STRATEGIES FOR LEAD FINDING AND LEAD OPTIMIZATION UTILIZING EXPERIMENTAL AND COMPUTATIONAL APPROACHES

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Lead Finding and Lead Optimization depend critically on our ability to integrate synthesis skills, automation technologies, design capabilities and medicinal chemistry knowledge into the discovery process. The discovery of novel Kv1.5 channel inhibitors, microtubule disassembly inhibitors, G6P-Translocase inhibitors, and factor Xa inhibitors will be discussed to describe various discovery strategies.

The voltage-gated potassium channel Kv1.5 is regarded as a promising target for the development of new atrial selective drugs with fewer side effects. Various approaches for lead finding including similarity search, rescaffolding, ligand- and structure-based design will be described. Emphasis will be given on synthetic strategies and the impact of automation technologies.

Besides synthetic small molecules natural products are a valuable source for novel lead structures. The impact of natural products on discovery will be briefly reviewed and illustrated based on selected project examples including microtubule disassembly inhibitors and G6P-Translocase inhibitors.

Factor Xa plays a critical role in the co-agulation pathways. Our efforts towards orally active agents will be described with an emphasis on aspects of multidimensional compound optimization.