Electronic Supplementary Material (ESI) for Journal of Materials Chemistry B.

Supporting Information

Dual Functional Amphiphilic Sugar-Coated AIE-Active Fluorescent Organic Nanoparticles for the Monitoring and Inhibition of Insulin Amyloid Fibrillation Based on Carbohydrate-Protein Interactions

Yan-ming Ji,‡[a] Wenyan Zhang,‡[bc] Jing-dong Zhang,[a] Xia-fen Li,[a] Fan-dong Yu,[a] Cui-yun Li,[a] Guang-jian Liu[a] and Guo-wen Xing*[a]

a College of Chemistry, Beijing Normal University, Beijing 100875, P. R. China.

b Department of Chemistry and Chemical Engineering, School of Chemistry and Biological Engineering, University of Science and Technology Beijing, Beijing 100083, P. R. China.

c Beijing Key Laboratory for Science and Application of Functional Molecular and Crystalline Materials, Beijing 100083, P. R. China

‡ Yan-ming Ji and Wenyan Zhang contributed equally to this work.

* Corresponding Author

Email: gwxing@bnu.edu.cn

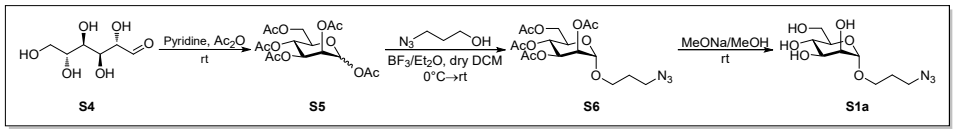
Table of Contents

1 Experimental Procedures

1.1 General

Unless otherwise noted, all chemicals were purchased at reagent grade and can be used without further purification. The human insulin was purchased from Med ChemExpress LLC. PBS buffer with pH 7.2-7.4 (0.01 M) was purchased from Beijing Solarbio Science & Technology Co., Ltd. All anaerobic reactions were performed under dry N2 atmosphere. All the reactions were monitored by thin-layer chromatography (TLC) on T-HSGF10025025 normal phase silica gel glass plates or 60 RP-18 F254s reversed phase silica gel glass plates, and visualized under Ultraviolet light, by dyeing with ninhydrin or by coloring with concentrated sulfuric acid-ethanol (7%) solution (after roasted). Flash column chromatography was performed on 200-300 mesh silica gel. Reversed phase chromatography was performed on SiliaSphere C18 (50 μm, 120 Å). Molecular exclusion chromatography was performed on Bio-Gel ® P-2 Media (45 - 90 μm). 1H and 13C NMR spectra were recorded on Bruker Avance III spectrometer (400 MHz) or JNM-ECZR spectrometer (400 and 600 MHz) with tetramethylsilane (TMS, δ= 0 ppm) as an internal standard. The residual peak of the solvent: Chloroform-d at 7.26 ppm (1H) and 77.16 ppm (13C), Methanol-d4 at 3.31 ppm (1H) and 49.00 ppm (13C). High resolution mass spectra were recorded on Bruker micrOTOF-QII mass spectrometer (ESI). Photoluminescence (PL) spectra were recorded on FS5 spectrofluorometer (Edinburgh Instruments Ltd.). Circular dichroism (CD) spectra were recorded on Applied Photophysics Ltd. Chirascan Spectrometer in a 1 cm quartz cuvette using a step resolution of 0.2 nm, a scan speed of 15 nm·min-1, a bandwidth of 2.0 nm. Each spectrum was the average of three scans. Transmission electron microscope (TEM) images were recorded on FEI Talos F200S (Thermo Fisher Scientific). All the PL and CD tests used secondary water.

1.2 Synthesis

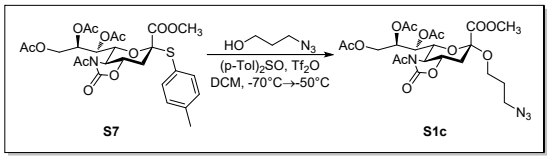


S1a: compound **S1a** was synthesized according to the methods reported in the previous article.[1-2]

S5: 99.9% yield (α:β = 6:1). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 6.09 (d, J = 1.9 Hz, 1H), 5.37-5.34 (m, 2H), 5.27 (t, J = 2.2 Hz, 1H), 4.29 (dd, J = 12.4, 4.9 Hz, 1H), 4.11 (dd, J = 12.5, 2.5 Hz, 1H), 4.08-4.02 (m, 1H), 2.18 (d, J = 3.3 Hz, 6H), 2.10 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H).

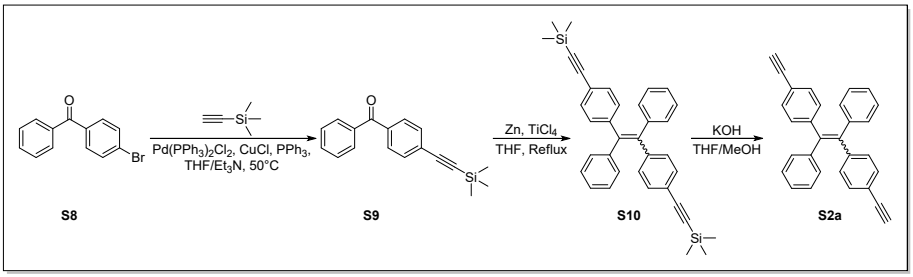
S6: 32.0% yield. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 5.36-5.27 (m, 2H), 5.26-5.22 (m, 1H), 4.82 (d, J = 1.7 Hz, 1H), 4.29 (dd, J = 12.2, 5.4 Hz, 1H), 4.12 (dd, J = 12.2, 2.5 Hz, 1H), 3.97 (ddd, J = 9.1, 5.4, 2.4 Hz, 1H), 3.82 (ddd, J = 9.9, 6.7, 5.6 Hz, 1H), 3.57-3.50 (m, 1H) 3.44 (t, J = 6.5 Hz, 2H), 2.16 (s, 3H), 2.11 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H), 1.93-1.87 (m, 2H).

S1a: 99.9% yield. ^{1}H NMR (600 MHz, CD_3OD), δ (ppm): 4.76 (s, 1H), 3.87-3.78 (m, 3H), 3.74-3.67 (m, 2H), 3.62 (t, J = 9.5 Hz, 1H), 3.55-3.48 (m, 2H), 3.45-3.39 (m, 2H), 1.90-1.84 (m, 2H).



S1c: compound **S7** and **S1c** was synthesized according to the methods reported in the previous article.[3]

S1c: 89.0% yield. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 5.57 (dd, J = 8.2, 1.3 Hz, 1H), 5.45-5.38 (m, 1H), 4.62 (dd, J = 9.4, 1.2 Hz, 1H), 4.37 (dd, J = 12.3, 2.8 Hz, 1H), 4.05-3.93 (m, 2H), 3.88-3.77 (m, 4H), 3.69 (dd, J = 11.0, 9.6 Hz, 1H), 3.40-3.33 (m, 3H), 2.83 (dd, J = 12.1, 3.5 Hz, 1H), 2.44 (s, 3H), 2.10-2.03 (m, 7H), 2.01 (s, 3H), 1.88-1.75 (m, 2H).

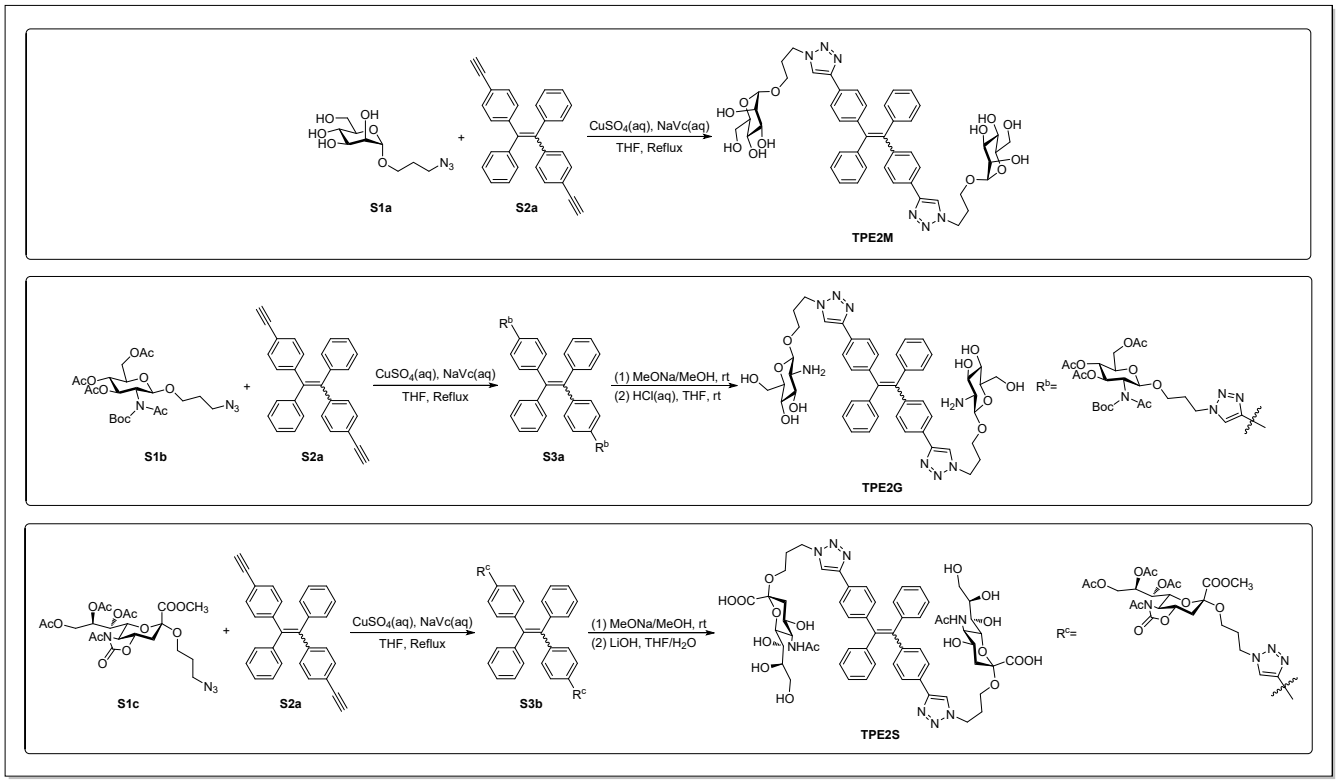


S2a: compound **S2a** was synthesized according to the methods reported in the previous article.[4]

S9: 88.6% yield. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.83-7.71 (m, 4H), 7.58 (dd, J = 10.4, 7.8 Hz, 3H), 7.49 (t, J = 7.8 Hz, 2H), 0.27 (s, 9H).

S10: 28.3% yield. ^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm): 7.20 (t, J = 7.9 Hz, 4H), 7.12-7.07 (m, 6H), 6.99-6.95 (m, 4H), 6.93 (dd, J = 8.2, 3.9 Hz, 4H), 0.22 (d, J = 8.6 Hz, 18H).

S2a: 88.8% yield. ^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm): 7.23 (dd, J = 13.5, 8.2 Hz, 4H), 7.14-7.09 (m, 6H), 6.98 (ddd, J = 14.5, 7.0, 4.2 Hz, 8H), 3.04 (d, J = 10.2 Hz, 2H).



TPE2M: compound **S1a** (58.4 mg, 0.2218 mmol) and compound **S2a** (35.3 mg, 0.0928 mmol) were dissolved in THF (8 mL) under nitrogen. Sodium ascorbate (0.037 M, 1 mL, aq.) and copper sulfate (0.019 M, 1 mL, aq.) were then added successively and stirred at 66 °C for 17 h. Then the reaction was cooled to room temperature, extracted with DCM, washed with saturated aqueous sodium chloride and dried over $MgSO_4$. After filtration, the solvent of mixture was evaporated. The residue was purified by Bio-Gel P-2 gel to obtain the crude product, and then purified by reversed phase column chromatography (H_2O : MeOH = 1 : 3, V/V) to obtain **TPE2M** (31.3 mg, 37.2% yield). ^{1}H NMR (600 MHz, CD_3OD), δ (ppm): 8.26 (d, J = 3.4 Hz, 2H), 7.57 (dd, J = 11.2, 8.0 Hz, 4H), 7.14-7.03 (m, 14H), 4.73 (d, J = 7.7 Hz, 2H), 4.54 (dq, J = 13.3, 6.6 Hz, 4H), 3.83-3.75 (m, 6H), 3.69 (dd, J = 11.1, 6.5 Hz, 4H), 3.60 (td, J = 9.6, 2.7 Hz, 2H), 3.55-3.49 (m, 2H), 3.45-3.39 (m, 2H), 2.22 (dq, J = 12.6, 6.4 Hz, 4H); ^{13}C NMR (150 MHz, CD_3OD), δ (ppm): 148.62, 148.59, 145.16, 145.12, 144.82, 144.74, 142.38, 133.04, 133.00, 132.45, 132.43, 132.37, 130.00, 129.91, 129.89, 129.02, 128.89, 127.89, 127.80, 126.17, 126.06, 122.51,

122.45, 101.85, 101.83, 74.88, 74.86, 72.65, 72.10, 72.09, 68.64, 66.68, 65.18, 62.94, 62.92, 49.60, 31.75, 31.28, 31.23, 20.28, 14.07; HRMS (ESI): m/z Calcd for $C_{48}H_{55}N_6O_{12}$ $[M+H]^+$ 907.3872, found: 907.3876.

S1b: compound **S1b** was synthesized according to the methods reported in the previous article.[5]

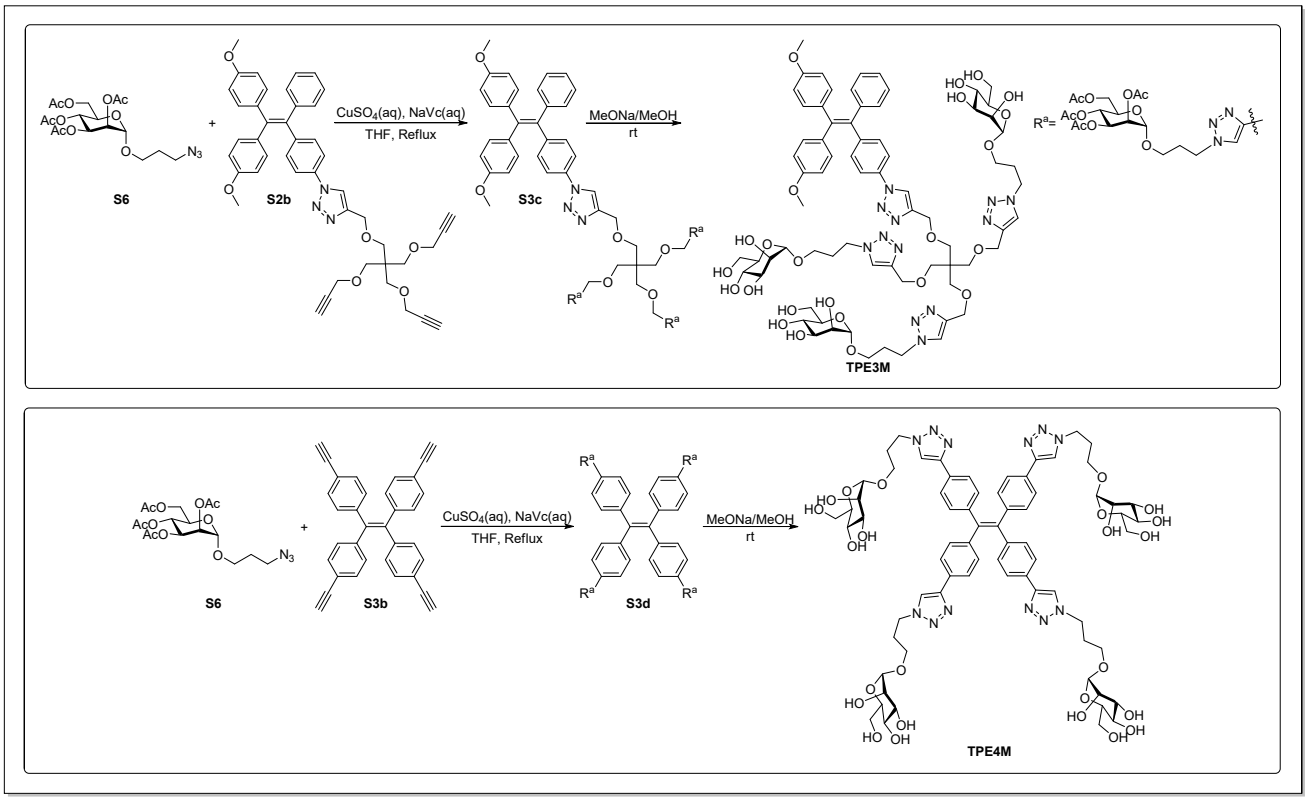
***tert*-Butoxycarbonyl & Acetyl protected TPE2G (S3a)**: compound **S1b** (182.0 mg, 0.3431 mmol) and compound **S2a** (50.0 mg, 0.1314 mmol) were dissolved in THF (10 mL) under nitrogen. Sodium ascorbate (0.052 M, 1 mL, aq.) and copper sulfate (0.027 M, 1 mL, aq.) were then added successively and stirred at 66 °C for 24h. After the disappearance of compound **S2a**, the reaction was cooled to room temperature, extracted with DCM, and dried over MgSO4. After filtration, the solvent of mixture was evaporated. The residue was purified by column chromatography (DCM : MeOH = 100 : 1, V/V) to obtain compound **S3a** (50.0 mg, 26.4% yield). 1H NMR (600 MHz, CDCl3), δ (ppm): 7.76 (d, J = 19.8 Hz, 2H), 7.60 (d, J = 7.3 Hz, 4H), 7.15-7.02 (m, 14H), 5.71 (dt, J = 18.7, 9.1 Hz, 2H), 5.25 (dd, J = 143.5, 7.6 Hz, 2H), 5.09 (dd, J = 11.9, 6.7 Hz, 2H), 4.92 (t, J = 8.2 Hz, 1H), 4.44 (t, J = 5.5 Hz, 4H), 4.27 (td, J = 12.8, 4.6 Hz, 2H), 4.20 (dd, J = 12.7, 6.7 Hz, 1H), 4.11 (td, J = 13.2, 1.3 Hz, 2H), 3.89-3.79 (m, 2H), 3.72 (d, J = 41.0 Hz, 2H), 3.54-3.46 (m, 2H), 2.38 (d, J = 51.9 Hz, 6H), 2.17 (s, 4H), 2.03 (m, 12H), 1.98 (dd, J = 18.9, 3.5 Hz, 6H), 1.58-1.52 (m, 18H); 13C NMR (100 MHz, CDCl3), δ (ppm): 170.65, 143.87, 143.85, 143.41, 143.39, 140.84, 140.42, 131.93, 131.90, 131.38, 131.37, 127.86, 127.73, 126.69, 126.63, 125.26, 125.09, 125.03, 100.28, 99.42, 85.04, 84.31, 77.22, 71.92, 71.86, 71.69, 71.09, 71.05, 70.35, 69.51, 69.35, 69.32, 65.85, 65.72, 62.08, 61.67, 56.63, 56.58, 34.88, 33.30, 33.29, 32.21, 32.19, 31.93, 31.51, 31.44, 30.20, 30.14, 29.70, 29.66, 29.37, 28.08, 27.94, 27.18, 26.92, 26.84, 26.40, 23.44, 22.70, 22.66, 20.78, 20.77, 20.69, 20.58, 14.13; HRMS (ESI): m/z Calcd for C74H89N8O22 [M+H]+ 1441.6085, found: 1441.6104.

TPE2G: compound **S3a** (50.0 mg, 0.0347 mmol) was dissolved in a solution of MeONa/MeOH (0.054 M, 1.0280 mL) under nitrogen atmosphere, adding extra 4 mL of methanol to it, and stirred for 20 h at room temperature. The reaction was neutralized with an IR-120 hydrogen ion resin. The pH was adjusted to about 7, then filtered, and the solvent was evaporated to give crude intermediate compound. Then, the crude compound was added to a round bottom flask containing a solution of THF (4 mL) and hydrochloric acid (1.0 M, 7 mL), and the reaction was stirred at room temperature for 15 h. After completion of the reaction, the solvent was removed by rotary evaporation, and the residual was purified by reversed phase column chromatography (H_2O : MeOH = 1 : 5, V/V) to obtain **TPE2G** (23.2 mg, 73.9% yield). ^{1}H NMR (400 MHz, CD_3OD), δ (ppm): 8.55 (d, J = 3.6 Hz, 2H), 7.59 (d, J = 8.2 Hz, 4H), 7.15-7.04 (m, 14H), 4.72-4.61 (m, 4H), 4.59 (dd, J = 8.3, 4.2 Hz, 2H), 3.99-3.90 (m, 2H), 3.84 (d, J = 11.8 Hz, 2H), 3.70-3.62 (m, 4H), 3.56-3.47 (m, 2H), 3.35-3.30 (m, 4H), 2.84 (dd, J = 8.4, 6.5 Hz, 2H), 2.29 (s, 4H); ^{13}C NMR (100 MHz, CD_3OD), δ (ppm): 148.00, 145.64, 144.65. 144.58, 142.44, 133.16, 133.11, 132.42, 132.39, 131.11, 129.07, 129.04, 128.94, 127.91, 126.33, 126.24, 123.42, 100.40, 78.54, 73.99, 71.77, 67.33, 62.18, 57.71, 57.61, 57.50, 57.29, 31.26, 17.50, 17.28, 17.12; HRMS (ESI): m/z Calcd for $C_{48}H_{57}N_8O_{10}$ $[M+H]^+$ 905.4192, found: 905.4198.

Methoxy & Acetyl protected TPE2S (S3b): compound **S1c** (100.0 mg, 0.1791 mmol) and compound **S2a** (27.3 mg, 0.0716 mmol) were dissolved in THF (13 mL) in a round bottom flask under nitrogen. Sodium ascorbate (0.028 M, 1 mL, aq.) and copper sulfate (0.014 M, 1 mL, aq.) were then added successively and stirred at 50 °C for 34h. After the disappearance of compound **S2a**, the reaction was cooled to room temperature, extracted with DCM and dried over $MgSO_4$. After filtration, the solvent of mixture was evaporated. The residue was purified by column chromatography (DCM : MeOH = 100 : 1, V/V) to obtain compound **S3b** (57.8 mg, 53.9% yield). ^{1}H NMR (600 MHz, $CDCl_3$,), δ (ppm): 7.82 (d, J = 2.2 Hz, 2H), 7.59 (d, J = 8.3 Hz, 4H), 7.14-7.04 (m, 14H), 5.57 (dt, J = 8.4, 1.4 Hz, 2H), 5.43 (ddd, J = 8.3, 7.0, 3.2 Hz, 2H), 4.62 (ddd, J = 9.3, 4.1, 1.7 Hz, 2H), 4.50 (dddd, J = 13.8, 10.1, 7.0, 4.3 Hz, 4H), 4.37 (ddd, J = 12.3, 4.1, 2.9 Hz, 2H), 4.00 (dddd, J = 12.2, 9.7, 5.4, 2.0 Hz, 4H), 3.90-3.85 (m, 2H), 3.77-3.69 (m, 8H), 3.40-3.36 (m, 2H), 2.84 (ddd, J = 12.1, 5.6, 3.6 Hz, 2H), 2.50 (d, J = 2.2 Hz, 6H), 2.21 (dt, J = 11.1, 5.6 Hz, 4H), 2.10 (dd, J = 6.0, 2.9 Hz, 14H), 2.01 (d, J = 4.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$), δ (ppm): 172.07, 170.79, 170.29, 170.27, 170.05, 168.71, 168.68, 153.62, 153.60, 143.72, 143.44, 143.41, 140.84, 131.92, 131.90, 131.39, 131.38, 127.85, 127.75, 126.69, 126.64, 125.16, 125.02, 120.09, 104.15, 99.93, 99.06, 75.55, 75.53, 74.82, 74.81, 71.72, 68.74, 68.73, 63.37, 62.33, 59.03, 53.42, 53.14, 47.39, 47.33, 36.49, 36.48, 31.94, 30.40, 29.71, 24.70, 22.70, 21.14, 20.94, 20.80, 14.12; HRMS (ESI): m/z Calcd for $C_{74}H_{81}N_8O_{26}$ $[M+H]^+$ 1497.5256, found: 1497.5266.

TPE2S: compound **S3b** (56.5 mg, 0.0377 mmol) was dissolved in a solution of MeONa/MeOH (0.054 M, 0.084 mL) under nitrogen atmosphere and add extra 3.5 mL of methanol to it. Then the mixture was stirred for 3 h at room temperature. After completion of the reaction, the reaction was neutralized with an IR-120 hydrogen ion resin, adjusting the pH to about 7. Then filtered, and the solvent was evaporated to give crude intermediate compound. Then, the crude compound, lithium hydroxide hydrate (26.0 mg, 0.6196 mmol), a solution of THF/H_2O (3 mL, 2 : 1, V/V) were added to a round bottom flask, and the reaction was stirred at room temperature over night. After the disappearance of reactant, the reaction was also

neutralized with an IR-120 hydrogen ion resin to adjust the pH to about 7. After filtration, the solvent was removed, and the residual was purified by Bio-Gel P-2 gel to obtain **TPE2S** (33.1 mg, 73.4% yield). ^{1}H NMR (400 MHz, CD_3OD), δ (ppm): 8.31 (s, 2H), 7.60 (t, J = 8.6 Hz, 4H), 7.20-7.00 (m, 14H), 4.54 (s, 4H), 3.82-3.51 (m, 20H), 2.89 (s, 6H), 2.78 (s, 2H), 2.16 (s, 2H), 1.60 (d, J = 6.5 Hz, 2H); HRMS (ESI): m/z Calcd for $C_{58}H_{69}N_8O_{18}$ $[M+H]^+$ 1165.4724, found: 1165.4708.



S2b: compound **S2b** was synthesized according to the methods reported in the previous article.[6]

Acetyl protected TPE3M (S3c): compound **S6** (69.1 mg, 0.1602 mmol) and compound **S2b** (33.2 mg, 0.0460 mmol) were dissolved in THF (5 mL) under nitrogen. Sodium ascorbate (0.034 M, 1 mL, aq.) and copper sulfate (0.018 M, 1 mL, aq.) were then added successively and stirred at 67 °C for 18 h. After completion of the reaction, the mixture was cooled to room temperature, extracted with DCM and dried over $MgSO_4$. And after filtration, the solvent of mixture was evaporated. The residue was purified by column chromatography (DCM : MeOH = 50 : 1, V/V) to obtain compound **S3c** (79.6 mg, 85.8% yield). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.96 (s, 1H), 7.66 (s, 3H), 7.50 (d, J = 8.2 Hz, 2H), 7.15 (dd, J = 17.1, 7.6 Hz, 5H), 7.03 (dd, J = 7.7, 1.3 Hz, 2H), 6.95 (dd, J = 11.5, 8.7 Hz, 4H), 6.65 (t, J = 8.1 Hz, 4H), 5.29 (d, J = 8.4 Hz, 6H), 5.24 (s, 3H), 4.81 (s, 3H), 4.60 (d, J = 12.5 Hz, 8H), 4.49 (s, 6H), 4.29 (dd, J = 12.1, 4.9 Hz, 3H), 4.09 (d, J = 11.9 Hz, 3H), 4.01 (s, 3H), 3.74 (s, 9H), 3.51 (d, J = 12.5 Hz, 11H), 2.24 (s, 6H), 2.15 (s, 9H), 2.08 (s, 9H), 2.04 (s, 9H), 1.99 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$), δ (ppm):170.61, 170.04, 169.91, 169.71, 158.43, 158.38, 158.33, 157.80, 157.79, 145.50, 145.20, 143.74, 141. 49, 140.78, 136.84, 135.86, 135.82, 133.97, 133.51, 132.70, 132.63, 132.56, 131.37, 127.93, 126.45, 119.69, 113.32, 113.09, 97.82, 69.48, 69.12, 68.74, 66.07, 64.85, 64.84, 62.45, 55.15, 55.12, 47.10, 47.09, 47.08, 47.07, 47.04, 30.22, 30.06, 30.05, 29.71, 29.69, 29.66, 20.89, 20.76, 20.73, 20.70; HRMS (ESI): m/z Calcd for $C_{96}H_{118}N_{12}O_{36}Na_2$ $[M+2Na]^{2+}$ 1030.3778, found: 1030.3789.

TPE3M: compound **S3c** (79.6 mg, 0.0395 mmol) and MeONa/MeOH (0.054 M, 0.22 mL) reagent were placed into a flask, and add extra 4 mL of methanol to it. The mixture was stirred for 22 h. Then the IR-120 hydrogen ion resin was added to the mixture until the pH of it was 7. At this stage the solid was filtered off, the filter cake was washed with methanol, and finally the solvent was removed by rotary evaporator. Then, the residue after evaporation of solvent was purified by reversed phase column chromatography (H_2O : MeOH = 1 : 3.5, V/V) to obtain **TPE3M** (5.8 mg, 9.7% yield). ^{1}H NMR (600 MHz, CD_3OD), δ (ppm): 8.42 (s, 1H), 7.93 (s, 3H), 7.61 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.18-7.12 (m, 3H), 7.06 (d, J = 6.9 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.5 Hz, 2H), 4.72 (s, 3H), 4.58 (s, 2H), 4.52 (s, 6H), 4.48 (dd, J = 11.5, 6.7 Hz, 6H), 3.84-3.79 (m, 6H), 3.77 (dd, J = 10.5, 5.2 Hz, 3H), 3.74-3.70 (m, 9H),

3.68 (dd, J = 9.6, 3.4 Hz, 3H), 3.62 (t, J = 9.6 Hz, 3H), 3.52 (d, J = 6.3 Hz, 3H), 3.50-3.45 (m, 8H), 3.41-3.37 (m, 3H), 2.20-2.15 (m, 6H); HRMS (ESI): m/z Calcd for $C_{72}H_{95}N_{12}O_{24}$ $[M+H]^+$ 1511.6576, found: 1511.6585.

1,1,2,2-tetrakis(4-ethynylphenyl)ethene (S3b): compound **S3b** was synthesized according to the methods reported in the previous article.[7]

Acetyl protected TPE4M (S3d): compound **S6** (79.5 mg, 0.1843 mmol) and compound **S3b** (17.7 mg, 0.0413 mmol) were added to a round bottom flask and dissolved with THF (4 mL) under N_2. Then sodium ascorbate (0.016 M, 1 mL, aq.) and copper sulfate (0.008 M, 1 mL, aq.) were added and the reaction was stirred at 67 °C for 21 h. After the disappearance of compound **S3b**, the reaction was cooled to room temperature, extracted with DCM, dried over $MgSO_4$, and the insoluble substance was filtered off. After the solvent of mixture was evaporated, the residue was purified by column chromatography (DCM : MeOH = 80 : 1, V/V) to obtain compound **S3d** (78.2 mg, 88.6% yield). ^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm): 7.77 (s, 4H), 7.61 (d, J = 8.1 Hz, 8H), 7.15 (d, J = 8.2 Hz, 8H), 5.34 (dd, J = 10.1, 3.4 Hz, 4H), 5.27 (s, 4H), 4.81 (s, 4H), 4.52 (ddd, J = 28.5, 13.8, 7.0 Hz, 8H), 4.28 (dd, J = 12.2, 5.4 Hz, 4H), 4.07 (dd, J = 12.2, 2.2 Hz, 4H), 4.00 (ddd, J = 9.8, 5.3, 2.2 Hz, 4H), 3.78-3.73 (m, 4H), 3.48-3.43 (m, 4H), 3.13-3.07 (m, 4H), 2.27 (ddd, J = 19.1, 13.4, 7.3 Hz, 8H), 2.15 (s, 12H), 2.04 (d, J = 7.0 Hz, 24H), 2.00 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 170.63, 170.12, 170.00, 169.72, 147.62, 143.42, 140.66, 131.97, 128.82, 125.24, 119.97, 97.79, 77.23, 69.46, 69.06, 68.77, 66.07, 64.52, 62.48, 60.41, 46.97, 45.83, 31.93, 29.99, 29.71, 29.67, 29.37, 25.66, 22.70, 21.06, 20.90, 20.73, 20.72, 20.71, 14.21, 14.13, 8.65; HRMS (ESI): m/z Calcd for $C_{102}H_{122}N_{12}O_{40}$ $[M+2H]^{2+}$ 1077.3935, found: 1077.3932.

TPE4M: compound **S3d** (78.2 mg, 0.0363 mmol) was dissolved in a solution of MeONa/MeOH (0.054 M, 1.65 mL) under nitrogen atmosphere and add extra 1 mL of methanol to it. Then the mixture was stirred for 30 h, and neutralize with IR-120 hydrogen ion resin to pH=7. After filtration of the turbid liquid, the solvent was removed and purified by reversed phase column chromatography (H2O : MeOH = 1 : 1.5, V/V) to obtain **TPE4M** (25.7 mg, 47.0% yield). 1H NMR (600 MHz, CD3OD), δ (ppm): 8.12 (s, 4H), 7.46 (d, J = 8.2 Hz, 8H), 6.99 (d, J = 8.3 Hz, 8H), 4.61 (s, 4H), 4.40 (p, J = 8.9 Hz, 8H), 3.69 (dd, J = 3.1, 1.6 Hz, 4H), 3.65 (dd, J = 12.0, 2.1 Hz, 4H), 3.61-3.56 (m, 12H), 3.50 (t, J = 9.7 Hz, 4H), 3.39 (ddd, J = 9.6, 5.5, 2.1 Hz, 4H), 3.32-3.27 (m, 4H), 2.08 (dt, J = 12.9, 6.6 Hz, 8H); 13C NMR (100 MHz, CD3OD), δ (ppm): 148.33, 145.72, 142.06, 132.99, 129.75, 127.09, 126.18, 122.69, 101.39, 101.17, 74.31, 72.24, 71.69, 68.15, 65.14, 62.33, 30.87; HRMS (ESI): m/z Calcd for C70H89N12O24 [M+H]+ 1481.6107, found: 1481.6117.

2 Results and Discussion

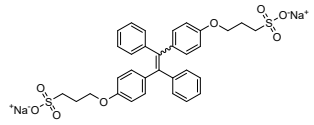
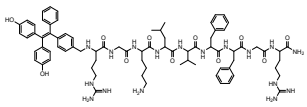
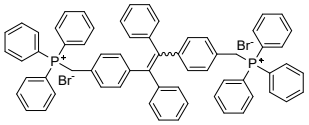
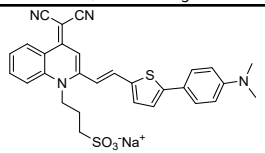
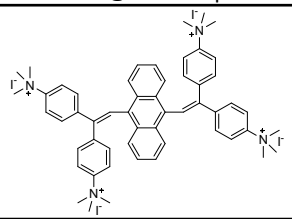
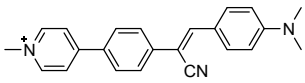
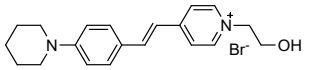
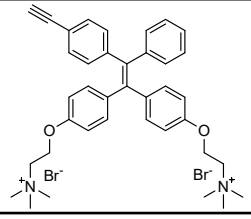
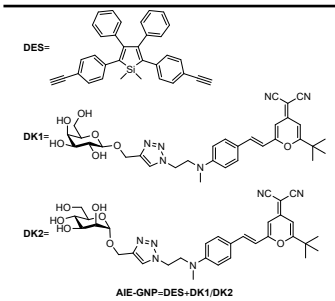
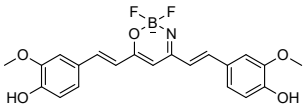
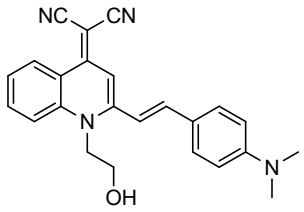
2.1 Summarize of amyloid fibrillation of monitoring and inhibition

Table S1. AIE-type fluorescent probes for monitoring and inhibition amyloid fibrillation.

Probe name	Type	Amyloid	Monitoring	Inhibition (I/P)[a]	Reference
BSPOTPE	*Turn-on*	Insulin fibrils	*ex situ* monitoring	*in situ* inhibition, I/P = 1/5 (Measurement for one week)	8
TPE-peptide	*Turn-on*	$A\beta_{1\text{-}40}$ fibrils Insulin fibrils Lysozyme fibrils	Detection and monitoring	-	9
TPE-TPP	*Turn-on*	α-synuclein oligomers and fibrils	Detection and monitoring	-	10
QM-FN-SO_3	*Off-on*	$A\beta_{42}$ fibrils	*in situ* mapping	-	11
DVAI@AuNCs-Apt	*Turn-on*	Insulin fibrils	Conformational monitoring	-	12
ASCP	*Ratiometric*	α-synuclein monomers and fibrils	Detection and monitoring	-	13
PD-BZ-OH	*Turn-on*	Hen egg white lysozyme fibrils	*in situ* nanoscale imaging	-	14
EPB@amyloid	*Turn-on*	$A\beta_{42}$ fibrils α-synuclein fibrils	High-throughput screening of small-molecule inhibitors	-	15
AIE-GNP	*Ratiometric*	$A\beta_{42}$ monomers and fibrils Lectins	Detection and discrimination between Aβ and lectin	-	16
Cur-N-BF_2	*Light-up*	$A\beta_{1\text{-}42}$ fibrils	Detection	Inhibition of Aβ fibrillation (I/P not mentioned) Disassembly of preformed Aβ fibrils Protection of neuronal cells	17
FB	*Turn-on*	$A\beta_{1\text{-}42}$ aggregates	Imaging of Aβ plaques and lipid droplets	-	18

[a] "-" represented no effects or not mentioned.

Table S2 The molecular structures of the corresponding probes in Table S1.

BSPOTPE	TPE-peptide	TPE-TPP	QM-FN-SO_3
			
DVAI@AuNCs-Apt	**ASCP**	**PD-BZ-OH**	**EPB@amyloid**
			
AIE-GNP	**Cur-N-BF_2**	**FB**	
			

2.2 Curve diagrams of fluorescence measurements

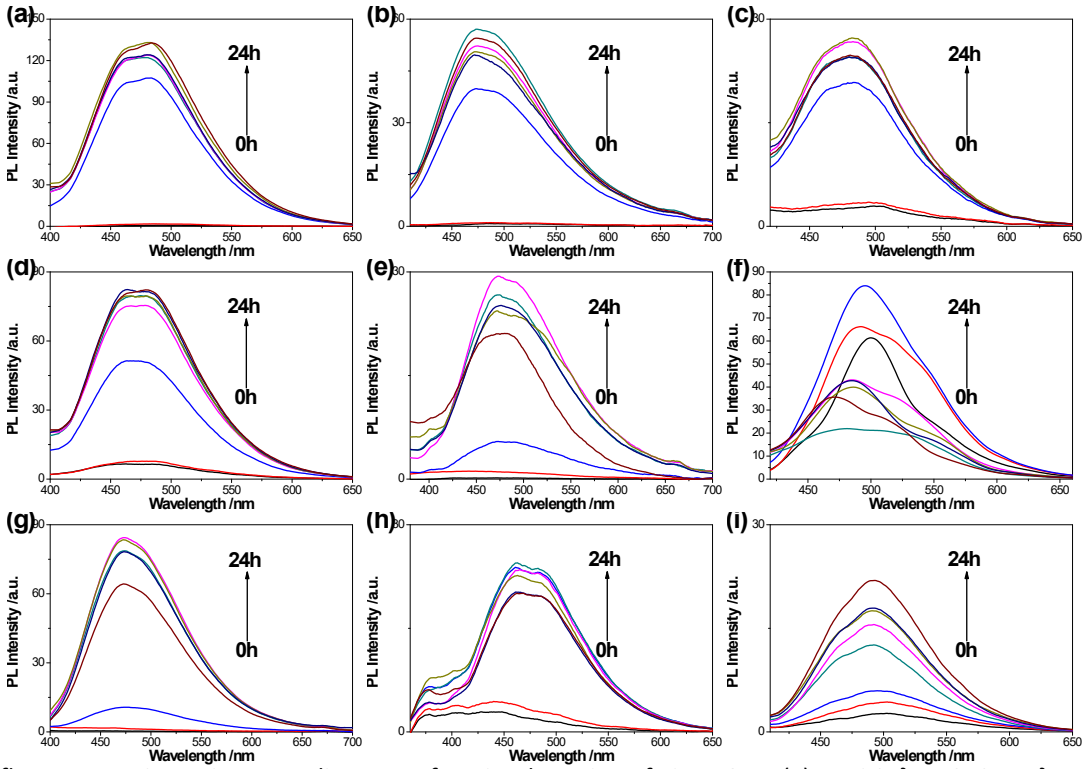


Fig. S1 The fluorescence intensity curve diagrams of ex situ detection of nine FONs. (a) TPE2G: λex=340nm, λem=480nm; (b) TPE3G: λex=330nm, λem=480nm; (c) TPE4G: λex=340nm, λem=480nm; (d) TPE2M: λex=330nm, λem=470nm; (e) TPE3M: λex=330nm, λem=480nm; (f) TPE4M: λex=345nm, λem=505nm; (g) TPE2S: λex=335nm, λem=473nm; (h) TPE3S: λex=330nm, λem=470nm; (i) TPE4S: λex=340nm, λem=492nm; Fluorescence measurements were performed in PBS buffer (10 mM, pH 7.4) at [FON] = 1 μM, [Insulin] = 5 μM.

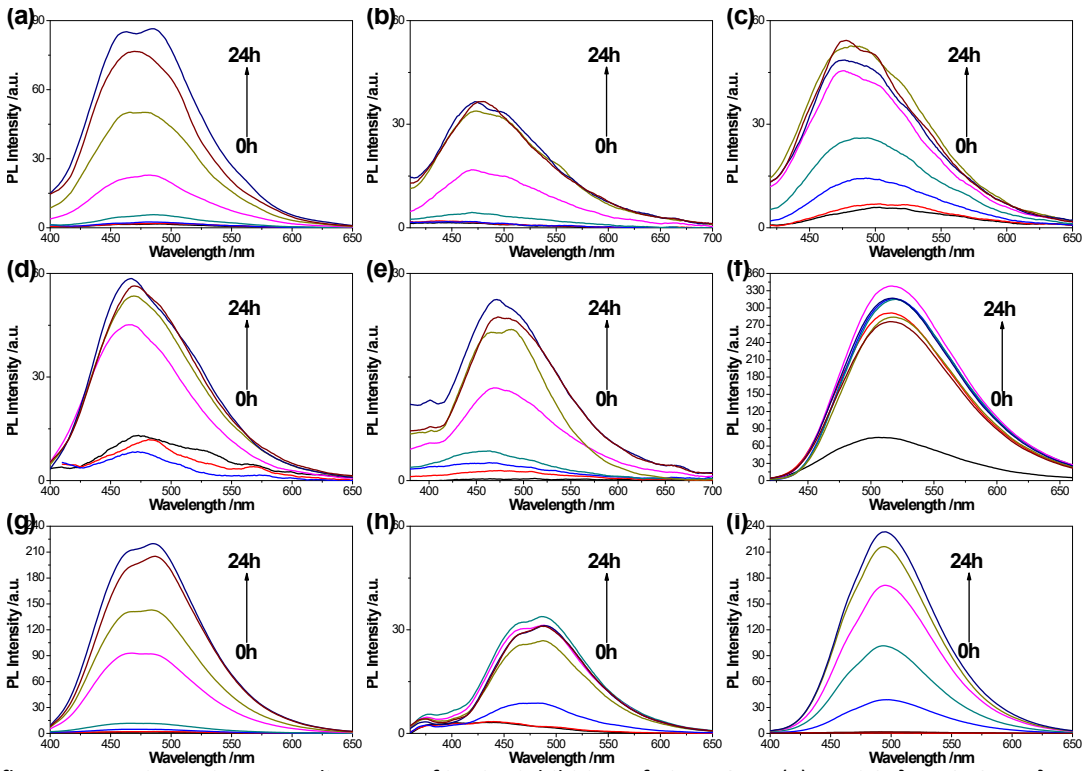


Fig. S2 The fluorescence intensity curve diagrams of in situ inhibition of nine FONs. (a) TPE2G: λex=340nm, λem=480nm; (b) TPE3G: λex=330nm, λem=480nm; (c) TPE4G: λex=340nm, λem=480nm; (d) TPE2M: λex=330nm, λem=470nm; (e) TPE3M: λex=330nm, λem=480nm; (f) TPE4M: λex=345nm, λem=505nm; (g) TPE2S: λex=335nm, λem=473nm; (h) TPE3S: λex=330nm, λem=470nm; (i) TPE4S: λex=340nm, λem=492nm; Fluorescence measurements were performed in PBS buffer (10 mM, pH 7.4) at [FON] = 1 μM, [Insulin] = 5 μM.

2.3 Curve diagrams of circular dichroism measurements

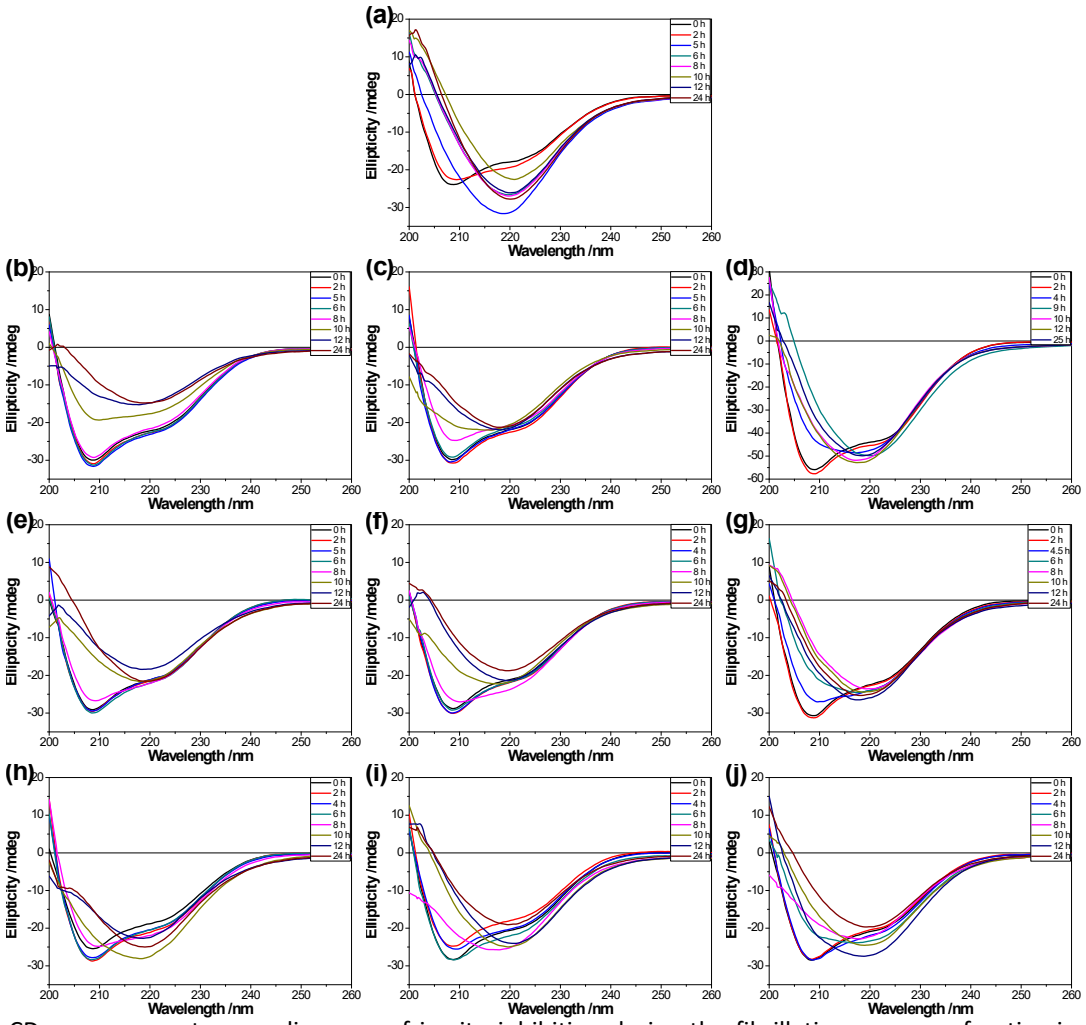


Fig. S3 The CD measurement curve diagrams of in situ inhibition during the fibrillation process of native insulin (a) and native insulin with nine FONs respectively: (b) TPE2G; (c) TPE3G; (d) TPE4G; (e) TPE2M; (f) TPE3M; (g) TPE4M; (h) TPE2S; (i) TPE3S; (j) TPE4S; CD measurements were performed in PBS buffer (10 mM, pH 7.4) at [Fluorescence inhibitor] = 1 μM, [Insulin] = 5 μM.

2.4 Images of TEM Experiments

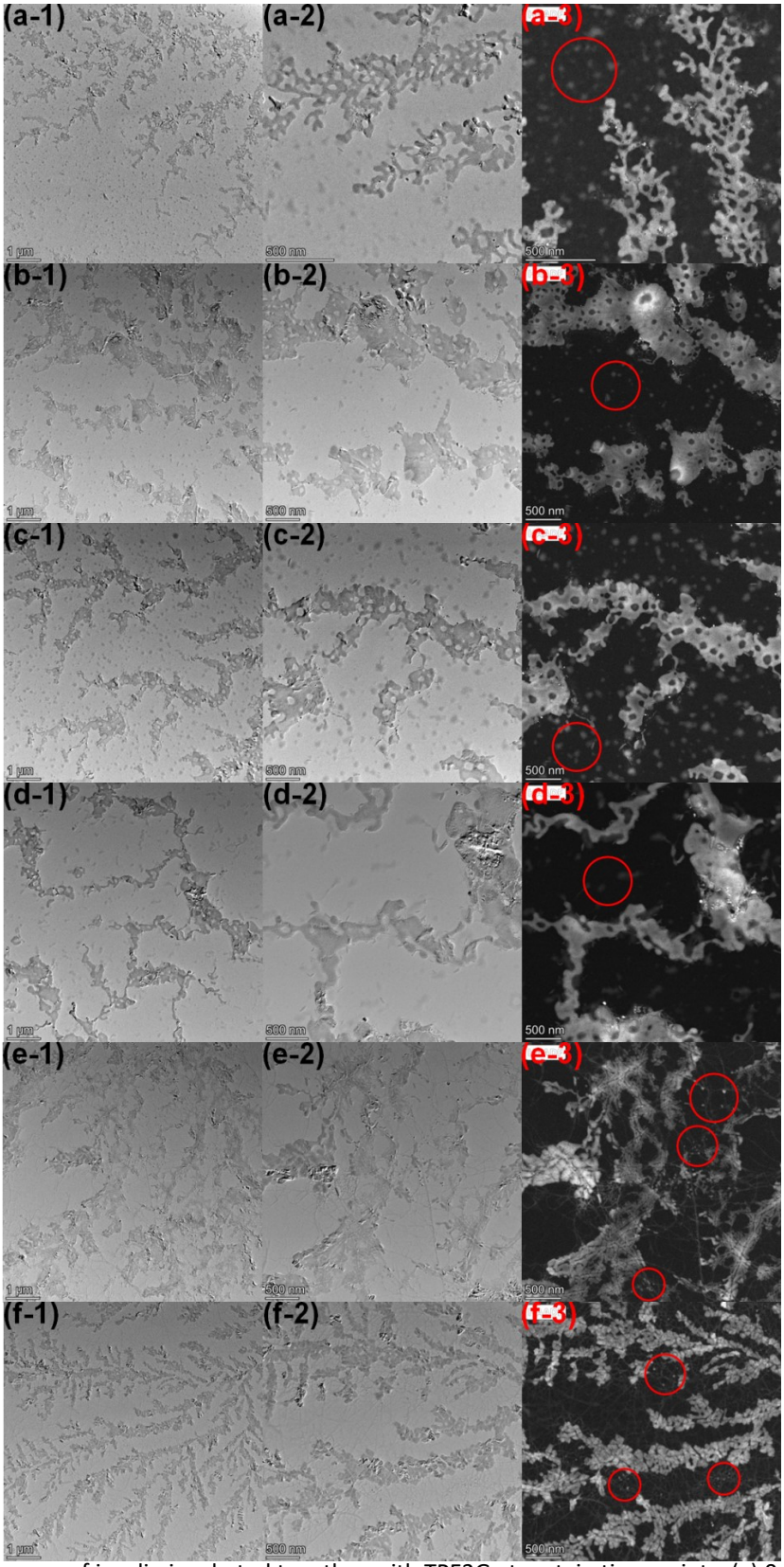


Fig. S4 TEM and STEM images of insulin incubated together with TPE2G at certain time points: (a) 0 hours; (b) 2 hours; (c) 5 hours; (d) 8 hours; (e) 9 hours; (f) 12 hours. The red circles marked the distribution of TPE2G.

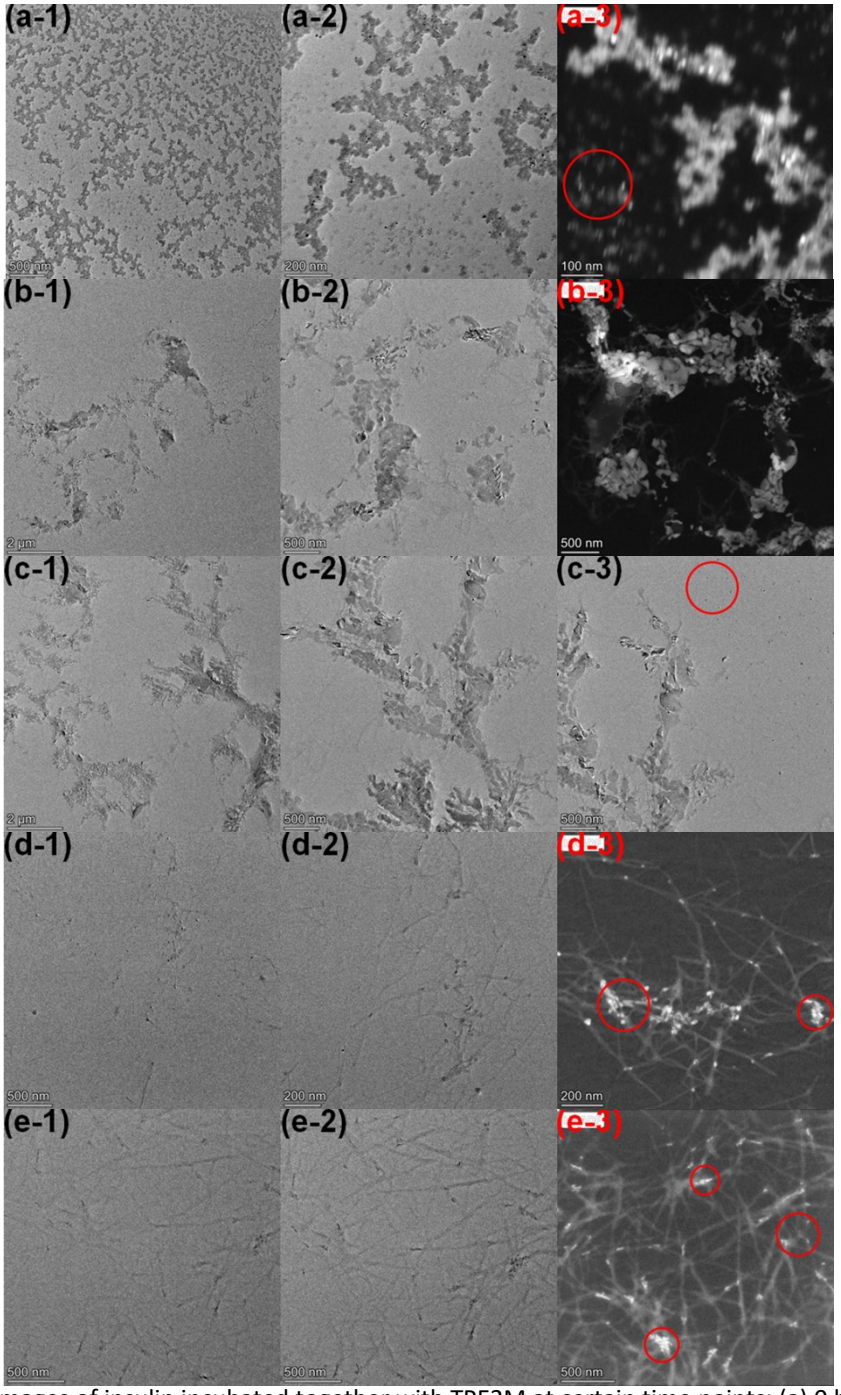


Fig. S5 TEM and STEM images of insulin incubated together with TPE2M at certain time points: (a) 0 hours; (b) 2 hours; (c) 4 hours; (d) 9 hours; (e) 12 hours. The red circles marked the distribution of TPE2M.

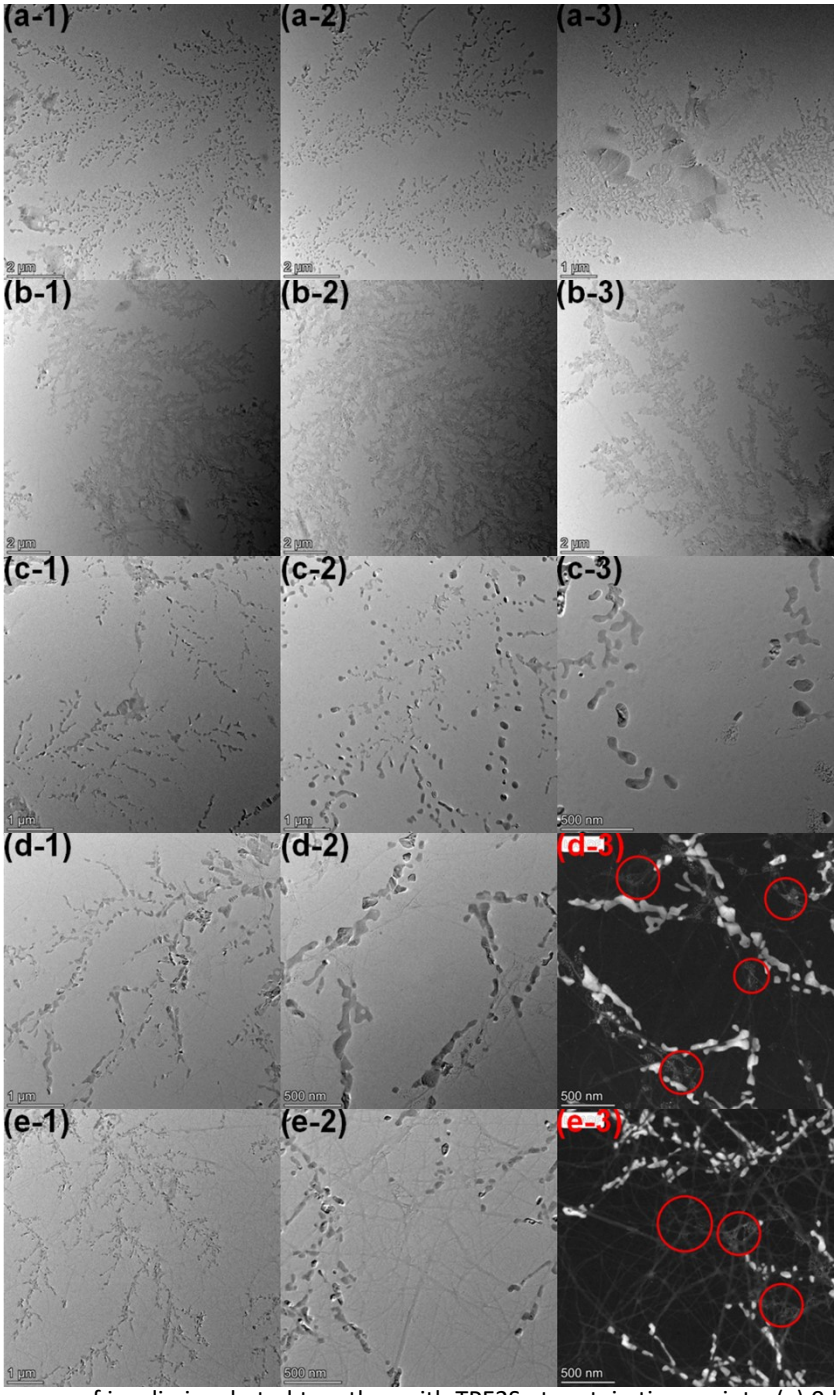


Fig. S6 TEM and STEM images of insulin incubated together with TPE2S at certain time points: (a) 0 hours; (b) 2 hours; (c) 4 hours; (d) 9 hours; (e) 12 hours. The red circles marked the distribution of TPE2S.

2.5 Images of molecular dynamics simulations

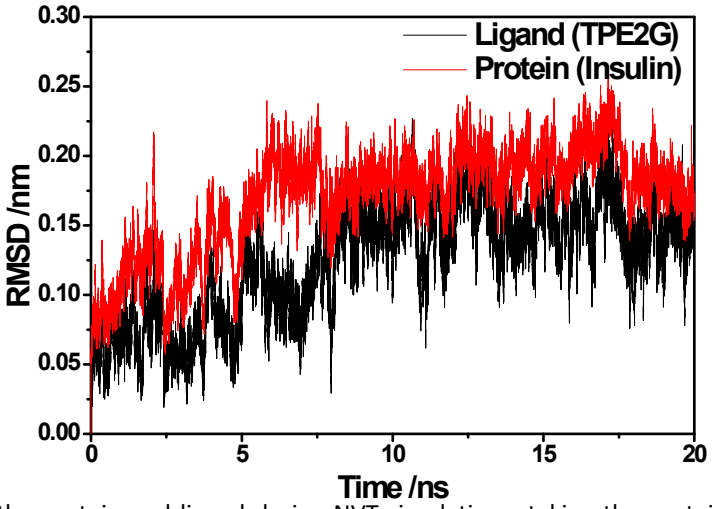


Fig. S7 RMSD line chart of the protein and ligand during NVT simulations, taking the protein backbone as the reference frame.

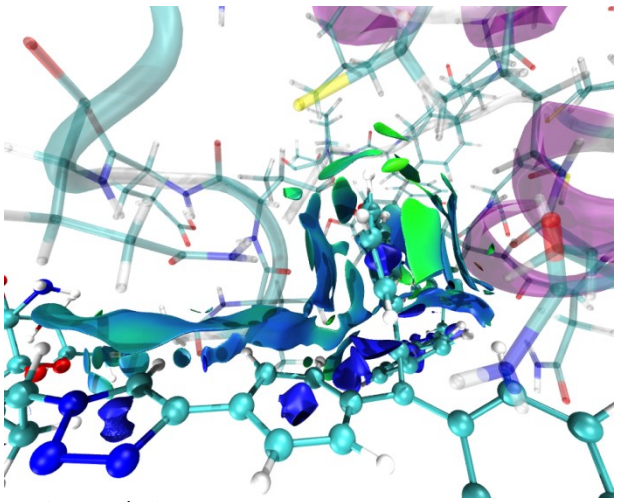


Fig. S8 The TFI image of weak interaction analysis.

3 References

1. J. A. Watt, S. J. Williams, *Org. Biomol. Chem.*, 2005, **3**, 1982-1992.
2. W. Hayes, H. M. I. Osborn, S. D. Osborne, R. A. Rastall, B. Romagnoli, *Tetrahedron*, 2003, **59**, 7983-7996.
3. G.-J. Liu, B. Wang, Y. Zhang, G.-W. Xing, X. Yang, S. Wang, *Chem. Commun.*, 2018, **54**, 10691-10694.
4. R. Hu, J. W. Y. Lam, J. Liu, H. H. Y. Sung, I. D. Williams, Z. Yue, K. S. Wong, M. M. F. Yuen, B. Z. Tang, *Polym. Chem.*, 2012, **3**, 1481-1489.
5. Y.-M. Ji, G.-J. Liu, C.-Y. Li, Y.-C. Liu, M. Hou, G.-W. Xing, *Chem. - Asian J.*, 2019, **14**, 3295-3300.
6. G.-J. Liu, Y. Zhang, L. Zhou, L.-Y. Jia, G. Jiang, G.-W. Xing, S. Wang, *Chem. Commun.*, 2019, **55**, 9869-9872.
7. K. Yuan, P. Guo-Wang, T. Hu, L. Shi, R. Zeng, M. Forster, T. Pichler, Y. Chen, U. Scherf, *Chem. Mater.*, 2015, **27**, 7403-7411.
8. Y. Hong, L. Meng, S. Chen, C. W. T. Leung, L.-T. Da, M. Faisal, D.-A. Silva, J. Liu, J. W. Y. Lam, X. Huang, B. Z. Tang, *J. Am. Chem.Soc.*, 2012, **134**, 1680-1689.
9. N. Pradhan, D. Jana, B. K. Ghorai, N. R. Jana, *ACS Appl. Mater. Interfaces*, 2015, **7**, 25813-25820.
10. C. W. T. Leung, F. Guo, Y. Hong, E. Zhao, R. T. K. Kwok, N. L. C. Leung, S. Chen, N. N. Vaikath, O. M. El-Agnaf, Y. Tang, W.-P. Gai, B. Z. Tang, *Chem. Commun.*, 2015, **51**, 1866-1869.
11. W. Fu, C. Yan, Z. Guo, J. Zhang, H. Zhang, H. Tian, W.-H. Zhu, *J. Am. Chem. Soc.*, 2019, **141**, 3171-3177.
12. Y. Jia, S. Guo, Q. Han, J. Zhu, X. Zhang, N. Na, J. Ouyang, *J. Mater. Chem. B*, 2021, **9**, 5128-5135.
13. N. R. Marzano, K. M. Wray, C. L. Johnston, B. P. Paudel, Y. Hong, A. van Oijen, H. Ecroyd, *ACS Chem. Neurosci.*, 2020, **11**, 4191-4202.
14. C. Fan, Y.-L. Wang, P.-J. Zhao, H.-Q. Qu, Y.-X. Su, C. Li, M.-Q. Zhu, *Bioconjugate Chem.*, 2020, **31**, 2303-2311.
15. L. Jia, W. Wang, Y. Yan, R. Hu, J. Sang, W. Zhao, Y. Wang, W. Wei, W. Cui, G. Yang, F. Lu, J. Zheng, F. Liu, *ACS Appl. Mater. Interfaces*, 2020, **12**, 31182-31194.
16. J.-D. Zhang, J. Mei, X.-L. Hu, X.-P. He, H. Tian, *Small*, 2016, **12**, 6562-6567.
17. Y. Yang, S. Li, Q. Zhang, Y. Kuang, A. Qin, M. Gao, F. Li, B. Z. Tang, *J. Mater. Chem. B*, 2019, **7**, 2434-2441.
18. Y. Wang, Y. Qiu, A. Sun, Y. Xiong, H. Tan, Y. Shi, P. Yu, G. Roy, L. Zhang, J. Yan, *Anal. Chim. Acta*, 2020, **1133**, 109-118.

4 Appendix: 1H NMR, 13C NMR and HRMS Spectrum of New Compounds

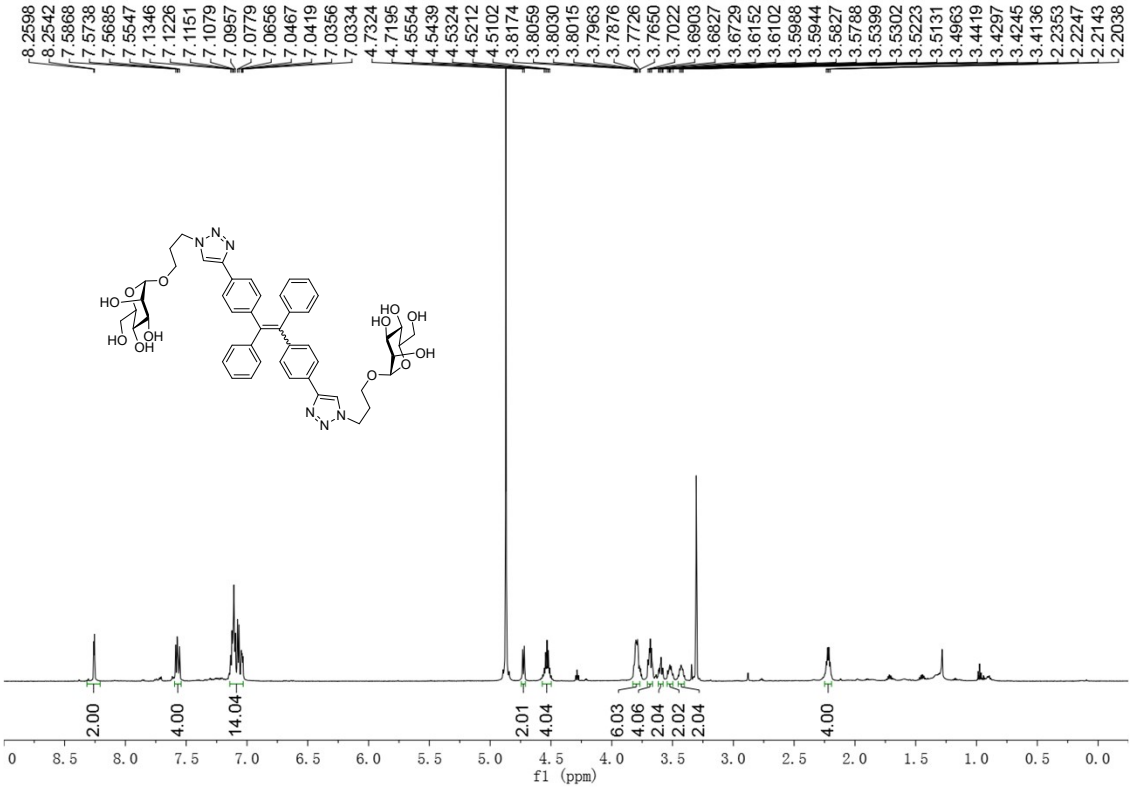


Fig. S9 ^{1}H NMR spectra of **TPE2M** (600 MHz, CD_3OD).

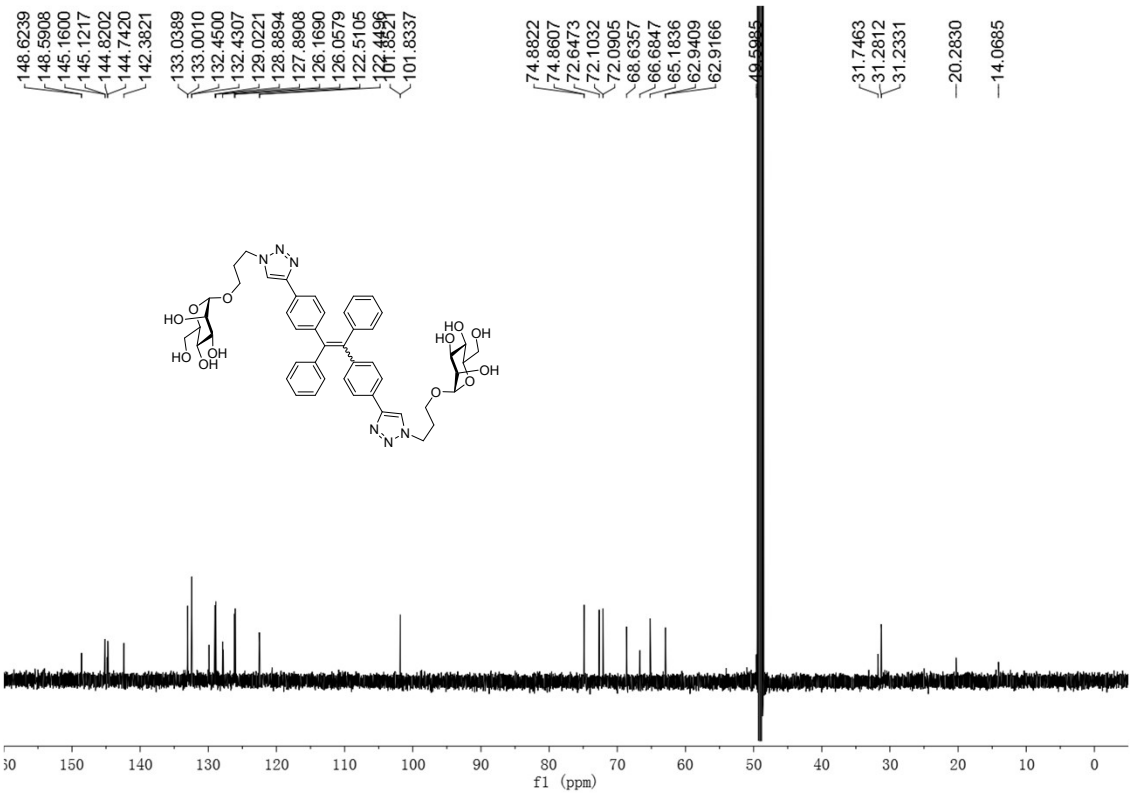
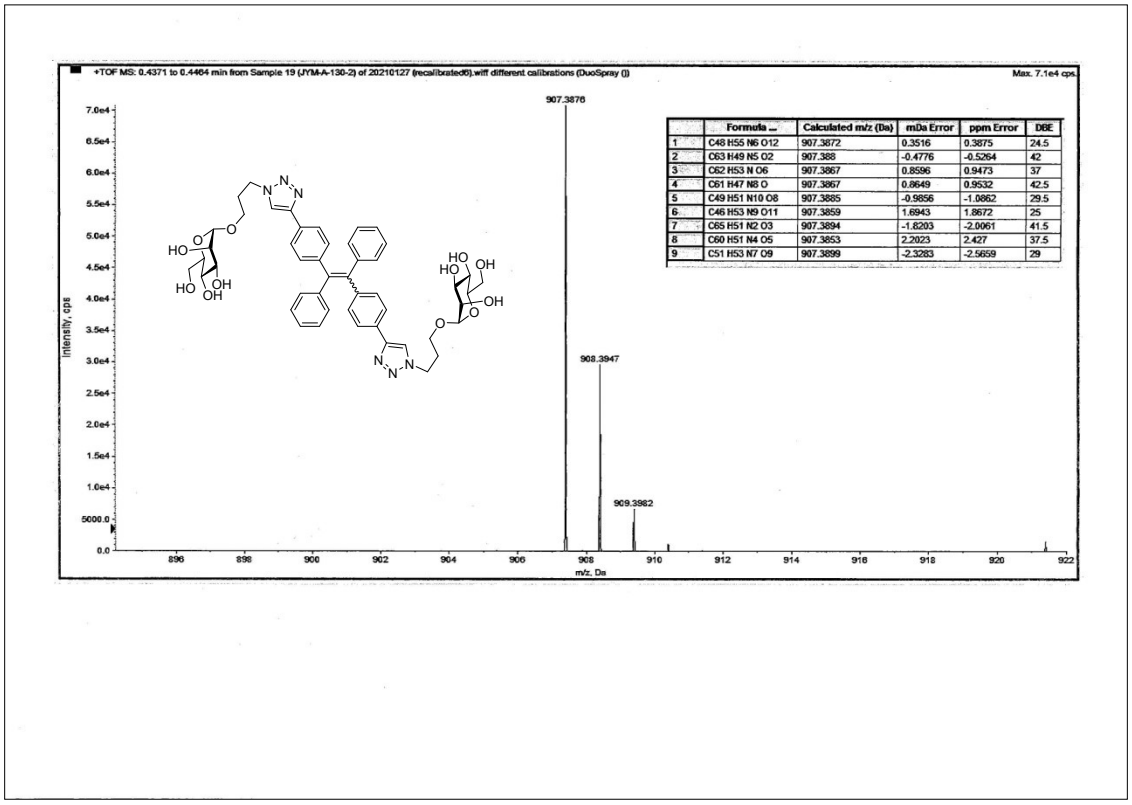


Fig. S10 ^{13}C NMR spectra of **TPE2M** (150 MHz, CD_3OD).



	Formula ...	Calculated m/z (Da)	mDa Error	ppm Error	DBE
1	C48 H55 N6 O12	907.3872	0.3516	0.3875	24.5
2	C63 H49 N5 O2	907.388	-0.4776	-0.5264	42
3	C62 H53 N O6	907.3867	0.8596	0.9473	37
4	C61 H47 N8 O	907.3867	0.8649	0.9532	42.5
5	C49 H51 N10 O8	907.3885	-0.9856	-1.0862	29.5
6	C46 H53 N9 O11	907.3859	1.6943	1.8672	25
7	C65 H51 N2 O3	907.3894	-1.8203	-2.0061	41.5
8	C60 H51 N4 O5	907.3853	2.2023	2.427	37.5
9	C51 H53 N7 O9	907.3899	-2.3283	-2.5659	29

Fig. S11 HRMS spectra of **TPE2M**.

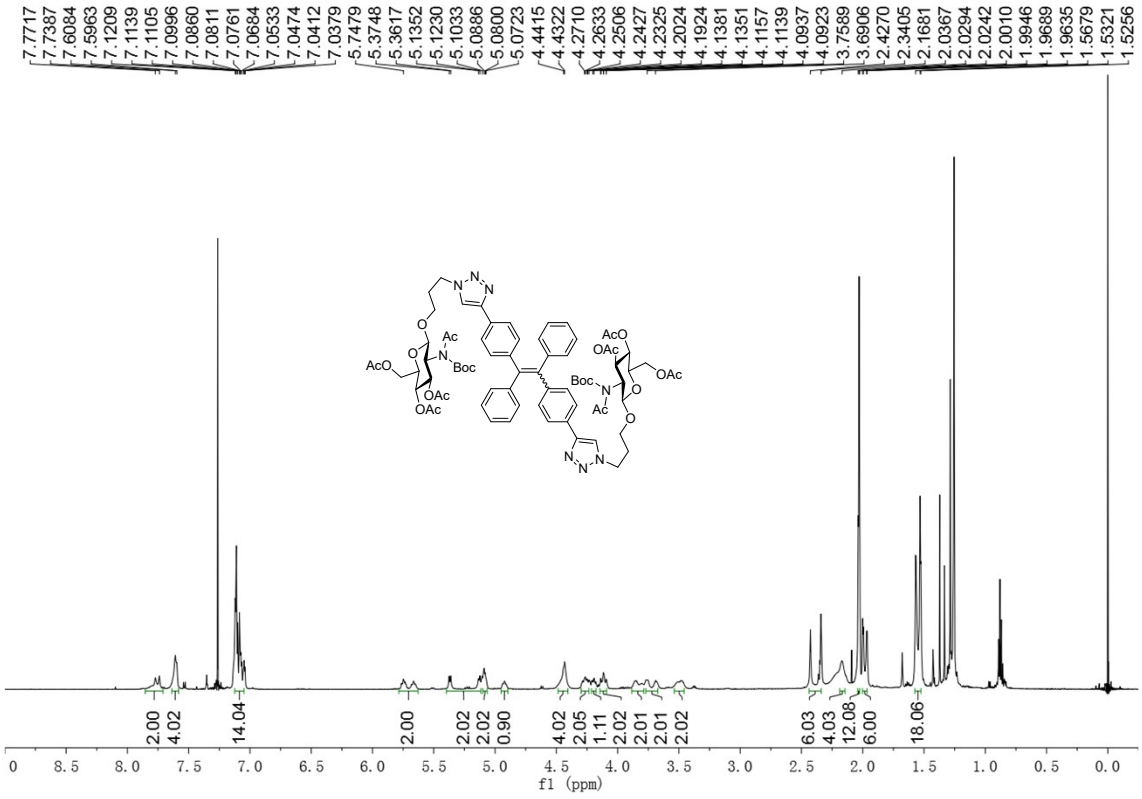


Fig. S12 ^{1}H NMR spectra of compound **S3a** (600 MHz, $CDCl_3$).

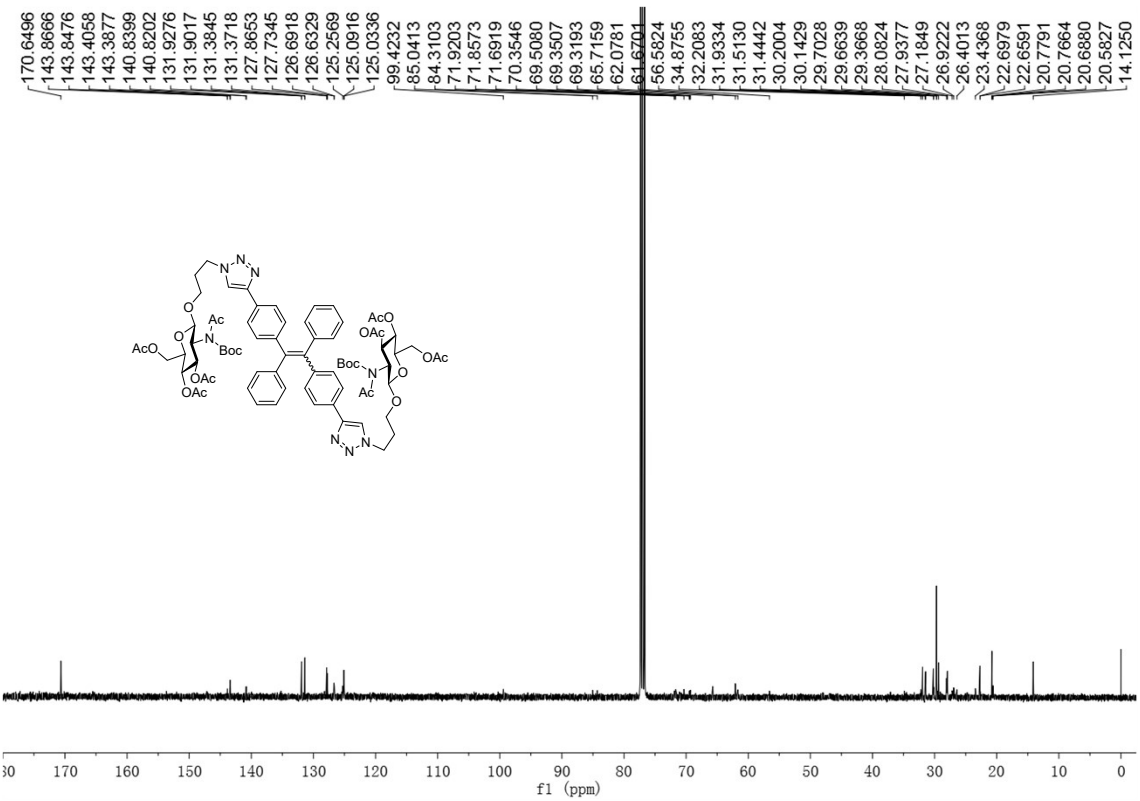


Fig. S13 ^{13}C NMR spectra of compound **S3a** (100 MHz, $CDCl_3$).

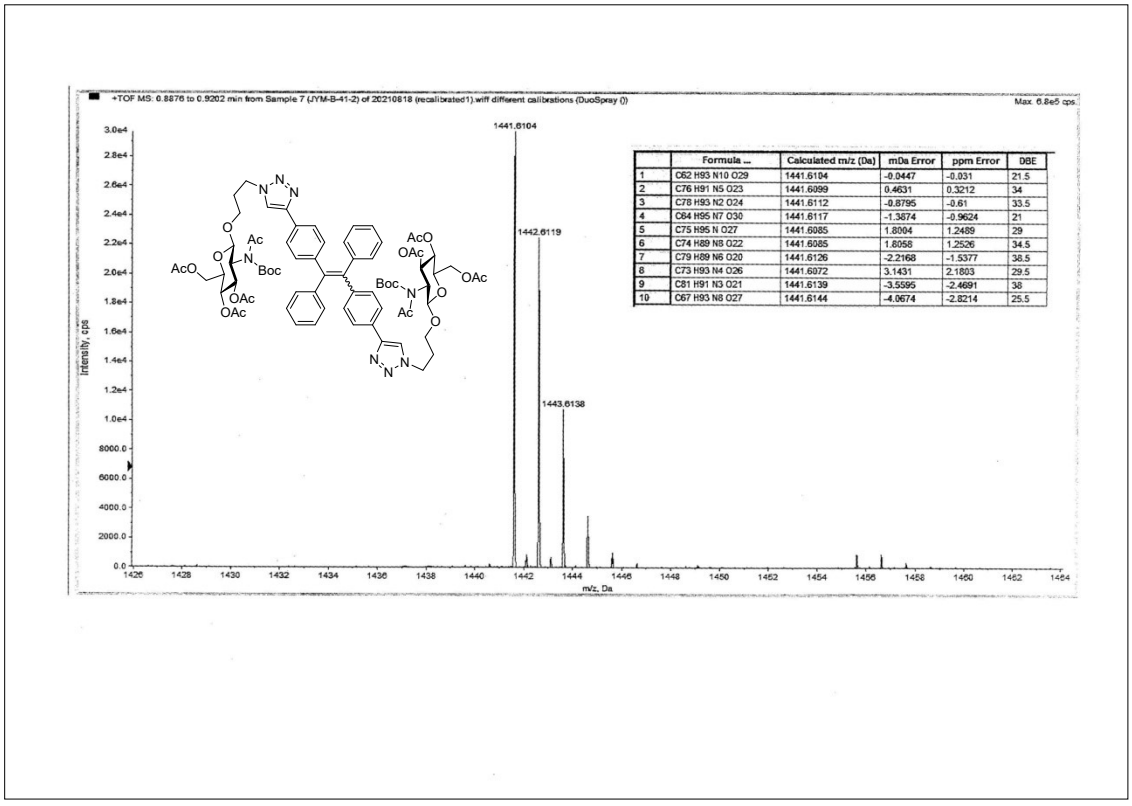


Fig. S14 HRMS spectra of compound **S3a**.

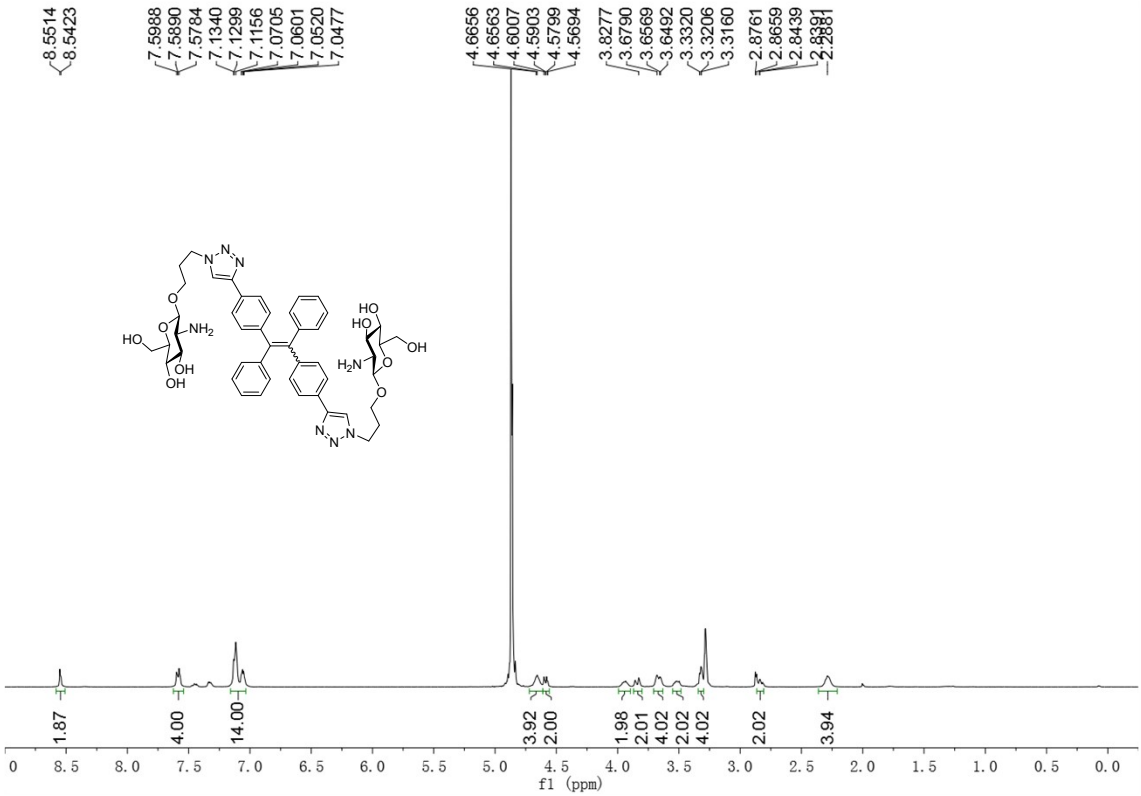


Fig. S15 ^{1}H NMR spectra of compound **TPE2G** (400 MHz, CD_3OD).

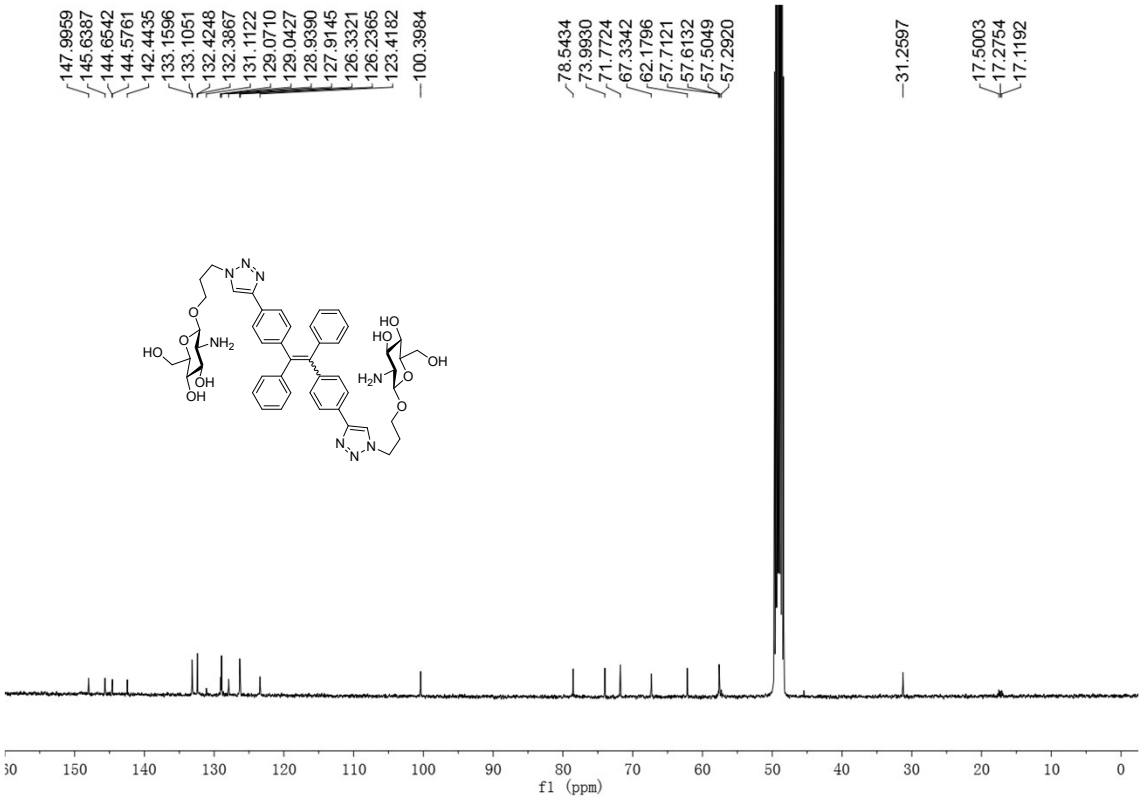
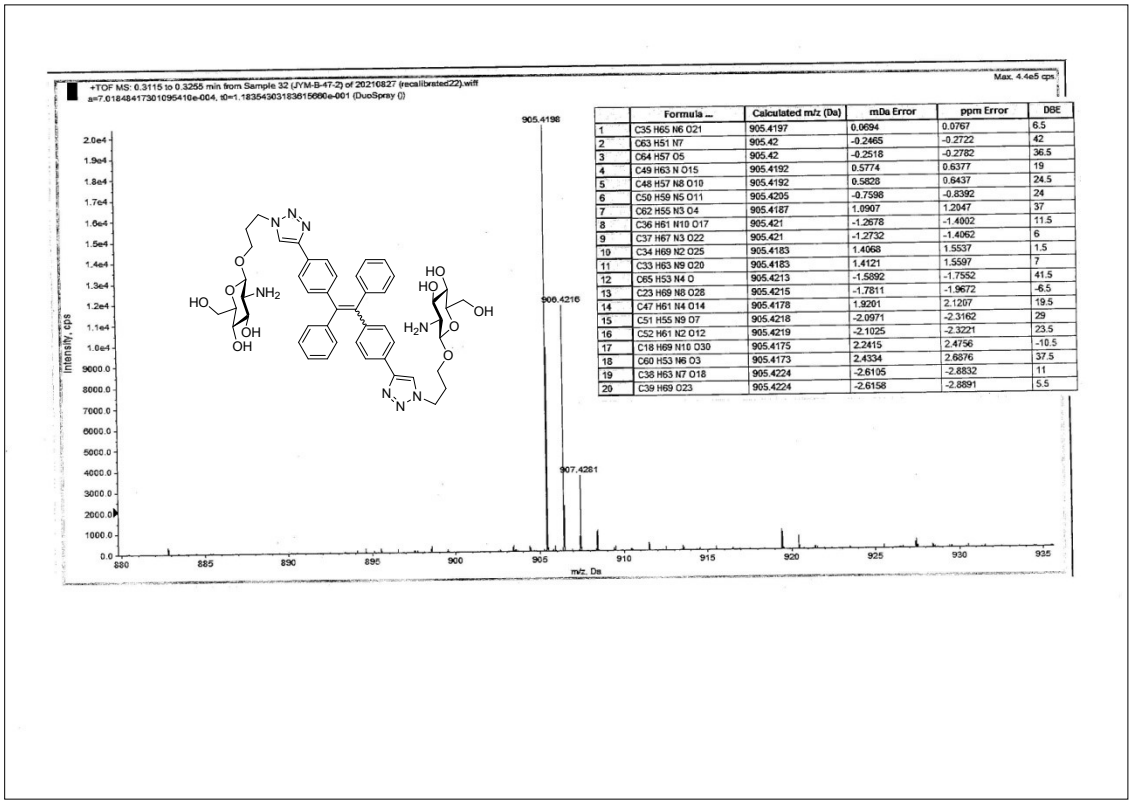


Fig. S16 ^{13}C NMR spectra of **TPE2G** (100 MHz, CD_3OD).



	Formula ...	Calculated m/z (Da)	mDa Error	ppm Error	DBE
1	C35 H65 N6 O21	905.4197	0.0694	0.0767	6.5
2	C63 H51 N7	905.42	-0.2465	-0.2722	42
3	C64 H57 O5	905.42	-0.2518	-0.2782	36.5
4	C49 H63 N O15	905.4192	0.5774	0.6377	19
5	C48 H57 N8 O10	905.4192	0.5828	0.6437	24.5
6	C50 H59 N5 O11	905.4205	-0.7598	-0.8392	24
7	C62 H55 N3 O4	905.4187	1.0907	1.2047	37
8	C36 H61 N10 O17	905.421	-1.2678	-1.4002	11.5
9	C37 H67 N3 O22	905.421	-1.2732	-1.4062	6
19	C34 H69 N2 O25	905.4183	1.4068	1.5537	1.5
11	C33 H63 N9 O20	905.4183	1.4121	1.5597	7
12	C65 H53 N4 O	905.4213	-1.5892	-1.7552	41.5
13	C23 H69 N8 O28	905.4215	-1.7811	-1.9672	-6.5
14	C47 H61 N4 O14	905.4178	1.9201	2.1207	19.5
15	C51 H55 N9 O7	905.4218	-2.0971	-2.3162	29
16	C52 H61 N2 O12	905.4219	-2.1025	-2.3221	23.5
17	C18 H69 N10 O30	905.4175	2.2415	2.4756	-10.5
18	C60 H53 N6 O3	905.4173	2.4334	2.6876	37.5
19	C38 H63 N7 O18	905.4224	-2.6105	-2.8832	11
20	C39 H69 O23	905.4224	-2.6158	-2.8891	5.5

Fig. S17 HRMS spectra of compound **TPE2G**.

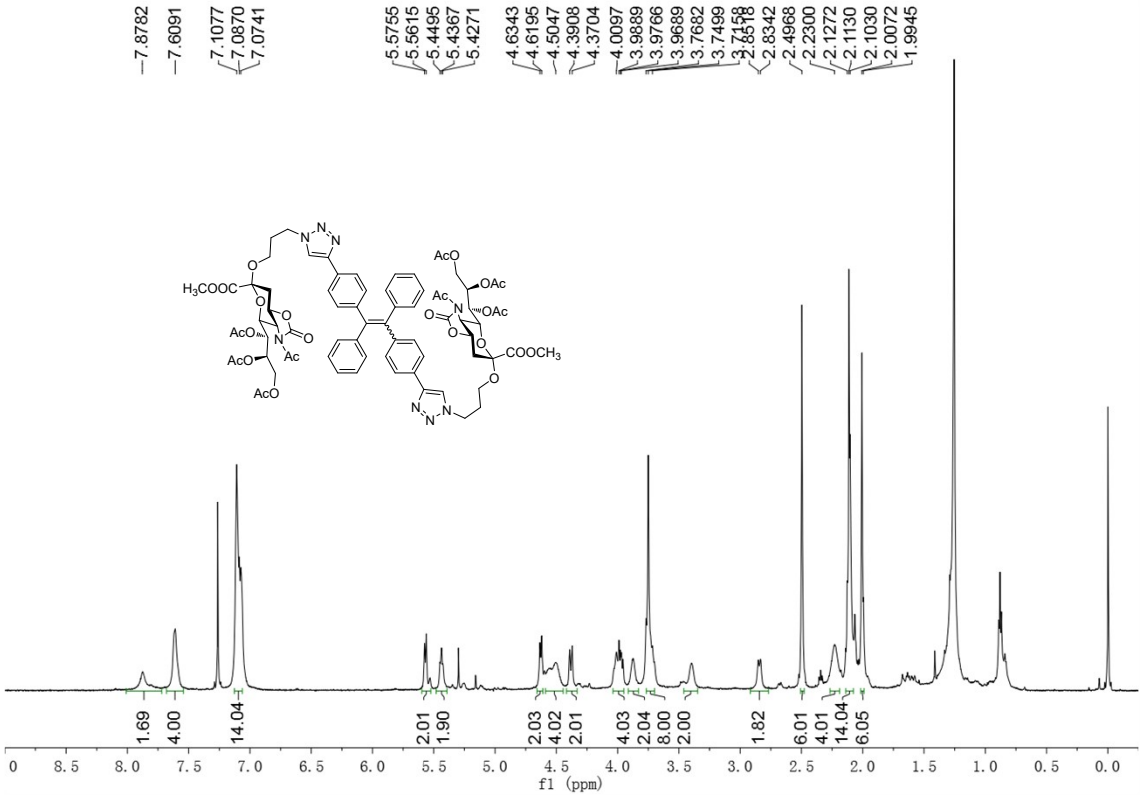


Fig. S18 ^{1}H NMR spectra of compound **S3b** (600 MHz, $CDCl_3$).

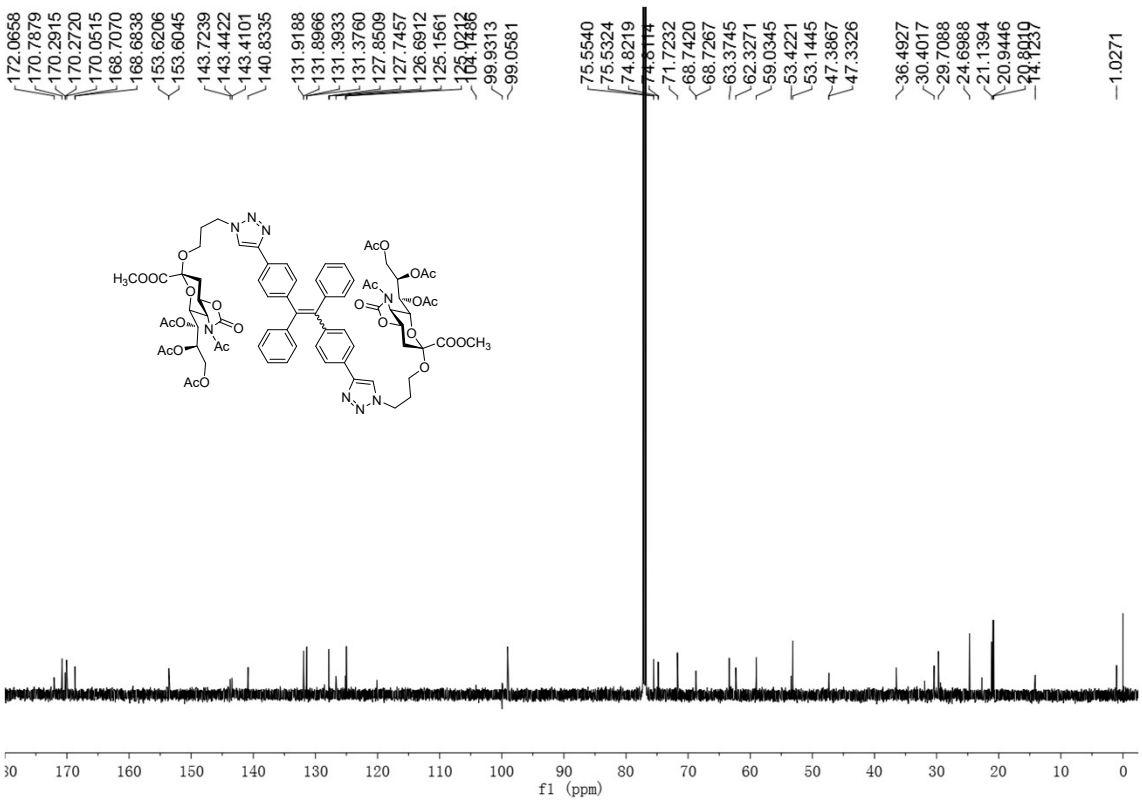


Fig. S19 ^{13}C NMR spectra of compound **S3b** (150 MHz, $CDCl_3$).

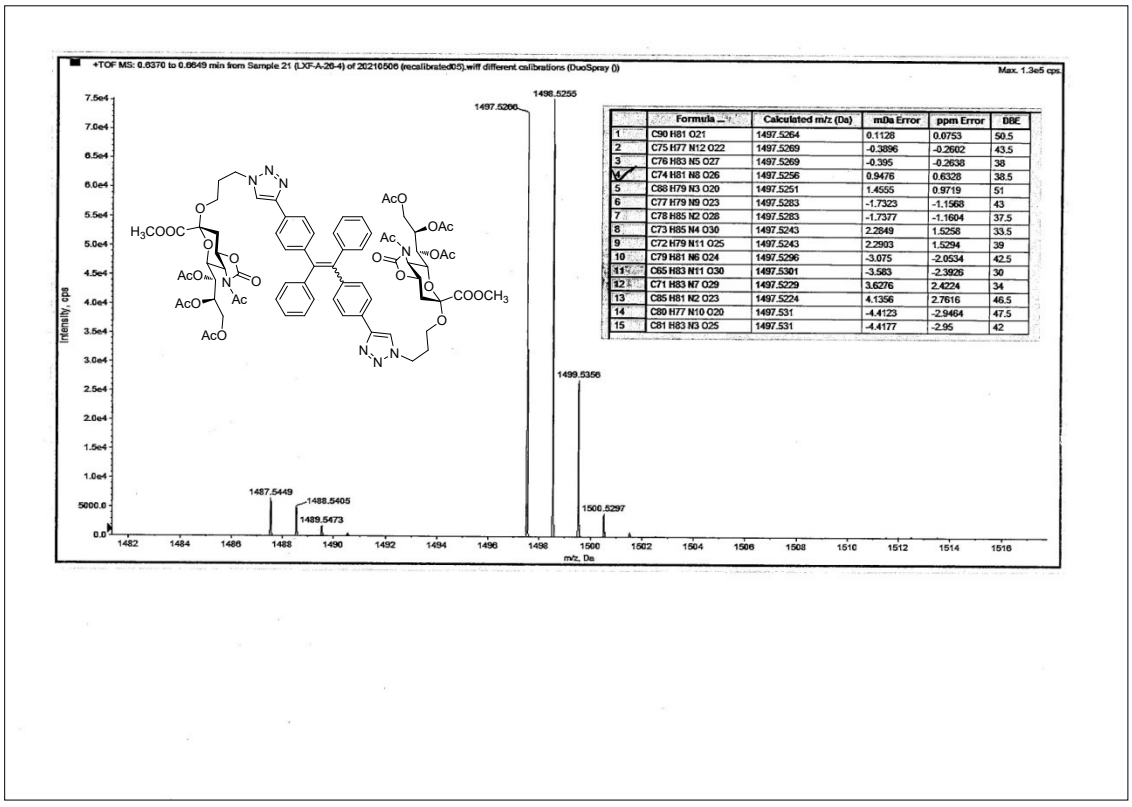


Fig. S20 HRMS spectra of compound **S3b**.

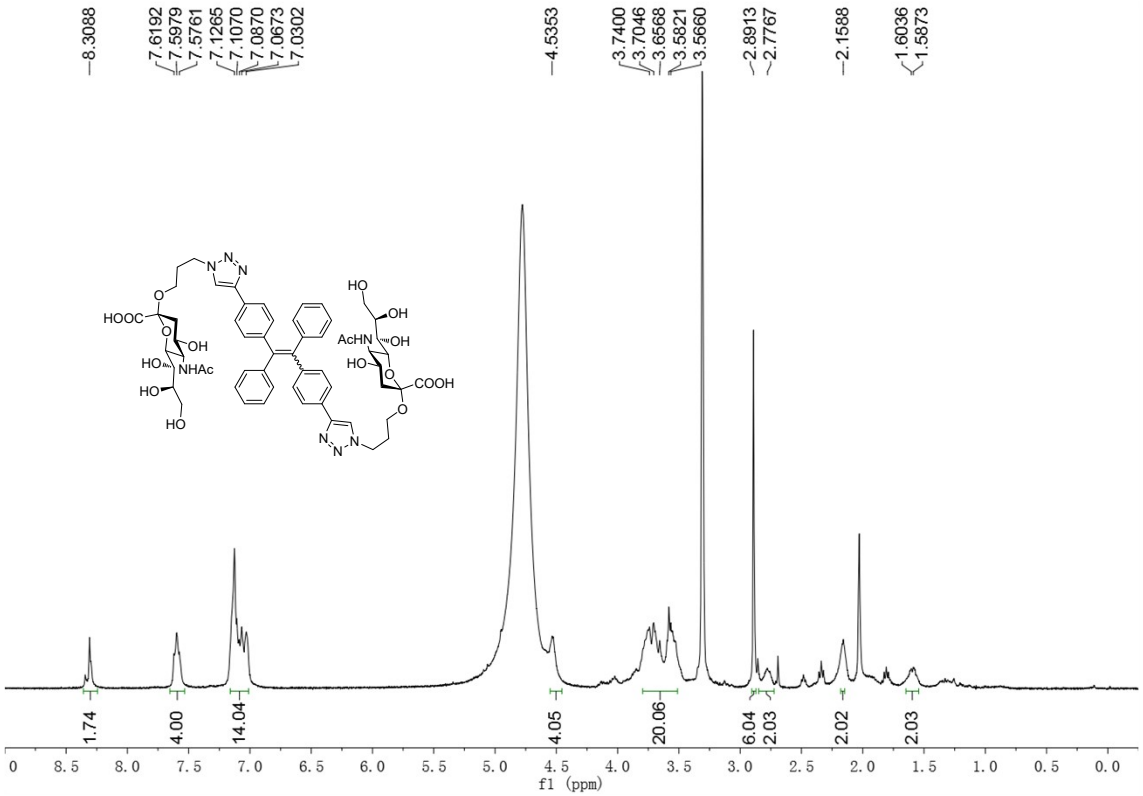


Fig. S21 ^{1}H NMR spectra of compound **TPE2S** (400 MHz, CD_3OD).

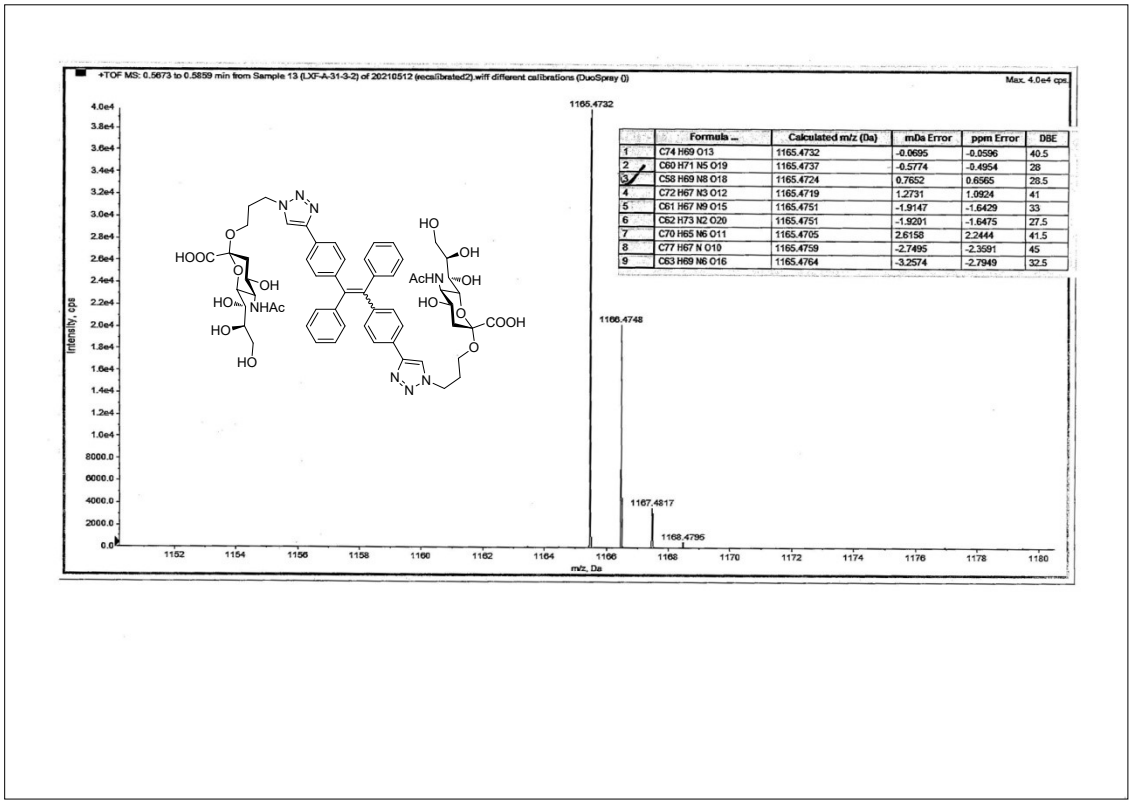


Fig. S22 HRMS spectra of compound **TPE2S**.

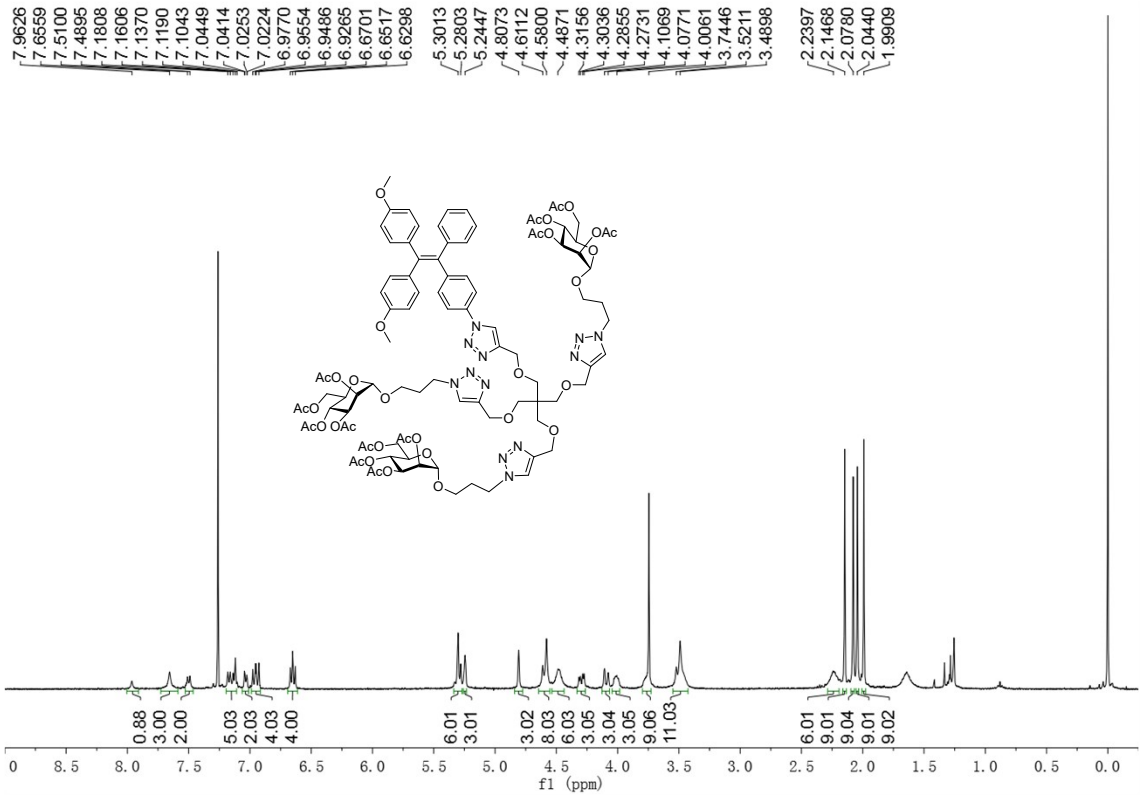


Fig. S23 ^{1}H NMR spectra of compound **S3c** (400 MHz, $CDCl_3$).

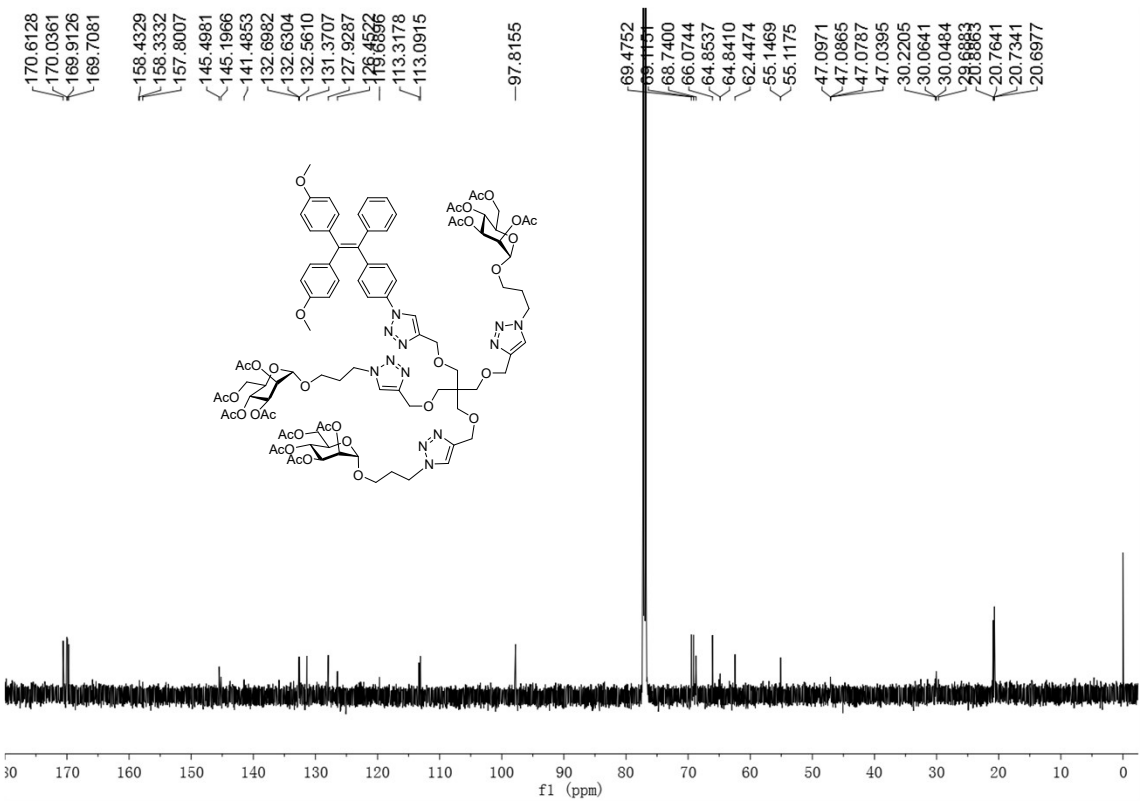


Fig. S24 ^{13}C NMR spectra of compound **S3c** (150 MHz, $CDCl_3$).

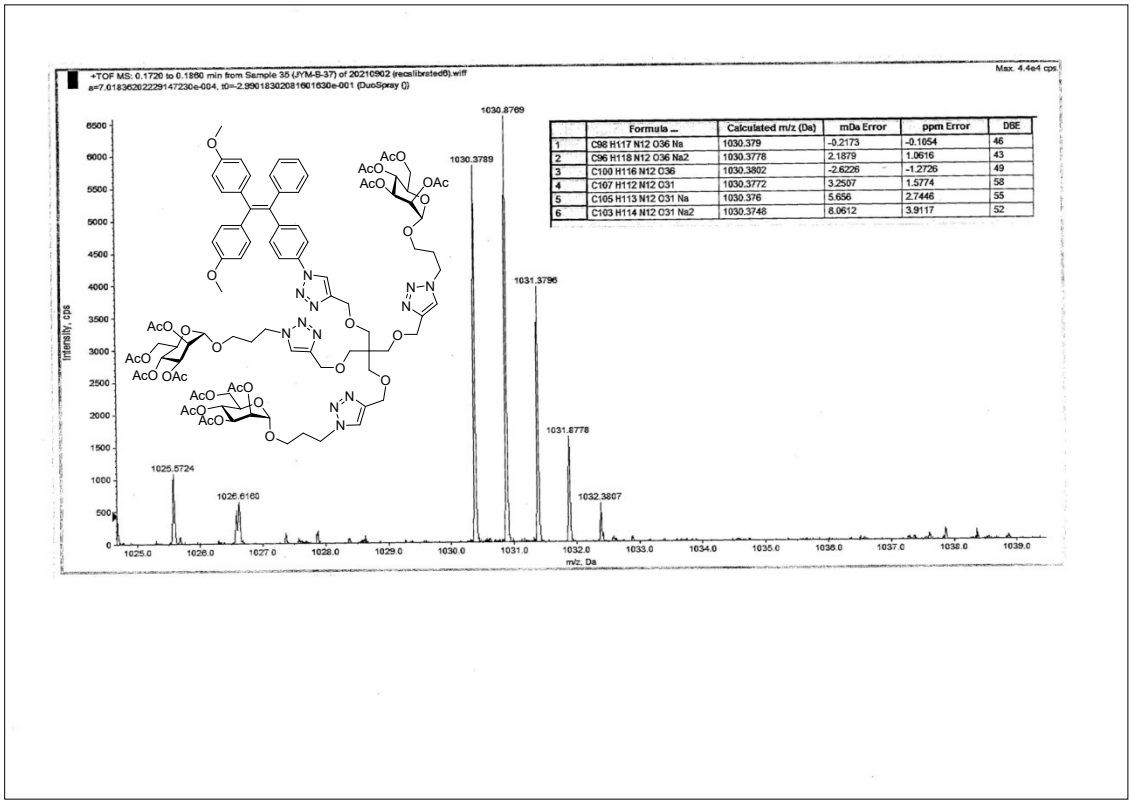


Fig. S25 HRMS spectra of compound **S3c**.

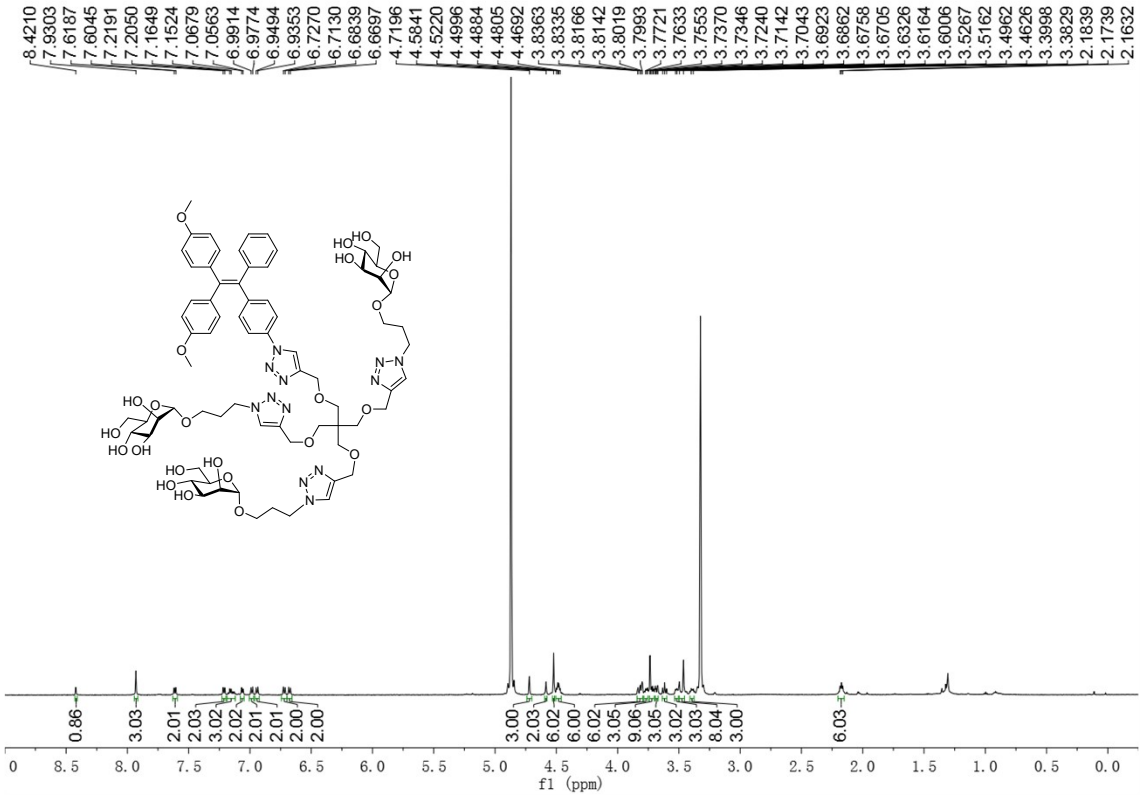


Fig. S26 ^{1}H NMR spectra of compound **TPE3M** (600 MHz, CD_3OD).

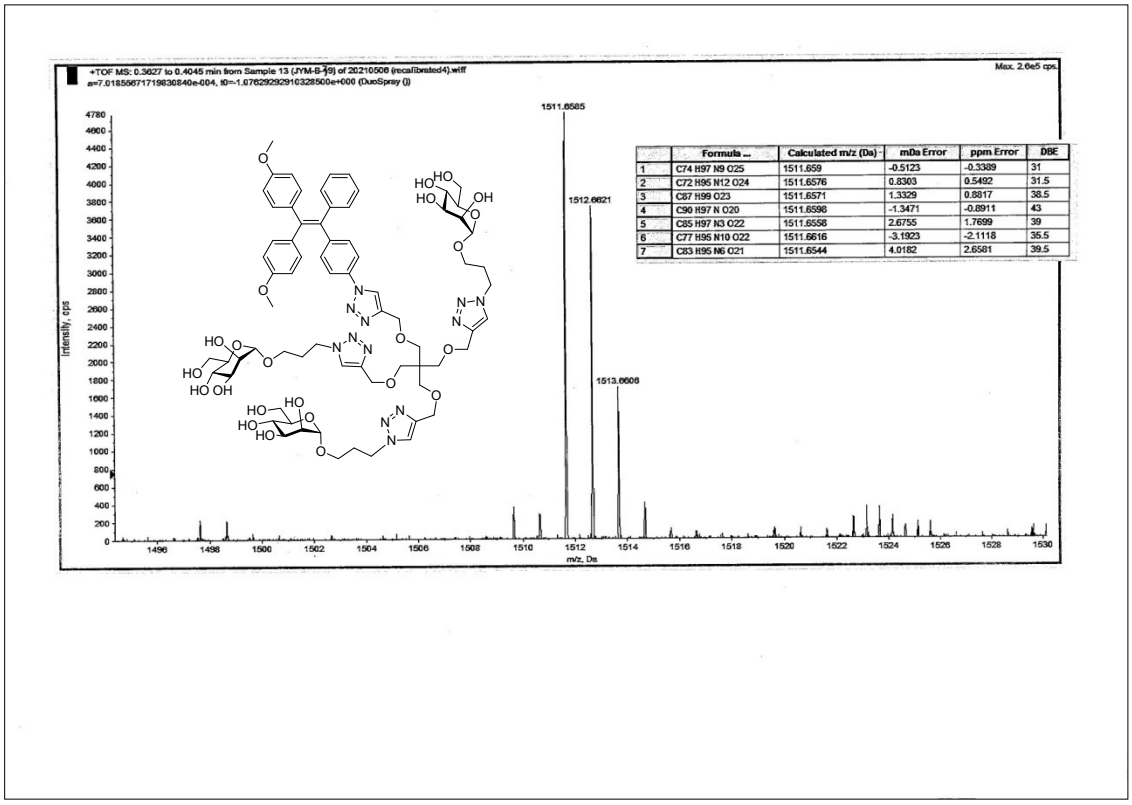


Fig. S27 HRMS spectra of compound **TPE3M**.

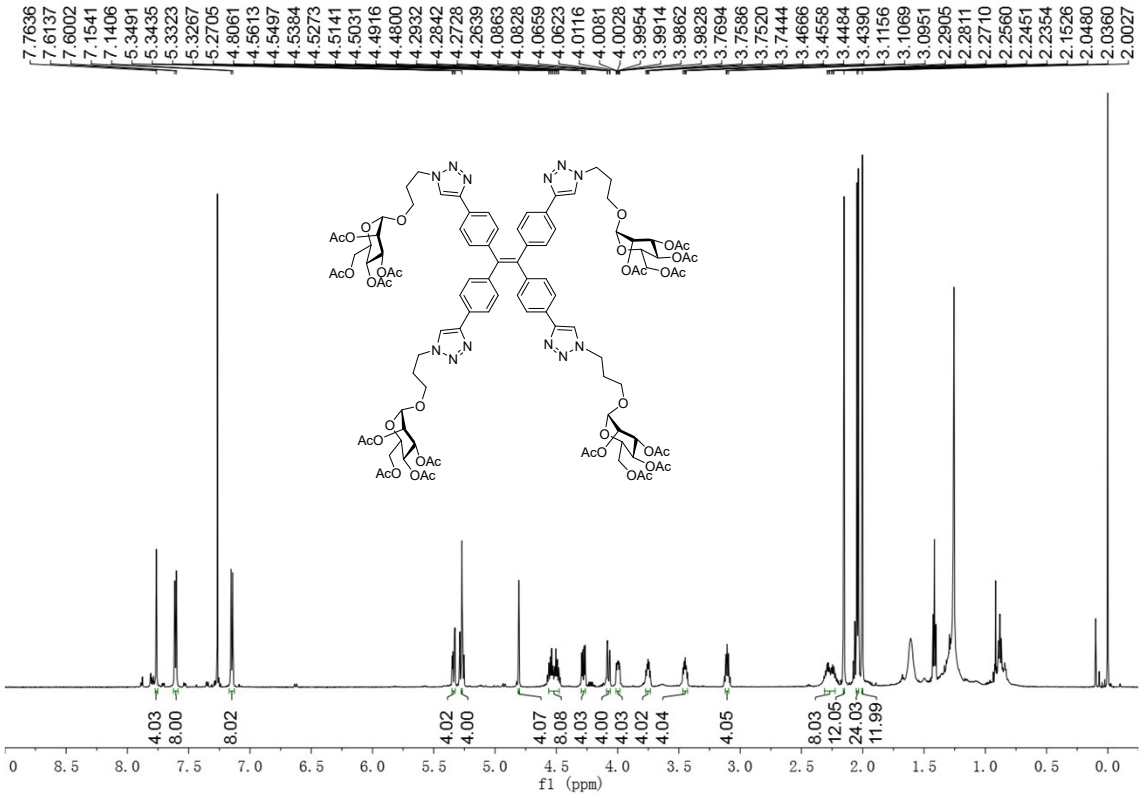


Fig. S28 ^{1}H NMR spectra of compound **S3d** (600 MHz, $CDCl_3$).

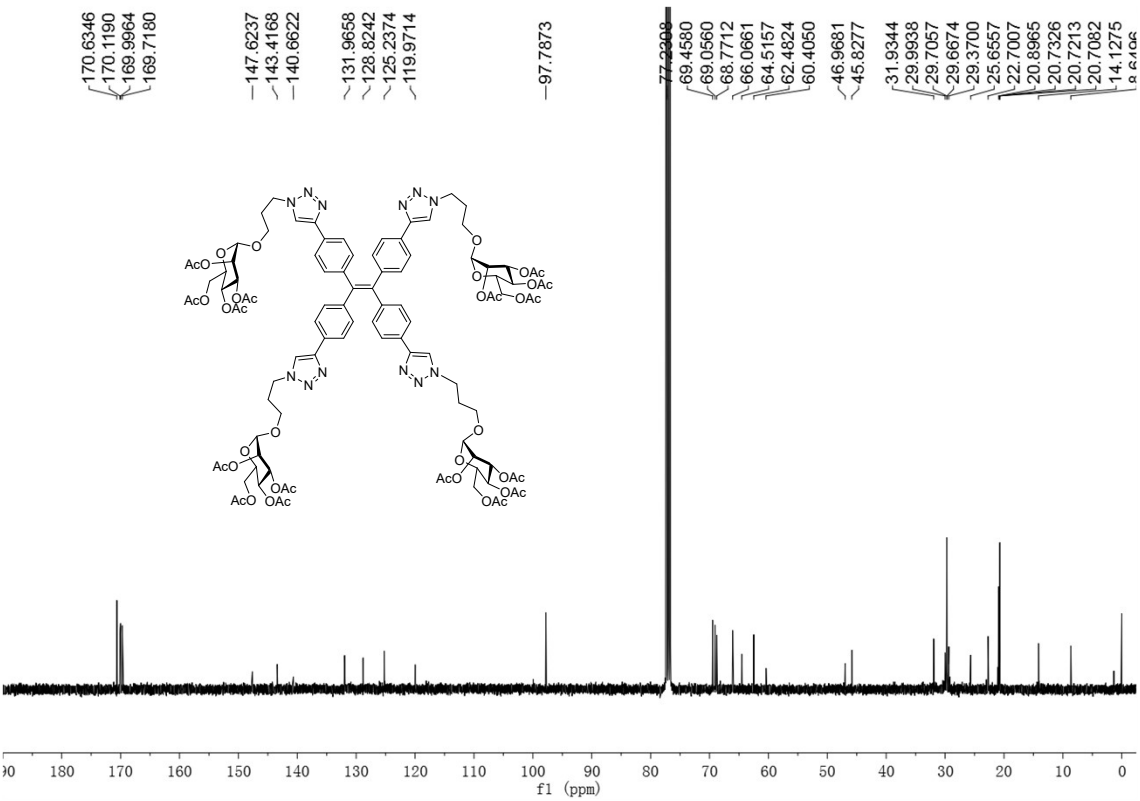


Fig. S29 ^{13}C NMR spectra of compound **S3d** (100 MHz, $CDCl_3$).

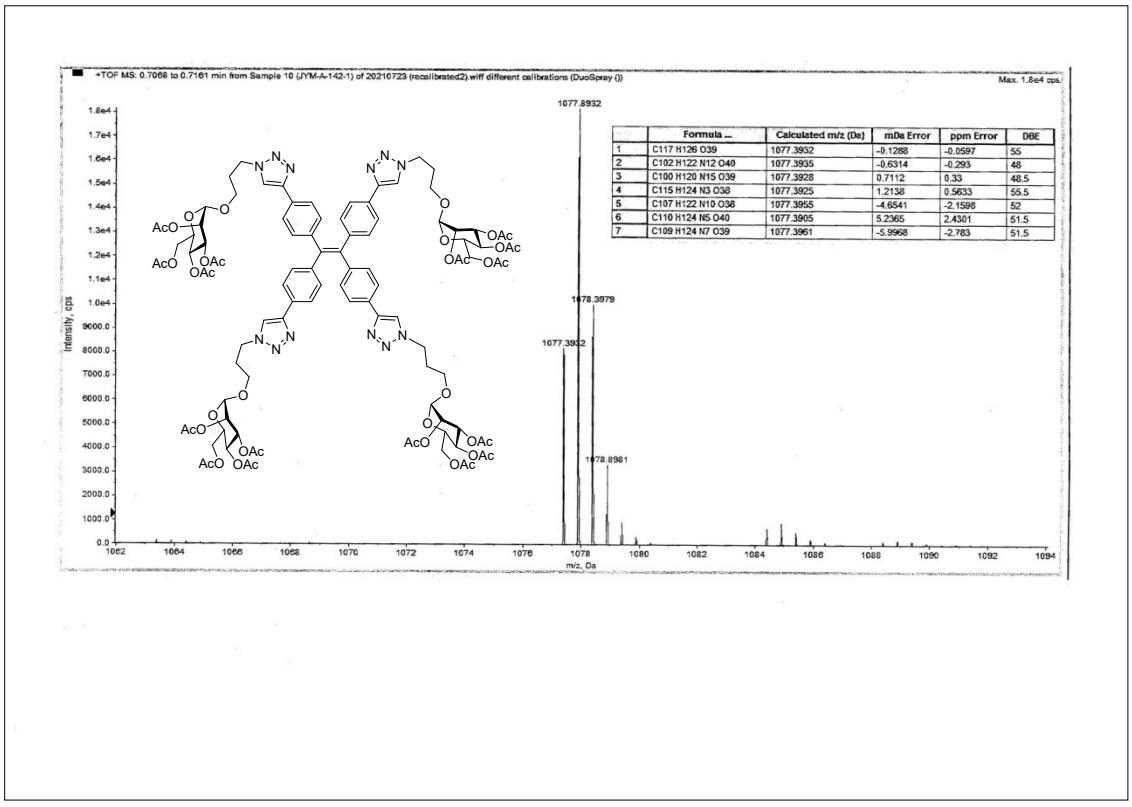


Fig. S30 HRMS spectra of compound **S3d**.

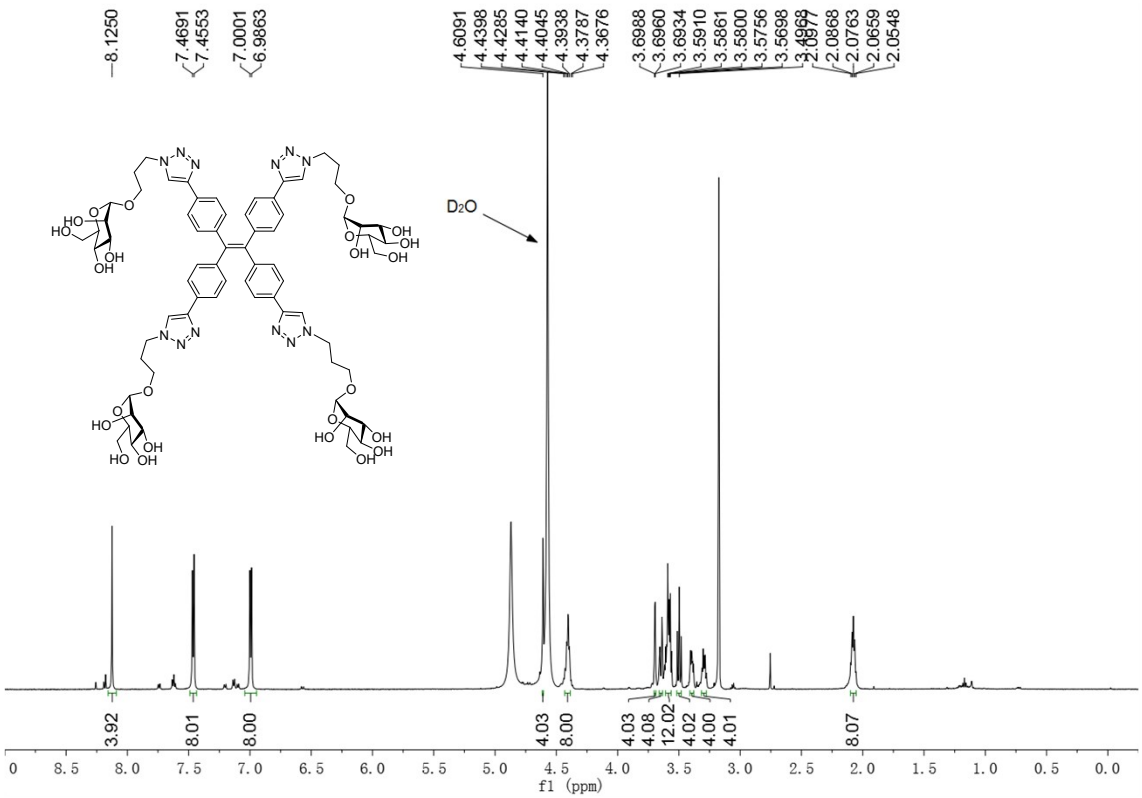


Fig. S31 ^{1}H NMR spectra of compound **TPE4M** (600 MHz, CD_3OD).

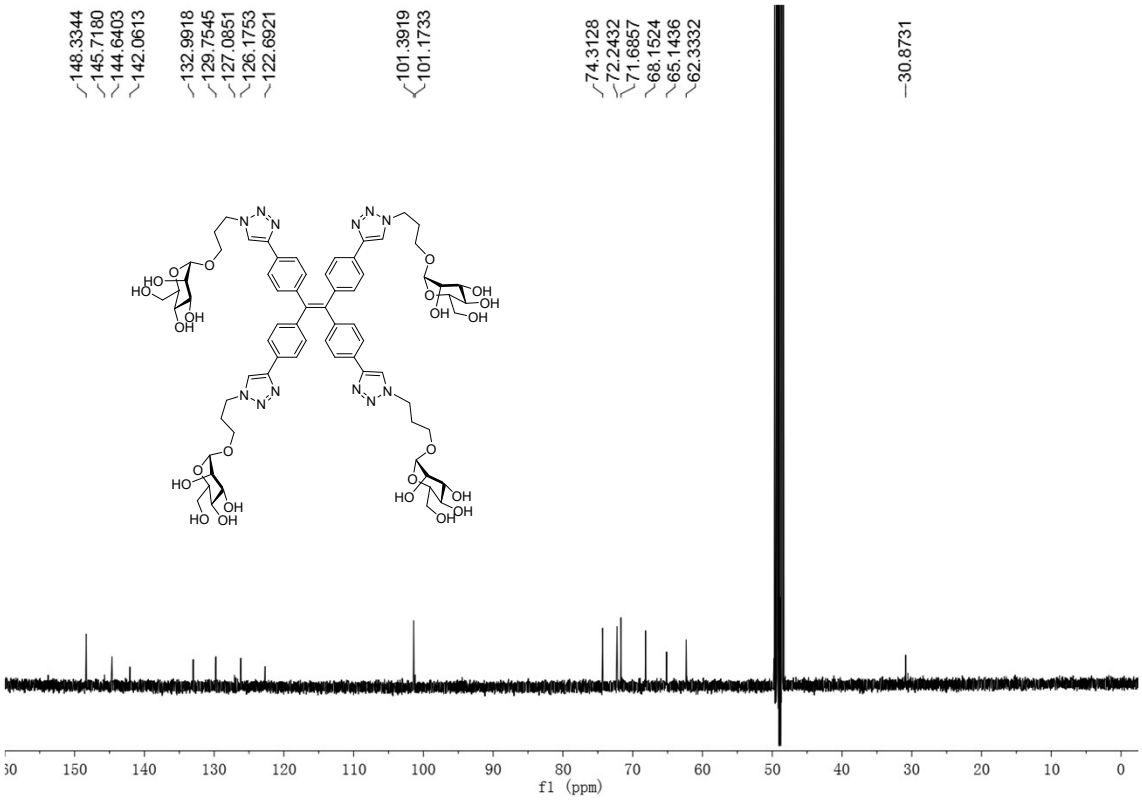
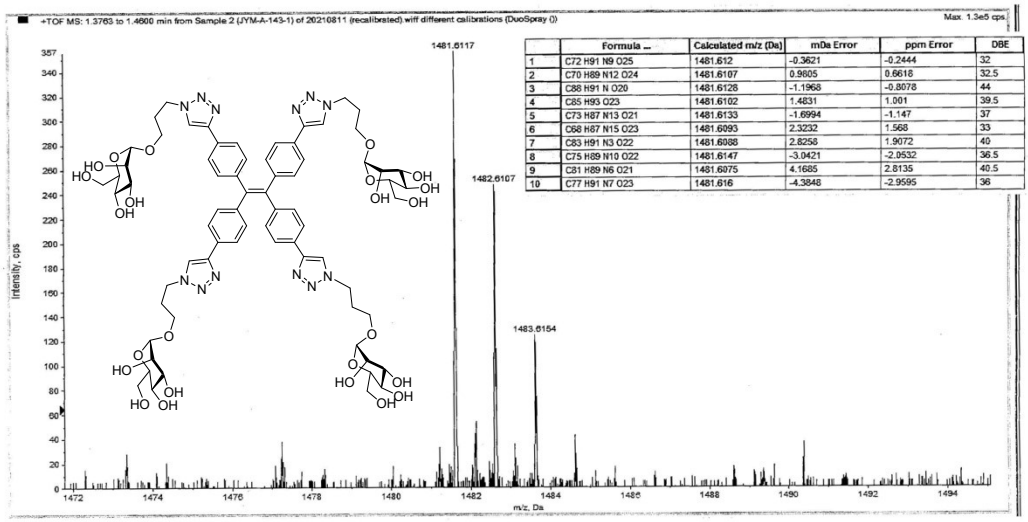


Fig. S32 ^{13}C NMR spectra of compound **TPE4M** (100 MHz, CD_3OD).



	Formula ...	Calculated m/z (Da)	mDa Error	ppm Error	DBE
1	C72 H91 N9 O25	1481.612	-0.3621	-0.2444	32
2	C70 H89 N12 O24	1481.6107	0.9805	0.6618	32.5
3	C88 H91 N O20	1481.6128	-1.1968	-0.8078	44
4	C85 H93 O23	1481.6102	1.4831	1.001	39.5
5	C73 H87 N13 O21	1481.6133	-1.6994	-1.147	37
6	C68 H87 N15 O23	1481.6093	2.3232	1.568	33
7	C83 H91 N3 O22	1481.6088	2.8258	1.9072	40
8	C75 H89 N10 O22	1481.6147	-3.0421	-2.0532	36.5
9	C81 H89 N6 O21	1481.6075	4.1685	2.8135	40.5
10	C77 H91 N7 O23	1481.616	-4.3848	-2.9595	36

Fig. S33 HRMS spectra of compound **TPE4M**.