Macrocycles - Conformational Sampling and Thermodynamic Characterization

Anna S. Kamenik,[a] Uta Lessel,[b] Julian E. Fuchs,[c] Thomas Fox,[*,b] and Klaus R. Liedl[*,a]

[a] Institute of General, Inorganic and Theoretical Chemistry, Center for Molecular Biosciences Innsbruck, University of Innsbruck, 6020 Innsbruck, Austria
[b] Medicinal Chemistry, Boehringer Ingelheim Pharma GmbH & Co. KG, 88397 Biberach, Germany
[c] Department of Medicinal Chemistry, Boehringer Ingelheim RCV GmbH & Co KG, 1120 Vienna, Austria

Macrocycles are of considerable interest as highly specific drug candidates, yet they challenge standard conformer generators with their large number of rotatable bonds and conformational restrictions. Here, we present a molecular dynamics-based routine that bypasses current limitations in conformational sampling and extensively profiles the free energy landscape of macrocycles in solution. We perform accelerated molecular dynamics simulations to capture a diverse conformational ensemble. By applying an energetic cutoff, followed by geometric clustering, we demonstrate the striking robustness and efficiency of the approach in identifying highly populated conformational states of cyclic compounds. The resulting structural and thermodynamic information is benchmarked against interproton distances from NMR experiments and conformational states identified by X-ray crystallography. Using model systems of varying size and flexibility, we show that the method reliably reproduces experimentally determined structural ensembles and is capable of identifying key conformational states that include the bioactive conformation. Thus, the described approach is a robust method to generate conformations of macrocycles and holds promise for structure-based drug design.