Design and Synthesis of Chimeric Activators for Restoration of Alternative Splicing

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Genome-wide analysis has estimated that >75% of human genes are alternatively spliced, allowing for the production of many protein isoforms from a single gene. Splicing is controlled by SR proteins, which bind to exonic splicing enhancers (ESEs) through RNA binding domains and recruit the splicosome via protein-protein interactions mediated by their RS domains. Defects in alternative splicing have been linked to several diseases, including Cystic Fibrosis, breast cancer, and Spinal Muscular Atrophy (SMA). SMA is a neurodegenerative disorder caused by the loss of survival of motor neuron 1 (*SMN1*) gene. A nearly identical copy of the gene, *SMN2*, contains a C→T transition on the ESE of exon 7, disrupting SR protein binding and resulting in substantial exon 7 skipping. Herein, we report our efforts toward the design and synthesis of two synthetic SR protein mimics and the experimental design to determine their ability to increase inclusion of exon 7 in *SMN2.*