Synthetic Multifunctional Pores with External and Internal Active Sites for Ligand Gating and Noncompetitive Blockage

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Supporting Information

General. Reagents for synthesis were purchased from Fluka, amino acid derivatives from Novabiochem, egg yolk phosphatidylcholine (EYPC) from Avanti polar lipids, HATU from Applied Biosystems, BODIPY-PC from Molecular Probes, fullerene (C60) from Alfa Aesar, CF, PE (MW 13600 g/mol), 1-pyrenebutyric acid, PLE, buffers, and salts from Sigma or Fluka-Aldrich. All reactions were performed under argon atmosphere. Unless stated otherwise, column chromatography was carried out on silica gel 60 (Fluka, 40-63 μm). Reverse phase column chromatography was performed using ODS (Fluka Silicagel 100 C18-Reverse Phase). Sephadex LH-20 was from Amersham Biosciences. Analytical (TLC) and preparative thin layer chromatography (PTLC) were performed in silica gel 60 (Fluka, 0.2 mm) and silica gel GF (Analtech, 1000 μm), respectively. Purity of the product was verified by using either Jasco HPLC system (PU-980, UV-970, FP-920) or Agilent 1100 Series. $[\alpha]^{20}_{D}$ values were recorded on a Jasco P-1030 Polarimeter, melting points (mp) on a heating table from Reichert (Austria), elemental analysis on a Vario EL instrument from Elementar. 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). ESI-MS and APCI-MS were performed on a Finnigan MAT SSQ 7000 instrument. ^{1}H and ^{13}C spectra were recorded (as indicated) on either a Bruker 300 MHz, 400 MHz or 500 MHz spectrometer and are reported as chemical shifts (δ) in ppm relative to TMS (δ = 0). Spin multiplicities are reported as a singlet (s), doublet (d), triplet (t), with coupling constants (*J*) given in Hz, or multiplet (m). ^{1}H and ^{13}C resonances were assigned with the aid of additional information from 2D NMR spectra [H,H-COSY, DEPT 135, HSQC and HMBC]. UV-Vis spectra were measured on a Varian Cary 1 Bio spectrophotometer. Fluorescence measurements were preformed on either a FluoroMax-2 or a FluoroMax-3, Jobin Yvon-Spex. The Mini-Extruder with a polycarbonate membrane, pore size 100 nm, used for LUV preparation was from Avanti polar lipids.

Abbreviations. Arg, *L*-Arginine; BOC: Butoxycarbonyl; BODIPY-PC: 2-(4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene-3-dodecanoyl)-1-hexadecanoyl-*sn*-glycero-3-phosphocholine; CF, 5(6)-carboxyfluorescein; DMF: *N,N*-Dimethylformamide; EDC: 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide, EYPC-LUVs: Egg yolk phosphatidylcholine

large unilamellar vesicles; Fmoc: 9-Fluorenylmethoxycarbonyl; *Gla*: -OCH_2CO- (H-Gla-OH: glycolic acid); HATU: *N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide; HBTU: *N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide; His: *L*-Histidine; HOBt: 1-Hydroxybenzotriazole; Leu: *L*-Leucine; PE: Poly-L-glutamic acid; PLE: porcine liver esterase; Pmc: 2,2,5,7,8,-Pentamethylchromane-6-sulfonyl; TEA: Triethylamine; TFA: Trifluoroacetic acid; Trt: Trityl.

H-His(Trt)-Leu-NH_2. This compound was prepared in 2 steps following previously reported procedures.[S1]

Z-Arg(Pmc)-His(Trt)-Leu-NH_2. EDC ·HCl (54 mg, 2.8 μmol), HOBt (35 mg, 2.6 μmol), Z-Arg(Pmc)-OH (138 mg, 2.4 μmol) and TEA (145 μl, 10.3 μmol) were added to a solution of H-His(Trt)-Leu-NH_2 (109 mg, 2.0 μmol) in CH_2Cl_2 (10 ml) at 0 °C. After stirring for 16 hours in the dark at rt, the reaction mixture was diluted with CH_2Cl_2, extracted with saturated aqueous $NaHCO_3$, washed with brine, extracted with 1 M aqueous $KHSO_4$, washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the crude product by column chromatography (CH_2Cl_2/MeOH 15:1) yielded pure Z-Arg(Pmc)-His(Trt)-Leu-NH_2 (203 mg, 90%) as colorless solid. $[\alpha]^{20}_D$ - 2.8 (*c* 1.00, MeOH); mp: 128.5 – 129.8 °C; IR: ν 3320 (m), 2960 (m), 1647 (s), 1532 (s), 1444 (s), 1418 (s), 1260 (s), 1102 (s), 1019 (s), 746 (s), 700 (s); ^{1}H NMR (500 MHz, CD_3OD): δ 7.36-7.23 (m, 15 H), 7.13-7.06 (m, 6H), 6.80 (s, 1H), 5.05 (d, ^2J (H,H) = 12.5 Hz, 1H), 4.91 (d, ^2J (H,H) = 12.5 Hz, 1H), 4.54 (dd, ^3J (H,H) = 7.6 Hz, ^3J (H,H) = 5.2 Hz, 1H), 4.32 (t, ^3J (H,H) = 7.3 Hz, 1H), 4.01 (dd, ^3J (H,H) = 7.7 Hz, ^3J (H,H) = 5.2 Hz, 1H), 3.16-3.06 (m, 2H), 3.02 (dd, ^2J (H,H) = 15.1 Hz, ^3J (H,H) = 5.2 Hz, 1H), 2.92 (dd, ^2J (H,H) = 15.1 Hz, ^3J (H,H) = 7.6 Hz, 1H), 2.61 (t, 2H, ^3J (H,H) = 6.9 Hz), 2.54 (s, 3H), 2.52 (s, 3H), 2.06 (s, 3H), 1.78 (t, 2H, ^3J (H,H) = 6.9 Hz), 1.75-1.45 (m, 7H), 1.27 (s, 6H), 0.88 (d, ^3J (H,H) = 5.8 Hz, 3H), 0.81 (d, ^3J (H,H) = 5.1 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 177.5 (s), 175.7 (s), 173.3 (s), 158.6 (s), 158.0 (s), 154.7 (s), 143.6 (s), 139.6 (d), 137.9 (s), 137.7 (s), 136.5 (s), 136.1 (s), 134.8 (s), 130.9 (d), 129.3 (d), 129.2 (d), 124.9 (s), 121.1 (d), 119.3 (s), 76.8 (s), 74.8 (s), 56.4 (d), 55.2 (d), 54.8 (d), 41.8 (t), 41.4 (t), 33.8 (t), 30.6 (t), 30.2 (t), 27.0 (q), 25.8 (d), 23.7 (q), 22.4 (t), 21.7 (q), 19.0 (q), 17.9 (q), 12.3 (q).; MS (ESI, MeOH/CH_2Cl_2 1/20): *m/z* (%) 1066.5 $[M + H]^+$; Anal. Calcd for $C_{59}H_{71}N_9O_8S$ (2 CH_3OH) (1130.41): C 64.81, H 7.04, N 11.15. Found: C 64.98, H 6.88, N 11.39.

H-Arg(Pmc)-His(Trt)-Leu-NH_2. $Pd(OH)_2$/C (10 mg) was added to a solution of Z-Arg(Pmc)-His(Trt)-Leu-NH_2 (1.58 g, 1.48 mmol) in MeOH (60 ml). The suspension was degassed and set under H_2-atmosphere. After stirring for 2 h, $Pd(OH)_2$/C was filtered off and the crude product was concentrated in vacuo. Purification by column chromatography (CH_2Cl_2/MeOH 10:1) yielded pure H-Arg(Pmc)-His(Trt)-Leu-NH_2 (1.07 g, 78%) as a colorless solid. $[\alpha]^{20}_D$ - 0.9 (*c* 1.00, MeOH); mp: 124 – 125 °C; IR: ν 3313 (m), 2931 (m), 1650 (s), 1545 (s), 1445 (s), 1106 (s), 746 (s), 701 (s); ^{1}H NMR (500 MHz, CD_3OD): δ 7.40-7.29 (m, 10 H), 7.15-7.07 (m, 6H), 6.78 (s, 1H), 4.57 (dd, ^3J (H,H) = 7.6 Hz, ^3J (H,H) = 5.4 Hz, 1H), 4.35 (dd, ^3J (H,H) = 9.5 Hz, ^3J (H,H) = 5.3 Hz, 1H), 3.27 (t, ^3J (H,H) = 6.2 Hz, 1H), 3.12-3.06 (m, 2H), 3.03 (dd, ^2J (H,H) = 14.9 Hz, ^3J (H,H) = 5.4 Hz, 1H), 2.90 (dd, ^3J (H,H) = 14.9 Hz, *J* (H,H) = 7.6 Hz, 1H), 2.63 (t, 2H, ^3J (H,H) = 6.8 Hz), 2.54 (s, 3H), 2.53 (s, 3H), 2.07 (s, 3H), 1.80 (t, 2H, ^3J (H,H) = 6.8 Hz), 1.70-1.37 (m, 7H), 1.28 (s, 6H), 0.91 (d, ^3J (H,H) = 6.3 Hz, 3H), 0.86 (d, ^3J (H,H) = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 177.4 (s), 177.2 (s), 173.3 (s), 154.7 (s), 143.6 (s), 139.6 (d), 137.5 (s), 136.5 (s), 136.1 (s), 134.9 (s),

130.9 (d), 129.3 (d), 129.2 (d), 124.9 (s), 121.3 (d), 119.3 (s), 76.9 (s), 74.8 (s), 55.4 (d), 54.6 (d), 52.9 (d), 42.0 (t), 41.6 (t), 33.8 (t), 33.0 (t), 31.4 (t, 27.0 (q), 25.9 (d), 23.6 (q), 22.4 (t), 21.8 (q), 18.9 (q), 17.9 (q), 12.3 (q); MS (ESI, MeOH/CH_2Cl_2 1/20): *m/z* (%) 932.5 $[M + H]^+$; Anal. Calcd for $C_{51}H_{65}N_9O_6S$ (CH_3OH) (964.23): C 64.77, H 7.21, N 13.07. Found: C 64.35, H 7.13, N 13.20.

Fmoc-His(Trt)-Arg(Pmc)-His(Trt)-Leu-NH_2. *General procedure A:* HBTU (360 mg, 0.949 mmol), Fmoc-His(Trt)-OH (380 mg, 0.614 mmol) and TEA (0.5 mL, 3.35 mmol) were added to a solution of H-Arg(Pmc)-His(Trt)-Leu-NH_2 (520 mg, 0.558 mmol) in CH_2Cl_2 (50 ml) at 0 °C. After stirring for 1 h in the dark at rt, the reaction mixture was diluted with CH_2Cl_2, and washed consecutively with saturated aqueous $NaHCO_3$, brine, 1 M aqueous $KHSO_4$, and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (CH_2Cl_2/MeOH 20:1) to give pure Fmoc-His(Trt)-Arg(Pmc)-His(Trt)-Leu-NH_2 (1.22 g, 73 %) as colorless solid. $[\alpha]^{20}_D$ - 9.1 (*c* 1.00, MeOH); mp: 145 – 146 °C; IR: ν 3315 (m), 2931 (m), 1661 (s), 1544 (s), 1493 (s), 1445 (s), 1107 (s), 743 (s), 700 (s); ^{1}H NMR (500 MHz, CD_3OD): δ 7.74 (d, ^3J (H,H) = 7.3 Hz, 2H), 7.52 (d, ^3J (H,H) = 7.4 Hz, 2H), 7.36-7.15 (m, 24H), 7.07-6.99 (m, 12H), 6.75 (s, 1H), 6.67 (s, 1H), 4.50 (dd, ^3J (H,H) = 8.3 Hz, ^3J (H,H) = 5.1 Hz, 1H), 4.36-4.28 (m, 2H), 4.26-4.13 (m, 3H), 4.04 (t, ^3J (H,H) = 6.9 Hz, 1H), 3.11-2.97 (m, 4H), 2.91-2.78 (m, 2H), 2.56 (t, 2H, ^3J (H,H) = 6.8 Hz), 2.52 (s, 3H), 2.50 (s, 3H), 2.03 (s, 3H), 1.73 (t, 2H, ^3J (H,H) = 6.8 Hz), 1.66-1.39 (m, 7H), 1.22 (s, 6H), 0.84 (d, ^3J (H,H) = 5.8 Hz, 3H), 0.78 (d, ^3J (H,H) = 5.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 177.6 (s), 174.5 (s), 174.1 (s), 173.4 (s), 158.4 (s), 158.0 (s), 154.7 (s), 145.2 (s), 145.1 (s), 143.6 (s), 139.8 (d), 139.7 (d), 137.8 (s), 137.7 (s), 136.5 (s), 136.1 (s), 134.9 (s), 130.9 (d), 130.8 (d), 129.3 (d), 129.2 (d), 128.8 (s), 128.2 (s), 126.3 (d), 124.9 (s), 121.2 (d), 121.0 (d), 120.9 (s), 119.3 (s), 76.9 (s), 76.8 (s), 74.8 (s), 68.2 (t), 57.0 (d), 55.4 (d), 55.0, 54.8 (d), 53.2, 48.3 (d), 41.7 (t), 41.4 (t), 33.8 (t), 30.8 (t), 29.9 (t), 27.0 (q), 25.8 (d), 23.7 (q), 22.4 (t), 21.7 (q), 19.0 (q), 18.0 (q), 12.4 (q); MS (ESI, MeOH/CH_2Cl_2 1/20): *m/z* (%) 1534.7 (100) $[M + H]^+$, 1556.4 (8) $[M + Na]^+$; Anal. Calcd for $C_{59}H_{71}N_9O_8S$ (2 CH_3OH) (1597.96): C 69.90, H 6.67, N 10.52. Found: C 69.78, H 6.45, N 10.73.

H-His(Trt)-Arg(Pmc)-His(Trt)-Leu-NH_2. *General procedure B*: A solution of Fmoc-His(Trt)-Arg(Pmc)-His(Trt)-Leu-NH_2 (200 mg, 0.13 mmol) in 4 ml DMF containing 5 % piperidine was stirred for 15 min at rt. Concentration in vacuo and purification of the crude product by column chromatography (CH_2Cl_2/MeOH 25:1, then 8:1) yielded pure H-His(Trt)-Arg(Pmc)-His(Trt)-Leu-NH_2 (164 mg, 96 %) as colorless powder. $[\alpha]^{20}_D$ - 4.2 (*c* 1.00, MeOH); mp: 148 - 149 °C; IR: ν 3315 (m), 2927 (m), 1652 (s), 1544 (s), 1445 (s), 1108 (s), 746 (s), 700 (s); ^{1}H NMR (500 MHz, CD_3OD): δ 7.38 (s, 1H), 7.37 (s, 1H), 7.35-7.25 (m, 18H), 7.14-7.02 (m, 12H), 6.75 (s, 1H), 6.65 (s, 1H), 4.50 (dd, ^3J (H,H) = 8.4 Hz, ^3J (H,H) = 5.1 Hz, 1H), 4.32 (m, 1H), 4.17 (dd, ^3J (H,H) = 7.7 Hz, ^3J (H,H) = 5.5 Hz, 1H), 3.58 (t, ^3J (H,H) = 6.5 Hz, 1H), 3.14-2.96 (m, 3H), 2.89 (dd, ^2J (H,H) = 14.5 Hz, ^3J (H,H) = 6.5 Hz, 1H), 2.83 (dd, ^2J (H,H) = 15.1 Hz, ^3J (H,H) = 8.4 Hz, 1H), 2.61 (t, ^3J (H,H) = 6.9 Hz, 2H), 2.53 (s, 3H), 2.52 (s, 3H), 2.06 (s, 3H), 1.78 (t, ^3J (H,H) = 6.9 Hz, 2H), 1.72-1.40 (m, 7H), 1.26 (s, 6H), 0.86 (d, ^3J (H,H) = 6.1 Hz, 3H), 0.80 (d, ^3J (H,H) = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 177.6 (s), 176.9 (s), 174.3 (s), 173.4 (s), 158.0 (s), 154.7 (s), 143.7 (s), 143.6 (s), 140.0 (d), 139.6 (d), 138.0 (d), 137.9 (s), 136.5 (s), 136.1 (s), 134.9 (s), 130.9 (d), 129.4 (d), 129.3 (d), 125.0 (s), 121.4 (d), 120.8 (d), 119.3 (s), 76.9 (s), 76.8 (s), 74.9 (s), 56.0 (d), 55.4 (d), 55.0 (d), 53.1 (d), 41.8 (t), 41.4 (t), 34.3 (t), 33.8 (t), 30.7 (t), 30.1 (t), 27.0 (q), 25.8 (d), 23.7 (q), 22.4 (t), 21.7 (q), 19.0 (q), 17.9 (q), 12.4 (q); MS (ESI, MeOH/CH_2Cl_2 1/20): *m/z*

(%) 1311.5 (100) $[M + H]^+$, 1333.6 (12) $[M + Na]^+$; Anal. Calcd for $C_{76}H_{88}N_{12}O_7S$ (3 CH_3OH) (1407.77): C 67.40, H 7.16, N 11.94. Found: C 67.32, H 6.73, N 12.16.

Fmoc-Leu-His(Trt)-Arg(Pmc)-His(Trt)-Leu-NH_2. Coupling of H-His(Trt)-Arg(Pmc)-His(Trt)-Leu-NH_2 (853 mg, 0.65 mmol) with Fmoc-Leu-OH (276 mg, 0.78 mmol) following the *general procedure A* and purification of the crude product by column chromatography (CH_2Cl_2/MeOH 20:1) yielded HPLC-pure (YMC-Pack SIL, CH_2Cl_2/MeOH 95/5 1 ml/min, t_R = 3.58 min) Fmoc-Leu-His(Trt)-Arg(Pmc)-His(Trt)-Leu-NH_2 (822 mg, 77%) as colorless solid. $[\alpha]^{20}_D$ - 2.0 (*c* 1.00, MeOH); mp: 146 – 147 °C; IR: ν 3316 (m), 2927 (m), 1655 (s), 1531 (s), 1445 (m), 1108 (s), 742 (s), 700 (s); ^{1}H NMR (500 MHz, CD_3OD): δ 7.74 (d, ^3J (H,H) = 7.6 Hz, 1H), 7.71 (d, ^3J (H,H) = 7.6 Hz, 1H), 7.54 (d, ^3J (H,H) = 7.6 Hz, 1H), 7.48 (d, ^3J (H,H) = 7.6 Hz, 1H), 7.38-7.16 (m, 24H), 7.06-6.95 (m, 12H), 6.74 (s, 1H), 6.70 (s, 1H), 4.47 (dd, ^3J (H,H) = 9.7 Hz, ^3J (H,H) = 4.3 Hz, 1H), 4.34-4.24 (m, 2H), 4.05-3.90 (m, 4H), 3.64-3.57 (m, 1H), 3.12-2.88 (m, 6H), 2.53 (s, 3H), 2.51 (m, 2H), 2.49 (s, 3H), 2.00 (s, 3H), 1.74-1.26 (m, 12H), 1.19 (s, 6H), 0.83 (d, ^3J (H,H) = 6.5 Hz, 3H), 0.83 (d, ^3J (H,H) = 6.5 Hz, 3H), 0.80 (d, ^3J (H,H) = 6.0 Hz, 3H), 0.78 (d, ^3J (H,H) = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 177.6 (s), 174.5 (s), 174.1 (s), 173.4 (s), 158.4 (s), 158.0 (s), 154.7 (s), 145.2 (s), 145.1 (s), 143.6 (s), 139.8 (d), 139.7 (d), 137.9 (s), 137.5 (s), 136.5 (s), 136.1 (s), 135.0 (s), 130.8 (d), 130.8 (d), 129.4 (d), 129.3 (d), 128.9 (s), 128.3 (s), 128.2 (s), 126.3 (d), 126.2 (d), 125.0 (s), 121.1 (d), 121.0 (d), 119.3 (s), 76.9 (s), 76.8 (s), 74.8 (s), 68.3 (t), 56.7 (d), 56.4 (d), 55.9 (d), 55.8 (d), 54.8 (s), 53.4 (d), 48.0 (d), 41.5 (t), 41.4 (t), 41.3 (t), 33.7 (t), 30.8 (t), 30.0 (t), 29.3 (t), 27.0 (q), 25.9 (d), 25.8 (d), 23.8 (t), 23.1 (t), 22.7 (t), 22.4 (t), 21.4 (q), 19.1 (q), 18.0 (q), 12.4 (q); MS (ESI, MeOH/CH_2Cl_2 1/20): *m/z* (%) 1647.5 (100) $[M + H]^+$, 1669.4 (34) $[M + Na]^+$; Anal. Calcd for $C_{97}H_{109}N_{13}O_{10}S$ (3 CH_3OH) (1743.17): C 68.90, H 6.99, N 10.45. Found: C 68.61, H 6.62, N 10.50.

H-Leu-His(Trt)-Arg(Pmc)-His(Trt)-Leu-NH_2. Deprotection of Fmoc-Leu-His(Trt)-Arg(Pmc)-His(Trt)-Leu-NH_2 (90 mg, 0.055 mmol) following the *general procedure B* and purification of the crude product by column chromatography (CH_2Cl_2/MeOH 15:1) yielded HPLC-pure (YMC-Pack SIL, CH_2Cl_2(0.1% TEA)/MeOH 85/15 1 ml/min, t_R = 3.36 min) H-Leu-His(Trt)-Arg(Pmc)-His(Trt)-Leu-NH_2 (60 mg, 77%) as colorless solid. $[\alpha]^{20}_D$ - 3.2 (*c* 1.00, MeOH); mp: 143.5 - 144 °C; IR (KBr): ν 3344 (m), 2955 (m), 1648 (s), 1528 (s), 1444 (s), 1125 (s), 747 (s), 700 (s); ^{1}H NMR (500 MHz, CD_3OD): δ 7.37 (s, 1H), 7.36 (s, 1H), 7.35–7.26 (m, 18H), 7.14-7.02 (m, 12H), 6.76 (s, 1H), 6.65 (s, 1H), 4.50 (dd, ^3J (H,H) = 7.3 Hz, ^3J (H,H) = 6.4 Hz, 1H), 4.48 (dd, ^3J (H,H) = 8.2 Hz, ^3J (H,H) = 5.6 Hz, 1H), 4.31 (m, 1H), 4.21 (dd, ^3J (H,H) = 7.9 Hz, ^3J (H,H) = 5.1 Hz, 1H), 3.36 (dd, ^3J (H,H) = 8.7 Hz, ^3J (H,H) = 5.5 Hz, 1H), 3.14-2.96 (m, 4H), 2.91-2.79 (m, 2H), 2.61 (m, 2H), 2.53 (s, 3H), 2.52 (s, 3H), 2.06 (s, 3H), 1.79 (t, ^3J (H,H) = 6.9 Hz, 2H), 1.76-1.28 (m, 10H), 1.27 (s, 6H), 0.86 (d, ^3J (H,H) = 6.8 Hz, 6H), 0.85 (d, ^3J (H,H) = 6.9 Hz, 3H), 0.79 (d, ^3J (H,H) = 5.7 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 177.6 (s), 174.1 (s), 173.9 (s), 173.4 (s), 158.0 (s), 154.7 (s), 143.6 (s), 139.8 (d), 139.7 (d), 137.9 (s), 137.5 (s), 136.5 (s), 136.1 (s), 134.9 (s), 130.9 (d), 130.8 (d), 129.4 (d), 129.3 (d), 124.9 (s), 121.4 (d), 120.8 (d), 119.3 (s), 76.9 (s), 76.8 (s), 74.8 (s), 55.4 (d), 55.2 (d), 54.8 (d), 54.3 (d), 53.1 (d), 44.9 (t), 41.7 (t), 41.4 (t), 41.3 (t), 33.8 (t), 31.4 (t), 30.8 (t), 30.0 (t), 27.0 (q), 26.4, 25.8 (d), 25.7 (d), 23.7 (q), 23.6 (q), 22.4 (q), 22.3 (t), 21.7 (q), 19.0 (q), 17.9 (q), 12.3 (q); MS (ESI, MeOH/CH_2Cl_2 1/50), *m/z* (%): 1425.0 (100) $[M + H]^+$, 1447.2 (12) $[M + Na]^+$; Anal. Calcd for $C_{82}H_{97}N_{13}O_8S$ (2 CH_3OH) (1488.88): C 67.76, H 7.11, N 12.23. Found: C 67.42, H 6.93, N 12.46.

$1^3,2^3,3^2,4^3,5^2,6^3,7^2,8^3$-octakis(*Gla*-OH)-*p*-octiphenyl. This compound was prepared in 9 steps following previously reported procedures.[S1]

$1^3,2^3,3^2,4^3,5^2,6^3,7^2,8^3$-Octakis(*Gla*-Leu-His(Trt)-Arg(Pmc)-His(Trt)-Leu-NH_2)-*p*-octiphenyl. A solution of $1^3,2^3,3^2,4^3,5^2,6^3,7^2,8^3$-octakis(*Gla*-OH)-*p*-octiphenyl (7.6 mg, 6.1 μmol) in dried DMF (0.8 ml), with HATU (25.8 mg, 67.9 μmol), and dried TEA (40.8 μl, 0.29 mmol) was stirred for 30 min at rt then H-Leu-His(Trt)-Arg(Pmc)-His(Trt)-Leu-NH_2 (83 mg, 58.2 μmol), was added. After stirring for 4 h at rt, the reaction mixture was concentrated *in vacuo*. Purification of the crude product by Sephadex LH-20 column (MeOH) yielded pure compound (7.5 mg, 10%) as a colorless solid. HPLC (YMC-Pack CN, 50 x 4 mm, CH_2Cl_2/(MeOH + 1% Et_3N) 97:3, 1 ml/min, t_R = 1.04 min); ^{1}H NMR (300 MHz, CD_3OD): δ 7.51-7.36 (m, 16H), 7.91 -7.35 (m, 270 H), 6.87 (m, 2H), 6.81-6.59 (m, 16H), 4.61 (s, 16H, overlapping with water), 4.52-3.87 (several m, 40H), 3.21-2.77 (m, 48 H), 2.63-2.37 (m, 64 H), 2.09-1.93 (m, 24 H), 1.83-1.34 (m, 96 H), 1.33-1.05 (m, 48 H), 0.92 - 0.49 (m, 96H); MS (ESI, CH_2Cl_2 / MeOH / CH_3CN / H_2O / acetic acid 13.2 / 26.4 / 44.4 / 14.4 / 1.2): *m/z* (%) 1385 (36) $[M+9H]^{9+}$, 1558 (54) $[M+8H]^{8+}$, 1781 (100) $[M+7H]^{7+}$, 2077 (50) $[M+6H]^{6+}$.

$1^3,2^3,3^2,4^3,5^2,6^3,7^2,8^3$-Octakis(*Gla*-Leu-His-Arg-His-Leu-NH_2)-*p*-octiphenyl (2). $1^3,2^3,3^2,4^3,5^2,6^3,7^2,8^3$-Octakis(*Gla*-Leu-His(Trt)-Arg(Pmc)-His(Trt)-Leu-NH_2)-*p*-octiphenyl (7.3 mg, 0.6 μmol) was dissolved in TFA (1ml). After stirring for 1h at rt, the reaction mixture was concentrated. Nonpolar impurities were removed by solid-liquid extraction (3 times with hexane). Purification of the product by RP HPLC (YMC-Pack ODS-A, 250 x 10 mm, H_2O/(MeOH + 1% TFA) 2:8, 2 ml/min, t_R = 5.13 min) yielded pure compound **2** (3.8 mg, quant) as a colorless solid. ^{1}H NMR (300 MHz, CD_3OD): δ 9.00-8.20 (several m, 64H), 4.70 (s, 16H, overlapping with water), 4.45-3.95 (several m, 40H), 3.22-2.95 (m, 48H), 1.87-1.10 (m, 80H), 0.98 - 0.47 (m, 96H).

$1^3,2^3,3^2,4^3,5^2,6^3,7^2,8^3$-Octakis(*Gla*-Leu-His-Leu-His-Leu-NH_2)-*p*-octiphenyl (2a). This compound was prepared in overall 19 steps following previously reported procedures.[S1]

$1^3,2^3,3^2,4^3,5^2,6^3,7^2,8^3$-Octakis(*Gla*-Leu-Arg-Leu-His-Leu-NH_2)-*p*-octiphenyl (2b). This compound was prepared in overall 19 steps following previously reported procedures.[S2]

Methyl 1-pyrene butyrate (5). To a solution of 1-pyrene butyric acid (100 mg, 347 μmol) in MeOH (10 ml) and toluene (2 ml), concentrated sulfuric acid (catalytic amount) was added and the reaction mixture was stirred at rt overnight. Solvents were removed *in vacuo*. The remaining oil was dissolved in ethyl acetate and washed with a saturated aqueous solution of $NaHCO_3$ and brine. Purification by column chromatography (CH_2Cl_2/petroleum ether 2/1) yielded pure **5** (83 mg, 79%) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (d, ^3J (H,H) = 9.2 Hz, 1H), 8.25-8.12 (m, 4H), 8.09-7.99 (m, 3H), 7.90 (d, ^3J (H,H) = 7.9 Hz, 1H), 3.74 (s, 3H), 3.44 (t, ^3J (H,H) = 7.5 Hz, 2H), 2.52 (t, ^3J (H,H) = 7.5 Hz, 2H), 2.25 (quintet, ^3J (H,H) = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2 (s), 135.2 (s), 130.8 (s), 130.3 (s), 129.3 (s), 128.1 (s), 126.9 (d), 126.8 (d), 126.8 (d), 126.1 (d), 125.4 (d), 124.4 (s), 124.4 (d), 124.3 (d), 124.2 (d), 122.8 (d), 51.0 (q), 33.0 (t), 32.1 (t), 26.2 (t); MS (APCI, DMSO/CH_2Cl_2 1:50): *m/z* 302.3 $[M^+]$.

Calix[4]arene 3a. This compound was prepared following previously reported procedures.[S3]

1-Pyrene butylsulfate, sodium salt (3b). Chlorosulfonic acid (170 µl, 2.5 mmol) was added slowly to ether (5 ml) at 0 °C. After addition was complete, a solution of 1-pyrene butanol (685 mg, 2.5 mmol) in ether (8 ml) was added to the acid-ether complex at 0 °C over 10 minutes with stirring. The mixture was stirred for an additional 30 minutes while purging with nitrogen to remove HCl formed. The mixture was then poured on to a mixture of 50% NaOH (1M) and ice (10 g), diluted with 10 ml isopropanol and 5 ml water and washed with 2 x 20 ml hexane. The alcohol-water layer was evaporated and the residue was chromatographed over ODS column using methanol as mobile phase. After drying in vacuum at 40 °C, the product **3b** was obtained as colorless powder (940 mg, 95% yield). ^{1}H NMR (400MHz, CD_3OD): δ 8.38 (d, ^{3}J(H,H)= 9.3 Hz, 1H), 8.19-8.14 (m, 4H), 8.06-8.02 (m, 2H), 8.01 (t, ^{3}J(H,H)= 7.6 Hz, 1H), 7.94 (d, ^{3}J(H,H)= 7.8 Hz, 1H), 4.13 (t, ^{3}J(H,H)= 6.3Hz, 2H), 3.43 (t, ^{3}J(H,H)= 7.6Hz, 2H), 2.00 (m, 2H), 1.89 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 136.7 (s), 131,0 (s), 129.8 (s), 128.2(s), 127.2 (d), 127.1 (d), 127.0 (d), 127.9 (d), 126.1 (d), 125.5 (d), 124.5 (d), 124.4(s), 124.4 (d), 124.3 (d), 123.2 (d), 67.4 (t), 32.5 (t), 29.0 (t), 27.9 (t); MS (ESI, MeOH): *m/z* (%) 353.3 (100) $[M - Na^+]^-$.

Fullerene 3d. This compound was prepared from C_{60} in overall 2 steps following previously reported procedures.[S4]

EYPC-LUVs⊃CF. Stock solutions of large unilamellar vesicles composed of egg yolk phosphatidylcholine loaded with CF were prepared by freeze-thaw-extrusion following the previously described method[S5] without change. Final conditions: ~5 mM EYPC; inside: 10 mM HEPES, 50 mM CF, 10mM NaCl, pH 7.4; outside: 10 mM HEPES, 107 mM NaCl, pH = 7.0.

Ligand-gating (Figures 2A, 2C•, S1; Table 1, S1). The following stock solutions were prepared and their pH was adjusted[S6] if necessary: 25,26,27,28-Tetra(hydroxycarbonyl methoxy)-*p-tert*-butyl calix[4]arene (**3a**, in 10 mM HEPES, 107 mM NaCl, pH = 7.0), 1-pyrenebutylsulfate (**3b**, in 10 mM HEPES, 107 mM NaCl, pH = 7.0), 1-pyrenebutyrate (**3c**, in DMSO), fullerene **3d** (in DMSO) and freshly purified (RP HPLC) *p*-octiphenyls **2**, **2a**, and **2b** (all in MeOH, concentrations confirmed by UV-vis spectroscopy[S7]).

*Calix[4]arene (**3a**, Fig. 2C, general procedure C):* EYPC-LUVs⊃CF (100 µl) were added to gently stirred, thermostated buffer (1.90 ml, 10 mM HEPES, 107 mM NaCl, pH = 7.0) in a fluorescence cuvette. Fluorescence emission intensity F_t (λ_{em} = 517 nm, λ_{ex} = 492 nm) was monitored as a function of time (*t*) during addition of calix[4]arene (**3a**, 20 µl of 0 - 1 mM, final concentration 0 - 10 µM), **2** (20 µl of 50 µM MeOH, final concentration 500 nM), and 40 µl 1.2% aq triton X-100. Fluorescence time courses were normalized to fractional emission intensity I^n using equation [S1]

$$I^n = (F_t - F_0) / (F_\infty - F_0) \qquad [S1],$$

where $F_0 = F_t$ at pore addition, $F_\infty = F_t$ at saturation after lysis. Obtained I^n was further converted into fractional pore activity *I* using equation [S2]

$$I = I^n / I^n_{MAX} \qquad [S2],$$

where I^n_{MAX} is I^n at saturation obtained under the conditions giving the highest activity. Fractional pore activities I were determined at 400 sec as a function of ligand concentration and fitted to the Hill equation [S3]

$$I = I_\infty + (I_0 - I_\infty) / \{1 + C_{ligand} / EC_{50})^n\} \qquad [S3],$$

where I_0 is I without ligand, I_∞ is I with excess ligand and n is the Hill coefficient, to give the effective concentration EC_{50}. Please note that addition of ligand **3a** *before* pore **2** included the intrinsic control experiment concerning inactivity of **3a** without **2**, which was found to be the case under experimental conditions.

*1-Pyrenebutylsulfate (**3b**):* Following the *general procedure C*, I_t was recorded during the addition of **3b** (final concentration, 0 – 10 μM, inactive without **2**) and rod **2** (0.5 μM). *1-Pyrenebutyrate (**3c**):* Measurements were done following the *general procedure C*. Rod **2** (0.1 μM) was added before the ligand **3c** (0 – 400 μM, inactive without **2**, see below and Fig. 2Bc). *Fullerene **3d**:* Following the *general procedure C*, using **3d** (0 – 100 nM, inactive without **2**) and **2** (0.1 μM). Dose response curves for **3a**-**d** are shown in Fig. S1, fit parameters in Tab. S1.

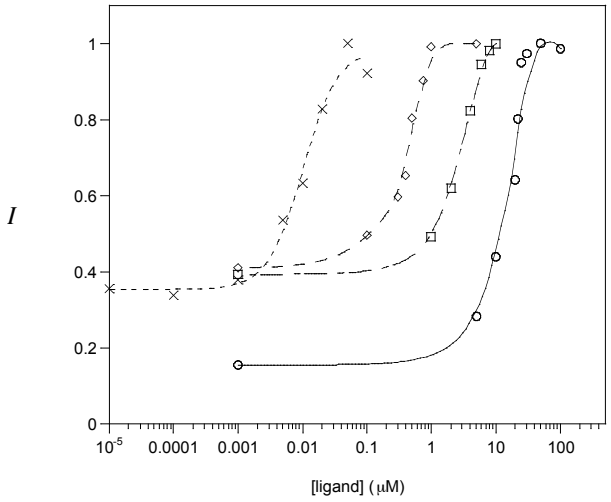

Figure S1. Fractional pore activity I as a function of concentration of calix[4]arene **3a** (◊), pyrenebutylsulfate **3b** (□), pyrenebutyrate **3c** (○) and fullerene **3d** (×).

Table S1. Fit parameters for the Hill equation [S3] for ligand gating in Fig. S1.

Parameters	$PySO_4$ (**3b**)	calix[4]arene (**3a**)	$PyCOO^-$ (**3c**)	C_{60} (**3d**)
I_0	0.40 ± 0.01	0.45 ± 0.03	0.19 ± 0.07	0.35 ± 0.03
I_∞	1.07 ± 0.03	1.01 ± 0.04	1.04 ± 0.01	0.99 ± 0.05
EC_{50} (μM)	2.9 ± 0.2	0.44 ± 0.04	15 ± 2	0.010 ± 0.002
n	1.8 ± 0.2	3.1 ± 0.7	2.5 ± 0.8	1.6 ± 0.5

Control Experiments with 2a and 2b. *Octiphenyl-LHLHL rod (**2a**, Fig. 2Bc and d):* Following the *general procedure C,* 1-pyrene butyrate (**3c**, 0 or 50 μM) and **2a** (1 μM) were subsequently added (Please note that addition of ligand **3c** *before* pore **2a** included the intrinsic control experiment concerning inactivity of **3c** without **2(a)**, see Fig. 2Bc, 180-200 s). *Octiphenyl-LRLHL rod (**2b**, Fig. S2):* Following the *general procedure C,* 1-pyrene butyrate (**3c**, 0 or 200 μM) and **2b** (0.5 μM) were subsequently added. Measurements and analyses were as described in the *general procedure C*.

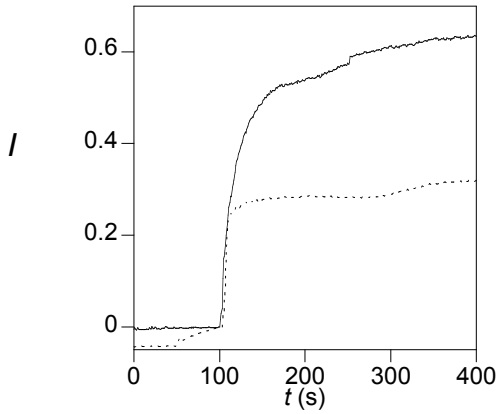

Figure S2. Fractional change in CF emission I^n as a function of time *t* during the addition of ligand **3c** (dotted line: 200 μM, solid line: 0 μM, 50 s) and rod **2b** (0.5 μM, at 100 s). Negligible activity of **3c** without **2(b)** could be observed at the high concentration of 200 μM **3c** (50-100 s dotted line), obviously irrelevant for blockage (not observed up to at least 50 μM **3c**, Fig. 2Bc, 180-200 s).

Pore Blockage (Fig. 2D•, 3S, Table 1, S2). Stock solutions of poly-L-glutamate and heparin were prepared in buffer (10 mM HEPES, 107 mM NaCl, pH = 7.0) and the pH was adjusted. Blocker stock solutions (20 μl) with different concentrations were added to 2 ml gently stirred EYPC-LUVs ⊃ CF suspension (pH 7.0) in a thermostated fluorescence cuvette prepared as described in above *general procedure C*. Then, ligand (**3a - c**) and finally rod **2** were added. Concentrations of the blocker ($C_{blocker}$), ligand (C_{ligand}) and rod (C_{rod}) are summarized in the Table S2 below. Fractional pore activity *I* was determined as a function of blocker concentration as described in above *general procedure C*. IC_{50} was determined by curve fitting of the obtained dose response curve to the Hill equation [S3']

$$I = I_\infty + (I_0 - I_\infty) / \{1 + (C_{blocker} / IC_{50})^n\} \qquad [S3'],$$

where I_0 is *I* without blocker, and I_∞ is *I* with excess blocker and *n* is Hill coefficient. Dose response curves for poly-L-glutamate (A) and heparin (B) are shown in Fig. S3, fit parameters in Tab. S3.

Table S2. Concentration of each component used for blockage experiments in Fig. S3.

Blocker	$C_{blocker}$	ligand	C_{ligand} (μM)	C_{rod} (μM)
PE	1 nM – 10 μM	**3a**	1	0.5
	1 nM – 10 μM	**3b**	6	0.5
	10 nM – 10 μM	**3c**	50	0.25
heparin	5.5 nM – 55 μM	**3a**	1	0.5
	5.5 nM – 55 μM	**3b**	6	0.5
	0.5 nM – 55 μM	**3c**	50	0.25

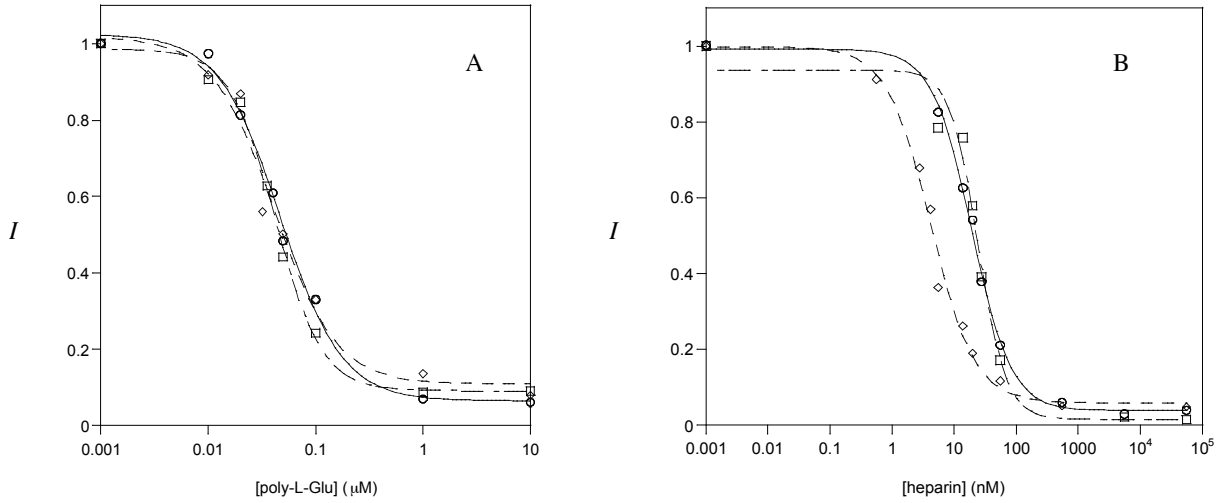

Figure S3. Fractional pore activity *I* as a function of concentration of PE (A), and heparin (B) in the presence of calix[4]arene **3a** (□), pyrenebutylsulfate **3b** (○) and pyrenebutyrate **3c** (◊).

Table S3. Fit parameters for the Hill equation [S3] for blockage experiments in Fig. S3.

Blocker	Ligand	I_0	I_∞	IC_{50} (nM)	n
heparin	**3a**	0.94 ± 0.06	0.02 ± 0.05	24.6 ± 3.3	1.9 ± 0.5
	3b	0.99 ± 0.02	0.04 ± 0.01	19.0 ± 1.2	1.4 ± 0.1
	3c	1.00 ± 0.04	0.06 ±0.03	4.2 ± 0.5	1.2 ± 0.2
PE	**3a**	0.99 ± 0.02	0.09 ± 0.02	42.2 ± 2.2	2.0 ± 0.2
	3b	1.02 ± 0.03	0.07 ± 0.02	47.0 ± 4.0	1.5 ± 0.2
	3c	1.02 ± 0.06	0.11 ± 0.05	41.0 ± 7.1	1.5 ± 0.4

Blockage during CF leakage (Fig. 2Bf). To a suspension of EYPC-LUVs⊃CF in buffer, prepared as in the *general procedure C*, 1-pyrenebutylsulfate (**3b**, 6 μM), rod (**2**, 0.5 μM), and PE (1 μM) were successively added. Measurement and analysis were as described in the *general procedure C*.

Intervesicular Transfer (Fig. 2Be). To a suspension of EYPC-LUVs⊃CF in buffer (250 μM), prepared as in the *general procedure C*, rod (**2**, 0.1 μM), 1-pyrenebutyrate (**3c**, 50 μM), and then EYPC-LUVs⊃CF (250 μM) were successively added. Measurement and analysis were as described in the *general procedure C*. Note that the activity was normalized relative to the fluorescence intensity after lysis. Without normalization, curves 2Bb and 2Be were superimposable before the addition of extra EYPC-LUVs⊃CF.

Fluorescence Resonance Energy Transfer Experiments (Fig. 2Cx, Dx). Stock solutions of large unilamellar vesicles composed of BODIPY-PC and EYPC were prepared by the extrusion method. Namely, solutions of EYPC (10 mg) and BODIPY-PC (20 μg) in $CHCl_3$/MeOH 1:1 were dried in vacuo (>2 h) to form thin films. The resulting films were hydrated with buffer [1 ml, 10 mM HEPES, 107 mM NaCl, pH 7.0] for > 30 min, freeze-thawed (5 times), extruded through a polycarbonate membrane (100 nm, >15 times). The obtained LUVs were used without further purification. The vesicle suspensions (42 μl) were diluted with 1.9 mL of HEPES buffer (pH 7.0), and excitation (λ_{em} = 530 nm, □) and emission spectra were recorded (λ_{ex} = 470 nm, ◊, λ_{ex} = 320 nm, ×, Fig. S4). Then, rod **2** was added (0.5 μM) and excitation (λ_{em} = 380 nm, ○) and emission spectra were recorded (λ_{ex} = 320 nm, +, Fig. S4). Subsequently, calix[4]arene **3a** was added in steps of 8 μl of 0.05 mM stock solution (final concentrations: 0.2 μM – 1 μM) and the emission spectra were recorded after each addition. Then, polyglutamate pE was added stepwise in an identical manner (4 μl of 10 μM stock solution, final concentrations: 0.02 μM – 1 μM), and the emission spectra were recorded again. The obtained spectra were normalized relative to the fluorescence emission intensity at 380 nm (Fig. 5S, summarized in Fig. 2Cx and 2D).

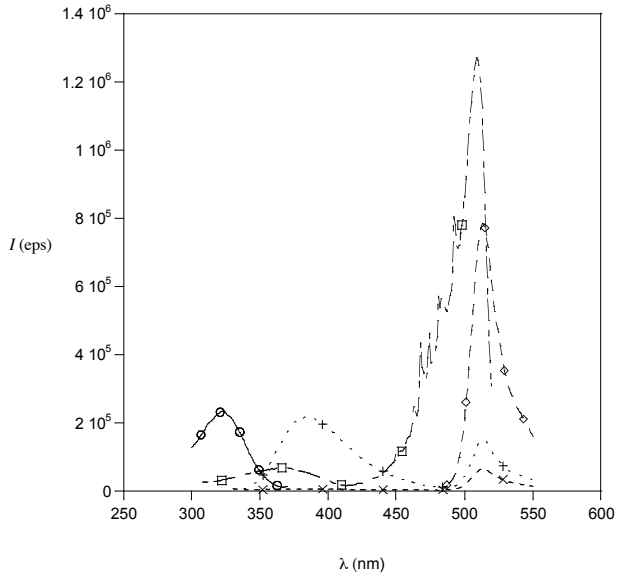

Figure S4. Excitation spectra of BODIPY-PC (□, λ_{em} = 530 nm) and rod **2** with BODIPY-PC (○, λ_{em} = 380 nm) and emission spectra of BODIPY-PC at λ_{ex}=470 nm (◊) and at λ_{ex}=320 nm with (+) and without rod **2** (×).

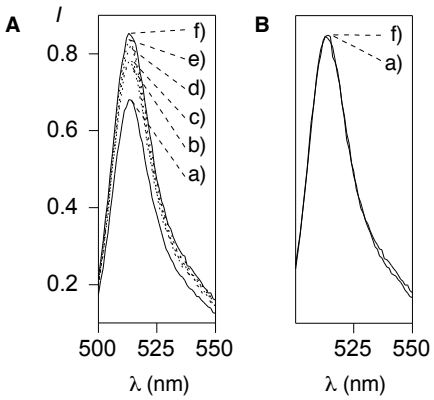

Figure S5. Changes in membrane affinity of **2** in response to ligands **3a** (A) and blocker pE (B). (A) Relative BODIPY emission I (λ_{ex} 320 nm) of EYPC-LUVs (250 μM EYPC) from β-BODIPY® FL C_{12}-HPC (BODIPY-PC, 0.2 mol%; λ_{ex} 506 nm, λ_{em} 513 nm) in presence of **2** (500 nM; λ_{ex} 320 nm, λ_{em} 380 nm) and **3a** (0 (a), 0.2 (b), 0.4 (c), 0.6 (d), 0.8 (e) and 1.0 μM (f)), calibrated to I = 1 at 380 nm (compare summary of data in Fig. 2Cx). (B) Same with EYPC-LUVs (250 μM EYPC, 0.2 mol% BODIPY-PC) **2** (500 nM), ligand **3a** (1 μM) and blocker pE (0 μM (a), 1 μM (f) (compare summary of data in Fig. 2Dx).

Brief Discussion of FRET Experiments. FRET experiments report on the average distance between donor and acceptor. In this case, the donor is the *p*-octiphenyl fluorophore in **2** (λ_{ex} 320 nm, λ_{em} 380 nm) and the acceptor is the BODIPY fluorophore in the middle of the membrane (λ_{ex} 506 nm, λ_{em} 513 nm), and a FRET experiment measures acceptor emission at 513 nm upon donor excitation at 320 nm. FRET experiments with the *p*-octiphenyl/BODIPY pair do not detect short-distance changes involved in rod reorientations (Föster radius R_0 = 36 ± 2 Å).[S7] Above FRET experiments report, therefore, on the concentration of membrane-bound pore. Increase in FRET with increasing concentration of ligand **3a** provides structural support that **3a** indeed promotes the binding of the pore to the membrane as designed (Fig. 5S, A). Unchanged FRET with increasing concentration of blocker pE at constant concentration ligand **3a** provides structural support that blockage by pE does not occur by removal of the pore from the membrane (*i.e.*, competitive blockage by ion exchange at the outer surface) and therefore demonstrates noncompetitive blockage consistent with complex **4** (Fig. 5S, B).

Pig Liver Esterase Assay in EYPC-LUVs⊃CF (Fig. 2E, F). Stock solutions of pig liver esterase (PLE, in 10 mM HEPES buffer, 107 mM NaCl, pH = 7.0) and methyl 1-pyrenebutyrate (**5**, in DMSO) were prepared. Rod **2** (0.1 μM) was added to 2 mL gently stirred EYPC-LUVs⊃CF suspension in a thermostated (37 °C) fluorescence cuvette, prepared as described in above *general procedure C*. Then, substrate **5** (20 µl of 60 mM stock solution, final concentration: 600 µM) and finally enzyme (20 µ1 of stock solutions, final concentration: 0.1 – 33 units/ml) were added (Fig. 2G). The fractional pore activity has been converted into 1-pyrenebutyrate concentration using the dose response curve (Fig. S1○). Initial velocities were estimated by fitting the product formation kinetics to linear function.

Control experiment performed with rod **2** (0.1 μM) and PLE (33 units/ml) but without substrate **5** did not show substantial increase in activity (Fig. S6).

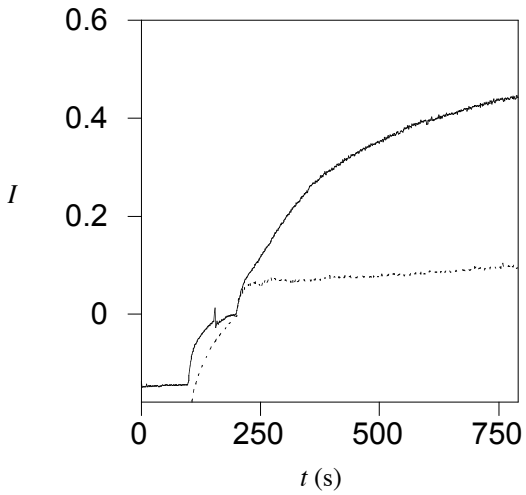

Figure S6. Fractional change in CF emission *I* as a function of time *t* during the addition of rod **2** (0.1 μM), substrate **5** (600 μM, solid line or 0 μM, dotted line) and PLE (33 units / ml).

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