BRIEF OUTLINE OF THE WORK

As GLP-1 is rapidly inactivated by DPP-IV enzyme, development of inhibitors of this enzyme was explored as a novel approach for the treatment of type 2 diabetes. Various experimental designs have been studied in depth to elucidate and confirm the mechanism of action and role of DPP-IV inhibitors. In the present work entitled “Therapeutic Management of Diabetes And Its Complications With Novel Targets” attempts were made in exploring the therapeutic utility of DPP-IV inhibitors in type 2 diabetes.

Chapter 1 described the general methodologies followed in the experimental sections of the thesis work. All the chemicals, equipment and other research materials utilised in carrying out the experiments were listed along with their source. General experimental procedures like compound preparation, dosing details, blood collection, plasma separation & clinical chemistry analysis, statistical tools employed in the studies undertaken, are outlined.

Proof of concept was established in chapter 2 with in vitro assays for enzyme specificity and selectivity using recombinant enzyme, human and rat plasma. Enzyme kinetic experiments were done to ascertain the nature of GRC 8011 kinetics and its site of binding on DPP-IV enzyme.

Chapter 3 forms the crux of the entire work wherein the test compound was screened in some of the important animal models to support, validate and substantiate the in vitro observations and the mechanism of action of DPP-IV inhibitors. The experiments included oral glucose tolerance test (OGTT) as an acute primary screening model for antihyperglycaemic activity. OGTT was carried out in C57BL/6J mice, a strain that is widely used for such studies. A dose response study was undertaken in this protocol to find out the ED$_{50}$ of GRC 8011. Having established the proof of concept with enzyme specificity and selectivity studies in vitro, pharmacodynamic studies were undertaken to establish a causal relationship between blood glucose and DPP-IV levels and confirm the in vitro findings. As DPP-IV
inhibitors exert their action by increasing/extendng the half life of the incretin hormone GLP-1, there by increasing insulin levels, experiments were conducted to determine the extent of increase in these parameters in blood in an OGTT model in C57BL/6J mice.

Based on the inputs and results obtained from the kinetic studies in rats and the dose-response studies in mice, repeated dose (subacute) experiments were planned in rats that were rendered type 2 diabetic with appropriate protocols. Dose levels in all the subacute experiments were fixed from the inputs obtained from toxicity and single dose efficacy studies.

Chapter 4 describes the pharmacokinetics of GRC 8011 carried out in wistar rats to profile the kinetic parameters of GRC 8011.

Chapter 5 elaborates the toxicity studies conducted in mice with GRC 8011. Acute toxicity study was conducted to explore the toxic potential of the compound. Based on the results obtained from acute toxicity study, three dose levels were chosen to carry out 4-week oral subacute toxicity study in mice. Detailed haematological and biochemical analyses were performed, and morphological and histological examination of vital organs was carried out to forecast on the consequences of long term exposure to the test compound.

GLP-1 agonists slow down gastric emptying, reduce food intake and produce a satiating effect. Chapter 6 examines whether DPP-IV inhibitors, whose mechanism of action is prolongation of half-life of GLP-1 enzyme, would affect food intake, gastrointestinal motility, etc. Attempts have been made to explore the utility of GRC 8011 in obesity and related complications of diabetes.

The thesis work ends with summary and conclusion.