

Expedient synthesis of trifunctional oligoethyleneglycol-amine linkers and their use for the preparation of PEG-based branched platforms.

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1 Material and methods

Experimental procedures

Unless otherwise indicated, reactions were carried out under an argon atmosphere in flame-dried glassware with magnetic stirring. Air and/or moisture-sensitive liquids were transferred *via* syringe. When required, solutions were degassed by argon bubbling through a needle. Organic solutions were concentrated by rotary evaporation at 25-80 °C at 15-30 torr. Analytical thin layer chromatography (TLC) was performed using plates cut from aluminium sheets (ALUGRAM Xtra SIL G/UV₂₅₄ from Macherey-Nagel). Visualization was achieved under a 254 or 365 nm UV light and by immersion in an appropriate revelation solution.

Materials.

All reagents were obtained from commercial sources and used without any further purifications. Anhydrous solvents used in experiments were obtained from Sigma-Aldrich or Alfa Aesar. Pd/C was purchased from Alfa Aesar (A12012 Palladium, 10% on carbon, Type 487, dry). Silica gel for column chromatography was purchased from Merck (Geduran® Si 60, 40-63 µm). Column flash chromatography was carried out using silica gel G-25 (40-63 µm) from Macherey-Nagel.

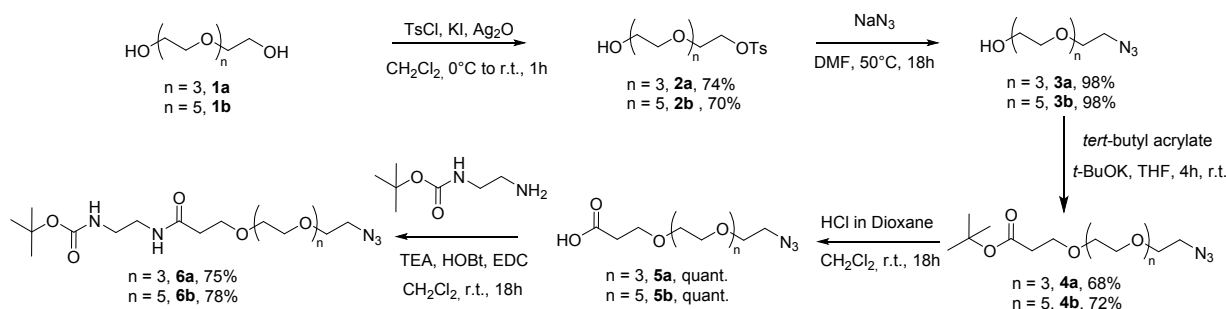
Instrumentation

NMR spectroscopy, ¹H and ¹³C NMR spectra were recorded respectively at 400 MHz and 100 MHz with a Bruker 400 spectrometer at 23 °C. Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad or a combination of the above), coupling constant (J, Hz) and integration.

High resolution mass spectra (HRMS) were obtained using an Agilent Accurate Mass QToF 6520 (PACSI Platform, Strasbourg University).

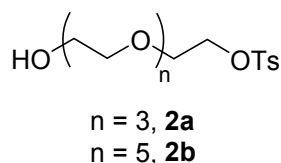
Semi-Preparative HPLC: The semi-preparative HPLC system consisted of a Waters 600 pump, a 2487 detector (Waters), a 5 mL sample loop. Column: Sunfire C₁₈ (150 mm × 19 mm i.d., 5 µm, Waters). Flow: 17 mL/min. Injection volume = 1 mL. Eluent A/B water/ACN, with 0.05% TFA. Gradient: 5% B to 95% B in 40 minutes and 10 minutes of re-equilibration. Detection: 254 nm.

2 Synthesis of hetero-bifunctional peg linkers



2a, 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate, $\text{C}_{15}\text{H}_{24}\text{O}_7\text{S}$, MW = 348.41 g/mol.¹

2b, 17-hydroxy-3,6,9,12,15-pentaoxaheptadecyl 4-methylbenzenesulfonate, $\text{C}_{19}\text{H}_{32}\text{O}_9\text{S}$, MW = 436.52 g/mol.²



General procedure: To a solution of ethylene glycol (**1a** or **1b**) in DCM (0.1 mmol/mL) at 0°C were added KI (0.2 eq.) and Ag_2O (1.5 eq.). Tosyl chloride (1.05 eq.) was then added portionwise and the reaction mixture was stirred at 0°C for 30 minutes. The mixture was then filtered through a pad of Celite® and evaporated. The crude material was purified by silica gel chromatography.

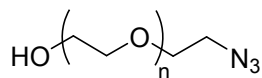
2a, gradient eluent for flash chromatography: Cyclohexane/EtOAc 7/3 to EtOAc. Yield: 77%. ^1H NMR (400 MHz, CDCl_3 , δ ppm): 7.80 (d, $J = 8.2$ Hz, 2H), 7.34 (d, $J = 7.6$ Hz, 2H), 4.16 (t, $J = 4.8$ Hz, 2H), 3.73 – 3.59 (m, 14H), 2.45 (s, 3H), the OH signal is missing. ^{13}C NMR (100 MHz, CDCl_3 , δ ppm): 144.8, 133.1, 129.8 (2C), 128.0 (2C), 72.5, 70.8 – 70.5, 69.2, 68.7, 61.8, 21.6.

2b, gradient eluent for flash chromatography: DCM to DCM/MeOH 95/5. Yield 88%. ^1H NMR (400 MHz, CDCl_3 , δ ppm): 7.77 (d, $J = 8.2$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H), 4.14 (t, $J = 4.8$ Hz, 2H), 3.72 – 3.53 (m, 22H), 2.42 (s, 3H), the OH signal is missing. ^{13}C NMR (100 MHz, CDCl_3 , δ ppm): 144.8, 133.1, 129.8 (2C), 128.0 (2C), 72.6, 70.7 – 70.3, 69.3, 68.7, 61.7, 21.6.

¹ J. Václavík, R. Zschoche, I. Klimánková, V. Matoušek, P. Beier, D. Hilvert and A. Togni, *Chem. Eur. J.*, 2017, **23**, 6490-6494.

² Z. Zhu, J. Wang, A. I. Lopez, F. Yu, Y. Huang, A. Kumar, S. Li, L. Zhang and C. Cai, *Biomater. Sci.*, 2015, **3**, 842-851.

3a, 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethan-1-ol, C₈H₁₇N₃O₄, MW = 219.24 g/mol.¹
3b, 17-azido-3,6,9,12,15-pentaoxaheptadecan-1-ol, C₁₂H₂₅N₃O₆, MW = 307.35 g/mol.²



n = 3, **3a**

n = 5, **3b**

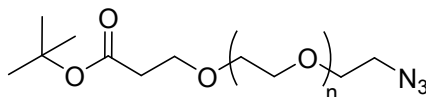
General procedure: To a solution of tosylate (**2a** or **2b**) in DMF (1 mmol/mL) was added NaN₃ (1.5 eq.). The reaction mixture was stirred at 50°C for 12 hours and filtered through a pad of celite. After concentration, DCM was added and the solution was washed with brine three times. The organic layer was dried over MgSO₄ and concentrated. The crude material was purified by silica gel flash chromatography (EtOAc to EtOAc/MeOH 9/1).

3a, Yield: 97%. ¹H NMR (400 MHz, CDCl₃, δ ppm): 3.75 – 3.71 (m, 2H), 3.69 – 3.66 (m, 10H), 3.62–3.61 (m, 2H), 3.39 (t, *J* = 5.0 Hz, 2H), the OH signal is missing. ¹³C NMR (100 MHz, CDCl₃, δ ppm): 72.6, 70.8 – 70.7, 70.5, 70.2, 61.9, 50.8.

3b, Yield: 96%. ¹H NMR (400 MHz, CDCl₃, δ ppm): 3.75 – 3.70 (m, 2H), 3.69 – 3.63 (m, 18H), 3.63–3.57 (m, 2H), 3.39 (t, *J* = 5.1 Hz, 2H). The OH signal is missing. ¹³C NMR (100 MHz, CDCl₃, δ ppm): 72.5, 70.7 – 70.6, 70.4, 70.0, 61.8, 50.7.

4a, *tert*-butyl 1-azido-3,6,9,12-tetraoxapentadecan-15-oate, C₁₅H₂₉N₃O₆, MW = 347.21 g/mol.³

4b, *tert*-butyl 1-azido-3,6,9,12,15,18-hexaoxahenicosan-21-oate, C₁₉H₃₇N₃O₈, MW = 435.52 g/mol.²



n = 3, **4a**

n = 5, **4b**

General procedure: To a solution of oligoethylene azide (**3a** or **3b**) in THF (0.3 mmol/mL) at 0°C was added *tert*-butyl acrylate (1.3 eq.). *t*-BuOK (0.1 eq.) was then added portionwise at 0°C and the reaction mixture was stirred at room temperature for 5 hours. After concentration, an aqueous solution of NaH₂PO₄ (1 M) was added and the mixture was extracted three times with EtOAc. The organic layers were dried over MgSO₄, filtered and evaporated. The crude material was purified by flash chromatography (Cyclohexane/EtOAc 8/2 to EtOAc).

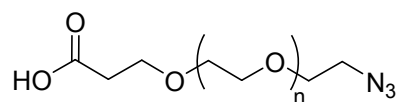
4a, Yield: 68%. ¹H NMR (400 MHz, CDCl₃, δ ppm): 3.72 – 3.59 (m, 16H), 3.39 (t, *J* = 5.2 Hz, 2H), 2.50 (t, *J* = 6.6 Hz, 2H), 1.44 (s, 9H). ¹³C NMR (100 MHz, CDCl₃, δ ppm): 169.9, 79.5, 69.7 – 69.6, 69.5, 69.4, 69.0, 65.9, 49.7, 35.3, 27.1 (3C).

4b, Yield: 72%. ¹H NMR (400 MHz, CDCl₃, δ ppm): 3.77 – 3.53 (m, 24H), 3.38 (t, *J* = 5.1 Hz, 2H), 2.49 (t, *J* = 6.6 Hz, 2H), 1.44 (s, 9H). ¹³C NMR (100 MHz, CDCl₃, δ ppm): 170.9, 80.5, 70.7 – 70.5, 70.4, 70.0, 66.9, 53.4, 50.7, 36.3, 28.1 (3C).

³ A. Garofalo, A. Parat, C. Bordeianu, C. Ghobril, M. Kueny-Stotz, A. Walter, J. Jouhannaud, S. Begin-Colina and D. Felder-Flesch, *New J. Chem.*, 2014, **38**, 5226-5239.

5a, 1-azido-3,6,9,12-tetraoxapentadecan-15-oic acid, C₁₁H₂₁N₃O₆, MW = 291.30 g/mol.⁴

5b, 1-azido-3,6,9,12,15,18-hexaoxahenicosan-21-oic acid, C₁₅H₂₉N₃O₈, MW = 379.41 g/mol.⁵



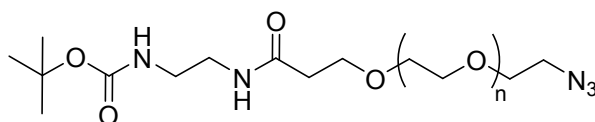
n = 3, **5a**

n = 5, **5b**

General procedure: To a solution of tert-butyl ester (**4a** or **4b**) in DCM (0.2 mmol/mL) was added a 4 M HCl solution in dioxane (15 eq., 4 M) and the reaction was stirred at room temperature for 12h. Concentration of the reaction mixture afforded the corresponding carboxylic acid.

5a, Yield: 99%. ¹H NMR (400 MHz, CDCl₃, δ ppm): 3.78 (t, *J* = 6.2 Hz, 2H), 3.70 – 3.63 (m, 14H), 3.40 (t, *J* = 5.2 Hz, 2H), 2.64 (t, *J* = 6.2 Hz, 2H), the CO₂H signal is missing. ¹³C NMR (100 MHz, CDCl₃, δ ppm): 175.6, 70.4 – 70.2, 69.8, 66.2, 50.5, 34.6.

5b, Yield: 99%. ¹H NMR (400 MHz, CDCl₃, δ ppm): 3.77 (t, *J* = 6.1 Hz, 2H), 3.70 – 3.61 (m, 22H), 3.39 (t, *J* = 5.0 Hz, 2H), 2.61 (t, *J* = 6.1 Hz, 2H), the CO₂H signal is missing. ¹³C NMR (100 MHz, CDCl₃, δ ppm): 174.8, 70.7 – 70.5, 70.3, 70.0, 66.5, 50.7, 35.0.



n = 3, **6a**

n = 5, **6b**

6a, *tert*-Butyl (1-azido-15-oxo-3,6,9,12-tetraoxa-16-azaoctadecan-18-yl)carbamate, C₁₈H₃₅N₅O₇, MW=433.5 g/mol.

6b, *tert*-Butyl (1-azido-21-oxo-3,6,9,12,15,18-hexaoxa-22-azatetracosan-24-yl)carbamate, C₂₂H₄₃N₅O₉, MW= 521.6 g/mol.

General procedure: To a solution of acid oligoethylene derivative (**5a** or **5b**) in DCM (0.5 mmol/mL) were added HOBt (1.3 eq.) and EDC (1.3 eq.). The solution was stirred 15 minutes at room temperature. A solution of *N*-boc ethylene diamine (1.1 eq.) and TEA (3 eq.) in DCM (0.5 mmol/mL of *N*-boc ethylene diamine) was added and the reaction was stirred at room temperature for 12 hours. After concentration, water was added and the solution was extracted with DCM. The crude material was purified by silica gel flash chromatography.

6a, Yield: 75%. Gradient eluent for flash chromatography: DCM to DCM/MeOH 9/1. Yield: 72%. ¹H NMR (400 MHz, CDCl₃, δ ppm): 6.92 (brs, 1H), 5.19 (brs, 1H), 3.72 (t, *J* = 5.7 Hz, 2H), 3.69 – 3.61 (m, 14H), 3.45 – 3.30 (m, 4H), 3.29 – 3.18 (m, 2H), 2.46 (t, *J* = 5.4 Hz, 2H), 1.46 (s, 9H). ¹³C NMR (100 MHz, CDCl₃, δ ppm): 172.1, 156.4, 79.1, 77.4, 77.1, 76.8, 70.6, 70.6, 70.5, 70.5, 70.3, 70.2, 79.0, 67.2, 50.7, 40.5, 39.1, 37.0, 28.4, 28.3. MS (ESI) *m/z*: 522.1 [M + H]⁺. HRMS (ESI, *m/z*): calcd for C₁₈H₃₅N₅NaO₇⁺ [M+Na]⁺ 456.2429; found 456.2426.

⁴ C. M. Steinkuhler, P. M. Gallinari, B. Osswald, N. Sewald, M. Ritzefeld and M. Frese, PCT Int. Appl., 2016146638, 2016.

⁵ S. Tamura, S. Inomata, M. Ebine, T. Genji, I. Iwakura, M. Mukai, M. Shoji, T. Sugai and M. Ueda, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 188-193.

6b, Yield: 78%. Gradient eluent for flash chromatography: EtOAc to EtOAc/MeOH 9/1. Yield: 84%. ^1H NMR (400 MHz, CDCl_3 , δ ppm): 6.87 (brs, 1H), 5.24 (brs, 1H), 3.75 – 3.62 (m, 24H), 3.40 (s, 4H), 3.29 – 3.20 (m, 2H), 2.46 (t, $J = 5.7$ Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3 , δ ppm): 172.2, 156.4, 79.2, 70.8 – 70.5, 70.4, 70.3, 70.0, 67.3, 50.7, 40.7, 39.7, 37.0, 28.5. MS (ESI) m/z : 434.2 $[\text{M} + \text{H}]^+$. HRMS (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{43}\text{N}_5\text{NaO}_9^+$ $[\text{M} + \text{Na}]^+$ 544.2953; found 544.2955.

3 Reductive azide dimerization

3.1 Optimization of reductive azide dimerization

The optimization of the reductive azide dimerization step was then performed using the hetero-bifunctional OEG_4 **4a** as model substrate. We screened several parameters, including the catalyst loading, the reactant concentration, the temperature and the solvent, and compared by ^1H -NMR spectroscopy the ratio between the expected dimer **8a** and the amine side-product **7a** resulting from the simple reduction. The ^1H -NMR ratios were determined by integrating the peaks corresponding to the protons located in the alpha position of the amine group (2 ^1H for compound **7a** and 4 ^1H for compound **8a**, **Figure 1**). The results are summarized in Table 1.

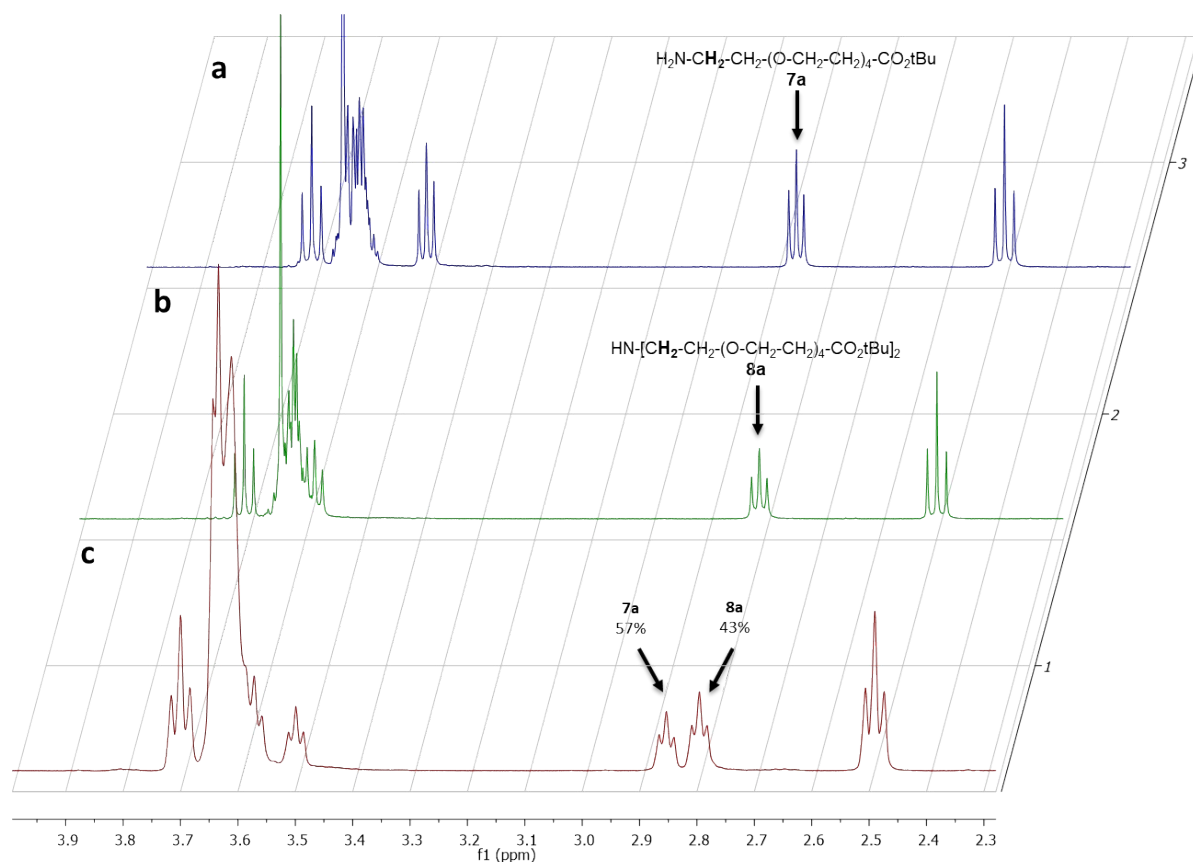
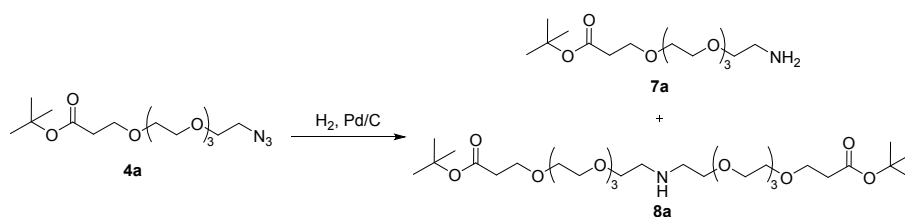


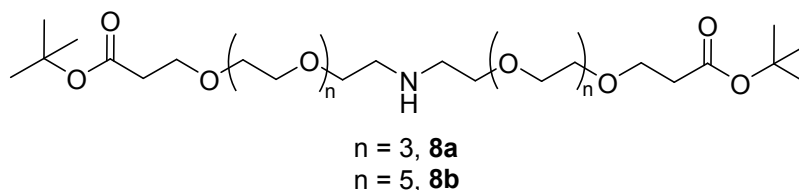
Figure 1 : Determination of dimer **8a and amine side-product **7a** ^1H NMR ratio.** a. Amine side-product **7a** ^1H NMR. b. Expected dimer **8a** ^1H NMR. c. Dimerization crude ^1H NMR, [azide **4a**] = 500 mM in EtOH, Pd/C 5% mol. (Table 1, entry 7).



Entry	[4a] mM	Solv.	T°C	Pd/C (mol%)	7a ^a	8a ^a
1	250	EtOH	20	1	82	18
2	250	EtOH	20	2,5	69	31
3	250	EtOH	20	5	58	42
4	250	EtOH	20	7.5	56	44
5	250	EtOH	20	10	56	44
6	100	EtOH	20	5	63	37
7	500	EtOH	20	5	57	43
8	700	EtOH	20	5	56	44
9	500	EtOH	0	5	61	39
10	500	EtOH	40	5	39	61
11	500	EtOH	50	5	25	75
12	500	EtOH	60	5	21	79
13	500	EtOAc	60	5	7	93
14	500	Diox.	60	5	7	93
15	500	THF	60	5	10	90

Table 1: Optimization of reductive azide dimerization. ^aratios determined by ^1H NMR spectroscopy by integrating the peaks corresponding to the protons located in the alpha position of the amine group.

3.2 Synthesis of trifunctional V-shaped *N,N*-bis-oligoelthyleneglycol-amine



8a, di-*tert*-butyl 4,7,10,13,19,22,25,28-octaoxa-16-azahentriacontane-1,31-dioate, $C_{30}H_{59}NO_{12}$, MW = 625.79 g/mol.

8b, di-*tert*-butyl 4,7,10,13,16,19,25,28,31,34,37,40-dodecaoxa-22-azatritetracontane-1,43-dioate, $C_{38}H_{75}NO_{16}$, MW = 802.00 g/mol.

General procedure: To a solution of azide derivative (**4a** or **4b**) in degassed dioxane (0.5 mmol/mL) was added Pd/C (0.05 eq.). The solution was stirred 4 hours at 60 °C under a hydrogen atmosphere. After cooling at room temperature, the mixture was diluted in DCM and filtered through a pad of Celite®. After concentration, the crude material was purified by flash chromatography (SiOH prelabably desactivated with a solution of DCM/MeOH/NH₄OH 9/0.9/0.1, eluent gradient DCM to DCM/MeOH/NH₄OH 9/0.9/0.1).

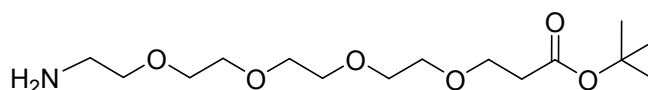
8a, Yield: 78%. ¹H NMR (400 MHz, CDCl₃, δ ppm): 3.71 (t, *J* = 6.6 Hz, 4H), 3.66 – 3.52 (m, 28H), 2.81 (t, *J* = 5.4 Hz, 4H), 2.50 (t, *J* = 6.6 Hz, 4H), 1.44 (s, 18H). The NH signal is missing. ¹³C NMR (100 MHz, CDCl₃, δ ppm): 169.8, 79.4 (2C), 69.60 – 69.4, 65.9, 48.2, 35.3, 27.11 (6C).

HRMS (ESI, *m/z*): calcd for $C_{30}H_{60}NO_{12}^+$ [M+H]⁺ 626.4110; found 626.4171.

8b, Yield: 74%. ¹H NMR (400 MHz, CDCl₃, δ ppm): 3.70 (t, *J* = 6.6 Hz, 4H), 3.66 – 3.55 (m, 44H), 2.80 (d, *J* = 5.4 Hz, 4H), 2.49 (t, *J* = 6.6 Hz, 4H), 1.44 (s, 18H). The NH signal is missing. ¹³C NMR (100 MHz, CDCl₃, δ ppm): 170.9, 80.5 (2C), 70.6 – 70.3, 66.9, 49.2, 36.3, 28.1 (6C). MS (ESI) *m/z*: 802.5 [M + H]⁺.

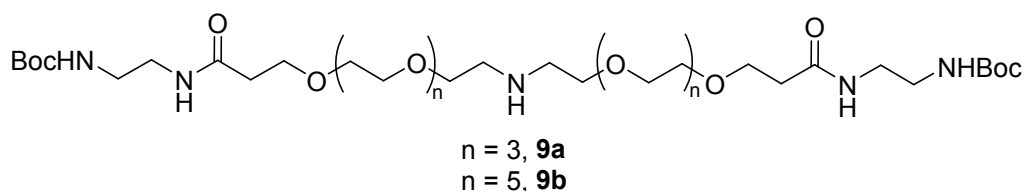
HRMS (ESI, *m/z*): calcd for $C_{38}H_{76}NO_{16}^+$ [M+H]⁺ 802.5157; found 802.5175.

Characterization of amine side-product **7a**:



7a, *tert*-butyl 1-amino-3,6,9,12-tetraoxapentadecan-15-oate,⁶ $C_{15}H_{31}NO_6$, MW = 321.41 g/mol. ¹H NMR (400 MHz, CDCl₃, δ ppm): 3.71 (t, *J* = 6.6 Hz, 2H), 3.67 – 3.58 (m, 12H), 3.51 (t, *J* = 5.2 Hz, 2H), 2.86 (t, *J* = 5.2 Hz, 2H), 2.50 (t, *J* = 6.6 Hz, 2H), 1.44 (s, 9H). The NH₂ signal is missing. ¹³C NMR (100 MHz, CDCl₃, δ ppm): 170.6, 80.1, 72.7, 70.3 – 70.0, 66.6, 41.3, 36.1, 27.9 (3C).

⁶ H. Herzner and H. Kunz, *Carbohydr. Res.*, 2007, **342**, 541-557.



9a, di-*tert*-Butyl (4,34-dioxo-7,10,13,16,22,25,28,31-octaoxa-3,19,35-triazaheptatriacontane-1,37-diyl)dicarbamate, $C_{36}H_{71}N_5O_{14}$, MW = 797.97 g/mol.

9b, di-*tert*-Butyl (4,46-dioxo-7,10,13,16,19,22,28,31,34,37,40,43-dodecaoxa-3,25,47-triazanonatetracontane-1,49-diyl)dicarbamate, $C_{44}H_{87}N_5O_{18}$, MW = 974.18 g/mol.

General procedure: To a solution of azide derivative (**6a** or **6b**) in degassed dioxane (0.5 mmol/mL) was added Pd/C (0.05 eq.). The solution was stirred 4 hours at 60 °C under a hydrogen atmosphere. After cooling at room temperature, the mixture was diluted in DCM and filtered through a pad of Celite®. After concentration, the crude material was purified by flash chromatography (SiOH prealably desactivated with a solution of DCM/MeOH/NH₄OH 9/0.9/0.1, eluent gradient DCM to DCM/MeOH/NH₄OH 9/0.9/0.1).

9a, Yield: 72%. ¹H NMR (400 MHz, CDCl₃, δ ppm): 6.95 (brs, 2H), 5.33 (brs, $J = 12.5$ Hz, 2H), 3.74 – 3.55 (m, 32H), 3.38 – 3.32 (m, 4H), 3.27 – 3.19 (m, $J = 5.3$ Hz, 4H), 2.80 (t, $J = 5.3$ Hz, 4H), 2.46 (t, $J = 5.8$ Hz, 4H), 1.43 (s, 18H). The NH signal is missing. ¹³C NMR (100 MHz, CDCl₃, δ ppm): 172.2, 156.4, 79.2 (2C), 77.4, 77.2, 77.0, 76.7, 70.6 – 70.2, 67.3, 49.2, 40.6, 39.7, 37.0, 28.5 (6C). MS (ESI) m/z : 974.4 [M + H]⁺.

HRMS (ESI, m/z): calcd for $C_{30}H_{60}NO_{12}^+$ [M+H]⁺ 798.5070; found 798.5049.

9b, Yield: 84%. ¹H NMR (400 MHz, CDCl₃, δ ppm): 6.93 (brs, 2H), 5.30 (brs, 2H), 3.72 (t, $J = 5.7$ Hz, 4H), 3.68 – 3.54 (m, 44H), 3.38 – 3.30 (m, 4H), 3.28 – 3.18 (m, 4H), 2.81 (t, $J = 5.2$ Hz, 4H), 2.46 (t, $J = 5.7$ Hz, 4H), 1.43 (s, 18H). The NH signal is missing. ¹³C NMR (100 MHz, CDCl₃, δ ppm): 171.7, 156.2, 78.5 (2C), 70.3 – 70.0, 67.0, 48.9, 40.2, 39.5, 36.7, 28.3 (6C). MS (ESI) m/z : 978.4 [M + H]⁺.

HRMS (ESI, m/z): calcd for $C_{30}H_{60}NO_{12}^+$ [M+H]⁺ 974.6119; found 974.6083.

3.3 Mechanistic study

To a solution of **4a** (1 eq., 1 g, 4.56 mmol) in EtOH (7.5 mL) was added Pd/C (5 %, 242 mg, 0.228 mmol). The mixture was stirred under atmospheric pressure of H₂. Aliquots were taken from the reaction mixture at regular intervals (0 min, 30 min, 1 h, 3 h and 22 h), filtered through a celite pad, concentrated under reduced pressure and analysed by ¹H NMR spectroscopy (**Figure 2**).

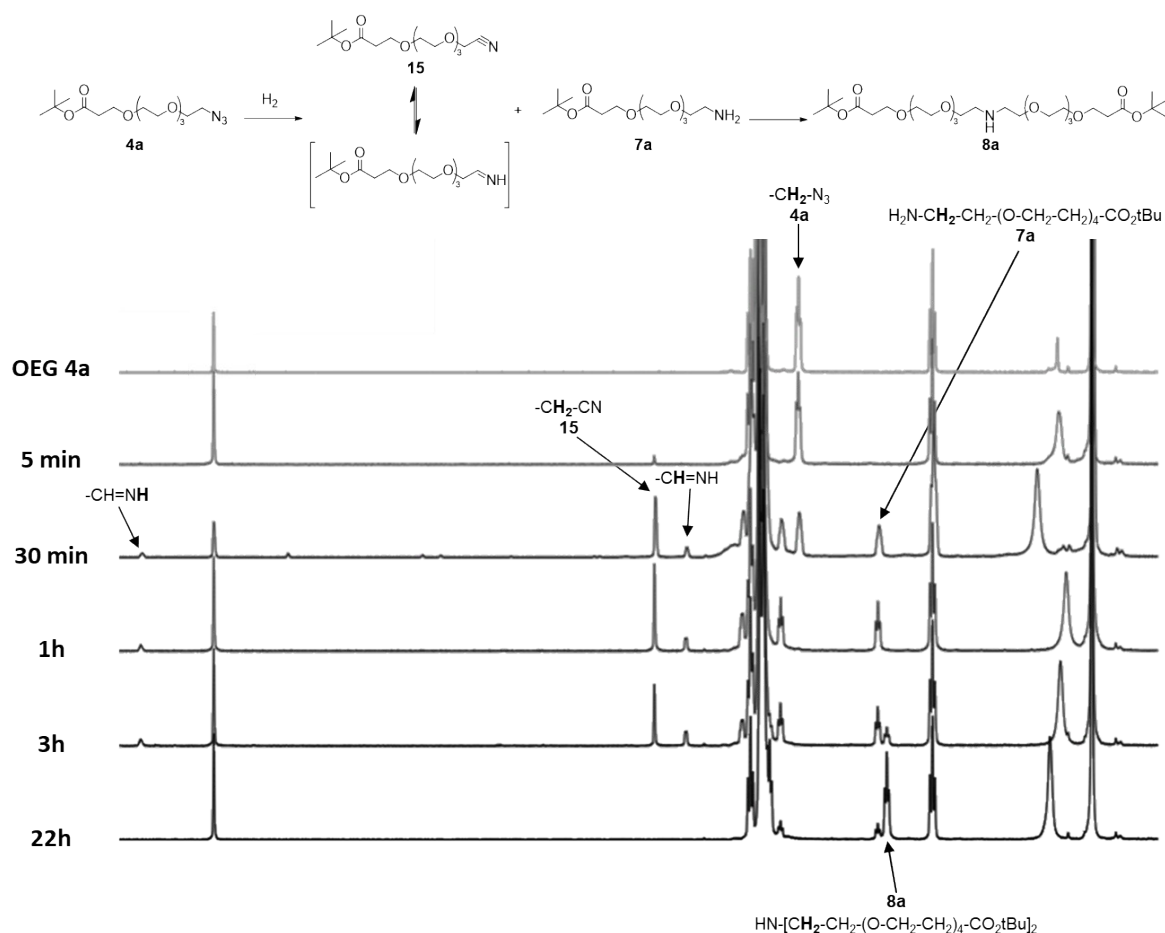
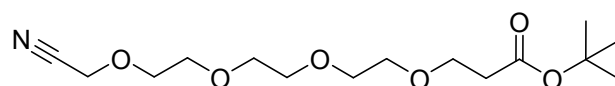


Figure 2 : ^1H NMR monitoring of reductive azide dimerization.

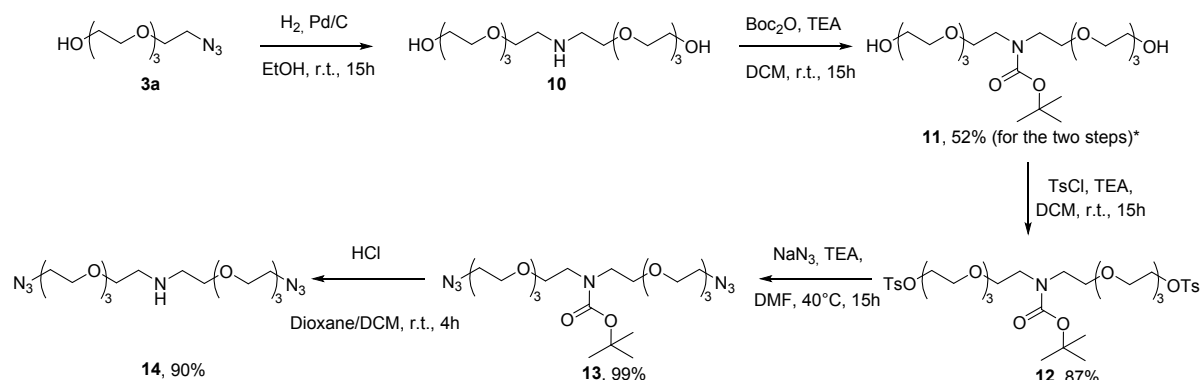
Characterization of nitrile intermediate **15**:



15, *tert*-butyl 1-cyano-2,5,8,11-tetraoxatetradecan-14-oate, $\text{C}_{15}\text{H}_{27}\text{NO}_6$, MW = 317.38 g/mol. ^1H NMR (400 MHz, CDCl_3 , δ ppm): 4.34 (s, 2H), 3.81 – 3.53 (m, 14H), 2.50 (t, $J = 6.6$ Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3 , δ ppm): 170.9, 116.0, 80.5, 70.7 – 70.3, 66.9, 56.7, 36.3, 28.1.

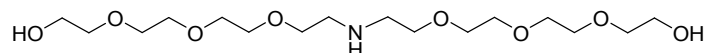
HRMS (ESI, m/z): calcd for $\text{C}_{15}\text{H}_{27}\text{NNaO}_6^+$ $[\text{M}+\text{Na}]^+$ 340.1730; found 340.1726.

4 Synthesis of *bis*-azido OEG amine



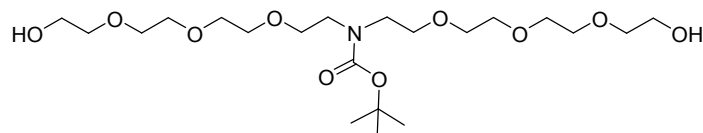
*Isolated yield after dimerization and *N*-boc protection.

10, 3,6,9,15,18,21-hexaoxa-12-azatricosane-1,23-diol, $\text{C}_{16}\text{H}_{35}\text{NO}_8$, MW = 369.46 g/mol



To a solution of **3a** (1 eq., 10 g, 45.6 mmol) in EtOH (72 mL) was added Pd/C (5 %, 0.28 g, 0.26 mmol). The mixture was stirred under atmospheric pressure of H_2 for 12 hours. The reaction mixture was diluted in DCM (150 mL) and filtered through a pad of Celite®. The crude material was used in the next step without purification.

11, *tert*-butyl bis(2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl)carbamate, $\text{C}_{21}\text{H}_{43}\text{NO}_{10}$, MW = 469.57 g/mol

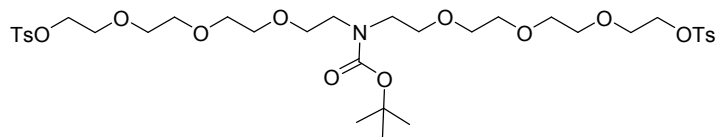


To a solution of **10** (1 eq., 8.43 g, 22.8 mmol) and TEA (3 eq., 9.51 mL, 68.4 mmol) in DCM (150 mL) was added Boc_2O (1.1 eq., 5.48 g, 25.1 mmol). The reaction mixture was stirred overnight at room temperature. 150 mL of an aqueous solution of NaH_2PO_4 (1M) were added and the mixture was extracted with DCM ($3 \times 150\text{mL}$). The crude material was purified by silica gel flash chromatography (EtOAc then DCM to DCM/MeOH 9/1) to afford **11** (5.6 g, 11.9 mmol, 52 %) as a yellowish oil.

^1H NMR (400 MHz, CDCl_3 , δ ppm): 3.73-3.71 (m, 4H), 3.66 – 3.56 (m, 24H), 3.45 – 3.42 (m, 4H), 1.44 (s, 9H). The OH signals are missing. ^{13}C NMR (100 MHz, CDCl_3 , δ ppm): 154.9, 79.0, 72.1, 70.1 – 69.8, 69.2 – 69.0, 60.9, 47.3 – 47.1, 27.9 (3C).

HRMS (ESI, m/z): Detected with loss of the Boc group, calcd for $\text{C}_{16}\text{H}_{35}\text{NNaO}_8^+$ [$\text{M-Boc}+\text{Na}$] $^+$ 392.2255; found 392.2271.

12, 12-(*tert*-butoxycarbonyl)-3,6,9,15,18,21-hexaoxa-12-azatricosane-1,23-diyl bis(4-methylbenzenesulfonate), C₃₅H₅₅NO₁₄S₂, MW = 777.94 g/mol

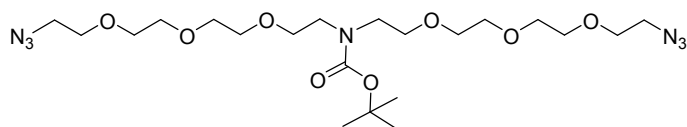


To a solution of dimer **11** (1 eq., 5.6 g, 11.9 mmol) in DCM (150 mL) under argon were added TEA (10 eq., 16.7 mL, 119 mmol) and DMAP (20 %, 0.291 g, 2.39 mmol). The reaction mixture was stirred 5 minutes at 0°C and tosyl chloride (4 eq., 9.09 g, 47.7 mmol) was added. The reaction mixture was stirred 2 hours at room temperature. 200 mL of DCM were added and the mixture was washed with an aqueous solution of NaHCO₃ (3 x 150 mL), dried over MgSO₄ and evaporated. The crude material was purified by silica gel flash chromatography (Cyclohexane/EtOAc 1/1 to EtOAc) to afford **12** (8.1 g, 10.4 mmol, 87 %) as a yellowish oil.

¹H NMR (400 MHz, CDCl₃, δ ppm): 7.66 (d, *J* = 8.1 Hz, 4H), 7.22 (d, *J* = 8.1 Hz, 4H), 4.02 (t, *J* = 4.5 Hz, 4H), 3.55 (t, *J* = 4.5 Hz, 4H), 3.48 – 3.40 (m, 20H), 3.34 – 3.24 (m, 4H), 2.31 (s, 6H), 1.32 (s, 9H). ¹³C NMR (100 MHz, CDCl₃, δ ppm): 155.1, 144.6, 132.8, 129.6 (4C), 127.7 (4C), 79.1, 70.4 – 70.0, 69.4, 69.1, 68.3, 47.7, 47.4, 28.2 (3C), 21.3.

HRMS (ESI, *m/z*): calcd for C₃₅H₅₅NNaO₁₄S₂⁺ [M+Na]⁺ 800.2956; found 800.2963.

13, *tert*-butyl bis(2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl)carbamate, C₂₁H₄₁N₇O₈, MW = 519.60 g/mol

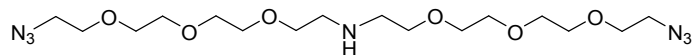


To a solution of **12** (1 eq., 8 g, 10.3 mmol) in DMF (60 mL) was added NaN₃ (4 eq., 2.67 g, 1.45 mL, 41.1 mmol) and the mixture was stirred overnight at 60°C. After concentration, 200 mL of DCM were added and the mixture was filtered through a pad of Celite® and washed with brine (3 x 150 mL). The organic layer was dried over MgSO₄ and evaporated to afford **13** (5.29 g, 10.2 mmol, 99 %) as a yellow oil.

¹H NMR (400 MHz, CDCl₃, δ ppm): 3.83 – 3.49 (m, 24H), 3.51 – 3.30 (m, 8H), 1.44 (s, 9H). ¹³C NMR (100 MHz, CDCl₃, δ ppm): 155.1, 79.1, 71.1, 70.5 – 69.1, 50.5, 47.7, 47.4, 42.6, 28.2 (3C).

HRMS (ESI, *m/z*): calcd for C₂₁H₄₁N₇NaO₁₄⁺ [M+Na]⁺ 542.2909; found 542.2928.

14, bis(2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl)amine, C₁₆H₃₃N₇O₆, MW = 419.48 g/mol

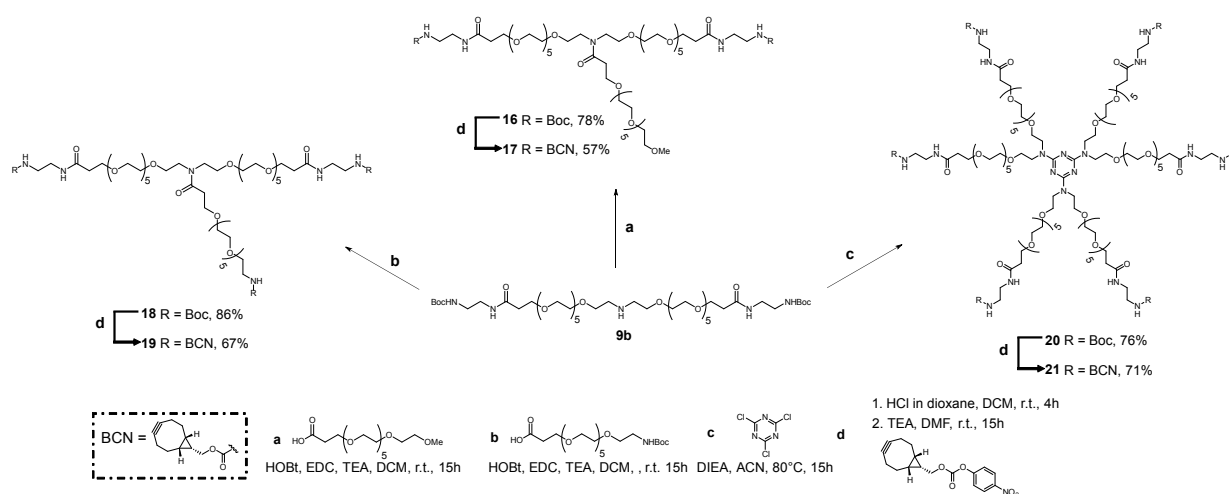


To a solution of **13** (1 eq., 5.25 g, 10.1 mmol) in DCM (65 mL) under argon was added a 4 M HCl solution in dioxane (15 eq., 4 M, 37.9 mL, 151 mmol). The reaction mixture was stirred overnight at room temperature. After concentration, the crude material was purified by silica gel flash chromatography (DCM to DCM/MeOH/NH₄OH 9/0.9/0.1) to afford **14** (3.8 g, 9.06 mmol, 90 %) as a yellow oil.

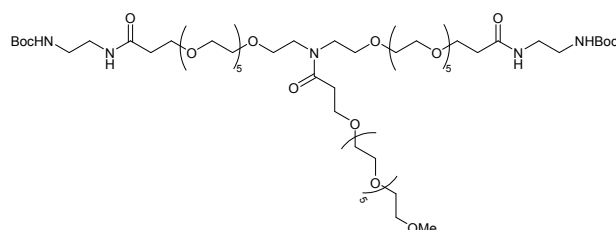
¹H NMR (400 MHz, CDCl₃, δ ppm): 3.72 – 3.54 (m, 24H), 3.39 (t, *J* = 4.9 Hz, 4H), 2.81 (t, *J* = 5.3 Hz, 4H). The NH signal is missing. ¹³C NMR (100 MHz, CDCl₃, δ ppm): 70.1, 69.8, 65.8, 50.6, 46.8.

HRMS (ESI, *m/z*): calcd for C₁₆H₃₃N₇NaO₆⁺ [*M*+Na]⁺ 442.2385; found 442.2384.

5 Synthesis of compact tri- and hexa-functional platforms



16, di-*tert*-butyl (4,46-dioxo-25-(2,5,8,11,14,17,20-heptaioxatricosan-23-oyl)-7,10,13,16,19,22,28,31,34,37,40,43-dodecaoxa-3,25,47-triazanonatetracontane-1,49-diyl)dicarbamate, C₆₀H₁₁₇N₅O₂₆, MW = 1324.61 g/mol



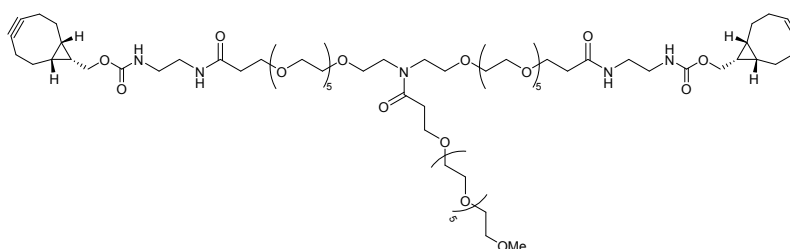
To a solution of 2,5,8,11,14,17,20-heptaioxatricosan-23-oic acid (1.1 eq., 166 mg, 0.452 mmol) in DCM (3 mL) were added HOBT (1.3 eq., 72.1 mg, 0.534 mmol) and EDC (1.3 eq., 82.9 mg, 0.534 mmol). The mixture was stirred at room temperature for 15 min. A solution of **9b** (1 eq., 400 mg, 0.411 mmol) and TEA (3 eq., 124 mg, 1.23 mmol) in DCM (5 mL) were then added and the reaction was stirred at room temperature for 15 h. 70 mL of water were added and the mixture was extracted with DCM (3 x 50 mL). The combined organic layers were dried over MgSO₄ and evaporated. The crude material was purified by silica gel flash

chromatography (gradient: EtOAc 5 min then DCM to DCM/MeOH 85/15) to afford **16** (424 mg, 0.32 mmol, 78 %) as a yellowish oil.

¹H NMR (400 MHz, CDCl₃, δ ppm): 6.90 (brs, 2H), 5.27 (brs, 2H), 3.76 (d, *J* = 6.2 Hz, 2H), 3.72 (t, *J* = 5.7 Hz, 4H), 3.68 – 3.50 (m, 72H), 3.37 (s, 3H), 3.36 – 3.30 (m, 4H), 3.27 – 3.11 (m, 4H), 2.68 (t, *J* = 6.8 Hz, 2H), 2.45 (t, *J* = 5.7 Hz, 4H), 1.43 (s, 18H). ¹³C NMR (100 MHz, CDCl₃, δ ppm): 172.1, 171.3, 156.3, 79.1, 71.9 (2C), 70.7 – 70.3, 70.2, 69.4, 69.3, 67.5, 67.2, 59.0, 48.7, 46.2, 40.6, 39.7, 37.0, 33.5, 28.4 (6C).

HRMS (ESI, *m/z*): calcd for C₆₀H₁₁₇N₅NaO₂₆⁺ [*M*+Na]⁺ 1346.7879; found 1346.7880.

17, bis(((1*R*,8*S*,9*S*)-bicyclo[6.1.0]non-4-yn-9-yl)methyl) (4,46-dioxo-25-(2,5,8,11,14,17,20-heptaotricosan-23-oyl)-7,10,13,16,19,22,28,31,34,37,40,43-dodecaoxa-3,25,47-triazanonatetracontane-1,49-diyl)dicarbamate, C₇₂H₁₂₅N₅O₂₆, MW = 1476.80 g/mol.

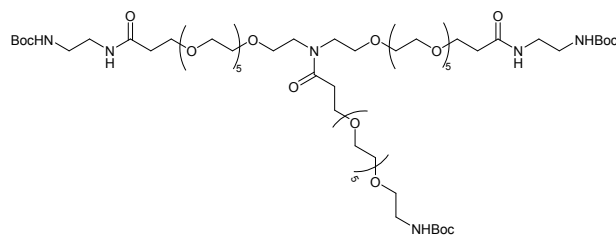


To a solution of **16** (1 eq., 225 mg, 0.16 mmol) in DCM (2 mL) was added a 4M HCl solution in dioxane (30 eq., 1.2 mL, 4.79 mmol). The mixture was stirred at room temperature for 4 h. After evaporation, the crude material was directly dissolved in DMF (2 mL). TEA (5 eq., 80.8 mg, 0.111 mL, 0.798 mmol) and (1*R*,8*S*,9*S*)-bicyclo[6.1.0]non-4-yn-9-ylmethyl (4-nitrophenyl) carbonate (3 eq., 150 mg, 0.479 mmol) were then added and the reaction was stirred for 15 h at room temperature. After concentration, 50 mL of water were added and the mixture was extracted with DCM (4 x 50mL). The combined organic layers were dried over MgSO₄ and evaporated. The crude material was purified by silica gel flash chromatography (gradient: EtOAc 5 min then DCM to DCM/MeOH 90/10) to afford **17** (175 mg, 0.107 mmol, 67 %) as a yellowish oil.

¹H NMR (400 MHz, DMSO-d₆, δ ppm): 7.84 (brs, 2H), 7.04 (brt, *J* = 5.2 Hz, 2H), 4.02 (d, *J* = 8.0 Hz, 4H), 3.62 – 3.38 (m, 78H), 3.23 (s, 3H), 3.14 – 3.02 (m, 4H), 3.04 – 2.92 (m, 4H), 2.58 (t, *J* = 6.8 Hz, 2H), 2.28 (t, *J* = 6.5 Hz, 4H), 2.17 (dd, *J* = 27.7, 11.0 Hz, 12H), 1.64 – 1.41 (m, 4H), 1.33 – 1.16 (m, 2H), 0.85 (t, *J* = 9.7 Hz, 4H). ¹³C NMR (125 MHz, CDCl₃, δ ppm): 172.4, 171.3, 157.1, 98.8, 71.9, 70.7 – 70.3, 70.2, 69.3, 69.3, 69.0, 67.5, 67.2, 59.0, 48.7, 46.2, 41.13, 39.5, 36.9, 33.5, 33.3, 29.7, 23.8, 22.8, 21.4.

HRMS (ESI, *m/z*): calcd for C₇₂H₁₂₅N₅NaO₂₆⁺ [*M*+Na]⁺ 1498.8505; found 1498.8567.

18, di-*tert*-butyl (25-(2,2-dimethyl-4-oxo-3,8,11,14,17,20,23-heptaotxa-5-azahexacosan-26-oyl)-4,46-dioxo-7,10,13,16,19,22,28,31,34,37,40,43-dodecaoxa-3,25,47-triazanonatetracontane-1,49-diyl)dicarbamate, C₆₄H₁₂₄N₆O₂₇, MW = 1408.85 g/mol

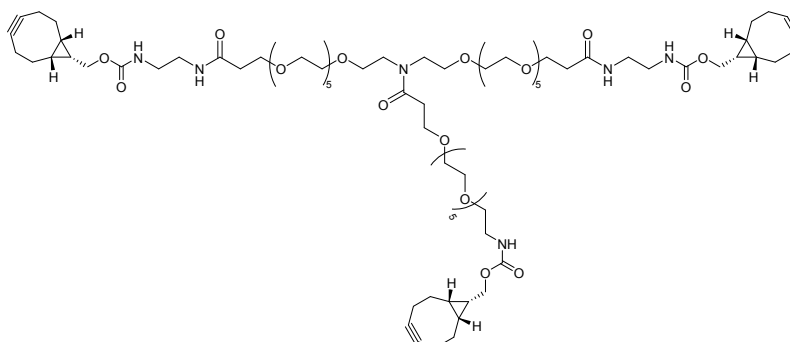


To a solution of 1-[[*(tert*-butoxy)carbonyl]amino}-3,6,9,12,15,18-hexaoxahenicosan-21-oic acid (1.1 eq., 204 mg, 0.452 mmol) in DCM (3 mL) were added HOBt (1.3 eq., 72.1 mg, 0.534 mmol) and EDC (1.3 eq., 82.9 mg, 0.534 mmol). The mixture was stirred at room temperature for 15 min. A solution of **9b** (1 eq., 400 mg, 0.411 mmol) and TEA (3 eq., 0.171 mL, 1.23 mmol) in DCM (5 mL) were then added and the reaction was stirred at room temperature for 15 h. 70 mL of water were added and the mixture was extracted with DCM (3 x 50 mL). The combined organic layers were dried over MgSO_4 and evaporated. The crude material was purified by silica gel flash chromatography (gradient: EtOAc 5 min then DCM to DCM/MeOH 85/15) to afford **18** (495 mg, 0.351 mmol, 86 %) as a yellowish oil.

^1H NMR (400 MHz, CDCl_3 , δ ppm): 6.91 (brs, 2H), 5.27 (brs, 2H), 5.07 (brs, 1H), 3.72 (t, J = 5.7 Hz, 4H), 3.70 (d, J = 6.9 Hz, 2H), 3.68 – 3.46 (m, 70H), 3.39 – 3.27 (m, 6H), 3.27 – 3.17 (m, 4H), 2.68 (t, J = 6.9 Hz, 2H), 2.45 (t, J = 5.7 Hz, 4H), 1.43 (s, J = 1.5 Hz, 27H). ^{13}C NMR (100 MHz, CDCl_3 , δ ppm): 171.9, 171.2, 156.3, 155.9, 78.8 (3C), 70.6, 70.5 – 70.0, 69.2, 69.2, 67.4, 67.1, 53.5, 48.6, 46.1, 40.4, 40.3, 39.6, 36.8, 33.4, 28.4 (6C), 28.3 (3C).

HRMS (ESI, m/z): calcd for $\text{C}_{64}\text{H}_{124}\text{N}_6\text{NaO}_{27}^+$ $[\text{M}+\text{Na}]^+$ 1431.8407; found 1431.8434.

19, *bis*((*(1R,8S,9S)*-bicyclo[6.1.0]non-4-yn-9-yl)methyl) (25-(1-((*(1R,8S,9S)*-bicyclo[6.1.0]non-4-yn-9-yl)-3-oxo-2,7,10,13,16,19,22-heptaoxa-4-azapentacosan-25-oyl)-4,46-dioxo-7,10,13,16,19,22,28,31,34,37,40,43-dodecaoxa-3,25,47-triazanonatetracontane-1,49-diyl)dicarbamate, $\text{C}_{82}\text{H}_{136}\text{N}_6\text{O}_{27}$, MW = 1638.01 g/mol.



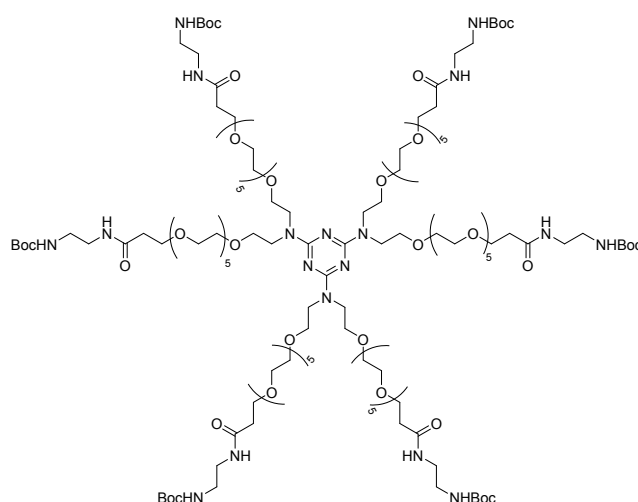
To a solution of **18** (1 eq., 225 mg, 0.16 mmol) in DCM (2 mL) was added a 4 M HCl solution in dioxane (30 eq., 4.79 mmol, 1.2 mL). The mixture was stirred at room temperature for 4 h. After evaporation the crude material was directly dissolved in DMF (5 mL). TEA (5 eq., 0.798 mmol, 0.111 mL) and (*(1R,8S,9S)*-bicyclo[6.1.0]non-4-yn-9-ylmethyl (4-nitrophenyl) carbonate (3 eq., 150 mg, 0.479 mmol) were then added and the reaction was stirred at room temperature for 15 h. After concentration, 50 mL of water were added and the mixture was extracted with DCM (50 x 4). The combined organic layers were dried over MgSO_4 and evaporated. The

crude material was purified by silica gel flash chromatography (gradient EtOAc 5 min then DCM to DCM/MeOH 90/10) to afford **19** (175 mg, 0.107 mmol, 67 %) as a yellowish oil.

^1H NMR (400 MHz, CDCl_3 , δ ppm): 6.95 (brs, 2H), 5.54 (brs, 2H), 5.30 (brs, 1H), 4.23 – 4.07 (m, 6H), 3.76 (t, $J = 7.1$ Hz, 2H), 3.72 (t, $J = 5.6$ Hz, 4H), 3.69 – 3.49 (m, 70H), 3.42 – 3.33 (m, 6H), 3.33 – 3.25 (m, 4H), 2.68 (t, $J = 7.0$ Hz, 2H), 2.46 (t, $J = 5.6$ Hz, 4H), 2.38 – 2.13 (m, 18H), 1.65 – 1.48 (m, 6H), 1.42 – 1.28 (m, 3H), 1.04 – 0.76 (m, $J = 8.7$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3 , δ ppm): 172.3, 171.3, 157.1, 156.8, 129.4, 98.8, 70.7, 70.5 – 70.1, 69.3, 69.3, 67.4, 67.2, 62.6, 53.4, 48.7, 46.2, 41.1, 40.8, 39.5, 36.9, 33.5, 29.0, 21.4, 20.1, 17.8.

HRMS (ESI, m/z): calcd for $\text{C}_{82}\text{H}_{136}\text{N}_6\text{NaO}_{27}^+$ $[\text{M}+\text{Na}]^+$ 1659.9346; found 1659.9337.

20, hexa-*tert*-butyl ((1,3,5-triazine-2,4,6-triyl)tris(4,46-dioxo-7,10,13,16,19,22,28,31,34,37,40,43-dodecaoxa-3,25,47-triazanonatetracontane-25,1,49-triyl))hexacarbamate, $\text{C}_{135}\text{H}_{258}\text{N}_{18}\text{O}_{54}$, MW = 1638.01 g/mol.

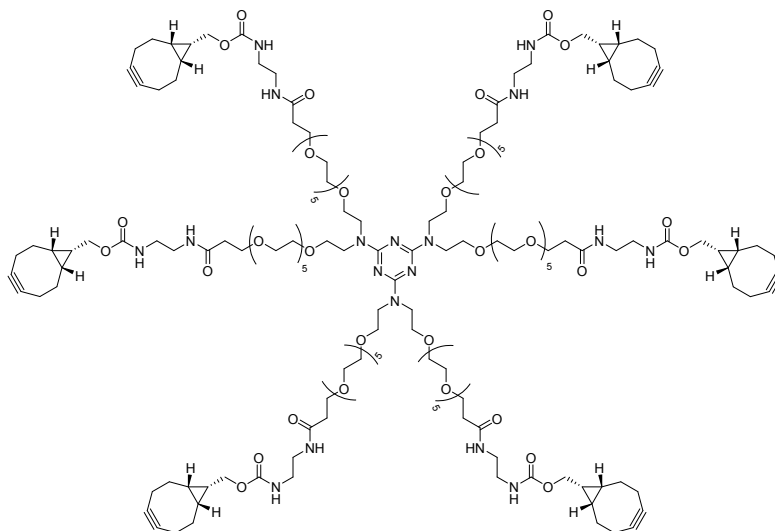


In a sealed tube, at room temperature, were introduced cyanuric chloride (1 eq., 16.4 mg, 0.00854 mL, 0.089 mmol), acetonitrile (2 mL), DIEA (5 eq., 57.5 mg, 0.0735 mL, 0.445 mmol) and **9b** (6 eq., 520 mg, 0.534 mmol). The reaction mixture was stirred at 120°C for 15 h. After concentration, 75 mL of an aqueous solution of citric acid (0.1M) were added and the solution was extracted three times with DCM (75 mL). The combined organic layers were dried over MgSO_4 and evaporated. The crude material was purified by silica gel flash chromatography (gradient EtOAc 5 min then DCM to DCM/MeOH 85/15) to afford **20** (203 mg, 0.0677 mmol, 76 %) as a yellow oil.

^1H NMR (400 MHz, CDCl_3 , δ ppm): 6.93 (brs, 6H), 5.30 (brs, 6H), 3.76 – 3.47 (m, 156H), 3.40 – 3.28 (m, 12H), 3.28 – 3.13 (m, 12H), 2.45 (t, $J = 5.6$ Hz, 12H), 1.43 (s, 54H). ^{13}C NMR (100 MHz, CDCl_3 , δ ppm): 172.0, 164.8, 156.3, 78.9 (6C), 70.5 – 70.1, 69.5, 67.2, 53.5, 47.7, 40.4, 39.7, 36.9, 28.4 (18C).

HRMS (ESI, m/z): calcd for $\text{C}_{135}\text{H}_{258}\text{N}_{18}\text{Na}_2\text{O}_{54}^{2+}$ $[\text{M}+2\text{Na}]^{2+}$ 1521.3907; found 1521.3896.

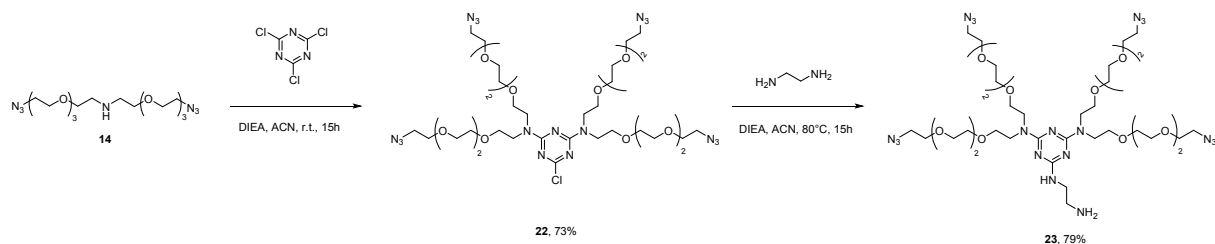
21, hexakis(((1*R*,8*S*,9*S*)-bicyclo[6.1.0]non-4-yn-9-yl)methyl) ((1,3,5-triazine-2,4,6-triyl)tris(4,4,6-dioxo-7,10,13,16,19,22,28,31,34,37,40,43-dodecaoxa-3,25,47-triazanonatetracontane-25,1,49-triyl))hexacarbamate, C₁₇₁H₂₈₂N₁₈O₅₄, MW = 3454.21 g/mol.



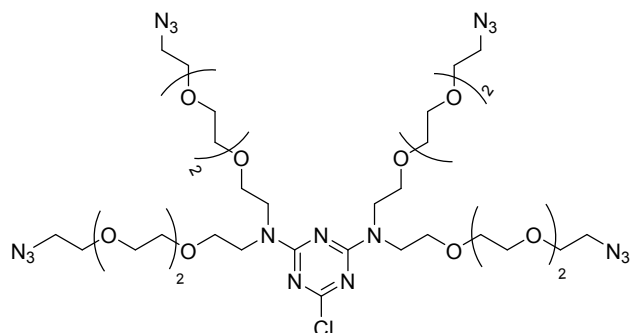
To a solution of **20** (1 eq., 200 mg, 0.0667 mmol) in DCM (1 mL) was added a 4M HCl solution in dioxane (30 eq., 0.5 mL, 2 mmol). The reaction was stirred at room temperature for 2 h. After concentration, the crude material was dissolved in DMF (1 mL). TEA (20 eq., 135 mg, 0.185 mL, 1.33 mmol) and (1*R*,8*S*,9*S*)-bicyclo[6.1.0]non-4-yn-9-ylmethyl (4-nitrophenyl) carbonate (6 eq., 126 mg, 0.4 mmol) were added and the reaction was stirred at room temperature for 15 h. 50 mL of water were added and the mixture was extracted with DCM (4 x 50 mL). The combined organic layers were dried over MgSO₄ and evaporated. The crude material was purified by silica gel flash chromatography (gradient EtOAc 5 min then DCM to DCM/MeOH 90/10) to afford **21** (164 mg, 0.0475 mmol, 71 %) as a yellowish oil.

¹H NMR (400 MHz, DMSO-d₆, δ ppm): 7.83 (brs, 6H), 7.03 (brs, 6H), 4.02 (d, *J* = 7.9 Hz, 12H), 3.72 – 3.36 (m, 156H), 3.12 – 3.03 (m, 12H), 3.03 – 2.94 (m, 12H), 2.28 (t, *J* = 6.5 Hz, 12H), 2.23 – 1.98 (m, 36H), 1.60 – 1.40 (m, 12H), 1.33 – 1.13 (m, 6H), 0.84 (t, *J* = 8.9 Hz, 12H).
HRMS (ESI, *m/z*): calcd for C₁₇₁H₂₈₂N₁₈Na₂O₅₄²⁺ [*M*+2*Na*]²⁺ 1749.4846; found 1749.9926.

6 Synthesis of hetero-functional OEG platforms



22, *N*²,*N*²,*N*⁴,*N*⁴-tetrakis(2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl)-6-chloro-1,3,5-triazine-2,4-diamine, C₃₅H₆₄ClN₁₇O₁₂, MW = 950.45 g/mol

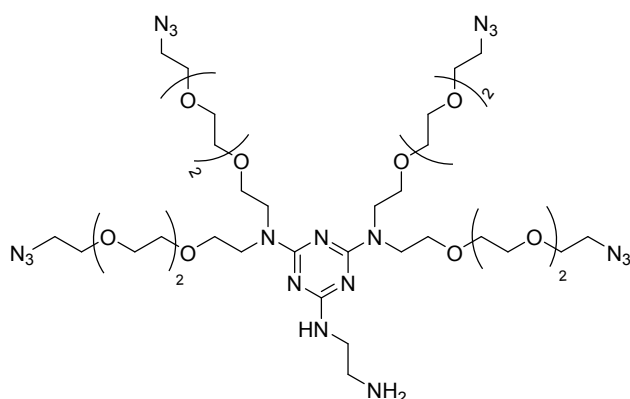


To a solution of **14** (2.1 eq., 700 mg, 1.54 mmol) in acetonitrile (5 mL) and DIEA (10 eq., 1.21 mL, 7.31 mmol) was added cyanuric chloride (1 eq., 134 mg, 0.73 mmol) and the reaction was stirred at room temperature for 5 hours. After concentration, 40 mL of a 10% HCl aqueous solution were added and the mixture was extracted with DCM. The combined organic layers were dried over MgSO₄ and evaporated. The crude material was purified by silica gel flash chromatography (Cyclohexane to EtOAc) to afford **22** (505 mg, 0.53 mmol, 73 %) as a colorless oil.

¹H NMR (400 MHz, CDCl₃, δ ppm): 3.78 (t, *J* = 5.6 Hz, 4H), 3.74 (t, *J* = 5.8 Hz, 4H), 3.70 – 3.54 (m, 48H), 3.39 (t, *J* = 5.0 Hz, 8H). ¹³C NMR (100 MHz, CDCl₃, δ ppm): 168.7, 164.5, 70.5 – 70.4, 70.2, 69.9, 69.2, 68.7, 50.5, 48.1, 47.7, 27.2.

HRMS (ESI, *m/z*): calcd for C₃₅H₆₄ClN₁₇NaO₁₂⁺ [*M*+Na]⁺ 972.4501; found 972.4490.

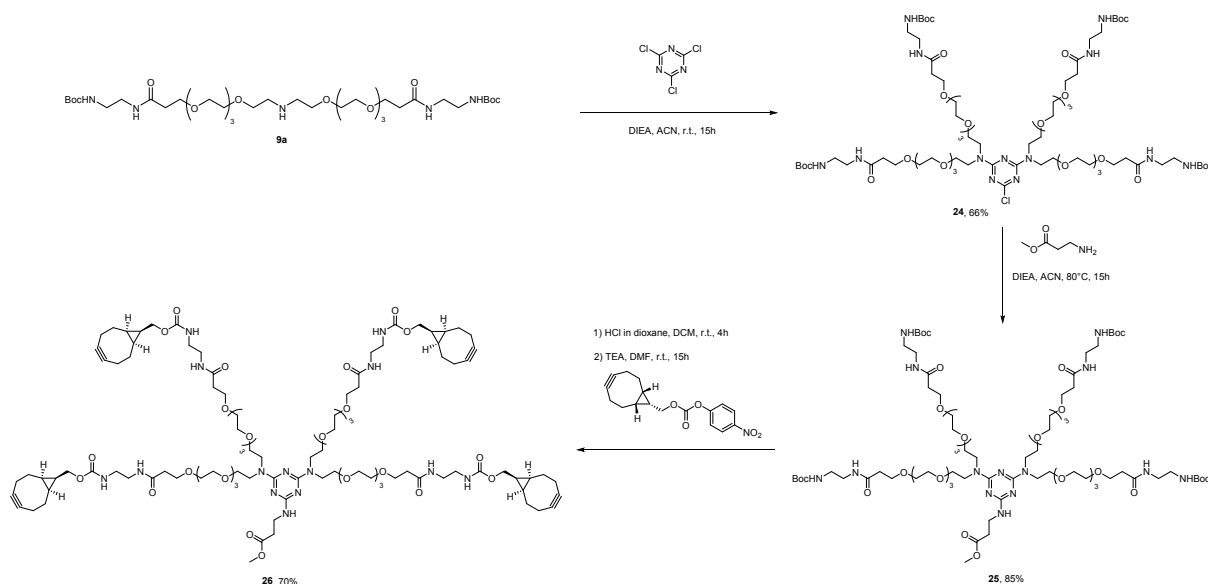
23, *N*²-(2-aminoethyl)-*N*⁴,*N*⁴,*N*⁶,*N*⁶-tetrakis(2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy) ethyl)-1,3,5-triazine-2,4,6-triamine, C₃₇H₇₁N₁₉O₁₂, MW = 974.10 g/mol



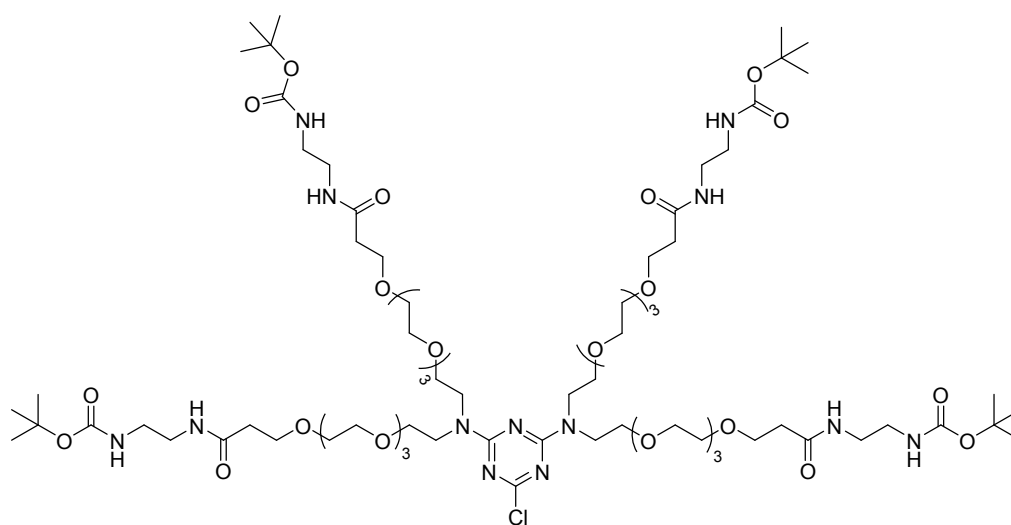
To a solution of **22** (1 eq., 500 mg, 0.53 mmol) and DIEA (20 eq., 1.74 mL, 10.50 mmol) in acetonitrile (5 mL) was added ethylene diamine (20 eq., 633 mg, 10.50 mmol). The reaction mixture was stirred at 80°C for 15 hours. After concentration, the crude material was directly purified by silica gel flash chromatography (DCM to DCM/MeOH/NH₄OH 9/0.9/0.1) to afford **23** (405 mg, 0.42 mmol, 79 %) as a yellowish oil.

^1H NMR (400 MHz, CDCl_3 , δ ppm): 4.94 (brt, $J = 5.7$ Hz, 1H), 3.66 (m, 58H), 3.45 – 3.31 (m, 10H), 2.87 (brm, 2H). ^{13}C NMR (100 MHz, CDCl_3 , δ ppm): 166.3, 165.0, 70.6 – 70.3, 70.0, 69.5, 69.3, 50.6, 47.6, 47.5, 43.6, 42.1.

HRMS (ESI, m/z): calcd for $\text{C}_{37}\text{H}_{72}\text{N}_{19}\text{O}_{12}$ $[\text{M}+\text{H}]^+$ 974.5602; found 974.5626.



24, tetra-*tert*-butyl ((6-chloro-1,3,5-triazine-2,4-diyl)*bis*(4,34-dioxo-7,10,13,16,22,25, 28,31-octaoxa-3,19,35-triazaheptatriacontane-19,1,37-triyl))tetracarbamate, $\text{C}_{75}\text{H}_{140}\text{ClN}_{13}\text{O}_{28}$, MW = 1707.46 g/mol

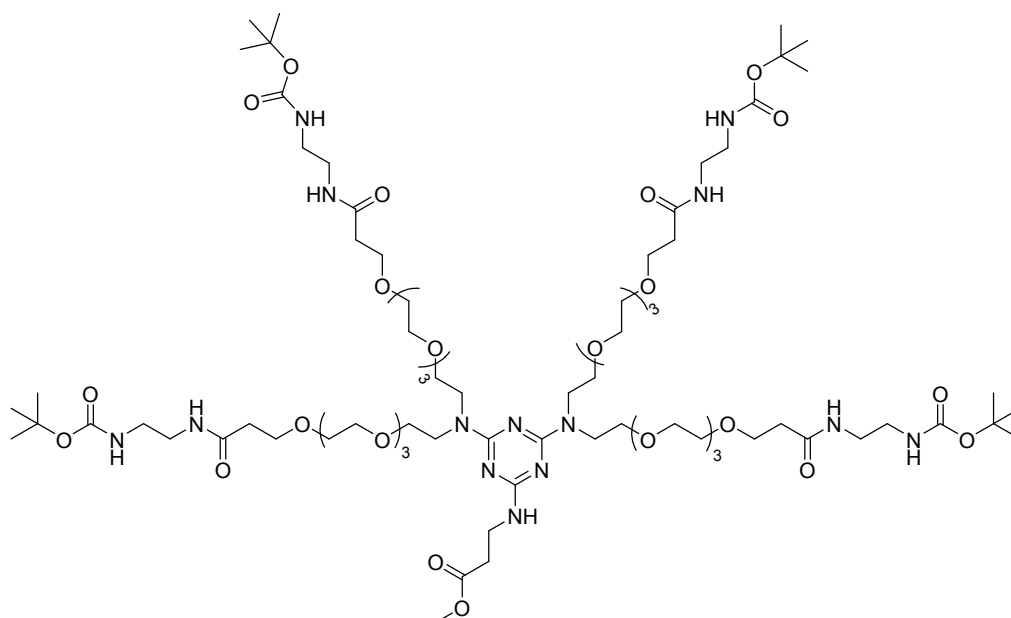


To a solution of **9a** (2.3 eq., 615 mg, 0.77 mmol) in acetonitrile (3 mL) and DIEA (10 eq., 0.554 mL, 3.35 mmol) was added cyanuric chloride (1 eq., 61.8 mg, 0.33 mmol) and the reaction was stirred at room temperature for 5 hours. After concentration, 40 mL of an aqueous solution of

NaHPO₄ 1M were added and the mixture was extracted with DCM (3 x 50 mL). The combined organic layers were dried over MgSO₄ and evaporated. The crude material was purified by silica gel flash chromatography (DCM to DCM/MeOH 90/10) to afford **24** (380 mg, 0.22 mmol, 66 %) as a clear yellow oil.

¹H NMR (400 MHz, CDCl₃, δ ppm): 6.96 (brs, 4H), 5.32 (brs, 4H), 3.80 – 3.68 (m, 16H), 3.61 (dd, *J* = 17.7, 9.8 Hz, 56H), 3.39 – 3.29 (m, *J* = 5.1 Hz, 8H), 3.27 – 3.16 (m, 8H), 2.45 (t, *J* = 5.7 Hz, 8H), 1.42 (s, 36H). ¹³C NMR (100 MHz, CDCl₃, δ ppm): 172.1, 168.8, 164.5, 156.3, 78.9, 70.5 – 70.1, 69.1, 68.8, 67.1, 48.1, 47.7, 40.3, 39.6, 36.8, 28.4 (12C). HRMS (ESI, *m/z*): calcd for C₇₅H₁₄₂ClN₁₃O₂₈ [M+2H]²⁺ 853.9882; found 853.9881.

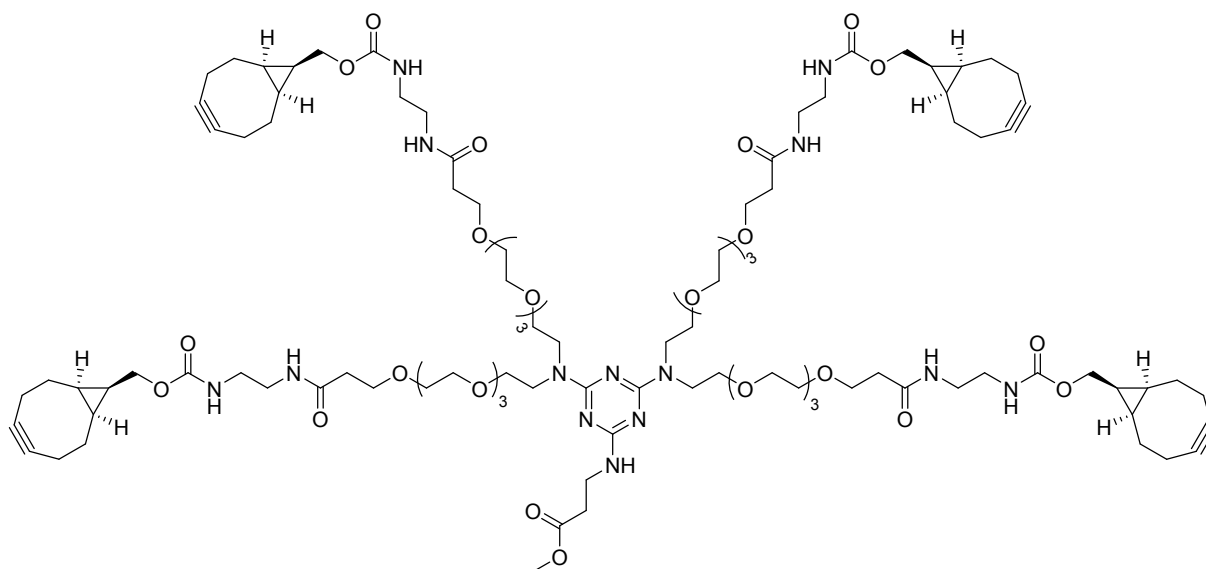
25, methyl 3-((4,6-bis(bis(2,2-dimethyl-4,9-dioxo-3,12,15,18,21-pentaoxa-5,8-diazatricosan-23-yl)amino)-1,3,5-triazin-2-yl)amino)propanoate, C₇₉H₁₄₈N₁₄O₃₀, MW = 1774.12 g/mol



To a solution of **24** (1 eq., 375 mg, 0.22 mmol) and DIEA (10 eq., 0.363 mL, 2.20 mmol) in acetonitrile (7 mL) was added methyl 3-aminopropionate hydrochloride (8 eq., 245 mg, 1.76 mmol). The reaction mixture was stirred at 80°C for 48 hours. After concentration, 70 mL of an aqueous solution of NaH₂PO₄ (1M) were added and the mixture was extracted with DCM (3 x 75mL). The crude material was purified by silica gel flash chromatography (DCM to DCM/MeOH 9/1) to afford **25** (330 mg, 0.19 mmol, 85 %) as a yellowish oil.

¹H NMR (400 MHz, CDCl₃, δ ppm): 6.98 (brs, 4H), 5.34 (brs, 4H), 3.85 – 3.47 (m, 77H), 3.39 – 3.27 (m, 8H), 3.28 – 3.14 (m, 8H), 2.60 (t, *J* = 6.2 Hz, 2H), 2.46 (t, *J* = 5.7 Hz, 8H), 1.43 (s, 36H). The NH signal is missing. ¹³C NMR (100 MHz, CDCl₃, δ ppm): 172.7, 172.0, 156.3, 78.9, 70.4 – 70.1, 69.4, 69.2, 67.1, 51.5, 47.6, 40.3, 39.6, 36.8, 36.3, 34.3, 28.4 (12C). HRMS (ESI, *m/z*): calcd for C₇₉H₁₅₀N₁₄O₃₀ [M+2H]²⁺ 887.5316; found 887.5310.

26, methyl 3-((4,6-bis(bis(1-((1*R*,8*S*,9*S*)-bicyclo[6.1.0]non-4-yn-9-yl)-3,8-dioxo-2,11,14,17,20-pentaoxa-4,7-diazadocosan-22-yl)amino)-1,3,5-triazin-2-yl)amino)propanoate, $C_{103}H_{164}N_{14}O_{30}$, MW = 2078.5 g/mol



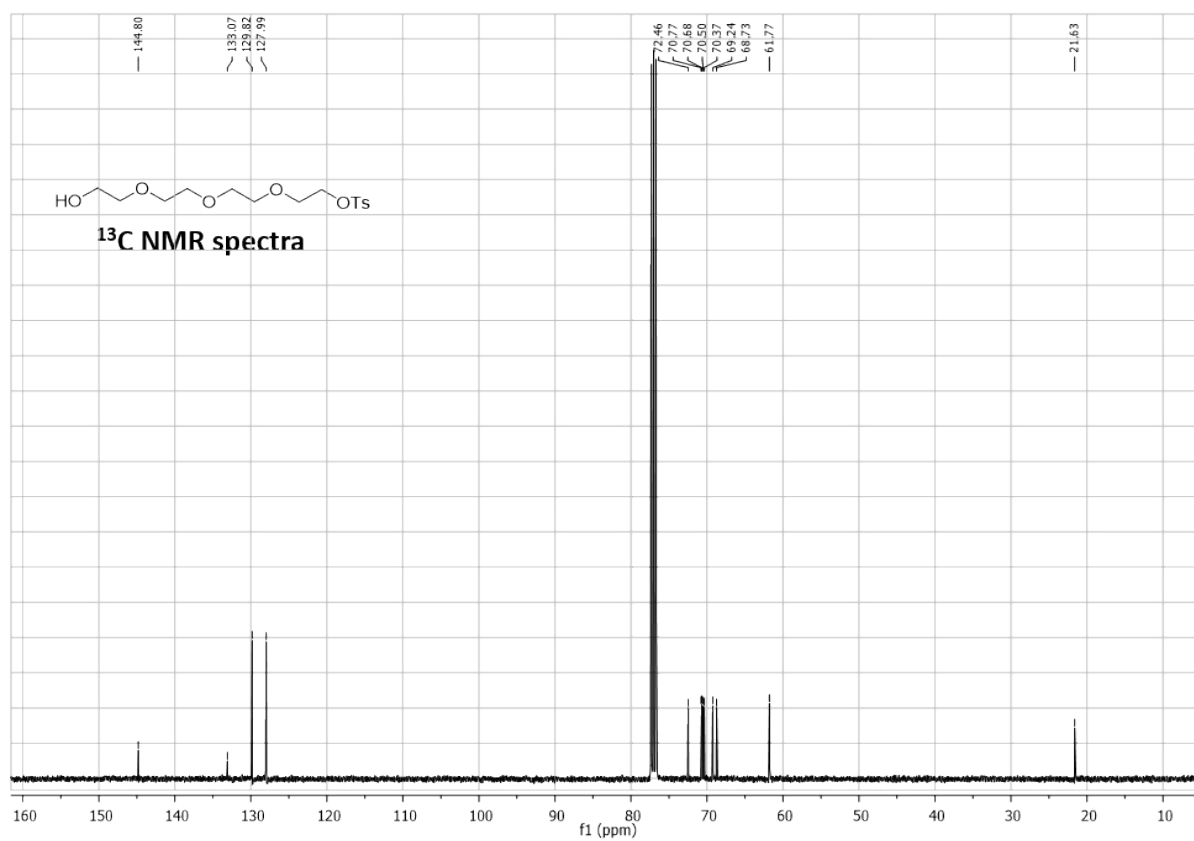
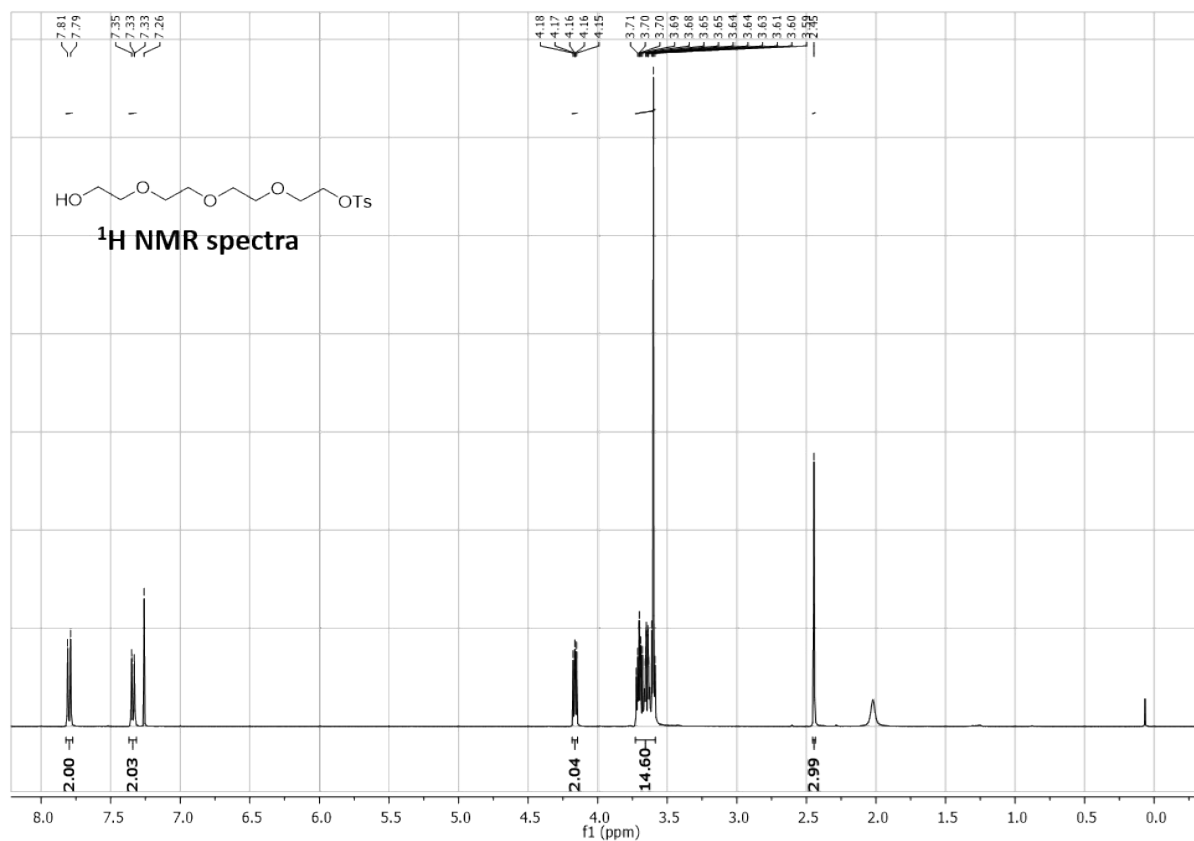
To a solution of **25** was added a 4M HCl solution in dioxane (60 eq., 2.37 mL, 9.47 mmol). The reaction mixture was stirred 5 hours and evaporated. The crude material was dissolved in DMF (5 mL) then TEA (10 eq., 159 mg, 0.219 mL, 1.58 mmol) and (1*R*,8*S*,9*S*)-bicyclo[6.1.0]non-4-yn-9-ylmethyl (4-nitrophenyl) carbonate (4 eq., 199 mg, 0.63 mmol) were added. The reaction mixture was stirred at room temperature for 15 hours. After concentration, 50 mL of water were added and the mixture was extracted with DCM (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The crude material was purified by silica gel flash chromatography (DCM to DCM/MeOH 9/1) to afford **26** (230 mg, 0.11 mmol, 70 %) as a yellowish oil.

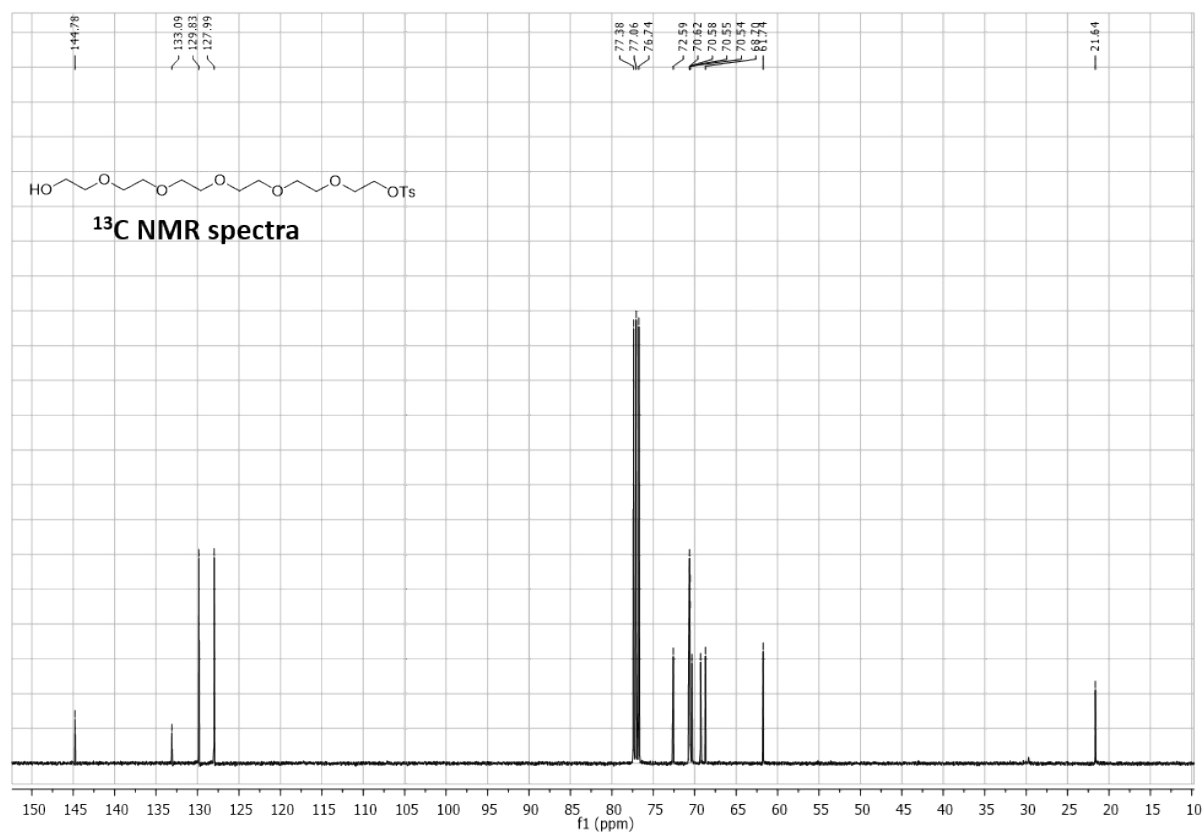
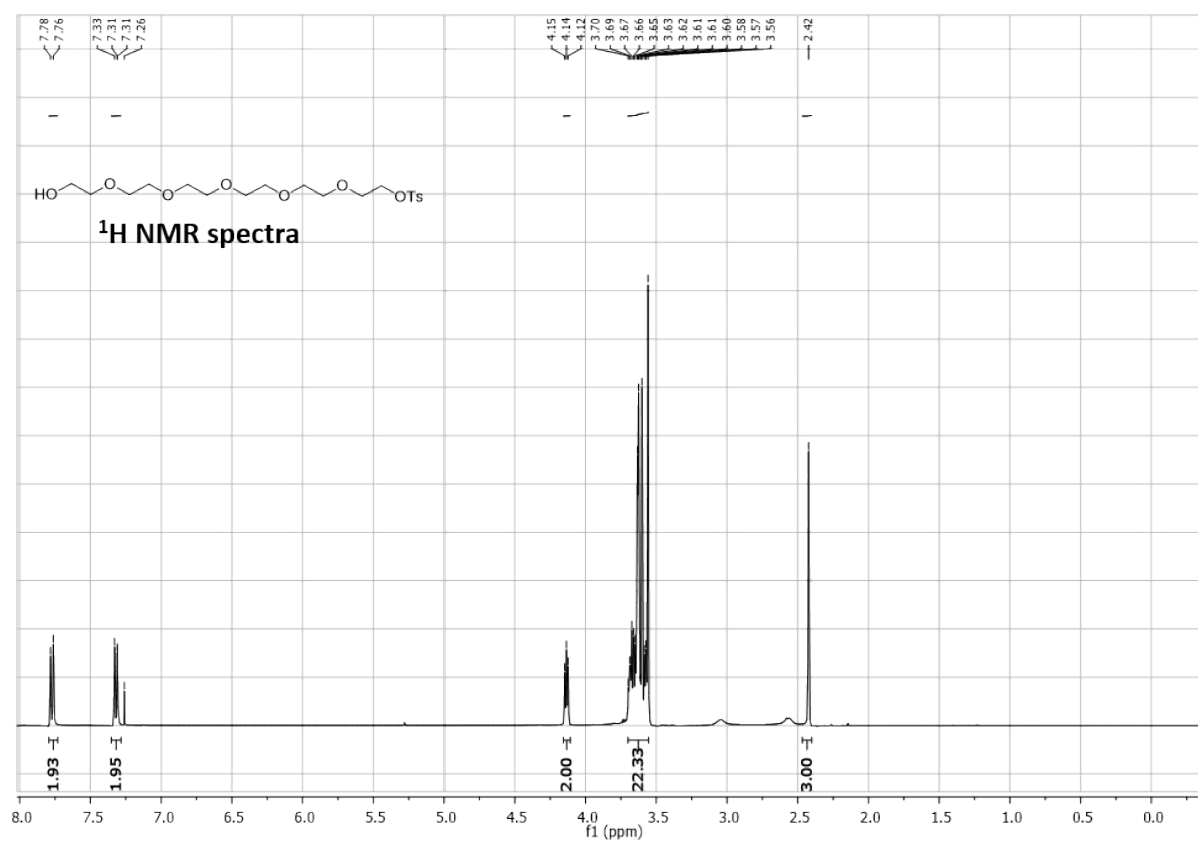
1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.01 (brs, 4H), 5.60 (brs, 4H), 5.33 (brs, 1H), 4.12 (d, J = 7.9 Hz, 8H), 3.78 – 3.47 (m, 77H), 3.42 – 3.31 (m, 8H), 3.33 – 3.20 (m, 8H), 2.60 (t, J = 6.2 Hz, 2H), 2.46 (t, J = 5.5 Hz, 8H), 2.36 – 2.13 (m, 24H), 1.56 (d, J = 11.4 Hz, 8H), 1.32 (dd, J = 18.6, 10.3 Hz, 4H), 0.92 (t, J = 9.6 Hz, 8H).

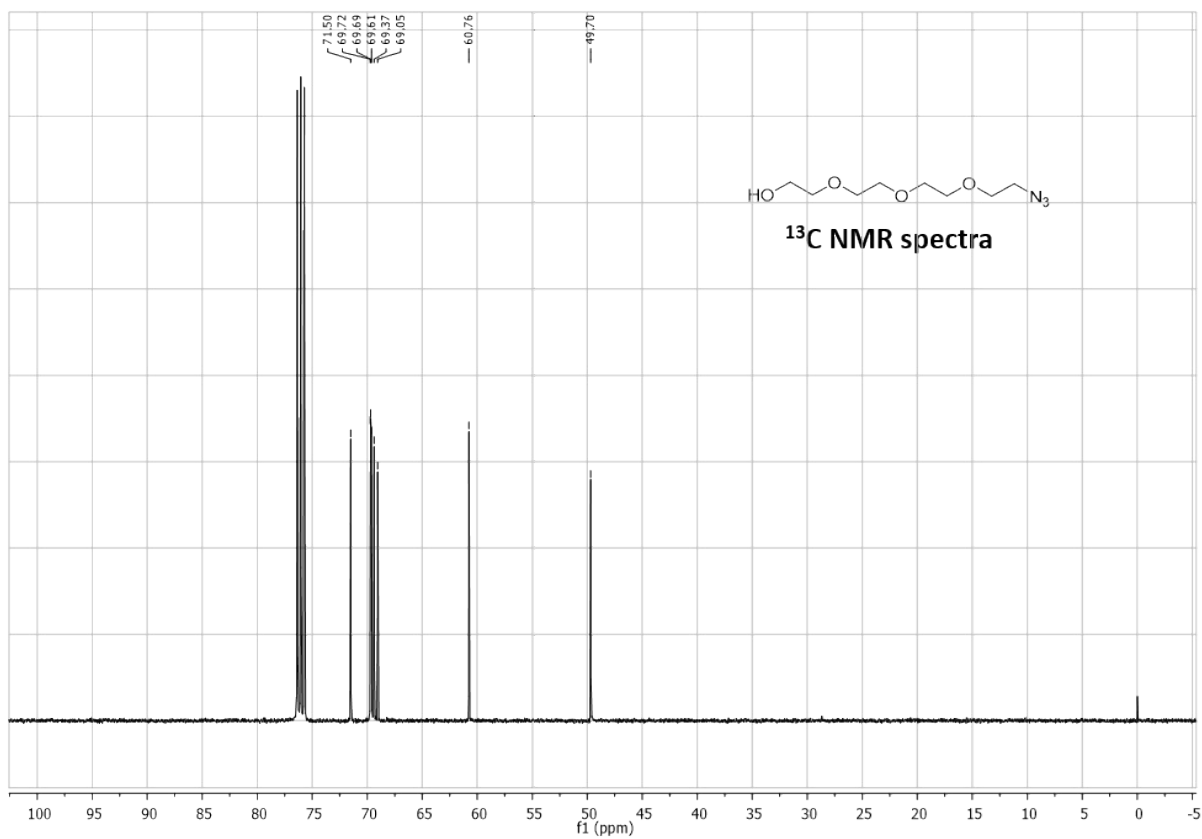
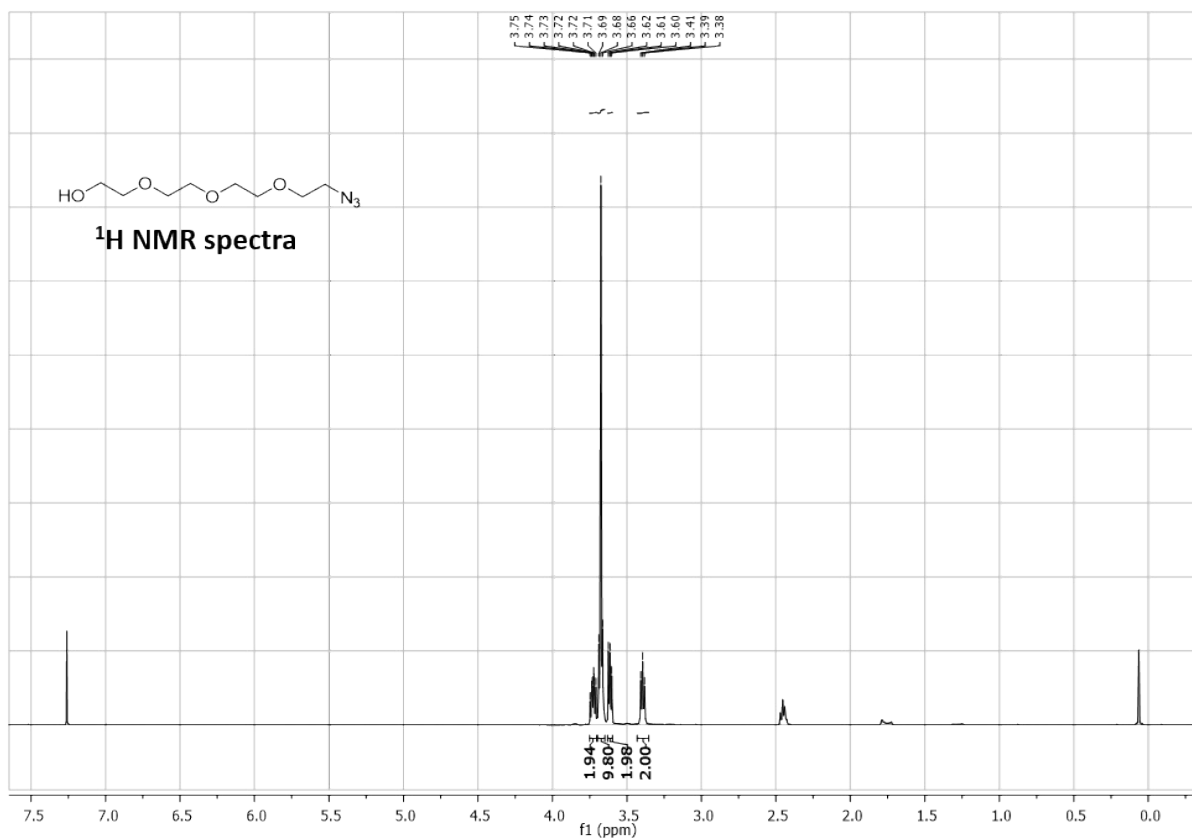
HRMS (ESI, m/z): calcd for $C_{103}H_{166}N_{14}O_{30}$ $[M+2H]^{2+}$ 1040.0958; found 1040.0949.

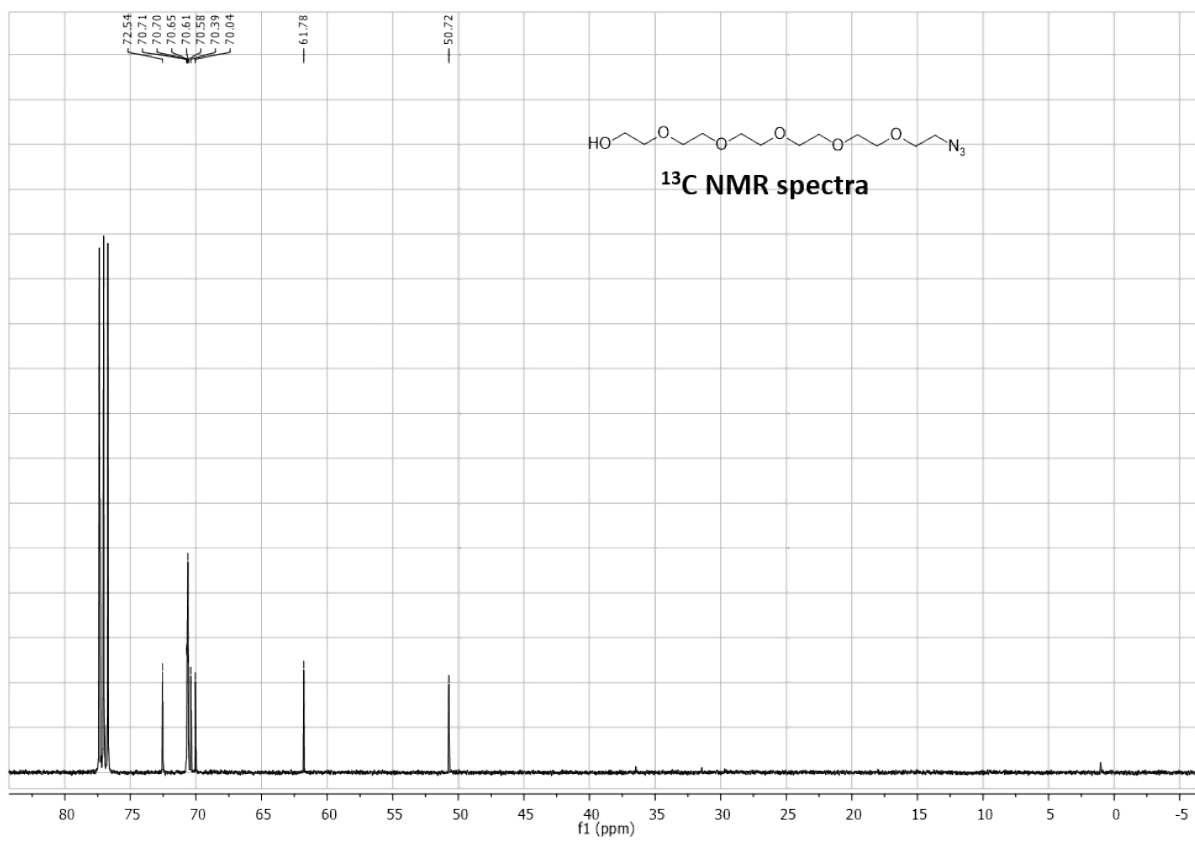
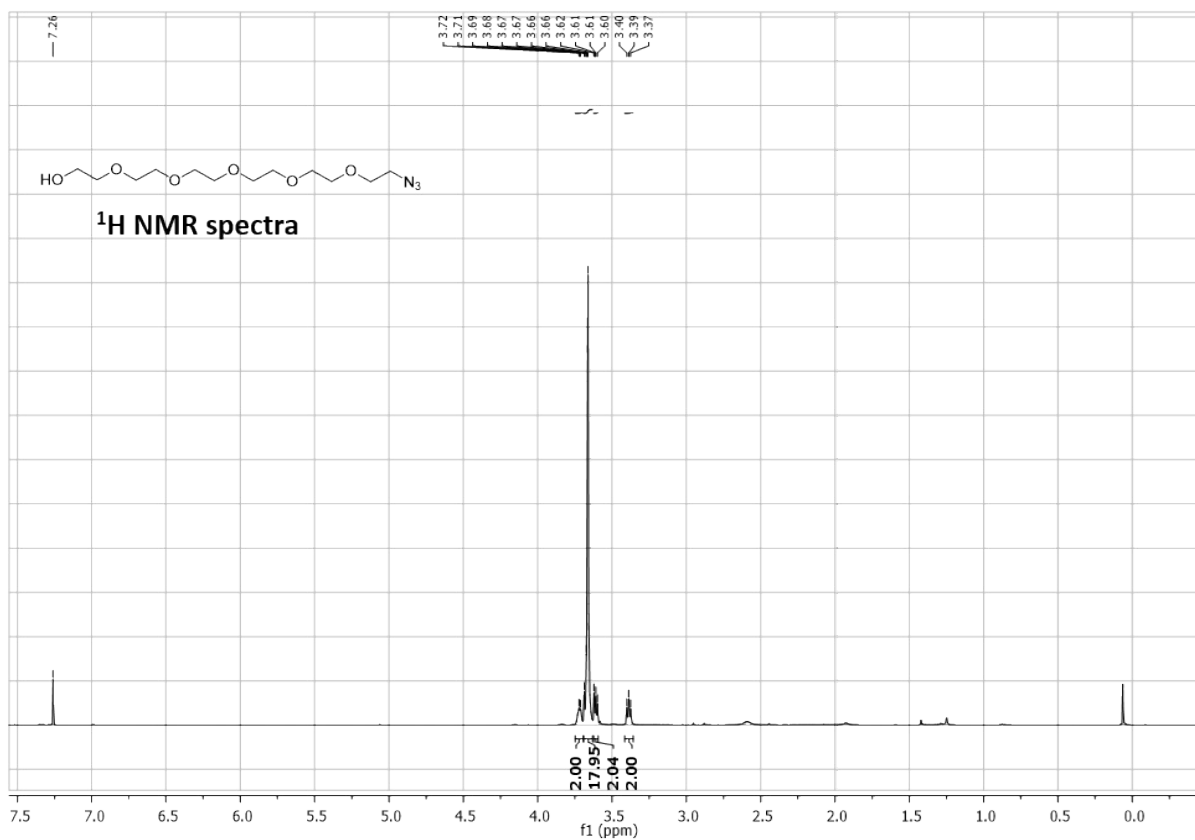
7 NMR spectra

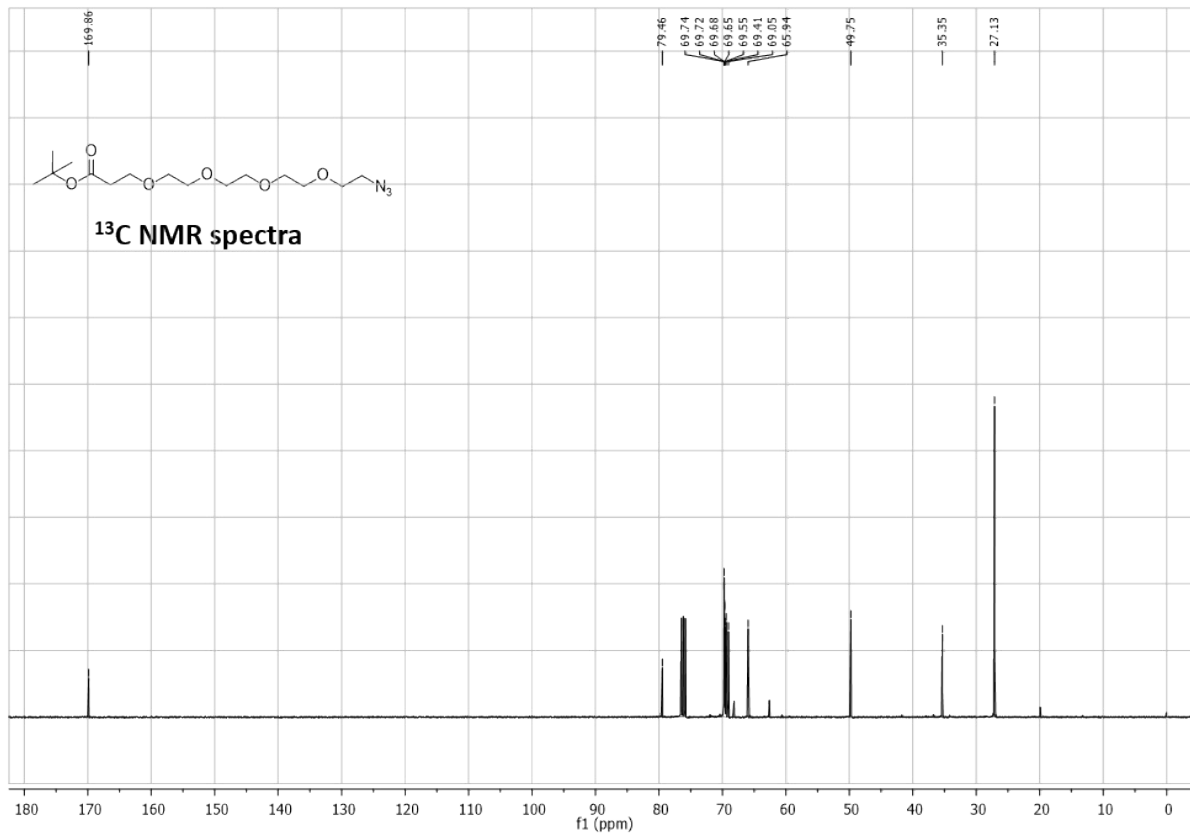
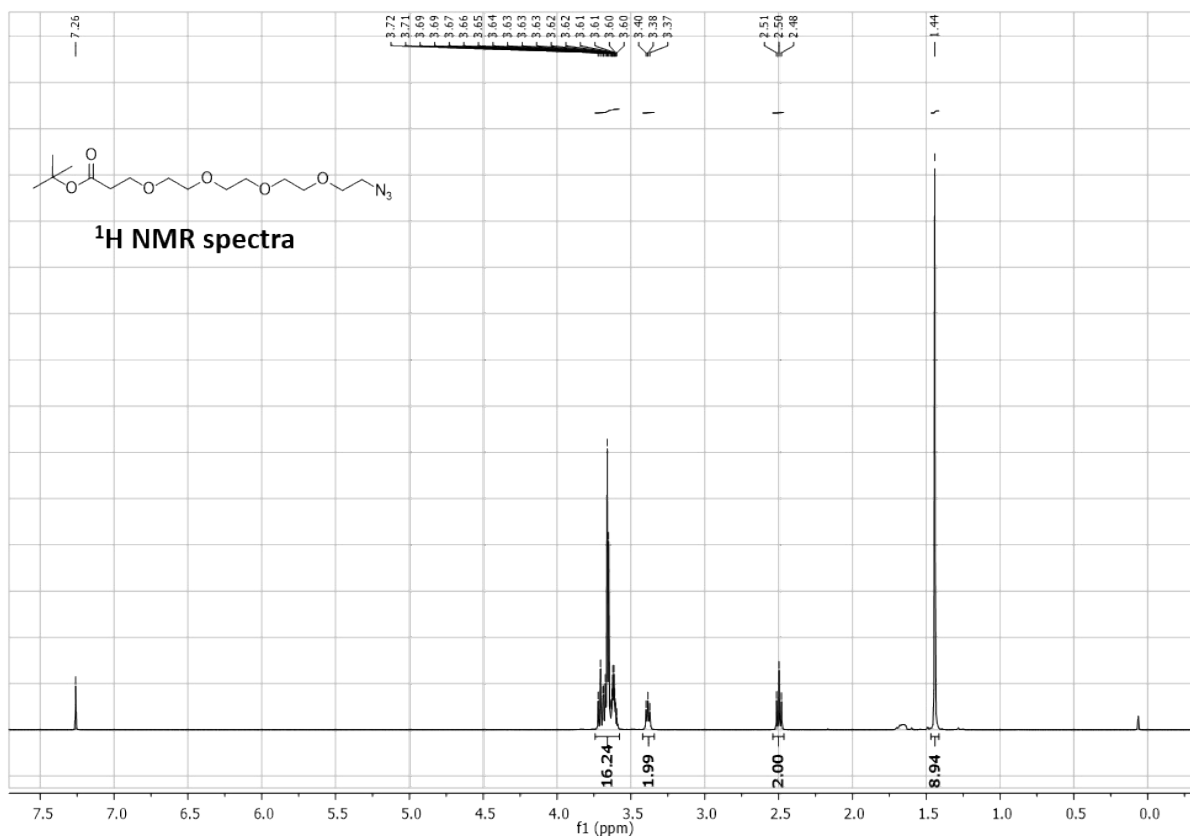
7.1 Hetero bifunctional peg linkers NMR spectra

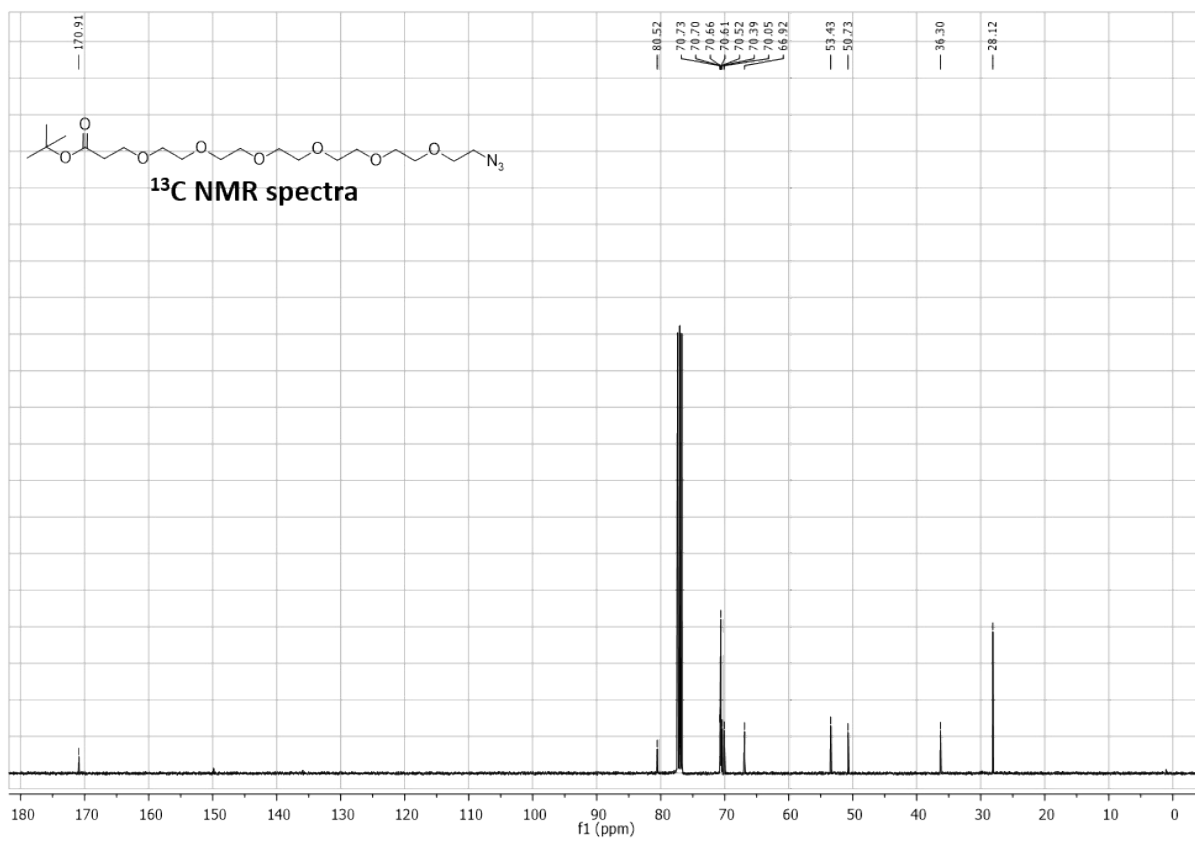
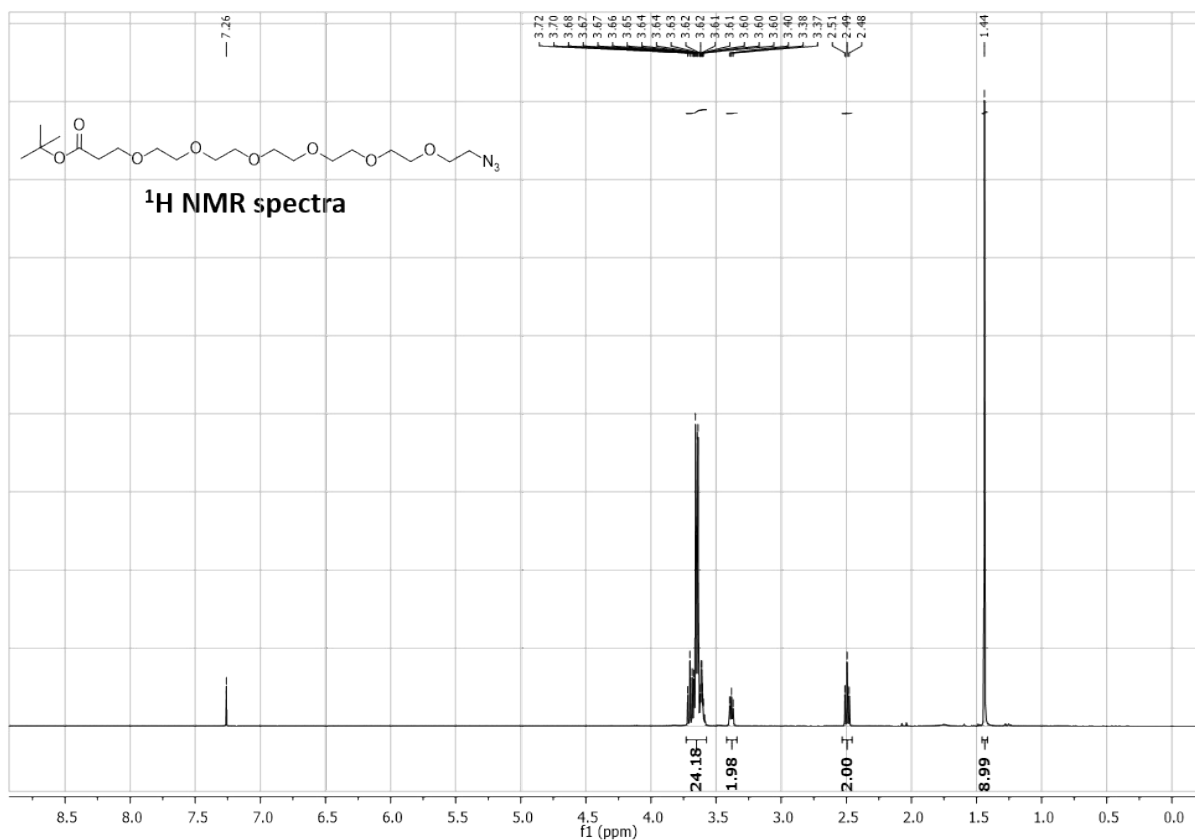


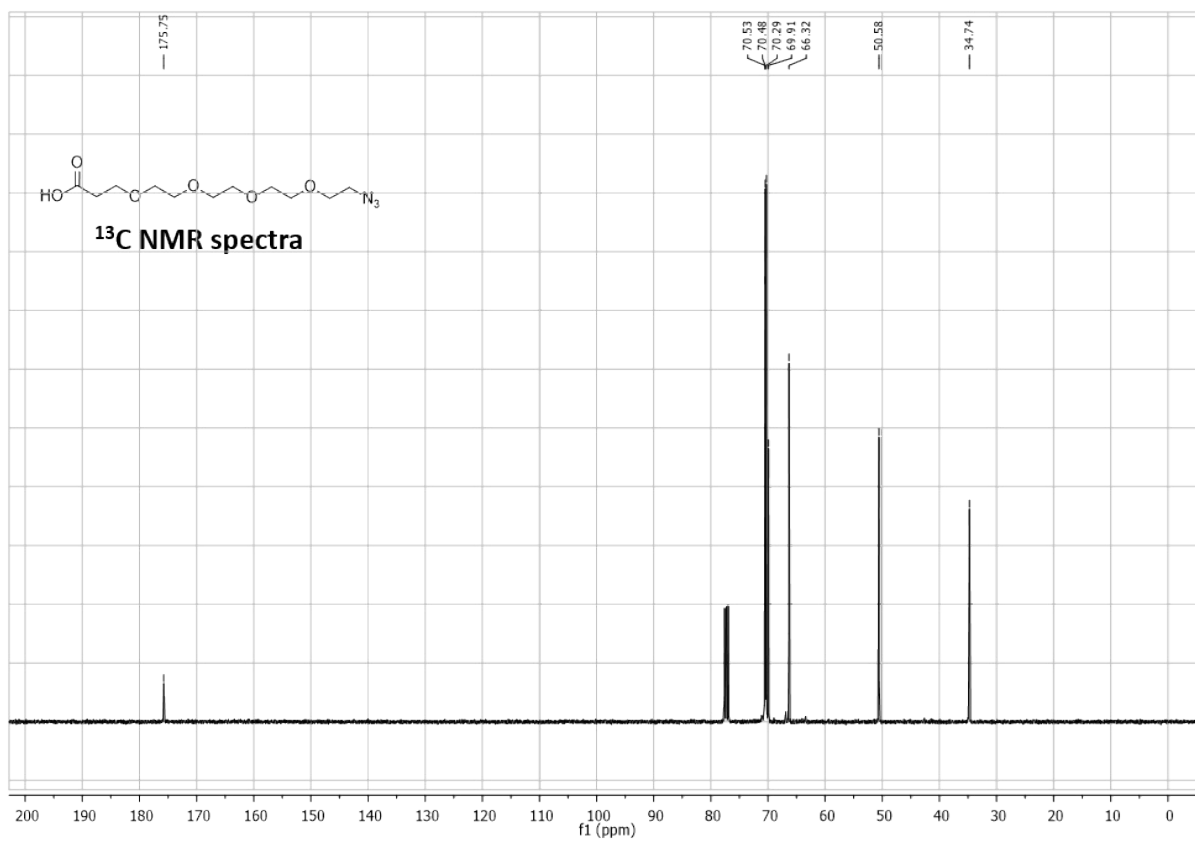
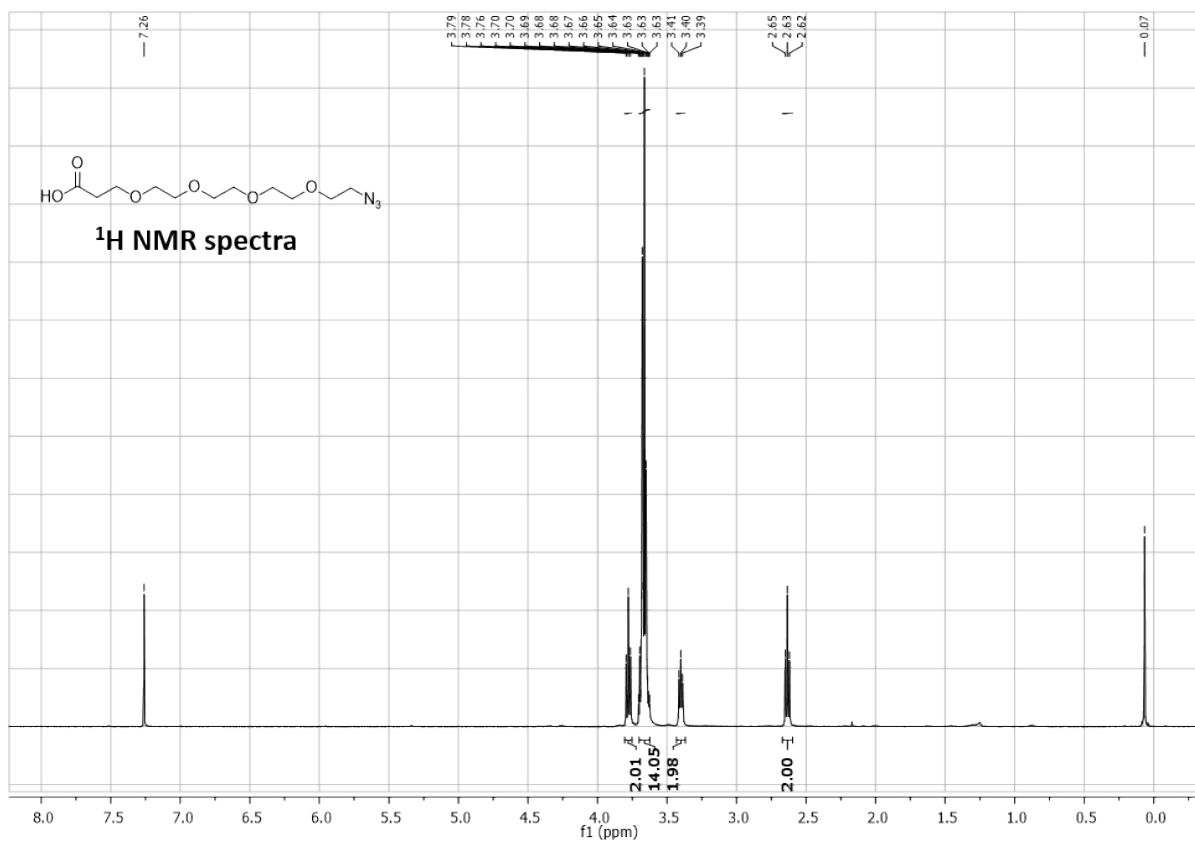


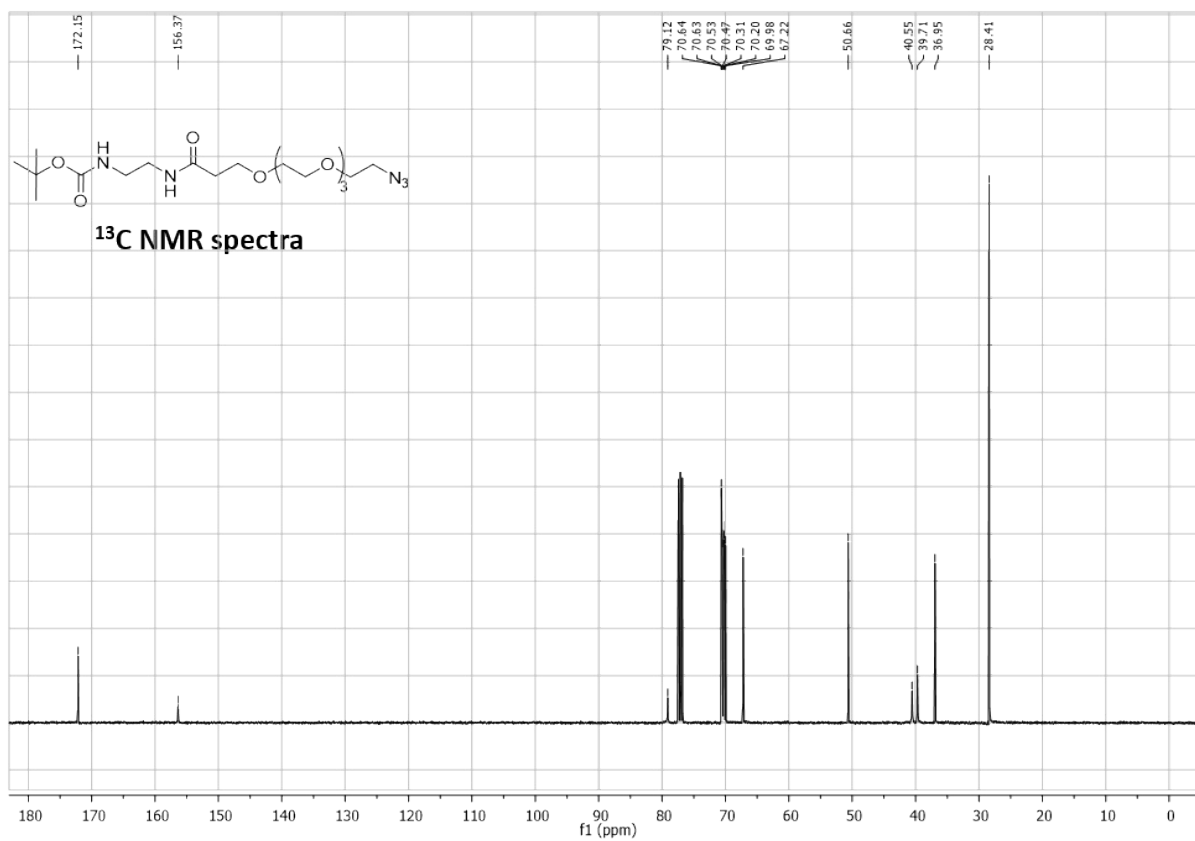
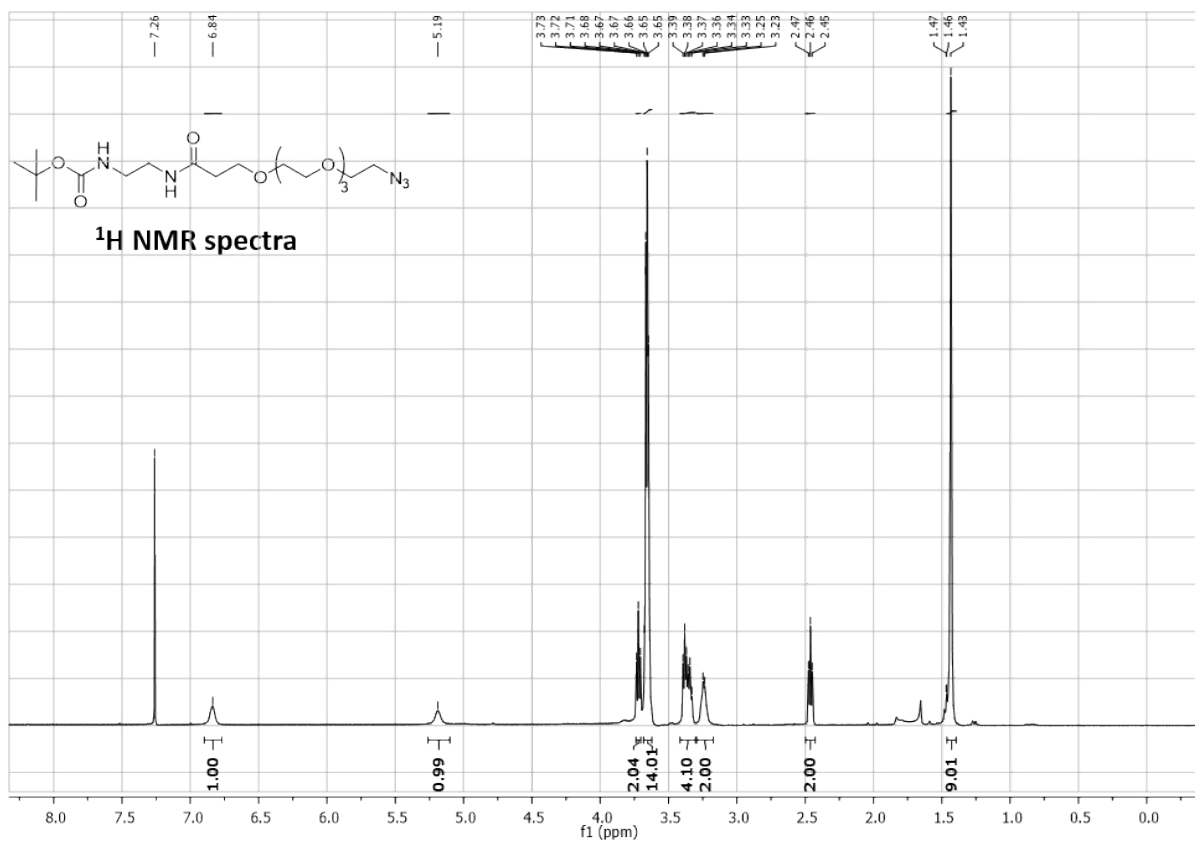


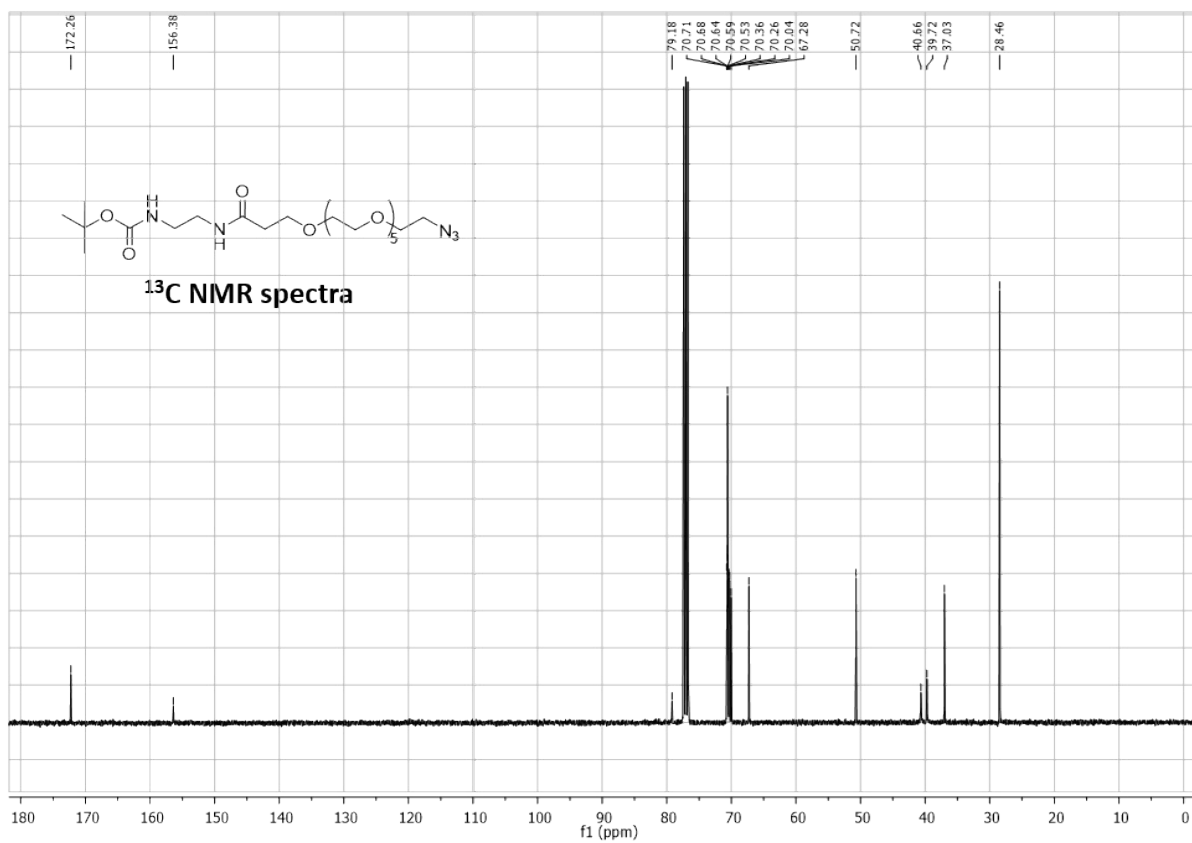
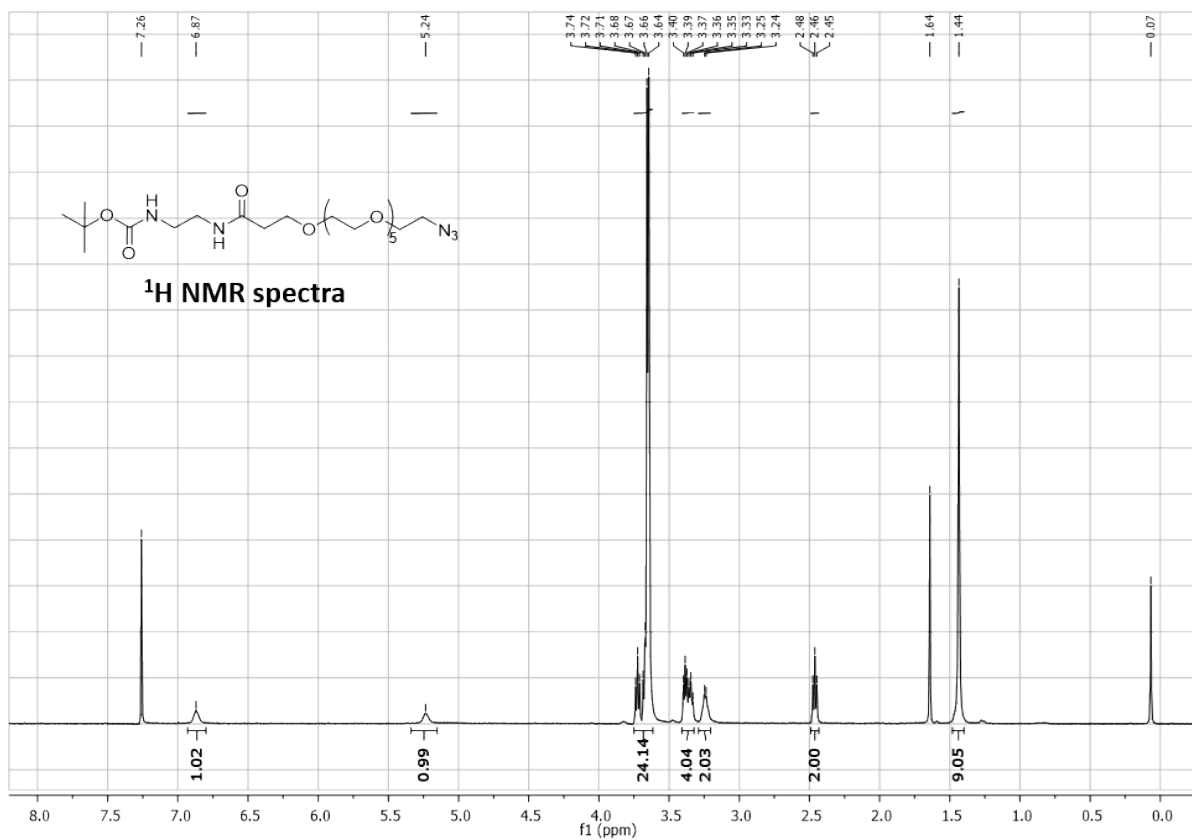




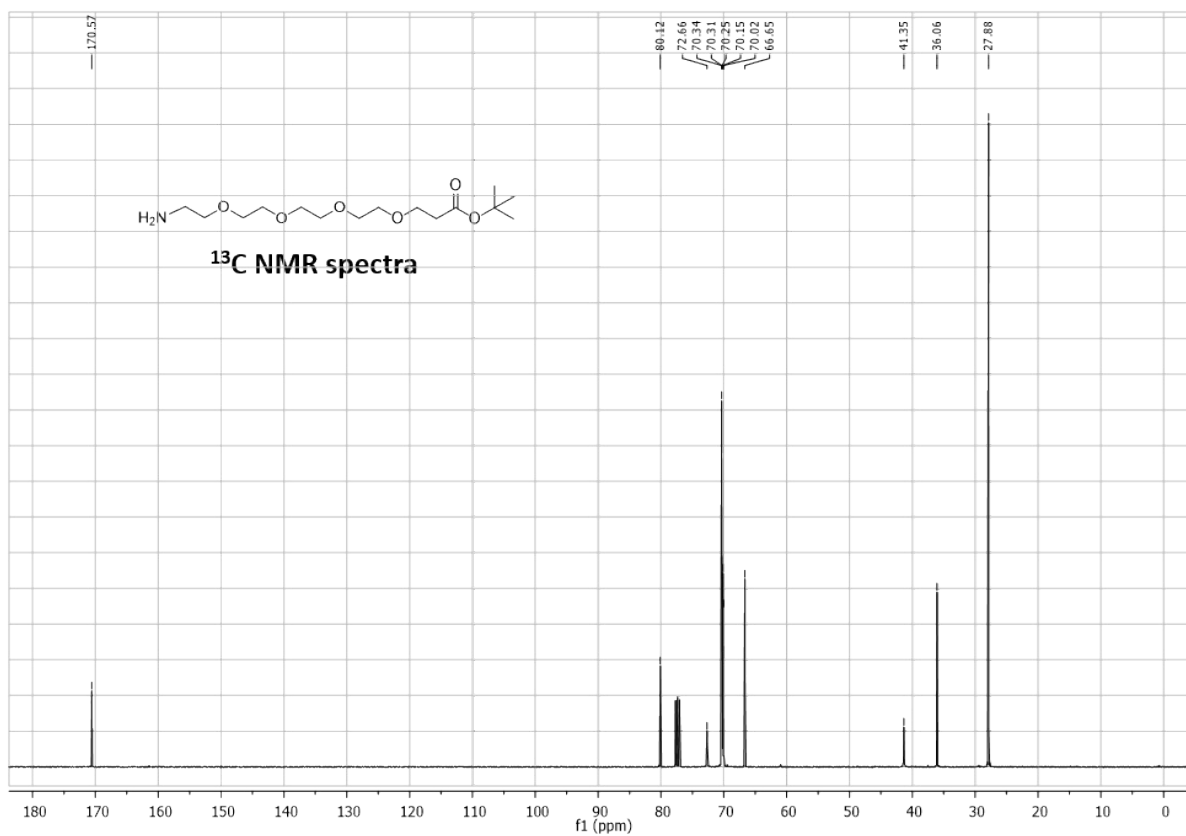
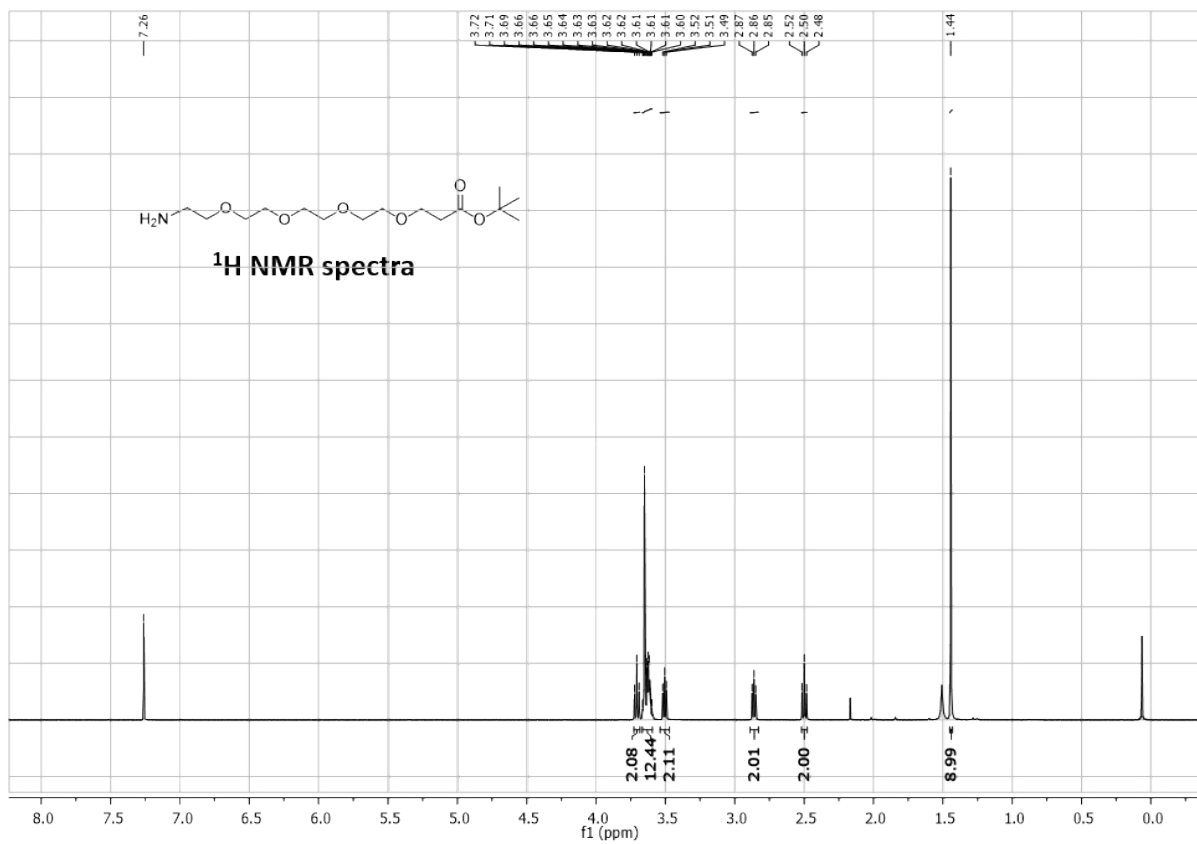


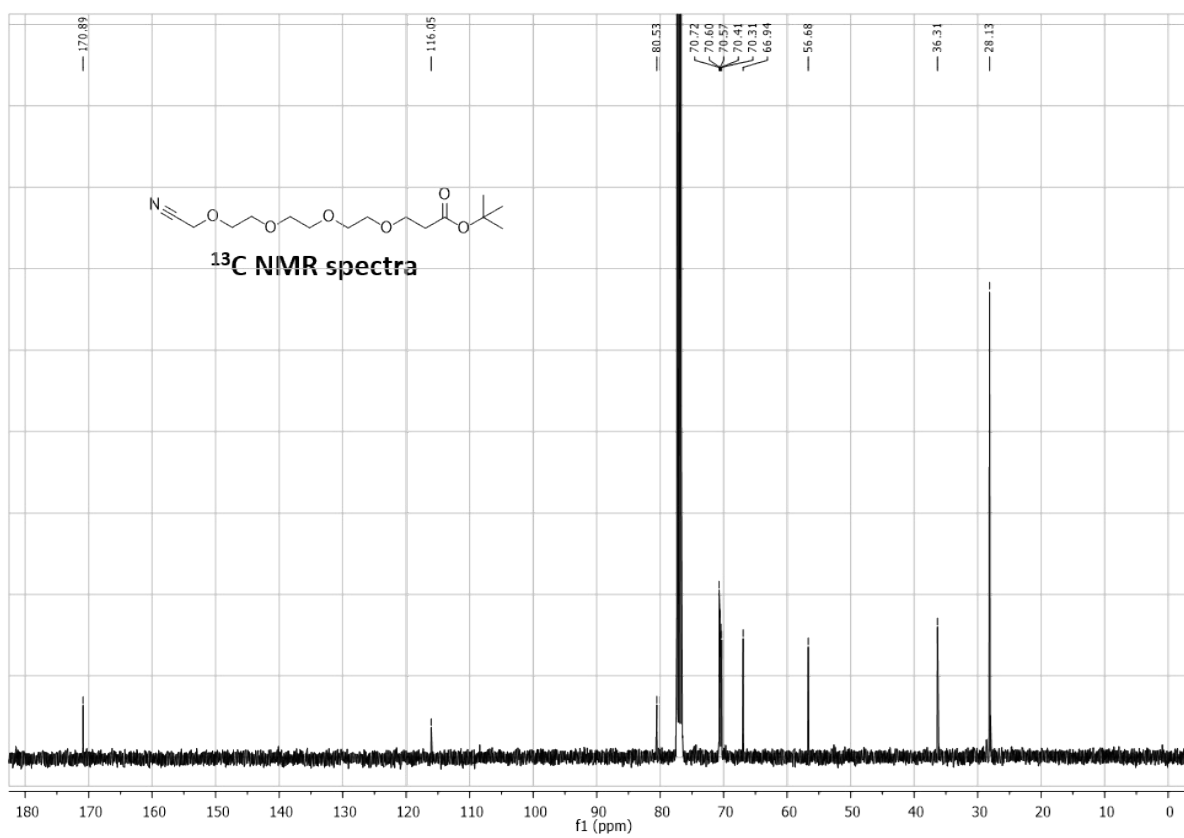
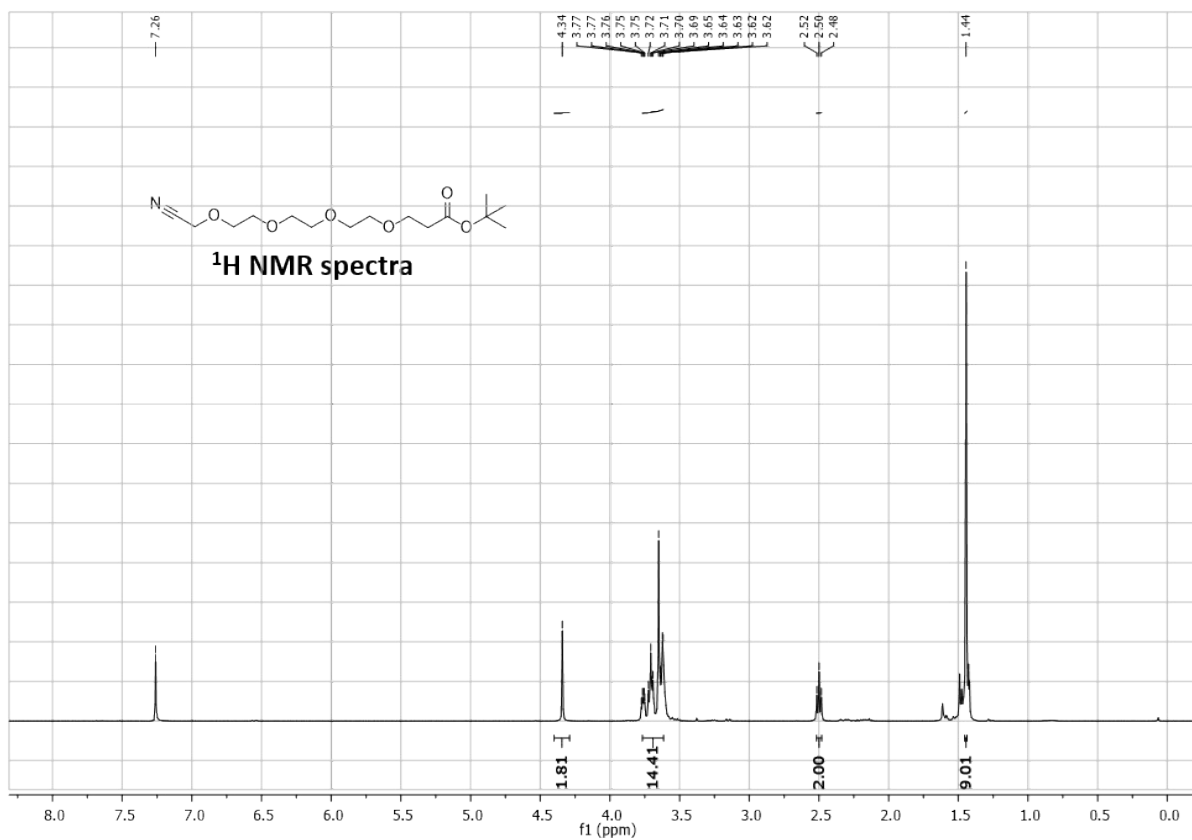


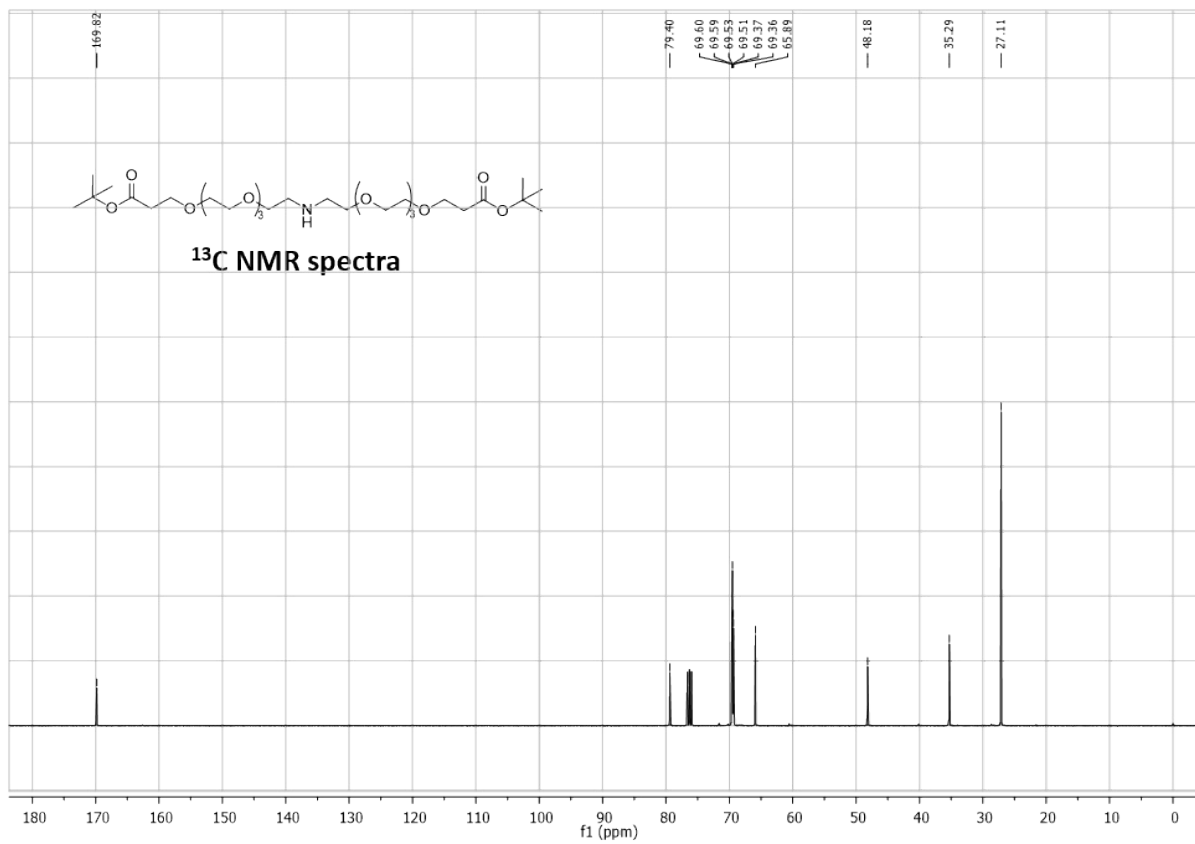
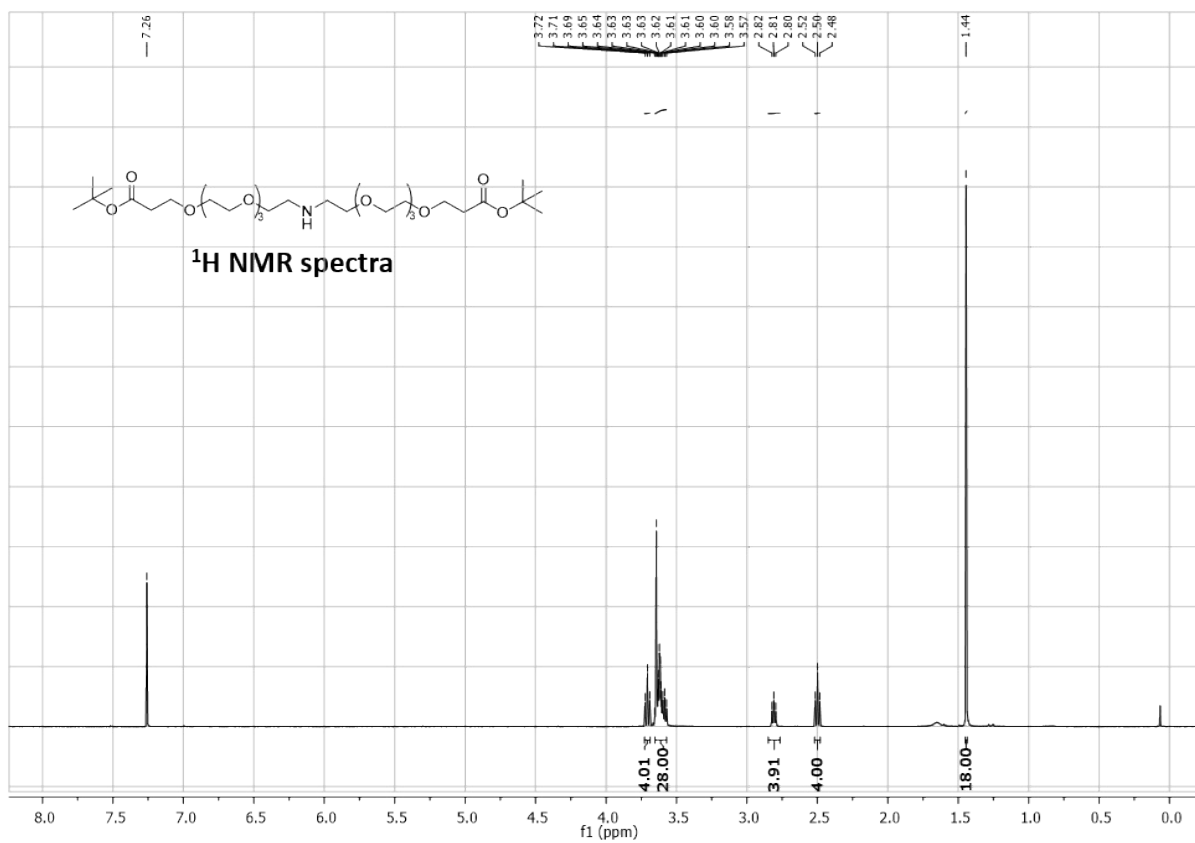


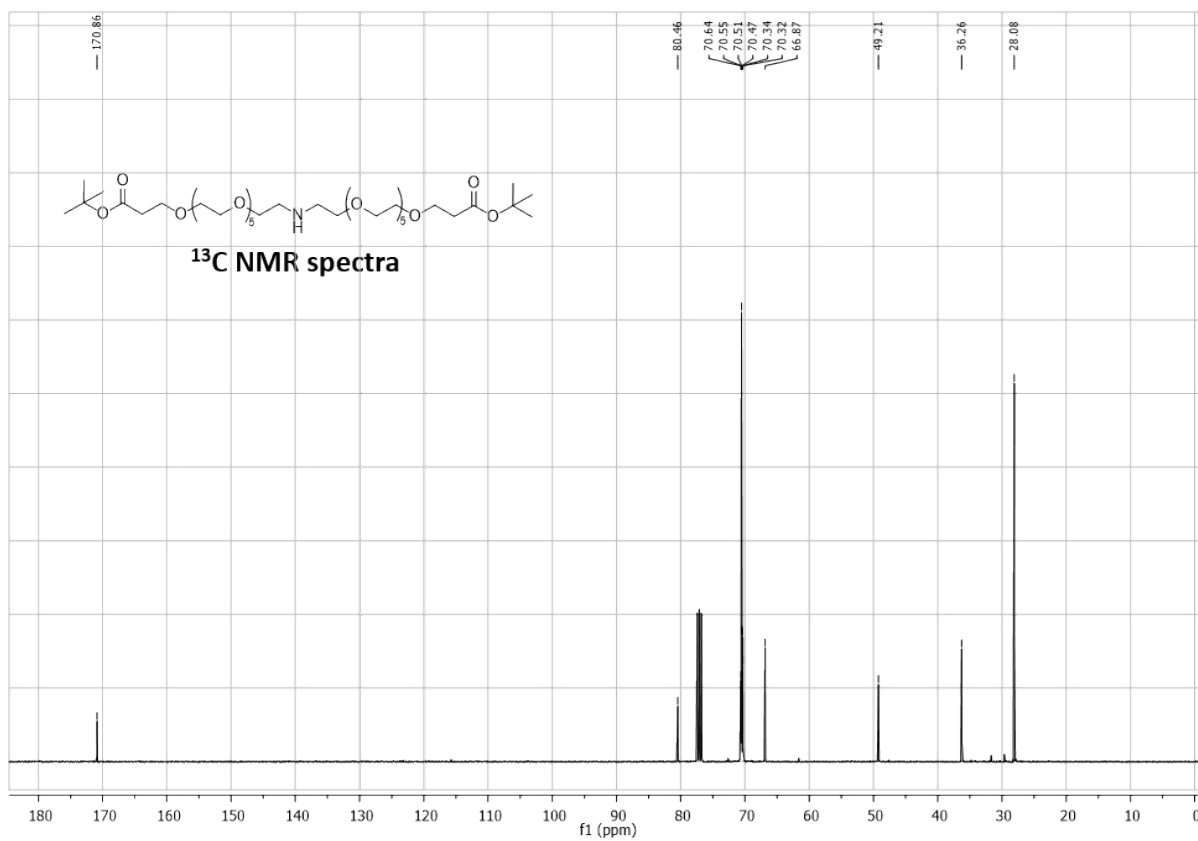
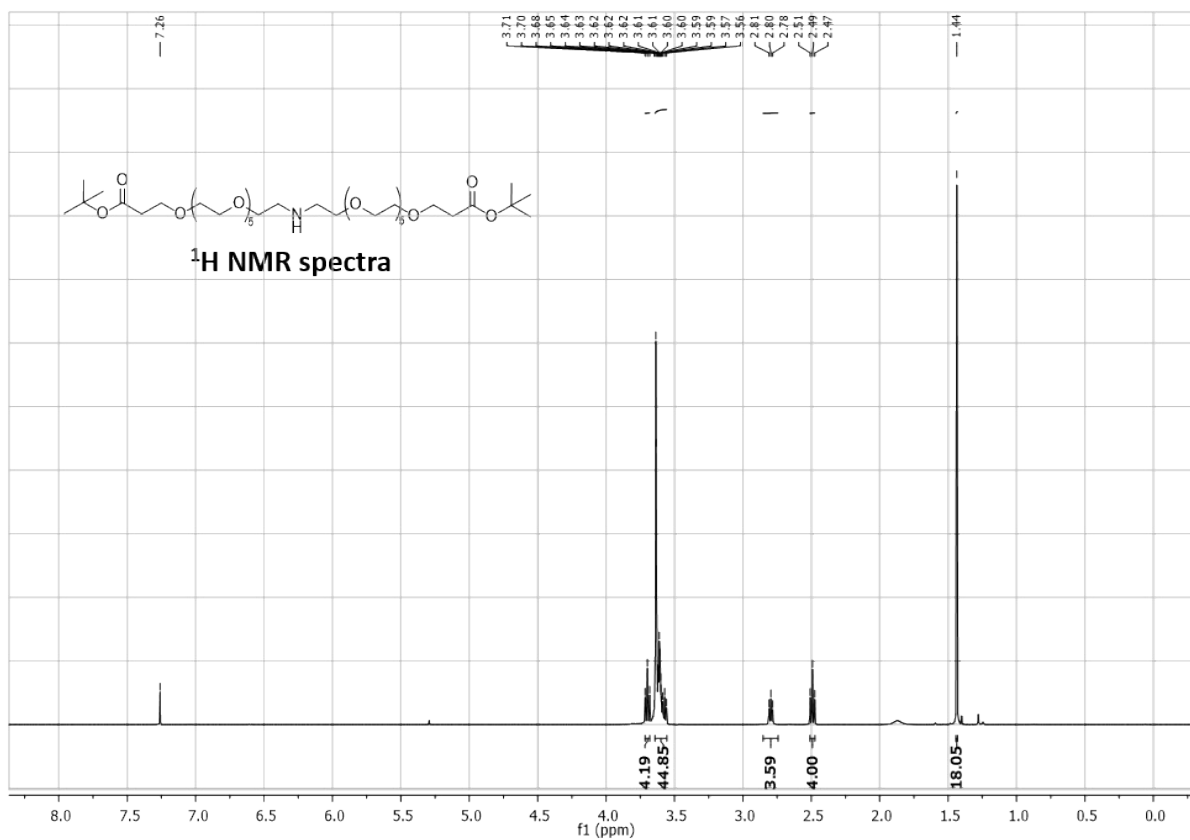


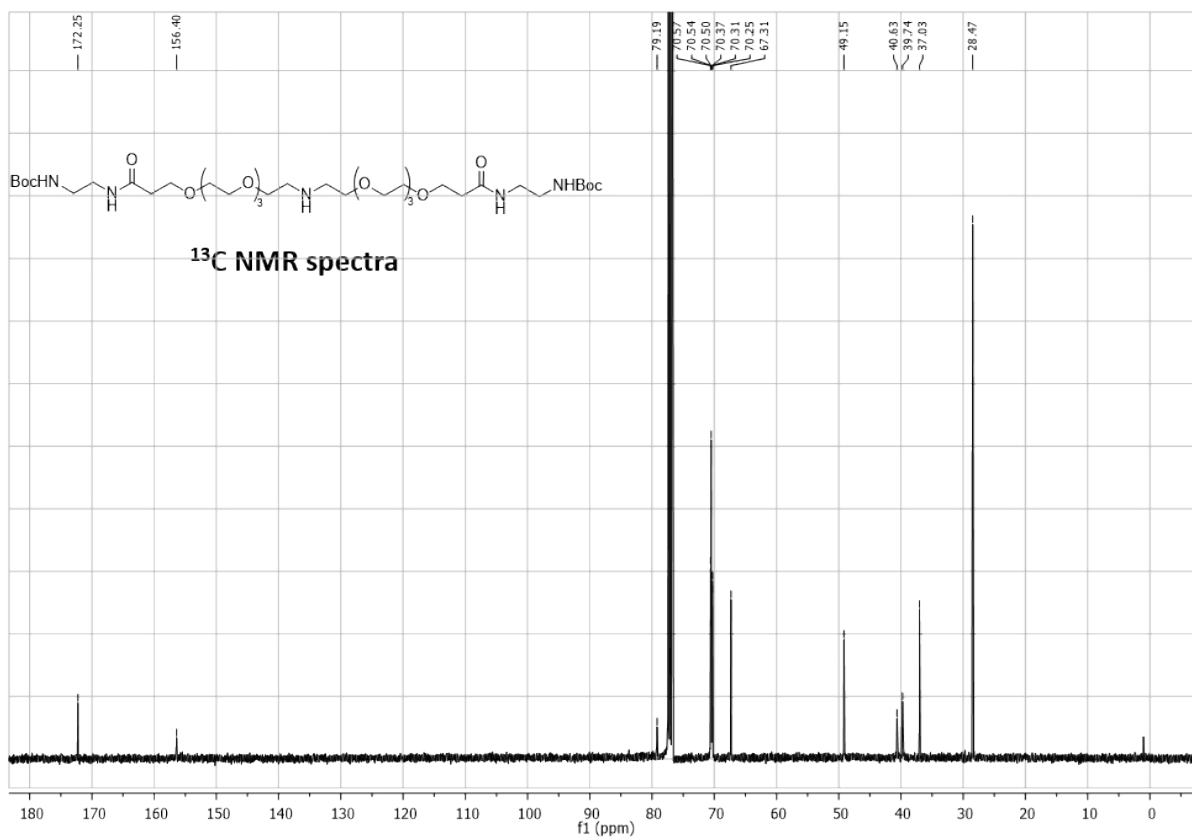
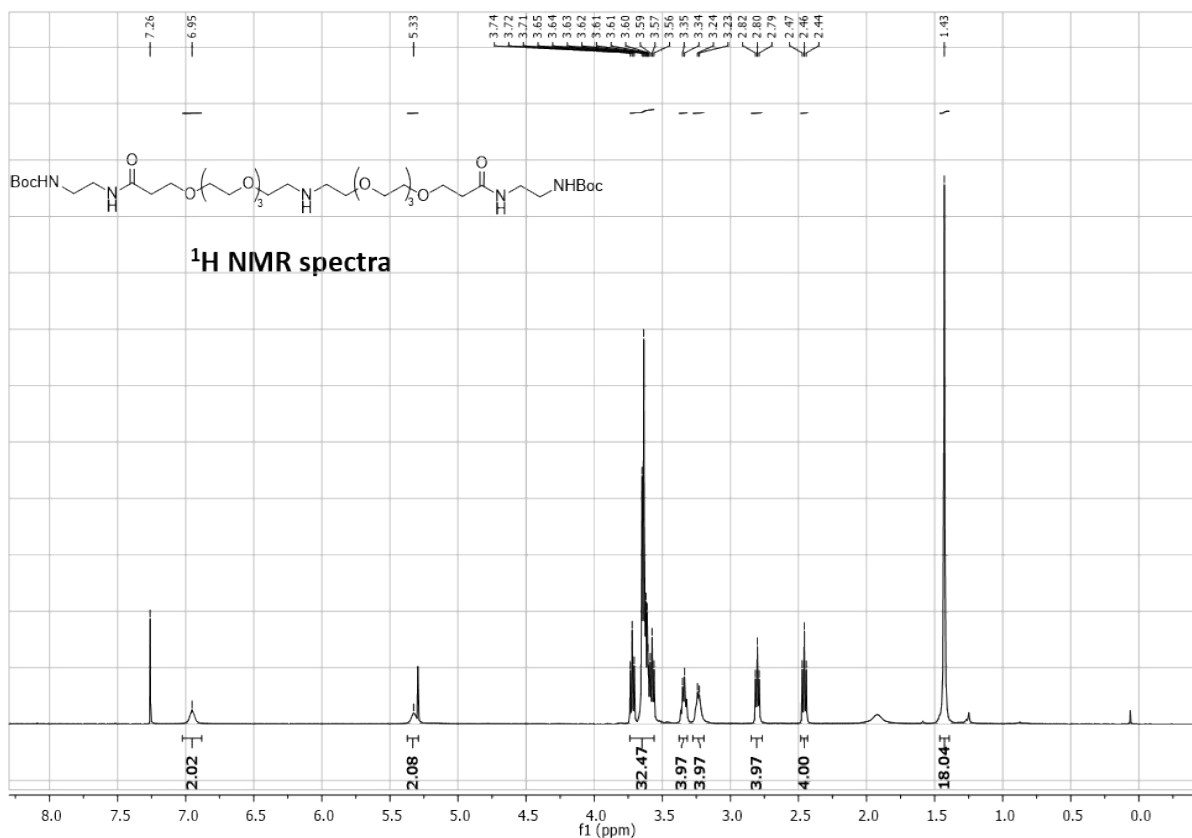
7.2 V-shaped N,N-bis-oligoethyleneglycol-amine NMR spectra

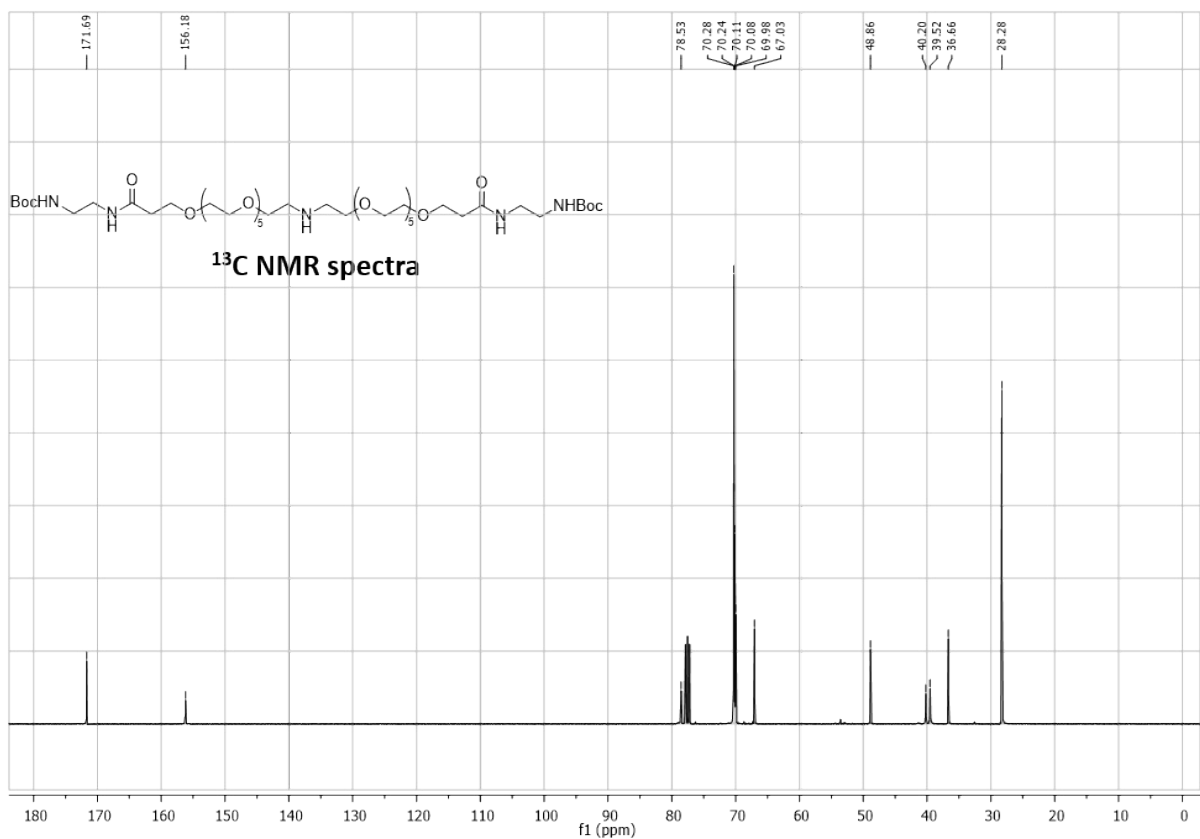
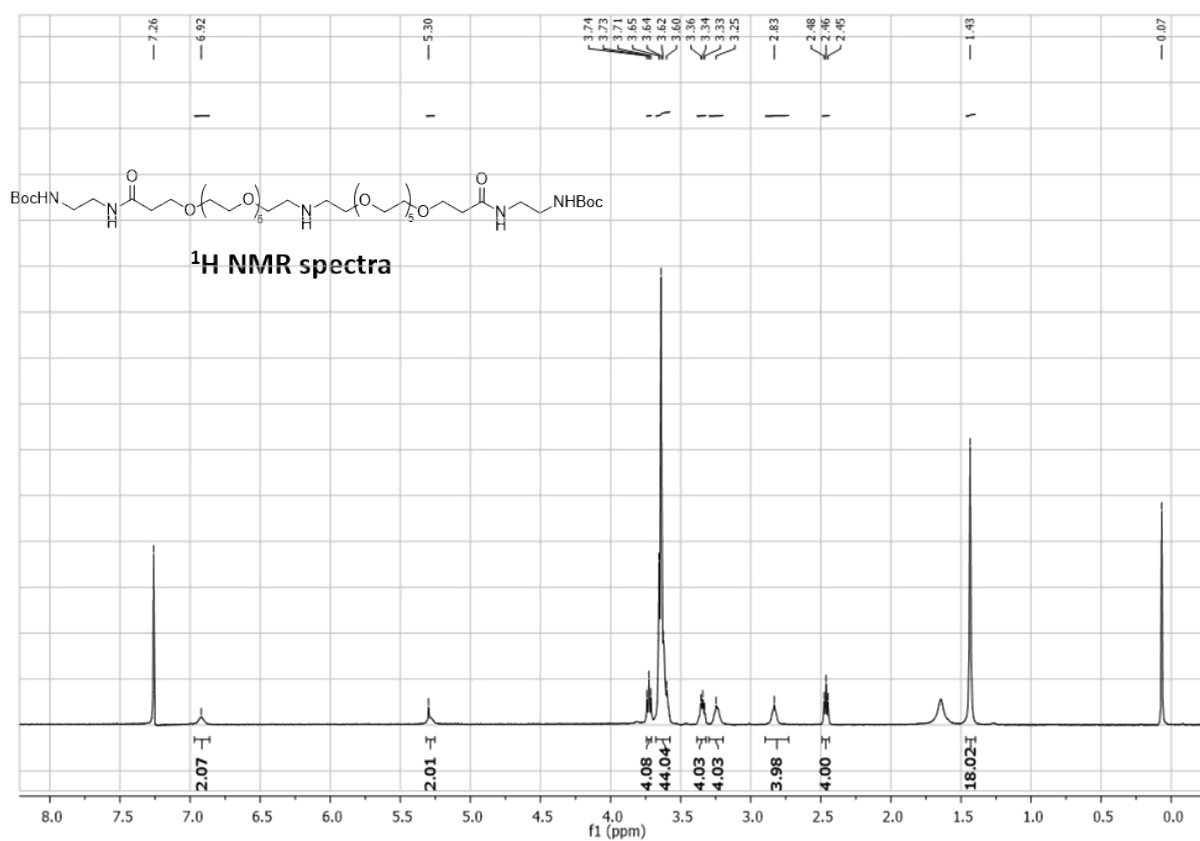




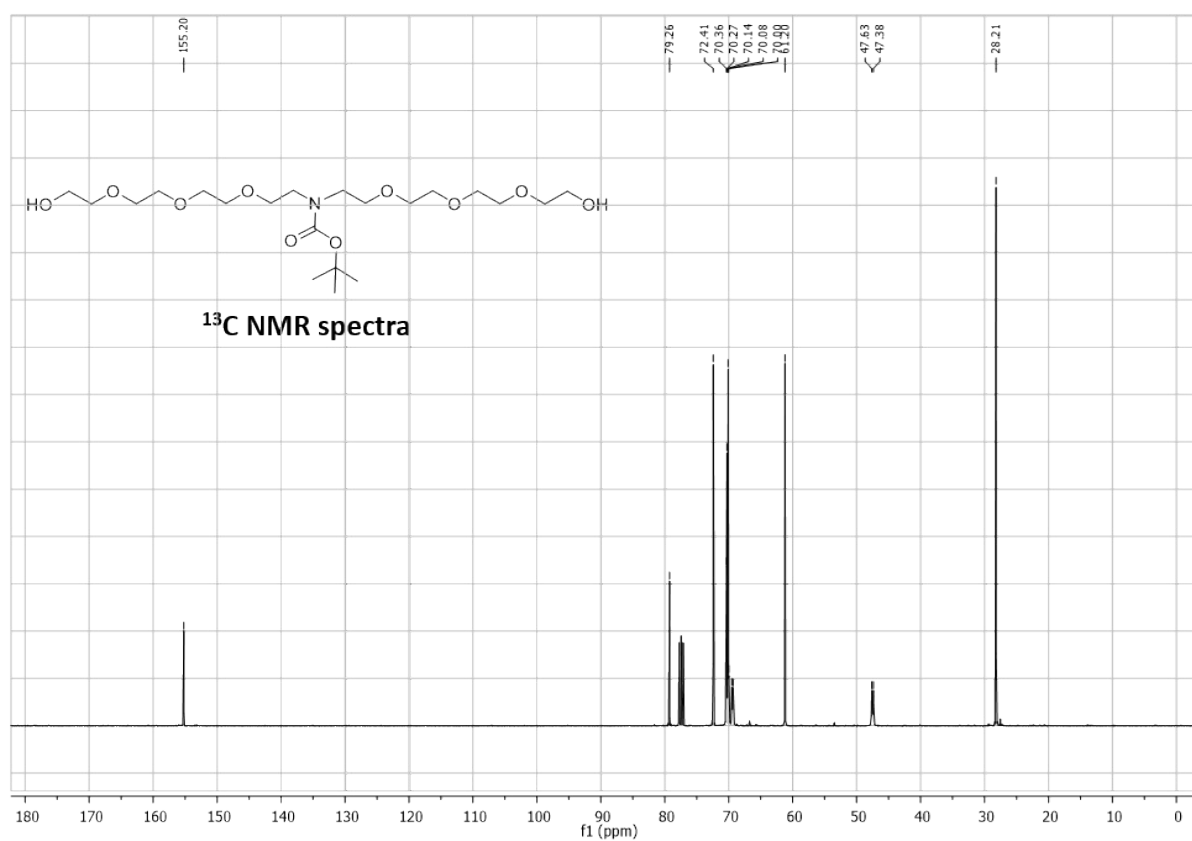
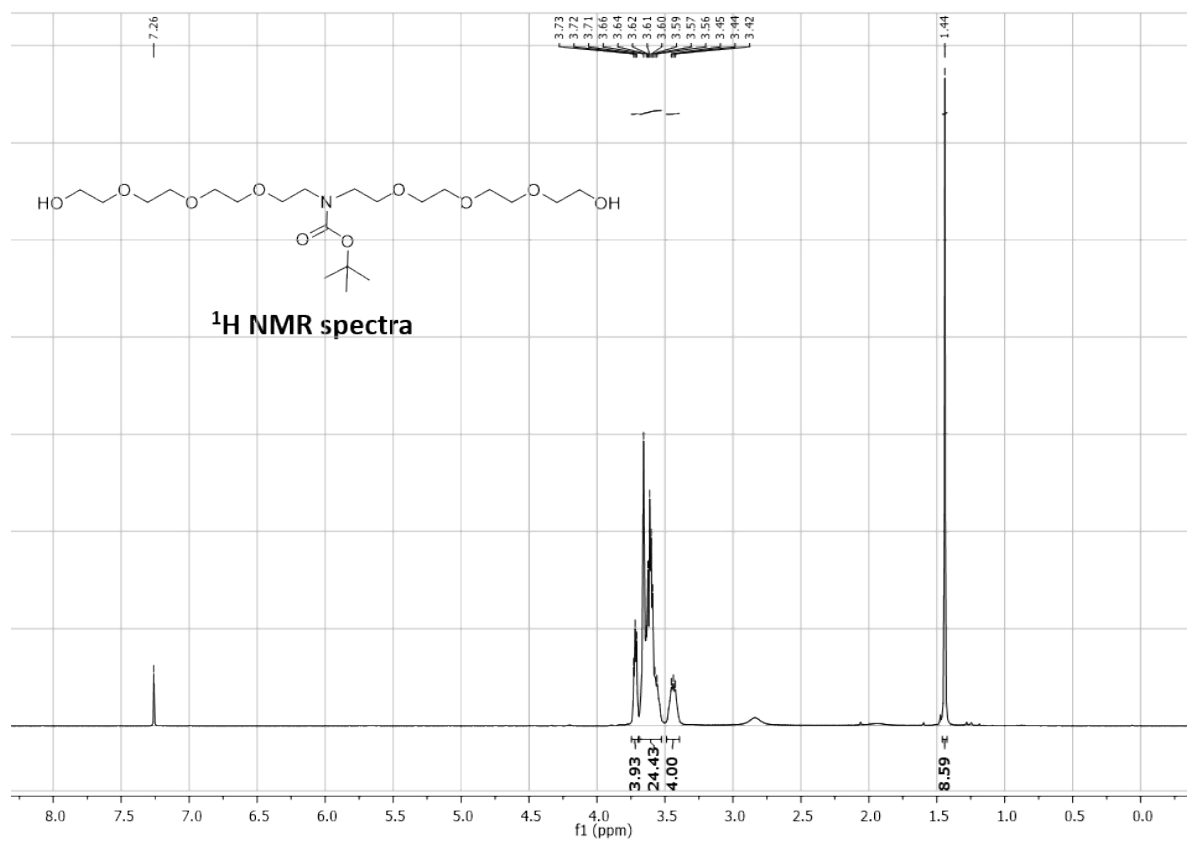


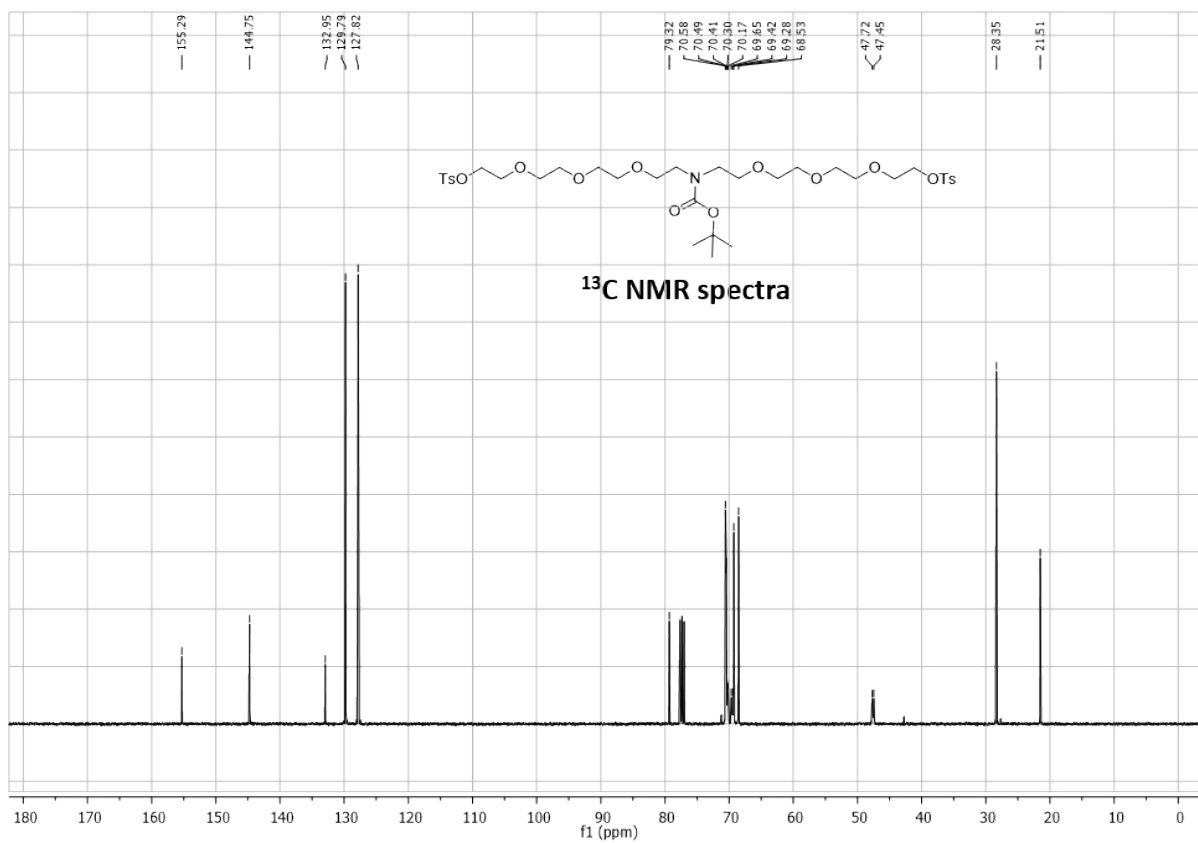
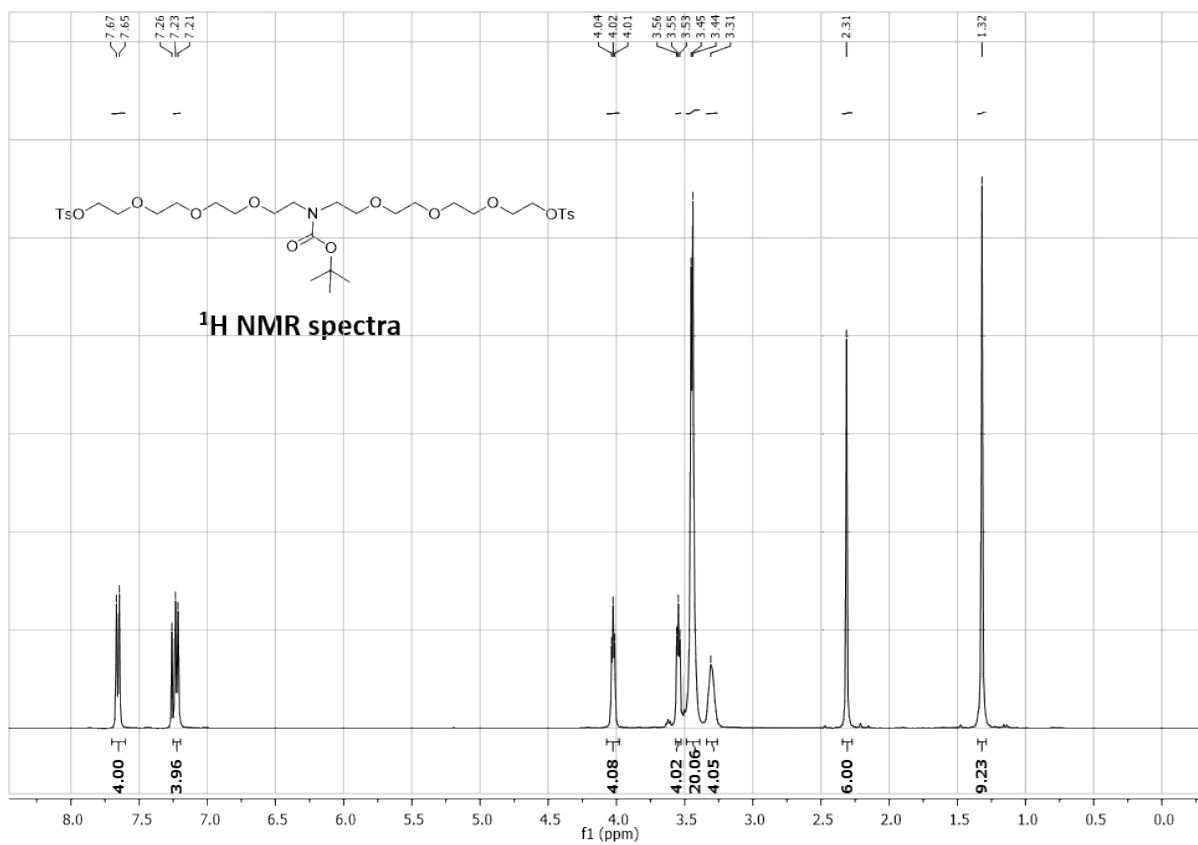


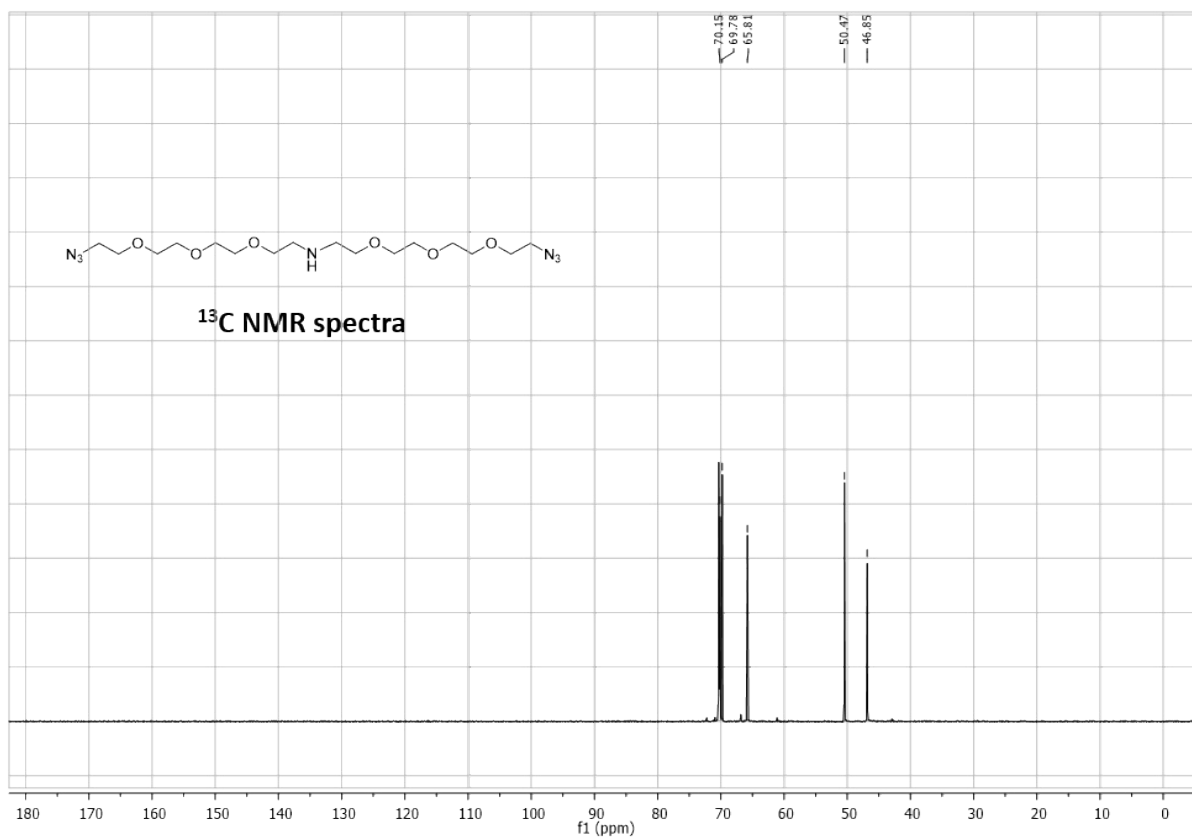
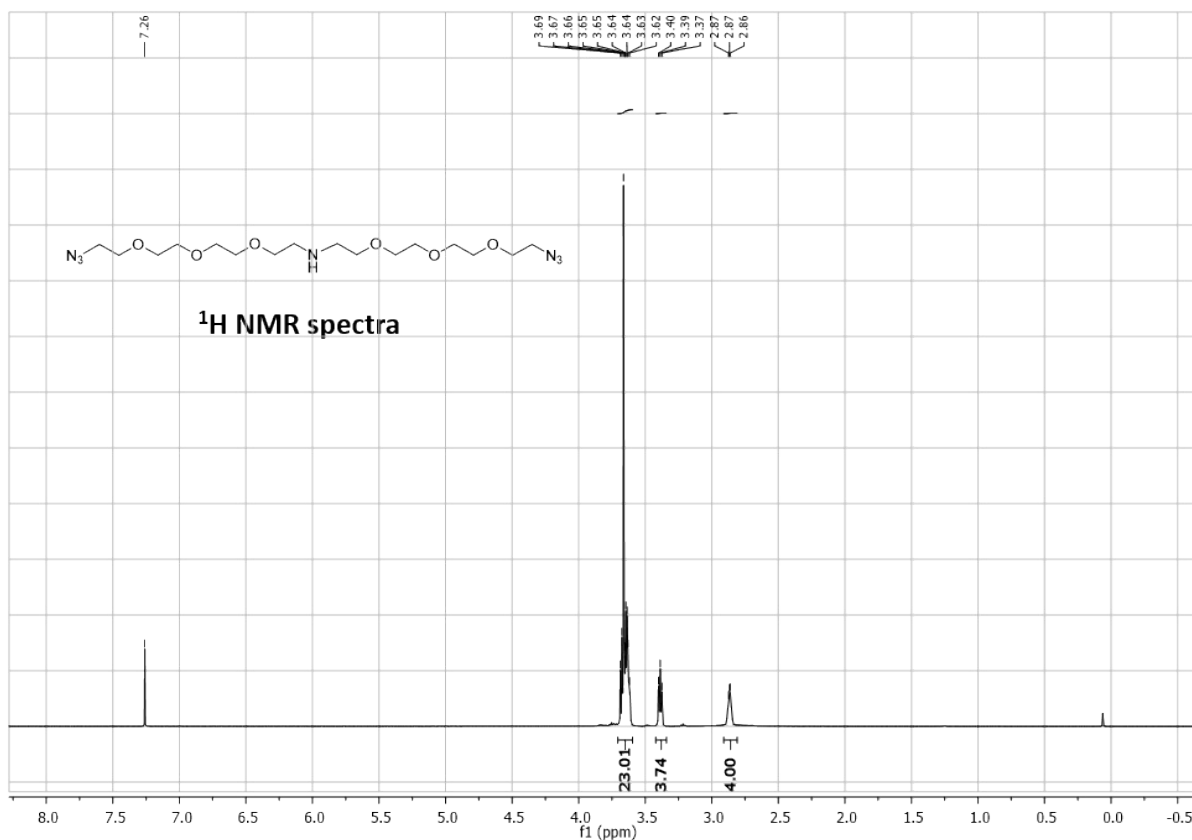




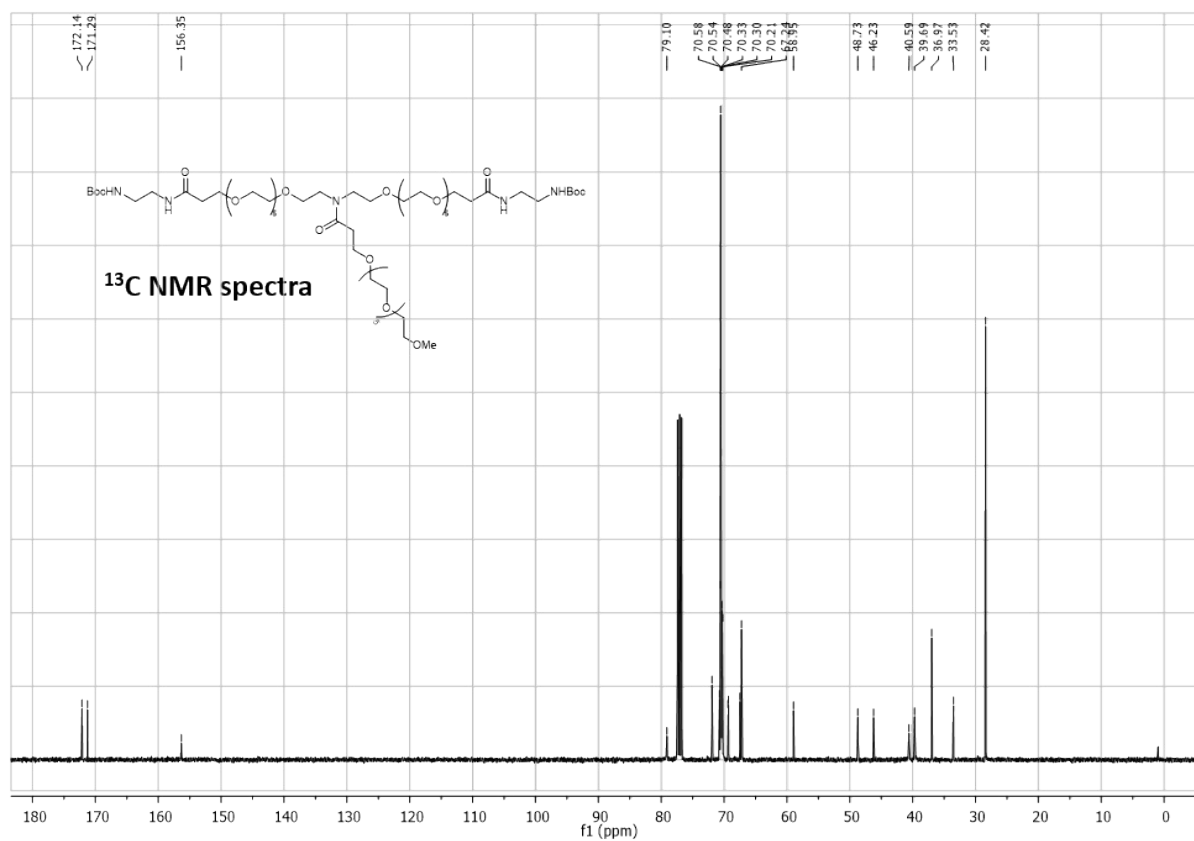
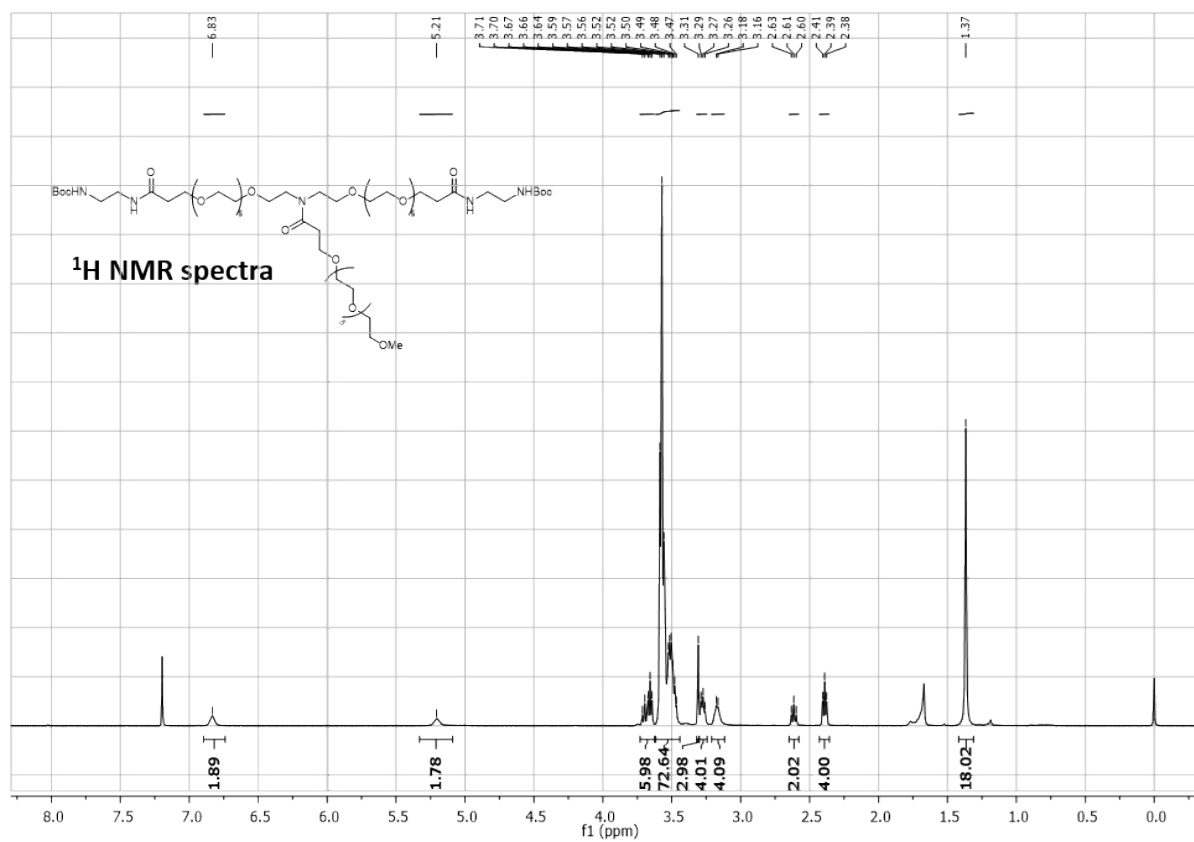
7.3 Bis-azido OEG amine NMR spectra

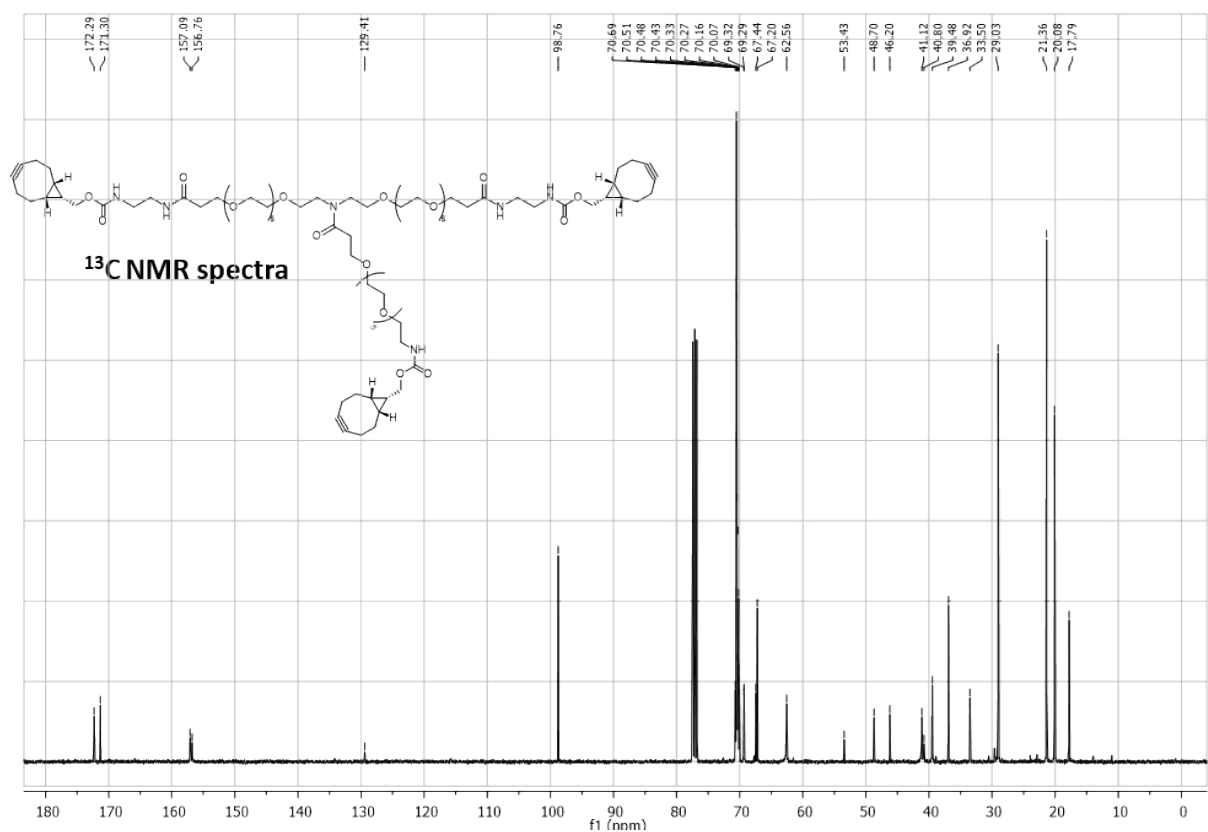
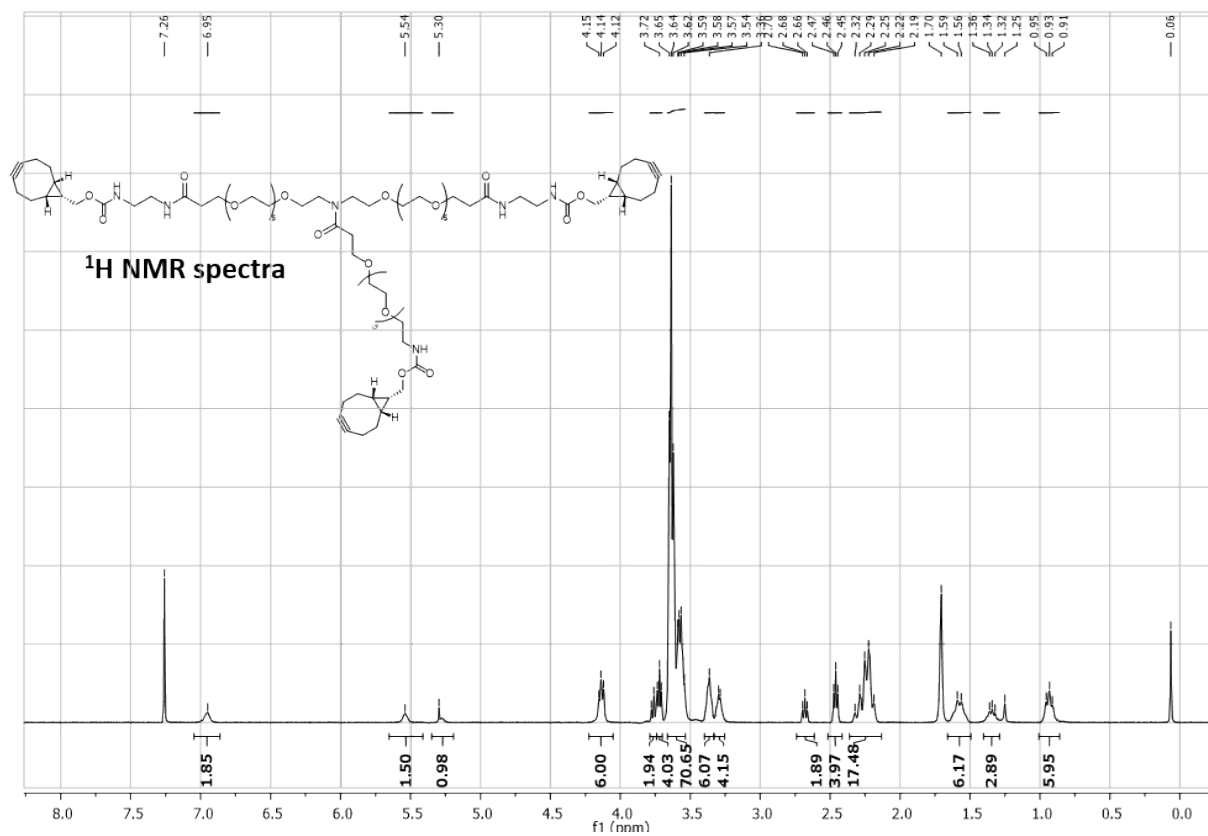


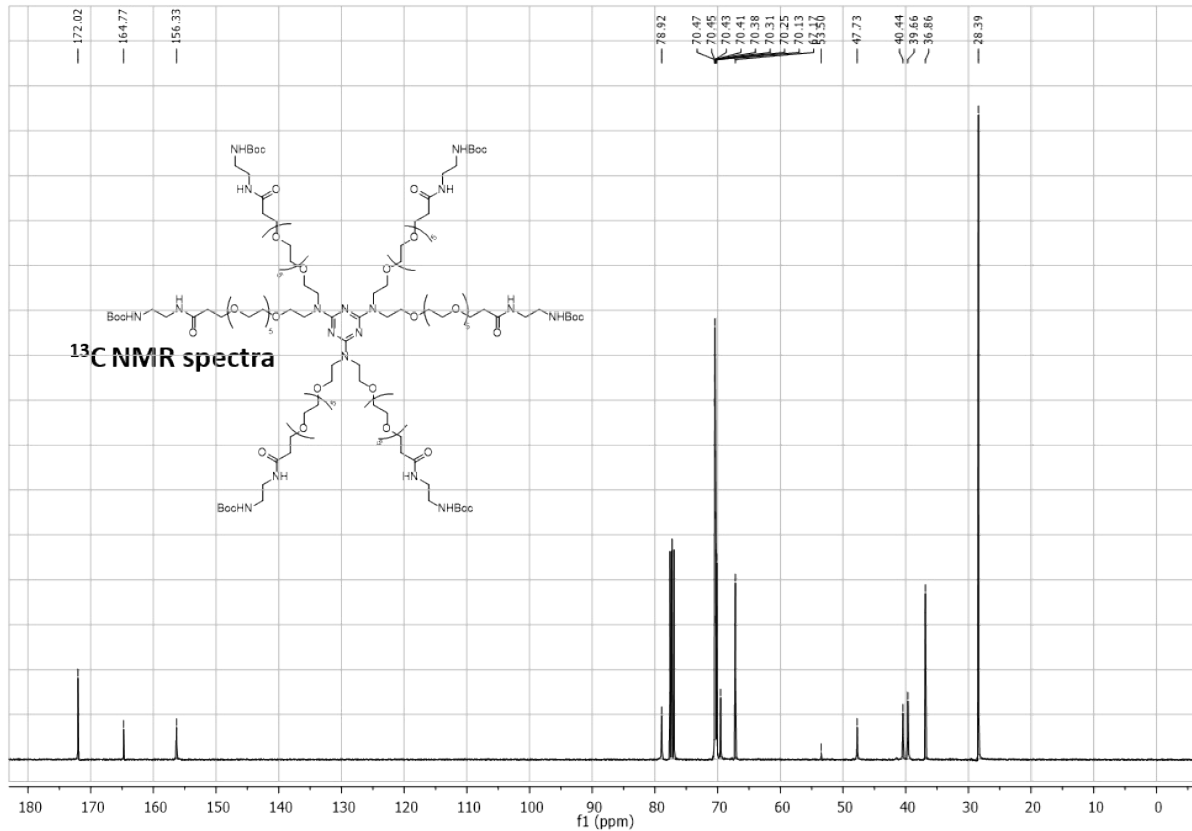
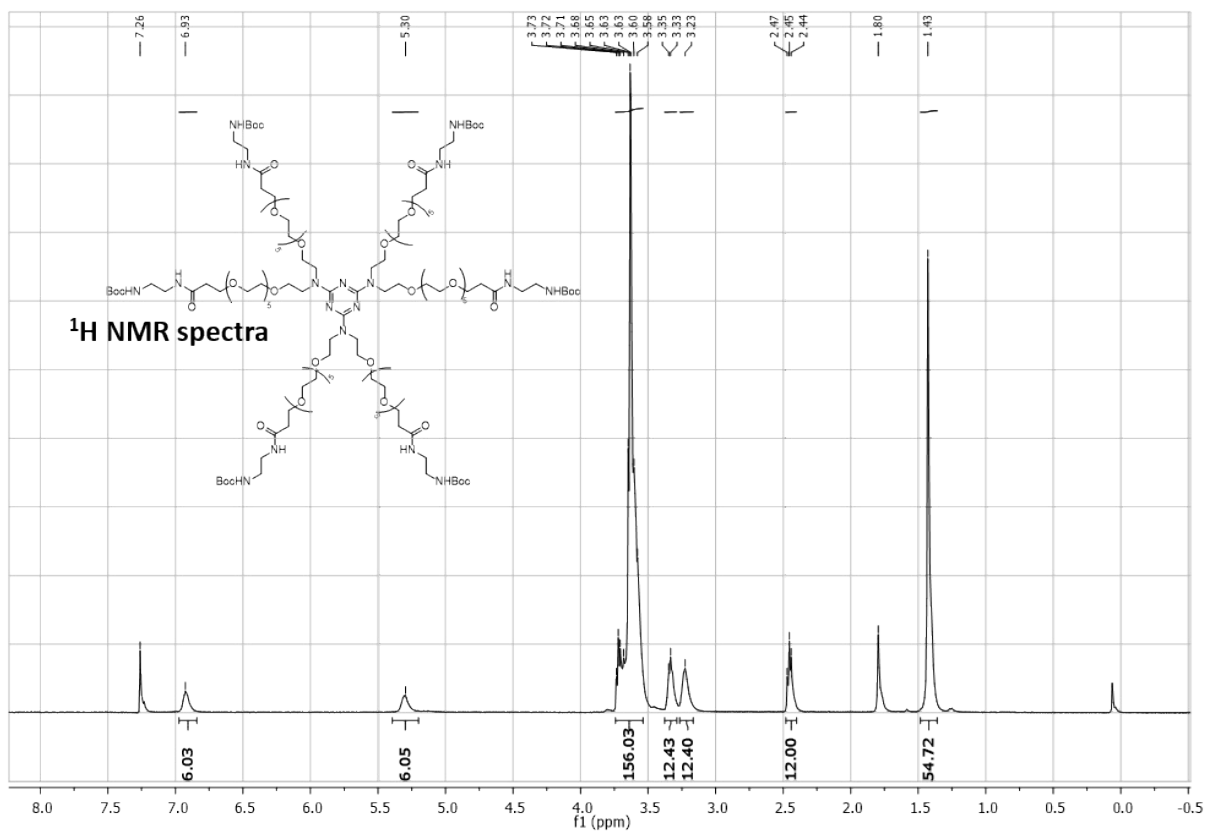


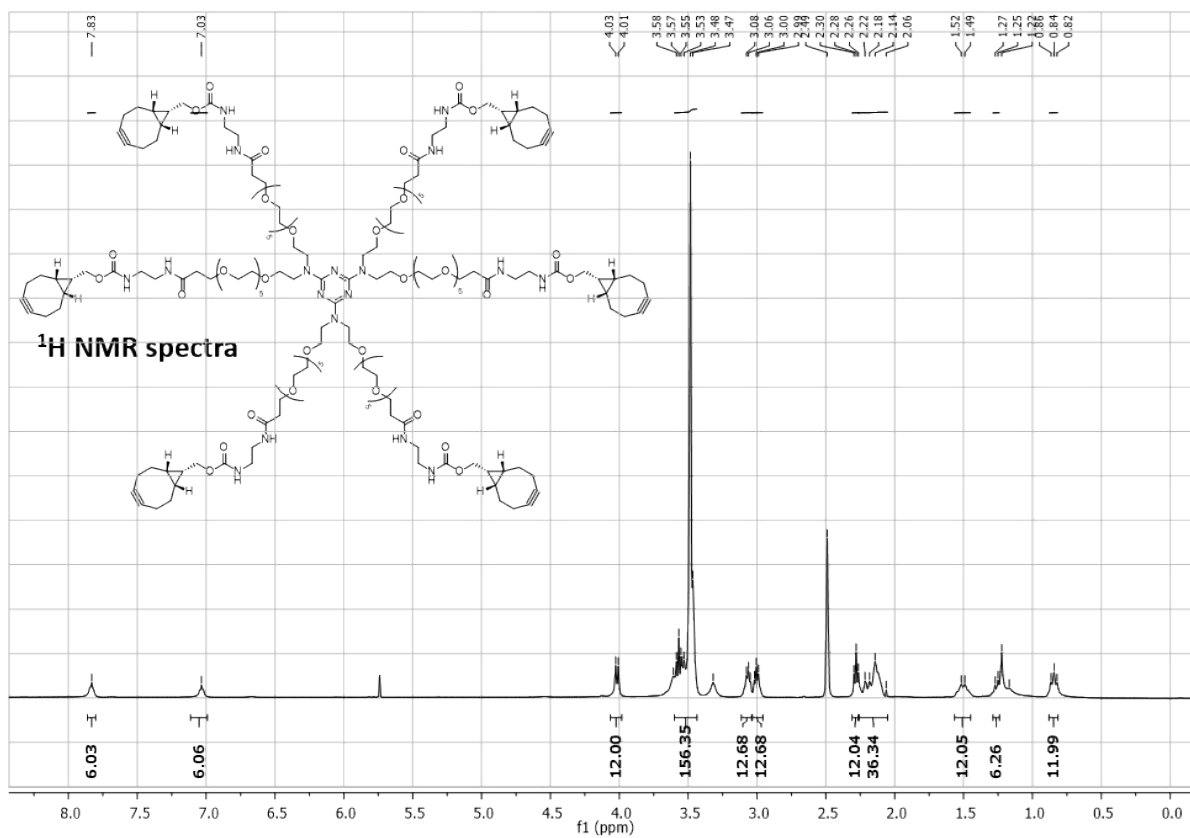


7.4 Compact tri- and hexa-functional platforms NMR spectra









7.5 hetero-functional OEG platforms NMR spectra

