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Control Self-Assembly of Hydrazide-Based Cyclic Hexamers: In or Out

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By moving the alkoxy group on the spacer from position 5 to position 4 to add another protocol for the algorithm for intermolecular and intramolecular hydrogen bonding interactions, highly regioselectivity of noncovalent synthesis of the hydrazide-based cyclic hexamers was achieved: one out of thirteen possible isomeric cyclic hexamers selectively formed and thus precise control of the two hydrazide units in the cyclic hexamers (in or out) was accomplished.

Self-assembly is a means of creating new materials and new functions[1–3]. The property of materials depends not only on the natures but also on the relative positions of functional groups[4–6]. Therefore precise control of self-assembly and precise location of functional groups in the resulting self-assembly structures are required for further applications in material design. The fact that the factors governing the self-assembly process are often very complicated and subtle makes it challenging to ensure to control at the molecular level. By properly and wisely encoding binding information into the molecular skeleton, programmable and controllable self-assembly might be achieved[7]. We report in this communication that by encoding the hydrazide-based monomer building blocks with proper hydrogen bonding sites, i. e., just moving the alkoxy group on the spacer from position 5 to position 4 to add another protocol for the algorithm for intermolecular and intramolecular hydrogen bonding interactions, highly regioselectivity of noncovalent synthesis of the cyclic hexamers was achieved: one out of thirteen possible isomeric cyclic hexamers selectively formed and thus precise position control of the two hydrazide units in the cyclic hexamers (in or out) was accomplished. Though this strategy was widely and intensively used by Gong et al[8–9]. to control linear or crescent conformation of oligoamide foldamers, the successful "in or out" control has never been reported for hydrogen bonding mediated cyclic oligomers.

Results

Recently by attaching two hydrazide-based[10–14] supramolecular synthons[15] to a 120° isophthalamide spacer and following a predefined algorithm for intermolecular and intramolecular hydrogen bonding, we successfully constructed a new kind of shape-persistent cyclic hexamers from nonheterocycle-based building blocks[16]. The self-assembly process is highly cooperative and thus the resulting cyclic hexamers have high kinetic and thermodynamic stability ($K_a = 3.67 \times 10^{16}$ M^{-5} in 3% DMSO-d_6/$CDCl_3$)[16]. The success of our strategy comes from the fact that the isophthalamide spacer unit prefers an *anti-syn* conformation[17–19]. This preference was further reinforced upon formation of cyclic hexamers. In the resulting cyclic hexamers the hydrazide unit attached to the amide group with an *anti* conformation is positioned inside and the other one attached to the *syn* amide group is positioned outside. Because there are two degenerated *anti-syn* conformations (Figure 1, top), the conformations of two amide groups are randomly adopted. When the monomer for self-assembly is symmetric, this makes no difference. But when hydrazide units with different ending groups are introduced, there should exist thirteen isomeric cyclic hexamers in solution (Figure S2): the hydrazide groups are positioned randomly inside or outside of the cyclic hexamers and there is no selectivity. We envision that if we move the alkoxy group on the spacer from position 5 to position 4, the *syn-anti* conformation can be fixed by highly favorable S(6) type[20,21] hydrogen bonding (Figure 1, bottom-left). With this spacer with fixed conformation in hand, we can locate precisely the two hydrazide units in the resulting cyclic hexamers. When two alkoxy groups are introduced to position 4 and

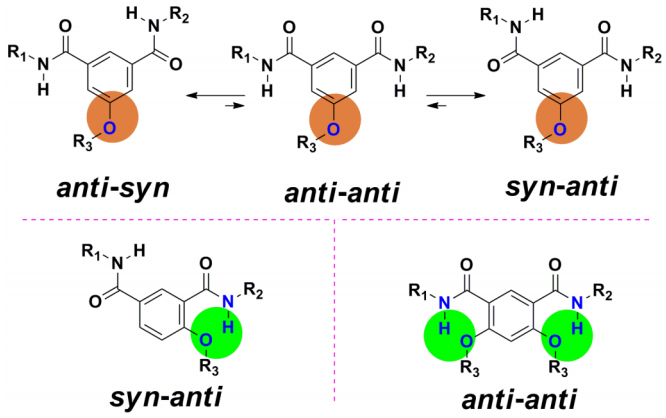

Figure 1 | Representation of conformation equilibrium of isophthalamide and conformation locking strategy by intramolecular hydrogen bonding.

position 6, the spacer is fixed in an *anti-anti* conformation and a linear supramolecular polymer instead of a cyclic hexamer should be observed (Figure 1, bottom-right).

To validate this idea, compounds **2** and **3** with 4-alkoxy substituted spacers (see Figure 2 for structure details) were designed and synthesized (see Supporting Information for more details). Unsymmetric compound **1** with a 5-alkoxy substituted spacer and symmetric compound **4** with two alkoxy groups on the isophthalamide spacer were also synthesized as controls. Benzyl and hexyl groups were introduced to the two hydrazide units respectively to disrupt symmetry. We envisioned that if this strategy is correct, the hydrazide unit adjacent to the S(6) type hydrogen bonding will be positioned on the inner side of the resulting cyclic hexamer and the other one be on the outer side. For example, in compound **2** where the hexyl group is attached the hydrazide unit adjacent to the S(6) type hydrogen bond, it is anticipated that the hexyl groups will be on the inner side and the benzyl groups attached to the other hydrazide unit be on the outer side (Figure 2). In the case of compound **3**, the conditions are reverse. While for the control compound **1**, because of two degenerated *anti-syn*/*syn-anti* conformations of the 1, 3-diamide spacer, there should be two suitable conformations **1** and **1′** for cyclic self-assembly in solution. The resulting cyclic hexamer should be composed of six monomers in two conformations. From theoretical perspective there should be thirteen possible isomeric cyclic hexamers (Figure S2). Thus the two hydrazide units of the monomer are arranged randomly on the inner and/or outer sides of the cyclic hexamer (see Figure 2). For compound **4** with a two-alkoxyl substituted spacer and two fold intramolecular hydrogen bonds for locking conformation, the monomer should be linear and the resulting self-assembly structure should be a linear supramolecular polymer.

Discussion

NMR studies first confirmed our hypothesis. Compounds **2** and **3** displayed almost the same ^{1}H (Figure S3) and ^{13}C NMR (Figure S4) spectra in DMSO-d_6 because of very similar structures, where these two compounds existed as monomers; While as shown in Figure 3 and Table 1, they showed well defined and quite different ^{1}H NMR spectra in $CDCl_3$. These spectra were similar to those for cyclic hexamers as we previously reported, where various analytical methods were used to fully characterize and confirm the self-assembly structures[16]. The ^{13}C NMR spectra (Figure 4 and Figure S4) in $CDCl_3$ also showed some differences. This might suggest formation of well-defined shape-persistent cyclic hexamers in solution, where the exchange of hydrazide units on the inner and outer sides was slow on the NMR time scale and two sets of signals were observed for the inner part and outer part. MALDI-TOF analysis in CH2Cl2 provided further information: two peaks at m/z = 5875 and m/z = 5878 corresponding to the cyclic hexamers were observed for compound **2** and **3** respectively (Figure S41). The control compound **1** showed an ill-resolved and very complicated ^{1}H NMR spectrum (Figure 3, bottom) under the same conditions, which might be composed of signals from thirteen possible isomeric cyclic hexamers. All the three compounds showed well defined ^{1}H NMR spectra corresponding to their chemical structures in hydrogen bonding competitive solvents such as DMSO-d_6.

By comparing with symmetrically substituted control compounds **5**, **6** with 5-alkoxy substituted spacers and **7**, **8** with 4-alkoxy substituted spacers, combined with NOESY and COSY analysis and peak splitting, full proton assignment was fulfilled (see Supporting Information for details). In all cases cross contacts between c′ and g_1&g_2, j and d′ were clearly observed in the NOESY spectra, which provided diagnostic evidences for the hexameric structures. The distances between the above mentioned protons in the same molecule are much too long for any cross contacts to be observed. The signals must result from intermolecular contacts among the molecules constituting the cyclic hexamers. Because of restriction of rotational freedom due to steric hindrance in confined space, geminal protons in NHCH_2 (g_1 and g_2, $g_1′$ and $g_2′$) and OCH_2 (n_1 and n_2) all displayed two separate sets of signals (Table 1 and Table S1). Typically when located on the inner side of the cyclic hexamer, hexyl-N*H* usually appeared at 6.5 ppm and Bn-N*H* at 6.9 ppm, pentyl-CH_2 at 2.2–2.6 ppm and Ph-CH_2 at 3.5–4.0 ppm; when located on the outer side, hexyl-N*H* usually appeared at 5.0–5.3 ppm and Bn-N*H* at 5.3–5.4 ppm, pentyl-CH_2 at 3.0–3.3 ppm and Ph-CH_2 at 3.8–4.4 ppm. In the ^{1}H NMR spectrum of compound **2**, signals for hexyl-N*H* and pentyl-CH_2, which were expected to be located on the inner side, appeared at 6.52 ppm and 2.22 ppm, 2.51 ppm respectively; signals for Bn-N*H* and Ph-CH_2, which were expected to be located on the outer side, appeared at 5.43 ppm and 4.33 ppm, 4.58 ppm respectively. In the case of compound **3**, hexyl-N*H* and pentyl-CH_2 signals appeared at 4.98 ppm and 2.75 ppm, 3.10 ppm respectively (outer side); Bn-N*H* and Ph-CH_2 signals appeared at 6.85 ppm and 3.48 ppm, 3.65 ppm respectively (inner side). In DMSO-d_6, all geminal protons in NHCH_2 and OCH_2 displayed only one set of signals. In all compounds hexyl-N*H* appeared at about 6.3 ppm and Bn-N*H* at 6.8 ppm, pentyl-CH_2 at 3.0 ppm and Ph-CH_2 at 4.3 ppm. All the results clearly showed that highly regioselectivity was achieved for the self-assembly process of compounds **2** and **3**. We precisely and selectively located the two hydrazide units inside or outside the resulting cyclic hexamers by strategy of intramolecular hydrogen bonding.

Another diagnostic evidence for the controlled self-assembly process came from ^{13}C NMR study (Figure 4). Two signals at about 43.9 ppm and 43.3 ppm were observed for the two NH*C*H_2Ph carbons in control compounds **6** and **8** in $CDCl_3$. Only one signal at about 43.1 ppm was observed for the two compounds in DMSO-d_6. The difference in chemical shifts might come from different chemical environments: upon formation of cyclic hexamers in $CDCl_3$, one NH*C*H_2Ph carbon is located on the inside and the other one on the outside. For compound **2** where the NH*C*H_2Ph group was expected to be located in the outside of the cyclic hexamer, a signal at about 44.0 ppm was observed; for compound **3** where the NH*C*H_2Ph group was expected to be located in the inside of the cyclic hexamer, a signal at about 43.3 ppm was observed.

Compound **4** showed a relatively simple and concentration-dependent ^{1}H NMR spectrum in $CDCl_3$ (Figure S6). The spectra displayed only one set of broad signals, which might suggest formation of a supramolecular polymer. With increasing concentrations in $CDCl_3$ signals for aromatic protons **h&i&e&d&f** and signal for **c** (N*H*) showed little high field shifts because of π-stacking; while signals for N*H***j&a** showed down field shift because of intermolecular hydrogen bonding.

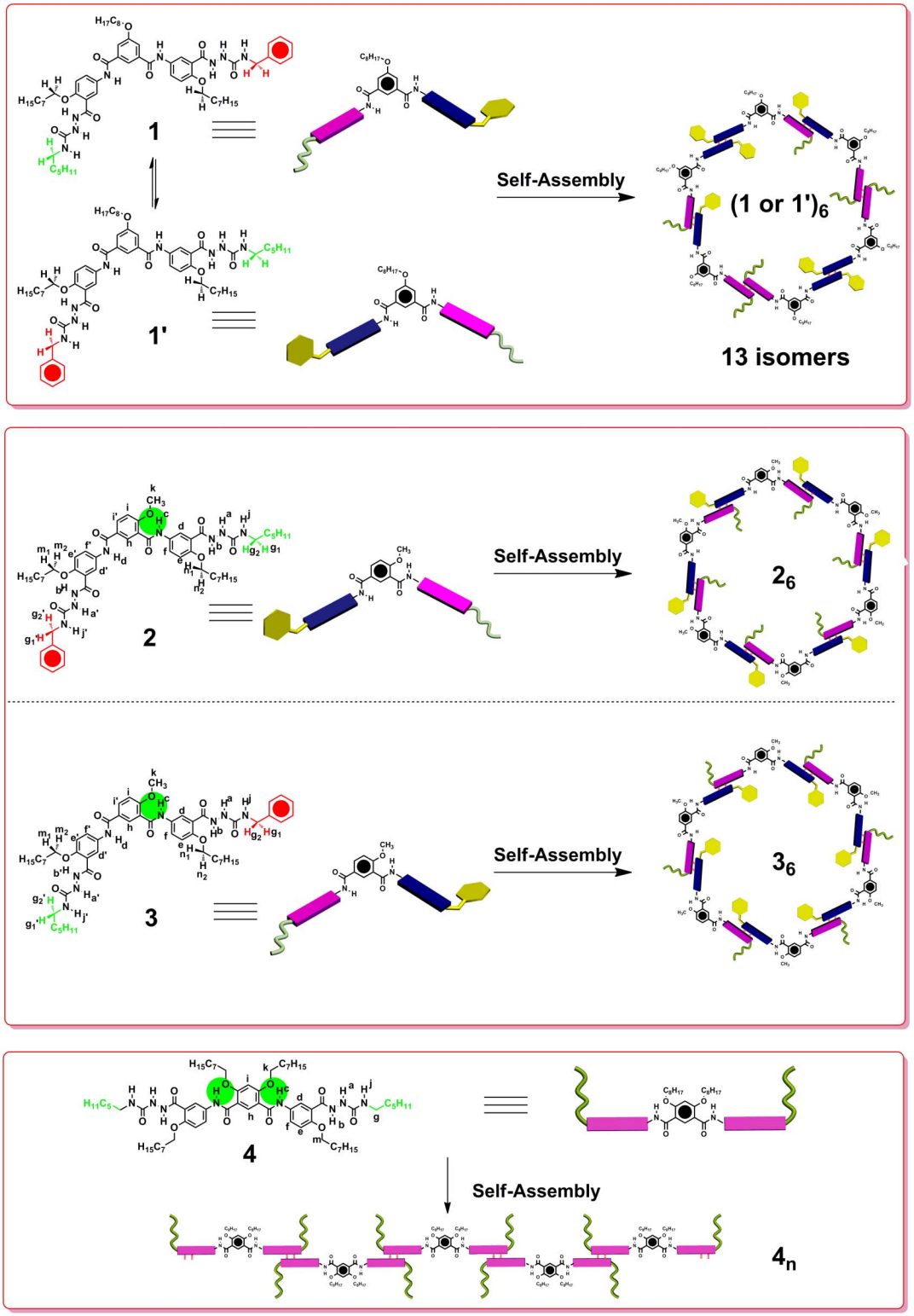

Figure 2 | Representation of self-assembly of compounds 1, 2, 3 and 4, with intramolecular hydrogen bonds which lock the conformation of spacer units highlighted with filled circles. H-labeling scheme is also showed.

In conclusion, just moving the alkoxy substitution on the spacer unit from position 5 to position 4 to add another protocol for the algorithm for intermolecular and intramolecular hydrogen bonding interactions, highly regioselectivity for the self-assembly process was achieved and we could precisely control the relative positions of the hydrazide units in the resulting cyclic hexamers. When two alkoxy groups were introduced, a supramolecular polymer instead of a cyclic hexamer was obtained. To the best of our knowledge, such a precise control has not been achieved in other hydrogen bonding mediated self-assembly systems[22–37]. Our strategy will provide a simple yet highly effective method for such a control. Application of this strategy will lead to precise location of functional groups attached to the monomer and thus modulate properties of materials based on this self-assembly system. This will provide new ideas and platforms for

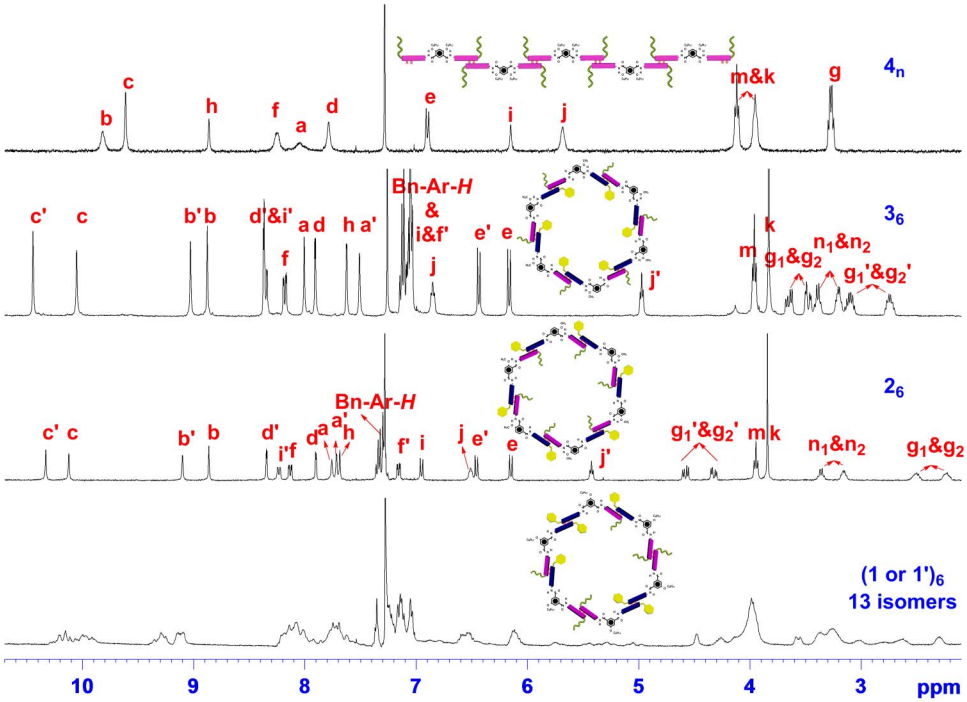

Figure 3 | ^{1}H NMR spectra for compounds 1, 2, 3 and 4 (from bottom up), 298 K, 400 MHz, 10 mM in $CDCl_3$, with proton signals assignment (for proton-labeling scheme see Figure 2).

the design and construction of new materials, which are underway in our lab.

Methods

All chemicals for synthesis were purchased from chemical companies and used without further purification. All NMR spectra were recorded at room temperature unless specifically indicated. The chemical shifts were reported using TMS as internal standard.

Synthesis of compound **1**: To a mixture of compound **16** (205 mg, 0.3 mmol) and compound **11** (124 mg, 0.3 mmol) in dry CH_2Cl_2 (10 mL) at room temperature was added **EDC·HCl** (96 mg, 0.5 mmol). The mixture was stirred at room temperature for 5 h, and then concentrated under reduced pressure. The pure product as a white solid (265 mg, 82%) was obtained by trituration from hot acetonitrile. ^{1}H NMR (400 MHz, 10 mM in DMSO-d_6, TMS, 298 K, ppm): δ 10.40 (s, 2H, N*H*), 9.77 (d, J = 2.8 Hz, 1H, N*H*NH), 9.74 (d, J = 2.8 Hz, 1H, N*H*NH), 8.32 (d, J = 2.0 Hz, 1H, Ar*H*), 8.20−8.15 (m, 4H, Ar*H*), 8.00 (d, J = 1.8 Hz, 1H, NHN*H*), 7.98 (d, J = 1.8 Hz, 1H, NHN*H*), 7.70 (s, 2H, Ar*H*), 7.34−7.16 (m, 7H, Ar*H*), 6.85 (t, J = 6.0 Hz, 1H, Urea-N*H*), 6.29 (t, J = 5.7 Hz, 1H, Urea-N*H*), 4.29 (d, J = 6.0 Hz, 2H, benzyl-CH_2), 4.17−4.08 (m, 6H, OCH_2), 3.08−3.00 (m, 2H, NHCH_2), 1.85−1.70 (m, 6H, CH_2), 1.52−1.20 (m, 38H, CH_2), 0.90−0.80 (m, 12H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, TMS, 298 K, ppm): δ 164.8, 164.2, 159.1, 158.2, 158.0, 153.2, 140.8, 136.7, 132.7, 128.6, 127.3, 127.0, 125.2, 123.3, 121.7, 121.6, 119.8, 116.9, 113.7, 69.5, 68.6, 43.2, 31.7, 31.5, 30.3, 29.30, 29.23, 29.18, 29.14, 29.02, 26.5, 26.02, 25.96, 22.58, 14.40, 14.35. MALDI-TOF MS: m/z 1099.7 [M+Na]$^+$). HRMS (MALDI$^+$) calc'd. For $C_{61}H_{88}N_8O_9$ [(M)]: 1076.6674, found: 1076.6668. Anal. Calcd for $C_{61}H_{88}N_8O_9 \cdot 3H_2O$: C 64.75, H 8.37, N 9.90. Found: C 64.76, H 8.19, N 10.66.

Synthesis of compound **2**: To a mixture of compound **24** (177 mg, 0.3 mmol) and compound **14** (122 mg, 0.3 mmol) in dry CH_2Cl_2 (10 mL) at room temperature was added **EDC·HCl** (96 mg, 0.5 mmol). The mixture was stirred at room temperature for 5 h, and then concentrated under reduced pressure. The pure product as a white solid (258 mg, 88%) was obtained by trituration from hot acetonitrile. ^{1}H NMR (400 MHz, DMSO-d_6, TMS, 298 K, ppm): δ 10.28 (s, 1H, N*H*), 10.23 (s, 1H, N*H*), 9.77 (d, J = 2.7 Hz, 1H, NHN*H*), 9.73 (d, J = 3.0 Hz, 1H, NHN*H*), 8.30 (d, J = 2.3 Hz, 1H, N*H*NH), 8.29 (d, J = 2.3 Hz, 1H, N*H*NH), 8.18−8.11 (m, 4H, Ar*H*), 7.98 (dd, J = 9.0 Hz, J = 2.8 Hz, 1H, Ar*H*), 7.89 (dd, J = 9.0 Hz, J = 2.7 Hz, 1H, Ar*H*), 7.35−7.20 (m, 6H, Ar*H*), 7.18 (d, J = 9.0 Hz, 1H, Ar*H*), 6.83 (t, J = 6.1 Hz, 1H, CH$_2$N*H*), 6.28 (t, J = 5.7 Hz, 1H, CH$_2$N*H*), 4.29 (d, J = 6.0 Hz, 2H, CH_2NH), 4.11 (m, 4H, OCH_2), 3.96 (s, 3H, OCH_3), 3.08−3.00 (m, 2H, NHCH_2), 1.85−1.70 (m, 4H, CH_2), 1.55−1.20 (m, 28H, CH_2), 0.90−0.82 (m, 9H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, TMS, 298 K, ppm): δ 164.4, 159.3, 158.3, 158.0, 153.0, 140.8, 132.9, 132.7, 132.1, 129.5, 128.6, 127.3, 127.1, 126.8, 125.5, 125.1, 124.5, 123.2, 122.5, 122.1, 121.7, 113.9, 113.7, 112.2, 69.5, 56.7, 43.1, 31.73, 31.70, 31.5, 30.3, 29.28, 29.21, 29.12, 29.09, 29.00, 26.4, 26.0, 25.9, 22.6, 14.42, 14.37. MALDI-TOF MS: m/z 1001.6 [M+Na]$^+$. HRMS (MALDI+) calc'd. For $C_{54}H_{74}N_8O_9$ [(M)]: 978.5579, found: 978.5583. Anal. Calcd for C54H74N8O9: C 66.23, H 7.62, N 11.44. Found: C 65.75, H 7.61, N 11.52.

Synthesis of compound **3**: To a mixture of compound **23** (175 mg, 0.3 mmol) and compound **11** (124 mg, 0.3 mmol) in dry CH_2Cl_2 (10 mL) at room temperature was added **EDC·HCl** (96 mg, 0.5 mmol). The mixture was stirred at room temperature

Table 1 | Chemical shifts for N**H**-CH_2- and NH-C**H**$_2$- in compounds **1**~**8** in $CDCl_3$ and DMSO-d_6

	In $CDCl_3$ [a]				In DMSO-d_6 [a]	
	N**H**-CH_2- inside	N**H**-CH_2- outside	NH-C**H**$_2$- inside	NH-C**H**$_2$- outside	N**H**-CH_2-	NH-C**H**$_2$-
Compound **1**	[b]	[b]	[b]	[b]	6.85, 6.29	4.29, 3.04
Compound **2**	6.52	5.43	2.51, 2.22	4.58, 4.33	6.83, 6.28	4.29, 3.04
Compound **3**	6.85	4.98	3.65, 3.48	3.10, 2.75	6.85, 6.27	4.28, 3.04
Compound **4**	5.68		3.27		6.27[c]	3.04[c]
Compound **5**	6.43	5.30	2.61, 2.24	3.29, 3.22	6.27	3.02
Compound **6**	6.89	5.41	4.03, 3.61	4.28, 3.95	6.85	4.27
Compound **7**	6.46	5.07	2.48, 2.18	3.30, 3.06	6.28	3.04
Compound **8**	6.91	5.29	3.70, 3.52	4.37, 3.88	6.85	4.29

[a]conditions: 10 mM in $CDCl_3$ or DMSO-d_6, 298 K, 400 MHz, δ in ppm.
[b]Because of ill-resolved spectrum in $CDCl_3$, the chemical shifts can't be determined.
[c]The concentration is less than 2 mM.

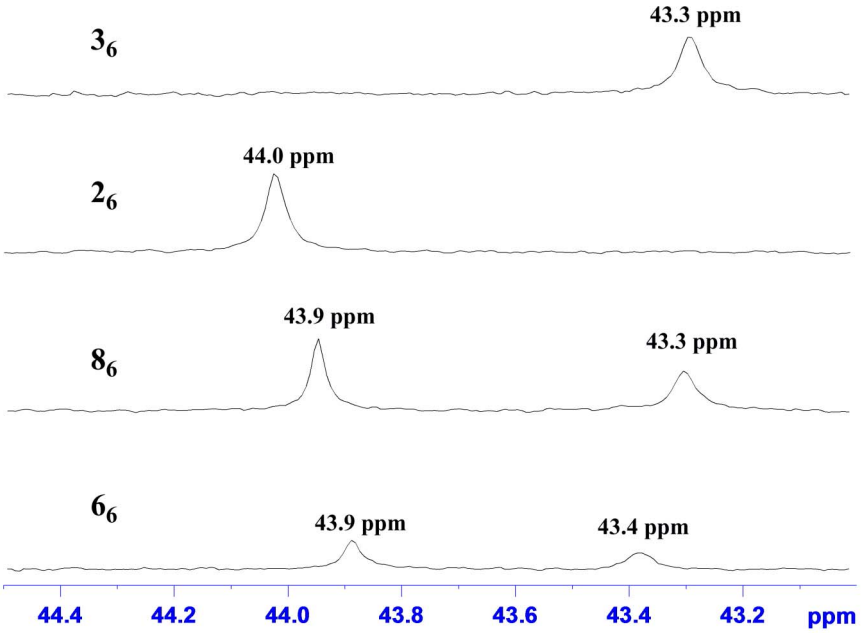

Figure 4 | Partial ^{13}C NMR spectra in $CDCl_3$ for compounds 6, 8, 2 and 3 (from bottom up) containing Benzyl groups, showing regions where NH-*C*H_2-Ph signals appear, 100 MHz, 298 K.

for 5 h, and then concentrated under reduced pressure. The pure product as a white solid (309 mg, 95%) was obtained by trituration from hot acetonitrile. ^1H NMR (400 MHz, DMSO-d_6, TMS, 298 K, ppm): δ 10.29 (s, 1H, N*H*), 10.23 (s, 1H, N*H*), 9.76 (d, J = 2.8 Hz, 1H, NHN*H*), 9.73 (d, J = 2.8 Hz, 1H, NHN*H*), 8.31 (d, J = 2.2 Hz, 1H, N*H*NH), 8.29 (d, J = 2.2 Hz, 1H, N*H*NH), 8.18−8.10 (m, 4H, Ar*H*), 7.98 (dd, J = 9.0 Hz, J = 2.7 Hz, 1H, Ar*H*), 7.88 (dd, J = 8.9 Hz, J = 2.7 Hz, 1H, Ar*H*), 7.35−7.15 (m, 8H, Ar*H*), 6.85 (t, J = 6.1 Hz, 1H, CH_2NH), 6.27 (t, J = 5.7 Hz, 1H, CH_2NH), 4.28 (d, J = 6.0 Hz, 2H, CH_2NH), 4.11 (m, 4H, OCH_2), 3.96 (s, 3H, OCH_3), 3.08−3.00 (m, 2H, $NHCH_2$), 1.85−1.70 (m, 4H, CH_2), 1.55−1.20 (m, 28H, CH_2), 0.90−0.82 (m, 9H, CH_3). 13C NMR (100 MHz, DMSO-d_6, TMS, 298 K, ppm): δ 164.4, 159.3, 158.3, 158.0, 152.99, 152.97, 140.8, 132.9, 132.7, 132.1, 129.5, 128.6, 127.3, 127.1, 126.8, 125.5, 125.2, 124.5, 123.2, 122.5, 122.0, 121.8, 113.9, 113.7, 112.2, 69.5, 56.7, 43.1, 31.72, 31.69, 31.5, 30.3, 29.28, 29.19, 29.12, 29.09, 29.01, 26.4, 25.99, 25.93, 22.57, 22.56, 14.41, 14.37. MALDI-TOF MS: m/z 1001.6 $[M+Na]^+$, 1017.6 $[M+K]^+$. Anal. Calcd for $C_{54}H_{74}N_8O_9 \cdot 1.5H_2O$: C 64.46, H 7.71, N 11.14. Found: C 64.46, H 7.45, N 11.09.

Synthesis of compound **4**: To a mixture of compound **25** (106 mg, 0.25 mmol) and compound **14** (203 mg, 0.5 mmol) in dry CH_2Cl_2 (10 mL) at room temperature was added **EDC·HCl** (115 mg, 0.6 mmol). The mixture was stirred at room temperature for 5 h, and then concentrated under reduced pressure. The pure product as a white solid (275 mg, 92%) was obtained by trituration from hot acetonitrile. ^1H NMR (400 MHz, $CDCl_3$, TMS, 298 K, ppm): δ 9.85−9.75 (br, 2H, N*H*NH), 9.61 (s, 2H, N*H*), 8.86 (s, 1H, Ar*H*), 8.25 (s, 2H, Ar*H*), 8.10−8.00 (br, 2H, NHN*H*), 7.79 (s, 2H, Ar*H*), 6.90 (d, J = 9.0 Hz, 2H, Ar*H*), 6.15 (s, 1H, Ar*H*), 5.72−5.65 (br, 2H, Urea-N*H*), 4.12 (t, J = 6.6 Hz, 4H, OCH_2), 4.00−3.90 (br, 4H, OCH_2), 3.31−3.24 (m, 4H, $NHCH_2$), 1.98−1.87 (m, 4H, CH_2), 1.85−1.74 (m, 4H, CH_2), 1.60−1.20 (m, 56H, CH_2), 0.95−0.84 (m, 18H, CH_3). MALDI-TOF MS: m/z 1221.9 $[M+Na]^+$). Anal. Calcd for $C_{68}H_{110}N_8O_{10}$: C 68.08, H 9.24, N 9.34. Found: C 68.09, H 9.18, N 9.34. The ^{13}C NMR spectrum recorded in nonpolar $CDCl_3$ has low S/N ratio; In hydrogen bonding competitive DMSO-d_6, the compound has limited solubility and it is difficult to record a ^{13}C NMR spectrum.

See Supporting Information (Part One) for synthetic details for other compounds.

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Author contributions

Performed the experiments: YY FH FJQ. Analyzed the data: YY MX QC. Contributed reagents/materials/analysis tools: JX. Wrote the paper: YY CFC.

Additional information

Supplementary information accompanies this paper at http://www.nature.com/scientificreports

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