Potential Supramolecular Cyclodextrin Dimers Using Nucleobase Pairs

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Received 11 June 2009

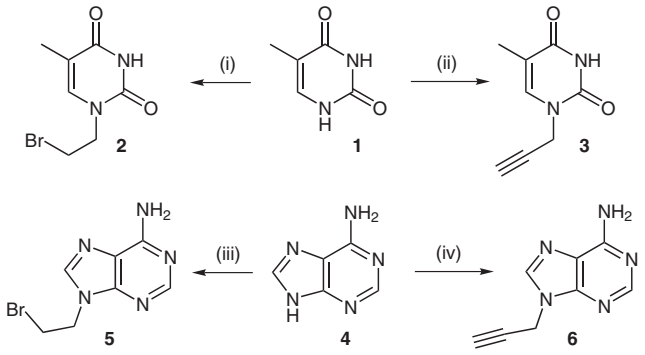
Abstract: The synthesis of six new cyclodextrin derivatives having nucleobase moiety is described. These two moieties are linked by different spacers, such as aminoethyl and 1,2,3-triazolyl groups. Example of association constants for complexation of adenine and thymine derivatives: K_{AT} = 385 M^{-1} using NMR methodology is reported. Study of interaction between four cyclodextrin derivatives and one adamantyl guest is described by ITC.

Key words: click chemistry, nucleobase, cyclodextrin

Cyclodextrins (CD) are a family of cyclic oligosaccharides composed of α-(1→4)-linked D-glucopyranose units in $^4C_1$ chair conformation. The most common CD have six, seven, and eight glucopyranose units and are referred to as α-, β-, and γ-CD, respectively. As a consequence of the structure, the molecule is hydrophilic and features a conical cavity that is essentially hydrophobic in nature. This property enables them to be successfully used as drug carrier,[1–3] separation reagents,[4–6] enzyme mimics,[7,8] photochemical sensors,[9,10] catalysis,[11,12] host–guest interactions,[13] and molecular recognition.[14] In comparison with CD monomers, CD dimers tethered by a spacer of different sizes and shapes have two hydrophobic cavities in a close vicinity.[15] This property may afford distinctly different apparent association abilities and molecular selectivities.[16] Various structural architectures of covalent CD dimers could be prepared but one challenge will be to obtain supramolecular CD dimers with noncovalent interactions such as H bonding, staking, electrostatic, and charge-transfer interactions. The equilibrium between the noncovalent dimers and the corresponding monomers could permit to modulate the association. Unexpectedly, these molecular organization behaviors have not been extensively investigated. The supramolecular assembly could be obtained by association of nucleobases such as adenine and thymine or guanine and cytosine. Few examples of CD derivative having nucleobase were described in the literature but only the study of CD monomers were reported.[17–21] In this paper, we reported our preliminary work regarding the synthesis of different CD monomers having a nucleobase such as adenine and thymine and their potential application for the formation of supramolecular CD dimers. The target compounds **8**, **9**, **11**, and **12** had three major structural variations and were novel CD derivatives. First modulation was the glycone moiety: amino-β-CD, azido-β-CD, or amino-permethylated β-CD derivatives. Second variation was the nature of the linker: aminoethyl group or 1,2,3-triazol-4-ylmethyl group. Third modulation was the nucleobase: adenine or thymine.

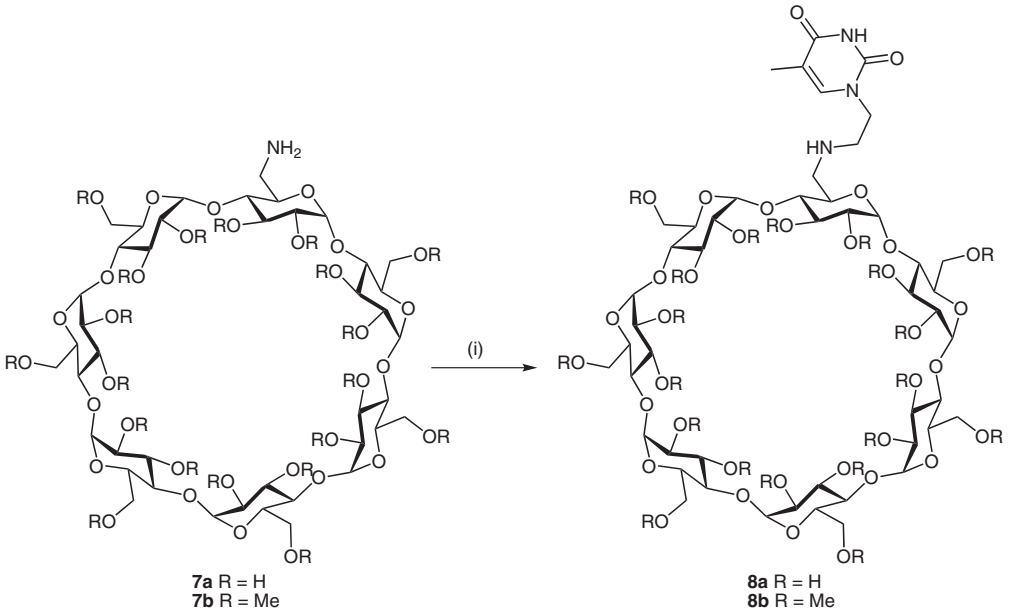
N-Alkylation of pyrimidine bases gave predominantly N1-monosubstituted and N1,N3-bis-substituted derivatives. In order to prepare regioselectively the N1-alkylated pyrimidine, silylation of the nucleobase was developed. Coupling of dibromoethane with silylated thymine (**1**) in presence of NaI at 105 °C without solvent furnished the bromide **2**[22–25] in 32% yield. Coupling of propargyl bromide with silylated thymine at 80 °C in acetonitrile gave the alkyne **3**[26,27] in 89% yield. The N9-alkylated adenine derivatives **5**[25] and **6**[26,27] were obtained from unprotected adenine (**4**). Starting from **4**, selective alkylation with dibromoethane and propargyl bromide using K_2CO_3 in DMF gave the derivatives **5** and **6** in 40 and 39% yields, respectively (Scheme 1).

The desired CD derivative **8a**[28] was obtained in 14% yield by the reaction of β-CD derivative **7a** with an excess of bromide **2** in anhydrous DMSO at 50 °C for 16 hours (Scheme 2). Starting from β-CD derivative **7a** and per-



Scheme 1 *Reaction conditions*: (i) HMDS, $(NH_4)_2SO_4$, reflux, 12 h then BrC_2H_4Br, NaI, 105 °C, 25 h (32%); (ii) BSA, MeCN, reflux, 12 h then $HCCCH_2Br$, reflux, 16 h (89%); (iii) BrC_2H_4Br, K_2CO_3, DMF, r.t., 24 h (40%); (iv) $HCCCH_2Br$, K_2CO_3, DMF, r.t., 24 h (39%).

SYNLETT 2009, No. 17, pp 2875–2879
Advanced online publication: 24.09.2009
DOI: 10.1055/s-0029-1217988; Art ID: G16909ST



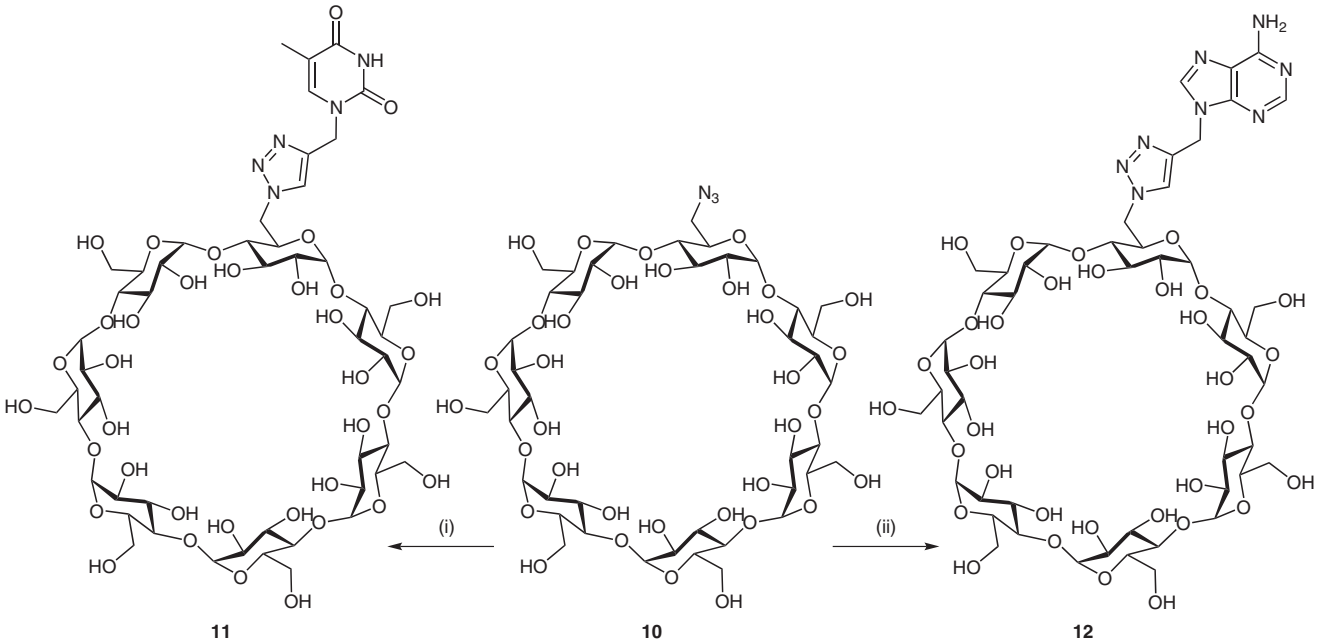
Scheme 2 *Reaction conditions*: (i) **2**, Et_3N, DMSO, 50 °C, 16 h.

methylated analogue **7b**, application of this procedure afforded the cyclodextrin derivatives **8b**, **9a**,**b**[29] in 16%, 38%, and 44% yields, respectively (Scheme 2 and Figure 1).

In order to modulate the nature of the linker, the Huisgen 1,3-dipolar cycloaddition of alkynes **3** and **6** and azide **10** was used for the synthesis of the target compounds **11** and **12** (Scheme 3).

1,2,3-Triazo-4-yl compound **11**[30] was prepared in 41% yield by treatment of azido derivative **10** with alkyne **3** in the presence of CuI in aqueous *t*-BuOH solution. Application of this procedure with the azido compound **10** and alkyne **6** furnished the CD derivative **12**[31] in 67% yield.

^{1}H NMR investigations were developed to estimate if the nucleobase moiety was oriented inside the CD cavity or outside. Liu et al. described the self inclusion of the nucleobase into the β-CD cavity with nucleobase-modified β-CD.[17] In our case, the ROESY spectrum of **8**, **9**, **11**, and **12** in D_2O showed the lack of NOE interactions between (i) the thymine protons (H6/CH_3) and (ii) the adenine protons (H2/H8) with the interior protons (H3/H5) of β-CD cavity, respectively. These results showed that the nucleobase moiety of **8**, **9**, **11**, and **12** was outside the β-CD cavity probably due to the presence of a linker: aminoethyl or 1,2,3-triazol group.



Scheme 3 *Reaction conditions*: (i) **3**, CuI, H_2O, *t*-BuOH, MW, 85 °C, 40 min (41%); (ii) **6**, CuI, H_2O, *t*-BuOH, MW, 85 °C, 40 min (67%).

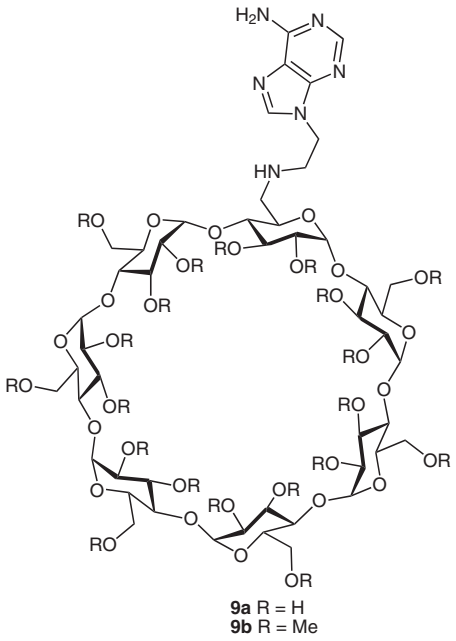


Figure 1 CD derivatives **9a** and **9b** having adenine nucleobase

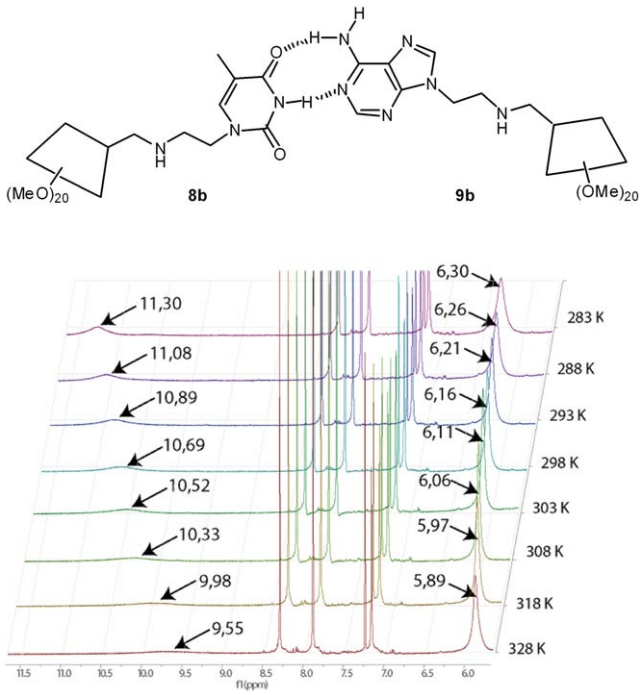


Figure 2 Supramolecular cyclodextrin dimers **8b** and **9b** using nucleobase pairs and the corresponding ^{1}H NMR spectra in $CDCl_3$ (25 mM, 500 MHz) with temperature variation from 283 K to 328 K.

The self-assembly property of CD derivatives **8b** and **9b** was studied by NMR spectroscopy in $CDCl_3$. The self aggregation for compounds **8b** and **9b** was shown by NMR titrations performed at 298 K. The association constant for homodimerization of **8b** and **9b** in $CDCl_3$ was $K_{TT} = 22$ M^{-1} and $K_{AA} = 16$ M^{-1}, respectively. Based on the NMR experiment data, the interactions between **8b** and **9b** in solution have been demonstrated, strong chemical shifts of signals of aromatic protons of both nucleobase moieties fully supporting the formation of hetero dimer (Figure 2). From 283 K to 328 K, remarkable shifts of both the thymine imino proton from $\delta = 11.3–9.5$ ppm and the adenine amino proton from $\delta = 6.3–5.9$ ppm were noticed. The association constant for hetero dimerization of **8b** and **9b** in a 1:1 stoichiometry was $K_{AT} = 385$ M^{-1}. These different values of K are in agreement with those obtained in the same experimental conditions for adenine and thymine alone.[32,33] In our case, the presence of cyclodextrin does not affect the interactions between nucleobases (AA, TT, or AT) in $CDCl_3$.

Adamantyl moiety has been selected as guest model since complexation of adamantyl derivatives with CD has been well documented.[34]

ITC experiments were carried out for measuring the thermodynamic parameters associated with the inclusion process of bisadamantyl derivative **13**[35] in several CD hosts, in pure water at 298 K (Table 1).

The experimental values for the guest/host ratio (n) were compatible with the expected ones. The association constants were slightly superior for the derivatives having nucleobase moiety than for pure β-CD ($78{\cdot}10^3$ vs. $46{\cdot}10^3$ M^{-1}, Table 1). These marginally enhanced binding abilities may result from additional interactions involving the nucleobase and/or the triazole ring with the guest **13**. It was notable that the mixture of **11** and **12** gave no significant enhancement of the association constant (Figure 4). This is probably due to the unfavorable hydrogen-bond formation between individual nucleobases (thymine and adenine) in water. Apparently, in water the presence of the guest dimer **13** (Figure 3) is not sufficient to drive the formation of noncovalent cyclodextrin dimer through a single base as designed.

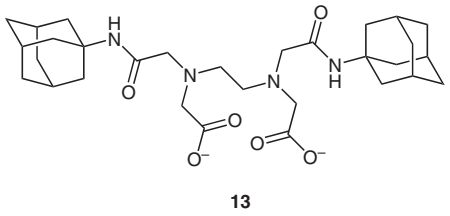


Figure 3 Bisadamantyl derivative **13**

In conclusion, nucleobase and cyclodextrin moieties were linked by aminoethyl and 1,2,3-triazol groups to provide six novel potential supramolecular elements. The apparent association constant between two nucleobase-appended permethylated cyclodextrin derivatives was determined by NMR in $CDCl_3$ ($K_{AT} = 385$ M^{-1}) supporting the formation of supramolecular hetero dimer of modified cyclodextrins. The association constant between these two novel cyclodextrin derivatives and one bisadamantyl guest in water was determined but no significant improvement was observed with regard to the parent compounds. In this study, the two desired interactions are orthogonal in the sense that AT and host–guest association occur in

Table 1 Apparent Association Constants and Thermodynamic Parameters Deduced from ITC for the Different Hosts[a]

Entry	Host	[Host] (mM)	n[a]	K_a ($\cdot 10^3$ M^{-1})	ΔH^0 (kJ mol^{-1})	$T\Delta S°$ (kJ.mol^{-1})	ΔG^0 (kJ mol^{-1})
1	β-CD	0.8	0.50 (1/2)	46 ± 2	–45.3 ± 0.3	–18.6 ± 0.4	–26.7 ± 0.1
2	**7a**	0.8	0.43 (1/2)	50 ± 3	–49.0 ± 0.2	–22.2 ± 0.3	–26.8 ± 0.1
3	**11**	0.8	0.43 (1/2)	77 ± 2	–51.1 ± 0.3	–23.3 ± 0.4	–27.8 ± 0.1
4	**12**	0.8	0.43 (1/2)	74 ± 2	–50.3 ± 0.3	–22.6 ± 0.4	–27.7 ± 0.1
5	**11** + **12**	0.4 + 0.4	0.43 (1/2)	78 ± 2	–51.1 ± 0.3	–23.3 ± 0.4	–27.8 ± 0.1

[a] Different hosts: β-CD, **7**, **11**, and **12** with the guest: bisadamantyl derivative **13** {[**13**] = 4.0 mM} in pure H_2O at 298 K.
[b] n: molar ratio (guest/host) of both components in the complex. The values in parentheses are theoretical values for the formation of complexes with all the binding sites of both guest and host occupied.

chloroform and water, respectively. Therefore, a screening of other solvents might result in a functioning system. Moreover, extension of this preliminary work to the synthesis of other novel cyclodextrin derivatives bearing nucleic acid oligomers, to strengthen the interaction in water, will be reported in due course.

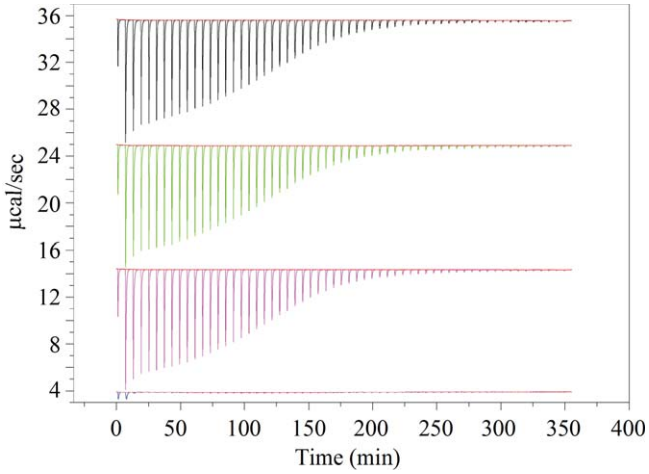


Figure 4 Calorimetric titration curve of **11** (a), **12** (b), **11** + **12** (c) or pure water (d) with **13** in water at 298 K. 5 µL injections of **13** {[**13**] = 4.0 mM} into host solution {[host] = 0.8 mM}

Acknowledgment

This work was supported by (i) the CNRS program; (ii) regional program from the Région Poitou-Charentes, France, and (iii) Biocydex.

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(28) **Selected Physical Data of Compound 8a**
MP 200 °C (decomp.). ^{1}H NMR (500 MHz, D_2O): δ = 7.48 (s, 1 H), 5.14–5.08 (m, 7 H), 4.30–4.10 (m, 3 H), 4.03–3.81 (m, 25 H), 3.72–3.50 (m, 15 H), 3.47 (m, 2 H), 3.39 (m, 1 H), 1.91 (s, 3 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 166.8, 153.0, 142.2, 111.5, 102.0–101.0, 83.3–80.8, 71.5–70.5, 67.5, 60.5–59.5, 48.8, 47.6, 45.0, 11.3 ppm. ESI-HRMS: *m/z* calcd $[M + H]^+$: 1286.4522; found: 1286.4581.

(29) **Selected Physical Data of Compound 8b**
Mp 200 °C (decomp.). ^{1}H NMR (500 MHz, D_2O): δ = 7.56 (s, 1 H), 5.36–5.24 (m, 5 H), 4.00 (s, 2 H), 3.89–3.54 (m, 33 H), 3.64–3.62 (m, 21 H), 3.55–3.52 (m, 21 H), 3.43–3.37 (m, 7 H), 3.41–3.40 (m, 21 H), 3.23 (br s, 2 H), 3.18 (br s, 2 H), 1.94 (s, 3 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 166.8, 152.4, 143.1, 110.6, 97.6–96.6, 81.4–75.9, 71.2–69.6, 59.9–58.1, 48.5, 47.4, 47.0, 11.43 ppm. ESI-HRMS: *m/z* calcd $[M + H]^+$: 1566.7532; found: 1565.7573.
Selected Physical Data of Compound 9a
Mp 200 °C (decomp.). ^{1}H NMR (500 MHz, D_2O): δ = 8.52 (s, 1 H), 8.40 (s, 1 H), 5.17–5.10 (m, 7 H), 4.38 (s, 2 H), 4.00–3.50 (m, 39 H) 3.31 (t, 1 H), 3.11 (m, 2 H), 2.95 (d, 1 H), 2.77 (m, 1 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 155.4, 152.2, 149.5, 142.5, 118.5, 102.0–101.7, 101.0, 83.5, 81.2–80.1, 73.1–70.2, 60.3–59.9, 48.2, 47.0, 43.2 ppm. ESI-HRMS: *m/z* calcd $[M + H]^+$: 1295,4637; found: 1295.4574.
Selected Physical Data of Compound 9b
Mp 200 °C (decomp.). ^{1}H NMR (500 MHz, D_2O): δ = 8.31 (s, 1 H), 8.23 (s, 1 H), 5.29–5.24 (m, 5 H), 5.17 (s, 1 H), 4.98 (s, 1 H), 4.44 (br s, 2 H), 3.88–3.51 (m, 26 H), 3.64–3.62 (m, 21 H), 3.55–3.52 (m, 21 H), 3.41–3.32 (m, 14 H), 3.41–3.40, (m, 21 H), 3.24 (br s, 2 H), 3.05 (br s, 2 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 155.5, 152.4, 149.3, 142.6,118.5, 97.7–96.5, 80.9–76.5, 71.1–70.7, 60.0–58.0, 48.1, 47.5, 43.2 ppm. ESI-HRMS: *m/z* calcd $[M + H]^+$: 1575.7673; found: 1575.7654.

(30) **Selected Physical Data of Compound 11**
Mp 200 °C (decomp.). ^{1}H NMR (500 MHz, D_2O): δ = 8.10 (s, 1 H), 7.66 (s, 1 H), 5.20 (s, 1 H), 5.10–5.03 (m, 9 H), 4.63 (s, 1 H), 4.30 (s, 1 H), 4.08–3.50 (m, 37 H), 3.01 (s, 1 H), 2.70 (s, 1 H), 1.92 (s, 3 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 167.1, 152.2, 142.4, 126.5, 111.2, 101.9–101.4, 83.2–80.5, 73.0–70.4, 60.3, 59.1, 51.4, 42.9, 11.3 ppm. ESI-HRMS: *m/z* calcd $[M + Na^+]$: 1346.4246; found: 1346.4211.

(31) **Selected Physical Data of Compound 12**
Mp 200 °C (decomp.). ^{1}H NMR (500 MHz, D_2O): δ = 8.29 (s, 1 H), 8.26 (s, 1 H), 7.99 (s, 1 H), 5.60 (s, 2 H), 5.15–5.00 (m, 7 H), 4.97 (d, 1 H), 4.59 (dd, 1 H), 4.11 (t, 1 H), 4.00–3.40 (m, 37 H), 2.78 (d, 1 H), 2.60 (d, 1 H) ppm. ^{13}C NMR (125 MHz, D_2O): δ = 155.6, 152.7, 148.9, 142.6, 142.1, 125.9, 118.6, 101.9, 81.3–80.4, 73.1–70.6, 60.0–58.8, 51.2, 38.4 ppm. ESI-HRMS: *m/z* calcd $[M + Na^+]$: 1355.4362; found: 1355.4363.

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