Supporting information

Novel Perfluorinated Triblock Amphiphilic Copolymers for Lipid-shelled Microbubble Stabilization

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Content:

Atri synthesis

11-(tert-butoxycarbonylamino)undecanoic acid (**1**) : 11-aminoundecanoic acid (2 g; 10 mmol) was dissolved in dry methanol (50 mL) then triethylamine (1.7 mL; 1.2 mol eq) and Boc_2O (2.18 g; 1 mol eq) were added. The mixture was heated at 55°C for 20 min. TLC control in CH_2Cl_2/MeOH (9:1) ascertained the end of the reaction. The solution was evaporated, taken up in diethyl ether and washed three times with 10% citric acid solution. The organic phase was dried over magnesium sulfate, filtered and concentrated. ^{1}H NMR of **1** (400 MHz, $CDCl_3$) δ 4.53 (bs, 1H); 3.10 (m, 2H); 2.34 (t, 2H); 1.63 (m, 2H); 1.44 (m, 11H); 1.27 (m, 11H). ^{13}C NMR of **1** (100 MHz, $CDCl_3$) δ 179.5; 156.3; 79.0; 40.6; 34.3; 30.2; 29.5; 28.3; 26.8; 24.6. MS of **1** m/z 325 $[M+Na]^+$.

PEGylation of 1: Compound **1** (0.15 mmol; 45.2 mg) was dissolved in dichloromethane (5 mL) and reacted with the three different amino-methoxy-polyethylene glycols (0.10 mmol; MW= 500, 1000, 2000 g mol^{-1}) in three different experiments. Triethylamine (0.5 mmol; 0.07 mL) and BOP (0.12 mmol; 53 mg) were added, and the mixture was stirred at room temperature for 2 h. It was then diluted with dichloromethane (10 mL), washed twice with saturated NaCl and dried over Na_2SO_4. Concentration followed by precipitation in diethyl ether gave respectively **2**, **3** and **4** after centrifugation and several washes with diethyl ether. ^{1}H NMR for **2** (400 MHz, $CDCl_3$) δ 6.25 (bs, 1H); 4.53 (bs, 1H); 3.80 (m, 2H); 3.63 (m, 40H); 3.53 (m, 4H); 3.43 (m, 2H); 3.36 (s, 3H); 3.08 (m, 2H), 2.15 (m, 2H); 1.59 (m, 2H); 1.42 (s, 11H); 1.25 (m, 12H). ^{13}C NMR for **2** (100 MHz, $CDCl_3$) δ 173.2; 153.6; 78.9; 71.8; 70.6; 69.9; 59.2; 40.7; 39.0; 36.0; 30.0; 29.1; 28.3; 26.7; 25.9. MS for **2** m/z 881 $[M+K]^+$. ^{1}H NMR for **3** (400 MHz, $CDCl_3$) δ 6.25 (bs, 1H); 4.53 (bs, 1H); 3.80 (m, 2H); 3.63 (m, 92H); 3.53 (m, 4H); 3.43 (m, 2H); 3.36 (s, 3H); 3.08 (m, 2H), 2.15 (m, 2H); 1.59 (m, 2H); 1.42 (s, 11H); 1.25 (m, 12H). ^{13}C NMR for **3** (100 MHz, $CDCl_3$) δ 173.3; 156.0; 78.9; 71.9; 70.5;

59.1; 46.1; 40.5; 39.0; 36.5; 29.9; 29.3; 28.5; 26.8; 25.8. MS for **3** m/z 1393.7 $[M+K]^+$. ^1H NMR for **4** (400 MHz, $CDCl_3$) δ 6.20 (bs, 1H); 4.53 (bs, 1H); 3.80 (m, 2H); 3.63 (m, 174H); 3.53 (m, 6H); 3.43 (m, 4H); 3.36 (s, 3H); 3.08 (m, 2H), 2.15 (m, 2H); 1.59 (m, 2H); 1.49 (m, 2H); 1.42 (s, 9H); 1.25 (m, 12H). ^{13}C NMR for **4** (100 MHz, $CDCl_3$) δ 173.5; 161.6; 155.8; 91.9; 80.7; 78.7; 71.9; 70.5; 68.8; 65.9; 58.9; 49.8; 45.8; 40.4; 39.0; 37.7; 36.7; 30.2; 29.2; 28.3; 26.6; 25.6; 15.4. MS for **4** m/z 2321 $[M+Na]^+$, 2337 $[M+K]^+$.

Boc deprotection: Compounds **2**, **3** and **4** (1.5 mmol) were treated with trifluoroacetic acid (1.5 mL) in CH_2Cl_2 (9 mL) (three separate reactions) under stirring at ambient temperature for 2 h. The reaction media were evaporated and traces of TFA removed by coevaporation with chloroform. The residues were washed with diethyl ether (caution: in the case of the 500 $g.mol^{-1}$ PEG, the product **5** is quite soluble in ether, it should then be washed at 0°C). Products **5**, **6** and **7** were obtained as white powders. ^1H NMR for **5** (400 MHz) $CDCl_3$ δ 7.34 (bs, 1H); 6.79 (bs, 3H); 3.64 (m, 44H); 3.44 (m, 2H); 3.38 (s, 3H); 2.90 (m, 2H); 2.20 (m, 2H); 1.63 (m, 4H); 1.29 (m, 12H). ^{13}C NMR for **5** (100 MHz, $CDCl_3$) δ 176.4; 159; 115; 71.5; 70.2; 69.1; 58.8; 40.4; 36.4; 39.5; 35.6; 29.8; 28.6; 27.4; 26.1; 25.4. MS for **5** m/z 743 $[M+H]^+$, 765 $[M+Na]^+$, 781 $[M+K]^+$. ^1H NMR for **6** (400 MHz) $CDCl_3$ δ 7.34 (bs, 1H); 6.90 (bs, 2H); 3.64 (m, 90H); 3.44 (m, 2H); 3.38 (s, 3H); 3.20 (m, 2H); 2.90 (m, 2H); 2.20 (m, 2H); 1.63 (m, 9H); 1.29 (m, 12H). MS for **6** m/z 1271 $[M+H]^+$, 1293 $[M+K]^+$. ^1H NMR for **7** (400 MHz) $CDCl_3$ δ 7.34 (bs, 1H); 6.79 (bs, 2H); 3.80 (m, 2H); 3.64 (m, 178H); 3.44 (m, 2H); 3.38 (s, 3H); 3.26 (m, 2H); 2.90 (m, 2H); 2.20 (m, 2H); 1.63 (m, 2H); 1.29 (m, 12H). ^{13}C NMR for **7** (100 MHz, $CDCl_3$) δ 176.5; 158.5; 115; 71.7; 70.1; 68.8; 58.5; 46.3; 40.4; 39.7; 38.8; 35.7; 28.8; 27.4; 26.3; 25.7. MS for **7** m/z 2221 $[M+H]^+$.

Atri500, 1000 and 2000: The above compounds **5**, **6** and **7** (1.5 mmol) were independently reacted with heptadecafluorodecyl isocyanate (0.88 g; 1.8 mmol) and triethylamine (4.5

mmol; 0.63 mL) in THF (10 mL). Completion of the reaction was determined by TLC using CH_2Cl_2/MeOH (8:2) as eluting solvent. The solution was evaporated, the residue was dissolved in a minimum amount of methanol. Purification was obtained using a short column loaded with ion exchange resin (Waters Rxn Cx sulfonate) eluted with methanol. The eluate was evaporated and the residue lyophilized in water to give respectively products **8**, **9** and **10**. ^{1}H NMR for **8** (400 MHz) $CDCl_3$ δ 6.48 (bs, 1H); 3.65 (m, 44H), 3.58 (m, 4H); 3.45 (m, 2H); 3.40 (m, 2H); 3.35 (s, 3H); 3.18 (m, 2H); 2.38 (m, 2H); 2.30 (m, 2H), 1.62 (m, 2H); 1.45 (m, 2H); 1.25 (m, 12H). ^{13}C NMR for **8** (100 MHz) $CDCl_3$ δ 173.7; 158.5; 71.9; 70.6; 70.2; 69.9; 59.0; 40.2; 39.1; 36.5; 32.5; 31.7; 30.1; 28.6; 26.7; 25.6. ^{19}F NMR for **8** (377 MHz) δ -81.7; -114.8; -122.7; -123.5; -124.4; -126.9. MS for **8** m/z = 1298.60 (M+Na). ^{1}H NMR for **9** (400 MHz) $CDCl_3$ δ 6.38 (m, 1H); 5.25 (m, 1H); 5.02 (m, 1H); 3.65 (m, 90H); 3.55 (m, 4H); 3.50 (m, 2H); 3.45 (m, 2H); 3.25 (s, 3H); 3.18 (m, 2H); 1.62 (m, 2H); 1.45 (m, 2H); 1.22 (m, 14H). ^{13}C NMR for **9** (100 MHz) $CDCl_3$ δ 173.4; 158.2; 71.9; 70.4; 70.1; 69.9; 59.0; 40.2; 39.0; 36.5; 36.0; 32.5; 30.1; 29.0; 26.6; 25.5. ^{19}F NMR for **9** (377 MHz) δ -81.5; -114.6; -115.2; -122.5; -123.3; -124.2; -126.8; -127.0. MS for **9** m/z = 1712.26 (M+Na). ^{1}H NMR for **10** (400 MHz) $CDCl_3$ δ 6.50 (bs, 1H); 5.20 (bs, 1H); 4.95 (bs, 1H); 3.81 (m, 2H); 3.64 (m, 204H); 3.55 (m, 6H); 3.44 (m, 4H); 3.37 (s, 3H); 3.13 (m, 2H); 2.35 (m, 2H); 2.17 (m, 2H); 1.61 (m, 2H); 1.46 (m, 2H); 1.27 (m, 12H). ^{13}C NMR for **10** (100 MHz) $CDCl_3$ δ 173.5; 158.4; 71.8; 70.3; 70.0; 69.0; 59.1; 40.1; 39.1; 36.6; 28.9; 26.8; 25.5. ^{19}F NMR for **10** (377 MHz) δ (from TFA) = -81.72; -114.94; -122.67; -123.71; -124.63; -127.12; -127.78. MS for **10** m/z = 2684.39; 2707.39 (M+Na); 2723.38 (M+K).

^{1}H, ^{13}C NMR and mass spectra for compounds 1, 5, 6, and 7.

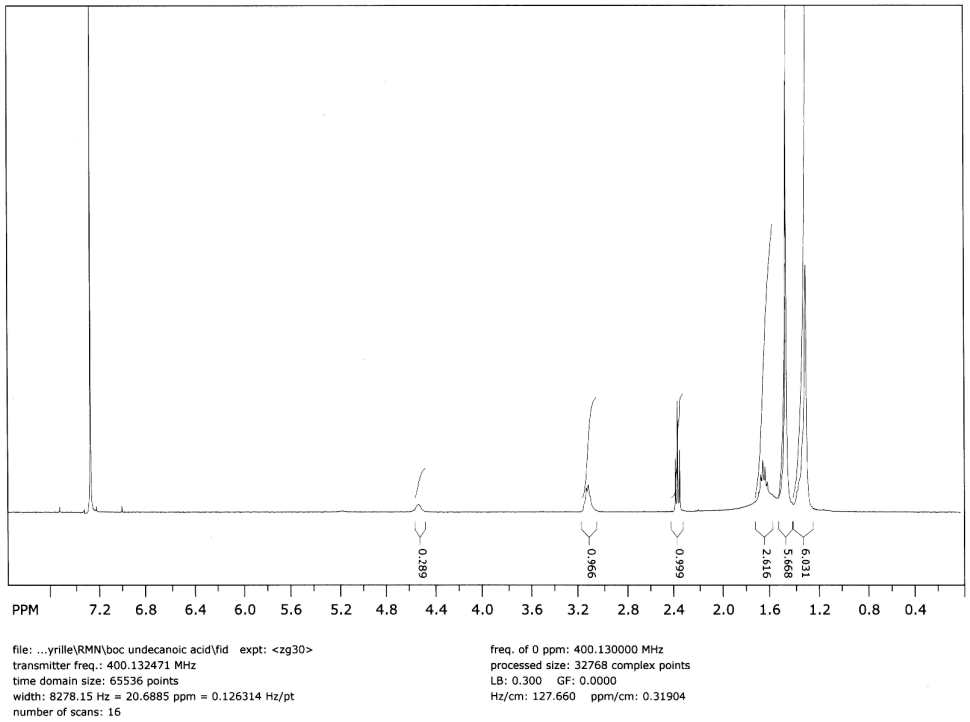

Figure S1. ^{1}H NMR spectrum for compound **1**.

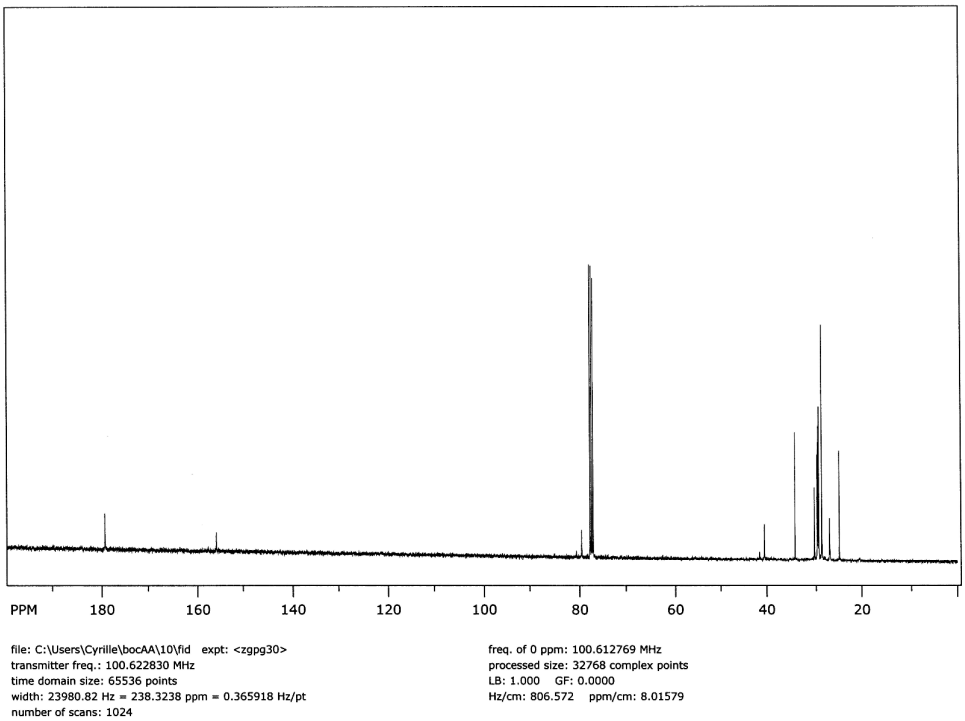

Figure S2. ^{13}C NMR spectrum for compound **1**.

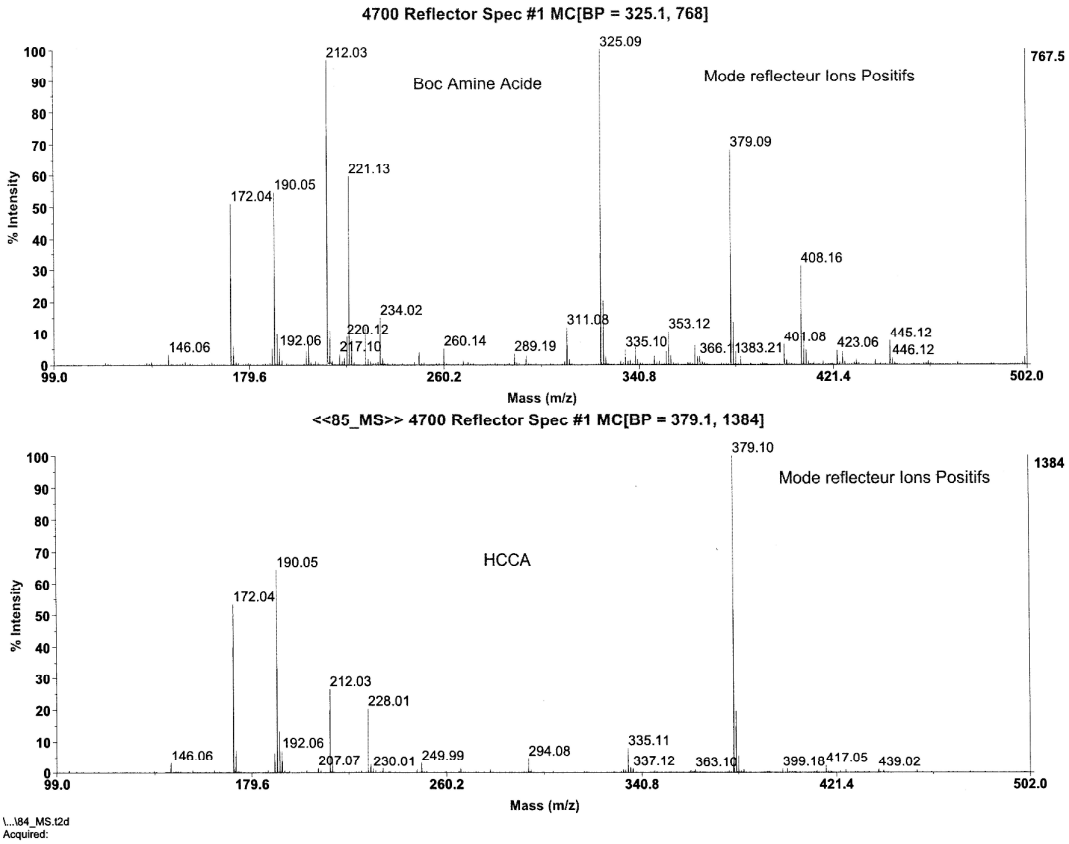

Figure S3. Mass spectrum for compound **1**.

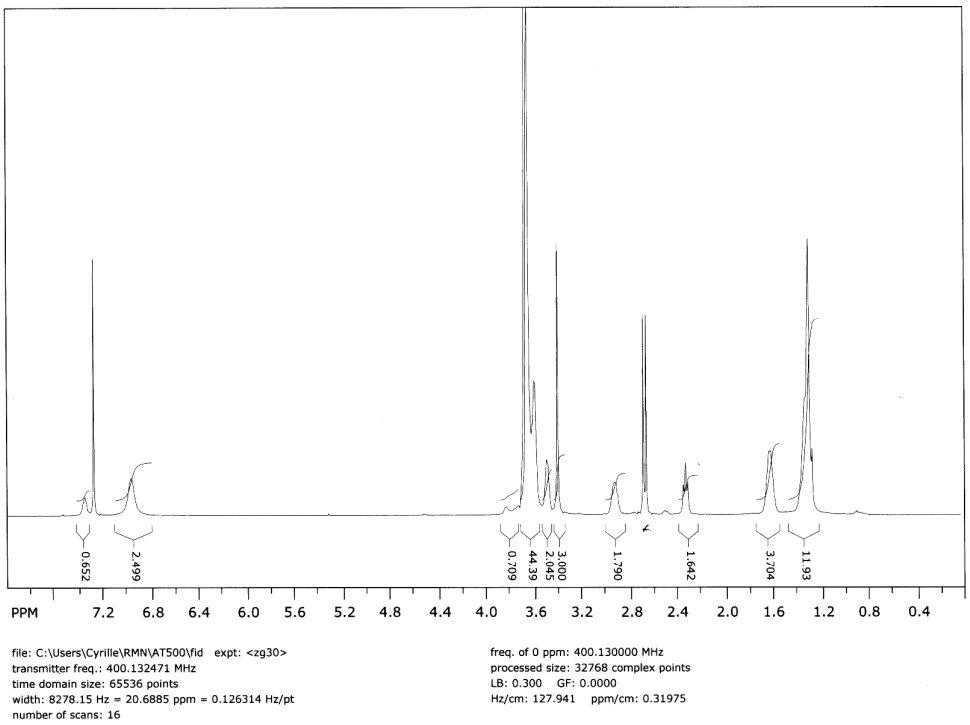

Figure S4. ^{1}H NMR spectrum for compound **5**.

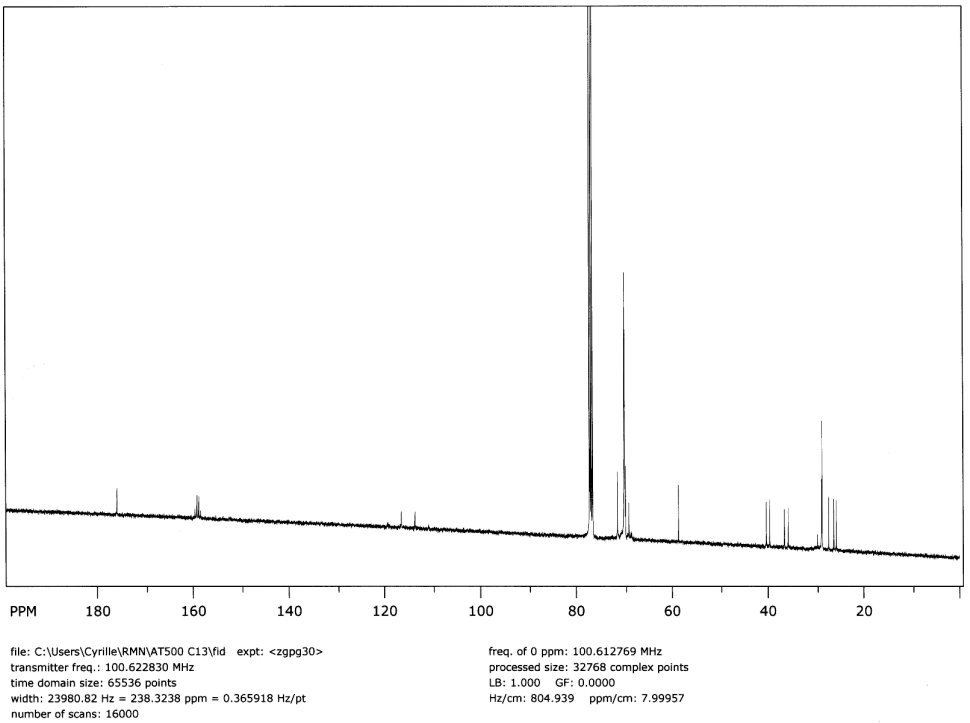

Figure S5. ^{13}C NMR spectrum for compound **5**.

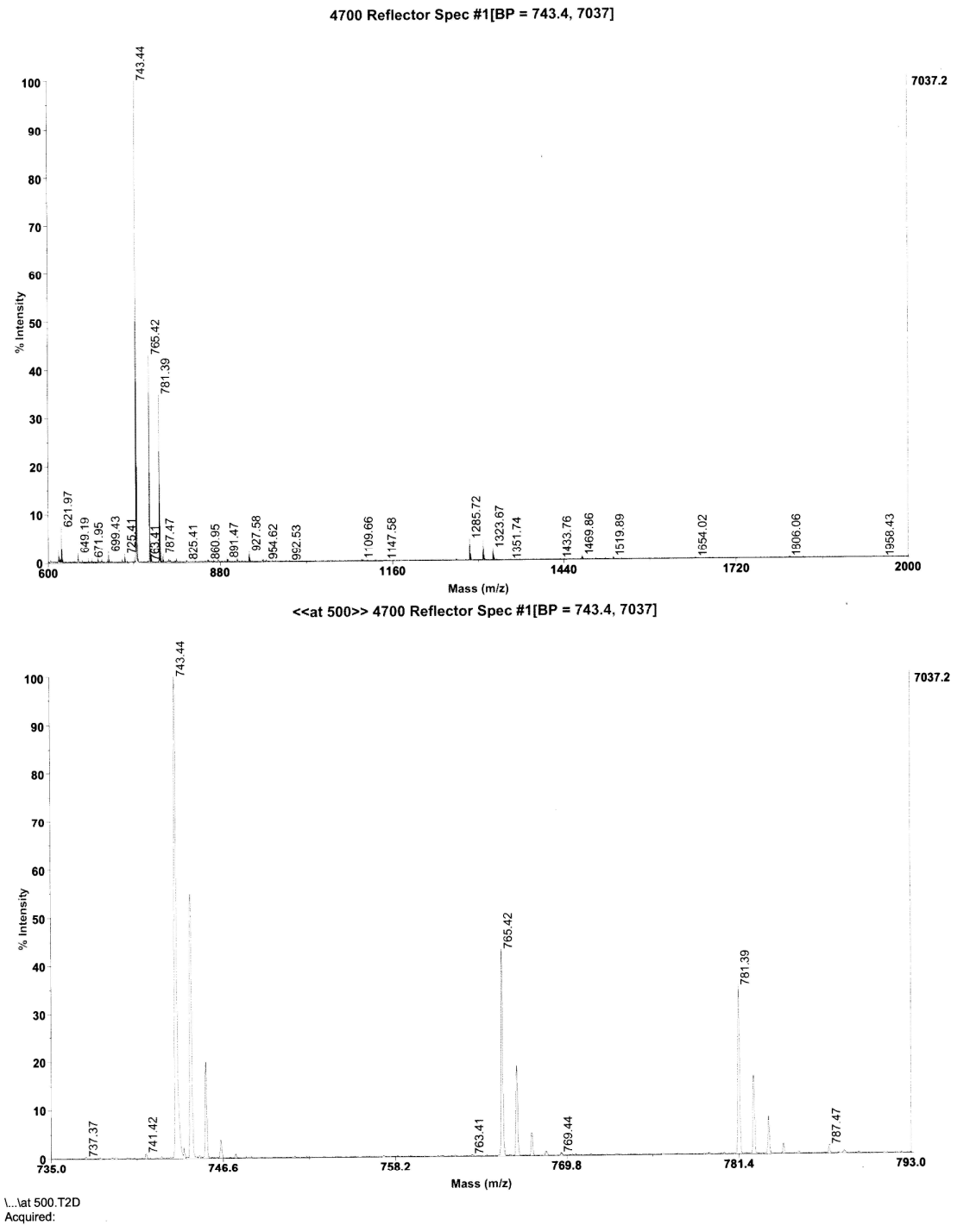

Figure S6. Mass spectrum for compound **5**.

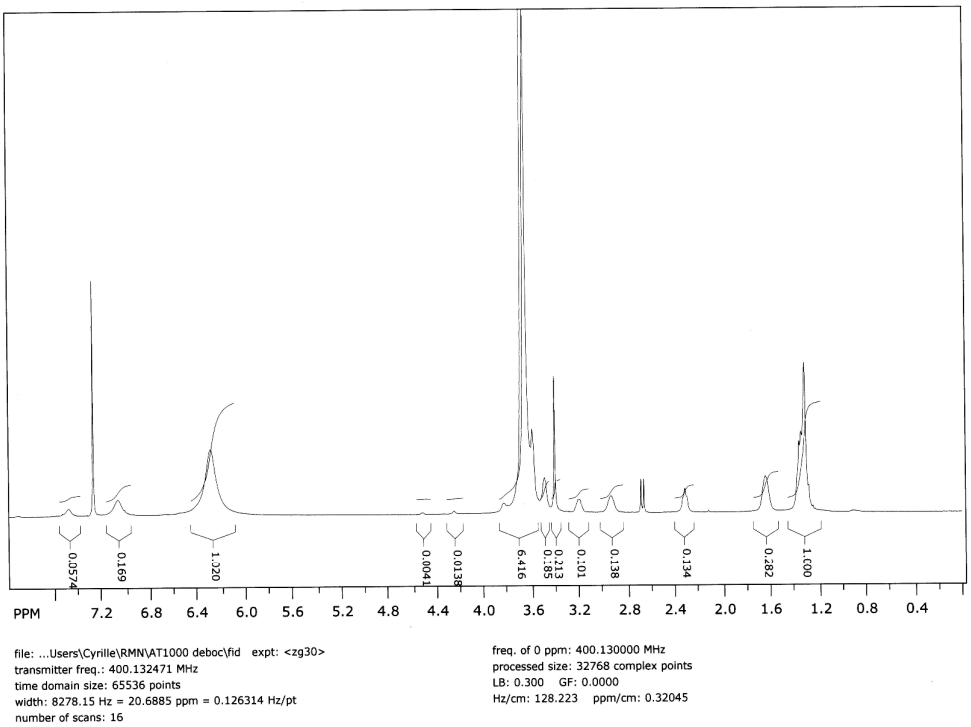

Figure S7. ^{1}H NMR spectrum for compound **6**.

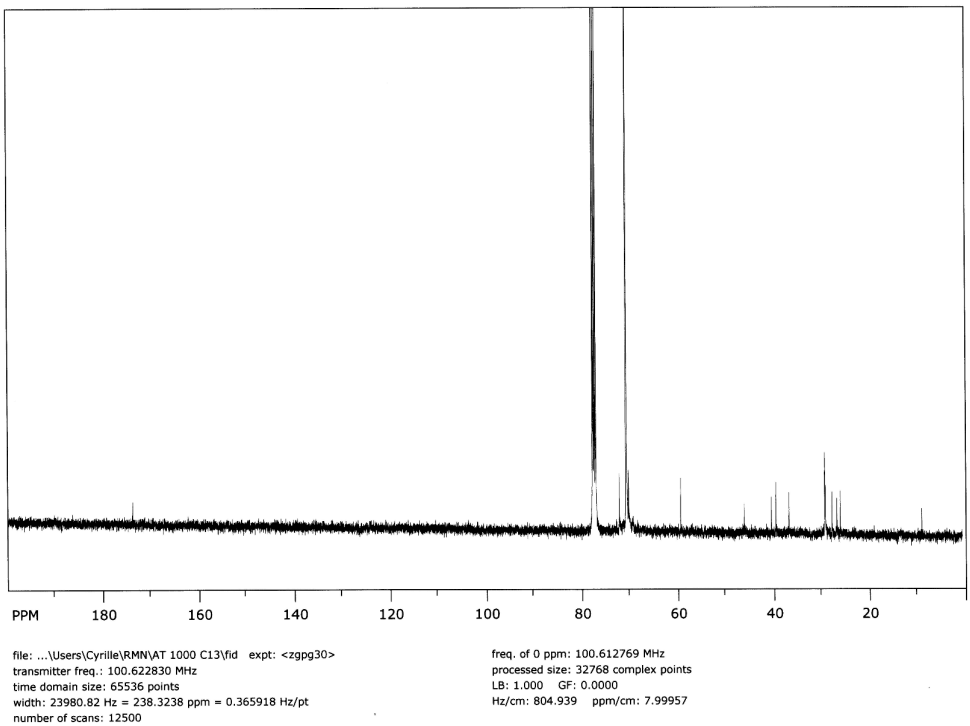

Figure S8. ^{13}C NMR spectrum for compound **6**.

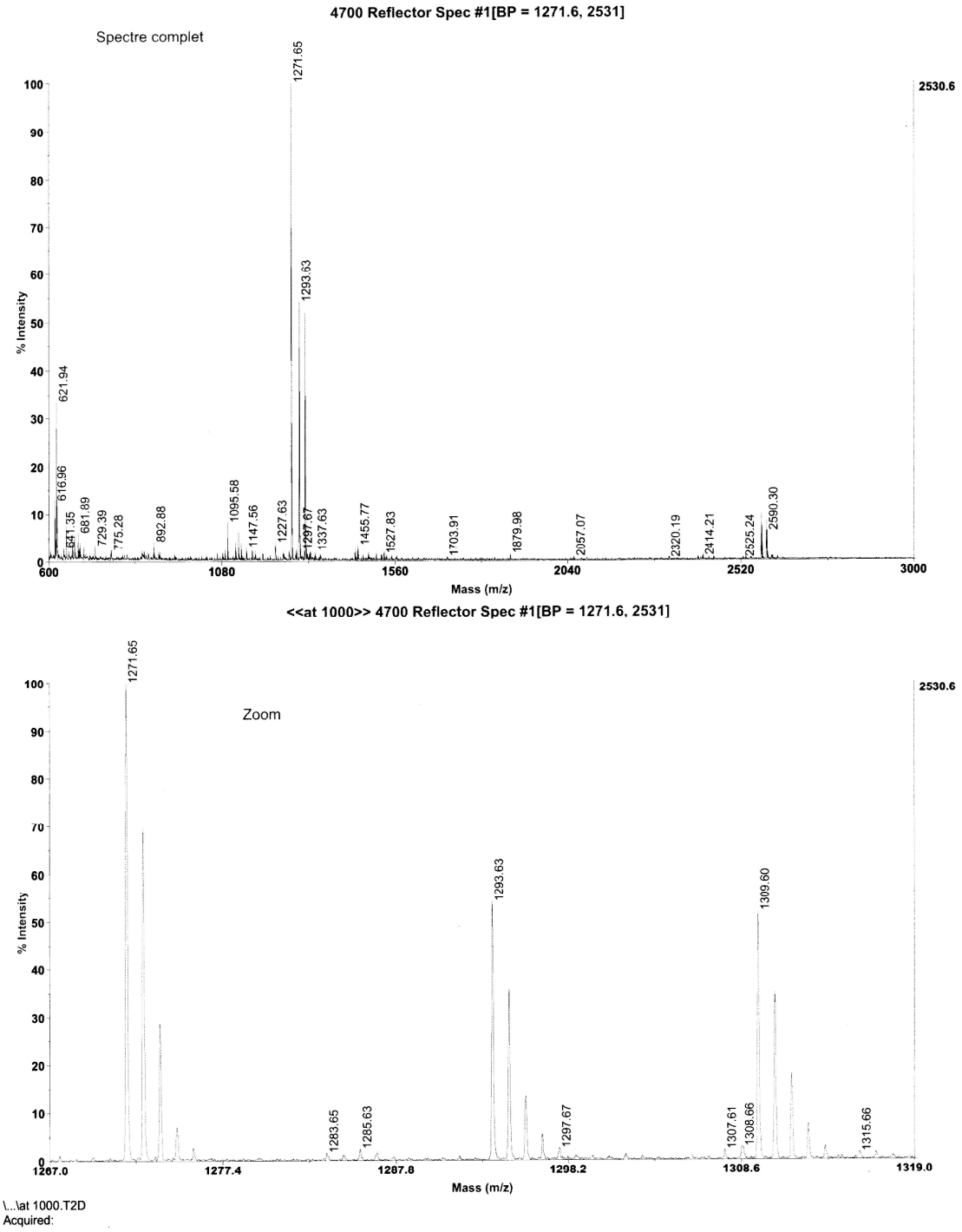

Figure S9. Mass spectrum for compound **6**.

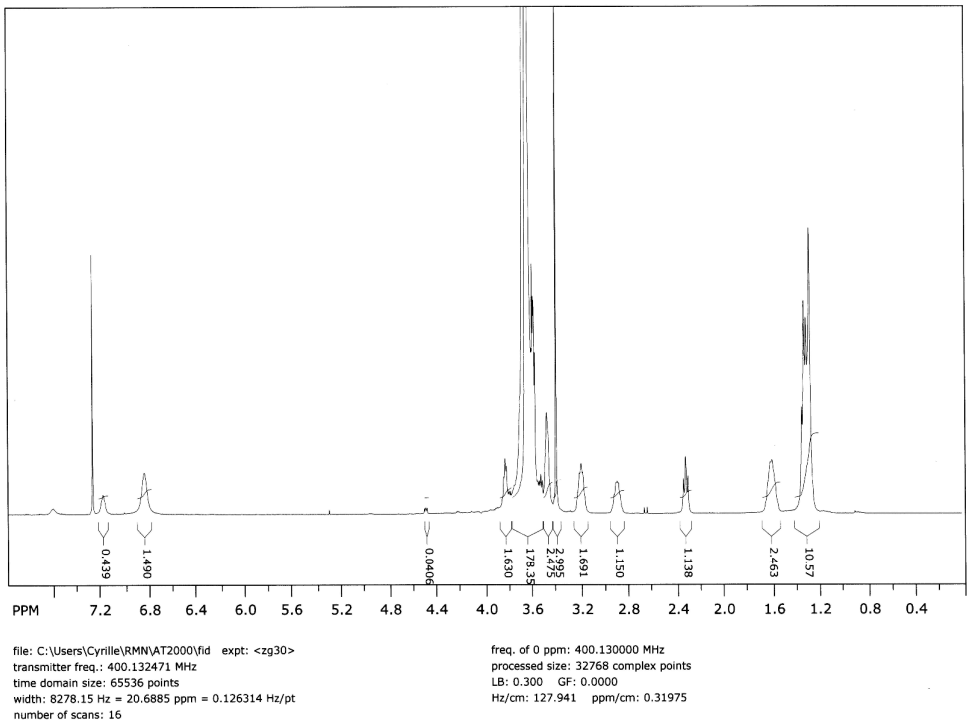

Figure S10. ^{1}H NMR spectrum for compound **7**.

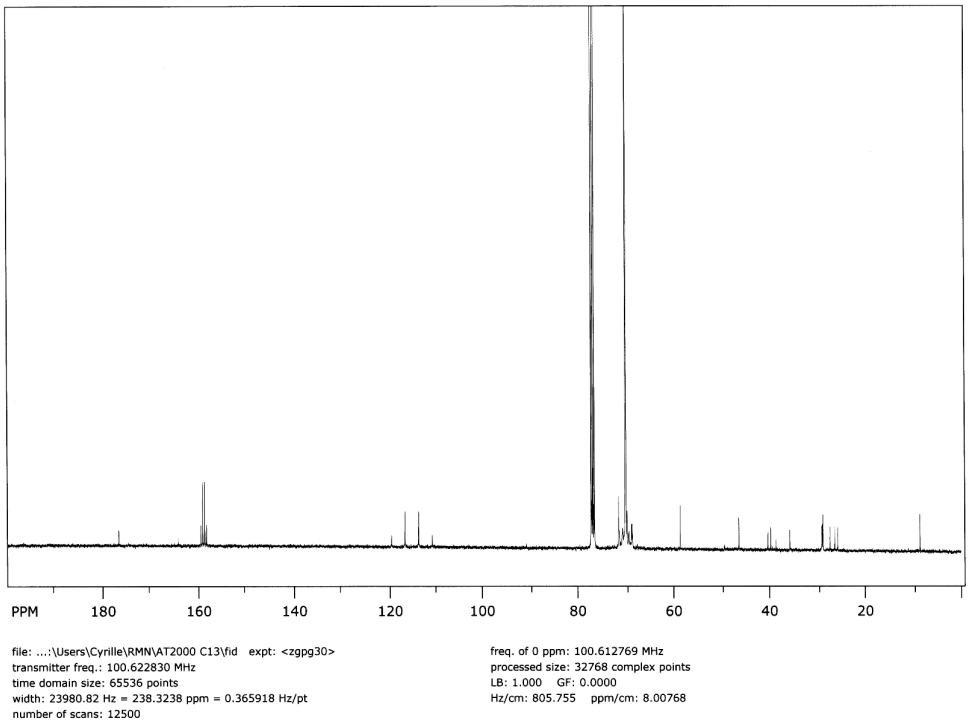

Figure S11. ^{13}C NMR spectrum for compound **7**.

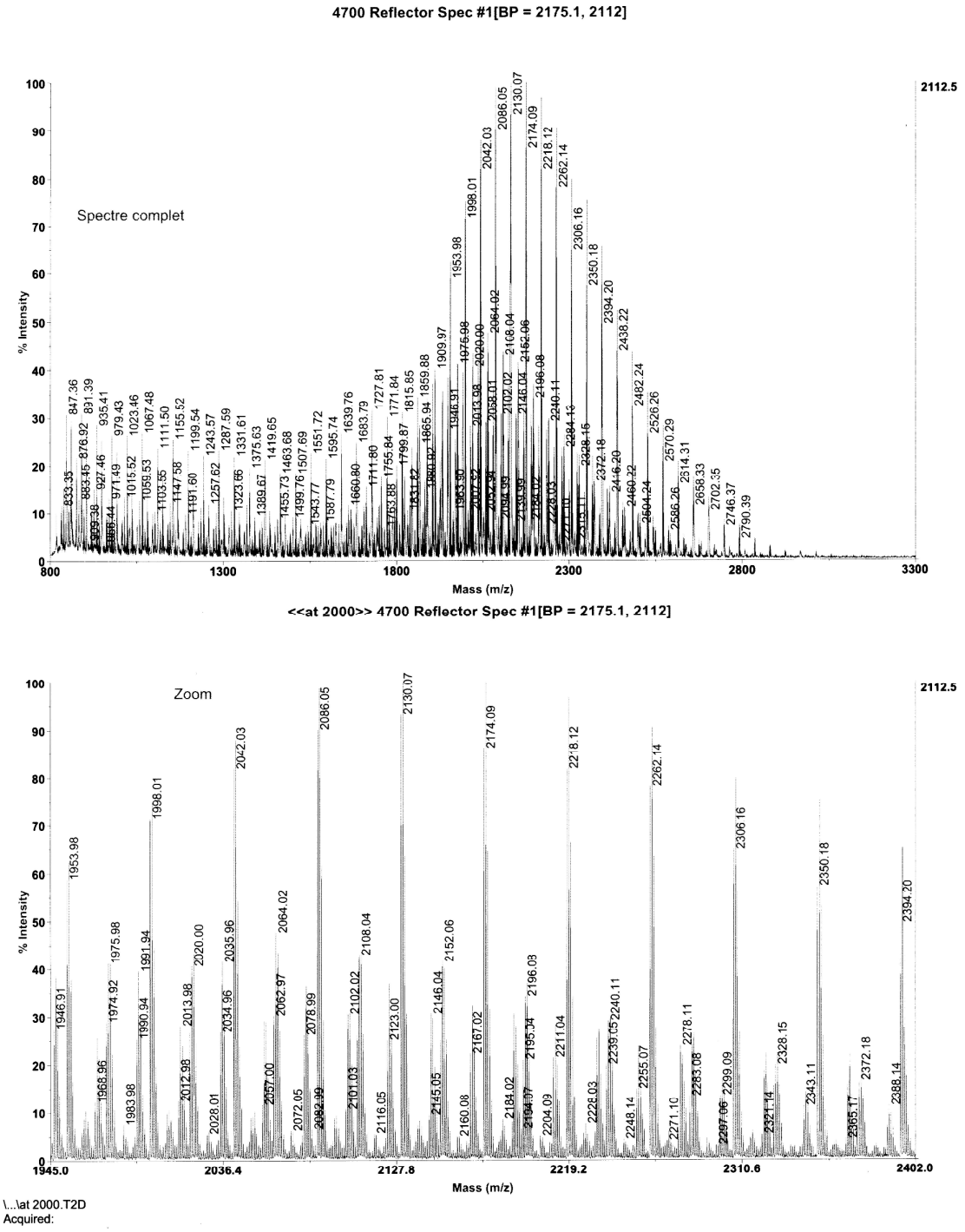

Figure S12. Mass spectrum for compound **7**.