Selective recognition of dual DNA-binding conjugates towards a G-quadruplex structure and its proximal duplex

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G-quadruplex (G4) structures are crucial in various biological processes such as transcriptional regulation, genome instability, and chromatin remodeling. Recently, studies using a genome-editing technique (CRISPR system) revealed a clear relationship between G4 formation and gene expression.[1] However, their specific targeting by ligands is still challenging. A genome-wide study identified over 700,000 G4-forming sequences,[2] and it is basically difficult for small molecules to target specific G4s, due to the structural similarities.

To overcome this issue, we developed a conjugate that recognizes both the G4 structure and its adjacent duplex (Figure 1).[3] This conjugate combines PyPDS, a known G4 ligand, with pyrrole−imidazole polyamide (PIP), which binds to the minor groove and can be customized to recognize any DNA sequence.[4] The binding of the synthesized conjugates to the target G4 and adjacent duplex was evaluated by thermal profiles of CD melting and UV melting assays. Furthermore, their enhanced selectivity was confirmed by fluorescent indicator displacement assay. Our research indicates that integrating G4 ligands with PIP can effectively target specific G4-forming sequences.

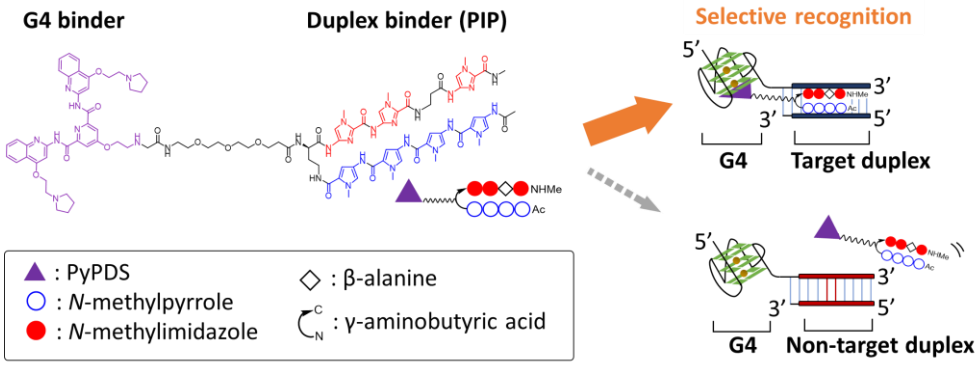

Figure 1. Chemical structures of a conjugate, and an illustration of selective DNA G4 recognition by a conjugate.

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