A unimolecular artificial cation channel based on cascaded hydrated acid groups

Pengyang Xin,* Hailong Yuan, Long Zhang, Qiuhui Zhu, Xunpeng Ning, Yufei Song, Yuqing Shu, and Yonghui Sun*

State Key Laboratory of Antiviral Drugs, Pingyuan Laboratory, NMPA Key Laboratory for Research and Evaluation of Innovative Drug, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, 453007 (China).

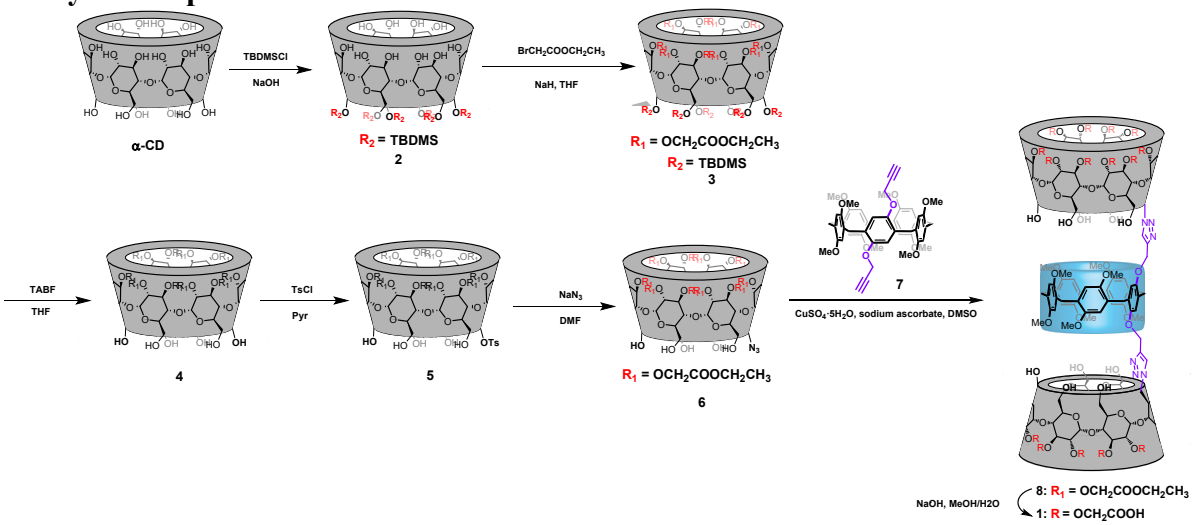
Email: pyxin27@163.com, syonghui1994@163.com

Contents

1. General:

Egg yolk L-α-phosphatidylcholine 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 NMR spectra were recorded on commercial instruments (400 MHz) at 298 K. Chemical shifts were referenced to solvent residue. Mass spectra were recorded with Bruker MicroTOF II spectrometer. The fluorescent experiments on vesicles were performed on V-arian Cary Eclipse fluorescence spectrophotometer. The conductance measurement on planar lipid bilayer was performed on Warner BC-535D Planar Lipid Bilayer Workstation.

2. Synthetic procedures and characterization data:



Compound 3. Compound **2** (500 mg, 0.30 mmol) and sodium hydride (432 mg, 18 mmol) was dispersed in dry THF at ice-bath under argon atmosphere for 1 h. Then, add 1.7 mL methyl bromoacetate by injection.The mixture was stirred for 2 h at ice-bath. After 2 h, it was moved to room temperature and reacted for 48 h. After quenching with methanol, the residue is concentrated under vacuum and dissolved in CH_2Cl_2. The solution was then washed with aqueous (3 × 100 mL). The organic layer was dried (Na_2SO_4), concentrated under vacuum. The product was purified by column chromatography (silica gel; PE: EA =2:1) afforded **3**.

3: Yield 80 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (d, J = 3.1 Hz, 1H), 4.75 (d, J = 15.4 Hz, 1H), 4.42 (dd, J = 16.0, 8.9 Hz, 2H), 4.15 (d, J = 16.6 Hz, 1H), 4.07 (d, J = 9.6 Hz, 1H), 3.63 (d, J = 11.3 Hz, 1H), 3.35 (dd, J = 9.5, 3.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.91, 170.71, 100.20, 81.24, 80.55, 80.20, 77.48, 77.36, 77.16, 76.84, 72.63, 70.96, 68.75, 62.26, 51.66, 51.58, 26.05, 18.42. HRMS: calcd for $C_{108}H_{192}NaO_{54}Si_6$ $[M+Na]^+$ 2544.0812, found 2545.0793.

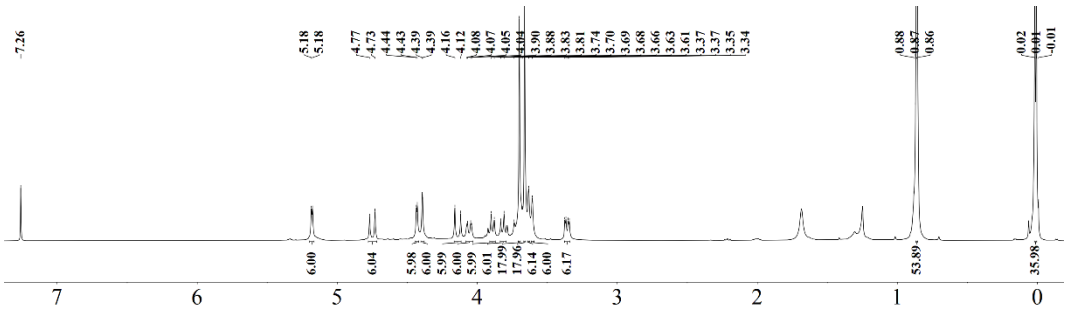


Figure S1. ^{1}H NMR spectrum of **3** in $CDCl_3$.

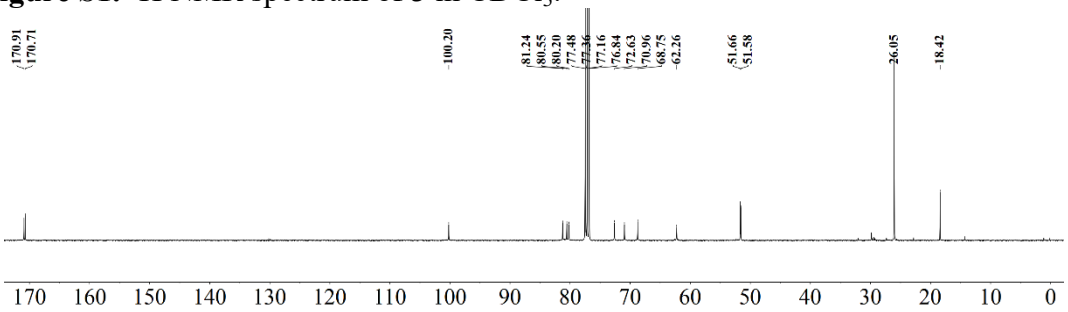


Figure S2. ^{13}C NMR spectrum of **3** in $CDCl_3$.

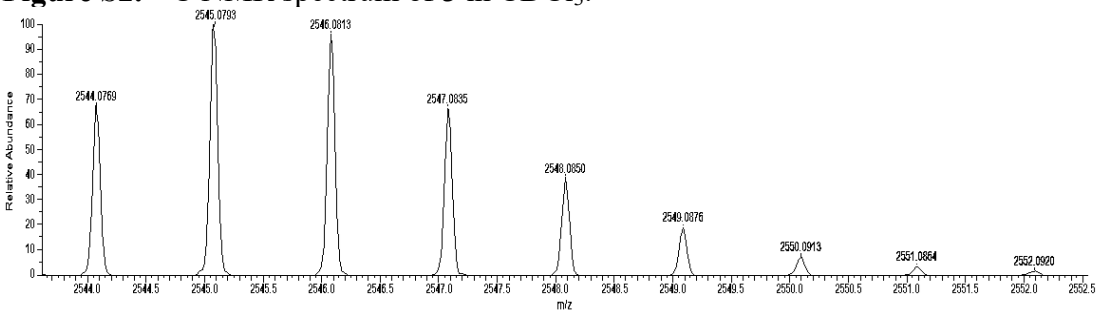


Figure S3. HR-MS of **3**.

Compound 4. Compound **3** (2 g, 0.79 mmol) and TBAF (tetrabutylammonium fluoride, 6 mL) was dissolved in dry THF. The mixture was stirred at 70 ℃ overnight. The residue concentrated under vacuum and purified by column chromatography (silica gel; DCM: MeOH =10:1) afforded **4**.

4: Yield: 76 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 5.33 (d, *J* = 3.6 Hz, 1H), 5.24 (d, *J* = 3.4 Hz, 1H), 5.20 (dd, *J* = 7.0, 3.6 Hz, 2H), 5.17 (d, *J* = 3.4 Hz, 1H), 5.03 (d, *J* = 3.2 Hz, 1H), 4.83 (dd, *J* = 15.5, 3.6 Hz, 2H), 4.70 (dd, *J* = 31.9, 15.4 Hz, 5H), 4.53-4.46 (m, 3H), 4.45-4.25 (m, 18H), 4.21-4.11 (m, 6H), 4.00 (dd, *J* = 39.2, 11.5 Hz, 6H), 3.79 (dd, *J* = 15.3, 8.2 Hz, 12H), 3.70 (d, *J* = 2.7 Hz, 18H), 3.67 (s, 18H), 3.64-3.54 (m, 6H), 3.43 (ddd, *J* = 14.1, 9.9, 3.6 Hz, 5H), 3.35 (td, *J* = 10.1, 3.4 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.97, 170.87, 170.81, 170.74, 170.69, 130.08, 130.05, 130.03, 128.19, 128.15, 99.89, 99.86, 99.83, 99.82, 99.79, 99.38, 99.34, 99.29, 99.23, 82.14, 82.09, 81.78, 81.76, 81.65, 81.60, 81.40, 81.36, 81.29, 81.22, 80.58, 80.47, 80.41, 80.16, 77.48, 77.36, 77.16, 76.84, 73.30, 73.26, 71.03, 70.96, 70.88, 70.77, 69.06, 68.98, 68.93, 68.80, 68.76, 68.71,

62.49, 62.39, 62.37, 62.27, 62.20, 62.16, 51.87, 51.83, 51.78, 32.04, 29.91, 29.83, 29.75, 29.69, 29.66, 29.62, 29.45, 29.38, 27.35, 25.67, 22.82, 21.82, 17.57, 14.25. HRMS: calcd for $C_{72}H_{108}NaO_{54}$ $[M+Na]^+$ 1859.5597, found 1859.5618.

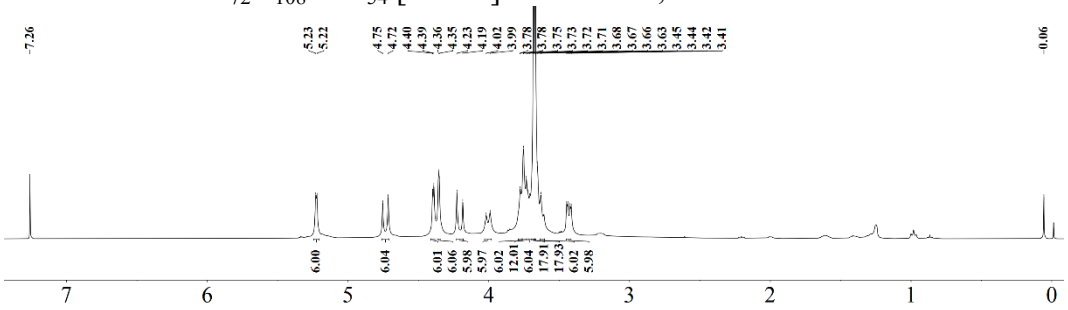


Figure S4. ^1H NMR spectrum of **4** in $CDCl_3$.

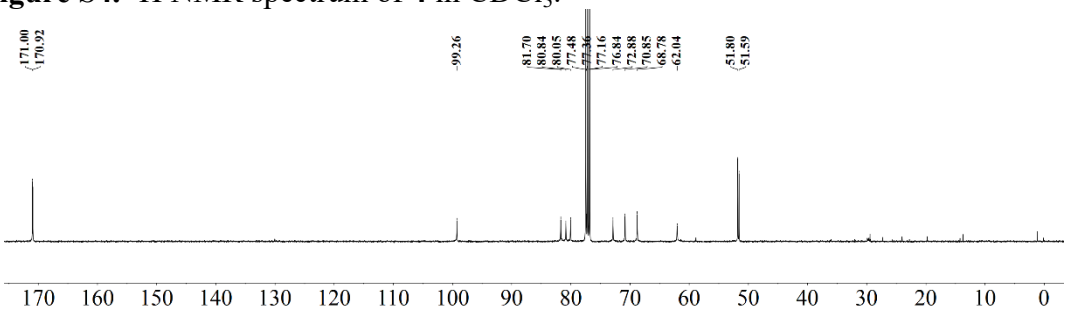


Figure S5. ^{13}C NMR spectrum of **4** in $CDCl_3$.

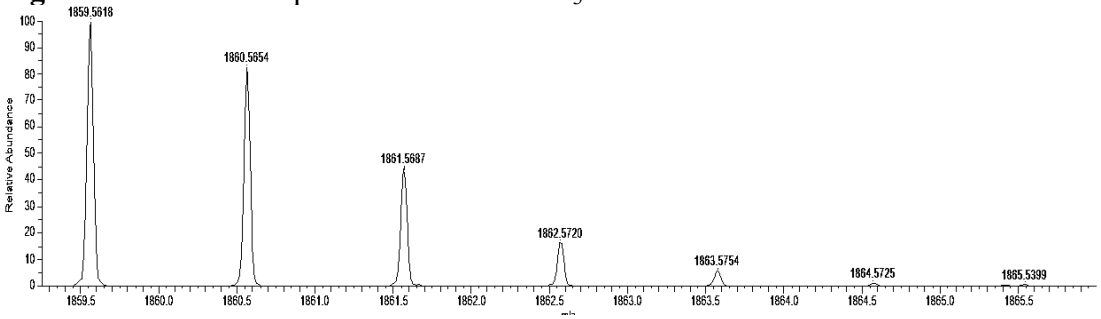


Figure S6. HR-MS of **4**.

Compound 5. Compound **4** (3 g, 1.6 mmol) was dissolved in dry pyridine at ice-bath. Then, add p-toluenesulfonyl chloride 5 mL (608 mg, 3.2 mmol) dissolved in pyridine dropwise within 10 minutes. The mixture was stirred for 24 h. After the reaction is completed, the residue is concentrated under vacuum and dissolved in CH_2Cl_2. The crude product was then washed with aqueous (3 × 100 mL) and then purified with SiliaSphere C18 reversed-phase column chromatography to obtain **5**.

5: Yield 2 %. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 5.33 (d, J = 3.6 Hz, 1H), 5.24 (d, J = 3.4 Hz, 1H), 5.20 (dd, J = 7.0, 3.6 Hz, 2H), 5.17 (d, J = 3.4 Hz, 1H), 5.03 (d, J = 3.2 Hz, 1H), 4.83 (dd, J = 15.5, 3.6 Hz, 2H), 4.70 (dd, J = 31.9, 15.4 Hz, 5H), 4.53-4.46 (m, 3H), 4.45-4.25 (m, 18H), 4.21-4.11 (m, 6H), 4.00 (dd, J = 39.2, 11.5 Hz, 6H), 3.79 (dd, J = 15.3, 8.2 Hz, 12H), 3.70 (d, J = 2.7 Hz, 18H), 3.67 (s, 18H), 3.64-3.54 (m, 6H), 3.43 (ddd, J = 14.1, 9.9, 3.6 Hz, 5H), 3.35

(td, J = 10.1, 3.4 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.97, 170.87, 170.81, 170.74, 170.69, 130.08, 130.05, 130.03, 128.19, 128.15, 99.89, 99.86, 99.83, 99.82, 99.79, 99.38, 99.34, 99.29, 99.23, 82.14, 82.09, 81.78, 81.76, 81.65, 81.60, 81.40, 81.36, 81.29, 81.22, 80.58, 80.47, 80.41, 80.16, 77.48, 77.36, 77.16, 76.84, 73.30, 73.26, 71.03, 70.96, 70.88, 70.77, 69.06, 68.98, 68.93, 68.80, 68.76, 68.71, 62.49, 62.39, 62.37, 62.27, 62.20, 62.16, 51.87, 51.83, 51.78, 32.04, 29.91, 29.83, 29.75, 29.69, 29.66, 29.62, 29.45, 29.38, 27.35, 25.67, 22.82, 21.82, 17.57, 14.25. HRMS: calcd for $C_{79}H_{114}NaO_{56}S$ $[M+Na]^+$ 2013.5685, found 2013.5719.

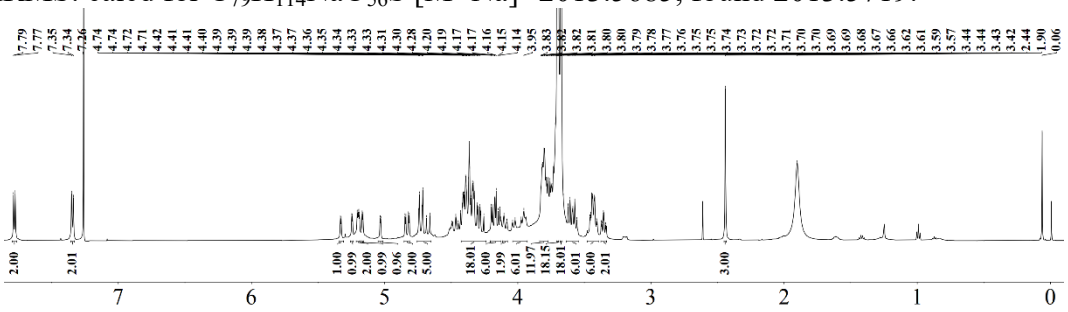


Figure S7. ^{1}H NMR spectrum of **5** in $CDCl_3$.

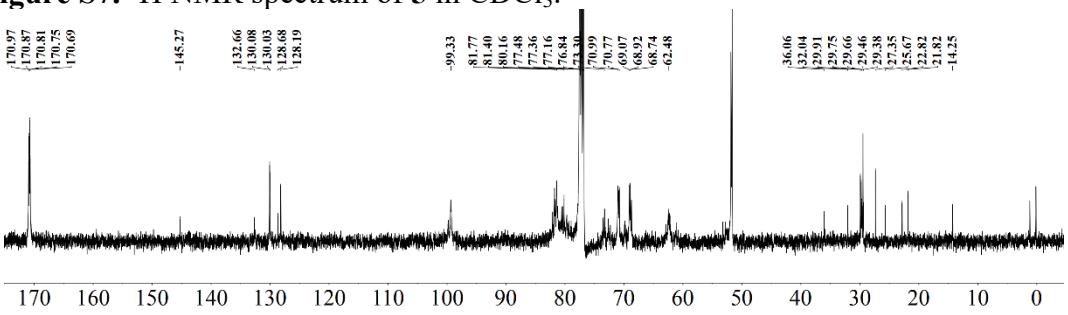


Figure S8. ^{13}C NMR spectrum of **5** in $CDCl_3$.

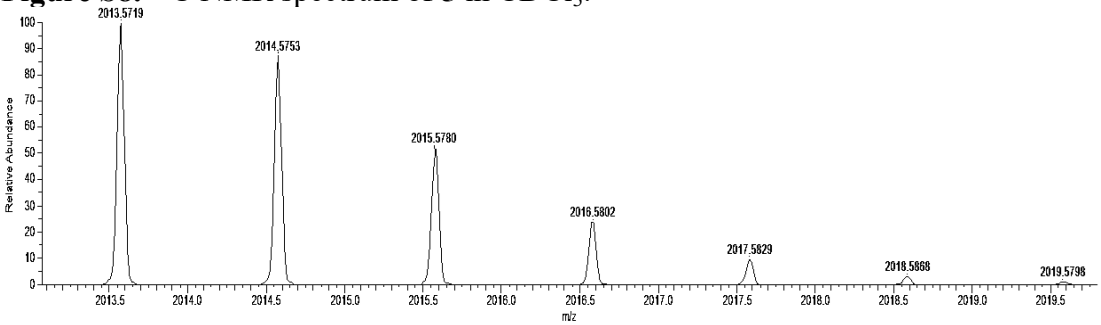


Figure S9. HR-MS of **5**.

Compound 6. Compound **5** (200 mg, 0.1 mmol) and NaN_3 (130 mg, 2 mmol) was dissolved in dry DMF. The mixture was stirred at 80 ℃ overnight. After the reaction is completed, the residue concentrated under vacuum and purified by column chromatography (silica gel; DCM: MeOH =10:1) afforded **6**.

6: Yield 89 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (dd, J = 24.7, 2.7 Hz, 2H), 5.15 (dd, J = 34.1, 6.5 Hz, 4H), 4.92-4.80 (m, 2H), 4.76-4.65 (m, 4H), 4.44-4.41 (m, 2H), 4.40 (d, J = 4.9 Hz, 2H), 4.38 (d, J = 5.5 Hz, 2H), 4.37-4.33 (m, 5H), 4.32 (s, 2H), 4.18 (dd,

J = 23.8, 13.5 Hz, 4H), 4.14 (s, 4H), 3.97-3.83 (m, 6H), 3.83-3.74 (m, 11H), 3.72 (s, 6H), 3.69 (dd, J = 10.6, 3.9 Hz, 36H), 3.65 (s, 2H), 3.58 (dd, J = 16.5, 8.0 Hz, 4H), 3.44 (dd, J = 10.9, 6.4 Hz, 6H), 2.69 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.06, 171.01, 170.90, 170.79, 170.77, 170.74, 130.15, 130.13, 129.88, 129.86, 129.62, 99.81, 99.79, 99.76, 99.74, 99.73, 99.39, 99.37, 99.34, 99.32, 99.30, 99.23, 99.05, 99.01, 98.97, 82.24, 82.12, 81.74, 81.59, 81.56, 81.47, 81.35, 80.87, 80.82, 80.45, 80.39, 80.01, 79.94, 79.91, 79.83, 79.42, 79.39, 79.08, 79.06, 77.37, 77.16, 76.95, 73.39, 73.35, 73.34, 73.19, 73.17, 72.48, 71.26, 70.99, 70.83, 70.75, 69.21, 68.92, 68.85, 68.71, 68.63, 62.49, 62.44, 62.39, 62.23, 62.21, 51.86, 51.84, 51.81, 51.79, 51.75, 51.62, 39.03, 32.03, 30.70, 30.45, 29.89, 29.83, 29.78, 29.65, 29.49, 29.45, 29.37, 29.34, 29.25, 29.11, 27.35, 27.30, 25.64, 24.11, 23.10, 22.82, 14.24, 14.17. HRMS: calcd for $C_{72}H_{107}N_3NaO_{53}$ $[M+Na]^+$ 1884.5561, found 1884.5685.

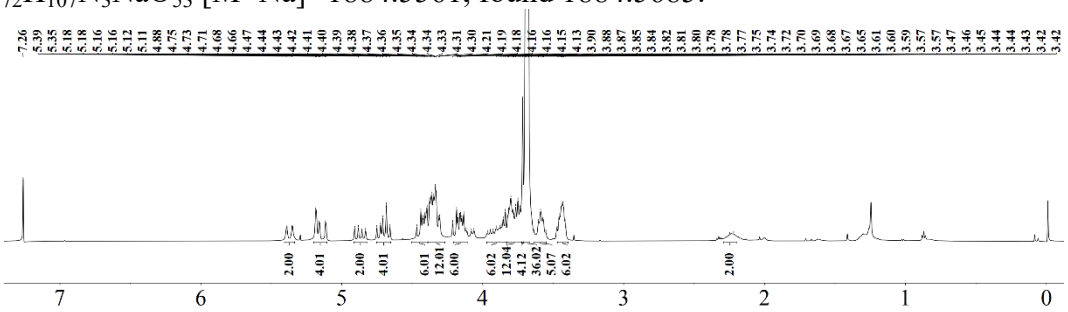


Figure S10. ^{1}H NMR spectrum of **6** in $CDCl_3$.

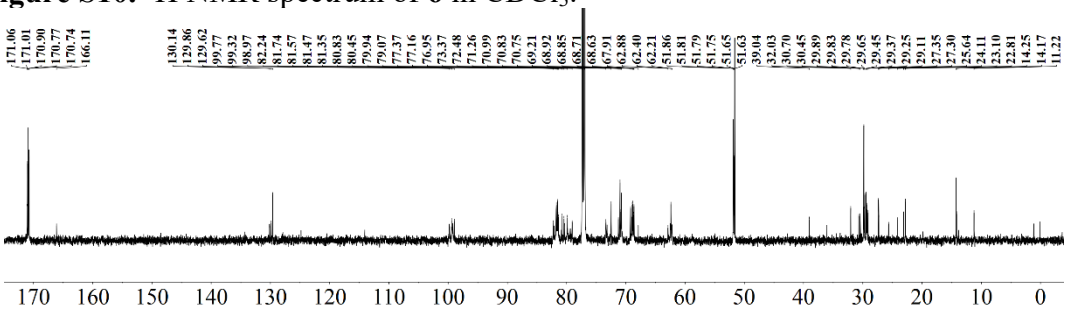


Figure S11. ^{13}C NMR spectrum of **6** in $CDCl_3$.

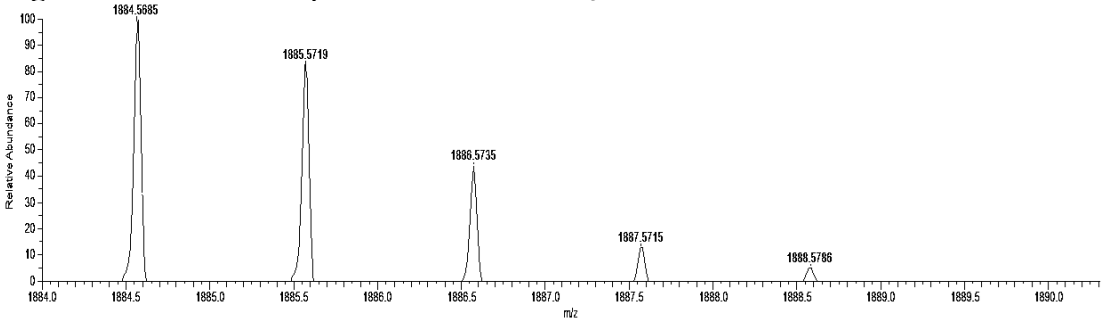


Figure S12. HR-MS of **6**.

Compound 8. Compound **6** (50 mg, 0.027 mmol) and Compound **7** was dissolved in DMSO (10 mL). The mixture was stirred for 15 minutes and then sodium L-ascorbate (608 mg, 3.2 mmol) and $CuSO_4 \cdot 5H_2O$ (11.20 mg, 0.045 mmol) was added. The

mixture was stirred for 24 h at room temperature. After the reaction is completed, 10 portions of water was added to the reaction mixture, and the obtained solution was freeze-dried. The crude product was purified using SiliaSphere C18 reversed-phase 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 **8** was obtained as white solid.

8: Yield: 48%. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.18 (d, *J* = 31.0 Hz, 2H), 7.00 (s, 2H), 6.80-6.76 (m, 6H), 6.71 (s, 2H), 5.43 (d, *J* = 20.3 Hz, 2H), 5.32-5.12 (m, 12H), 5.05-4.94 (m, 6H), 4.71-4.52 (m, 24H), 4.40-4.28 (m, 24H), 4.21 (t, *J* = 16.2 Hz, 12H), 3.92-3.77 (m, 12H), 3.72 (d, *J* = 8.9 Hz, 18H), 3.68 (d, *J* = 9.0 Hz, 30H), 3.64 (s, 24H), 3.62-3.57 (m, 72H), 3.55-3.48 (m, 12H), 3.45 (d, *J* = 10.1 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 170.47, 170.46, 170.44, 170.41, 170.38, 170.30, 170.26, 170.24, 170.18, 170.16, 170.13, 170.08, 170.06, 149.92, 149.87, 129.70, 127.57, 127.50, 127.44, 127.38, 113.37, 113.33, 113.27, 113.21, 98.59, 98.52, 98.43, 98.39, 98.25, 98.21, 98.03, 81.18, 79.64, 79.20, 72.26, 70.10, 67.97, 67.71, 60.07, 55.47, 55.24, 51.43, 51.40, 51.37, 51.34, 51.14, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 35.16, 31.32, 29.13, 29.07, 29.02, 28.88, 28.78, 28.64, 26.61, 25.15, 22.13, 13.99. HRMS: calcd for $C_{193}H_{264}N_6NaO_{116}$ $[M+3Na]^{3+}$ 1530.8228, found 1530.8215.

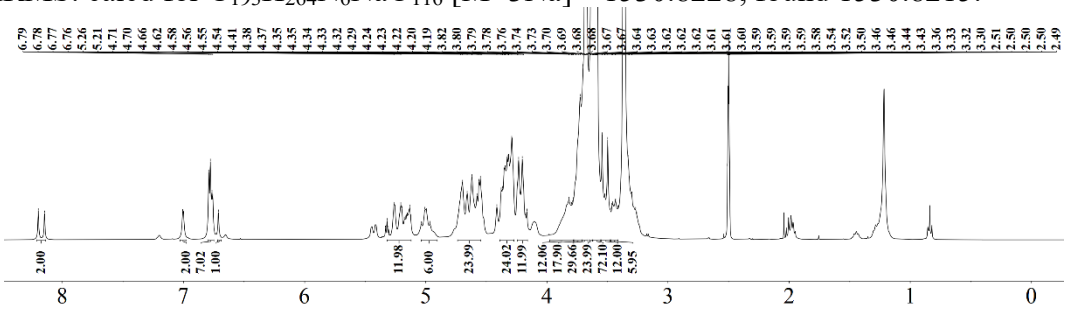


Figure S13. ^{1}H NMR spectrum of **8** in DMSO-*d6*.

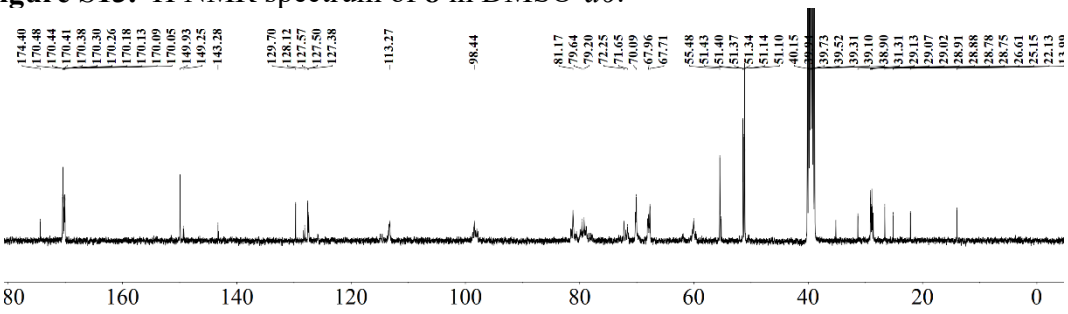


Figure S14. ^{13}C NMR spectrum of **8** in DMSO-*d6*.

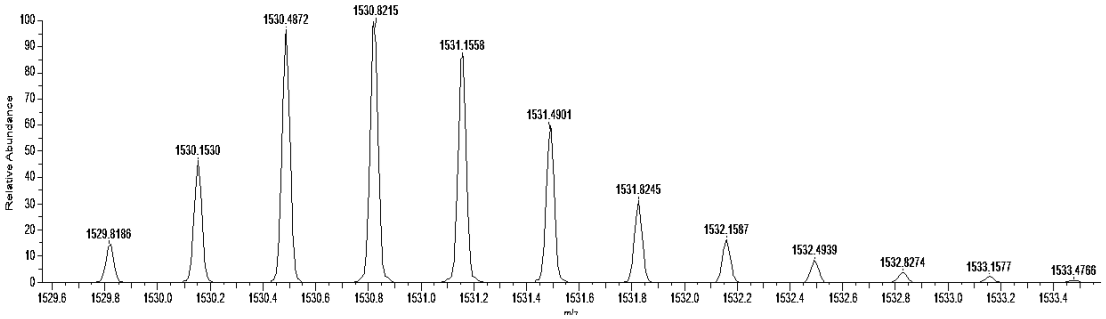


Figure S15. HR-MS of **8**.

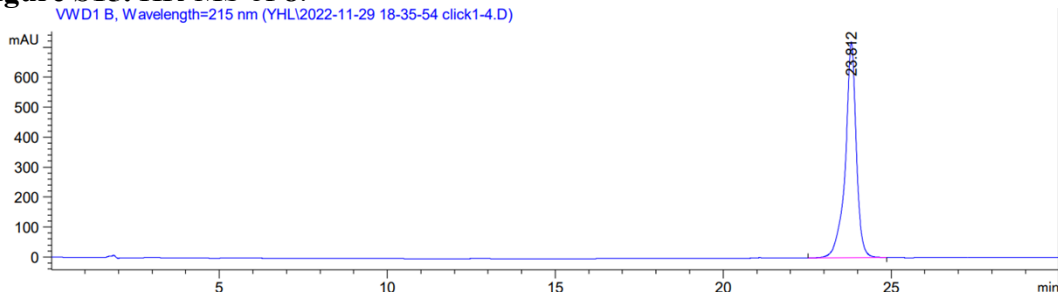


Figure S16. HPLC analytic trace of **8.**

Compound 1. Compound **8** (20 mg,0.005 mmol) was dissolved in MeOH/H_2O (3/0.5 mL) and then NaOH (1M) solution was droped to the mixture solution under ice bath conditions. The mixture was stirred at room temperature for 48 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 using SiliaSphere C18 reversed-phase 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 **8** was obtained as white solid.

1: Yield 64 %. HPLC retention time: 13.836 min, purity: 94.38%. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.40 (s, 17H), 8.19 (d, *J* = 22.3 Hz, 2H), 7.01 (s, 2H), 6.78 (d, *J* = 12.0 Hz, 8H), 5.46-5.30 (m, 4H), 5.16 (s, 12H), 4.98 (s, 6H), 4.70-4.49 (m, 24H), 4.38-4.04 (m, 48H), 3.79 (s, 12H), 3.67 (s, 36H), 3.55-3.40 (m, 36H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 171.99, 171.91, 171.36, 171.24, 150.01, 149.42, 143.20, 129.79, 128.25, 127.65, 127.57, 127.45, 113.32, 99.39, 80.90, 80.46, 78.60, 72.41, 70.39, 67.75, 60.24, 55.58, 40.13, 39.92, 39.71, 39.50, 39.29, 39.08, 38.87, 29.14, 28.95, 26.69, 22.19, 14.07. HRMS: calcd for $C_{169}H_{216}N_6NaO_{116}$ $[M+3H]^{3+}$ 1396.7156, found 1396.7448.

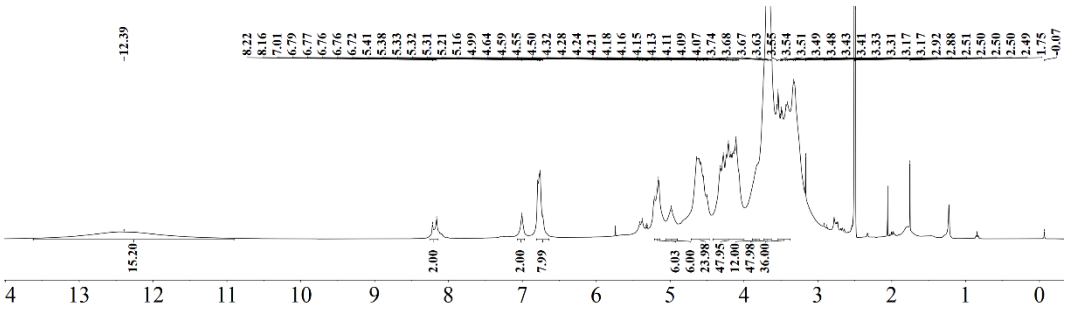


Figure S17. ^{1}H NMR spectrum of **1** in DMSO-*d6*.

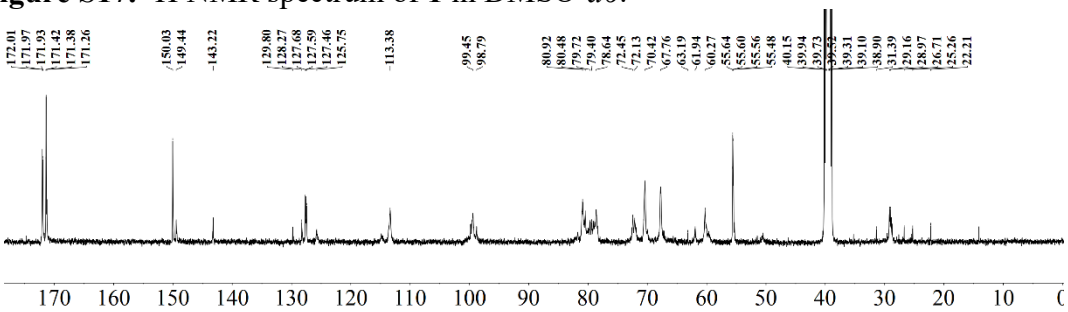


Figure S18. ^{13}C NMR spectrum of **1** in DMSO-*d6*.

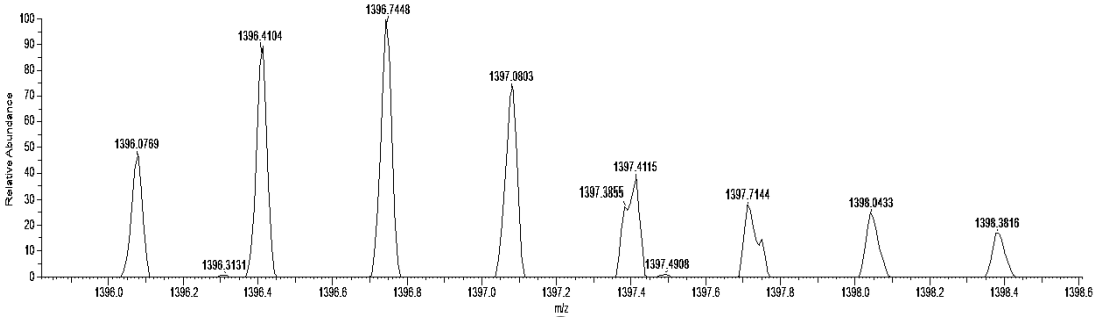


Figure S19. HR-MS of **1**.

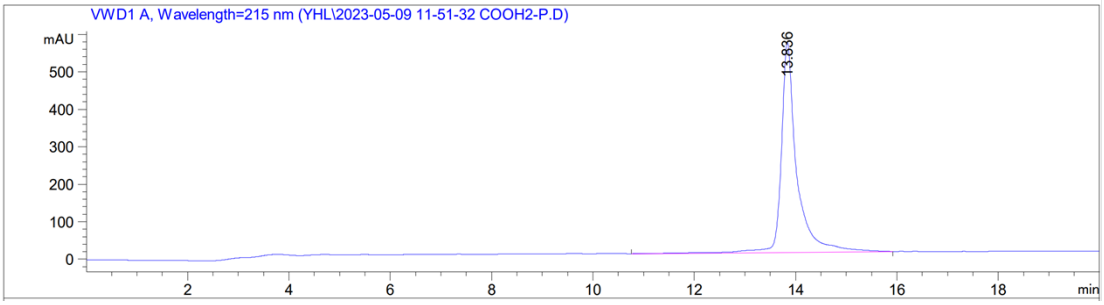


Figure S20. HPLC analytic trace of **1.**

3. Ionophoric experiment with HPTS assay:

(a) Preparation of HPTS containing large unilamellar vesicles (LUVs): EYPC (15 mg, 20 μmol) in EtOH (0.15 mL) was diluted with EtOH (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 (1.5 mL, HEPES (10 mM), KCl (100 mM), pH = 7.2) containing 8-hydroxypyrene-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).[3] 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 via polycarbonate membrane (0.2 μm) suspension nine times 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), KCl (100 mM, pH=6.0/pH=8.0) and the prepared vesicle suspension (13.3 mM, 100 uL) were placed in a fluorimetric cuvette. To the cuvette, the solution of compound **1** in DMSO (5 uL) was added to reach a required channel concentration (molar ratio relative to lipid, represented by *x* (%)) with gentle stirring. Fluorescent intensity (It) was continuously monitored at 510 nm (excitation at 460 nm) in 13 min. Then, Triton aqueous solution (50%, 10 uL) was added with gentle stirring. The intensity was monitored until the fluorescent intensity (I_t) 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.

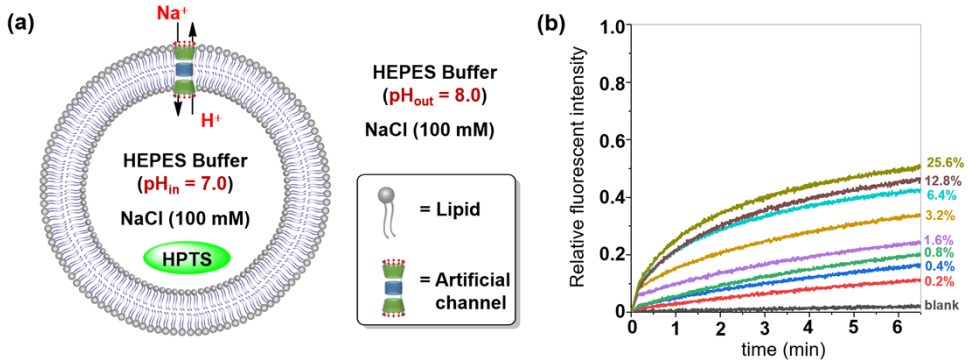


Figure S21. (a) Schematic diagram of fluorescent vesicles containing HPTS probes (λ_{ex}=460 nm, λ_{em}=510 nm); (b) Under the condition of pH_{out}=8, the change curve of HPTS fluorescence intensity in vesicles over time after adding compound **1** with equal gradient and different concentrations.

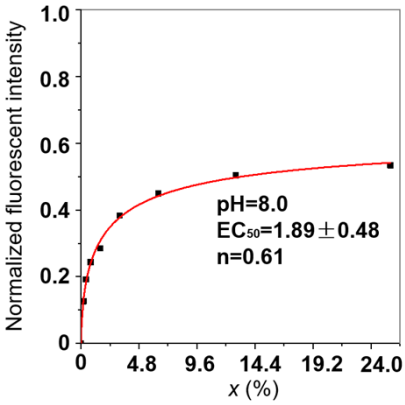


Figure S22. The dose-response curves and EC_{50} values obtained through Hill equation

fitting under pH_{out}=8.0.

4. 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) Fluorescence experiment: 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.

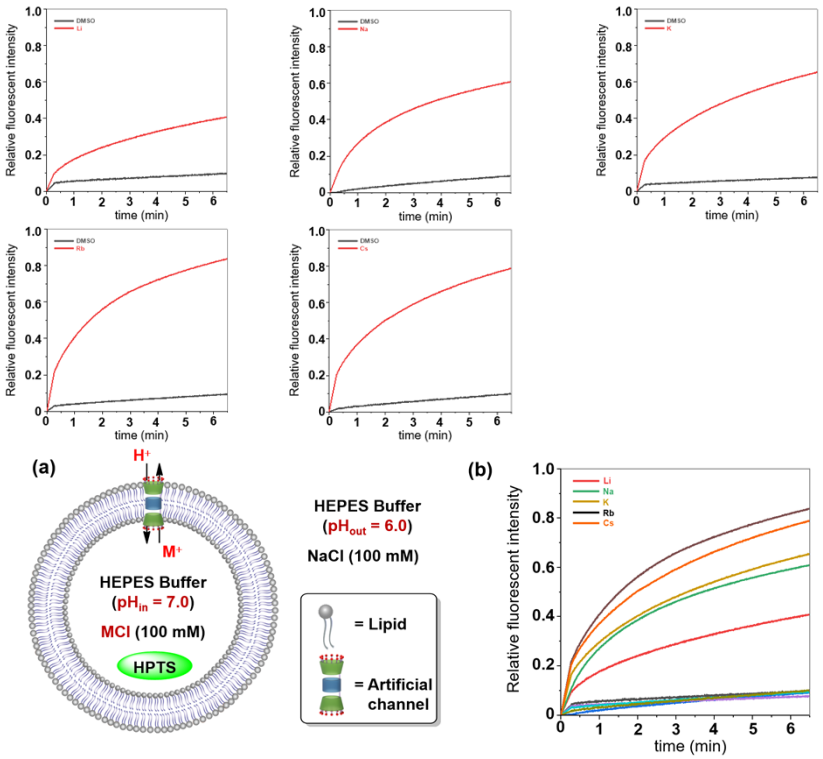


Figure S23. (a) Schematic diagram of fluorescent vesicles containing HPTS probes; **(b)** Under the condition of pH_{out}=6, by changing the type of buffer salt solution in the inner liquid (M^+=Li^+, Na^+, K^+, Rb^+, Cs^+) and adding compound **1**, the fluorescence intensity of HPTS in the vesicles changes over time.

5. Rocedures for planar lipid bilayer conductance experiments:

The solution of 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, 1.0 mL). 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 210 Hz. The conductance (γ) was obtained by further analyzing the data using the Clampfit software.

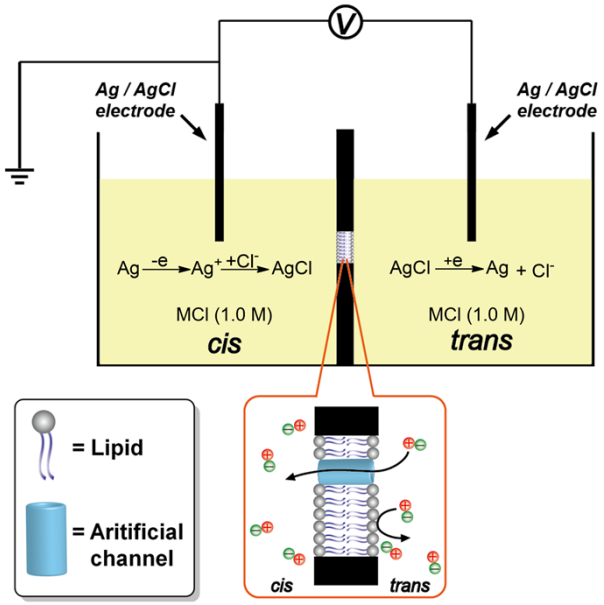


Figure S24. Schematic representation for the patch clamp experiments with planar lipid bilayer. The redox reactions on both Ag/AgCl electrodes are inserted to illustrate the nature of charge balance during K^+ transmembrane transport.

For the single-channel conductance measurement, two chambers were charged with N-2-hydroxyethylpiperazine-N'-2-ethanesulphonic acid (HEPES) buffer (10 mM HEPES, 1 M KCl, pH 7.5, 1 mL). And the solution of compound **1** in DMSO(0.01 mM, 1 μL) 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.[3]

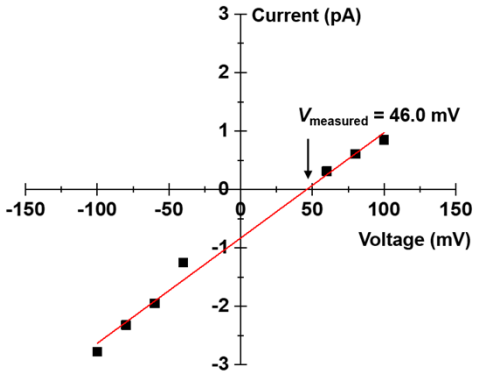


Figure S25. *I-V* plots of **1** by using unsymmetrical solution at both side of the bilayer. *cis* chamber: KCl (1 M), *trans* chamber: KCl (0.25 mM).

6. References

[1] J. Cao, Y. Shang, B. Qi, X. Sun, L. Zhang, H. Liu, H. Zhang, X. Zhou, Synthesis of pillar[n]arenes (n = 5 and 6) with deep eutectic solvent choline chloride 2$FeCl_3$. *RSC Adv.* 2015, **5**, 9993.

[2] D. M. Vriezema, M. C. Aragonès, J. A. A. W, Elemans, J. J. L. M. Cornelissen, A. E. Rowan, R. J. M. Nolte, Self-Assembled Nanoreactors. *Chem. Rev.* 2005, **105**, 1445.

[3] L. Shi, W. Zhao, Z. Jiu, J. Guo, Q. Zhu, Y. Sun, B. Zhu, J. Chang, P. Xin, *Angew. Chem. Int. Ed.*, 2024, **63**, e202403667.