Rational Design of Alternating Bisamidine-Melamine Oligomers as Potential Therapeutics for Myotonic Dystrophy Type 1

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Myotonic dystrophy type 1 (DM1) is the most common form of muscular dystrophy among adults, affecting 1 in 8000 worldwide. The disease originates from the expanded trinucleotide (CTG)n repeats in 3'-UTR of DMPK gene. The widely accepted pathogenesis involves toxic RNA gain-of-function of the corresponding transcript, CUGexp. The CUGexp RNA forms a hairpin structure that sequesters one of the key splicing regulators, MBNL1 (Muscleblind-like protein 1), leading to the mis-splicing of >100 pre-mRNAs. We have previously reported a rational design of a bisamidinium-based small molecule ligand 1 that selectively binds to CUGexp. Utilizing its groove-binding mode and the optimized structure of this ligand, we used facile chemistry to synthesize oligomer 3 with alternating bisamidinium and triaminotriazine fragments. These oligomers show higher binding affinity to the RNA target compared to the original ligand. Aditionally, they have been shown to disrupt nuclear foci, a hallmark of the disease, in both DM1 model cells and DM1 patient-derived myoblasts. The oligomers reduce the toxic RNA level in DM1 model cell culture and affect more downstream events such as reversing the mis-splicing of IR minigene. Furthermore, the oligomers also show excellent activity in DM1 Drosophila models, improving the climbing ability of the adult flies upon oral treatment.