**Non-covalent and covalent ligands to target G-quadruplex secondary structures**

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DNA and RNA containing runs of 3 or 4 adjacent guanines may spontaneously arrange into four-stranded DNA supramolecular structures called G-quadruplexes (G4).1 These non-canonical structures are likely to form in G-rich regions throughout the genome and thus are assumed to have functional roles in key biological processes, such as replication, transcription, repair, and recombination,2 and thereby they represent potential barriers for the enzymatic machineries involved in these processes. However, the dynamic nature of these structures makes their identification in live cells extremely challenging; therefore, G4 actual formation *in vivo* is still a matter of debate. G4 can be stabilized by small synthetic molecules (G4 ligands),3 hence, the latter represent a new family of DNA drugs assumed to act region selectively at specific genomic G-rich loci including telomeres, oncogene promoters, tandem mini satellites that have higher propensity to generate quadruplexes.4 In general, G4 ligands do not display acute cytotoxicity and produce diverse cellular effects, suggesting that targeting of genomic G4 is characterized by different accessibility. Consequently, it is highly important to follow G4 ligand distribution in cells and identify precisely their binding sites genome-wide; this knowledge will enhance understanding in regard to characterization and exploitation of drug responses. These objectives will be achieved by the construction of specifically tagged G4-selective small molecules that will act as molecular reporters enabling visualization of G4 in cells5,6 and photoactivatable covalent agents.7

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