Dimeric ligands as selective binders of CUG repeats

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CUG repeats in RNA are considered to be the causative agent of mytonic dystrophy type 1 (DM1) through its ability to sequester muscleblind-like (MBNL) proteins. The regular and repeating structures of the CUG repeats offer an opportunity for rational drug design. In particular, the development of specific inhibitors of MBNL binding to CUG repeats. Previously, a triaminotriazine-acridine conjugate was developed and found to exhibit high nanomolar binding to UU mismatches in the CUG sequence. This compound consists of an intercalator and a recognition unit that were designed to form a base triplet with the UU mismatch. To improve this lead compound in terms of binding affinity and selectivity, our general approach is ligand oligomerization, starting with dimerization of the ligand. For efficient bis-intercalation, the length and nature of the linker was varied. Keeping the recognition unit and the intercalator the same, a small library of dimeric ligands was made using different types of linkers. Isothermal titration calorimetry (ITC) and a gel shift assay were used to study the binding affinity and inhibition of MBNL1-RNA complex formation. The K_d of the most potent dimer to $d(CTG)_6$, was 8.7 μM similar to the corresponding monomer (K_d=9.3 μM). Possible explanations for this finding will be presented along with future plans.