

## Supporting Information

### Structure-based tuning of $T_m$ in lipid-like ionic liquids. Insights from

### $Tf_2N^-$ salts of gene transfection agents

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#### Synthesis of new ILs

Ionic liquids **1**, **2**, and **5** were prepared by the anion metathesis of the corresponding chloride salts (obtained commercially from Avanti Polar Lipids) with aqueous  $KN(SO_2CF_3)_2$ . Either of two metathesis procedures can be used. In procedure (1), the chloride salt of interest is added to water (~0.10g/ 2 mL) and the suspended material ultrasonicated until dissolution is complete, indicating the formation of stable liposomes of the cationic lipid. To the clear, colorless aqueous solution of liposome is added, in one portion, 1 mol eq. of  $KN(SO_2CF_3)_2$  in water (~0.10g/3mL). A milky emulsion is formed immediately, which settles into two distinct phases over a period of several days. Alternately, distinct phases may be more quickly achieved by centrifugation. In either event, the upper (aqueous) layer is discarded once settling is complete. The water-immiscible material is then washed with 2 x 2 mL portions of water, each of which is, in turn, separated from the hydrophobic salt and discarded. The lipophilic salt is then taken up into  $CH_2Cl_2$ , and a small amount of anhydrous  $MgSO_4$  added. The dehydrating agent is subsequently separated by filtration, and the pure IL is isolated by removal of the  $CH_2Cl_2$  *in vacuo*. Save for mechanical losses, the ILs are formed in quantitative yields. In procedure (2), the initial cationic lipid chloride salt is dissolved in  $CHCl_3$ , and this solution vigorously stirred together overnight with an aqueous solution of  $KN(SO_2CF_3)_2$ . The two liquid phases are allowed to separate, and the lower (organic) phase separated, dried over  $MgSO_4$  and worked-up as in procedure (1). The ILs formed were identical (NMR) regardless of the synthetic approach used.

Finally, in both procedures, the ILs were dried at 70 °C under mechanical pump vacuum for at least eight hours prior to examination by DSC. Also after drying, the salts were characterized by <sup>1</sup>H- and <sup>13</sup>C-NMR and ESI-MS (all spectra included in supplemental); all gave negative tests for residual Cl<sup>-</sup> ion.

**IL 1:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ<sub>H</sub> 4.38 (d, 2H); 4.02 (m, 1H); 3.68 (d, 2H); 3.21 (s, 9H); 3.34 (m, 4H); 1.58 (m, 8H); 1.25 (s, 52H); 0.88 (t, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ<sub>C</sub> 173.22; 173.00; 126.12. 121.88, 117.83; 113.38; 66.73; 65.45; 62.88; 54.78; 54.62; 54.34; 31.91; 29.77; 29.54; 29.33; 29.15; 27.23; 22.69; 14.21; 14.12; 13.77; MS (EI): m/z 666.7 (M<sup>+</sup>, calcd 666.6).

**IL 2:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ<sub>H</sub> 5.34 (m, 4H); 4.38 (d, 2H); 4.04 (m, 1H); 3.72 (d, 2H); 3.26 (s, 9H); 3.35 (m, 4H); 2.01 (m, 8H); 1.59- 1.70 (m, 4H); 1.26-1.30 (m, 40H); 0.88 (t, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ<sub>C</sub> 173.26; 173.20; 130.09; 130.05; 129.68; 121.83, 117.87; 117.58; 117.49; 113.30; 66.51; 65.50; 62.90; 54.45; 31.94; 29.74; 29.69; 29.56; 29.53; 29.39; 29.34; 22.70; 14.11; MS (EI): m/z 662.7 (M<sup>+</sup>, calcd 662.6).

**IL 3:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ<sub>H</sub> 8.75 (s, 1H); 7.31 (d, 1H); 7.27 (d, 1H); 4.16 (t, 2H); 3.95 (s, 3H); 1.75-1.95 (m, 2H); 1.20-1.45 (m, 30H); 0.88 (t, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ<sub>C</sub> 136.35; 126.35; 123.84; 122.32; 122.10; 117.86; 113.61; 50.45; 36.56; 32.12; 30.26; 29.90; 29.85; 29.78; 29.67; 29.55; 29.50; 29.07; 26.33; 22.88; 14.30.

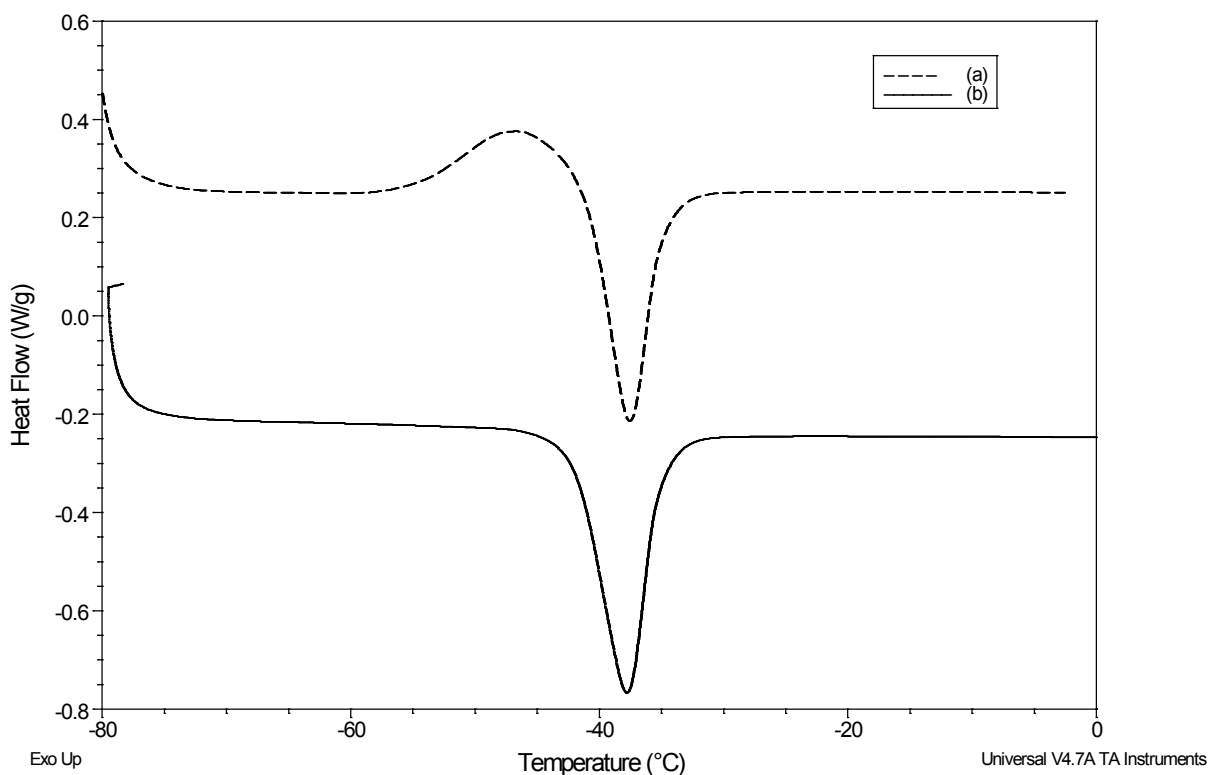
**IL 4:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ<sub>H</sub> 7.17 (d, 1H); 7.13 (d, 1H); 5.20-5.40 (m, 2H); 3.99 (t, 2H); 3.75 (s, 3H); 2.55 (s, 3H); 1.90-2.05 (m, 4H); 1.65-1.85 (m, 2H); 1.10-1.40 (m, 22H); 0.84 (t, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ<sub>C</sub> 143.85; 130.19; 129.85; 126.34; 122.72; 122.08; 120.93; 117.83; 113.56; 48.98; 35.44; 32.06; 29.93; 29.85; 29.69; 29.47; 29.43; 29.31; 29.11; 27.38; 27.33; 26.46; 22.84; 14.27; 9.69.

**IL 5:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ<sub>H</sub> 5.31-5.36 (m, 4H); 3.96 (m, 1H); 3.42-3.70 (m, 8H), 3.22 (s, 9H); 1.99-2.17 (m, 8H); 1.53-1.57 (m, 4H); 1.26-1.28 (m, 44H); 0.87 (t, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ<sub>C</sub> 130.49; 130.31; 130.28; 126.70, 122.46; 118.20; 113.95; 73.90; 72.55; 69.88; 55.41; 53.95; 32.43; 30.29; 30.05; 29.89; 29.84; 27.73; 26.30; 21.53; 21.50; 14.62; MS (EI): m/z 634.7 (M<sup>+</sup>, calcd 634.6).

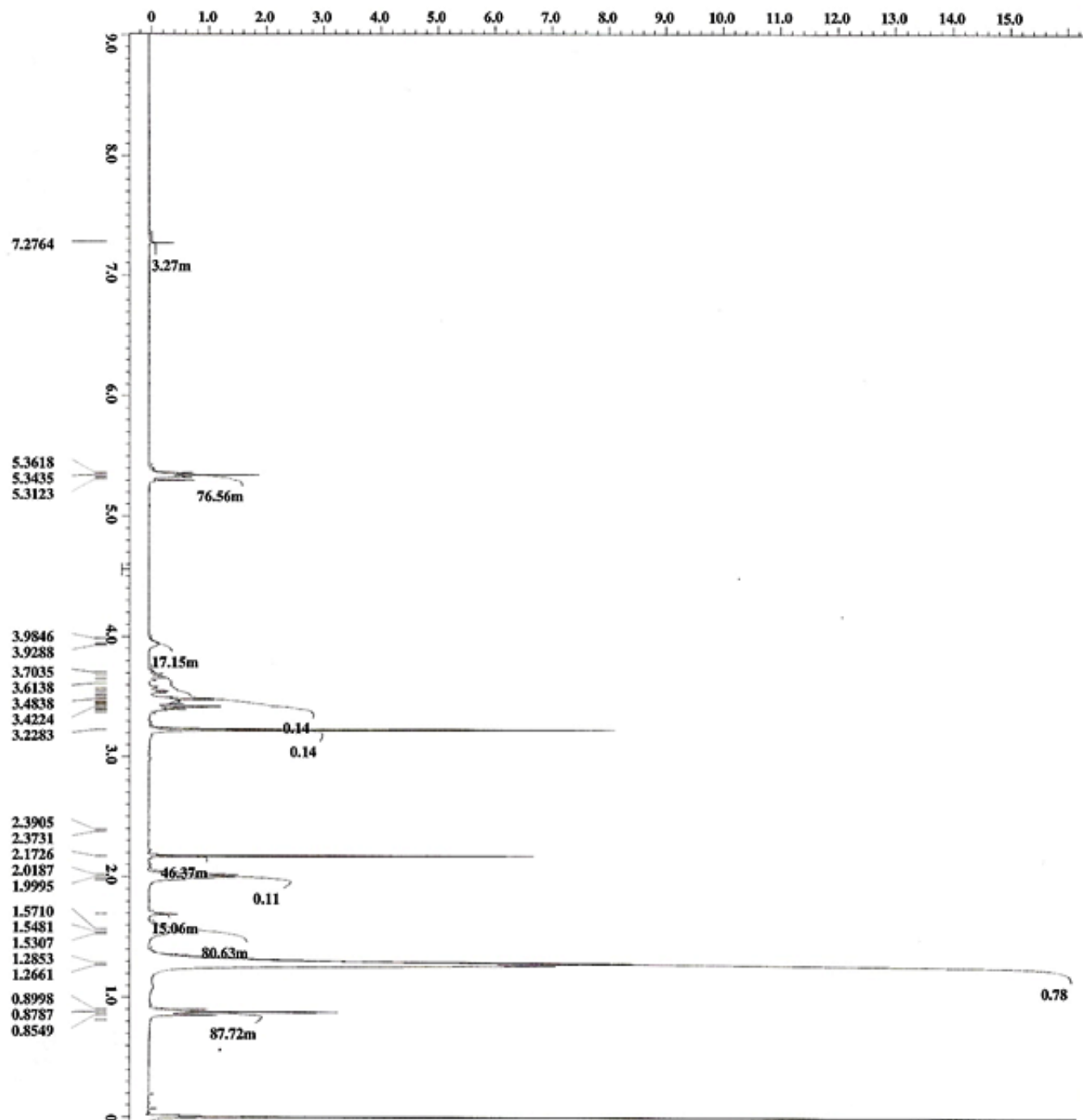
For the synthesis of **3**, **4** and **6** compounds, see the ref. 2a

### DSC Determinations

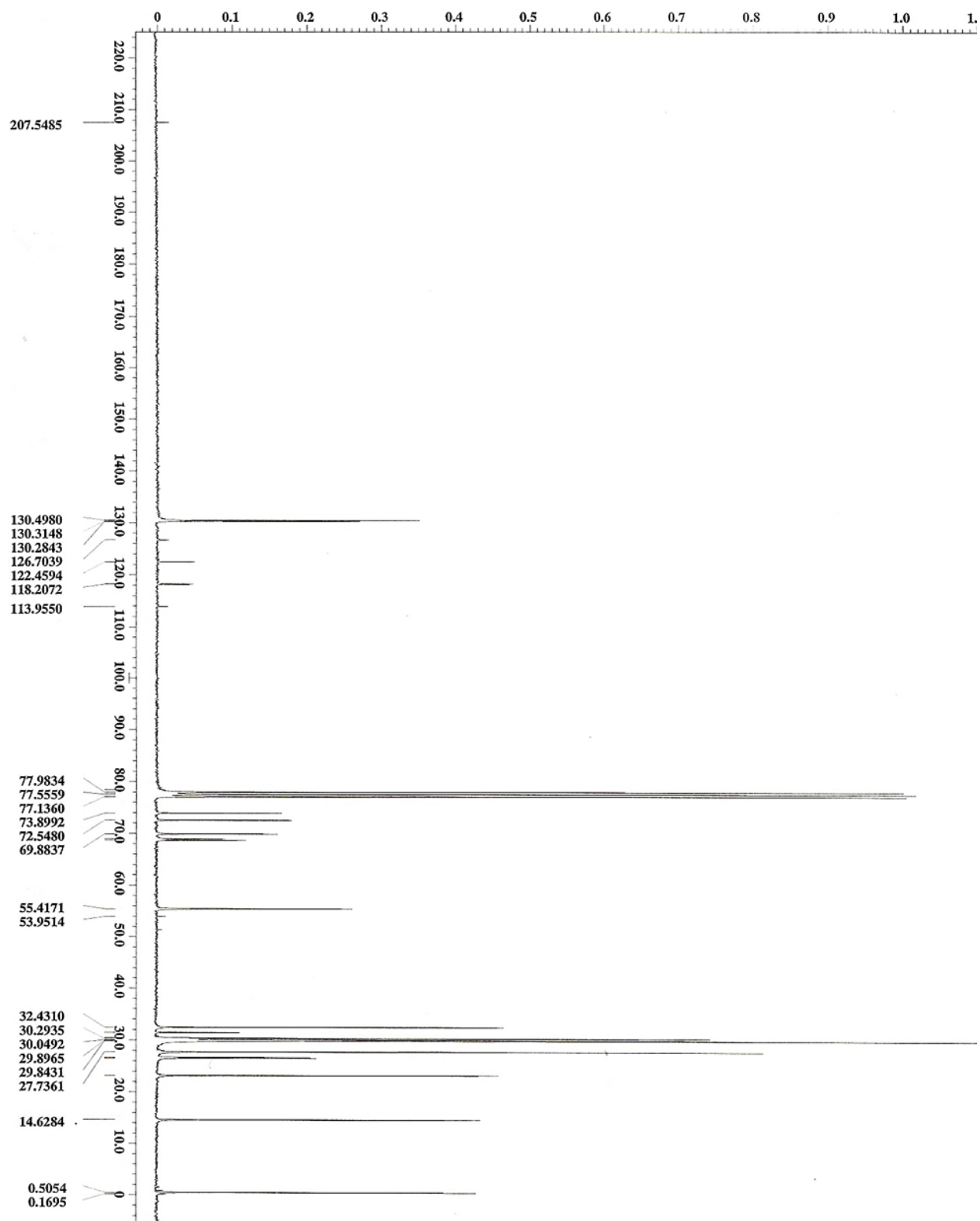
DSC curves were obtained using a TA Instruments Q2000 Differential Scanning Calorimeter with cooling/heating rates of 10°C/min. Sample sizes ranged from 5-20 mg. As is routine in DSC experiments on lipids (and many polymers), thermal pre-treatment of the samples were helpful in obtaining clean phase transitions (see example below).



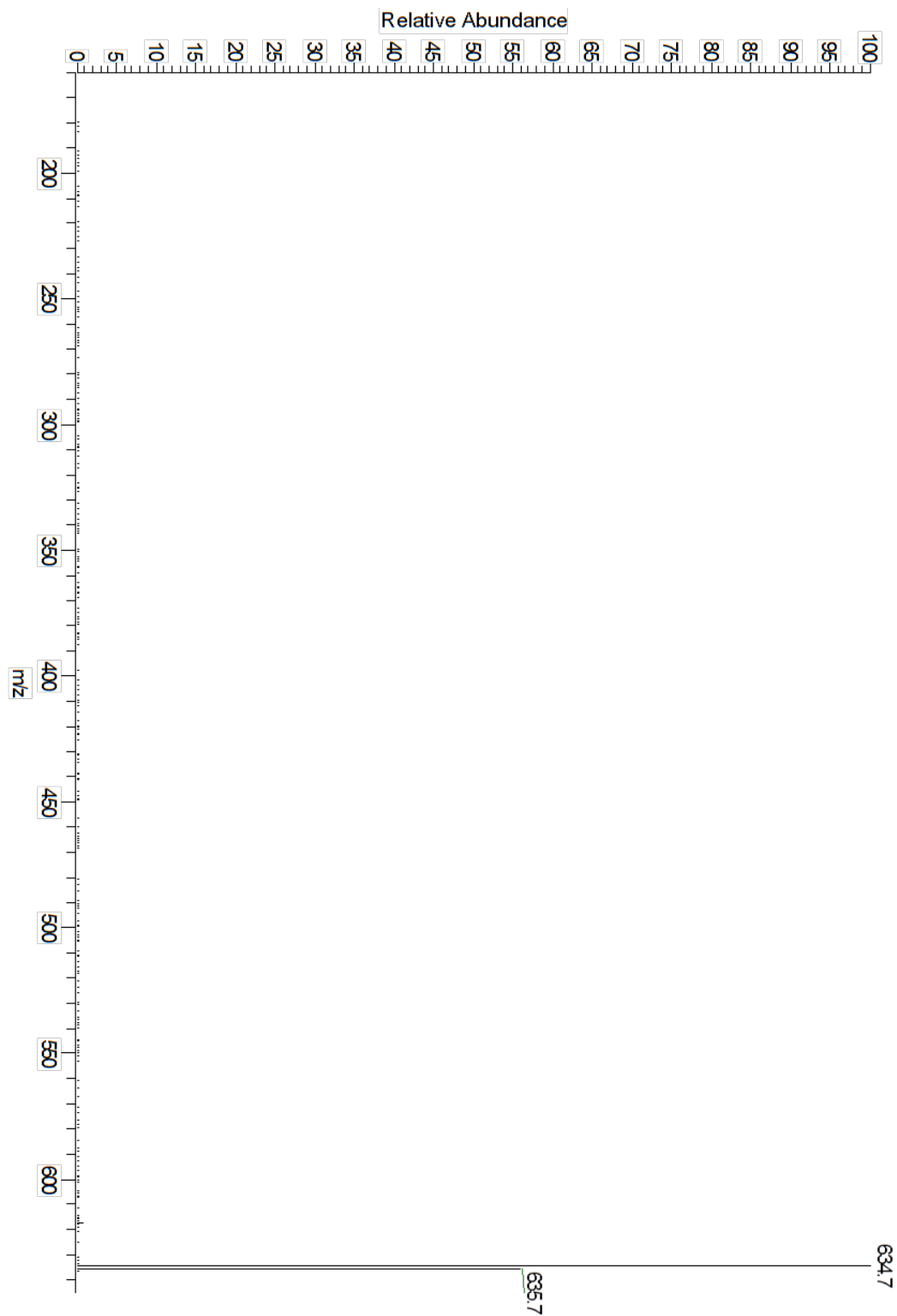
DSC curves for **5** (above) obtained using different heating procedures. Curve (a) was obtained by heating the sample at 75°C under N<sub>2</sub> for 10 minutes, followed by cooling at 10°C/min to -80°C and subsequent heating at 10°C/min, the last segment of which is shown. Curve (b) was obtained with the same pretreatment at 75°C and cooling to -80°C; however, in this run the sample was heating at 10°C/min to -43°C to initiate the exotherm, cooled at 10°C/min back to -80°C and then heated at 10°C to record the curve shown.



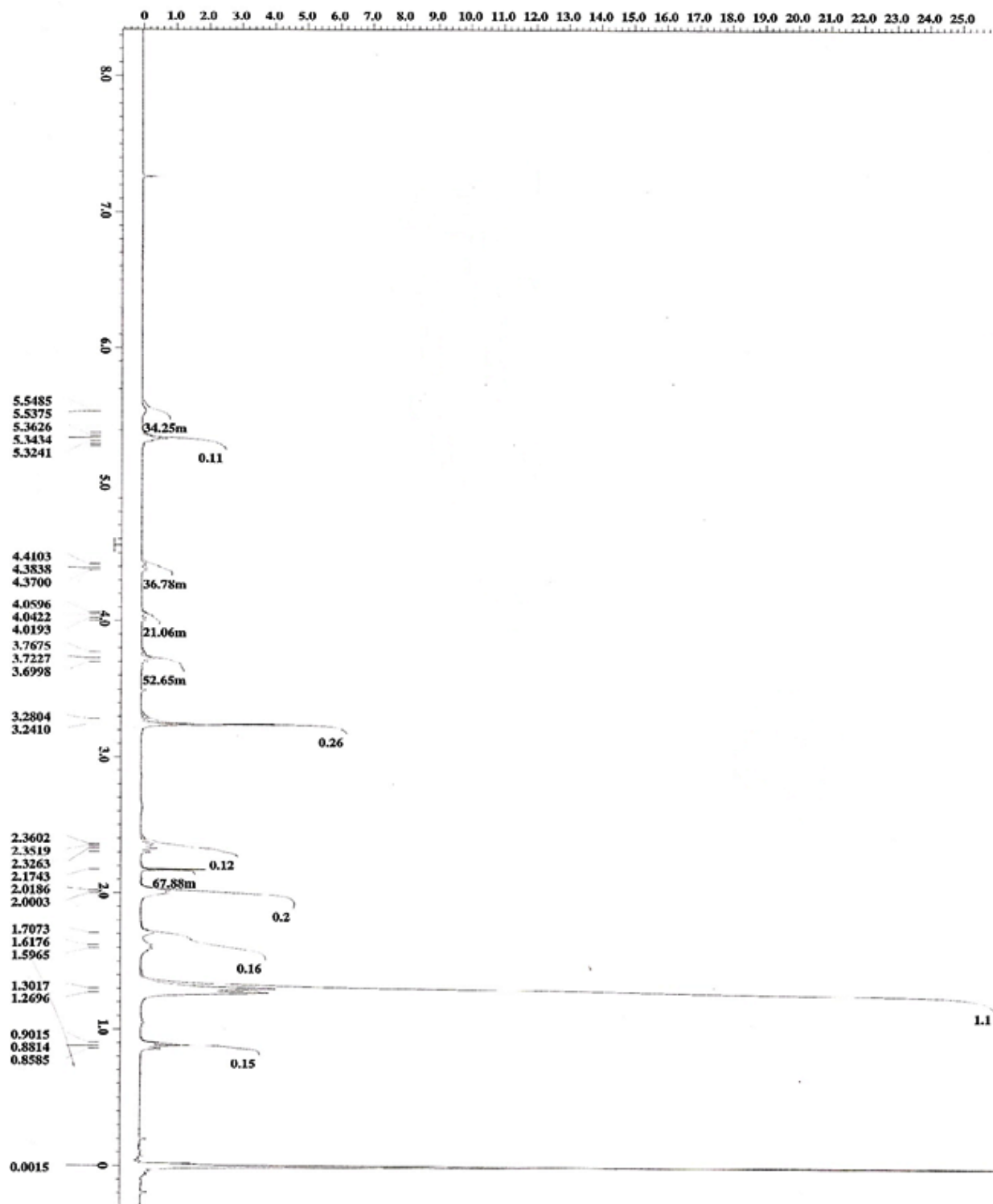
<sup>1</sup>H-NMR spectrum of 5



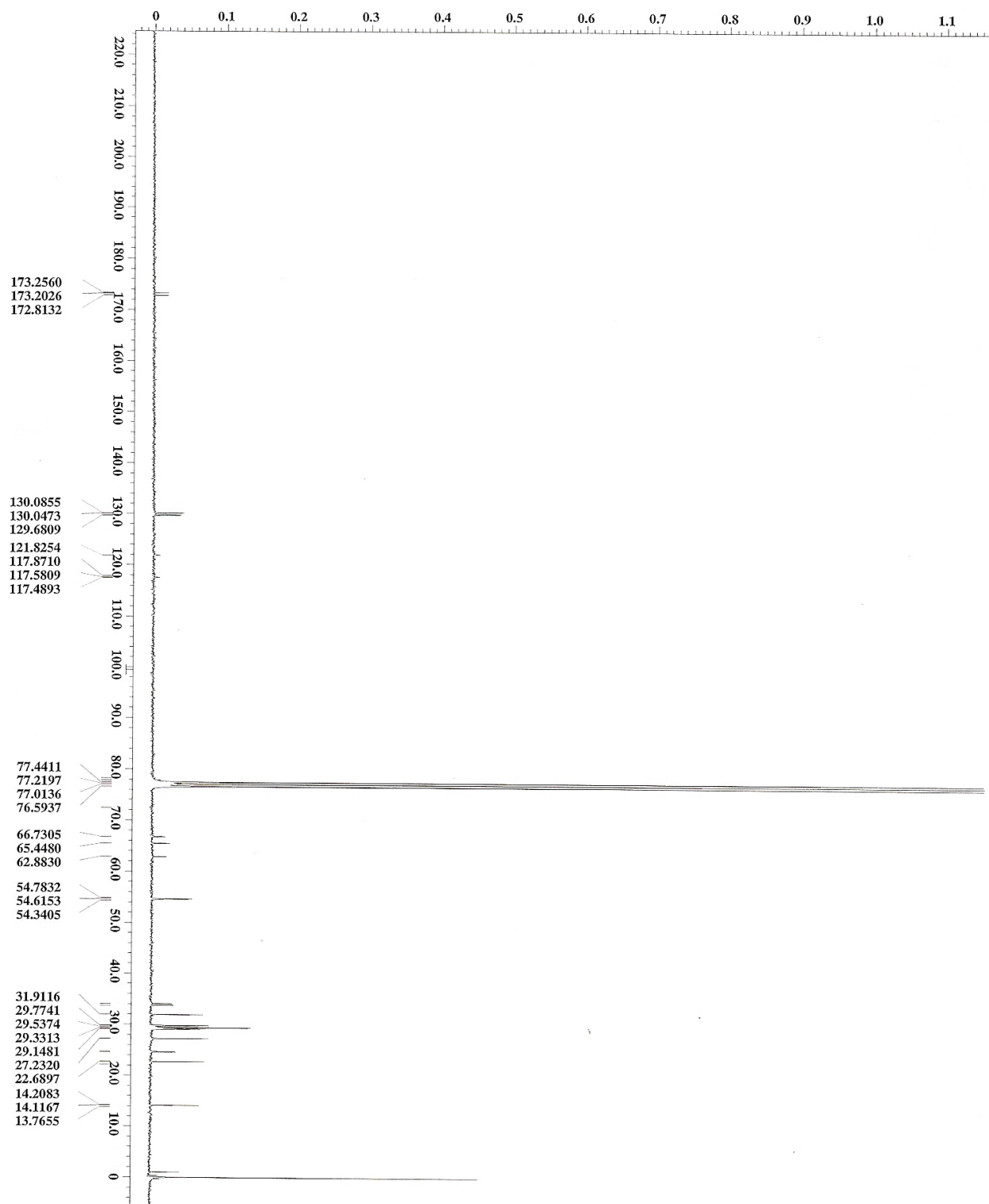
$^{13}\text{C}$ -NMR spectrum of 5



EI-MS spectrum of 5

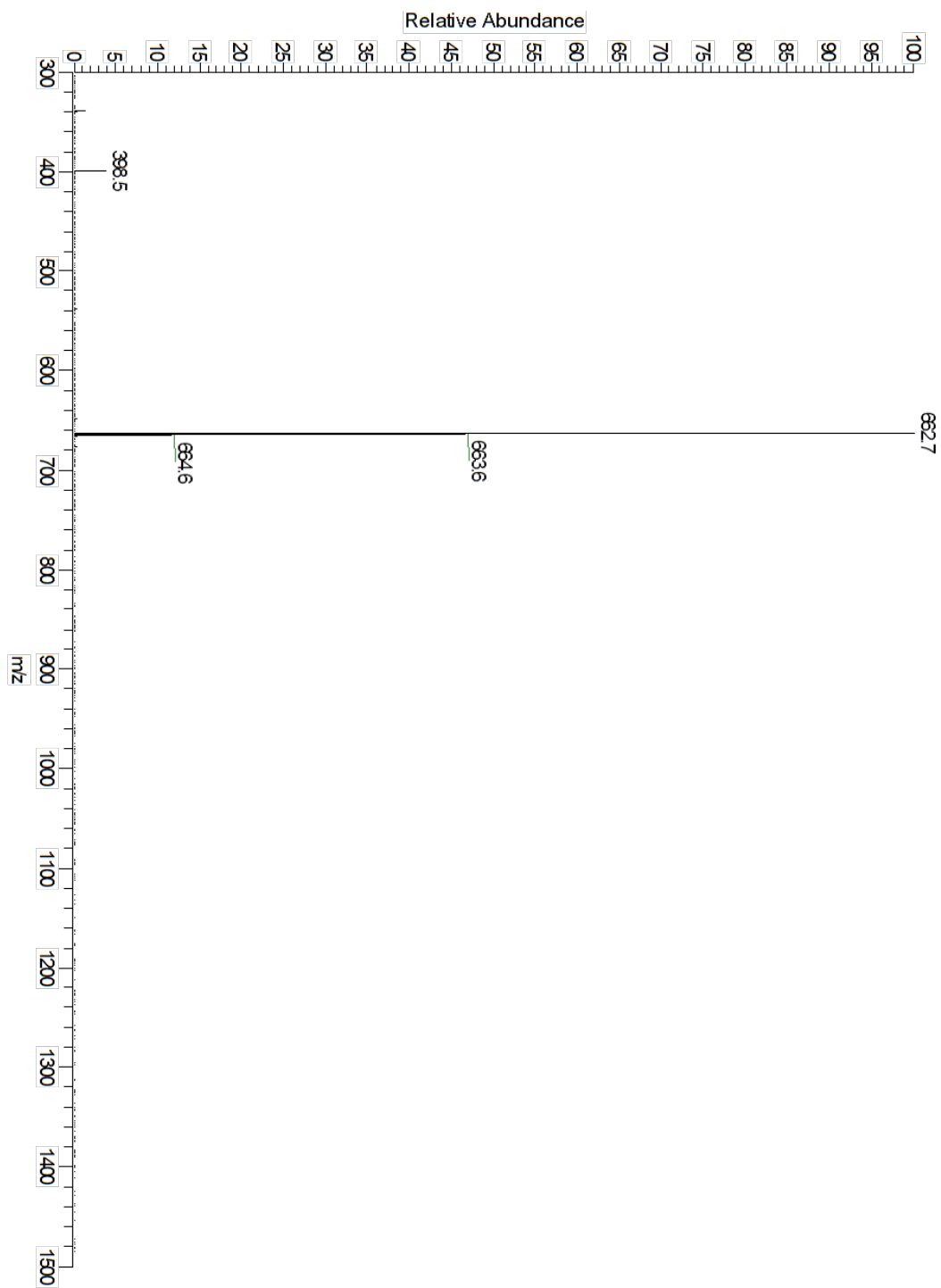


<sup>1</sup>H-NMR spectrum of 2

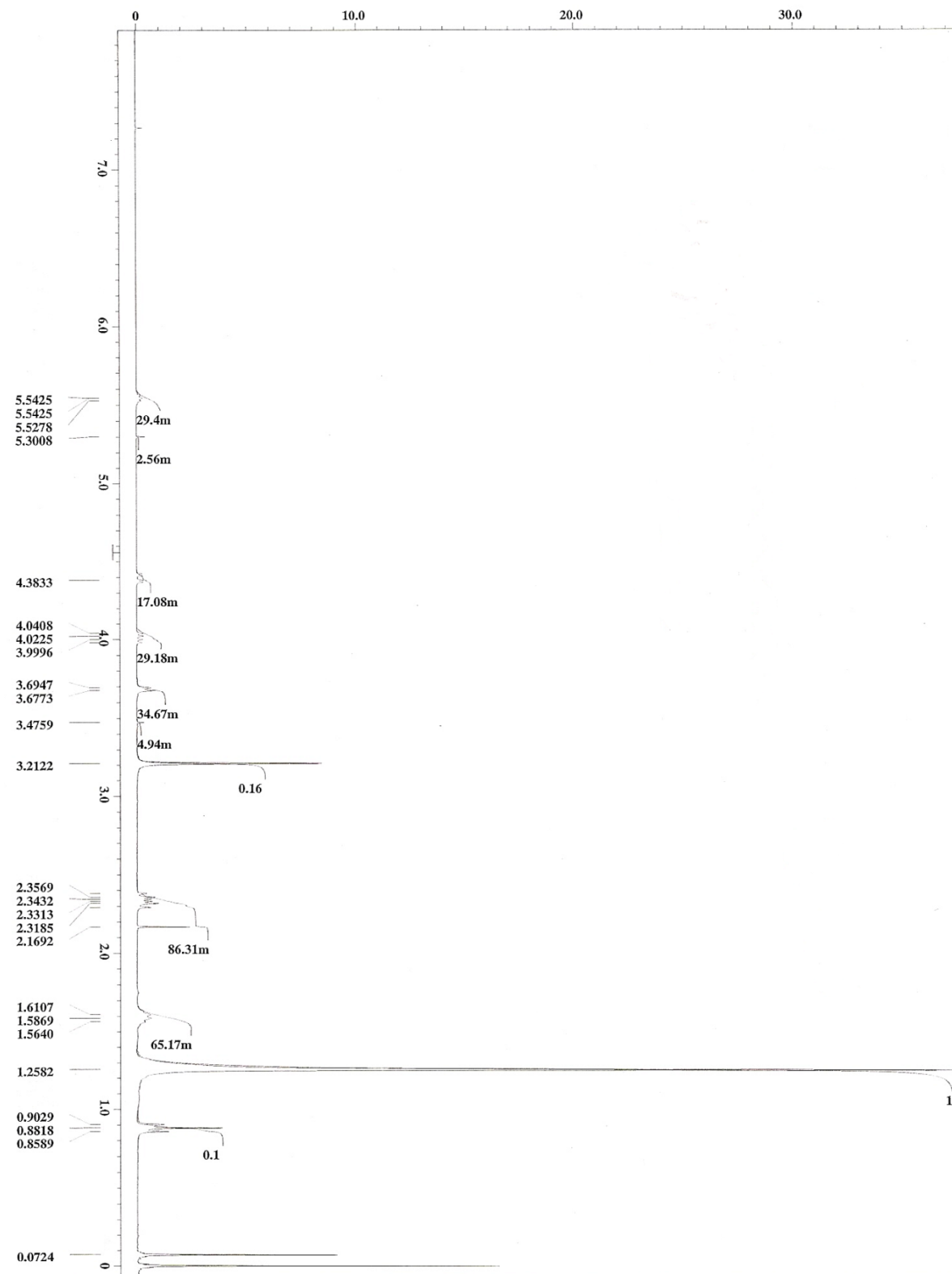


$^{13}\text{C}$ -NMR spectrum of 2

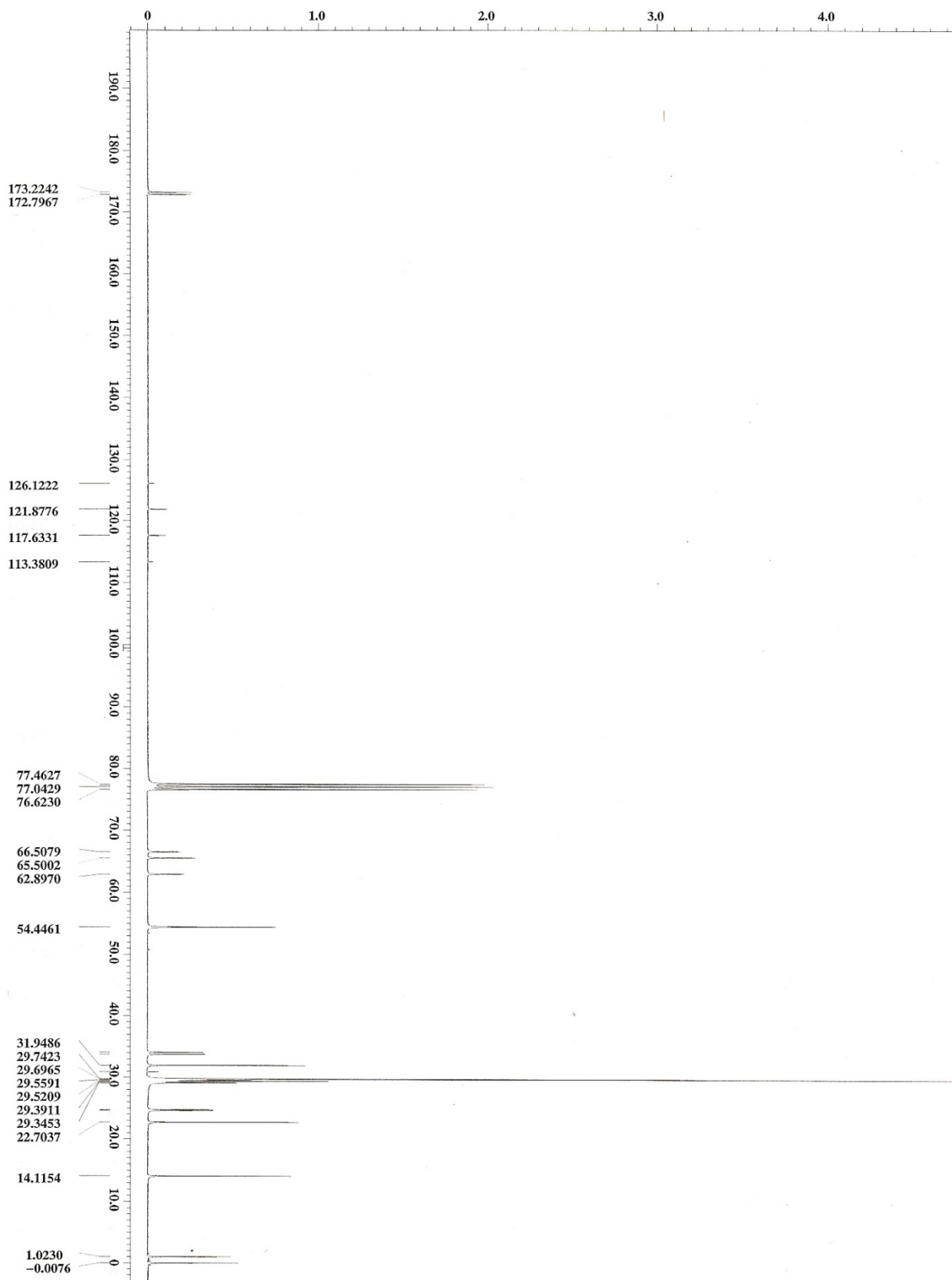




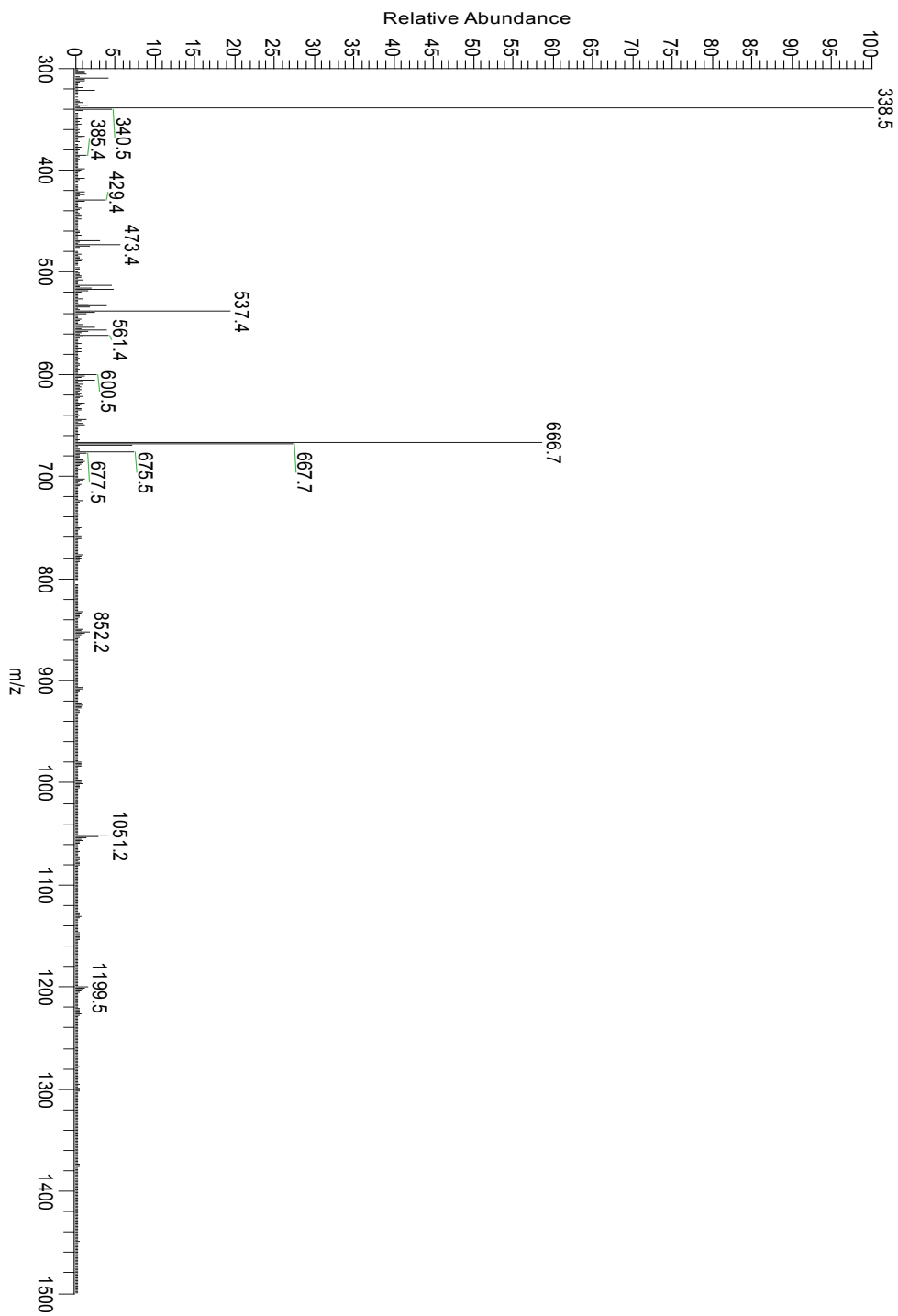
EI-MS spectrum of 2



<sup>1</sup>H-NMR spectrum of 1



$^{13}\text{C}$ -NMR spectrum of 1



EI-MS spectrum of 1