Study of the Binding Strength and Selectivity of Inhibitors by CDK2/CDK4 Protein Systems: QM/MM Interaction Energy as a Descriptor of Biological Activity

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Cyclin-dependent-kinases (CDK) are enzymes involved in regulation of the cell cycle in all eukaryotic organisms (Malumbres y cols., 2005). This study considers the CDK2 enzyme, which is over-expressed in cancer cells contributing to the deregulated cell growth, becoming an important therapeutic target for cancer treatment through the inhibition of the enzyme by small molecules embedded in the ATP binding pocket.

However, the study of the inhibitory capacity of a set of molecules does not depend only on its potency of inhibition, but also on its selectivity for CDK2 over other highly homologous members of the cyclin-dependent kinases family. Therefore, the CDK4 enzyme will be studied as well, which shares about 70% identity with CDK2 in their binding sites.

By means of several computational methods the binding potency and selectivity of a set of CDK2 and CDK4 inhibitors will be studied, evaluating also the correlation between the interaction energy and the experimental data of biological activity through use of QM/MM hybrid methods of calculation, thus identifying the residues of the active site that are critical for selectivity.

A set of 7 inhibitors were selected to evaluate the selectivity for CDK2 and CDK4, which have in common the chemical group aminoimidazo[1,2-a]pyridines.

Molecular modeling technique called molecular docking was use to predict the position and orientations of the ligands into the ATP binding pocket of CDKs. Then, the structures obtained from docking were optimized using hybrid QM/MM calculation methods. The inhibitor was treated with quantum mechanics while the rest of the protein-ligand complex was treated with molecular mechanics.

Moreover, the convergence of interaction energy with the system size was evaluated using the Density Functional Theory (DFT-B3LYP) method with the lacvp** basis set. To do so, the largest inhibitor was chosen and then four molecular models were constructed, considering first the residues that establish hydrogen bonds and adding after to this small minimized model system all amino acids within 2, 5 y 7 Å from the inhibitor.
Once the optimal size of active site is determined, the interaction energy of whole protein-ligand structure will be evaluated, considering the QM/MM approach previously used to determine the optimal system size.

It is expected that a statistical correlation, between obtained interaction energy and the known biological activity of CDK/inhibitor complexes measured by the IC$_{50}$ value, could be found.

ACKNOWLEDGEMENTS:
J.A.M. and I.A. acknowledge the financial support through project FONDECYT No 11100177.