Heterocycl. Commun., Vol. 16(4-6), pp. 269–273, 2010 • Copyright © by Walter de Gruyter • Berlin • New York. DOI 10.1515/HC.2010.013

# Synthesis of thymidine derivatives bearing aromatic oligoamides with rigidified backbone

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## Abstract

Novel thymidine derivatives carrying dimeric, tetrameric and hexameric aromatic oligoamide moieties with the backbone rigidified by the intramolecular three-center hydrogen bonds have been synthesized as potential hosts for specific molecular recognition.

**Keywords:** aromatic oligoamides; 3′,5′-O-diacetyl-5-aminomethyl-2′-deoxyuridine; rigidified backbone; three-center hydrogen bonds; thymidine.

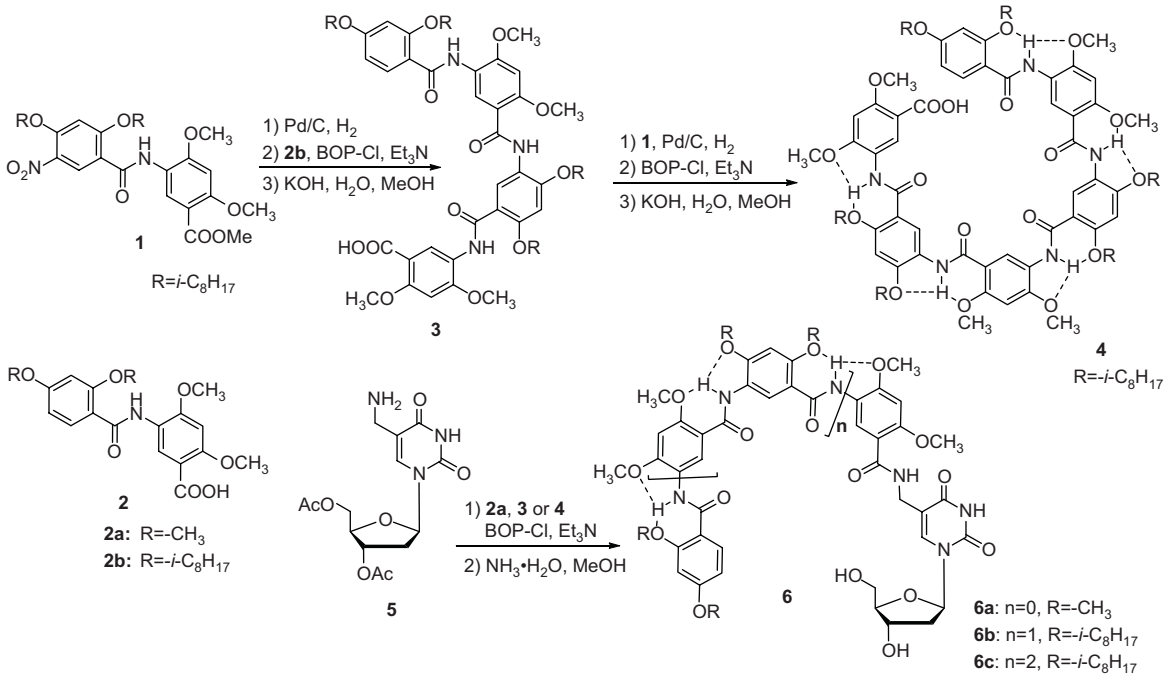
## Introduction

Modifications of deoxyribonucleosides have produced a large number of compounds with important biochemical and biological activities (Tollin et al., 1968). For example, 3′-azido-3′-deoxythymidine is known as an important antiviral agent, which is the first drug against human HIV (Mitsuya et al., 1985). In addition, several modified thymidine derivatives have shown anticancer activities (Dreyer and Dervan, 1985; Boorstein and Teebor, 1989; Asseline et al., 1996; Hurley and Tor, 1998; Verma and Eckstein, 1998). Recently, thymidine has been the focus of much attention to tailor its function and application by modifications, such as for drug discovery, catalysis, nucleobase pairing investigation and crystal structure study (Jiang et al., 2007; Salon et al., 2007, 2008, 2010; Sheng et al., 2007, 2010; Caton-Williams and Huang 2008; Sheng and Huang 2008, 2010; Hassan et al., 2010; Gan et al., 2011). The aromatic oligoamides containing the intramolecular three-center hydrogen bonds have demonstrated various interesting properties and functions, such as facilitating catalysis, forming ion-channel and permitting molecular recognition (Gong, 2008; Helsel et al., 2008). The intramolecular hydrogen bonds are able to rigidify the conformation of oligoamide backbone, leading to the formation of macrocycles (Yuan et al., 2004a) and foldamers (Yuan et al., 2004b). Furthermore, the acyclic and cyclic oligoamides are able to form cavities that favorably recognize molecules, such as guanidine and arginine (Pedersen, 1967; Kyba et al., 1977; Lehn et al., 1979; Kremer et al., 1994; Takeshita et al., 1994; Schrader, 1998; Bell et al., 1999; Sanford et al., 2005; Schugand et al., 2005; Zheng et al., 2008; Yamato et al., 2009). We envision that the oligoamides could help functionalize thymidine for molecular specific recognition. Therefore, we decided to synthesize the thymidine derivatives containing the aromatic oligoamides with rigidified backbone. Moreover, synthesis of these thymidine derivatives enables construction of new molecule-sensing DNAs with these recognition elements. Herein we report the first synthesis of novel thymidine derivatives with the incorporated aromatic oligoamides as potential molecular sensing moieties.

3′,5′-O-Diacetyl-5-aminomethyl-2′-deoxyuridine (**5**) was synthesized according to the literature using thymidine as starting material (Shiau et al., 1980). The aromatic oligoamides foldamers **3** and **4** were synthesized from building blocks **1** and **2** (Yuan et al., 2005), the synthetic procedures were shown in Scheme 1.

## Results and discussion

Compounds **1** and **2** were prepared from commercially available 2,4-dihydroxybenzoic acid following the known procedure (Yuan et al., 2005) with a total yield of 80% and 73%, respectively. The solubility of aromatic oligomers in organic solvents was greatly improved by introducing more soluble iso-octyl groups as side chains. The synthesis of tetramer **3** was achieved by coupling **2b** with the amine obtained by reduction of **1**, followed by hydrolysis and acidification. Hexamer **4** was synthesized in a similar manner, by coupling **3** with the amine obtained from **1**. It was noteworthy that bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl), the coupling reagent, was more efficient than N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC) for the formation of amide bonds in these coupling reactions. Furthermore, dryness of the acid and amine affects the coupling yield considerably. Because compound **5** was obtained by reduction of the corresponding azide in ethanol, the residual solvent wrapped in the sticky product was difficult to remove and thus caused the side reaction, significantly reducing the yield of the coupling reaction between **5** and **2a** (**3** or **4**). In addition, the yield decreased sharply from 63% in **6a** to 39% in **6c** as the backbone of the oligoamides extends from dimer to hexamer, indicative of the steric effect of the crowdedness. The purification on silica gel ($CH_2Cl_2$/ethyl acetate=35:1) and




**Scheme 1** Synthesis of the thymidine derivatives containing aromatic oligoamides.

deacetylation with $NH_3{\cdot}H_2O$ afforded **6a**–**6c**. The H-1′ signals of the thymidine derivatives appeared at approximately 6.1 ppm, and the amide signals of three-center hydrogen bonds shifted slightly downfield to 9.7 ppm. Along with the results from HRMS data, the NMR clearly demonstrated the integrity of **6a**–**6c**. As a typical example, the HRMS of **6c** is shown in Figure 1.

## Conclusions

In summary, by modification on the 5-position of thymidine, the aromatic oligoamide dimer, tetramer and hexamer were successfully introduced to thymidine. The structures of the target molecules were confirmed by $^1$H- and $^{13}$C-NMR and ESI-HRMS. These thymidine derivatives with the folded backbone enforced by three-center hydrogen bonds could have potential application as molecular sensors and regulators, providing the nucleoside with molecular recognition property. Success of the synthesis has encouraged us to further study and prepare other thymidine derivatives with increased solubility in more polar solvents, such as ethanol or even water, and to introduce the modified nucleosides into oligonucleotides.

## Experimental section

### General procedures

HRMS spectra were recorded on a Waters Q-TOF-Premier spectrometer. NMR spectra were recorded on a Bruker DRX 400 spectrometer at 400 MHz ($^1$H) and at 100 MHz ($^{13}$C). Materials were obtained from commercial suppliers and were used without further purification unless otherwise noted. Tetrahydrofuran (THF) was dried by refluxing over sodium/benzophenone immediately prior to use. Dichloromethane was distilled from $CaH_2$ prior to use.

**5-(5-(5-(2,4-Bis(isooctyloxy)benzamido)-2,4-dimethoxybenzamido)-2,4-bis(isooctyloxy)benzamido)-2,4-dimethoxybenzoic acid (3)** Dry THF (50 ml) was added to a mixture of compound **1** (1.60 g, 2.59 mmol) and 10% Pd/C (200 mg). The solution was stirred under one atmosphere of hydrogen at room temperature for 10 h. The mixture was then filtered and the solvent was evaporated. The residue was dried under reduced pressure and then added to a mixture of dimer **2b** (1.60 g, 2.8 mmol), $Et_3N$ (1.0 g, 10 mmol), and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) (0.89 g, 3.5 mmol) in dry $CH_2Cl_2$ (100 ml). The mixture was stirred overnight under argon. A white solid (1.55 g) was obtained after removing the solvent and triturating with methanol. Then 1 M KOH solution (20 ml) and MeOH (30 ml) were added, the solution was acidified to pH=4–5 with 1 M HCl and heated under reflux (70°C) for 8 h. The solvent was removed, and the residue was washed with water (3×20 ml) and dried to afford a white solid, 1.53 g in 78% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 9.69 (s, 1H), 9.68 (s, 1H), 9.63 (s, 1H), 9.10 (s, 1H), 9.08 (s, 1H), 9.06 (s, 1H), 8.26 (d, J=8.8 Hz, 1H), 6.61 (dd, J=8.8, 2.1 Hz, 1H), 6.53 (s, 1H), 6.50 (d, J=2.1 Hz, 1H), 6.49 (s, 1H), 6.43 (s, 1H), 4.02 (d, J=2.1 Hz, 6H), 3.98 (d, J=6.9 Hz, 4H), 3.96 (s, 3H), 3.94 (s, 3H), 3.92–3.88 (m, 4H), 1.97–1.80 (m, 3H), 1.80–1.66 (m, 5H), 1.65–1.18 (m, 31H), 0.99–0.80 (m, 21H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.9, 163.2, 163.0, 162.6, 158.3, 157.0, 154.6, 153.7, 153.0, 152.2, 134.2, 124.4, 122.2, 121.7, 121.4, 115.0, 105.8, 99.7, 96.4, 95.5, 95.0, 72.5, 71.9, 71.4, 70.7, 56.5, 56.5, 55.9, 55.8, 39.4, 39.1, 38.9, 38.7, 30.5, 30.2, 30.1, 29.1, 28.9, 28.8, 23.8, 23.5, 23.4, 23.0, 23.0, 14.1, 14.0, 14.0, 11.1, 10.8, 10.6, 8.7. ESI-HRMS *m/z*, calcd for $C_{64}H_{93}N_3O_{13}$ $[M+H]^+$

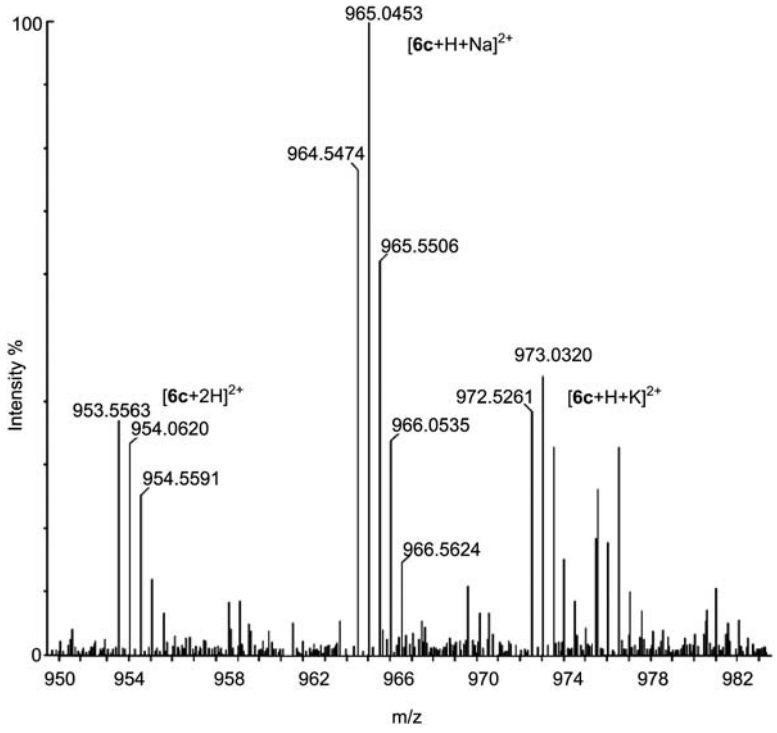



**Figure 1** The ESI-HRMS spectrum of compound **6c.**

1112.6742, $[M+Na]^+$ 1134.6606, $[M+K]^+$ 1150.6345, found $[M+H]^+$ 1112.6709, $[M+Na]^+$ 1134.6605, $[M+K]^+$ 1150.6376.

**5-(5-(5-(5-(5-(2,4-Bis(isooctyloxy)benzamido)-2,4-dimethoxybenzamido)-2,4-bis(isooctyloxy)benzamido)-2,4-dimethoxybenzamido)-2,4-bis(isooctyloxy)benzamido)-2,4-dimethoxybenzoic acid (4)** Tetramer **3** (2.67 g, 2.4 mmol) was added to a solution of the amine prepared from compound **1** (1.52 g, 2.47 mmol), $Et_3N$ (1.1 g, 11 mmol) and BOP-Cl (0.85 g, 3.4 mmol) in dry $CH_2Cl_2$ (100 ml). The mixture was stirred overnight under argon. After removing the solvent and triturating with methanol, a white solid (3.54 g) was obtained. Then 1 M KOH (40 ml) and MeOH (60 ml) were added, the solution was acidified to pH=4–5 with 1 M HCl and heated under reflux (70°C) for 7 h. The solvent was removed, and the solid residue was washed with water (3×20 ml) and dried to afford a white powder, 3.06 g in 76% yield. $^1$HMNR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 9.59 (s, 1H), 9.56 (s, 1H), 9.55 (s, 1H), 9.52 (s, 1H), 9.39 (s, 1H), 9.08 (s, 1H), 9.02 (s, 1H), 8.98 (s, 1H), 8.92 (s, 1H), 8.85 (s, 1H), 8.18 (d, J=8.8 Hz, 3H), 6.54–6.51 (dd, J=2.4, 8.8 Hz, 2H), 6.46 (s, 1H), 6.45 (s, 1H), 6.43 (s, 1H), 6.43 (s, 1H), 6.42 (s, 2H), 3.98–3.92 (m, 12H), 3.91–3.89 (m, 4H), 3.88 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.84–3.81 (m, 2H), 3.79 (s, 3H), 1.85–1.76 (m, 6H), 1.47–1.40 (m, 12H), 1.38–1.34 (m, 12H), 1.29–1.15 (m, 24H), 0.90–0.74 (m, 36H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.8, 163.3, 163.1, 163.1, 162.9, 158.3, 155.6, 154.9, 154.8, 154.0, 153.9, 153.4, 153.1, 152.5, 134.2, 125.3, 122.4, 121.9, 121.8, 121.6, 121.5, 114.8, 114.0, 113.8, 113.7, 109.1, 105.8, 99.7, 96.2, 96.1, 95.0, 72.4, 72.3, 72.0, 71.4, 70.7, 56.8, 56.6, 56.6, 56.3, 56.0, 55.9, 49.8, 49.6, 49.5, 49.4, 49.2, 39.3, 39.0, 38.9, 38.6, 30.4, 30.1, 30.0, 29.1, 28.8, 28.8, 28.7, 23.8, 23.5, 23.4, 23.3, 23.0, 23.0, 14.0, 14.0, 13.9, 13.9, 11.1, 10.6, 10.6, 10.6, 10.5. ESI-HRMS *m/z*, calcd for $C_{96}H_{139}N_5O_{19}$ $[M+2H]^{2+}$ 834.5127, $[M+H+K]^{2+}$ 853.4907, found $[M+2H]^{2+}$ 834.5162, $[M+H+K]^{2+}$ 853.4971.

**5-(5-(2,4-Dimethoxybenzamido)-2,4-dimethoxybenzamido) methyl-2′-deoxyuridine (6a)** Dry $CH_2Cl_2$ (80 ml) was added to a round-bottle flask containing compound **5** (670 mg, 1.79 mmol) and dimer **2a** (1.08 g, 2.90 mmol), followed by sequential addition of BOP-Cl (0.8 g, 3.15 mmol) and $Et_3N$ (1.0 g, 10 mmol). The mixture was stirred for 10 h at room temperature. The solvents were removed under reduced pressure, and the crude mixture was washed with brine (3×20 ml), followed by extraction with ethyl acetate and drying over $Na_2SO_4$. A white solid (2.6 g) was obtained after removal of the solvent, which was then transferred to 7.5 M ammonia in $CH_3OH$ solution (25 ml). The mixture was stirred overnight, filtered, washed with water (2×30 ml) and dried under reduced pressure to provide 2.44 g of a white solid in 63% yield. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.01 (s, 1H), 9.31 (s, 1H), 9.10 (s, 1H), 8.30 (t, J=6.1 Hz, 1H), 8.24 (d, J=8.8 Hz, 1H), 7.78 (s, 1H), 6.61 (dd, J=8.8, 2.3 Hz, 1H), 6.47 (d, J=2.2 Hz, 1H), 6.42 (s, 1H), 6.32 (dd, J=8.8, 5.6 Hz, 1H), 5.29–5.20 (m, 1H), 4.46–4.29 (m, 3H), 4.26–4.17 (m, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.92 (s, 3H), 3.85 (s, 3H), 2.43 (ddd, J=14.0, 5.6, 1.6 Hz, 1H), 2.34 (dd, J=14.0, 5.6 Hz, 1H). $^{13}$C NMR (100 MHz, DMSO) δ 164.1, 163.5, 163.4, 161.6, 158.5, 154.2, 151.5, 150.2, 137.7, 128.8, 128.7, 121.9, 121.3, 113.8, 113.2, 110.7, 106.5, 98.7, 96.1, 87.4, 84.1, 70.4, 61.4, 56.7, 56.5, 56.4, 55.6, 36.2. ESI-HRMS *m/z*, calcd for $C_{28}H_{32}N_4O_{11}$ $[M+H]^+$ 601.2146, $[M+Na]^+$ 623.1965, $[M+K]^+$ 639.1705, found $[M+H]^+$ 601.2191, $[M+Na]^+$ 623.1941, $[M+K]^+$ 639.1691.

**5-(5-(5-(5-(2,4-Bis(isooctyloxy)benzamido)-2,4-dimethoxybenzamido)-2,4-bis(isooctyloxy)benzamido)-2,4-dimethoxybenzoamido)methyl-2′-deoxyuridine (6b)** Compound **5** (140 mg, 0.410 mmol), tetramer **3** (181 mg, 0.163 mmol), BOP-Cl (0.1 g, 0.4 mmol) and $Et_3N$ (0.12 g, 1.2 mmol) were added to dry $CH_2Cl_2$ (50 ml), and the reaction mixture was stirred overnight. The solution was washed with water (3×20 ml).

After removing the solvent, it was subjected to column chromatography (AcOEt/$CH_2Cl_2$, 1:35) to afford a white foam (146 mg), which was immediately mixed with of 7.5 M ammonia in $CH_3OH$ (50 ml), and the mixture was stirred overnight. The mixture was concentrated under reduced pressure and filtered. The residue was washed with brine (3×20 ml) and dried under reduced pressure to give 102 mg of a white solid in 58% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 9.87 (s, 1H), 9.83 (s, 1H), 9.35 (s, 1H), 9.17 (s, 1H), 8.83 (s, 1H), 8.67 (s, 1H), 8.31 (s, 1H), 8.20 (d, J=8.8 Hz, 1H), 7.96 (s, 1H), 6.62 (d, J=8.8 Hz, 1H), 6.56 (s, 1H), 6.51 (s, 1H), 6.49 (s, 2H), 6.39 (s, 1H), 5.07 (s, 1H), 4.88 (s, 2H), 4.32 (d, J=25.9 Hz, 2H), 4.11 (dd, J=44.2, 19.9 Hz, 4H), 4.03 (s, 3H), 4.02–3.97 (m, 4H), 3.96 (s, 3H), 3.95 (s, 3H), 3.93 (s, 3H), 3.90 (d, J=5.6 Hz, 2H), 2.54–2.41 (m, 1H), 2.31 (dd, J=18.4, 11.6 Hz, 1H), 1.90 (dtd, J=18.1, 12.2, 6.1 Hz, 3H), 1.74 (dt, J=12.1, 5.9 Hz, 1H), 1.41 (t, J=7.3 Hz, 16H), 1.29 (d, J=28.3 Hz, 16H), 1.00–0.77 (m, 24H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 164.5, 163.9, 163.5, 162.4, 162.3, 158.4, 154.8, 150.7, 121.9, 121.5, 114.4, 113.6, 113.3, 111.2, 96.5, 87.9, 84.6, 70.98, 61.9, 57.3, 56.9, 56.8, 56.7, 39.1, 30.3, 30.1, 30.1, 29.9, 28.9, 28.7, 28.6, 28.5, 23.7, 23.5, 23.4, 23.3, 23.0, 22.9, 14.3, 14.2, 14.2, 11.0, 10.8, 8.8. ESI-HRMS *m/z*, calcd for $C_{74}H_{106}N_6O_{17}$ $[M+Na]^+$ 1373.7512, found $[M+Na]^+$ 1373.7486.

**5-(5-(5-(5-(5-(5-(2,4-Bis(isooctyloxy)benzamido)-2,4-dimethoxybenzamido)-2,4-bis(isooctyloxy)benzamido)-2,4-dimethoxybenzamido)-2,4-bis(isooctyloxy)benzamido)-2,4-dimethoxybenzaamido)methyl-2′-deoxyuridine (6c)** Compound **5** (121 mg, 0.35 mmol), hexamer **4** (320 mg, 0.19 mmol), BOP-Cl (0.1 g, 0.4 mmol) and $Et_3N$ (0.12 g, 1.2 mmol) were added to dry $CH_2Cl_2$ (20 ml). The reaction mixture was stirred at room temperature overnight, followed by quenching with water. After removing the solvents, the crude mixture was purified by silica gel column chromatography (EA/$CH_2Cl_2$, 1:40) to afford a white foam (223 mg). After addition of 7.5 M ammonia in $CH_3OH$ solution (25 ml), the mixture was stirred overnight, filtered, washed with water (3×20 ml) and dried under reduced pressure to afford 122 mg of a white solid in 39% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 9.68 (s, 1H), 9.61 (s, 1H), 9.58 (s, 2H), 9.33 (s, 1H), 9.01 (s, 1H), 9.00 (s, 1H), 8.97 (s, 1H), 8.59 (s, 1H), 8.29 (s, 1H), 8.16 (d, J=8.8 Hz, 1H), 7.93 (s, 1H), 7.41 (s, 1H), 6.53 (d, J=8.8 Hz, 1H), 6.47 (s, 1H), 6.46 (s, 1H), 6.42 (s, 4H), 6.38 (d, J=6.4 Hz, 1H), 4.98 (s, 1H), 4.93 (s, 1H), 4.72 (s, 1H), 4.40 (d, J=10.2 Hz, 1H), 4.26–4.09 (m, 2H), 4.07–3.72 (m, 30H), 2.48 (d, J=7.6 Hz, 1H), 2.34–2.23 (m, 1H), 1.92–1.73 (m, 12H), 1.54–1.14 (m, 45H), 0.94–0.71 (m, 33H). $^{13}$C NMR (100 MHz, DMSO) δ 164.0, 163.4, 163.0, 162.1, 161.9, 158.0, 154.4, 154.3, 153.6, 152.4, 152.0, 151.8, 150.2, 137.9, 133.8, 133.2, 129.0, 123.3, 121.7, 121.5, 121.4, 121.0, 114.0, 113.3, 113.1, 113.0, 110.7, 106.9, 99.7, 97.7, 96.3, 96.2, 87.4, 84.1, 72.3, 72.0, 71.5, 70.4, 70.3, 61.4, 57.0, 56.5, 56.4, 56.2, 38.6, 38.4, 38.3, 38.1, 29.9, 29.7, 29.6, 28.4, 28.2, 28.1, 23.3, 23.1, 23.1, 23.0, 22.5, 22.4, 13.8, 13.7, 13.7, 10.9, 10.6, 10.4. ESI-HRMS *m/z*, calcd for $C_{106}H_{152}N_8O_{23}$ $[M+2H]^{2+}$ 954.0580, $[M+H+Na]^{2+}$ 965.0490, $[M+H+K]^{2+}$ 973.0360, found $[M+2H]^{2+}$ 954.0620, $[M+H+Na]^{2+}$ 965.0453, $[M+H+K]^{2+}$ 973.0320.

## Acknowledgements

The authors thank the National Natural Science Foundation of China (20774059), SRF for ROCS, SEM (20071108-18-16), and Distinguished GCC Cancer Clinicians and Scientists Award. We also thank Prof. Pengchi Deng in Analytical and Testing Center of Sichuan University for NMR analyses.

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