We are interested in exploring how introducing specific structural modifications into peptides and other small molecules effects thermodynamics in protein-ligand interactions. This is arguably one of the most challenging problems in contemporary molecular recognition in biological systems and in the applied field of drug discovery. One common design strategy for increasing ligand binding affinity is to introduce conformational constraints in order to preorganize a flexible molecule in the conformation that corresponds to its biologically active conformation. The fundamental premise for this approach is the general belief that there will be a smaller entropic penalty on binding for the constrained molecule relative to its flexible counterpart that will lead to increased affinity, provided the two ligands interact in the same way with water and the protein so binding enthalpies for the two ligands are approximately the same.

Another successful tactic for improving ligand binding affinity is to increase its hydrophobicity by introducing aliphatic and/or aromatic substituents. This design rationale owes its origin to the common interpretation of the hydrophobic effect, which suggests that enhanced potency will accompany the entropic gain associated with desolvation of nonpolar surfaces. However, it is now increasingly apparent that the prevailing paradigms regarding the energetic consequences associated with making such changes in ligand structure upon the resultant binding energetics are not necessarily valid. Recent results from our laboratories relevant to how ligand preorganization and added nonpolar surface area affect binding enthalpies and entropies in protein-ligand interactions will be presented.