C60: A highly flexible scaffold for bioorganic design: From HIV protease inhibition to pharmacophore presentation.

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A general principle of bioorganic design is that the more flexible a ligand is, the lower its affinity for its target will be. Conversely, one of the main strategies for increasing the binding affinity of ligands is to limit their conformational freedom. This reduction in conformational freedom leads to a significant reduction in the entropic cost of complex formation, with a commensurate decrease in binding free energy (i.e. higher affinity). The fullerenes can effectively be used for bioorganic design because they are a completely conformationally restricted surface upon which may be placed the key moieties required for binding.

We have taken advantage of this unique fullerene property in two arenas, which will be the focus of this presentation: 1) C60 fullerene based inhibitors of the HIV-1 protease and 2) C60 based pharmacophore scaffolds. While the targeting of the HIV protease takes advantage of its unique chemical and steric complementarity to the C60 fullerene core, fullerenes have potentially even broader possible applications as scaffolds to present pharmacophores, or binding determinants. This ability hinges on two key factors, the ability for moieties attached to the C60 surface to span biochemically reasonable distances and more importantly to do this in a conformationally restricted manner. The talk will focus on the application of these principles to design of antagonists for biochemically relevant targets, including third generation design of HIV protease inhibitors.