The Binding Modes of Diminazene Aceturate with c-MYC G-quadruplexes

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G-quadruplexes (G4s) are higher-order DNA structures typically present at promoter regions of genes and telomeres. Stabilization of proto-oncogene c-MYC (G4) using small molecules serves as an attractive strategy for anticancer therapeutics. Recent studies showed that diminazene, DMZ, (or berenil) is a tight binder of G-quadruplexes; hence, DMZ serves as a suitable platform for the development of new potent G-quadruplex ligands because its toxicology profile is already known. However, there lacks a structural and energetic understanding of the specific binding modes. Therefore, it is interesting to understand the mechanism of distinct binding modes of DMZ and how it influences the overall flexibility of the G-quadruplex. In this study, we investigated the mechanism underlying the binding of DMZ to c-MYC G4 variants using molecular dynamics (MD) simulations. The results show that DMZ can bind to c-MYC G4 via three binding distinct binding modes that include end stacking (5' and 3'), loop binding, and groove binding. Overall, the results suggest that DMZ based drugs that target the loops of G4s can serve as an efficient strategy to design newer drugs for cancer therapeutics. Future work will apply more sophisticated enhanced sampling methodologies to this challenging system to elucidate the free-energy landscape that allows identifying low-energy ligand binding modes and the presence of higher energy prebinding states.