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Substituted indanylacetic acids as PPAR-α–γ activators

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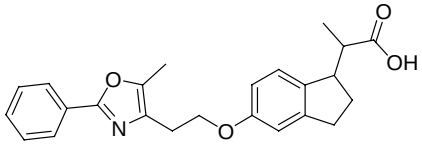
Abstract—A series of oxazole-substituted indanylacetic acids were prepared which show a spectrum of activity as ligands for PPAR nuclear receptor subtypes.

Peroxisome-proliferator activated receptors (PPARs) are pharmaceutical targets of great importance. Their wide-ranging effects on key transcriptional pathways for lipid handling, insulin sensitivity, inflammation and other functions have led to marketed drugs and vast clinical and preclinical research efforts.[1–4] While the first successful compounds in this field have been PPAR-γ agonists, there is strong evidence that dual-acting PPARα–γ ligands may be of even greater benefit. Both insulin sensitivity and dyslipidemia could potentially be treated through such balanced activity. Indeed, several compounds of this type have been reported, some of which have advanced to human clinical trials.[5]

Many of the known PPAR agonists contain substituted arylacetic/propionic acids or acid isosteres. Molecular modeling and docking studies led us to the hypothesis that appropriately substituted indanylacetic acids, structures previously uninvestigated in this field, would be efficacious. This head group was combined with the substituted oxazoles found in many PPAR ligands,[6] as in our prototype compound **1**.



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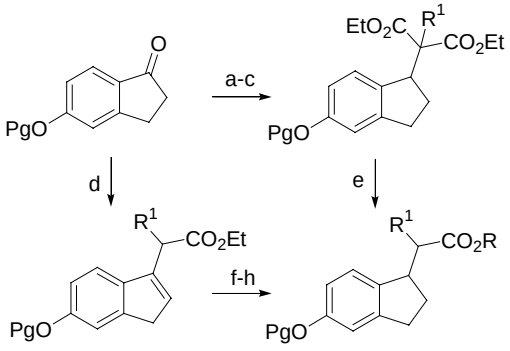
Synthesis of these compounds required the corresponding phenol, which was initially prepared according to Scheme 1. Starting from the commercially available



Scheme 1. Reagents: (a) diethyl malonate, $TiCl_4$; (b) H_2, Pd/C; (c) R^1I, KO(*t*-Bu); (d) Zn, $BrCH_2CO_2Et$; (e) LiCl, aq DMSO; (f) KOH, aq MeOH; (g) H_2, $ClRh(Ph_3P)_3/Et_3N$, EtOH/THF; (h) MeI/$NaHCO_3$, DMF. Pg = protecting group (Bn or Me).

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5-methoxy or 5-benzyloxyindanones, the branched acidic chain could be introduced through several methods. Knoevenagel condensation with diethylmalonate followed by reduction and alkylation provided an intermediate that could be decarboxylated to the desired compounds. This route suffered from variable yields; however, and produced mixtures of all four possible stereoisomers. More direct approaches were also attempted. However, Horner–Emmons–Wadsworth reactions of the starting indanone failed with branched phosphonates, and alkylation of the unsubstituted indanylacetic acid (R^1 = H) was very low-yielding. In-plane steric hindrance from the adjacent aryl ring is presumably the cause of both difficulties.

We then developed a route based on a Reformatsky reaction with ethyl α-bromobutanoate, which yielded only the endocyclic alkene on workup. This ester could be hydrogenated to yield a mixture of diastereomers. Unless otherwise indicated, the compounds presented here were prepared by this route and contain between 50% and 75% of the *SR*/*RS* diastereomers. We later found that the corresponding carboxylate could be hydrogenated stereoselectively to the desired *RR*/*SS* racemate with Wilkinson's catalyst and re-esterified, with optional resolution of the intermediate acid as its quinine salt. These methods have been detailed in a separate publication.[7]

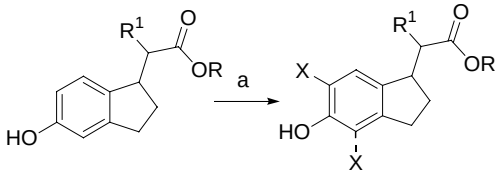
These intermediates could be further substituted as shown in Scheme 2. Bromination of the phenols gave mainly 6-bromo products, with small amounts of the 4,6-dibromo adducts. Friedel–Crafts acylation showed similar selectivity.

Elaboration of these indanylacetates to the final compounds was straightforward (Scheme 3). Deprotection of the phenol (via hydrogenolysis or demethylation) and Mitsunobu coupling with an appropriate heterocyclic alcohol completed the general scaffold. The heterocyclic intermediates were prepared by known procedures, specifically through Dakin–West reactions of aspartate esters and subsequent closure to provide substituted oxazoles.[8] Attempts to alkylate the phenol through more conventional ether syntheses led to unacceptable amounts of elimination for all the oxazolylethyl-leaving groups investigated. After coupling, the bromoindanyl compounds could be elaborated by Suzuki coupling at the R^2 position. In either case, hydrolysis of the ester then furnished the desired PPAR ligands.

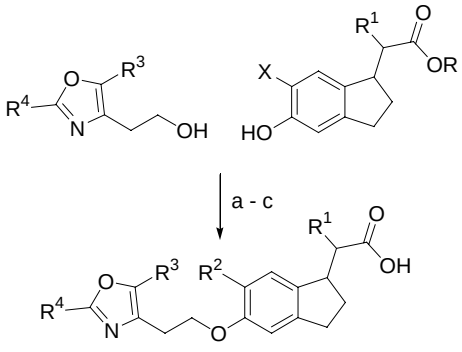
The final compounds[9] were first evaluated by FRET assays, using human ligand-binding domains for PPAR-α and PPAR-γ, and the known co-activator CBP.[10] Active compounds were then profiled in a cellular transactivation assay.[11] (Data from this assay are not presented here, as they showed almost all compounds of reasonable potency could be classified as full agonists comparable to rosiglitazone.)

Since the acid moiety is crucial for PPAR binding, our initial efforts surveyed a range of groups at the α-position (Table 1). Even when assayed as mixtures of diastereomers, the SAR trends were clear. The PPAR-α activity was sensitive to changes in this region, as shown by the shift in potency between **3** and **4**. Bulky groups near the carboxyl (e.g., **2**, **7**, and **8**) abrogated activity at both subtypes. On the basis of these studies, we selected the α-ethyl group for the majority of our compounds.

The utility of the substituted oxazolylethyl chain became clear when other heterocycles, amines, and chain lengths[12] were investigated (Table 2). Save for pyrazoles (e.g., **15**) and the chain-shortened analog **22**, none of the

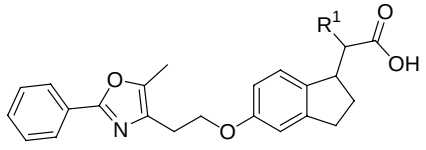


Scheme 2. Reagents: (a) Br_2, dioxane or $AlCl_3$/RCOCl.



Scheme 3. Reagents: (a) ADDP/Ph_3P, THF; (b, if X = Br) $NaHCO_3$/$R^2B(OH)_2$/$(Ph_3P)_4Pd$ or $Pd(dppf)Cl_2$, aq DME; (c) LiOH, aq MeOH.

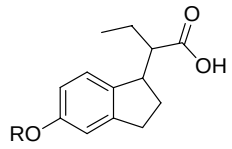
Table 1. EC_{50} values (in nM) for α-substituted PPAR ligands

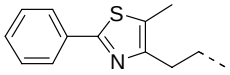
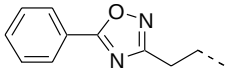
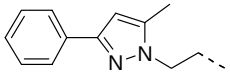
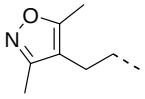
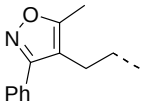
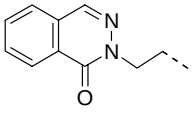
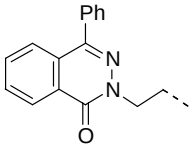
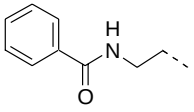
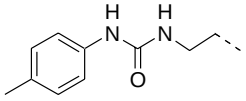
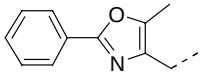
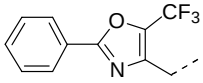
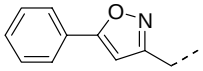
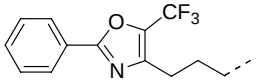
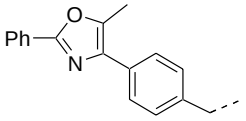


Compound	R^1	PPAR-α FRET EC_{50} (nM)	PPAR-γ FRET EC_{50} (nM)
1	CH_3	1000	104
2	*gem*-Dimethyl	6000	5640
3	CH_3CH_2	141	42
4	CF_3CH_2	5790	177
5	Cyclopropyl	795	160
6	$CH_3CH_2CH_3$	3890	52
7	$PhCH_2CH_2CH_2$	>10,000	3180
8	Phenyl	7260	9560
9	CO_2H	>10,000	1860
10	CO_2Et	308	68
11	CH_3O	670	45
12	CH_3CH_2O	500	12

Values are means of at least three experiments. DR = diastereomeric ratio.

Table 2. EC_{50} values (in nM) for various heterocyclic substituents



Compound	R^4	PPAR-α FRET EC_{50} (nM)	PPAR-γ FRET EC_{50} (nM)
13		979	85
14		1040	>10,000
15		232	196
16		>10,000	>10,000
17		>10,000	>10,000
18		>10,000	>10,000
19		>10,000	>10,000
20		>10,000	>10,000
21		>10,000	>10,000
22		1220	632
23		1000	>10,000
24		670	>10,000
25		232	>10,000
26		>10,000	>10,000

Values are means of at least three experiments.

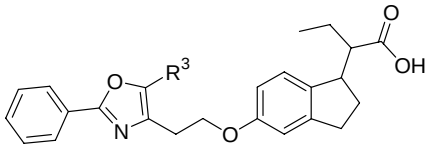
variations were successful, although some retained modest activity against PPAR-α. Even relatively small variations such as the oxadiazole **14** were not well tolerated. Compounds **18** and **19** represent left-hand heterocycles reported[13] for another series of PPAR ligands, which did not maintain potency when attached to our indanylacetic head group.

We then returned to the oxazole series and the Dakin–West reaction sequence[14] to investigate substituents at this R^3 site. The results in Table 3 suggest that the methyl group was already optimal. The PPAR-α activity appeared to be very sensitive to steric effects here, while PPAR-γ activity was relatively unaffected.

We investigated a similar short run of substituents at the 6-position of the indane, keeping the other regions of the molecule at their standard settings (Table 4). These modifications generally lowered activity at PPAR-γ, some drastically. None of the changes were sufficiently compelling enough for us to abandon the original unsubstituted indane core.

Other regions of the molecule seemed more promising for generating balanced PPAR activity without increasing the molecular weight and lipophilicity of the compounds. To this end, the 2-oxazolyl position became

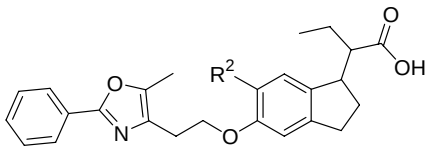
Table 3. EC_{50} values (in nM) for 5-oxazoyl substituents



Compound	R^3	PPAR-α FRET EC_{50} (nM)	PPAR-γ FRET EC_{50} (nM)
27	H	383	306
3	CH_3	141	42
28	CH_3CH_2	354	46
29	$(CH_3)_2CH$	>10,000	347
30	Phenyl	>10,000	617

Values are means of at least three experiments.

Table 4. EC_{50} values (in nM) for 6-indanyl substituents



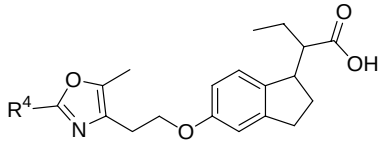
Compound	R^2	PPAR-α FRET EC_{50} (nM)	PPAR-γ FRET EC_{50} (nM)
3	H	141	42
31	Cl	127	294
32	Br	181	>10,000
33	CH_3CO	327	>10,000
34	Phenyl	58	290
35	4-Chlorophenyl	45	168
36	4-Methoxyphenyl	23	124

Values are means of at least three experiments.

the target of a large SAR effort, some results of which are shown in Table 5.

Several broad SAR trends can be discerned. Activity at both PPAR subtypes is well maintained in these compounds compared to modifications in other regions. Alkyl, aryl, and heteroaryl groups all show reasonable potency. The main SAR restrictions appear to be the decreased activities, especially at PPAR-α, of *ortho*-substituted rings (**43**, **52**, **64**, and **65**), also seen in the relative potencies of the naphthyl compounds **68** and **69**. Steric considerations at the distal end of the aryl ring may explain the low activities of compounds **59**, **62**, and **67**, an effect again most noticeable at PPAR-α.

Table 5. EC_{50} values (in nM) for 2-oxazoyl substituents



Compound	R^4	PPAR-α FRET EC_{50} (nM)	PPAR-γ FRET EC_{50} (nM)
37	Benzyl	718	330
38	(4-Fluoro)benzyl	204	523
39	Phenoxymethyl	61	45
40	(4-Chlorophenoxy)methyl	53	104
41	Cyclopentyl	202	212
42	Cyclohexyl	111	136
3	Phenyl	141	42
43	2-Methylphenyl	637	153
44	3-Methylphenyl	271	34
45	4-Methylphenyl	65	45
46	4-Ethylphenyl	109	40
47	4-Isopropylphenyl	119	22
48	4-(*n*-Butyl)phenyl	82	16
49	4-(*tert*-Butyl)phenyl	240	19
50	3-Methoxyphenyl	254	1
51	4-Methoxyphenyl	199	42
52	2-Fluorophenyl	559	49
53	3-Fluorophenyl	336	61
54	4-Fluorophenyl	137	59
55	4-Chlorophenyl	92	206
56	3-Trifluoromethyl	171	21
57	4-Trifluoromethyl	58	205
58	3,4-Dimethylphenyl	38	32
59	3,5-Bis(trifluoromethyl)phenyl	1170	247
60	3-Fluoro-4-methylphenyl	46	43
61	4-Fluoro-3-methylphenyl	75	77
62	3,4-Dimethoxy	1130	84
63	3,4-(Methylenedioxy)phenyl	354	14
64	2,6-Difluorophenyl	523	368
65	2.4-Dichlorophenyl	5480	738
66	3.4-Dichlorophenyl	91	94
67	(4-Phenyl)phenyl	3280	43
68	1-Naphthyl	451	113
69	2-Naphthyl	104	16
70	2-Furyl	745	396
71	6-(Dihydrobenzofuranyl)	65	6
72	2-Benzothienyl	287	37
73	3-(5-Methyl)isoxazoyl	827	762

Values are means of at least three experiments. DR = diastereomeric ratio.

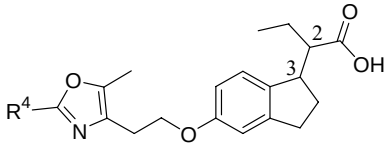
A final consideration in these structures is the stereochemistry of the indanylacetic acid region. As mentioned above, late in our SAR program we developed a stereoselective route to these compounds, but we previously had separated the individual enantiomers by chiral HPLC with a Chiracel® AD column. This method along with X-ray crystallographic analysis of a chiral α-methylbenzylamine salt (see footnote 11 in Ref. 7) provided the assignments in Table 6.

A striking chiral effect was made clear by these studies. There is a strong preference at both PPAR subtypes for the *S* chirality at the carboxylic acid center, and the *R*,*R* combination was seen to be particularly unfavorable.

We evaluated several of the most active compounds with balanced PPAR activity in animal models of type II diabetes and dyslipidemia. Preliminary PK studies showed generally good oral exposure. A 3 mpk oral dose of 45d in db/db[15] and hApoA1 transgenic[16] mice showed C_{max} values of 2980 and 2550 μg/l, and AUC values of 11600 and 8060 μg*h/l, respectively, values which are very compatible with qd dosing.

On oral administration (10 mpk) in db/db mice compound **45d** caused a 45% decrease in blood glucose levels ($p < 0.01$ relative to vehicle). By comparison, the PPAR-γ agonist rosiglitazone showed a 55% decrease at a dose of 30 mpk in a positive control group. In hApoA1 mice, a 10 mpk dose of **45d** showed a roughly 15% increase in serum HDL, which did not achieve statistical significance. The 30 mpk dose, however, elevated HDL by 30%, which was statistically significant relative to vehicle ($p < 0.001$) and indistin-

Table 6. EC_{50} values (in nM) for 6-indanyl substituents



Compound	R^4	2,3-Chirality	PPAR-α FRET EC_{50} (nM)	PPAR-γ FRET EC_{50} (nM)
3a	Phenyl	*SR*	26	19
3b		*RS*	350	95
3c		*RR*	>10,000	605
3d		*SS*	62	6
45a	4-Methylphenyl	*SR*	48	83
45b		*RS*	1520	>10,000
45c		*RR*	>10,000	>10,000
45d		*SS*	78	30
54a/b	4-Fluorophenyl	*SR*/*RS*	37	154
54c		*RR*	868	>10,000
54d		*SS*	94	46
66a/b	3,4-Dichlorophenyl	*SR*/*RS*	29	131
66c		*RR*	63	225
66d		*SS*	57	46

Values are means of at least three experiments.

guishable from a 100 mpk dose of the PPAR-α agonist fenofibrate. At the same time, **45d** lowered serum triglycerides in this model by 45% ($p < 0.01$ relative to vehicle) at 10 mpk and by 60% at 30 mpk ($p < 0.001$). These significant and complementary effects on glucose and triglyceride levels established this series of compounds as worthy of further development.

Acknowledgments

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10. Test compounds were incubated in 96-well plates with europium-labeled anti-GST antibody, GST-tagged PPAR ligand-binding domain, biotinylated CREB-binding protein, and streptavidin-labeled APC (Wallac, AD0065). The plate was read in a fluorimeter with an excitation wavelength of 340 nm and emission wavelengths of 615 and 640 nm.
11. CV-1 cells were seeded in 96-well plates at 2.5×10^4 cells per well, grown overnight in standard media containing 10% fetal bovine serum, and then transiently transfected using the Lipofectamine/Plus procedure. Each well was transfected with plasmids containing the Gal4/PPAR-LBD fusion, UAS/firefly luciferase and renilla luciferase. After an overnight incubation with media containing 10% FBS treated with charcoal/dextran, test compounds were added and the cells were incubated for an additional 24 h. The plates were processed using the Promega Dual Luciferase kit and read on a Packard Topcount. EC_{50} values were determined based on a dose–response and the percent maximum stimulation was assessed by comparison to reference compounds.
12. 5-Trifluoromethyl compounds: (a) Kawase, M.; Miyamae, H.; Kurihara, T. *Chem. Pharm. Bull.* **1998**, *46*, 749; Oxadiazole preparation adapted from: (b) Showell, G. A.; Gibbons, T. L.; Kneen, C. O.; MacLeod, A. M.; Merchant, K.; Saunders, J.; Freedman, S. B.; Patel, S.; Baker, R. *J. Med. Chem.* **1991**, *34*, 1086.
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15. Male db/db mice ($n = 8$/group) were provided with ad lib access to water and chow. Test compound or vehicle (0.5% methylcellulose) was administered by oral gavage once daily for 14 days. After the final dose, the animals were euthanized and blood was collected and analyzed for glucose levels.
16. Male hApoA1 mice ($n = 16$/group) were provided with ad lib access to water and chow. Test compound or vehicle (0.5% methylcellulose) was administered by oral gavage once daily for eight days. After the final dose, animal were euthanized, and serum was prepared from the collected blood and analyzed for triglyceride content.