Conformational Sampling of Macrocycles: Recent Progress

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Macrocyclic molecules have been shown to be orally bioavailable ligands for targets such as GPCRs and protein-protein interfaces. Greater exploitation of macrocycles in drug discovery has been stymied by a lack of computational methods to investigate their properties, including their conformational space. Here we present extensive validation of a rapid, atom-based method for macrocycle conformational sampling, using datasets drawn from the CSD and the PDB. We compare the performance of the method to other approaches to the same problem to identify avenues for future improvement.