Electronic Supplementary Information

for

Light-Responsive Dual-Functional Biodegradable Mesoporous Silica Nanoparticles with Drug Delivery and Lubrication Enhancement for the Treatment of Osteoarthritis

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1 Materials and Methods

Cetyltrimethylammonium chloride (CTAC, >98%), 2,2-Azodiisobutyronitrile (AIBN, >99%) and tetraethyl orthosilicate (TEOS, >98%) were purchased from J&K Scientific Co., Beijing, China. 4-Aminoazobenzene (>98%) and (3-isocyanatopropyl)-triethoxysilane (3-ICPES, >95%) were obtained from Aladdin Co., China. Deuterium oxide (D_2O) and dimethyl sulfoxide-d6 (DMSO-d6) used in the nuclear magnetic resonance (NMR) experiments were obtained from InnoChem Co., Beijing, China. 2-Methacryloyloxyethyl phosphorylcholine (MPC, >98%) was purchased from Joy-Nature Technology Institute, Nanjing, China. Mono-6-thio-β-CD (CD-SH) was synthesized by Binzhou Zhiyuan Biotechnology Co., Ltd., Shandong, China. Hydrochloric acid (HCl, 37%), triethanolamine (TEA, >99%), toluene, methanol, tetrahydrofuran (THF), N,N-dimethylformamide (DMF) and other chemical reagents were purchased from Beijing Chemical Reagent Co., Beijing, China. Aggrecan (Agg) and a disintegrin and metalloproteinase with thrombospondin 5 (ADAMTS5) enzyme-linked immunosorbent assay (ELISA) kits were obtained from Cloud-Clone Corp., Houston, USA. Interleukin-6 (IL-6) and matrix metalloproteinases (MMP13) ELISA kits, simulated body fluid (SBF), as well as other biological reagents used in the bio-experiments were purchased from Solarbio Science & Technology Co., Ltd., Beijing, China. The water used in this work was deionized water with a resistivity of 18.2 MΩ·cm.

The morphologies of bMSNs and modified bMSNs were evaluated using transmission electron microscopy (TEM, H-7650B, Hitachi, Japan). The molecular weight distribution (weight-average molecular weight, M_w) and the corresponding

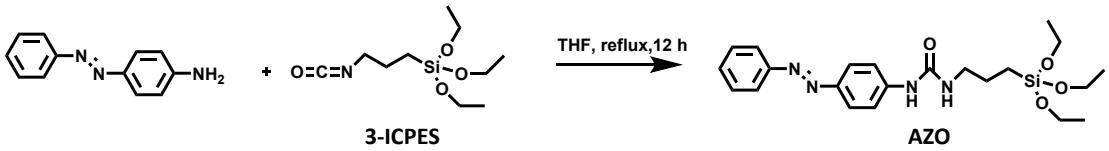
polymer dispersity index (PDI) of CD-PMPC were examined on a gel permeation chromatography (GPC) system (Viscotek TDA305max, Malvern Instruments, UK) using 0.1 M sodium nitrate as the diluent with a flow rate of 0.7 mL/min. The chemical structures of CD-PMPC and AZO were confirmed by ^{1}H NMR spectra on a JNM-ECS400 spectrometer (JEOL, Japan) using D_2O and DMSO-d6 as the solvents, respectively. UV-vis absorption spectra of AZO and diclofenac sodium (DS) were recorded on a Metash UV-6100A spectrometer (Shanghai, China). X-ray photoelectron spectroscopy (XPS) spectra of bMSNs and modified bMSNs were recorded on a 250XI XPS system (Thermo Scientific, USA). The modification of bMSNs was confirmed by Fourier transform infrared (FTIR) spectra using a Nicolet 6700 transform infrared spectrometer (Thermo Scientific, USA). Thermogravimetric analysis (TGA) of the bMSNs was performed on a Q5000IR instrument (TA Instruments, USA) with a heating rate of 10 °C/min in the range from 25 °C to 800 °C. X-ray diffraction spectrum (XRD) was conducted using a Bruker AXS D8 Diffractometer (Bruker, Germany) with 2θ range from 0.6° to 10°. The mesostructure characterization of bMSNs and modified bMSNs was obtained using a Quantachrome SI-MP equipment (Quantachrome Instruments, USA) based on Brunauer–Emmett–Teller (BET) model and Barrett-Joyner Halenda (BJH) model. The lubrication properties of bMSNs and modified bMSNs in aqueous solution were evaluated using a universal material tribometer (UMT-3, Centre for Tribology Inc., California, USA) via a series of tribological tests. The mouse MC3T3-E1 osteoblastic cells obtained from the Shanghai Cell Bank of the Chinese Academy of Sciences were cultured in minimum essential medium (MEM,

Hyclone) supplemented with 10% fetal bovine serum (FBS, Invitrogen) and maintained in an incubator at 37 °C with 5% CO_2 and 95% humidity. The cell compatibility and viability were evaluated by Cell Counting Kit-8 (CCK-8, Dojindo Kagaku, Japan) assay and Live/Dead cell-mediated cytotoxicity kit (Life Technologies), with the stained living and dead cells imaged by a confocal laser scanning microscope (LSM710META, Zeiss, Germany).

Briefly, the MC3T3-E1 cells were seeded in six-well plates with a density of 5×10^4 cells/well and treated with 5 nM of tumor necrosis factor (TNF-α) to stimulate the inflammatory conditions in cells. After incubation for 6 h, the cells were treated with 0.1 mg/mL of bMSNs, bMSNs/DS, bMSNs-AZO/DS, bMSNs-AZO/CD-PMPC or bMSNs-AZO/CD-PMPC/DS for 12 h. Then, the cell supernatants were collected and stored at -20 ^oC for later analysis. The ELISA assays were performed according to the corresponding instructions for determining protein concentrations. Taking MMP13 as a representative, the collected supernatants were added to a 96-well plate pre-coated with MMP13 monoclonal antibody, and immunosorbented by biotinylated anti-mouse MMP13 antibody at 37 °C for 1 h. Then, horseradish peroxidase labeled streptavidin was added to bind biotins and catalyze the color development of tetramethylbenzidine (TMB). The absorption was measured at 450 nm immediately after adding termination solution. The protein concentrations were calculated by comparing the OD value of samples with the standards. Each sample was repeated at least three times to give an error bar in the graphs.

2□ Preparation and Synthesis

2.1. Synthesis of AZO[S1]



Scheme S1. Synthesis route of AZO.

4-Aminoazobenzene (0.197 g, 1.0 mmol) and 3-ICPES (0.272 g, 1.1 mmol) were dissolved in 60 mL of THF and heated at 70 ℃ under nitrogen atmosphere. After being stirred for 12 h, the solvent was evaporated to dryness and the residue was recrystallized in hexane/THF to get the AZO (62% yield). The ^{1}H NMR spectrum of AZO was shown in Figure S1.

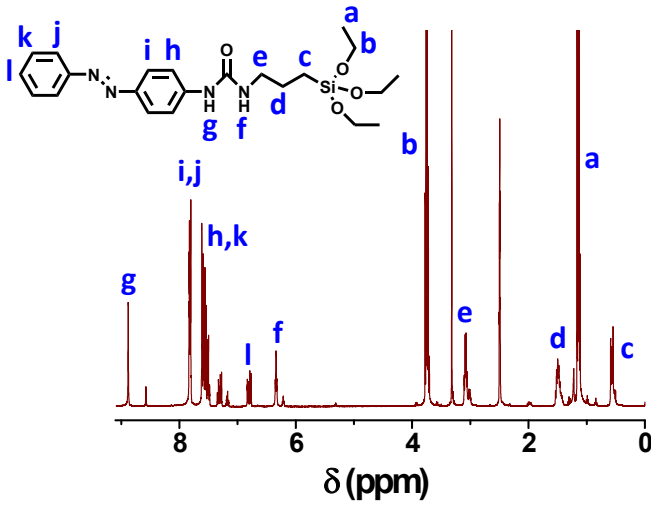
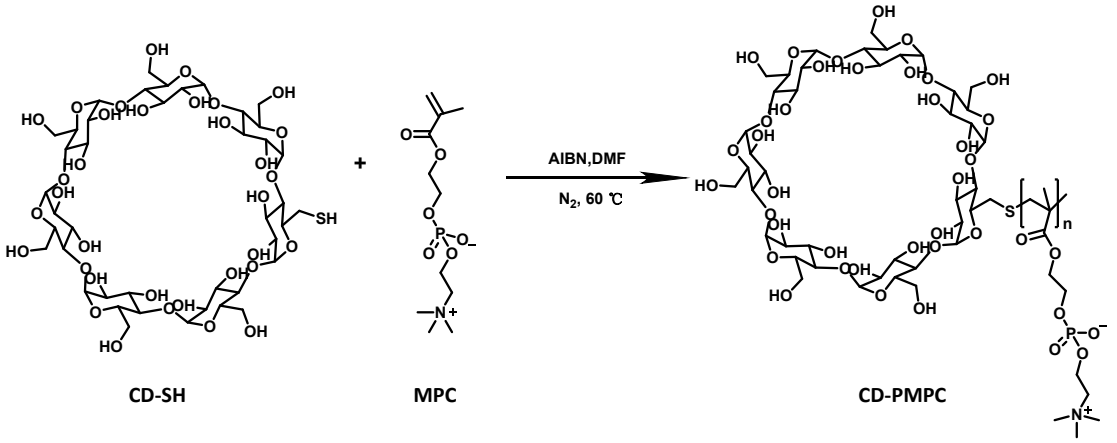


Figure S1. ^{1}H NMR spectrum of AZO in DMSO-d6 at 25 °C.

2.2. Synthesis of CD-PMPC[S2]



Scheme S2. Synthesis route of CD-PMPC.

MPC (0.59 g, 2.0 mM), CD-SH (0.115 g, 0.1 mM) and AIBN (0.01 g, 0.06 mM) were mixed in 20 mL of anhydrous DMF, and then the mixture was kept in an oil bath at 60 °C for 12 h under the protection of nitrogen. Finally, the solution was dialyzed (molecular weight cut off 3500 dialysis bags) against deionized water for 7 d and lyophilized to obtain the white solid product CD-PMPC. The ^{1}H NMR spectrum of CD-PMPC was shown in Figure S2. The GPC analysis of CD-PMPC indicated that the M_w of the polymer is 69.3 kDa with a polydispersity of 2.3.

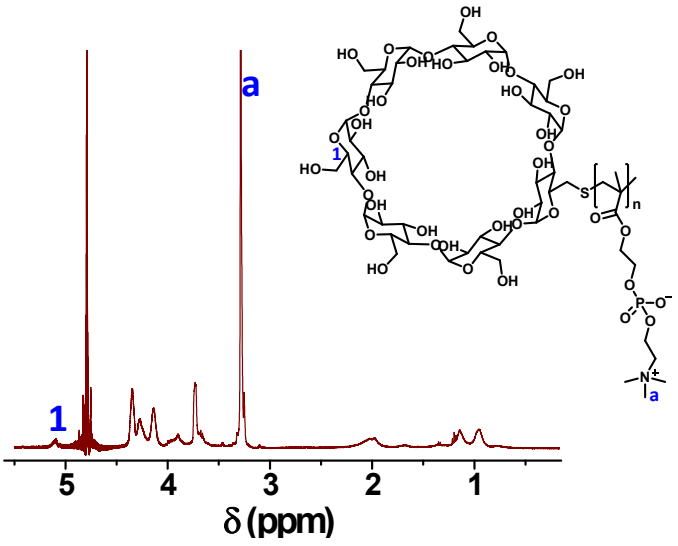


Figure S2. ^{1}H NMR spectrum of CD-PMPC in D_2O at 25 °C.

2.3. Preparation of biodegradable mesoporous silica nanoparticles (bMSNs)

The bMSNs were synthesized according to a previous literature.[S3] Briefly, 8.00 g of CTAC and 0.18 g of TEA were added into 60 mL of deionized water, and the mixture was stirred at 60 °C for 1 h to dissolve the solids absolutely. Then, 1.00 mL of TEOS and 19.00 mL of cyclohexane were added gently into the mixture to form an organic phase above the aqueous phase. The mixture was stirred at 60 °C with a speed of 90 rpm for 72 h. The resulting product bMSNs in aqueous phase was collected by adding methanol and centrifugation (8000 rpm, 10 min). The CTAC template was removed by dispersing the bMSNs in acidic methanol solution and refluxing at 60 °C for 24 h. Finally, the solid was washed with methanol, centrifuged at 8000 rpm for 10 min, and dried under vacuum to get the bMSNs.

2.4. Preparation of Azobenzene modified biodegradable mesoporous silica nanoparticles (bMSNs-AZO)

100 mg of bMSNs and 10 mg of AZO were dispersed in 30 mL of toluene, and then the mixture was kept refluxed and stirred for 12 h. The product was centrifugated at 8000 rpm for 10 min, washed with toluene and methanol sequentially, and dried under vacuum to get the bMSNs-AZO.

2.5. Preparation of CD-PMPC modified bMSNs-AZO (bMSNs-AZO/CD-PMPC)

30 mg of bMSNs-AZO was dispersed in 10 mL of deionized water, and then 6 mg, 12 mg and 18 mg of CD-PMPC was added, respectively. The mixed solutions were stirred in dark condition for 24 h to make the azobenzene group and CD form host-guest

complex. The nanoparticles were collected by centrifugation, washed with deionized water and dried under vacuum to get bMSNs-AZO/CD-PMPC 1, bMSNs-AZO/CD-PMPC 2, and bMSNs-AZO/CD-PMPC 3, respectively.

3□ Material Characterization

3.1. XPS spectra of bMSNs and modified bMSNs

The deconvolution analysis of the XPS spectra for N 1s and P 2p was illustrated in Figure S3-5. Figure S3 showed one N 1s peak of bMSNs-AZO located at 399 eV, which could be assigned to N atom in −NH−CO− and −N=N− groups in AZO. Compared with Figure S3, the N 1s spectrum of bMSNs-AZO/CD-PMPC in Figure S4 gave two peaks located at 399 eV and 402 eV, which was attributed to the N atom in −NH−CO− and −N=N− groups, and $-N^{+}(NH_3)_3$ group, respectively. In the P 2p region of bMSNs-AZO/CD-PMPC, the single peak centered at 132 eV, corresponding to the P atom in $-OPOCH_2-$ groups (Figure S5). All the above results indicate the successful modification of azobenzene and CD-PMPC on bMSNs.

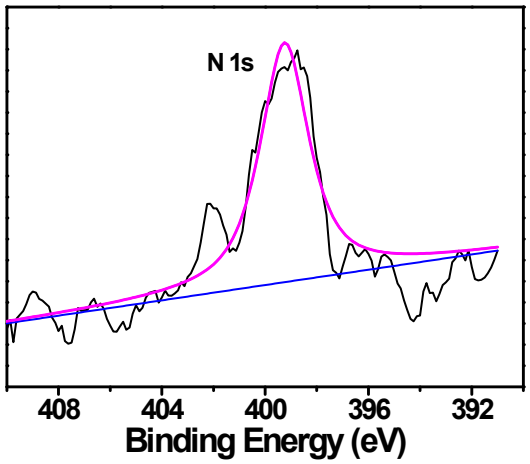


Figure S3. XPS spectrum of bMSNs-AZO (N 1s).

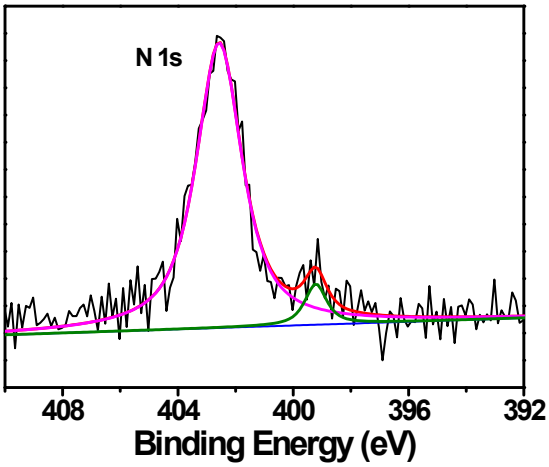


Figure S4. XPS spectrum of bMSNs-AZO/CD-PMPC (N 1s).

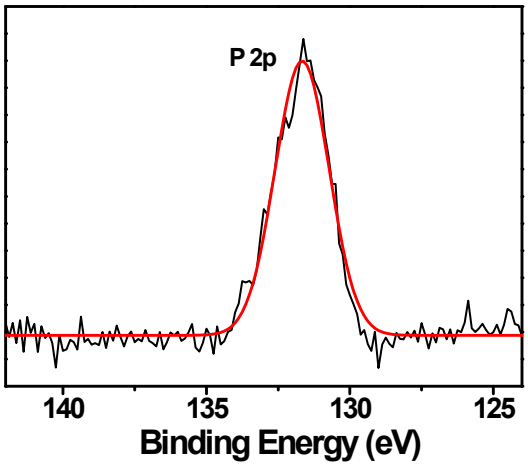


Figure S5. XPS spectrum of bMSNs-AZO/CD-PMPC (P 2p).

3.2. N_2 adsorption and desorption isotherm of bMSNs and modified bMSNs

The nitrogen adsorption and desorption isotherm curves and the pore size distribution curves of bMSNs, bMSNs-AZO and bMSNs-AZO/CD-PMPC were depicted in Fig. 2h-i. The physicochemical parameters of bMSNs, bMSNs-AZO and bMSNs-AZO/CD-PMPC were summarized in Table S1. The nitrogen adsorption-desorption isotherm curves of the three samples showed a typical IV type isotherm with a hysteresis loop, demonstrating the existence of mesoporous channels in the nanoparticles. Based on the

BET and the BJH model, the surface area and the pore volume were calculated to be 733 m^2/g and 2.98 mL/g for bMSNs, 593 m^2/g and 2.59 mL/g for bMSNs-AZO, and 378 m^2/g and 1.32 mL/g for bMSNs-AZO/CD-PMPC, respectively.

Table S1. Physicochemical parameters of bMSNs, bMSNs-AZO and bMSNs-AZO/CD-PMPC.

Sample	S_{BET} (m^2/g)	V_p (mL/g)	Pore size (nm)
bMSNs	733	2.98	9.39
bMSNs-AZO	593	2.59	9.14
bMSNs-AZO/CD-PMPC	378	1.32	8.59

3.3. *In vitro* biodegradation of bMSNs and modified bMSNs

The *in vitro* biodegradation experiments of bMSNs and modified bMSNs were carried out by dispersing 5 mg of nanoparticles in 20 mL of simulated body fluid (pH 6.0) solution under 37 ℃ with slight shaking. At 0 d, 1 d, 5 d and 10 d, 0.1 mL of solution was taken out and collected by centrifugation for TEM observation.

The TEM images in Figure S6 indicated that the bMSNs, bMSNs-AZO and bMSNs-AZO/CD-PMPC nanoparticles experienced rapid degradation, including the erosion at the surface as well as the bulk of the nanoparticles, which resulted in the breakdown of the mesoporous structure as time increased. The degradability of the silica nanoparticles was attributed to the loose mesoporous structure with a low cross-linking degree, and this may avoid accumulation of the nanoparticles *in vivo* and promote the application of bMSNs in clinics.

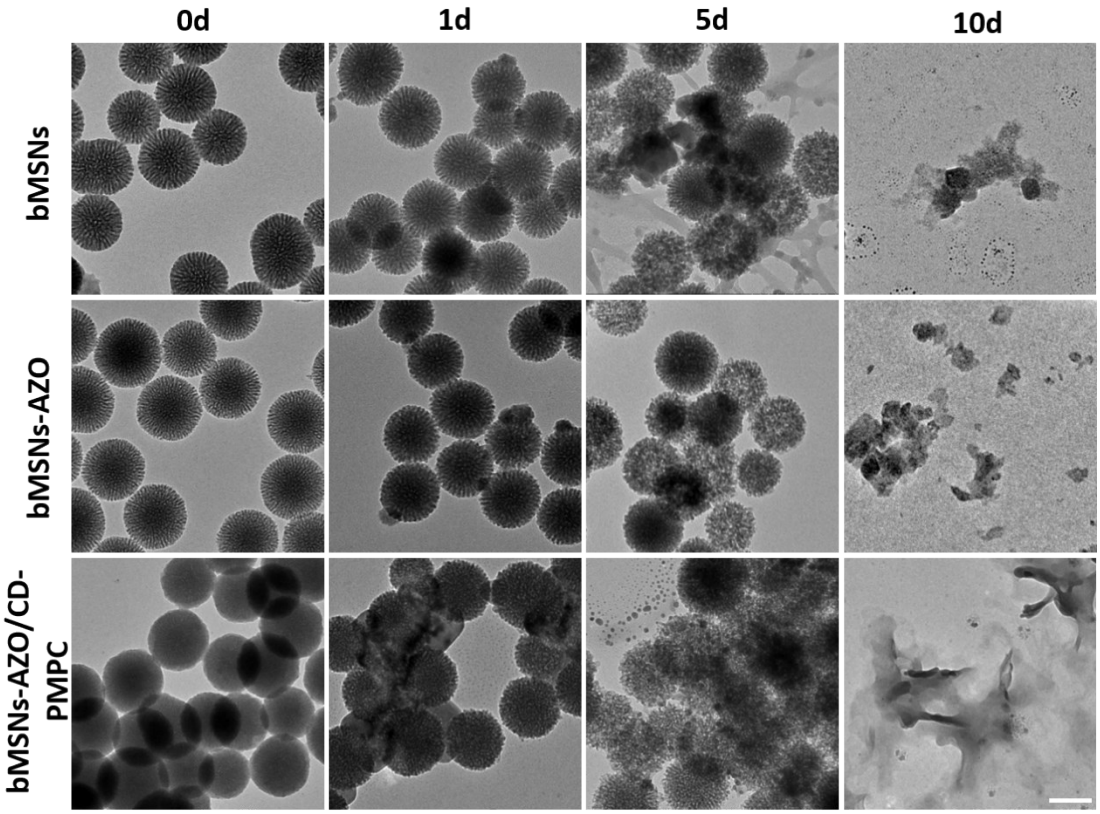


Figure S6. TEM images showing the biodegradation behavior of the bMSNs, bMSNs-AZO and bMSNs-AZO/CD-PMPC nanoparticles in simulated body fluid at 37 °C (bar = 100 nm).

3.4. UV-vis spectra and ^{1}H NMR spectra of AZO and AZO/β-CD

The UV-vis spectra of AZO in Figure S7 indicated that the visible light with a wavelength of 450 nm could induce isomerization with or without passing through nude mouse shin. The absorption band at the maximum absorption wavelength (λ_{max}) declined with increasing the irradiation time, and reached equilibrium in 600 s. In the presence of nude mouse skin, the visible light was weakened with a slight decrease of AZO isomerization. For comparison, the UV-vis spectra of AZO/β-CD with a molar ratio of 1:1 were also tested at different irradiation times with/without passing through nude mouse skin. It could be seen from the spectra that the Abs value at λ_{max} decreased

when β-CD was added. This phenomenon was attributed to AZO entering the cavity of β-CD with high hydrophobicity and high electron density, indicating the formation of host-guest complex between AZO and β-CD.[S4-8] By considering the reduction of the maximum Abs value after irradiation, the isomerization degree in AZO (Figure S7a) and AZO/β-CD (Figure S7c) was calculated to be 27.1% and 28.1%. In a similar manner, the ^{1}H NMR spectra of AZO (C_{AZO} = 1 mM) and AZO/β-CD (molar ratio = 1:1, C_{AZO} = 1 mM) with/without irradiation were also recorded (Figure S8). The mixed solutions were irradiated at 450 nm for 10 min to ensure the trans-to-cis isomerization of AZO. After visible light irradiation, the intensity of the peaks at 6.80 and 7.32 ppm increased while the intensity of the peaks at 7.56 and 7.82 ppm decreased, which were ascribed to the $H_{h,k}$ and $H_{i,j}$ in cis isomer and trans isomer of AZO, respectively. Besides, the peaks corresponding to H_g were split into two parts, suggesting the proton environmental variation after photoisomerization. These results indicated that the isomerization of AZO occurred in both AZO and AZO/β-CD. The comparison between the original spectra and the spectra after irradiation allowed for the calculation of the isomerization degree, and the isomerization degree in AZO and AZO/β-CD was calculated to be 28.3% and 29.1%.

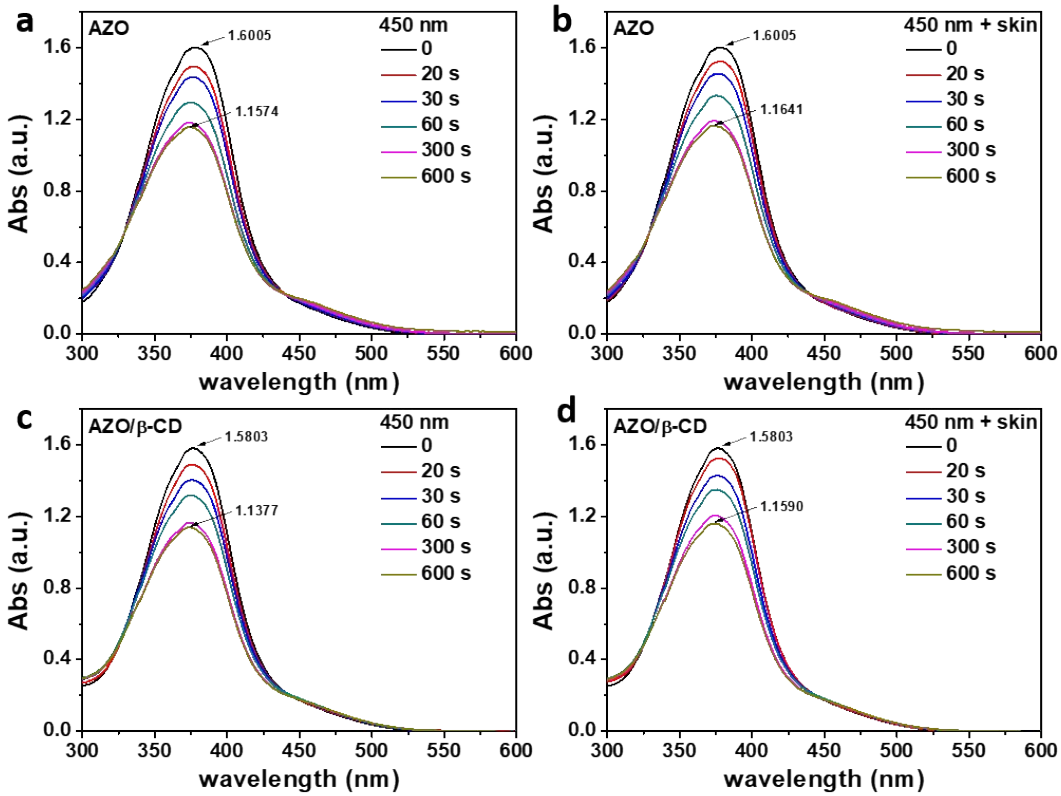


Figure S7. The UV-vis spectra of AZO (C_{AZO} = 0.06 mM, a and b) and AZO/β-CD (molar ratio = 1:1, C_{AZO} = 0.06 mM, c and d) in dark condition and after irradiation with visible light (450 nm) at different times with/without passing through nude mouse skin (solvent: dimethyl sulfoxide). The Abs values at the maximum absorption wavelength (λ_{max}) of AZO and AZO/β-CD after irradiation for 0 s and 600 s were given in the figure.

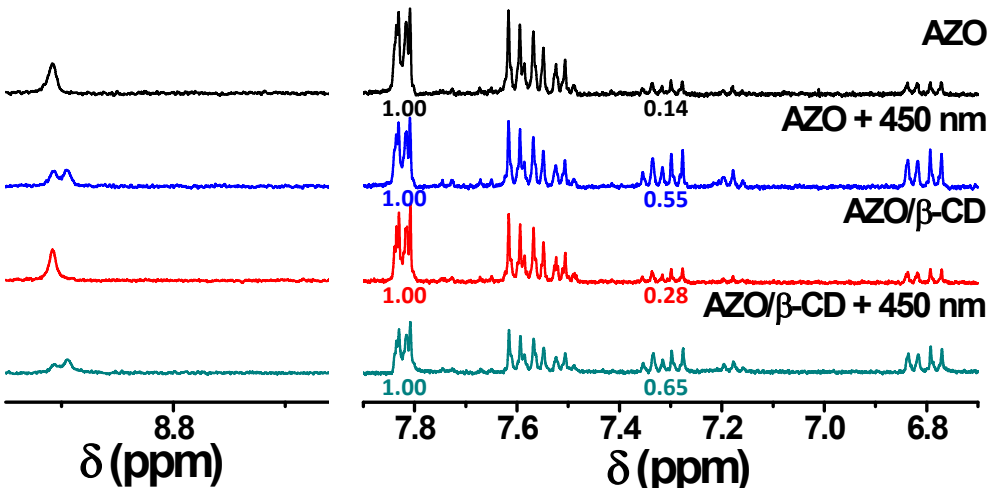


Figure S8. The ^{1}H NMR spectra of AZO (C_{AZO} = 1 mM) and AZO/β-CD (molar ratio

= 1:1, C_{AZO} = 1 mM) in dark condition and after irradiation with visible light (450 nm) for 600 s in DMSO-d6. The integral values of the peaks at 7.32 ppm and 7.82 ppm were given below the corresponding peak by setting the integral of the peak at 7.82 ppm as 1.00.

4□ Drug Loading and Controlled Release Experiments

4.1. DS loading process

30 mg of bMSNs-AZO and 5 mg of DS were dispersed in 10 mL of deionized water, and the solutions were stirred in dark condition for 24 h. Then, 6 mg, 12 mg and 18 mg of CD-PMPC was added and stirred in dark condition for another 24 h to obtain the DS loaded bMSNs-AZO/CD-PMPC-1, bMSNs-AZO/CD-PMPC-2 and bMSNs-AZO/CD-PMPC-3, respectively. The nanoparticles were collected by centrifugation, washed with deionized water and dried under vacuum overnight. The drug loading capacity (LC, %) and encapsulation efficiency (EE, %) were calculated according to the Equations S1-2.

$$LC\ (\%) = \frac{amount\ of\ loaded\ DS}{amount\ of\ DS\text{-}loaded\ nanoparticles} \times 100 \quad (S1)$$

$$EE\ (\%) = \frac{amount\ of\ loaded\ DS}{amount\ of\ added\ DS} \times 100 \quad (S2)$$

For bMSNs, bMSNs-AZO/CD-PMPC 1, bMSNs-AZO/CD-PMPC 2 and bMSNs-AZO/CD-PMPC 3, the DS loading capacity was calculated to be 2.10%, 2.86%, 3.91% and 4.20%, while the encapsulation efficiency was calculated to be 21.46%, 29.47%, 40.71% and 43.92%. The drug loading capacity of bMSNs-AZO/CD-PMPC increased along with the CD-PMPC concentration used in the modification process. This was considered to be attributed to the binding between DS and CD, as DS adsorbed on the surface of the silica nanoparticles could form complexes with CD to some extent, and

similar results were previously reported in the literature.[S9]

4.2. DS release experiment

The release of DS from bMSNs-AZO/CD-PMPC 1, bMSNs-AZO/CD-PMPC 2 and bMSNs-AZO/CD-PMPC 3 nanoparticles were examined by dialysis process. Typically, 8 mg of DS-loaded nanoparticles were sonicated uniformly in 2 mL of phosphate buffer saline (PBS) and put into a dialysis bag (molecular weight cut off 3500). The dialysis bag was immersed in 18 mL of PBS. At regular intervals, 2 mL of DS-containing PBS was taken out for UV-vis measurements and 2 mL of fresh PBS was added. The calibration curve of DS and the release curves of DS from different bMSNs-AZO/CD-PMPC nanoparticles were shown in Figure S9-12.

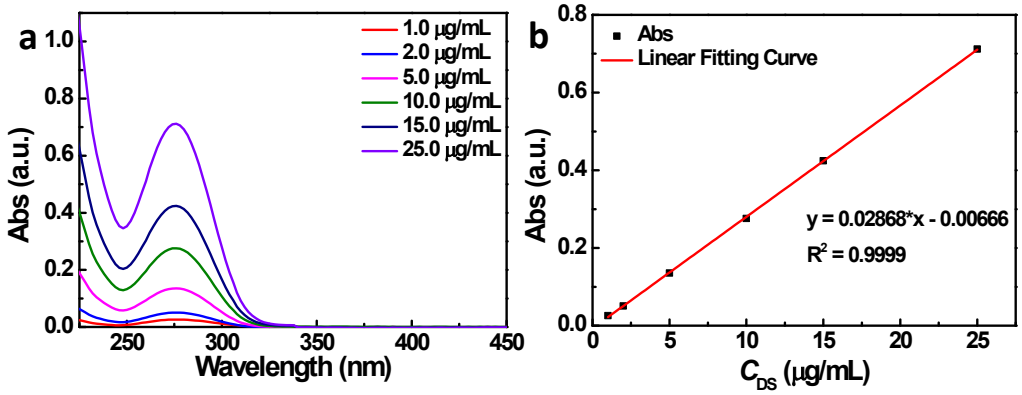


Figure S9. (a) The UV-vis spectra of DS with different concentrations; (b) calibration curve of DS with different concentrations.

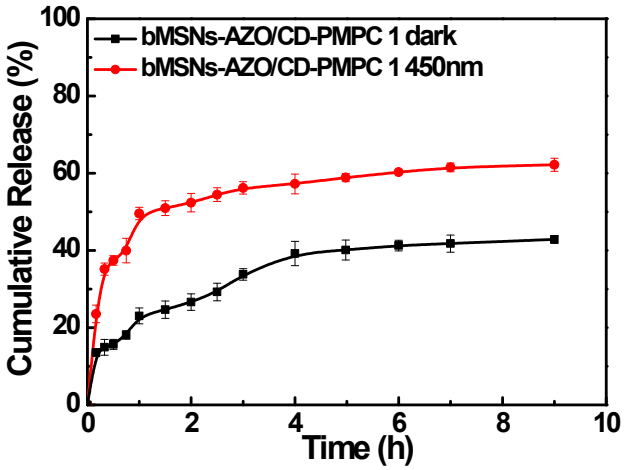


Figure S10. The release curves of DS from bMSNs-AZO/CD-PMPC 1 in the dark and with the irradiation of visible light (450 nm).

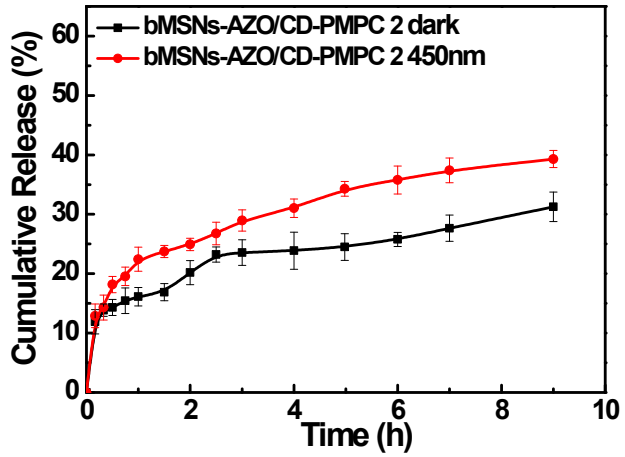


Figure S11. The release curves of DS from bMSNs-AZO/CD-PMPC 2 in the dark and with the irradiation of visible light (450 nm).

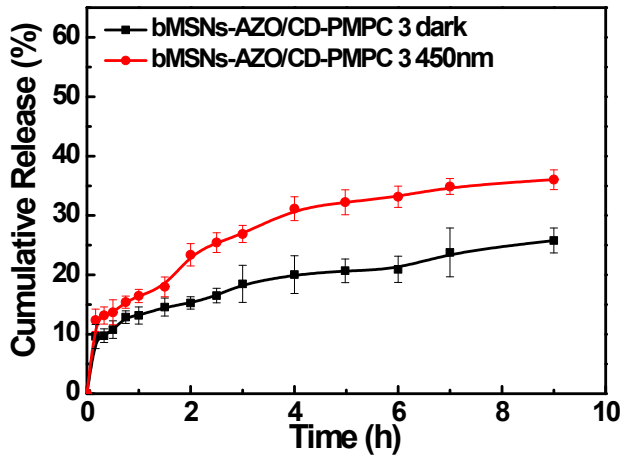


Figure S12. The release curves of DS from bMSNs-AZO/CD-PMPC 3 in the dark and

with the irradiation of visible light (450 nm).

5□ Tribological Tests of bMSNs and Modified bMSNs

The lubrication properties of bMSNs-AZO/CD-PMPC with different CD-PMPC concentrations were evaluated by a series of tribological tests. Figure S13-15 depicted the COF values of bMSNs-AZO/CD-PMPC under different test conditions. The results demonstrated that the COF value decreased with the increase in the concentration of bMSNs-AZO/CD-PMPC. Additionally, it seemed to experience a gradually decreasing trend with the increase in the loading force and scanning rate, which indicated that the lubrication enhancement was based on hydration lubrication mechanism.[S10] Combining all the results, the bMSNs-AZO/CD-PMPC nanoparticles could efficiently enhance the lubrication owing to the hydration layer formed around the zwitterionic charged groups in CD-PMPC.

To verify the lubrication property of detached CD-PMPC from silica nanoparticles after visible light irradiation, the tribological tests of CD-PMPC, bMSNs and bMSNs-AZO samples before and after visible light irradiation were performed, with the results illustrated in Figure S16. The concentration of CD-PMPC used in this experiment was consistent with that of bMSNs-AZO/CD-PMPC-2. The result illustrated that the visible light irradiation had negligible effect on the COF values of these samples as no obvious change was detected, which confirmed that both free and combined CD-PMPC could provide excellent lubrication performance in the aqueous solution.

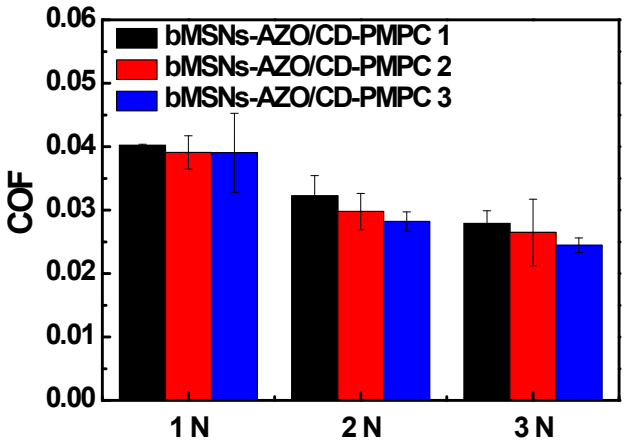


Figure S13. The lubrication properties of bMSNs-AZO/CD-PMPC-1, bMSNs-AZO/CD-PMPC-2 and bMSNs-AZO/CD-PMPC-3 at different loading forces (concentration: 2.0 mg/mL; scanning rate: 2 Hz).

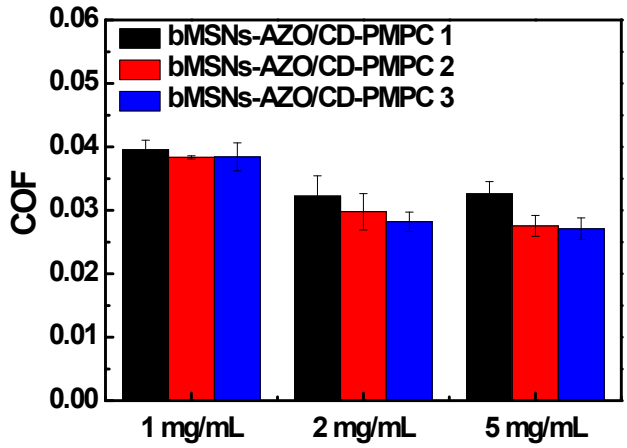


Figure S14. The lubrication properties of bMSNs-AZO/CD-PMPC-1, bMSNs-AZO/CD-PMPC-2 and bMSNs-AZO/CD-PMPC-3 at different concentrations of nanoparticles (scanning rate: 2 Hz; loading force: 2 N).

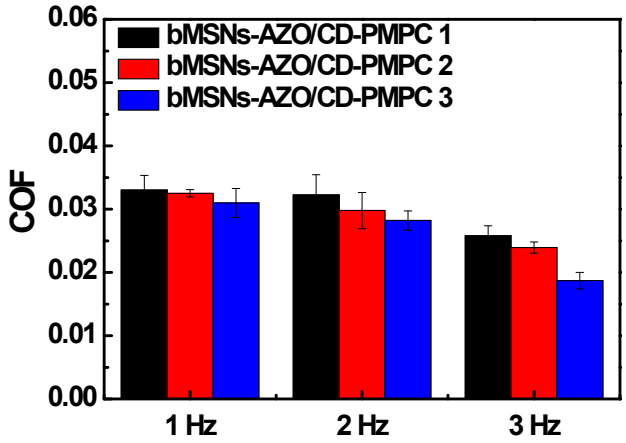


Figure S15. The lubrication properties of bMSNs-AZO/CD-PMPC-1, bMSNs-AZO/CD-PMPC-2 and bMSNs-AZO/CD-PMPC-3 at different scanning rates (concentration: 2.0 mg/mL; loading force: 2 N).

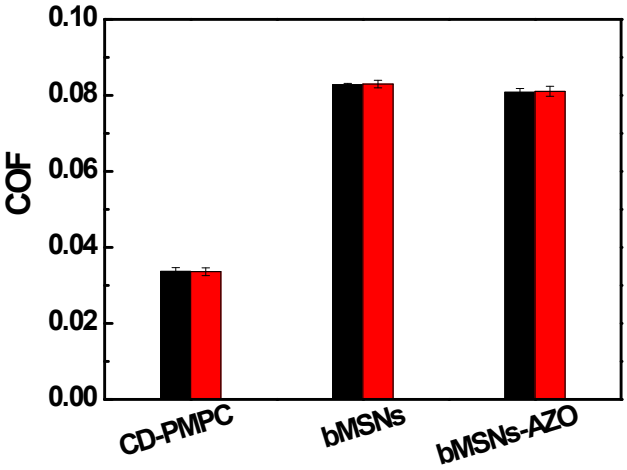


Figure S16. The lubrication property of CD-PMPC (0.8 mg/mL), bMSNs (2.0 mg/mL) and bMSNs-AZO (2.0 mg/mL) before and after visible light irradiation (scanning rate: 2.0 Hz; loading force: 2 N).

6□ *In Vitro* Cytotoxicity

The cell cytotoxicity of bMSNs and bMSNs-AZO/CD-PMPC was examined using the CCK-8 assay. Briefly, the mouse MC3T3-E1 osteoblastic cells were cultured in a 96-well plate at a density of 5×10^3 cells/well, and then bMSNs and bMSNs-AZO/CD-

PMPC with different concentrations were added and incubated for 24 h. Afterward, 0.5 mg/mL of bMSNs or bMSNs-AZO/CD-PMPC were chosen as a representative to investigate cell cytotoxicity on 1, 3 and 5 days. Finally, 50 μL of CCK-8 solution was added into each well, and the absorbance of the solution at 450 nm was measured using an Infinite F50 instrument (Tecan, Switzerland) after incubation for 2 h. The results were shown in Figure S17-18.

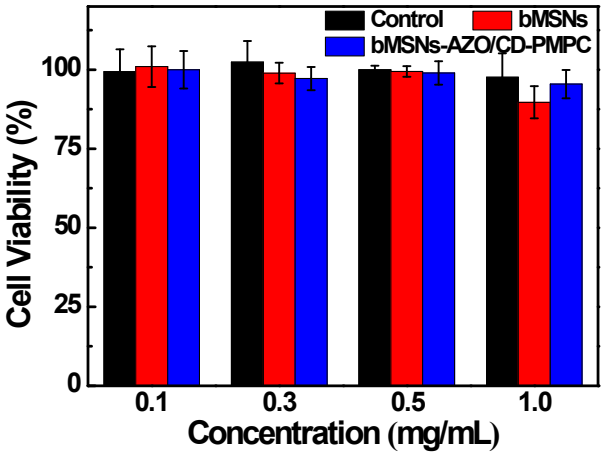


Figure S17. Cell viability of the MC3T3-E1 cells after incubation with different concentrations of bMSNs or bMSNs-AZO/CD-PMPC.

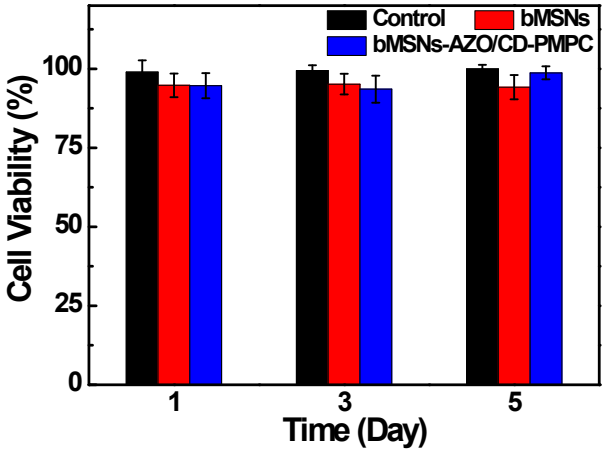


Figure S18. Cell viability of the MC3T3-E1 cells after incubation with 0.5 mg/mL of bMSNs or bMSNs-AZO/CD-PMPC for 1, 3 and 5 days.

7□ The Protein Expression Levels in bMSNs and Modified bMSNs Treated MC3T3-E1 Cells

The protein expression levels of IL-6, MMP13, ADAMTS5 and Agg in the MC3T3-E1 cells treated with 5 nM of TNF-α and then cultured with 0.1 mg/mL of bMSNs, bMSNs-AZO/CD-PMPC, bMSNs/DS, bMSNs-AZO/DS or bMSNs-AZO/CD-PMPC/DS were also examined and the corresponding results were depicted in Figure S19. As shown in Figure S19, bMSNs-AZO/CD-PMPC treated group induced lower protein expression levels of IL-6, MMP13 and ADAMTS5 and higher protein expression level of Agg to some extent compared with bMSNs treated group, which could be attributed to the anti-inflammatory effect of PMPC.[S11] After encapsulating DS, the bMSNs/DS, bMSNs-AZO/DS and bMSNs-AZO/CD-PMPC/DS treated groups could effectively downregulate the expression levels of IL-6, MMP13 and ADAMTS5 and upregulate the expression level of Agg. For bMSNs/DS and bMSNs-AZO/DS treated groups, the protein expression levels of IL-6, MMP13, ADAMTS5 and Agg showed no obvious differences, indicating that the drug molecule DS played an important role in reducing inflammation. The introduction of bMSNs-AZO/CD-PMPC/DS to the MC3T3-E1 cells resulted in the lowest protein expression levels of IL-6, MMP13 and ADAMTS5 and the highest protein expression level of Agg, owing to the combination effect of drug molecule and PMPC. All the above results proved that the modified silica nanoparticles bMSNs-AZO/CD-PMPC through supramolecular interaction of AZO and CD-PMPC showed the best anti-inflammatory effect among the tested groups, which could effectively release the drug molecules.

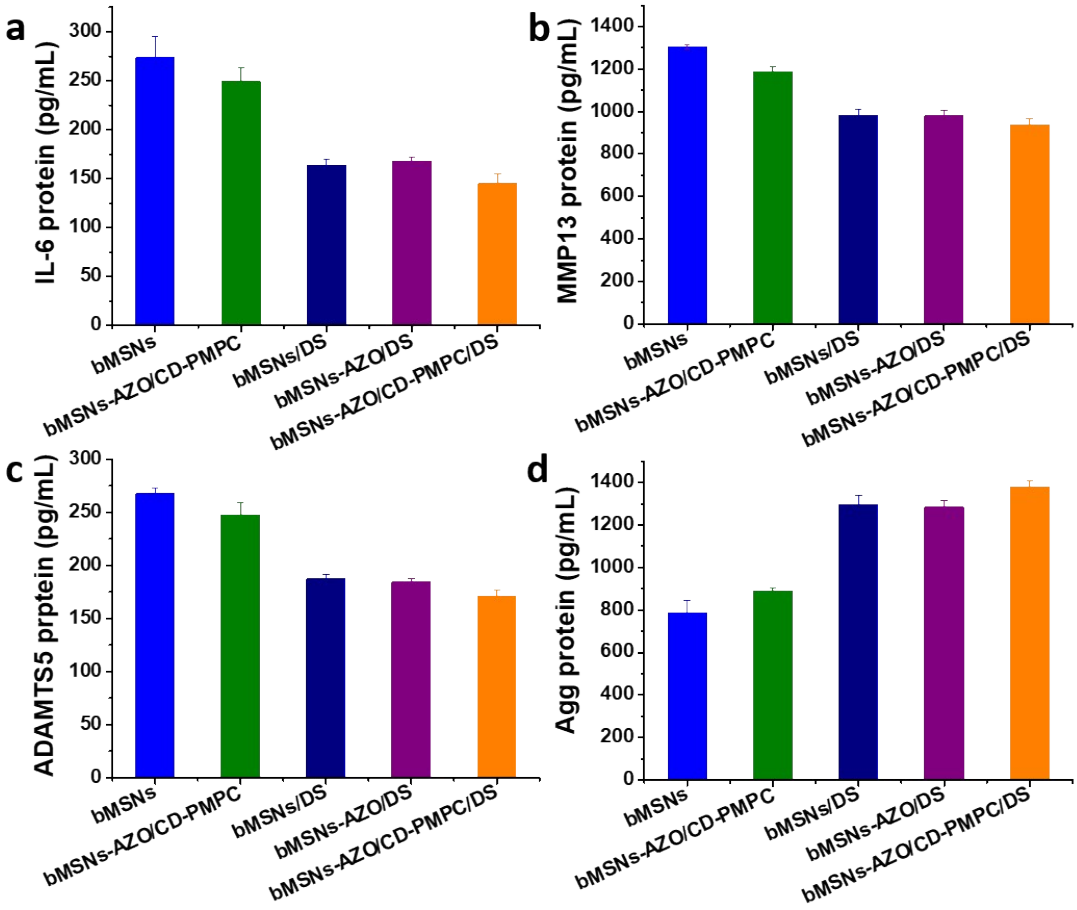


Figure S19. The protein expression levels of IL-6 (a), MMP13 (b), ADAMTS5 (c) and Agg (d) in the MC3T3-E1 cells treated with 5 nM of TNF-α and then cultured with 0.1 mg/mL of bMSNs, bMSNs-AZO/CD-PMPC, bMSNs/DS, bMSNs-AZO/DS or bMSNs-AZO/CD-PMPC/DS for 12 h, measured by ELISA kits.

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