

## Supporting Information

### **A charge-reversal prodrug activated by tumor-acidity for selective cancer chemotherapy**

Bing Liu<sup>1†</sup>, Guanchun Wang<sup>2†\*</sup>, Qianjun Yang<sup>3†</sup>, Yang Yu<sup>1</sup>, Yue Su<sup>2</sup>, Wei Huang<sup>2</sup>,  
Ping Wang<sup>2</sup>, Deyue Yan<sup>2\*</sup> & Ping Huang<sup>1\*</sup>

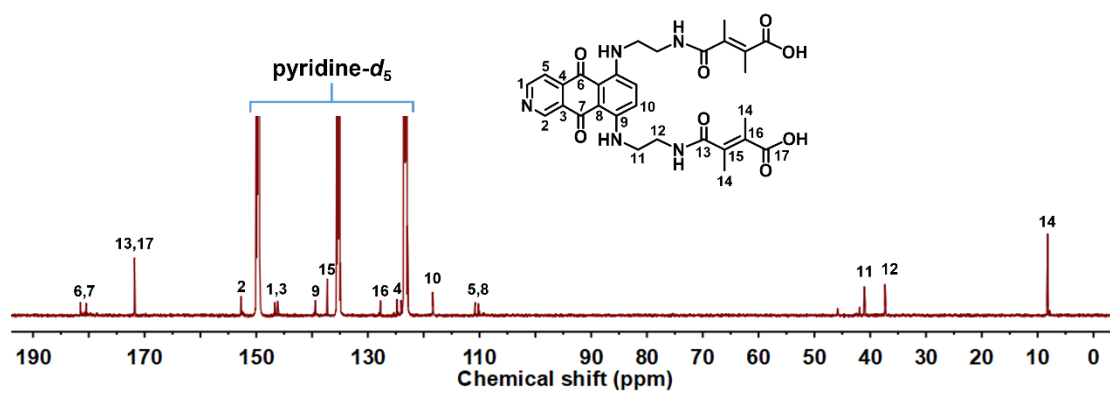
*<sup>1</sup>The First Affiliated Hospital of Harbin Medical University, School of Stomatology, Harbin Medical University, Harbin 150001, China*

*<sup>2</sup>School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, Shanghai 200240, China*

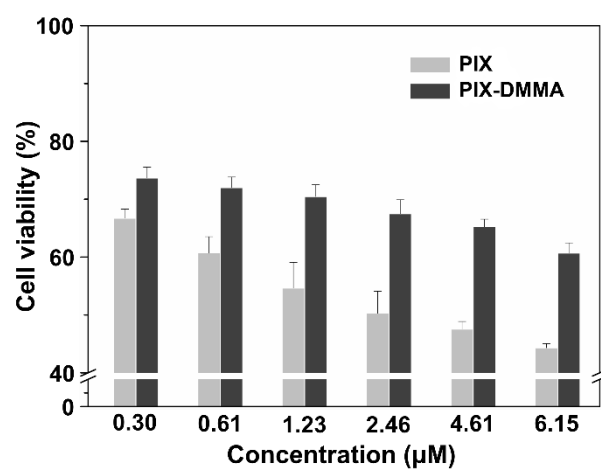
*<sup>3</sup>Department of Pharmacy, Shanghai Sixth People's Hospital affiliated Shanghai Jiao Tong University School of Medicine, Shanghai 200233, China*

<sup>†</sup>These authors contributed equally to this work.

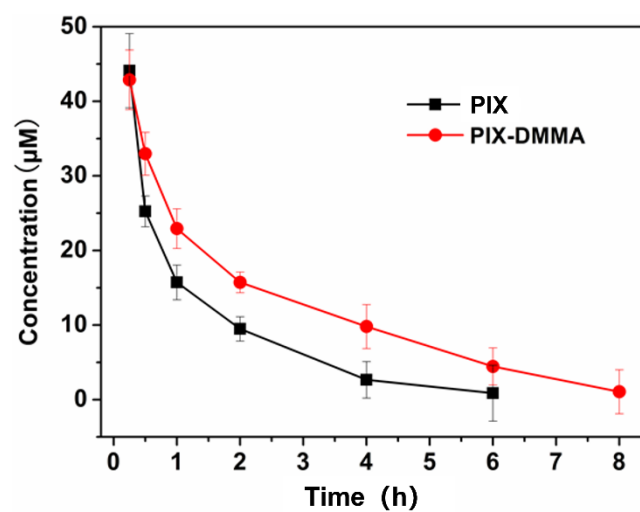
\*Corresponding authors: (email: wangguanchun@sjtu.edu.cn; dyyan@sjtu.edu.cn; hp158@sjtu.edu.cn)



**Fig. S1**  $^{13}\text{C}$  NMR spectrum of the PIX-DMMA prodrug in  $\text{pyridine-}d_5$ .



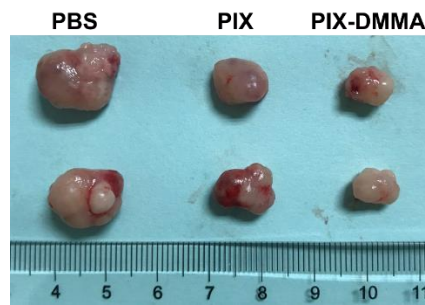
**Fig. S2** The cell viability of NIH/3T3 cells measured by the MTT method against PIX and PIX-DMMA with different concentrations (Data are presented as average  $\pm$  error (n = 5)).



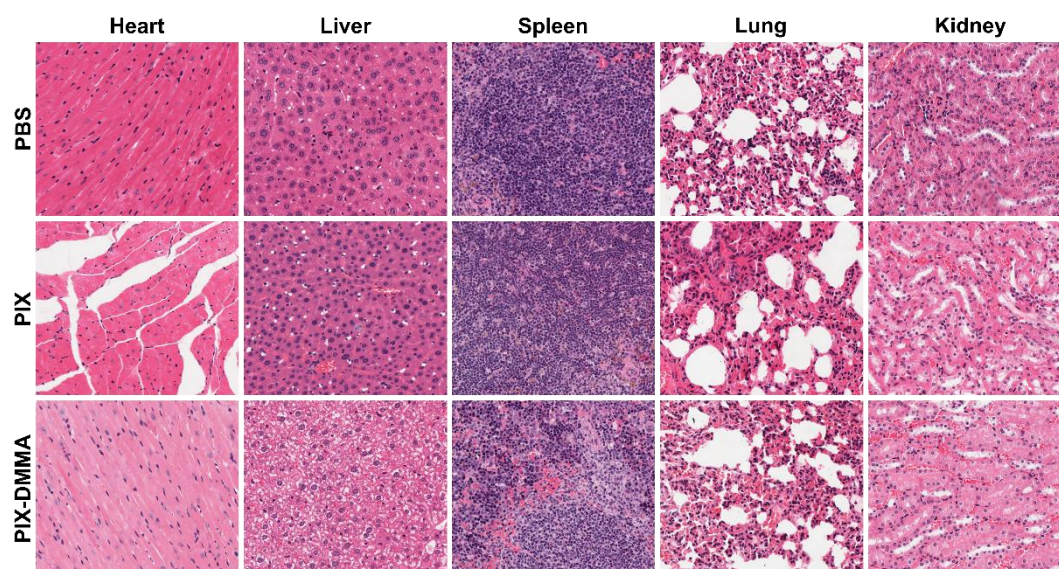
**Fig. S3** Representative plasma concentration-time profiles of PIX-DMMA and PIX after *iv* injection into rats.



**Fig. S4** The photo of mice treated with different formulations during the 21-day therapeutic period.



**Fig. S5** Representative tumors separated from animals after intravenous injection of PBS, PIX, and PIX-DMMA prodrug.



**Fig. S6** The H&E photographs of heart, liver, spleen, lung, and kidney sections of LoVo tumor-bearing mice after being treated by intravenous injection of PBS, PIX, and PIX-DMMA prodrug for 21 days (magnification  $\times 100$ ).