Supplementary Information (SI) for RSC Advances.

Synthetic Cation Channel: Reconstructing the Ion Permeation Pathway of TRPA1 in an Artificial System

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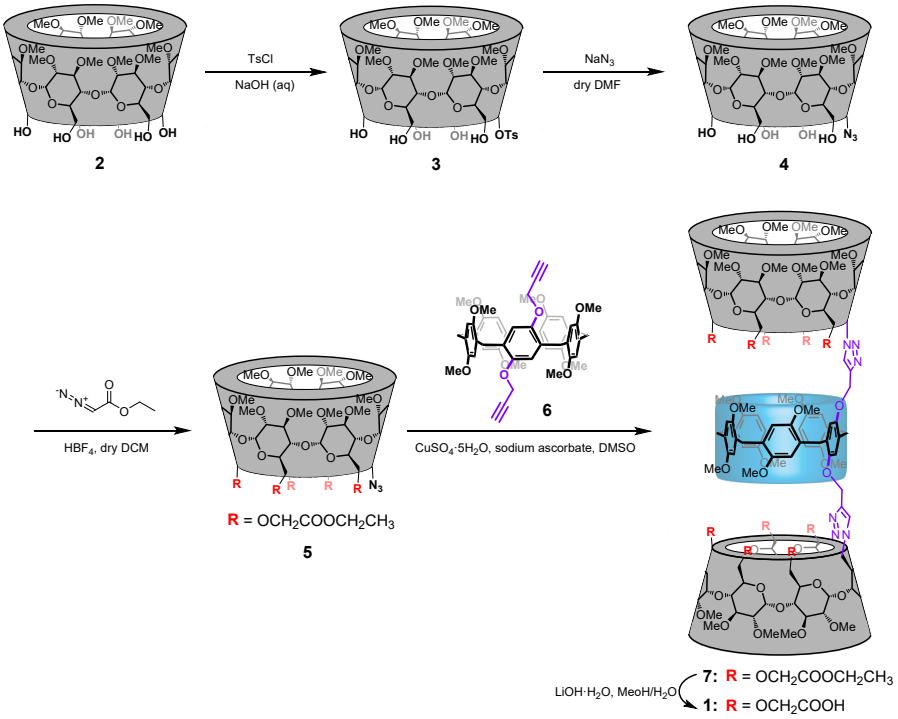
Contents:

1. General:

Egg yolk L-α-phosphatidylcholine (EYPC)was obtained from Sigma-Aldrich as ethanol solution (100 mg/mL). 1,2-diphytanoyl-sn-glycero-3-phosphocholine (diPhyPC) was obtained from Avanti Polar Lipids as chloroform solution (10 mg/mL). The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on commercial instruments (Bruker AVANCE III HD 600 MHz, Bruker AVANCE NEO 400 MHz) at 298 K. Chemical shifts were referenced to solvent residue. Mass spectra were recorded with Bruker Micro TOF II spectrometer and Thermo Fisher LC-HRMS spectrometer. The fluorescent experiments on vesicles were performed on Varian Cary Eclipse fluorescence spectrophotometer. The conductance measurement on planar lipid bilayer was peformed on Warner BC-535D Planar Lipid Bilayer Workstation.

2. Synthetic procedures and characterization data for 1:



Compound 2. Compound **2** was synthesized according to the reported procedure.[1]

2: Yield: 75%.^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (d, J = 3.6 Hz, 6H), 4.10 (d, J = 11.8 Hz, 6H), 3.81 (dd, J = 10.1, 5.3 Hz, 6H), 3.72 (dd, J = 12.1, 5.5 Hz, 6H), 3.64 (s, 18H), 3.53 (dd, J = 9.8, 8.5 Hz, 6H), 3.49 (s, 18H), 3.38 (t, J = 9.1 Hz, 6H), 3.15 (dd, J = 9.8, 3.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 99.2, 82.3, 82.0, 81.9, 73.1, 62.3, 61.8, 58.2. HRMS: calcd for $C_{48}H_{85}O_{30}$ $[M+H]^+$: 1141.5047, found 1141.5348.

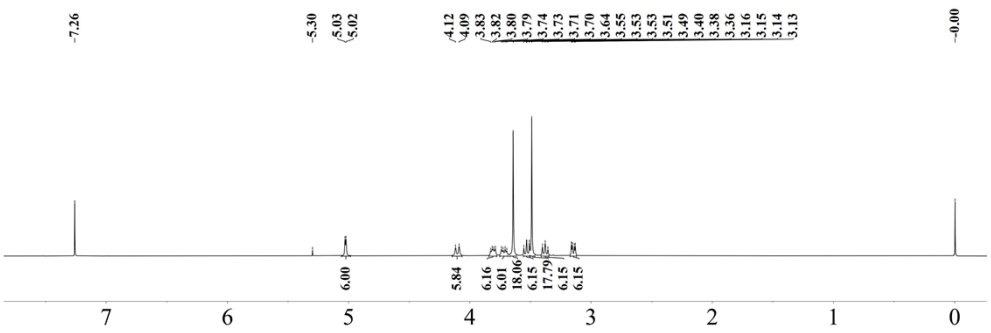


Figure S1. ^{1}H NMR spectrum of **2** in $CDCl_3$.

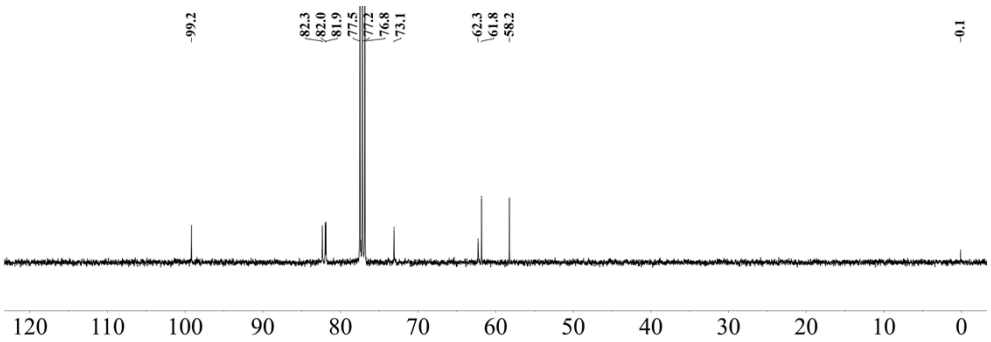


Figure S2. ^{13}C NMR spectrum of **2** in $CDCl_3$.

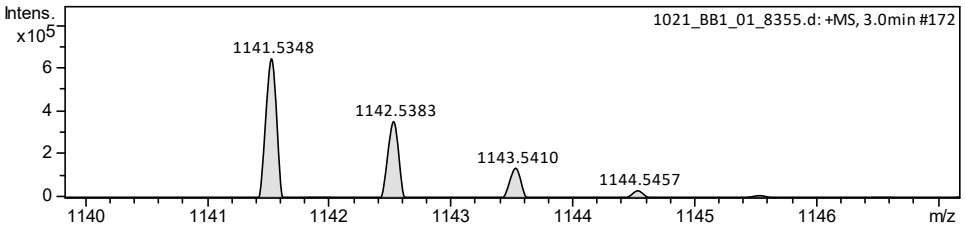


Figure S3. HR-MS of **2**.

Compound 3. Compounds **2** (200 mg, 0.18 mmol) was dissolved in dry pyridine (10 mL), and the reaction mixture was stirred at -5°C. Subsequently, a solution of p-toluenesulfonyl chloride (TsCl, 130mg, 0.65mmol) dissolved in dry pyridine (10 mL) was added dropwise to the reaction mixture over a period of 30 minutes. The reaction mixture was stirred under nitrogen atmosphere at room temperature for 18 hours. Then, the reaction mixture was quenched with water (5 mL), and then concentrated under reduced pressure. The residue was then dissolved in dichloromethane (DCM, 250 mL) and washed with water, dried over anhydrous Na_2SO_4. After removing of the solvent, the obtained crude product was purified by column chromatography on silica gel to yield **3** as a white solid.

3: Yield: 31%.^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.09 (d, *J* = 3.6 Hz, 1H), 5.02 (dd, *J* = 10.0, 3.6 Hz, 3H), 4.96 (d, *J* = 3.6 Hz, 1H), 4.80 (d, *J* = 3.5 Hz, 1H), 4.63 (dd, *J* = 11.1, 4.2 Hz, 1H), 4.39 (dd, *J* = 11.2, 1.8 Hz, 1H), 4.12-3.98 (m, 5H), 3.91 (ddd, *J* = 9.7, 4.3, 1.9 Hz, 1H), 3.85-3.71 (m, 12H), 3.68-3.59 (m, 22H), 3.56-3.50 (m, 6H), 3.49 (s, 3H), 3.47-3.46 (m, 12H), 3.43 (s, 3H), 3.40 (ddd, *J* = 10.4, 8.7, 2.4 Hz, 3H), 3.34 (td, *J* = 9.1, 4.1 Hz, 2H), 3.15-3.10 (m, 4H), 3.05 (dd, *J* = 9.9, 3.4 Hz, 1H), 2.99 (dd, *J* = 9.8, 3.5 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.1, 133.0, 130.0, 128.2, 99.3, 99.2, 99.2, 99.0, 98.9, 82.7,

82.4, 82.3, 82.2, 82.1, 82.0, 81.9, 81.8, 81.7, 81.6, 81.5, 81.4, 81.4, 73.3, 73.1, 73.1, 72.8, 72.3, 70.3, 69.8, 62.7, 62.6, 62.5, 62.4, 62.2, 62.0, 61.8, 61.8, 61.7, 61.7, 59.1, 58.5, 58.4, 58.1, 58.0, 24.2, 21.8, 19.9, 13.8. HRMS: calcd for $C_{55}H_{90}O_{32}S$ $[M+H]^+$: 1295.5136, found 1295.5503.

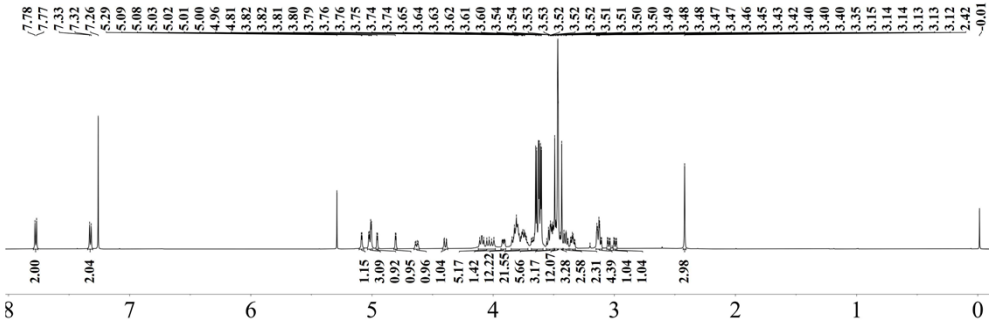


Figure S4. ^1H NMR spectrum of **3** in $CDCl_3$.

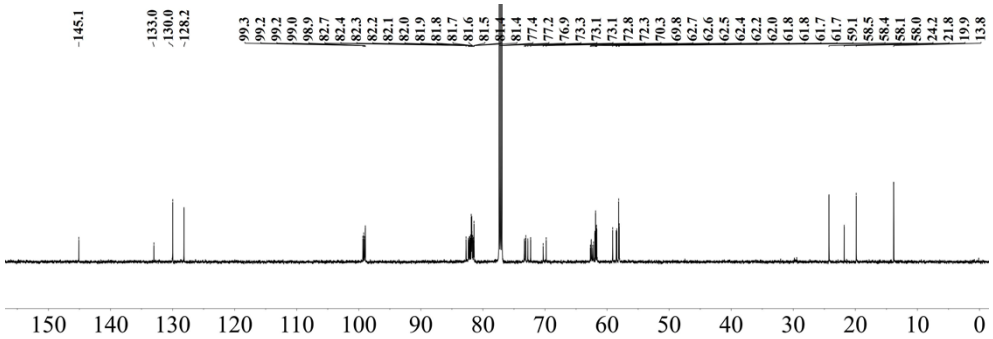


Figure S5. ^{13}C NMR spectrum of **3** in $CDCl_3$.

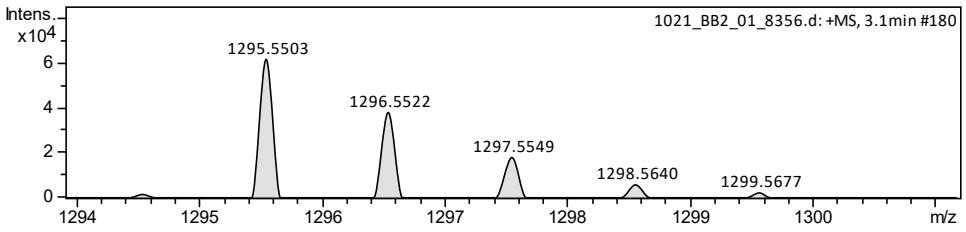


Figure S6. HR-MS of **3**.

Compound 4. Compounds **3** (200 mg, 0.15 mmol) and NaN_3 (100 mg, 1.54 mmol) was dissolved in dry DMF (5 mL). The reaction mixture was stirred under nitrogen atmosphere at 80°C for 18 hours. Then, the reaction mixture was concentrated under reduced pressure. The residue was then dissolved in dichloromethane (DCM, 100 mL) and washed with water, dried over anhydrous Na_2SO_4. After removing of the solvent, the obtained crude product was purified by column chromatography on silica gel to yield **4** as a white solid.

4: Yield: 83%.^1H NMR (600 MHz, $CDCl_3$) δ 5.09 (dd, J = 11.4, 3.6 Hz, 2H), 5.04-4.97 (m, 4H), 4.24 (t, J = 6.3 Hz, 2H), 4.14-4.06 (m, 3H), 4.04-3.96 (m, 2H), 3.88-3.83 (m, 2H), 3.79 (s, 5H), 3.74 (s, 6H), 3.67 (d, J = 12.0 Hz, 6H), 3.64-3.61 (m, 12H), 3.57-3.53 (m, 4H), 3.53-3.50 (m, 9H), 3.48 (dd, J = 4.7, 2.6 Hz, 12H), 3.43 (t, J = 9.1 Hz, 1H), 3.38 (s, 4H), 3.14 (dt, J = 6.3, 3.5 Hz, 6H), 2.49-2.20 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 99.57, 99.40, 99.27, 99.12, 98.98, 98.91, 82.98, 82.73, 82.62, 82.31, 82.11, 81.93, 81.84, 81.77, 81.35, 73.16, 72.71, 71.10, 62.46, 61.99, 61.84,

61.72, 61.61, 58.71, 58.50, 58.19, 58.14, 58.09, 58.05, 53.56, 51.93. HRMS: calcd for $C_{48}H_{83}NaN_3O_{29}$ $[M+Na]^+$: 1188.5004, found: 1188.5295.

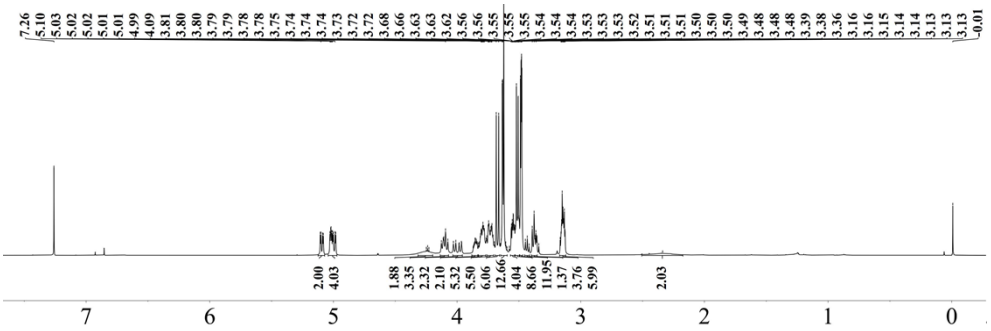


Figure S7. ^{1}H NMR spectrum of **4** in $CDCl_3$.

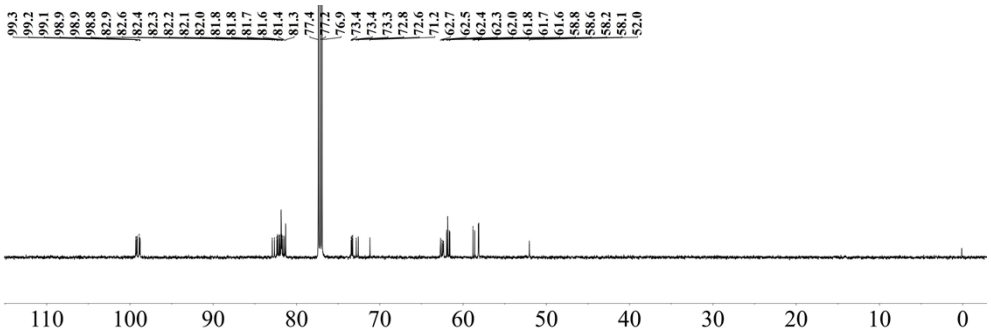


Figure S8. ^{13}C NMR spectrum of **4** in $CDCl_3$.

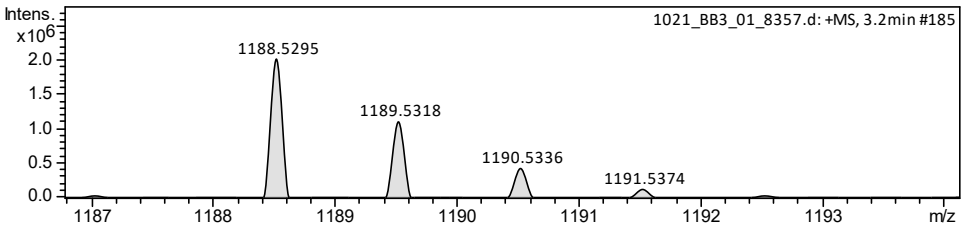


Figure S9. HR-MS of **4**.

Compound 5. Compounds **4** (100 mg, 0.08 mmol) and ethyl diazoacetate (110 mg, 0.92 mmol) were dissolved in dry DCM (3 mL). Subsequently, a solution of HBF_4 (12.3 μmol of HBF_4 dissolved in 0.1 mL of DCM) was added to the reaction mixture over a period of 30 minutes. The reaction mixture was stirred under nitrogen atmosphere at room temperature for 24 hours. Then, 2% aqueous $NaHCO_3$ solution (2 mL) was added to the reaction mixture and stirred for an additional 5 minutes. The reaction mixture was diluted with DCM (10 mL), and the organic layer was collected. After drying the organic layer over anhydrous Na_2SO_4 and removal of the solvent, the crude product obtained was purified by silica gel column chromatography, affording **5** as a white solid.

5: Yield: 55%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.11-5.03 (m, 6H), 4.22-4.09 (m, 20H), 4.04-3.98 (m, 5H), 3.94-3.77 (m, 13H), 3.70-3.60 (m, 25H), 3.53-3.45 (m, 25H), 3.19-3.13 (m, 6H), 1.26-1.24 (t, J = 6.0 Hz, 15H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 170.1, 100.3, 100.1, 99.7, 83.4, 82.6, 82.5, 82.3, 82.1, 82.1, 82.0, 81.3, 81.3, 81.2, 81.1, 77.4, 77.2, 76.9, 71.5, 71.3, 71.2, 71.1, 70.5, 70.3, 68.9, 68.8, 68.7, 62.0, 61.9, 60.8, 60.7, 60.7, 60.7, 58.1, 58.0, 57.9, 14.3. HRMS: calcd for $C_{68}H_{113}NaN_3O_{39}$

[M+Na]$^+$: 1618.6843, found: 1618.6820.

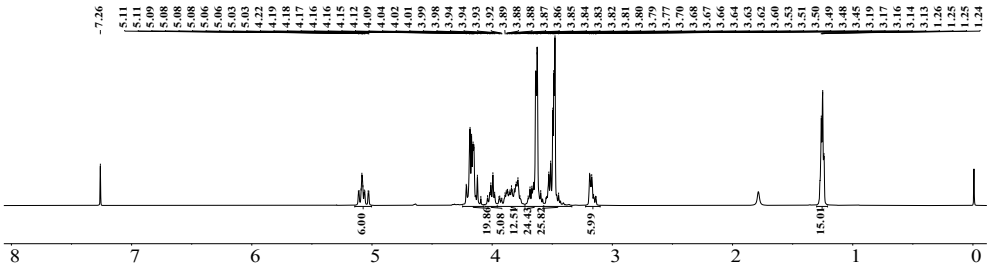


Figure S10. ^{1}H NMR spectrum of **5** in $CDCl_3$.

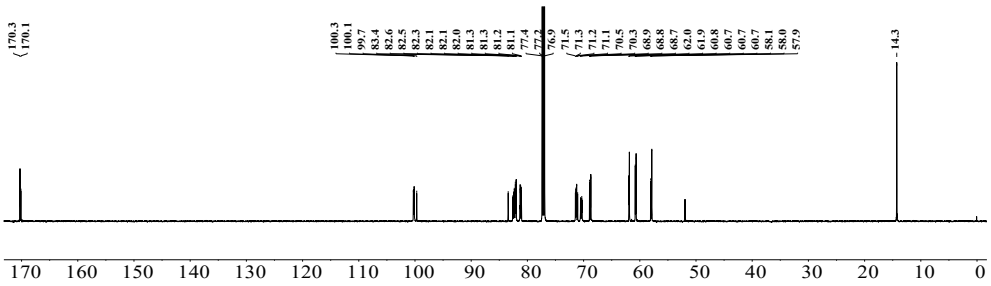


Figure S11. ^{13}C NMR spectrum of **5** in $CDCl_3$.

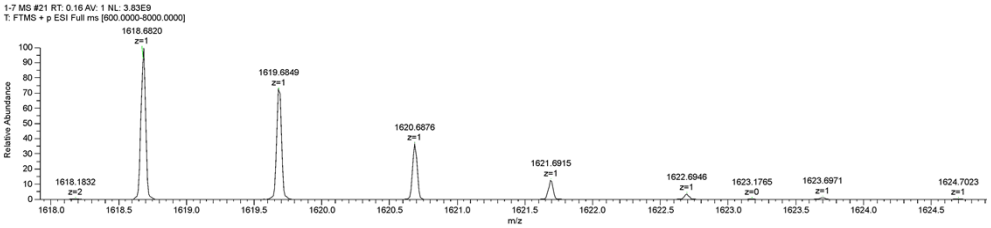


Figure S12. HR-MS of **5**.

Compound 6. Compound **6** was synthesized according to the reported procedure.[2]
7: Yield: 48%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (s, 2H), 6.80 (s, 2H), 6.78 (s, 2H), 6.75 (s, 2H), 6.72 (s, 2H), 4.48 (d, J = 2.4 Hz, 4H), 3.80-3.76 (m, 10H), 3.68 (d, J = 5.9 Hz, 12H), 3.64 (d, J = 1.8 Hz, 12H), 1.99 (t, J = 2.4 Hz, 2H). HRMS: calcd for $C_{49}H_{50}O_{10}Na$ [M+Na]$^+$: 821.3297, found 821.3278.

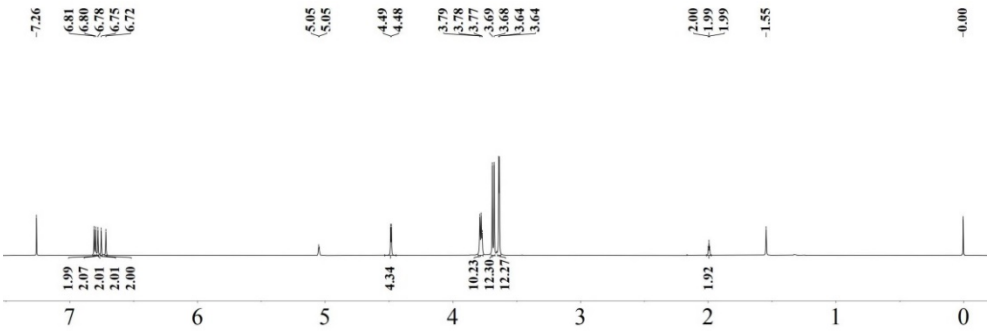


Figure S13. ^{1}H NMR spectrum of **6** in $CDCl_3$.

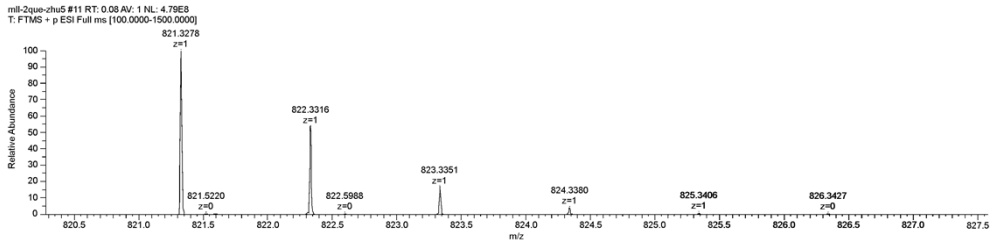


Figure S14. HR-MS of **6**.

Compound 7. To a solution of compound **5** (200 mg, 0.12 mmol) and **6** (40 mg, 0.05 mmol) in DMSO (10 mL) was added sodium ascorbate (99.3 mg, 0.5 mmol). The mixture was stirred for 15 minutes and then $CuSO_4 \cdot 5H_2O$ (62.7 mg, 0.25 mmol) was added. The reaction mixture was stirred at room temperature for 48 h. Then, 10 portions of water was added to the reaction mixture, and the obtained solution was freeze-dried. The crude product was purified by preparative reverse phase HPLC (Agilent 1260) using SBC18 column (21.2 × 250 mm, 7 μm) with A (100% water) and B (100% acetonitrile) as eluent. The linear gradient from 95% A and 5% B to 5% A and 95% B over 60 min was used in the purification process. The compound **7** was obtained as white solid.

7: Yield: 54%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 18.0 Hz, 2H), 7.00 (d, *J* = 18.0 Hz, 2H), 7.01-6.76 (m, 6H), 6.69 (s, 2H), 5.40 (s, 2H), 5.11-5.03 (m, 18H), 4.89-4.73 (m, 3H), 4.20-4.11 (m, 23H), 4.08-3.98 (m, 23H), 3.85 (d, *J* = 6.0 Hz, 12H), 3.79-3.74 (m, 8H), 3.72-3.70 (m, 30H), 3.68-3.63 (m, 38H), 3.62 (s, 8H), 3.57-3.55 (m, 16H), 3.51-3.49 (m, 36H), 3.44 (d, *J* = 12.0 Hz, 16H), 3.25 (s, 2H), 3.20 (s, 6H), 3.15 (d, *J* = 6.0 Hz, 2H), 2.91 (s, 2H), 1.28-1.21 (m, 16H), 1.17-1.12 (m, 6H), 1.10-1.00 (m, 8H), 0.86-0.82 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 150.6, 144.3, 128.5, 128.2, 125.7, 113.6, 100.4, 100.1, 82.3, 82.1, 81.4, 77.4, 77.2, 76.9, 71.4, 70.4, 69.0, 68.8, 62.0, 61.9, 60.8, 60.7, 58.1, 57.9, 55.9, 29.5, 14.3, 14.1, 13.8. HRMS: calcd for $C_{185}H_{276}N_6Na_2O_{88}$ $[M+2Na]^{2+}$: 2018.8578, found: 2018.8538.

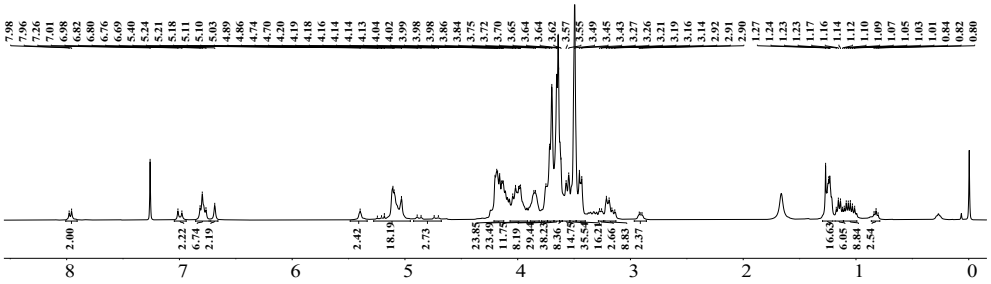


Figure S15. ^{1}H NMR spectrum of **7** in $CDCl_3$.

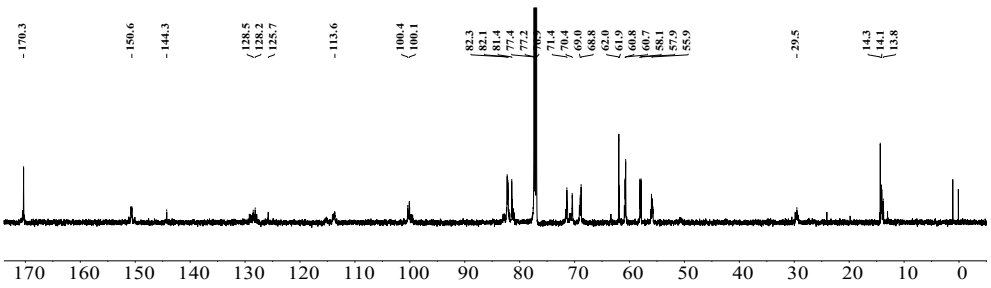


Figure S16. ^{13}C NMR spectrum of **7** in $CDCl_3$.

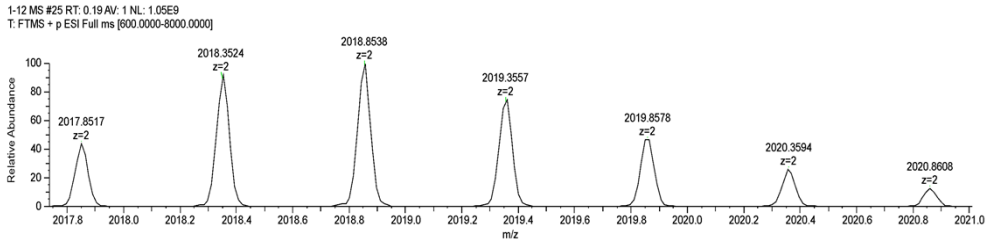


Figure S17. HR-MS of **7**.

Compound 1. To a solution of compound **7** (120 mg, 0.03 mmol) in MeOH/H_2O (3/0.5 mL) was added LiOH•H_2O (72 mg, 3 mmol). The mixture was stirred at room temperature for 24 h and then the MeOH was removed under reduced pressure. The residual solution was diluted with water (10 mL) and then acidified with aqueous HCl solution (1 M). Then, the mixture was centrifuged, and the resulting solid was washed with water. The crude product was purified by preparative reverse phase HPLC (Agilent 1260) using SBC18 column (21.2 × 250 mm, 7 μm) with A (100% water) and B (100% acetonitrile) as eluent. The linear gradient from 95% A and 5% B to 5% A and 95% B over 50 min was used in the purification process. The compound **1** was obtained as white solid.

1: Yield: 68%.^1H NMR (400MHz,DMSO-*d6*) δ 8.11 (s, 2H), 6.98 (s, 2H), 6.79-6.74 (m, 8H), 5.36-5.33 (m, 3H), 5.25-5.21 (m, 2H), 5.09-5.01 (m, 12H), 4.97-4.92 (m, 2H), 4.76-4.65 (m, 3H), 4.13-4.07 (m, 5H), 4.04-3.91 (m, 30H), 3.88-3.78 (m, 19H), 3.74-3.63 (m, 51H), 3.61-3.57 (m, 13H), 3.55-3.46 (m, 58H), 3.39 (s, 10H), 3.29 (d, *J* = 4.0 Hz, 10H), 3.18-3.12 (m, 5H), 3.07-2.98 (m, 11H), 2.75 (d, *J* = 4.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-*d6*) δ 171.7, 171.6, 150.0, 149.9, 149.9, 149.3, 149.3, 142.8, 142.8, 128.3, 127.5, 127.4, 113.2, 113.2, 98.8, 81.5, 81.4, 81.2, 81.1, 81.0, 70.7, 69.9, 68.1, 61.0, 61.0, 57.3, 57.3, 57.2, 55.5, 55.4, 40.1, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9, 28.9. HRMS: calcd for $C_{165}H_{236}N_6Na_2O_{88}$ $[M+2Na]^{2+}$: 1878.7012, found 1878.7119.

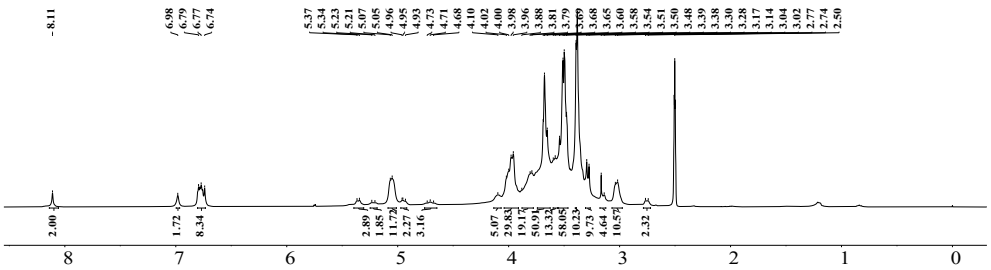


Figure S18. ^{1}H NMR spectrum of **1** in DMSO-*d6*.

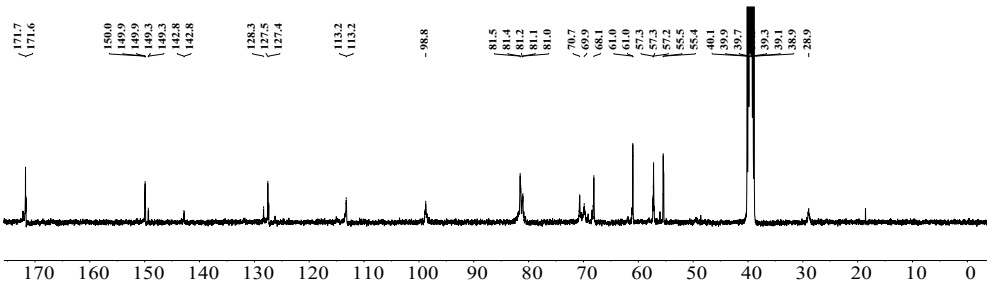


Figure S19. ^{13}C NMR spectrum of **1** in DMSO-*d6*.

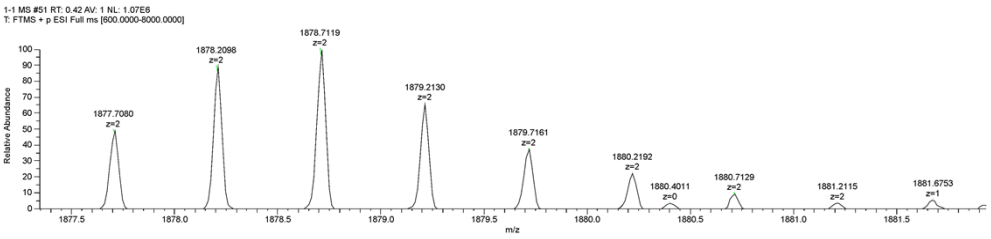


Figure S20. HR-MS of **1**.

3. Computational studies for 1:

The semiempirical tight-binding based quantum chemistry method GFN2-xTB was employed to obtain the reasonable model of molecule **1**.[3] Calculated results indicated that **1**'s optimal structure adopts a tubular conformation (Figure S21). Based on the optimized structure, the length and diameter of **1** were measured using Multiwfn software.[4, 5] Computational results shown that the maximal length and minimum tubular diameter of **1** is 34.81 and 2.03 Å, respectively. The detailed Cartesian coordinates of the optimized structure of molecule **1** are provided in the appendix at the end of the ESI (section 11).

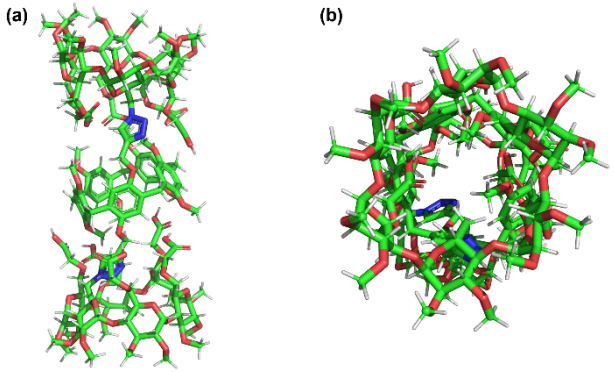


Figure S21. a) Side view and b) top view of the optimized structures of molecule **1**.

4. Ionophoric experiment with HPTS assay:

(a) Preparation of HPTS containing large unilamellar vesicles (LUVs): Egg yolk L-α-phosphatidylcholine (EYPC, 20 mg) was diluted with $CHCl_3$ (5.0 mL), the solution was transferred to a round-bottomed flask and then evaporated under reduced

pressure, and the resulting thin film was dried under high vacuum for 3 h. The lipid film was hydrated with N-2-hydroxyethylpiperazine-N'-2-ethanesulphonic acid (HEPES) buffer solution (2 mL, HEPES (10 mM), NaCl (100 mM), pH = 7) containing 8-hydrox-ypyrene-1,3,6-trisulfonic acid (HPTS, 0.1 mM) at 40 ℃ for 2 h to give a milky suspension (gently vortexing after every 0.5 h to ensure the lipid film complete hydrated under nitrogen protection). The resulting suspension was subjected to ten freeze-thaw cycles by using liquid N_2 to freeze and warm water bath to thaw. The suspension was extruded nine times through polycarbonate membrane (0.2 μm) and then dialyzed with membrane tube (MWCO = 14000) against the same HEPES buffer solution (200 mL, without HPTS) for six times to remove un-entrapped HPTS and produce vesicle suspension ([lipid] = 13.3 mM).

(b) Fluorescent experiments: HEPES buffer solution (2.0 mL, HEPES (10 mM), NaCl (100 mM), pH=6.0) and the prepared vesicle suspension (13.3 mM, 100 uL) were placed in a fluorometric cuvette. To the cuvette, the solution of compound **1** in DMSO (5 μL) was added to reach a required channel concentration (molar ratio relative to lipid, represented by x) with gentle stirring. Fluorescent intensity (I_t) was continuously monitored at 510 nm (excitation at 460 nm) in 6.5 min. Then, Triton aqueous solution (20%, 10 μL) was added with gentle stirring. The intensity was monitored until the fluorescent intensity (I_∞) did not change. The collected data were then normalized into the fractional change in fluorescence given by $(I_t\text{-}I_0)/(I_\infty\text{-}I_0)$, where I_0 is the initial intensity.

5. pH-sensitive ionophoric experiment with HPTS assay:

(a) Preparation of HPTS containing LUVs: The preparation protocol for LUVs follows the steps described in section 3(a).

(b) Fluorescent experiments: The external HEPES buffer solutions were adjusted to pH 4.0, 5.0, 6.0, 8.0, 9.0 or 10.0 by using HCl or KOH. Then, the external HEPES buffer solution (2.0 mL, HEPES (10 mM), NaCl (100 mM)) at the corresponding pH value, along with the prepared vesicle suspension (13.3 mM, 100 uL), was added to the cuvette. To the cuvette, the solution of compound **1** in DMSO (5 μL) was added to reach a required channel concentration (x = 1.6%, molar ratio relative to lipid, represented by x) with gentle stirring. Fluorescent intensity (I_t) was continuously monitored at 510 nm (excitation at 460 nm) in 6.5 min. Then, Triton aqueous solution (20%, 10 μL) was added with gentle stirring. The intensity was monitored until the fluorescent intensity (I_∞) did not change. The collected data were then normalized into the fractional change in fluorescence given by $(I_t\text{-}I_0)/(I_\infty\text{-}I_0)$, where I_0 is the initial intensity.

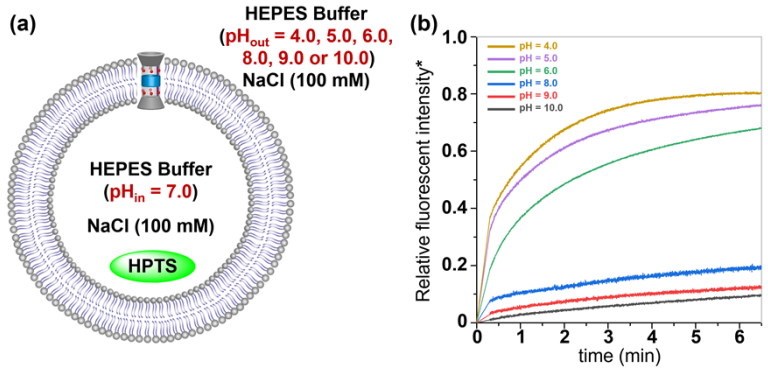


Figure S22. (a) Schematic representation for the HPTS assay across different pH conditions. (b) Changes in the fluorescence intensity of HPTS (λex = 460 nm, λem = 510 nm) in vesicles with time after the addition of **1** (x = 1.6%) at different external pH conditions (*baseline corrected).

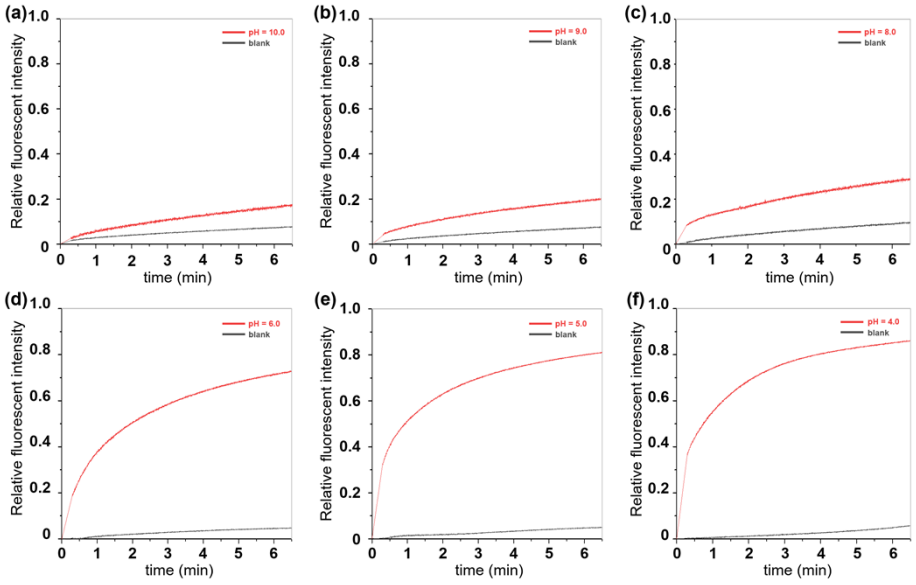


Figure S23. (a)-(f) Changes in the fluorescence intensity of HPTS (λex = 460 nm, λem = 510 nm) in vesicles with time after the addition of **1** (x = 1.6%) at different external pH conditions, without baseline correction.

(c) Procedures for the HPTS assay under alkaline condition: HEPES buffer solution (2.0 mL, HEPES (10 mM), NaCl (100 mM), pH=8.0) and the prepared vesicle suspension (13.3 mM, 100 uL) were placed in a fluorometric cuvette. To the cuvette, the solution of compound **1** in DMSO (5 μL) was added to reach a required channel concentration with gentle stirring. Fluorescent intensity (I_t) was continuously monitored at 510 nm (excitation at 460 nm) in 6.5 min. Then, Triton aqueous solution (20%, 10 μL) was added with gentle stirring. The intensity was monitored until the fluorescent intensity (I_∞) did not change. The collected data were then normalized into the fractional change in fluorescence given by $(I_t\text{-}I_0)/(I_\infty\text{-}I_0)$, where I_0 is the initial intensity.

6. Cation transport experiment with HPTS assay:

(a) Preparation of HPTS containing LUVs: The preparation protocol for LUVs

follows the steps described in section 3(a), with the sole modification of substituting the 100 mM NaCl within the internal LUVs buffer with MCl (100 mM, M = Li^+, Na^+, K^+, Rb^+ and Cs^+).

(b) Fluorescent experiments: HEPES buffer solution (2.0 mL, HEPES (10 mM), NaCl (100 mM), pH=6.0) and the prepared vesicle suspension (13.3 mM, 100 uL) were placed in a fluorometric cuvette. To the cuvette, the solution of compound **1** in DMSO (5 μL) was added to reach a required channel concentration (molar ratio relative to lipid, represented by x) with gentle stirring. Fluorescent intensity (I_t) was continuously monitored at 510 nm (excitation at 460 nm) in 6.5 min. Then, Triton aqueous solution (20%, 10 μL) was added with gentle stirring. The intensity was monitored until the fluorescent intensity (I_∞) did not change. The collected data were then normalized into the fractional change in fluorescence given by $(I_t\text{-}I_0)/(I_\infty\text{-}I_0)$, where I_0 is the initial intensity.

7. Procedures for the FCCP-HPTS assay:

(a) Preparation of HPTS containing LUVs: The preparation protocol for LUVs follows the steps described in section 3(a), with the sole modification of substituting the 100 mM NaCl within the internal LUVs buffer with 100 mM KCl.

(b) Fluorescent experiments: HEPES buffer solution (2.0 mL, HEPES (10 mM), NaCl (100 mM), pH=6.0) and the prepared vesicle suspension (13.3 mM, 100 uL) were placed in a fluorometric cuvette. The solution of compound **1** (x = 0.8 %), carbonyl cyanide 4-(trifluoromethoxy) phenyl hydrazone (FCCP, 0.5 μM), and a mixture of compound **1**/FCCP were added to the cuvette separately. Fluorescent intensity (I_t) was continuously monitored at 510 nm (excitation at 460 nm) in 6.5 min. Then, Triton aqueous solution (20%, 10 μL) was added with gentle stirring. The intensity was monitored until the fluorescent intensity (I_∞) did not change. The collected data were then normalized into the fractional change in fluorescence given by $(I_t\text{-}I_0)/(I_\infty\text{-}I_0)$, where I_0 is the initial intensity.

8. Procedures for the VA-HPTS assay:

(a) Preparation of HPTS containing LUVs: The preparation protocol for LUVs follows the steps described in section 3(a), with the sole modification of substituting the 100 mM NaCl within the internal LUVs buffer with 100 mM KCl.

(b) Fluorescent experiments: HEPES buffer solution (2.0 mL, HEPES (10 mM), NaCl (100 mM), pH=6.0) and the prepared vesicle suspension (13.3 mM, 100 uL) were placed in a fluorometric cuvette. The solution of compound **1** (x = 0.8 %), valinomycin (VA, 5 pM), and a mixture of compound **1**/VA were added to the cuvette separately to reach a required channel concentration with gentle stirring. Fluorescent intensity (I_t) was continuously monitored at 510 nm (excitation at 460 nm) in 6.5 min. Then, Triton aqueous solution (20%, 10 μL) was added with gentle stirring. The intensity was monitored until the fluorescent intensity (I_∞) did not change. The collected data were then normalized into the fractional change in fluorescence given by $(I_t\text{-}I_0)/(I_\infty\text{-}I_0)$, where I_0 is the initial intensity.

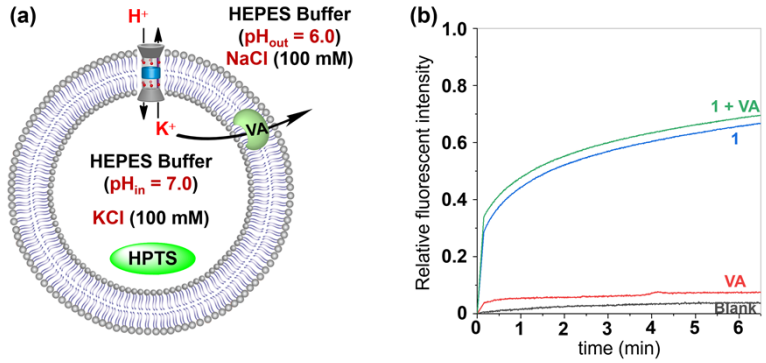


Figure S24. (a) Schematic representation for the FCCP-HPTS assay. (b) Changes in the fluorescence intensity of HPTS after the addition of **1** and VA.

In VA-HPTS assay, the presence of VA will selectively mediate the K^+ transport from inside to outside because of the concentration gradient, and further result in the influx of H^+ or the efflux of OH^- through compound **1** to sustain the overall charge balance. Once the flow rates of H^+ or OH^- are higher than that of K^+, the significant increase of the fluorescence intensity of HPTS will be observed. However, compared with the individual addition of channel **1** (66.7 %), the co-injection of channel **1** and VA did not improve the fluorescence intensity of HPTS significantly (69.6 %). These observations suggesting that K^+ possess higher flow rate than that of H^+ or OH^- during the transport process.

9. Procedures for planar lipid bilayer conductance experiments:

The solution of 1,2-diphytanoyl-sn-glycero-3-phosphocholine (diPhyPC) in chloroform (10 mg/mL, 20 μL) was evaporated with nitrogen gas to form a thin film and re-dissolved in *n*-decane (8 μL). The lipid solution (0.5 μL) was injected on to the aperture (diameter = 200 μm) of the Delrin® cup (Warner Instruments, Hamden, CT) and then evaporated with nitrogen gas. In a typical experiment for measurement of the channel conductance for an ion, the chamber (*cis* side) and the Delrin cup (*trans* side) were filled with aqueous KCl solution (1.0 M). Ag-AgCl electrodes were applied directly to the two solutions and the cis one was grounded. Planar lipid bilayer was formed by painting the lipids solution (1.0 μL) around the pretreated aperture and by judgment of capacitance (100-120 pF). Membrane currents were measured using a Warner BC-535D bilayer clamp amplifier and were collected by PatchMaster (HEKA) with sample interval at 10 kHz and then filtered with an 8-pole Bessel filter at 1 kHz (HEKA). The data were analyzed by FitMaster (HEKA) with a digital filter at 110 Hz. The conductance (γ) was obtained by further analyzing the data using the Clampfit software.

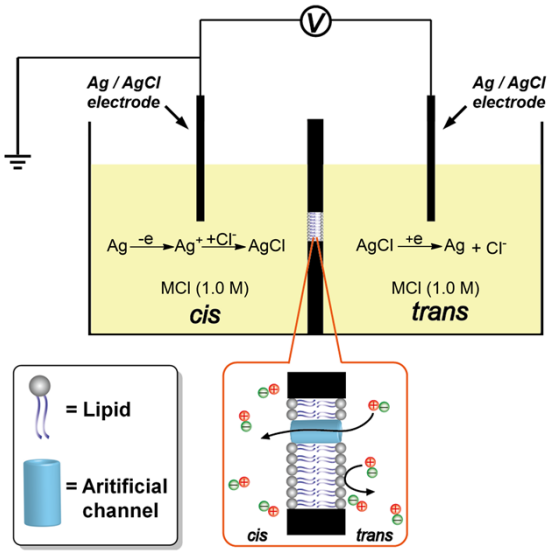


Figure S25. Schematic representation for the patch clamp experiments with planar lipid bilayer. The redox reactions on both Ag/AgCl electrodes are inserted to illustrate the nature of charge balance during M^+ transmembrane transport.

For the single-channel conductance measurement, two chambers were charged with KCl (1 M, 1 mL). And the solution of compound **1** in DMSO (0.25 mM, 1 uL) was added to the *cis* compartment, and the solution was stirred for 5 min.

For the measurement of the transport selectivity of K^+ over Cl^-, the KCl solutions (0.25 M and 1 M) were added to the both side of the bilayer (diPhyPC), *cis* chamber: KCl (1.0 M), *trans* chamber: KCl (0.25 M). The solution of compound **1** in DMSO (0.25 mM, 1 uL) was added to the *cis* compartment and the solution was stirred for 5 min. The measured reversal potentials obtained from the *I-V* plots needed adjustment, accounting for the redox potential produced by disparate voltage drops at the electrode-solution interface in different electrolyte concentrations. The PK^+/PCl^- values were calculated from the equation derived from Goldman-Hodgin-Katz equation.[6]

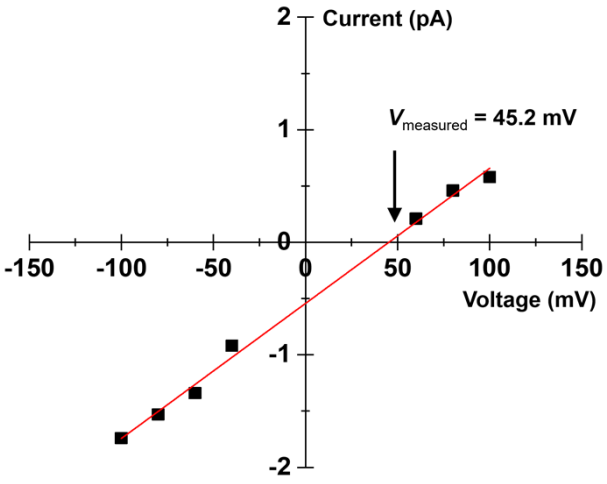


Figure S26. *I-V* plots of **1** by using unsymmetrical solution at both side of the bilayer. *cis* chamber: KCl (1 M KCl, 1 mL), *trans* chamber: (0.25 M KCl, 1 mL).

10. References

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11. Appendix

The cartesian coordinate of optimized structure of 1

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H	-0.34890000	-2.13560000	-4.42490000
H	-0.52030000	-0.57090000	-3.61090000
H	-3.82930000	-0.65160000	-5.29140000
H	-4.84280000	0.32340000	-7.30130000
H	-3.76870000	1.51450000	-8.09030000
H	-0.23310000	-3.34710000	-2.41950000
H	-3.51320000	-3.81730000	2.73940000
H	-3.00800000	-2.10250000	2.68090000
H	-2.29110000	-1.27350000	5.19230000
H	0.34570000	-2.46960000	7.45770000
H	-0.84030000	-1.14580000	7.22560000
H	0.44960000	-2.86260000	2.14090000
H	0.91350000	-2.29560000	4.20210000
H	0.45160000	-0.78390000	3.37740000
H	1.50330000	-0.74650000	4.82810000
H	4.60940000	-5.12970000	-1.34940000
H	4.29940000	-3.75380000	-2.44950000

H	3.67910000	-5.36710000	-2.85460000
H	2.24230000	5.02780000	-3.45430000
H	2.27780000	3.25400000	-3.26630000
H	3.79190000	4.15570000	-3.47390000
H	0.37840000	4.46410000	-2.34950000
H	-4.97150000	2.18730000	1.99770000
H	-3.38350000	1.52380000	2.47510000
H	-4.86570000	0.55350000	2.69670000
O	-0.10370000	-4.90670000	-10.76820000
C	1.23560000	-5.07070000	-10.32830000
C	2.09660000	-4.38680000	-11.41630000
C	3.56770000	-4.40180000	-10.97330000
C	3.67330000	-3.62320000	-9.64210000
O	3.30020000	-2.28320000	-9.77370000
C	3.96110000	-1.35090000	-8.92040000
C	4.89770000	-0.48830000	-9.79540000
O	5.90240000	-1.25850000	-10.41690000
C	5.42100000	0.69140000	-8.96600000
O	6.41270000	1.47340000	-9.57670000
C	4.19480000	1.50320000	-8.48390000
O	3.43880000	0.68430000	-7.63160000
C	2.89500000	-0.49270000	-8.21380000
C	2.21580000	-1.28530000	-7.07380000
O	2.98670000	-1.35180000	-5.89410000
O	3.44280000	1.99100000	-9.55820000
C	2.88310000	3.28870000	-9.43760000
C	1.59870000	3.31430000	-8.58340000
O	0.89070000	4.54230000	-8.72670000
C	0.50310000	4.89030000	-10.02630000
C	1.78910000	5.05750000	-10.86950000
C	2.55570000	3.72480000	-10.88510000
O	3.69600000	3.74600000	-11.71240000
O	1.58930000	5.64680000	-12.12390000
O	-0.39160000	3.97150000	-10.57810000
C	-1.77800000	4.19930000	-10.37770000
C	-2.47470000	3.79060000	-11.69600000
C	-3.99540000	3.89570000	-11.49740000
C	-4.37910000	2.89130000	-10.38630000
O	-4.03270000	1.58230000	-10.72340000
C	-4.84030000	0.52910000	-10.21610000
C	-4.05750000	-0.31700000	-9.18820000
O	-4.73450000	-1.52220000	-8.85930000
C	-5.06110000	-2.36270000	-9.94680000
O	-3.94230000	-2.82300000	-10.63310000

C	-3.44740000	-4.12370000	-10.31370000
C	-2.33890000	-4.08700000	-9.23750000
C	-2.86210000	-3.75600000	-7.83770000
O	-3.87980000	-4.67060000	-7.46140000
O	-1.68430000	-5.33750000	-9.11270000
C	-1.07120000	-5.79130000	-10.28660000
C	-2.18240000	-6.04210000	-11.33160000
C	-2.88260000	-4.70780000	-11.62840000
O	-3.85210000	-4.80540000	-12.64690000
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C	-6.03710000	-1.57130000	-10.85480000
O	-6.70950000	-2.34900000	-11.80360000
C	-5.28640000	-0.34980000	-11.40600000
O	-6.00580000	0.38380000	-12.36810000
O	-3.77420000	3.32250000	-9.19110000
C	-2.34430000	3.38650000	-9.19000000
C	-1.98100000	4.02400000	-7.83870000
O	-2.23250000	3.13690000	-6.76270000
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C	1.83310000	3.18480000	-7.07030000
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O	2.90090000	-4.29450000	-8.68340000
C	1.50810000	-4.42020000	-8.95220000
C	0.98150000	-5.22380000	-7.75470000
O	0.29140000	-4.36360000	-6.87150000
O	4.49270000	-4.02490000	-11.95390000
O	1.88180000	-4.92750000	-12.69850000
H	1.48090000	-6.14250000	-10.27410000
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H	3.85360000	-5.43150000	-10.71640000
H	4.70520000	-3.70710000	-9.27580000
H	4.53990000	-1.88130000	-8.15500000
H	4.30050000	-0.09520000	-10.62610000
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H	4.54230000	2.33120000	-7.84870000
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H	2.09820000	-2.31990000	-7.39670000
H	1.22750000	-0.85680000	-6.86520000
H	3.62530000	3.96780000	-8.99250000
H	0.95980000	2.47920000	-8.90520000
H	0.02820000	5.87700000	-9.91360000
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H	-2.54930000	4.95070000	-7.72300000
H	-0.91670000	4.25660000	-7.82960000
H	2.24940000	2.20410000	-6.84640000
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H	1.02980000	-3.43060000	-8.95900000
H	1.85830000	-5.65800000	-7.25950000
H	0.30480000	-6.02660000	-8.06670000
C	-4.49610000	4.00990000	14.00060000
H	-4.12650000	4.99600000	14.29490000
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H	-5.33890000	0.95870000	14.88100000
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H	-7.19660000	-1.40750000	12.75160000
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H	1.84240000	5.57610000	15.66160000
C	4.67570000	2.61120000	14.43950000
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H	5.48790000	2.61440000	15.16370000

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C	-4.59750000	-5.18420000	11.33260000
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H	-5.06880000	-3.03120000	-12.90280000
H	-6.70310000	-3.28730000	-13.56630000
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H	-7.41370000	1.30970000	-11.13000000
C	-4.43000000	2.81720000	-13.61060000
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H	5.41930000	4.61060000	-12.23100000
C	6.25070000	1.76290000	-10.95910000
H	6.42290000	0.87070000	-11.56670000
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H	7.01710000	2.50420000	-11.17960000
C	6.99470000	-1.66590000	-9.62100000
H	7.63690000	-0.81850000	-9.36190000
H	6.68000000	-2.17330000	-8.70390000
H	7.55140000	-2.36670000	-10.24100000
C	4.21410000	-2.84320000	-12.68900000
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H	3.99760000	-2.00640000	-12.02780000
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H	2.11570000	-6.43890000	-13.98160000
H	3.53020000	-6.17290000	-12.93590000
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H	-1.83270000	-5.39880000	-14.02520000
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H	-0.74350000	-6.79840000	-14.17650000
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H	0.01410000	3.10030000	-4.53050000
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H	-2.46620000	5.57120000	6.99440000
H	-1.40870000	5.60350000	8.42610000
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O	-0.06880000	4.00030000	6.04000000
O	0.12880000	6.16720000	6.49490000
H	0.97560000	6.07320000	5.96360000
C	3.15860000	5.19190000	7.61920000
H	4.04990000	4.77380000	8.09490000
H	3.09730000	6.26970000	7.82970000
C	3.19930000	4.97160000	6.10750000

O	2.42570000	5.52250000	5.35260000
O	4.11570000	4.13190000	5.72090000
H	3.95510000	3.83280000	4.77920000
C	5.29560000	0.96820000	6.54700000
H	5.48800000	1.61660000	5.68050000
H	6.03220000	1.17570000	7.32410000
C	5.43620000	-0.48820000	6.09700000
O	6.34620000	-1.21010000	6.41130000
O	4.43740000	-0.81860000	5.31270000
H	4.43900000	-1.76560000	5.02040000
C	2.42630000	-4.17540000	5.64500000
H	2.68570000	-5.02010000	6.29300000
H	1.40750000	-4.35130000	5.28300000
C	3.38590000	-4.14490000	4.46990000
O	4.30570000	-3.37090000	4.35120000
O	3.11550000	-5.08180000	3.57460000
H	3.70140000	-5.01290000	2.80220000
C	-3.84490000	0.98820000	6.16650000
H	-4.04530000	1.07600000	5.09160000
H	-4.44520000	1.74010000	6.69230000
C	-2.37630000	1.33790000	6.40450000
O	-1.69440000	0.85300000	7.26880000
O	-1.97640000	2.22340000	5.51680000
H	-1.12830000	2.67120000	5.77970000
C	-4.88980000	-4.12810000	-6.65420000
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C	-4.41860000	-3.37190000	-5.41750000
O	-5.08220000	-2.49740000	-4.91270000
O	-3.23290000	-3.73400000	-4.98100000
H	-2.91570000	-3.11110000	-4.27220000
C	0.24030000	-4.85650000	-5.54480000
H	-0.58930000	-4.34590000	-5.05370000
H	0.06740000	-5.93860000	-5.53330000
C	1.57170000	-4.51780000	-4.86370000
O	2.55240000	-5.21040000	-4.94720000
O	1.51110000	-3.35960000	-4.23990000
H	2.38590000	-3.02620000	-3.91850000
C	2.82320000	-0.26470000	-5.01720000
H	3.34540000	0.63200000	-5.37090000
H	1.75640000	-0.01580000	-4.90530000
C	3.37350000	-0.63140000	-3.65230000
O	3.52700000	-1.76270000	-3.25850000
O	3.66520000	0.43680000	-2.94260000

H	4.08670000	0.20910000	-2.06710000
C	2.47090000	5.48300000	-6.64380000
H	3.12560000	5.97000000	-5.91200000
H	2.72050000	5.86110000	-7.64330000
C	1.03740000	5.92270000	-6.35460000
O	0.50900000	6.83730000	-6.92850000
O	0.46590000	5.22210000	-5.38960000
H	-0.48700000	5.45390000	-5.27340000
C	-3.35190000	3.42940000	-5.97320000
H	-4.22780000	3.68710000	-6.58630000
H	-3.58610000	2.53170000	-5.39520000
C	-3.12430000	4.56660000	-4.98550000
O	-2.24790000	5.39210000	-5.04620000
O	-4.07970000	4.59200000	-4.06440000
H	-3.91260000	5.29030000	-3.40980000