Solvent-free synthesis of novel chiral unsymmetrical urea molecular tweezers under microwave irradiation

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Seven novel chiral unsymmetrical urea molecular tweezers based on 1, 3-phenoxyacetic acid have been designed and synthesised using solid K_2CO_3 as supporter in the solvent-free conditions under microwave irradiation. This method is simple, fast, efficient and eco-friendly. The structures of target compounds were characterised by IR, ^{1}H NMR, MS spectra and elemental analyses and their molecular recognition properties were investigated by UV-Vis spectral titration. The preliminary results indicated that these molecular tweezers possess good selectivity for D/L amino acid methyl esters and some anions.

Keywords: chiral unsymmetrical urea, molecular tweezer, microwave irradiation, molecular recognition

Molecular recognition is a basic characteristic in biological systems.[1–3] Molecular tweezers, as one kind of new model of artificial receptors developed in recent years, have created more and more attention in the field of supramolecular chemistry because their natural occurring cavities can provide appropriate microenvironments for substrates.[4–11] A chiral unsymmetrical urea is an ideal building block for the construction of molecular tweezers due to two acid NH groups in the molecule. However, to the best of our knowledge, the use of chiral unsymmetrical disubstituted ureas as building blocks for the construction of molecular tweezer has rarely been reported.

Moreover, the technique of microwave irradiation in solvent-free conditions has become a valuable tool in organic synthesis because of the advantages such as reducing reaction time, getting cleaner reactions, improving yields, simplifying work-up and designing energy-saving protocols.[12–14] In continuation of our ongoing programme to synthesise molecular tweezers using microwave activation,[15–20] we now report a facile and rapid synthetic method in the solid state using microwaves to synthesise chiral unsymmetrical urea-type molecular tweezers. The molecular tweezers shown in Scheme 1 have a cavity in which four NH groups direct towards the centre of the cavity, and the NH group could form hydrogen bonds with substrates in the process of molecular recognition. We can expect that this kind of molecular tweezer possesses good molecular recognition properties for guest molecules. The synthetic route is depicted in Scheme 1. An amino acid **1** is progressed through a urea **2** to the urea **3**, which is coupled with the diacid **4** to yield the required tweezer **5**.

Results and discussion

Synthetic condition of target compound **5a–g**

The supporters significantly affect the yields of the receptors. We found that only trace amounts of **5b** could be detected by TLC analysis when using silica gel H, an artificial zeolite, Al_2O_3 as supporter and irradiating for 7 min, whereas the receptor **5b** was obtained in the yield of 86% when using K_2CO_3 as supporter and irradiating for 7 min. To determine the optimum conditions of this reaction, we investigated the effects of microwave irradiation power and time. It was found that the highest yield of compound **5** can be obtained in 450 W for 7–10 min. The typical results are shown in Table 1. As shown in Table 1, the distinct features of this method include short reaction time, high yields of products and the simple reaction set-up, which is eco-friendly to the environment.

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Recognition abilities of molecular tweezers **5a**, **5d**, **5e** *and* **5g**

The recognition abilities of molecular tweezers **5a**, **5d**, **5e** and **5g** for *D/L*-Val-OMe, *D/L*-Phe-OMe, NO_3^- and $H_2PO_4^-$ have been investigated by UV-Vis spectra titration. The association constant (*Ka*) and Gibbs free energy changes ($-\Delta G^0$) were determined.

Different volumes of guests NO_3^- and $H_2PO_4^-$ solution were added into defined amounts of hosts **5a**, **5d**, **5e** and **5g** respectively. Their characteristic UV absorbance was measured in this process. The phenomenon was: (1) with guest NO_3^- adding into **5a**, **5d**, **5e** and **5g** respectively, the characteristic UV absorbance of hosts had not changed regularly; (2) with guest $H_2PO_4^-$ adding into **5a**, **5d**, **5e** and **5g**, the UV absorbance of hosts had risen in regularity. The results indicated **5a**, **5d**, **5e** and **5g** had no obvious recognition abilities for NO_3^- but were good for $H_2PO_4^-$. The UV-Vis plot of **5d** for $H_2PO_4^-$ is shown in Fig. 1.

$$\frac{1}{\Delta A} = \frac{1}{aKa[G]_0} + \frac{1}{a} \quad (1)$$

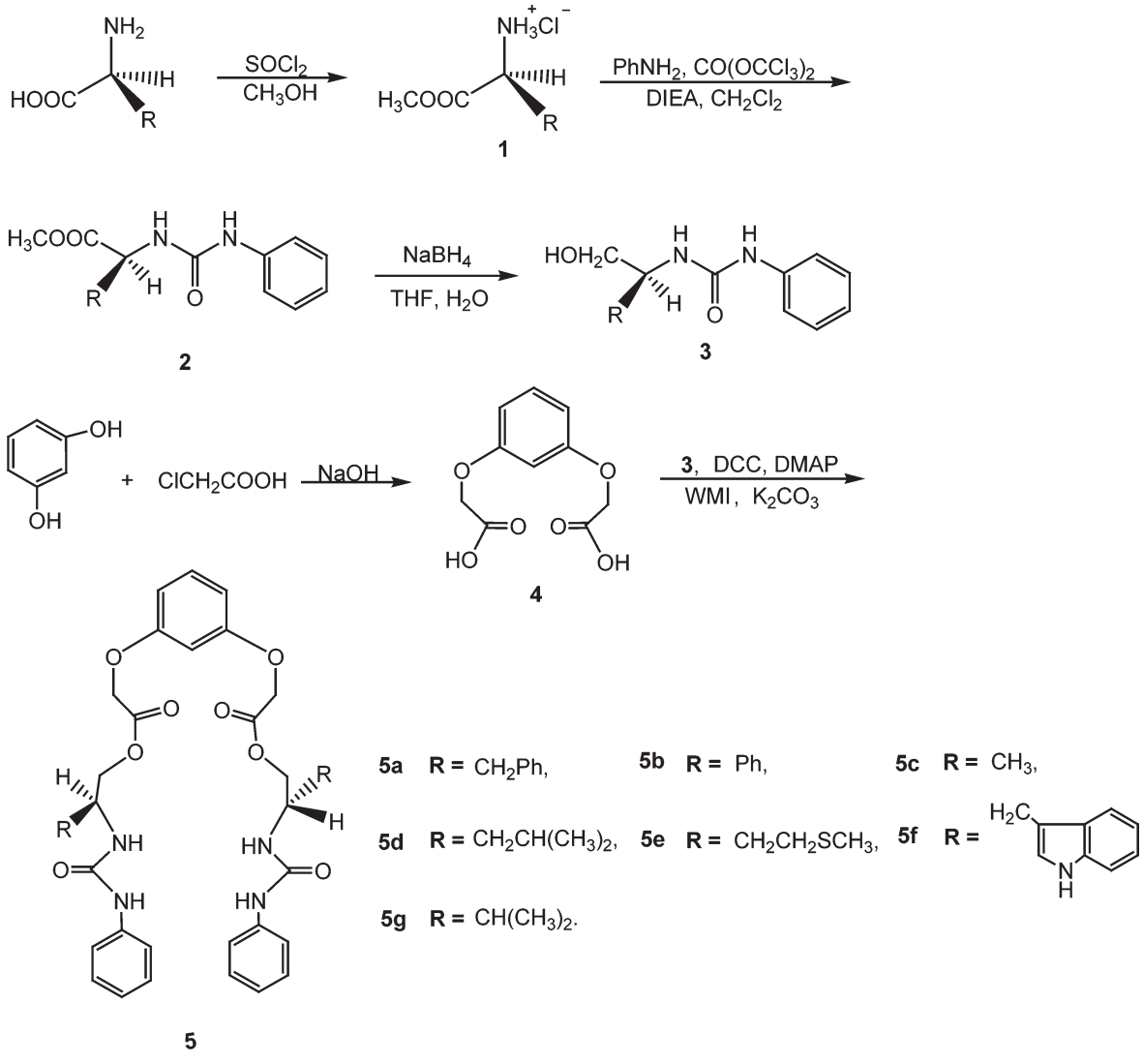
$$\Delta G^0 = -RTLnKa \quad (2)$$

According to equations (1) and (2),[21] when $[G]_0 >> [H]_0$, the plots of $1/[G]_0$ versus $1/\Delta A$ were measured. The plot gave a straight line (Fig. 2). It showed that molecular tweezers **5d** have the ability to form a complex with the guest molecules examined. The supramolecular complexes consisted of 1:1 host and guest molecules. According to the intercept and the slope of the line, we calculated the association constants (*Ka*). The free energy change ($-\Delta G^0$) was obtained according to equation (2). Association constants (*Ka*) and free energy changes ($-\Delta G^0$) for the inclusion complexes of **5a**, **5d**, **5e** and **5g** with $H_2PO_4^-$ are listed in Table 2. The good recognition abilities of **5a**, **5d**, **5e** and **5g** for $H_2PO_4^-$ may be explained because their size and shape are more complementary and matching than NO_3^-.

Association constants (*Ka*), free energy changes ($-\Delta G^0$) and K_L/K_D for the inclusion complexes of **5a**, **5d**, **5e**, **5g** with *D/L*-Val-OMe and *D/L*-Phe-OMe are listed in Table 3. As shown in Table 3, these receptors showed good chiral recognition for *L*-amino acid methyl esters, the maximum K_L/K_D of molecular tweezer **5e** reaches 9.35 for *D/L*-Val-OMe. The details of molecular recognition of these molecular tweezers are under further study.

Experimental

Melting points were determined on a micro-melting point apparatus and the thermometer was uncorrected. Infrared spectra were obtained on a 1700 Perkin-Elmer FTIR using KBr disks. ^{1}H NMR spectra were recorded on a Varian INOVA 400 MHz spectrometer using TMS as internal standard. Mass spectra were determined on a Finnigan



Scheme 1

Table 1 Synthesis of molecular tweezers **5a–g** in solvent-free conditions under microwave irradiation

Entry	T/min	Yield/%
5a	7	84
5b	8	86
5c	10	81
5d	10	82
5e	10	81
5f	7	82
5g	10	83

LCQ^{DECA} instrument. Elemental analysis was performed on a Carlo-Erba-1106 autoanalyser. All reactions were performed in a commercial microwave reactor (XH-100A, 100-1000 W, Beijing Xianghu Science and Technology Development Co. Ltd, Beijing, P.R. China). All the solvents were purified before use. Optical rotations were measured on a Wzz-2B polarimeter. Intermediates **1**, **2**, **3** and **4** were prepared following a reported procedure.[22,23]

Microwave preparation of **5a–g**

Compounds **3a–g** (1.2 mmol), compound **4** (0.5 mmol), DCC (1.2 mmol), a small amount of DMAP and K_2CO_3 (2.0 g) were added to a small flask at room temperature and mixed thoroughly. Then the mixture was irradiated by microwaves at 450 W for 7–10 min. The reaction was monitored by TLC until it was completed. After cooling to room temperature, the reaction mixture was extracted with CH_2Cl_2 (15 mL × 2). The extracted liquid was washed with 10% $NaHCO_3$ (15 mL × 2), brine (15 mL × 2), and finally dried over anhydrous Na_2SO_4. The solvent was evaporated to give the crude product which was purified by column chromatography on silica gel H with

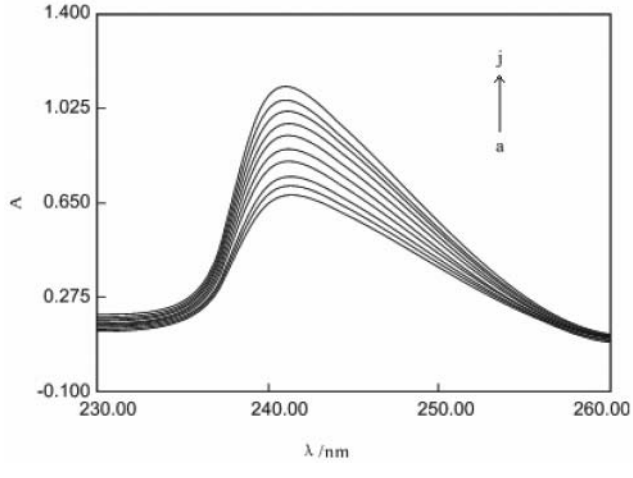


Fig. 1 UV-Vis spectra of molecular tweezers **5d** (4.5×10^{-4} molL^{-1}) in the presence of $H_2PO_4^-$ (a) 0 (b) 0.8×10^{-2} (c) 1.6×10^{-2} (d) 2.4×10^{-2} (e) 3.2×10^{-2} (f) 4.0×10^{-2} (g) 4.8×10^{-2} (h) 5.6×10^{-2} (i) 6.4×10^{-2} (j) 7.2×10^{-2} mol·L^{-1} with λ_{max} at 244.0 nm.

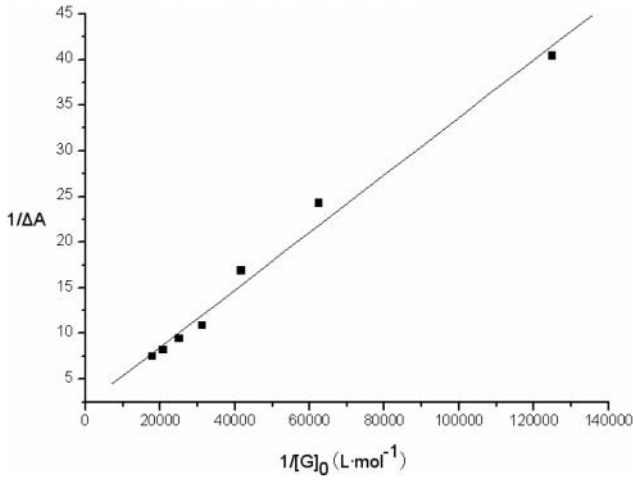


Fig. 2 Typical plot of $1/\Delta A$ versus $1/[G]_0$ for the inclusion complex of molecular tweeze **5d** with $H_2PO_4^-$ in DMSO/$CHCl_3$ (V/V=1:2) at 25 °C.

Table 2 Association constants (Ka) and Gibbs free energy changes ($-\Delta G^0$) for the inclusion complexes of molecular tweezers **5a**, **5d**, **5e** and **5g** with $H_2PO_4^-$ in DMSO/$CHCl_3$ (V/V = 1:2) at 25 °C

Host	Guest[a]	*Ka* /M^{-1}	$-\Delta G^0$/KJ·mol^{-1}
5a	$H_2PO_4^-$	8762.32	22.49
5d	$H_2PO_4^-$	22489.56	24.83
5e	$H_2PO_4^-$	7055.12	21.95
5g	$H_2PO_4^-$	3723.45	19.86

[a] The association constants and Gibbs free energy changes for NO_3^- are not listed because the host molecules have no recognition ability for NO_3^-.

Table 3 Association constants (*Ka*) and free energy changes ($-\Delta G^0$) for the inclusion complexes of molecular tweezers **5a**, **5d**, **5e** and **5g** with amino acid methyl esters in DMSO/$CHCl_3$ (V/V=1:2) at 25 °C

Host	Guest	*Ka*/L·mol^{-1}	$-\Delta G^0$ (KJ·mol^{-1})	K_L/K_D
5a	*D*-Phe-OMe	733.26	16.35	
	L-Phe-OMe	1766.96	18.56	2.42
	D-Val-OMe	179.21	12.86	
	L-Val-OMe	849.75	16.71	4.74
5d	*D*-Phe-OMe	264.23	13.81	
	L-Phe-OMe	2082.35	18.93	7.88
	D-Val-OMe	158.14	12.55	
	L-Val-OMe	1392.25	17.93	8.81
5e	*D*-Phe-OMe	107.25	11.58	
	L-Phe-OMe	788.26	16.52	7.36
	D-Val-OMe	31.21	8.52	
	L-Val-OMe	290.04	14.05	9.35
5g	*D*-Phe-OMe	763.89	16.49	
	L-Phe-OMe	1253.39	17.67	**1.64**
	D-Val-OMe	611.16	15.89	
	L-Val-OMe	635.23	15.99	**1.04**

dichloromethane/ethyl acetate as eluant. The physical and spectra data of the compounds **5a–g** are as follows.

5a: White crystal, yield 84%, m.p. 73-75 °C, [α]20 D–25.4 (c 0.20, DMF); IR (KBr) (cm^{-1}): 3348, 3030, 2955, 1761, 1651, 1599, 1520, 1495, 1441, 1155; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.46 (s, 2H, PhNHCO), 7.36 (d, J = 7.6 Hz, 4H, ArH), 7.31 (t, J = 8.0 Hz, 4H, ArH), 7.22–7.18 (m, 10H, ArH), 7.12 (t, J = 8.4 Hz, 1H, ArH), 6.90 (t, J = 7.6 Hz, 2H, ArH), 6.58–6.54 (m, 3H, ArH), 6.21 (d, J = 7.6 Hz, 2H, CONH), 4.85–4.75 (m, 4H, OCH_2CO), 4.17–4.14 (m, 4H, OCH_2), 4.08–4.03 (m, 2H, NCH), 2.82–2.70 (m, 4H, $PhCH_2$); ESI-MS *m/z* (%): 753 ([M+Na]$^+$, 100). Ana1.Calcd for $C_{42}H_{42}N_4O_8$: C, 69.03; H, 5.79; N, 7.67. Found: C, 69.11; H, 5.77; N, 7.65%.

5b: Pale yellow crystal, yield 86%, m.p. 162–164 °C, [α]20 D+98.3 (c 0.10, DMF); IR (KBr) (cm^{-1}): 3326, 3034, 1763, 1646, 1599, 1554, 1495, 1156, 1077; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.55 (s, 2H, PhNHCO), 7.39–7.35 (m, 12H, ArH), 7.31–7.28 (m, 2H, ArH), 7.23 (t, J = 7.6 Hz, 4H, ArH), 7.08 (t, J = 8.4 Hz, 1H, ArH), 6.91 (t, J = 7.2 Hz, 2H, ArH), 6.85 (d, J = 8.4 Hz, 2H, CONH), 6.48–6.41 (m, 3H, ArH), 5.11–5.06 (m, 2H, NCH), 4.72 (s, 4H, OCH_2CO), 4.38 (d, J = 6.0 Hz, 4H, OCH_2), ESI-MS *m/z* (%): 725 ([M+Na]$^+$, 100). Ana1. Calcd for $C_{40}H_{38}N_4O_8$: C, 68.36; H, 5.45; N, 7.97. Found: C, 68.44; H, 5.43; N, 7.94%.

5c: White crystal, yield 81%, m.p. 154–156 °C, [α]20 D-36.1 (c 0.30, DMF); IR (KBr) (cm^{-1}): 3316, 2978, 1766, 1635, 1598, 1563, 1495, 1441, 1079; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.43 (s, 2H, PhNHCO), 7.39 (d, J = 7.6 Hz, 4H, ArH), 7.23 (t, J = 8.0 Hz, 4H, ArH), 7.15 (t, J = 8.4 Hz, 1H, ArH), 6.90 (t, J = 7.2 Hz, 2H, ArH), 6.55 (t, J = 8.0 Hz, 3H, ArH), 6.15 (d, J = 8.0 Hz, 2H, CONH), 4.83–4.74 (m, 4H, OCH_2CO), 4.13-4.06 (m, 4H, OCH_2), 4.00- 3.94 (m, 2H, NCH), 1.09 (d, J = 6.4 Hz, 6H, CH_3); ESI-MS *m/z* (%): 601 ([M+Na]$^+$, 100). Ana1.Calcd for $C_{30}H_{34}N_4O_8$: C, 62.27; H, 5.92; N, 9.68. Found: C, 62.35; H, 5.91; N, 9.65%.

5d: White crystal, yield 82%, m.p. 75–77 °C, [α]20 D-63.8 (c 0.20, DMF); IR (KBr) (cm^{-1}): 3357, 2958, 1760, 1652, 1600, 1553, 1496, 1441, 1085; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.41 (s, 2H, PhNHCO), 7.39 (d, J = 8.4 Hz, 4H, ArH), 7.23 (t, J = 7.6 Hz, 4H, ArH), 7.12 (t, J = 7.6 Hz, 1H, ArH), 6.90 (t, J = 7.2 Hz, 2H, ArH), 6.54 (d, J = 7.6 Hz, 3H, ArH), 6.08 (d, J = 8.4 Hz, 2H, CONH), 4.81–4.71 (m, 4H, OCH_2CO), 4.16–4.02 (m, 4H, OCH_2), 4.00–3.94 (m, 2H, NCH), 1.67–1.60 (m, 2H, CH), 1.34–1.19 (m, 4H, CH_2), 0.89–0.84 (m, 12H, CH_3); ESI-MS *m/z* (%): 685 ([M+Na]$^+$, 100). Ana1.Calcd for $C_{36}H_{46}N_4O_8$: C, 62.24; H, 7.00; N, 8.45. Found: C, 62.35; H, 6.98; N, 8.43%.

5e: Pale yellow crystal, yield 81%, m.p. 60–62 °C, [α]20 D-21.4 (c 0.20, DMF); IR (KBr) (cm^{-1}): 3358, 2916, 1761, 1654, 1598, 1557, 1498, 1440, 1084; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.43 (s, 2H, PhNHCO), 7.39 (d, J = 8.0 Hz, 4H, ArH), 7.24 (t, J = 7.6 Hz, 4H, ArH), 7.14 (t, J = 8.4 Hz, 1H, ArH), 6.91 (t, J = 7.2 Hz, 2H, ArH), 6.54 (t, J = 8.0 Hz, 3H, ArH), 6.20 (d, J = 8.4 Hz, 2H, CONH), 4.82–4.73 (m, 4H, OCH_2CO), 4.20–4.10 (m, 4H, OCH_2), 4.04–3.97 (m, 2H, NCH), 2.56–2.43 (m, 4H, SCH_2), 2.04 (s, 6H, SCH_3), 1.80–1.61 (m, 4H, CH_2); ESI-MS *m/z* (%): 699 ([M+H]$^+$, 100). Ana1.Calcd for $C_{34}H_{42}N_4O_8S_2$: C, 58.43; H, 6.06; N, 8.02. Found: C, 58.55; H, 6.08; N, 8.00%.

5f: White crystal, yield 82%, m.p. 130–132 °C, [α]20 D-32.1.4 (c 0.20, DMF); IR (KBr) (cm^{-1}): 3365, 2925, 1750, 1648, 1599, 1553, 1494, 1439, 1311, 1219, 1157, 1089, 743; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.88 (s, 2H, NH), 8.51 (s, 2H, PhNHCO), 7.60 (d, J = 7.6 Hz, 2H, ArH), 7.39–7.33 (m, 6H, ArH), 7.23 (t, J = 7.6 Hz, 4H, ArH), 7.14–7.05 (m, 5H, ArH), 7.00 (t, J = 7.6 Hz, 2H, indole-CH), 6.90 (t, J = 7.6 Hz, 2H, ArH), 6.58–6.52 (m, 3H, ArH), 6.21 (d, J = 8.0 Hz, 2H, CONH), 4.84–4.74 (m, 4H, OCH_2CO), 4.23–4.20 (m, 2H, NCH), 4.17–4.08 (m, 4H, OCH_2), 2.90 (d, J = 6.4 Hz, 4H, CH_2); ESI-MS *m/z* (%): 809 ([M+H]$^+$, 100). Ana1.Calcd for $C_{46}H_{44}N_6O_8$: C, 68.30; H, 5.48; N, 10.39. Found: C, 68.41; H, 5.46; N, 10.35%.

5g: White crystal, yield 83%, m.p. 70–72 °C, [α]20 D + 28.9 (c 0.20, DMF);IR (KBr) (cm^{-1}): 3351, 2964, 1762, 1652, 1599, 1553, 1497, 1441, 1088; ^{1}H NMR (400 MHz, DMSO-d_6,) δ: 8.44 (s, 2H, PhNHCO), 7.40 (d, J = 8.0 Hz, 4H, ArH), 7.23 (t, J = 7.6 Hz, 4H, ArH), 7.10 (t, J = 8.4 Hz, 1H, ArH), 6.90 (t, J = 7.2 Hz, 2H, ArH), 6.52 (d, J = 8.4 Hz, 3H, ArH), 6.14 (d, J = 9.2 Hz, 2H, CONH), 4.79–4.70 (m, 4H, OCH_2CO), 4.21–4.08 (m, 4H, OCH_2), 3.79–3.73 (m, 2H, NCH), 1.79–1.75 (m, 2H, CH), 0.89 (d, J = 6.8 Hz, 12H, CH_3), ESI-MS *m/z* (%): 657 ([M+Na]$^+$, 100). Ana1.Calcd for $C_{34}H_{42}N_4O_8$: C, 64.34; H, 6.67; N, 8.83. Found: C, 64.45; H, 6.65; N, 8.80%.

We thank the Natural Science Foundation of the State Ethnic Affairs Commission of P.R.China (Project No.09XN08) for the financial support.

Received 1 October 2010; accepted 18 October 2010
Paper 1000381 doi: 10.3184/174751911X556837
Published online: 21 January 2011

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