Supporting information for: Cyclodextrin Ion Channels
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General Information

Reagents and general chemicals were purchased from Aldrich. Unless specified, all solvents were used as supplied without further purification. Analytical thin-layer chromatography (TLC) was performed on E. Merck aluminium-backed silica gel (Silica Gel F254); compounds were identified by charring with a solution of paranilaldehyde in aqueous sulfuric acid and ethanol. NMR spectra were recorded with either (i) a Bruker AMX spectrometer operating at 300 MHz for \(^1\)H nuclei, 75 MHz for \(^13\)C nuclei, and 282MHz for \(^19\)F nuclei, or (ii) a Bruker AMX spectrometer operating at 500MHz for \(^1\)H nuclei, and 126 MHz for \(^13\)C nuclei. Low resolution mass spectra were recorded with a Q-TOF II (MicroMass/Waters, Milford MA) with 4000m/z max quadrapole. Samples were prepared as 1mg/ml solutions in acetonitrile:water, and diluted by a factor of ten; 0.1% trifluoroacetic acid was added to generate more ions. High resolution mass spectra (accurate to 0.5 ppm) were obtained on an LTQ Orbitrap Velos from Thermo Scientific with 200-2000 mass range and 300 nL/min liquid infusion with samples prepared as 10 ng/µL solutions in methanol.

Per-6'-azido \(\alpha\)- and \(\beta\)-cyclodextrins were prepared as described in Ashton et al.¹

Cyclodextrin Channel Precursors- single tailed

4-Aminoethynylbenzene and ethisterone (P1) were commercially available. The cholate propargyl ester P2 was prepared as described by Zhang et al² with the modifications given below. Alkynes P3 – P11 were prepared by acylation.

![Chemical structures](image-url)
**General procedure**, illustrated with compound **P9**.

In a flame-dried 25ml round-bottom flask equipped with a septum and stir bar, anhydrous K$_2$CO$_3$ (1.22g, 8.9mmol, 1.5 eqv.) and hex-5-yn-1-amine (579mg, 5.9mmol, 1.0 eqv.) was slurried in dry THF and cooled to 0°C. Per-fluoropentanoyl chloride (2.5g, 8.9mmol, 1.5 eqv.) was added drop-wise to the rapidly stirred solution. The reaction was allowed to warm to room temperature. After 2 hours, the reaction was quenched by careful addition of MeOH before filtering. The solvent was carefully removed under reduced pressure (the product is slightly volatile). Chromatography on silica gel with 1:5 EtOAc:Hex as eluent gives 273mg product (40%) as a clear, colorless oil.

**P3:**

MS - m/z calculated for C$_{13}$H$_{14}$O$_2$ = 202.1; found 202.0; $^1$H - (300 MHz; CDCl$_3$): δ8.01 (s, 2H), 7.42 (s, 4H), 4.34 (s, 2H), 2.27 (d, J = 2.7, 2H), 1.95 (s, 1H), 1.92-1.84 (m, 2H), 1.71-1.66 (m, 2H); $^{13}$C-NMR (75MHz; CDCl$_3$): δ166.6, 132.9, 130.6, 129.5, 128.3, 83.9, 64.4, 27.8, 25.1, 18.1.

Fig. S1: $^1$H-NMR and $^{13}$C- spectra of P3
P4

$^1$H-NMR (300 MHz; CDCl$_3$): $\delta$ 4.03 (t, J = 6.4, 2H), 2.21 (t, J = 7.4, 3H), 2.17 (td, J = 7.2, 2.4, 3H), 1.89 (t, J = 2.7, 1H), 1.72-1.51 (m, 7H), 0.88 (t, J = 7.4, 3H); $^{13}$C-NMR (126MHz; CDCl$_3$): $\delta$ 173.5, 83.8, 69.1, 63.8, 36.3, 27.5, 25.3, 18.8, 17.4, 13.8.

Fig. S2: $^1$H-NMR and $^{13}$C- spectra of P4
**P5**

MS - m/z calculated for C\textsubscript{10}H\textsubscript{17}NO = 167.1; found 168.0; \textsuperscript{1}H-NMR (300 MHz; CDCl\textsubscript{3}): \( \delta \) 5.52 (s, 1H), 3.25 (q, J = 6.4, 2H), 2.19 (td, J = 6.7, 2.7, 2H), 2.11 (t, J = 7.5, 2H), 1.93 (t, J = 2.7, 1H), 1.67-1.52 (m, 6H), 0.91 (t, J = 7.4, 3H); \textsuperscript{13}C-NMR (75MHz; CDCl\textsubscript{3}): \( \delta \) 173.4, 84.0, 68.7, 38.86, 38.78, 28.7, 25.7, 19.2, 18.1, 13.8

Fig. S3: \textsuperscript{1}H-NMR and \textsuperscript{13}C- spectra of P5
**P6**

MS - m/z calculated for C$_{10}$H$_9$F$_7$O$_2$ = 294.0; found 293.8

$^1$H-NMR (300 MHz; CDCl$_3$): δ 4.40 (t, J = 6.4, 2H), 2.24 (td, J = 6.9, 2.7, 2H), 1.96 (t, J = 2.7, 1H), 1.92-1.83 (m, 2H), 1.66-1.56 (m, 2H); $^{19}$F (282 MHz; CDCl$_3$): delta -119.39 (q, J = 8.6, 1F), -127.02 (s, 1F). The terminal CF$_3$ is characteristically at higher chemical shift (ca. -80 ppm) than the range probed here (-100 to 200 ppm). The observed 9 Hz coupling is for $^4$J F-F; $^{13}$C-NMR (126 MHz; CDCl$_3$): delta 82.9, 69.3, 68.2, 27.2, 24.4, 18.0. Insufficient signal intensity for quaternary carbon detection.

Fig. S4: Partial $^{19}$F-NMR, $^1$H-NMR and $^{13}$C-NMR spectra of **P6**
**P7**

MS - m/z calculated for C_{10}H_{10}F_{7}NO = 293.0; found 293.0; ¹H-NMR (300 MHz; CDCl₃): δ 6.36 (s, br, 1H), 3.37 (dd, J = 6.8, 0.7, 2H), 2.19 (td, J = 6.7, 2.7, 2H), 1.92 (t, J = 2.7, 1H), 1.72-1.62 (m, 2H), 1.56-1.46 (m, 2H); ¹⁹F-NMR - (282 MHz; CDCl₃): delta -120.77 (q, J = 8.8, 2F), -127.03 (s, 2F). CF₃ fluorines were out of probed range; ¹³C-NMR (126MHz; CDCl₃): δ 157.7 (t), 118.8 (qt), 108.5 (tt), 83.7, 68.4, 39.4, 28.3, 25.5, 17.6.

Fig. S5: ¹H-NMR and ¹³C-NMR spectra of **P7**
**P8**

MS - m/z calculated for C_{11}H_{10}F_{9}NO = 343.0; found 342.9; ^1H-NMR (300 MHz; CDCl₃): δ 6.33 (s, A), 3.37 (q, J = 6.5 Hz, B), 2.19 (td, J = 6.7, 2.7 Hz, C), 1.91 (t, J = 2.7 Hz, D), 1.72-1.62 (m, E), 1.56-1.48 (m, F); ^19F-NMR - (282 MHz; CDCl₃): δ-119.94 (td, J = 12.0, 2.3 Hz, A), -123.42--123.55 (m, B), -125.90 (dt, J = 12.0, 7.7, 4.2 Hz, C); ^13C-NMR (126MHz; CDCl₃): δ 157.73 (t, J = 25.7 Hz, A), 83.73 (s, B), 69.33 (s, C), 39.88 (s, D), 28.16 (s, E), 25.52 (s, F), 18.17 (s, G).

Fig. S6: ^1H-NMR and Partial ^19F-NMR spectrum of P8
P9
MS - m/z calculated for C_{14}H_{22}O_4+H^+ = 255.15909; found 255.15912; \textsuperscript{1}H-NMR (500 MHz; CDCl\textsubscript{3}): \delta 4.10 (q, J = 7.1, 2H), 4.08 (q, J = 6.8, 2H), 2.30-2.28 (m, 4H), 2.21 (td, J = 6.9, 2.7, 2H), 1.94 (t, J = 2.7, 1H), 1.74-1.54 (m, 8H), 1.23 (t, J = 7.1, 3H); \textsuperscript{13}C-NMR (126MHz; CDCl\textsubscript{3}): \delta 173.3, 83.8, 68.7, 63.8, 60.3, 34.0, 27.7, 24.9, 24.4, 18.1, 14.2.

Fig. S7: \textsuperscript{1}H-NMR and \textsuperscript{13}C-NMR spectra of P9
**P10**

MS - m/z calculated for C_{14}H_{24}O_{2} = 224.2; found 224.2; \(^1^H\)-NMR (300 MHz; CDCl\(_3\)): \(\delta\) 4.02 (t, J = 6.4, 2H), 2.23 (septet, J = 7.4, 2H), 2.16 (td, J = 7.0, 2.7, 2H), 1.88 (t, J = 2.7, 1H), 1.68 (dd, J = 8.1, 0.9, 2H), 1.58-1.50 (m, 5H), 1.26-1.18 (m, 14H), 0.83-0.79 (m, 5H); \(^{13}\)C-NMR (75MHz; CDCl\(_3\)): delta 68.6, 63.7, 34.3, 31.6, 29.1, 28.9, 27.8, 24.9, 24.7, 22.6, 18.0. Neither of the quaternary carbons had enough intensity to be resolved from the baseline.

Fig. S8: \(^1^H\)-NMR and \(^{13}\)C-NMR spectra of **P10**
**P11**

MS - m/z calculated for C_{14}H_{25}NO = 223.2; found 223.0; $^1$H-NMR (300 MHz; CDCl$_3$): $\delta$ 5.40 (s, 1H), 3.21 (q, J = 6.4, 2H), 2.16 (td, J = 6.7, 2.7, 2H), 2.08 (t, J = 7.6, 2H), 1.88 (t, J = 2.7, 1H), 1.61-1.43 (m, 7H), 1.23 (t, J = 6.9, 8H), 0.81 (t, J = 6.8, 3H); $^{13}$C-NMR (126MHz; CDCl$_3$): $\delta$ 172.8, 83.8, 68.5, 39.1, 37.3, 31.7, 29.3, 29.0, 28.7, 25.83, 25.74, 22.5, 18.1, 14.1.

Fig. S9: $^1$H-NMR and $^{13}$C-NMR spectra of **P11**
In a flame-dried 50 mL flask equipped with a stir bar, 10 mL of dry CH₂Cl₂ was added, into which 5-aminohex-1yne (500 mg, 5.15 mmol, 1.0 eqv) was dissolved. Hexylisocyanate (656 mg, 5.15 mmol, 1.0 eqv) was then added, and the reaction mixture stirred at room temperature. After 1 hour, the solvent was removed under vacuum to give white needles. This was further purified by chromatography on silica gel (30 g, EtOAc:Hex 1:1) to give 990 mg of a white solid (85%).

MS (EI) - m/z calculated for C₁₃H₂₄N₂O = 224.2; found 224.0; ¹H-NMR (300 MHz; CDCl₃): δ 4.13 (s, 2H), 3.13 (q, J = 6.3, 2H), 3.08 (dd, J = 12.8, 7.1, 2H), 2.16 (td, J = 6.7, 2.7, 2H), 1.88 (t, J = 2.7, 1H), 1.57-1.40 (m, 12H), 1.26-1.21 (m, 7H), 0.82 (t, J = 6.7, 3H); ¹³C-NMR (126MHz; CDCl₃): δ 84.0, 68.7, 40.9, 40.1, 31.4, 30.0, 29.1, 26.4, 25.6, 22.4, 18.0, 14.1

Fig. S10: ¹H-NMR and ¹³C-NMR spectra of P₁₂
Coupling of propargyl amine to cholic acid follows a procedure modified from ref 2. Cholic acid (4.94 g, 12.1mmol, 1.0 equiv.), propargyl amine (1.0 g, 18.2mmol, 1.5 equiv.), and dimethylaminopyridine (0.148 g, 1.21mmol, 0.1 equiv.) were combined in 50 mL of dichloromethane, and this light yellow heterogenous solution was stirred at room temperature for 30 minutes, after which dicyclohexylcarbodimide (2.75 g, 13.3mmol, 1.1 equiv.) was added and the solution stirred for a further 24 hours. Directly applying the concentrated solution to a silica gel column, using 10% MeOH in CH₂Cl₂ as an eluent gives 5.4 g as a clear glass (34%).

MS - m/z calculated for C₂₇H₄₃NO₄⁺H⁺ = 446.327, C₂₇H₄₃NO₄⁺Na⁺ = 468.309; found 446.31, 468.24; ¹H-NMR (300 MHz; CDCl₃): δ 6.99 (s, 1H), 3.95 (s, br, 2H), 3.88 (s, br, 1H), 3.76 (s, br, 1H), 3.36 (s, br, 1H), 2.20 (t, J = 2.4, 1H), 2.21-2.01 (m, 5H), 1.82-1.19 (m, 19H), 0.94 (s, br, 5H), 0.82 (s, 3H), 0.60 (s, 3H). Signals are in general broad for this compound;

¹³C-NMR (126MHz; CDCl₃): δ 174.1, 80.2, 73.2, 72.1, 71.3, 68.3, 46.7, 46.1, 41.7, 39.2, 35.7, 34.6, 33.1, 31.4, 30.7, 28.8, 28.3, 27.7, 26.1, 23.2, 22.6, 17.7, 12.5.

Fig. S11: ¹H-NMR and ¹³C-NMR spectra of P2
Cyclodextrin Channel Precursors- twin tailed

General Procedure, illustrated with P14

In a 5mL flask equipped with a reflux condensor, the propargyl malonate ester (1.0 g, 5.88 mmol, 1.0 eqv) and 1-amino-3-ethoxypropane (1.4 g, 1.6 mL, 13.5mol, 2.3 eqv) was combined. The solution was heated to 100 °C for 4hours.On cooling, this mixture was directly chromatographed on silica gel (EtOAc:Hex 1:4, gradient to 4:1) to give 1.305 g of white needles (71%).

MS - m/z calculated for C_{16}H_{28}N_{2}O_{4}Na^+ = 335.1948; found 335.209; \textsuperscript{1}H-NMR (300 MHz; CDCl\textsubscript{3}): \delta 7.13 (s, br, 2H), 3.48-3.43 (m, 8H), 3.34 (q, J = 6.0, 4H), 3.08 (t, J = 7.6, 1H), 2.71 (dd, J = 7.6, 2.7, 2H), 2.03 (t, J = 2.6, 1H), 1.75 (quintet, J = 6.2, 4H), 1.18 (t, J = 7.0, 6H); \textsuperscript{13}C-NMR (75MHz; CDCl\textsubscript{3}): \delta 168.8, 80.6, 71.4, 69.2, 66.7, 53.7, 38.3, 29.1, 21.3, 15.4

Fig. S12: \textsuperscript{1}H-NMR and \textsuperscript{13}C-NMR spectra of P14
**P13**

MS - m/z calculated for C_{15}H_{32}N_{2}O_{2} + Na^+ = 331.2358; found 331.63; \(^1\)H-NMR (300 MHz; CDCl\(_3\)) \(\delta\) 6.91 (s, br, 2H), 3.22 (q, \(J = 6.4\), 4H), 3.15 (t, \(J = 7.6\), 1H), 2.72 (dd, \(J = 7.6\), 2.7, 2H), 2.03 (t, \(J = 2.6\), 1H), 1.50-1.45 (m, 4H), 1.31-1.22 (m, 12H), 0.85 (t, \(J = 6.8\), 6H); \(^{13}\)C-NMR (75MHz; CDCl\(_3\)): delta 169.1, 80.4, 71.1, 53.3, 39.8, 31.4, 29.3, 26.5, 22.5, 21.5, 14.0.

Fig. S13: \(^1\)H-NMR and \(^{13}\)C-NMR spectra of **P13**
**P15**

MS - m/z calculated for C₁₄H₂₄N₂O₄+Na⁺ = 307.163; found 307.16; **¹H-NMR (300 MHz; CDCl₃):** δ 6.98 (s, 2H), 3.44 (t, J = 5.9, 4H), 3.36 (q, J = 6.0, 4H), 3.32 (s, 6H), 3.09 (t, J = 7.5, 1H), 2.73 (dd, J = 7.5, 2.7, 2H), 2.04 (t, J = 2.7, 1H), 1.76 (qd, J = 6.4, 5.9, 4H); **¹³C-NMR (126MHz; CDCl₃):** δ 169.0, 80.6, 71.0, 70.9, 58.7, 52.9, 37.8, 29.0, 20.8.

Fig. S14: **¹H-NMR and **¹³C-NMR spectra of **P15
The monoprotected propylene diamine (P16) was prepared and purified as described. In a 25 mL flask equipped with a reflux condensor, P16 (6.0 g, 34.5 mmol, 2.5 equiv.) and dimethylpropargylmalonate (2.34 g, 13.8 mmol, 1.0 equiv.) was combined. The viscous, light-yellow oil was heated to reflux for 80 minutes; on cooling it solidifies to a brown-red solid. This solid is soluble in hot EtOAc and only sparingly soluble when cold. The product was first recrystallized from ethyl acetate (30 mL) to give a white powder, and then chromatographed (silica gel, 10% MeOH in dichloromethane) to give 1.43 g of a crystalline white solid (25%).

MS - m/z calculated for C_{22}H_{38}N_{4}O_{6}+H^+ = 455.3, found 455.3; $^1$H-NMR (300 MHz; CDCl$_3$): $\delta$ 3.26 (dt, J = 3.3, 1.6, 2H), 3.19-3.16 (m, 4H), 3.02 (t, J = 6.7, 4H), 2.66 (dd, J = 7.7, 2.7, 2H), 2.32 (t, J = 2.7, 1H), 1.60 (quintet, J = 6.7, 4H), 1.39 (s, 18H); $^{13}$C-NMR (175MHz; CDCl$_3$):$\delta$ 169.2, 156.7, 80.3, 79.1, 69.8, 52.2, 37.9, 36.3, 29.2, 26.4, 19.2

Fig. S15: $^1$H-NMR and $^{13}$C-NMR spectra of P17
A one-pot deprotection–coupling procedure was used in the preparation of bis-amides P18 and P19. **General procedure** illustrated for bis-butylamide P18. Carbamate P16 (200 mg, 0.44mmol, 1.0 eqv.) was stirred in 4 mL acetonitrile and 4 mL dichloromethane. Methanol (70 µL, 1.76mmol, 4.0 eqv.) was added, followed by NaI (263 mg, 1.76mmol, 4.0 eqv.), upon the addition of which the solution becomes homogenous. Butyryl chloride (249 µL, 3.52mmol, 8.0 eqv.) was added and the reaction vessel capped immediately, and stirred vigorously at room temperature for 40 minutes. Anhydrous K$_2$CO$_3$ (1.21 g, 8.8mmol, 20 eqv.) was added and let stir overnight, during which the color of the solution turns substantially lighter. The heterogeneous solution was filtered, solvent evaporated, and chromatographed (silica gel, gradient from 5% MeOH in CH$_2$Cl$_2$ to 10% MeOH in CH$_2$Cl) to yield 116 mg of a white powder (67%).

$^1$H-NMR (300 MHz; CDCl$_3$): $\delta$ 2.77-3.17 (m, 8H), 2.71 (dd, $J = 7.7$, 2.7, 2H), 2.37 (t, $J = 7.4$, 1H), 2.16 (t, $J = 7.4$, 4H), 1.72-1.57 (m, 8H), 0.94 (t, $J = 7.4$, 6H); $^{13}$C-NMR (75MHz; MeOD-d$_4$): $\delta$ 176.29, 176.20, 170.8, 81.6, 71.9, 54.2, 39.18, 39.13, 38.1, 37.78, 37.66, 30.3, 20.45, 20.40, 14.1. Slow amide rotation observed in methanol, resulting in double sets of certain peaks.

![Fig. S16: $^1$H-NMR and $^{13}$C-NMR spectra of P18](image-url)
P19

$^1$H-NMR (500 MHz; MeOH-d$_4$): δ 3.24 (dt, J = 6.7, 3.4, 4H), 3.20 (t, J = 6.8, 4H), 2.71 (dd, J = 7.7, 2.7, 2H), 2.37 (t, J = 2.6, 1H), 2.18 (t, J = 7.6, 4H), 1.68 (quintet, J = 6.8, 4H), 1.61 (dt, J = 15.0, 7.5, 4H), 1.36-1.29 (m, 9H), 0.92 (t, J = 7.1, 7H);

$^{13}$C-NMR (126MHz; CDCl$_3$); δ 81.7, 72.0, 54.5, 38.2, 37.8, 37.3, 32.7, 30.3, 26.9, 23.6, 20.6, 14.5

Fig. S17: $^1$H-NMR and $^{13}$C-NMR spectra of P19
Click Chemistry using Cul as Catalyst

**General procedure.** In a sample vial equipped with a stir-bar, alkyne (8.0 equiv., 1.15 equiv. per azide), per-6-azido α- or β-cyclodextrin (1.0 equiv.), and Cul (2.1 equiv., 0.3 equiv. per azide) were dissolved in 1:1 DMF:water. The sample vial was capped, sealed with teflon tape, and heated to 100°C. The solution remains heterogenous throughout. After 2 hours, the dark green-to-orange reaction mixture was cooled to room temperature, and directed applied on a silica gel column, using 10:2:1 acetonitrile:water:NH₄OH(aq) as eluent. The copper salt is retained as a thin blue band on top of the column. Evaporation of solvent with a stream of air gives desired products in 20-75% yields. Air evaporation is preferable to the usual procedure of rotary evaporation; some amphiphilic products foam under vacuum.

**βCD-Tz-6AmF5 from P8**

MS (MALDI-TOF) - m/z calculated for C₁₁₉H₁₃₃N₃₈F₆₃O₃₅+2H⁺ = 1856.9336. Found 1856.9341; ¹H-NMR (500 MHz; MeOH-d₄): δ 7.68 (s, A), 5.12 (d, J = 3.5 Hz, B), 4.54 (d, J = 12.3 Hz, C), 4.31 (dd, J = 14.4, 6.1 Hz, D), 4.14 (ddd, J = 9.5, 6.1, 3.2 Hz, E), 3.87 (t, J = 9.3 Hz, F), 3.43 (dd, J = 9.8, 3.4 Hz, G), 3.28 (t, J = 9.3 Hz, H), 2.58-2.51 (m, I), 1.59 (d, J = 4.8 Hz, J).

¹³C-NMR (126 MHz; MeOH-d₄): δ 159.26 (t, J = 25.8 Hz, A), 148.75 (s, B), 125.42 (s, C), 118.88 (qt, J = 287.9, 33.2 Hz, D), 114-106 (m, E, F, G'), 104.00 (s, G), 84.93 (s, H), 74.22 (s, I), 74.04 (s, J), 71.62 (s, K), 51.64 (s, L), 40.87 (s, M), 29.43 (s, N), 27.47 (s, O), 25.73 (s, P); ¹⁹F-NMR - (282 MHz; MeOH-d₄): δ -120.06--121.01 (m, A), -124.15--124.73 (m, B), -126.93--127.36 (m, C); Elemental Analysis - Expected C 38.50, H 3.61, N 10.56. Found C 37.59, H 3.73, N 10.40. Analysis for oxygen unavailable due to interference by fluorine.
Fig. S18: $^1$H-NMR spectrum of $\beta$CD-Tz-6AmF5

Fig. S19 $^{13}$C-NMR spectrum of $\beta$CD-Tz-6AmF5
Fig. S20: $^{19}$F-NMR spectrum of βCD-Tz-6AmF5
**βCD-Tz-Cholamide from P2**

MS - m/z calculated for C\textsubscript{231}H\textsubscript{364}N\textsubscript{28}O\textsubscript{56}+3Na\textsuperscript{3+} = 1498, C\textsubscript{231}H\textsubscript{364}N\textsubscript{28}O\textsubscript{56}+2Na+K\textsuperscript{3+} = 1504; found 1497.7, 1504.8; \textsuperscript{1}H-NMR (500 MHz; DMSO-d\textsubscript{6}): δ 8.15 (s, 1H), 7.71 (s, 1H), 5.07 (s, 1H), 4.44-4.01 (m, 7H), 3.77-3.61 (m, 3H), 3.27 (d, J = 59.3, 8H), 2.27-2.09 (m, 2H), 1.95 (s, 2H), 1.67 (t, J = 19.7, 5H), 1.39-1.14 (m, 10H), 0.89 (d, J = 5.3, 4H), 0.80 (s, 4H), 0.56 (s, 3H); \textsuperscript{13}C-NMR (500 MHz; DMSO-d\textsubscript{6}): δ 172.5, 144.4, 124.3, 101.5, 82.7, 72.3, 71.9, 71.1, 70.5, 66.4, 46.3, 45.8, 41.6, 41.4, 35.5, 34.9, 34.5, 33.8, 32.5, 31.7, 30.4, 28.6, 27.4, 26.3, 22.9, 22.7, 17.2, 12.4.

Fig. S21: \textsuperscript{1}H-NMR and \textsuperscript{13}C-NMR spectra of βCD-Tz-Cholamide
βCD-Tz-Ethisterone from P1

MS - m/z calculated for C_{180}H_{255}N_{22}O_{42}+2H^{+} = 1749.4478; found 1749.4511; ^1H-NMR (500 MHz; MeOH-d₄): δ 7.81 (s, V), 5.70 (s, U), 5.15 (d, J = 3.4 Hz, T), 4.77 (d, J = 12.8 Hz, S), 4.60 (s, R), 4.52 (d, J = 15.1 Hz, Q), 4.18-4.16 (m, P), 3.88 (t, J = 9.3 Hz, O), 3.40 (dd, J = 9.8, 3.3 Hz, N), 3.19 (t, J = 9.3 Hz, M), 2.52-2.44 (m, L), 2.26 (m, K), 2.14 (s, J), 2.00 (dd, J = 9.5, 3.3 Hz, I), 1.94-1.88 (m, H), 1.82-1.78 (m, G), 1.67-1.55 (m, F), 1.46-1.36 (m, E), 1.30-1.23 (m, D), 1.03-0.99 (m, C), 0.71-0.65 (m, B), 0.58-0.53 (m, A); ^13C-NMR (126 MHz; MeOH-d₄): δ 202.15 (A), 175.07 (B), 154.73 (C), 126.50 (D), 124.35 (E), 103.73 (F), 84.25 (G), 83.00 (H), 74.36 (I), 73.86 (J), 71.75 (K), 55.43 (L), 51.61 (M), 40.17 (N), 38.05 (O), 37.60 (P), 37.14 (Q), 34.94 (R), 34.31 (S), 34.02 (T), 33.35 (U), 25.08 (V), 21.96 (W), 17.86 (X), 15.15 (Y).

Fig. S22: ^1H-NMR spectrum of βCD-Tz-Ethisterone

Fig. S23: ^13C-NMR spectrum of βCD-Tz-Ethisterone
\textbf{αCD-Tz-Ethisterone} from \textit{P1}
MS - m/z calculated for C_{162}H_{222}N_{18}O_{36}+2H^{2+} = 1499.8153; found 1499.8164; \textsuperscript{1}H-NMR (500 MHz; MeOD-d_{4}/CDCl_{3}): \delta 7.76 (s, 1H), 5.69 (s, 1H), 5.10 (s, 1H), 4.54 (s, 1H), 4.40 (s, 1H), 4.08 (s, 1H), 3.95 (t, J = 9.2, 1H), 3.40-3.38 (m, 1H), 3.17 (s, 1H), 2.45 (m, 3H), 2.29-2.21 (m, 3H), 1.99-1.38 (m, 17H), 1.25-1.19 (m, 6H), 1.06-0.99 (m, 6H), 0.72-0.60 (m, 3H); \textsuperscript{13}C-NMR (126MHz; MeOD-d_{4}/CDCl_{3}): \delta 201.9, 174.8, 154.7, 125.9, 124.1, 103.3, 82.6, 74.3, 73.1, 54.9, 39.9, 37.2, 36.7, 34.7, 34.1, 33.8, 32.9, 24.8, 21.6, 17.9, 15.0.

Fig. S24: \textsuperscript{1}H-NMR and \textsuperscript{13}C-NMR spectrum of \textbf{αCD-Tz-Ethisterone}
Click Chemistry using CuSO$_4$ as Catalyst

*General procedure* illustrated with compound $\beta$CD-Tz-6AmF4. In a 1 dram sample vial equipped with a small stir-bar, alkyne P5 (250 mg, 0.814mmol, 7.7 eqv.), per-6-azido-$\beta$-cyclodextrin (139 mg, 0.106mmol, 1.0 eqv.), CuSO$_4$.5H$_2$O (21.3mg, 0.085mmol, 0.8 eqv.), sodium ascorbate (68 mg, 0.34mmol, 3.2 eqv.) were combined and dissolved in 2 mL DMSO. The resulting light-brown solution was left to stir at room-temperature for 24 hours. At the end of the reaction, the mixture was quenched into 100 mL ice-cold water; filtration gives a light green powder that was redissolved in methanol. Solid-liquid extraction by addition of Chelex-100 for a minimum of three times gives a clear, colorless solution, which was evaporated by a stream of air, chromatographed (silica gel, 20% MeOH: chloroform) to give 119 mg of a white powder (33%).
**βCD-Tz-6EsPh from P3**

MS - m/z calculated for C\textsubscript{133}H\textsubscript{161}N\textsubscript{21}O\textsubscript{42}+Na\textsuperscript{+} = 1374.5553; found 1374.5525. \textsuperscript{1}H-NMR (500 MHz; DMSO-d\textsubscript{6}): δ 7.84 (dd, J = 6.1, 2.2, 3H), 7.61-7.51 (m, 2H), 7.42-7.38 (m, 3H), 5.01 (s, 1H), 4.24-3.95 (m, 5H), 3.64 (s, 1H), 2.32 (s, 2H), 1.55 (t, J = 46.9, 5H). Possibly related to aggregate formation, the signals for \textbf{β}\textsuperscript{b}CD-Tz-6EsPh are extremely broad in both methanol-d\textsubscript{4} as well as DMSO-d\textsubscript{6}. \textsuperscript{13}C-NMR (126MHz; DMSO-d\textsubscript{6}): δ 166.3, 146.9, 133.8, 130.4, 129.7, 129.3, 123.9, 102.4, 83.6, 73.0, 72.6, 70.3, 65.0, 50.5, 28.5, 25.9, 25.0.

**Fig. S25:** \textsuperscript{1}H-NMR and \textsuperscript{13}C-NMR spectrum of \textbf{β}CD-Tz-6EsPh
**βCD-Tz-6Es4** from P4

MS - m/z calculated for C_{112}H_{175}N_{21}O_{42}^2+ = 1244.6191, found 1244.6167; \(^1^H\)-NMR (500 MHz; MeOD-d₄): δ 7.73 (s, 1H), 5.16 (d, J = 3.6, 1H), 4.39 (dd, J = 14.5, 5.7, 1H), 4.17 (ddd, J = 9.4, 5.6, 3.6, 1H), 4.08-4.02 (m, 2H), 3.90 (t, J = 9.3, 1H), 3.44 (dd, J = 9.8, 3.4, 1H), 2.60-2.48 (m, 2H), 2.27 (t, J = 7.3, 2H), 1.65-1.59 (m, 6H), 0.93 (t, J = 7.3, 3H); \(^1^3^C\)-NMR (126MHz; MeOD-d₄): δ 175.4, 148.7, 125.6, 103.7, 84.6, 74.3, 73.9, 71.8, 65.3, 51.5, 37.2, 29.4, 26.9, 25.9, 19.7, 14.2.

Fig. S26: \(^1^H\)-NMR and \(^1^3^C\)-NMR spectrum of **βCD-Tz-6Es4**
\textbf{βCD-Tz-6Am4 from P5}

MS - m/z calculated for C_{112}H_{182}N_{28}O_{35} + Na^+ = 2503.3, found 2503.4; $^1$H-NMR (500 MHz; MeOD-d$_4$): δ 7.75 (s, 1H), 5.17 (d, J = 3.6, 1H), 4.57 (d, J = 14.2, 1H), 4.43-4.41 (s, br, 1H), 4.22-4.19 (s, br, 1H), 3.90 (d, J = 8.3, 2H), 3.45 (d, J = 9.5, 1H), 3.14 (t, J = 6.3, 2H), 2.57 (s, br, 2H), 2.14 (t, J = 7.4, 2H), 1.61 (7, J = 7.4, 6H), 1.50 (6, J = 7.1, 2H), 0.92 (t, J = 7.4, 3H); $^{13}$C-NMR (126MHz; CDCl$_3$): δ 176.1, 148.9, 125.7, 103.7, 84.5, 74.3, 73.9, 71.6, 51.6, 40.6, 40.1, 39.2, 30.2, 27.9, 26.0, 20.6, 14.2

Fig. S27: $^1$H-NMR and $^{13}$C-NMR spectrum of βCD-Tz-6Am4
**βCD-Tz-6EsF4 from P6**

MS - m/z calculated for C_{112}H_{126}N_{21}F_{49}O_{42}+2Na^{2+} = 1707.4; found 1707; \(^1\)H-NMR (500 MHz; MeOD-d₄): \(\delta\) 7.74 (s, 1H), 5.17 (s, br, 1H), 4.55 (d, J = 12.9, 1H), 4.42-4.39 (m, 1H), 4.20 (s, br, 1H), 3.93 (t, J = 8.7, 1H), 3.53 (t, J = 6.4, 2H), 3.46-3.44 (m, 1H), 3.33-3.25 (m, 1H), 2.59-2.51 (m, 2H), 1.64-1.50 (m, 4H); \(^1^3\)C-NMR (126MHz; MeOD-d₄): \(\delta\) 163.1 (t, J = 24), 149.0, 125.6, 119.6 (qt, J = 286.81, 34.39), 110.4 (m, 112.75-107.96), 103.7, 84.5, 74.2, 73.9, 71.6, 62.7, 51.5, 33.3, 26.9, 26.1.

**Fig. S28:** \(^1\)H-NMR and \(^1^3\)C-NMR spectrum of βCD-Tz-6EsF4
\( \beta \text{CD-Tz-6Es6Es2 from P9} \)

MS - m/z calculated for C\(_{147}\)H\(_{231}\)N\(_{21}\)O\(_{56}\) = 3186.5876; found [M+H]\(^+\); \(^1\)H-NMR (500 MHz; CDCl\(_3\)): \( \delta \) 7.74 (s, 1H), 5.17 (s, 1H), 4.57-4.39 (m, 2H), 4.19 (s, 1H), 4.10 (q, J = 7.1, 4H), 4.04 (s, 2H), 3.93-3.89 (m, 2H), 3.46-3.44 (m, 1H), 2.56 (s, 2H), 2.32 (s, 6H), 1.63-1.61 (m, 11H), 1.23 (t, J = 7.1, 4H); \(^{13}\)C-NMR (126MHz; CDCl\(_3\)): \( \delta \) 175.21, 175.16, 148.7, 125.6, 103.7, 84.5, 74.3, 73.9, 71.7, 65.3, 61.6, 34.9, 29.4, 26.9, 26.0, 25.6, 14.8.

Fig. S29: \(^1\)H-NMR and \(^{13}\)C-NMR spectrum of \( \beta \text{CD-Tz-6Es6Es2} \).
**βCD-Tz-6Es8 from P10**

MS - m/z calculated for C_{140}H_{231}N_{21}O_{42}+2H^2+ = 1440.8388; found 1440.8376; $^1$H-NMR (500 MHz; MeOD-d$_4$): δ 7.73 (s, 1H), 5.16 (d, J = 3.6, 1H), 4.57-4.54 (m, 1H), 4.39 (t, J = 13.3, 1H), 4.17 (s, 1H), 4.03 (s, br, 2H), 3.91 (m, 1H), 3.45 (s, br, 1H), 2.57 (s, br, 2H), 2.27 (t, J = 7.7, 6H), 1.63-1.58 (m, 13H), 1.35-1.30 (m, 32H), 0.90 (d, J = 14.1, 11H); $^{13}$C-NMR (126MHz; MeOD-d$_4$): δ 178.5, 175.5, 148.7, 125.6, 103.7, 84.6, 74.3, 73.9, 71.7, 65.3, 51.6, 35.5, 35.3, 33.0, 30.41, 30.26, 26.4, 23.8, 14.6.

Fig. S30: $^1$H-NMR and $^{13}$C-NMR spectrum of βCD-Tz-6Es8
$\beta$CD-Tz-6Am8 from P11
MS - m/z calculated for C$_{140}$H$_{238}$N$_{26}$O$_{35}$+2H$^{2+}$ = 1437.3947; found 1437.3942; $^1$H-NMR (500 MHz; MeOD-d$_4$): $\delta$ 7.73 (s, 1H), 5.16 (d, J = 3.6, 1H), 4.57-4.54 (m, 1H), 4.41 (dd, J = 14.4, 5.4, 1H), 4.19-4.17 (m, 1H), 3.91 (t, J = 9.3, 1H), 3.44 (dd, J = 9.8, 3.3, 1H), 3.14 (t, J = 6.9, 2H), 2.57-2.52 (m, 2H), 2.16 (t, J = 7.6, 2H), 1.59 (dt, J = 14.3, 7.2, 5H), 1.49 (t, J = 7.2, 2H), 1.33-1.29 (m, 10H), 0.90 (q, J = 4.4, 3H); $^{13}$C-NMR (126MHz; CDCl$_3$): $\delta$ 176.3, 148.9, 125.6, 103.7, 84.5, 74.3, 73.9, 71.7, 51.6, 40.2, 37.4, 33.1, 30.5, 30.29, 30.15, 27.9, 27.3, 26.0, 23.8, 14.7.

*Fig. S31:* $^1$H-NMR and $^{13}$C-NMR spectrum of $\beta$CD-Tz-6Am8
**βCD-Tz-6Ur8 from P12**

MS - m/z calculated for C_{133}H_{231}N_{35}O_{35}+2H^{2+} = 1440.8781; found 1440.8781; \(^1\)H-NMR (500 MHz; MeOD-\(d_4\)): \(\delta\) 7.73 (s, 1H), 5.17 (s, 1H), 4.53 (d, J = 12.2, 1H), 4.40-4.38 (m, 1H), 4.19-4.17 (m, 1H), 3.91 (t, J = 9.1, 1H), 3.47-3.45 (m, 1H), 3.09 (t, J = 7.0, 4H), 2.52 (t, J = 8.0, 2H), 1.62-1.55 (m, 2H), 1.46 (q, J = 6.9, 4H), 1.35-1.31 (m, 6H), 0.90 (t, J = 6.9, 3H); \(^{13}\)C-NMR (126MHz; MeOD-\(d_4\)): \(\delta\) 161.4, 148.9, 125.6, 103.7, 84.5, 74.3, 73.9, 71.7, 51.5, 41.3, 40.9, 32.9, 31.5, 31.1, 27.8, 26.1, 23.8, 14.6.

Fig. S32: \(^1\)H-NMR and \(^{13}\)C-NMR spectrum of \(\beta\)CD-Tz-6Ur8
Click Chemistry using Cu/AlO(OH) as Catalyst

The preparation of catalyst $P_{20}$ proceeded as described Park et al. Briefly: CuCl$_2$·2H$_2$O (400 mg), EtOH (8.0 g), and pluronic P123 (4.0 g) were combined, the mixture was stirred at room temperature for 30 minutes, after which Al(sec-OBu)$_3$ (9.1 g, 37 mmole$^\dagger$) was added slowly. The heterogeneous solution was heated to 160 °C (reflux) for 3 h, and gelation was effected by dropwise addition of water (3.0 mL) through the top of the condenser. The reaction was stirred for another 30 minutes, cooled and kept at room temperature overnight. The baby-blue solid was filtered, washed with acetone, and dried in an oven overnight to give $P_{20}$ as a green solid. This insoluble solid is kept in the oven (120 °C) as it absorbs moisture readily to return to the blue color, and used as is without further characterization.

General procedure illustrated with compound $\beta$CD-Tz-MalAm3Am6. In a 1 dram sample vial, alkyne $P_{19}$ (93 mg, 0.206mmol, 8.0 equiv.), per-6-azido-$\beta$-cyclodextrin (33.7 mg, 0.0257mmol, 1.0 equiv.), Cu/AlO(OH) ($P_{20}$, 60mg), triethylamine (86 µL, 0.62mmol, 24 equiv.) was combined in 1 mL DMF to give a heterogenous solution. The sample vial was capped, sealed with teflon tape, and further wrapped with parafilm to prevent evaporation of triethylamine. The reaction was then heated to 80 °C in an oil bath, and the previously light-green heterogeneous solution turns to a dark-brown almost immediately at this temperature. This is allowed to stir for 24 hours. For workup, the reaction is first cooled to room temperature, and then centrifuged. The light brown solution, now free of solid catalyst, was chromatographed (silica gel, using dichloromethane:MeOH 9:1 gradient to 1:1 as eluent) to give 45 mg of a light-yellow crystalline material (39%).
**βCD-Tz-MalAm3Am6 from P19**

MS - m/z calculated for C_{210}H_{357}N_{49}O_{56} = 4461.6593; found [M+H]^+; \(^1\)H-NMR (300 MHz; CDCl\(_3\)): \(\delta\) 7.73 (s, 1H), 5.11 (s, 1H), 4.59 (s, 1H), 4.30 (s, 1H), 4.11 (s, 1H), 3.87-3.84 (m, 2H), 3.48-3.44 (m, 2H), 3.25-3.03 (m, 15H), 2.19 (t, J = 6.7, 6H), 1.69-1.68 (m, 5H), 1.61 (t, J = 7.1, 7H), 1.35-1.29 (m, 14H), 0.91 (t, J = 6.5, 10H); \(^{13}\)C-NMR (126MHz; CDCl\(_3\)): \(\delta\) 176.4, 171.6, 145.8, 126.4, 103.8, 84.6, 74.4, 73.9, 71.9, 38.5, 38.0, 37.4, 32.8, 30.48, 30.43, 27.0, 23.6, 14.6.

Fig. S33: \(^1\)H-NMR and \(^{13}\)C-NMR spectrum of βCD-Tz-MalAm3Am6
**βCD-Tz-MalAm3O1 from P15**

MS - m/z calculated for C_{340}H_{231}N_{35}O_{56}+H+Na^{2+} = 1661.3; found 1661.7; $^1$H-NMR (300 MHz; CDCl$_3$): δ 7.69 (s, 1H), 5.11 (d, J = 3.3, 1H), 4.55 (d, J = 9.0, 1H), 4.38 (d, J = 9.2, 1H), 4.14 (t, J = 4.1, 1H), 3.86 (t, J = 9.2, 1H), 3.64 (t, J = 7.6, 1H), 3.47-3.44 (m, 2H), 3.41-3.36 (m, 6H), 3.30 (s, 6H), 3.28-3.07 (m, 7H), 1.76-1.69 (m, 5H), 1.31 (t, J = 7.3, 2H).

Fig. S34: $^1$H-NMR spectrum of βCD-Tz-MalAm3O1
**CD-Tz-MalAm3O2 from P14**

MS - m/z calculated for $\text{C}_{158}\text{H}_{259}\text{N}_{35}\text{O}_{56} = 3494.849$; found [M+H]$^+$; $^1$H-NMR (500 MHz; MeOD): $\delta$ 7.70 (s, 1H), 5.11 (d, J = 3.3, 1H), 4.57 (d, J = 14.0, 1H), 4.39 (d, J = 8.8, 1H), 4.13 (s, 1H), 3.87 (t, J = 9.2, 1H), 3.67-3.60 (m, 2H), 3.51-3.41 (m, 12H), 3.27 (d, J = 11.9, 5H), 3.07 (s, 2H), 1.92 (s, 1H), 1.73 (dt, J = 17.0, 8.9, 4H), 1.17 (m, 6H); $^{13}$C-NMR (126MHz; CDCl$_3$): delta 171.3, 145.8, 126.0, 103.8, 84.6, 74.4, 73.9, 72.0, 69.3, 67.4, 55.0, 51.6, 38.44, 38.38, 38.30, 30.7, 15.8

Upon conjugation, the alkyl tails appear to have broken symmetry due to slow amide rotation. This is manifested in non-equivalent amide carbons (171 ppm), as well as overlapping terminal methyl proton triplets at 1.17 ppm.

![Fig. S35: $^1$H-NMR and $^{13}$C-NMR spectrum of βCD-Tz-MalAm3O2](image)

**References**