Molecular Modelling for Macrocycle Design

Dan Sindhikara[1], Lingle Wang[1], Tatjana Braun[2]

[1]*Schrodinger, Inc., 120 West 45th Street, New York 10036, United States*

[2]*Schrödinger GmbH, Q7 23, 68161 Mannheim, Germany*

Macrocycles are an important and growing class of clinical drug candidates due to their structural diversity, wide range of physicochemical properties, and promising biological activities. However, macrocycles are often more difficult to work with than typical drug-like small molecules, both synthetically and computationally.

Here, we present a toolkit for computational macrocycle design introduced by Schrödinger over the last few years. Key component is a new macrocycle sampling approach based on established protein structure prediction algorithms that has shown excellent accuracy, robustness, and speed on a diverse benchmarking data set of 208 macrocycles. [1]

The new sampling technology is at the core of a variety of macrocyclic workflows: macrocycle bioactive conformer stability calculation, membrane permeability predictions [2], and binding mode determination using ligand-receptor docking with Glide.

Furthermore, the results of an adapted FEP+ [3] protocol for calculating binding free energies of macrocycles are presented. [4] The approach allows studying both ring size changes and cyclization of acyclic precursors. Applied to seven pharmaceutically relevant data sets 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 below 1 kcal/mol.

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