Structural dynamics of Interaction between human telomeric DNA G-quadruplex 21-mer and naphthalene diimide compound MM4

Christian Solis-Calero, Hernandes H Carvalho

Stabilization of G-quadruplex DNA structures (GQ) by small molecules has been recognized as a promising strategy for developing new anticancer agents. In particular, the stabilization of GG in the human telomeric sequence by small molecules can result in telomerase inhibition and telomere uncapping, leading to senescence or apoptosis of tumor cells. A experimentally determined human telomeric DNA GQ 21-mer has been investigated for their interaction with naphthalene diimide compound MM4 by employing molecular dynamics (MD) simulations. We compare the dynamics of this GQ structure in presence and absence of MM4, and because the MM4 ligand could have different protonation states in its two N-methyl-piperazine groups, the MD simulations also include one with the MM4 protonated in both groups, and other without them. Our results show significant differences between these simulations, showing the GQ without MM4 ligand higher flexibility and the GQ with charged MM4 ligand less flexibility, what could be explained but the electrostatic interactions of MM4 and phosphate groups of GQ and it could explain a possible higher stabilization effect. Because the interactions of the studied molecular complex are also characterized by a large aromatic core involved in π-π stacking, we also determined their interaction energy using density functional theory (DFT) considering only the G-quartets and the naphthalene diimide moiety.