Sonication-induced self-assembly of flexible tris(ureidobenzyl)amine: from dimeric aggregates to supramolecular gels

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Supporting Information

1. General information

All reactions were conducted under Ar atmospheres. Chemicals were treated as follows: THF, toluene, and hexane, distilled from Na/benzophenone; CH_2Cl_2, MeCN, distilled from CaH_2 (for reactions) or simple distillation (chromatography); Hexane (for chromatography), methanol, and simple distillation; $CDCl_3$ (Acros), Other materials not listed were used as received from common commercial sources.

NMR spectra were obtained on Bruker 300 and 400 spectrometers, and referenced to TMS (^1H, ^{13}C). Melting points (Mp) were determined using a Focus X-4 apparatus (made in China) and were not corrected. Ultrasound irradiation was performed by using a Kun Shan KQ-5200 DE ultrasound cleaner (max. power, 200 W, 40 KHz; Kunshan Ultrasound Instrument Co, Kunshan China). SEM images were obtained by using a SHIMADZU SSX-550 scanning electronic microscope. Low-resolution electrospray ionization mass spectra (LR-ESI-MS) were obtained on Finnigan Mat TSQ 7000 instruments. High-resolution electrospray ionization mass spectra (HR-ESI-MS) were recorded on an Agilent 6540Q-TOF LCMS equipped with an electrospray ionization (ESI) probe operating in positive-ion mode with direct infusion.

2. ^{1}H NMR spectra of 1a in different polar solvents

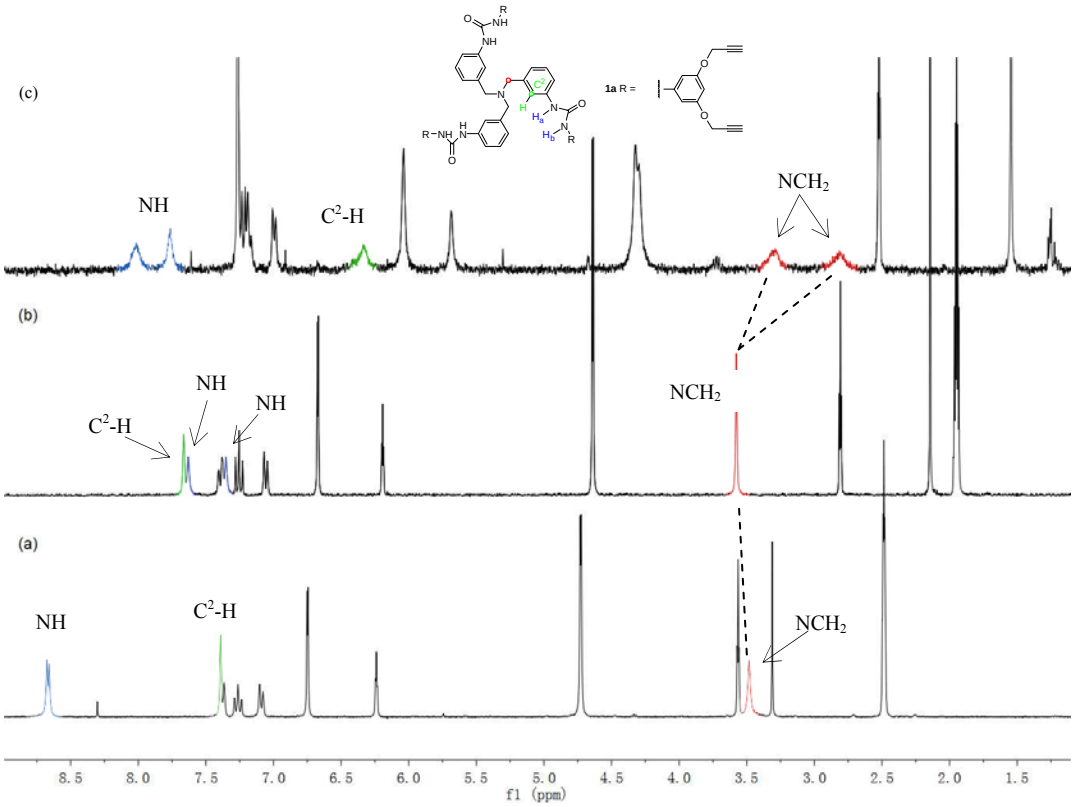


Fig. S1 ^{1}H NMR spectra of **1a** (300 MHz, 295 K) (a): in DMSO-d_6; (b): CD_3CN; (c): $CDCl_3$. Respectively.

3. ^{1}H NMR spectra of 1b in different polar solvents

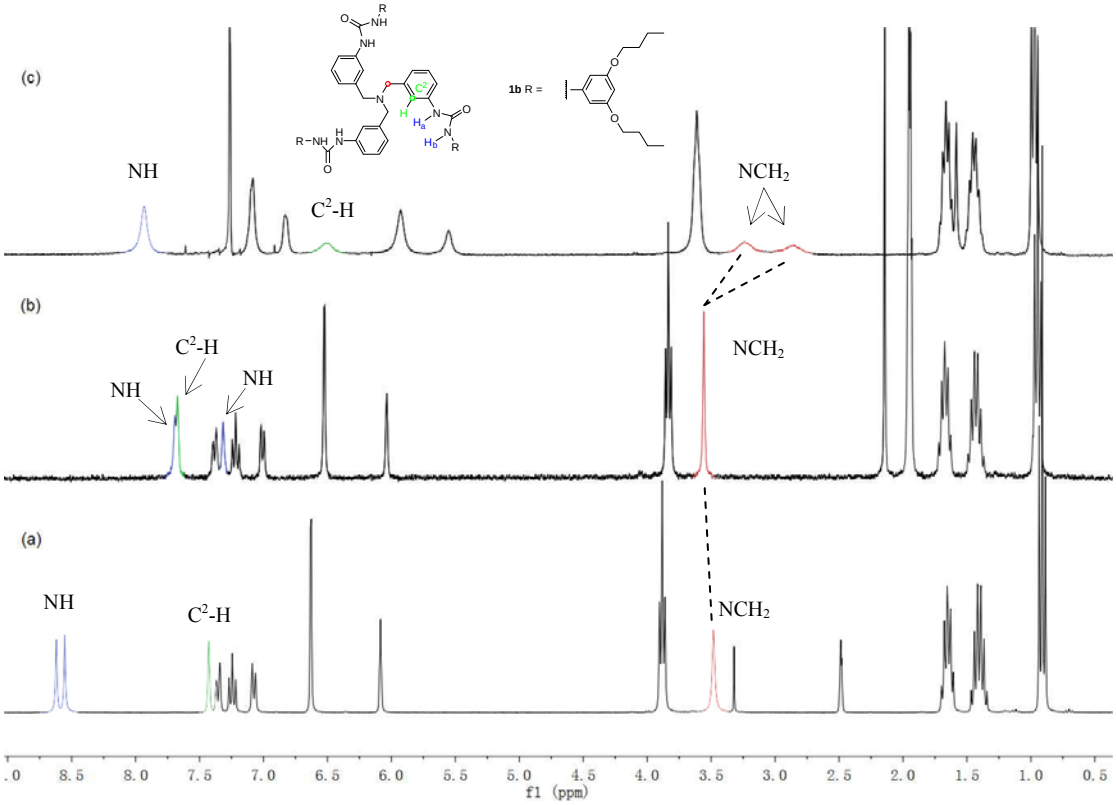


Fig. **S2** ^{1}H NMR spectra of **1b** (300 MHz, 295 K) (a): in DMSO-d_6; (b): CD_3CN; (c): $CDCl_3$. Respectively.

4. ^{1}H NMR spectra of 1c in different polar solvents

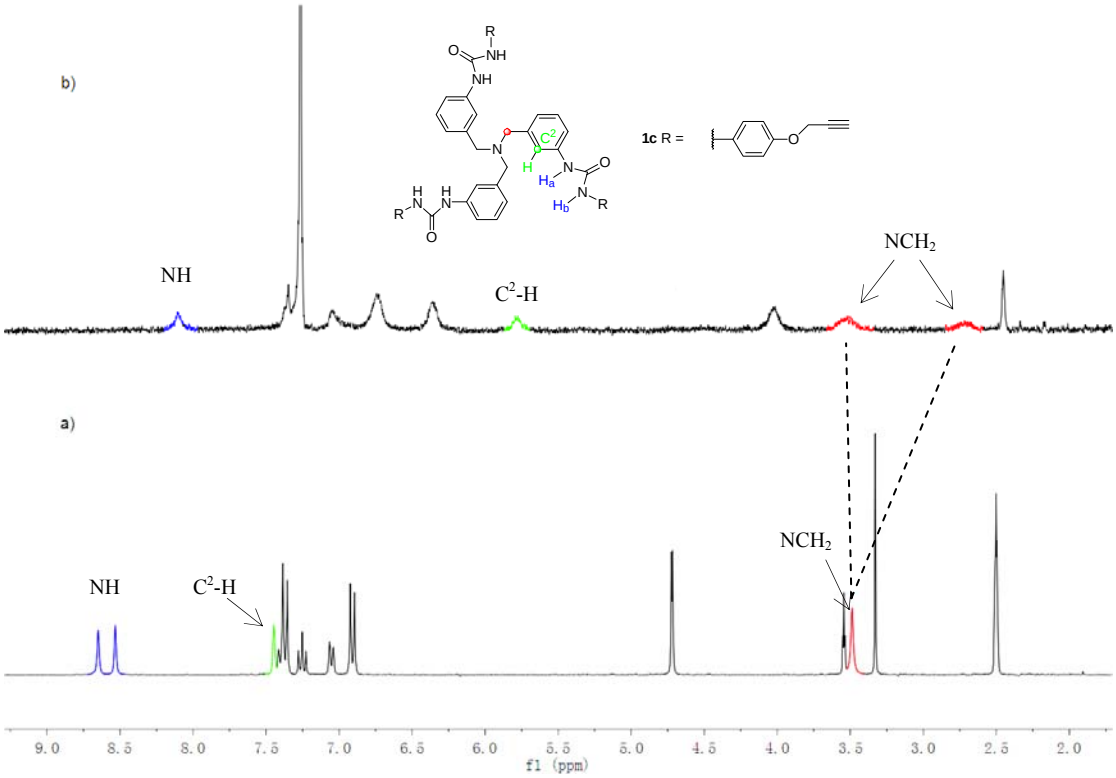


Fig. **S3** ^{1}H NMR spectra of **1c** (300 MHz, 295 K) (a): in DMSO-d_6; (b): $CDCl_3$. Respectively.

5. ^{1}H NMR spectra of 1d in different polar solvents

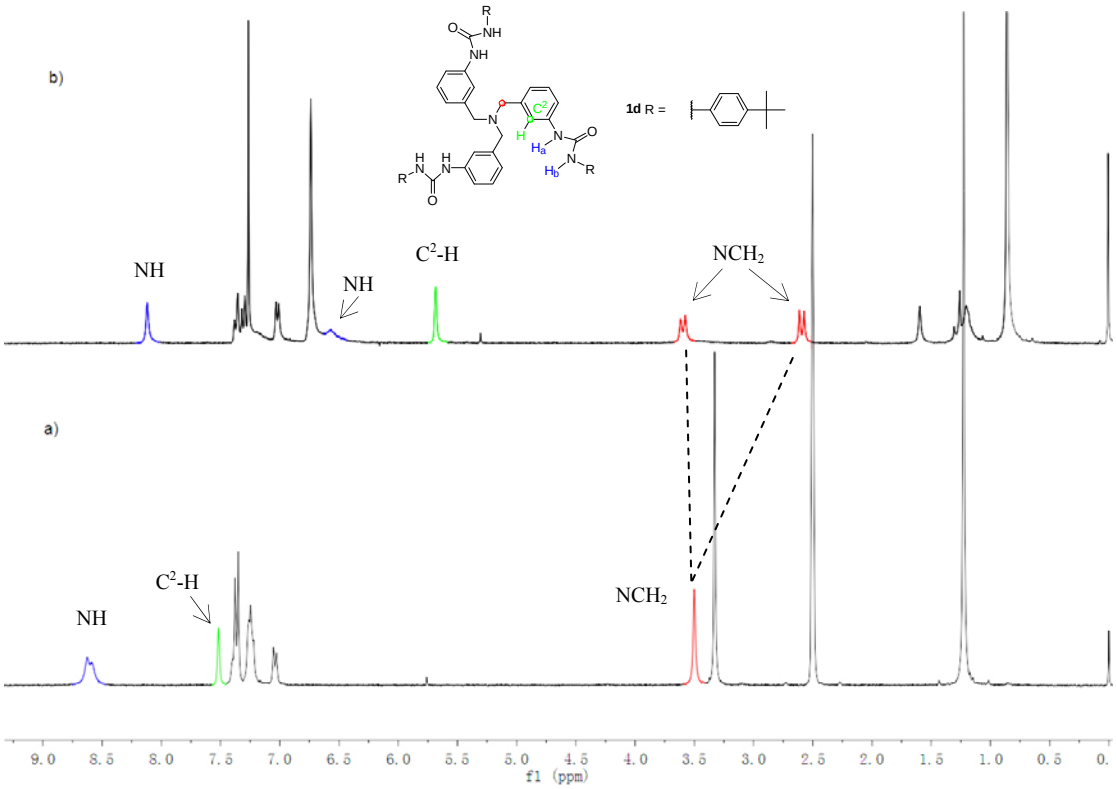


Fig. S4 ^{1}H NMR spectra of **1d** (300 MHz, 295 K) (a): in DMSO-d_6; (b): $CDCl_3$. Respectively.

6. ^{1}H, ^{1}H ROESY spectrum of a solution of 1b•1b

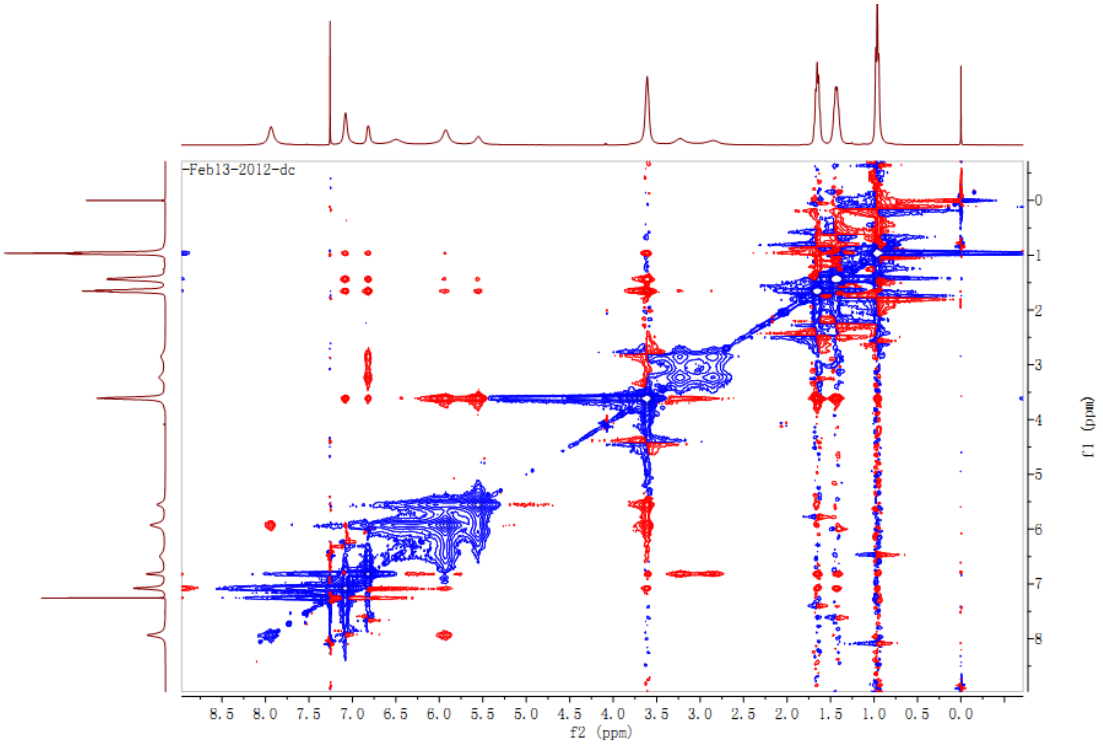
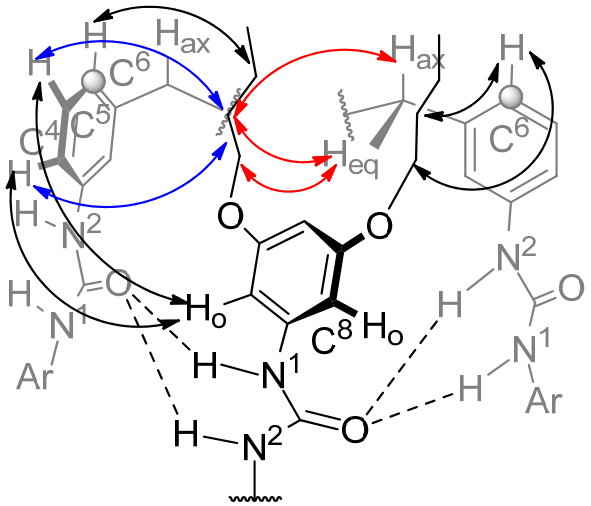


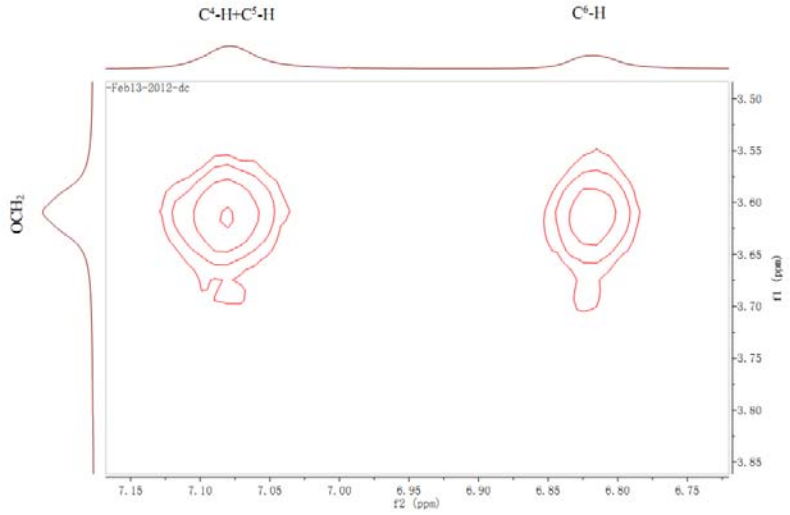
Fig. S5 ^{1}H, ^{1}H ROESY spectrum of a solution of **1b•1b** in $CDCl_3$ (400 MHz, 1.2 × 10^{-2} M) at 298 K.



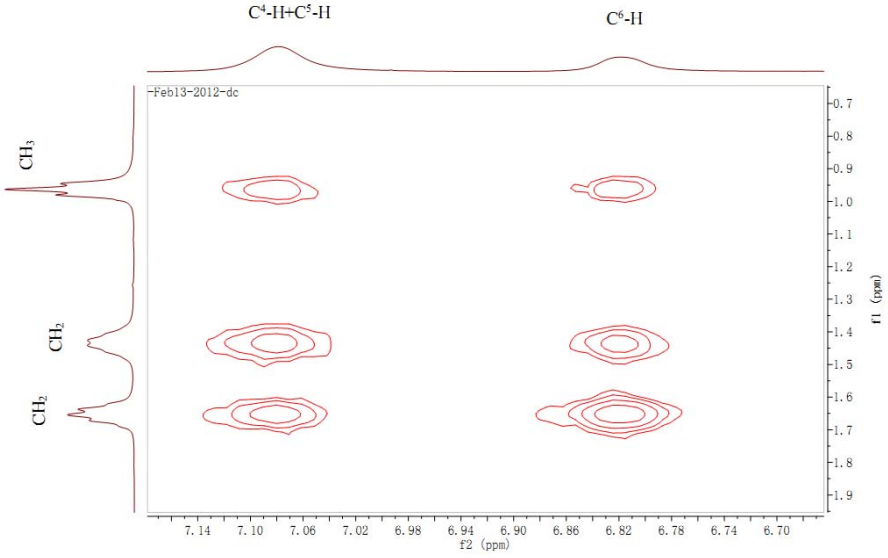
Intermolecular (solid arrows) NOE interactions found within the dimeric capsules **1b•1b** in the ROESY spectrum of a solution in $CDCl_3$ (400 MHz, 1.2 × 10^{-2} M) at 298 K.

Part of ^{1}H, ^{1}H ROESY spectrum of a solution of **1b•1b** in $CDCl_3$:

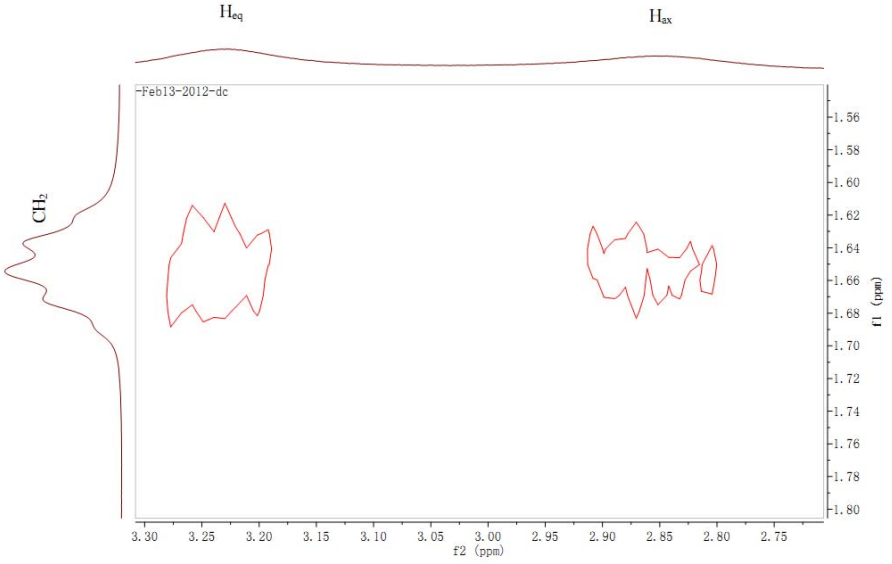
a)



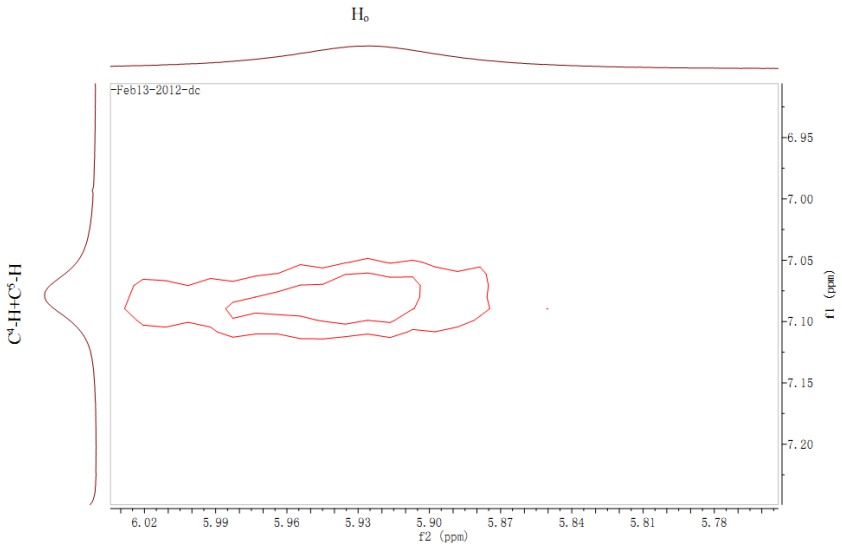
b)



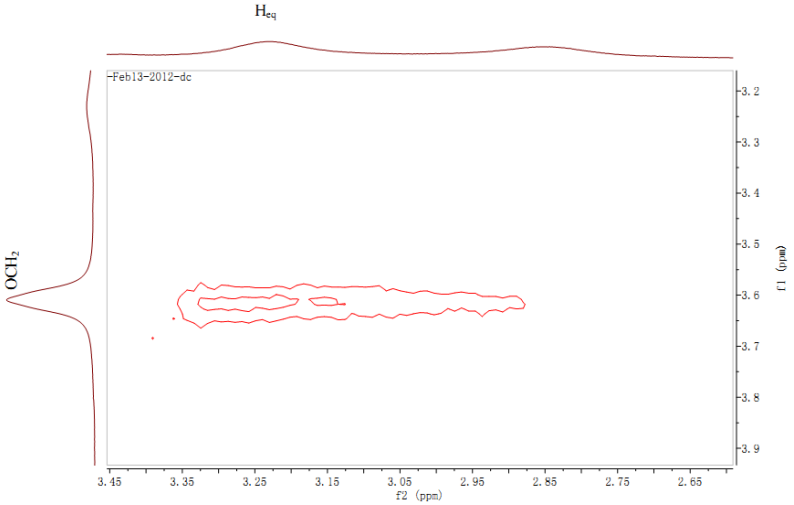
c)



d)


Ho
-Feb13-2012-dc
C4-H+C5-H
6.95
7.00
7.05
7.10
7.15
7.20
f1 (ppm)
6.02
5.99
5.96
5.93
5.90
5.87
5.84
5.81
5.78
f2 (ppm)

e)


Heq
-Feb13-2012-dc
OCH2
3.2
3.3
3.4
3.5
3.6
3.7
3.8
3.9
f1 (ppm)
3.45
3.35
3.25
3.15
3.05
2.95
2.85
2.75
2.65
f2 (ppm)

7. ^{1}H, ^{1}H ROESY spectrum of a solution of 1d•1d

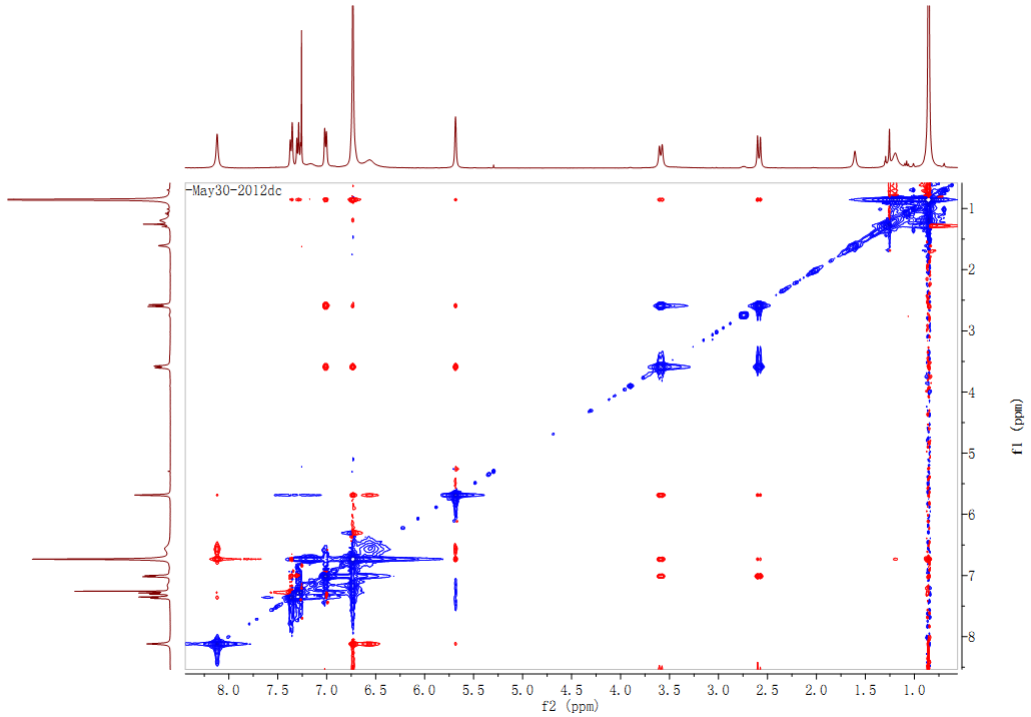
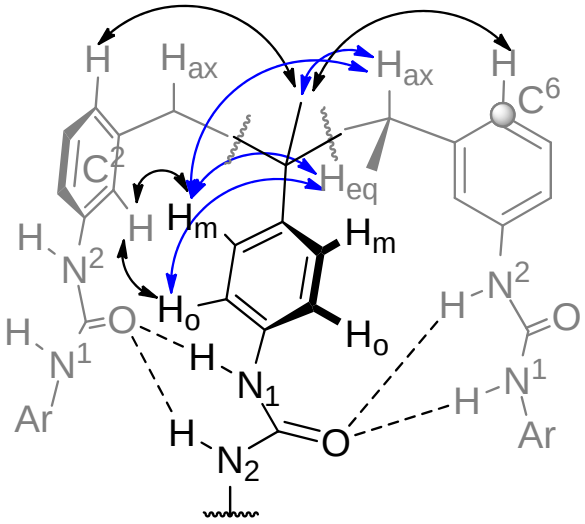


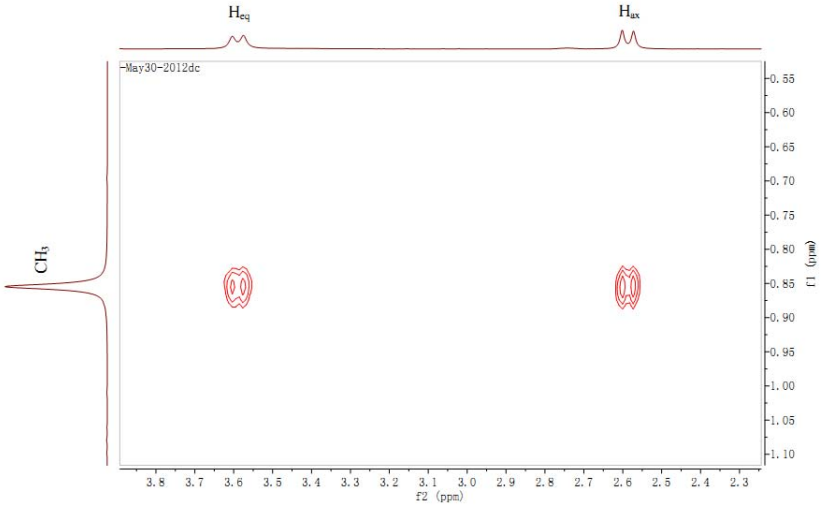
Fig. S6 ^{1}H, ^{1}H ROESY spectrum of a solution of **1d•1d** in $CDCl_3$ (400 MHz, 1.8×10^{-2} M) at 298 K.



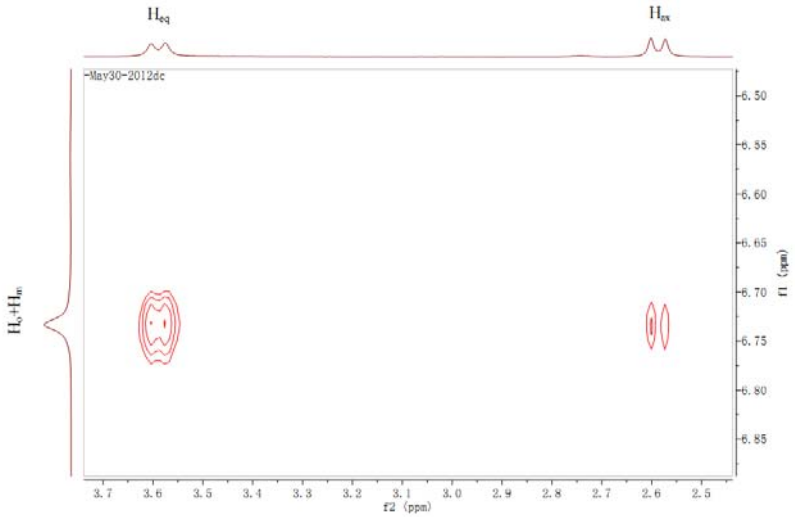
Intermolecular (solid arrows) NOE interactions found within the dimeric capsules **1d•1d** in the ROESY spectrum of a solution in $CDCl_3$ (400 MHz, 1.8×10^{-2} M) at 298 K.

Part of ^{1}H, ^{1}H ROESY spectrum of a solution of **1d•1d** in $CDCl_3$:

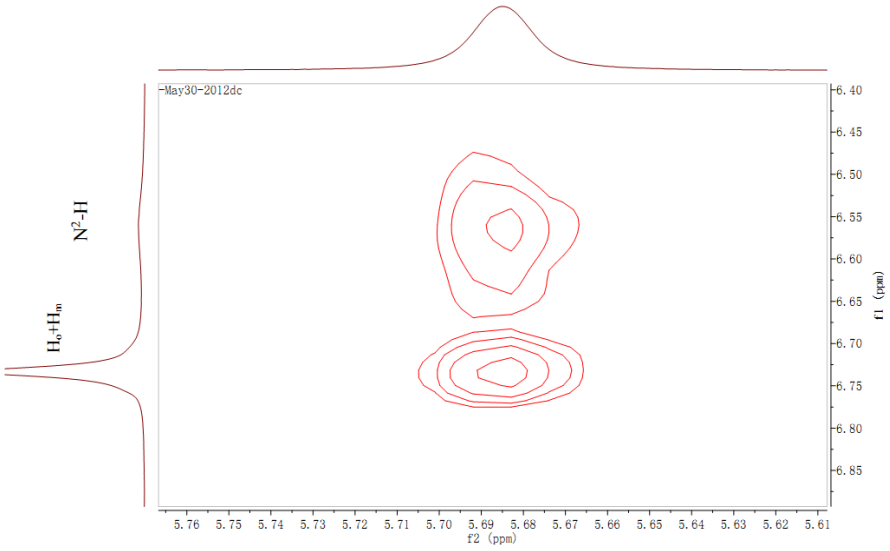
a)



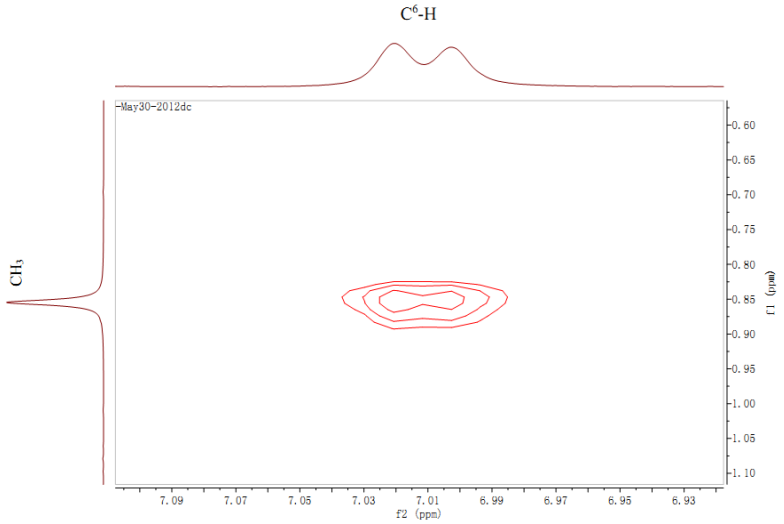
b)



c)



d)


C6-H
CH3
-May30-2012dc
0.60
0.65
0.70
0.75
0.80
0.85
0.90
0.95
1.00
1.05
1.10
f1 (ppm)
7.09
7.07
7.05
7.03
7.01
6.99
6.97
6.95
6.93
f2 (ppm)

8. DOSY NMR spectrum of a solution of 1a-b in $CDCl_3$

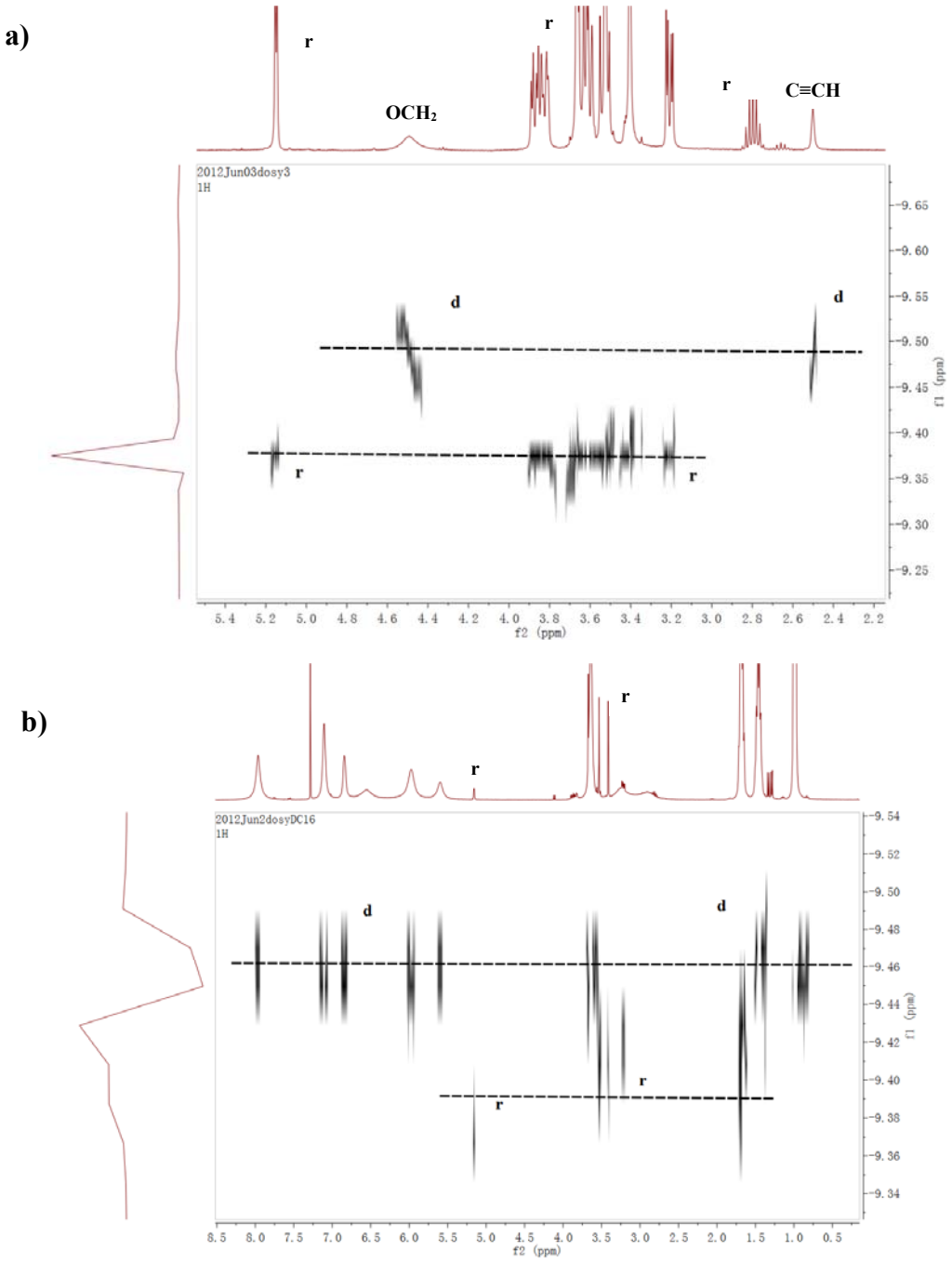


Fig. S7 Part of the DOSY-NMR spectrum (400 MHz, 298 K) of (a) a strurated solution of compound **1a** in $CDCl_3$ (b) a 20 mM solution of compound **1b** in $CDCl_3$. Signals originating from dimeric aggregates are labeled "d", and those from heptakis(2,3,6-tri-*O*-methyl)-*β*-cyclodextrin (*M* = 1429 g/mol) added as internal reference are labeled "r". Diffusion constants are given relative to the diffusion constant of the internal reference.

9. Gelation properties of tripodal tris-urea 1a

Table. S8 Gelation properties of tripodal tris-urea **1a**[a]

solvents	State	CGC	solvents	State	CGC
dichloromethane	I		acetone	S	
chloroform	P		DMSO	S	
methanol	P		water	I	
ethanol	I		acetonitrile	G	15 mg/mL
toluene	P		CH_2Cl_2/MeOH = 10/1	G	20 mg/mL
diethyl ether	I		$CHCl_3$/MeOH = 10/1	G	20 mg/mL
toluene	P				

[a]CGC: critical gelation concentration, the minimum concentration necessary for gelation of solvents. I: insoluble at solvent reflux temperature; P: precipitates; S: soluble at room temperature (solubility > 20 mg/mL); G: gel.

10. Concentration-dependent ^{1}H NMR spectroscopy of 1a in CD_3CN

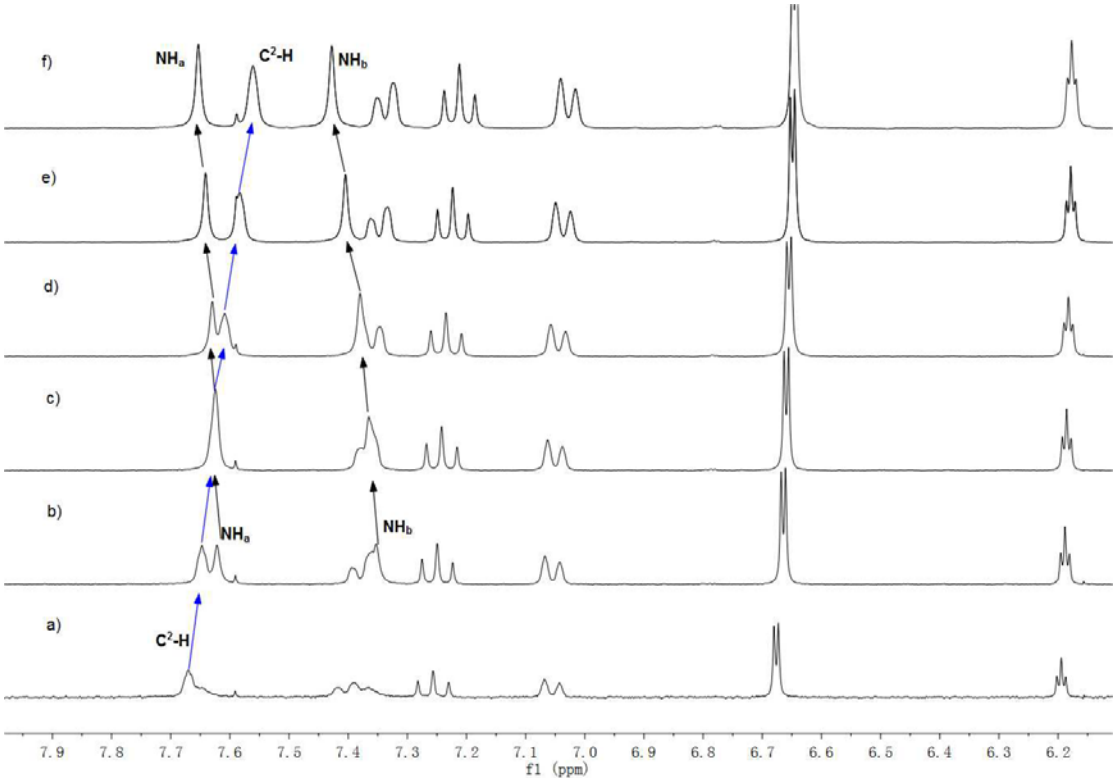


Fig. S9 Partial ^{1}H NMR spectra of tris-urea **1a** (300 MHz, CD_3CN, 295 K) at various concentrations: a) 1.3 mg/mL; b) 3.6 mg/mL; c) 7.2 mg/mL; d) 10.7 mg/mL; e) 14.8 mg/mL; f) 20.1 mg/mL, respectively.

11. The solvent-tuning experiment of gel 1a

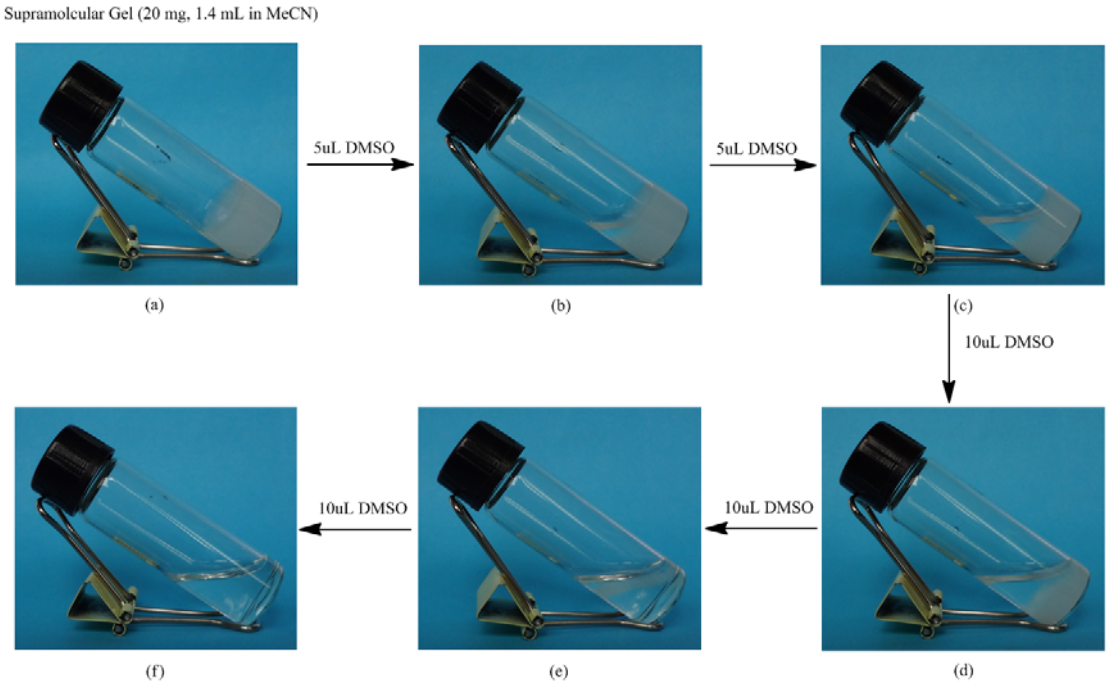


Fig. S10 The solvent-tuning experiment of gel **1a** (20 mg, 1.4 mL in MeCN) with different volume (μL) and equivalent (eq.) of DMSO-d_6: (a) 0.0 (b) 5 μL, 3.5 eq. (c) 10.0 μL, 7 eq. (d) 20 μL, 14 eq. (e) 30.0 μL, 21 eq. (f) 40.0 μL 28 eq.

12. The ^{1}H NMR titration of 1a with DMSO-d_6 in CD_3CN

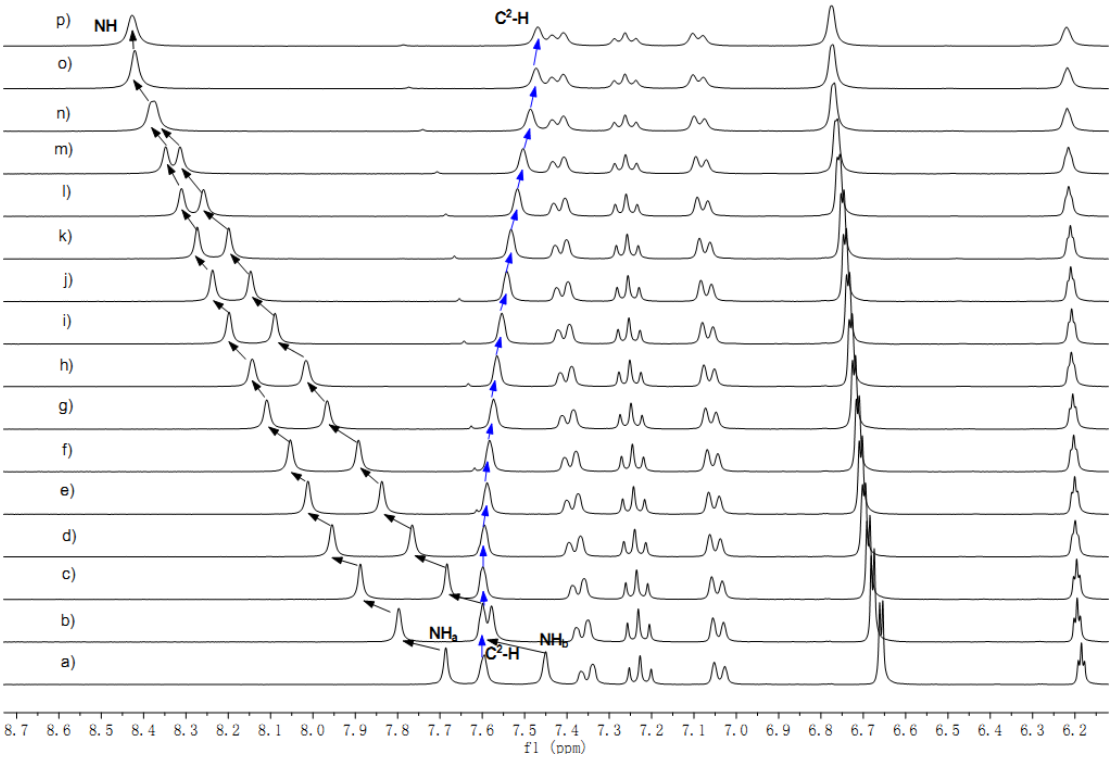
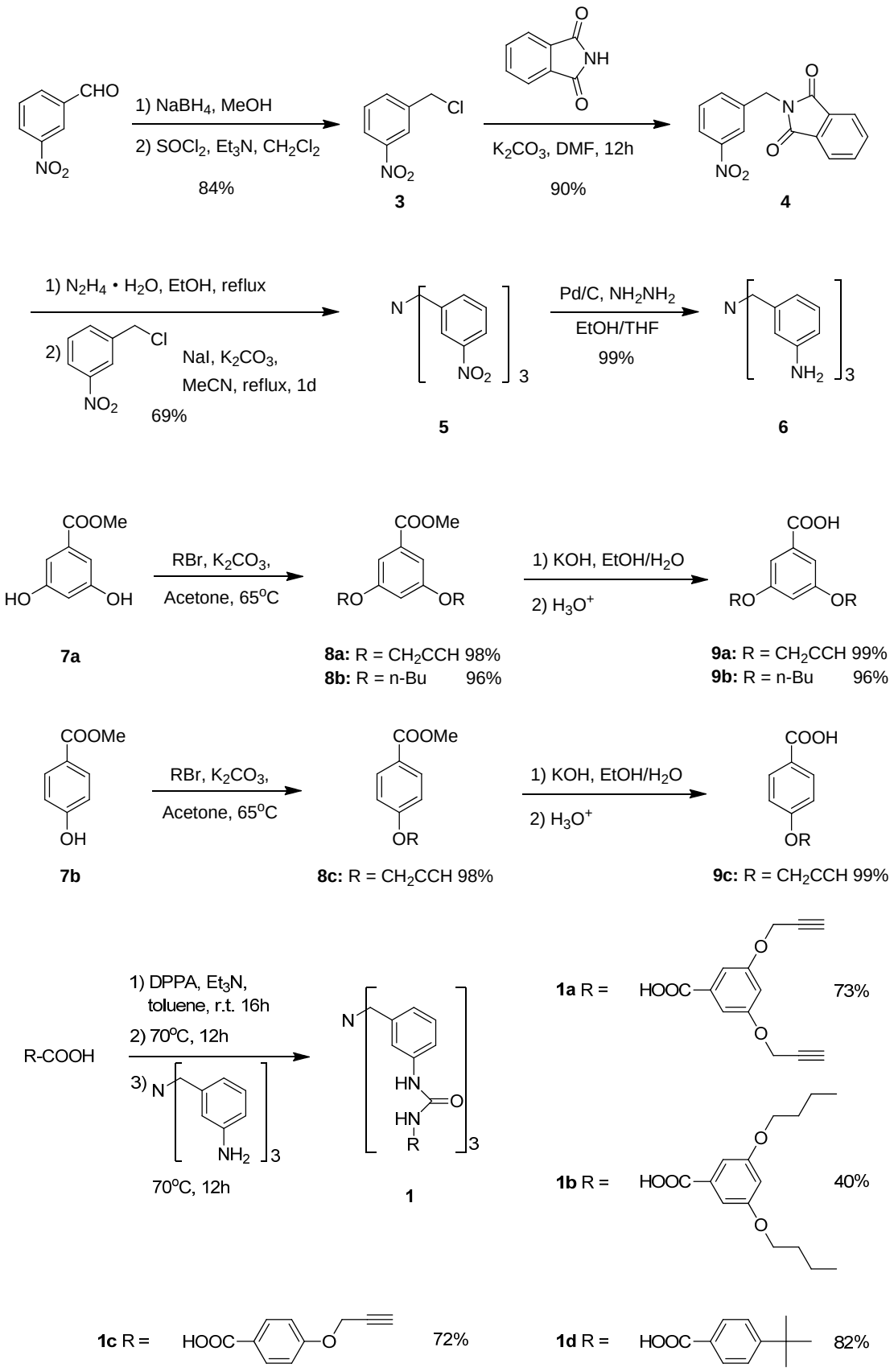


Fig. S11 Partial ^{1}H NMR spectra (CD_3CN, 0.6 mL, 295 K, 300 MHz) of **1a** at a concentration of 14.8 mM with different volume (μL) of DMSO-d_6: (a) 0.0, (b) 2.0 μL, (c) 4.0 μL, (d) 6.0 μL, (e) 8.0 μL, (f) 10.0 μL, (g) 13.0 μL, (h) 16.0 μL, (i) 20.0 μL, (j) 25.0 μL, (k) 30.0 μL, (l) 40.0 μL, (m) 50.0 μL, (n) 70.0 μL, (o) 90.0 μL, (p)100.0 μL.

13. Synthesis of the tri(urea)s 1



Scheme S1 Synthesis of the Tris-(ureas) **1a-d**.

3-nitrobenzyl chloride (3)[S1]: 3-nitrobenzaldehyde (5.67 g, 37.5 mmol) was dissolved in methanol (120.0 mL) and $NaBH_4$ (2.26 g, 60.0 mmol) was added. After 1 h, the mixture was assayed by TLC (no residual substrate). The solvent was removed by rotary evaporation. Then ethyl acetate (100 mL) and water (100 mL) were added. The organic layer was separated. The aqueous phase was extracted with ethyl acetate (2 × 50 mL). The combined organic phases were washed with water (100 mL) and brine (100 mL), and dried (Na_2SO_4). The solvents were removed by rotary evaporation. The residue was filtered through a short silica gel column with hexane. The solvent was removed from the filtrate by rotary evaporation to give a yellow liquid. The liquid was dissolved in dry CH_2Cl_2 (80 mL) with Et_3N (11 mL) and transferred to a round bottom flask. Then $SOCl_2$ (4.8 g, 40.0 mmol) was slowly added with stirring in 10 min. After 3 h, the solvent was removed by rotary evaporation at 45 °C and the residue was chromatographed on silica gel (4.0 × 20.0 cm column) with n-hexane/CH_2Cl_2 (4:1 *v/v*). The solvents were removed from the product fractions to give yellow solid **3** (5.40 g, 31.5 mmol, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.21 (s, 1H, ArH), 8.21 (dd, 1H, J = 8.1 Hz, J = 1.2 Hz, ArH), 7.93 (d, 1H, J = 7.8 Hz, ArH), 7.71 (t, 1H, J = 8.1 Hz, ArH), 4.94 (s, 2H, CH_2Cl). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 44.7, 123.3, 123.4, 129.8, 134.5, 139.4, 148.3.

2-(3-nitrobenzyl)isoindoline-1,3-dione (4)[S2]: A mixture of phtalimide (1.91 g, 13.0 mmol) and K_2CO_3 (2.50 g, 18.1 mmol) in dry DMF (40 mL) was stirred at 70 °C for 6 h. 3-nitrobenzyl chloride (1.71 g, 10 mmol) was added and the reaction mixture still was stirred at 70 °C for 12 h. After cooling to room temperature, the mixture was poured on ice/H_2O (300 mL) and the aqueous phase was extracted with $CHCl_3$ (3 × 50 mL). The combined organic phases were washed with water (100 mL) and brine (100 mL), and dried (Na_2SO_4). The solvents were removed by rotary evaporation. The residue was filtered through a short silica gel column with hexane. The solvent was removed from the filtrate by rotary evaporation and the residue was chromatographed

on silica gel (2.5 × 20.0 cm column) with n-hexane/CH_2Cl_2 (1:1 *v/v*) to give a white solid **4** (2.53 g, 9.0 mmol, 90%). ESI-MS: Calcd. for $C_{15}H_{10}N_2O_4$: 282.06; Found: 305.00 $[M + Na]^+$ (70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.28 (t, 1H, J = 1.8, ArH), 8.15 (dd, 1H, J = 8.1 Hz, J = 1.8 Hz, ArH), 7.91-7.86 (m, 2H, ArH), 7.82-7.74 (m, 3H, ArH), 7.71 (t, 1H, J = 8.1 Hz, ArH), 4.95 (s, 2H, NCH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 40.8, 123.0, 123.5, 123.6, 129.8, 131.9, 134.3, 134.7, 138.2, 148.4, 167.8.

Tri(3-nitrobenzyl)amine (5)[S3]: The compound **4** (1.20 g, 4.3 mmol) was dissolved in EtOH (75 mL) with N_2H_4•H_2O (5 mL) and transferred to a round bottom flask. The mixture was stirred at reflux temperature for 6 h. After cooling to room temperature, the solvent was removed and aqueous $NaHCO_3$ (150 mL) was added and the resulting solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine (100 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and to give yellow oil 3-nitrobenzylamine[S4] (0.65 g, 4.3 mmol, 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.23 (s, 1H, ArH), 8.12 (d, 1H, J = 8.1 Hz, ArH), 7.68 (d, 1H, J = 7.8 Hz, ArH), 7.51 (t, 1H, J = 7.8 Hz, ArH), 4.23 (s, 2H, NCH_2), 1.52 (br, 2H, NH_2).

A Schlenk flask was charged with above 3-nitrobenzylamine (0.65 g, 4.3 mmol), 3-nitrobenzyl chloride (1.71 g, 10.0 mmol), K_2CO_3 (1.80 g, 13.0 mmol) and NaI (1.95 g, 13.0 mmol) and dry acetonitrile (40 mL), and fitted with a condenser. The reaction mixture was stirred at reflux for 24 h. After cooling, the inorganic salts were filtered and washed with cold acetonitrile. The solvent removed, and the residue was purified by silica gel chromatography (2.5 × 20.0 cm column) eluting with AcOEt/hexanes (1:4 *v/v*) to afford tri(3-nitrobenzyl)amine as a yellow soild (1.26 g,

2.98 mmol, 69%). ESI-MS: Calcd. for $C_{21}H_{18}N_4O_6$: 422.12; Found: 423.05 $[M + H]^+$ (80%). 445.05 $[M + Na]^+$ (100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.21 (s, 3H, ArH), 8.14 (d, 3H, J = 8.1 Hz, ArH), 7.74 (d, 3H, J = 7.5 Hz, ArH), 7.55 (t, 3H, J = 7.8 Hz, ArH), 3.72 (s, 6H, NCH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 57.5, 122.5, 123.6, 130.3, 135.7, 141.6, 148.2.

Tri(3-aminobenzyl)amine (6)[S5]: Tri(3-nitrobenzyl)amine (0.55 g, 1.3 mmol) was dissolved in EtOH/THF (20/15 mL) and 10% Pd/C (0.06 g) was added. Hydrazine hydrate (3 ml, 48 mmol) was added when the reaction mixture was heated at 80 °C. After 6 h, the mixture was assayed by TLC (no residual substrate). The mixture was filtered through Celite and the filter cake was discarded. The solvent was removed and the residue was purified by silica gel chromatography (2.0 × 20.0 cm column) eluting with CH_2Cl_2/MeOH (70:1, *v/v*) to afford **6** as a yellow solid (0.42 g 1.3 mmol, 99%). ESI-MS: Calcd. for $C_{21}H_{24}N_4$: 322.20; Found: 333.15 $[M + H]^+$ (100%). ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm) 7.09 (t, 3H, J = 7.8 Hz, ArH), 6.80 (d, 3H, J = 7.6 Hz, ArH), 6.75 (s, 3H, ArH), 6.55 (dd, 3H, J = 8.0 Hz, J = 1.6 Hz ArH), 3.63 (br, 6H, NH_2), 3.47 (s, 6H, NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 58.0, 113.7, 115.4, 119.2, 129.0, 141.0, 146.3.

Compound (8): A Schlenk flask was charged with Compound **7a** (2.0 g, 11.9 mmol), RBr (**a:** 3.45 g, 29.0 mmol; **b:** 4.11 g, 30 mmol), K_2CO_3 (4.84 g, 35.0 mmol), and Acetone (50 mL), and fitted with a condenser. The mixture was stirred for 16 h at 70 °C, cooled to ~20 °C. The mixture was filtered and the solvent was removed. The residue was chromatographed on silica gel (4.0 × 20.0 cm column) with n-hexane/CH_2Cl_2 (4:1 *v/v*). The solvents were removed from the product fractions to get compound **8**.

8a[S6]**:** white solid (2.85 g, 11.6 mmol, 98%). ESI-MS: Calcd. for $C_{14}H_{12}O_4$: 244.07; Found: 245.05 $[M + H]^+$ (40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.60 (d, 2H, J = 2.4 Hz, ArH), 6.82 (t, 1H, J = 2.4 Hz, ArH), 4.72 (d, 4H, J = 2.4 Hz, OCH_2), 3.95 (s, 3H, $COOCH_3$), 2.55 (t, 2H, J = 2.4 Hz, CCH). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 52.3, 56.1, 76.0, 78.0, 107.5, 108.9, 132.2, 158.5, 166.4.

8b[S7]**:** colorless liquid (3.20 g, 11.4 mmol, 96%). ESI-MS: Calcd. for $C_{16}H_{24}O_4$: 280.17; Found: 281.10 $[M + H]^+$ (100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.16 (d, 2H, J = 2.1 Hz, ArH), 6.64 (t, 1H, J = 2.1 Hz, ArH), 3.98 (t, 4H, J = 6.6 Hz, OCH_2), 3.90 (s, 3H, $COOCH_3$), 1.72-1.81 (m, 4H, CH_2), 1.45-1.53 (m, 4H, CH_2), 0.97 (t, 6H, J = 7.5 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 13.8, 19.2, 31.2, 53.1, 68.0, 106.6, 107.6, 131.8, 160.2, 167.0.

methyl *p*-propargyloxybenzoate (8c) [S8]**:** A Schlenk flask was charged with Compound **7b** (4.56 g, 30.0 mmol), propargyl bromide (4.69 g 39.0 mmol), K_2CO_3 (7.0 g, 50.0 mmol), and acetone (50 mL), and fitted with a condenser. The mixture was stirred for 18 h at 65 °C, cooled to ~20 °C. The mixture was filtered and the solvent was removed. The residue was chromatographed on silica gel (4.0 × 20.0 cm column) with n-hexane/CH_2Cl_2 (1:1 *v/v*). The solvents were removed from the product fractions to get white solid **8c** (5.60 g, 29.4 mmol, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.01 (d, 2H, J = 9.0 Hz, ArH), 7.00 (d, 2H, J = 9.0 Hz, ArH), 4.75 (d, 2H, J = 2.4 Hz, OCH_2), 3.89 (s, 3H, $COOCH_3$), 2.55 (t, 1H, J = 2.4 Hz, CCH).

Compound (9): To a solution of KOH (2.24 g, 40.0 mmol) in ethanol (90 mL) and H_2O (10 mL) was added compound **8** (**a:** 2.0 g, 8.2 mmol; **b:** 2.0 g, 7.1 mmol). After stirring at 25 °C for 16 h, the mixture was assayed by TLC (no residual substrate). The solvent was removed and the residue was dissolved in a mixture of AcOEt (100 mL) and H_2O (100 mL), and concentrated HCl solution was added in small portions until the pH reached 1. The layers were separated, and the organic

layer was washed with an aqueous 10% HCl (2 × 100 mL), and then with brine (100 mL). The organic phase was dried ($MgSO_4$) and evaporated to get compound **9**.

9a[S6]**:** white solid (1.9 g, 8.2 mmol, 99%). ESI-MS: Calcd. for $C_{13}H_{10}O_4$: 230.06; Found: 228.95 $[M - H]^-$ (100%). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 13.12 (br, 1H, COOH), 7.17 (d, 2H, J = 2.4 Hz, ArH), 6.85 (t, 1H, J = 2.4 Hz, ArH), 4.85 (d, 4H, J = 2.1 Hz, OCH_2), 3.61 (t, 2H, J = 2.4 Hz, CCH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 56.3, 79.0, 79.3, 107.4, 108.9, 133.3, 158.7, 167.2.

9b[S7]**:** white solid (1.8 g, 6.8 mmol, 95%). ESI-MS: Calcd. for $C_{15}H_{22}O_4$: 266.15; Found: 265.10 $[M - H]^-$ (100%). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 12.97 (br, 1H, COOH), 7.03 (d, 2H, J = 2.4 Hz, ArH), 6.71 (t, 1H, J = 2.4 Hz, ArH), 3.98 (t, 4H, J = 6.6 Hz, OCH_2), 1.64-1.73 (m, 4H, CH_2), 1.37-1.49 (m, 4H, CH_2), 0.93 (t, 6H, J = 7.5 Hz, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.1, 19.1, 31.1, 67.9, 106.0, 107.7, 133.2, 160.2, 167.5.

***p*-propargyloxybenzoic acid (9c)**[S8]**:** To a solution of KOH (2.5 g, 44.6 mmol) in ethanol (90 mL) and H_2O (10 mL) was added compound **8c** (1.5 g, 7.9 mmol). After stirring at 25 °C for 16 h, the mixture was assayed by TLC (no residual substrate). The solvent was removed and the residue was dissolved in a mixture of AcOEt (100 mL) and H_2O (100 mL), and concentrated HCl solution was added in small portions until the pH reached 1. The layers were separated, and the organic layer was washed with an aqueous 10% HCl (2 × 100 mL), and then with brine (100 mL). The organic phase was dried ($MgSO_4$) and evaporated to get compound **9c**. white solid (1.38 g, 7.8 mmol, 99%). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 12.67 (br, 1H, COOH), 7.91 (dt, 2H, J = 6.9 Hz, J = 1.2 Hz, ArH), 7.07 (dt, 2H, J = 6.6 Hz, J = 1.2 Hz, ArH), 4.90 (d, 2H, J = 1.8 Hz, OCH_2), 3.62 (t, 1H, J = 1.8 Hz, CCH).

Tri(urea)s 1a-b: To a solution of compound **9** (**a:** 1.04 g, 4.5 mmol; **b:** 1.22 g 4.5 mmol) in toluene (30 mL) was added DPPA (1.38 g, 5.0 mmol) and Et_3N (0.51 g, 5.0 mmol).After stirring The reaction mixture was stirred at 25 °C for 12 h, The reaction mixture was heated at 70 °C for 7 h, and tri(3-aminobenzyl)amine (**6**) (0.34 g, 1.0 mmol) was added. The reaction was then stirred at 70 °C for 7 h. The reaction mixture was evaporated and the residue was chromatographed on silica gel (2.5 × 20.0 cm column) with CH_2Cl_2/MeOH (80:1 *v/v*). The solvents were removed from the product fractions to give tri(urea)s **1**.

1a: white solid (0.74 g, 0.73 mmol, 73%). M.p. 148-152 °C. ESI-MS: Calcd. for $C_{60}H_{51}N_7O_9$: 1013.37; Found: 1036.25 $[M + Na]^+$ (100%). HR-ESI-MS: *m/z* calcd for $[M + Na]^+$ $C_{60}H_{51}N_7NaO_9$, 1036.3646; Found 1036.3659, error 1.2 ppm. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.69 (s, 3H, NH), 8.68 (s, 3H, NH), 7.41 (s, 3H, ArH), 7.39 (d, 3H, J = 7.8 Hz, ArH), 7.28 (t, 3H, J = 7.8 Hz, ArH), 7.11 (d, 3H, J = 7.5 Hz, ArH), 6.67 (d, 6H, J = 2.1 Hz, ArH), 6.26 (t, 3H, J = 2.1 Hz, ArH), 4.75 (d, 12H, J = 2.4 Hz, OCH_2), 3.58 (t, 6H, J = 2.4 Hz, CCH), 3.50 (s, 6H, NCH_2).^{1}H NMR (300 MHz, CD_3CN) δ (ppm): 7.65 (s, 3H, ArH), 7.63 (s, 3H, NH), 7.37 (d, 3H, J = 7.5 Hz, ArH), 7.36 (s, 3H, NH), 7.25 (t, 3H, J = 7.5 Hz, ArH), 7.05 (d, 3H, J = 7.5 Hz, ArH), 6.66 (d, 6H, J = 2.4 Hz, ArH), 6.18 (t, 3H, J = 2.1 Hz, ArH), 4.63 (d, 12H, J = 2.1 Hz, OCH_2), 3.56 (s, 6H, NCH_2), 2.81 (t, 6H, J = 2.4 Hz, CCH). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.02 (s, 6H, NH), 7.76 (s, 6H, NH), 7.17-7.23 (m, 12H, ArH), 6.99 (d, 6H, J = 6.9 Hz, ArH), 6.34 (s, 6H, ArH), 6.04 (s, 12H, ArH), 5.69 (s, 6H, ArH), 4.31 (s, 24H, OCH_2), 3.29 (br, 6H, NCH_2), 2.82 (br, 6H, NCH_2), 2.52 (t, 12H, J = 2.4 Hz, CCH). ^{13}C NMR (75 MHz, CD_3CN) δ (ppm): 55.6, 57.2, 75.9, 78.6, 96.3, 98.9, 118.1, 120.1, 123.4, 128.7, 138.9, 140.5, 141.0, 153.1, 158.9.

1b: colorless solid (0.45 g, 0.40 mmol, 40%). M.p. 120-124 °C. ESI-MS: Calcd. for $C_{66}H_{87}N_7O_9$: 1121.66; Found: 1122.55 $[M + H]^+$ (35%), 1144.55 $[M + Na]^+$ (100%). HR-ESI-MS: *m/z* calcd for $[M + Na]^+$ $C_{66}H_{87}N_7NaO_9$, 1144.6463; Found 1144.6476, error 1.1 ppm. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.64 (s, 3H, NH), 8.57 (s, 3H,

NH), 7.45 (s, 3H, ArH), 7.37 (d, 3H, J = 8.4 Hz, ArH), 7.26 (t, 3H, J = 7.8 Hz, ArH), 7.10 (d, 3H, J = 7.5 Hz, ArH), 6.65 (d, 6H, J = 2.1 Hz, ArH), 6.10 (t, 3H, J = 2.1 Hz, ArH), 3.90 (t, 12H, J = 6.3 Hz, OCH_2), 3.50 (s, 6H, NCH_2). 1.63-1.72 (m, 12H, CH_2), 1.36-1.49 (m, 12H, CH_2), 0.93 (t, 18H, J = 7.5 Hz, CH_3). ^{1}H NMR (300 MHz, CD_3CN) δ (ppm): 7.69 (s, 3H, NH), 7.67 (s, 3H, ArH), 7.38 (d, 3H, J = 7.5 Hz, ArH), 7.32 (s, 3H, NH), 7.22 (t, 3H, J = 7.8 Hz, ArH), 7.01 (d, 3H, J = 6.9 Hz, ArH), 6.53 (d, 6H, J = 1.8 Hz, ArH), 6.04 (t, 3H, J = 1.8 Hz, ArH), 3.84 (d, 12H, J = 6.6 Hz, OCH_2), 3.56 (s, 6H, NCH_2), 1.63-1.72 (m, 12H, CH_2), 1.37-1.49 (m, 12H, CH_2), 0.95 (t, 18H, J = 7.5 Hz, CH_3). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.93 (s, 12H, NH), 7.08-7.13 (m, 12H, ArH), 6.83 (s, 6H, J = 6.6 Hz, ArH), 6.50 (s, 6H, ArH), 5.92 (s, 12H, ArH), 5.54 (s, 6H, ArH), 3.61 (s, 24H, J = 6.6 Hz, OCH_2), 3.24 (br, 6H, NCH_2), 2.85 (br, 6H, NCH_2), 1.62-1.72 (m, 24H, CH_2), 1.39-1.51 (m, 24H, CH_2), 0.98 (t, 36H, J = 7.2 Hz, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.2, 19.2, 31.2, 57.6, 67.5, 95.3, 97.3, 117.4, 118.9, 122.5, 129.2, 140.0, 141.8, 152.9, 160.5.

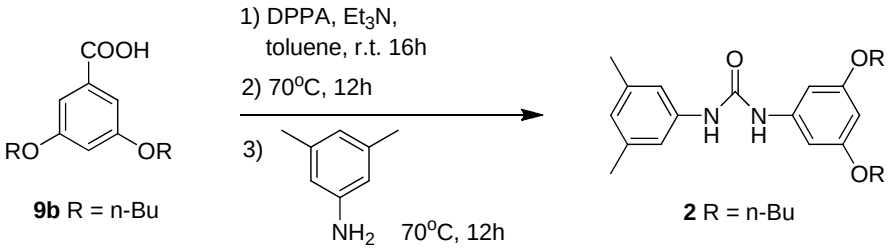
Tri(urea)s 1c: To a solution of compound **9c** (0.8 g, 4.5 mmol) in toluene (30 mL) was added DPPA (1.38 g, 5.0 mmol) and Et_3N (0.51 g, 5.0 mmol).After stirring The reaction mixture was stirred at 25 °C for 12 h, The reaction mixture was heated at 70 °C for 7 h, and tri(3-aminobenzyl)amine (**6**) (0.34 g, 1.0 mmol) was added. The reaction was then stirred at 70 °C for 7 h. The reaction mixture was evaporated and the residue was chromatographed on silica gel (2.5 × 20.0 cm column) with CH_2Cl_2/MeOH (80:1 *v/v*). The solvents were removed from the product fractions to give white solid. (0.61 g, 0.72 mmol, 72%). M.p. 238-243 °C. ESI-MS: Calcd. for $C_{51}H_{45}N_7O_6$: 851.34; Found: 852.25 $[M + H]^+$ (50%), 874.25 $[M + Na]^+$ (90%). HR-ESI-MS: *m/z* calcd for $[M + Na]^+$ $C_{51}H_{45}N_7NaO_6$, 874.3329; Found 874.3323, error 0.7 ppm. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.65 (s, 3H, NH), 8.53 (s, 3H, NH),

3.45 (s, 3H, ArH), 7.41-7.36 (m, 9H, ArH), 7.25 (t, 3H, J = 7.8 Hz, ArH), 7.05 (d, 3H, J = 7.5 Hz, ArH), 6.91 (d, 6H, J = 9.0 Hz, ArH), 4.72 (d, 6H, J = 2.4 Hz, OCH_2), 3.54 (t, 3H, J = 2.4 Hz, CCH), 3.49 (s, 6H, NCH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 56.1, 57.5, 78.5, 80.0, 115.6, 117.2, 118.7, 120.3, 122.3, 129.2, 133.9, 140.2, 140.3, 152.8, 153.2.

Tris{3-[N′-(4-*tert*-butylphenyl)ureido]benzyl}amine (**1d**): To a solution of 4-(*tert*-butyl)benzoic acid (0.24 g, 1.35 mmol) in toluene (30 mL) was added DPPA (0.41 g, 1.5 mmol) and Et_3N (0.17g, 1.5 mmol).After stirring The reaction mixture was stirred at 25 °C for 12 h, The reaction mixture was heated at 70 °C for 7 h, and tri(3-aminobenzyl)amine (**6**) (0.10 g, 0.3 mmol)was added. The reaction was then stirred at 70 °C for 7 h. The reaction mixture was evaporated to 2~3 mL, Et_2O (20 mL) was added carefully and the white precipitate was formed, the white solid was filtered off and dried under vacuum to give white solid **1d** (0.21 g, 0.24 mmol, 82%). M.p. 215-218 °C. ESI-MS: Calcd. for $C_{54}H_{63}N_7O_3$: 857.50; Found: 858.45 $[M + H]^+$ (50%), 880.40 $[M + Na]^+$ (100%). HR-ESI-MS: *m/z* calcd for $[M + Na]^+$ $C_{54}H_{63}N_7NaO_3$, 880.4890; Found 880.4887, error 0.3 ppm. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.63 (s, 3H, NH), 8.59 (s, 3H, NH), 7.52 (s, 3H, ArH), 7.40-7.35 (m, 9H, ArH), 7.26-7.22 (m, 9H, ArH), 7.04 (d, 3H, J = 2.4 Hz, ArH), 3.50 (s, 6H, NCH_2), 1.23 (s, 27H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 31.7, 34.3, 57.5, 117.2, 118.5, 118.7, 122.3, 125.8, 129.1, 137.5, 140.2, 140.3, 144.4, 153.0.

Tris{3-[N′-(4-n-butylphenyl)ureido]benzyl}amine (**1e**): The tri(3-aminobenzyl)amine (**6**) (0.064 g, 0.193 mmol) was dissolved in dry CH_2Cl_2 (15 mL) and the appropriate isocyanate (0.14 g, 0.76 mmol) was added and stirred at 25 °C for 18 h, the solvent was removed and Et_2O (20 mL) was added. After several minutes' sonications, the insoluble white solid **1e** was filtered off and dried under vacuum.

1e[S5]**:** white solid (0.160 g, 0.186 mmol, 96%). ESI-MS: Calcd. for $C_{54}H_{63}N_7O_3$: 857.50; Found: 858.45 $[M + H]^+$ (25%), 880.40 $[M + Na]^+$ (100%). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.62 (s, 3H, NH), 8.55 (s, 3H, NH), 7.51 (s, 3H, ArH), 7.39-7.33 (m, 9H, ArH), 7.25 (t, 3H, J = 7.8 Hz, ArH), 7.08-7.04 (m, 9H, ArH), 3.50 (s, 6H, NCH_2), 2.48 (t, 6H, J = 7.8 Hz, $ArCH_2$) 1.45-1.55 (m, 6H, CH_2), 1.22-1.34 (m, 6H, CH_2), 0.89 (t, 9H, J = 7.5 Hz, CH_3).

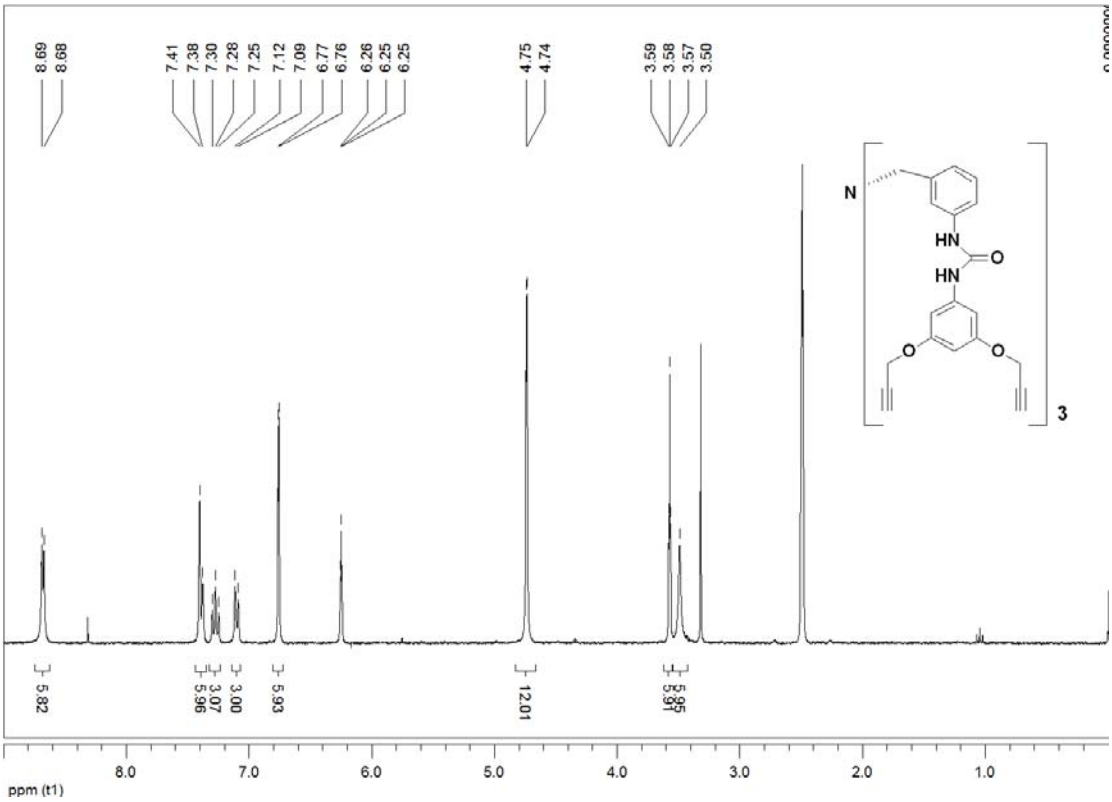


1-(3,5-dibutoxyphenyl)-3-(3,5-dimethylphenyl)urea (2): To a solution of compound **9b** (0.4 g 1.5 mmol) in toluene (25 mL) was added DPPA (0.47 g, 1.7 mmol) and Et_3N (0.17 g, 1.7 mmol).After stirring The reaction mixture was stirred at 25 °C for 12 h, The reaction mixture was heated at 70 °C for 7 h, and 3,5-dimethylaniline (0.16 g, 1.3 mmol)was added. The reaction was then stirred at 70 °C for 7 h. The reaction mixture was evaporated and the residue was chromatographed on silica gel (2.0 × 20.0 cm column) with CH_2Cl_2/MeOH (200:1 v/v). The solvents were removed from the product fractions to give white solid (0.50 g, 1.3 mmol, 99%). M.p. 152-154 °C ESI-MS: Calcd. for $C_{23}H_{32}N_2O_3$: 384.24; Found: 385.20 $[M + H]^+$ (100%). HR-ESI-MS: m/z calcd for $[M + H]^+$ $C_{23}H_{33}N_2O_3$, 385.2491; Found 385.2493, error 0.5 ppm. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.56 (s, 1H, NH), 8.45 (s, 1H, NH), 7.05 (s, 2H, ArH), 6.61 (s, 1H, ArH), 6.33 (s, 2H, J = 2.1 Hz, ArH), 6.10 (t, 1H, J = 2.1 Hz, ArH), 3.90 (t, 4H, J = 6.3 Hz, OCH_2), 2.23 (s, 6H, CH_3). 1.63-1.72 (m, 4H, CH_2), 1.36-1.49 (m, 4H, CH_2), 0.93 (t, 6H, J = 7.5 Hz, CH_3). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.11 (br, 2H, NH), 6.90 (s, 2H, ArH), 6.71 (s, 1H, ArH), 6.53 (s, 2H,

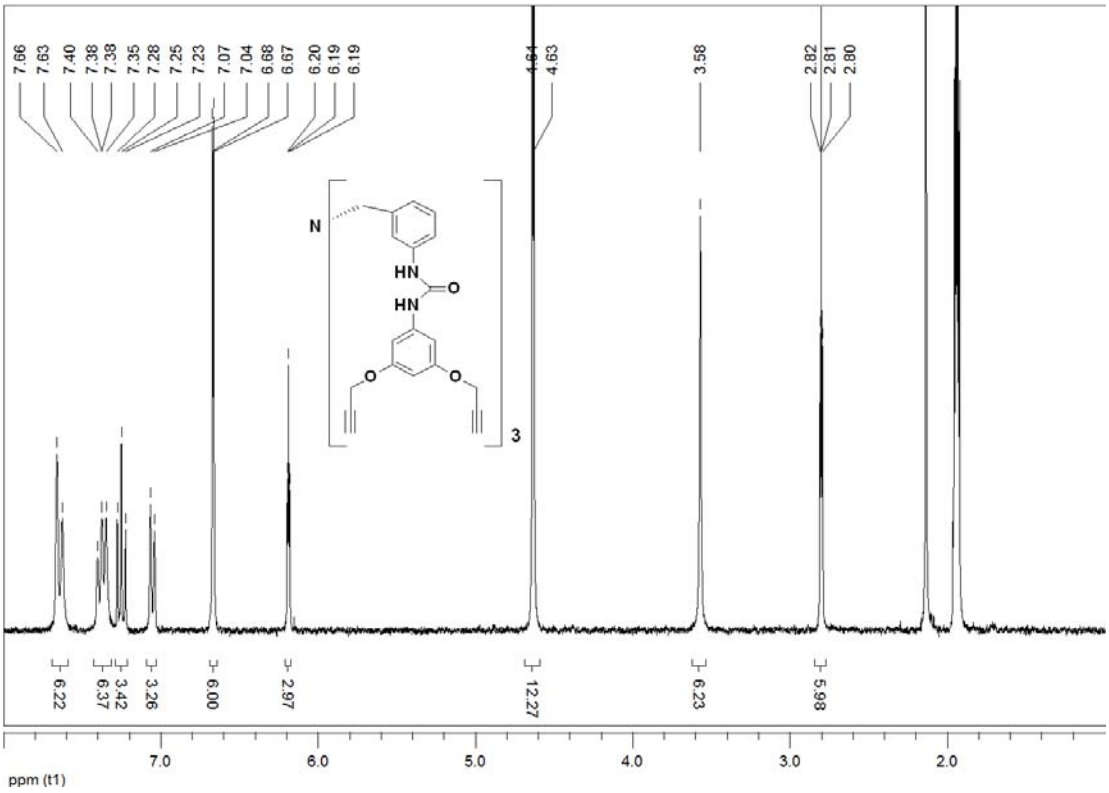
J = 2.1 Hz, ArH), 6.18 (t, 1H, *J* = 2.1 Hz, ArH), 3.85 (t, 4H, *J* = 6.6 Hz, OCH_2), 2.22 (s, 6H, CH_3). 1.64-1.74 (m, 4H, CH_2), 1.37-1.49 (m, 4H, CH_2), 0.93 (t, 6H, *J* = 7.5 Hz, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 14.2, 19.2, 21.6, 31.2, 67.5, 95.3, 97.2, 116.4, 123.9, 138.2, 139.9, 141.8, 152.8, 160.5.

NMR Spectra

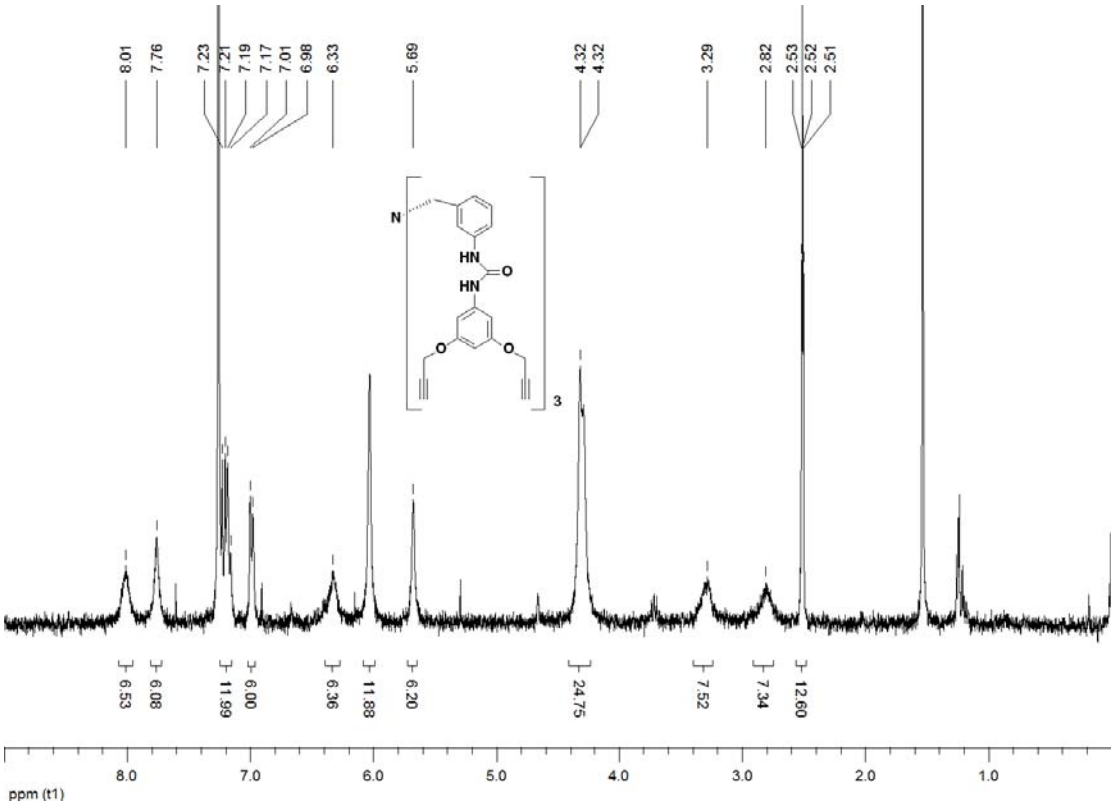
^{1}H NMR of **1a** (DMSO-d_6, 300 MHz).



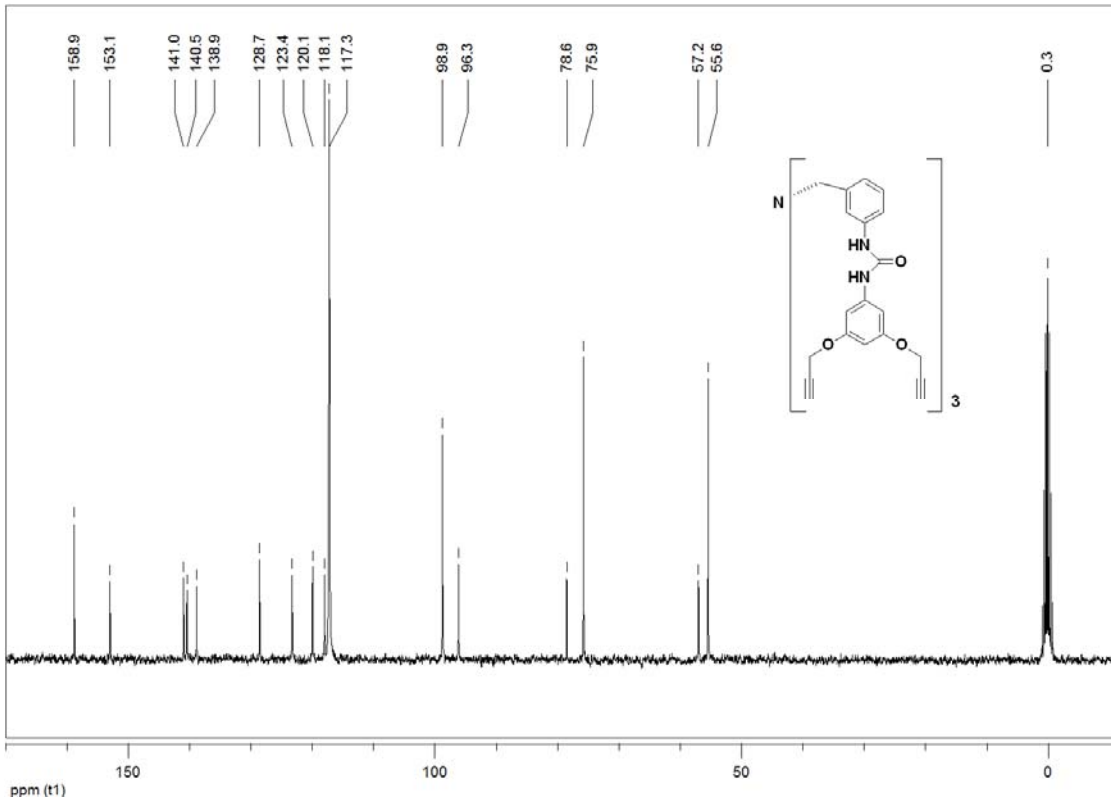
^{1}H NMR of **1a** (CD_3CN, 300 MHz).



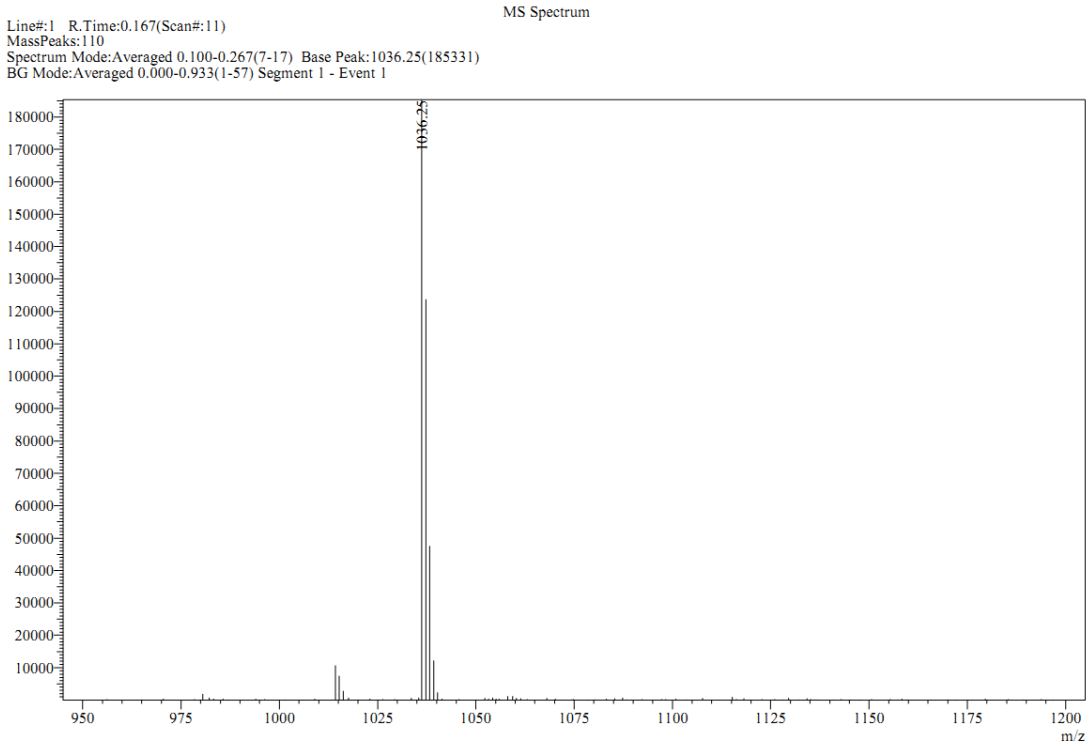
^{1}H NMR of **1a** ($CDCl_3$, 300 MHz).



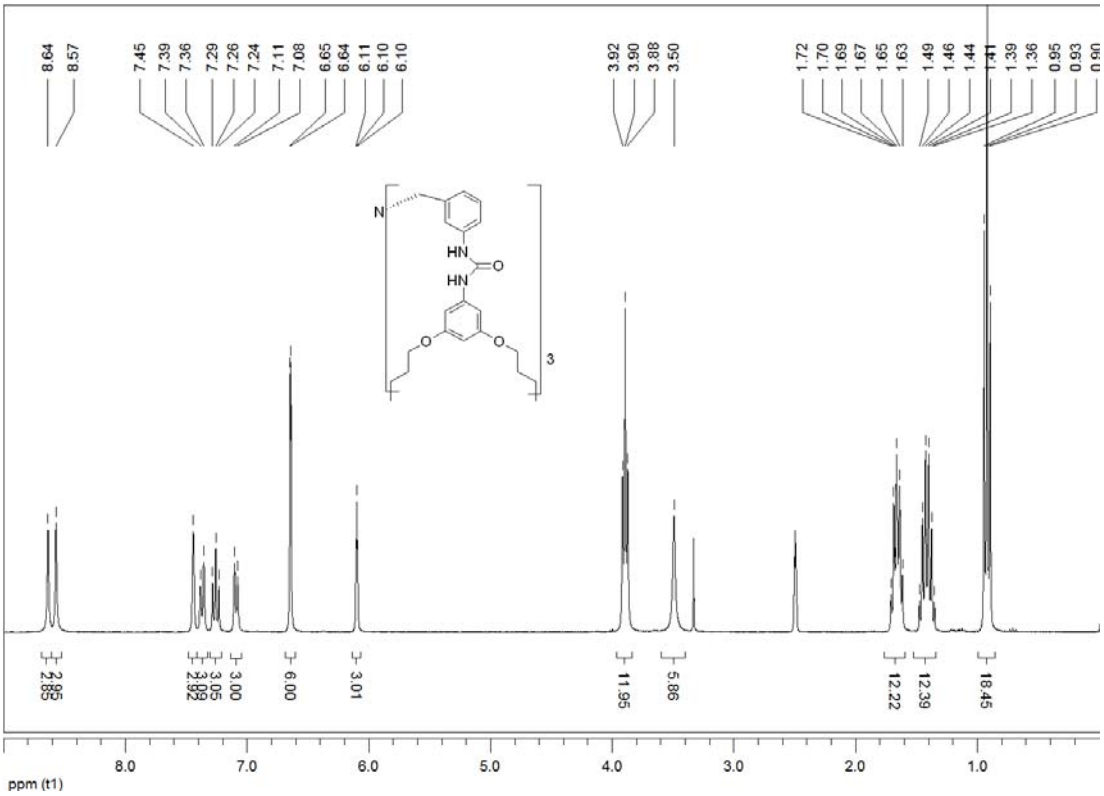
^{13}C NMR of **1a** (CD_3CN, 75 MHz).



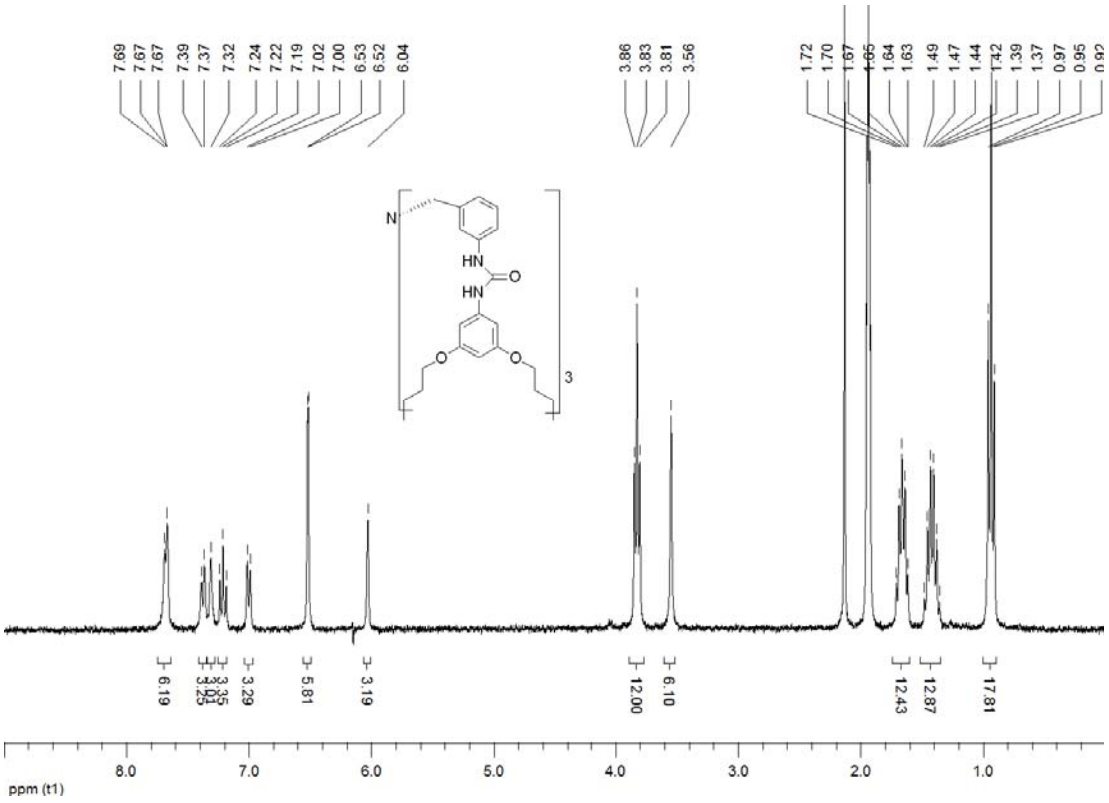
ESI-MS of **1a**



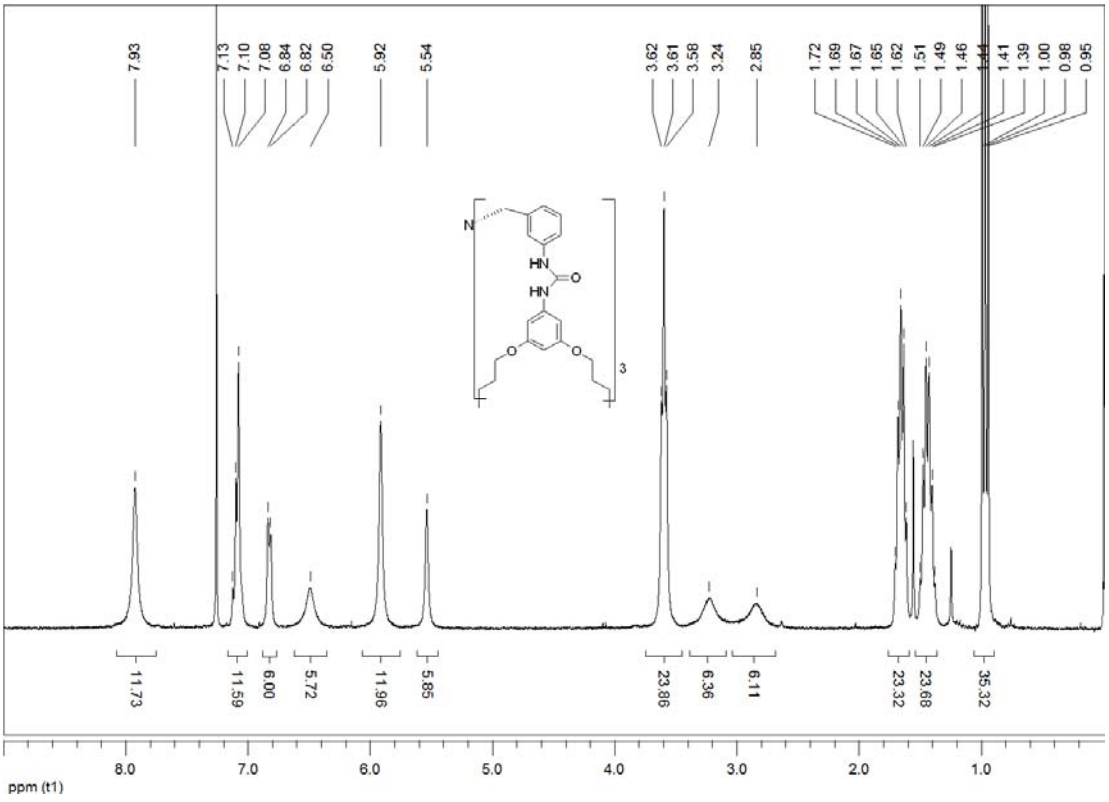
^{1}H NMR of **1b** (DMSO-d_6, 300 MHz).



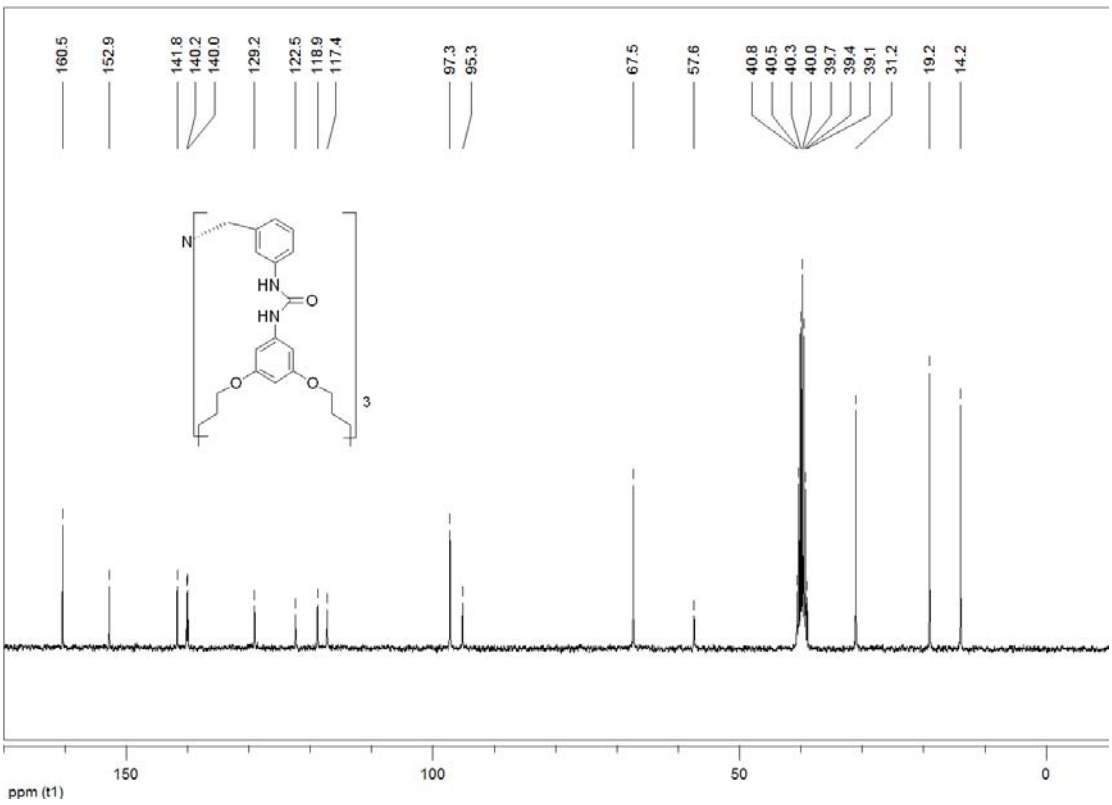
^{1}H NMR of **1b** (CD_3CN, 300 MHz).



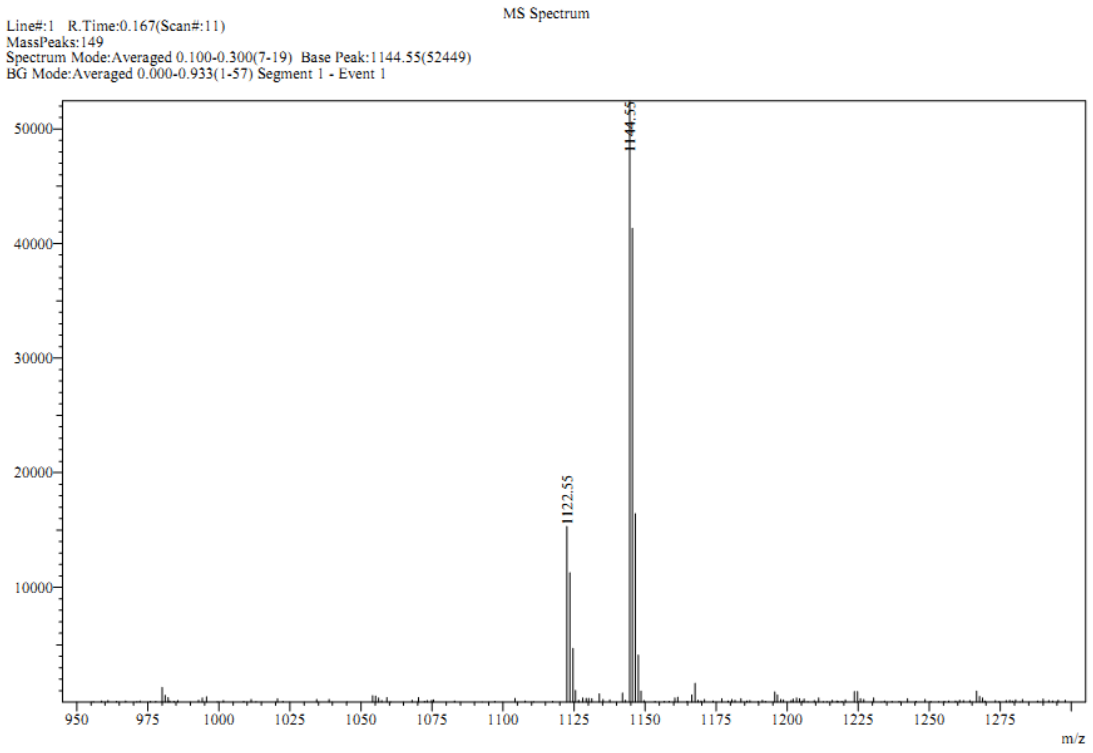
^{1}H NMR of **1b** ($CDCl_3$, 300 MHz).



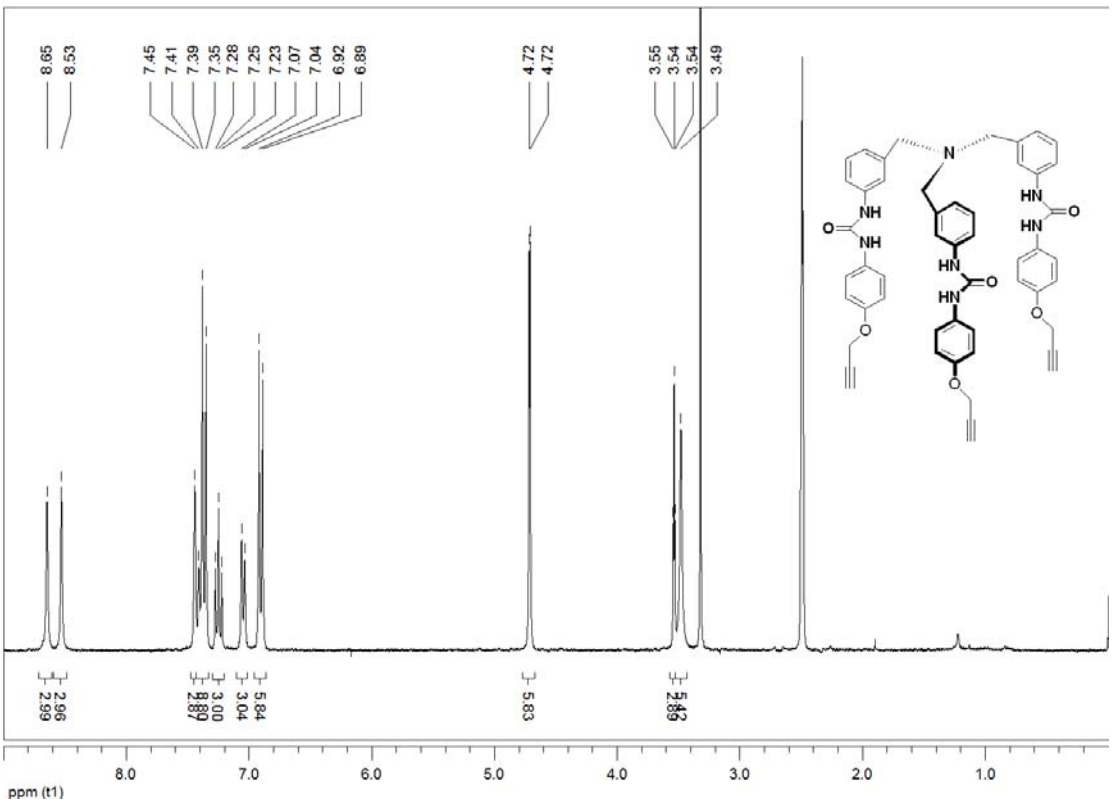
^{13}C NMR of **1b** (DMSO-d_6, 75 MHz).



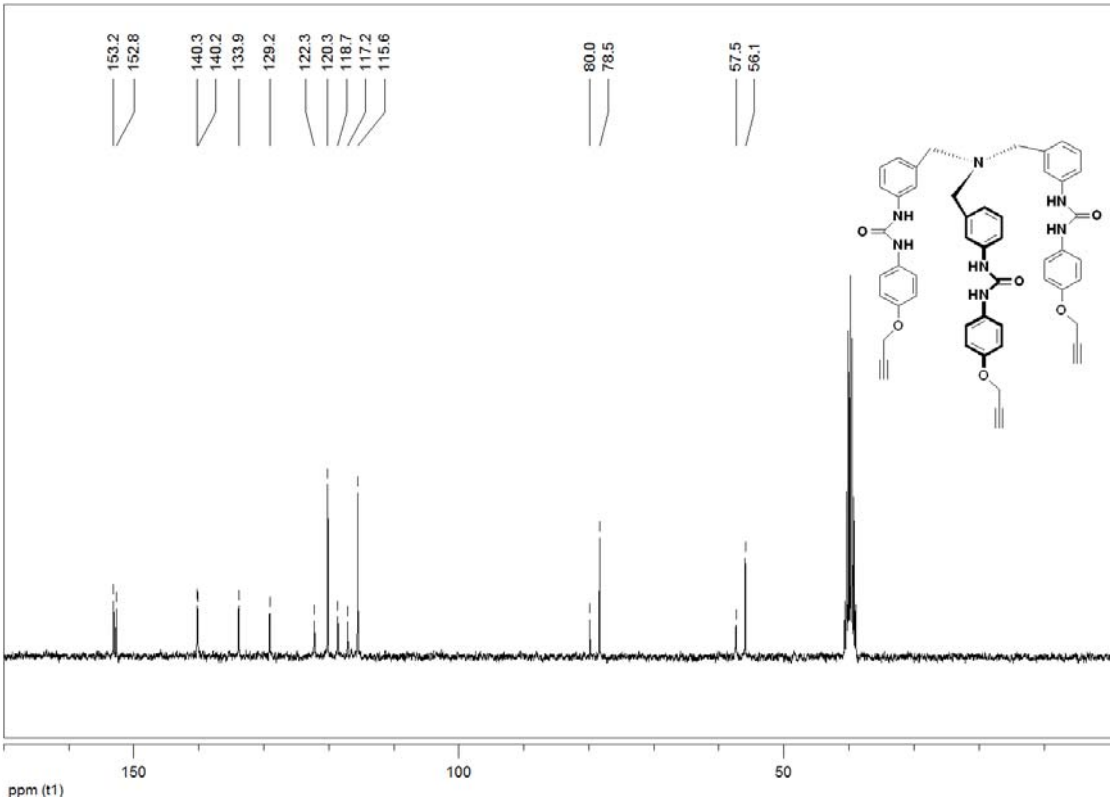
ESI-MS of **1b**



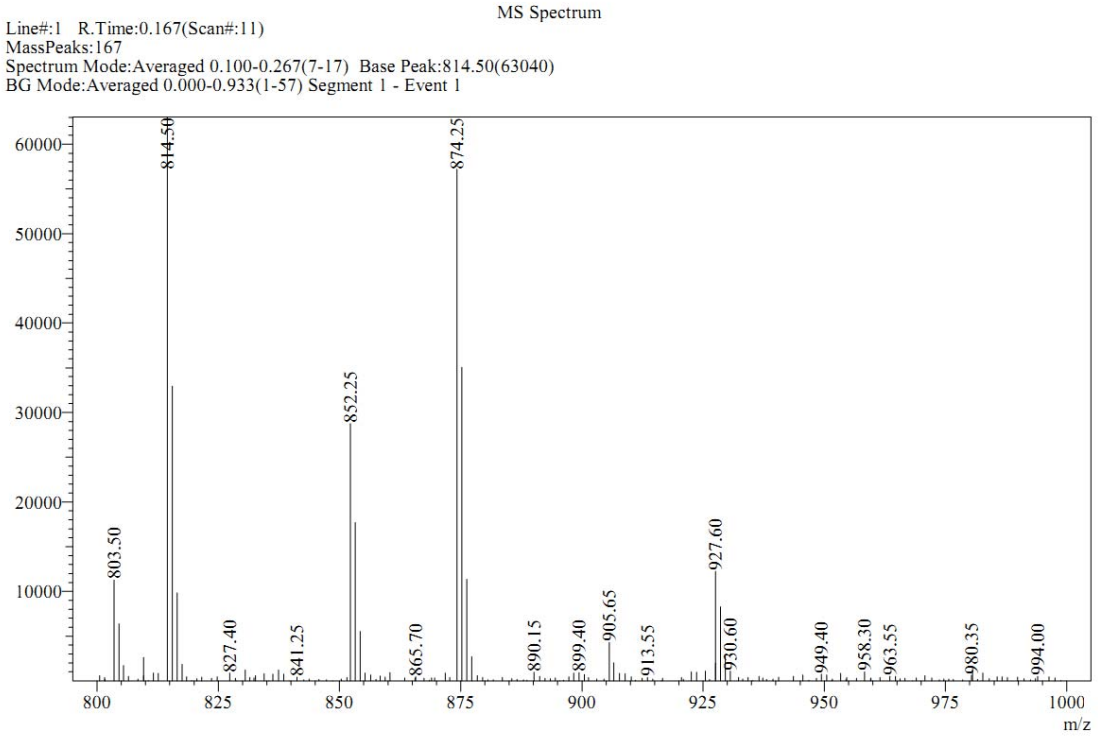
^{1}H NMR of **1c** (DMSO-d_6, 300 MHz).



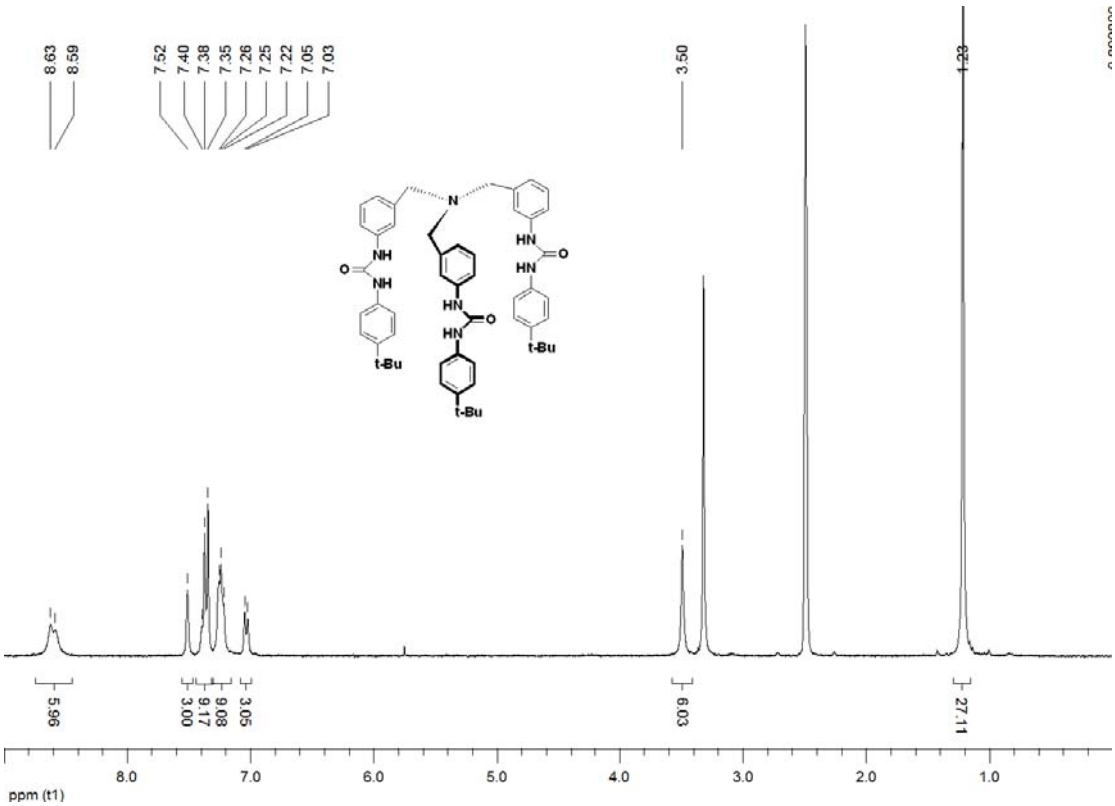
^{13}C NMR of **1c** (DMSO-d_6, 75 MHz).



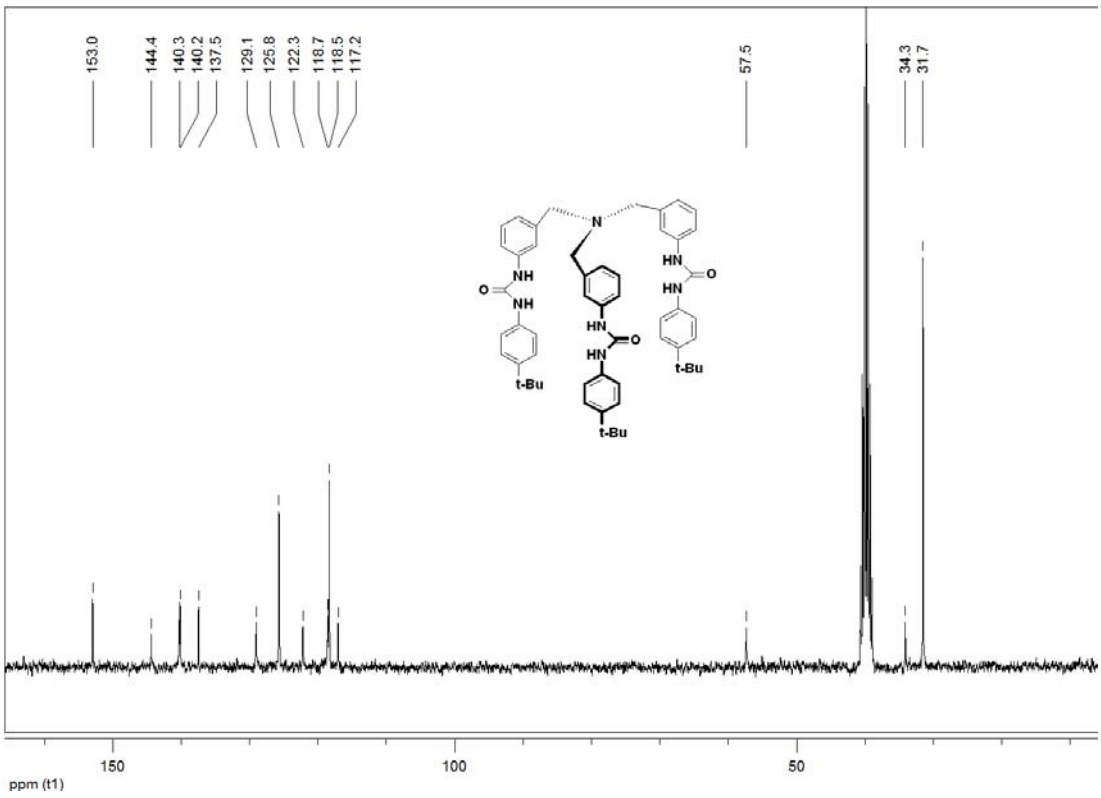
ESI-MS of **1c**



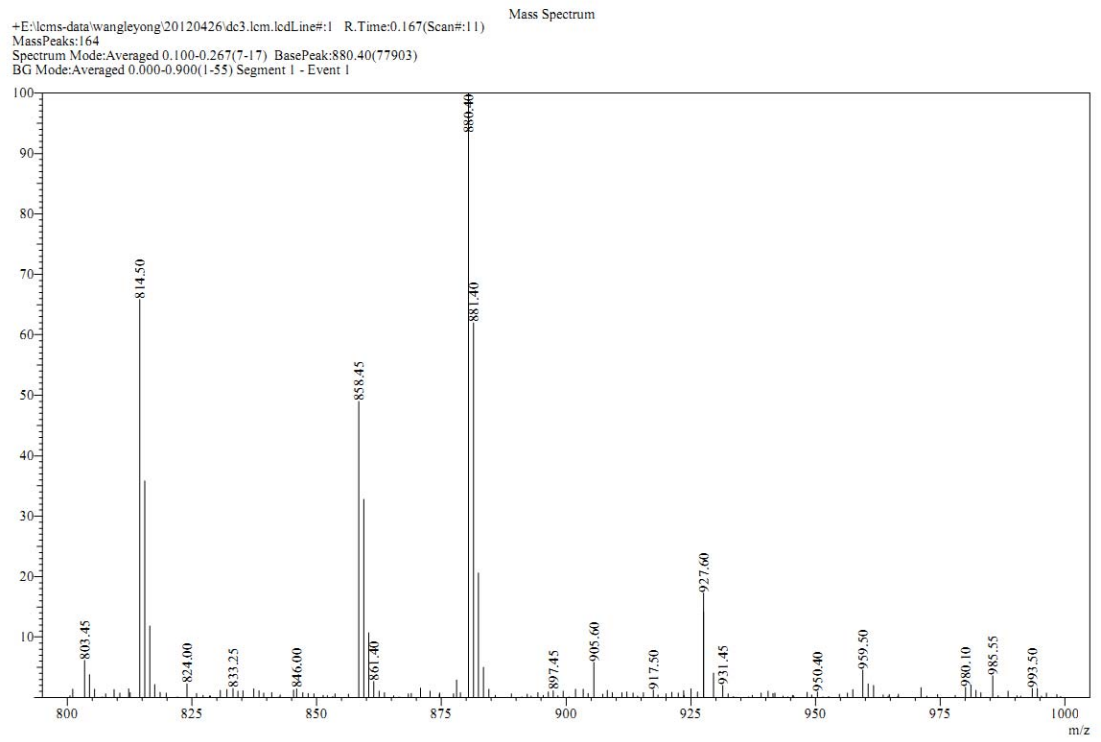
^{1}H NMR of **1d** (DMSO-d_6, 300 MHz).



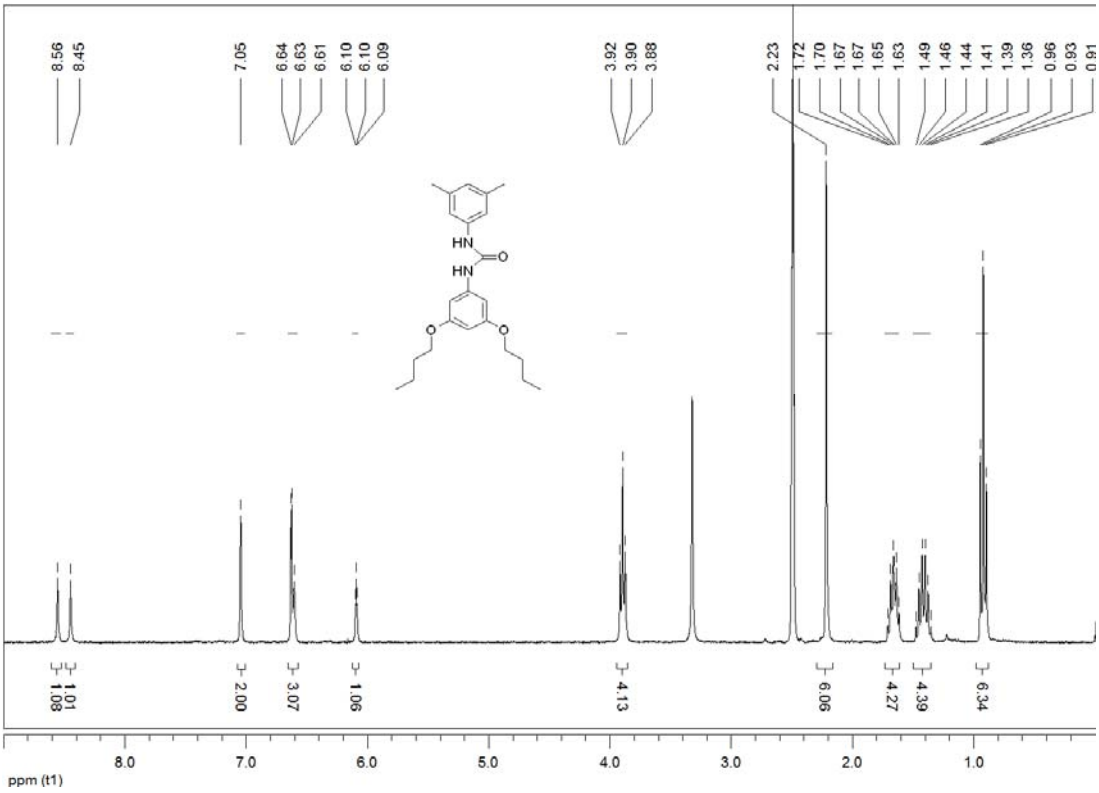
^{13}C NMR of **1d** (DMSO-d_6, 75 MHz).



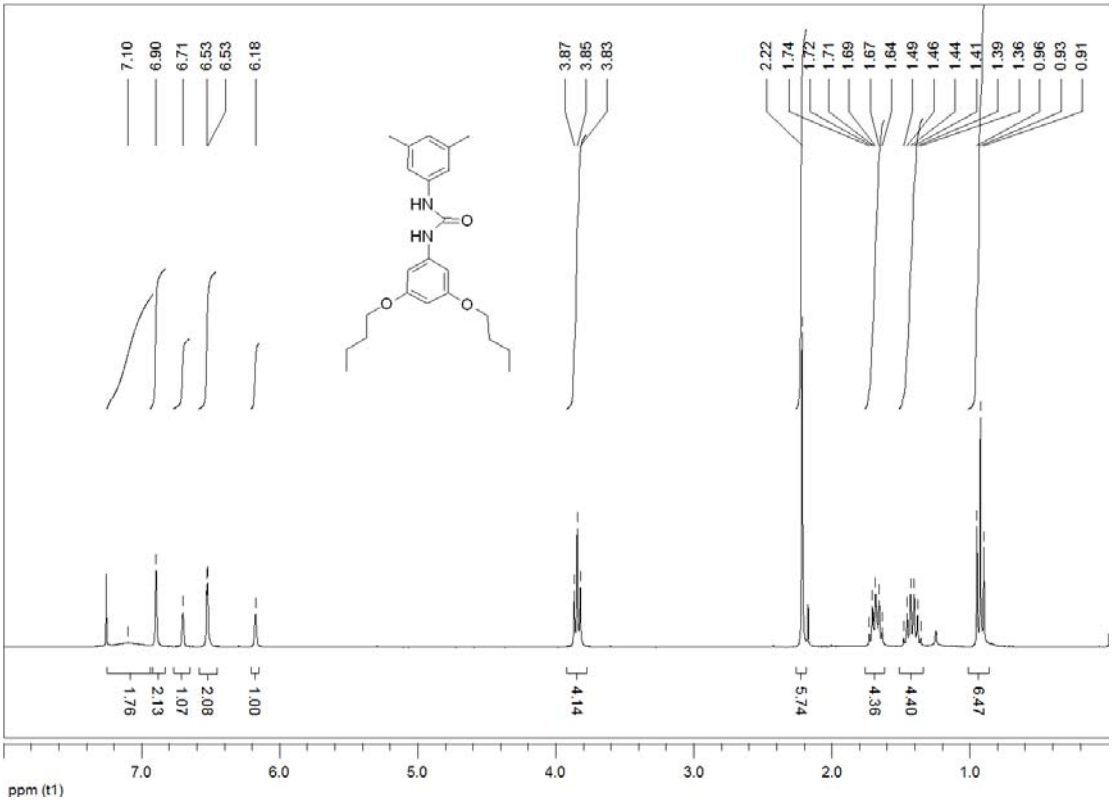
ESI-MS of **1d**



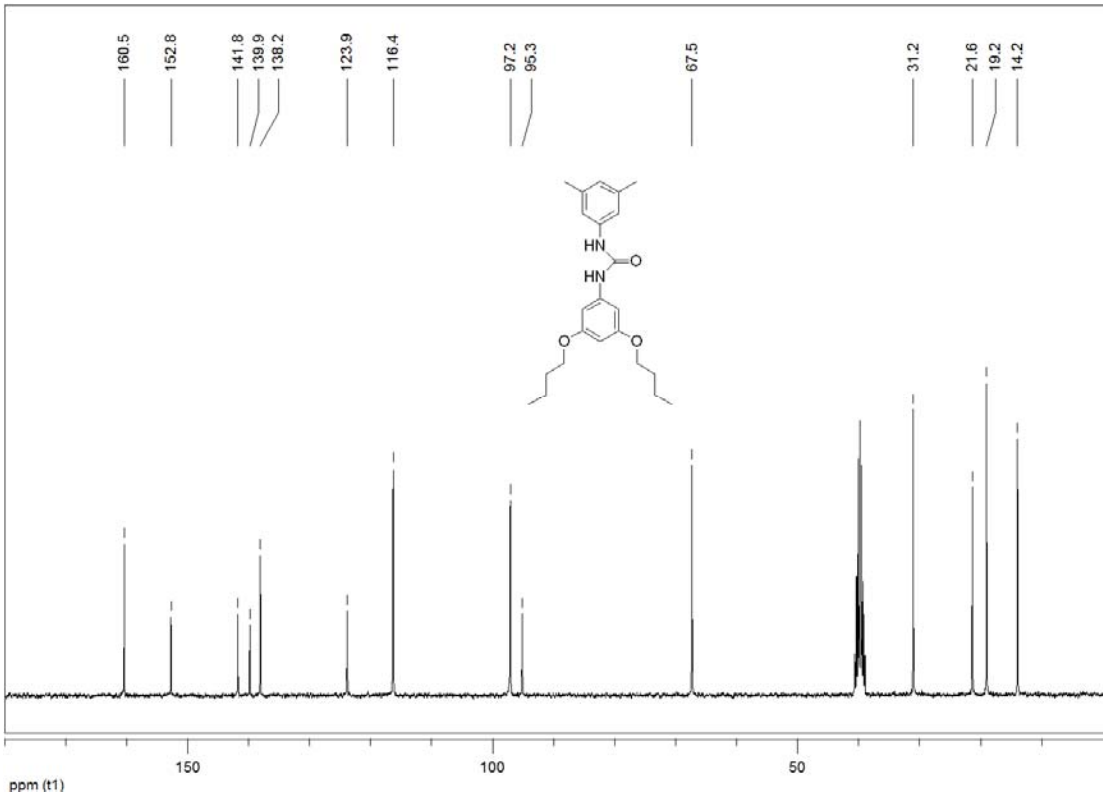
^{1}H NMR of 1-(3,5-dibutoxyphenyl)-3-(3,5-dimethylphenyl)urea **2** (DMSO-d_6, 300 MHz).



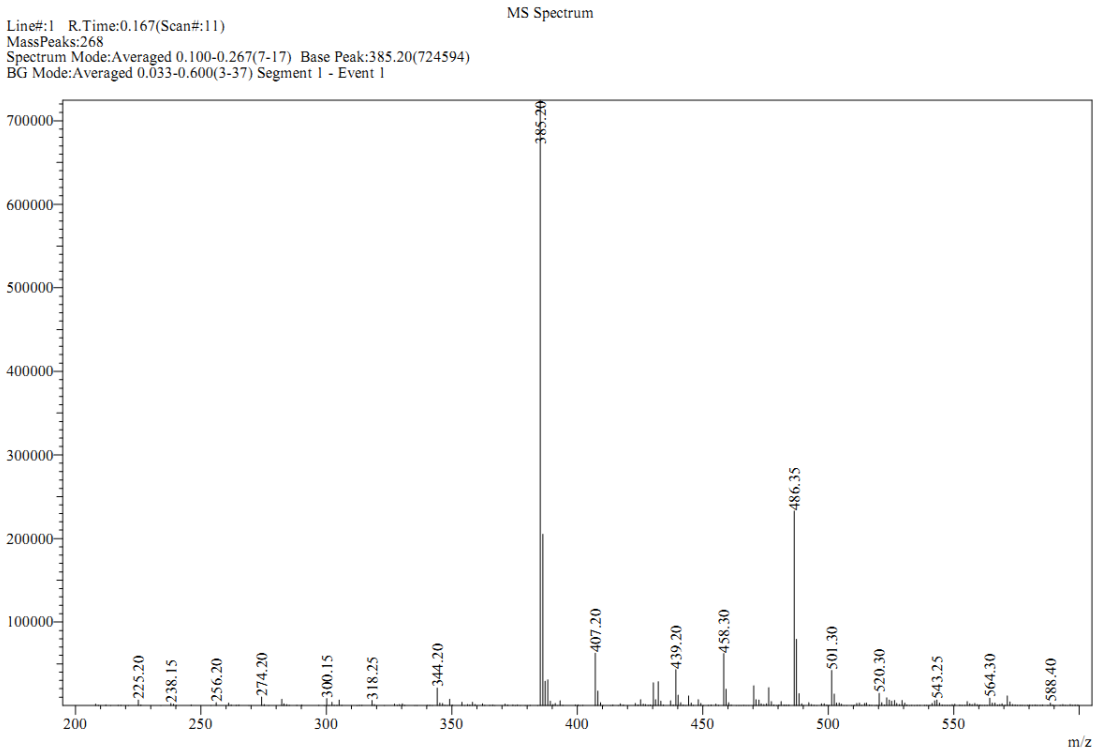
^{1}H NMR of 1-(3,5-dibutoxyphenyl)-3-(3,5-dimethylphenyl)urea **2** ($CDCl_3$, 300 MHz).



^{13}C NMR of 1-(3,5-dibutoxyphenyl)-3-(3,5-dimethylphenyl)urea **2** (DMSO-d_6, 75 MHz).



ESI-MS of 1-(3,5-dibutoxyphenyl)-3-(3,5-dimethylphenyl)urea **2**



14. X-ray crystallography data of 1a

X-ray data from a red needle crystal were measured at 296(2) K on a Bruker SMART APEX II CCD diffractometer (Mo Kα radiation, λ = 0.71073 Å). The collected diffraction data were reduced by using the SAINT program and empirical absorption corrections were done by using the SADABS program. Final unit cell parameters were determined by least-squares refinement from the data set. The structures were solved by direct method and refined by least-squares method on F^2 by using the SHELXTL-PC software package.[S9] All non-H atoms were anisotropically refined and all hydrogen atoms were inserted in the calculated positions.

Table 1. Crystal data and structure refinement for **1a**

CCDC number	869084
Empirical formula	$C_{120}H_{104}N_{14}O_{19}$
Formula weight	2046.17
Temperature	296(2)
Wavelength	0.71073 Å
Crystal system	hexagonal
Space group	$R\bar{3}$
a	20.2892(9) Å
b	20.2892(9) Å
c	23.219(2) Å
α	90.00°
β	90.00°
γ	120.00°
Volume	8277.6(12) $Å^3$
Z	3
Density (calculated)	1.231 g/cm^3
Absorption coefficient	0.085
F(000)	3222
Crystal size	0.28 × 0.24 × 0.22 mm^3

Theta range for data collection	2.47 to 22.51°
Index ranges	-25<=h<=16, -24<=k<=25, -28<=l<=28
Reflections collected	16687
Independent reflections	3618 [R(int) = 0.0535]
Completeness to theta = 24.71°	100 %
Absorption correction	Psi-scan
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.031
Final R indices [I > 2sigma(I)]	$R1$ = 0.0479, $wR2$ = 0.1144
R indices (all data)	$R1$ = 0.0694, $wR2$ = 0.1226
Largest diff. peak and hole	0.161 and -0.185 e·Å^{-3}

Reference:

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