Scope and Plan of Present Investigations
SCOPE AND PLAN OF PRESENT INVESTIGATIONS

According to the recent estimates, the human population worldwide appears to be in the midst of an epidemic of diabetes mellitus in particular of type 2 diabetes mellitus and insulin resistance. Despite the great strides that have been made in the understanding and management of type 2 diabetes mellitus and insulin resistance, diabetes related complications are increasing unabated. Various experimental models for diabetes mellitus are though present for investigators to explore numerous physiological and biochemical defects observed during the progression of disease. Moreover, there will always be physiological, pathological and morphological differences among different animal models of diabetes mellitus. The purpose of present study was to standardize/develop suitable animal models for type 2 diabetes mellitus and insulin resistance which can mimic the disease present in the human being. However, an unavoidable reality is that none of models are perfectly equivalent to the human disease state. Parallel to this, recent developments in understanding the pathophysiology of disease process have opened up several new avenues to identify and develop novel therapies to combat the diabetic plague and insulin resistance by developing new class of agents that have insulin resistant reversal potential. Concurrently, identification of new classes of drugs provides an exciting opportunity for the development of new types of therapeutics management for diabetes mellitus and insulin resistance.

The entire work presented in this thesis has been divided into four chapters. Review of literature for diabetes mellitus, its therapeutics and consequences of alcoholism has been arranged before results and discussion part of the thesis.

The first chapter gives an overview on alcoholism and its impact on carbohydrate metabolism. This chapter deals with effects of alcohol intake on various biochemical serum parameters and on regulatory enzymes of carbohydrate metabolism (glucose-6-phosphatase, glycogen phosphorylase, phosphofructokinase, pyruvate kinase, lactate dehydrogenase, alcohol dehydrogenase and protein tyrosine phosphatase etc.) in insulin sensitive and insulin insensitive tissues (liver, muscle and kidney). Significant alterations in these biochemical parameters upon alcohol feeding to rats are the novel findings. These findings will help in delineating the molecular mechanism(s) caused to insulin sensitivity and insulin resistance in alcoholism. This chapter also contains the details of experimental procedures in the manner as they were carried out in the lab.
The second chapter delineates the evaluation of rationally designed antidiabetic molecules in various animal models for diabetes mellitus and insulin resistance. This chapter details the antihyperglycemic effects of large number of synthetic compounds belonging to various chemical series on postprandial hyperglycemia in normal rats and on sucrose challenged streptozotocin-induced diabetic rats. The compounds, which were showing significant antihyperglycemic activity in these experimental diabetes models, were also tested in db/db mice i.e. animal model for insulin resistance. Identification of few lead antihyperglycemic molecules is the main achievement of this section. This chapter also provide new chemical leads for the development of insulin resistant reversal agents.

The third chapter describes the evaluation of target based design of antidiabetic agents (glucose-6-phosphatase, glycogen phosphorylase and protein tyrosine phosphatase inhibitors). The results demonstrated moderate to high level of inhibitory action by some of the tested molecules; in vivo activity of these lead molecules will be the main achievement of this section.

The chapter four contains the details of insulin resistance in alcoholism. This chapter also devoted on antidiabetic agents which can reverse insulin resistance in alcoholism. Two of the evaluated compounds displayed significant improvement on insulin resistance in alcoholism is the main achievement of this section.

Suffice to say that investigations made in the present study provide an overview of multiple aspects of the pathophysiology of diabetes mellitus and insulin resistance in alcoholism; multi-model therapeutic effect(s) of synthetic compounds as antihyperglycemic and insulin resistant reversal agents.