Supporting Information (SI)

Lactose Targeting Oxaliplatin Prodrug Loaded Micelles for More Effective Chemotherapy of Hepatocellular Carcinoma

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Synthesis of small molecules

Synthesis of Compound 3 and 4

Compound **3** and **4** were synthesized as previously described [29]. Briefly, 2,2-bis-(bromomethyl)propane-1,3-diol (8.0 g, 30 mmol) and NaN_3 (8 g, 125 mmol) were dissolved in 100 mL DMF in a 250 mL flask. The solution was stirred at 110 °C overnight and filtered. After evaporation of the solvent, the resulting solid was dissolved in 100 mL DCM. The filtrate was obtained and evaporated, and the residue was partitioned with 20 mL aq. NaCl and 100 mL diethyl ether. The organic phase was dried with anhydrous Na_2SO_4 and concentrated to yield 18 g (98% yield) of crude 2,2-bis(azidomethyl) propane-1,3-diol (**3**) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ3.62 (s, 4H), 3.42 (s, 4H).

Compound 3 (5.7 g, 30 mmol) and Pd/C (2 g, 10% Pd/C, 50% wet with water) were dissolved in 50 mL ethanol in a 500 mL high pressure autoclave. The system was purged with nitrogen 3 times, and then pressurized to 1.3 MPa with hydrogen and stirred overnight. The mixture was filtered, and the filtrate was evaporated to dryness to yield 4.0 g (98%) of crude **4** as white solids. ^{1}H NMR ($CDCl_3$, 400 MHz): δ3.26 (s, 4H), 2.44 (s, 4H).

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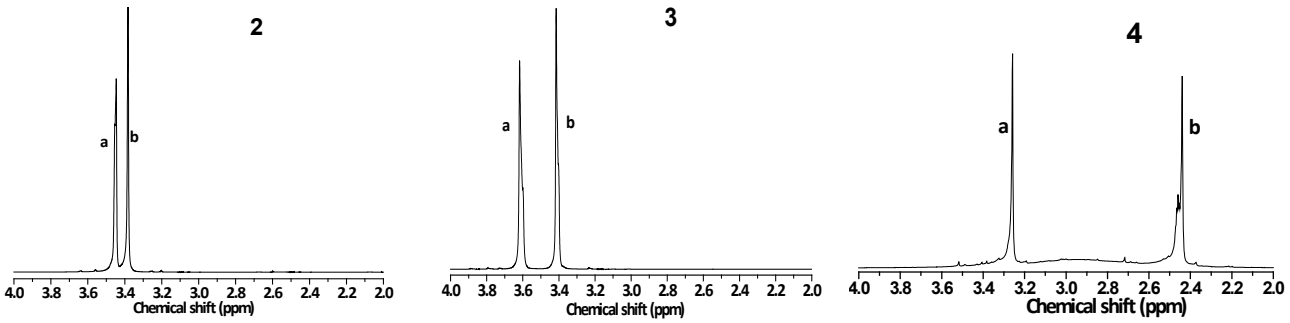

(A) (B) (C)

Fig. S1 ^{1}H NMR spectra of Compound 2, 3, and 4.

The structure of **2, 3,** and **4** were characterized by ^{1}H NMR. As can be seen in Fig. S1, the peaks a and b at 3.38 and 3.45 ppm in Fig. S1 (A) are assigned to the methylene protons of OH-C$\underline{H}_2$-C and Br-C$\underline{H}_2$-C of **2**). The peaks marked with a (3.62 ppm) and b (3.41 ppm) in Fig. S1 (B) can be assigned to the methylene protons of OH-C$\underline{H}_2$-C and N_3-C$\underline{H}_2$-C of 3. The peaks a (3.26 ppm) and b (2.44 ppm) in Fig. S1(c) are assigned to the methylene protons of OH-C$\underline{H}_2$-C and NH_2-C$\underline{H}_2$-C of **4**.

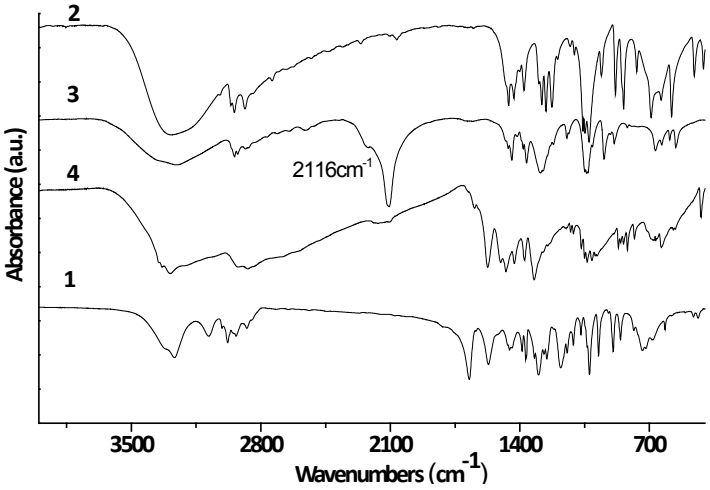

Fig. S2 FT-IR spectra of Compound 2, 3, 4, and 1.

The structure of 1, 2, 3 and 4 were determined by FTIR. The wide peak at 3274 cm^{-1} in Fig. S2(1) is assigned to the OH stretching of **2**. In Fig. S2 (3), the peak at 2116 cm^{-1} is assigned to the N_3 stretching of 3. After N_3 groups are converted to NH_2 groups, the peak at 2116 cm^{-1} disappears, and the sharp peak at 3290 cm^{-1}, belonging to the NH_2 stretching of **4,** appears. After the NH_2 groups are protected by Boc groups, the new peak at 1672 cm^{-1} in Fig. S2 (1) appears and is assigned to the C=O stretching.

Synthesis of 1 (Scheme 1). Compound 4 was dissolved in 50 mL MeCN, and aqueous NaOH (2.4 g, 60 mmol in

100 mL of H_2O) and then Boc_2O (16 g, 72 mmol) were added. The mixture was stirred for 6 h, and the resulting white precipitate was collected and washed several times with water. The white powder was dried under vacuum to yield 10 g (quantitative) of **1**, and the product was recrystallized two times in methanol. ^{1}H NMR (DMSO$_{-d6}$, 300 MHz): δ1.37 (s, 18 H), 2.86 (d, 4H), 3.19 (d, 4H), 4.29 (t, 2H), 6.57 (t, 2H). Elem. Anal. Calc. for $C_{15}H_{30}N_2O_6$: C, 53.87; H, 9.04; N, 8.38; O, 28.71. Found: C, 53.69; H, 8.95; N, 8.44; O, 28.92.

Synthesis and subsequent deprotection of polyurethanes PU-Boc (PU-Boc and PUs)

The PU-Boc was synthesized in two steps, with PEG as soft segment, and HDI and **1** as hard segment. The number average molecular weight of PEG was 1.5 kg/mol. The molar ratios of PEG/HDI/**1** were 1:1.5:0.5, 1:2.0:1.0 and 1:2.5:1.5, their corresponding polymers are coded as PU-Boc0.5, PU-Boc1.0, PU-Boc1.5. A typical synthetic procedure for PU-Boc1.5 was as follows: dried PEG (6.0 g, 4 mmol) was dissolved in THF (20 ml) in a dried polymerization bottle equipped with a magnetic stirring bar. The reaction bottle was immersed in an oil bath at 90 °C for 30 min to dissolve PEG completely. A solution of HDI (1.76 g, 10.5 mmol) in THF (20 ml) and a solution of $Sn(Oct)_2$ in toluene (2.0×10^{-4} mol/ml, 1 ml) were added, respectively. After 2 hours, a solution of **1** (2.01 g, 6 mmol) in THF (30 ml) was added and the reaction solution was stirred at 90 °C for 6 h. The product was precipitated in ether and dried to constant weight under vacuum. A certain quantity of PU-Boc1.5 (5 g) was dissolved in CH_2Cl_2 (15 ml) in a 50 ml flask immersed in ice bath, and CF_3COOH (15 ml) was added. The mixture was stirred for 60 min, and precipitated in ether. The precipitates were collected and dried under vacuum until constant weight. After the dried product was dissolved in water, saturated $NaHCO_3$ solution was added to the solution until the pH of the solution reached near 7.5. The solution was dialyzed against pure water for 2 days and then lyophilized to obtain the polyurethane containing free amino groups (PU1.5). Three typical PU samples are coded as PU0.5, PU1.0, and PU1.5, where the numbers denote the molar ratios of **1**/PEG.

Synthesis of polymer conjugates

Synthesis of PU-LA conjugate. PU1.5 (500 mg, 0.47 mmol NH_2 groups) was dissolved in 20 ml water, lactobionic acid (LA, 33 mg, 0.094 mmol), NHS (21 mg, 0.18 mmol) and EDC·HCl (34 mg, 0.18 mmol) were added in turn. The solution was stirred at room temperature for 12 h and then dialyzed for 2 days to remove un-reacted LA, and lypophilized.

Synthesis of PU-Pt conjugate. PU1.5 (500 mg, 0.47 mmol NH_2 groups) was dissolved in 20 ml water, OxaPt(IV) (270 mg, 0.51 mmol), NHS (0.117 g, 1 mmol) and EDC·HCl (0.19 g, 1 mmol) were added in turn. The

solution was stirred at room temperature for 12 h and then dialyzed for 3 days to remove un-reacted OxaPt(IV), and lypophilized.

Synthesis of PU-LA/Pt conjugate. PU1.5-LA (300 mg, 0.23 mmol NH_2 groups) was dissolved in 20 ml water, OxaPt(IV) (150 mg, 0.28 mmol) was added, and then NHS (53 mg, 0.46 mmol) and EDC·HCl (87 mg, 0.46 mmol) were added. The solution was stirred at room temperature for 12 h and then dialyzed for 3 days to remove un-reacted OxaPt(IV), and lypophilized.

Synthesis of Rhodamine B labeled drug conjugates PU/RhB and PU-LA/RhB

Rhodamine B (RhB) (90 mg, 0.18 mmol) was dissolved in 20 ml water, to which NHS (41 mg, 0.36 mmol) and EDC·HCl (68 mg, 0.36 mmol) were added. The solution was stirred at room temperature for 24 h. Then the reaction mixture was added into a solution of PU or PU-LA in water and the reaction lasted 24 h. The solution was dialyzed for 6 days to remove un-reacted Rhodamine B, and finally lyophilized to obtain PU/RhB and PU-LA/RhB

Thermogravity analysis (TGA) of PU/Pt (a), PU-LA/Pt (b) and PU (c)

Thermogravity analysis (TGA) of PU/Pt (a), PU-LA/Pt (b) and PU (c) were determined by Perkin Elmer Pyris Diamond TG/DTA at a heating rate of 10k/min under air from 25 to 900 °C. The remaining weights of PU/Pt (a), PU-LA/Pt (b) and PU(c) are 7.1%, 6.0% , and 1.2%, respectively.

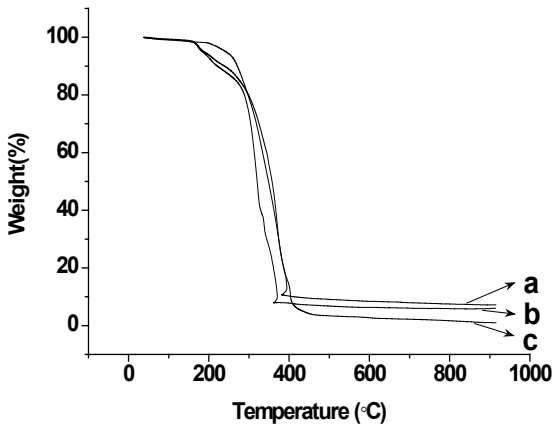

Fig. S3: The TGA curves of PU/Pt (a), PU-LA/Pt (b) and PU(c).