ABSTRACT

The chronic metabolic Type 2 Diabetes mellitus (T2D) is epidemic disease spread all over world characterized by hyperglycaemia, which is a major risk factor for cardiovascular diseases. Proteases are attractive targets for small molecule drug discovery because of their role in metabolism, immune regulation, signal transduction and apoptosis. Dipeptidyl peptidase IV (DPP4) is serine protease enzyme, involved in the degradation of incretin hormones such as glucagon-like peptide (GLP-1) and glucose-dependent insulino tropic polypeptide (GIP). The inhibition of DPP4 provides a new strategy to prolong the insulino tropic actions of GLP-1 and GIP for the treatment of T2D. Despite intensive efforts for more than two decades relatively very few DPP4 inhibitors have entered into the market and most of them were discontinued from clinical trials because of severe toxicities that are associated with DPP4 isoforms. Hence, the design and development of potent, selective DPP4 inhibitors over DPP8, DPP9 and QPP is a major challenge in current drug discovery.

The aim of this current thesis work could be to lead to a better understanding of the specific concerns on DPP4 activity and selectivity. The understanding of active site residues of DPP4 isoforms, structure activity relationship of inhibitors could help to achieve desired activity, selectivity by introducing specific chemotype with appropriate substitution groups. The purpose of this thesis work is to explore and exploit Molecular modeling approaches such as structure-based design (homology modeling, docking and core hopping), ligand-based design (pharmacophore modeling, QSAR) have been carried out on different classes of DPP4 inhibitors provided substantial design clues for the development of novel, potent, selective DPP4 molecules.