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Indanylacetic acids as PPAR-δ activator insulin sensitizers

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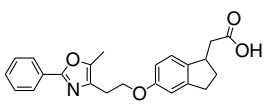
Abstract—A series of indane acetic acid derivatives were prepared which show a spectrum of activity as insulin sensitizers and PPAR-α and PPAR-δ ligands. In vivo data are presented for insulin sensitizers with selectivity for PPAR-δ over PPAR-α.

Peroxisome proliferator-activated receptors (PPARs) are part of the nuclear receptor superfamily and have captured the interest of the pharmaceutical industry as drug targets.[1,2] The PPAR receptors regulate lipid metabolism, with fatty acid catabolism controlled by PPAR-α and PPAR-δ, and lipid storage and adipogenesis by PPAR-γ.[3,4] PPAR-γ agonists such as rosiglitazone and pioglitazone are marketed for the treatment of diabetes.[5] Dual acting PPAR-α/-γ compounds for type II diabetes have been investigated by a number of pharmaceutical companies[6] including ourselves,[7] since the combined profile of insulin resistance and dyslipidemia could be treated through such activities. Since PPAR-δ also has great promise in treating dyslipidemia,[8,9] the industry has also moved into the area of PPAR pan agonists (α, γ, δ).[10,11]

The PPAR-γ/-δ combination remains relatively unexplored, however.[11,12] A recent publication reported by Lilly Research Laboratories[13] describes PPAR-γ/-δ agonists as novel euglycemic agents with a reduced weight gain profile, and we have observed reduced weight gain also with our dual activator when compared to Rosiglitazone (data not disclosed).

Many of the PPAR agonists to date (generally γ or dual α/γ agonists) contain an aryl ring with a 1–3 atom spacer to an acid or an acid isostere. A recent paper from our group[7] used a substituted indane acetic acid as a head group for molecules which showed potent PPAR-α/-γ agonist activity. Compounds such as **1** without substitution α to the acid were more selective for PPAR-δ over PPAR-α (see examples in Table 1). Insulin receptor induction was also measured as a readout of insulin-sensitizing activity.



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Racemic and chiral syntheses of our indane acetic acid derivatives have been published.[14–16] The synthesis of the chiral indane phenol is shown in Scheme 1. Starting

Keywords: PPAR; Insulin sensitizer; Indane acetic acids.
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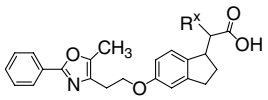
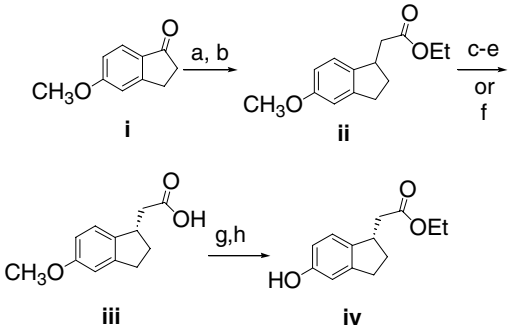
Table 1. SAR of α substituted indane acetic acids



Compound	R^X	Fret δ EC_{50} (nM)	Fret α EC_{50} (nM)	α/δ
1	H	27	890	32
2	CH_3	120	220	1.8
3	CH_2CH_3	590	130	0.22
4	OCH_3	4400	670	0.15

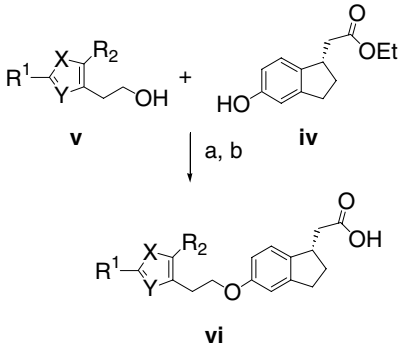


Scheme 1. Reagents and conditions: (a) Zn powder, CuCl, ethyl bromoacetate; (b) H_2, Pd/C; (c) NaOH, EtOH; (d) (*S*)-(−)-1-phenethylamine; (e) HCl (99% ee, 27% over 5 steps); (f) amano lipase PS (98% ee, 45% over 3 steps); (g) TMSCl, EtOH, 98%; (h) EtSH, $AlCl_3$, DCM, 99%.

from the commercially available 5-methoxyindanone (**i**), Reformatsky reaction with ethyl bromoacetate gives the coupled olefin. Subsequent hydrogenation gives the ethyl ester of the indane acetic acid (**ii**). The separation of the two enantiomers was achieved using one of the two methods shown in Scheme 1. Resolution of the free acid through its (*S*)-(−)-1-phenethylamine salt followed by aqueous HCl gave the chiral acid (99% ee). Alternatively, enzymatic hydrolysis (Amano Lipase PS) gave the acid in 98% ee. In either case, the acid was reesterified using TMSCl and EtOH, followed by the methyl ether cleavage using $AlCl_3$ and ethanethiol.

The synthesis can then be completed by coupling a heterocyclic alkylalcohol (**v**) (prepared by various methods previously published by our group[15]) with the indane phenol **iv** (Scheme 2), followed by hydrolysis of the ester.

Our indane acetic acid derivatives (**vi**) were evaluated by FRET assays using the PPAR-δ and PPAR-α ligand binding domains and the biotinylated TRAP 220 coactivator protein, and streptavidin-labeled APC.[17] Active compounds were then tested in a cellular transactivation assay (results not shown), which generally paralleled the FRET data, and in a cell based insulin receptor assay (Insulin sensitivity-IS)[18] in mouse 3T3L1 preadipocytes.



Scheme 2. Reagents and conditions: (a) ADDP/Ph_3P, THF, ~80%; (b) LiOH, aq MeOH, ~80%.

The two PPAR activities showed different SARs. Table 1 shows the effects of substitution α to the acid, in which the initial evaluations of diastereomeric mixtures showed a trend. The trend suggests the smaller the α substitution the more active the mixture at PPAR-δ and the greater the selectivity over PPAR-α. To reduce the number of chiral centers, we chose to concentrate our efforts on the α-unsubstituted series which also had the best selectivity for PPAR-δ over -α.

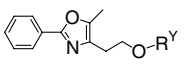
Chromatographic resolution[19] of the remaining chiral center showed that the *S*-enantiomer of **1** had an EC_{50} of 11 nM at PPAR-δ, 2400 nM at PPAR-α, and 246 nM at m-IS (*R*-enantiomer PPAR-δ EC_{50} = 1.3μM). Chiral assignments were confirmed by X-ray. Subsequently, all analogs were made with the (*S*) intermediate (Scheme 1).

The acetic acid substitution of **1** appears to be optimal (Table 1). Substitutions around the indane in the 4, 6, and 7 positions (counting around the indane starting from the acetic acid substituted position) all resulted in inactive compounds (not shown). Replacement of the indane moiety by a six-membered ring led to loss of PPAR-δ activity (**5**), as did replacement by a tetrahydrofuran moiety (**6**). Substitution of the 2 and 3 positions of the indane (**7** and **8**) resulted in weakly active compounds (Table 2).

Extensive SAR work was then devoted to the heterocyclic region and its aryl substituent (Table 3). Starting with the 5-methyloxazole moiety, the 4-substitution on the phenyl ring seemed more desirable for PPAR-δ activity and m-IS, than 3-substitution. Very few compounds were explored with substitution in the 2 position. 2-Substituted compounds were made in previous programs with substitution α to the acid[7] which resulted in compounds with weak PPAR-γ activity when compared to compounds with 3- and 4-substitution. (In the thiazole series the 2-F compound **32**, Table 4, also had weak insulin sensitivity.)

Replacements of the oxazole by thiazoles and imidazoles are shown in Table 4. (Pyrazoles were also prepared, but no compounds made had activity in the insulin sensitivity assay.) The thiazole compounds (**24**–**38**) have comparable PPAR-δ activity and insulin-sensitizing activity to the oxazoles (**9**–**23**) but seem to be generally more

Table 2. SAR of substituted indane acetic acids and other modification to the indane



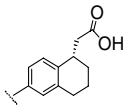
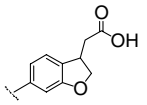
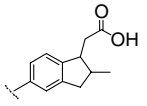
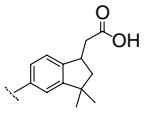
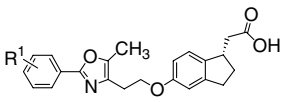
Compound	R^Y	Fret δ EC_{50} (nM)	m-IS EC_{50} (nM)	Fret α EC_{50} (nM)
5		3140 (50%)		2190 (58%)
6		10,000		10,000 (15%)
7		883	5440 (58%)	7470 (11%)
8		6480 (38%)	253 (66%)	10,000 (7.5%)

Table 3. SAR of substitution on the phenyl of 2-phenyl oxazoles



Compound	R^1	Fret δ EC_{50} (nM)	m-IS EC_{50} (nM)	Fret α EC_{50} (nM)
9	H	14	231	2464
10	4-MeO	3	29	798
11	3-MeO	18	82	1890
12	4-Et	3	27	78
13	4-*t*-Bu	21	nd	546
14	4-*i*-Pr	1	33	300
15	3-F	13	371	1690
16	4-F	7	354	504
17	4-Ph	6	45	2718
18	4-Me	4	24	444
19	3-Me	64	101	1152
20	4-CN	35	301	9975
21	3-CN	73	164	10,001
22	3-Cl	13	200	1573
23	4-Cl	3	212	1188

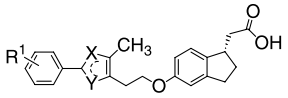
selective versus PPAR-α. The imidazole analogs prefer *N*-substitution on the *Y* position, but substituents larger than a methyl on the imidazole nitrogen were inactive in the m-IS assay (not shown). The methyl analogs made again show a preference for 4-substituted aryls. The reversed oxazoles were also made but lacked insulin-sensitizing activity (not shown). The phenol ether chain was also modified, but 1-carbon and 3-carbon lengths resulted in compounds with modest insulin-sensitizing activity.

Finally, substituents in the 5 position of the oxazoles (R^2, Table 5) were explored. Ethyl substitution increased the selectivity for PPAR-δ over PPAR-α while maintaining the profile of the oxazole series. However, groups larger than ethyl (**50**, **51**) showed decreased activity in the insulin sensitization assay.

The most active and selective compounds were evaluated through in vivo animal models of type II diabetes and dyslipidemia. Preliminary PK studies showed that the oxazoles and thiazoles had good oral exposure when dosed as a suspension at 3 mg/kg, with the thiazole series showing generally better blood levels. In vitro, the thiazoles had similar insulin sensitivity and PPAR-δ activity to the oxazoles but were more selective for PPAR-δ over PPAR-α. Interestingly, when compared in vivo, the oxazoles outperformed the thiazoles in both the type II diabetes model and the dyslipidemia model (perhaps due to increased protein binding of the thiazoles). Compound **17** (3 mg/kg po) lowered blood glucose by the same amount as rosiglitazone (10 mg/kg po) in the db/db mouse model. In the hApoA1 mouse model, compound **17** raised serum HDL by 29% and lowered serum triglycerides by 38% when dosed orally at 30 mg/kg. By comparison, the potent PPAR-δ selective compound GW 501516 raised serum HDL by 30% and lowered serum triglycerides by 33% at 10 mg/kg po. (The higher dose of **17** was required, we believe, because GW 501516 has similar PPAR-δ activity in mouse and human, while **17** is much more active at PPAR-δ in the human than the mouse.)

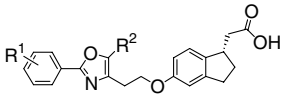
Thus, the in vitro PPAR-δ activity and increases in insulin sensitivity seen with compound **17** seemed to translate well in vivo, and this complementary activity was felt worthy of further investigation. When this series of compounds was explored in toxicology studies no prohibitive findings were observed.

Table 4. SAR of substitution on the phenyl of 2-phenylthiazoles and SAR on the phenyl of 2-phenyl-1-me-imidazoles



Compound	R^1	X	Y	Fret δ (nM)	m-IS (nM) (% agon)	Fret α (nM)
24	H	S	N	11	267 (60%)	10,000
25	4-Me	S	N	0.8	65	594
26	3,4-OCH_2O	S	N	5	66	1210
27	4-MeO	S	N	4	166	3280
28	3-MeO	S	N	61	32	6960
29	4-*i*Pr	S	N	5	25	559
30	4-F	S	N	7	544	2270
31	3-F	S	N	47	140	6530
32	2-F	S	N	116	1620	10,000
33	4-Cl	S	N	1.5	970	10,000
34	4-EtO	S	N	30	165	10,000
35	3-Me	S	N	272	50	6790
36	3-CF_3	S	N	30	45	10,000
37	4-CF_3O	S	N	2	225	7940
38	4-Ph	S	N	13	270	10,000
39	4-Ph	N	NMe	28	71	10,000
40	4-Ph	NMe	N	309	54	10,000
41	4-Et	N	NMe	31	155	10,000
42	4-Et	NMe	N	347	103	10,000
43	4-MeO	N	NMe	86	5560 (41%)	10,000
44	4-MeO	NMe	N	10,000	644 (56%)	10,000
45	H	N	NMe	257	5940 (19%)	10,000
46	H	NMe	N	10,000	608 (55%)	10,000

Table 5. SAR of substitution on the phenyl of 2-phenyloxazoles with substitution on the 5 position of the oxazole



Compound	R^1	R^2	Fret δ EC_{50} (nM)	m-IS EC_{50} (nM) (% agon)	Fret α EC_{50} (nM)
47	H	Et	7	186	10,000
48	4-Me	Et	5	30	1020
49	4-Et	Et	11	35	2530
50	H	Pr	10	3000 (32)	10,000
51	H	PhEt–	607	>3000 (9%)	10,000

Acknowledgments

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17. BAY compounds were incubated with europium-labeled anti-GST antibody, GST-tagged human PPAR-δ ligand binding domain, biotinylated TRAP220 coactivator protein, and streptavidin-labeled APC. The samples were placed in a fluorimeter with an excitation wavelength of 340 nm and emission wavelengths of 615 and 665 nm.
18. *Insulin receptor binding in 3T3-L1 cells treated with compounds:* 3T3-L1 cells were seeded at 9300 cells per well in Costar flat-bottomed TC and incubated for 1 week until they were 2 days post-confluent. The cells were then treated for 2 days with differentiation media (Dulbecco's modified Eagle's medium (DMEM), 100 μg/mL Penicillin/Streptomycin, 2 mM L-Glutamine, 10% Fetal Bovine Serum) containing 0.5 μM human insulin-like growth factor (IGF-1) and test compounds. After treatment, the media were replaced with differentiation media, and the cells were incubated for 4 days. The cells were then assayed for insulin receptor activity. After washing the cells with buffer, they were incubated with 0.1 nM [^{125}I]-insulin and (+/−) 100 nM unlabeled insulin, and incubated at room temperature for 1 h. The cells were then washed 3× with buffer, dissolved with 1 N NaOH, and counted on a γ counter. An EC_{50} value was determined if a plateau was attained and percent maximum stimulation was assessed.
19. Chiral HPLC method: chiralpak AD-H 4.6 × 250 mm. A = hexane (0.4% TFA) B = IPA. 10% B at 1 mL/min. UV = 280 nM.