Molecular Design in Drug Discovery: Applications and Challenges

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Molecular Design plays an important role in modern Drug Discovery. It is applied in lead generation for identification and fine-tuning of suitable hits and leads. Furthermore, in lead optimization Molecular Design plays a pivotal role in turning lead series into preclinical candidates.

This presentation outlines Molecular Design principles in particular in small molecule lead optimization. For example, application of our SALI Explorer in structure-activity relationships (SAR) fosters the early identification of SAR hot spots within lead series. Subsequent quantitative structure-activity relationship is then applied to optimize compounds against the target of interest.

Most often lead series suffer from poor ADMET profiles and/or anti-target activities which have to be taken into account in optimization. We have implemented several predictive data mining tools in the field of ADMET- and anti-target (e.g. hERG, CYPs) modeling. A few examples outline the scope and applicability of these tools for Medicinal Chemists and Drug Designers. In addition, in silico profiling of molecules against off-targets allows fast and early identification of liabilities of putative lead series.

The ultimate challenge of multidimensional compound optimization (MDCO) requires an early definition of the candidate profile in order to derive the multidimensionality of the problem. Suitable fitness functions can then be derived and applied in MDCO.

The increasing interest in peptides and biologicals (e.g. proteins, antibodies) as drugs opens new opportunities for Molecular Modeling. For example, peptide design becomes more and more important in order to synthesize only the most important peptides while taking into account their physicochemical properties. In the field of antibodies, Molecular Design plays an important role to ensure proper physicochemical properties (e.g. solubility, aggregation) of the biologicals.