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O-Arylmandelic Acids as Highly Selective Human PPAR α/γ Agonists

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Abstract—A new class of *O*-arylmandelic acid PPAR agonists show excellent anti-hyperglycemic efficacy in a db/db mouse model of DM2. These PPARα-weighted agonists do not show the typical PPARγ associated side effects of BAT proliferation and cardiac hypertrophy in a rat tolerability assay.

A remarkable body of research has appeared on the pharmacology of the peroxisome proliferator activated receptors γ (PPARγ, NR1C3) and α (PPARα, NR1C1) in the last 5–7 years.[1] Both the therapeutic promise and the biological complexity of these nuclear hormone receptor agonists in the treatment of hyperglycemia associated with type 2 diabetes (DM2) and of dyslipidemia are impressive.[2] The clinical use of PPARγ agonists in DM2 has been plagued with mechanism based side effects including weight gain, fluid retention and edema. Further worrisome indications include adipose tissue proliferation, fatty changes in bone marrow and significant increases in heart weight in rodents.[3] Dual PPARγ/α agonists have also shown very promising efficacy in rodent models and in humans but with the same PPARγ mediated side effects. The first example, Farglitazar, was eventually dropped from development due to requirements for additional clinical trials to address concerns with edema, CHF and fluid retention.[4]

The fibrate hypolipidemics have, by comparison, an excellent tolerability profile. Extensive clinical studies with fibrates also indicate that PPARα could play a role in the management of insulin resistance and hyperglycemia. Multiple clinical studies with bezafibrate, fenofibrate and Gemfibrozil show modest but significant improvements in glucose homeostasis and insulin sensitivity with normal clinical doses of the fibrates.[5] These clinically marginal but reproducible responses led us to investigate a novel structure series for insulin sensitizing utility. This family of agonists shows modest efficacy on the hPPARγ receptor but exceptional efficacy on the hPPARα receptor. Potent and selective h/mPPARα/γ agonists from this series also show excellent efficacy as insulin sensitizers in insulin resistant db/db mice. As the efficacy of these PPAR agonists appears to be driven primarily by PPARα activation, the possibility of identifying effective antidiabetic PPAR agonists with reduced or eliminated PPARγ mechanism based side effects exists.

The unique mandelic acid PPAR agonist **1** (Fig. 1) was discovered as a PPAR ligand with micromolar hPPARγ affinity but nanomolar affinity for hPPARα, K_i 63 nM.

The mandelate **1** proved to be an agonist of remarkable intrinsic efficacy in a hPPARαGAL4 chimer transactivation assay.[6] In cell based functional assays, other fibrate analogues such as fenofibric acid (**13**), EC_{50}

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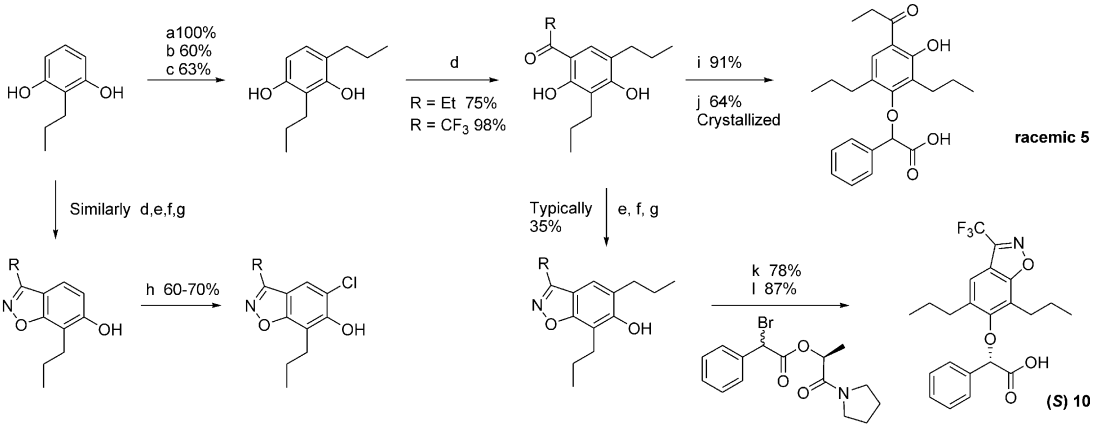


Scheme 1. (a) Excess allylbromide K_2CO_3 acetone Δ; (b) 1,2-Cl_2benzene Δ; (c) H_2, Pd/C EtOAc; (d) R=CF_3 $(CF_3CO)_2O$ $AlCl_3$ CH_2Cl_2. R=Et; CH_3CH_2COONa TfOH Δ; (e) 10 equiv NH_2OH-HCl 10 equiv NaAcO Δ; (f) Ac_2O Neat; (g) Pyr Δ; (h) $(iBu)_2NH$ $SOCl_2$ Toluene 50 °C; (i) Cs_2CO_3 Me α-Br-phenylacetate; (j) NaOHaq CH_3OH; (k) Li *t*BuO THF. Addition of anion to 0.83 equiv bromide 0 °C; (l) 2 equiv LiOOH aq THF.

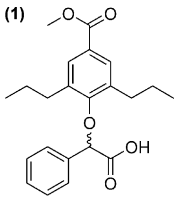


Figure 1.

>10,000 nM, or more potent proprietary structures, GW-2331, EC_{50} 240 nM,[2] typically show similar maximum inductions in a luciferase reporter assays, which will be defined here as 100%. The mandelic acid **1** shows good potency in functional assays, with a 33 nM inflection point, but a remarkable 2100% maximum induction. A survey of the PPAR affinity and efficacy for some related analogues showed this to be a general and interesting property of this series dependent on the ortho, ortho disubstitution pattern of **1**, as reported in Table 1. Monosubstituted analogues of **1** are inactive.[7] All members of this class of compounds proved to be remarkably selective for hPPARγ and α over hPPARδ (NR1C2). All showed no or trace displacement in the analogous hPPARδ binding assay up to 50 μM.

Given a unique class of PPARα-weighted dual PPARα/γ agonists, we initiated a study to explore the utility of these agonists in DM2. Affinity for the PPAR subtypes as well as agonist efficacy were studied in established in vitro assays. EC_{50} values are reported from the HTRF assay[9] due to difficulties generating accurate EC_{50} values from the very high % activation PPARαGAL4 TA signal. The nature of the HTRF assay allows only 100% full agonist responses. The analogues of Table 2 show 560% to 1380% maximal induction in hPPARαGAL4 TA assays. Due to well known differences in PPAR response between the human and murine PPARα receptor,[8] both hPPARα and mPPARα agonist potency were confirmed in PPARαGAL4 chimer transfection assays. Potency was generally similar in this series of agonists. None of the analogues show better than 60% induction at 3 μM on the hPPARγGAL4 TA assay. The in vivo pharmacology of this family of agonists was studied in established db/db ($lepr^{db\text{-}3J}$/$lepr^{db\text{-}3J}$) mouse model of DM2[6] as well as a normal Sprague–Dawley (SD) rat to assess lipid lowering.[10] The well known PPARγ mediated side effects of brown adipose tissue (BAT) proliferation, heart weight increase, hematocrit decreases and body weight gain were also monitored in these two week studies in normal male SD rats.[3]

Table 1. Ortho substituent effects in **1**

	Ortho substituent		Binding affinity	
	2	6	K_i PPARα	K_i PPARγ
1	*n*Pr	*n*Pr	63	1100
2	Me	*n*Pr	28	5940
3	Cl	*n*Pr	57	8530
4	Me	Me	225	>10,000

A family of o,o-disubstituted mandelate analogues related to **1** shows very good efficacy in the db/db diabetes model and good lipid lowering efficacy in the rat. This family of PPARα weighted agonists is also well tolerated in these models without the mechanism based side effects typical seen with PPARγ weighted insulin sensitizers.

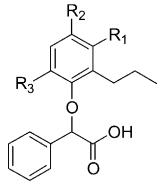
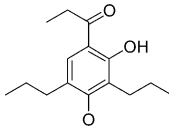
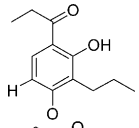
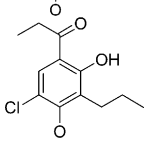
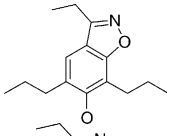
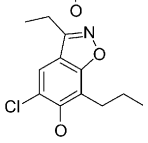
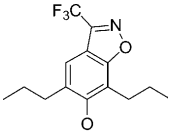
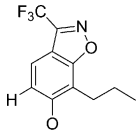
As the ester function of the lead **1** is clearly poorly suited to in vivo studies, a survey was run to find suitable replacements for this residue. Several good to superior substituents were rapidly identified. The keto phenols and benzisoxazoles of Scheme 1 represent carbonyl surrogate substitutions found to be successful in vivo in previous SAR work on PPAR agonists.[11] The direct substitution of a ketone for the ester of **1** was found to be photolytically unstable. The keto phenol analogue **5** of Scheme 1 is chemically and metabolically stable. Synthesis of the required phenols is analogous to previously reported methods, as shown in Scheme 1.

The 2-(aryloxy)-2-arylacetic acids were prepared from the above phenols via simple condensations. The required α-halophenylacetic acid derivatives are readily available from either the parent arylacetic acids by deprotonation and quenching with TMS-Cl followed by *N*-bromosuccinimide or by bromination of the corre-

sponding 2-aryl(2-hydroxy)acetic acid.[12] The single enantiomers of the 2-(aryloxy)-2-arylacetic acids are readily available via a known route described by P. N. Devine et al.[13] An electrophilic partner incorporating a lactamide chiral auxillary is used. The detailed chemistry of this diastereoselective condensation and the preparation of typical mandelate lactamide esters is well described in this paper. Cleavage of the ester yields the desired acid product. The enantiomeric excess of the final product was typically determined using chiral stationary phase OD-R HPLC columns. Typical *ee* for a batch of (S)**10** was >96%. The enantiomers were assigned based on the correlation reported by Devine.

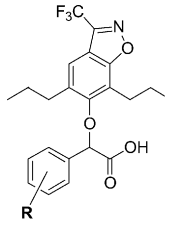
The results detailed in Table 2 show good retention of the desired affinity and efficacy on the PPARα receptor for all of the *o*,*o*-disubstituted ester surrogate analogues. The ketophenol analogue **5** resembles the lead ester **1** in PPARα receptor selectivity, affinity and agonist efficacy. The mono ortho substituted analogue **6** loses almost all affinity for the receptors. As demonstrated by **11**, mono-ortho substituted analogues with reasonable affinity can

Table 2.

		PPAR Binding affinity[a] nM		PPAR α/γ HTRF inflection nM		db/db Mouse FPG Correction	
		K_i α	K_i γ	hα	hγ	Dose mpk	FPG corr.%
	BRL49653	NA	136	NA	14	10	57
5		81	WA	37	1090	30 10	55 42
6		WA	WA	ND	WA		
7		293	985	804	3760		
8		61	2680	80	560		
9		38	WA	162	1120	15 5	47 10
10		37	956	15	365	30	91
10	(R)	WA	WA	ND	3149		
10	(S)	12	618	ND	194	10	50
11		98	WA	836	4600	30	−5
12	Wy-14643	NA murine PPAR α	NA 100	WA	ND	30	20
13	Fenofibric acid	35,000	NA	WA	ND	150	17

[a]The apparent K_i was calculated from the Cheng-Prusoff equation using the IC_{50} determined in the previously described SPA binding assay at 15 C.[16] WA = Weakly active. Did not titrate. NA = Not active. ND = Not done.

Table 3.

		PPAR Binding affinity[a] nM		PPAR α/γ HTRF inflection nM		db/db Mouse FPG correction	
		K_i α	K_i γ	hα	hγ	Dose mpk	FPG corr.%
10	R=H	37	956	15	365	30	91
						10	78
						3	46
						1	35
14	p-Cl	105	175	10	110	10	74
						3	31
15	*i*-Pr	36	87	14	38	10	61
						3	31
16	p-CF_3	18	104	23	79	10	83
						3	41
						1	21
17	p-OCH_2 (2-pyridyl)	64	268	19	47	10	90
						3	51
18	p-CH_2CH_2 (2-pyridyl)	65	197	28	110	10	75

[a]As for Table 2.

Table 4.

	Dose mpk po	Total Cholesterol % change	TG % change	Heart weight gms	Body weight gms	BAT weight gms
Control				1.10±0.13	298±16	0.49±0.07
Control				1.14±0.06	309±19	0.33±0.05
BRL 49653	30	+1	**−47**	1.38±0.17	310±21	**0.74±0.09**
BRL 49653	30	+1	−15	1.35±0.09	322±16	**0.63±0.09**
13 Fenofibrate	150	**−18**	−23	1.18±0.10	308±41	0.33±0.11
5	10	**−36**	**−64**	1.11±0.08	290±15	0.29±0.05
5	30	−7	−8	1.06±0.08	294±15	0.34±0.13
9	30	−9	−11	1.22±0.02	312±24	0.34±0.06
10	30	**−27**	**−52**	1.05±0.10	**276±21**	0.28±0.09
14	30	**−23**	**−56**	1.17±0.11	297±15	0.22±0.08
16	30	**−32**	**−41**	1.14±0.09	318±24	0.27±0.05
17	30	**−38**	**−47**	1.15±0.03	297±16	0.42±0.24

Values with statistically significant differences versus vehicle control as determined by Student's *t*-test are indicated in bold.

be identified in optimized series. Efficacy in the animal model is, however, lost.

Conversion of the ketophenol to a benzisoxazole analogue similarly retained affinity and efficacy on PPARα with some gain in affinity on PPARγ. The direct ethyl analogue **8** resembles the lead **1** closely while the more lipophilic trifluromethyl benzisoxazole **10** shows both improved affinity and potency on PPARα as well as better affinity for PPARγ. The observed PPAR affinity is due to the **10(S)** enantiomer as determined by enantioselective synthesis. The **10(R)** enantiomer shows no affinity for PPAR beyond the level of that expected for the residual **10(S)** enantiomer contaminant.

The C57BL/6J db/db ($lepr^{db\text{-}3J}$/$lepr^{db\text{-}3J}$) mouse is a well established model of DM2 which has been used to characterize a host of PPARγ and γ/α agonists as insulin sensitizers. The evaluation of the current h/mPPARα weighted agonists in the db/db model gave very promising results dosed p.o. q.d. as shown in Tables 2 and 3. Comparison of the correction of fasting plasma glucose (FPG) was made to the FPG correction observed for rosiglitazone (BRL49653) dosed near its ED_{50}, 10 mpk q.d., in each study. BRL shows an average 57% correction of hyperglycemia ($n=30$, SD 19). The PPARα selective agonists **5** and **9**, dosed at 30 and 15 mpk q.d., respectively, showed very good efficacy similar to BRL. The observed correction of hyperglycemia is unusual but not unprecedented for a selective PPARα agonist.[14,15] The potent mPPARα agonist pirinixic acid (Wy-14643 **12**), however, shows little or no effect on FPG in this model. The slightly less PPARα selective agonist **10** shows excellent dose dependent correction of hyperglycemia with an ED_{50} near 3 mpk (Table 3). Plasma clearance and AUC in the SD rat are both good for compounds **5** and **10**, but bio-availability is somewhat low for **10** at 11%.[17] An investigation of the effect

of substitution on the alpha phenyl ring of **10** is reported in Table 3.

Simple para substitution of **10** improved bioavailability consistently to ~80% for **14**, **17** or **18** with good efficacy in the db/db model and a modest increase in affinity for PPARγ. Effects on potency and receptor selectivity were modest. All para substituted analogues showed a trend to increased affinity for PPARγ. Any efficacy correlation to this increased PPARγ activation could easily be masked by small exposure differences in this set. What fraction of the efficacy is contributed by PPARγ driven effects is perhaps best judged by tracking the PPARγ driven side effects.

The mechanism-based side effects seen with PPARγ agonists are clinically significant. Weight gains up to 12 pounds over one year with pioglitazone and over 9 pounds with rosiglitazone are seen. Incidence of edema is up to 16% in pioglitazone combination therapy and 8.4% in rosiglitazone therapy. Side effects are serious enough to limit the clinical use of PPARγ agonist in some DM2 patients.[18] These and further mechanism based effects are faithfully recapitulated in normal rats.[3] Additional effects in rodents include plasma volume expansion, brown adipose tissue (BAT) proliferation and significant increases in heart weight.

A two-week assay was conducted to compare the mandelate PPARα/γ agonists to the same dose of the PPARγ agonist rosiglitazone for tolerability and lipid lowering effects.[10] Results are reported in Table 4. BAT proliferation and heart weight increases were tracked as the most sensitive markers of PPARγ mediated toxicity. Doses of one to three times the efficacious dose used in the db/db DM2 model were used. Daily administration of rosiglitazone (30 mkd) increased heart weight by 18–25%. BAT depot mass was increased by 51–91%. Serum chemistry values showed a decrease in TG but not cholesterol with rosiglitazone, while the PPARα/γ agonists decreased both TG and cholesterol significantly for all except one dose of compound **5**. The co-regulated BAT proliferation and heart weight increase phenomena related to PPARγ were not seen with any of the PPARα/γ agonists reported here. The most prominent and unsurprising finding was a PPARα driven increase in liver weight for all of the mandelate analogues tested.[8]

The mandelate PPAR agonists described here are characterized by a PPARα selective to balanced PPARα/γ affinity and exceptional intrinsic efficacy in the PPARαGAL4 chimer TA assay. These ortho, ortho- disubstituted arylmandelates are very effective at correcting hyperglycemia in very insulin resistant db/db mice at doses equal to or less than the clinically proven PPARγ selective insulin sensitizer, rosiglitazone. Both PPARα selective and PPARα/γ mixed mandelate agonists show good efficacy. Pharmacokinetic parameters in SD rat are consistently good to excellent for the series. Both types of agonists are superior to rosiglitazone in a rat tolerability model of the known, clinically relevant, mechanism based toxicities caused by PPARγ agonists. The inference from the superior tolerability, without signs of PPARγ mechanism based toxicity, would be that the efficacy in the rodent DM2 model is driven largely by PPARα activation. This phenomenon has been reported by both Glaxo and Boehringer-Mannheim scientists for GW9578[14] and BM17.0744.[15] In the case of BM 17.0744, the same favorable ratio of efficacy to PPARγ mechanism based toxicity is reported. The mechanism of this efficacy is under active investigation in rodents.

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We would like to thank Dr. Gerard Kieczykowski, Amanda Makarewicz and Glenn Reynolds for supplies of starting materials. Additional technical support for biological evaluation was provided by; Margaret Wu, John Ventre, Chhabi Biswas and Neelam Sharma.

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for PPARγ. The mean EC_{50} is 21 nM SD 5.6 SEM 2.5. Compound **3** of ref 11 is used as a full agonist (100%) reference PPARα. The mean EC_{50} is 9.9 nM SD 4.9 SEM 0.2. The db/db mouse model is run as described for 11 days. Correction of FPG is reported as the degree of mean glucose lowering as percentage of the difference between vehicle treated db/db mice versus lean control mice at day 11.

7. All new compounds gave consistent 400 MHz ^{1}H NMR spectra and satisfactory LCMS data. Experimental procedures and spectra for the analogues reported here are disclosed in WO02064094.

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10. Male Sprague–Dawley rats (~200 g body weight) from Charles River were housed 3 rats/cage and provided ad lib access to rodent chow (Purina #5008) and water. Body weights were measured prior to dosing and on days 1, 4, 6, 8, 11 and 14 of dosing. Animals ($n = 6$ to 7 per group) received once-a-day oral dosing by gavage with compounds at the doses indicated or with vehicle (0.5% methylcellulose; 10 mL/kg). Twenty-four h following the last dose, animals were euthanatized via CO_2 inhalation. The indicated tissues and organs were removed and weighed. Serum was prepared from the blood sample and assayed for serum chemistry. Statistical significance was determined by Student's *t*-test compared with vehicle.

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17. Pharmacokinetics studies were performed in fasted male Sprague–Dawley rats. Doses used were 0.5 mpk iv and 2.0 mpk po. po nAUC, Cl, F and $t_{1/2}$ for **5** and **10** are; **5** 272 μM-Hr, 0.19 mL/min-kg, 88%, 7.7 Hr. and **10** 67, 0.08, 11, 10.5.

18. See; Avandia/Rosiglitazone NDA Submission 021-071, 5/25/1999. http://www.fda.gov/cder/foi/nda/99/21071Avandia.htm Medical review p. 26–37. Actos/Pioglitazone NDA. Submission 021073, 7/15/1999 http://www.fda.gov/cder/foi/nda/99/021073AActosmedrP3.pdf Medical review part 3, p 36–40.