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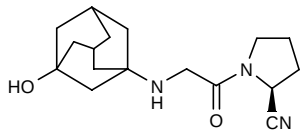
Vildagliptin

Prop INN

Agent for Type 2 Diabetes
Dipeptidyl-Peptidase IV Inhibitor

LAF-237
NVP-LAF-237

1-[2-(3-Hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2(*S*)-carbonitrile



$C_{17}H_{25}N_3O_2$

Mol wt: 303.4035

CAS: 274901-16-5

EN: 291074

Abstract

Type 2 diabetes is characterized by chronic hyperglycemia due to the body's progressive inability to efficiently utilize insulin. The majority of individuals who develop this form of diabetes will eventually require drug therapy to control the disease and minimize the risk of complications. The incretin hormone glucagon-like peptide-1 (GLP-1) has a spectrum of effects that mimic the requirements of antidiabetic therapy. This serine protease is degraded by the enzyme dipeptidyl-peptidase IV (DPP-IV), and the development of inhibitors of this enzyme has been a recent focus in diabetes research. Vildagliptin is a highly selective, orally active DPP-IV inhibitor. In obese, fatty Zucker rats, vildagliptin significantly decreased glucose excursions and stimulated insulin secretion following a glucose challenge. Long-term metabolic control and cardiovascular risk factors were also shown to improve in obese, insulin-resistant cynomolgus monkeys. Clinical studies in patients with type 2 diabetes have demonstrated significant decreases in fasting plasma glucose and 24-h mean glucose in patients receiving vildagliptin compared to placebo-treated patients. Significant improvement in the rates of change in HbA1c compared to placebo following treatment for 1 year provided evidence for a role for vildagliptin in modifying the progression of type 2 diabetes. The drug is well tolerated, and pharmacokinetic studies have indicated that it can be safely coadministered with glibenclamide with no need for dose adjustment. Vildagliptin is currently in phase III clinical development.

Synthesis

Reaction of adamantan-1-amine (I) with HNO_3 and H_2SO_4 gives 3-nitroadamantan-1-amine (II), which is hydrolyzed with KOH in hot water to yield 3-hydroxyadamantan-1-amine (III). On the other hand, reaction of chloroacetyl chloride (IV) with L-prolinamide (V) by means of K_2CO_3 in THF gives 1-(chloroacetyl)-L-prolinamide (VI), which is treated with trifluoroacetic anhydride in THF to yield the corresponding nitrile (VII). Finally, 3-hydroxyadamantan-1-amine (III) is condensed with 1-(chloroacetyl)-L-prolinenitrile (VII) by means of K_2CO_3 in dichloromethane (1, 2). Scheme 1.

Introduction

Diabetes is a group of diseases characterized by chronic hyperglycemia. Adult-onset or type 2 diabetes (formerly known as non-insulin-dependent diabetes mellitus, or NIDDM) accounts for over 90% of the diabetic population in developed countries, and although a genetic predisposition to the disease is a predominant factor in its development, lifestyle factors also contribute significantly. Individuals who develop type 2 diabetes are progressively less able to efficiently utilize insulin produced by the β-cells of the pancreas. Diet and exercise may initially improve glycemic control, but 90% of patients will eventually require pharmacological intervention (3).

One area of focus in the development of drugs for the treatment of type 2 diabetes is the hormonal regulation of insulin secretion. The naturally occurring incretin hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) are potent insulinotropic hormones which are vital in the control of glucose homeostasis. GLP-1 stimulates the body's ability to produce insulin in response to raised blood glucose levels, inhibits the release of glucagon following meals and slows the rate of nutrient absorption into the bloodstream. The development of type 2 diabetes may be slowed, or even

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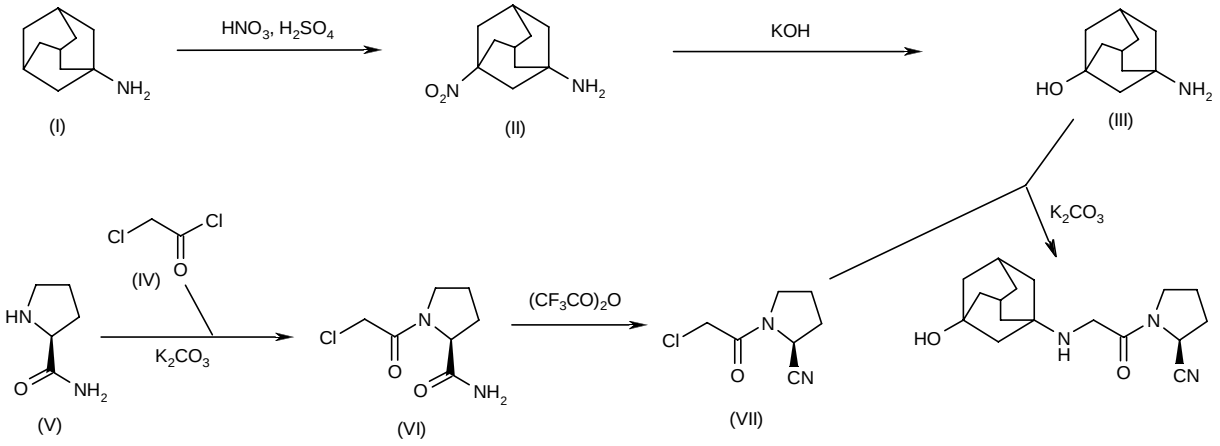
Scheme 1: Synthesis of Vildagliptin



prevented, by extending the duration of action of endogenous GLP-1. The serine protease dipeptidyl-peptidase IV (DPP-IV) inactivates GLP-1, and acts as a catalyst in the processes of signal transduction during the immune response leading to the development of type 2 diabetes. By preserving GLP-1 levels, DPP-IV inhibition stimulates insulin gene expression and biosynthesis and increases the expression of the glucose-sensing mechanism in β-cells. It also promotes genes involved in the differentiation of β-cells and may play a role in mediating peripheral glucose uptake (3-10).

Vildagliptin (NVP-LAF-237, LAF-237; Novartis) is a potent, selective, stable, orally active DPP-IV inhibitor with antihyperglycemic properties, currently in phase III clinical trials as a potential new treatment for type 2 diabetes.

Pharmacological Actions

In vitro DPP-IV inhibition and selectivity assays were performed with extracts from human colon carcinoma Caco-2 cells and using human, rat and monkey plasma as the source of DPP-IV. In the primary assays, vildagliptin demonstrated potent inhibition of DPP-IV enzyme activity, with an IC_{50} value of 3.5 nM in the Caco-2 cell assay and values of 2.3 and 2.7 nM in the rat and human plasma assays, respectively. Vildagliptin was highly specific for DPP-IV, showing > 75,000-fold selectivity relative to other enymes profiled. No significant binding was observed at 10 μM in over 100 other receptor and enzyme assays (1, 11).

The effect of vildagliptin on DPP-IV activity, active GLP-1 levels and glucose and insulin excursions was studied in obese Zucker (*fa/fa*) rats, a model of type 2 diabetes. In an oral glucose tolerance test, conducted over 90 min, plasma DPP-IV activity was inhibited by over 90% within 10 min and throughout the study following a single oral dose of 10 μmol/kg. Rats treated with vildagliptin exhibited GLP-1 levels 60% higher than those of vehicle-treated controls immediately prior to glucose challenge. Following the challenge, GLP-1 levels peaked at 5 min and were almost 5 times the levels observed in the control group (13.5 pM *vs.* 2.8 pM). Vildagliptin also significantly decreased glucose excursions and stimulated insulin secretion following the glucose challenge. Plasma insulin levels peaked at 15 min at twice those of vehicle-treated controls, and returned to baseline levels after 45 min. The glucose-stimulated insulin release index was approximately 5-fold greater in vildagliptin-treated rats (1, 11).

Further studies in GK rats, a model of moderate type 2 diabetes, have confirmed the effects of vildagliptin on glucose tolerance. In GK rats treated with vildagliptin 10 mg/kg twice daily for 8 weeks, a significant reduction in glucose AUC was observed during an oral glucose tolerance test compared with vehicle-treated controls. However, there was no improvement in diurnal glycemia after 4 weeks of treatment, nor any significant decrease in glycated hemoglobin (HbA1c) after 8 weeks in rats treated with vildagliptin. In addition, no differences in food intake or body weight were observed (12). The lack of effect of vildagliptin on caloric intake and body weight was confirmed in another study in obese candy-fed rats (13).

Zucker diabetic fatty (ZDF) rats were administered vildagliptin at a dose of 10 mg/kg twice daily for 3 weeks. These rats demonstrated a significant reduction in blood glucose levels during an oral glucose tolerance test following the first dose compared with vehicle-treated rats (1086 mmol/l/min *vs.* 1246 mmol/l/min). However, after 3 weeks, no differences in glucose AUC were observed, although plasma DPP-IV activity was significantly reduced and there was a significant 2-fold increase in intact GLP-1 levels in rats treated with vildagliptin compared with vehicle-treated controls. This study indicated

that vildagliptin was unable to prevent the progression of diabetes in these rats, also shown by its lack of effect on HbA1c levels, food intake or body weight (14).

Vildagliptin was then investigated in combination with pioglitazone, an insulin sensitizer. Obese Zucker rats were administered vildagliptin 3 mg/kg p.o. 4 times daily, either alone or in combination with pioglitazone, for 10 days. During an oral glucose tolerance test, vildagliptin increased glucose-stimulated insulin release by 87%. Although by itself it had no significant effect on the glucose excursion, the combined effect of vildagliptin and pioglitazone reduced the glucose excursion by 61% compared to vehicle-treated rats, resulting in glucose levels equivalent to normal, insulin-sensitive lean rats. The combined treatment also significantly increased the glucose clearance rate and rapidly restored glucose levels to normal, whereas vildagliptin alone had no effect on the glucose clearance rate (15).

The effects of vildagliptin on glucose and insulin responses to a glucose challenge have also been studied in mouse models of diabetes. In *ob/ob* mice treated with a single dose of vildagliptin (5 mg/kg), plasma insulin was elevated 4-fold at 15 min after glucose challenge. The glucose excursion was minimized under both glucose and saline challenge conditions, as shown by an approximate 15% rise in peak plasma glucose levels following glucose challenge in vildagliptin-treated mice, compared with a 60% rise in the vehicle-treated group. Following saline challenge, glucose levels fell by over 40% in mice treated with vildagliptin. In this study, as well as another experiment in C57 mice, administration of vildagliptin (3 mg/kg) significantly suppressed DPP-IV activity during an oral glucose tolerance test (16, 17).

Cynomolgus monkeys were used to assess the acute and chronic effects of vildagliptin. In the acute administration study, oral glucose tolerance tests were performed 3 weeks apart in anesthetized, obese, insulin-resistant monkeys. Prior to the tests, monkeys were administered vildagliptin (1 μmol/kg) or vehicle. Following the glucose challenge, peak plasma GLP-1 levels were significantly greater in animals treated with vildagliptin compared with vehicle-treated controls. The glucose excursion was also significantly decreased (15%) in vildagliptin-treated animals. In addition, these animals exhibited a 35% reduction in gastric emptying during the oral glucose tolerance test (18).

The effect of vildagliptin on metabolic control and cardiovascular risk factors was investigated in obese, insulin-resistant cynomolgus monkeys that were either normoglycemic or had established diabetes and were receiving insulin therapy. Vildagliptin (1 μmol/kg once daily) was administered for 10 weeks. At the end of the study, all animals demonstrated a significant decrease in HbA1c, which was more pronounced in the diabetic group. Fasting plasma insulin was also significantly reduced, more so in the nondiabetic group, and there was a trend towards a decrease in fasting plasma glucose. Risk factors for the development of diabetic complications, *i.e.*, plasma fibrinogen and plasminogen activator inhibitor-1 (PAI-1), were also significantly reduced at 10 weeks (10% and 30%, respectively) (19).

Pharmacokinetics and Metabolism

Pharmacokinetic and pharmacodynamic studies were performed in anesthetized cynomolgus monkeys administered vildagliptin 1 μmol/kg by oral gavage or 0.4 μmol/kg i.v. The absolute oral bioavailability was > 90%. The peak plasma concentration (C_{max}) following the oral dose was 293 nM at 72 min, with a terminal elimination half-life of 90 min. Maximal inhibition (approximately 95%) of plasma DPP-IV activity was observed at 2 h postdose and > 50% inhibition persisted for at least 10 h, consistent with a once-daily dosing regimen (1).

Clinical Studies

The risk of reactive hypoglycemia in subjects administered glibenclamide and vildagliptin, and the effect of the combined administration on levels of GLP-1 and GIP, were investigated in a randomized, double-blind, crossover study in 16 healthy male subjects. Although the minimal glucose concentration during an oral glucose tolerance test was significantly lower when glibenclamide was given, the combination of vildagliptin and glibenclamide did not significantly increase the risk of hypoglycemia. The incremental responses of total GLP-1 and GIP to an oral glucose load were significantly reduced by vildagliptin alone, but not by glibenclamide alone, and there was no interaction when the treatments were combined (20, 21).

The potential for a pharmacokinetic interaction or acute clinical safety issues with the combined administration of vildagliptin and glibenclamide was also examined in 15 patients with type 2 diabetes in a randomized, crossover study. Following 5 weeks' treatment with glibenclamide alone, patients received either vildagliptin 100 mg twice daily or placebo for 28 days. Glibenclamide treatment was continued throughout the crossover period, and vildagliptin was administered alone for the final 5 days of the study. No pharmacokinetic interactions were observed; peak plasma concentrations, AUC values and half-lives of the compounds were not significantly affected when given in combination. The combined therapy was also well tolerated, with no hypoglycemic events. The study supported the combined therapy of both agents without the need for dose adjustment (22).

The effect of vildagliptin on model-assessed β-cell function was evaluated in 9 patients with type 2 diabetes not previously treated with oral agents. Patients were treated with vildagliptin 100 mg twice daily or placebo for 28 days. At the end of the treatment period, plasma levels of intact GLP-1 and GIP had more than doubled in the active treatment group, and fasting plasma glucose and 24-h mean glucose were significantly decreased compared to placebo-treated patients. The β-cell response to

glucose was amplified by vildagliptin, as shown by a significantly higher insulin secretion rate at each glucose level, although β-cell sensitivity was not significantly affected. The study demonstrated improved β-cell function via enhanced secretory tone (23).

A randomized, double-blind, crossover trial was conducted in 12 patients with type 1 diabetes treated by insulin pump to assess the mechanism of suppression of postprandial glucagon secretion by vildagliptin. Patients received vildagliptin 100 mg twice daily or placebo for 28 days. Vildagliptin significantly reduced the postprandial glucose exposure in the first 2 h (12%) and overall glucose exposure (10%). These findings indicated that the glucagonostatic effect of vildagliptin was mediated via an endocrine effect, rather than being dependent on endogenous insulin secretion (24).

The effects of vildagliptin were assessed in a multicenter, double-blind trial in 40 patients with type 2 diabetes controlled by diet alone. The patients received vildagliptin 100 mg/day or placebo for 4 weeks. At the end of the treatment period, postprandial active GLP-1 was significantly increased, and fasting and postprandial glucose was significantly reduced. Insulin secretion was maintained despite lower glucose levels. Vildagliptin was well tolerated, and the study demonstrated its ability to improve metabolic control in this group of patients (25).

A double-blind, placebo-controlled study was also conducted in 100 previously untreated patients with type 2 diabetes. Patients in the vildagliptin-treated group (n=72) received 25 mg twice daily for 12 weeks. There was a significant decrease in HbA1c from baseline to endpoint in patients treated with vildagliptin compared with placebo-treated patients. Patients with a higher HbA1c at baseline (8-9.5%) had a greater response relative to placebo (–1.2%), and 47% of patients treated with vildagliptin with a baseline HbA1c > 7% had values below 7% at the end of the study. Fasting plasma glucose and 4-h mean postprandial glucose decreased significantly, and the insulin response corrected for peak glucose and 4-h mean postprandial C-peptide levels increased significantly in patients taking vildagliptin relative to placebo. Adverse events with a suspected relationship to study treatment were reported by 15.7% and 10.7% of patients in the vildagliptin and placebo groups, respectively. The study further demonstrated the safety and efficacy of vildagliptin as monotherapy in patients with type 2 diabetes (26).

The long-term efficacy of vildagliptin was evaluated in patients with type 2 diabetes inadequately treated with metformin. An initial 12-week study was extended for 40 weeks, and HbA1c was measured periodically over the 52-week period. Patients continued to receive metformin at a dose of 1500-3000 mg/day, and additionally received either vildagliptin 50 mg 4 times daily or placebo. In the first 12 weeks of the study, fasting plasma glucose, mean postprandial glucose and peak postprandial glucose excursions were significantly reduced in patients taking vildagliptin compared to those in the placebo group. Mean baseline HbA1c was 7.6% in the vildagliptin group and 7.8% in the placebo group. This had increased to 8.3% in the placebo group at week 52, with a rate of increase from week 12 to week 52 of 0.0656% per month. The mean HbA1c from week 12 to week 52 in the vildagliptin group was 7.1%; the rate of change was significantly less than in the placebo group, and not significantly different from zero. The percentage of patients with a baseline HbA1c of at least 7.0% who achieved an endpoint value of < 7.0% was 41.7% in the vildagliptin group compared with only 10.7% in the placebo group. Vildagliptin was generally well tolerated, and the study indicated that the drug may play a role in modifying the progression of type 2 diabetes (27-29).

During the first quarter of 2004, vildagliptin advanced into phase III clinical development (30).

Source

Novartis AG (CH).

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