Electronic Supplementary Information

Mass Spectrometric Imaging and Monitoring of In Vivo Glutathione-triggered Cisplatin Release from Nanoparticle in Kidney

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MATERIALS AND METHODS

Chemicals. Dichloromethane (DCM), methanol and diethyl ether (Et_2O) were ordered from RCI Labscan (Bangkok, Thailand). Thioctic acid, ethylenediamine (EDA), *N*,*N*'-carbonyldiimidazole (CDI), and 1H-pyrazole-1-carboxamidine hydrochloride (PCAC) were purchased from Meryer (Shanghai, China).

NMR spectroscopy. The ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR were obtained from Bruker Advance–III 400 spectrometers operating at 101 and 400 MHz, accordingly, and the chemical shifts are quoted in ppm. ^{1}H and ^{13}C chemical shifts were assigned relatively to solvent chemical shift values ($CDCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.16 ppm; CD_3OD: ^{1}H, 3.31 ppm; ^{13}C, 49.00 ppm; $(CD_3)_2CO$: ^{1}H, 29.84 ppm; ^{13}C, 206.26 ppm), and the data were processed by MestReNova Software (Mestrelab).

Mass Spectrometry. Bruker Autoflex Mass Spectrometer (MALDI–TOF) and Thermo Fisher Scientific UPLC–Q exactive focus hybrid quadrupole-orbitrap mass spectrometer in positive ion mode (ESI–MS) were performed to gather the high-resolution mass spectra.

Preparation of thioctic monomer: The monomer was prepared according to the literature.[S1] Thioctic acid (7.84 g, 38 mmol) was first dissolved in 250 mL of DCM followed by addition of carbonyldiimidazole (CDI, 8.12 g, 50 mmol). The solution was stirred for 10 min until observable bubbles was formed. The solution was added dropwise to a round bottom flask containing ethylenediamine (20 mL, 300 mmol, in 70 mL DCM) under vigorous stirring at 0 °C for 40 min and room temperature for another 40 min. The resulted solution was washed with brine to remove the salt byproducts for three times. The organic layer was collected and condensed to the volume of about 100 mL using a rotary evaporator. To the above solution, a minimum amount of 1H-pyrazole-1-carboxamidine hydrochloride (4.39 g, 30 mmol) was added to the solution in order to ensure a complete reaction with the intermediate. The solution was stirred at room temperature for 6 h. Next, the solution was condensed to allow the

formation of sticky yellow solid. The yellow organic layer was washed with DCM and MeOH/Et_2O (v/v, 1:9) to remove pyrazole byproducts. The yellow solid was collected by drying over high vacuum for 12 h. The ^1H NMR and $^{13}C\{^1H\}$ NMR of the thioctic monomer were obtained from Bruker Advance–III 400 spectrometers operating at 101 and 400 MHz, accordingly, and the chemical shifts are quoted in ppm. ^1H and ^{13}C chemical shifts were assigned relatively to solvent chemical shift values, and the data were processed by MestReNova Software (Mestrelab). Bruker Autoflex Mass Spectrometer (MALDI–TOF) and Thermo Fisher Scientific UPLC–Q exactive focus hybrid quadrupole-orbitrap mass spectrometer in positive ion mode (ESI–MS) were performed to gather the high-resolution mass spectra of the synthesized monomer.

SYNTHESIS

General scheme

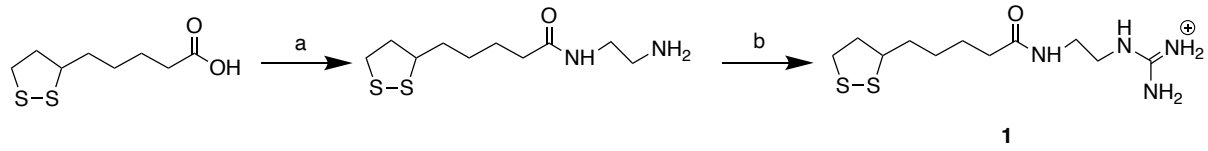

Figure S1 Synthetic scheme of **Monomer** (**1**). a) EDA, CDI, DCM, 40 min in ice bath and 30 min at room temperature, b) PCAC, DCM, 18 h at room temperature.

Monomer (1). ^1H NMR (400 MHz, methanol-d_4) δ 3.65 – 3.51 (m, 1H), 3.37 – 3.29 (m, 4H), 3.21 – 3.05 (m, 2H), 2.46 (m, J = 12.0, 6.7, 5.3 Hz, 1H), 2.24 (t, J = 7.5 Hz, 2H), 1.89 (dq, J = 13.6, 6.9 Hz, 1H), 1.77 – 1.56 (m, 4H), 1.55 – 1.36 (m, 2H). ^{13}C NMR (101 MHz, methanol-d_4) δ 176.96, 158.86, 57.54, 42.08, 41.32, 39.35, 36.71, 35.71, 29.87, 26.54. HRMS (MALDI-TOF): $C_{11}H_{23}N_4OS_2^+$ $[M+H]^+$: calculated 291.1306; found 291.1283.

NMR AND MASS SPECTRA

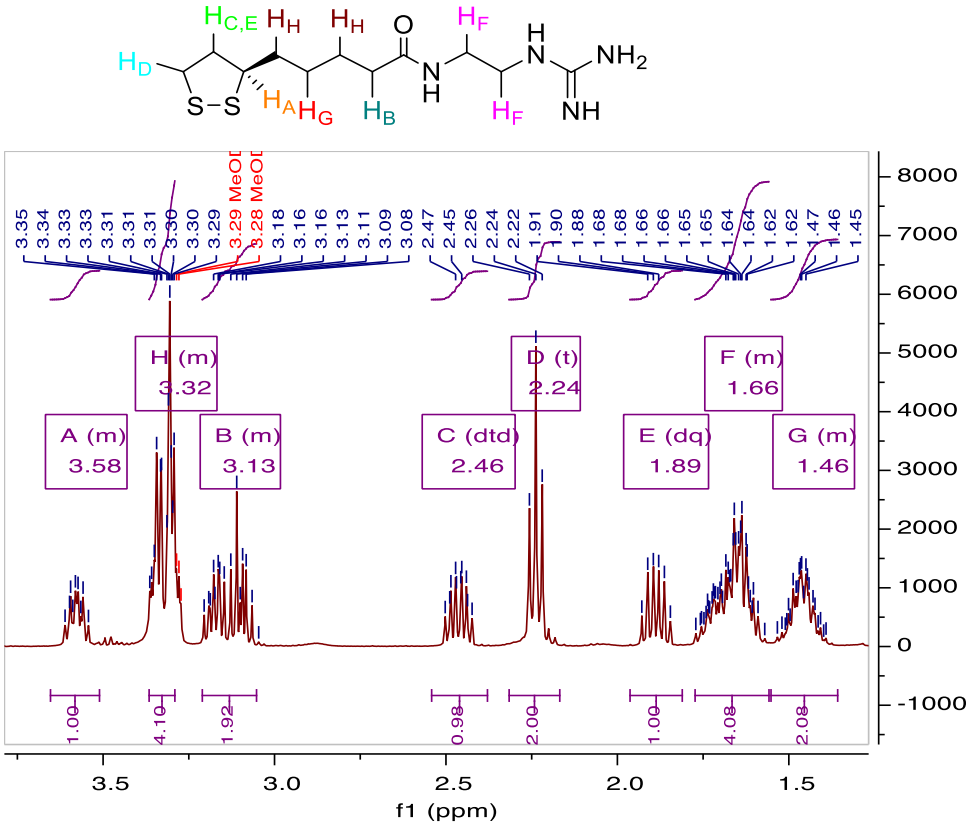

Figure S2. 1H NMR spectrum (400 MHz, methanol-d_4) of **Monomer** (1).

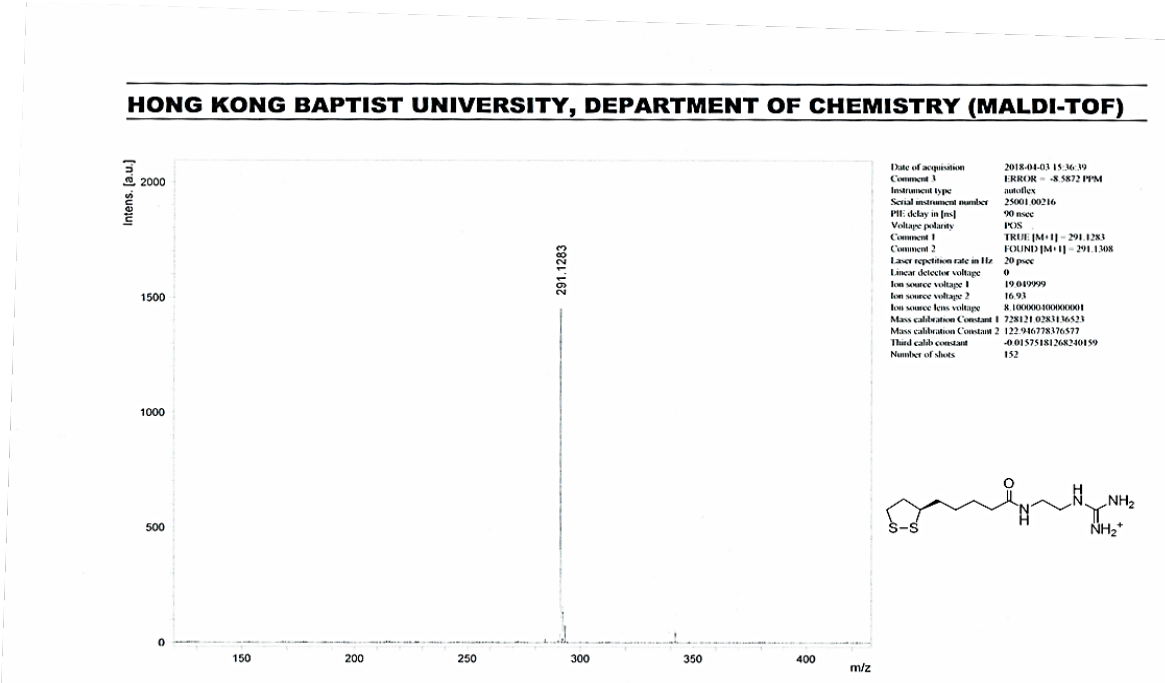

Figure S3. HRMS (MALDI–TOF) analysis of **Monomer (1)**: $C_{11}H_{23}N_4OS_2^+$ $[M+H]^+$: calculated 291.1306; found 291.1283.

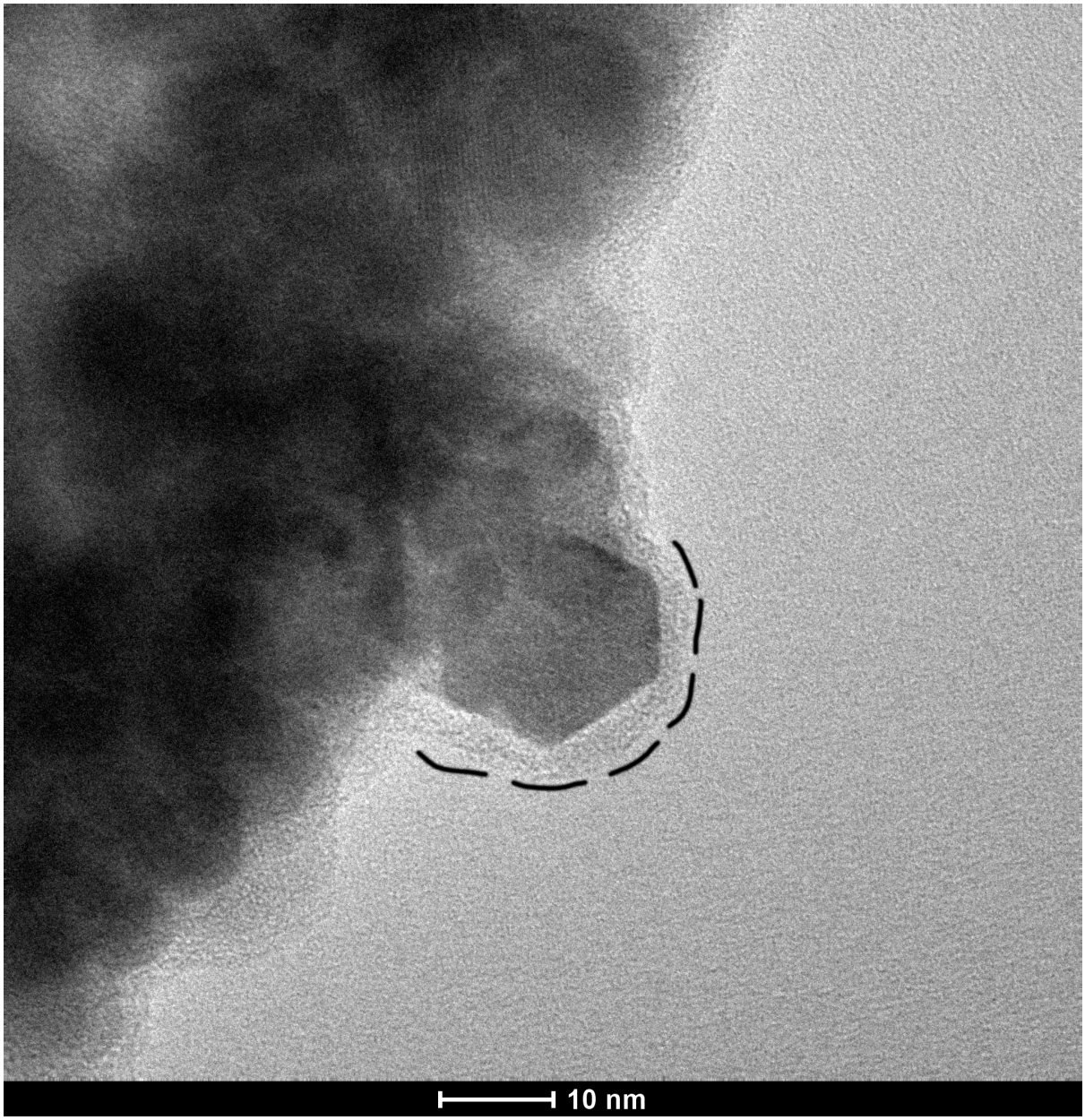

Figure S4. TEM image of *h*Fe3O4-MPS-CPD indicating the polymer layer on the particle surface.

TABLE

Table S1 Loading conditions and efficiency of cisplatin in *h*Fe_3O_4-MPS-CPD.

Solvent	Cisplatin concentration	Pt/Fe ratio
H_2O	1.0	1.4%
DMF	16.0	3.1%
DMF/ H_2O (v/v, 1:1)	9.0	7.9%
acetone	2.4	23.4%

REFERENCE

(S1) E. K. Bang, G. Gasparni, G. Molinard, A. Roux, N. Sakai and S. Matile, *J. Am. Chem. Soc.,* 2013, **135**, 2088-2091.