Supporting Information

Synthetic chloride transporters with the binding mode observed in a ClC chloride channel

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Contents
1. Synthesis and characterization of new compounds
2. X-ray crystallographic analysis
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4. Transport experiments
General: All reagents were purchased from commercial suppliers and used without further purification. If it is necessary, anhydrous reagents were purchased. CH$_2$Cl$_2$ was purified by drying over CaH$_2$ followed by distillation. Thin layer chromatography (TLC) was performed on Merck (silica gel 60, F-254, 0.25 mm). Silica gel 60 (230 ~ 240 mesh, Merck) was used for column chromatography. Melting points were determined with a Barnsted Electrochemical (IA9100). The NMR (Bruker Avance II spectrometer) chemical shifts were reported in ppm downfield relative to the residual protonated solvent peaks (for $^1$H NMR spectra: CD$_3$CN 1.94 ppm; DMSO-$d_6$ 2.50 ppm, for $^{13}$C NMR spectra: CD$_3$CN 1.32 ppm; DMSO-$d_6$ 39.52 ppm). Routine mass analyses were performed with photodiode array detector using electron spray ionization (ESI) or atmospheric pressure chemical ionization (APCI). Fluorescence spectra were measured with HITACHI-F4500. The elemental analysis data were obtained from Organic Chemistry Research Center at Sogang University.

1. **Synthesis and characterization of new compounds**

![Diagram](attachment:diagram.png)

$2a$: I$_2$ (6.8 g, 1 equiv) diluted in EtOH (100 ml) was dropwise added to a round bottom flask charged with 4-t-butylaniline (4 g, 27 mmol), Ag$_2$SO$_4$ (8.4 g, 1 equiv) and EtOH (100 ml). The solution was stirred vigorously for 4 h at room temperature. The reaction mixture was filtered through Celite and the organic solvent was evaporated. The concentrated mixture was dissolved in CH$_2$Cl$_2$ and was washed with saturated NaHCO$_3$ solution and brine, dried over anhydrous Na$_2$SO$_4$ and concentrated. The reaction mixture was purified by column chromatography (silica gel, 1:3 (v/v) ethyl acetate in hexane) to give $2a$ as brown liquid. (6.9 g, 75%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.47 (s, 1H), 7.12 (d, $J = 8.5$ Hz, 1H), 6.70 (d, $J = 8.4$ Hz, 1H), 4.98 (s, 2H, NH), 1.19 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 144.2, 143.2, 135.6, 126.5, 114.4, 84.5, 33.8, 31.4 ppm; HR-MS(ESI) m/z Calcd for C$_{10}$H$_{14}$IN 275.0171, found : 275.0177.
3a: 2a (4.8 g, 17 mmol) in CH₂Cl₂ (100 ml, 0.17 M) and saturated NaHCO₃ aqueous solution (100 ml) was stirred and triphosgene (5.2 g, 1 equiv) was added in several portions. The reaction mixture was vigorously stirred at room temperature. The resulting suspension was washed with saturated NaHCO₃ solution and brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was recrystallized with MeOH to give 3a (6.2 g, 62%) as white solid. mp > 250 ºC (dec); ¹H NMR (400 MHz, DMSO–d₆) δ 8.44 (s, 2H, NH), 7.77 (s, 2H), 7.59 (d, J = 8.6 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 1.26 (s, 18H); ¹³C NMR (100 MHz, DMSO–d₆) δ 153.0, 148.2, 137.5, 135.3, 125.7, 124.1, 92.8, 33.9, 31.0; Anal. Caled for C₂₁H₂₆I₂N₂O: C, 43.8; H, 4.55; N, 4.9, found: C, 43.7; H, 4.55; N, 5.0%

4a: A Schlenk flask charged with 3a (1 g, 1.7 mmol), CuI (3.3 mg, 0.01 equiv) and Pd(PPh₃)₂Cl₂ (12.2 mg, 0.01 equiv) were evacuated under vacuum and back filled with nitrogen (two times). Anhydrous THF (10 ml), TEA (10 ml) and 3-methyl-1-butyn-3-ol (0.51 ml, 3 equiv) were added, the solution was degassed, refilled with N₂, and stirred at 55-58 ºC for 19 h. The mixture was cooled down to room temperature, filtered through Celite and organic solvent was evaporated. The residue was dissolved in CH₂Cl₂, washed with saturated NaHCO₃ aqueous solution and brine, dried over anhydrous Na₂SO₄ then concentrated. The mixture was purified by short column chromatography (CH₂Cl₂) to get 4a (0.7 g, 83%) as white solid.; mp > 197 ºC (dec); ¹H NMR (400 MHz, DMSO–d₆) δ 8.44 (s, 2H, NH), 7.87 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H), 7.30 (s, 2H), 5.44 (s, 2H, OH), 1.48 (s, 12H), 1.26 (s, 18H); ¹³C NMR (100 MHz, DMSO–d₆) δ 157.7, 150.3, 142.3, 133.8, 131.3, 126.5, 118.2, 106.3, 82.5, 69.1, 39.1, 36.8, 36.2.; HR-MS-FAB (m/z) Caled for C₃₁H₄₀N₂O₃: 488.3039, found: 488.3038; Anal. Caled for C₃₁H₄₀N₂O₃: C, 76.2; H, 8.25; N, 5.7, found: C, 76.0; H, 8.0; N, 5.9%

Compound 4b-h were prepared following the procedures described above for the synthesis of 4a.
4b: Mp 174 ~ 178 °C; $^1$H NMR (400 MHz, DMSO–$d_6$) δ 9.13 (s, 2H, NH), 8.24 (d, $J = 9.2$ Hz, 2H), 7.90 (overlapped, 4H), 5.53 (s, 2H, OH), 4.26 (t, $J = 6.6$ Hz, 4H), 1.69 (qn, $J = 6.8$ Hz, 4H), 1.52 (s, 12H), 1.41 (m, 4H), 0.96 (t, $J = 7.0$ Hz, 6H); $^{13}$C NMR (100 MHz, DMSO–$d_6$) δ: 164.7, 151.6, 143.2, 133.4, 129.8, 123.9, 120.2, 112.7, 102.8, 75.7, 64.4, 63.9, 31.3, 30.2, 18.7, 13.6; LR-MS(ESI) m/z Calcd for C$_{33}$H$_{40}$N$_2$O$_7$ [M-H$^+$]: 575.28, found: 575.26; Anal. Calcd for C$_{33}$H$_{40}$N$_2$O$_7$: C, 68.8; H, 7.0; N, 4.9. Found: C, 68.8; H, 7.0, N, 4.9%}

4c: Mp 139 ~ 143 °C; $^1$H NMR (400 MHz, DMSO–$d_6$) δ 9.26 (s, 2H), 8.23 (d, $J = 9.6$ Hz, 2H), 7.91 (overlapped, 4H), 5.61 (s, 2H), 4.25 (t, $J = 6.4$ Hz, 4H), 1.70 (qn, $J = 6.8$ Hz, 4H), 1.51 (s, 12H), 1.26 ~ 1.39 (overlapped, 20H), 0.87 (t, $J = 6.4$ Hz, 6H); $^{13}$C NMR (100 MHz, DMSO–$d_6$) δ: 164.7, 151.6, 143.2, 133.4, 129.8, 123.9, 120.1, 112.65, 102.8, 75.7, 64.7, 64.0, 31.3, 31.2, 28.6, 28.5, 28.1, 25.4, 22.0, 13.9; LR-MS(ESI) m/z Calcd for C$_{41}$H$_{56}$N$_2$O$_7$ [M-H$^+$]: 687.40, found: 687.34; Anal. Calcd for C$_{41}$H$_{56}$N$_2$O$_7$: C, 71.5; H, 8.2; N, 4.0. Found: C, 71.5; H, 8.2; N, 4.0%

4d: Mp 102 ~ 105 °C; $^1$H NMR (250 MHz, DMSO–$d_6$) δ 9.06 (s, 2H), 8.24 (d, $J = 8.5$ Hz, 2H), 7.87 (overlapped, 4H), 5.47 (s, 2H), 4.26 (t, $J = 6.5$ Hz, 4H), 1.72 ~ 1.10 (overlapped, 32 H), 0.89 (d, $J = 5.5$Hz, 6H), 0.81 (d, $J = 6.7$ Hz, 12H); $^{13}$C NMR (100 MHz, DMSO–$d_6$) δ: 165.1, 152.0, 146.7, 133.9, 130.2, 124.4, 120.5, 113.0, 103.2, 76.2, 64.4, 63.5, 36.9, 35.4, 31.8, 19.8, 27.8, 24.4, 22.9, 22.8, 19.8;
LR-MS(ESI) m/z Calcd for C_{45}H_{64}N_{2}O_{7} [M-H]\textsuperscript{+}: 743.46, found: 743.47; Anal. Calcd for C_{45}H_{64}N_{2}O_{7}: C, 72.55; H, 8.7; N, 3.8. found: C, 72.55; H, 9.2; N, 3.8%

4e: Mp: 83 ~ 87 °C; \textsuperscript{1}H NMR (250 MHz, DMSO–\textit{d}_{6}) \delta 9.09 (s, 2H, NH), 8.25 (d, J = 9.2 Hz, 2H), 7.92 (overlapped, 4H), 5.49 (s, 2H, OH), 4.37 (t, J = 3.7 Hz, 4H), 3.73 (t, J = 4.5 Hz, 4H), 3.56 (t, J = 4.0 Hz, 4H), 3.48 (t, J = 3.3 Hz, 4H), 3.35 (t, J = 6.5, 4H), 1.51 (s, 12H), 1.44 (qn, J = 4.0 Hz, 4H), 1.33 (m, 4H), 0.83 (t, J = 7.2 Hz, 6H); \textsuperscript{13}C NMR (100 MHz, DMSO–\textit{d}_{6}) \delta 165.1, 152.0, 143.8, 134.0, 130.4, 124.2, 120.6, 113.1, 103.3, 76.2, 70.5, 70.3, 69.9, 68.8, 64.5, 64.4, 31.8, 31.7, 19.3, 14.2; LR-MS(ESI) m/z Calcd for C_{41}H_{56}N_{2}O_{11} [M-H\textsuperscript{+}]: 751.38, found: 751.36 ; Anal. Calcd for C_{41}H_{56}N_{2}O_{11}: C, 65.4; H, 7.5; N, 3.7; found: C, 65.5; H, 7.5; N, 3.7%

4f: Mp 149 ~ 152 °C; \textsuperscript{1}H NMR (400 MHz, DMSO–\textit{d}_{6}) \delta 8.73 (s, 2H, NH), 7.99 (d, J = 9.6, 2H), 7.39 (d, J = 7.6, 2H), 7.38 (s, 2H), 5.48 (s, 2H, OH), 1.49 (s, 12H); \textsuperscript{13}C NMR (100 MHz, DMSO–\textit{d}_{6}) \delta 152.0, 138.3, 131.3, 128.8, 126.5, 122.8, 115.1, 103.0, 75.5, 63.9, 31.4; Anal. Calcd for C_{23}H_{22}Cl_{2}N_{2}O_{3}: C, 62.0; H, 5.0; N, 6.3. Found: C, 62.0; H, 4.9; N, 6.3%

4g: Mp:114 ~ 117 °C; \textsuperscript{1}H NMR (400 MHz, DMSO–\textit{d}_{6}) \delta 8.54 (s, 2H, NH), 7.92 (d, J = 8.4, 2H), 7.41 (s, 2H), 7.39 (d, J = 9.0, 2H), 5.15 (s, 2H, OH), 1.65 (t, J = 6.8, 8H), 0.96 (t, J = 7.2, 12H); \textsuperscript{13}C NMR (100 MHz, DMSO–\textit{d}_{6}) \delta 152.0, 138.2, 131.3, 128.8, 126.7, 123.0, 115.7, 100.9, 77.8, 70.7, 33.6, 8.5;
LR-MS(ESI) m/z Calcd for C_{27}H_{30}Cl_2N_2O_3 [M-H^+] : 499.16, found : 499.07; Anal. Calcd for C_{27}H_{30}Cl_2N_2O_3: C, 64.6; H, 6.0; N, 5.5. Found: C, 64.7; H, 6.0, N, 5.6%

4h: Mp 70 ~ 72 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.78 (s, 2H, NH), 7.94 (d, \(J = 8.8\), 2H), 7.38 (m, 4H), 5.44 (s, 2H, OH), 1.93 (m, 2H), 1.57 (d, \(J = 6.0\), 4H), 1.57 (s, 6H), 0.94 (d, \(J = 6.8\), 12H), \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 152.0, 138.2, 131.1, 128.8, 126.6, 122.9, 115.5, 102.5, 76.8, 66.7, 51.6, 30.6, 34.4, 24.2, 24.1; LR-MS(ESI) m/z Calcd for C_{29}H_{34}Cl_2N_2O_3 [M-H^+] : 527.19, found : 527.12; Anal. Calcd for C_{29}H_{34}Cl_2N_2O_3: C, 66.8; H, 6.5; N, 5.2. Found: C, 65.8; H, 6.5, N, 5.3%

2. X-ray crystallographic analysis

Complex 4f • TBA^+Cl^- : Single crystals were grown as follow: 4f (10 mg) and TBA^+Cl^- (3 equiv) were dissolved in 50:1 (v/v) toluene/CH_2Cl_2 (10 ml) and \(n\)-heptane was added to the solution until no precipitate was formed. Slow diffusion of \(n\)-heptane into a toluene/CH_2Cl_2 solution over a few days yielded single crystals suitable for the X-ray diffraction.

A crystal of complex 4f • TBA^+Cl^- was coated with paratone oil and the diffraction data measured at 193 K with Mo K\(\alpha\) radiation on an X-ray diffraction camera system using an imaging plate equipped with a graphite crystal incident beam monochromator. The RapidAuto software\[^{[S1]}\] was used for data collection and data processing. Structure was solved by direct method and refined by full-matrix least-squares calculation with the SHELXTL software package.\[^{[S2]}\]

One ligand, one chloride anion and one tetrabutylammonium cation were observed as an asymmetric unit. A terminal methyl residue of the tetrabutylammonium cation is statistically disordered. All non-hydrogen atoms are refined anisotropically; the hydrogen atoms were assigned isotropic displacement coefficients U(H) = 1.2U (C) and 1.5U (C methyl), and their coordinates were allowed to ride on their respective atoms. All hydrogen atoms involved in hydrogen bonding interaction with the chloride anion are found in difference Fourier map and refined with isotropic

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displacement coefficients.

Final least-squares refinement of the structure converged at a final $R_1 = 0.0497$ and $wR_2 = 0.1120$ for 4808 reflections with $I > 2\sigma(I)$; $R_1 = 0.1247$ and $wR_2 = 0.1503$ for all 9561 reflections. The largest different peak and hole were 0.390 and $-0.417 \text{ e}\cdot\text{Å}^{-3}$, respectively.

A summary of the crystal and some crystallography data is given in Table S1. CCDC-875574 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK.

![Figure S1. Top view (left) and side view (right) of ORTEP plots for the crystal structure of $4f\cdot\text{TBA}^+\text{Cl}^-$ with 50% probability ellipsoids. The counter cation and CH hydrogen atoms were all omitted for clarity.](image)

**Table S1.** Crystal data and structure refined for $4f\cdot\text{TBA}^+\text{Cl}^-$.  

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<td>Density (calculated)</td>
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Absorption coefficient 0.256 mm\(^{-1}\)
F(000) 1552
Crystal size 0.29 x 0.22 x 0.16 mm\(^3\)
Theta range for data collection 3.18 to 27.48°.
Index ranges -17<=h<=17, -24<=k<=24, -22<=l<=21
Reflections collected 40579
Independent reflections 9561 [R(int) = 0.0806]
Completeness to theta = 27.48° 99.6 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 0.9602 and 0.9294
Refinement method Full-matrix least-squares on F\(^2\)
Data / restraints / parameters 9561 / 0 / 469
Goodness-of-fit on F\(^2\) 1.056
Final R indices [I>2sigma(I)] R1 = 0.0497, wR2 = 0.1120
R indices (all data) R1 = 0.1247, wR2 = 0.1503
Extinction coefficient 0.0037(5)
Largest diff. peak and hole 0.390 and -0.417 e.Å\(^{-3}\)

Table S2. Hydrogen bonds length and bonds angles for 4f•TBA\(^+\)Cl\(^-\) [Å and °].

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<th>d(H...A)</th>
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<td>3.121(2)</td>
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3. Binding study

$^1$H NMR titrations: Each stock solution of receptor ($5.0 \times 10^{-4}$ M) and TBA$^+\text{Cl}^-$ ($5.0 \times 10^{-3}$ M) was prepared in 1% (v/v) H$_2$O/CD$_3$CN ($5.0 \times 10^{-4}$ M) at 24 ± 1 °C. The $^1$H NMR spectrum of receptor (500 µL) was taken first to determine the chemical shift of free host, and then aliquots of TBA$^+\text{Cl}^-$ (at first 10 µL and finally 200 µL) were added to the receptor stock solution and the spectrum was recorded after each addition. The association constant ($K_a$, M$^{-1}$) was determined by non-linear least square fitting of the titration curve$^{[S3]}$ as show below.

![1H NMR spectral changes of 4a upon addition of TBA$^+\text{Cl}^-$](Image)

**Figure S2.** $^1$H NMR spectral changes of 4a upon addition of TBA$^+\text{Cl}^-$ (top), and titration curves (bottom) plots for NH (left) and OH (right): the experimental data (dots) are fitted to theoretical ones (lines) with the association constant, $K_a = (5.1 \pm 0.6) \times 10^3$ M$^{-1}$.

Figure S3. $^1$H NMR spectral changes of 4b upon addition of TBA$^+\text{Cl}^-$ (top), and titration curves (bottom) plots for NH (left) and OH (right): the experimental data (dots) are fitted to theoretical ones (lines) with the association constant, $K_a = (8.5 \pm 0.2) \times 10^3 \text{M}^{-1}$. 
Figure S4. $^1$H NMR spectral changes of 4c upon addition of TBA$^-$Cl$^-$ (top), and titration curves (bottom) plots for NH (left) and OH (right): the experimental data (dots) are fitted to theoretical ones (lines) with the association constant, $K_a = (8.0 \pm 0.1) \times 10^3 \text{M}^{-1}$. 
Figure S5. $^1$H NMR spectral changes of 4d upon addition of TBA$^+$Cl$^-$ (top), and titration curves (bottom) plots for NH (left) and OH (right): the experimental data (dots) are fitted to theoretical ones (lines) with the association constant, $K_a = (9.2 \pm 0.1) \times 10^3 \text{M}^{-1}$. 
Figure S6. $^1$H NMR spectral changes of 4e upon addition of TBA$^+$Cl$^-$ (top), and titration curves (bottom) plots for NH (left) and OH (right): the experimental data (dots) are fitted to theoretical ones (lines) with the association constant, $K_a = (8.7 \pm 0.2) \times 10^3$ M$^{-1}$. 
Figure S7. $^1$H NMR spectral changes of 4f upon addition of TBA$^+$Cl$^-$ (top), and titration curves (bottom) plots for NH (left) and OH (right): the experimental data (dots) are fitted to theoretical ones (lines) with the association constant, $K_a = (1.7 \pm 0.1) \times 10^4$ M$^{-1}$. 
Figure S8. $^1$H NMR spectral changes of 4g upon addition of TBA$^+$Cl$^-$ (top), and titration curves (bottom) plots for NH (left) and OH (right): the experimental data (dots) are fitted to theoretical ones (lines) with the association constant, $K_a = (1.3 \pm 0.1) \times 10^4$ M$^{-1}$.
Figure S9. $^1$H NMR spectral changes of 4h upon addition of TBA$^+$Cl$^-$ (top), and titration curves (bottom) plots for NH (left) and OH (right): the experimental data (dots) are fitted to theoretical ones (lines) with the association constant, $K_a = (1.7 \pm 0.1) \times 10^4 \text{M}^{-1}$. 
4. Transport experiments

1) Preparation of POPC vesicles

The solution of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) (Avanti) in chloroform was evacuated and dried under vacuum for 6 h to form a lipid thin film. The film was rehydrated by vortexing for 5 min with the internal solution (200 mM NaNO₃ and 1mM lucigenin and 10 mM phosphate buffer, pH 7.2). Then, the lipid suspension was to complete eight freeze–thaw cycles and allowed to age for 1 h at room temperature followed by extruding 27 times through a 200 nm polycarbonate membrane (Avanti, The Mini-Extruder set). The resulting vesicles were separated from unencapsulated lucigenin by the Sephadex G-50 column (eluent 200 mM NaNO₃ and 10 mM phosphate buffer, pH 7.2).

2) Transport Experiments

Unilamellar POPC vesicles, prepared as described above, were diluted in an external solution (200 mM NaNO₃ and 10 mM phosphate buffer, pH 7.2) to the lipid concentration was 1 mM. 2 mL of POPC stock solution was transferred to the cuvette and 30 µL of 2 M NaCl and DMSO solution of receptor were added to start the experiment. The chloride influx to the lipid bilayer was detected by fluorescence spectrophotometer. After 400 s, 10% Triton X-100 was added to lipid solution to lyse the vesicles.
**Figure S10.** Transport experiments with vesicles containing 100 mM Na$_2$SO$_4$, 1 mM lucigenin and 10 mM phosphate buffer pH 7.2, and suspended in phosphate buffer solution (pH = 7.2) containing 200 mM NaNO$_3$ and 30 mM NaCl. The DMSO solution of receptor 4h (1 mol% relative to POPC) was injected at 0 s. Sulfate is a highly polar anion and challenging to pass through the lipid membrane.

**Figure S11.** Transport experiments with vesicles containing 200 mM NaNO$_3$, 1 mM lucigenin and 10 mM phosphate buffer pH 7.2, and suspended in phosphate buffer solution (pH = 7.2) containing 200 mM NaNO$_3$ and 30 mM NaCl or KCl. The DMSO solution of receptor 4h (1 mol% relative to POPC) was injected at 0 s.
Figure S12. Transport experiments with the different amounts of 4h (POPC/4h 100:1 to 1600:1) in the vesicles containing 200 mM NaNO₃, 1 mM lucigenin and 10 mM phosphate buffer pH 7.2, and suspended in phosphate buffer solution (pH = 7.2) containing 200 mM NaNO₃ and 30 mM NaCl.

At each receptor concentration, the reaction rate was calculated by first order integrated rate expression.

\[
\frac{(I_0-I_f)}{(I_0-I_f)} = 1 - e^{-k_{abs}t}
\]

Figure S13. A Plot of transport rates versus concentrations of 4h.