Synthetic Small Molecule Ligands for Internal RNA Secondary Structure

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Small molecule inhibitors and agonists of protein function are well established as the dominant therapeutic method for treating diseases in the clinic. However, only a small percentage of proteins contain appropriate binding sites for small molecule ligands, limiting the extent of the genome that can be covered by drugs that target proteins. Efforts to expand treatment options upstream of protein function include antisense oligonucleotides, DNA binding small molecules, and RNA interference. Targeting of mRNA by small molecule ligands, by taking advantage of unique features of RNA secondary structure, could lead to the selective silencing of protein translation as a treatment for disease states.

A spirocyclic small molecule natural product has previously been disclosed as an *in vitro* ligand for bulged regions in DNA. Based on the structure-activity relationships and molecular recognition principles of this molecule, a simpler synthetic analog has been designed as a putative RNA ligand. The core scaffold has been synthesized and derivatives prepared, which will be assessed for their binding activity in RNA bulges and internal loops.