tional approaches for the structure prediction of protein-protein complexes are so-called scoring and objective functions, which quantify the structural correctness of the predictions.

Here, we evaluate the DrugScore^{PPI} statistical potentials previously developed for *in silico* alanine scanning and hot spot prediction on given structures of protein-protein complexes [2] as such a scoring and objective function. We do so in connection with the computationally efficient protein-protein docking algorithm FRODOCK [3]. Our results show that the DrugScore^{PPI} potentials balance well different types of interactions important for protein-protein recognition, which is remarkable given that these potentials have not been specifically designed for the prediction of protein-protein complex structures [1].

The results are discussed in view of the influence of crystal packing and the type of protein-protein complex docked. Finally, a simple criterion is provided with which to estimate *a priori* if unbound docking with DrugScore^{PPI}/FRODOCK will be successful [1].

The ability to accurately and efficiently predict protein-protein complex structures is expected to impact the development of drugs and diagnostics that interfere with such complexes, and to foster our basic understanding of evolutionary processes and signaling in biological systems.

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P-75: Identification of novel tubulin inhibitors by parallel virtual screening protocol of reaction-based combinatorial library of combretastatin CA-4 derivatives

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Microtubules are cytoskeletal filaments consisting of αβ-tubulin heterodimers and are involved in a wide range of cellular functions. In the mitotic phase, microtubules are in dynamic equilibrium with tubulin dimers by assembling the tubulin into microtubules or disassembling microtubules to tubulin [1]. Disruption of the dynamic equilibrium can induce arresting cell cycle and lead to apoptosis. Hence, the compounds that could inhibit tubulin polymerization or interrupt microtubule depolymerization would be useful in the treatment of cancer [2]. In recent decades, mostly natural products, targeting tubulin have been discovered and developed; some of them are already in clinical use, such as epothilone, paclitaxel, and combrestatin A-4 (CA-4) [3].

We present here an application of parallel virtual screening protocol to identification of novel CA-4 analogs. Based on the elaborated synthesis protocol for the CA-4 analogs, the virtual combinatorial library (VCL) was created using CombiGlide. The library consisted of 1339 structures was obtained by the direct linking of four different cores (*cis*-stilbenes, α-phenylcinnamic acids, N-methylimidazoles and oxazoles as *cis*-restricted analogs) with available reagents. Next, the potency of each VCL compound was evaluated by means of developed screening protocol, which combined different evaluation models, such

as 3D pharmacophore, QSAR models and post-docking scoring method based on Structural Interaction Fingerprints (SIFt) for two tubulin crystals (PDB ID: 1SA0 and 1SA1). Final ranking list was obtained by combining all rankings using consensus scoring method [4]. Based on the final scores the 16 diverse structures, with different level of predicted activity, were selected and synthesized.

The ability of compounds to inhibit tubulin polymerization was evaluated experimentally and showed good correlation with our predictions.

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P-77: PTP1B – Combining Inhibitory Activity with Selectivity

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Protein Tyrosine Phosphatase 1B (PTP1B) has now been known for about 20 years as a promising target. However, the search for selective and potent inhibitors is still ongoing [1,2]: While PTP1B is important for regulating insulin signaling in healthy humans, its activity increases with type 2 diabetes and obesity as well as mammary and ovarian carcinoma [3,4]. Especially selectivity over the closely related TCPTP remains a challenge; the impact of TCPTP inhibition in vivo is still not thoroughly discovered, but judged on the fate of TCPTP knockout mice which die soon after birth selectivity over TCPTP seems advisable to avoid severe side effects [5]. We present a work-flow that aims at increasing selectivity while maintaining high affinity levels with high ligand efficiency (LE).

By dividing the binding site into an activity and a selectivity relevant part, available protein-ligand crystal structures and known inhibitors are exploited to build 3D pharmacophore models for each site separately, which were then used to virtually screen for fragments with high LE. The molecular building blocks discovered that way are used to create a combinatorial database of potentially highly active and selective inhibitors of PTP1B. Ensemble docking experiments are used to investigate the way of binding for the resulting assembled molecules. Additionally, molecular dynamics simulations for both PTP1B and TCPTP are performed in order to identify subtle differences in binding site rigidity that can be used to increase inhibitor selectivity.

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