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Discovery of *para*-alkylthiophenoxyacetic acids as a novel series of potent and selective PPARδ agonists

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Abstract—A novel series of potent and selective PPARδ agonists, *para*-alkylthiophenoxyacetic acids, was identified. The synthesis and structure–activity relationships are described.

The peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors acting as metabolic sensors regulating the expression of genes involved in glucose and lipid homeostasis. Agonists of the PPARα subtype,[1,2] such as LOPID® (gemfibrozil) and TRICOR® (fenofibrate), and agonists of the PPARγ subtype,[3,4] such as AVANDIA® (rosiglitazone maleate) and ACTOS® (pioglitazone HCl), are used for the treatment of dyslipidemia and diabetes, respectively. PPARδ subtype is also involved in lipid metabolism and, unlike the other two PPAR receptors, is ubiquitously expressed, but the highest expression levels are found in tissues with high lipid metabolism including adipose, skeletal muscle, developing brain, intestine, and heart.[5] PPARδ subtype has both distinct and overlapping functions, particularly with PPARα, as there are many common target genes.[6] PPARδ subtype may also act in a regulatory or complimentary manner to PPARα or PPARγ activities based on in vitro and knockout mice studies.[7,8]

The synthesis and development of a potent and selective PPARδ agonist, GW501516, has provided a greater understanding of the role of PPARδ and the potential clinical utility of selective agonists.[9] In obese, dyslipidemic, and hyperinsulinemic rhesus monkeys treatment with GW501516 resulted in an increase in high density lipoprotein cholesterol (HDL-C), a decrease in triglycerides, and an improvement in the atherogenic profile (decreases in small dense LDL particles) with little effect on glucose (although insulin levels were decreased in monkeys).[9] The increase in HDL-C was attributed to gene induction by PPARδ activation of the ABC-A1 transporter, a key gene involved in reverse cholesterol transport and HDL-C metabolism. There was also an increase in cholesterol efflux in lipid-loaded macrophages, further implicating a role for PPARδ in modulating HDL-C levels and reverse cholesterol transport. In early clinical studies with normal male volunteers, GW501516 increased circulating HDL-C and decreased triglycerides, although the decrease in triglycerides was not statistically significant.[10] On the other hand, in overweight, dyslipidemic males with the metabolic syndrome, treatment with GW501516 had no marked effect on HDL-C but rather significantly decreased plasma total cholesterol, apolipoprotein B levels and improved remnant particle clearance.[11] These data indicate that PPARδ agonists may have clinical utility in the treatment of dyslipidemia, obesity, and diabetes, and may complement the actions of existing therapies such as the widely used statins.

The structures of GW501516 and another published PPARδ agonist, L-165041, are shown in Figure 1.[12] Compared with the PPARα and γ subtypes, reports on selective PPARδ agonists remain limited,[13] and new potent and selective agonists are needed to shed light on the further understanding of pharmacological responses to the PPARδ activation. In this paper, we report the identification of the Y-shaped molecules (listed in Table 1) as highly potent and highly selective PPARδ agonists.

Keywords: PPARδ agonists; Y-shaped molecules; Dyslipidemic.
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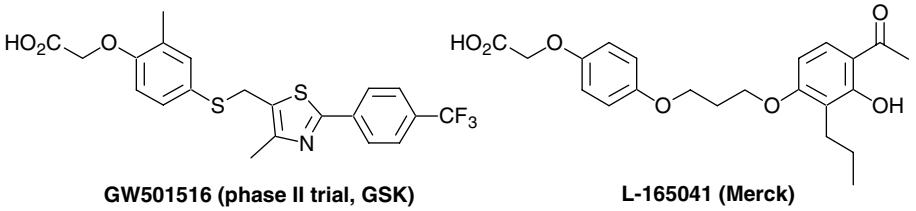
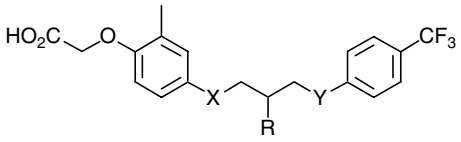


Figure 1. Structures of selective PPARδ agonists.

Table 1. Activity of compounds **1**–**19** in cell based transactivation assay against human PPARδ receptor[a]



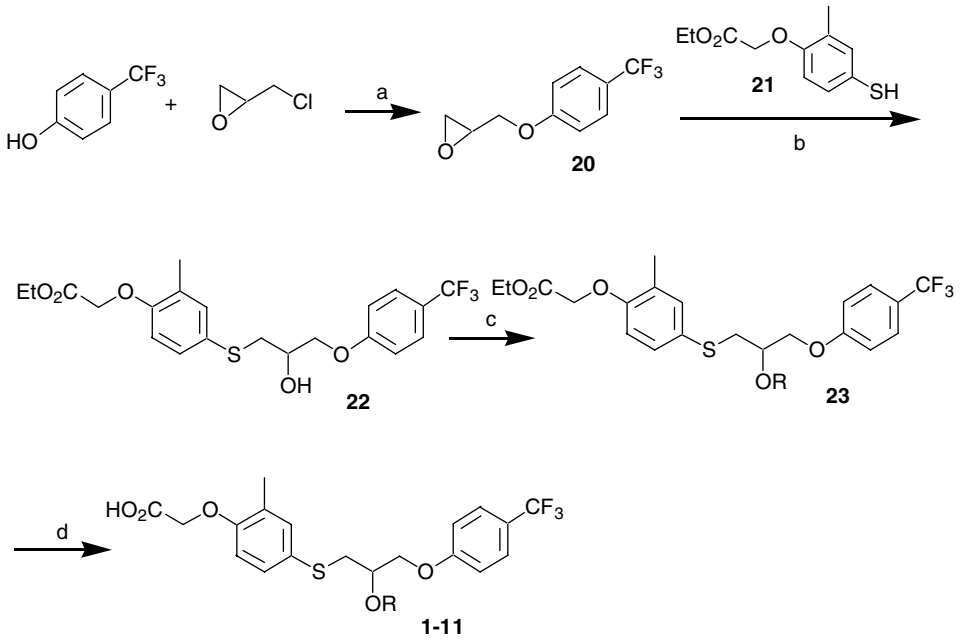
Compound	X	Y	R	Human PPARδEC50 (nM)	Efficacy (%)
1	S	O	OH	79.0	114
2	S	O	OMe	18.8	95
3	S	O	OEt	3.4	98
3*R* [b]	S	O	OEt(*R*)	1.9	105
3*S* [b]	S	O	OEt(*S*)	25.0	93
4	S	O	O(*n*-Pr)	4.3	104
5	S	O	O(*n*-Bu)	7.0	105
6	S	O	OAllyl	3.9	97
7	S	O	OMOM	6.3	94
7*R* [b]	S	O	OMOM(*R*)	2.1	98
7*S* [b]	S	O	OMOM(*S*)	70.0	77
8	S	O	OBn	60.0	107
9	S	O	OCH_2CO_2H	126	84
10	S	O	O(4-methoxylphenyl)	62.1	95
11	S	O	O(4-*n*-propylcarbonylphenyl)	23.9	93
12	S	O	CH_2OEt	4.6	87
13	S	O	CH_2O(4-trifluoromethylphenyl)	17.0	79
14	S	O	Me	7.4	81
15	S	O	Et	0.06	109
15*R* [b]	S	O	Et(*R*)	0.03	102
16	S	CH_2	OEt	6.9	102
17	S	CH_2	OMSM	15.2	103
18	O	O	OEt	24.3	102
19	S=O	O	OEt(*R*)	>3000	3.4
GW501516				1.0[c]	

[a] EC_{50}s of all the compounds are >1 μM in PPARα and PPARγ assays.
[b] *R* and *S* represent the absolute configurations, respectively. ee% > 99%.
[c] The data was reported in Ref. 12b.

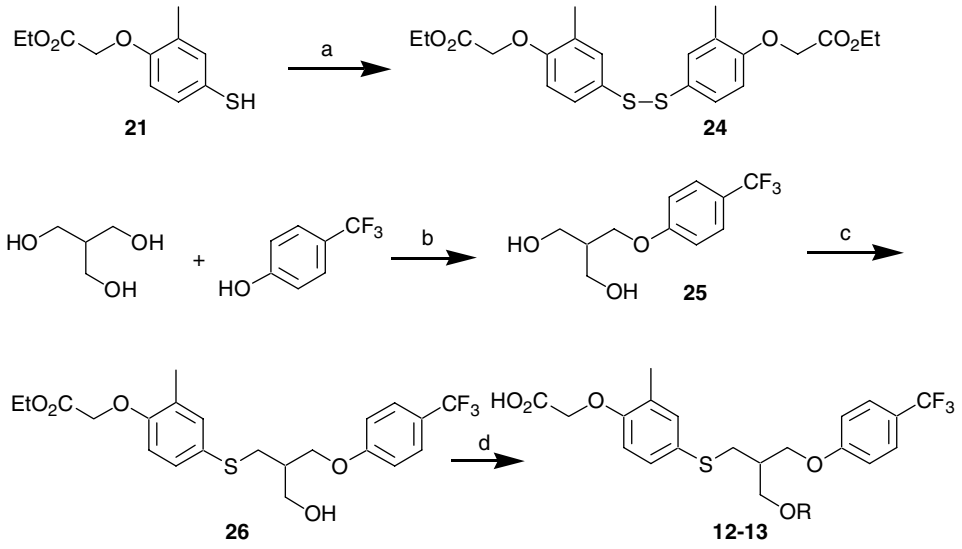
The general synthesis of compounds **1**–**11** is outlined in Scheme 1. The epoxide **20** was obtained from *para*-trifluoromethylphenol and epichlorohydrin under basic condition.[14] The epoxide opening[15] with thiophenol **21**[16] prepared by reduction of the corresponding sulfonyl chloride with tin in refluxing HCl ethanol solution afforded the common intermediate alcohol **22**. Alkylation of the alcohol **22** and subsequent hydrolysis of the ester **23** yielded compounds **1**–**11**. The enantiomeric compounds **3R**, **3S** and **7R**, **7S** were derived from the corresponding enantiomeric epoxides **20**, which were obtained from the corresponding enantiomeric epoxypropanol and trifluoromethylphenol under Mitsunobu condition. Compounds **16**–**18** were synthesized in a similar fashion to Scheme 1.

Scheme 2 illustrates the synthesis of compounds **12**–**13**. Dimerization[17] of **21** to give **24** was affected by $Ba(MnO_4)_2$ in high yield. The diol **25**, generated from 2-(hydroxymethyl)-1,3-propanediol by Mitsunobu reaction, reacted with disulfide **24** in the presence of n-Bu_3P in pyridine providing monoalcohol **26**.[18] Subsequent transformations of the intermediates gave the compounds **12** and **13**.

Preparations of compounds **14**, **15**, and **15*R*** are exemplified by the synthesis of **15*R*** in Scheme 3. The enantiomeric alcohol **27** was prepared according to literature procedures.[19] Protection of the hydroxyl group with TBSCl followed by reduction of the ester with DIBALH gave alcohol **28**. Activation of the



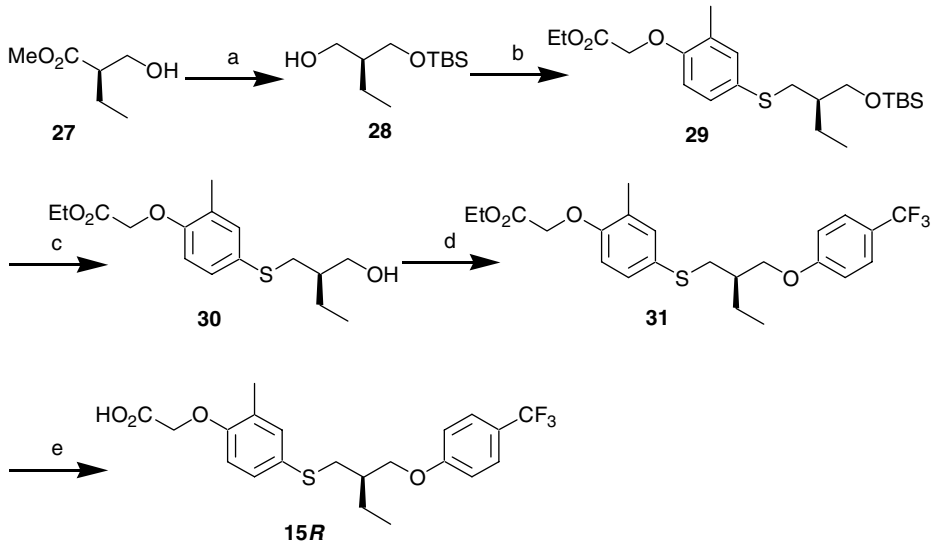
Scheme 1. Reagents and condition: (a) Cs_2CO_3, dioxane, 100 °C 80%; (b) TBAF (cat), THF, 85%; (c) NaH, RI, THF or DMF for esters of **2–5**, **8–9,** 10–80%; *i*Pr_2NEt, RBr or MOMCl, THF for esters of **6–7**, 58–79%; ADDP, Ph_3P, phenol, CH_2Cl_2 for esters of **10–11**, 68–73%; (d) LiOH, H_2O, THF, 90–95%.



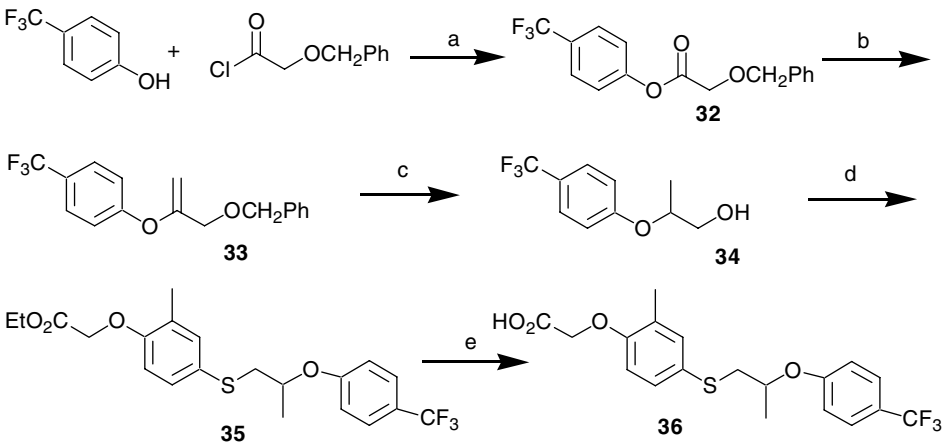
Scheme 2. Reagents: (a) $Ba(MnO_4)_2$, CH_2Cl_2, 89%; (b) DIAD, Ph_3P, DMF, THF, 17%; (c) *n*-Bu_3P, **24**, Py, 55%; (d) i—NaHMDS, EtOTf, THF for the ethyl ester of **12**, 47%; DIAD, Ph_3P, *para*-trifluoromethylphenol for the ethyl ester of **13**, 79%; ii—LiOH, H_2O, THF, 84–88%.

hydroxyl group as mesylate followed by nucleophilic replacement with thiophenol under basic condition yielded sulfide **29**. After removal of TBS group, Mitsunobu reaction gave compound **31**, which led to acid **15*R*** upon hydrolysis.

All the compounds investigated show weak activity in both PPARα and PPARγ assays ($EC_{50} > 1$ μM). The PPARδ functional transactivation data for compounds **1–18** are listed in Table 1, and the structure–activity relationship (SAR) is summarized here. First, ethoxy group (compound **3**) seems to be preferred among the alkoxyl substituents examined (compounds **1–7**). The best side chain, however, is the simple ethyl group with subnanomolar potency (compounds **15** and **15*R***). Second, branching with phenyl rings on the side chain (compounds **8**, **10**, **11**, and **13**) diminishes the potency, so does the polar group (compound **9**). Third, the molecules with X = S, Y = CH_2 (compounds **16–17**) are inferior to the counterparts with X = S and Y = O (compounds **3** and **7**). Fourth, replacement of the sulfur atom with sulfoxide reduces the potency dramatically. For example, the sulfoxide **19**, readily available by oxidation of corresponding sulfide **3** with hydrogen peroxide, shows greater than 3 μM EC_{50}. Finally, the molecules with *R* configuration are at least 13-fold more potent



Scheme 3. Reagents: (a) i—TBSCl, Imidazole, 92%; ii—DIBALH, 88%; (b) i—MsCl, Et_3N; ii—Cs_2CO_3, **21**, 61%; (c) TBAF, 81%; (d) DIAD, Ph_3P, *para*-trifluoromethylphenol, 69%; (e) LiOH, 88%.



Scheme 4. Reagents: (a) Et_3N, 94%; (b) Tebbe reagent, THF, 80%; (c) Pd/C, H_2, EtOH, THF, 91%; (d) MsCl, Et_3N; Cs_2CO_3, **21**, 11%; (e) LiOH, H_2O, THF, 62%.

than the corresponding *S* enantiomers (compounds **3*R*** versus **3*S*** and **7*R*** versus **7*S***).

In addition, we investigated the effect of the backbone length on the PPARδ potency. To that end, compound **36** was synthesized (Scheme 4). Olefination[20] of the ester **32** with Tebbe reagent yielded enol ether **33**. Concurrent reduction of the enol ether and removal of the benzyl group was achieved by Pd-C and H_2 to give alcohol **34**. Activation of the hydroxy group and subsequent displacement with thiophenol **21** produced sulfide **35**, which was then hydrolyzed to acid **36**. A dramatic drop in potency (EC_{50} of this analog is 211 nM) was observed by the removal of one methylene group, suggesting the backbone length is critical to achieving good potency.

In summary, we identified a novel series of highly potent and highly selective PPARδ agonists with the Y-shaped structure. However, it seems to us that the Y-shaped molecules with a short side arm are better than those with larger aryl groups. The compound **15*R***, for example, is very potent and possesses a favorable pharmacokinetic (PK) profile. The oral bioavailability in rat is 84% with high maximum plasma concentration (C_{max} = 8872 ng/mL), rapid oral absorption (T_{max} = 0.5 h), high plasma exposure (AUC = 13567 ng-h/mL), and long plasma duration ($t_{1/2}$ = 8.2 h). In addition, we also demonstrated that the lengths of both backbone and side chain, as well as the chirality at the Y intersection, are all pivotal to PPARδ agonist activity.

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