Long Abstract

The cyclin-dependent protein kinase 2 (CDK2) belongs to a family of proteins that play important roles in cellular processes, carrying out a major post-translational modifications, reversible phosphorylation, and they are responsible for regulating the cell cycle and its proper development in all eukaryotes. They also require the physical association with cyclins to achieve optimal enzyme activity and they are regulated by phosphorylation and dephosphorylation events.

Research on the molecular mechanisms by which these molecules act has led to the understanding of many cellular processes such as cell cycle irregularities leading to different types of cancer. In cancer cells with uncontrolled cell proliferation has been shown that activity of this protein is altered, this due to the loss of function of natural inhibitors of CDK2, either because they were mutated, deleted or silenced in tumors. This condition makes this protein a target of interest for the development of a possible therapy for these diseases.

Available crystallographic structures of a group of 12 CDK2-inhibitor complexes in which inhibitors have in common two heterocyclic cores named imidazopyrazine and pyrazolo-pirimidine, were used as systems under study. In addition, biological activity reported, as IC$_{50}$ values is also available.

Based on this experimental data for these CDK2/inhibitor complexes, we tested a computational methodology to evaluate if the computational calculated affinity of these complexes is related or not with biological activity (IC$_{50}$ values) reported previously.

We performed long molecular dynamics simulations for the 12 CDK2/inhibitor complexes to have an appropriate system for performing calculations of affinity and interaction energies. These calculations were performed using the method MM-GBSA (Molecular Mechanics - Generalized Born Surface Area), which provides the free energy of binding.

If this approximation gives correct results, the computational method could be considered predictive when applied to new CDK2/inhibitor complexes, at least when used with chemical systems related with set of compounds studied.