DNA G-quadruplex ligands for cancer therapy

Alexandra Paulo

Department of Medicinal Chemistry, Faculty of Pharmacy, University of Lisbon

Av. Prof. Gama Pinto, 1749-003 Lisboa, Portugal

Email: mapaulo@ff.ul.pt

DNA containing repetitive guanine (G)-rich sequences can form higher-order structures, the G-quadruplexes (G4). The analysis of human genome has revealed an elevated frequency of occurrence of these sequences, notably in telomeres and promoter regions of oncogenes, thus suggesting that G4 may naturally act as regulatory elements, particularly in cell proliferation processes. Several studies have shown evidence for the existence of G4 in eukaryotic telomeres and promoters of some oncogenes and that small molecules stabilizing G4 are able to downregulate the oncogene transcription in tumor cell lines, inhibit telomerase activity and induce cancer cell growth arrest. However, from a drug discovery perspective, we are still giving the first steps and some challenges need to be faced, in particular the fact that, (i) there are still restricted diversity in available small-molecule G4 ligands and (ii) these have low affinity and selectivity for G4.

The main aim of this project is to contribute to the construction of a chemically diverse library of G4 ligands and to use it to understand the ligands' structural requirements for selective and efficient binding to different G4. In this communication we will present the effects of indolo[3,2-*b*]quinoline derivatives on DNA G4 stabilization determined by a FRET melting assay, inhibition of cancer cell proliferation and KRAS protein expression. Molecular modelling studies were also used to rationalize structure-activity relationships.

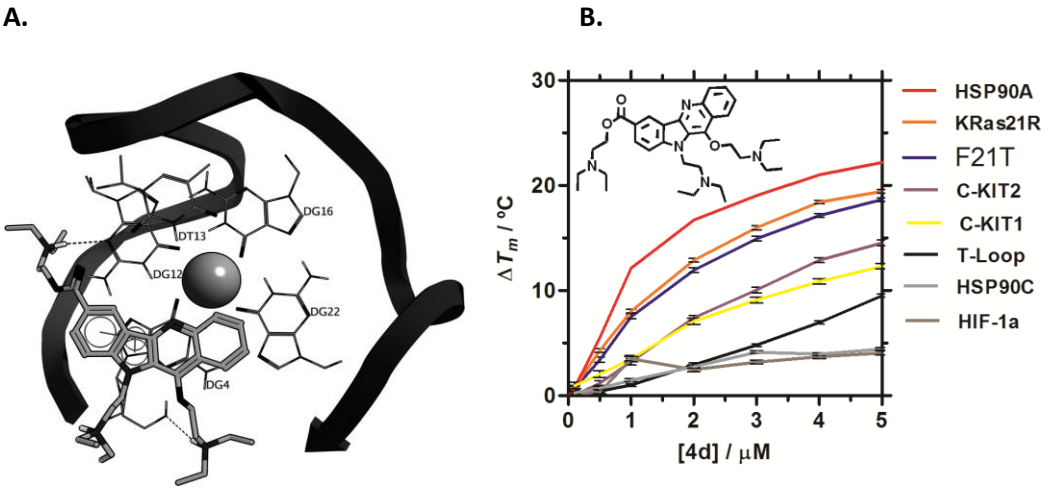

Figure 1. **A.** Top view of the predicted pose upon docking with MOE of **4d** and the optimized 21-mer hybrid-type2 G4 structure (PDB 2JPZ). **B.** Concentration-dependent FRET melting profile of G4 structures and T-Loop DNA complexed with **4d**. (From: Lavrado et al. Chem MedChem 2013, 8, 1648-61)

Acknowledgements: FCT for financial support through project grants PEst-OE/SAU/UI4013/2011, EXPL/QEQ-MED/0502/2012 and postdoctoral grant: SFRH/BPD/72903/2010.