Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.
This journal is © The Royal Society of Chemistry 2015

ELECTRONIC SUPPORTING INFORMATION

Synthesis and Biological Evaluation of Hybrid G-Quadruplex-HSP90 Ligand Conjugates As Telomerase Inhibitors

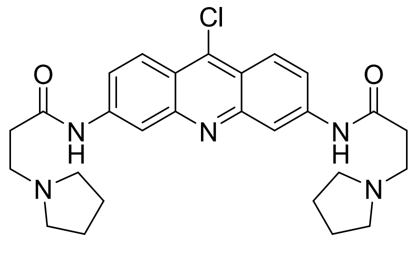
S. Roe,[a] M. Gunaratnam,[b] C. Spiteri,[a] P. Sharma,[a] R. D. Alharthy,[c] S. Neidle[b] and J. E. Moses[a*]

[a.*] *School of Chemistry, University of Nottingham, University Park, NG7 2RD, UK*
Tel: ++44 (0)115 951 3533*; E-mail:* john.moses@nottingham.ac.uk
[b.] *School of Pharmacy, University College London, WC1N 1AX, UK*
[c.] *Department of Chemistry, King Abdulaziz University, Saudi Arabia*

Experimental:

General: ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker AV(III) 500 (Cryoprobe) (500 MHz (^{1}H) and 125 MHz (^{13}C)), Bruker AV(III) 400 Bruker AV 400 Bruker DPX 400 (400MHz (^{1}H) and 100 MHz (^{13}C)) spectrometers. Chemical shifts are expressed in parts per million (ppm) and the spectra are calibrated to residual solvent signals of $CDCl_3$ (7.26 (^{1}H) and 77.0 (^{13}C)). Coupling constant are given in hertz (Hz) and the following notations indicate the multiplicity of the signals: s (singlet), d (doublet), brd (broad doublet), t (triplet), q (quartet), p (pentet), m (multiplet). High Resolution Mass Spectra were recorded on VG micron Autospec or Bruker microTOF. Fourier Transform Infrared Spectroscopy (FT-IR) spectra were obtained on Perkin Elmer 1600 series or Bruker Tensor 27 spectrometer. UV absorption was measured on Philips PU8720 series UV/VIS spectrometer. Thin layer chromatography were carried on Merck precoated silica gel plates (60F-254) or Merck aluminium backed aluminium oxide 60 F_{254} coated plates and visualised using ultra violet light or $KMnO_4$ solution or *p*-anisaldehyde solution. Column chromatography was performed at ambient temperature using Merck silica gel 60 (0.063-0.200 mm) or BDH neutral aluminium oxide, and eluents containing c.$NH_{3(aq)}$ refer to the mixed eluent with the water removed prior to use. THF was freshly distilled from sodium-benzophenone; dichloromethane was dried over calcium hydride. Acetone and solid CO_2 was used to obtain -78 °C. Where necessary, reaction requiring anhydrous conditions were performed in dry solvents in flame dried or oven-dried apparatus under nitrogen or argon atmosphere.

3,6-Bis(3-pyrrolidin-1-ylpropionamido)-9-chloroacridine (2)

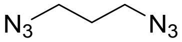


Compound 3,6-Bis[3-(pyrrolidino)propionamido]-9(10H)-acridone (5.78 g, 12.2 mmol) was slowly added at reflux $POCl_3$ (87 mL) over 10 minutes (care: HCl evolution), then heated at reflux for a further 3 h. The reaction mixture was cooled to 0° C and anhydrous diethyl ether was added to precipitate the product, which was then isolated by filtration. Solids were washed with diethyl ether, then redissolved in chloroform (100 mL) and water (100 mL) and made basic with dilute ammonia. The organic phase was collected, washed with brine (50 mL) and evaporated to dryness to give the title compound (4.85 g, 81%) as a dark yellow powder; R_f 0.73 (85:10:5 dichloromethane / methanol / triethylamine); δ_H (400 MHz, $CDCl_3$) 11.72 (2H, s), 8.35 (2H, d, *J* 9.4 Hz), 8.12 (2H, *J* 1.8 Hz), 7.98 (2H, dd, *J* 9.4 and 1.8 Hz), 2.94 (4H, t, *J* 6.2 Hz), 2.77 (8H, m), 2.65 (4H, t, *J* 6.2 Hz), 1.99 (8H, m); δ_C (101 MHz, $CDCl_3$) 171.46, 150.27, 141.20, 140.62, 125.61, 121.74, 120.79, 115.06, 53.19, 51.36, 34.77, 23.78; *m/z* (ESI) 516.2 ($M+Na^+$, 7%), 494.2 ($M+H^+$, 100), 411.2 (88), 328.1 (51), 286.1 (21); HRMS: Found 494.2304. $C_{27}H_{33}Cl_1N_5O_2$ ($M+H^+$) Requires 494.2317.

General Procedure for the Preparation of Diazidoalkanes

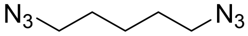
The dibromoalkane (1 mmol) and sodium azide (2.5 mmol) in water (2 mL) were placed in a 10 mL crimp-sealed thick-walled glass microwave tube along with a magnetic stirrer. The reaction tube was placed inside the cavity of a Biotage Initiator™ microwave synthesiser and heated to 120-140° C for 1-4 hours. After completion of the reaction as monitored by ^{1}H NMR, the diazide was extracted with diethyl ether and the combined organic layers dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* afforded the product as colourless-pale yellow oil.

1,3-Diazidopropane



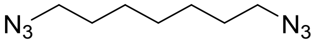
The reaction of 1,3-dibromo-propane (2.15 g, 7.3 mmol) and sodium azide (1.18 g, 18.2 mmol) was carried out as described in the general procedure and afforded the title compound (0.72 g, 78%) as a colourless oil; R_f 0.50 (6:1 hexane / ethyl acetate); δ_H (400 MHz, $CDCl_3$) 3.42 (4H, t, J 6.5 Hz), 1.83 (2H, p, J 6.5 Hz).

1,5-Diazidopentane



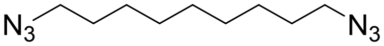
The reaction of 1,5-dibromopentane (1.61 g, 7.0 mmol) and sodium azide (1.14 g, 17.5 mmol) was carried out as described in the general procedure and afforded the title compound (1.01 g, 94%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 3.29 (4H, t, J 6.8 Hz), 1.59-1.68 (4H, m), 1.42-1.51 (2H, m).

1,7-Diazidoheptane



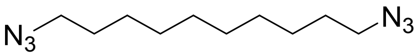
The reaction of 1,7-dibromoheptane (1.61 g, 6.3 mmol) and sodium azide (1.02 g, 15.6 mmol) was carried out as described in the general procedure and afforded the title compound as a solution in diethyl ether which was used directly in the next reaction; δ_H (400 MHz, $CDCl_3$) 3.27 (4H, t, J 6.91 Hz), 1.60 (4H, m), 1.33-1.43 (6H, m).

1,9-Diazidononane



The reaction of 1,9-dibromononane (1.61 g, 5.6 mmol) and sodium azide (0.91 g, 14.1 mmol) was carried out as described in the general procedure and afforded the title compound as a solution in diethyl ether which was used directly in the next reaction; δ_H (400 MHz, $CDCl_3$) 3.27 (4H, t, *J* 7.0 Hz), 1.61 (4H, m), 1.29-1.43 (10H, m).

1,9-Diazidodecane

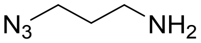


The reaction of 1,10-dibromodecane (1.61 g, 5.4 mmol) and sodium azide (0.87 g, 13.4 mmol) was carried out as described in the general procedure and afforded the title compound as a solution in diethyl ether which was used directly in the next reaction; δ_H (400 MHz, $CDCl_3$) 3.26 (4H, t, *J* 7.0 Hz), 1.60 (4H, m), 1.27-1.41 (12H, m).

General Procedure for the Preparation of Azido-aminoalkanes:

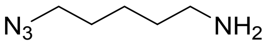
To a solution of the di-azide (1 mmol) in diethyl ether (1 mL), ethyl acetate (1 mL) and 5% aqueous hydrochloric acid (3 mL) was added triphenylphosphine (0.98 mmol) portionwise over 1 hour at 0º C and stirred for 16 hours at room temperature. The organic layer was discarded and the aqueous layer was washed with (3 × 6 mL) CH_2Cl_2. The resultant aqueous phase was basified with sodium hydroxide (pH>12), and then extracted with (3 × 6 mL) CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give pure amino azide.

1-Azido-3-aminopropane (9)



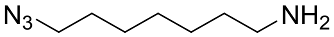
The reaction of 1,3-diazidopropane (2.42 g, 19.2 mmol) according to the general procedure afforded the title compound (0.90 g, 55%) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) 3.40 (2H, t, *J* 6.8 Hz), 2.83 (2H, t, *J* 6.8 Hz), 1.75 (2H, p, *J* 6.8 Hz), 1.31 (2H, br s).

1-Azido-5-aminopentane (10)



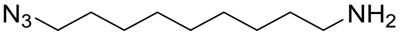
The reaction of 1,5-diazidopentane (1.30 g, 8.5 mmol) according to the general procedure afforded the title compound (0.85 g, 81%) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) 3.27 (2H, t, *J* 6.9 Hz), 2.70 (2H, t, *J* 6.8 Hz), 1.62 (2H, m), 1.36-1.51 (4H, m), 1.19 (2H, br s).

1-Azido-7-aminoheptane (11)



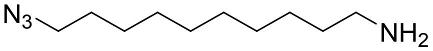
The reaction of 1,7-diazidoheptane (2.28 g, 12.5 mmol) according to the general procedure afforded the title compound (0.86 g, 52%) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) 3.24 (2H, t, *J* 6.9 Hz), 2.66 (2H, t, *J* 7.0 Hz), 1.58 (2H, m), 1.26-1.48 (10H).

1-Azido-9-aminononane (12)



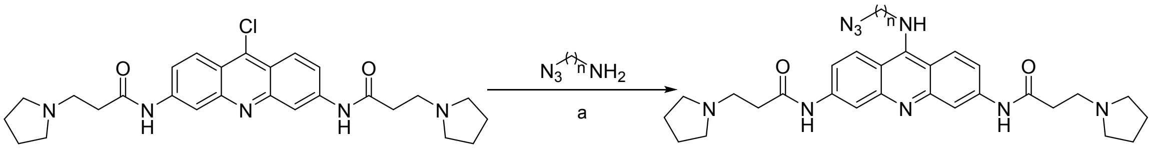
The reaction of 1,9-diazidononane (2.37 g, 11.3 mmol) according to the general procedure afforded the title compound (0.41 g, 23%) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) 3.23 (2H, t, *J* 6.9 Hz), 2.65 (2H, t, *J* 7.0 Hz), 1.55 (2H, m), 1.23-1.47 (14H).

1-Azido-10-aminodecane (13)



The reaction of 1,10-diazidodecane (2.41 g, 10.7 mmol) according to the general procedure afforded the title compound (0.27 g, 15%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 3.25 (2H, t, *J* 6.9 Hz), 2.67 (2H, t, *J* 7.0 Hz), 1.55 (2H, m), 1.24-1.49 (16H, m).

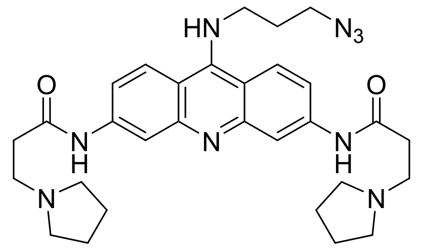
Tethering of the amino-azide linkers to bis-amidochloroacridine (2):



Reagents: a) $CHCl_3$, reflux, 16 h

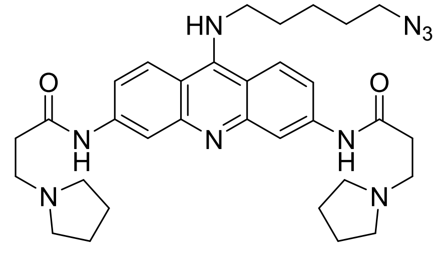
Coupling of the amino azides with the bis-amidochloroacridine (**2**) went in good yields in $CHCl_3$. (Purification was achieved by column chromatography on silica with 85:10:5, DCM:MeOH:$NH_{3(aq)}$).

N-[9-(3-Azido-propylamino)-6-(3-pyrrolidin-1-yl-propionylamino)-acridin-3-yl]-3-pyrrolidin-1-yl-propionamide (14)



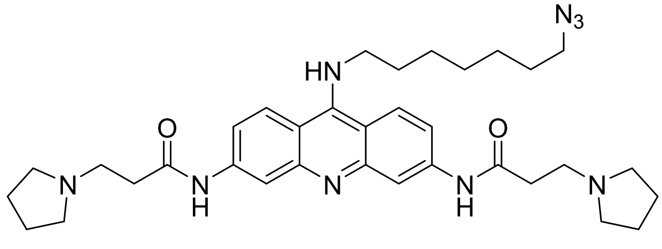
To a solution of the 3,6-bisamido-9-chloroacridine (**2**, 0.45 g, 0.9 mmol) in $CHCl_3$ (4.5 mL) was added 1-azido-3-aminopropane (**9**, 100 mg, 1.0 mmol), and the resultant mixture was stirred at reflux for 40 hours. The reaction mixture was made basic with saturated aqueous K_2CO_3 solution (3 mL), then extracted with $CHCl_3$ (3 × 5 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by column chromatography over silica gel (eluting with 85:10:5 CH_2Cl_2:MeOH:c.$NH_{3(aq)}$) gave the *title compound* (300 mg, 59%) as an amorphous yellow glass; R_f 0.17 (90:6:4 CH_2Cl_2:CH_3OH:c.$NH_{3(aq)}$); ν_{max} ($CHCl_3$)/cm^{-1} 2968, 2102 (azide), 1675 (amide), 1613; δ_H (400 MHz, $CDCl_3$) 11.60 (2H, br s), 7.82-8.06 (4H, m), 7.77 (2H, s), 5.28 (1H, br s), 3.88 (2H, t, *J* 6.2 Hz), 3.52 (2H, t, *J* 6.2 Hz), 2.88 (4H, t, *J* 5.6 Hz), 2.70 (8H, m), 2.59 (4H, t, *J* 5.6 Hz), 2.01 (2H, p, *J* 6.2 Hz), 1.92 (8H, m); δ_C (75 MHz, $CDCl_3$) 171.3, 150.6, 150.3, 140.6, 123.7, 117.8, 115.2, 113.5, 53.1, 51.3, 49.5, 48.3, 34.7, 30.3, 23.6; *m/z* (ESI) 558.3 ($M+H^+$, 100%), 476.3 (6), 279.7 (27); HRMS: Found 580.3109. $C_{30}H_{39}N_9NaO_2$ ($M+Na^+$) Requires 580.3119.

N-[9-(5-Azido-pentylamino)-6-(3-pyrrolidin-1-yl-propionylamino)-acridin-3-yl]-3-pyrrolidin-1-yl-propionamide (15)



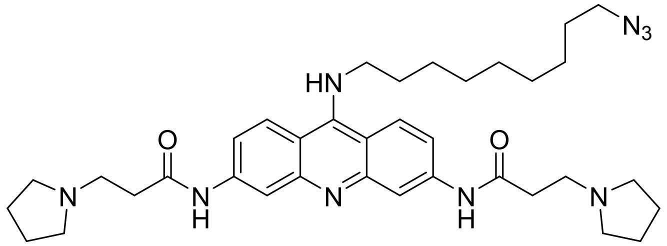
To a solution of the 3,6-bisamido-9-chloroacridine (**2**, 0.70 g, 1.4 mmol) in $CHCl_3$ (7 mL) was added 1-azido-5-aminopentane (**10**, 200 mg, 1.3 mmol), and the resultant mixture was stirred at reflux for 40 hours. The reaction mixture was made basic with saturated aqueous K_2CO_3 solution (8 mL), then extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by column chromatography over silica gel (eluting with 85:10:5 CH_2Cl_2:MeOH:c.$NH_{3(aq)}$) gave the title compound (531 mg, 64%) as an amorphous yellow glass; R_f 0.43 (85:10:5 CH_2Cl_2:CH_3OH:c.$NH_{3(aq)}$); ν_{max} ($CHCl_3$)/cm^{-1} 2938, 2819, 2100 (azide), 1674 (amide), 1613; δ_H (400 MHz, $CDCl_3$) 11.56 (2H, br s), 8.00 (2H, d, *J* 9.3 Hz), 7.91 (2H, m), 7.72 (2H, s), 5.03 (1H, br s), 3.78 (2H, t, *J* 7.2 Hz), 3.26 (2H, t, *J* 6.7 Hz), 2.87 (4H, t, *J* 5.8 Hz), 2.69 (8H, m), 2.58 (4H, t, *J* 5.8 Hz), 1.92 (8H, m), 1.78 (2H, p, *J* 7.4 Hz), 1.62 (2H, m), 1.50 (2H, m); δ_C (101 MHz, $CDCl_3$) 171.3, 150.8, 150.2, 140.5, 123.8, 117.2, 114.7, 113.0, 53.0, 51.2, 51.0, 50.1, 34.7, 31.0, 28.4, 23.9, 23.5; *m/z* (ESI) 586.4 (M+H$^+$, 100%), 392.2 (12), 293.7 (18); HRMS: Found 586.3601. $C_{32}H_{44}N_9O_2$ (M+H$^+$) Requires 586.3612.

N-[9-(7-Azido-heptylamino)-6-(3-pyrrolidin-1-yl-propionylamino)-acridin-3-yl]-3-pyrrolidin-1-yl-propionamide (16)



To a solution of the 3,6-bisamido-9-chloroacridine (**2**, 0.63 g, 1.3 mmol) in $CHCl_3$ (9.5 mL) was added 1-azido-5-aminoheptane (**11**, 300 mg, 1.9 mmol), and the resultant mixture was stirred at reflux for 40 hours. The reaction mixture was made basic with saturated aqueous K_2CO_3 solution (10 mL), then extracted with $CHCl_3$ (3 × 15 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by column chromatography over silica gel (eluting with 90:6:4 CH_2Cl_2:CH_3OH:c.$NH_{3(aq)}$) gave the title compound (500 mg, 64%) as an amorphous yellow glass; R_f 0.33 (90:6:4 CH_2Cl_2:CH_3OH:c.$NH_{3(aq)}$); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2750, 2100 (azide), 1674 (amide), 1613; δ_H (400 MHz, $CDCl_3$) 11.57 (2H, br s), 7.95 (2H, d, *J* 8.7 Hz), 7.84 (2H, d, *J* 8.7 Hz), 7.66 (2H, s), 5.29 (1H, br s), 3.68 (2H, m), 3.13 (2H, t, *J* 6.8 Hz), 2.77 (4H, m), 2.57 (8H, m), 2.49 (4H, m), 1.78 (8H, m), 1.66 (2H, m), 1.45 (2H, m), 1.16-1.35 (6H, m); δ_C (101 MHz, $CDCl_3$) 171.1, 150.7, 150.5, 140.4, 123.7, 117.2, 114.9, 112.8, 52.9, 51.1, 51.0, 50.3, 34.6, 31.2, 28.6, 28.4, 26.5, 26.3, 23.4; *m/z* (ESI) 614.4 (M+H$^+$, 100%), 420.2 (17), 308.2 (28), 307.7 (72); HRMS: Found 614.3914. $C_{34}H_{48}N_9O_2$ (M+H$^+$) Requires 614.3925.

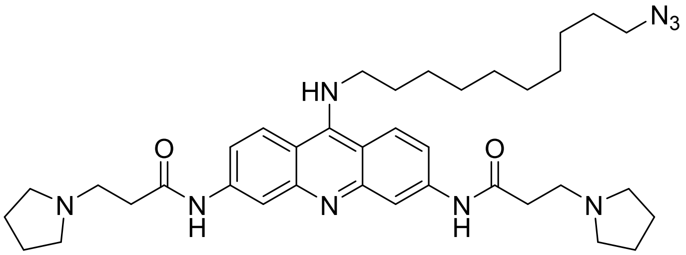
N-[9-(9-Azido-nonylamino)-6-(3-pyrrolidin-1-yl-propionylamino)-acridin-3-yl]-3-pyrrolidin-1-yl-propionamide (17)



To a solution of the 3,6-bisamido-9-chloroacridine (**2**, 0.54 g, 1.1 mmol) in $CHCl_3$ (5.4 mL) was added 1-azido-9-aminononane (**12**, 300 mg, 1.6 mmol), and the resultant mixture was stirred at reflux for 40 hours. The reaction mixture was made basic with saturated aqueous K_2CO_3 solution (10 mL), then extracted with $CHCl_3$ (3 × 15 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by column chromatography over silica gel (eluting with 90:6:4 CH_2Cl_2:CH_3OH:c.$NH_{3(aq)}$) gave the title compound (252 mg, 36%) as an amorphous yellow glass; R_f 0.26 (90:6:4 CH_2Cl_2:CH_3OH:c.$NH_{3(aq)}$); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2965, 2099 (azide), 1674 (amide), 1613; δ_H (400 MHz, $CDCl_3$) 11.57 (2H, br s), 8.03 (2H, d, *J* 9.2 Hz), 7.99 (2H, m), 7.71 (2H, s), 5.29 (1H, br s), 3.81 (2H, t, *J* 6.8 Hz), 3.26 (2H, t, *J* 6.8 Hz), 2.90 (4H, t, *J* 6.4 Hz), 2.73 (8H, m), 2.61 (4H, t, *J* 6.4 Hz), 1.82 (8H, m), 1.78

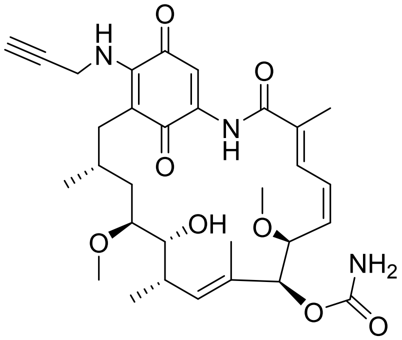
(2H, m), 1.59 (2H, m), 1.27-1.44 (10H, m); δ_C (101 MHz, $CDCl_3$) 171.4, 151.0, 150.6, 140.7, 123.8, 117.7, 115.3, 113.2, 53.2, 51.5, 51.4, 50.8, 34.8, 31.9, 29.3, 29.2, 29.0, 28.8, 26.8, 26.6, 23.8; *m/z* (ESI) 642.4 ($M+H^+$, 94%), 448.3 (12), 322.2 (42), 321.7 (100); HRMS: Found 642.4222. $C_{35}H_{52}N_9O_2$ ($M+H^+$) Requires 642.4238

N-[9-(10-Azido-decylamino)-6-(3-pyrrolidin-1-yl-propionylamino)-acridin-3-yl]-3-pyrrolidin-1-yl-propionamide (18)



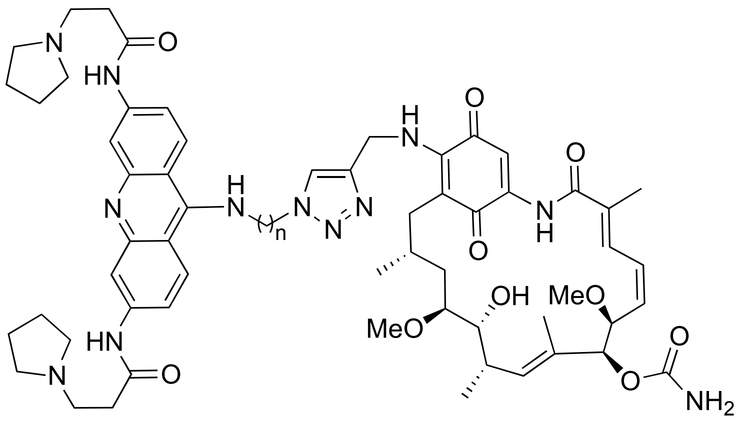
To a solution of the 3,6-bisamido-9-chloroacridine (**2**, 0.17 g, 0.3 mmol) in $CHCl_3$ (1.7 mL) was added 1-azido-10-aminodecane (**13**, 100 mg, 0.5 mmol), and the resultant mixture was stirred at reflux for 40 hours. The reaction mixture was made basic with saturated aqueous K_2CO_3 solution (4 mL), then extracted with $CHCl_3$ (3 × 5 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by column chromatography over silica gel (eluting with 90:6:4 CH_2Cl_2:CH_3OH:c.$NH_{3(aq)}$) gave the title compound (114 mg, 52%) as an amorphous yellow glass; R_f 0.29 (90:6:4 CH_2Cl_2:CH_3OH:c.$NH_{3(aq)}$); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2931, 2100 (azide), 1672 (amide), 1613; δ_H (400 MHz, $CDCl_3$) 11.57 (2H, br s), 7.99 (2H, d, *J* 9.1 Hz), 7.73 (2H, dd, *J* 9.1 and 1.6 Hz), 7.71 (2H, s), 3.82 (2H, t, *J* 6.8 Hz), 3.59 (2H, m), 2.85 (4H, t, *J* 6.4 Hz), 2.66 (8H, m), 2.58 (4H, t, *J* 6.4 Hz), 1.87 (8H, m), 1.75 (2H, m), 1.53 (2H, m), 1.20-1.45 (12H, m); *m/z* (ESI) 656.4 ($M+H^+$, 1%), 631.4 (100), 316.7 (28), 316.2 (70); HRMS: Found 656.4385. $C_{37}H_{54}N_9O_2$ ($M+H^+$) Requires 656.4395.

17-Propargylamino-17-demethoxygeldanamycin (6)



To a solution of Geldanamycin (**4**, 506 mg, 0.9 mmol) in dimethylformamide (11.7 mL) in a flame dried flask under nitrogen was added a solution of propargylamine (104 μL, 1.6 mmol) in DMF (1 mL) slowly via syringe pump over a period of 1 hour at room temperature. The mixture was then stirred at room temperature for an additional 16 hours. Concentration of the reaction mixture *in vacuo* at 50 ºC followed by repeated dissolution and re-concentration from chloroform gave the title compound (516.8 mg, 98%) as a purple solid; R_f 0.35 (95:5 CH_2Cl_2/ CH_3OH); ν_{max} ($CHCl_3$)/cm^{-1} 3620.7, 1727.9, 1688.6, 1579.7; δ_H (400 MHz, $CDCl_3$) 9.08 (1H, s), 7.29 (1H, s), 6.94 (1H, d, *J* 11.4 Hz), 6.57 (1H, t, *J* 11.4 Hz), 6.31 (1H, t, *J* 5.5 Hz), 5.82-5.90 (2H, m), 5.18 (1H, s), 4.90 (2H, br s), 4.27-4.33 (3H, m), 3.95 (1H, br m), 3.54-3.60 (1H, br m), 3.41-3.46 (1H, br m), 3.35 (3H, s), 3.26 (3H, s), 2.68-2.78 (2H, br m), 2.40 (1H, s), 2.31-2.38 (1H, br m), 2.02 (3H, s), 1.79 (3H, s), 1.63-1.77 (2H, m), 0.95-1.02 (7H, m); δ_C (101 MHz, $CDCl_3$) 183.59, 181.55, 168.31, 156.09, 143.90, 140.71, 135.89, 134.88, 133.56, 132.85, 126.95, 126.47, 110.26, 109.08, 81.56, 81.27, 81.11, 78.18, 73.93, 72.58, 57.08, 56.69, 35.39, 34.92, 34.35, 32.25, 28.55, 22.85, 12.77, 12.57, 12.35; *m/z* (ESI) 1189.6 (2M+Na$^+$, 90.5%), 606.3 (M+Na$^+$, 100), 491.3 (14.8); HRMS: Found 606.2773. $C_{31}H_{41}N_3NaO_8$ (M+Na$^+$) Requires 606.2786.

General Procedure for the Preparation of Geldanamycin-bis-amido-acridine analogues:



GA-G4 conjugates

SR372: n = 3 **SR361**: n = 5
SR362: n = 7 **SR374**: n = 9
SR375: n = 10

To a solution of the acridine-azide (**14-18**, 1 equiv) and the propargyl-Geldanamycin (**6**, 1 equiv), in a mixture of (1:1 ^{t}butanol : water) (20 vols) was added anhydrous $CuSO_4$ (5 mol%) followed by sodium ascorbate (0.2 equiv). The reaction mixture was stirred at room temperature for 16 hours after which time the azide had been consumed according to TLC in either (90:6:4 CH_2Cl_2:CH_3OH:c.$NH_{3(aq)}$ or 85:10:5 CH_2Cl_2:CH_3OH:c.$NH_{3(aq)}$) and a fine brown solid had formed. The reaction mixture was concentrated *in vacuo* diluted with water (50 vols), then stirred for 30 minutes. The mixture was filtered and the collected solid washed with 3 × $CHCl_3$ (30 vols) to remove any residual starting materials. Mass spectrometry data were collected in MeOH.

Triazole product	linker length, n	Yield (%)[b]
SR372	3	0[a]
SR361	5	45
SR362	7	62
SR374	9	31
SR375	10	16

a) reaction failed; b) yields are based on isolated solids that have not been purified.

SR361: HRMS (ESI) (*m/z*): $[M\text{-}H]^+$ calcd for $C_{63}H_{83}N_{12}O_{10}$, 1167.6350; found 1167.6231.

SR362: HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{65}H_{88}N_{12}O_{10}$, 1196.6736; found 1196.6718.

SR374: HRMS (ESI) (*m/z*): $[M+H]^+$ calcd for $C_{67}H_{93}N_{12}O_{10}$, 1225.7132; found 1225.7126.

SR375: HRMS (ESI) (*m/z*): $[M]^+$ calcd for $C_{68}H_{94}N_{12}O_{10}$, 1238.7204; found 1238.7124.

References:

(1) T. R. Chan, *Org. Lett.,* 2004, **6**, 2853.

(2) In *PCT Int. Appl., 9501342, 12 Jan 1995.*

(3) C. Martins, M. Gunaratnam, J. Stuart, V. Makwana, O. Greciano, A. P. Reszka, L. R. Kelland and S. Neidle, *Bioorganic & Medicinal Chemistry Letters,* 2007, **17**, 2293-2298.

(4) Y. Ju, D. Kumar, R. S. Varma, *J. Org. Chem.,* 2006, **71**, 6697-6700.

(5) A. R. Katritzky, N. K. Meher, S. Hanci, R. Gyanda, S. R. Tala, S. Mathai, R. S. Duran, S. Bernard, F. Sabri, S. K. Singh and J. Doskocz, *J. Polymer Sci. Polymer Chem.,* 2008, 238-256.

(6) D. D. Diaz, K. Rajagopal, E. Strable, J. Schneider and M. G. Finn, *J. Am. Chem. Soc.* 2006, **128**, 6056-6057.

(7) A. H. Sommers and J. D. Barnes, *J. Am. Chem. Soc.,* 1957, **79**, 3491-3492.

(8) A. J. Lampkins, E. J. O'Neil and B.D. Smith, *J. Org. Chem.,* 2008, **73**, 6053-6058.

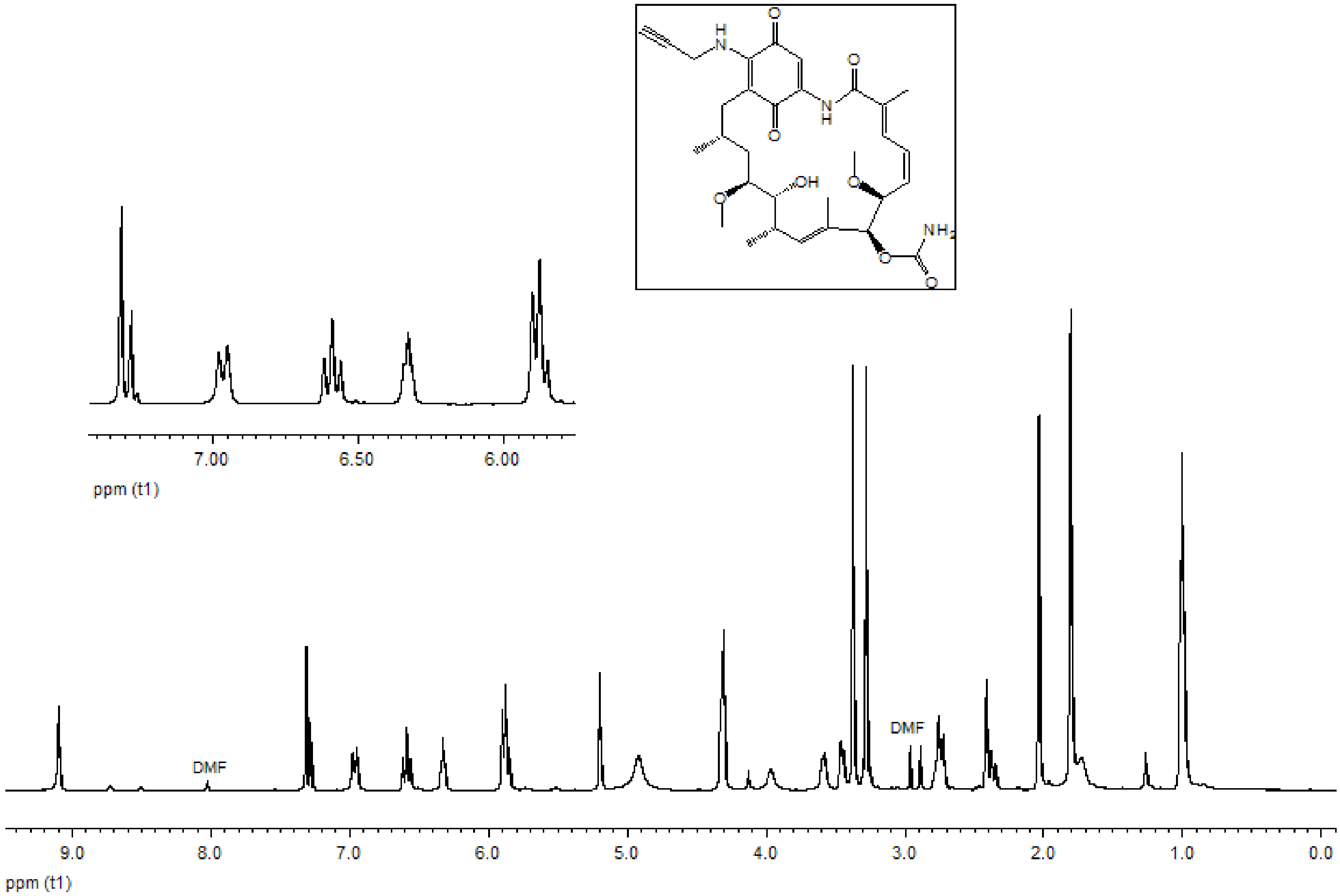
(9) Z. –S. Hou, Y.-B. Tan, K. Kim and Q.-F. Zhou, *Polymer,* 2006, **47**, 742-750.

(10) M. Wyk and E. Strauss, *Chem. Commun.,* 2007, **4**, 398-400.

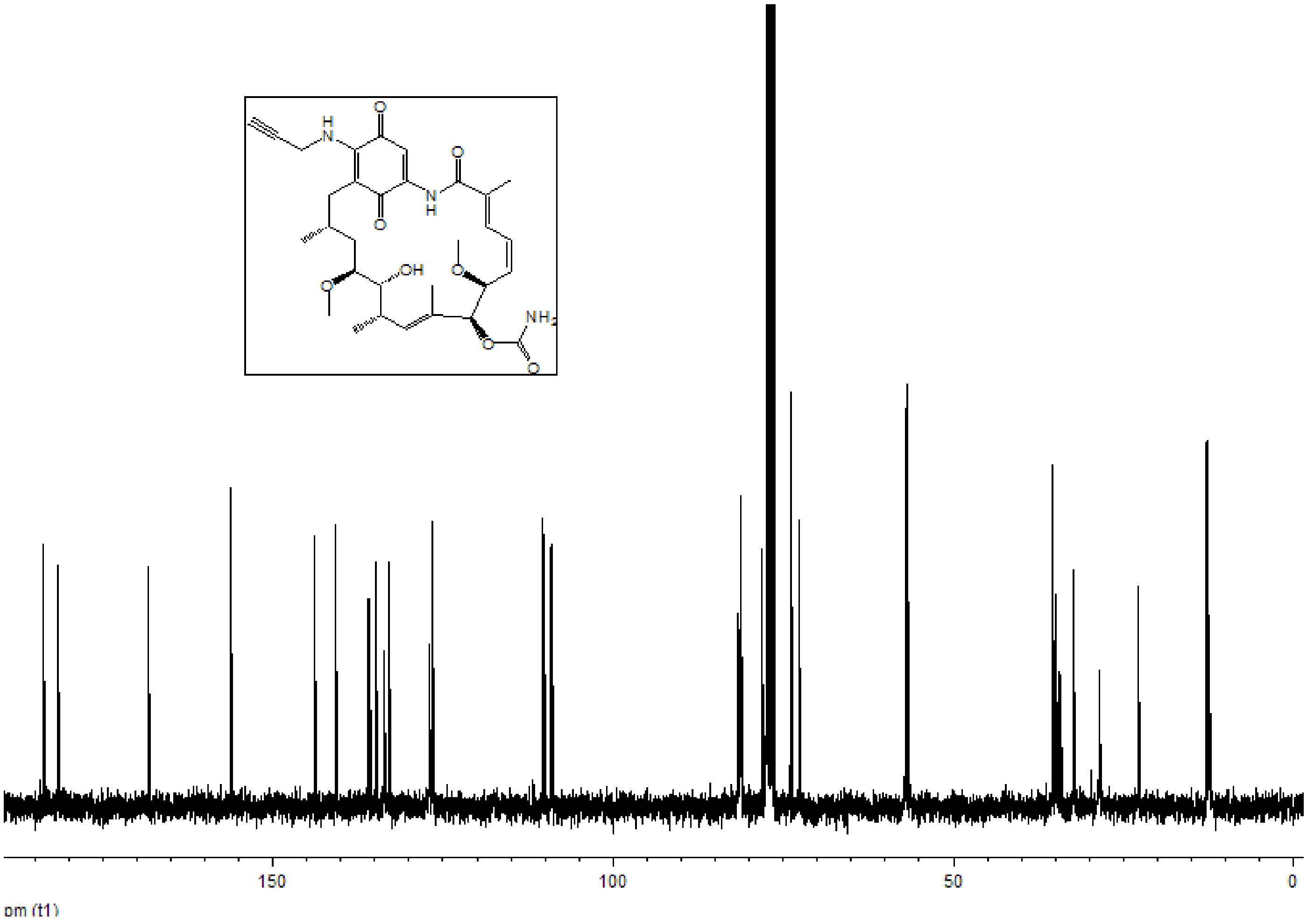
(11) I. A. Inverarity, R. F. H. Viguier, P. Cohen and A. N. Hulme, *Bioconjugate Chemistry,* 2007, **18**, 1593-1603.

(12) In *Jung, M.E.; Ouk, S.; Sawyers, C.L.; Chen, C.D.; Welsbie, D., PCT Int. Appl., 2005, 44 pp. WO 2005099693 A2 20051027 CAN 143:432632 AN 2005:1154369.*

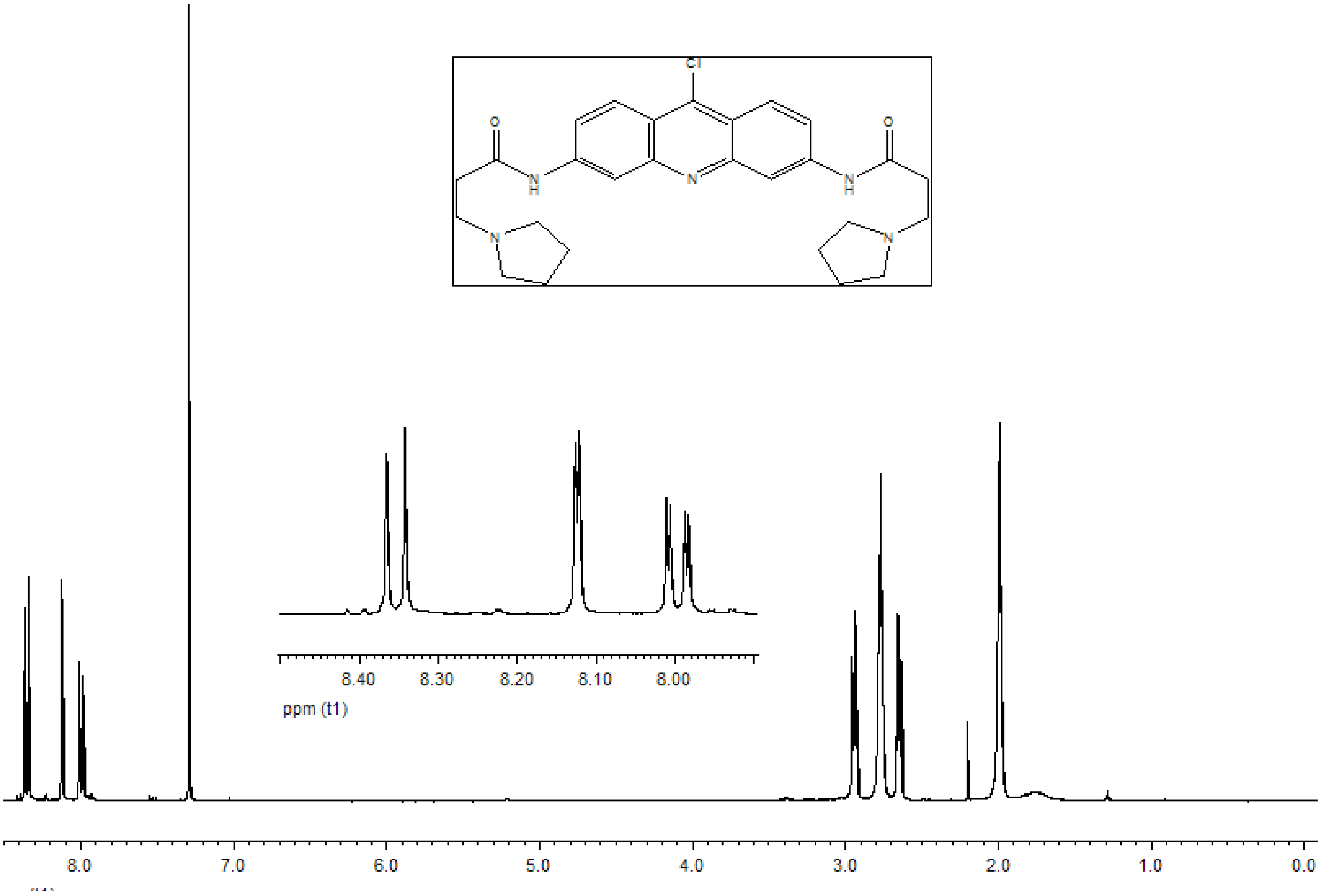
(13) In *Zundel, M.; Peschke, B., PCT Int. Appl. 2006, 142pp. WO 2006084888, A2 20060817, CAN 145:249515, AN 2006:815931.*

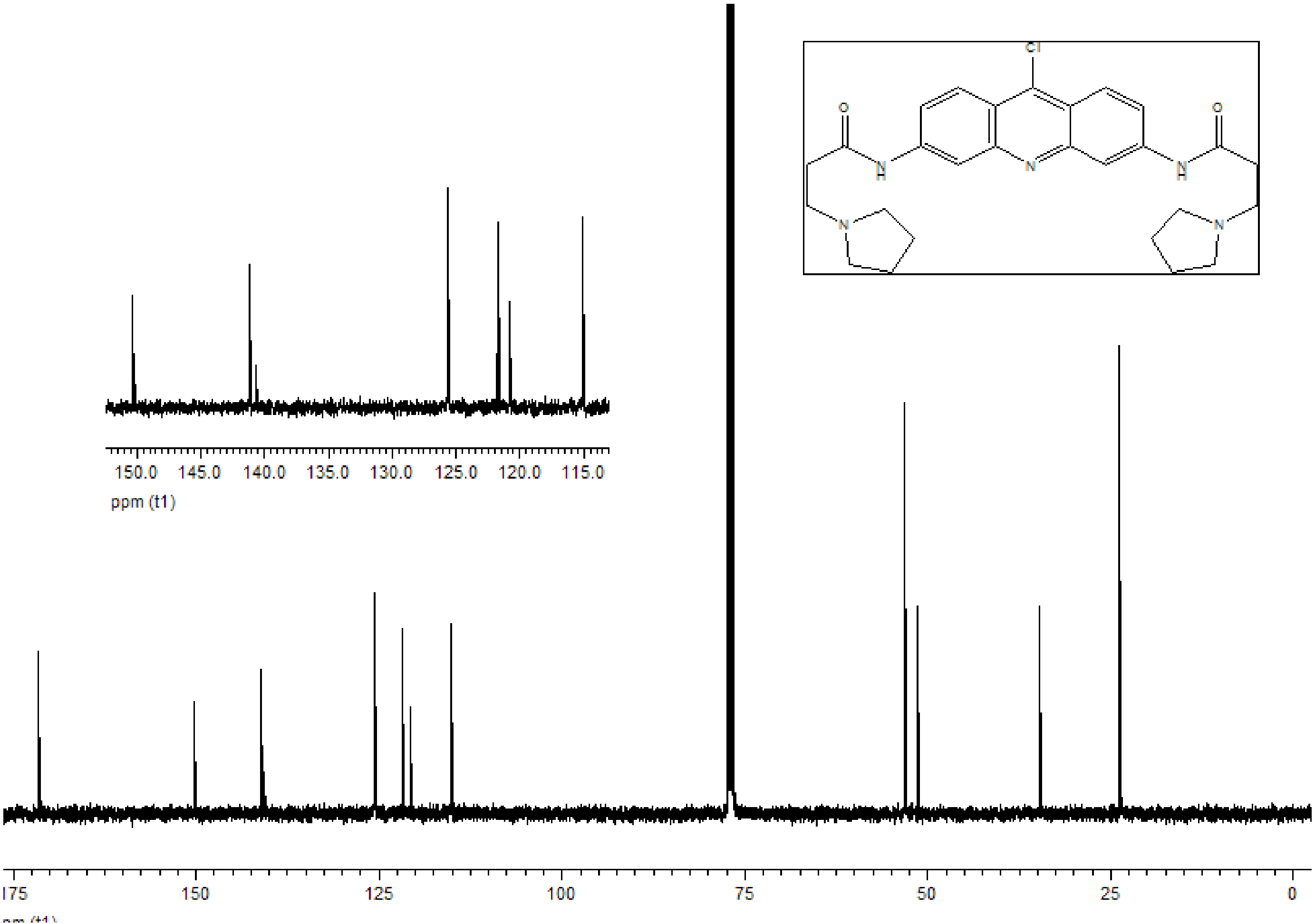


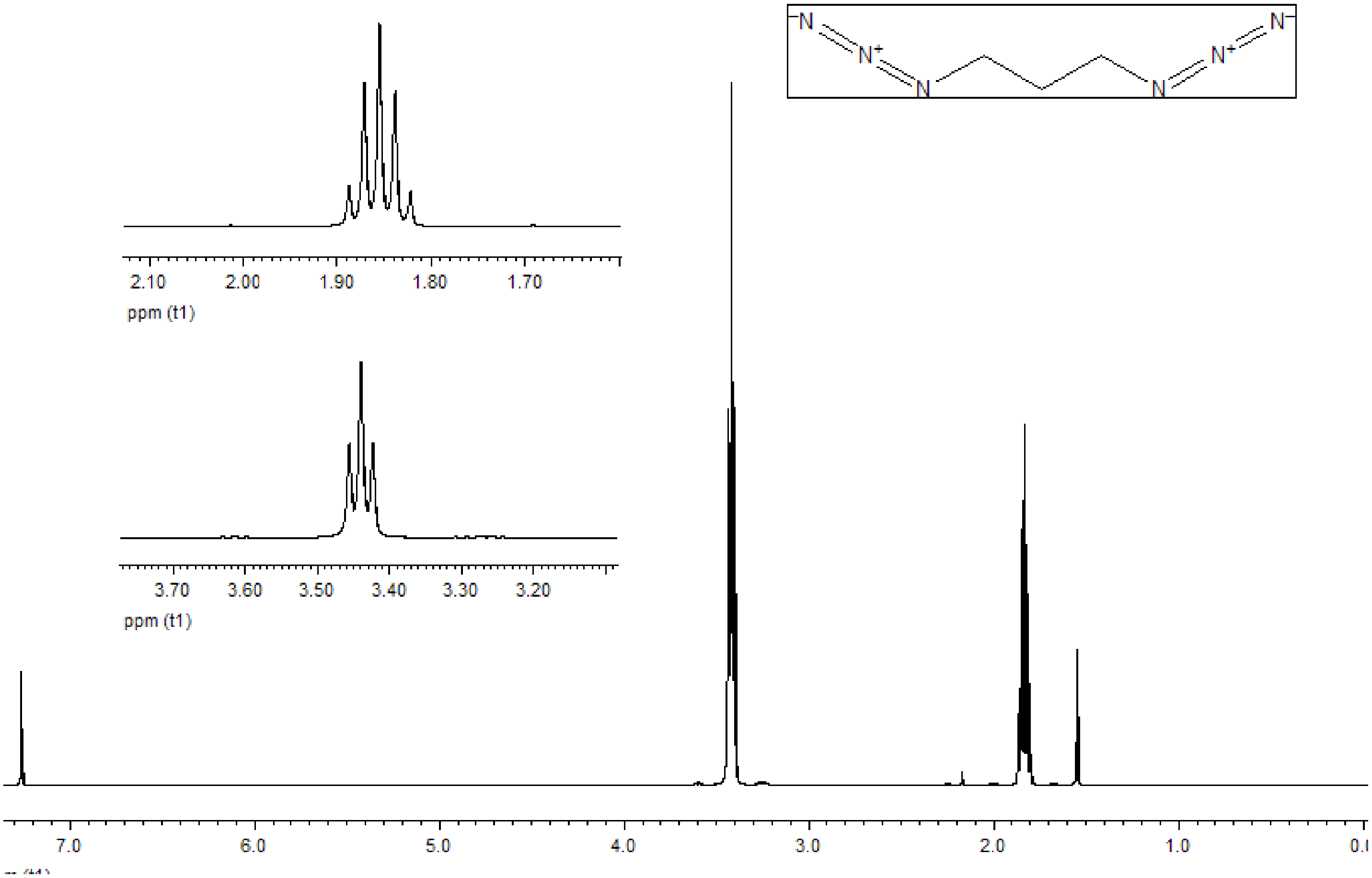
H
N
O
O
N
H
O
O
OH
O
O
NH2
O
7.00
6.50
6.00
ppm (t1)
DMF
DMF
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

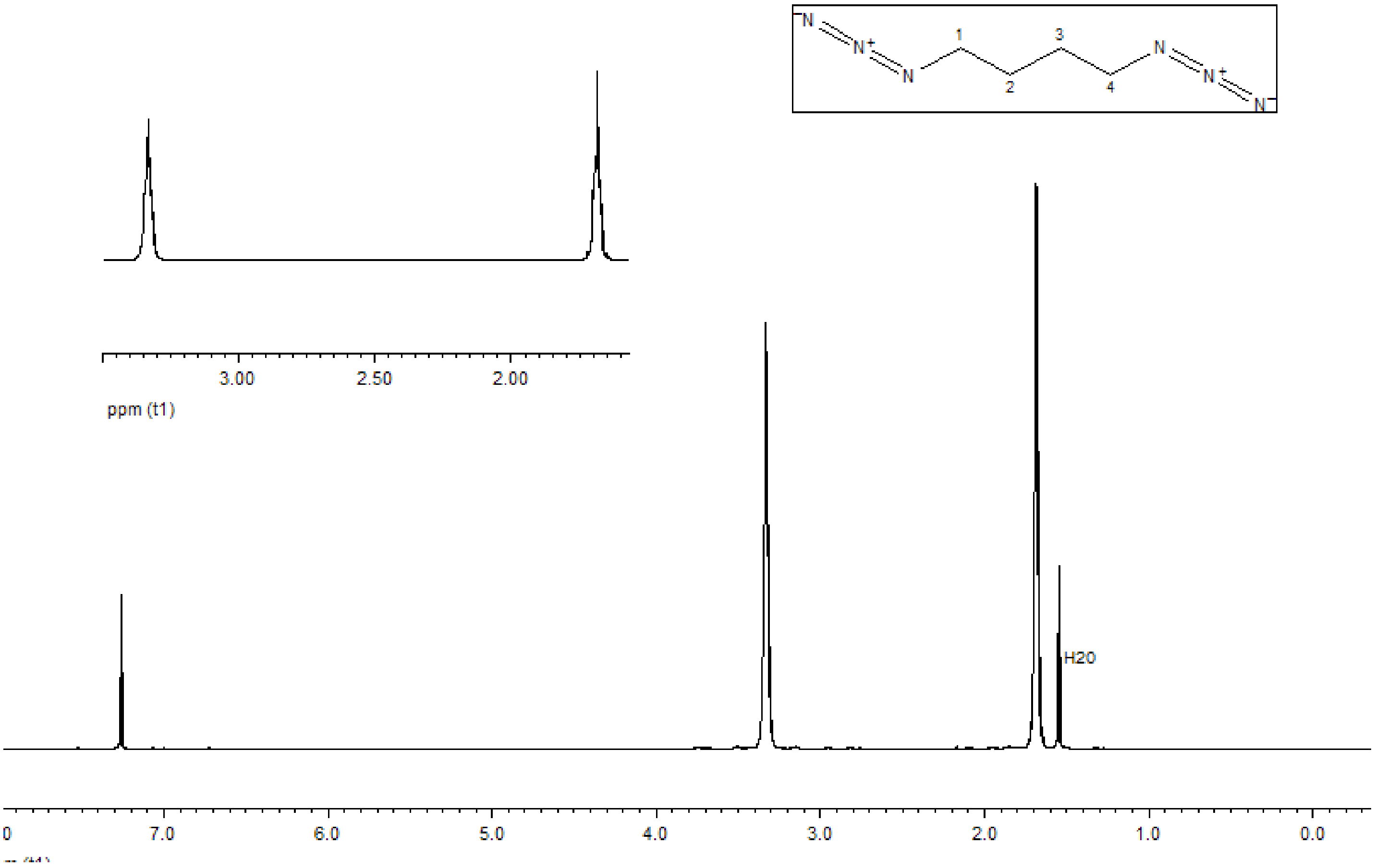


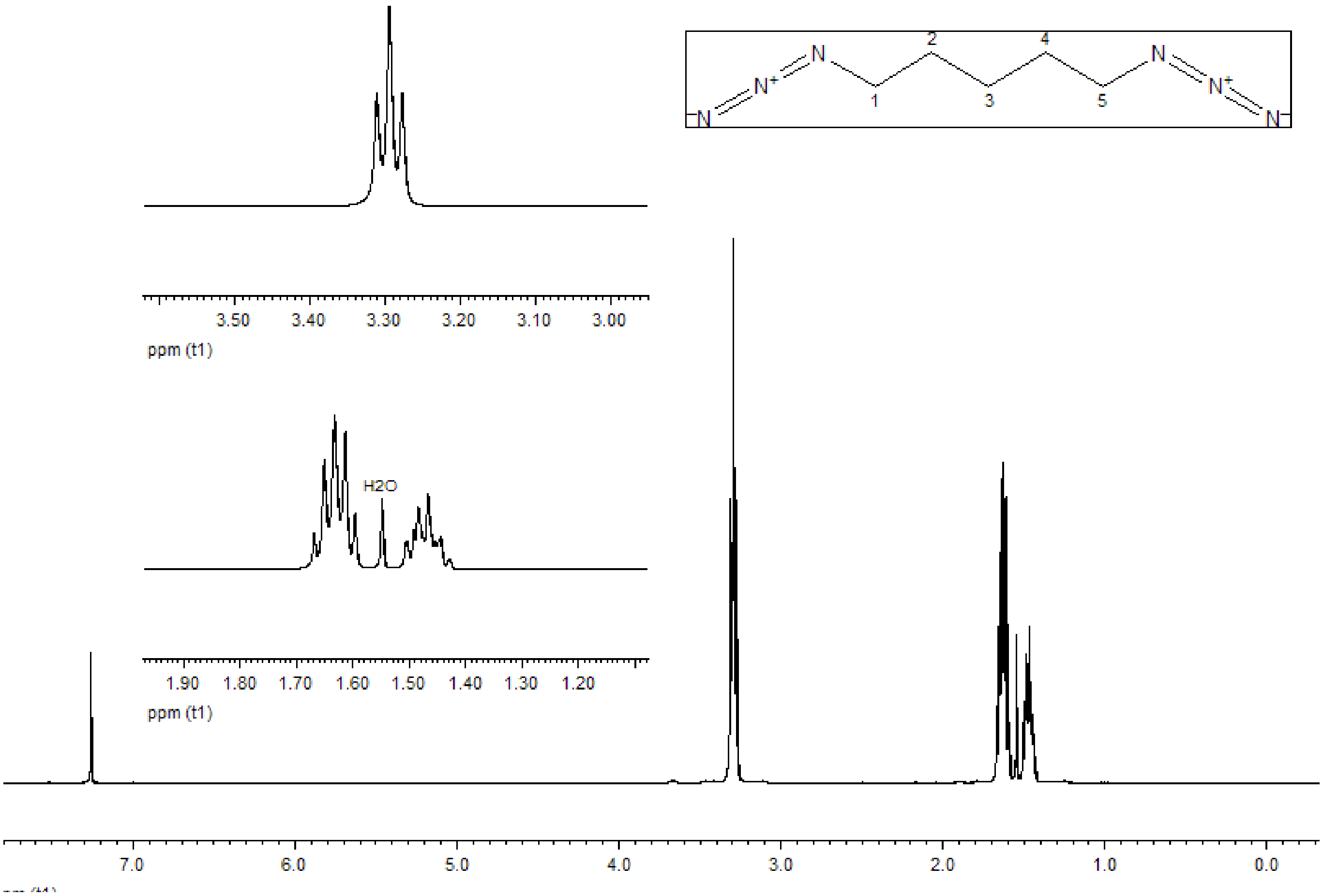
H
N
O
O
N
H
O
O
OH
O
O
NH2
O
150
100
50
0
pm (t1)


Cl
O
N
H
N
O
N
H
N
N
8.40
8.30
8.20
8.10
8.00
ppm (t1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

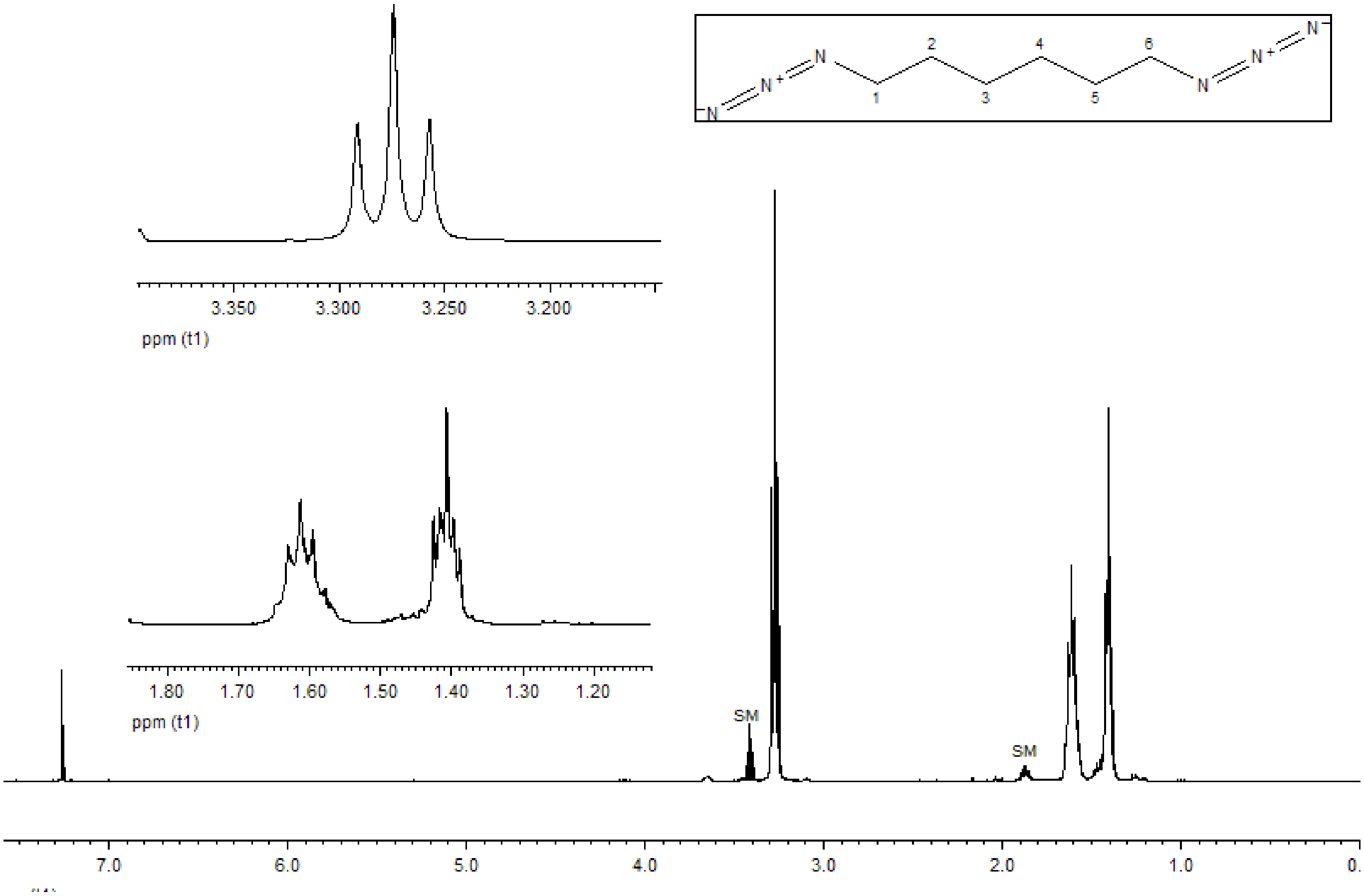

Cl
O
N
H
N
O
N
H
N
N
150.0
145.0
140.0
135.0
130.0
125.0
120.0
115.0
ppm (t1)
175
150
125
100
75
50
25
0


N
N+
N
N
N+
N
2.10
2.00
1.90
1.80
1.70
ppm (t1)
3.70
3.60
3.50
3.40
3.30
3.20
ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.

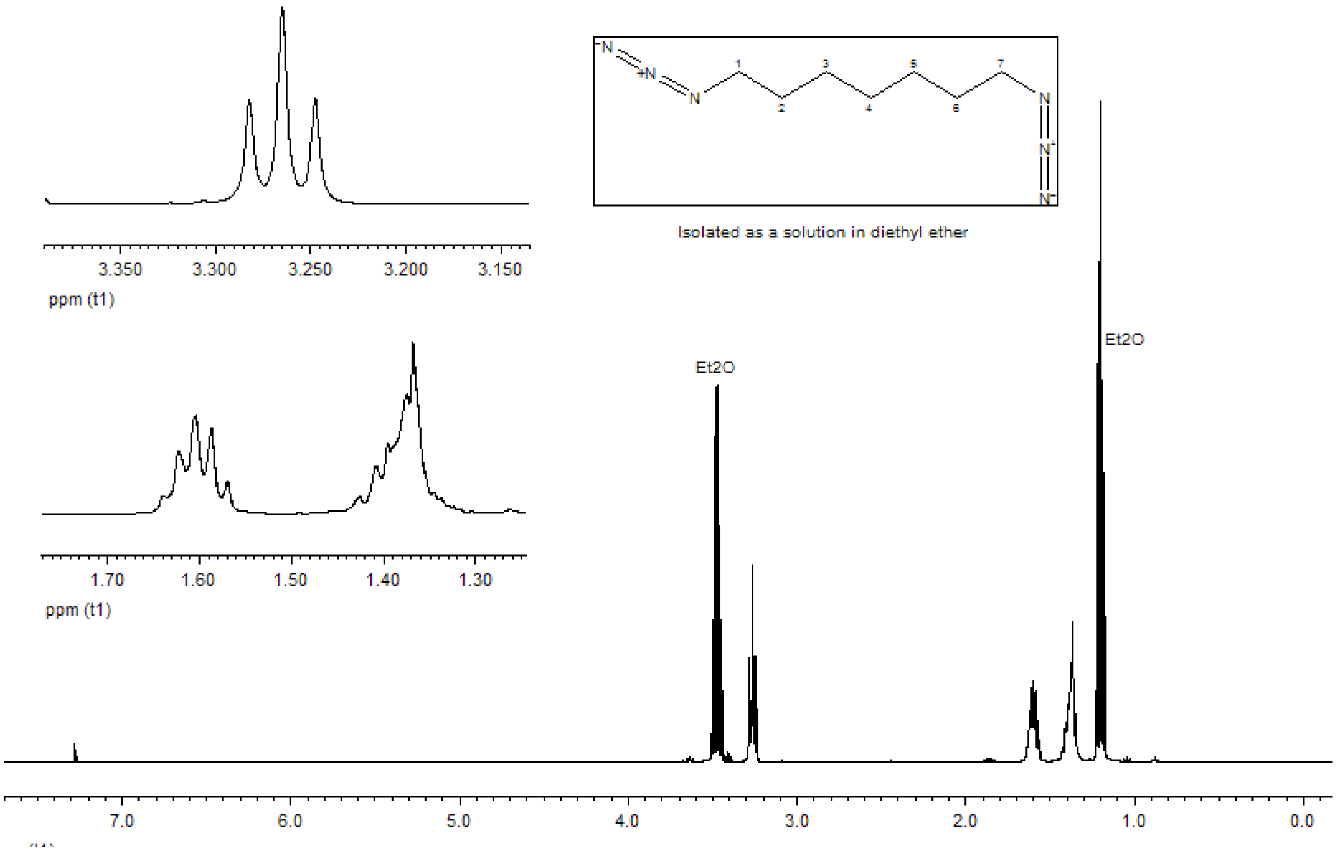

N
N+
N
1
2
3
4
N
N+
N
3.00
2.50
2.00
ppm (t1)
H2O
0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

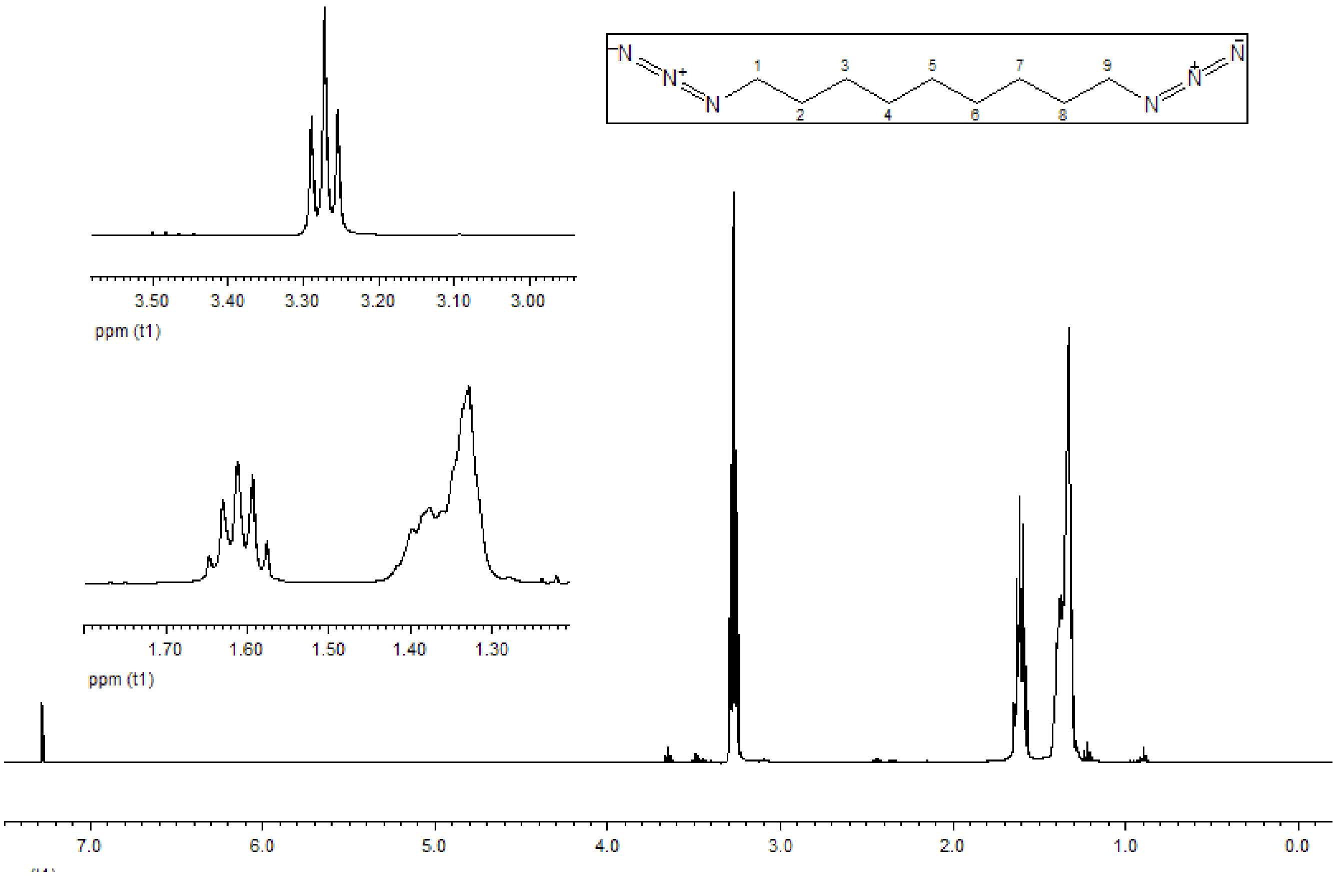


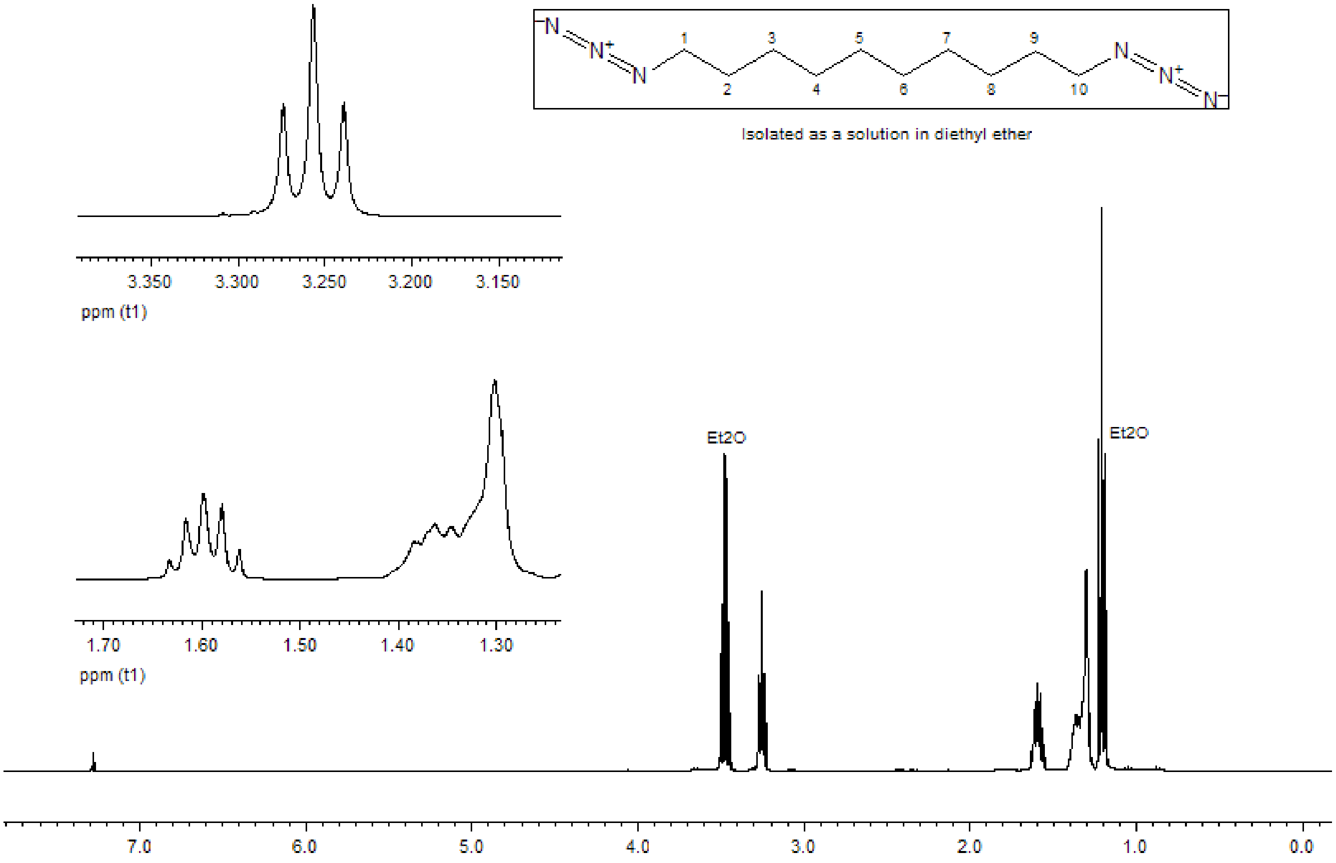
N
N+
N
1
2
3
4
5
N
N+
N
3.50
3.40
3.30
3.20
3.10
3.00
ppm (t1)
H2O
1.90
1.80
1.70
1.60
1.50
1.40
1.30
1.20
ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

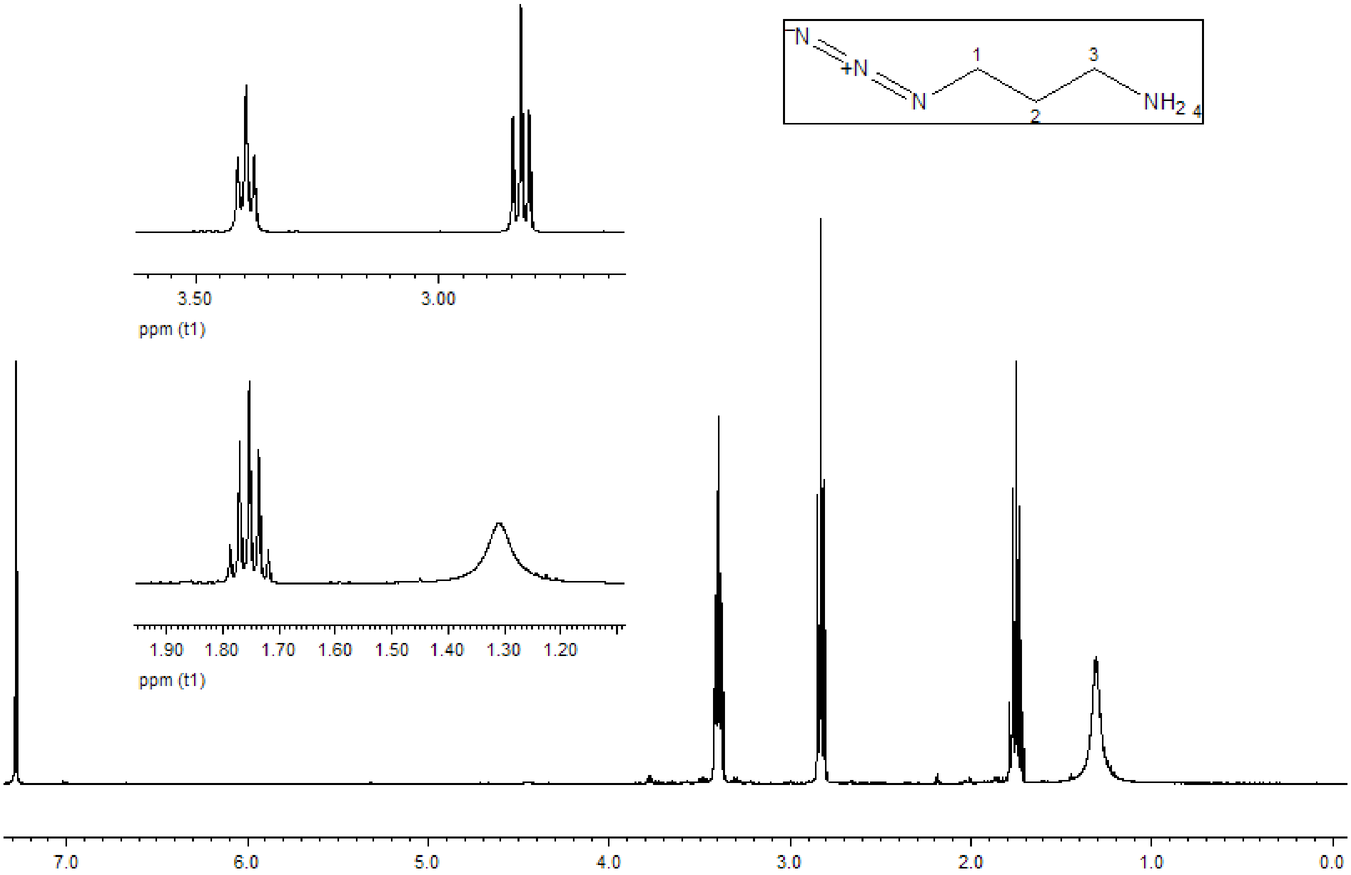


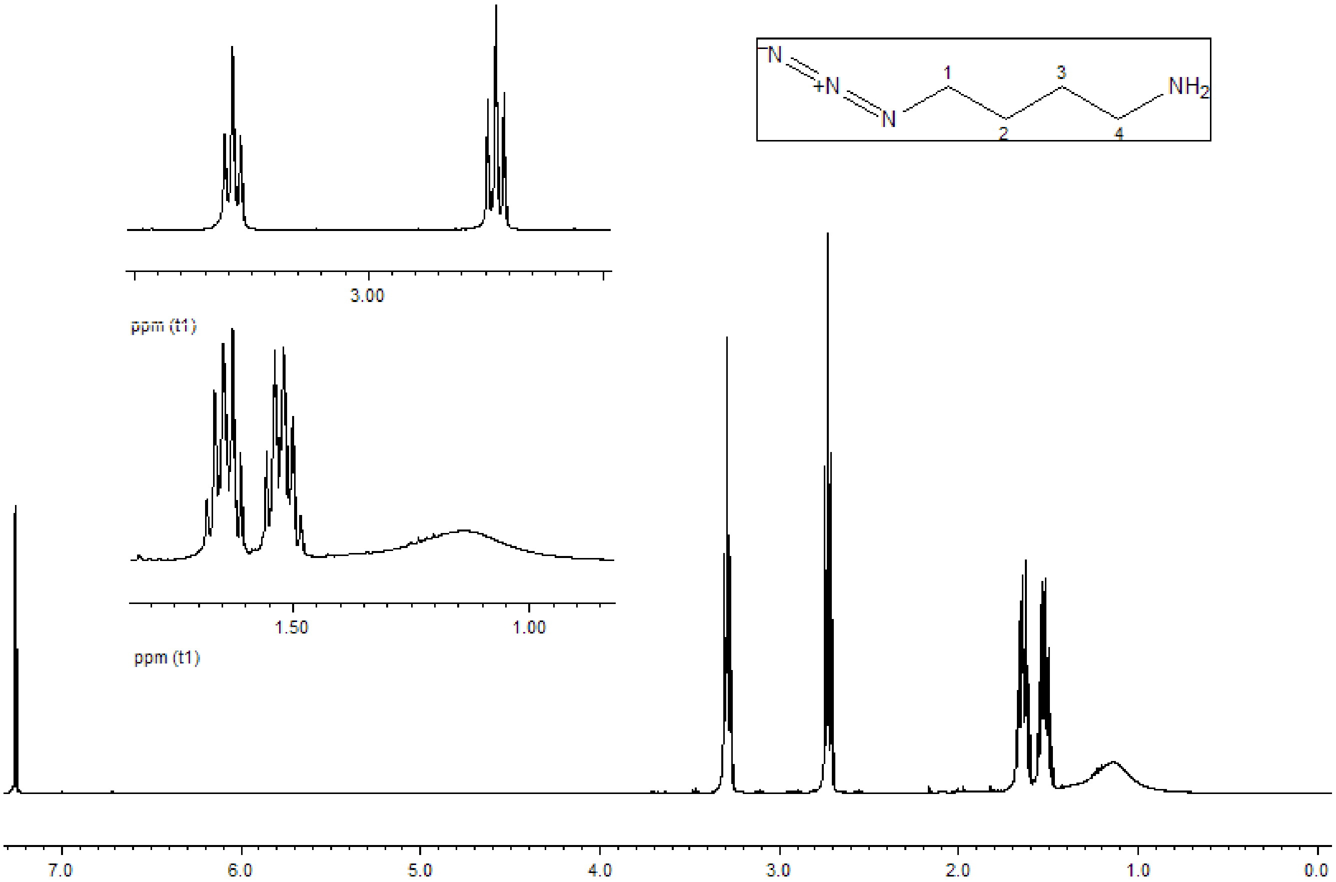
N
N+
N
1
2
3
4
5
6
N
N+
N
3.350
3.300
3.250
3.200
ppm (t1)
1.80
1.70
1.60
1.50
1.40
1.30
1.20
ppm (t1)
SM
SM
7.0
6.0
5.0
4.0
3.0
2.0
1.0


Isolated as a solution in diethyl ether

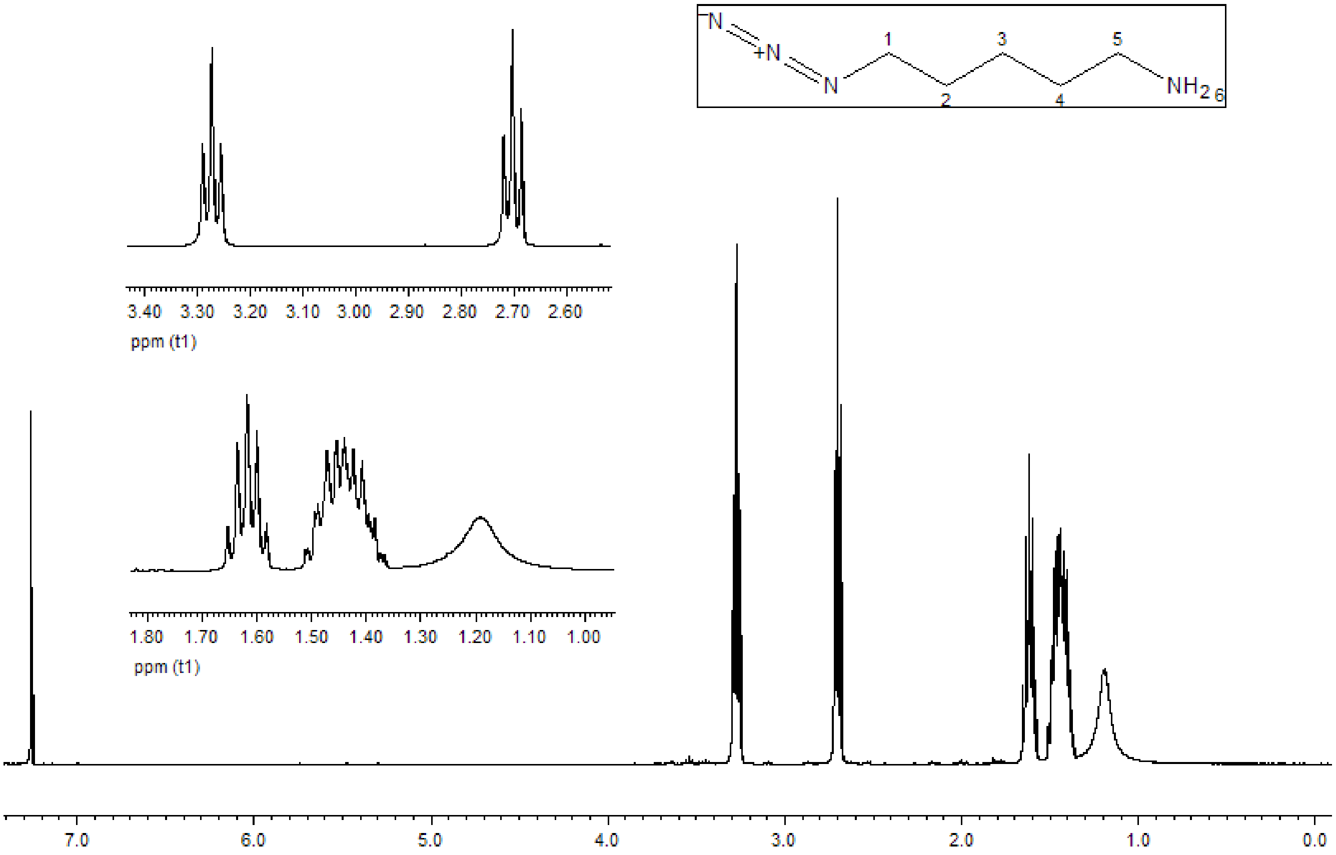



N
N+
N
1
2
3
4
5
6
7
8
9
10
N
N+
N
Isolated as a solution in diethyl ether
3.350
3.300
3.250
3.200
3.150
ppm (t1)
1.70
1.60
1.50
1.40
1.30
ppm (t1)
Et2O
Et2O
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


N
+N
N
1
2
3
NH2 4
3.50
3.00
ppm (t1)
1.90
1.80
1.70
1.60
1.50
1.40
1.30
1.20
ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

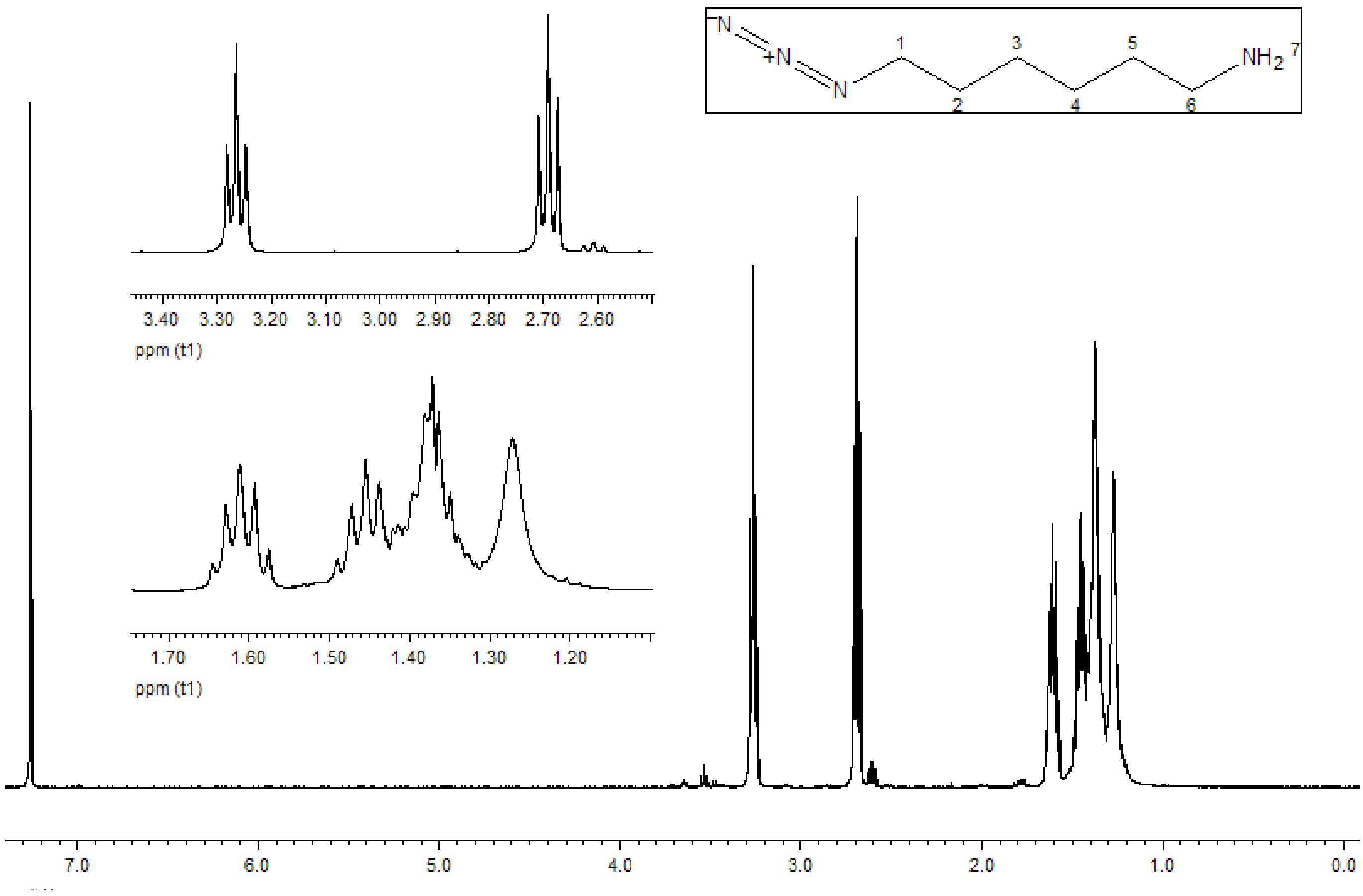


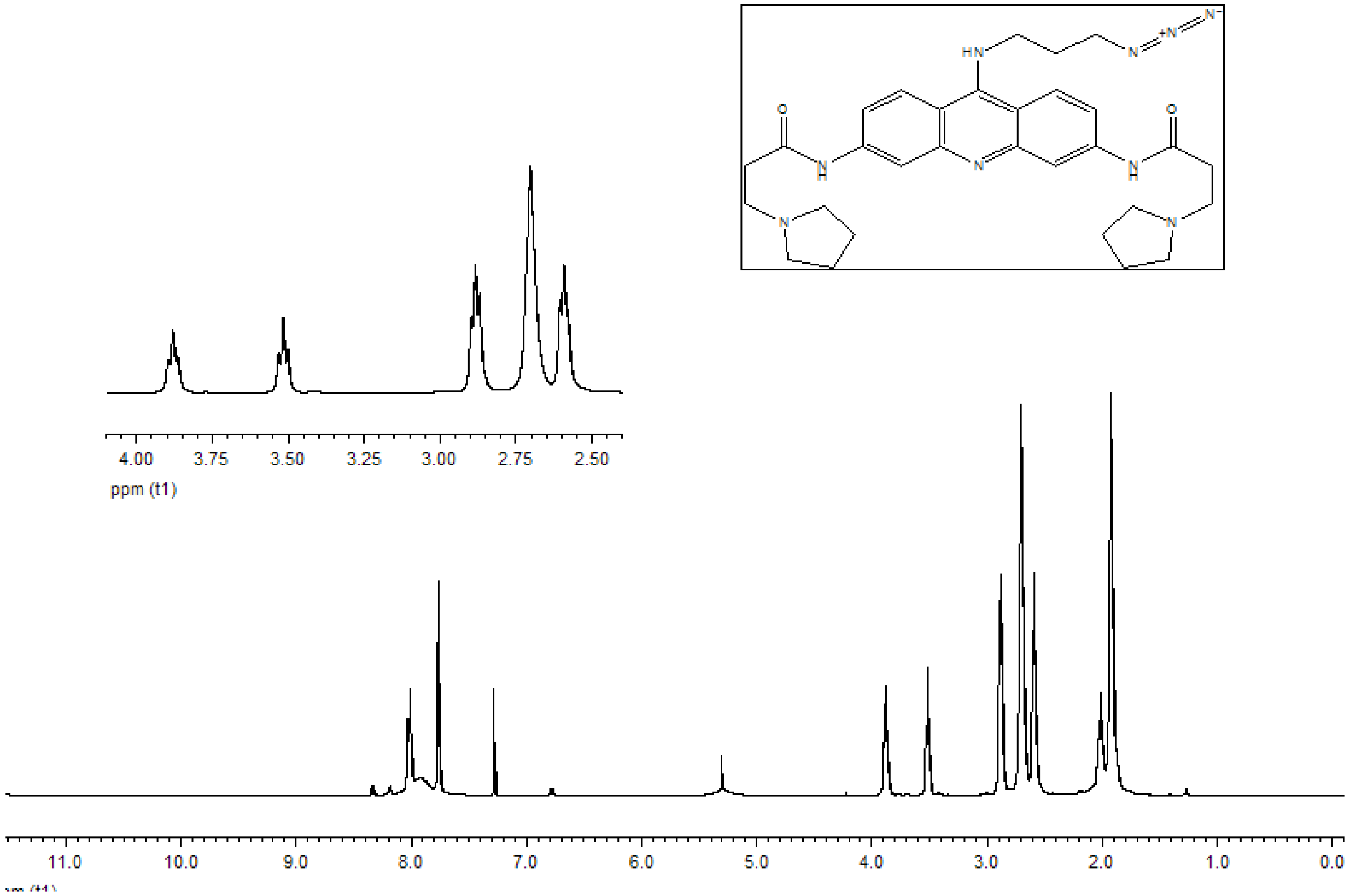
N
+N
N
1
2
3
4
NH2
3.00
ppm (t1)
1.50
1.00
ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

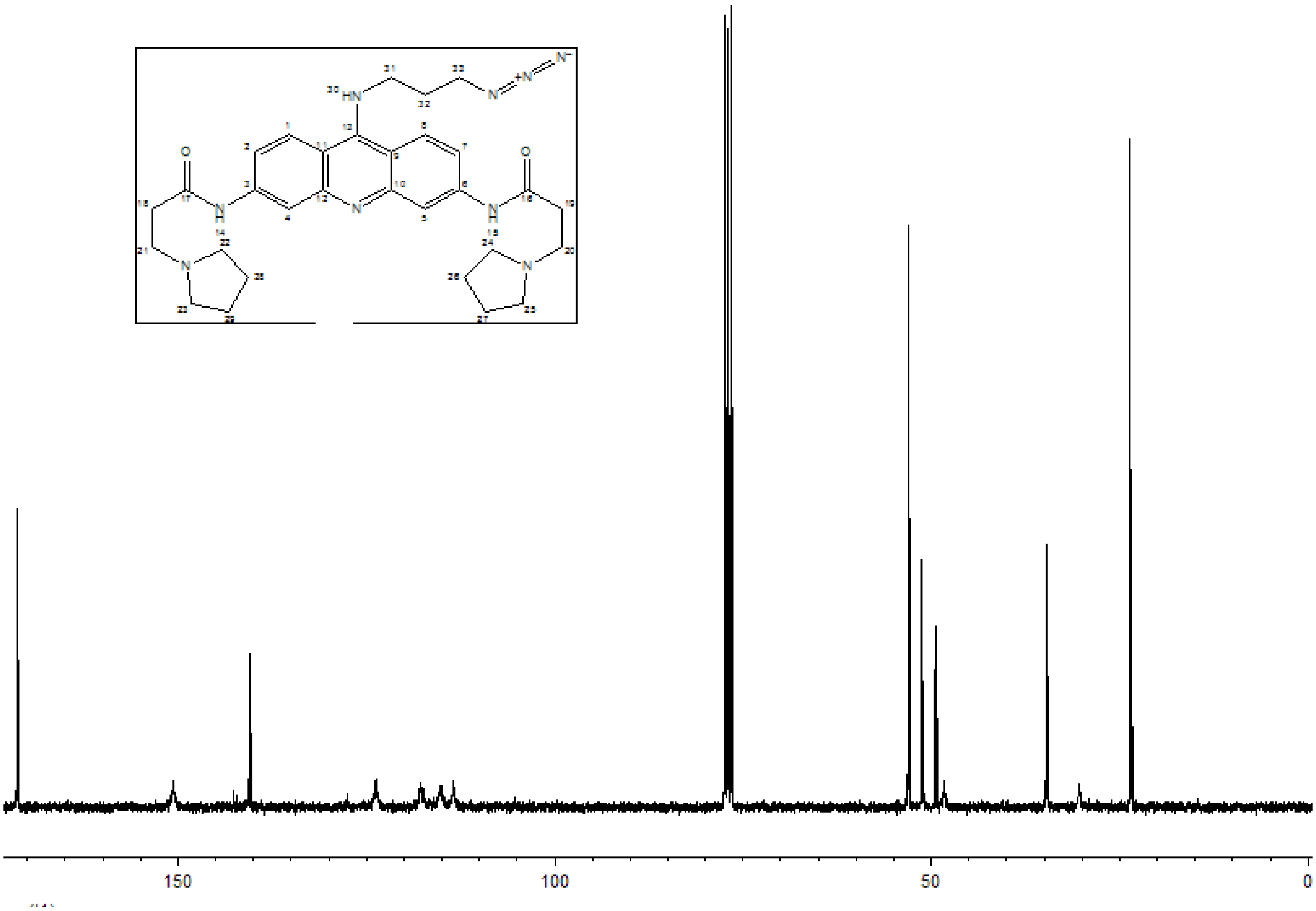


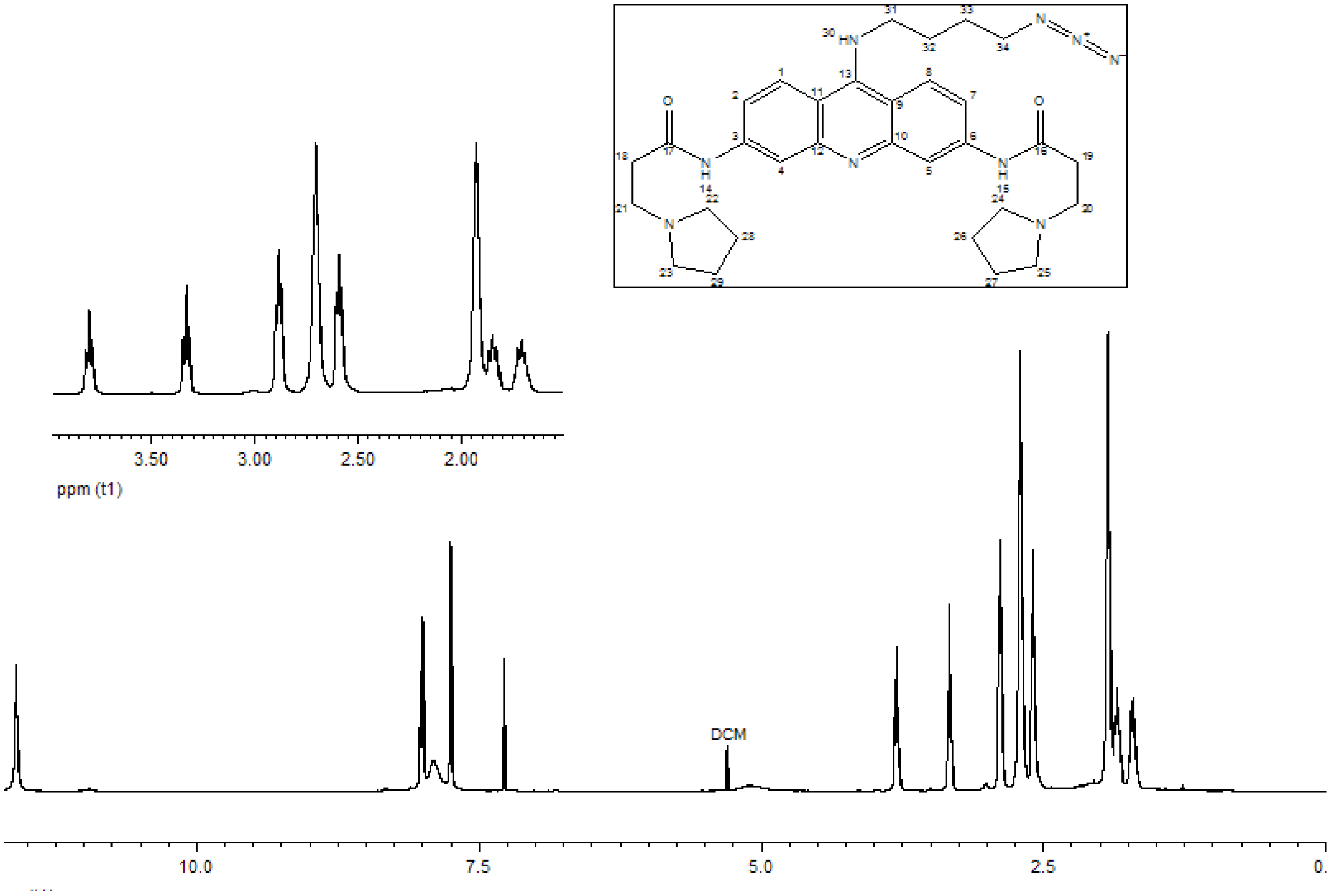
N
+N
N
1
2
3
4
5
NH2 6
3.40
3.30
3.20
3.10
3.00
2.90
2.80
2.70
2.60
ppm (t1)
1.80
1.70
1.60
1.50
1.40
1.30
1.20
1.10
1.00
ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

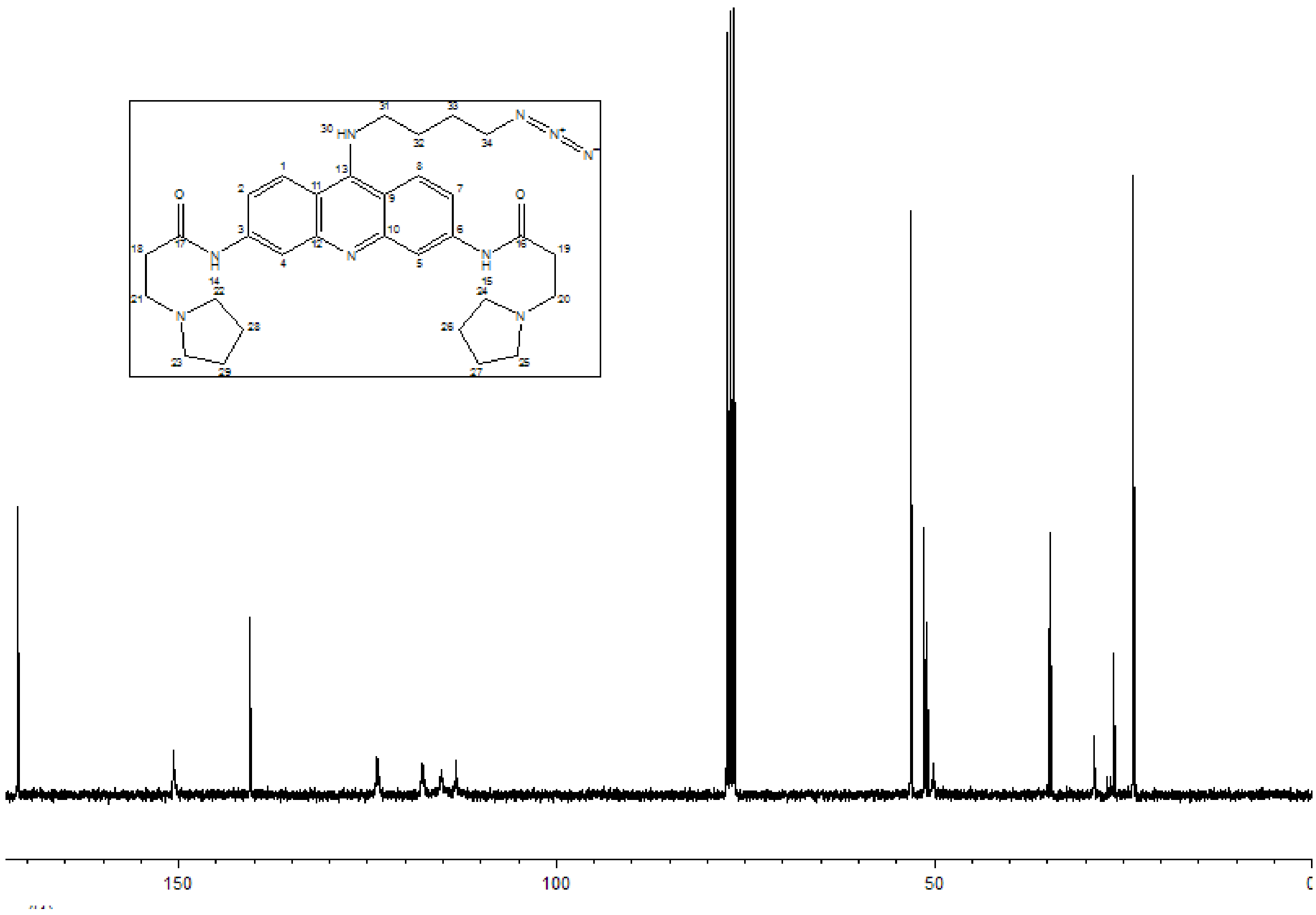
ELECTRONIC SUPPORTING INFORMATION

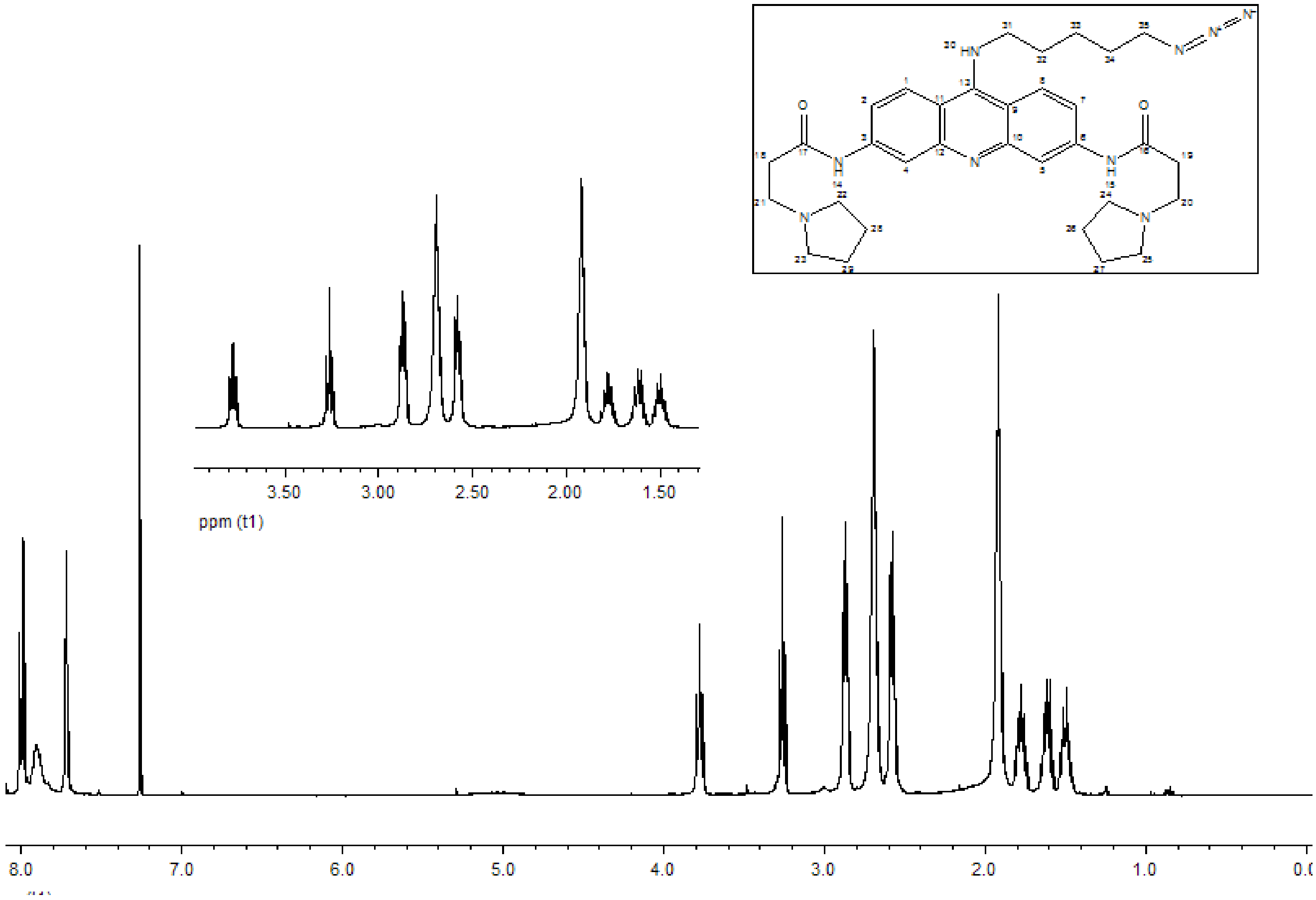


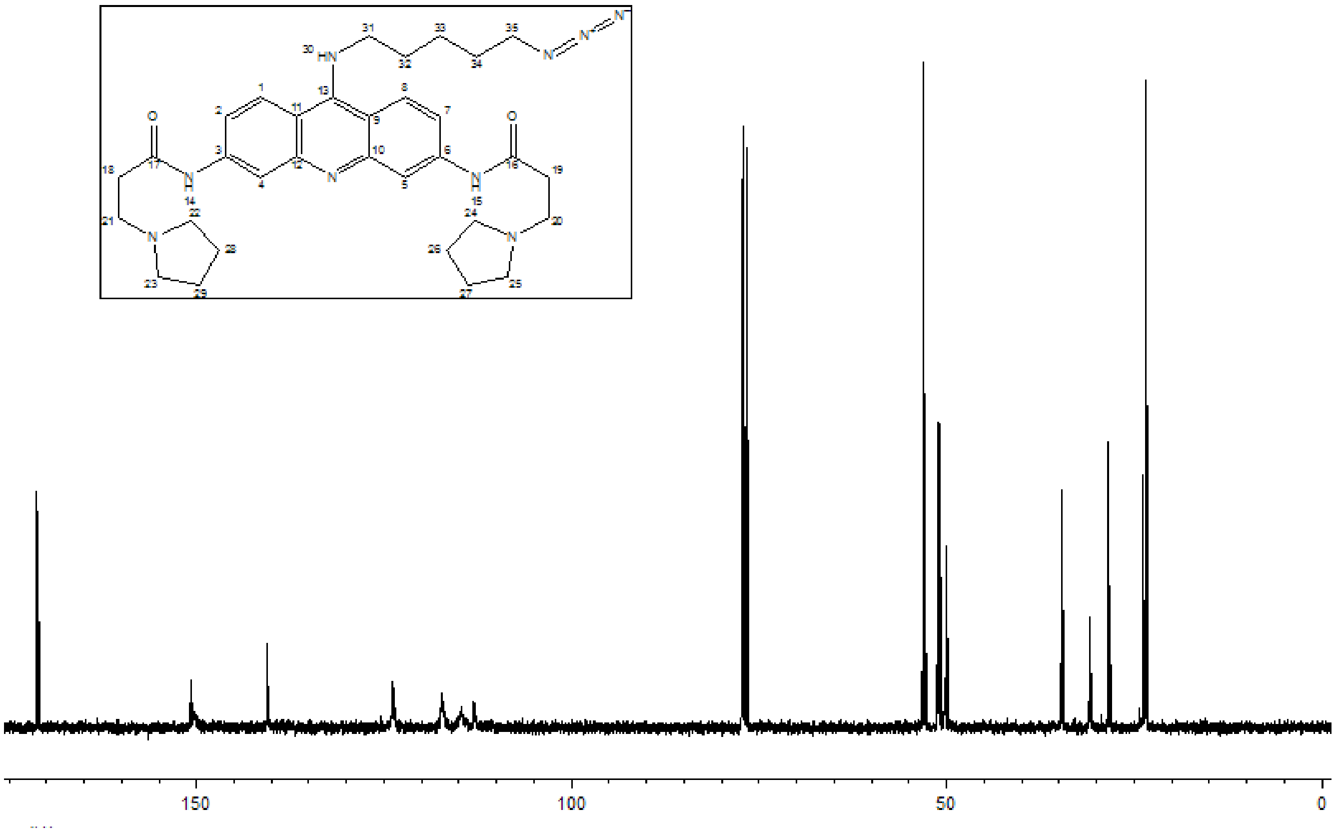


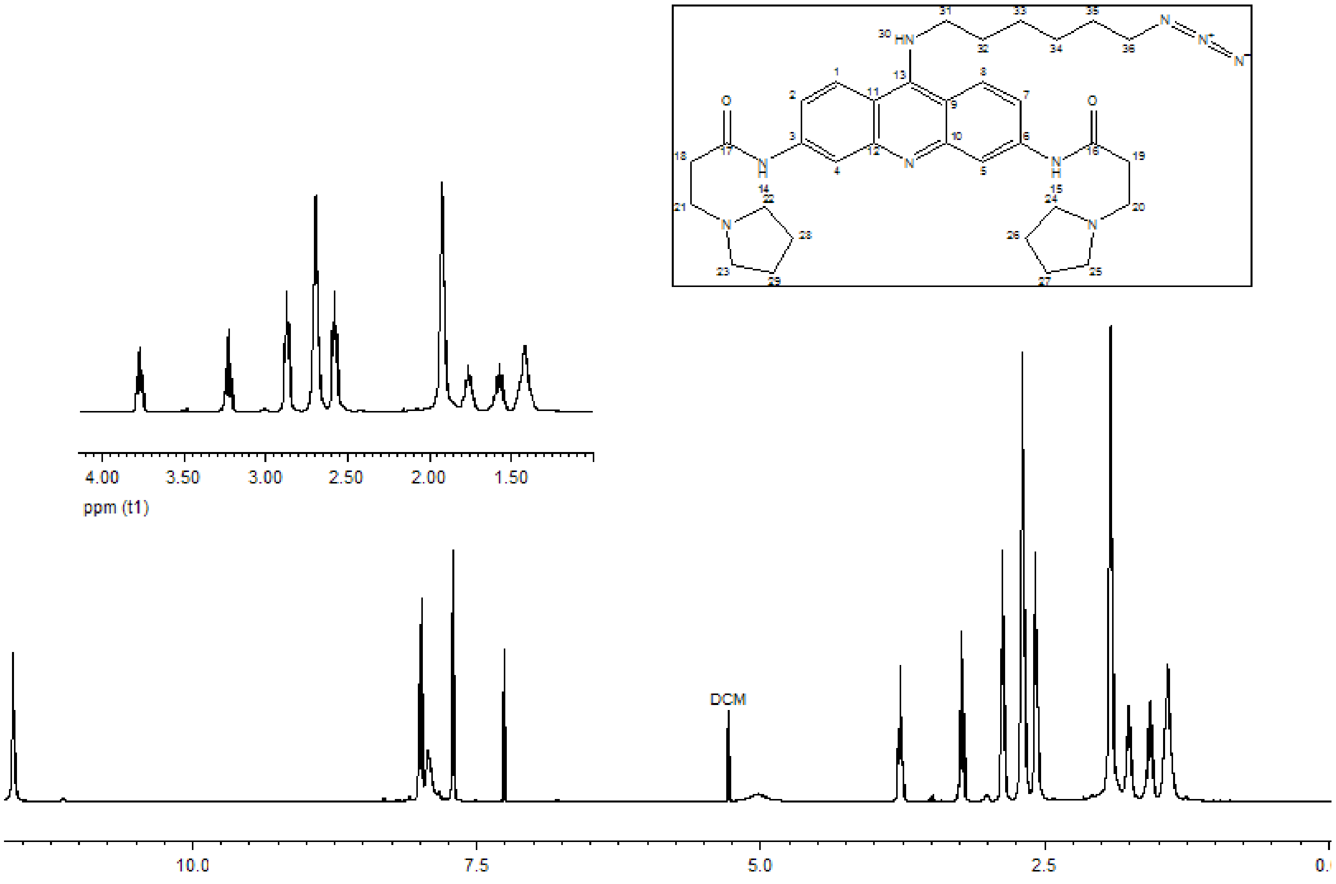

HN
N
O
150
100
50
0

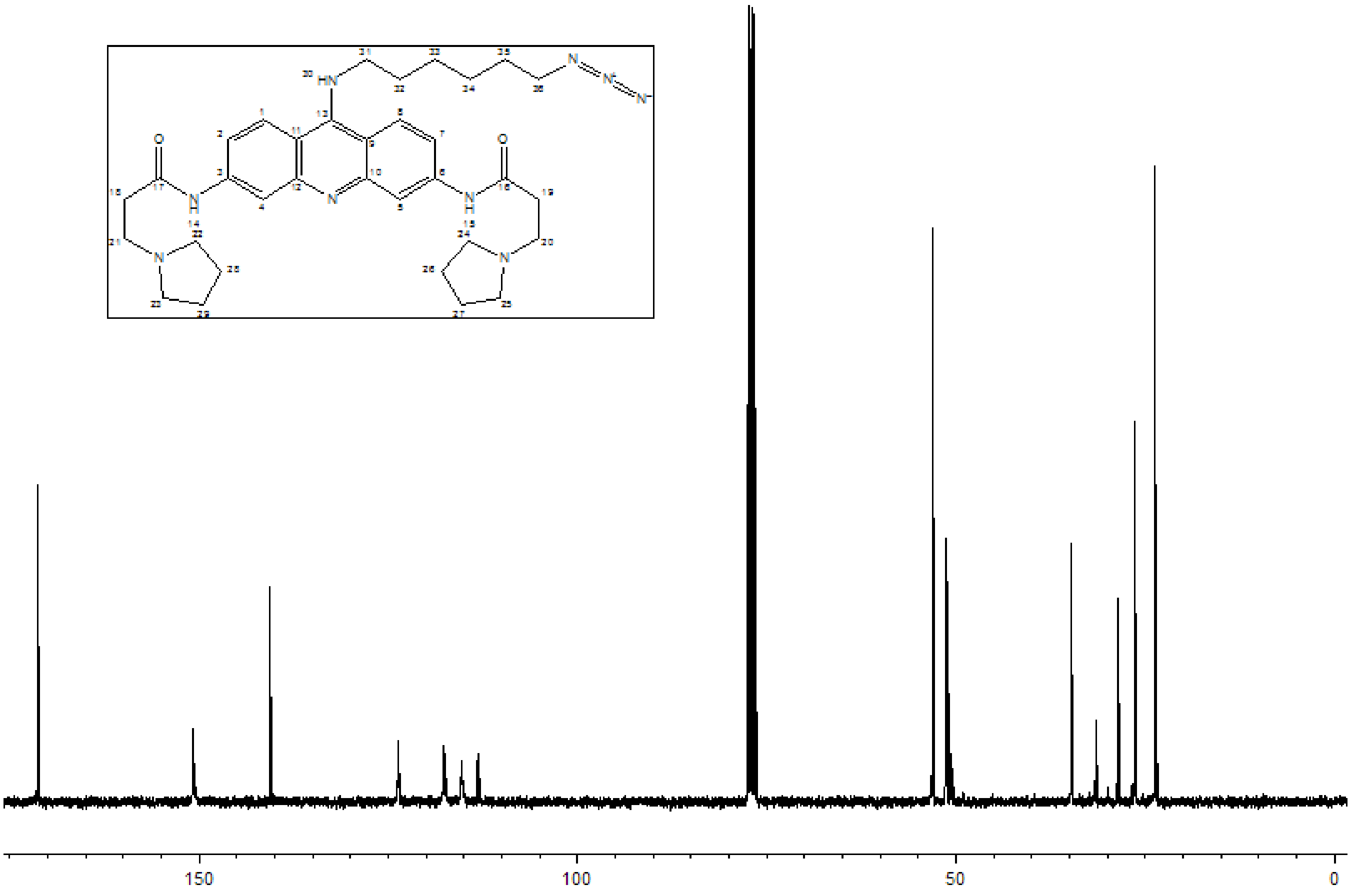

HN
N
O
3.50
3.00
2.50
2.00
ppm (t1)
DCM
10.0
7.5
5.0
2.5
0.

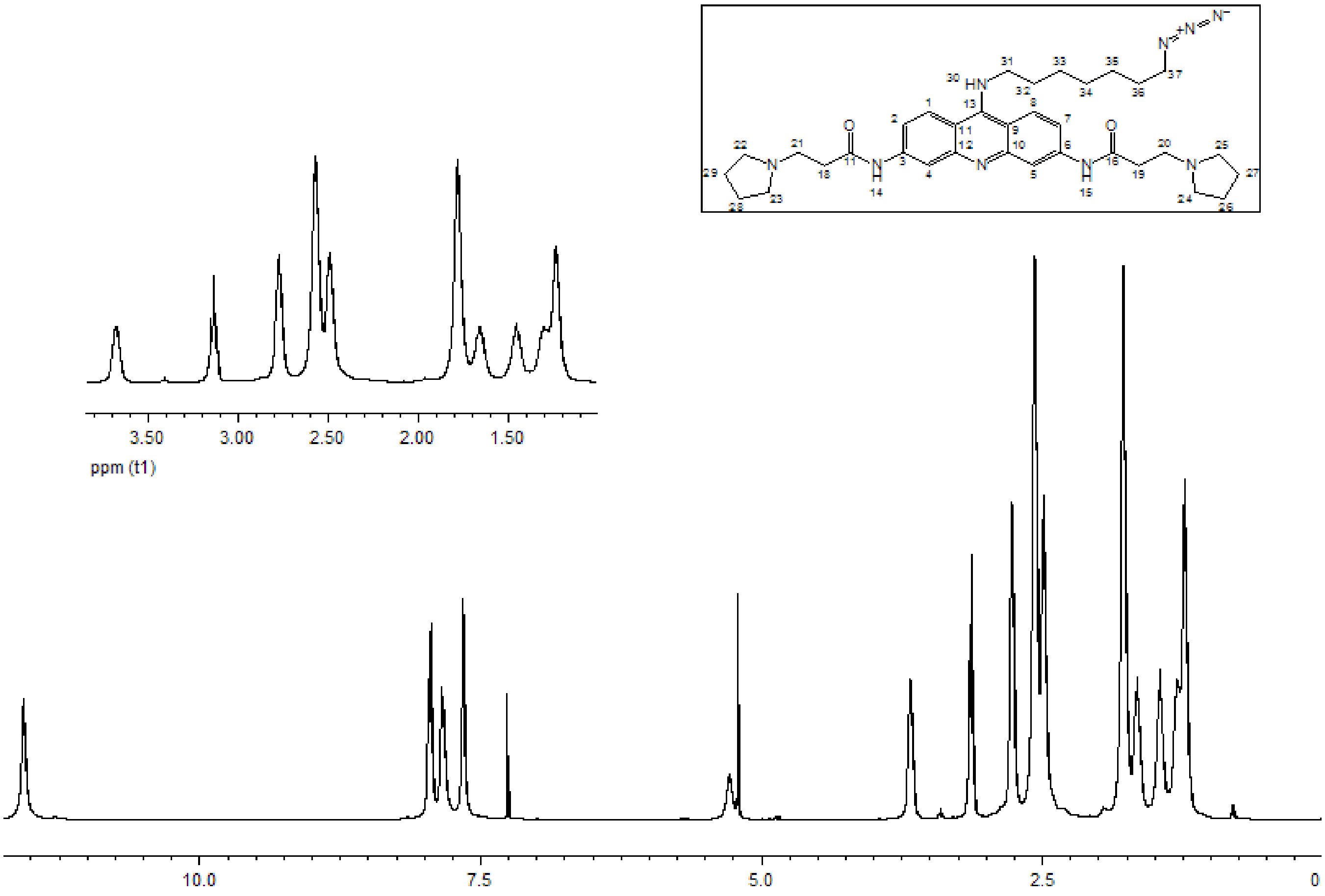

30 HN
31
32
33
34
N
N+
N-
1
2
3
4
5
6
7
8
9
10
11
12
13
N
O
O
17
16
18
19
NH
14
NH
15
21
20
N
N
22
23
24
25
26
27
28
29
150
100
50

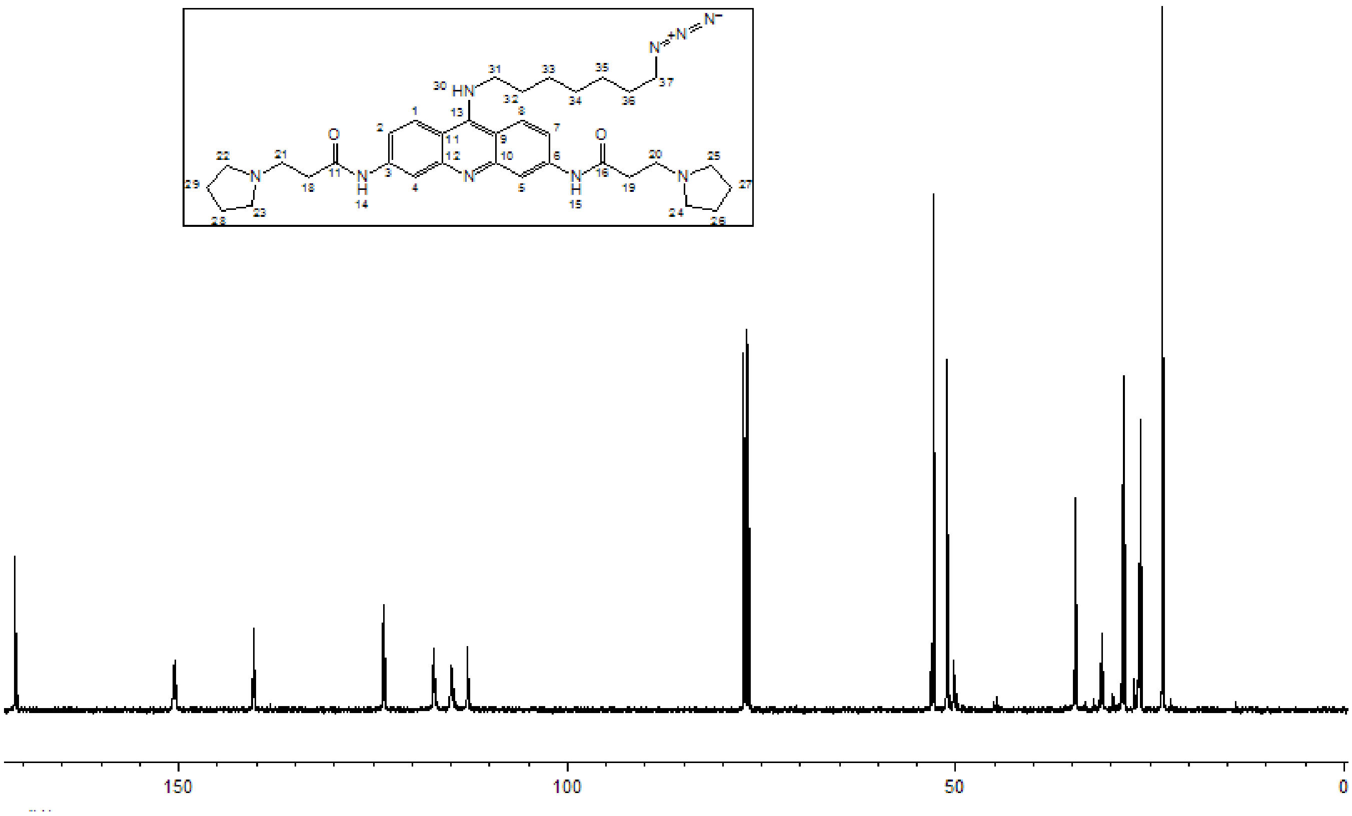

30 HN
31
32
33
34
35
N
N+
N-
1
2
3
4
5
6
7
8
9
10
11
12
13
N
O
O
17
16
18
19
NH
14
NH
15
21
20
N
N
22
23
24
25
26
27
28
29
3.50
3.00
2.50
2.00
1.50
ppm (t1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0


150
100
50
0


4.00
3.50
3.00
2.50
2.00
1.50
ppm (t1)
DCM
10.0
7.5
5.0
2.5
0.


HN
N
N⁺
N⁻
O
O
N
H
N
H
N
N
N
150
100
50
0


N⁺
N⁻
HN
O
O
N
H
N
H
N
N
N
3.50
3.00
2.50
2.00
1.50
ppm (t1)
10.0
7.5
5.0
2.5
0


N
N
N
HN
O
O
NH
NH
N
N
N
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
150
100
50
0