Novel Euglycemic and Hypolipidemic Agents. 1[†]

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A series of [[(heterocyclyl)ethoxy]benzyl]-2,4-thiazolidinediones have been synthesized by the condensation of corresponding aldehyde **1** and 2,4-thiazolidinedione followed by hydrogenation. Both unsaturated thiazolidinedione **2** and its saturated counterpart **3** have shown antihyperglycemic activity. Many of these compounds have shown superior euglycemic and hypolipidemic activity compared to troglitazone (CS 045). The indole analogue DRF-2189 (**3g**) was found to be a very potent insulin sensitizer, comparable to BRL-49653 in genetically obese C57BL/6J-*ob*/*ob* and 57BL/KsJ-*db*/*db* mice. Pharmacokinetic and tissue distribution studies conducted on BRL-49653 and DRF-2189 (**3g**) indicate that these drugs are well-distributed in target tissues. On the basis of euglycemic activity as well as enhanced selectivity against reduction of triglycerides in plasma, DRF-2189 (**3g**) has been selected for further evaluation.

Introduction

Diabetes is the root 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 suffer from type 2 diabetes, i.e., non-insulin-dependent diabetes mellitus (NIDDM), which is characterized by insulin resistance and hyperglycemia.[1] It has been estimated that a large number of type 2 diabetics remain undiagnosed. Several epidemiological and clinical studies[2] indicate a direct relationship between hyperglycemia and long-term complications such as neuropathy, nephropathy, retinopathy, atherosclerosis, and coronary artery disease. Therefore, it is essential to control blood glucose levels during the early stages of the disease.[3] The treatment generally prescribed for NIDDM has been a combination of diet, exercise, and a hypoglycemic agent,[4] commonly sulfonylureas and biguanides. Sulfonylureas, which are insulin secretagogues, stimulate insulin secretion from pancreatic β-cells and are often known to induce severe hypoglycemia[5] and weight gain.[6] In addition, both primary and secondary treatment failure rates with sulfonylureas are high, leading to complications.[7] Therefore, drugs that reverse the insulin resistance without stimulating insulin release from β-cells[8,9] fulfill a major medical need in the treatment of NIDDM and hence the potentials to reduce long-term complications of NIDDM. Since the pioneering discovery of ciglitazone by a group of scientists at Takeda,[10] which effectively reduces insulin resistance by potentiating insulin action in genetically diabetic and/or obese animals, several new thiazolidine-2,4-diones have been developed. Pioglitazone,[11] troglitazone (CS 045),[12] englitazone,[13] BRL-49653,[14] and many others are in various stages of clinical development (Chart 1).

In rodent models of obesity, insulin resistance, and hyperglycemia, thiazolidinediones ameliorate insulin resistance and normalize plasma glucose and insulin without causing hypoglycemia even at very high doses.[15] However, due to the unsatisfactory efficacy and safety profile of these agents,[16] there has been concern about thiazolidinediones as antidiabetic drugs. Recently, troglitazone has been marketed in the United States as Rezulin and in Japan as Noscal.[17] The encouraging reports from clinicians on troglitazone as well as set back due to its liver toxicity have rekindled the interest among pharmaceutical companies. Therefore, there has been a resurgence of interest in the development of novel antihyperglycemic agents that can control hyperglycemia without causing hypoglcemia.[18−21] Recent symposia at San Francisco,[22a] Washington,[22b] and Boston[22c] have attracted a large number of pharmaceutical companies which are involved in this effort.

Recently, some of the indole derivatives have been implicated in lowering blood glucose with a single dose in KKAy mice (50 mg/kg).[23] Certain imidazoline-containing compounds have been found to decrease plasma glucose in a dose-dependent manner following an oral glucose load in healthy human subjects.[24,25] More recently, BRL-49653 has advanced to phase III in clinical trials. Our strategy for the discovery of potent euglycemics involved the search for novel thiazolidinediones which are superior to or at least as active as BRL-49653.

We believed that the methyl group on N of BRL-49653, if incorporated in a ring with or without the help of a carbon or heteroatom as shown in structure A, might change the pharmacological profile of the compound in the desired direction and perhaps improve the potency of the compound, as has been observed in other cases.[20,21d] Recently, we have reported our preliminary

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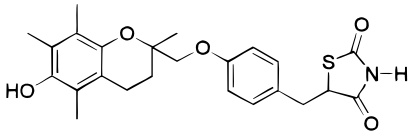
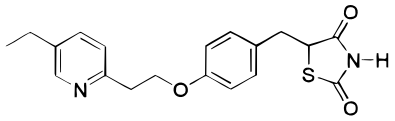
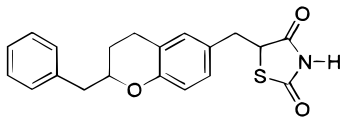
Chart 1



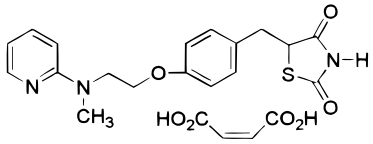
Troglitazone (CS 045) (Sankyo)
(Launched in1997 in the US and Japan)



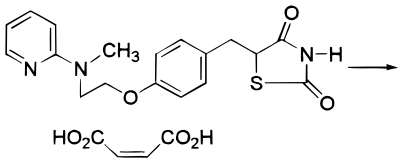
Pioglitazone (Takeda)
(Launched in 1997 in Japan)



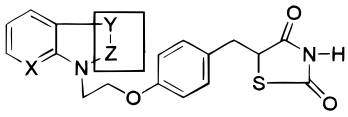
Englitazone (Pfizer)
(Phase II)



BRL-49653 (SKB)
(Phase III)



BRL-49653



A (1)

finding on a few selected indole and benzimidazole derivatives having good euglycemic activities.[26] We now report the synthesis, structure−activity relationship (SAR), and biological studies of several [[(heterocyclic)-ethoxy]benzyl]-2,4-thiazolidinediones.

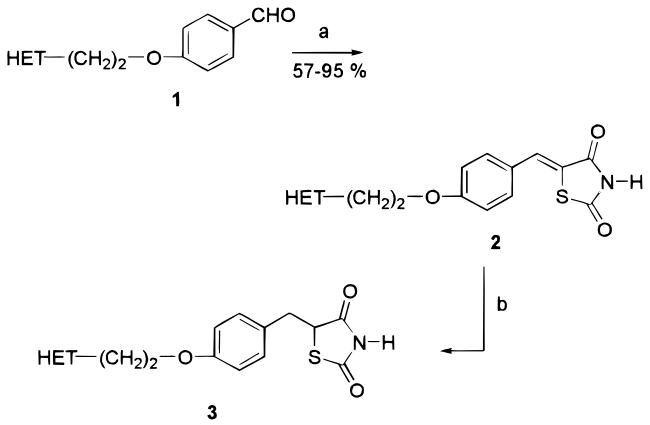
Chemistry

A general strategy to synthesize thiazolidinediones **2** and **3** is shown in Scheme 1. The aldehydes **1** undergo Knöevenagal condensation with 2,4-thiazolidinedione in the presence of piperidinium benzoate in refluxing toluene with azeotropic removal of water to give good to excellent yield (57−95%) of benzylidenes **2** which crystallize on cooling. The benzylidene-2,4-thiazolidinedione derivatives **2** could be reduced by either catalytic hydrogenation or magnesium/methanol.

In all the cases, the olefinic bond was reduced with hydrogen in 1,4-dioxane using 10% palladium on carbon as catalyst to give 5-benzyl-2,4-thiazolidinediones **3**. In most of the cases, more than a stoichiometric amount of Pd−C (10%) was required for complete hydrogenation of the olefinic bond due to poisoning of the catalyst. In order to overcome the problem of using stoichiometric amounts of 10% Pd−C, we attempted to employ magnesium/methanol for reduction of the olefinic bond using the electron-transfer technique of Watt et al.[27] However, in many cases, reduction of C=C bond in heterocyclic moieties was also observed as a side product or sometimes as the major product.

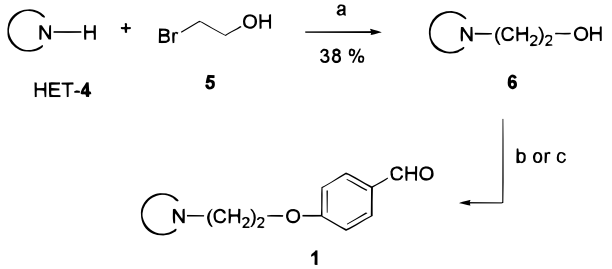
The aldehydes **1** in turn were prepared by two different routes shown in Schemes 2 and 3. The reaction of heterocyclic amines **4** with 2-bromoethanol (**5**) gave *N*-ethanol compounds **6** (38%) which were reacted with 4-fluorobenzaldehyde to give the aldehydes **1** (Scheme 2). Alternatively, Mitsunobu-type coupling

Scheme 1[a]



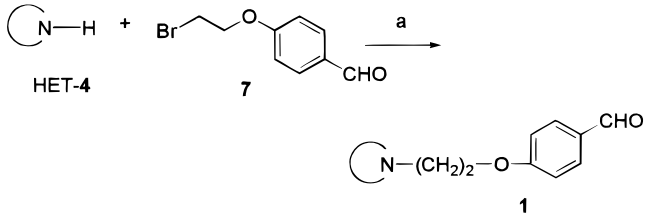
[a] (a) 2,4-Thiazolidinedione, piperidine, C_6H_5COOH, toluene, Δ, 57−95% yield; (b) H_2/10% Pd−C, 70−96% yield.

Scheme 2[a]



[a] (a) KOH−DMSO, 38% yield; (b) 4-fluorobenzaldehyde, NaH, DMF, 42% yield; (c) 4-hydroxybenzaldehyde, DEAD, Ph_3P, 39% yield.

Scheme 3[a]



[a] (a) KOH−DMSO, NaH−DMSO, NaH−DMF, or K_2CO_3−DMF, 33−89% yield.

of **6** with 4-hydroxybenzaldehyde in the presence of Ph_3P−DEAD gave only moderate yield of **1** (39%).

However, in both cases, the reaction led to formation of some unidentified side products. Thus, an alternate route was examined (Scheme 3). Dibromoethane was

treated with 4-hydroxybenzaldehyde in acetone in the presence of K_2CO_3 as base to give 4-(2-bromoethoxy)-benzaldehyde (**7**)[28] in good yield (60−70%). The aldehyde **7** was then treated with various heterocycles **4** to give the aldehydes **1** in 30−89% yield.

Results and Discussion

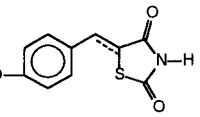
We examined several 2,4-thiazolidinediones, including troglitazone, in *db*/*db* mice. (cf. vide infra). A dose of 100, 200, 400, or 800 mg/kg troglitazone was administered to *db*/*db* mice for 9 days, and the plasma glucose level was examined. The reduction in plasma glucose level at each dose was 32%, 41%, 44%, and 52%, respectively. As observed by others,[29] approximately 25% of the animals did not show any response to troglitazone, and the maximum reduction in plasma glucose observed with troglitazone (800 mg/kg) was only 52%, at which point the plasma glucose in *db*/*db* mice (15 ± 1 mM) had still not reached the level of lean littermates (8 ± 1 mM). Although the mechanism of action of this class of compounds (glitazones) is not fully understood, recent studies suggest that most of the glitazone class of compounds bind to PPARγ (peroxisome proliferator-activated receptors), a member of the steroid/thyroid hormone receptor superfamily of transcription factors.[30,31] However, it is not clear whether binding of these glitazones to both PPARγ_1 and PPARγ_2 is necessary for their antihyperglycemic activity.[22b,d] It has also been observed that various other classes of compounds which bind to PPARγ receptor do not show antihyperglycemic activity.[31a] Thus, it appears that there may be other receptors which may play a crucial role in maintaining the antihyperglycemic activity of the glitazone class of compounds.[32] Moreover, since skeletal muscle is the predominant insulin-sensitive tissue accounting for >80% of insulin-regulated glucose disposal, an increase in glucose disposal in adipocytes alone is unlikely to account for euglycemic activity of thiazolidinediones.[33] Thus, we chose to follow a direct in vivo screening procedure in *db*/*db* mice.

We prepared a series of indole and azaindole analogues (Table 1) and evaluated their antihyperglycemic activity. We first examined several unsaturated 2,4-thiazolidinediones (**2a**−**l**) and compared their activities against those of troglitazone or compound **8** (Table 1). In cases where the antihyperglycemic activities were comparable to that of compound **8**, we synthesized the corresponding saturated analogues (**3a,d,g,l**) and compared their euglycemic activities with those of troglitazone or BRL compound **9** (cf. BRL-49653 is the maleate salt of compound **9**) (Table 1).

Pharmacokinetic studies on troglitazone have been reported by Horikoshi et al.[29] which indicate poor oral bioavailability. Pharmacokinetic studies on BRL compound **9** and BRL-49653 suggest that both compounds are present at higher plasma concentration than troglitazone. Also BRL-49653 (log *P* 1.32)[14b] is much more hydrophilic and is one of the most potent compounds of the glitazone class with a minimally effective dose of 3 μmol kg^{-1} of diet.[14b] On the basis of these observations on oral bioavailability and potency, we surmised that it might be possible to modify the structure of BRL compounds **8** and **9** and obtain a novel glitazone with the desired biological properties.

With a view to achieving this goal, ring closure of BRL compound **8** with the help of a methylene bridge, as shown in eq 1 (where X = N; Y = Z = CH), resulted in the azaindole analogue **2a**, which showed fair glycemic control (Table 1, entry 1) but far superior reduction (79%) in plasma triglyceride (TG). On saturating, this thiazolidinedione **2a** gave compound **3a** which is comparable to BRL compound **9** (Table 1, entries 14 vs 18). However, the saturated compound **3a** did not show a significant difference in plasma glucose reduction or triglyceride reduction in *db*/*db* mice as compared to its unsaturated counterpart **2a** (Table 1, entries 1 vs 14; **2a** vs **3a**). Similarly, on comparison of **3a** (Table 1, entry 14) with compound **9** (Table 1, entry 18), compound **3a** is inferior in euglycemic but superior in hypolipidemic activity. Further, the benzimidazole derivative **2b** was synthesized and evaluated. There was no significant change in the percent reduction of plasma glucose or TG (Table 1, entries 1 vs 2). We then examined imidazole derivative **2c** (Table 1, entry 3) which is a smaller heterocycle that does not have an aromatic benzene ring like **2a** or **2b**. Although hypolipidemic activity of **2c** was comparable to that of **2a,b**, their euglycemic activity was very poor. Hence, a systematic alteration in the structure was considered, and the 2,3-dihydroindole derivative **2d** and its saturated analogue **3d** were evaluated for euglycemic and hypolipidemic activities. Surprisingly, the unsaturated thiazolidinedione **2d** showed far superior euglycemic activity (Table 1, entry 4, 61% reduction in plasma glucose) as compared to its saturated analogue **3d** (Table 1, entry 15, 33% reduction in plasma glucose). In contrast, reduction in triglyceride for both the compounds **2d** (83% reduction in TG) and **3d** (79% reduction in TG) was nearly the same (Table 1, entries 4 vs 15). While this suggests that both **2d** and **3d** might act via a similar mechanism for the reduction of triglyceride, the reason for the difference in their euglycemic activities is not clear. It is possible that different mechanisms are responsible for euglycemic and hypolipidemic activity. For example, it is known that ligands which activate PPARγ cause a reduction in blood sugar, whereas ligands which bind to PPARα cause a reduction in triglyceride.[31b] We have not carried out studies to prove the above in the case of the thiazolidinediones reported in Table 1. On the other hand, Wilson et al.[31b] examined binding and activation studies of a few thiazolidinediones for PPARα, -γ, and -δ receptors and concluded that thiazolidinediones in general do not activate PPARα and -δ receptors even at high concentrations. Thus, the hypolipidemic activity of thiazolidinedione may be associated with a receptor type which is yet to be identified.

In order to obtain further insight into the structure−activity relationship, we examined several indole derivatives (**2e**−**k**). Effect of various substituents on indole ring was examined. The presence of an electron-withdrawing group such as COOH or COOMe (**2e**,**f**) or electron-donating group such as methyl (**2i**,**j**) has a deleterious effect on the euglycemic as well as hypolipidemic activities of these thiazolidinediones. It appears that substituents at C_2 and C_3 positions of the indole ring are not tolerated. We selected thiazolidinedione **2g**, having no substituent on the indole ring, for further

Table 1. Euglycemic and Hypolipidemic Activities of HET–$(CH_2)_2$–O– 

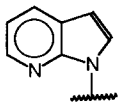
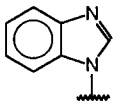
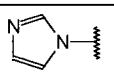
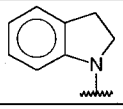
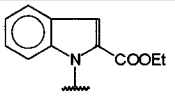
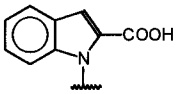
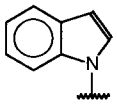
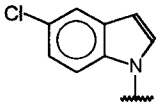
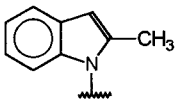
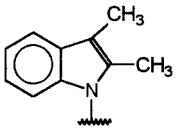
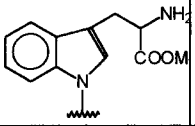
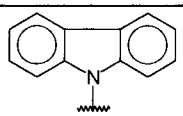
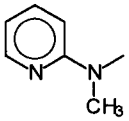
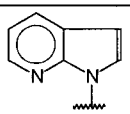
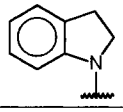
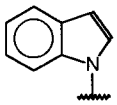
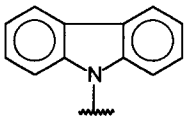
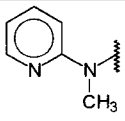
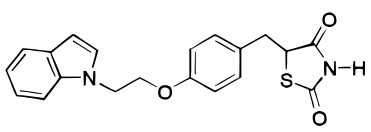
S.No.	Compd No.	HET	DB	Yield %	mp (°C)	*Clog P*[c]	Dose (mg/kg)	BG[a]	Tg[b]
1.	2a		Yes	81	205	3.02	200	36	79
2.	2b		Yes	92	258-260	3.30	200	33	76
3.	2c		Yes	78	210	1.70	200	13	72
4.	2d		Yes	94	179	4.28	200	61	83
5.	2e		Yes	82	184	4.91	200	0	13
6.	2f		Yes	84	115	4.22	200	12	0
7.	2g		Yes	78	216	4.31	200	33	37
8.	2h		Yes	91	206	5.07	200	39	11
9.	2i		Yes	95	235	4.81	200	16	41
10.	2j		Yes	94	254	5.26	200	40	2
11.	2k		Yes	71	180	3.15	100	27	64
12.	2l		Yes	95	277-278	5.70	100	0	44
13.	Compound 8[c]		Yes	87	193-194	2.95	10 100	15 56	17 32
14.	3a		No	70	195	2.90	200	33	74
15.	3d		No	83	143-144	4.16	200	33	79

Table 1 (Continued)

S.No.	Compd No.	HET	DB	Yield %	mp (°C)	*Clog P*[e]	Dose (mg/kg)	BG[a]	Tg[b]
16.	3g		No	92	103	4.20	100	74	77
17.	3l		No	80	214	5.58	100	0	21
18.	Compound 9[c]		No	52	153-155	2.84	10 100 200	15 71 67	11 46 55
19.		Troglitazone[d]	No	77	180-181	2.7	200	41	
20.		BRL-49653[c]	No	76	123	1.32[f]	10	55	37

[a] Percent reduction in BG (blood glucose). [b] Percent reduction in triglyceride (TG) after 9 days of dosing in *db*/*db* mice via oral gavage. [c] Compound **8**, compound **9**, and BRL-49653 were prepared by reported procedure.[14b] BRL-49653 is the maleate salt of BRL compound **9**. [d] Troglitazone was prepared by the reported method, and log *P* value is quoted from ref 29. [e] The program used to calculate Clog *P* was obtained from BioByte Corp. USA and is used without any correction. [f] The value of log *P* for BRL-49653 is quoted from ref 14b. DB, double bond; dotted line, optional double bond.

study and synthesized saturated thiazolidinedione **3g** (DRF-2189) which was very effective in reducing blood glucose (74%) and triglyceride (77%) with the blood glucose level reaching levels close to that of the lean littermate (8 ± 1 mM). We also examined the tryptophan derivative **2k** and carbazole **21**. Interestingly, tryptophan derivative **2k** showed poor euglycemic and moderate hypolipidemic activities, whereas compound **2l** which has a planar heterocyclic moiety is completely devoid of any activity (Table 1, entries 11 and 12). The saturated thiazolidinedione analogue **3l** (Table 1, entry 16) also did not show any euglycemic activity. Clearly, despite having planar heterocycle moieties (**2g** vs **2l** and **3g** vs **3l**), the enormous difference in euglycemic activity might be due to the large size of the carbazole moiety. Thus it appears that the size of heterocyclic moiety plays a crucial role in binding to the receptor site responsible for euglycemic activity. Also when one tries to rationalize the shape of the heterocyclic moiety (**3g** vs **3d**), the planar heterocycle is preferred. Although both **3g**,**d** may have similar steric requirements, their potencies differ remarkably. The compound **3g** showed very good euglycemic and hypolipidemic activity, whereas **3d** is markedly inferior. This might be associated with the shape of the heterocycle (**3g** is planar, whereas **3d** is puckered). Hence, we selected DRF-2189 (**3g**) for further evaluation as a potential development candidate.



DRF - 2189 (3g)

Comparison of **3g** with troglitazone was carried out at 200 mg/kg dose. At this dose troglitazone reduced plasma glucose and triglycerides by 24% and 50%, respectively, while DRF-2189 (**3g**) reduced plasma glucose and triglyceride by 74% and 77%, respectively. Thus, it seems that DRF-2189 (**3g**) might have greater efficacy at this dose compared to troglitazone. With an aim to compare the efficacy of DRF-2189 with BRL-49653, we carried out dose−response studies in *db*/*db* and *ob*/*ob* mice examining the percent reduction of plasma glucose and triglycerides. We examined DRF-2189 (**3g**), BRL compound **9**, and BRL-49653 at 100 mg/kg/day/po in *db*/*db* mice. Interestingly, all three compounds showed similar reduction in plasma glucose (71−72%) and normalized glucose in plasma (i.e., 8 ± 1 mM). Hence we examined all three compounds at a lower dose of 10 mg/kg/day in *db*/*db* mice for 9 days. We observed that DRF-2189 and BRL-49653 reduced the blood glucose by 51−55% (plasma glucose: 12.5 ± 1 mM), whereas BRL compound **9** did not produce a significant reduction. Further dose−response studies were carried out using DRF-2189 (1, 3, and 10 mg/kg) and BRL-49653 (1, 3, and 10 mg/kg) in *db*/*db* mice and compared with studies of troglitazone (100, 200, and 800 mg/kg). The results are shown in Figure 1.

From these results it is clear that DRF-2189 and BRL-49653 are approximately equipotent, whereas troglitazone even at 800 mg/kg dose was less effective in reducing plasma glucose. The reductions in triglyceride for DRF-2189 and BRL-49653 were not significantly different in *db*/*db* mice; however, the reduction of cholesterol was observed with the 3 and 10 mg/kg dose of DRF-2189 (**3g**) (10−15% reduction in total cholesterol), whereas BRL-49653 did not show improvement in cholesterol. Further, oral glucose tolerance test (OGTT) carried out after 9 days of treatment in *db*/*db* mice with DRF-2189 (**3g**) (AUC, 68% reduction) and BRL-49653 (AUC, 61% reduction) showed comparable potency.

Both the drugs were consequently evaluated in *ob*/*ob* mice. After similar dosage (10 mg/kg/day) for both drugs for 14 days, the glucose and triglyceride in the blood plasma were determined. In both cases the percent reduction in blood glucose (51−59%) and triglyceride (53−55%) was found to be similar. Having found comparable potency of DRF-2189 (**3g**) with BRL-49653, we decided to study the pharmacokinetics and tissue distribution of both drugs. Both BRL-49653 and

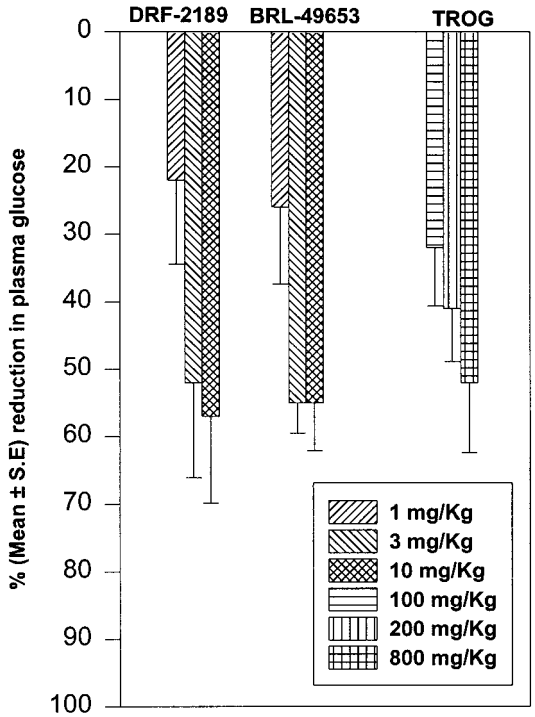


Figure 1. Comparison of percent reduction in random blood sugar (RBS) in *db*/*db* mice using 1, 3, or 10 mg/kg DRF-2189 and BRL-49653 with troglitazone (100, 200, and 800 mg/kg).

Table 2. Pharmacokinetic Parameters for DRF-2189 and BRL-49653 at 10 mg/kg/po in Wistar Rats

parameter	DRF-2189[a]	BRL-49653[b]
$AUC_{0-\infty}$ (μg h mL^{-1})	129.3 ± 46.3	59.2 ± 19.0
C_{max} (μg mL^{-1})	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
half-life (h)	3.28 ± 1.4	1.02 ± 0.24

[a] Results are mean ± SD of three animals. [b] Results are mean ± SD of six animals.

DRF-2189 were administered at a single oral dose of 10 mg/kg in Wistar rats, and blood samples were collected and analyzed as described in the Experimental Section. Results of these studies are presented in Table 2.

The results indicate that the systemic exposure ($AUC_{0-\infty}$) for DRF-2189 is more than twice that for BRL-49653. There are considerable differences in their C_{max}, T_{max}, K_{el}, and $t_{1/2}$. DRF-2189 is absorbed slowly, reaches a maximum plasma level in 3−4 h, and is eliminated slowly ($t_{1/2}$ 3.2 h) as compared to BRL-49563 which is absorbed rapidly (t_{max} 0.5 h) and is also eliminated rapidly with a half-life of about 1 h (Figure 2).

Although C_{max} for DRF-2189 is much lower (14.5 ± 2.4 μg/mL^{-1}) compared to that for BRL-49653 (29.4 ± 6.0 μg/mL^{-1}), longer plasma residence time of DRF-2189 accounts for higher systemic exposure. However, the question of distribution of drug candidate into target tissues needs to be addressed before selection of the preclinical lead candidate. We carried out tissue distribution studies for both BRL-49653 and DRF-2189 in Wistar rats. After single dosing of BRL-49653 and DRF-2189, the animals were sacrificed at a time when drug concentrations are maximum in the plasma (i.e., at t_{max}), and the concentration of drug in various target tissues was determined. Tissue distribution studies for

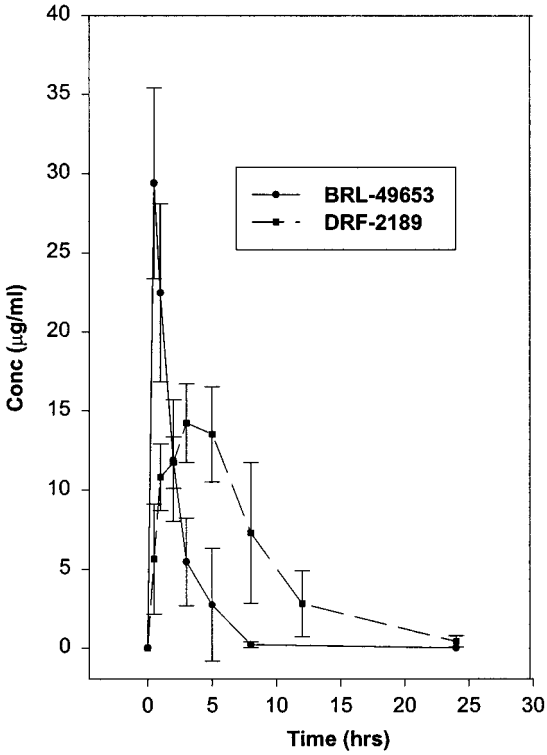


Figure 2. Comparison of drug plasma levels of BRL-49653 (●) and DRF-2189 (■) in Wistar rats at various time intervals.

Table 3. Tissue Levels for DRF-2189 and BRL-49653 at 10 mg/kg/po in Wistar Rats[a]

tissue	DRF-2189	BRL-49653
liver (μg g^{-1})	10.01 (0.85)	10.90 (0.40)
subcutaneous fat (μg g^{-1})	1.50 (0.13)	14.32 (0.53)
brown fat (μg g^{-1})	1.23 (0.10)	2.10 (0.08)
skeletal muscle (μg g^{-1})	0.85 (0.07)	0.87 (0.03)
heart (μg g^{-1})	2.45 (0.21)	1.63 (0.06)
blood (μg mL^{-1})	7.24 (0.62)	13.76 (0.51)
plasma (μg mL^{-1})	11.76 (1.00)	27.16 (1.00)

[a] The animals were sacrificed at t_{max} (i.e., 3 h for DRF-2189 and 1 h for BRL-49653), and the drug concentration in various target tissues was determined. The numbers in parentheses are tissue/plasma ratios.

these molecules (Table 3) indicated that both drugs were present in the plasma and liver in large amounts, but concentrations were relatively low in skeletal muscle, brown fat, and the heart.

One striking difference between the two molecules is that BRL-49653 showed relatively high concentrations in subcutaneous fat (tissue to plasma (t/p) ratio = 0.53) as compared to DRF-2189 (t/p ratio = 0.13). In contrast, the concentration of DRF-2189 in liver was relatively higher (t/p ratio = 0.85) as compared to that for BRL-49653 (t/p ratio = 0.4). These studies suggest that both compounds are well-distributed in various tissues. The high concentrations in the pharmacological target sites such as liver and subcutaneous fat may be important for their pharmacological action.

We have carried out preliminary toxicity studies (LD_{50}) for both DRF-2189 and BRL-49653, and both compounds seem to have a similar LD_{50} profile. Detailed toxicity studies will be carried out later.

To conclude, the indole-containing thiazolidine-2,4-dione (DRF-2189) has potential to have a better euglycemic and hypolipidemic profile. The further progress

of this compound into clinical trials depends on its safety and efficacy.

Experimental Section

Biological Procedure. Male C57BL/KsJ-*db*/*db* and C57BL/6J-*ob*/*ob* mice were obtained at 6 weeks of age from Jackson Laboratories (Bar Harbor, ME) and maintained at 25 ± 2 °C on a 12-h light/dark cycle. Animals were given standard laboratory chow (National Institute of Nutrition, Hyderabad, India) and water, ad libitum.

The *db*/*db* mice were used for experiments at 8 weeks of age. Four to six animals were used in each treatment group. In *db*/*db* mice, the test compounds were administered at different doses orally for 9 days. Troglitazone (200 and 800 mg/kg) and BRL-49653 (1, 3, and 10 mg/kg) were used as standard drugs. The control animals were given vehicle (0.5% carboxymethylcellulose, dose 10 mL/kg). The blood sample (25−50 μL) was collected from the retro-orbital sinus through heparinized capillary tubes in EDTA-containing tubes at different time intervals. In *db*/*db* mice, blood samples were collected after 1 h of drug administration on days 0, 3, 6, and 9 of treatment. Only selected compounds were tested in *ob*/*ob* mice. The *ob*/*ob* mice were used for experiments at 10 weeks of age, and blood samples were collected on days 0 and 14 of treatment as described above. After centrifugation, plasma was separated for glucose, cholesterol, and triglyceride estimations using commercial kits (Dr. Reddy's Laboratories Diagnostic Division, India). The percent reduction in plasma glucose level was calculated.[34]

Oral glucose tolerance test (OGTT) was performed after 9 days of treatment (*db*/*db*). Mice were fasted overnight (*db*/*db*) and challenged with glucose (3 g/kg/po). Blood samples were collected at 0, 30, 60, and 120 min for measuring plasma glucose levels. The improvement in glycemic control was calculated as the percent reduction in the area under the plasma glucose content versus time curve (AUC). The AUC was calculated using the trapezoidal rule.

Similarly, OGTT was performed in *ob*/*ob* mice after 14 days of treatment; however, the mice were challenged with glucose (3 g/kg/po) after a 5-h fast. Blood samples were collected and examined as described earlier.

Pharmacokinetics and Tissue Distribution Studies. All studies were carried out in Wistar rats obtained from National Institute of Nutrition (Hyderabad, India). The animals (175−200 g) were fasted 12 h before starting the experiment and had free access to water throughout. Animals were fed 3 h after drug administration.

(a) Single-Dose Pharmacokinetics. Animals were dosed with the drug at 10 mg/kg/po as 0.5% CMC suspension, and 0.4 mL of blood sample was collected into heparinized microfuge tubes at different time points (0, 0.5, 1, 2, 3, 5, 8, 12, and 24 h) from the orbital sinus. The samples were analyzed by HPLC to generate drug plasma concentration versus time profiles (Figure 2).

Pharmacokinetic parameters such as $AUC_{0-\infty}$, K_{el}, $t_{1/2}$, C_{max}, and t_{max} were calculated using noncompartmental model analysis. $AUC_{0-\infty}$ is the area under the plasma concentration versus time curve extrapolated to infinity, K_{el} is the elimination rate constant, C_{max} is the observed maximum plasma concentration, and t_{max} is the time at which C_{max} is achieved. The pharmacokinetic parameters for DRF-2189 and BRL-49653 are summarized in Table 2.

(b) Tissue Distribution Studies. Tissue distribution studies were carried out in Wistar rats. The drug was administered to two animals (10 mg/kg/po) following which the animals were sacrificed at t_{max}. Various tissues/organs were isolated, perfused with phosphate buffer (pH 5.8) to remove blood, and homogenized in buffer (1:4 ratio). Blood/plasma was collected from each animal just before sacrifice. The tissue homogenates were analyzed by HPLC for drug content, and tissue concentrations were measured and are expressed as μg g^{-1} of wet tissue (Table 3).

Analysis of Plasma/Tissue Samples. (a) Sample Preparation. To 0.1 mL of plasma was added internal standard, and the drug was extracted from the plasma using 2.0 mL of extracting solvent. For DRF-2189, troglitazone (3 μg) was used as internal standard and the extraction solvent was ethyl acetate−dichloromethane (6:4, v/v), whereas for BRL-49653, another thiazolidinedione analogue (1 μg) was used as internal standard and a mixture of dichloromethane−methanol (2:1, v/v) was used as extraction solvent. The organic layer (1.5 mL) was evaporated to dryness and reconstituted in 200 μL of methanol−water (50:50); 100 μL of the sample was analyzed by HPLC. In case of tissue homogenates, sample preparation was carried out with 0.5 mL of homogenate and the amount of internal standard added was 15 μg. The calibration, control, and recovery samples were prepared by spiking blank plasma/liver homogenate and were processed similarly.

(b) HPLC Assay. The HPLC system consisted of a Waters LC Module-1, Perkin Elmer LC-240 fluorescence detector, Millennium software, and a HiChrom C_{18} (ODS) column (5 μm, 4.6 mm × 250 mm). Analysis of DRF-2189 was carried out using 0.05 M NaH_2PO_4 buffer−acetonitrile−methanol (22.5:37.5:40, v/v, pH 5.0) as mobile phase at a flow rate of 1.0 mL/min, and the excitation and emission wavelengths were 280 and 320 nm, respectively. Under these conditions, the retention times for DRF-2189 and troglitazone were 10.8 and 13.9 min, respectively. For analysis of BRL-49653, mobile phase was 0.05 M NaH_2PO_4 buffer (pH 5)−methanol−acetonitrile (22:12:55, v/v) at a flow rate of 1.0 mL/min, and the excitation and emission wavelengths were 317 and 370 nm, respectively. Under these conditions, the retention times for BRL-49653 and standard were 7.5 and 8.7 min, respectively. The assay methods were validated to ensure specificity, linearity, recovery, accuracy, and precision. The limits of quantitation for DRF-2189 and BRL-49653 from plasma were 200 and 50 ng/mL, respectively. The response was linear up to 50 μg/mL for both methods. The absolute recoveries for both methods were >95%.

Chemical Methods. Thin layer chromatography was performed on silica gel plates (60 F254; Merck). Flash chromatography was performed on silica gel (SRL 230−400 mesh). Melting points were recorded on Veego melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained with a Varian Gemini 200-MHz spectrometer and are reported as parts per million (ppm) downfield to TMS. The infrared spectra were recorded on a Perkin Elmer FT-IR 1600 spectrometer. The mass spectra were obtained with an HP 5989A mass spectrometer. 4-(2-Bromoethoxy)benzaldehyde[28] and ethyl indole-2-carboxylate[35] were prepared according to literature procedures. Indole, 7-azaindole, 3-methylindole, 2,3-dimethylindole, 5-chloroindole, benzimidazole, and imidazole were purchased and used directly. Compound **8**, compound **9**, and BRL-49653 were prepared by a reported procedure.[14b] Troglitazone was prepared by the method reported by Horikoshi et al.[29]

General Method of Preparation of 4-[2-(Heterocyclyl)-ethoxy]benzaldehyde. To a solution of an appropriate heterocycle **4** (10.0 mmol) in dry DMSO (15.0 mL) at 25 °C was added an appropriate base (11.0 mmol), and the mixture stirred for 0.25−1 h. A solution of 4-(2-bromoethoxy)benzaldehyde (**7**) (12.0 mmol) in dry DMSO (5 mL) was added and stirred further for 0.5−6 h. To the reaction mixture was added water (20 mL), and it was extracted with EtOAc (2 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was chromatographed over silica gel using a mixture (3:7−8:2) of ethyl acetate and petroleum ether as eluent to yield pure compound (30−79%).

4-[2-(7-Aza-1-indolyl)ethoxy]benzaldehyde (1a). The title compound **1a** was prepared by the general procedure using azaindole (1.81 g, 10.0 mmol), aldehyde **7** (2.75 g, 12.0 mmol), and KOH (1.43 g, 25.0 mmol) in 89% yield (2.68 g): IR ν_{max}(KBr) 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.89 (s, 1 H), 8.32 (d, J = 3.0 Hz, 1 H), 7.95 (d, J = 6.0 Hz, 1 H), 7.80 (d, J = 8.72 Hz, 2 H), 7.40 (d, J = 3.0 Hz, 1 H), 7.15−6.95 (m, 1 H), 6.98 (d, J = 8.72 Hz, 2 H), 6.48 (d, J = 3.0 Hz, 1 H), 4.75 (t, J = 5.30 Hz, 2 H), 4.40 (t, J = 5.30 Hz, 2 H).

4-[2-(1-Benzimidazolyl)ethoxy]benzaldehyde (1b). The title compound was prepared by the general procedure using benzimidazole (1.18 g, 10.0 mmol), aldehyde **7** (2.52 g, 10.0 mmol), and NaH (290 mg, 12.0 mmol) in 51% yield (1.36 g): IR ν_{max} (KBr) 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.90 (s, 1 H), 8.00−7.70 (m, 1 H), 7.85 (d, J = 8.70 Hz, 2 H), 7.60−7.50 (m, 1 H), 7.50−7.20 (m, 3 H), 6.98 (d, J = 8.70 Hz, 2 H), 4.64 (t, J = 5.2 Hz, 2 H), 4.40 (t, J = 5.2 Hz, 2 H).

4-[2-(1-Imidazolyl)ethoxy]benzaldehyde (1c). The title compound was prepared by the general procedure using imidazole (0.34 g, 5.0 mmol), aldehyde **7** (1.26 g, 5.5 mmol), and NaH (152 mg, 6.0 mmol, 95%) in 77% yield (0.83 g): IR ν_{max} (KBr) 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.92 (s, 1 H), 7.85 (d, J = 8.70 Hz, 2 H), 7.65 (s, 1 H), 7.10 (d, J = 5.0 Hz, 2 H), 6.98 (d, J = 8.70 Hz, 2 H), 4.40 (d, J = 5.30 Hz, 2 H), 4.30 (d, J = 5.30 Hz, 2 H).

4-[2-(2-Carbethoxy-1-indolyl)ethoxy]benzaldehyde (1e). The title compound (2.4 g, 75%) was prepared by the general procedure using ethyl indole-2-carboxylate (1.75 g, 10.0 mmol), aldehyde **7** (2.29 g, 10.0 mmol), and K_2CO_3 (2.76 g, 20.0 mmol) as base: IR ν_{max} (KBr) 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.91 (s, 1 H), 7.90 (d, J = 8.72 Hz, 2 H), 7.65 (d, J = 6.0 Hz, 1 H), 7.85 (d, J = 6.0 Hz, 1 H), 7.36 (t, J = 6.0 Hz, 1 H), 7.22−7.05 (m, 2 H), 7.10 (d, J = 8.72 Hz, 2 H), 4.92 (t, J = 5.0 Hz, 2 H), 4.50−4.30 (m, 4 H), 1.45 (t, J = 6.50 Hz, 3 H).

Synthesis of 4-[2-(1-Indolyl)ethoxy]benzaldehyde (1g). Method A: The aldehyde was prepared by the general procedure using indole (1.17 g, 10.0 mmol), sodamide (429 mg, 11.0 mmol), and aldehyde **7** (2.75 g, 12.0 mmol) to yield 2.10 g (79%) of **1g**: IR ν_{max} (neat) 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.86 (s, 1 H), 7.79 (d, J = 8.72 Hz, 2 H), 7.64 (d, J = 7.89 Hz, 1 H), 7.42 (d, J = 7.88 Hz, 1 H), 7.40−7.05 (m, 3 H), 6.94 (d, J = 8.72 Hz, 2 H), 6.53 (d, J = 2.91 Hz, 1 H), 4.58 (t, J = 5.49 Hz, 2 H), 4.38 (t, J = 5.49 Hz, 2 H).

Method B (Scheme 2), Step A, Synthesis of 1-(2-Hydroxyethyl)indole (6g): To a stirred suspension of KOH (2.18 g, 38.4 mmol) in dry DMSO (25 mL) was added a solution of indole (3 g, 25.6 mmol) in DMSO (5 mL) dropwise at 25 °C. After stirring for 5 min a clear solution was observed to which bromoethanol (1.81 mL, 3.2 g, 25.6 mmol) was added, and it was further stirred for 30 min. The reaction mixture was diluted with EtOAc (100 mL) and washed with water (3 × 25 mL) and brine. The EtOAc layer was dried over anhydrous Na_2SO_4 and concentrated to yield 3.5 g of crude compound which was purified by column chromatography using a mixture of EtOAc−petroleum ether (1:9) as eluent to afford 1.56 g (38%) of **6g**: IR ν_{max} (neat) 3376 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.64 (d, J = 7.67 Hz, 1 H), 7.37 (d, J = 7.6 Hz, 1 H), 7.24 (d, J = 6.14 Hz, 1 H), 7.22−7.02 (m, 2 H), 6.52 (d, J = 2.9 Hz, 1 H), 4.26 (t, J = 5.28 Hz, 2 H), 4.0−3.85 (m, 2 H); MS m/z (relative intensity) 161 (M^+, 19), 130 (100).

Step B, Procedure 1: To a stirred suspension of NaH (30 mg, 1.2 mmol, 95%) in dry DMF (3 mL) was added a solution of 1-(2-hydroxyethyl)indole (**6g**) (161 mg, 1.0 mmol) in DMF (1 mL) dropwise at 25 °C, and the mixture stirred for 30 min. The reaction mixture was cooled to 0 °C, and 4-fluorobenzaldehyde (116 μL, 136 mg, 1.1 mmol) was added and stirred for 2 h at 0−25 °C. The reaction was quenched with ice and the mixture extracted with EtOAc (3 × 15 mL). The combined EtOAc layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to yield 250 mg of crude reaction mixture, which was purified by column chromatography using EtOAc−petroleum ether (1:9) as eluent to afford 110 mg (42%) of **1g**.

Step B, Procedure 2: To a solution of 1-(2-hydroxyethyl)-indole (**6g**; 161 mg, 1.0 mmol), 4-hydroxybenzaldehyde (122 mg, 1.0 mmol), and triphenylphosphine (315 mg, 1.2 mmol) in dry THF (3 mL) was added diethyl azodicarboxylate (189 μL, 209 mg, 1.2 mmol) at 25 °C, and the mixture stirred for 3 h at the same temperature. THF was removed under reduced pressure, and the resultant residue was dissolved in EtOAc (10 mL), washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated to yield 200 mg of crude product. The crude compound was purified by column chromatography to afford 103 mg (39%) of **1g**.

4-[2-(5-Chloro-1-indolyl)ethoxy]benzaldehyde (1h). 5-Chloroindole (2.0 g, 13.2 mmol) was reacted by general procedure with aldehyde **7** (3.4 g, 14.5 mmol) and KOH (1.48 g, 26.4 mmol) to afford the title compound, 2.75 g (69%): IR ν_{max} (KBr) 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.86 (s, 1 H), 7.79 (d, J = 8.72 Hz, 2 H), 7.59 (d, J = 1.75 Hz, 1 H), 7.40−7.15 (m, 3 H), 6.92 (d, J = 8.72 Hz, 2 H), 6.46 (d, J = 3.0 Hz, 1 H), 4.54 (t, J = 5.30 Hz, 2 H), 4.34 (t, J = 5.30 Hz, 2 H).

4-[2-(3-Methyl-1-indolyl)ethoxy]benzaldehyde (1i). The title compound was prepared by the general procedure using 3-methylindole (3.0 g, 22.9 mmol), aldehyde **7** (6.3 g, 27.48 mmol), and KOH (2.57 g, 45.8 mmol) in 57% yield (3.68 g): IR ν_{max} (KBr) 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.88 (s, 1 H), 7.80 (d, J = 8.72 Hz, 2 H), 7.56 (d, J = 6.0 Hz, 1 H), 7.37 (d, J = 6.0 Hz, 1 H), 7.30−7.05 (m, 3 H), 6.91 (d, J = 8.72 Hz, 2 H), 4.51 (t, J = 5.30 Hz, 2 H), 4.32 (d, J = 5.30 Hz, 2 H), 2.30 (s, 3 H).

4-[2-(2,3-Dimethyl-1-indolyl)ethoxy]benzaldehyde (1j). The title compound was prepared by the general procedure using 2,3-dimethylindole (2.0 g, 13.8 mmol), aldehyde **7** (4.42 g, 19.28 mmol), and KOH in 55% yield (2.22 g): IR ν_{max} (KBr) 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.85 (s, 1 H), 7.72 (d, J = 8.67 Hz, 2 H), 7.50 (d, J = 7.10 Hz, 1 H), 7.30 (d, J = 7.10 Hz, 1 H), 7.20−7.05 (m, 2 H), 6.89 (d, J = 8.67 Hz, 2 H), 4.50 (t, J = 5.82 Hz, 2H), 4.27 (t, J = 5.82 Hz, 2 H), 2.43 (s, 3 H), 2.25 (s, 3 H).

4-[2-(1-Carbazolyl)ethoxy]benzaldehyde (1l). The title compound (3.92 g, 52%) was prepared by the general procedure using carbazole (4.0 g, 24 mmol), aldehyde **7** (7.12 g, 31.0 mmol), and KOH (2.68 g, 47.8 mmol): IR ν_{max} (KBr) 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.85 (s, 1 H), 8.12 (d, J = 7.5 Hz, 2 H), 7.77 (d, J = 8.72 Hz, 2 H), 7.52−7.46 (m, 4 H), 7.32−7.23 (m, 2 H), 6.90 (d, J = 8.72 Hz, 2 H), 4.78 (t, J = 5.58 Hz, 2 H), 4.45 (t, J = 5.58 Hz, 2 H).

General Method To Prepare 5-[[4-[2-(Heterocyclyl)-ethoxy]phenyl]methylene]thiazolidine-2,4-diones 2a−l. A mixture of 4-[2-(heterocyclyl)ethoxy]benzaldehyde **1** (10 mmol), thiazolidine-2,4-dione (10 mmol), benzoic acid (1.3 mmol), and piperidine (1.5 mmol) in 25 mL of toluene was refluxed for 1 h with continuous removal of water using a Dean−Stark water separator. The reaction mixture was cooled to room temperature, and the resultant crystalline compound was filtered, washed with water, and dried to afford the pure product **2a**−**l** (71−99%).

5-[[4-[2-(7-Aza-1-indolyl)ethoxy]phenyl]methylene]-thiazolidine-2,4-dione (2a). The title compound (3.27 g, 81%) was prepared by the general procedure using **1a** (2.40 g, 8.9 mmol) and thiazolidine-2,4-dione (1.05 g, 8.9 mmol): mp 205 °C; IR ν_{max} (KBr) 1738, 1704 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 12.10 (bs, 1 H, D_2O exchangeable), 8.35 (d, J = 3.0 Hz, 1 H), 7.9 (d, J = 5.0 Hz, 1 H), 7.70 (s, 2 H), 7.46 (d, J = 8.72 Hz, 2 H), 7.25−7.0 (m, 1 H), 7.01 (d, J = 8.72 Hz, 2 H), 6.42 (d, J = 3.0 Hz, 1 H), 4.68 (t, J = 5.30 Hz, 2 H), 4.40 (t, J = 5.20 Hz, 2 H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 167.73, 167.43, 159.53, 146.93, 142.11, 131.70, 131.34, 129.09, 128.24, 125.75, 120.64, 120.01, 115.45, 115.03, 99.10, 66.58, 43.07; MS m/z (relative intensity) (M^+ − 1, 15), 118 (100). Anal. Calcd for $C_{19}H_{15}N_3SO_3$ (365.41): C, 62.45; H, 4.13; N, 11.50. Found: C, 62.00; H, 4.63; N, 11.40.

5-[[4-[2-(1-Benzimidazolyl)ethoxy]phenyl]methylene]-thiazolidine-2,4-dione (2b). The title compound (6.72 g, 92%) was prepared by the general procedure using **1b** (5.32 g, 20.0 mmol) and thiazolidine-2,4-dione (2.34 g, 20.0 mmol): mp 258−260 °C; IR ν_{max} (KBr) 1748, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 12.10 (bs, 1 H, D_2O exchangeable), 8.20 (s, 1 H), 7.71 (s, 1 H), 7.75−7.60 (m, 2 H), 7.52 (d, J = 8.30 Hz, 2 H), 7.40−7.20 (m, 2 H), 7.05 (d, J = 8.30 Hz, 2 H), 4.68 (t, J = 4.47 Hz, 2 H), 4.43 (t, J = 4.47 Hz, 2 H); ^{13}C NMR (DMSO-d_6) 168.15, 167.72, 161.02, 159.61, 144.50, 143.29, 133.96, 132.12, 131.61, 125.98, 122.45, 121.66, 120.83, 119.42, 115.40, 110.74, 66.71, 43.69; MS m/z (relative intensity) 365 (M^+, 18), 131

(100). Anal. Calcd for $C_{19}H_{15}N_3SO_3$ (365.41): C, 62.45; H, 4.13; N, 11.50. Found: C, 62.17; H, 4.20; N, 11.46.

5-[[4-[2-(1-Imidazolyl)ethoxy]phenyl]methylene]-thiazolidine-2,4-dione (2c). The title compound (0.95 g, 78%) was prepared by the general procedure using **1c** (0.83 g, 3.84 mmol) and thiazolidine-2,4-dione (0.495 g, 4.2 mmol): mp 250 °C dec; IR ν_{max} (KBr) 1740, 1705 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 12.05 (bs, 1 H, D_2O exchangeable), 7.72 (s, 1 H), 7.62 (s, 1 H), 7.45 (d, J = 8.20 Hz, 2 H), 7.20 (s, 1 H), 7.04 (d, J = 8.20 Hz, 2 H), 6.90 (bs, 1 H), 4.40 (t, J = 4.02 Hz, 2 H), 4.25 (t, J = 4.02 Hz, 2 H). Anal. Calcd for $C_{15}H_{13}N_3SO_3$ (315.35): C, 57.13; H, 4.15; N, 13.32. Found: C, 57.01; H, 4.10; N, 13.00.

5-[[4-[2-(1-Indolinyl)ethoxy]phenyl]methylene]-thiazolidine-2,4-dione (2d). To a stirred solution of 5-[[4-[2-(1-indolyl)ethoxy]phenyl]methylene]thiazolidine-2,4-dione (**2f**) (3.64 g, 10.0 mmol) in glacial acetic acid (30 mL) at 20 °C was added $NaCNBH_3$ (1.86 g, 30.0 mmol) in one portion, and the mixture was heated at 70 °C with continuous stirring for 1 h. The precipitated compound was filtered and washed with water to furnish **2d** (3.44 g, 94%): mp 175 °C; IR ν_{max} (KBr) 1742, 1689, 1592 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 12.08 (bs, 1 H, D_2O exchangeable), 7.78 (s, 1 H), 7.52 (d, J = 8.72 Hz, 2 H), 7.10−6.90 (m, 4 H), 6.78−6.52 (m, 2 H), 4.26 (t, J = 5.3 Hz, 2 H), 3.62−3.40 (m, 4 H), 3.0 (t, J = 5.30 Hz, 2 H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 167.68, 167.27, 159.81, 151.52, 131.55, 129.07, 126.77, 125.50, 123.94, 120.29, 117.19, 114.78, 106.26, 65.99, 53.44, 48.00, 28.10; MS m/z (relative intensity) (M^+ + 1, 16), 132 (100). Anal. Calcd for $C_{20}H_{18}N_2SO_3$ (366.43): C, 65.55; H, 4.95; N, 7.64. Found: C, 65.33; H, 4.88; N, 7.61.

5-[[4-[2-(2-Carbethoxy-1-indolyl)ethoxy]phenyl]methylene]thiazolidine-2,4-dione (2e). The title compound (2.8 g, 82%) was prepared by the general procedure using **1e** (2.62 g, 7.8 mmol) and thiazolidine-2,4-dione (0.96 g, 7.8 mmol): mp 184 °C; IR ν_{max} (KBr) 1738, 1711, 1683 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 12.12 (bs, 1 H, D_2O exchangeable), 7.76 (s, 1 H), 7.64 (d, J = 7.89 Hz, 1 H), 7.57 (d, J = 8.39 Hz, 2 H), 7.49 (d, J = 8.72 Hz, 2 H), 7.40−7.30 (m, 1 H), 7.20−7.10 (m, 1 H), 7.07 (d, J = 8.72 Hz, 2 H), 4.86−4.79 (m, 2 H), 4.50−4.30 (m, 4 H), 1.42 (t, J = 7.10 Hz, 3 H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 167.72, 167.35, 159.65, 159.15, 135.66, 132.02, 131.88, 131.52, 125.91, 125.72, 122.53, 122.35, 121.28, 120.58, 115.15, 109.40, 107.17, 76.67, 65.55, 60.42, 14.00. Anal. Calcd for $C_{23}H_{20}N_2SO_5$ (436.47): C, 63.29; H, 4.61; N, 6.41. Found: C, 63.20; H, 4.51; N, 6.21.

5-[[4-[2-(2-Carboxyindol-1-yl)ethoxy]phenyl]methylene]-thiazolidine-2,4-dione (2f). To a stirred solution of 5-[[4-[2-(2-carbethoxyindol-1-yl)ethoxy]phenyl]methylene]thiazolidine-2,4-dione (0.972 g, 2.23 mmol) in 1,4-dioxane (8 mL) was added a 1 M solution of KOH (4.5 mL, 4.5 mmol) at 25 °C, and the mixture stirred for 1 h. Dioxane was removed under reduced pressure at 60 °C. The resultant syrup was dissolved in 6.0 mL of water and acidified to pH 2.0, with 6 N HCl. A white solid precipitated out, which was filtered and dried over P_2O_5 in a desiccator for 12 h to afford 765 mg (84%) of **2f**: mp 115 °C; IR ν_{max} (KBr) 3040, 1736, 1688 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 12.08 (bs, 1 H, D_2O exchangeable), 7.78 (s, 1 H), 7.70−7.40 (m, 4 H), 7.38 (t, J = 6.70 Hz, 1 H), 7.20−7.0 (m, 4 H), 4.80 (t, J = 5.30 Hz, 2 H), 4.40 (t, J = 5.30 Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 167.99, 167.48, 160.83, 159.87, 135.81, 132.15, 131.75, 126.76, 125.86, 125.73, 122.52, 121.34, 120.56, 115.45, 109.53, 107.20, 76.83, 65.72. Anal. Calcd for $C_{21}H_{16}N_2SO_5$ (408.42): C, 61.70; H, 3.95; N, 6.92. Found: C, 61.88; H, 4.03; N, 7.02.

5-[[4-[2-(1-Indolyl)ethoxy]phenyl]methylene]-thiazolidine-2,4-dione (2g). The title compound (12.28 g, 78%) was prepared by the general procedure using **1g** (11.4 g, 43.0 mmol), thiazolidine-2,4-dione (5.03 g, 43.0 mmol), benzoic acid (0.68 g, 5.5 mmol), and piperidine (0.61 mL, 0.53 g, 6.4 mmol): mp 216 °C; IR ν_{max} (KBr) 1748, 1692 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 12.05 (bs, 1 H, D_2O exchangeable), 7.67 (s, 1 H), 7.56 (d, J = 7.56 Hz, 1 H), 7.53 (t, J = 7.56 Hz, 1 H), 7.43 (d, J = 8.72 Hz, 2 H), 7.30 (d, J = 3.0 Hz, 1 H), 7.18 (t, J = 7.56 Hz, 1 H), 7.06 (d, J = 7.56 Hz, 1 H), 6.97 (d, J = 8.72 Hz, 2 H), 6.45 (d, J = 2.90 Hz, 1 H), 4.59 (t, J = 4.75 Hz, 2 H), 4.37 (t, J = 4.75 Hz, 2 H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 167.63, 167.21, 159.37, 135.61, 131.59, 131.47, 128.29, 128.02, 125.69, 121.01, 120.44, 120.29, 118.94, 114.79, 109.23, 100.91, 66.88, 44.89; MS m/z (relative intensity) 364 (M^+, 30), 130 (100). Anal. Calcd for $C_{20}H_{16}N_2SO_3$ (364.42): C, 65.91; H, 4.42; N, 7.71. Found: C, 65.86; H, 4.31; N, 7.66.

5-[[4-[2-(5-Chloro-1-indolyl)ethoxy]phenyl]methylene]-thiazolidine-2,4-dione (2h). The title compound (3.46 g, 91%) was prepared by the general procedure using aldehyde **1h** (2.75 g, 9.20 mmol) and thiazolidine-2,4-dione (1.2 g, 10.1 mmol): mp 206 °C; IR ν_{max} (KBr) 1738, 1705 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 12.10 (bs, 1 H, D_2O exchangeable), 7.67 (s, 1 H), 7.54 (s, 1 H), 7.49 (d, J = 8.1 Hz, 1 H), 7.41 (d, J = 8.49 Hz, 2 H), 7.31 (d, J = 2.90 Hz, 1 H), 7.14 (d, J = 8.1 Hz, 1 H), 6.94 (d, J = 8.49 Hz, 2 H), 6.44 (d, J = 2.90 Hz, 1 H), 4.57 (t, J = 4.90 Hz, 2 H), 4.35 (t, J = 4.90 Hz, 2 H); MS m/z (relative intensity) 398 (M^+, 46), 164 (100). Anal. Calcd for $C_{20}H_{15}ClN_2SO_3$ (398.86): C, 60.22; H, 3.79; N, 7.02. Found: C, 59.81; H, 4.00; N, 6.96.

5-[[4-[2-(3-Methyl-1-indolyl)ethoxy]phenyl]methylene]-thiazolidine-2,4-dione (2i). The title compound (4.9 g, 95%) was prepared by the general procedure using **1i** (3.84 g, 13.76 mmol) and thiazolidine-2,4-dione (1.61 g, 13.70 mmol): mp 235 °C; IR ν_{max} (KBr) 1738, 1710 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 12.05 (bs, 1 H, D_2O exchangeable), 7.68 (s, 1 H), 7.53 (d, J = 7.8 Hz, 1 H), 7.41 (d, J = 8.72 Hz, 2 H), 7.39 (d, J = 7.80 Hz, 1 H), 7.20 (t, J = 7.47 Hz, 1 H), 7.08 (t, J = 7.47 Hz, 1 H), 7.01 (s, 1 H), 6.93 (d, J = 8.72 Hz, 2 H), 4.51 (t, J = 5.31 Hz, 2 H), 4.32 (t, J = 5.31 Hz, 2 H), 2.31 (s, 3 H). Anal. Calcd for $C_{21}H_{18}N_2SO_3$ (378.44): C, 66.65; H, 4.79; N, 7.40. Found: C, 66.70; H, 4.81; N, 7.33.

5-[[4-[2-(2,3-Dimethyl-1-indolyl)ethoxy]phenyl]methylene]thiazolidine-2,4-dione (2j). The title compound (2.0 g, 94%) was prepared by the general procedure using aldehyde **1j** (1.60 g, 5.46 mmol) and thiazolidine-2,4-dione (0.70 g, 6.0 mmol): mp 254 °C; IR ν_{max} (KBr) 1749, 1694, 1584 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 12.10 (bs, 1 H, D_2O exchangeable), 7.67 (s, 1 H), 7.50−7.30 (m, 2 H), 7.42 (d, J = 8.72 Hz, 2 H), 7.20−6.95 (m, 2 H), 6.91 (d, J = 8.72 Hz, 2 H), 4.52 (t, J = 5.30 Hz, 2 H), 4.29 (t, J = 5.30 Hz, 2 H), 2.44 (s, 3 H), 2.23 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 167.90, 167.40, 159.72, 135.76, 132.81, 131.98, 131.62, 128.24, 125.69, 125.09, 120.48, 120.21, 118.43, 117.48, 115.16, 109.05, 105.54, 67.15, 41.93, 9.92, 8.64; MS m/z (relative intensity) 392 (M^+, 37), 158 (100). Anal. Calcd for $C_{22}H_{20}N_2SO_3$ (392.47): C, 67.32; H, 5.13; N, 7.13. Found: C, 67.00; H, 5.00; N, 6.97.

5-[[4-[2-(Methyltryptophan-1-yl)ethoxy]phenyl]methylene]thiazolidine-2,4-dione (2k). The title compound was prepared in three steps as follows. **Step A, Preparation of 4-[2-[Methyl-*N*-(*tert*-butoxycarbonyl)tryptophan-1-yl]-ethoxy]benzaldehyde:** The title compound was prepared by the general procedure using *N*-(*tert*-butoxycarbonyl)tryptophan methyl ester (2.0 g, 6.31 mmol), 4-(2-bromoethoxy)benzaldehyde (1.45 g, 6.31 mmol), and NaH (154 mg, 6.31 mmol) in 38% (1.1 g) yield: IR ν_{max} (KBr) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.86 (s, 1 H), 7.80 (d, J = 8.72 Hz, 2 H), 7.55 (d, J = 7.47 Hz, 1 H), 7.36 (d, J = 8.21 Hz, 1 H), 7.30−7.08 (m, 2 H), 7.01 (s, 1 H), 6.94 (d, J = 8.72 Hz, 2 H), 5.20−4.90 and 4.70−4.50 (m, 1 H), 4.51 (t, J = 5.40 Hz, 2 H), 4.33 (t, J = 5.40 Hz, 2 H), 3.65 (s, 3 H), 3.35−3.05 (m, 2 H), 1.42 (s, 9 H).

Step B, Preparation of 5-[[4-[2-[Methyl-3-*N*-(1-butoxycarbonyl)tryptophan-1-yl]ethoxy]phenyl]methylene]thiazolidine-2,4-dione: The title compound was prepared by the general procedure using 4-[2-[methyl-*N*-(*tert*-butoxycarbonyl)-tryptophan-1-yl]ethoxy]benzaldehyde (2.25 g, 5.54 mmol) and thiazolidine-2,4-dione (0.71 g, 6.09 mmol) in 71% (2.20 g) yield: mp 140−142 °C; IR ν_{max} (KBr) 1730, 1710, 1690 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 12.05 (bs, 1 H, D_2O exchangeable), 9.40 (bs, 1 H, D_2O exchangeable), 7.59 (d, J = 7.80 Hz, 1 H), 7.41 (d, J = 8.72 Hz, 2 H), 7.32−7.01 (m, 4 H), 6.92 (d, J = 8.72 Hz, 2 H), 5.30−5.08 and 4.28−4.10 (m, 1 H), 4.51 (t, J = 4.80 Hz, 2 H), 4.30 (t, J = 4.80 Hz, 2 H), 4.20−4.00 (m, 1

H), 3.70 (s, 3 H), 3.30 (d, J = 5.30 Hz, 2 H), 1.40 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 190.31, 172.89, 167.84, 167.39, 160.02, 155.32, 136.14, 133.63, 132.20, 128.31, 126.87, 125.98, 121.90, 119.38, 118.99, 118.67, 115.11, 109.31, 79.94, 66.92, 54.05, 52.26, 45.25, 27.95.

Step C, Hydrolysis of 5-[[4-[2-[3-methyl-*N*-(1-butoxycarbonyl)tryptophan-1-yl]ethoxy]phenyl]methylene]thiazolidine-2,4-dione: To a stirred solution of 5-[[4-[2-[3-[2-(*tert*-butoxycarbonylamino)-2-(carbomethoxy)ethyl]indolyl]-ethoxy]phenyl]methylene]thiazolidine-2,4-dione (1.70 g, 3.0 mmol) in 1,4-dioxone (15 mL) was added concentrated HCl (4.0 mL) at room temperature, and stirring was continued for 3 h. Dioxane was removed under reduced pressure, and the resultant residue was dissolved in water (50 mL) and neutralized with saturated aqueous K_2CO_3 solution. A white solid precipitated out, which was filtered and dried under vacuum to yield 0.89 g of **2k** (64%): mp 180 °C; IR ν_{max} (KBr) 1744, 1697 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 12.10 (bs, 1 H, D_2O exchangeable), 7.66 (s, 1 H), 7.54 (d, J = 7.47 Hz, 1 H), 7.43 (d, J = 8.72 Hz, 2 H), 7.42 (s, 1 H), 7.30−7.00 (m, 4 H), 6.96 (d, J = 8.72 Hz, 2 H), 4.54 (t, J = 4.88 Hz, 2 H), 4.35 (t, J = 4.88 Hz, 2 H), 3.90−3.70 (m, 1 H), 3.66 (s, 3 H), 3.30−3.10 (m, 1 H), 3.10−2.90 (m, 1 H). Anal. Calcd for $C_{24}H_{23}N_3SO_5$ (466.14): C, 61.84; H, 5.10; N, 9.01. Found: C, 61.77; H, 5.00; N, 8.88.

5-[[4-[2-(1-Carbazolyl)ethoxy]phenyl]methylene]-thiazolidine-2,4-dione (2l). The title compound was prepared by the general procedure using **1l** (2.5 g, 7.9 mmol) and thiazolidine-2,4-dione (0.93 g, 7.9 mmol) in 95% (3.1 g) yield: mp 277−278 °C; IR ν_{max} (KBr) 1752, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 12.12 (bs, 1 H, D_2O exchangeable), 8.07 (d, J = 7.48 Hz, 2 H), 7.65 (s, 1 H), 7.60 (d, J = 8.30 Hz, 2 H), 7.47 (t, J = 8.30 Hz, 2 H), 7.39 (d, J = 7.89 Hz, 2 H), 7.23 (t, J = 7.48 Hz, 2 H), 6.91 (d, J = 7.89 Hz, 2 H), 4.80 (t, J = 4.89 Hz, 2 H), 4.46 (t, J = 4.89 Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 167.97, 167.42, 159.72, 140.23, 132.00, 131.67, 125.68, 122.18, 120.45, 120.17, 119.22, 118.96, 115.17, 109.59, 66.75, 41.91; MS m/z (relative intensity) 414 (M$^+$, 6), 180 (100). Anal. Calcd for $C_{24}H_{18}N_2SO_3$ (414.47): C, 69.54; H, 4.37; N, 6.75. Found: C, 69.31; H, 4.32; N, 6.70.

General Procedure of Preparation of 5-[[4-2-(Heterocyclyl)ethoxy]phenyl]methyl]thiazolidine-2,4-diones 3. A solution of the appropriate thiazolidine-2,4-dione **2** (1.0 g) in 1,4-dioxane (35 mL) was added to 10% Pd−C (1.5 g) and hydrogenated at 60 psi for 36−60 h. The mixture was filtered through a bed of Celite, and the filtrate was evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel using a mixture of ethyl acetate and petroleum ether as an eluent to yield pure compound.

5-[[4-[2-(7-Azaindol-1-yl)ethoxy]phenyl]methyl]thiazolidine-2,4-dione (3a). The title compound was prepared by the general procedure using **2a** (1.0 g, 2.74 mmol) and 10% Pd−C (1.5 g) in 70% (0.70 g) yield: mp 195 °C; IR ν_{max} (KBr) 1744, 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 11.78 (bs, 1 H, D_2O exchangeable), 8.38 (d, J = 5.0 Hz, 2 H), 7.96 (d, J = 8.7 Hz, 1 H), 7.48 (d, J = 5.0 Hz, 1 H), 7.20−7.12 (m, 1 H), 7.18 (d, J = 8.70 Hz, 2 H), 6.86 (d, J = 8.70 Hz, 2 H), 6.50 (d, J = 5.0 Hz, 1 H), 4.78 (t, J = 5.30 Hz, 2 H), 4.44 (dd, J = 9.0, 6.0 Hz, 1 H), 4.40 (t, J = 5.30 Hz, 2 H), 3.42 (dd, J = 14.5, 6.0 Hz, 1 H), 3.06 (dd, J = 14.5, 9.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 175.30, 171.28, 157.05, 146.87, 142.06, 130.10, 129.09, 128.55, 128.21, 120.02, 115.40, 114.95, 99.00, 66.26, 52.95, 43.24, 36.68; MS m/z (relative intensity) 368 (M$^+$+ 1, 16), 118 (100). Anal. Calcd for $C_{19}H_{17}N_3SO_3$ (367.42): C, 62.11; H, 4.66; N, 11.43. Found: C, 62.50; H, 4.00; N, 11.50.

5-[[4-[2-(1-Indolinyl)ethoxy]phenyl]methyl]thiazolidine-2,4-dione (3d). To a stirred solution of 5-[[4-[2-(1-indolyl)-ethoxy]phenyl]methyl]thiazolidine-2,4-dione (**3g**) (1.2 g, 3.20 mmol) in 10 mL of glacial acetic acid was added sodium cyanoborohydride (609 mg, 9.8 mmol) at 20 °C in portions, and the mixture stirred for 1 h at the same temperature. The reaction mixture was diluted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The resultant residue was crystallized from dichloromethane to furnish 1.0 g (83%) of pure compound: mp 143−144 °C; IR ν_{max} (KBr) 1736, 1697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.12 (bs, 1 H, D_2O exchangeable), 7.20−7.00 (m, 4 H), 6.88 (d, J = 8.72 Hz, 2 H), 6.68 (t, J = 7.0 Hz, 1 H), 6.55 (d, J = 7.0 Hz, 1 H), 4.50 (dd, J = 10.0, 6.0 Hz, 1 H), 4.18 (t, J = 5.30 Hz, 2 H), 3.60−3.40 (m, 5 H), 3.12 (dd, J = 14.0, 10.0 Hz, 1 H), 2.98 (t, J = 7.60 Hz, 2 H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 173.88, 169.88, 156.14, 150.55, 128.76, 127.81, 126.97, 125.57, 122.69, 115.74, 113.68, 112.88, 105.02, 82.24, 64.44, 52.13, 51.72, 46.77, 26.87; MS m/z (relative intensity) 368 (M$^+$, 9), 139 (100). Anal. Calcd for $C_{20}H_{20}N_2SO_3$ (368.14): C, 65.15; H, 5.42; N, 7.60. Found: C, 65.50; H, 5.20; N, 7.60.

5-[[4-[2-(1-Indolyl)ethoxy]phenyl]methyl]thiazolidine-2,4-dione (3g). The title compound (0.92 g, 92%) was prepared by the above general procedure using compound **2g** (1.0 g, 2.75 mmol) and 10% Pd−C (1.5 g): mp 103 °C; IR ν_{max} (KBr) 1754, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 8.18 (bs, 1 H, D_2O exchangeable), 7.65 (d, J = 7.4 Hz, 1 H), 7.39 (d, J = 8.30 Hz, 1 H), 7.30−7.15 (m, 2 H), 7.08 (d, J = 8.72 Hz, 2 H), 6.76 (d, J = 8.72 Hz, 2 H), 6.50 (d, J = 2.92 Hz, 2 H), 4.50 (t, J = 5.52 Hz, 2 H), 4.43 (dd, J = 9.45, 3.75 Hz, 1 H), 4.23 (t, J = 5.52 Hz, 2 H), 3.39 (dd, J = 14.11, 3.74 Hz, 1 H), 3.04 (dd, J = 14.11, 9.45 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 174.64, 170.95, 157.64, 135.99, 130.28, 128.57, 128.32, 128.17, 121.58, 121.00, 119.48, 114.72, 109.16, 101.59, 66.77, 53.56, 45.52, 37.50; MS m/z (relative intensity) 367 (M$^+$ + 1, 19), 130 (100). Anal. Calcd for $C_{20}H_{18}N_2SO_3$ (366.41): C, 65.50; H, 4.95; N, 7.64. Found: C, 65.50; H, 4.49; N, 7.62.

5-[[4-[2-(Carbazol-1-yl)ethoxy]phenyl]methyl]thiazolidine-2,4-dione (3l). The title compound was prepared by the above general procedure using **2l** (1.25 g, 3.02 mmol) and 10% Pd−C (1.62 g) in 80% (1.0 g) yield: mp 214 °C; IR ν_{max} (KBr) 1755, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 11.89 (bs, 1 H, D_2O exchangeable), 8.06 (d, J = 7.47 Hz, 2 H), 7.57 (d, J = 8.30 Hz, 2 H), 7.45 (t, J = 7.47 Hz, 2 H), 7.21 (t, J= 8.20 Hz, 2 H), 7.07 (d, J = 8.20 Hz, 2 H), 6.72 (d, J = 8.20 Hz, 2 H), 4.75 (t, J = 5.80 Hz, 2 H), 4.42 (dd, J = 9.0, 6.0 Hz, 1 H), 4.35 (t, J = 5.30 Hz, 2 H), 3.37 (dd, J = 14.0, 6.0 Hz, 1 H), 2.99 (dd, J = 14.0, 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 175.76, 171.74, 157.12, 140.26, 130.34, 128.87, 125.66, 122.16, 120.16, 118.91, 114.22, 109.60, 66.25, 53.03, 42.04, 36.27; MS m/z (relative intensity) 416 (M$^+$, 11), 180 (100). Anal. Calcd for $C_{24}H_{20}N_2SO_3$ (416.48): C, 69.15; H, 4.84; N, 6.73. Found: C, 69.50; H, 4.81; N, 6.78.

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References

(1) (a) DeFronzo, R. A. The triumvirate: β cell, muscle, liver a collusion responsible for NIDDM. *Diabetes* **1988**, *37*, 667. (b) Turner, R. C.; Mathews, D. R.; Clark, A.; O'Rahilly, S.; Rudenski, A. S.; Levy, J. *Clin. Endrocrinol. Metab.* **1988**, *2*, 327. (c) Reaven, G. M. *Diabetes* **1988**, *37*, 1595−1607.

(2) (a) Feldt-Rasmussen, B.; Mathiesen, E.; Deckert, T. Effect of Two Years of Strict Metabolic Control on Progression of Inapient Nephropathy in Insulin-Dependent Diabetes. *Lancet* **1986**, *2*, 1300−1304. (b) Dahl-Jorgensen, K.; Brinchmann-Hansen, O.; Hanssen, K. F.; Ganes, T.; Kierulf, P.; Smeland, E.; Sandvik, L.; Aagenaes, O. Effect of Near-Normoglycemia for Two Years on Progression of Early Diabetic Retinopathy, Nephropathy, and Neuropathy; The Oslo Study. *Br. Med. J.* **1986**, *293*, 1195−1199. (c) Pirart, J. Diabetes Mellitus and its Degenerative Complications, A Prospective Study of 4,400 Patients Observed between 1947 and 1973. *Diabetes Care* **1978**, *1*, 168−188, 252−263.

(3) Jaspan, J. B. Monitoring and Controlling the Patient with Non-Insulin Dependent Diabetes Mellitus. *Metabolism* **1987**, *36* (Suppl. 1), 22−27.

(4) Gerich, J. E. Oral Hypoglycemic Agents. *N. Engl. J. Med.* **1989**, *321*, 1231−1245.

(5) (a) Goldman, J. M. Oral Hypoglycemic Agents: an Update of Sulfonylureas. *Drugs Today* **1989**, *25*, 689−695. (b) Kolterman, O. G.; Prince, M. J.; Olefsky, J. M. Insulin Resistance in Non-

Insulin Dependent Diabetes Mellitus. Impact of sulfonylureas agents *in vivo* and *in vitro*. *Am. J. Med.* **1983**, *74* (Suppl. 1A), 82−101. (c) Bailey, C. J. Hypoglycemic and anti-hyperglycemic drugs for the control of diabetic. *Proc. Nutr. Soc.* **1991**, *50*, 619−630.

(6) (a) Holman, R. R.; Turner, R. C. Oral Agents and Insulin in the treatment of Non-Insulin-Dependent Diabetes-Mellitus. In *Text Book of Diabetes*; Pickup, J. C., Williams, G., Eds.; Blackwell Scientific Publications: London, 1991; pp 462−476. (b) Ferrannini, E. The Insulin Resistance Syndrome. *Curr. Opin. Nephrol. Hypertens.* **1992**, *1*, 291−298.

(7) (a) The Diabetes Control and Complications Trials (DCCT). *N. Engl. J. Med.* **1993**, *329*, 683−689. (b) American Diabetic Association. *Diabetes* **1993**, *43*, 1555−1558.

(8) Steiner, K. E.; Lien, E. L. Hypoglycemic Agents which do not Release Insulin. In *Progress in Medicinal Chemistry*; Ellis, G. P., West, C. B., Eds.; Elsevier: Oxford, 1987; Vol. 24, pp 209−248.

(9) (a) Larson, E. R.; Clark, D. A.; Stevenson, R. W. New Approaches to Diabetes. *Annu. Rep. Med. Chem.* **1989**, *25*, 205−213. (b) Colea, J. R.; Tanis, S. P. Recent advances in the discovery and development of potential antidiabetic agents. *Annu. Rep. Med. Chem.* **1992**, *27*, 219−226. (c) Dow, R. L.; Kreutter, D. K. Recent Advancements in the Discovery and Development of Agents for the Treatment of Diabetes. *Annu. Rep. Med. Chem.* **1995**, *30*, 159−168. (d) Hulin, B.; McCarthy, P. A.; Gibbs, E. M. The Glitazone Family of Antidiabetic Agents. *Curr. Pharmacol. Des.* **1996**, *2*, 85−102. (e) Hulin, B. New Hypoglycemic Agents. *Prog. Med. Chem.* **1994**, *31*, 1−58.

(10) Sohda, T.; Mizuno, K.; Tawada, H.; Sugiyama, Y.; Fujita, T.; Kawanatsu, Y. Studies on Antidiabetic agents. II Synthesis of 5-[4-(1-Methylcyclohexylmethoxy)benzyl]thiazolidine-2,4-dione and its derivatives. *Chem. Pharm. Bull.* **1982**, *30*, 3563−3573, 3580−3600.

(11) (a) Momose, Y.; Meguro, K.; Ikeda, H.; Hatanaka, C.; Oi, S.; Sohda, T. Studies on antidiabetic agents X synthesis and biological activities of pioglitazone and related compounds. *Chem. Pharm. Bull.* **1991**, *39*, 1440−1445. (b) Meguro, K.; Fujita, T. EP 0155845, 1985; *Chem. Abstr.* **1986**, *104*, 186401a. (c) Sugiyama, Y.; Taketomi, S.; Shimara, Y.; Ikeda, H.; Fujita, T. Effects of Pioglitazone on Glucose and Lipid metabolism in Wistar fatty rats. *Arzneim. Forsch. Drug Res.* **1990**, *40*, 263−267.

(12) (a) Yoshioka, T.; Fujita, T.; Kanai, T.; Aizawa, Y.; Kurumada, T.; Hasegawa, K.; Horikoshi, H. Studies on Hindered Phenols and analogous. 1. Hypolipidemic Agents with ability to Inhibit Lipid peroxidation. *J. Med. Chem.* **1989**, *32*, 421−428. (b) Yoshioka, T.; Kotazata, E.; Yamazaki, M.; Hasegawa, K. Thiazolidinedione Derivatives, Their preparation and compositions containing them. EP 0139421, 1984; *Chem. Abstr.* **1985**, *103*, 540685.

(13) (a) Clark, D. A.; Goldstein, S. W.; Volkmann, R. A.; Eggler, J. F.; Holland, G. F.; Hulin, B.; Stevenson, R. W.; Kreutter, D. K.; Gibbs, E. M.; Krupp, M. N.; Merrigan, P.; Kelbaugh, P. L.; Andrews, E. G.; Tickner, D. L.; Suleske, R. T.; Lamphere, C. H.; Rajeckas, F. J.; Kappeler, W. H.; McDermott, R. E.; Hutson, N. J.; Johnson, M. R. Substituted Dihydrobenzopyran and Dihydrobenzofuran Thiazolidine-2,4-diones and Hypoglycemic Agents. *J. Med. Chem.* **1991**, *34*, 319−325. (b) Eggler, J. F.; Holland, G. F.; Johnson, M. R.; Volkmann, R. A. Hypoglyceamic Thiazolidinediones. U.S. Patent 4,738,972, 1985; *Chem. Abstr.* **1987**, *107*, 39794 q. (c) Stevenson, R. W.; Hutson, N. J.; Krapp, M. N.; Volkmann, R. A.; Holland, G. F.; Eggler, J. F.; Clark, D. A.; McPherson, R. K.; Haell, K. L.; Danburg, B. H.; Gibbs, E. M.; Krentler, D. K. Actions of Novel antidiabetic agents Englitazone in Hyperglycemic Hyperinsulinemic ob/ob mice. *Diabetes* **1990**, *39*, 1218−1227.

(14) (a) Cantello, B. C. C.; Cawthorne, M. A.; Haigh, D.; Hindley, R. M.; Smith, S. A.; Thurlby, P. L. The Synthesis of BRL-49653 - A Novel and Potent antihyperglycemic agent. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1181−1184. (b) Cantello, B. C. C.; Cawthorne, M. A.; Cottam, G. P.; Duff, P. T.; Haigh, D.; Hindley, R. M.; Lister, C. A.; Smith, S. A.; Thurlby, P. L. [(ω-(Heterocyclylamino)alkoxy]-benzyl]-2,4-thiazolidinediones as potent antihyperglycemic agents. *J. Med. Chem.* **1994**, *37*, 3977−3985.

(15) Fujita, T.; Sugiyama, Y.; Taketomi, S.; Sohda, T.; Kawamastsu, Y.; Iwatsuka, H.; Suzuoki, Z. Reduction of Insulin Resistance in Obese and/or Diabetic Animals by 5-[4-(1-Methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878, U,63287, Ciglitazone), a New Antidiabetic Agent. *Diabetes* **1983**, *32*, 804−810.

(16) (a) Williams, D. G.; Deldar, A.; Jordan, W. H.; Gries, C.; Long, G. G.; Dimarchi, R. D. Subchronic Toxicity of the Thiazolidinedione, Tanabe 174, in Rat and Dog. *Diabetes* **1993**, *42* (Suppl 1), 59A (Abstr. 186). (b) Deldar, A.; William, G.; Stevenes, C. Pathogenesis of Thiazolidinedione induced haemotoxocity in the dog. *Diabetes* **1993**, *42* (Suppl. 1), 57A (Abstr. 179).

(17) Troglitazone is being marketed in the United States as Rezulin and in Japan as Noscal.

(18) (a) Kauramatsu, Y.; Fujita, T. Thiazolidine derivatives and pharmaceutical compositions comprising them. U.S. Patent 4 438 141; *Chem. Abstr.* **1980**, *93*, 114506v. (b) Kauramatsu, Y.; Fujita, T. Thiazolidine derivatives. U.S. Patent 4 461 902; *Chem. Abstr.* **1983**, *99*, 212516s. (c) Meguro, K.; Fujita, T. 5-(4-Hydroxybenzyl)-2,4-dioxothiazolidine derivatives. U.S. Patent 4 775 687; *Chem. Abstr.* **1987**, *106*, 138436k. (d) Krueger, B. W.; Hoffman, H.; Roos, E.; Behrenz, W. Insecticidal Synergists. U.S. Patent 4 678 777; *Chem. Abstr.* **1986**, *104*, 22072z. (e) Meguro, K.; Fujita, T. Thiazolidinedione derivatives and their uses. U.S. Patent 4 725 610; *Chem. Abstr.* **1986**, *105*, 172446c. (f) Meguro, K.; Fujita, T. Thiazolidinedione derivatives and their medicinal compositions. U.S. Patent 4 582 839; *Chem. Abstr.* **1986**, *104*, 186401a. (g) Meguro, K.; Fujita, T. Thiazolidine derivatives and their uses. U.S. Patent 4 687 777. *Chem. Abstr.* **1986**, *105*, 226543c. (h) Eggler, J.; Holland, G. Thiazolidinedione derivatives as hypoglycemics and their preparations. *Chem. Abstr.* **1989**, *110*, 75483h. (i) Clark, D. A. Preparation of (benzopyranyl-methyl)thiazolidinediones as hypoglycemic and anticholesteremic agents. U.S. Patent 4 791 125; *Chem. Abstr.* **1988**, *111*, 23503v. (j) Clark, D. A.; Goldstein, S. W.; Hulin, B.; U.S. Patent 4 791 125, 1988. (k) Fujiwara, T.; Yoshioka, S.; Yoshioka, T.; Ushiyama, I.; Horikoshi, H. Characterization of New Oral Antidiabetic Agent CS-045. *Diabetes* **1988**, *37*, 1549−1558. (l) Clark, D. A.; Goldstein, S. W.; Hulin, B. U.S. Patent 5 036 079. (m) Hulin, B.; Clark, D. A.; Goldstein, S. W.; McDermott, R. E.; Dambek, P. J.; Kappeler, W. H.; Lamphere, C. H.; Lewis, D. M.; Rizzi, J. P. Novel Thiazolidine-2,4-diones as Potent Euglycemic Agents. *J. Med. Chem.* **1992**, *35*, 1853−1864. (n) Sohda, T.; Mizuno, K.; Momose, Y.; Ikeda, H.; Fujita, T.; Meguro, K. Studies on Antidiabetic Agents. 11. Novel Thiazolidinedione Derivatives as Potent Hypoglycemic and Hypolipidemic Agents. *J. Med. Chem.* **1992**, *35*, 2617−2626.

(19) For Non-thiazolidinedione-like agents, see: Kees, K. L.; Cheeseman, R. S.; Prozialeck, D. H.; Steiner, K. E. Perfluoro-N-[4-(1H-tetrazol-5-ylmethyl)phenyl]alkanamides. A New Class of Oral Antidiabetic Agents. *J. Med. Chem.* **1989**, *32*, 11−13.

(20) For 2,4-oxazolidinediones, see: Dow, R. L.; Bechle, B. M.; Chou, T. T.; Clark, D. A.; Hulin, B.; Stevenson, R. W. Benzyloxazolidine-2,4-diones as Potent Hypoglycemic Agents. *J. Med. Chem.* **1991**, *34*, 1538−1544.

(21) (a) Goldstein, S. W.; McDermott, R. E.; Gibbs, E. M.; Stevenson, R. W. Hydroxyurea Derivatives as Hypoglycemic Agents. *J. Med. Chem.* **1993**, *36*, 2238−2240. (b) Kees, K. L.; Caggiano, T. J.; Steiner, K. E.; Fitzgerald, J. J., Jr.; Kates, M. J.; Christos, T. E.; Kulishoff, J. M., Jr.; Moore, R. D.; McCaleb, M. L. Studies on New Acidic Azoles as Glucose Lowering Agents in Obese, Diabetic db/db mice. *J. Med. Chem.* **1995**, *38*, 617−628. (c) See ref 18b. (d) See ref 18d. (e) Yoshioka, T.; Kitazawa, E.; Kurumada, T.; Mitsuo, Y.; Hasegawa, K.; Fujita, T. Chroman thiazolidine derivatives as hypoglycemic agents and aldose reductase inhibitors and process for their preparation. EP 207 581, *Chem. Abstr.* **1987**, *106*, 119879r. (f) See ref 18k. (g) Yoshioka, T.; Fujita, T.; Kanai, T.; Aizawa, Y.; Kurumada, T.; Hasegawa, K.; Horikoshi, H. Studies on Hindered Phenols and Analogues. 1. Hypolipidemic and Hypoglycemic Agents with Ability to Inhibit Lipid Peroxidation. *J. Med. Chem.* **1989**, *32*, 421−428. (h) Kees, K. L.; Cheeseman, R. S. Preparation of hypoglycemic 5-[[(hydroxyiminocyclohexyl)methoxy]benzyl]-2,4-thiazolidinediones. U.S. Patent 4 728 739; *Chem. Abstr.* **1988**, *109*, 6505j. (i) Ijima, I.; Ozeka, M.; Okumura, K.; Inamasu, M. EP 283035-A, 1988; U.S. Patent 4 824 833. (j) Cantello, B. C. C.; Hindley, R. M. Urea and thiourea derivatives of thiazolidinedione, a process for their preparation, their pharmaceutical compositions. EP 295 828a; *Chem. Abstr.* **1989**, *110*, 135231m. (k) See ref 181.

(22) (a) 56 Annual Meeting of American Diabetes Association, Moscone Centrem, San Francisco, CA, June 8−11, 1996. (b) Insulin Resistance, Novel Drug Development Strategies for type-2 Diabetes and Obesity. International Business Communication, Oct. 31−Nov. 1, 1996. (c) 57th Annual Meeting and Scientific Session, American Diabetes Association, Boston, MA, June 21−24, 1997. (d) Elbrect, A.; Chen, Y.; Cullinan, C. A.; Hayes, N.; Leibowitz, M. D.; Moller, D. E.; Beger, J. Molecular Cloning, Expression and Characterization of Human Peroxisome Proliferator Activated Receptor γ_1 and γ_2. *Biochem. Biophys. Res. Commun.* **1996**, *224*, 431−437.

(23) Youngolale, G. A.; Sih, J. C.; Tanis, S. P.; Lin, C.-H. Preparation of α-amino indole-3-acetic acid useful as antidiabetic, antiobesity and antiatherosclerotic agents. WO 90 05721; *Chem. Abstr.* **1990**, *113*, 211831m.

(24) Berlin, I.; Chalon, S.; Rosenzweig, P.; Fuseau, E.; Pueeh, A. *J. Fundam. Clin. Pharmacol.* **1993**, *7*, 348.

(25) Berlin, I.; Rosenzweig, P.; Chalon, S.; Fuseau, E.; Landult, C.; Cesselin, F.; Blacker, C.; Puech, A. *J. Clin. Pharmacol. Ther.* **1994**, *95*, 338.

(26) Lohray, B. B.; Bhushan, V.; Bheema Rao, P.; Madhavan, G. R.; Murali, N.; Rao, K. N.; Reddy, K. A.; Rajesh, B. M.; Reddy, P. G.; Chakrabarti, R.; Rajagopalan, R. Novel Thiazolidinedione Derivatives as Potent Euglycemic and Hypolipidemic Agents. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 785−788.

(27) Watt, S. D.; Profitt, J. A.; Corey, E. J. A Reagent for α,β-Reduction of conjugated Nitriles. *J. Org. Chem*. **1975**, *40*, 127−128.

(28) Nate, H.; Matsuki, K.; Tsunashima, A.; Ohtsuka, H.; Sekine, Y. Synthesis of 2-phenylthiazolidine derivatives as cardiotonic agents. II. 2-(phenylpiperazinoalkoxyphenyl)thiazolidine-3-thiocarboxyamides and corresponding carboxyamides. *Chem. Pharm. Bull.* **1987**, *35*, 2394.

(29) Horikoshi, H.; Yoshio, T.; Kawasaki, T.; Nakamura, K.; Matsunuma, N.; Yamaguchi, K.; Sasahara, K. Troglitazone (CS-045), A New Antidiabetic Drug. *Annu. Rep. Sankyo Res. Lab.* **1994**, *46*, 1−57.

(30) (a) Issemann, I.; Green, S. Activation of a member of the steroid hormone receptor superfamily by Peroxisome proliferator. *Nature* **1990**, *347*, 645−650. (b) Clawla, A.; Schwarz, E. J.; Dimaculangan, D. D.; Lazar, M. A. Peroxisome proliferator activated receptor (PPARγ): adipose-predominant expression and induction early in adipocyte differentiation. *Endocrinology* **1994**, *135* (2), 798−800. (c) Kilewer, S. A.; Forman, B. M.; Blumberg, B.; Ong, E. S.; Borgmeyer, U.; Manglesdorf, D. J.; Umesono, K.; Evans, R. M. Differential Expression and Activation of a family of Murine Peroxisome Proliferatory-activated Receptors. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 7355.

(31) (a) Forman, B. M.; Tontonoz, P.; Chen, J.; Brun, R. P.; Spiegelman, B. M.; Evans, R. M. 15-Deoxy-$\Delta^{12,14}$-Prostaglandin J_2 is a ligand for the Adipocyte Determination Factor PPARγ. *Cell* **1995**, *83*, 803−812. (b) Willson, T. M.; Cobb, J. E.; Cowan, D. J.; Wiethe, R. W.; Correa, I. D.; Prakash, S. R.; Beck, K. D.; Moore, L. B.; Kliewer, S. A.; Lehmann, J. M. The Structure Activity Relationship between Peroxisome Proliferator-Activated Receptor γ Agonism and the antihyperglycemic activity of Thiazolidinediones. *J. Med. Chem*. **1996**, *39*, 665.

(32) Lehmann, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkison, W. O.; Willson, T. M.; Kliewer, S. A. An Antidiabetic Thiazolidinediones as a High Affinity Ligands for Peroxisome Proliferator-Activated Receptor γ (PPARγ). *J. Biol. Chem*. **1995**, *270*, 12953−12956.

(33) Flier, J. S. The Adipocyte Storage Depot or Node on the Energy Information Super highway. *Cell* **1995**, *80*, 15−18.

(34) Calculation: The percent reduction was calculated according to the formula: $1 - [(TT/OT)/(TC/OC)] \times 100$, where TT, test day treated; OT, zero day treated; TC, test day control; OC, zero day control Statistics: All results are expressed as mean ± SE. The AUC was calculated according to trapezoidal rule. ANOVA was used for testing for significance between the control and treated groups. *P* value which is <0.05 is considered as significant.

(35) Noland, W. E.; Baude, F. J. *Organic Synthesis*; John Wiley & Sons: New York, 1963; Collect. Vol. IV, p 567.

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