Electronic Supplementary Information (ESI)

Entirely Oligosaccharide–based Supramolecular Amphiphiles Constructed via Host–guest Interactions as Efficient Drug Delivery Platforms

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Experimental Section

Materials: propargylamine(98%, Aladdin), 2-bromoethylamine hydrobromide (98%, Aladdin), sodium azide (98%, shanghai sanyou chemical reagent Co.Ltd), magnesium sulfate (sichuan xilong Co.Ltd), triphenyllphosphine (95%, Aladdin), sodiun methoxide (97%, Aladdin), iodine (98%, beijing kehuagong chemical technology Co.Ltd.), ferrocenecarboxylic acid (98%,Aladdin), propargyl alcohol (98%,Aladdin), 4-dimethylaminopyridine (DMAP, 99%, Aladdin), dicyclohexylcarbodiimide (99%, Aladdin), pyridinium toluene-4-sulphonate (98%,sigma-aldrich), 2-methyoxypropene (97%, sigma-aldrich), pentamethyldiethylenetrimine (98%, Aladdin), DOX·HCl (98%, Aladddin), Superdry dimethyl sulfoxide (DMSO, J&K) were used as received. β-cyclodextrin (β-CD, 98%, A&B chemical reagent Co.LTD) was recrystallized twice from distilled water and dried in vaccum chamber at 100℃ for two days. N,N-dimethylformamide was obtained by divacuum distillation over over CaH_2. Deionized water was used throughout this study.

Measurements: The ^1H NMR spectra were recorded on a JEOL-ECS 400M nuclear magnetic resonance instrument using dimethyl sulfoxide-d_6 (DMSO-d_6), deuterated chloroform ($CDCl_3$) or deuterium oxide (D_2O) as the solvents and TMS as the internal reference. FT-IR spectra were recorded on a Bio-Rad Win-IR instrument with the potassium bromide (KBr) method. The transmmission electron microscope (TEM) was performed on JEOL JEM-2100. Mass spectrometry analysis was performed on a

Bruker Daltonics autoflex III smartbeam provided with an electrospray ionizeation source (ESI) in positive mode.

Synthesis of maltoheptaose (MH): Maltoheptaose was prepared according to the literature (Farkas, E.; Janossy, L.; Harangi, J.; Kandra, L. L.; Liptak, A. *Carbohyd. Res.* **1997,** 303, 407-415.). The MS m/z: calcd for $C_{42}H_{72}O_{36}Na$ ($M+Na^+$), 1175.9186; found, 1175.1492.

Syntehsis of N-Maltoheptaosyl-3-acetamido-1-propyne(MH-C≡CH): Dispersion of maltoheptaose (1.0g, 0.867mmol) in anhydrous propargylamine (1.19mL, 17.4mmol) was stirred strongly for seven days until maltoheptaose totally dissolved in propargylamine (room temperature). The mixture is poured into methy alcohol (10mL) to dissolve and then depositted in dichloromethane (30mL). The white precipitation is centrifuged and washed several times uing the blend solution of methy alcohol and dichloromethane (CH_3OH:CH_2Cl_2=1:3, v/v, 120mL). The obtained white solid is promptly added into the mixed solution of acetic anhydride and methy alcohol (acetic anhydride:CH_3OH=1:20, v/v, 100mL) and stirred at room temperature for the night. Remove the methy alcohol in the above reacting solution under reduced pressure and the trace amount of acetic anhydride is taken out by co-evaporating method with the bi-component solvent of methy alcohol and methybenzene (CH_3OH:methybenzene=1:1, v/v). The crude product is dissolved into a spot of distilled water and obtain the pure product through freeze drying. ^1H NMR (400 MHz ppm, D_2O):δ 5.29 and 4.95 (2×d, 1H), 5.23-5.15 (m, 6H), 4.24-3.45 (m,44H), 3.03 and 2.92(2×s, 1H, H of alkynyl group), 2.72 and 2.66(2×s, 3H, $NCOCH_3$). The MS

m/z: calcd for $C_{47}H_{76}O_{36}NNa$ ($M+Na^+$), 1254.0041; found, 1254.3642.

Synthesis of 3-Azidopropylamine: The solution of 2-bromopropylamine hydrobromide (9.76g, 44.6mmol) in Water (40mL) and the solution of sodium azide (8.7g, 133mmol) in water (40mL) is mixed up and warmed to 90℃ with stirring for fourteen hours. Then the reacting solution is cooled in ice-water bath and added NaOH (10.418g, 260.5mmol) to the cooling solution stirring until the NaOH is absolutely dissolved. The reacting solvent is extracted by diethyl ether. The organic phase is collected and added magnesium sulfate as water absorbent. Then the solution is filtered at atmospheric pressure and removed diethyl ether by reduced pressure distillation. The oily product is stored in refrigerator. ^1H NMR (400 MHz ppm,$CDCl_3$):δ 3.20(t, 2H, CH_2NH_2), 2.62(t, 2H,CH_2N_3), 1.61-1.54(m, 2H).

Synthesis of N-Maltoheptaosyl-3-Azidopropylamine (MH-N_3): A dispersion of maltoheptaose (1.0g, 0.867mmol) in oily 3-Azidopropylamine (1.19mL) was stirred strongly for seven days until maltoheptaose totally dissolved in 3 (room temperature). The mixture is poured into methy alcohol (10mL) to dissolve and then depositted in dichloromethane (30mL). The white precipitation is centrifuged and washed several times uing the blend solution of methy alcohol and dichloromethane (CH_3OH:CH_2Cl_2=1:3, v/v, 120mL). The obtained white solid is promptly added into the mixed solution of acetic anhydride and methy alcohol (acetic anhydride:CH_3OH=1:20, v/v, 100mL) and stirred at room temperature for the night. Remove the methy alcohol in the above reacting solution under reduced pressure and the trace amount of acetic anhydride is taken out by co-evaporating method with the

bi-component solvent of methy alcohol and methybenzene (CH_3OH:methybenzene=1:1, v/v). The crude product is dissolved into a spot of distilled water and obtained the pure product through freeze drying. ^{1}NMR(400 MHz, ppm, D_2O):δ5.20 (d, 6H), 4.86 (d, 1H), 4.10-3.43 (m, 44H), 2.65 (s, 3H, NCOCH3), 2.30(m, 2H). The MS m/z:calcd for $C_{47}H_{80}O_{36}N_4Na$ ($M+Na^+$), 1300.0467; found, 1299.3161.

Synthesis of β-CD-$(I)_7$: Triphenyllphosphine (18.6 g, 70mmol) is dissolved in 40mL anhydrous N,N-dimethylformamide with stirring, while iodine that is dissolved in 30mL anhydrous N,N-dimethylformamide is added dropwise in fifteen minutes. β-cyclodextrin (5.68g, 5mmol) is dissolved in 30mL anhydrous N,N-dimethylformamide and then charily added into the above solution. After the addition is finished and the brownish black reacting solution is increased to 70℃. The reaction is sustained for 24 hours under nitrogen atmosphere. The obtained solution is evaporated an amount of N,N-dimethylformamide under vaccum environment and then added 10mL 3mol/L ice-cold solution of sodiun methoxide of methyl alcohol stirring for an hour. The cooled methy alcohol is poured into the mixed solution and is centrifuged to get yellow solid. The obtained precipitation is extracted for 24 hours using methyl alcohol and dried in vaccum at 25℃. ^{1}H NMR (400 HMz, ppm, DMSO-d_6): 6.06-5.86 (m, 14H ,b,c-OH), 4.96 (s, 7H), 3.85-3.15 (m, 42H,).

Synthesis of β-CD-$(N_3)_7$: β-CD-$(I)_7$ (4.62g, 2.6mmol) is dissolved in 50mL anhydrous N,N-dimethylformamide and added sodium azaid (2.02g, 31mmol). The suspension is heated to 70℃ and stirred for 36 hours under the protection of nitrogen. The obtained

mixture is concentrated by vacuum rotary evaporation to remove an amount of N,N-dimethylformamide and then is precipitated in plenty of water to gain white solid. The solid is washing with water and putting in vaccum drying chamber. ^{1}H NMR (400MHz, ppm, DMSO-d_6): 5.72-5,62 (m, 14H, b,c-OH), 4.82-4.78 (s, 7H,), 3.71-3.22 (m, 42H). The MS m/z: calcd for $C_{42}H_{63}O_{28}N_{21}Na$ ($M+Na^{+}$), 1332.9908, found, 1332.1396.

Synthesis of Fc-modified propargyl alcohol(Fc-C≡CH): Ferrocenecarboxylic acid (0.5g, 2.2mmol) as well as propargyl alcohol (0.114g, 2.0mmol) are dissolved in 15mL anhydrous dichloromethane, then 4-dimethylaminopyridine (DMAP) (0.02414g, 0.2mmol) and dicyclohexylcarbodiimide (DCC) (0.4485g, 2.2mmol) is added. Under the nitrogen protection the mixed solvent is stirred for 24 hours at room temperature. Then the dicyclohexylcarbodiimide is removed by filtration. The obtained mixture is evaporated by vacuum decompression and the final product is collected by column chromatography. (hexane:ethyl acetate=8.5:1). ^{1}H NMR (400MHz, ppm, $CDCl_3$): 4.85-4.83 (m, 2H), 4.81-4.80 (m, 2H), 4.43-4.41 (m, 2H), 4.25-4.24 (m, 5H), 2.49-2.48 (m, 1H).

Synthesis of AcMH-N_3: MH-N_3 (0.1g, 0.086mmol), pyridinium toluene-4-sulphonate (6mg, 24μmol) as well as 2-methyoxypropene (0.5mL 5.3mmol) are dissolved in 1.5mL dimethyl sulfoxide solution. After the addition is complete, the reaction sealed away from light is sustained for 0.5 hour under nitrogen condition. Then 0.4mL triethylamine was added to quench the reaction. The reacting solution is poured into 50mL distilled water and centrifuged to gain the white solid. The product is washing

with water for three times and freeze-dried the pure product for several days. ^{1}H NMR (400MHz, ppm, DMSO-d_6): 4.02-2.93 (m, 44H), 2.61 and 2.29 (s, 2H), 2.24 and 2.04 (s, 3H,), 1.65-1.55 (m, 2H), 1.276(s, H of acetal group).

Synthesis of MH_4-β-CD: MH_4-β-CD was prepared by an alkyne-azide click reaction. Briefly, β-CD-$(N_3)_7$ (0.05g, 0.0765mmol), N-Maltoheptaosyl-3-acetamido-1-propyne (0.6g, 0.535mmol) and pentamethyldiethylenetrimine (PMDETA, 112μL, 0.535mmol) is dissolved in 15mL anhydrous dimethyl sulfoxide (DMSO). After freeze-thaw for three times, cuprous bromide (CuBr, 0.08g, 0.535mmol) is added to the shrek tube under nitrogen condition. The reaction is conducted for three days at 50℃. When the reaction is finished, the obtained solution is dialyzed (MWCO 6KDa) against N,N-dimethylformamide for two days against as well as distilled water for another two days.

Synthesis of Fc-AcMH: Fc-C≡CH (0.022g, 0.081mmol), AcMH-N_3 (0.1g, 0.081mmol) as well as pentamethyldiethylenetrimine (PMDETA, 25.2μL, 0.081mmol) is dissolved in 10mL anhydrous dimethyl sulfoxide (DMSO). After freeze-thaw three times repeatedly, the solutiom is added cuprous bromide (CuBr, 0.011g, 0.081mmol). Then is proceed for three days at 40℃ under nitrogen atmosphere. The gained solution is dialyzed (MWCO 2KDa) against methyl alcohol for two days and against distilled water for another two days. ^{1}H NMR(400HMz, ppm, DMSO-d_6): 8.18 (s, 1H), 5.74-5.35 (m, 7H), 5.221 (s, 2H), 5.08-4.81 (m, 7H), 4.729 (s, 2H), 4.45 (s, 2H), 4.10 (s, 5H), 3.419-3.478 (m, 21H), 3.31 (s, H of methoxy group and H_2O), 1.18 (s, H of acetal group).

Synthesis of supramolecular micelles: MH_4-β-CD (10mg) as well as five times of the equivalent of Fc-AcMH (2mg) are dissolved in 1mL dimethyl sulfoxide (DMSO). The mixed solution is sonicated for three hours and is shaken in a thermostated shaker at 250 rpm at room temperature for 12 hours to form inclusion complexation efficiently. The 14mL distilled water is injected at the rate of 0.5mL/h by squirt pump. After the addition is complete, the obtained solution is stirred for five hours and is dialyzed (MWCO 6KDa) against disstilled water for 48 hours. The supramolecular micells is collected by lyophilization.

For the preparation of DOX loaded micelles, firstly DOX·HCl is dissolved in 100μl dimethyl sulfoxide (DMSO) and added excessive triethylamine (TEA, 3 equiv. of DOX·HCl) shaken for a while in dark. Then the solution of free DOX is added to the above solution of inclusion complexation of dimethyl sulfoxide (DMSO). The mixed solution is put into table concentrator shaken for 12 hour continuely. The addition of 12ml distilled water is fulfilled through syringe pump at the rate of 0.5ml/h. The obtained solution is stirred for another five hours and is dialyzed (MWCO 6KDa) against deionized water to remove the DOX that is not loaded in the micelles. In the end, the drug loaded micells is harvested by freeze drying and stored in a refrigerator.

Determination of the concentration of the critical micelle: The CMC value was investigated by a fluorescence method using pyrene as a probe to demonstrate the formation of micelles and the influence of the composition of block copolymers on the properties of micelles.

Characterization of nanoparticles: The morphology of the nanoparticles was observed through TEM. The TEM samples were prepared by dropping nanoparticle solution on a carbon-coated copper grid for several times and the concentration of the solution is 1 mg/mL. The size of the nanoparticles were measured by DLS with a concentration of 0.5 mg/mL.

Control of micellar morphology: In order to determine whether the effect of the rate of adding water on the morphology of the nanoparticles, we did the following experiment: MH_4-β-CD (10mg) as well as five times of the equivalent of Fc-AcMH (2mg) are dissolved in 1mL dimethyl sulfoxide (DMSO). The mixed solution is sonicated for three hours and is shaken in a thermostated shaker at 250 rpm at room temperature for 12 hours to form inclusion complexation efficiently. The 3mL distilled water is injected at the rate of 0.5mL/h by squirt pump. After the addition is complete, the obtained solution is stirred for five hours and is dialyzed (MWCO 6KDa) against disstilled water for 48 hours. The supramolecular micells is collected by lyophilization. Also, we did the experiment to determine whether the amount of added water made a difference on the morphology of the nanoparticles: MH_4-β-CD (10mg) as well as five times of the equivalent of Fc-AcMH (2mg) are dissolved in 1mL dimethyl sulfoxide (DMSO). The mixed solution is sonicated for three hours and is shaken in a thermostated shaker at 250 rpm at room temperature for 12 hours to form inclusion complexation efficiently. The 14 mL distilled water is injected at the rate of 1 mL/h by squirt pump. After the addition is complete, the obtained solution is

stirred for five hours and is dialyzed (MWCO 6KDa) against disstilled water for 48 hours. The supramolecular micells is collected by lyophilization.

In vitro drug loading study: The quantitative determination of drug loading content (DLC) and the encapsulation efficiency (EE) is based on the a calibration curve (λ_{ex}=235nm). The DLC and DLE of the prepared drug-loaded micelles is calculated according to the equations listed bellow:

$$DLC(wt\%) = \frac{weight\,of\,drug\,in\,nanocapsules}{weight\,of\,nanocapsules} \times 100\%$$

$$EE(wt\%) = \frac{weight\,of\,drug\,in\,nanocapsules}{weight\,of\,totally\,used\,in\,nanocapsules} \times 100\%$$

In vitro drug release study: The in vitro release of the supramolecular amphiphiles micelles is fulfilled in phosphate buffer at pH=7.4 and sodium citrate buffer at pH=4.0. Specificaly,1ml solution containing 1mg drug-loaded micelles is encased in dialysis tube (MWCO=2500Da). The tube is infused in 25ml buffer solution , transformed it to shaking table at 200 rpm while the temperature of the interior of the shaking table at 37℃ constantly. Sodium hypochlorite is added to the the dialysate as to study the redox-responsive property of the micelles. 3ml solvent of the exterior dialysate is extracted and displaced by 3ml fresh release medium at the regular time that is setting in advance. The amount of the DOX released from the micelles is confirmed by a calibration curve via ultraviolet and visible spectrophotometer at 235nm.

In vitro cytotoxicity assay: The cytotoxicity of free DOX, blank micells and drug-loaded micelles against SW620 are assessed via methyl thiazolyl tetrezolium (MTT) assay. SW620 cells are seeded into 96-well cultural plate, which is incubated

for 24 hours at 37℃. The distinguishing forms of DOX with differential concentration from 0.5 μg/ml to 20 μg/ml are applied to while the amount of DOX is corresponding to drug- loaded DOX as well as the amount of materials is corresponding to all groups containing micelles. After all addition is complete, the cells is incubated for another 48 hours. Subsequently the MTT solution is taken the place in the cells, the MTT solution is replaced by dimethyl sulfoxide after 4 hours. The absorbance is detected by the thermo scientific microplate. The cell growth inhibition rate is calculated based on the formulation below:

$$Cell\ \text{Viability}(\%) = \frac{the\,absorbance\,of\ samples}{the\,absorbance\,of\ control} \times 100\%$$

In vitro phagocytic cellular uptake: SW620 cells were seeded in the 6-well plate at 2×10^5 per well and incubated in 2ml complete dulbecco's modified eagle medium (DEME) for 24 hours. Then the culture medium was removed and culture media containing a given amount of DOX-loaded micelles was replenished at a final DOX concemtration of 10μg/ml. The cells were cultured for another 3 hours and washed three times with phosphate buffer solution (PBS). Afterwards the cells were blended with 4% paraformaldehyde for 30 min at room temperature and washed with phosphate buffer solution (PBS) for three times again. The cells were incubated with 4',6-diamidino-2-phenylindole (DAPI, blue) for 20 min for the sake of staining the nuclei. The images of SW620 cells were acquired by fluorescence microscope.

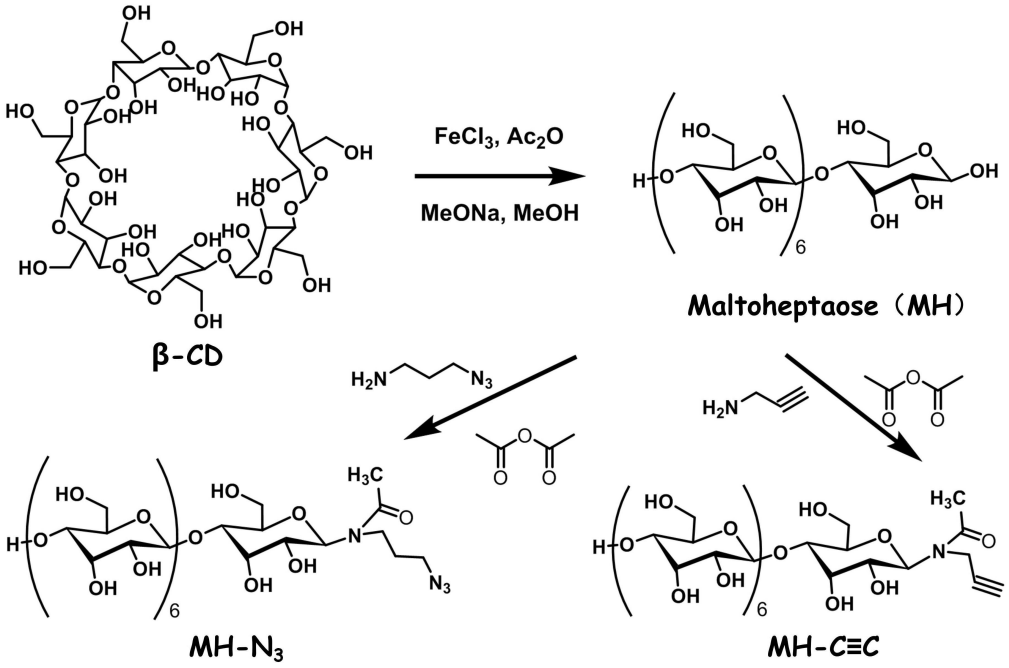
The number of MH-C≡CH linking to the β-CD: The number of MH-C≡CH linking to the β-CD was calculated via the following equation, where x is the number of MH-C≡CH:

$$\frac{7(x+1)}{x} = 8.75$$

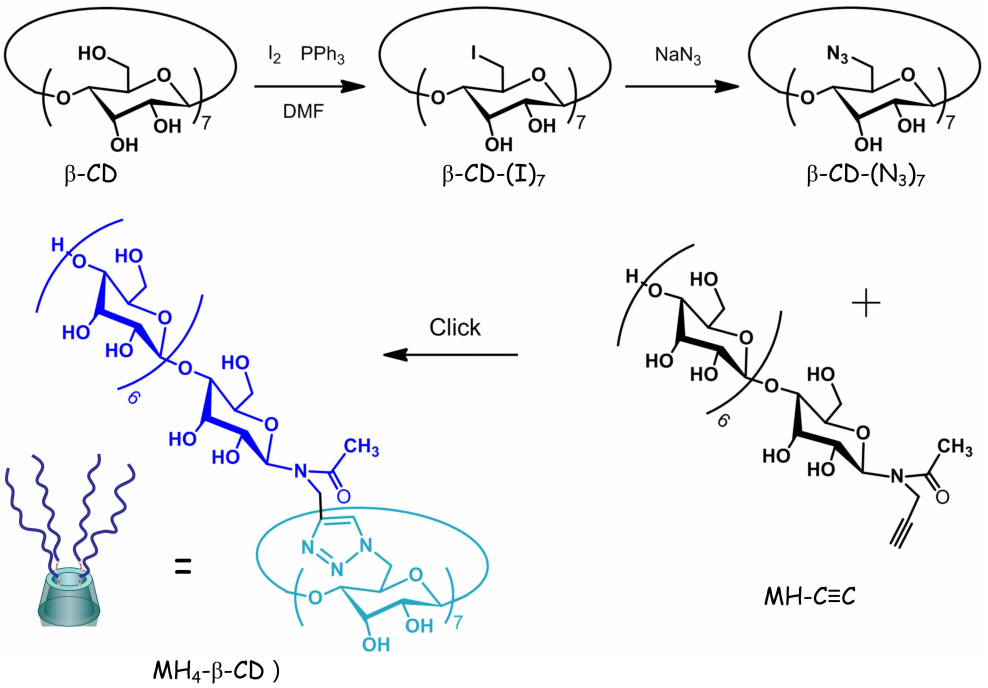
We calculated that there are four MH-C≡CH attached to β-CD. Due to the lipophilic property of the methyl group on DMSO, the linear chain of maltoheptaose could not strench well but aggregate resulting to the multiplicity of the peaks of one proton on the ^{1}H NMR spectroscopy.

ESI-II

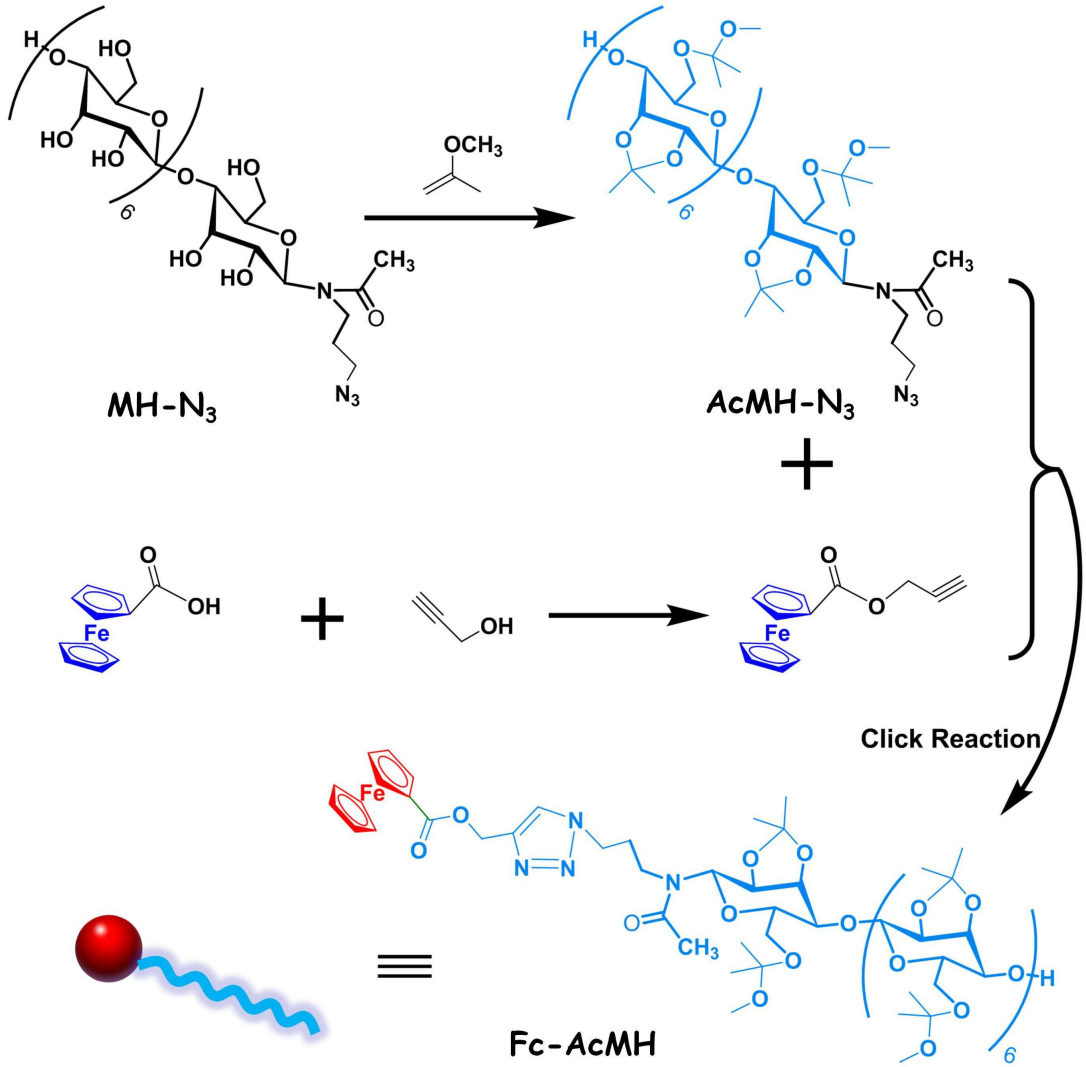
Fabrication and Characterization



Scheme S1. Synthetic route for MH-N_3 and MH-C≡CH.



Scheme S2. Synthesis route for β-CD -$(I)_7$, β-CD- $(N_3)_7$, MH_4-β-CD.



Scheme S3. Synthesis route for Fc-AcMH.

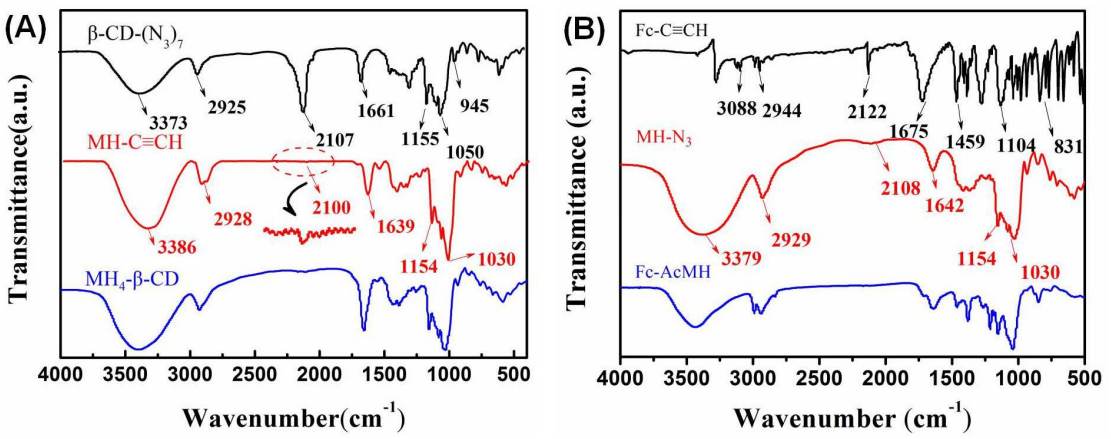


Fig. S1 The FT-IR spectra of β-CD-(N_3)7, MH-C ≡ CH, MH_4-β-CD (A); and the FT-IR spectra of Fc-C≡CH, MH-N_3, Fc-AcMH (B).

The information about the FT-IR spectra is displayed in the following figure. β-CD-N_3 shown in figure (A), the very broad absorption band centered at 3373cm^{-1} is assigned to the OH stretching vibration of hydroxyl groups, the absorption with maximum at 2925cm^{-1} belongs to the valence vibrations of C-H bonds in the CH and CH_2 groups, the absorption band at 2107 cm^{-1} is confirmed to the stretching vibration of azide group, the band at 1661cm^{-1} is due to HOH bending of physical absorbed water,and the 1155cm^{-1}, 1050cm^{-1} and 945cm^{-1} correspond to the absorption by C-O, C-O-C of glucose units and C-O-C of rings respectively. MH-C≡CH shown in figure (A), the wide band is registered with the absorption maximum at 3386 cm^{-1}, which is caused by the valence vibrations of O-H bonds; the absorption band at 2928cm^{-1} belongs to the valence vibrations of C-H; the absorption band centered at 2169 cm^{-1} is assigned to the valence vibration of alkinyl group; the band at the absorption at 1639 cm^{-1} is confirmed to the stretching vibration of amide group; and the 1154cm^{-1}, 1030cm^{-1} correspond to the absorption by C-O, C-O-C of glucose units. While in the spectrum of MH4-β-CD, the absorption of alkinyl group and azide group almostly disappeared, which confirmed that MH_4-β-CD was successfully synthesized. Fc-C≡CH shown in figure (B), the absorption band at 3088cm^{-1} is assigned to the C-H stretching vibration of cyclopenta (Cp ring), the absorption with maximum at 2944cm^{-1} belongs to the valence vibrations of

C-H bonds; the absorption band at 2122cm^{-1} is attributed to the valence vibrations of alkynyl group; the band at 1672cm^{-1} is identified as valence vibrations of C=O, the absorption band at 1459, 1104cm^{-1} are attributed to the C-C deformation vibrations of Cp ring and C-H deformation vibrations of Cp respectively, the absorption at around 831cm^{-1} is regarded as bending vibrations π C-H of Cp ring. MH-N_3 shown in figure (B), the wide band is registered with the absorption maximum at 3379 cm^{-1}, which is caused by the valence vibrations of O-H bonds; the absorption band at 2929 cm^{-1} belongs to the valence vibrations of C-H; the absorption band centered at 2108cm^{-1} is assigned to the valence vibration of azide group; the band at the absorption at 1642 cm^{-1} is confirmed to the stretching vibration of amide group; and the 1154cm^{-1}, 1030cm^{-1} correspond to the absorption by C-O, C-O-C of glucose units. While in the spectrum of Fc-AcMH, the absorption of alkinyl group and azide group disappeared, which confirmed that Fc-AcMH was successfully synthesized. The detailed FT-IR spectra was added in the ESI file.

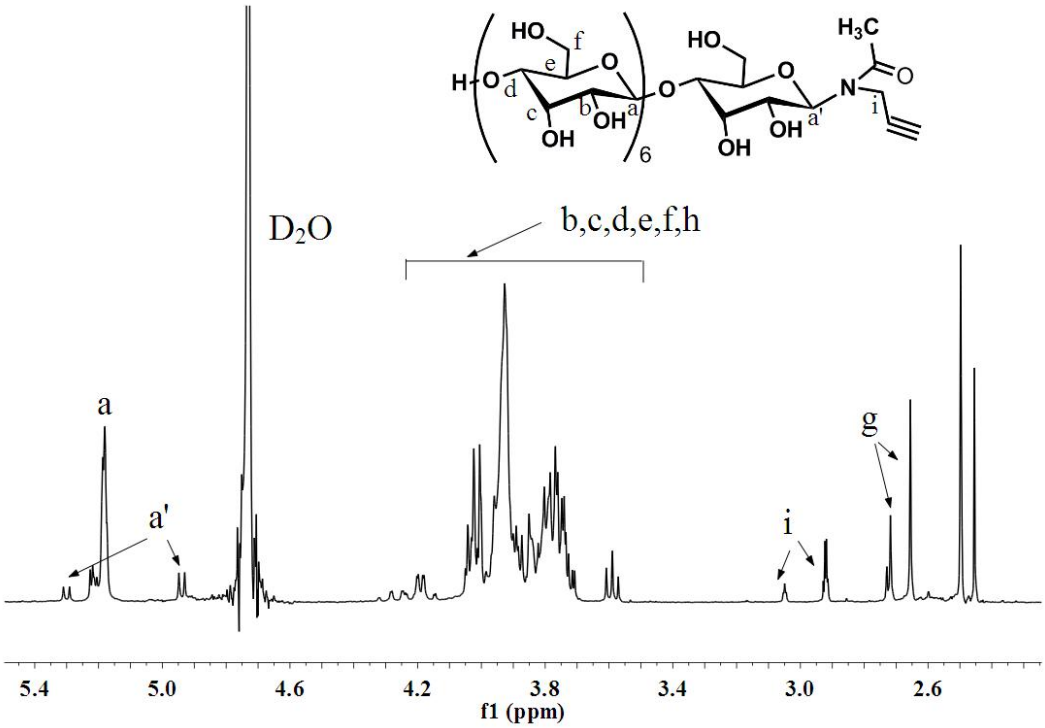


Fig. S2 ^{1}H NMR of MH-C≡CH.

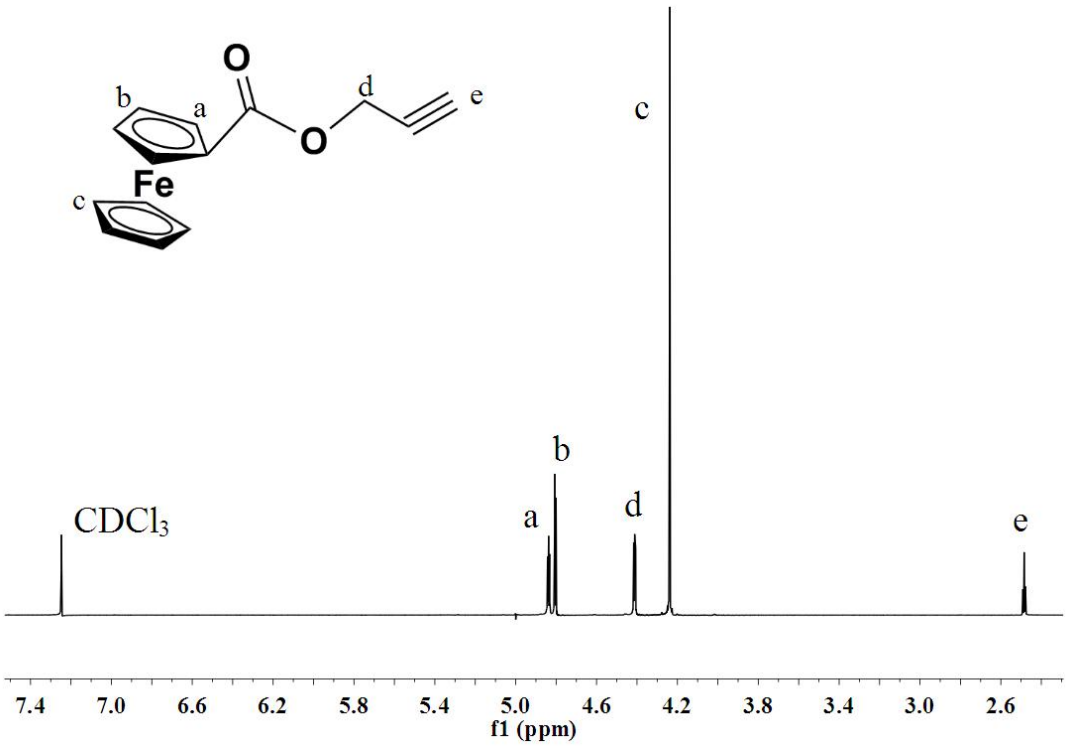


Fig. S3 ^{1}H NMR of Fc-C≡CH.

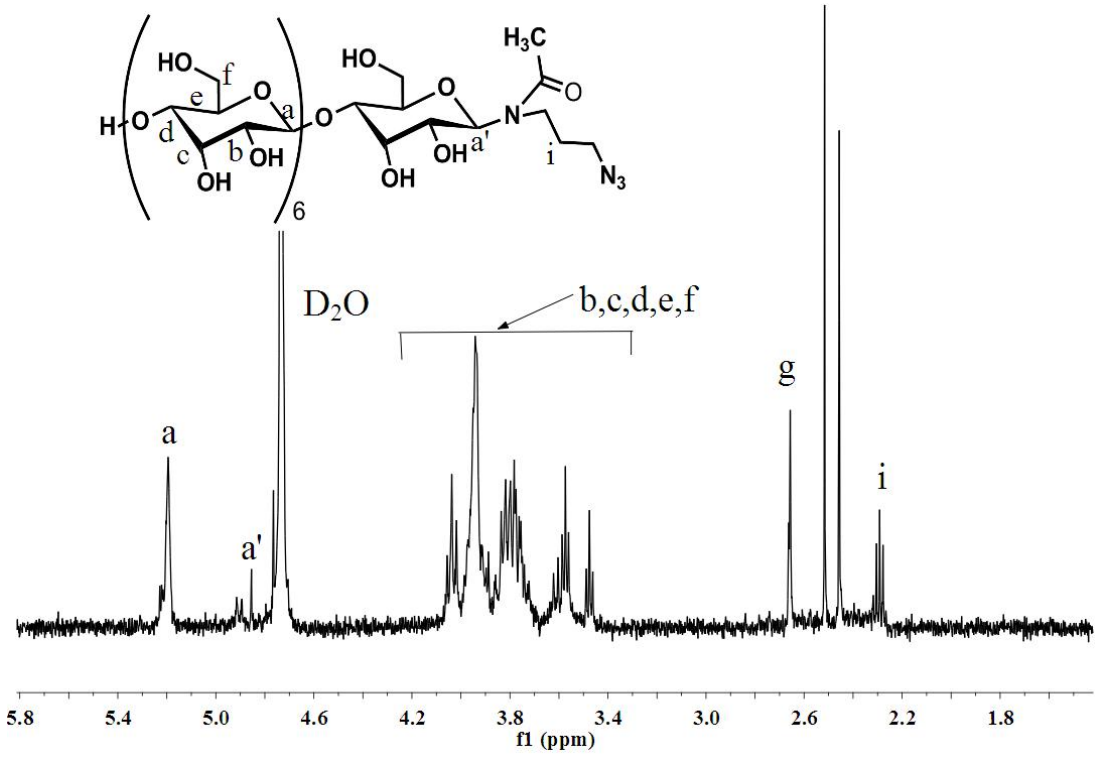


Fig. S4 ^{1}H NMR of MH-N_3.

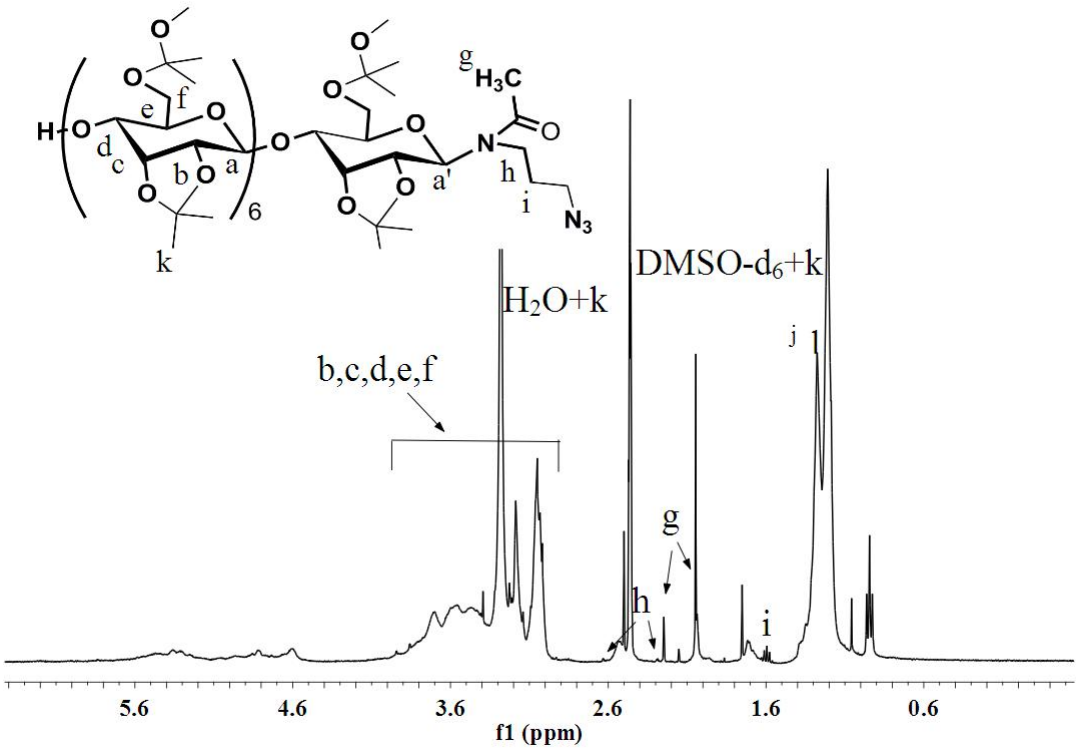


Fig. S5 ^{1}H NMR of AcMH-N_3.

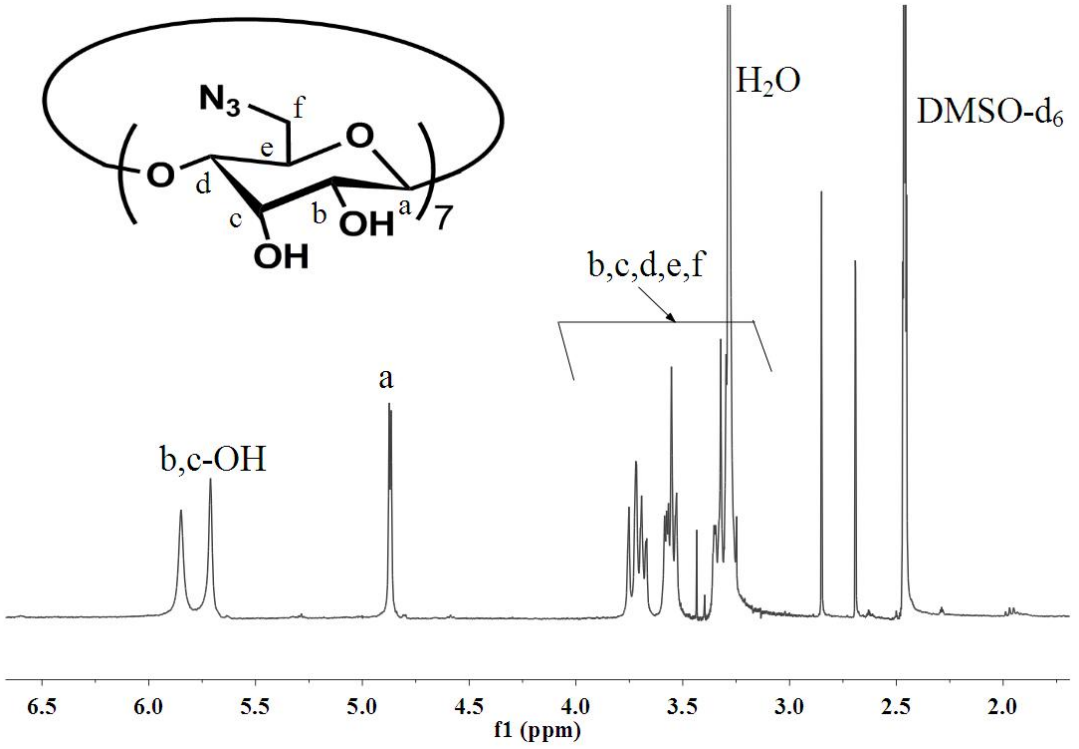


Fig. S6 ^{1}H NMR of β-CD-$(N_3)_7$.

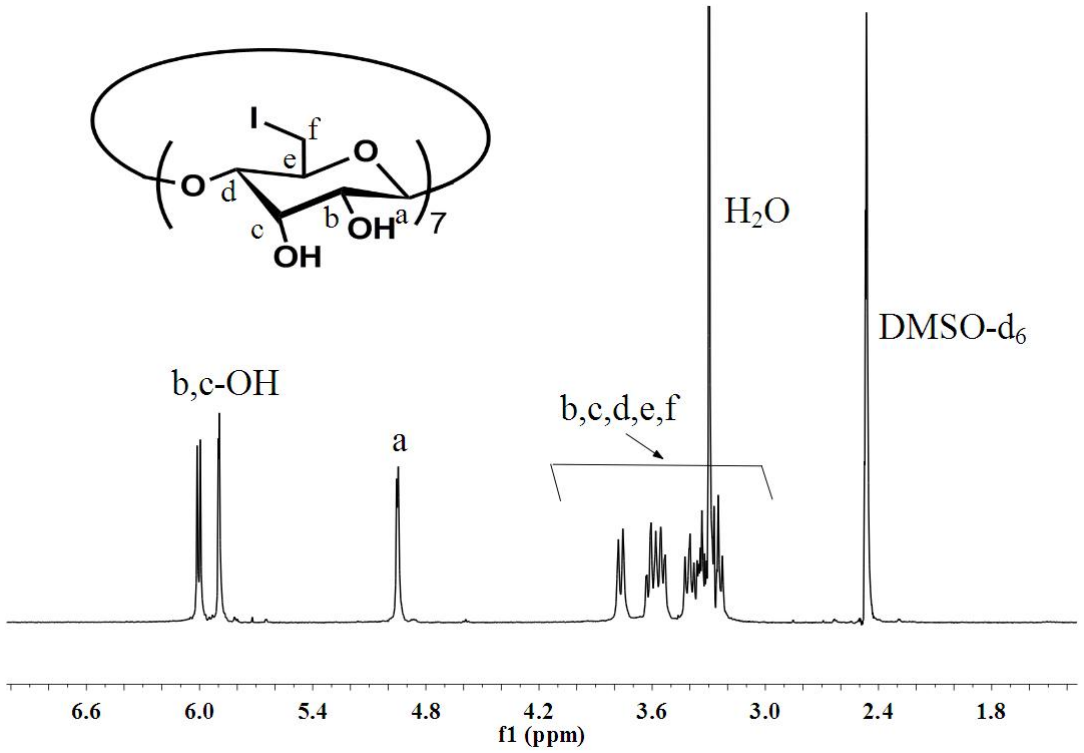


Fig. S7 ^{1}H NMR of β-CD-(I)$_{7}$.

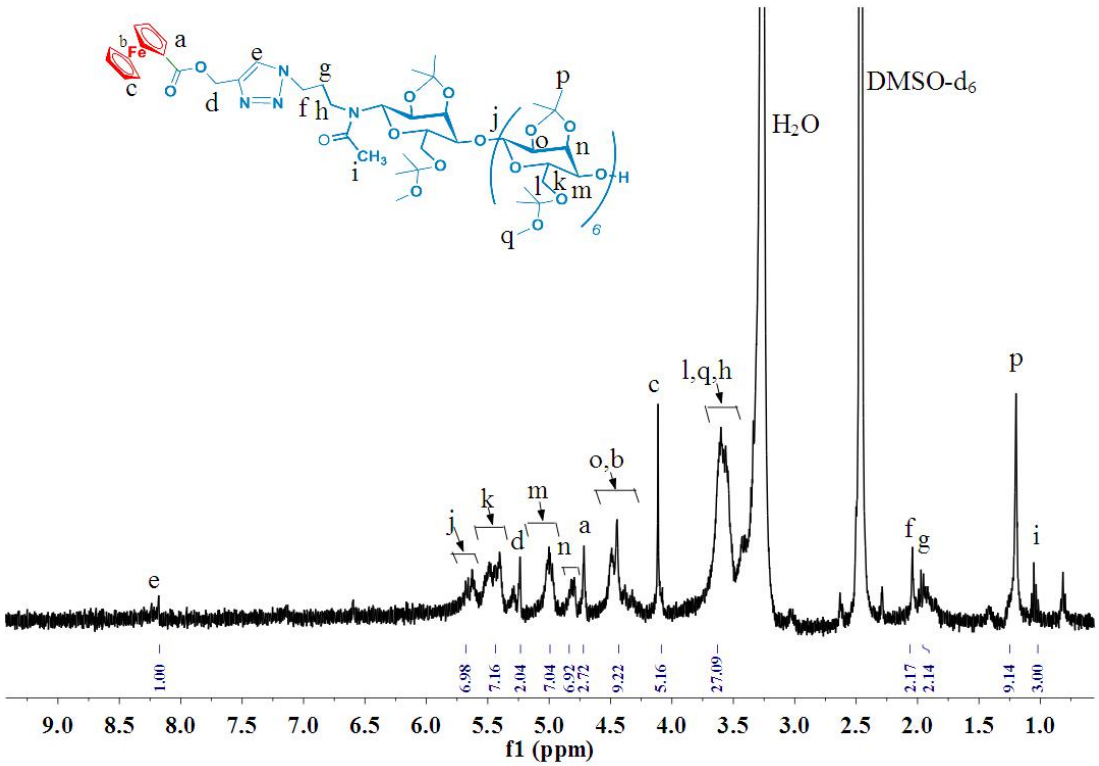


Fig. S8 ^{1}H NMR of Fc-AcMH.

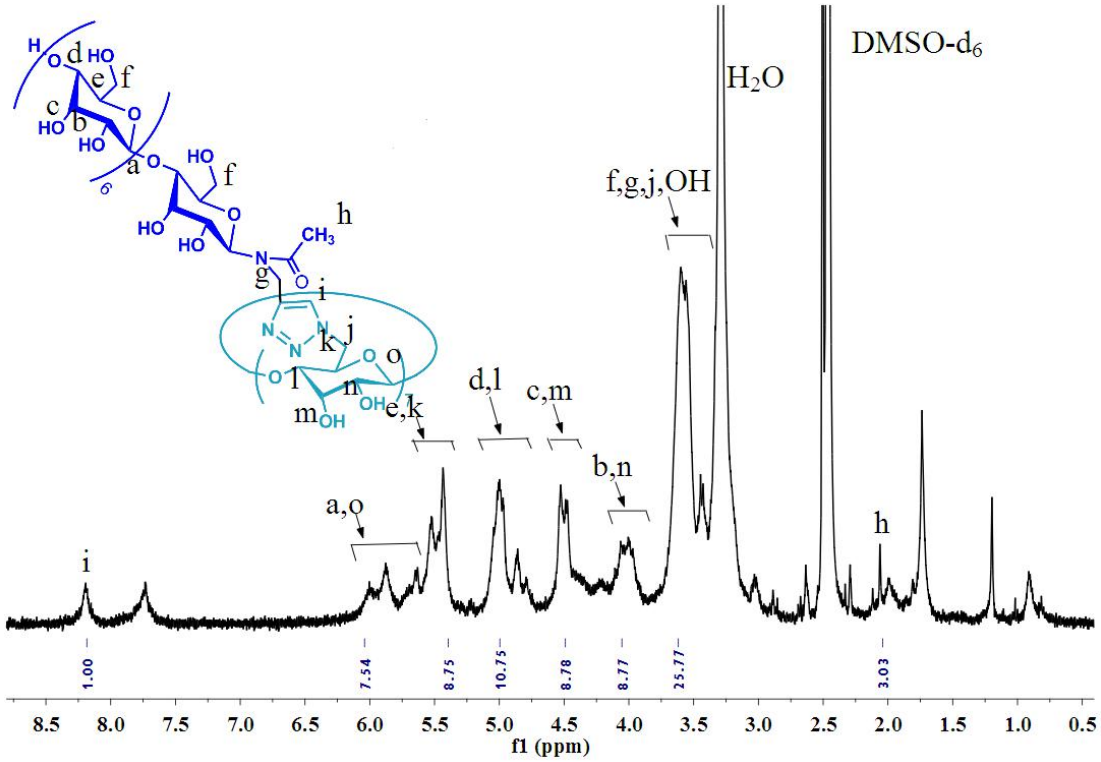


Fig. S9 ^{1}H NMR of MH_4-β-CD.

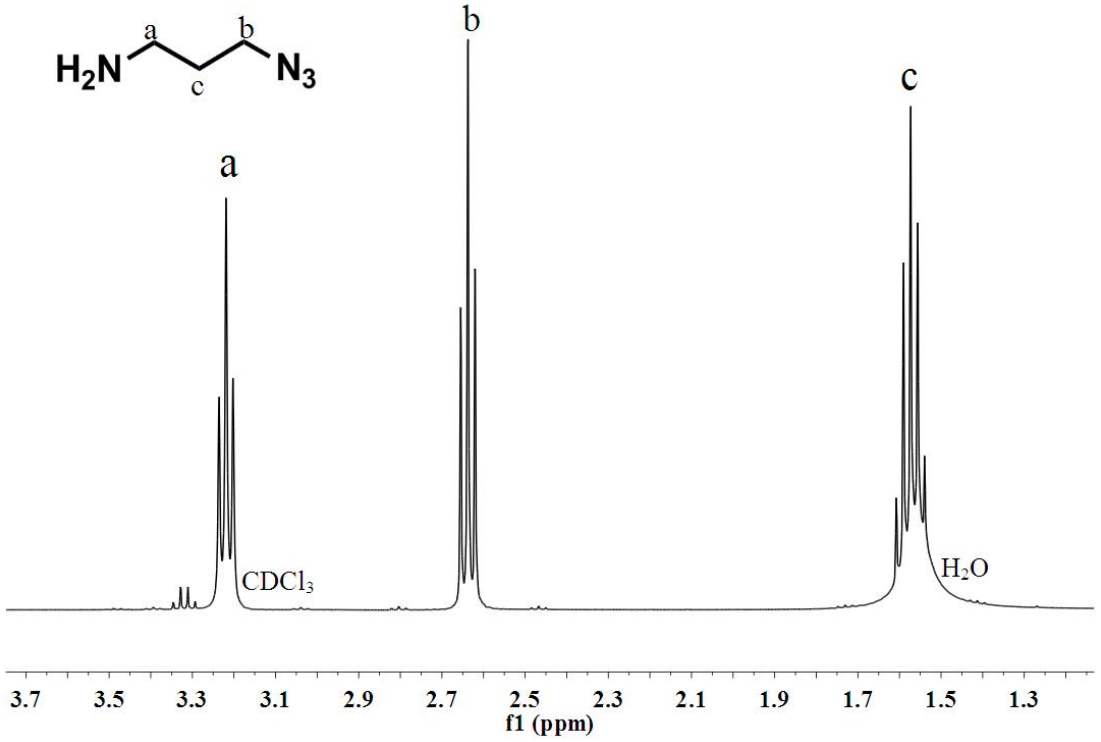


Fig. S10 ^{1}H NMR of 3-Azidopropylamine

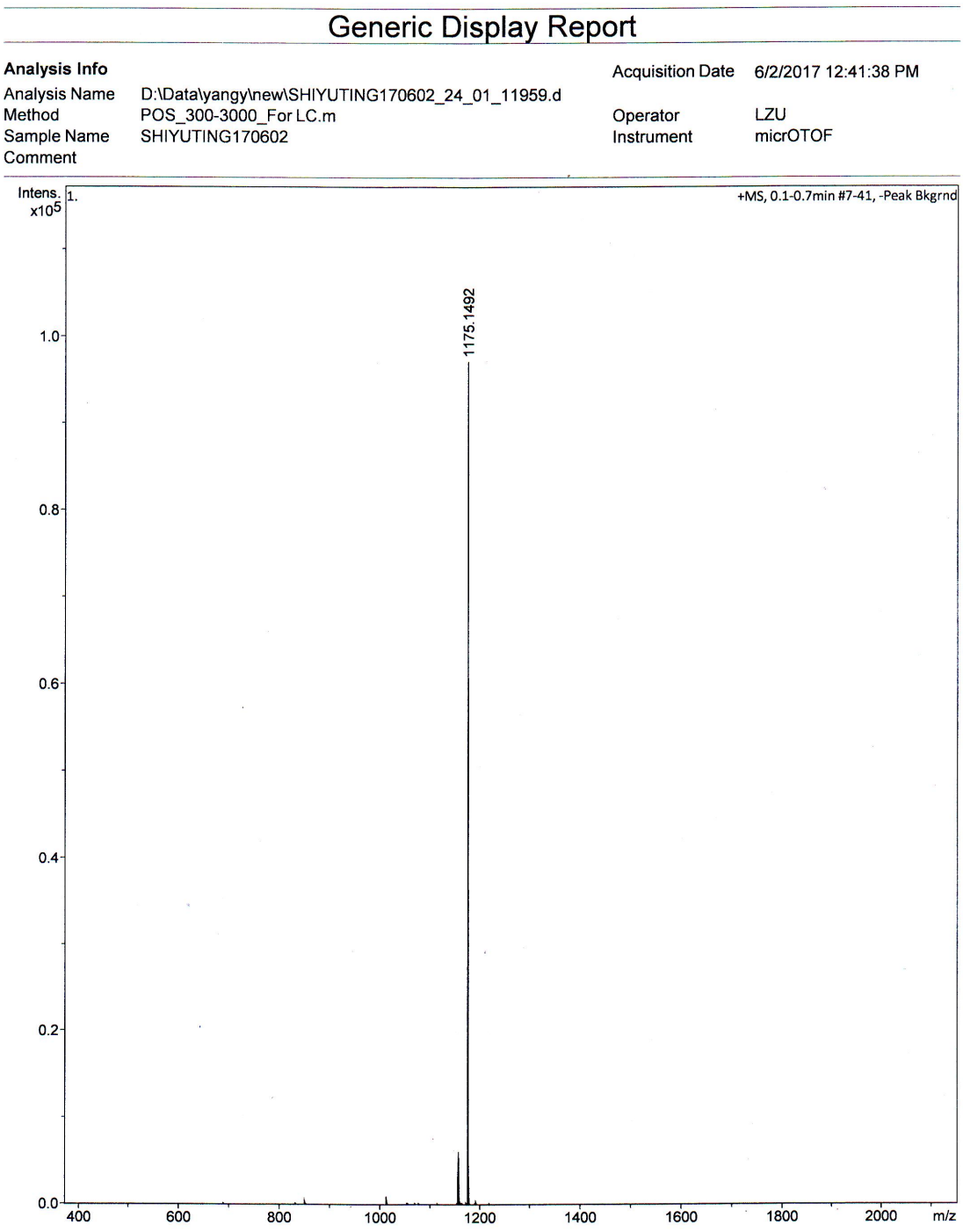


Fig. S11 The MS of MH

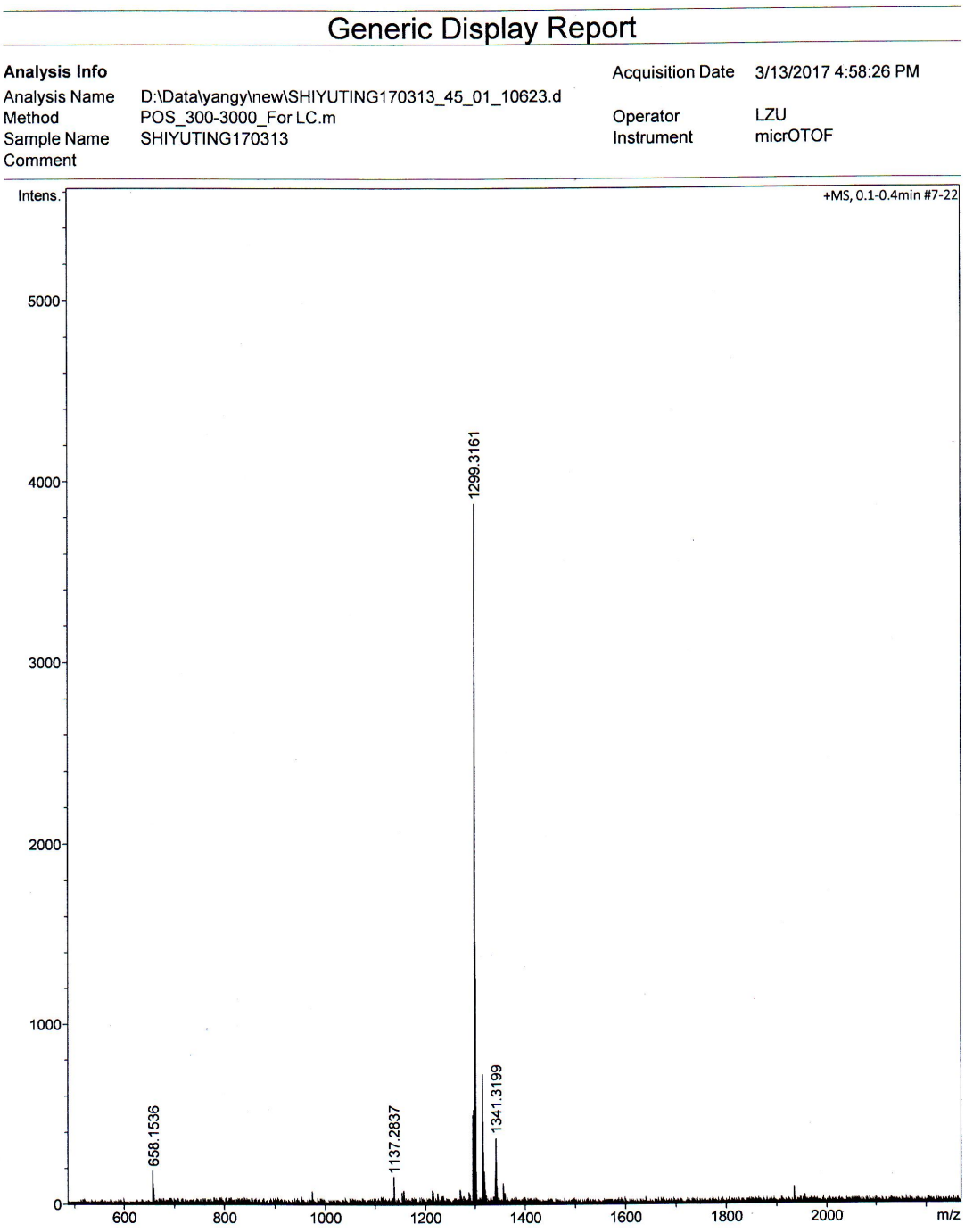


Fig. S12 The MS of MH-N_3.

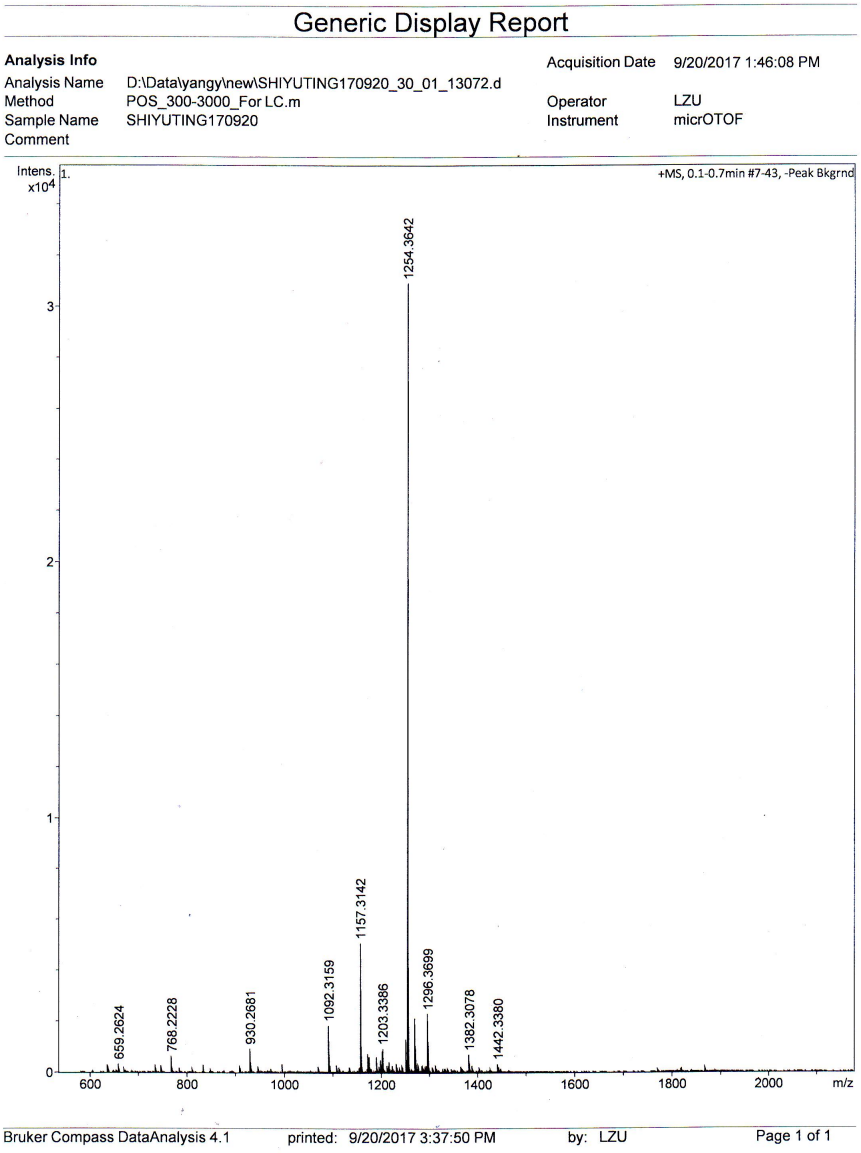


Fig. S13 The MS of MH-C≡CH.

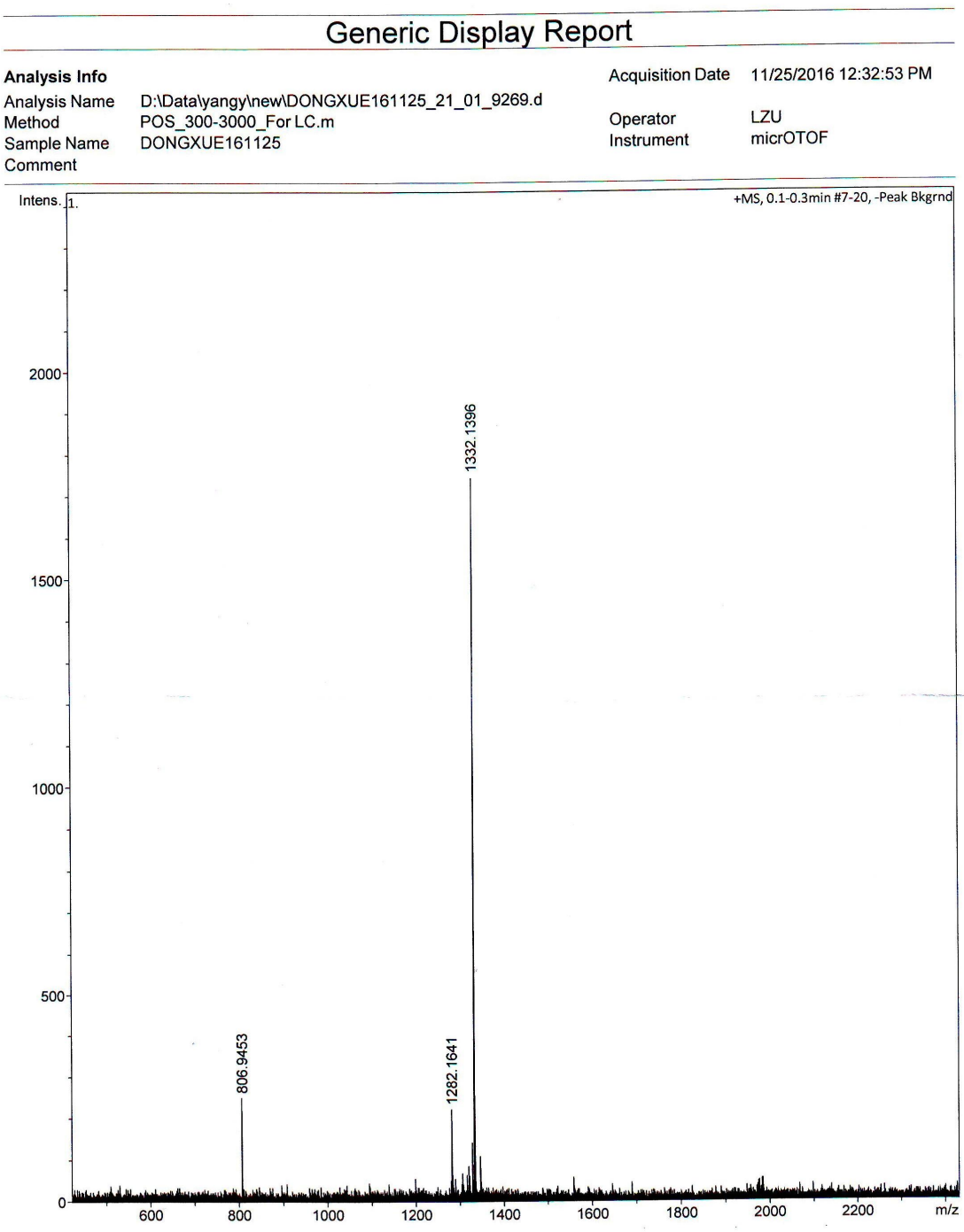


Fig. S14 The MS of β-CD-$(N_3)_7$.

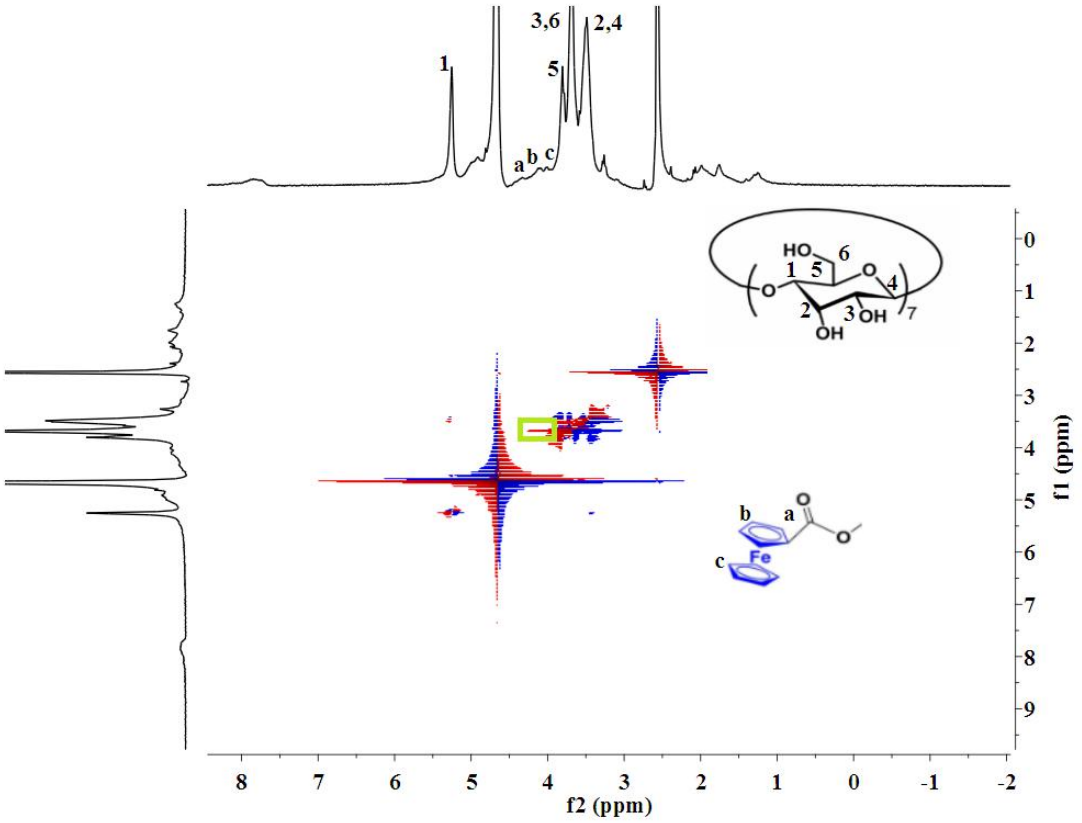


Fig. S15 2D NOESY NMR spectrum of Fc-AcMH and MH_4-β-CD in D_2O.

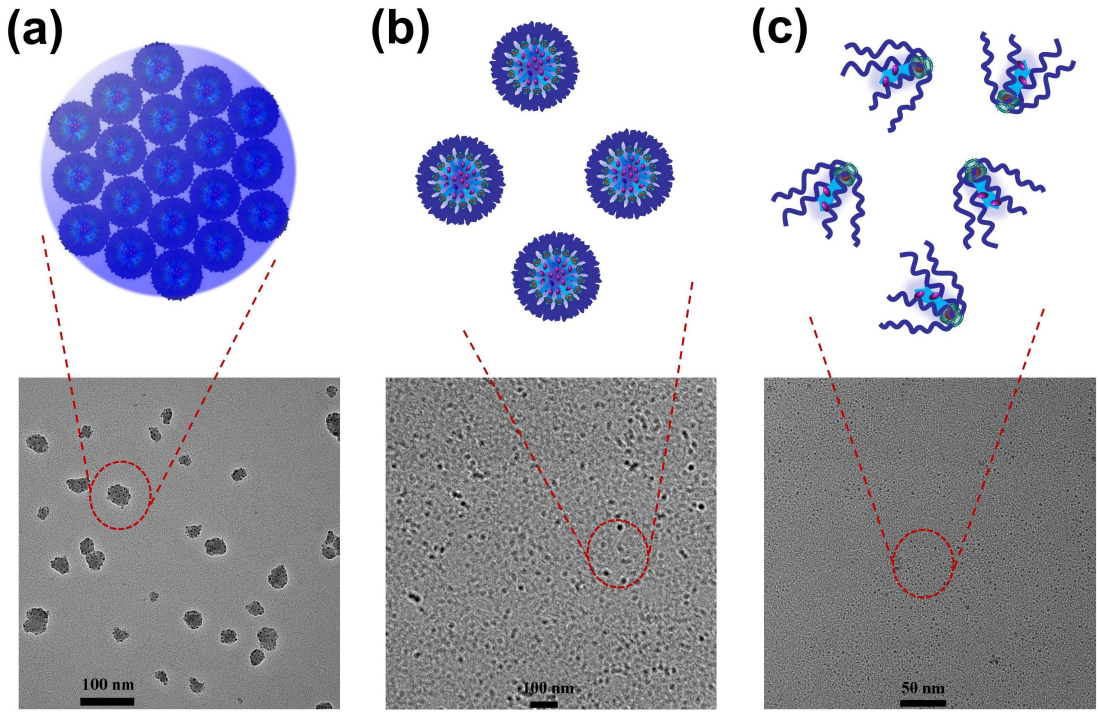


Fig. S16 The TEM of (a) DOX-loaded nanoparticles formed by DOX-loaded primary micelles, 14 mL distlled water, 0.5mL/h, (b) DOX-loaded primary micelles formed by DOX-loaded monolecular micelles,14mL distilled water, 1mL/h and (c) DOX-loaded monolecular micelles, 3mL distilled water, 0.5mL/h.

As shown in Fig. S16, monolecular micelles (c) formed by the single supermolecules MH_4-β-CD-AcMH, which also chould be self-assembled into primary micelles (b) with segregated AcMH cores and MH shells, and primary micelles further aggregate into large nanoparticles (a). According to the experimental results, we found that the slower the injection and the more water made it easier to form monolecular micelles.

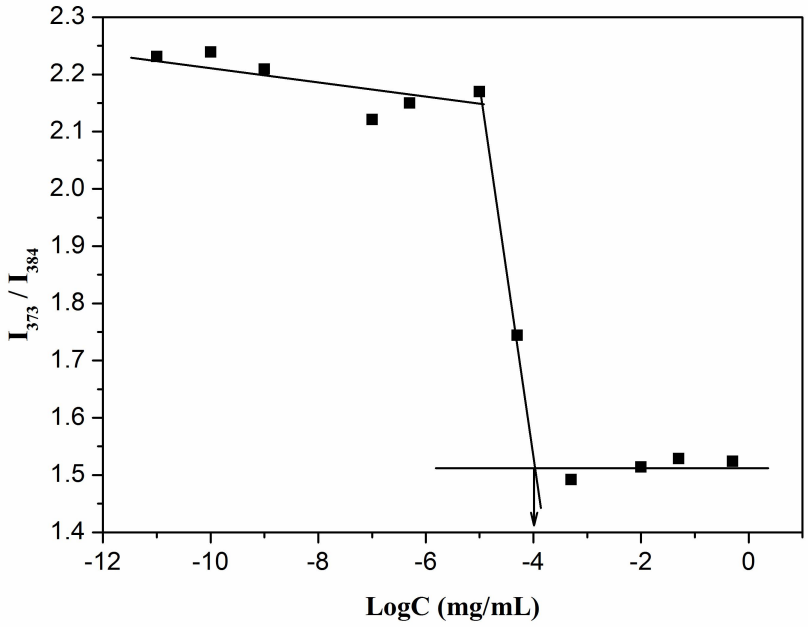


Fig. S17 I_{373}/I_{384} intensity ratios from ptrene excitation spectra as a function of concentration of MH_4-β-CD-AcMH supramolecular copolymer in PBS at pH 7.4.

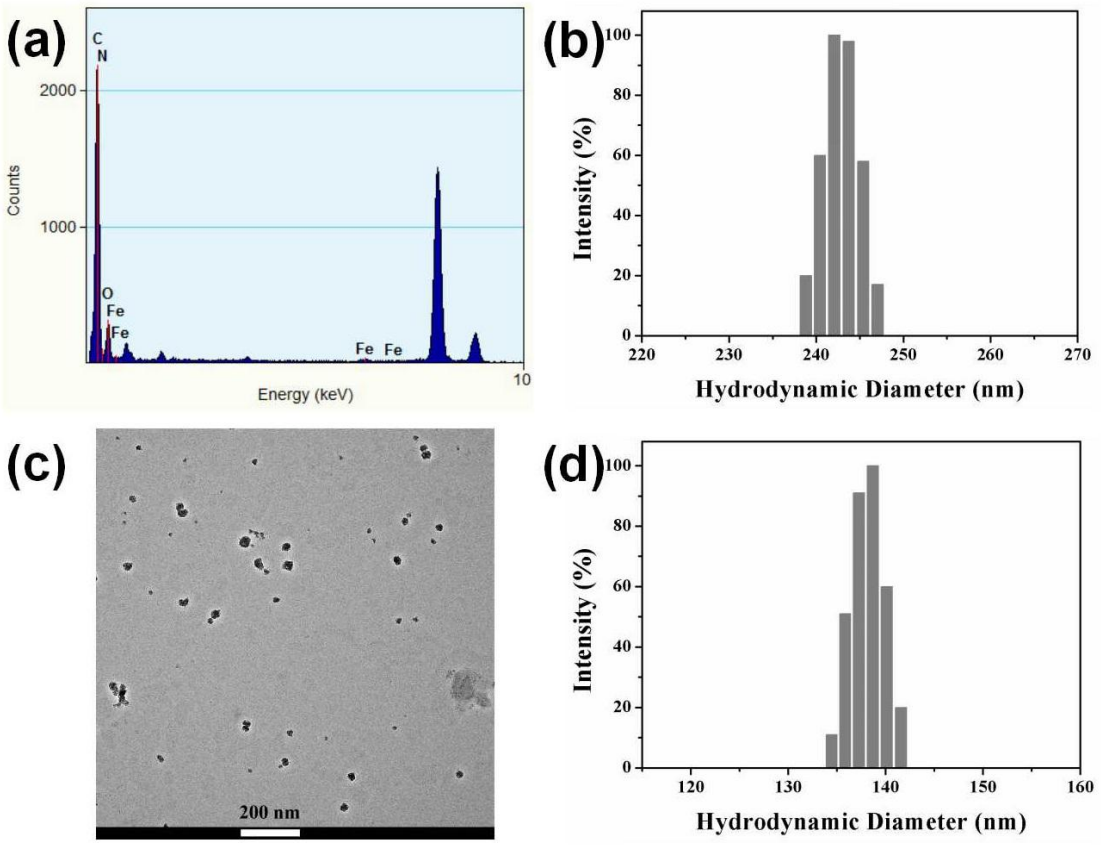


Fig. S18 (a) The EDX of the the dark black spots dotting in the nanoparticles. (b) The DLS of the drug-loaded nanoparticles. (c) The TEM of blank nanoparticles. (d) The DLS of the blank nanoparticles.

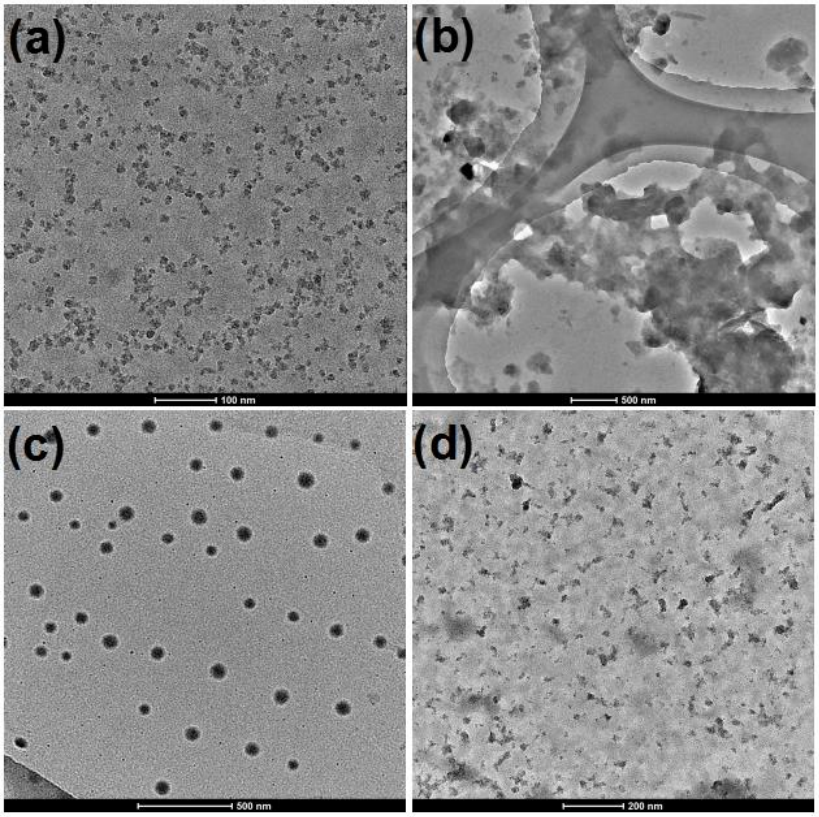


Fig. S19 TEM micrographs of MH_4-β-CD-AcMH at pH=4.0 for 24h(a), 48h(b) as well as pH =4.0 and 0.1M NaClO for 24h(C), 48h(D), respectively.