Development of Spirocyclic Ligands for Bulged RNA Secondary Structure

S. Todd Meyer and Paul J. Hergenrother

The ability to target mRNA selectively with small molecules would represent an important complement to standard therapeutic agents, which largely target proteins. Owing to its single-stranded nature, RNA is prone to adopt a number of distinct secondary structures, including hairpin loops, internal loops, and bulged regions. One possible approach to targeting RNA is the development and *in vitro* evaluation of modules that selectively target individual types of RNA secondary structure. A new class of compounds that bind selectively to bulged regions of RNA has been developed through careful design of molecular architecture. A core scaffold has been designed and synthesized, and an initial library of spirocyclic compounds prepared and evaluated for RNA binding activity. These minimally charged compounds show good affinity and selectivity for bulges as compared to other types of secondary structure.