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In vitro anti-hyperglycemic activity of 4-hydroxyisoleucine derivatives

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ABSTRACT

The nonproteinogenic amino acid, 4-hydroxyisoleucine (**1**) has been isolated in large quantities from the fenugreek (*T. foenum-graecum*) seeds. Few novel derivatives (**3**–**11** and **13**–**18**) were prepared from the naturally occurring 4-hydroxyisoleucine (**1**) and screened for their *in vitro* glucose uptake stimulatory effect in L-6 skeletal muscle cells. The derivatives **6**, **7**, **8**, **10** and **11** exhibited better glucose uptake stimulatory activity than parent compound, 4-hydroxyisoleucine at 5 and 10 μM concentrations and compounds **7** and **11** enhanced translocation of insulin sensitive glucose transporters-4 in skeletal muscle cells.

Introduction

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both (Mitra, 2008). The chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys and nerves, as well as an increased risk for cardiovascular disease (CVD). It affects all age group worldwide. In 1985, an estimated 30 million people around the world were diagnosed with diabetes; in 2000, that figure rose to over 150 million; and in 2012, the International Diabetes Federation (IDF) estimated that 371 million people had diabetes (International Diabetes Federation, 2012, www.idf.org/diabetesatlas). That number is projected to rise up to 552 million (or 1 in 10 adults) by 2030, which equates to 3 new cases per second (International Diabetes Federation, 2012, www.idf.org/diabetesatlas).

The main pathophysiological feature of type 2 diabetes mellitus is insulin resistance, characterized by reduced ability of target tissues, such as the liver, skeletal muscle, and adipose, to respond to insulin (Reaven, 1995). This includes impairment in the insulin stimulated translocation of GLUT4 to cell surface and resulting defect in insulin-stimulated glucose uptake in peripheral tissues like skeletal muscle and fat. Hence, interventions with ability to stimulate glucose uptake might be important for the treatment of diabetes mellitus. Although numerous oral anti-hyperglycemic drugs exist along with insulin, there is no promising therapy for type 2 diabetes mellitus.

Natural products have played a key role in the discovery of antidiabetic drugs (Fig. 1) (Kanaujia et al., 2010) Metformin is currently used as antidiabetic agent in the treatment of type 2 diabetes. Metformin and its analogues (Shapiro et al., 1959) were synthesized on the basis of a natural product lead, that is, galegine (Bailey and Day, 1989). Acarbose, a complex of oligosaccharides isolated from *Actinoplanes* sp., was discovered by Bayer pharmaceuticals for a search of α-glucosidase inhibitors (Shu, 1998). Acarbose is an antidiabetic agent to treat type 2 diabetes. Few plant-derived unusual amino acids have been reported for their anti-hyperglycemic activity. Hypoglycin A and B isolated from the fruits of *Blighia sapida*, which are chemically related to lysine were reported for their anti-hyperglycemic activity (Hassall and Reyle, 1954; Feng and Patrick, 1958). Enormous amount of research work is going on 4-hydroxyisoleucine (4-HIL), due to its broad range of pharmaceutical activities as insulinotropic, anti-dyslipidemic, and anti-hyperglycemic agent (Sauvaire et al., 1998; Narender et al., 2006)

The 4-hydroxyisoleucine was first isolated as free acid from fenugreek (*T. foenum-graecum*) seeds (Fowden et al., 1973) and structure was validated by X-ray crystallography (Alcock et al., 1989), establishing the absolute stereochemistry as 2S, 3R, 4S. Further, the SAR studies indicated that the absolute configuration

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