Anti-Target Optimization in Medicinal Chemistry: Do in silico tools help?

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Pharmaceutical drug research is a multi-objective optimization problem not only concerned with potency, efficacy, and selectivity, but additionally with finding a suitable compromise also by reducing physicochemical and pharmacokinetic liabilities of early hits.

Phaenomenological models that describe chemical features responsible for a pharmacological effect and provide an optimization rationale are highly desired over classical black box QSAR models that connect molecular descriptors with some target property. Nevertheless, fast and effective alerts with about eighty percent accuracy can be obtained by classical QSAR and allow for prioritization within HTS analysis, compound purchase and virtual compound profiling datasets, when applied in the context of clusters and not taken literally for any specific compound.

Most important for predictive models are high quality data sets. These should be acceptably large, internally diverse and with similar profile to the warehouse to predict. With our dataset for human serum albumine binding it is not only possible to create a highly predictive HSA model but also an satisfactory model for fraction unbound in human as derived from calculated HSA.

On the other hand, the dataset used for the creation of CypScore as a tool for the prediction of cytochrome P450 mediated metabolic lability prediction is much smaller, but favorably matches the observed variety of metabolic reactions. CypScore is presented as an example for a phaenomenological model, based on specific AM1 quantum-chemical atomic reactivity models for the most important phase-I reactions. Instead of a diffuse metabolic stability value, it hints to the most attractive molecular regions for chemical modifications.

The dataset available to us for hERG inhibition is much too limited to create global models of the quality needed for lead optimization. topoHERG, a knowlededgebase approach for the classification of hERG inhibition based on pharmacophore-similarity which allows to learn from successful chemical modifications in near neighborhoods, is presented as a proof-of-concept study that currently lacks from the small structural data basis. topoHERG is compared with decision tree and SVM black box models with larger applicability domain but lower accuracy.

