Fig. S1: Impacts of drug treatment after 1 hour and 24 hours (**A**) Percent of cells with detectable nucleolus after 1 hour of treatment and 24 hours treatment. (**B**) Percent of cells with detectable cleaved-caspase (cell death) staining after 1 hour of treatment and 24 hours treatment (**C**) Cell size measurements after 1 hr of treatment and 24hrs treatment. (**D**) Immunofluorescent images of DAPI, Cleaved-caspase (CC) and Fibrillarin (nucleolar marker) after 24 hours treatment. (**E**) Example of cleaved caspase-positive cell. Scale bar = 5μm(A) Immunofluorescent images of DAPI, Cleaved-caspase (CC) and Fibrillarin (nucleolar marker) for cells at 24 hr drug treatment. Scale bar = 5μm. *ns* = not significant, **P<0.01; **** P<0.0001. Ordinary one-way ANOVA with multiple comparisons.
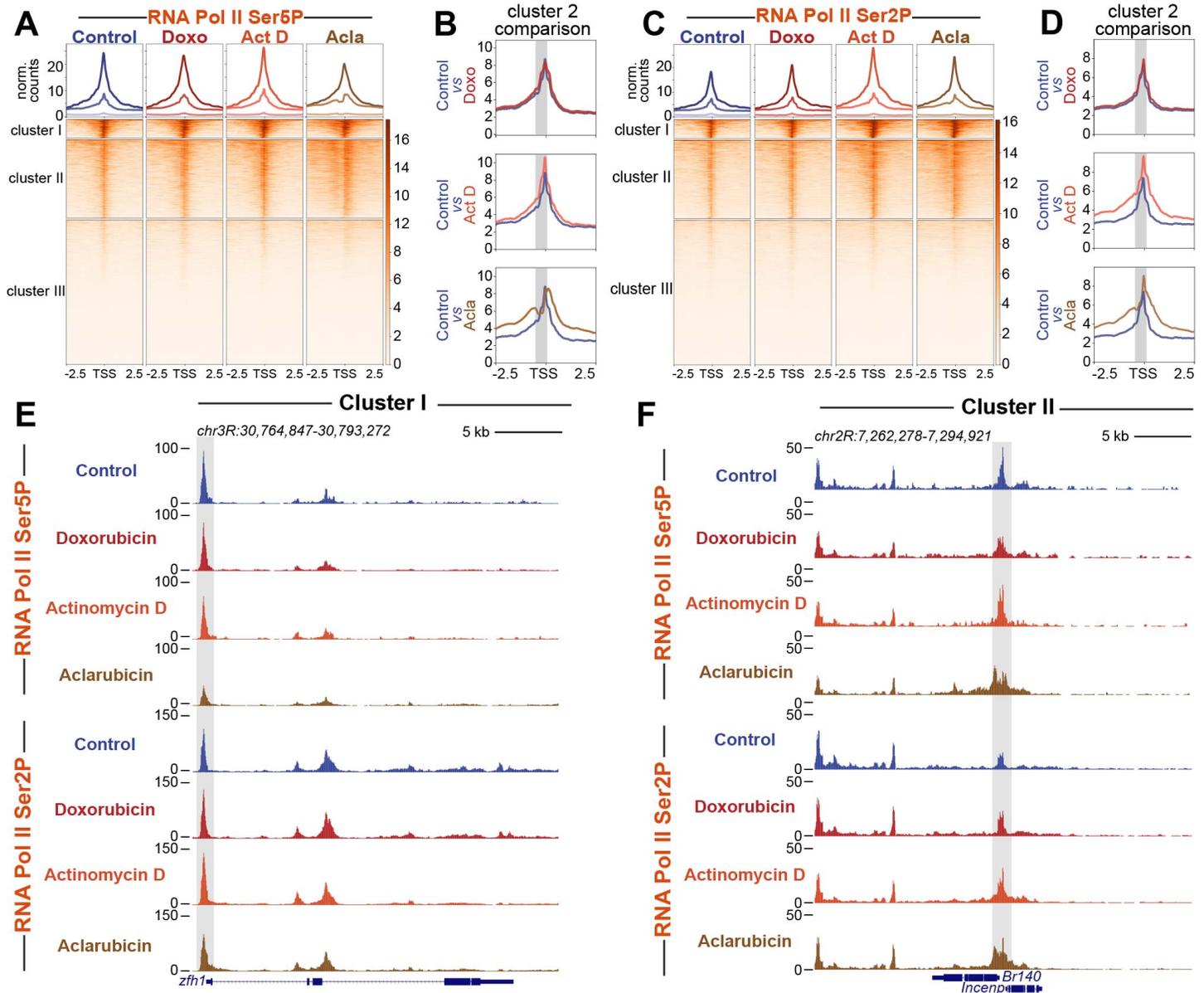
Fig. S2: Drug treatment impacts the relative distribution of RNA Pol II Ser5P and Ser2P (**A**) Heatmap aligned to the transcriptional start site (TSS) of all promoters showing normalized counts of RNA Pol II ser5P CUT&Tag signal clustered via k-means clustering derived from CUTAC datasets (k=3). (**B**) Enlarged comparison of accessibility differences between different drug groups and controls. Gray box marks upstream promoter region. (**C**) Heatmap aligned to TSS of all promoters showing normalized counts of RNA Pol II Ser2P CUT&Tag signal clustered via k-means clustering (k=3) derived from CUTAC datasets. (**D**) Enlarged comparison of G-quadruplex differences between different drug groups and controls. Gray box marks upstream promoter region. (**E**) Representative UCSC browser track snapshot of RNA Pol II ser5P and RNA Pol II Ser2P distribution at Cluster I gene. (**F**) Representative UCSC browser track snapshot of RNA Pol II ser5P and RNA Pol II Ser2P distribution at Cluster II gene.
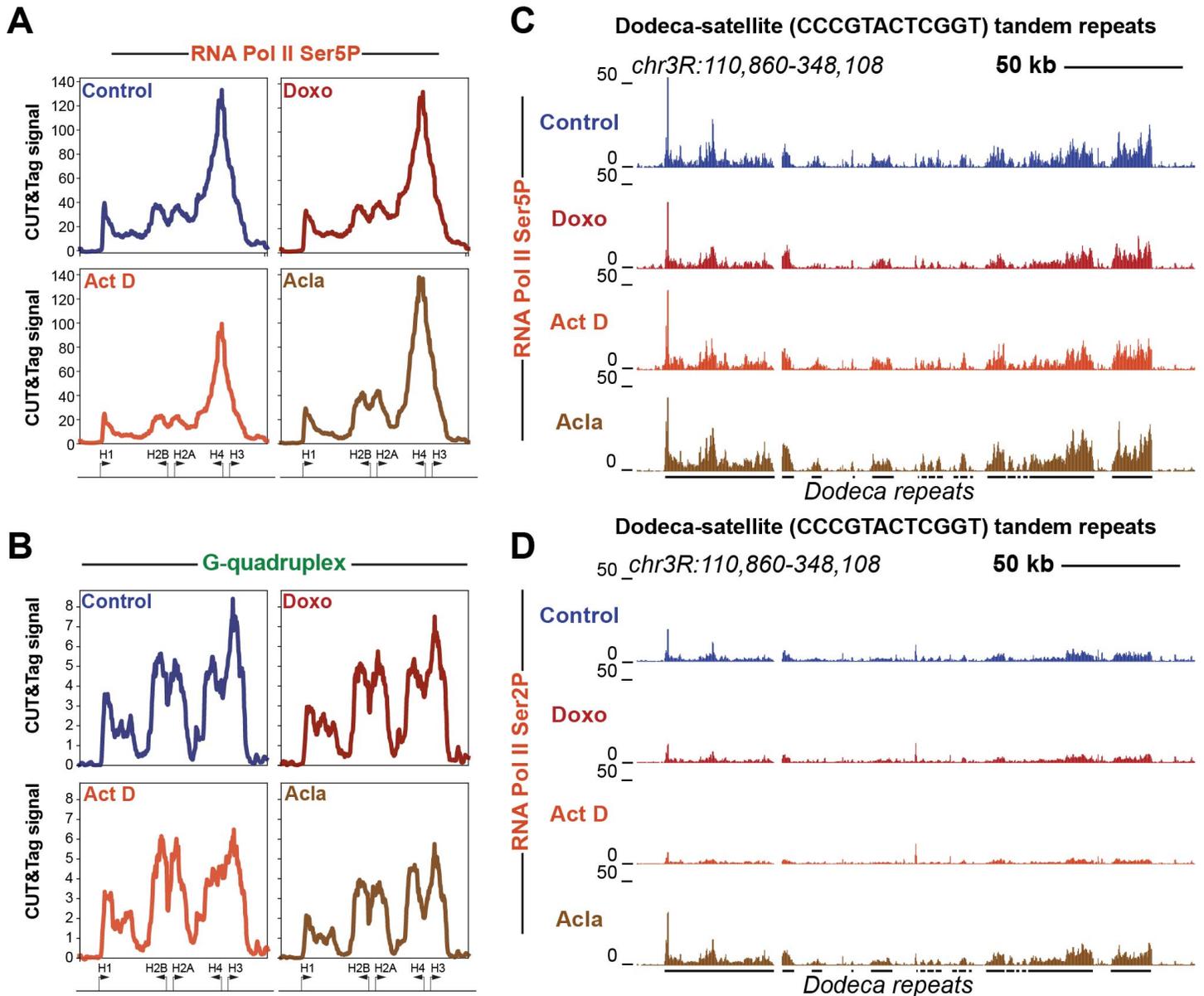
Fig. S3: Promoter distance and orientation effects RNA Pol II, G-quadruplexes, accessibility, and torsion. Heatmaps of CUT&Tag data targeting RNA Pol II ser5P (**A**) RNA Pol II ser2P (**B**) and G-quadruplexes (**C**) aligned to the transcriptional start site (TSS) of all promoters sorted by distance to nearest upstream promoter element and plotted in descending order. (**D**) Plot showing CUTAC chromatin accessibility signal for promoters less than 2kb apart and greater than 2kb apart. Median shown as black bar with 95% confidence interval. (**E**) Plot showing fold change of CUTAC chromatin accessibility centered on the TSS for doxorubicin *vs* control (E), actinomycin D *vs* control (**F**) and aclarubicin *vs* control (**G**) Horizontal dotted line indicates 1-fold. Vertical dotted line indicates TSS. (**H**) Plot showing TMP-seq signal for promoters less than 2kb apart and greater than 2kb apart. **** = p< 0.0001 Kruskal-Wallis test with multiple comparisons for panel D.

Fig. S4: Histone cluster and Dodeca-satellite repeats show distinct responses to drug treatment (**A**) Average coverage plot of histone clusters showing CUT&Tag data targeting RNA Pol II ser5P. (**B**) Average coverage plot of histone clusters showing CUT&Tag data targeting G-quadruplexes. Arrows at the bottom of average plots indicate approximate positions of histone genes. (**C**) UCSC browser track snapshot of CUT&Tag data targeting RNA Pol II ser5P at Dodeca-satellite repeats. (**D**) UCSC browser track snapshot of CUT&Tag data targeting RNA Pol II ser2P at Dodeca-satellite repeats. Black lines below the browser tracks indicate location of Dodeca-satellite repeats.