Small Molecules Targeting the Toxic RNA in Myotonic Dystrophy Type 2

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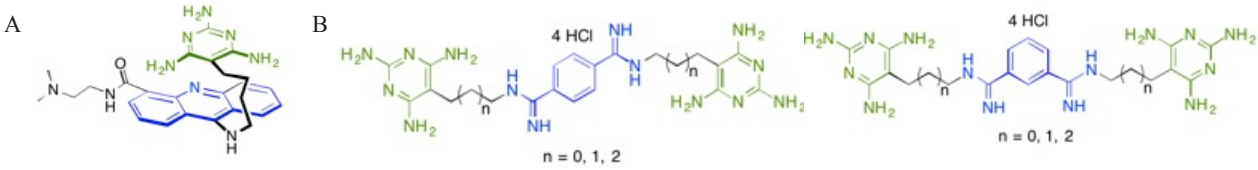
Myotonic dystrophy type 2 (DM2) is caused by an expansion of CCTG repeats in the zinc-finger protein gene (ZNF9) in chromosome 3. Pathogenesis of the disease involves a toxic RNA gain-of-function. The transcribed CCUG repeats sequester a significant alternative splicing regulator, muscleblind-like protein 1 (MBNL1), blocking MBNL1 from its normal function, thereby leading to the disease phenotype. We report a series of ligands that inhibit the MBNL1-r(CCUG)$_n$ interaction as potential therapeutic agents for DM2. They are based on bisamidinium groove binder with triaminopyrimidine recognition unit. Compared to the previously reported triaminopyrimidine-acridine conjugate (ligand **2**), which is poorly water-soluble and not cell-permeable, these new ligands are perfectly water-soluble with very low cytotoxicity. The optimized ligand maintained the inhibition potency of low micromolar K_i value to MBNL1-r(CCUG)$_8$. More importantly, the ligands are the first to show the dispersion of the MBNL1-r(CCUG)$_n$ disease foci in DM2 model cell culture.



A. Ligand **1**. Triaminopyrimidine-acridine conjugate. B. Bisamidinium-based ligands with different substitution patterns and linker lengths.

Poly(phthalaldehyde) and Poly(vinyl carbonate sulfone)s as UV and Thermally Degradable Packaging for Transient Electronics

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Transient electronics capable of programmed self-destruction eliminates the need to recover environmental sensors, biomedical implants, and clandestine devices. Current packaging relies on bulk water as the sole trigger, limiting the application of these electronics in wet environment. We explore additional triggers by investigating two low-ceiling-temperature polymers: cyclic poly(phthalaldehyde) (cPPA) and poly(olefin sulfone)s. Blend films of cPPA and photoacid generator degrade upon UV irradiation, leading to termination of the on-board electronics within 20 min. We also show the thermal degradation of poly(vinyl *tert*-butyl carbonate sulfone), which decomposes into volatile molecules at 80 °C in 20 min, leaving <5 wt% residue. We are currently determining the degradation kinetics and mechanism to enable designs of new transient packaging responsive to fluoride, radio frequency, and humidity.