Targeting DNA/RNA Recognition Motifs Related to Myotonic Dystrophy (DM) Diseases with Janus-Wedge Containing Heterocycles

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Myotonic dystrophy type 1 (DM1) and type 2 (DM2) are muscle diseases caused by the expansion of $(CTG)_n$ and $(CCTG)_n$ repeats in DNA, respectively. The corresponding RNA transcripts, $(CUG)_n$ for DM1 and $(CCUG)_n$ for DM2, are found to form nuclear inclusions which in turn sequester muscleblind (MBNL) proteins. The lowering of free MBNL proteins by the RNA-repeats-mediated sequestration is proposed to lead to the disease.

By developing Janus-wedge containing heterocycles that are capable of selectively binding to the U-U and the C-U mismatches in the $(CUG)_n$ and the $(CCUG)_n$ repeats, respectively, a reversal of disease phenotype may be possible by inhibiting the sequestration of the MBNL protein from binding to RNA repeats. This poster will describe the synthesis and evaluation of ligands targeted to CUG and CCUG repeats.