Development of Enforced Stacked Intercalators for DNA/RNA Mismatch Recognition

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Myotonic dystrophy type 1 (DM1) is one of >30 inheritable diseases whose origin can be traced to unstable repeating sequences in genomic DNA. DM1 is caused in part by the dysregulation of alternative pre-mRNA splicing that arises from the sequestration of proteins in the muscleblind-like (MBNL) family by expanded, non-coding r(CUG) trinucleotide repeats (TNR). Most therapeutic approaches have focused on developing agents that strongly and selectively bind the toxic r(CUG)exp, thereby inhibiting its sequestration of MBNL proteins. Another approach would be to bind the expanded CTG repeats (CTG)n in DNA. Most models propose that TNR expansion occurs in DNA metabolic processes including replication, transcription, and mismatch repair. Our acridine-triaminotriazine ligands target these mismatches through hydrogen-bonding recognition. However, they also exhibited significant cytotoxicity, which was attributed to off-target binding arising from nonspecific intercalation of the acridine unit in unstacked conformers into RNA & DNA sequences. To prevent this nonspecific intercalation, we have rationally designed macrocyclic ligands that enforce π-stacking between the acridine and triaminotriazine units. We have exciting preliminary results that show our macrocyclic design greatly increases binding selectivity and also reduces cytotoxicity by around 20-fold.

Synthesis of Cycloparaphenyleneacetylene Using Alkyne Metathesis: C_{70} Complexation and Cu-Free Triple Click Reaction

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Despite the great advances in conjugated molecular belts such as cycloparaphenylene-acetylene (CPPA) cycloparaphenylene (CPP), the macrocyclization step remains the bottle neck in the synthesis. Here, a CPPA derivative is prepared in high yield using alkyne metathesis followed by reductive aromatization. The cavity size was suitable for binding C70 and the strained alkyne bonds enabled three copper-free azide-alkyne cycloadditions.