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TArget Specific Scoring FUNction (tassfun)

The aim of this project, supervised by Dr. Niklas Blomberg (GSI CompChem AZ Mölndal) and Dr. Rebecca Wade (EML Research, Heidelberg), is to develop target specific scoring functions based on COMparative BINding Energy (COMBINE) analysis for designing new specific inhibitors mainly against thrombin, urokinase type plasminogen activator (uPA) and factor Xa (fXa), under consideration of the anti-target trypsin. For this, 3D structures of complexes consisting of a receptor and a small molecule inhibitor should be analyzed by calculating electrostatic and van de Waals interaction energies, which are correlated with bioactivity values by Partial Least Square (PLS) and variable selection.

At the moment, the COMBINE analyses are focused on published crystal structures of the above mentioned receptors inhibited by ligands with a common structural element of a 2-(2-phenol)indole or a 2-(2-phenol)benzimidazole moiety. For over 200 ligands, SDF files with K_i values, SMILES strings and 2D structure information were created at AstraZeneca and were checked against the corresponding PDB files.

Until now, two COMBINE analyses for uPA and trypsin with 18 and 8 different ligands, respectively, plus alternative receptor conformations, were done. In both cases, even with small training sets, a promising correlation of functional groups and bioactivity could be shown. In these analyses, only structures of complexes were used, where structures were available in the Protein Data Bank with already given hydrogens. For doing further COMBINE analysis without any given hydrogen positions, we have established a semi-automatic procedure for adding hydrogens in the correct state. This procedure relies on the InsightII and WHATIF programs and requires scripts written for this purpose.

In the next steps, SDF files will be integrated together with coordinates of complexes and other data in a database. The necessary tools for doing database queries and visualisation of results will be realized in collaboration with the group of Dr. Isabel Rojas (EML Research, Heidelberg). First concepts have already been discussed.

Tools will be developed to integrate the generating and docking of ligand structures in cases where no 3D structures are available and COMBINE models will be made for other targets (eg. thrombin and fXa).