Electronic supplementary materials *Mendeleev Commun.*, 2018, **28**, 626–628

Synthesis of new binary porphyrin–cyanine conjugates and their self-aggregation in organic-aqueous media

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Materials. Calcium hydride, phosphorus pentoxide, and organic solvents purchased from domestic manufacturers. 4-Hydroxybenzaldehyde, pyrrole and silica gel G60 were supplied by Merck. Dichloromethane were distilled over phosphorus pentoxide; pyrrole and THF over calcium hydride. **IR spectra** (4000-500 cm^{-1}) were recorded in KBr pellets on an Infralyum FT 02 Fourier transform spectrometer (Lumex Instruments Research and Production Company) in the region 4000-300 cm^{-1} with a resolution of 1 cm^{-1}. **NMR** (^{1}H and ^{13}C) spectra were measured in $CDCl_3$ or $(CD_3)_2SO$ on a Bruker MSL-300 pulse Fourier transform spectrometer in the JRC PMR IGIC RAS. Tetramethylsilane was used as an external standard. **MALDI mass spectra** were recorded on a Bruker autoflex speed time-of-flight (TOF) mass spectrometer (Bruker Daltonics Inc., Germany) equipped with a solid-state ultraviolet (UV) laser of 355 nm (1 kHz repetition rate, 1000 shots for each spectrum) operating in positive reflectron mode. MALDI mass spectra were recorded by using stainless-steel targets (MTP 384 ground steel; Bruker Daltonics Inc., Germany) containing 384 cells for the deposition of an analyte mixed with a reactive matrix. **Electronic spectra** were recorded on a TermoSpectronic Helios Alpha spectrophotometer in quartz cuvettes with an optical path length of 1 cm. **Fluorescence spectra** were measured on a Cary Eclipse spectrofluorometer (Agilent). **Dynamic light scattering spectra** were measured using the Photocor Complex dynamic and static light scattering spectrometer (Photokor Ltd., Russia) in the JRC PMR IGIC RAS. The measurements were carried out at a scattering angle of 90° in a thermostated cell at 25 °C. The average correlation function for each of the samples was obtained by averaging 10 curves taken with an accumulation of 10 s. The average hydrodynamic diameter of the particles, weighted by the contribution to the scattering intensity, was determined using the regularization method (DynaLS software).

10,15,20-Tris(4-hexadecyloxyphenyl)-5-(4-hydroxyphenyl)porphyrin **1**. To a boiled mixture of propionic acid (8 ml), acetic acid (4 ml) and nitrobenzene (2 ml), 4-hydroxybenzaldehyde (55 mg, 0.45 mmol) and 4-hexadecyloxybenzaldehyde (467 mg, 1.35 mmol) were added. The mixture was refluxed for 15 min. Then a solution of pyrrole (120 mg, 1.8 mmol) in nitrobenzene (2 ml) was added dropwise, and the mixture was refluxed for 2 h. The mixture was cooled and dissolved in hexane (100 ml) from which precipitation of porphyrin crystals occurs. The precipitate was filtered and dried, then chromatographed on silica gel G60 (system CH_2Cl_2:hexane= 5:1). Yield: 80 mg (13%). UV-vis, λmax/nm (lgε): 419.8 (5.86), 516.0 (5.2), 555.6 (4.08), 593.4 (3.82), 650.4 (3.74). ^{1}H NMR ($CDCl_3$, δ, ppm, 300 MHz): 9.5 (8H, br s, H2, H3, H7, H8, H12, H13, H17, H18), 8.2 (6H, d., *J*=8.30 Hz, 2-H), 8.01 (2H, d., *J*=8.44 Hz, 2-H), 7.53 (6H, d., *J*=8.58 Hz, 3-H), 7.28 (2H, d., *J*=8.84 Hz, 3-H), 4.2 (6H, m., -OC$\underline{H}_2$), 2.9 (6H, m., -OCH$_2$C$\underline{H}_2$), 2.6-2.2 (72H, br m, -(O(CH$_2$)$_2$(C$\underline{H}_2$)$_{12}$CH$_2$CH$_3$), 1.8 (6H, м., -C$\underline{H}_2$CH$_3$), 1.0 (9H, m, -CH$_2$C$\underline{H}_3$); ^{13}C-NMR ($CDCl_3$), δ, ppm: 157.72, 134.35, 131.18, 130.68, 118.60, 113.45, 111.45, 76.20, 75.78, 75.35, 70.77, 69.72, 69.42, 68.67, 67.07, 66.44, 57.85, 30.70, 28.50, 25.01, 21.47, 12.89 IR-spectrum, ν/cm^{-1}: 3436 (O-H bond), 1073 (Ph-O-R). MALDI-TOF-MS: calcd for $C_{92}H_{126}N_4O_4$ (M+H)+: 1351.99, found: 1351.993.1719.

5-(4-Aminophenyl)-10,15,20-tris(4-hexadecyloxyphenyl)porphyrin **2**. 5-(4-Acetamidophenyl) precursor was obtained from pyrrole (13 mg, 1.93 mmol), 4-hexadecyloxybenzaldehyde (500 mg, 1.45 mmol) and 4-acetamidobenzaldehyde (80 mg, 0.49 mmol) similarly to the above symthesis of **1**. Yield: 0.09 g (13%). The thus obtained semi-product (0.09, 0.07 mmol) was dissolved in trifluoroacetic acid (8 ml) and then conc. HCl (10 ml) was added. The mixture was stirred at 70°C for 48 h, then cooled, treated with CH_2Cl_2/H_2O system (1:1, 100 ml), the organic layer was washed two times with 10% Na_2CO_3. Purification by column chromatography on silica gel G 60 afforded 130 mg (95%) of product **2**. EAS ($CHCl_3$) λmax/nm (lgε): 422.8 (5.98); 518.4 (5.36); 556.4 (4.21); 597.8 (4.01); 650.2 (3.81). ^{1}H NMR ($CDCl_3$, δ, ppm, 300 MHz): 8.93-9.00 (8H, m, H2, H3, H7, H8, H12, H13, H17, H18), 8.13 (6H, d, *J*=8.44 Hz, 2-H), 8.02 (2H, d, *J*=8.44 Hz, 2-H), 7.34 (6H, d, *J*=8.25 Hz, 3-H), 7.10 (2H, d, *J*=8.44 Hz, 3-H), 4.28 (6H, t, *J*=6.60 Hz, -OC$\underline{H}_2$), 4.14 (2H, m, NH$_2$), 1.95-2.07 (6H, br m, -OCH$_2$C$\underline{H}_2$), 1.63-1.71 (6H, br m, -O(CH$_2$)$_2$C$\underline{H}_2$), 1.30-1.58 (72H, br m, -O(CH$_2$)$_3$(C$\underline{H}_2$)$_{12}$CH$_3$), 0.96 (9H, br m, AlkC$\underline{H}_3$), -2.70 (2H, br s, N$\underline{H}$). NMR ^{13}C ($CDCl_3$, δ, ppm.): 157.6, 150.95, 147.87, 135.9, 132.8, 127.2, 119.35, 118.45, 67.07, 31.05, 29.28, 29.00, 24.35, 21.95, 13.03. IR-spectrum ν/cm^{-1}: 3428 (PhNH2), 1241, 1050 (δ arC-O-alkC). MALDI-TOF-MS: calcd for $C_{92}H_{127}N_5O_3$: 1349.99, found: 1349.645.

3,3-Dimethyl-1-(6-oxo-6-{4-[10,15,20-tris(4-hexadecyloxyphenyl)porphyrin-5-yl]phenoxy}-hexyl)-2-[(1E,3E,5E)-5-(1,3,3-trimethyl-1,3-dihydro-2H-indol-2-ylidene)penta-1,3-dien-1-yl]-3H-indolium bromide **3**. To a solution of 1-(5-carboxypentyl)-3,3-dimethyl-2-[(1*E*,3*E*,5*E*)-5-(1,3,3-trimethyl-1,3-dihydro-2*H*-indol-2-ylidene)penta-1,3-dien-1-yl]-3*H*-indolium bromide (Cy5COOH, 30 mg, 0.06 mmol) in dry CH_2Cl_2 (4 ml), $SOCl_2$ (8 μl) was added. The mixture was boiled for 2 h, then evaporated *in vacuo* to remove excess $SOCl_2$. To a stirred solution of compound **1** (65 mg, 0.48 mmol) and DMAP (11 mg, 1.5 eq) in dry THF (4 ml), the above-prepared Cy5C(O)Cl in THF (2 ml) was added dropwise. The mixture was stirred at room temperature for 24 h, then treated with CH_2Cl_2/H_2O system (1:1, 15 ml), the organic layer was dried over Na_2SO_4. The product was isolated by column chromatography on silica gel G60 (gradient EtOAc to 10:1 EtOAc–MeOH). EAS ($CHCl_3$) λmax/nm (lgε): 425 (4.83); 557 (3.99); 602 (4.09); 650 (4.39). ^{1}H NMR ($CDCl_3$, δ, ppm, 300 MHz): 8.92-8.97 (8H, m, H2, H3, H7, H8, H12, H13, H17, H18), 8.20 (2H, br, 2-H), 8.08 (1H, s, for H – j), 8.02 (6H, br, 2-H), 7.58-7.75 (4H, m, for H – a, H – d, H – e, H – h), 7.16-7.29 (4H, m, for H – b, H – c, H – g, H – f), 7.16-7.33 (8H, br, for 3-H, 1H, s, for 1H, s, 1H, s), 6.88-6.91 (1H, m, for H – l), 5.74 (1H, s, H – m), 5.55 (1H, m, for H – k), 5.19 (1H, m, for H – i), 4.29-4.35 (2H, m, N-C$\underline{H}_2$$CH_2$), 4.19-4.26 (6H, m, -OC$\underline{H}_2$), 3.38 (3H, br, N-C$\underline{H}_3$), 2.64 (2H, d, *J*=4.27 Hz, N-$(CH_2)_4$C$\underline{H}_2$C(O)), 2.18 (6H,s, -$C(CH_3)_2$), 2.01 (6H, s, -$C(CH_3)_2$), 1.69-1.77 (6H, br m, -OCH_2C$\underline{H}_2$), 1.60-1.68 (2H, m, for NCH_2C$\underline{H}_2$, 6H, m, for -$O(CH_2)_2$C$\underline{H}_2$), 1.22-1.36 (72H, many multiples, -$O(CH_2)_3(C\underline{H}_2)_{12}CH_3$), 0.91-0.98 (9H, br m, AlkC$\underline{H}_3$). MALDI-TOF-MS: calcd for $C_{92}H_{127}N_5O_3$: 1349.99, found: 1349.645. Yield 12 mg (10%). MALDI-TOF-MS: calcd for $C_{124}H_{163}BrN_6O_5$: 1895.19, found: 1896.04 [M+1].

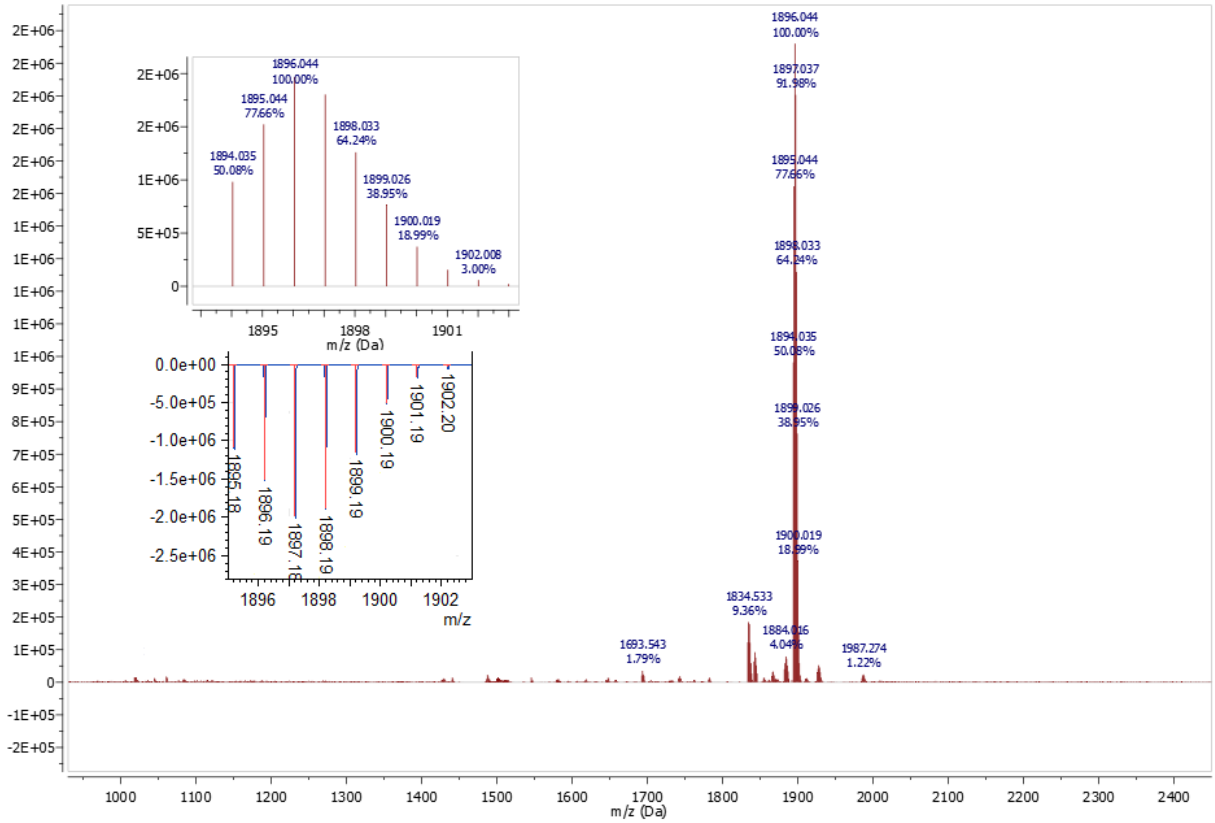

Figure S1. MS of conjugate **3** and its calculated mass spectrum (reflected).

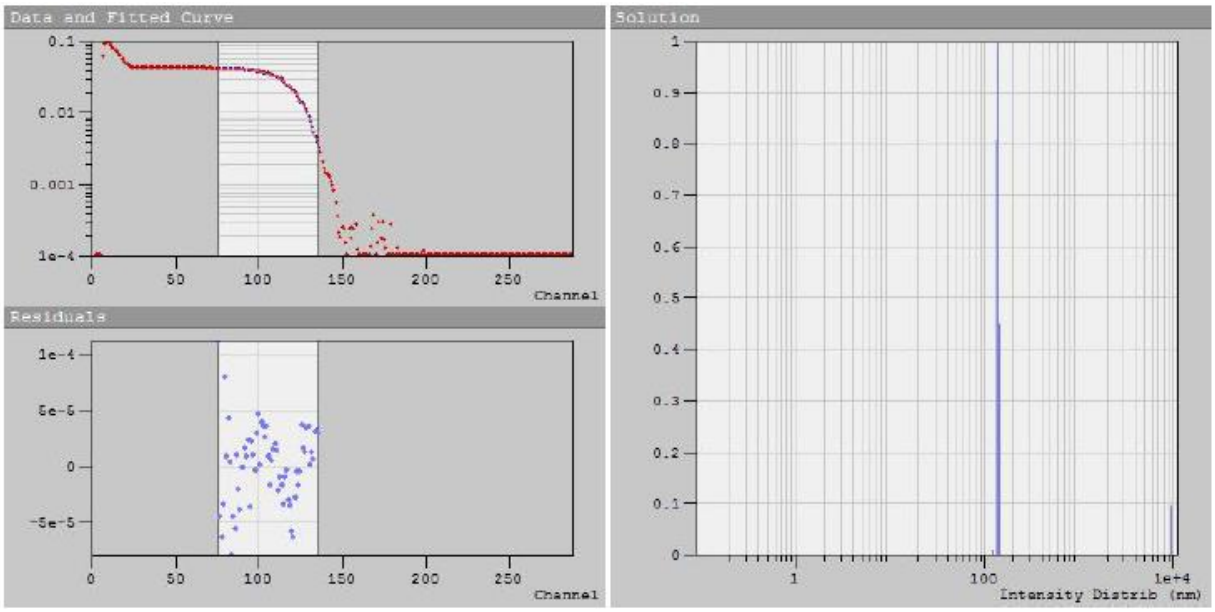

Figure S2. Particle size of conjugate **3** in THF/H_2O ratio=50:50.

3,3-Dimethyl-1-(6-oxo-6-{4-[10,15,20-tris(4-hexadecyloxyphenyl)porphyrin-5-yl]phenylamino}-hexyl)-2-[(1E,3E,5E)-5-(1,3,3-trimethyl-1,3-dihydro-2H-indol-2-ylidene)penta-1,3-dien-1-yl]-3H-indolium bromide **4**. A solution of Cy5COOH (20 mg, 0.04 mmol), *N*-hydroxysuccinimide (NCS, 23 mg, 0.2 mmol) and DIPEA (11 mg, 0.08 mmol) in dry $CHCl_3$ (6 ml) was stirred for 1 h under argon. Then 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC, 15.3 mg, 0.08 mmol) and compound **2** (27 mg, 0.02 mmol) were added, and the resulting solution was stirred for 24 h. The reaction mixture was washed several times with water (20 ml), the organic layer was dried over Na_2SO_4 and concentrated on rotary evaporator. The product was isolated by column chromatography on silica gel G60 (gradient EtOAc to 10:1 EtOAc–MeOH). Yield: 15 mg (20%). EAS ($CHCl_3$) λmax/nm (lgε): 422 (4.74); 550 (3.92); 597 (3.99); 649 (3.27). ^{1}H NMR ($CDCl_3$, δ, ppm, 300 MHz): 8.90-8.97 (8H, m, H2, H3, H7, H8, H12, H13, H17, H18), 8.24 (2H, br, 2-H), 8.09 (1H, s, for H – j), 8.01 (6H, br, 2-H), 7.55-7.74 (4H, m, for H – a, H – d, H – e, H – h), 7.15-7.30 (4H, m, for H – b, H – c, H – g, H – f), 7.20-7.31 (8H, br, for 3-H, 1H, s, for 1H, s, 1H, s), 6.80-6.90 (1H, m, for H – l), 5.75 (1H, s, H – m), 5.65 (1H, m, for H – k), 5.18 (1H, m, for H – i), 4.28-4.34 (2H, m, N-CH_2CH_2), 4.18-4.26 (6H, m, -OC$\underline{H}_2$), 3.35 (3H, br, N-CH_3), 2.68 (2H, m, N-$(CH_2)_4C\underline{H}_2C(O)$), 2.20 (6H,s, -$C(C\underline{H}_3)_2$), 2.07 (6H, s, -$C(C\underline{H}_3)_2$), 1.68-1.76 (6H, br m, -$OCH_2C\underline{H}_2$), 1.59-1.71 (2H, m, for $NCH_2C\underline{H}_2$, 6H, m, for -$O(CH_2)_2C\underline{H}_2$), 1.20-1.38 (72H, several multiplets, -$O(CH_2)_3(C\underline{H}_2)_{12}CH_3$), 0.91-0.98 (9H, br m, AlkCH_3). MALDI-TOF-MS: calcd for: 1894.20, found: 1817.724 [M^+-Br].

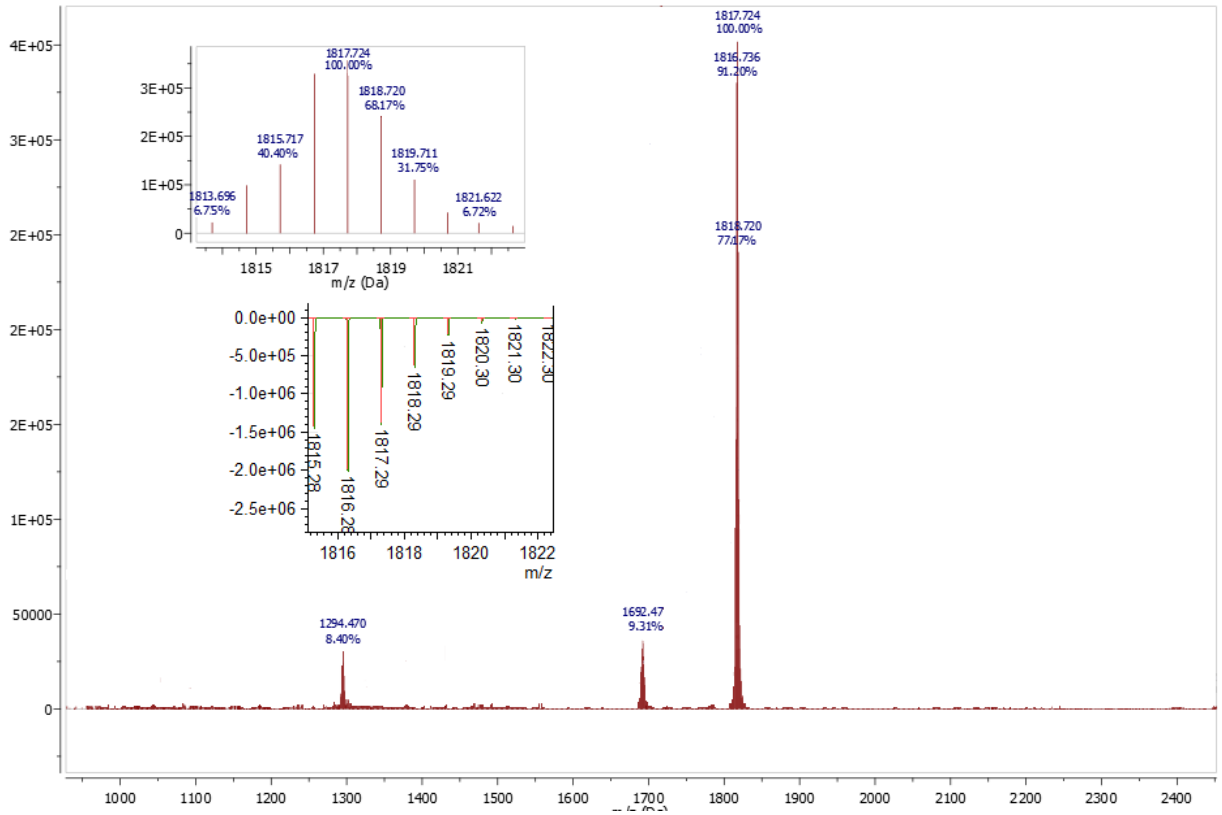

Figure S3. MS of comjugate **4** and its calculated mass spectrum (reflected).

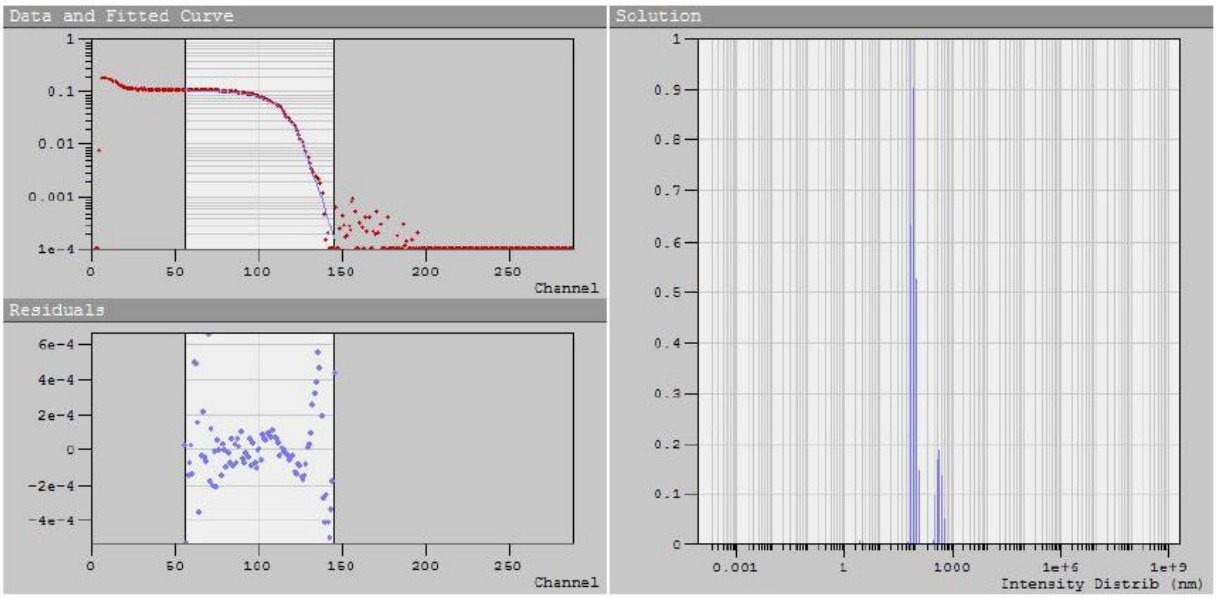

Figure S4. Particle size of conjugate **4** in THF/H_2O ratio=50:50.