Supporting Information

Mechanosensitive Membrane Probes: Push-Pull Papillons

Heorhii V. Humeniuk,[a] Giuseppe Licari,[a,b] Eric Vauthey,[a] Naomi Sakai[a] and Stefan Matile[a]*

[a] *Department of Organic Chemistry, University of Geneva, CH-1211 Geneva 4, Switzerland,*

[b] *Current address: Department of Chemistry, University of Illinois at Urbana−Champaign, Urbana, Illinois 61801-3028, USA.*

stefan.matile@unige.ch

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1. Materials and Methods

As in references (*S1*) and (*S2*), reagents for synthesis were purchased from Sigma-Aldrich, Fluka, Acros and Alfa-Aesar, buffers and salts of the best grade available from Fluka or Sigma-Aldrich and used as received.

1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC), were purchased from Avanti Polar Lipids. Large unilamellar vesicles were prepared using a Mini-Extruder from Avanti Polar Lipids (pore size 100 nm).

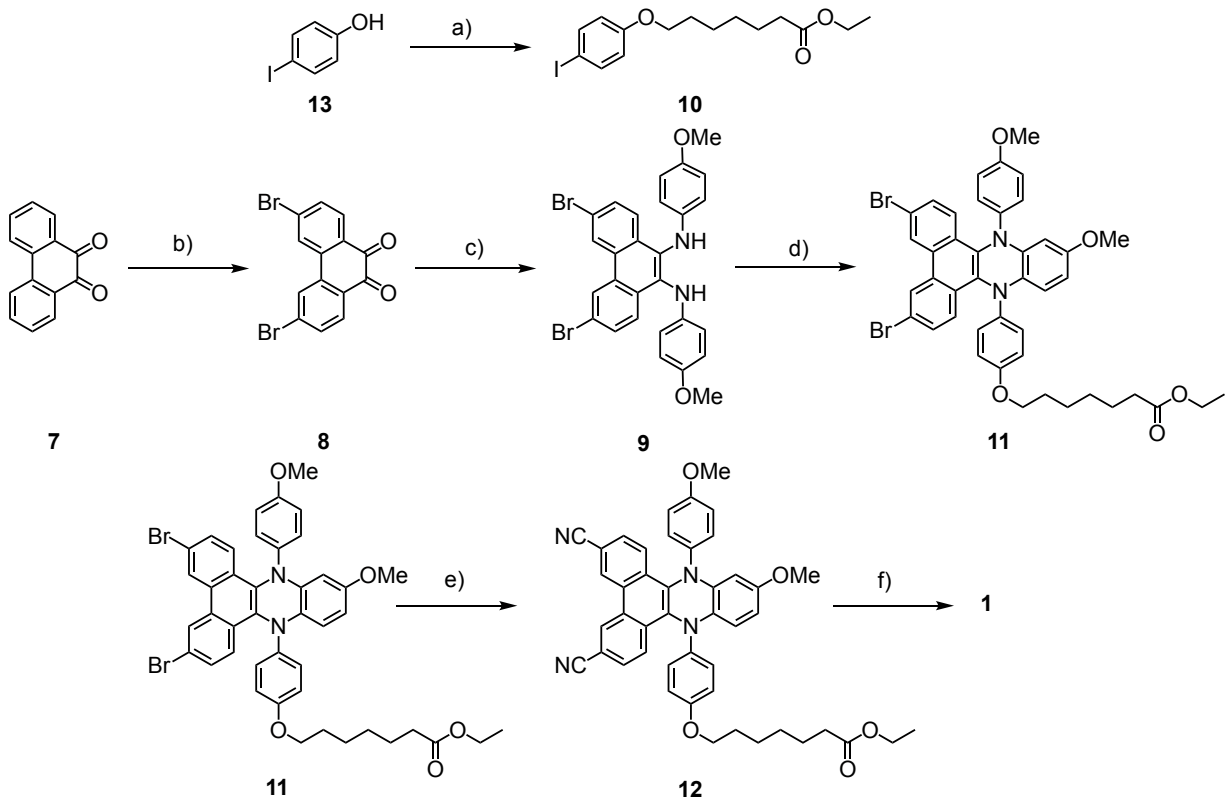
Unless stated otherwise, column chromatography was carried out on silica gel 60 (Fluka, 40–63 μm) or silica gel (SiliaFlash® P60, SILICYCLE, 230–400 mesh). Analytical (TLC) and preparative thin layer chromatography (PTLC) were performed on TLC silica gel 60 F254 (Merck) and SilicaPlate TLC (SILICYCLE, 1000 mm) respectively. UV–Vis spectra were recorded on a JASCO V–650 spectrophotometer equipped with a stirrer and a temperature controller and are reported as maximal absorption wavelength λ in nm. Fluorescence measurements were performed with a FluoroMax–4 NIR spectrofluorometer (Horiba Scientific) equipped with a stirrer and a temperature controller. Spectral corrections were applied unless stated otherwise. All the spectra were corrected by subtraction of the corresponding blank (solvent or lipid vesicles). Melting points (Mp) were recorded on a Büchi Melting Point M-565. IR spectra were recorded on a Perkin Elmer Spectrum One FT–IR spectrometer (ATR, Golden Gate) and are reported in cm^{-1} with band intensities indicated as s (strong), m (medium), w (weak), b (broad).

^{1}H and ^{13}C NMR spectra were recorded (as indicated) either on a Bruker 400 MHz or 500 MHz spectrometer and are reported as chemical shifts (δ) in ppm relative to (residual) solvent signal. Spin multiplicities are reported as a singlet (s), doublet (d), triplet (t), quartet (q), with coupling constants (J) given in Hz, or multiplet (m). ^{13}C Resonances were assigned with the aid of additional information from DEPT135 spectra.

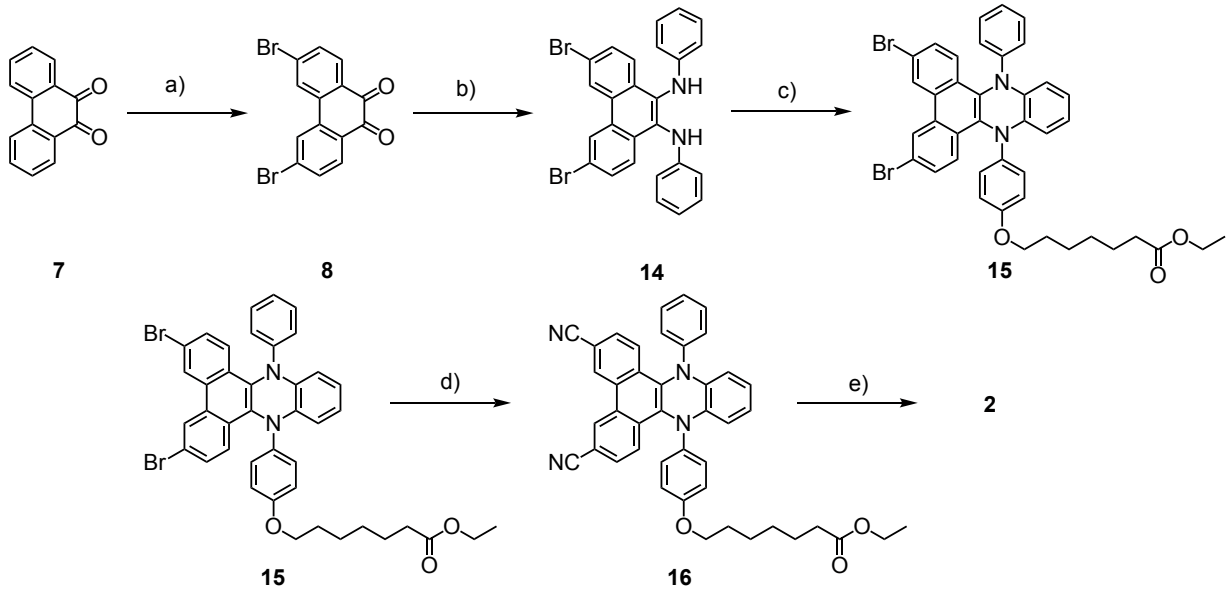
ESI–MS were performed on a ESI API 150EX and are reported as *m/z* (%, [assignment]). Accurate mass determinations using ESI (HRMS) were performed on a Sciex QSTAR Pulsar mass spectrometer.

Abbreviations. BPO: Benzoyl peroxide; Calcd: Calculated; CAN: Ammonium cerium(IV) nitrate; DMF: *N,N*-Dimethylformamide; DCE: 1,2-dichloroethane; DOPC: 1,2-Dioleoyl-*sn*-glycero-3-phosphocholine; DPPC: 1,2-Dipalmitoyl-*sn*-glycero-3-phosphocholine; L_d: Liquid disordered; LUVs: Large unilamellar vesicles; NMP: *N*-Methyl-2-pyrrolidone; PE: Petroleum ether; rt: Room temperature; S_o: Solid ordered; TBAB: Tetrabutylammonium bromide; TCB: 1,2,4-Trichlorobenzene; THF: Tetrahydrofuran; Tris: Tris(hydroxymethyl)aminomethane.

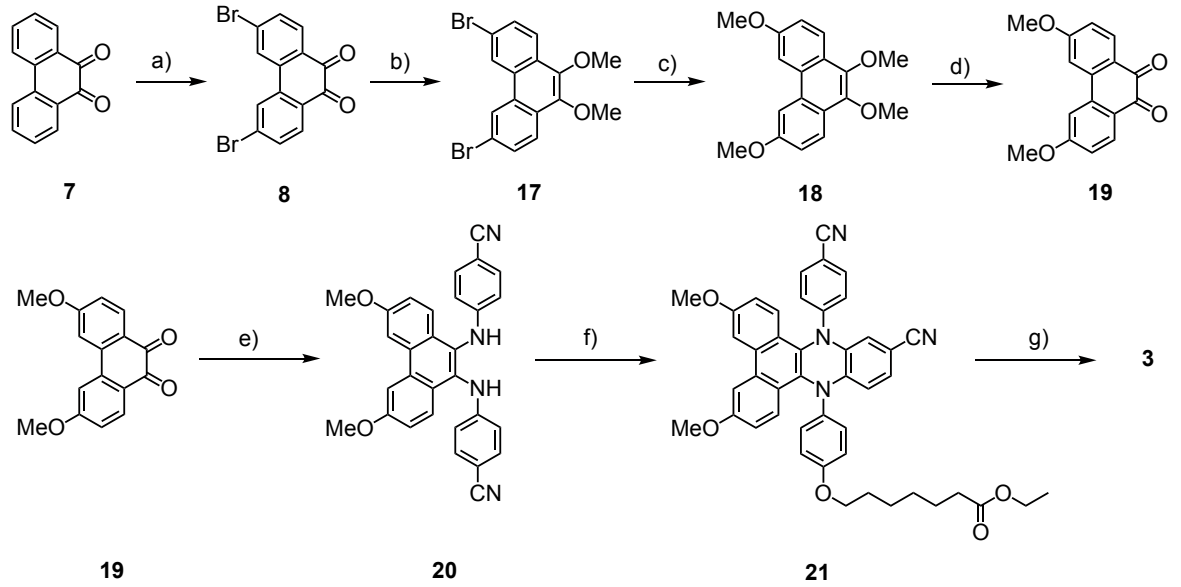
2. Synthesis



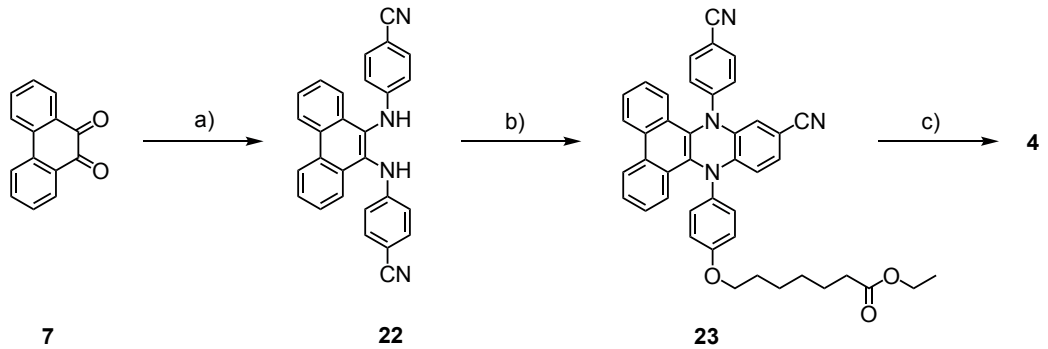
Scheme S1. a) Ethyl 7-bromoheptanoate, K_2CO_3, DMF, 70 °C overnight, 81%; b) Br_2, BPO, nitrobenzene, 110 °C, overnight, 57%; c) 1. 4-Methoxyaniline, pyridine, $TiCl_4$, CH_2Cl_2, rt, overnight; 2. Hydrazine hydrate, Pd/C, THF, rt, 2 h, 31% over two steps; d) **10**, K_2CO_3, $Cu(OTf)_2$, 1,2,4-trichlorobenzene, 210 °C, overnight, 5%; e) CuCN, NMP, 150 °C, overnight, 8%; f) Me_3SnOH, DCE, reflux, 3 h, 49%.



Scheme S2. a) Br_2, BPO, nitrobenzene, 110 °C, overnight, 57%; b) 1. aniline, pyridine, $TiCl_4$, CH_2Cl_2, rt, overnight; 2. Hydrazine hydrate, Pd/C, THF, rt, 2 h, 86% over two steps; c) **10**, K_2CO_3, $Cu(OTf)_2$, 1,2,4-trichlorobenzene, 210 °C, overnight, 23%; d) CuCN, NMP, 150 °C, overnight, 41%; e) Me_3SnOH, DCE, reflux, 4 h, 71%.



Scheme S3. a) Br_2, BPO, nitrobenzene, 110 °C, overnight, 57%; b) 1. $Na_2S_2O_4$, TBAB, THF, H_2O, rt, 20 min; 2. $(CH_3)_2SO_4$, NaOH, THF, H_2O, rt, 20 min, 76%; c) NaOMe, CuBr, MeOH, toluene, 80 °C, overnight, 75%; d) CAN, CH_3CN, rt, 30 min, 88%; e) 1. 4-aminobenzonitrile, pyridine, $TiCl_4$, CH_2Cl_2, rt, overnight; 2. Hydrazine hydrate, Pd/C, THF, rt, 2 h, 78% over two steps; f) **10**, K_2CO_3, $Cu(OTf)_2$, TCB, 210 °C, overnight, 72%; g) Me_3SnOH, DCE, reflux, 3 h, 61%.



Scheme S4. a) 1. 4-Aminobenzonitrile, pyridine, $TiCl_4$, CH_2Cl_2, rt, overnight; 2. Hydrazine hydrate, Pd/C, THF, rt, 2 h, 61%; b) **10**, K_2CO_3, $Cu(OTf)_2$, TCB, 210 °C, overnight, 51%; c) Me_3SnOH, DCE, reflux, 4 h, 82%.

Compound 10 was synthesized following the literature procedures (*S3*).

Compound 8 was synthesized following the literature procedures (*S4*).

Compound 9. To a solution of **8** (3.66 g, 10.0 mmol) and 4-methoxyaniline (5.41 g, 44.0 mmol) in anhydrous CH_2Cl_2 (130 mL), under N_2, pyridine (8.14 mL, 100 mmol) was added and the solution was cooled to 0 °C. Then, $TiCl_4$ (3.63 mL, 33.0 mmol) was added dropwise and reaction mixture was stirred at rt overnight. Then, the solution was diluted with CH_2Cl_2 (250 mL), stirred for 10 min, and filtered to remove the solid. The solvent was evaporated and residual viscous dark oil was subjected to next step. Crude product was dissolved under N_2 in 120 mL of MeOH/THF 1:1, Pd/C (10%, 50 mg) was added followed by hydrazine hydrate (6 mL). The reaction mixture was stirred at rt for 2 hours followed by filtration through Na_2SO_4/celite 1:1. The filtrate was evaporated to dryness and the solid residue was purified by flash chromatography (SiO_2, PE/CH_2Cl_2 1:2), affording **9** as a yellow-green powder (1.8 g, 31%). R_f (PE/CH_2Cl_2 1:1): 0.31; Mp: 153 – 154 °C (decomp.); IR (neat): 3305 (w), 2951 (w), 2832 (w), 1609 (w), 1584 (m), 1503 (s), 1449 (m), 1390 (m), 1300 (m), 1232 (s), 1178 (m), 1167 (m), 1104 (m), 1032 (s), 929 (w), 812 (s), 757 (m), 719 (m), 683 (m), 626 (m), 556 (m); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.77 (d, ^4J (H,H) = 2.0 Hz, 2H), 7.82 (d, ^3J (H,H) = 8.8 Hz, 2H), 7.60 (dd, ^3J (H,H) = 8.8 Hz, ^4J (H,H) = 2.0 Hz, 2H), 6.75 – 6.66 (m, 4H), 6.65 – 6.55 (m, 4H), 5.82 (s, 2H), 3.70 (s, 6H); ^{13}C NMR (101 MHz, CD_2Cl_2): 154.8 (C), 140.7 (C), 132.0 (C), 131.2 (CH), 131.0 (C), 129.8 (C), 127.5 (CH), 126.6 (CH), 121.3 (C), 118.1 (CH), 115.5 (CH), 56.3 (CH_3); ESI–MS (–ve, $CHCl_3$/MeOH 1:1): 579/577/575 (50/100/50, $[M–H]^–$), 564/562/560 (50/100/50, $[M–Me–H]^–$).

Compound 11. To a solution of **9** (460 mg, 0.80 mmol) and **10** (200 mg, 0.53 mmol) in TCB (6 mL), K_2CO_3 (221 mg, 1.60 mmol) and $Cu(OTf)_2$ (72 mg, 0.20 mmol) were added. The mixture was stirred at 210 °C under air overnight. TCB was removed by vacuum distillation to give a black residue. After cooling to rt, the residue was diluted with CH_2Cl_2 (20 mL), stirred for 10 min, and filtered. The filtrate was purified by flash chromatography (SiO_2, PE/CH_2Cl_2 1:2) and subsequently by PTLC (SiO_2, PE/EtOAc 4:1) to afford **11** as a lemon-yellow powder (20 mg, 5%). R_f (PE/CH_2Cl_2 1:3): 0.72; Mp: 83 – 84 °C; IR (neat): 2929 (m), 2856 (w), 1730 (m), 1612 (w), 1591 (w), 1503 (s), 1442 (m), 1393 (w), 1376 (w), 1346 (w), 1238 (s), 1204 (s), 1174 (s), 1100 (m), 1032 (m), 826 (s), 762 (w), 736 (m), 638 (w), 594 (w), 550 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.74 (d, ^4J (H,H) = 1.8 Hz, 2H), 7.99 (d, ^3J (H,H) = 8.8 Hz, 1H), 7.94 (d, ^3J (H,H) = 8.8 Hz, 1H), 7.62 (dd, ^3J (H,H) = 8.7 Hz, ^3J (H,H) = 1.9 Hz, 1H),

7.58 (dd, ^{3}J (H,H) = 8.8 Hz, ^{3}J (H,H) = 1.9 Hz, 1H), 7.53 (d, ^{3}J (H,H) = 8.7 Hz, 1H), 7.19 (d, ^{4}J (H,H) = 2.8 Hz, 1H), 7.04 (d, ^{3}J (H,H) = 9.0 Hz, 2H), 6.89 (d, ^{3}J (H,H) = 9.0 Hz, 2H), 6.83 (dd, ^{3}J (H,H) = 8.7 Hz, ^{4}J (H,H) = 2.8 Hz, 1H), 6.71 – 6.58 (m, 4H), 4.07 (q, ^{3}J (H,H) = 7.1 Hz, 2H), 3.86 (s, 3H), 3.80 (t, ^{3}J (H,H) = 6.5 Hz, 2H), 3.68 (s, 3H), 2.25 (t, ^{3}J (H,H) = 7.5 Hz, 2H), 1.73 – 1.57 (m, 4H), 1.43 – 1.33 (m, 4H), 1.21 (t, ^{3}J (H,H) = 7.1 Hz, 4H); ^{13}C NMR (101 MHz, CD_2Cl_2): 174.0 (C), 158.1 (C), 156.3 (C), 155.1 (C), 146.1 (C), 143.1 (C), 142.0 (C) 138.0 (C), 137.9 (C), 137.5 (C), 137.3 (C), 131.1 (CH), 130.9 (C), 130.9 (CH), 130.7 (C), 129.2 (C), 128.9 (C), 127.3 (CH), 126.8 (C), 126.7 (CH), 126.4 (CH), 126.3 (CH), 124.9 (C), 123.6 (C), 122.2 (CH), 122.2 (CH), 121.3 (C), 120.2 (CH), 119.7 (CH), 115.4 (CH), 115.3 (C), 114.8 (CH), 114.8 (CH), 111.6 (CH), 110.7 (CH), 68.7 (CH_2), 60.6 (CH_2), 56.3 (CH_3), 55.9 (CH_3), 34.7 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 26.2 (CH_2), 25.4 (CH_2), 14.6 (CH_3); ESI–MS (+ve, $CHCl_3$/MeOH/HCOOH 50:50:0.1): 827/825/823 (50/100/50, $[M+H]^+$).

Compound 12. To a solution of **11** (75 mg, 0.091 mmol) in dry NMP (1.5 mL), CuCN (150 mg, 1.67 mmol) was added. The mixture was stirred at 140 °C under N_2 overnight. After cooling, the mixture was diluted with CH_2Cl_2 (10 mL), stirred for 10 min, and filtered. The filtrate was purified by flash chromatography (SiO_2, PE/CH_2Cl_2 5:1 to 1:2) and subsequently by PTLC (SiO_2, CH_2Cl_2) to afford **12** as an orange glassy solid (5.1 mg, 8%). R_f (PE/CH_2Cl_2 1:3): 0.25; Mp: 103 – 104 °C; IR (neat): 2934 (w), 2859 (w), 2227 (m), 1731 (m), 1610 (w), 1579 (w), 1504 (s), 1467 (w), 1437 (m), 1381 (w), 1335 (w), 1246 (m), 1212 (m), 1107 (w), 1033 (m), 888 (w), 825 (m), 648 (w), 590 (w), 558 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.88 (d, ^{4}J (H,H) = 1.2 Hz, 2H), 8.20 (d, ^{3}J (H,H) = 8.6 Hz, 1H), 8.16 (d, ^{3}J (H,H) = 8.6 Hz, 1H), 7.72 (dd, ^{3}J (H,H) = 8.6 Hz, ^{4}J (H,H) = 1.2 Hz, 1H), 7.69 (dd, ^{3}J (H,H) = 8.6 Hz, ^{4}J (H,H) = 1.2 Hz, 1H), 7.56 (d, ^{3}J (H,H) = 8.8 Hz, 1H), 7.20 (d, ^{4}J (H,H) = 2.7 Hz, 1H), 7.07 (d, ^{3}J (H,H) = 9.1 Hz, 2H), 6.92 (d, ^{3}J (H,H) = 9.1 Hz, 2H), 6.86 (dd, ^{3}J (H,H) = 8.8 Hz, ^{4}J (H,H) = 2.7 Hz, 2H), 6.71 (d, ^{3}J (H,H) = 9.1 Hz, 2H), 6.66 (d, ^{3}J (H,H) = 9.1 Hz, 2H), 4.07 (q, ^{3}J (H,H) = 7.1 Hz, 2H), 3.87 (s, 3H), 3,82 (t, ^{3}J (H,H) = 6.5 Hz, 2H) 3.69 (s, 3H), 2.25 (t, ^{3}J (H,H) = 7.5 Hz, 2H), 1.72 – 1.56 (m, 4H), 1.44 – 1.29 (m, 4H), 1.21 (t, ^{3}J (H,H) = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 174.0 (C), 158.4 (C), 156.9 (C), 155.6 (C), 145.5 (C), 142.8 (C), 141.6 (C), 140.0 (C), 139.6 (C), 136.5 (C), 132.8 (C), 132.5 (C), 129.9 (CH), 129.7 (CH), 129.2 (C), 129.0 (C), 128.7 (CH), 127.0 (CH), 126.1 (CH), 123.2 (CH), 121.0 (CH), 119.5 (C), 119.4 (C), 115.6 (CH), 115.1 (CH), 111.1 (CH), 110.7 (C), 68.7 (CH_2), 60.6 (CH_2), 56.4 (CH_3), 56.0 (CH_3), 34.7 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 26.2 (CH_2), 25.4 (CH_2), 14.6 (CH_3); ESI–MS (+ve, $CHCl_3$/MeOH/HCOOH 50:50:0.1): 718 (100, $[M+H]^+$).

Compound 1. To a solution of **12** (4.5 mg, 0.0063 mmol) in DCE (0.5 mL), under N_2, Me_3SnOH (20 mg, 0.1 mmol) was added. The mixture was stirred at reflux for 3 hours, and then cooled. CH_2Cl_2 (10 mL) and saturated aqueous solution of $KHSO_4$ (10 mL) were added. The organic layer was separated and washed additionally with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by PTLC (SiO_2, CH_2Cl_2/MeOH 98:2) afforded **1** as an orange powder (2.1 mg, 49%). R_f (CH_2Cl_2/MeOH 96:4): 0.28; Mp: 258 – 259 °C; IR (neat): 3356 (br), 2922 (s), 2853 (s), 2227 (m), 1727 (m), 1607 (m), 1504 (s), 1435 (s), 1246 (s), 1074 (s), 874 (m), 824 (m), 713 (w), 648 (w), 602 (m), 555 (m) ; ^{1}H NMR (500 MHz, DMSO-d_6): 9.62 (d, ^4J (H,H) = 1.5 Hz, 2H), 8.13 (d, ^3J (H,H) = 8.5 Hz, 1H), 8.10 (d, ^3J (H,H) = 8.5 Hz, 2H), 7.99 (dd, ^3J (H,H) = 8.5 Hz, ^4J (H,H) = 1.5 Hz, 1H), 7.96 (dd, ^3J (H,H) = 8.5 Hz, ^4J (H,H) = 1.5 Hz, 1H), 7.68 (d, ^3J (H,H) = 8.8 Hz, 1H), 7.33 (d, ^3J (H,H) = 2.8 Hz, 1H), 7.29 – 7.22 (m, 2H), 7.09 – 7.02 (m, 2H), 6.89 (dd, ^3J (H,H) = 8.8 Hz, ^4J (H,H) = 2.8 Hz, 1H), 6.83 – 6.77 (m, 2H), 6.77 – 6.71 (m, 2H), 3.86 – 3.79 (m, 5H), 3.66 (s, 3H), 2.09 (t, ^3J (H,H) = 7.4 Hz, 2H), 1.62 (p, ^3J (H,H) = 6.7 Hz, 2H), 1.46 (p, ^3J (H,H) = 7.4 Hz, 2H), 1.37 – 1.29 (m, 4H); ^{13}C NMR (126 MHz, DMSO-d_6): 174.9 (C), 157.2 (C), 155.8 (C), 154.5 (C), 144.5 (C), 141.8 (C), 140.7 (C), 138.6 (C), 138.2 (C), 135.4 (C), 131.2 (C), 131.0 (C), 129.8 (CH), 129.8 (CH), 129.6 (CH), 129.4 (C), 128.8 (CH), 128.6 (CH), 126.2 (CH), 124.9 (C), 124.9 (C), 123.0 (CH), 120.7 (CH), 119.0 (C), 118.9 (C), 115.0 (CH), 114.6 (CH), 110.6 (CH), 110.1 (C), 109.4 (C), 109.4 (C), 67.5 (CH_2), 55.6 (CH_3), 55.2 (CH_3), 29.0 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 25.3 (CH_2), 24.9 (CH_2); HRMS (ESI, +ve) calcd for $C_{43}H_{36}N_4O_5$ ($[M+H]^+$): 689.2759, found: 689.2755.

Compound 14. To a solution of **8** (1.47 g, 4.00 mmol) in anhydrous CH_2Cl_2 (75 mL), under N_2, aniline (1.60 mL, 17.6 mmol) and pyridine (3.3 mL, 40 mmol) were added and the solution was cooled to 0 °C. Then, $TiCl_4$ (1.45 mL, 13.2 mmol) was added dropwise and reaction mixture was stirred at rt overnight. Then, the solution was diluted with CH_2Cl_2 (150 mL), stirred for 15 min, and filtered to remove the solid. The solvent was evaporated and viscous red oil was subjected to next step. Crude product was dissolved under N_2 in 60 mL of THF, Pd/C (10%, 20 mg) was added followed by hydrazine hydrate (3 mL). The reaction mixture was stirred at rt for 1 hour followed by filtration through Na_2SO_4/celite 1:1. The filtrate was evaporated to dryness and the solid residue was purified by flash chromatography (SiO_2, PE/CH_2Cl_2 2:1), affording **14** as a yellow-green powder (1.8 g, 86%). R_f (PE/CH_2Cl_2 1:1): 0.9; Mp: 192 – 193 °C (decomp.); IR (neat): 3330 (m), 3045 (w), 1697 (w), 1585 (s), 1492 (s), 1438 (m), 1376 (m), 1346 (m), 1317 (m), 1287 (m), 1244 (m), 1177 (w), 1099 (m), 1078 (m), 1021 (m), 918 (w), 873 (w), 846 (m), 808 (s), 750 (s), 691 (s), 655 (m), 572 (m); ^{1}H NMR (400

MHz, CD_2Cl_2): 8.80 (d, ^4J (H,H) = 1.8 Hz, 2H), 7.87 (d, ^3J (H,H) = 8.8 Hz, 2H), 7.63 (dd, ^3J (H,H) = 8.8 Hz, ^4J (H,H) = 1.8 Hz, 2H), 7.12 (t, ^3J (H,H) = 7.9 Hz, 4H), 6.81 (t, ^3J (H,H) = 7.3 Hz, 2H), 6.60 (d, ^3J (H,H) = 7.8 Hz, 4H), 5.90 (s, 2H); ^{13}C NMR (101 MHz, CD_2Cl_2): 146.7 (C), 131.7 (C), 131.1 (CH), 130.9 (C), 129.9 (CH), 129.8 (C), 127.4 (CH), 126.4 (CH), 121.5 (C), 120.5 (CH), 115.9 (CH); ESI–MS (–ve, $CHCl_3$/MeOH/HCOOH 50:50:0.1): 519/517/515 (50/100/50, $[M–H]^–$).

Compound 15. To a solution of **14** (350 mg, 0.67 mmol) and **10** (170 mg, 0.45 mmol) in TCB (5 mL), K_2CO_3 (182 mg, 1.32 mmol) and $Cu(OTf)_2$ (61 mg, 0.17 mmol) were added. The mixture was stirred at 210 °C under air overnight. TCB was removed by vacuum distillation to give a black residue. After cooling, the residue was dissolved in CH_2Cl_2 (20 mL), stirred for 10 min, and filtered. The filtrate was purified by flash chromatography (SiO_2, PE/CH_2Cl_2 3:1 to 1:2) to afford **15** as a pale-yellow powder (79 mg, 23%). R_f (PE/CH_2Cl_2 1:1): 0.4; Mp: 75 – 76°C; IR (neat): 2934 (w), 2861 (w), 1728 (m), 1589 (m), 1574 (m), 1504 (s), 1484 (s), 1430 (m), 1394 (m), 1346 (m), 1238 (s), 1197 (s), 1097 (m), 1023 (m), 857 (m), 814 (s), 748 (s), 689 (s), 618 (w), 555 (m); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.75 (d, ^4J (H,H) = 1.9 Hz, 2H), 7.99 (d, ^3J (H,H) = 8.8 Hz, 1H), 7.94 (d, ^3J (H,H) = 8.8 Hz, 1H), 7.75 – 7.68 (m, 2H), 7.66 (dd, ^3J (H,H) = 8.8 Hz, ^4J (H,H) = 1.9 Hz, 1H), 7.58 (dd, ^3J (H,H) = 8.8 Hz, ^4J (H,H) = 1.9 Hz, 1H), 7.37 – 7.28 (m, 2H), 7.10 – 7.05 (m, 2H), 7.04 – 7.00 (m, 2H), 6.97 – 6.91 (m, 2H), 6.89 – 6.80 (m, 1H), 6.66 – 6.58 (m, 2H), 4.07 (q, ^3J (H,H) = 7.1 Hz, 2H), 3.79 (t, ^3J (H,H) = 6.5 Hz, 2H), 2.25 (t, ^3J (H,H) = 7.5 Hz, 2H), 1.72 – 1.54 (m, 4H), 1.44 – 1.28 (m, 4H), 1.21 (t, ^3J (H,H) = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 174.0 (C), 156.0 (C), 148.9 (C), 145.9 (C), 143.4 (C), 141.5 (C), 139.1 (C), 136.9 (C), 131.3 (CH), 131.1 (C), 130.9 (CH), 130.5 (C), 129.5 (CH), 129.2 (C), 128.8 (C), 128.0 (CH), 126.9 (CH), 126.7 (CH), 126.5 (CH), 126.5 (CH), 126.4 (CH), 125.7 (CH), 125.4 (CH), 122.6 (CH), 121.8 (CH), 121.6 (C), 121.3 (C), 117.0 (CH), 115.4 (CH), 68.6 (CH_2), 60.6 (CH_2), 34.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 26.2 (CH_2), 25.4 (CH_2), 14.6 (CH_3); HRMS (ESI, +ve) calcd for $C_{41}H_{36}Br_2N_2O_3$ ($[M+H]^+$): 763.1165, found: 763.1156.

Compound 16. To a solution of **15** (270 mg, 0.36 mmol) in dry NMP (5 mL), CuCN (640 mg, 7.2 mmol) was added. The mixture was stirred at 140 °C under N_2 overnight. After cooling, the mixture was diluted with CH_2Cl_2 (100 mL), stirred for 10 min, and filtered. The filtrate was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, PE/CH_2Cl_2 1:1) afforded **16** as a yellow powder (94 mg, 41%).

R_f (CH_2Cl_2): 0.22; Mp: 242 – 243 °C; IR (neat): 3069 (w), 2925 (m), 2854 (m), 2227 (m), 1732 (s), 1608 (m), 1581 (m), 1503 (s), 1486 (s), 1436 (m), 1386 (w), 1332 (w), 1239 (s), 1177 (s), 1116 (w), 1031 (m), 890 (m), 822 (s), 751 (s), 694 (m), 624 (w), 582 (s); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.86 (d, ^4J (H,H) = 1.4 Hz, 1H), 8.85 (d, ^4J (H,H) = 1.3 Hz, 1H), 8.19 (d, ^3J (H,H) = 8.5 Hz, 1H), 8.14 (d, ^3J (H,H) = 8.6 Hz, 1H), 7.79 – 7.70 (m, 3H), 7.67 (dd, ^3J (H,H) = 8.6 Hz, ^4J (H,H) = 1.5 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.16 – 7.03 (m, 4H), 6.96 – 6.86 (m, 3H), 6.71 – 6.63 (m, 2H), 4.07 (q, ^3J (H,H) = 7.1 Hz, 2H), 3.81 (t, ^3J (H,H) = 6.5 Hz, 2H), 2.25 (t, ^3J (H,H) = 7.5 Hz, 2H), 1.74 – 1.54 (m, 4 H), 1.45 – 1.30 (m, 4H), 1.21 (t, ^3J (H,H) = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 174.0 (C), 156.7 (C), 148.7 (C), 145.4 (C), 142.5 (C), 141.2 (C), 140.9 (C), 138.4 (C), 132.8 (C), 132.3 (C), 130.2 (CH), 129.7 (CH), 129.7 (CH), 129.5 (C), 128.7 (CH), 128.7 (CH), 127.8 (CH), 126.9 (CH), 126.3 (CH), 125.9 (CH), 125.8 (CH), 125.1 (CH), 123.9 (CH), 122.5 (CH), 119.5 (C), 119.3 (C), 117.4 (CH), 115.7 (CH), 111.1 (C), 110.8 (C), 68.7 (CH_2), 60.6 (CH_2), 34.7 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 26.2 (CH_2), 25.4 (CH_2), 14.6 (CH_3); HRMS (ESI, +ve) calcd for $C_{43}H_{36}N_4O_4$ ([M+H]$^+$): 657.2860, found: 657.2861.

Compound 2. To a solution of **16** (87 mg, 0.13 mmol) in DCE (2.5 mL), under N_2, Me_3SnOH (240 mg, 1.3 mmol) was added. The mixture was stirred at reflux for 4 hours. After cooling, CH_2Cl_2 (20 mL) and saturated aqueous solution of $KHSO_4$ (20 mL) were added. The organic layer was separated and washed additionally with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH 99:1) afforded **2** as a yellow powder (59 mg, 71%). R_f (CH_2Cl_2/MeOH 98:2): 0.13; Mp: 255 – 256 °C; IR (neat): 3064 (w), 2927 (m), 2856 (w), 2228 (m), 1744 (w), 1704 (m), 1608 (m), 1580 (m), 1502 (s), 1486 (s), 1434 (m), 1385 (m), 1329 (m), 1242 (s), 1198 (s), 1182 (s), 1031 (m), 887 (s), 838 (s), 823 (s), 751 (s), 694 (s), 581 (s); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.81 (d, ^4J (H,H) = 1.4 Hz, 1H), 8.80 (d, ^4J (H,H) = 1.4 Hz, 1H), 8.16 (d, ^3J (H,H) = 8.5 Hz, 1H), 8.11 (d, ^3J (H,H) = 8.6 Hz, 1H), 7.80 – 7.71 (m, 3H), 7.65 (dd, ^3J (H,H) = 8.6 Hz, ^4J (H,H) = 1.4 Hz, 1H), 7.43 – 7.33 (m, 2H), 7.15 – 6.99 (m, 4H), 6.95 – 6.83 (m, 3H), 6.72 – 6.60 (m, 2H), 3.81 (t, ^3J (H,H) = 6.5 Hz, 2H), 2.32 (t, ^3J (H,H) = 7.5 Hz, 2H), 1.76 – 1.49 (m, 4 H), 1.49 – 1.33 (m, 4H); ^{13}C NMR (101 MHz, CD_2Cl_2): 179.2 (C), 156.7 (C), 148.7 (C), 145.4 (C), 142.5 (C), 141.2 (C), 140.9 (C), 138.3 (C), 132.8 (C), 132.3 (C), 130.2 (CH), 129.7 (CH), 129.7 (CH), 129.4 (C), 128.7 (CH), 128.6 (CH), 127.8 (CH), 126.9 (CH), 126.2 (CH), 125.9 (CH), 125.8 (CH), 125.1 (CH), 123.9 (CH), 122.5 (CH), 119.5 (C), 119.4 (C), 117.5 (CH), 115.7 (CH), 111.0 (C), 110.7 (C), 68.7 (CH_2), 34.2 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 26.2 (CH_2), 25.1 (CH_2); HRMS (ESI, +ve) calcd for $C_{41}H_{32}N_4O_3$ ([M+H]$^+$): 629.2547, found: 629.2557.

Compounds 17 – 19 were synthesized following the literature procedures (*S4*).

Compound 20. To a solution of **19** (800 mg, 3.0 mmol) and 4-aminobenzonitrile (1.56 g, 13.2 mmol) in anhydrous CH_2Cl_2 (75 mL), under N_2, pyridine (2.5 mL, 30 mmol) was added and the solution was cooled to 0 °C. Then, $TiCl_4$ (1.1 mL, 9.9 mmol) was added dropwise and reaction mixture was stirred at rt overnight. Then, the solution was diluted with CH_2Cl_2 (250 mL), stirred for 10 min, and filtered to remove the solid. The solvent was evaporated and viscous amber oil was subjected to next step. Crude product was dissolved under N_2 in 75 mL of THF, Pd/C (10%, 40 mg) was added followed by hydrazine hydrate (3 mL). The reaction mixture was stirred at rt for 1 hour followed by filtration through Na_2SO_4/celite 1:1. The filtrate was evaporated to dryness and the solid residue was purified by flash chromatography (SiO_2, CH_2Cl_2), affording **20** as a pale-yellow powder (1.1 g, 78%). R_f (CH_2Cl_2): 0.21; Mp: 234 – 235 °C (decomp.); IR (neat): 3355 (w), 3285 (w), 2928 (w), 2834 (w), 2216 (s), 1598 (s), 1506 (s), 1465 (m), 1436 (m), 1322 (m), 1231 (s), 1169 (s), 1130 (m), 1116 (m), 1055 (m), 1021 (m), 932 (w), 825 (s), 811 (s), 728 (s), 697 (w), 542 (s); ^{1}H NMR (400 MHz, $C_2D_2Cl_4$): 7.96 (d, ^4J (H,H) = 2.1 Hz, 2H), 7.81 (d, ^3J (H,H) = 9.0 Hz, 2H), 7.26 (d, ^3J (H,H) = 8.6 Hz, 4H), 7.17 (dd, ^3J (H,H) = 9.0 Hz, ^4J = 2.1 Hz, 2H), 6.44 (d, ^3J (H,H) = 8.6 Hz, 4H), 5.95 (s, 2H), 3.95 (s, 6H); ^{13}C NMR (101 MHz, $C_2D_2Cl_4$): 159.4 (C), 150.8 (C), 134.5 (CH), 131.9 (C), 128.6 (C), 127.0 (CH), 125.0 (C), 120.9 (C), 117.8 (CH), 114.7 (CH), 106.0 (CH), 101.3 (C), 56.5 (CH_3); HRMS (ESI, +ve) calcd for $C_{30}H_{22}N_4O_2$ ($[M+H]^+$): 471.1816, found: 471.1813.

Compound 21. To a solution of **20** (270 mg, 0.57 mmol) and **10** (140 mg, 0.38 mmol) in TCB (4 mL), K_2CO_3 (157 mg, 1.14 mmol) and $Cu(OTf)_2$ (54 mg, 0.15 mmol) were added. The mixture was stirred at 210 °C under air overnight. TCB was removed by vacuum distillation, obtaining a black residue. After cooling to rt, the residue was diluted with CH_2Cl_2 (20 mL), stirred for 10 min, and filtered. The filtrate was purified by flash chromatography (SiO_2, PE/CH_2Cl_2 1:1 to 1:9) to afford **21** as a pale-yellow powder (191 mg, 72%). R_f (CH_2Cl_2): 0.33; Mp: 96 – 97 °C; IR (neat): 2933 (w), 2861 (w), 2222 (m), 1727 (m), 1608 (m), 1594 (m), 1503 (s), 1438 (m), 1361 (m), 1331 (m), 1266 (m), 1234 (s), 1201 (m), 1173 (s), 1113 (m), 1026 (s), 817 (s), 707 (w), 547 (s) ; ^{1}H NMR (400 MHz, CD_2Cl_2): 8.05 – 8.01 (m, 2H), 7.95 (d, ^3J (H,H) = 8.9 Hz, 1H), 7.92 – 7.87 (m, 2H), 7.77 (d, ^3J (H,H) = 8.4 Hz, 1H), 7.63 (dd, ^3J (H,H) = 8.4 Hz, ^4J (H,H) = 1.9 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.29 (dd, ^3J (H,H) = 9.0 Hz, ^4J (H,H) = 2.4 Hz, 1H), 7.13 – 7.06 (m, 3H), 6.91 – 6.84 (m, 2H), 6.76 – 6.69 (m, 2H), 4.07 (q, ^3J (H,H) = 7.2 Hz, 2H), 4.04 (s, 3H), 3.98 (s, 3H), 3.84 (t, ^3J (H,H) = 6.5 Hz, 2H), 2.26 (t, ^3J

(H,H) = 7.5 Hz, 2H), 1.75 –1.57 (m, 4H), 1.46 – 1.30 (m, 4H), 1.21 (t, ^{3}J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 174.0 (C), 159.1 (C), 159.0 (C), 157.4 (C), 152.5 (C), 151.3 (C), 140.5 (C), 139.5 (C), 136.0 (C), 133.8 (CH), 132.3 (C), 131.7 (CH), 131.5 (CH), 131.4 (C), 131.0 (C), 126.7 (CH), 125.7 (CH), 125.7 (CH), 124.3 (CH), 123.8 (C), 123.3 (C), 119.8 (C), 119.0 (C), 117.9 (CH), 116.9 (CH), 115.8 (CH), 115.6 (CH), 107.8 (C), 105.9 (CH), 105.9 (CH), 104.2 (C), 68.7 (CH_2), 60.6 (CH_2), 56.2 (CH_3), 56.1 (CH_3), 34.7 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 26.2 (CH_2), 25.4 (CH_2), 14.6 (CH_3); HRMS (ESI, +ve) calcd for $C_{45}H_{40}N_4O_5$ ($[M+H]^+$): 717.3072, found: 717.3087.

Compound 3. To a solution of **21** (180 mg, 0.25 mmol) in DCE (2.5 mL), under N_2, Me_3SnOH (560 mg, 3.1 mmol) was added. The mixture was stirred at reflux for 4 hours. After cooling to rt, the mixture was diluted with CH_2Cl_2 (20 mL) and saturated aqueous solution of $KHSO_4$ (20 mL). The organic layer was separated and washed additionally with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH 98:2) afforded **3** as a pale-yellow powder (105 mg, 61%). R_f (CH_2Cl_2/MeOH): 0.19; Mp: 135 – 136 °C; IR (neat): 2933 (w), 2859 (w), 2223 (m), 1703 (m), 1607 (m), 1594 (m), 1503 (s), 1437 (m), 1360 (m), 1267 (m), 1233 (s), 1173 (s), 1115 (m), 1027 (s), 947 (w), 817 (s), 707 (w), 546 (s); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.05 – 8.01 (m, 2H), 7.95 (d, ^{3}J (H,H) = 8.9 Hz, 1H), 7.92 – 7.87 (m, 2H), 7.76 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 7.62 (dd, ^{3}J (H,H) = 8.4 Hz, ^{4}J (H,H) = 1.9 Hz, 1H), 7.42 – 7.34 (m, 2H), 7.29 (dd, ^{3}J (H,H) = 9.0 Hz, ^{4}J (H,H) = 2.4 Hz, 1H), 7.13 – 7.05 (m, 3H), 6.92 – 6.84 (m, 2H), 6.75 – 6.69 (m, 2H), 4.03 (s, 3H), 3.97 (s, 3H), 3.83 (t, ^{3}J (H,H) = 6.5 Hz, 2H), 2.33 (t, ^{3}J (H,H) = 7.5 Hz, 2H), 1.76 –1.57 (m, 4H), 1.48 – 1.30 (m, 4H); ^{13}C NMR (101 MHz, CD_2Cl_2): 179.4 (C), 159.1 (C), 159.0 (C), 157.4 (C), 152.5 (C), 151.3 (C), 140.6 (C), 139.5 (C), 136.0 (C), 133.8 (CH), 132.3 (C), 131.7 (CH), 131.5 (CH), 131.4 (C), 131.0 (C), 126.7 (CH), 125.7 (CH), 125.6 (CH), 124.3 (CH), 123.8 (C), 123.3 (C), 119.8 (C), 119.0 (C), 117.9 (CH), 116.9 (CH), 115.8 (CH), 115.6 (CH), 107.8 (C), 106.0 (CH), 105.9 (CH), 104.1 (C), 68.7 (CH_2), 56.2 (CH_3), 56.1 (CH_3), 34.3 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 26.2 (CH_2), 25.1 (CH_2); HRMS (ESI, +ve) calcd for $C_{43}H_{36}N_4O_5$ ($[M+H]^+$): 689.2759, found: 689.2732.

Compound 22. To a solution of **7** (520 mg, 2.5 mmol) and 4-aminobenzonitrile (1.4 g, 11 mmol) in anhydrous CH_2Cl_2 (75 mL), under N_2, pyridine (2.0 mL, 25 mmol) was added and the solution was cooled to 0 °C. Then, $TiCl_4$ (0.92 mL, 8.3 mmol) was added dropwise and reaction mixture was stirred at rt overnight. Then, the solution was diluted with CH_2Cl_2 (250

mL), stirred for 10 min, and filtered to remove the solid. The solvent was evaporated and viscous amber oil was subjected to next step. Crude product was dissolved under N_2 in 75 mL of THF, Pd/C (10%, 40 mg) was added followed by hydrazine hydrate (3 mL). The reaction mixture was stirred at rt for 1 hour followed by filtration through Na_2SO_4/celite 1:1. The filtrate was evaporated to dryness and the solid residue was purified by flash chromatography (SiO_2, CH_2Cl_2), affording **22** as a pale-yellow powder (0.63 g, 61%). R_f (CH_2Cl_2): 0.28; Mp: 228 – 229 °C (decomp.); IR (neat): 3297 (s), 3073 (w), 2925 (w), 2854 (w), 2216 (s), 1600 (s), 1513 (s), 1487 (s), 1425 (w), 1384 (m), 1326 (s), 1263 (m), 1171 (m), 1033 (w), 1003 (w), 948 (w), 886 (w), 862 (w), 823 (s), 765 (m), 724 (m), 622 (m), 540 (m); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.81 (d, ^3J (H,H) = 8.3 Hz, 2H), 8.01 (d, ^3J (H,H) = 8.1 Hz, 2H), 7.75 (t, ^3J (H,H) = 7.2 Hz, 2H), 7.62 (t, ^3J (H,H) = 7.5 Hz, 2H), 7.38 (d, ^3J (H,H) = 8.8 Hz, 4H), 6.55 (d, ^3J (H,H) = 8.8 Hz, 4H), 6.12 (s, 2H); ^{13}C NMR (101 MHz, $C_2D_2Cl_4$): 149.9 (C), 134.1 (CH), 130.6 (C), 130.1 (C), 129.6 (C), 128.0 (CH), 127.9 (CH), 124.7 (CH), 123.6 (CH), 120.3 (C), 114.6 (CH), 101.4 (C); HRMS (ESI, +ve) calcd for $C_{28}H_{18}N_4$ ($[M+H]^+$): 411.1604, found: 411.1607.

Compound 23. To a solution of **22** (630 mg, 1.54 mmol) and **10** (398 mg, 1.06 mmol) in TCB (8 mL), K_2CO_3 (424 mg, 3.08 mmol) and $Cu(OTf)_2$ (140 mg, 0.38 mmol) were added. The mixture was stirred at 210 °C under air overnight. TCB was removed by vacuum distillation, obtaining a black residue. After cooling to rt, the residue was diluted with CH_2Cl_2 (20 mL), stirred for 10 min, and filtered. The filtrate was purified by flash chromatography (SiO_2, PE/CH_2Cl_2 3:1 to 1:3) to afford **23** as a pale-yellow powder (352 mg, 51%). R_f (CH_2Cl_2): 0.2; Mp: 82 – 83 °C; IR (neat): 3067 (w), 2935 (w), 2861 (w), 2222 (m), 1727 (m), 1593 (m), 1503 (s), 1490 (s), 1374 (w), 1335 (m), 1296 (m), 1240 (s), 1175 (s), 1098 (m), 1034 (m), 946 (w), 814 (s), 759 (s), 725 (s), 597 (m); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.76 (d, ^3J (H,H) = 8.0 Hz, 2H), 8.07 (dd, ^3J (H,H) = 8.3 Hz, ^4J (H,H) =1.4 Hz, 1H), 8.01 (dd, ^3J (H,H) = 8.4 Hz, ^4J (H,H) =1.3 Hz, 1H), 7.93 (d, ^4J (H,H) = 1.8 Hz, 1H), 7.80 (d, ^3J (H,H) = 8.5 Hz, 1H), 7.75 – 7.61 (m, 4H), 7.45 (ddd, ^3J (H,H) = 8.2 Hz, ^3J (H,H) = 7.0 Hz, ^4J (H,H) = 1.2 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.16 – 7.09 (m, 2H), 6.92 – 6.85 (m, 2H), 6.78 – 6.71 (m, 2H), 4.07 (q, ^3J (H,H) = 7.1 Hz, 2H), 3.84 (t, ^3J (H,H) = 6.5 Hz, 2H), 2.26 (t, ^3J (H,H) = 7.5 Hz, 2H), 1.71 (p, ^3J (H,H) = 6.8 Hz, 2H), 1.60 (p, ^3J (H,H) = 7.5 Hz, 2H), 1.48 – 1.29 (m, 4H), 1.21 (t, ^3J (H,H) = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 174.0 (C), 157.6 (C), 152.3 (C), 151.1 (C), 140.3 (C), 139.3 (C), 138.2 (C), 133.9 (CH), 133.1 (C), 131.8 (CH), 131.6 (CH), 131.3 (C), 130.1 (C), 129.0 (C), 128.5 (C), 128.3 (CH), 127.6 (CH), 127.4 (CH), 126.0 (CH), 125.1 (CH), 124.1 (CH), 124.0 (CH), 123.8 (C), 123.8 (CH), 119.7 (C), 118.9 (C), 115.8 (CH), 115.6 (CH), 108.0

(C), 104.4 (C), 68.7 (CH_2), 60.6 (CH_2), 34.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 26.2 (CH_2), 25.4 (CH_2), 14.6 (CH_3); HRMS (ESI, +ve) calcd for $C_{43}H_{36}N_4O_3$ ($[M+H]^+$): 657.2860, found: 657.2858.

Compound 4. To a solution of **23** (340 mg, 0.52 mmol) in DCE (4 mL), under N_2, Me_3SnOH (0.94 g, 5.2 mmol) was added. The mixture was stirred at reflux for 4 hours. After cooling to rt, the mixture was diluted with CH_2Cl_2 (20 mL) and saturated aqueous solution of $KHSO_4$ (20 mL). The organic layer was separated and washed additionally with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH 99:1) afforded **4** as a pale-yellow powder (269 mg, 82%). R_f (CH_2Cl_2/MeOH 98:2): 0.13; Mp: 130 – 131 °C; IR (neat): 3074 (w), 2933 (w), 2860 (w), 2223 (m), 1703 (m), 1593 (m), 1504 (s), 1490 (s), 1430 (m), 1334 (m), 1295 (s), 1240 (s), 1175 (s), 1110 (m), 1036 (w), 1010 (w), 945 (w), 823 (s), 758 (s), 724 (s), 596 (m); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.75 (d, ^3J (H,H) = 8.2 Hz, 2H), 8.07 (dd, ^3J (H,H) = 7.9 Hz, ^4J (H,H) =1.5 Hz, 1H), 8.00 (dd, ^3J (H,H) = 8.4 Hz, ^4J (H,H) =1.3 Hz, 1H), 7.92 (d, ^4J (H,H) = 1.9 Hz, 1H), 7.79 (d, ^3J (H,H) = 8.4 Hz, 1H), 7.75 – 7.59 (m, 4H), 7.45 (ddd, ^3J (H,H) = 8.2 Hz, ^3J (H,H) = 7.0 Hz, ^4J (H,H) = 1.1 Hz, 1H), 7.42 – 7.34 (m, 2H), 7.17 – 7.08 (m, 2H), 6.92 – 6.84 (m, 2H), 6.78 – 6.69 (m, 2H), 3.84 (t, ^3J (H,H) = 6.5 Hz, 2H), 2.33 (p, ^3J (H,H) = 6.8 Hz, 2H), 1.76 – 1.56 (m, 4H), 1.46 – 1.32 (m, 4H); ^{13}C NMR (101 MHz, CD_2Cl_2): 179.4 (C), 157.6 (C), 152.4 (C), 151.2 (C), 140.3 (C), 139.3 (C), 138.2 (C), 133.9 (CH), 133.2 (C), 131.8 (CH), 131.6 (CH), 131.3 (C), 130.1 (C), 129.0 (C), 128.5 (C), 128.3 (CH), 127.6 (CH), 127.4 (CH), 126.0 (CH), 125.1 (CH), 124.2 (CH), 124.0 (CH), 123.9 (C), 123.8 (CH), 119.7 (C), 118.9 (C), 115.8 (CH), 115.6 (CH), 108.0 (C), 104.3 (C), 68.7 (CH_2), 34.3 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 26.2 (CH_2), 25.1 (CH_2); HRMS (ESI, +ve) calcd for $C_{41}H_{32}N_4O_3$ ($[M+H]^+$): 629.2547, found: 629.2556.

3. Fluorescence Spectroscopy in LUVs

The large unilamellar vesicles (LUVs) made of DOPC and DPPC were prepared according to the procedures reported in (*S2*).

To a 2 mL gently stirred, thermostated buffer (55 °C, 10 mM Tris, 100 mM NaCl, pH 7.4) in a quartz cuvette were added DOPC or DPPC LUVs (5.0 μL of 30 mM, 75 μM lipid in a cuvette) followed by the probe **1**, **2**, **3** or **4** (10 μL of 0.1 mM in DMSO, 0.5 μM). The solution was stirred at 55 °C and emission was measured at different time (λ_{ex} = 415 nm, λ_{em} = 602 nm

for probe **1**; λ_{ex} = 415 nm, λ_{em} = 595 nm for probe **2**; λ_{ex} = 355 nm, λ_{em} = 592 nm for probe **3**; λ_{ex} = 355 nm, λ_{em} = 609 nm for probe **4**) until no changes were detected.

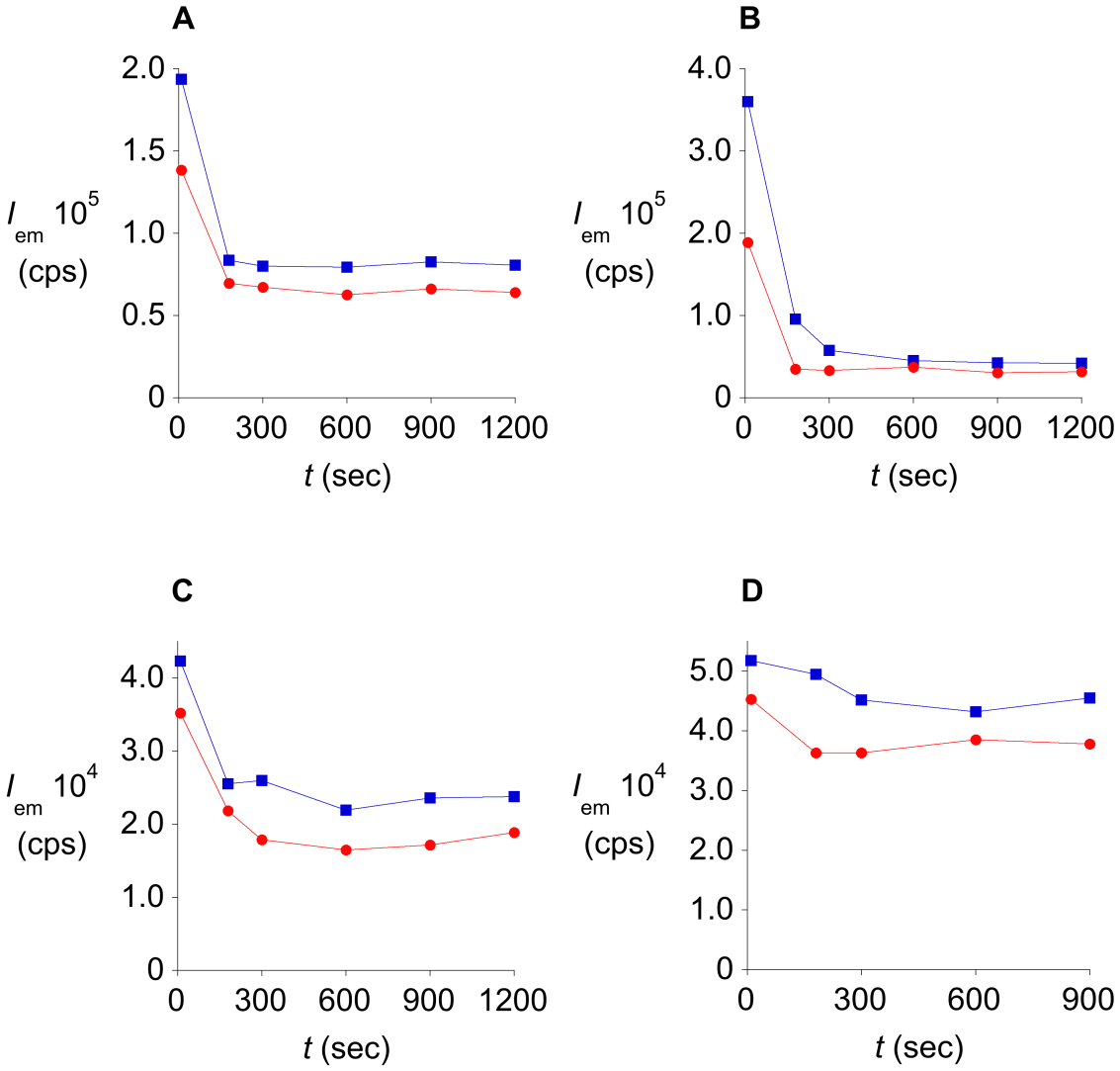
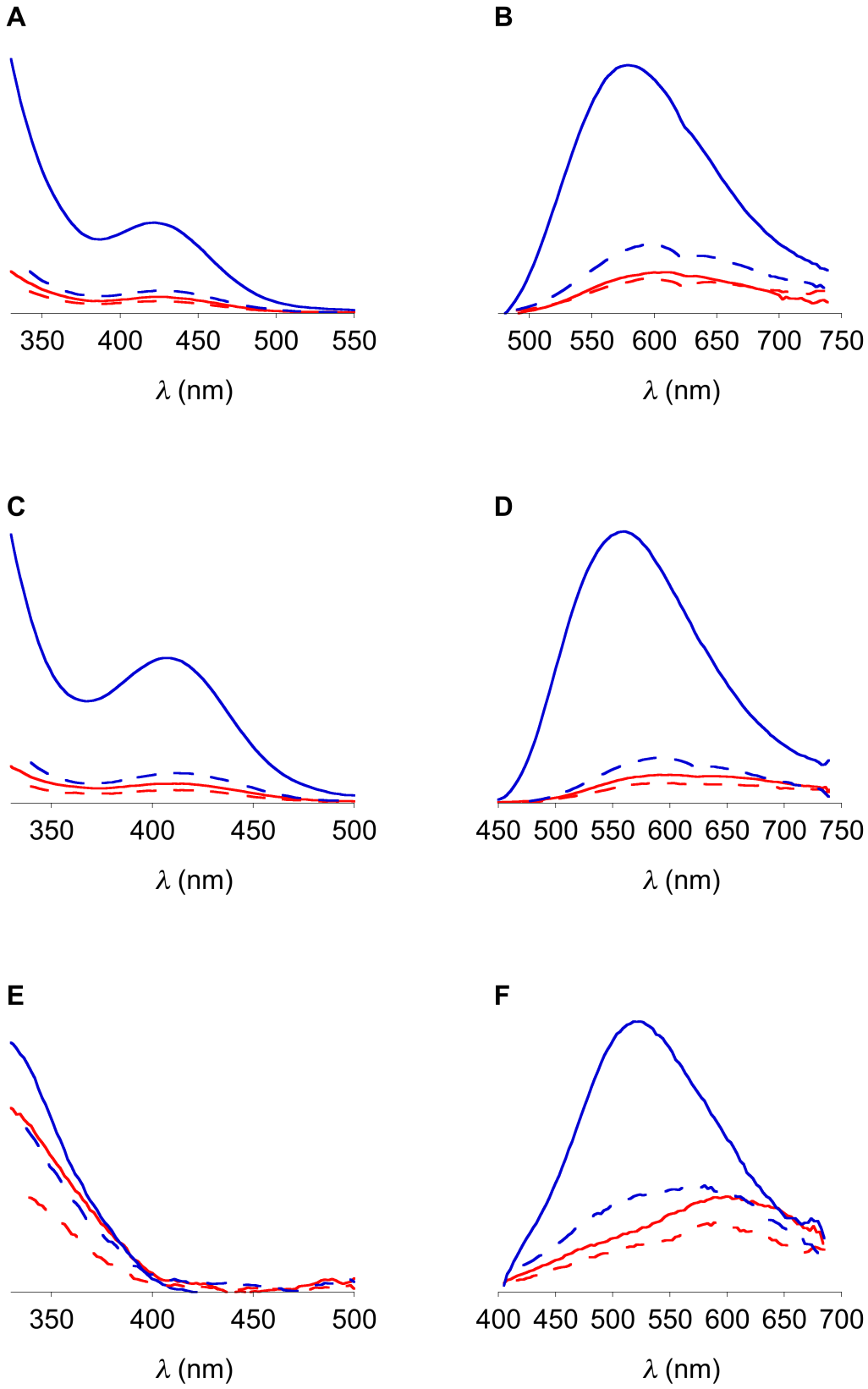


Figure S1. Partition kinetics in DOPC (red circles) and DPPC LUVs (blue squares) of probes **1** (A), **2** (B), **3** (C) and **4** (D) at 55 °C.

To a 2 mL gently stirred, thermostated buffer (55 °C, 10 mM Tris, 100 mM NaCl, pH 7.4) in a quartz cuvette, DOPC or DPPC LUVs (5.0 μL of 30 mM, 75 μM lipid in a cuvette) and the probe **1**, **2**, **3** or **4** (10 μL of 0.1 mM in DMSO, 0.5 μM) were added. The solution was stirred at 55 °C for 20 minutes before the emission and the excitation spectra were acquired (λ_{ex} = 415 nm, λ_{em} = 600 nm for probe **1**; λ_{ex} = 415 nm, λ_{em} = 600 nm for probe **2**; λ_{ex} = 355 nm, λ_{em} = 600 nm for probe **3**; λ_{ex} = 355 nm, λ_{em} = 600 nm for probe **4**). The temperature was

then lowered to 25 °C and the solution was kept at this temperature for 15 minutes before the emission and excitation spectra were acquired under the same conditions.



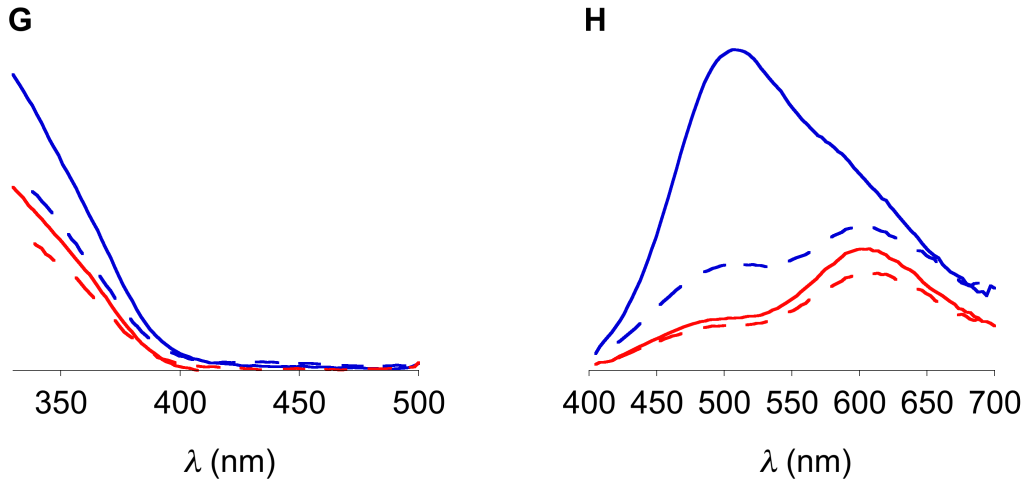
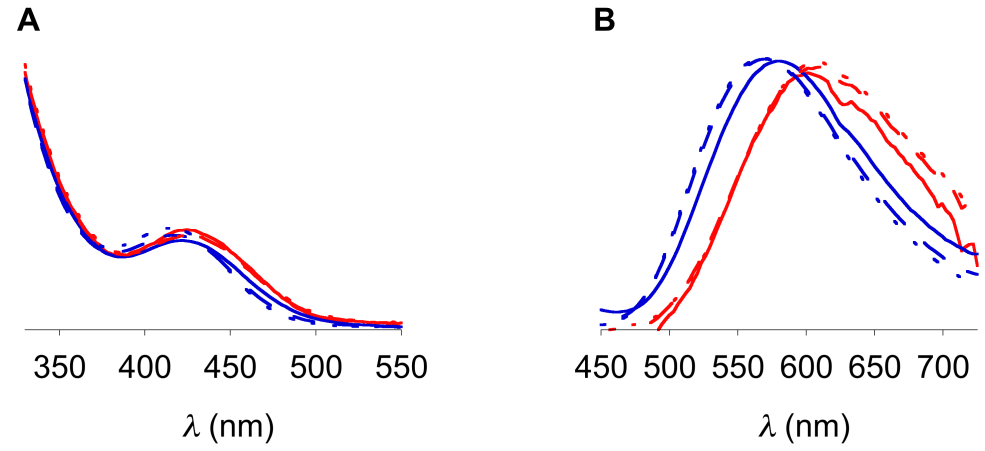


Figure S2. Excitation (A, C, E, G) and emission (B, D, F, H) spectra in DPPC LUVs (solid) and DOPC LUVs (dashed) at 55 °C (red) and 25 °C (blue) of probes **1** (A and B), **2** (C and D), **3** (E and F) and **4** (G and H).

To a 2 mL gently stirred, thermostated buffer (55 °C, 10 mM Tris, 100 mM NaCl, pH 7.4), DPPC LUVs (5.0 μL of 30 mM, 75 μM lipid in a cuvette) and probes at different concentrations (10 μL of 0.1 mM in DMSO, 0.5 μM; 13 μL of 0.15 mM in DMSO, 1.0 μM; 15 μL of 0.27 mM in DMSO, 2.0 μM) were added. The solutions were stirred at 55 °C for 45 minutes before the emission and the excitation spectra were acquired (λ_{ex} = 415 nm, λ_{em} = 600 nm for probe **1**; λ_{ex} = 415 nm, λ_{em} = 600 nm for probe **2**; λ_{ex} = 415 nm, λ_{em} = 600 nm for probe **3**; λ_{ex} = 415 nm, λ_{em} = 600 nm for probe **4**). The temperature was then lowered to 25 °C and the solutions were kept at this temperature for 10 minutes before the emission and excitation spectra were acquired under the same conditions.



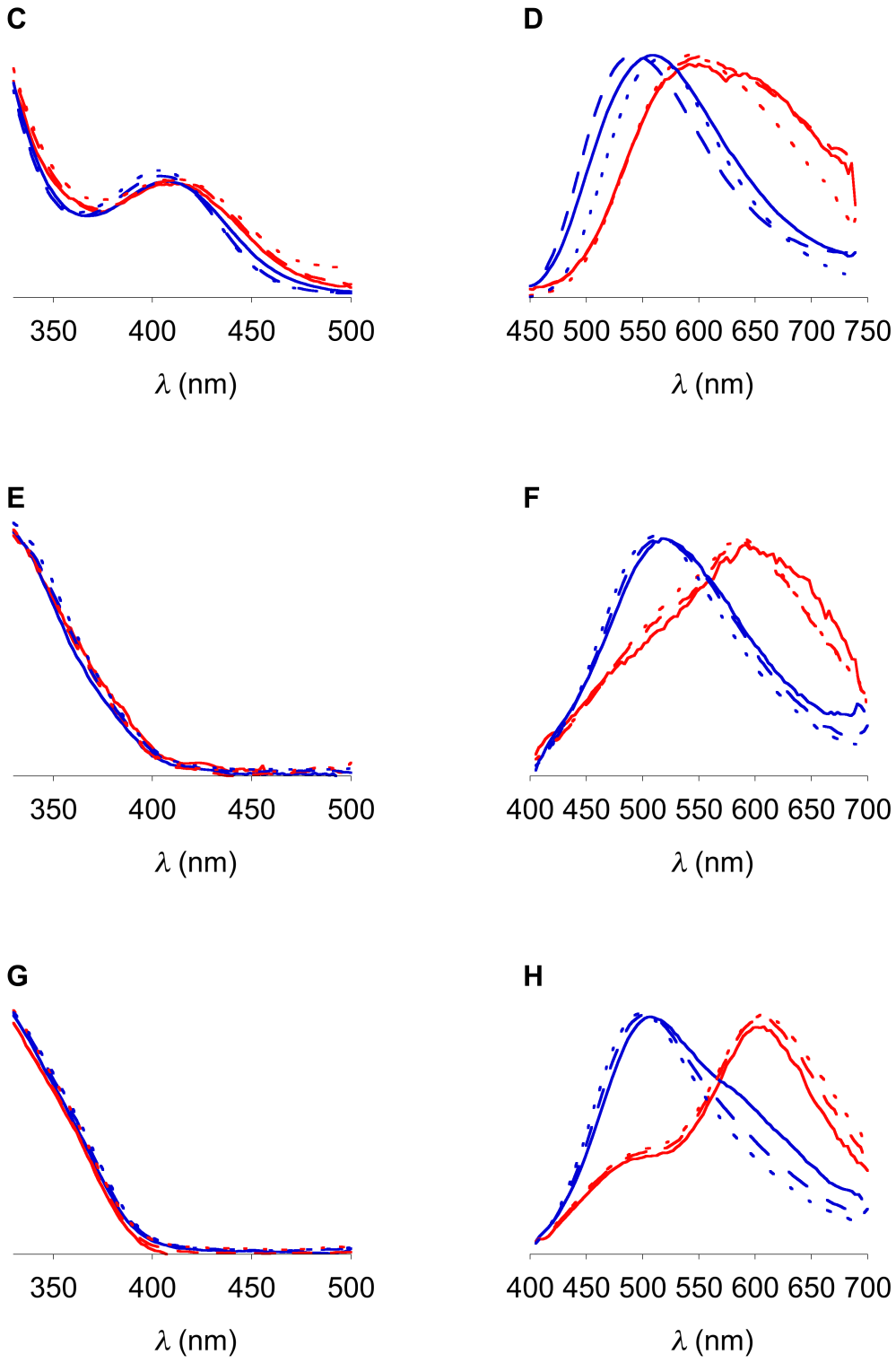


Figure S3. Normalized excitation (A, C, E, G) and emission (B, D, F, H) spectra in DPPC LUVs at 55 °C (red) and 25 °C (blue) of probes **1** (A and B), **2** (C and D), **3** (E and F) and **4** (G and H) at concentration 0.5 μM (solid), 1.0 μM (dashed) and 2.0 μM (dotted).

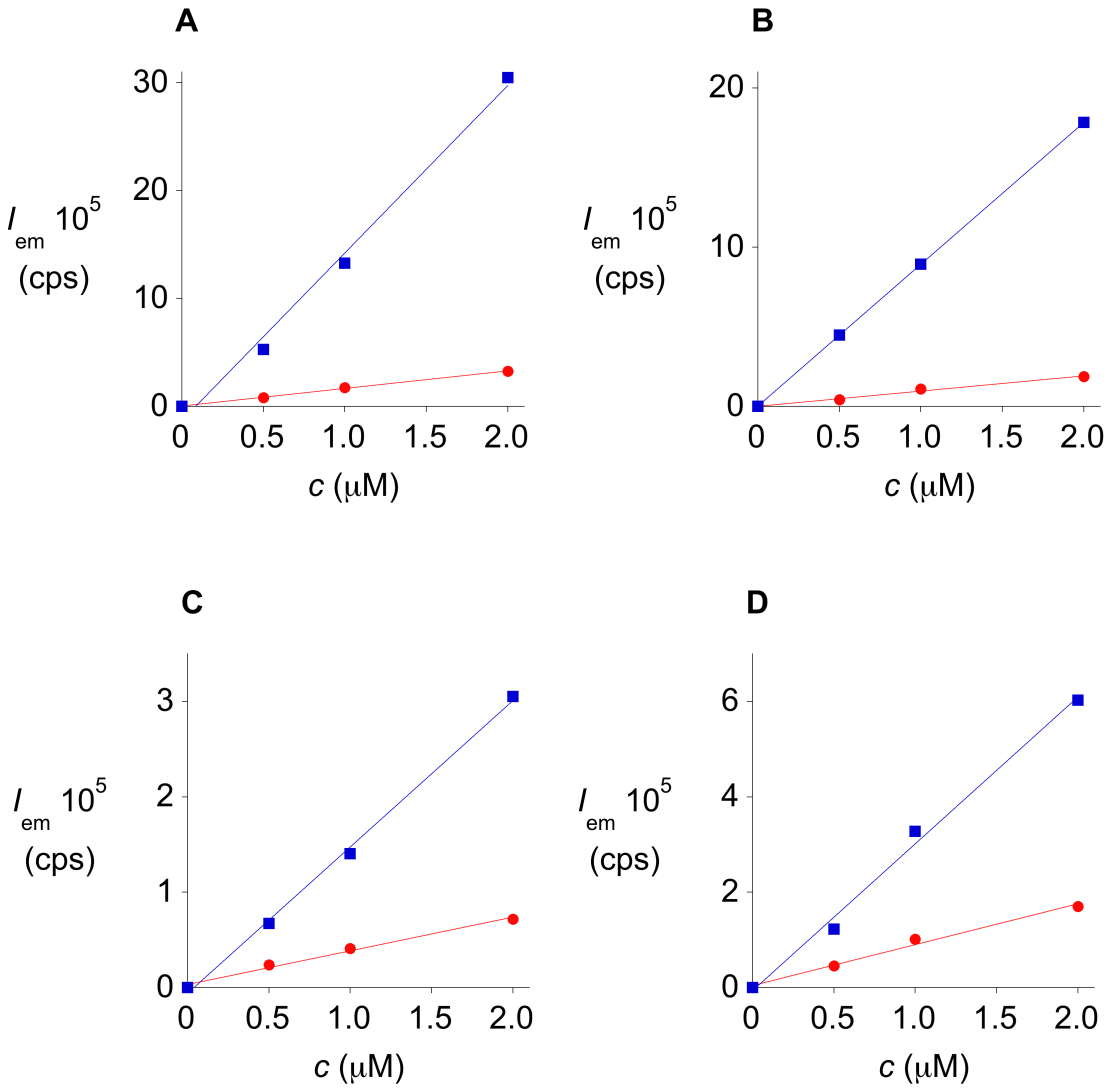


Figure S4. Fluorescence intensity as a function of concentration of **1** (λ_{e1} = 578 nm, λ_{e2} = 602 nm, A), **2** (λ_{e1} = 553 nm, λ_{e2} = 595 nm, B), **3** (λ_{e1} = 515 nm, λ_{e2} = 592 nm, C) and **4** (λ_{e1} = 508 nm, λ_{e2} = 609 nm, D) in DPPC LUVs at 55 °C (red circles, λ_{e2}) and 25 ºC (blue squares, λ_{e1}).

4. Fluorescence Spectroscopy in Organic Solvents

In a typical experiment, 10 μM solutions of compound **1**, **2**, **3** and **4** (20 μL of 1 mM in DMSO) were prepared in air saturated solvents of different polarity. The solutions were stirred at 25 °C for 10 minutes before absorption and emission spectra were acquired. Fluorescence quantum yields were evaluated based on external standard Fluorescein in 0.1 M NaOH (compound **1** and **2**) and Coumarin 1 in EtOH (compound **3** and **4**) using the equation (S1).

$$\Phi = \Phi_{\mathrm{STD}} \frac{I}{I_{\mathrm{STD}}} \frac{OD_{\mathrm{STD}}}{OD} \frac{n^2}{n_{\mathrm{STD}}^2} \qquad \text{(S1)}$$

where Φ_{STD} is the standard quantum yield (Fluorescein, $\Phi_{\mathrm{STD}} = 0.91$ (*S5*); Coumarin 1, $\Phi_{\mathrm{STD}} = 0.73$ (*S6*)), I is the area of the emission intensity of the sample, I_{STD} is the area of the emission intensity of the standard, OD is the optical density of the sample, OD_{STD} is the optical density of the standard, n is the refractive index of the sample, n_{STD} is the refractive index of the standard.

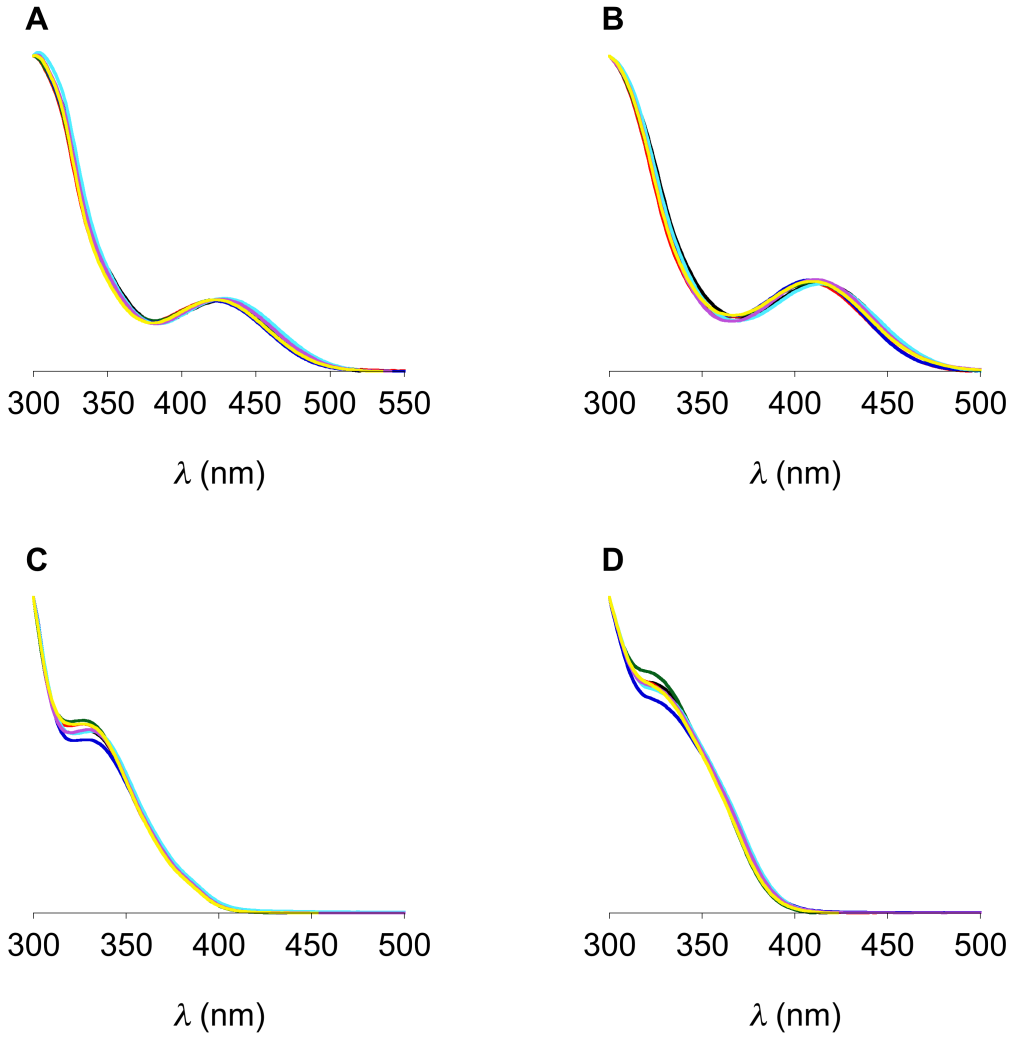


Figure S5. Normalized absorption spectra of compounds **1** (A), **2** (B), **3** (C) and **4** (D) recorded in toluene (blue), EtOAc (red), THF (purple), CH_2Cl_2 (black), CH_3CN (yellow), DMF (cyan), MeOH (olive).

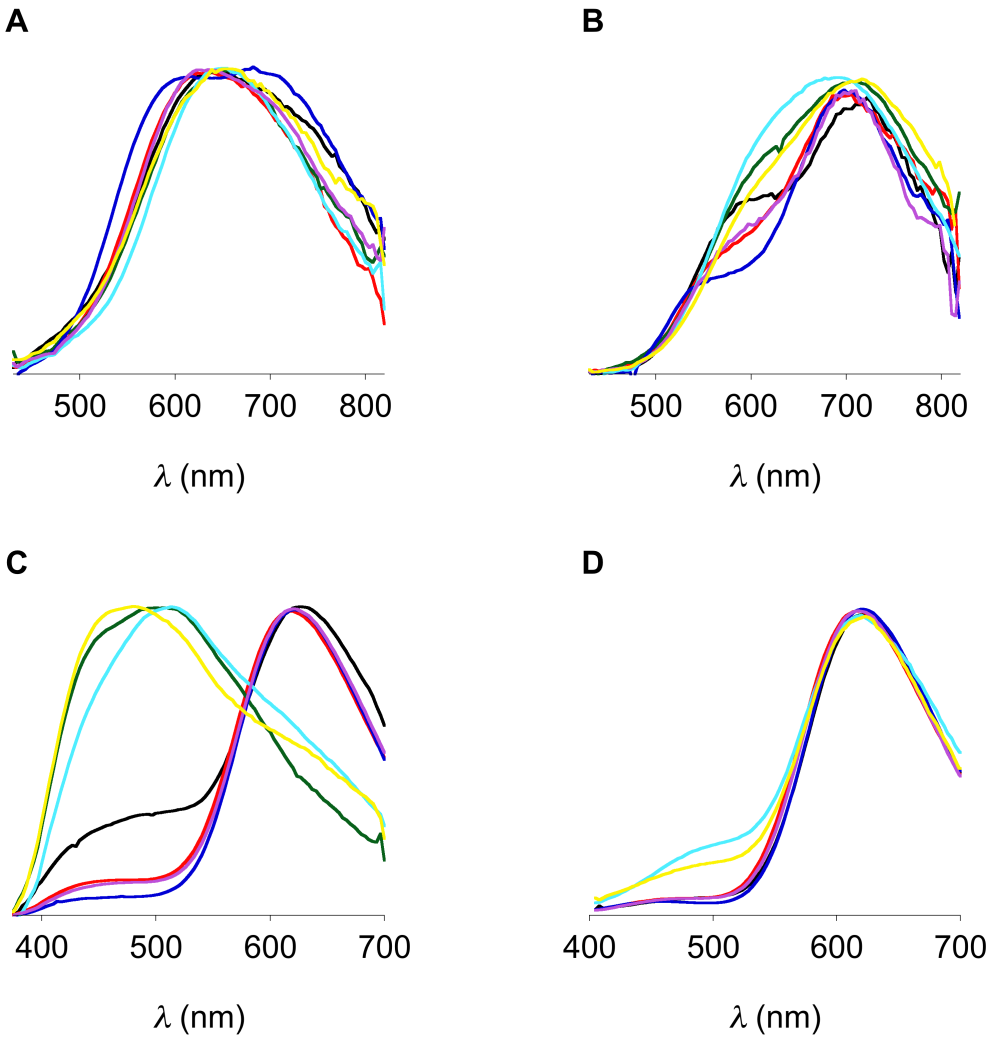


Figure S6. Normalized emission spectra of compounds **1** (λ_{ex} = 415 nm, A), **2** (λ_{ex} = 415 nm, B), **3** (λ_{ex} = 355 nm, C) and **4** (λ_{ex} = 355 nm, D) recorded in toluene (blue), EtOAc (red), THF (magenta), CH_2Cl_2 (black), CH_3CN (yellow), DMF (cyan), MeOH (olive).

Table S1. Photophysical properties of **1** and **2** in various solvents.

Cmpd[a]	**1**				**2**			
Solvent	λ_{abs}[b] (nm)	ε[c] ($mM^{-1}cm^{-1}$)	λ_{em}[d] (nm)	Φ[e] (%)	λ_{abs}[b] (nm)	ε[c] ($mM^{-1}cm^{-1}$)	λ_{em}[d] (nm)	Φ[e] (%)
Toluene	422	5.2	682	0.4	408	8.2	689	0.3
EtOAc	423	5.5	644	0.2	408	8.3	686	0.5
THF	427	5.5	653	0.2	412	8.5	710	0.8
CH_2Cl_2	428	5.6	638	0.2	413	9.2	715	0.4
CH_3CN	422	5.2	637	0.1	408	8.3	702	0.2
DMF	429	5.3	640	0.3	414	8.0	673	0.3
MeOH	423	5.5	682	0.1	410	8.3	709	0.2

[a]Compounds, Scheme S1–S2. [b]Wavelength of absorption maxima. [c]Extinction coefficient. [d]Wavelength of emission maxima. [e]Fluorescence quantum yield.

Table S2. Photophysical properties of **3** and **4** in various solvents.

Cmpd[a]	**3**				**4**			
Solvent	λ_{abs}[b] (nm)	ε[c] ($mM^{-1}cm^{-1}$)	λ_{em}[d] (nm)	Φ[e] (%)	λ_{abs}[b] (nm)	ε[c] ($mM^{-1}cm^{-1}$)	λ_{em}[d] (nm)	Φ[e] (%)
Toluene	318	28.3	616	0.1	321	25.2	620	3.7
EtOAc	327	28.8	619	0.7	323	26.8	620	2.6
THF	330	29.4	620	1.7	325	26.9	618	2.9
CH_2Cl_2	328	32.4	623	0.8	322	30.7	626	2.2
CH_3CN	318	28.5	485	0.1	326	24.6	622	0.6
DMF	332	28.4	521	0.1	323	26.7	616	0.8
MeOH	327	27.1	520	0.1	323	27.7	614	<0.1

[a]Compounds, Scheme S3–S4. [b]Wavelength of absorption maxima. [c]Extinction coefficient. [d]Wavelength of emission maxima. [e]Fluorescence quantum yield.

5. Fluorescence Spectroscopy in Methanol–Glycerol Mixtures

In a typical experiment, 10 μM solutions of compound **1**, **2**, **3** and **4** (20 μL of 1 mM in DMSO) were prepared in air saturated mixtures of methanol–glycerol (100:0, 80:20, 60:40, 50:50, 40:60, 20:80, 0:100) with various viscosities. The solutions were stirred at 25 °C for 10 minutes before emission spectra was acquired (λ_{ex}= 415 nm for **1** and **2**; λ_{ex}= 355 nm for **3** and **4**).

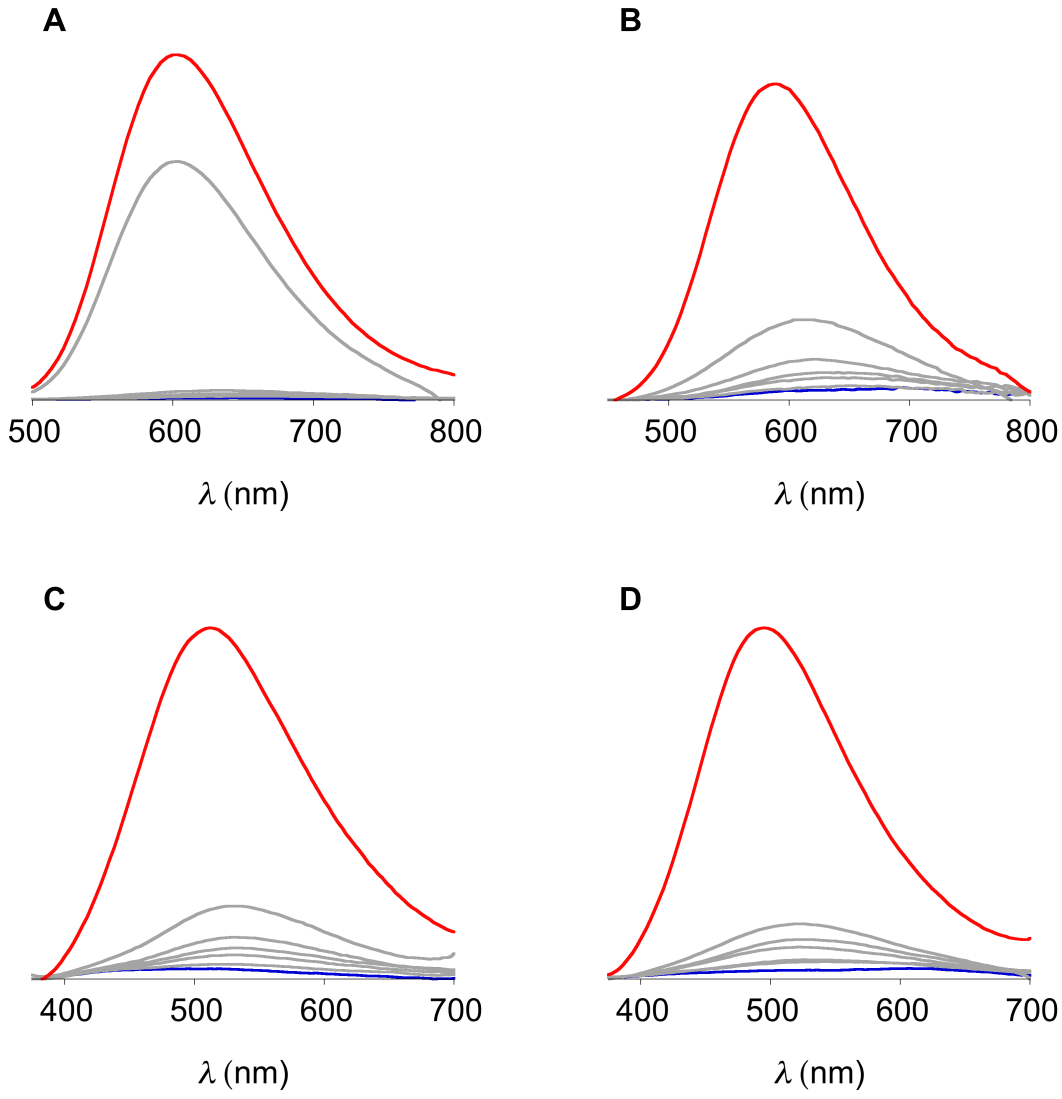


Figure S7. Emission spectra of compounds **1** (λ_{ex} = 415 nm, A), **2** (λ_{ex} = 415 nm, B), **3** (λ_{ex} = 355 nm, C) and **4** (λ_{ex} = 355 nm, D) recorded in methanol–glycerol (blue line – 100:0 methanol–glycerol; red line – 0:100 methanol–glycerol).

6. Fluorescence Spectroscopy in Water

To a 2 mL gently stirred thermostated buffer (55 °C, 10 mM Tris, 100 mM NaCl, pH 7.4) probes (from a stock solution in DMSO at 1 mM) were added to achieve the desired final concentrations of 0.313, 0.625, 1.25, 2.5 and 5.0 μM respectively. The solutions were stirred at 55 °C for 10 minutes before the emission spectra was acquired (λ_{ex} = 415 nm for **1** and **2**; λ_{ex} = 355 nm for **3** and **4**). Afterwards, the temperature was lowered to 25 °C and the solutions were kept at this temperature for 10 minutes before the emission was acquired under the same conditions.

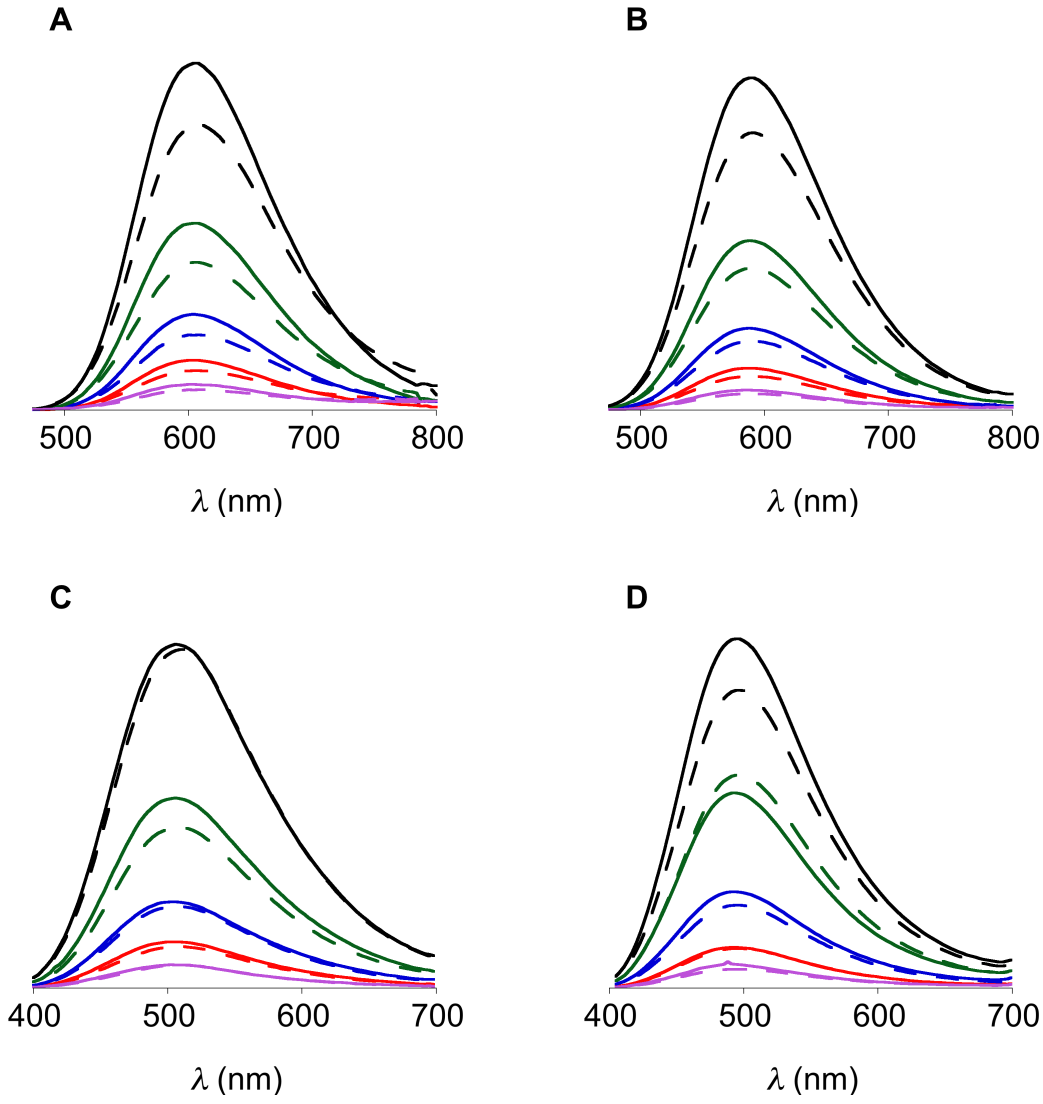


Figure S8. Emission spectra of compounds **1** (A), **2** (B), **3** (C) and **4** (D) at 25 °C (solid) and 55 °C (dashed) at different concentrations: 0.313 μM (pink), 0.625 μM (red), 1.25 μM (blue), 2.5 μM (olive), 5 μM (black).

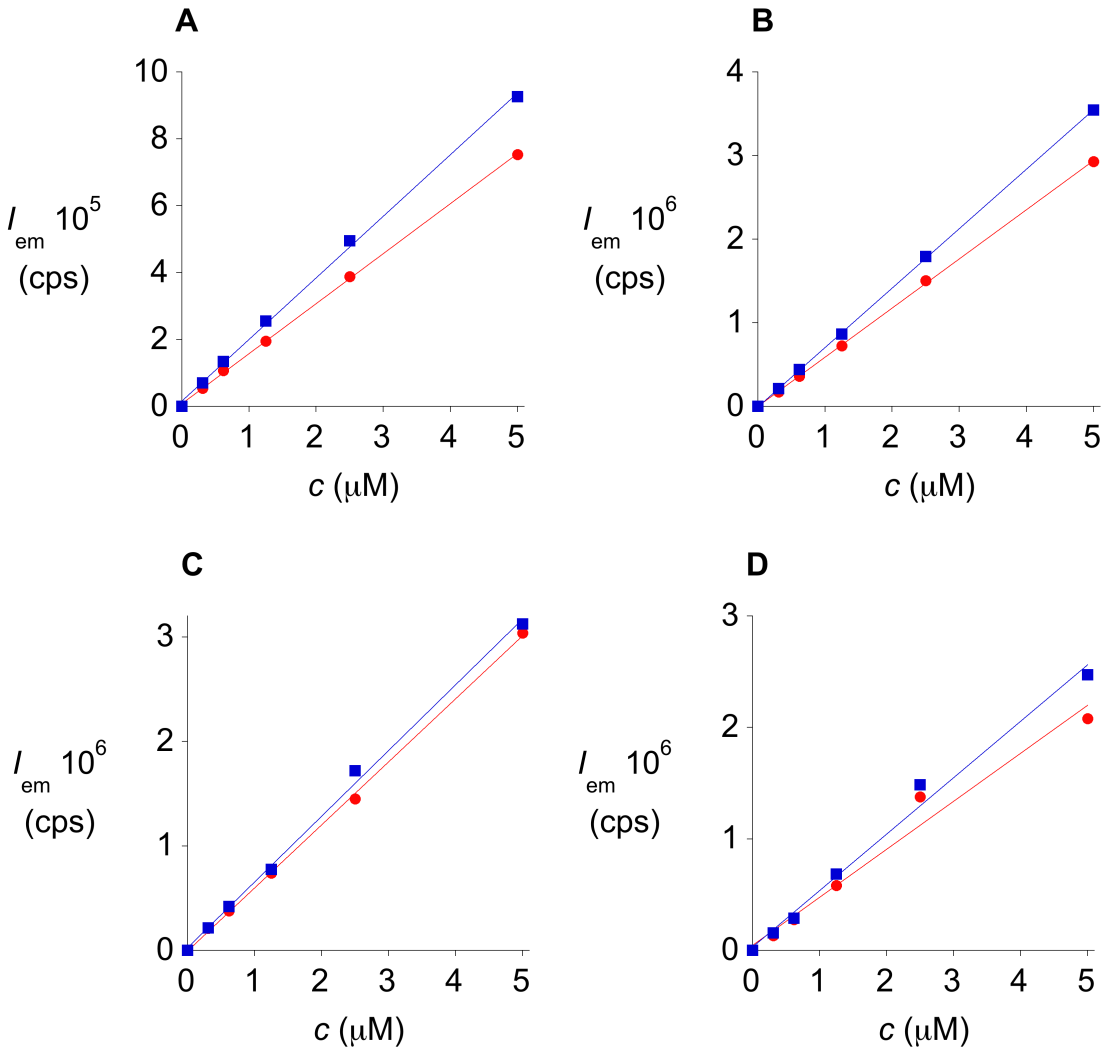


Figure S9. Fluorescence intensity as a function of concentration of **1** (λ_{em} = 603 nm, A), **2** (λ_{em} = 585 nm, B), **3** (λ_{em} = 504 nm, C) and **4** (λ_{em} = 490 nm, D) at 25 °C (blue squares) and 55 °C (red circles) in buffer.

Table S3. Characteristics of push-pull papillon probes **1** – **4** in bulk.

Cmpd[a]	Toluene 25 °C		H_2O 25 °C		Glycerol 25 °C	
	$\lambda_{e1}/\lambda_{e2}$[b]	$I_{b/p}$[c]	$\lambda_{e1}/\lambda_{e2}$[b]	$I_{b/p}$[c]	$\lambda_{e1}/\lambda_{e2}$[b]	$I_{b/p}$[c]
1	608/682	0.9	603/–	>20	601/–	>20
2	565/689	0.3	585/–	>20	582/–	>20
3	446/616	<0.1	504/–	>20	515/–	>20
4	464/620	<0.1	490/–	>20	490/–	>20

[a]Compounds, see Scheme S1–S4. [b]Wavelength of the first (e1) and second emission maxima (e2), in nm. [c]Fluorescence intensity ratio $I_{b/p} = I_{e1} / I_{e2}$.

Table S4. Characteristics of push-pull papillon probes **1** – **4** in LUVs.

Cmpd[a]	DPPC 25 °C		DPPC 55 °C	DOPC 25 °C	DOPC 55 °C
	$\lambda_{e1}/\lambda_{e2}$[b]	$I_{b/p}$[c]	$I_{b/p}$[c]	$I_{b/p}$[c]	$I_{b/p}$[c]
1	578/602	1.1	0.8	0.9	0.9
2	553/595	1.2	0.8	0.8	0.8
3	515/592	1.6	0.7	0.9	0.6
4	508/609	1.9	0.4	0.8	0.5

[a]Compounds, see Scheme S1–S4. [b]Wavelength of the first (e1) and second emission maxima (e2), in nm. [c]Fluorescence intensity ratio $I_{b/p} = I_{e1} / I_{e2}$.

7. Quantum Chemistry Calculations

All calculations were performed at the DFT level of theory using the CAM-B3LYP/6-31+G(d,p) combination of functional and basis set (*S7*) with the implicit polarized continuum model representation for water (*S8*). The electron densities and molecular orbitals were rendered with VMD 1.9.4 (*S9*) at isovalue 0.02. All calculations were performed with Gaussian09 software (rev. C) (*S10*).

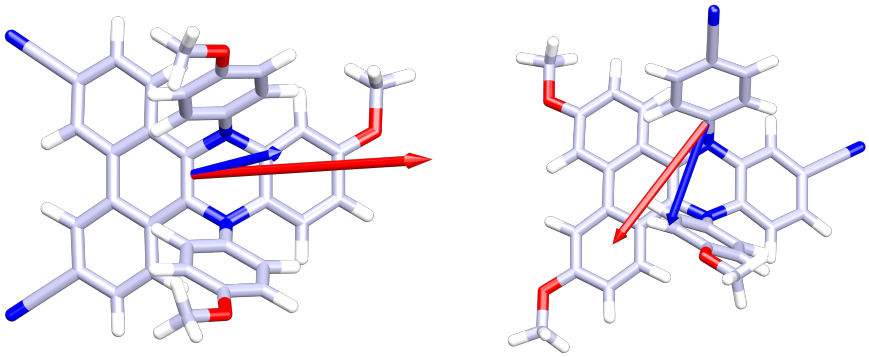


Figure S10. Calculated permanent dipole moment of compound **1** (left) and **3** (right) for ground state (blue vector) and for first excited state in non-equilibrium geometry (vertical transition, red vector).

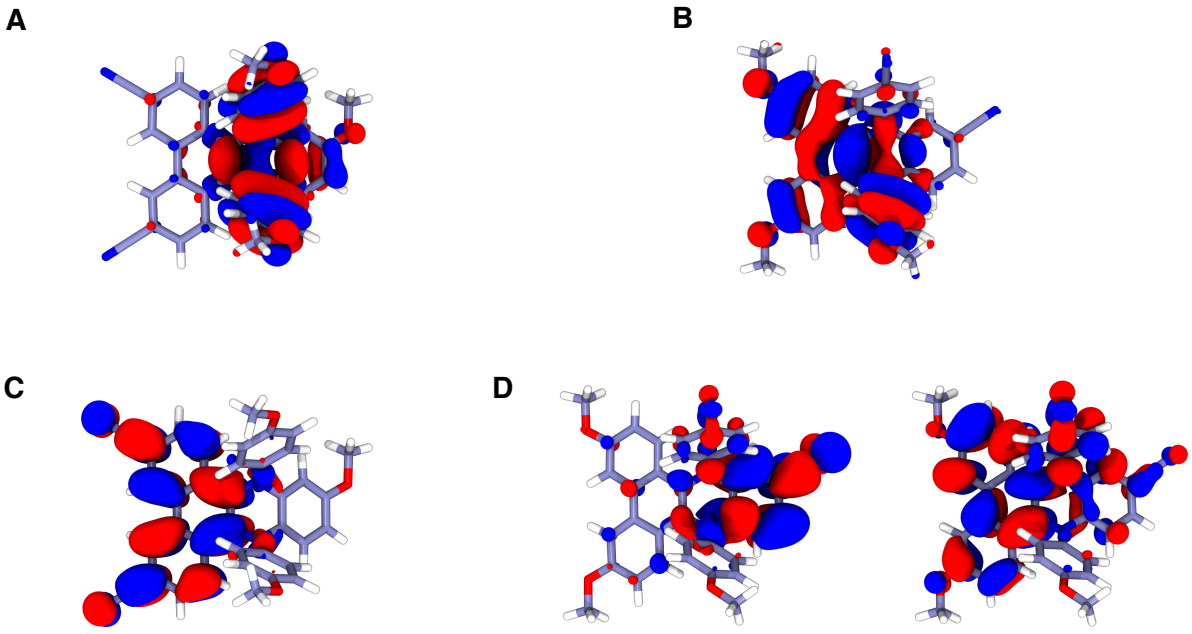


Figure S11. Frontier molecular orbitals of **1** (A: HOMO, C: LUMO) and **3** (B: HOMO, D: LUMO and LUMO+1) in the ground state optimized geometry involved in the first excited state.

Table S5. Molecular orbital contributions to the first excited state for compounds under investigation.

Cmpd[a]	λ_{abs}[b] (nm)	f[c]	Contribution[d]
1	384	0.27	HOMO → LUMO (90%)
2	375	0.33	HOMO → LUMO (87%)
3	322	0.60	HOMO → LUMO (66%) HOMO → LUMO+1 (14%)
4	319	0.57	HOMO → LUMO (71%) HOMO → LUMO+1 (14%)

[a]Compounds, Scheme S1–S4. [b]Calculated lowest-lying absorption. [c]Oscillator strength. [d]Main molecular orbital contribution.

8. References

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The original data can be found at:

https://doi.org/10.26037/yareta:5b2y3rzii5hufg6hpled2yyrlm

9. NMR Spectra

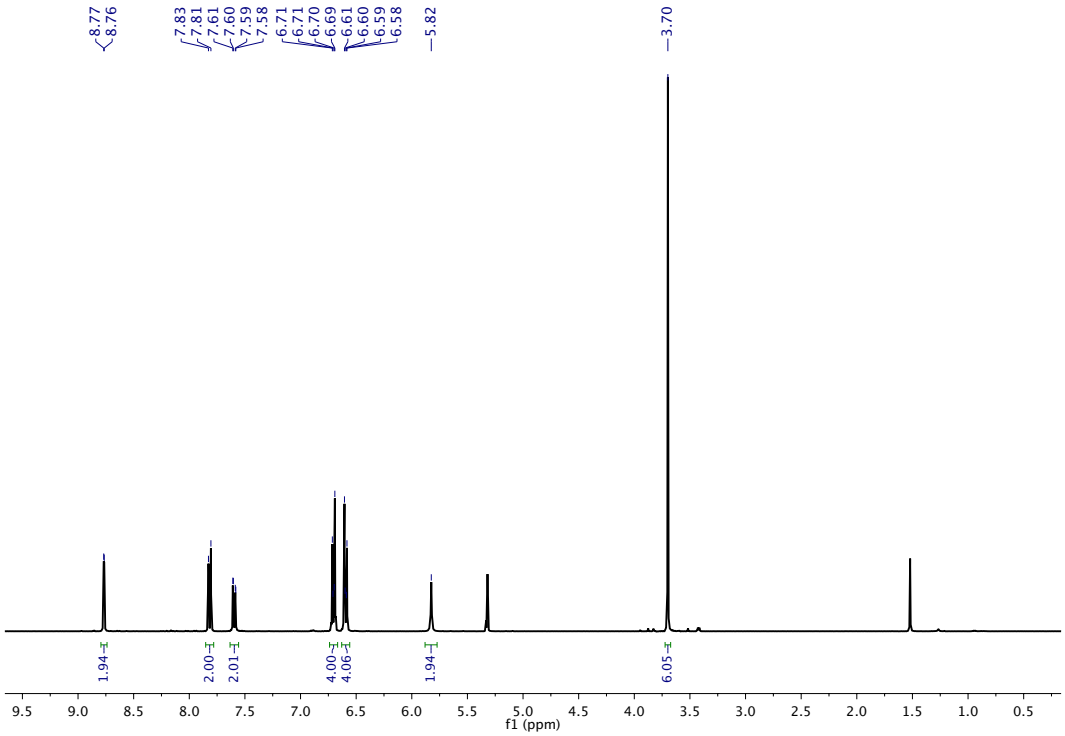

Figure S12. ^{1}H NMR spectrum of **9** in CD_2Cl_2.

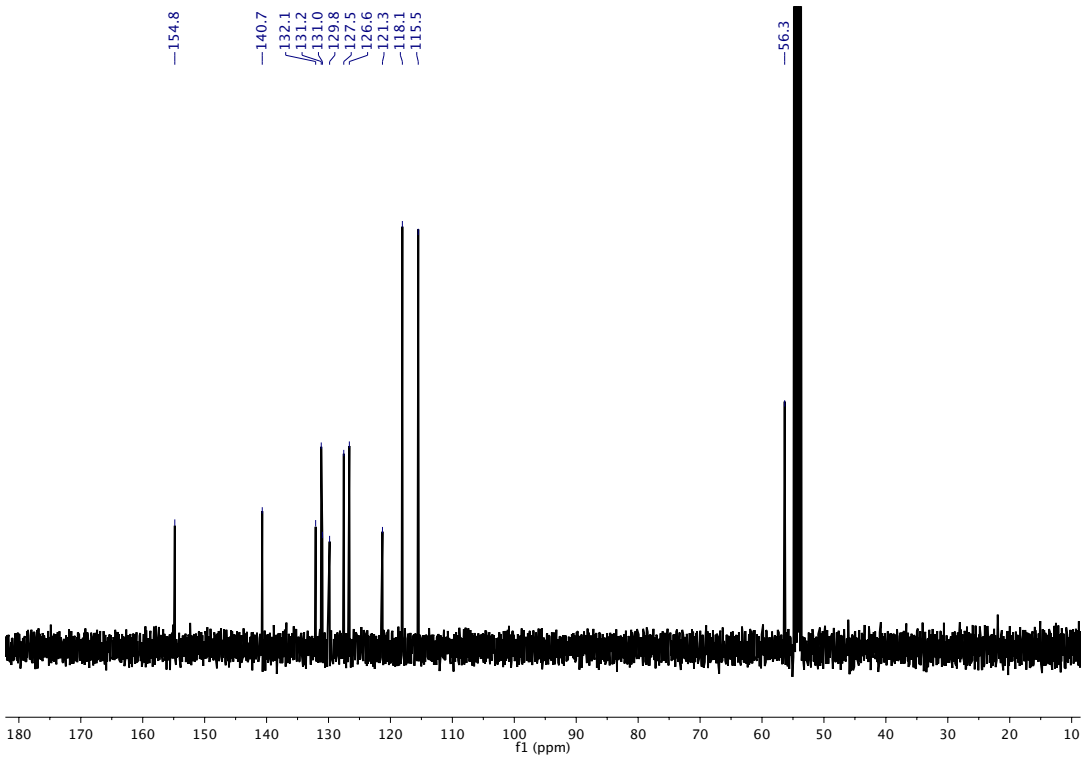

Figure S13. ^{13}C NMR spectrum of **9** in CD_2Cl_2

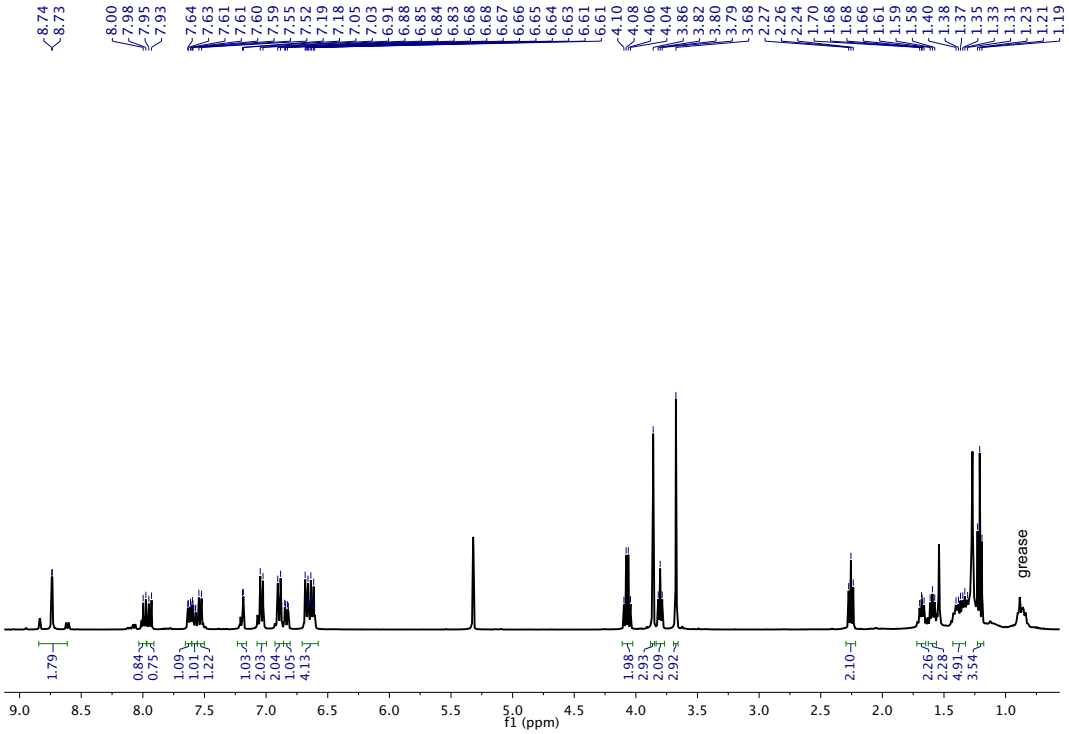

Figure S14. ^{1}H NMR spectrum of **11** in CD_2Cl_2.

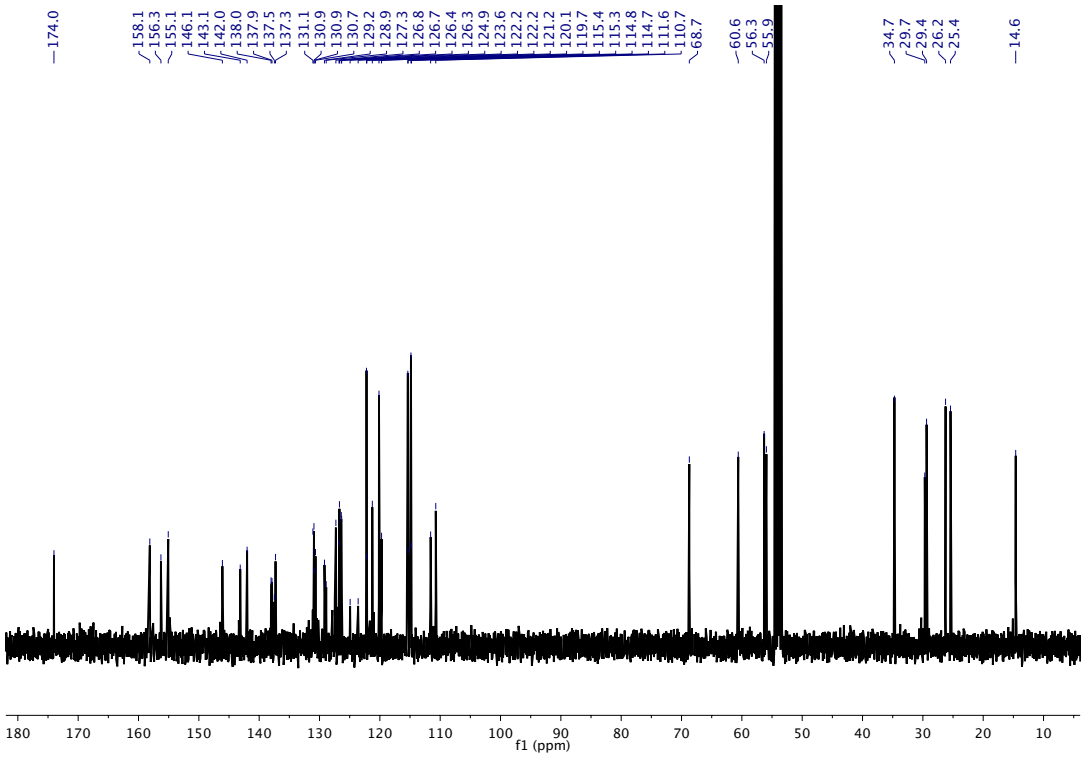

Figure S15. ^{13}C NMR spectrum of **11** in CD_2Cl_2.

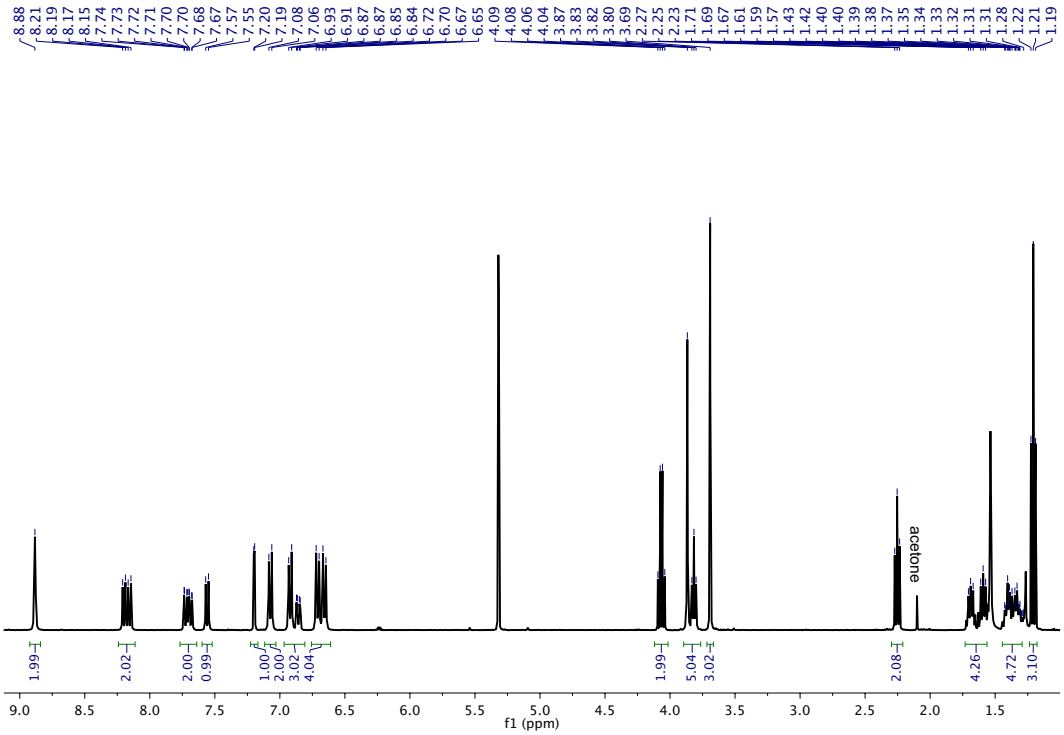

Figure S16. ^{1}H NMR spectrum of **12** in CD_2Cl_2.

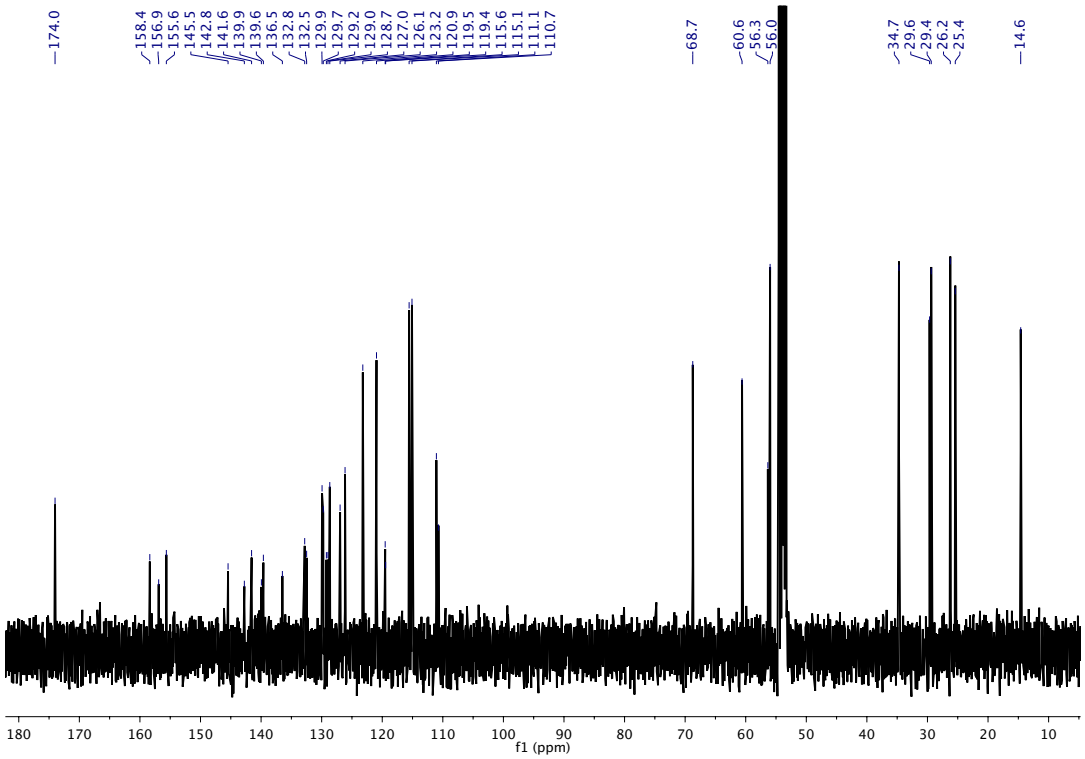

Figure S17. ^{13}C NMR spectrum of **12** in CD_2Cl_2.

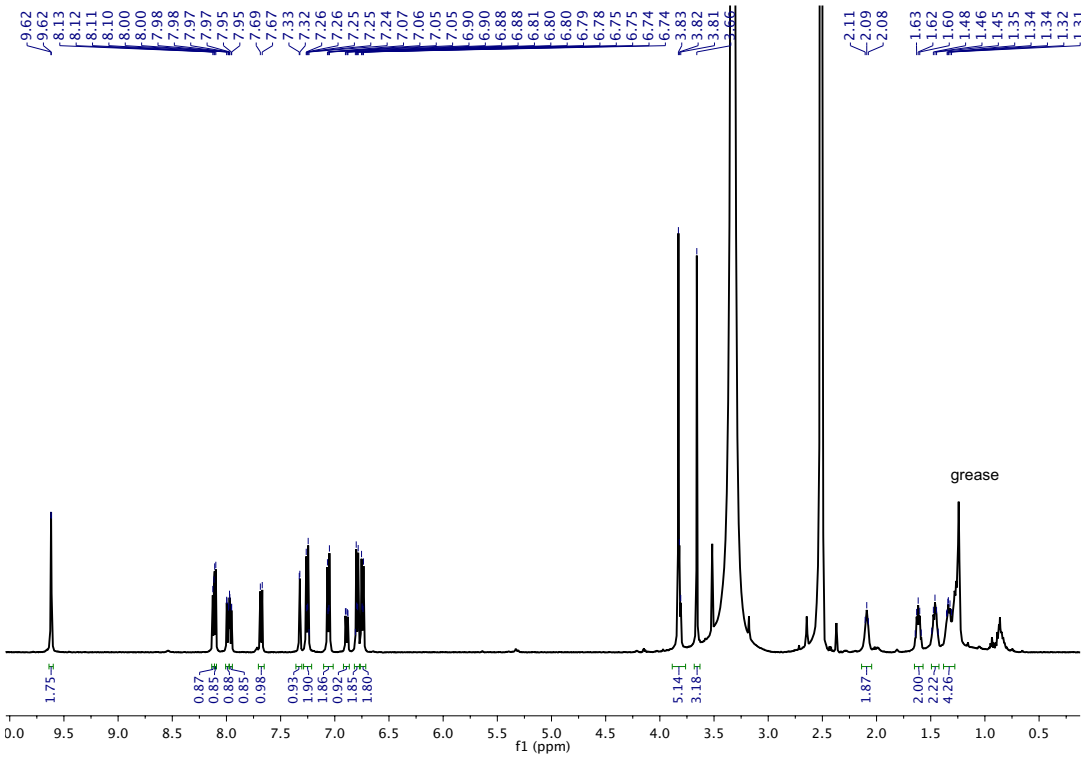

Figure S18. ^{1}H NMR spectrum of **1** in DMSO-d_6.

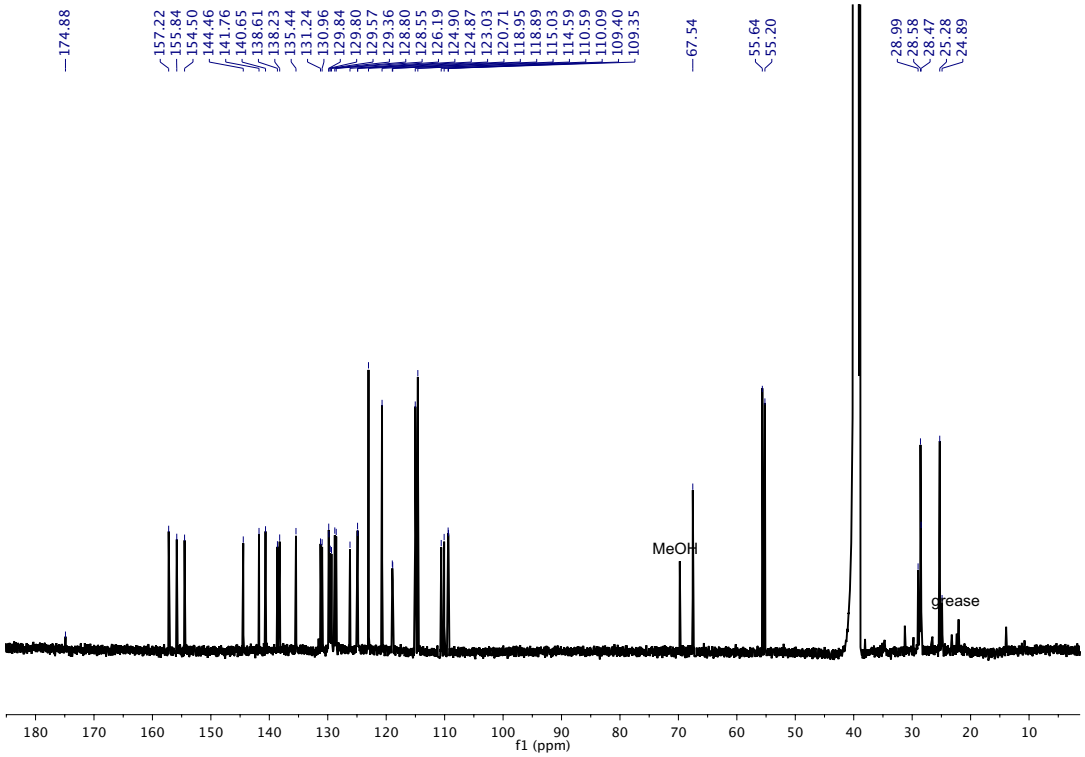

Figure S19. ^{13}C NMR spectrum of **1** in DMSO-d_6.

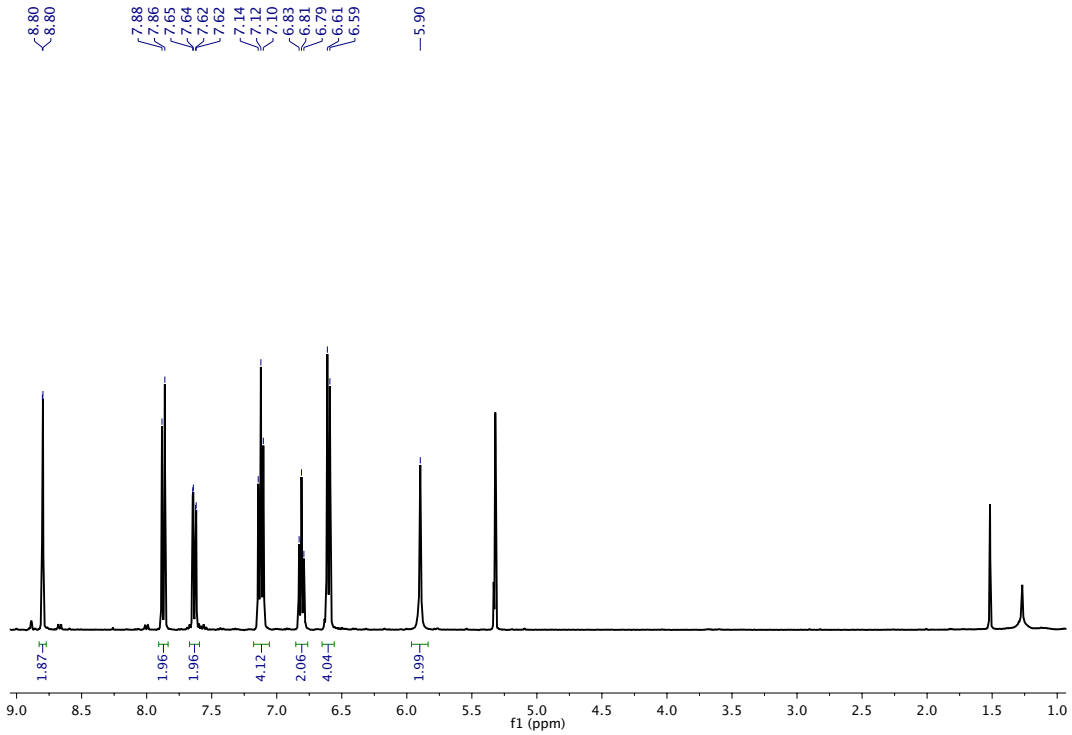

Figure S20. ^{1}H NMR spectrum of **14** in CD_2Cl_2.

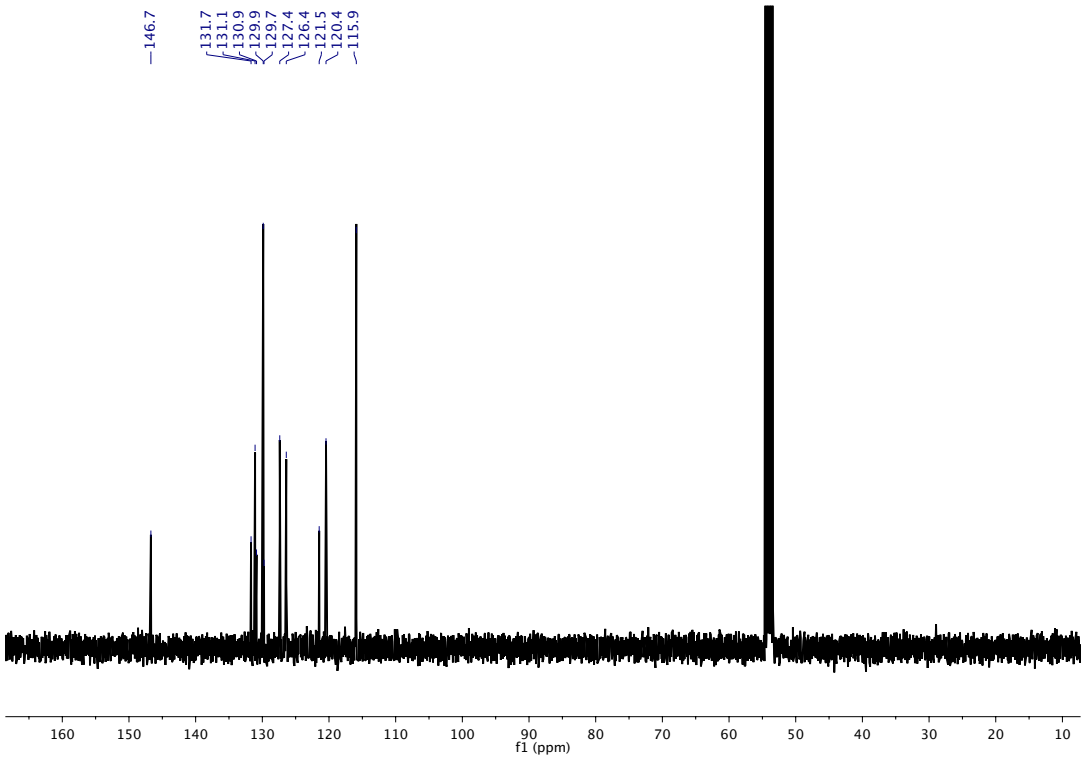

Figure S21. ^{13}C NMR spectrum of **14** in CD_2Cl_2.

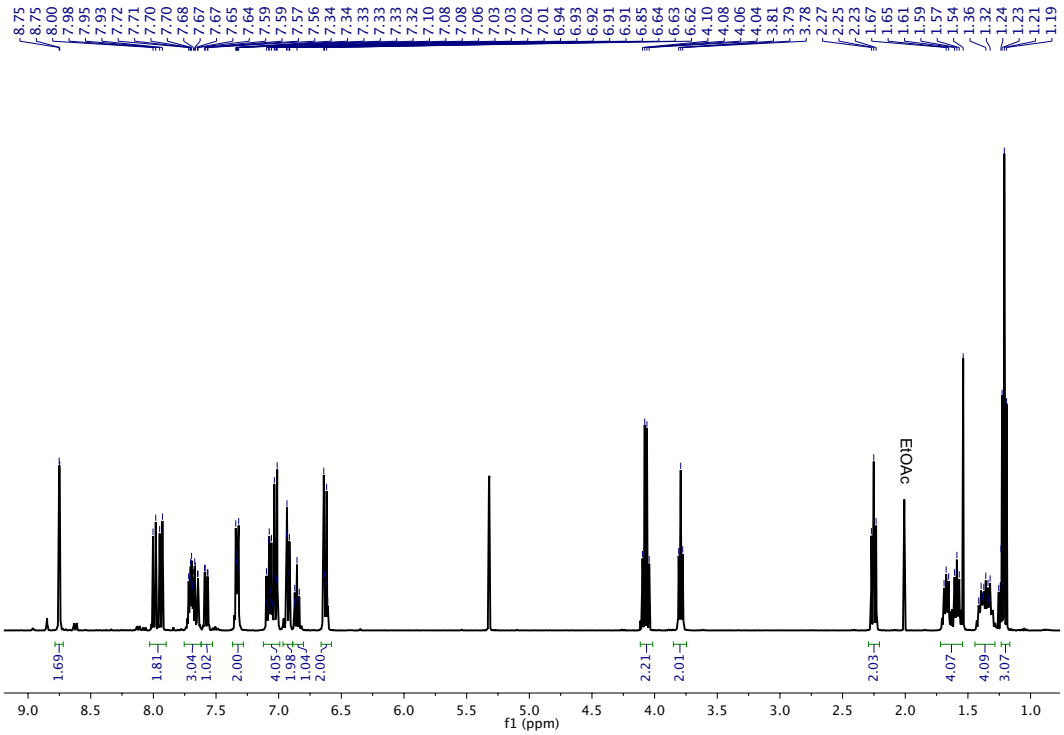

Figure S22. ^{1}H NMR spectrum of **15** in CD_2Cl_2.

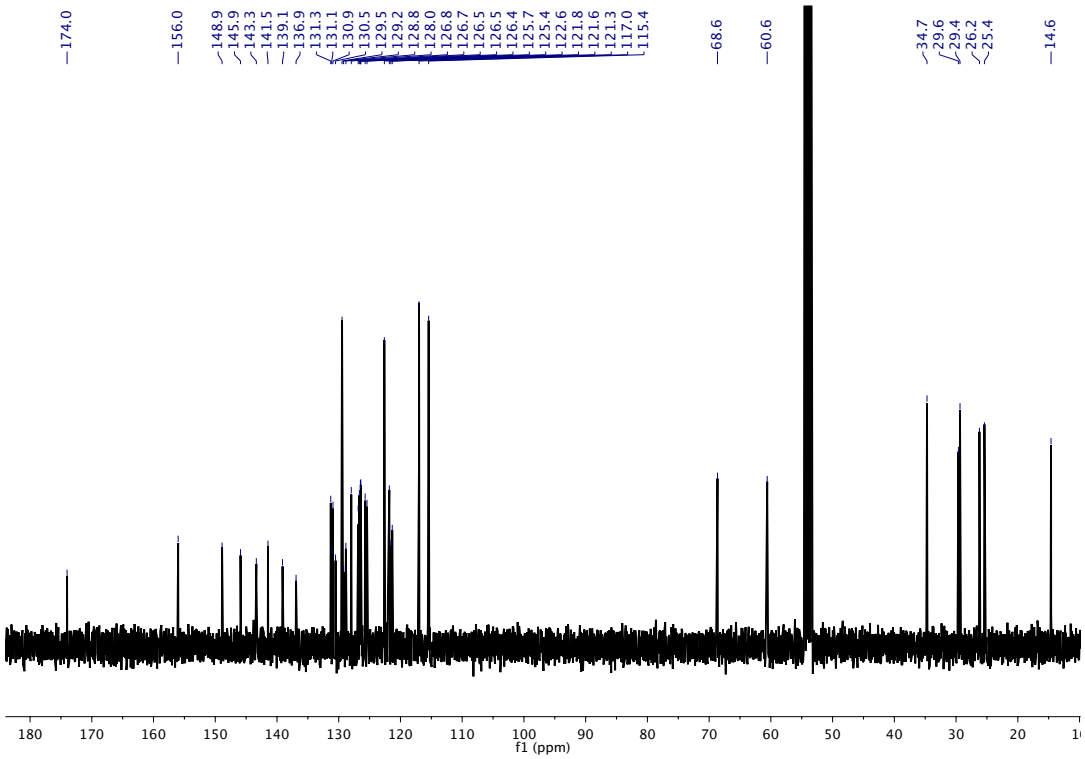

Figure S23. ^{13}C NMR spectrum of **15** in CD_2Cl_2.

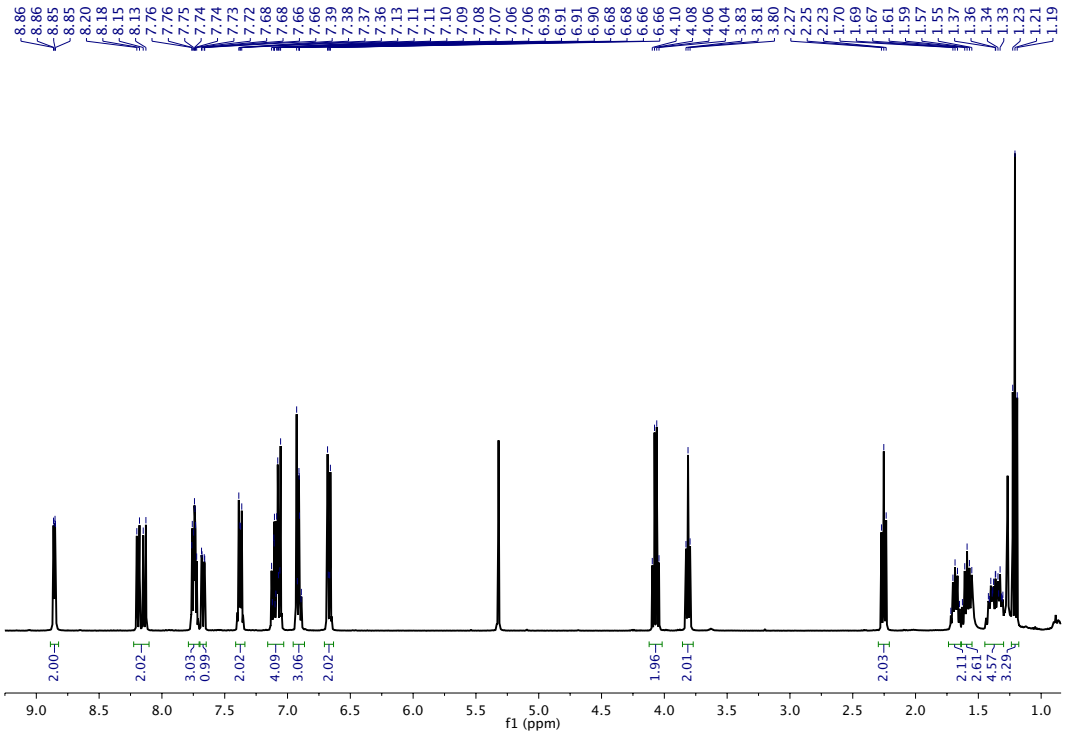

Figure S24. ^{1}H NMR spectrum of **16** in CD_2Cl_2.

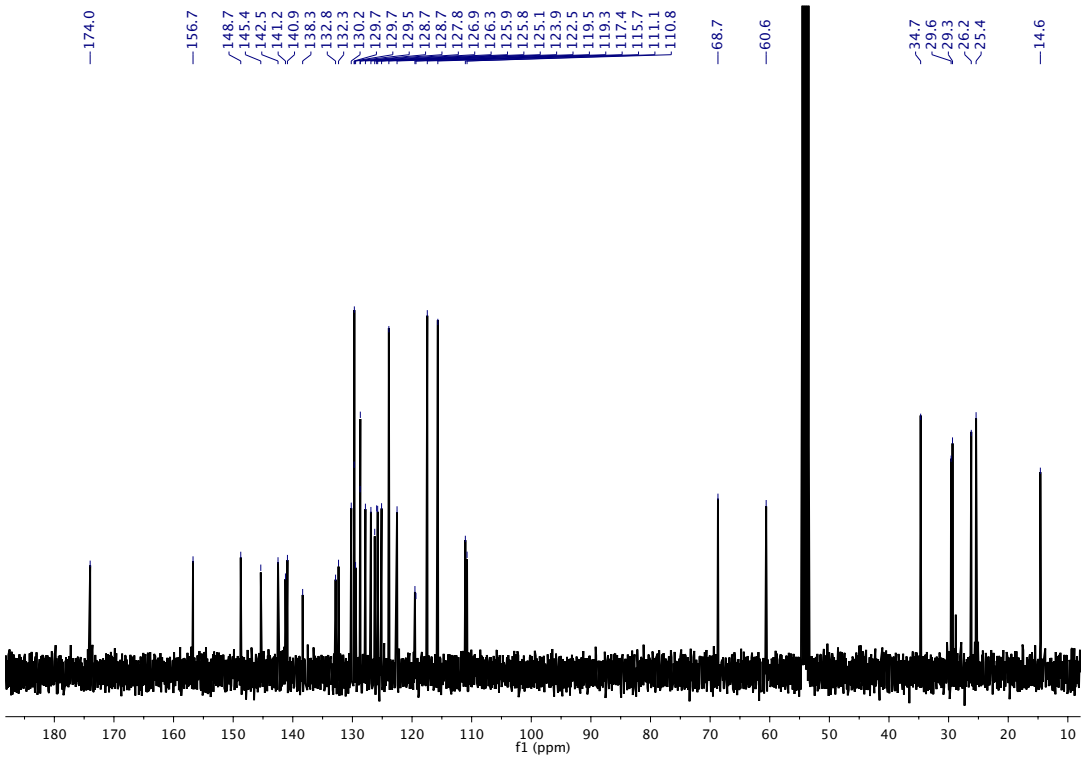

Figure S25. ^{13}C NMR spectrum of **16** in CD_2Cl_2.

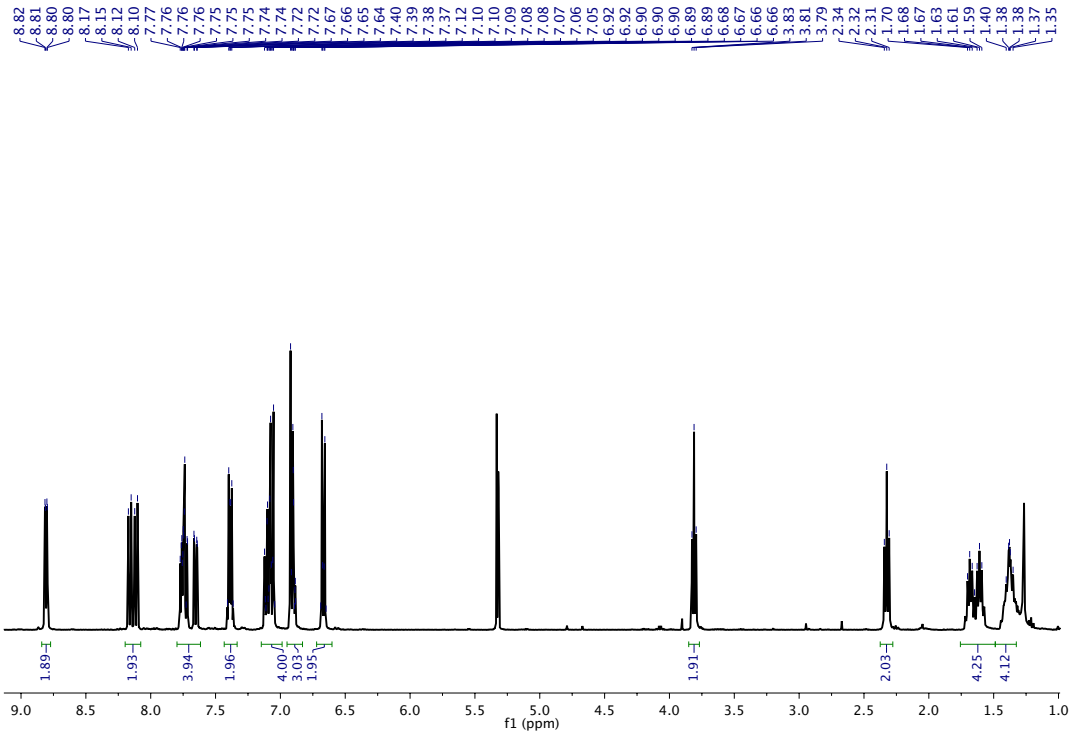

Figure S26. ^{1}H NMR spectrum of **2** in CD_2Cl_2.

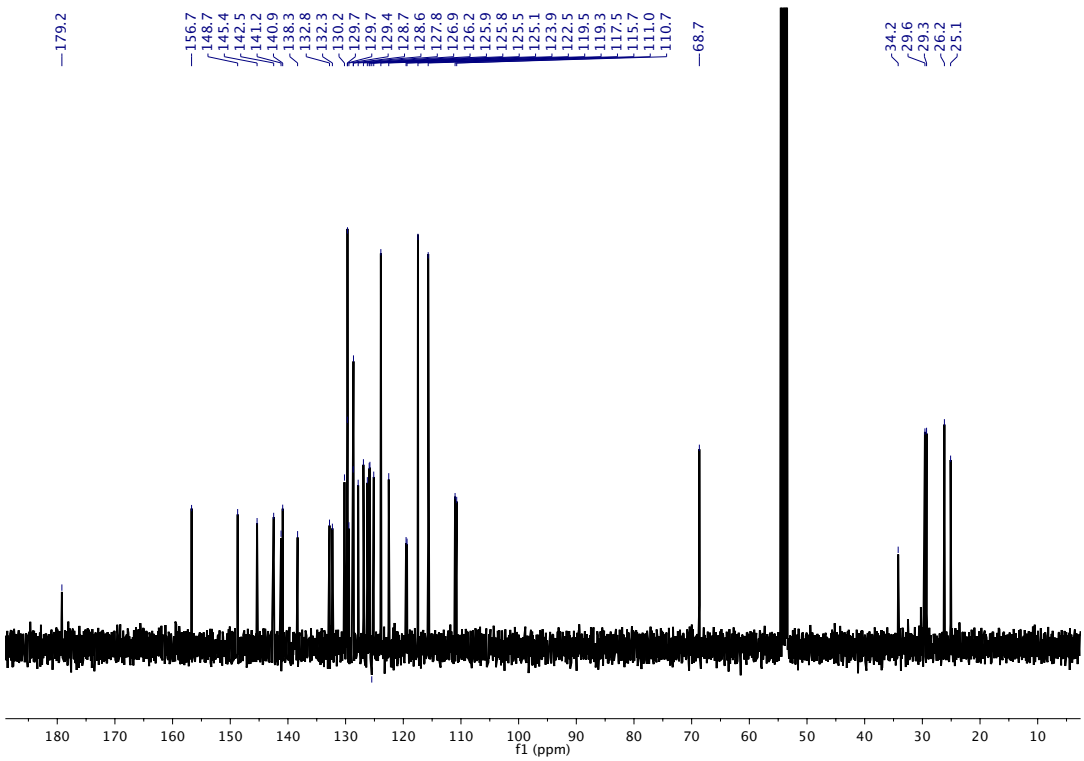

Figure S27. ^{13}C NMR spectrum of **2** in CD_2Cl_2.

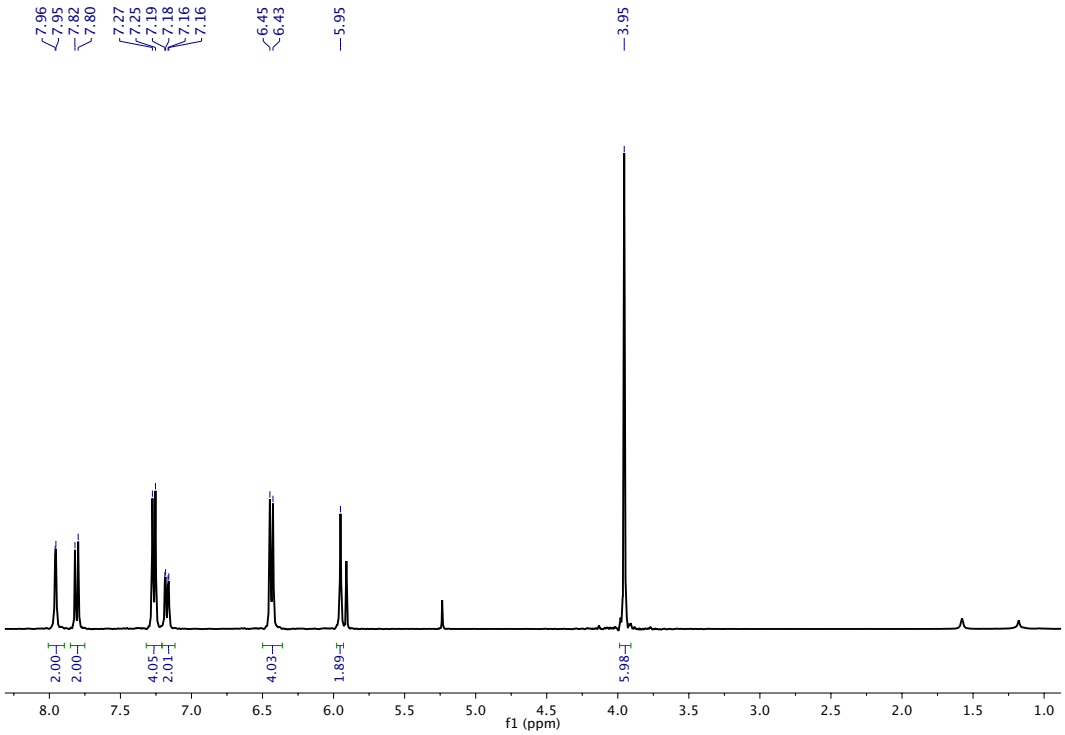

Figure S28. ^{1}H NMR spectrum of **20** in $C_2D_2Cl_4$.

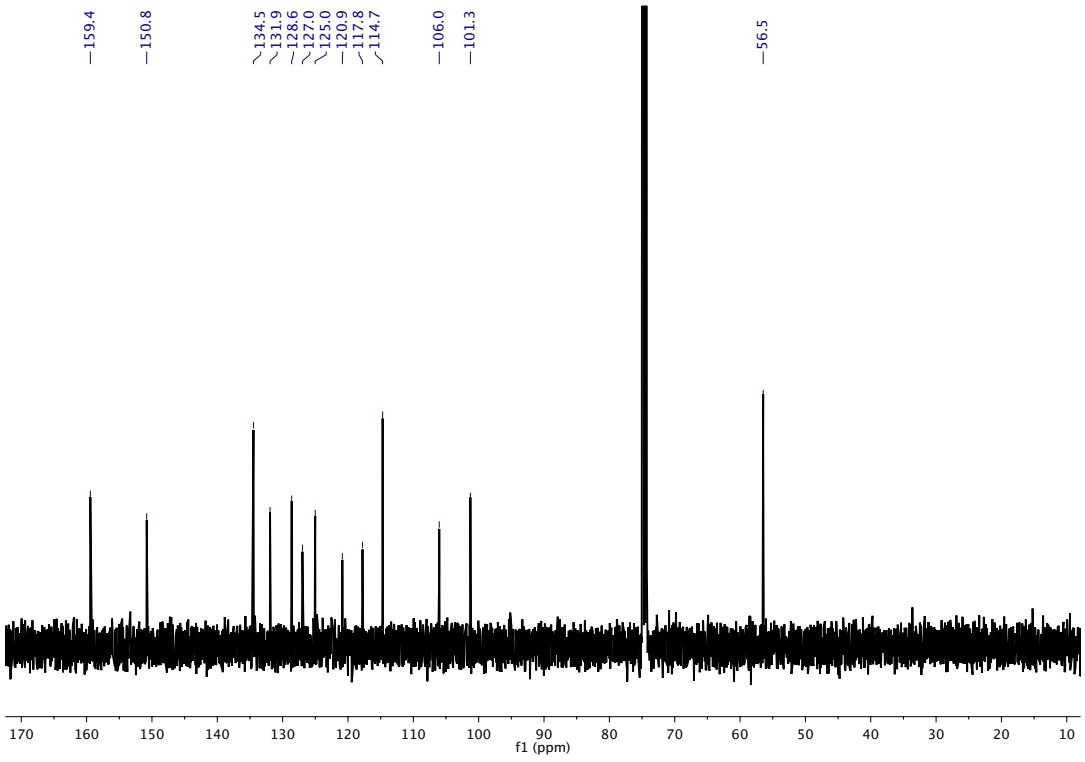

Figure S29. ^{13}C NMR spectrum of **20** in $C_2D_2Cl_4$.

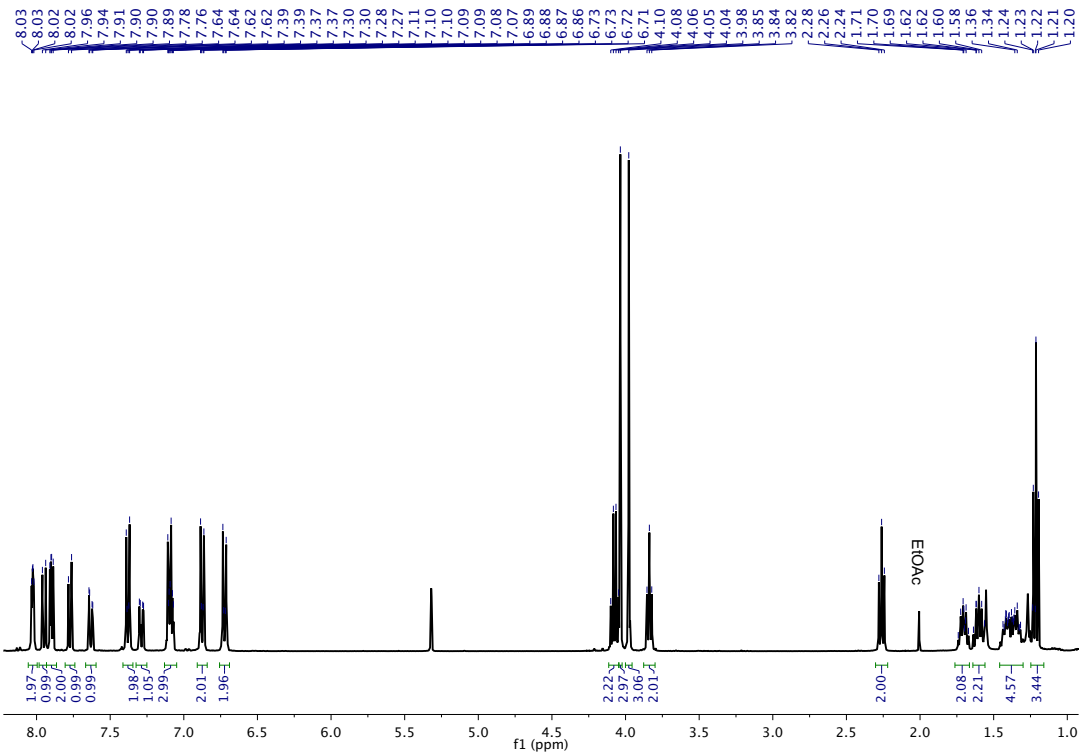

Figure S30. ^{1}H NMR spectrum of **21** in CD_2Cl_2.

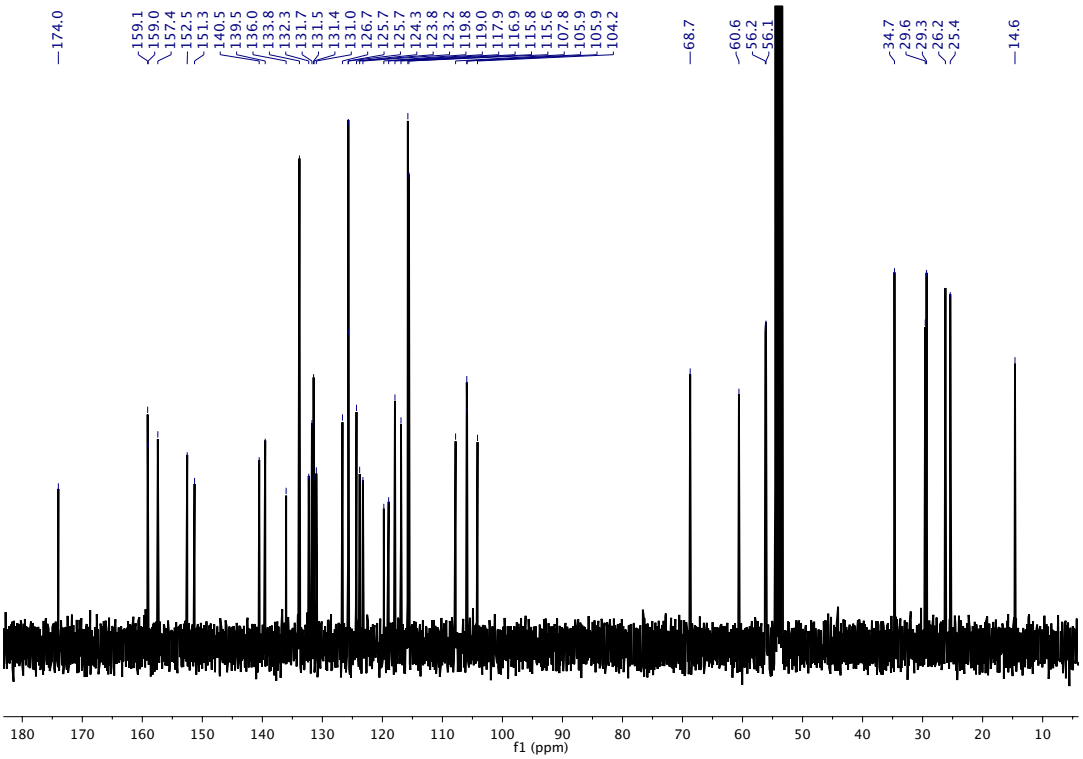

Figure S31. ^{13}C NMR spectrum of **21** in CD_2Cl_2.

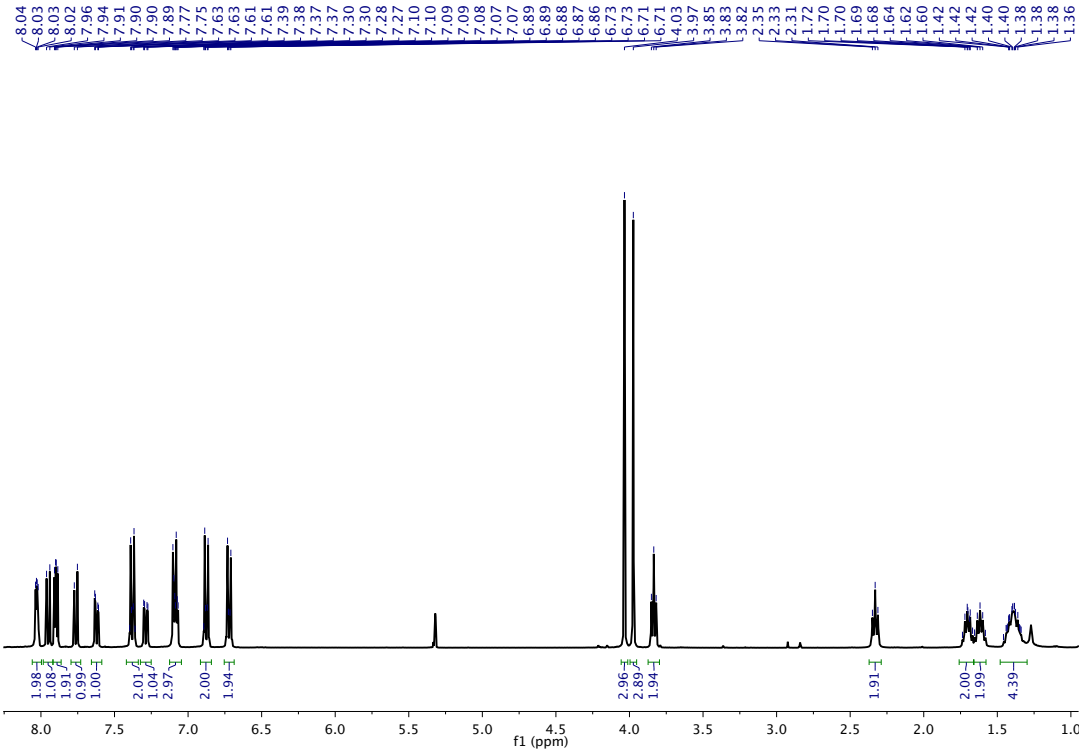

Figure S32. ^{1}H NMR spectrum of **3** in CD_2Cl_2.

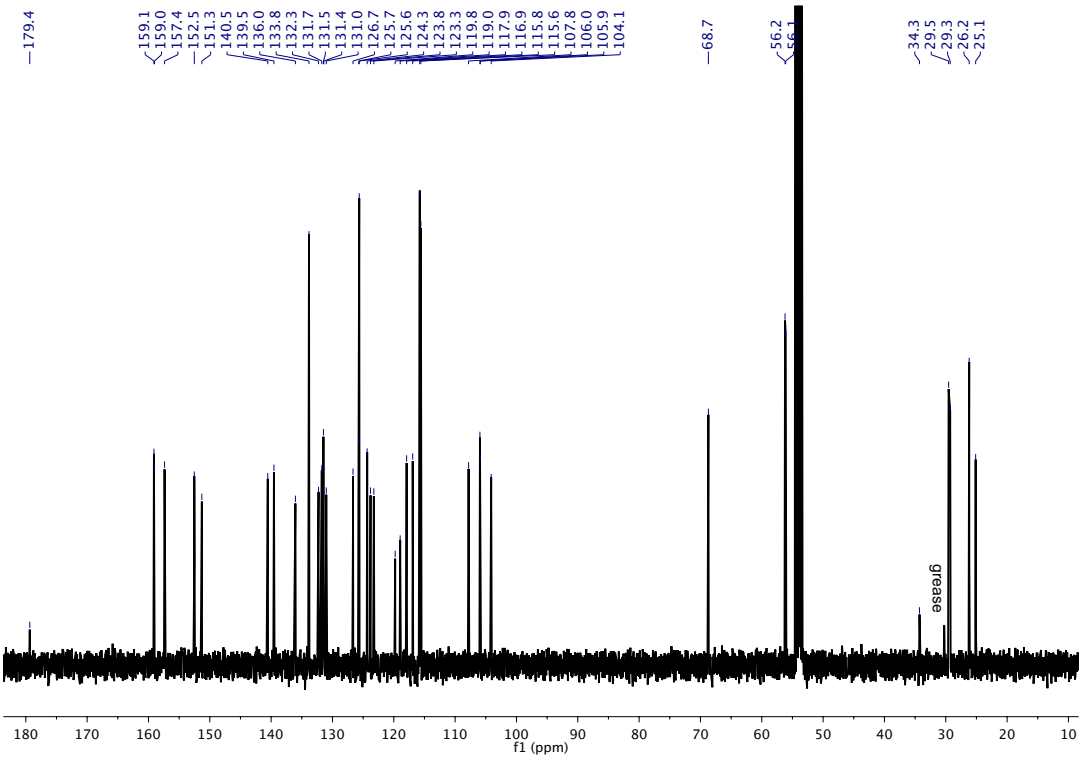

Figure S33. ^{13}C NMR spectrum of **3** in CD_2Cl_2.

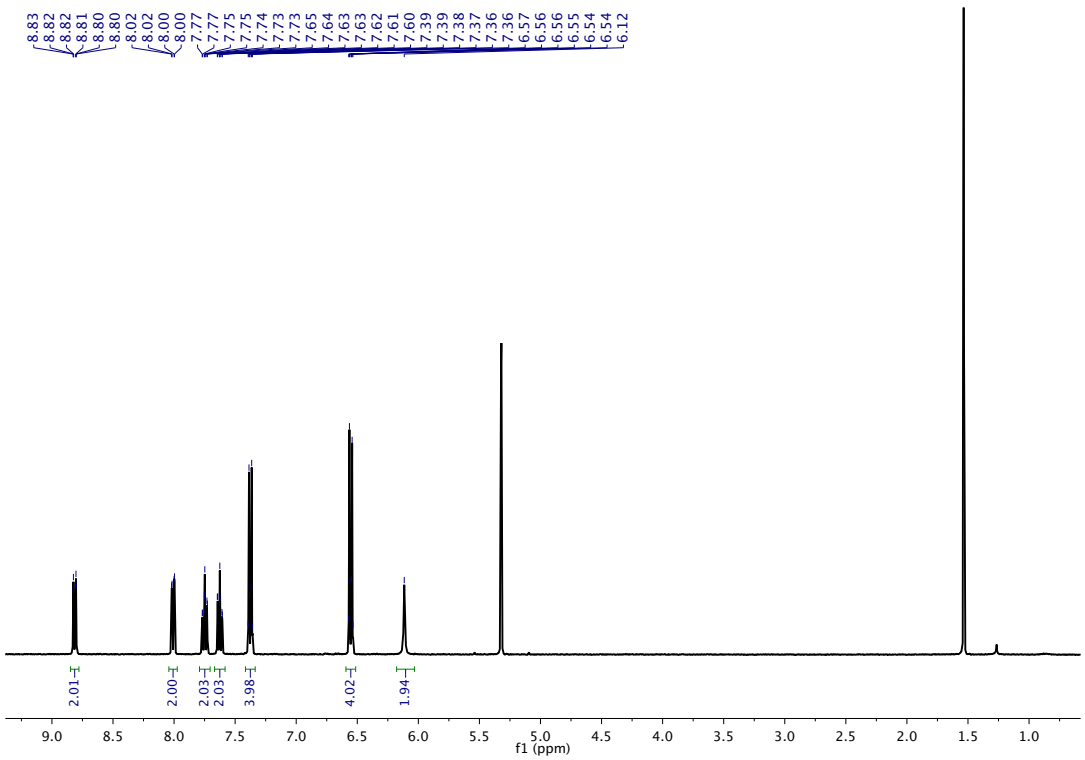

Figure S34. ^{1}H NMR spectrum of **22** in CD_2Cl_2.

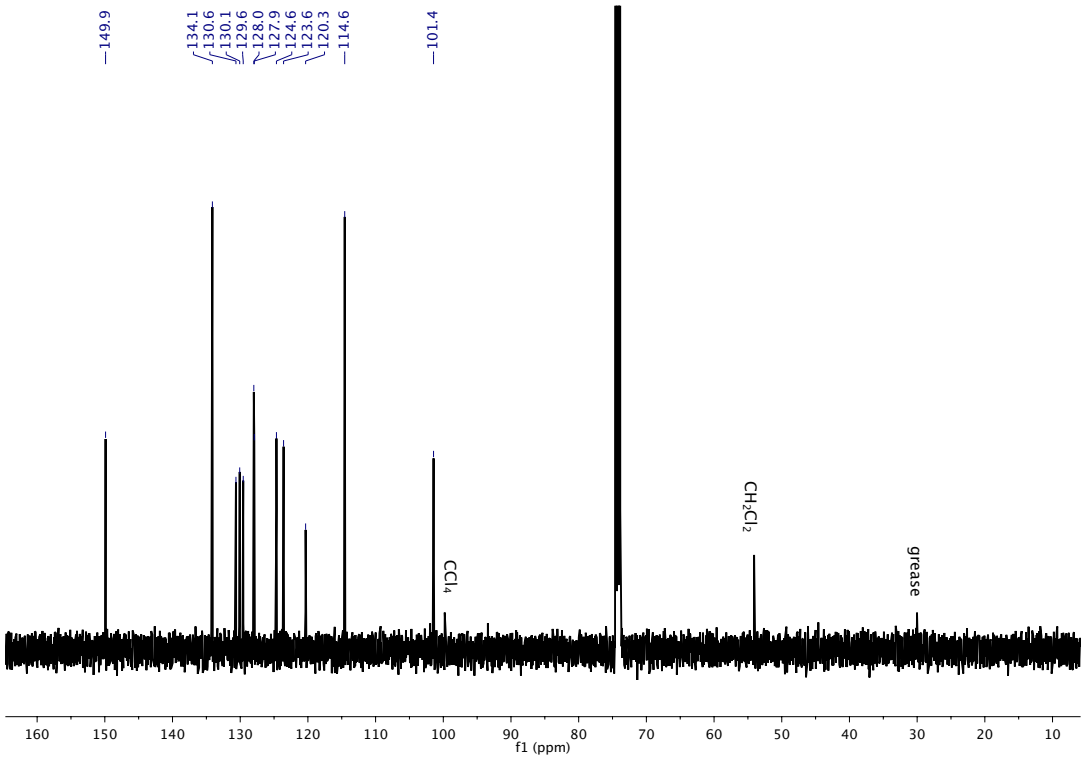

Figure S35. ^{13}C NMR spectrum of **22** in $C_2D_2Cl_4$.

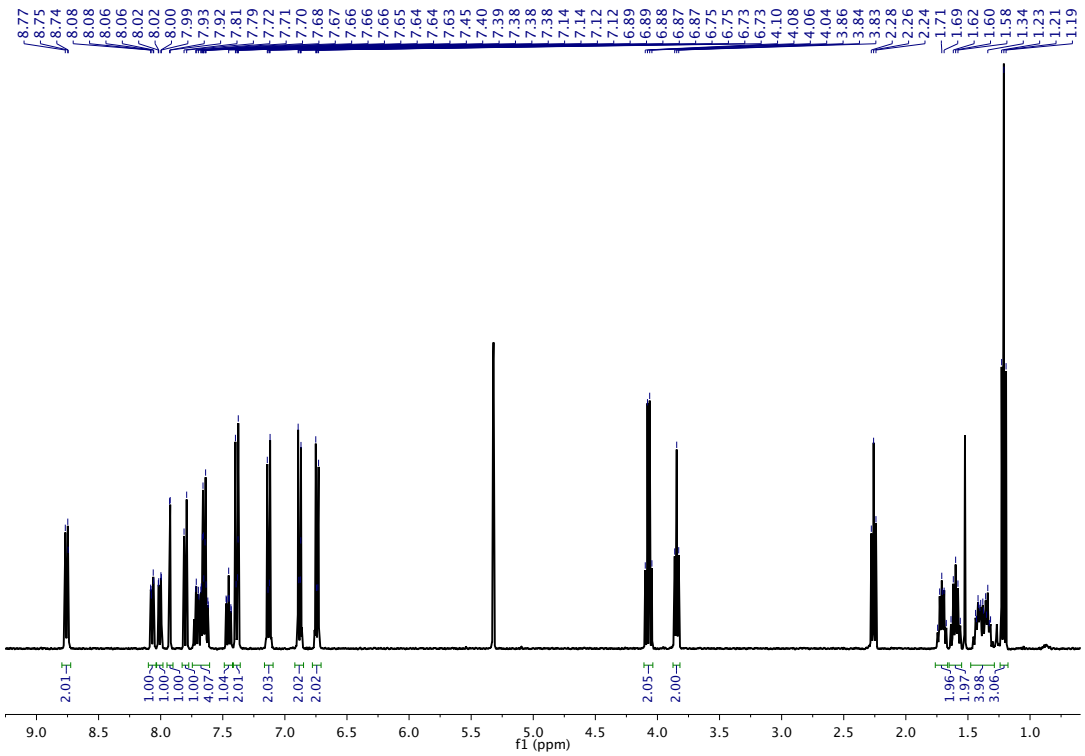

Figure S36. ^{1}H NMR spectrum of **23** in CD_2Cl_2.

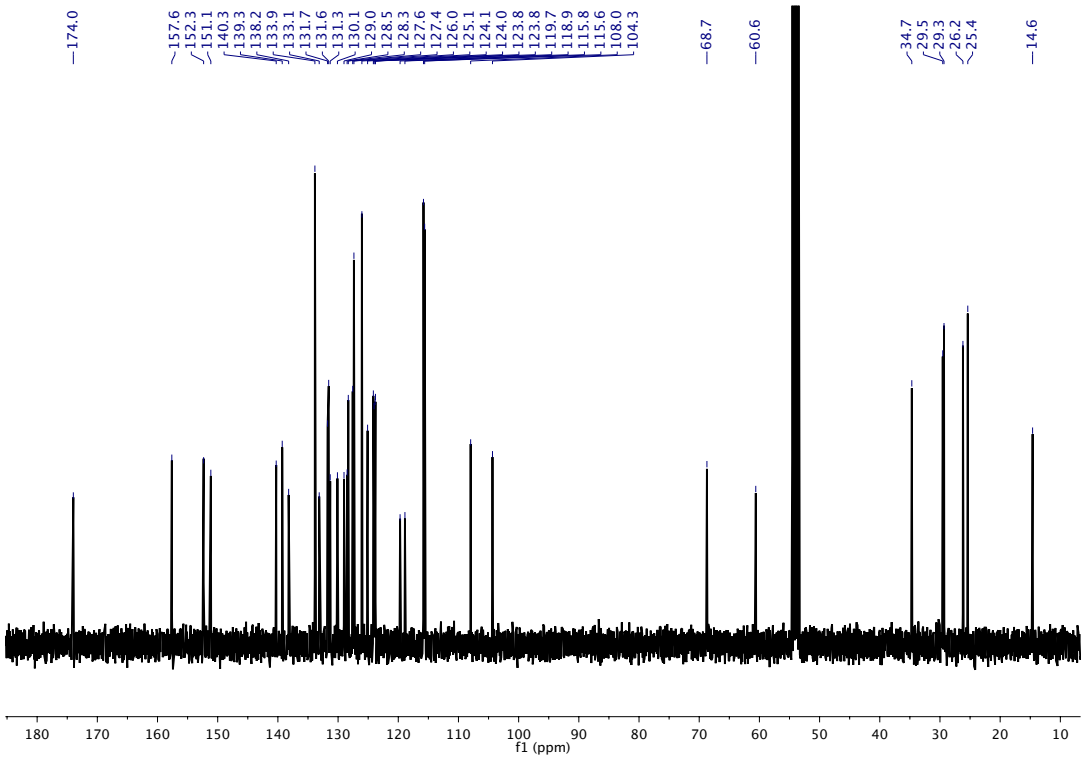

Figure S37. ^{13}C NMR spectrum of **23** in CD_2Cl_2.

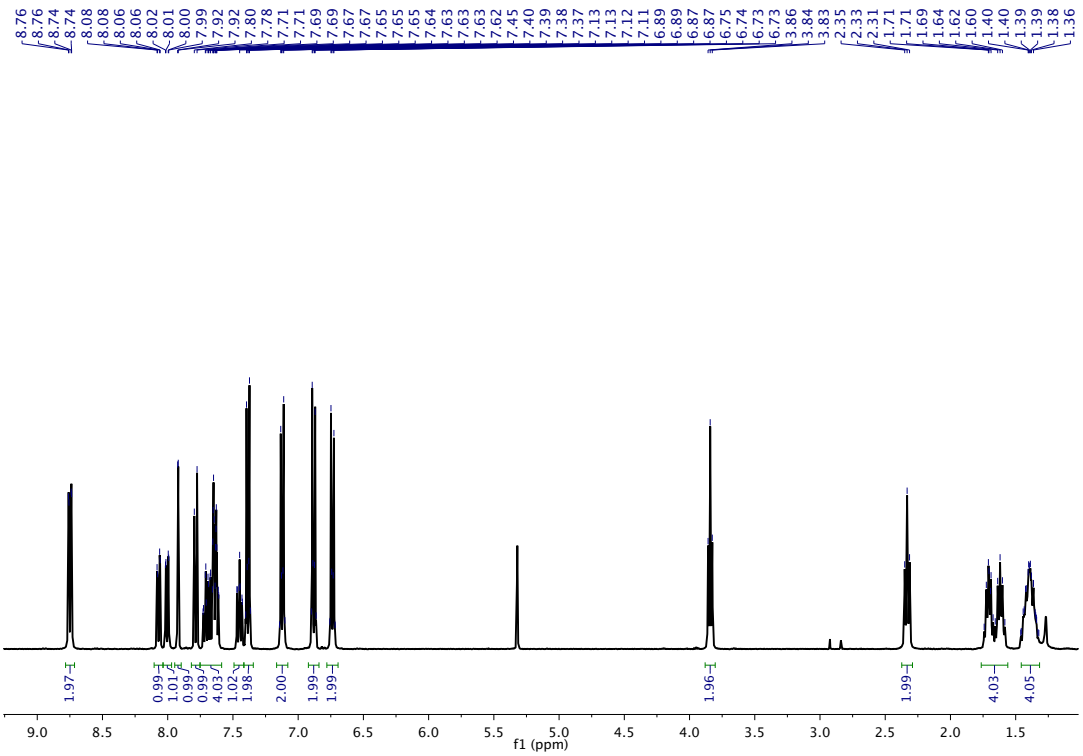

Figure S38. ^{1}H NMR spectrum of **4** in CD_2Cl_2.

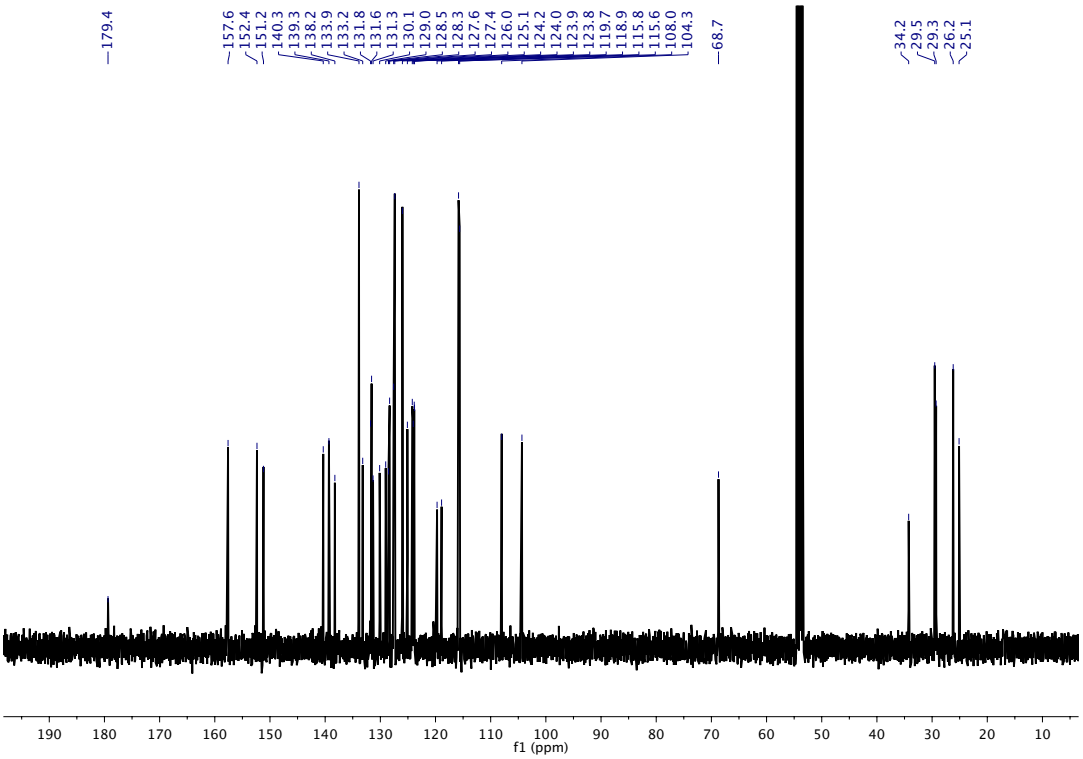

Figure S39. ^{13}C NMR spectrum of **4** in CD_2Cl_2.