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Editors
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CHAPTER 6

RECENT PERSPECTIVES OF CHALCONE-BASED MOLECULES AS PROTEIN TYROSINE PHOSPHATASE 1B (PTP1B) INHIBITORS

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ABSTRACT

Diabetes mellitus (DM) is a heterogeneous group of disorders which is characterized by increased blood sugar level, altered metabolism of lipids, carbohydrates, and proteins and increased risk of complications from vascular disease. Protein Tyrosine Phosphatase 1B (PTP1B) has gained adequate notice due to its crucial role in type 2 diabetes (t2D) and obesity as a negative regulator of the insulin and leptin-signaling pathway. PTP-1B is primarily responsible for dephosphorylation of the insulin receptor and thus down regulates insulin signaling. PTP1B inhibitors are the latest candidate for the management of diabetes, where they prevent dephosphorylation of the insulin receptor and consequently increase insulin level. Natural products have been reported to exhibit promising anti-diabetic activity. Chalcones or 1,3-diphenyl-2*E*-propene-1-one, the open chain intermediate in aurones synthesis of flavones containing benzylideneacetophenone scaffold, where the two aromatic nuclei are joined by a three-carbon α, β

unsaturated carbonyl bridge have shown tremendous PTP1B inhibition. In this chapter, a concrete focus on pharmacology, mechanism of action, and structural aspects along with substituents required for modulating PTP1B has been discussed. Still, none of these inhibitors have gained adequate attention at present and need to be explored and evaluated properly in terms of efficacy and toxicity to develop as therapeutic agents/formulations for the management of diabetes in future.

6.1 INTRODUCTION

Diabetes Mellitus (DM) is a heterogeneous group of disorders which is characterized by increased blood sugar level, altered metabolism of lipids, carbohydrates, and proteins and increased risk of complications from vascular disease [1]. The chronic hyperglycemic conditions are associated with dysfunction and failure of major organs like heart, eyes, nerves, blood vessels and kidneys [2]. The American Diabetes Association (ADA) defines that DM is characterized by polyuria, polydipsia, polyphagia, glycosuria, unexplained weight loss and random plasma glucose concentration of greater than 200 mg/dL along with fasting plasma glucose concentration of greater than 126 mL/dL [3]. Variations in normal glucose homeostasis occur by numerous factors like impaired insulin secretion, hepatic gluconeogenesis and reduced uptake of glucose by skeletal muscle, adipose tissues and liver [4]. In the case of type I diabetes, the body does not produce enough insulin that is required to convert sugar, starches, etc. into energy. Type II diabetes (t2D) is a condition characterized by situation where cells do not properly use insulin as a result of "resistance" [5]. The most prominent features of type II diabetes is decreased sensitivity of muscle and adipose cells to insulin. T2D is often characterized by intrinsic problems like compliance, ineffectiveness and hypoglycemic episodes with insulin and the sulfonylureas. Administration of glitazones are not effective in all t2D patients, therefore, the great need for more effective orally administered agents particularly ones that normalize both glucose and insulin levels still remains a challenge [6]. Insulin is secreted in two discrete phases from pancreatic β-cells which influence the magnitude of both fasting and postprandial blood glucose concentrations. In the beginning, a rapid release of insulin occurs, when the glucose concentration