3D-QSAR and molecular docking studies of 2-Pyrimidinecarbonitrile derivatives as inhibitors against falcipain

*Plasmodium falciparum* (*P. falciparum*) is the most virulent human malaria pathogen that causes hundreds of millions infected annually. According to the World Health Organization report 2010, the estimated number of malaria cases are 225 million that result in 781,000 deaths ([http://www.who.int/malaria/en/](http://www.who.int/malaria/en/)).

*P. falciparum* depends on hemoglobin hydrolysis as a source of amino acids for protein synthesis. Hemoglobin proteolysis may be essential for survival, because *P. falciparum* has a limited capacity for *de novo* amino acid synthesis. The genome sequence analysis of *P. falciparum* predicted over 30 cysteine proteases. Among these predicted proteases, four falcipains have been biochemically characterized and closely resembled the papain family. The papain superfamily cysteine proteases are involved in a number of cellular processes and are important virulence factors in the pathogenesis of parasitic diseases. The best characterized function of the cysteine protease family members- falcipain-2 and falcipain-3 is the hemoglobin hydrolysis in erythrocytic trophozoites. These two enzymes are therefore the most relevant therapeutic targets for malaria.

In the present work, we performed molecular modeling studies of the falcipain-3 inhibitors using three-dimensional quantitative structure–activity relationship (3D-QSAR) and docking approaches. Ligand-based 3D-QSAR approach and receptor-based (molecular docking) studies have been found to be important in further development of novel potent inhibitors. Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Indices Analysis (CoMSIA) are two 3D-QSAR methods that have been successfully employed in drug design. CoMFA approach describes the molecular properties by 3D steric and electrostatic fields, evaluated over a lattice of points. Partial Least-Squares (PLS) method is used in order to correlate the variation of these properties with the variation of the biological response. Similar to the usual CoMFA approach, Klebe et al., proposed CoMSIA method. In CoMSIA approach, similarity indices are calculated at regularly placed grid points for the aligned molecules. CoMSIA uses a Gaussian-type distance-dependent function to assess five fields of different physicochemical properties like steric, electrostatic, hydrophobic, hydrogen bond donor and
hydrogen bond acceptor descriptors. Both the 3D-QSAR methods give contour maps as output that can be used to gain general insights into the topological features of the binding site.

In the conventional ligand-based QSAR method, the active conformations are obtained by minimizing the molecules and selecting those with lower energy. While the receptor-based conformation determination by molecular docking takes into account the features of the binding pocket. The ligand based 3D-QSAR and receptor based molecular docking methods are often complementary to each other. The molecular docking of inhibitors into the active site of a protein identifies the binding orientations and the protein-inhibitor interactions responsible for the observed activity. The molecular docking of 2-Pyrimidinecarbonitrile analogs into the active site of falcipain was carried out using GOLD (Genetic Optimization of Ligand Docking) software. The docking conformation with the highest GOLD score was selected as the best pose and these conformations provided binding position and interactions in the falcipain-inhibitor complexes.

Both molecular docking and 3D-QSAR studies rendered complementary information and the 3D contour maps derived from the CoMFA and CoMSIA models provided crucial clues that were used to design (in silico) new molecules with high predicted inhibitory activity.