Supporting Information for

An Iterative Route To "Decorated" Ethylene Glycol-based Linkers

Genliang Lu, Sang Lam and Kevin Burgess*

Texas A & M University, Chemistry Department, P.O. Box 30012, College Station

Texas 77842, USA.

burgess@tamu.edu

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General Experimental

Unless otherwise indicated, all NMR data were collected at room temperature in $CDCl_3$ with internal $CHCl_3$ as the reference (δ 7.27 ppm for ^1H and 77.00 ppm for ^{13}C). MS were measured under ESI, MALDI or APCI conditions. Analytical thin-layer chromatography (TLC) was carried out on commercial Merck silica gel 60 plates, 0.25 μm thickness, with fluorescent indicator (F-254) or stained with aqueous $KMnO_4$ solution. Column chromatography was performed with 40-63 μm silica gel. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone; other solvents were used as received. Unless otherwise specified, all reactions were carried out under an atmosphere of dry nitrogen in oven-dried (at least 6 h at 140 ^oC) glassware.

2-(2-{2-[2-(4-Methylbenzenesulfonyl)ethoxy]ethoxy}ethyl)isoindole-1,3-dione (2). To a solution of 2-{2-[2-(2-hydroxyethoxy)ethoxy]ethyl}isoindole-1,3-dione[1] (12.00 g, 42.97 mmol), triethylamine (11.9 mL, 86.0 mmol) and trimethylamine hydrochloride (0.41 g, 4.30 mmol) in acetonitrile (100 mL) was added *p*-toluenesulfonyl chloride (12.29 g, 64.46 mmol) slowly at 0 °C under nitrogen. The mixture was stirred at 0 °C for 20 min and at room temperature for 40 min under nitrogen. The reaction mixture was poured into water, extracted with EtOAc and dried over Na_2SO_4. The crude product was purified by flash chromatography eluting with EtOAc/hexane (1 : 3) and EtOAc/hexane (1 : 1) to afford **2** (17.81 g, 96%) as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, J = 5.5, 3.0 Hz, 2 H), 7.78 (d, J = 7.0 Hz, 2 H), 7.71 (dd, J = 5.5, 3.0 Hz, 2 H), 7.33 (d, J = 7.5 Hz, 2 H), 4.09 (t, J = 4.8 Hz, 2 H), 3.87 (t, J = 5.8 Hz, 2 H), 3.69 (t, J = 6.0 Hz, 2 H), 3.62 (t, J = 4.8 Hz, 2 H), 3.58-3.56 (m, 2 H), 3.53-3.51 (m, 2 H), 2.44 (s, 3 H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 168.2, 144.7, 133.9, 132.9, 132.0, 129.8, 127.9, 123.2, 70.6, 70.0, 69.1, 68.6, 67.9, 37.2, 21.6; HRMS (ESI) calcd for $C_{21}H_{24}NO_7S$ $(M+H)^+$ 434.1273, found 434.1244.

General Procedure for the Synthesis of TEG Linkers 1, 6, 8 and 10. To a solution of tosylate (1.0 mmol) in acetonitrile was added sodium azide (3.0-5.0 mmol). The mixture was refluxed for 40-48 h under N_2. The suspension was cooled, diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated to yield TEG linkers as yellow oils.

2-{2-[2-(2-Azidoethoxy)ethoxy]ethyl}isoindoline-1,3-dione (1). Treatment of **2** (6.502 g, 15.00 mmol) and sodium azide (2.925 g, 45.00 mmol) in acetonitrile (35 mL) for 48 h afforded **1** (4.16 g, 91%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.5, 3.0 Hz, 2 H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2 H), 3.91 (t, *J* = 4.5 Hz, 2 H), 3.76 (t, *J* = 4.8 Hz, 2 H), 3.67-3.65 (m, 2 H), 3.63-3.61 (m, 4 H), 3.31 (t, *J* = 5.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 133.9, 132.1, 123.2, 70.6, 70.1, 70.0, 68.0, 50.6, 37.2; MS (APCI, m/z) 305 $(M+H)^+$; HRMS (ESI) calcd for $C_{14}H_{16}N_4O_4$ $(M+H)^+$ 305.1250, found 305.1239.

2-[2-(2-{2-[4-({2-[2-(2-Azidoethoxy)ethoxy]ethoxy}methyl)-1*H*-1,2,3-triazol-1-yl]ethoxy}ethoxy)ethyl]isoindoline-1,3-dione (6). Treatment of **5** (3.90 g, 6.0 mmol) and sodium azide (1.17 g, 18.0 mmol) in acetonitrile (40 mL) for 40 h afforded **6** (2.89 g, 93%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.0, 3.0 Hz, 2 H), 7.73 (s, 1 H), 7.73 (dd, *J* = 5.0, 3.0 Hz, 2 H), 4.69 (s, 2 H), 4.47 (t, *J* = 5.0 Hz, 2 H), 3.91 (t, *J* = 5.5 Hz, 2 H), 3.81 (t, *J* = 5.0 Hz, 2 H), 3.73 (t, *J* = 5.0 Hz, 2 H), 3.72-3.66 (m, 10 H), 3.63-3.61 (m, 2 H), 3.58-3.55 (m, 2 H), 3.38 (t, *J* = 5.0 Hz, 2 H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 168.2, 144.9, 140.0, 132.0, 123.8, 123.2, 70.63, 70.59, 70.57, 70.48, 70.0, 69.9, 69.6, 69.4, 68.0, 64.5, 50.6, 50.1, 37.2, several signals account for more than one carbon; MS (MALDI, m/z) 540 $(M+Na)^+$; HRMS (ESI) calcd for $C_{23}H_{32}N_7O_7$ $(M+H)^+$ 518.2363, found 518.2360.

2-(2-{2-[2-(4-{[2-(2-{2-[4-({2-[2-(2-Azidoethoxy)ethoxy]ethoxy}methyl)-1*H*-1,2,3-triazol-1-yl]ethoxy}ethoxy)ethoxy]methyl}-1*H*-1,2,3-triazol-1-yl)ethoxy]ethoxy}-ethyl)isoindoline-1,3-dione (8). Treatment of **7** (2.15 g, 2.50 mmol) and sodium azide (0.488 g, 7.5 mmol) in acetonitrile (13 mL) for 40 h afforded **8** (1.758 g, 96%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 5.5, 3.0 Hz, 2 H), 7.72 (s, 1 H), 7.70 (s, 1 H), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2 H), 4.65 (s, 4 H), 4.50 (t, *J* = 5.0 Hz, 2 H), 4.44 (t, *J* = 5.0 Hz, 2 H), 3.87 (t, *J* = 5.8 Hz, 2 H), 3.84 (t, *J* = 5.0 Hz, 2 H), 3.78 (t, *J* = 5.0 Hz, 2 H), 3.71-3.53 (m, 24 H), 3.36 (t, *J* = 5.3 Hz, 2 H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 144.8, 144.7, 134.0, 132.0, 123.76, 123.74, 123.2, 70.56, 70.52, 70.50, 70.43, 70.40, 70.37, 69.9, 69.8, 69.54, 69.49, 69.38, 69.36, 67.9, 64.5, 64.4, 50.6, 50.1, 50.0, 37.1, several signals account for more than one carbon; MS (MALDI, m/z) 731 $(M+Na)^+$; HRMS (ESI) calcd for $C_{32}H_{47}N_{10}O_{10}$ $(M+H)^+$ 731.3477, found 731.3481.

2-{2-[2-(2-{4-[(2-{2-[2-(4-{[2-(2-{2-[4-({2-[2-(2-Azidoethoxy)ethoxy]ethoxy}methyl)-1*H*-1,2,3-triazol-1-yl]ethoxy}ethoxy)ethoxy]methyl}-1*H*-1,2,3-triazol-1-yl)ethoxy]-ethoxy}ethoxy)methyl]-1*H*-1,2,3-triazol-1-yl}ethoxy)ethoxy]ethyl}isoindoline-1,3-dione (10). Treatment of **9** (0.215 g, 0.20 mmol) and sodium azide (0.065 g, 1.0 mmol) in acetonitrile (4 mL) for 40 h afforded **10** (0.145 g, 77%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 5.5, 3.0 Hz, 2 H), 7.72-7.69 (m, 5 H), 4.64 (s, 4 H), 4.63 (s, 2 H), 4.50 (t, *J* = 5.0 Hz, 4 H), 4.44 (t, *J* = 5.0 Hz, 2 H), 3.87 (t, *J* = 5.8 Hz, 2 H), 3.84 (t,

J = 5.0 Hz, 4 H), 3.78 (t, *J* = 5.0 Hz, 2 H), 3.71-3.51 (m, 32 H), 3.36 (t, *J* = 5.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 144.8, 144.7, 134.0, 132.0, 128.5, 125.9, 123.82, 123.79, 123.2, 70.61, 70.57, 70.55, 70.48, 70.46, 70.42, 70.0, 69.9, 69.6, 69.5, 69.42, 69.41, 68.0, 64.5, 64.44, 64.43, 50.6, 50.15, 50.12, 37.1, several signals account for more than one carbon; HRMS (ESI) calcd for $C_{41}H_{62}N_{13}O_{13}$ $(M+H)^+$ 944.4584, found 944.4586.

2-{2-[2-(Prop-2-ynyloxy)ethoxy]ethoxy}ethanol (4)[2]. To a solution of triethylene glycol (15.02 g, 100 mmol) in distilled THF (75 mL) at 0 ^{o}C under nitrogen was added sodium hydride (2.60 g, 65 mmol, 60%) slowly. The mixture was stirred at 0 ^{o}C for 30 min under nitrogen. Propargyl bromide (5.40 mL, 7.44 g, 50 mmol) was injected slowly to the reaction flask. The mixture was stirred at 0 ^{o}C for 2 h and at 25 °C for 20 h. The mixture was poured into water, extracted with CH_2Cl_2 and dried over Na_2SO_4. The crude product was purified by flash chromatography eluting with EtOAc/hexane (3 : 2) to afford **4** as a yellow oil (7.102 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.19 (d, *J* = 2.5 Hz, 2H), 3.71 (t, *J* = 6.0 Hz, 2H), 3.60-3.70 (m, 8H), 3.59 (t, *J* = 5.5 Hz, 2H), 2.61 (s, 1H), 2.43 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 79.5, 74.6, 72.4, 70.5, 70.3, 70.2, 69.0, 61.6, 58.3.

2-{2-[2-(Prop-2-ynyloxy)ethoxy]ethoxy}ethyl 4-methylbenzenesulfonate (3). To a solution of **4** (10.28 g, 54.62 mmol), triethylamine (19.0 mL, 136.5 mmol) and trimethylamine hydrochloride (0.522 g, 5.46 mmol) in acetonitrile (140 mL) was added *p*-toluenesulfonyl chloride (20.82 g, 109.24 mmol) slowly at 0 °C under nitrogen. The mixture was stirred at 0 °C for 50 minutes and at room temperature for 30 min under nitrogen. The reaction mixture was poured into water, extracted with EtOAc and dried over $MgSO_4$. The crude product was purified by flash chromatography eluting with

EtOAc/hexane (1 : 3) to afford **3** (16.19 g, 87%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 (d, *J* = 8.5 Hz, 2 H), 7.34 (d, *J* = 8.5 Hz, 2 H), 4.19 (d, *J* = 2.0 Hz, 2H), 4.15 (t, *J* = 5.0 Hz, 2H), 3.67-3.69 (m, 4H), 3.64-3.65 (m, 2H), 3.59 (s, 4H), 2.45 (s, 3H), 2.43 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.7, 132.9, 129.8, 127.9, 79.6, 74.5, 70.7, 70.5, 70.4, 69.2, 69.0 68.6, 58.3, 21.6; MS (APCI, m/z) 365 $(M+Na)^+$; HRMS (ESI) calcd for $C_{16}H_{23}O_6S$ $(M+H)^+$ 343.1215, found 343.1194.

General Procedure for the Synthesis of TEG Linkers 5, 7, 9, 13 and 14. To a solution of azide **1** (**6**, **8** or **10**) (1.0 mmol) and alkyne (1.0-1.3 mmol) in THF (2.5 mL) under nitrogen was added copper turnings (0.064 g), H_2O (2.5 mL) and $CuSO_4$ (0.20 mL, 0.20 mmol, 1.0 N in H_2O). The reaction mixture was stirred at 25 °C under nitrogen for 17-48 h. The solvents were removed under reduced pressure and the crude product was purified by flash chromatography over silica to afford TEG Linkers as yellow oils.

2-{2-[2-(2-{4-[(2-{2-[2-(4-Methylbenzenesulfonyl)ethoxy]ethoxy}ethoxy)methyl]-1*H*-1,2,3-triazol-1-yl}ethoxy)ethoxy]ethyl}isoindoline-1,3-dione (5). Treatment of **1** (1.826 g, 6.00 mmol) and **3** (2.67 g, 7.80 mmol) for 20 h according to the general procedure described above, eluting with EtOAc/hexane (3 : 1) and EtOAc to afford **5** (3.90 g, 100 %) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 (dd, *J* = 5.0, 3.0 Hz, 2 H), 7.79 (d, *J* = 8.5 Hz, 2 H), 7.75 (s, 1 H), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2 H), 7.34 (d, *J* = 8.5 Hz, 2 H), 4.68 (s, 2 H), 4.46 (t, *J* = 5.3 Hz, 2 H), 4.15 (t, *J* = 5.0 Hz, 2 H), 3.90 (t, *J* = 5.8 Hz, 2 H), 3.80 (t, *J* = 5.0 Hz, 2 H), 3.72 (t, *J* = 5.8 Hz, 2 H), 3.67-3.70 (m, 4 H), 3.61-3.64 (m, 2 H), 3.56-3.60 (m, 8 H), 2.45 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.2, 144.8, 134.0, 132.9, 132.0, 129.8, 127.9, 123.9, 123.2, 70.7, 70.52, 70.49, 70.48, 69.9, 69.6, 69.4, 69.2, 68.6, 68.0, 64.4, 50.8, 50.2, 37.2, 21.6, several signals account for

more than one carbon; MS (ESI, m/z) 647 $(M+H)^+$; HRMS (ESI) calcd for $C_{30}H_{39}N_4O_{10}S$ $(M+H)^+$ 647.2387, found 647.2396.

2-[2-(2-{2-[4-({2-[2-(2-{4-[(2-{2-[2-(4-Methylbenzenesulfonyl)ethoxy]ethoxy}ethoxy)-methyl]-1*H*-1,2,3-triazol-1-yl}ethoxy)ethoxy]ethoxy}methyl)-1*H*-1,2,3-triazol-1-yl]ethoxy}ethoxy)ethyl)]isoindoline-1,3-dione (7). Treatment of **6** (1.035 g, 2.00 mmol) and **3** (0.684 g, 2.0 mmol) for 20 h according to the general procedure described above, eluting with EtOAc/MeOH (10 : 1) and EtOAc/MeOH (10/2) to afford **7** (1.457 g, 85 %) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84 (dd, *J* = 6.0 Hz, 3.0 Hz, 2 H), 7.79 (d, *J* = 8.4 Hz, 2 H), 7.75 (s, 1 H), 7.73 (s, 1 H), 7.72 (dd, *J* = 6.0 Hz, 3.5 Hz, 2 H), 7.33 (d, *J* = 8.5 Hz, 2H), 4.67 (s, 2 H), 4.66 (s, 2 H), 4.52 (t, *J* = 5.0 Hz, 2 H), 4.45 (t, *J* = 5.0 Hz, 2 H), 4.17-4.14 (m, 2 H), 3.91-3.86 (m, 4 H), 3.80 (t, *J* = 5.3 Hz, 2 H), 3.70-3.55 (m, 24 H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.2, 144.8, 144.7, 134.0, 132.9, 132.0, 129.8, 128.4, 127.9, 125.8, 123.8, 123.2, 70.6, 70.45, 70.43, 70.41, 70.37, 69.8, 69.5, 69.4, 69.2, 68.6, 67.9, 64.5, 64.4, 50.11, 50.09, 37.2, 21.6, several signals account for more than one carbon; MS (MALDI, m/z) 860 $(M+Na)^+$; HRMS (ESI) calcd for $C_{39}H_{54}N_7O_{13}S$ $(M+H)^+$ 860.3500, found 860.3496.

2-(2-{2-[2-(4-{[2-(2-{2-[4-({2-[2-(2-{4-[(2-{2-[2-(4-Methylbenzenesulfonyl)ethoxy]-ethoxy}ethoxy)methyl]-1*H*-1,2,3-triazol-1-yl}ethoxy)ethoxy]ethoxy}methyl)-1*H*-1,2,3-triazol-1-yl]ethoxy}ethoxy)ethoxy]methyl}-1*H*-1,2,3-triazol-1-yl)ethoxy]ethoxy}ethyl)isoindoline-1,3-dione (9). Treatment of **8** (0.730 g, 1.00 mmol) and **3** (0.445 g, 1.3 mmol) for 42 h according to the general procedure described above, eluting with $CHCl_3$/MeOH (95 : 5) to afford **9** (0.854 g, 80 %) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.5, 3.0 Hz, 2 H), 7.77 (d, *J* = 8.5 Hz, 2 H), 7.74 (s, 1

H), 7.73 (s, 1 H), 7.71 (s, 1 H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2 H), 7.32 (d, *J* = 8.5 Hz, 2 H), 4.66 (s, 2 H), 4.64 (s, 4 H), 4.51 (t, *J* = 5.3 Hz, 4 H), 4.45 (t, *J* = 5.0 Hz, 2 H), 4.13 (t, *J* = 4.8 Hz, 2 H), 3.88 (t, *J* = 5.8 Hz, 2 H), 3.85 (t, *J* = 5.3 Hz, 4 H), 3.79 (t, *J* = 5.3 Hz, 2 H), 3.71 (t, *J* = 5.8 Hz, 2H), 3.69-3.65 (m, 8 H), 3.62-3.59 (m, 16 H), 3.56-3.54 (m, 6 H), 2.43 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 144.8, 144.7, 134.0, 132.9, 132.0, 129.8, 127.9, 123.8, 123.2, 70.7, 70.48, 70.46, 70.45, 70.40, 69.9, 69.5, 69.4, 69.2, 68.6, 68.0, 64.5, 64.49, 64.44, 64.43, 50.15, 50.12, 37.2, 21.6, several signals account for more than one carbon; MS (MALDI, m/z) 1095.5 $(M+Na)^+$; HRMS (ESI) calcd for $C_{48}H_{69}N_{10}O_{16}S$ $(M+H)^+$ 1073.4614, found 1073.4664.

***tert*- Butyl 2-{2-[2-(2-{[1-(2-{2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethoxy]-ethoxy}ethyl)-1*H*-1,2,3-triazol-4-yl]methoxy}ethoxy)ethoxy]ethoxy}acetate (13).** Treatment of **6** (0.525 g, 1.015 mmol) and **12** (0.393 g, 1.3 mmol) for 17 h according to the general procedure described above, eluting with $CHCl_3$/MeOH (95 : 5) to afford **13** (0.760 g, 91 %) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.5, 3.0 Hz, 2 H), 7.81 (s, 1 H), 7.72 (s, 1 H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2 H), 4.66 (brs, 4 H), 4.53 (brs, 2 H), 4.46 (t, *J* = 4.8 Hz, 2 H), 4.01 (s, 2 H), 3.89-3.85 (m, 4 H), 3.80 (t, *J* = 5.0 Hz, 2 H), 3.71-3.54 (m, 26 H), 1.46 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 168.2, 134.0, 132.0, 123.2, 81.4, 70.6, 70.5, 70.46, 70.42, 70.40, 69.8, 69.6, 69.5, 68.9, 67.9, 64.4, 50.3, 37.1, 28.0, several signals account for more than one carbon; HRMS (ESI) calcd for $C_{38}H_{58}N_7O_{13}$ $(M+H)^+$ 820.4093, found 820.4077.

5-[2-(2-{2-[{1-[2-(2-{2-[(1-{2-[2-(2-{[1-(2-{2-[2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethoxy]ethoxy}ethyl)-1*H*-1,2,3-triazol-4-yl]methoxy}ethoxy)ethoxy]ethyl}-1*H*-1,2,3-triazol-4-yl)methoxy]ethoxy}ethoxy)ethyl]-1*H*-1,2,3-triazol-4-yl}methoxy]-

ethoxy}ethoxy)ethyl]-1*H*-1,2,3-triazol-4-yl]pentanoic acid (14). Treatment of **10** (0.110 g, 0.117 mmol), 6-heptynoic acid (0.044 g, 0.350 mmol), copper turnings (20 mg), $CuSO_4$ (0.10 mL, 1 N), THF (2 mL) and water (2 mL) for 48 h according to the general procedure described above, eluting with MeOH to afford **14** (0.030 g, 24 %) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.5, 3.5 Hz, 2 H), 7.78 (s, 1 H), 7.74 (s, 1 H), 7.73 (s, 1 H), 7.71 (dd, *J* = 5.5, 3.5 Hz, 2 H), 7.55 (s, 1 H), 4.68 (s, 2H), 4.67 (s, 2 H), 4.66 (s, 2 H), 4.54-4.51 (m, 4 H), 4.49 (t, *J* = 5.5 Hz, 2 H), 4.46 (t, *J* = 5.0 Hz, 2 H), 3.89 (t, *J* = 5.8 Hz, 2 H), 3.86 (t, *J* = 4.8 Hz, 4 H), 3.83 (t, *J* = 4.8 Hz, 2 H), 3.79 (t, *J* = 5.3 Hz, 2 H), 3.71 (t, *J* = 5.8 Hz, 2 H), 3.70-3.66 (m, 6 H), 3.63-3.54 (m, 22 H), 2.74 (t, *J* = 6.8 Hz, 2 H), 2.37 (t, *J* = 6.8 Hz, 2 H), 1.76-1.67 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 168.2, 147.6, 144.7, 144.5, 134.0, 132.0, 124.2, 123.9, 123.2, 122.2, 70.6, 70.45, 70.42, 70.40, 70.37, 69.9, 69.5, 69.4, 69.39, 69.38, 69.33, 68.0, 64.36, 64.31, 64.0, 50.3, 50.2, 50.1, 37.2, 33.7, 28.6, 25.3, 24.3, several signals account for more than one carbon; MS (MALDI, m/z) 1070.7 $(M+Na)^+$; HRMS (ESI) calcd for $C_{48}H_{72}N_{13}O_{15}$ $(M+H)^+$ 1070.5271, found 1070.5255.

***tert*-Butyl 2-(2-{2-[2-(prop-2-ynyloxy)ethoxy]ethoxy}ethoxy)acetate (12).** To a solution of **4** (2.823 g, 15.00 mmol) in distilled THF (30 mL) at 0 ^{o}C under nitrogen was added sodium hydride (0.84 g, 21.0 mmol, 60%) slowly. The mixture was stirred at 0 ^{o}C for 30 min. under nitrogen. *tert*-Butyl bromoacetate (4.43 mL, 5.85 g, 30.0 mmol) was injected slowly to the reaction flask. The mixture was stirred at 0 ^{o}C for 1 h and at 25 °C for 12 h. The mixture was poured into water, extracted with CH_2Cl_2 and dried over $MgSO_4$. The crude product was purified by flash chromatography eluting with EtOAc/hexane (1 : 1) to afford **12** as a yellow oil (2.40 g, 53%). ^{1}H NMR ($CDCl_3$, 300

MHz) δ 4.21 (d, *J* = 2.7 Hz, 2 H), 4.03 (s, 2 H), 3.73-3.66 (m, 12 H), 2.43 (t, *J* = 2.3 Hz, 1 H), 1.48 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 81.5, 79.6, 74.5, 70.7, 70.59, 70.57 (two carbons), 70.4, 69.1, 69.0, 58.4, 28.1; HRMS (ESI) calcd for $C_{15}H_{26}Na$ $(M+Na)^+$ 325.1627, found 325.1637.

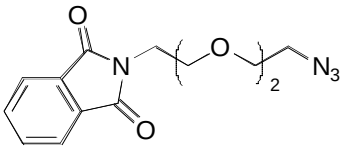
***tert*- Butyl 3-{2-[2-(2-{[1-(2-{2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethoxy]-ethoxy}ethyl)-1*H*-1,2,3-triazol-4-yl]methoxy}ethoxy)ethoxy]ethyl}tetrahydro-pyrimidine-1(2*H*)-carboxylate (11).** To a solution of **5** (0.200 g, 0.309 mmol) and mono-Boc-piperazine[3] (0.058 g, 0.309 g) in CH_3CN (4 mL) under nitrogen was added K_2CO_3 (0.21 g, 1.55 mmol). The mixture was refluxed for 20 h. The suspension was cooled, diluted with water, extracted with CH_2Cl_2 and dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude product was purified by flash chromatography over silica eluting with MeOH to afford **11** (0.12 g, 59%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.5, 3.0 Hz, 2 H), 7.72 (s, 1 H), 7.71 (dd, *J* =5.5, 3.0 Hz, 2 H), 4.67 (s, 2 H), 4.45 (t, *J* = 5.0 Hz, 2 H), 3.89 (t, *J* = 5.8 Hz, 2 H), 3.79 (t, *J* = 5.3 Hz, 2 H), 3.71 (t, *J* = 5.8 Hz, 2 H), 3.70-3.59 (m, 12 H), 3.56-3.54 (m, 2 H), 3.43 (t, *J* = 4.8 Hz, 4 H), 2.61 (t, *J* = 5.5 Hz, 2 H), 2.46 (brs, 4 H), 1.44 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 154.6, 144.8, 133.9, 132.0, 123.7, 123.2, 79.5, 70.46, 70.43 (two carbons), 70.3, 69.8, 69.5, 69.4, 68.6, 67.9, 64.5, 57.7, 53.2, 50.1, 43.8, 37.1, 28.3; HRMS (ESI) calcd for $C_{32}H_{49}N_6O_9$ $(M+H)^+$ 661.3561, found 661.3543.

Outline of Approach for Calculations

The following approach was used to obtain estimates of molecular lengths for the extended conformations of the linkers. The molecules were drawn in Chem3D (CambridgeSoft Corp.) in extended forms, then minimized with their molecular mechanics routine. End-to-end lengths of the molecules were measured using the ruler function in Chem3D.

References

1. Sato, H.; Hayashi, E.; Yamada, N.; Yatagai, M.; Takahara, Y. *Bioconjugate Chem.* **2001**, 12, 701-710.
2. (a) Hansen, T. M.; Engler, M. M.; Forsyth, C. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2127-2130; (b) Fujii, K.; Hatano, K.; Nakamura, K.; Umeyama, H. Jpn. Kokai Tokkyo Koho, **2001**, JP 2001064238. (c) Fujii, K.; Hatano, K.; Oka, A. Jpn. Kokai Tokkyo Koho, **2000**, JP 2000355505.
3. (a) Wallen, E. A. A.; Christiaans, J. A. M.; Jarho, E. M.; Forsberg, M. M.; Venalainen, J. I.; Mannisto, P. T.; Gynther, J. *J. Med. Chem*. **2003**, 46, 4543-4551. (b) Carpino, L. A.; Mansour, E. M. E.; Cheng, C. H.; Williams, J. R.; MacDonald, R.; Knapczyk, J.; Carman, M. *J. Org. Chem*. **1983**, 48, 661-665.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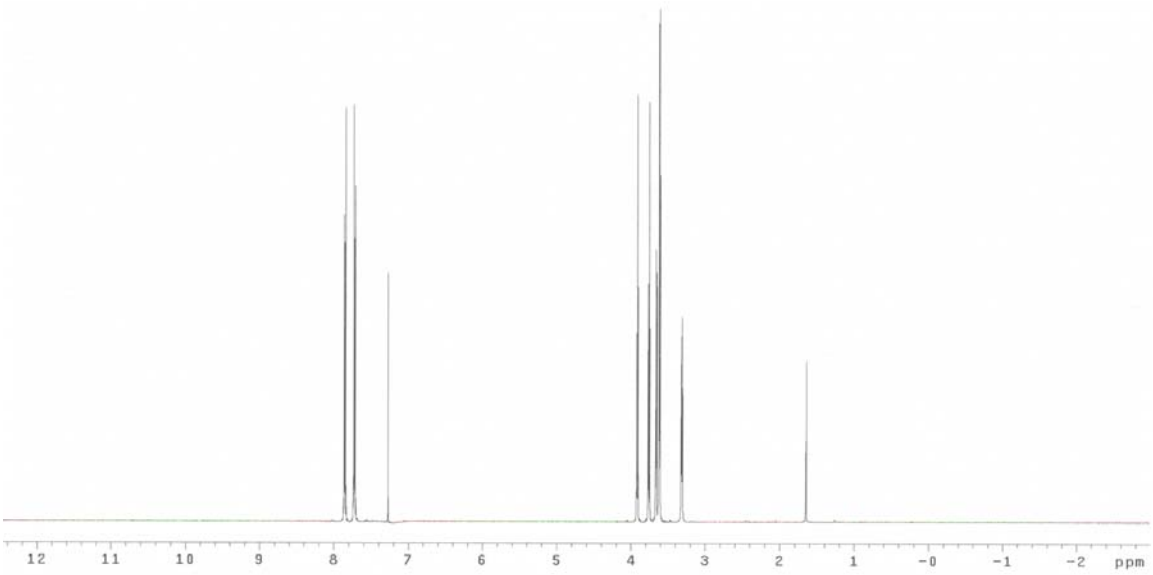
N
O
2
N3
O

1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10
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8
7
6
5
4
3
2
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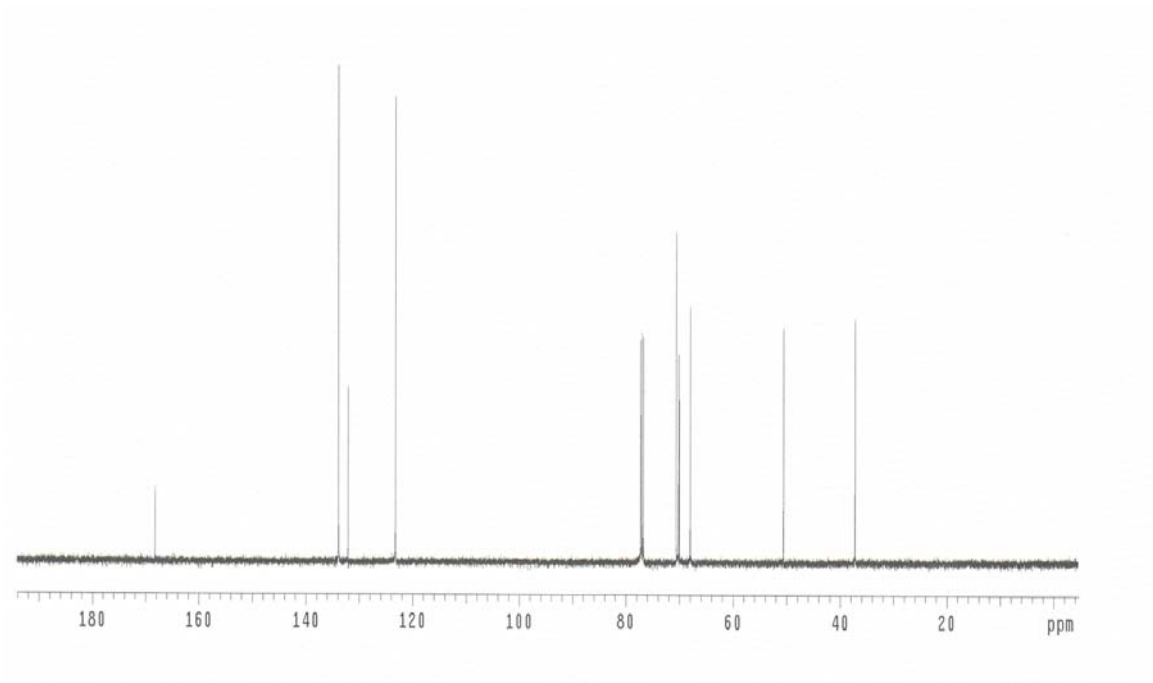
-0
-1
-2
ppm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40
20
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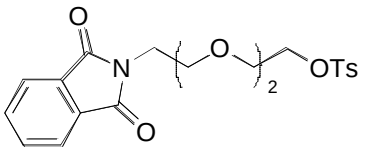
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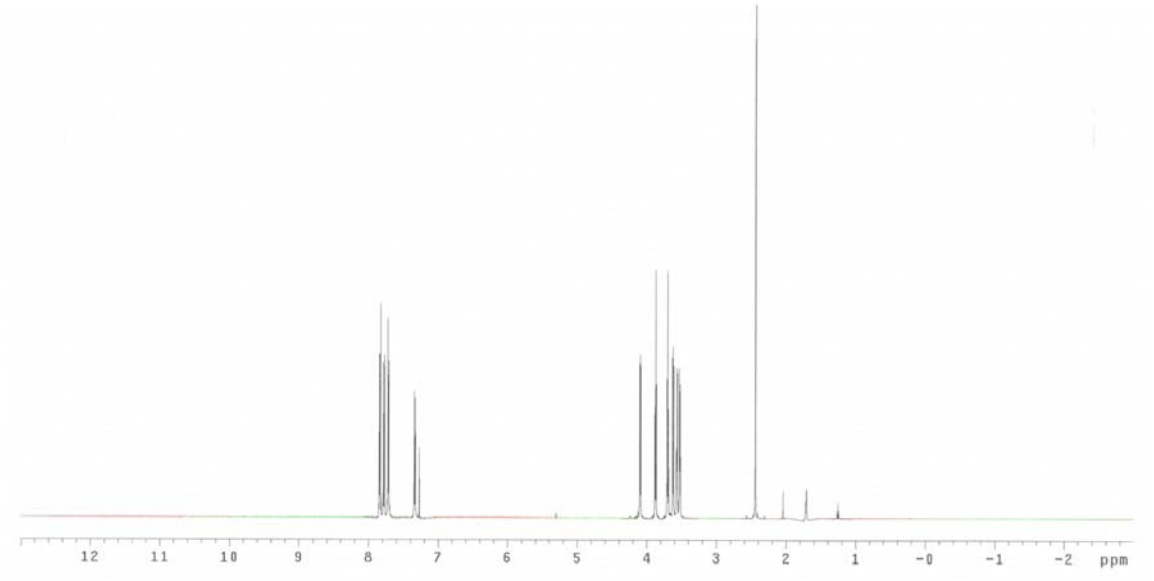
N
O
O
2
OTs
O

2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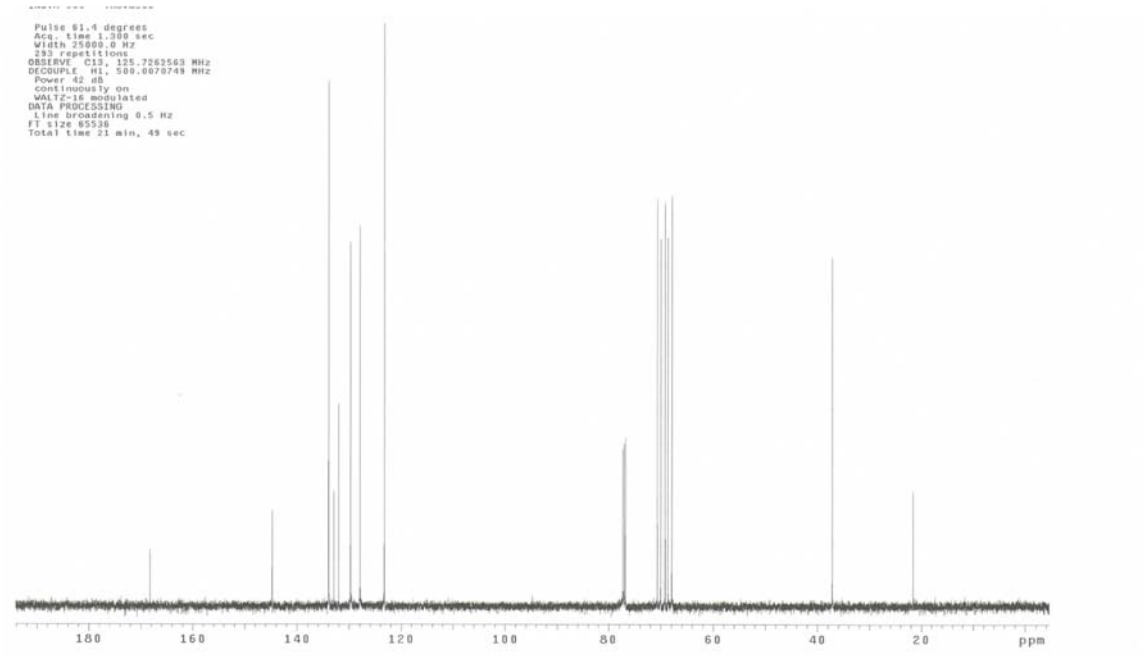
-2
ppm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DECOUPLE H1, 500.0870749 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
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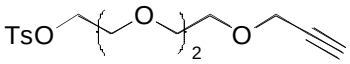
140
120
100
80
60
40
20
ppm



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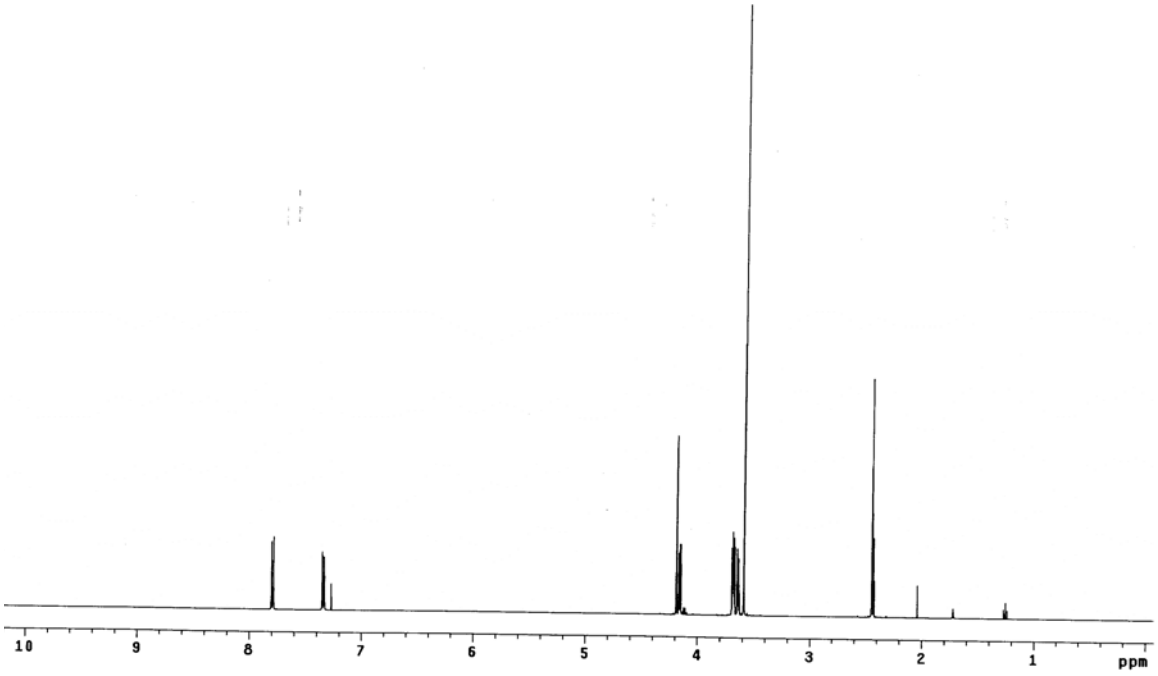

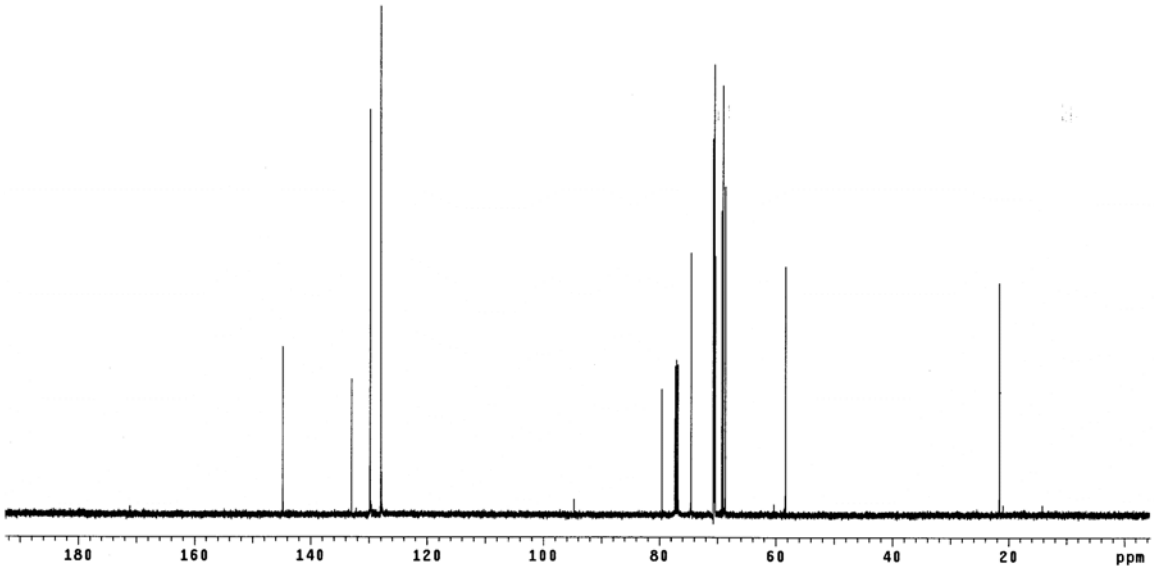

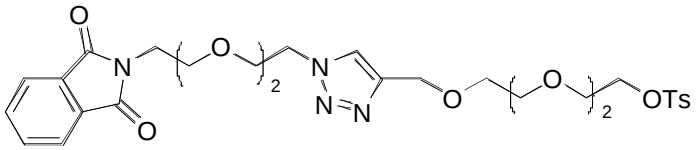
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N
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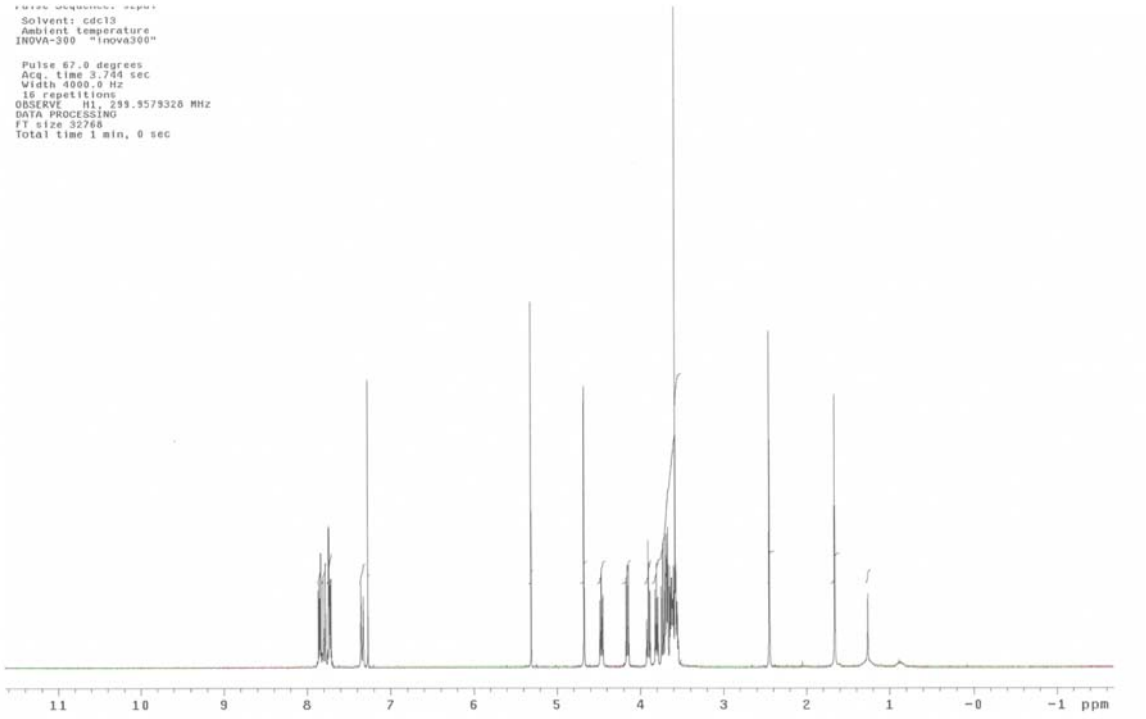
2
N
N
N
O
O
2
OTs
O

5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Pulse 67.0 degrees
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Width 4000.0 Hz
16 repetitions
OBSERVE H1, 299.9579328 MHz
DATA PROCESSING
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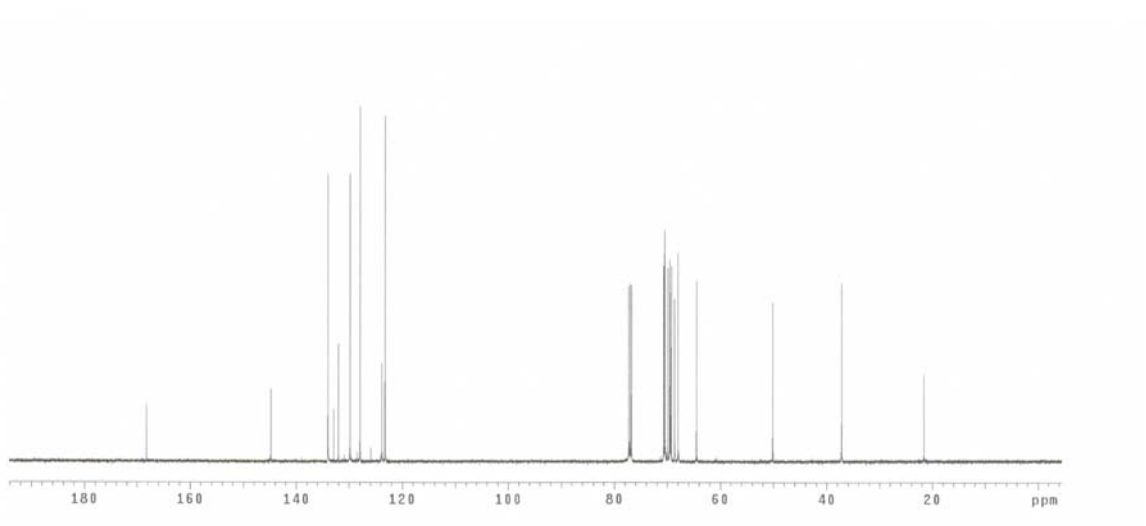
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm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20
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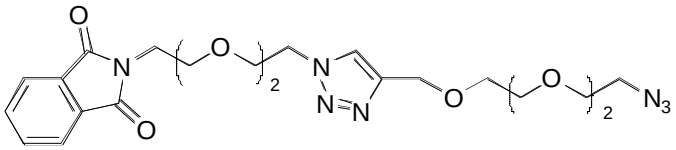

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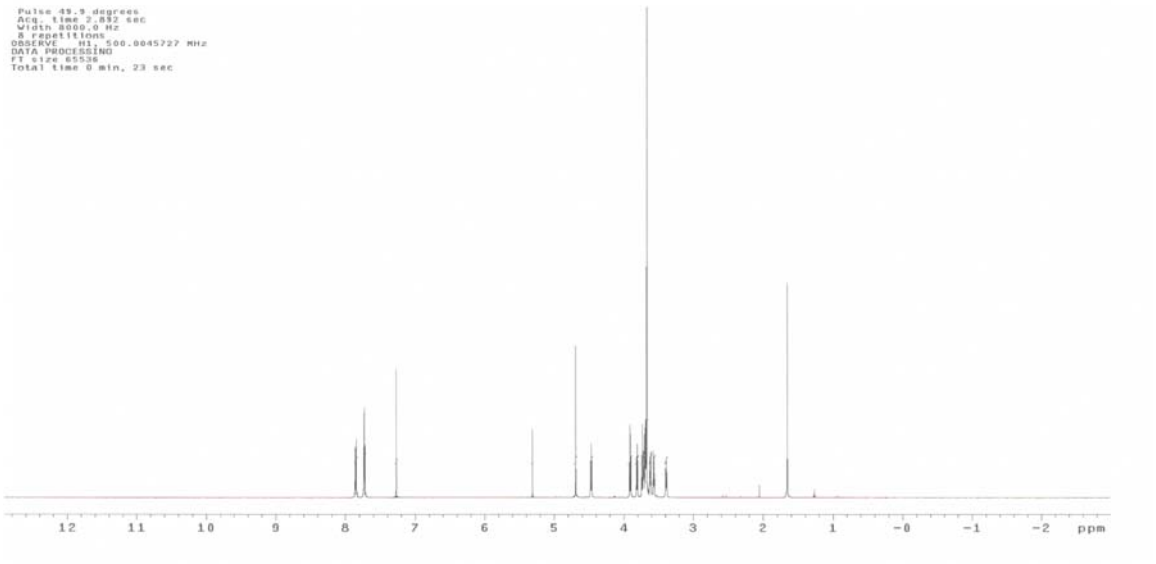
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Acq. time 2.882 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 500.0045727 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 23 sec
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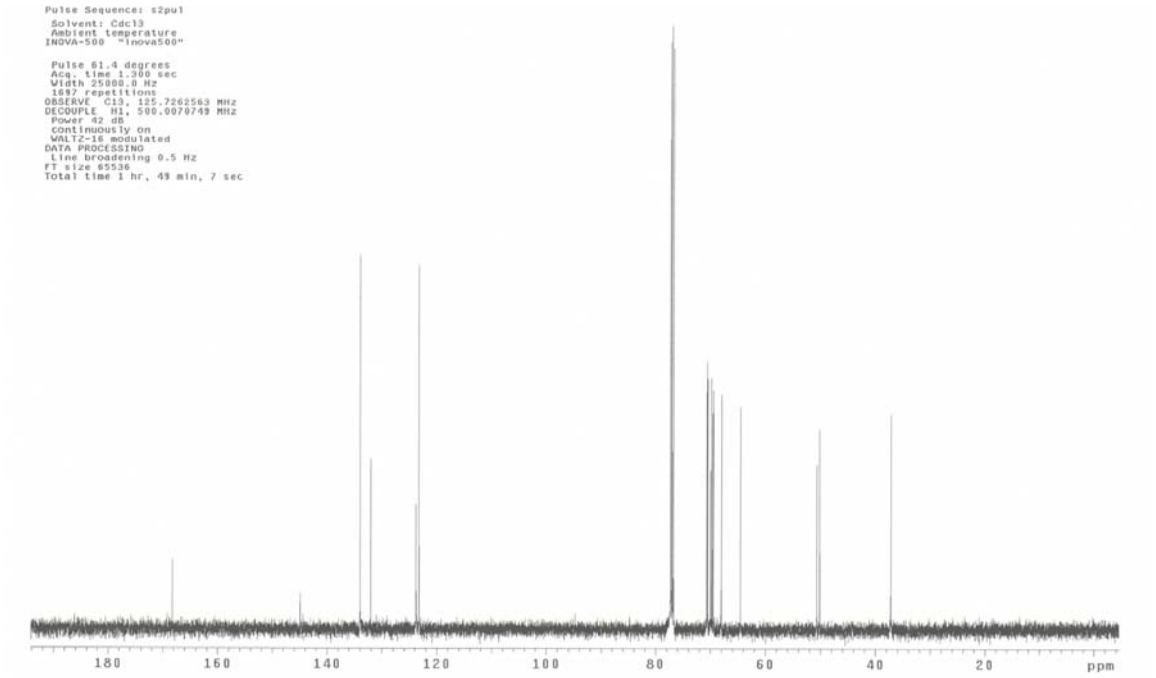
11
10
9
8
7
6
5
4
3
2
1
-0
-1
-2
ppm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Pulse 61.4 degrees
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Width 25000.0 Hz
1697 repetitions
OBSERVE C13, 125.7262563 MHz
DECOUPLE H1, 500.0070749 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
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FT size 65536
Total time 1 hr, 49 min, 7 sec
180
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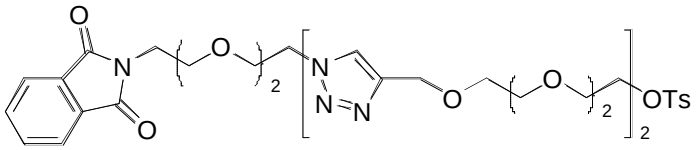
140
120
100
80
60
40
20
ppm



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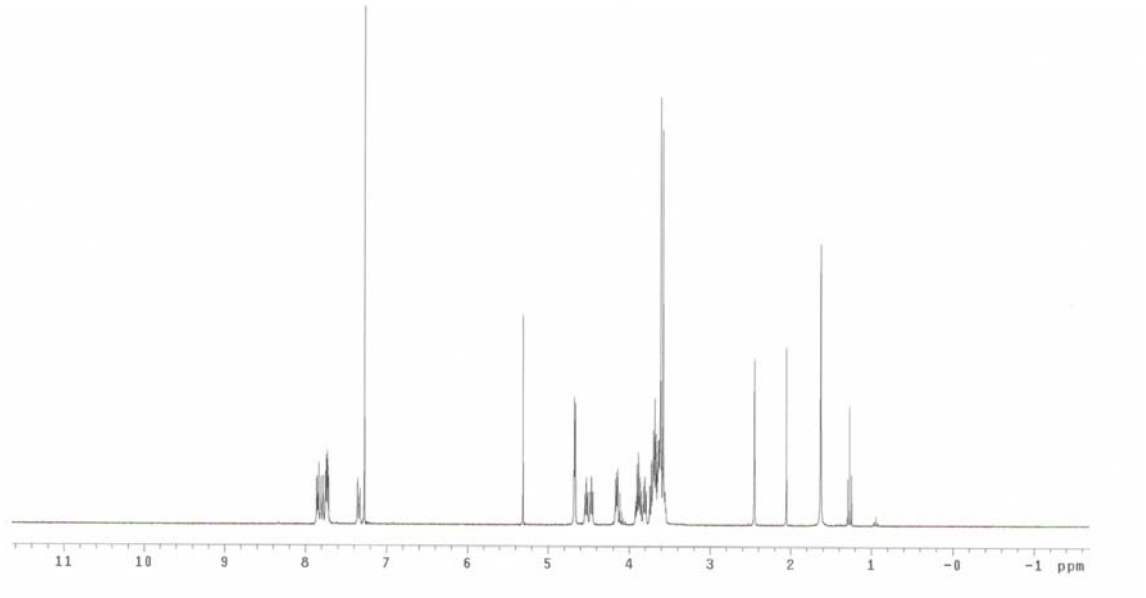

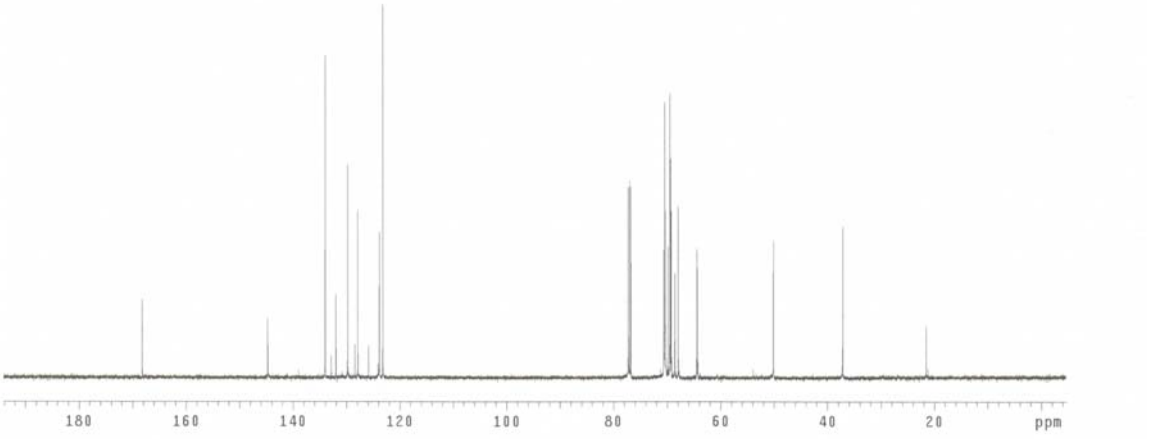

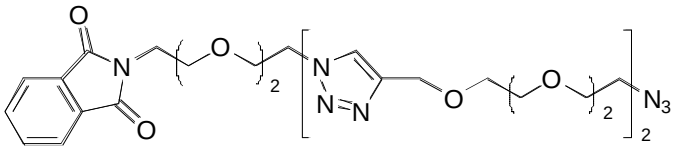

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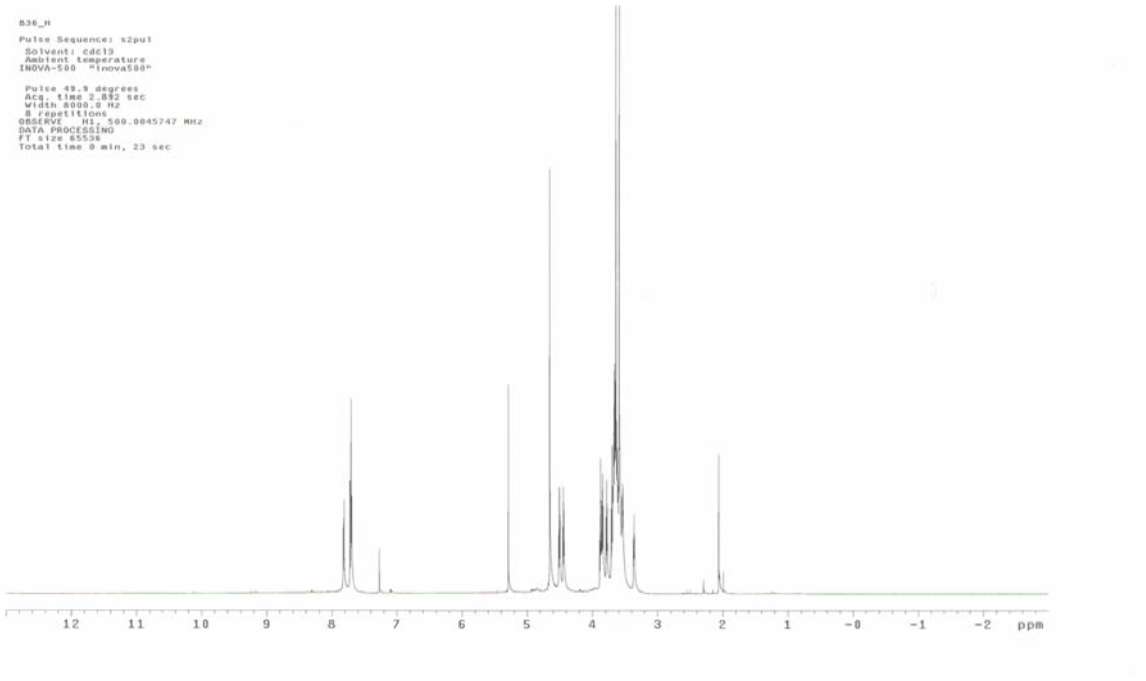
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Solvent: cdcl3
Ambient temperature
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Pulse 49.9 degrees
Acq. time 2.882 sec
Width 8000.0 Hz
8 repetitions
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DATA PROCESSING
FT size 65536
Total time 0 min, 23 sec
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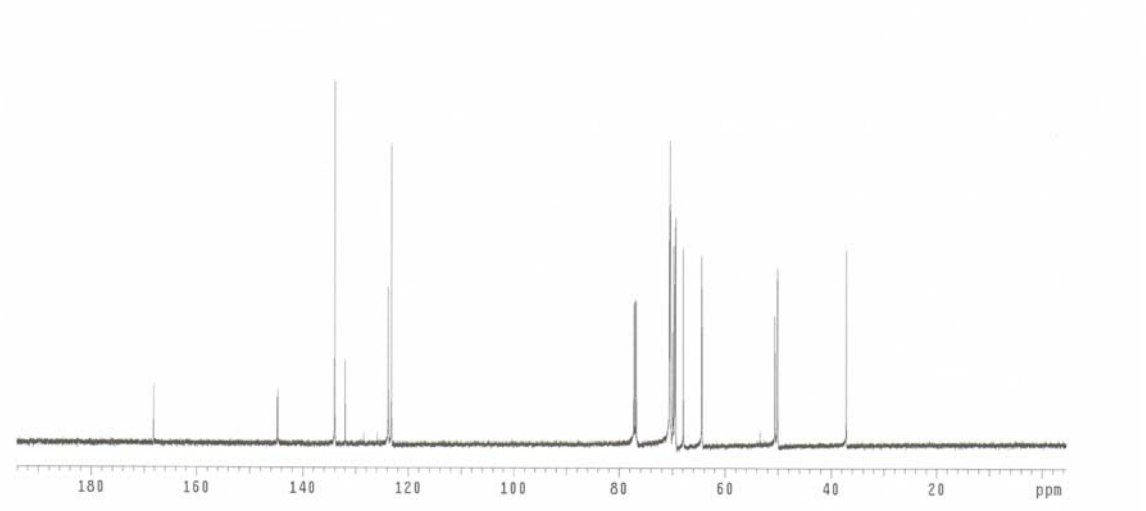
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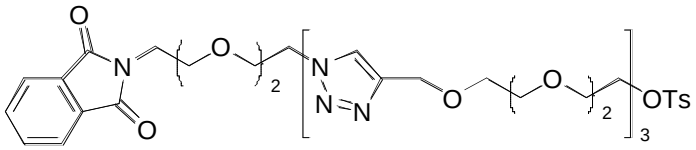

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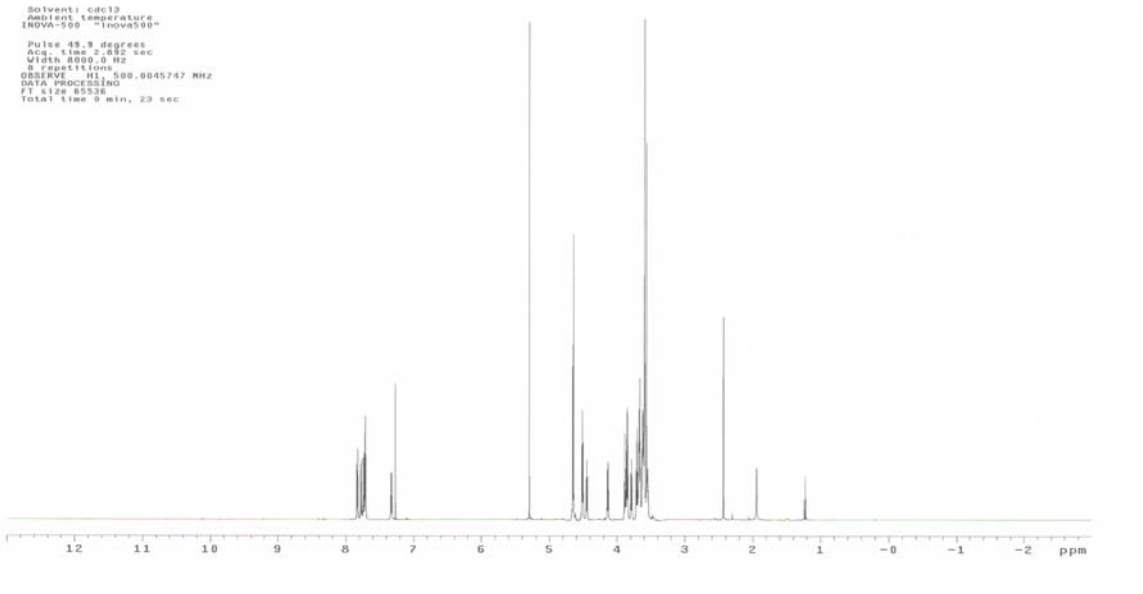
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Pulse 49.9 degrees
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Width 8000.0 Hz
8 repetitions
OBSERVE H1, 500.0045747 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 23 sec
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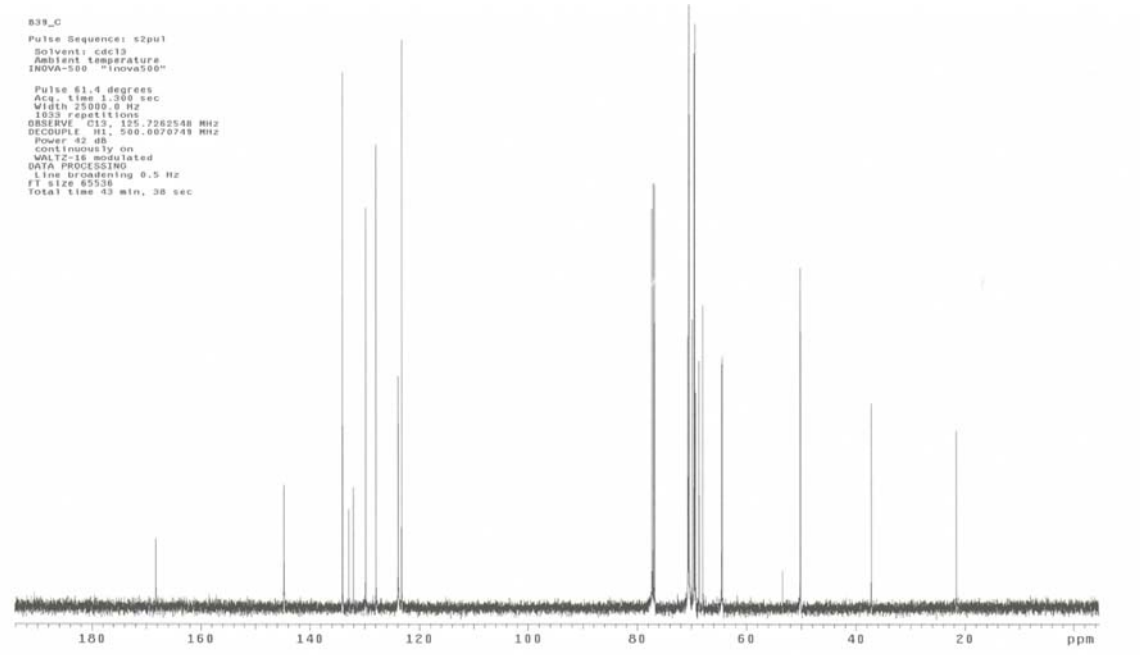
11
10
9
8
7
6
5
4
3
2
1
-0
-1
-2
ppm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Ambient temperature
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Width 25000.0 Hz
1033 repetitions
OBSERVE C13, 125.7262548 MHz
DECOUPLE H1, 500.0070749 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
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FT size 65536
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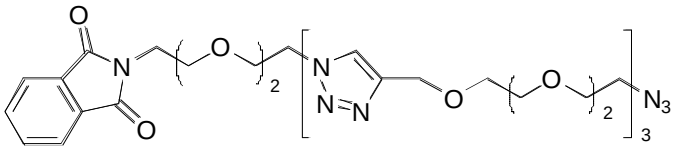
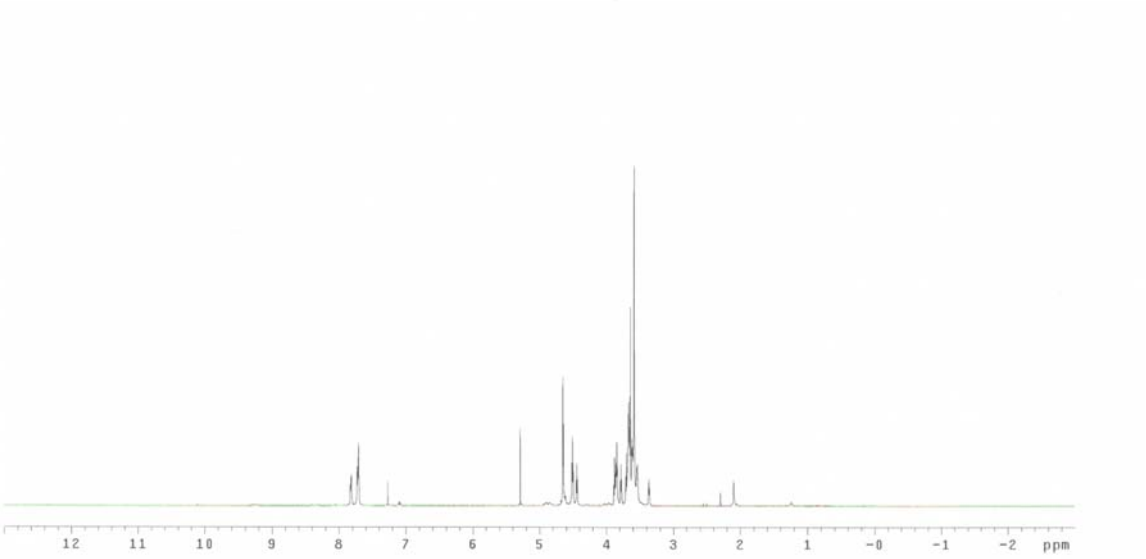
140
120
100
80
60
40
20
ppm



10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10
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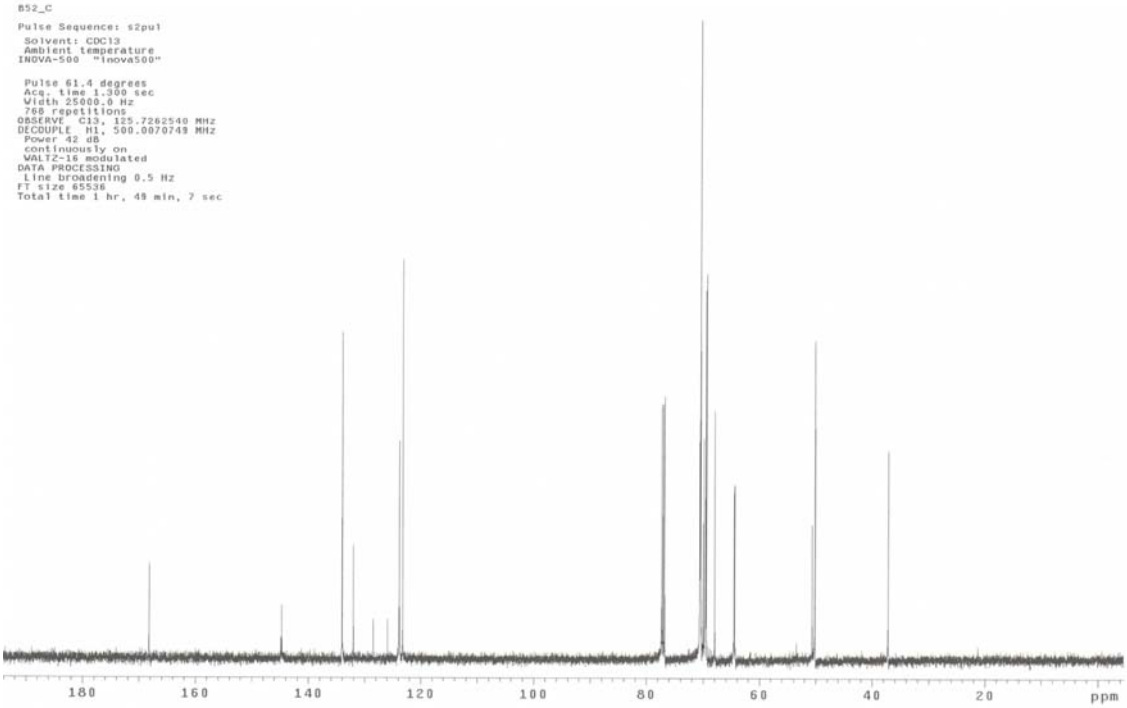
6
5
4
3
2
1
-0
-1
-2
ppm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Ambient temperature
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Pulse 61.4 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
760 repetitions
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DECOUPLE H1, 500.0070749 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
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FT size 65536
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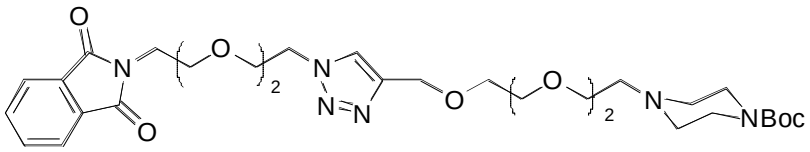
140
120
100
80
60
40
20
ppm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N=N
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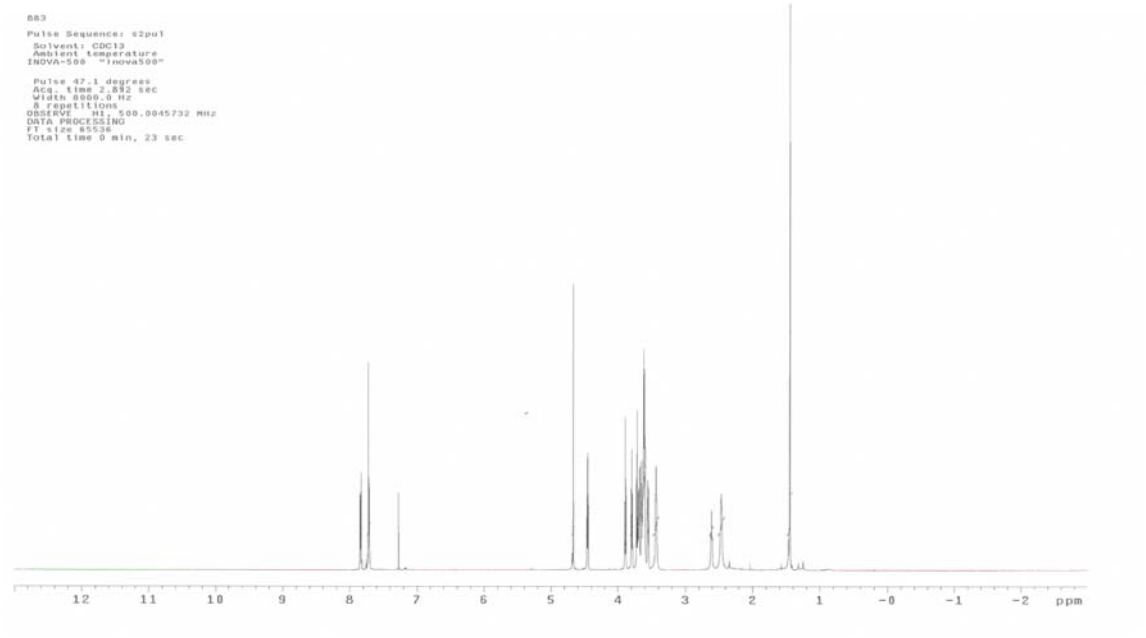
2
N
NBoc
O

11


883
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Solvent: CDCl3
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Pulse 47.1 degrees
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Width 8000.0 Hz
8 repetitions
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DATA PROCESSING
FT size 65536
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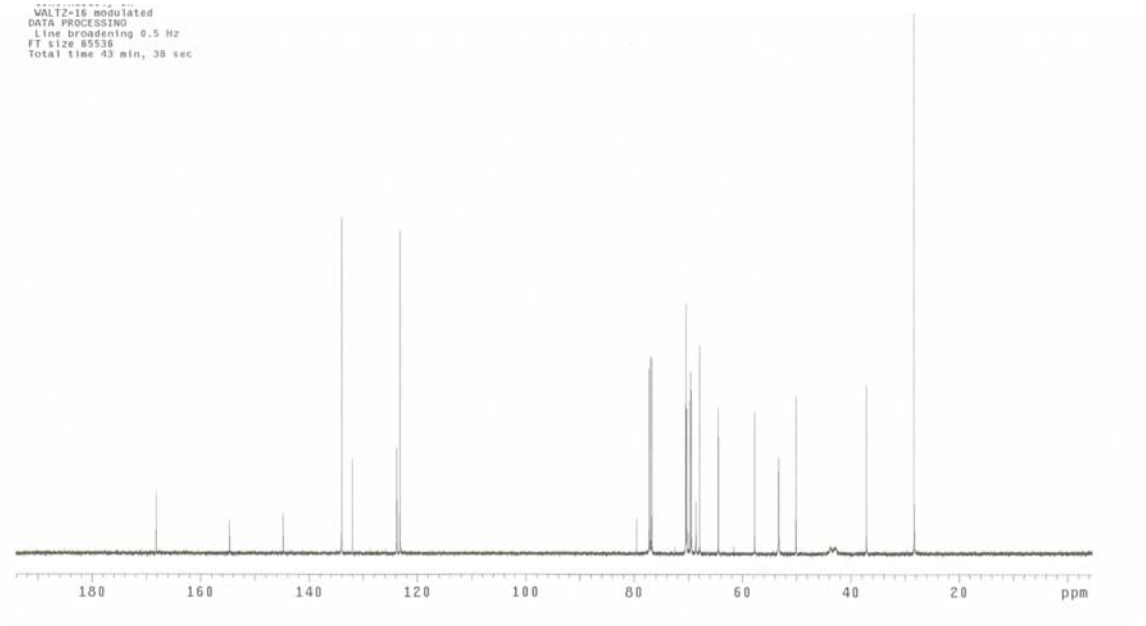
11
10
9
8
7
6
5
4
3
2
1
-0
-1
-2
ppm


WALTZ-16 modulated
DATA PROCESSING
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FT size 65536
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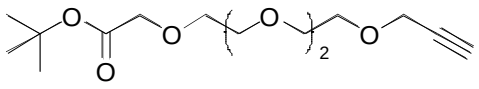
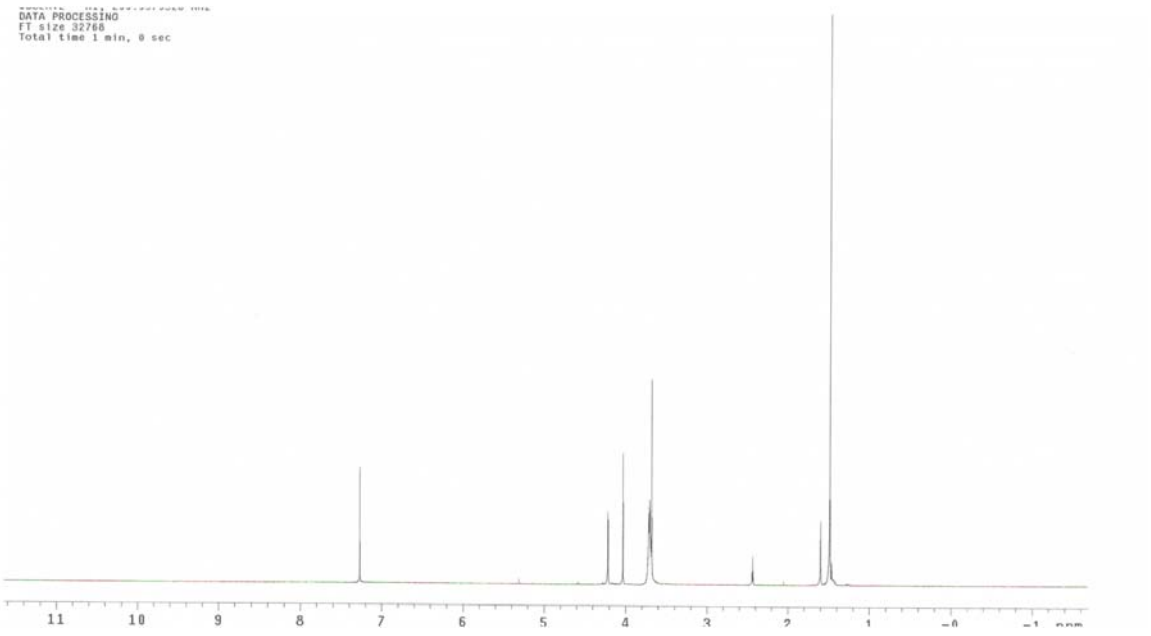
160
140
120
100
80
60
40
20
ppm



12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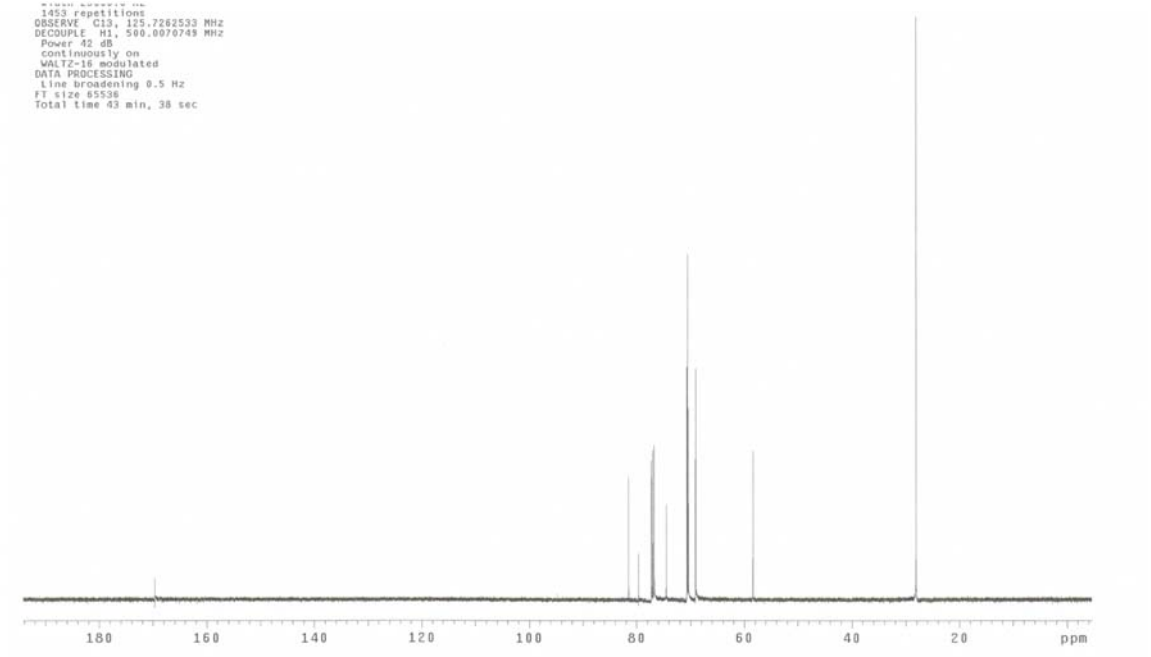
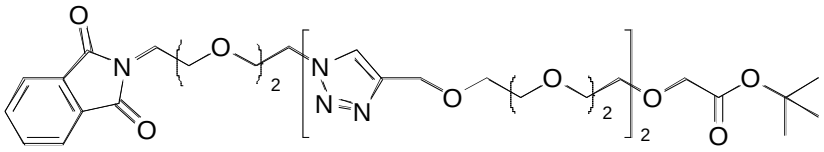
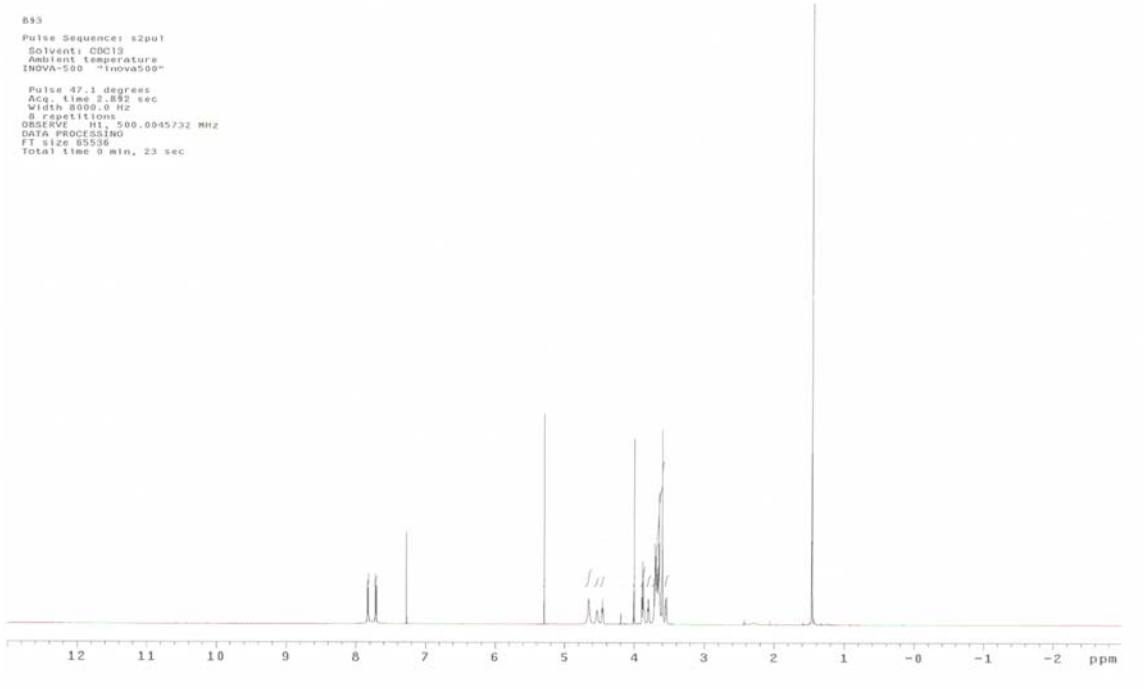
10
9
8
7
6
5
4
3
2
1
0
-1 ppm


1453 repetitions
OBSERVE C13, 125.7262533 MHz
DECOUPLE H1, 500.0070749 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 43 min, 38 sec
180
160
140
120
100
80
60
40
20
ppm



13


893
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Solvent: CDCl3
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Pulse 47.1 degrees
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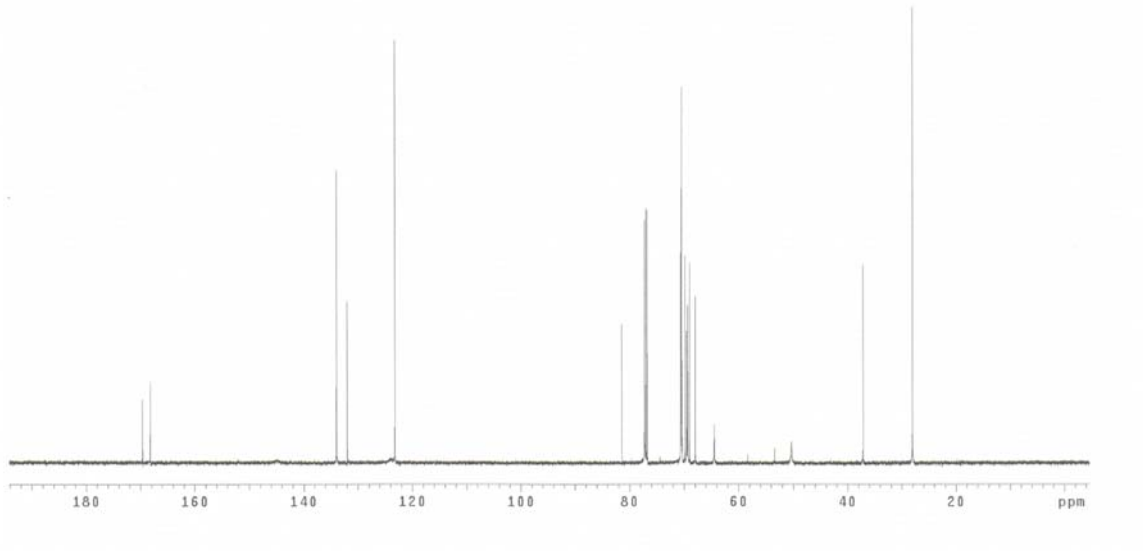
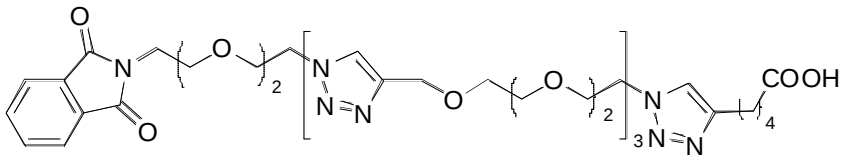
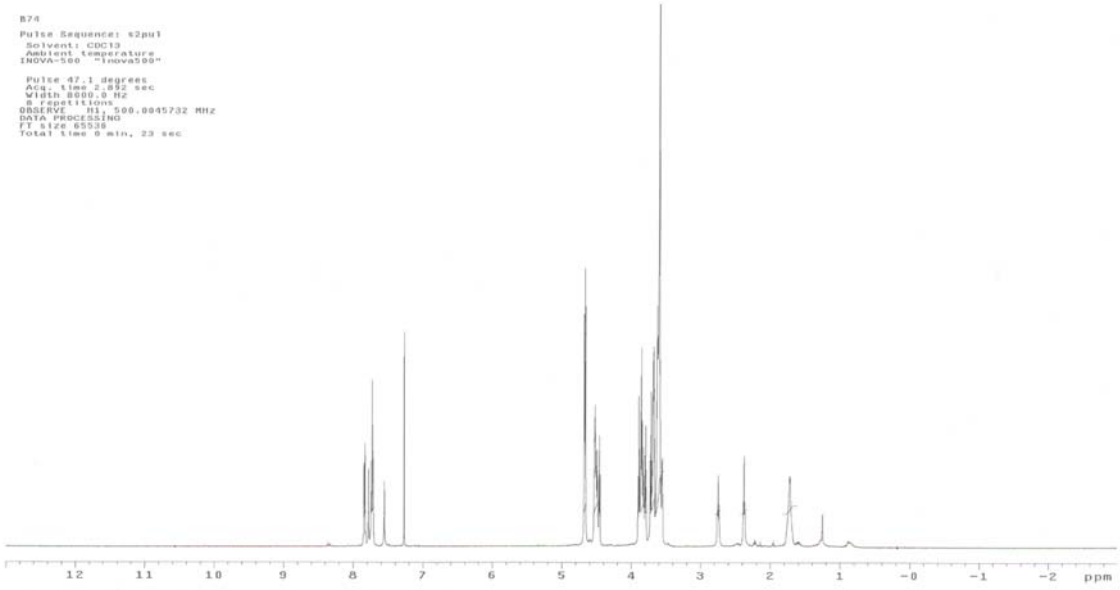
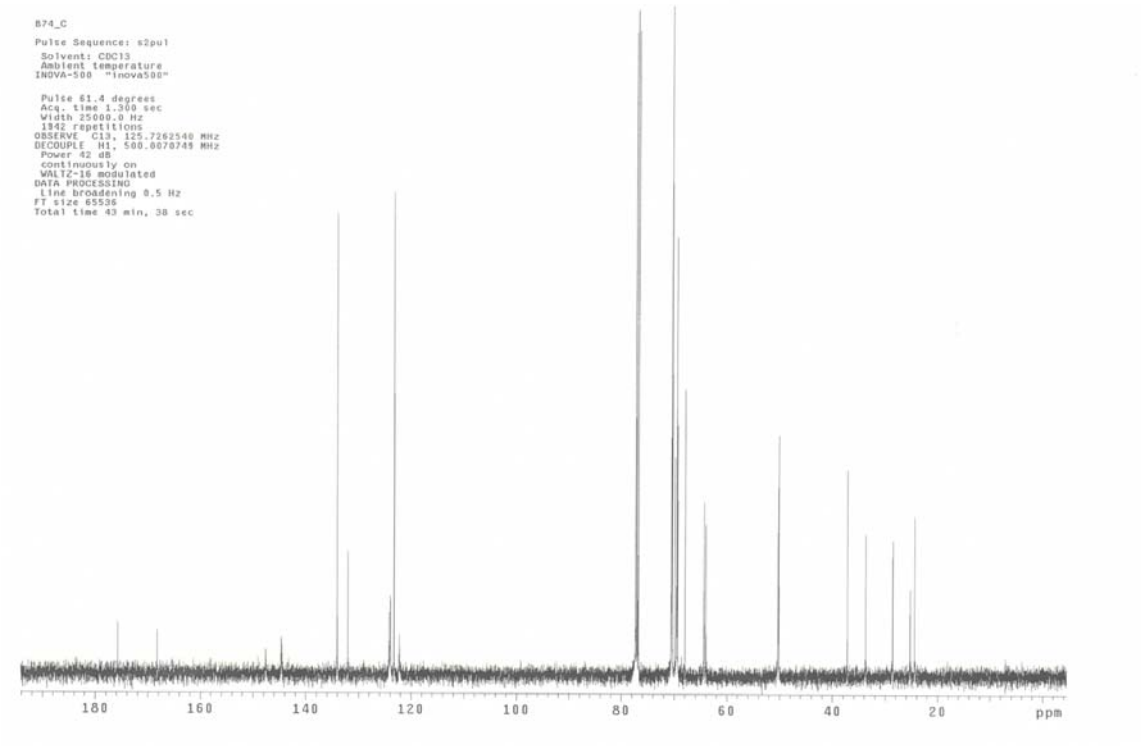
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 500.0045732 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 23 sec
12 11 10 9 8 7 6 5 4 3 2 1 -0 -1 -2 ppm


180 160 140 120 100 80 60 40 20 ppm


O
N
O
2
N
N
N
O
O
2
N
3
N
N
COOH
4

14


B74
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-500 "inova500"
Pulse 47.1 degrees
Acq. time 2.892 sec
Width 8000.0 Hz
8 repetitions
OBSERVE H1, 500.0045732 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 23 sec
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
-2
ppm


B74_C
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-500 "inova500"
Pulse 61.4 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
1842 repetitions
OBSERVE C13, 125.7262540 MHz
DECOUPLE H1, 500.0070745 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 43 min, 38 sec
180
160
140
120
100
80
60
40
20
ppm