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5-Aryl Thiazolidine-2,4-diones as Selective PPARγ Agonists

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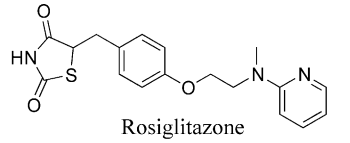
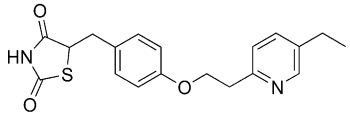
Abstract—A series of 5-aryl thiazolidine-2,4-diones containing 4-phenoxyphenyl side chains was designed, synthesized, and evaluated for PPAR agonist activities. One such compound **28** exhibited comparable levels of glucose correction to rosiglitazone in the *db*/*db* mouse type 2 diabetes animal model.

Type 2 diabetes is a chronic disease characterized by insulin resistance in the liver and peripheral tissues accompanied by a defect in pancreatic β-cells.[1,2] Between 1997 and 1999, a new class of drugs called 'glitazones'[3] was approved by the FDA for the treatment of type 2 diabetes (Fig. 1). These agents share a common partial chemical structure: thiazolidine-2,4-diones (TZD). Glitazones correct hyperglycemia by enhancing tissues' sensitivity to insulin. Because of this mechanism of action, glitazone treatment is not associated with dangerous hypoglycemic incidents that have been observed with conventional sulfonylurea agents and insulin therapy. In the mid-1990s, the molecular target of glitazones was reported to be the peroxisome proliferator-activated receptor-γ (PPARγ).[4–7] The PPARs are a group of nuclear receptors that act as transcriptional factors which play a major role in the regulation of lipid metabolism and storage.[8–10]



Rosiglitazone



Pioglitazone

Figure 1. Currently marketed glitazone antidiabetic drugs.

To date, a large number of compounds containing TZD moiety have been synthesized and tested for PPAR agonist activities.[11] Several of these have reportedly entered clinical studies. While the vast majority of TZD-containing antidiabetic agents reported in the literature have a methylene group bridging the TZD and the phenyl group (5-benzyl TZDs), we and others have independently found that compounds with a TZD directly connected to the phenyl group (5-aryl TZDs) can be potent and selective PPAR agonists.[12,13] Herein, we would like to report the results of our SAR studies on 5-aryl-thiazoline-2,4-diones.[14]

The design of 5-aryl TZD structure came from the phenylacetic acid series that had been studied earlier in our laboratories:[15] a TZD was introduced as a carboxylic acid surrogate (Fig. 2). Some of the partial structures of 5-aryl-TZDs **11**–**30** (Scheme 1) and our SAR interests were derived from our previous work in the phenylacetic acid series.[16,17]

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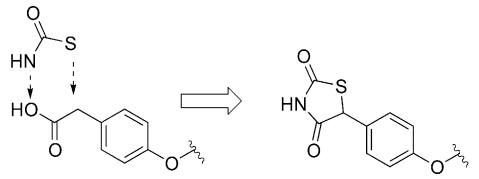


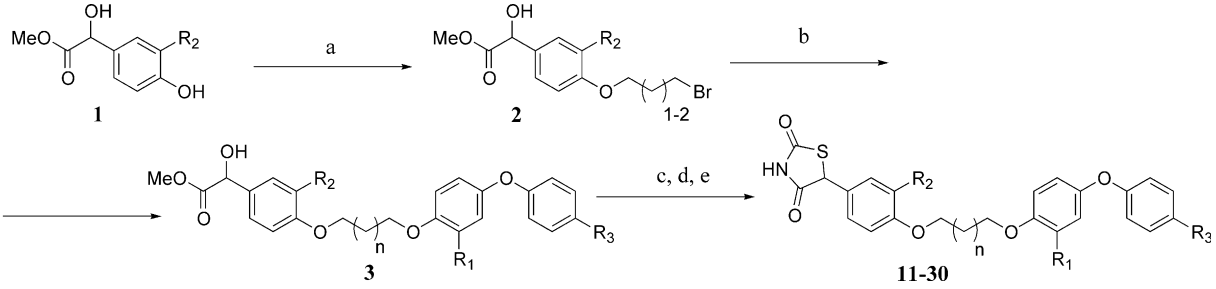
Figure 2. 5-Aryl TZD as a phenylacetic acid replacement.

General synthesis of 5-aryl thiazolidine-2,4-diones is depicted in Scheme 1. Thus, appropriately substituted mandelates were treated with 1,3-dibromopropane or 1,4-dibromobutane and cesium carbonate in DMF at 65 °C to form an ether linkage yielding **2**. Compound **2** was coupled with *para*-substituted 4-phenyoxyphenols such as **8**, **9**, or **10** giving rise to **3**. A standard TZD formation protocol was applied to these mandelate derivatives to give the final compounds **11**–**30**.[18] Synthesis of substituted 4-phenoxyphenols is shown in Scheme 2. A variety of *para*-substituted phenols **4** underwent an addition–elimination reaction with 4-fluorobenzadehyde in refluxing *N,N*-dimethylacetamide to give **5**. Subsequent Baeyer–Villiger oxidation of the aldehydes yielded phenols **6**. From compound **6**, allyl ether formation followed by Claisen rearrangement and hydrogenation of the resulting 2-allyl-4-phenoxyphenols gave **8**. Synthesis of substituted phenoxyphenols **9** and **10** was conducted in the similar fashion as described in Scheme 2.

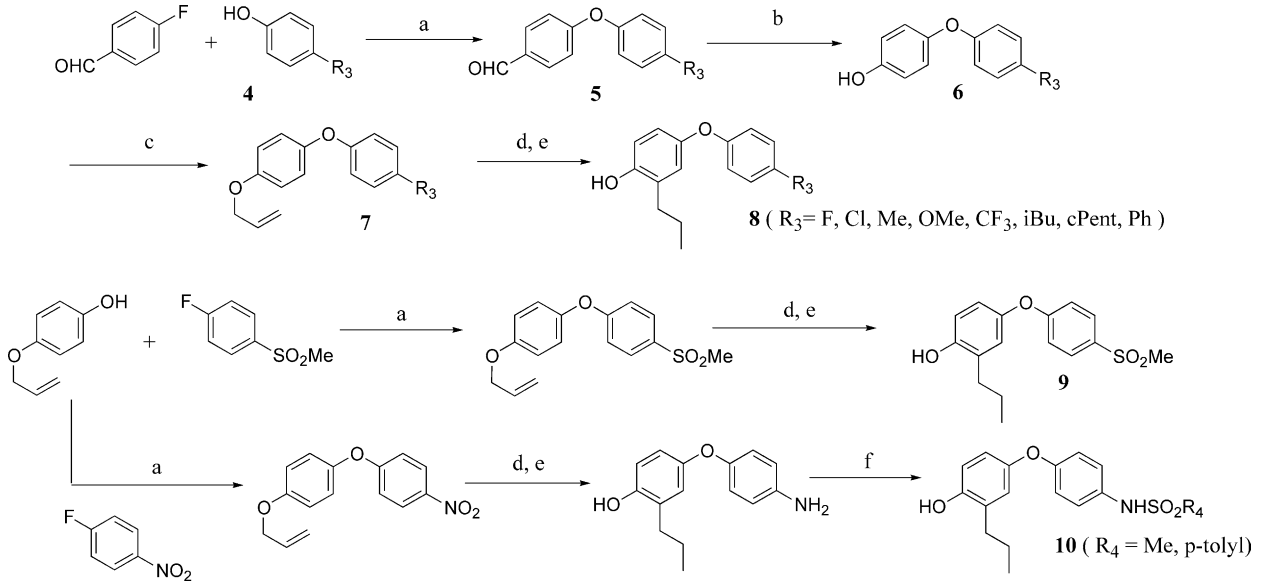
Table 1 summarizes the in vitro activities of compounds **11**–**30**. By and large, compounds are chronologically arranged in the table as the SAR evolved. The initial set of compounds **11**–**14** were synthesized to investigate into the effects of R_1 group and the tether length. Although based on the data of a small number of examples, compounds with a three methylene tether appeared to give superior PPARγ activities than corresponding four methylene tethered ones. The SAR of R_1 group seemed to be fairly restricted. Based on these findings, we decided to continue our SAR studies while keeping these structural features constant: (three methylene tether and $R_1 = {}^n\text{Pr}$). We have revisited the issues of tether length and R_1 group from time to time as we continued SAR studies and we observed these structural features generally gave the best results.[19]

In general, we used the binding assay as a tool to identify inactive compounds and viewed the results of transactivation assays as more meaningful estimation of functional activity because of the nature of nuclear receptors.

Next, we became interested in studying the effects of R_2 and R_3 groups. In addition to improving the potency,



Scheme 1. (a) $Br(CH_2)_{3\text{-}4}Br$, Cs_2CO_3, DMF, 65 °C, 74–80%; (b) **8**, **9**, **10**, 4-phenoxyphenol, or 2-isobutyl-4-phenoxyphenol, Cs_2CO_3, DMF, 65 °C, 71–82%; (c) $SOCl_2$, Py rt 85–90%; (d) thiourea, NaOAc, EtOH refl. 70–79%; (e) aq–HCl, EtOH, refl. 75–83%.



Scheme 2. (a) K_2CO_3, *N,N*-dimethylacetamide, refl. 56–76%; (b) mCPBA 62–75%; (c) allylbromide, K_2CO_3, acetone 95%; (d) *o*-dichlorobenzene, refl.; (e) H_2, Pd/C 56–70% (two steps); (f) (i) TBS-Cl, imidazole, DMF; (ii) R_4SO_2Cl, Et_3N, CH_2Cl_2; (iii) TBAF 70% (three steps).

Table 1. In vitro human PPAR activities of compounds **11–30**

Compd	*n*	R_1	R_2	R_3	Binding IC_{50} (μM)[a]			Transactivation EC_{50} (μM)[b]		
					α	δ	γ	α	δ	γ
11	1	^{n}Pr	H	H	50	>10	0.18	>3	>3	0.3
12	2	^{n}Pr	H	H	>50	>10	3.0	>3	>3	1.0
13	1	^{i}Bu	H	H	0.34	0.16	0.48			
14	1	H	H	H	>50	>50	>15			
15	1	^{n}Pr	F	H		2.0		>3	>3	0.3
16	1	^{n}Pr	Cl	H	>50	0.88	0.43	>3	>3	0.7
17	1	^{n}Pr	Me	H	>50	6.0	6.7	>3	>3	0.1
18	1	^{n}Pr	OMe	H	>50	>10	1.0	>3	>3	0.4
19	1	^{n}Pr	*n*Pr	H	>50	1.0	0.12	>3	3	0.2
20	1	^{n}Pr	H	Me	>50	>50	2.6			
21	1	^{n}Pr	H	CF_3	>50	>50	1.8			
22	1	^{n}Pr	H	*i*Bu	>50	>50	0.13	>3	>3	0.03
23	1	^{n}Pr	H	*c*-Pentyl	>50	>50	0.18			
24	1	^{n}Pr	H	Ph	>50	>50	0.13	>3	>3	0.02
25	1	^{n}Pr	H	F	>50	>50	0.82	>50	>50	0.06
26	1	^{n}Pr	H	Cl	>50	>50	2.0	3	>3	0.08
27	1	^{n}Pr	H	OMe	>50	>50	0.46	>10	>3	0.03
28	1	^{n}Pr	H	SO_2Me	>50	>50	0.25	>3	>3	0.12
29	1	^{n}Pr	H	$NHSO_2Me$	>50	>50	2.0			
30	1	^{n}Pr	H	$NHSO_2$-4-tolyl	>50	>50	5.7	>3	>3	0.5
Rosiglitazone					>50	>50	0.25	>3	>3	0.02

All data SD ± 15% ($n = 3$).
[a]Binding affinities were measured using radioligands following published procedure.[20]
[b]Agonist activities were measured in PPAR-GAL4 chimeric COS-1 cells following published procedure.[20] The EC_{50} refers to the concentration yielding a 50% response relative to the standard. All compounds were full agonists.

we were interested in finding out if these positions are metabolically labile, being *ortho* or *para* to the phenol ethers. In light of the potency and selectivity, when the data of compounds **11** and **15–19** are compared, introduction of substituents at R_2 position increases binding affinity to undesired PPARδ, albeit not the functional activity. The SAR studies of R_3 group proved to be more fruitful. Introduction of a hydrophobic group of an intermediate size (**22–28**) improved the functional activity toward PPARγ up to 10-fold from the original compound **11**.

Table 2 summarizes the results of pharmacokinetic studies of selected compounds in rat. Comparing the data of compounds **11** and **15**, it appears that the introduction of a fluorine group at R_2 position did not alter the clearance in rats. The R_2 position of **11** may not be a major metabolic site. Compound **24** suffered from poor absorption presumably due to the lipophilic phenyl group at R_3 position. Compounds **25–28** generally had modest clearance and fair to good oral bioavailability.

Finally, compounds with good functional activity and desirable pharmacokinetic profiles were tested for efficacy in *db*/*db* mouse: an obese animal model characterized by severe insulin resistance and marked hyperglycemia. The results are summarized in Table 3.

Table 2. Pharmacokinetic profiles of compounds **11**, **15**, and **24–28** in rat

Compd	iv (0.5 mg/kg)		po (2 mg/kg)	
	Clp[a] (mL/min/kg)	$t_{1/2}$[b] (h)	nAUC[c] (μM h)	F[d] (%)
11	2.3 ± 0.2	2.3 ± 0.6	13.8 ± 1.7	89
15	2.9 ± 0.3	1.7 ± 0.3	7.43 ± 2.5	63
24	2.8 ± 0.1	2.2 ± 0.2	0.70 ± 0.2	6
25	3.6 ± 0.4	2.1 ± 0.3	5.97 ± 0.8	63
26	2.9 ± 0.3	5.4 ± 0.9	6.70 ± 1.0	58
27	1.1 ± 0.2	2.8 ± 0.5	11.7 ± 0.5	39
28	2.1 ± 0.2	2.8 ± 0.2	11.8 ± 2.4	84
Rosiglitazone	2.7 ± 0.5	1.2 ± 0.3	16.4 ± 6.9	85

Fasted male Sprague–Dawley rats ($n = 3$), which have been surgically cannulated in the femoral artery and vein, received an intravenous dose by bolus injection into the femoral vein, or an oral gavage dose. Blood samples were taken serially at selected time points from the femoral arterial cannula.
[a]Clearance.
[b]Half life.
[c]Dose-normalized AUC.
[d]Bioavailability.

Table 3. In vivo efficacy of compounds **11**, **15**, and **25–28** in *db*/*db* mice

Compd	Dose (mpk)	Glucose[a] correction (%)	Triglyceride[b] correction (%)
11	10	77	74
15	10	43	50
25	10	78	71
26	10	86	80
27	10	67	67
28	10	86	78
28	5	62	55
Rosiglitazone	10	67	74
Rosiglitazone	5	46	52

Male *db*/*db* mice (12–13 weeks of age, $n = 7$) and non-diabetic mice (lean control, $n = 7$) were provided ad libitum access to rodent chow and water and received once-a-day oral dosing of the sodium-salts of tested compounds by gavage with vehicle (0.25% methylcellulose) for 11 days. Blood was collected from the tail for measurement of plasma levels of glucose and triglyceride. For further experimental details, see ref 20.
[a]SD ± 15%.
[b]SD ± 20%.

The glucose and triglyceride levels correction of the tested compounds was generally in good accordance with PPARγ agonist activities and PK profiles of the compounds. For example, compounds **11** and **15** have the same level of PPARγ transactivation activity but compound **15** showed slightly weaker efficacy because of its lower exposure (nAUC). Compounds **11** and **28** have essentially the same PK profiles but compound **28** is more efficacious because of its superior PPARγ agonist activity. Compound **28** exhibited higher levels of glucose and triglyceride correction to rosiglitazone despite its weaker functional activity in vitro. This might be perhaps caused by the longer half life ($t_{1/2}$) of **28**.

In conclusion, we have identified a series of novel 5-arylthiazolidine-2,4-diones as potent and selective PPARγ agonists. In the SAR studies, this class of compounds generally maintained a high level of receptor subtype (PPARγ) selectivity and exhibited good oral efficacy in *db*/*db* mice. One such compound **28** exhibited comparable levels of glucose and triglyceride correction to rosiglitazone in the *db*/*db* mouse studies.

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