Preface

Diabetes is a disease characterized by high levels of blood glucose resulting from defects in insulin production, insulin action or both. Type 2 diabetes is typically a polygenic disease that results from a complex interplay between genetic predisposition and environmental factors such as diet, degree of physical activity and age. The long-term effects of elevated blood sugar are damage to the eyes, heart, feet, kidneys, nerves and blood vessels. People with diabetes will increase from 175 million in 2000 to 350 millions in 2030, with the biggest increase expected in India and China. The rising incidence of type 2 diabetes has begun to surface in children at an alarming rate, in some countries representing up to 80% of all the cases of diabetes reported in the pediatric population. These numbers suggest a dramatic increase and alarming health and economic threat due to diabetes particularly in India and China. Therefore there is an urgent requirement to address the unmet medical need in the management of diabetes.

The first chapter of this thesis gives an overview of the role of Dipeptidyl Peptidase-IV (DPP-IV) and its inhibitors in the development of anti-diabetic agents with the main emphasis on the recent developments in this area of study. After brief introduction of the incretins, we have concentrated mainly on different kinds of inhibitors and their clinical status.

The second chapter of the thesis deals with the development of synthetic methodology and biological evaluation of peptidomimetics as DPP-IV inhibitors. The chapter begins with a concise introduction of Valine pyrrolidide as a DPP-IV inhibitor followed by the basis of work. The next section deals with the study of the effect of different amine components in the peptidomimetics containing Val and Ile on the inhibition potential. As our major goal is to enhance metabolic stability, modifications like N-methylation, guanidinylation and thioxylation have been performed and synthesis and characterization of compounds are described followed by the experimental details. The last section of the chapter describes DPP-IV inhibition assay followed by the results and discussion.

In the third chapter, synthesis of dipeptide amides has been described with the objective to compare the effect of Proline and Thiaproline amides on the inhibition potential followed by the discussion on the biological data.
In the fourth chapter, the normal peptide bond, which is susceptible to peptidases has been replaced with modified peptide bond i.e. reduced peptide bond. We have discussed the synthesis of new DPP-IV inhibitors with reduced peptide bond and have chosen four different amino acids and four different amines to explore their effect on inhibition.

The chapter five of the thesis comprises the molecular modeling studies on the pyrrolidine containing derivatives. The beginning of the chapter gives a brief introduction to QSAR and deals with the basic requirements and approaches involved in QSAR studies. In this chapter, we have discussed CoMFA and CoMSIA investigation of the pyrrolidine based analogues as DPP-IV inhibitors.