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## Supplementary information

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### 3 **Rational design of a new cytarabine-based prodrug for** 4 **highly efficient oral delivery of cytarabine**

5 Jing Zhang,<sup>a</sup> Di Zhang,<sup>a</sup> Xu Hu,<sup>a</sup> Ruiling Liu,<sup>a</sup> Zhonghao Li,<sup>b</sup> Yuxia Luan<sup>a\*</sup>

6 <sup>a</sup> School of Pharmaceutical Science, Shandong University, 44 West Wenhua Road,  
7 Jinan, Shandong Province 250012, China, E-mail: yuxialuan@sdu.edu.cn.

8 <sup>b</sup> Key Laboratory of Colloid & Interface Chemistry, Shandong University, Ministry of  
9 Education, 250100, China.

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15 **Conditions for HPLC-MS**

16 **1. HPLC**

17 A C18 column (150 mm × 4.6 mm i.d. 5 mm, Thermo) coupled with a Phenomenex  
18 C18 guard column (4 mm × 3.0 mm i.d. 5 mm) conducted the quantitative analysis.  
19 Column temperature: 25 °C. The The gradient elution conditions for HPLC-  
20 MSmeasurements was shown in Table S1. The flow rate was 0.6 mL min<sup>-1</sup>.

21 **2. MS**

22 A triple quadrupole mass spectrometer (Agilent 1260)was equipped with an ESI  
23 (electrospray ionization)source. IS was 5500 V, TEM was 650 °C, and the scanning  
24 mode was used to monitor the positive ion scanning mode. GAS1 and GAS2 were  
25 both 60 psi, CAD was 6 psi and CUR was 15 psi.

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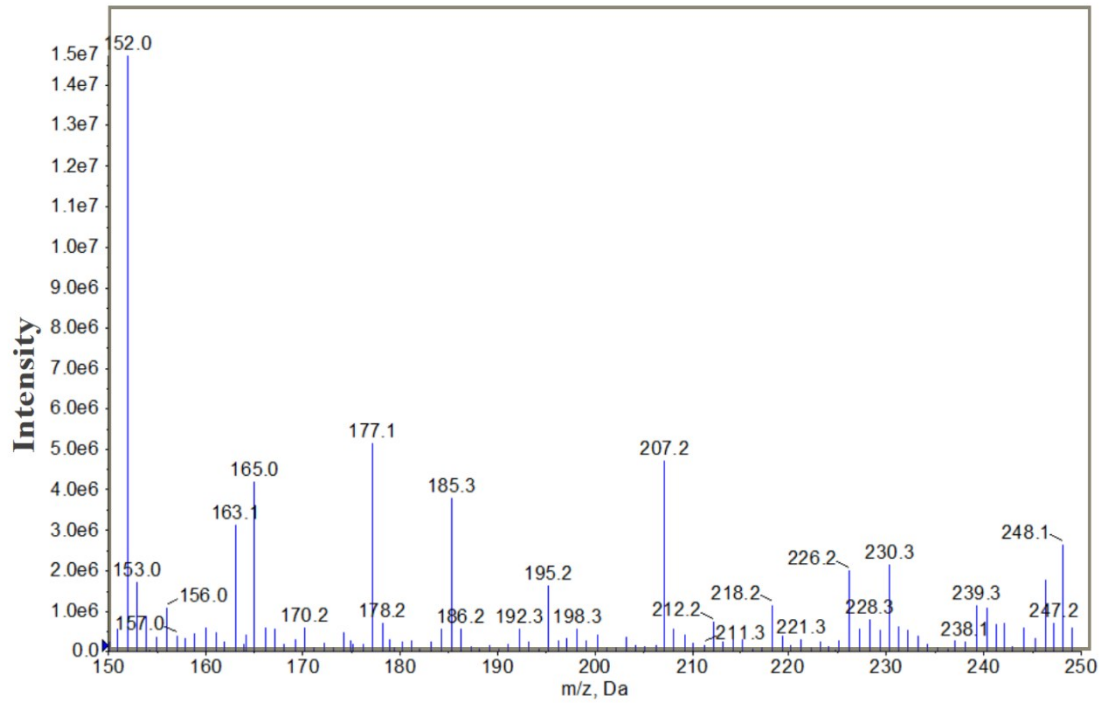
28 **Table S1.** The gradient elution conditions for HPLC-MS/MS measurements.

Time (min)	0-2	2-4	4-12	12-16.5
methanol (%)	20	20→90	90→95	95

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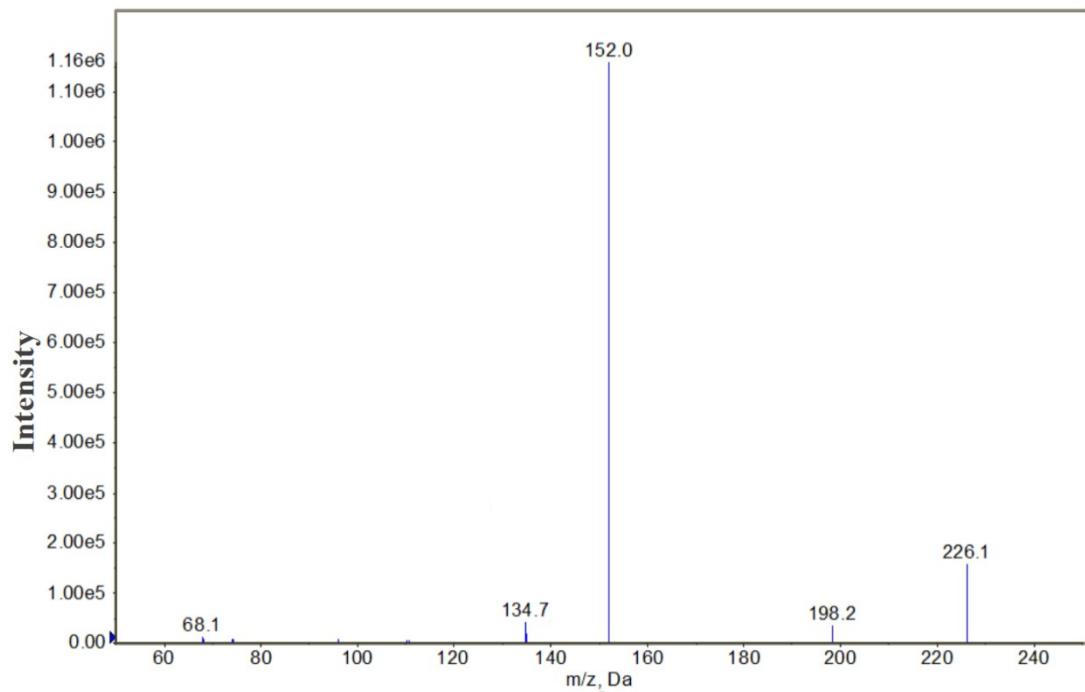


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33 **Fig. S1.** The first-order mass spectra of acyclovir.

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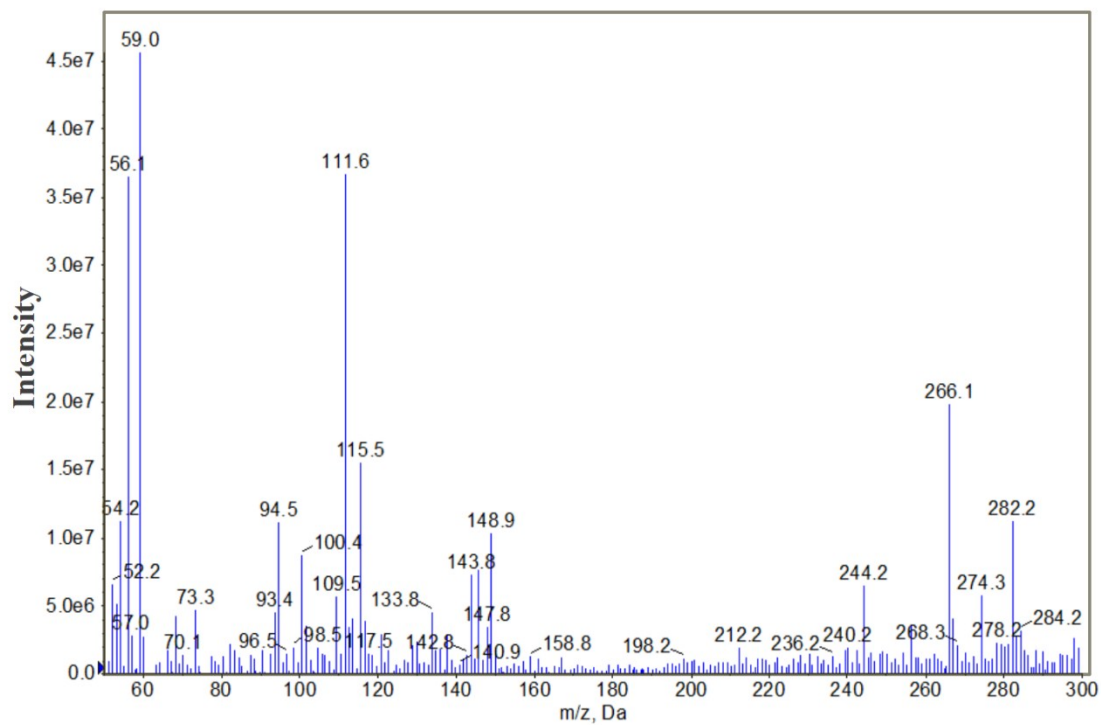
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37 **Fig. S2.** The second-order mass spectra of acyclovir.

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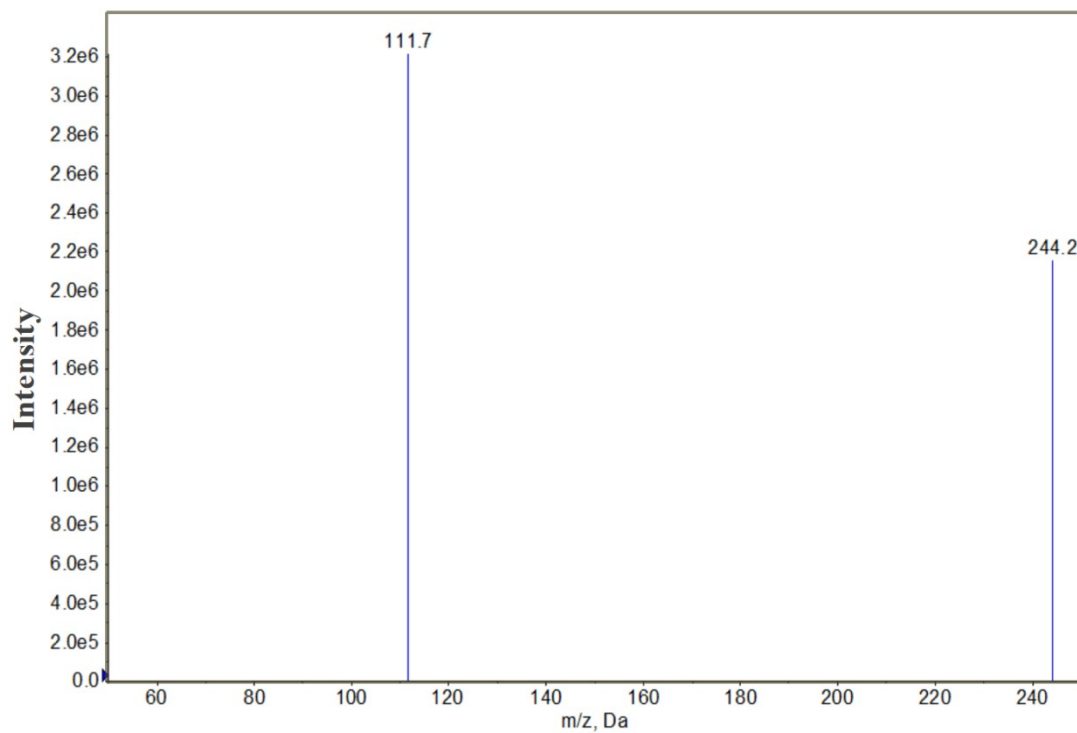


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40 **Fig. S3.** The first-order mass spectra of Ara-C.

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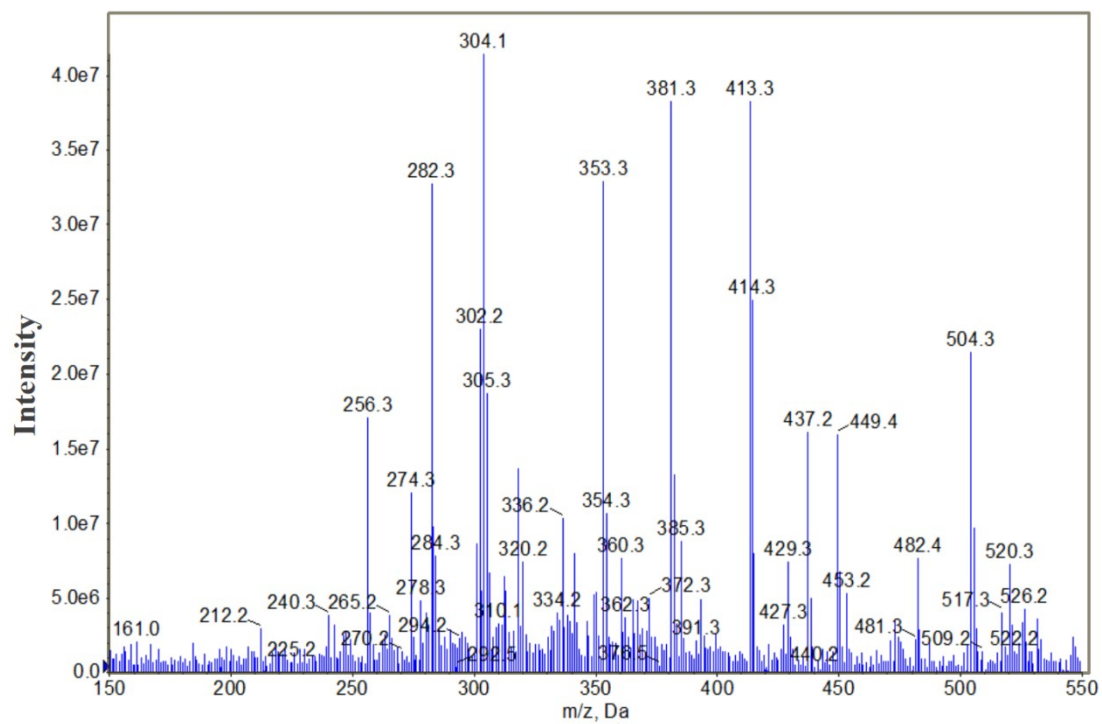
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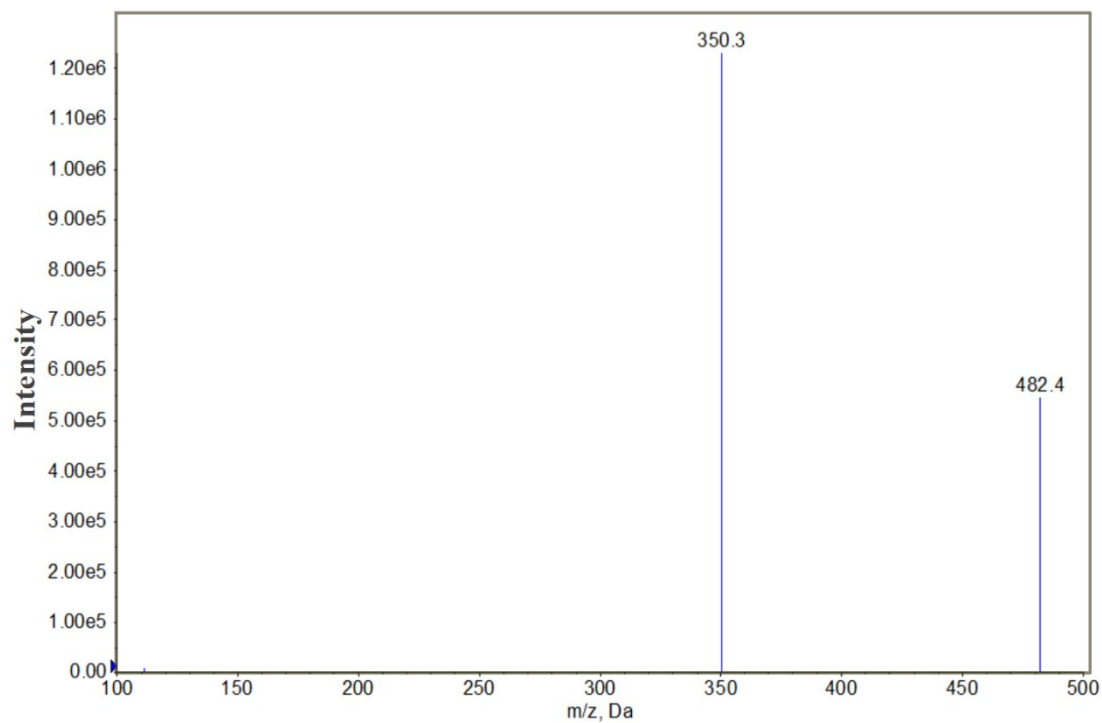
44 **Fig. S4.** The second-order mass spectra of Ara-C.

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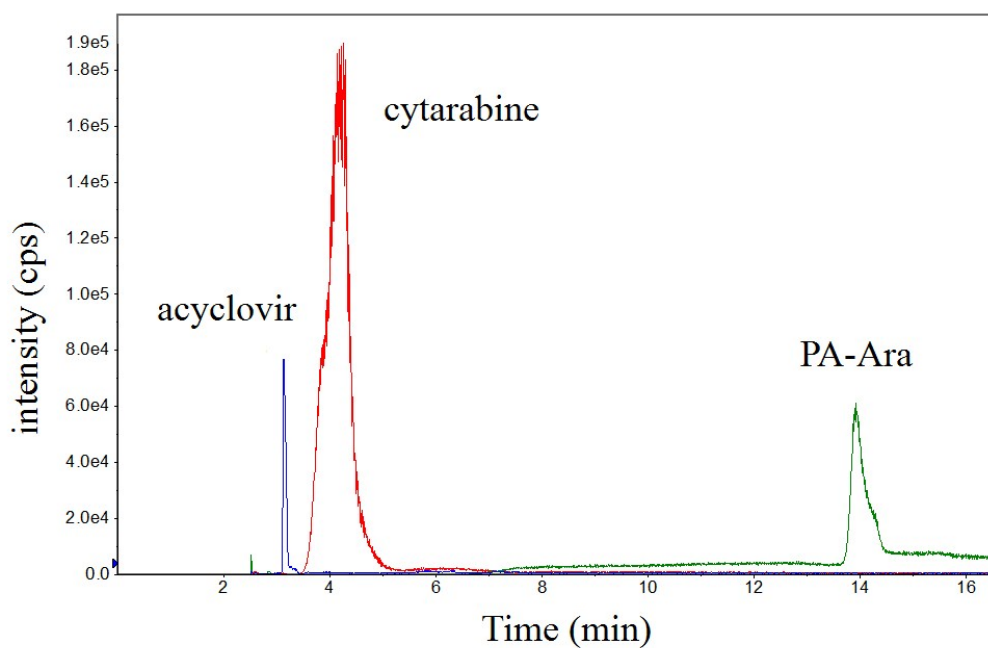
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47 Fig. S5. The first-order mass spectra of PA-Ara.



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49 Fig. S6. The second-order mass spectra of PA-Ara.

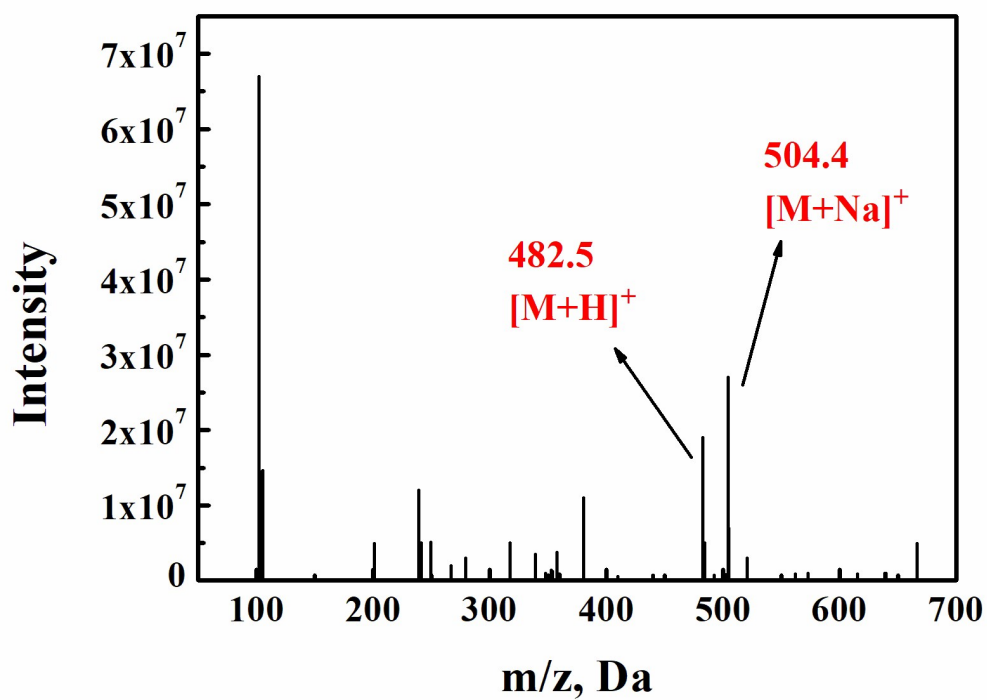


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51 **Fig. S7.** The chromatograms of acyclovir ( $m/z$  226 $\rightarrow$ 152), cytarabine ( $m/z$  244 $\rightarrow$ 112)

52 and PA-Ara ( $m/z$  482 $\rightarrow$ 350) in rat plasma samples.

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55 **Fig. S8.** Mass spectra of prodrug PA-Ara.