Design, synthesis and biological evaluation of water-soluble per-*O*-methylated cyclodextrin-C₆₀ conjugates as anti-influenza virus agents

Xiaolei Zhu ^a, Sulong Xiao ^c, Demin Zhou ^c, Matthieu Sollogoub ^a, Yongmin Zhang ^{a,b,*}

^a Sorbonne Universités, UPMC Univ Paris 06, Institut Parisien de Chimie Moléculaire, CNRS UMR 8232, 4 place Jussieu, 75005 Paris, France

^b Institute for Interdisciplinary Research, Jiangnan University, Wuhan Economic and Technological Development Zone, 430056 Wuhan, China

^c State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China

* Corresponding author.

E-mail: yongmin.zhang@upmc.fr

Abstract:

The most common fullerene member C₆₀ displays many biological applications, such as, anticancer, human immunodeficiency virus and hepatitis C virus inhibitors, O₂ uptake inhibitor and vectors for drug and DNA. Nevertheless, the innate hydrophobicity of C₆₀ constrains its further development. We introduced cyclodextrins to enhance the water-solubility of C₆₀. Nine cyclodextrin-C₆₀ conjugates, including seven α -cyclodextrin-C₆₀ conjugates and two γ -cyclodextrin-C₆₀ conjugates, were designed and synthesized. All of these conjugates did not show obvious cytotoxicity. The anti-influenza virus activity of nine conjugates was assessed. Two γ -cyclodextrin-C₆₀ conjugates, which were relatively more water-soluble, exerted higher inhibition with IC₅₀ values of 87.73 μ M and 75.06 μ M, respectively, than seven α -cyclodextrin-C₆₀ conjugates.

Keywords: Anti-influenza virus; Synthesis; Cyclodextrin-C₆₀ conjugates; Water-soluble

1. Introduction

Influenza is a common disease to both humans and animals. The respiratory diseases and secondary bacterial infection caused by influenza virus increase the life-threatening risk, especially for elder people [1]. There are three types of influenza viruses, which are A, B and C. Influenza virus A is the major one to cause morbidity and mortality. Currently, two classes of anti-influenza drugs (neuraminidase inhibitors and M2 ion channel protein inhibitors) have been approved by the FDA for the interruption of specific processes in influenza infection. However, the emergence of drug-resistant influenza viruses has limited the use of those drugs, illustrating the urgent need to develop novel anti-influenza drugs [2, 3].

C₆₀ serves as radical scavenger, reactive oxygen species (ROS) producer under irradiation, human immunodeficiency virus (HIV) and hepatitis C virus (HCV) inhibitors, O₂ uptake inhibitor, drug and DNA vectors [4, 5]. Nevertheless, its poor water-solubility limits the further development of C₆₀. The functionalization of C₆₀ not only ameliorates the water-solubility of C₆₀, but also gives a possibility to discover new application of C₆₀ in biology. Bis(phenethylamincuccinate) C₆₀ (**C1**) is firstly reported to inhibit HIV through interaction with the large hydrophobic pocket of HIV aspartic protease (**Figure 1**) [6]. Further study has shown that the modified C₆₀s with amino acid group (**C2** and **C3**) inhibit HIV reverse transcriptase and C₆₀ derivatives with quaternary ammonium salts (**C4** and **C5**) have HCV RNA-dependent RNA polymerase inhibition activities [7]. Fmoc protected C₆₀ derivative (**C6**) exhibits potent HIV aspartic protease inhibition [8]. Echegoyen, Llano *et al.* have characterized the mechanism of C₆₀ derivatives with quaternary ammonium salts in HIV inhibition. These derivatives prevent HIV-1 maturation with protease-independent way [25]. Even though some progress has been made by the aforementioned researches, the C₆₀ derivatives with structural novelty and their mechanism in virus inhibition are still open issues. Based on these studies, we choose cyclodextrins (CDs) as functionalization groups to enhance the water-solubility of C₆₀ and conduct research on other virus inhibition.

CDs, composed of 6, 7 and 8 saccharides (α -CD, β -CD and γ -CD, respectively), are ideal candidates to improve the water-solubility of C₆₀. Because of the relatively easy synthesis of β -CD derivatives, a lot of work was focused on β -CD-C₆₀ conjugates and β -CD/C₆₀ micelle, which displayed photodynamic activity on DNA cleavage and HeLa cells inhibition [9-12, 15]. γ -CD with the largest cavity is capable to encapsulate C₆₀ [13, 16]. γ -CD/C₆₀ complexes serve as photosensitizers and two γ -CD-C₆₀ conjugates generate the highest singlet oxygen compared to other CD-C₆₀ conjugates [14, 16-19].

There are few studies on α -CD-C₆₀ conjugates and their biological applications in the literature. We previously reported that α -CD-C₆₀ conjugate (**C7**) inhibits HCV entry into the host cells with IC₅₀ value of 0.17 μ M [5]. In order to increase the family of α -CD-C₆₀ conjugates, we designed and synthesized seven α -CD-C₆₀ conjugates (**Figure 2**). However, these α -CD-C₆₀ conjugates did not display the promising inhibitory activity against HCV (unpublished data). Here we evaluated the anti-influenza A/WSN/33 (H1N1) virus activity of seven α -CD-C₆₀ conjugates and two reported γ -CD-C₆₀ conjugates (**Figure 2**) [19].

Figure 1. The reported antiviral C_{60} derivatives

Figure 2. Nine CD- C_{60} conjugates

2. Results and discussion

2.1 Chemistry

Scheme 1. Synthetic routes of CD- C_{60} conjugates **1** and **2**. Reagents and conditions: (i) $\text{N}_3(\text{CH}_2)_6\text{OTs}$ or $\text{N}_3(\text{CH}_2)_{12}\text{OTs}$ or $\text{N}_3\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OTs}$, NaH, dry DMF, 80 °C, 72h; (ii) $\text{HS}(\text{CH}_2)_3\text{SH}$, dry Et_3N , dry MeOH, r.t., 7d; (iii) $(\text{HOOC}(\text{CH}_2)_6\text{OCO})_2\text{CH}_2$ or $(\text{HOOC}(\text{CH}_2)_{11}\text{OCO})_2\text{CH}_2$ or $(\text{HOOCCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCO})_2\text{CH}_2$, EDC HCl, HOBT, dry DCM, r.t.; (iv) CBr_4 (or I_2), DBU, C_{60} , dry PhMe, r.t.; (v) $\text{N}_3(\text{CH}_2)_6\text{OTs}$ or $\text{N}_3(\text{CH}_2)_{12}\text{OTs}$ or $\text{N}_3\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OTs}$, NaH, dry DMF, r.t., 6h; (vi) CH_3I , NaH, dry DMF, r.t., overnight; $\text{HS}(\text{CH}_2)_3\text{SH}$, dry Et_3N , dry MeOH, r.t., 7d.

As shown in **Scheme 1**, monol and diol of per-*O*-methylated CDs [20] were alkylated to obtain **5** and **8**, respectively. Because -OH at position 2 is more acidic than position 6 and position 3, the alkylation condition of diol per-*O*-methylated CDs is milder than that of monol of per-*O*-methylated CDs. The remaining OH group of compound **8** was methylated to give compound **9** quantitatively. The alkylated compounds were converted to amino CD derivatives **6** and **9**. Then, **6** and **9** were coupled with $(\text{HOOCR}_2\text{OCO})_2\text{CH}_2$, which gave dimer **7** and **10**, respectively. **7** and **10** were attached to C_{60} , yielding **1** and **2** via Bingel-Hirsch cyclopropanation.

The $\alpha\text{-CD}$ - C_{60} conjugates **3** and **4** with one $\alpha\text{-CD}$ moiety were synthesized through the same methodology (**Scheme 2**). Since the condensed compounds **11a** and **13a** with -OH groups could not be attached to C_{60} directly, the free -OH groups of **11a** and **13a** were first methylated, before C_{60} was conjugated with **12a** and **14a** to afford **3** and **4**, respectively.

Scheme 2. Synthetic routes of CD- C_{60} conjugates **3** and **4**. Reagents and conditions: (i) $(\text{HOOC}(\text{CH}_2)_6\text{OCO})_2\text{CH}_2$ (1.0 eq.), EDC HCl, HOBT, dry DCM, r.t., overnight; (ii) CH_3I , NaH, dry DMF, 4 Å M.S., r.t., overnight; (iii) CBr_4 , DBU, C_{60} , dry PhMe, r.t.

We estimated visually the water-solubility of nine conjugates at r.t., which was: **2d** > **1d** > **2c** > **2a** > **2b** > **1a** > **1b**, **3**, **4**. It was obviously inferred that γ -CD is a better water-solubilizing reagent than α -CD and the hydrophilic linker at the secondary rim is beneficial to give water-soluble conjugate.

2.2 SAR of anti-influenza A/WSN/33 (H1N1) virus activity

As part of our biological profiling [21], a cytopathic effect (CPE) reduction assay and a CellTiter-Glo assay were utilized in parallel to evaluate the antiviral activity of nine CD- C_{60} conjugates (**1a-1b**, **1d**, **2a-2d**, **3**, **4**) against the influenza A/WSN/33 (H1N1) virus that was propagated in MDCK cells [22]. Firstly, the CellTiter-Glo assay displayed that all tested compounds had no obvious cytotoxicity against uninfected MDCK cells at a concentration of 100 μM (**SI Figure 1**). Then, the CPE reduction assay was carried out to screen the antiviral activity. All the conjugates were preliminarily tested at one concentration (100 μM) and oseltamivir (OSV), an inhibitor of influenza neuraminidase, was used as a positive control. As shown in **Figure 3**, all the α -CD- C_{60} conjugates had no anti-influenza virus activity at the concentration of 100 μM , except for compounds **1d** and **2d**. These two γ -CD- C_{60} conjugates **1d** and **2d** displayed significant anti-influenza virus activity (58.5 and 66.9 %, respectively) at 100 μM , which suggested that the C_{60} conjugates with γ -CD moieties were more effective than that with α -CD moieties. Interestingly, **1d** and **2d** had also higher water-solubility than seven α -CD- C_{60} conjugates, indicating that the anti-influenza activity of CD- C_{60} conjugates may relate to the water-solubility of the conjugates. Moreover, compared to α -CD- C_{60} conjugates, γ -CD- C_{60} conjugates displayed much less aggregation in aqueous solution, which was evaluated by the generation of singlet oxygen species [19, 26]. The further work will focus on the design and synthesis of water-soluble CD- C_{60} conjugates with less aggregation.

After the preliminary screening at one concentration, conjugates **1d** and **2d** were selected to undergo dose response assays. The concentrations of compounds **1d** and **2d** required to inhibit viral replication by 50% (IC_{50}) are summarized in **Table 1**. Although conjugates **1d** and **2d** showed about half potent anti-influenza activity than that of OSV (IC_{50} : 87.73 and 75.06 μM vs 33.6 μM , respectively), they can be used as new lead compounds of anti-influenza inhibitor for further structural modification.

Figure 3. Cytopathic effect-based screening of nine CD-C₆₀ conjugates. 0.5% DMSO (final concentration) was used as the negative; oseltamivir was utilized as a positive control. Error bars indicate standard deviations of triplicate experiments.

Table 1. *In vitro* anti-influenza virus activity of the active CD-C₆₀ conjugates

Compound	IC ₅₀ (μM) ^a
1d	87.73 ± 6.9
2d	75.06 ± 5.1
OSV	33.6 ± 2.2 [21]

^a Concentration inhibiting viral replication by 50%. The values are means of at least three independent determinations; the corresponding standard deviations are noted.

3. Conclusion

We designed and synthesized nine CD-C₆₀ conjugates. Cyclodextrin moieties enhanced apparently the water-solubility of C₆₀. CD-C₆₀ conjugates with γ-CD attachment and hydrophilic spacer of moderate length are the most water-soluble. Then, their anti-influenza A/WSN/33 (H1N1) virus activity in MDCK cells was evaluated. All of the conjugates did not show obvious cytotoxicity at the concentration of 100 μM. The most water-soluble conjugates **1d** and **2d** displayed the highest anti-influenza virus activity. Although the inhibitory efficiency of **1d** and **2d** was only half of that of OSV, C₆₀ derivatives are firstly reported to exhibit anti-influenza virus activity. According to our previous study, one of the obvious differences between α-CD-C₆₀ conjugates and γ-CD-C₆₀ conjugates could be the less aggregation in aqueous solution of γ-CD-C₆₀ conjugates [19, 26]. Further studies along this line are currently ongoing.

4. Experimental section

4.1 Chemistry

General information

All of the reactants were purchased from commercial sources and used without further purification. DCM and PhMe were degassed, and dried on alumina using Pure SolvTM systems. DMF and NEt₃ were dried over 4 Å molecular sieve and stored under argon. HRMS were recorded on a Bruker microTOF spectrometer, using Agilent ESI-L Low Concentration Tuning-Mix as reference. NMR spectra were recorded on a Bruker AM-400 MHz or Bruker Avance II 600 MHz using the signal of the residual solvent as an internal reference. The NMR assignments were determined by COSY and HSQC experiments.

The synthetic protocols and the NMR assignments of γ-CD derivatives **1d** and **2d** were reported in our previous work [19].

4.1.1 6-azidoalkyl permethylated α-CD **5a**

To a solution of 6^A-monol-α-CD^{Me} [23] (218 mg, 0.18 mmol) in dry DMF (4 mL), NaH (22 mg, 3.0 eq., 0.54 mmol) was added at 0 °C under argon. The reaction mixture was stirred at r.t. for 1 h. Then 6-azidoethyl 4-methylbenzenesulfonate (107 mg, 2.0 eq., 0.36 mmol) in dry DMF (1 mL) was added. The reaction mixture was stirred at 80 °C overnight. CH₃OH was added dropwise to quench the reaction at 0 °C. The reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over MgSO₄, filtrated and concentrated. The residue was purified by flash chromatography (eluent: cyclohexane/acetone 4:1, then 3.5:1) to give the product **5a** (172 mg, 83%) as a white foam. *R*_f = 0.35 (Cyclohexane/Acetone = 1:1). ¹H NMR (400 MHz,

CDCl₃, 300K): δ 1.31-1.39 (m, 4H, 2 $\times$ H₉, 2 $\times$ H₁₀), 1.51-1.65 (m, 4H, 2 $\times$ H₈, 2 $\times$ H₁₁), 3.16 (m, 6H, 6 $\times$ H₂), 3.23 (t, 2H, J = 6.82 Hz, 2 $\times$ H₁₂), 3.38 (m, 15H, 5 $\times$ OCH₃(C₆)), 3.47 (m, 18H, 6 $\times$ OCH₃(C₂)), 3.54 (m, 12H, 6 $\times$ H₃, 6 $\times$ H₄), 3.62 (m, 18H, 6 $\times$ OCH₃(C₃)), 3.78 (m, 6H, 6 $\times$ H₅), 5.03 (m, 6H, 6 $\times$ H₁), 3.33 - 3.90 (m, 14H, 2 $\times$ H₇, 6 $\times$ H_{6a}, 6 $\times$ H_{6b})ppm; ¹³C NMR (100 MHz, CDCl₃, 300K): δ 25.86, 26.72, 28.94, 29.64 (4C, C₈, C₉, C₁₀, C₁₁), 51.50 (1C, C₁₂), 57.94, 57.97, 58.00 (6C, 6 $\times$ OCH₃(C₂)), 59.04, 59.10, 59.15 (5C, 5 $\times$ OCH₃(C₆)), 61.88, 61.90, 61.92 (6C, 6 $\times$ OCH₃(C₃)), 69.57 (1C, C₇), 71.31, 71.34 (6C, 6 $\times$ C₅), 71.41, 71.58, 71.62, 71.67 (6C, 6 $\times$ C₆), 81.37, 81.42, 81.44, 82.29, 82.33, 82.39, 82.41, 82.48, 82.58, 82.61 (18C, 6 $\times$ C₂, 6 $\times$ C₃, 6 $\times$ C₄), 100.21, 100.24, 100.25, 100.30, 100.35 (6C, 6 $\times$ C₁). **HRMS (ESI)**: m/z calcd for C₅₉H₁₀₅N₃O₃₀ [M + Na]⁺ 1358.6675, found 1358.6666 (mass accuracy of 0.7 ppm).

4.1.2 6-aminoalkyl permethylated α -CD **6a**

To a solution of compound **5a** (268 mg, 0.20 mmol) in dry MeOH (6 mL) was added propane-1,3-dithiol (0.91 mL, 45 eq., 9.0 mmol), dry NEt₃ (1.3 mL, 45 eq., 9.0 mmol) at r.t. under N₂. The reaction mixture was stirred at r.t. for 7 days. The solvent was removed by evaporation. The residue was subjected to flash chromatography (eluent: dichloromethane/methanol 30:1, then 3:1) to give the product **6a** (234 mg, 89%) as a white foam. **R_f** = 0.2 (DCM/MeOH = 4:1). ¹H NMR (400 MHz, CDCl₃, 300K): δ 1.34 (m, 4H, 2 $\times$ H₉, 2 $\times$ H₁₀), 1.48 (m, 2H, 2 $\times$ H₁₁), 1.58 (m, 2H, 2 $\times$ H₈), 2.55 (br, 2H, -NH₂), 2.71 (t, 2H, J = 6.82 Hz, 2 $\times$ H₁₂), 3.16 (m, 6H, 6 $\times$ H₂), 3.38 (m, 15H, 5 $\times$ OCH₃(C₆)), 3.47 (m, 18H, 6 $\times$ OCH₃(C₂)), 3.58 (m, 12H, 6 $\times$ H₃, 6 $\times$ H₄), 3.63 (m, 18H, 6 $\times$ OCH₃(C₃)), 3.79 (m, 6H, 6 $\times$ H₅), 5.03 (m, 6H, 6 $\times$ H₁), 3.33 - 3.90 (m, 14H, 2 $\times$ H₇, 6 $\times$ H_{6a}, 6 $\times$ H_{6b})ppm; ¹³C NMR (100 MHz, CDCl₃, 300K): δ 26.06, 26.80 (2C, C₉, C₁₀), 29.83 (1C, C₈), 32.57 (1C, C₁₁), 41.73 (1C, C₁₂), 57.96, 57.98, 58.02 (6C, 6 $\times$ OCH₃(C₂)), 59.06, 59.12, 59.17 (5C, 5 $\times$ OCH₃(C₆)), 61.91 (6C, 6 $\times$ OCH₃(C₃)), 69.56 (1C, C₇), 71.31, 71.35 (6C, 6 $\times$ C₅), 71.54, 71.58, 71.68 (6C, 6 $\times$ C₆), 82.28, 82.33, 82.38, 82.48, 82.57, 82.63 (18C, C₂, C₃, C₄), 100.06, 100.21, 100.25, 100.28, 100.35 (6C, C₁)ppm. **HRMS (ESI)**: m/z calcd for C₅₉H₁₀₈NO₃₀ [M + Na]⁺ 1310.6951, found 1310.6900 (mass accuracy of 3.9 ppm).

4.1.3 6-permethylated α -CD dimer **7a**

To a solution of 7,7'-(malonylbis(oxy))diheptanoic acid (23 mg, 0.064 mmol) in dry DCM (10mL) was added EDC HCl (37 mg, 3 eq., 0.19 mmol) and HOBT (29 mg, 3 eq., 0.19 mmol). After stirring at r.t. for 2 h, compound **6a** (184 mg, 2.2 eq., 0.14 mmol) was added. The reaction mixture was stirred at r.t. for 48 h. After washed with H₂O (3 $\times$ 3 mL), brine (3 mL), dried with MgSO₄, the solvent was removed by evaporation. The residue was subjected to flash chromatography (eluent: ethyl acetate/methanol 9:1, then 7:1) to give the product **7a** (140 mg, 75%) as a white foam. **R_f** = 0.1 (Cyclohexane/Acetone = 1:3). ¹H NMR (400 MHz, CDCl₃, 300K): δ 1.31 (m, 8H, 4 $\times$ H₉, 4 $\times$ H₁₀), 1.34 (m, 4H, 4 $\times$ H₁₇), 1.35 (m, 4H, 4 $\times$ H₁₆), 1.44 (m, 4H, 4 $\times$ H₁₁), 1.58 (m, 4H, 4 $\times$ H₈), 1.62 (m, 4H, 4 $\times$ H₁₅), 1.64 (m, 4H, 4 $\times$ H₁₈), 2.14 (t, 4H, 4 $\times$ H₁₄), 3.13-3.22 (m, 12H, 12 $\times$ H₂), 3.21 (m, 4H, 4 $\times$ H₁₂), 3.35 (s, 2H, -COCH₂CO-), 3.39 (m, 30H, 10 $\times$ OCH₃(C₆)), 3.44 (m, 4H, 4 $\times$ H₇), 3.48 (m, 36H, 12 $\times$ OCH₃(C₂)), 3.54 (m, 24H, 12 $\times$ H₃, 12 $\times$ H₄), 3.63 (m, 36H, 12 $\times$ OCH₃(C₃)), 3.82 (m, 12H, 12 $\times$ H₅), 3.62-3.94 (m, 24H, 12 $\times$ H_{6a}, 12 $\times$ H_{6b}), 4.12 (t, 4H, J = 6.61 MHz, 4 $\times$ H₁₉), 4.95 (d, 2H, J = 4.0 Hz, 2 $\times$ H₁), 5.04 (m, 10H, 10 $\times$ H₁), 5.68 (t, 2H, 2 $\times$ -NH-)ppm; ¹³C NMR (100 MHz, CDCl₃, 300K): δ 25.65, 25.69, 25.98, 28.45, 28.94, 29.75, 29.84, 29.85 (16C, 2 $\times$ C₈, 2 $\times$ C₉, 2 $\times$ C₁₀, 2 $\times$ C₁₁, 2 $\times$ C₁₅, 2 $\times$ C₁₆, 2 $\times$ C₁₇, 2 $\times$ C₁₈), 36.71 (2C, 2 $\times$ C₁₄), 39.55 (2C, 2 $\times$ C₁₂), 41.81 (1C, -COCH₂CO-), 57.96, 57.98, 58.01 (12C, 12 $\times$ OCH₃(C₂)), 59.09, 59.16, 59.22 (10C, 10 $\times$ OCH₃(C₆)), 61.93, 61.96, 61.98 (12C, 12 $\times$ OCH₃(C₃)), 65.60 (2C, 2 $\times$ C₁₉), 71.24, 71.29, 71.31 (12C, 12 $\times$ C₅), 71.50, 71.53, 71.57, 71.63 (12C, 12 $\times$ C₆), 69.45 (2C, 2 $\times$ C₇), 81.36, 81.41, 81.44, 82.27, 82.32, 82.33, 82.38, 82.41, 82.59, 82.61, 82.64 (36C, 12 $\times$ C₂, 12 $\times$ C₃, 12 $\times$ C₄), 100.10, 100.23, 100.27, 100.33, 100.38 (12C, 12 $\times$ C₁), 166.81 (2C, 2 $\times$ C₂₀), 172.93 (2C, 2 $\times$ C₁₃)ppm. **HRMS (ESI)**: m/z calcd for C₁₃₅H₂₃₈N₂O₆₆ [M + 2Na]²⁺ 1494.7557, found 1494.7640 (z = 2⁺, mass accuracy of -5.6 ppm).

4.1.4 2:1 per-*O*-methylated α -CD-C₆₀ conjugate **1a**

To a solution of compound **7a** (126 mg, 0.043 mmol), CBr₄ (35 mg, 2.5 eq., 0.11 mmol), C₆₀ (154 mg, 5 eq., 0.21 mmol) in dry PhMe (15 mL), DBU was added under argon. The reaction mixture was stirred at r.t. for 24h. The reaction mixture was directly chromatographed, eluting first with toluene to recover the excess of C₆₀, then cyclohexane/acetone = 1:1 to provide the product **1a** (14 mg, 9%) as a brown foam. **R_f** = 0.2 (Cyclohexane/Acetone = 1:3). [α]_D²⁰ = +123.5 (CHCl₃, c = 0.02). ¹H NMR (400 MHz, CDCl₃, 300K): δ 1.25-1.45 (m, 16H, 4 $\times$ H₉, 4 $\times$ H₁₀, 4 $\times$ H₁₇, 4 $\times$ H₁₆), 1.48 (m, 4H, 4 $\times$ H₁₁), 1.58 (m, 4H, 4 $\times$ H₈), 1.66 (m, 4H, 4 $\times$ H₁₅), 1.84 (m, 4H, 4 $\times$ H₁₈), 2.14 (t, 4H, 4 $\times$ H₁₄), 3.12-3.19 (m, 12H, 12 $\times$ H₂), 3.21 (m, 4H, 4 $\times$ H₁₂), 3.39 (m, 30H, 10 $\times$ OCH₃(C₆)), 3.65, 3.89 (m, 4H, 4 $\times$ H₇), 3.48 (m, 36H, 12 $\times$ OCH₃(C₂)), 3.54 (m, 24H, 12 $\times$ H₃, 12 $\times$ H₄), 3.63 (m, 36H, 12 $\times$ OCH₃(C₃)), 3.82 (m, 12H, 12 $\times$ H₅), 3.41-3.86 (m, 24H, 24 $\times$ H₆), 4.48 (t, 4H, J = 8 MHz, 4 $\times$ H₁₉), 5.04 (m, 12H, 12 $\times$ H₁), 5.65 (t, 2H, 2 $\times$ -NH-)ppm; ¹³C NMR (100 MHz, CDCl₃, 300K): δ 25.77, 25.89, 26.01, 28.58, 29.03, 29.42, 29.78, 29.89 (16C, 2 $\times$ C₈, 2 $\times$ C₉, 2 $\times$ C₁₀, 2 $\times$ C₁₁, 2 $\times$ C₁₅, 2 $\times$ C₁₆, 2 $\times$ C₁₇, 2 $\times$ C₁₈), 36.79 (2C, 2 $\times$ C₁₄), 39.62 (2C, 2 $\times$ C₁₂), 57.96, 57.99, 58.03 (12C, 12 $\times$ OCH₃(C₂)), 59.10, 59.15, 59.22 (10C, 10 $\times$ OCH₃(C₆)), 61.91, 61.92, 61.95 (12C, 12 $\times$ OCH₃(C₃)), 67.47 (2C, 2 $\times$ C₁₉), 69.53 (2C, 2 $\times$ C₇), 71.30, 71.36 (12C, 12 $\times$ C₅), 71.57, 71.63, 71.74 (14C, 12 $\times$ C₆, 2 $\times$ sp³-C₆₀), 71.78 (1C, 1 $\times$ C₂₁), 81.38, 81.43, 81.46, 82.29, 82.34, 82.41, 82.60 (36C, 12 $\times$ C₂, 12 $\times$ C₃, 12 $\times$ C₄), 100.10, 100.23, 100.27 (12C, 12 $\times$ C₁), 139.12, 141.10, 142.04, 142.34, 143.13, 143.18, 143.25, 144.03, 144.75, 144.78, 144.84, 145.04, 145.30, 145.34, 145.41, 145.47 (58C, 58 $\times$ sp²-C₆₀), 163.78 (2C, 2 $\times$ C₂₀), 173.00 (2C, 2 $\times$ C₁₃) ppm. **HRMS (ESI)**: m/z calcd for C₁₉₅H₂₃₆N₂O₆₆ [M + 2Na]²⁺ 1853.7478, found 1853.7431 (z = 2⁺, mass accuracy of 2.5 ppm).

4.1.5 6-azidoalkyl permethylated α -CD **5b**

To a solution of 6^A-monol- α -CD^{Me} [23] (200mg, 0.17 mmol) in dry DMF (5 mL) was added NaH (20 mg, 3.0 eq., 0.50 mmol) at 0 °C. After stirred at room temperature for 2h, 12-azidododecyl 4-methylbenzenesulfonate (95 mg, 1.5 eq., 0.25 mmol) in dry DMF (1 mL) was added at 0 °C. The reaction mixture was stirred at 80 °C for 24h. CH₃OH was added dropwise to quench the reaction at 0 °C. The reaction mixture was extracted with ethyl acetate (3 $\times$ 15 mL). The combined organic

layers were washed with brine (3 × 15 mL), dried over MgSO₄, filtrated and concentrated. The residue was purified by chromatography (eluent: cyclohexane/acetone 1:1) to afford the product **5b** (137 mg, 80%) as a white foam. R_f = 0.15 (cyclohexane/acetone = 1:1). **¹H NMR** (400 MHz, CDCl₃, 300K) : δ 1.21-1.36 (m, 16H, 2 × H₉, 2 × H₁₀, 2 × H₁₁, 2 × H₁₂, 2 × H₁₃, 2 × H₁₄, 2 × H₁₅, 2 × H₁₆), 1.57 (m, 4H, 2 × H₁₇, 2 × H₈), 3.13-1.16 (m, 6H, 6 × H₂), 3.23 (t, 2H, J = 6.8 Hz, 2 × H₁₈), 3.37 (m, 15H, 5 × OCH₃(C₆)), 3.46, 3.47 (m, 18H, 6 × OCH₃(C₂)), 3.55 (m, 12H, 6 × H₃, 6 × H₄), 3.62 (m, 18H, 6 × OCH₃(C₃)), 3.68 (m, 1H, 1 × H_{7a}), 3.76 (m, 6H, 6 × H₅), 3.83 (m, 1H, 1 × H_{7b}), 3.39-3.86 (12H, 6 × H_{6a}, 6 × H_{6b}), 5.03 (m, 6H, 6 × H₁)ppm; **¹³C NMR** (100 MHz, CDCl₃, 300K) : δ 26.32, 26.82, 28.94, 29.25, 29.57, 29.64, 29.67, 29.69, 29.74, 29.82 (10C, 1 × C₈, 1 × C₉, 1 × C₁₀, 1 × C₁₁, 1 × C₁₂, 1 × C₁₃, 1 × C₁₄, 1 × C₁₅, 1 × C₁₆, 1 × C₁₇), 51.64 (1C, 1 × C₁₈), 57.94, 57.96, 57.98 (6C, 6 × OCH₃(C₂)), 59.05, 59.08, 59.12 (5C, 5 × OCH₃(C₆)), 61.89 (6C, 6 × OCH₃(C₃)), 69.62 (1C, 1 × C₇), 71.31, 71.33 (6C, 6 × C₅), 71.54, 71.56, 71.60, 71.63 (6C, 6 × C₆), 81.37, 81.43, 82.32, 82.37, 82.53, 82.58 (18C, 6 × C₂, 6 × C₃, 6 × C₄), 100.01, 100.19, 100.22, 100.26, 100.28 (6C, 6 × C₁)ppm. **HRMS (ESI)**: m/z calcd for C₆₅H₁₁₇N₃O₃₀ [M + Na]⁺ 1442.7620, found 1442.7610 (mass accuracy of 0.7 ppm).

4.1.6 6-aminoalkyl permethylated α -CD **6b**

To a solution of **5b** (40 mg, 0.028 mmol) in dry MeOH (2 mL) was added propane-1,3-dithiol (0.17 mL, 45 eq., 1.26 mmol) and dry triethylamine (0.17 mL, 44 eq., 1.23 mmol). The reaction mixture was stirred at r.t. for 7 days. The solvent was evaporated. The residue was subjected to flash chromatography (eluent: DCM/MeOH 30:1, then 5:1) to give the product **6b** (37 mg, 95%) as a white foam. R_f = 0.3 (DCM/MeOH = 5:1). **¹H NMR** (400 MHz, CDCl₃, 300K) : δ 1.20-1.36 (m, 16H, 2 × H₉, 2 × H₁₀, 2 × H₁₁, 2 × H₁₂, 2 × H₁₃, 2 × H₁₄, 2 × H₁₅, 2 × H₁₆), 1.60 (m, 2H, 2 × H₈), 1.71 (m, 2H, 2 × H₁₇), 2.94 (t, 2H, J = 7.7 Hz, 2 × H₁₈), 3.15 (m, 6H, 6 × H₂), 3.37, 3.38 (m, 15H, 5 × OCH₃(C₆)), 3.47 (m, 18H, 6 × OCH₃(C₂)), 3.55 (m, 12H, 6 × H₃, 6 × H₄), 3.62, 3.63 (m, 18H, 6 × OCH₃(C₃)), 3.68 (m, 1H, 1 × H_{7a}), 3.76 (m, 6H, 6 × H₅), 3.84 (m, 1H, 1 × H_{7b}), 3.40-3.81 (12H, 6 × H_{6a}, 6 × H_{6b}), 5.03 (m, 6H, 6 × H₁)ppm; **¹³C NMR** (100 MHz, CDCl₃, 300K) δ 25.09 (1C, 1 × C₈), 27.89 (1C, 1 × C₁₇), 26.76, 29.25, 29.50, 29.56, 29.67, 29.79, 29.82, 29.95 (8C, 1 × C₉, 1 × C₁₀, 1 × C₁₁, 1 × C₁₂, 1 × C₁₃, 1 × C₁₄, 1 × C₁₅, 1 × C₁₆), 40.21 (1C, 1 × C₁₈), 58.04, 58.06, 58.09 (6C, 6 × OCH₃(C₂)), 59.17, 59.19, 59.23 (5C, 5 × OCH₃(C₆)), 61.98, 62.00 (6C, 6 × OCH₃(C₃)), 69.72 (1C, 1 × C₇), 71.41, 71.44 (6C, 6 × C₅), 71.66, 71.71, 71.82 (6C, 6 × C₆), 81.48, 81.53, 82.35, 82.40, 82.44, 82.47, 82.60, 82.62, 82.66 (18C, 2 × C₂, 2 × C₃, 2 × C₄), 100.08, 100.28, 100.30, 100.35, 100.38 (6C, 6 × C₁)ppm. **HRMS (ESI)**: m/z calcd for C₆₅H₁₂₀NO₃₀ [M + H]⁺ 1394.7890, found 1394.7880 (mass accuracy of 0.7 ppm).

4.1.7 6-permethylated α -CD dimer **7b**

To a solution of 12,12'-(malonylbis(oxy))didodecanoic acid (43 mg, 0.085 mmol) in dry DCM (4mL) was added EDC HCl (44 mg, 3.0 eq., 0.23 mmol) and HOBT (35 mg, 3.0 eq., 0.23 mmol). After the reaction mixture was stirred at r.t. for 2h, compound **6b** (215 mg, 2.2 eq., 0.15 mmol) was added. The reaction mixture was stirred for 48 h. After washed with H₂O (3 × 3 mL), brine (1 × 3 mL), dried over MgSO₄ and filtrated, the solvent was evaporated. The residue was purified by silica gel chromatography (eluent: cyclohexane/acetone 1.5:1) to give the product **7b** (123 mg, 49%) as a white foam. R_f = 0.3 (Cyclohexane/Acetone = 1:1). **¹H NMR** (400 MHz, CDCl₃, 300K) : δ 1.50 (m, 4H, 4 × H₁₇), 1.61 (m, 4H, 4 × H₂₁), 1.62 (m, 4H, 4 × H₂₉), 1.20-1.70 (m, 64H, 4 × H₈, 4 × H₉, 4 × H₁₀, 4 × H₁₁, 4 × H₁₂, 4 × H₁₃, 4 × H₁₄, 4 × H₁₅, 4 × H₁₆, 4 × H₂₂, 4 × H₂₃, 4 × H₂₄, 4 × H₂₅, 4 × H₂₆, 4 × H₂₇, 4 × H₂₈), 2.14 (t, 4H, J = 8.0 Hz, 4 × H₂₀), 3.16 (m, 12H, 12 × H₂), 3.20 (m, 4H, 4 × H₁₈), 3.35 (s, 2H, 2 × H₃₂), 3.38, 3.39 (m, 30H, 10 × OCH₃(C₆)), 3.48 (m, 36H, 12 × OCH₃(C₂)), 3.56 (m, 24H, 12 × H₃, 12 × H₄), 3.63, 3.64 (m, 36H, 12 × OCH₃(C₃)), 3.69, 3.85 (m, 4H, 4 × H₇), 3.80 (m, 12H, 12 × H₅), 3.42-3.86 (m, 24H, 24 × H₆), 4.12 (t, 4H, J = 8.0 Hz, 4 × H₃₀), 5.04 (m, 12H, 12 × H₁), 5.47 (br, 2H, 2 × -NH-)ppm; **¹³C NMR** (100 MHz, CDCl₃, 300K) : δ 25.92, 25.96, 26.36, 27.09, 28.60, 29.32, 29.47, 29.49, 29.59, 29.64, 29.71, 29.75, 29.77, 29.81, 29.86 (38C, 2 × C₈, 2 × C₉, 2 × C₁₀, 2 × C₁₁, 2 × C₁₂, 2 × C₁₃, 2 × C₁₄, 2 × C₁₅, 2 × C₁₆, 2 × C₁₇, 2 × C₂₁, 2 × C₂₂, 2 × C₂₃, 2 × C₂₄, 2 × C₂₅, 2 × C₂₆, 2 × C₂₇, 2 × C₂₈, 2 × C₂₉), 37.08 (2C, 2 × C₃₀), 39.63 (2C, 2 × C₁₈), 41.85 (1C, 1 × C₃₂), 57.96, 57.98, 58.01 (12C, 12 × OCH₃(C₂)), 59.09, 59.12, 59.16 (10C, 10 × OCH₃(C₆)), 61.92 (12C, 12 × OCH₃(C₃)), 65.84 (2C, 2 × C₃₀), 69.61 (2C, 2 × C₇), 71.34, 71.36 (12C, 12 × C₅), 71.57, 71.63, 71.72 (12C, 12 × C₆), 81.39, 81.45, 82.30, 82.35, 82.39, 82.42, 82.56, 82.61 (36C, 12 × C₂, 12 × C₃, 12 × C₄), 100.03, 100.22, 100.25, 100.28, 100.32 (12C, 12 × C₁), 166.81 (2C, 2 × C₃₁), 173.13 (2C, 2 × C₁₉)ppm. **HRMS (ESI)**: m/z calcd for C₁₅₇H₂₈₂N₂O₆₆ [M + 2Na]²⁺ 1648.9278, found 1648.9256 (z = 2⁺, mass accuracy of 1.3 ppm).

4.1.8 2:1 6-permethylated α -CD-C₆₀ conjugate **1b**

To a solution of C₆₀ (10 mg, 0.014 mmol) in 8 mL dry PhMe was added the solution of **7b** (44 mg, 1.0 eq., 0.014 mmol) in dry PhMe (2 mL) under Ar. I₂ (4 mg, 1.23 eq., 0.017 mmol) was added. DBU (4.5 μ L, 2.23 eq., 0.030 mmol) was added to the reaction mixture at 0 °C. After stirred for 2h at room temperature, the reaction mixture was diluted with ethyl acetate (20 mL). After washed with brine (3 × 5 mL), dried over MgSO₄, filtrated and concentrated. The residue was subjected to flash chromatography (eluent: toluene, then cyclohexane/acetone 1.5:1) to give the product **1b** as a brown foam (27 mg, 53%). R_f = 0.4 (cyclohexane/acetone = 1:1). **[α]_D²⁰** = +91.6 (CHCl₃, c = 0.025). **¹H NMR** (400 MHz, CDCl₃, 300K) : δ 1.46 (m, 4H, 4 × H₁₇), 1.61 (m, 4H, 4 × H₂₁), 1.18-1.65 (m, m, 64H, 4 × H₈, 4 × H₉, 4 × H₁₀, 4 × H₁₁, 4 × H₁₂, 4 × H₁₃, 4 × H₁₄, 4 × H₁₅, 4 × H₁₆, 4 × H₂₂, 4 × H₂₃, 4 × H₂₄, 4 × H₂₅, 4 × H₂₆, 4 × H₂₇, 4 × H₂₈), 1.82 (m, 4H, 4 × H₂₉), 2.13 (t, 4H, J = 8 Hz, 4 × H₂₀), 3.15 (m, 12H, 12 × H₂), 3.20 (m, 4H, 4 × H₁₈), 3.37, 3.38 (m, 30H, 10 × OCH₃(C₆)), 3.27 (m, 36H, 12 × OCH₃(C₂)), 3.62, 3.63 (m, 36H, 12 × OCH₃(C₃)), 3.50-3.64 (24H, 12 × H₃, 12 × H₄), 3.76 (m, 12H, 12 × H₅), 3.69, 3.83 (m, 4H, 4 × H₇), 3.30-3.84 (m, 24H, 24 × H₆), 4.48 (t, 4H, J = 8.0 Hz, 4 × H₃₀), 5.01-5.05 (m, 12H, 12 × H₁), 5.48 (t, 2H, J = 4.0 Hz, 2 × -NH-)ppm; **¹³C NMR** (100 MHz, CDCl₃, 300K) : δ 25.96, 26.12, 26.35, 27.04, 27.09, 28.73, 29.35, 29.41, 29.46, 29.50, 29.53, 29.64, 29.68, 29.75, 29.77, 29.81, 29.86 (38C, 2 × C₈, 2 × C₉, 2 × C₁₀, 2 × C₁₁, 2 × C₁₂, 2 × C₁₃, 2 × C₁₄, 2 × C₁₅, 2 × C₁₆, 2 × C₁₇, 2 × C₂₁, 2 × C₂₂, 2 × C₂₃, 2 × C₂₄, 2 × C₂₅, 2 × C₂₆, 2 × C₂₇, 2 × C₂₈, 2 × C₂₉), 37.04 (2C, 2 × C₃₀), 39.64 (2C, 2 × C₁₈), 57.95, 57.97, 58.00 (12C, 12 × OCH₃(C₂)), 59.08, 59.11, 59.15 (10C, 10 × OCH₃(C₆)), 61.92, 67.59, 69.61 (12C, 12 × OCH₃(C₃)), 67.59 (2C, 2 × C₃₀), 67.61 (2C, 2 × C₇), 77.31, 77.34 (12C, 12 × C₅), 71.84 (1C, 1 × C₃₂), 71.54, 71.57, 71.58, 71.61, 71.67, 71.70 (14C, 12 × C₆, 2 × sp³-C₆₀), 81.37, 81.43, 82.33, 82.37, 82.54, 82.59 (36C, 12 × C₂, 12 × C₃, 12 × C₄), 100.02, 100.21, 100.24, 100.27, 100.31 (12C, 12 × C₁), 139.10,

141.06, 142.03, 142.32, 143.10, 143.13, 143.99, 144.71, 144.80, 145.30, 145.37, 145.52 (58C, 58 × sp²-C₆₀), 163.78 (2C, 2 × C₃₁), 173.09 (2C, 2 × C₁₉)ppm. **HRMS (ESI):** *m/z* calcd for C₂₁₇H₂₈₀N₂O₆₆ [M + 2Na]²⁺ 2007.9200, found 2007.9254 (*z* = 2, mass accuracy of -2.7 ppm).

4.1.9 2-azidoalkyl α-CD **8a**

To a solution of 2^A,3^B-diol-α-CD^{Me} [23] (238 mg, 0.20 mmol) in dry DMF, NaH (16 mg, 2.0 eq., 0.40 mmol) was added 0 °C under Ar. Then the reaction mixture was stirred at r.t. for 1 h. Then 6-azidohexyl 4-methylbenzenesulfonate (94 mg, 1.6 eq., 0.32 mmol) in dry DMF (1 mL) was added. The reaction mixture was stirred at r.t. for 6 h. CH₃OH was added dropwise to quench the reaction at 0 °C. The reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with H₂O (3 × 10 mL), brine (10 mL), dried with MgSO₄, filtrated and the solvent was removed by evaporation. The residue was subjected to flash chromatography (eluent: cyclohexane/acetone 4:1, then 3.5:1) to give the product **8a** (168 mg, 64%) as a white foam. *R_f* = 0.15 (cyclohexane/acetone = 2:1). **¹H NMR** (400 MHz, CDCl₃, 300K): δ 1.33 (m, 4H, 2 × H₉, 2 × H₁₀), 1.55 (m, 2H, 2 × H₁₁), 1.63 (m, 2H, 2 × H₈), 3.13 (m, 4H, 4 × H₂), 3.20 (m, 1H, 1 × H₂^B), 3.22 (t, 2H, *J* = 6.7 Hz, 2 × H₁₂), 3.27 (m, 1H, 1 × H₂^A), 3.37, 3.38 (m, 18H, 6 × OCH₃(C₆)), 3.44, 3.45, 3.51 (m, 15H, 5 × OCH₃(C₂)), 3.58, 3.60 (m, 15H, 5 × OCH₃(C₃)), 3.44-3.62 (m, 11H, 5 × H₃, 6 × H₄), 3.58-3.89 (20H, 12 × H₆, 6 × H₅, 2 × H₇), 4.03 (t, 1H, *J*₁ = 9.2 Hz, *J*₂ = 9.6 Hz, 1 × H₃^B), 4.91 (d, 1H, *J* = 4.0 Hz, 1 × H₁^A), 4.98 (d, 1H, *J* = 4.0 Hz, 1 × H₁), 5.00 (m, 3H, 3 × H₁), 5.06 (d, 1H, *J* = 4.0 Hz, 1 × H₁^B)ppm; **¹³C NMR** (100 MHz, CDCl₃, 300K): δ 25.25, 26.36 (2C, 1 × C₉, 1 × C₁₀), 28.74 (1C, 1 × C₁₁), 29.55 (1C, 1 × C₈), 51.34 (1C, 1 × C₁₂), 57.74, 57.78 (5C, 5 × OCH₃(C₂)), 57.94, 57.98 (6C, 6 × OCH₃(C₆)), 59.04, 59.08, 59.11, 59.14, 59.19 (5C, 5 × OCH₃(C₃)), 70.02, 71.15, 71.20, 71.30, 71.36, 71.59, 71.78 (7C, 6 × C₅, 1 × C₃^B), 71.17, 71.25, 71.43, 71.45, 71.67 (6C, 6 × C₆), 72.71 (1C, 1 × C₇), 81.01, 81.19, 81.27, 81.38, 82.24, 82.29, 82.32, 82.39, 82.45, 82.50, 82.57, 82.67, 82.91, 83.80 (17C, 6 × C₂, 5 × C₃, 6 × C₄), 100.12, 100.17, 100.38, 100.41, 101.46 (6C, 6 × C₁)ppm. **HRMS (ESI):** *m/z* calcd for C₅₈H₁₀₃N₃O₃₀ [M + Na]⁺ 1344.6519, found 1344.6551 (mass accuracy of -2.4 ppm).

4.1.10 2-aminoalkyl permethylated α-CD **9a**

To a solution of **8a** (249 mg, 0.19 mmol) in dry DMF (4 mL) was added NaH (23 mg, 3.0 eq., 0.57 mmol) at 0 °C. After stirred at r.t. for 2h, CH₃I (0.037 mL, 3.0 eq., 0.57 mmol) was added at 0 °C. The reaction mixture was stirred at r.t. overnight. The excess NaH was quenched by MeOH. The reaction mixture was diluted with ethyl acetate (20 mL), washed with H₂O (1 × 5 mL), brine (3 × 5 mL), dried over MgSO₄, filtrated and concentrated. The residue was used for further reaction without purification. Dry methanol (4 mL) dissolved the residue. Propane-1,3-dithiol (0.86 mL, 45 eq., 8.6 mmol) and dry triethylamine (0.86 mL, 34 eq., 6.4 mmol) were added at r.t. under N₂. The reaction mixture was stirred at r.t. for 7 days. The solvent was removed by evaporation. The residue was purified by silica gel chromatography (eluent: DCM/MeOH 30:1, then 3:1) to give the product **9a** (167 mg, 67%) as a white foam. *R_f* = 0.5 (DCM/MeOH = 3:1). **¹H NMR** (400 MHz, CDCl₃, 300K): δ 1.35 (m, 4H, 2 × H₉, 2 × H₁₀), 1.51 (m, 2H, 2 × H₁₁), 1.62 (m, 2H, 2 × H₈), 2.72 (t, 2H, *J* = 7.0 Hz, 2 × H₁₂), 3.15 (m, 5H, 5 × H₂), 3.21 (dd, 1H, *J*₁ = 3.3 Hz, *J*₂ = 9.4 Hz, 1 × H₂), 3.38 (m, 20H, 2 × H₇, 6 × OCH₃(C₆)), 3.47, 3.48 (m, 15H, 5 × OCH₃(C₂)), 3.54 (m, 12H, 6 × H₃, 6 × H₄), 3.60, 3.61, 3.62, 3.63 (m, 18H, 6 × OCH₃(C₃)), 3.77 (m, 6H, 6 × H₅), 3.62-3.90 (m, 12H, 12 × H₆), 4.95 (d, 1H, *J* = 3.3 Hz, 1 × H₁), 5.03 (m, 5H, 5 × H₁)ppm; **¹³C NMR** (100 MHz, CDCl₃, 300K): δ 25.82, 26.79 (2C, 1 × C₉, 1 × C₁₀), 30.11 (1C, 1 × C₈), 32.21 (1C, 1 × C₁₁), 41.51 (1C, 1 × C₁₂), 57.93, 57.99, 58.04, 58.22 (5C, 5 × OCH₃(C₂)), 59.04, 59.05, 59.09 (6C, 6 × OCH₃(C₆)), 61.73, 61.86, 61.91, 61.94, 62.28 (6C, 6 × OCH₃(C₃)), 70.68 (1C, 1 × C₇), 71.23, 71.27, 71.30, 71.35 (6C, 6 × C₅), 71.55, 71.59, 71.64, 71.68 (6C, 6 × C₆), 81.27, 81.31, 81.37, 81.40, 82.02, 82.30, 82.36, 82.42, 82.49, 82.57, 82.60, 82.67 (18C, 6 × C₂, 6 × C₃, 6 × C₄), 100.17, 100.23, 100.38, 100.50, 100.57 (6C, 6 × C₁)ppm. **HRMS (ESI):** *m/z* calcd for C₅₉H₁₀₈NO₃₀ [M + H]⁺ 1310.6951, found 1310.6949 (mass accuracy of 0.1 ppm).

4.1.11 2-permethylated α-CD dimer **10a**

To a solution of 7,7'-(malonylbis(oxy))diheptanoic acid (14 mg, 0.038 mmol) in dry DCM (8 mL) was added EDC HCl (22 mg, 3.0 eq., 0.11 mmol) and HOBt (18 mg, 3 eq., 0.11 mmol). After stirring at r.t. for 2 h, compound **9a** (104 mg, 2.1 eq., 0.79 mmol) was added. The reaction mixture was stirred at r.t. for 24 h. After washed with H₂O (3 × 3 mL), brine (1 × 3 mL), dried over MgSO₄, filtrated and concentrated. The residue was purified by silica gel chromatography (eluent: EtOAc/MeOH 15:1, then 10:1) to give the product **10a** (74 mg, 66%) as a white foam. *R_f* = 0.1 (Cyclohexane/Acetone = 1:1). **¹H NMR** (400 MHz, CDCl₃, 300K): δ ¹H NMR (400M, CDCl₃, 300K) δ 1.30-1.42 (m, 20H, 4 × H₈, 4 × H₉, 4 × H₁₀, 4 × H₁₆, 4 × H₁₇), 1.46 (m, 4H, 4 × H₁₁), 1.62 (m, 8H, 4 × H₁₈, 4 × H₁₅), 2.14 (t, 4H, *J* = 7.6 Hz, 4 × H₁₄), 3.14 (m, 10H, 10 × H₂), 3.20 (m, 6H, 4 × H₁₂, 2 × H₂), 3.34 (s, 2H, 2 × H₂₁), 3.38 (m, 36H, 12 × OCH₃(C₆)), 3.40 (m, 4H, 4 × H₇), 3.47, 3.48 (m, 30H, 10 × OCH₃(C₂)), 3.53 (m, 24H, 12 × H₃, 12 × H₄), 3.60, 3.62, 3.63 (m, 36H, 12 × OCH₃(C₃)), 3.77 (m, 12H, 12 × H₅), 3.61-3.92 (m, 24H, 24 × H₆), 4.12 (t, 4H, *J* = 6.7 Hz, 4 × H₁₉), 4.95 (d, 2H, *J* = 3.3 Hz, 2 × H₁), 5.03 (m, 10H, 10 × H₁), 5.70 (t, 2H, *J* = 5.0 Hz, 2 × -NH-) ppm; **¹³C NMR** (100 MHz, CDCl₃, 300K): δ 25.51, 25.55, 25.59, 26.73, 28.30, 28.80, 29.61, 29.97 (16C, 2 × C₈, 2 × C₉, 2 × C₁₀, 2 × C₁₁, 2 × C₁₅, 2 × C₁₆, 2 × C₁₇, 2 × C₁₈), 36.56 (2C, 2 × C₁₄), 39.41 (2C, 2 × C₁₂), 41.68 (1C, 1 × C₂₁), 57.81, 57.85, 57.87, 58.12 (12C, 12 × OCH₃(C₂)), 58.93, 58.97 (12C, 12 × OCH₃(C₆)), 61.61, 61.72, 61.78, 61.81, 62.18 (12C, 12 × OCH₃(C₃)), 65.47 (2C, 2 × C₁₉), 70.55 (2C, 2 × C₇), 71.12, 71.15, 71.17, 71.23 (12C, 12 × C₅), 71.41, 71.48, 71.53 (12C, 12 × C₆), 81.25, 81.29, 81.35, 81.39, 81.99, 82.28, 82.30, 82.36, 82.42, 82.50, 82.58, 82.59, 82.60, 82.64 (36C, 12 × C₂, 12 × C₃, 12 × C₄), 100.17, 100.24, 100.33, 100.53, 100.61 (12C, 12 × C₁), 166.79 (2C, 2 × C₂₀), 173.00 (2C, 2 × C₁₃)ppm. **HRMS (ESI):** *m/z* calcd for C₁₃₅H₂₃₈N₂O₆₆ [M + 2Na]²⁺ 1494.7557, found 1494.7499 (*z* = 2⁺, mass accuracy of 3.9 ppm).

4.1.12 2:1 2-permethylated α-CD-C₆₀ conjugate **2a**

To a solution of compound **10a** (90 mg, 0.031 mmol), CBr₄ (25 mg, 2.5 eq., 0.072 mmol), C₆₀ (110 mg, 5.0 eq., 0.15 mmol) in dry PhMe (11 mL), DBU (0.011 mL, 2.5 eq., 0.072 mmol) was added under argon. The reaction mixture was stirred at r.t. for 24h. The reaction mixture was directly chromatographed, eluting first with

toluene to recover the excess of C₆₀, then cyclohexane/acetone = 1:1 to provide the product **2a** (22 mg, 20%) as a brown foam. **R_f** = 0.5 (cyclohexane/acetone = 1:2). **¹H NMR** (600 MHz, CDCl₃, 300K): δ 1.30-1.69 (m, 28H, 4 $\times$ H₈, 4 $\times$ H₉, 4 $\times$ H₁₀, 4 $\times$ H₁₁, 4 $\times$ H₁₅, 4 $\times$ H₁₆, 4 $\times$ H₁₇), 1.84 (m, 4H, 4 $\times$ H₁₈), 2.17 (t, 4H, J = 7.6 Hz, 4 $\times$ H₁₄), 3.14 (m, 10H, 10 $\times$ H₂), 3.20 (m, 6H, 2 $\times$ H₂, 4 $\times$ H₁₂), 3.39 (m, 36H, 12 $\times$ OCH₃(C₆)), 3.40 (m, 4H, 4 $\times$ H₇), 3.48, 3.49 (m, 30H, 10 $\times$ OCH₃(C₂)), 3.55 (m, 24H, 12 $\times$ H₃, 12 $\times$ H₄), 3.60, 3.62, 3.63, 3.64 (m, 36H, 12 $\times$ OCH₃(C₃)), 3.78 (m, 12H, 12 $\times$ H₅), 3.62-3.92 (m, 24H, 12 $\times$ H_{6a}, 12 $\times$ H_{6b}), 4.48 (t, 4H, J = 6.4 Hz, 4 $\times$ H₁₉), 4.96 (d, 2H, J = 3.0 Hz, 2 $\times$ H₁), 5.04 (m, 10H, 10 $\times$ H₁), 5.72 (t, 2H, J = 5.8 Hz, 2 $\times$ -NH-)ppm; **¹³C NMR** (150 MHz, CDCl₃, 300K): δ 25.77, 25.90, 26.93, 29.04, 29.83, 30.01, 30.14 (14C, 2 $\times$ C₈, 2 $\times$ C₉, 2 $\times$ C₁₀, 2 $\times$ C₁₁, 2 $\times$ C₁₅, 2 $\times$ C₁₆, 2 $\times$ C₁₇), 28.57 (2C, 2 $\times$ C₁₈), 36.76 (2C, 2 $\times$ C₁₄), 39.58 (2C, 2 $\times$ C₁₂), 57.96, 57.97, 58.02, 58.03, 58.28 (10C, 10 $\times$ OCH₃(C₂)), 59.08, 59.12, 59.15 (12C, 12 $\times$ OCH₃(C₆)), 61.77, 61.88, 61.94, 61.97, 62.34 (12C, 12 $\times$ OCH₃(C₃)), 67.46 (2C, 2 $\times$ C₁₉), 70.69 (2C, 2 $\times$ C₇), 71.26, 71.29, 71.32, 71.37, 71.52 (12C, 12 $\times$ C₅), 71.55, 71.57, 71.63, 71.67, 71.69 (14C, 12 $\times$ C₆, 2 $\times$ sp³-C₆₀), 71.80 (1C, 1 $\times$ C₂₁), 81.27, 81.32, 81.37, 81.41, 81.43, 81.45, 82.03, 82.31, 82.33, 82.39, 82.45, 82.53, 82.60, 82.62, 82.66, 82.68 (36C, 12 $\times$ C₂, 12 $\times$ C₃, 12 $\times$ C₄), 100.18, 100.20, 100.26, 100.35, 100.55, 100.62 (12C, 12 $\times$ C₁), 139.12, 141.10, 142.03, 142.34, 143.13, 143.17, 143.24, 144.02, 144.75, 144.78, 144.83, 145.03, 145.30, 145.33, 145.41, 145.47 (58C, 58 $\times$ sp²-C₆₀), 163.78 (2C, 2 $\times$ C₂₀), 172.87 (2C, 2 $\times$ C₁₃)ppm. **HRMS (ESI)**: m/z calcd for C₁₉₅H₂₃₆N₂O₆₆ [M + 2Na]²⁺ 1853.7478, found 1853.7538 ($z = 2^+$, mass accuracy of -3.2 ppm).

4.1.13 2-azidoalkyl α -CD **8b**

To a solution of 2^A,3^B-diol- α -CD^{Me} (252 mg, 0.21 mmol) [23] in dry DMF (5 mL), NaH (25 mg, 3.0 eq., 0.64 mmol) was added 0 °C under Ar. Then the reaction mixture was stirred at room temperature for 1 h. Then 12-azidododecyl 4-methylbenzenesulfonate (121 mg, 1.5 eq., 0.32 mmol) in dry DMF (1 mL) was added. The reaction mixture was stirred at room temperature for 6 h. CH₃OH was added dropwise to quench the reaction at 0 °C. The reaction mixture was extracted with ethyl acetate (3 $\times$ 20 mL). The combined organic layers were washed with H₂O (1 $\times$ 10 mL), brine (3 $\times$ 10 mL), dried over MgSO₄, filtrated and concentrated. The residue was purified by silica gel chromatography (eluent: cyclohexane/acetone = 4:1, then 3.5:1) to give the product **8b** (193 mg, 65%) as a white foam. **R_f** = 0.4 (cyclohexane/acetone = 5:4). **¹H NMR** (400 MHz, CDCl₃, 300K): δ 1.21-1.40 (m, 16H, 2 $\times$ H₉, 2 $\times$ H₁₀, 2 $\times$ H₁₁, 2 $\times$ H₁₂, 2 $\times$ H₁₃, 2 $\times$ H₁₄, 2 $\times$ H₁₅, 2 $\times$ H₁₆), 1.58 (m, 2H, 2 $\times$ H₁₇), 1.60 (m, 2H, 2 $\times$ H₈), 3.17 (m, 4H, 4 $\times$ H₂), 3.25 (m, 3H, 1 $\times$ H₂^B, 2 $\times$ H₁₈), 3.30 (m, 1H, 1 $\times$ H₂), 3.40, 3.41 (m, 18H, 6 $\times$ OCH₃(C₆)), 3.48, 3.49, 3.54 (m, 15H, 5 $\times$ OCH₃(C₂)), 3.56 (11H, 5 $\times$ H₃, 6 $\times$ H₄), 3.62, 3.63, 3.64 (m, 15H, 5 $\times$ OCH₃(C₃)), 3.79 (m, 6H, 6 $\times$ H₅), 3.65-3.90 (m, 14H, 2 $\times$ H₇, 6 $\times$ H_{6a}, 6 $\times$ H_{6b}), 4.07 (t, 1H, J = 9.2 Hz, 1 $\times$ H₃^B), 4.97 (d, 1H, J = 3.0 Hz, 1 $\times$ H₁), 5.05 (m, 4H, 4 $\times$ H₁), 5.10 (d, 1H, J = 3.0 Hz, 1 $\times$ H₁)ppm; **¹³C NMR** (100 MHz, CDCl₃, 300K): δ 25.69, 26.93, 28.85, 29.15, 29.31, 29.45, 29.48, 29.51, 29.56, 29.58, 29.73 (10C, 1 $\times$ C₈, 1 $\times$ C₉, 1 $\times$ C₁₀, 1 $\times$ C₁₁, 1 $\times$ C₁₂, 1 $\times$ C₁₃, 1 $\times$ C₁₄, 1 $\times$ C₁₅, 1 $\times$ C₁₆, 1 $\times$ C₁₇), 51.49 (1C, 1 $\times$ C₁₈), 57.67, 57.72, 57.87, 57.91 (5C, 5 $\times$ OCH₃(C₂)), 58.98, 59.02, 59.04, 59.07, 59.13 (6C, 6 $\times$ OCH₃(C₆)), 61.81, 61.87, 61.96 (5C, 5 $\times$ OCH₃(C₃)), 70.07, 71.19, 71.25, 71.31, 71.63, 71.80 (7C, 6 $\times$ C₅, 1 $\times$ C₇), 71.40 (1C, 1 $\times$ C₃^B), 71.22, 71.34, 71.48, 71.71, 73.05 (6C, 6 $\times$ C₆), 80.95, 81.14, 81.21, 81.26, 81.32, 82.18, 82.22, 82.27, 82.34, 82.39, 82.52, 82.61, 82.84, 83.73 (17C, 6 $\times$ C₂, 5 $\times$ C₃, 6 $\times$ C₄), 100.06, 100.11, 100.31, 100.34, 101.46 (6C, 6 $\times$ C₁)ppm. **HRMS (ESI)**: m/z calcd for C₆₄H₁₁₅N₃O₃₀ [M + Na]⁺ 1428.7458, found 1428.7502 (mass accuracy of -3.1 ppm).

4.1.14 2-aminoalkyl α -CD **9b**

To a solution of **8b** (163 mg, 0.12 mmol) in dry DMF (4 mL) was added NaH (14 mg, 3.0 eq., 0.35 mmol) at 0 °C. After stirred at r.t. for 2h, CH₃I (0.015 mL, 0.23 mmol) was added at 0 °C. The reaction mixture was stirred at r.t. overnight. The excess NaH was quenched by MeOH. The reaction mixture was diluted with ethyl acetate (20 mL), washed with H₂O (1 $\times$ 5mL), brine (3 $\times$ 5 mL), dried over MgSO₄, filtrated and concentrated. The residue was used for further reaction without purification. Dry methanol (7 mL) dissolved the residue. Propane-1,3-dithiol (0.73 mL, 45.0 eq., 5.4 mmol) and dry NEt₃ (0.75 mL, 45.0 eq., 5.4 mmol) were added at r.t. under nitrogen. The reaction mixture was stirred at r.t. for 7 days. The solvent was removed by evaporation. The residue was subjected to flash chromatography (eluent: DCM/MeOH 30:1, then 5:1) to give the product **9b** (166 mg) quantitatively as a white foam. **R_f** = 0.5 (DCM/MeOH = 3:1). **¹H NMR** (400 MHz, CDCl₃, 300K): δ 1.20-1.40 (m, 18H, 2 $\times$ H₈, 2 $\times$ H₉, 2 $\times$ H₁₀, 2 $\times$ H₁₁, 2 $\times$ H₁₂, 2 $\times$ H₁₃, 2 $\times$ H₁₄, 2 $\times$ H₁₅, 2 $\times$ H₁₆), 1.44 (m, 2H, 2 $\times$ H₁₇), 2.70 (t, 2H, J = 7.0 Hz, 2 $\times$ H₁₈), 3.16 (m, 5H, 5 $\times$ H₂), 3.22 (dd, 1H, J_1 = 3.3 Hz, J_2 = 9.7 Hz, 1 $\times$ H₂), 3.39 (m, 2H, 2 $\times$ H₇), 3.40 (m, 18H, 6 $\times$ OCH₃(C₆)), 3.48, 3.49 (m, 15H, 5 $\times$ OCH₃(C₂)), 3.55 (m, 12H, 6 $\times$ H₃, 6 $\times$ H₄), 3.62, 3.63, 3.64, 3.66 (m, 18H, 6 $\times$ OCH₃(C₃)), 3.78 (m, 6H, 6 $\times$ H₅), 3.65-3.91 (m, 12H, 6 $\times$ H_{6a}, 6 $\times$ H_{6b}), 4.97 (d, 1H, J = 3.0 Hz, 1 $\times$ H₁), 5.05 (m, 5H, 5 $\times$ H₁)ppm; **¹³C NMR** (100 MHz, CDCl₃, 300K): δ 26.12, 27.02, 29.62, 29.68, 29.81, 30.25 (10C, 1 $\times$ C₈, 1 $\times$ C₉, 1 $\times$ C₁₀, 1 $\times$ C₁₁, 1 $\times$ C₁₂, 1 $\times$ C₁₃, 1 $\times$ C₁₄, 1 $\times$ C₁₅, 1 $\times$ C₁₆, 1 $\times$ C₁₇), 42.17 (1C, 1 $\times$ C₁₈), 57.97, 57.97, 58.03, 58.08, 58.25 (5C, 5 $\times$ OCH₃(C₂)), 59.10, 59.14 (6C, 6 $\times$ OCH₃(C₆)), 61.76, 61.91, 61.96, 61.99, 62.33 (6C, 6 $\times$ OCH₃(C₃)), 70.96 (1C, 1 $\times$ C₇), 71.16, 71.24, 71.33, 71.40 (6C, 6 $\times$ C₅), 71.52, 71.58, 71.62, 71.68, 71.73 (6C, 6 $\times$ C₆), 81.30, 81.32, 81.40, 81.43, 82.05, 82.08, 82.17, 82.19, 82.33, 82.34, 82.39, 82.43, 82.49, 82.54, 82.63, 82.65, 82.67, 82.69, 82.71 (18C, 6 $\times$ C₂, 6 $\times$ C₃, 6 $\times$ C₄), 100.20, 100.24, 100.42, 100.53, 100.67 (6C, 6 $\times$ C₁)ppm. **HRMS (ESI)**: m/z calcd for C₆₅H₁₂₀NO₃₀ [M + H]⁺ 1394.7890, found 1394.7877 (mass accuracy of 0.9 ppm).

4.1.15 2-permethylated α -CD dimer **10b**

To a solution of 12,12'-(malonylbis(oxy))didodecanoic acid (23 mg, 0.045 mmol) in dry DCM (5mL) was added EDC HCl (26 mg, 3.0 eq., 0.14 mmol) and HOBT (21 mg, 3.0 eq., 0.14 mmol). After the reaction mixture was stirred for 2h at r.t., compound **9b** (126 mg, 2 eq., 0.090 mmol) was added. The reaction mixture was stirred for 24 h. After washed with H₂O (3 $\times$ 3 mL), brine (3 mL), dried over MgSO₄, the solvent was evaporated. The residue was purified by silica gel chromatography (eluent: cyclohexane/acetone 1:1) to give the product **10b** (50 mg, 34%) as a white foam. **R_f** = 0.2 (cyclohexane/acetone = 1:1). **¹H NMR** (400 MHz, CDCl₃, 300K): δ 1.20-1.35 (m, 64H, 4 $\times$ H₈, 4 $\times$ H₉, 4 $\times$ H₁₀, 4 $\times$ H₁₁, 4 $\times$ H₁₂, 4 $\times$ H₁₃, 4 $\times$ H₁₄, 4 $\times$ H₁₅, 4 $\times$ H₁₆, 4 $\times$ H₂₂, 4 $\times$ H₂₃, 4 $\times$ H₂₄, 4 $\times$ H₂₅, 4 $\times$ H₂₆, 4 $\times$ H₂₇, 4 $\times$ H₂₈), 1.45 (m, 4H, 4 $\times$ H₁₇), 1.61 (m, 4H, 4 $\times$ H₂₁), 1.64 (m, 4H, 4 $\times$ H₂₉), 2.13 (t, 4H, J = 7.5 Hz, 4 $\times$ H₂₀), 3.15 (m, 10H, 10 $\times$ H₂), 3.21 (m, 6H, 4 $\times$ H₁₈, 2 $\times$ H₂), 3.34 (s, 2H, 2 $\times$ H₃₂),

3.38 (m, 36H, 12 × OCH₃(C₆)), 3.39 (m, 4H, 4 × H₇), 3.47, 3.48 (m, 30H, 10 × OCH₃(C₂)), 3.54 (m, 24H, 12 × H₃, 12 × H₄), 3.60, 3.62, 3.64 (m, 36H, 12 × OCH₃(C₃)), 3.77 (m, 12H, 12 × H₅), 3.62-3.90 (m, 24H, 12 × H_{6a}, 12 × H_{6b}), 4.11 (t, 4H, *J* = 6.6 Hz, 4 × H₃₀), 4.96 (d, 2H, *J* = 3.4 Hz, 2 × H₁), 5.03 (m, 10H, 10 × H₁), 5.48 (t, 2H, *J* = 6.4 Hz, 2 × -NH-)ppm; ¹³C NMR (100 MHz, CDCl₃, 300K): δ 25.90, 25.95, 26.08, 27.07, 28.57, 29.31, 29.39, 29.45, 29.48, 29.58, 29.62, 29.66, 29.69, 29.72, 29.74, 29.79, 29.83, 30.20 (38C, 2 × C₈, 2 × C₉, 2 × C₁₀, 2 × C₁₁, 2 × C₁₂, 2 × C₁₃, 2 × C₁₄, 2 × C₁₅, 2 × C₁₆, 2 × C₁₇, 2 × C₂₁, 2 × C₂₂, 2 × C₂₃, 2 × C₂₄, 2 × C₂₅, 2 × C₂₆, 2 × C₂₇, 2 × C₂₈, 2 × C₂₉), 37.03 (2C, 2 × C₂₀), 39.64 (2C, 2 × C₁₈), 41.84 (1C, 1 × C₃₂), 57.92, 57.97, 58.01, 58.20 (10C, 10 × OCH₃(C₂)), 59.07, 59.11 (12C, 12 × OCH₃(C₆)), 61.73, 61.88, 61.93, 61.96, 62.31 (12C, 12 × OCH₃(C₃)), 65.76 (2C, 2 × C₃₀), 70.88 (2C, 2 × C₇), 71.21, 71.27, 71.35 (12C, 12 × C₅), 71.53, 71.58, 71.62, 71.68 (12C, 12 × C₆), 81.23, 81.28, 81.33, 81.38, 82.00, 82.28, 82.34, 82.39, 82.49, 82.58, 82.62, 82.66 (36C, 12 × C₂, 12 × C₃, 12 × C₄), 100.16, 100.22, 100.37, 100.49, 100.64 (12C, 12 × C₁), 166.81 (2C, 2 × C₃₁), 173.12 (2C, 2 × C₁₉)ppm. **HRMS (ESI)**: *m/z* calcd for C₁₅₇H₂₈₂N₂O₆₆ [M + 2Na]²⁺ 1648.9284, found 1648.9270 (mass accuracy of 0.8 ppm).

4.1.16 2:1 2-methylated α-CD-C₆₀ conjugate 2b

To a solution of C₆₀ (11 mg, 0.015 mmol), **10b** (50 mg, 1.0 eq., 0.015 mmol) and I₂ (5 mg, 1.23 eq., 0.02 mmol) in 11 mL dry toluene was added DBU (5.2 μL, 2.23 eq., 0.035 mmol) at 0 °C under Ar. After stirred for 1.5 h at room temperature, the reaction mixture was purified by silica gel chromatography (eluent: toluene, then cyclohexane/acetone = 1:1) to give the product **2b** as a brown foam (17 mg, 29%). **R_f** = 0.3 (cyclohexane/acetone = 1:1). ¹H NMR (600 MHz, CDCl₃, 300K): δ 1.20-1.54 (m, 68H, 4 × H₈, 4 × H₉, 4 × H₁₀, 4 × H₁₁, 4 × H₁₂, 4 × H₁₃, 4 × H₁₄, 4 × H₁₅, 4 × H₁₆, 4 × H₁₇, 4 × H₂₂, 4 × H₂₃, 4 × H₂₄, 4 × H₂₅, 4 × H₂₆, 4 × H₂₇, 4 × H₂₈), 1.62 (m, 4H, 4 × H₂₁), 1.83 (m, 4H, 4 × H₂₉), 2.14 (t, 4H, 4 × H₂₀), 3.06-3.21 (m, 16H, 12 × H₂, 4 × H₁₈), 3.33 (m, 36H, 12 × OCH₃(C₆)), 3.42, 3.43 (m, 30H, 10 × OCH₃(C₂)), 3.50 (m, 24H, 12 × H₃, 12 × H₄), 3.55, 3.57, 3.58 (m, 36H, 12 × OCH₃(C₃)), 3.72 (m, 12H, 12 × H₅), 3.37-3.85 (m, 28H, 12 × H_{6a}, 12 × H_{6b}, 4 × H₇), 4.49 (t, 4H, *J* = 6.5 Hz, 4 × H₃₀), 4.96 (d, 2H, 2 × H₁), 5.06 (m, 10H, 10 × H₁), 5.47 (br, 2H, 2 × -NH-)ppm; ¹³C NMR (150 MHz, CDCl₃, 300K): δ 28.89 (2C, 2 × C₂₉), 26.10, 26.27, 27.25, 29.49, 29.61, 29.65, 29.77, 29.82, 29.84, 29.95, 30.02 (36C, 2 × C₈, 2 × C₉, 2 × C₁₀, 2 × C₁₁, 2 × C₁₂, 2 × C₁₃, 2 × C₁₄, 2 × C₁₅, 2 × C₁₆, 2 × C₁₇, 2 × C₂₁, 2 × C₂₂, 2 × C₂₃, 2 × C₂₄, 2 × C₂₅, 2 × C₂₆, 2 × C₂₇, 2 × C₂₈), 37.20 (2C, 2 × C₂₀), 39.78 (2C, 2 × C₁₈), 58.10, 58.16, 58.22, 58.38 (10C, 10 × OCH₃(C₂)), 59.16, 59.20, 59.23 (12C, 12 × OCH₃(C₆)), 61.84, 61.97, 62.02, 62.05, 62.39 (12C, 12 × OCH₃(C₃)), 67.73 (2C, 2 × C₃₀), 71.10, 71.14, 71.40, 71.46, 71.48, 71.49, 71.53, 71.57, 71.73, 71.77, 71.83, 71.89, 72.04 (29C, 12 × C₅, 12 × C₆, 2 × C₇, 2 × sp³-C₆₀, 1 × C₃₂), 81.47, 81.49, 81.60, 81.64, 82.24, 82.50, 82.52, 82.56, 82.62, 82.67, 82.68, 82.70, 82.74, 82.75, 82.79, 82.84 (36C, 12 × C₂, 12 × C₃, 12 × C₄), 100.32, 100.36, 100.52, 100.64, 100.74 (12C, 12 × C₁), 139.27, 141.23, 142.20, 142.49, 143.27, 143.30, 143.36, 144.16, 144.88, 144.97, 145.16, 145.47, 145.54, 145.71 (58C, 58 × sp²-C₆₀), 163.92 (2C, 2 × C₃₁), 173.21 (2C, 2 × C₁₉)ppm. **HRMS (ESI)**: *m/z* calcd for C₂₁₇H₂₈₀N₂O₆₆ [M + 2Na]²⁺ 2007.9200, found 2007.9271 (mass accuracy of -3.5 ppm).

4.1.17 2-azidoalkyl α-CD **8c**

To a solution of 2^A,3^B-diol-α-CD^{Me} (92 mg, 0.079 mmol) [23] in dry DMF (3 mL) was added NaH (10 mg, 3 eq., 0.24 mmol) at 0 °C. After stirred at r.t. for 2h, 2-(2-azidoethoxy)ethyl 4-methylbenzenesulfonate (33 mg, 1.5 eq., 0.12 mmol) in dry DMF (1 mL) was added. The reaction mixture was stirred at r.t. for 6h. MeOH was added dropwise to quench the reaction. The reaction mixture was extracted with EtOAc (30 mL), washed with H₂O (1 × 5 mL), brine (3 × 5 mL), dried over MgSO₄, filtrated and concentrated. The residue was purified by silica gel chromatography (cyclohexane/acetone 2.5:1) to give the product **8c** (51 mg, 49%) as a white foam. **R_f** = 0.3 (cyclohexane/acetone = 1:1). ¹H NMR (400 MHz, CDCl₃, 300K): δ 3.14 (m, 5H, 5 × H₂), 3.20 (dd, 1H, *J*₁ = 3.1 Hz, *J*₂ = 10 Hz, 1 × H₂^B), 3.38 (m, 2H, 2 × H₁₀), 3.37, 3.38 (m, 18H, 6 × OCH₃(C₆)), 3.40, 3.54 (m, 11H, 5 × H₃, 6 × H₄), 3.45, 3.46, 3.50 (m, 15H, 5 × OCH₃(C₂)), 3.59, 3.60, 3.61, 3.62 (m, 15H, 5 × OCH₃(C₃)), 3.58-4.0 (m, 18H, 2 × H₇, 2 × H₈, 2 × H₉, 6 × H_{6a}, 6 × H_{6b}), 3.77 (m, 6H, 6 × H₅), 4.04 (t, 1H, *J* = 9.6 Hz, 1 × H₃^B), 5.01 (m, 5H, 5 × H₁), 5.07 (d, 1H, *J* = 3.3 Hz, 1 × H₁^B)ppm; ¹³C NMR (100 MHz, CDCl₃, 300K): δ 50.59 (1C, 1 × C₁₀), 57.82, 57.84, 57.94, 57.96 (5C, 5 × OCH₃(C₂)), 59.05, 59.09, 59.13, 59.17 (6C, 6 × OCH₃(C₆)), 61.89, 61.94, 61.98 (5C, 5 × OCH₃(C₃)), 69.95 (1C, 1 × C₈), 70.59 (1C, 1 × C₇), 71.34, 71.44, 71.48, 71.54, 71.72, 71.77 (7C, 6 × C₆, 1 × C₉), 70.16, 71.26, 71.30, 71.39, 71.46, 71.84 (6C, 6 × C₅), 71.80 (1C, 1 × C₃^B), 81.07, 81.24, 81.30, 81.40, 82.24, 82.27, 82.35, 82.44, 82.46, 82.58, 82.66, 82.68, 82.84, 83.75 (17C, 6 × C₂, 5 × C₃, 6 × C₄), 100.05, 100.15, 100.20, 100.36, 100.42, 101.47 (6C, 6 × C₁)ppm. **HRMS (ESI)**: *m/z* calcd for C₅₆H₉₉N₃O₃₁ [M + Na]⁺ 1332.6155, found 1332.6137 (mass accuracy of 1.3 ppm).

4.1.18 2-aminoalkyl permethylated α-CD **9c**

To a solution of **8c** (185 mg, 0.14 mmol) in dry DMF (7 mL) was added NaH (17 mg, 3 eq., 0.42 mmol). After stirred for 2h, CH₃I (0.018 mL, 2 eq., 0.28 mmol) was added at 0 °C. The reaction mixture was stirred at r.t. overnight. The excess NaH was quenched by MeOH. The reaction mixture was diluted with ethyl acetate (30 mL), washed with H₂O (1 × 5 mL), brine (3 × 10 mL), dried over MgSO₄, filtrated and concentrated. The residue was used for further reaction without purification. Dry methanol (9 mL) dissolved the residue. Propane-1,3-dithiol (0.85 mL, 45 eq., 6.3 mmol) and dry triethylamine (0.88 mL, 44 eq., 6.3 mmol) were added at room temperature under N₂. The reaction mixture was stirred at room temperature for 7 days. The solvent was removed by evaporation. The residue was purified by silica gel chromatography (eluent: DCM/MeOH 30:1, then 3:1) to give the product **9c** (165 mg, 91%) as a white foam. **R_f** = 0.2 (DCM/MeOH = 5:1). ¹H NMR (400 MHz, CDCl₃, 300K): δ 2.86 (t, 2H, *J* = 5.3 Hz, 2 × H₁₀), 3.14 (m, 5H, 5 × H₂), 3.29 (m, 1H, 1 × H₂^A), 3.38 (m, 18H, 6 × OCH₃(C₆)), 3.52 (m, 2H, 2 × H₇), 3.53 (m, 12H, 6 × H₃, 6 × H₄), 3.62, 3.63 (m, 18H, 6 × OCH₃(C₃)), 3.47 (m, 15H, 5 × OCH₃(C₂)), 3.67 (m, 2H, 2 × H₇), 3.77 (m, 6H, 6 × H₅), 3.86 (m, 2H, 2 × H₈), 3.62-3.90 (m, 12H, 6 × H_{6a}, 6 × H_{6b}), 4.99 (d, 1H, *J* = 3.0 Hz, 1 × H₁^A), 5.03 (m, 5H, 5 × H₁)ppm; ¹³C NMR (100M, CDCl₃, 300K): δ 41.87 (1C, 1 × C₁₀), 57.94, 57.99, 58.03, 58.15 (5C, 5 × OCH₃(C₂)), 59.06, 59.10 (6C, 6 × OCH₃(C₆)), 61.72, 61.86, 61.91, 61.94, 62.14 (6C, 6 × OCH₃(C₃)), 69.96 (1C, 1 × C₈), 70.69 (1C, 1 × C₇), 71.29, 71.35 (6C, 6 × C₅), 71.49, 71.52, 71.60, 71.70 (6C, 6 × C₆), 72.69 (1C, 1 × C₉), 81.34, 81.38, 81.41, 81.47, 81.72, 82.08, 82.32, 82.36, 82.42, 82.52, 82.58, 82.63, 82.66 (18C, 6 × C₂,

6 × C₃, 6 × C₄), 100.19, 100.25, 100.37, 100.45, 100.68 (6C, 6 × C₁)ppm. **HRMS (ESI):** *m/z* calcd for C₅₇H₁₀₄NO₃₁ [M + H]⁺ 1298.6587, found 1298.6595 (mass accuracy of -0.7 ppm).

4.1.19 2-permethylylated α-CD dimer 10c

To a solution of 8,10-dioxo-4,7,11,14-tetraoxaheptadecanedioic acid (17 mg, 0.05 mmol) in dry DCM (5 mL) was added EDC HCl (29 mg, 3 eq., 0.15 mmol) and HOBt (23 mg, 3.0 eq., 0.15 mmol). After stirred at r.t. for 2h, compound **9c** (129 mg, 2 eq., 0.1 mmol) was added. The reaction mixture was stirred at r.t. overnight, then diluted with DCM (20 mL), washed with H₂O (5 × 3 mL), brine (5 × 1 mL), dried over MgSO₄, filtrated and concentrated. The residue was purified by silica gel chromatography (DCM/ MeOH 15:1) to afford the product **10c** (95 mg, 67%) as a white foam. *R_f* = 0.3 (DCM/MeOH = 10:1). **¹H NMR** (400 MHz, CDCl₃, 300K) : δ 2.46 (t, 4H, *J* = 5.9 Hz, 4 × H₁₂), 3.13 (m, 10H, 10 × H₂), 3.29 (m, 2H, 2 × H₂^A), 3.37 (m, 36H, 12 × OCH₃(C₆)), 3.42 (s, 2H, 2 × H₁₇), 3.46 (m, 32H, 10 × OCH₃(C₂), 2 × H_{10b}), 3.54 (m, 24H, 12 × H₃, 12 × H₄), 3.37 (m, 2H, 2 × H_{10a}), 3.60, 3.61, 3.62 (m, 36H, 12 × OCH₃(C₃)), 3.65 (m, 4H, 4 × H₁₄), 3.73 (m, 4H, 4 × H₁₃), 3.76 (m, 12H, 12 × H₅), 3.82 (m, 4H, 4 × H₈), 3.52 (m, 4H, 4 × H₉), 3.48, 3.90 (m, 28H, 12 × H_{6a}, 12 × H_{6b}, 4 × H₇), 4.25 (t, 4H, *J* = 5.0 Hz, 4 × H₁₅), 4.97 (d, 2H, *J* = 3.0 Hz, 2 × H₁^A), 5.02 (m, 10H, 10 × H₁), 6.53 (t, 2H, *J* = 5.4 Hz, 2 × -NH-)ppm; **¹³C NMR** (100 MHz, CDCl₃, 300K) : δ 36.92 (2C, 2 × C₁₂), 39.42 (2C, 2 × C₁₀), 41.32 (1C, 1 × C₁₇), 57.90, 57.92, 57.99, 58.28 (10C, 10 × OCH₃(C₂)), 59.00, 59.07, 59.09 (12C, 12 × OCH₃(C₆)), 61.72, 61.82, 61.85, 61.88, 61.90, 62.09 (12C, 12 × OCH₃(C₃)), 64.53 (2C, 2 × C₁₅), 68.77 (2C, 2 × C₁₄), 67.45 (2C, 2 × C₁₃), 69.75 (2C, 2 × C₈), 69.87 (2C, 2 × C₉), 71.23, 71.26, 71.32, 71.34, 71.44 (12C, 12 × C₅), 71.48, 71.51, 71.55, 71.62 (12C, 12 × C₆), 70.63 (2C, 2 × C₇), 81.27, 81.33, 81.36, 81.40, 81.45, 81.53, 81.61, 82.07, 82.27, 82.30, 82.33, 82.40, 82.49, 82.57, 82.62 (36C, 12 × C₂, 12 × C₃, 12 × C₄), 100.15, 100.22, 100.24, 100.52, 100.57 (12C, 12 × C₁), 166.45 (2C, 2 × C₁₆), 171.03 (2C, 2 × C₁₁)ppm. **HRMS (ESI):** *m/z* calcd for C₁₂₇H₂₂₂N₂O₇₀ [M + Na]⁺ 2918.3765, found 2918.3753 (mass accuracy of 0.4 ppm).

4.1.20 2:1 2-permethylylated α-CD-C₆₀ conjugate 2c

To a solution of C₆₀ (15 mg, 0.020 mmol), **10c** (59 mg, 1 eq., 0.020 mmol) and I₂ (6 mg, 1.23 eq., 0.025 mmol) in 14 mL dry toluene was added DBU (6.8 μL, 2.23 eq., 0.045 mmol) at 0 °C under argon. After stirred at r.t. for 1.5h, the reaction mixture was subjected to flash chromatography (eluent: PhMe, then DCM/MeOH 17:1) to give the product **2c** as a brown foam (28 mg, 39%). *R_f* = 0.4 (DCM/MeOH = 10:1). *[α]_D²⁰* = +40.8 (CHCl₃, *c* = 0.012). **¹H NMR** (400 MHz, CDCl₃, 300K) : δ 2.47 (t, 4H, *J* = 6.0 Hz, 4 × H₁₂), 3.16 (m, 10H, 10 × H₂), 3.30 (m, 2H, 2 × H₂^A), 3.38 (m, 36H, 12 × OCH₃(C₆)), 3.41 (m, 2H, 2 × H_{10a}), 3.47, 3.48 (m, 30H, 10 × OCH₃(C₂)), 3.48 (m, 2H, 2 × H_{10b}), 3.54 (m, 24H, 12 × H₃, 12 × H₄), 3.55 (m, 4H, 4 × H₉), 3.61, 3.62, 3.63 (36H, 12 × OCH₃(C₃)), 3.77 (m, 12H, 12 × H₅), 3.82 (m, 4H, 4 × H₁₃), 3.84 (m, 4H, 4 × H₁₄), 3.60-3.93 (m, 32H, 12 × H_{6a}, 12 × H_{6b}, 4 × H₇, 4 × H₈), 4.62 (t, 4H, *J* = 5.0 Hz, 4 × H₁₅), 4.98 (d, 2H, *J* = 3.0 Hz, 2 × H₁^A), 5.04 (m, 10H, 10 × H₁), 6.50 (t, 2H, *J* = 5.0 Hz, 2 × -NH-)ppm; **¹³C NMR** (100 MHz, CDCl₃, 300K) : δ 37.02 (2C, 2 × C₁₂), 39.50 (2C, 2 × C₁₀), 57.96, 58.03, 58.32 (10C, 10 × OCH₃(C₂)), 59.06, 59.11, 59.15 (12C, 12 × OCH₃(C₆)), 61.77, 61.87, 61.91, 61.92, 61.95, 62.15 (12C, 12 × OCH₃(C₃)), 66.22 (2C, 2 × C₁₅), 67.56 (2C, 2 × C₁₃), 68.70 (2C, 2 × C₁₄), 69.88 (2C, 2 × C₉), 70.64 (2C, 2 × C₇), 71.27, 71.30, 71.37, 71.48, 71.55, 71.57, 71.59, 71.65, 71.65 (29C, 2 × C₈, 1 × C₁₇, 2 × sp³-C₆₀, 12 × C₅, 12 × C₆), 81.30, 81.36, 81.40, 81.44, 81.46, 81.53, 81.71, 82.12, 82.34, 82.44, 82.53, 82.62 (36C, 12 × C₂, 12 × C₃, 12 × C₄), 100.19, 100.26, 100.55, 100.61 (12C, 12 × C₁), 139.19, 141.08, 141.97, 142.33, 143.12, 143.17, 144.02, 144.77, 144.83, 145.26, 145.33, 145.42 (58C, 58 × sp²-C₆₀), 163.51 (2C, 2 × C₁₁), 170.90 (2C, 2 × C₁₆)ppm. **HRMS (ESI):** *m/z* calcd for C₁₈₇H₂₂₀N₂O₇₀ [M + Na]⁺ 3638.3675, found 3638.3726 (mass accuracy of -1.4 ppm).

4.1.21 6-alkyl α-CD 11a

To a solution of 7,7'-(malonylbis(oxy))diheptanoic acid (42 mg, 0.12 mmol) in dry DCM (7 mL) was added EDC HCl (22 mg, 1.0 eq., 0.12 mmol) and HOBt (18 mg, 1.0 eq., 0.12 mmol). After stirred at r.t. for 1h, **6a** (50 mg, 0.33 eq., 0.038 mmol) was added. After stirred at r.t. overnight, the reaction mixture was diluted with 20 mL by DCM, washed with water (2 × 5 mL), brine (1 × 5 mL), dried over MgSO₄, filtrated and concentrated. The residue was purified by silica gel chromatography (eluent: DCM/MeOH 15:1). The product **11a** (41 mg, 65%) was obtained as a white foam. *R_f* = 0.3 (cyclohexane/acetone = 1 : 1). **¹H NMR** (400 MHz, CDCl₃, 300K): δ 1.25-1.35 (m, 6H, 2 × H₈, 2 × H₉, 2 × H₁₀), 1.37 (m, 8H, 2 × H₁₇, 2 × H₂₅, 2 × H₁₆, 2 × H₂₆), 1.50 (m, 2H, 2 × H₁₁), 1.66 (m, 8H, 2 × H₁₈, 2 × H₂₄, 2 × H₁₅, 2 × H₂₇), 2.17 (t, 2H, *J* = 7.26 Hz, 2 × H₁₄), 2.31 (t, 2H, *J* = 7.26 Hz, 2 × H₂₈), 3.16 (m, 6H, 6 × H₂), 3.22 (m, 2H, 2 × H₁₂), 3.36 (s, 2H, 2 × H₂₁), 3.38, 3.39 (5 × s, 15H, 5 × OCH₃(C₆)), 3.48 (m, 20H, 2 × H₇, 6 × OCH₃(C₂)), 3.49-3.61 (m, 12H, 6 × H₃, 6 × H₄), 3.63, 3.64 (m, 19H, 1 × H_{6a}^A, 6 × OCH₃(C₃)), 3.66-3.87 (m, 6 × H₅, 10 × H₆), 3.89 (dd, 1H, *J*₁ = 3.12 Hz, *J*₂ = 10.66 Hz, 1 × H_{6b}^A), 4.13 (m, 4H, 2 × H₁₉, 2 × H₂₃), 5.03 (m, 6H, 6 × H₁), 5.65 (t, *J* = 5.10 Hz, 1 × -NH-)ppm; **¹³C NMR** (100MHz, CDCl₃, 300K): δ 24.85, 25.57, 25.69, 25.71, 25.96, 26.89, 28.39, 28.45, 28.69, 28.95, 29.69 (12C, 1 × C₈, 1 × C₉, 1 × C₁₀, 1 × C₁₁, 1 × C₁₅, 1 × C₁₆, 1 × C₁₇, 1 × C₁₈, 1 × C₂₄, 1 × C₂₅, 1 × C₂₆, 1 × C₂₇), 34.00 ((1C, 1 × C₂₈), 36.75 ((1C, 1 × C₁₄), 39.66 (1C, 1 × C₁₂), 41.99 (1C, 1 × C₂₁), 57.97, 58.00, 58.03 (6C, 6 × OCH₃(C₂)), 59.04, 59.12, 59.18 (5C, 5 × OCH₃(C₆)), 61.89, 61.92, 61.95 (6C, 6 × OCH₃(C₃)), 65.55, 65.65 (2C, 1 × C₁₉, 1 × C₂₃), 69.53 (1C, 1 × C₆^A), 71.31, 71.36 (6C, 6 × C₅), 71.51 (1C, 1 × C₇), 71.60, 71.70 (5C, 5 × C₆), 81.40, 81.48, 81.50, 82.25, 82.33, 82.38, 82.57, 82.59, 82.62 (18C, 6 × C₂, 6 × C₃, 6 × C₄), 100.06, 100.21, 100.25, 100.31, 100.35 (6C, 6 × C₁), 166.74, 166.76 (2C, 1 × C₂₀, 1 × C₂₂), 173.60, 176.02 (2C, 1 × C₁₃, 1 × C₂₉)ppm. **HRMS (ESI):** *m/z* calcd for C₇₆H₁₃₃N₃O₃₇ [M - H]⁻ 1651.8620, found 1651.8555 (mass accuracy of 3.9 ppm).

4.1.22 6-alkyl α-CD 12a

To a solution of **11a** (64 mg, 0.039 mmol) in dry DMF (3 mL) was added K₂CO₃ (11mg, 2 eq., 0.078 mmol) and CH₃I (3 μ L, 1.3 eq., 0.05 mmol). After stirred at r.t. overnight, the reaction mixture was diluted with DCM (20 mL), washed with water (1 $\times$ 5 mL), brine (3 $\times$ 5 mL), dried with MgSO₄, filtrated and concentrated. The residue was purified by silica gel chromatography (eluent: cyclohexane/acetone 2:1) to give the product **12a** (42 mg, 65%) as a white foam. **R_f** = 0.5 (cyclohexane: acetone = 1: 1.2). **¹H NMR** (400 MHz, CDCl₃, 300K): δ 1.32 (m, 12H, 2 $\times$ H₈, 2 $\times$ H₉, 2 $\times$ H₁₆, 2 $\times$ H₂₅, 2 $\times$ H₁₇, 2 $\times$ H₂₆), 1.46 (m, 2H, 2 $\times$ H₁₁), 1.61 (m, 8H, 2 $\times$ H₁₈, 2 $\times$ H₂₄, 2 $\times$ H₁₅, 2 $\times$ H₂₇), 2.11 (t, J = 7.36 Hz, 2 $\times$ H₁₄), 2.28 (t, J = 7.36 Hz, 2 $\times$ H₂₈), 3.13 (m, 6H, 6 $\times$ H₂), 3.19 (m, 2H, 2 $\times$ H₁₂), 3.33 (s, 2H, 2 $\times$ H₂₁), 3.35, 3.36 (5 $\times$ s, 15H, 5 $\times$ OCH₃(C₆)), 3.43 (m, 2H, 2 $\times$ H₇), 3.46 (6 $\times$ s, 18H, 5 $\times$ OCH₃(C₂)), 3.47-3.60 (m, 12H, 6 $\times$ H₂, 6 $\times$ H₃), 3.61 (6 $\times$ s, 18H, 6 $\times$ OCH₃(C₃)), 3.63 (s, 3H, 3 $\times$ H₃₀), 3.64-3.85 (m, 17H, 1 $\times$ H_{6a}^A, 6 $\times$ H₅, 10 $\times$ H₆), 3.87 (dd, 1H, 1 $\times$ H_{6b}^A), 4.09 (m, 4H, 2 $\times$ H₁₉, 2 $\times$ H₂₃), 5.02 (m, 6H, 6 $\times$ H₁), 5.56 (t, 1H, J = 5.83 Hz, 1 $\times$ -NH-)ppm; **¹³C NMR** (100 MHz, CDCl₃, 300K): δ 24.84, 25.54, 25.56, 25.59, 25.92, 26.99, 28.38, 28.76, 28.83, 29.68, 29.75 (12C, 1 $\times$ C₈, 1 $\times$ C₉, 1 $\times$ C₁₀, 1 $\times$ C₁₁, 1 $\times$ C₁₅, 1 $\times$ C₁₆, 1 $\times$ C₁₇, 1 $\times$ C₁₈, 1 $\times$ C₂₄, 1 $\times$ C₂₅, 1 $\times$ C₂₆, 1 $\times$ C₂₇), 34.06 (1C, 1 $\times$ C₂₈), 36.66 (1C, 1 $\times$ C₁₄), 39.49 (1C, 1 $\times$ C₁₂), 41.73 (1C, 1 $\times$ C₂₁), 51.59 (1C, 1 $\times$ C₃₀), 57.90, 57.92, 57.95 (6C, 6 $\times$ OCH₃(C₂)), 59.01, 59.07, 59.13 (5C, 5 $\times$ OCH₃(C₆)), 61.84, 61.86, 61.90 (6C, 6 $\times$ OCH₃(C₃)), 65.35, 65.38 (2C, 1 $\times$ C₁₉, 6 $\times$ C₂₃), 69.47 (1C, 1 $\times$ C₆^A), 71.25, 71.30 (6C, 6 $\times$ C₅), 71.48, 71.55, 71.64 (6C, 5 $\times$ C₆, 1 $\times$ C₇), 81.32, 81.37, 81.40, 82.23, 82.28, 82.34, 82.36, 82.53, 82.57 (18C, 6 $\times$ C₂, 6 $\times$ C₃, 6 $\times$ C₄), 100.02, 100.15, 100.20, 100.25, 100.31 (6C, 6 $\times$ C₁), 170.21, 170.30 (2C, 1 $\times$ C₂₀, 1 $\times$ C₂₂), 172.83, 174.15 (2C, 1 $\times$ C₁₃, 1 $\times$ C₂₉)ppm. **HRMS (ESI): m/z** calcd for C₇₇H₁₃₅NO₃₇ [M + Na]⁺ 1688.8605, found 1688.8608 (mass accuracy of -0.1 ppm).

4.1.23 α -CD^{Me}-C₆₀ conjugate 3

To a solution of **12a** (42 mg, 0.025 mmol), C₆₀ (91 mg, 5 eq., 0.13 mmol), CBr₄ (21 mg, 2.5 eq., 0.65 mmol) in dry toluene (8 mL) was added DBU (9.4 μ L). The brown reaction mixture was stirred overnight, which was subjected to silica chromatography directly (eluent: toluene to remove the excess of C₆₀, then cyclohexane/acetone 2.5:1). The product **3** was obtained (9 mg, 15%) as a foam. **R_f** = 0.5 (cyclohexane/acetone = 1: 1). **[α]_D²⁰** = +56.3 (CHCl₃, c = 0.024). **¹H NMR** (400 MHz, CDCl₃, 300K): δ 1.32-1.42 (m, 6H, 2 $\times$ H₈, 2 $\times$ H₉, 2 $\times$ H₁₀), 1.43 (m, 8H, 2 $\times$ H₁₆, 2 $\times$ H₂₆, 2 $\times$ H₁₇, 2 $\times$ H₂₅), 1.46 (m, 2H, 2 $\times$ H₁₁), 1.66 (m, 4H, 2 $\times$ H₁₅, 2 $\times$ H₂₇), 1.85 (m, 4H, 2 $\times$ H₁₈, 2 $\times$ H₂₄), 2.14 (t, 2H, J = 8.01 Hz, 2 $\times$ H₁₄), 2.32 (t, 2H, J = 7.72 Hz, 2 $\times$ H₂₈), 3.16 (m, 6H, 6 $\times$ H₂), 3.23 (m, 2H, 2 $\times$ H₁₂), 3.38, 3.39, 3.40 (5 $\times$ s, 15H, 5 $\times$ OCH₃(C₆)), 3.48 (m, 2H, 2 $\times$ H₇), 3.49 (6 $\times$ s, 18H, 6 $\times$ OCH₃(C₂)), 3.51-3.61 (m, 12H, 6 $\times$ H₃, 2 $\times$ H₄), 3.64, 3.65 (6 $\times$ s, 18H, 6 $\times$ OCH₃(C₃)), 3.66 (m, 1H, 1 $\times$ H_{6a}^A), 3.67 (s, 3H, 3 $\times$ H₃₀), 3.62-3.87 (m, 6 $\times$ OCH₃(C₃), 6 $\times$ H₅, 10 $\times$ H₆), 3.90 (dd, 1H, J_1 = 3.60 Hz, J_2 = 11.39 Hz, 1 $\times$ H_{6b}^A), 4.49 (m, 4H, 2 $\times$ H₁₉, 2 $\times$ H₂₃), 5.05 (m, 6H, 6 $\times$ H₁), 5.51 (t, 1H, J = 5.34 Hz, 1 $\times$ -NH-)ppm; **¹³C NMR** (100 MHz, CDCl₃, 300K): δ 24.98, 25.73, 25.85, 26.01, 27.01, 28.86, 28.99, 29.84, 29.90 (10C, 1 $\times$ C₈, 1 $\times$ C₉, 1 $\times$ C₁₀, 1 $\times$ C₁₁, 1 $\times$ C₁₅, 1 $\times$ C₁₆, 1 $\times$ C₁₇, 1 $\times$ C₂₅, 1 $\times$ C₂₆, 1 $\times$ C₂₇), 28.57 (2C, 1 $\times$ C₁₈, 1 $\times$ C₂₄), 34.17 (1C, 1 $\times$ C₂₈), 36.85 (1C, 1 $\times$ C₁₄), 39.67 (1C, 1 $\times$ C₁₂), 51.76 (1C, 1 $\times$ C₃₀), 57.98, 58.00, 58.04 (6C, 6 $\times$ OCH₃(C₂)), 59.10, 59.15, 59.22 (5C, 5 $\times$ OCH₃(C₆)), 61.92, 61.95, 61.98 (6C, 6 $\times$ OCH₃(C₃)), 67.52 (2C, 1 $\times$ C₁₉, 1 $\times$ C₂₃), 69.61 (1C, 1 $\times$ C₆^A), 71.32, 71.33, 71.38, 71.57, 71.62, 71.72, 71.73, 71.81 (16C, 6 $\times$ C₅, 5 $\times$ C₆, 1 $\times$ C₂₁, 2 $\times$ sp³-C₆₀, 1 $\times$ C₇), 81.39, 81.40, 81.45, 81.47, 82.31, 82.35, 82.44, 82.49, 82.62, 82.65 (18C, 6 $\times$ C₂, 6 $\times$ C₃, 6 $\times$ C₄), 100.10, 100.24, 100.28, 100.34, 100.40 (6C, 6 $\times$ C₁), 139.10, 139.14, 141.10, 141.13, 142.04, 142.35, 143.14, 143.18, 143.25, 144.04, 144.78, 144.85, 145.04, 145.29, 145.32, 145.34, 145.42, 145.49, 145.49 (58C, 58 $\times$ sp²-C₆₀), 163.77, 163.81 (2C, 1 $\times$ C₂₀, 1 $\times$ C₂₂), 172.78, 174.17 (2C, 1 $\times$ C₁₃, 1 $\times$ C₂₉)ppm. **HRMS (ESI): m/z** calcd for C₁₃₇H₁₃₃NO₃₇ [M + Na]²⁺ 1214.9170, found 1214.9124 (z = 2⁺, mass accuracy of 3.8 ppm).

4.1.24 2-alkyl α -CD **13a**

To a solution of 7,7'-(malonylbis(oxy))diheptanoic acid (77 mg, 0.21 mmol) in dry DCM (6 mL) was added EDC HCl (41 mg, 1 eq., 0.21 mmol) and HOBt (33 mg, 1 eq., 0.21 mmol). The reaction mixture was stirred at r.t. for 2h and **9a** (140 mg, 0.5 eq., 0.11 mmol) was added. After stirred overnight at r.t., the reaction mixture was diluted with DCM (20 mL), washed with water (2 $\times$ 7 mL), brine (1 $\times$ 5 mL), dried over MgSO₄, filtrated and concentrated. The residue was purified by silica gel chromatography (eluent: DCM/MeOH 9:1) to give the product **13a** (106 mg, 60%) as a white foam. **R_f** = 0.2 (DCM/MeOH = 6:1). **¹H NMR** (400 MHz, CDCl₃, 300K): δ 1.29-1.40 (m, 16H, 2 $\times$ H₈, 2 $\times$ H₉, 2 $\times$ H₁₀, 2 $\times$ H₁₁, 2 $\times$ H₁₆, 2 $\times$ H₁₇, 2 $\times$ H₂₅, 2 $\times$ H₂₆), 1.62 (m, 2H, 2 $\times$ H₁₅), 1.64 (m, 6H, 2 $\times$ H₁₈, 2 $\times$ H₂₄, 2 $\times$ H₂₇), 2.17 (t, 2H, J = 7.22 Hz, 2 $\times$ H₁₄), 2.31 (t, 2H, J = 7.22 Hz, 2 $\times$ H₂₈), 3.12-3.18 (m, 5H, 5 $\times$ H₂), 3.22 (m, 3H, 1 $\times$ H₂^A, 2 $\times$ H₁₂), 3.35 (s, 2H, 2 $\times$ H₂₁), 3.39 (6 $\times$ s, 18H, 6 $\times$ OCH₃(C₆)), 3.41 (m, 2H, 2 $\times$ H₇), 3.48 (m, 15H, 5 OCH₃(C₂)), 3.49-3.60 (m, 12H, 6 $\times$ H₃, 6 $\times$ H₄), 3.61, 3.63, 3.64 (6 $\times$ s, 18H, 6 $\times$ OCH₃(C₃)), 3.65-3.86 (m, 17H, 6 $\times$ H₅, 11 $\times$ H₆), 3.91 (dd, 1H, J_1 = 10.88 Hz, J_2 = 3.81 Hz, 1 $\times$ H₆), 4.13 (m, 4H, 2 $\times$ H₁₉, 2 $\times$ H₂₃), 4.95 (d, 1H, J = 3.04 Hz, 1 $\times$ H₁^A), 5.04 (m, 5H, 5 $\times$ H₁), 5.71 (t, 1H, J = 5.53 Hz, 1 $\times$ -NH-)ppm; **¹³C NMR** (100 MHz, CDCl₃, 300K): δ 22.81, 24.85, 25.57, 25.68, 25.72, 28.39, 28.45, 28.69, 28.94, 29.48, 29.60 (12C, 1 $\times$ C₈, 1 $\times$ C₉, 1 $\times$ C₁₀, 1 $\times$ C₁₁, 1 $\times$ C₁₅, 1 $\times$ C₁₆, 1 $\times$ C₁₇, 1 $\times$ C₁₈, 1 $\times$ C₂₄, 1 $\times$ C₂₅, 1 $\times$ C₂₆, 1 $\times$ C₂₇), 33.93 (1C, 1 $\times$ C₂₈), 36.72 (1C, 1 $\times$ C₁₄), 39.65 (1C, 1 $\times$ C₁₂), 42.11 (1C, 1 $\times$ C₂₁), 57.95, 57.98, 58.02, 58.28 (5C, 5 $\times$ OCH₃(C₂)), 59.05, 59.10, 59.12 (6C, 6 $\times$ OCH₃(C₆)), 61.74, 61.83, 61.91, 61.94, 62.31 (6C, 6 $\times$ OCH₃(C₃)), 65.54, 65.63 (2C, 1 $\times$ C₁₉, 1 $\times$ C₂₃), 70.75 (1C, 1 $\times$ C₇), 71.29, 71.34, 71.38 (6C, 6 $\times$ C₅), 71.56, 71.63, 71.68 (6C, 6 $\times$ C₆), 81.32, 81.42, 81.96, 82.33, 82.45, 82.52, 82.61 (18C, 6 $\times$ C₂, 6 $\times$ C₃, 6 $\times$ C₄), 100.18, 100.25, 100.31, 100.53, 100.53, 100.59 (6C, 6 $\times$ C₁), 166.73 (2C, 1 $\times$ C₂₀, 1 $\times$ C₂₂), 173.59, 176.03 (2C, 1 $\times$ C₂₉, 1 $\times$ C₁₃)ppm. **HRMS (ESI): m/z** calcd for C₇₆H₁₃₃NO₃₇ [M + Na]⁺ 1674.8449, found 1674.8490 (mass accuracy of -2.5 ppm).

4.1.25 2-alkyl α -CD **14a**

To a solution of **13a** (55 mg, 0.03 mmol) and K₂CO₃ (9 mg, 2 eq., 0.06 mmol) in dry DMF (2 mL) was added MeI (3 μ L, 1.5 eq., 0.045 mmol) at r.t.. After stirred overnight, the reaction mixture was extracted with DCM (20 mL), washed with brine (5 $\times$ 5 mL), dried over MgSO₄, filtrated and concentrated. The residue was purified by silica gel chromatography (eluent: cyclohexane/acetone 1.5:1) to give the product **14a** (45 mg, 81%) as a white foam. **R_f** = 0.5 (DCM: MeOH = 8:1). **¹H**

NMR (400 MHz, CDCl₃, 300K) : δ 1.29 – 1.54 (m, 16H, 2 $\times$ H₈, 2 $\times$ H₉, 2 $\times$ H₁₀, 2 $\times$ H₁₁, 2 $\times$ H₁₆, 2 $\times$ H₁₇, 2 $\times$ H₂₅, 2 $\times$ H₂₆), 1.62 (m, 8H, 2 $\times$ H₁₈, 2 $\times$ H₂₄, 2 $\times$ H₁₅, 2 $\times$ H₂₇), 2.12 (t, 2H, J = 7.78 Hz, 2 $\times$ H₁₄), 2.28 (t, 2H, J = 7.5 Hz, 2 $\times$ H₂₈), 3.13 (m, 5H, 5 $\times$ H₂), 3.19 (m, 1H, 1 $\times$ H₂^A), 3.20 (m, 2H, 2 $\times$ H₁₂), 3.33 (s, 2H, 2 $\times$ H₂₁), 3.37 (6 $\times$ s, 18H, 6 $\times$ OCH₃(C₆)), 3.39 (m, 2H, 2 $\times$ H₇), 3.46, 3.47 (5 $\times$ s, 15H, 5 $\times$ OCH₃(C₂)), 3.48-3.59 (m, 12H, 6 $\times$ H₃, 6 $\times$ H₄), 3.59-3.63 (m, 18H, 6 $\times$ OCH₃(C₃)), 3.64 (s, 3H, 3 $\times$ H₃₀), 3.65-3.85 (m, 17H, 6 $\times$ H₅, 11 $\times$ H₆), 3.89 (dd, 1H, J_1 = 3.54 Hz, J_2 = 10.64 Hz, 1 $\times$ H₆), 4.09 (m, 4H, 2 $\times$ H₁₉, 2 $\times$ H₂₃), 4.94 (d, 1H, J = 2.92 Hz, 1 $\times$ H₁^A), 5.02 (m, 5H, 5 $\times$ H₁), 5.61 (t, 1H, J = 6.01 Hz, 1 $\times$ -NH-)ppm; **¹³C NMR** (100 MHz, CDCl₃, 300K) : δ 24.85, 25.57, 25.62, 25.69, 26.83, 28.36, 28.39, 28.77, 28.86 (12C, 1 $\times$ C₈, 1 $\times$ C₉, 1 $\times$ C₁₀, 1 $\times$ C₁₁, 1 $\times$ C₁₅, 1 $\times$ C₁₆, 1 $\times$ C₁₇, 1 $\times$ C₁₈, 1 $\times$ C₂₄, 1 $\times$ C₂₅, 1 $\times$ C₂₆, 1 $\times$ C₂₇), 34.06 (1C, 1 $\times$ C₂₈), 36.69 (1C, 1 $\times$ C₁₄), 39.49 (1C, 1 $\times$ C₁₂), 41.73 (1C, 1 $\times$ C₂₁), 51.61 (1C, 1 $\times$ C₃₀), 57.90, 57.96, 57.96, 58.21 (5C, 5 $\times$ OCH₃(C₂)), 59.01, 59.06 (6C, 6 $\times$ OCH₃(C₆)), 61.71, 61.82, 61.88, 61.91, 62.27 (6C, 6 $\times$ OCH₃(C₃)), 65.48 (2C, 1 $\times$ C₁₉, 1 $\times$ C₂₃), 70.65 (1C, 1 $\times$ C₇), 71.21, 71.24, 71.27, 71.33 (6C, 6 $\times$ C₅), 71.51, 71.57, 71.61 (6C, 6 $\times$ C₆), 81.22, 81.26, 81.32, 81.37, 81.41, 81.97, 82.25, 82.28, 82.33, 82.39, 82.47, 82.54, 82.56, 82.61 (18C, 6 $\times$ C₂, 6 $\times$ C₃, 6 $\times$ C₄), 100.13, 100.20, 100.30, 100.49, 100.57 (6C, 6 $\times$ C₁), 170.22, 170.31 (2C, 1 $\times$ C₂₀, 1 $\times$ C₂₂), 172.86 (1C, 1 $\times$ C₂₉), 174.16 (1C, 1 $\times$ C₁₃)ppm. **HRMS (ESI)**: m/z calcd for C₇₇H₁₃₅NO₃₇ [M + Na]⁺ 1688.8605, found 1688.8654 (mass accuracy of -2.9 ppm).

4.1.26 α -CD^{Me}-C₆₀ conjugate 4

To a solution of **14a** (113 mg, 0.068 mmol), C₆₀ (244 mg, 5 eq., 0.34 mmol) and CBr₄ (113 mg, 5 eq., 0.34 mmol) in dry toluene (21 mL) was added DBU (25 μ L, 2.5 eq., 0.17 mmol) at r.t. under Ar. After stirred for overnight, the brown reaction mixture was subjected to silica chromatography directly (toluene to remove the excess of C₆₀, then cyclohexane / acetone 2 : 1) to give the product **4** (40 mg, 25%) as a brown foam. **R_f** = 0.3 (cyclohexane/acetone = 1 : 1). **[α]_D²⁰** = +51.69 (CHCl₃, c = 0.039). **¹H NMR** (600 MHz, CDCl₃, 300K) : δ 1.41 (m, 6H, 2 $\times$ H₁₆, 2 $\times$ H₂₆, 2 $\times$ H₉), 1.48 (m, 4H, 2 $\times$ H₁₇, 2 $\times$ H₂₅), 1.49 (m, 2H, 2 $\times$ H₁₀), 1.50 (m, 2H, 2 $\times$ H₁₁), 1.60 (m, 2H, 2 $\times$ H₈), 1.64 (m, 4H, 2 $\times$ H₁₅, 2 $\times$ H₂₇), 1.84 (m, 4H, 2 $\times$ H₁₈, 2 $\times$ H₂₄), 2.16 (t, J = 7.49 Hz, 2 $\times$ H₁₄), 2.32 (t, J = 7.49 Hz, 2 $\times$ H₂₈), 3.15 (m, 5H, 5 $\times$ H₂), 3.21 (m, 3H, 1 $\times$ H₂^A, 2 $\times$ H₁₂), 3.39 (6 $\times$ s, 18H, 6 $\times$ OCH₃(C₆)), 3.40 (m, 2H, 2 $\times$ H₇), 3.48 (5 $\times$ s, 15H, 5 $\times$ OCH₃(C₂)), 3.49-3.59 (m, 12H, 6 $\times$ H₃, 6 $\times$ H₄), 3.60, 3.61, 3.62, 3.63, 3.64 (6 $\times$ s, 18H, 6 $\times$ OCH₃(C₃)), 3.66 (s, 3H, 3 $\times$ H₃₀), 3.67-3.87 (m, 17H, 6 $\times$ H₅, 11 $\times$ H₆), 3.90 (dd, 1H, J_1 = 3.54 Hz, J_2 = 10.64 Hz, 1 $\times$ H₆), 4.48 (m, 4H, 2 $\times$ H₁₉, 2 $\times$ H₂₃), 4.95 (d, 1H, J = 2.99 Hz, 1 $\times$ H₁^A), 5.04 (m, 5H, 5 $\times$ H₁), 5.56 (t, 1H, J = 5.60 Hz)ppm; **¹³C NMR** (150 MHz, CDCl₃, 300K) : δ 24.97, 25.73, 25.76, 25.83, 25.84, 26.91, 28.85, 28.98, 30.12 (10C, 1 $\times$ C₈, 1 $\times$ C₉, 1 $\times$ C₁₀, 1 $\times$ C₁₁, 1 $\times$ C₁₅, 1 $\times$ C₁₆, 1 $\times$ C₁₇, 1 $\times$ C₂₅, 1 $\times$ C₂₆, 1 $\times$ C₂₇), 28.59 (2C, 1 $\times$ C₁₈, 1 $\times$ C₂₄), 34.09 (1C, 1 $\times$ C₂₈), 36.79 (1C, 1 $\times$ C₁₄), 39.55 (1C, 1 $\times$ C₁₂), 51.72 (1C, 1 $\times$ C₃₀), 57.96, 58.02, 58.27 (5C, 5 $\times$ OCH₃(C₂)), 59.07, 59.11, 59.14 (6C, 6 $\times$ OCH₃(C₆)), 61.76, 61.87, 61.93, 61.96, 62.32 (6C, 6 $\times$ OCH₃(C₃)), 67.42 (2C, 1 $\times$ C₁₉, 1 $\times$ C₂₃), 71.26, 71.29, 71.32, 71.37, 71.41, 71.53, 71.56, 71.62, 71.66, 71.68, 71.79 (15C, 6 $\times$ C₅, 6 $\times$ C₆, 2 $\times$ sp³-C₆₀, 1 $\times$ C₂₁), 81.26, 81.31, 81.36, 81.38, 81.40, 81.42, 81.45, 82.01, 82.29, 82.32, 82.37, 82.40, 82.43, 82.46, 82.51, 82.55, 82.58, 82.61, 82.64, 82.67 (18C, 6 $\times$ C₂, 6 $\times$ C₃, 6 $\times$ C₄), 100.16, 100.18, 100.24, 100.33, 100.53, 100.61 (6C, 6 $\times$ C₁), 139.08, 139.13, 141.08, 141.10, 142.03, 142.33, 143.12, 143.16, 143.23, 144.01, 144.74, 144.76, 144.78, 144.82, 145.02, 145.28, 145.30, 145.32, 145.40, 145.47 (58C, 58 $\times$ sp²-C₆₀), 163.75, 163.79 (2C, 1 $\times$ C₂₀, 1 $\times$ C₂₂), 172.80 (1C, 1 $\times$ C₂₉), 174.16 (1C, 1 $\times$ C₁₃)ppm. **HRMS (ESI)**: m/z calcd for C₁₃₇H₁₃₃NO₃₇ [M + Na]⁺ 2406.8449, found 2406.8508 (mass accuracy of -2.5 ppm).

4.2 Cytotoxicity test

Cells were seeded in 96-well plates in DMEM supplemented with 10% FBS and cultured overnight at 37 °C in 5% CO₂. Then the tested compounds were added and the cells were further incubated at 37 °C in 5% CO₂ for 40 hours. Cell viability was assessed using the CellTiter-Glo assay kit as recommended by the supplier, and the plates were read using a plate reader (Tecan Infinite M2000 PRO; Tecan Group Ltd., Männedorf, Switzerland) Viability was calculated using the background-corrected absorbance as follows:

Viability (%) = A of experiment well/A of control well $\times$ 100%.

4.3 Cytopathic effect (CPE) reduction assay

The assay was performed as reported by Noah et al. with some modifications [24]. MDCK cells were seeded into 96-well plates, incubated overnight and infected with influenza virus (MOI = 0.1) suspended in DMEM supplemented with 1% FBS, containing 2 μ g/mL TPCK-treated trypsin and tested compound, with a final DMSO concentration of 1% in each well. After incubation for 40h, CellTiterGlo reagent (Promega Corp., Madison, WI, USA) was added and the plates were read using a plate reader (Tecan Infinite M2000 PRO™; Tecan Group Ltd., Männedorf, Switzerland).

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