# [SC2] Conformational Sampling and Binding Affinity Prediction of Macrocycles

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When optimizing ligand binding to a target protein during the drug design process, macrocyclization can be an effective way to generate compounds with restricted conformational space compared to their acyclic counterparts and with the potential to improve potency, selectivity, metabolic stability and their physicochemical properties. But in the context of computationally-driven drug design, this diverse class of chemical structures provides some challenges particularly regarding how to handle conformational flexibility and thus binding affinity predictions.

Here, we will first introduce a method for evaluating the propensity of a macrocyclic compound to adopt a conformation similar that of a known active linear compound in the binding site. This method can be used as a fast screening tool for prioritizing macrocycles by leveraging the assumption that the propensity for the known bioactive substructural conformation relates to the affinity.

Then we will discuss our recent algorithm for exploring macrocyclic conformational space and the results of a benchmarking study will be reported. A dataset of 208 structures was curated from the Cambridge Structural Database, the Protein Data Bank and the Biologically Interesting Molecule Reference Dictionary. A conformational search algorithm using the program Prime reproduces the crystal structure conformations in a highly accurate way and is fast compared to other published approaches. The sampling algorithm is also used in the context of a membrane permeability prediction protocol for macrocyles.
Finally, results for binding affinity prediction using the FEP+ framework for macrocycles will be presented. We have applied the method to 7 pharmaceutically interesting data sets taken from recent drug discovery projects including 33 macrocyclic ligands covering a diverse chemical space. The predicted binding free energies are in excellent agreement with experimental data, with an overall root mean square error (RMSE) of the predictions below 1 kcal/mol.