Synthetic Small Molecule Ligands for 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 scaffold has previously been disclosed as an *in vitro* ligand for bulged regions in DNA. In order to investigate the potential of compounds of this type to bind bulges in RNA, a modified synthetic approach to this scaffold has been devised, and the parent alcohol has been functionalized. A library of small molecules based on this scaffold has been prepared and their *in vitro* binding activity assessed through a fluorescence-based assay.