Supporting Information for

Modular platform of Carbohydrates-modified Supramolecular Polymers Based on Dendritic Peptide Scaffolds

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Abbreviations

calc. calculated
DCM dichloromethane
DMF N,N-dimethylformamide
MeOH methanol
PyBOP Benzotriazol-1-yl-oxy-tripyrrolidinophosphonium-hexafluorophosphate
SEC size exclusion chromatography
TFA trifluoroacetic acid
DCC dicyclohexylcarbodiimide
DIC N,N'-Diisopropylcarbodiimide
TMS-CHN2 (Trimethylsilyl)diazomethane
HBTU O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
DIPEA N,N-diisopropylethylamine
TEA trimethylamine
HOBr Hydroxybzentriazole
TIPS triisopropylsilane
HATU 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HOAt 1-hydroxy-7-azabenzotriazole

Materials and Methods
All materials were used as purchased unless otherwise specified. N-methylmorpholine, N-benzyloxycarbonyl-6-aminohexanoic acid, TFA, DMF, N,N-diisopropylcarbodiimide, dimethyl sulfoxide-d6 (DMSO-d6), dicyclohexylcarbodiimide, (trimethylsilyl)diazomethane, HBTU and sodium methoxide were purchased from Sigma-Aldrich. ((tert-Butoxycarbonyl) aminoxy) acetic acid, N,N-Diisopropylethylamine, anhydrous ethanol, and CDCl3 were purchased from J&K Scientific. Chloroform, n-hexane, acetic acid, ethyl acetate, petroleum ether, and methanol were
purchased from Sinopharm Chemical Reagent Co., Ltd. Maltotriose, maltpentaose, maltoheptaose, sialyl Lewis-X, and mannotriose were purchased from Beijing InnoChem Science & Technology Co., Ltd.

**Thin-layer chromatography (TLC):** Analytes were detected by using silica-coated aluminum plates 60 F254 by Merck KGaA (Darmstadt, Germany) with fluorescent indicator and irradiating with UV light at a wavelength of 254 nm to observe the absorption. Staining of carbohydrates or carbohydrate-containing substances was performed using a 1:1 mixed solution of 50 mL of ethanol, 2.7 mL of concentrated sulfuric acid, and 0.1 mL of m-methoxyphenol. Vanillin-staining (detecting double bond or hydroxyl group) was performed using a mixed solution of 100 mL of methanol solution, 1.0 g of vanillin, 12 mL of acetic acid and 4 mL of concentrated sulfuric acid. Ninhydrin-staining (detecting amines) was performed using 1.5 g of ninhydrin dissolved in 500 mL of methanol and 15 mL of acetic acid. Color reaction proceeds upon heating.

**Dynamic light scattering (DLS):** DLS was taken by Zeta sizer Nano ZS90 from Malvern Instruments.

**Size exclusion chromatography (SEC):** SEC was performed using the Sephadex LH-20 (GE Healthcare Bio-Sciences) as the stationary phase and DMF (HPLC grade) as the mobile phase. The product was analyzed using thin layer chromatography (TLC).

**Nuclear Magnetic Resonance (NMR):** The 1H and 13C-NMR-spectra were performed on an Avance II 400 (400 MHz) or Avance III 600 (600 MHz) by Bruker (Rheinstätten, Germany). The measurements were carried out in deuterated solvents. The measured coupling constants were calculated in Hertz (Hz) by using chemical shifts (δ/ppm) relative to residual solvent protons. The spectra were analyzed by using the software MestReNova 10.0.2 of MESTRELAB RESEARCH (Santiago de Compostela, Spain). The multiplicity of the signals is reported as follows: bs = broad singlet, s = singlet, d = doublet, t = triplet, q = quadruplet and m = multiplet.

**Mass spectrometry:** The spectra were performed on Micro TOF by Bruker (Rheinstätten, Germany) and QTOF Ultima 3 by Micromass (Eschborn, Germany), using ESI (electrospray ionization).

**Transmission Electron Microscopy (TEM):** The TEM measurements were performed on a Tecnai T12 by FEI (Hillsboro, USA). Electron micrographs were recorded on a 4k × 4k CMOS camera by TVIPS (Oslo, Norway). The copper grids CF300-CU by Electron Microscopy Sciences (Hatfield, USA) were glow-discharged before use. 5 µL of the probes were adsorbed on the grid for 2 min. The grids were then stained for 1 min with 1.0% uranyl acetate by Polysciences (Warminster, USA), and the grids were dried by filter papers.

**Solid phase peptide synthesis (SPPS):** A CS136XT peptide synthesizer by CS Bio (Menlo Park, USA) was employed for SPPS. A 2 chloro-trityl ether-modified polystyrene resins by Iris Biotech (Marktredwitz, Germany) with loadings of 1.0–1.6 mmol/g and crosslinked (1% divinylbenzene) were used as solid support. SPPS grade reagents and solvents were used for peptide synthesis.1

**Cytotoxicity assay (CCK-8):** The cytotoxicity of carbohydrate-modified peptide supramolecular polymers was assessed by detecting the dehydrogenase activity of cells and using the CCK-8 kit. RAW264.7 cells were grown in RPMI 1640 medium supplemented with 10% FBS, 1% antibiotics, and incubating at 37 °C, 5% CO2. Different concentrations of supramolecular polymers (7.5 µg/mL ~ 125 µg/mL) were incubated with cells for 24 hours, and then 10% CCK-8 reagent was added to them and incubated for 2 hours. Absorbance at 450 nm was detected by absorption light microplate reader.
Enzyme-linked immunosorbent assay (ELISA): RAW264.7 cells were incubated with carbohydrate-modified peptide supramolecular polymers (10 μg/mL, 100μg/mL) for 24 h. After collected the supernatant solutions (1500 rpm, 10 min), IL-6 and TNF-α were detected by BioLegend ELISA kit. The experimental steps were as follows: The coated antibody was incubated overnight at 4 °C, then blocked the ELISA dilution for 2 h. After adding the standard or detection sample and incubate for 2 hours, the detection antibody was added and incubated for 1 h. Then the avidin-HRP was added and incubated for 30 minutes, and 3,3',5,5'-tetramethylbenzidine (TMB, catalyzed by HRP to produce a soluble blue product, absorbance at 370 nm) was employed for color reaction. After adding stop solution for TMB substrate (maximum absorbance change to 450 nm), the absorbance at 450 nm was detected by absorption light microplate reader.

Figure S1. Hydrodynamic sizes and TEM images of three-branched 3-M3 assemblies. Assembly was performed using a 25 µM aqueous solution (water) of triple-branched 3-M3 monomer at room temperature.

Figure S2. TEM images of 3-FITC assemblies. Self-assembly was performed using a 25 μM aqueous solution (water) of 3-FITC monomer at room temperature.
Figure S3. The cytotoxic effect of glycopeptide supramolecular polymers on macrophages. The control group used PBS buffer.

Figure S4. Cytokine release of macrophages induced by the two-branched glycopeptide supramolecular polymers. The production of a) TNF-α, and b) IL-6 after 24h incubation with 2-M3, 2-M5, and 2-M7. The control group used PBS buffer.

Synthesis of precursor

\[
\text{PL1: PL1 as prepared as described in previous work.}^{2}
\]

HR-TOF-MS (ESI, pos.), m/z: [M+H]\(^+\) 249.1813 (calc. 249.1809).

\(^1\)H NMR (400 MHz, Chloroform-\(d\)): \(\delta\) 6.79 (t, \(J = 5.9\) Hz, 1H), 3.50 (d, \(J = 5.3\) Hz, 4H), 3.36 (dt, \(J = 11.6, 6.0\) Hz, 5H), 3.05 (q, \(J = 6.0\) Hz, 2H), 2.63 (t, \(J = 5.8\) Hz, 2H), 1.37 (s, 9H).

\(^13\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 156.03, 78.03, 73.58, 69.99, 69.96, 69.61, 41.84, 28.69.
Synthesis of P1: P0 (410 mg, 2.14 mmol) was dissolved in a mixed solvent of toluene and methanol (10 mL/1 mL), and trimethylsilyldiazomethane (TMS-CHN$_2$) (1.39 mL, 2.19 mmol, 2.0 M in n-hexane) was slowly added to P0. The solution was stirred at room temperature for 1 h. The solvent was removed by rotary evaporation, and the product was purified by silica gel column chromatography with n-hexane/ethyl acetate (3/1, v/v), and dried through rotary evaporated.

HR-TOF-MS (ESI, pos.), m/z: [M+Na]$^+$ 228.0833 (calc. 228.0842).

$^1$H NMR (400 MHz, Chloroform-$d$): $\delta$ 7.79 (s, 1H), 4.46 (s, 2H), 3.80 (s, 3H), 1.49 (s, 9H).

$^{13}$C NMR (100 MHz, Chloroform-$d$): $\delta$ 170.16, 156.31, 82.31, 72.62, 52.18, 28.29.

Synthesis of P2: P1 (436 mg, 2.13 mmol) was dissolved in 10 mL of N,N-Dimethylformamide (DMF), and sodium hydride (98 mg, 2.65 mmol) was added. The solution was stirred at room temperature for 20 min. Then methyl iodide (160 $\mu$L, 2.57 mmol) was added slowly, with stirring continued for 2 h at room temperature. The solvent was removed by rotary evaporation and chloroform was added. It was washed three times with saturated brine, dried with anhydrous sodium sulfate, filtered and spin-dried and passed through a column. The product was purified by silica gel column chromatography with n-hexane/ethyl acetate (3/1, v/v) to obtain 189 mg of product, and dried through rotary evaporated.

HR-TOF-MS (ESI, pos.), m/z: [M+Na]$^+$ 242.0994 (calc. 242.0999).

$^1$H NMR (400 MHz, Chloroform-$d$): $\delta$ 4.50 (s, 2H), 3.80 (s, 3H), 3.23 (s, 3H), 1.51 (s, 9H).

$^{13}$C NMR (100 MHz, Chloroform-$d$): $\delta$ 169.73, 157.74, 82.01, 71.88, 51.93, 38.39, 28.20.

Synthesis of P3: 35 mg of P2 was dissolved in 4 mL of methanol/water (3/1, v/v). The flask was settled at 5 °C with stirring for 30 min. Sodium hydroxide was dissolved in methanol to make a 28% w/v solution, then added 30 $\mu$L to the cooled P2 solution, and stirred at 5 °C for 1 h. The system was warmed at room temperature and neutralized with acid resin. After filtration and drying, 15 mg of the product was obtained.

HR-TOF-MS (ESI, pos.), m/z: [M+Na]$^+$ 228.1679 (calc. 228.0642).

$^1$H NMR (400 MHz, Chloroform-$d$): $\delta$ 4.50 (s, 2H), 3.80 (s, 3H), 3.23 (s, 3H), 1.51 (s, 9H).

$^{13}$C NMR (100 MHz, Chloroform-$d$): $\delta$ 169.73, 157.74, 82.01, 71.88, 51.93, 38.39, 28.20.

Synthesis of P3-NHS or P0-NHS: 1 eq of P3 or P0 was dissolved in DCM, and added 1.5 eq of
NHS. After stirring, dicyclohexylcarbodiimide (DCC) (1.5 eq) was added to the reaction system, and the mixture was stirred at room temperature for 1 h. The product was purified by silica gel column chromatography (gradient elution with ethyl acetate and petroleum ether), and dried through rotary evaporation.

**Synthesis of Fmoc-FFF:** Fmoc-FFF was prepared as described in previous work.\(^1\)

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 12.79\) (bs, 1H), 8.36 (d, 1H), 8.07 (d, 1H), 7.87 (d, 2H), 7.60 (t, 2H), 7.54 (d, 1H), 7.40 (tdd, 2H), 7.33 - 7.03 (m, 17H), 4.58 (td, 1H), 4.46 (td, 1H), 4.20 (td, 1H), 4.16 - 4.05 (m, 3H), 3.10 - 2.75 (m, 5H), 2.70 - 2.62 (m, 1H).

**Synthesis of two-branched oligosaccharide-tripeptide.**

Synthesis of A3: Fmoc-FFF (200 mg, 0.293 mmol) was dissolved in DMF, Ethyl cyanoglyoxylate-2-oxime (42 mg, 0.293 mmol) was added. Then \(N,N'\)-Diisopropylcarbodiimide (DIC) was slowly added in an ice-water bath. After stirring for 1 h in an ice-water bath, the DMF solution of PL1 was slowly added. Stirring in ice-water bath for 1 h, then the mixture was slowly warmed to room temperature overnight. The product was roto-evaporated to remove the solvent, and directly added Trifluoroacetic acid (TFA) / Dichloromethane (DCM) (1/1, \(v/v\)) for deprotection, then dried through rotary evaporation.

A2, HR-TOF-MS (ESI, pos.), m/z: \([\text{M+Na}]^+ 934.4369\) (calc. 934.4361).

A3, HR-TOF-MS (ESI, pos.), m/z: \([\text{M+Na}]^+ 834.3824\) (calc. 834.3837).

A4, HR-TOF-MS (ESI, pos.), m/z: \([\text{M+Na}]^+ 612.3156\) (calc. 612.3156).

A4, \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta 8.52\) (d, \(J = 8.3\) Hz, 1H), 8.17 (s, 1H), 7.70 (d, \(J = 6.8\) Hz, 1H), 7.04 - 7.34 (m, 15H), 4.48 (s, 2H), 3.54 - 2.60 (m, 17H), 2.46 (s, 1H), 1.23 (t, \(J = 7.3\) Hz, 2H).

Synthesis of A5: A4 (37 mg, 0.063 mmol) was dissolved in DMF. Then P0-NHS (36 mg, 0.126 mmol) was added, and the mixture was stirred at room temperature for 24 h. The product was roto-evaporated to remove the solvent and separated by SEC with the DMF as eluent.

HR-TOF-MS: (ESI, pos.), m/z: \([\text{M+Na}]^+ 958.4531\) (calc. 958.4532).

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta 10.25\) (m, 2H), 8.52 - 7.83 (m, 4H), 7.53 - 6.86 (m, 15H), 4.52
(m, 3H), 4.15 (s, 1H), 4.12 - 3.94 (m, 3H), 3.50 (d, J = 6.1 Hz, 3H), 3.46 - 3.02 (m, 13H), 3.02 - 2.62 (m, 6H), 1.40 (d, J = 5.0 Hz, 17H), 1.27 - 1.14 (m, 2H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 170.93, 168.44, 129.67, 129.58, 128.50, 128.40, 126.67, 81.05, 74.85, 69.99, 53.64, 38.64, 28.46, 28.42, 28.38, 7.64.

Synthesis of A6: The A5 was added TFA/DCM (1/1, v/v) for deprotection. HR-TOF-MS: (ESI, pos.), m/z: [M+Na]$^{+}$ 758.3486 (calc. 758.3484).

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.40 - 8.00 (m, 5H), 7.31 - 7.11 (m, 15H), 4.63 - 4.44 (m, 3H), 4.38 - 4.20 (m, 3H), 3.50 - 3.22 (m, 19H).

Synthesis of 2-M3: A6 (5 mg, 6.79 $\mu$mol) was dissolved in DMF, and 40 $\mu$mol of maltotriose was added. After adjusted the pH of the mixture to 3.7 with acetic acid, the mixture was stirred at room temperature for 48 h. The excess maltotriose was removed by dialysis, then the solution was dried by lyophilization.

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.55 - 7.45 (m, 1H), 7.39 - 6.83 (m, 15H), 5.50 (s, 2H), 5.40 (s, 2H), 5.00 (s, 4H), 4.52 (s, 5H), 4.37 (s, 7H), 3.12 - 2.66 (m, 11H), 1.36 - 1.04 (m, 7H).

Synthesis of 2-M5: Similar with 2-M3.

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.27 - 7.88 (m, 3H), 7.30 - 7.06 (m, 15H), 5.40 (s, 1H), 4.66 - 3.75 (m, 7H), 3.04 - 2.61 (m, 7H), 1.42 - 1.02 (m, 5H).

Synthesis of 2-M7: Similar with 2-M3.

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.22 (s, 2H), 7.99 (s, 1H), 7.22 (d, J = 9.5 Hz, 15H), 5.87 (s, 1H), 5.58 (s, 8H), 5.52 (s, 4H), 5.41 (s, 3H), 5.02 (d, J = 11.5 Hz, 12H), 4.72 - 4.18 (m, 17H), 4.08 (s, 6H), 3.83 (s, 7H), 3.64 (s, 21H), 3.53 - 3.01 (m, 75H), 2.01 (d, J = 13.6 Hz, 11H), 1.35 - 1.03 (m, 11H).

Synthesis of three-branched oligosaccharides-tripeptide.
Synthesis of **C2**: C2 was prepared as described in previous work.¹

![Diagram of C2](image)

Synthesis of **D1**: D1 was prepared as described in previous work.³

![Diagram of D1](image)

Synthesis of **D2**: Fmoc-FFF (168 mg, 0.248 mmol) was dissolved in DMF, and Ethyl cyanoglyoxylate-2-oxime (42 mg, 0.293 mmol) was added, and then DIC was slowly added in an ice-water bath. After stirring for 1 h, D1 (100 mg, 0.124 mmol) in DMF solution was slowly added. After stirred in ice-water bath for 1 h, the mixture was slowly warmed to room temperature overnight. After roto-evaporated to remove the solvent, the product was deprotected by piperidine, and separated by semi-preparative HPLC with methanol/water (2/1, v/v). The product was acidified with 10 mM HCl, then the solution was dried by lyophilization.

Maldi-TOF-MS: m/z: [M+Na]⁺ 1268.5 (calc. 1269).

¹H NMR (400 MHz, DMSO-d₆): δ 8.66 (t, J = 8.8 Hz, 1H), 8.43 (d, J = 8.2 Hz, 1H), 8.08 - 7.79 (m, 3H), 7.33 - 7.12 (m, 15H), 7.02 (s, 1H), 4.73 - 4.60 (m, 1H), 4.51 (q, J = 7.7 Hz, 1H), 3.60 – 3.20 (s, 63H), 2.04 (t, J = 7.4 Hz, 2H), 1.41 (q, J = 7.5 Hz, 2H), 1.29 (q, J = 7.3 Hz, 2H), 1.16 (d, J = 7.5 Hz, 2H).
Synthesis of B4: B4 was prepared as described in previous work. B4 was synthesized by solid phase peptide synthesis on a CS136XT by CS Bio (Menlo Park, USA). A TentaGel R Trityl resin loaded with Bis-(2-aminoethyl)-ether (0.5 g, 0.5 mmol/g loading capacity, 0.25 mmol), purchased from Rapp Polymere (Tübingen, Germany), was used as solid support. The chain was elongated using the Fmoc-protected amino acids, Fmoc-aminohexanoic acid (Fmoc-Ahx-OH) and 3 × Fmoc-L-Phe-OH. For the coupling reactions, amino acid (1.0 mmol, 4.0 eq. relative to resin loading capacity) were pre-activated in DMF with HBTU (1.0 mmol, 4.0 eq.), HOBt (1.0 mmol, 4.0 eq.) and DIPEA (1.5 mmol, 6.0 eq.). The solution was then transferred to the reactor and shook during 40 min for the actual coupling. After several washing steps, the cleavage of the terminal Fmoc-group was achieved by treatment with a solution of piperidine in DMF (20 %) for 5 min and another 20 min. After the attachment of the third phenylalanine, the free N-terminus was reacted with a mixture of C2 (1.0 mmol, 4.0 eq.), HATU (1.0 mmol, 4.0 eq.) and HOAt (1.0 mmol, 4.0 eq.) in DMF. Finally, B4 could be cleaved from the resin using a mixture of TFA/TIPS/H2O (9.5/0.25/0.25). The filtrate was codistilled three times with toluene, the remainder suspended in water and subjected to lyophilization.

HR-TOF-MS (ESI, pos.), m/z: [M+Na]+ 1042.3571 (calc. 1042.3595).

1H NMR (600 MHz, DMSO-d6): δ 8.28 - 8.14 (m, 3H), 7.85 (d, J = 6.4 Hz, 5H), 7.29 - 7.08 (m, 14H), 4.51 (dd, J = 8.6, 4.7 Hz, 2H), 4.46 (td, J = 8.5, 6.4 Hz, 1H), 4.01 (d, J = 1.8 Hz, 4H), 3.78 (d, J = 4.2 Hz, 2H), 3.64 (s, 5H), 3.56 (s, 2H), 3.42 (d, J = 5.8 Hz, 3H), 3.39 (s, 3H), 3.23 (d, J = 5.7 Hz, 2H), 3.06 - 2.88 (m, 7H), 2.88 - 2.80 (m, 1H), 2.80 - 2.73 (m, 1H), 2.73 - 2.64 (m, 1H), 2.05 (t, J = 7.5 Hz, 2H), 1.49 - 1.40 (m, 2H), 1.29 (d, J = 7.2 Hz, 2H), 1.15 (d, J = 7.2 Hz, 2H).

13C NMR (150 MHz, DMSO-d6): δ 178.54, 178.15, 172.27, 170.53, 170.31, 168.76, 166.15, 137.60, 137.58, 137.37, 129.65 - 128.74 (m), 128.52 - 127.50 (m), 126.76 - 125.88 (m), 118.30, 116.31, 69.16, 66.31, 55.40 - 53.30 (m), 52.57, 38.65, 38.46, 38.13, 38.00, 37.51, 35.30, 33.44, 32.15, 28.80, 26.07, 25.01.

Synthesis of B5: B4 (20 mg, 19.60 μmol) was dissolved in DMF. After adding P0-NHS, the mixture was stirred for 24h at room temperature. The product was roto-evaporated to remove the solvent, and was separated by SEC with the DMF as eluent.

HR-TOF-MS (ESI, pos.), m/z: [M+Na]+ 1215.4275 (calc. 1215.4283).

1H NMR (400 MHz, DMSO-d6): δ 10.31 (s, 1H), 8.28 - 8.08 (m, 3H), 8.02 (t, J = 5.6 Hz, 1H), 7.80 (td, J = 5.7, 2.6 Hz, 2H), 7.40 - 6.94 (m, 15H), 4.51 (ddd, J = 17.8, 8.7, 4.8 Hz, 3H), 4.17 (s, 2H), 4.01 (s, 4H), 3.78 (d, J = 1.9 Hz, 2H), 3.65 (s, 5H), 3.53 - 3.13 (m, 18H), 3.13 - 2.62 (m, 8H), 2.05 (t, J = 7.5 Hz, 2H), 1.42 (s, 11H), 1.30 (t, J = 7.6 Hz, 2H), 1.25 - 1.05 (m, 2H).

13C NMR (100 MHz, DMSO-d6): δ 178.59, 172.65, 170.95, 170.70, 169.18, 168.51, 138.01, 129.71, 129.62, 129.56, 128.54, 128.46, 128.31, 126.75, 126.70, 126.64, 81.10, 75.19, 69.40, 69.05, 54.49, 54.32, 52.98, 38.89, 38.84, 38.63, 38.47, 37.96, 35.69, 33.87, 32.58, 29.20, 28.39, 26.48, 25.44.

Synthesis of B6: In the mixed solution of MeOH and THF (1:1), 19 mg of B5 was added. Then 33 eq of 0.1 M LiOH was slowly added, and the mixture was stirred at room temperature for 1 h. After neutralizing with an equal amount of HCl (1 M), the solvent was removed by rotary evaporation, and the mixture was separated by SEC with the DMF as eluent, then the solution was dried by lyophilization.
Synthesis of **B7**: **B6** (20 mg, 18.96 μmol) and **D2** (48 mg, 37.31 μmol) were dissolved in DMF, then DIPEA (6.5 μL, 37.31 μmol) and Ethyl cyanoglyoxylate-2-oxime (5.3 mg, 37.31 μmol) were added. After stirring for 5 min, DIC (5.74 μL, 37.31 μmol) was added. The solution was stirred overnight at room temperature, and then the solvent was removed by rotary evaporation. The product was separated by SEC with the DMF as eluent.

$^1$H NMR (400 MHz, DMSO-d$_6$): δ 8.17 (s, 9H), 7.80 (d, $J = 5.9$ Hz, 3H), 7.37 - 6.89 (m, 50H), 4.64 - 4.48 (m, 10H), 4.16 (s, 1H), 3.59 (s, 17H), 3.56 - 3.44 (m, 100H), 3.42 (d, $J = 5.3$ Hz, 18H), 3.23 (s, 21H), 3.13 - 2.60 (m, 27H), 2.02 (s, 6H), 1.41 (d, $J = 6.1$ Hz, 11H), 1.33 - 1.21 (m, 7H), 1.20 - 1.06 (m, 6H).

Synthesis of **B8**: The **B7** was added TFA/DCM (1/1, v/v) for deprotection.

**Synthesis of 3-triM**: Similar with 2-M3.

$^1$H NMR (400 MHz, DMSO-d$_6$): δ 8.61 - 7.98 (m, 7H), 7.80 (s, 3H), 7.40 - 6.87 (m, 45H), 4.56 (s, 5H), 4.48 (s, 3H), 4.42 (s, 1H), 3.59 (s, 17H), 3.56 - 3.48 (m, 87H), 3.42 (d, $J = 5.2$ Hz, 19H), 3.33 (s, 43H), 3.23 (s, 22H), 2.93 (s, 21H), 2.01 (d, $J = 7.1$ Hz, 6H), 1.40 (s, 7H), 1.26 (d, $J = 12.4$ Hz, 9H), 1.18 - 0.93 (m, 7H).

**Synthesis of 3-SA**: Similar with 2-M3.

$^1$H NMR (400 MHz, DMSO-d$_6$): δ 8.17 (s, 10H), 7.80 (s, 3H), 7.35 - 6.93 (m, 45H), 6.85 (d, $J = 2.4$ Hz, 2H), 6.64 (d, $J = 8.9$ Hz, 1H), 5.32 (s, 3H), 4.68 - 4.42 (m, 9H), 3.59 (s, 24H), 3.49 (d, $J = 4.0$ Hz, 75H), 3.41 (s, 17H), 3.23 (s, 18H), 3.08 - 2.61 (m, 20H), 2.12 - 1.93 (m, 10H), 1.36 (s, 26H), 1.23 (s, 44H), 1.16 (s, 22H).
Synthesis of 3-M3: Similar with 3-triM and 3-SA.

**B11**, HR-TOF-MS (ESI, pos.), m/z: [M+Na]+ 1229.4446 (calc. 1229.4440).

1H NMR (400 MHz, DMSO-d6): δ 8.45 - 7.64 (m, 7H), 7.21 (dd, J = 11.7, 3.8 Hz, 17H), 4.46 (d, J = 5.9 Hz, 4H), 4.27 (s, 2H), 3.89 (d, J = 9.5 Hz, 5H), 3.53 - 3.14 (m, 33H), 3.07 (s, 3H), 3.04 - 2.61 (m, 11H), 2.04 (t, J = 7.4 Hz, 4H), 1.43 (s, 11H), 1.30 (s, 3H), 1.15 (d, J = 6.5 Hz, 3H).

**B12**, 1H NMR (400 MHz, DMSO-d6): δ 8.19 (s, 8H), 7.80 (s, 4H), 7.40 - 6.83 (m, 45H), 4.45 - 4.64 (m, 8H), 3.59 (s, 12H), 3.49 (t, J = 2.8 Hz, 79H), 3.22 (s, 22H), 2.02 (s, 9H), 1.58 - 1.38 (m, 12H), 1.25 (d, J = 16.1 Hz, 20H), 1.14 (s, 9H), 0.84 (d, J = 7.0 Hz, 5H).

**B13**, 1H NMR (400 MHz, DMSO-d6): δ 8.47 - 8.02 (m, 10H), 7.79 (d, J = 6.2 Hz, 4H), 7.31 - 6.89 (m, 45H), 4.70 - 4.37 (m, 9H), 4.26 (s, 1H), 3.59 (s, 12H), 3.49 (t, J = 2.8 Hz, 80H), 3.41 (dd, J = 5.8, 3.6 Hz, 14H), 3.23 (s, 17H), 3.06 (s, 2H), 3.05 - 2.97 (m, 9H), 2.97 - 2.88 (m, 9H), 2.02 (t, J = 6.4 Hz, 6H), 1.64 (p, J = 5.7 Hz, 5H), 1.55 (q, J = 5.5 Hz, 3H), 1.42 (s, 11H), 1.32 - 1.21 (m, 8H), 1.13 (d, J = 8.7 Hz, 6H).

**B14**, 1H NMR (400 MHz, DMSO-d6): δ 8.50 - 8.00 (m, 8H), 7.80 (s, 4H), 7.40 - 6.83 (m, 45H), 4.62 - 4.43 (m, 8H), 3.59 (s, 12H), 3.49 (t, J = 2.8 Hz, 79H), 3.22 (s, 22H), 2.02 (s, 9H), 1.60 - 1.38 (m, 12H), 1.32 - 1.21 (m, 20H), 1.19 - 1.02 (m, 9H), 0.85 (t, J = 6.7 Hz, 5H).

**3-M3**, 1H NMR (400 MHz, DMSO-d6): δ 8.21 (m, 7H), 7.79 (s, 3H), 7.34 - 6.88 (m, 45H), 4.71 - 4.36 (m, 11H), 4.19 (d, J = 4.2 Hz, 2H), 3.03 - 2.77 (m, 19H), 2.01 (d, J = 7.5 Hz, 8H), 1.41 (d, J = 7.4 Hz, 10H), 1.19 - 1.05 (m, 13H).
Synthesis of 3-FITC: B4 (25 mg, 24.5 μmol) and FITC (95 mg, 245 μmol) was added to a 10 mL round-bottomed flask and dissolved in DMF. Then a catalytic amount of TEA was added. The reaction was stirred overnight at room temperature. After the reaction was completed, the mixture was dialyzed for 2 d. After lyophilization and demethylation, the product was reacted with D2 (Similar with B13). And the final product was purified by semi-preparative HPLC with methanol/water (2/1, v/v), then dried by lyophilization.

B16, $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.23 (d, $J = 2.0$ Hz, 3H), 8.06 - 7.62 (m, 7H), 7.35 - 7.01 (m, 15H), 6.81 - 6.63 (m, 17H), 6.63 - 6.44 (m, 12H), 4.53 (d, $J = 18.7$ Hz, 2H), 4.00 - 3.78 (m, 4H), 3.78 - 3.66 (m, 6H), 3.41 (s, 3H), 3.23 (d, $J = 7.4$ Hz, 1H), 3.12 - 2.78 (m, 15H), 2.19 (s, 2H), 1.69 - 1.28 (m, 8H), 1.28 - 1.17 (m, 2H).

3-FITC, $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.70 - 6.79 (m, 45H), 6.75 - 6.22 (m, 9H), 3.69 - 3.36 (m, 108H), 3.00 (s, 18H), 1.22 - 1.19 (m, 22H).
Figure S1. Mass spectrum of PL1.

Figure S2. $^1$H-NMR spectrum (400 MHz, CDCl$_3$) of PL1.

Figure S3. $^{13}$C-NMR spectrum (100 MHz, DMSO-$d_6$) of PL1.
Figure S4. Mass spectrum of P1.

Figure S5. $^1$H-NMR spectrum (400 MHz, CDCl$_3$) of P1.
Figure S6. $^{13}$C-NMR spectrum (100 MHz, CDCl$_3$) of P1.

Figure S7. COSY spectrum (400 MHz, CDCl$_3$) of P1.

Figure S8. HSQC spectrum (400 MHz, CDCl$_3$) of P1.
Figure S9. HMBC spectrum (400 MHz, CDCl₃) of P1.

Figure S10. Mass spectrum of P2.
Figure S11. $^1$H-NMR spectrum (400 MHz, CDCl$_3$) of P2.

Figure S12. $^{13}$C-NMR spectrum (400 MHz, CDCl$_3$) of P2.
Figure S13. HSQC spectrum (400 MHz, CDCl$_3$) of P2.

Figure S14. HMBC spectrum (400 MHz, CDCl$_3$) of P2.
Figure S15. Mass spectrum of P3.

Figure S16. $^1$H-NMR spectrum (400 MHz, CDCl$_3$) of P3.
Figure S17. $^{13}$C-NMR spectrum (400 MHz, CDCl$_3$) of P3.

Figure S18. $^1$H-NMR spectrum (400 MHz, DMSO-$d_6$) of Fmoc-FFF.
Figure S19. Mass spectrum of A2.

Figure S20. Mass spectrum of A3.

Figure S21. Mass spectrum of A4.
Figure S22. $^1$H-NMR spectrum (400 MHz, DMSO-$d_6$) of A4.

Figure S23. Mass spectrum of A5.
**Figure S24.** $^1$H-NMR spectrum (400 MHz, DMSO-$d_6$) of A5.

**Figure S25.** $^{13}$C-NMR spectrum (100 MHz, DMSO-$d_6$) of A5.
Figure S26. Mass spectrum of A6.

Figure S27. $^1$H-NMR spectrum (400 MHz, DMSO-$d_6$) of A6.
Figure S28. $^1$H-NMR spectrum (400 MHz, DMSO-$d_6$) of 2-M3.

Figure S29. $^1$H-NMR spectrum (400 MHz, DMSO-$d_6$) of 2-M5.

Figure S30. $^1$H-NMR spectrum (400 MHz, DMSO-$d_6$) of 2-M7.
Figure S31. Mass spectrum of D2.

Figure S32. $^1$H-NMR spectrum (400 MHz, DMSO-$d_6$) of D2.
Figure S33. Mass spectrum of B4.

Figure S34. $^1$H-NMR spectrum (600 MHz, DMSO-$d_6$) of B4.
Figure S35. $^{13}$C-NMR spectrum (100 MHz, DMSO-$d_6$) of B4.

Figure S36. COSY spectrum (DMSO-$d_6$) of B4.

Figure S37. HSQC spectrum (DMSO-$d_6$) of B4.
Figure S38. HMBC spectrum (DMSO-$d_6$) of B4.

Figure S39. Mass spectrum of B5.

Figure S40. $^1$H-NMR spectrum (400 MHz, DMSO-$d_6$) of B5.
Figure S41. $^{13}$C-NMR spectrum (100 MHz, DMSO-$d_6$) of B5.

Figure S42. COSY spectrum (DMSO-$d_6$) of B5.

Figure S43. HSQC spectrum (DMSO-$d_6$) of B5.
Figure S44. HMBC spectrum (DMSO-$d_6$) of B5.

Figure S45. $^1$H-NMR spectrum (400 MHz, DMSO-$d_6$) of B7.

Figure S46. $^1$H-NMR spectrum (400 MHz, DMSO-$d_6$) of 3-triM.
Figure S47. $^1$H-NMR spectrum (400 MHz, DMSO-$d_6$) of 3-SA.

Figure S48. Mass spectrum of B11.
Figure S49. $^1$H-NMR spectrum (400 MHz, DMSO-$d_6$) of B11.

Figure S50. $^1$H-NMR spectrum (400 MHz, DMSO-$d_6$) of B12.

Figure S51. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$) of B13.

Figure S52. $^1$H-NMR spectrum (400 MHz, DMSO-$d_6$) of B14.
Figure S53. $^1$H-NMR spectrum (400 MHz, DMSO-$d_6$) of 3-M3.

Figure S54. $^1$H-NMR spectrum (400 MHz, DMSO-$d_6$) of B16.

Figure S55. $^1$H-NMR spectrum (400 MHz, DMSO-$d_6$) of 3-FITC.
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