

Doxorubicin Dimerization Causes the Precipitation of Doxorubicin

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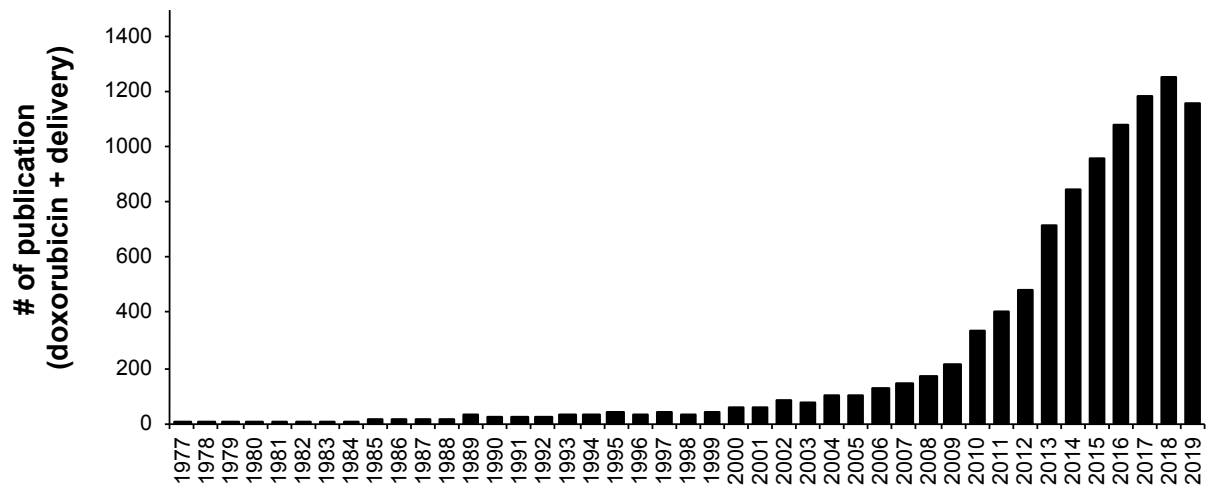


Figure S1. Number of publications of doxorubicin delivery study searched by PubMed (doxorubicin + delivery). Data retrieved: September 23, 2020.

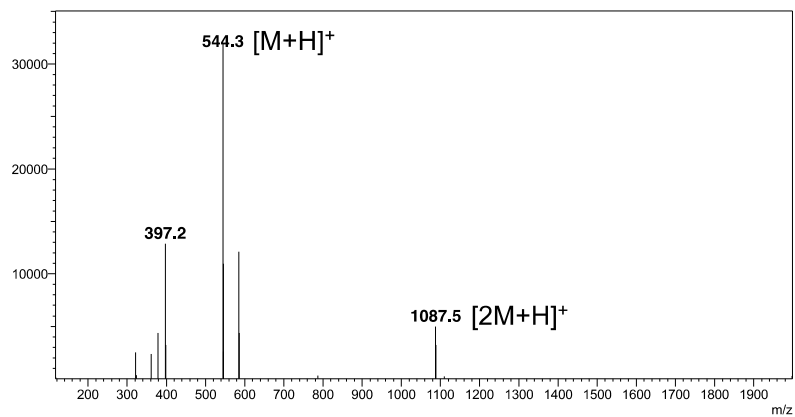
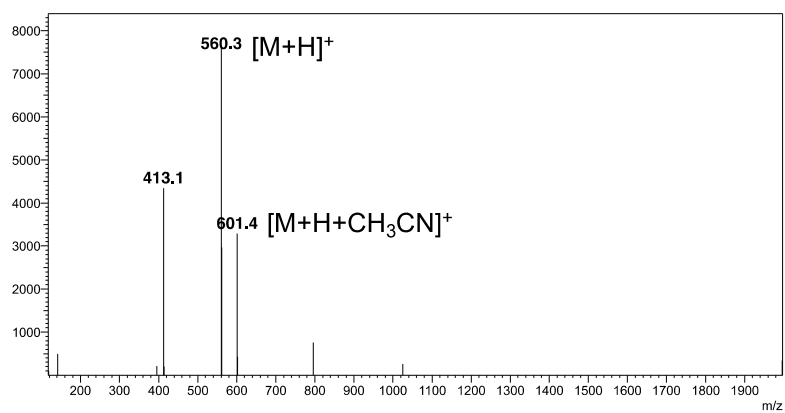
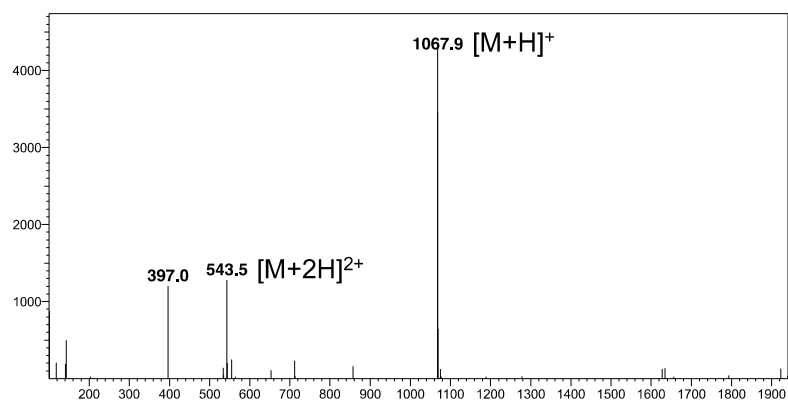
A**B****C**

Figure S2. Mass spectrum of DOX (A), the DOX monomer derivative (B), and the DOX dimer (C) analyzed using LC/MS (shown in Fig. 2D).

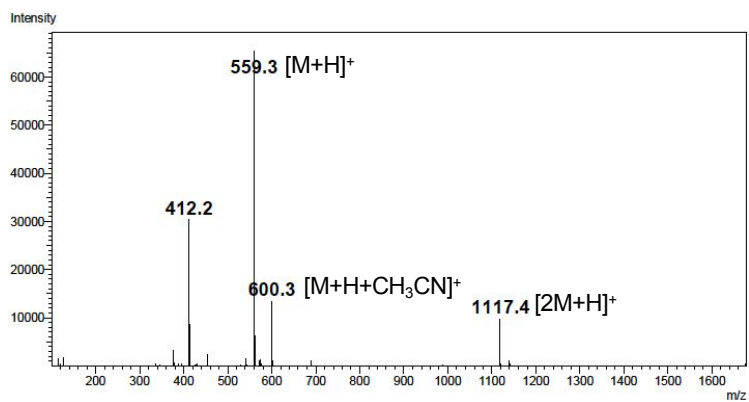
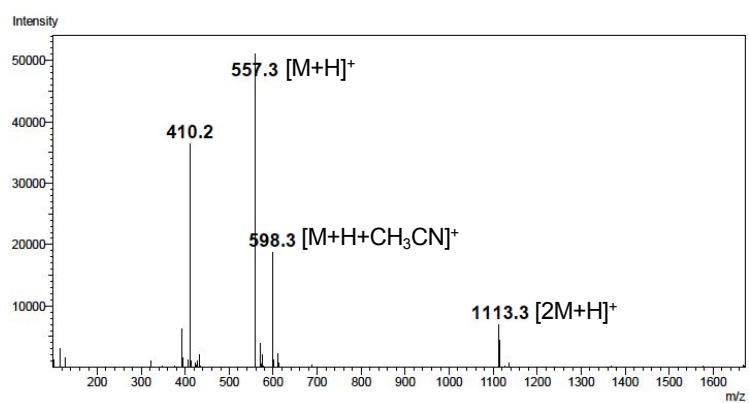
A**B**

Figure S3. Mass spectrum of DOX oxime (A) and oxidized DOX oxime (B) shown in figure 4A.

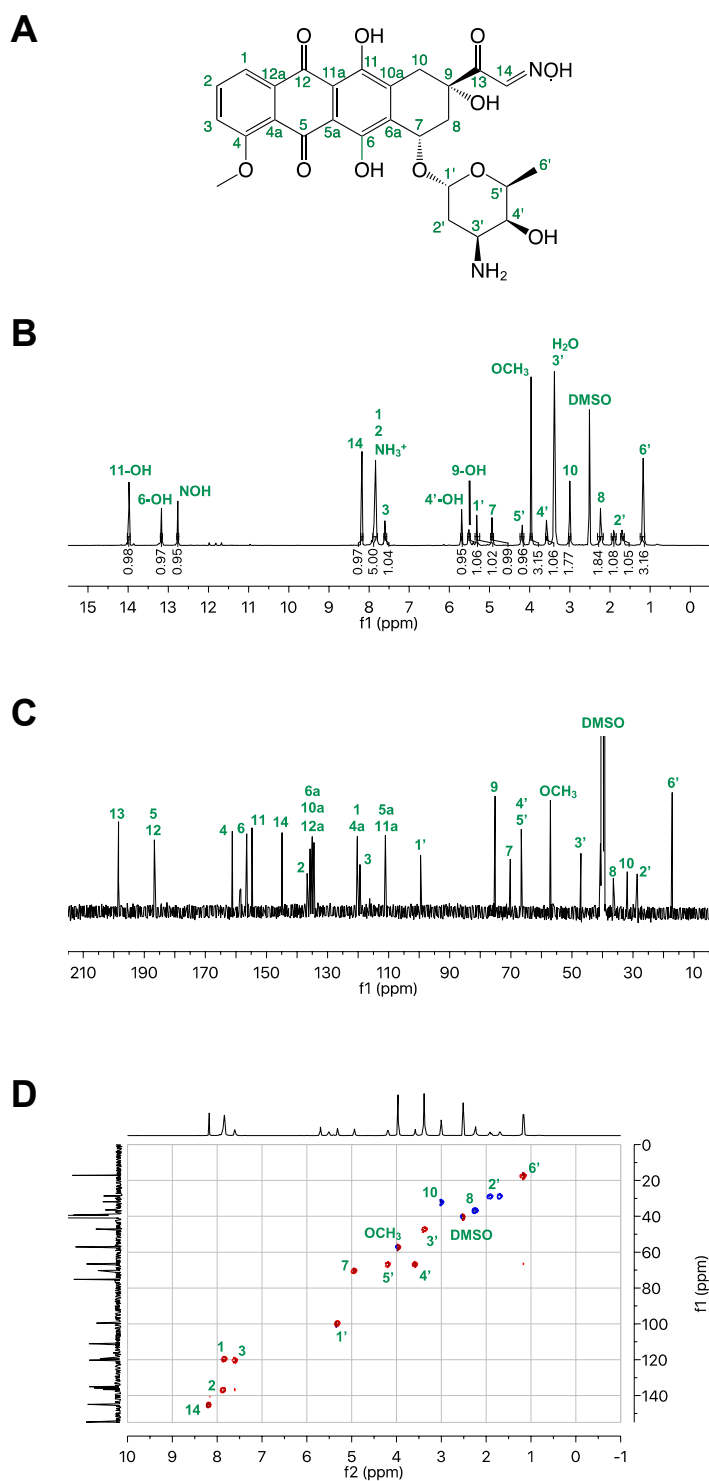


Figure S4. NMR spectra of oxidized DOX oxime. (A) Structure of oxidized DOX oxime. (B) ^1H -NMR spectrum. (C) ^{13}C -NMR spectrum. (D) ^1H - ^{13}C HSQC spectrum.

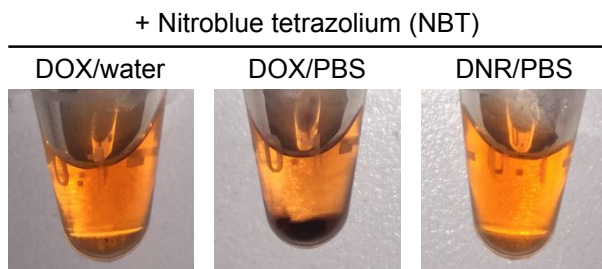


Figure S5. Nitroblue tetrazolium (NBT) test. NBT (VWR, Radnor, PA, USA) was added to 1 mg/mL DOX in PBS, DOX in water, and DNR in PBS at final concentration of 0.5 mg/mL and incubated for 24 h at 37°C.

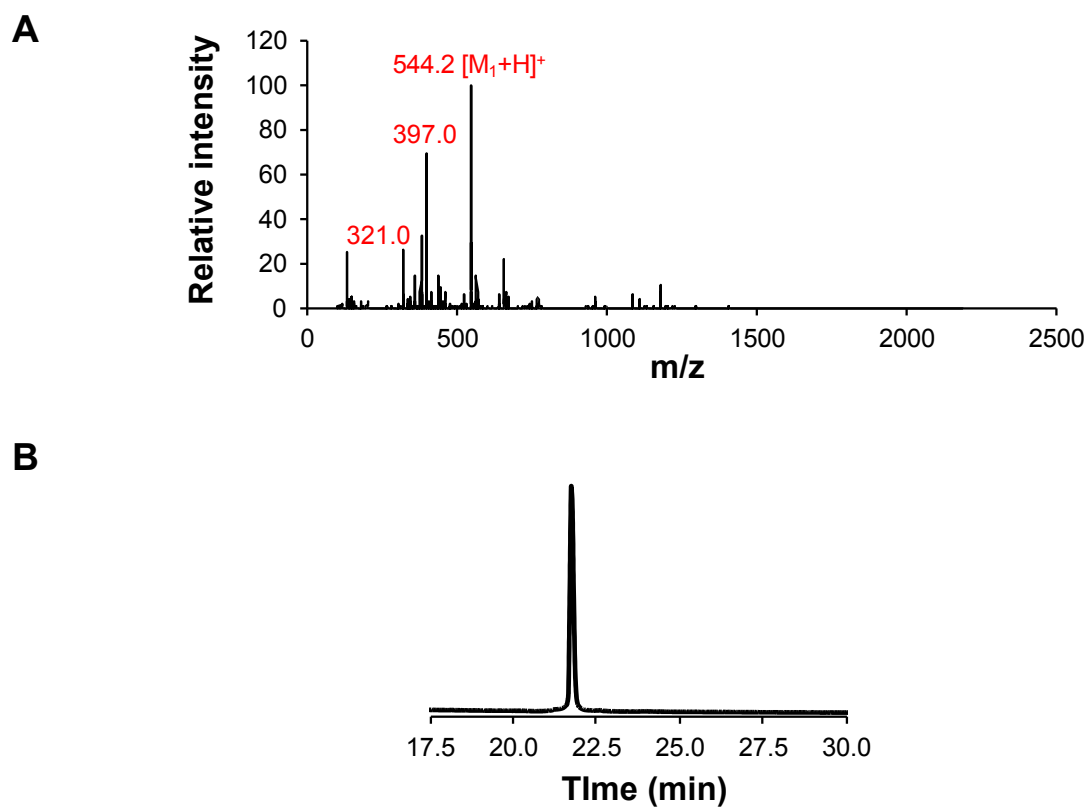


Figure S6. Mass spectrum (A) and HPLC chromatogram (B) of DOX precipitate formed by mixing with heparin.