Abstract No: TI 10

In silico identification of natural product inhibitors of HMG-CoA reductase

Archchana Ganeshalingam[1] and Chinthaka N. Ratnaweera[2*]

[1] *College of Chemical Sciences, Institute of Chemistry Ceylon, Rajagiriya 10107, Sri Lanka*

[2] *Department of Chemistry, Faculty of Science, University of Ruhuna, Matara 81000, Sri Lanka*

**Corresponding author: nadun@chem.ruh.ac.lk*

Coronary heart diseases such as hypercholesterolemia along with cancer and AIDS are the most studied diseases in the world. Inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA reductase) which is the rate determining enzyme in the cholesterol synthesizing mevalonate pathway has been proven to control serum cholesterol levels. At present, statins have been extensively used as a medication to lower the serum cholesterol level. They have HMG CoA like moiety hence act as competitive reversible inhibitors. It has been found that the use of statins results in certain side effects. Since hypercholesterolemia is a chronic condition needing lifelong therapy, the use of natural product-based drugs can be more beneficial. Therefore, in this study, natural product compounds isolated from various plants that are used as drugs for hypercholesterolemia in ayurvedic medicine have been investigated for their inhibitor activity against the enzyme applying molecular docking and molecular dynamics. HMG CoA reductase is a tightly associated tetramer with a bipartite active site. The crystal structure of HMG CoA reductase (PDB ID: 3CCZ) was retrieved from the RCSB PDB database. For the initial model, only chains A and B were retained while the remaining chains and all other non-standard residues were removed using Chimera. The stability of the model was investigated through a 100 ns molecular dynamic simulation. Subsequently, selected compounds were docked to the enzyme using the Autodock Vina algorithm in PyRx software. Several commercially available statins were considered as references. The complex with the highest negative binding affinity was studied with a 100 ns molecular dynamic simulation. Results revealed that reference molecules showed binding affinities ranging from -6.4 to -8.2 kcal/mol. Several natural product ligands show comparable binding affinities (>7.0 kcal/mol) to the references and show drug likeliness. Coclaurine emerge as a promising candidate for further studies making a stable complex, stabilized after 25 ns from the start of the simulation with the highest negative binding affinity of -7.6 kcal/mol with two significant hydrogen bonds and showing drug likeliness.

Keywords: Hypercholesterolemia, Natural product inhibitors, *in-silico* study

Abstract No: TI 11

A Computational Study of Cyclin-dependent Kinases 1 (CDK1) butyrolactone I complex and the Role of Mg Ion in the Active Site

Chanikya D. Jayawardana[1] and Chinthaka N. Ratnaweera[2*]

[1] *College of Chemical Sciences, Institute of Chemistry Ceylon, Rajagiriya 10107, Sri Lanka*

[2] *Department of Chemistry, Faculty of Science, University of Ruhuna, Matara 81000, Sri Lanka*

**Corresponding author: nadun@chem.ruh.ac.lk*

Cyclin-dependent kinases (CDK) 1, 2, 4, and 6 are the protein kinases that play a pivotal role in the cell cycle regulating of all eukaryotic organisms by phosphorylating proteins needed during the cell division cycle. Phosphorylation of protein kinase requires the assistance of a divalent metal ion, usually Mg^{2+} ion to facilitate the transfer of a phosphate group onto a particular residue (serine, threonine, or tyrosine) in a substrate. However, only CDK1 is required for the successful completion of the M-phase of the cell cycle. Therefore, inhibition of CDK1 is emerging as a drugable target for diseases caused by unregulated cell proliferation. Butyrolactone I is a

natural product with certain bioactivities that have been isolated from the endophytic fungus *Aspergillus terreus*. Experimental studies have revealed that butyrolactone I inhibits the activities of both CDK1 and CDK2. However, its inhibitory mechanism and the role of Mg^{2+} ion remain uninvestigated. In this study, the effect of butyrolactone I on the CDK1-cyclin B complex in the presence and absence of Mg^{2+} ion in the active site was evaluated by applying a computational methodology. The currently available CDK1 crystal structures do not contain any Mg^{2+} ion, therefore, our first step was to position the Mg^{2+} ion in the CDK1 crystal structure (PDB ID:5HQ0) based on the structural information of CDK2 (PDB ID:1HCK). The stability of the two models (with $Mg^{2+}$and without Mg^{2+}) were investigated by conducting a 200 ns molecular dynamics simulation. The root mean square deviation (RMSD) of the structures with respective to the starting structures were almost stable during the last 100 ns. Subsequently, butyrolactone I was docked into the active site of both models using Autodock Vina, and further molecular dynamic simulation of 200 ns was conducted for the best docking poses of each complex. Stable RMSD values indicated the stability of protein-ligand complex. MM-GBSA binding free energy calculations were conducted to further assess the stability of the complexes. Accordingly, the butyrolactone I CDK1 complex was more favorable in the absence of Mg^{2+} ion (ΔG = -25.50 kcal/mol) than its presence (ΔG = -19.2 kcal/mol).

Keywords: CDK1, Mg^{2+} ion, Butyrolactone I, Computational chemistry

Abstract No: TI 23

A study on complexation, stoichiometry and binding of selected anionic organic pollutants and protonated polyaza macrocycles

Danushka M. Kumarasinghe and Isurika R. Fernando*

Department of Chemistry, Faculty of Applied Sciences, University of Sri Jayewardenepura, Nugegoda 10250, Sri Lanka

**Corresponding author: isurika.fernando@sjp.ac.lk*

Anionic organic pollutants (AOPs) generated by industrial and laboratory processors are accumulated in the environment while causing health problems for human beings. Therefore, this research project is focused on a fundamental study of the removal of three selected AOPs, namely dianions of hydroquinone, catechol and resorcinol from the environment using a supramolecular approach. Two electron deficient, PPAMs, namely PPAM1 and PPAM2 with different cavity sizes and shapes were synthesized by using a 1:1 molar mixture of diethylenetriamine along with a dialdehyde, terephthalaldehyde and isophthalaldehyde separately as starting materials by carrying out an imine metathesis, a reduction with sodium borohydride followed by a protonation with perchloric acid in order to obtain aqueous medium soluble macrocycle. After characterization of the PPAM1 and PPAM2 using spectroscopic techniques, the complexation is driven by ionic interactions between hexa-cationic PPAMs and dianionic AOPs in an aqueous solution was characterized by UV-visible spectroscopy and fluorescence spectroscopy. Stoichiometry and the binding constant between each PPAM with dianions of hydroquinone, resorcinol and catechol were determined using fluorescence spectroscopy by employing the Job's plot method and dilution method, respectively. The Job's plots of each PPAM and AOP used in this study demonstrated 1:2 stoichiometry between the PPAM and AOP indicating a partial displacement of the counter ion of the macrocycles. Binding constants between PPAMs and AOPs were calculated using the Benesi – Hildebrand equation. Among the three AOPs used in this study, dianions of hydroquinone exhibited the highest binding constants of 2.85×10^6 $mol^{-2}dm^6$ and 2.58×10^6 $mol^{-2}dm^6$ with PPAM1 and with PPAM2, respectively. The dianions of resorcinol exhibited the lowest binding constant of 8.21×10^5 $mol^{-2}dm^6$ and 8.12×10^5 $mol^{-2}dm^6$ for PPAM1 and PPAM2, respectively. In conclusion, fluorescence spectroscopy evidenced the complexation between PPAMs and AOPs. The cavity size and shape of the PPAM as well as the position of the dianions in AOPs