SCIENTIFIC UTILITY OF THE WORK

Type 2 diabetes is associated with insulin resistance in peripheral tissues, impaired glucose-stimulated insulin secretion from pancreatic β-cells and elevated hepatic gluconeogenesis. Current therapeutic approaches do not adequately address the metabolic defects underlying this disease. Thus, novel targets that increase pancreatic β-cell function and glucose-dependent insulin secretion, enhance insulin action at target tissues, stimulate carbohydrate and fat catabolism and decrease endogenous glucose production are being explored at various research centres worldwide. Inhibition of DPP-IV enzyme is one of such targets that enhance insulin secretion. US FDA has recently approved Sitagliptin, a DPP-IV inhibitor, for the treatment of diabetes.

By potentiating incretin activity, DPP-IV inhibitors are likely to be effective in treating mild to moderate diabetes. They enhance concentrations of the active forms of both incretin hormones precisely when they are most needed (i.e. following meal ingestion), resulting in improved postprandial glucose control. Since the actions of both GLP-1 and GIP are glucose dependent, DPP-IV inhibition has the additional advantage that it carries a minimal risk of hypoglycaemia. Further support to this therapeutic approach emerged from studies in animals lacking DPP-IV enzyme and in long term studies involving DPP-IV inhibitors [47,71]. Clinical studies of type 2 diabetes corroborated these findings with improved metabolic control, increased insulin secretion, reduced glucagon secretion, favourable tolerability and safety during a treatment period of up to 1 year [79,80].

All the above findings led to the pursuit of adopting DPP-IV inhibitors for the development of a novel pharmacotherapy for the treatment of type 2 diabetes. At present, the commercially available drugs either enhance insulin secretion (e.g., sulfonylureas) or action (e.g., thiazolidinediones). However, most of these drugs are associated with body weight gain or hypoglycaemia, and are of little value in case of β-cell failure. As a result, newer therapies with better safety and efficacy profiles are being explored. With its novel characteristics in controlling elevated blood glucose
levels in response to nutrient ingestion without causing hypoglycaemia and its positive attributes in a host of associated parameters of interest, GRC 8011, a DPP-IV inhibitor was studied extensively in the current thesis work, and attempts have been made in validating and justifying the scientific utility of work.