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Aryloxazolidinediones: Identification of Potent Orally Active PPAR Dual α/γ Agonists

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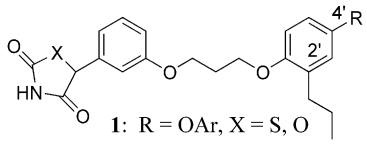
Abstract—A series of novel aryloxazolidine-2,4-diones was synthesized. A structure–activity relationship study of these compounds led to the identification of potent, orally active PPAR dual α/γ agonists. Based on the results of efficacy studies in the db/db mice model of type 2 diabetes and the desired pharmacokinetic parameters, compound **12** was selected for further profiling.

Type 2 insulin-resistant diabetes is a heterogeneous disorder that accounts for 120 million patients worldwide and the number is likely to grow over 200 million over next decade. This is a complex disease and invariably type 2 diabetic patients population also display cardiovascular factors including hypertension and dyslipidemia.[1,2] In the past 3 years, two new drug candidates, Avandia (rosiglitazone) and Actos (pioglitazone) have been introduced in the US market as novel therapy for type 2 diabetes. Both Avandia and Actos are PPARγ agonists and elicit their insulin sensitizing effect through binding and activating PPARγ nuclear receptor. Recently, scientists at Kyorin Pharmaceutical Co. have disclosed a novel antidiabetic KRP-297, a first published example of a dual PPARα and PPARγ agonist.[3] PPARα is the molecular target for the fibrate class of lipid-modulating drugs[4] and incorporation of additional PPARα activity into compounds with PPARγ agonist activity may offer improved alternatives towards control of hyperglycemia and hypertriglyceridemia in type 2 diabetic patients.[5]

In the previous communication, we disclosed the results of our efforts that led to the identification of compounds of type **1** (X = S) as potent dual PPARα/γ agonists.[6] Unlike the classical glitazones, **1** has the thiazolidine-2,4-dione ring directly attached to the phenyl ring. Based on their excellent efficacy in the established rodent models of type 2 diabetes and desirable PK profile, we initiated synthesis of various meta linked aryl TZD analogues to find replacement(s) for the C-4′-aryloxy substituents and extended these efforts to include the synthesis of oxazolidine-2,4-diones (OZDs, **1**: X = O) as bioisosteric replacement for the corresponding TZD ring.[7,8]



1: R = OAr, X = S, O

In the earlier structure–activity relationship (SAR) studies en route to identifying **1**, we had established the need for the three carbon methylene tether and *n*-propyl group as the optimal substituent at the C-2′ position for potency and selectivity. Further studies identified C-4′ position as an important site for additional structural modifications. Herein, we report the results of this SAR study that resulted in the identification of potent and in vivo efficacious OZD analogues.

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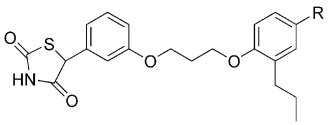
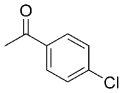
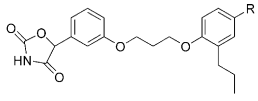
Table 1. In vitro human PPAR activities of compounds **1–11**

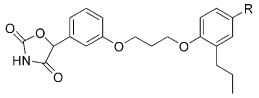


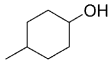
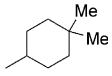
Compd	R	Binding IC_{50} (μM)[13]			Transactivation EC_{50} (μM)[10]		
		α	δ	γ	α	δ	γ
1		0.028	>50	0.057	0.026	>3	0.014
2		1.4	>50	0.037	0.035	>3	0.039
3		0.21	>50	0.085	ND	ND	ND
4		0.042	0.92	0.063	ND	ND	ND
5		0.09	0.17	0.019	>3	>3	0.167
6		>10	>50	0.144	>3	>3	0.051
7		0.037	0.14	0.03	ND	ND	ND
8		0.12	>50	0.064	0.13	>3	0.11
9		0.062	>50	0.15	0.17	>3	0.21
10		0.046	>50	0.059	0.076	>3	0.08
11		0.08	>5	0.34	0.053	>3	0.081

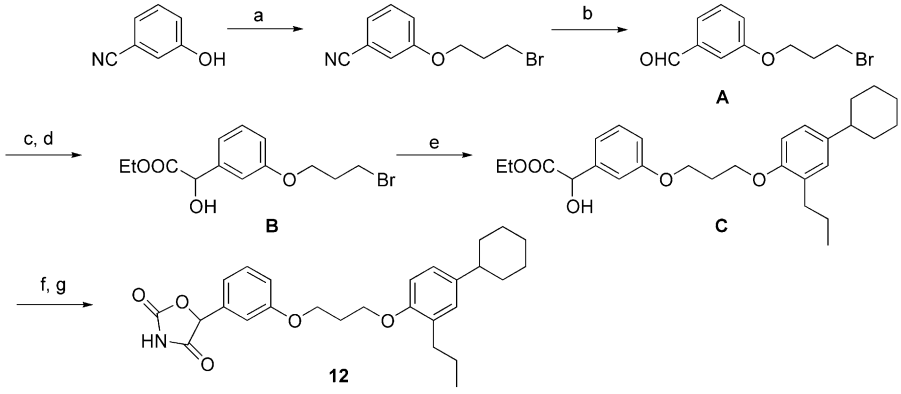
The preparation of the thiazolidine-2,4-diones (Table 1) has been described.[9] The synthetic route used to prepare OZD analogues **12–20** (Table 2) is illustrated in Scheme 1 with the synthesis of **12**. Commercially available 3-hydroxybenzonitrile was converted to aldehyde **A** by first alkylating with 1,3-dibromopropane and then reducing the nitrile with DIBALH. The aldehyde was then transformed to mandelate **B** via intermediacy of a cyanohydrin. Coupling of the mandelate with 2-propyl-4-cyclohexylphenol provided intermediate **C**. Conversion of the ester to corresponding amide using methanolic ammonia followed by treatment of the amide with diethylcarbonate and sodium methoxide in methanol gave the desired oxazolidine-2,4-dione derivative **12**. The preparation of 2-propyl-4-cyclohexylphenol is described in Scheme 2. 4-Cyclohexylphenol (**D**, R = cyclohexyl) was first alkylated with allyl bromide and then subjected to Claisen rearrangement to provide intermediate **E**. Hydrogenation of the allylic olefin furnished the desired phenol **F**. The starting phenols **D** were either commercially available or could be easily synthesized using conventional chemistry.

As stated earlier, our initial goal was to find a suitable replacement for the C-4′ phenoxy substituent of compound **1**. The obvious starting point would be to explore the corresponding saturated ring analogue as shown for compound **2.** This analogue, though equipotent to **1** in its binding affinity to PPARγ receptor, was 90-fold less active on the PPARα receptor. However, in the functional GAL4-PPAR transactivation assay,[10] **2** was indistinguishable from **1** at both PPARγ and PPARα receptors. This compound unfortunately suffered from poor PK properties which resulted in poor in vivo efficacy in lowering glucose and triglycerides in the db/db mice model. Oral administration of compound **2** to male Sprague–Dawley (SD) rats (2 mg/kg) resulted in low bioavailability (10%) and dose

Table 2. In vitro human PPAR activities of compounds **12–20**



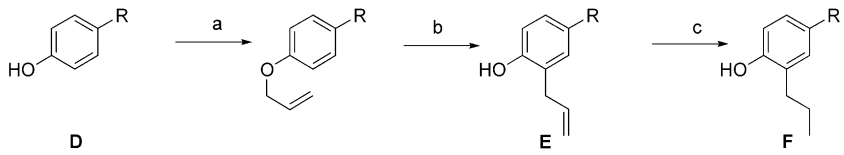
Compd	R	Binding IC_{50} (μM)[13]			Transactivation EC_{50} (μM)[10]		
		α	δ	γ	α	δ	γ
12		0.29	>50	0.49	0.055	>3	0.019
13		2.64	1.51	0.45	2	>3	0.09
14		0.61	>50	0.64	0.054	>3	0.035
15		0.63	3.85	1.06	ND	ND	ND
16		>15	>50	1.16	ND	ND	ND
17		>15	>50	0.18	ND	ND	ND
18		0.59	>50	0.54	>3	>3	>3
19		3.3	>50	1.76	>3	>3	0.09
20		2.88	>50	0.75	ND	ND	ND



Scheme 1. Reagents: (a) $Br(CH_2)_3Br$, K_2CO_3, DMF; (b) DIBALH; (c) TMSCN, NaCN, 18-crown-6; (d) HCl (gas), EtOH; (e) 2-propyl-4-cyclohexylphenol, K_2CO_3, DMF; (f) NH_3, MeOH; (g) $(C_2H_5O)_2CO$, MeONa, MeOH.

normalized AUC of 0.3 μM h. The higher homologe **3** also suffered from poor PK in SD rats. As compared to **2**, which showed dual PPARγ and PPARα receptors agonism, the corresponding cyclopentyloxy ring analogue **4** displayed non-selective binding to all three PPAR γ, α, and δ receptors. Replacement of the oxygen linker of **1** with carbonyl afforded compound **5**, which also showed non-selective binding. However, an improvement in the binding selectivity favoring PPARγ was noted with analogue **6** bearing a *para*-chloro substituent on the phenyl ring. But, this binding selectivity was lost as observed in compound **7**, where the carbonyl group was masked in a benzisoxazole moiety.

Interestingly, when compared to phenyl ketone **5**, the corresponding cyclohexyl ketone analogue **8** displayed the desired PPARγ and PPARα receptor affinity in both the binding and functional assays. Despite this good potency, compound **8** suffered from poor PK in SD rats with 7.8% bioavailability and dose normalized AUC of 0.07 μM h and a high clearance of 29.47 mL/min/kg. In an attempt to improve upon the metabolic stability and



Scheme 2. Reagents: (a) CH_2=$CHCH_2Br$, K_2CO_3, acetone; (b) 1,2-dichlorobenzene, reflux; (c) H_2, Pd/C, MeOH.

Table 3. In vivo efficacy of selected dual agonists in db/db mice

Compd	Dose (mpk)	Glucose correction (%)	Triglyceride correction (%)
2	10	34	7
8	10	29	57
9	10	87	31
10	10	46	41
11	10	91	85
12	10	76	77
14	10	45	53
Rosiglitazone	10	67	74
KRP-297	100	51	60

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.[10]

also to further probe the SAR, compounds **9**–**11** were synthesized. All three compounds displayed dual PPARγ and PPARα binding as well as functional agonism.

While **9** and **10** suffered from poor PK profile, compound **11** showed promising PK profile with 27% oral bioavailability, $t_{1/2}$ of 3.6 h and dose normalized AUC of 1.1 μM h for a 2-mpk po dose in SD rats. As seen from Table 3, compound **11** when dosed orally at 10 mpk for 11 days produced 91% glucose correction and 85% triglycerides reduction in the db/db mice model of type 2 diabetes. It is noteworthy that although weaker in its binding affinity for both PPARγ and PPARα receptors when compared to **1**, compound **11** was not significantly different in functional assay, which was reflected in the excellent in vivo efficacy.

Optimization studies established that the C-4′ cyclohexyl was a suitable replacement for the phenoxy group of **1**. Next, we decided to explore the utility of the OZD as a bioisosteric replacement for the corresponding thiazolidine-2,4-dione (TZD) ring. With this objective, the aryl OZD **12** was synthesized and evaluated. Compound **12** was found equipotent in both binding affinity and functional potency to the corresponding TZD analogue **11**. In the db/db mice, **12** produced 76% glucose correction and lowered triglycerides by 77% reflecting correlation between in vitro potency and in vivo efficacy. Interestingly, switching cyclohexyl ring of **12** a with the phenyl ring resulted in non-selective binding as revealed by compound **13**. The effects of the ring size variations at C-4′ were probed with synthesis of analogues **14** and **15**. In order to minimize the metabolic oxidation sites of the cyclohexyl ring of **12**, the substituted cyclohexyl derivatives **18**–**19** as well as the tetrahydropyran analogue **20** were synthesized.[11,12]

Analogues **16** and **17** were found to be selective PPARγ agonists while **18**–**20** displayed decreased binding affinity and activation potency for PPARγ and PPARα receptors as compared to compound **12**.

In summary, we have identified through a systematic structure–activity relationship study, a novel series of potent, orally efficacious 5-aryloxazolidine-2,4-diones (OZDs) as dual PPARα/γ agonists.

Acknowledgements

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References and Notes

1. Moller, D. E. *Nature* **2001**, *414*, 821.
2. Smith, A.; Fogelfeld, L.; Bakris, G. *Emerg. Drugs* **2000**, *5*, 441.
3. Nomura, M.; Kinoshita, S.; Satoh, H.; Maeda, T.; Murakami, K.; Tsunoda, M.; Miyachi, H.; Awano, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 553.
4. Wilson, T. M.; Brown, P. J.; Sternbach, D. D.; Henke, B. R. *J. Med. Chem.* **2000**, *43*, 527.
5. Murakami, K.; Tobe, K.; Ide, T.; Mochizuki, T.; Ohashi, M.; Akanuma, Y.; Yazaki, Y.; Kadowaki, T. *Diabetes* **1998**, *47*, 1841.
6. Desai, R. C.; Han, W.; Metzger, E. J.; Bergman, J. P.; Gratale, D. F.; MacNaul, K. L.; Berger, J. P.; Doebber, T. W.; Leung, K.; Moller, D. E.; Heck, J. V.; Sahoo, S. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2795.
7. Schnur, R.; Morville, M. *J. Med. Chem.* **1986**, *29*, 770.
8. Dow, R. L.; Bechle, B. M.; Chou, T. T.; Clark, D. A.; Hulin, B.; Stevenson, R. W. *J. Med. Chem.* **1991**, *34*, 1538.
9. Sahoo, S. P.; Tolman, R. L.; Han, W.; Bergman, J.; Santini, C.; Lombardo, V.; Desai, R.; Boueres, J. K.; Gratale, D. F. US Patent 6,008,237, 1999.
10. Berger, J. P.; Leibowitz, M. D.; Doebber, T. W.; Elbrecht, A.; Zhang, B.; Zhou, G.; Biswas, C.; Cullinan, C. A.; Hayes, N. S.; Li, Y.; Tanem, M.; Venture, J.; Wu, S. M.; Berger, G. D.; Mosley, R.; Marquis, R.; Santini, C.; Sahoo, S. P.; Tolman, R. L.; Smith, R. G.; Moller, D. E. *J. Biol. Chem.* **1999**, *274*, 6718.
11. Compounds **16** and **17** were identified as major metabolites following incubation of **12** with human liver microsomes. The details of metabolism studies of **12** will be published elsewhere.
12. The preparation of compounds **16**–**20** has been described: Desai, R. C.; Sahoo, S. P.; Bergman, J. P.; Lombardo, V. K.; Metzger, E. J.; Koyama, H. US Patent 6,465,497, 2002.
13. Adams, A. D.; Yuen, W.; Hu, Z.; Santini, C.; Jones, B. A.; MacNaul, K. L.; Berger, J. P.; Doebber, T. B.; Moller, D. E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 931.