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Redefining the Essential Molecular Aspects that Drive Interactions Between Small Molecules and G-Quadruplex DNA

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Abstract
G-Quadruplex (G4) structures are secondary nucleic acid structures located in guanine-rich regions of DNA and RNA sequences, involved in gene regulation and cellular maintenance. Efforts to target G4s in a therapeutic setting are scarce, mainly due to vague details about the binding interactions between the ligands and the G4 structure combined with the lack of emphasis on drug-like properties early in the ligand development process. Furthermore, the ability to target specific G4 structures with small drug-like molecules remains a big challenge to overcome in the field. In this thesis, extensive organic synthesis developments coupled with computational-aided design and orthogonal *in vitro* assays has been used in tandem to reveal in-depth knowledge about ligand-to-G4 interactions. First, a macrocyclic approach was applied to design and discover novel G4 ligands which showed that macrocycles offer a solid foundation for ligand design. Next, computational tools to optimise the macrocyclic molecular conformation were used based on the macrocycles' abilities to stack on the G4 surface. In addition, macrocyclic, and non-macrocyclic ligands that bound G4 with high potency were shown to correlate with electron-deficient electrostatic potential (ESP) maps. The frequent inclusion of cationic residues in G4 ligands and their enhancement on ligand-to-G4 binding was, thereof, ascribed to their impact on the electrostatic character of the ligands' arene-arene interactions with the G4 surface, and not through direct electrostatic ionic interactions. In addition, the dispersion energetic component in the arene-arene interactions between the G4 ligand and the G4 was discovered to be paramount for ligand-to-G4 binding. The implementation of these descriptors in practice resulted in the discovery of potent G4 binders with adequate pharmacokinetic (PK) properties, accentuating the significance of understanding the molecular interactions between ligands and G4s in rational ligand design. Finally, a G4 ligand conjugated to an oligonucleotide was demonstrated as a modular approach to achieve selective binding of a ligand to a specific G4 structure.

Keywords
G-Quadruplexes, DNA, Oncogenes, G4 ligands, heterocycles, macrocycles, organic synthesis, molecular interactions, rational compound design, medicinal chemistry.

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