**Supporting Information**

**for**

# Phosphatase-triggered cell-selective release of a Pt(IV)-backboned prodrug-like polymer for improved therapeutic index

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## Supporting Figures and Tables

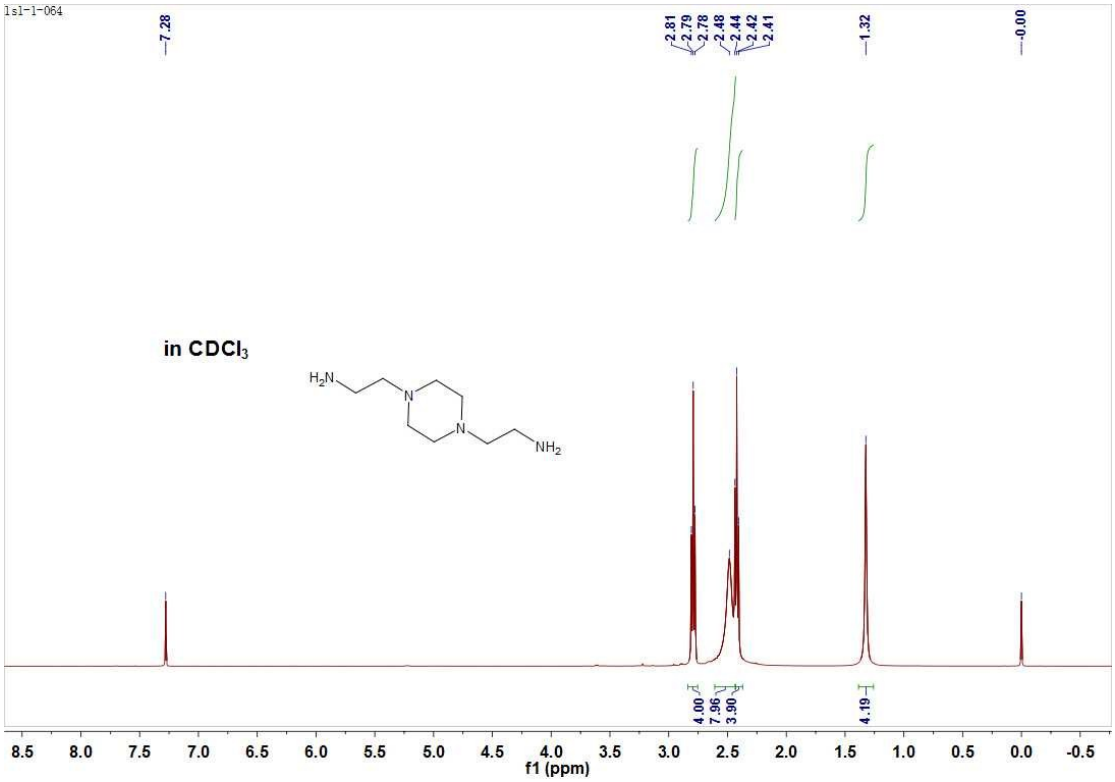



**Fig. S1**. $^{1}H$ NMR spectrum of DAEP in $CDCl_3$.

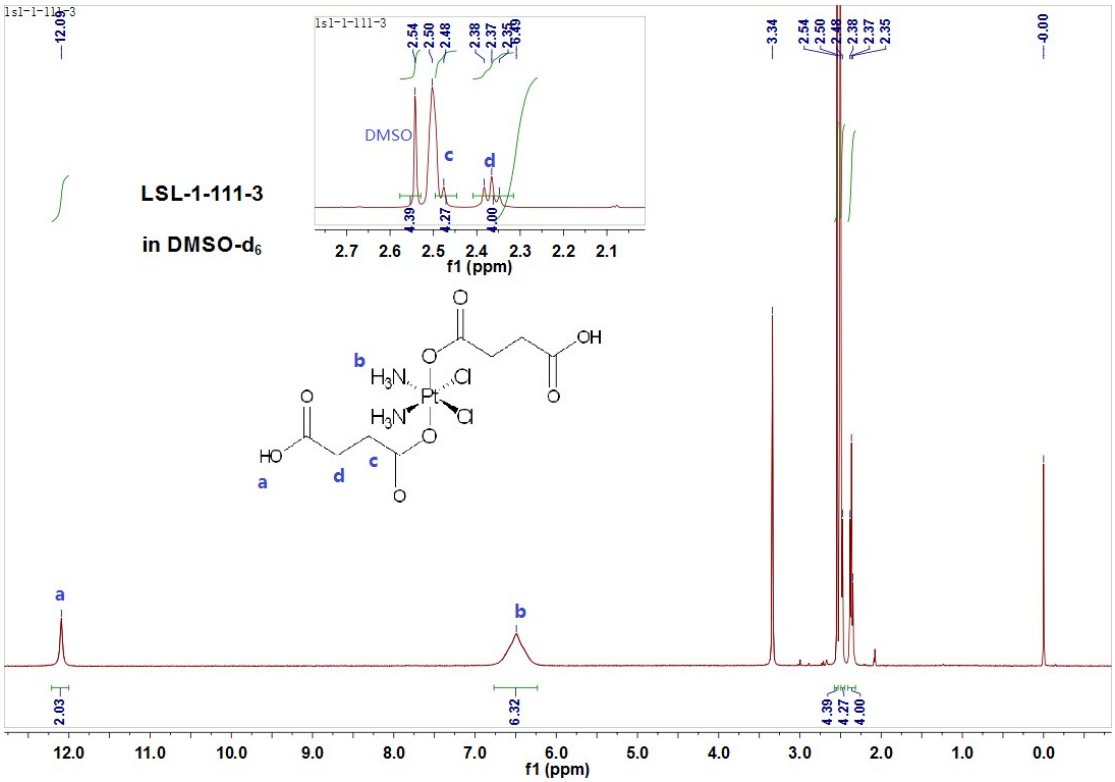



**Fig. S2**. $^{1}$H NMR spectrum of DSP in DMSO-$d_6$.

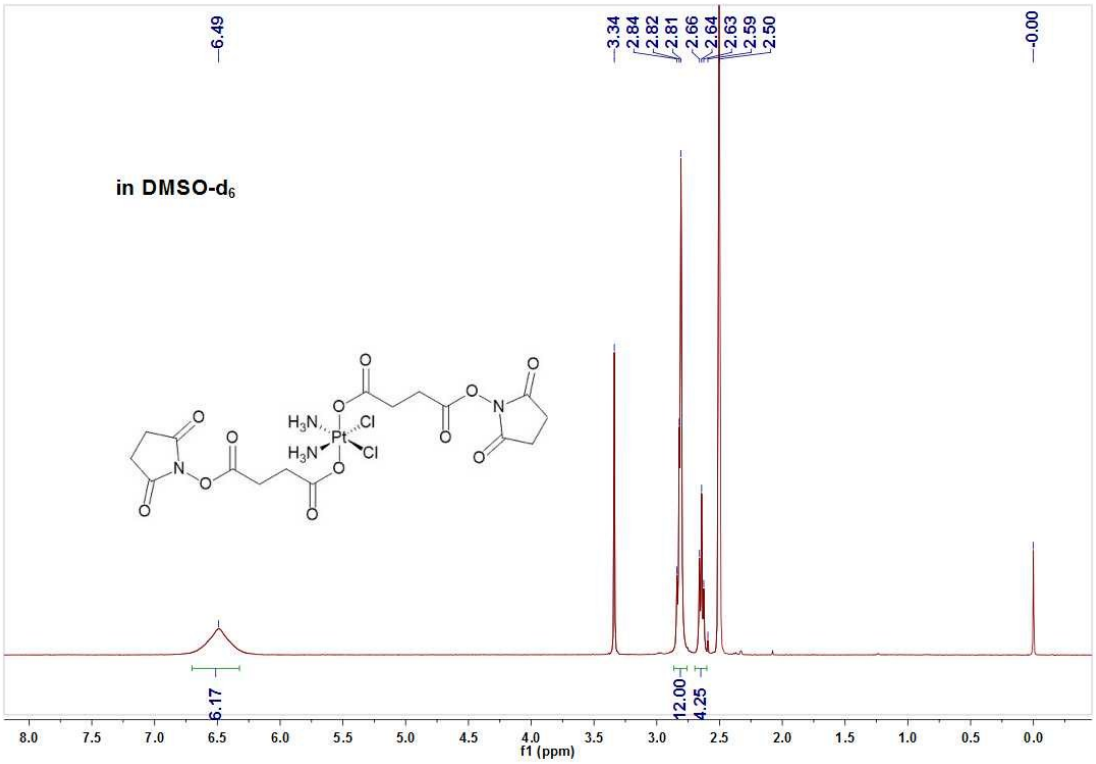



**Fig. S3**. $^{1}$H NMR spectrum of Pt-NHS in DMSO-$d_6$.

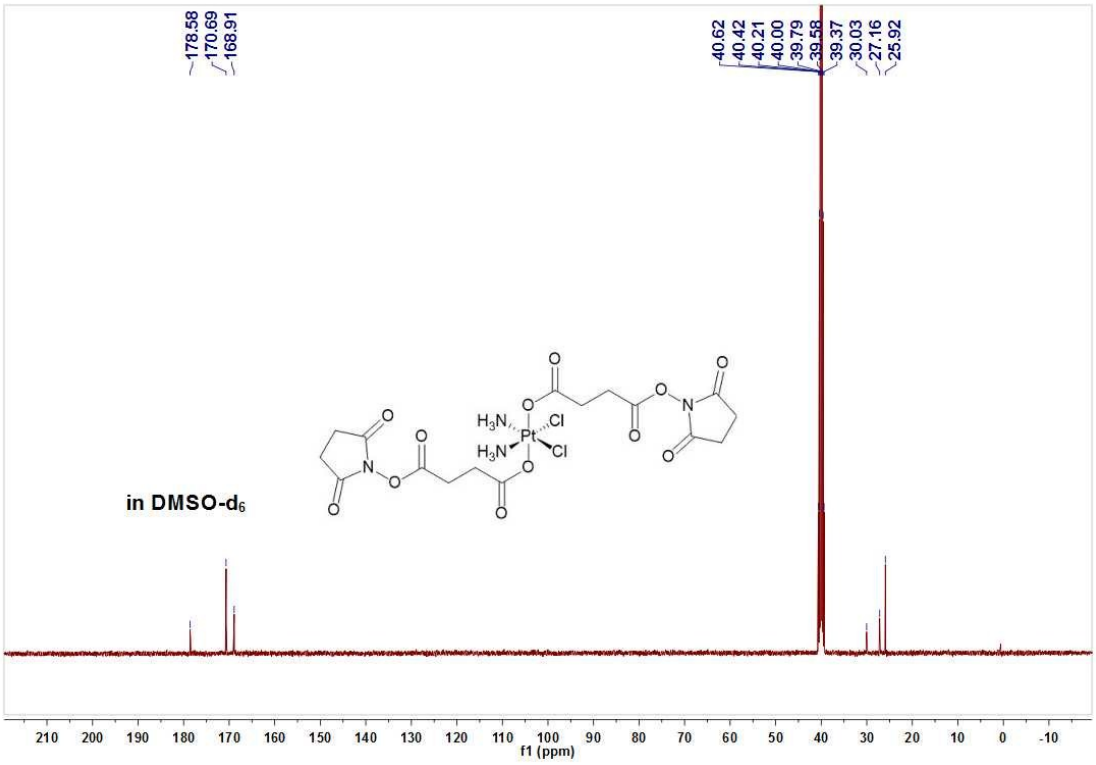



**Fig. S4**. $^{13}$C NMR spectrum of Pt-NHS in DMSO-$d_6$.

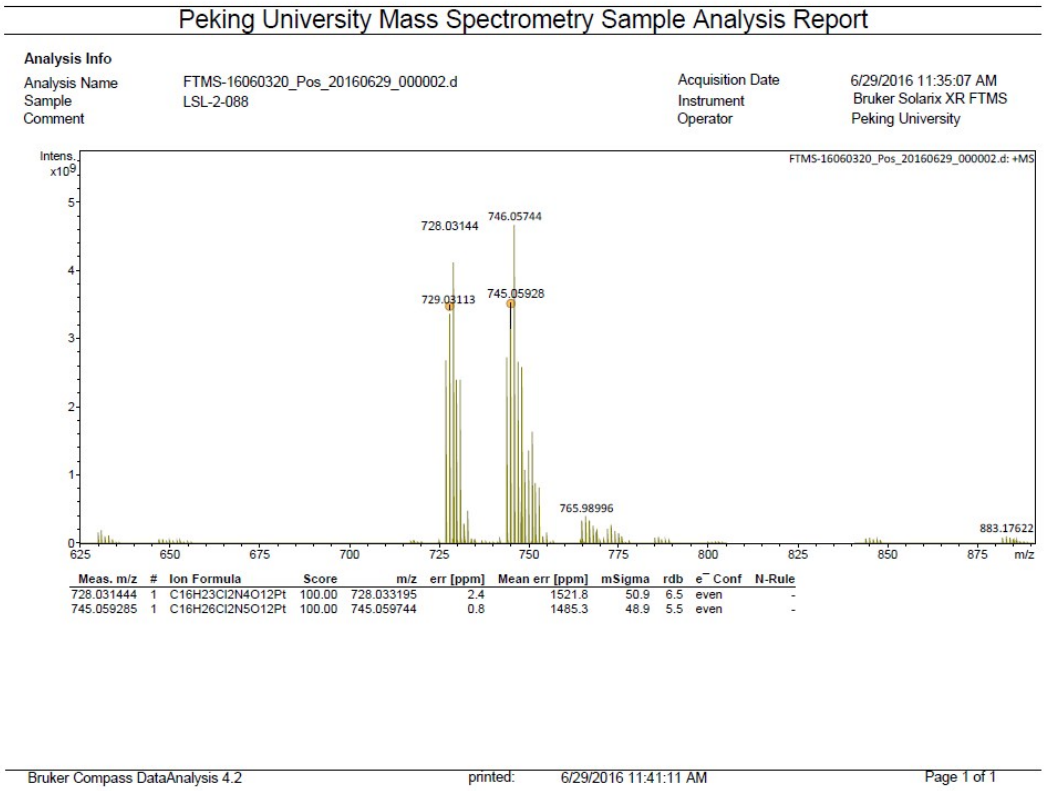



**Fig. S5**. HR-ESI-MS spectrum of Pt-NHS.

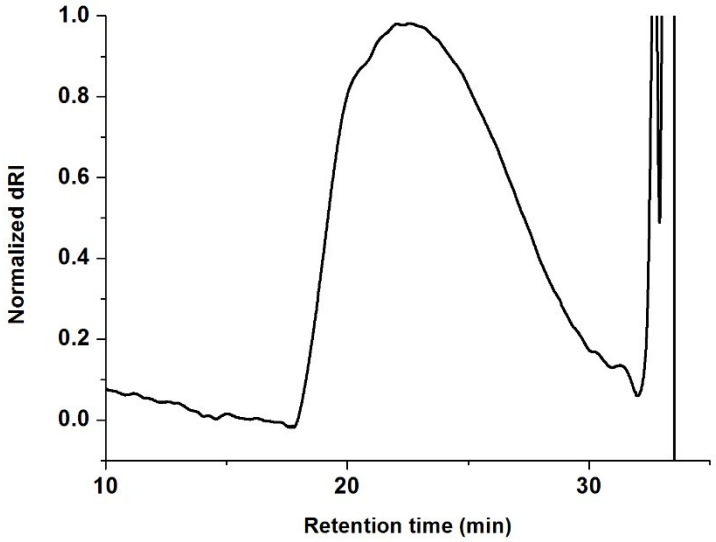



**Fig. S6.** GPC curve of P(DSP-DAEP).

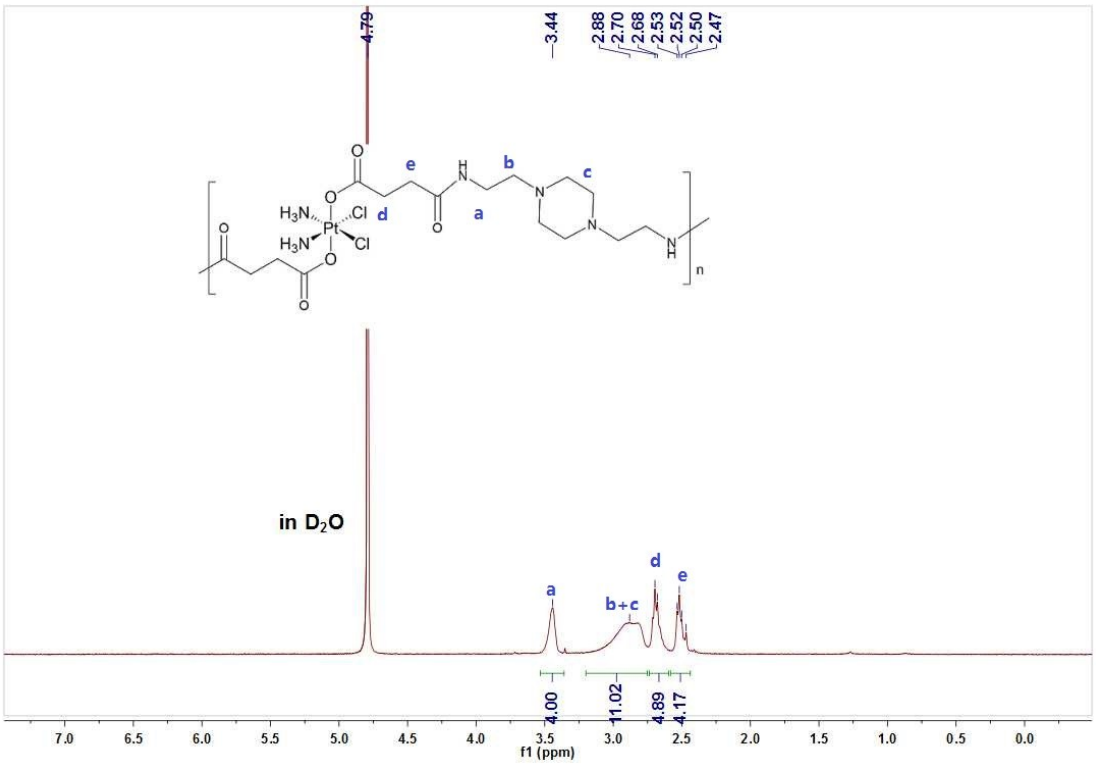
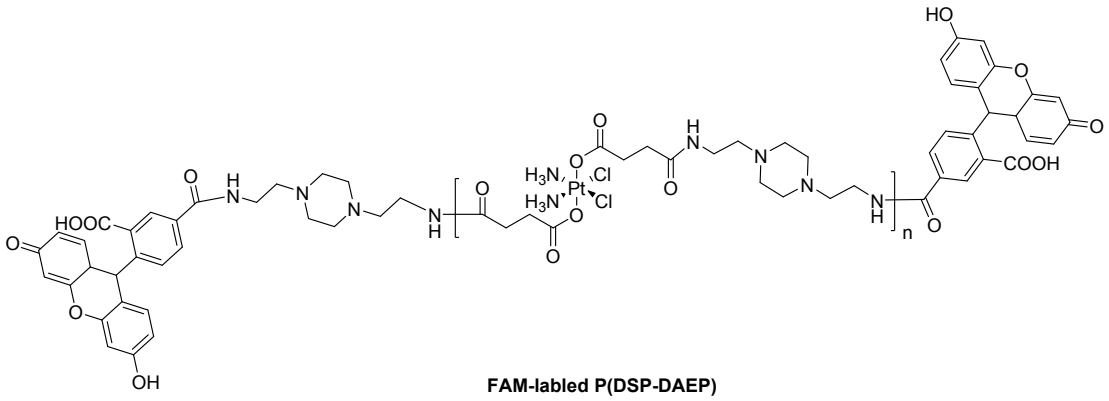



**Fig. S7**. $^{1}$H NMR spectrum of P(DSP-DAEP) in $D_2O$.




**Scheme S1.** The chemical structure of FAM-labeled P(DSP-DAEP).

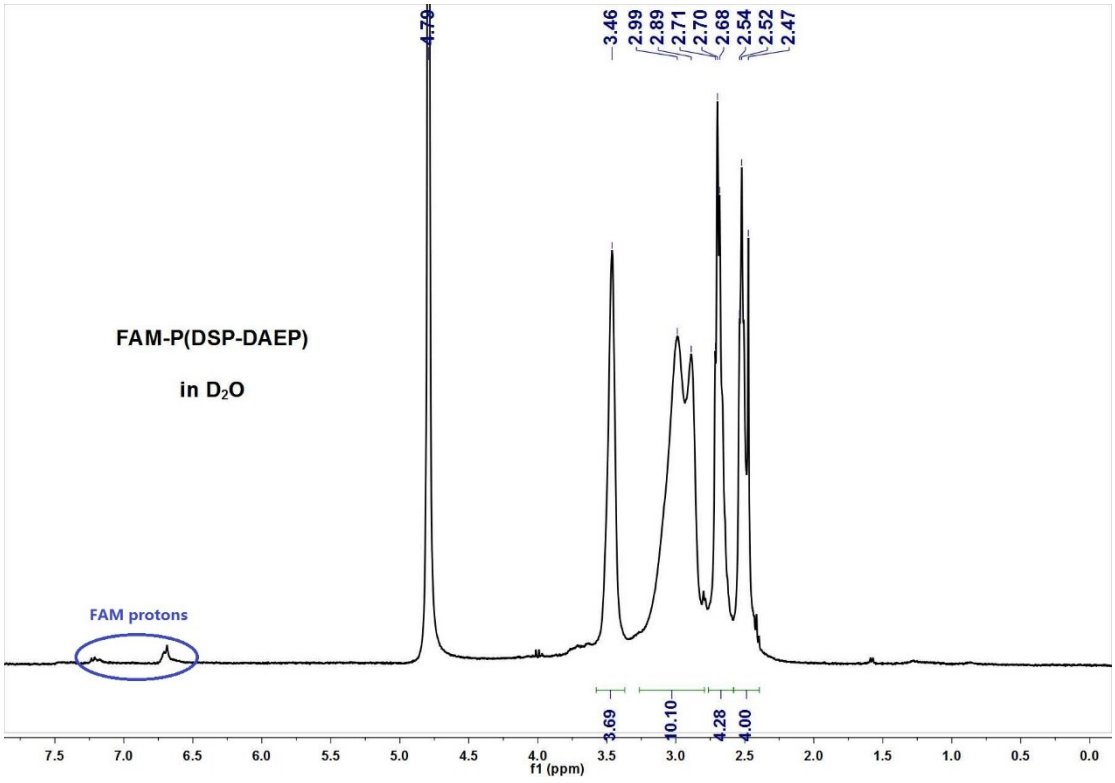
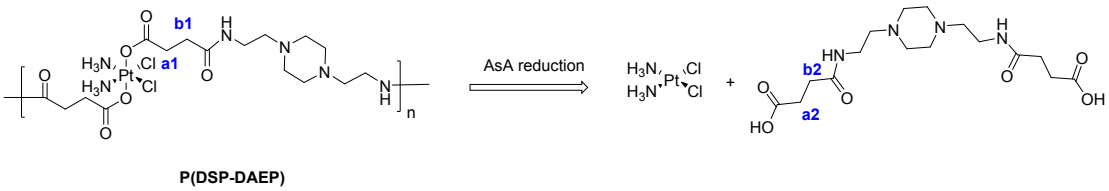



**Fig. S8**. $^{1}H$ NMR spectrum of FAM-P(DSP-DAEP) in $D_2O$.

**Quantification of reductive degradation of polymer P(DSP-DAEP)**

The disappearance of the methylene **a1** peak (δ 2.68 ppm) and appearance of the **a2** (δ 2.48 ppm) peak was quantified by using $^{1}$H NMR in comparison with the original polymer.




**Scheme S2.** Polymer degradation upon the ascorbic acid reduction.

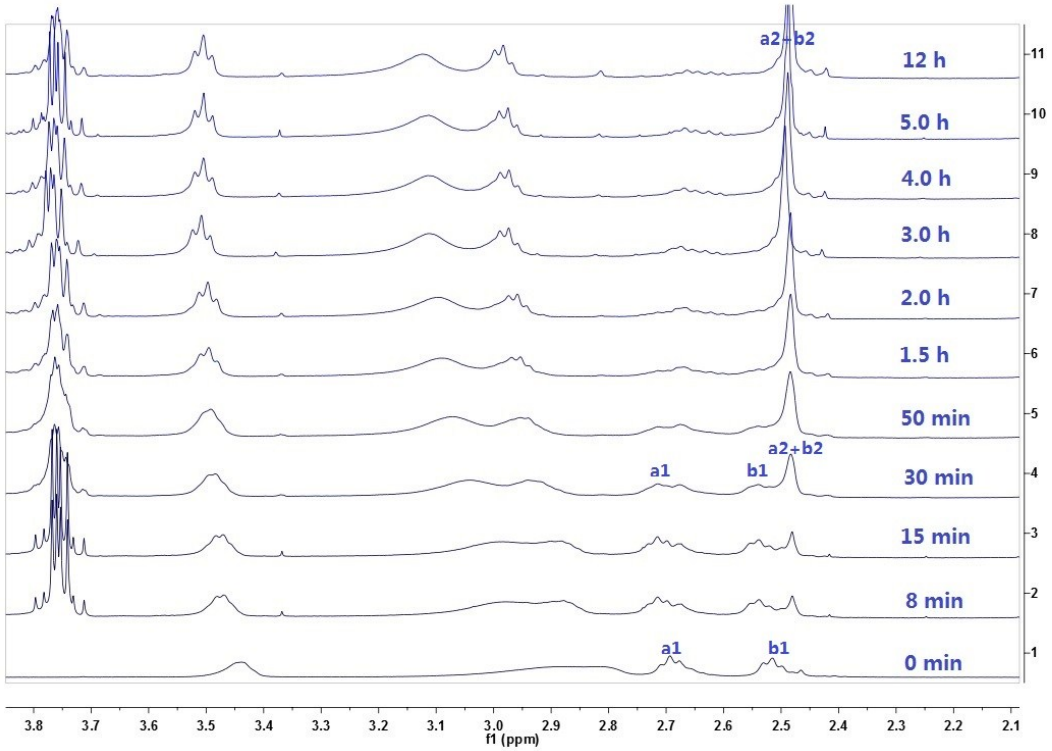
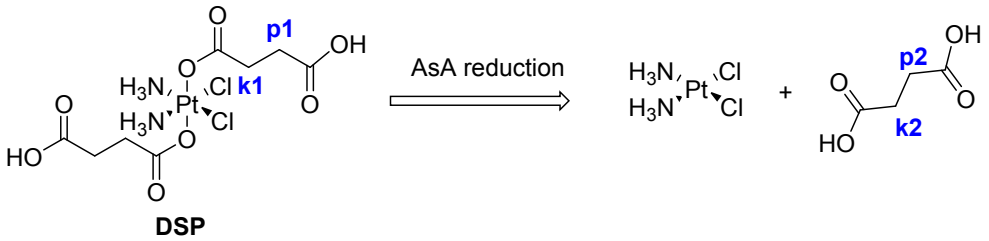



**Fig. S9**. Stacked $^{1}$H NMR spectrum of P(DSP-DAEP) with the ascorbic acid for various periods of incubation time at 37 °C.




**Scheme S3.** DSP degradation upon the ascorbic acid reduction.

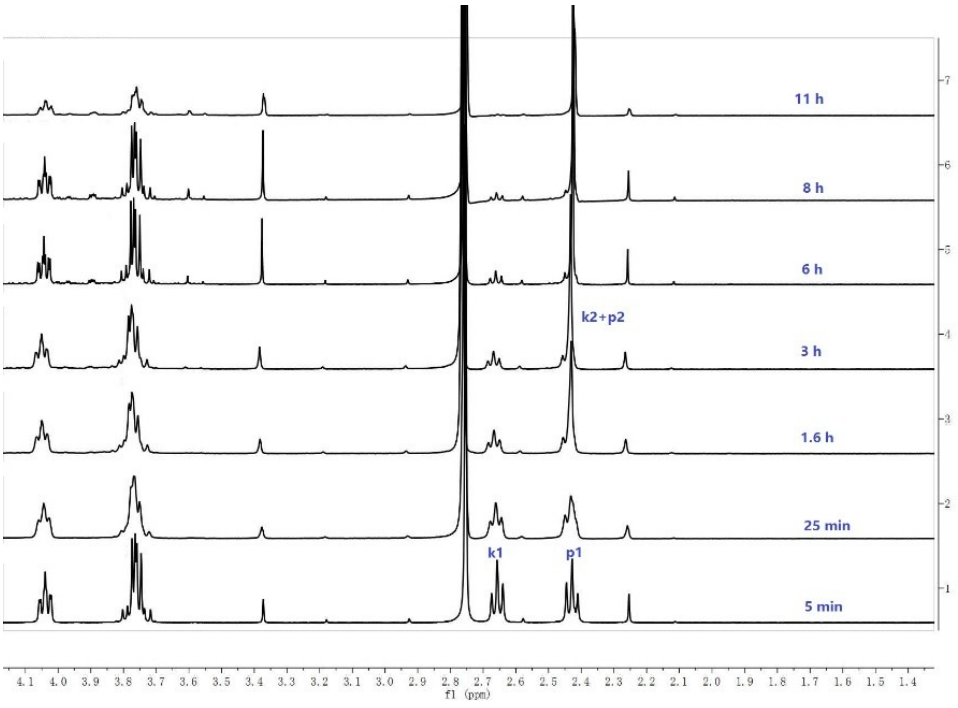



**Fig. S10**. Stacked $^{1}$H NMR spectrum of DSP with the ascorbic acid for various periods of incubation time at 37 °C.

**Electrochemistry**

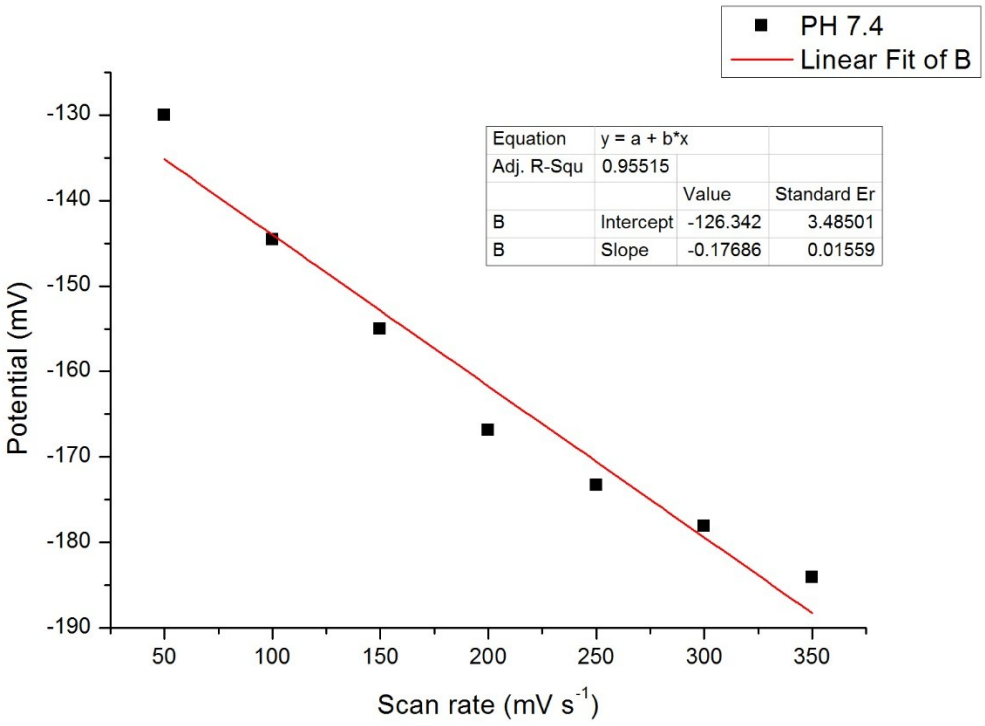



**Fig. S11**. Plot of reduction peak potential maxima of P(DSP-DAEP) at pH 7.4 as a function of scan rate.

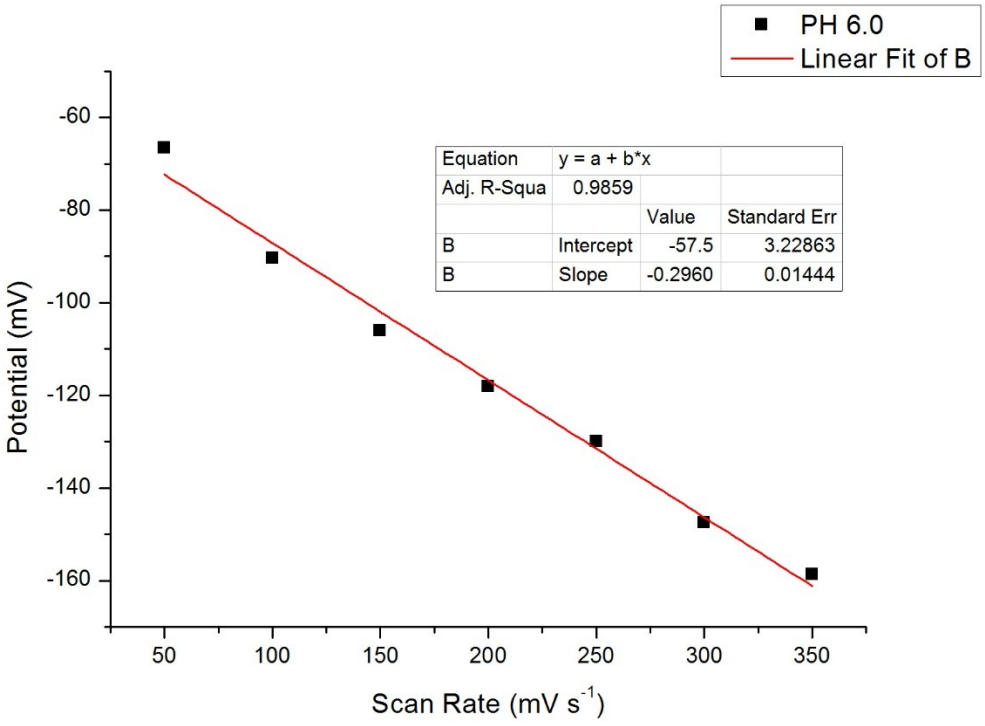



**Fig. S12.** Plot of reduction peak potential maxima of P(DSP-DAEP) at pH 6.0 as a function of scan rate.

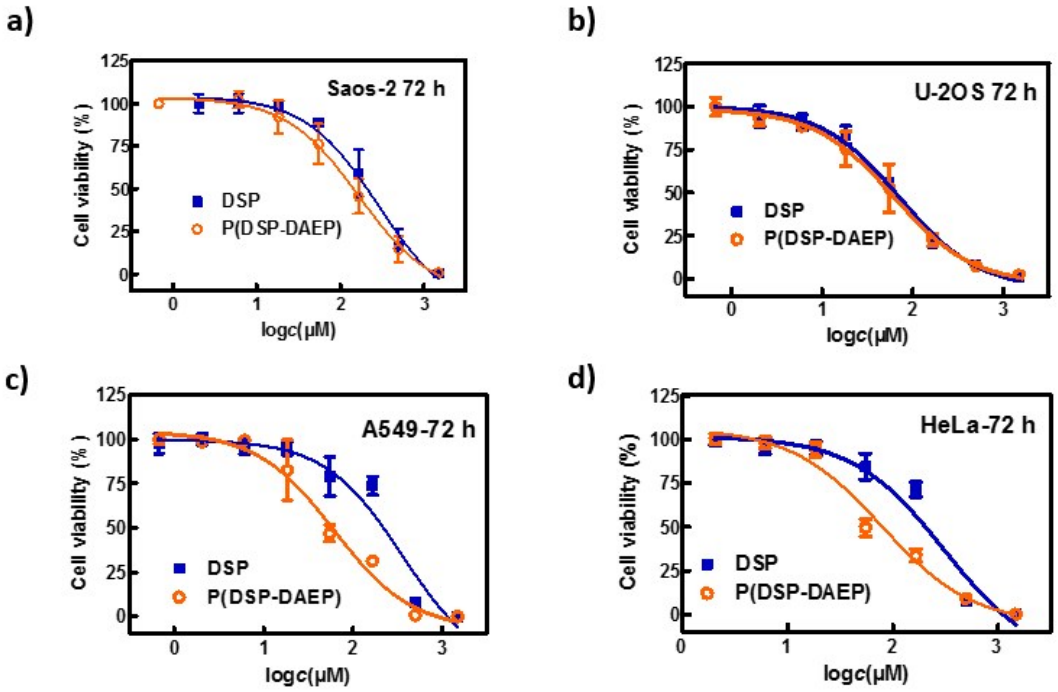



**Fig. S13.** Cell viability assays of DSP and P(DSP-DAEP) in Saos-2, U-2OS, A549 and HeLa cells.

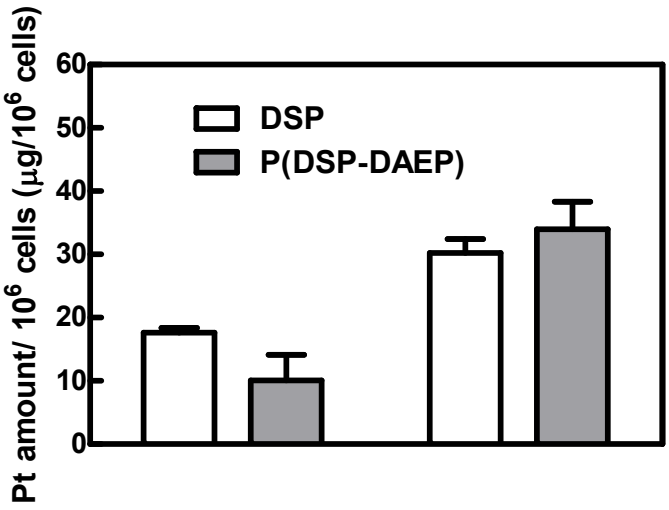



**Fig.S14.** Intracellular Pt amount of DSP and P(DSP-DAEP) in HeLa at 20 μM and 60 μM based on Pt at 37 ℃ incubated for 3 h.

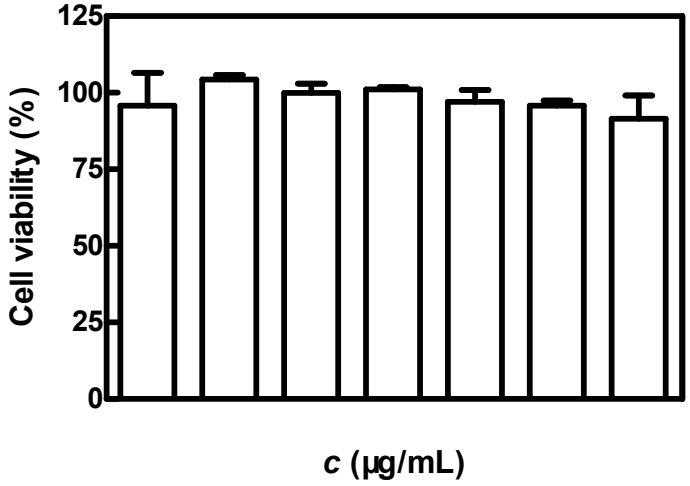



**Fig. S15**. Cell viability assay of DAEP in HeLa for 72 h.

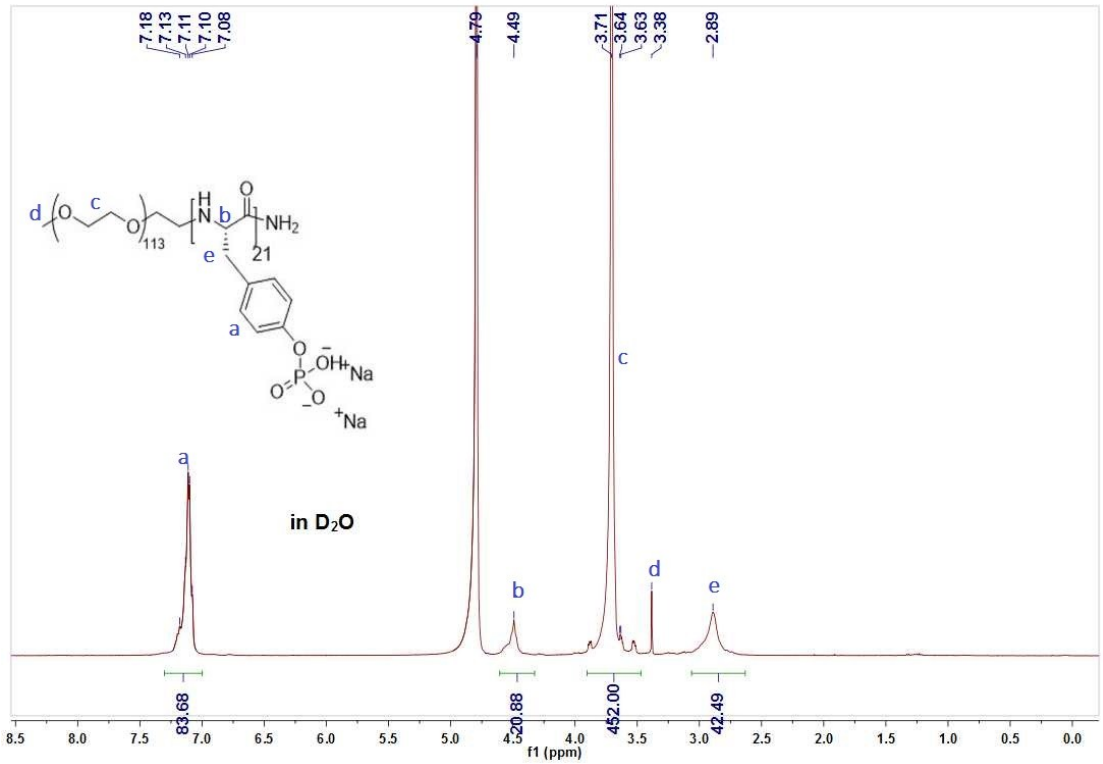



**Fig. S16**. $^{1}$H NMR spectrum of mPEG-*b*-PpY in $D_2O$.

**Table S1** Size and zeta potential of Pt-PIC with different feeding ratio of P/Pt

| P/Pt | Size (nm) | Zeta potential (mV) | Drug loading (%) |
|---|---|---|---|
| 3:1 | 213 | -72 | 13.1 |
| 2:1 | 178 | -71 | 17.3 |
| 1:1 | 250 | -23 | 21.8 |

**Table S2.** Size, zeta potential, and polydispersity index of Pt-PIC, ALP-treated Pt-PIC and ALP-treated mPEG-*b*-PpY.

| | Pt-PIC | ALP-treated Pt-PIC | ALP-treated mPEG-*b*-PpY |
|---|---|---|---|
| Eff.Diam.[a] (nm) | 177.9 | 56.4 | 61.7 |
| PDI[b] | 0.36 | 0.34 | 0.33 |
| Zeta potential (mV) | -71.2 | -28.7 | -36.3 |

[a] Mean hydrodynamic diameters at 25 $^{o}$C. [b] Polydispersity index determined by dynamic light scattering.

**Dephosphorylation process of mPEG-PpY and Pt-PIC with ALP measured by $^{31}P$ NMR**

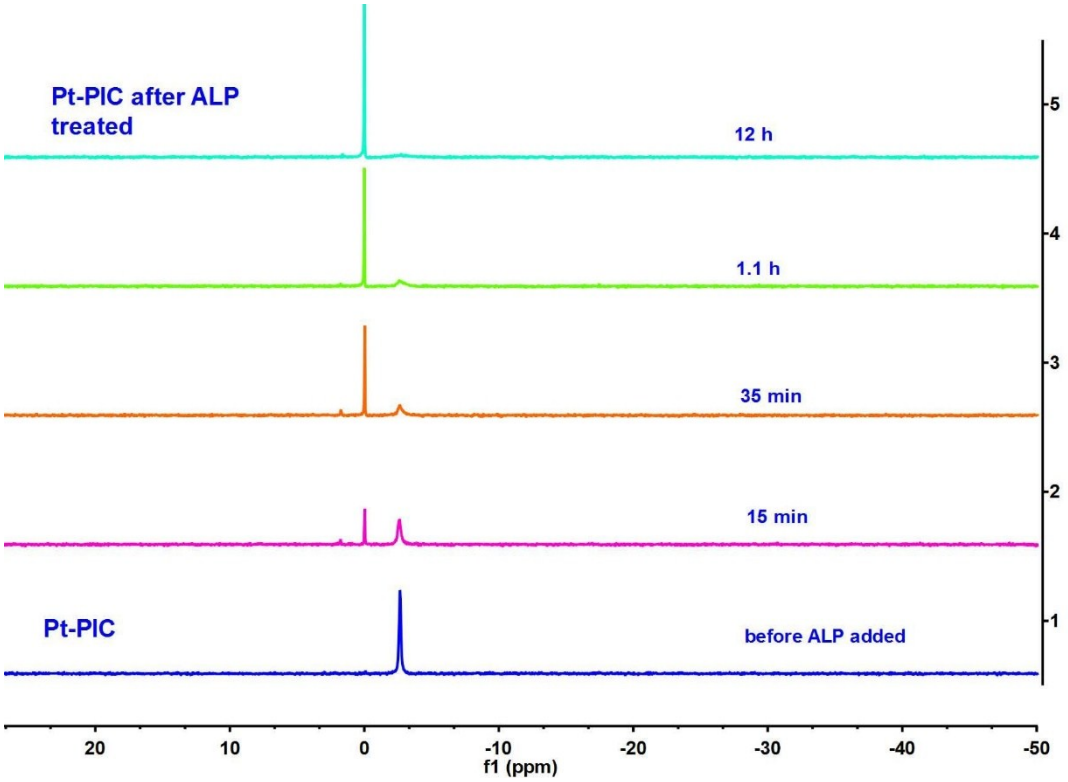



**Fig. S17.** Stacked $^{31}P$ NMR spectrum of Pt-PIC with the treatment of ALP for various periods of incubation time at 37 °C.

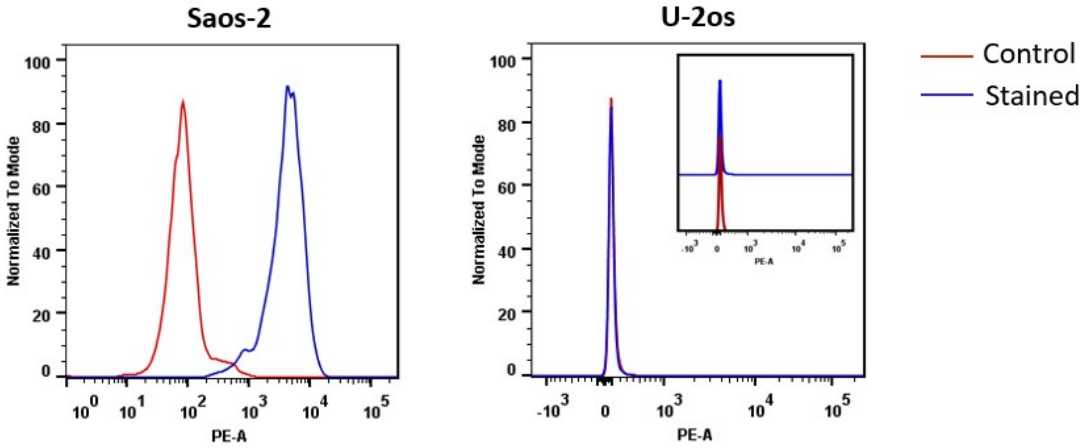



**Fig. S18.** The ALP expression levels of Saos-2 and U-2OS analyzed by flow cytometry assay.

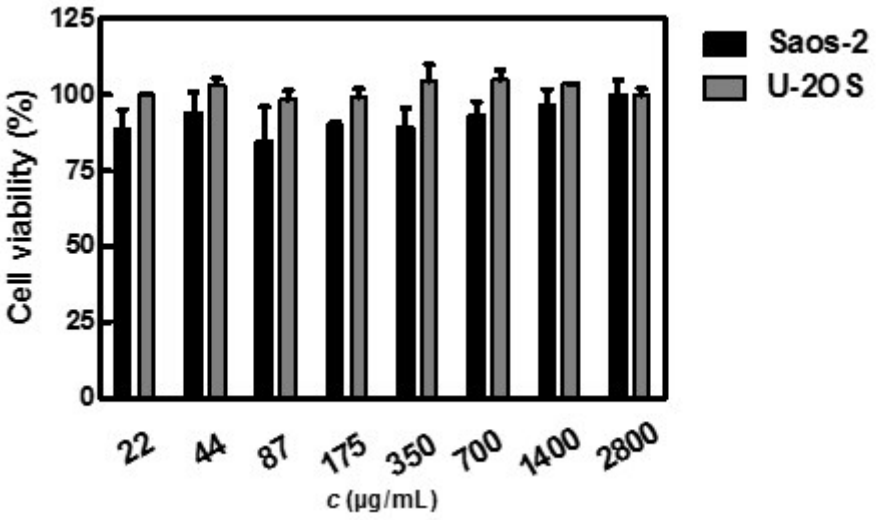



**Fig. S19.** Cytotoxicity of mPEG-*b*-PpY.

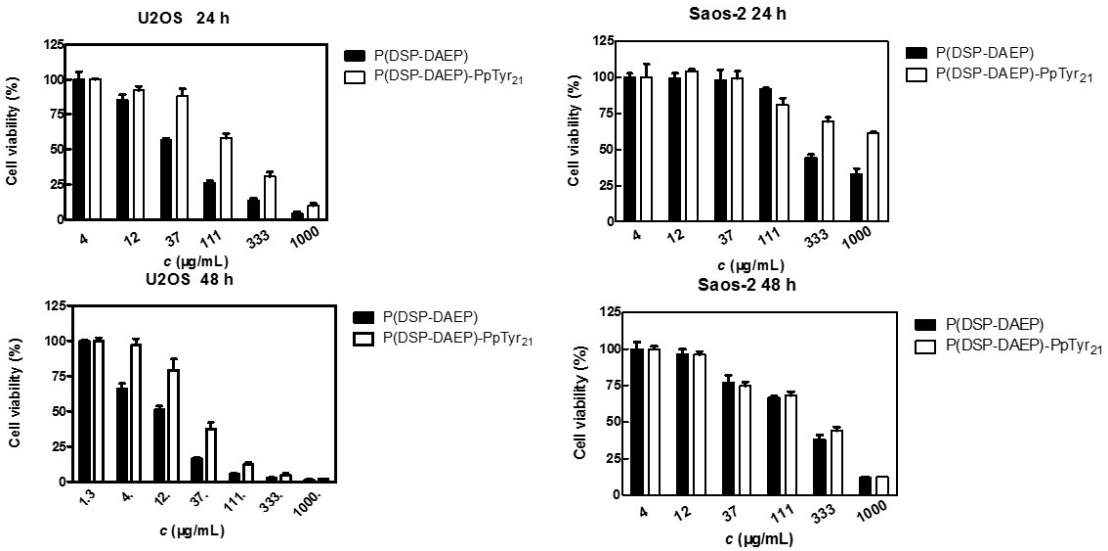



**Fig. S20**. in *vitro* cytotoxicity of P(DSP-DAEP) and Pt-PIC in Saos-2(ALP positive) and U-2OS (ALP negative) cell lines.