

Supporting Information

A paclitaxel prodrug with bifunctional folate and albumin binding moiety for both passive and active targeted cancer therapy

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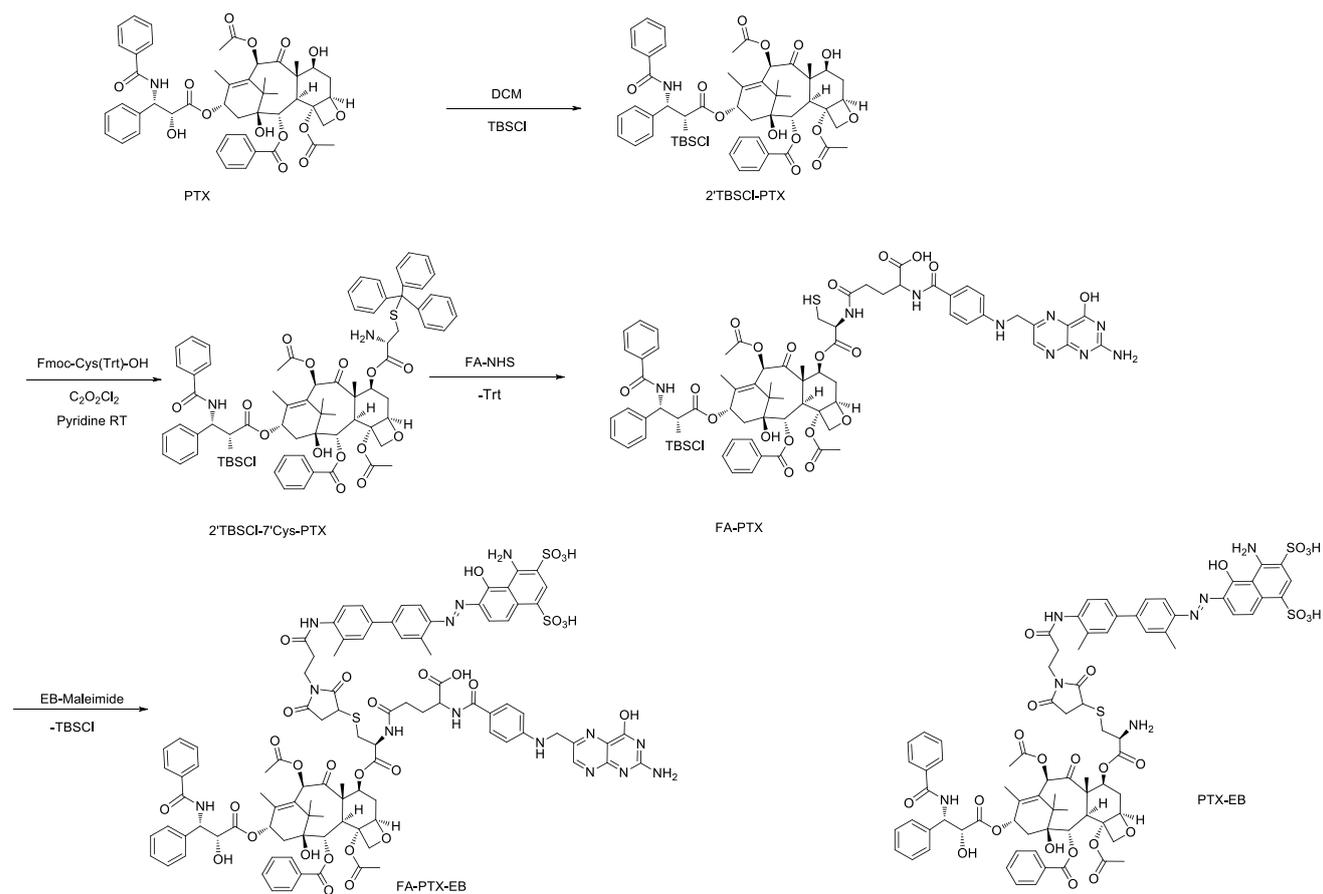
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Scheme S1. Synthetic Scheme for EB-conjugated FA-PTX prodrugs.

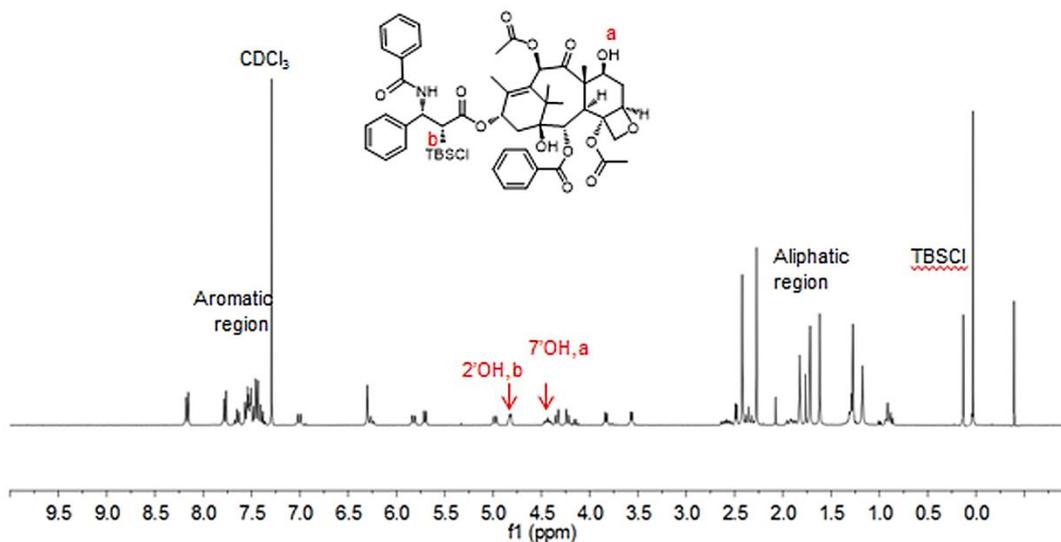


Figure S1. ¹H NMR spectrum of 2'-TBSCSI-PTX. ¹H NMR (400 MHz, CDCl₃): = 8.27 - 7.29 (m, 15 H), 7.07 (d, J = 9.0 Hz, 1 H), 6.36 - 6.20 (m, 2 H), 5.74 (d, J = 9.0 Hz, 1 H), 5.69 (d, J = 7.5 Hz, 1 H), 4.98 (d, J = 9.4 Hz, 1 H), 4.66 (s, 1 H), 4.43 (d, J = 5.5 Hz, 1 H), 4.33 (d, J = 8.1 Hz, 1 H), 4.22 (d, J = 8.8 Hz, 1 H), 3.83 (d, J = 7.5 Hz, 1 H), 2.63 - 2.51 (m, 4 H), 2.49 - 2.35 (m, 2 H), 2.23 (s, 3 H), 2.13 (dd, J = 8.8, 14.9 Hz, 1 H), 1.97 - 1.85 (m, 4 H), 1.69 (s, 3 H), 1.24 (s, 3 H), 1.14 (s, 3 H), 0.80 (s, 9 H), -0.04 (s, 3 H), -0.29 (s, 3 H).

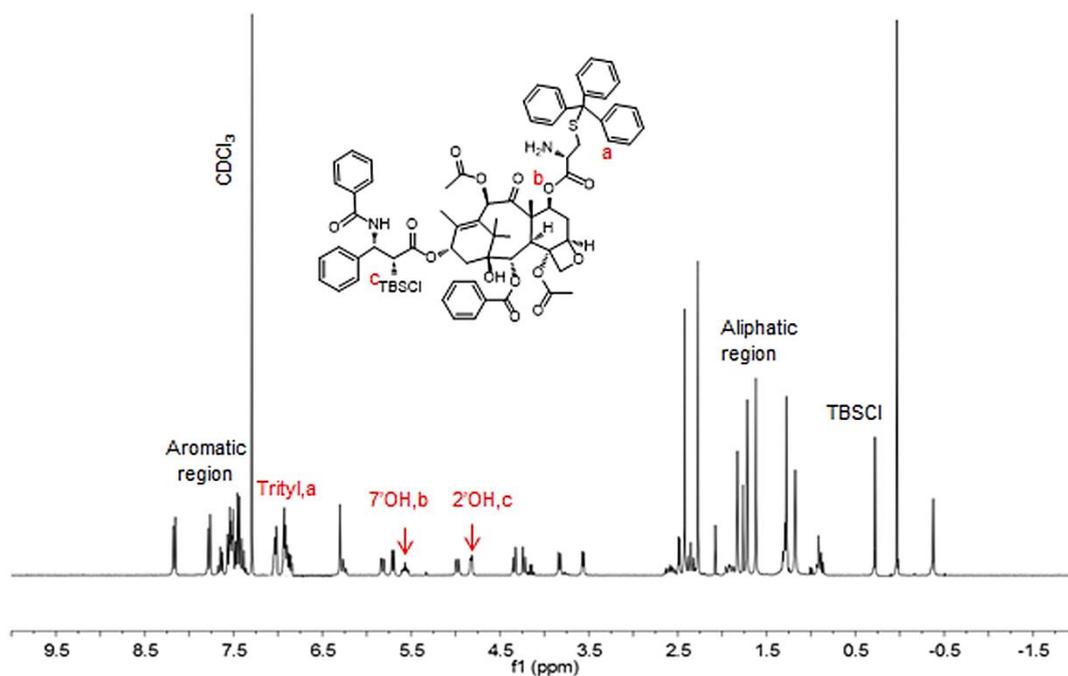


Figure S2. ¹H NMR spectrum of 2'-TBSCl-7'PTX-Cys. ¹H NMR (400 MHz, CDCl₃):= 8.10 -7.08 (m, 15 H), 7.08 (d, *J* = 9.2 Hz, 2 H), 6.33 (s, 1 H), 6.24 (t, *J* = 9.2 Hz, 1 H), 5.69 - 5.78 (m, 2 H), 5.54 - 5.63 (m, 1 H), 4.35 (d, *J* = 8.8 Hz, 1 H), 4.25 (d, *J* = 8.4 Hz, 1 H), 3.97 (d, *J* = 6.6 Hz, 1 H), 2.69 - 2.48 (m, 4 H), 2.42 (dd, *J* = 9.8, 15.1 Hz, 1 H), 2.03 - 1.88 (m, 1 H), 1.81 (s, 3 H), 1.68 - 1.39 (m, 8 H), 1.20 (s, 3 H), 1.16 (s, 3 H), 0.91 (s, 9 H), 0.80 (s, 9 H).

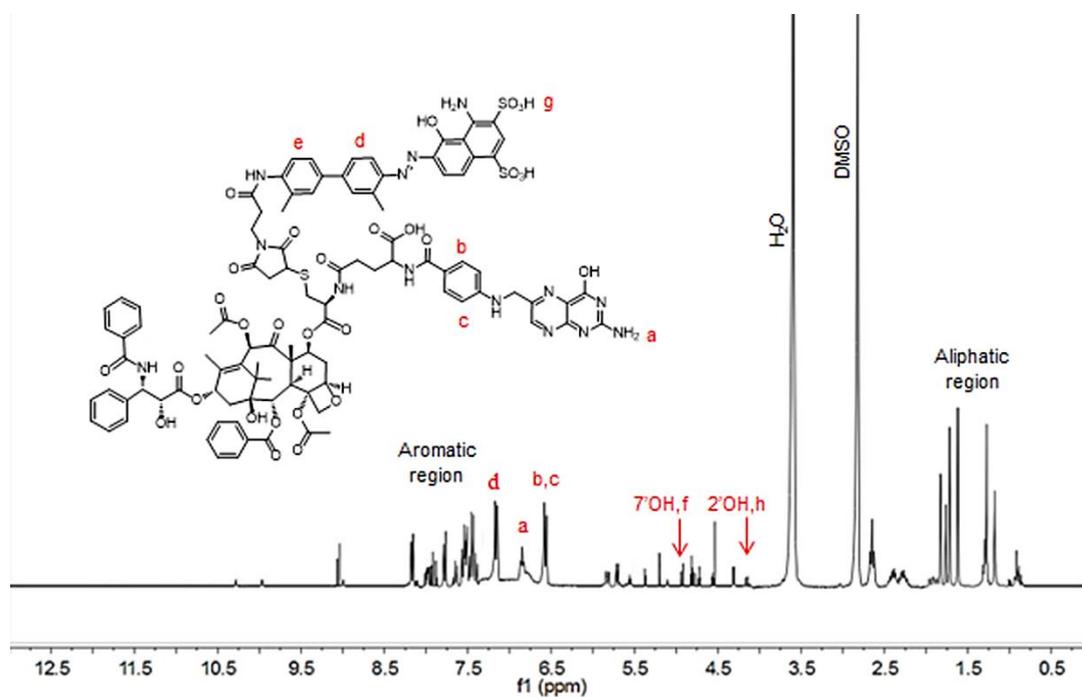


Figure S3. ¹H NMR spectrum of FA-PTXFA-PTX-EB. ¹H NMR (400 MHz, DMSO) 11.53 (s, 1H), 8.52 (s, 1H), 8.02 (m, 4H), 7.94 (m, 2H), 7.77 (t, *J*=7.4 Hz, 1H), 7.63-7.29 (m, 10H), 7.58 (d, *J*=8.1 Hz, 2H), 7.14 (s, 1H), 7.08 (s, 1H), 6.95 (s, 1H), 6.78 (m, 4H), 6.10 (d, *J*=8.1 Hz, 2H), 5.80 (d, *J*=8.1 Hz, 1H), 5.35 (d, *J*=5.7 Hz, 1H), 4.80 (m, 2H), 4.70 (s, 1H), 4.41 (d, *J*=4.9 Hz, 2H), 4.11 (m, 1H), 4.01 (s, 2H), 3.58 (d, *J*=6.8 Hz, 1H), 3.86-3.04 (m, 10H), 2.81-2.00 (m, 8H), 2.12 (s, 3H), 1.90-1.81 (m, 6H), 1.83 (s, 3H), 1.59 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H).

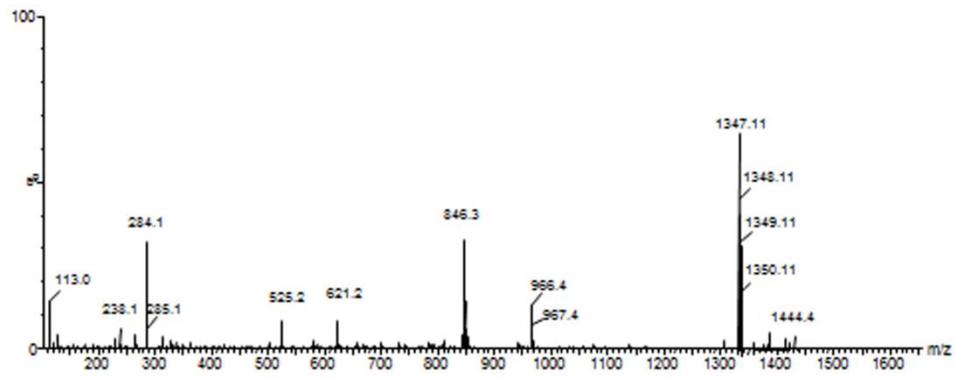


Figure S4: 2'-TBSCI-7'PTX-Cys LC-MS: $[M + H]^+ = 1347.11$, calc.: 1348.11.

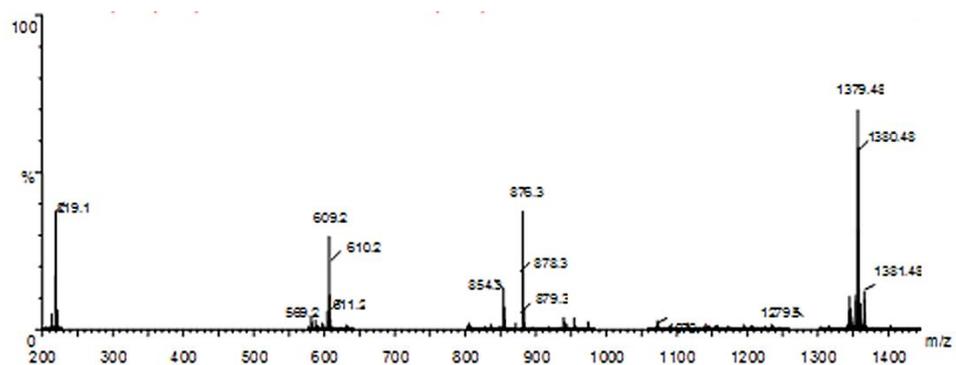


Figure S5: FA -7'PTX-Cys-HS LC-MS: $[M + H]^+ = 1379.48$, calc.: 1380.48.

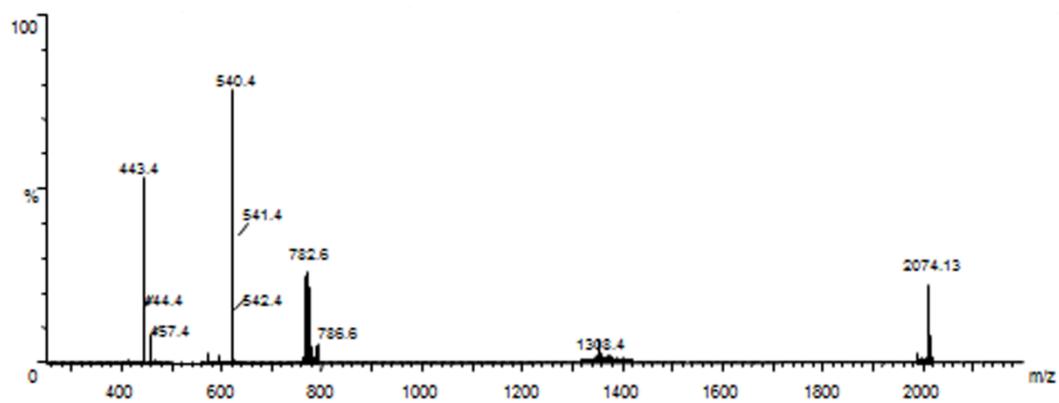


Figure S6. FA-PTX-EB, LC-MS: $[M + H]^+ = 2073.13$, calc.:2074.13.

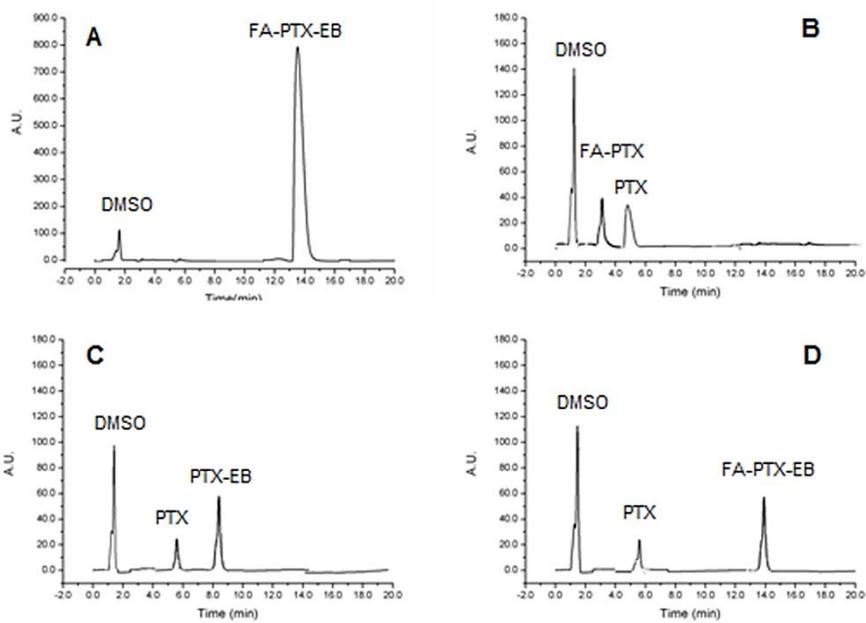


Figure S7. *In vitro* and *in vivo* release of PTX from PTX prodrugs was measured by HPLC.

The FA-PTX-EB prodrug was purified by HPLC (A), the PTX released from FA-PTX (B), the PTX released from PTX-EB (C), and the PTX released from FA-PTX-EB (D).

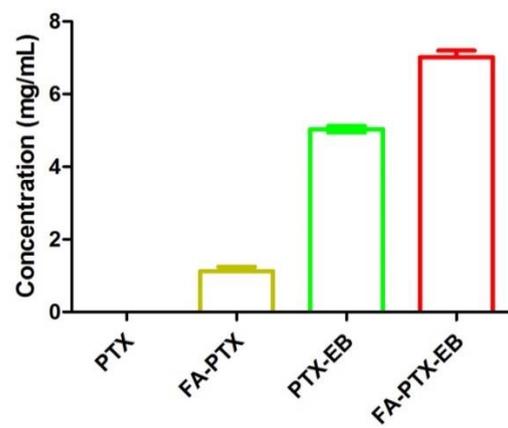


Figure S8. The solubility of PTX, FA-PTX, PTX-EB, and FA-PTX-EB.

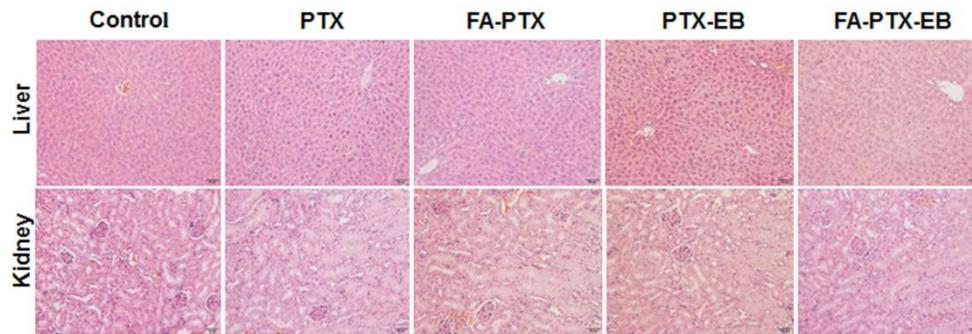


Figure S9. Tissue H&E staining of liver and kidney excised from nude mice 21 days after administration of PTX, FA-PTX, PTX-EB, and FA-PTX-EB.