IN SILICO APPROACHES GENERATING NOVEL COMPOUND SERIES IN LEAD OPTIMIZATION

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Lead optimization (LO) is undoubtedly the major bottleneck in pre-clinical drug discovery. In LO utilizing typically 3-4 optimization cycles several goals should be achieved at the same time including: improved activity, selectivity, chemical and biological stability, enhanced bioavailability and safety. This process requires normally between 8 to 16 months depending on the target or the therapeutic area. In order to address the need to reduce the overall timeline, we developed an integrated *in silico* approach, which accelerates the re-design process after each iteration cycle. The key elements of this approach are library design and filtering/ focusing tools that define the LO library for the subsequent cycle.

In the library design we utilize several proprietary approaches for 'lead multiplying':

- 2D analog search based on structural similarity to the best compounds in the preceding iteration, selected from in-house or publicly available databases,
- A unique medicinal chemistry knowledge base (EMIL: Example Mediated Innovation for Lead evolution), which contains several thousands of structural "evolution" examples for bioanalogous sub-structural replacements
- Novel chemogenomics approach to increase the selectivity based on the genetic divergence of target family members ('selectivity jumping').

The subsequent filtering process comprises several *in silico* tools of various functions:

- 3D virtual screening if crystal structure or homology model is available
- *In silico* ADMETox filtering using the latest edition of Pallas^{TM} software
- Synthetic Feasibility Analysis and Scoring
- Diversity selection ensures that all the relevant structural features are represented

In the present talk we describe the elements of this integrated *in silico* approach for LO together with case studies in the area of various target families (e.g. kinases, MMPs etc.).