Supporting Information
for
Synthesis of uniform cyclodextrin thioethers
to transport hydrophobic drugs

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Experimental procedures for CD derivatives 1b₂, 3a₁, 4a₁,
3b₂, 4b₁, and 3c₁

1b₂: Heptakis(6-deoxy-6-ethylsulfanyl)-β-cyclodextrin

4.00 g (2.54 mmol) heptakis-(6-deoxy-6-bromo)-β-cyclodextrin was added to a
solution of 100 mL DMF and 4.49 g (53.38 mmol, 21 equiv) sodium ethanethiolate
under vigorously stirring. The reddish brown solution is stirred for another 120 h at 90 °C. After cooling down to rt, the product is precipitated in 1.3 L of ice water and stirred for another 2.5 h. A white solid (3.15 g, 86%) is obtained after filtration and drying in vacuo.

\[^1\text{H-NMR:}\] \[\delta/\text{ppm (DMSO-}d_6, 400 \text{ MHz) = 1.17 (dd, 3H, H-8, }^2\text{J=4.8 Hz, }^3\text{J=6 Hz), 2.59 (q, 2H, H-7, }^2\text{J=4.8 Hz, }^3\text{J=12 Hz), 2.78-2.83 (dd, 1H, H-6b, }^2\text{J=8 Hz, }^3\text{J=12 Hz), 3.09 (d, 1H, H-6a, }^3\text{J=8 Hz), 3.35-3.37 (m, 2H, H-2,4), 3.61 (dd, 1H, H-3, }^2/3\text{J=8 Hz,), 3.76-3.79 (m, 1H, H-5), 4.89 (d, 1H, H-1, }^3\text{J=4 Hz), 5.86 (bs, 1H, OH-3), 5.94 (bs, 1H, OH-2).\]

\[^{13}\text{C-NMR:}\] \[\delta/\text{ppm (DMSO-}d_6, 100 \text{ MHz) = 14.9 (C-8), 26.3 (C-7), 32.9 (C-6), 71.4 (C-5), 72.3 (C-2), 72.6 (C-3), 84.9 (C-4), 102.0 (C-1).}\]

\[^{\text{MS(ESI):}}\] m/z = 1465.43 [M+Na]^+.\]

\[^{\text{CHN:}}\] for C\textsubscript{56}H\textsubscript{98}O\textsubscript{28}S\textsubscript{7} (M = 1443.82 g/mol)

Calculated: C (46.58 %), H (6.84 %)

Found: C (47.22 %), H (6.81 %).

**3a₁:** Hexakis[6-deoxy-6-methylsulfanyl-2-(2-(2-methoxyethoxy)ethoxy)ethyl]-α-cyclodextrin
0.82 g (20.5 mmol) NaH (60 wt % dispersion in mineral oil, Sigma-Aldrich) was washed twice with 10 mL of n-pentane under N₂ and stirred at rt for 1 h. After addition of 1.96 g (1.7 mmol) hexakis(6-deoxy-6-methylsulfanyl)-α-CD dissolved in 50 mL of DMF, 5.62 g (20.5 mmol) 2-(2-(2-methoxyethoxy)ethoxy)ethyl iodide and 7 mg (0.016 mmol) tetra-n-butylammonium iodide were added and the resulting reaction mixture was stirred at 60 °C under N₂ for 6 d. The reaction was quenched by addition of 10 mL of methanol and stirred at rt for further 30 min. The solvents were completely removed by vacuum distillation (bath temperature 70 °C, 1 mbar) and the residue was dissolved in 40 mL of water and neutralized by addition of 1 M HCl. The crude product was purified by nanofiltration in water (500 Da, Nadir PM NP030, Microdyn-Nadir GmbH, Wiesbaden, Germany) and a yellowish oil (1.44 g, 42%) was obtained after lyophilization.

\[^{1}H\text{-NMR}\quad \delta/\text{ppm (DMSO-d}_6, 400 \text{ MHz)} \quad = \quad 5.00 \text{ (bs, 1H, H-1)}, \quad 4.61 \text{ (bs, 1H, OH-3)}, \quad 3.89-3.95 \text{ (m, 1H, H-8a)}, \quad 3.78-3.80 \text{ (m, 1H, H-5)}, \quad 3.81 - 3.86 \text{ (m, 1H, H-3)}, \quad 3.71-3.77 \text{ (m, 1H, H-8b)}, \quad 3.50-3.55 \text{ (m, 10H, H-10, 11, 12, 13)} \quad 3.43-3.45 \text{ (m, 1H, H-4)}, \quad 3.41 - 3.42 \text{ (m, 2H, H-9)}, \quad 3.34 - 3.37 \text{ (m, 1H, H-2)}, \quad 3.23 \text{ (s, 3H, O-CH}_3\text{)}, \quad 3.05-3.08 \text{ (m, 1H, H-6a)}, \quad 2.74-2.79 \text{ (m, 1H, H-6b)}, \quad 2.07 \text{ (s, 3H, H-7).}

\[^{13}C\text{-NMR}: \quad \delta/\text{ppm (DMSO-d}_6, 100 \text{ MHz)} \quad = \quad 100.2 \text{ (C-1)}, \quad 85.9 \text{ (C-4)}, \quad 80.2 \text{ (C-2)}, \quad 72.8 \text{ (C-3)}, \quad 71.3 \text{ (C-9)}, \quad 70.8 \text{ (C-8)}, \quad 70.7 \text{ (C-5)}, \quad 69.5-69.9 \text{ (C-10, C-11, C-12, C-13)}, \quad 58.1 \text{ (O-CH}_3\text{)}, \quad 35.1 \text{ (C-6)}, \quad 16.2 \text{ (C-7).}
4a₁: Hexakis[6-deoxy-6-methylsulfanyl-2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)ethyl]-α-cyclodextrin

0.42 g (10.4 mmol) NaH (60 wt % dispersion in mineral oil, Sigma-Aldrich) was washed twice with 10 mL of n-pentane under N₂ and stirred at rt for 1 h. After addition of 1.00 g (0.87 mmol) hexakis(6-deoxy-6-methylsulfanyl)-α-cyclodextrin dissolved in 50 mL of DMF, 2.25 g (10.4 mmol) 2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)ethyl iodide and 3 mg (0.008 mmol) tetra-n-butylammonium iodide were added and the resulting reaction mixture was stirred at 80 °C under N₂ for 7 d. The reaction was quenched by addition of 10 mL of methanol and stirred at rt for further 30 min. The solvents were completely removed by vacuum distillation (bath temperature 70 °C, 1 mbar) and the residue was dissolved in 50 mL of water and neutralized by addition of 1 M HCl. The crude product was purified by crossflow nanofiltration in water (1 kDa, Pall Minimate TFF Capsule) and a brown yellowish oil (0.204 g, 10%) was obtained after lyophilization.

TLC: \[ R_f (EE:iPrOH:NH₄OH:H₂O 7:7:5:2 v/v) = 0.58. \]

\(^1\)H-NMR \[ δ/\text{ppm} \ (\text{DMSO-d}_6, 400 \text{ MHz}) = 5.02 \ (d, 1H, H-1, \ ^3J= 3.0 \text{ Hz}), 4.64 \ (s, 1H, OH-3), 3.98-3.94 \ (m, 1H, H-8a), 3.85-3.81 \ (m, 1H, H-3), 3.81-3.77 \ (m, 1H, H-5), 3.77-3.74 \ (m, 1H, H-8b), 3.53-3.52 \ (m, 12H, H-9, H-10, H-11, H-12, H-13, H-14), 3.45-3.42 \ (m, 2H, H-15), 3.36-3.35 \ (m, 1H, H-2), \]
3.25 (s, 3H, O-CH₃), 3.10-3.07 (m, 1H, H-6a), 2.81-2.75 (m, 1H, H-6b), 2.09 (s, 3H, H-7).

δ/ppm (DMSO-d₆, 100 MHz) = 100.2 (C-1), 85.9 (C-4), 80.1 (C-2), 72.8 (C-3), 71.3 (C-9), 70.8 (C-8), 70.7 (C-5), 69.8-69.6 (C-10, C-11, C-12, C-13, C-14, C-15), 58.1 (O-CH₃), 35.2 (C-6), 16.2 (C-7).

m/z = 2316.49 [M+Na]⁺.

3b₂: Heptakis[6-deoxy-6-ethylsulfanyl-2-(2-(2-methoxyethoxy)ethoxy)ethyl]-β-cyclodextrin

0.358 g (9.70 mmol) NaH (60 wt % dispersion in mineral oil, Sigma-Aldrich) was washed twice with 10 mL of n-pentane under N₂ and stirred at rt for 1 h. After addition of 1.00 g (0.69 mmol) heptakis(6-deoxy-6-methylsulfanyl)-β-CD dissolved in 40 mL of DMF, 2.66 g (9.70 mmol) 2-(2-(2-methoxyethoxy)ethoxy)ethyl iodide and 3 mg (0.008 mmol) tetra-n-butylammonium iodide were added and the resulting reaction mixture was stirred at rt under N₂ for 3 d. The reaction was quenched by addition of 10 mL of methanol and stirred at rt for further 30 min. The solvents were completely removed by vacuum distillation (bath temperature 70 °C, 1 mbar) and the residue was dissolved in 40 mL of water and neutralized by addition of 1 M HCl. The crude product
was purified by crossflow nanofiltration in water (1kDa, Pall Minimate TFF Capsule) and a yellowish oil (1.51 g, 89%) was obtained after lyophilization.

^1H-NMR δ/ppm (DMSO-d₆, 400 MHz) = 5.03 (bs, 1H, H-1), 4.87 (bs, 1H, OH-3), 3.97-3.99 (m, 1H, H-9a), 3.72-3.78 (m, 3H, -CH₂-CH₂-O), 3.50 – 3.53 (m, 8H, -CH₂-CH₂-O), 3.39 – 3.44 (m, 4H, -CH₂-CH₂-O), 3.24 (s, 3H, O-CH₃), 3.03-3.06 (m, 1H, H-6a), 2.82-2.86 (m, 1H, H-6b), 2.58 (q, 2H, H-7), 1.63 (dd, 3H, H-8).

^13C-NMR: δ/ppm (DMSO-d₆, 100 MHz) = 100.4 (C-1), 85.1 (C-4), 80.6 (C-2), 72.5 (C-3), 71.3 (C-10), 71.1 (C-9) 70.7 (C-5), 69.6-69.9 (C-11, C-12, C-13, C-14), 58.1 (O-CH₃), 32.7 (C-6), 26.4 (C-7), 14.8 (C-8).

ESI-MS: m/z= 2489.00 [M+Na]^+.

4b₁: Heptakis[6-deoxy-6-methylsulfanyl-2-(2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)ethyl)]-β-cyclodextrin

0.36 g (8.92 mmol) NaH (60 wt % dispersion in mineral oil, Sigma-Aldrich) was washed twice with 10 mL of n-pentane under N₂ and stirred at rt for 1 h. After addition of 1.01 g (0.74 mmol) heptakis(6-deoxy-6-methylsulfanyl)-β-cyclodextrin dissolved in 50 mL of DMF, 2.84 g (8.92 mmol) 2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)ethyl
iodide and 3 mg (0.008 mmol) tetra-n-butylammonium iodide were added and the resulting reaction mixture was stirred at 80 °C under N₂ for 7 d. The reaction was quenched by addition of 10 mL of methanol and stirred at rt for further 30 min. The solvents were completely removed by vacuum distillation (bath temperature 70 °C, 1 mbar) and the residue was dissolved in 50 mL of water and neutralized by addition of 1 M HCl. The crude product was purified by crossflow nanofiltration in water (1 kDa, Pall Minimate TFF Capsule) and a brown yellowish oil (0.277 g, 14%) was obtained after lyophilization.

¹H-NMR \[\delta/\text{ppm} \ (\text{DMSO-d}_6, \ 400 \text{ MHz}) = 5.03 \ (d, 1\text{H}, \ H-1, \ ^3J = 3.0 \text{ Hz}), \ 4.89 \ (s, \ 1\text{H}, \ OH-3), \ 4.00-3.94 \ (m, \ 1\text{H}, \ H-8a), \ 3.78-3.70 \ (m, \ 1\text{H}, \ H-8b), \ 3.53-3.50 \ (m, \ 12\text{H}, \ H-9, \ H-10, \ H-11, \ H-12, \ H-13, \ H-14), \ 3.44-3.38 \ (m, \ 4\text{H}, \ H-2, \ H-4, \ H-15), \ 3.24 \ (s, \ 3\text{H}, \ O-\text{CH}_3), \ 3.10-3.06 \ (m, \ 1\text{H}, \ H-6a), \ 2.78-2.69 \ (m, \ 1\text{H}, \ H-6b), \ 2.08 \ (s, \ 3\text{H}, \ H-7).\]

¹³C-NMR: \[\delta/\text{ppm} \ (\text{DMSO-d}_6, \ 100 \text{ MHz}) = 100.6 \ (C-1), \ 85.6 \ (C-4), \ 80.6 \ (C-2), \ 72.6 \ (C-3), \ 71.3 \ (C-9), \ 70.8 \ (C-8), \ 70.7 \ (C-5), \ 69.8-69.6 \ (C-10, \ C-11, \ C-12, \ C-13, \ C-14, \ C-15), \ 58.1 \ (O-\text{CH}_3), \ 35.1 \ (C-6), \ 16.0 \ (C-7).\]

ESI-MS: \[m/z = 2699.55 [\text{M+Na}]^+.\]
3c₁: Octakis[6-deoxy-6-methylsulfanyl-2-(2-(2-methoxyethoxy)ethoxy)ethyl]-γ-cyclodextrin

0.418 g (10.4 mmol) NaH (60 wt % dispersion in mineral oil, Sigma-Aldrich) was washed twice with 10 mL of n-pentane under N₂ and stirred at r.t. for 1 h. After addition of 1.01 g (0.65 mmol) octakis(6-deoxy-6-methylsulfanyl)-γ-cyclodextrin dissolved in 50 mL of DMF, 2.90 g (10.6 mmol) 2-(2-(2-methoxyethoxy)ethoxy)ethyl iodide and 3 mg (0.008 mmol) tetra-n-butylammonium iodide were added and the resulting reaction mixture was stirred at 60°C under N₂ for 4 d. The reaction was quenched by addition of 10 mL of methanol and stirred at r.t. for further 30 min. The solvents were completely removed by vacuum distillation (bath temperature 70 °C, 1 mbar) and the residue was dissolved in 50 mL of water and neutralized by addition of 1 M HCl. The crude product was purified by crossflow nanofiltration in water (1 kDa, Pall Minimate TFF Capsule) and a yellowish oil (1.57 g, 89%) was obtained after lyophilization.

TLC: R₁ (EE:iPrOH:NH₄OH:H₂O 7:7:5:2 v/v) = 0.82.

¹H-NMR δ/ppm (DMSO-d₆, 400 MHz) = 5.10 (d, 1H, H-1, 3J =3.0 Hz), 4.84 (bs, 1H, OH-3), 3.92-3.96 (m, 1H, H-8a), 3.76-3.80 (m, 1H, H-8b), 3.73-3.76 (m, 1H, H-5), 3.68-3.70 (m, 1H, H-3), 3.50-3.53 (m, 8H, H-10, 11, 12, 13)
3.41-3.44 (m, 1H, H-9), 3.38–3.41 (m, 2H, H-2), 3.35–3.38 (m, 1H, H-4),
3.23 (s, 3H, O-CH$_3$), 3.05-3.10 (m, 1H, H-6a), 2.71-2.76 (m, 1H, H-6b),
2.09 (s, 3H, H-7).

$^{13}$C-NMR: δ/ppm (DMSO-d$_6$, 100 MHz) = 99.8 (C-1), 84.1 (C-4), 80.7 (C-2), 72.3 (C-3),
71.3 (C-9), 71.0 (C-8) 70.7 (C-5), 69.5-69.9 (C-10, C-11, C-12, C-13),
58.0 (O-CH$_3$), 35.1 (C-6), 16.1 (C-7).

ESI-MS: m/z = 2729.32 [M+Na]$^+$. 