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Review Article

Indole-containing thiazolidine-2,4-diones as novel euglycemic and hypolipidemic agents: DRF-2189

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CONTENTS

Introduction

Diabetes is the seminal cause of several chronic and progressive diseases which adversely affect a number of organs, including the nervous and vascular systems. More than 90% of diabetic patients are noninsulin-dependent, *i.e.*, type II diabetes (noninsulin-dependent diabetes mellitus; NIDDM). Type II diabetes is a metabolic disorder characterized by hyperglycemia and insulin resistance (1-3) and leads to several secondary complications such as neuropathy, nephropathy, retinopathy, atherosclerosis and other coronary artery diseases (4-6). In type II diabetes, although the pancreatic B cells are capable of producing insulin, insulin is unable to act in all the target tissues due to a metabolic disorder (7). This abnormality which leads to hyperinsulinemia, is referred to as insulin resistance. Detailed etiology of diabetes is a matter of debate and the mechanism of development of insulin resistance is still unclear (8, 9), although elevated circulating lipids have been recently proposed to be a cause (10-13).

Despite our poor understanding of the cause of insulin resistance, several thiazolidinediones (TZD) have been developed which act as insulin sensitizers in animal models of diabetes such as db/db or ob/ob mice. These animals also have insulin resistance and mimic the type II diabetes observed in humans (14). Recently attempts have been made to correlate the action of insulin normalizers (also glucose normalizers) with certain nuclear receptors such as peroxisome proliferator activated receptor-γ (PPAR-γ) (15-22). It has been suggested that thiazolidine-2,4-diones activate PPAR-γ which leads to a cascade of events responsible for their insulin normalizing effect (23). However, other studies (24), including some of our own observations (25), do not fully corroborate this hypothesis. Some TZDs have also been found to have triglyceride (TG) lowering activity in addition to plasma glucose lowering effects. It has been speculated that TG lowering activities of these TZDs are due to agonist activity with another nuclear receptor, PPAR-α (26, 27). Thus, TZDs that exhibit both PPAR-α and PPAR-γ agonist activities may be able to control plasma glucose and TG levels effectively, presumably reducing the secondary complications in diabetic patients (23).

A specific advantage of TZDs as insulin sensitizers is that they may be able to prevent the progression of diabetes and related complications without the risk of hypoglycemia. Over the past decade and after the pioneering discovery of ciglitazone by a group of scientists at Takeda (28), several TZDs of diverse structures have been developed. Troglitazone (Sankyo) has been on the market since 1997 (29-31). Pioglitazone (Takeda) and rosiglitazone (SmithKline Beecham) have recently been approved in the U.S. (32-36) and englitazone (Pfizer) is in phase II development (37-39) (Fig. 1). Other compounds are also undergoing clinical evaluation (40). However, due to the unsatisfactory efficacy and safety profile of these agents, there has been concern about TZDs as antidiabetic drugs. Nevertheless, the encouraging clinical reports on troglitazone (regardless of the liver toxicity reported in a limited number of patients) (41-43), have generated interest among the pharmaceutical industry to develop newer TZD analogs (44-64).

Recently, some of the indole derivatives have been implicated in lowering blood glucose with a single dose in KKAy mice (50 mg/kg) (64). Certain imidazoline-containing compounds (and other related analogs) have been found to decrease plasma glucose in a dose-dependent manner following oral glucose load in healthy human subjects (65-67).

Herein we describe the structure-activity relationships of various indole-containing and related TZDs, including pharmacological, pharmacokinetic and toxicity profiles, as well as the effect of TZDs on PPAR nuclear receptors.

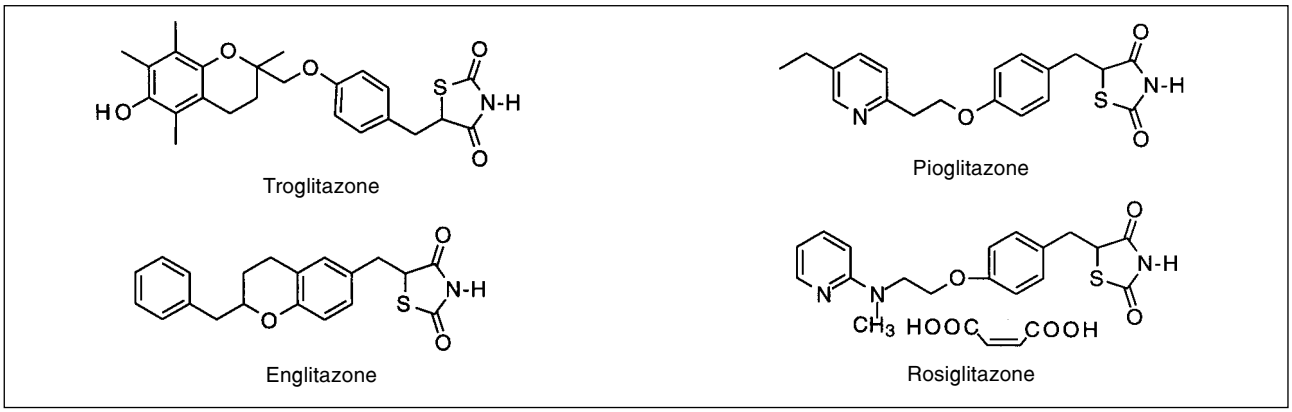


Fig. 1. Chemical structures of insulin-sensitizing thiazolidinediones.

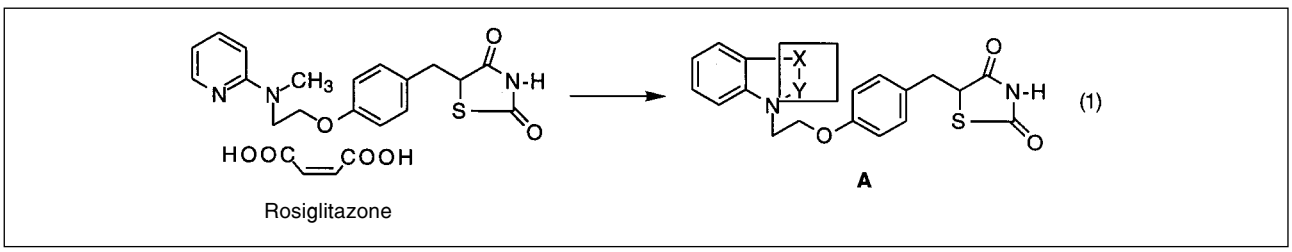


Fig. 2. Approach to modifying rosiglitazone.

Structure-activity relationship studies

One of the TZDs in development, rosiglitazone, was approved in May of this year by the FDA. We hypothesized that the incorporation of a methyl group on the nitrogen of rosiglitazone in a ring with or without a carbon or heteroatoms (Fig. 2, structure **A**), would improve the pharmacological profile of the compound and possibly increase its potency, as was observed in other cases (68).

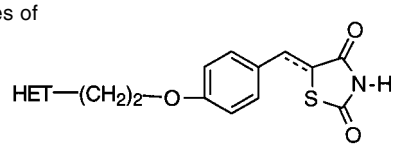
Based on this assumption, several TZDs containing indole and related heterocycles (69) in the structural motif of **A** were synthesized and evaluated in animal models of diabetes and compared with troglitazone and rosiglitazone. Some of the selected examples are presented in Table I.

Initially, several unsaturated TZDs were examined at a dose of 200 mg/kg/day in db/db mice as an initial screening method and were compared with the same dose of the standard drug troglitazone. As seen in Table I, the azaindole (**1**) and benzimidazole (**2**) derivatives of unsaturated TZDs were as potent as troglitazone (**11**) in euglycemic and TG lowering activity. However, the corresponding indole derivative (**3**) showed poor TG lowering activity. On the other hand, dihydroindole (**4**) was distinctly superior in euglycemic and TG lowering activities to troglitazone (**11**) and the 2-methylaminopyridine derivative (**5**). It is noteworthy that (**5**) is the unsaturated TZD analog of rosiglitazone. Thus, further structure-activity relationship studies were carried out with the saturated TZD analogs of azaindole (**6**), dihydroindole (**7**) and indole (**8**), comparing results with those from the saturated 2-methylaminopyridine derivative (**9**), of which rosiglitazone is the maleate salt. Although all the compounds showed good euglycemic and excellent to good TG lowering activities and were superior to the pyridine analog (**9**), the indole derivative (**8**; DRF-2189) was found to be the most potent euglycemic and hypolipidemic agent.

Comparative studies were carried out in db/db mice using DRF-2189 (**8**) and rosiglitazone (**10**) at doses of 1, 3 and 10 mg/kg/day, and the results were compared with those for troglitazone doses of 100, 200 and 800 mg/kg. The dose-dependent reductions in plasma glucose and TG levels are shown in Figure 3. As can be seen, DRF-2189 and rosiglitazone were approximately equipotent, whereas troglitazone even at 800 mg/kg was less effective in reducing plasma glucose. The reductions in plasma glucose and TG for DRF-2189 and rosiglitazone were not significantly different in db/db mice. The oral ED_{50} for plasma glucose lowering for DRF-2189 was 3 mg/kg and higher doses (10 and 30 mg/kg) did not further reduce the blood sugar level. Similarly, plasma TG lowering activity was found to be the highest (~ 53% reduction in plasma TG) with 1 mg/kg; once again, higher doses did not further reduce TG levels. Furthermore, DRF-2189 also reduced plasma insulin levels by 79%, similar to rosiglitazone (10 mg/kg).

DRF-2189 was further evaluated in ob/ob mice at 20 mg/kg for 14 days. Treatment resulted in reductions in plasma glucose and TG levels of 56% and 50%, respec-

Table I: Euglycemic and hypolipidemic activities of



Compound	HET	DB	Dose (mg/kg)	PG[a]	TG[a]
1		Yes	200	36 ± 6	79 ± 10
2		Yes	200	33 ± 6	76 ± 8
3		Yes	200	33 ± 7	37 ± 14
4		Yes	200	61 ± 5	83 ± 7
5		Yes	100	56 ± 6	32 ± 12
6		No	200	33 ± 9	74 ± 10
7		No	200	33 ± 8	79 ± 9
8		No	100	74 `± 8	77 ± 10
9		No	100	71 ± 5	46 ± 12
10		No	10	55 ± 7	37 ± 10
11	Troglitazone	No	200	41 ± 8	66 ± 8

[a]Percentage reduction in plasma glucose and triglyceride after 9 days of dosing in db/db mice. DB = double bond; dotted line = optional double bond. Compound **10** is the maleate salt of compound **9**.

tively. In addition, a 22% reduction in cholesterol was also observed, an effect not found with rosiglitazone. A glucose tolerance test performed in ob/ob mice after 15 days of treatment led to a 68% reduction in AUC (70). In contrast, troglitazone-treated animals showed only a 30% improvement in glucose clearance. When high fat-fed Sprague Dawley rats were treated with DRF-2189 (10 and 30 mg/kg), significant reductions in TG (47 and 30%), total cholesterol (11 and 41%), LDL cholesterol (13 and 47%) and VLDL (47 and 36%) were observed, as well as an increase in HDL cholesterol (80 and 79%). In contrast, rosiglitazone at the same doses did not have any effect on the above parameters. It should be pointed out that improved management of lipid profiles is essential for patients with a high risk of coronary artery disease and in this regard, DRF-2189 was superior to rosiglitazone.

Toxicity studies

In acute toxicity studies, DRF-2189 (300 mg/kg) caused no behavioral changes and the LD_{50} was 800 mg/kg i.p. Thus, the therapeutic safety window of this compound appears to be quite wide. In subcutaneous toxicity studies, animals treated with a dose 16 times higher than the ED_{50} dose of DRF-2189 did not exhibit any adverse behavioral changes and there were no significant changes in body weight or food consumption. After 28 days of treatment with DRF-2189 (50 mg/kg/day), a nonsignificant reduction in hemoglobin (12%), packed cell volume (9%) and an increase in heart weight (13%) were observed; no change in liver weight was observed. No treatment-related changes were seen after biochemical and histological examination of various organs, further indicating the safety of this compound.

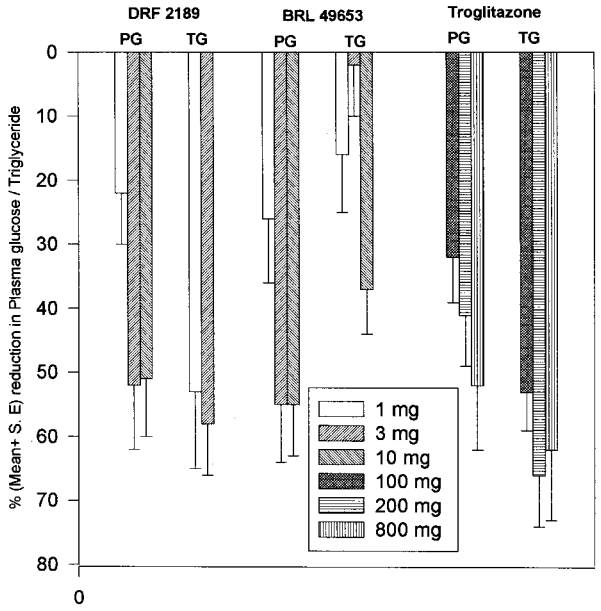


Fig. 3. Reductions in plasma glucose and triglyceride with various doses of DRF-2189, rosiglitazone (BRL 49653) and troglitazone.

Oral bioavailability and pharmacokinetic studies

Pharmacokinetic studies were performed in Wistar rats administered DRF-2189 at oral and i.v. doses of 1, 3 and 10 mg/kg (71). DRF-2189 was absorbed slowly, attaining C_{max} at 2-3 h and was eliminated with a $t_{1/2}$ of 3 h. C_{max} and $AUC_{0-\infty}$ values increased linearly (r^2 = 0.99) with dose, while elimination $t_{1/2}$ was independent of dose (Fig. 4).

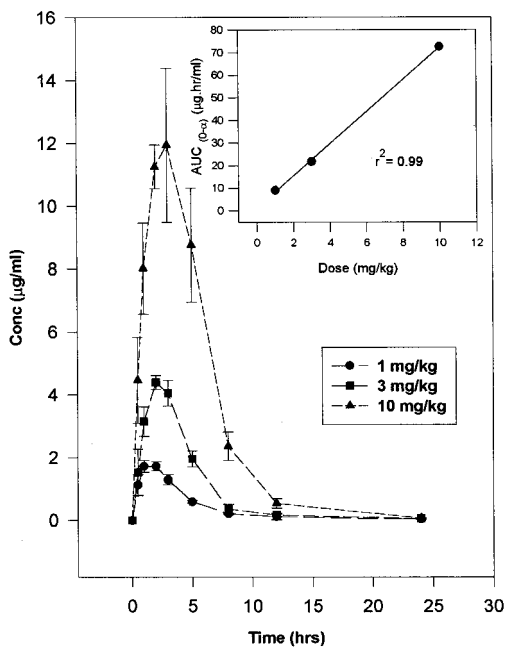


Fig. 4. Bioavailability of DRF-2189 in Wistar rats.

Table II: Pharmacokinetic parameters for DRF-2189 and rosiglitazone (100 mg/kg/p.o.) in Wistar rats.

Parameters	DRF-2189[a]	Rosiglitazone[b]
$AUC_{0-\infty}$ (µg.h/ml)	129.3 ± 46.3	59.2 ± 19.0
C_{max} (µg/ml)	14.54 ± 2.4	29.4 ± 6.0
t_{max} (h)	3.67 ± 1.2	0.5 ± 0.0
K_{el} (h^{-1})	0.25 ± 0.14	0.72 ± 0.18
$t_{1/2}$ (h)	3.28 ± 1.4	1.02 ± 0.24

[a]Results are mean ± SD of 3 animals; [b]Results are mean ± SD of 6 animals.

Table III: Tissue levels for DRF-2189 and rosiglitazone (10 mg/kg/p.o.) in Wistar rats[a].

Tissue (µg/g)	DRF-2189	Rosiglitazone
Liver	10.01 (0.85	10.90 (0.40)
Subcutaneous fat	1.50 (0.13)	14.32 (0.53
Brown fat	1.23 (0.10)	2.10 (0.08)
Skeletal muscle	0.85 (0.07)	0.87 (0.03)
Heart	2.45 (0.21)	1.63 (0.06)
Blood	7.24 (0.62)	13.76 (0.51)
Plasma	11.76 (1.00)	27.16 (1.00)

[a]Animals were sacrificed at t_{max} (3 h for DRF-2189 and 1 h for rosiglitazone), and the drug concentration in various target tissues was determined. Numbers in parentheses are tissue/plasma ratios.

No major metabolites of DRF-2189 were formed, as indicated by HPLC analysis of plasma constituents (72). The fractional bioavailability was found to be about 44%. Comparative pharmacokinetic studies (69) of DRF-2189 and rosiglitazone are summarized in Table II. As can be seen, systemic exposure ($AUC_{0-\infty}$) for DRF-2189 was more than twice that of rosiglitazone. There were considerable differences in C_{max}, t_{max}, K_{el} and $t_{1/2}$ values between the two compounds. Although C_{max} for DRF-2189 was much lower than rosiglitazone, longer plasma residence time of DRF-2189 accounted for higher systemic exposure.

Tissue distribution studies

Tissue distribution of DRF-2189 and rosiglitazone are shown in Table III. It can be seen from the results that both drugs were present in large amounts in plasma and liver, although concentrations were relatively low in skeletal muscle, brown fat and heart (69). Despite the large quantities of DRF-2189 in the liver, no indication of liver toxicity was observed. This finding is significant considering that troglitazone is known to cause liver damage (41-43).

Peroxisome proliferator activated receptor studies

Several TZDs are known to have agonist activity at the peroxisome proliferator activated receptor (PPAR), a member of the steroid thyroid hormone receptor superfamily of transcription factors (15-23). These nuclear receptors (PPAR-α and PPAR-γ) regulate the transcription of a number of genes responsible for carbohydrate and lipid metabolism (23). In a HEK 293 cell assay, DRF-2189 at a concentration of 1 mM showed 3-fold activation which compared favorably with troglitazone (3-fold transactivation of PPAR-γ). Surprisingly, despite having similar euglycemic activity, PPAR-γ transactivation by rosiglitazone (6-fold) was better than DRF-2189. However, the fact that PPAR-γ transactivation may be an underlying mechanism of action of these drugs corroborates the present study. In contrast, although DRF-2189 showed a much improved lipid profile as compared to rosiglitazone, the transactivation of PPAR-α by both compounds was not high.

Conclusions

The indole-containing TZD, DRF-2189, was shown to be a very potent and efficacious antidiabetic compound which was superior to troglitazone and comparable to rosiglitazone in terms of euglycemic and hypolipidemic activities. In addition, DRF-2189 possessed a better lipid profile, including reductions in total cholesterol, VLDL, LDL and an increase in beneficial HDL-cholesterol, activities which are not associated with other TZDs such as troglitazone and rosiglitazone. This additional benefit indicates that DRF-2189 could be a potential treatment for a larger population of patients with diabetes type II-related complications and coronary artery disease. Moreover, preliminary toxicity studies showed that the compound appears to be safe. Thus, DRF-2189 is a good candidate for further development as an antidiabetic drug for the treatment of type II diabetes and related complications.

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