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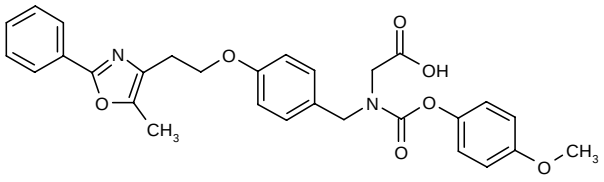
Muraglitazar

Prop INN; USAN

Treatment of Type 2 Diabetes
Dual PPARα/γ Agonist

BMS-298585

2-[*N*-(4-Methoxyphenoxycarbonyl)-*N*-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]benzyl]amino]acetic acid
N-(4-Methoxyphenoxycarbonyl)-*N*-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]benzyl]glycine



$C_{29}H_{28}N_2O_7$
Mol wt: 516.5472
CAS: 331741-94-7
EN: 303122

Abstract

Adult-onset, or type 2, diabetes is characterized by the body's inability to effectively utilize insulin, which leads to defects in carbohydrate, fat and protein metabolism. The peroxisome proliferator-activated receptors (PPARs) play a key role in the regulation of dietary fat storage and PPAR agonists, which act as insulin sensitizers, have shown therapeutic potential in the treatment of blood glucose and lipid abnormalities in patients with type 2 diabetes. Muraglitazar is a PPAR agonist with dual PPARα/γ subtype activity. In preclinical studies, diabetic *db/db* mice and hamsters fed a high-fat diet showed significant reductions in fasting and fed glucose, plasma insulin and triglycerides in response to muraglitazar administration. A significant reduction in both triglyceride and cholesterol content of the liver was also observed. In patients with type 2 diabetes, treatment with muraglitazar resulted in dose-dependent improvements in 24-h mean glucose concentrations, with corresponding decreases in fasting triglycerides, LDL cholesterol and total cholesterol. Muraglitazar is currently in phase III clinical development.

Synthesis

Condensation of 2-(5-methyl-2-phenyloxazol-4-yl)-ethanol (I) with 4-hydroxybenzaldehyde (II) by means of PPh_3 and DEAD in THF gives the aryl ether (III), which is reductocondensed with glycine *tert*-butyl ester (IV) by means of $NaBH_4$ in THF to afford *N*-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]benzyl]glycine *tert*-butyl ester (V). Reaction of compound (V) with 4-methoxyphenyl chloroformate (VI) — obtained by reaction of 4-methoxyphenol (VII) with phosgene in toluene — by means of polyvinylpyridine (PVP) in dichloromethane provides carbamate (VIII), which is finally hydrolyzed at the *tert*-butyl ester group with trifluoroacetic acid (1). Scheme 1.

Introduction

Diabetes is a chronic syndrome characterized by hyperglycemia resulting from defects in insulin secretion and utilization. Abnormal insulin action on its target tissues results in defects in carbohydrate, fat and protein metabolism. Type 2 diabetes, or adult-onset diabetes, accounts for over 90% of the diabetic population in developed countries. It is characterized by an inability of the body to effectively utilize insulin. The insulin resistance, or metabolic syndrome, is associated with factors including impaired glucose tolerance, obesity, hypertension and an increased risk of atherosclerotic disease. The peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptor isoforms that play a key role in the regulation of dietary fat storage and are a target for the development of treatments for type 2 diabetes, obesity and cardiovascular disease. Agonists at these receptors act as insulin sensitizers, and PPARα and γ receptor subtypes show different tissue and ligand specificities: PPARγ agonists improve glycemic control and dyslipidemia in type 2 diabetic patients by downregulating cytokines in adipose tissue, while agonists of the PPARα subtype improve the atherogenic lipoprotein profile of insulin resistance (2, 3).

Muraglitazar (BMS-298585) is a novel oxybenzylglycine analogue with selective and balanced dual

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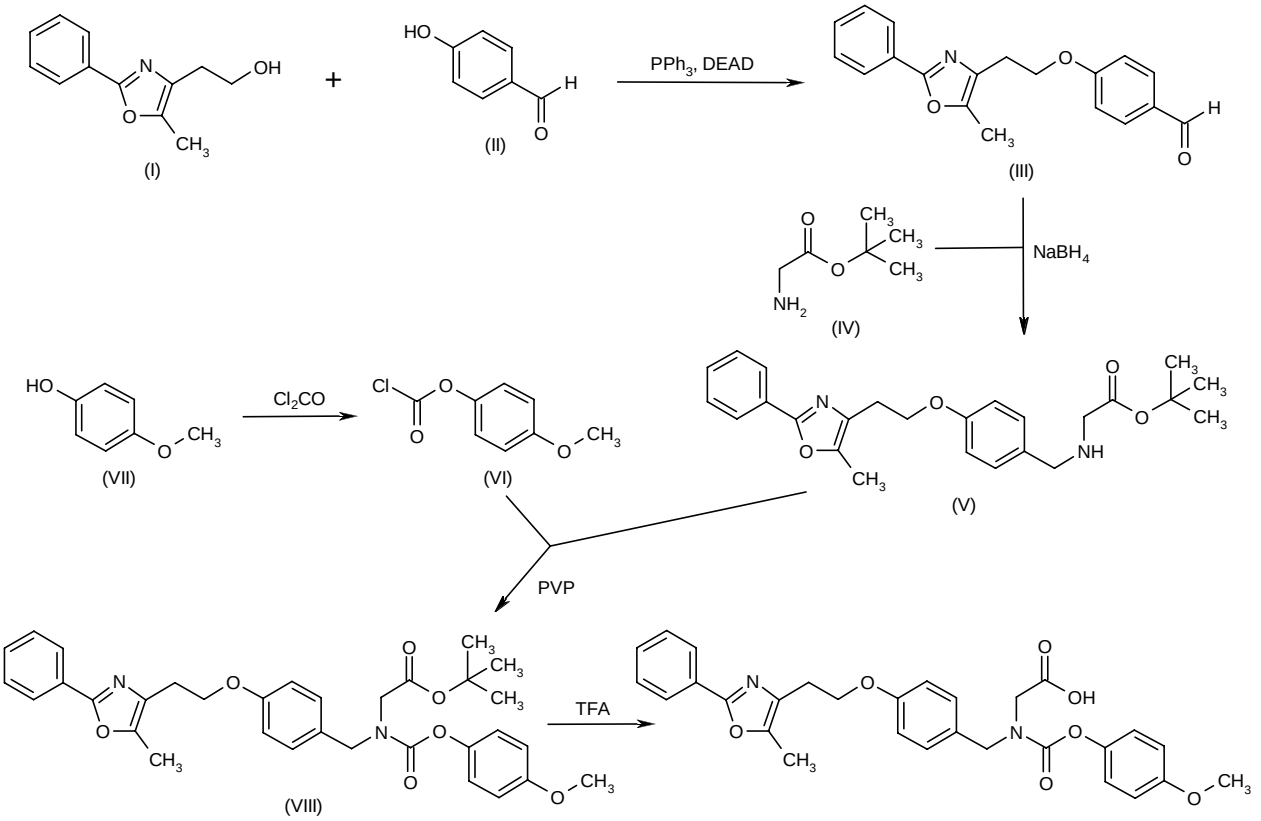
Scheme 1: Synthesis of Muraglitazar



agonist activity at PPARα/γ receptors, which is being developed under a global alliance between Bristol-Myers Squibb and Merck & Co. for the treatment of blood glucose and lipid abnormalities in patients with type 2 diabetes. Phase III clinical trials are in progress (4).

Pharmacological Actions

Receptor binding assays showed that muraglitazar has high binding affinity at both PPARα and PPARγ receptors, with IC_{50} values of 0.42 and 0.14 μM, respectively. It had no binding or functional activity at a wide variety of other nuclear hormone receptors. It displayed potent agonist activity at these receptors *in vitro*, with respective EC_{50} values of 0.24 and 0.12 μM in cells transfected with PPARα and PPARγ receptors. The activation of both PPARα and γ receptors was also demonstrated *in vivo* in genetic and diet-induced mouse models of diabetes and hyperlipidemia. PPARα activation was demonstrated by induction of the acyl-CoA oxidase gene and suppression of the apolipoprotein CIII (apoCIII) gene in the liver of *db/db* mice and suppression of very-low-density lipoprotein (VLDL) secretion in C57BL/6 mice following administration of muraglitazar. PPARγ activation was indicated by the induction of the lipoprotein lipase gene in *db/db* mouse white adipose tissue (5, 6).

Muraglitazar (1 mg/kg/day) was administered to *db/db* mice for 7 and 14 days. There were significant reductions in insulin and triglyceride levels, as well as significant reductions in fasting glucose (36% after 7 days) and fed glucose levels (46% after 14 days). In mice fed a high-fat/sucrose diet, administration of muraglitazar (10 mg/kg/day) for 14 days resulted in normalization of fasting plasma glucose, triglycerides and VLDL+LDL cholesterol. There was also a significant reduction in liver lipid content (6).

Muraglitazar was also evaluated in hamsters fed a high-fat diet. These hamsters develop dyslipidemia, insulin resistance and obesity, and as a model may be more predictive than mice in the assessment of lipid-lowering agents. Induction or suppression of the genes involved in PPARα and PPARγ activation consistent with that observed in *db/db* mice (6) was seen following oral administration of muraglitazar. Treatment with muraglitazar (10 mg/kg/day) for 4 weeks resulted in normalization of fasting plasma triglycerides, VLDL+LDL cholesterol, free fatty acids and liver lipid content. Fasting

plasma glucose was also significantly reduced (19%). Administration of a higher dose of 30 mg/kg/day for 4 weeks resulted in a 41% reduction in fasting plasma glucose (7).

The lipid content of liver samples was analyzed in C57BL/6 mice and Golden Syrian hamsters fed a high-fat diet and treated with muraglitazar or the PPARγ-selective agonist rosiglitazone (10 mg/kg/day for 2 and 4 weeks). In both models, there was a significant reduction in both triglyceride and cholesterol content of the liver (39% and 63%, respectively, in hamsters) in animals treated with muraglitazar, but not rosiglitazone. Importantly, these reductions were achieved without any associated increase in liver weight (8).

In another study, Golden Syrian hamsters on a high-fat diet were treated with muraglitazar (30 mg/kg/day) for 45 days. Inguinal white adipose tissue RNA showed a 10-fold induction of uncoupling protein 1 (UCP1) gene isoform expression. Histological analysis showed a 60% increase in total adipocyte cell count per tested area, indicating a decrease in the average size of the cells. Muraglitazar-treated hamsters also showed a 14% increase in basal oxygen consumption compared with control animals. These changes confirmed the PPARγ-agonist activity of muraglitazar, enhancing preadipocyte differentiation, promoting apoptosis of large mature adipocytes and stimulating the transcription of the UCP1 gene (9).

Severely diabetic *db/db* mice were treated with muraglitazar at doses of 0.1-30 mg/kg/day for 4 weeks. A progressive, dose-dependent lowering of plasma triglycerides, free fatty acids, glucose and insulin was observed. The metabolic abnormalities observed in untreated *db/db* mice, evidenced by low plasma adiponectin levels and 3-4-fold elevated corticosterone levels, were normalized by treatment with a muraglitazar dose of 3 mg/kg/day. The highest dose also improved polyuria, with a decrease in urine output from 12 ml to 1.9 ml (10).

The effect of muraglitazar on macrophage foam cells was assessed in order to evaluate its potential to retard atherogenesis. THP-1 macrophage cells were induced to differentiate, then treated for 24 h *in vitro* with muraglitazar 10 μM. The expression of multiple genes involved in reverse cholesterol transport was induced by up to 5.9-fold (apoE). There was also a 78% increase in cholesterol efflux from THP-1 cells and the secretion of monocyte chemoattractant protein-1 (MCP-1) was inhibited (IC_{50} = 0.19 μM) (11).

Pharmacokinetics and Metabolism

The pharmacokinetics of muraglitazar were evaluated in mice, rats, beagle dogs and cynomolgus monkeys. The absolute oral bioavailability ranged from 64% to 88% in the mouse, rat and monkey, while in dogs, the bioavailability was approximately 18%. The terminal elimination half-life was 2.4 h in dogs and 7.3 h in rats (5, 12).

The disposition and metabolic profile of [^{14}C]-muraglitazar were evaluated in rats, dogs, monkeys and humans. The parent compound was the major circulating radioactive component. The main route of excretion was the feces as phase I metabolites via biliary elimination of glucuronides. The metabolic pathways were qualitatively similar in the species studied, with involvement of multiple cytochrome P-450 and UDP-glucuronosyltransferase isozymes (13).

A randomized, placebo-controlled, ascending-dose study assessed the safety and pharmacokinetics of muraglitazar in healthy subjects. Following single doses of 0.5, 1.5, 5, 25, 100 and 300 mg, muraglitazar was rapidly absorbed, with a dose-related increase in C_{max} and AUC values. The mean half-life ranged between 19 and 27 h and the overall pharmacokinetic profile supported once-daily administration. Muraglitazar was well tolerated and no serious adverse events were reported (14).

Clinical Studies

The efficacy and tolerability of muraglitazar were evaluated in a randomized, multiple-ascending-dose study in patients with type 2 diabetes, where up to 10 patients (fasting serum glucose of 150-280 mg/dl) per group received muraglitazar at doses of 1.5, 5.0 or 20 mg or placebo once daily for 28 days. Dose-dependent improvements in 24-h mean glucose concentrations were obtained, with mean decreases from baseline of 24, 76 and 100 mg/dl, respectively, following treatment with 1.5, 5.0 and 20 mg muraglitazar. There was also a trend for a reduction in fasting plasma insulin. Corresponding pronounced lipid-lowering effects were also observed, with a dose-dependent decrease in fasting triglycerides and decreases in LDL cholesterol, total cholesterol, small dense LDL and VLDL, and increases in HDL cholesterol. In addition, muraglitazar decreased apoCIII and nonesterified fatty acids in a dose-dependent manner. Muraglitazar was well tolerated at all dose levels and no serious adverse events were reported (15-17).

Phase III clinical trials with muraglitazar are ongoing, and regulatory filing with the U.S. FDA is anticipated during 2005 (4).

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