

Synthesis, Biological Evaluation and Molecular Modeling of Urea-Containing MraY Inhibitors[†]

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ELECTRONIC SUPPLEMENTARY INFORMATION

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[†] Electronic supplementary information (ESI) available: 1. Numbering system, 2. ¹H and ¹³C NMR spectra of all new compounds.

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Experimental procedure for the synthesis of primary amines **13c-e** and **13h-k**

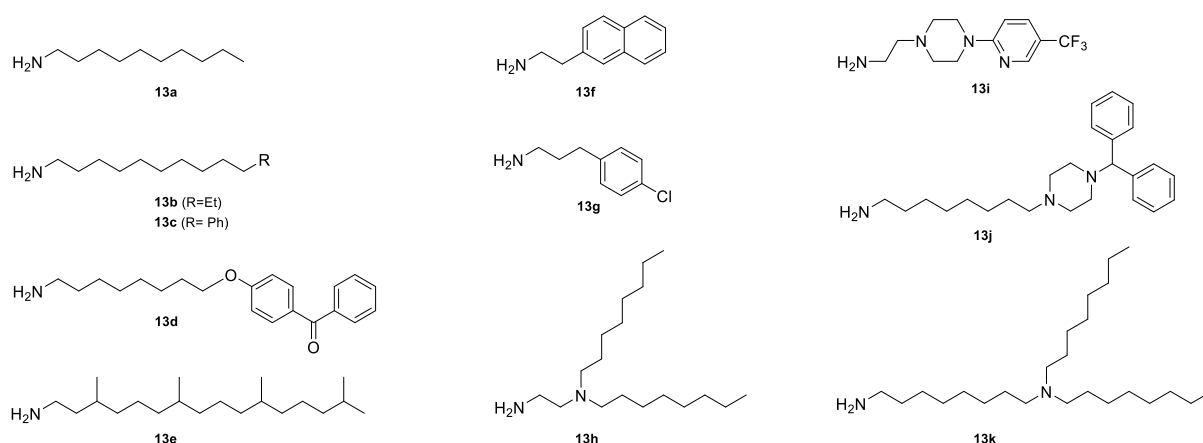


Fig. 1S Structure of the selected primary amines **13a-k**.

10-phenyldecan-1-amine **13c**.

To a solution of 10-phenyl-1-azide (380 mg, 1.46 mmol, 1 equiv) in THF (4 mL) was added triphenylphosphine (768 mg, 2.93 mmol, 2 equiv.) and pure water (1 mL). The reaction mixture was stirred at r.t. for 18 h. and concentrated *in vacuo*. Flash chromatography of the residue (Cyclo/EtOAc 1/1; then EtOAc 100% and EtOAc/MeOH 7/3) afforded the compound **13c** as a white powder (315 mg, 92% yields): R_f 0.1 (EtOAc/MeOH 7/3); IR (film) 3379, 2925, 2853, 1645, 1352, 1275, 1261, 749; ^1H NMR δ 7.26 – 7.01 (m, 5 H, $\text{H}_{12}\text{H}_{13}\text{H}_{14}$), 2.64 (t, $J_{\text{H1-H2}} = 7.1$ Hz, 2 H, H_1), 2.54 – 2.50 (m, 2 H, H_{10}), 1.57 – 1.49 (m, 2 H, H_9), 1.43 – 1.37 (m, 2 H, H_2), 1.27–1.16 (m, 12 H, $\text{H}_3\text{--H}_8$); ^{13}C NMR (126 MHz, CDCl_3) δ 143.0 (C_{11}), 128.5 (C_{12}), 128.3 (C_{13}), 125.6 (C_{14}), 42.3 (C_1), 36.1 (C_{10}), 34.0 (C_2), 31.6 (C_9), 29.7 (C_4), 29.6 (C_8), 29.6 (C_5 , C_7), 29.4 (C_6), 27.0 (C_3); HRMS APCI $^+$ calcd for $\text{C}_{16}\text{H}_{27}\text{N}_1$ ($\text{M} + \text{H}$) $^+$ 234.2216, found 234.2215.

4-(8'-Amino-octanyloxy)-benzophenone **13d**.

To a solution of compound **18** (60 mg, 170 μmol , 1 equiv.) in THF (17 mL) was added triphenylphosphine (179 mg, 683 μmol , 4 equiv.) and pure water. The reaction mixture was stirred at r.t. for 18 h. and then concentrated *in vacuo*. Flash chromatography of the residue (Cyclo/EtOAc 1/1; then EtOAc 100% and EtOAc/MeOH 7/3) afforded compound **13d** as a white powder (32 mg, 98% yield): R_f 0.10 (EtOAc/MeOH 7/3); IR (film): 3279, 2926, 2853, 1641, 1602, 1506, 1473, 1444, 1317, 1307, 1290, 1250, 1174, 1149, 939, 846, 740; ^1H NMR δ 7.82 (d, $J_{\text{H2-H3}} = 8.8$ Hz, 2 H, H_2), 7.78 – 7.72 (m, 2 H, H_7), 7.56 (t, $J_{\text{H9-H8}} = 7.4$ Hz, 1H, H_9), 7.47 (t, $J_{\text{H8-H9}} = J_{\text{H8-H7}} = 7.4$ Hz, 2 H, H_8), 6.95 (d, $J_{\text{H3-H2}} = 8.8$ Hz, 2 H, H_3), 4.04 (t, $J_{\text{H1'-H2'}} = 6.5$ Hz, 2 H, $\text{H}_{1'}$), 2.68 (t, $J_{\text{H8'-H7'}} = 7.0$ Hz, 2 H, $\text{H}_{8'}$), 1.86 – 1.78 (m, 2 H, $\text{H}_{2'}$), 1.50 – 1.42 (m, 4 H, $\text{H}_{7'}\text{H}_{3'}$), 1.38–1.32 (m, 6 H, $\text{H}_{6'}\text{H}_{5'}\text{H}_{4'}$); ^{13}C NMR δ 195.7 (C_5), 163.0 (C_4), 138.5 (C_6), 132.7 (C_2), 131.9 (C_9), 130.1 (C_1), 129.8 (C_7), 128.3 (C_8), 114.1 (C_3), 68.4 ($\text{C}_{1'}$), 42.3 ($\text{C}_{8'}$), 33.8 ($\text{C}_{7'}$), 29.5 ($\text{C}_{4'}$), 29.4 ($\text{C}_{6'}$), 29.2 ($\text{C}_{2'}$), 26.9 ($\text{C}_{5'}$), 26.1 ($\text{C}_{3'}$); HRMS APCI $^+$ calcd for $\text{C}_{21}\text{H}_{28}\text{NO}_2$ ($\text{M} + \text{H}$) $^+$ 326.2115, found 326.21149.

3,7,11,15-tetramethylhexadecan-1-amine **13e**.

To a solution of 3,7,11,15-tetramethylhexadecan-1-azide (75 mg, 232 μmol , 1 equiv) in THF (3 mL) was added triphenylphosphine (121 mg, 463 μmol , 2 equiv.) and pure water (1 mL). The reaction mixture was stirred at r.t. for 12 h and concentrated *in vacuo*. Flash chromatography of the residue (Cyclo/EtOAc 1/1; then EtOAc 100% and EtOAc/MeOH 7/3) afforded the compound **13e** as a colorless oil (67 mg, 98% yield): R_f 0.15 (EtOAc/MeOH 7/3); IR (film) 2954, 2925, 2868, 1463, 1377, 1275, 1260,

1262, 1136, 938, 875, 799, 764; ^1H NMR δ 2.85 – 2.68 (m, 2 H, H_1), 2.32 (s, 2 H, NH_2), 1.62 – 1.43 (m, 4 H, CH), 1.48 – 1.00 (m, 20 H, CH_2), 0.93 – 0.79 (m, 15 H, CH_3); HRMS APCI $^+$ calcd for $\text{C}_{20}\text{H}_{44}\text{N}_1$ ($\text{M} + \text{H}$) $^+$ 298.3468, found 298.3468. Other spectral data were in agreement with literature.¹

***N,N*-dioctylethane-1,2-diamine 13h.**

The compound 20 (75 mg, 180 μmol , 1 equiv.) was dissolved in MeOH (10 mL) and hydrazine monohydrate (28 μL , 904 μmol , 5 equiv.) was added dropwise. The reaction mixture was stirred for 12 h at 80 $^\circ\text{C}$. Solvent were removed *in vacuo* and the product was then dissolved in DCM, filtered through a celite pad, and rinsed with DCM. The diamine 13h was obtained in quantitative yield and analyzed: IR (film): 3005, 2954, 2924, 2854, 1643, 1573, 1467, 1365, 1275, 1260, 1206, 1153, 1094, 1021, 936, 764, 750; ^1H NMR δ 3.11 (bs, 1 H, NH_2), 2.75 (t, $J_{\text{H}_1-\text{H}_2} = 5.5$ Hz, 2 H, H_1), 2.48 (t, $J_{\text{H}_2-\text{H}_1} = 5.5$ Hz, 2 H, H_2), 2.43 – 2.35 (m, 4 H, H_3), 1.40 (bs, 4 H, H_4), 1.25 (s, 10 H, H_5 – H_9), 0.86 (t, $J_{\text{H}_{10}-\text{H}_9} = 6.8$ Hz, 6 H, H_{10}); ^{13}C NMR δ 56.7 (C_2), 54.4 (C_3), 39.6 (C_1), 31.9, 29.7, 29.4, 27.6, 27.2 (C_4), 22.5, 14.2 (C_{10}); HRMS APCI $^+$ calcd for $\text{C}_{18}\text{H}_{41}\text{N}_2$ ($\text{M} + \text{H}$) $^+$ 285.3264, found 285.3268.

2-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)ethan-1-amine 13i.

The compound 21 (50 mg, 123 μmol , 1 equiv.) was dissolved in MeOH (8 mL) and hydrazine monohydrate (19 μL , 618 μmol , 5 equiv.) was added dropwise. The reaction mixture was stirred for 12 h at 80 $^\circ\text{C}$. The solvent were removed *in vacuo*, the product was then dissolved in DCM, filtered through a celite pad, and rinsed with DCM. The amine 13i was obtained in quantitative yield: IR (film) 3006, 2985, 2924, 2552, 1614, 1508, 1458, 1329, 1275, 1260, 1169, 1116, 1082, 764, 750; ^1H NMR δ 8.41 – 8.37 (m, 1 H, H_5), 7.62 (d, $J_{\text{H}_3-\text{H}_2} = 9.0$ Hz, 1 H, H_3), 6.63 (d, $J_{\text{H}_2-\text{H}_3} = 9.0$ Hz, 1 H, H_2), 3.68 – 3.63 (m, 4 H, H_7), 2.84 (t, $J_{\text{H}_7-\text{H}_6} = 6.1$ Hz, 2 H, H_9), 2.60 – 2.53 (m, 4 H, H_6), 2.48 (t, $J_{\text{H}_8-\text{H}_9} = 6.1$ Hz, 2 H, H_8); ^{13}C NMR δ 160.5 (C_1), 145.8 (C_5), 134.5 (C_3), 125.71 (CF_3), 115.3 (C_4), 105.6 (C_2), 61.2 (C_6), 53.0 (C_8), 44.8 (C_7), 38.8 (C_9); HRMS APCI $^+$ calcd for $\text{C}_{12}\text{H}_{18}\text{F}_3\text{N}_4$ ($\text{M} + \text{H}$) $^+$ 275.1478, found 275.14726.

8'-(4-benzhydrylpiperazin-1-yl)octan-1-amine 13j.

To a solution of compound 17 (35 mg, 86 μmol , 1 equiv.) in dry THF (9 mL) was added triphenylphosphine (90 mg, 345 μmol , 4 equiv.) and pure water. The reaction mixture was stirred at r.t. for 18 h and then concentrated *in vacuo*. Flash chromatography of the residue (Cyclo/EtOAc 1/1; then EtOAc 100% and EtOAc/MeOH 7/3) afforded the compound 13j as a white powder (32 mg, 98% yield): Rf 0.15 (EtOAc/MeOH 7/3); IR (film): 3362, 3060, 3026, 2927, 2853, 2808, 2770, 1597, 1491, 1451, 1376, 1305, 1281, 1187, 1151, 1008, 850, 757, 700; ^1H NMR δ 7.34 (d, $J_{\text{H}_7-\text{H}_8} = 8.5$, 4H, H_7), 7.18 (dd, $J_{\text{H}_8-\text{H}_9} = 8.5$, $J_{\text{H}_8-\text{H}_7} = 7.5$ Hz, 4H, H_8), 7.09 (t, $J_{\text{H}_9-\text{H}_8} = 7.5$ Hz, 2 H, H_9), 4.14 (s, 1 H, H_5), 2.62 (dd, $J_{\text{H}_8'-\text{a}}-\text{H}_8'-\text{b} = 13.7$, $J_{\text{H}_8'-\text{H}_7'} = 6.7$ Hz, 2 H, H_8'), 2.38 (bs, 1 H, H_9 , H_3), 2.31 – 2.20 (m, 2 H, H_1'), 1.38 (s, 4 H, H_2 , H_2'), 1.28 – 1.14 (m, 8 H, H_6' , H_3'); ^{13}C NMR δ 142.9 (C_6), 128.5 (C_8), 128.0 (C_7), 127.0 (C_9), 76.40 (C_5), 58.9 (C_1'), 53.6 (C_8'), 52.0 ($\text{C}_3 = \text{C}_2$), 42.0 (C_7'), 33.0 (C_2'), 29.6 (C_6'), 29.4 (C_3'), 27.7 (C_5'), 26.9 (C_4'); HRMS APCI $^+$ calcd for $\text{C}_{25}\text{H}_{38}\text{N}_3$ ($\text{M} + \text{H}$) $^+$ 380.3060, found 380.3049.

***N,N*-dioctyloctane-1,8-diamine 13k.**

To a solution of compound 19 (50 mg, 127 μmol , 1 equiv.) in dry THF (13 mL) was added triphenylphosphine (132 mg, 506 μmol , 4 equiv.) and pure water. The reaction mixture was stirred at r.t. for 18 h and then concentrated *in vacuo*. Flash chromatography of the residue (Cyclo/EtOAc 1/1; then EtOAc 100% and EtOAc/MeOH 7/3) afforded the compound 13k as a colorless oil (46 mg, 98% yield): Rf 0.15 (EtOAc/MeOH 7/3); IR (film): 2925, 2854, 2095, 1681, 1574, 1465, 1260, 1275, 1203, 1181, 1137, 764, 750; ^1H NMR δ 3.90 (bs, 2 H, NH_2), 2.70 (t, $J_{\text{H}_1-\text{H}_2} = 7.1$ Hz, 2 H, H_1), 2.60 – 2.51 (m, 6 H, H_8 , H_9), 1.48 (s, 6 H, H_{10} , H_7), 1.27 (s, 30 H), 0.87 (t, $J_{\text{H}_{16}-\text{H}_{15}} = 6.8$ Hz, 6 H, H_{16}); ^{13}C NMR δ 53.7 (C_8), 53.6 (C_9), 41.9 (C_1), 31.9 (C_7), 29.5, 29.4, 29.3, 27.5, 27.3, 26.7, 25.8, 22.7, 14.2 (C_{16}); HRMS APCI $^+$ calcd for $\text{C}_{24}\text{H}_{53}\text{N}_2$ ($\text{M} + \text{H}$) $^+$ 369.4203, found 369.4209.

8-azido-octyl methanesulfonate 16.

To a solution of 1,8-octanediol (2.0 g, 13.7 mmol) in dry DCM (100 mL) was added triethylamine (4.38 mL, 31.46 mmol, 2.3 equiv.) at 0 °C under argon. The reaction was stirred for 30 min prior to addition of methanesulfonyl chloride (2.43 mL, 31.46 mmol, 2.3 equiv.). The temperature was allowed to slowly warm to room temperature, the reaction mixture was quenched with water (20 mL) and the aqueous phase was extracted with DCM. The combined organic layers were washed with brine, dried and concentrated *in vacuo*. The crude white powder (3.27g, 10.8 mmol, 1 equiv.) was then dissolved in dry DMF (120 mL), then sodium azide (667 mg, 10.27 mmol, 0.95 equiv.) was added and the reaction mixture was stirred overnight at 90 °C. After solvent removal *in vacuo*, 150 mL of EtOAc was added and the organic phase was washed four times with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting pale yellow oil was purified by flash chromatography (Cyclohexane/EtOAc 9/1) to give compound 16 as a white powder (1.29 g, 48% yield): R_f 0.25 (Cyclohexane/EtOAc 9/1); IR (film): 2930, 2857, 2096, 1715, 1612, 1466, 1353, 1255, 1260, 1174, 974, 940, 750; ¹H NMR δ 4.23 (t, *J*_{H1-H2} = 6.6 Hz, 2 H, H₁), 3.26 (t, *J*_{H8-H7} = 6.9 Hz, 2 H, H₈), 3.00 (s, 6 H, H₉), 1.82 – 1.69 (m, 2 H, H₂), 1.66 – 1.56 (m, 2 H, H₇), 1.45 – 1.20 (m, 8 H, H₆₋₅₋₄₋₃); ¹³C NMR δ 70.1 (C₁), 52.0 (C₈), 37.5 (C₉), 29.2 (C₇), 29.0 (C₅), 29.0 (C₄), 28.9 (C₂), 26.7 (C₆), 25.4 (C₃); HRMS APCI⁺ calcd for C₉H₂₀O₃N₃ (M + H)⁺ 250.1220, found 250.1218.

1-(8'-azido-octyl)-4-benzhydrylpiperazine 17.

To a solution of compound 16 (70 mg, 280 μmol) in dry CH₃CN (100 mL) was added triethylamine (66 μL, 417 μmol, 1.7 equiv.) and 1-benzhydrylpiperazine (85 mg, 336 μmol, 1.2 equiv.) at 0 °C under argon. The reaction was stirred for 16 h at 90 °C and then concentrated *in vacuo*. The resulting pale yellow oil was purified by flash chromatography (Cyclohexane/EtOAc 7/3) to give compound 17 as a white powder (99 mg, 88% yield): R_f 0.25 (Cyclohexane/EtOAc 7/3); IR (film): 3026, 2931, 2855, 2808, 2094, 1595, 1491, 1451, 1301, 1278, 1261, 1151, 1008, 757, 746, 700; ¹H NMR δ 7.33 (d, *J*_{H7-H8} = 7.3 Hz, 4 H, H₇), 7.18 (t, *J*_{H8-H7} = 7.6 Hz, 4 H, H₈), 7.09 (t, *J*_{H9-H8} = 7.3 Hz, 2 H, H₉), 4.14 (s, 1 H, H₅), 3.16 (t, *J*_{H8'-H7'} = 7.0 Hz, 2 H, H_{8'}), 2.38 (bs, 8 H, H₂, H₃), 2.30 – 2.17 (m, 2 H, H_{1'}), 1.57 – 1.45 (m, 2 H, H_{7'}), 1.41 – 1.37 (m, 2 H, H_{2'}), 1.29 – 1.18 (m, 8 H, H_{3'-H6'}); ¹³C NMR (126 MHz, CDCl₃) δ 142.9 (C₆), 128.5 (C₈), 128.0 (C₇), 127.0 (C₉), 76.37 (C₅), 58.9 (C_{1'}), 53.6 (C₂), 52.0 (C₃), 51.6 (C_{8'}), 29.5, 29.1, 28.9, 27.6, 26.9 26.7 (C_{2'-C7'}); HRMS APCI⁺ calcd for C₂₅H₃₆N₅ (M + H)⁺ 406.2965, found 406.29585.

4-(8'-Azido-octanyloxy)-benzophenone 18.

To a solution of compound 16 (50 mg, 200 μmol, 1 equiv.) in dry DMF (10 mL) was added 4-hydroxybenzophenone (79 mg, 400 μmol, 2 equiv.), K₂CO₃ (55mg, 400 μmol, 2 equiv.) and KI (6.6 mg, 40 μmol, 0.2 equiv.) under argon. The reaction was stirred for 16 h at 80 °C and then concentrated *in vacuo*. The resulting pale yellow oil was purified by flash chromatography (Cyclohexane/EtOAc 7/3) to give compound 18 as a white powder (61 mg, 87% yield): R_f 0.25 (Cyclohexane/EtOAc 7/3); IR (film): 2933, 2857, 2094, 1854, 1660, 1507, 1446, 1325, 1305, 1280, 1250, 1172, 1148, 922, 844, 764, 742; ¹H NMR δ 7.82 (d, *J*_{H2-H3} = 8.8 Hz, 2 H, H₂), 7.79 – 7.74 (m, 2 H, H₇), 7.6 (t, *J*_{H9-H8} = 7.4 Hz, 1 H, H₉), 7.47 (t, *J*_{H8-H9} = *J*_{H8-H7} = 7.6 Hz, 2 H, H₈), 6.95 (d, *J*_{H3-H2} = 8.8 Hz, 2 H, H₃), 4.04 (t, *J*_{H1'-H2'} = 6.5 Hz, 2 H, H_{1'}), 3.26 (t, *J*_{H8'-H7'} = 6.9 Hz, 2 H, H_{8'}), 1.86 – 1.77 (m, 2 H, H_{2'}), 1.65 – 1.56 (m, 2 H, H_{7'}), 1.50-1.46 (m, 2 H, H_{3'}), 1.37 (s, 2 H, H_{6'}), 1.34 – 1.23 (m, 4 H, H_{5'}, H_{4'}); ¹³C NMR δ 195.6 (C₅), 163.0 (C₄), 138.5 (C₆), 132.7 (C₂), 131.9 (C₉), 130.1 (C₁), 129.8 (C₇), 128.3 (C₈), 114.1 (C₃), 68.3 (C_{1'}), 51.6 (C_{8'}), 29.3 (C_{7'}), 29.1 (C_{2'}), 29.2 (C_{3'}), 28.9 (C_{6'}), 27.0 (C_{5'}), 26.0 (C_{4'}); HRMS APCI⁺ calcd for C₂₁H₂₅N₃O₂ (M + H)⁺ 352.2020, found 352.20225.

8-azido-*N,N*-dioctyloctan-1-amine 19.

To a solution of compound 16 (70 mg, 280 μmol) in dry CH₃CN (100 mL) was added triethylamine (66 μL, 417 μmol, 1.7 equiv.) and dioctylamine (103 μL, 337 μmol, 1.2 equiv.) at 0 °C under argon. The reaction was stirred for 16 h at 90 °C and then concentrated *in vacuo*. The resulting pale yellow oil was purified by flash chromatography (Cyclohexane/EtOAc 7/3) to give the product 19 as a colorless

oil (111 mg, 59% yield): Rf 0.30 (Cyclohexane/EtOAc 7/3); IR (film): 2925, 2854, 2095, 1694, 1582, 1466, 1377, 1275, 1260, 1090, 839, 764, 722; ^1H NMR δ 3.25 (t, $J_{\text{H8-H7}} = 7.0$ Hz, 2 H, H₈), 2.45 (s, 6 H, H₁, H₉), 1.68 – 1.55 (m, 2 H, H₇), 1.47 (s, 6 H, H₁₀, H₂), 1.38 – 1.33 (m, 2 H, H₆), 1.37 – 1.20 (m, 26 H, H₃, H₄, H₅, H₁₁ – H₁₅), 0.88 (t, $J_{\text{H16-H15}} = 6.9$ Hz, 6 H, H₁₆); ^{13}C NMR δ 54.0 (C₁ = C₉), 51.6 (C₈), 32.0, 29.6, 29.5, 29.4, 29.2, 28.9 (C₇), 27.7 (C₂), 27.6 (C₁₀), 26.8 (C₆), 22.7, 14.2 (C₁₆); HRMS APCI⁺ calcd for C₂₄H₅₁N₄ (M + H)⁺ 395.4108, found 395.40986.

N-phthalimido-10-(9-(dioctylamino)ethyl) 20.

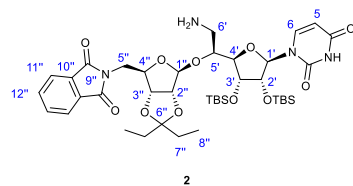
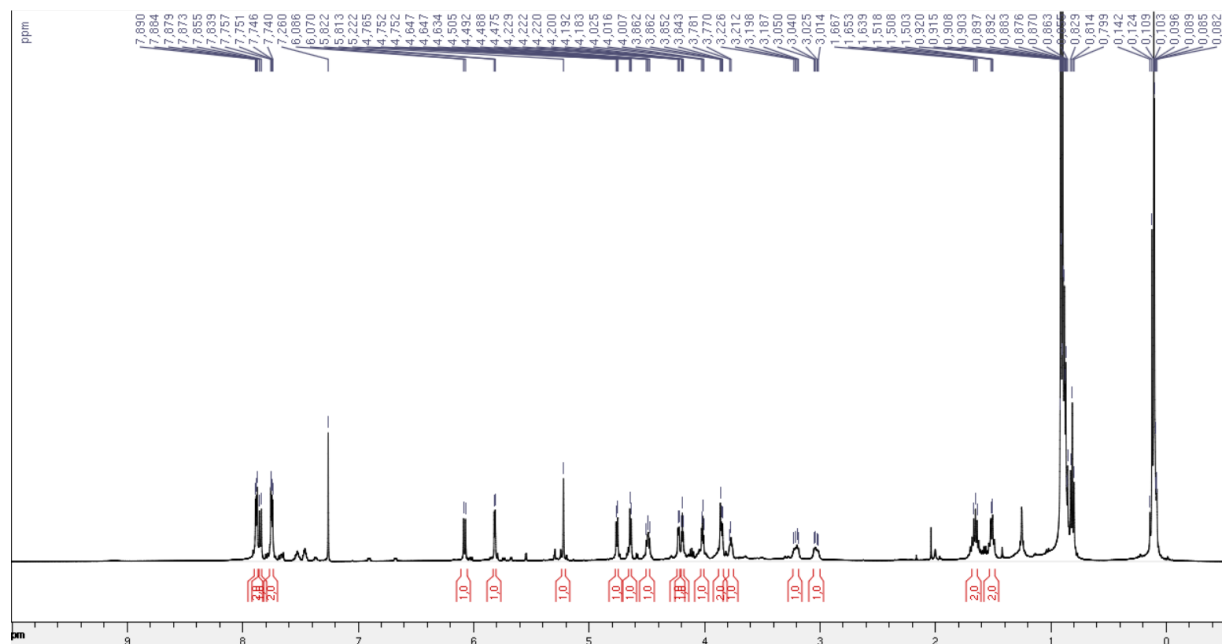
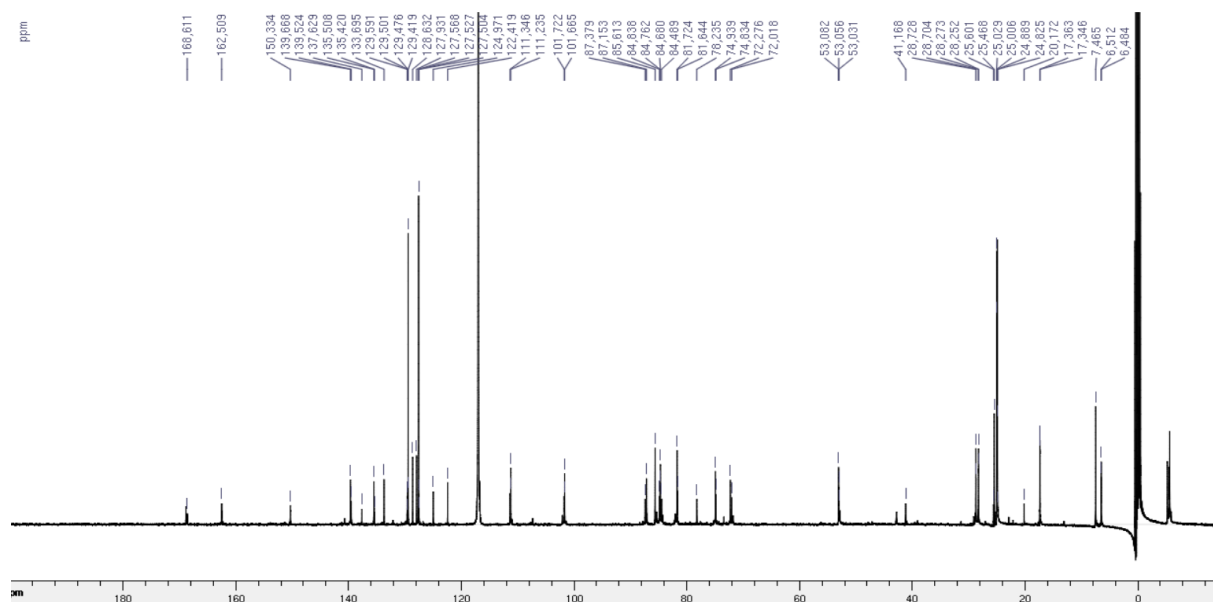
To a solution of 1-phthalimido-2-bromoethane (75 mg, 295 μmol , 1 equiv.) in dry CH₃CN (30 mL) were successively added K₂CO₃ (40 mg, 295 μmol , 1 equiv.) and dioctylamine (90 μL , 295 μmol , 1 equiv.) at 0 °C under argon. The reaction was stirred for 16 h at 90 °C and then concentrated *in vacuo*. The resulting pale yellow oil was purified by flash chromatography (Cyclohexane/EtOAc 7/3) to give compound 20 as a colorless oil (90 mg, 74% yield): Rf 0.25 (Cyclohexane/EtOAc 7/3); IR (film): 3726, 3692, 2926, 2856, 2354, 2342, 1774, 1751, 1467, 1394, 1087, 871, 719; ^1H NMR δ 7.86–7.81 (m, 2 H, H₁₃), 7.72–7.68 (m, 2 H, H₁₄), 3.75 (t, $J_{\text{H10-H9}} = 6.8$ Hz, 2 H, H₁₀), 2.69 (t, $J_{\text{H9-H10}} = 6.8$ Hz, 2 H, H₉), 2.50 – 2.36 (m, 4 H, H₈), 1.36 (dd, $J_{\text{H7-H8}} = J_{\text{H7-H6}} = 7.4$ Hz, 4 H, H₇), 1.30 – 1.21 (m, 4 H, H₆), 1.20 (bs, 8 H, H₂₋₅), 0.87 (t, $J_{\text{H1-H2}} = 7.1$ Hz, 6H, H₁); ^{13}C NMR δ 168.5 (C₁₁), 133.9 (C₁₄), 132.4 (C₁₂), 123.2 (C₁₃), 54.4 (C₈), 51.6 (C₉), 36.4 (C₁₀), 31.9, 29.7, 29.5, 27.6, 27.4 (C₇), 22.8 (C₆), 14.2 (C₁); HRMS APCI⁺ calcd for C₂₆H₄₃N₂O₂ (M + H)⁺ 415.3319, found 415.3312.

2-(2-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)ethyl) phthalimide 21.

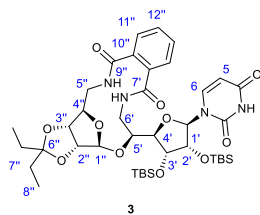
To a solution of 1-phthalimido-2-bromoethane (70 mg, 275 μmol , 1 equiv.) in dry CH₃CN (27 mL) were successively added K₂CO₃ (38 mg, 275 μmol , 1 equiv.) and 1-[5-(trifluoromethyl)pyridin-2-yl]piperazine (63 mg, 275 μmol , 1 equiv.) under argon. The reaction was stirred for 16 h at 90 °C and then concentrated *in vacuo*. The resulting pale yellow oil was purified by flash chromatography (Cyclohexane/EtOAc 7/3) to give the compound 21 as a colorless oil (100 mg, 90% yield): Rf 0.35 (Cyclohexane/EtOAc 7/3); IR (film): 2988, 2821, 1773, 1750, 1612, 1586, 1508, 1396, 1327, 1317, 1276, 1258, 1244, 1167, 1111, 1081, 1009, 944, 813, 764, 750, 720; ^1H NMR δ 8.37 (s, 1 H, H₅), 7.88 – 7.81 (m, 2 H, H₁₂), 7.76 – 7.70 (m, 2 H, H₁₃), 7.60 (d, $J_{\text{H3-H2}} = 9.0$ Hz, 1 H, H₃), 6.60 (d, $J_{\text{H2-H3}} = 9.0$ Hz, 1 H, H₂), 3.86 (t, $J_{\text{H9-H8}} = 5.9$ Hz, 2 H, H₉), 3.57 (bs, 4 H, H₇), 2.69 (t, $J_{\text{H8-H9}} = 5.9$ Hz, 2 H, H₈), 2.61 (bs, 4 H, H₆); ^{13}C NMR δ 208.1 (C₁₀), 168.5 (C₁), 145.9 (C₅), 134.5 (C₃), 134.4 (C₁₁), 134.0 (C₁₃), 132.3 (C₁₂), 123.4 (CF₃), 105.7 (C₂), 55.8 (C₆), 52.8 (C₈), 44.9 (C₇), 35.3 (C₉), 31.03; HRMS APCI⁺ calcd for C₂₀H₂₀F₃N₄O₂ (M + H)⁺ 405.1533, found 405.15234.

¹H and ¹³C Spectra

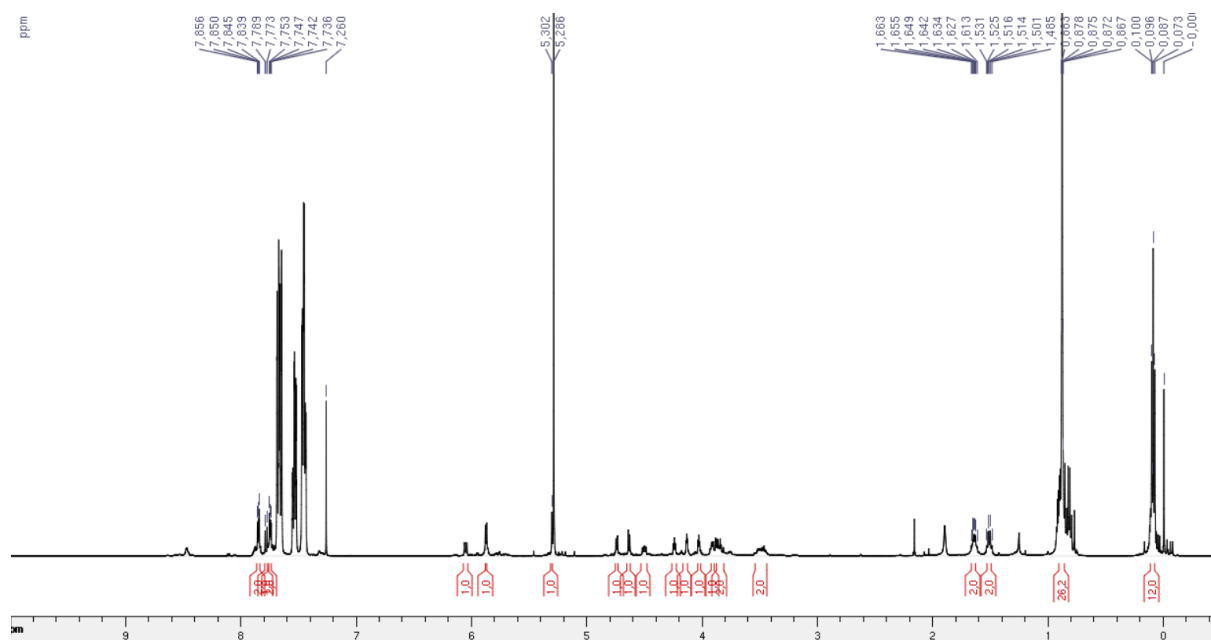
Compound 2

¹H NMR, 500 MHz (CDCl₃) ^{13}C NMR, 125 MHz (CDCl_3)

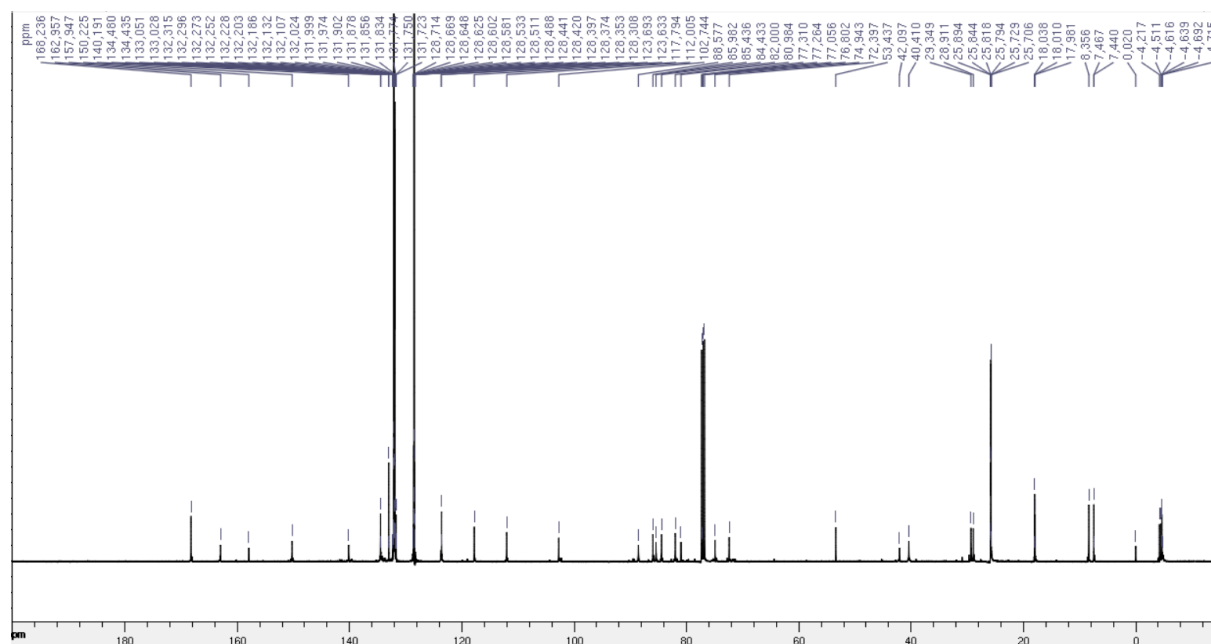
Side product 3



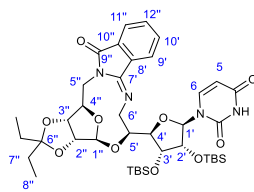
^1H NMR, 500 MHz (CDCl_3)



^{13}C NMR, 125 MHz (MeOD)

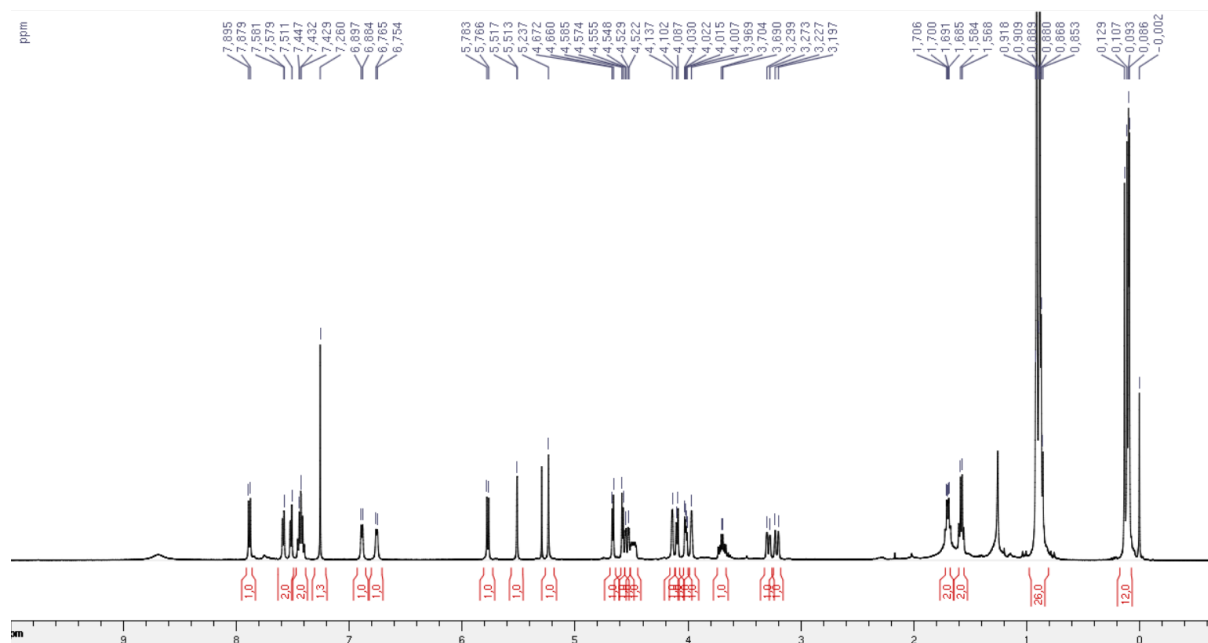


Side product 4

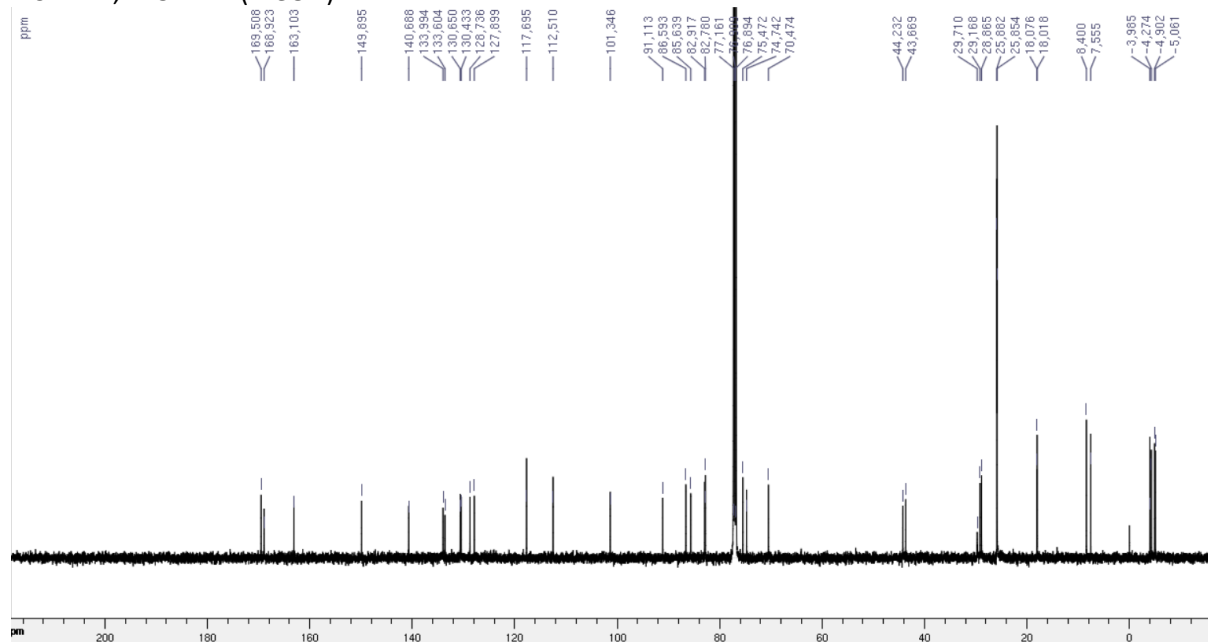


4

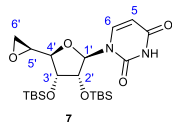
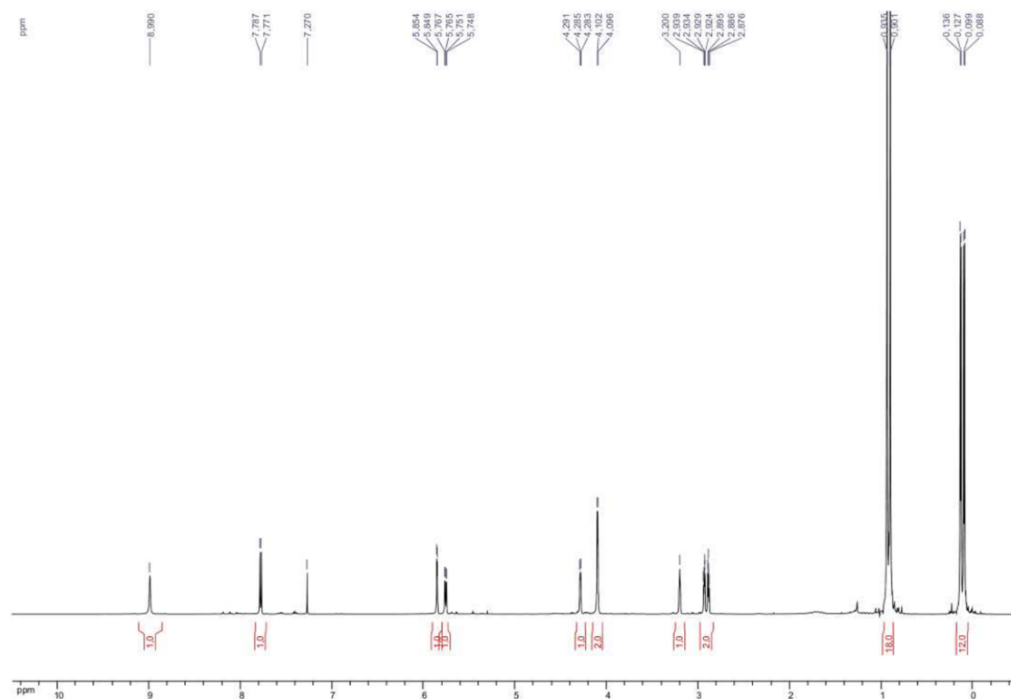
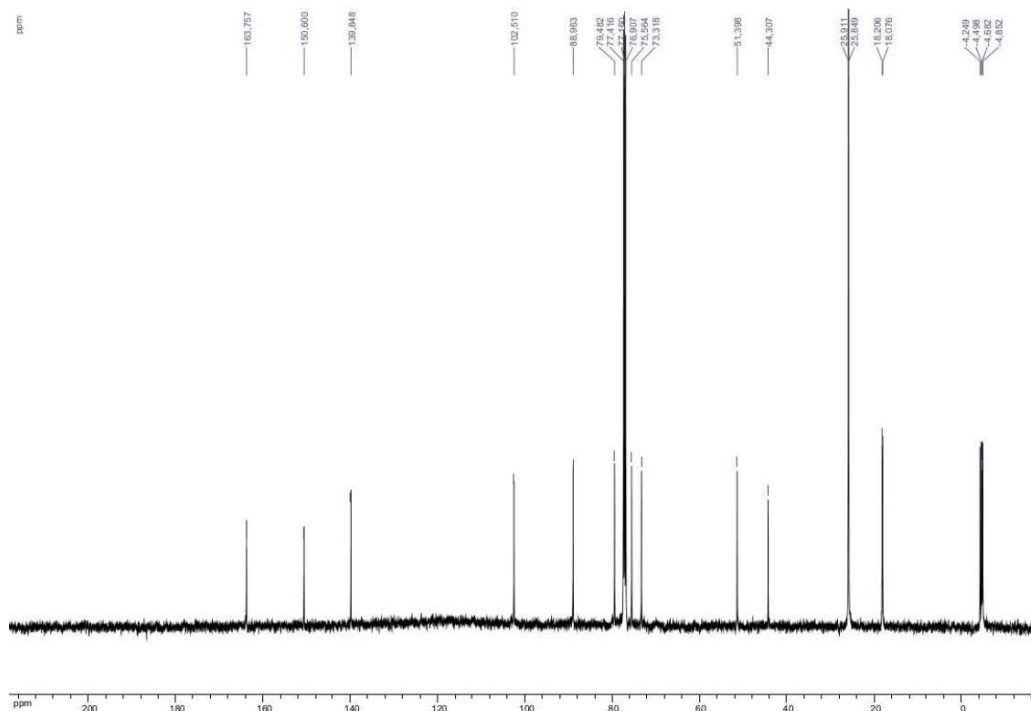
^1H NMR, 500 MHz (CDCl_3)



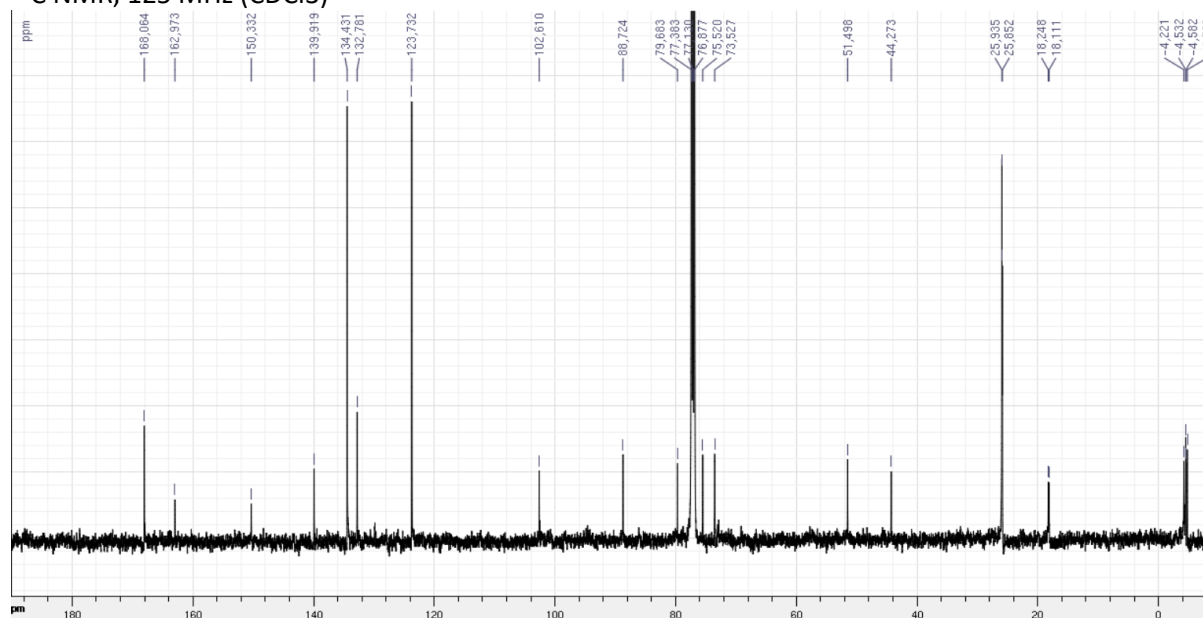
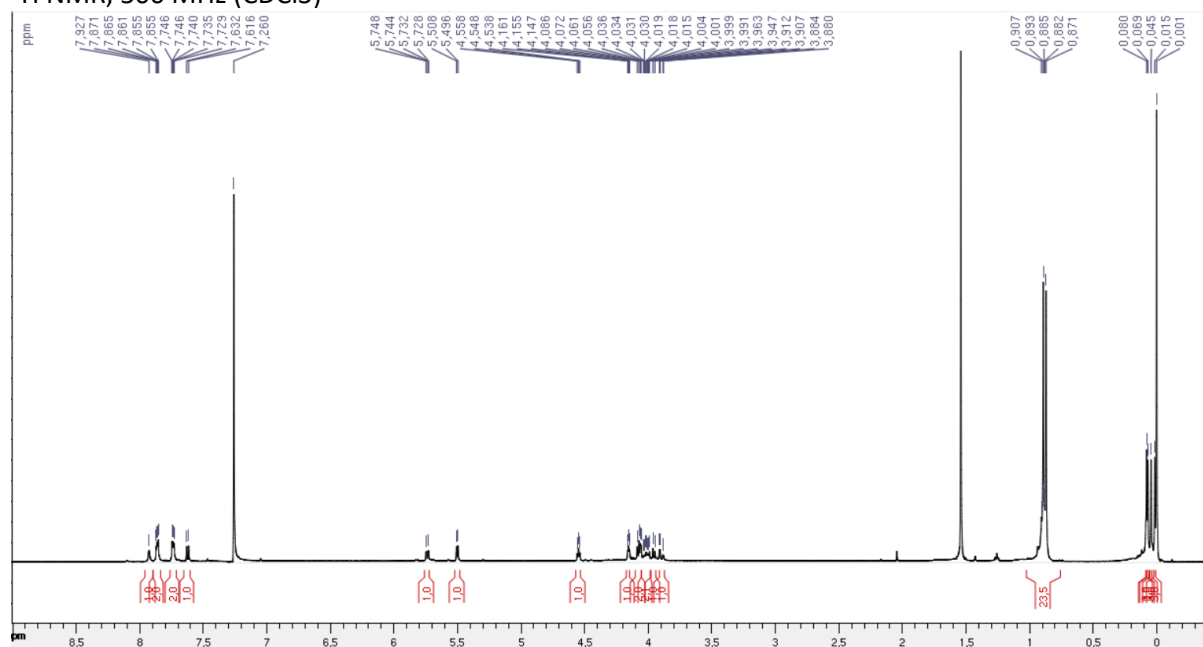
^{13}C NMR, 125 MHz (MeOD)



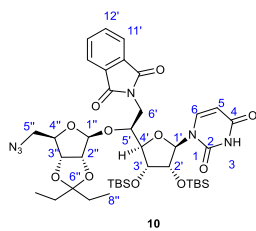
Compound 7

¹H NMR, 500 MHz (CDCl₃) ^{13}C NMR, 125 MHz (CDCl_3)

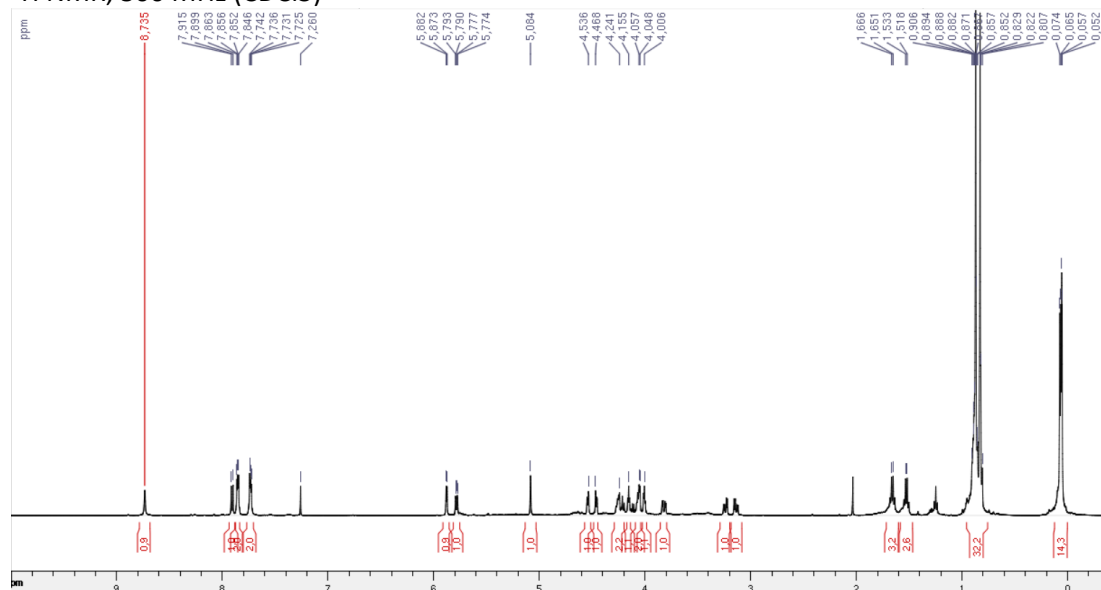
8



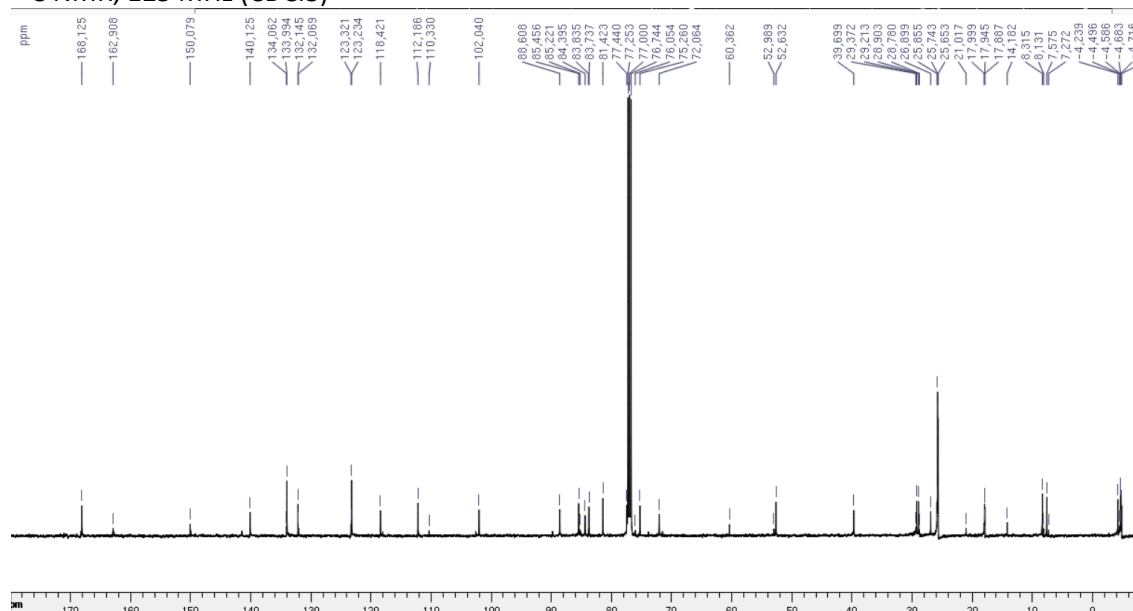
1'',5''-Dideoxy-2'',3''-O-isopentylidene-5''-azido-1''-[2',3'-O-isopropylidene-5'(S)-phthalimidomethyl-uridiny]-β-D-ribofuranose 10



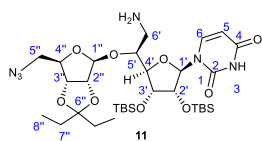
¹H NMR, 500 MHz (CDCl₃)



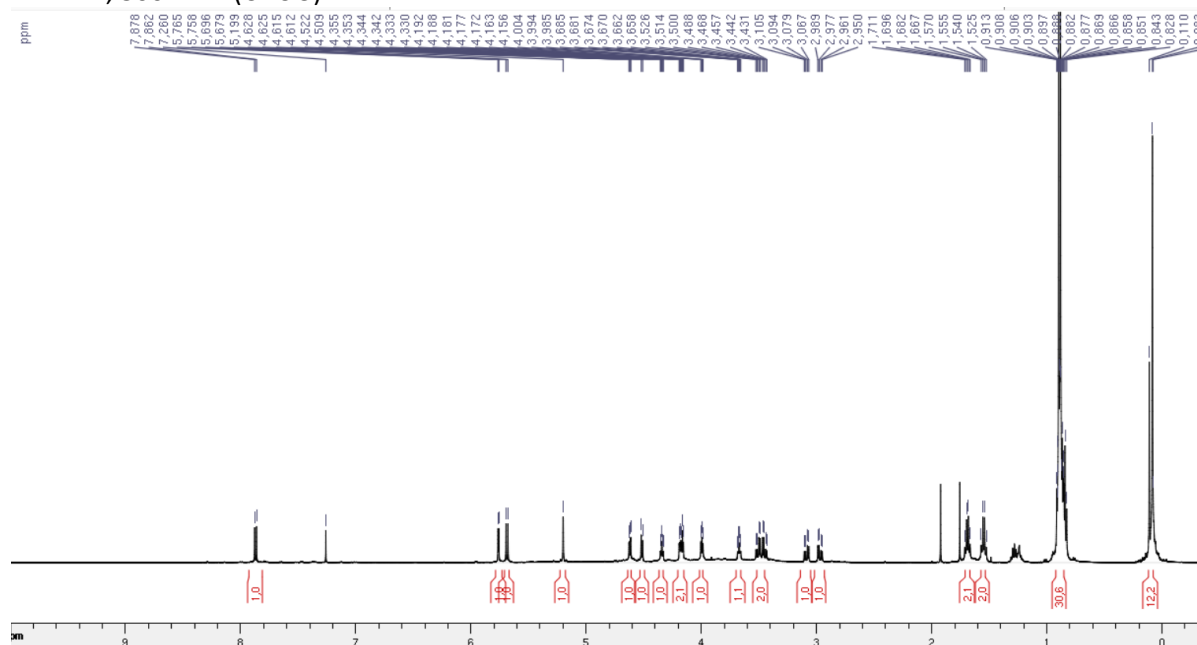
¹³C NMR, 125 MHz (CDCl₃)



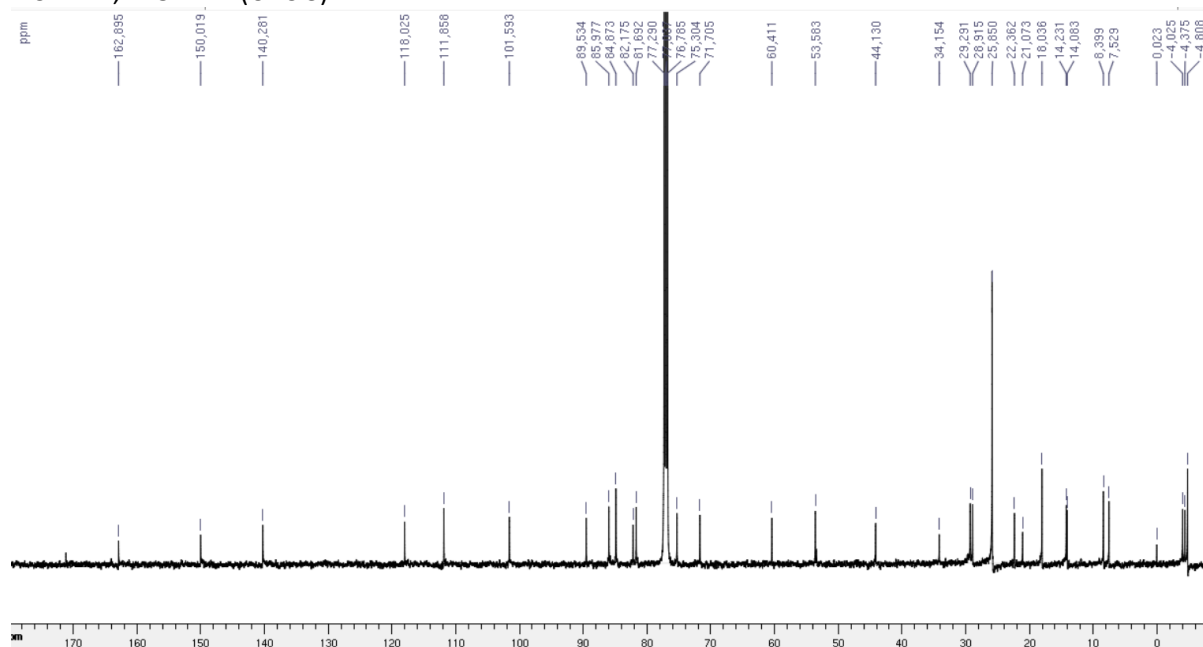
1'',5''-Dideoxy-2'',3''-O-isopentylidene-5''-azido-1''-[2',3'-O-isopropylidene-5'(S)-aminomethyl-uridiny]-β-D-ribofuranose 11



¹H NMR, 500 MHz (CDCl₃)

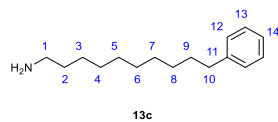


¹³C NMR, 125 MHz (CDCl₃)

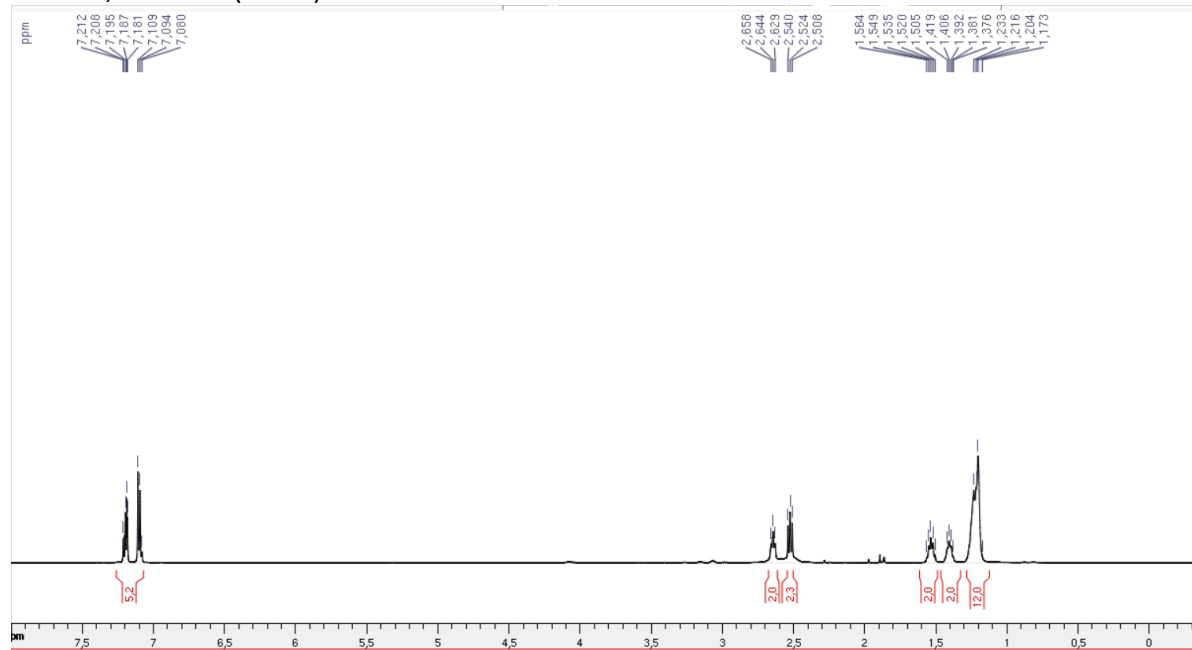


12

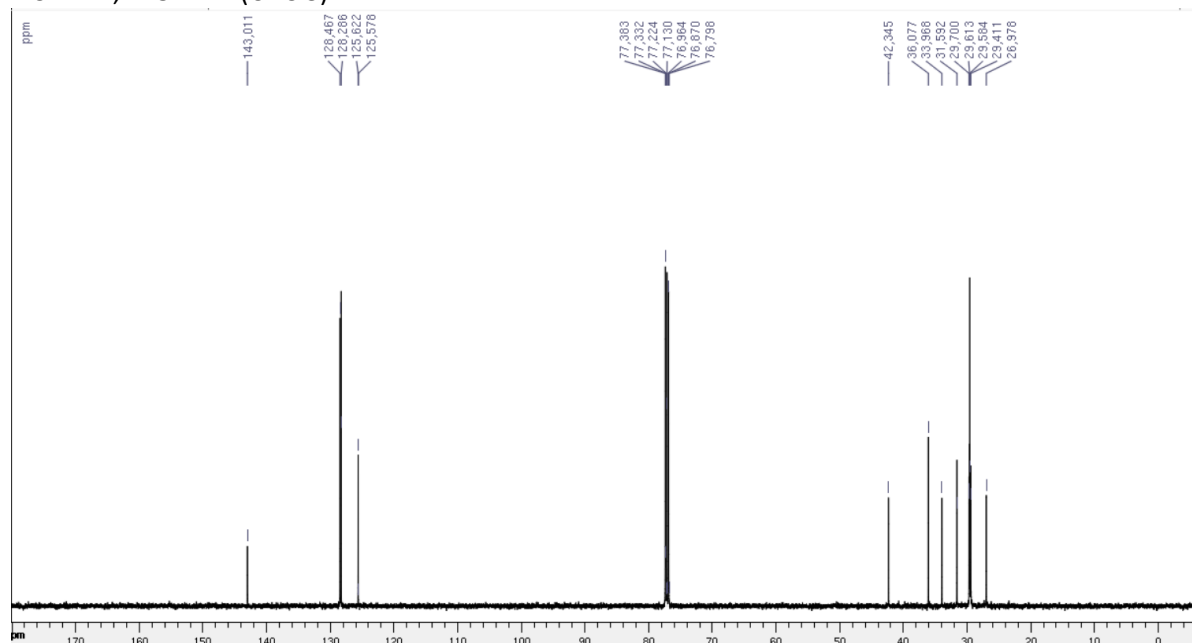
10-phenyldecan-1-amine 13c



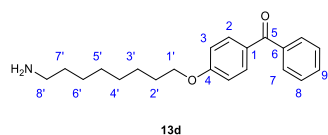
^1H NMR, 500 MHz (CDCl_3)



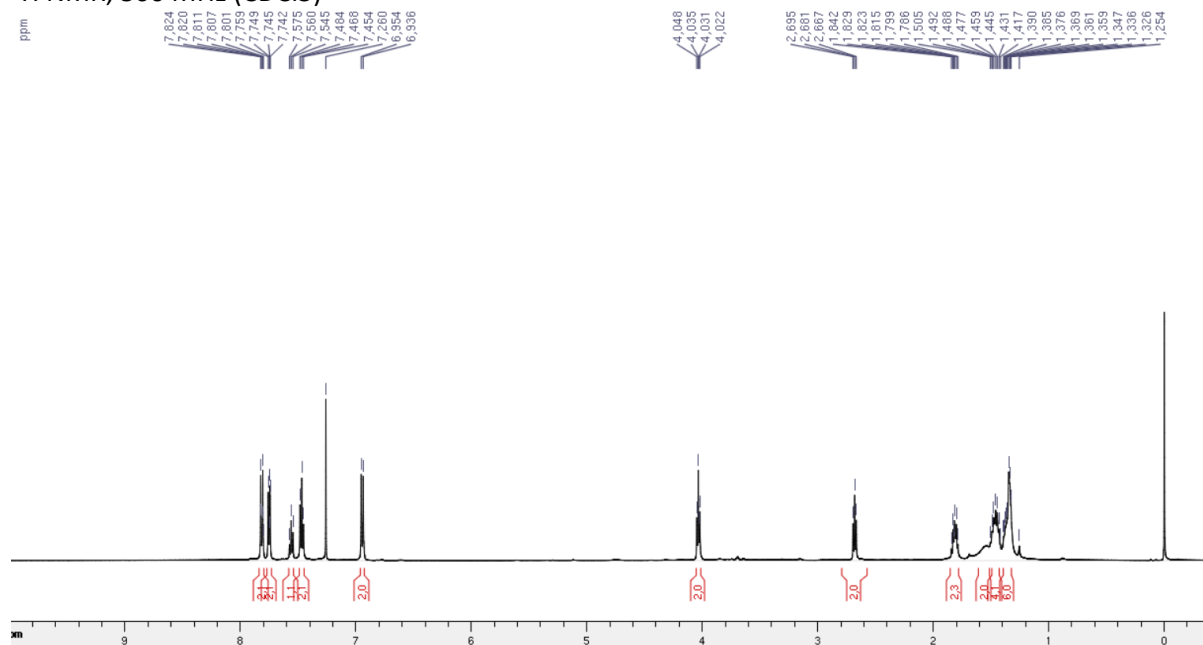
^{13}C NMR, 125 MHz (CDCl_3)



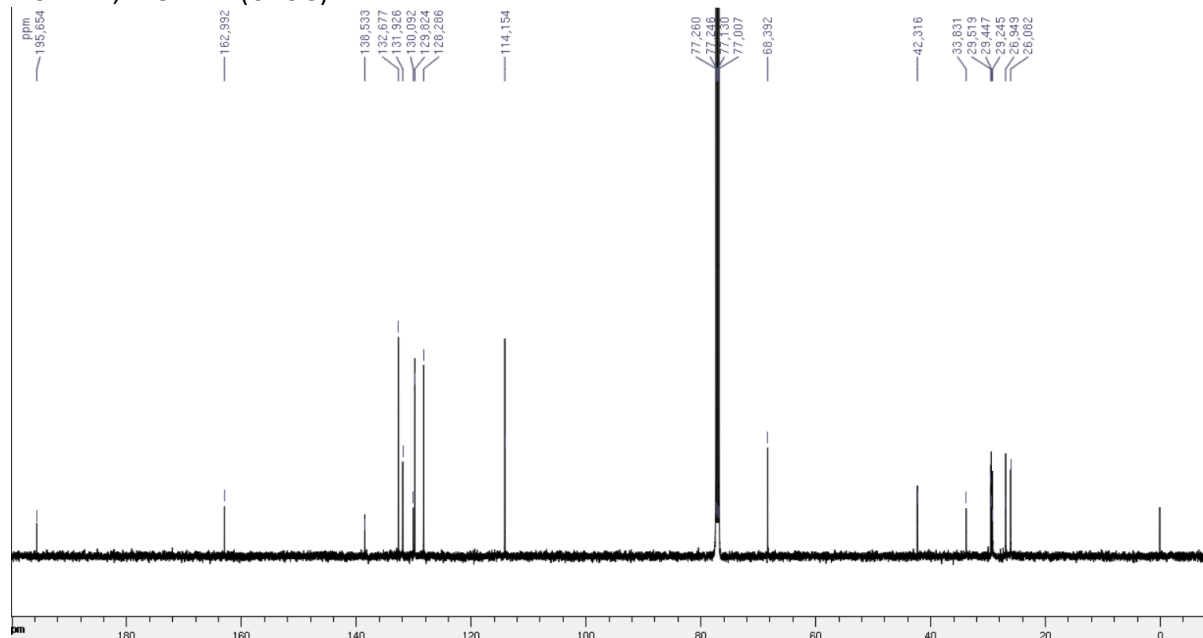
4-(8'-Amino-octanyloxy)-benzophenone 13d



¹H NMR, 500 MHz (CDCl₃)



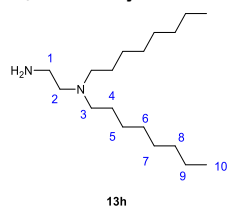
¹³C NMR, 125 MHz (CDCl₃)



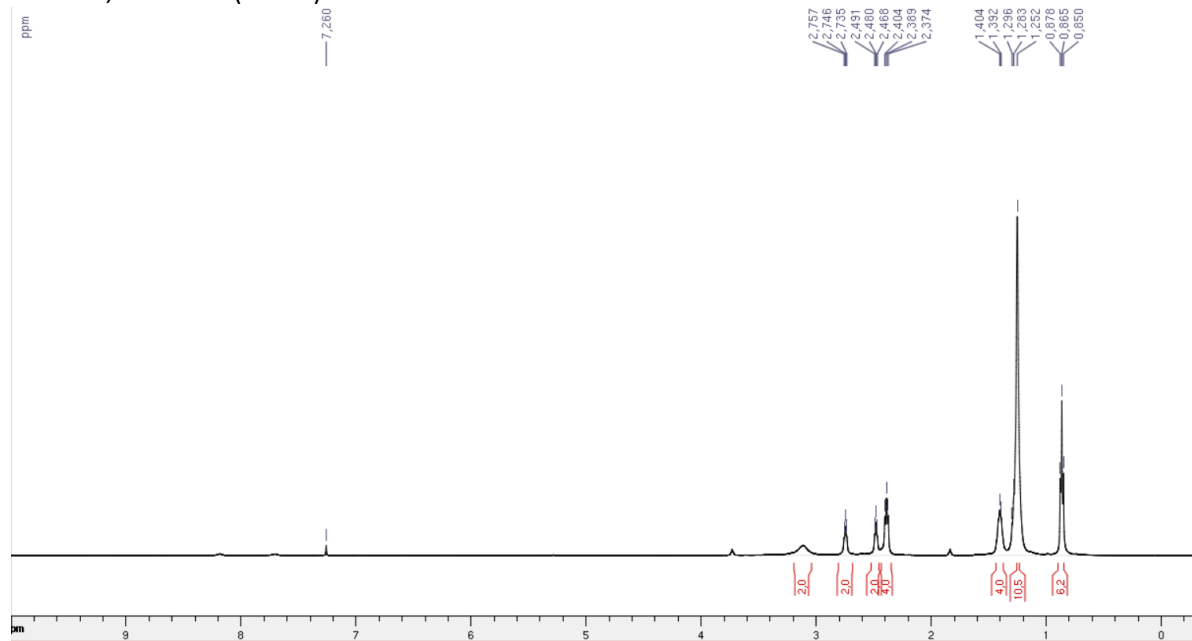
13e

¹H NMR spectrum (CDCl₃) of 1,2-dibromoethane. The spectrum shows a triplet at 1.260 ppm (3H, integration 3.0), a quartet at 1.130 ppm (2H, integration 2.0), a multiplet at 1.066 ppm (2H, integration 2.0), and a triplet at 0.838 ppm (3H, integration 3.0). A reference peak for TMS is at 0.0 ppm. The x-axis is labeled 'ppm' and ranges from 0 to 10.

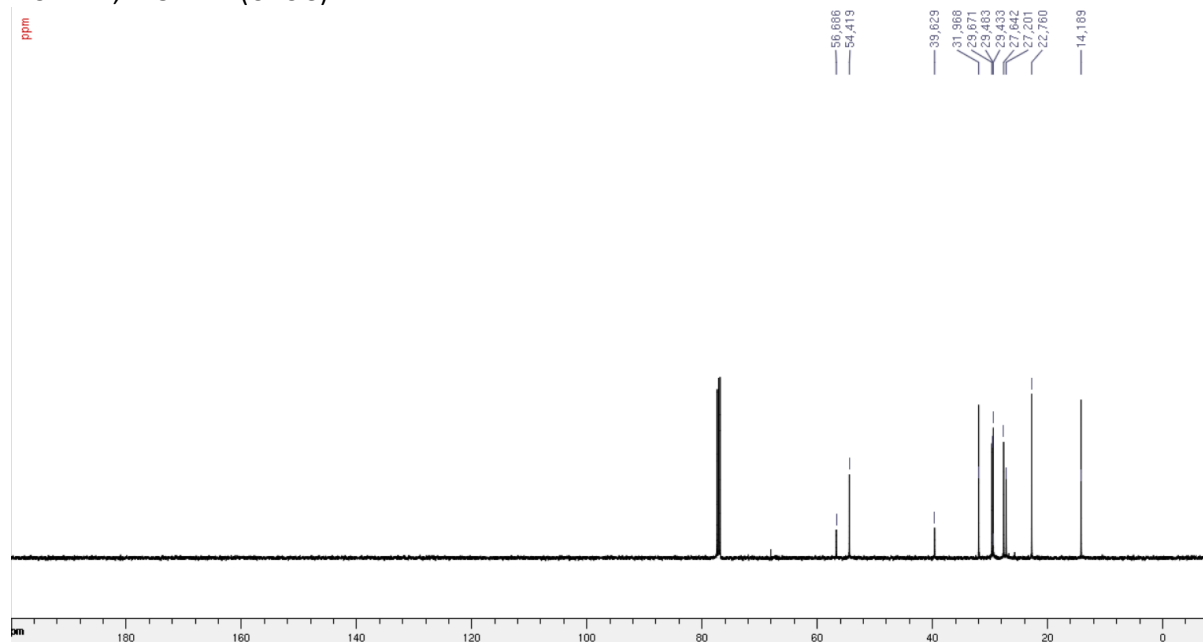
N,N-dioctylethane-1,2-diamine 13h



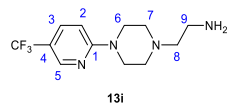
¹H NMR, 500 MHz (CDCl₃)



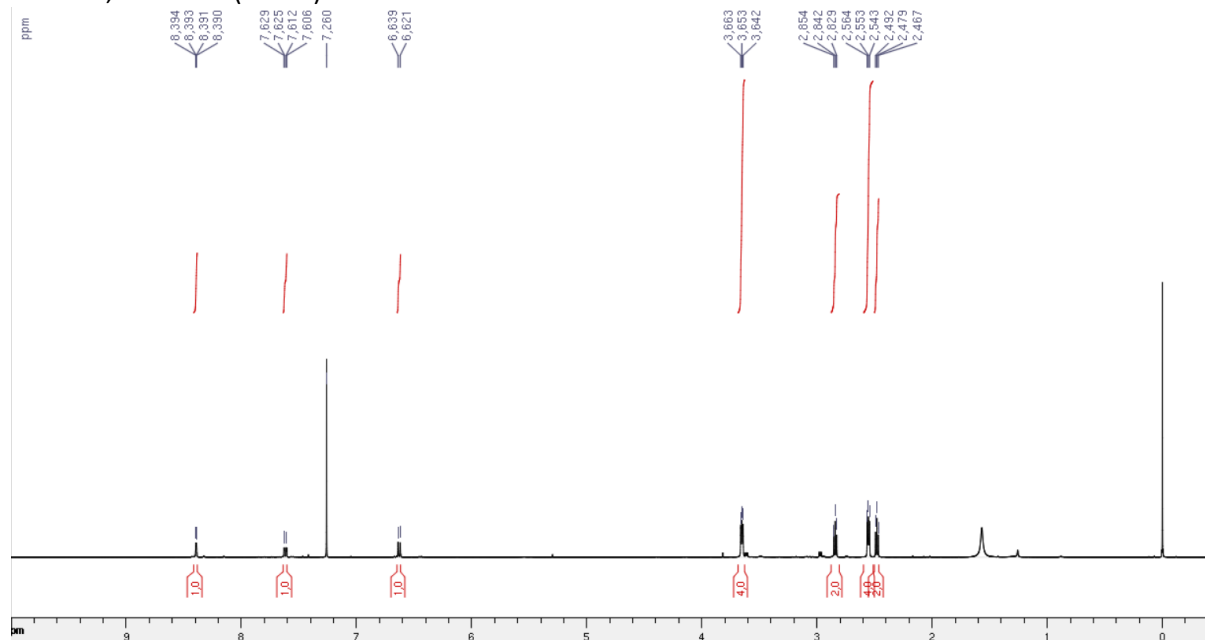
¹³C NMR, 125 MHz (CDCl₃)



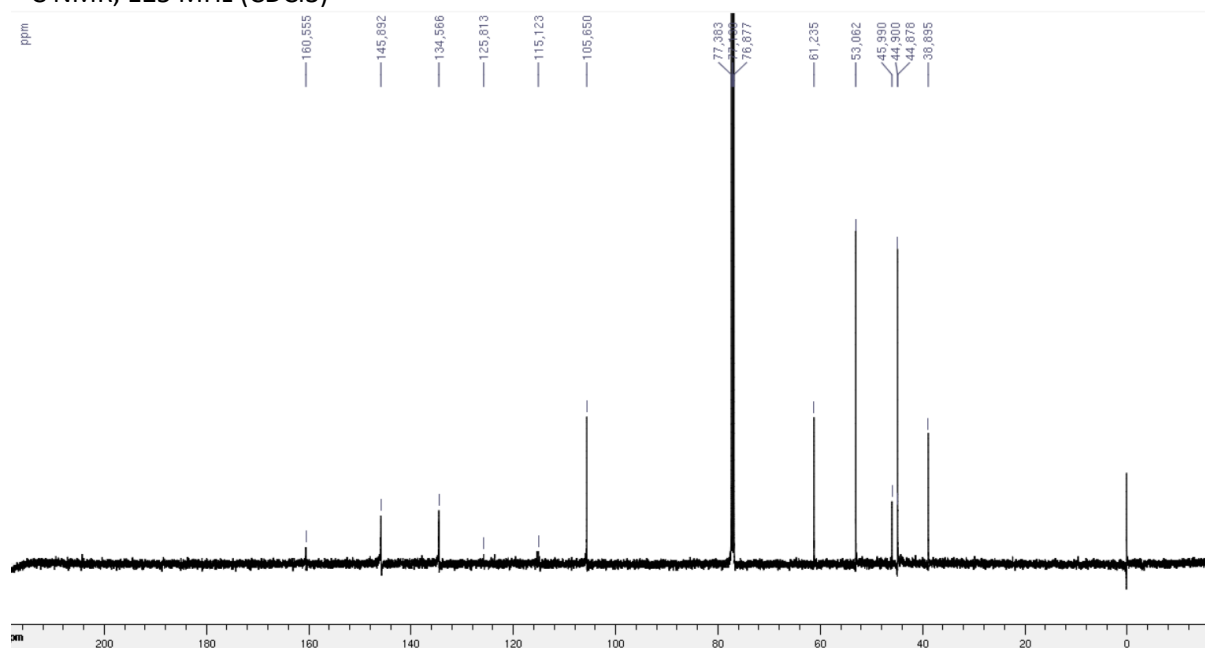
2-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)ethan-1-amine 13i



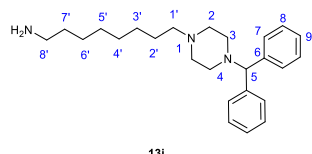
¹H NMR, 500 MHz (CDCl₃)



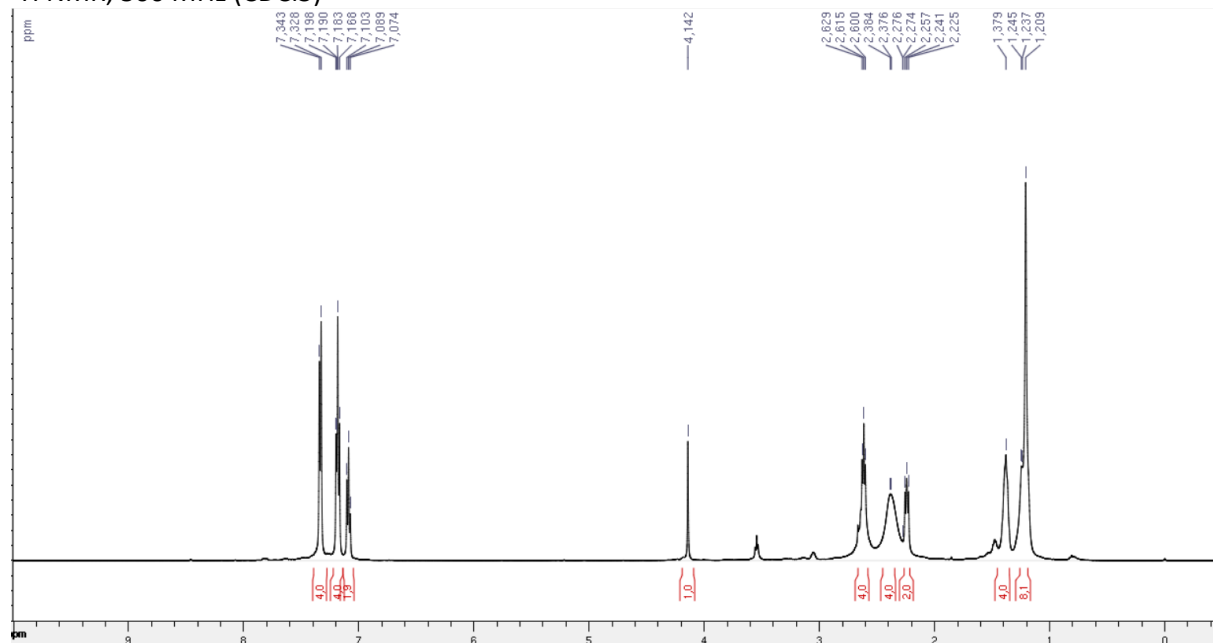
¹³C NMR, 125 MHz (CDCl₃)



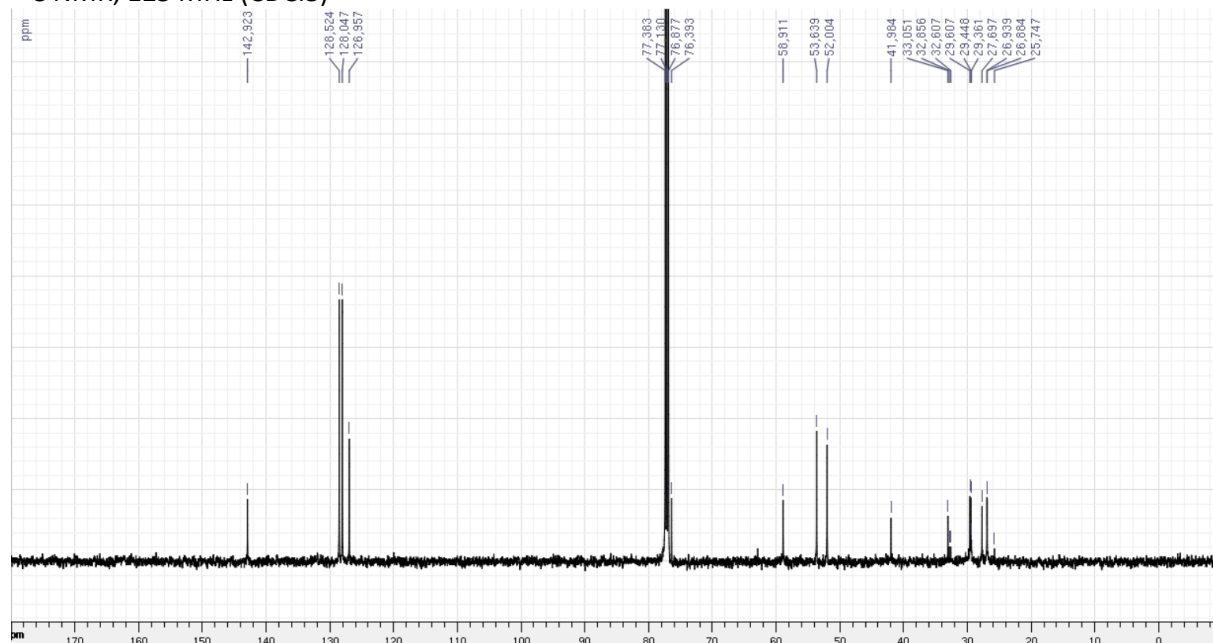
8'-(4-benzhydrylpiperazin-1-yl)octan-1-amine 13j



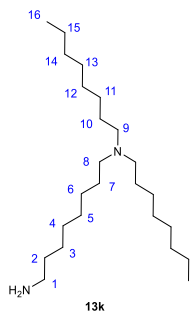
^1H NMR, 500 MHz (CDCl_3)



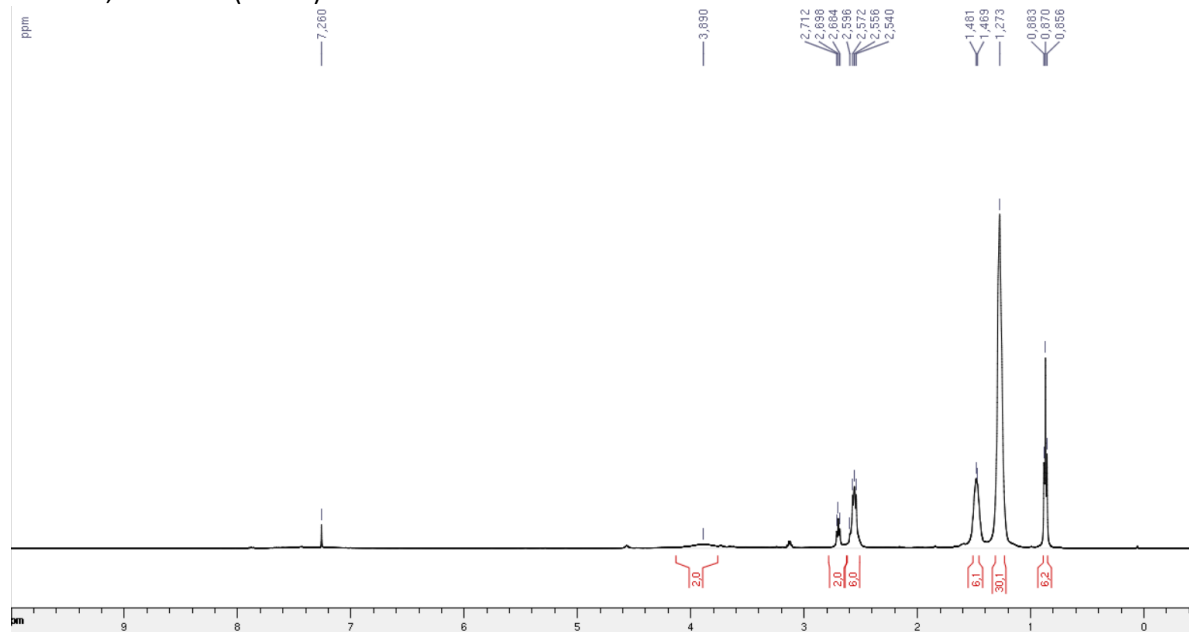
^{13}C NMR, 125 MHz (CDCl_3)



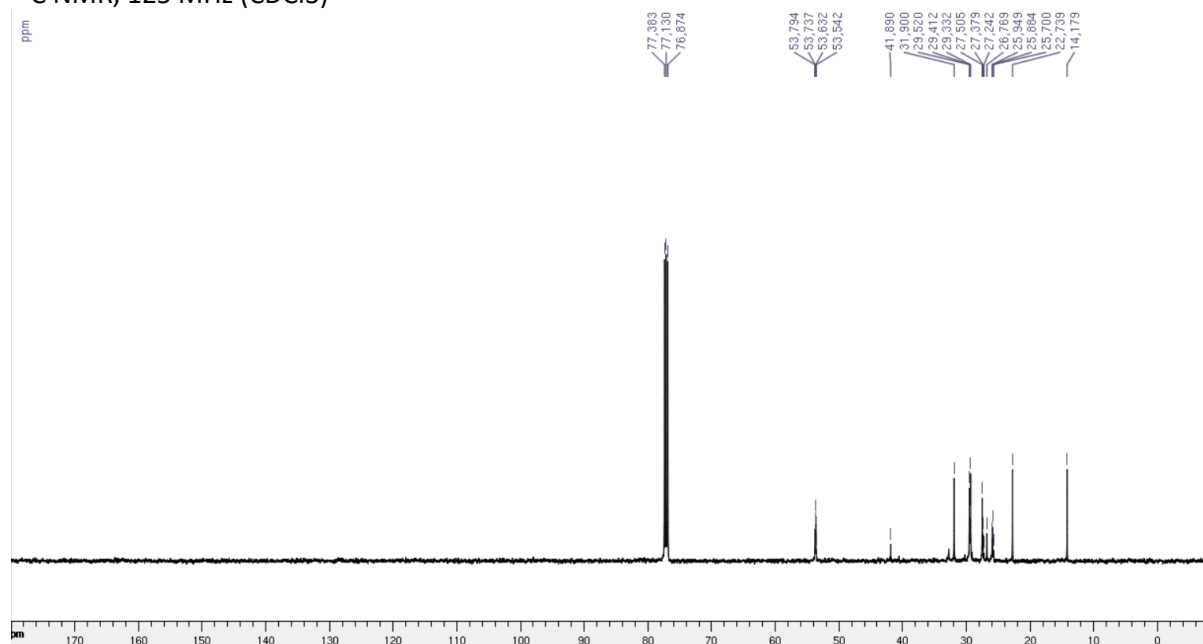
***N,N*-dioctyloctane-1,8-diamine 13k**



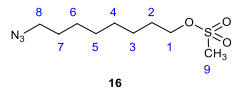
^1H NMR, 500 MHz (CDCl_3)



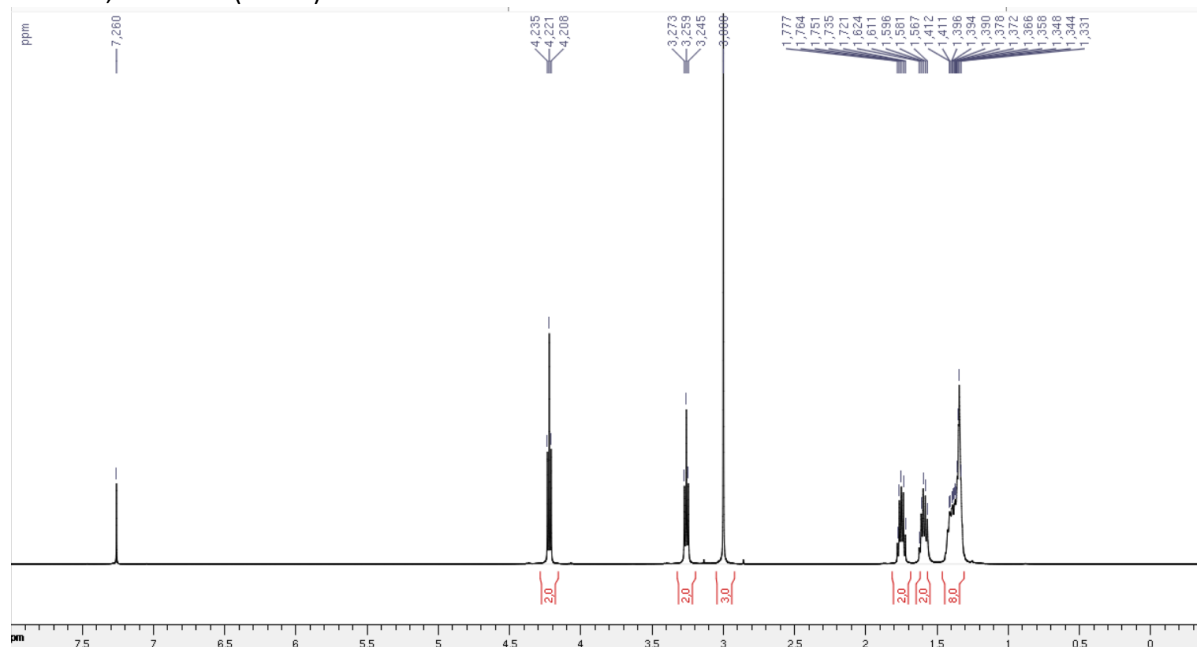
^{13}C NMR, 125 MHz (CDCl_3)



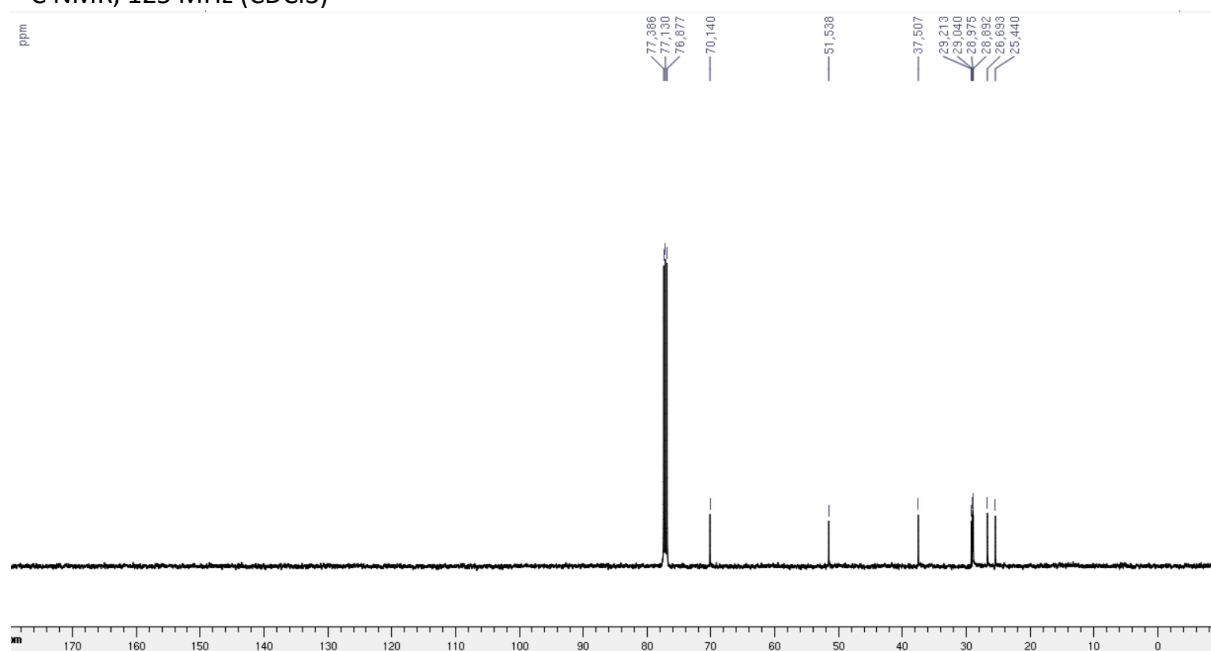
8-azidoctyl methanesulfonate **16**



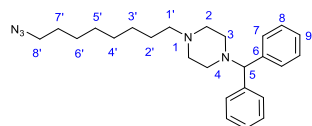
¹H NMR, 500 MHz (CDCl₃)



¹³C NMR, 125 MHz (CDCl₃)

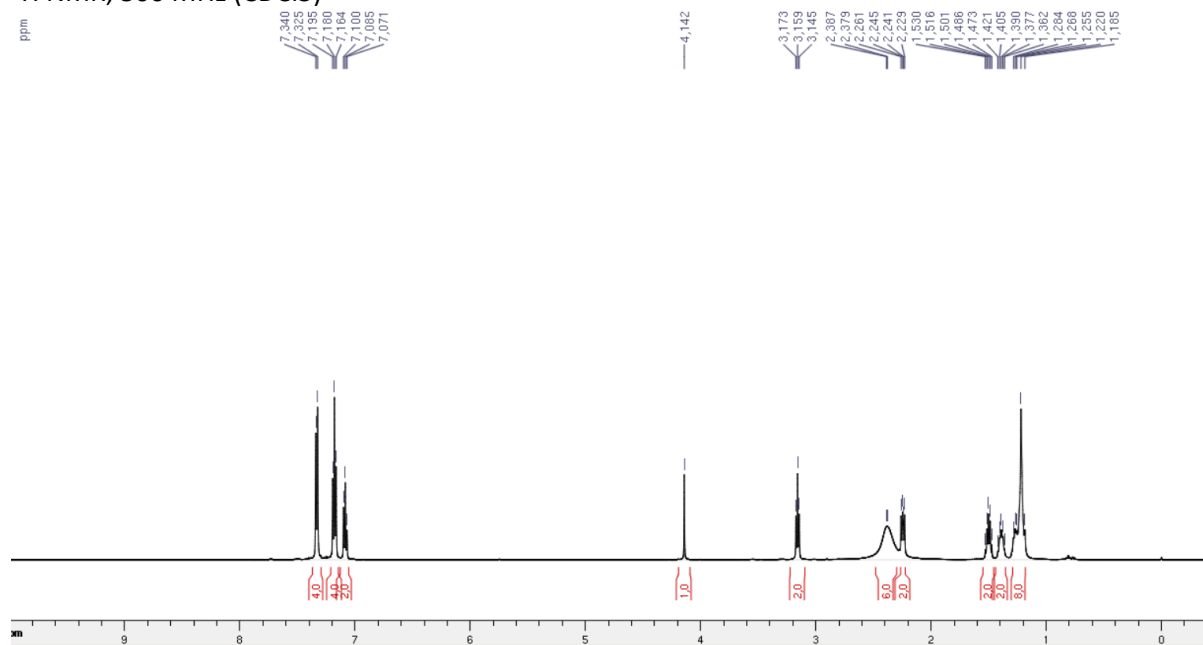


1-(8'-azidooctyl)-4-benzhydrylpiperazine 17

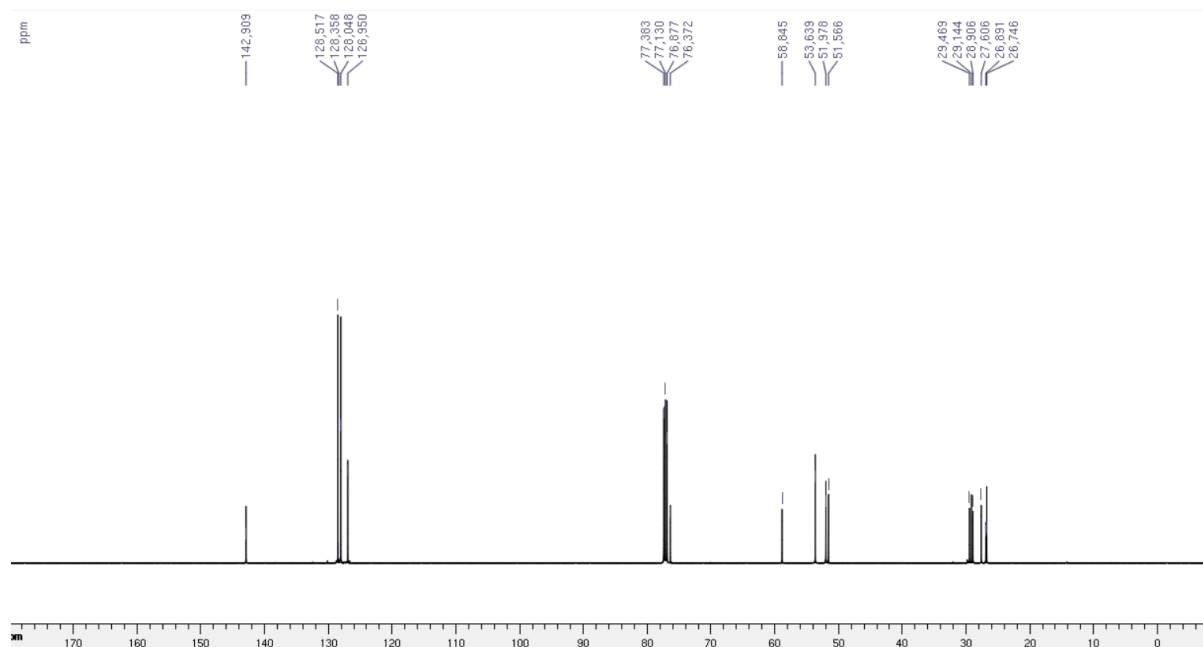


17

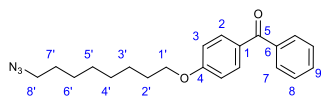
¹H NMR, 500 MHz (CDCl₃)



¹³C NMR, 125 MHz (CDCl₃)

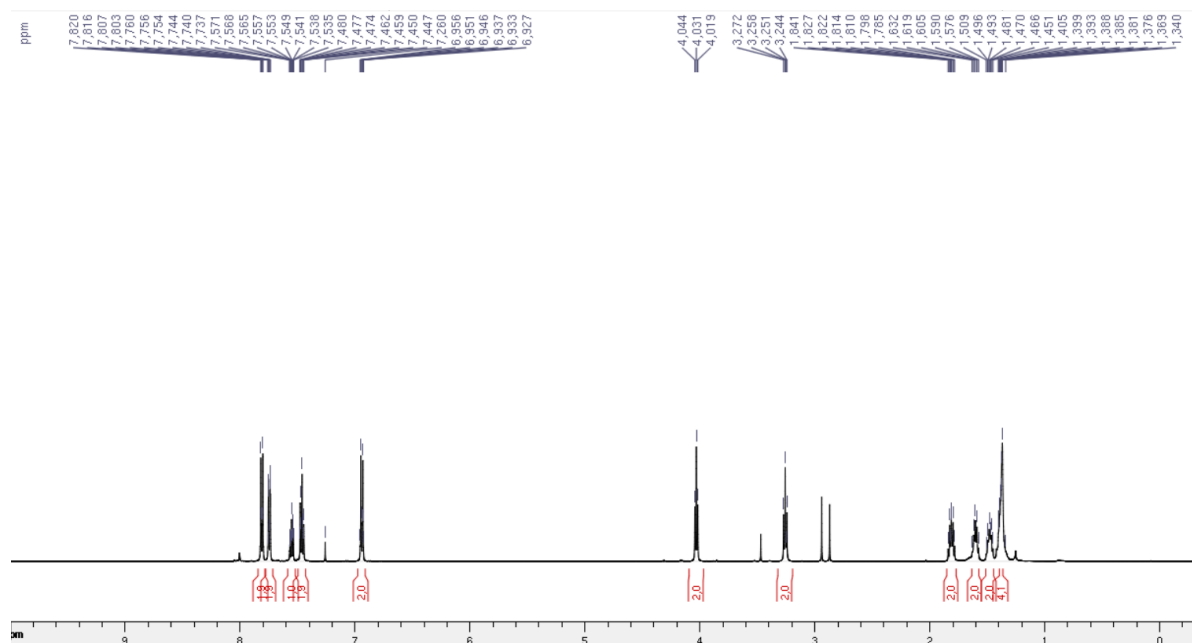


4-(8'-Azido-octanyloxy)-benzophenone 18

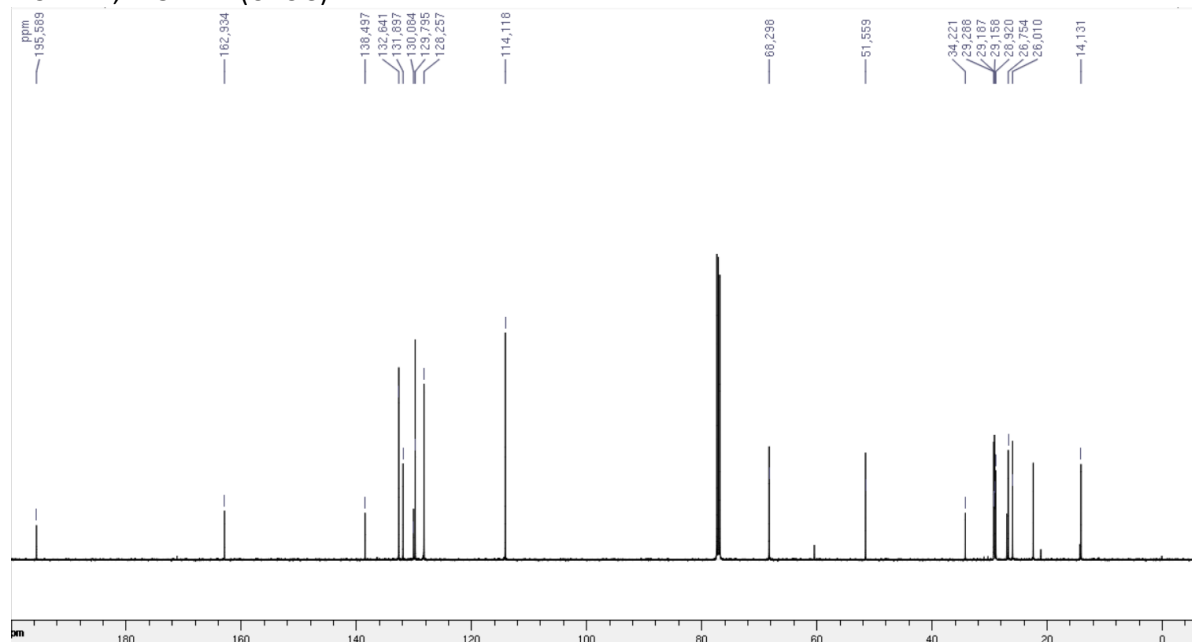


18

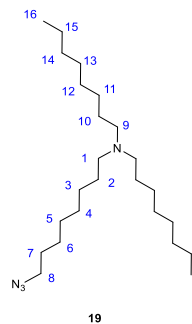
¹H NMR, 500 MHz (CDCl₃)



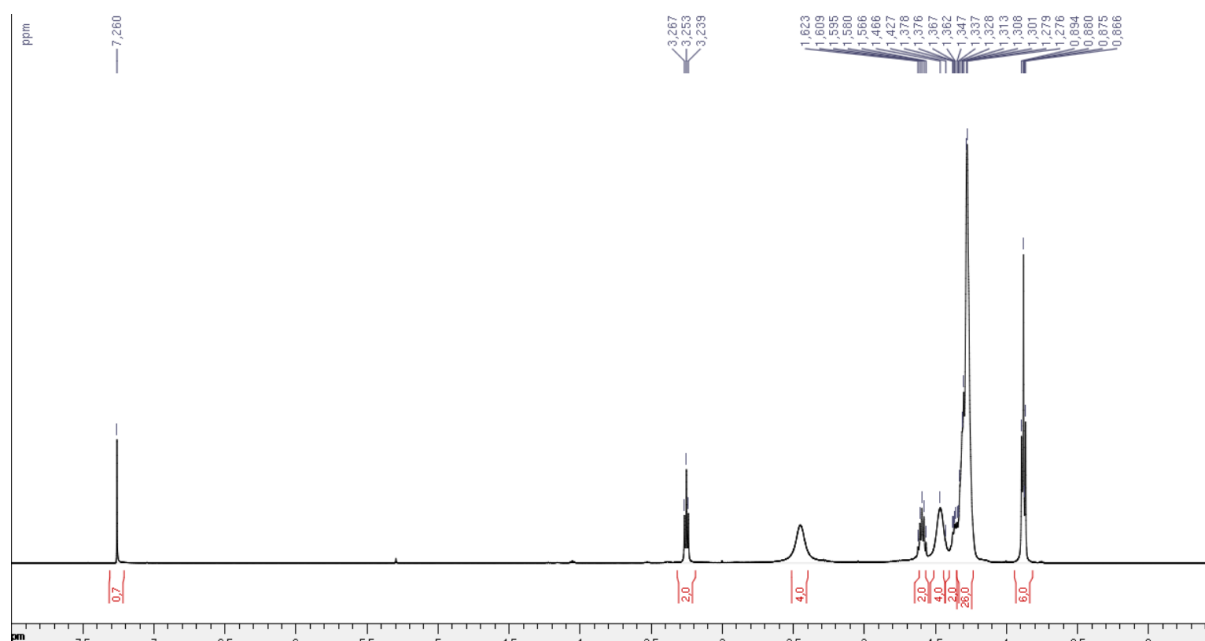
¹³C NMR, 125 MHz (CDCl₃)



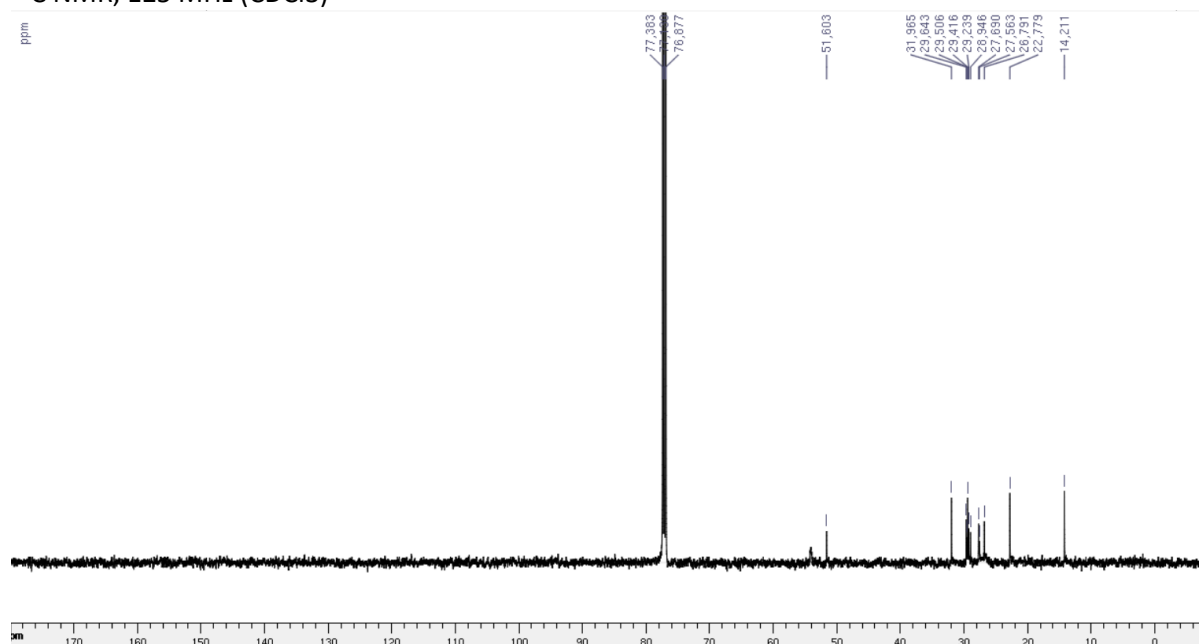
8-azido-*N,N*-dioctyloctan-1-amine 19



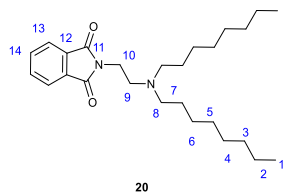
^1H NMR, 500 MHz (CDCl_3)



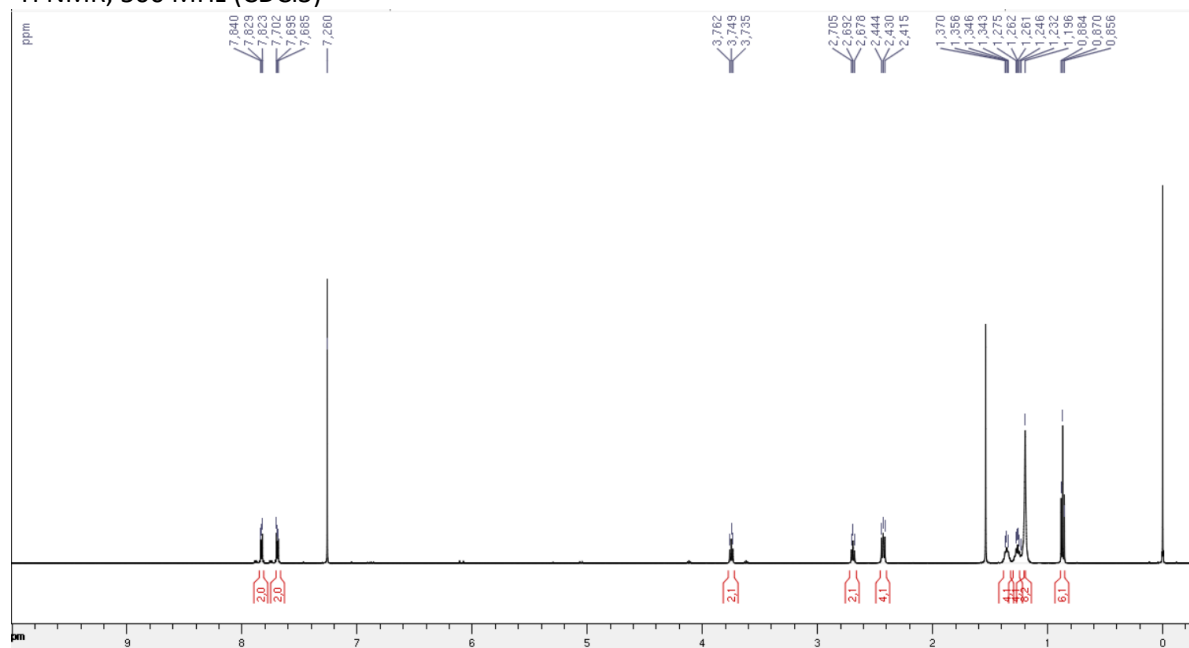
^{13}C NMR, 125 MHz (CDCl_3)



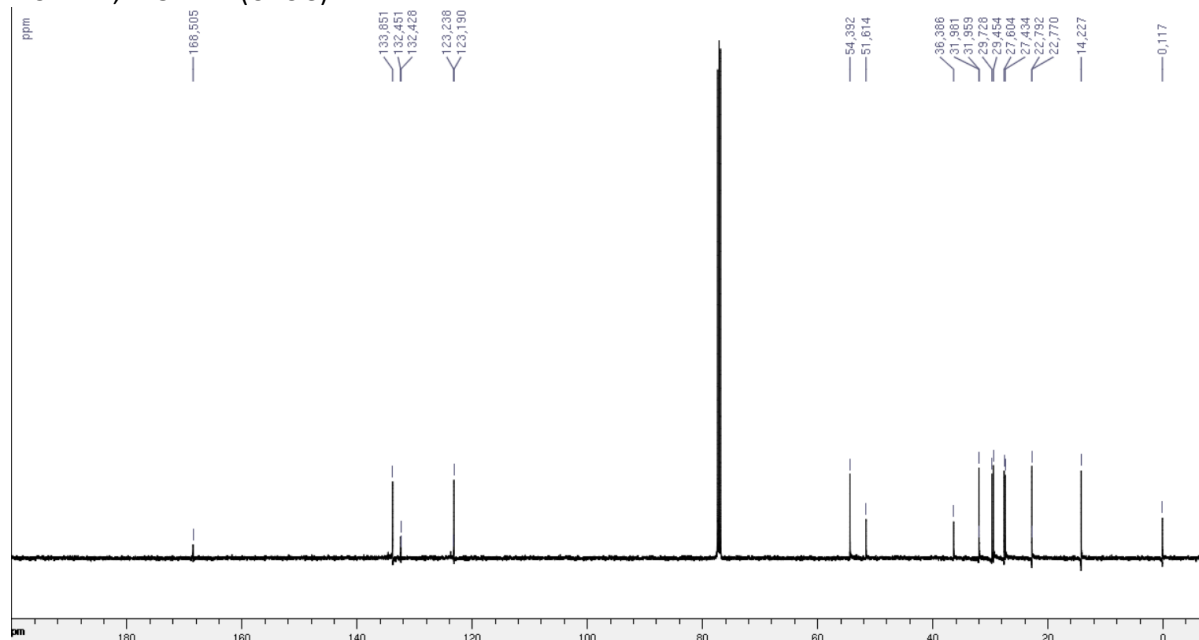
N-phtalimido-10-(9-(dioctylamino)ethyl) 20



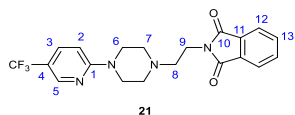
¹H NMR, 500 MHz (CDCl₃)



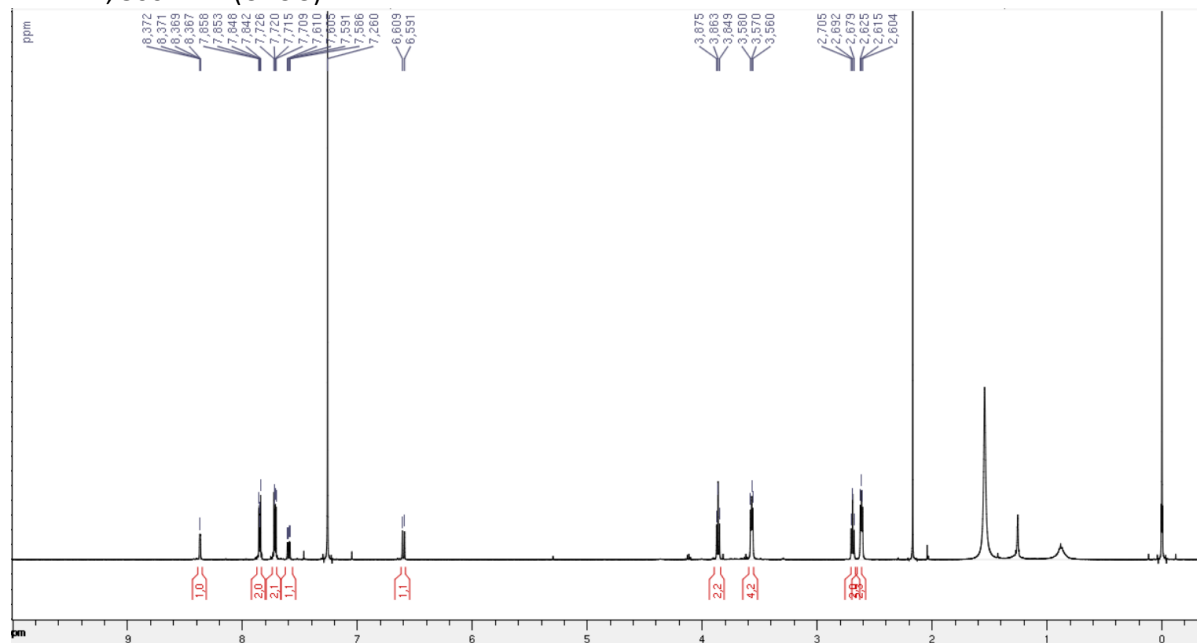
¹³C NMR, 125 MHz (CDCl₃)



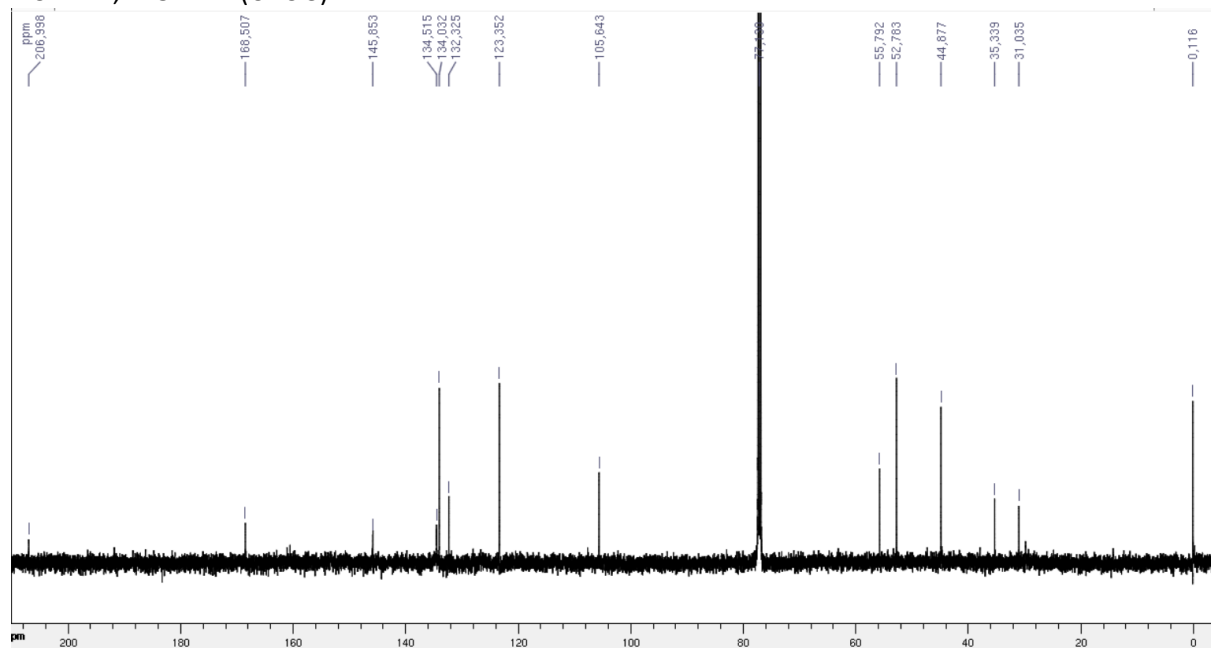
2-(2-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)ethyl) phthalimide 21



¹H NMR, 500 MHz (CDCl₃)



¹³C NMR, 125 MHz (CDCl₃)



Chemical structure of compound 23a, showing a pyridine ring substituted with a sugar derivative and a long alkyl chain. The structure is labeled 23a at the bottom.

Chemical shift (ppm)

162.995
158.218
150.134
140.485
118.169
112.049
101.813
89.658
85.965
85.096
84.989
81.723
80.573
77.384
77.130
76.876
75.126
71.834
53.818
41.938
40.875
40.833
38.352
31.998
29.680
29.653
29.630
29.416
27.022
26.955
26.506
25.929
25.890
25.842
25.773
22.779
18.104
14.205
8.469
7.607
0.100
-4.021
-4.379

ppm

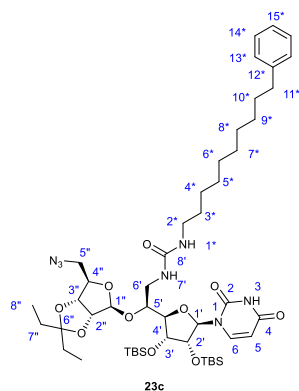
23b

Chemical shifts (ppm): 8.239, 7.806, 7.790, 7.780, 7.680, 5.750, 5.733, 5.713, 5.707, 5.695, 5.690, 5.200, 4.614, 4.611, 4.602, 4.588, 4.538, 4.525, 4.385, 4.382, 4.222, 4.222, 4.214, 4.205, 4.125, 4.100, 4.100, 4.100, 4.115, 4.110, 4.014, 4.005, 3.996, 3.833, 3.826, 3.516, 3.493, 3.483, 3.479, 3.467, 3.148, 3.144, 3.133, 1.727, 1.712, 1.687, 1.683, 1.643, 1.579, 1.564, 1.549, 1.534, 1.310, 1.296, 1.286, 1.283, 1.254, 0.946, 0.941, 0.931, 0.931, 0.926, 0.914, 0.911, 0.896, 0.895, 0.888, 0.885, 0.863, 0.855, 0.845, 0.839, 0.822, 0.119, 0.113, 0.108, 0.104, 0.092, 0.085, 0.081, 0.075, 0.068.

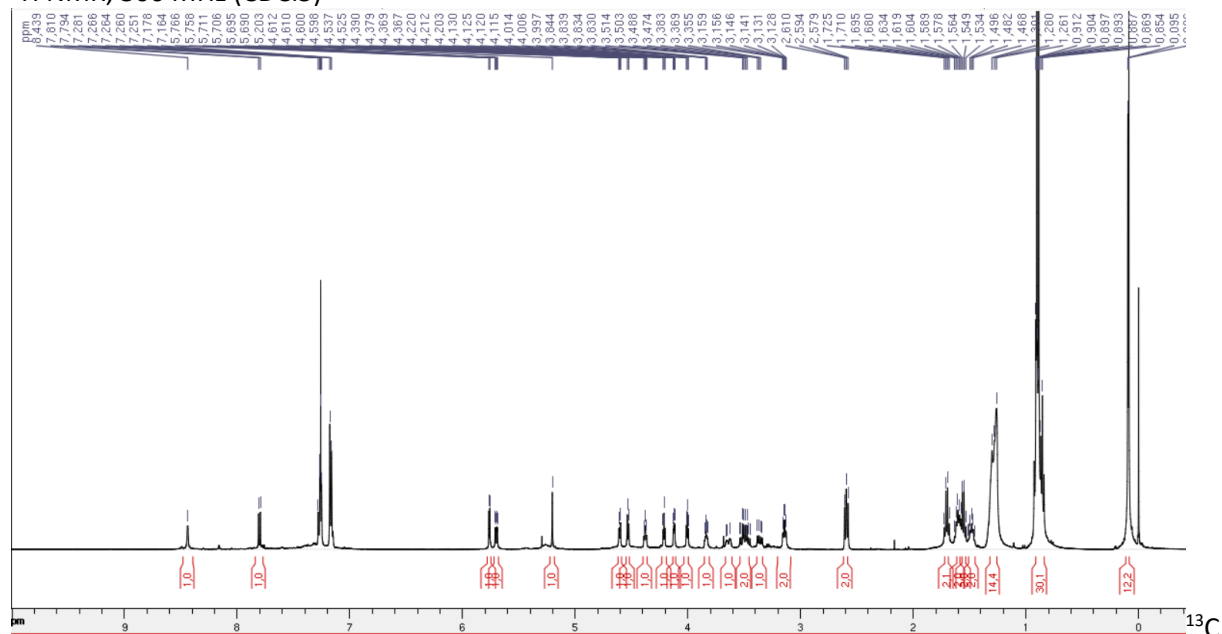
Integration values: 12.2, 31.7, 1.9.

13C NMR spectrum of compound 1. The x-axis represents chemical shift in ppm, ranging from 0 to 170. The spectrum shows several sharp peaks. Key peaks are labeled with their chemical shift values: 163.375, 158.320, 150.319, 140.433, 118.119, 112.009, 101.736, 89.565, 84.980, 81.716, 77.383, 76.877, 75.166, 71.779, 53.776, 53.754, 42.841, 40.146, 31.996, 29.779, 29.751, 29.722, 29.693, 29.613, 29.584, 23.482, 23.433, 23.404, 25.800, 25.873, 22.768, 16.001, 14.189, 0.448, -4.378, and -4.855. A large solvent peak is visible at 77.383 ppm.

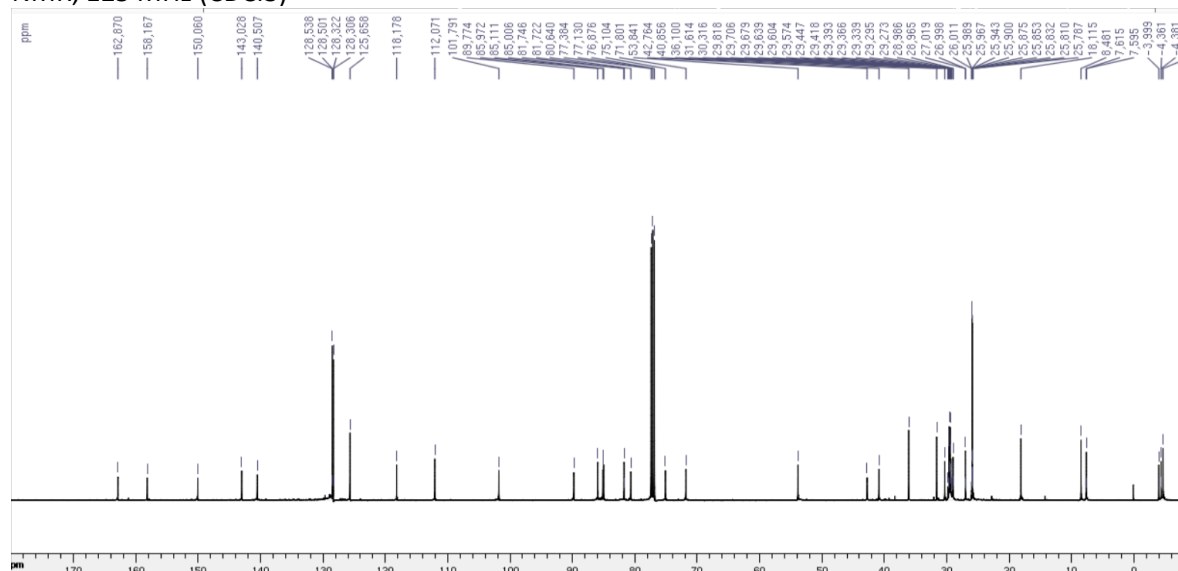
Compound 23c



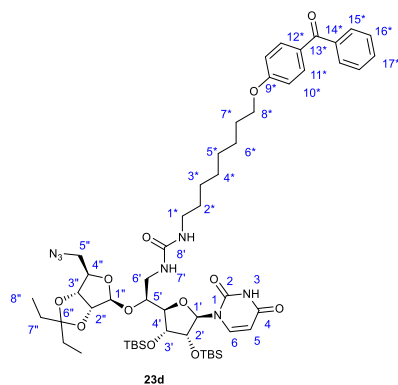
¹H NMR, 500 MHz (CDCl₃)



NMR, 125 MHz (CDCl₃)



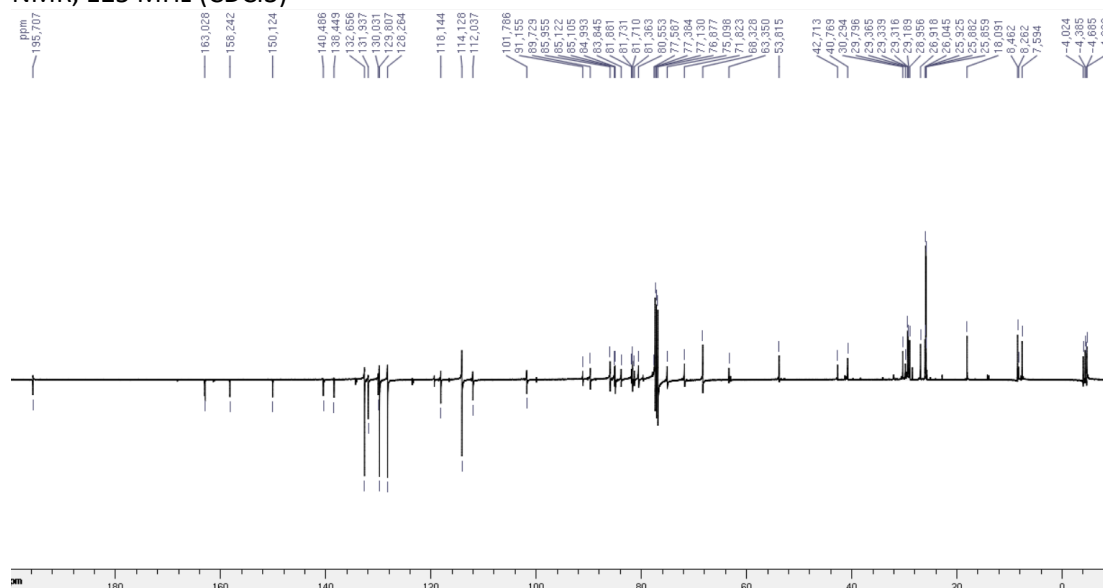
Compound 23d



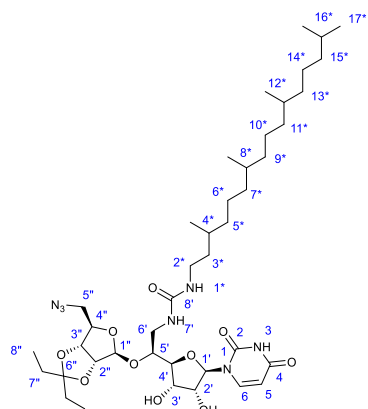
¹H NMR, 500 MHz (CDCl₃)



NMR, 125 MHz (CDCl₃)

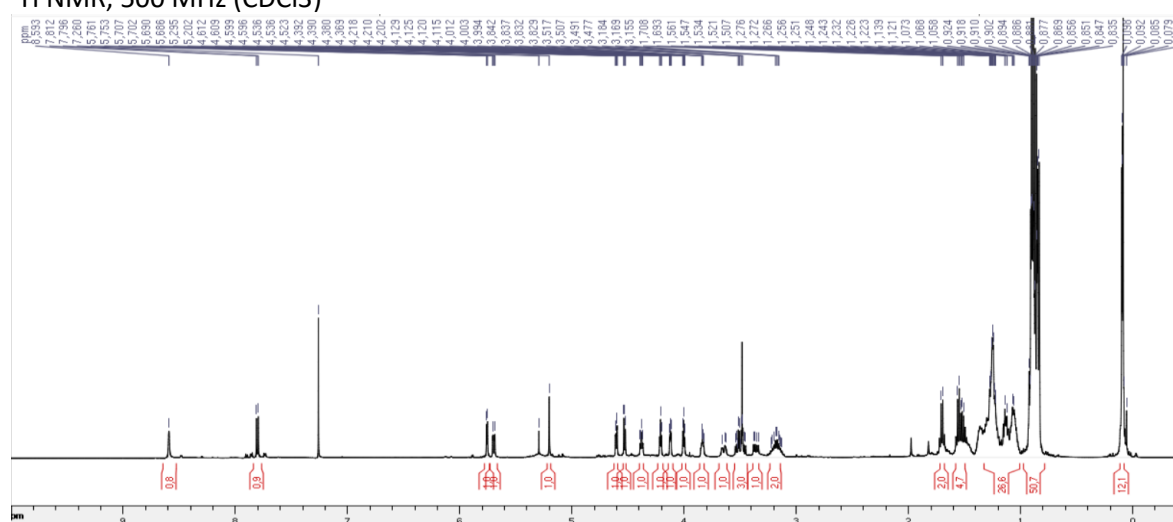


Compound 23e

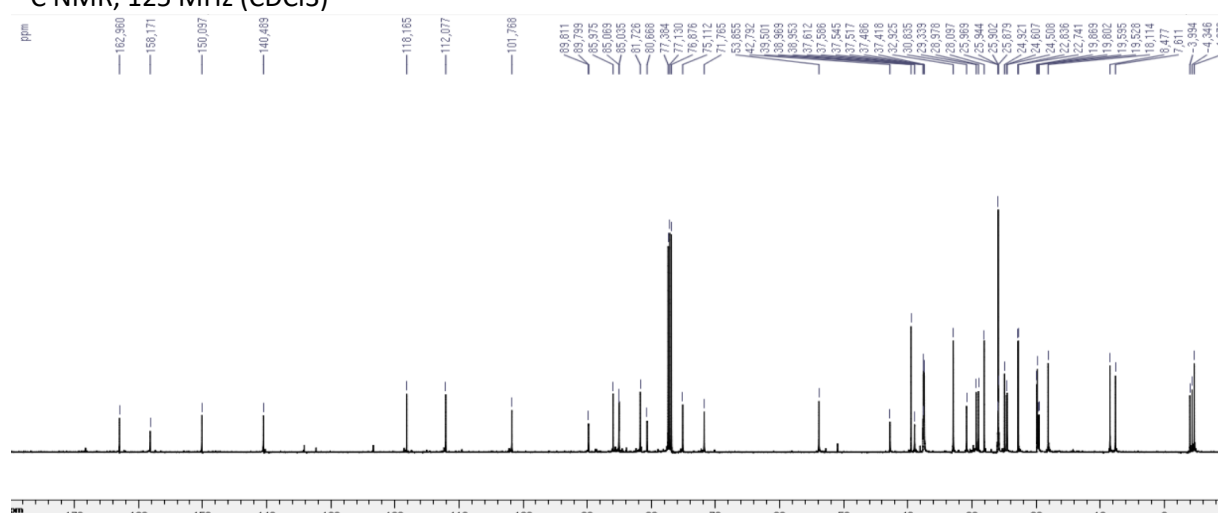


23e

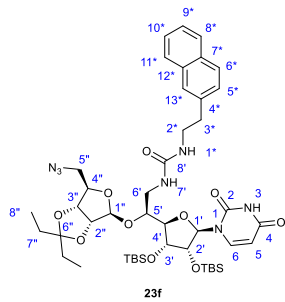
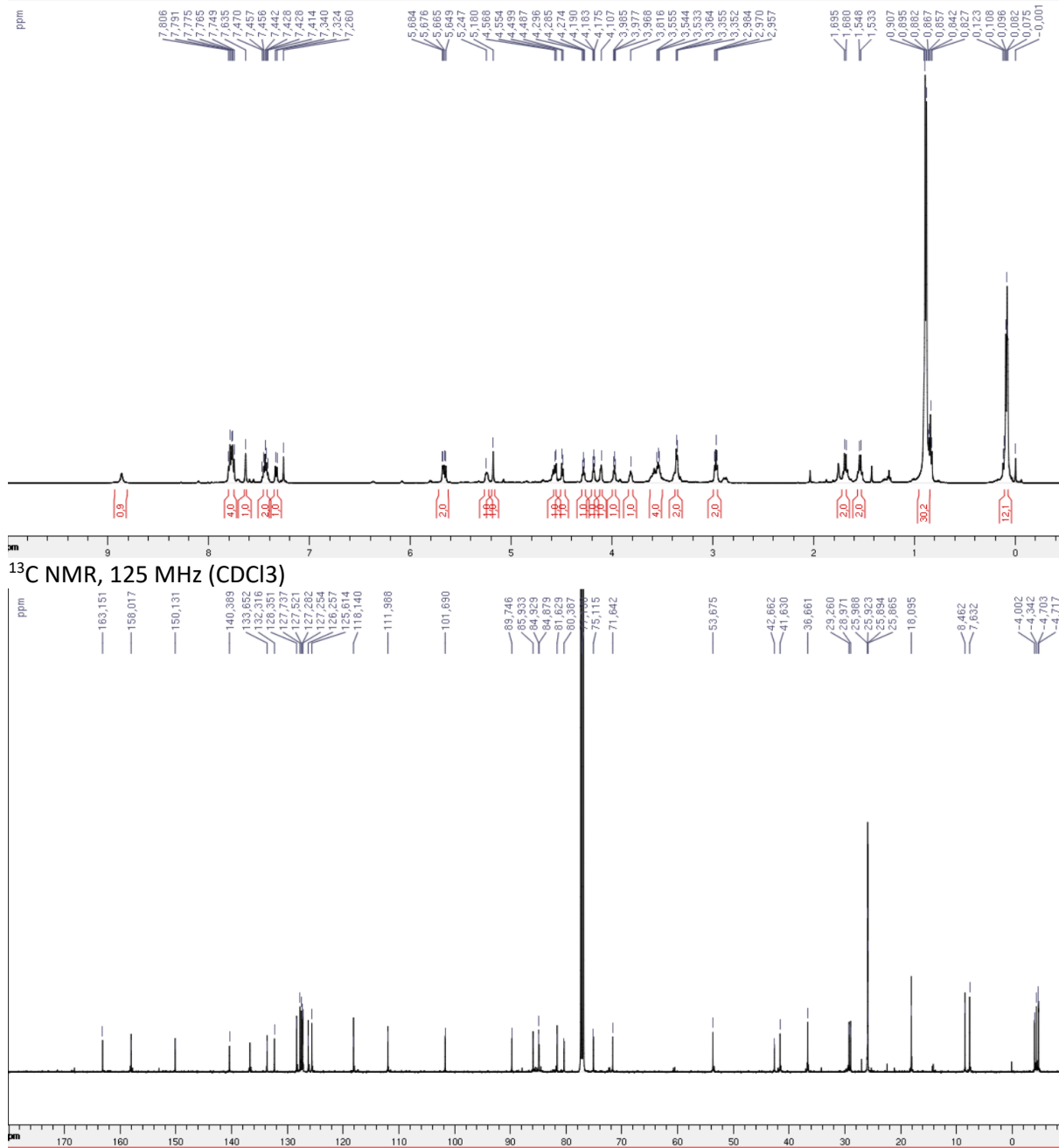
¹H NMR, 500 MHz (CDCl₃)



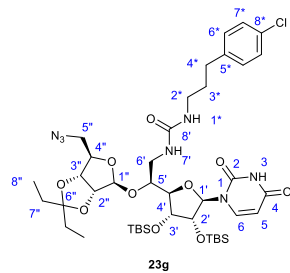
¹³C NMR, 125 MHz (CDCl₃)



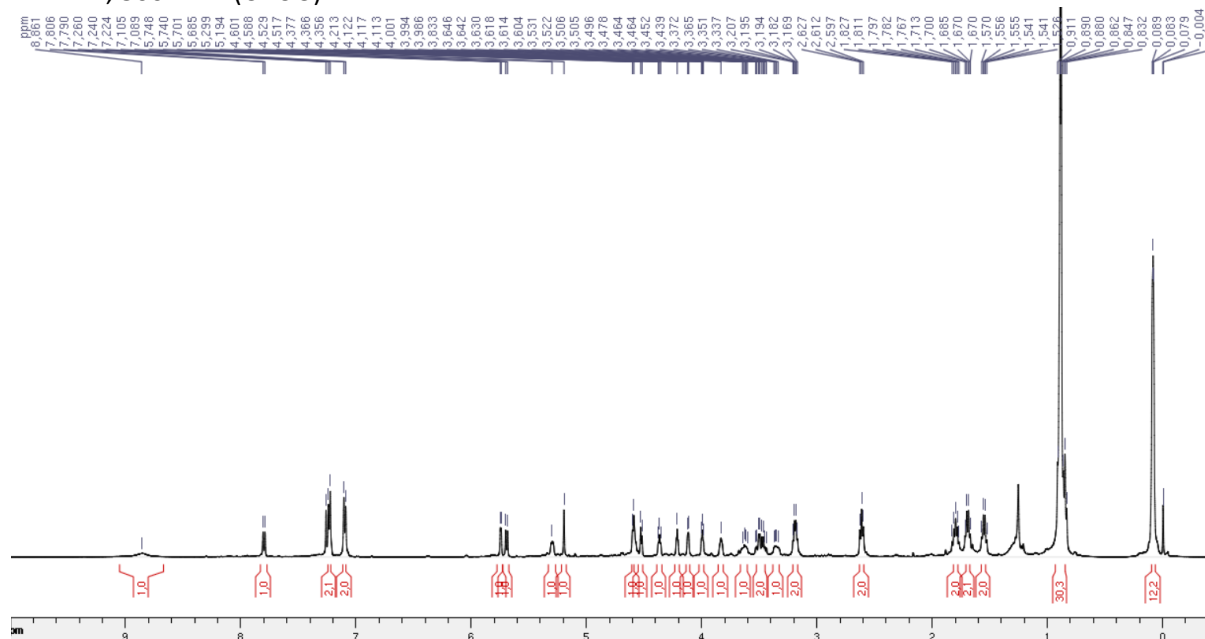
Compound 23f

¹H NMR, 500 MHz (CDCl₃)

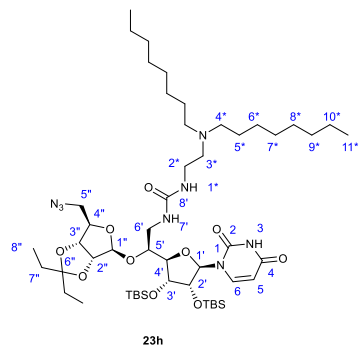
Compound 23g



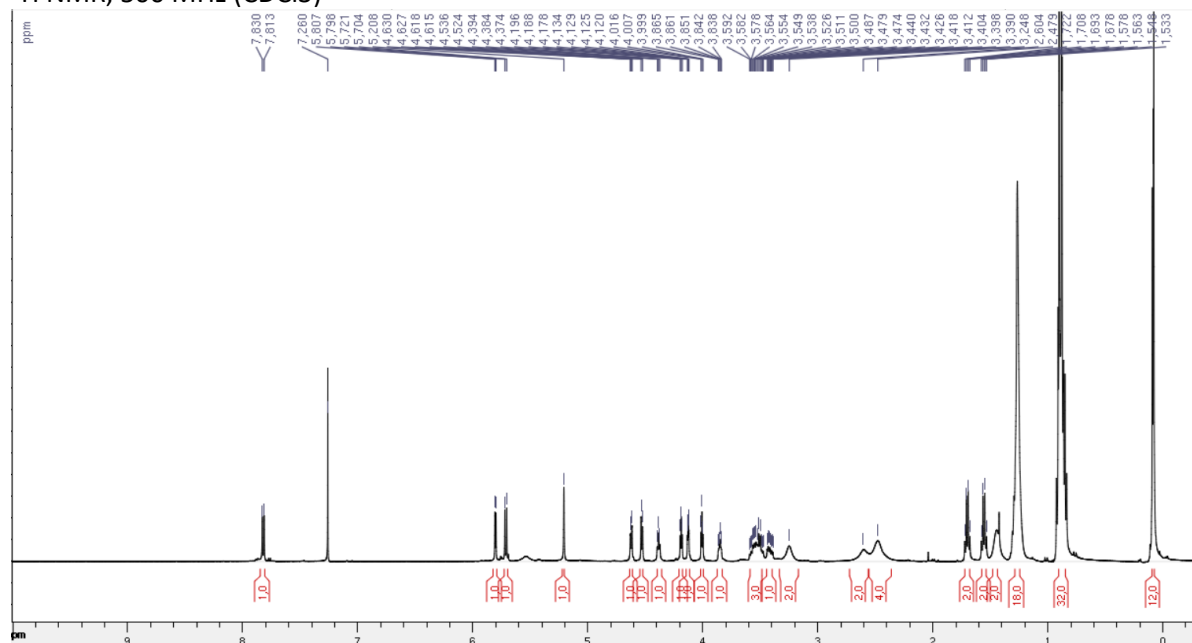
¹H NMR, 500 MHz (CDCl₃)



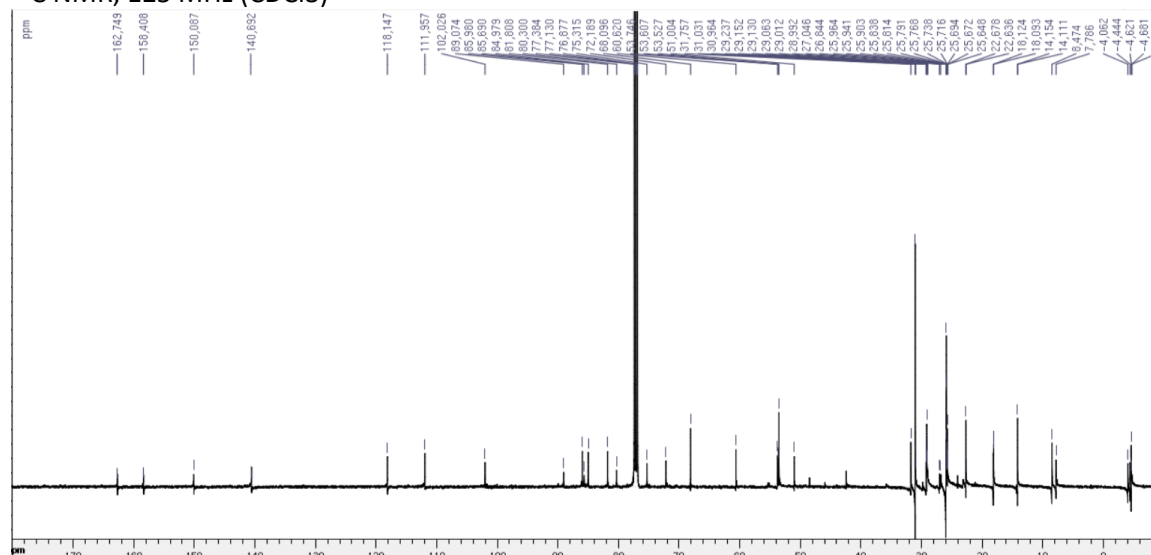
Compound 23h



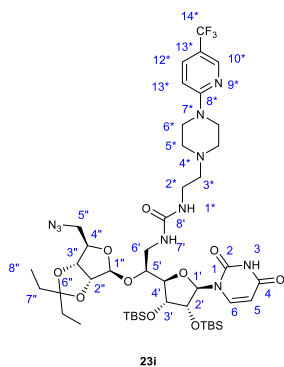
¹H NMR, 500 MHz (CDCl₃)



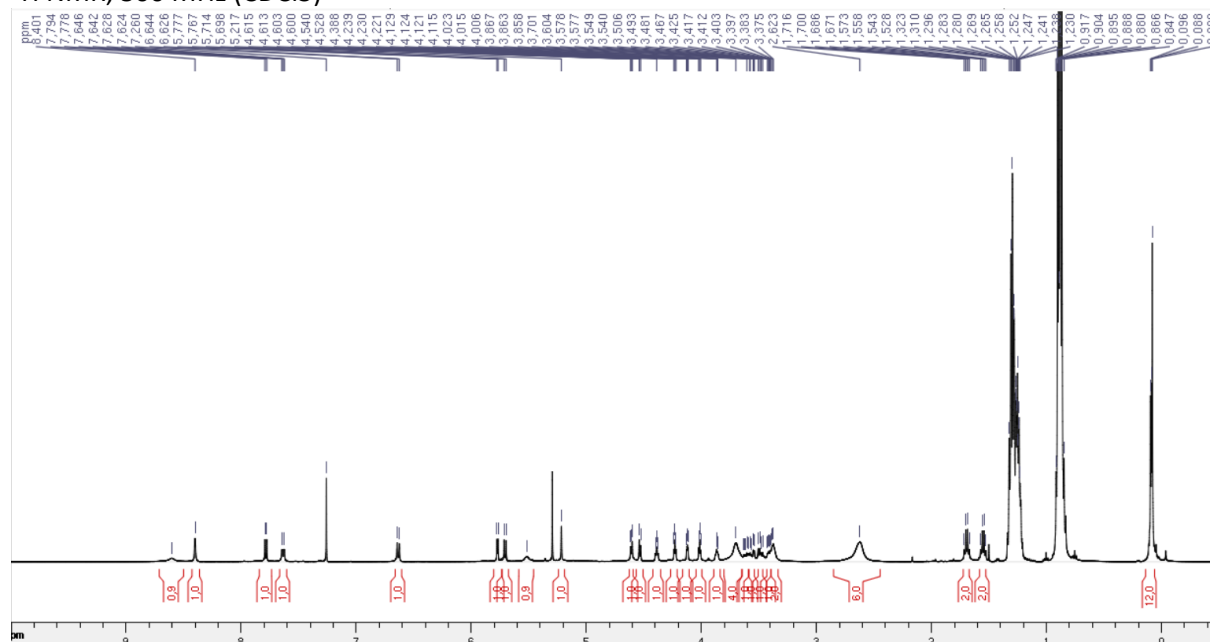
¹³C NMR, 125 MHz (CDCl₃)



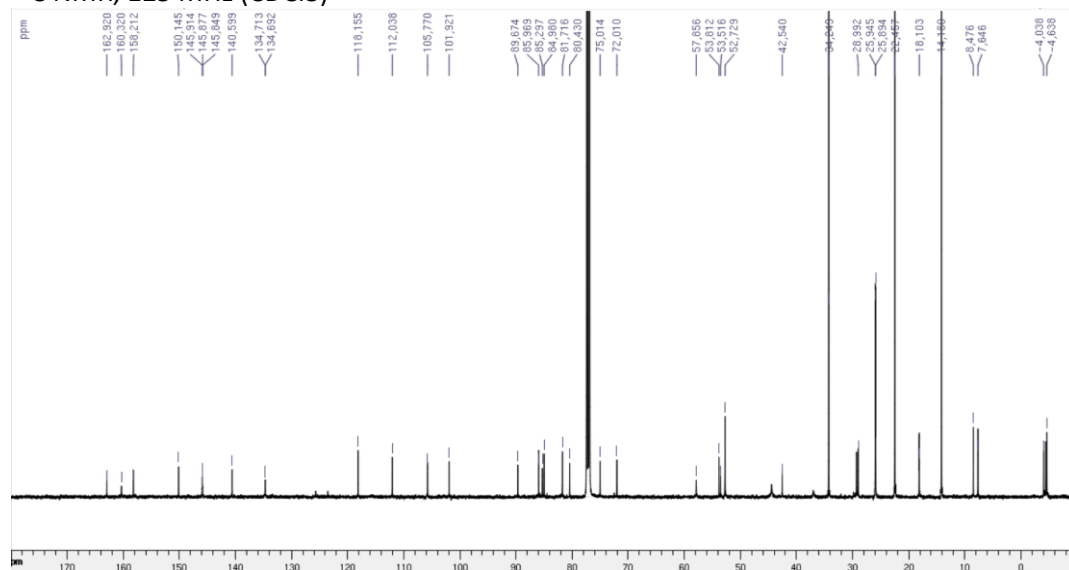
Compound 23i



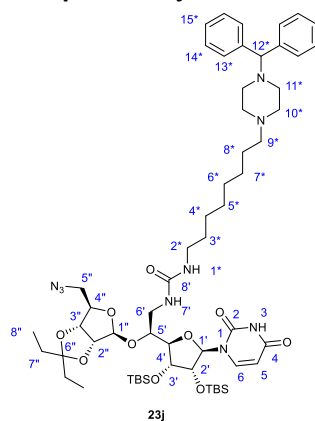
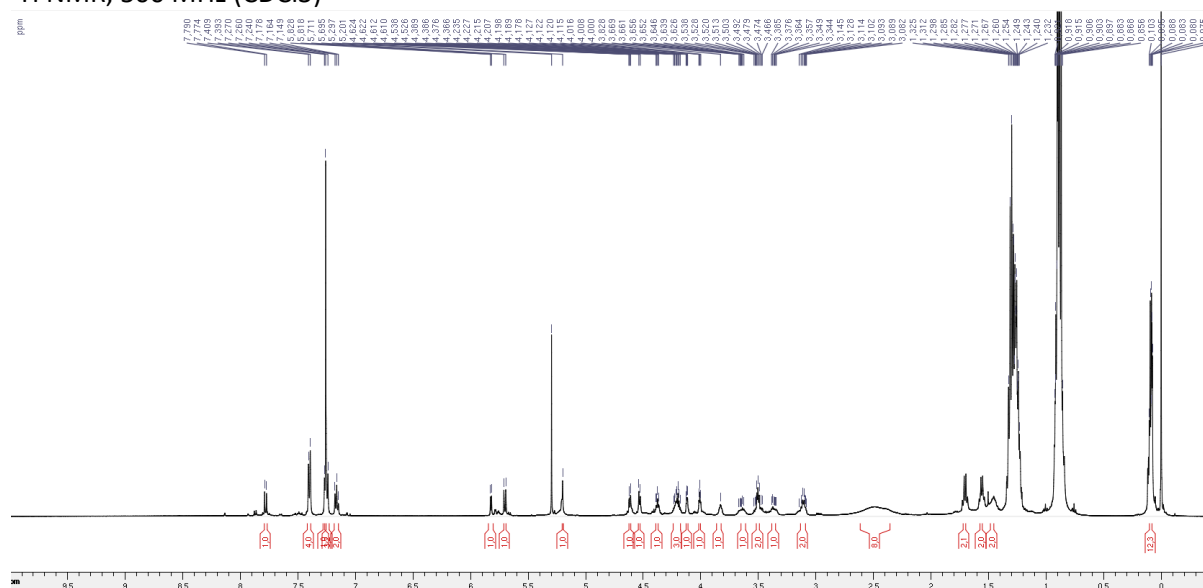
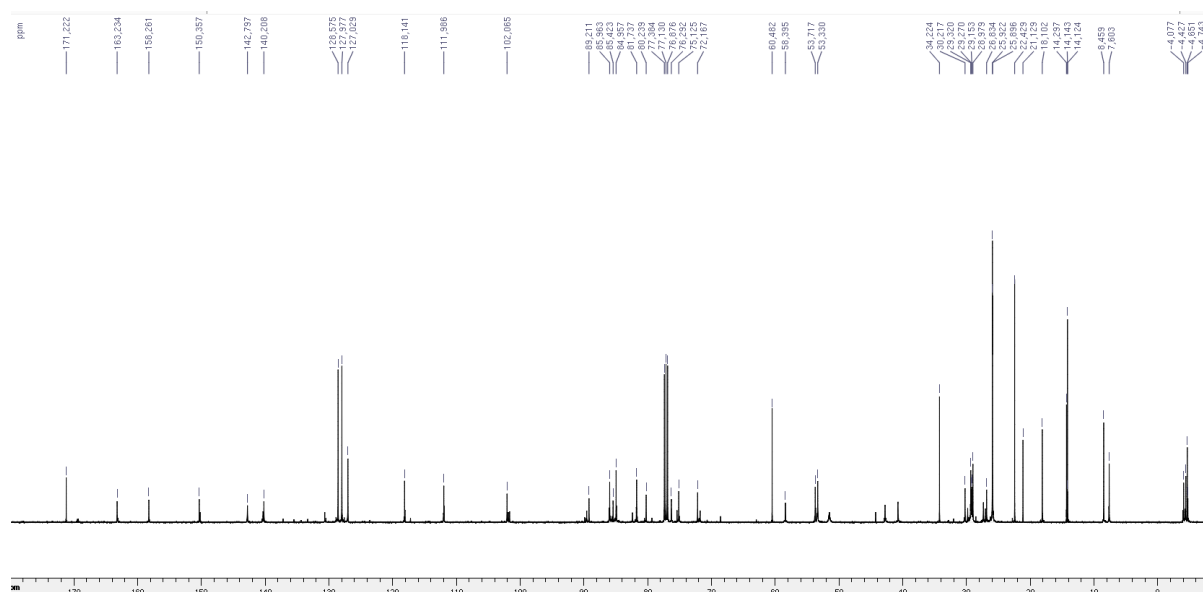
¹H NMR, 500 MHz (CDCl₃)



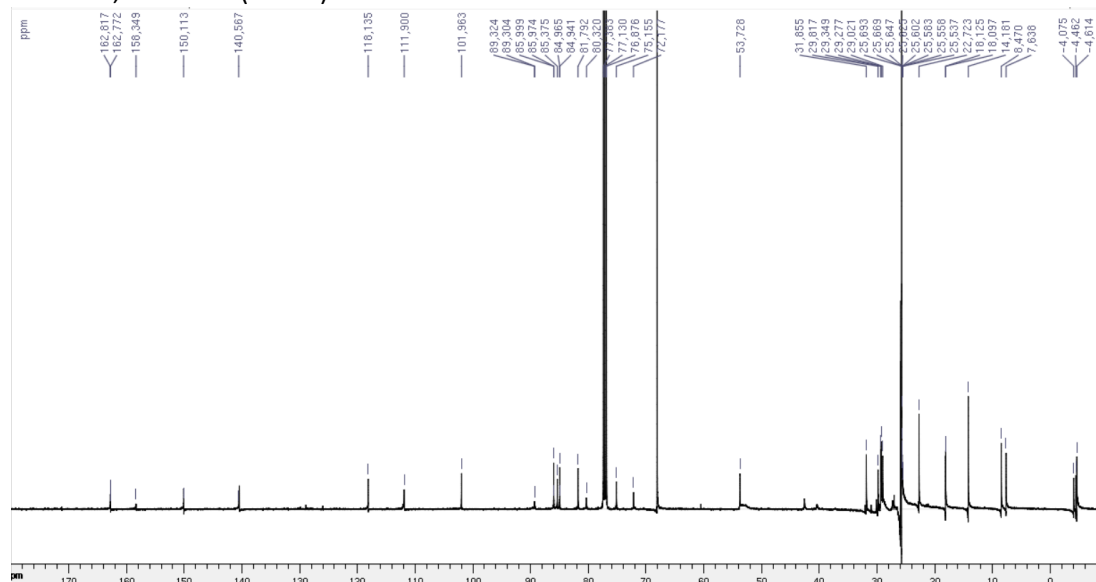
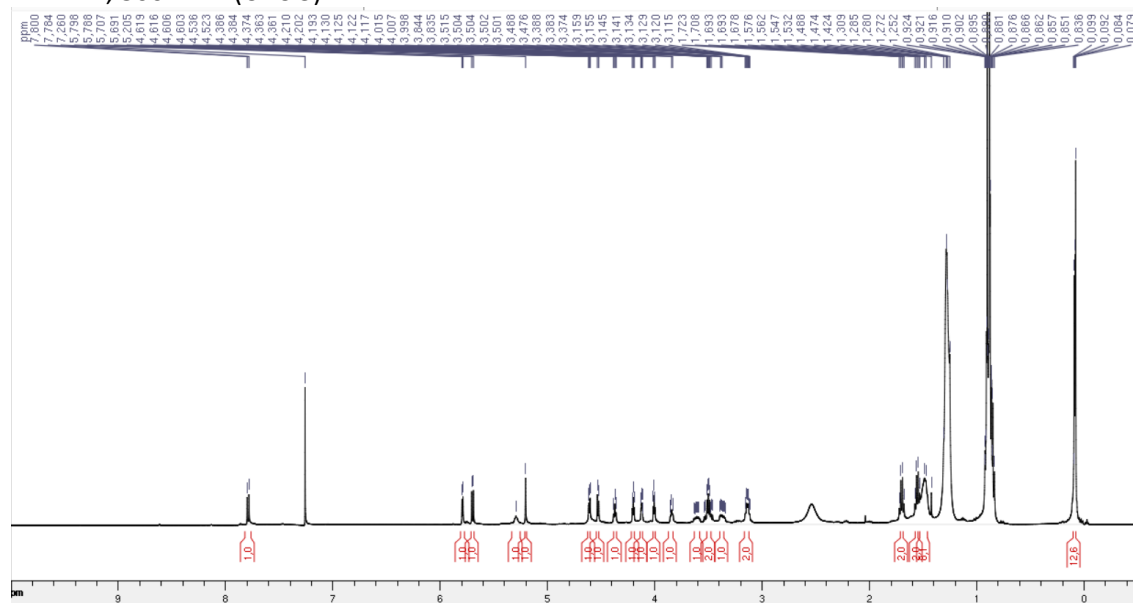
¹³C NMR, 125 MHz (CDCl₃)



Compound 23j

¹H NMR, 500 MHz (CDCl₃)¹³C NMR, 125 MHz (CDCl₃)

Chemical structure of compound **23k**, showing a complex molecule with a pyrimidine ring, a sugar moiety, and a long alkyl chain. The structure is labeled with 17 carbon atoms (1* to 17*) and 8 nitrogen atoms (8* to 17*). The pyrimidine ring is substituted with a TBSO group at position 2 and a TBSO group at position 4. The sugar moiety is a pyranose ring with a TBSO group at position 2' and a TBSO group at position 4'. The long alkyl chain is attached to the nitrogen at position 10*.



¹H NMR spectrum (CDCl₃) of compound 10. The spectrum displays several peaks with corresponding chemical shifts (ppm) and integration values (H).

Chemical Shift (ppm)	Integration (H)
7.864, 7.848	1.0
5.822, 5.817, 5.715, 5.699, 5.113, 4.144, 4.135, 4.130, 4.125, 4.111, 4.101, 4.053, 4.055, 4.065, 4.042, 4.034, 4.019, 3.974, 3.965, 3.914, 3.905, 3.895, 3.560, 3.551, 3.532, 3.522, 3.382, 3.367, 3.345, 3.330, 3.268, 3.266, 3.241, 3.124, 3.110, 3.096, 3.044, 3.024, 3.019, 2.559	10.0
2.5	2.1
1.293	14.4
0.912, 0.898, 0.865	3.2

Chemical structure of compound **24b**, showing a pyrazole ring system linked to a sugar moiety and a long alkyl chain. The structure is labeled with carbon numbers 1 through 13, indicating the positions of various atoms and functional groups.

[illegible]

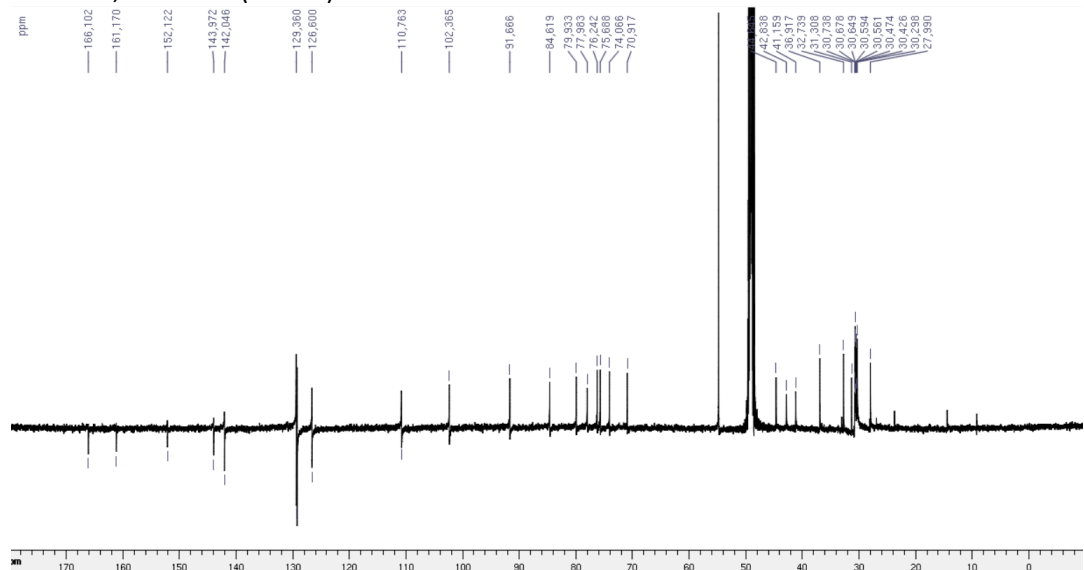
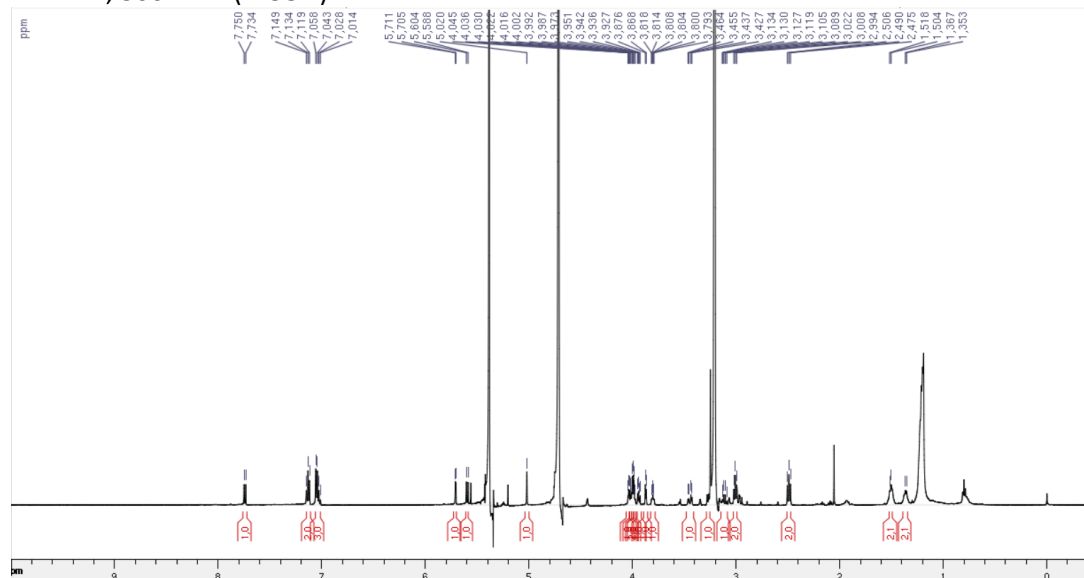
ppm

—166,116
—161,191
—152,143
—142,076
—110,779
—102,384
—91,620
—84,643
—79,968
—78,024
—76,244
—75,679
—74,047
—70,551
—44,650
—42,534
—41,166
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—39,520
—30,772
—30,744
—30,522
—30,457
—29,616
—23,713
—14,413

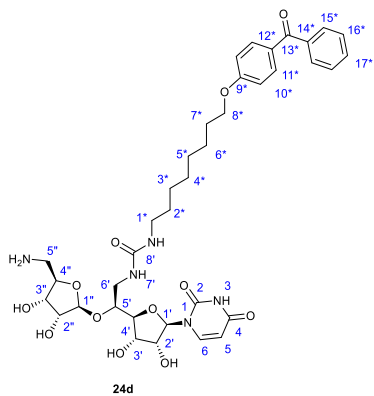
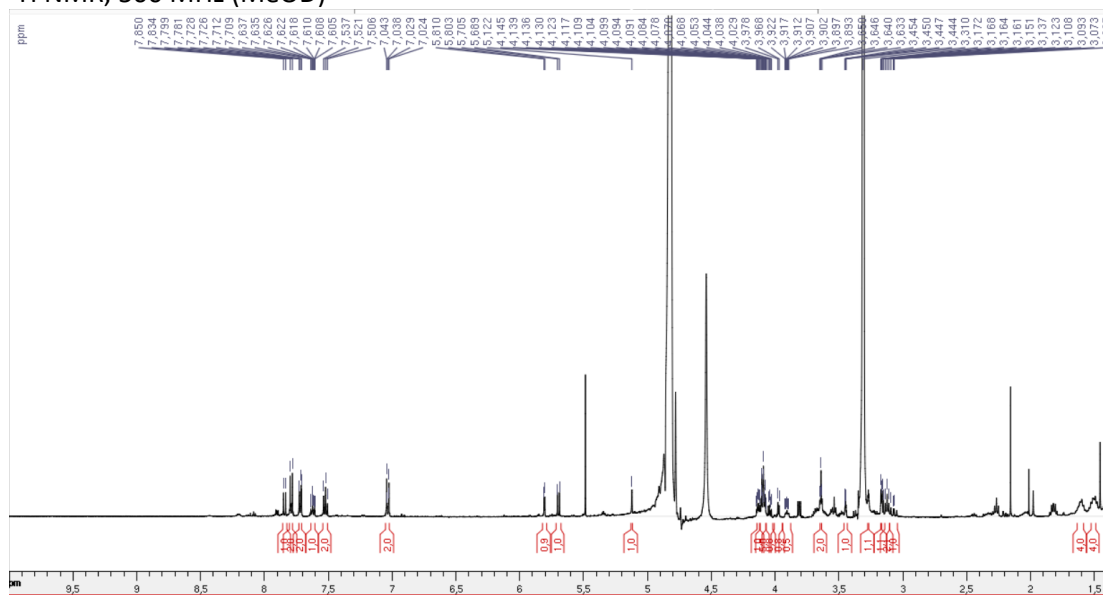
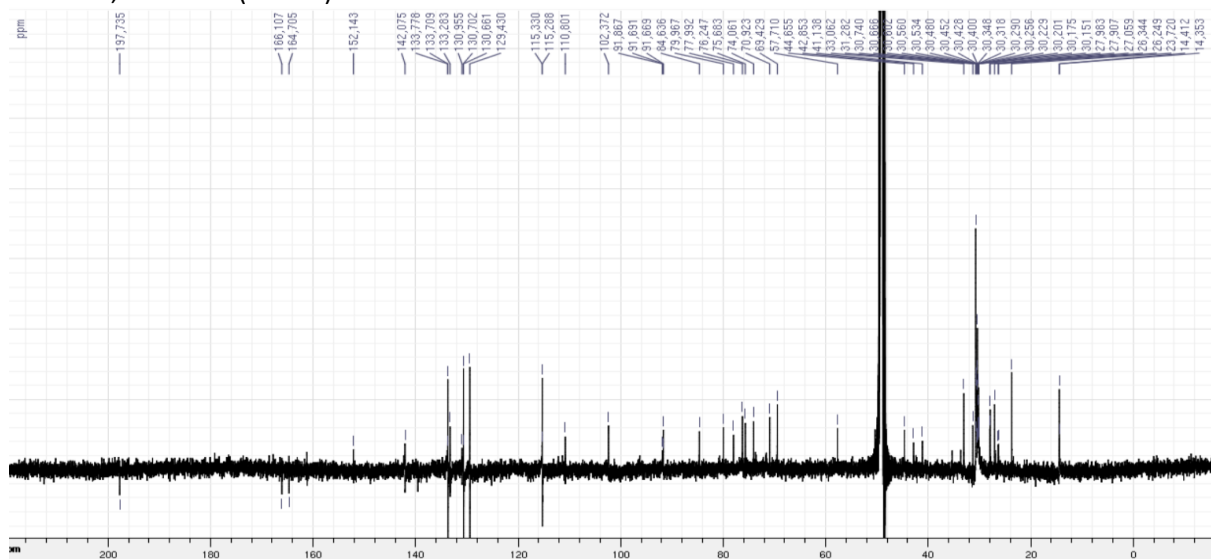
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

10

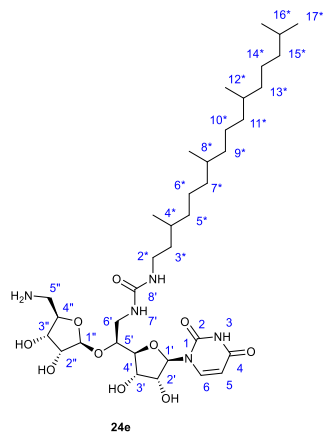
24c



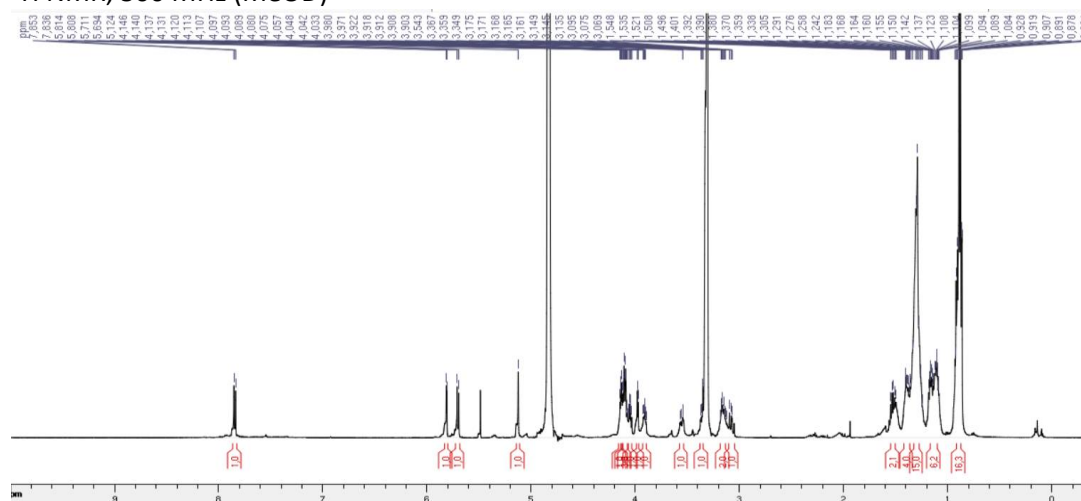
Compound 24d

¹H NMR, 500 MHz (MeOD)¹³C NMR, 125 MHz (MeOD)

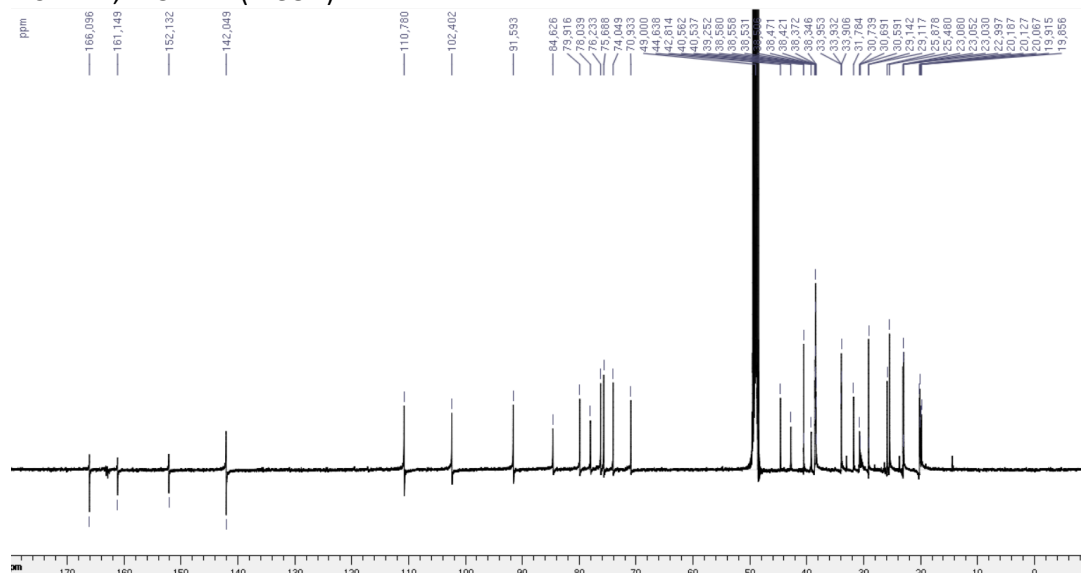
Compound 24e

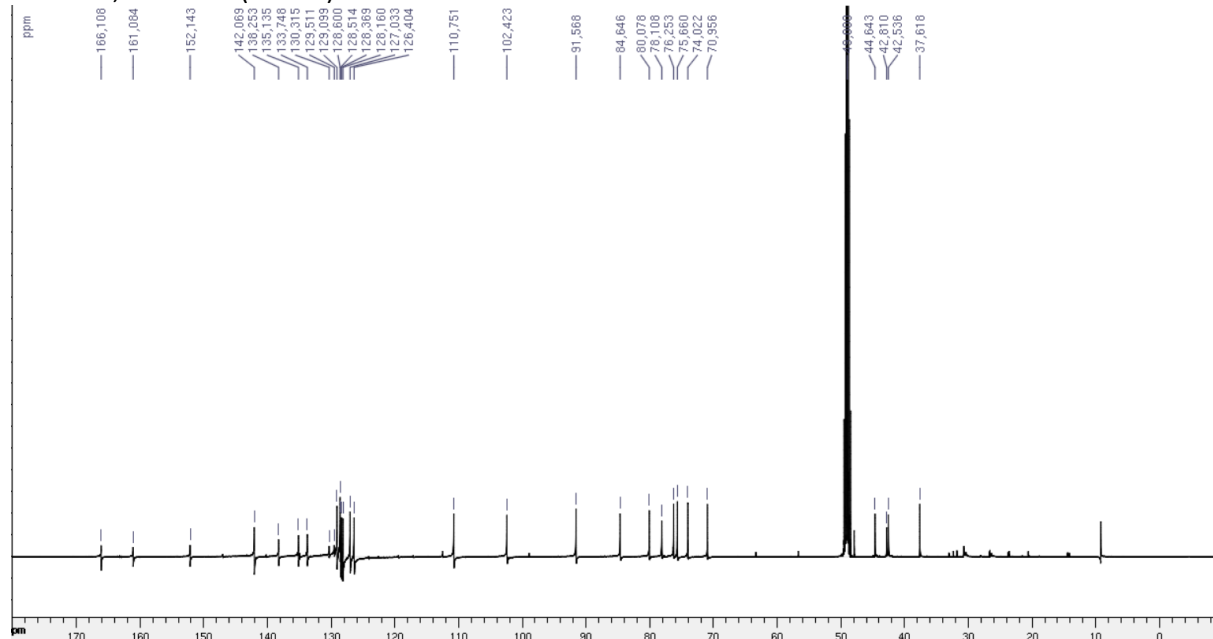
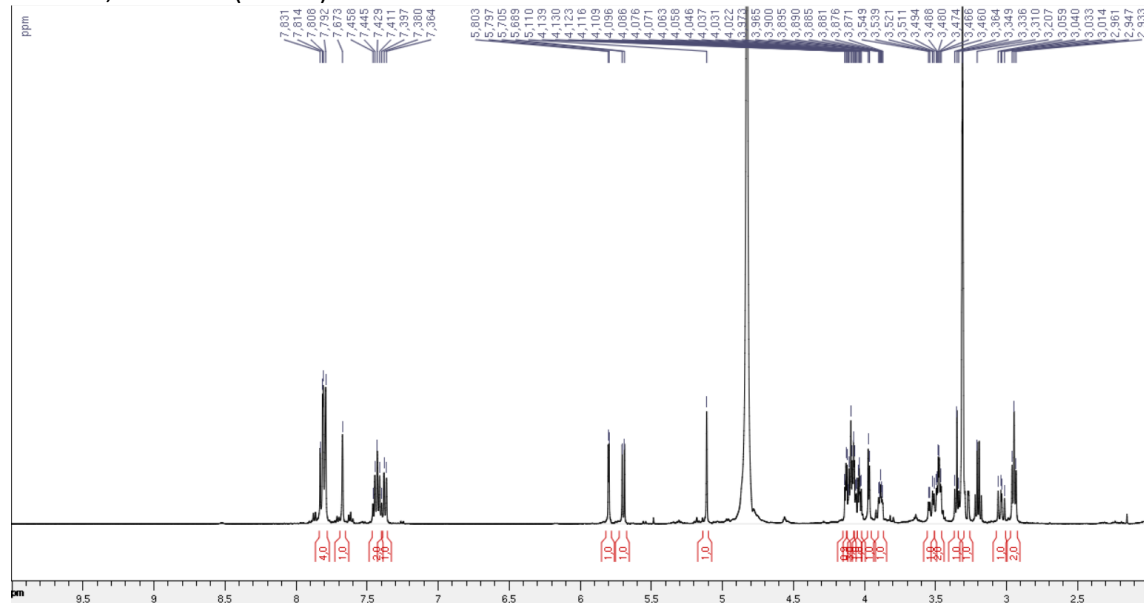


¹H NMR, 500 MHz (MeOD)

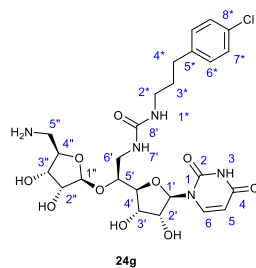


¹³C NMR, 125 MHz (MeOD)

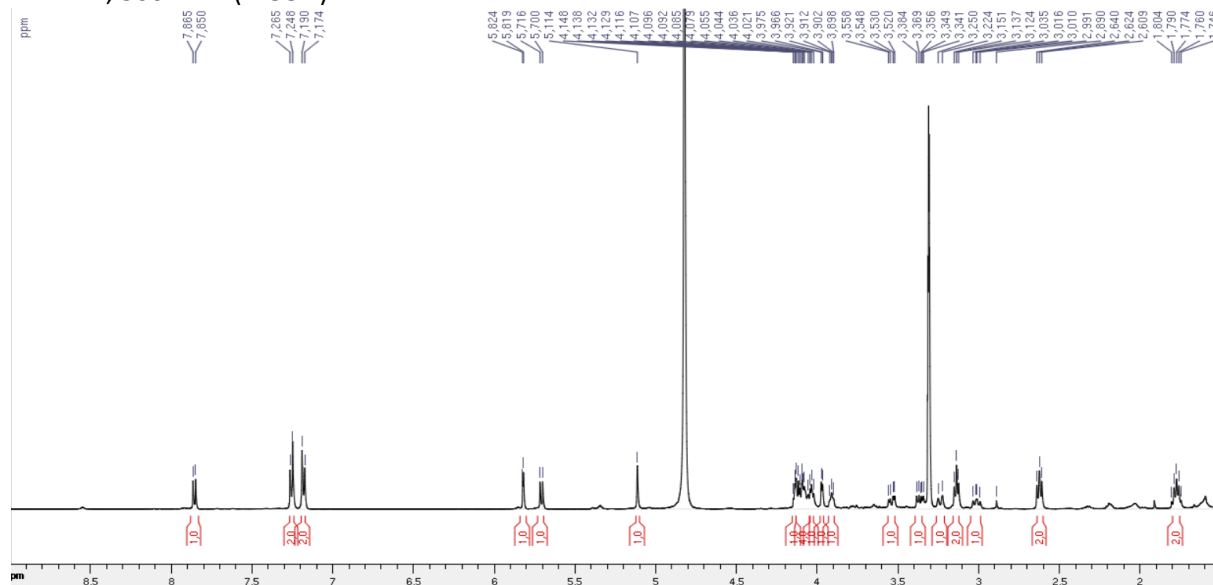




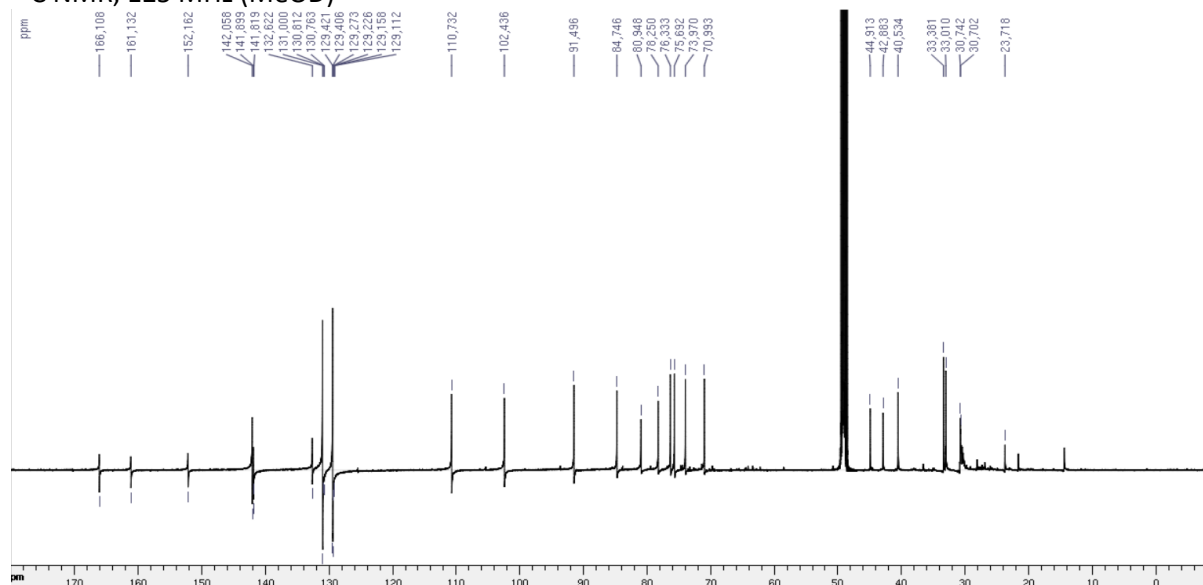
Compound 24g



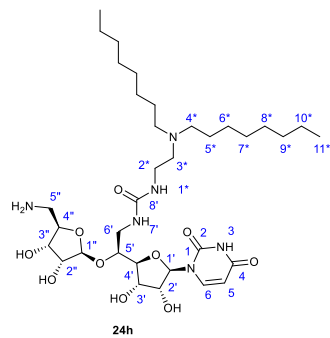
¹H NMR, 500 MHz (MeOD)



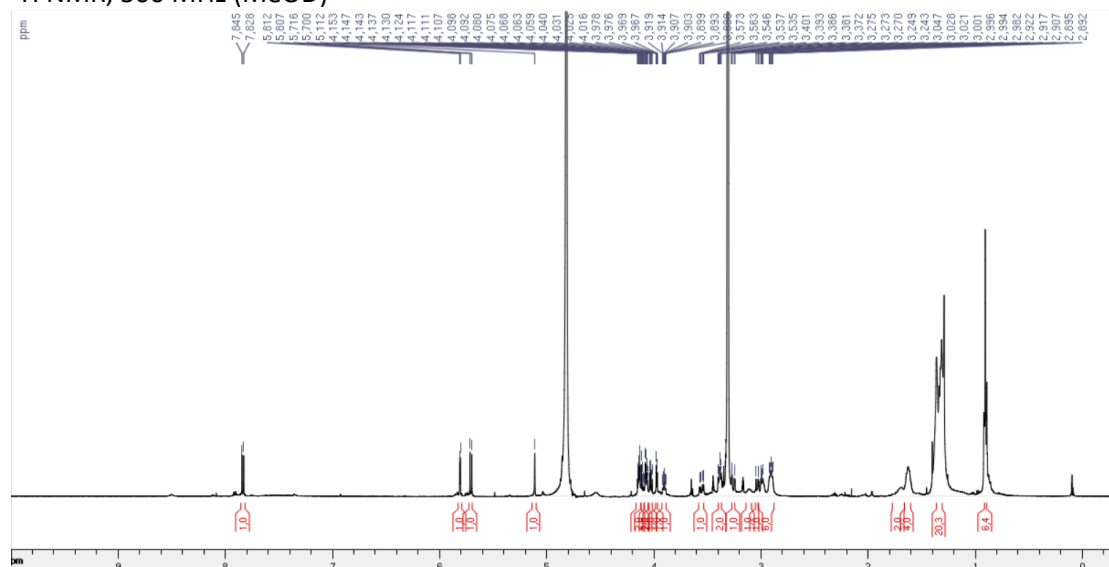
¹³C NMR, 125 MHz (MeOD)



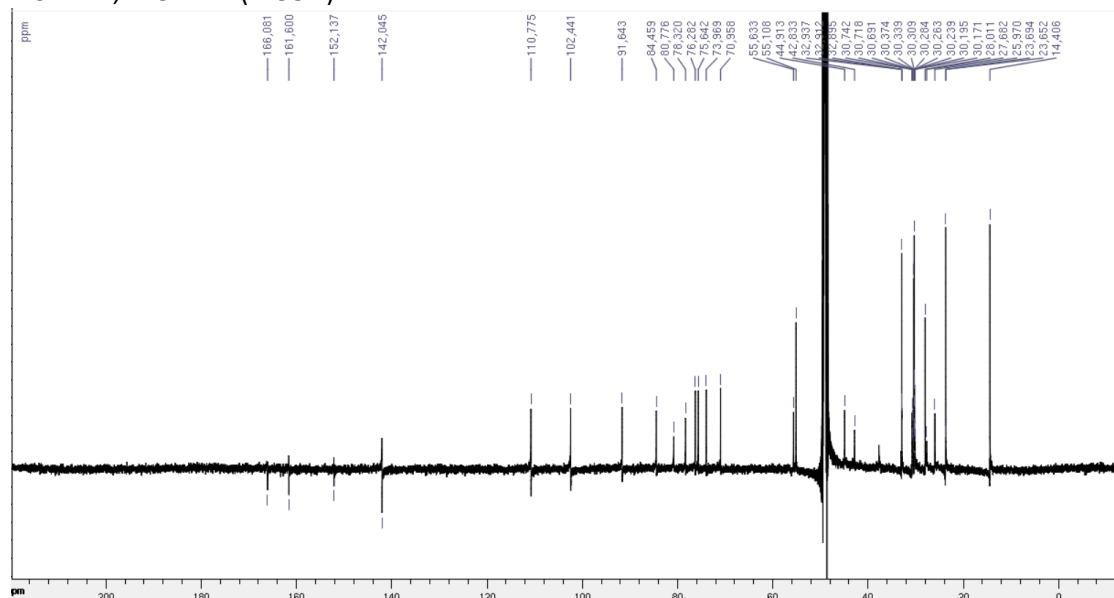
Compound 24h



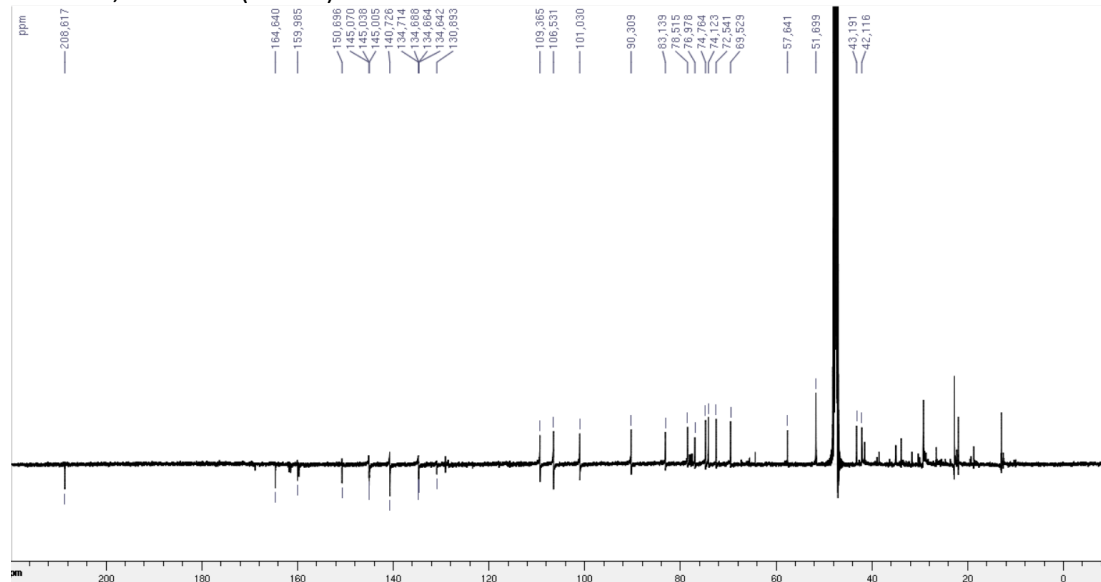
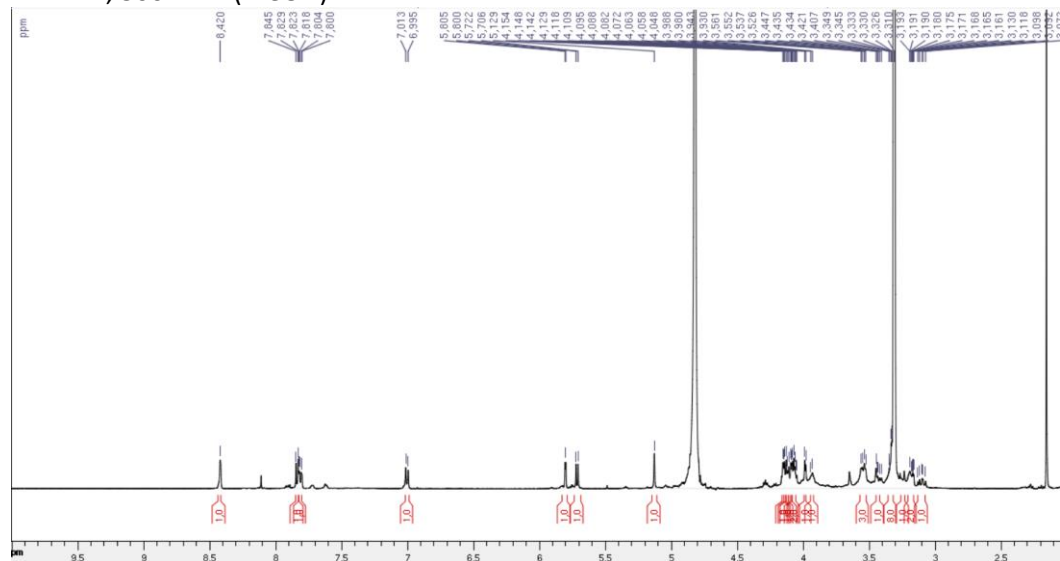
¹H NMR, 500 MHz (MeOD)



¹³C NMR, 125 MHz (MeOD)



Chemical structure of compound **24i**, featuring a complex molecule with a 4-aminopyranose derivative linked to a 4-oxo-1,2,3,4-tetrahydropyridine derivative via a carbamate bridge. The pyranose ring is substituted with a trifluoromethylphenyl group and a 4-aminophenyl group. The pyridine ring is substituted with a trifluoromethyl group and a 4-aminophenyl group. The structure is labeled with ¹⁴C and ¹⁵N isotopes.



¹H NMR spectrum of compound 10 in CDCl₃. The spectrum shows peaks from 0 to 8 ppm. Key features include a triplet at ~0.9 ppm (3H), a multiplet at ~1.5 ppm (2H), a multiplet at ~2.5 ppm (2H), a multiplet at ~3.5 ppm (2H), a multiplet at ~4.0 ppm (2H), a multiplet at ~4.5 ppm (2H), a multiplet at ~5.5 ppm (2H), a multiplet at ~6.5 ppm (2H), and a multiplet at ~7.5 ppm (2H). Integration values are shown below the peaks.

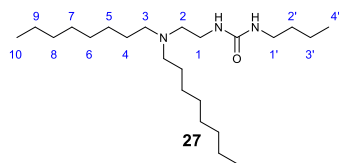
Chemical shifts (ppm) for compound 10:

- 166.086
- 161.193
- 152.151
- 142.831
- 142.074
- 139.810
- 138.871
- 138.541
- 128.463
- 128.425
- 110.834
- 110.803
- 102.452
- 91.555
- 84.787
- 79.866
- 78.103
- 76.398
- 74.870
- 75.647
- 74.008
- 70.982
- 58.035
- 53.509
- 50.076
- 44.813
- 42.873
- 41.659
- 31.230
- 30.739
- 30.696
- 30.584
- 30.449
- 30.180
- 30.153
- 30.123
- 30.054
- 30.027
- 30.004
- 27.796
- 27.592
- 25.169
- 25.114
- 23.716

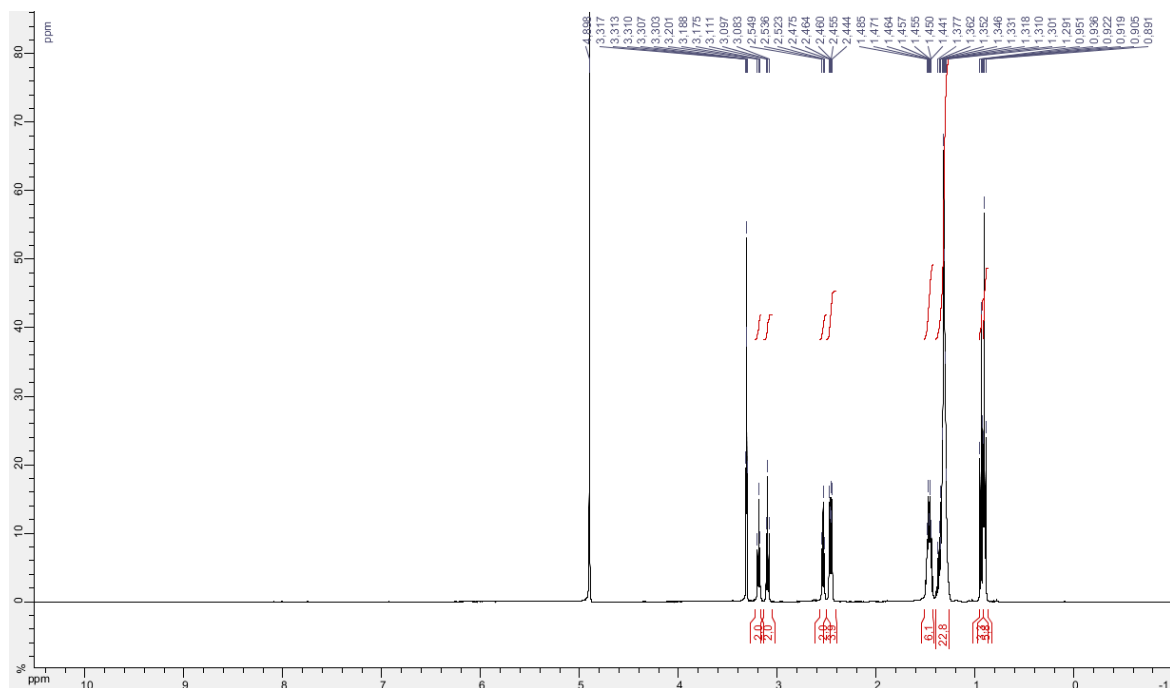
24k

166.073
161.185
152.140
142.045
110.802
102.421
91.561
84.730
79.935
78.071
76.241
75.800
74.622
70.350
54.321
54.271
54.246
44.612
42.863
41.110
32.866
31.288
30.747
30.225
30.173
30.157
27.879
27.608
24.952
24.887
23.886
14.580

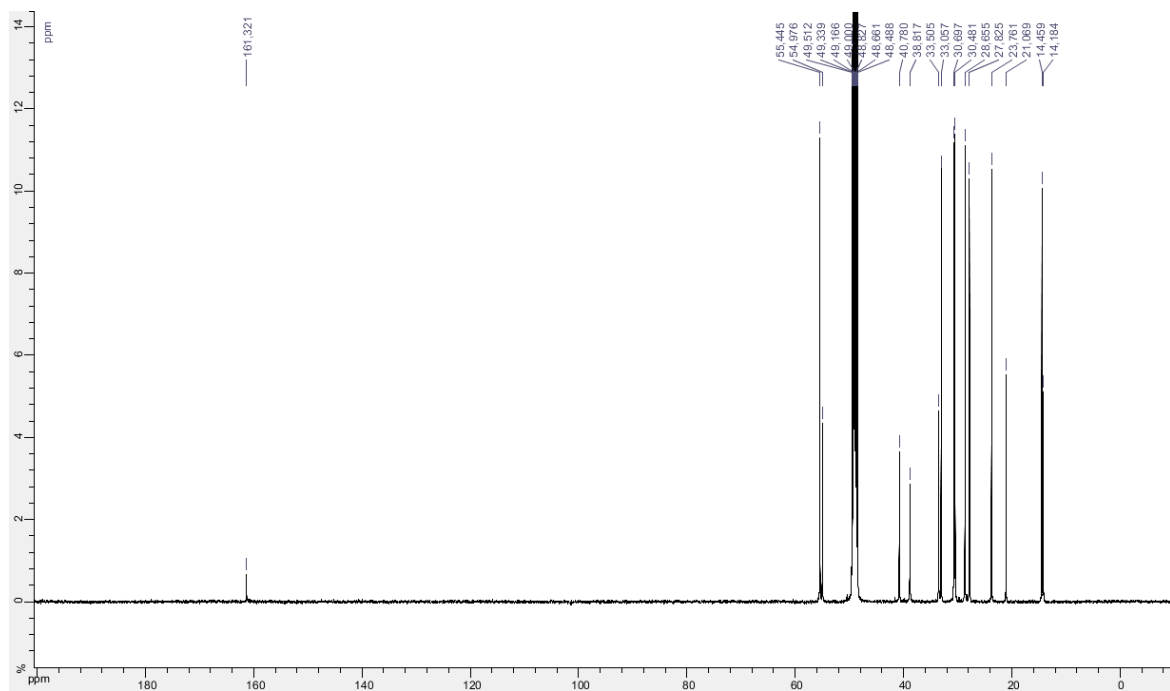
1-butyl-3-(2-(dioctylamino)ethyl)urea 27



¹H NMR, 500 MHz (MeOD)



¹³C NMR, 500 MHz (MeOD)



¹H Spectra of compound 7

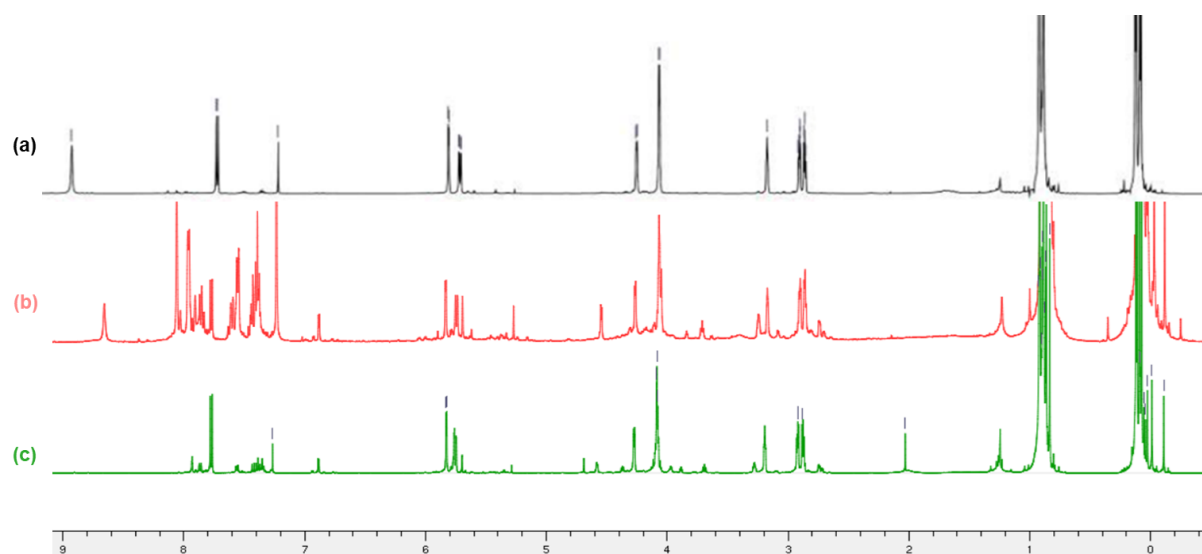


Fig. 2S Comparison of the ¹H NMR spectra of the crude compound **7** according to the experimental conditions: (a) compound **6** (10 g), *m*CPBA, 4 equiv., CH₂Cl₂/Phosphate buffer pH7 : 2/1, 30 °C, 16 h; (b) compound **6** (10 g), *m*CPBA, 4 equiv., CH₂Cl₂, 30 °C, 16 h; (c) compound **6** (1 g), *m*CPBA, 4 equiv., CH₂Cl₂, 30 °C, 16 h