Design, analysis and virtual screening of an *in silico* dynamic combinatorial compound library with focus on protein-protein interaction inhibitors

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Enabling the protein target to direct the synthesis of its strongest binder via dynamic combinatorial chemistry is an interesting strategy for *de-novo* design and identification of new bioactive compounds. Employing a reversible reaction in solution with different building blocks an enrichment of the strongest binder occurs, since it is removed from equilibrium during binding to the protein target. One successful example is the formation of acylhydrazones from aldehydes and hydrazides which led to the identification of new inhibitors of endothiapepsin. [1]

As commercial compound collections show low hit rates for protein-protein interaction (PPI) targets due to a non-suitable chemical space, *de-novo* design of small molecule libraries within a new chemical space is of uttermost importance for the elucidation of PPI inhibitors. [2] For this purpose chemoinformatics tools were utilized for the analysis of the acylhydrazone libraries chemical space. Usage of an *in-silico* reaction between all available aldehydes and hydrazides contained in the ZINC database (http://zinc.docking.org) created a virtual library of about 1.2 billion highly diverse acylhydrazones of appropriate physicochemical properties.

Previous high-throughput docking studies by Koch et al. identified an acylhydrazone based inhibitor of the PPI between mycobacterial thioredoxin reductase and thioredoxin. [3] Therefore it can ideally be screened for new inhibitors of the thioredoxin reductase as proof of concept study employing the dynamic combinatorial chemistry approach for a highly diverse subset of the newly obtained acylhydrazone library.

We will present the results of the exhaustive chemoinformatics based analysis of the virtual acylhydrazone library together with the docking results leading to aldehyde and hydrazide building blocks for *in-vitro* application of the dynamic combinatorial chemistry approach.

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[2] O. Sperandio, C. H. Reynès, A.-C. Camproux, B. O. Villoutreix, *Drug Discov. Today*., **2010,** *15* (5-6), 220–229.

[3] O. Koch, T. Jäger, K. Heller, P. C. Khandavalli, J. Pretzel, K. Becker, L. Flohé, P. M. Selzer, *J. Med. Chem.,* **2013,** *56* (12), 4849–4859.