Thermodynamics of Naphthalene Diimide Derived Ligand Binding to G-Quadruplex

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ABSTRACT

The non-covalent interactions between naphthalene diimide derived ligands containing cationic substituents attached by short saturated alkyl chains and human telomeric G-quadruplex DNA have the potential to stabilize the G-quadruplex secondary structure and inhibit telomeric repair mechanisms. The inhibition of the maintenance of telomeric DNA has the potential to provide a therapeutic approach to inhibit cancer cell growth. In this study four naphthalene diimide based ligands were analyzed in order to elucidate the principal factors determining contributing to the G-quadruplex-ligand binding. Three possible modes of binding and their respective and Gibbs free energies for two naphthalene diimide based di-N-alkylpyridinium substituted ligands have been determined using a molecular docking technique and compared with experimental results. The structures obtained from the molecular docking calculations, were analyzed using the ab-initio based fragment molecular orbital (FMO) method in order to determine the major enthalpic contributions to the binding and types of interactions between the ligand and specific residues of the G-quadruplex. A computational methodology for the efficient and inexpensive ligand optimization based on the estimation of binding affinities of the naphthalene diimide derived ligands to G-quadruplex is proposed.