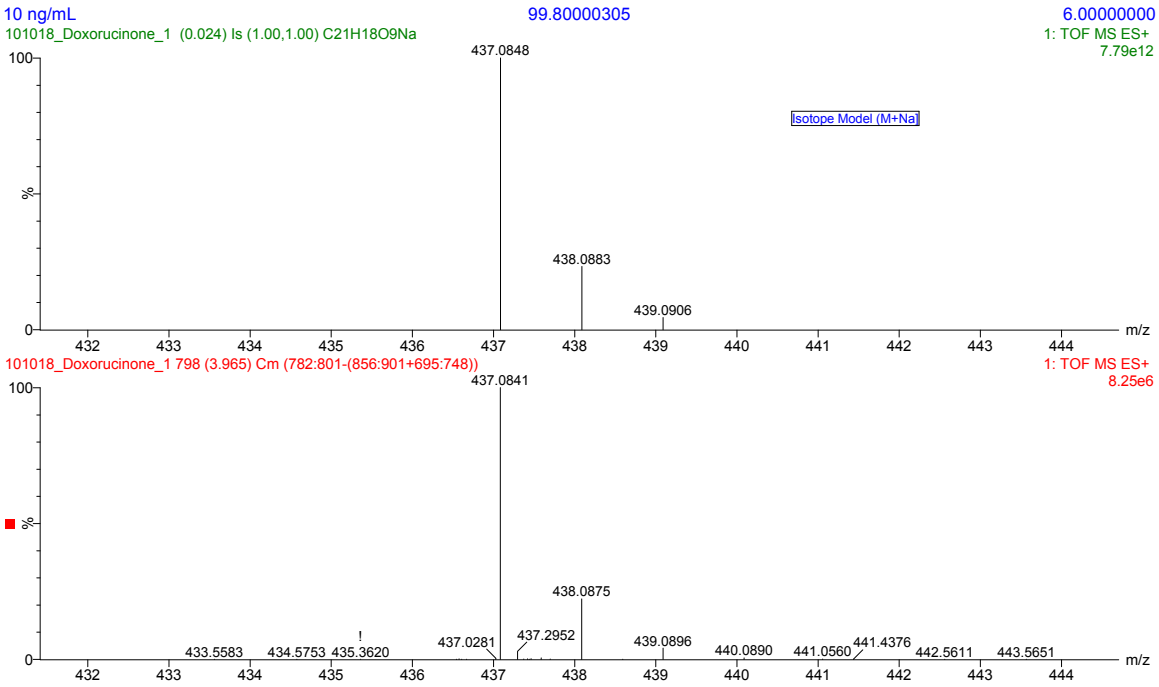
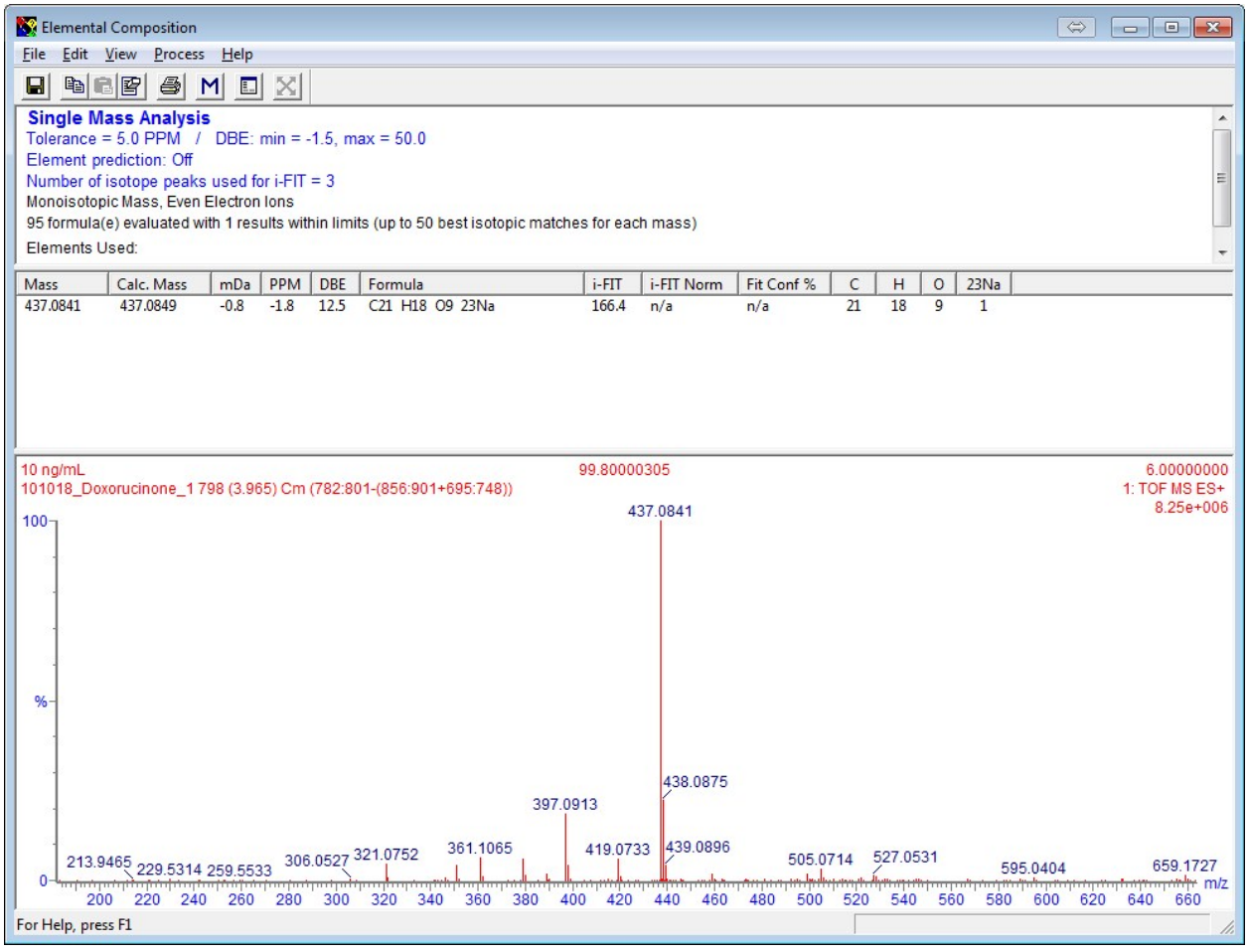
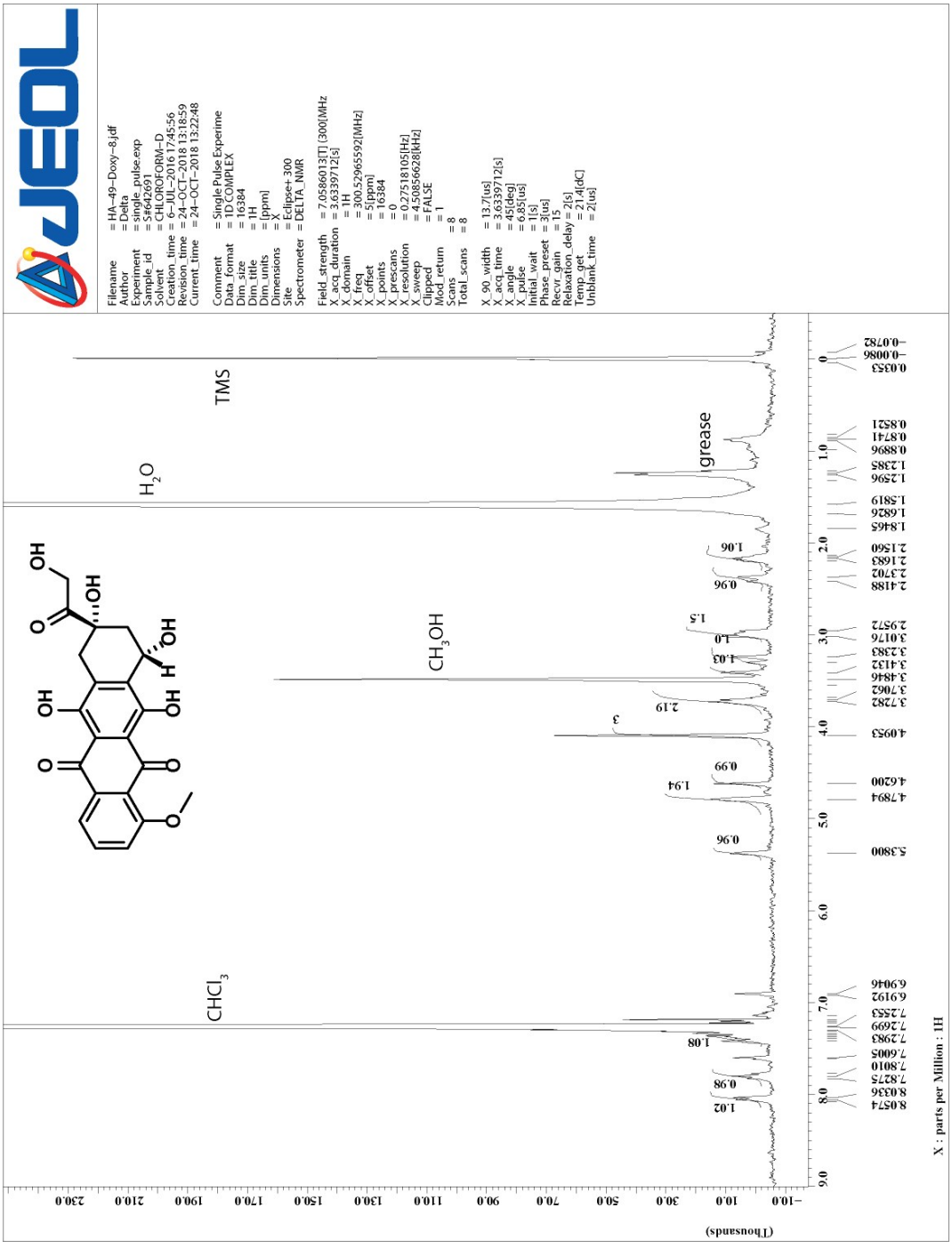
## Supplementary Data

**High Resolution Mass Spectrometry data for DOXY:** (ES+) m/z calculated for $C_{21}H_{18}O_9Na$ $[M+H]^+$ 437.0848, found 437.0841.

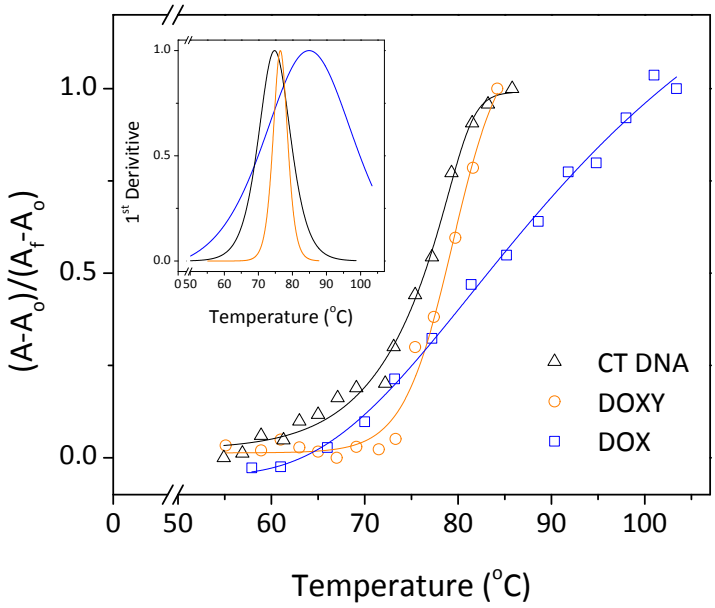


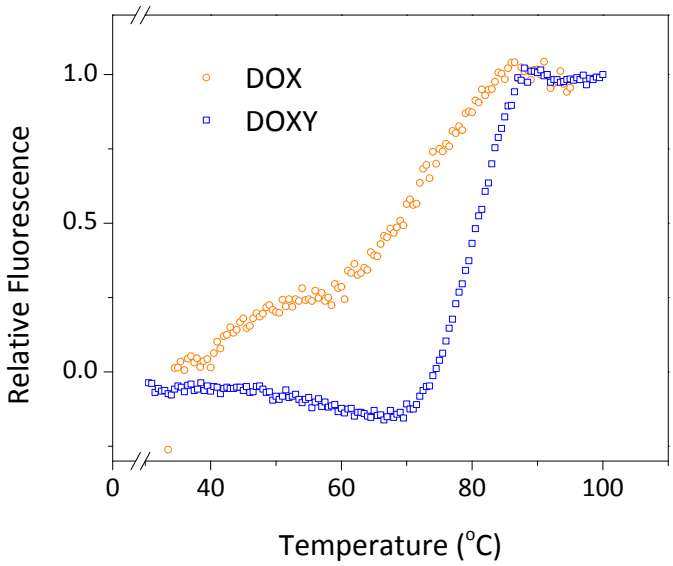
**$^{1}$H NMR spectrum for DOXY:**



**Melting Data:** The figure below shows an overlay of the melting curves of CT DNA, and CT DNA bound to DOX and DOXY at a ratio of 10:1 [DNA]:[drug]. The data was fit to a sigmoidal curve and the inset shows an overlay of the first-derivative of the fitted curve.




In addition to the absorbance-based method described in the manuscript, melting curves were also measured using a PCR instrument, BIO-RAD DNA Engine Opticon 2. In this method, the fluorescence of either DOX or DOXY were monitored as the temperature increased over 0.5 °C increments with 10 s hold times. An increase in fluorescence was observed as the temperature increased due to the increased concentration of free drug upon melting of the helix. Samples were prepared in triplicate with 30 μM CT DNA and [DNA]/[Drug] ratios between 3 and 50 using the FAM™ dye setting. Samples were vortexed prior to measurement. Data was analyzed using the first derivative method provided in the instrumentation software. Advantages of this method include small volume samples (50 μL), small temperature step-sizes (0.5 °C), and a 96 well-plate sample holder that makes possible running several trials of each ratio simultaneously. Comparing our data to control data was more challenging in this method, however, because it is not possible to run CT DNA alone and the instrument has fixed excitation and emission wavelengths that limit the drugs that can be used. The figure below shows an overlay of melting curves, using this method, for DOX and DOXY bound to CT DNA. At [DNA]/[DOX] = 25, $T_m$ = 80 °C compared to $T_m$ = 71 °C at [DNA]/[DOXY] = 30. The higher melting point of DOX bound to CT DNA is consistent with an intercalative binding mode. If the binding mode of DOXY was the same, we would expect to see similar $T_m$ values, instead of a $\Delta T_m$ of 9 °C.


DOX
DOXY
Relative Fluorescence
1.0
0.5
0.0
0
40
60
80
100
Temperature (°C)