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5-Aryl Thiazolidine-2,4-diones: Discovery of PPAR Dual α/γ Agonists as Antidiabetic Agents

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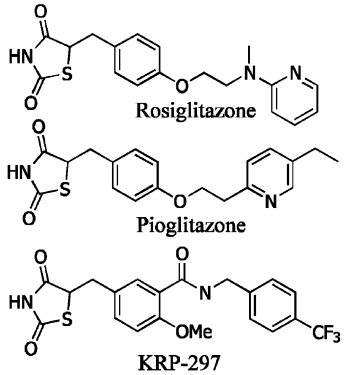
Abstract—A novel series of 5-aryl thiazolidine-2,4-diones based dual PPARα/γ agonists was identified. A number of highly potent and orally bioavailable analogues were synthesized. Efficacy study results of some of these analogues in the db/db mice model of type 2 diabetes showed them superior to rosiglitazone in correcting hyperglycemia and hypertriglyceridemia.

Type 2 diabetes is a debilitating disease characterized by hyperglycemia due to insulin resistance (IR) in the liver and peripheral tissues. In the US, approximately 16 million people suffer from type 2 diabetes and an additional 14 million have impaired glucose tolerance.[1] This disease is associated with a high degree of morbidity and mortality. Several epidemiological and clinical studies implicate NIDDM with dyslipidemia, accelerated arthrosclerosis and hypertension resulting in the increased incidences of renal failure, heart attacks and strokes.[2] The primary therapy for NIDDM include lifestyle modifications with emphasis on caloric restrictions, exercise and oral hypoglycemic agents such as sulfonylureas and biguanides. Sulfonylureas which stimulate insulin release from pancreatic β-cells are often only moderately effective and can induce hypoglycemia, weight gain and are subject to both primary and secondary failure.[3,4] Therefore, an attractive approach would be to attenuate IR without stimulating insulin secretion.

Following the initial report of a novel antidiabetic agent ciglitazone[5] from Takeda laboratories, the PPAR gamma agonists (benzylthiazolidinedione, TZDs) have emerged as a new class of antidiabetic agents. The TZDs are a group of pharmacological agents that enhance insulin action (insulin sensitizers) and promote glucose utilization in peripheral tissues.

In the US troglitazone (Rezulin)[6] was the first drug approved in the class followed by rosiglitazone (Avandia)[7] and pioglitazone (Actos).[8]



Although their exact mechanism of action has not been completely elucidated, it has been demonstrated that TZDs elicit their pharmacological actions by binding and activating nuclear receptor PPARγ.[9,10] PPARγ is mainly expressed in insulin sensitive tissues such as adipocytes and to a lesser extent in muscle and liver. It is

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hypothesized that their activation by TZDs affect the expression of a number of genes involved in lipid and glucose metabolism and preadipocyte differentiation.[11,12] Both rosiglitazone and pioglitazone are potent agonists of PPARγ. Recently, a group of Japanese scientists at Kyorin Pharmaceutical Co. have disclosed KRP-297, a novel antidiabeic agent.[13] Unlike rosiglitazone and pioglitazone, KRP-297 is the first published example of PPARγ and PPARα dual agonist. In a comparative study in ob/ob mice, KRP-297 demonstrated superior efficacy to pioglitazone in reducing glucose, insulin and triglyceride levels.[13]

PPARα is found primarily in the liver and is the molecular target for the fibrate class of lipid-modulating drugs.[14] Considering the potential benefits of fibrates in the treatment of coronary disease in diabetic patients,[15] the combined profile of dual PPARα/γ agonist(s) would offer an attractive option for the management of hyperglycemia and hypertriglyceridemia. We have recently reported a novel series of 5-aryl thaizolidene-2,4-diones as selective PPARγ agonists as represented with **11**[16] (Fig. 1). Unlike the classical PPAR gamma agonists, **11** has thiazolidene-2,4-dione ring directly attached to the phenyl ring. Also, a common feature in this series is the *para* relationship between the thiazolidene-2,4-dione ring and the 3-carbon methylene linker.

With the objective of further probing the SAR, we decided to explore the corresponding *meta*-linked TZD analogues typified by **12** (Fig. 1). Described below are the results of this investigation.

The general synthesis of 5-aryl thaizolidene-2,4-diones is described in Scheme 1. Thus, mandelate **1** was alkylated with 1,3-dibromoropropane to give **2**. Coupling of **2** with appropriate phenol **8** furnished **3**. Application of the standard TZD-forming protocol to **3** provided final compounds **12–26**.[17] The synthesis of substituted 4-phenoxy phenols **8** is shown in Scheme 2. A variety of phenols (**4**) underwent an addition–elimination reaction with 4-fluorobenzaldehyde in DMA to give **5**. Bayer-Villager oxidation followed by allyl ether formation, Claisen rearrangement and finally hydrogenation of the olefin transformed **5** to **8**.

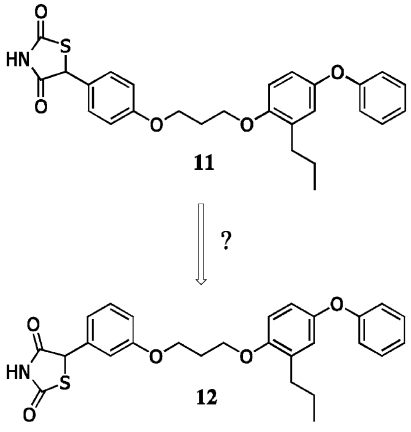
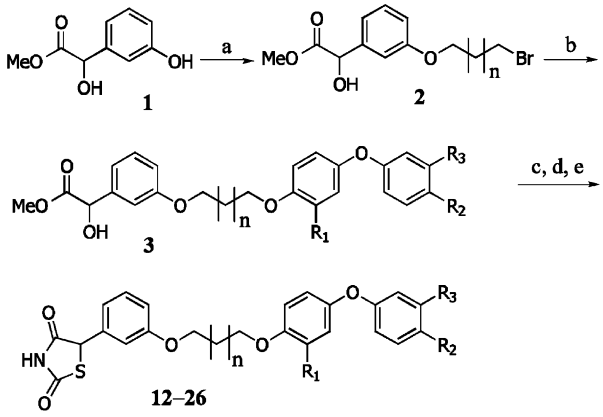
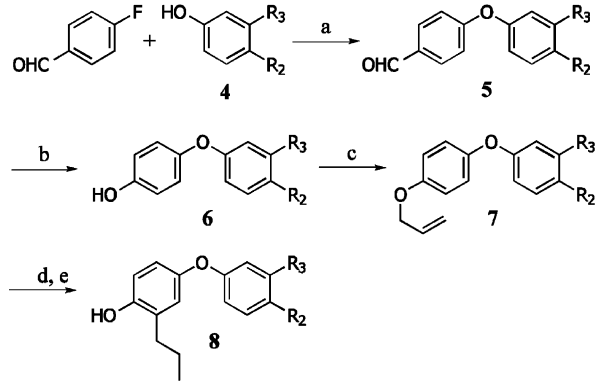


Figure 1. *p*-Aryl TZD versus *m*-aryl TZD.

The results of the in vitro activities of compounds **12–26** are summarized in Table 1. In contrast to the *para* linked analogue **11**, the very *first* synthesized *meta* linked analogue **12** displayed potent activity at both the PPARα and PPARγ receptors in the binding and transactivation assays. Encouraged by this initial result, we decided to further pursue this series. However, before undertaking further work in this series, it was essential that, as in the case of the *para* linked series, we establish the need for the three carbon methylene tether and *n*-propyl group at R_1 for the selectivity and potency.[16] As seen for the data for compound **13**, the absence of propyl group furnished a potent but a non-selective PPAR agonist, while extending the tether with an additional methylene group as in the case of analogue **14** gave PPARγ selective agonist. With these requirements satisfied, a series of R_2 substituted analogues **15–23** were synthesized with a dual objective of probing SAR and also to block a site of potential metabolic oxidation. In general, lipophilic substituents at R_2 showed 3- to 10-fold reduced affinity for PPARγ receptor and weak activity at the PPARα receptor. With the introduction of chloro and fluoro substituents, as in the case of compounds **20** and **21**, a trend towards dual PPARα/γ activity was restored though there was a some loss



Scheme 1. (a) $Br(CH_2)_{3-4}Br$, Cs_2CO_3, DMF, 65 °C; (b) **8**, Cs_2CO_3, DMF, 65 °C; (c) $SOCl_2$, Py, rt; (d) thiourea, NaOAc, EtOH, refl; (e) aqHCl, EtOH, refl.



Scheme 2. (a) K_2CO_3, *N,N*-dimethylacetamide, refl; (b) *m*CPBA; (c) allylbromide, K_2CO_3, acetone; (d) *o*-dichlorobenzene, refl; (e) H_2, Pd/C.

Table 1. In vitro human PPAR activities of compounds **11**–**26**

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		>50	>10	0.18	>3	>3	0.3
12	1	*n*Pr	H		0.028	>10	0.057	0.026	>3	0.014
13	1	H	H		0.047	0.19	0.076	ND	ND	ND
14	2	*n*Pr	H		>5	3	0.195	ND	ND	ND
15	1	*n*Pr	*i*Pr		2.1	>50	0.17	>3	>3	0.167
16	1	*n*Pr	*t*Bu		>10	>50	0.335	ND	ND	ND
17	1	*n*Pr	*i*Bu		>10	>50	0.291	ND	ND	ND
18	1	*n*Pr	*c*-Pentyl		2.0	>50	0.33	>3	>3	0.123
19	1	*n*Pr	Ph		>10	>50	0.226	>3	>3	0.353
20	1	*n*Pr	Cl		0.1	>50	0.073	0.18	>3	0.165
21	1	*n*Pr	F		0.028	>5	0.077	0.066	>3	0.085
22	1	*n*Pr	OMe		2.55	>10	0.3	>3	>3	0.069
23	1	*n*Pr	OH		0.95	3.8	0.03	>3	>3	0.023
24	1	*n*Pr	Cl	Cl	0.068	>50	0.064	0.082	>3	0.047
25	1	*n*Pr	Cl	Me	0.162	>50	0.056	0.156	>3	0.027
26	1	*n*Pr	F	Me	0.112	>50	0.078	0.085	>50	0.106
Rosiglitazone					>50	>50	0.25	>3	>3	0.02

[a]Binding affinities were measured using radioligands following published procedure.[19]
[b]Agonist activities were measured in PPAR-GAL4 chimeric COS-1 cells following published procedure.[18] The EC_{50} refers to the concentration yielding a 50% response relative to the standard. ND, not run.

Table 2. Pharmacokinetic profiles of compounds **12**, **15**, **20**, **21**, **24**, and **26** in SD rats

Compd	iv (0.5 mg/kg)		po (2 mg/kg)	
	Clp[a] (mL/min/kg)	$t_{1/2}$[b] (h)	nAUC[c] (μMh)	F[d] (%)
12	9.5±0.3	1.5±0.3	21.78±0.9	62
15	6.1±0.8	3.3±2.0	0.3±0.04	6
20	9.7±1.7	2.9±0.1	1.5±0.22	44
21	10.2±0.42	1.3±0.2	3.3±0.14	66
24	7.9±1.1	2.2±1.4	0.8±0.24	19
26	10.5±0.37	3.3±0.2	0.6±0.15	20
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 selected dual agonists in db/db mice

Compd	Dose (mpk)	Glucose correction (%)	Triglyceride correction (%)
12	10	91±4.7	67±3.9
20	10	86±7.5	68±1.4
21	10	90±4.6	76±6.0
24	10	79±5.9	77±3.5
26	10	78±8.5	69±5.5
Rosiglitazone	10	67±6.2	74±3.3

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.[18]

(10-fold) in functional activity. Finally, adding substituents at R_3 as in examples **24**–**26** did not alter the PPARα/γ selectivity.

The pharmacokinetic study data on selected analogues is recorded in Table 2. Compound **12** has an overall superior PK parameters with 62% bioavailability and dose normalized AUC of 21.78 μM h in rats. The corresponding fluoro substituted analogue **21** did not show any decrease in the clearance possibly indicating that R_2 position may not be a major site for metabolic oxidation in rats. Surprisingly, the normalized AUC for this analogue was about 7-fold less when compared to **12**. Based on the functional activity and desirable PK parameters, compounds **12**, **20**, **21**, **24**, and **26** were selected for efficacy studies in highly insulin resistant, obese and hyperglycemic db/db mice as described by Berger et al.[18] As seen from the data in Table 3, the glucose and triglycerides correction correlated well with the functional activity and PK profile of the compound. For example, compounds **12** and **21** are essentially identical in their efficacy, whereas analogues **24** and **26** are comparatively slightly less efficacious, potentially due to lower exposure and short half life. It is interesting to note that despite much lower exposure (>25-fold) and around 4-fold lower bioavailability, both **24** and **26** demonstrated comparable blood glucose correction with respect to rosiglitazone.

In summary, we have identified a potent series of 5-aryl thaizolidene-2,4-diones class of dual PPARα/γ agonists. Changing the point of attachment of thaizolidene-2,4-dione ring onto the phenyl ring from the *para* to *meta* orientation with respect to the three carbon methylene tether transformed PPARγ selective agonists to dual PPARα/γ agonists. A number of highly potent and orally active analogues were synthesized. In the db/db mice model of diabetes, these compounds displayed superior efficacy when compared to the benchmark rosiglitazone.

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