Drugs of the Future 2001, 26(4): 354-363

CCC: 0377-8282/2001

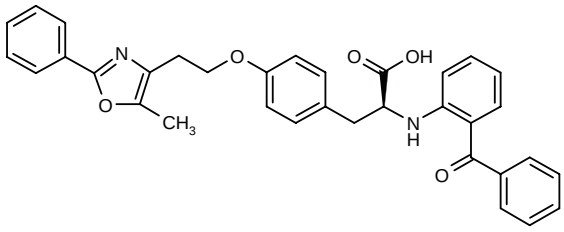
Farglitazar

USAN

Antidiabetic
PPARγ Agonist

GI-262570

2(*S*)-(2-Benzoylphenylamino)-3-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl]propionic acid
N-(2-Benzoylphenyl)-*O*-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethyl]-L-tyrosine



$C_{34}H_{30}N_2O_5$ Mol wt: 546.6200

CAS: 196808-45-4
CAS: 274687-78-4

EN: 255618

Synthesis

Condensation of L-tyrosine methyl ester (I) with 2-benzoylcyclohexanone (II) in the presence of Pd/C in boiling anisole provides the vinylogous amide intermediate (III) which, in the reaction conditions, experiences a dehydrogenation to furnish benzophenone (IV). Coupling of (IV) with 2-(5-methyl-2-phenyloxazol-4-yl)ethanol (V) under Mitsunobu conditions affords ether (VI). Finally, the ester function of (VI) is hydrolyzed with LiOH to give farglitazar (1, 2). Scheme 1.

Description

M.p. 148-50 °C.

Introduction

Diabetes mellitus encompasses several diseases characterized by chronic hyperglycemia with disturbances in fat, carbohydrate and protein metabolism due to abnormal insulin secretion and/or action. The World Health Organization (WHO) reported for the year 2000 that there were 154.4 million diabetics worldwide with no indication that prevalence is stabilizing. WHO predicts that there will be approximately 300 million individuals with diabetes by the year 2005 (3).

Diabetes is classified into 4 major subtypes. Type 1 diabetes, also known as juvenile-onset diabetes (previously referred to as insulin-dependent diabetes mellitus or IDDM), is due to the autoimmune destruction of pancreatic β cells resulting in the inability of the pancreas to produce insulin. Type 1 diabetes can be caused by autoimmune, genetic and/or environmental factors and accounts for 5-10% of all reported cases in the Western world. It usually develops before the age of 40 with most cases presenting before the age of 20. In contrast, type 2 diabetes, or adult-onset diabetes (previously referred to as noninsulin-dependent diabetes mellitus or NIDDM), accounts for over 90% of the diabetic cases reported in the Western world. In general, individuals suffering from type 2 diabetes produce sufficient amounts of insulin although their bodies cannot use it effectively. Genetic predisposition and environmental factors contribute to its development and risk factors include obesity, physical inactivity, family history of diabetes, prior history of gestational diabetes, impaired glucose tolerance and race/ethnicity. Other types of diabetes are much less frequent and include gestational diabetes, drug-induced diabetes and diabetes secondary to illness or infection (3).

Several drugs are available for the treatment of diabetes mellitus including various insulin formulations (*e.g.*, very short-acting, short-acting, intermediate-acting, long-acting and biphasic insulins) in addition to biguanides, sulfonylureas, α-glucosidase inhibitors, insulin sensitizers and insulin secretagogues. Moreover, the search for new agents is ongoing. One novel class of antidiabetic agents that appear to be effective as a treatment for diabetes are peroxisome proliferator-activated receptor (PPAR) agonists such as the thiazolidinediones (3-7). PPARs are a family of transcription factors that play a crucial role in regulating the storage and catabolism of dietary fats and, since their cloning, they have become the target for the development of compounds to treat human metabolic diseases. Three PPAR subtypes have been identified, the α, γ and δ forms, which are products of distinct genes

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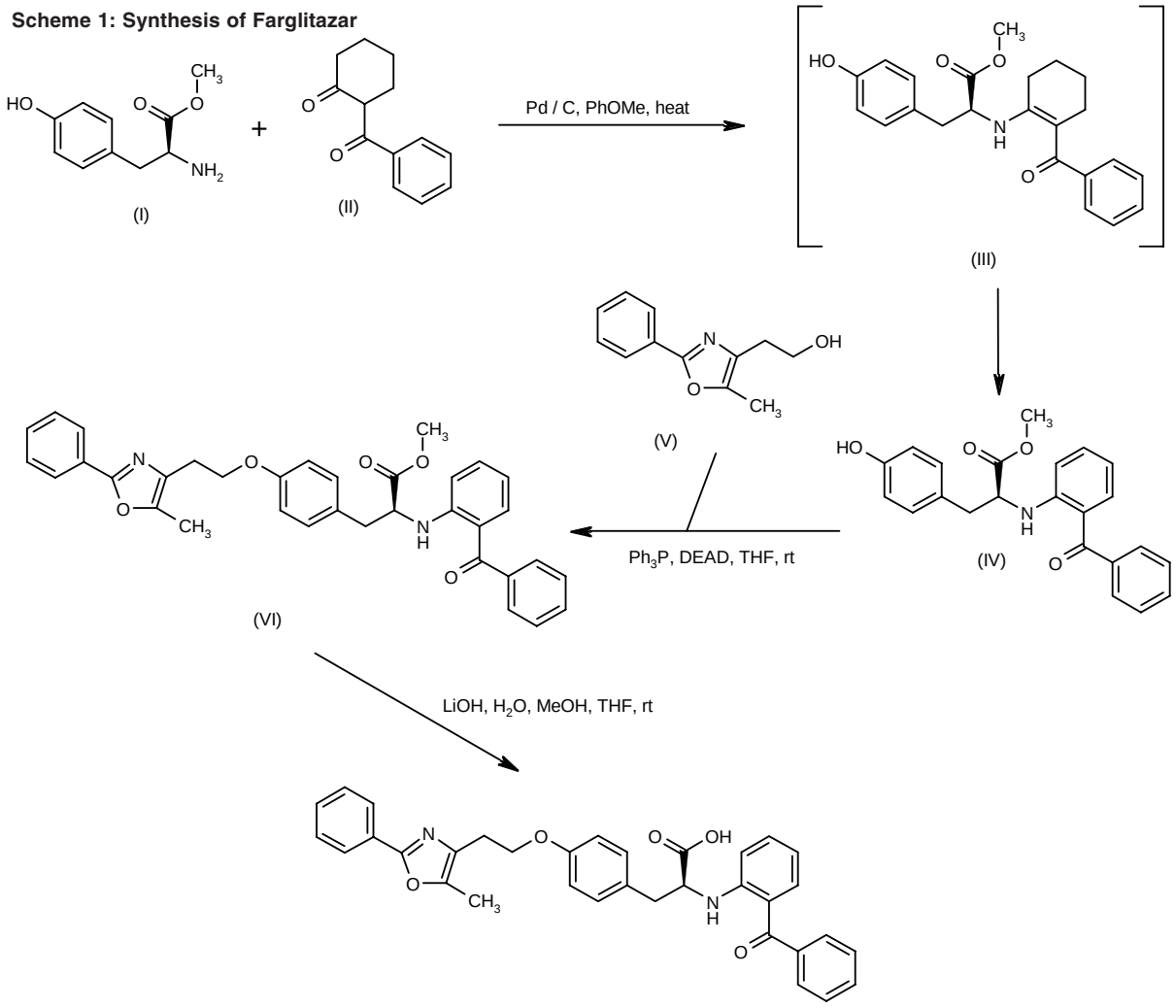
Scheme 1: Synthesis of Farglitazar



(8-13). The PPARγ subtype is mainly expressed in adipose tissue and 3 isoforms, PPARγ1, PPARγ2 and PPARγ3, exist with PPARγ1 the most prominent form (14-16). Studies have demonstrated that several endogenous fatty acids, eicosanoids, prostaglandins and their metabolites can modulate PPARγ activity, suggesting that these compounds may be the natural ligands for this receptor (5, 17-20). PPARγ forms heterodimers with another nuclear receptor, the 9-*cis*-retinoic acid receptor (RXR). PPARγ/RXR heterodimers bind to DNA and are the actual functional transcription factor within cells (Fig. 1) (21).

The PPARγ receptor is a particularly attractive target for antidiabetic therapy and PPAR agonists currently under development for the treatment of type 2 diabetes are shown in Table I. Thiazolidinediones (*e.g.*, troglitazone, rosiglitazone, pioglitazone) were the first high-affinity PPARγ agonists discovered and they have been developed for the last 15 years (22). Thiazolidinediones are insulin sensitizers. These agents do not increase insulin secretion or the number or affinity of insulin receptor binding sites but are thought to amplify postreceptor events in the insulin signaling cascade (23, 24). However, a number of thiazolidinediones possibly due to their structure and/or mechanism of action are associated with a poor safety profile and have been discontinued (25). Hence, a series of potent, selective nonthiazolidinedione tyrosine-based PPARγ agonists have been developed as antihyperglycemic, antihyperlipidemic agents. Of these compounds, farglitazar (GI-262570) has emerged as a promising agent for the treatment of diabetes and has been selected for further development (2).

Pharmacological Actions

Farglitazar is a nonthiazolidinedione with high-affinity binding to the human PPARγ. *In vitro* studies in which the PPAR ligand binding domains for murine and human PPARα, PPARγ and PPARδ were fused to the yeast

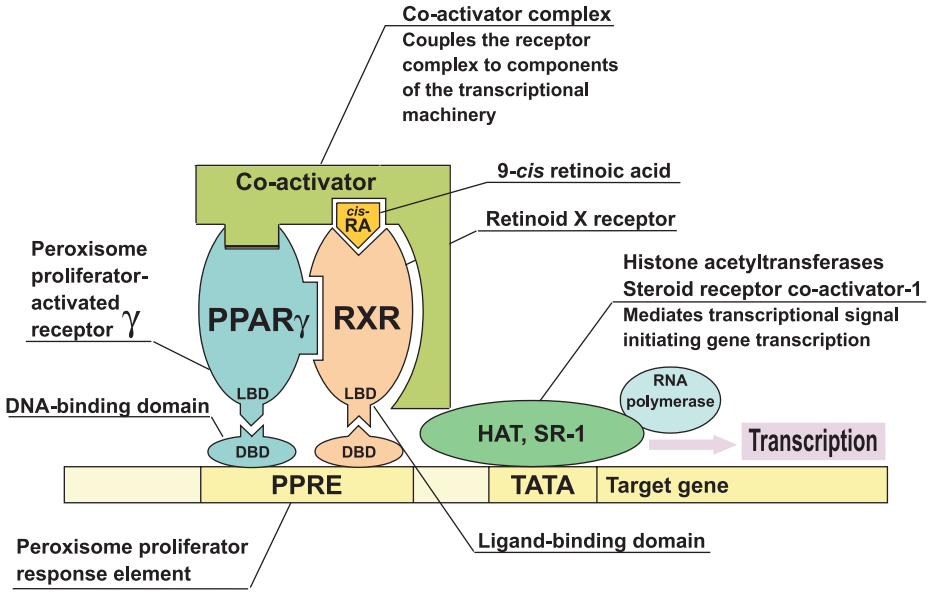


Fig. 1. The PPARγ/RXR complex. The PPARγ/RXR heterodimer binds to DNA and regulates transcription. (This figure is also in an animated format and can be found in the Prous Science Drug R&D Backgrounders database.)

transcription factor GAL4 DNA binding domain and subsequently transiently transfected along with a reporter construct to drive expression of secreted placental alkaline phosphatase (SPAP) and β-galactosidase in CV-1 cells, showed that farglitazar was inactive (at 10 μM) at the human PPARδ but bound to human PPARα and PPARγ with EC_{50} values of 0.45 and 0.00034 μM, respectively. The agent was inactive at both the murine PPARα and PPARδ while binding to murine PPARγ with an EC_{50} value of 0.00035 μM. Results indicate that farglitazar is more than 1000-fold more selective for PPARγ than PPARα and PPARδ. Farglitazar also displayed lipogenetic activity in an *in vitro* assay examining the ability of the agent to induce differentiation of C3H10T1/2 stem cells to adipocytes; an EC_{50} value of 1.5 nM was obtained (2, 24, 26).

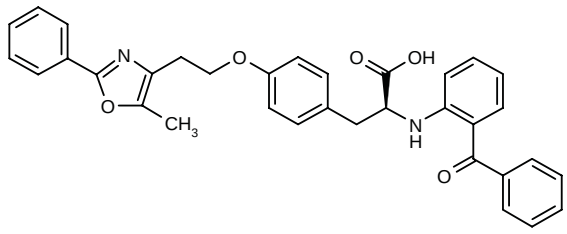
Farglitazar binds to the human PPARγ/RXRα heterodimer with K_i values of 1 nM which is approximately 50-fold higher than that of rosiglitazone (2, 26). Farglitazar bound preferentially to PPARγ complexed with RXRα as compared to rosiglitazone and pioglitazone. Farglitazar displayed a 9-fold preference (*vs.* 4-fold for thiazolidinediones) for binding to the PPARγ/RXRα complex as compared to the uncomplexed PPARγ. Similar binding results were obtained with the PPARγ/cAMP response element binding protein (CBP) complex. Thus, results demonstrated that farglitazar was more effective in stabilizing transcriptionally relevant receptor complexes than thiazolidinediones. Crystal structure analysis revealed that farglitazar bound to the human PPARγ/RXRα complex in a U-shaped confirmation occupying about 40% of a hydrophobic pocket that rosiglitazone cannot access and interacted directly with the PPARγ AF-2 helix. These results may be an explanation for why farglitazar possesses a greater affinity for PPARγ (26-28).

The antihyperglycemic and antihyperlipidemic activity of farglitazar was demonstrated in *in vivo* studies using male db/db mice and Zucker diabetic fatty (ZDF) rats as models of type 2 diabetes. In db/db mice, administration of the agent (5 mg/kg p.o. b.i.d. for 14 days) resulted in decreases in nonfasted glucose, triglycerides, free fatty acids and insulin of 65, 37, 56 and 54%, respectively. Glucose levels of ZDF rats treated with 0.3, 1, 3 or 5 mg/kg farglitazar (p.o. b.i.d.) for 14 days were 465 ± 32.7, 343 ± 55.2, 218 ± 36.3 and 168 ± 21.8 mg/dl, respectively, as compared to 462 ± 20.3 mg/dl in rats treated with the vehicle. HbA1c (9.25 ± 0.30, 8.37 ± 0.52, 6.89 ± 0.43 and 6.36 ± 0.32%, respectively, *vs.* 9.48 ± 0.18%) and free fatty acid (0.91 ± 0.06, 0.57 ± 0.07, 0.31 ± 0.03 and 0.24 ± 0.04 mEq/l, respectively, *vs.* 0.96 ± 0.08 mEq/l) were also decreased in treated animals as compared to controls. Triglyceride levels were reduced in animals treated with the 1, 3 and 5 mg/kg doses (564 ± 91, 215 ± 22 and 186 ± 33 mg/dl, respectively, *vs.* 810 ± 72 mg/dl) (2, 29).

Long-term glycemic efficacy of farglitazar (3 mg/kg/day) was shown in an *in vivo* study using ZDF rats treated at either 6 weeks (prior to the onset of diabetes), 8 weeks (when animals were diabetic but insulin levels were still rising) or 10 weeks (when animals were diabetic and insulin levels were falling). All treated ZDF rats showed decreased levels of serum fatty acid and triglycerides. ZDF rats treated with the agent at 6 or 8 weeks displayed normal fed glucose levels throughout the 24 weeks of the study (< 200 mg/dl). Moreover, HbA1c levels of ZDF animals treated at 6 or 8 weeks were not

Table I: PPAR agonists for type 2 diabetes.

Drug Name	Source	Target	Status
1. Farglitazar	GlaxoSmithKline	PPAR-γ	Phase III
2. JTT-501 (PNU-182716)	Japan Tobacco/Pharmacia	PPAR-γ	Phase II/III
3. AR-H039242*	AstraZeneca	PPAR (not specified)	Phase II
4. MCC-555	Mitsubishi Chem./Johnson & Johnson	PPAR-γ	Pgase II
5. AR-H049020*	AstraZeneca	PPAR (not specified)	Phase I/II
6. CS-011 (CI-1037)	Sankyo/Pfizer	PPAR-γ	Phase I
7. GW-409544X	Ligand/GlaxoSmithKline	PPAR-α/PPAR-γ	Phase I
8. KRP-297	Kyorin/Merck & Co.	PPAR-α/PPAR-γ	Phase I
9. RG-12525	Aventis	PPAR-γ	Clinical trials
10. BM-15.2054	Roche	PPAR-γ	Preclinical
11. CLX-0940*	Calyx	PPAR-α	Preclinical
12. CLX-0921*	Calyx	PPAR-γ	Preclinical
13. DRF-2189	Dr. Reddy's Research Foundation	PPAR-γ	Preclinical
14. GW-1929	GlaxoSmithKline	PPAR-γ	Preclinical
15. GW-9820	GlaxoSmithKline	PPAR-γ	Preclinical
16. LR-90	Lipha	PPAR-α/PPAR-γ	Preclinical
17. LY-510929*	Ligand/Lilly	PPAR (not specified)	Preclinical
18. NIP-221*	Nissan Chemical	PPAR-γ	Preclinical
19. NIP-223*	Nissan Chemical	PPAR-γ	Preclinical
20. JTP-20993	Japan Tobacco	PPAR-γ	Preclinical



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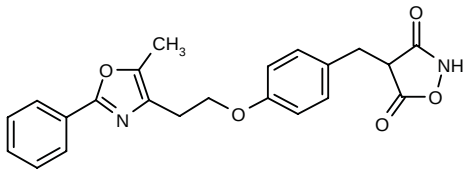

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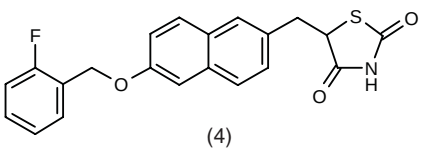

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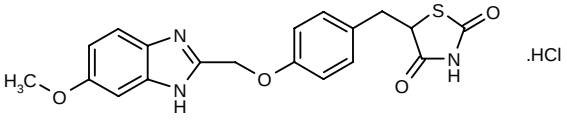

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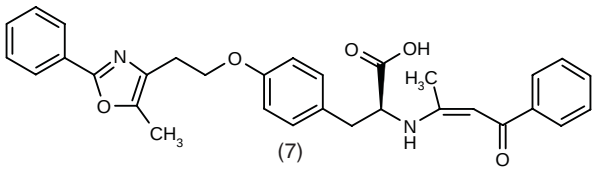

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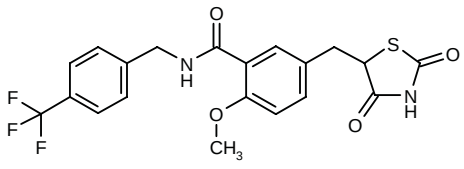

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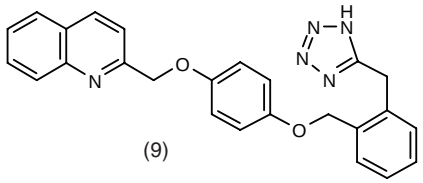

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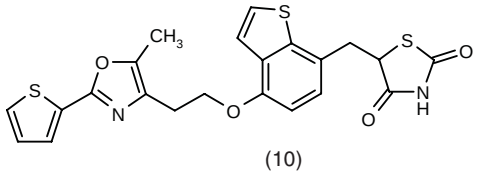

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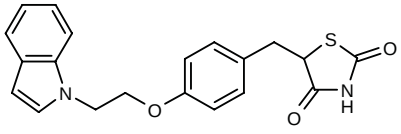

(13)

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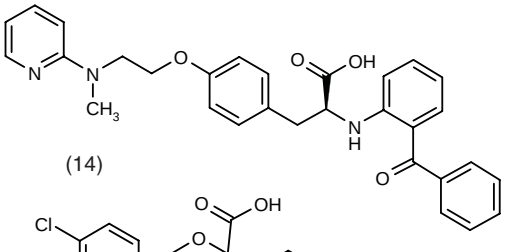
Table I: PPAR agonists for type 2 diabetes (Cont.).



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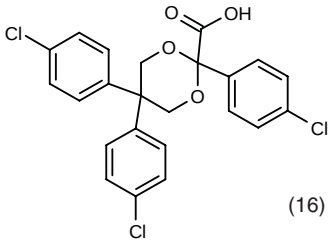

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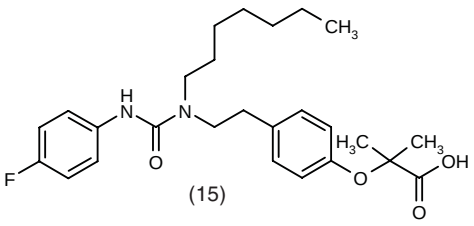

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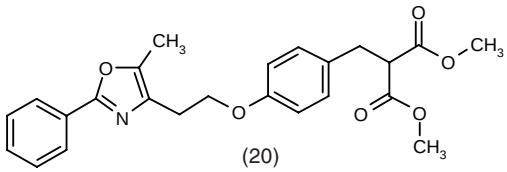

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significantly different from levels of lean littermates (5.6 ± 0.1 and 5.8 ± 0.1, respectively, *vs.* 5.8 ± 0.2). Insulin levels decreased in animals treated at 6 or 8 weeks to levels that were sustained although still considered hyperinsulinemic. In contrast, although ZDF animals treated at 10 weeks displayed an initial decrease in glucose levels with treatment (only 3 of 10 rats reached levels of < 200 mg/dl), levels gradually rose to values indicating severe diabetes. These results demonstrated that ZDF rats with early diabetes respond to farglitazar treatment by reverting to normal glycemia. However, if treatment was delayed, animals progressed so that glycemia could not be adequately controlled (30).

A study conducted in spontaneously obese hyperinsulinemic rhesus monkeys demonstrated that treatment with farglitazar (0.1, 0.5 and 1 mg/kg p.o. b.i.d. for 4 weeks/dose) significantly improved the prediabetic symptoms of metabolic syndrome X. Treated animals exhibited significant reductions in insulin (63%) and triglyceride (54%) levels and a 23% increase in HDL cholesterol as compared to baseline. Fasting glucose also significantly and dose-dependently decreased with levels normalized; no hypoglycemia was observed (31).

Pharmacokinetics

The pharmacokinetics of farglitazar were reported from the results of a randomized, double-blind, placebo-controlled, ascending dose, 6-way crossover trial in 10 healthy men (23-46 years). Each subject received 4 of 5 single farglitazar doses (0.5, 1.5, 5, 15 and 40 mg p.o. solution), a 5 mg dose of an oral farglitazar suspension and a placebo dose. Farglitazar treatment was well tolerated with no adverse events or significant alterations in laboratory parameters or cardiovascular parameters seen. Both AUC_{∞} (44 ± 13, 111 ± 26, 355 ± 69, 963 ± 222 and 2636 ± 642 ng·h/ml, respectively) and C_{max} (20 ± 5, 48 ± 12, 168 ± 35, 378 ± 56 and 1173 ± 225 ng/ml, respectively) were dose-proportional for doses of 0.5, 1.5, 5, 15 and 40 mg. $T_{1/2}$ values for the respective doses were 3.0 ± 1.9, 3.9 ± 0.5, 4.9 ± 0.8, 4.9 ± 0.4 and 5.3 ± 0.9 h (32).

Studies have also demonstrated that multiple farglitazar dosing has no clinically significant effect on the pharmacokinetics of warfarin or digoxin. A double-blind, placebo-controlled study conducted in 22 healthy subjects administered warfarin (individually dosed) on days 1-14 and farglitazar (10 mg) or placebo on days 15-25 reported that the AUC_{24} and C_{max} values for (*R*)- and (*S*)-warfarin were decreased by 20% with combination treatment. However, the mean prothrombin time on day 24 was 17.4 ± 2.4 and 17.2 ± 1.5 s for subjects receiving warfarin + farglitazar and warfarin + placebo, respectively, indicating no effects on digoxin pharmacodynamics (33).

A randomized, double-blind, placebo-controlled study in 24 healthy subjects administered digoxin on days 1-14 and farglitazar (10 mg) or placebo on days 15-25 showed no significant differences in the pharmacokinetics of digoxin in subjects treated with combination therapy as compared to treatment with digoxin + placebo. AUC_{0-24} and C_{max} values for subjects treated with digoxin + farglitazar and digoxin + placebo were 19.52 and 8.35 ng·h/ml and 2.30 and 2.15 ng/ml, respectively (34).

A model to prospectively predict the absolute change in HbA1c levels at 3 months during treatment with farglitazar (0.25, 1, 2, 5 and 10 mg) has been described. The glucose indirect response model linked to a caternary chain HbA1c model was constructed and results obtained were compared to data from 2- and 12-week farglitazar trials performed in patients with type 2 diabetes. Results obtained with the model generally agreed with the actual results except for the predicted absolute changes in HbA1c from baseline for the two highest doses (best case: –1.2 and –1.5 predicted for 5 and 10 mg, respectively, *vs.* –1.4 and –1.9 for actual trial, respectively) (35) (Box 1).

Box 1: Prospective comparison of clinical trial simulation and actual phase II results for farglitazar (35) [Prous Science CSline database].

Design	Dose-finding clinical study
Population	Patients with diabetes mellitus
Treatments	Farglitazar, 0.25 mg o.d. x 14 wks Farglitazar, 1 mg o.d. x 14 wks Farglitazar, 2 mg o.d. x 14 wks Farglitazar, 5 mg o.d. x 14 wks Farglitazar, 10 mg o.d. x 14 wks
Results	HbA1c levels in worst case mode, change @ 14 wks: G10 (–0.7%) ≥ G5 (–0.6%) ≥ G2 (–0.4%) ≥ G1 (–0.2) ≥ G0.25 (–0.1) in most likely model: G10 (–1.2%) ≥ G5 (–1.0%) ≥ G2 (–0.7%) ≥ G1 (–0.5) ≥ G0.25 (–0.2) in best case model: G10 (–1.5%) ≥ G5 (–1.2%) ≥ G2 (–0.8%) ≥ G1 (–0.6) ≥ G0.25 (–0.3) in actual trial: G10 (–1.9%) ≥ G5 (–1.4%) ≥ G2 (–0.8%) ≥ G1 (–0.4) ≥ G0.25 (–0.2)
Conclusions	Farglitazar was effective in diabetes mellitus

Box 2: Farglitazar improves metabolic control in patients with type 2 diabetes (36) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled, dose-finding clinical study
Population	Patients with noninsulin-dependent diabetes mellitus (n = 35)
Treatments	Farglitazar, 1.5 mg o.d. x 14 d (n = 8) Farglitazar, 7 mg o.d. x 14 d (n = 7) Farglitazar, 21 mg o.d. x 14 d (n = 8) Placebo (n = 12)
Results	24-h least square glucose levels, change *vs.* P @ 14 d: F21* (–22.2%) ≥ F7* (–14.8%) ≥ F1.5 (–9.6) [*p <0.05 *vs.* P] 24-h least square insulin levels, change *vs.* P @ 14 d: F21* (–32.3%) ≥ F7* (–27.7%) ≥ F1.5 (–9.4) [*p <0.05 *vs.* P] 24-h least square triglyceride levels, change *vs.* P @ 14 d: F21* (–38.0%) ≥ F7* (–29.6%) ≥ F1.5 (–11.4) [*p <0.05 *vs.* P]
Conclusions	Farglitazar improved metabolic control in noninsulin-dependent diabetes mellitus

Clinical Studies

Farglitazar (1.5, 7 or 21 mg once daily for 14 days) was shown to improve metabolic control in patients with type 2 diabetes in a randomized, double-blind, placebo-controlled trial conducted in a total of 35 patients. Significant reductions in glucose were observed for all doses (9.6, 14.8 and 22.2%, respectively) and significant decreases in insulin (27.7 and 32.3%, respectively) and triglycerides (29.6 and 38%, respectively) were seen with doses of 7 and 21 mg. The decreases observed were sustained for 24 h postdosing (36) (Box 2).

The efficacy of farglitazar (1, 2, 5 and 10 mg once daily for 12 weeks) as a monotherapy for improving glycemic control in type 2 diabetes patients was demonstrated in a randomized, double-blind, placebo-controlled trial conducted in a total of 376 patients. Treatment was well tolerated and the safety profile obtained for farglitazar was similar to that observed with other PPARγ agonists in that dose-related weight gain, peripheral edema and decreases in hemoglobin were observed. Although a dose of 0.25 mg/day was ineffective, treatment for 12 weeks with 1, 2, 5 and 10 mg farglitazar resulted in significant dose-related reductions in HbA1c (–0.4, –0.8, –1.4 and –1.9, respectively) and fasting serum glucose as compared to placebo. Decreases in fasting serum glucose were significant as early as 2-4 weeks (–0.6, –1.1, –1.9 and –3.0, respectively, *vs.* +1.2 in placebo at 4 weeks), further decreasing at 4-8 weeks and subsequently stabilizing by 8-12 weeks (–0.5, –1.6, –2.7 and –3.7, respectively, *vs.* –1.2 in placebo at 12 weeks). Over 70% of the patients treated with the 5 or 10 mg dose had reductions in fasting serum glucose of 1.67 mmol/l or more. Moreover, over 40% of the patients treated with the 5 or 10 mg doses exhibited reductions in HbA1c levels of 0.7% or greater. Significant improvements in triglycerides (–6, –13, –30 and –43% change from baseline at 12 weeks, respectively, *vs.* +3% in placebo) and HDL-cholesterol (+4, +13, +12 and +15% changes from baseline at 12 weeks, vs. 0% in placebo) were also observed with all doses and apolipoprotein B levels decreased 8-14% with the 5 and 10 mg doses (37, 38) (Boxes 3 and 4).

A multicenter, randomized, double-blind, placebo-controlled study conducted in 385 patients with type 2

Box 3: Effects of monotherapy with farglitazar on glycemic control in type 2 diabetes mellitus patients (37) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled, dose-finding clinical study
Population	Farglitazar, in noninsulin-dependent diabetes mellitus (n = 376)
Treatments	Farglitazar, 0.25 mg o.d. x 12 wks (n = 64) Farglitazar, 1 mg o.d. x 12 wks (n = 59) Farglitazar, 2 mg o.d. x 12 wks (n = 61) Farglitazar, 5 mg o.d. x 12 wks (n = 58) Farglitazar, 10 mg o.d. x 12 wks (n = 67) Placebo (n = 67)
Results	Fasting serum glucose levels (mmol/l), change @ 4 wks: F10* (–3.0) ≥ F5* (–1.9%) ≥ F2* (–1.1) ≥ F1* (–0.6) ≥ P (1.2) [*p <0.05 *vs.* P]; @ 12 wks: F10* (–3.7) ≥ F5* (–2.7%) ≥ F2* (–1.6) ≥ F1* (–0.5) ≥ P (1.2) [*p <0.05 *vs.* P] HbA1c levels (mmol/l), change @ 12 wks: F10 (–0.7) ≥ F5 (–0.3) ≥ F2 (0.3) ≥ F1 (0.7) ≥ P (1.1)
Conclusions	Farglitazar improved metabolic control in noninsulin-dependent diabetes mellitus

Box 4: Efficacy of monotherapy with farglitazar in patients with type 2 diabetes mellitus (38) [Prous Science CSline database].

Design	Randomized, dose-finding, double-blind, placebo-controlled clinical study
Population	Patients with type 2 diabetes mellitus (n = 376)
Treatments	Farglitazar, 0.25 mg p.o. o.d. x 12 wks (n = 64) Farglitazar, 1 mg p.o. o.d. x 12 wks (n = 59) Farglitazar, 2 mg p.o. o.d. x 12 wks (n = 61) Farglitazar, 5 mg p.o. o.d. x 12 wks (n = 58) Farglitazar, 10 mg p.o. o.d. x 12 wks (n = 67) Placebo (n = 67)
Results	Triglycerides levels, % change @ 12 wks: F10* (–43) ≥ F5* (–30) ≥ F2** (–13) ≥ F1 (–6) ≥ P (3) [*p <0.001, **p <0.05 *vs.* P] ; in patients with hypertriglyceridemia @ 12 wks: F10 (–53) ≥ F5 (–44) ≥ F2 (–19) ≥ F1 (–18) ≥ P(–7) HDL-cholesterol levels, % change @ 12 wks: F10* (15) ≥ F2** (13) ≥ F5** (12) ≥ F1 (4) ≥ P (0) [*p <0.001, **p <0.005 *vs.* P]
Conclusions	Farglitazar enhanced overall metabolic control in patients with type 2 diabetes mellitus by improving dyslipemia and hyperglycemia

Box 5: Effect of farglitazar in combination with glibenclamide on metabolic control in patients with type 2 diabetes (39) [Prous Science CSline database].

Design	Randomized, placebo-controlled, dose-finding clinical study
Population	Patients with noninsulin-dependent diabetes mellitus inadequately controlled on glibenclamide (n = 385)
Treatments	Glibenclamide, 15 mg p.o. o.d x 12 wks +Farglitazar, 0.25 mg o.d. x 12 wks (n = 122) Glibenclamide, 15 mg p.o. o.d x 12 wks + Farglitazar, 1 mg o.d. x 12 wks (n = 53) Glibenclamide, 15 mg p.o. o.d x 12 wks + Farglitazar, 2 mg o.d. x 12 wks (n = 48) Glibenclamide, 15 mg p.o. o.d x 12 wks + Farglitazar, 5 mg o.d. x 12 wks (n = 54) Glibenclamide, 15 mg p.o. o.d x 12 wks + Farglitazar, 10 mg o.d. x 12 wks (n = 52) Glibenclamide, 15 mg p.o. o.d x 12 wks + Placebo (n = 56)
Adverse events	F10: hypoglycemic symptoms
Results	Fasting serum glucose levels (mmol/l), change *vs.* P @ 12 wks: F10* (–5.4) ≥ F5* (–4.7%) ≥ F1* (–2.0) ≥ F2** (–1.7) [*p <0.001 *vs.* P; **p <0.005 *vs.* P] Patients (%) with ≥ 1.67 mmol/l reduction in fasting serum glucose levels: F10* (90) ≥ F5* (87%) ≥ F1** (54) ≥ F2** (53) ≥ P (31) [*p <0.001 *vs.* P; **p <0.05 *vs.* P] HbA1c levels (mmol/l), change *vs.* P @ 12 wks: F10* (–2.1) ≥ F5* (–1.9%) ≥ F1* (–0.7) ≥ F2** (–0.5) [*p <0.001 *vs.* P; **p <0.05 *vs.* P] Patients (%) with ≥ 0.7% reduction in HbA1c levels: F10* (92) ≥ F5* (87%) ≥ F1** (50) ≥ F2 (38) ≥ P (22) [*p <0.001 *vs.* P; **p <0.005 *vs.* P]
Conclusions	Farglitazar improved metabolic control in noninsulin-dependent diabetes mellitus patients inadequately controlled on glibenclamide

Box 6: Efficacy of combination treatment with farglitazar and glibenclamide in patients with type 2 diabetes mellitus (40) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled, dose-finding, multicenter clinical studyy
Population	Patients with type 2 diabetes mellitus inadequately controlled with glibenclamide (n = 385)
Treatments	Farglitazar, 0.25 mg p.o. o.d. + Glibenclamide, 15 mg/d p.o. x 12 wks Farglitazar, 0.5 mg p.o. o.d. + Glibenclamide, 15 mg/d p.o. x 12 wks Farglitazar, 1 mg p.o. o.d. + Glibenclamide, 15 mg/d p.o. x 12 wks (n = 53) Farglitazar, 2 mg p.o. o.d. + Glibenclamide, 15 mg/d p.o. x 12 wks (n = 48) Farglitazar, 5 mg p.o. o.d. + Glibenclamide, 15 mg/d p.o. x 12 wks (n = 54) Farglitazar, 10 mg p.o. o.d. + Glibenclamide, 15 mg/d p.o. x 12 wks (n = 52) Placebo + Glibenclamide, 15 mg/d p.o. x 12 wks (n = 56)
Results	Triglyceride levels, % change @ 12 wks: F10* (–40) ≥ F5* (–32) ≥ F2** (–16) ≥ F1*** (–15) > P (2) [*p <0.001, **p <0.005, ***p <0.05 *vs.* P] ; in patients with hypertriglyceridemia @ 12 wks: F10 (–48) ≥ F5 (–42) ≥ F1 (–23) ≥ F2 (–20) > P (–11) HDL-cholesterol levels, % change @ 12 wks: F10* (23) ≥ F5* (21) ≥ F2** (13) ≥ F1** (12) > P (1) [*p <0.001, **p <0.05 *vs.* P]
Conclusions	Farglitazar in combination with glibenclamide enhanced overall metabolic control in patients with type 2 diabetes mellitus by improving HDL-cholesterol and triglyceride levels

diabetes who were inadequately controlled on glibenclamide alone (15 mg) showed the efficacy of combination farglitazar (1, 2, 5 or 10 mg/day) + glibenclamide (15 mg) treatment for 12 weeks. Cotreatment was well tolerated with dose-related weight gain, peripheral edema and decreases in hemoglobin observed with farglitazar treatment. A higher incidence of hypoglycemic symptoms was noted in the group receiving combination glibenclamide + 10 mg farglitazar. Combination treatment with all doses resulted in significant decreases in fasting serum glucose (–2, –1.7, –4.7 and –5.4, respectively) and HbA1c (–0.7, –0.5, –1.9, –2.1, respectively) at 12 weeks; doses of 0.25 and 0.5 mg were ineffective. Over 85% of the patients on combination therapy including the 5 and 10 mg farglitazar doses exhibited decreases in fasting serum glucose of 1.67 mmol/l or more and decreases in HbA1c of 0.7% or more. Significant improvements in triglycerides (–15, –16, –32, –40%, respectively, vs. +2% in placebo) and HDL-cholesterol (+12, +13, +21 and +23%, respectively, *vs.* +1% in placebo) were also observed at 12 weeks with combination treatment; the greatest improvements in these parameters were observed in those patients with mild to moderate hypertriglyceridemia (fasting triglycerides > 150 mg/dl) at baseline (39, 40) (Boxes 5 and 6).

Farglitazar is currently undergoing phase III development for the treatment of type 2 diabetes (41).

Manufacturer

GlaxoSmithKline plc (GB).

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