CHAPTER - 3

SCOPE OF WORK
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The current thesis work mainly focused on diabetes and obesity to explore and exploit novel anti-diabetic and anti-obesity molecules. T2D is a chronic metabolic disease, affecting 6% population all over world. The total number of diabetic patients worldwide is projected to increase to 350 million by 2025. In India has a share of 33 million diabetics. It is forecasted that India will have 40 million diabetics by 2010 and 74 million by 2025. The main causes of T2D are insulin resistance and failure of insulin secretion. The raising pandemic of T2D is also caused by increase in obesity among population. Several marketed anti-diabetic drugs are so effective in controlling T2D, though these drugs have several limitations such as low efficacy and more severe complications such as congestive heart failure, pulmonary edema and kidney failure. Also, nearly 30-40% of the patients are not adequately controlled with the existing drugs and requires subcutaneous Insulin injections. Hence there is a need for the development of newer drugs based on the knowledge about key targets involved in the disease to increase their efficiency and reduce severe complications which are related to diabetes. Further, most people who get type 2 diabetes are overweight, and losing weight is often the first step in controlling type 2 diabetes. Therefore there is requirement to address both disease conditions via a single target or combination of targets for which NCE can be designed.

DPP4 is serine protease enzyme regulates incretin hormones (GLP-1 and GIP) and chemokines. Inhibiting DPP4 helps to activate the appropriate physiological responses to food intake by increasing the level of incretins that stimulate insulin secretion; suppressing glucose production, slow digestion and decrease appetite. The knockout mice
experiments were confirmed the involvement of DPP4 in both obesity and diabetes. Hence DPP4 is considered as promising target for both diabetes and obesity. In animal models, long term treatment with DPP4 inhibitors has lead to improved physiological response to glucose and delayed onset of diabetes. In addition to improvement in glucose management and weight management, DPP4 knockout mice did not show any major adverse effect. Several inhibitors were designed and tested for DPP4 activity and checked cross reactivity of DPP4 isoforms such as DPP2, DPP8, DPP9 and QPP. Several clinical candidates of DPP4 were discontinued because of adverse effects associated with DPP4 gene family. Hence, the major concern in development of potent and selective anti-diabetic drugs through DPP4 inhibition is selectivity over other peptidases such as DPP8, DPP9, and QPP. However, comprehensive understanding of active site residues of DPP4 gene related enzymes, structure activity relationship of inhibitors helps to achieve desired selectivity by introducing specific chemotype with appropriate substitution groups.

Rational design of therapeutic agents has gained increased attention and several computational approaches have been attempted in the lead finding and optimization towards different druggable targets. Currently very limited molecular modeling work has been carried on DPP4 target and this information is not sufficient to exploit and explore novel potent DPP4 inhibitors. Hence, the detailed molecular modeling approaches such as structure-based design and ligand-based design have been carried out on different classes of DPP4 inhibitors provided substantial design clues for the development of novel, potent, selective DPP4 molecules.

The DPP8 and DPP9 are known to be monomeric and its three dimensional structure is unknown. Hence the need to develop homology models of DPP8, DPP9 based
on the X-ray crystal structure of DPP4 for investigating activity and selectivity aspects. The sequence alignments could help in identifying template structures for making better homology models. Also the sequence analysis provides valuable information about secondary structure of proteins, ligand binding residues, mutation hotspots and residues important for enzymatic activity. The homology models can be used to identify different binding pockets, putative active site residues, binding mode of different classes of inhibitors and its structure activity relationships. Further, these models can be used to explore the probable ligand-protein interactions to understand the exact mechanism of DPP proteins. The pharmacophore models provide a rational hypothetical picture of the primary chemical features that are responsible for activity. The atom-based 3D-QSAR approach is used to understand steric electrostatic structural features in terms regression maps for better ligand design by introducing appropriate substitution groups. The docking study could help in identifying key amino acid residues that are responsible for gaining DPP4 activity and selectivity. The Molecular modeling approaches can be used to screen large library of molecules for exploring novel compounds.