Abstract

Various novel derivatives of substituted thiazolidine and pyrrolidine were designed and synthesized as Dipeptidyl peptidase-IV (DPP-IV) inhibitors. Based on the in vivo DPP-IV activity, selected molecules were further evaluated for their ADME profiling and oral activity in various animal models. TRC8156 (IC50=10 µM) has shown good in vivo profile at 30 µM/kg dose level. TRC 8156 has been found potent, selective, competitive, reversible, 1,2,3-triazole substituted pyrrolidine DPP-IV inhibitor. Several in vitro and in vivo studies have been conducted to confirm its in vivo activity and selectivity. TRC8156 has been found to be orally bioavailable and active in various animal models. The development of TRC8156 has been focused on its ADME and in-vivo profile in various animal models. TRC8156 (IC50= 88 nM) has shown good in-vivo profile and potency in various animal models.

1. Introduction

Diabetes mellitus is a metabolic condition in which the body fails to produce enough insulin or the action of insulin is reduced. Glucagon like peptide (GLP-1), produced by L-cell in distal small bowel, stimulates glucose dependent insulin secretion. However, as effects are achieved as a result of signal transduction by Dipeptidyl peptidase-IV (DPP-IV) the mechanism of inactivation action of DPP-IV involves interaction with a specific receptor belonging to the glucagon family of G-protein coupled receptor located on the pancreatic tissue, which results in increase in AMP in results in increased insulin release. DPP-IV is known to cause little action without the glycogen when given to insulin sensitive normal weight animals. DPP-IV is an abundant and widely distributed serine protease. It is located on endothelial cells of the blood vessels and other tissue. It is present at very high levels in the heart and lungs, and in lower levels in the liver and kidneys. It plays a major role during glucose metabolism and the control of blood glucose levels. It can lead to diabetes mellitus, where the body fails to produce enough insulin or the body becomes resistant to its effects. DPP-IV inhibitors have many advantages like increased insulin release and suppressed glucagon release in a glucose-dependent manner. Hence the prior studies of this type of hypoglycemic effect and weight gain that were observed with other dipeptidyl peptidase-IV inhibitors (DPP-IV).

Since the knowledge of the rapid inactivation of GLP-1 by DPP-IV was established in mid 1990s, the widely accepted strategy is to develop an oral drug as DPP-IV inhibitor. There are several orally available DPP-IV inhibitors that are commercially available. GLP1R agonists have been developed, but their pharmacokinetic profile is not ideal and they are only used in conjunction with a DPP-IV inhibitor. Less attention has been given to the development of novel DPP-IV inhibitors. DPP-IV inhibitors have been rationally designed and synthesized as DPP-IV inhibitors. These in vitro and in vivo studies have been conducted to confirm its in vivo activity and selectivity. TRC8156 has been found to be orally bioavailable and active in various animal models. The development of TRC8156 has been focused on its ADME and in-vivo profile in various animal models. TRC8156 (IC50= 88 nM) has shown good in-vivo profile and potency in various animal models.

2. Design and Synthesis

We have designed compounds based on the structural similarity of known ligands. Fig. 2 shows a typical mechanism of enzyme. We have considered various molecules for designing the compounds like, pseudopeptides, pseudosugars, acylated pseudosugars, and thiazolidines. The hypothesis is that pyrrolidine, sulfonyl, and thiazolidine are the pharmacophoric elements in novel designed pyrrolidine DPP-IV inhibitors. We have designed novel pyrrolidine DPP-IV inhibitors, and synthesized several other DPP-IV inhibitors are in the advanced development stage and some of them are selected to be tested in vivo and structure is shown in Fig. 1.

3. Results and Discussions

The in vitro DPP-IV activity of all the synthesized compounds was evaluated in the Hela cell assay. Comparative data for a series of DPP-IV inhibitors were presented in Table 1. Structure activity relationship of synthesized compounds has been described in Fig. 3. TRC8156 was found potent, selective, competitive, reversible DPP-IV inhibitor. It has excellent in vivo activity and high selectivity for its ADME and in-vivo profile in various animal models. TRC8156 was selected to be tested in safety evaluation as shown in Table 2. TRC8156 was found orally bioavailable and active in various animal models. TRC8156 has been found to be orally bioavailable and active in various animal models.