Just as iron rusts from disuse,  
Even so does inaction spoil the intellect.  

- Leonardo da Vinci

Preface

Diabetes mellitus is a metabolic disease that afflicts around 6% of the world population both in developed and under developed countries. Increasing luxurious life style is an important contributing factor to the disease, spreading with high rapidity and likely to affect 300 million people by the year 2010. Type 2, the most common form of diabetes prevalent both in children and adults, accounts for more than 90% of all diabetes. This is one of the diseases responsible for major health and financial burden to the world community. Currently diet, exercise and oral antidiabetic agents are prescribed for the treatment of disease. Sulfonylurea, metformin and thiazolidinedione are the most important drugs used for the management of type 2 diabetes. However, these therapies are not ideal as they suffer from side effects. Sulfonylureas cause hypoglycemia and extrapancreatic effects that limit their use for the treatment of diabetes. Metformin and thiazolidinedione are associated with side effects of lactic acidosis/weight gain and hepatotoxicity respectively. Thus, there is need to develop drugs free from side effects of hypoglycemia, obesity and hepatotoxicity. Until 1980s antidiabetic compounds used to be discovered through cell assay of molecules obtained by synthesis or isolated from natural sources. Recent advances in molecular pharmacology; proteomics and medicinal chemistry have given better insight of the disease process which led to develop mechanistic approach for drug designing and is a crux of today's drug development.

Recent development in the analytical facilities has dramatically improved the diagnosis and management of the disease. Advent of liquid chromatography based biochemical separation followed by cloning technology during last two decades have made possible to obtain individual drug targets for screening compounds for desired activity. Currently, numerous antidiabetic drug targets such as glucose-6-phosphatase, glycogen synthetase, fructose-1,6-bisphosphatase, glucokinase and protein tyrosinephosphatase 1B (PTP1B) etc are available for in vitro screening. The knowledge of antidiabetic targets and modern techniques such as high throughput screening (HTS) for in vitro evaluation of compounds have expedited the process of drug testing. This in turn is supported by solid phase chemistry and parallel synthesis of compounds that made available enough number of
compounds for HTS. The success of these developments could be realized with the discovery of a potent glucokinase activator RO-28-1675 and PTP1B inhibitor a hydroxamic acid derivative in short span of time. Thus, it is pertinent to focus efforts to develop novel potent antidiabetic drugs with least side effects.

With this objective attempts have been made to synthesize rationally designed efficacious antidiabetic agents with least side effects. The entire work presented in this thesis has been divided into six chapters. The first chapter gives an overview of various approaches and developments for treatment of diabetes mellitus. The second chapter delineates the synthesis and evaluation of rationally designed suitably functionalized quinazolines both in streptozotocin (STZ) and sucrose loaded rat models. Attempts have been also made to establish structure activity relationship. The third chapter of the thesis is devoted on the synthesis of suitably designed various pyrrole derivatives to evaluate their antihyperglycemic activity. Some of the compounds have also been transformed to porphyrins and metalloporphyrins to assess their antidiabetic activity. The chapter 4 describes synthesis of suitably functionalized bicyclic heterobiaryls to explore their glucose-6-phosphatase inhibitory activity. Some of the evaluated compounds displayed significant inhibitory activity. Based on the screening results attempts have been made to establish structure activity relationship. Chapter 5 of the thesis is the synthesis of rationally designed thiouriedo alkanoic acids esters as glucose-6-phosphatase inhibitors to assess their antihyperglycemic activity but only a few of them displayed significant inhibitory property. The chapter 6 delineates diversity oriented synthesis of biaryls to explore their glucose-6-phosphatase inhibitory activity. The screening of the synthesized compounds demonstrated moderate to high level of inhibitory property.