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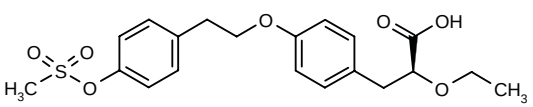
Tesaglitazar

Prop INN

Treatment of Type 2 Diabetes
Treatment of Metabolic Syndrome
PPARα/PPARγ Agonist

AR-H039242XX
AZ-242
Galida™

2(*S*)-Ethoxy-3-[4-[2-[4-(methylsulfonyloxy)phenyl]ethoxy]phenyl]propionic acid



$C_{20}H_{24}O_7S$

Mol wt: 408.4686

CAS: 251565-85-2

EN: 259635

Abstract

Peroxisome proliferator-activated receptors (PPARs) modulate gene expression in the process of lipid metabolism. Tesaglitazar is a novel, dual PPAR agonist which binds to and activates both α and γ receptor subtypes with similar high potency. It is currently being developed for the treatment of insulin resistance-related glucose and lipid abnormalities associated with type 2 diabetes and the metabolic syndrome. In rodent models of insulin resistance, tesaglitazar has been shown to improve insulin sensitivity and to have beneficial effects on fatty acid and glucose metabolism. In nondiabetic subjects with abnormalities characteristic of insulin resistance, there were significant dose-dependent reductions in fasting triglycerides, glucose and insulin in subjects treated with tesaglitazar. The drug is currently in phase III trials.

Synthesis

Tesaglitazar can be prepared by several ways:

1) Reaction of 2-(4-hydroxyphenyl)ethanol (I) with MsCl and triethylamine in dichloromethane gives the bismesylate (II), which is condensed with 4-hydroxybenzaldehyde (III) by means of K_2CO_3 in acetonitrile to yield the 4-substituted benzaldehyde (IV). Condensation of benzaldehyde (IV) with the phosphonium salt (V) by means of tetramethylguanidine (TMG) in chloroform affords the acrylic ester (VI), which is reduced with H_2 over Pd/C in ethyl acetate to provide the propionic ester (VII). Hydrolysis of the ester (VII) with LiOH in THF/water gives the racemic propionic acid derivative (VIII), which is condensed with (*R*)-phenylglycinol (IX) by means of EDC, HOBt and diisopropylethylamine in dichloromethane to yield amide (X) as a diastereomeric mixture that is separated by crystallization and chromatography. Finally, the desired (2*S*)-diastereomer (XI) is treated with H_2SO_4 in hot dioxane/water (1). Scheme 1.

2) Condensation of 4-(benzyloxy)benzaldehyde (XII) with the phosphonium salt (V) by means of tetramethylguanidine gives the acrylic ester (XIII), which is hydrogenated with H_2 over Rh/C in methanol to yield the propionic ester (XIV). Hydrolysis of ester (XIV) with LiOH in dioxane/water affords the racemic free acid (XV), which is condensed with (*R*)-phenylglycinol (IX) by means of EDC, HOBt and diisopropylethylamine in dichloromethane to provide amide (XVI) as a diastereomeric mixture that is separated by crystallization and chromatography. The desired (2*S*)-diastereomer (XVII) is hydrolyzed with H_2SO_4 in hot dioxane/water to furnish the chiral propionic acid (XVIII), which is esterified with EtOH and HCl to give the ethyl ester (XIX). Hydrogenolysis of the benzyl ether group of compound (XIX) with H_2 over Pd/C in ethyl acetate yields the phenolic derivative (XX), which is condensed with the bismesylate (II) by means of K_2CO_3 in acetonitrile to afford the adduct (XXI). Finally, the ethyl ester group of (XXI) is hydrolyzed with LiOH in THF/water (1). Scheme 2.

3) Reaction of chloroacetic acid (XXI) with sodium ethoxide (XXIII) in ethanol gives 2-ethoxyacetic acid ethyl ester (XXIV), which is condensed with 4-methoxybenz-

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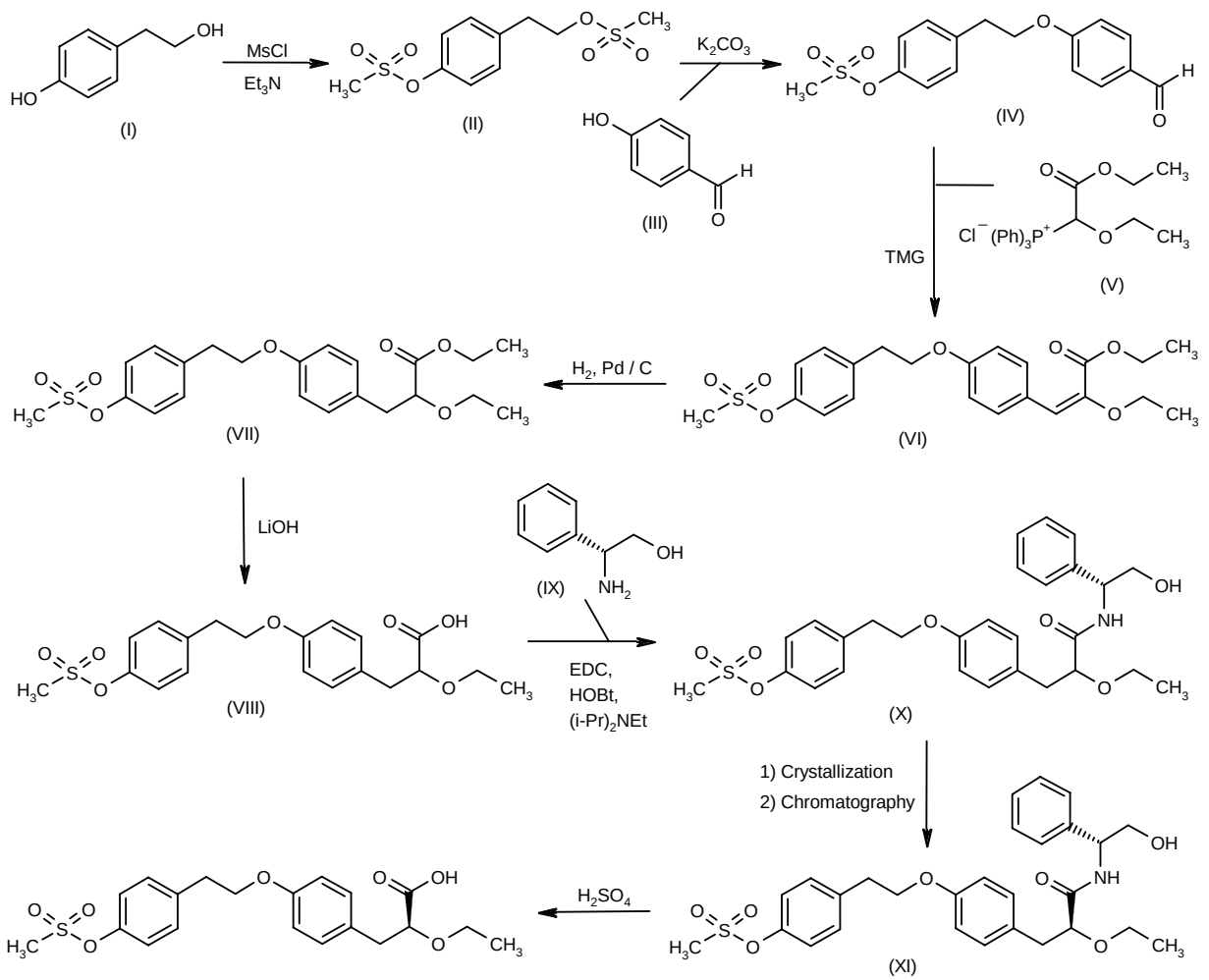
Scheme 1: Synthesis of Tesaglitazar

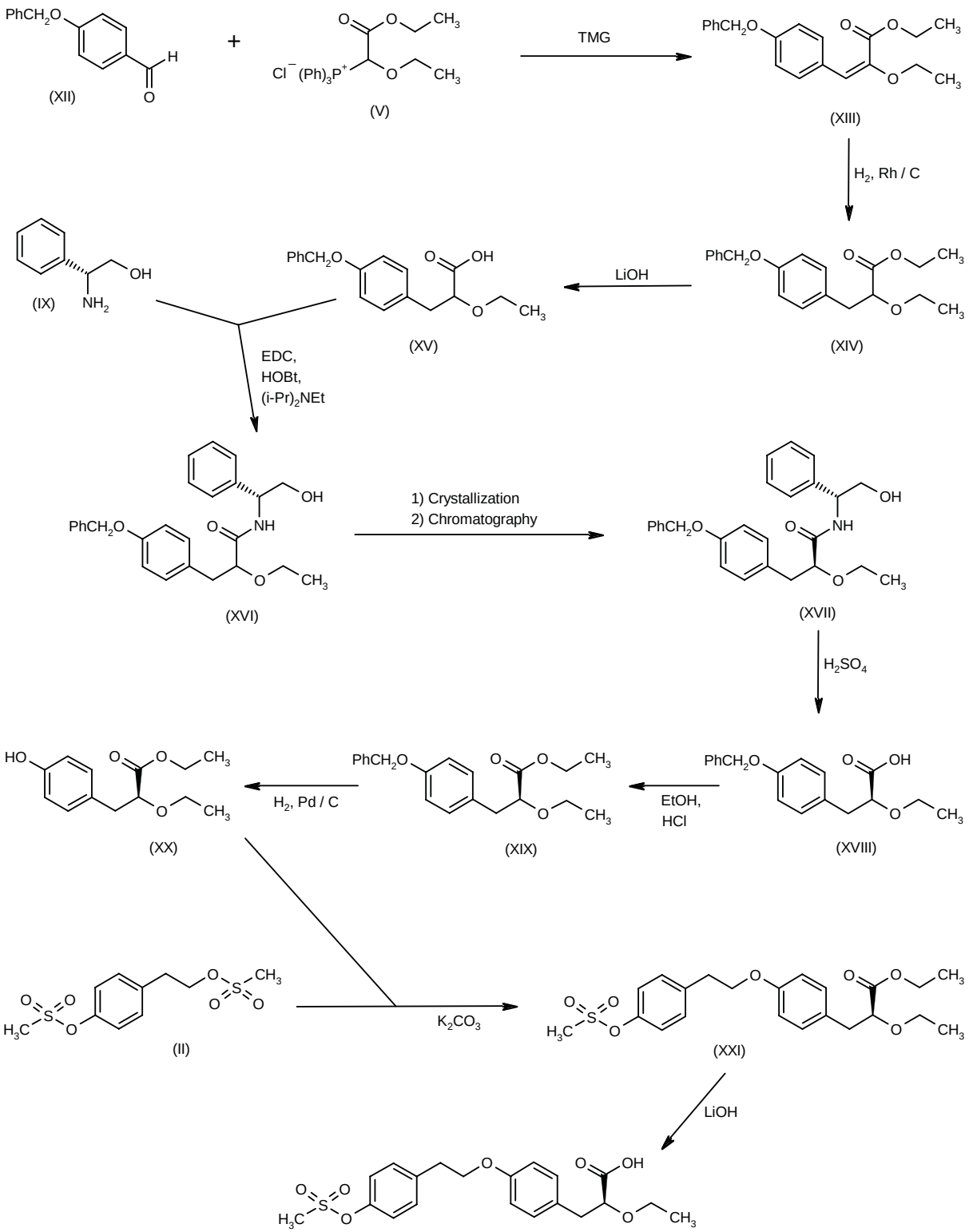


aldehyde (XXV) by means of *t*-BuOK in THF to yield 2-ethoxy-3-(4-methoxyphenyl)-2-propenoic acid ethyl ester (XXVI). Hydrolysis of ester (XXVI) with NaOH in hot ethanol/water affords the propenoic acid derivative (XXVII), which is reduced with H_2 over Pd/C in ethanol to provide racemic 2-ethoxy-3-(4-methoxyphenyl)propionic acid (XXVIII). Optical resolution of mixture (XXVIII) is performed by salt formation with 1(*S*)-(1-naphthyl)ethylamine (XXIX) followed by crystallization to give the diastereomeric salt (XXX), which is treated with NaOH, followed by acidification with HCl to yield 2(*S*)-ethoxy-3-(4-methoxyphenyl)propionic acid (XXXI). Demethylation of compound (XXXI) by reaction with NaOH and octanethiol in NMP affords 2(*S*)-ethoxy-3-(4-hydroxyphenyl)propionic acid (XXXII), which is esterified with ethanol/HCl to provide the corresponding ethyl ester (XXXIII). Condensation of ester (XXXIII) with the bismesylate (II) by means of either K_2CO_3 in 2-butanone or Na_2CO_3 in acetone provides 2(*S*)-ethoxy-3-[4-[2-[4-(methanesulfonyloxy)-phenyl]ethoxy]phenyl]propionic acid ethyl ester (XXI), which is finally hydrolyzed with NaOH or LiOH in acetone/water (2). Scheme 3.

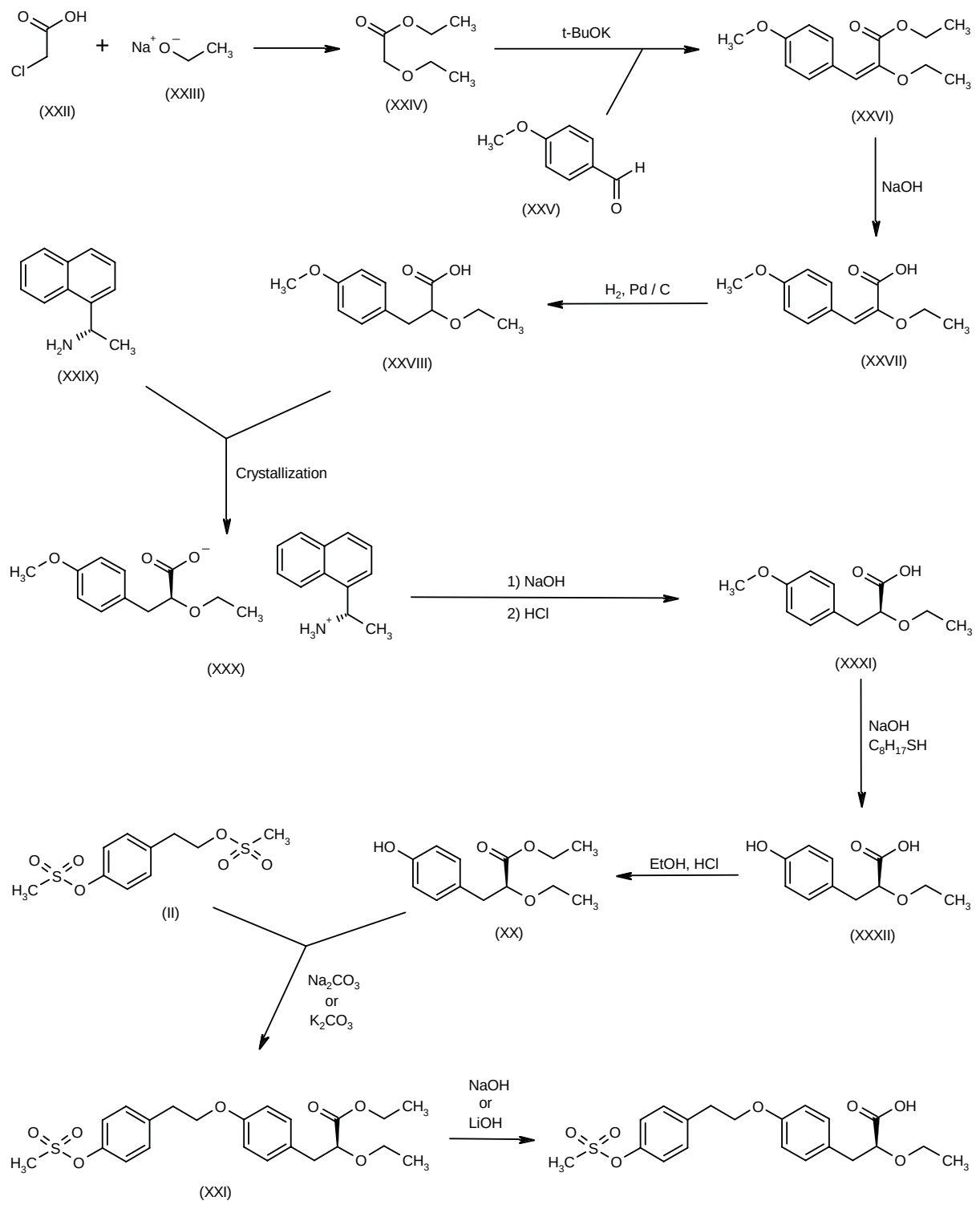
Introduction

Insulin resistance associated with the metabolic syndrome and type 2 diabetes is related to abnormalities in fatty acid metabolism and can lead to an increased risk in cardiovascular disease. Peroxisome proliferator-activated receptors (PPARs) are ligand-activated nuclear receptors or transcription factors, which modulate gene expression in the process of lipid metabolism. There are PPAR subtypes, α and γ, which have different tissue and ligand specificities. PPARγ expression is mainly in adipose tissue, while the α subtype is expressed mainly in liver,

Scheme 2: Synthesis of Tesaglitazar



Scheme 3: Synthesis of Tesaglitazar



skeletal muscle and heart. PPARγ agonists improve glycemic control and dyslipidemia in type 2 diabetic patients while the α subtype improves the atherogenic lipoprotein profile of insulin resistance. Tesaglitazar (AZ-242; Galida™), a single enantiomer dihydrocinnamate derivative, is a novel, combined PPARα/γ agonist which binds and activates both receptor subtypes with similar high potency. It is being developed as an oral treatment for insulin resistance-related glucose and lipid abnormalities associated with type 2 diabetes and the metabolic syndrome. It is currently in phase III trials (3-5).

Pharmacological Actions

The effects of tesaglitazar on insulin resistance and carbohydrate and lipid metabolism have been studied in rodents. The treatment of obese, diabetic (ob/ob) mice with tesaglitazar resulted in normalization of hyperglycemia and a reduction in insulin levels. Groups of untreated obese and lean mice were used as controls. In mice treated with tesaglitazar 1 μmol/kg/day, there was a significant reduction in plasma triglycerides, insulin and glucose levels compared with obese controls. Triglyceride levels were reduced to lower levels in the tesaglitazar-treated ob/ob mice than those of lean control mice. The effect was dose-dependent in the range of doses administered, 0.01-5 μmol/kg/day for 8 days. Tesaglitazar 1 μmol/kg/day for 1 week also restored insulin sensitivity and decreased insulin secretion in obese, insulin-resistant (fa/fa) Zucker rats during euglycemic clamp studies. Glucose infusion rates in fasted animals were 27 and 30 μmol/min in the lean control and tesaglitazar-treated obese rats, respectively, compared with 4.3 μmol/min in the obese control group. The impaired insulin-mediated suppression of free fatty acids in untreated obese rats under clamp conditions was also restored following tesaglitazar treatment. These studies have established the efficacy of tesaglitazar in improving insulin resistance and correcting glucose and fatty acid metabolic abnormalities in ob/ob mice and obese Zucker rats (4).

In a double transgenic human mouse model, tesaglitazar (1 μmol/kg/day) had a broader activity profile in reducing diet-induced insulin resistance and associated dyslipidemia than selective PPARα or PPARγ agonists alone (6).

The effect of tesaglitazar on metabolic responses to an oral glucose/lipid load was also studied in obese Zucker rats. Obese rats were treated with tesaglitazar 3 μmol/kg/day for 4 weeks and responses compared with those in lean, insulin-sensitive controls and obese insulin-resistant controls. Following a 7-h fast, rats were gavaged with a glucose/triglyceride test meal. Treatment with tesaglitazar resulted in normalization of fasting plasma glucose, improved glucose tolerance, substantially reduced fasting and post-randial insulin, and normalized fasting triglycerides and lipid tolerance compared with untreated obese rats. Postprandial free fatty acid production was also completely restored to lean control levels (7).

The insulin-sensitizing action of tesaglitazar was assessed in Wistar rats with mild, dietary-induced insulin resistance. Rats were fed a high-fat diet for 3 weeks. A group given tesaglitazar 1 μmol/kg/day for 7 days was compared with an untreated group. There was a significant reduction in basaal plasma insulin in the tesaglitazar-treated group, 33.1 mU/l, compared with 51.7 mU/l in the untreated group. There was also a significant increase in glucose infusion rate in the tesaglitazar-treated group during euglycemic clamp studies. Studies using a fatty acid tracer demonstrated that the insulin-sensitizing action of tesaglitazar was accompanied by an 83% increase in fatty acid uptake into epididymal white adipose tissue under basal conditions (8).

A simultaneous multitracer assessment of whole body and *in vivo* tissue-specific free fatty acid and glucose metabolism was also made in Zucker rats. Obese rats were treated with tesaglitazar 3 μmol/kg/day for 3 weeks. In euglycemic clamp studies, rats treated with tesaglitazar required significantly higher glucose infusion rates than obese controls, 187 *versus* 39 μmol/kg/min. The effects of tesaglitazar on individual tissues under clamp conditions were also significantly different to the effects in individual tissues in the control group: there was lower free fatty acid utilization in skeletal muscle, liver, heart and adipose tissue, and increased glucose utilization in contracting muscles and adipose tissue. The glycogen stores in skeletal muscles and liver were reduced to the levels observed in a group of lean control rats (9).

In another study, *in vivo* tissue-specific rates of glucose utilization were also assessed using tracers in Zucker rats. Obese rats were treated with tesaglitazar 3 μmol/kg/day for 3 weeks. Euglycemic clamp studies showed that skeletal muscle glucose utilization in obese rats was almost unresponsive to the insulin elevation postprandially under clamp conditions. Treatment with tesaglitazar lowered basal insulin to levels observed in lean controls. The ability of insulin to increase the rate of glucose utilization in skeletal muscle was restored in rats treated with tesaglitazar (10).

Pharmacokinetics and Metabolism

In an open, randomized, crossover study, 8 healthy male subjects received a single oral or i.v. dose of 1 mg [^{14}C]-tesaglitazar and tesaglitazar. Maximum concentrations of tesaglitazar were reached after approximately 1 h, indicating rapid absorption of the drug. The absolute bioavailability was approximately 100%. The plasma concentration-time profiles were almost identical following administration of either [^{14}C]-tesaglitazar or tesaglitazar, indicating low systemic metabolite concentrations. Their half-lives were in the order of 45 h. The drug was well tolerated and the pharmacokinetic profile supported a once-daily administration for tesaglitazar (11).

The effect of tesaglitazar on the major drug-metabolizing human cytochrome P450 enzymes has been studied using *in vitro* enzyme systems expressed in yeast. At

Table I: Clinical studies of tesaglitazar (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Type 2 diabetes mellitus	Randomized, open, crossover	Tesaglitazar, 1 mg (after an overnight fast) Tesaglitazar, 1 mg (after a high-calorie breakfast)	20	Tesaglitazar was well tolerated and showed no differences in systemic exposure or absorption when administered with or without food	13
Insulin resistance	Randomized, double-blind	Tesaglitazar, 0.1 mg x 12 wk Tesaglitazar, 0.25 mg x 12 wk Tesaglitazar, 0.5 mg x 12 wk Tesaglitazar, 1.0 mg x 12 wk Placebo	390	Tesaglitazar was well tolerated and was associated with dose-dependent increases in the particle size of LDL and the plasma levels of HDL-cholesterol, as well asreductions in the plasma levels of fasting triglycerides, total cholesterol, free fatty acids, fasting insulin, glucose and Homeostasis Model Assessment scores	15

concentrations much higher than those anticipated *in vivo*, tesaglitazar had no effect on any of the enzymes investigated. The results indicate that tesaglitazar is unlikely to cause any clinically significant cytochrome P450-based drug interactions (12).

Another study has demonstrated that tesaglitazar absorption is not affected by food intake. The effect of food on the pharmacokinetics of tesaglitazar 1 mg was evaluated in an open, randomized, crossover study in healthy male subjects. The estimated geometric mean for the fed/fasted ratio for AUC and C_{max} were 0.99 and 0.82. The observed 90% confidence intervals were within the limits defined for equivalence of the 2 regimens. Tesaglitazar was well tolerated and there were no clinically significant abnormalities in vital signs or routine laboratory parameters (13) (Table I).

In these studies, plasma and urine concentrations of tesaglitazar were assayed using validated reverse-phase liquid chromatography and mass spectrometry methods (14).

Clinical Studies

The effects of tesaglitazar on the glucose and lipid abnormalities associated with insulin resistance have been studied in nondiabetic subjects with abnormalities characteristic of this condition. Four doses of tesaglitazar (0.1-1 mg) were compared with placebo in a 12-week study of 390 subjects. There were significant dose-dependent reductions in fasting triglycerides, glucose and insulin at doses of 0.25 mg tesaglitazar and above. There was also a dose-dependent significant increase in low density lipoprotein particle size, indicating a switch to a less atherogenic pattern. Tesaglitazar was well tolerated and there were no dose-dependent adverse events reported. The study demonstrated that tesaglitazar improves the metabolic abnormalities associated with insulin resistance and has a beneficial effect on the risk factors for atherosclerosis (15) (Table I).

The clinical potential of tesaglitazar is currently under evaluation in phase III studies in patients with type 2 diabetes.

Source

AstraZeneca plc (GB).

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