FROM LEADS TO DRUGS

Hugo Kubinyi

University of Heidelberg, Germany
E-mail kubinyi@t-online.de

The optimization of a lead structure is an evolutionary procedure. Medicinal chemists follow the similarity principle, based on the experimental experience that structural analogs most often have similar biological properties. Whereas there are many exceptions to this general observation, all rational lead optimizations are based on this concept. Every improvement of certain properties of a lead results in further structural modifications. This process ends when the final candidate has all desired properties to proceed to preclinical profiling and clinical investigation.

General procedures for lead structure modification are (bio)isosteric replacement of atoms and groups, formation of rings (rigidization), cleavage of rings, modification of side chains and linkers, use of „privileged“ structural elements, selective optimization of side activities (SOSA approach), virtual screening, structure-based ligand design, computer-aided ligand design, fragment-based ligand design, modification of ADME properties, prodrugs, soft drugs, and targeted drugs. Selected examples will illustrate most of these principles.