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Alogliptin Benzoate

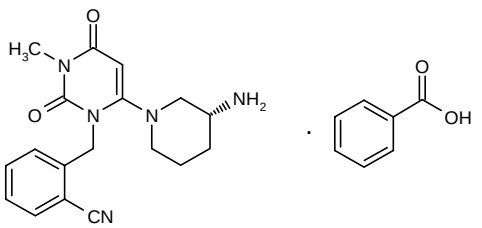
Dipeptidyl-Peptidase IV (DPP IV) Inhibitor
Treatment of Type 2 Diabetes

Prop INNM; USAN

SYR-322

2-[6-[3(*R*)-Aminopiperidin-1-yl]-3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-ylmethyl]benzonitrile benzoate

InChI=1/C18H21N5O2.C7H6O2/c1-21-17(24)9-16(22-8-4-7-15(20)12-22)23(18(21)25)11-14-6-3-2-5-13(14)10-19;8-7(9)6-4-2-1-3-5-6/h2-3,5-6,9,15H,4,7-8,11-12,20H2,1H3;1-5H,(H,8,9)/t15-;/m1./s1



$C_{25}H_{27}N_5O_4$
Mol wt: 461.5132

CAS: 850649-62-6

CAS: 850649-61-5 (free base)

EN: 405286

Abstract

The prevalence of type 2 diabetes is rapidly increasing and currently available medications for the treatment of type 2 diabetes are commonly associated with secondary failure. Alogliptin (SYR-322), a potent, highly selective inhibitor of the serine protease dipeptidyl-peptidase IV (DPP IV), is a new investigational drug developed for the treatment of type 2 diabetes. Orally administered alogliptin demonstrated antidiabetic effects in preclinical studies in mice, rats, dogs and monkeys, as well as a good safety profile. Early clinical studies demonstrated that alogliptin can be safely co-administered with antidiabetic drugs such as pioglitazone, glyburide, metformin and warfarin without the need for dose adjustment. Alogliptin also demonstrated efficacy in reducing glucose and increasing insulin levels and proved to be well tolerated in healthy subjects and patients with type 2 diabetes. Global phase III clinical trials of alogliptin as monotherapy and in combination with other antidiabetic drugs for the treatment of type 2 diabetes are currently ongoing, and an NDA was recently submitted to the FDA.

Synthesis*

Alogliptin benzoate can be prepared as follows. 6-Chlorouracil (I) is alkylated with 2-(bromomethyl)benzonitrile (II) in the presence of NaH and LiBr in DMF/DMSO to produce the *N*-benzyluracil derivative (III), which is further alkylated with iodomethane and NaH in DMF/THF to yield the 1,3-disubstituted uracil (IV) (1-3). Intermediate (IV) is alternatively obtained by alkylation of 6-chloro-3-methyluracil (V) with 2-(bromomethyl)benzonitrile (II) by means of diisopropylethylamine in hot NMP (3). Subsequent displacement of chlorouracil (IV) with 3(*R*)-aminopiperidine dihydrochloride (VI) in the presence of either $NaHCO_3$ in hot methanol or K_2CO_3 in aqueous isopropanol provides alogliptin (1-3), which is isolated as the corresponding benzoate salt by treatment with benzoic acid in ethanol (3). Scheme 1.

Background

Diabetes affects millions of people worldwide and is considered one of the main threats to human health in the 21st century. In 2006, the World Health Organization (WHO) estimated that over 180 million people worldwide had diabetes, and the number is projected to double by 2030. Over time, uncontrolled diabetes can damage body systems, including the heart, blood vessels, eyes, kidneys and nerves. According to the WHO, approximately 1.1 million people died from diabetes in 2005, and it is estimated that diabetes-related deaths will increase by more than 50% in the next decade. Globally, the socioeconomic burden of diabetes is substantial (4-6).

There are two main types of diabetes, type 1 and type 2 diabetes. Type 2 diabetes accounts for over 90% of all diabetes cases globally. Type 1 diabetes is characterized by insulin deficiency, primarily caused by autoimmune-

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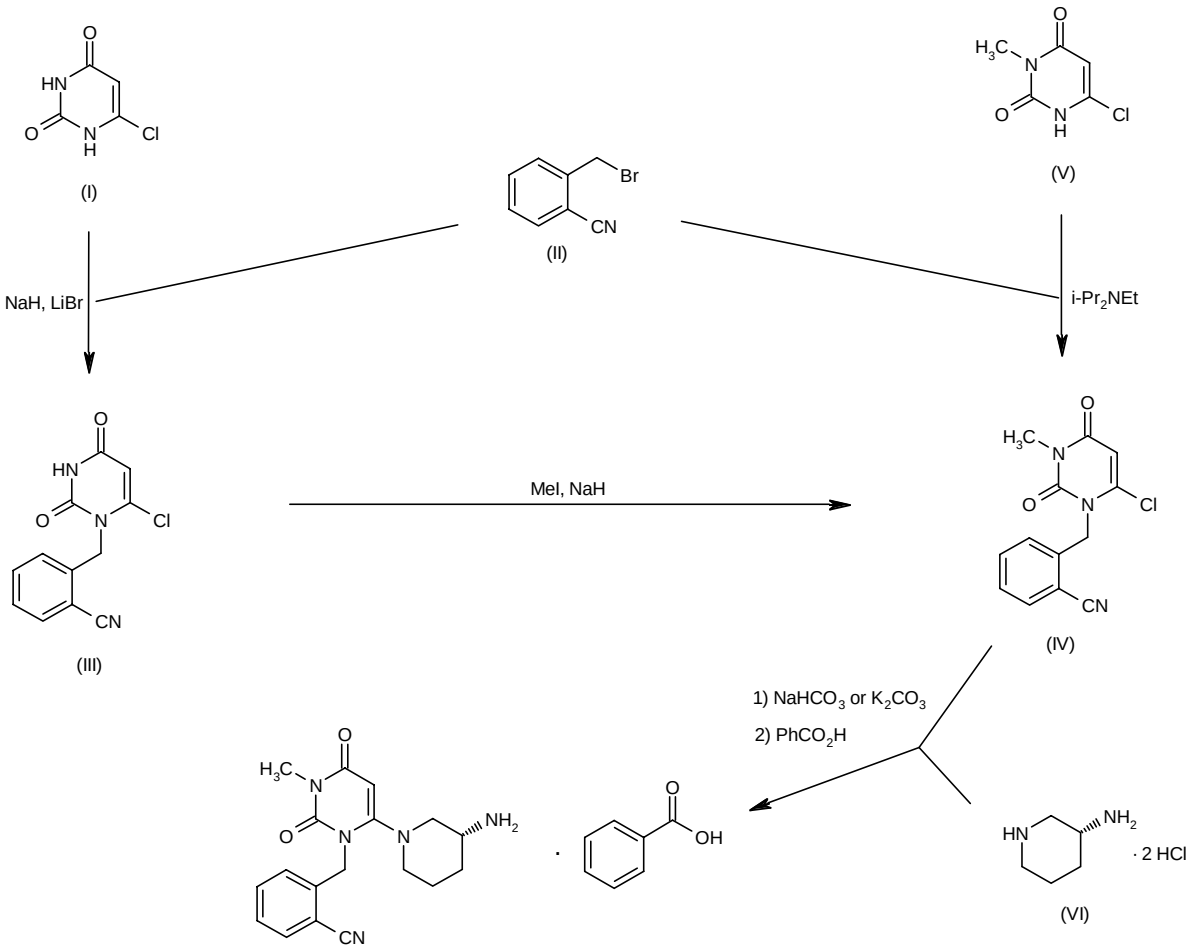
Scheme 1: Synthesis of Alogliptin Benzoate



mediated destruction of pancreatic islet β-cells, and type 2 diabetes is characterized by abnormal insulin secretion and concomitant insulin resistance (4, 5, 7). To prevent the development of ketoacidosis, people with type 1 diabetes must take exogenous insulin for survival. Although those with type 2 diabetes are not dependent on exogenous insulin as much as subjects with type 1 diabetes, they may require exogenous insulin to control blood glucose levels (4).

As diabetes has become a global health concern, research interest in the condition has rapidly increased. In addition to studies on prevention, many studies with the aim of developing new interventions for the treatment of diabetes, especially type 2 diabetes, have been conducted (4, 8). Currently available medications for the treatment and management of type 2 diabetes include metformin, sulfonylureas, thiazolidinediones and insulin. However, these therapies are commonly associated with secondary failure and may cause hypoglycemia (9). Insulin resistance and progressively worsening hyperglycemia caused by reduced β-cell function are major challenges in managing type 2 diabetes (10).

Evidence suggested that patients with insulin resistance do not develop hyperglycemia until their β-cells are unable to produce enough insulin. New agents that can enhance insulin secretion from islet β-cells in a sustained glucose-dependent manner could therefore hold promise for the treatment of type 2 diabetes. One promising approach is based on inhibition of the serine protease dipeptidyl-peptidase IV (DPP IV), a postproline dipeptidyl aminopeptidase that belongs to the S9b peptidase family of proteolytic enzymes. It is known that DPP IV plays a key role in maintaining glucose homeostasis by controlling the incretin activity of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP, also known as gastric inhibitory polypeptide). Preclinical studies have shown that inhibition of DPP IV can increase endogenous concentrations of GLP-1 and GIP, enhance insulin secretion and improve glucose tolerance. In addition, studies have shown that a selective inhibitor of DPP

IV can improve plasma glucose concentrations in patients with type 2 diabetes. Inhibition of DPP IV is therefore recognized as a novel therapeutic approach for the treatment of type 2 diabetes (11).

With the assistance of structure-based design and optimization, the Takeda subsidiary Takeda San Diego (formerly Syrrx) developed a series of small molecules with a heterocyclic structure, known as the SYR series of compounds, as DPP IV inhibitors. Among these highly potent compounds, alogliptin benzoate (SYR-322) demonstrated encouraging antidiabetic efficacy in early studies. Oral alogliptin is currently undergoing phase III clinical development for the treatment of type 2 diabetes (2, 12, 13).

Preclinical Pharmacology

Alogliptin inhibited DPP IV with an IC_{50} of 7 nM. The agent also proved highly selective relative to DPP II, DPP VIII, DPP IX, PREP, FAP/seprase and tryptase. The mean peak inhibition of DPP IV in rats after a single dose of 10 mg/kg was > 85% and inhibition lasted for over 12 h. The mean peak inhibition of DPP IV in dogs after a single oral dose of alogliptin (3 mg/kg) was > 95%, maximum inhibition being observed at 0.5 h and significant inhibition being sustained through 12 h postdosing. The mean peak inhibition after a single oral dose of alogliptin (2-30 mg/kg) in monkeys was > 80 and nearly maximum inhibition of DPP IV was observed at 24 h postdosing. Improvement in glucose tolerance and increase in plasma insulin levels were observed in C57BL6 mice administered a single oral dose of alogliptin (14).

The antidiabetic effects of oral alogliptin were first evaluated in *ob/ob* mice, a model of type 2 diabetes. The animals received alogliptin mixed with the diet once daily for 4 weeks. Alogliptin inhibited plasma DPP IV activity in a dose-dependent manner (24% and 62%, respectively, at doses of 2.8 and 14.1 mg/kg/day). Doses of 2.8 and 14.1 mg/kg/day also increased active GLP-1 by approximately 2.3- and 5.3-fold, respectively. Moreover, alogliptin decreased glycosylated hemoglobin (HbA1c; 0.4% and 0.7%, respectively, for doses of 2.8 and 14.1 mg/kg/day), glucagon (26% and 23%, respectively, for doses of 2.8 and 14.1 mg/kg/day) and plasma triglycerides (51% and 42%, respectively, for doses of 2.8 and 14.1 mg/kg/day), and increased plasma insulin and pancreatic insulin content by 1.5- and 1.9-fold, respectively (15, 16).

The effects of oral alogliptin on glucose tolerance and β-cell function were further studied in *ob/ob* mice. In this study, the mice received a higher dose of alogliptin (42.2 mg/kg/day) for 4 weeks. After 4 weeks, alogliptin decreased plasma DPP IV activity by 80% and increased plasma and pancreatic insulin content by 2- and 2.5-fold, respectively. In addition, alogliptin decreased HbA1c and glucose AUC by 0.9% and 25%, respectively. Compared to untreated mice, animals treated with alogliptin showed increased insulin staining in β-cells, indicating improved β-cell function. Treatment with alogliptin did not influence body weight or food consumption. Preclinical studies conducted in *ob/ob* mice therefore suggest that treatment with alogliptin may lead to effective glycemic control and β-cell preservation (15, 16).

In further studies in *ob/ob* mice, combination of alogliptin (41.5 mg/kg/day) and pioglitazone (4.1 mg/kg/day) once daily in the diet for 4 weeks was associated with enhanced glycemic control (17).

The effects of alogliptin on β-cell function were also evaluated in a rat model of sulfonylurea-induced secondary failure (neonatally streptozotocin-injected diabetic Wister-Kyoto rats [N-STZ-1.5 rats] with glibenclamide-induced secondary failure). A single dose of alogliptin (1 mg/kg) significantly decreased glucose excursions and stimulated insulin secretion, similar to in N-STZ-1.5 rats without sulfonylurea-induced secondary failure, whereas single doses of glibenclamide (10 mg/kg), a sulfonylurea, or nateglinide (50 mg/kg), a nonsulfonylurea insulin secretagogue, had no effect (18).

The efficacy of alogliptin alone or in combination with pioglitazone, a thiazolidinedione, was assessed in diabetic rodent models. In N-STZ-1.5 rats, treatment with alogliptin for 4 weeks significantly reduced HbA1c and significantly increased pancreatic insulin content, with a minimum effective dose of 3 mg/kg/day. In male *db/db* mice, concomitant treatment with alogliptin (56.5 ± 3.1 mg/kg/day) and pioglitazone (14.1 ± 0.8 mg/kg/day) mixed with the diet for 3 weeks led to synergistic effects; concomitant treatment significantly decreased plasma glucose concentrations (239 ± 81 mg/dl for the treated group *vs.* 499 ± 59 mg/dl for controls) and significantly increased pancreatic insulin content (200 ± 138 ng/mg for the treated group *vs.* 44 ± 17 ng/mg for controls). A decrease in the plasma glucagon concentration (59% *vs.* control) was also observed after combination therapy (19).

Pharmacokinetics and Metabolism

The pharmacokinetics of alogliptin were evaluated in rats, beagle dogs and cynomolgus monkeys. After a single oral dose, alogliptin was rapidly absorbed, with peak plasma concentrations observed at 2.3, 0.4 and 1.0 h after dosing, respectively, in rats, dogs and monkeys. The absolute oral bioavailability ranged from about 45% to 87% across all species. The $t_{1/2}$ values for alogliptin in rats, dogs and monkeys were 2.3, 3.0 and 5.7 h, respectively (14).

In healthy male subjects, single doses of oral alogliptin were also rapidly absorbed, with median t_{max} ranging from 1 to 2 h at doses of 25, 50, 100, 200, 400 and 800 mg. The mean AUC and C_{max} of alogliptin increased with dose. The mean $t_{1/2}$ of alogliptin ranged from 12.4 to 21.4 h. At 72 h, 60-70% of the dose was excreted unchanged in urine (20, 21).

The pharmacokinetics of oral alogliptin were further evaluated in patients with type 2 diabetes. In this study, patients received 25, 100 or 400 mg alogliptin or placebo once daily for 14 days. Alogliptin was again rapidly absorbed, with a median t_{max} of approximately 1.0 h. AUC_{0-24} and C_{max} increased in a dose-proportional man-

ner on days 1 and 14, and increased by approximately 34% and 9%, respectively, after 14 days. On day 14, the mean $t_{1/2}$ ranged from 12.5 to 21.1 h. Minimal accumulation of alogliptin was observed (22).

In an open-label study, 8 subjects with moderate hepatic impairment (Child-Pugh score of 7-9) and 8 healthy subjects received a single oral dose of alogliptin of 25 mg. Blood and urine pharmacokinetic analysis revealed that the AUC and the C_{max} of alogliptin were lower in subjects with moderate hepatic impairment than in healthy subjects. No clinically significant changes in AUC and C_{max} were observed for M-I, a minor metabolite of alogliptin, in subjects with moderate hepatic impairment. The results of this study indicate that alogliptin can be administered to subjects with moderate hepatic impairment without the need for dose adjustment (23).

Clinical Studies

In the above-mentioned randomized, double-blind, placebo-controlled phase I study in 36 healthy male subjects receiving single rising doses of alogliptin (25, 50, 100, 200, 400 or 800 mg) or placebo, alogliptin produced rapid, almost complete and sustained inhibition of plasma DPP IV activity, leading to increased intact GLP-1 concentrations. The peak and total exposure of plasma GLP-1 was 2- and 3-fold greater, respectively, in the alogliptin groups compared to the placebo group. The treatment was well tolerated. Results of this phase I study suggest the suitability of once-daily dosing (20, 21).

The efficacy and tolerability of multiple doses of alogliptin were also assessed in the double-blind, randomized, placebo-controlled trial in patients with type 2 diabetes. The patients were assigned to receive alogliptin (25, 100 or 400 mg) or placebo once daily for 14 days. A total of 54 subjects completed the study. Alogliptin substantially inhibited plasma DPP IV activity, with peak inhibition ranging from 93.8% to 98.9% across all doses tested on days 1 and 14. The median time to peak inhibition was 1.0-2.5 h. At 72 h after the last dose on day 14, mean inhibition ranged from 66.3% to 81.6%. Statistically significant decreases (–39.9, –48.6 and –68.3 mg/dl, respectively) from baseline (day 1) in mean postprandial plasma glucose concentrations were observed on day 14 for all alogliptin doses. All doses were well tolerated (22).

A series of global phase III clinical trials of alogliptin are under way for the treatment of diabetes (24-32). Takeda recently submitted an NDA with the FDA seeking approval of alogliptin for the treatment of type 2 diabetes (33).

Drug Interactions

The potential pharmacokinetic interactions between alogliptin and pioglitazone were investigated in an open-label, randomized, crossover trial in 30 healthy subjects. The subjects received 25 mg alogliptin once daily for 12 days, 45 mg pioglitazone once daily for 12 days and 25 mg alogliptin once daily plus 45 mg pioglitazone once daily for 12 days, with a 10-day washout between each treatment period. Pharmacokinetic parameters measured on day 12 indicated that there were no pharmacokinetic interactions between alogliptin and pioglitazone: no clinically significant changes in AUC_{0-24}, C_{max} or t_{max} were observed for alogliptin or pioglitazone (34).

The potential pharmacokinetic interaction between alogliptin and glyburide was also evaluated in an open-label trial in 24 healthy subjects. In this study, the subjects received 5 mg glyburide on day 1, 25 mg alogliptin from day 3 to day 9 and 25 mg alogliptin plus 5 mg glyburide on day 10. Plasma pharmacokinetic parameters measured on day 10 did not show clinically significant changes in AUC, C_{max} and t_{max} for glyburide. Since glyburide is a cytochrome P-450 CYP2C9 substrate, the results of this study indicate that alogliptin is probably not a CYP2C9 inhibitor. Alogliptin can therefore be co-administered with glyburide and other CYP2C9 substrates without the need for dose adjustment (35).

A randomized, open-label, crossover study examined the potential pharmacokinetic interactions between alogliptin and metformin in 36 healthy subjects. The subjects were assigned to receive 100 mg alogliptin once daily for 6 days, 1000 mg metformin twice daily for 6 days and 100 mg alogliptin once daily along with 1000 mg metformin twice daily for 6 days. Analyses of blood and urine samples collected at 96 h after dosing on day 6 of each period revealed that co-administration did not lead to clinically significant changes in AUC_{0-tau}, C_{max} and t_{max} for alogliptin or metformin (36).

In a randomized, single-blind, placebo-controlled, multiple-dose study, 36 healthy male subjects received both alogliptin and warfarin to evaluate the potential for drug interactions. Dose levels of warfarin were titrated over a 9-day period before alogliptin was co-administered. A total of 30 subjects completed the study. The study demonstrated that 25 mg alogliptin once daily co-administered with a stable dose of warfarin for 7 days did not significantly change the pharmacokinetic and pharmacodynamic parameters of warfarin, suggesting that alogliptin and warfarin can be administered concomitantly without the need for dose adjustment (37).

Source

Takeda Pharmaceutical Co., Ltd. (JP).

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