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Rivoglitazone Hydrochloride

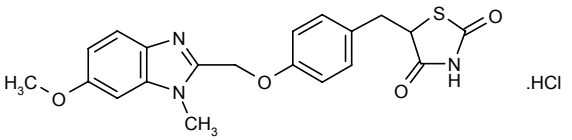
Rec INN; USAN

PPARγ Agonist
Insulin Sensitizer
Treatment of Diabetes

CI-1037
CS-011
DE-101
R-106056

(±)-5-[4-(6-Methoxy-1-methylbenzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione hydrochloride

InChI=1/C20H19N3O4S/c1-23-16-10-14(26-2)7-8-15(16)21-18(23)11-27-13-5-3-12(4-6-13)9-17-19(24)22-20(25)28-17/h3-8,10,17H,9,11H2,1-2H3,(H,22,24,25)



$C_{20}H_{20}ClN_3O_4S$
Mol wt: 433.908

CAS: 299176-11-7

CAS: 185428-18-6 (free base)

CAS: 918309-86-1 (hydrate)

EN: 281436

Abstract

The complex metabolic disorder type 2 diabetes is a leading cause of morbidity and mortality worldwide and thus a health and economic burden. Daiichi Sankyo has developed a new thiazolidinedione candidate for the treatment of type 2 diabetes, rivoglitazone hydrochloride (CS-011). In vitro, rivoglitazone demonstrates increased agonist activity at the peroxisome proliferator-activated receptor PPARγ compared to rosiglitazone, with in vivo and clinical studies confirming its enhanced antidiabetic activity compared with other thiazolidinediones. Rivoglitazone is currently undergoing phase II/III clinical development for the treatment of type 2 diabetes.

Synthesis

Rivoglitazone hydrochloride can be synthesized by three related methods:

Alkylation of 5-(4-hydroxybenzyl)-3-tritylthiazolidine-2,4-dione (I) with methyl bromoacetate (II) in the presence of cesium carbonate affords the protected aryloxy acetate (III), which by cleavage of the trityl group by means of acetic acid in dioxane at 80 °C provides compound (IV). Finally, ester (IV) is condensed with the phenylenediamine (V) in the presence of HCl (1, 2). Scheme 1.

Chlorination of the aryloxyacetic acid (VI) with thionyl chloride and DMF in acetonitrile followed by coupling with *N*-methyl-5-methoxy-2-nitroaniline (VII) in the presence of DMAP yields amide (VIII), which is finally submitted to catalytic hydrogenation of the nitro group in the presence of Pd/C and HCl (3). Scheme 1.

Alternatively, coupling of aryloxyacetic acid (VI) with the Boc-protected phenylenediamine (IX) by means of propylphosphonic acid cyclic anhydride (T3P) in $AcOEt/CH_2Cl_2$ gives amide (X), which is deprotected and cyclized upon refluxing with methanolic hydrochloric acid (4, 5). Scheme 1.

The intermediates (V), (VII) and (IX) can be prepared as follows:

Reaction of 5-chloro-2-nitroaniline (XI) with sodium methoxide in methanol/dioxane affords 5-methoxy-2-nitroaniline (XII), which is protected as the *N*-Boc derivative (XIII) by treatment with di-*tert*-butyl dicarbonate in the presence of DMAP. Methylation of compound (XIII) with iodomethane and NaH followed by deprotection of the resulting *N*-methyl carbamate (XIV) in acidic medium provides 5-methoxy-*N*-methyl-2-nitroaniline (VII). Alternatively, condensation of 2,4-dichloronitrobenzene (XV) with methylamine in DMF at 75-80 °C yields nitroaniline (XVI), which undergoes chloride group displacement with methanolic sodium methoxide, producing the target intermediate (VII) (3). Then, reduction of the nitro group of

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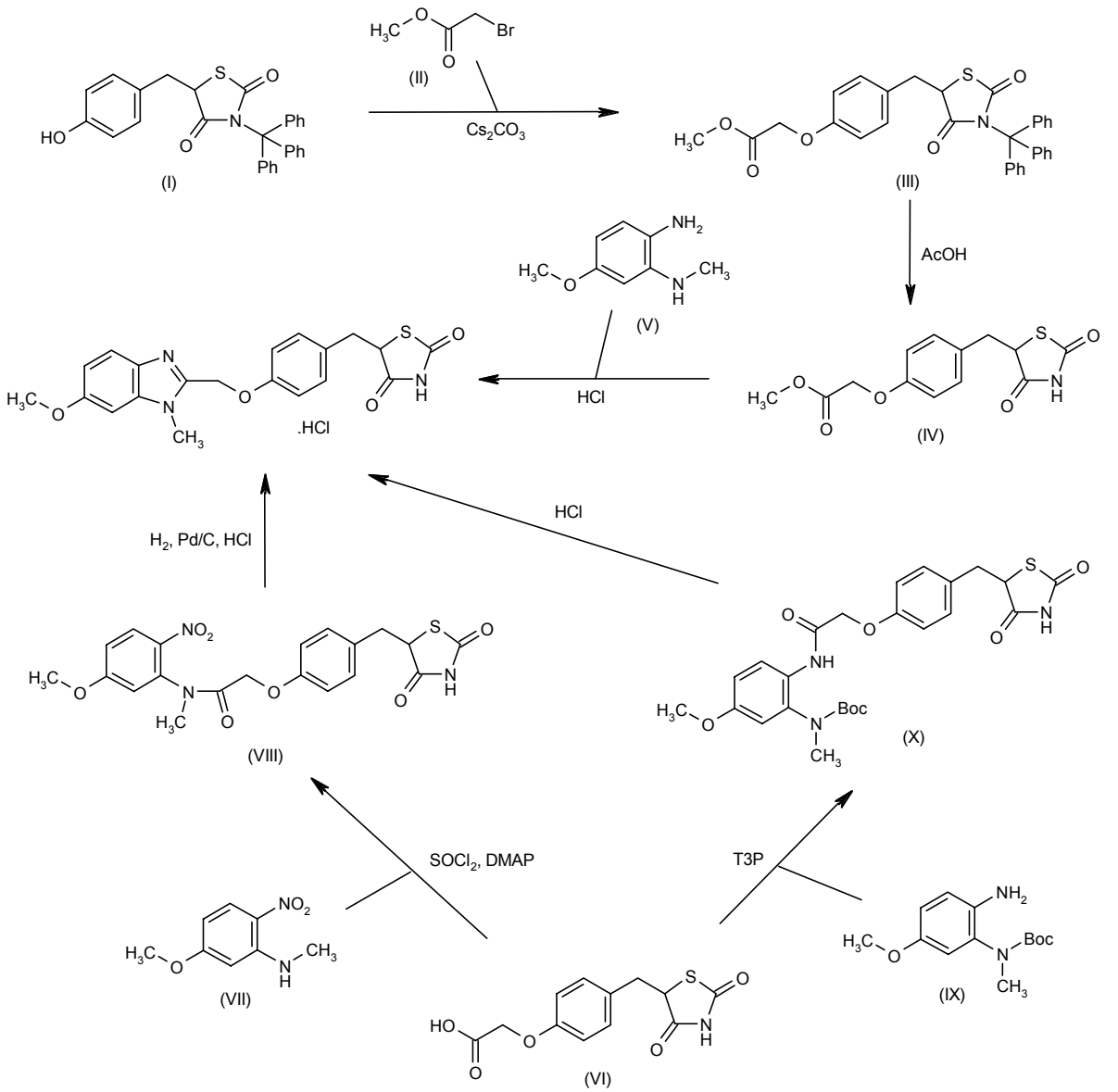
Scheme 1: Synthesis of Rivoglitazone Hydrochloride



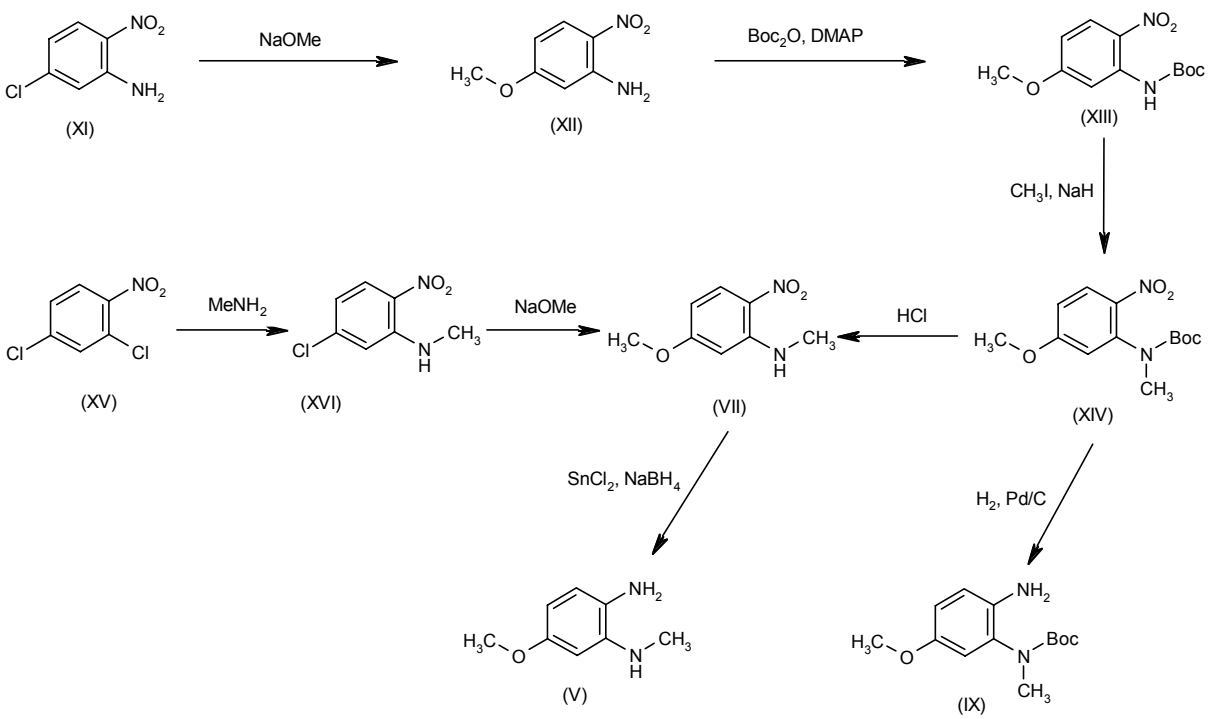
(VII) with $SnCl_2$-$NaBH_4$ provides phenylenediamine (V) (1) and the monoprotected diamine (IX) is obtained by catalytic hydrogenation of the *N*-Boc nitroaniline (XIV) in the presence of Pd/C in toluene (5). Scheme 2.

Background

Type 2 diabetes is a complex metabolic disorder characterized by hyperglycemia resulting from a deficiency of insulin secretion and a reduced response of target tissues to insulin (insulin resistance). Type 2 diabetes is a leading cause of morbidity and mortality associated with a substantial economic and health burden. It has been reported that there are now 150 million people with diabetes worldwide and that this number will rise to 300 million by 2025 (6). Successful management of type 2 diabetes requires strict control of glycemia, as well as other risk factors, to prevent disease progression. Despite the availability of multiple classes of oral antidiabetic drugs and insulin, the majority of patients fail to achieve or maintain tight glycemic control over time, raising their risk of serious vascular complications (7).

The thiazolidinediones (commonly known as glitazones) are a class of drugs that directly decrease insulin resistance by enhancing insulin action in skeletal muscle, adipose tissue and the liver via an agonist interaction with

Scheme 2: Synthesis of the Intermediates (V), (VII) and (IX)



the peroxisome proliferator-activated receptor PPARγ (8, 9). Thiazolidinediones currently available for the treatment of type 2 diabetes are included in Table I.

Daiichi Sankyo is developing rivoglitazone hydrochloride (CS-011) as a new thiazolidinedione candidate for the treatment of type 2 diabetes. Two phase II studies are planned but not yet recruiting patients. Both of these studies will investigate the efficacy of rivoglitazone after 12 weeks of treatment in patients with type 2 diabetes using a randomized, double-blind, placebo-controlled design, with one study making a direct comparison with pioglitazone (10, 11). An actively recruiting phase III study is also under way to assess the efficacy and safety of rivoglitazone as a monotherapy for type 2 diabetes in patients currently suboptimally controlled by diet and exercise or with nonthiazolidinedione antihyperglycemic monotherapy, with pioglitazone as the study comparator (12). A 6-month multicenter phase II/III study that investigated the effects of rivoglitazone on glycemic control in newly identified type 2 diabetes patients or diabetics not adequately treated with other antidiabetic agents (versus placebo and pioglitazone) was recently completed (13).

Preclinical Pharmacology

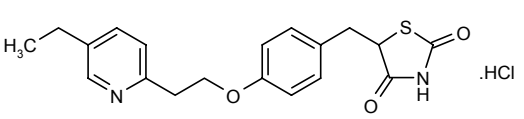
Mouse PPARγ chimera assays indicated that rivoglitazone has 3-fold more potent PPARγ receptor-dependent transactivity than rosiglitazone (EC_{50} = 160 nM vs. 490 nM), along with an enhanced ability to induce the differentiation of adipocytes from 3T3 L1 cells (EC_{50} = 5 nM vs. 15 nM) (14). Affinity binding studies have confirmed that the (*S*)-enantiomer of rivoglitazone is responsible for its PPARγ-agonist activity (15).

Studies in *db/db* mice have indicated that the (*R*)-enantiomer of rivoglitazone is converted to the (*S*)-enantiomer following administration but the glucose-lowering activity of the racemate and the enantiomers was not significantly different. Once-daily dosing at 0.03. 0.1, 0.3 and 1 mg/kg p.o. for 1 week decreased plasma glucose levels dose-dependently (15). Investigations in obese Zucker diabetic fatty and *db/db* mice have demonstrated that rivoglitazone modifies glucose (ED_{50} to reduce plasma glucose = 0.20 mg/kg p.o.) and lipid metabolism (ED_{50} to reduce triglycerides = 0.093 mg/kg p.o.) with up to 100-fold greater potency compared with other thiazolidinediones (rosiglitazone and pioglitazone). Furthermore, rivoglitazone did not appear to affect the expression of PPARα target genes involved in cardiac function, suggesting that it may be associated with reduced oxidative stress in the diabetic heart (16, 17).

Further comparisons with rosiglitazone in diabetic animal models have shown that rivoglitazone can be administered at lower doses to normalize plasma glucose levels; the potency of rivoglitazone versus rosiglitazone was enhanced 141-, 8- and 9-fold , respectively, in the ZDF rat model, KK mice and *db/db* mice. Rivoglitazone also

Table I: Thiazolidinediones in clinical evaluation for type 2 diabetes (from Prous Science Integrity®).

Product	Source	Phase
1. Pioglitazone hydrochloride (Actos, Glustin, Zactos)	Lilly/Novo Nordisk/Takeda	L-1999
2. Rosiglitazone maleate (Avandia)	GlaxoSmithKline	L-1999
3. Balaglitazone	Dr. Reddy's Laboratorios/Rheoscience	III
4. Rivoglitazone	Daiichi Sankyo	III
5. Lobeglitazone sulfate	Chong Kun Dang Pharm.	II
6. Netoglitazone	Mitsubishi Tanabe Pharma/ Perlegen Sciences	II



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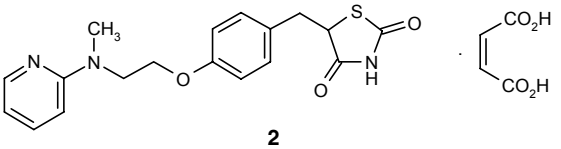

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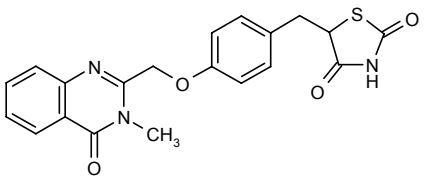

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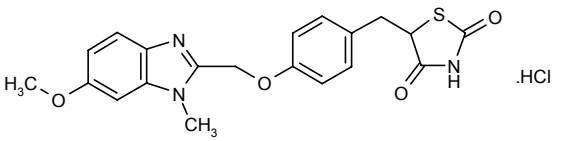

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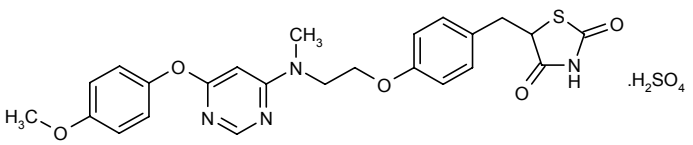

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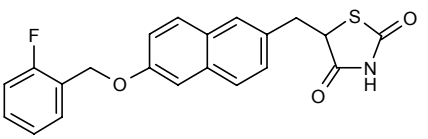

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demonstrated a prolonged plasma half-life and area under the curve (AUC) compared with rosiglitazone when given at a dose of 1 mg/kg ($t_{1/2}$ = 12.2 h vs. 1.88 h; AUC = 32,000 ng.h/ml vs. 5350 ng.h/ml) (14, 18).

Pharmacokinetics and Metabolism

A randomized (3:1), double-blind, placebo-controlled study investigating rivoglitazone at doses of 1, 2.5, 5 and 10 mg in 48 healthy male volunteers revealed dose-related increases in C_{max} and AUC, with a $t_{1/2}$ of 10-15 h, supporting once-daily dosing. Steady state was achieved within 5 days of dosing and an accumulation ratio ranging from 1.11 to 1.42 with once-daily dosing was recorded, and the compound was well tolerated (19).

An open-label, single-dose (10 mg), randomized, crossover study in healthy volunteers confirmed that administration with a high-fat meal does not impact on the drug's C_{max} or AUC. Rivoglitazone was also well tolerated in this study, with a relative bioavailability for tablets of 73% that of an oral solution formulation (20).

Safety

Assessment of the cardiovascular safety of rivoglitazone was carried out in a randomized, double-blind, parallel-group study of corrected Q-T parameters ($Q\text{-}T_c$) in healthy subjects after once-daily treatment for 7 days. Rivoglitazone at oral doses of 3 and 10 mg did not affect $Q\text{-}T_c$ values compared with placebo, with clear differences seen versus the active comparator moxifloxacin (21).

Clinical Studies

Rivoglitazone was shown to significantly and dose-dependently increase plasma adiponectin levels in healthy volunteers up to 5 mg following treatment for 14 days (19, 22).

A 6-week, double-blind, randomized, proof-of-concept study assessed the safety and efficacy of rivoglitazone compared with placebo and open-label pioglitazone in 426 patients with type 2 diabetes. Rivoglitazone was generally well tolerated at 0.5, 2 and 5 mg once daily, with dose-dependent drug-related mild adverse events (AEs). Fluid retention-related AEs (i.e., edema and weight gain) were more common at higher doses (approx. 15%). Rivoglitazone doses of 0.5, 2 and 5 mg provided a decrease of 13, 39 and 57 mg/dl in fasting plasma glucose levels, respectively, compared with 19 mg/dl for pioglitazone (30 mg). A dose-dependent increase in adiponectin levels (a marker of insulin sensitivity) was also noted (5.1, 16.8 and 26.0 μg/ml, respectively, versus

7.6 μg/ml for pioglitazone). These data suggest efficacy for rivoglitazone across a 10-fold dose range. Rivoglitazone demonstrated enhanced glycemic control and reduced lipid levels to a greater extent versus pioglitazone (23, 24).

Rivoglitazone and pioglitazone were also compared in a 26-week, double-blind, randomized trial with a primary outcome of change in baseline HbA1c. While HbA1c was significantly increased on placebo and unchanged on rivoglitazone 1 mg and pioglitazone 45 mg, it was significantly decreased on rivoglitazone 2 and 3 mg (0.4% and 0.5%, respectively). Target HbA1c of 7.0% or less was achieved by 45% and 44%, respectively, on rivoglitazone 2 and 3 mg, 36% on pioglitazone, 30% on rivoglitazone 1 mg and 8% on placebo. Changes in fasting plasma glucose were consistent with changes in HbA1c, and rivoglitazone dose-dependently decreased triglyceride levels (9.5%, 14.5% and 20.7%, respectively, on 1, 2 and 3 mg; 8.0% on pioglitazone) and increased HDL cholesterol levels (11.3%, 10.2% and 13.7%, respectively; 8.3% on pioglitazone). No treatment-related serious adverse events were seen and the most common were peripheral edema and weight gain (25).

Drug Interactions

A subanalysis of an open-label, randomized, crossover study demonstrated that the potent cytochrome P-450 CYP3A4 inhibitor itraconazole does not have a clinically significant effect on the steady-state pharmacokinetics of rivoglitazone (26).

Sources

Daiichi Sankyo; Santen is developing the compound (DE-101) under license for corneal and conjunctival epithelial disorders associated with dry eye (phase II).

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