

# **Hierarchically Theranostic Nanomedicine: MRI Contrast Agents as the Physical Vehicle Anchor for High Drug Loading and Triggered on-demand Delivery**

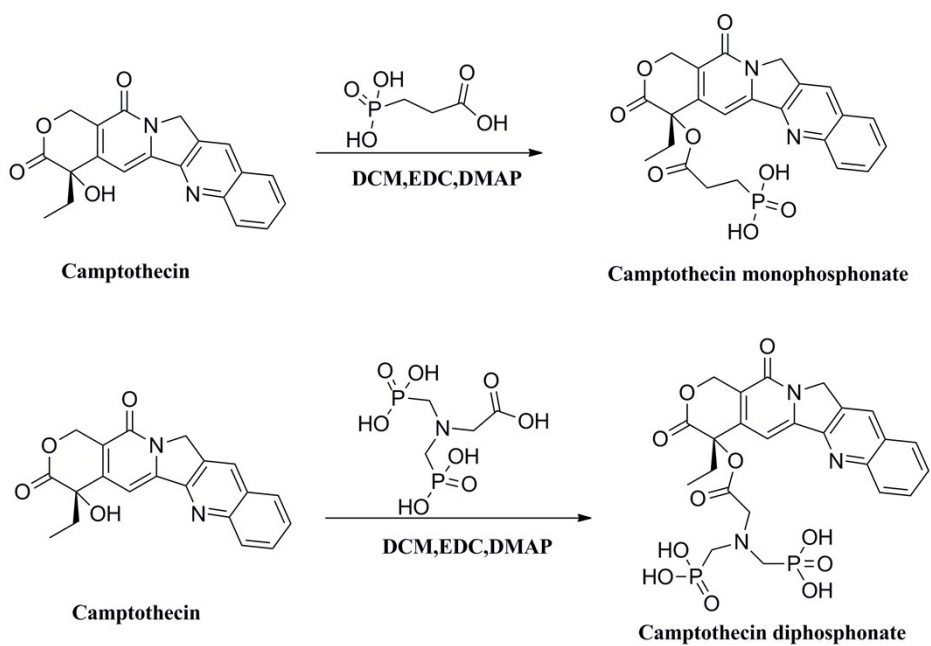
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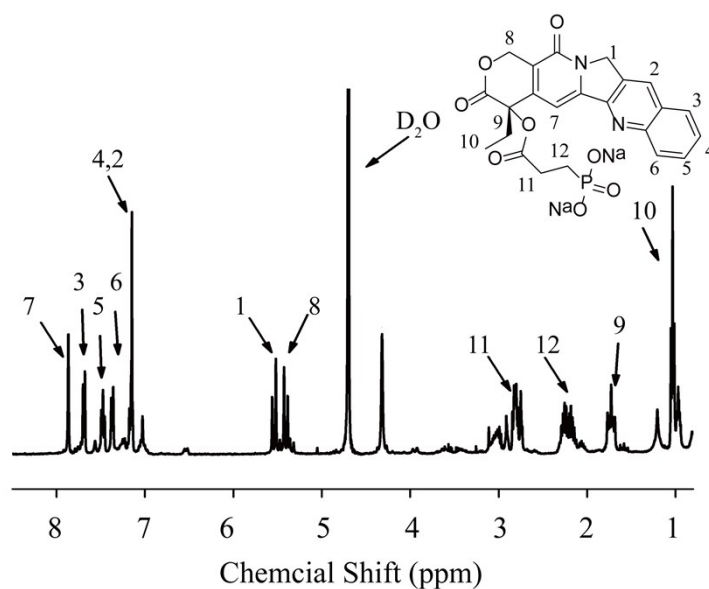
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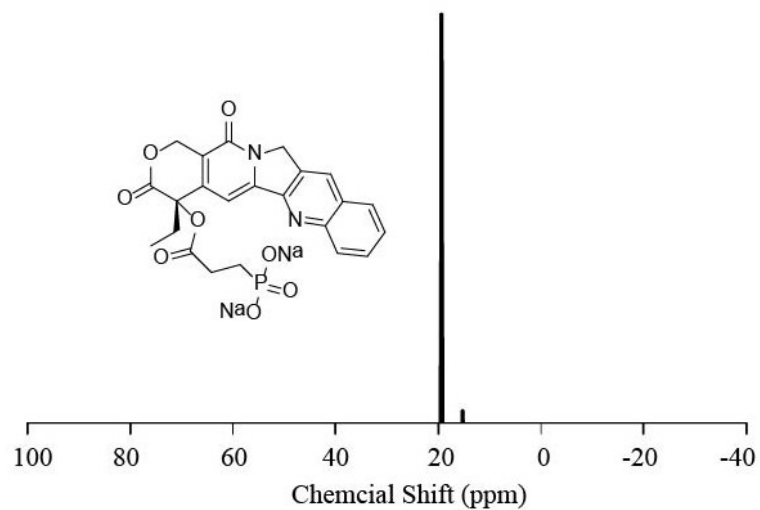
Email: zhaoyj@tju.edu.cn (Y Zhao)



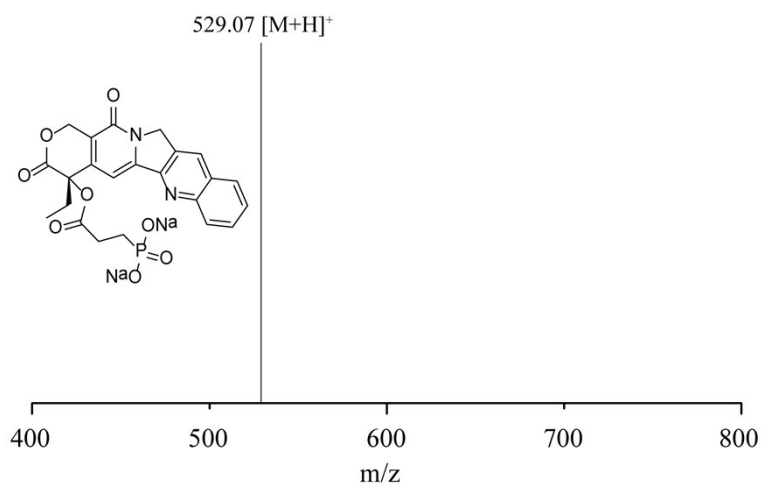
**Scheme S1.** Synthetic route of camptothecin monophosphate (CPT-P) and camptothecin diphosphate (CPT-2P).



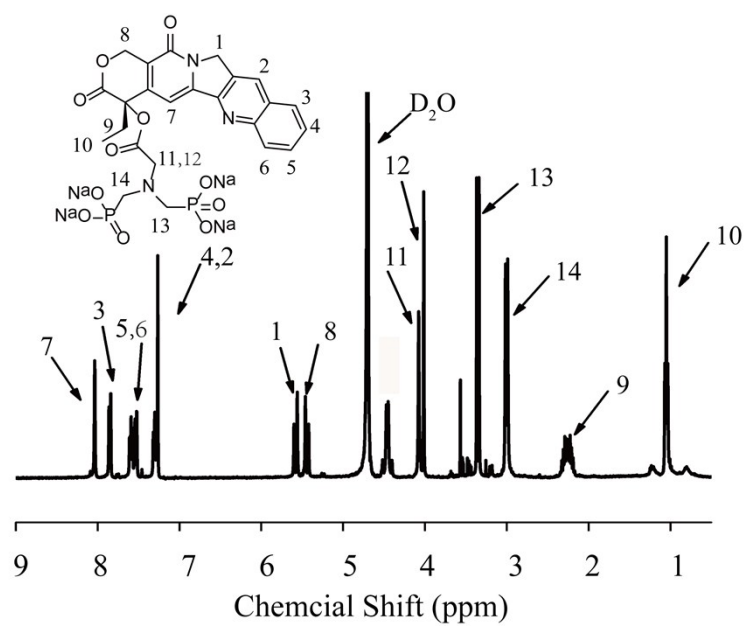
**Figure S1.**  $^1\text{H}$  NMR spectrum of camptothecin phosphate (CPT-P) ( $\text{D}_2\text{O}$ ).



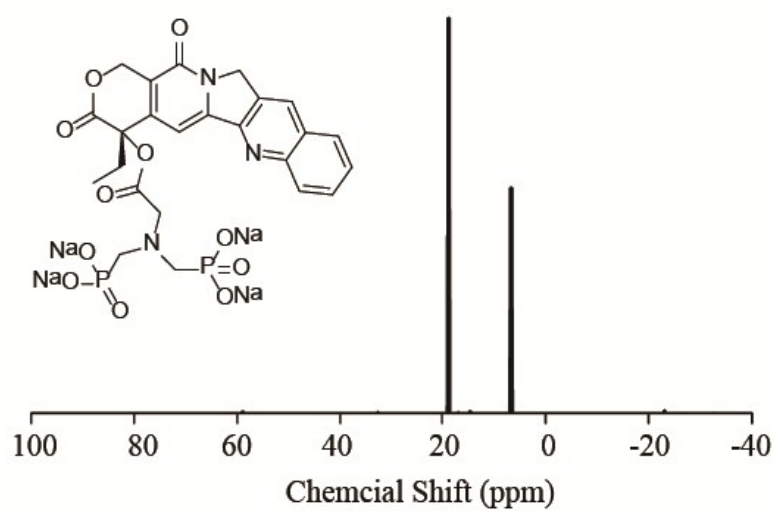
**Figure S2.**  $^{31}\text{P}$  NMR spectrum of camptothecin phosphate (CPT-P) ( $\text{D}_2\text{O}$ ).



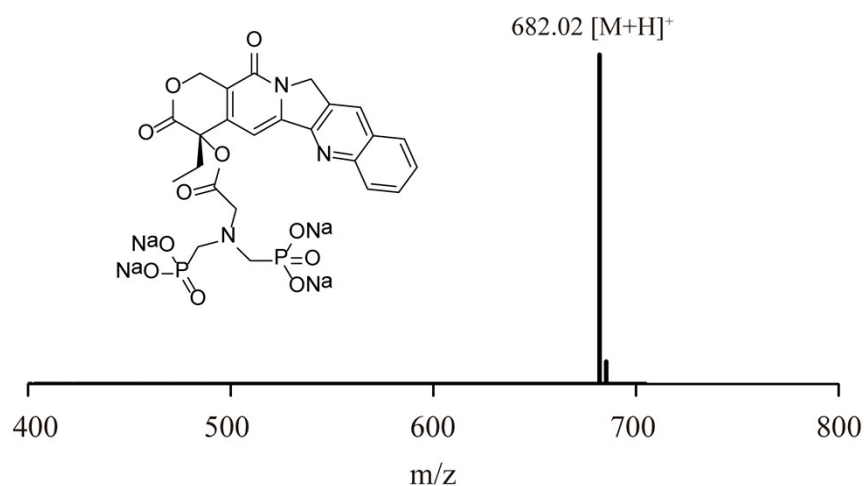
**Figure S3.** The mass spectrum of camptothecin phosphate (CPT-P).



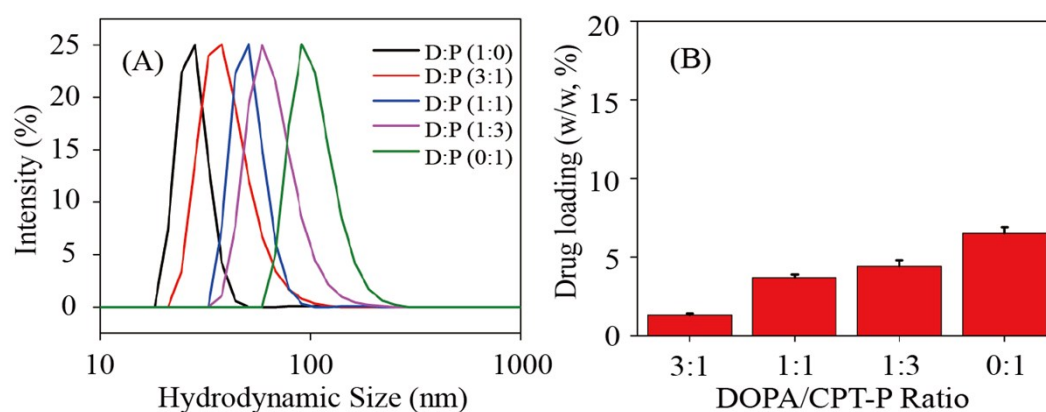
**Figure S4.**  $^1\text{H}$  NMR spectrum of camptothecin diphosphate (CPT-2P) ( $\text{D}_2\text{O}$ ).



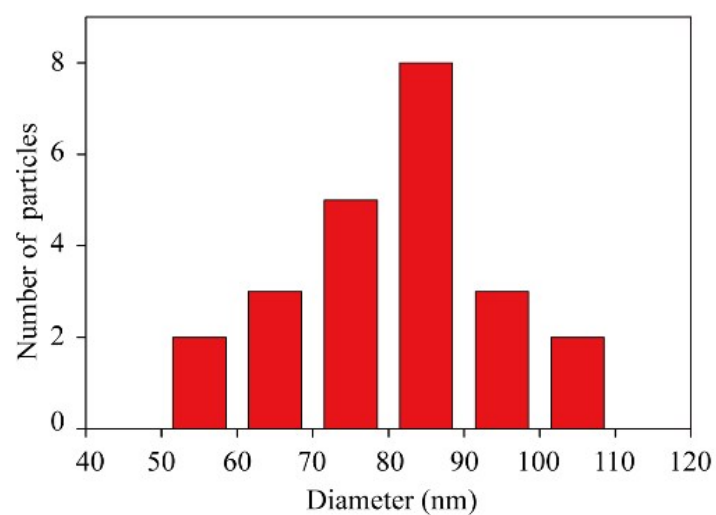
**Figure S5.**  $^{31}\text{P}$  NMR spectrum of camptothecin diphosphate (CPT-2P) ( $\text{D}_2\text{O}$ ).



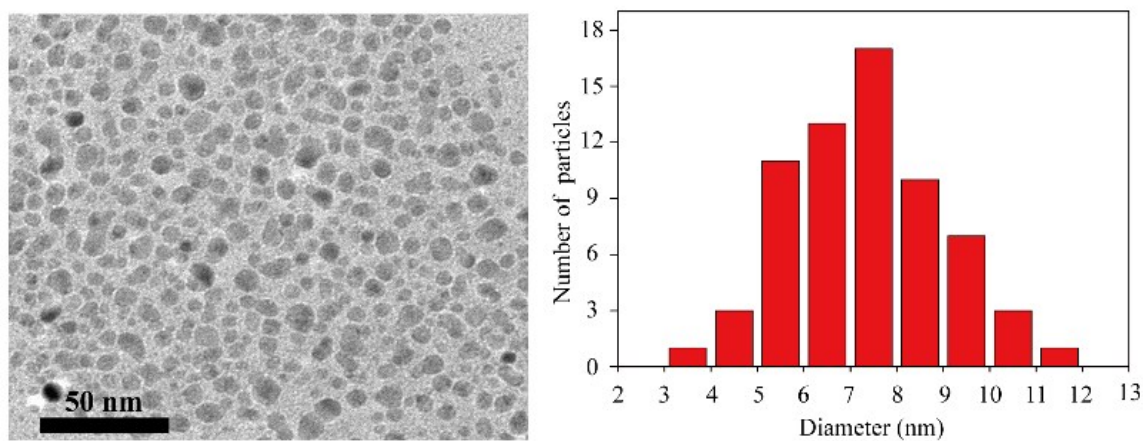
**Figure S6.** The mass spectrum of camptothecin diphosphate (CPT-2P).



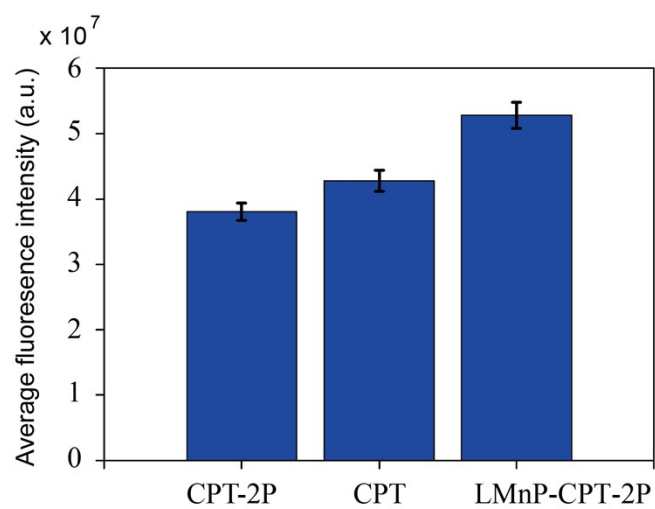
**Figure S7.** The influence of dioleoylphosphatidic acid (DOPA or D) and camptothecin monophosphonate (CPT-P or P) ratio on the particle size and drug loading in hybrid nanocarriers. (A) The hydrodynamic sizes of the hybrid nanocarrier when the mixture of a DOPA lipid and a model drug (CPT-P) at different molar ratios (D:P) were supplemented for the particle fabrication; (B) The drug loadings of four types of hybrid nanocarrier in corresponding to different D:P ratio.



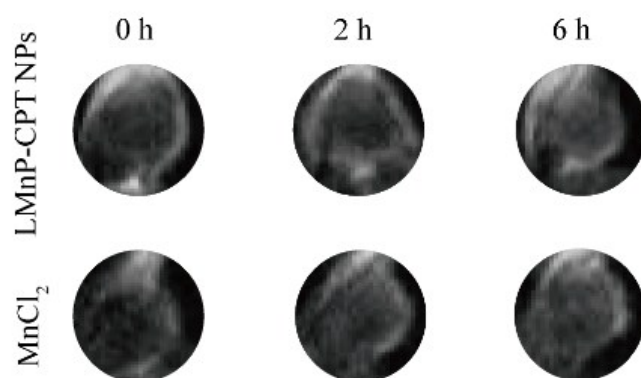
**Figure S8.** The number-based size and size distribution of micelles based on the TEM analysis in Figure 1D.



**Figure S9.** The TEM size of LMnP core and corresponding number-based size and size distribution histogram.



**Figure S10.** The average drug fluorescence intensity when three samples (CPT-2P, CPT and LMnP-CPT-2P) were incubated with 4T1 cells for 4 hours. The data were extracted from Figure 3B.



**Figure S11.** The enlarged MR images of tumor in Figure 4A.

**Table S1.** Significant comparison of three different formulations in terms of IC<sub>50</sub>. Free CPT ( $3.9 \pm 0.3 \mu\text{M}$ ), free CPT-2P ( $6.4 \pm 1.0 \mu\text{M}$ ), LMnP-CPT-2P nanocarrier ( $5.4 \pm 0.3 \mu\text{M}$ ).

Samples	Significant Difference
Free CPT vs. Free CPT-2P	Yes ( $p < 0.05$ )
Free CPT vs. LMnP-CPT-2P Nanocarrier	Yes ( $p < 0.05$ )
Free CPT-2P vs. LMnP-CPT-2P Nanocarrier	No ( $p > 0.05$ )