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Fragment-based identification of multi-target ligands by self-organizing map alignment

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In the recent years the prevalent paradigm in drug discovery of „one drug – one target – one disease", following the assumption that highly selective ligands would avoid unwandted side effects caused by binding to seconday non-theratpeutic targets, got reconsidered. The results of post-genomic and network biology showed that proteins rarely act in isolated systems but rather as a part of a highly connected network [1]. It was further shown that the efficacy of several approved drugs is traced back to the fact that they act on multiple targets [2]. Therefore inhibiting a single target of such a network might not lead to the desired therapeutic effect. These findings lead to a shift towards polypharmacology [3] and the rational design of selective multi-target drugs, which have often improved efficacy [4]. But the design of multi target drugs is still a great challenge in regard of a sufficient activity on each target as well as an adequate pharmacokinetic profile [5]. Early design strategies tried to link the pharmacophors of known inhibitors, however these methods often lead to high molecular weight and low ligand efficiency.

We present a new approach based on self-organizing maps [3,6] (SOM) for the identification of multi-target fragments. We describe a workflow that initially identifies multi-target relevant substructures with a combination of maximum common substructure search and the alignment of multiple SOMs. Furthermore, these substructures are trained together with a fragment library on additional SOMs to find new multi-target fragments, validated by saturation transfer difference (STD)-NMR and biochemical assay systems. We used our approach for the identification of new dual-acting inhibitors of 5-Lipoxygenase (5-LO) and soluble Epoxide Hydrolase

(sEH), both enzymes located in the arachidonic acid cascade and involved in inflammatory processes, pain and cadiovascular diseases.

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