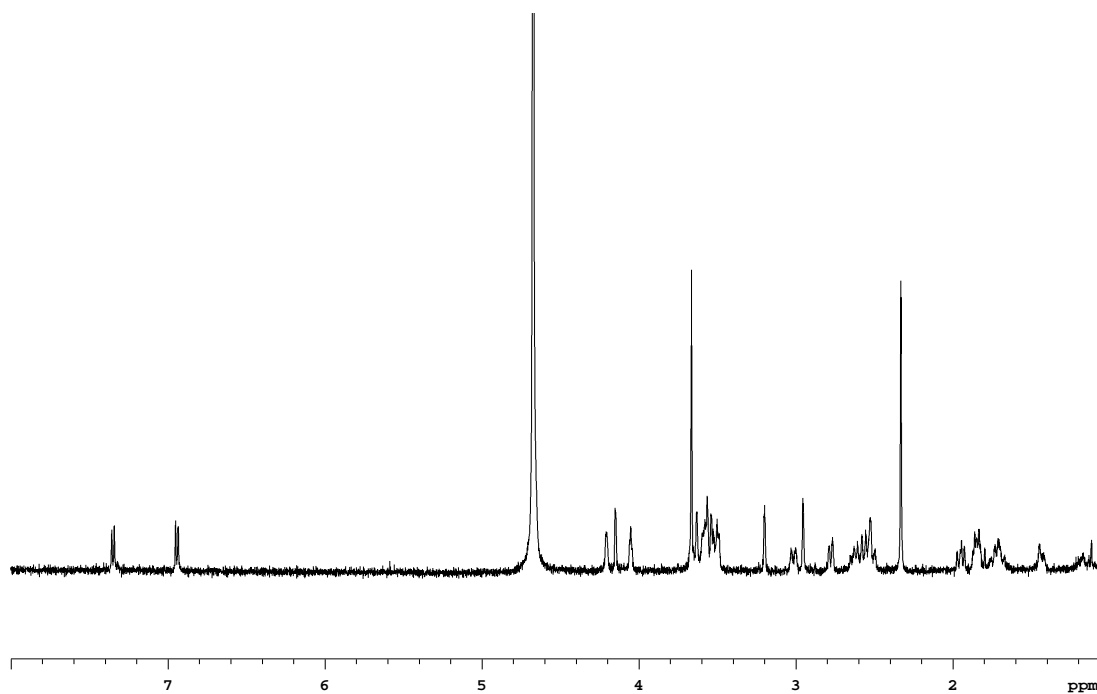
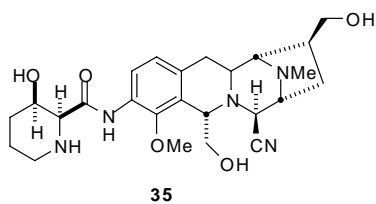
33



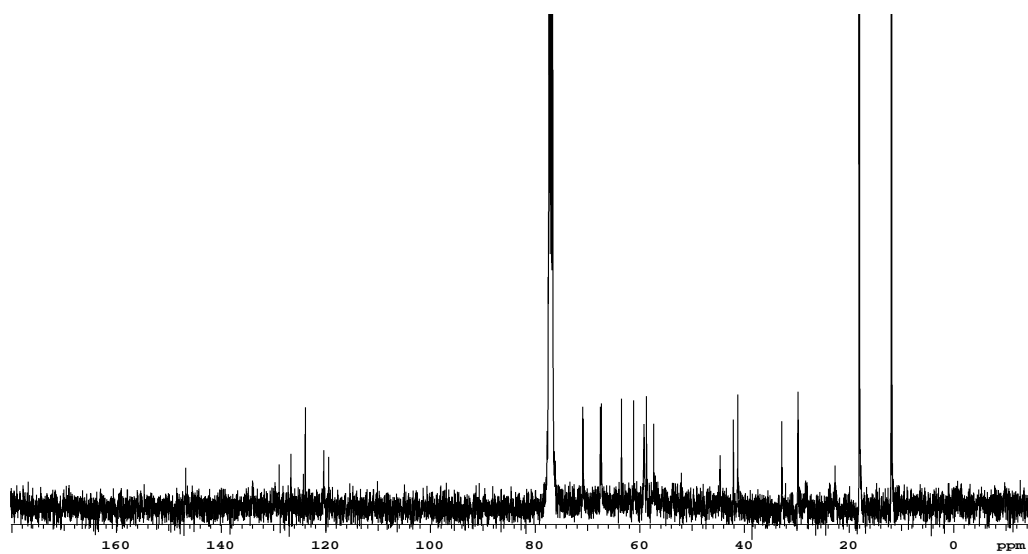
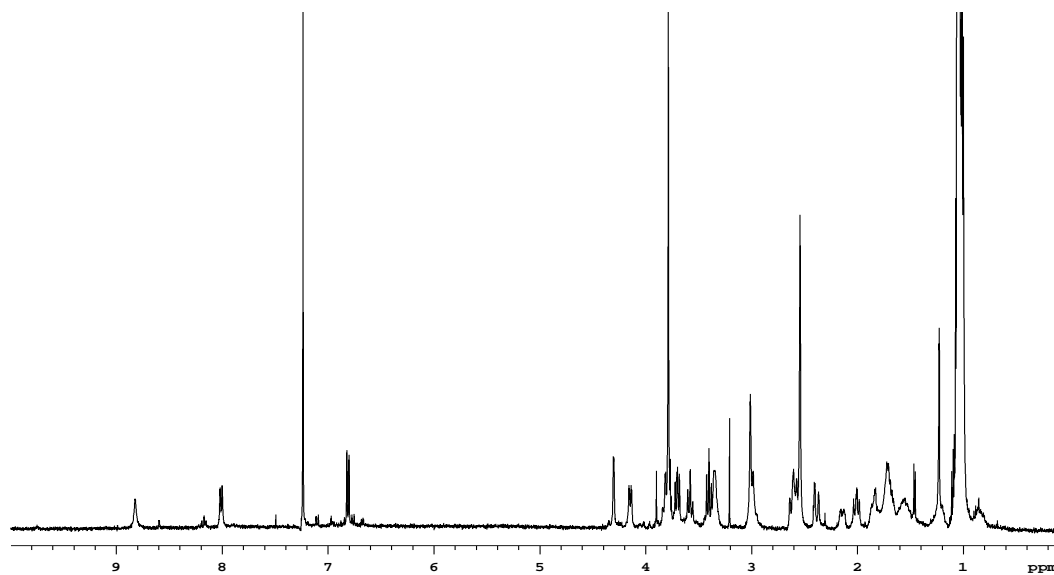
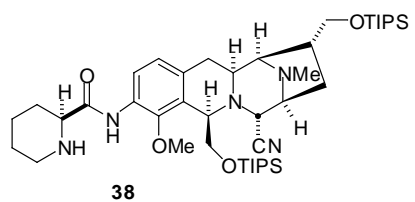
Compound **33**: ^1H -NMR (500 MHz) and ^{13}C -NMR (125 MHz) in D_2O (vs. $\text{d}_4\text{-MeOH}$)



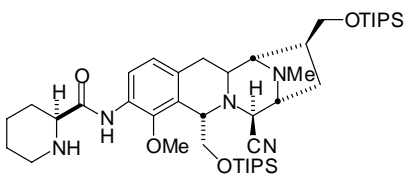
Compound **34**: $^1\text{H-NMR}$ (400 MHz) and $^{13}\text{C-NMR}$ (100 MHz) in CDCl_3



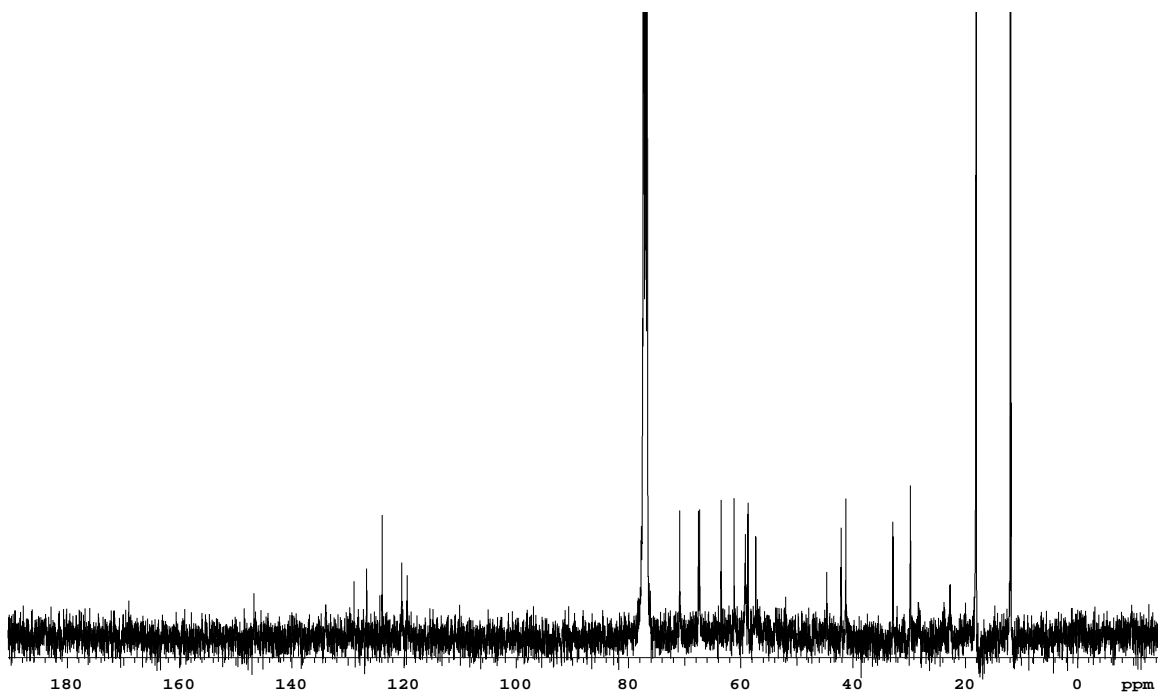
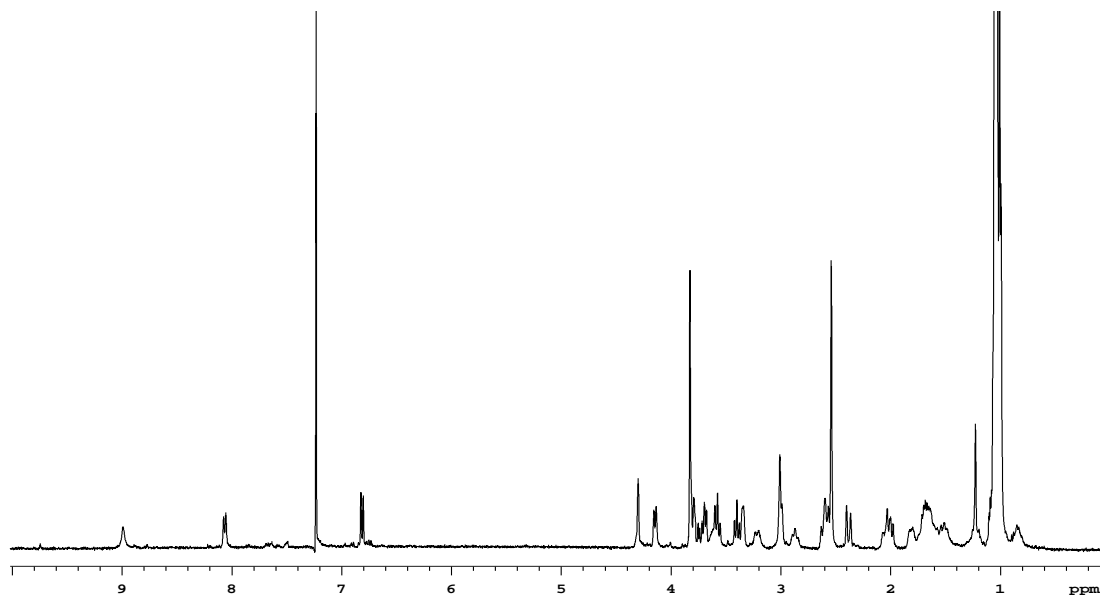
Compound **35**: ¹H-NMR (500 MHz) and ¹³C-NMR (125 MHz) in D₂O (vs. d₄-MeOH)



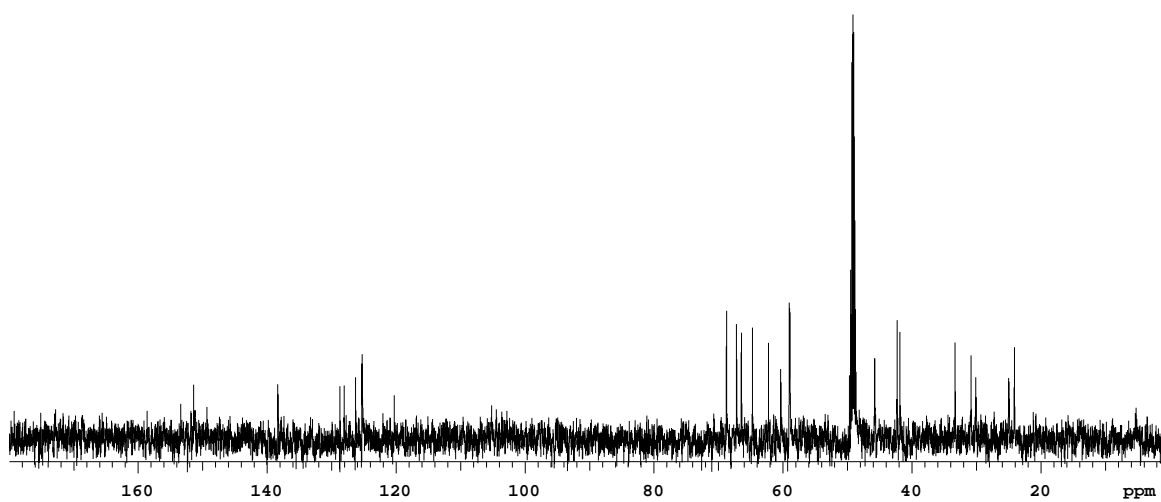
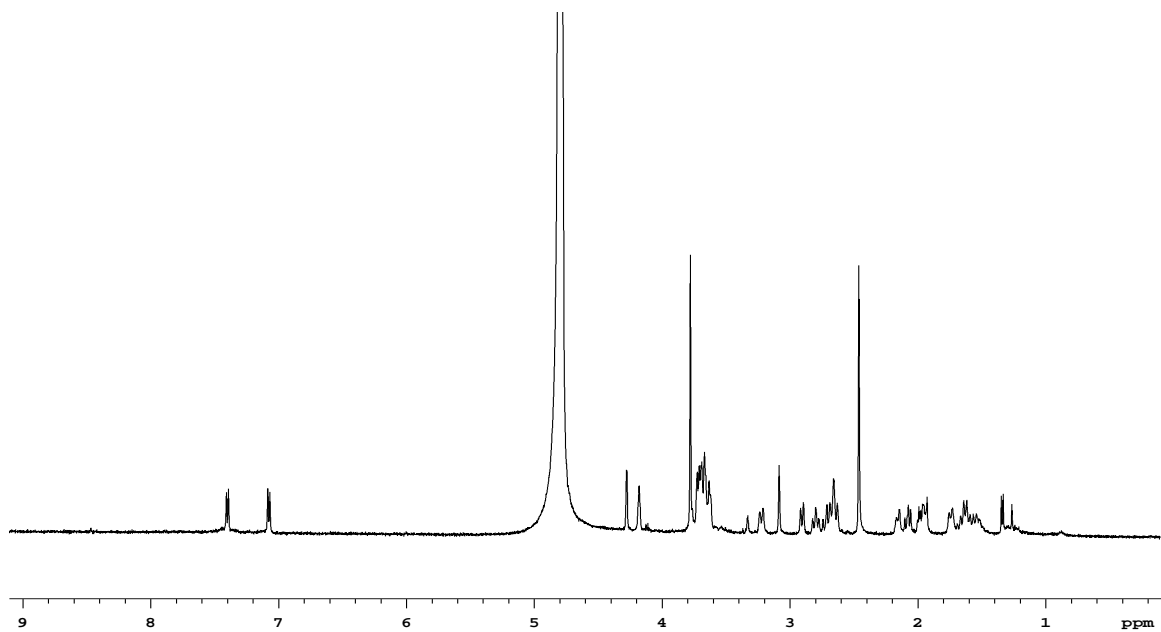
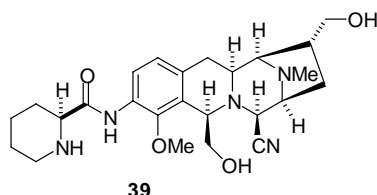
Compound **38**: ^1H -NMR (400 MHz) and ^{13}C -NMR (100 MHz) in CDCl_3



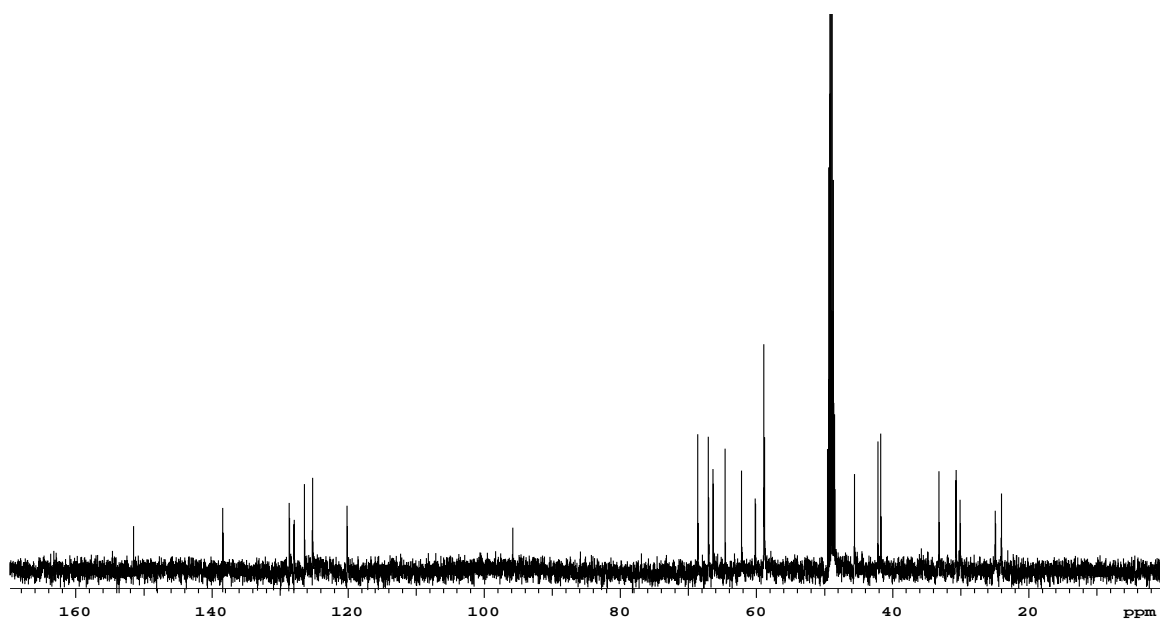
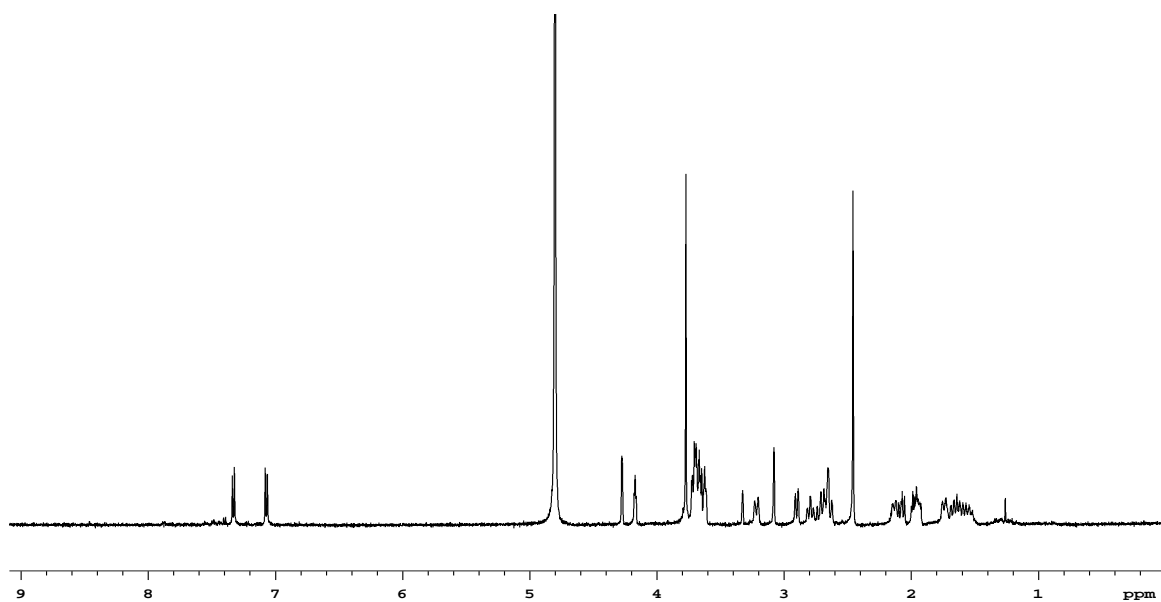
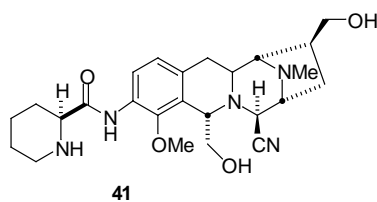
40



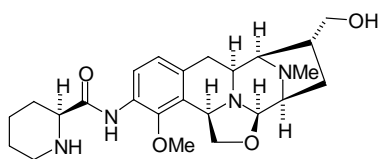
Compound **40**: ^1H -NMR (400 MHz) and ^{13}C -NMR (100 MHz) in CDCl_3



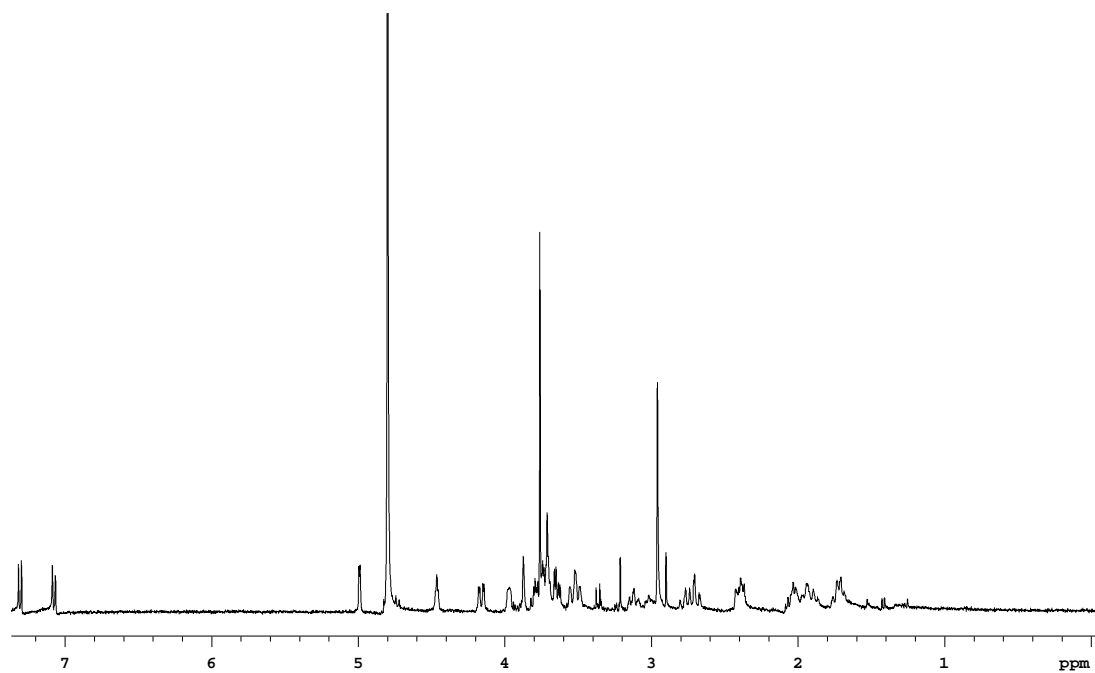
Compound **39**: ^1H -NMR (500 MHz) and ^{13}C -NMR (125 MHz) in D_2O (vs. d_4MeOH)



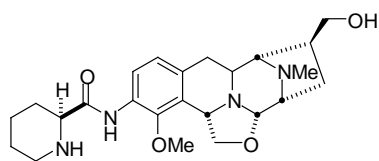
Compound **41**: ^1H -NMR (500 MHz) and ^{13}C -NMR (125 MHz) in D_2O (vs. d_4MeOH)



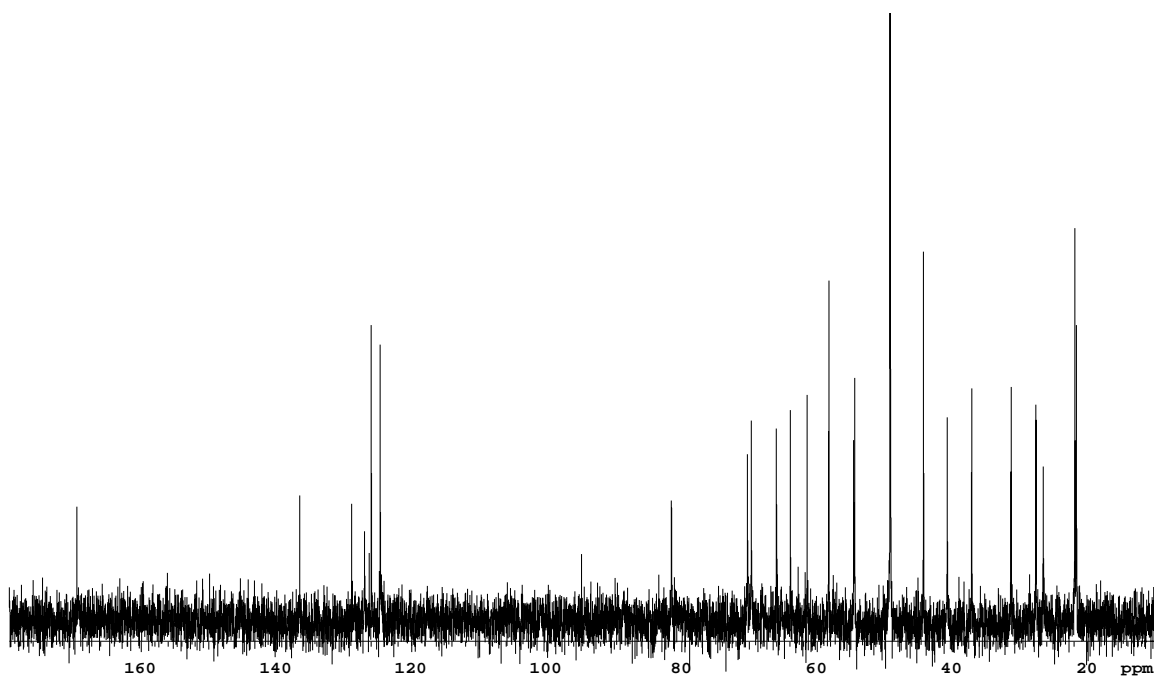
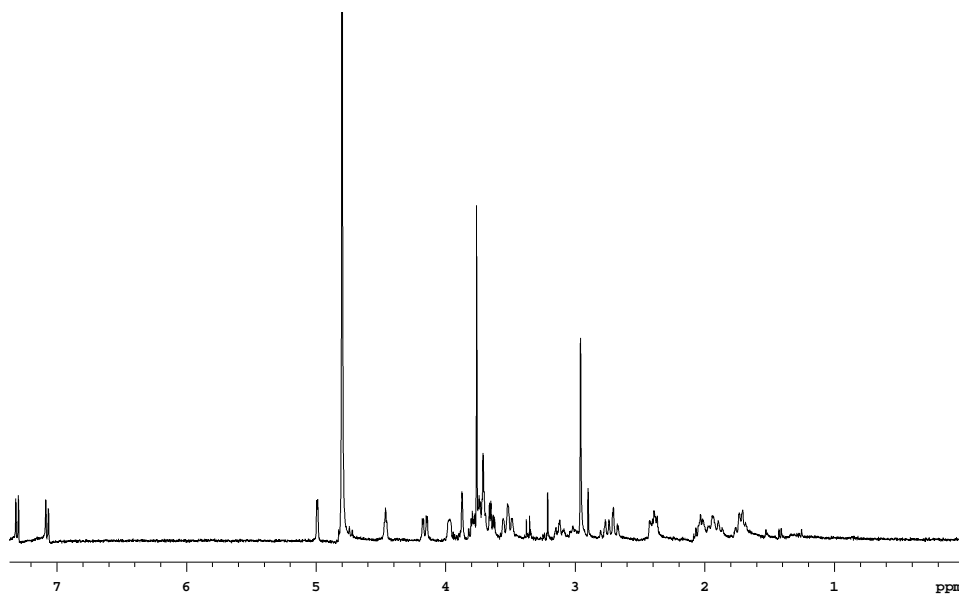
42



Compound **42**: ^1H -NMR (400 MHz) in D_2O



43



Compound **43**: ^1H -NMR (400 MHz) and ^{13}C -NMR (100 MHz) in D_2O (vs. d_4MeOH)