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. ^{1}H and ^{13}C NMR spectra* of all new compounds.

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

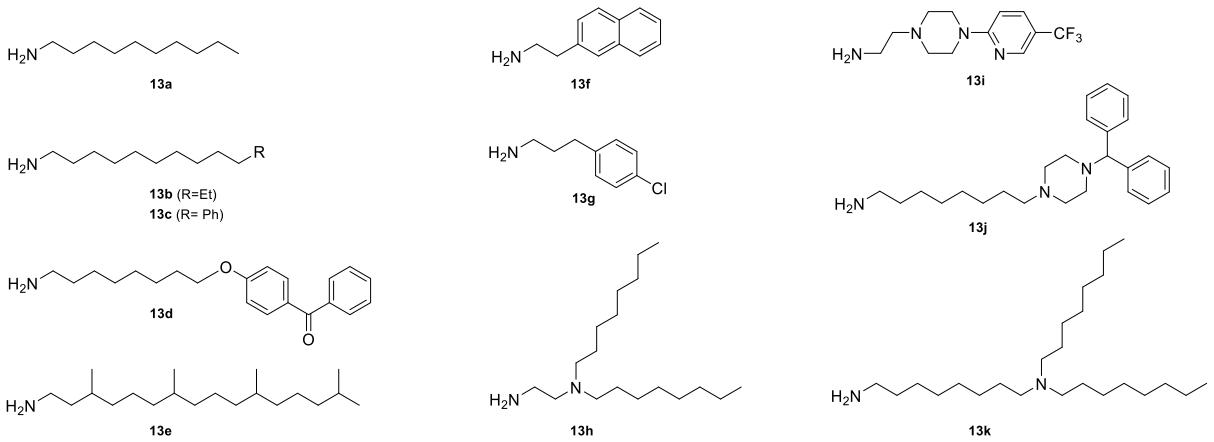


Fig. 1S Structure of the selected primary amines **13a-k**.

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; ^{1}H NMR δ 7.26 – 7.01 (m, 5 H, $H_{12}H_{13}H_{14}$), 2.64 (t, $J_{H1\text{-}H2}$ = 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, H_3-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 $C_{16}H_{27}N_1$ $(M + H)^+$ 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): Rf 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, JH2-H3 = 8.8 Hz, 2 H, H2), 7.78 – 7.72 (m, 2 H, H7), 7.56 (t, JH9-H8 = 7.4 Hz, 1H, H9), 7.47 (t, JH8-H9 = JH8-H7 = 7.4 Hz, 2 H, H8), 6.95 (d, JH3-H2 = 8.8 Hz, 2 H, H3), 4.04 (t, JH1'-H2' = 6.5 Hz, 2 H, H1'), 2.68 (t, JH8'-H7' = 7.0 Hz, 2 H, H8'), 1.86 – 1.78 (m, 2 H, H2'), 1.50 – 1.42 (m, 4 H, H7' H3'), 1.38-1.32 (m, 6 H, H6' H5' H4'); 13C NMR δ 195.7 (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), 68.4 (C1'), 42.3 (C8'), 33.8 (C7'), 29.5 (C4'), 29.4 (C6'), 29.2 (C2'), 26.9 (C5'), 26.1 (C3'); HRMS APCI+ calcd for C21H28NO2 (M + 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; ^{1}H 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 $C_{20}H_{44}N_1$ $(M + H)^+$ 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 °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; ^{1}H NMR δ 3.11 (bs, 1 H, NH_2), 2.75 (t, $J_{H1\text{-}H2}$ = 5.5 Hz, 2 H, H_1), 2.48 (t, $J_{H2\text{-}H1}$ = 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, $J_{H10\text{-}H9}$ = 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 $C_{18}H_{41}N_2$ $(M + H)^+$ 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 °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; ^{1}H NMR δ 8.41 – 8.37 (m, 1 H, H_5), 7.62 (d, $J_{H3\text{-}H2}$ = 9.0 Hz, 1 H, H_3), 6.63 (d, $J_{H2\text{-}H3}$ = 9.0 Hz, 1 H, H_2), 3.68 – 3.63 (m, 4 H, H_7), 2.84 (t, $J_{H7\text{-}H6}$ = 6.1 Hz, 2 H, H_9), 2.60 – 2.53 (m, 4 H, H_6), 2.48 (t, $J_{H8\text{-}H9}$ = 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 $C_{12}H_{18}F_3N_4$ $(M + H)^+$ 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; ^{1}H NMR δ 7.34 (d, $J_{H7\text{-}H8}$ = 8.5, 4H, H_7), 7.18 (dd, $J_{H8\text{-}H9}$ = 8.5, $J_{H8\text{-}H7}$ = 7.5 Hz, 4H, H_8), 7.09 (t, $J_{H9\text{-}H8}$ = 7.5 Hz, 2 H, H_9), 4.14 (s, 1 H, H_5), 2.62 (dd, $J_{H8'a\text{-}H8'b}$ = 13.7, $J_{H8'\text{-}H7'}$ = 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 (C_3 = 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 $C_{25}H_{38}N_3$ $(M + H)^+$ 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; ^{1}H NMR δ 3.90 (bs, 2 H, NH_2) 2.70 (t, $J_{H1\text{-}H2}$ = 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, $J_{H16\text{-}H15}$ = 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 $C_{24}H_{53}N_2$ $(M + H)^+$ 369.4203, found 369.4209.

8-azidooctyl 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): Rf 0.25 (Cyclohexane/EtOAc 9/1); IR (film): 2930, 2857, 2096, 1715, 1612, 1466, 1353, 1255, 1260, 1174, 974, 940, 750; ^{1}H NMR δ 4.23 (t, $J_{H1\text{-}H2}$ = 6.6 Hz, 2 H, H_1), 3.26 (t, $J_{H8\text{-}H7}$ = 6.9 Hz, 2 H, H_8), 3.00 (s, 6 H, H_9), 1.82 – 1.69 (m, 2 H, H_2), 1.66 – 1.56 (m, 2 H, H_7), 1.45 – 1.20 (m, 8 H, $H_{6\text{-}5\text{-}4\text{-}3}$); ^{13}C NMR δ 70.1 ($C_1$), 52.0 ($C_8$), 37.5 ($C_9$), 29.2 ($C_7$), 29.0 ($C_5$), 29.0 ($C_4$), 28.9 ($C_2$), 26.7 ($C_6$), 25.4 ($C_3$); HRMS APCI$^+$ calcd for $C_9H_{20}O_3N_3$ $(M + H)^+$ 250.1220, found 250.1218.

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

To a solution of compound 16 (70 mg, 280 µmol) in dry CH_3CN (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): Rf 0.25 (Cyclohexane/EtOAc 7/3); IR (film): 3026, 2931, 2855, 2808, 2094, 1595, 1491, 1451, 1301, 1278, 1261, 1151, 1008, 757, 746, 700; ^{1}H NMR δ 7.33 (d, $J_{H7\text{-}H8}$ = 7.3 Hz, 4 H, H_7), 7.18 (t, $J_{H8\text{-}H7}$ = 7.6 Hz, 4 H, H_8), 7.09 (t, $J_{H9\text{-}H8}$ = 7.3 Hz, 2 H, H_9), 4.14 (s, 1 H, H_5), 3.16 (t, $J_{H8'\text{-}H7'}$ = 7.0 Hz, 2 H, $H_{8'}$), 2.38 (bs, 8 H, H_2, H_3), 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, $H_{3'}$-$H_{6'}$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.9 (C_6), 128.5 (C_8), 128.0 (C_7), 127.0 (C_9), 76.37 (C_5), 58.9 ($C_{1'}$), 53.6 (C_2), 52.0 (C_3), 51.6 ($C_{8'}$), 29.5, 29.1, 28.9, 27.6, 26.9 26.7 ($C_{2'}$-$C_{7'}$); HRMS APCI$^+$ calcd for $C_{25}H_{36}N_5$ $(M + H)^+$ 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.), K_2CO_3 (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): Rf 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; ^{1}H NMR δ 7.82 (d, $J_{H2\text{-}H3}$ = 8.8 Hz, 2 H, H_2), 7.79 – 7.74 (m, 2 H, H_7), 7.6 (t, $J_{H9\text{-}H8}$ = 7.4 Hz, 1 H, H_9), 7.47 (t, $J_{H8\text{-}H9}$ = $J_{H8\text{-}H7}$ = 7.6 Hz, 2 H, H_8), 6.95 (d, $J_{H3\text{-}H2}$ = 8.8 Hz, 2 H, H_3), 4.04 (t, $J_{H1'\text{-}H2'}$ = 6.5 Hz, 2 H, $H_{1'}$), 3.26 (t, $J_{H8'\text{-}H7'}$ = 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, $H_{5'}$, $H_{4'}$); ^{13}C NMR δ 195.6 (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), 68.3 ($C_{1'}$), 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 $C_{21}H_{25}N_3O_2$ $(M + H)^+$ 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 CH_3CN (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; ^{1}H NMR δ 3.25 (t, $J_{H8\text{-}H7}$ = 7.0 Hz, 2 H, H_8), 2.45 (s, 6 H, H_1, H_9), 1.68 – 1.55 (m, 2 H, H_7), 1.47 (s, 6 H, $H_{10,}$ H_2), 1.38 – 1.33 (m, 2 H, H_6) 1.37 – 1.20 (m, 26 H, H_3, H_4, H_5, H_{11} - H_{15}), 0.88 (t, $J_{H16\text{-}H15}$ = 6.9 Hz, 6 H, H_{16}); ^{13}C NMR δ 54.0 (C_1 = C_9), 51.6 (C_8), 32.0, 29.6, 29.5, 29.4, 29.2, 28.9 (C_7), 27.7 (C_2), 27,6 (C_{10}), 26.8 (C_6), 22.7, 14.2 (C_{16}); HRMS APCI$^+$ calcd for $C_{24}H_{51}N_4$ $(M + H)^+$ 395.4108, found 395.40986.

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

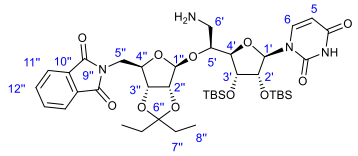
To a solution of 1-phthalimido-2-bromoethane (75 mg, 295 µmol, 1 equiv.) in dry CH_3CN (30 mL) were successively added K_2CO_3 (40 mg, 295 µmol, 1 equiv.) and dioctylamine (90 µL, 295 µmol, 1 equiv.) at 0 °C under argon. The reaction was stirred for 16 h at 90 °C and then concentrated *in vacuo*. The 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; ^{1}H NMR δ 7.86-7.81 (m, 2 H, H_{13}), 7.72-7.68 (m, 2 H, H_{14}), 3.75 (t, $J_{H10\text{-}H9}$ = 6.8 Hz, 2 H, H_{10}), 2.69 (t, $J_{H9\text{-}H10}$ = 6.8 Hz, 2 H, H_9), 2.50 – 2.36 (m, 4 H, H_8), 1.36 (dd, $J_{H7\text{-}H8}$ = $J_{H7\text{-}H6}$ = 7.4 Hz, 4 H, H_7), 1.30 – 1.21 (m, 4 H, H_6), 1.20 (bs, 8 H, $H_{2\text{-}5}$) 0.87 (t, $J_{H1\text{-}H2}$ = 7.1 Hz, 6H, H_1); ^{13}C NMR δ 168.5 (C_{11}), 133.9 (C_{14}), 132.4 (C_{12}), 123.2 (C_{13}), 54.4 (C_8), 51.6 (C_9), 36.4 (C_{10}), 31.9, 29.7, 29.5, 27.6, 27.4 (C_7), 22.8 (C_6), 14.2 (C_1); HRMS APCI$^+$ calcd for $C_{26}H_{43}N_2O_2$ $(M + H)^+$ 415.3319, found 415.3312.

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

To a solution of 1-phthalimido-2-bromoethane (70 mg, 275 µmol, 1 equiv.) in dry CH_3CN (27 mL) were successively added K_2CO_3 (38 mg, 275 µmol, 1 equiv.) and 1-[5-(trifluoromethyl)pyrid-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; ^{1}H NMR δ 8.37 (s, 1 H, H_5), 7.88 – 7.81 (m, 2 H, H_{12}), 7.76 – 7.70 (m, 2 H, H_{13}), 7.60 (d, $J_{H3\text{-}H2}$ = 9.0 Hz, 1 H, H_3), 6.60 (d, $J_{H2\text{-}H3}$ = 9.0 Hz, 1 H, H_2), 3.86 (t, $J_{H9\text{-}H8}$ = 5.9 Hz, 2 H, H_9), 3.57 (bs, 4 H, H_7), 2.69 (t, $J_{H8\text{-}H9}$ = 5.9 Hz, 2 H, H_8), 2.61 (bs, 4 H, H_6); ^{13}C NMR δ 208,1 (C_{10}), 168.5 (C_1), 145.9 (C_5), 134.5 (C_3), 134.4 (C_{11}), 134.0 (C_{13}), 132.3 (C_{12}), 123.4 (CF_3), 105.7 (C_2), 55.8 (C_6), 52.8 (C_8), 44.9 (C_7), 35.3 (C_9), 31.03; HRMS APCI$^+$ calcd for $C_{20}H_{20}F_3N_4O_2$ $(M + H)^+$ 405.1533, found 405.15234.

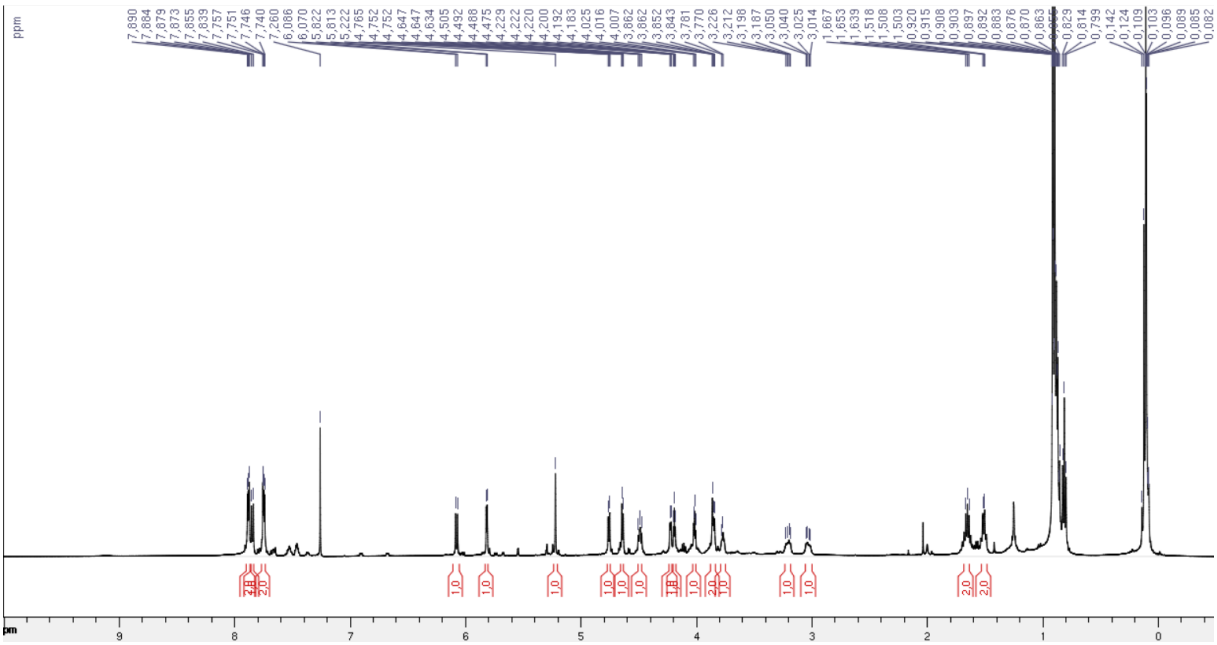
^{1}H and ^{13}C Spectra

Compound 2

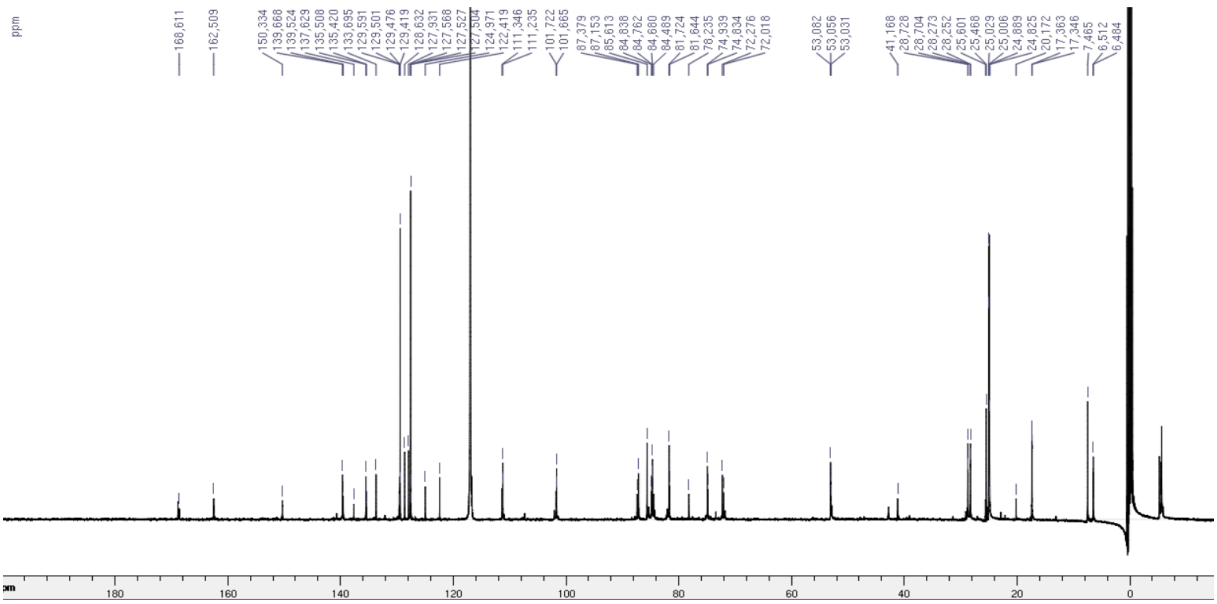


2

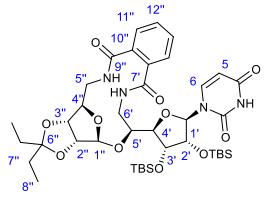
^{1}H NMR, 500 MHz ($CDCl_3$)



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

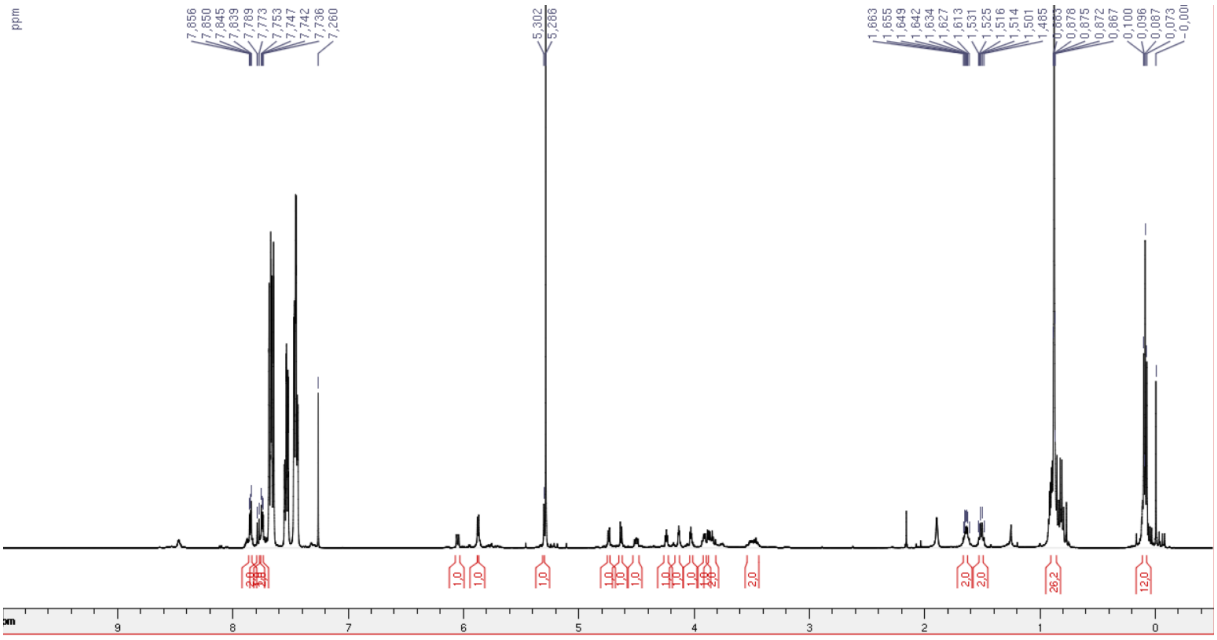


Side product 3

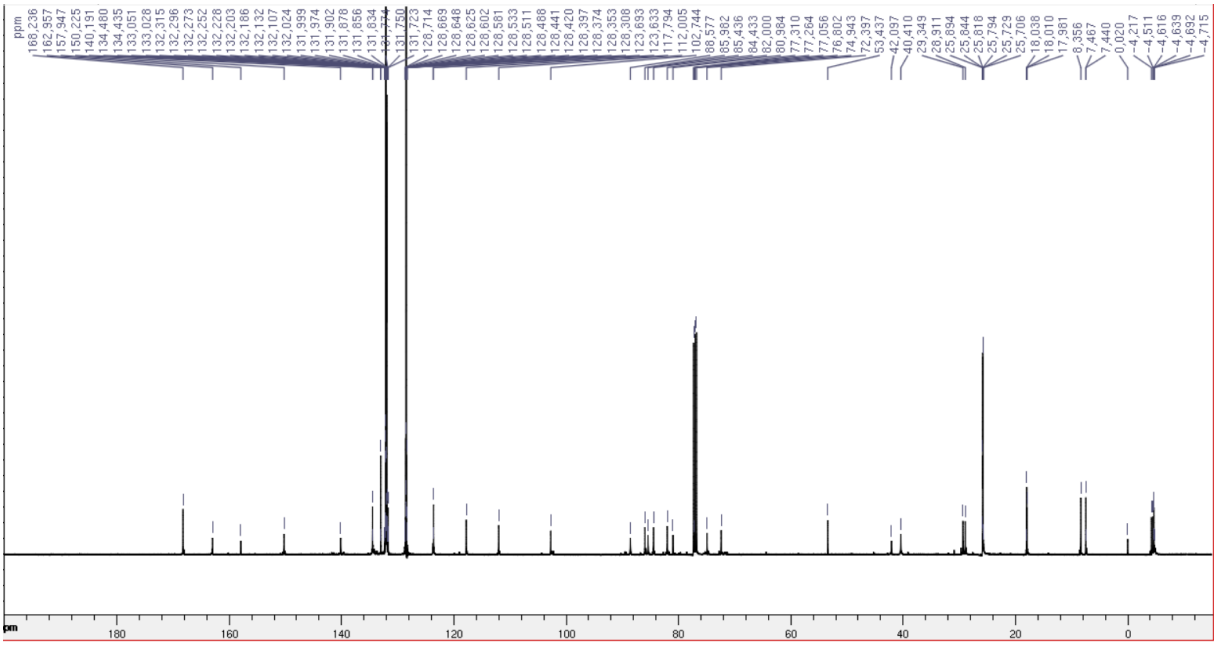


3

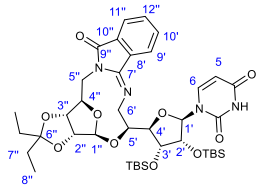
^{1}H NMR, 500 MHz ($CDCl_3$)



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

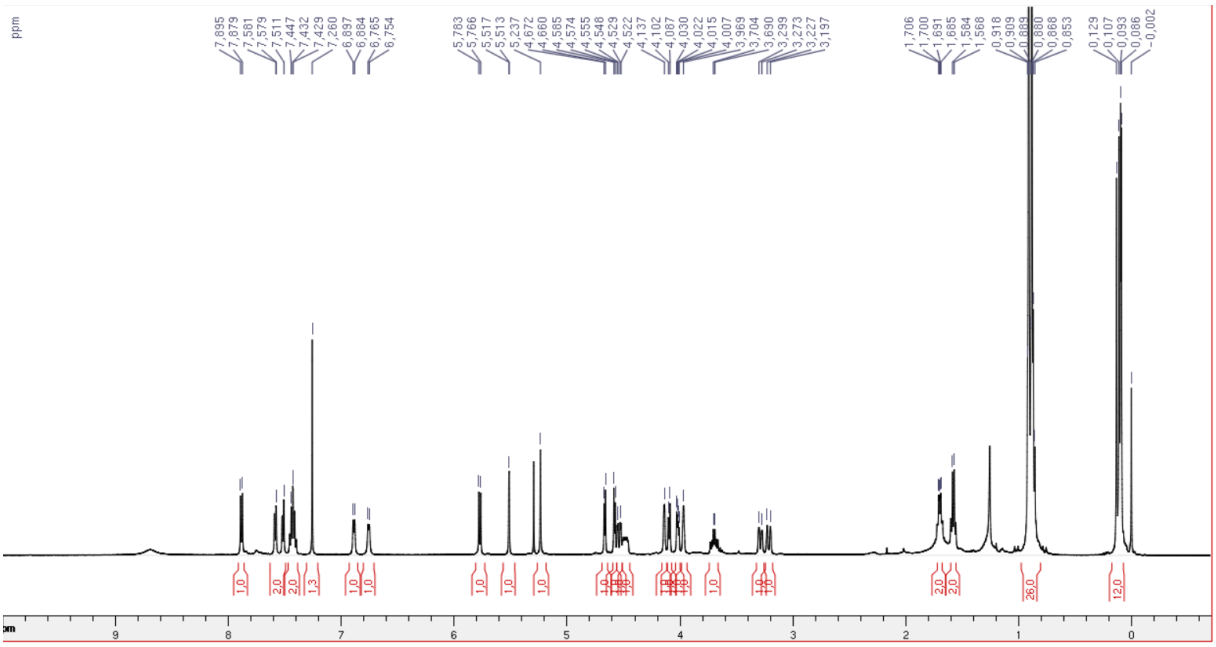


Side product 4

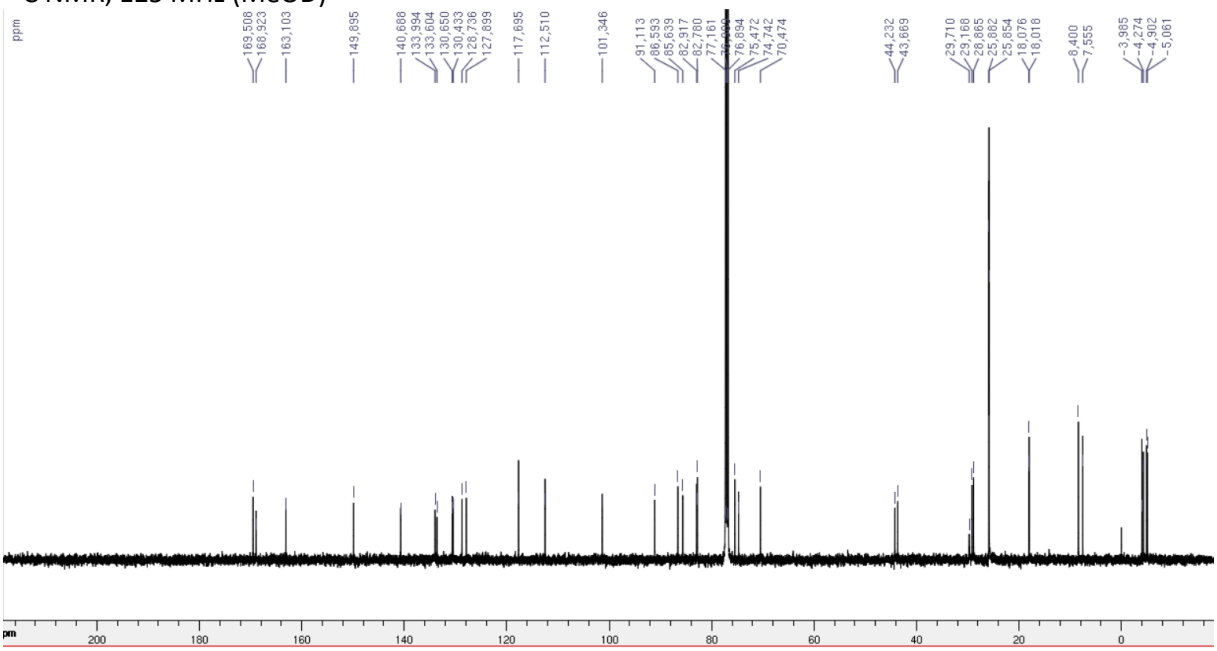


4

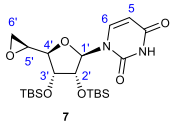
^{1}H NMR, 500 MHz ($CDCl_3$)



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

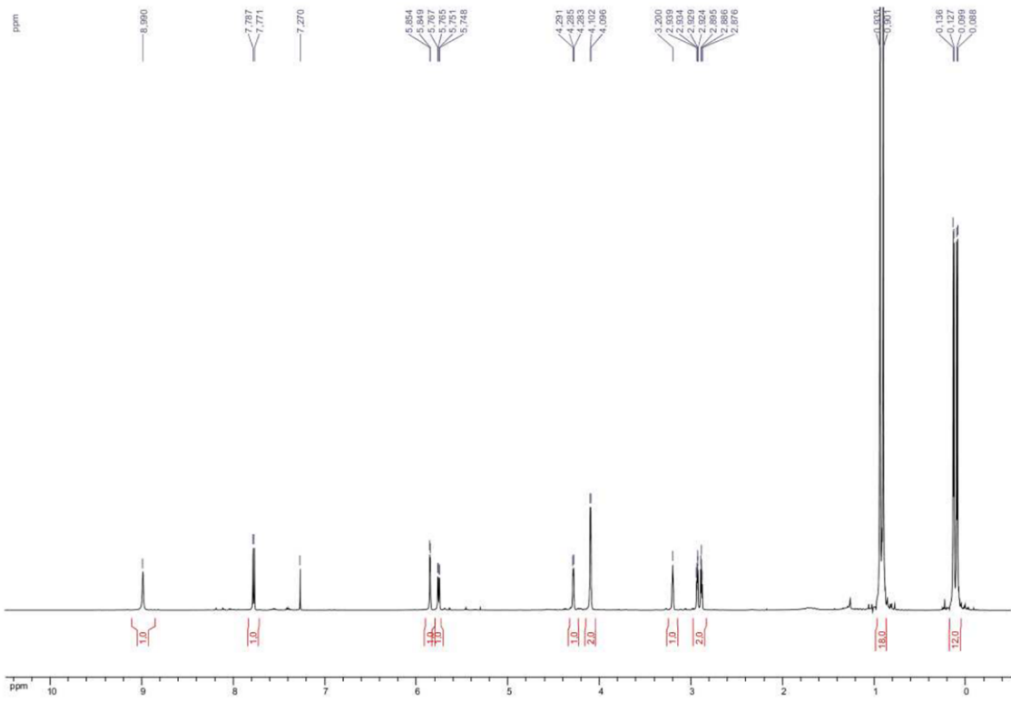


Compound 7

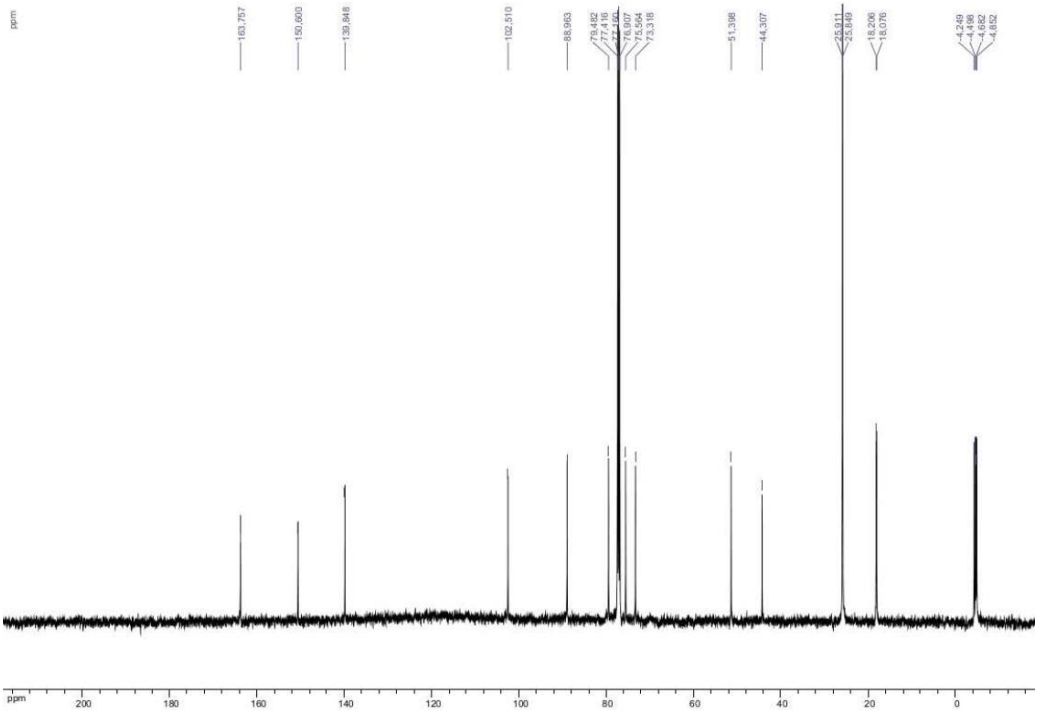


7

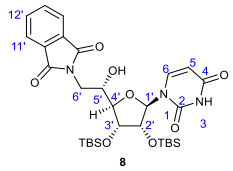
^{1}H NMR, 500 MHz ($CDCl_3$)



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

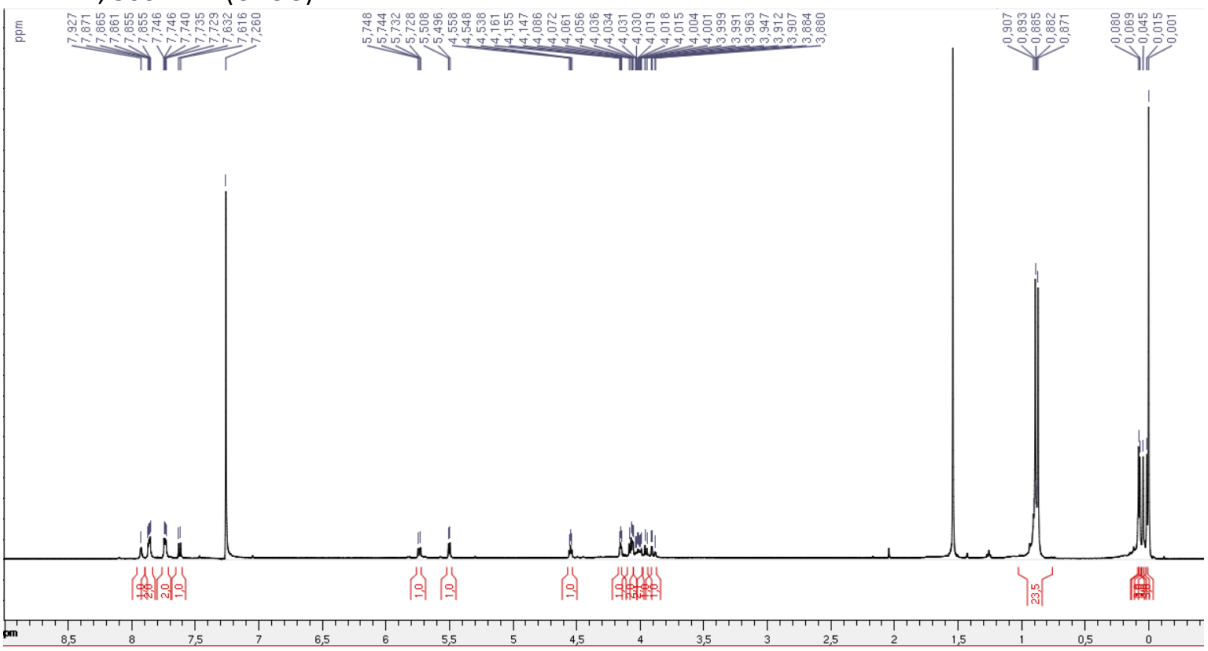


5’(S)-C-(Phthalimidomethyl)-2’,3’-di-O-(tert-butyldimethylsilyl)uridine 8

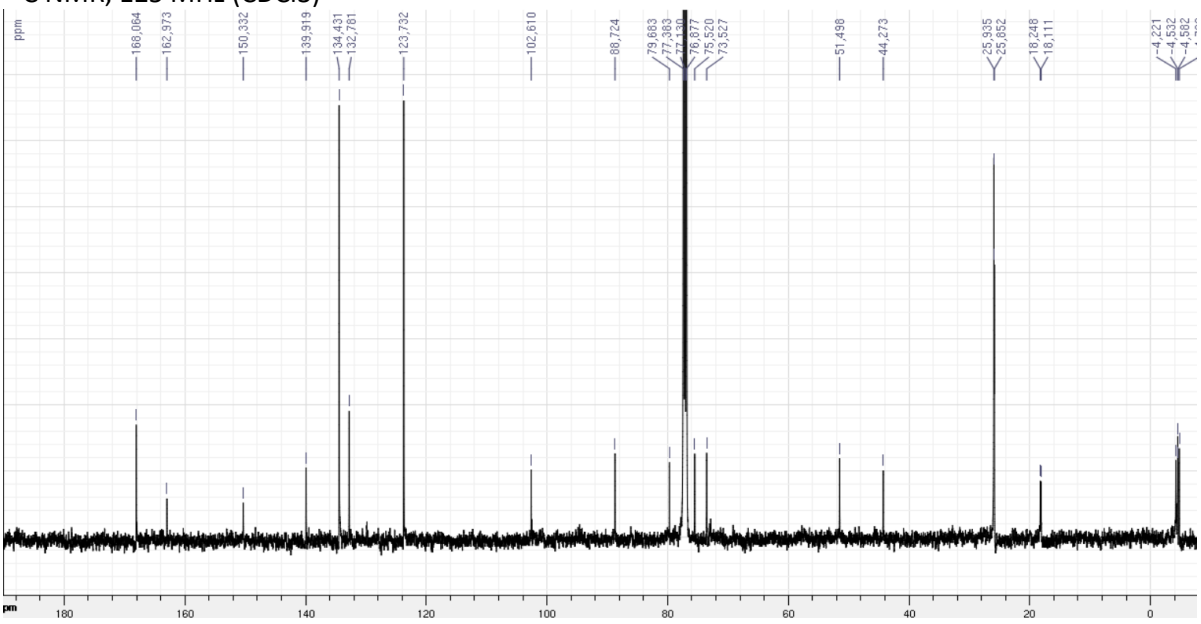


8

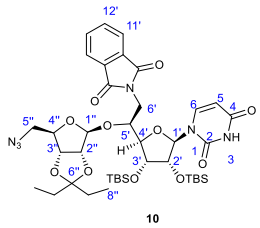
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

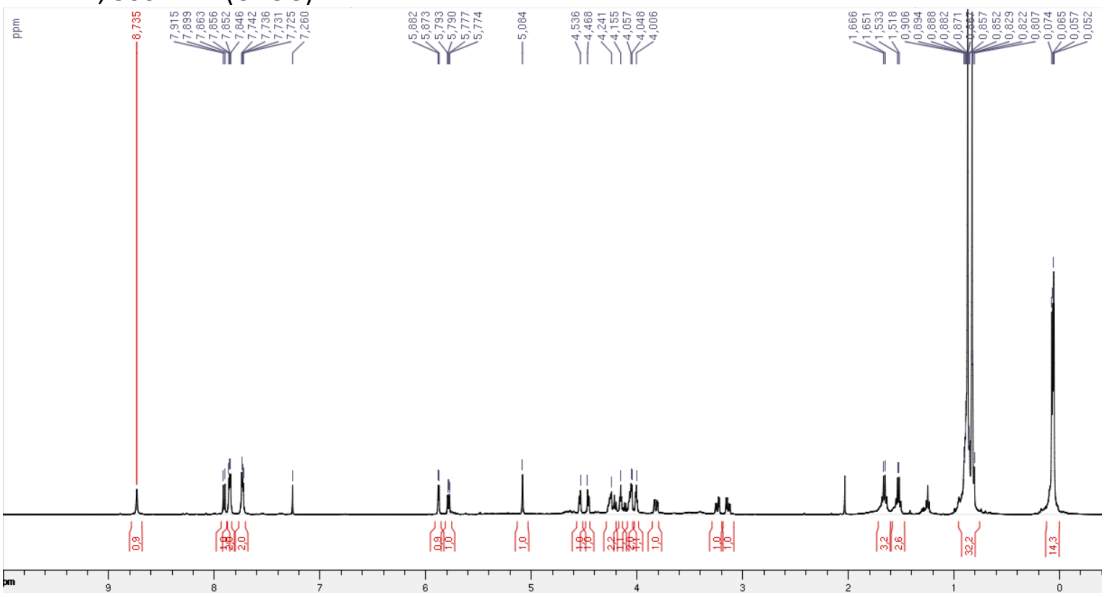


1’’,5’’-Dideoxy-2’’,3’’-O-isopentylidene-5’’-azido-1’’-[2’,3’-O-isopropylidene-5’(S)-phthalimidomethyl-uridinyl]-β-D-ribofuranose 10

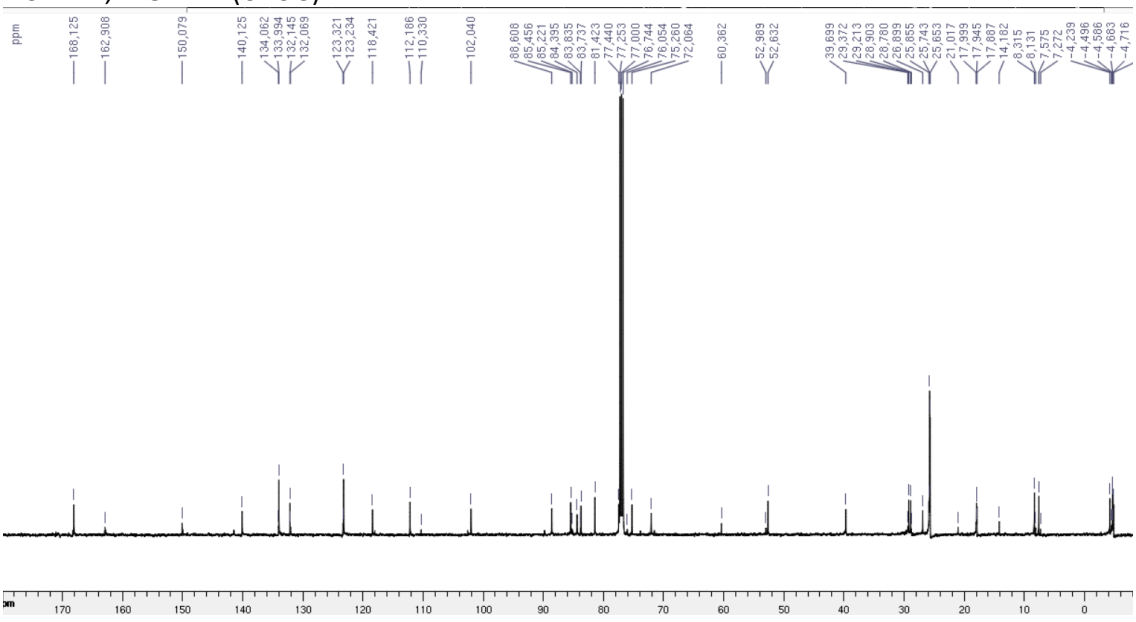


10

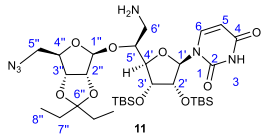
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

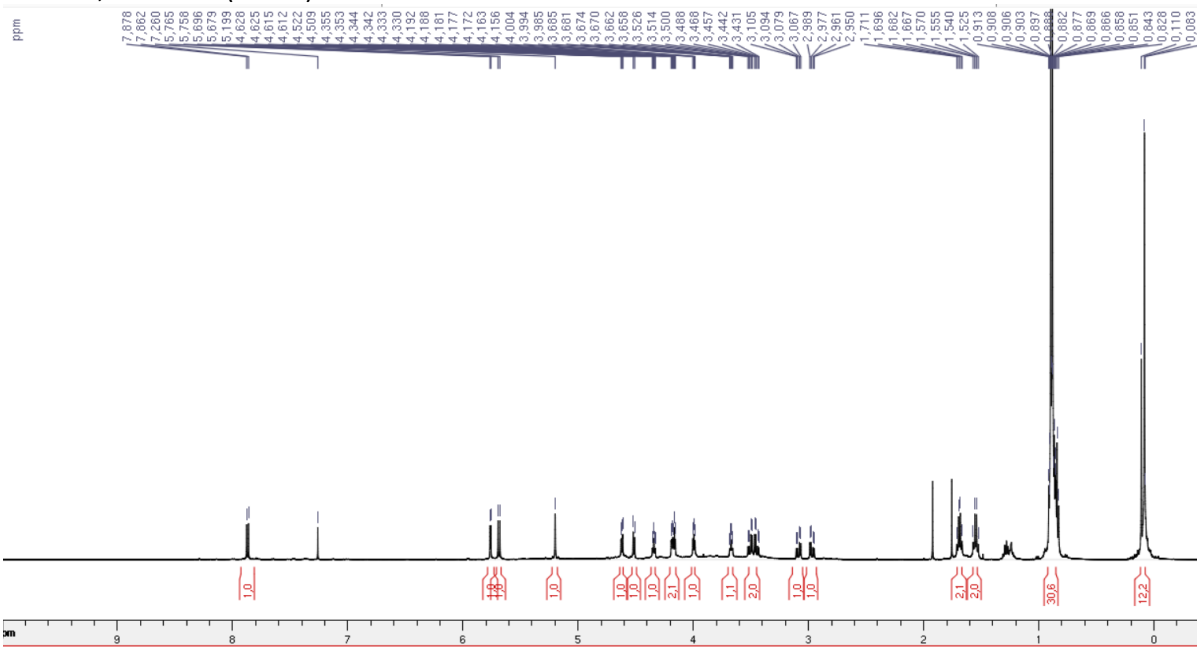


1’’,5’’-Dideoxy-2’’,3’’-O-isopentylidene-5’’-azido-1’’-[2’,3’-O-isopropylidene-5’(S)-aminomethyl-uridinyl]-β-D-ribofuranose 11

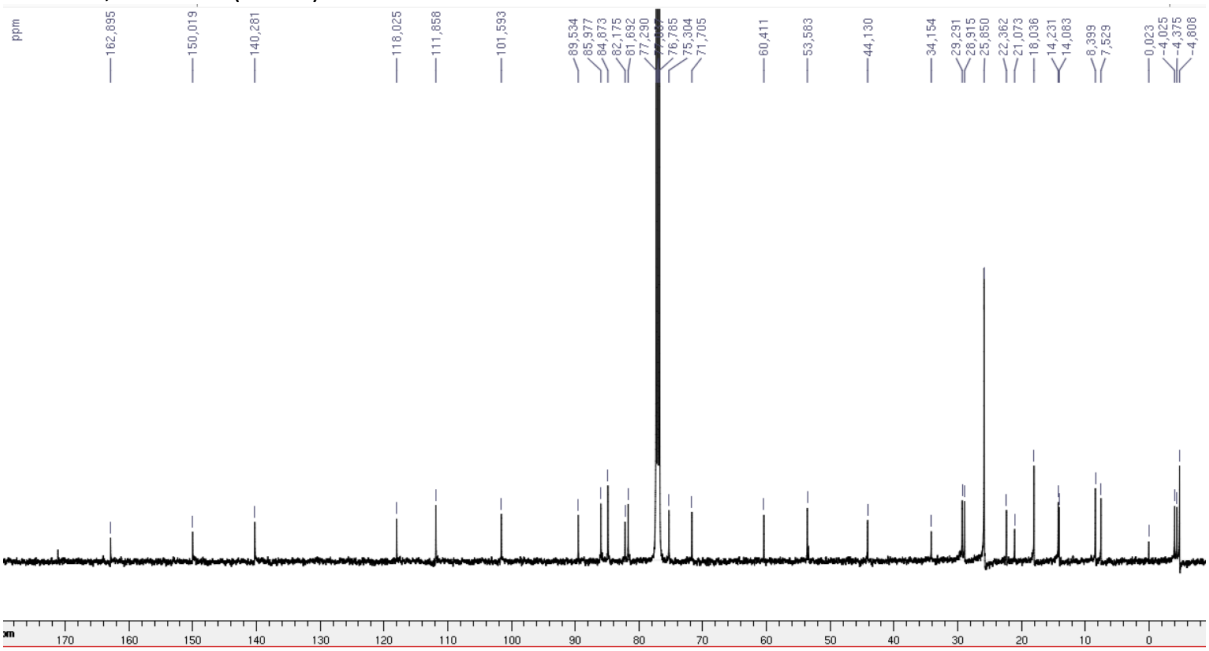


11

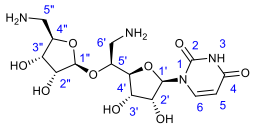
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

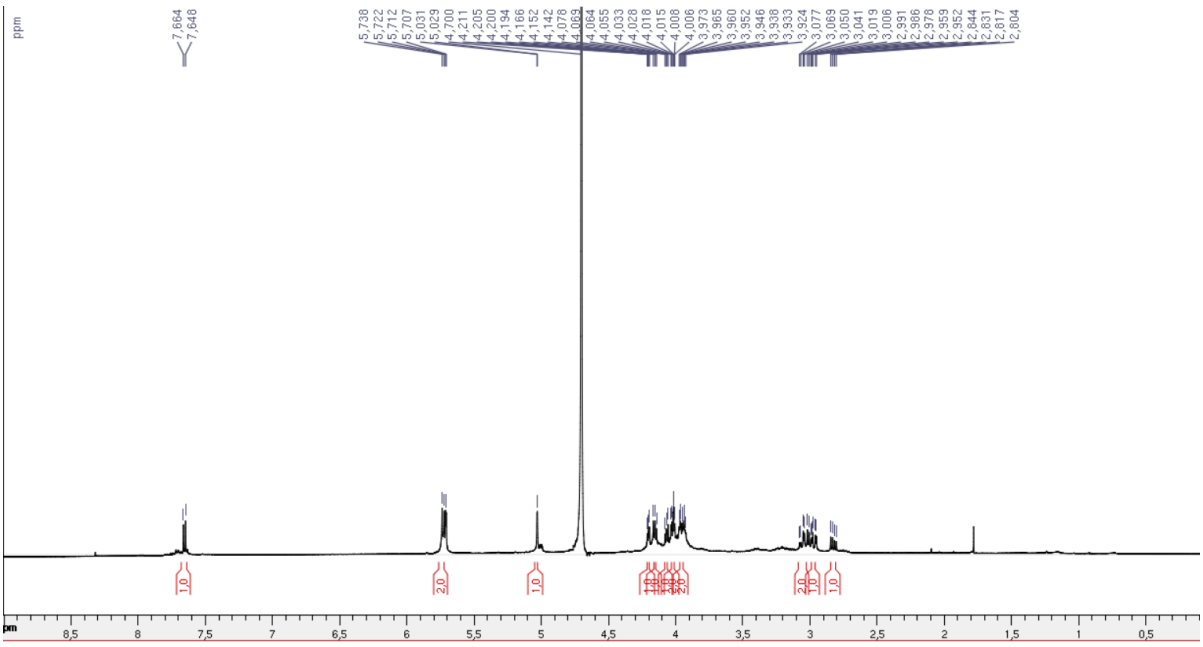


Compound **12**

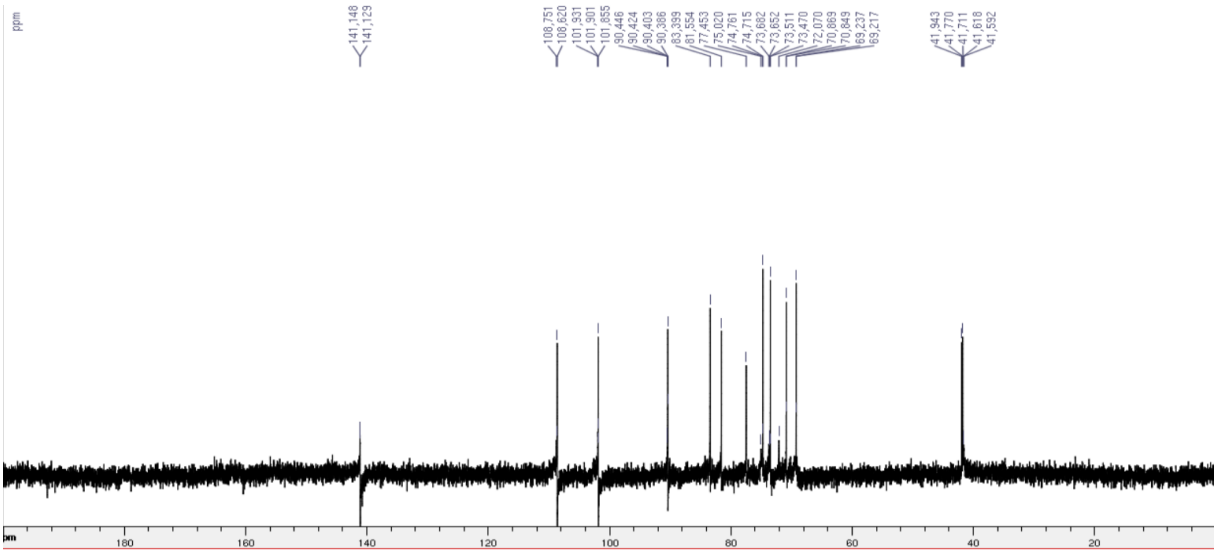


12

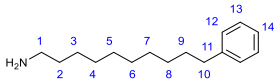
^{1}H NMR, 500 MHz (D_2O)



^{13}C NMR, 125 MHz (D_2O)

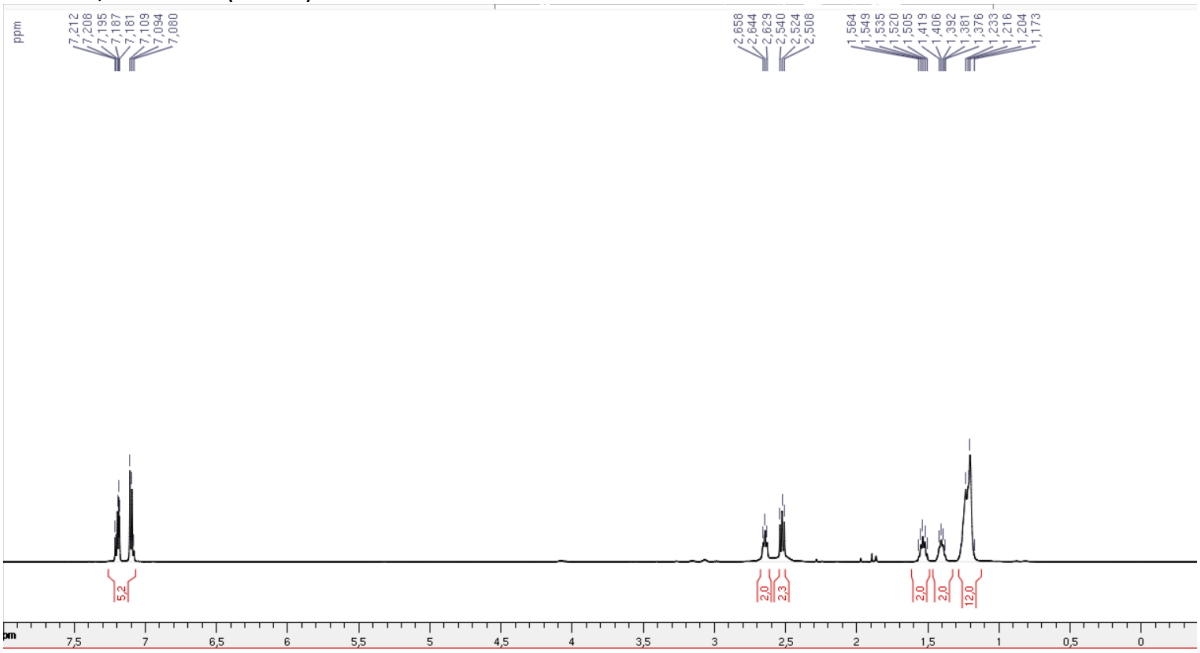


10-phenyldecan-1-amine 13c

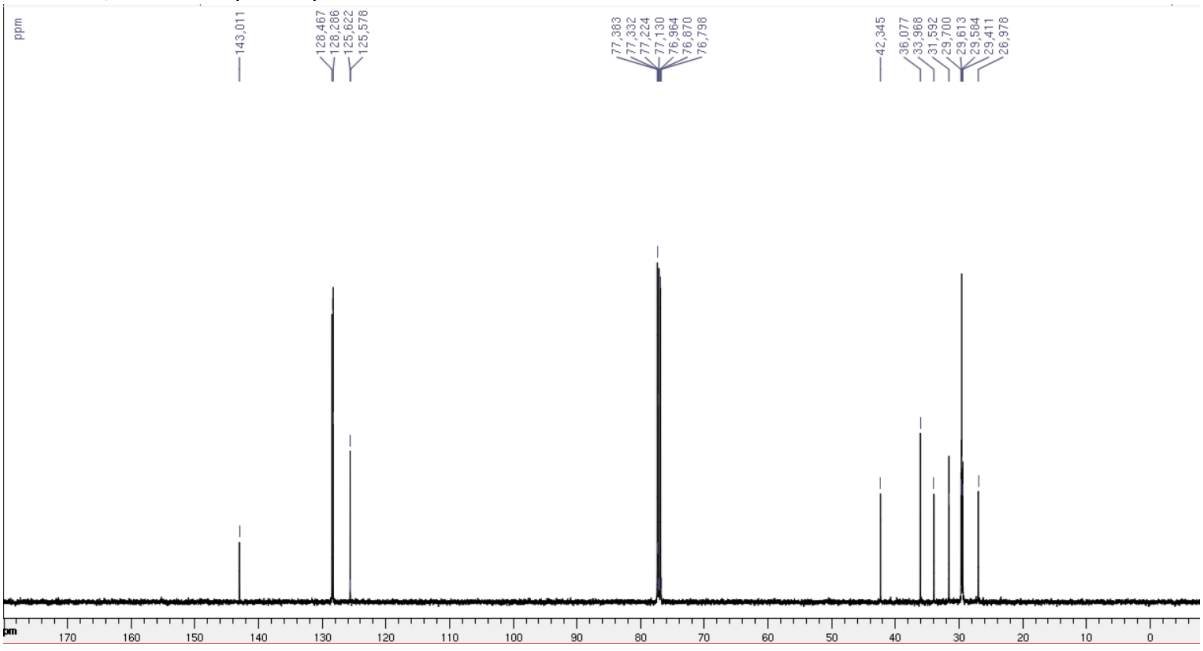


13c

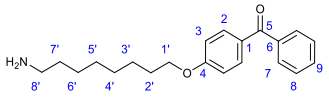
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

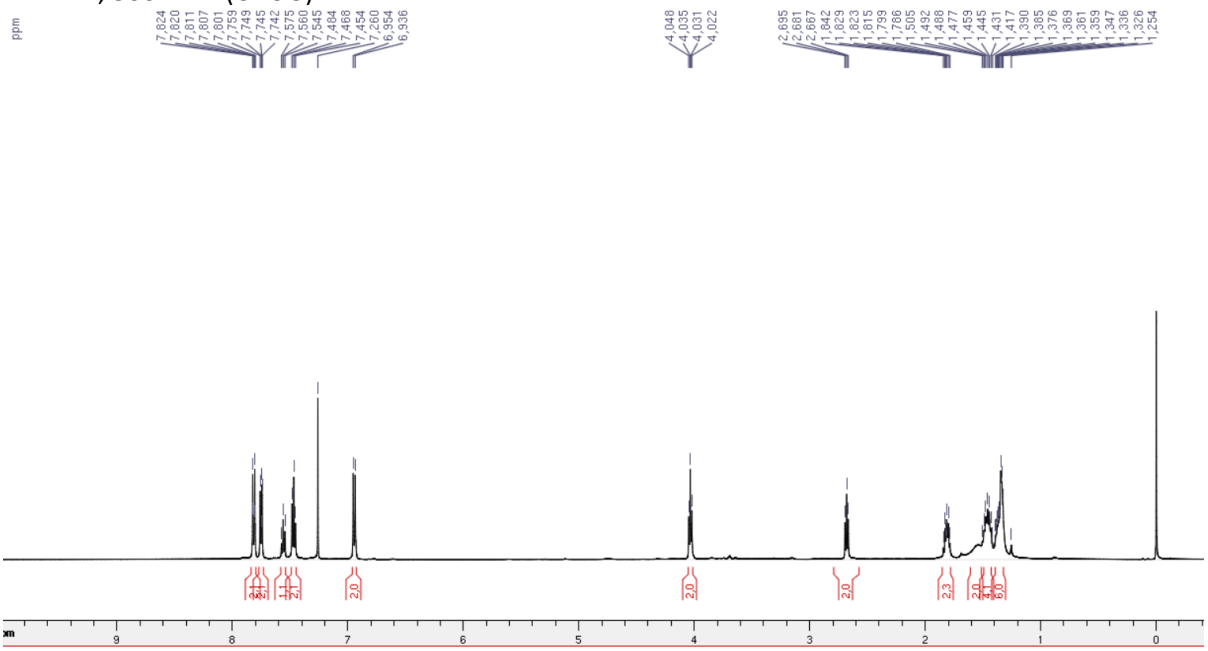


4-(8’-Amino-octanyloxy)-benzophenone 13d

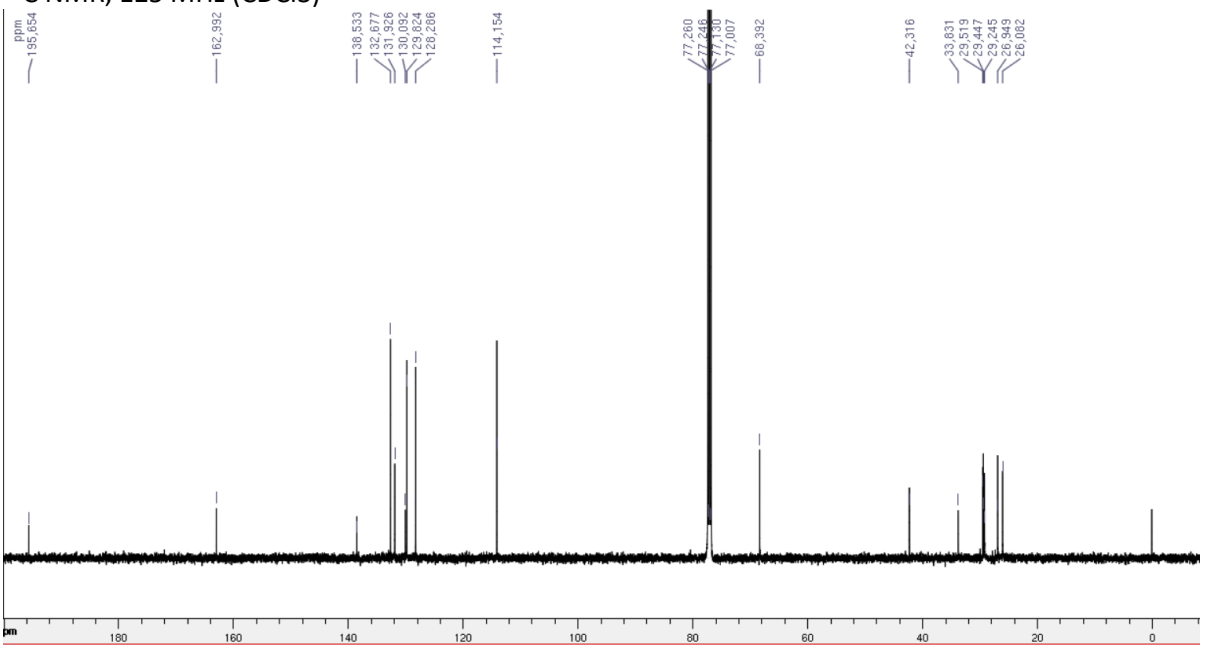


13d

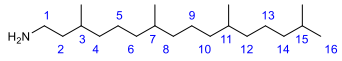
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

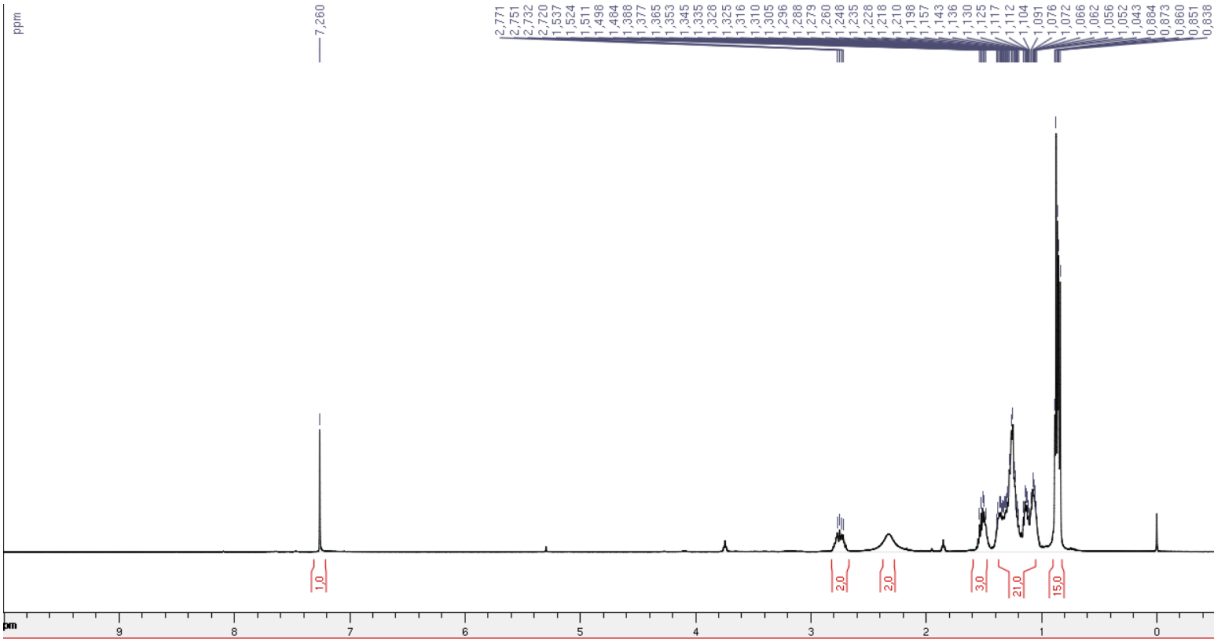


3,7,11,15-tetramethylhexadecan-1-amine 13e

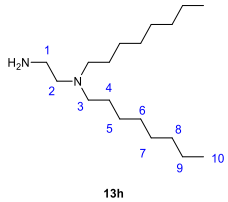


13e

^{1}H NMR, 500 MHz (CDCl3)

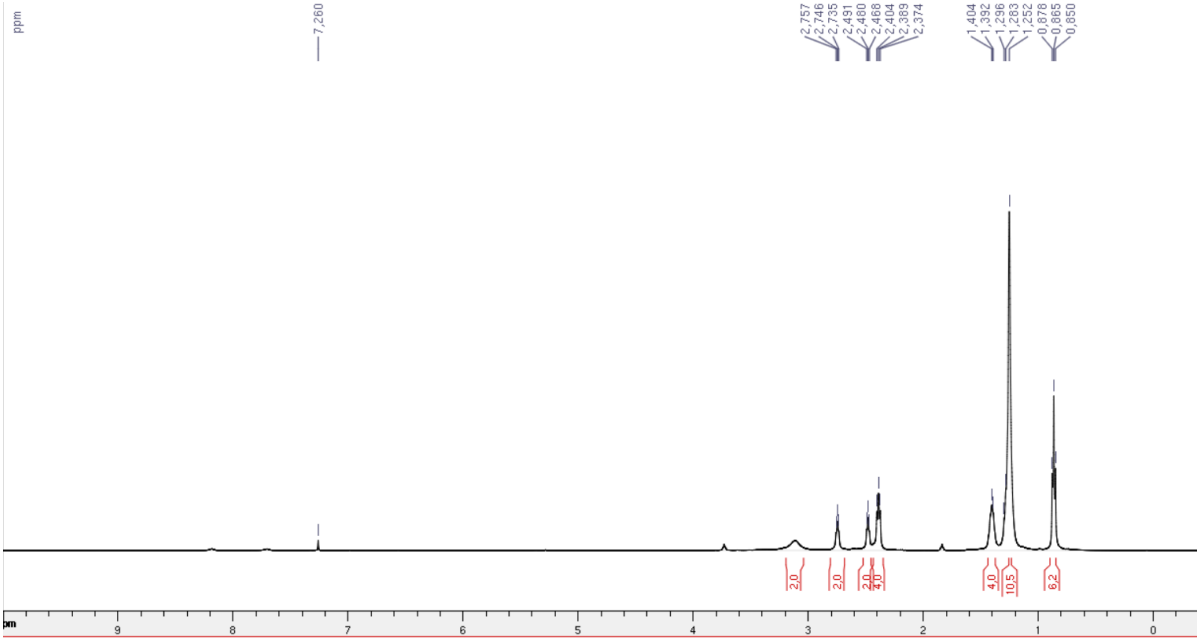


N,N-dioctylethane-1,2-diamine 13h

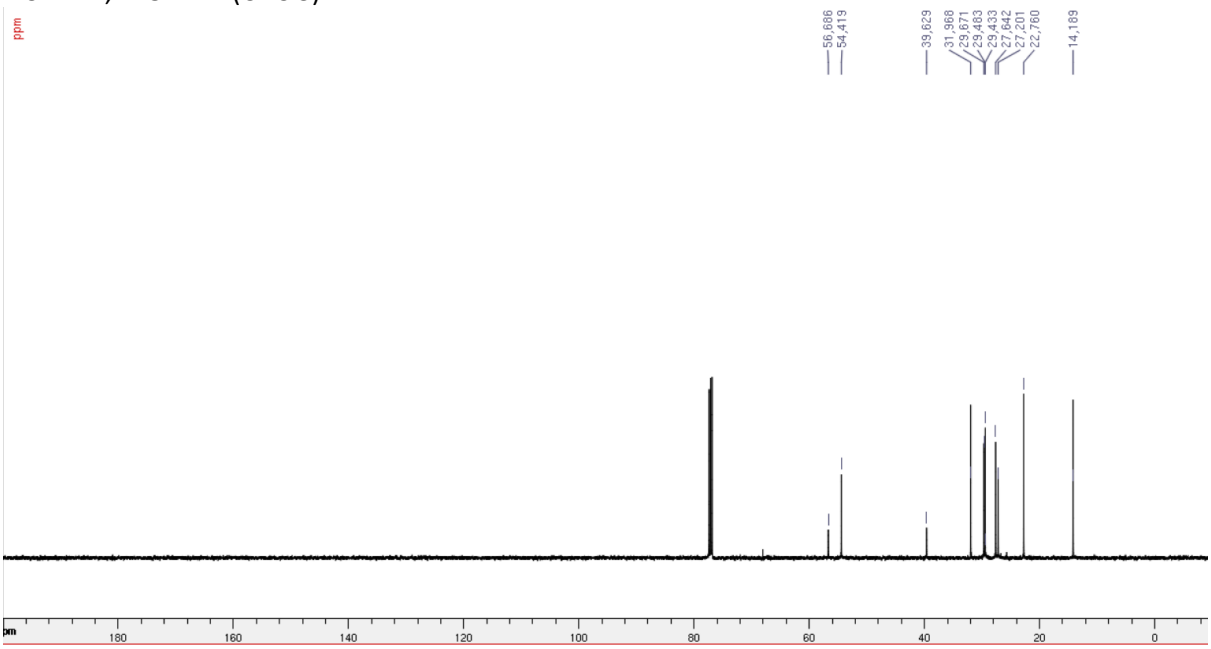


13h

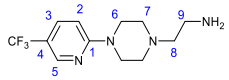
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

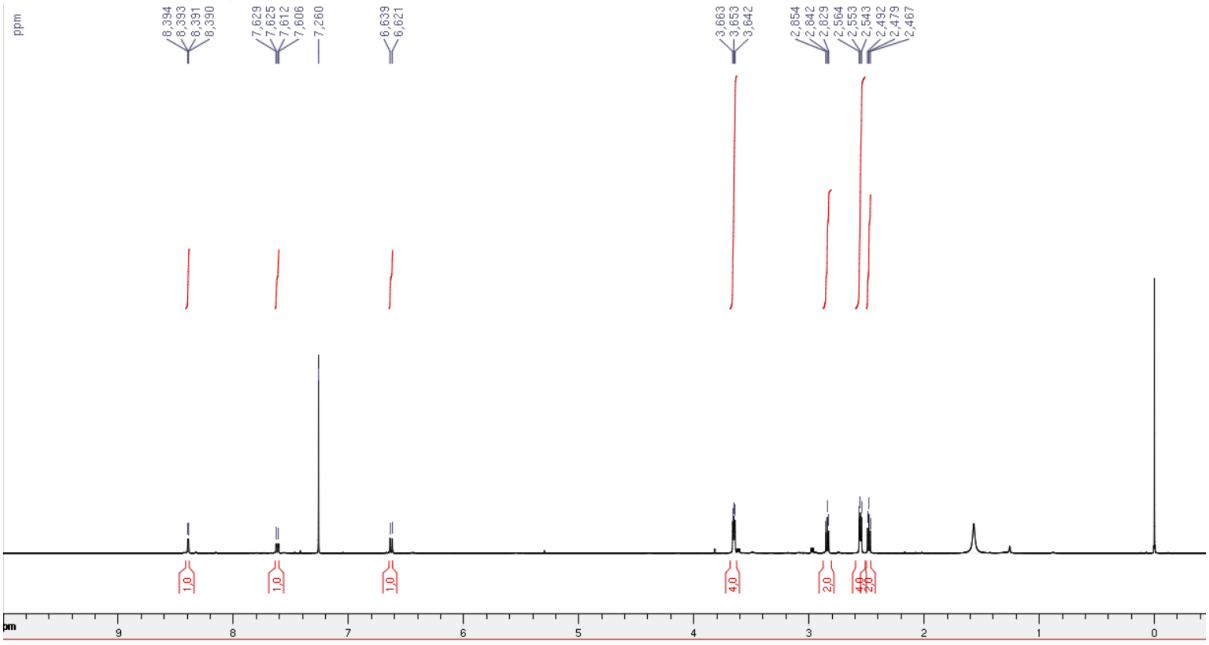


2-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)ethan-1-amine 13i

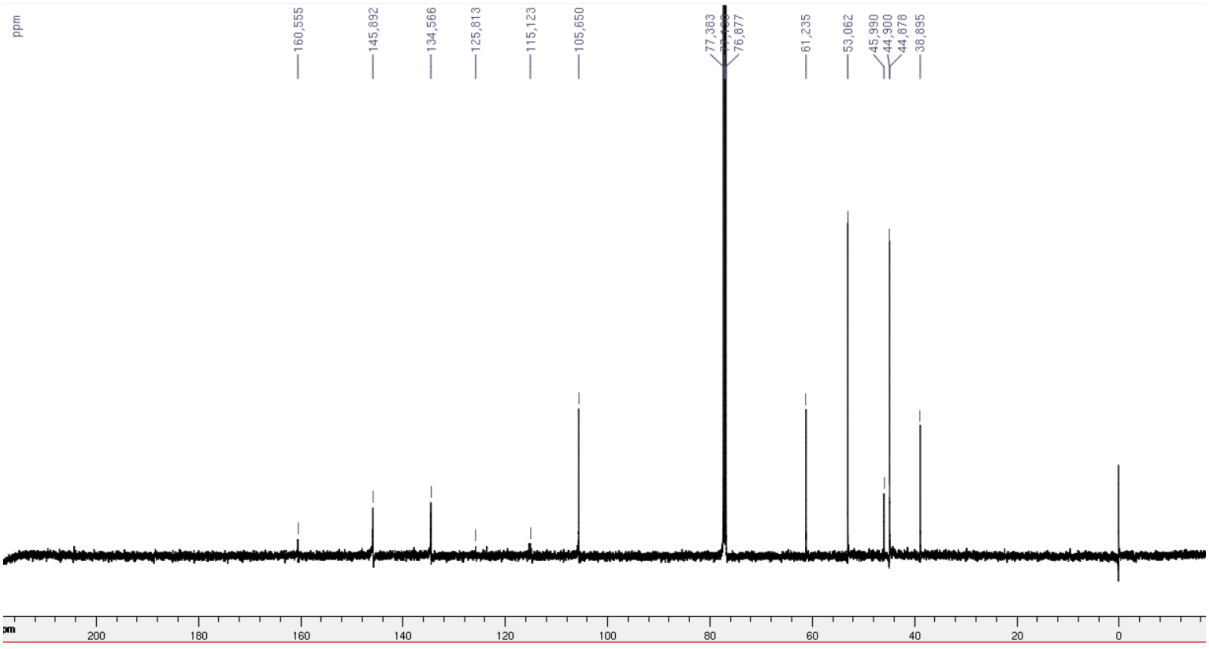


13i

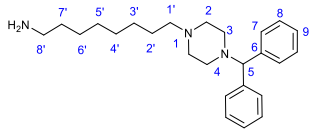
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

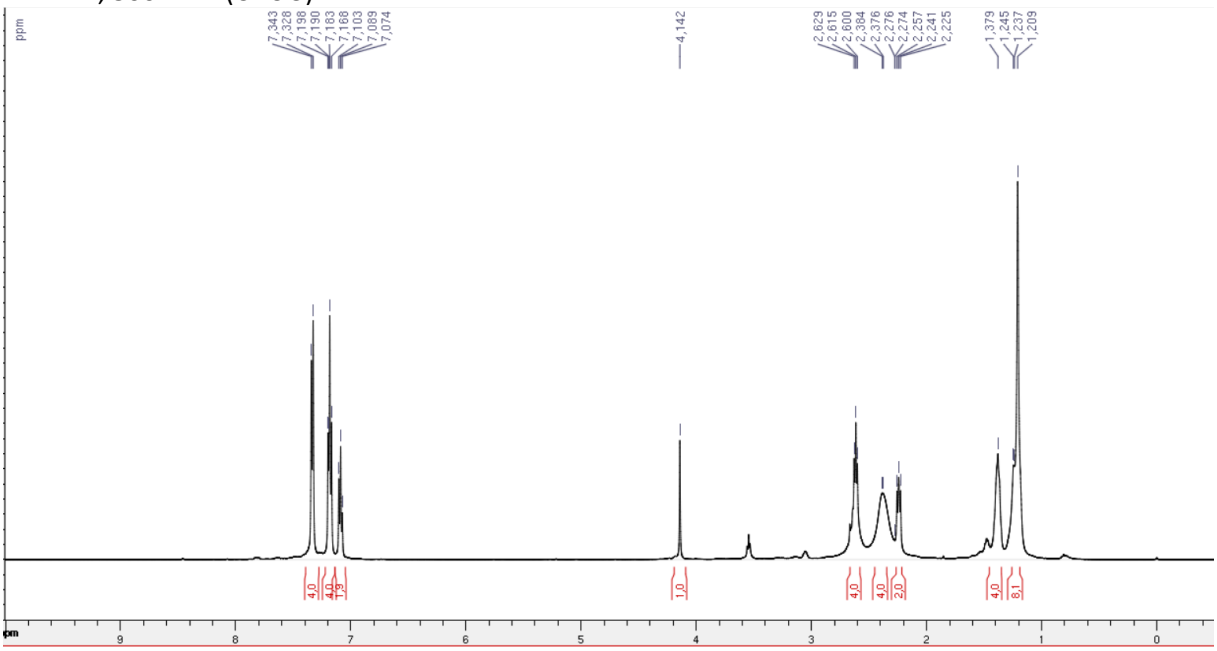


8'-(4-benzhydrylpiperazin-1-yl)octan-1-amine 13j

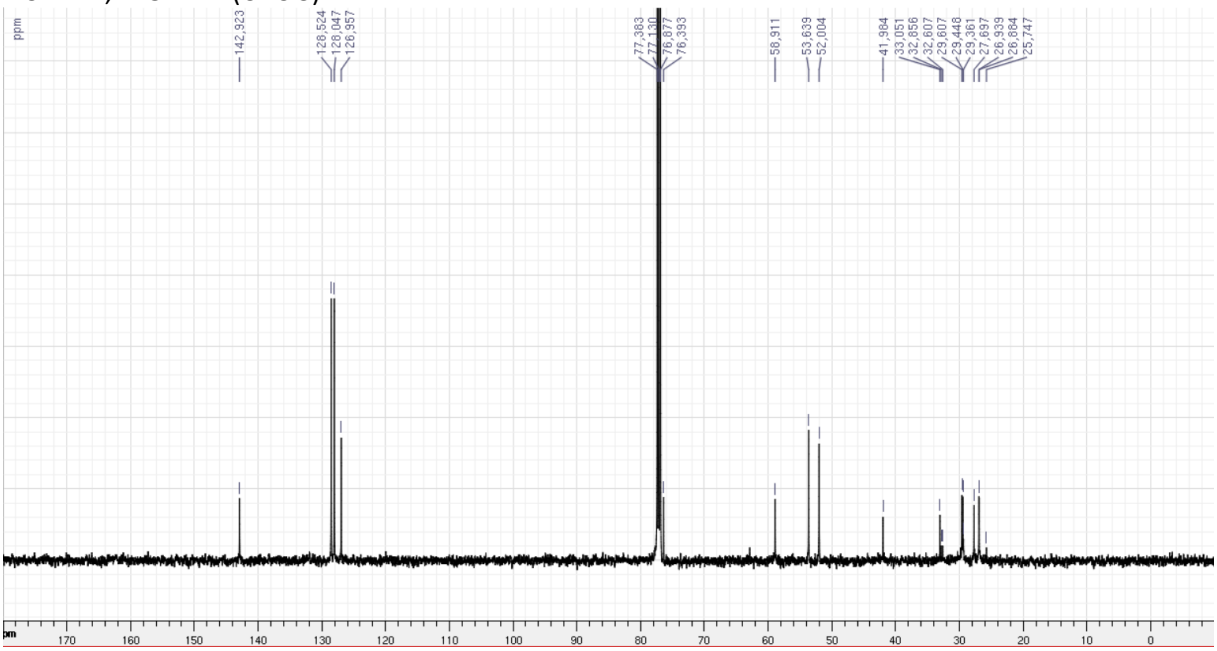


13j

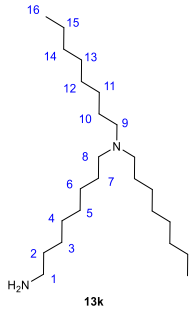
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

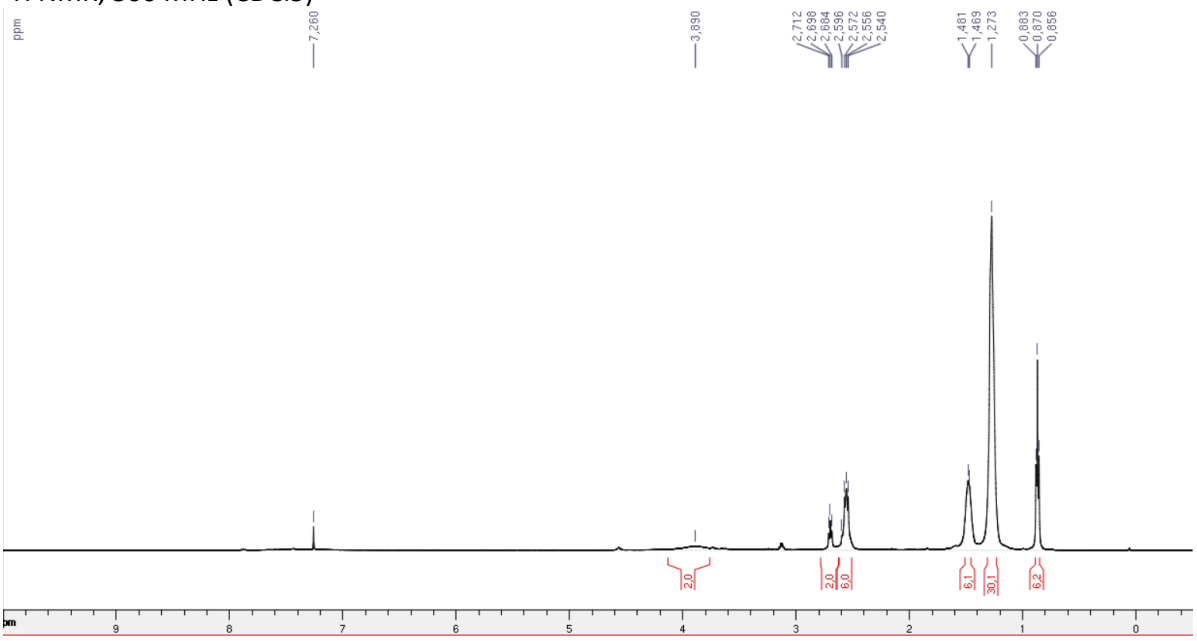


***N*,*N*-dioctyloctane-1,8-diamine 13k**

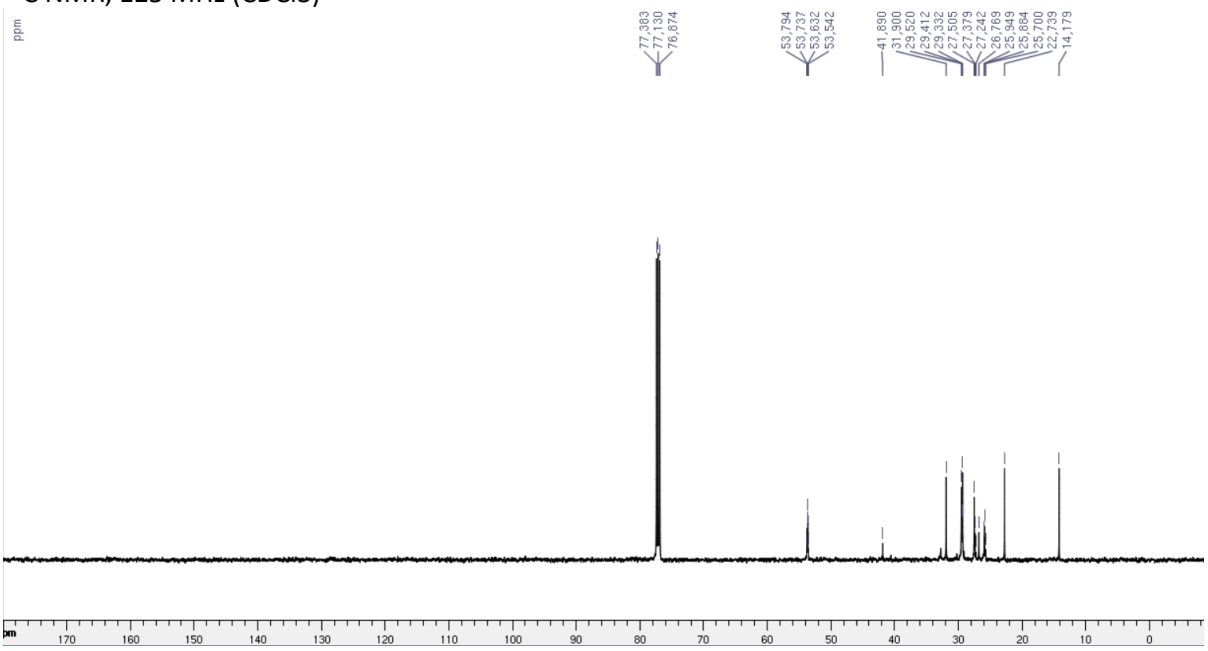


13k

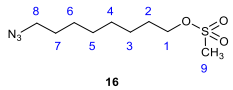
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

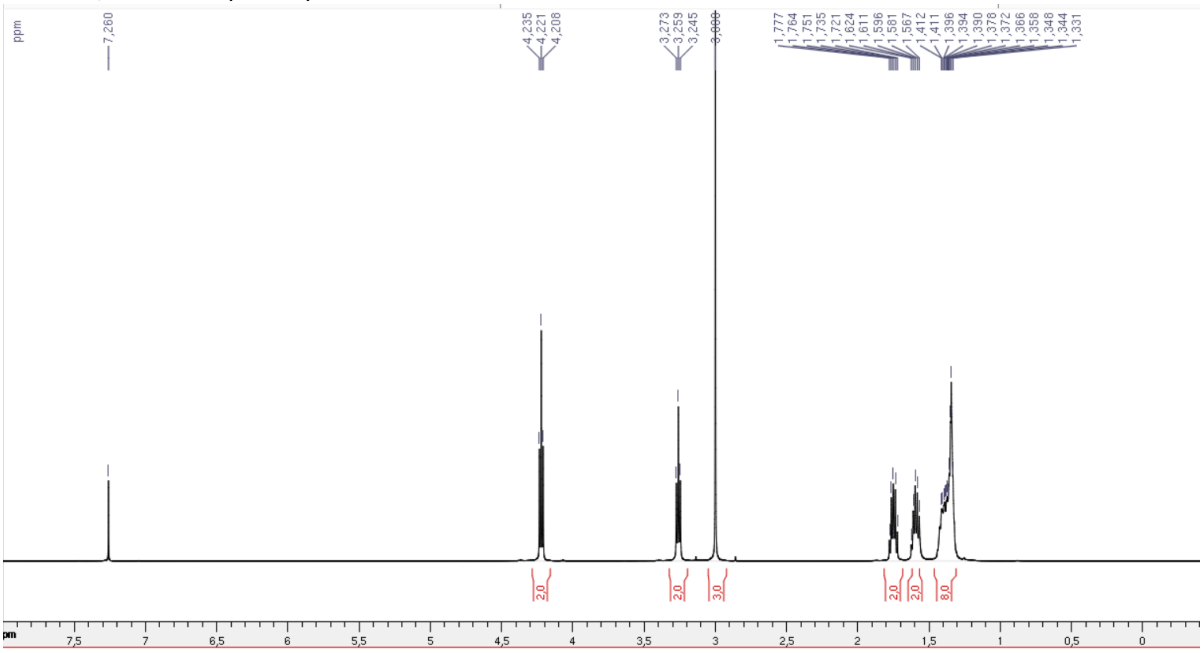


8-azidooctyl methanesulfonate 16

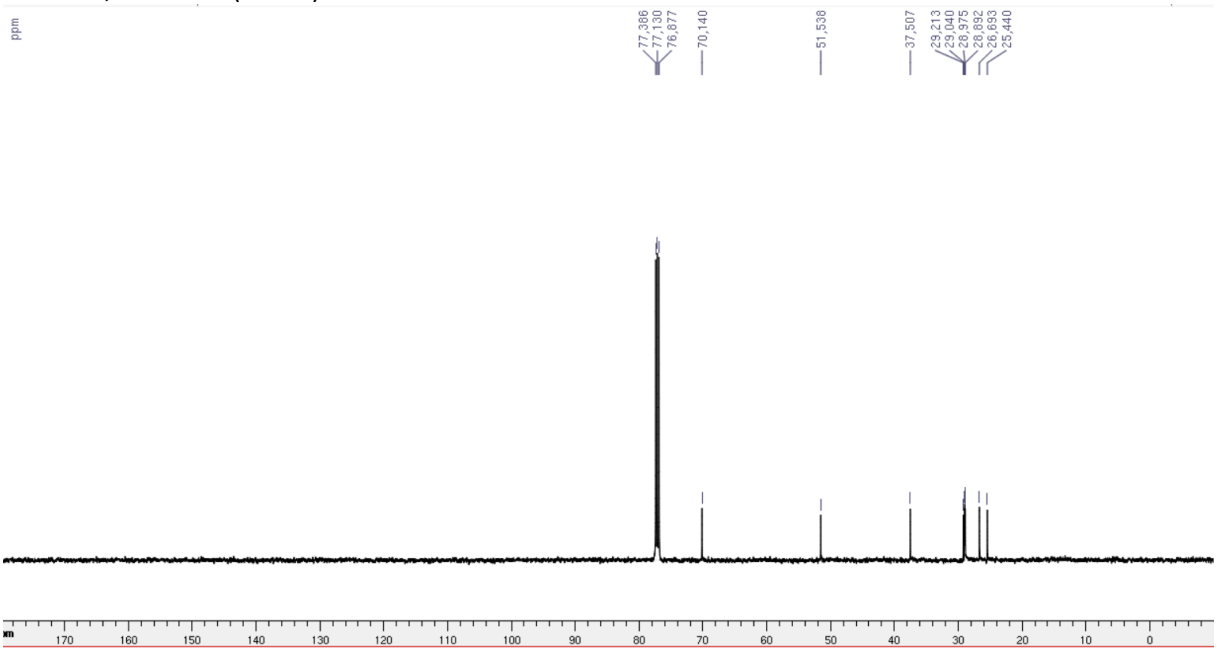


16

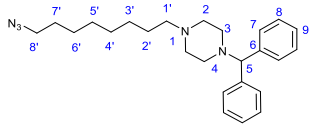
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

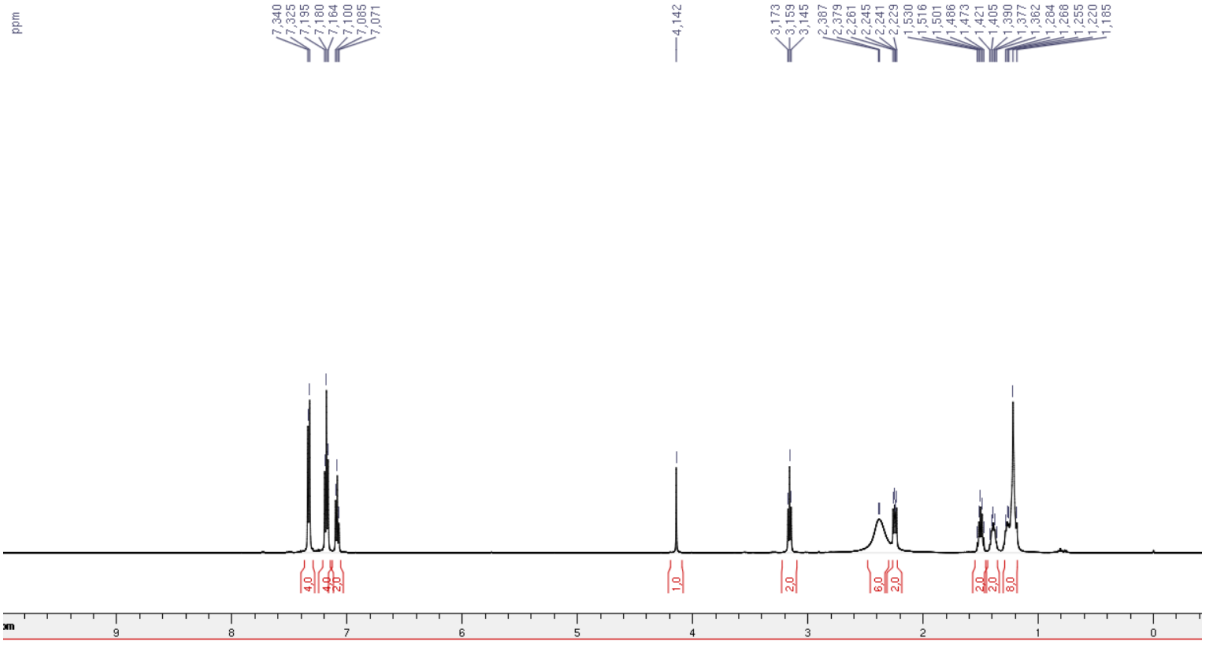


1-(8'-azidooctyl)-4-benzhydrylpiperazine 17

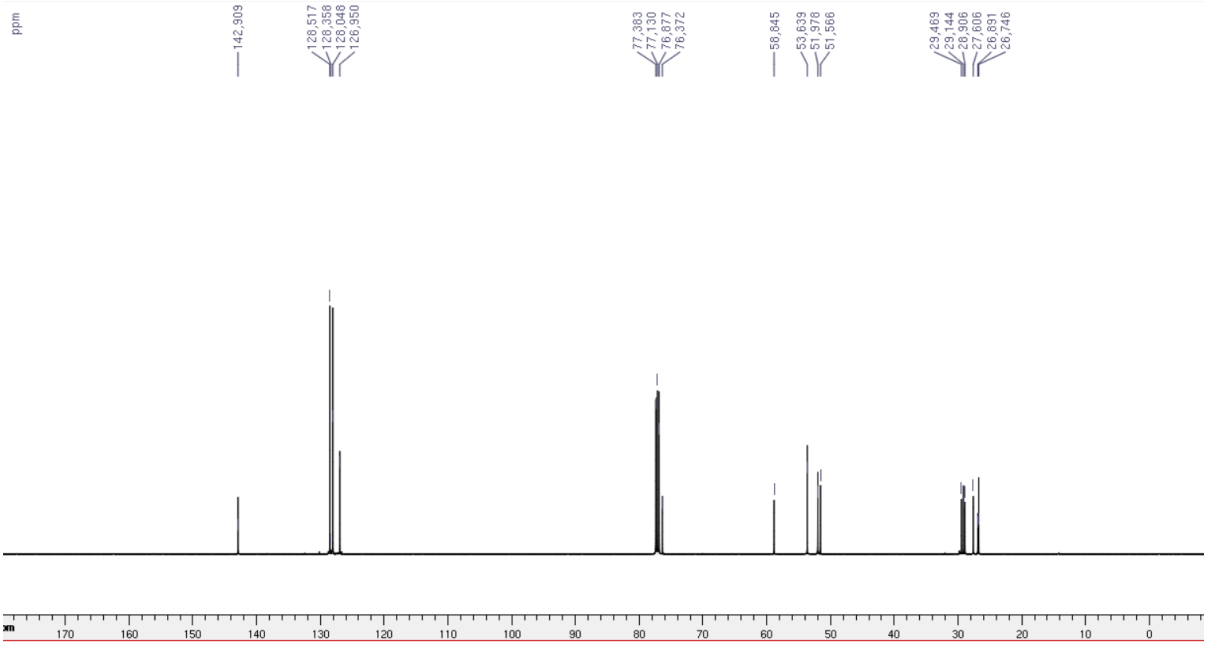


17

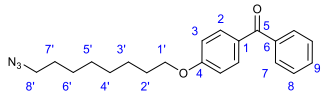
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

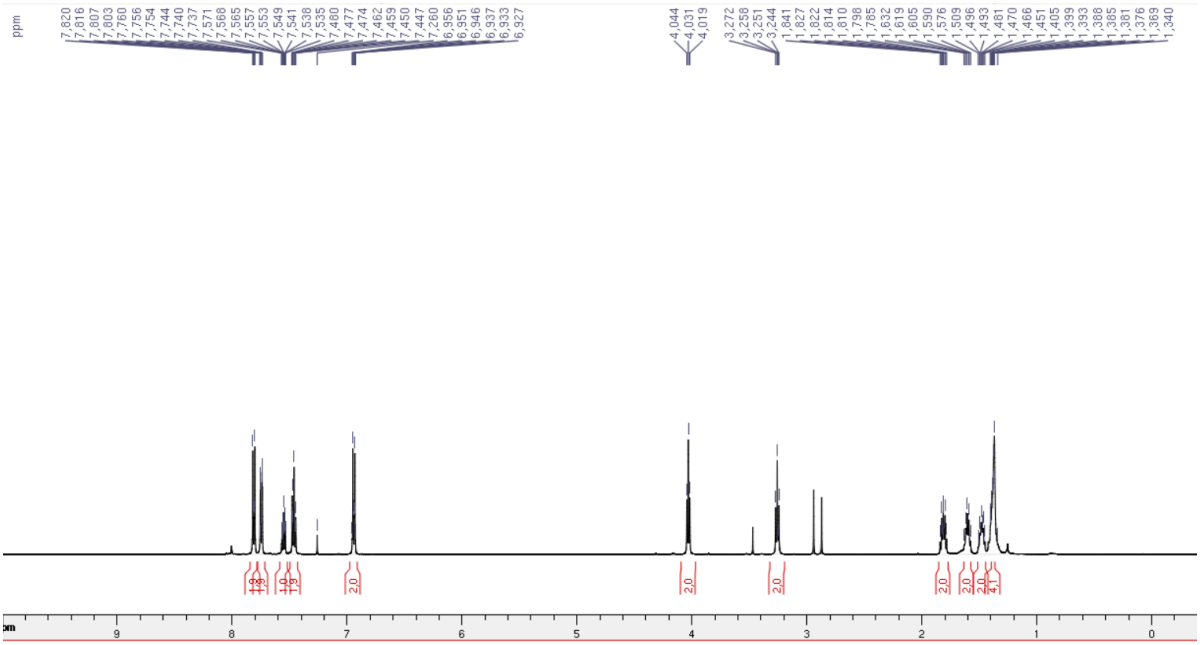


4-(8’-Azido-octanyloxy)-benzophenone 18

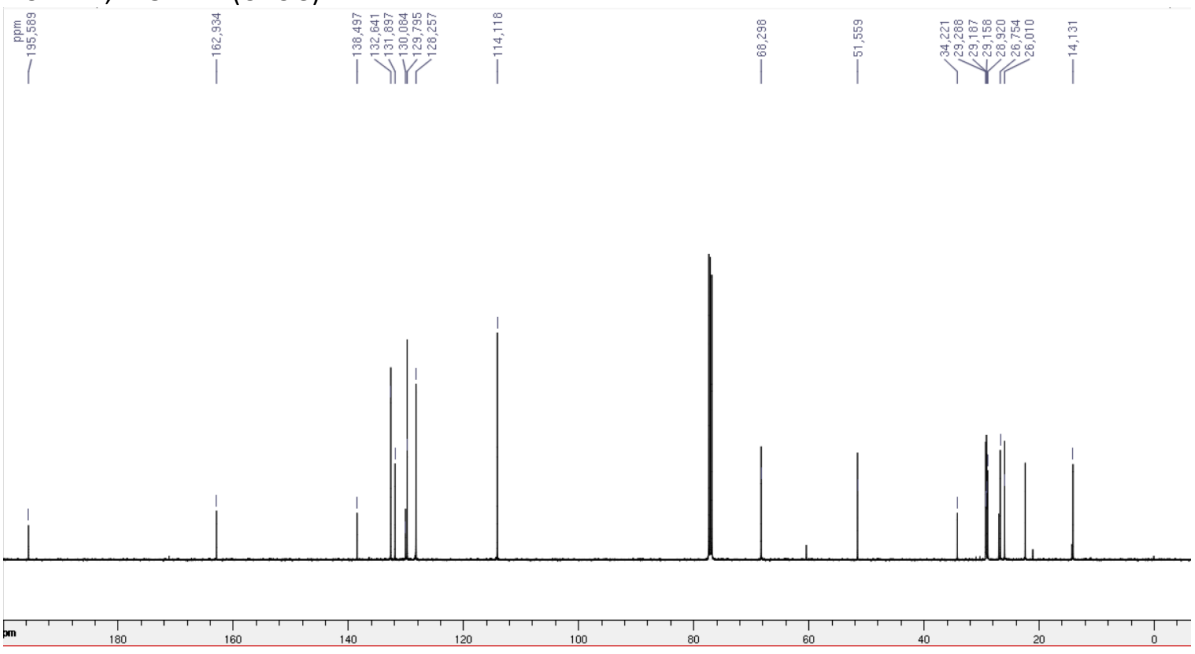


18

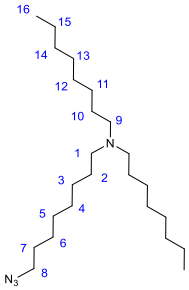
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

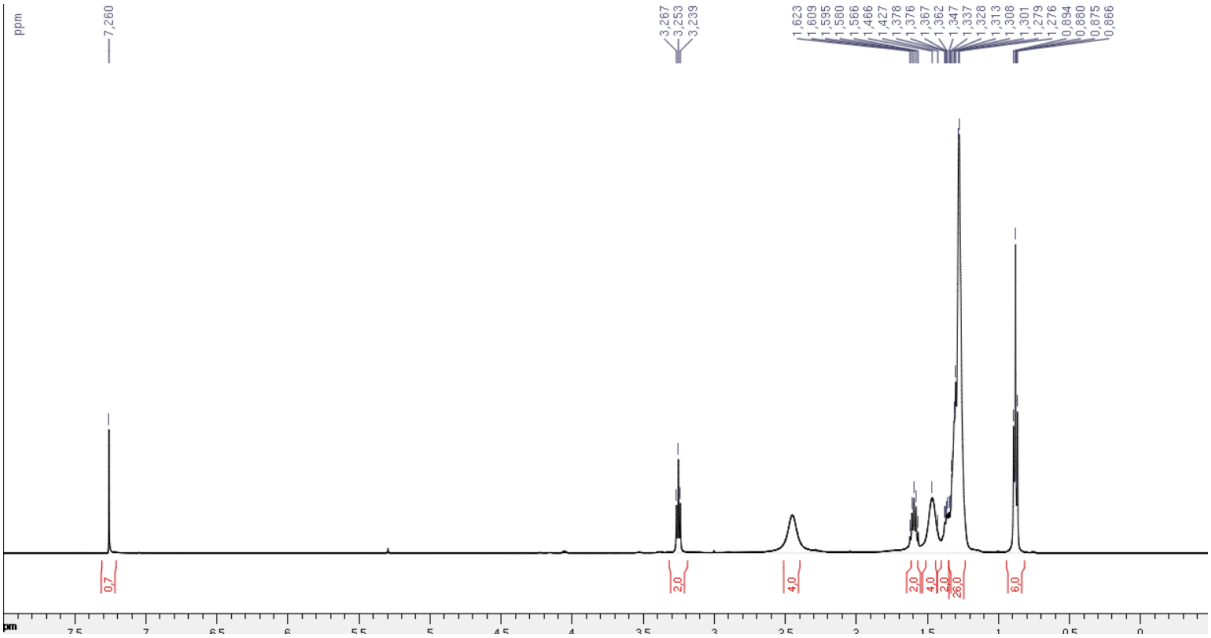


8-azido-*N*,*N*-dioctyloctan-1-amine 19

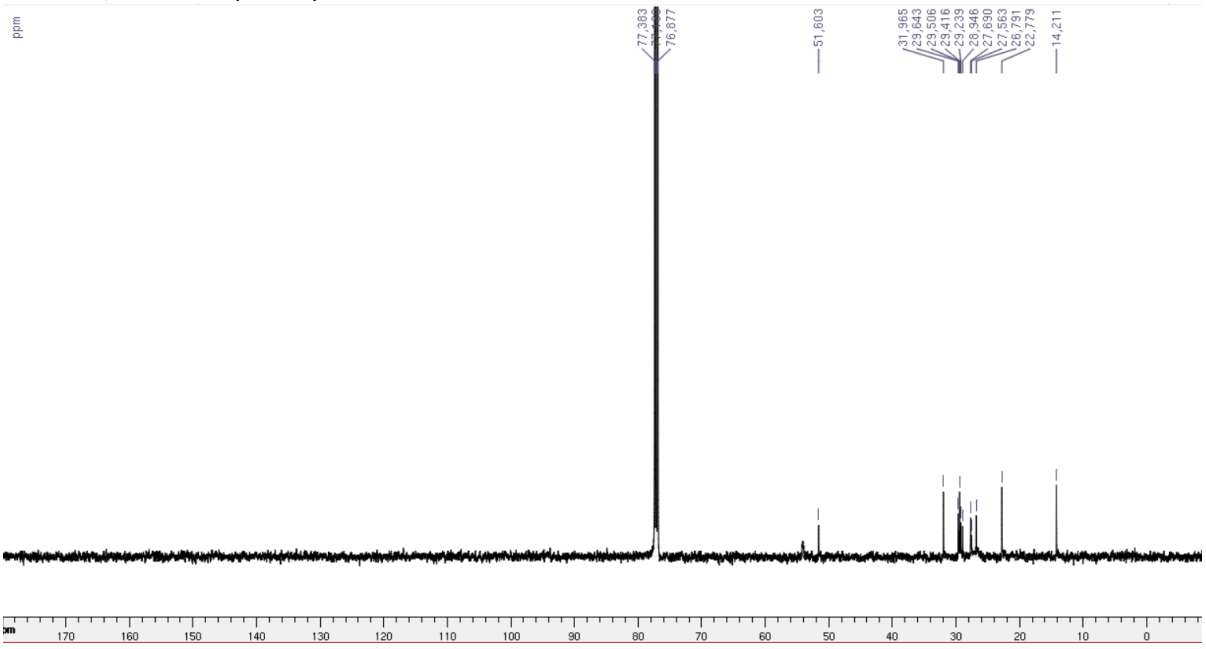


19

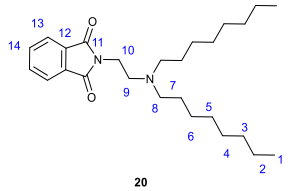
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

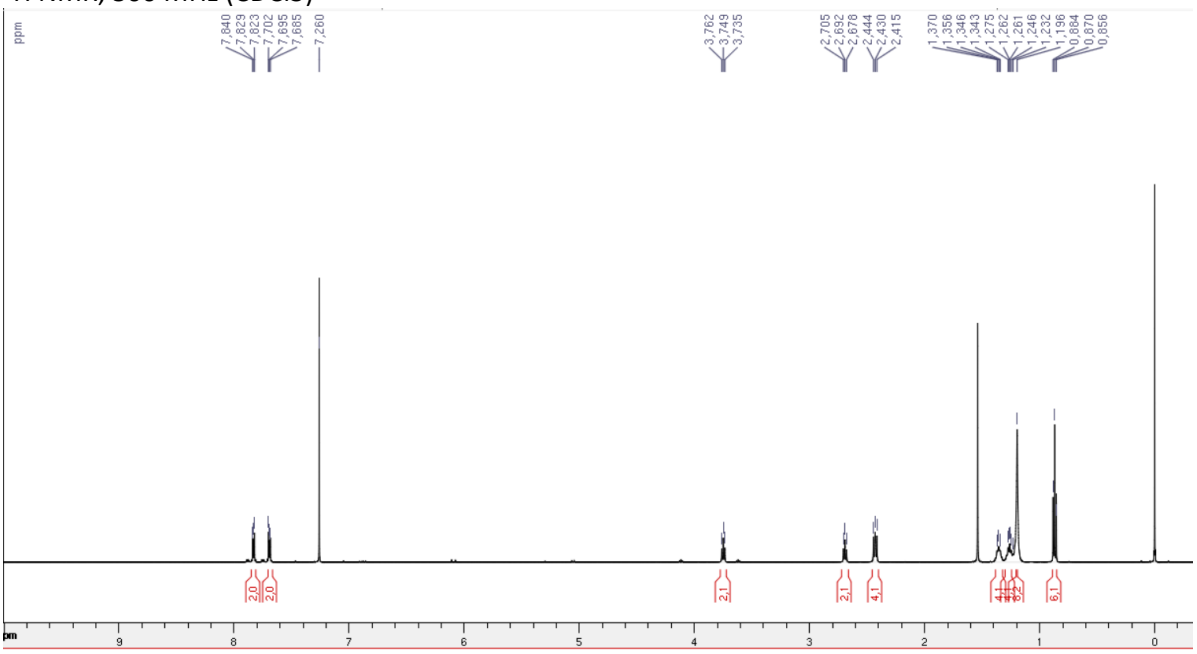


_N_-phtalimido-10-(9-(dioctylamino)ethyl) 20

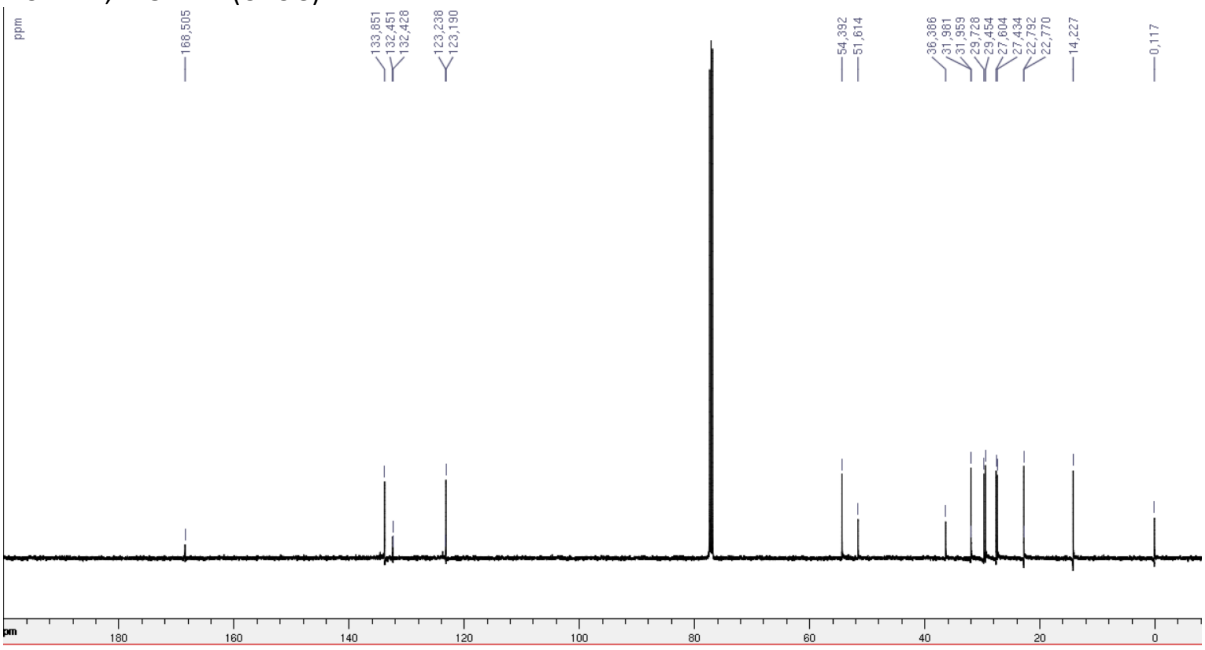


20

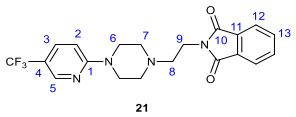
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

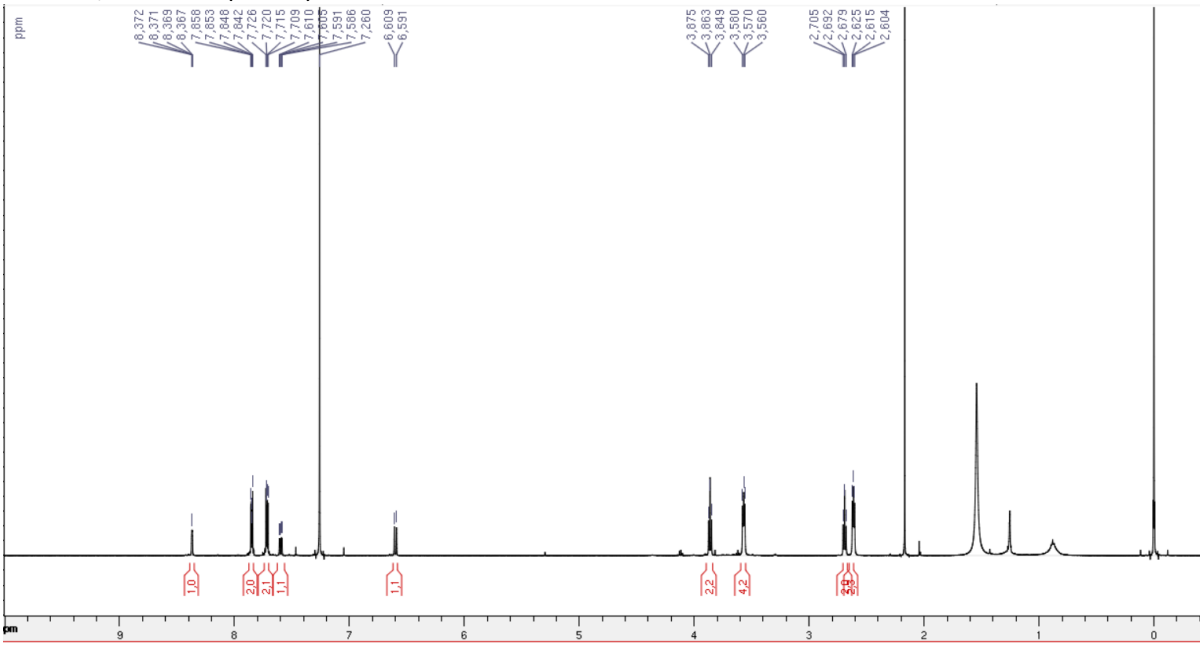


2-(2-(4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)ethyl) phtalimide 21

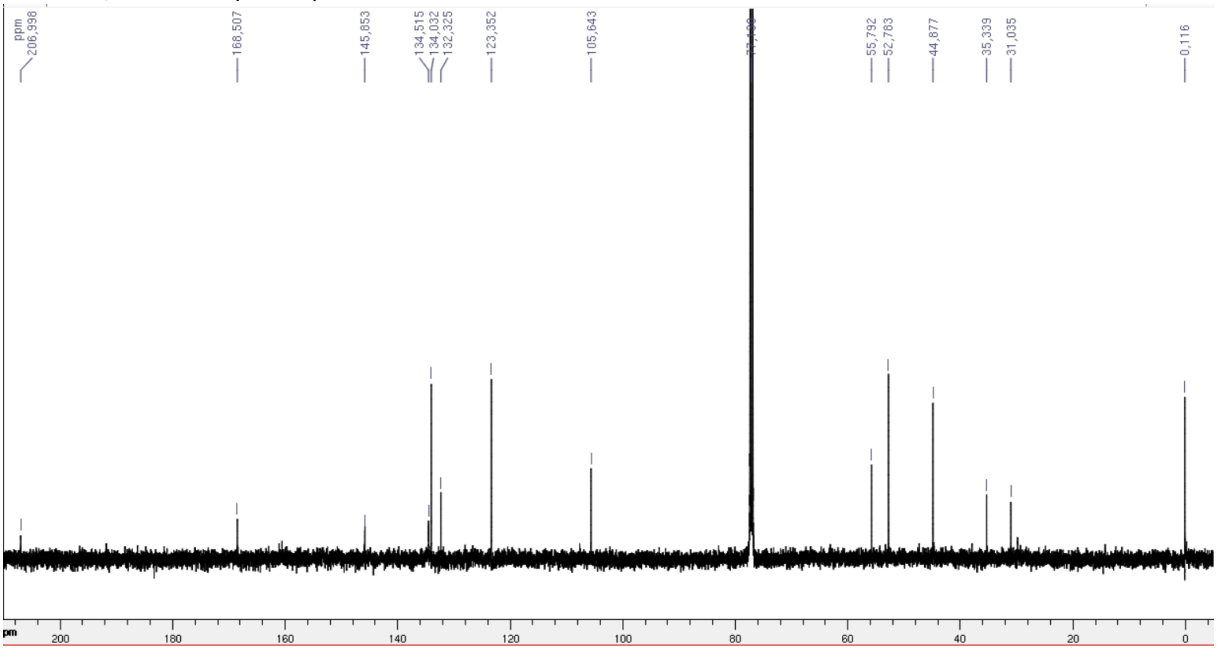


21

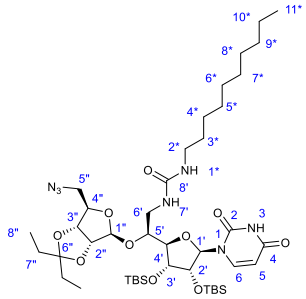
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

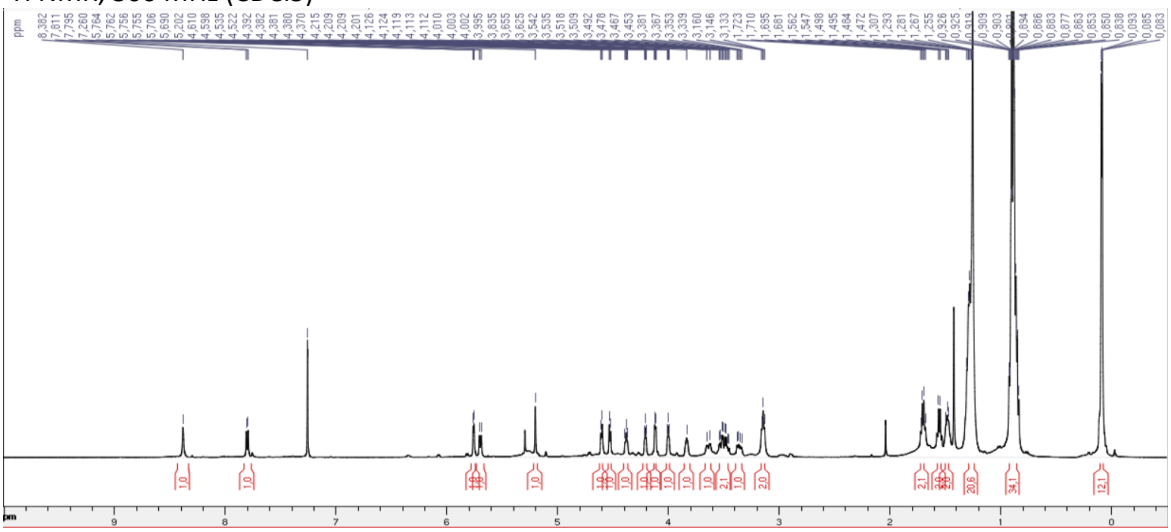


Compound 23a

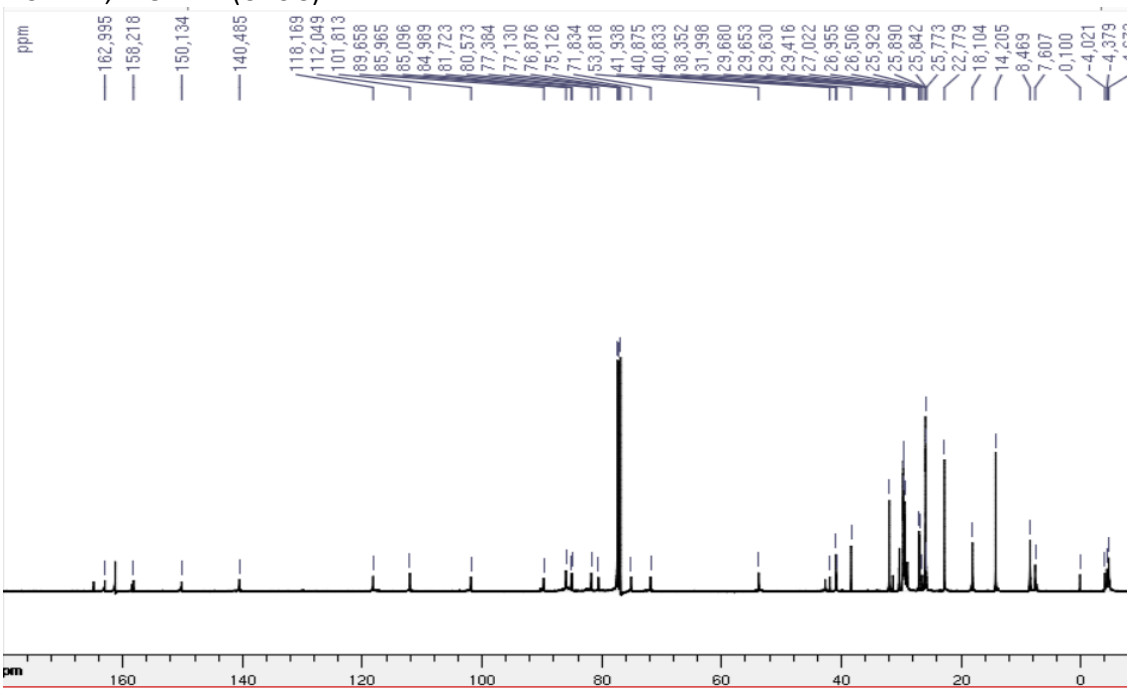


23a

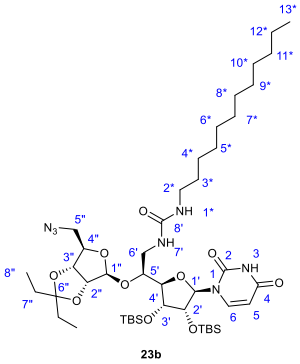
^{1}H NMR, 500 MHz (CDCl3)



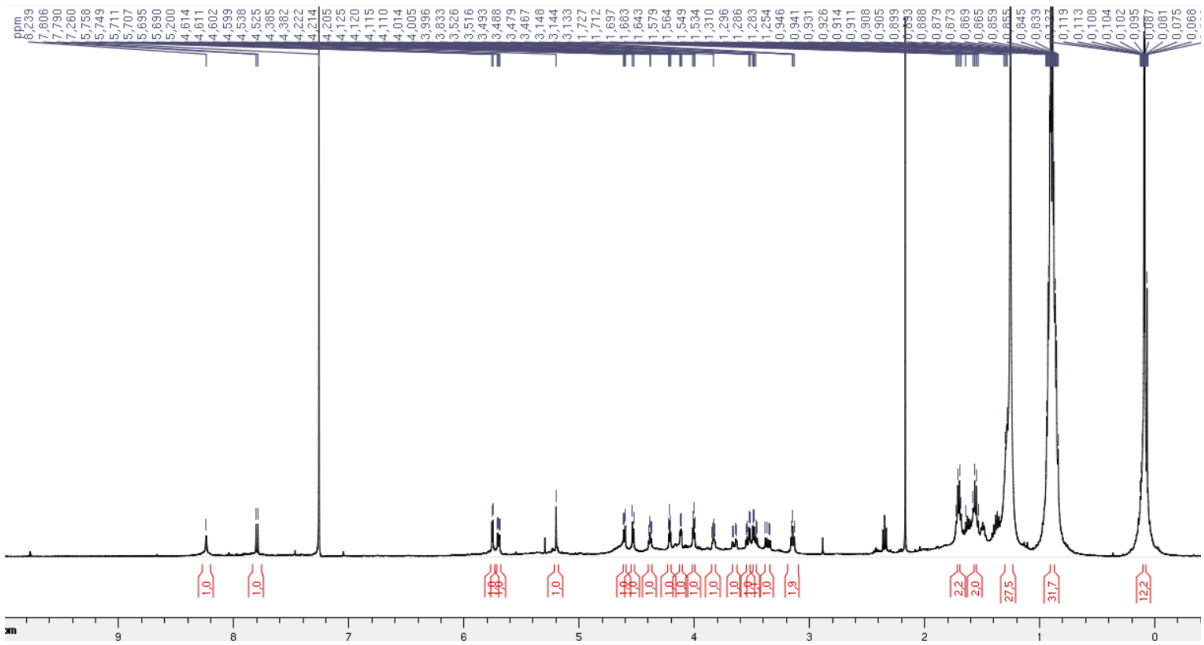
^{13}C NMR, 125 MHz (CDCl3)



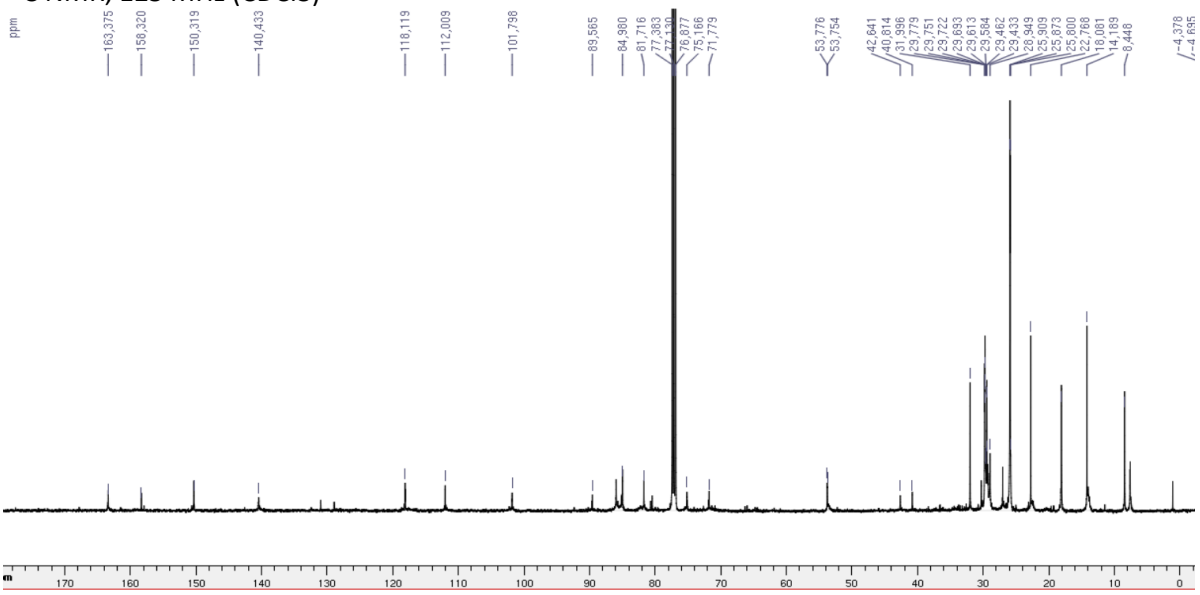
Compound 23b



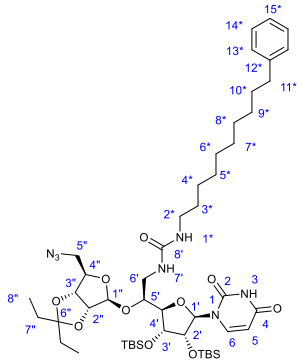
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

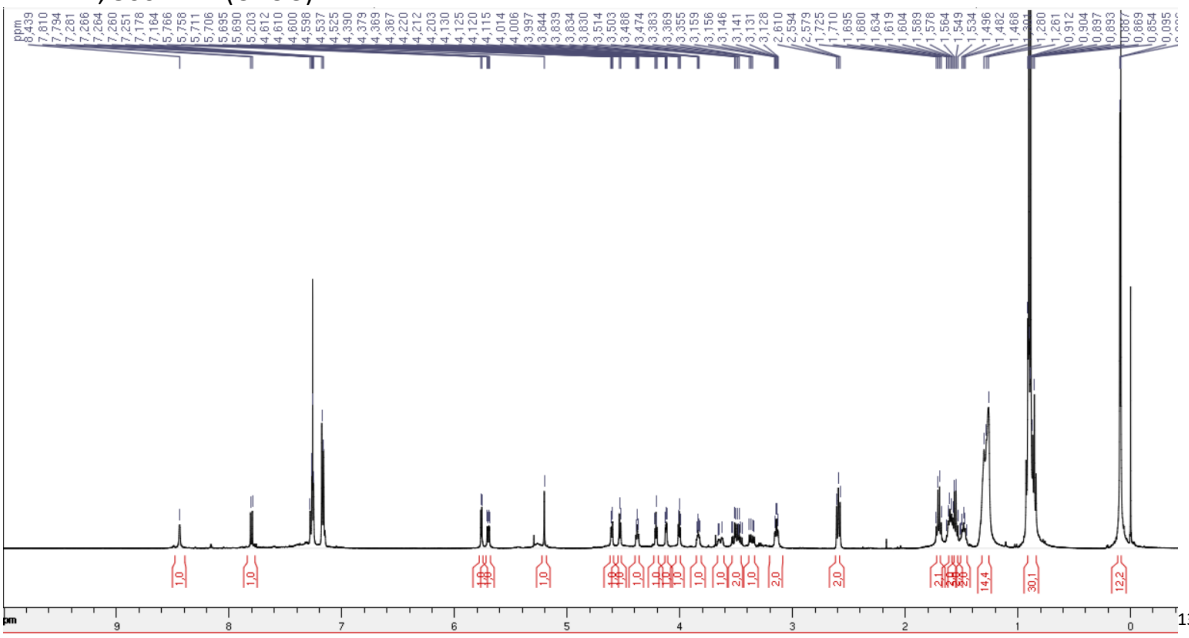


Compound 23c

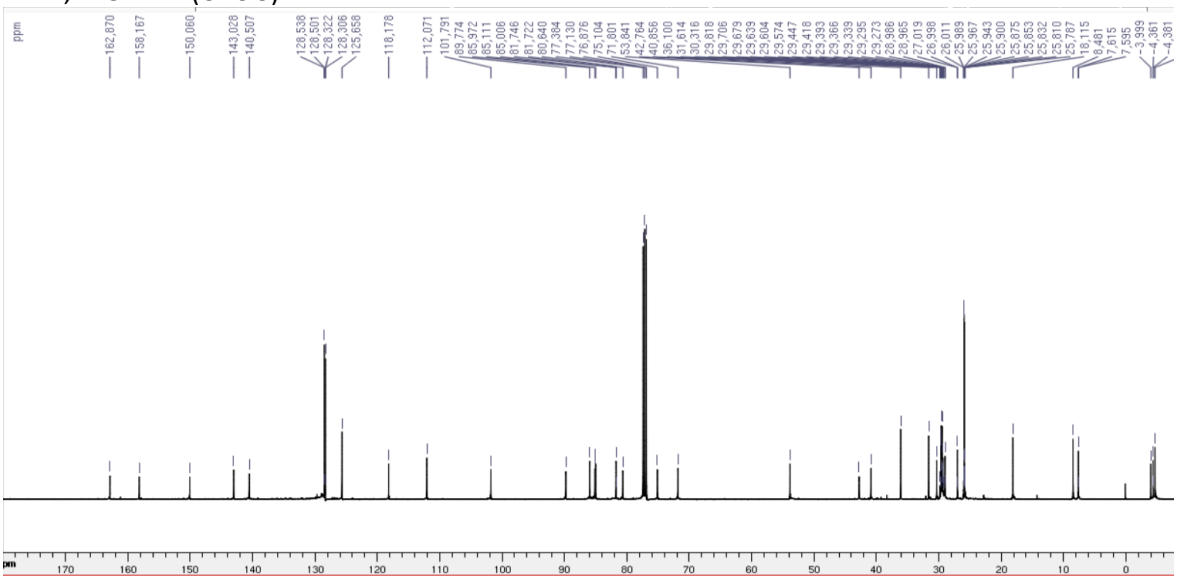


23c

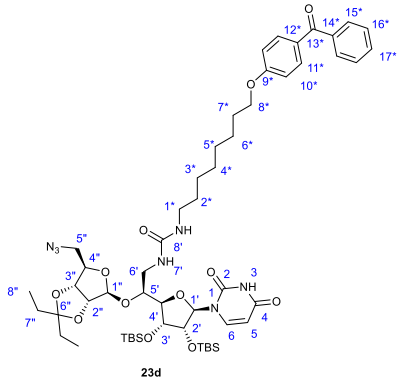
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

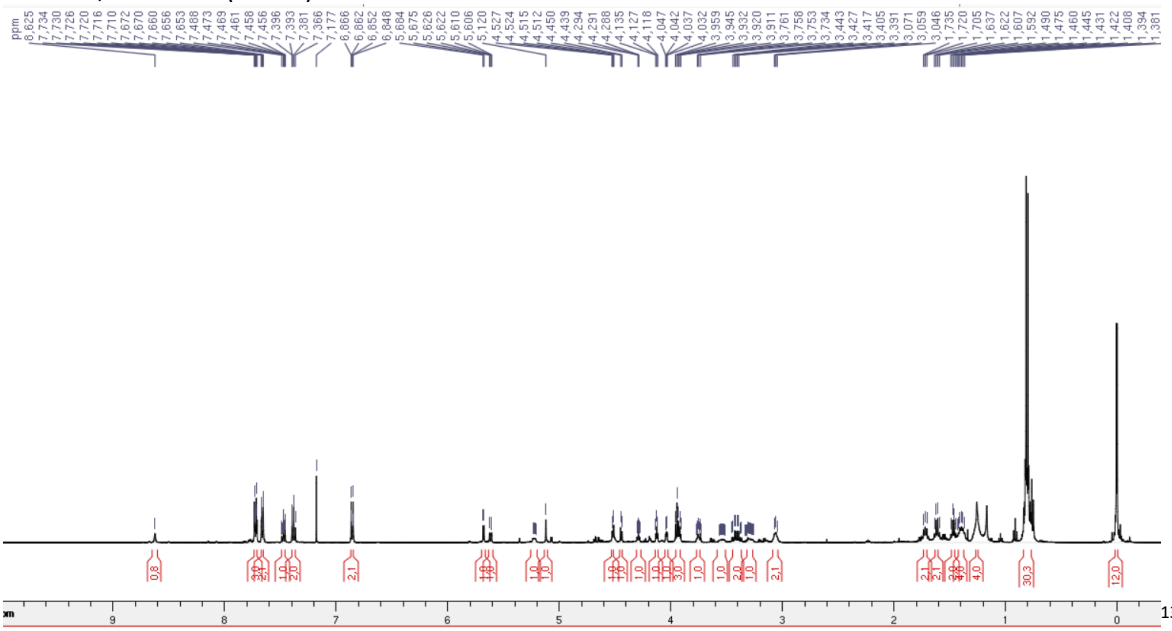


Compound 23d

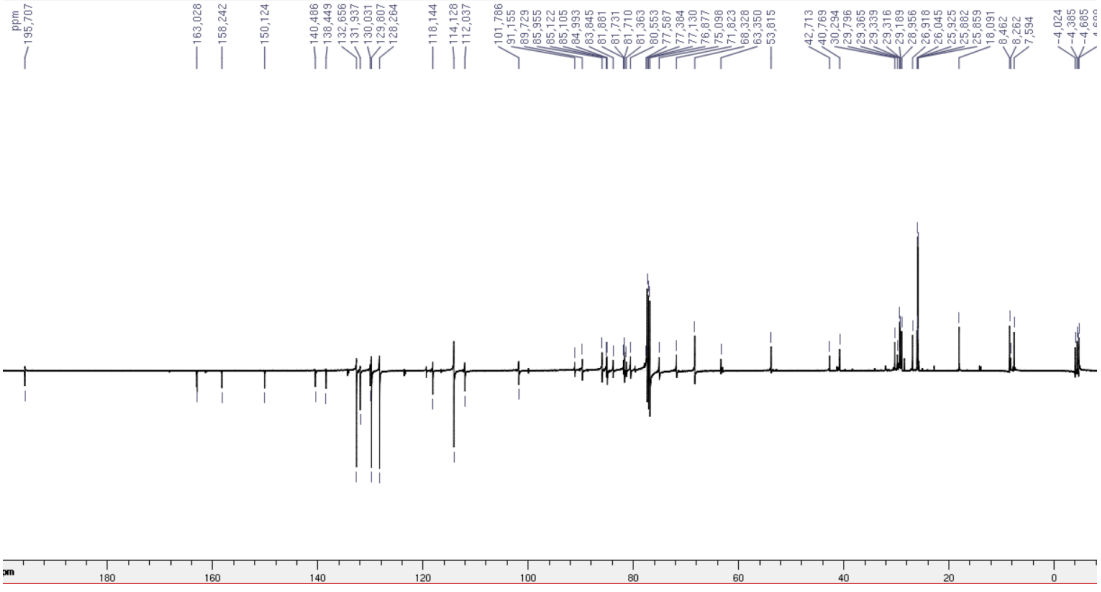


23d

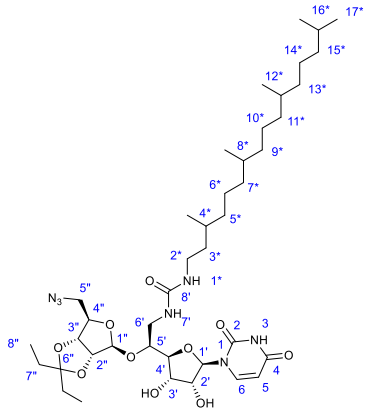
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

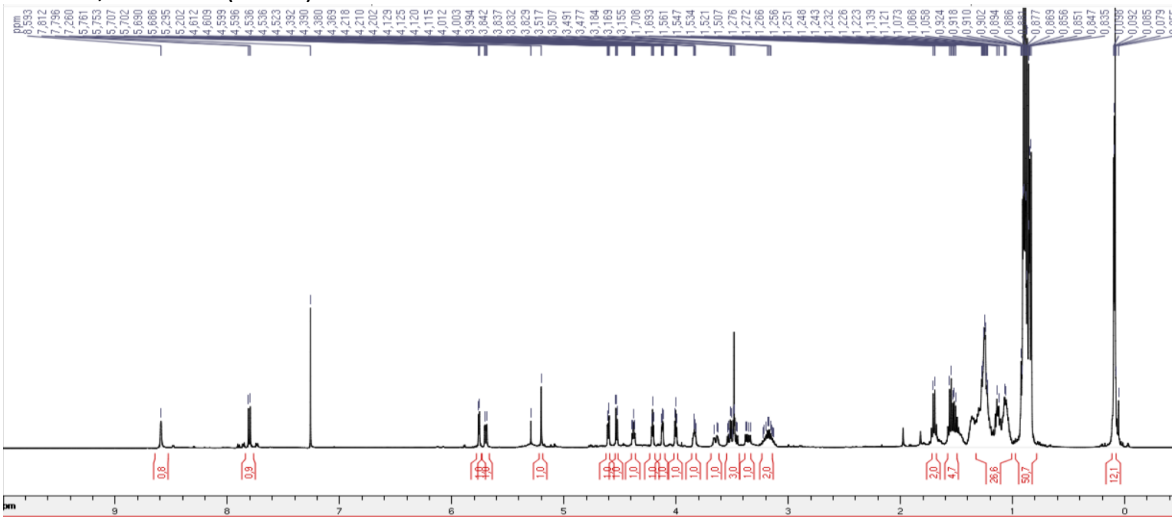


Compound 23e

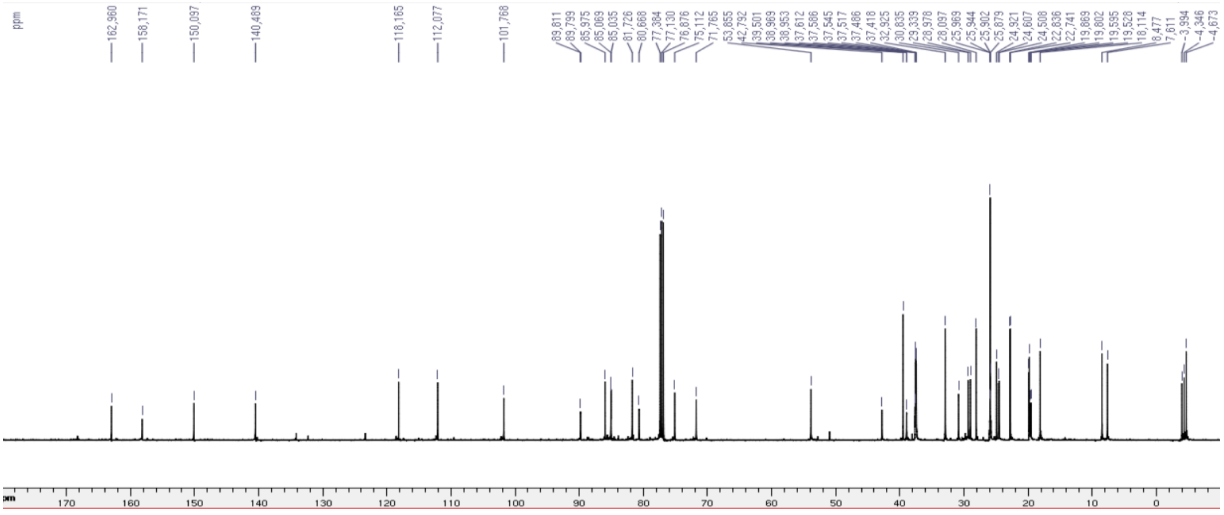


23e

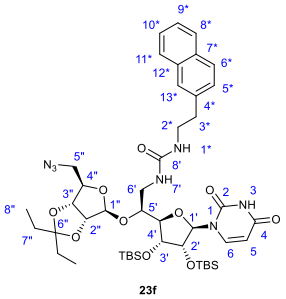
^{1}H NMR, 500 MHz (CDCl3)



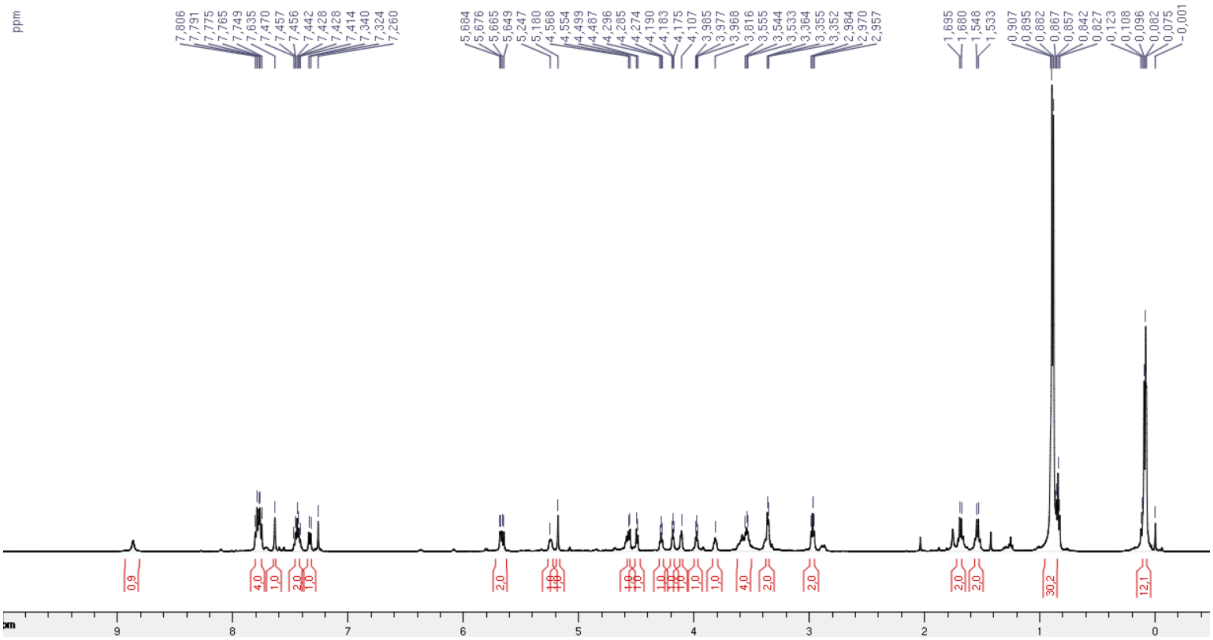
^{13}C NMR, 125 MHz (CDCl3)



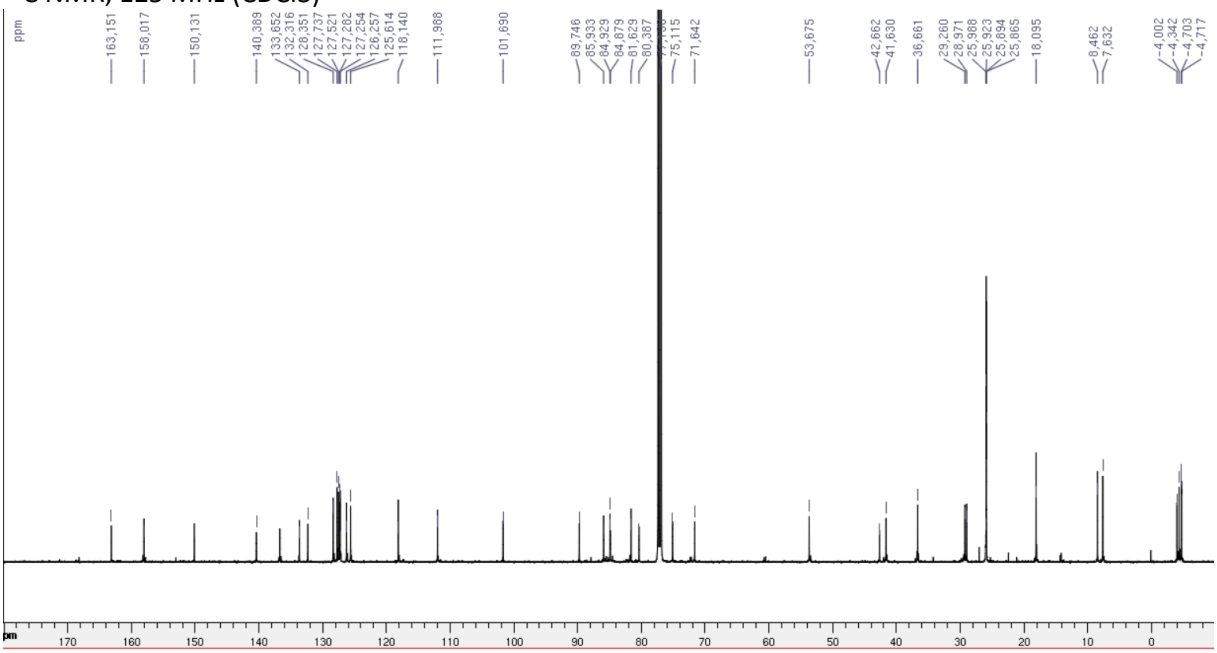
Compound 23f



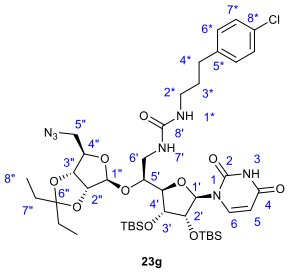
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

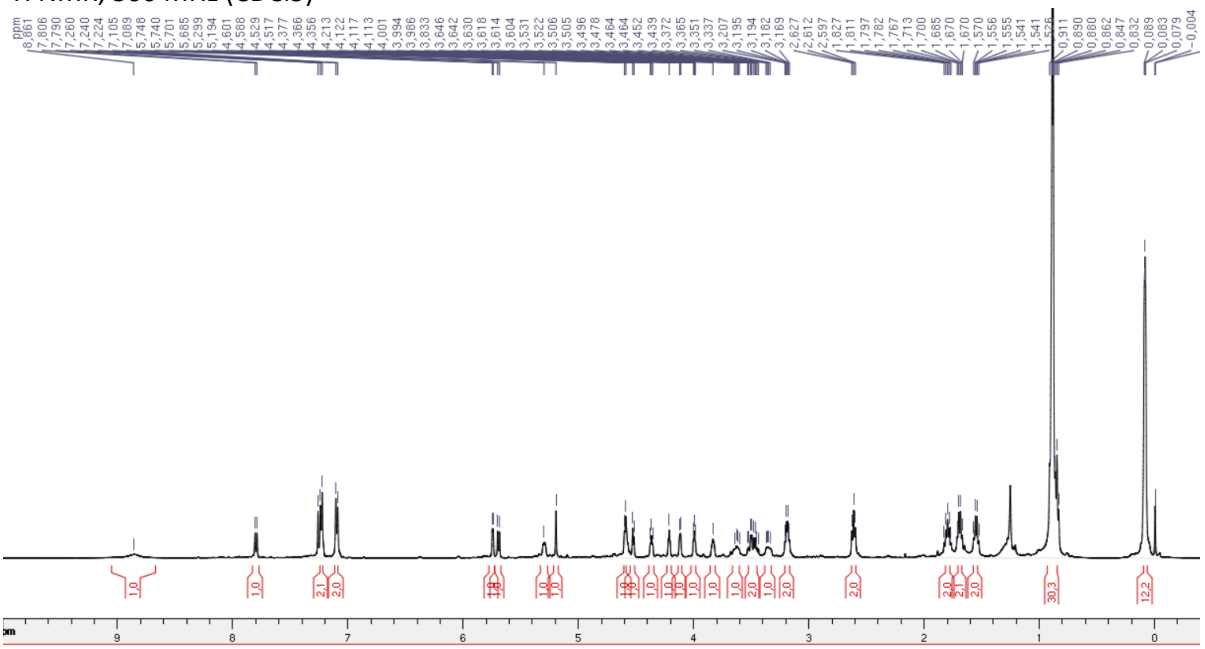


Compound 23g

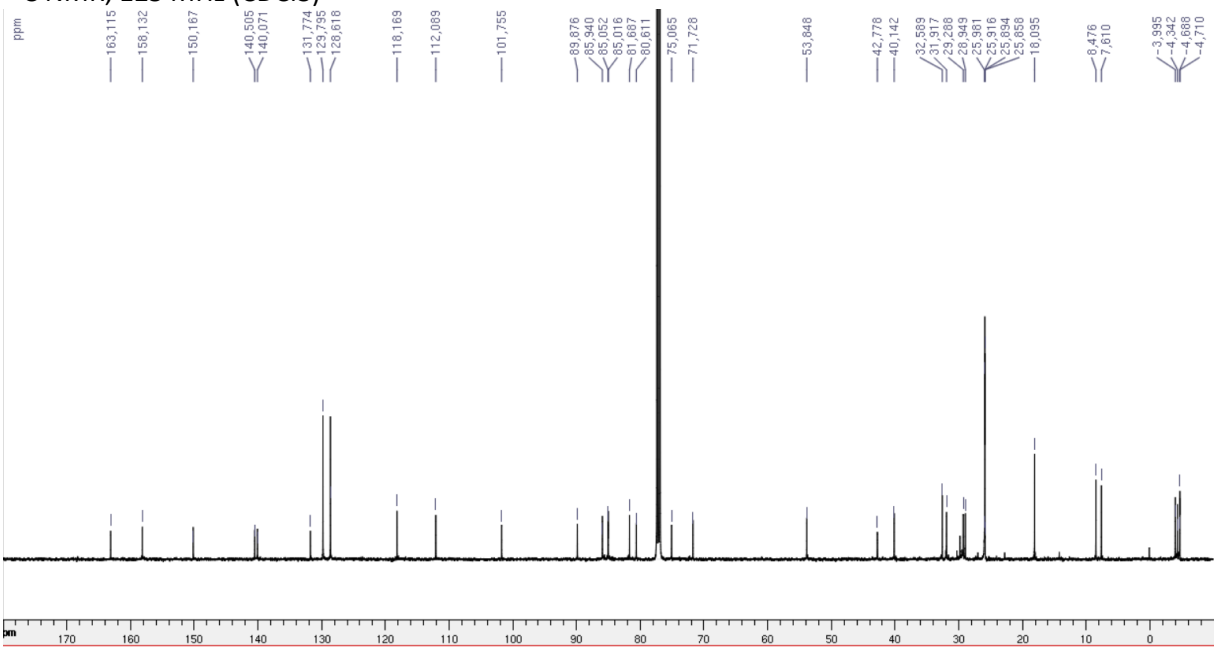


23g

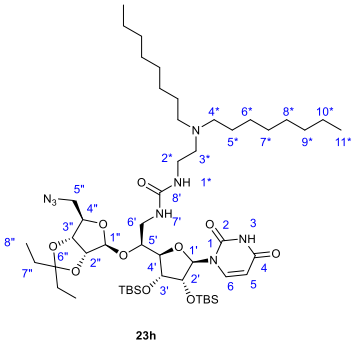
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

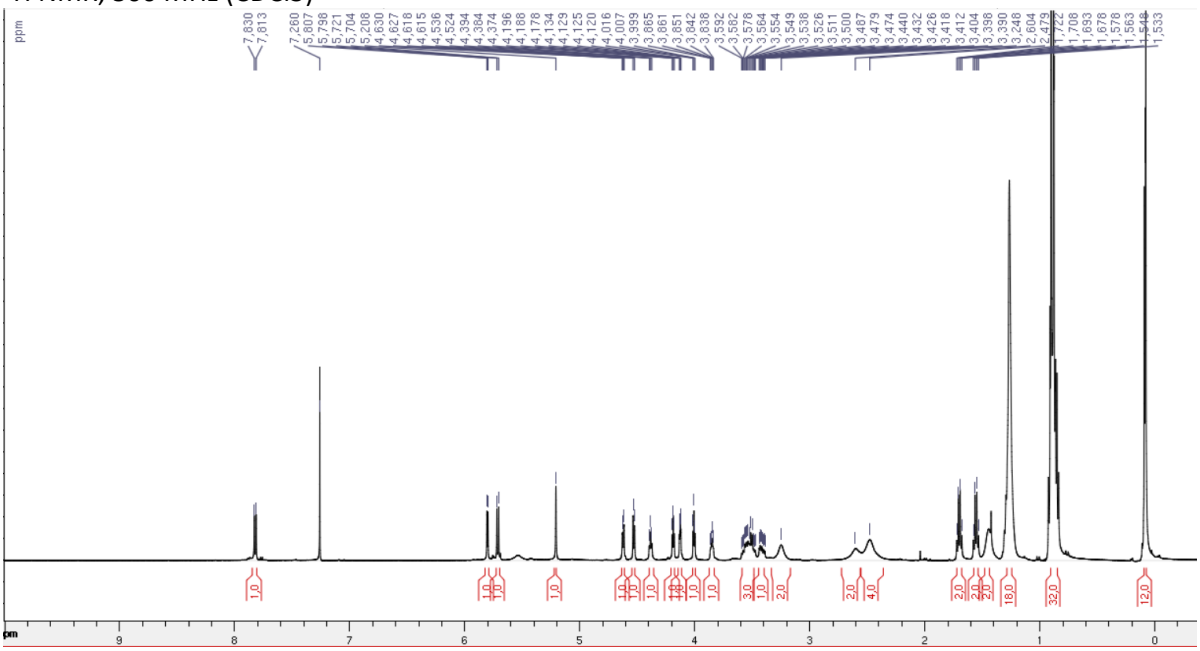


Compound 23h

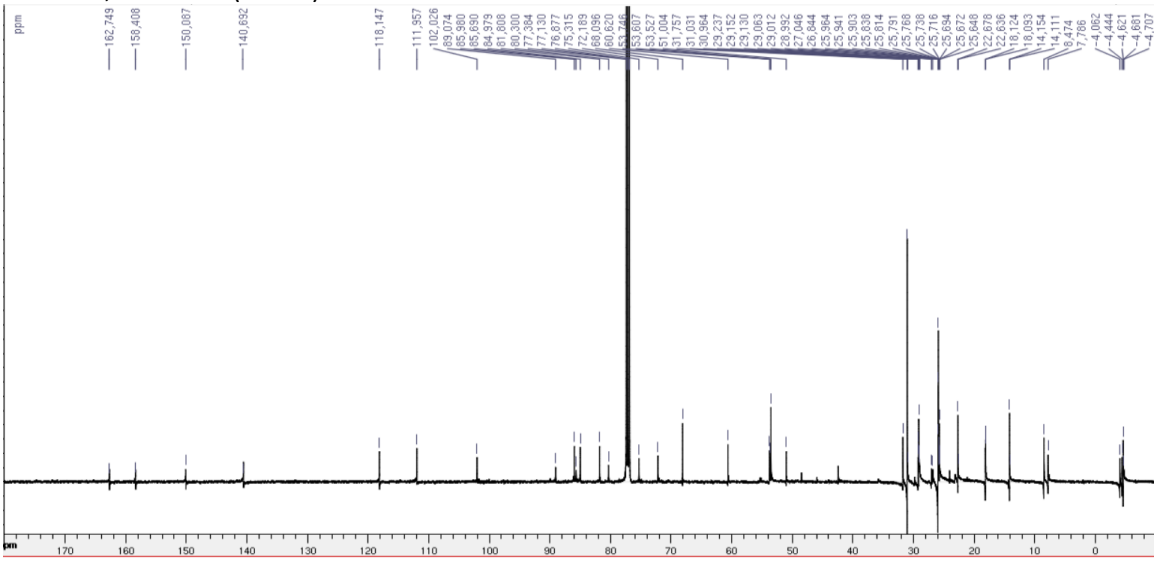


23h

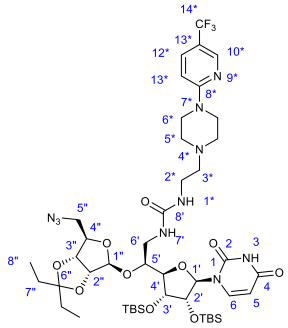
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

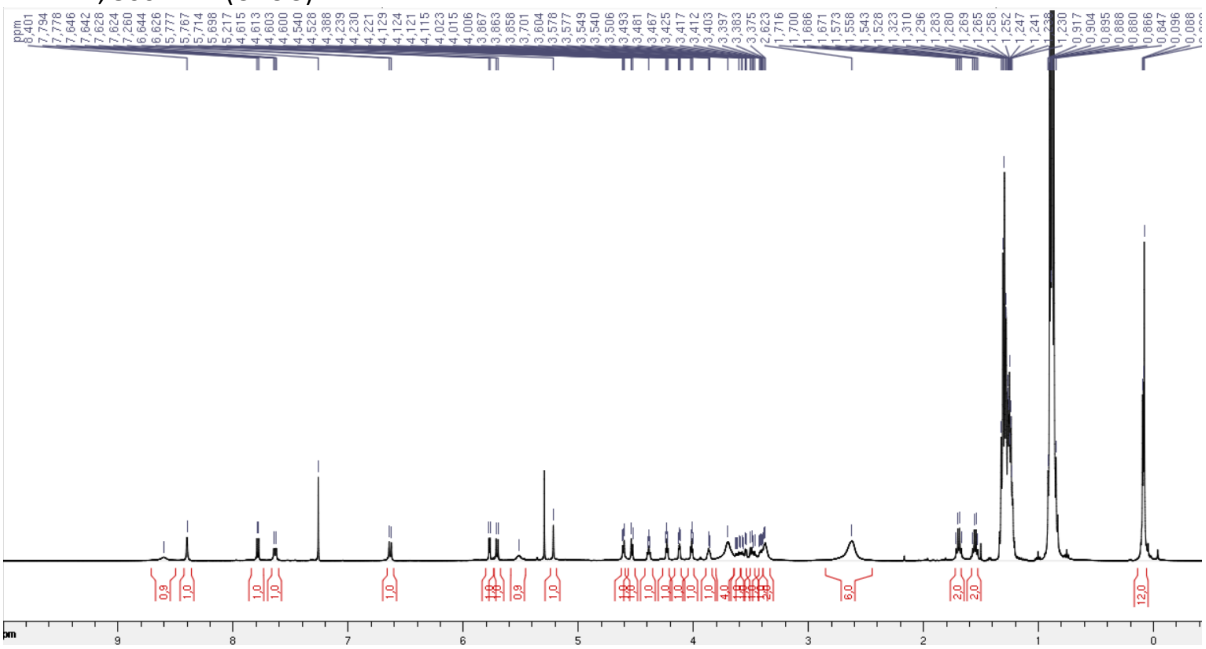


Compound 23i

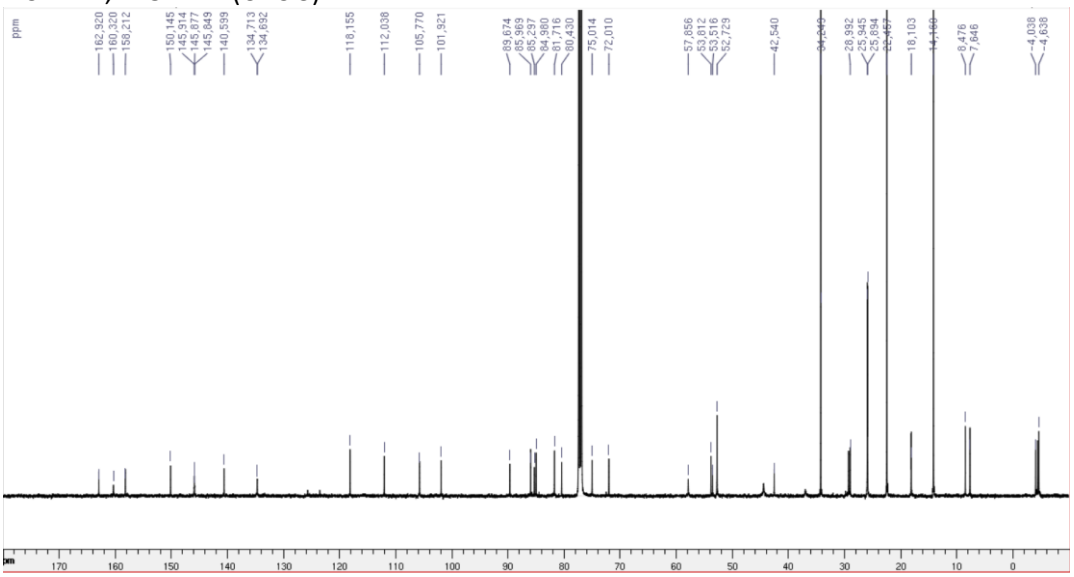


23i

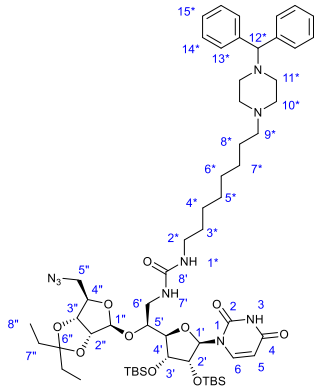
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

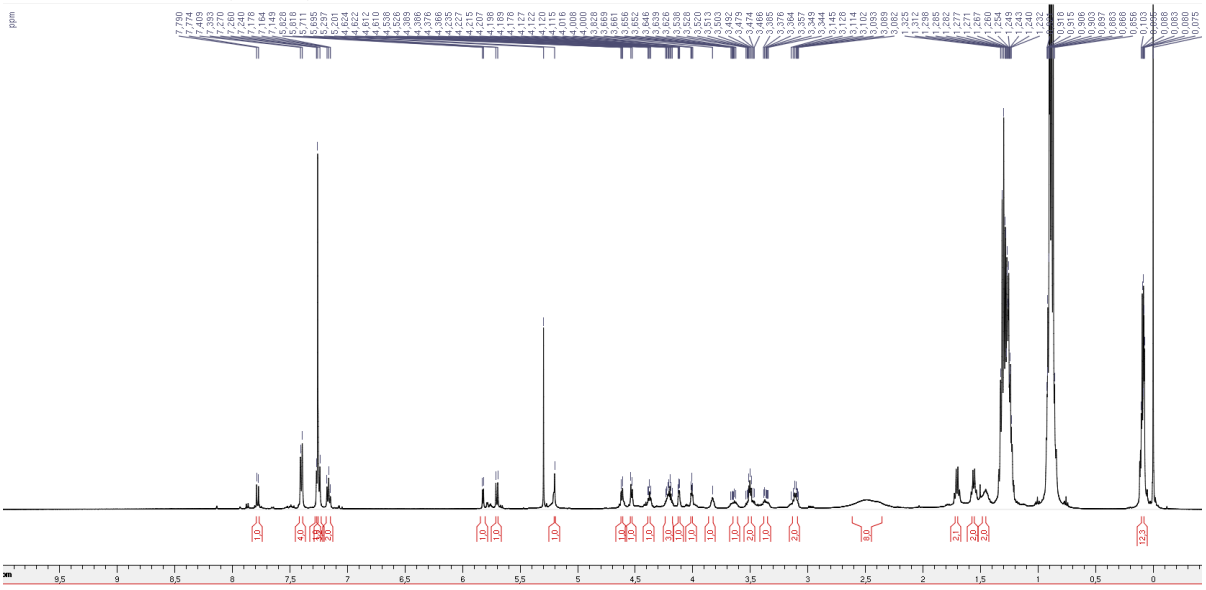


Compound 23j

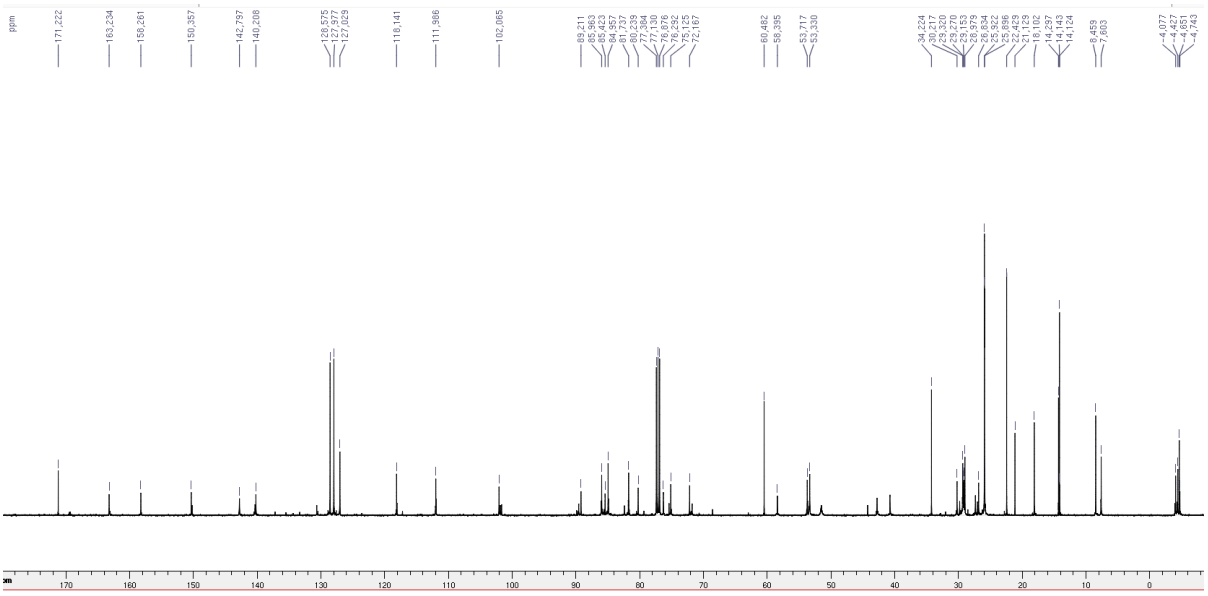


23j

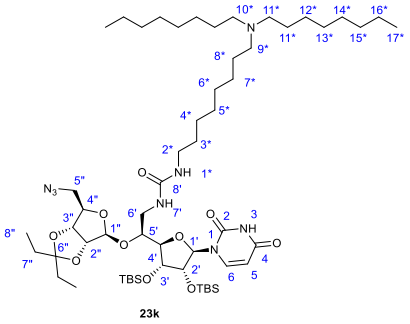
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

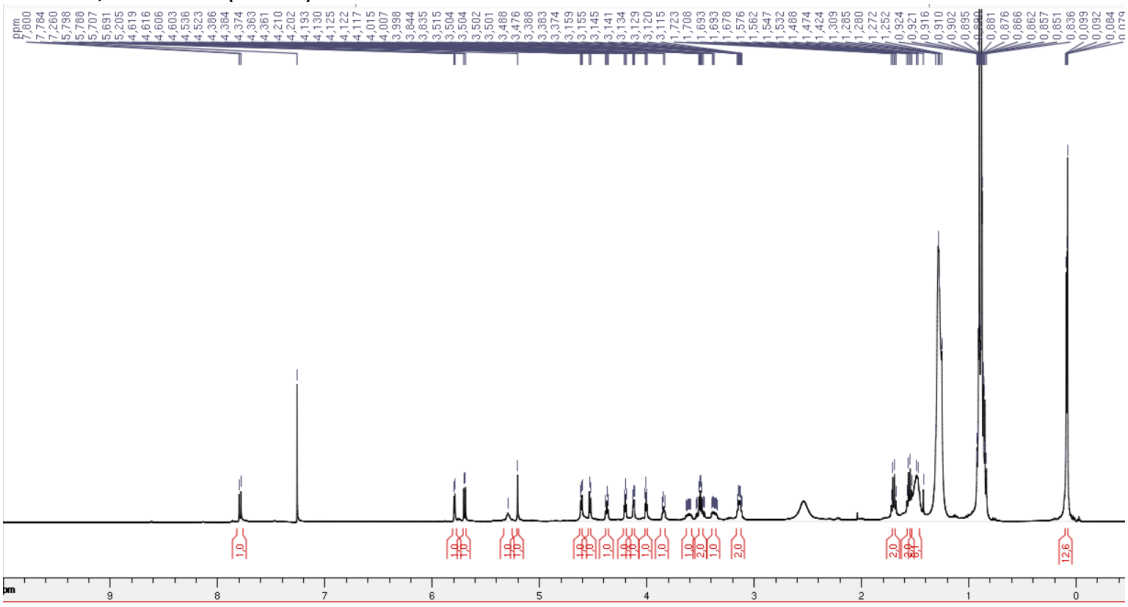


Compound 23k

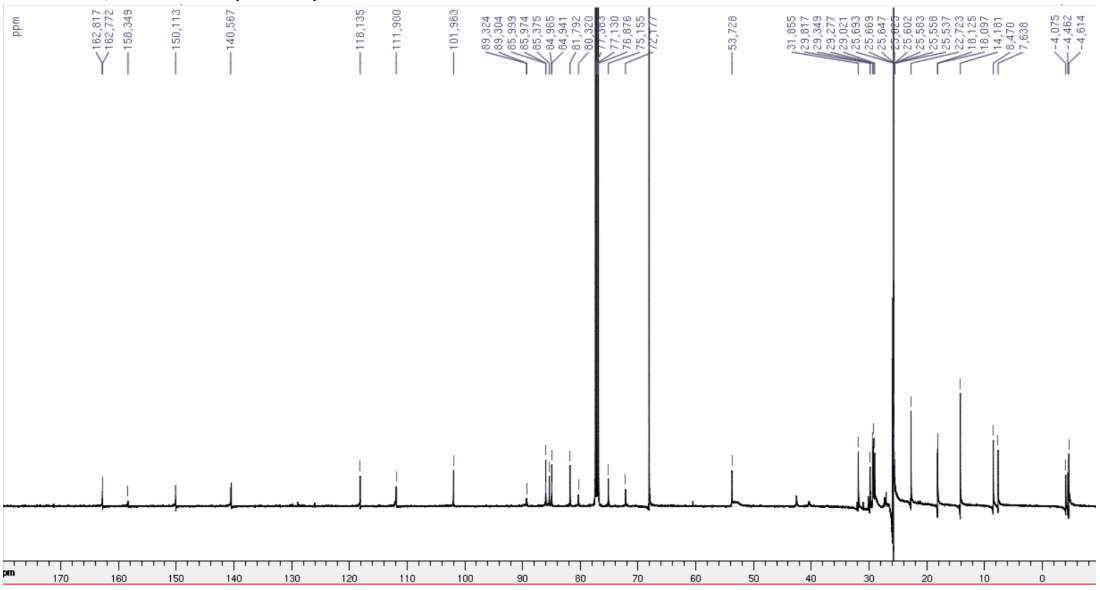


23k

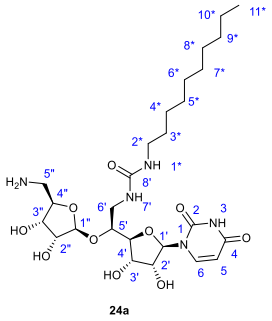
^{1}H NMR, 500 MHz (CDCl3)



^{13}C NMR, 125 MHz (CDCl3)

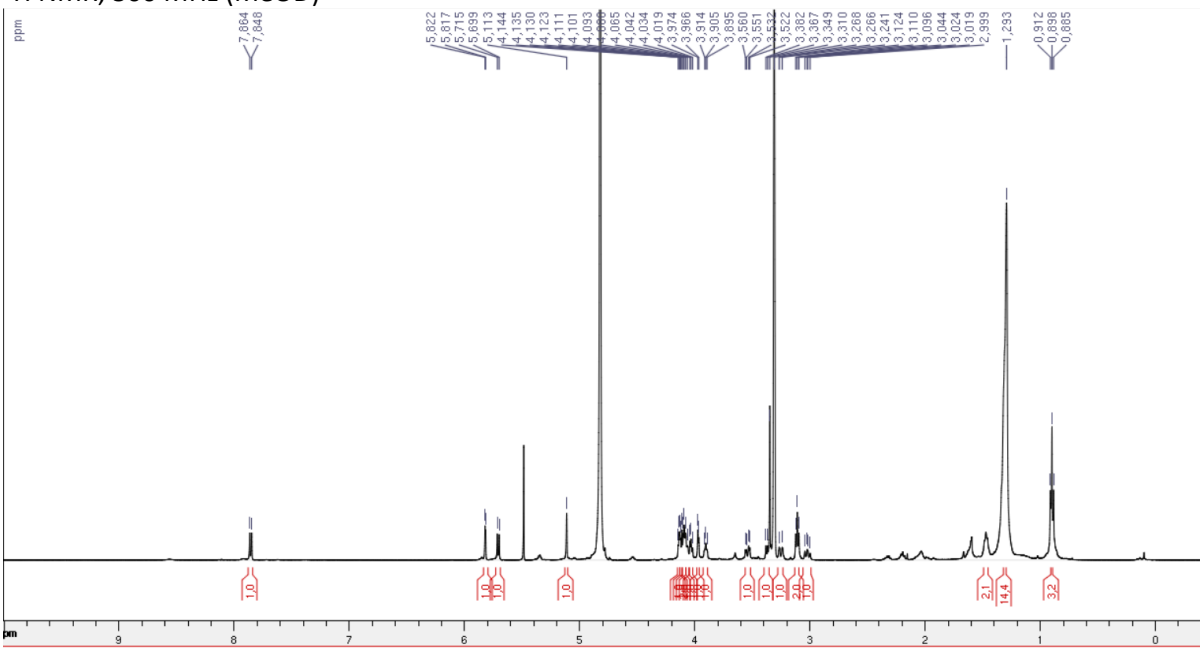


Compound 24a

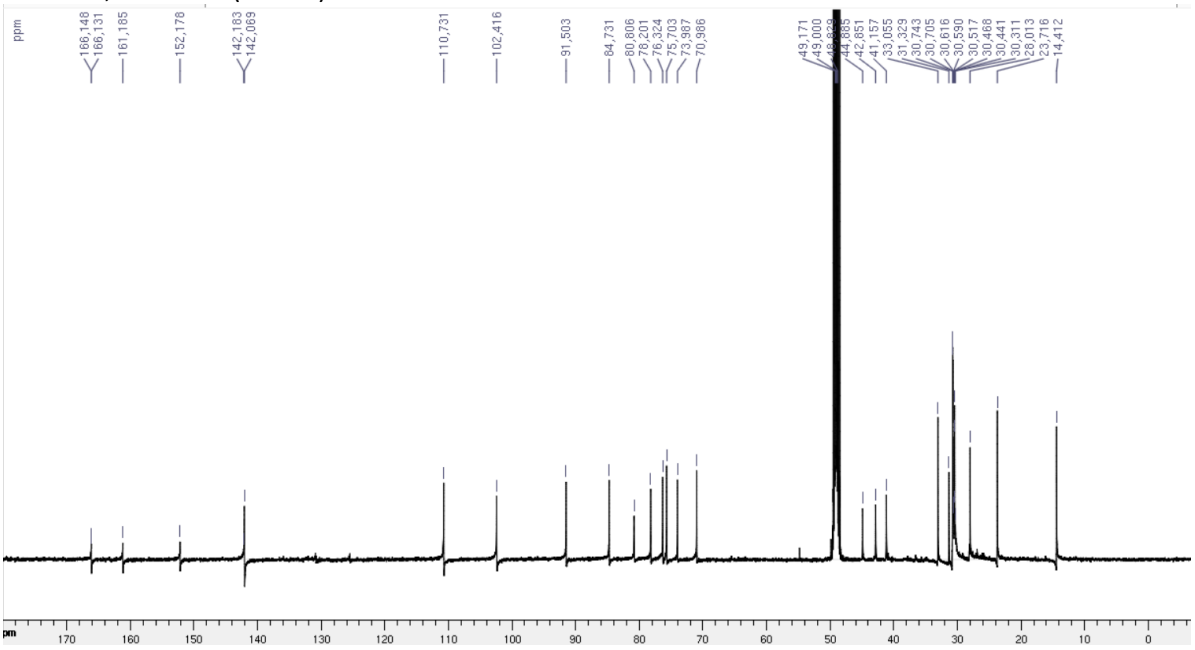


24a

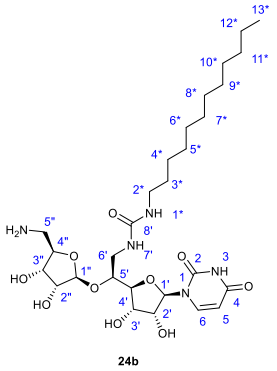
^{1}H NMR, 500 MHz (MeOD)



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

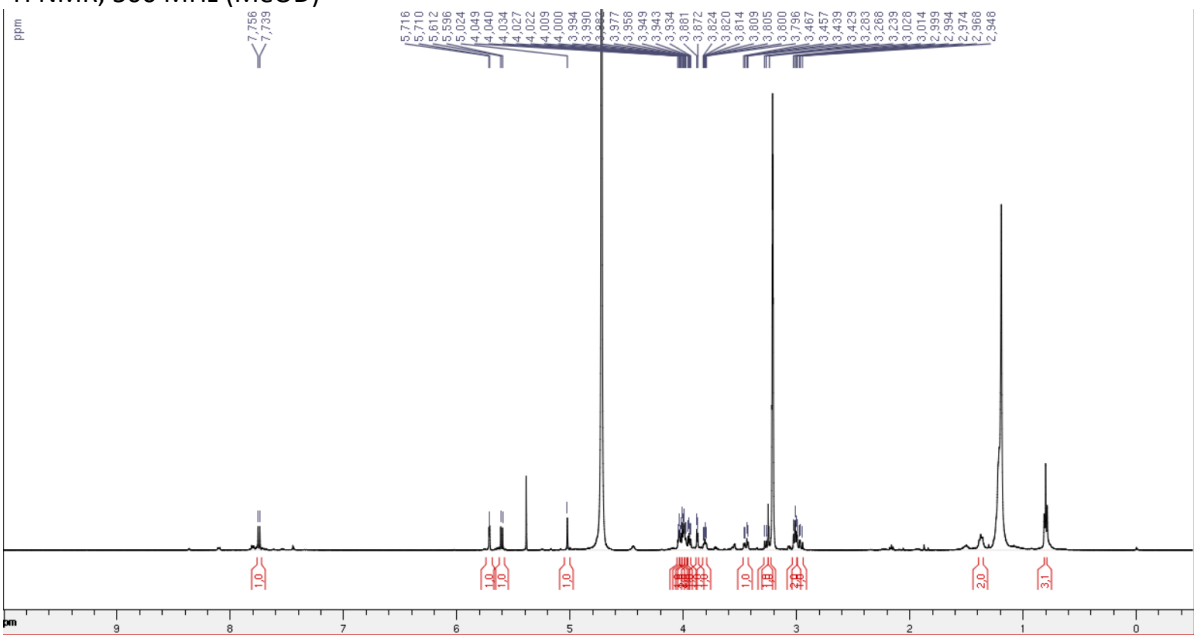


Compound 24b

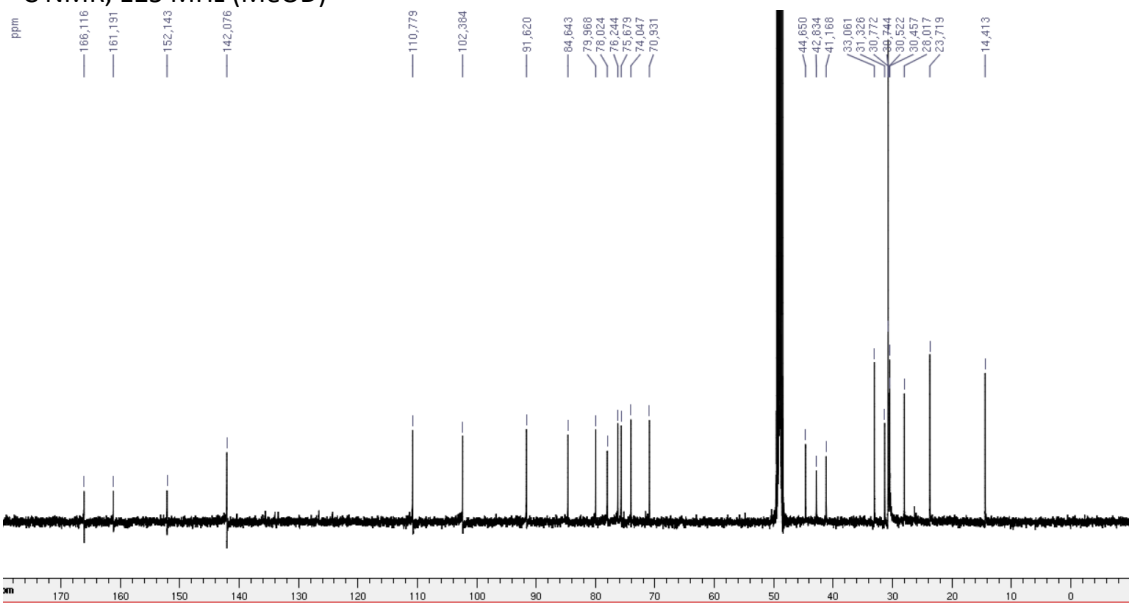


24b

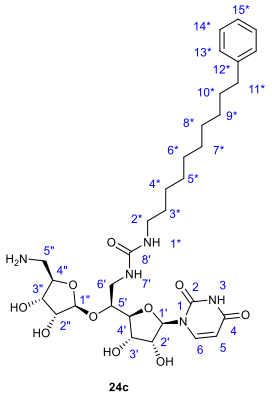
^{1}H NMR, 500 MHz (MeOD)



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

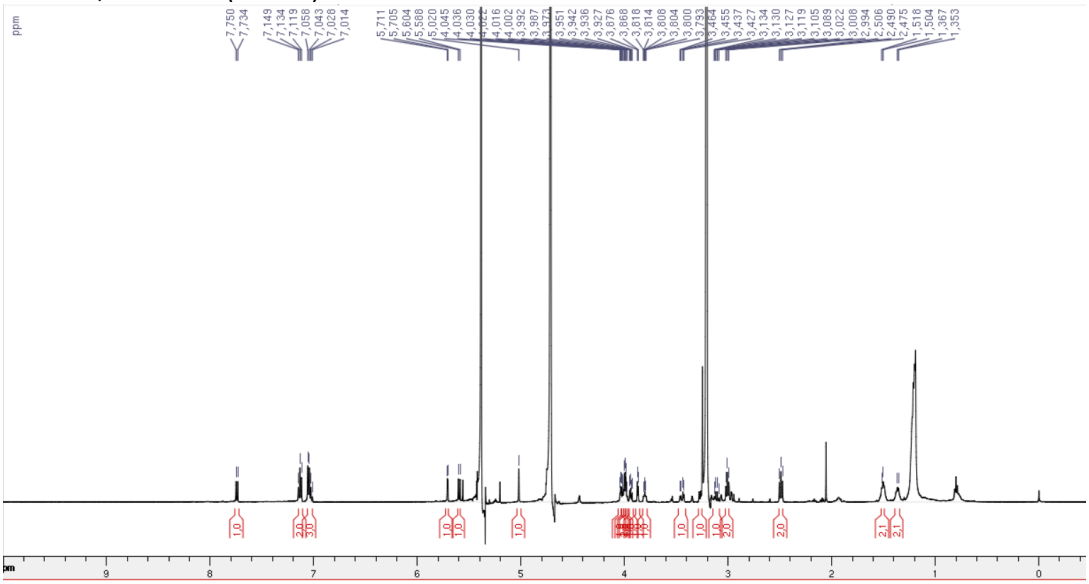


Compound 24c

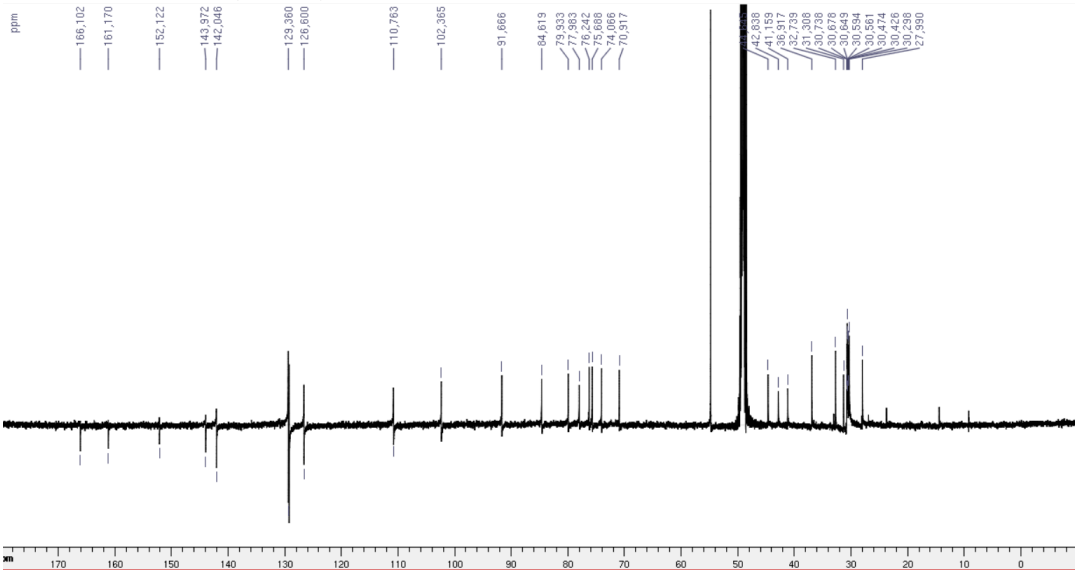


24c

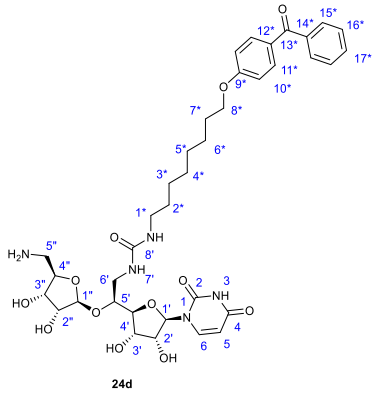
^{1}H NMR, 500 MHz (MeOD)



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

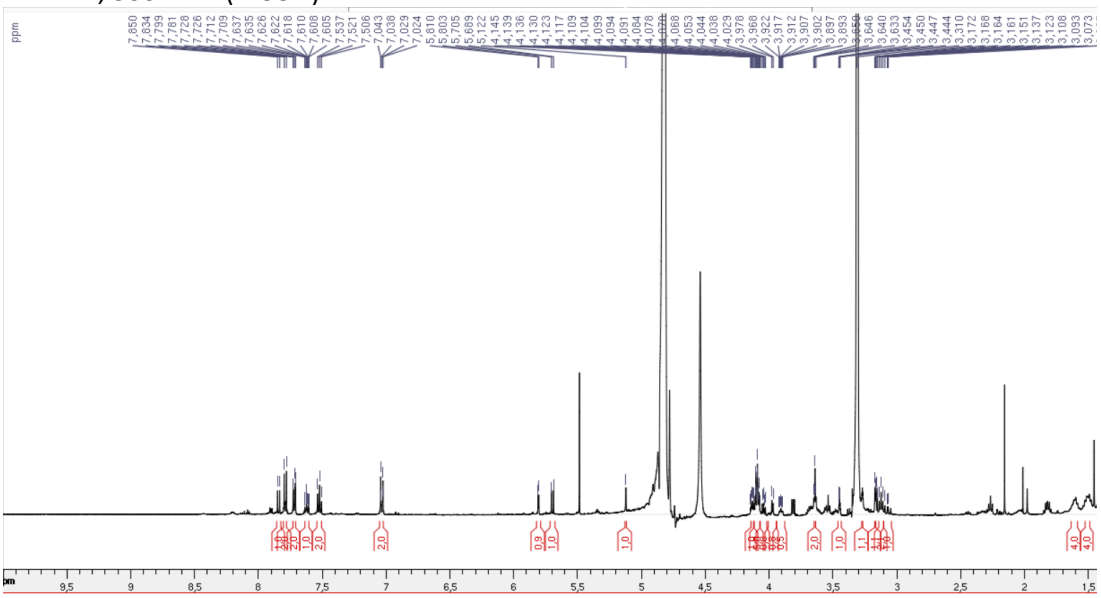


Compound 24d

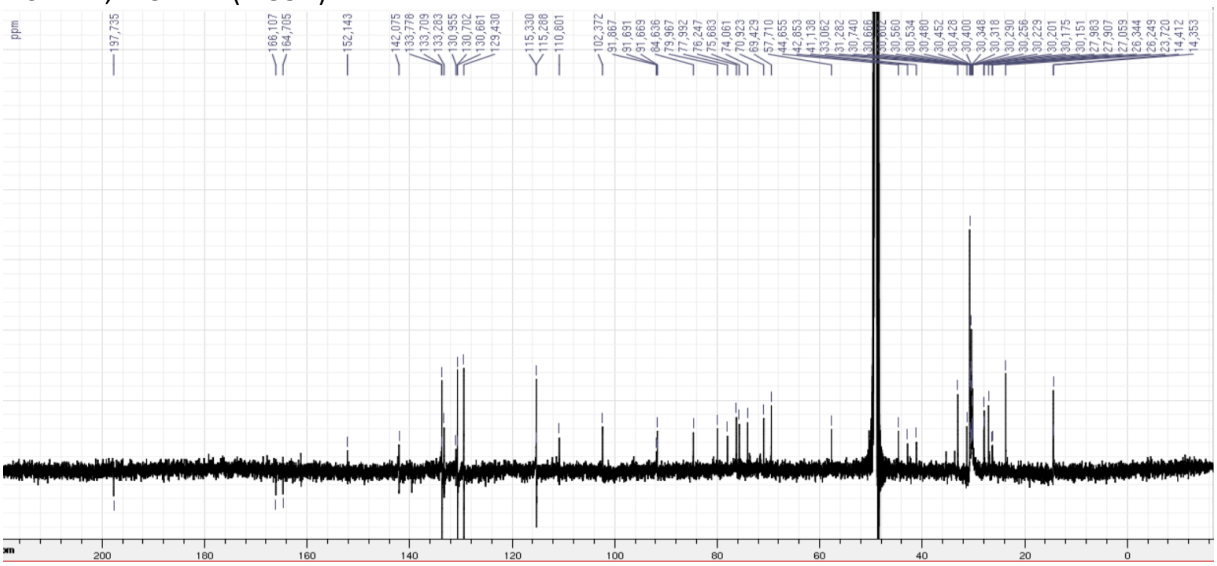


24d

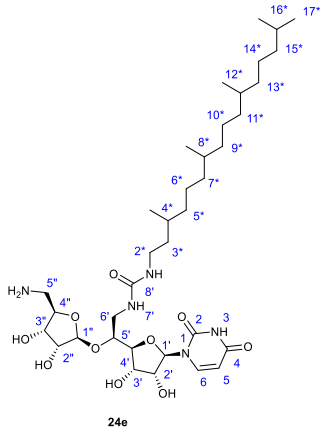
^{1}H NMR, 500 MHz (MeOD)



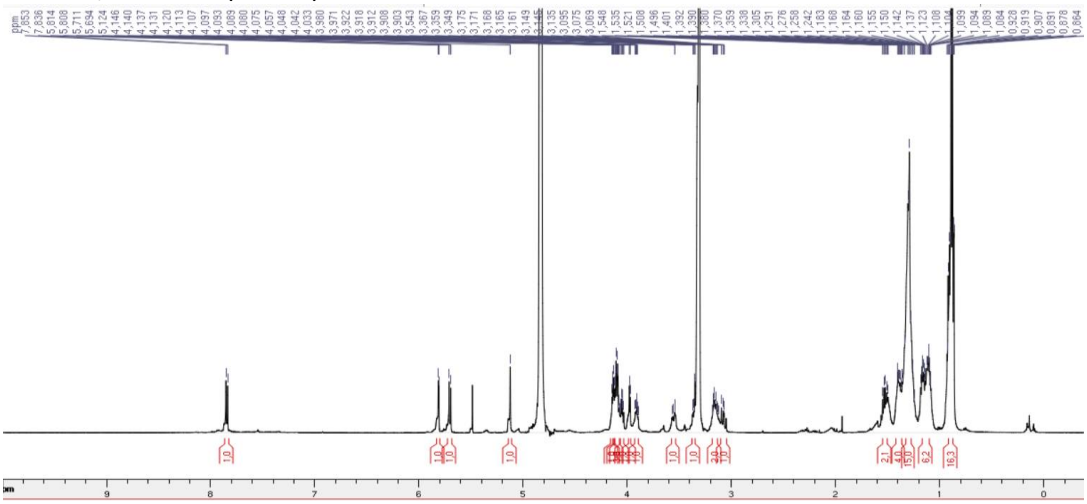
^{13}C NMR, 125 MHz (MeOD)



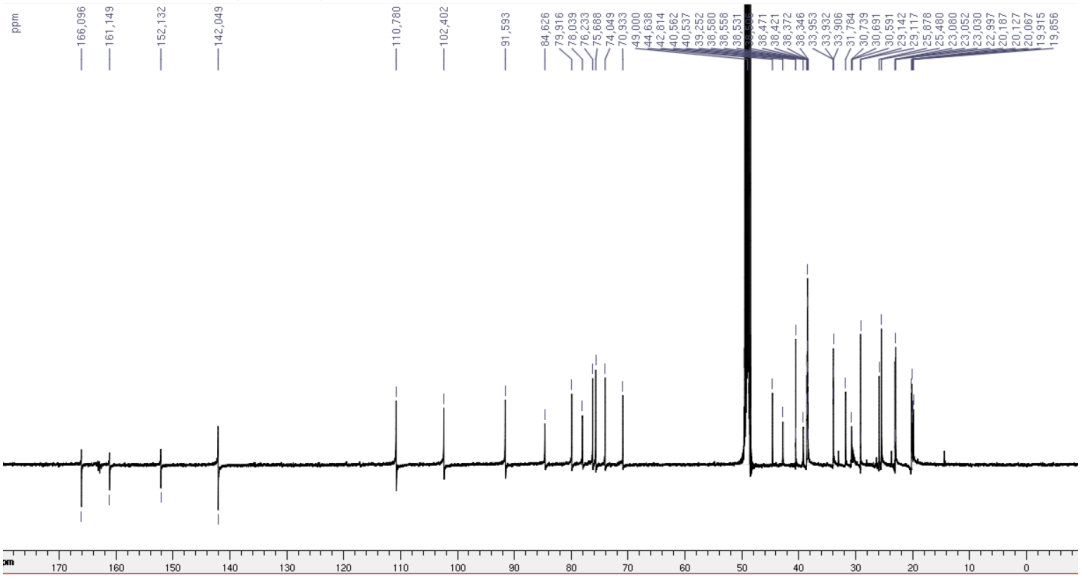
Compound 24e



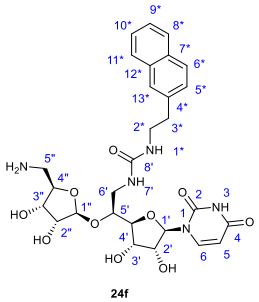
^{1}H NMR, 500 MHz (MeOD)



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

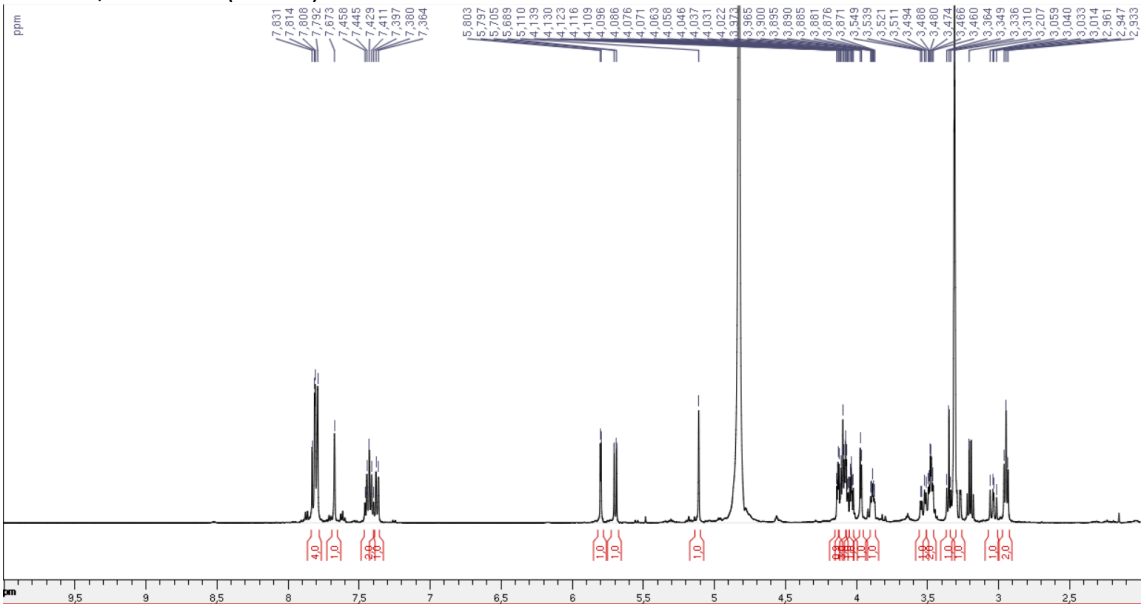


Compound 24f

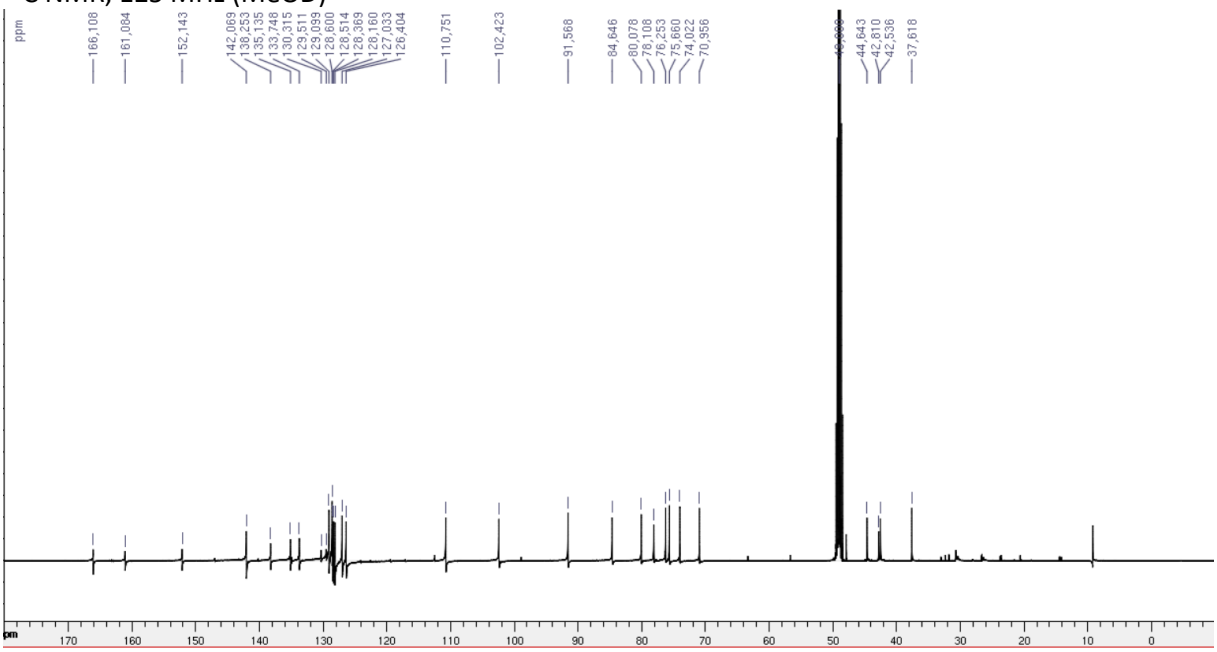


24f

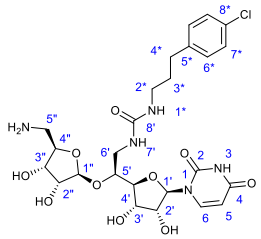
^{1}H NMR, 500 MHz (MeOD)



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

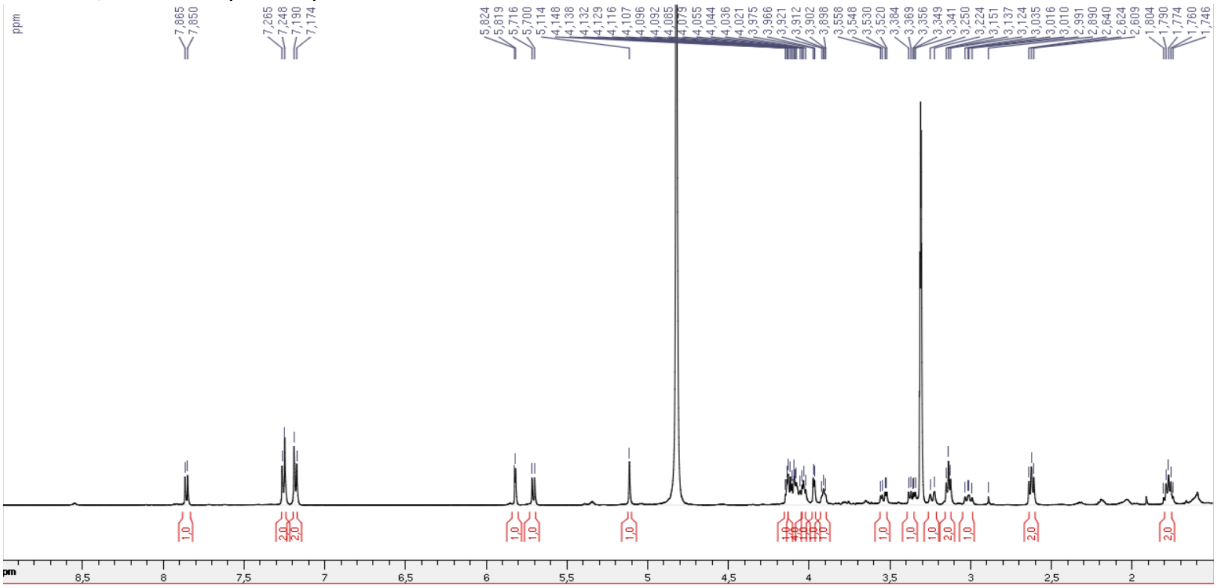


Compound 24g

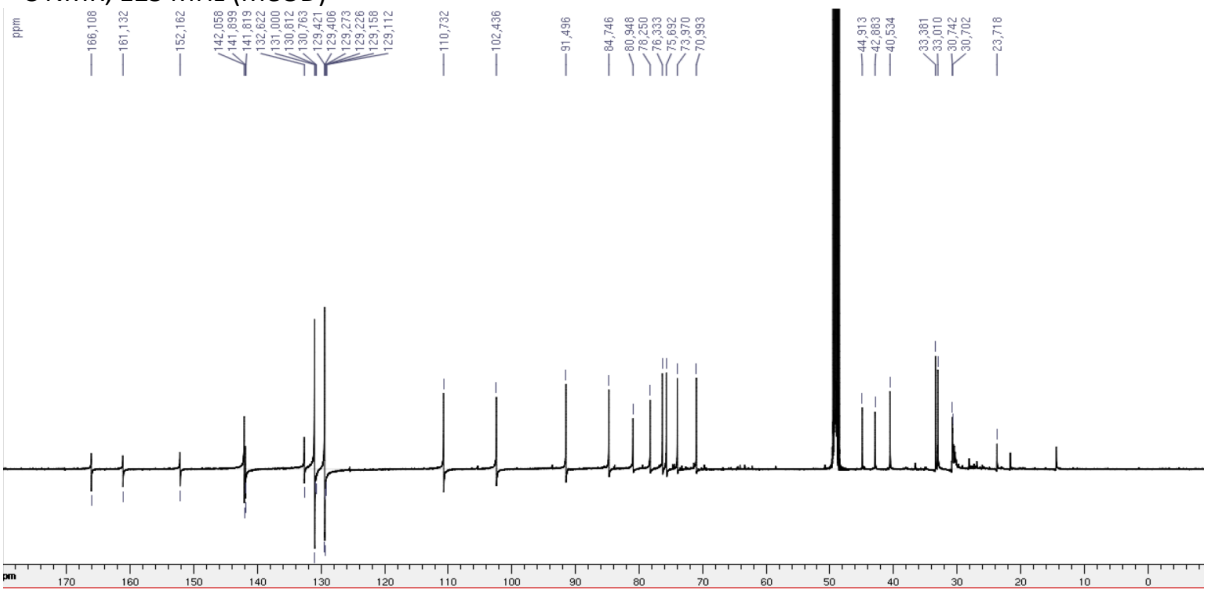


24g

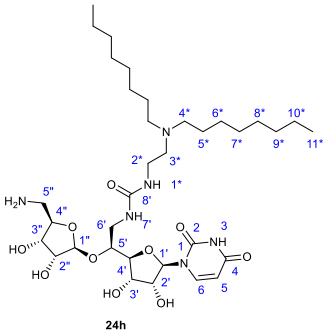
^{1}H NMR, 500 MHz (MeOD)



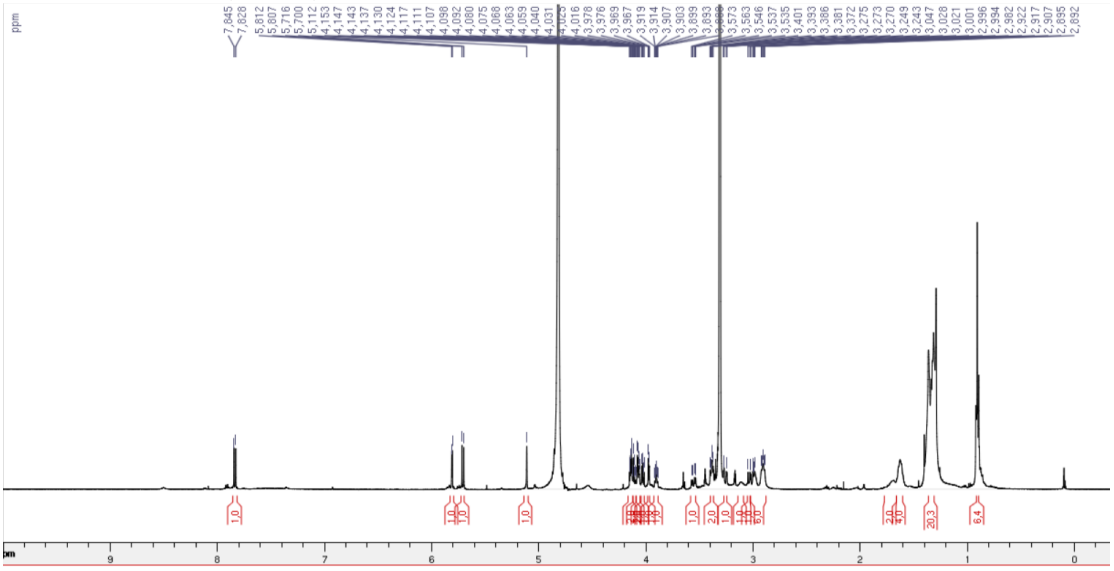
^{13}C NMR, 125 MHz (MeOD)



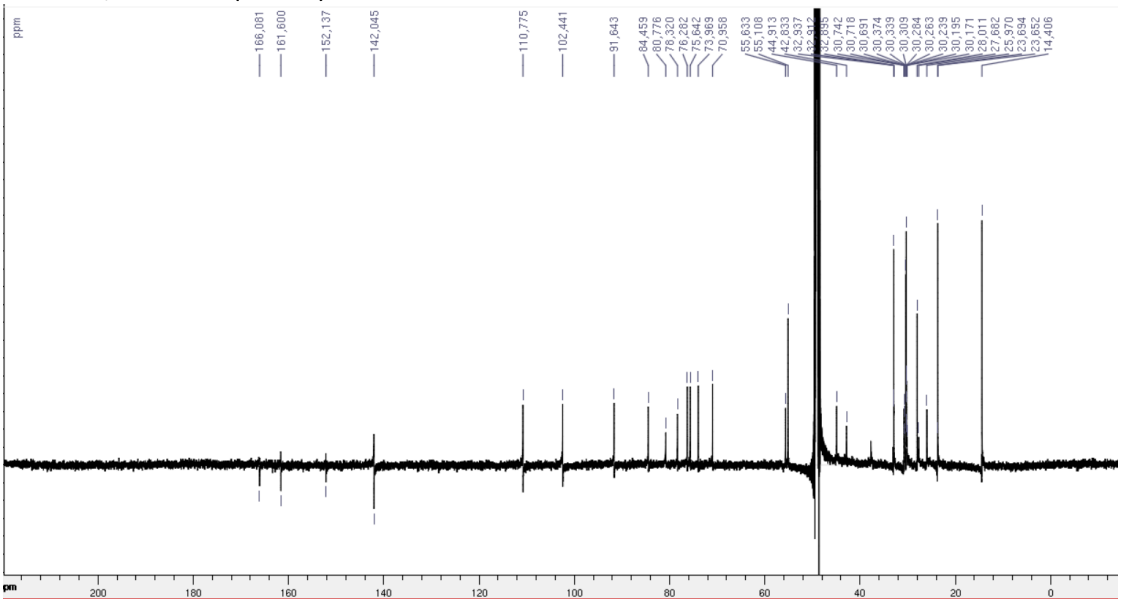
Compound 24h



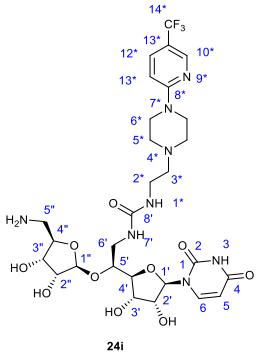
^{1}H NMR, 500 MHz (MeOD)



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

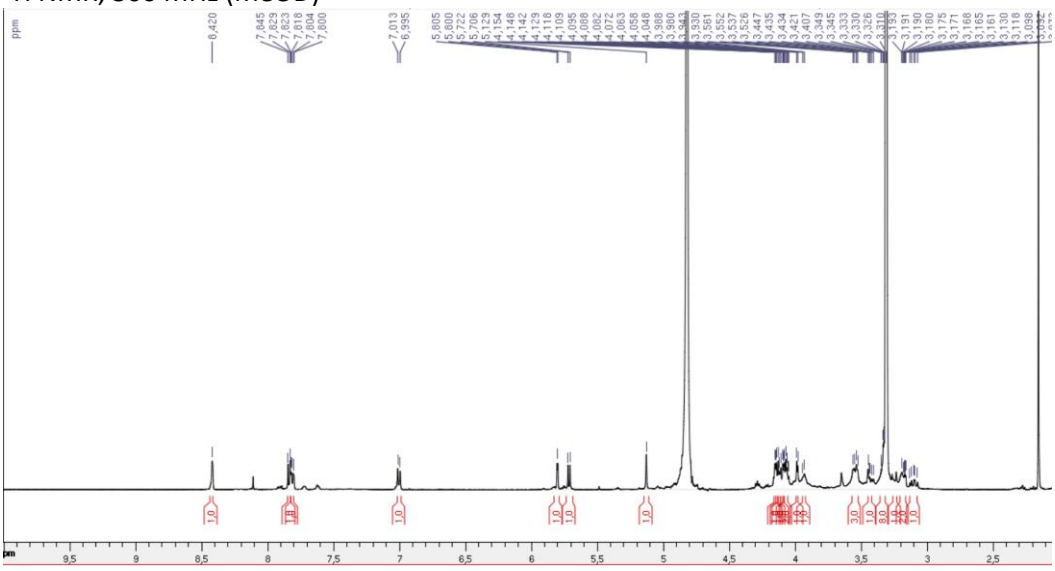


Compound 24i

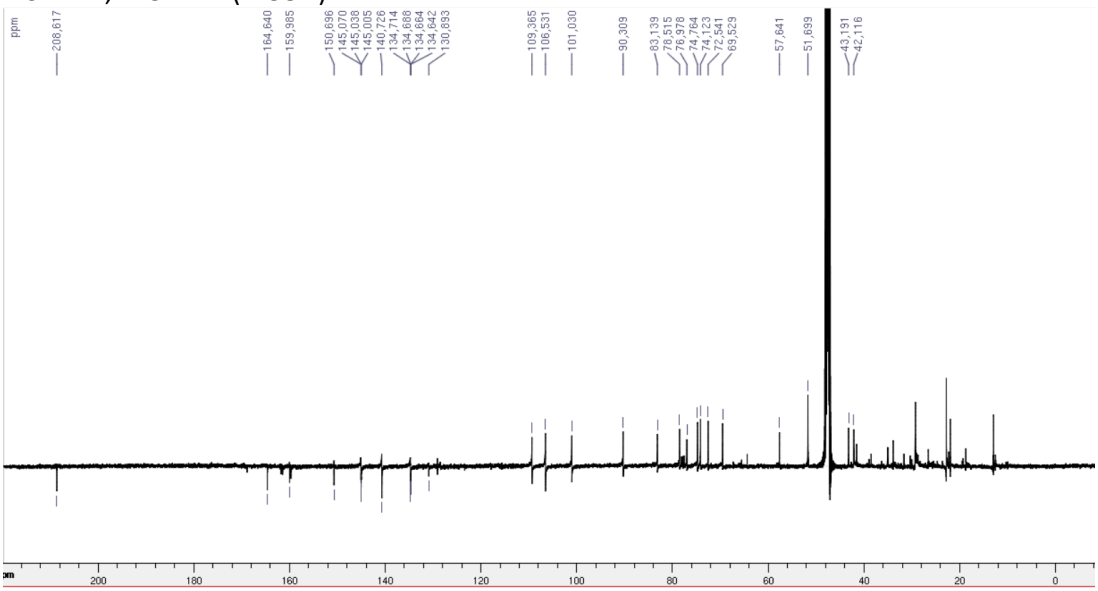


24i

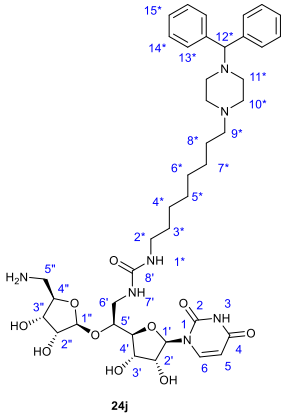
^{1}H NMR, 500 MHz (MeOD)



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

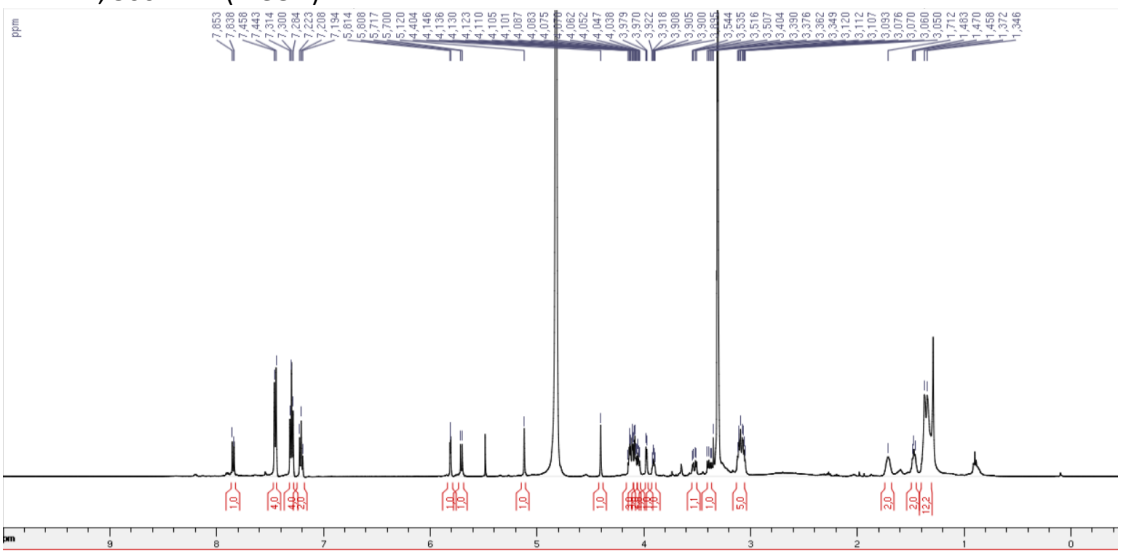


Compound 24j

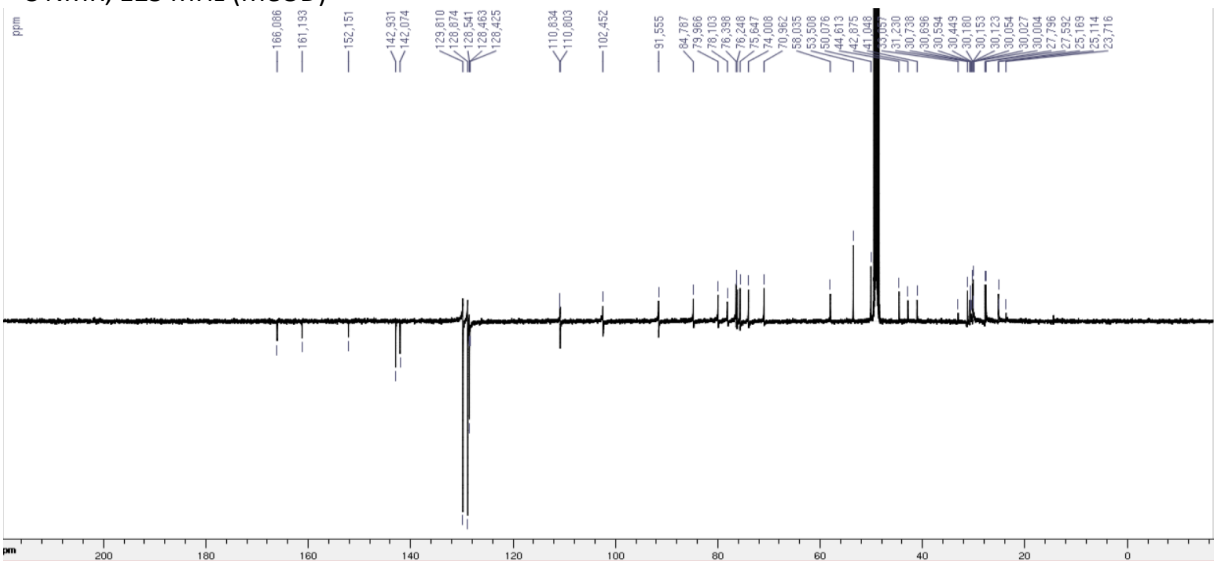


24j

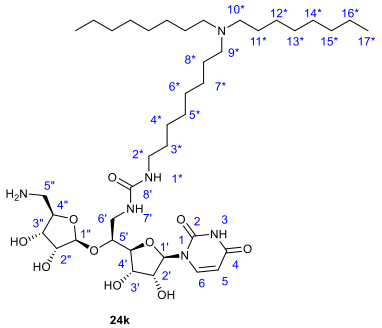
^{1}H NMR, 500 MHz (MeOD)



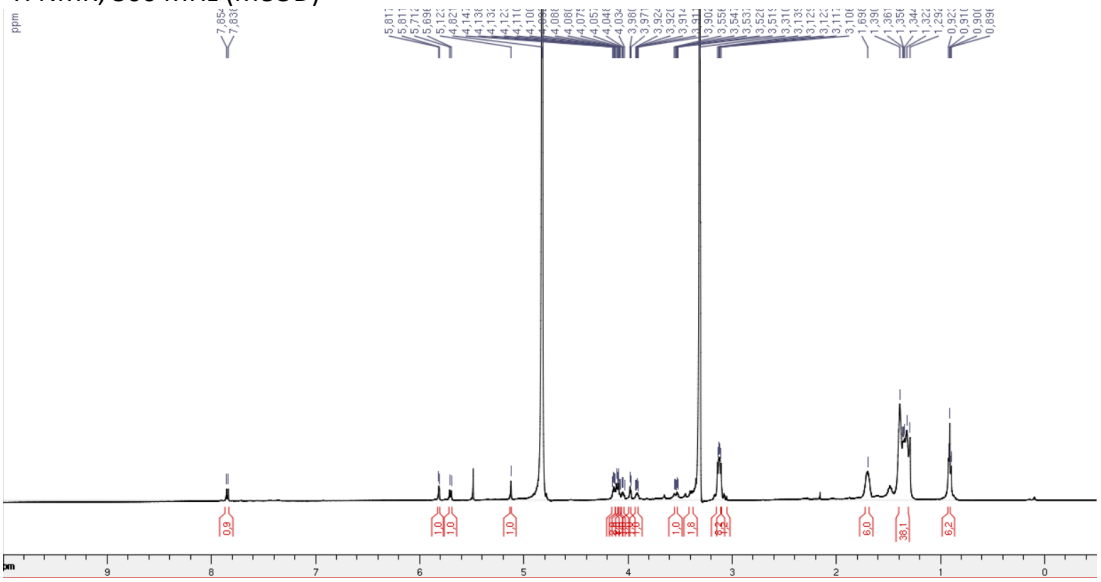
^{13}C NMR, 125 MHz (MeOD)



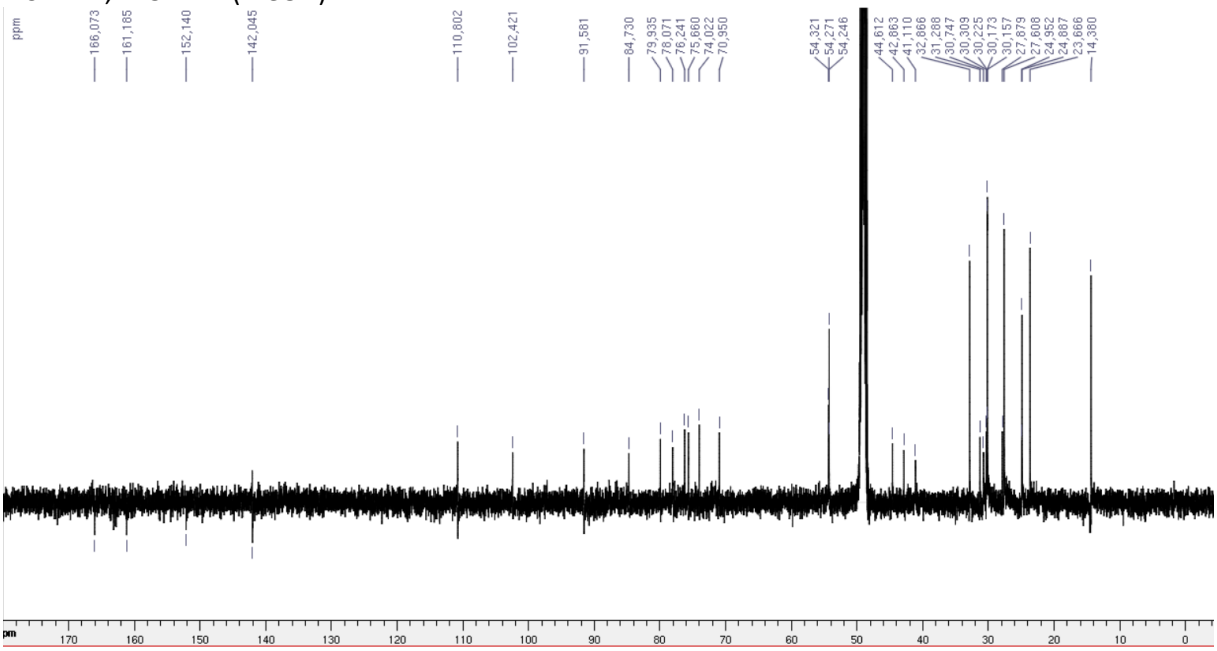
Compound 24k



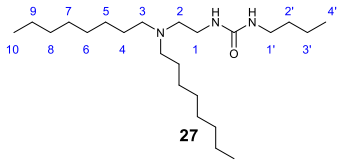
^{1}H NMR, 500 MHz (MeOD)



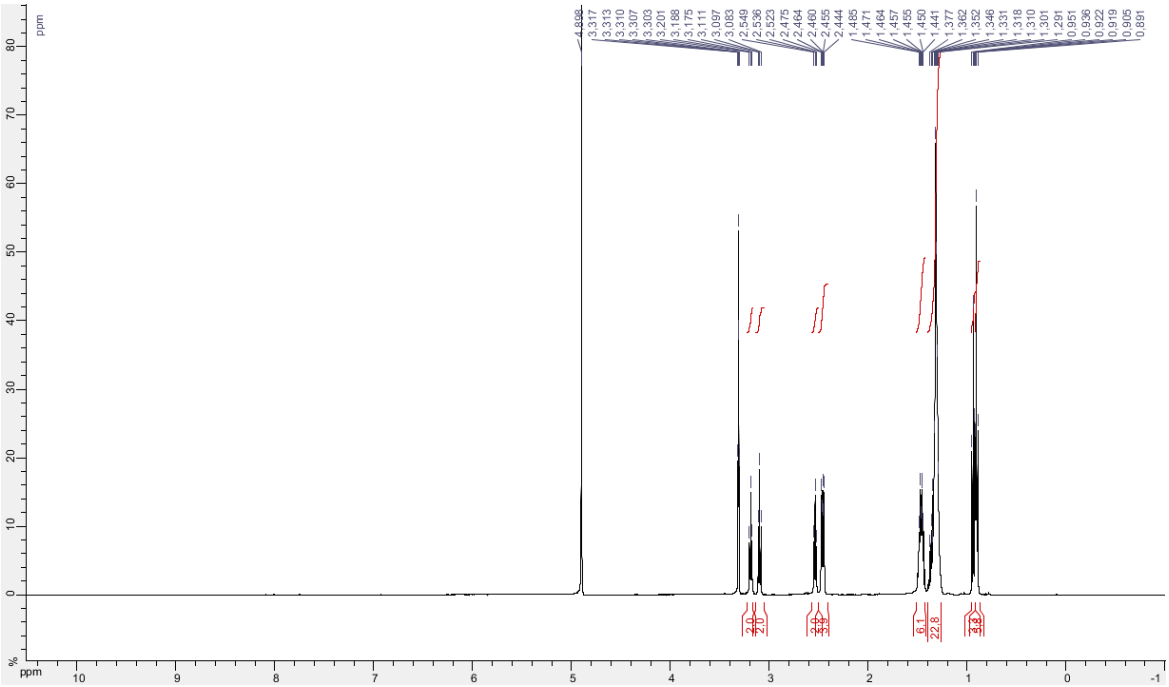
^{13}C NMR, 125 MHz (MeOD)



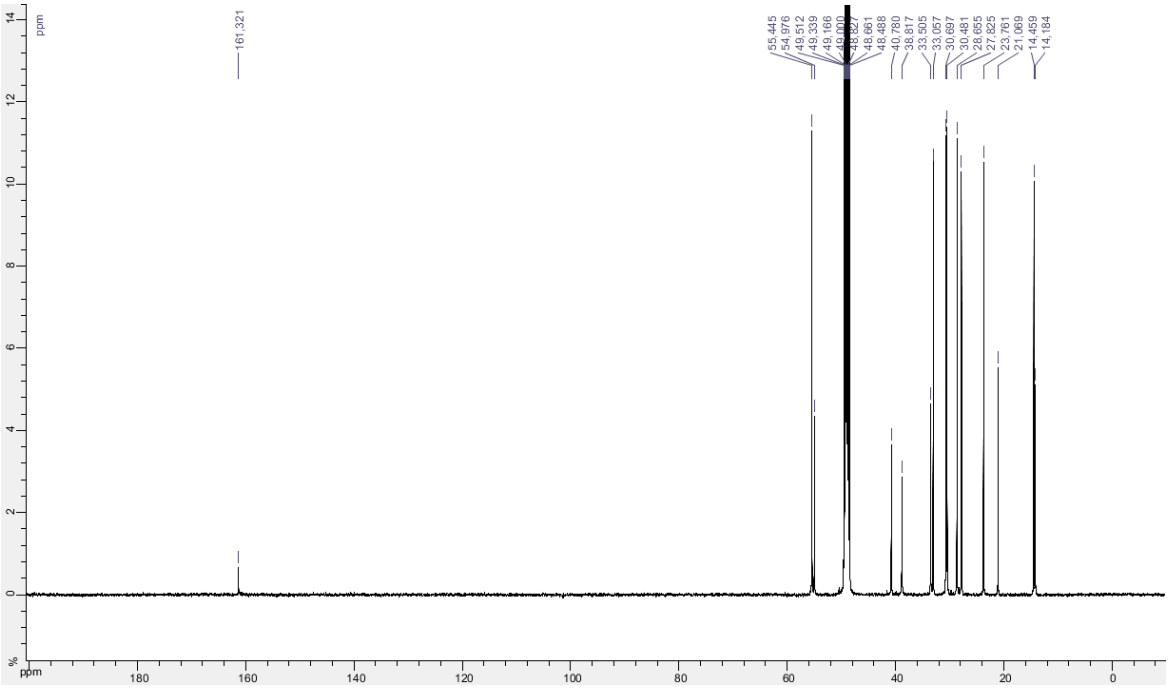
1-butyl-3-(2-(dioctylamino)ethyl)urea 27



^{1}H NMR, 500 MHz (MeOD)



^{13}C NMR, 500 MHz (MeOD)



^{1}H Spectra of compound 7

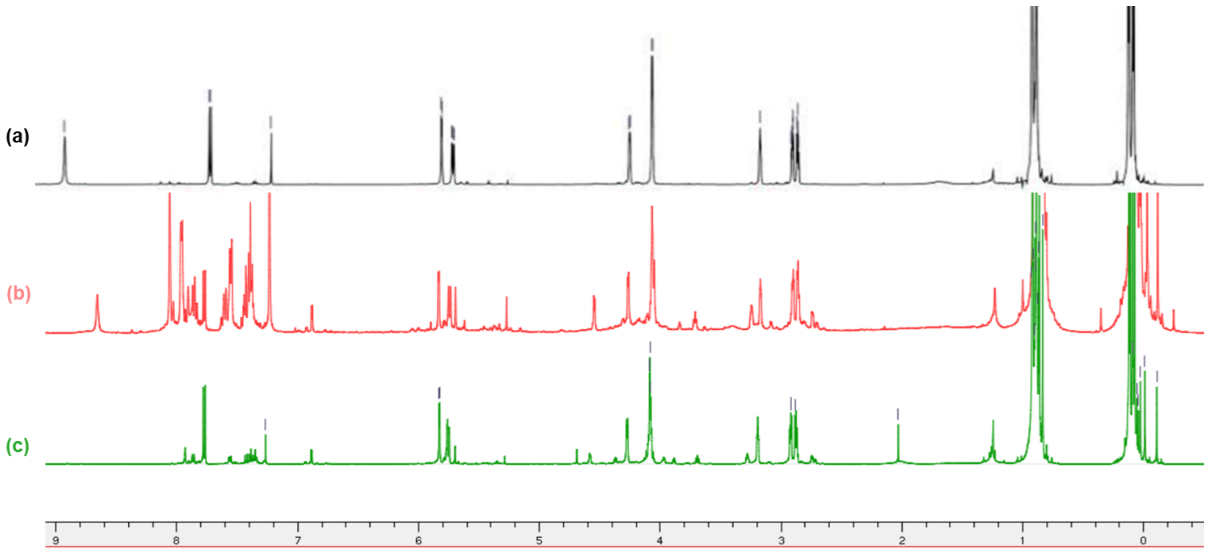


Fig. 2S Comparison of the 1H NMR spectra of the crude compound **7** according to the experimental conditions: (a) compound **6** (10 g), *m*CPBA, 4 equiv., CH_2Cl_2/Phosphate buffer pH7 : 2/1, 30 °C, 16 h; (b) compound **6** (10 g), *m*CPBA, 4 equiv., CH_2Cl_2, 30 °C, 16 h; (c) compound **6** (1 g), *m*CPBA, 4 equiv., CH_2Cl_2, 30 °C, 16 h