Development of Benzdiamidinium Ligands as Potential Therapeutic Agents for Myotonic Dystrophy Desease

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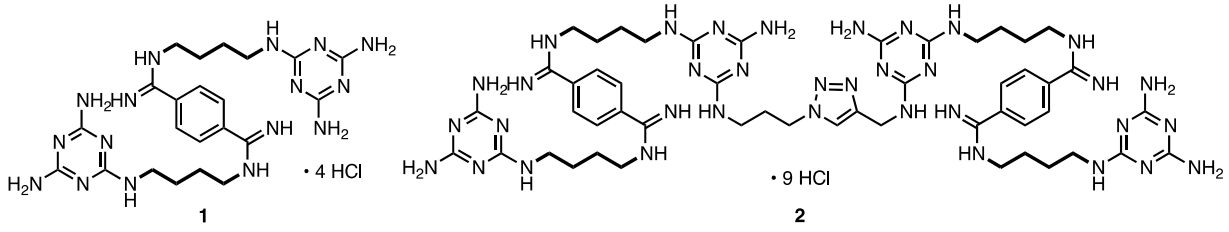
Myotonic dystrophy type 1 (DM1), the most common form of muscular dystrophy, is caused by a progressive expansion of the trinucleotide dCTG repeat. The transcribed rCUG repeat sequesters the muscleblind-like protein (MBNL1) into nuclear foci, leading to the abnormal regulation of alternative splicing of more than 100 pre-mRNAs. Herein, we report our successful efforts to discover and develop small molecule inhibitors of the r(CUG)$_n$-MBNL1 complex. For example, ligand **1** selectively binds to CUG repeats and displaces MBNL1 from its complex with the RNA in a DM1 cell model, serving as a lead MBNL1-(CUG)^{exp} inhibitor in our group. The measured K_I of **1** is 8 μM. Structural modifications of ligand **1** have led to a dimeric ligand **2** whose in vitro K_I is 1000-fold lower. Ligand **2** is cell permeable, relatively non-toxic to HeLa cells, and capable of dissolving up to 80% of nuclear foci at a low concentration, leading to reversal of IR splicing in a DM1 cell model.



The Design, Synthesis, and Analysis of Small Molecules that Accumulate in Gram-Negative Bacteria

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Multidrug resistant Gram-negative bacteria have emerged as a major public health concern. The outer membranes of these pathogens are highly impermeable to most small molecules, making them intrinsically resistant to many clinically used antibiotics, including drugs of last resort such as vancomycin and daptomycin. Due to the complexity of the system, very little is known about the properties a small molecule must possess in order to accumulate in Gram-negative bacteria; such information has the potential to greatly accelerate the antibiotic discovery process. Herein we describe the development of a method to study the physicochemical properties necessary for small molecule accumulation in Gram-negative bacteria, as well as insights gained using this method.