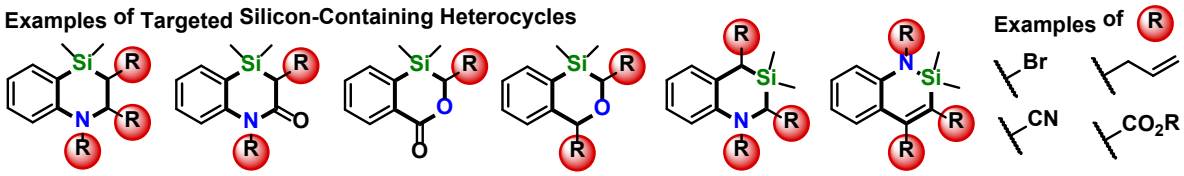
Synthesis and Functionalization of Novel Silicon-Containing Heterocycles for Drug Discovery

Scott Barraza and Scott E. Denmark

Silicon and its unique properties represent an untapped source of solutions for drug discovery and design, from potency to ADMET. The basis of silicon's underutilization may be attributed to a lack of synthetic methods for accessing cyclic organosilicon compounds. This research focused on the development of synthetic methods for constructing silicon-containing heterocycles that may serve as building blocks for application in drug discovery. Targets were selected based on predicted stability and biological potential, and were composed of silicon-containing benzannulated heterocycles that incorporated at least one other heteroatom (O or N). The program was executed in two-phases, (1) the synthesis of unfunctionalized silicon-containing heterocyclic cores, and (2) the elaboration of these cores into diverse functionalized heterocycles. This design allowed for the study of silicon's effect on these novel ring systems and comparison to analogous classical heterocycles.



Development of Aldehyde Bisamidinium Ligands for the Treatment of Myotonic Dystrophy Type 1 (DM1)

Brenda Andrade and Steven C. Zimmerman

Developing treatments for the rare trinucleotide repeat disorder myotonic dystrophy type 1 (DM1) is a challenging process because of the diseases' complex pathogenesis. Primary effort towards developing therapies has been focused on generating small molecules to disrupt the complex that forms between DM1 generated toxic RNA (CUG)exp repeats and Muscleblind-like 1 (MBNL1) protein, a key-splicing regulator. Using a RNA-groove binder with a U-U mismatch recognition unit, we have been able to selectively target r(CUG)exp and recover some of the phenotypes in model systems, however full recovery has not been observed.
Current work is focused on enhancing ligand potency by using the dynamic covalent chemistry of reversible imine formation.