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Benzoyl 2-methyl indoles as selective PPARγ modulators

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Abstract—Routine screening for human PPAR ligands yielded compounds **1** and **2**, both of which were sub-micromolar hPPARγ agonists. Synthetic modifications of these leads led to a series of potent substituted 3-benzyl-2-methyl indoles, a subset of which were noted to be selective PPARγ modulators (SPPARγMs). SPPARγM **24** displayed robust anti-diabetic activity with an improved therapeutic window in comparison to a PPARγ full agonist in a rodent efficacy model.

Non-insulin dependent or Type 2 diabetes mellitus (T2DM) affects a significant number of people in the industrialized world, and is expected to be a growing medical concern as the post-World War II generation ages. Onset of T2DM most often occurs in middle age, but younger people are more frequently being diagnosed. The sedentary lifestyles in developed countries, combined with high caloric intake, are contributing factors in T2DM. Type 2 diabetic patients suffer a variety of symptoms, including hyperglycemia, hyperlipidemia, atherosclerosis, and obesity. Insulin resistance combined with pancreatic β-cell dysfunction play a central role in the etiology of type 2 diabetes; with insulin resistance usually occurring first, followed by insulin insufficiency.[1] Peroxisome proliferator-activated receptor gamma (PPARγ) is a transcription factor known to mediate adipocyte differentiation.[2] Synthetic agonists of PPARγ including pioglitazone[3] and rosiglitazone[4] have been shown clinically to provide beneficial decreases in elevated plasma glucose levels in T2DM patients.

Glitazones, while efficacious, exhibit significant liabilities; they are associated with edema and weight gain in man. In addition, cardiac hypertrophy is observed in preclinical rodent models. These adverse effects preclude pioglitazone and rosiglitazone from being used as front-line therapy in T2DM, suggesting that pursuit of a safer second generation human PPARγ (hPPARγ) agonist is desirable.

Selective PPARγ modulators (SPPARγMs), which are also known as hPPARγ partial agonists, have recently attracted much interest. Selective modulation of the hPPARγ nuclear receptor theoretically could provide significant anti-diabetic activity while concurrently reducing or eliminating PPARγ-mediated side-effects such as increased adipogenesis.[5,6] Berger recently disclosed the SPPARγM nTZDpa,[7] which in comparison with PPARγ full agonists demonstrates attenuation of body weight gain, adipose depot size, cardiac weight gain, and adipocyte gene expression in a rodent model of T2DM. Equally important was the marked reduction of hyperglycemia and hyperinsulinemia seen in these same models. Others have reported compounds (Fmoc-Leu[8] and YM440[9]) that modulate PPARγ with improved in vivo profiles relative to full agonists; while GW0072[10] and L-764406[11] have been shown to be hPPARγ partial agonists in vitro. The antagonist LG100641 reportedly blocks TZD-induced PPARγ activation and adipocyte differentiation in vitro.[12]

Sample collection screening directed at identifying new and structurally diverse leads active on hPPARγ provided the 2-methyl indoles **1** and **2** as selective, sub-micromolar receptor agonists. The indole core is present

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Keywords: PPAR; Indole; Selective PPAR modulator.

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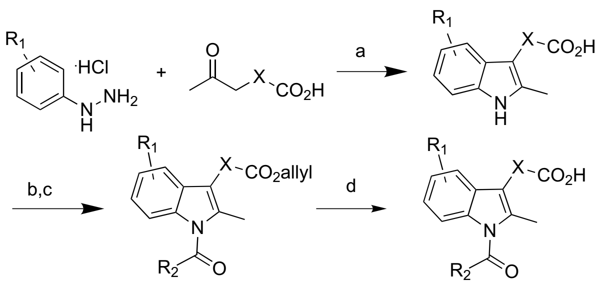
in a large number of pharmacologically active compounds. In fact, indomethacin,[13] nTZDpa,[7] and 2,3-disubstituted indole 5-acetic acids[14] are all indoles that have been reported to be PPARγ agonists. Modification of the 2-methyl indole leads and their effects on in vitro measures of hPPARγ agonism and in vivo efficacy, toxicity, and pharmacokinetics in rodent models are disclosed below.

Modifications were made at four individual sites of the indole core of compound **3** (Fig. 1). Scrutiny of the screening actives and a limited synthetic survey established that the methyl group is optimal at C-2. Modification of the side chain at C-3 as well as variations at R_1 (C-4 to C-7) and COR_2 (N-1) were undertaken using known synthetic procedures. The indoles were prepared by treating a phenylhydrazine and a methyl ketone with phosphoric acid in refluxing toluene (the Fischer indole synthesis). Initially, the choices for the C-3 side chain were limited to various aliphatic acids. The methyl ketones were either commercially available or prepared in short sequences from available precursors. Following acylation of the indole, catalytic cleavage of the allyl ester by the method of McCombie provided the final products.[15,16] A general preparative sequence is shown below (Scheme 1).



Scheme 1. Reagents and conditions: (a) H_3PO_4, toluene, reflux; (b) Cs_2CO_3, allyl iodide, DMF; (c) NaHMDS, R_2COCl, THF; (d) $Pd(PPh_3)_4$, dimedone, DIEA, DMF.

All new compounds were evaluated as ligands for the three human PPAR isoforms (γ, δ, and α) in competition binding assays.[7,17] With rare exception, active compounds were selective hPPARγ ligands. Those of adequate binding potency were then assessed for agonist activity in a COS-1 cell-based transactivation assay (TA) using transiently co-transfected pcDNA3-PPAR/GAL4 chimer and pUAS(5X)-tk-luc reporter vectors.[7]

A wide array of substituents are tolerated at the indole 5-position (R_1); among those leading to potent analogs are methoxy, trifluoromethoxy, isopropyl, fluoro, propyl, phenoxy, and *N*,*N*-dimethylcarbamate. Substitution at the 4, 6, or 7 positions of the indole was poorly tolerated. Variation of the chain length at C-3 indicates that five to six methylenes are optimal for a straight chain, whereas the bulkier *gem*-dimethyl substituted chains can be shorter. A limited number of benzoyl group substituents (COR_2) retain activity; only the 2-napthoyl and 4-methoxybenzoyl groups were notable improvements over the 4-chlorobenzoyl screening leads. Substitution of 4-chlorobenzyl for 4-chlorobenzoyl at N-1 led to >50-fold reduction in hPPARγ binding; transactivation activity was not measured. Combining the most favorable X, R_1, and COR_2 substituents leads to very potent hPPARγ full agonists (IC_{50}'s of <40 nM in the binding assay). Unsurprisingly, these long chain alkyl compounds suffer from poor pharmacokinetic profiles and in general fared poorly in rodent efficacy models.

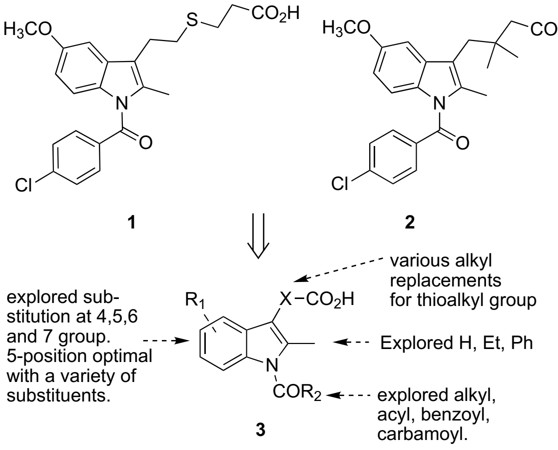
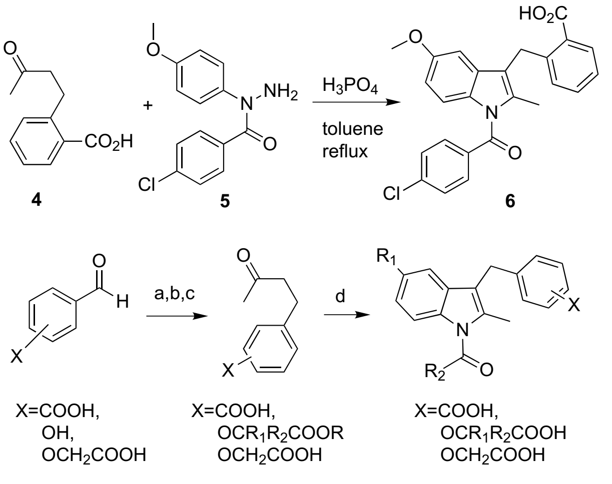


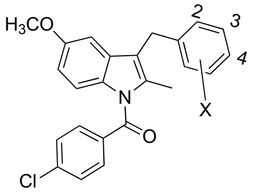
Figure 1. Screening leads and initial synthetic survey.

A series of substituted 3-benzylic indoles[18] were designed that preserved the lipophilic nature of the acid-bearing side chain while maintaining the carboxylate in a similar position. Introduction of a benzylic moiety could possibly improve pharmacokinetics relative to the metabolically soft long-chain aliphatics. Preparation of the first of these 3-benzylic indoles involved the reaction of the benzoic acid intermediate **4** with the indomethacin synthetic intermediate **5** to give indole **6**. Intermediate **4** is easily accessible; the route shown in Scheme 2 below can be used to make **4** or any number



Scheme 2. Reagents and conditions: (a) $Ph_3P{=}CHCOCH_3$/THF/reflux; (b) H_2/10% Pd–C/EtOAc; (c) (if needed) $BrCR_1R_2COOR$/K_2CO_3/DMF; (d) Fischer indole reaction using acylhydrazines like **5** or a phenylhydrazine ($ArNHNH_2$) followed by acylation and ester hydrolysis.

Table 1. In vitro activity of 3-benzyl indoles **6**–**17**



	Position/X substituent	hPPARγ binding (SPA) IC_{50} (μM)[a]	PPARγ TA EC_{50} (μM)[c]	PPARγ TA % max @ 3 μM
6	2; CO_2H	6.28	ND[d]	ND
7	3; CO_2H	0.208	0.28	33%
8	4; CO_2H	4.69	ND	ND
9	2; OCH_2CO_2H	0.333	0.191	50%
10	3; OCH_2CO_2H	0.099 ± 0.024[b]	0.077	25%
11	4; OCH_2CO_2H	>10	ND	ND
12	2; $OCH(Me)CO_2H$	0.084	0.014	97%
13	3; $OCH(Me)CO_2H$	0.049	0.019 ± 0.005[b]	42%
14	4; $OCH(Me)CO_2H$	2.14	ND	ND
15	2; $OC(Me)_2CO_2H$	0.079	0.012	86%
16	3; $OC(Me)_2CO_2H$	0.045	0.019	59%
17	4; $OC(Me)_2CO_2H$	0.914	ND	ND

[a] Compounds **6**–**17** do not bind hPPARα. Compound **10** and **16** bind hPPARδ modestly (1.25 and 4.22 μM IC_{50}'s, respectively); all others not active on hPPARδ. All data SD ± 15% (*n* = 3).

[b] Average of two experiments. Data presented as mean ± SEM.

[c] The EC_{50} is reported; this is the compound concentration at which 50% of a given compounds' intrinsic maximal response has been reached. The standard reference full agonist is rosiglitazone (EC_{50} = 0.023 μM; 100% maximum activation at 3.0 μM). Activation levels can be compared between compounds; those that reach a nearly equivalent maximal activation to rosiglitazone are considered full agonists, while those reaching 20–60% of rosiglitazones' maximal activation are deemed partial agonists. A graphical representation of this can be seen in Figure 2.

[d] Not done = ND.

of positional isomers or analogs. The ketones were directly converted to the desired *N*-acylindoles via Fischer indole synthesis with **5**. Alternatively, Fischer indole synthesis with the ketone and a phenylhydrazine ($ArNHNH_2$) followed by *N*-acylation and ester hydrolysis provided the desired indole as outlined in Scheme 1.

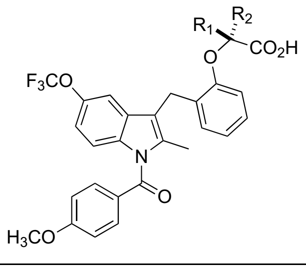
The initial 3-benzyl indoles prepared were 2-, 3-, and 4-benzoic acid and phenoxyacetic acid analogs (**6**–**11**, Table 1). Generally, the benzoic acid analogs were weak ligands, with only *meta*-analog **7** showing sub-micromolar binding affinity. Improvement in potency was noted with the phenoxyacetic acid analogs; the *ortho* (**9**) and *meta* (**10**) analogs both exhibit sub-micromolar γ-binding affinity. Compound **10** also bound hPPAR*δ* weakly. In the TA assay analogs **7**, **9**, and **10** showed useful functional activity. Further elaboration of the phenoxyacetic acids led to a series of compounds substituted at the carbon α to the carboxylate. These lactates (**12**, **13**) and isobutyrates (**15**, **16**) led to another 2- to 4-fold improvement in binding affinity and transactivation potency. The addition of the methyl groups ameliorated off-target hPPARδ activity; compound **16** improved hPPARγ specificity 10-fold versus compound **10**.

A series of compounds was then prepared that incorporated all of the optimized substituents at R_1, COR_2 and the benzylic side chain at C-3. These 'hybrids' include R_1 as trifluoromethoxy, COR_2 as 4-methoxybenzoyl and the benzylic side chains as *ortho*- and *meta*-lactates and isobutyrates. The individual (*R*) and (*S*) isomers of the lactates[19] were prepared as well.

The *ortho*-lactates and isobutyrates are potent full agonists of hPPARγ, with all analogs except the (*R*)-lactate exhibiting binding IC_{50}'s and transactivation EC_{50}'s ⩽6 nM. Data is shown in Table 2 below.

The *meta*-lactates and isobutyrates in the 'hybrid' series were potent partial agonists of hPPARγ; they activate hPPARγ in the COS1 cell line to ⩽50% of the maximum of the comparator full agonist rosiglitazone. Closer

Table 2. In vitro activity of *o*-benzyl indoles **18**–**22**



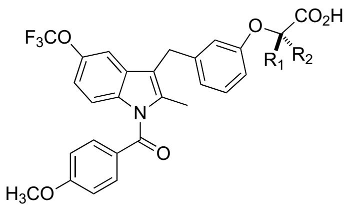
	R_1	R_2	hPPARγ binding (SPA) IC_{50} (μM)[a]	PPARγ TA EC_{50} (μM)	PPARγ TA % max @ 3 μM
18	*rac*-Me	—	0.001	0.003	83%
19	H	(*R*)-Me	0.023	0.021	47%
20	(*S*)-Me	H	0.002	0.002	97%
21	*rac*-Et	—	0.003	0.006	67%
22	Me	Me	0.001	0.050	75%

[a] Compounds **18**–**22** do not bind hPPARα or hPPARδ. All data SD ± 15% (*n* = 3). *rac* = racemic.

examination of the profiles of the earlier benzyl indoles (Table 1) also shows that the *meta*-analogs (carboxylate, phenoxyacetate, lactate, and isobutyrate) were hSPPARγMs. All of the analogs in this 'hybrid' series were <5 nM ligands of hPPARγ; maximum activation of these analogs ranged from 24% to 42% at 3 μM compound concentration with nanomolar EC_{50}'s in the TA assay. The actual data is shown in Table 3 below; the graph in Figure 2 compares compound **24** with rosiglitazone in the transactivation assay.

Expansion of the SAR was undertaken to correlate the structural parameters to partial agonism and to identify when SPPARγM-like behavior transitions to full agonism or even antagonism. These alterations are illustrated in Figure 3. *N*-(Di- and tri-chlorobenzoyl) substituents revert to full agonism while *N*-(2-napthoyl) analogs retain the partial agonist character of the 4-chloro- and 4-methoxybenzoyl substituents. Variation of the length of the benzylic methylene bridge was attempted ($n = 0$–3). A partial agonist was prepared from the $n = 0$ series ($R_1 = R_2 = CH_3$), while the $n = 2$–3 analogs are full agonists ($R_1 = CH_3/R_2 = H$; (*R*)-lactates). For $n = 1$, every compound prepared with the 'hybrid' core structure was a hSPPARγM, indicating that there is a fairly tight structural constraint regarding full versus partial agonism. Also in the $n = 1$ class, substitution on the benzylic methylene attenuated functional activity; the cyclopropyl and dimethyl compounds were very weak partial agonists. When $X_n = C(CH_3)_2$, potency dropped off sharply relative to compound **24**. However, with $X_n = O$ at the benzylic methylene position a hSPPARγM that is equipotent with **24** is obtained.

Table 3. In vitro activity of *m*-benzyl indoles **23**–**28**



	R_1	R_2	hPPARγ/δ/α binding (SPA) IC_{50} (μM)	PPARγ TA EC_{50} (μM)	PPARγ TA % max @ 3 μM
23	*rac*-Me	—	0.001/>15/3.90	0.002	24%
24	H	(*S*)-Me	0.001/>15/>15	0.002	21%
25	(*R*)-Me	H	0.003/>15/1.65	0.002	34%
26	*rac*-Et	—	0.003/>15/1.64	0.003	36%
27	*rac*-*n*Pr	—	0.004/>50/2.75	0.002	42%
28	Me	Me	0.003/>15/2.77	0.006	24%

All data SD ± 15% ($n = 3$). *rac* = racemic.

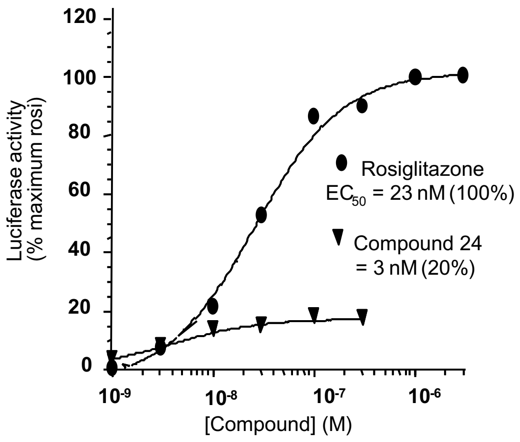


Figure 2. Human PPARγ transactivation of rosiglitazone and compound **24**.

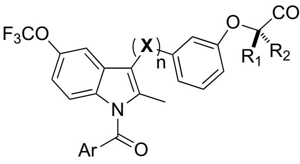


Figure 3. Structural survey of *meta*-indole lead class: $n = 0$–3, Ar = 2-napthoyl, 4-Cl-benzoyl, 2,4-Cl-benzoyl, 2,4,6-Cl-benzoyl, X = CH_2, $C(CH_3)_2$, $C(CH_2CH_2)$, O.

Following the identification of multiple hSPPARγMs with good intrinsic potency in vitro, it was necessary to determine whether these compounds would retain useful in vivo efficacy in diabetes models while exhibiting an enhanced safety profile with respect to known PPARγ mechanism-based liabilities. Easily monitored liabilities include weight gain, cardiac hypertrophy, and brown adipose tissue (BAT) accumulation. Armed with numerous SPPARγMs, in vivo testing in rodent models was used to ascertain whether this objective could be attained. The incorporation of the more metabolically robust 3-benzylic indole side chain improved pharmacokinetics in Sprague–Dawley (SD) rats versus the 3-aliphatic compounds described above, validating one of the hypotheses posited earlier. *Db*/*db* mice,[20] a genetic model of obese, insulin resistant T2DM, were then used to evaluate the in vivo efficacy of analogs with adequate pharmacokinetic profiles. While a number of SPPARγMs were tested in pharmacokinetics and in the *db*/*db* mouse model, only representative compound **24** is described in detail (Table 4). SPPARγM **24** effectively reduces hyperglycemia in the *db*/*db* model at 3 and 10 mg/kg/day for 11 days (79% and 90% correction, respectively). Rosiglitazone is effective as well, but slightly less so under these test conditions (10 mg/kg/day, 60% glucose correction). Body weight gain measured in the *db*/*db* mouse amounted to only 4% at 3 and 10 mg/kg/day of **24**, while a 10% body weight gain was noted for rosiglitazone at 10 mg/kg/day. PPARγ-mediated toxicities were evaluated by dosing lean Sprague–Dawley rats[21,22] with high doses of the requisite PPARγ ligand for 14 days, followed by analysis of serum chemistries, necropsy, and organ weight determination. There were two notable differences between compound **24** and rosiglitazone in this study. Compound **24** resulted in a 3.5% heart weight increase and a 45% BAT weight increase at a plasma exposure 100 times greater than the exposure needed for efficacy in *db*/*db*

Table 4. In vivo data of Compound **24** versus rosiglitazone

	db/db Mouse[20]			Normal Sprague–Dawley rats[21]		
	Glucose correction[a] (dose, mg/kg)	Body weight gain (dose, mg/kg)	Plasma AUC of parent drug (dose, mg/kg)	Heart wt. (dose, mg/kg)	Brown adipose tissue wt. (BAT) (dose, mg/kg)	Plasma AUC of parent drug (dose, mg/kg)
Vehicle	None	ND	None	1.13 ± 0.06 g	0.31 ± 0.03	None
24	90 ± 11% (10)[b]	4% (10)	8.7 μM h (3)	1.17 ± 0.09 g (30)	0.45 ± 0.05 (30)	20.2 μM h (2)
	79 ± 15% (3)[c]	4% (3)				955 μM h (30)
Rosiglitazone	60 ± 17%[b] (10)	10% (10)	317 μM h (10)	1.41 ± 0.07 g (150)	0.88 ± 0.15 (150)	1607 μM h (150)
				1.37 ± 0.08 g (30)		

[a] Glucose correction is calculated as the percent correction of nonfasting hyperglycemia present in vehicle control db/db mice relative to normal glucose levels in control db/lean mice, all on day 11 of dosing. Data is presented as mean glucose correction ± SEM.

[b] Average of two experiments.

[c] Average of four experiments.

mice, while rosiglitazone resulted in a 23% heart weight increase and a 183% BAT weight increase at an exposure only five times greater than the exposure needed for efficacy in *db/db* mice. Based upon these findings, we conclude that SPPARγM **24** possesses important pharmacological advantages relative to the PPARγ full agonist rosiglitazone in these models.

During the course of these investigations, structural modifications of full hPPARγ agonists **1** and **2** led to the identification of a series of potent partial agonists or hSPPARγMs, typified by the *meta*-lactate substituted 3-benzylic indole **24**. The series of compounds described here feature improved pharmacokinetics as compared to the original screening leads, while also demonstrating excellent efficacy in rodent diabetes models. Further evaluation demonstrated that separation of efficacy from hPPARγ mechanism-based liabilities can be achieved in rodent models. These results indicate that hSPPARγMs are attractive candidates for future development.

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