Classical and Non-classical Structure-based Drug Design

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Structure-based drug design is usually described as an iterative process in which knowledge of the three-dimensional structure of a receptor-ligand complex reveals details of the binding interface that can be improved by chemical modification of the ligand. These structure-based changes as evaluated by *in vitro* or *in vivo* assay, and improved ligands are subjected to additional cycles of structure determination, improvement and evaluation. Our studies on caspase-3, PTP-1B and other targets provide examples of such classical structure-based drug design. On occasion, however, structural studies lead to surprising results that produce unexpected effects on the inhibitor-development process. In both the caspase and PTP projects, early structures revealed that the apparent improvement in binding potency was inconsistent with program goals and this knowledge led to termination of the compound classes involved. In work on both nuclear receptors and kinases, knowledge of structure-based selectivity led to the design of novel assays that have effectively discriminated compounds on their biological properties. These studies demonstrate that structure-based drug design studies can not only lead to ligand optimization but to prioritization of compound classes and to the design of novel methods of discriminating among compounds based on their biological properties.

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