MDM2 CASE STUDY: COMPUTATIONAL PROTOCOL UTILIZING PROTEIN FLEXIBILITY IMPROVES LIGAND BINDING MODE PREDICTIONS

Physics, Astronomy and Materials Science

Missouri State University, July 28th, 2016

Master of Materials Science

Anthony Ascone

ABSTRACT

Recovery of the P53 tumor suppressor pathway via small molecule inhibitors of onco-protein MDM2 highlights the critical role of computational methodologies in targeted cancer therapies. Molecular docking programs in particular, provide a quantitative ranking of predicted binding geometries based on binding free energy allowing for the screening of large chemical libraries in search of lead compounds for cancer therapeutics. This study found improved binding mode predictions of medicinal compounds to MDM2 using the popular docking programs AutoDock and AutoDock Vina, while adopting a rigid-ligand/flexible-receptor protocol. Crystal structures representing small molecule inhibitors bound to MDM2 were selected and a total of 12 rotatable bonds was supplied to each complex and distributed systematically between the ligand and binding site residues. Docking results were evaluated in terms of the top ranked binding free energy and corresponding RMSD values from the experimentally known binding site. Results show lowest RMSD values coincide with a rigid ligand, while the protein retained the majority of flexibility. This study suggests the future implementation of a rigid-ligand/flexible-receptor protocol may improve accuracy of high throughput screenings of potential cancer drugs targeting the MDM2 protein, while maintaining manageable computational costs.

KEYWORDS: molecular docking, MDM2, autodock, autodock vina, drug discovery