Self-Assemblies of Nucleolipid Supramolecular Synthons Show Unique Self-Sorting and Cooperative Assembling Process

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Electronic Supplementary Information

1. Materials: Tert-butyl(chloro)dimethylsilane (TBDMS-Cl), 4,4′-dimethoxytrityl chloride (DMT-Cl), octanoic acid, dodecanoic acid, palmatic acid, stearic acid, oleic acid, cytidine and dry pyridine were purchased from Sigma-Aldrich. EDC (1-(3-dimethyl aminopropyl)-3-ethyl carbodiimide hydrochloride) and 4-dimethylaminopyridine were obtained from Avra synthesis private limited. Myristic acid was procured from Fluka. Adenosine and guanosine were obtained from Sisco Research Laboratories and uridine from Molychem. Silicon wafers (N-type without dopant) were purchased from Sigma-Aldrich.

2. Instrumentation: NMR spectra were recorded on 400 MHz Jeol ECS-400 spectrometer and Bruker 500 MHz spectrometer. The morphology of gels was analyzed by using Zeiss Ultra Plus field-emission scanning electron microscope (FESEM). Powder X-ray diffraction (PXRD) spectra were obtained at room temperature using Bruker D8 Advance diffractometer (Cu Kα radiation, λ = 1.5406 Å). Rheology measurements were carried out in Anton Paar MCR 302 instrument. Single crystal X-ray data for structure determination were collected from Bruker APEX II DUO diffractometer using MoKα (λ = 0.71073 Å) and CuKα (λ = 1.54178 Å) graphite monochromated radiation. Mass measurements were recorded on Applied Biosystems 4800 Plus MALDI TOF/TOF analyzer and Water Synapt G2 High Definition mass spectrometers.

3. Synthesis of nucleolipids

Synthesis of 5′-*O*-TBDMS-adenosine (2): To a suspension of adenosine (1.0 g, 3.7 mmol, 1.0 equiv.) in anhydrous DMF (20 mL/g) was added TBDMS-Cl (0.68 g, 4.5 mmol, 1.2 equiv.) and imidazole (0.51 g, 7.5 mmol, 2.0 equiv.). The reaction mixture was allowed to stir at RT for 12 h under nitrogen atmosphere. The reaction mixture was diluted with dichloromethane and extracted with $NaHCO_3$ and dried over sodium sulfate. The organic extract was evaporated and the residue was purified by silica gel column chromatography (7% methanol in dichloromethane) to afford the product **2** as a solid (80%). TLC (CH_2Cl_2:MeOH = 95:5); R_f = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.29 (s, 1H), 8.14 (s, 1H), 7.31 (br, 2H), 5.91 (d, *J* = 5.2 Hz, 1H), 5.55 (d, *J* = 6.0 Hz,1H), 5.21 (d, *J* = 5.6 Hz, 1H), 4.55–4.51 (m, 1H), 4.19–4.16 (m, 1H), 3.97–3.94 (m, 1H), 3.88 (dd, J_1 = 11.4 Hz, J_2 = 3.8 Hz, 1H), 3.75 (dd, J_1 = 11.2 Hz, J_2 = 4.0 Hz, 1H), 0.88–0.86 (m, 9H), 0.05–0.04 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 156.0, 152.7, 149.4, 138.9, 119.0, 87.4, 84.4, 73.7, 69.9, 62.9, 25.8, 18.1, -5.4, -5.4; HRMS: m/z Calcd. for $C_{16}H_{28}N_5O_4Si$ $[M+H]^+$ = 382.1911, found = 382.1910.

General procedure for the synthesis of 2′,3′-*O*-disubstituted adenosine nucleolipids (4a–4d). 5′-*O*-TBDMS-adenosine **2** (1.0 equiv.), fatty acid (dodecanoic acid, myristic acid, palmitic acid and stearic acid, 2.0 equiv.), EDC (2.0 equiv.) and DMAP (0.2 equiv.) were dissolved in anhydrous pyridine (10 mL/g) under nitrogen atmosphere at RT. The reaction mixture was stirred overnight at RT. The reaction mixture was diluted with dichloromethane and extracted using water and dried over sodium sulfate. The organic extract was evaporated and the residue was purified by silica gel column chromatography (2% methanol in dichloromethane) to afford the product (**3a**–**3d**). Characterization data for **3a–3d** is provided below.

5′-*O*-TBDMS-adenosine nucleolipid (**3a**–**3d**) was dissolved in anhydrous THF and TBAF (1M in THF) was added drop wise under nitrogen atmosphere and the reaction mixture was stirred at RT for 30 min. The mixture was diluted with dichloromethane and extracted using

water and dried over sodium sulfate. The organic extract was evaporated and the residue was purified by silica gel column chromatography (2.5% methanol in dichloromethane) to afford adenosine nucleolipid **4a**–**4d** in good yields**.** Characterization data for **4a–4d** is provided below.

General procedure for the synthesis of 2′,3′-*O*-disubstituted uridine nucleolipids (7a–7e): 5′-*O*-DMT–protected uridine **6**[S1] (1.0 equiv), fatty acid (octanoic acid, dodecanoic acid, myristic acid, palmitic acid and oleic acid, 2.1 equiv), EDC (2.1 equiv) and DMAP (0.3 equiv) were dissolved in anhydrous dichloromethane (10 mL/g of **6**). The reaction mixture was stirred for 12 h at room temperature under nitrogen atmosphere. After completion of the reaction, the reaction mixture was diluted with dichloromethane and extracted using saturated NH_4Cl solution and dried over sodium sulfate. The product was treated with 3% trichloroacetic acid (TCA) in dichloromethane for 30 min at RT to remove DMT group. The solvent was evaporated, and the resultant residue was purified by silica gel column chromatography (40% ethyl acetate in hexane) to obtain the uridine nucleolipids (**7a**–**7e**). Characterization data for **7a–7e** is provided below.

Characterization data for compounds 4a-4d and 7a-7e

Compound 3a: Colourless solid, 82% yield. TLC (CH_2Cl_2:MeOH = 95:5); R_f = 0.48; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.31 (br, 1H), 8.24 (br, 1H), 6.34 (d, J = 6.8 Hz, 1H), 6.28–6.26 (br, 2H), 5.74–5.71 (m, 1H), 5.54–5.52 (m, 1H), 4.31–4.26 (m, 1H), 3.95 (dd, J_1 = 11.4 Hz, J_2 = 2.2 Hz, 1H), 3.89 (dd, J_1 = 11.2 Hz, J_2 = 2.0 Hz, 1H), 2.37 (t, J = 7.4 Hz, 2H), 2.26 (t, J = 7.6 Hz, 2H), 1.69–1.62 (m, 2H), 1.56–1.49 (m, 2H), 1.26–1.20 (m, 32H), 0.96 (s, 9H), 0.89–0.85 (m, 6H), 0.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.8, 172.3, 155.7, 153.1, 150.2, 138.6, 119.5, 85.1, 84.5, 74.3, 71.8, 63.3, 34.2, 33.9, 32.1, 29.8, 29.8, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 26.1, 25.1, 25.0, 24.8, 22.8, 18.6, 14.2, -5.3; HRMS: m/z Calcd. for $C_{40}H_{72}N_5O_6Si$ $[M+H]^+$ = 746.5252, found = 746.5242.

Compound 3b: Colourless solid, 88% yield. TLC (CH_2Cl_2:MeOH = 95:5); R_f = 0.32; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.34 (s, 1H), 8.22 (s, 1H), 6.35 (d, J = 7.2 Hz, 1H), 5.92 (br, 2H), 5.73 (dd, J_1 = 7.0 Hz, J_2 = 5.4 Hz, 1H), 5.54 (dd, J_1 = 5.2 Hz, J_2 = 2.4 Hz, 1H), 4.29–4.27 (m, 1H), 3.95 (dd, J_1 = 11.4 Hz, J_2 = 2.2 Hz, 1H), 3.89 (dd, J_1 = 11.6 Hz, J_2 = 2.2 Hz, 1H), 2.37 (t, J = 7.4 Hz, 2H), 2.26 (t, J = 7.6 Hz, 2H), 1.68–1.60 (m, 2H), 1.55–1.47 (m, 2H), 1.29–1.20 (m, 40H), 0.96 (s, 9H), 0.89–0.85 (m, 6H), 0.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.8, 172.3, 155.6, 153.3, 150.3, 138.6, 119.7, 85.0, 84.4, 74.2, 71.8, 63.3, 34.2, 33.9, 32.1, 29.8, 29.8, 29.8, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 26.1, 25.0, 24.8, 22.8, 18.6, 14.3, -5.3, -5.3; HRMS: m/z Calcd. for $C_{44}H_{80}N_5O_6Si$ $[M+H]^+$ = 802.5878, found = 802.5880.

Compound 3c: Colourless solid, 70% yield. TLC (CH_2Cl_2:MeOH = 95:5); R_f = 0.41; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.32 (s, 1H), 8.24 (s, 1H), 6.35 (d, J = 6.8 Hz, 1H), 6.16 (br, 2H), 5.73 (dd, J_1 = 6.8 Hz, J_2 = 5.2 Hz, 1H), 5.53 (dd, J_1 = 5.4 Hz, J_2 = 2.2 Hz, 1H), 4.29–4.28 (m, 1H), 3.95 (dd, J_1 = 11.4 Hz, J_2 = 2.2 Hz, 1H), 3.89 (dd, J_1 = 11.6 Hz, J_2 = 2.0 Hz, 1H), 2.37 (t, J = 7.4 Hz, 2H), 2.26 (t, J = 7.6 Hz, 2H), 1.67–1.60 (m, 2H), 1.55–1.47 (m, 2H), 1.29–1.20 (m, 48H), 0.96 (s, 9H), 0.89–0.86 (m, 6H), 0.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.9, 172.3, 155.7, 153.2, 150.2, 138.6, 119.5, 85.0, 84.4, 74.3, 71.8, 63.3, 34.2, 33.9, 32.1, 29.9, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 26.1, 25.1, 25.0,

24.8, 22.8, 18.6, 14.3, -5.3; HRMS: m/z Calcd. for $C_{48}H_{88}N_5O_6Si$ $[M+H]^+$ = 858.6505, found = 858.6500.

Compound 3d: Colourless solid, 72% yield. TLC (CH_2Cl_2:MeOH = 95:5); R_f = 0.42; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.35 (s, 1H), 8.22 (s, 1H), 6.35 (d, J = 6.8 Hz, 1H), 5.83 (br, 2H), 5.73 (dd, J_1 = 6.8 Hz, J_2 = 5.2 Hz, 1H), 5.54 (dd, J_1 = 5.2 Hz, J_2 = 2.4 Hz, 1H), 4.29–4.27 (m, 1H), 3.95 (dd, J_1 = 11.2 Hz, J_2 = 2.4 Hz, 1H), 3.89 (dd, J_1 = 11.6 Hz, J_2 = 2.4 Hz, 1H), 2.37 (t, J = 7.4 Hz, 2H), 2.26 (t, J = 7.6 Hz, 2H), 1.68–1.60 (m, 2H), 1.55–1.49 (m, 2H), 1.31–1.20 (m, 56H), 0.96 (s, 9H), 0.89–0.86 (m, 6H), 0.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.8, 172.3, 155.6, 153.4, 150.4, 138.7, 119.8, 85.0, 84.4, 74.2, 71.8, 63.3, 34.2, 33.9, 32.1, 29.9, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 26.1, 25.0, 24.8, 22.8, 18.6, 14.3, -5.3, -5.3; HRMS: m/z Calcd. for $C_{52}H_{96}N_5O_6$ Si $[M+H]^+$ = 914.7130, found = 914.7141.

Compound 4a: Colourless solid, 73% yield. TLC (CH_2Cl_2:MeOH = 95:5); R_f = 0.48; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.33 (s, 1H), 7.81 (s, 1H), 6.62 (br, 1H), 6.05–6.03 (br, 1H), 6.01–6.00 (m, 2H), 5.70–5.69 (m, 1H), 4.34 (br, 1H), 3.98 (dd, J_1 = 13.0 Hz, J_2 = 1.4 Hz, 1H), 3.87–3.84 (m, 1H), 2.39 (t, J = 7.6 Hz, 2H), 2.23 (t, J = 7.6 Hz, 2H), 1.69–1.62 (m, 2H), 1.56–1.48 (m, 2H), 1.26–1.22 (m, 32H), 0.89–0.85 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.6, 171.9, 156.2, 152.9, 148.8, 140.3, 121.3, 88.9, 86.8, 72.8, 72.8, 62.8, 34.3, 33.8, 32.1, 29.8, 29.8, 29.7, 29.7, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 25.1, 24.8, 22.8, 14.2; HRMS: m/z Calcd. for $C_{34}H_{58}N_5O_6$ $[M+H]^+$ = 632.4387, found = 632.4377.

Compound 4b: Colourless solid, 83% yield. TLC (CH_2Cl_2:MeOH = 95:5); R_f = 0.36; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.34 (br, 1H), 7.81 (s, 1H), 6.62 (d, J = 10.8 Hz, 1H), 6.01–6.00 (m, 1H), 5.95–5.80 (br, 2H), 5.70 (dd, J_1 = 4.4 Hz, J_2 = 0.8 Hz, 1H), 4.34 (br, 1H), 3.99–3.96 (m, 1H), 3.89–3.83 (m, 1H), 2.39 (t, J = 7.4 Hz, 2 H), 2.23 (t, J = 7.6 Hz, 2H), 1.70–1.62 (m, 2H), 1.58–1.47 (m, 2H), 1.32–1.22 (m, 40H), 0.89–0.85 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.6, 171.9, 156.1, 152.9, 148.9, 140.3, 121.4, 100.1, 88.9, 86.8, 72.8, 72.8, 62.8, 34.3, 33.8, 32.1, 29.8, 29.8, 29.8, 29.8, 29.7, 29.7, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 25.1, 24.8, 22.8, 14.2; HRMS: m/z Calcd. for $C_{38}H_{66}N_5O_6$ $[M+H]^+$ = 688.5013, found = 688.5002.

Compound 4c: Colourless solid, 75% yield. TLC (CH_2Cl_2:MeOH = 95:5); R_f = 0.37; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.35 (br, 1H), 7.81 (s, 1H), 6.59 (d, J = 11.2 Hz, 1H), 6.01–6.00 (m, 1H), 5.85–5.73 (br, 2H), 5.70 (dd, J_1 = 4.6 Hz, J_2 = 0.6 Hz, 1H), 4.34 (br, 1H), 4.00–3.97 (m, 1H), 3.89–3.83 (m, 1H), 2.39 (t, J = 7.6 Hz, 2H), 2.23 (t, J = 7.6 Hz, 2H), 1.68–1.63 (m, 2H), 1.56–1.47 (m, 2H), 1.31–1.22 (m, 48H), 0.89–0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.6, 171.9, 156.1, 152.9, 148.9, 140.3, 121.4, 88.9, 86.9, 72.8, 72.8, 62.8, 34.3, 33.8, 32.1, 29.9, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 25.1, 24.8, 22.8, 14.3; HRMS: m/z Calcd. for $C_{42}H_{74}N_5O_6$ $[M+H]^+$ = 744.5639, found = 744.5622.

Compound 4d: Colourless solid, 87% yield. TLC (CH_2Cl_2:MeOH = 95:5); R_f = 0.38; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.35 (s, 1H), 7.80(s, 1H), 6.61 (d, J = 11.2 Hz, 1H), 6.03–5.98 (m, 2H), 5,71–5.70 (m, 2H), 4.34 (br, 1H), 4.00–3.97 (m, 1H), 3.89–3.83 (m, 1H), 2.39 (t, J = 7.6 Hz, 2H), 2.23 (t, J = 7.4 Hz, 2H), 1.68–1.60 (m, 2H), 1.56–1.48 (m, 2H), 1.29–1.23 (m, 56H), 0.89–0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.6, 171.9, 156.1, 153.0, 148.9, 140.3, 121.4, 100.2, 88.9, 86.9, 72.8, 62.8, 34.3, 33.8, 32.1, 29.9, 29.8,

29.8, 29.7, 29.6, 29.5, 29.5, 29.4, 29.4, 29.2, 25.1, 24.8, 22.8, 14.3; HRMS: m/z Calcd. for $C_{46}H_{82}N_5O_6$ $[M+H]^+$ = 800.6265, found = 800.6265.

Compound 7a: Colourless solid, 73% yield over two steps. TLC (CH_2Cl_2:MeOH = 95:5); R_f = 0.29; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.04 (br, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 6.06–6.03 (m, 1H), 5.78 (d, *J* = 8.0 Hz, 1H), 5.48–5.45 (m, 2H), 4.19–4.18 (m, 1H), 3.92 (dd, J_1 = 12.2 Hz, J_2 = 2.2 Hz, 1H), 3.86 (dd, J_1 = 12.4 Hz, J_2 = 2.0 Hz, 1H), 2.38–2.29 (m, 4H), 1.66–1.54 (m, 4H), 1.30–1.25 (m, 16H), 0.90–0.85 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 173.1, 172.7, 163.2, 150.5, 140.9, 103.3, 87.9, 83.7, 73.0, 71.1, 62.0, 34.1, 33.9, 31.8, 29.2, 29.1, 29.1, 29.0, 25.0, 24.8, 22.7, 14.2; HRMS: m/z Calcd. for $C_{25}H_{41}N_2O_8$ $[M+H]^+$ = 497.2863, found = 497.2855.

Compound 7b: Colourless solid, 78% yield over two steps. TLC (CH_2Cl_2:MeOH = 95:5); R_f = 0.42; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.78 (br, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 6.05–6.01 (m, 1H), 5.78 (dd, J_1 = 8.2 Hz, J_2 = 2.2 Hz, 1H), 5.49–5.45 (m, 2H), 4.20–4.18 (m, 1H), 3.95 (dd, J_1 = 12.0 Hz, J_2 = 2.0 Hz, 1H), 3.86 (dd, J_1 = 12.0 Hz, J_2 = 2.4 Hz, 1H), 2.38–2.29 (m, 4H), 1.66–1.54 (m, 4H), 1.29–1.25 (m, 32H), 0.89–0.85 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 173.1, 172.7, 163.0, 150.4, 140.9, 103.4, 88.0, 83.7, 73.0, 71.0, 62.0, 34.1, 33.9, 32.1, 29.8, 29.6, 29.5, 29.4, 29.3, 29.2, 25.0, 24.8, 22.8, 14.3; HRMS: m/z Calcd. for $C_{33}H_{57}N_2O_8$ $[M+H]^+$ = 609.4115, found = 609.4107.

Compound 7c: Colourless solid, 81% yield over two steps. TLC (CH_2Cl_2:MeOH = 95:5); R_f = 0.23; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.82 (br, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 6.05–6.01 (m, 1H), 5.78 (d, *J* = 8.0 Hz, 1H), 5.48–5.45 (m, 2H), 4.19–4.18 (m, 1H), 3.95 (dd, J_1 = 11.8 Hz, J_2 = 1.8 Hz, 1H), 3.86 (dd, J_1 = 12.0 Hz, J_2 = 2.0 Hz, 1H), 2.38–2.29 (m, 4H), 1.66–1.54 (m, 4H), 1.29–1.25 (m, 40 H), 0.89–0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 173.0, 172.6, 162.9, 150.4, 140.8, 103.4, 88.1, 83.7, 73.0, 71.0, 62.0, 34.2, 34.0, 32.1, 29.8, 29.8, 29.8, 29.6, 29.5, 29.4, 29.4, 29.3, 29.2, 25.0, 24.9, 22.8, 14.2; HRMS: m/z Calcd. for $C_{37}H_{65}N_2O_8$ $[M+H]^+$ = 665.4741, found = 665.4729.

Compound 7d: Colourless solid, 70% yield over two steps. TLC (CH_2Cl_2:MeOH = 95:5); R_f = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.41 (br, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 6.04–6.01 (m, 1H), 5.77 (dd, *J* = 8.0 Hz, 1H), 5.48–5.45 (m, 2H), 4.20–4.19 (m, 1H), 3.96 (dd, J_1 = 12.0 Hz, J_2 = 2.0 Hz, 1H), 3.86 (dd, J_1 = 12.2 Hz, J_2 = 2.2 Hz, 1H), 2.38–2.30 (m, 4H), 1.64–1.55 (m, 4H), 1.30–1.25 (m, 48H), 0.89–0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 173.1, 172.6, 162.7, 150.3, 140.7, 103.4, 88.1, 83.6, 73.0, 71.0, 62.0, 34.2, 33.9, 32.1, 29.9, 29.8, 29.8, 29.6, 29.5, 29.4, 29.3, 29.2, 25.0, 24.9, 22.8, 14.3; HRMS: m/z Calcd. for $C_{41}H_{73}N_2O_8$ $[M+H]^+$ = 721.5367, found = 721.5358.

Compound 7e: Colourless solid, 74% yield over two steps. TLC (CH_2Cl_2:MeOH = 95:5); R_f = 0.38; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.79 (br, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 6.04–6.02 (m, 1H), 5.78 (d, *J* = 8.0 Hz, 1H), 5.47–5.46 (m, 2H), 5.38–5.29 (m, 4H), 4.19–4.18 (m, 1H), 3.95 (dd, J_1 = 12.0 Hz, J_2 = 2.2 Hz, 1H), 3.86 (dd, J_1 = 12.2 Hz, J_2 = 2.0 Hz, 1H),2.38–2.26 (m, 8H), 2.01–1.99 (m, 4H), 1.62–1.58 (m, 4H), 1.30–1.26 (m, 40 H), 0.89–0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 173.0, 172.7, 163.1, 159.5, 150.4, 140.9, 130.2, 129.8, 103.3, 88.0, 83.7, 73.1, 71.0, 62.0, 34.1, 33.9, 32.1, 29.9, 29.9, 29.7, 29.5, 29.3, 29.3, 29.2, 27.4, 27.3, 25.0, 24.8, 22.8, 14.2; HRMS: m/z Calcd. for $C_{45}H_{76}N_2O_8Na$ $[M+Na]^+$ = 795.5499, found = 795.5486.

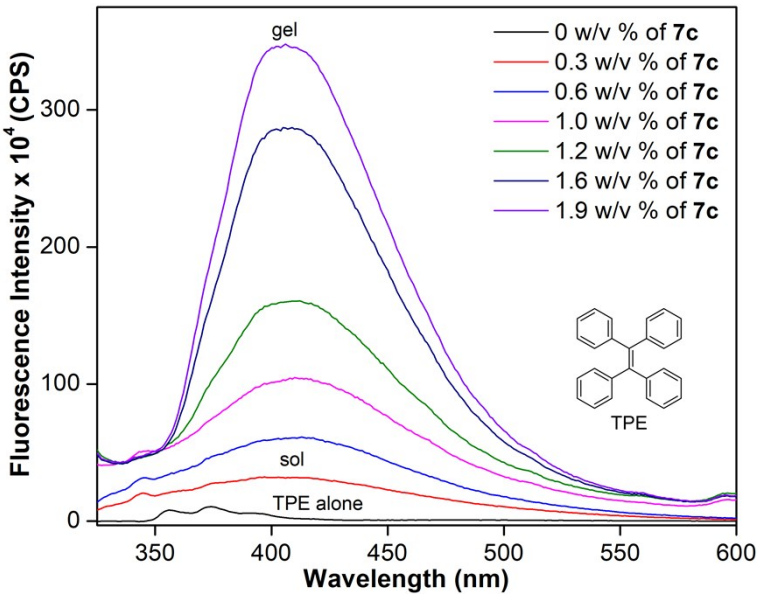


Fig. S1 Fluorescence emission spectra of TPE (50 μM) in DMSO containing different concentrations of **7c** ranging from 4.5 mM (0.3 w/v %)–28.6 mM (1.9 w/v %). A weighed amount of nucleolipid **7c** was dissolved in DMSO containing TPE (50 μM) by heating. The hot solution was transferred to a quartz cuvette (1 mm path length). The sample was cooled to RT and emission spectrum was recorded. Samples were excited at 306 nm with an excitation and emission slit width of 3 nm and 3 nm, respectively.

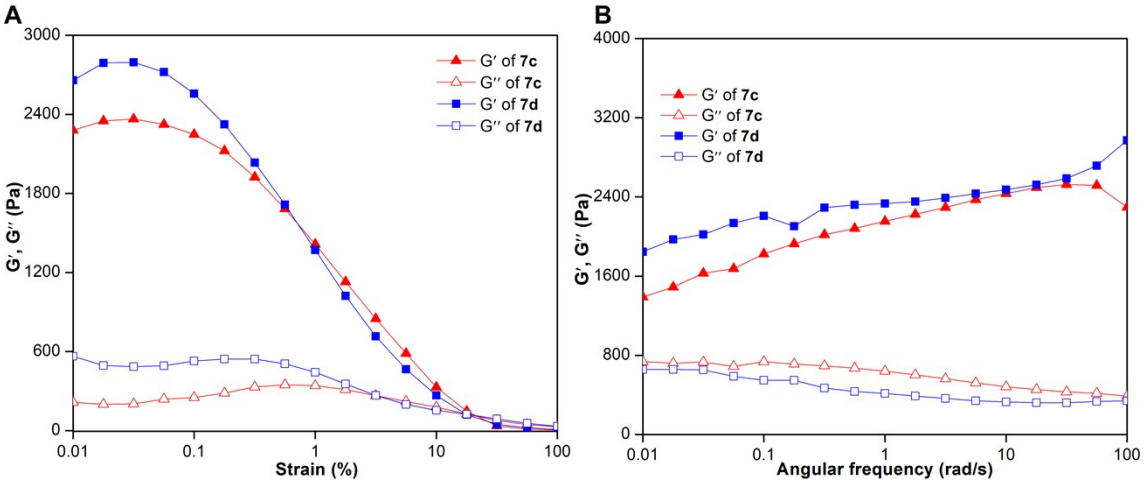


Fig. S2 (**A**) Strain sweep at constant oscillating frequency (10 Hz) plot for uridine nucleolipid gels **7c** (1.2 w/v %) and **7d** (0.7 w/v %) formed in DMSO at respective CGC. (**B**) Frequency sweep at constant strain (0.1 %) plot for the same.

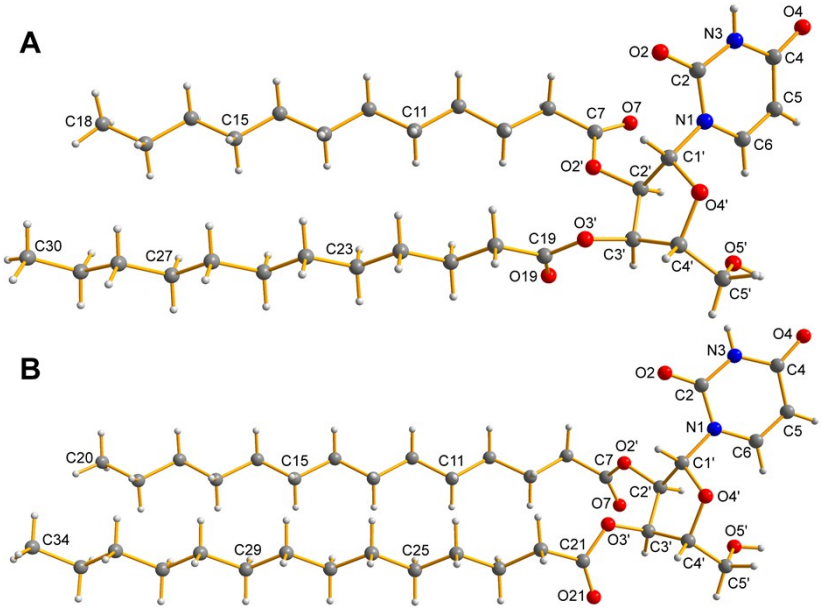


Fig. S3 X-ray crystal structure of nucleolipid **7b** (**A**) and **7c** (**B**) showing one molecule in the unit cell. Nucleobase adopts an *anti* conformation relative to the sugar ring with C2′-endo sugar puckering. Atoms are coded as follows: off white, hydrogen; dark gray, carbon; blue, nitrogen; red, oxygen.

Table S1. Crystallographic data for nucleolipid 7b

Compound identity	**7b**
Empirical formula	$C_{33}\ H_{56}\ N_2O_8$
Formula weight	608.80
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2
Unit cell dimensions	a = 16.404(8) α = 90
	b = 5.345(3) β = 96.154(10)
	c = 38.959(18) γ = 90
Volume	3396(3) $Å^3$
Z	4
Density (calculated)	1.191 Mg/cm^3
Absorption coefficient (μ)	0.085 mm^{-1}
F(000)	1328
Crystal size	0.30 X 0.16 X 0.06 mm^3
Theta range for data collection	2.63 to 19.00
Index ranges	-17<=h<=17, -5<=k<=5, -42<=l<=42
Reflections collected	14394
Independent reflections	4195 [R(int) = 0.0592]
Completeness to theta = 24.86	95.4 %
Absorption correction	MULTI-SCAN
Max. and min. Transmission	0.984 and 0.995
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4195 / 1 / 391
Goodness-of-fit on F^2	1.117
Final R indices [I>2sigma(I)]	R1 = 0.0619, wR2 = 0.1527
R indices (all data)	R1 = 0.0745, wR2 = 0.1630
Largest diff. Peak and hole	0.191 and -0.245 $e.Å^{-3}$
CCDC	1831323

Table S2. Crystallographic data for nucleolipid 7c

Compound identity	**7c**
Empirical formula	$C_{37}H_{64}N_2O_8$
Formula weight	664.90
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2
Unit cell dimensions	a = 83.98(4) α = 90
	b = 7.173(4) β = 94.66(2)
	c = 7.066(3) γ = 90
Volume	4242(3) $Å^3$
Z	4
Density (calculated)	1.041 Mg/cm^3
Absorption coefficient (μ)	0.072 mm^{-1}
F(000)	1456
Crystal size	0.40 X 0.25 X 0.12 mm^3
Theta range for data collection	2.85 to 24.01
Index ranges	-110<=h<=110, -9<=k<=9, -6<=l<=9
Reflections collected	32581
Independent reflections	9804 [R(int) = 0.1700]
Completeness to theta = 25.242	97.8 %
Absorption correction	MULTI-SCAN
Max. and min. Transmission	0.582 and 0.746
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9804 / 13 / 427
Goodness-of-fit on F^2	0.972
Final R indices [I>2sigma(I)]	R1 = 0.0833, wR2 = 0.1736
R indices (all data)	R1 = 0.2197, wR2 = 0.2163
Largest diff. Peak and hole	0.325 and -0.321 $e.Å^{-3}$
CCDC	1831324

Table S3. H-bonding distances and angles, torsional angles measured from the crystal structure of uridine nucleolipids **7b** and **7c**.

nucleolipid	hydrogen bond	distance (Å)	angle (°)	torsion angle (χ) (°)
7b	N3H---O4	1.949(4)	173.6(3)	C2-N1-C1′-O4′, –124.3(4)
	O2---HO5′	2.010(4)	151.9(3)	
	O4---HN3	1.949(5)	173.6(3)	
	O5′H---O2	2.010(5)	151.9(3)	
7c	N3H---O4	1.938(3)	167.8(3)	C2-N1-C1′-O4′, –138.9(5)
	O2---HO5′	1.993(3)	160.6(3)	
	O4---HN3	1.938(3)	167.8(3)	
	O4---HC5	2.270(3)	165.6(4)	
	C5H---O4	2.270(3)	165.6(4)	
	O5′H---O2	1.993(3)	160.6(3)	

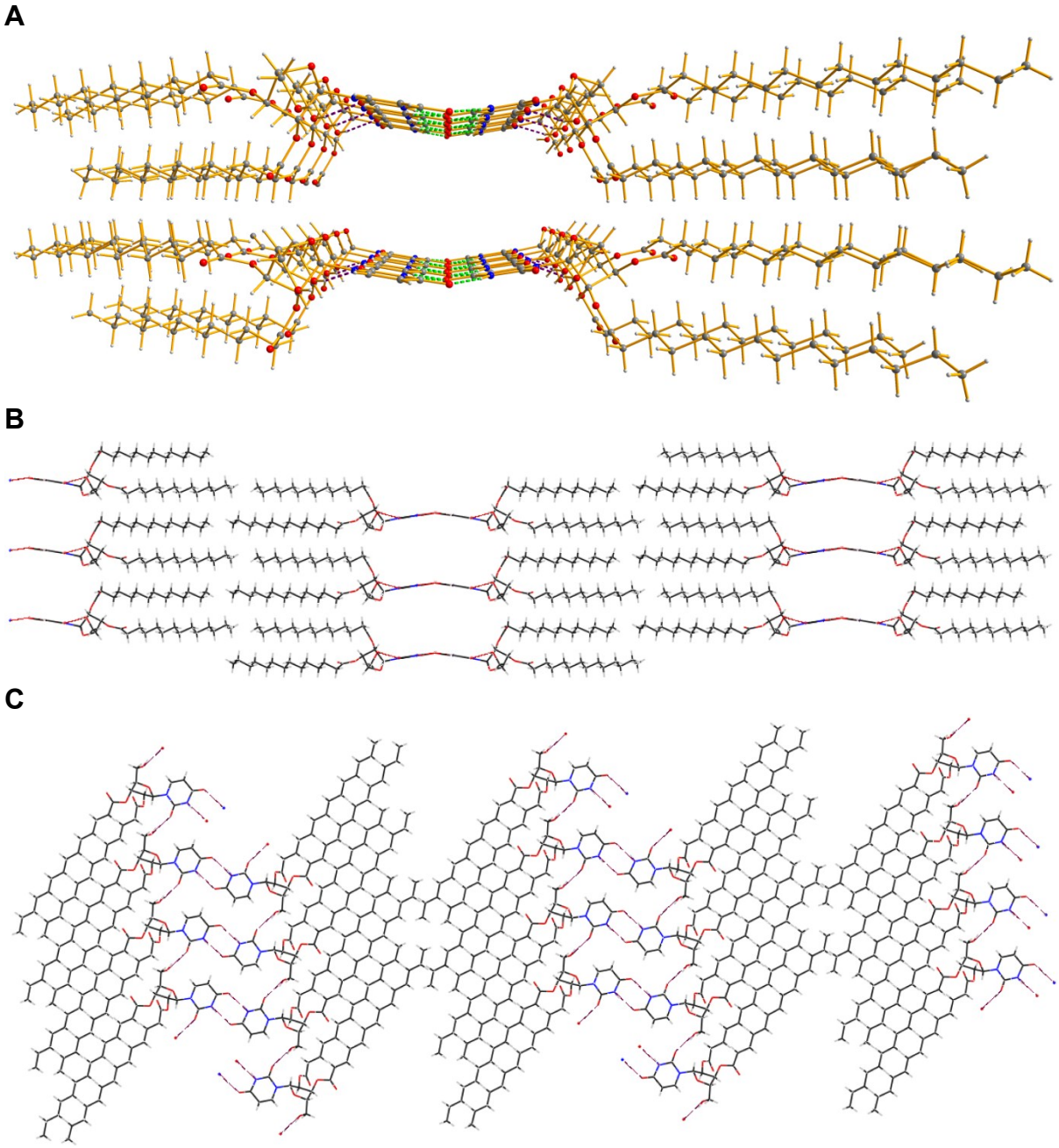
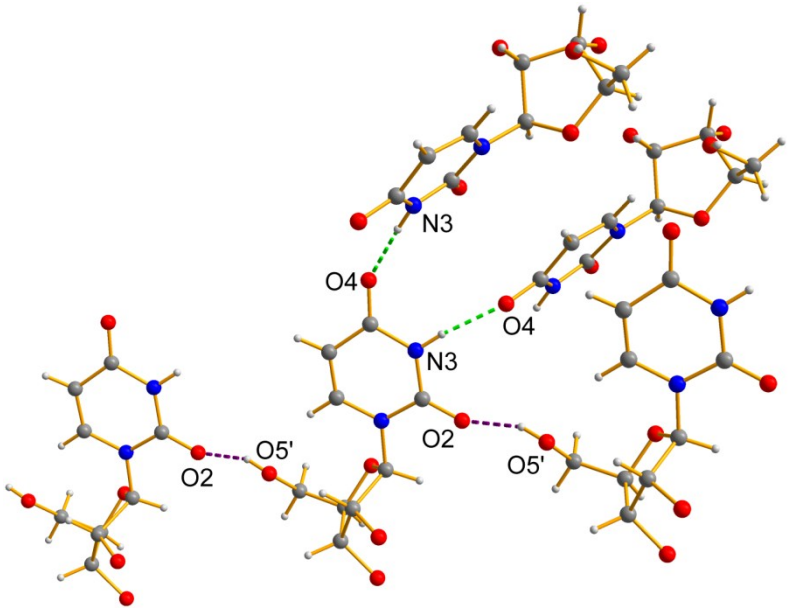


Fig. S4 (**A**) X-ray crystal structure showing a complete view of the non-covalent interactions between nucleolipids of **7c** along the crystallographic c-axes. Two 1D sheets join together through interlayer hydrophobic interactions. Base pairing is shown in green dashed lines and other H-bonds are denoted in violet dashed lines. (**B**) Packing structure of **7c** along the crystallographic c-axes showing the head to head and tail to tail interactions between the nucleolipids. (**C**) Packing diagram of **7c** along the crystallographic b-axes. Atoms are coded as follows: off white, hydrogen; dark gray, carbon; blue, nitrogen; red, oxygen.

A



B

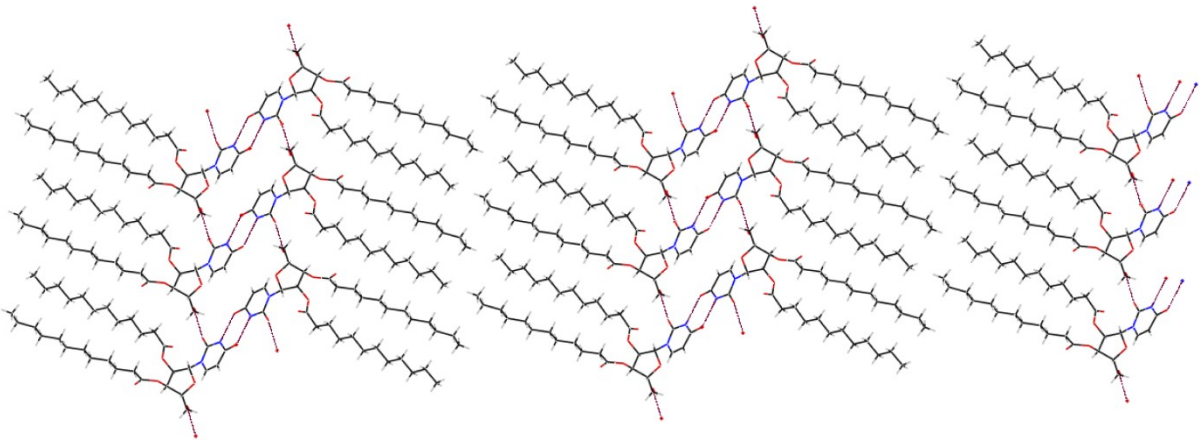


Fig. S5 (**A**) Crystal packing of **7b** along the crystallographic b-axes showing the H-bonding pattern, which is not the same as in **7c**. The alkyl chains and hydrogen atoms other than the nucleosides are not shown for clarity. (**B**) Packing diagram of **7b** along the crystallographic b-axes. Atoms are coded as follows: off white, hydrogen; dark gray, carbon; blue, nitrogen; red, oxygen.

4. Variable temperature ^{1}H NMR experiments: Gels of **7c** (1.2 w/v %) and **7d** (0.7 w/v %) in *d6*-DMSO at respective CGC were formed in individual NMR tubes by heating and cooling steps. ^{1}H NMR was recorded on a 500 MHz spectrometer as a function of increasing temperature. The temperature of the sample was elevated from 25 °C to 60 °C with an increment of 5 °C and equilibration time of 10 min. The spectrum was recorded at every 5 °C interval.

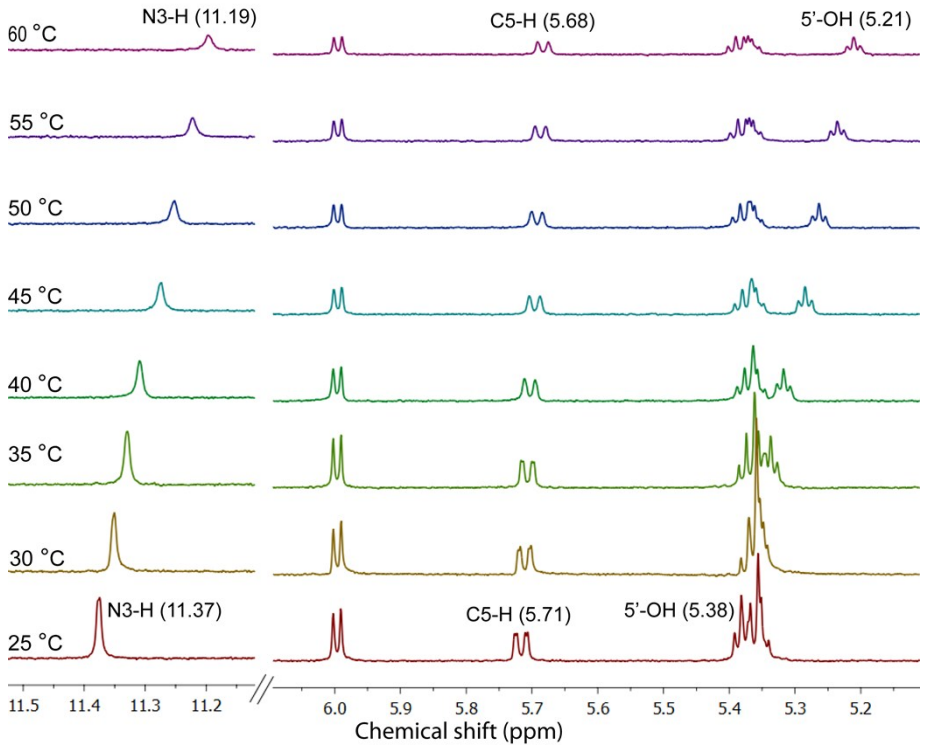


Fig. S6 Partial ^{1}H NMR spectrum of nucleolipid gel of **7d** (0.7 w/v %) in *d6*-DMSO as a function of increasing temperature. N3-H, C5-H and 5′-OH atoms, which are involved in the intermolecular H-bonding in crystalline state, show progressive upfield shift in their proton signal during gel-sol transition ($\Delta\delta$ = 0.18, 0.03, 0.17 ppm). This result indicates that the H-bonding interactions in the crystal structure and in gel state are similar.

5. Powder X-ray diffraction (PXRD) analysis of uridine nucleolipids: Gels of **7c** and **7d** in DMSO at respective CGC were formed on a glass slide by drop-casting method. The glass slide was placed in a vacuum desiccator and dried under vacuum for nearly 15 h to obtain the xerogels. PXRD spectrum was recorded using Bruker D8 Advance diffractometer with CuKα source (1.5406 Å). Diffraction data were collected at 2θ angle from 1° to 30° using a 0.01° step size and 0.5 s per step. Low angle diffraction data was collected by keeping the motorized divergence slit in automatic mode so as to maintain the X-ray beam footprint on the sample to 12 x 12 mm. Further, the position sensitive detector (Lynxeye) channels were reduced to minimize the background X-ray scattering entering the detector.[S2]

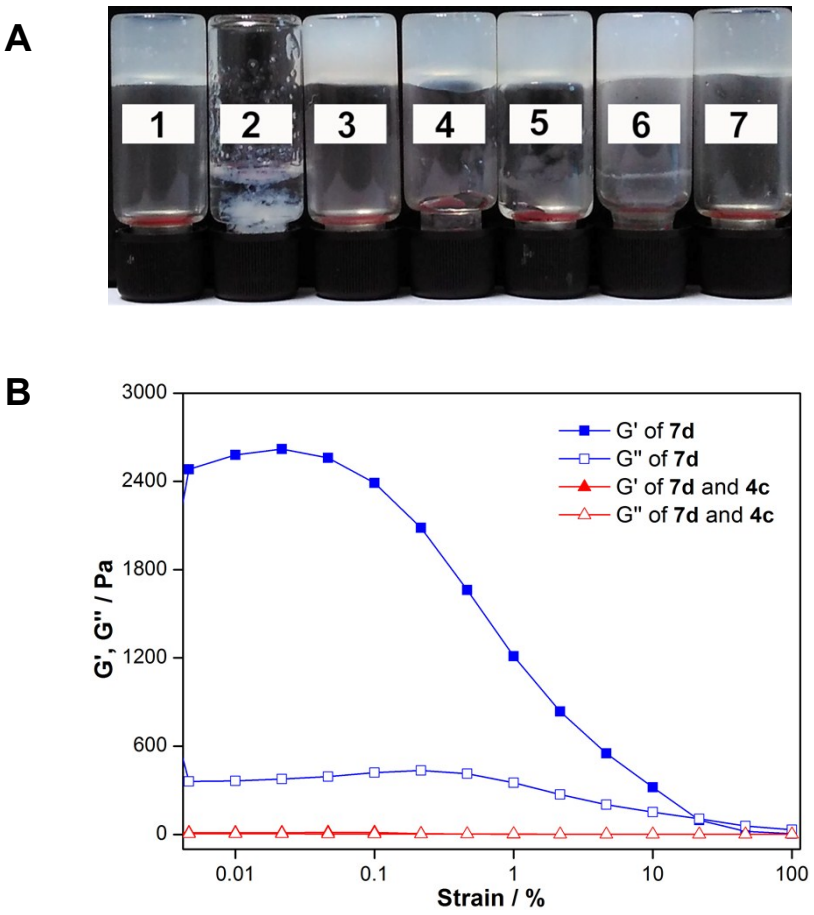


Fig. S7 (**A**) Inverted vial experiment to study the effect of addition of adenosine nucleolipid **4c**, uridine nucleolipid **7c** and nucleosides on the gelation ability of uridine nucleolipid **7d**. Vial 1: Gel of **7d** in DMSO at CGC. Vial 2: 1:1 mixture of **7d** and **4c** in DMSO. Vial 3: co-assembly of a 1:1 mixture of **7d** and **7c** in DMSO. Vials 4–7: 1:1 mixture of **7d** and nucleosides adenosine, guanosine, cytidine and uridine, respectively, in DMSO.
(**B**) A comparison of strain sweep rheological measurement of nucleolipid organogel **7d** (0.7 w/v % CGC, blue lines) and a 1:0.5 mixture (partial gel) of **7d** and **4c** in DMSO at constant oscillating frequency. G′ and G″ lines of the mixture overlay on one another. The storage modulus (G′) of organogel of **7d** dramatically decreased from 2483 Pa to 14 Pa for the partial gel made of a mixture of **7d** and **4c**, which suggests that adenosine nucleolipid destabilized the gel of uridine nucleolipid.

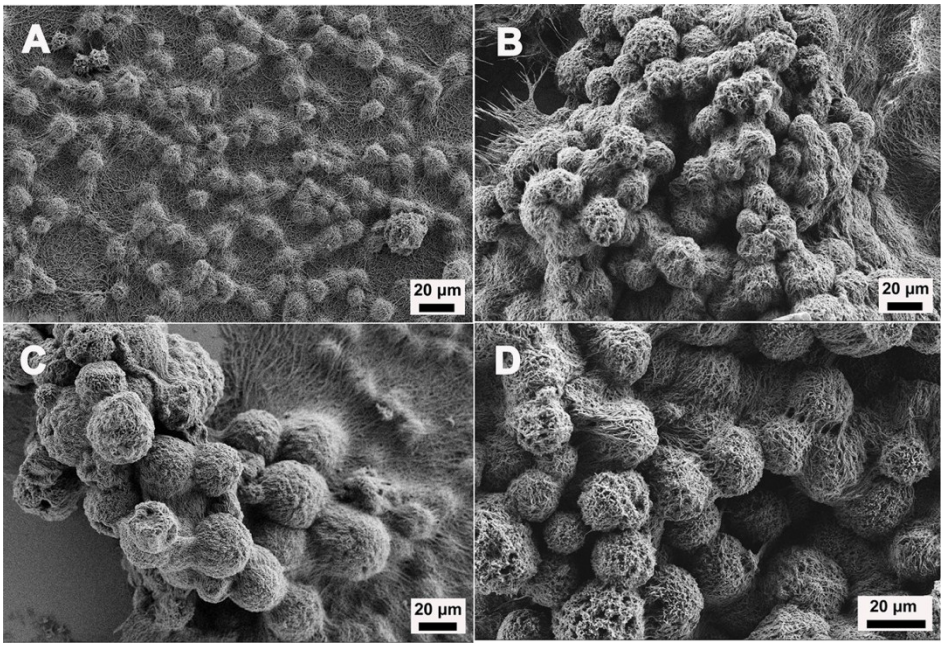


Fig. S8 FESEM images of xerogels of different mixtures of uridine nucleolipid **7d** and adenosine nucleolipid **4c**. Molar ratio of **7d** to **4c**. (**A**) 1:0.5; (**B**) 1:1; (**C**) 1:1.5; (D) 1:2.

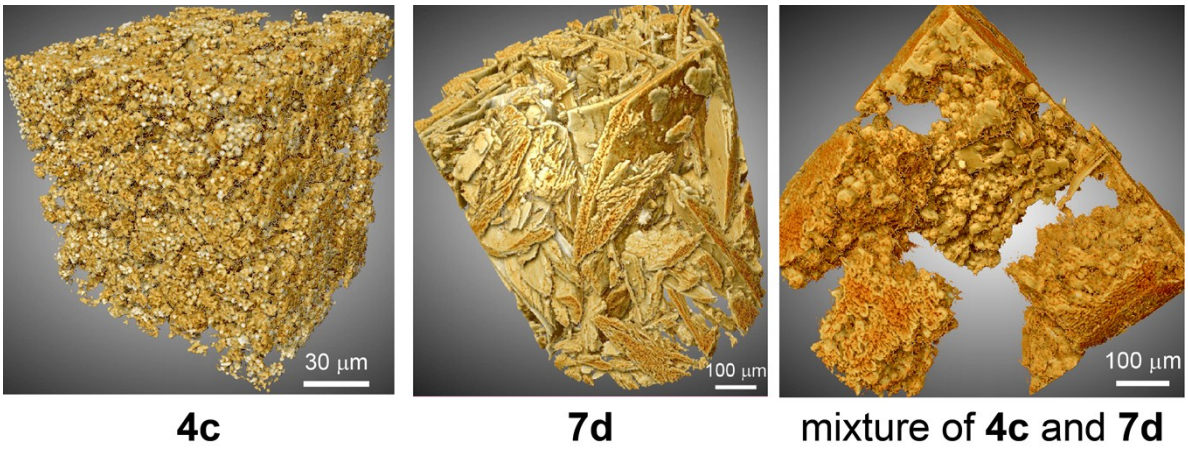


Fig. S9 3D rendered X-ray tomography images of individual and mixture of nucleolipids. For clarity, Fig. 6, column 3 has been depicted here in a larger size.

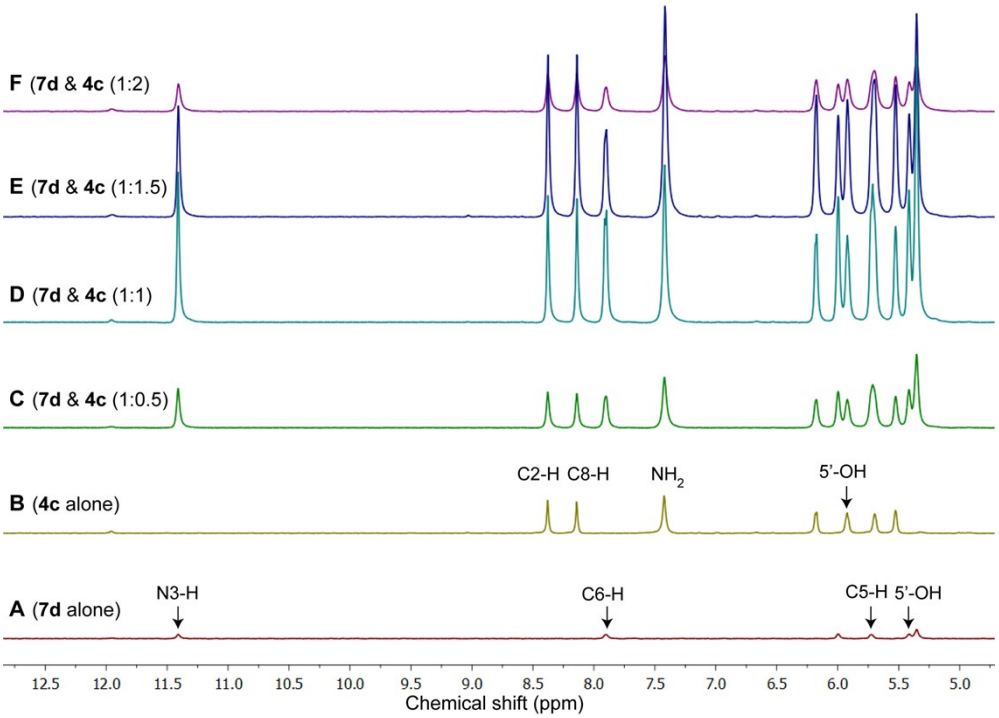


Fig. S10 Partial ^{1}H NMR spectrum of (**A**) uridine nucleolipid gel **7d** (0.7 w/v %) and (**B**) adenosine nucleolipid **4c** (0.7 w/v %) in *d6*-DMSO. **C**–**F:** ^{1}H NMR spectrum of different mixtures of **7d** and **4c**. H atoms of nucleosides that can potentially form H-bonds and aromatic protons did not exhibit discernible changes in their chemical shift.

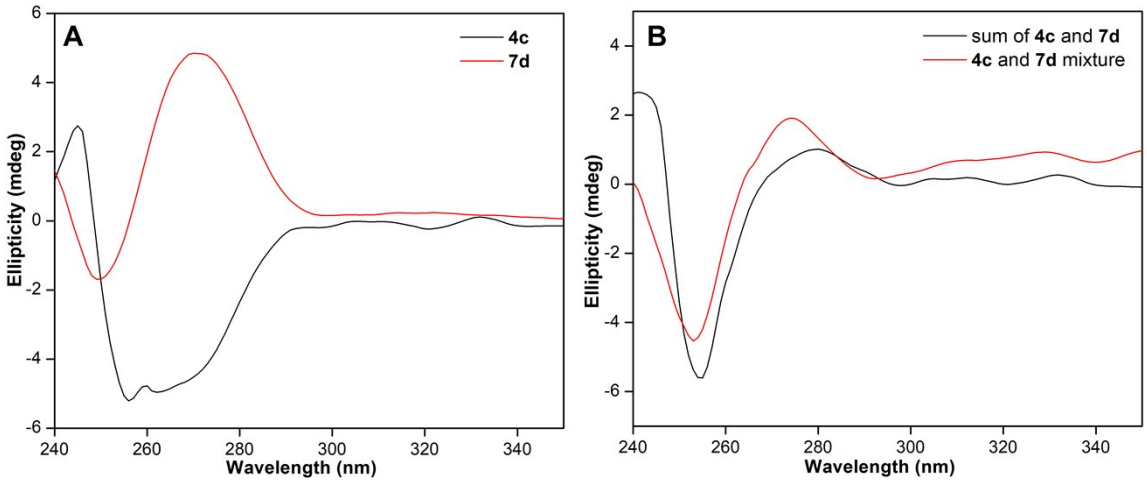


Fig. S11 (**A**) CD spectrum of **4c** and **7d** in DMSO (0.5 mM). (**B**) CD spectrum of a 1:1 mixture of **4c** and **7d** and sum of the CD spectra of individual assembles of **4c** and **7d**. Spectra were collected from 350 to 240 nm on a Jasco J-815 CD spectrometer using 1 nm bandwidth at 25°C. Experiments were performed in duplicate wherein each spectrum was an average of three scans. The spectrum of DMSO without nucleolipid was subtracted from all the sample spectra.

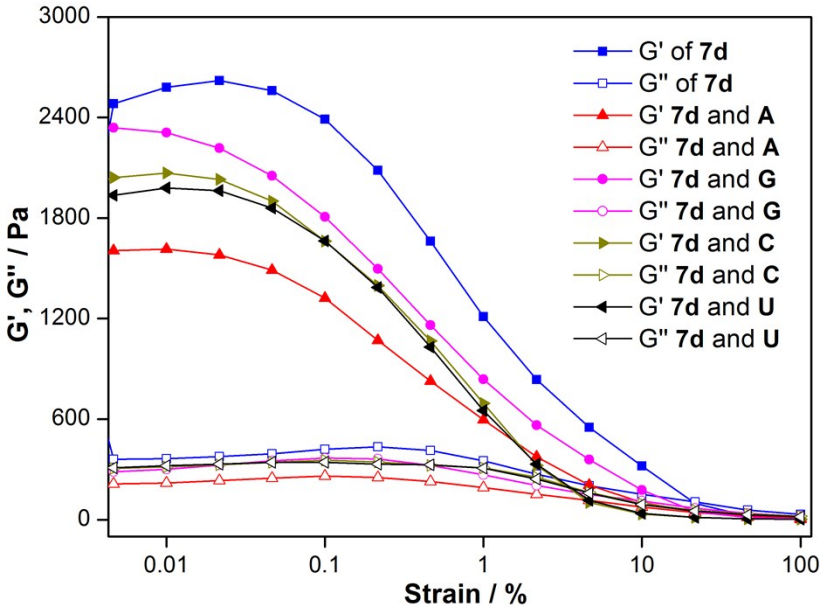


Fig. S12 Comparison of strain sweep rheological measurement of a 1:1 mixture of uridine nucleolipid gel **7d** in DMSO (0.7 w/v %, CGC) and nucleosides (A = adenosine, G = guanosine, C = cytidine and U = uridine) at constant oscillating frequency.

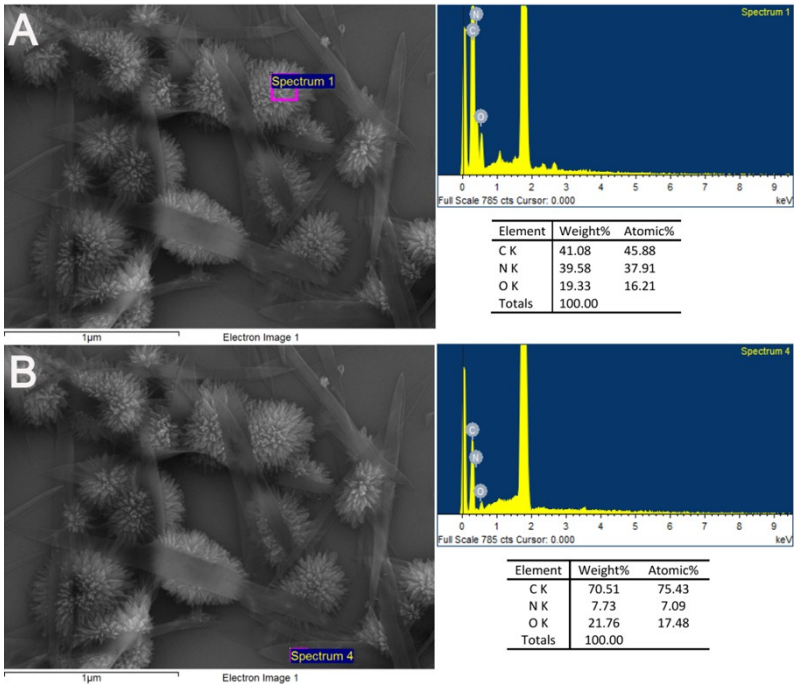


Fig. S13 EDAX analysis of SEM images obtained from a mixture of uridine nucleolipid **7d** and adenosine. (**A**) Spectrum 1 (top) shows the elemental composition of the cluster. (**B**) Spectrum 4 (bottom) elemental composition of the sheet. The compositions were similar for different clusters and sheets, respectively. A comparison of carbon content suggests that the cluster is composed of adenosine and sheets are made of uridine nucleolipid **7d**.

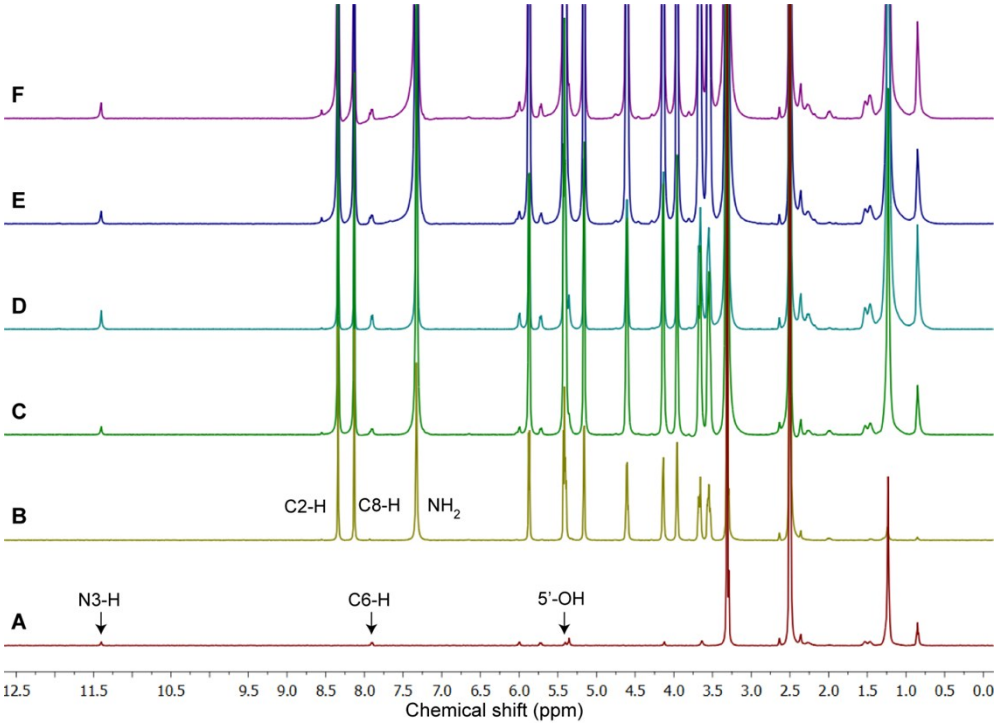


Fig. S14 ^{1}H NMR spectrum of (**A**) uridine nucleolipid gel **7d** (0.7 w/v %, CGC) and (**B**) adenosine (0.7 w/v %) in *d6*-DMSO. **C**–**F:** ^{1}H NMR spectrum of a mixture of **7d** and adenosine at different ratios. 1:0.5 (**C**), 1:1 (**D**), 1:1.5 (**E**) and 1:2 (**F**). H atoms of nucleosides that can potentially form H-bonds and aromatic protons did not exhibit discernible changes in their chemical shift.

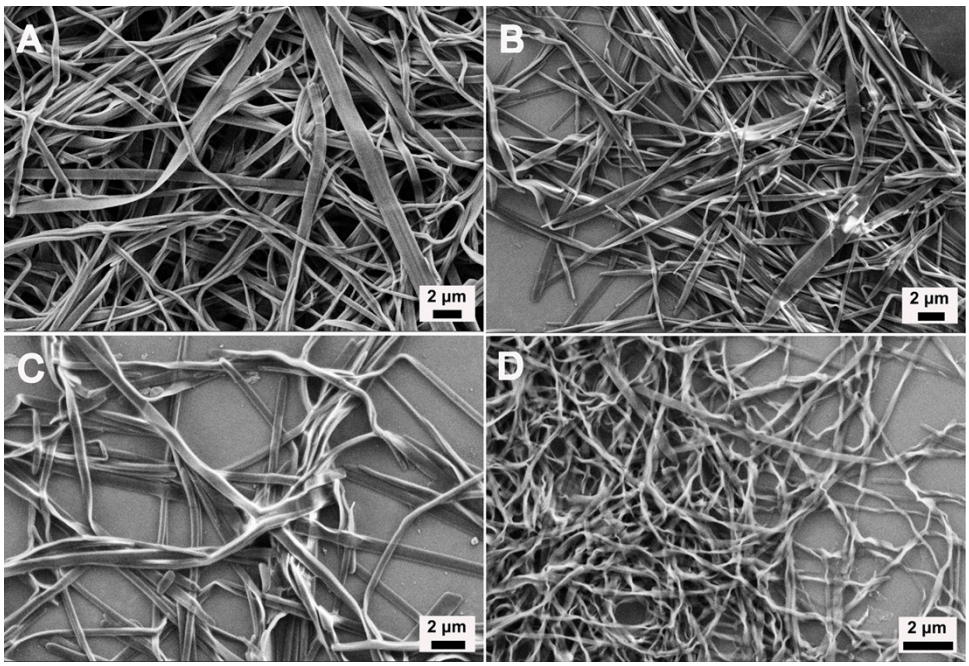


Fig. S15 FESEM images of xerogels of (**A**) uridine nucleolipid gel **7d** (0.7 w/v %, CGC) and a mixture of (**B**) **7d** and guanosine (equiv. 1:1), (**C**) **7d** and cytidine (equiv. 1:1), (**D**) **7d** and uridine (equiv. 1:1) in DMSO.

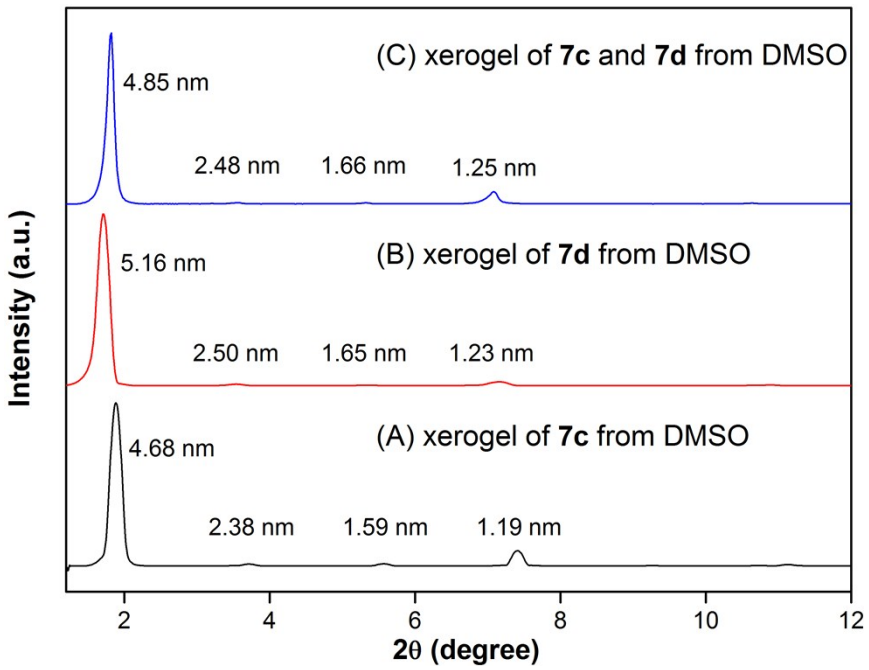


Fig. S16 Comparison of PXRD spectrum of xerogels of **7c** (A), **7d** (B) and 1:1 mixture of **7c** and **7d** (C). Layer spacing (nm) for diffraction peaks is given.

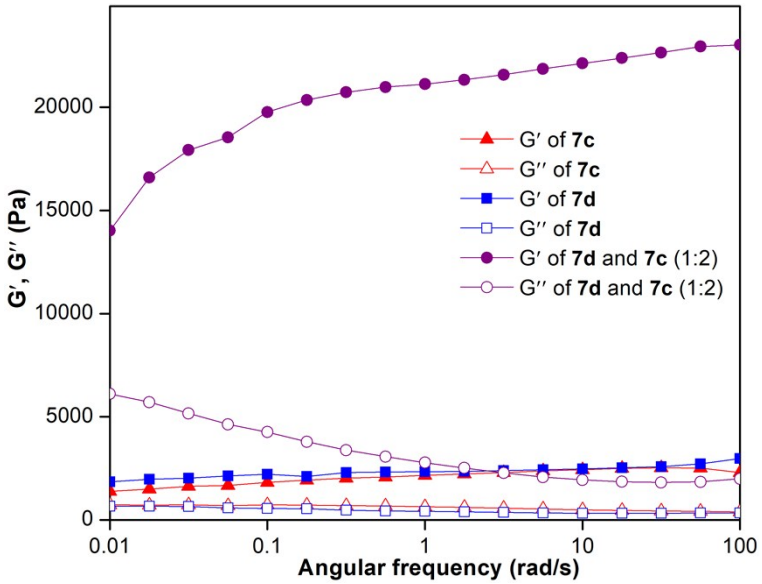


Fig. S17 Comparison of frequency sweep rheological measurement of nucleolipid gel **7c** (1.2 w/v %), **7d** (0.7 w/v %) and gel formed by a 1:2 mixture of **7d** (9.7 mM) and **7c** (19.4 mM) at constant strain (0.1%).

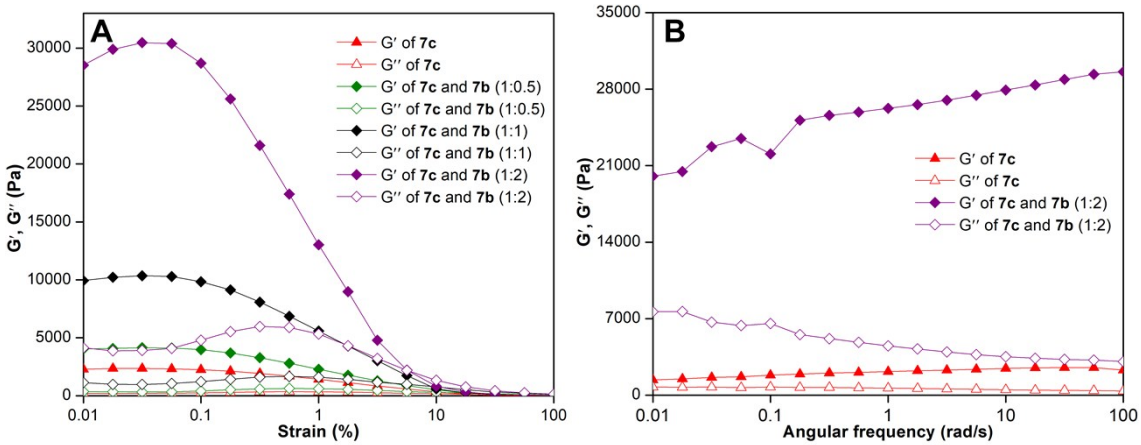


Fig. S18 Rheological measurement of nucleolipid gels. (**A**) Comparison of strain sweep of nucleolipid gel **7c** (1.2 w/v %) and gels formed by different mixtures of **7c** and **7b** at constant oscillating frequency. (**B**) Frequency sweep at constant strain (0.1 %) plot for nucleolipid gel **7c** (1.2 w/v %, 18 mM) and gels formed by 1:2 mixture of **7c** (18 mM) and **7b** (36 mM).

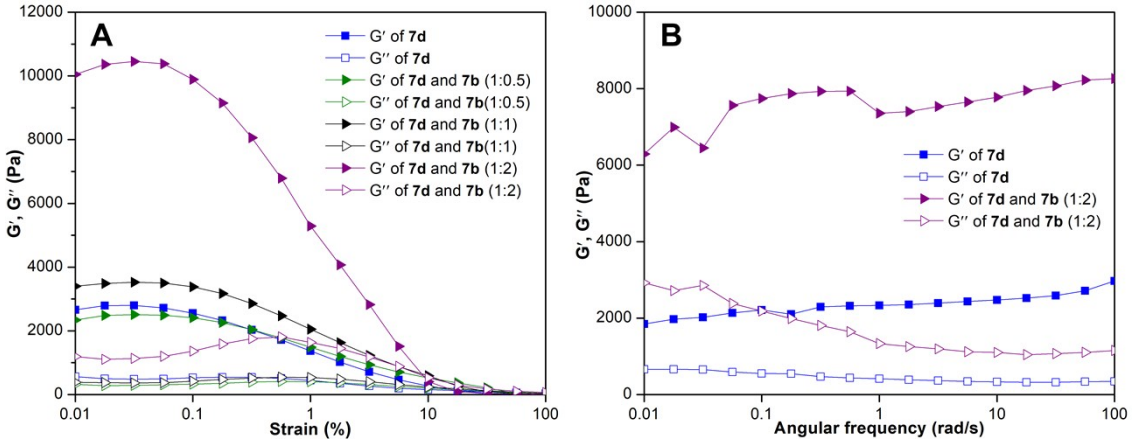
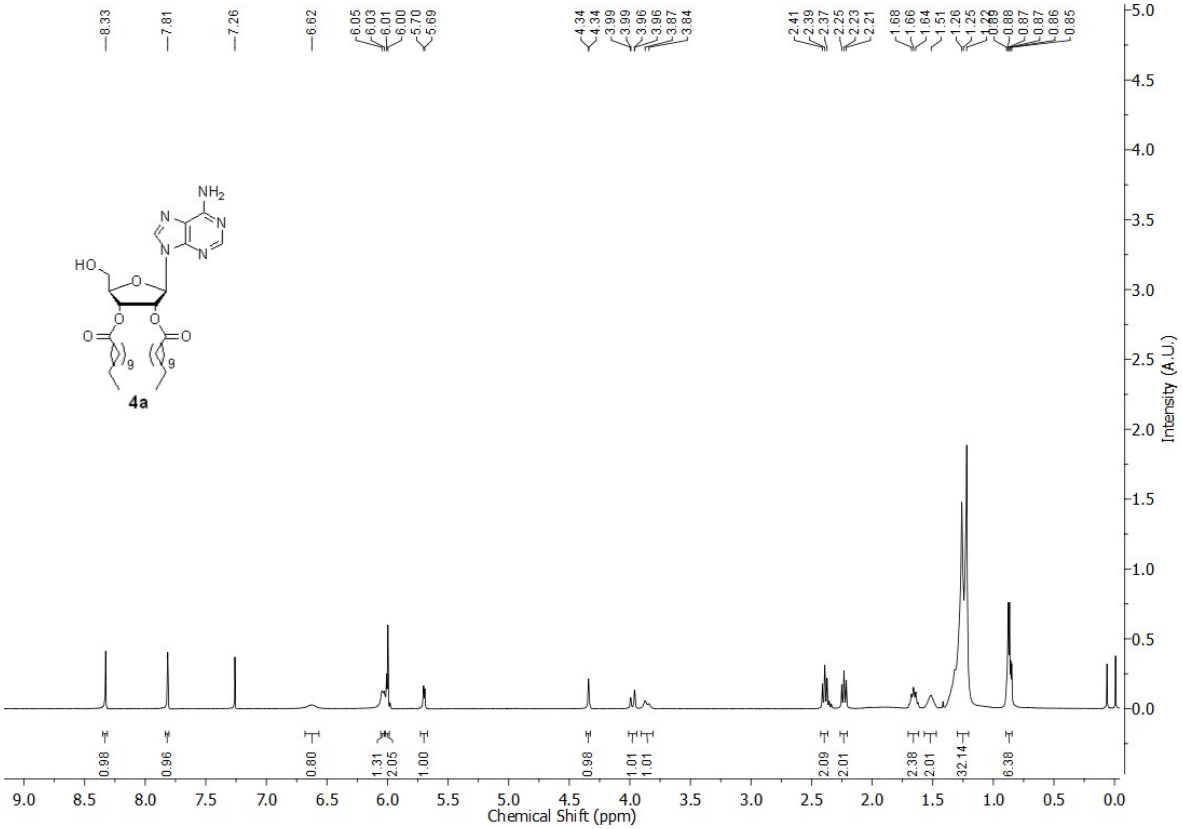


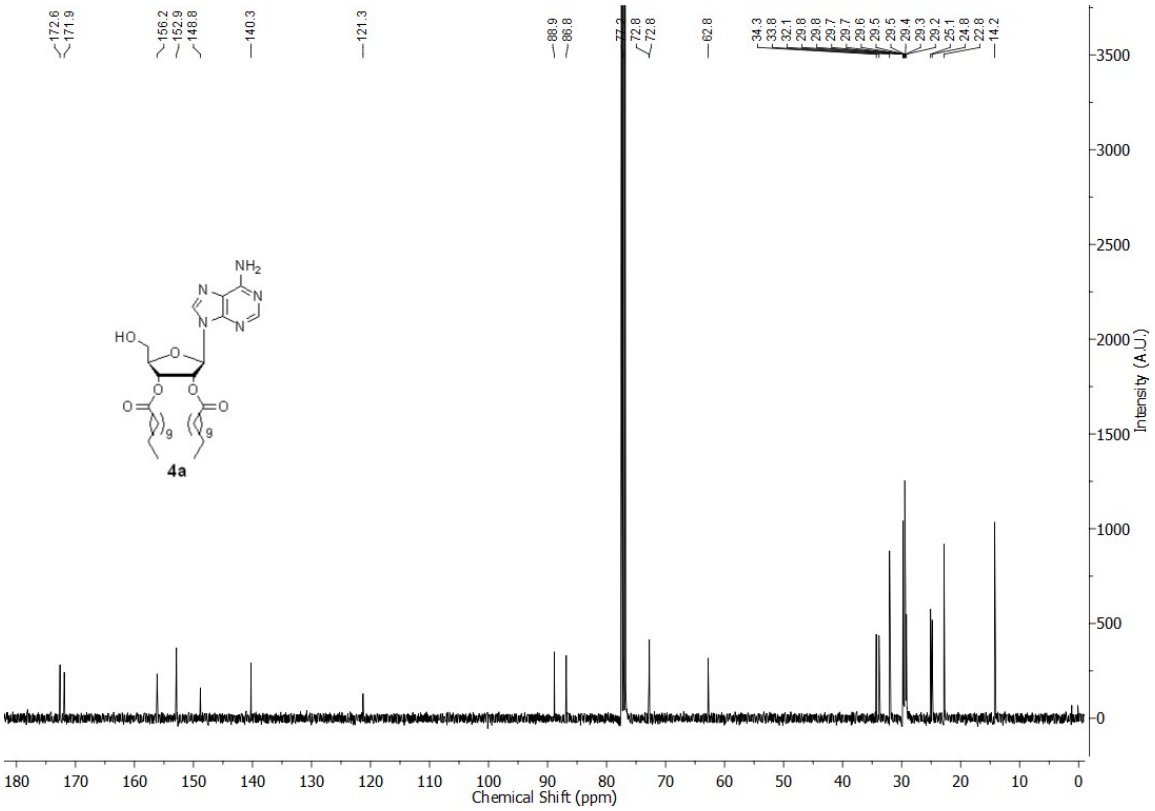
Fig. S19 Rheological measurement of nucleolipid gels. (**A**) Comparison of strain sweep of nucleolipid gel **7d** (0.7 w/v %) and gels formed by different mixtures of **7d** and **7b** at constant oscillating frequency. (**B**) Frequency sweep at constant strain (0.1 %) plot for nucleolipid gel **7d** (0.7 w/v %) and gels formed by 1:2 mixture of **7d** (9.7 mM) and **7b** (19.4 mM).

6. NMR spectra

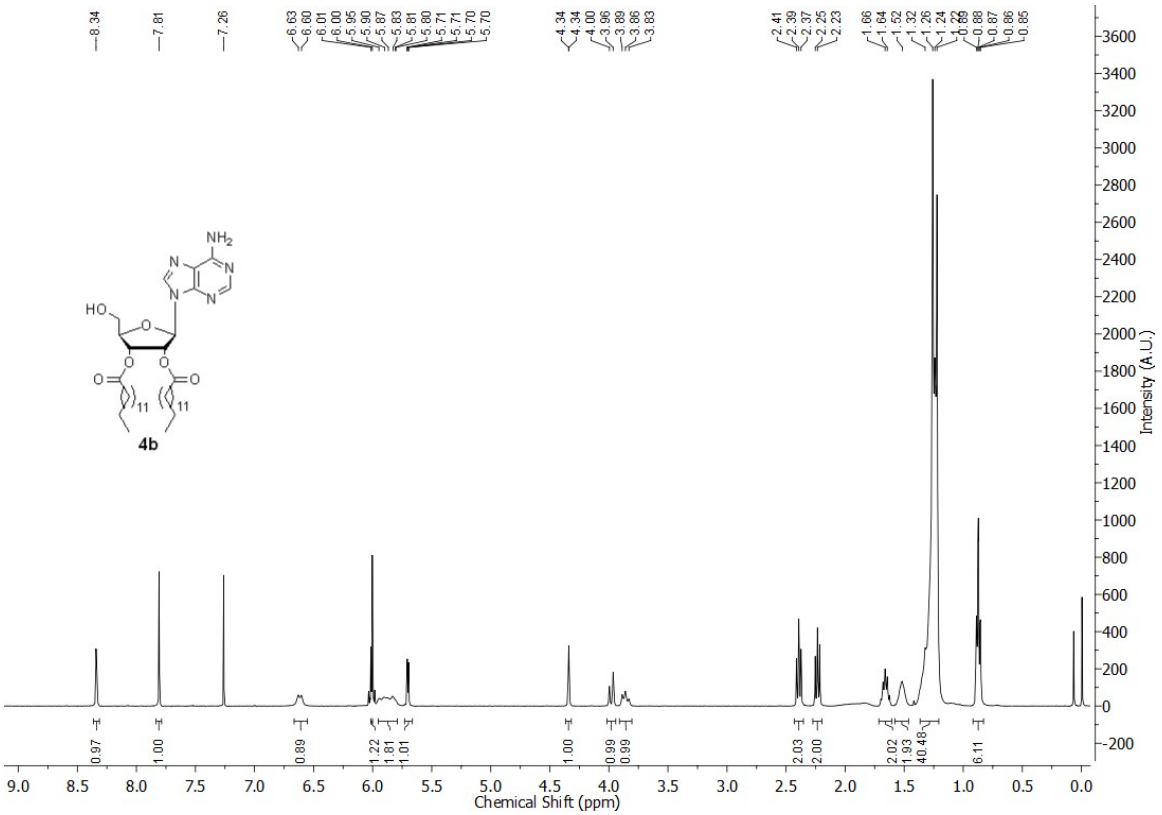
^{1}H NMR of nucleolipid **4a** in $CDCl_3$



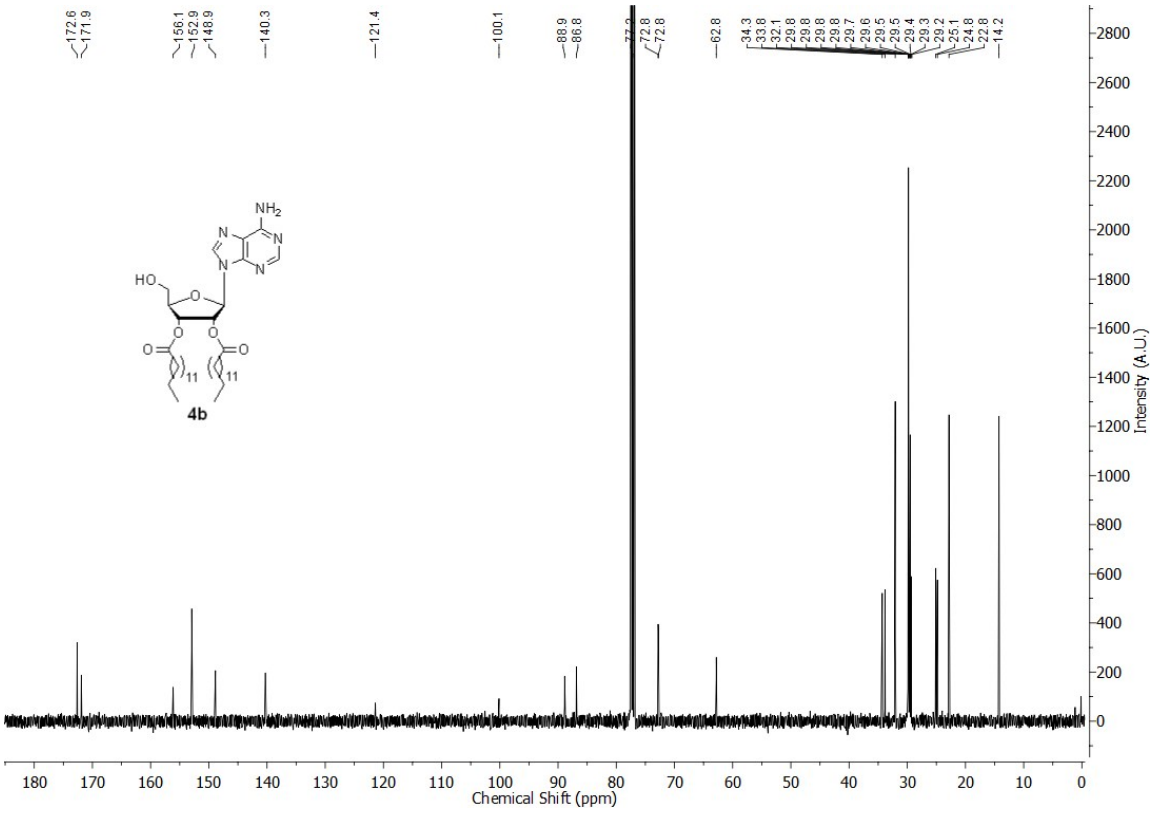
^{13}C NMR of nucleolipid **4a** in $CDCl_3$



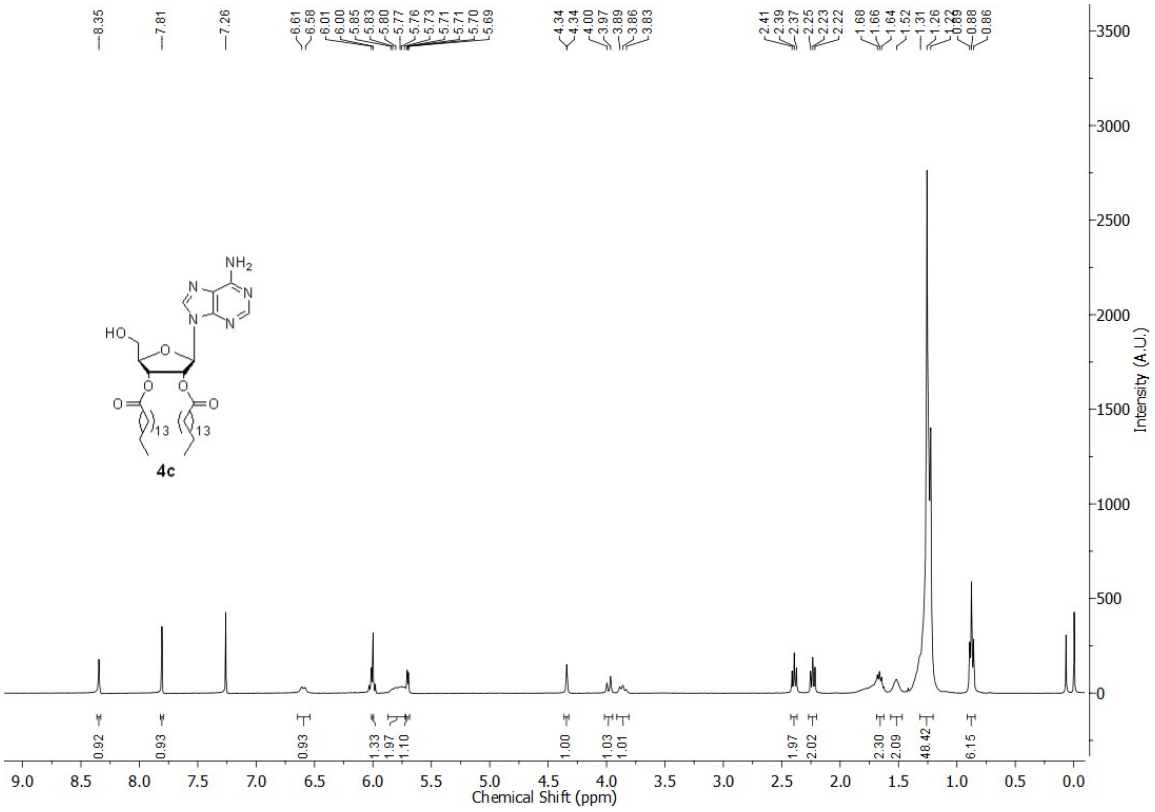
^{1}H NMR of nucleolipid **4b** in $CDCl_3$



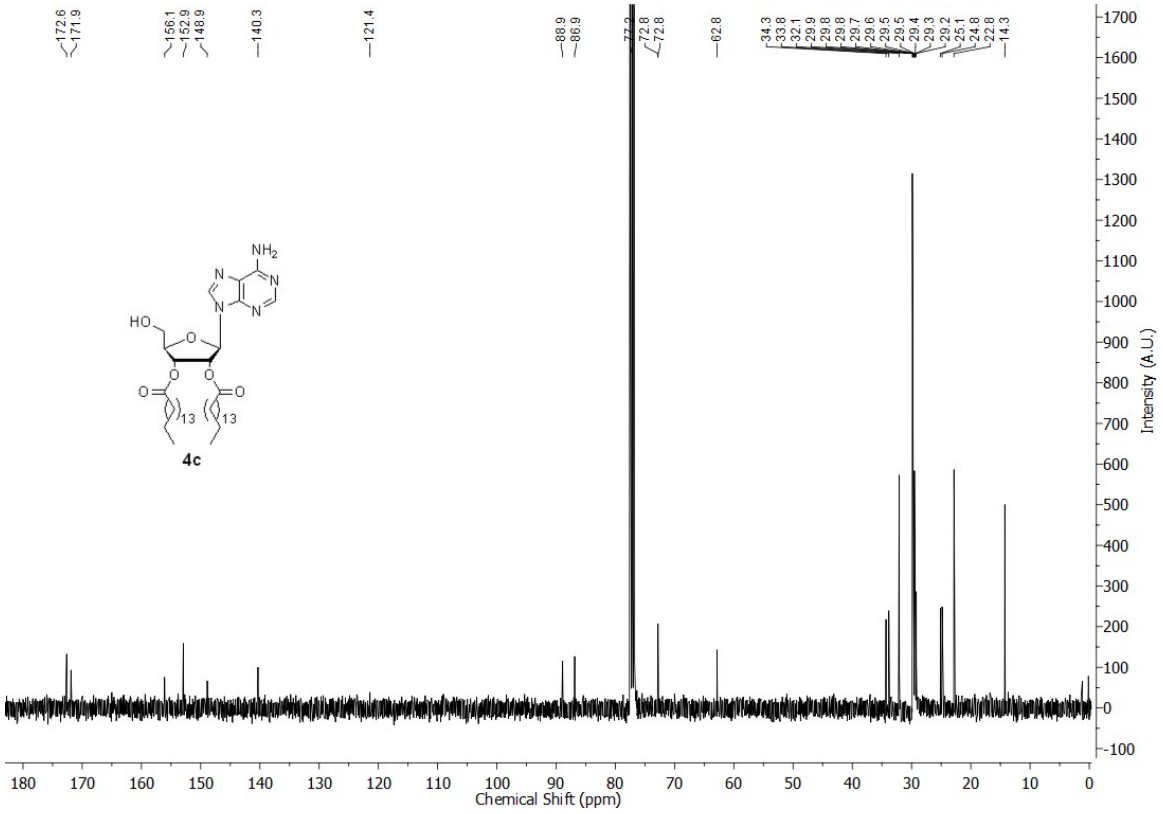
^{13}C NMR of nucleolipid **4b** in $CDCl_3$



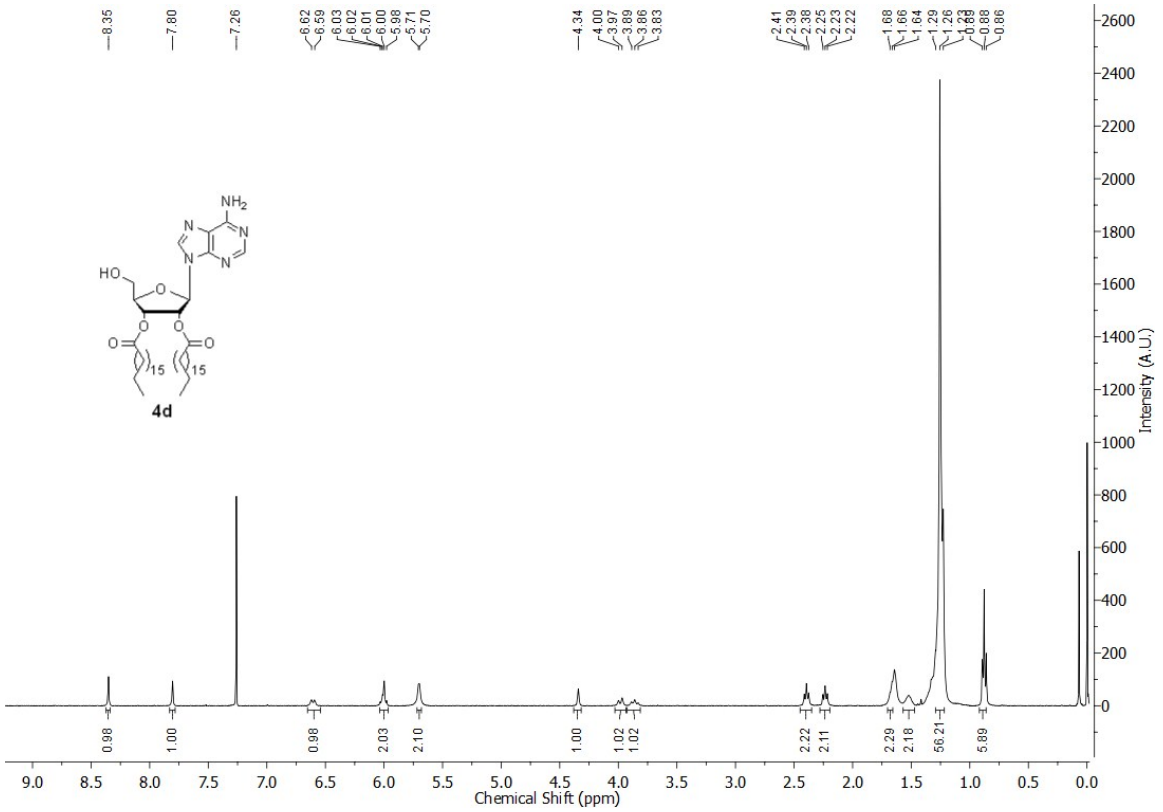
^{1}H NMR of nucleolipid **4c** in $CDCl_3$



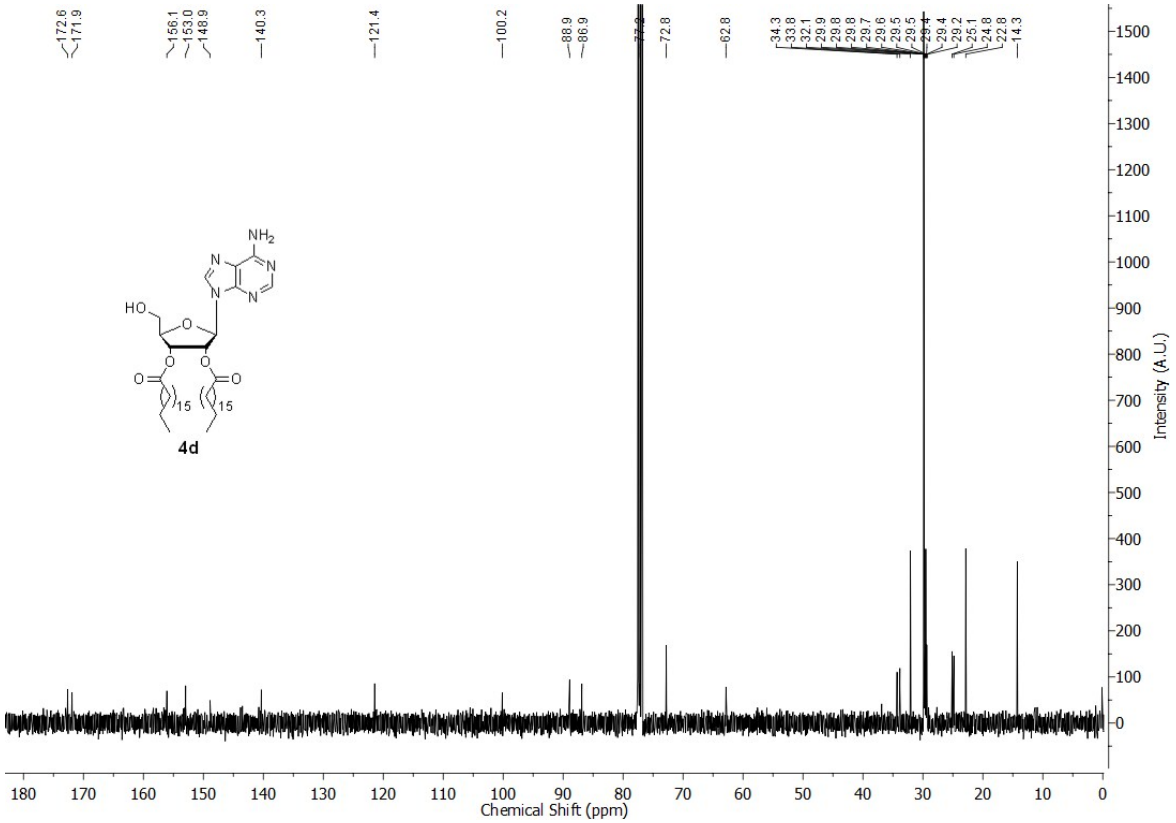
^{13}C NMR of nucleolipid **4c** in $CDCl_3$



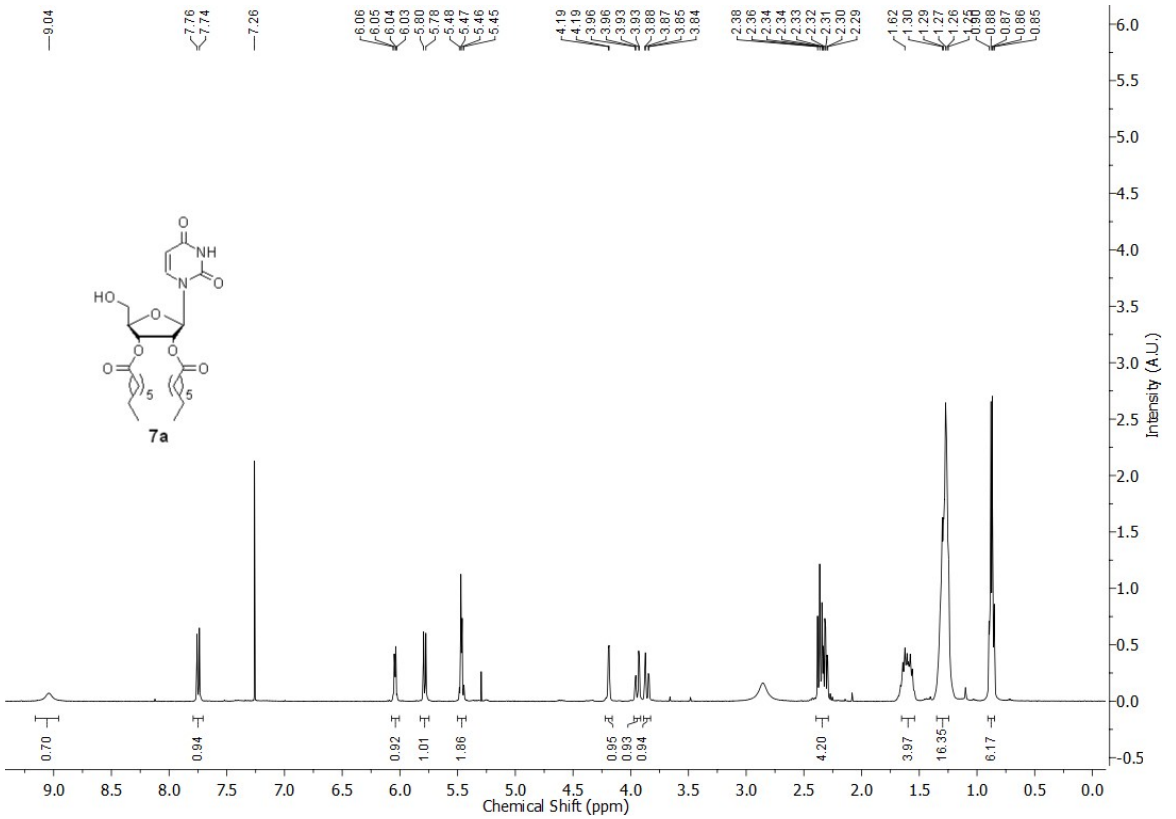
^{1}H NMR of nucleolipid **4d** in $CDCl_3$



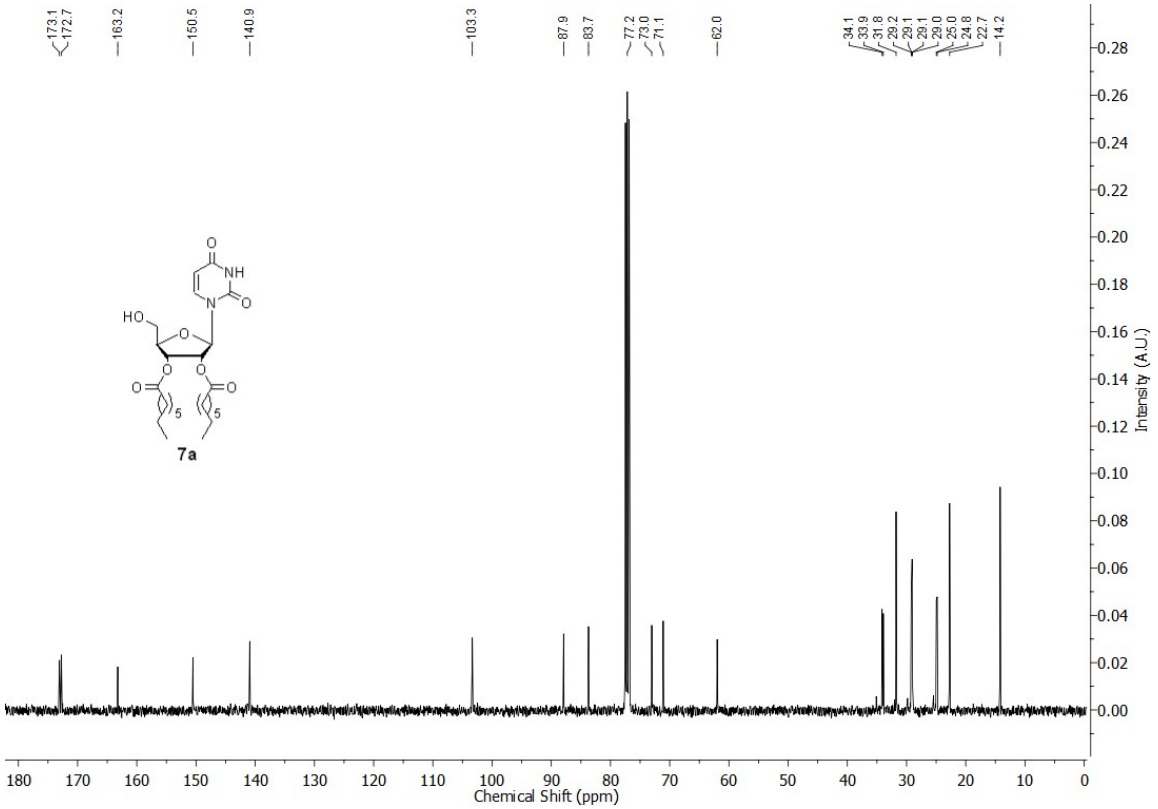
^{13}C NMR of nucleolipid **4d** in $CDCl_3$



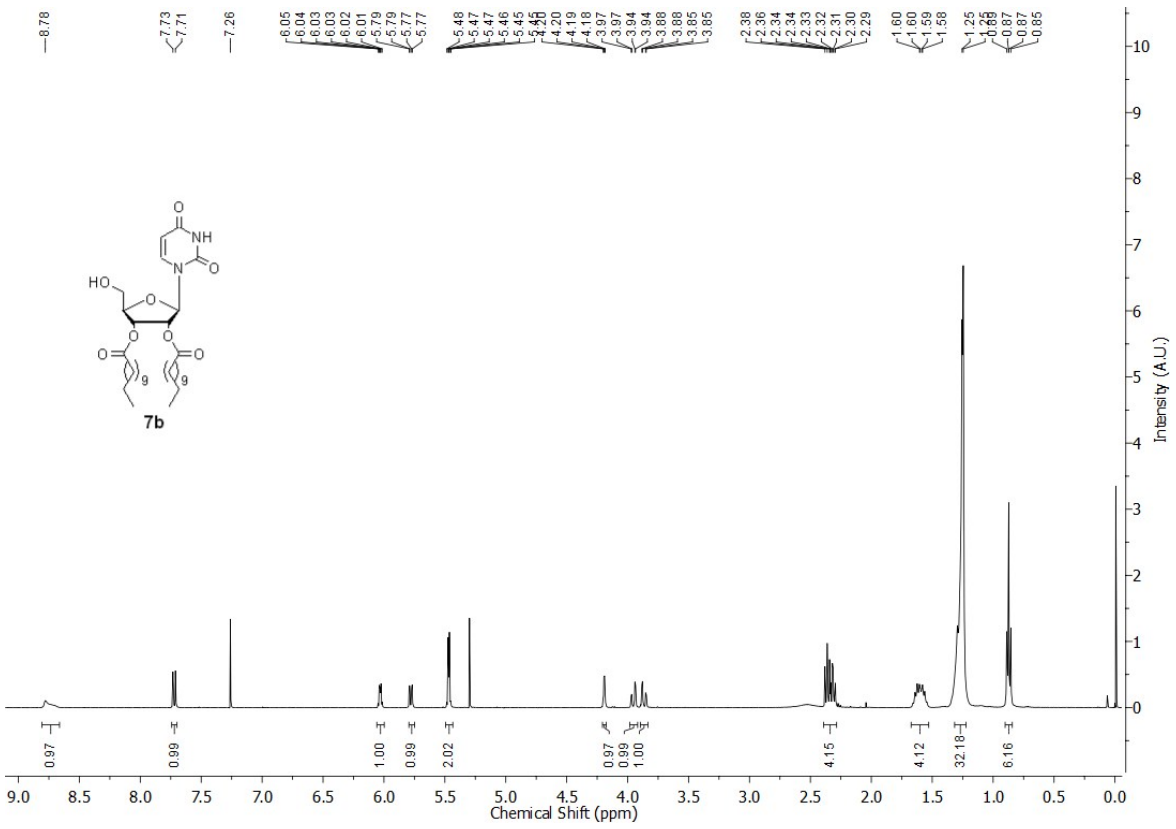
^{1}H NMR of nucleolipid **7a** in $CDCl_3$



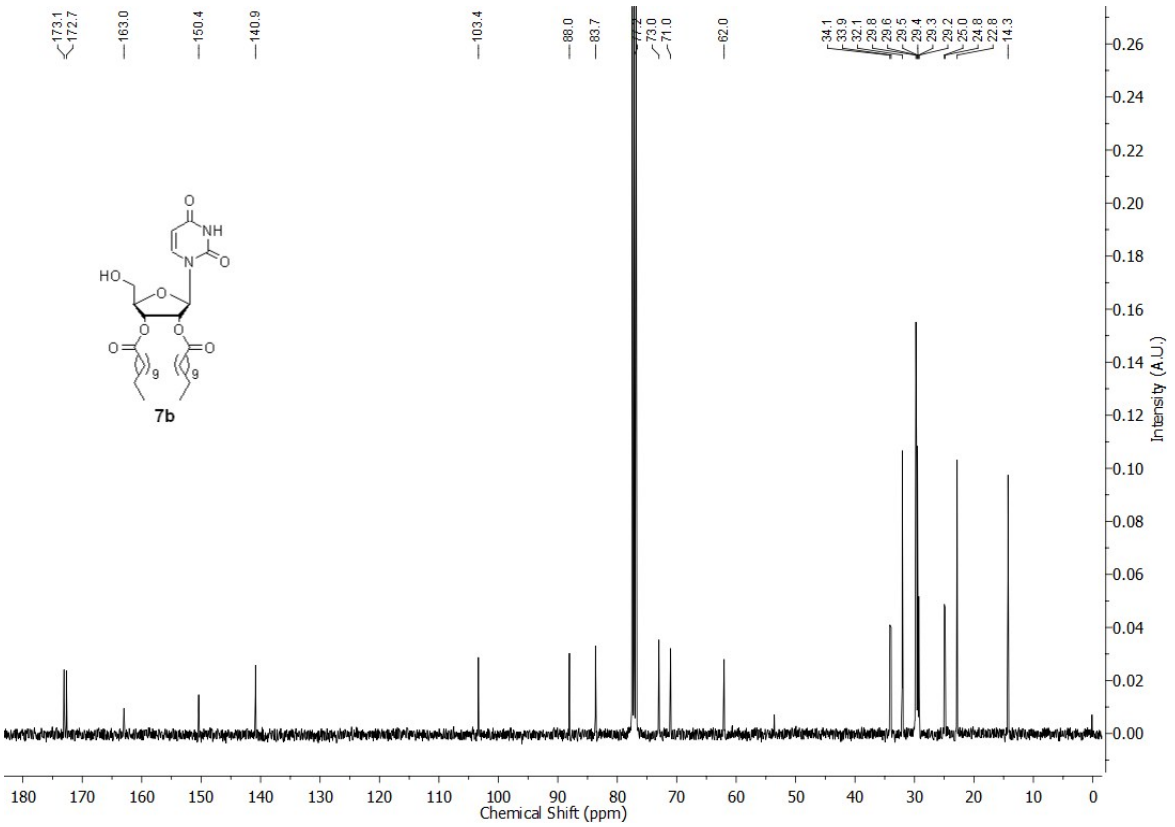
^{13}C NMR of nucleolipid **7a** in $CDCl_3$



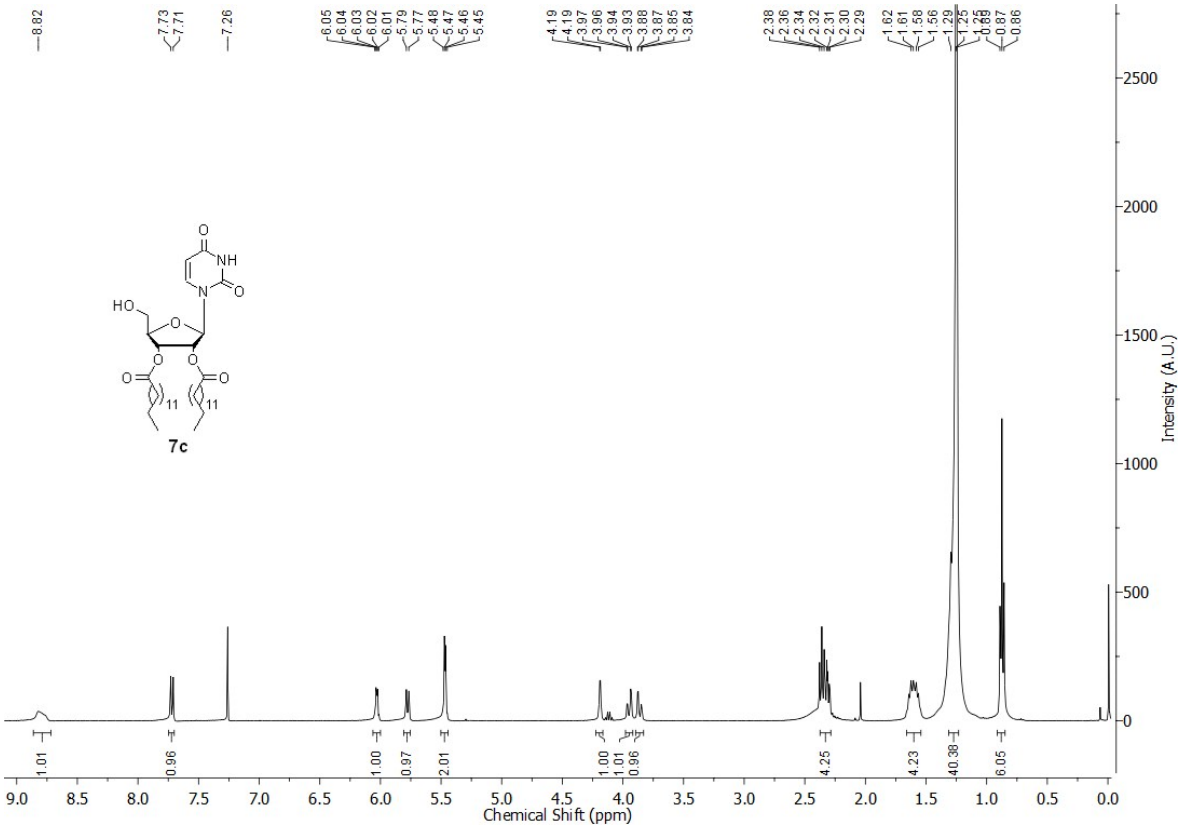
^{1}H NMR of nucleolipid **7b** in $CDCl_3$



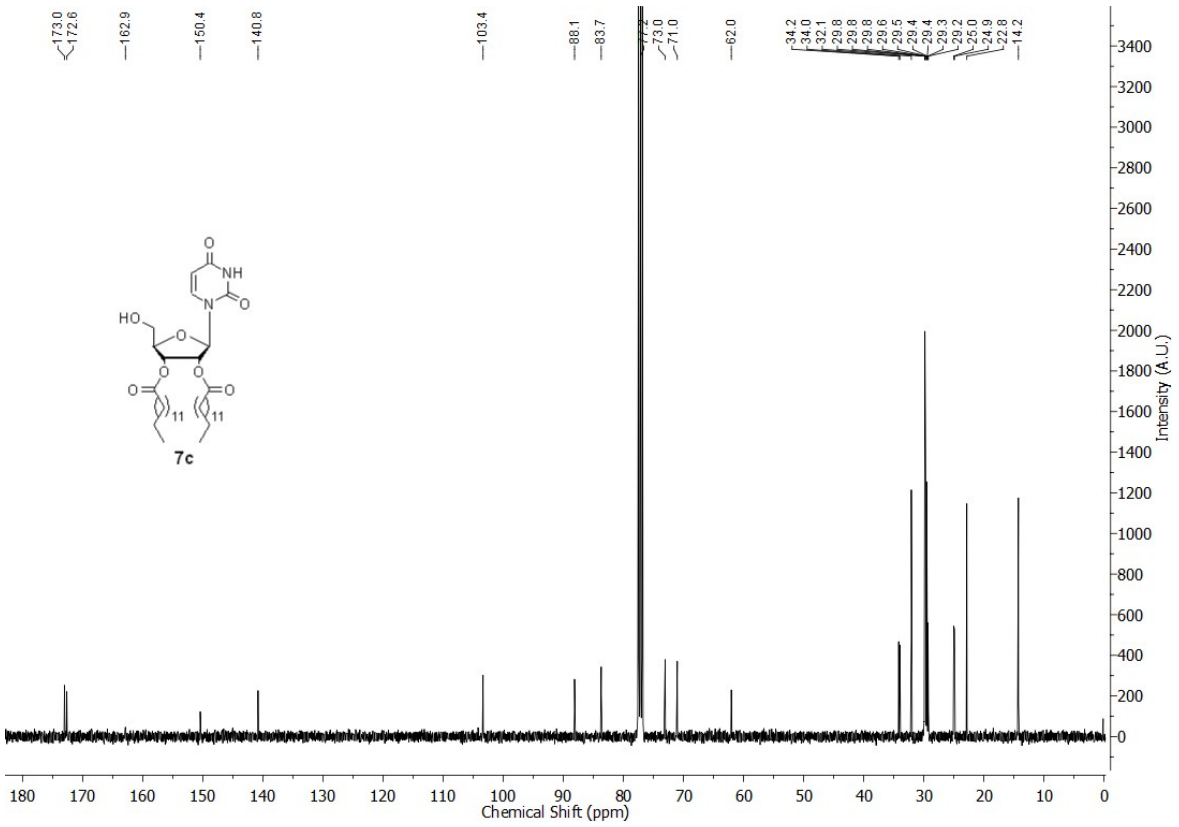
^{13}C NMR of nucleolipid **7b** in $CDCl_3$



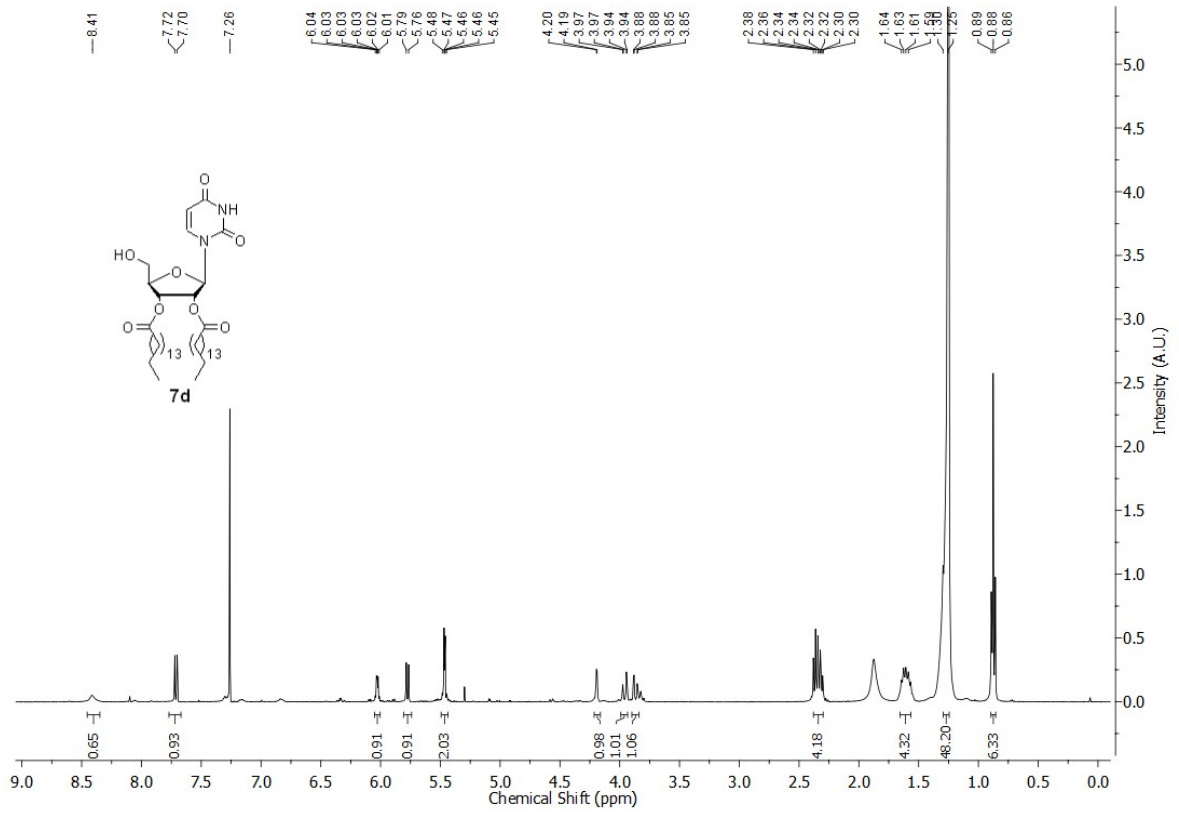
^{1}H NMR of nucleolipid **7c** in $CDCl_3$



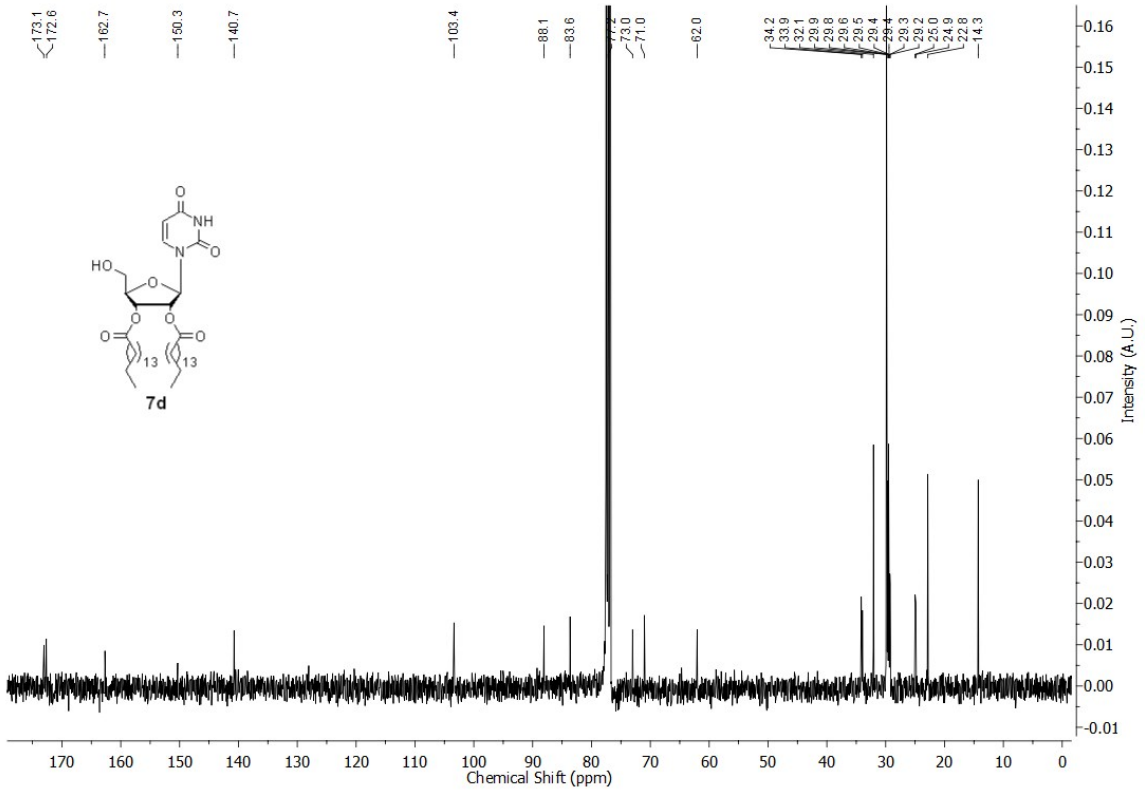
^{13}C NMR of nucleolipid **7c** in $CDCl_3$



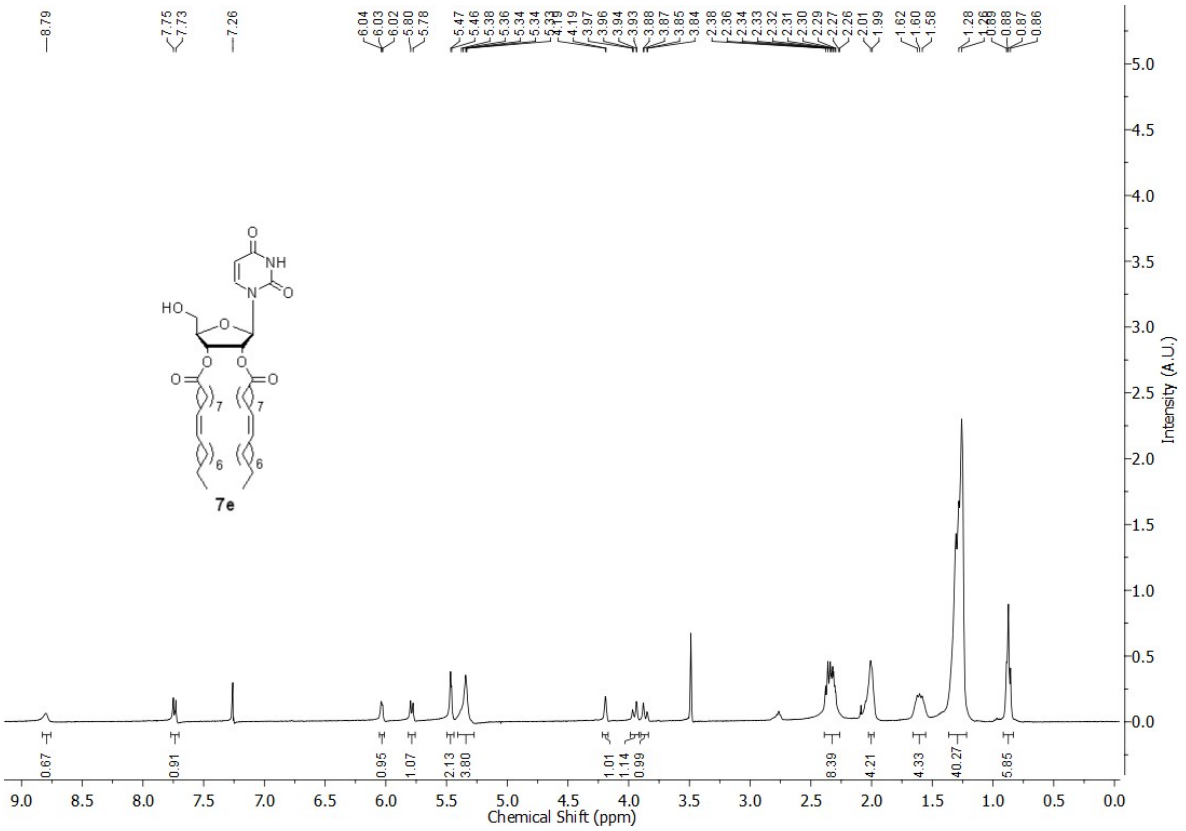
^{1}H NMR of nucleolipid **7d** in $CDCl_3$



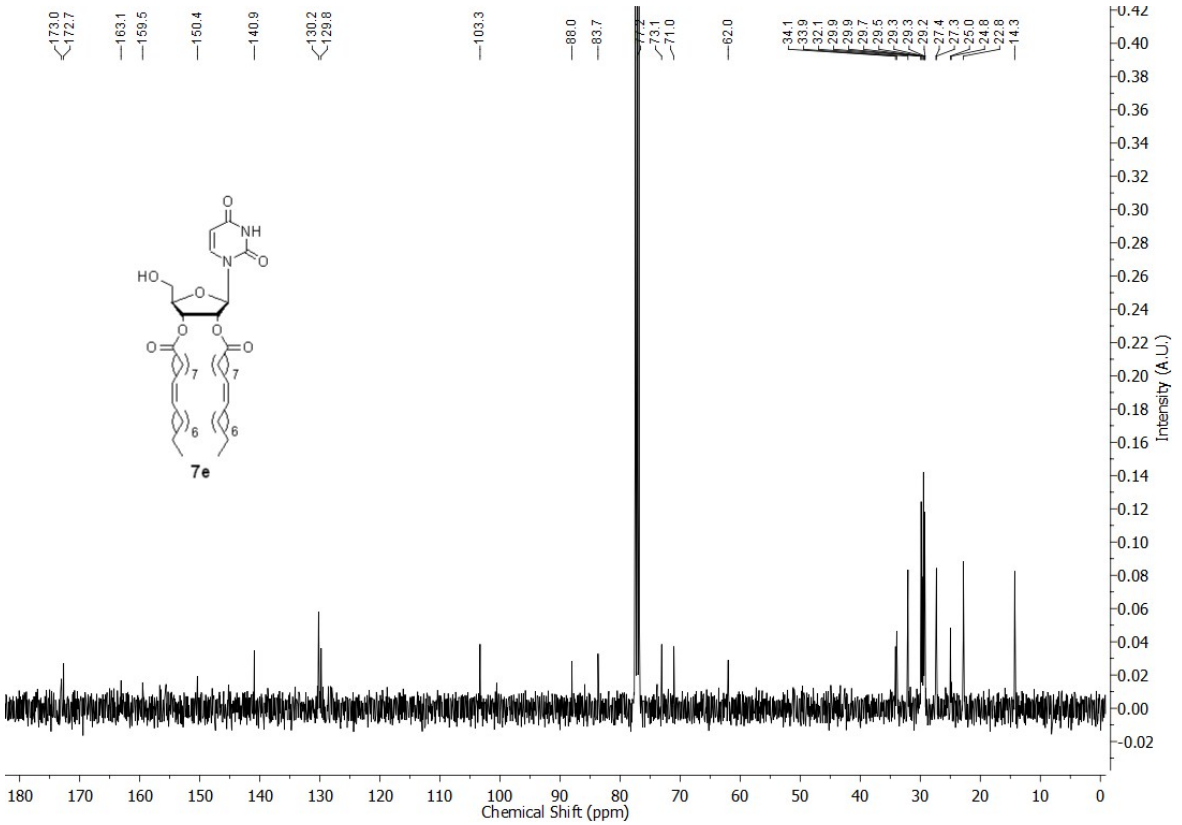
^{13}C NMR of nucleolipid **7d** in $CDCl_3$



^{1}H NMR of nucleolipid **7e** in $CDCl_3$



^{13}C NMR of nucleolipid **7e** in $CDCl_3$



7. References

S1. K. Shah, H. Wu, T. M. Rana, *Bioconjugate Chem.*1994, **5**, 508–512.

S2. A. Nuthanakanti, S. G. Srivatsan, *ACS Appl. Mater. Interfaces* 2017, **9**, 22864–22874.