SUPPORTING INFORMATION

Modulating the cellular uptake of platinum drugs with glycopolymers

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Experimental Part

Materials

D-Glucose (99%, Aldrich), D-galactose (99%, Aldrich) and D-fructose (99%, Aldrich) were used without further purification. Methacrylic acid (MAA, 99%, Aldrich) was passed through basic alumina column to remove inhibitor and stored at -20 °C. 2,2′-Azobis(isobutyronitrile) (AIBN, 98%, Fluka) was recrystallized from methanol. 4-Dimethylaminopyridine (DMAP; 94%, Aldrich), fluorescein O-methacrylate (FMA, 97%, Aldrich), methacrylic anhydrate (94%, Aldrich), sulfuric acid (95-98%, Ajax Finechem), acetone (HPLC grade, Ajax Finechem), dichloromethane (DCM; anhydrous, >99.8%, Aldrich), and N,N-dimethylformamide (DMF; 99%, Ajax Finechem) were used as received. Dioxane (99%, Ajax Finechem) and pyridine (99%, Ajax Finechem) were purified by vacuum distillation. Triethyl amine (Et_3N, 99.5%, Aldrich), diethyl ether (Et_2O anhydrous, 99%, Ajax Finechem), sodium chloride (99.8%, Aldrich), petroleum spirit (BR 40-60 °C, 90%, Ajax Finechem), tetrahydrofuran (THF; 99.7%, Ajax Finechem), dimethylsulfoxide-d_6 (DMSO; Cambridge Isotope Laboratories), chloroform-*d* ($CDCl_3$; Cambridge Isotope Laboratories), chloroform ($CHCl_3$; 99.8%, Aldrich), N,N dimethylacetamide (DMAc; Aldrich, HPLC grade), methanol (APS, HPLC grade), magnesium sulfate (70%, Ajax Finechem) and toluene (Aldrich, purum) were used as received. The RAFT agent 4-cyanopentanoic acid dithiobenzoate (CPADB) was prepared according to the procedure described elsewhere [1]. Unless otherwise specified, all chemicals were reagent grade and were used as received.

Instrumentation

Gel Permeation Chromatography (GPC)

The conventional gel permeation chromatography (GPC) measurements were carried out with a Shimadzu modular system, comprising of an auto-injector, a Phenomenex Phenogel 5.0 mm bead-size guard column (50 x 7.5 mm), four linear Phenomenex columns (10^5, 10^4, 10^3 and 500 Å), and a differential refractive index detector. The eluent used was N,Ndimethylacetamide (DMAc) (0.05% w/v LiBr, 0.05% w/v BHT) at 50 ºC with a flow rate of 1 mL/min. The apparent molecular weights ($M_{w,GPC}$ and $M_{n,GPC}$) and polydispersities (M_w/M_n) were determined with a calibration based on linear PS standards ranging from 162 to $2x10^6$ g/moL. Additionally, water GPC (water containing 0.02% w/v NaN_3) was performed using a Shimadzu modular system comprising a DGU-12A solvent degasser, an LC-10AT pump, a CTO-10A column oven, and a RID-10A refractive index detector (flow rate: 0.8 mL/min). The system was equipped with a Polymer Laboratories 5.0 mm bead-size guard column (50 × 7.8 mm^2) followed by three 300 × 7.8 mm linear PL columns (30, 40 and 50 respectively in type). Calibration was conducted with PEO standards ranging from 500 to 500,000 g/moL.

Nuclear Magnetic Resonance (NMR) Spectrometry

NMR spectra were conducted using a Bruker Avance III 300 spectrometer (300 MHz). All chemical shifts are recorded in ppm (δ) relative to tetramethylsilane (δ=0 ppm), referenced to the chemical shifts of residual solvent resonances (^{1}H and ^{13}C).

Dynamic Light Scattering (DLS)

Dynamic light scattering studies of the nanoparticle solutions at 1 mg/mL in an aqueous medium were conducted using a Malvern Instruments Zetasizer Nano ZS instrument equipped with a 4 mV He–Ne laser operating at λ = 633 nm, an avalanche photodiode detector with high quantum efficiency, and an ALV/LSE-5003 multiple tau digital correlator electronics system.

Transmission Electron Microscopy (TEM)

The sizes and morphologies of the nanoparticles were observed using a transmission electron microscope JEOL1400 TEM at an accelerating voltage of 100 kV. The nanoparticle solutions in water (1 mg/mL) was deposited onto formvar-coated copper grid (200 mesh) for 10 min. The excess liquid was removed by filter paper. After grid being dried, the samples were imaged without staining.

Thermogravimetric analysis (TGA)

The loading content and loading efficiency of platinum onto glyco-block copolymers were determined by using a Perkin-Elmer Thermogravimetric Analyzer (Pyris 1 TGA). Analyses were conducted over a temperature range of 25-800 ºC with a programmed temperature increment of 20 ºC per min.

Inductively coupled plasma-mass spectrometer (ICP-MS)

The Perkin-Elmer ELAN 6000 inductively coupled plasma-mass spectrometer (Perkin-Elmer, Norwalk, CT, U.S.A.) was used for quantitative determinations of platinum in drug release experiment. All samples were carried out at an incident ratio frequency power of 1200 W. The plasma argon gas flow of 12 L/min with an auxiliary argon flow of 0.8 L/min was used in all cases, and the nebulizer gas flow was adjusted to maximize ion intensity at 0.93 L/min as indicated by the mass flow controller. The element/mass detected was ^{195}Pt and the internal standard used was ^{193}Ir. Replicate time was set to 900 ms and the dwell time was set to 300 ms. Peak hopping was the scanning mode employed and the number of sweeps/readings was set to three. Ten replicates were measured at a normal resolution. The samples were treated with aqua regia solution at 90 ºC for 2 h to digest platinum.

Synthetic procedures

Synthesis of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucose (β-AcGlc) (1)

β-AcGlc, **1**, was prepared according to modified literature procedure [2]. To a 250 mL of round-bottomed flask sodium acetate (6.064 g, 0.074 mol) and acetic anhydride (63 mL, 0.666 mol) were added and the mixture was heated at 140 °C. During that period glucose (12 g, 0.066 mol) was added slowly. After 45 min. the reaction mixture was poured into ice-cold water (500 mL) by stirring vigorously and precipitation of compound was observed after five

minutes. The solid phase was collected by filtration and washed extensively with water. The crude product was then purified by crystallization. The compound was dissolved in warmed ethanol and kept in refrigeration for one night. After decantation of solution, white solid was then transferred to a centrifuge tube and lyophilized. (Yield: 14.73 g, 57%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.71(d, 1H, H-1 $J_{1,2}$= 9 Hz), 5.28 (dd, 1H, H-4, $J_{4,3}$= 3Hz, $J_{4,5}$= 3 Hz), 5.18-5.08 (m, 2H, H-3, H-2), 4.28 (dd, 1H, H-6, $J_{6,6'}$= 6 Hz, $J_{6,5}$= 3 Hz), 4.28 (dd, 1H, H-6', $J_{6',6}$ = 3 Hz, $J_{6',5}$= 3 Hz), 4.07 (m, 1H, H-5), 2.11, 2.08, 2.03, 2.03, 2.01 (15H, OC=OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 170.65, 170.14, 169.42, 169.28, 168.99 (O*C*=OCH_3), 91.73 (C-1), 71.82 (C-4), 72.75 (C-5), 70.25 (C-2), 67.76 (C-3), 61.47 (C-6), 20.85, 20.73, 20.63 20.62, 20.51 (5C, OC=O*C*H_3).

Synthesis of 1,2,3,4,6-penta-*O*-acetyl-D-galactose (β-AcGal) (2)

A similar procedure was repeated for the preparation of β-AcGal. To a 250 mL of round-bottomed flask was added sodium acetate (6.064 g, 0.074 mol) and acetic anhydride (63 mL, 0.666 mol), and the mixture was heated at 140 °C for 45 minutes. During that period galactose (12 g, 0.066 mol) was added slowly. Then the reaction mixture was poured into ice-cold water (500 mL) by stirring vigorously and precipitation of compound was observed after five minutes. The solid phase was collected by filtration and washed extensively with water. The crude product was then purified by crystallization. The compound was dissolved in warmed ethanol and kept in refrigeration for one night. After decantation of solution, white solid was then transferred to a centrifuge tube and lyophilized. (Yield: 12.27 g, 47%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.69 (d, 1H, H-1 $J_{1,2}$ = 6 Hz), 5.43 (d, 1H, H-4, $J_{4,3}$ = 3Hz, $J_{4,5}$ = 3Hz), 5.33 (dd, 1H, H-2, $J_{2,1}$ = 18Hz, $J_{2,3}$ = 3Hz,), 5.10 (dd, 1H, H-3, $J_{3,2}$ = 3Hz, $J_{3,4}$= 3Hz,), 4.21-4.14 (m, 2H, H-6, H-5), 4.07 (m, 1H, H-6'), 2.18,2.14, 2.06, 2.06, 2.01 (15H, OC=OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 170.34, 170.12, 169.96, 169.37, 168.98 (O*C*=OCH_3), 92.15 (C-1), 71.70 (C-5), 70.83 (C-3), 67.82 (C-2), 66.79 (C-4), 61.02 (C-6), 20.86, 20.64, 20.64 20.61, 20.53 (5C, OC=O*C*H_3).

Synthesis of 2,3:4,5 di-*O*-isopropylidene β-D-fructopyranose (i*pr*Fruc1) (3)

*ipr*Fruc1, **3**, was prapared according to literature procedure [3]. To a flame-dried two necked 1 L of round-bottomed flask was added D-fructose (36 g, 0.199 mol). It was dried under vacumm for 2 h. Then a cooled solution of conc. sulfuric acid (35 mL) in acetone (700 mL)

was added to the flask and left to stir for 1.5 h at room temperature. After that, the reaction mixture was cooled in an ice bath. The sodium hydroxide solution was prepared in water and gradually added to the reaction mixture with stirring. Acetone was evaporated and resulting solution was extracted with CH_2Cl_2. The extracts were washed with water and dried by anhydrous sodium sulphate and evaporated to a crystalline solid. (Yield: 39.10 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.63 (dd, *J* = 7.9, 2.6 Hz, 1H), 4.36 (d, $_J$ = 2.6 Hz, 1H), 4.26 (ddd, *J* = 7.9, 1.9, 0.8 Hz, 1H), 3.94 (dd, *J* = 13.0, 1.9 Hz, 1H), 3.79 (dd, *J* = 13.0, 0.8 Hz, 1H), 3.78 – 3.62 (m, 2H), 1.56 (s, 3H), 1.50 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.08, 108.52, 103.07, 71.00, 70.79, 70.06, 65.54, 61.27, 26.45, 25.76, 25.33, 23.96.

Synthesis of 1,2:4,5 di-*O*-isopropylidene β-D-fructopyranose (i*pr*Fruc3) (4)

A similar procedure was repeated for the preparation of *ipr*Fruc1. To a flame-dried two necked 1 L of round-bottomed flask was added D-fructose (36 g, 0.199 mol). It was dried under vacumm for 2 h. Then a cooled solution of conc. sulfuric acid (3.5 mL) in acetone (700 mL) was added to the flask and left to stir for 1.5 h at room temperature. After that, the reaction mixture was cooled in an ice bath. The sodium hydroxide solution was prepared in water and gradually added to the reaction mixture with stirring. Acetone was evaporated and resulting solution was extracted with CH_2Cl_2. The extracts were washed with water and dried by anhydrous sodium sulphate and evaporated to a crystalline solid. (Yield: 20.81 g, 40%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.19-3.96 (m, 6H), 3.65 (d, *J*=6.9 Hz, 1H), 1.52 (s, 3H), 1.50 (s, 3H), 1.43 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 111.86, 109.37, 104.55, 77.30, 73.34, 72.23, 70.33, 60.67, 27.94, 26.37, 26.28, 25.95.

Synthesis of 2-(2',3',4',6'-tetra-*O*-acetyl-D-glucosyloxy) ethyl methacrylate (AcGlcMA) (5)

AcGlcMA, **5**, was prepared according to modified published procedure [4]. AcGlc (5.00 g, 12.80 mmol) and 2-hydroxyethyl methacrylate, (HEMA) (1.86 mL, 15.37 mmol), were added into a 250 mL two-neck round-bottom flask together with molecular sieves (4 A^o). Anhydrous CH_2Cl_2 (80 mL) was added to the stirred flask under nitrogen flow. The reaction started when boron trifluoride diethyl etherate ($BF_3O(Et)_2$) (7.90 mL, 64.04 mmol) was introduced over 30 min via a gastight syringe while maintaining the flow of nitrogen through the flask. After purging the solution for another 20 min, the flask was sealed and left stirring at room temperature for 36 h to allow maximum conversion. The reaction mixture was

filtered through a sintered glass funnel pouring into ice-water (100 mL) and extracted. CH_2Cl_2 solution were washed (aqueous $NaHCO_3$, water), dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure, and the resulting oily light yellow mixture was purified by column chromatography using hexane/ethyl acetate (1.5/1) as eluent. The light yellow oil was obtained with the R_f value of 0.4. (Yield: 4.95 g, 84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.09 (m, 1H, H11), 5.57 (m, 1H, H11'), 5.20 – 5.14 (dd, 1H, H4, $J_{4,3}$= 6 Hz, $J_{4,5}$ = 3 Hz), 5.10 – 5.03 (dd, 1H, H2, $J_{2,1}$ = 9 Hz, $J_{2,3}$ = 6 Hz), 5.01 – 4.95 (dd, 1H, H3), 4.56 – 4.54 (d, 1H, H1), 4.33 – 4.20 (m, 3H, H6, H8), 4.13 – 4.07 (dd, 1H, $J_{6,6'}$= 3 Hz, $J_{6',5}$ = 1.5 Hz, H6'), 4.06 – 3.78 (dm 2H, H7), 3.75 – 3.60 (m, 1H, H5), 2.06, 2.00, 1.98, 1.97 (12H, OC=OCH_3), 1.92 (dd, 3H, H12).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 170.69, 170.29, 169.40, 169.27 (4 × O*C*=OCH_3), 167.11 (C9), 136.01 (C10), 125.94 (C11), 100.75 (H1), 70.88 (C3), 71.07 (C5), 68.26 (C2), 67.48 (C6), 63.39 (C4), 61.84 (C8), 61.28 (C7), 20.74, 20.62, 20,60, 20.58 (4C, OC=O*C*H_3), 18.28 (C12).

Synthesis of 2-(2',3',4',6'-tetra-*O*-acetyl-D-galactosyloxy) ethyl methacrylate (AcGalMA) (6)

AcGalMA, **6**, was prepared according to similar procdure described for the synthsis of compound **5**. AcGal (5.00 g, 12.80 mmol) and 2-hydroxyethyl methacrylate, (HEMA) (1.86 mL, 15.37 mmol), were added into a 250 mL two-neck round-bottom flask together with molecular sieves (4 A^o). Anhydrous CH_2Cl_2 (80 mL) was added to the stirred flask under nitrogen flow. The reaction started when boron trifluoride diethyl etherate ($BF_3O(Et)_2$) (7.90 mL, 64.04 mmol) was introduced over 30 min via a gastight syringe while maintaining the flow of nitrogen through the flask. After purging the solution for another 20 min, the flask was sealed and left stirring at room temperature for 36 h to allow maximum conversion. The reaction mixture was filtered through a sintered glass funnel pouring into ice-water (100 mL) and extracted. CH_2Cl_2 solution were washed (aqueous $NaHCO_3$, water), dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure, and the resulting oily light yellow mixture was purified by column chromatography using hexane/ethyl acetate (2/1) as eluent. The light yellow oil was obtained with the R_f value of 0.45. (Yield: 5.06g, 86%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.07 (m, 1H, H11), 5.54 (m, 1H, H11'), 5.34 – 5.32 (dd, 1H, H4, $J_{4,3}$= 3.4 Hz, $J_{4,5}$ = 0.9 Hz), 5.19 – 5.13 (dd, 1H, H2, $J_{2,1}$ = 8.0 Hz, $J_{2,3}$ = 10.4 Hz), 4.98 – 4.93 (dd, 1H, H3), 4.51–4.48 (d, 1H, H1), 4.28 – 4.21 (m, 2H, H8), 4.11 – 4.07 (m, 2H, H7), 4.04 – 3.97 (m, 1H, H6), 3.89 – 3.84 (dt, 1H, H5, $J_{5,6}$ = 6.6 Hz), 3.82 – 3.74 (m, 1H, H6'), 2.09, 1.99, 1.96, 1.92 (12H, OC=OCH_3), 1.89 (dd, 3H, H12).
^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 170.36, 170.22, 170.12, 169.32 (4 × O*C*=OCH_3), 167.09 (C9), 136.09 (C10), 125.87 (C11), 101.24 (H1), 70.88 (C3), 70.74 (C5), 68.66 (C2), 67.38 (C6), 67.01 (C4), 63.47 (C8), 61.28 (C7), 20.64, 3 × 20.56 (4C, OC=O*C*H_3), 18.26 (C12).

Synthesis of 1-*O*-methacryloyl 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (*ipr*FrucMA1) (7)

A solution of 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (3.0 g, 11.52 mmol) in anhydrous dichloromethane (165 mL), pyridine (6 mL) and 4-dimethylaminopyridine (1.0 g, 8.18 mmol) at 0 ℃ was treated dropwise with a solution of methyl acrylate anhydride (2.2 mL, 13.25 mmol) in dichloromethane (5 mL). After it was stirred for 48 h at room temperature, the mixture was poured into ice-cold saturated $NaHCO_3$ solution (165 mL), and the organic layer was withdrawn. The aqueous layer was extracted with CH_2Cl_2, and combined organic layers were dried using $MgSO_4$ and concentrated under reduced pressure. The product was purified by flash column chromatography. (Yield: 3.21 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.17 (dq, *J* = 1.8, 0.9 Hz, 1H), 5.62 (dd, *J* = 1.9, 1.3 Hz, 1H), 4.64 (dd, *J* = 7.9, 2.7 Hz, 1H), 4.50 (dd, *J* = 11.9, 0.6 Hz, 1H), 4.40 (dd, *J* = 2.7, 0.6 Hz, 1H), 4.27 (ddd, *J* = 7.9, 1.9, 0.8 Hz, 1H), 4.17 (dd, *J* = 11.9, 0.7 Hz, 1H), 3.96 (dd, *J* = 13.0, 1.9 Hz, 1H), 3.79 (dt, *J* = 13.0, 0.8 Hz, 1H), 1.99 (dt, *J* = 1.6, 0.8 Hz, 3H), 1.56 (s, 3H), 1.50 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H).

Synthesis of 3-*O*-methacryloyl 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (*ipr*FrucMA3) (8)

The synthesis of 3-*O*-methacryloyl 1,2 4,5-di-*O*-isopropylidene-β-D-fructopyranose followed the same procedure as that of 1-O-methacryloyl 2,3 4,5-di-O-isopropylidene-β-D-fructopyranose (Yield: 3.33 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (dq, *J* = 1.9, 1.0 Hz, 1H), 5.66 (p, *J* = 1.6 Hz, 1H), 5.22 (d, *J* = 8.0 Hz, 1H), 4.38 (dd, *J* = 8.0, 5.3 Hz, 1H), 4.27 (ddd, *J* = 5.3, 2.4, 1.0 Hz, 1H), 4.25 – 4.06 (m, 2H), 3.99 (d, *J* = 9.3 Hz, 1H), 3.84 (d, *J* = 9.3 Hz, 1H), 2.00 (dd, *J* = 1.6, 1.0 Hz, 3H), 1.61 (s, 3H), 1.52 (s, 3H), 1.41 (s, 3H), 1.39 (s,

3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.72, 135.70, 126.67, 112.08, 109.67, 103.80, 75.02, 73.75, 71.69, 70.41, 60.41, 27.81, 26.40, 26.38, 26.11, 18.31.

Preparation of 1,2-diaminocyclopentane-platinum(II) (DACP-Pt)

250 mg (0.6 mmol) of potassium tetrachloroplatinate were dissolved in 400 μL of water and placed to stir at 40 °C. A solution of 600 mg (3.61 mmol) of KI in 1 ml of warm water was added to the platinum solution and the temperature was risen slowly to 70 °C, as soon as the temperature was reached the mixture was cooled down to room temperature. The solid impurities were filtrated and a solution of 102 mg (0.589 mmol) of (1S,2S)-*trans*-1,2-cyclopentanediamine dihydrochloride in 1 mL of water was added. The mixture was stirred for 20 min at room temperature and the yellow crystalline compound was filtrated using a millipore filtration system, washed with ice-cold ethanol followed by ether and air dry. (Yield: 219 mg, 68%)

219 mg (0.399 mmol) of the diiodo derivate was added in small portions to a solution of 243 mg (0.779 mmol) of silver sulphate in 15 mL of water. The suspension was heated, with stirring, at 75 °C for 15 min. The mixture was filtered to separate the AgI precipitated. The solution was freeze dried to obtain a pale yellow powder (Yield: 98 mg, 57%). The acquated species was used for conjugation to the polymers. The dichloride species was obtained by treating the water solution with excess of NaCl, the bright yellow precipitate was filtered using a Millipore filtration system and washed with ice-cold ethanol followed by ether and air dry.

Synthesis of polymers

Preparation of poly(2-(2',3',4',6'-tetra-*O*-acetyl-D-glucosyloxy) ethyl methacrylate (PAcGlcMA)

PAcGlcMA was synthesized using RAFT polymerization. AcGlcMA (1.50 g, 3.258 mmol), CPADB (0.012 g, 0.043 mmol), FMA (0.013 g, 0.032 mmol) and AIBN (0.891 mg, 5.529 μmol) were loaded into a 100 mL round bottom flask along with 1,4-dioxane (3.25 mL) as a solvent. The solution was three freeze-pump-thaw (FPT) cycles. The vial was placed in a preheated oil bath at 70 °C to react for 7 h. The monomer conversions were determined using ^1H NMR by taking crude mixtures from the aliquots and dissolving them into $CDCl_3$. The conversion was calculated from the relative integration of monomer's vinylic peak ($CH=CH_2$, 5.6-6.2 ppm) and its anomoric peak at 4.56-4.54 ppm. The final polymer from the crude

solution was precipitated in 10-fold excess of hexane/diethyl ether (2/1) two times and dried under reduced pressure at room temperature for 24 hours. Then polymer was purified by precipitation in hexane two times. The obtained polymer was dried under vacuum for 24 h at room temperature.

Preparation of poly(2-(2',3',4',6'-tetra-*O*-acetyl-D-galactosyloxy) ethyl methacrylate (PAcGalMA)

PAcGalMA was synthesized using RAFT polymerization. AcGalMA (1.50 g, 3.258 mmol), CPADB (0.012 g, 0.043 mmol), FMA (0.013 g, 0.032 mmol) and AIBN (0.891 mg, 5.529 μmol) were loaded into a 100 mL round bottom flask along with 1,4-dioxane (3.25 mL) as a solvent. The solution was degassed by three FPT cycles. The vial was placed in a preheated oil bath at 70 °C to react for 7 h. The monomer conversions were determined using ^{1}H NMR by taking crude mixtures from the aliquot and dissolving it into $CDCl_3$. The conversion was calculated from the relative integration of monomer's vinylic peak ($CH=CH_2$, 5.7-6.2 ppm) and its anomoric peak at 4.51-4.48 ppm. The final polymer from the crude solution was precipitated in 10-fold excess of hexane/diethyl ether (2/1) two times and dried under reduced pressure at room temperature for 24 hours. Then polymer was purified by precipitation in hexane two times. The obtained polymer was dried under vacuum for 24 h at room temperature.

Preparation of poly(1-*O*-methacryloyl-2,3:4,5-di-O-isopropylidene-β-D-fructopyranose) P(iprFrucMA1)

In a Schlenk tube, 1-*O*-methacryloyl-2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (1 g, 3.045 mmol), CPADB (17 mg, 0.060 mmol), FMA (12 mg, 0.030 mmol), and AIBN (1.25 mg, 7.613 μmol) were dissolved in 1,4-dioxane (4.3 mL), respectively. Then the tube was degassed by three FPT cycles. The polymerization was carried out at 70 ℃ and stopped at 11 h by cooling the solution in ice water. The polymer solution was poured into a large excess of ether for precipitation. The viscous polymer was dried under vacuum for 24 h. The conversion of polymerization was determined by ^{1}H NMR.

Preparation of poly(3-*O*-methacryloyl-1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose) P(iprFrucMA3)

In a Schlenk tube, 3-*O*-methacryloyl-1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (1 g, 3.045 mmol), CPADB (17 mg, 0.060 mmol), FMA (12 mg, 0.030 mmol), and AIBN (1.25

mg, 7.613 μmol) were dissolved in 1,4-dioxane (4.3 mL), respectively. Then the tube was degassed by three FPT cycles. The polymerization was carried out at 70 ℃ and stopped at 15 h by cooling the solution in ice water. The polymer solution was poured into a large excess of ether for precipitation. The viscous polymer was dried under vacuum for 24h. The conversion of polymerization was determined by ^{1}H NMR.

General procedure for the chain extension of MacroRAFT Agents with methyl methacrylic acid

A typical procedure was described as follows: MacroRAFT Agent (100 mg, 4. 29 μmol, Table 1 Entry 1 , based on $M_{n,NMR}$= 23300), MAA (55.42 mg, 0.643 mmol), AIBN (1.072 μmol) were dissolved in 1,4-dioxane (1.1 mL). The tube was degassed by three FPT cycles. The polymerization was carried out at 70 ℃ and stopped by cooling the solution in ice water in an appropriate time. The polymer solution was poured into a large excess of *n*-hexane for precipitation. After cenrifugation, the viscous polymer was dried under vacuum for 24h. The conversion of polymerization was determined by ^{1}H NMR.

Deprotection of Glyco-block copolymers

The deacetylation of block copolymers were carried out in basic conditions. In a typical protocol, P(AcGlcMA$_{50}$-*b*-MAA$_{116}$) and/or P(AcGalMA$_{50}$-*b*-MAA$_{112}$) (0.100 g) were dissolved in $CHCl_3$/CH_3OH mixture (20 mL, 1/1; v/v) separately. The solution was degassed with nitrogen for 20 min. The freshly prepared sodium methoxide (25 wt. % in methanol) in a solution of dry methanol (0.092 M) was introduced into each mixture by droping the appropriate quantity (0.25 eq. per acetyl group,) via a syringe. The reaction mixtures were stirred for 3 h at room temperature. After that, the solvent was removed under vacumm at 35 ºC. The residual 2 mL polymer solution was subsequently dialyzed against distilled water for 2 days (molecular weight cutoff; MWCO 3500). The deprotected copolymers were recovered by lyophilization. (Yield: 0.065 g, 87% for P(AcGlcMA$_{50}$-*b*-MAA$_{116}$), Yield: 0.064 g, 86% for P(AcGalMA$_{50}$-*b*-MAA$_{112}$)). In contrast to the acetyl protective group, polymer P(FrucMA1$_{44}$-*b*-MAA$_{116}$) and P(FrucMA3$_{34}$-*b*-MAA$_{94}$) were readily obtained by hydrolysis of acetonide groups of P(*ipr*FrucMA1$_{44}$-*b*-MAA$_{116}$) and P(*ipr*FrucMA3$_{34}$-*b*-MAA$_{94}$) (0.100 g) in TFA/H_2O mixture (2 mL, 6:1 v/v) with stirring at room temperature for 3 h followed by dialyzed against deionized water for two days (MWCO 3500). The deprotected polymer was dried by freeze dryer. (Yield: 0.065 g, 87% for P(AcGlcMA$_{50}$-*b*-MAA$_{116}$), Yield: 0.064 g, 86% for P(AcGalMA$_{50}$-*b*-MAA$_{112}$)).

Attachment of DACP-Pt onto glyco-block copolymers and drug release experiment

Micelles containing a DACP-Pt drug were prepared as previously reported procedure by our group. DACP-Pt-loaded micelles were spontaneously formed from the treatment of the carboxylic moieties of copolymers with the platinum of DACP-Pt in water. As a general procedure: 10 mg of glyco-block copolymer polymer was dissolved in water (5 mL). DACP-Pt solution (1 eq. for two carboxylic acids) in 5 mL of water was added to the solution via syringe pump at a rate of 0.2 ml/h . The sample was then purified by dialyzing against water using membrane dialysis (MWCO 3500) to remove unbound DACP-Pt. The water was replaced 3 times every 2 h.

The release profile of DACP-Pt from 4 mL DACP-Pt–loaded glyco-block micelles were studied using a dialysis tube (MWCO = 3500) at 37 °C in pH 7.4 PBS (150 mL). At predetermined time intervals, 2 ml aliquots of the aqueous solution were withdrawn from the release media and another 2 ml fresh PBS was added into the release media. Then the concentration of DACP-Pt released was determined using an ICP-MS.

Cells culture and Cytotoxicity assay

The human ovarian carcinoma A2780cells were grown in a ventilated tissue culture flask T-75 using Roswell Park Memorial Institute (RPMI-1640) media containing 10% foetal bovine serum (FBS) and antibiotics. The human breast carcinoma MCF-7 and MB-MDA-231 cell lines were grown in the T-75 flasks using Dulbecco's modified Eagle's medium (DMEM)containing 10% FBS and antibiotics. The cells were incubated at 37 ºC under a 5% CO_2 humidified atmosphere and passaged every 2–3 days when monolayers at around 80% confluence were formed.

The cells were seeded at a density of 4,000 cells per well in 96-well plates containing 200 μL of growth medium and incubated for 24 h. The medium was then replaced with fresh medium (200 μL) containing various concentrations of the material being tested.

After 48 h incubation, cells were fixed with trichloroacetic acid 10% w/v (TCA) before washing, incubated at 4 ºC for 1 h, and then washed five times with tap water to remove TCA, growth medium, and low molecular weight metabolites. Plates were air dried and then stored until use. TCA-fixed cells were stained for 30 min with 0.4% (w/v) SRB dissolved in 1% acetic acid. At the end of the staining period, SRB was removed and cultures were

quickly rinsed five times with 1% acetic acid to remove the unbound dye. Then the cultures were air dried until no conspicuous moisture was visible. The bound dye was shaken for 10 min. The absorbance at 570 nm of each well was measured using a microtiter plate reader scanning spectrophotometer BioTek's PowerWave™ HT Microplate Reader and the KC4™ Software. All experiments were repeated three times.

Dose–response curves were plotted (values were expressed as the percentage of control, medium only) and IC_{50} inhibitory concentrations were obtained using the software Graph Pad PRISM 6.

Cell viability (%) = $(OD_{490,sample} - OD_{490,blank})/ (OD_{490,control} - OD_{490,blank}) \times 100$

Cellular Uptake Studies Using Laser Scanning Confocal Microscopy (LSCM)

Cells were seeded in 35 mm Fluorodishes (World Precision Instruments) with a density of 2 × 10^5 cells per well in 2 mL of medium. Micelles were loaded to the cells at a working concentration of 100 μg/mL and incubated in a humidified incubator (5% CO_2/ 95% air atmosphere at 37 ºC) for 6 h. After incubation, the cells were washed thrice with PBS. A laser scanning confocal microscope system (Zeiss LSM 780) consisted of, an argon laser (excitation wavelengths: 405nm) connected to a Zeiss Axio Observer.Z1 inverted microscope (oil immersion × 100/1.4 NA objective) was used for observation. The Zen2011 imaging software (Zeiss) was used for imaging acquisition and processing.

Flow cytometry

Cells were seeded in 6-well tissue culture palte at a density of 5 × 10^5 cells per well and cultured for 2 d. Micelles were loaded to the cells at a working concentration of 100 μg/mL and incubated in a humidified incubator (5% CO_2/ 95% air atmosphere at 37 ºC) for 6 h. After incubation, the cells were washed thrice with cold PBS. The cells were treated with trypsin, centrifuged and resuspended in cold serum free medium before measurements. The flow cytometry assay was performed with BD FACSCanto II Analyzer (BD Biosciences, San Jose, USA).

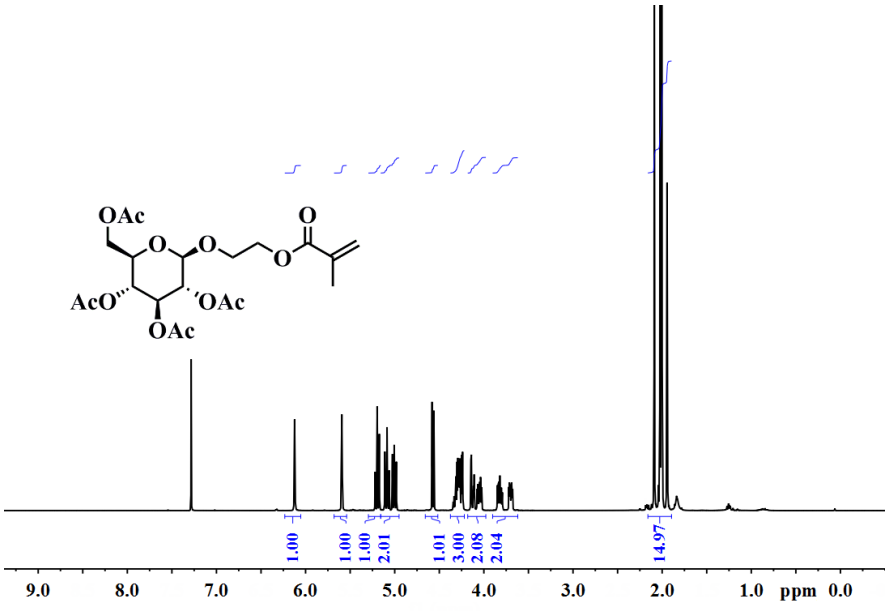

Figure S1: ^{1}H NMR spectrum of 2-(2',3',4',6'-tetra-*o*-acetyl-D-glucosyloxy) ethyl methacrylate (AcGlcMA) (**5**) in $CDCl_3$.

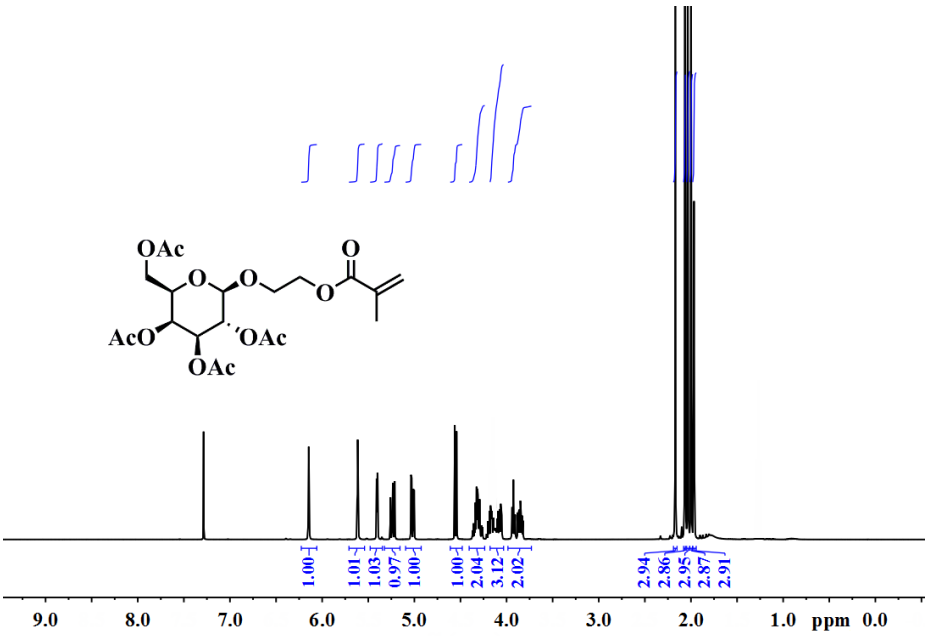

Figure S2: ^{1}H NMR spectrum of 2-(2',3',4',6'-tetra-*o*-acetyl-D-glactosyloxy) ethyl methacrylate (AcGalMA) (**6**) in $CDCl_3$.

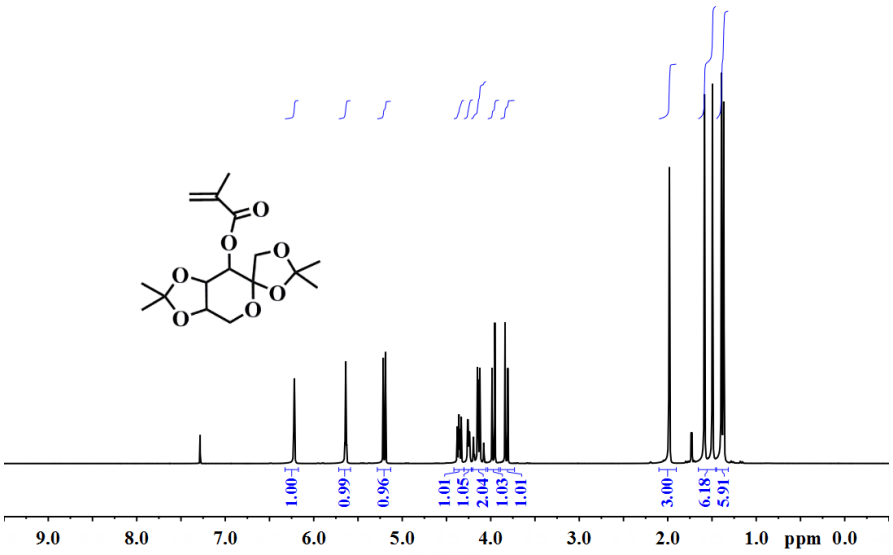

Figure S3: ^{1}H NMR spectrum of 3-O-methacryloyl 1,2:4,5-di-O-isopropylidene-β-D-fructopyranose (*ipr*FrucMA3) (**8**) in $CDCl_3$.

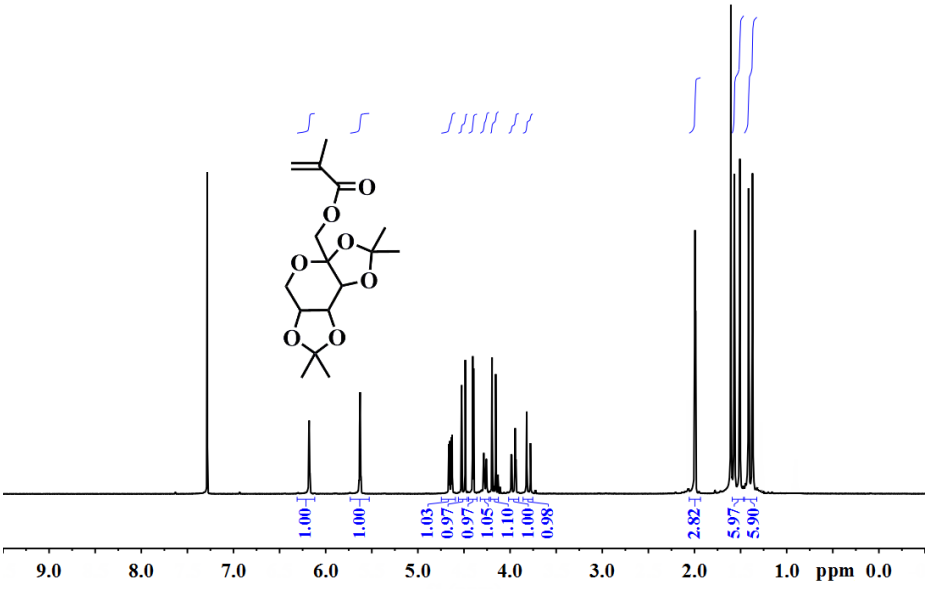

Figure S4: ^{1}H NMR spectrum of 1-O-methacryloyl 2,3:4,5-di-O-isopropylidene-β-D-fructopyranose (*ipr*FrucMA1) (**7**) in $CDCl_3$.

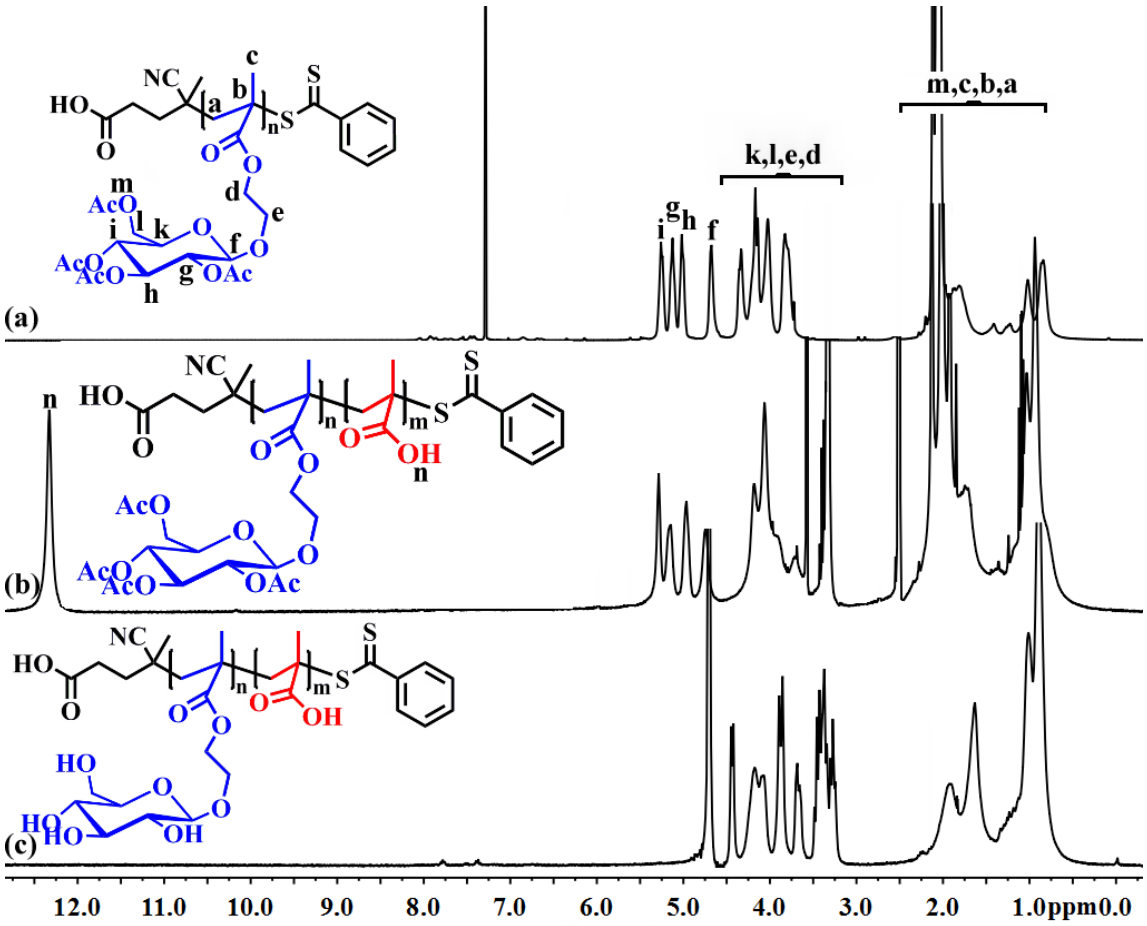

Figure S5: ^{1}H NMR spectra of a) P(AcGlcMA) MacroRAFT agent in $CDCl_3$;b) P(AcGlcMA-*b*-MAA) block copolymer before deprotection reaction in DMSO-d_6; c) P(GlcMA-*b*-MAA) block copolymer in D_2O after deprotection reaction.

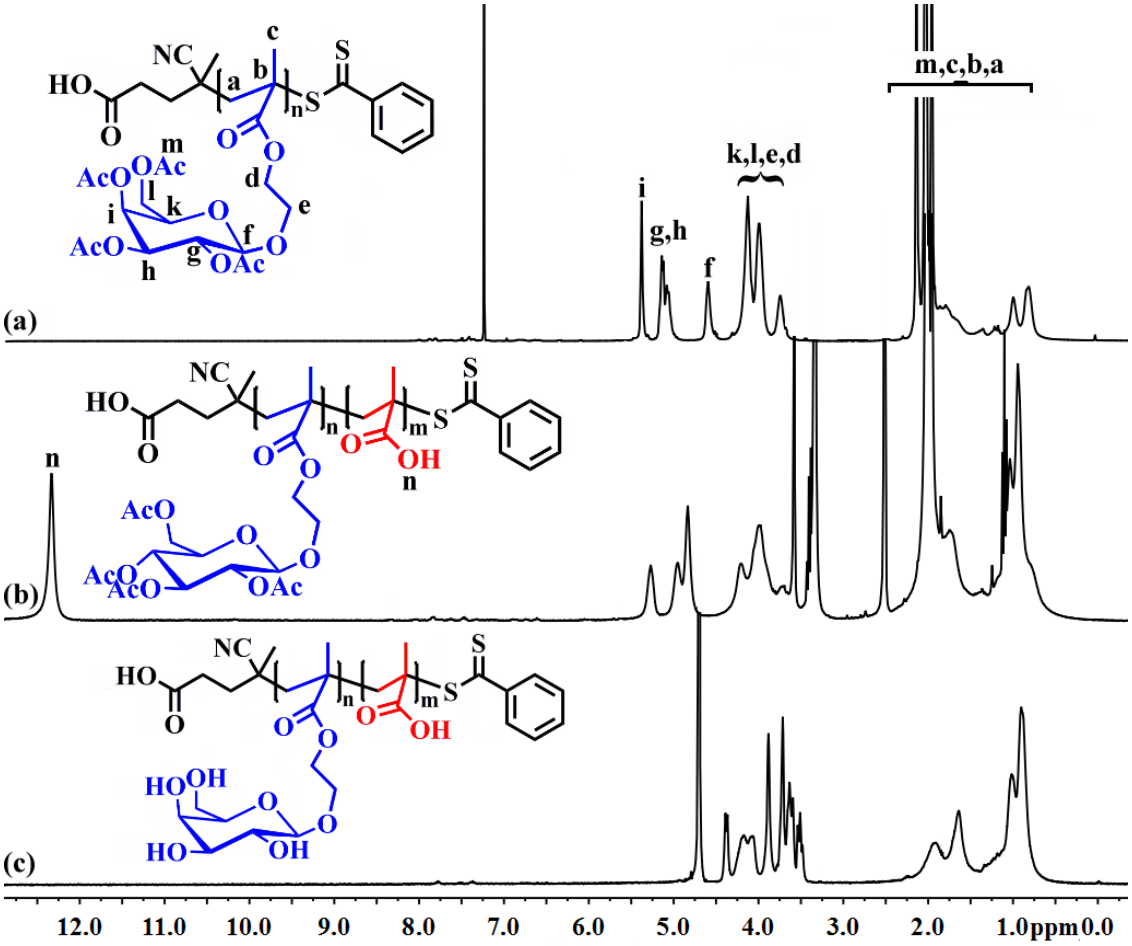

Figure S6: ^{1}H NMR spectra of a) P(AcGalMA) MacroRAFT agent in $CDCl_3$;b) P(AcGalMA-*b*-MAA) block copolymer before deprotection reaction in DMSO-d_6; c) P(GalMA-*b*-MAA) block copolymer in D_2O after deprotection reaction.

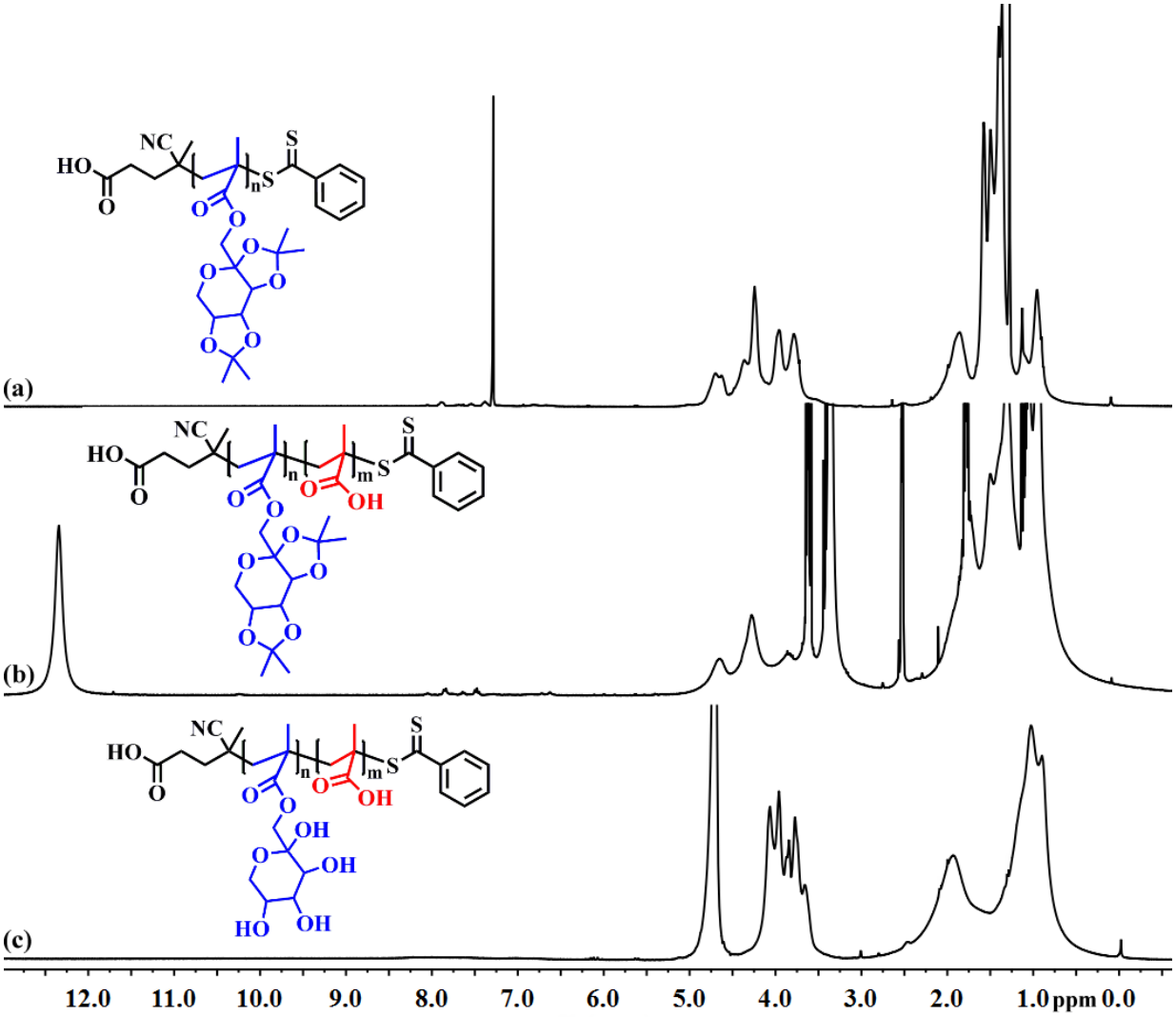

Figure S7: ^{1}H NMR spectra of a) P(*ipr*FrucMA1) MacroRAFT agent in $CDCl_3$;b) P(*ipr*FrucMA1-*b*-MAA) block copolymer before deprotection reaction in DMSO-d_6; c) P(FrucMA1-*b*-MAA) block copolymer in D_2O after deprotection reaction.

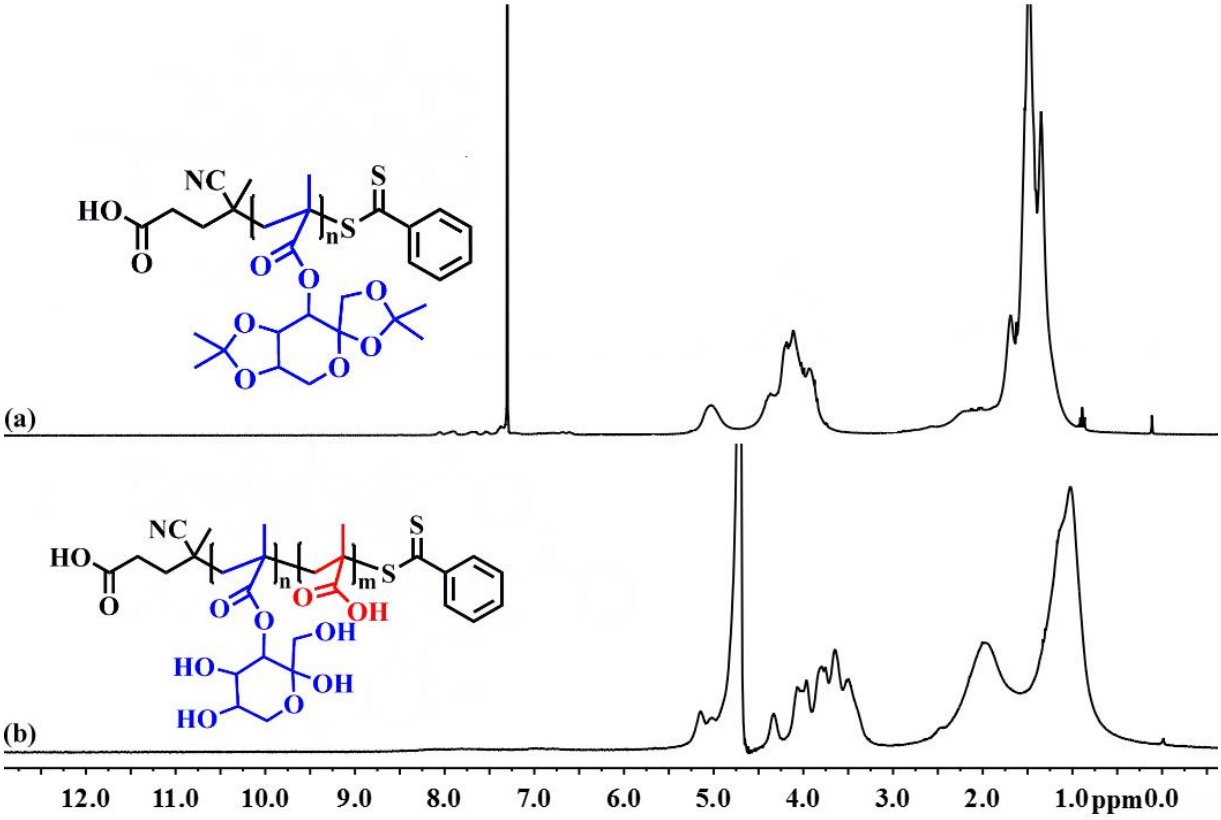

Figure S8: ^{1}H NMR spectra of a) P(*ipr*FrucMA3) MacroRAFT agent in $CDCl_3$; b) P(FrucMA1-*b*-MAA) block copolymer in D_2O after deprotection reaction.

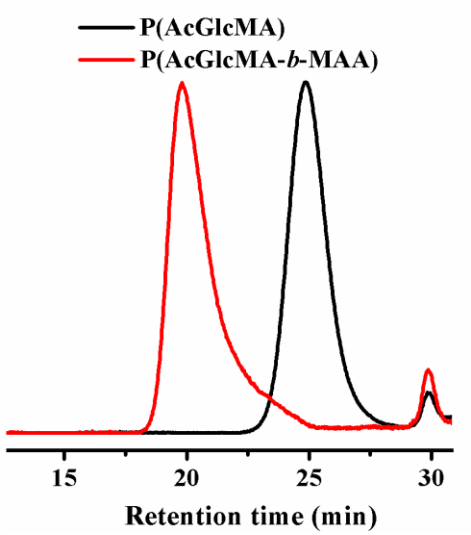

Figure S9. GPC traces of P(AcGlcMA-*b*-MAA) glycoblock copolymer and its precursors P(AcGlcMA) MacroRAFT recorded with RI detector in DMAc at 50 ºC.

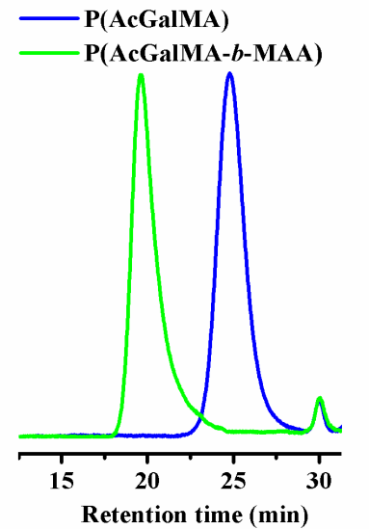

Figure S10. GPC traces of P(AcGalMA-*b*-MAA) glycoblock copolymer and its precursors P(AcGalMA) MacroRAFT recorded with RI detector in DMAc at 50 ºC.

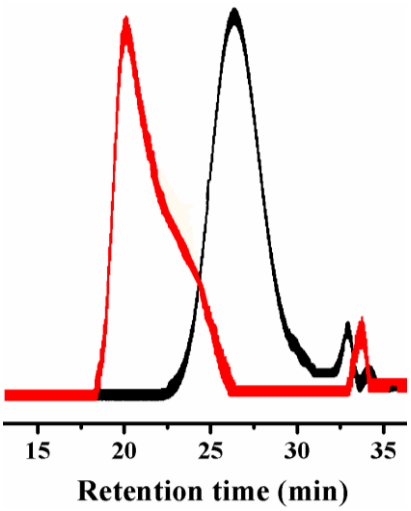

Figure S11. GPC traces of P(*ipr*FrucMA1-*b*-MAA) glycoblock copolymer (red) and its precursors P(*ipr*FrucMA1$_{44}$) MacroRAFT (black) recorded with RI detector in DMAc at 50 ºC.

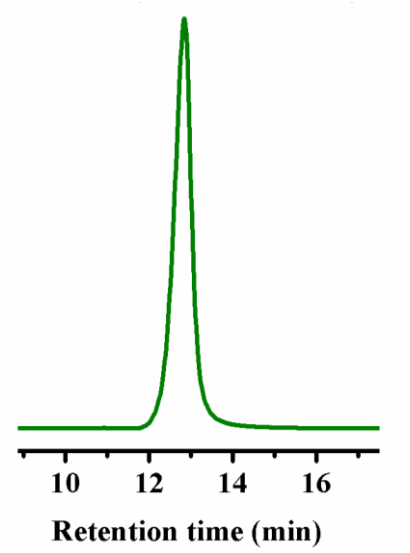

Figure S12. A GPC trace of P(GlcMA-*b*-MAA) glycoblock copolymer after deprotection reaction recorded with RI detector in water at 25 ºC.

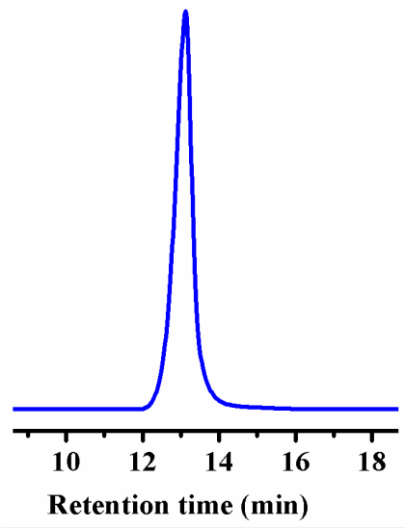

Figure S13. A GPC trace of P(GalMA-*b*-MAA) glycoblock copolymer after deprotection reaction recorded with RI detector in water at 25 ºC.

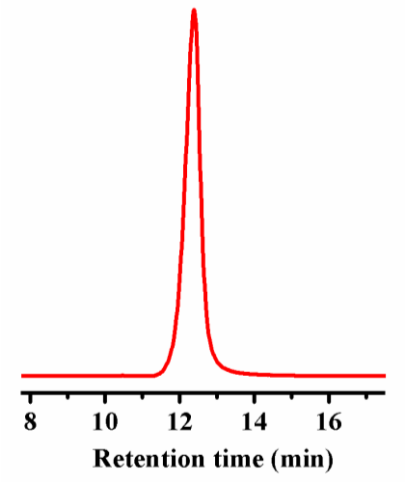

Figure S14. A GPC trace of P(*ipr*FrucMA1-*b*-MAA) glycoblock copolymer after deprotection reaction recorded with RI detector in water at 25 ºC.

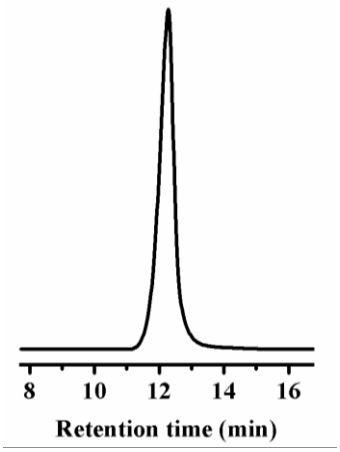

Figure S15. A GPC trace of **P(*ipr*FrucMA3-*b*-MAA)** glycoblock copolymer after deprotection reaction recorded with RI detector in water at 25 ºC.

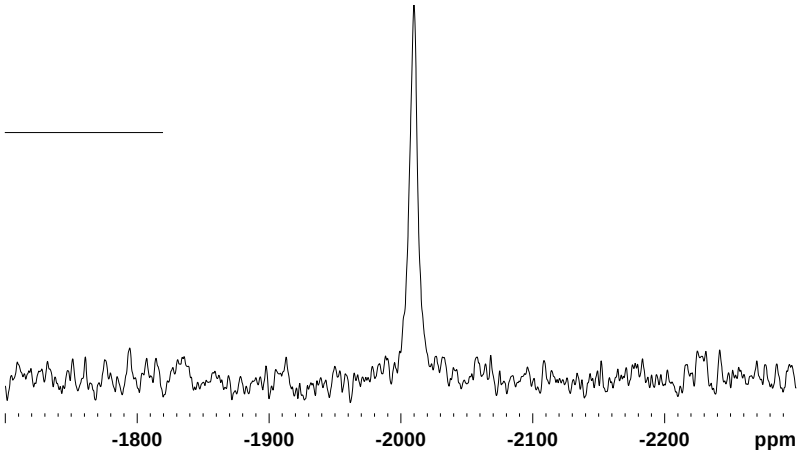

Figure S16. 400 MHtz ^{195}Pt NMR of 1,2-diaminocyclohexyl-dichloro platinum(II) in DMF/D_2O.

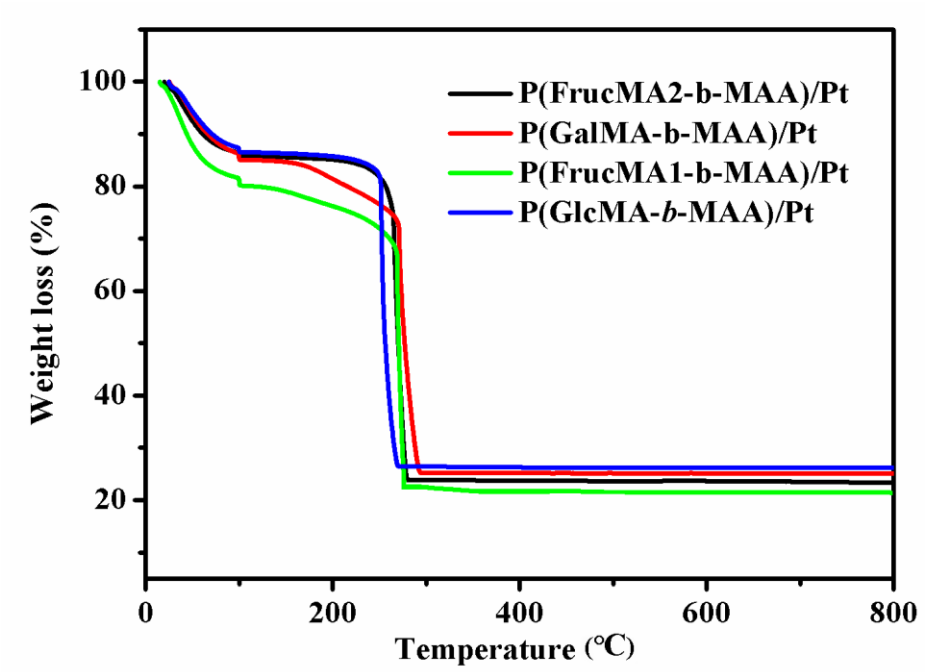

Figure S17. TGA curves of polymers after platinum drug conjugation.

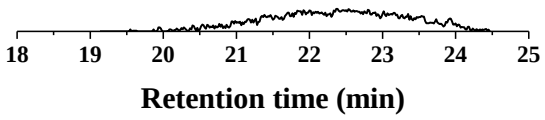

Figure S18. GPC trace after platination indicating that most block copolymer has been crosslinked into the micelle

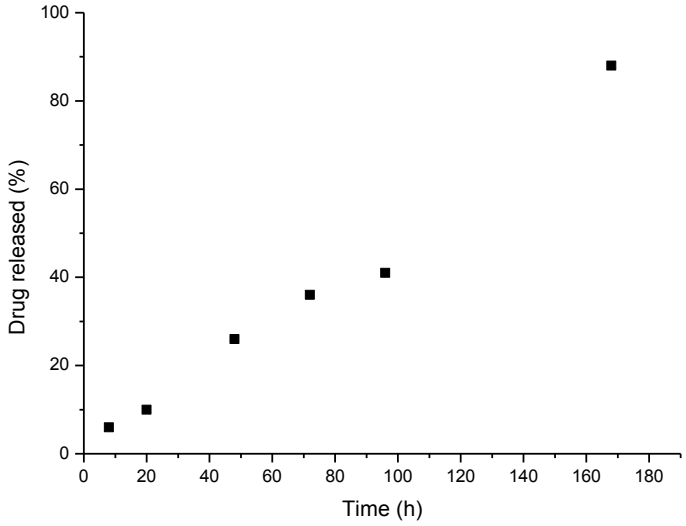

Figure S19. In vitro release profile of DACPPt from P(FrucMA1_{44}-*b*-MAA_{116})/Pt micelles in PBS (pH 7.4) at 37 ºC. The amount of platinum in the solutions was determined by ICP-MS

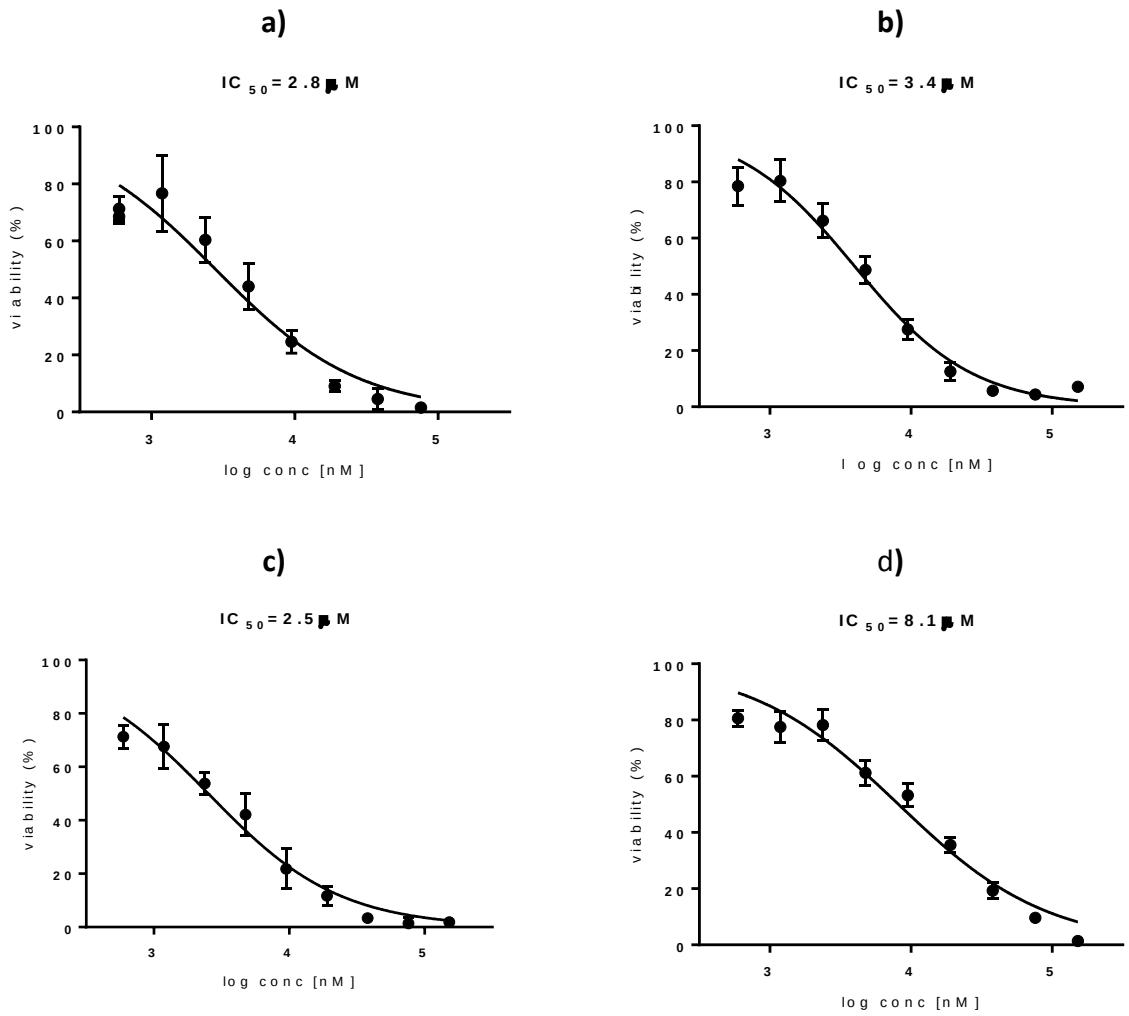

Figure S20. Cytotoxicity assays of Pt-polymer conjugates micelle against A2870 cells **a)** P(GlcMA-*b*-MAA)/Pt, **b)** P(GlcMA-*b*-MAA)/Pt, **c)** P(FrucMA1-*b*-MAA)/Pt, **d)** P(FrucMA3-*b*-MAA)/Pt for 24 h

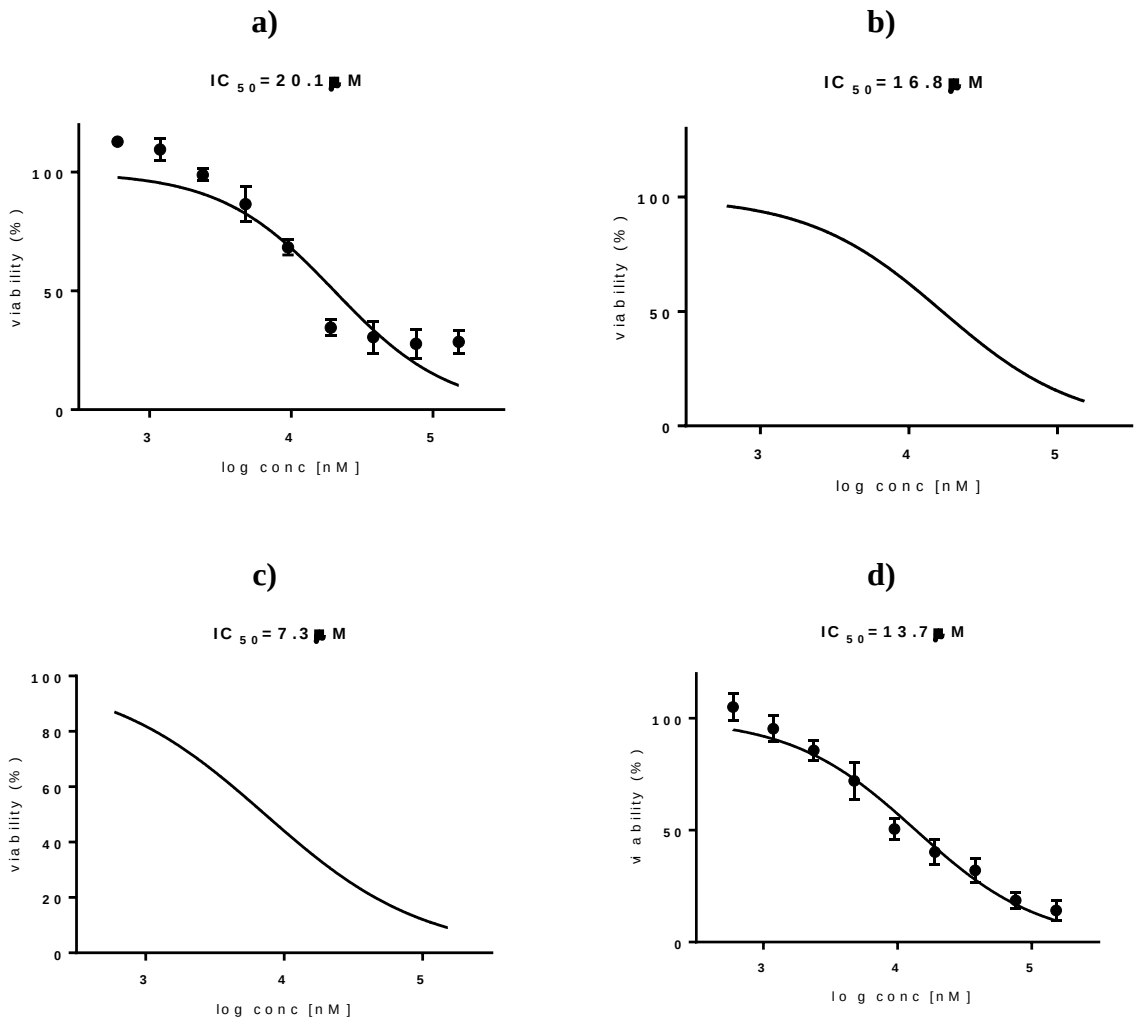

Figure S21. Cytotoxicity assays of Pt-polymer conjugates micelle against MCF-7 cells **a)** P(GlcMA-*b*-MAA)/Pt, **b)** P(GlcMA-*b*-MAA)/Pt, **c)** P(FrucMA1-*b*-MAA)/Pt, **d)** P(FrucMA3-*b*-MAA)/Pt for 24 h

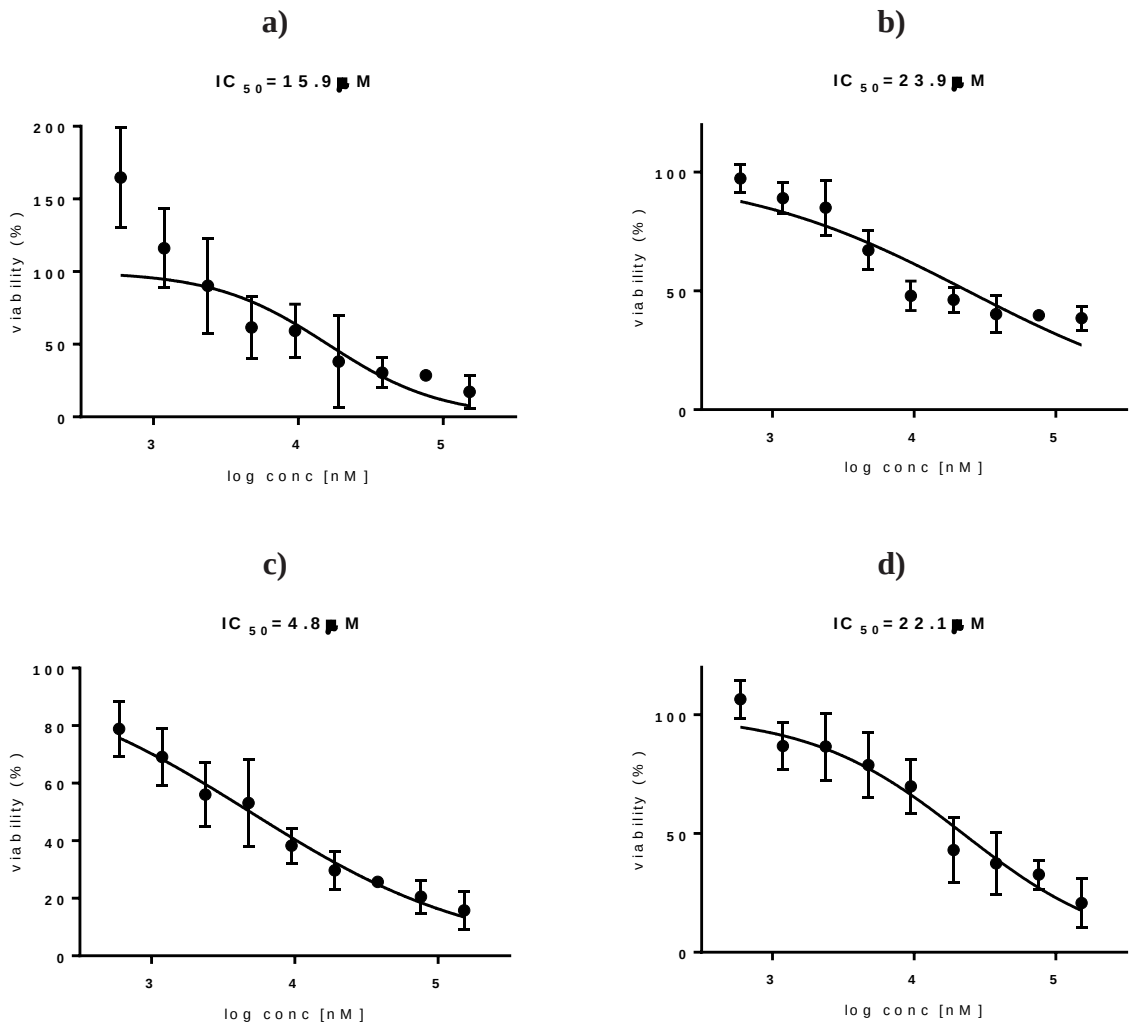

Figure S22. Cytotoxicity assays of Pt-polymer conjugates micelle against MDA-MB-231 a) P(GlcMA-*b*-MAA)/Pt, b) P(GlcMA-*b*-MAA)/Pt, c) P(FrucMA1-*b*-MAA)/Pt, d) P(FrucMA3-*b*-MAA)/Pt for 24 h.

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