

HYDRAmers: Design, synthesis and characterization of different generation novel Hydra-like dendrons based on multifunctionalized adamantane

Giuseppe Lamanna,* Julie Russier, Cécilia Ménard-Moyon, and Alberto Bianco*

CNRS, Institut de Biologie Moléculaire et Cellulaire, Laboratoire d'Immunologie et Chimie Thérapeutiques, 15 Rue René Descartes, 67084 Strasbourg, France

Supporting Information

General Experimental Details.

All starting materials, chemicals and anhydrous solvents were obtained from Sigma-Aldrich commercial suppliers and used without purification. ^1H and ^{13}C NMR spectra were recorded using a Bruker 300, 400 or 600 MHz spectrometer; the residual solvent protons were used to reference the chemical shift in ppm. Coupling constants (J) are reported in Hertz (Hz), and splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Infrared spectra (IR) were measured on a Perkin Elmer Spectrum One ATR-FT-IR spectrometer. ESI-Mass spectra were recorded on ThermoFisher Finnigan LCQ Advantage Max instrument. MALDI-TOF and elemental analyses were performed at Mass and Micro-Analytical Facility Core of the University of Strasbourg. MALDI-TOF analyses were carried on a Bruker Daltonics MALDI-TOF/TOF Autoflex II or III spectrometer in positive ion mode using dithranol as the matrix. The following compounds were synthesized according to literature procedures: 1,3,5-triphenyladamantane,¹ 1,3,5-triphenyl-7-bromoadamantane (**1**).²

1,3,5-Triphenyl-7-acetylaminoadamantane (2).

To a suspension of 1-Bromo-3,5,7-triphenyladamantane **1** (2.5 g, 5.6 mmol) in 200 mL of acetonitrile was added concentrated sulfuric acid (3.6 mL, 67.2 mmol) and the resulting mixture was refluxed for 24 h. After concentration of the solvent, the reaction mixture was poured into ice water and the product was extracted with ethyl acetate (3x150 mL). The combined organic layers were dried over Na_2SO_4 , filtered and evaporated *in vacuo* to give the acetamide **2** as a white solid (1.9 g, 4.5 mmol, 80% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 7.44 (d, $J = 9.0$ Hz, 6H), 7.19-7.36 (m, 9H), 5.41 (s, 1H), 2.30 (s, 6H), 2.11 (s, 6H), 1.97 (s, 3H); ^{13}C NMR (CDCl_3 , 300 MHz) δ 169.78, 148.37, 128.32, 126.21, 124.95, 54.86, 47.26, 45.27, 39.73, 24.57. FT-IR (neat, v/cm^{-1}) 3240, 3048, 2932, 1625, 1539, 1495, 750, 697. MS (ESI) m/z : 422.6 $[\text{M} + \text{H}]^+$. Anal. Calcd for $\text{C}_{30}\text{H}_{31}\text{NO}$: C 85.47; H 7.41; N 3.32. Found: C 85.11; H 7.05; N 3.74.

1,3,5-Tricarboxy-7-acetylaminoadamantane (3).

To a solution of 1,3,5-Triphenyl-7-acetylaminoadamantane **2** (1.6 g, 3.8 mmol) and periodic acid (39.0 g, 171.0 mmol) in 100 mL of CCl₄/MeCN/H₂O (3:2:3), kept at 0 °C, was added RuCl₃·xH₂O (0.27 g, 1.3 mmol) and the resulting mixture was stirred at rt for 3 days. Then the reaction mixture was poured into ice water and the excess of oxidant was destroyed by Na₂SO₃ addition. The aqueous layer was washed with ethyl acetate (1x100 mL), acidified with 2 N HCl to pH 1, and extracted with ethyl acetate (4x100 mL). The combined organic layers were dried over Na₂SO₄ and the solvent was removed *in vacuo* to give the tricarboxylic acid **3** as a brown solid (1.0 g, 3.2 mmol, 85% yield), which was used without further purification in the next step. ¹H NMR (DMSO-d₆, 300 MHz) δ 12.53 (br s, 3H), 1.93 (s, 6H), 1.75 (s, 3H), 1.70-1.82 (m, 6H); ¹³C NMR (DMSO-d₆, 300 MHz) δ 176.58, 169.12, 51.58, 41.90, 40.78, 38.51, 23.60. MS (ESI) m/z: 326.2 [M + H]⁺.

1,3,5-Tricarboxy-7-tert-butoxycarbonylaminoadamantane (4).

A solution of 1,3,5-Tricarboxy-7-acetylaminoadamantane **3** (1.2 g, 3.7 mmol) in a mixture of 20 mL water and 4 mL concentrated HCl was refluxed for 24 h. After cooling to room temperature the solution was washed with ethyl acetate (2x25 mL) and the aqueous phase was evaporated to obtain the 1,3,5-Tricarboxy-7-aminoadamantane as a white solid (1.0 g, 3.5 mmol, 95% yield), which was used without further purification in the next step. ¹H NMR (DMSO-d₆, 300 MHz) δ 12.33 (br s, 3H), 8.40 (br s, 2H), 1.85 (s, 6H), 1.71-1.86 (m, 6H); ¹³C NMR (DMSO-d₆, 300 MHz) δ 175.74, 51.88, 41.82, 39.71, 37.98. MS (ESI) m/z: 284.3 [M + H]⁺. To a solution of 1,3,5-Tricarboxy-7-aminoadamantane (1.4 g, 5.1 mmol) in 70 mL of methanol were added NEt₃ (3.5 mL, 25.6 mmol) and Boc₂O (3.3 g, 15.3 mmol). The solution was stirred at 50 °C for 24 h and a second portion of Boc₂O (1.6 g, 7.6 mmol) together with NEt₃ (1.7 mL, 12.8 mmol) was added again. After stirring for additional 24 h at 50 °C, the solvent was evaporated and the crude reaction was dissolved in 50 mL of water, acidified with 2 N HCl to pH 1 and extracted with ethyl acetate (3x60 mL). Drying of the combined organic layers over Na₂SO₄ and evaporation of the solvent gave the Boc-protected amine **4** as a beige solid (1.3 g, 3.4 mmol, 67% yield). ¹H NMR (DMSO-d₆, 300 MHz) δ 12.44 (br s, 3H), 6.73 (br s, 1H), 1.86 (s, 6H), 1.68-1.83 (m, 6H), 1.37 (s, 9H); ¹³C NMR (DMSO-d₆, 300 MHz) δ 176.57, 153.96, 77.53, 50.71, 41.91, 40.91, 38.43, 28.20. FT-IR (neat, ν/cm⁻¹) 3351, 2980, 1693, 1666, 1521, 1248, 1162, 675. MS (ESI) m/z: 284.2 [M + H - Boc]⁺. Anal. Calcd for C₁₈H₂₅NO₈: C 56.39; H 6.57; N 3.65. Found: C 56.29; H 6.83; N 3.55.

1,3,5-Tri(5-methoxycarbonyl-pentylcarbamoyl)-7-tert-butoxycarbonylaminoadamantane (5).

To a solution of 1,3,5-Tricarboxy-7-tert-butoxycarbonylaminoadamantane **4** (0.4 g, 1.0 mmol) in 10 mL of dry DMF were added EDCI (1.1 g, 6.0 mmol) and HOBt (0.8 g, 6.0 mmol) and the

resulting mixture was stirred at rt for 30 min. Then a solution of methyl-6-aminohexanoate hydrochloride (0.8 g, 4.5 mmol) and *N*-diisopropylethylamine (1.6 mL, 9.0 mmol) in 10 mL of dry DMF was added and the reaction was stirred at 65 °C for 72 h. After addition of AcOEt (100 mL), the organic phase was washed with saturated aqueous NH₄Cl solution (2x100 mL), saturated aqueous NaHCO₃ solution (2x100 mL) and brine (1x100 mL), dried over Na₂SO₄ and filtered. The solvent was removed *in vacuo* and the crude product was purified by column chromatography on silica gel (eluent: AcOEt) to yield the desired compound **5** as an orange solid (0.5 g, 0.65 mmol, 65% yield). ¹H NMR (CDCl₃, 300 MHz) δ 5.85 (t, *J* = 5.5 Hz, 3H), 4.65 (s, 1H), 3.65 (s, 9H), 3.18-3.25 (m, 6H), 2.29 (t, *J* = 7.3 Hz, 6H), 2.00 (s, 6H), 1.79-1.94 (m, 6H), 1.56-1.66 (m, 6H), 1.43-1.53 (m, 6H), 1.39 (s, 9H), 1.27-1.36 (m, 6H); ¹³C NMR (CDCl₃, 300 MHz) δ 174.87, 174.01, 154.11, 79.49, 51.97, 51.50, 43.25, 41.82, 39.33, 39.26, 33.76, 29.07, 28.39, 26.23, 24.35. FT-IR (neat, v/cm⁻¹) 3338, 2934, 2860, 1730, 1634, 1522, 1245, 1158. MS (ESI) *m/z*: 766.8 [M + H]⁺, 710.7 [M + H - *t*-Bu]⁺. Anal. Calcd for C₃₉H₆₄N₄O₁₁: C 61.24; H 8.43; N 7.32. Found: C 60.99; H 8.41; N 7.00.

1,3,5-Tri(5-methoxycarbonyl-pentylcarbamoyl)-7-aminoadamantane (6).

1,3,5-Tri(5-methoxycarbonyl-pentylcarbamoyl)-7-*tert*-butoxycarbonylaminoadamantane **5** (0.30 g, 0.4 mmol) was dissolved in a mixture of 1 mL TFA and 4 mL CH₂Cl₂ and the resulting solution was stirred at rt for 1 h. Evaporation of the solvent *in vacuo* afforded the amine **6** as an orange oil (0.26 g, 0.4 mmol, quantitative). ¹H NMR (CDCl₃, 300 MHz) δ 8.20 (br s, 2H), 6.97 (m, 3H), 3.64 (s, 9H), 3.12-3.23 (m, 6H), 2.29 (t, *J* = 7.3 Hz, 6H), 1.91-2.15 (m, 12H), 1.40-1.63 (m, 12H), 1.23-1.33 (m, 6H); ¹³C NMR (CDCl₃, 300 MHz) δ 175.10, 174.83, 54.03, 51.66, 43.27, 40.07, 39.75, 38.30, 33.65, 28.40, 25.96, 24.20. FT-IR (neat, v/cm⁻¹) 3346, 2939, 2860, 1732, 1627, 1534, 1200, 1132, 720. MS (ESI) *m/z*: 665.7 [M + H]⁺. Anal. Calcd for C₃₄H₅₆N₄O₉: C 61.42; H 8.49; N 8.43. Found: C 60.99; H 8.41; N 8.11.

1,3,5-Tri(5-carboxy-pentylcarbamoyl)-7-*tert*-butoxycarbonylaminoadamantane (7).

To a solution of 1,3,5-Tri(5-methoxycarbonyl-pentylcarbamoyl)-7-*tert*-butoxycarbonylaminoadamantane **5** (0.100 g, 0.13 mmol) in 10 mL of MeOH/H₂O (1:1) was added KOH (0.044 g, 0.78 mmol) and the reaction mixture was stirred at 60 °C for 24 h. Then the solution was diluted with water (50 mL), acidified with 2 N HCl to pH 2 and extracted with ethyl acetate (3x60 mL). Drying of the combined organic layers over Na₂SO₄ and evaporation of the solvent yielded the desired product **7** as a colorless solid (0.085 g, 0.117 mmol, 90% yield). ¹H NMR (CD₃OD, 300 MHz) δ 3.26-3.35 (m, 6H), 2.40 (t, *J* = 7.3 Hz, 6H), 2.09 (s, 6H), 1.92-2.02 (m, 6H), 1.58-1.78 (m, 12H), 1.53 (s, 9H), 1.41-1.51 (m, 6H); ¹³C NMR (CD₃OD, 300 MHz) δ 178.11, 177.50, 156.55, 79.95, 53.01, 44.60, 42.61, 40.40, 34.81, 30.10, 28.86, 27.40, 25.74. FT-IR (neat, v/cm⁻¹) 3362, 2932, 2865, 1702, 1616, 1529, 1159, 745. MS (ESI) *m/z*: 723.7 [M + H]⁺, 667.6 [M + H - *t*-Bu]⁺, 623.6 [M + H - Boc]⁺. Anal. Calcd for C₃₆H₅₈N₄O₁₁: C 59.82; H 8.09; N 7.75. Found: C 59.23; H 8.10; N 7.23.

Synthesis of 2nd generation dendron (8).

To a solution of 1,3,5-Tri(5-carboxy-pentylcarbonyl)-7-*tert*-butoxycarbonylaminoadamantane **7** (0.060 g, 0.083 mmol) in 3 mL of dry DMF were added EDCI (0.110 g, 0.581 mmol) and HOBt (0.078 g, 0.581 mmol) and the resulting mixture was stirred at rt for 30 min. Then a solution of 1,3,5-Tri(5-methoxycarbonyl-pentylcarbonyl)-7-aminoadamantane **6** (0.250 g, 0.373 mmol) and *N*-diisopropylethylamine (0.300 mL, 1.660 mmol) in 2 mL of dry DMF was added and the reaction was stirred at 65 °C for 72 h. After addition of AcOEt (60 mL), the organic phase was washed with saturated aqueous NH₄Cl solution (2x60 mL), saturated aqueous NaHCO₃ solution (2x60 mL) and brine (1x60 mL), dried over Na₂SO₄ and filtered. The solvent was removed *in vacuo* and the crude product was purified by column chromatography on silica gel (eluent: AcOEt/MeOH 20:1) to give the dendron **8** as a beige solid (0.203 g, 0.076 mmol, 92% yield). ¹H NMR (CD₃OD, 600 MHz) δ 3.65 (s, 27H), 3.16-3.20 (m, 24H), 2.32 (t, *J* = 7.5 Hz, 18H), 2.13 (t, *J* = 7.5 Hz, 6H), 2.07 (s, 18H), 1.99 (s, 6H), 1.83-1.92 (m, 24H), 1.57-1.64 (m, 24H), 1.48-1.53 (m, 24H), 1.42 (s, 9H), 1.29-1.35 (m, 24H); ¹³C NMR (CD₃OD, 600 MHz) δ 177.97, 177.91, 175.77, 175.71, 156.47, 79.82, 54.23, 53.05, 52.07, 44.59, 44.55, 42.66, 42.30, 40.55, 40.46, 40.37, 37.75, 34.69, 30.24, 30.11, 28.92, 27.53, 27.39, 26.80, 25.70. FT-IR (neat, v/cm⁻¹) 3331, 2932, 2860, 1724, 1631, 1525, 1161. MS (MALDI-TOF) *m/z*: 2685.960 [M + Na]⁺, 2563.916 [M + H - Boc]⁺. Anal. Calcd for C₁₃₈H₂₂₀N₁₆O₃₅: C 62.23; H 8.33; N 8.41. Found: C 62.31; H 8.34; N 8.10.

2nd generation dendron-(COOH)₉ (9).

To a solution of G2 dendron **8** (0.100 g, 0.037 mmol) in 8 mL of MeOH/H₂O (1:1) was added KOH (0.042 g, 0.751 mmol) and the reaction mixture was stirred at 60 °C for 24 h. Then the solution was diluted with water (30 mL), acidified with 2 N HCl to pH 2 and extracted with ethyl acetate (4x50 mL). Drying of the combined organic layers over Na₂SO₄ and evaporation of the solvent yielded the desired product **9** as a colorless solid (0.075 g, 0.029 mmol, 80% yield). ¹H NMR (CD₃OD, 600 MHz) δ 3.17-3.20 (m, 24H), 2.26 (t, *J* = 7.5 Hz, 18H), 2.16 (t, *J* = 7.5 Hz, 6H), 2.08 (s, 18H), 1.99 (s, 6H), 1.85-1.93 (m, 24H), 1.57-1.63 (m, 24H), 1.50-1.55 (m, 24H), 1.41 (s, 9H), 1.32-1.37 (m, 24H); ¹³C NMR (CD₃OD, 600 MHz) δ 178.95, 178.23, 178.18, 176.10, 156.70, 80.01, 54.50, 53.26, 44.79, 44.73, 42.85, 42.46, 40.74, 40.64, 40.62, 37.94, 36.04, 30.30, 30.29, 29.11, 27.71, 27.68, 26.97, 26.29. FT-IR (neat, v/cm⁻¹) 3350, 2935, 2863, 1701, 1621, 1529, 1153. MS (MALDI-TOF) *m/z*: 2559.031 [M + Na]⁺, 2480.826 [M - *t*-Bu]⁺, 2437.181 [M - Boc]⁺. Anal. Calcd for C₁₂₉H₂₀₂N₁₆O₃₅: C 61.07; H 8.03; N 8.83. Found: C 61.37; H 8.10; N 8.86.

2nd generation dendron-NH₂ (10).

G2 dendron **8** (0.100 g, 0.037 mmol) was dissolved in a mixture of 0.1 mL TFA and 2 mL CH₂Cl₂ and the resulting solution was stirred at rt for 1 h. Evaporation of the solvent *in vacuo* afforded the amine **10** as an orange oil (0.095 g, 0.037 mmol, quantitative). ¹H NMR (CD₃OD,

400 MHz) δ 3.64 (s, 27H), 3.16-3.20 (m, 24H), 2.32 (t, $J = 7.4$ Hz, 18H), 2.14 (t, $J = 7.2$ Hz, 6H), 2.07 (s, 18H), 1.83-1.99 (m, 30H), 1.57-1.65 (m, 24H), 1.47-1.54 (m, 24H), 1.28-1.36 (m, 24H); ^{13}C NMR (CD_3OD , 400 MHz) δ 177.89, 176.61, 175.79, 175.71, 54.22, 53.05, 52.07, 44.63, 44.53, 42.29, 41.63, 40.55, 40.40, 39.84, 37.68, 34.66, 30.16, 30.06, 27.38, 27.37, 26.74, 25.66. FT-IR (neat, v/cm^{-1}) 3341, 2937, 2860, 1730, 1629, 1532, 1140. MS (MALDI-TOF) m/z : 2586.439 $[\text{M} + \text{Na}]^+$, 2564.316 $[\text{M} + \text{H}]^+$. Anal. Calcd for $\text{C}_{133}\text{H}_{212}\text{N}_{16}\text{O}_{33}$: C 62.32; H 8.34; N 8.74. Found: C 62.29; H 8.31; N 8.80.

Synthesis of 3rd generation dendron (11).

To a solution of 1,3,5-Tri(5-carboxy-pentylcarbamoyle)-7-*tert*-butoxycarbonylaminoadamantane **7** (0.009 g, 0.012 mmol) in 2 mL of dry DMF were added EDCI (0.016 g, 0.084 mmol) and HOBT (0.011 g, 0.084 mmol) and the resulting mixture was stirred at rt for 30 min. Then a solution of G2 dendron **10** (0.090 g, 0.035 mmol) and *N*-diisopropylethylamine (0.040 mL, 0.240 mmol) in 3 mL of dry DMF was added and the reaction was stirred at 65 °C for 72 h. After addition of AcOEt (50 mL), the organic phase was washed with saturated aqueous NH_4Cl solution (2x50 mL), saturated aqueous NaHCO_3 solution (2x50 mL) and brine (1x50 mL), dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo* and the crude product was purified by column chromatography on silica gel (eluent: AcOEt/MeOH 20:1) to give the dendron **11** as a yellow solid (0.083 g, 0.010 mmol, 83% yield). ^1H NMR (CD_3OD , 600 MHz) δ 3.65 (s, 81H), 3.16-3.19 (m, 78H), 2.32 (t, $J = 7.5$ Hz, 54H), 2.13 (t, $J = 7.5$ Hz, 24H), 2.07 (br s, 72H), 1.98 (br s, 6H), 1.84-1.92 (m, 78H), 1.58-1.64 (m, 78H), 1.48-1.53 (m, 78H), 1.42 (s, 9H), 1.29-1.35 (m, 78H); ^{13}C NMR (CD_3OD , 600 MHz) δ 177.96, 177.94, 177.93, 175.82, 175.80, 175.79, 54.26, 53.99, 52.08, 44.58, 42.34, 42.32, 40.50, 40.48, 40.41, 40.40, 37.80, 37.77, 34.72, 34.71, 30.27, 30.16, 30.14, 28.93, 27.60, 27.55, 27.43, 27.42, 26.85, 26.82, 25.74, 25.72. FT-IR (neat, v/cm^{-1}) 3331, 2931, 2860, 1727, 1628, 1530, 1426, 1161. MS (MALDI-TOF) m/z : 8351 $[\text{M} + \text{H}]^+$, 7701 $[\text{M} - \text{G1}]^+$, 5773 $[\text{M} - \text{G2}]^+$. Anal. Calcd for $\text{C}_{435}\text{H}_{688}\text{N}_{52}\text{O}_{107}$: C 62.51; H 8.30; N 8.71. Found: C 62.59; H 8.40; N 8.77.

Solubilization of the dendrons

Prior to incubation with the different cell lines, compounds **7**, **9** and **11** were solubilized in 50 % DMSO to achieve a 2 mM stock solution. More in details, 150 μl solutions were obtained dissolving the different dendrimers in 75 μl of DMSO followed by the addition of three aliquots (25 μl) of PBS. Different concentrations of DMSO were used as control in the cytotoxicity tests.

Cell cultures

Human HeLa cells (cervix epithelioid carcinoma) and mouse macrophages cell line (RAW 264.7) were obtained from American Type Culture Collection (ATCC). Both cellular types were cultured under controlled atmosphere (37°C, 5% CO_2) in RPMI 1640 supplemented with 10% heat inactivated Fetal Bovine Serum (FBS) and 100 U/ml gentamycin. In addition, for the murine cell line, the culture medium contained 2- β -mercaptoethanol (50 μM) and HEPES (20 mM).

When confluency reached 70-80%, HeLa and RAW 264.7 cells were trypsinized or detached with a phosphate buffer saline (PBS)-EDTA (2 mM) solution, respectively, and subcultured in T75 cm² flasks at a density of 50000 cells/ml.

Before *in vitro* cytotoxicity assessments, either HeLa or RAW 264.7 were removed from the culture flasks, reseeded in 24 well plates (250000 and 450000 cells/well, respectively, in 500 µl complete medium) and allowed to adhere overnight.

The media was then removed and replaced with 500 µl of fresh medium containing different concentrations of compounds **7**, **9** and **11** (from 1.6 to 100 µM). After 24 hours of incubation, cells were harvested and processed for propidium iodide (PI) staining or intracellular lactate dehydrogenase (LDH) release evaluation.

Cell viability

PI is a fluorescent vital dye that stains DNA in cells that have lost their plasma membrane integrity (late stage of apoptosis or death). After treatment with compound **7**, **9** and **11**, the cells were collected, washed twice in PBS, resuspended in PBS-PI solution (1 µg/ml) and incubated at room temperature for 15-20 minutes. The fluorescence of 10000 individual cells was then measured by flow cytometry (FACS Calibur, Becton-Dickinson, USA) and data were analyzed using FlowJo software.

The content of the cytosolic LDH was also evaluated as an indicator of cellular viability/proliferation using the CytoTox 96® Non-Radioactive Cytotoxic Assay (Promega), following the manufacturer's instructions. Briefly, after the cells were washed and harvested, they were resuspended in 200 µl of the provided lysis solution, incubated 45 minutes at 37°C and centrifuged (5 min; 13400 g at 4°C). Then, 50 µl of cellular lysate was allowed to react with the equivalent volume of LDH substrate mix (30 minutes at room temperature protected from light), Stop solution was added and absorbance was determined using a plate reader (λ=490 nm). In this case, the detected amount of LDH in the lysate is representative of the cells that survived the dendron subadministration.

References

1. (a) Reichert, V. R.; Mathias, L. J. *Macromolecules* **1994**, *27*, 7015-7023. (b) Newman, H. *Synthesis* **1972**, 692-693.
2. Nasr, K.; Pannier, N.; Frangioni, J. V.; Maison, W. *J. Org. Chem.* **2008**, *73*, 1056-1060.

Figure S1. ^1H NMR spectra (CDCl_3 , 300 MHz) of G1 dendron **5**.

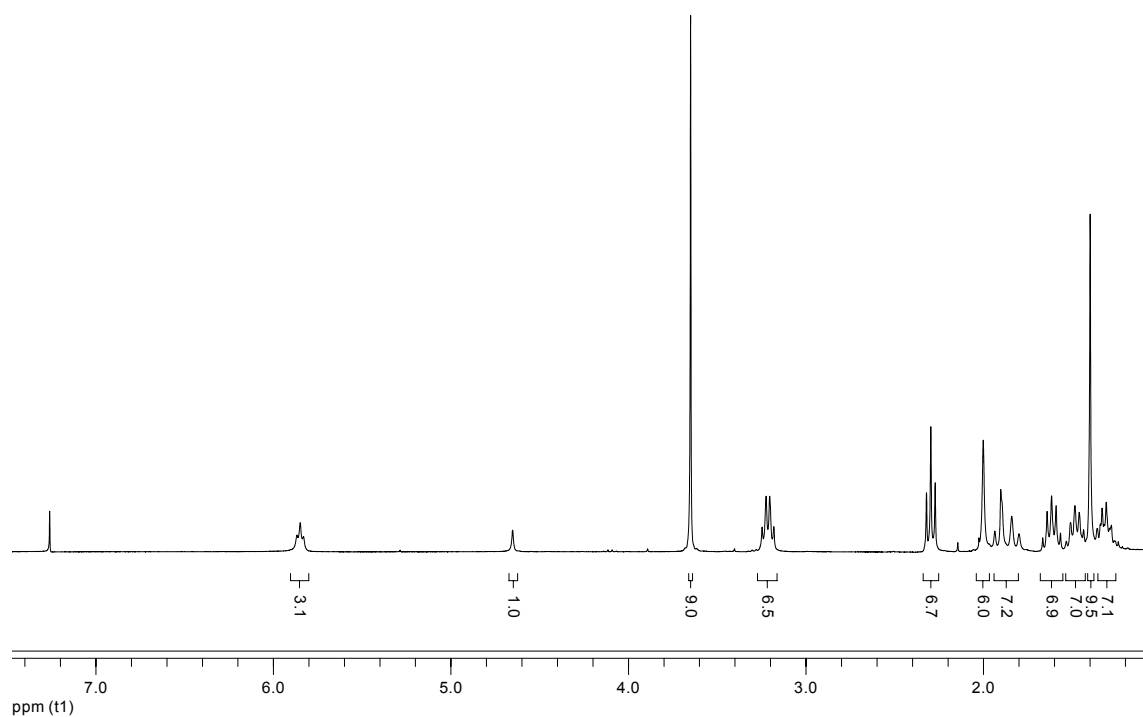


Figure S2. ^{13}C NMR spectra (CDCl_3 , 300 MHz) of G1 dendron **5**.

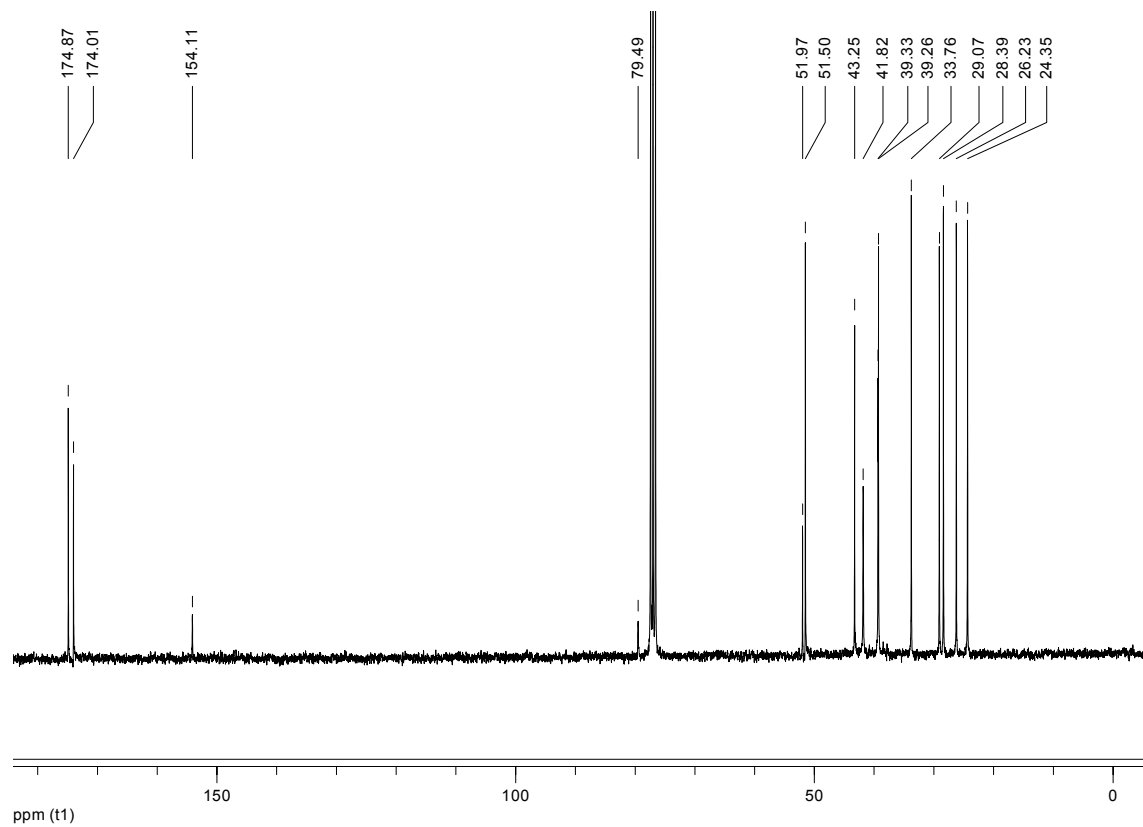


Figure S3. ^1H NMR spectra (CD_3OD , 600 MHz) of G2 dendron **8**.

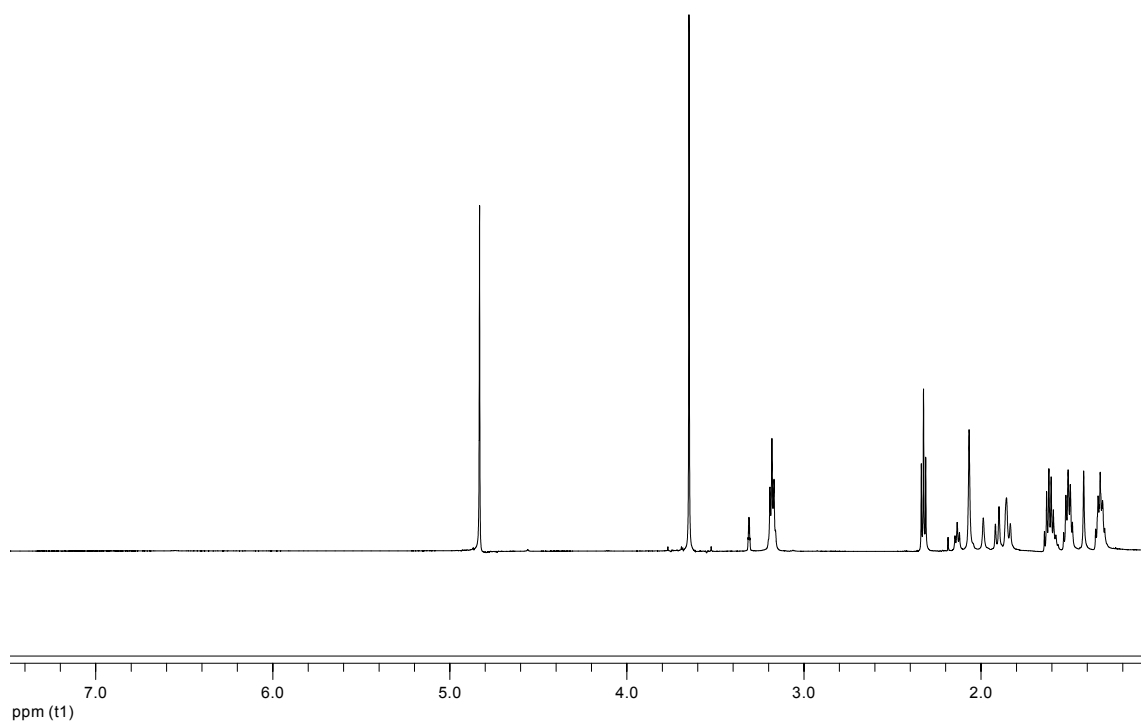


Figure S4. ^{13}C NMR spectra (CD_3OD , 600 MHz) of G2 dendron **8**.

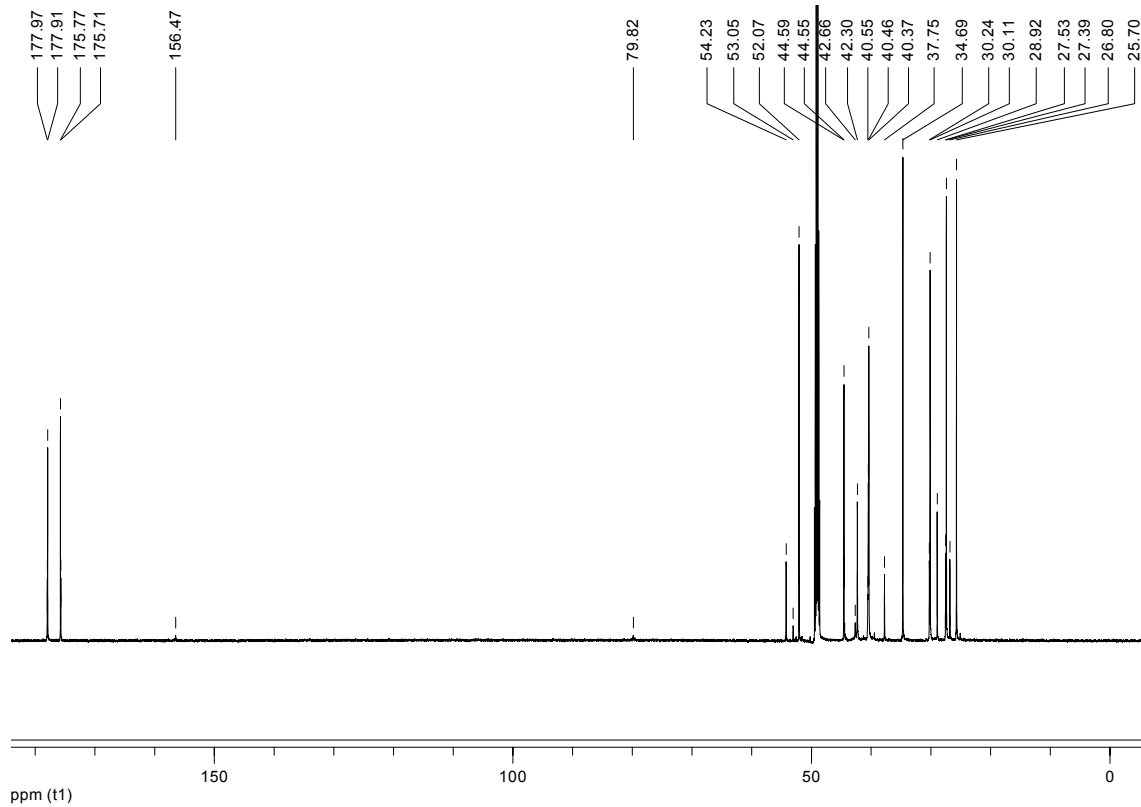


Figure S5. ^1H NMR spectra (CD_3OD , 600 MHz) of G3 dendron **11**.

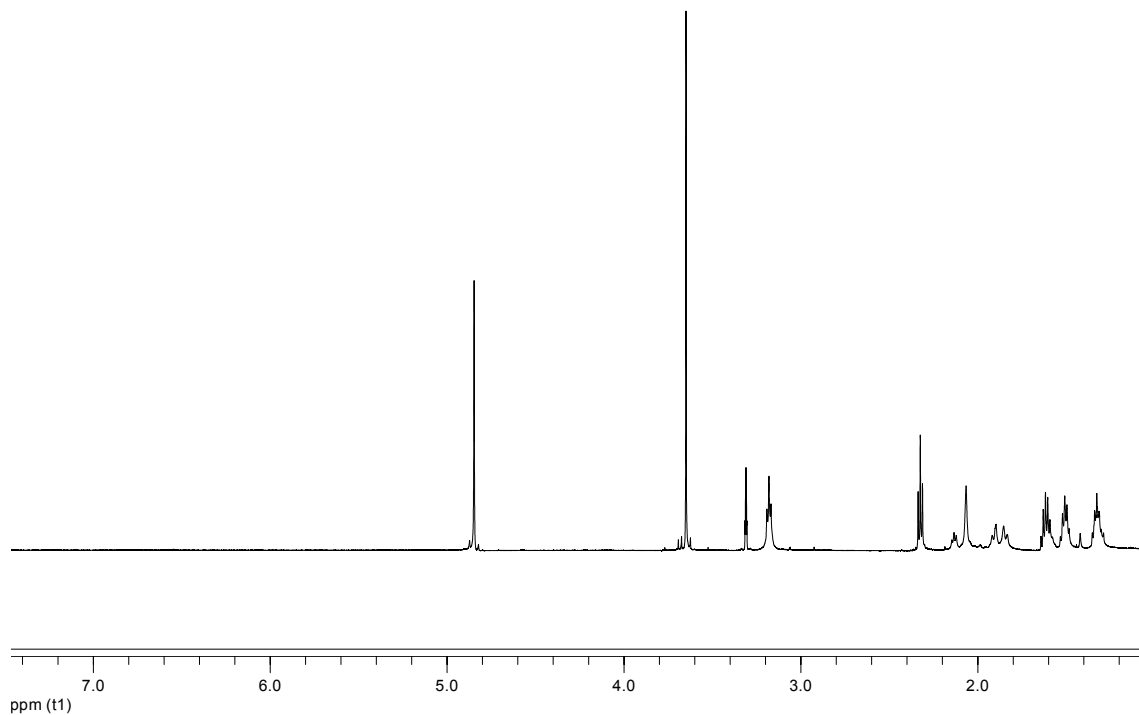


Figure S6. ^{13}C NMR spectra (CD_3OD , 600 MHz) of G3 dendron **11**.

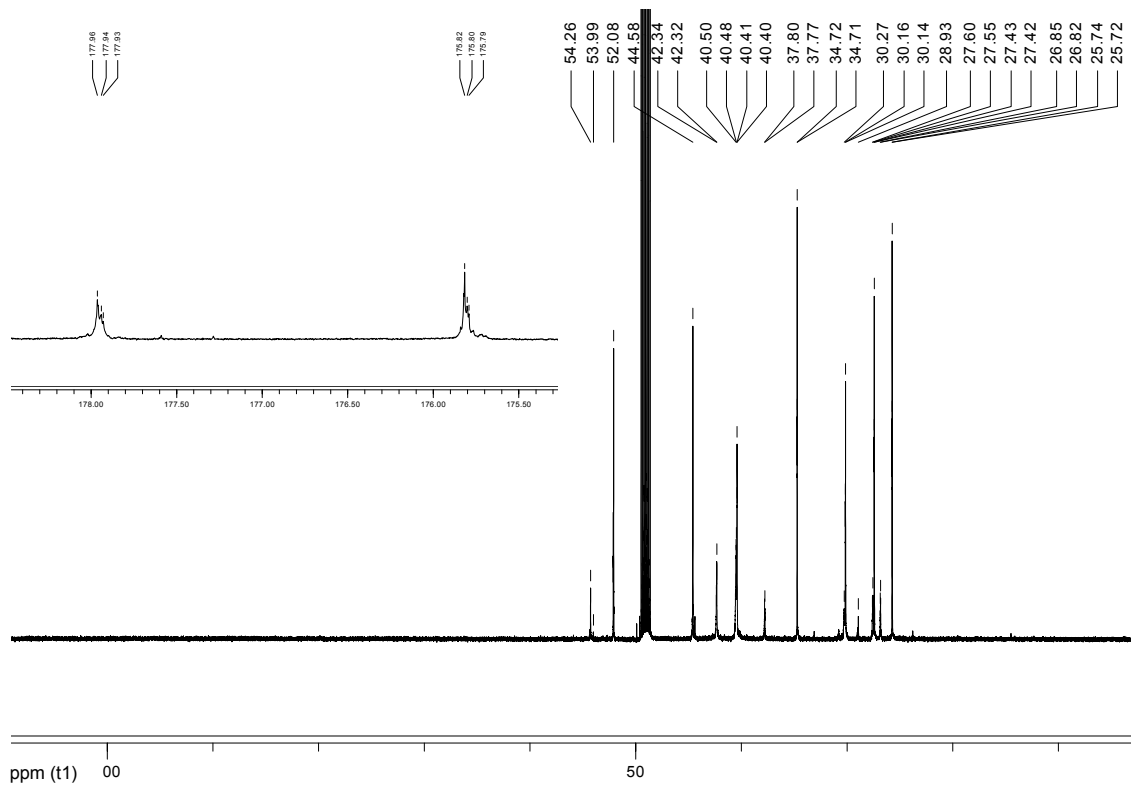


Figure S7. MALDI-TOF spectra of G2 dendron **8**.

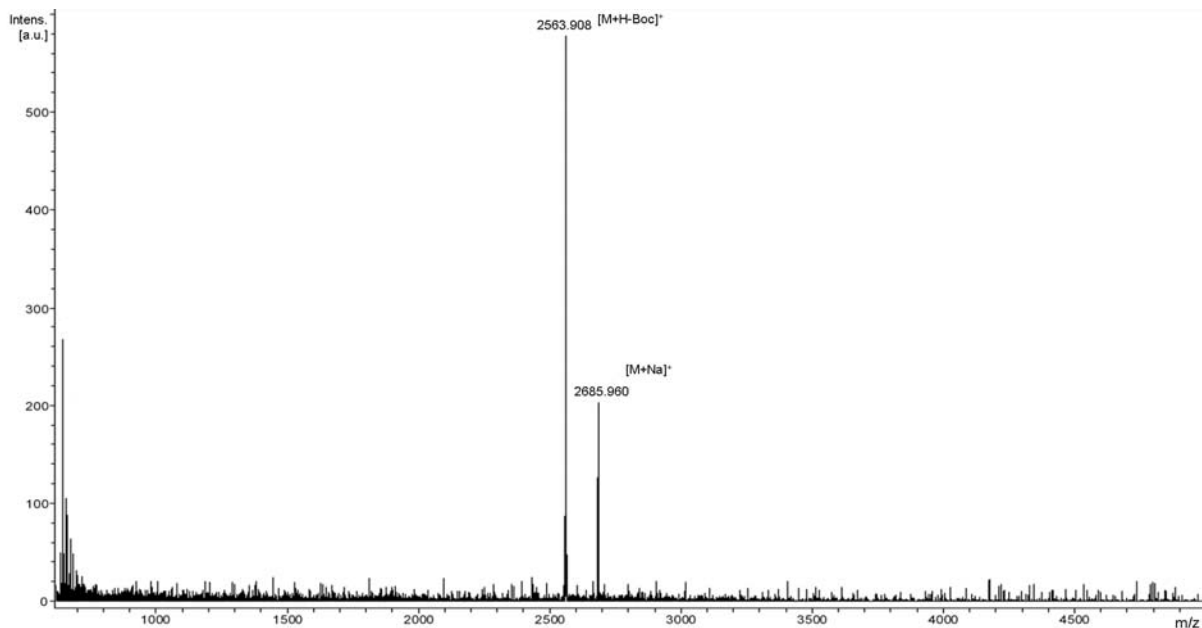


Figure S8. MALDI-TOF spectra of G3 dendron **11**. The assignment of the mass values for each peak needs to take into account a standard error of ± 10 Da due to the low resolution at very high masses.

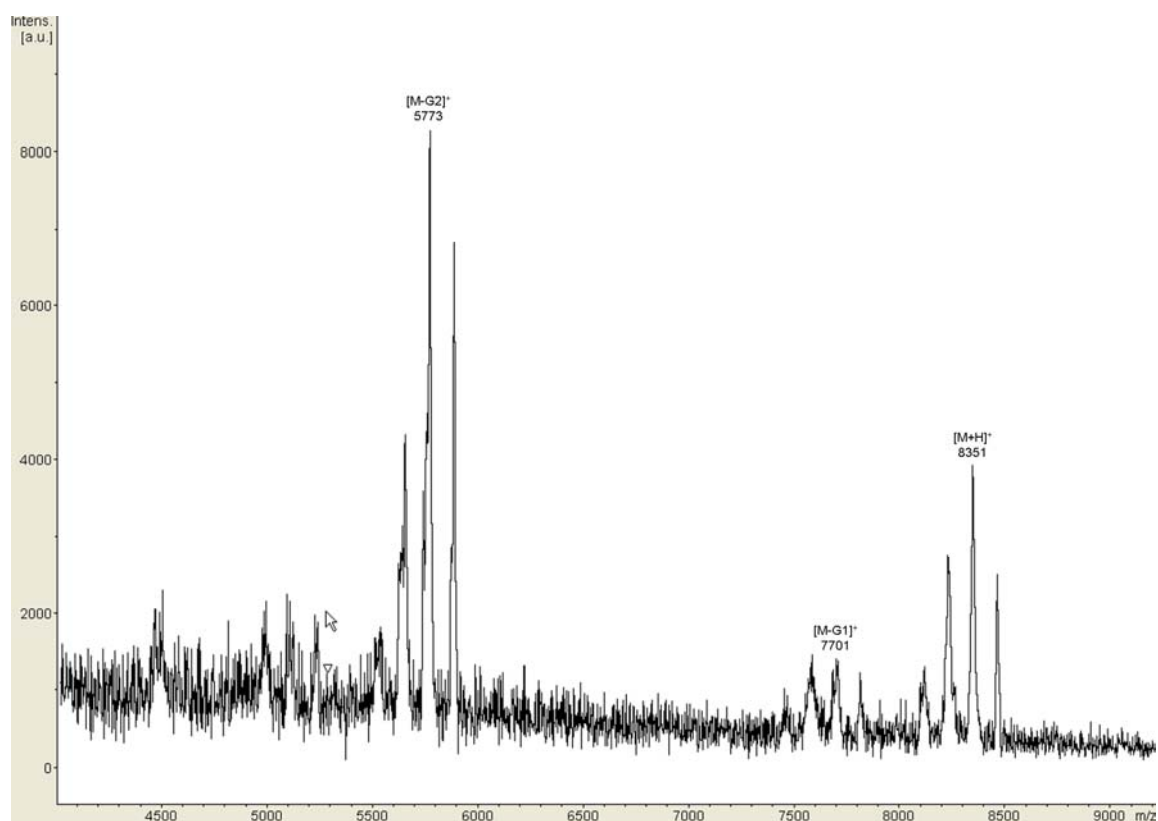


Figure S9. HeLa and RAW 264.7 cells were treated during 24 hours with different concentrations (from 1.6 to 100 μM) of compound **7** (G1 dendron; cyan bar), **9** (G2 dendron; blue bar) and **11** (G3 dendron; purple bar). Cell viability was then evaluated by propidium iodide staining (a) and (c), and lactate dehydrogenase content of cell lysates (b) and (d). The data demonstrate that none of the compounds had a significant impact on cell viability, even at the highest concentrations.

