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Abstract

Fragment-based docking was used to select a conformation for virtual screening from a molecular dynamics trajectory of the West Nile virus nonstructural 3 protease. This conformation was chosen from an ensemble of 100 molecular dynamics snapshots because it optimally accommodates benzene, the most common ring in known drugs, and two positively charged fragments (methylguanidinium and 2-phenylimidazoline). The latter fragments were used as probes because of the large number of hydrogen bond acceptors in the substrate binding site of the protease. Upon high-throughput docking of a diversity set of 18694 molecules and pose filtering, only five compounds were chosen for experimental validation, and two of them are active in the low micromolar range in an enzymatic assay and a tryptophan fluorescence quenching assay. Evidence for specific binding to the protease active site is provided by nuclear magnetic resonance spectroscopy. The two inhibitors have different scaffolds (diphenylurea and diphenyl ester) and are promising lead candidates because they have a molecular weight of about 300 Da.