Synthesis and Identification of [1,2,4]Thiadiazole Derivatives as a New Series of Potent and Orally Active Dual Agonists of Peroxisome Proliferator-Activated Receptors α and δ

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Cardiovascular disease is the most common cause of morbidity and mortality in developed nations. To effectively target dyslipidemia to reduce the risk of cardiovascular disease, it may be beneficial to activate the peroxisome proliferator-activated receptors (PPARs) PPARα and PPARδ simultaneously through a single molecule. Replacement of the methylthiazole of **5** (the PPARδ selective agonist) with [1,2,4]thiadiazole gave compound **13**, which unexpectedly displayed submicromolar potency as a partial agonist at PPARα in addition to the high potency at PPARδ. Optimization of **13** led to the identification of **24** as a potent and selective PPARα/δ dual agonist. Compound **24** and its close analogs represent a new series of PPARα/δ dual agonists. The high potency, significant gene induction, excellent PK profiles, and good in vivo efficacies in three animal models may render compound **24** as a valuable pharmacological tool in elucidating the complex roles of PPARα/δ dual agonists and as a potential treatment of the metabolic syndrome.

Introduction

Cardiovascular disease (CVD[a]) is the most common cause of morbidity and mortality in developed nations.[1] Atherogenic dyslipidemia, characterized by an abnormal circulating lipid profile, including low levels of high-density lipoprotein cholesterol (HDL-C), elevated levels of small-dense low-density lipoprotein cholesterol (LDL-C), or elevated triglycerides (TG), is often found in patients who are obese, have type 2 diabetes, or the metabolic syndrome.[2−4] These individuals are at high risk for premature CVD. While LDL-C is prone to accumulate in the arterial wall, leading to the formation of atherosclerotic cholesterol-laden foam cells,[5] HDL-C may play a protective role in removing excess cholesterol from peripheral cells and returning it to the liver.[6]

The peroxisome proliferator-activated receptors (PPARs) belong to the nuclear hormone receptor superfamily and consist of three members, PPARα, PPARγ, and PPARδ. PPARα is expressed mainly in tissues involved in lipid oxidation such as liver, kidney, adrenal glands, cardiac muscle, and skeletal muscles. PPARα regulates the expression of genes involved in lipid metabolism.[7] The fibrate drugs, such as fenofibrate **1** and ciprofibrate **2** (Figure 1), have been used for the clinical treatment of dyslipidemia by lowering serum triglycerides and free fatty acid (FFA) levels and raising HDL-C since the 1970s.[8] Several studies have provided evidence that the hypolipidemic effect of the fibrate drugs is attributed to the activation of PPARα.[9] PPARγ is expressed in adipose tissue, macrophages, and vascular smooth muscles.[7] PPARγ was identified as a key regulator for insulin sensitivity, and two PPARγ agonists, rosiglitazone **3** and pioglitazone **4**, have been used for the clinical treatment of type 2 diabetes since 1999.[10] In contrast, the biological role of PPARδ and the potential clinical utility of its ligand were unclear, in part, due to its broad tissue expression[11] and lack of good chemical tools to study its pharmacology. Recently, a potent and selective PPARδ agonist, **5** (GW501516, phase II clinical trial), was developed and shown to increase plasma HDL-C levels together with decreasing LDL-C and triglycerides in obese and dyslipidemic rhesus monkeys.[12] In addition, while one study supported an atheroprotective effect of PPARδ agonists in $LDLR^{-/-}$ mice,[13] other data suggested that PPARδ activation may attenuate the metabolic syndrome, including obesity.[14] To effectively target dyslipidemia to reduce the risk of cardiovascular diseases, it may be beneficial to activate PPARα and PPARδ simultaneously through a single molecule. To date, there are only two series of PPARα/δ dual agonists [**6** (GW2433)[15] and **7**[16]] with in vitro data reported. This paper describes our finding of [1,2,4]-thiadiazole derivatives as a new series of potent and orally active PPARα/δ dual agonists.

Chemistry

The synthesis of the first target molecule **13** is shown in Scheme 1. Cyclocondensation of 4-trifluoromethylbenzamide **8** with chlorocarbonylsulfenyl chloride at 60 °C gave the [1,3,4]-oxathiazol-2-one **9** intermediate. Reaction of **9** with ethyl cyanoformate at 160 °C with the extrusion of CO_2 provided the desired [1,2,4]thiadiazole-5-carboxylic acid ethyl ester **10**. Reduction of the ethyl ester with $NaBH_4$ resulted in the formation of primary alcohol **11**. Conversion of **11** to its mesylate, followed by S-alkylation with thiophenoxide **12**[17] and base hydrolysis of the ethyl ester, gave the desired target molecule **13**.

The synthesis of its geminal dimethyl analog **15** is shown in Scheme 2. Conversion of **11** to the mesylate, followed by S-alkylation with 4-mercapto-2-methylphenol, provided phenol **14**. O-Alkylation of **14** with 2-bromoisobutyric acid gave the

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[a] Abbreviations: CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PPARs, peroxisome proliferator-activated receptors; FFA, free fatty acid; TG, triglycerides; FXR, farnesoid X receptor; LXR, liver X receptor; RXR, retinoic acid X receptor; GR, glucocorticoid receptor; RAR, retinoic acid receptor; ABC-A1, ATP-binding cassette transporter A1; CPT-1, carnitine palmitoyltransferase type1; DMAP, (dimethylamino)pyridine; TFA, trifluoroacetic acid; NMP, 1-methyl-2-pyrrolidinone; DPPA, diphenylphosphoryl azide.

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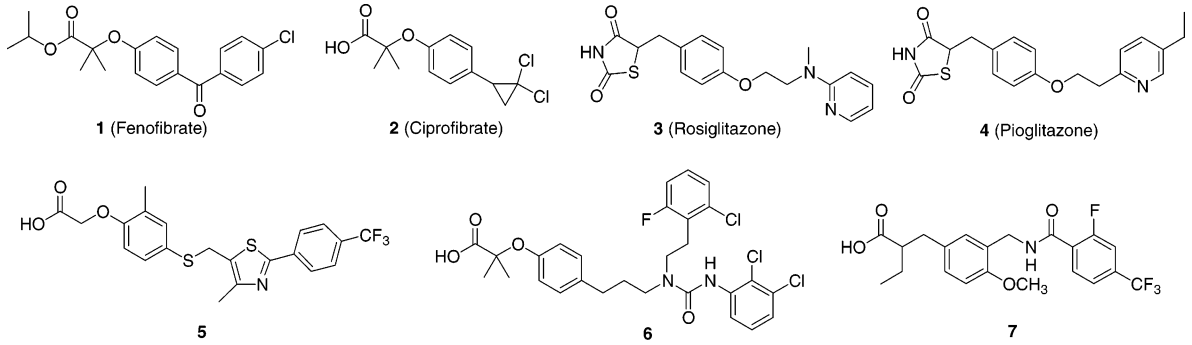
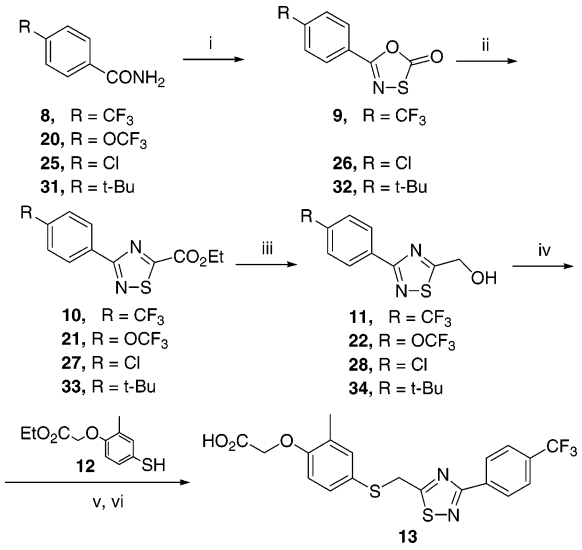


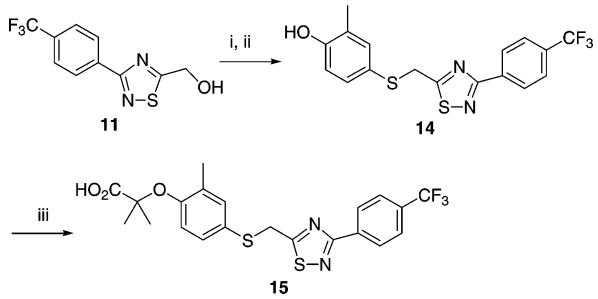
Figure 1. Structures of representative PPAR agonists: PPARα (**1**, **2**), PPARγ (**3**, **4**), PPARδ (**5**), and PPARα/δ (**6**, **7**).

Scheme 1[a]



[a] (i) Chlorocarbonylsulfenyl chloride, toluene, 60 °C, 39−70%; (ii) ethyl cyanoformate, 1,2-dichlorobenzene, 160 °C, 81−97%; (iii) $NaBH_4$, EtOH, 70−100%; (iv) MsCl, Et_3N, CH_2Cl_2; (v) **12**, CH_3CN, Cs_2CO_3, 64% (two steps); (vi) NaOH, MeOH−H_2O, 97%.

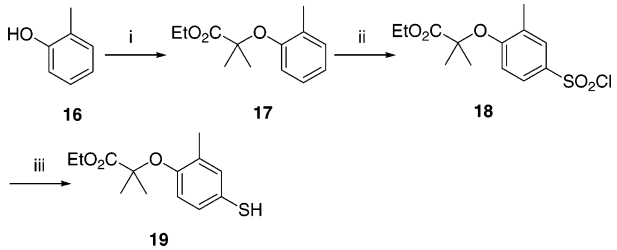
Scheme 2[a]



[a] (i) MsCl, Et_3N, CH_2Cl_2; (ii) 4-mercapto-2-methylphenol, CH_3CN, Cs_2CO_3, 95% (two steps); (iii) NaH, THF, 60 °C, 2-bromoisobutyric acid, 21%.

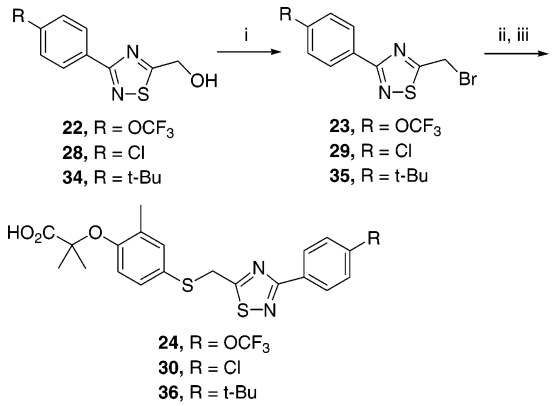
desired compound **15**. The synthesis of the corresponding OCF_3 analog **24**, Cl analog **30**, or *t*-Bu analog **36** could also be accomplished in a slightly different manner when compared to that of CF_3 analog **15**. Therefore, we first prepared the thiophenoxide **19**, followed by S-alkylation of the right-hand biheteroaryl moiety to give **24**, **30**, or **36**. The synthesis of **19** is shown in Scheme 3. O-Alkylation of 2-methylphenol **16** with 2-bromo-2-methylpropionic acid ethyl ester generated **17**. Treatment of **17** with excess $ClSO_3H$ at 0 °C, with the temperature being allowed to warm to 20 °C slowly, gave the chlorosulfonyl derivative **18**. Reduction of **18** with $SnCl_4$ provided the thiophenoxide **19** in quantitative yield. The required key

Scheme 3[a]



[a] (i) $EtO_2CC(Me)_2Br$, Cs_2CO_3, dioxane, 100 °C, 68%; (ii) $ClSO_3H$, 0−20 °C, 47%; (iii) $SnCl_4$, HCl, EtOH, reflux, 100%.

Scheme 4[a]



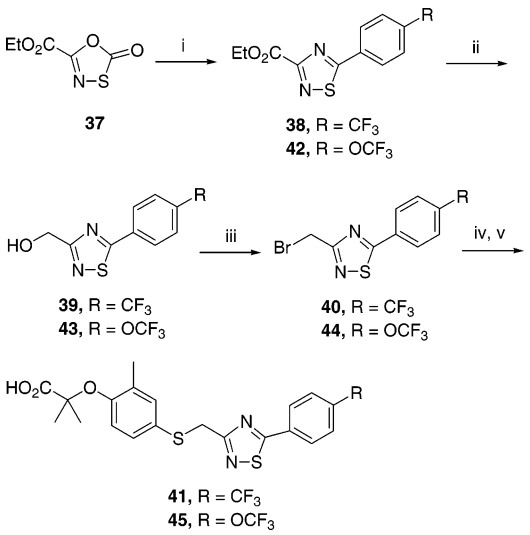
[a] (i) PPh_3, CBr_4, CH_2Cl_2, 0−20 °C, 55−81%; (ii) **19**, CH_3CN, Cs_2CO_3; (iii) NaOH, MeOH−H_2O, 47−74% (two steps).

intermediate **22** needed for the synthesis of the OCF_3 analog **24** was prepared in the same method as that of **11** (Scheme 1). Once the alcohol **22** was obtained, reaction of **22** with PPh_3/CBr_4 afforded the primary bromide **23** smoothly (Scheme 4). S-Alkylation of **23** with thiophenoxide **19**, followed by base hydrolysis, generated the OCF_3 analog **24**. The synthesis of Cl analog **30** and *t*-Bu analog **36** is identical to that of **24**.

The synthesis of reverse-thiadiazole analog **41** (or **45**) is shown in Scheme 5. Reaction of 2-oxo[1,3,4]oxathiazole-5-carboxylic acid ethyl ester **37**[18] with 4-trifluoromethylbenzonitrile at 160 °C provided [1,2,4]thiadiazole-3-carboxylic acid ethyl ester **38**. Reduction of **38** with $NaBH_4$ generated the alcohol **39**. Reaction of **39** with PPh_3/CBr_4 afforded the bromide **40**, followed by S-alkylation with **19**, and base hydrolysis provided desired target **41**.

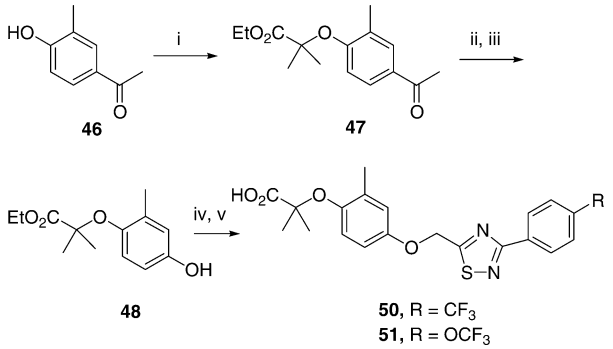
The synthesis of oxygen-link target **50** (or **51**) is shown in Scheme 6. O-Alkylation of phenol **46** with 2-bromo-2-methylpropionic acid ethyl ester gave **47**. Oxidation of **47** with *m*-CPBA, followed by base hydrolysis, provided phenol **48**. Alkylation of **48** with the bromide **49** (or **23**), followed by base hydrolysis, afforded target **50** (or **51**).

Scheme 5[a]



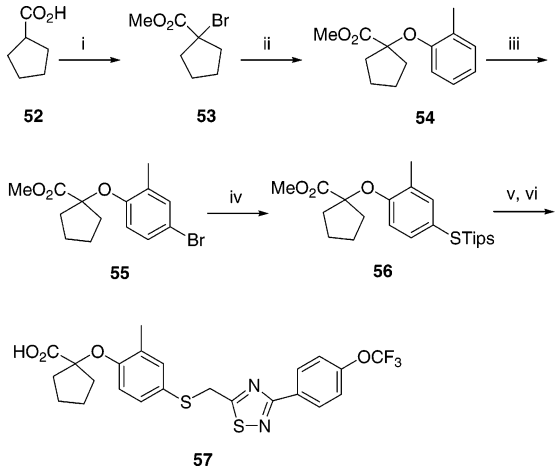
[a] (i) 4-Trifluoromethylbenzonitrile, 1,2-dichlorobenzene, 160 °C, 4−34%; (ii) $NaBH_4$, EtOH, 93−94%; (iii) PPh_3, CBr_4, CH_2Cl_2, 0−20 °C, 72−87%; (iv) **19**, CH_3CN, Cs_2CO_3. (v) NaOH, MeOH−H_2O, 50−74% (two steps).

Scheme 6[a]



[a] (i) 2-Bromo-2-methylpropionic acid ethyl ester, Cs_2CO_3, dioxane, 100 °C, 57%; (ii) *m*CPBA, TsOH, CH_2Cl_2, 38 °C, 82%; (iii) NaOEt, EtOH−THF, 81%; (iv) **49** (or **23**), CH_3CN, Cs_2CO_3; (v) NaOH, MeOH−H_2O, 71−72% (two steps).

Scheme 7[a]



[a] (i) $ClSO_3H$, Br_2, 1,2-dichloroethane, reflux; MeOH, 86%; (ii) 2-methylphenol, CH_3CN, Cs_2CO_3,70 °C, 22%; (iii) NBS, CH_3CN, 95%; (iv) NaH, toluene, triisopropylsilanethiol, $Pd(PPh_3)_4$, THF, 90 °C, 82%; (v) **23**, TBAF, THF, 0 °C, 94%; (vi) NaOH, MeOH−H_2O, 68%.

The synthesis of cyclopentyl analog **57** is shown in Scheme 7. Treatment of cyclopentanecarboxylic acid **52** with $ClSO_3H$ and Br_2 gave bromide **53**. Alkylation of **53** with 2-methylphenol, followed by bromination with NBS, afforded bromide **55**. Reaction of **55** with triisopropylsilanethiol in the presence of $Pd(PPh_3)_4$ gave the thio analog **56**. S-Alkylation of **56** with bromide **23** in the presence of TBAF, followed by base hydrolysis, resulted in the target **57**.

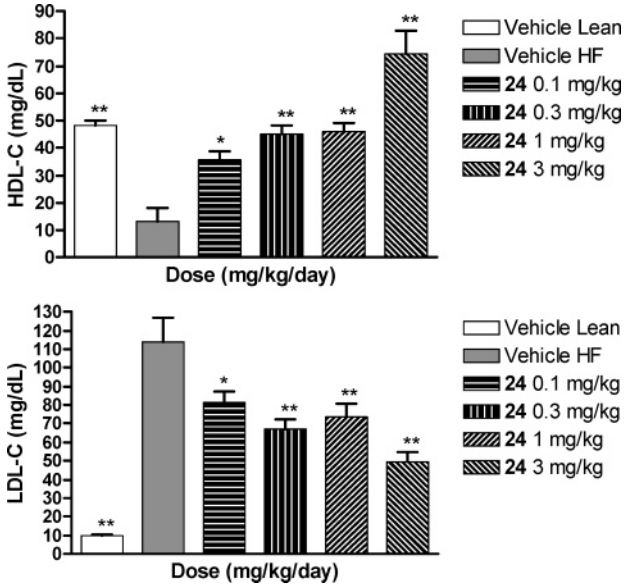


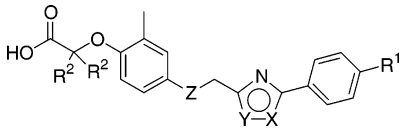
Figure 2. Effects of **24** on serum HDL-C and LDL-C levels in hypercholesterolemic rat treated via oral gavage (0.1−3 mg/kg) for 8 days. Bars represent means ± SEM ($n = 8$ rat per group; $*p < 0.05$, $**p < 0.01$ relative to vehicle HF).

Results and Discussion

Lead Generation. During this study, HEK293 cells were grown in DMEM/F-12 medium supplemented with 10% FBS and glutamine. The cells were cotransfected with DNA constructs containing the ligand-binding domains of either PPARα, PPARγ, or δ-Gal4 chimeric receptors. The steady-Glo luciferase assay kit was used for measuring luciferase reporter activity. Percent efficacies for PPARα, PPARδ, and PPARγ activation were reported relative to PPARα agonist (compound **2.1**),[19] PPARδ agonist (compound **f**),[20] and rosiglitazone, respectively.

A primary goal of our PPARs research programs has been the identification of a functionally potent and selective PPARδ agonist with optimal in vivo efficacy and maximum safety margin. Since **5** is the first reported potent and selective PPARδ agonist, we were interested in conducting structure−activity relationship (SAR) studies with respect to **5** as the lead molecule. It seems that the methyl-substituted thiazole of **5** may contribute uniquely to its high functional potency and selectivity at PPARδ; therefore, we first screened various five-membered or six-membered heteroaryls or heterocycles in all three human PPARs cotransfection assays to see if we could uncover any new series that may meet our program goal. In summary, replacement of the methylthiazole of **5** with [1,2,4]thiadiazole gave compound **13**. Unexpectedly, **13** displayed submicromolar potency as a partial agonist at PPARα ($EC_{50} = 468$ nM, 42%, Table 1) in addition to the retained high potency and high activity at PPARδ ($EC_{50} = 10$ nM, 79%) and no activity at PPARγ ($EC_{50} > 3000$ nM). Therefore, while maintaining the similar shape and size of the entire molecule, a simple replacement of the methylthiazole to the thiadiazole resulted in the conversion of a highly potent and selective PPARδ agonist (~1000-fold selectivity as shown in **5**, Table 1) to a PPARα/δ dual agonist (only ~47-fold selectivity for δ over α as observed in **13**). Since geminal dimethyl substitution of the acidic head moiety appears to be

Table 1. Activities of Compounds in Human PPAR Co-Transfection Assays



						EC_{50} (SEM,[a] nM (% resp)		
compd	R^2	Z	Y	X	R^1	PPARα[b]	PPARδ[c]	PPARγ[d]
13	H	S	S	N	CF_3	468 ± 10 (42)	10 ± 2 (79)	>3000
15	CH_3	S	S	N	CF_3	79 ± 9 (51)	6 ± 2 (76)	407 ± 31 (25)
24	CH_3	S	S	N	OCF_3	33 ± 1 (44)	3 ± 1 (73)	>3000
30	CH_3	S	S	N	Cl	186 ± 10 (38)	18 ± 2 (72)	>3000
36	CH_3	S	S	N	t-Bu	64 ± 13 (64)	93 ± 7 (48)	>3000
41	CH_3	S	N	S	CF_3	425 ± 12 (38)	26 ± 3 (67)	>3000
45	CH_3	S	N	S	OCF_3	656 ± 13 (47)	58 ± 3 (55)	>3000
50	CH_3	O	S	N	CF_3	94 ± 2 (71)	3 ± 1 (79)	>3000
51	CH_3	O	S	N	OCF_3	94 ± 7 (80)	12 ± 2 (83)	>3000
57		S	S	N	OCF_3	736 ± 16 (31)	>1000	>3000
5						1100[e]	1[e]	850[e]

[a] EC_{50} is the concentration of test compounds needed to induce 50% of the maximum luciferase activity. The EC_{50} value is the average of more than two separate tests. SEM: standard error of the mean. [b] The internal PPARα agonist (compound **2.1**)[19] was used as the standard. [c] The internal PPARδ agonist (compound **f**)[20] was used as the standard. [d] Rosiglitazone was used as the standard. [e] The data was reported in ref 17c.

Table 2. Induction of Selected Target Genes by **24** in Primary Human Skeletal Muscle Cells

concn, nM	ABC-A1	CPT-1	Pa9
1	1.9 ± 0.3[a]	3 ± 0.9	4.1 ± 1
10	2 ± 0.1	2.6 ± 0.5	6.5 ± 0.2
100	4.7 ± 1.3	5.9 ± 0.7	9.9 ± 1.2
1000	5.4 ± 0.2	11.4 ± 3.2	22.4 ± 5.4

[a] Fold increase over vehicle were expressed as mean ± SEM (standard error mean) of triplicate samples.

beneficial for many PPARα agonists, including **1**, **2**, and **6**, we decided to explore PPARs activities of the geminal dimethyl analog of **13**. Indeed, **15** displayed 6-fold improved potency at PPARα (EC_{50} = 79 nM, 51%) and even slightly higher potency at PPARδ (EC_{50} = 6 nM, 76%) compared to that of **13**. Meanwhile, **15** also exhibited submicromolar potency but with low activity at PPARγ (EC_{50} = 407 nM, 25%). Overall, with the incorporation of the additional geminal dimethyl group to the [1,2,4]thiadiazole series, **15** displayed better potency at both PPARα and PPARδ than the corresponding CH_2 analog **13**. This observation is also consistent with another PPARδ agonist series reported recently.[21]

We then examined the impact of other phenyl ring substituents on PPARs activities. Replacing the CF_3 substituent with OCF_3 gave **24**. Interestingly, OCF_3 analog **24** displayed ~2-fold higher potency at PPARα (EC_{50} = 33 nM, 44%) and ~2-fold higher potency at PPARδ (EC_{50} = 3 nM, 73%), but with abolished activity at PPARγ (EC_{50} > 3000 nM) compared to CF_3 analog **15**. Up to this point, **24** behaves as a quite potent and selective PPARα/δ dual agonist. It is unclear if the high potency of **24** observed at both PPARα and PPARδ may derive from the increasing steric bulk of OCF_3 or from the H-bond-acceptor capability of the oxygen atom. We thus prepared sterically less bulky Cl analog **30** and sterically more bulky *t*-Bu analog **36** to get more insights. Compound **30** exhibited >2-fold reduced potency at PPARα (EC_{50} = 186 nM, 38%) and 3-fold reduced potency at PPARδ (EC_{50} = 18 nM, 72%) and maintained no activity at PPARγ (EC_{50} > 3000 nM) compared to that of CF_3 analog **15**. Meanwhile, **36** displayed about equal potency with higher activity at PPARα (EC_{50} = 64 nM, 64%) and 16-fold reduced potency with lower activity at PPARδ (EC_{50} = 93 nM, 48%) compared to that of CF_3 analog **15**. From these four examples (**15**, **24**, **30**, and **36**), it seems the high potency observed at both PPARα and PPARδ of **24** may not derive from the steric bulkiness at the 4-position of the phenyl group.

We turned our interest to examine the reverse-[1,2,4]-thiadiazole series to see if the specific orientation of the five-membered thiadiazole ring is critical to the potency or selectivity observed at PPARs. The representative CF_3 analog **41** and OCF_3 analog **45** of reverse-[1,2,4]thiadiazole were thus synthesized. Compound **41** displayed 5-fold reduced potency with slightly lower activity at PPARα (EC_{50} = 425 nM, 38%) and 4-fold reduced potency at PPARδ (EC_{50} = 26 nM, 67%) compared to that of **15**. Even with the assumed more favorable OCF_3-substituent, **45** displayed 8-fold reduced potency at PPARα (EC_{50} = 656 nM, 47%) and 10-fold reduced potency at PPARδ (EC_{50} = 58 nM, 55%) compared to that of **15**. It appears that the reverse-[1,2,4]thiadiazole analogs may not have the favorable interactions with the ligand-binding pockets of PPARα and PPARδ as the [1,2,4]thiadiazole analogs have.

Since the oxygen atom may behave as the bioisostere of the sulfur atom in some cases, we decided to synthesize the oxygen-link analogs of **15** and **24**. Compound **50**, the oxygen-link CF_3 analog, exhibited slightly lower potency but higher activity at PPARα (EC_{50} = 94 nM, 71%) and ~2-fold higher potency at PPARδ (EC_{50} = 3 nM, 79%) compared to that of the sulfur-link CF_3 analog **15**. Therefore, the replacement of a sulfur atom with an oxygen atom led to an interesting potent PPARα/δ dual agonist **50**, although it is not as potent as **24** at PPARα. Replacing the CF_3 substituent with OCF_3 in the oxygen-link series resulted in the formation of **51**. Compound **51** exhibited slightly lower potency but higher activity at PPARα (EC_{50} = 94 nM, 80%) and ~2-fold reduced potency at PPARδ (EC_{50} = 12 nM, 83%) compared to that of **15**. Overall, in the oxygen-link series, the OCF_3 analog **51** does not seem to have more favorable interaction with the ligand-binding pockets of PPARα and PPARδ than that of the CF_3 analog **50**. This observation is not consistent with the previous result observed between CF_3 analog **15** and OCF_3 analog **24** in the sulfur-link series. The nonparallel SAR suggests that the oxygen atom is not an equivalent bioisostere to the sulfur atom in this series.

Since we already demonstrated that the incorporation of the geminal dimethyl group in the acidic head moiety improved

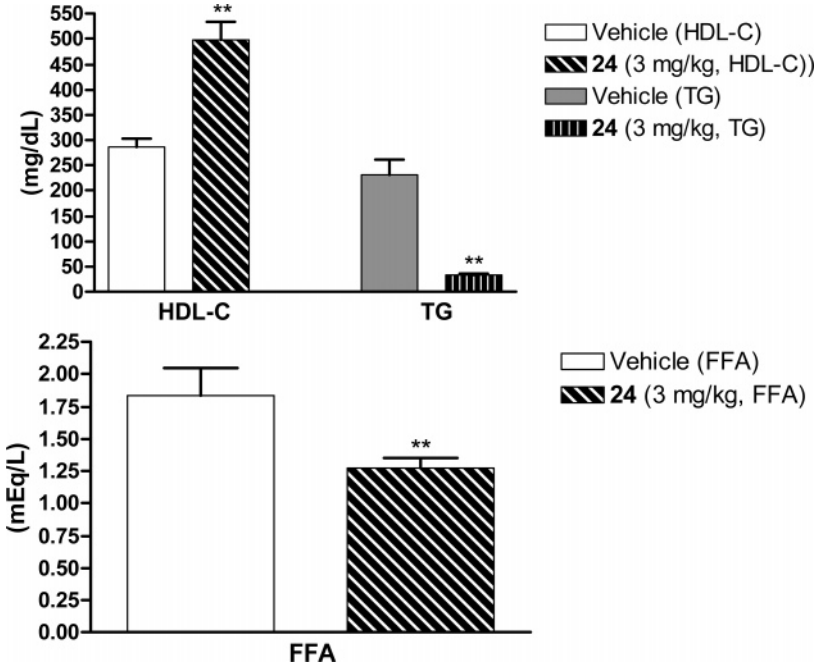


Figure 3. Effects of **24** on HDL-C, TG, and FFA levels in male hApoA1 transgenic mice dosed orally (3 mg/kg) for 7 days. Bars represent means ± SEM ($n = 8$ mice per group; $*p < 0.05$, $**p < 0.01$ relative to vehicle control).

the potencies at both PPARα and PPARδ (**15** versus **13**), we would like to see if we could further enhance the potency by introducing a sterically bulkier group. Unfortunately, installation of a cyclopentyl group as in **57** not only lowered the potency and the activity at PPARα ($EC_{50} = 736$ nM, 31%) but also abolished the activities at both PPARδ ($EC_{50} > 1000$ nM) and PPARγ ($EC_{50} > 3000$ nM). In summary, as compared to **5**, these [1,2,4]thiadiazole derivatives appear as a new series of potent and selective PPARα/δ dual agonists. In addition, there was no cross-activity of **24** against several nuclear hormone receptors, such as farnesoid X receptor (FXR), liver X receptor (LXR), retinoic acid X receptor (RXR), glucocorticoid receptor (GR), and retinoic acid receptor (RAR).

To determine the activity of these compounds on the human receptor, we employed real time PCR to measure the expression levels of a panel of genes involved in lipid metabolism and energy expenditure. The cell types utilized in these experiments were primary human skeletal muscles cells. To date, **24** induced several target genes in a dose-dependent manner (Table 2). For example, a robust induction of ATP-binding cassette transporter A1 (ABC-A1)[22] by **24** was detected in skeletal muscles (1.9-fold increase at 1 nM to 5.4-fold increase at 1000 nM). Since ABC-A1 is involved in lipid and protein metabolism, the induction of this gene by **24** suggests PPARα/δ dual agonists may play an important role in this function. Meanwhile, a significant induction of carnitine palmitoyltransferase type 1 (CPT-1)[23] by **24** (3-fold at 1 nM to 11.4-fold at 1000 nM) suggests that **24** may be involved in fatty acid oxidation. In addition, a strong induction of a new PPARα target gene, Pa9,[24] was also observed (4.1-fold at 1 nM to 22.4-fold at 1000 nM).

Most of the compounds displayed very good pharmacokinetic profiles in rat. For example, using 10% Solutol in D5W for intravenous formulation and 0.5% methylcellulose for oral gavage formulation, when dosing at 3 mg/kg, **24** displayed high maximum plasma concentration ($C_{max} = 6675 \pm 779$ ng/mL), rapid oral absorption ($T_{max} = 0.8$ h), high plasma drug exposure (AUC = 22033 ± 2375 ng h/mL), long plasma duration ($t_{1/2} = 5.3 \pm 2.3$ h), low systemic clearance (CL = 2.2 ± 0.2 mL/min.kg), and high oral bioavailability ($F = 96\%$).

In Vivo Studies. The ability of compound **24** to affect lipid/cholesterol homeostasis in vivo was first examined in a hypercholesterolemic rat model. The high-cholesterol diet fed hypercholesterolemic rat displayed about a 3.7-fold lower HDL-C level (13 mg/dL, Figure 2) than the rat fed standard chow (48 mg/dL). Compound **24** dose-dependently (from 0.1 to 3 mg/kg/d) increased serum HDL-C levels (from 35 to 74 mg/dL) after these rats were dosed orally for 8 days. With this hypercholesterolemic rat model, a PPARδ selective agonist will generally normalized HDL-C levels to that of vehicle lean rats (data not shown), but the current PPARα/δ dual agonist **24** is able to increase the HDL-C levels even 50% higher than that of vehicle lean rats. In addition, while the hypercholesterolemic rat displayed about 11-fold elevated LDL-C levels (113 mg/dL, Figure 2) than the rat fed standard chow (10 mg/dL), **24** attenuated the high LDL-C levels (from 82 to 49 mg/dL) in a dose-related manner. On the other hand, **24** exhibited no effect on serum triglycerides and no effect on liver weight except at the 3 mg/kg high dose (~50% increase), which may be attributed to its PPARα activity.[25]

The capability of **24** to affect lipid homeostasis was next examined in the human apoA1 transgenic mouse model. Since apoA1 is the primary protein component of HDL-C, a human apoA1 transgenic mouse model has proven useful in the testing of PPARα and PPARδ hypolipidemic compounds.[26] Male hApoA1 mice were dosed orally with 3 mg/kg of **24** for 7 days. Compound **24** caused significant increase in HDL-C (74% increase, from 287 to 499 mg/dL, Figure 3) and reductions in triglycerides (85% decrease, from 230 to 34 mg/dL) and in free fatty acids (31% decrease, from 1.84 to 1.27 mequiv/L) compared to that of vehicle control group.

The ob/ob mice are obese, insulin resistant with hypertriglyceridemia and hyperglycemia, and have been used as a rodent model of obesity-induced insulin resistance. Seven-week-old female ob/ob mice were dosed orally with **24** for 11 days. Compound **24** significantly reduced serum TG (80% decrease, from 492.9 to 98.9 mg/dL, Table 3), serum glucose (51% decrease, from 630.9 to 308.7 mg/dL), and serum FFA (58% decrease, from 1.2 to 0.5 mequiv/L). Meanwhile, liver weights

Table 3. Effect of **24** on Serum TG, Glucose, FFA, and Liver Weight in ob/ob Mice[a]

dose, mg/kg	TG,[b] mg/dL	gluc,[b] mg/dL	FFA,[b] mequiv/L	liver wt,[b] g
vehicle	492.9 ± 40.4	630.9 ± 23.4	1.2 ± 0.1	3.0 ± 0.2
1	98.9 ± 5.4	308.7 ± 24.7	0.5 ± 0.1	4.5 ± 0.1

[a] Seven-week-old female ob/ob mice dosed orally with **24** for 11 days. [b] Mean value ± SEM ($n = 8$), $p < 0.01$ versus vehicle control.

increased (50% increase, from 3 to 4.5 g) similar to the effect observed with PPARα agonists. The good in vivo efficacy of **24** observed in the mouse model is consistent with the good potency displayed in the mouse PPARα HD assay ($EC_{50} = 127$ nM).

Conclusion

In an attempt to rationalize the unexpected potent and selective PPARα/δ dual agonist activity, **24** was docked into all three PPAR isotypes. Unfortunately, docking energies and binding modes experiments revealed little about SAR selectivity. Nonetheless, compound **24** and its close analogs represent a new series of PPARα/δ dual agonists. The high potency, high selectivity, significant gene induction, excellent PK profiles, and good in vivo efficacies in three animal models may render compound **24** as a valuable pharmacological tool in elucidating the complex roles of PPARα/δ dual agonists and as a potential treatment of the metabolic syndrome.

Experimental Section

Chemistry. ^{1}H NMR spectra were measured on a Bruker AC-300 (300 MHz) spectrometer using tetramethylsilane as an internal standard. Elemental analyses were obtained by Quantitative Technologies Inc. (Whitehouse, NJ), and the results were within 0.4% of the calculated values unless otherwise mentioned. Melting points were determined in open capillary tubes with a Thomas-Hoover apparatus and were uncorrected. Electrospray mass spectra (MS-ES) were recorded on a Hewlett-Packard 59987A spectrometer. High-resolution mass spectra (HRMS) were obtained on a Micromass Autospec. E. spectrometer.

General Procedure for the Synthesis of 9, 26, and 32. 5-(4-Trifluoromethylphenyl)[1,3,4]oxathiazol-2-one (9). The reaction mixture of 4-trifluoromethylbenzamide **8** (2.57 g, 13.6 mmol) and chlorocarbonylsulfenyl chloride (3.57 g, 27.2 mmol) in toluene (35 mL) was heated at 60 °C for 15 h and concentrated. CH_2Cl_2 was added and the mixture was filtered. The white solid was washed with CH_2Cl_2 and dried under high vacuum to give 922 mg (36%) of 4-trifluoromethylbenzamide **8** as recovered starting material. The filtrate was concentrated and column chromatographed (EtOAc/hexane) to provide 1.31 g (39%) of **9** as white crystals: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, $J = 8.2$ Hz, 2 H), 7.77 (d, $J = 8.3$ Hz, 2 H).

5-(4-Chlorophenyl)[1,3,4]oxathiazol-2-one (26). Using **25** and following the procedure as in the preparation of **9** gave **26** (63%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, $J = 8.6$ Hz, 2 H), 7.48 (d, $J = 8.6$ Hz, 2 H).

5-(4-*tert*-Butylphenyl)[1,3,4]oxathiazol-2-one (32). Using **31** and following the procedure as in the preparation of **9** gave **32** (70%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (m, 2 H), 7.50 (m, 2 H), 1.35 (s, 9 H).

General Procedure for the Synthesis of 10, 21, 27, and 33. 3-(4-Trifluoromethylphenyl)[1,2,4]thiadiazole-5-carboxylic Acid Ethyl Ester (10). A reaction mixture of **9** (448 mg, 1.81 mmol) and ethyl cyanoformate (722 mg, 7.29 mmol) in 1,2-dichlorobenzene (7 mL) was heated at 160 °C for 20 h. After cooling down to room temperature, the reaction mixture was purified by column chromatography to give 505 mg (92%) of **10** as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, $J = 8.1$ Hz, 2 H), 7.76 (d, $J = 8.2$ Hz, 2 H), 4.57 (q, $J = 7.1$ Hz, 2 H), 1.49 (t, $J = 7.1$ Hz, 3 H); MS (ES) *m/z* 303 ($M + H^+$).

3-(4-Trifluoromethoxyphenyl)[1,2,4]thiadiazole-5-carboxylic Acid Ethyl Ester (21). Using **20** and following the procedure as in the preparation of **9** and **10** gave **21** (97%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (m, 2 H), 7.33 (dd, $J = 8.9$, 0.8 Hz, 2 H), 4.56 (q, $J = 7.1$ Hz, 2 H), 1.49 (t, $J = 7.1$ Hz, 3 H).

3-(4-Chlorophenyl)[1,2,4]thiadiazole-5-carboxylic Acid Ethyl Ester (27). Using **26** and following the procedure as in the preparation of **10** gave **27** (94%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (m, 2 H), 7.47 (m, 2 H), 4.55 (q, $J = 7.1$ Hz, 2 H), 1.48 (t, $J = 7.1$ Hz, 3 H); MS (ES) *m/z* 269 ($M + H^+$).

3-(4-*tert*-Butylphenyl)[1,2,4]thiadiazole-5-carboxylic Acid Ethyl Ester (33). Using **32** and following the procedure as in the preparation of **10** gave **33** (81%) as a yellowish crystal: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (m, 2 H), 7.51 (m, 2 H), 4.55 (q, $J = 7.1$ Hz, 2 H), 1.48 (t, $J = 7.1$ Hz, 3 H), 1.37 (s, 9 H); MS (ES) *m/z* 291 ($M + H^+$).

General Procedure for the Synthesis of 11, 22, 28, and 34. [3-(4-Trifluoromethylphenyl)[1,2,4]thiadiazol-5-yl]methanol (11). To a solution of **10** (200 mg, 0.662 mmol) in EtOH (10 mL) at room temperature was added $NaBH_4$ (64 mg, 1.7 mmol). After stirring for 2 h, a few drops of water were added to quench the excess of hydride. EtOH was evaporated, and the residue was partitioned between CH_2Cl_2 and water. The organic phase was dried and concentrated to provide 167 mg (97%) of **11** as off-white crystals: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, $J = 8.1$ Hz, 2 H), 7.74 (d, $J = 8.2$ Hz, 2 H), 5.20 (s, 2 H), 2.65 (brs, 1 H); MS (ES) *m/z* 261 ($M + H^+$).

[3-(4-Trifluoromethoxyphenyl)[1,2,4]thiadiazol-5-yl]methanol (22). Using **21** and following the procedure as in the preparation of **11** gave **22** (70%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (m, 2 H), 7.31 (d, $J = 8.1$ Hz, 2 H), 5.17 (d, $J = 5.8$ Hz, 2 H), 1.26 (t, $J = 7.1$ Hz, 1 H); MS (ES) *m/z* 277 ($M + H^+$).

[3-(4-Chlorophenyl)[1,2,4]thiadiazol-5-yl]methanol (28). Using **27** and following the procedure as in the preparation of **11** gave **28** (87%) as an off-white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (m, 2 H), 7.45 (m, 2 H), 5.17 (s, 2 H); MS (ES) *m/z* 227 ($M + H^+$).

[3-(4-*tert*-Butylphenyl)[1,2,4]thiadiazol-5-yl]methanol (34). Using **33** and following the procedure as in the preparation of **11** gave **34** (100%) as an off-white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (m, 2 H), 7.50 (m, 2 H), 5.16 (s, 2 H), 1.36 (s, 9 H); MS (ES) *m/z* 249 ($M + H^+$).

{2-Methyl-4-[3-(4-trifluoromethylphenyl)[1,2,4]thiadiazol-5-ylmethylsulfanyl]phenoxy}acetic Acid (13). A mixture of **11** (88 mg, 0.34 mmol), methanesulfonyl chloride (58 mg, 0.51 mmol), and triethylamine (70 mg, 0.69 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 1.5 h. The mixture was washed with water and the aqueous phase was back-extracted with CH_2Cl_2. The combined organic layers were dried and concentrated to provide 111 mg of the mesylate as a yellow solid.

A mixture of the crude mesylate (111 mg) and (4-mercapto-2-methylphenoxy)acetic acid ethyl ester **12** (111 mg, 0.491 mmol) in CH_3CN (4 mL) was degassed under N_2 for about 15 min. After the addition of Cs_2CO_3 (214 mg, 0.656 mmol), the mixture was stirred overnight under N_2, concentrated, and purified by column chromatography (EtOAc/hexane) to give 102 mg (64%, 2 steps) of the ethyl ester as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, $J = 8.1$ Hz, 2 H), 7.71 (d, $J = 8.2$ Hz, 2 H), 7.30 (d, $J = 1.7$ Hz, 1 H), 7.23 (dd, $J = 8.6$, 2.2 Hz, 1 H), 6.62 (d, $J = 8.5$ Hz, 1 H), 4.61 (s, 2 H), 4.41 (s, 2 H), 4.24 (q, $J = 7.1$ Hz, 2 H), 2.25 (s, 3 H), 1.27 (t, $J = 7.1$ Hz, 3 H); MS (ES) *m/z* 491 ($M + Na^+$). Anal. ($C_{19}H_{15}F_3N_2O_3S_2 \cdot 0.5H_2O$) C, H, N.

A mixture of ethyl ester (77 mg, 0.16 mmol) and 2 M NaOH (0.30 mL, 0.60 mmol) in MeOH (4 mL) was stirred under N_2 for 30 min and concentrated. EtOAc and water were added, and the mixture was acidified with concentrated HCl. The organic phase was separated and the aqueous phase was extracted with EtOAc. The combined organic layers were dried and concentrated to give 70 mg (97%) of **13** as an off-white solid: ^{1}H NMR (300 MHz,

MeOH-d_4) δ 8.37 (d, J = 8.1 Hz, 2 H), 7.78 (d, J = 8.3 Hz, 2 H), 7.28 (s, 1 H), 7.26 (m, 1 H), 6.76 (d, J = 8.3 Hz, 1 H), 4.66 (s, 2 H), 4.53 (s, 2 H), 2.20 (s, 3 H); MS (ES) *m/z* 441 ($M + H^+$); FAB-HRMS (M^+) calcd 440.0476, found 440.0465.

2-Methyl-4-[3-(4-trifluoromethylphenyl)[1,2,4]thiadiazol-5-ylmethylsulfanyl]phenol (14). To a solution of **11** (795 mg, 3.06 mmol) in CH_2Cl_2 (30 mL) at 0 °C were added methanesulfonyl chloride (518 mg, 4.52 mmol) and triethylamine (617 mg, 6.11 mmol). The mixture was stirred at room temperature for 1 h and then partitioned between water and CH_2Cl_2 (80 mL). The organic layer was washed with brine, dried, concentrated, and column chromatographed (EtOAc/hexane) to provide 859 mg (83%) of the mesylate as a white solid.

A mixture of the mesylate (210 mg, 0.621 mmol) and 4-mercapto-2methylphenol (126 mg, 0.897 mmol) in CH_3CN (8 mL) was degassed under N_2 for about 10 min. After the addition of Cs_2CO_3 (242 mg, 0.742 mmol), the mixture was stirred at room temperature for 40 min, concentrated, and purified by column chromatography (EtOAc/hexane) to give 228 mg (95%) of **14** as a white crystalline solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J = 8.0 Hz, 2 H), 7.71 (d, J = 8.2 Hz, 2 H), 7.26 (s, 1 H), 7.20 (dd, J = 8.0, 2.1 Hz, 1 H), 6.71 (d, J = 8.2 Hz, 1 H), 4.83 (s, 1 H), 4.40 (s, 2 H), 2.21 (s, 3 H); MS (ES) *m/z* 383 ($M + H^+$).

2-Methyl-2-{2-methyl-4-[3-(4-trifluoromethylphenyl)[1,2,4]thiadiazol-5-ylmethylsulfanyl]phenoxy}propionic Acid (15). To a solution of **14** (39 mg, 0.10 mmol) in THF (1 mL) was added NaH (20 mg, 0.50 mmol; 60% in mineral oil) and the mixture was heated at 60 °C for 30 min, during which the solution changed to blue and then brown. 2-Bromoisobutyric acid (34 mg, 0.20 mmol) was added, and the mixture was heated at the same temperature for 1 h, acidified with 1 N HCl, and diluted with CH_2Cl_2. The organic phase was separated, washed with brine, dried, concentrated, and column chromatographed (EtOAc/hexane) to isolate 10 mg (21%) of **15** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J = 8.0 Hz, 2 H), 7.71 (d, J = 8.2 Hz, 2 H), 7.28 (m, 1 H), 7.18 (dd, J = 8.4, 2.4 Hz, 1 H), 6.72 (d, J = 8.5 Hz, 1 H), 4.43 (s, 2 H), 2.20 (s, 3 H), 1.61 (s, 6 H); MS (ES) *m/z* 469 ($M + H^+$). Anal. ($C_{21}H_{19}F_3N_2O_3S_2$·0.3 H_2O) C, H. N.

2-Methyl-2-*o*-tolyloxypropionic Acid Ethyl Ester (17). To a mixture of 2-bromo-2-methylpropionic acid ethyl ester (8.27 mL, 64.0 mmol) and 2-methylphenol (7.60 g, 70.2 mmol) in dioxane (100 mL) was added Cs_2CO_3 (31.3 g, 96.0 mmol). After the mixture was refluxed at 100 °C for 4 h and allowed to cool to room temperature, the solvent was evaporated under reduced pressure. The residue was dissolved in Et_2O, washed with 1 N NaOH, dried, and concentrated to give 9.69 g (68%) of **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J = 7.3 Hz, 1 H), 7.03 (t, J = 7.6 Hz, 1 H), 6.87 (t, J = 7.3 Hz, 1 H), 6.66 (d, J = 8.2 Hz, 1 H), 4.24 (q, J = 7.1 Hz, 2 H), 2.23 (s, 3 H), 1.59 (s, 6 H), 1.25 (t, J = 7.1 Hz).

2-(4-Chlorosulfonyl-2-methylphenoxy)-2-methylpropionic Acid Ethyl Ester (18). To a flask containing **17** (11.3 g, 0.051 mol) at 0 °C was slowly added $ClSO_3H$ (15.2 mL, 0.229 mol). The temperature was allowed to warm to room temperature and the solution was stirred for 1 h. Upon stirring, the reaction mixture was poured into ice. The solid was filtered, washed with water, and vacuum-dried to give 7.7 g (47%) of **18**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 2.5 Hz, 1 H), 7.75 (dd, J = 8.9, 2.5 Hz, 1 H), 6.67 (d, J = 8.8 Hz, 1 H), 4.23 (q, J = 7.1 Hz, 2 H), 2.31 (s, 3 H), 1.70 (s, 6 H), 1.22 (t, J = 7.1 Hz); MS (ES) *m/z* 343 ($M + Na^+$).

2-(4-Mercapto-2-methylphenoxy)-2-methylpropionic Acid Ethyl Ester (19). To a solution of **18** (2.00 g, 6.25 mmol) in EtOH (7.8 mL) were added HCl in dioxane (4.0 M, 7.8 mL, 31 mmol) and tin powder (3.70 g, 31.2 mmol). The mixture was refluxed for 3 h, poured into ice, and extracted with CH_2Cl_2 (50 mL × 3). The organic layers were combined and dried over Na_2SO_4. After filtration, the filtrate was concentrated to give 3.37 g (~100%) of **19**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 2.0 Hz, 1 H), 7.00 (dd, J = 8.4, 2.4 Hz, 1 H), 6.56 (d, J = 8.4 Hz, 1 H), 4.23 (q, J = 7.1 Hz, 2 H), 3.31 (s, 1 H), 2.18 (s, 3 H), 1.57 (s, 6 H), 1.25 (t, J = 7.1 Hz); MS (ES) *m/z* 255 ($M + H^+$).

General Procedure for the Synthesis of 23, 29, and 35. 5-Bromomethyl-3-(4-trifluoromethoxyphenyl)[1,2,4]thiadiazole (23). To a solution of **22** (679 mg, 2.46 mmol) in CH_2Cl_2 (10 mL) were added carbon tetrabromide (896 mg, 2.70 mmol) and triphenylphosphine (707 mg, 2.70 mmol). The mixture was stirred at 0 °C for 1 h and room temperature for 1 h, concentrated, and purified by column chromatography to give 678 mg (81%) of **23** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (m, 2 H), 7.31 (dd, J = 8.9, 0.8 Hz, 2 H), 4.82 (s, 2 H); MS (ES) *m/z* 339 ($M + H^+$).

5-Bromomethyl-3-(4-chlorophenyl)[1,2,4]thiadiazole (29). Using **28** and following the procedure as in the preparation of **23** gave **29** (65%) as an off-white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (m, 2 H), 7.45 (m, 2 H), 4.81 (s, 2 H).

5-Bromomethyl-3-(4-*tert*-butylphenyl)[1,2,4]thiadiazole (35). Using **34** and following the procedure as in the preparation of **23** gave **35** (55%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (m, 2 H), 7.49 (m, 2 H), 4.82 (s, 2 H), 1.36 (s, 9 H); MS (ES) *m/z* 313 ($M + H^+$).

General Procedure for the Synthesis of 24, 30, and 36. 2-Methyl-2-{2-methyl-4-[3-(4-trifluoromethoxyphenyl)[1,2,4]thiadiazol-5-ylmethylsulfanyl]phenoxy}propionic Acid (24). To a mixture of **23** (73 mg, 0.22 mmol) and 2-(4-mercapto-2-methylphenoxy)-2-methyl-propionic acid ethyl ester **19** (52 mg, 0.21 mmol) in CH_3CN (1.5 mL) and DMF (0.1 mL) was added Cs_2CO_3 (100 mg, 0.31 mmol). After stirring at room temperature for 15 min, the mixture was concentrated. The residue was diluted with EtOAc, washed with water and brine, dried, concentrated, and column chromatographed to give 82 mg (78%) of **24-ethyl ester**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 8.9 Hz, 2 H), 7.29 (dd, J = 8.9, 0.9 Hz, 1 H), 7.26 (m, 2 H), 7.13 (dd, J = 8.5, 2.4 Hz, 1 H), 6.56 (d, J = 8.5 Hz, 1 H), 4.40 (s, 2 H), 4.20 (q, J = 7.1 Hz, 2 H), 2.18 (s, 3 H), 1.58 (s, 6 H), 1.20 (t, J = 7.1 Hz, 3 H); MS (ES) *m/z* 513 ($M + H^+$). Anal. ($C_{23}H_{23}F_3N_2O_4S_2$) C, H, N.

A solution of **24-ethyl ester** (80 mg, 0.16 mmol) in MeOH (1.0 mL) and THF (1.0 mL) was treated with 2 N NaOH (1.0 mL, 2.0 mmol) for 4 h and concentrated. The residue was diluted with EtOAc and water and acidified with concentrated HCl. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phases were washed with brine, dried, concentrated, and column chromatographed to provide 71 mg (95%) of **24**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.8 Hz, 2 H), 7.30−7.23 (m, 3 H), 7.17 (d, J = 8.4 Hz, 1 H), 6.72 (d, J = 8.4 Hz, 1 H), 4.42 (s, 2 H), 2.20 (s, 3 H), 1.60 (s, 6 H); MS (ES) *m/z* 507 ($M + Na^+$). Anal. ($C_{21}H_{19}F_3N_2O_4S_2$) C, H, N.

2-{4-[3-(4-Chlorophenyl)[1,2,4]thiadiazol-5-ylmethylsulfanyl]-2-methylphenoxy}-2-methylpropionic Acid (30). Using **29** and following the procedure as in the preparation of **24** gave **30** (64%) as a light yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (m, 2 H), 7.42 (m, 2 H), 7.28 (d, J = 2.2 Hz, 1 H), 7.18 (dd, J = 8.5, 2.4 Hz, 1 H), 6.72 (d, J = 8.5 Hz, 1 H), 4.42 (s, 2 H), 2.19 (s, 3 H), 1.61 (s, 6 H); MS (ES) *m/z* 435 ($M + H^+$). Anal. ($C_{20}H_{19}ClN_2O_3S_2$) C, H, N.

2-{4-[3-(4-*tert*-Butylphenyl)[1,2,4]thiadiazol-5-ylmethylsulfanyl]-2-methylphenoxy}-2-methylpropionic Acid (36). Using **35** and following the procedure as in the preparation of **24** gave **36** (47%) as a yellow gummy solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (m, 2 H), 7.47 (m, 2 H), 7.28 (d, J = 2.3 Hz, 1 H), 7.17 (dd, J = 8.5, 2.4 Hz, 1 H), 6.72 (d, J = 8.5 Hz, 1 H), 4.43 (s, 2 H), 2.19 (s, 3 H), 1.60 (s, 6 H), 1.35 (s, 9 H); MS (ES) *m/z* 457 ($M + H^+$). Anal. ($C_{24}H_{28}N_2O_3S_2$) C, H, N.

General Procedure for the Synthesis of 38 and 42. 5-(4-Trifluoromethylphenyl)[1,2,4]thiadiazole-3-carboxylic Acid Ethyl Ester (38). A mixture of **37** (1.77 g, 10.1 mmol) and 4-trifluoromethylbenzonitrile (8.63 g, 50.5 mmol) in 1,2-dichlorobenzene (10 mL) was heated at 160 °C for 4 days. After cooling down to room temperature, the mixture was purified by column chromatography to provide 120 mg (3.9%) of **38** as light brown crystals: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 8.1 Hz, 2 H), 7.80 (d, J = 8.2 Hz, 2 H), 4.56 (q, J = 7.1 Hz, 2 H), 1.50 (t, J = 7.1 Hz, 3 H); MS (ES) *m/z* 303 ($M + H^+$).

5-(4-Trifluoromethoxyphenyl)[1,2,4]thiadiazole-3-carboxylic Acid Ethyl Ester (42). Using 4-trifluoromethoxybenzonitrile and following the procedure as in the preparation of **38** gave **42** (34%) as a yellow gummy solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (m, 2 H), 7.37 (d, J = 8.0 Hz, 2 H), 4.55 (q, J = 7.1 Hz, 2 H), 1.49 (t, J = 7.1 Hz, 3 H); MS (ES) *m/z* 319 (M + H$^+$).

General Procedure for the Synthesis of 39 and 43. [5-(4-Trifluoromethylphenyl)[1,2,4]thiadiazol-3-yl]methanol (39). Using **38** and following the procedure as in the preparation of **11** gave **39** (93%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 8.1 Hz, 2 H), 7.78 (d, J = 8.2 Hz, 2 H), 5.01 (s, 2 H); MS (ES) *m/z* 261 (M + H$^+$).

[5-(4-Trifluoromethoxyphenyl)[1,2,4]thiadiazol-3-yl]methanol (43). Using **42** and following the procedure as in the preparation of **39** gave **43** (94%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (m, 2 H), 7.35 (d, J = 8.2 Hz, 2 H), 4.99 (s, 2 H), 2.70 (brs, 1 H).

General Procedure for the Synthesis of 40 and 44. 3-Bromomethyl-5-(4-trifluoromethylphenyl)[1,2,4]thiadiazole (40). Using **39** and following the same procedure as in the preparation of **23** gave **40** (72%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.2 Hz, 2 H), 7.78 (d, J = 8.2 Hz, 2 H), 4.71 (s, 2 H); MS (ES) *m/z* 323 (M + H$^+$).

3-Bromomethyl-5-(4-trifluoromethoxyphenyl)[1,2,4]-thiadiazole (44). Using **43** and following the same procedure as in the preparation of **40** gave **44** (87%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (m, 2 H), 7.35 (d, J = 8.1 Hz, 2 H), 4.69 (s, 2 H); MS (ES) *m/z* 341 (M + H$^+$).

General Procedure for the Synthesis of 41 and 45. 2-Methyl-2-{2-methyl-4-[5-(4-trifluoromethylphenyl)[1,2,4]thiadiazol-3-ylmethylsulfanyl]phenoxy}propionic Acid (41). Using **40** and following the same procedure as in the preparation of **24** gave **41** (50%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 8.1 Hz, 2 H), 7.76 (d, J = 8.2 Hz, 2 H), 7.28 (d, J = 2.3 Hz, 1 H), 7.18 (dd, J = 8.5, 2.3 Hz, 1 H), 6.73 (d, J = 8.5 Hz, 1 H), 4.37 (s, 2 H), 2.19 (s, 3 H), 1.60 (s, 6 H); MS (ES) *m/z* 469 (M + H$^+$). Anal. ($C_{21}H_{19}F_3N_2O_3S_2$) C, H, N.

2-Methyl-2-{2-methyl-4-[5-(4-trifluoromethoxyphenyl)[1,2,4]-thiadiazol-3-ylmethylsulfanyl]phenoxy}propionic Acid (45). Using **44** and following the same procedure as in the preparation of **41** gave **45** (74%) as a white gummy solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (m, 2 H), 7.33 (d, J = 8.1 Hz, 2 H), 7.27 (s, 1 H), 7.17 (dd, J = 8.5, 2.4 Hz, 1 H), 6.73 (d, J = 8.5 Hz, 1 H), 4.35 (s, 2 H), 2.19 (s, 3 H), 1.60 (s, 6 H); MS (ES) *m/z* 485 (M + H$^+$). Anal. ($C_{21}H_{19}F_3N_2O_4S_2$) C, H, N.

2-(4-Acetyl-2-methylphenoxy)-2-methylpropionic Acid Ethyl Ester (47). A mixture of 2-bromo-2-methylpropionic acid ethyl ester (7.93 g, 40.65 mmol), **46** (6.10 g, 40.65 mmol), and cesium carbonate (13.2 g, 40.65 mmol) was refluxed in dioxane (100 mL) for 18 h. After cooling, the mixture was partitioned between ethyl acetate and water. The organic layers were dried and concentrated. Purification by column chromatography (EtOAc/hexane) gave compound **47** (6.169 g, 57%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 1.5 Hz, 1H), 7.67−7.70 (dd, J = 2.1, 8.6 Hz, 1H), 6.60−6.63 (d, J = 8.6 Hz, 1H), 4.19−4.26 (q, J = 7.1 Hz, 2H), 2.53 (s, 3H), 2.27 (s, 3H), 1.66 (s, 6H), 1.24 (t, J = 7.1 Hz, 3H); MS (ES) *m/z* 265 (M + H$^+$).

2-(4-Hydroxy-2-methylphenoxy)-2-methylpropionic Acid Ethyl Ester (48). Compound **47** (2.14 g, 8.10 mmol) was dissolved in CH_2Cl_2 (25 mL). *m*CPBA (77 wt %, 3.18 g, 14.17 mmol) and TsOH monohydrate (154 mg, 0.81 mmol) were added. The mixture was stirred at refluxing for 4 h and cooled. Solid $Na_2S_2O_3$ was added, followed by saturated aqueous $Na_2S_2O_3$, $NaHCO_3$, and brine. The organic phase was dried and evaporated. Purification by column chromatography (eluting with EtOAc/hexane) gave acetate (1.858 g, 82%) as a light yellow oil: ^{1}HNMR (300 MHz, $CDCl_3$) δ 6.88 (d, J = 2.8 Hz, 1H), 6.74−6.78 (dd, J = 2.8, 8.8 Hz, 1H), 6.66 (d, J = 8.8 Hz, 1H), 4.20−4.27 (q, J = 7.1 Hz, 2H), 2.26 (s, 3H), 2.22 (s, 3H), 1.58 (s, 6H), 1.23−1.27 (t, J = 7.1 Hz, 3H); MS (ES) *m/z* 298 (M + H$^+$).

The acetate (1.858 g, 6.63 mmol) was dissolved in THF (10 mL). NaOEt in EtOH (2.68 M, 6.63 mmol) was added. The mixture was stirred at 20 °C for 2 h and concentrated. The residue was partitioned between EtOAc and H_2O. The organic phase was dried and concentrated. Purification by column chromatography (eluting with EtOAc/hexane) provided compound **48** (1.28 g, 81%) as a light yellow oil: ^{1}HNMR (300 MHz, $CDCl_3$) δ 6.62−6.65 (m, 2H), 6.48−6.52 (dd, J = 8.7, 3.0 Hz, 1H), 4.51 (s, 1H), 4.22−4.29 (q, J = 7.1 Hz, 2H), 2.19 (s, 3H), 1.53 (s, 6H), 1.26−1.30 (t, J = 7.1 Hz, 3H); MS (ES) *m/z* 261 (M + Na).

General Procedure for the Synthesis of 50 and 51. 2-Methyl-2-{2-methyl-4-[3-(4-trifluoromethylphenyl)[1,2,4]thiadiazol-5-ylmethoxy]phenoxy}propionic Acid (50). O-Alkylation of **48** with the bromide **49** (CF_3 analog of **23**) and following the same procedure as in the preparation of **24** gave **50** (71%) as a white solid: ^{1}H NMR (300 MHz, MeOH-d_4) δ 8.48 (d, J = 8.2 Hz, 2 H), 7.81 (d, J = 8.3 Hz, 2 H), 6.95 (s, 1 H), 6.83 (s, 2 H), 5.56 (s, 2 H), 2.23 (s, 3 H), 1.54 (s, 6 H); MS (ES) *m/z* 453 (M + H$^+$). Anal. ($C_{21}H_{19}F_3N_2O_4S$) C, H, N.

2-Methyl-2-{2-methyl-4-[3-(4-trifluoromethoxyphenyl)[1,2,4]-thiadiazol-5-ylmethoxy]phenoxy}propionic Acid (51). O-Alkylation of **48** with the bromide **23** and following the same procedure as in the preparation of **50** gave **51** (72%) as a white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 8.39 (d, J = 8.8 Hz, 2 H), 7.41 (d, J = 8.4 Hz, 2 H), 6.94 (d, J = 2.5 Hz, 1 H), 6.83 (m, 2 H), 5.54 (s, 2 H), 2.23 (s, 3 H), 1.53 (s, 6 H); MS (ES) *m/z* 469 (M + H$^+$). Anal. ($C_{21}H_{19}F_3N_2O_5S$) C, H, N.

1-Bromocyclopentanecarboxylic Acid Methyl Ester 53. To a solution of cyclopentanecarboxylic acid (1.14 g, 10.0 mmol) in 1,2-dichloroethane (50 mL) were added bromine (1.60 g, 10.0 mmol) and chlorosulfonic acid (1.17 g, 10.0 mmol). The reaction mixture was refluxed for 2 h and concentrated. The residue was dissolved in MeOH (30 mL) and the mixture was refluxed overnight. After removal of the solvent, the residue was diluted with Et_2O, washed with water (×2) and brine, dried over Na_2SO_4, filtered, and concentrated to give 1.79 g (86%) of **53**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 3 H), 2.33−2.28 (m, 4 H), 2.03−1.95 (m, 2 H), 1.85−1.75 (m, 2 H).

1-*o*-Tolyloxycyclopentanecarboxylic Acid Methyl Ester 54. To a solution of 2-methylphenol (90 mg, 0.83 mmol) in CH_3CN (2 mL) was added Cs_2CO_3 (678 mg, 2.08 mmol), followed by **53** (207 mg, 1.0 mmol). The mixture was heated at 70 °C for 4.5 h, diluted with water, and extracted with Et_2O. The extracts were dried, concentrated, and column chromatographed (EtOAc/hexane 1/12) to give 52 mg (22%) of **54**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J = 7.3 Hz, 1 H), 7.03 (m, 1 H), 6.83 (td, J = 7.4, 0.7 Hz, 1 H), 6.45 (d, J = 8.1 Hz, 1 H), 3.73 (s, 3 H), 2.29−2.17 (m, 4 H), 2.23 (s, 3 H), 1.84−1.76 (m, 4 H); MS (ES) *m/z* 235 (M + H$^+$).

1-(4-Bromo-2-methylphenoxy)cyclopentanecarboxylic Acid Methyl Ester 55. To a solution of **54** (76 mg, 0.32 mmol) in CH_3CN (1.5 mL) was added *N*-bromosuccinimide (63 mg, 0.35 mmol). After stirring at room temperature for 1.5 h, additional *N*-bromosuccinimide (29 mg, 0.16 mmol) was added and the mixture was stirred for another 1 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (CH_2Cl_2/hexane 1/1) to provide 95 mg (95%) of **55**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 0.5 Hz, 1 H), 7.13 (dd, J = 8.6, 2.4 Hz, 1 H), 6.32 (d, J = 8.7 Hz, 1 H), 3.73 (s, 3 H), 2.28−2.12 (m, 4 H), 2.19 (s, 3 H), 1.82−1.77 (m, 4 H); MS (ES) *m/z* 314 (M + H$^+$).

1-(2-Methyl-4-triisopropylsilanylsulfanylphenoxy)-cyclopentanecarboxylic Acid Methyl Ester 56. To a suspension of NaH (17 mg, 0.43 mmol; 60% in mineral oil) in toluene (1.5 mL) was added triisopropylsilanethiol (82 mg, 0.43 mmol). After stirring at room temperature for 30 min, to the mixture were added a solution of **55** (122 mg, 0.390 mmol) in THF (1 mL) and tetrakis-(triphenylphosphine) palladium (45 mg, 0.039 mmol), and the mixture was degassed under N_2. After heating at 90 °C for 4 h, the solvents were evaporated and the residue was purified by column chromatography (EtOAc/hexane 1/8) to afford 135 mg (82%) of **56**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 1.8 Hz, 1 H), 7.13

(dd, $J = 8.5$, 2.3 Hz, 1 H), 6.32 (d, $J = 8.5$ Hz, 1 H), 3.70 (s, 3 H), 2.25−2.13 (m, 4 H), 2.16 (s, 3 H), 1.82−1.77 (m, 4 H), 1.27−1.19 (m, 3 H), 1.07 (s, 9 H), 1.04 (s, 9 H); MS (ES) *m/z* 423 ($M + H^+$).

1-{2-Methyl-4-[3-(4-trifluoromethoxyphenyl)[1,2,4]thiadiazol-5-ylmethylsulfanyl]phenoxy}cyclopentanecarboxylic Acid 57. To a mixture of **23** (53 mg, 0.18 mmol) and **56** (76 mg, 0.18 mmol) in THF (0.5 mL) at 0 °C was added 1.0 M tetrabutylammonium fluoride (0.18 mL, 0.18 mmol) in THF dropwise. After stirring at the same temperature for 15 min, the mixture was concentrated and the residue was purified by column chromatography to afford 88 mg (94%) of **57-methyl ester** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, $J = 8.9$ Hz, 2 H), 7.30−7.26 (m, 3 H), 7.14 (dd, $J = 8.5$, 2.2 Hz, 1 H), 6.37 (d, $J = 8.5$ Hz, 1 H), 4.39 (s, 2 H), 3.70 (s, 3 H), 2.27−2.12 (m, 4 H), 2.18 (s, 3 H), 1.80−1.76 (m, 4 H); MS (ES) *m/z* 525 ($M + H^+$).

Using **57-methyl ester** and follow the same base hydrolysis procedure as in the preparation of **50** gave **57** (68%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (m, 2 H), 7.30−7.27 (m, 3 H), 7.17 (dd, $J = 8.5$, 2.3 Hz, 1 H), 6.50 (d, $J = 8.5$ Hz, 1 H), 4.40 (s, 2 H), 2.36−2.27 (m, 2 H), 2.21−2.15 (m, 2 H), 2.18 (s, 3 H), 1.82−1.78 (m, 4 H). Anal. ($C_{23}H_{21}F_3N_2O_4S_2$) C, H, N.

Biology. PPARs Assays. All cell culture and cotransfection reagents were purchased from Invitrogen (Carlsbad, CA) with the exception of the charcoal-treated FBS (Hyclone; Logan, UT). HEK293 cells were grown in DMEM/F-12 medium supplemented with 10% FBS and glutamine. The Steady-Glo Luciferase Assay Kit (Promega; Madison, WI) was used for measuring luciferase reporter activity. For a 175 cm^2 tissue culture flask, 100×10^5 of HEK293 cells were seeded in the growth medium and incubated at 37 °C in 5%CO_2 incubator until the cells were 80% confluent. Then the cells were cotransfected with DNA constructs containing the ligand-binding domains of either PPARα, PPARγ, or δ-Gal4 chimeric receptors and Gal4-luciferase reporter using DMRIE-C transfection reagent and OPTI-MEM reduced serum medium according to the manufacturer's instructions. On the following day, the DNA-containing medium was replaced with 30 mL of 5% charcoal-treated FBS growth medium. After 6 h, the cells were replated at a density of 50 000 cells/well in 96-well plates and incubated overnight at 37 °C in a 5% CO_2 incubator. Cells were treated with 5 μL of compound or vehicle (0.1% DMSO) solution and incubated for 24 h at 37 °C in 5%CO_2 incubator. The next day, luciferase activity was measured with the Steady-Glo Luciferase Assay kit according to the manufacturer's instructions.

Induction of Selected Genes. Human peripheral blood lymphocytes were freshly prepared (ABS Inc., Wilmington, DE) and total RNA was isolated from the cells following manufacturer's instruction (Trizon method, Invitrogen Inc.). PCR primers and fluorescent probes (TagMan probe) were designed using the software PrimerDesign (Applied Biosystems, Foster City, CA). The sequences of the primers and TaqMan probe for PDHK4 (GanBank accession number U54617) are 5′-TGCATTTTTGCGACAAGAATTG (forward), 5′-TTGGGTCGGGAGGATATCAA (reverse), and 5-FAM-CTGTGAGACTCGCCAACATTCTGAAGGA-TAMRA-3. The sequences of the primers and TaqMan probe for CPT1 (GanBank accession number NM_001876) are 5′-CATTCCTTCCCATTCGTAGC (forward), 5′-AGCTGCACAAAGGCGTCTG (reverse), and 5-FAM-AGGAATCATCAAGAAATGTCGCACGAGC-TAMRA-3 (TaqMan). They were synthesized by Keystone Labs (Camarillo, CA). Reverse transcription (RT) was conducted following manufacturer's instruction using TaqMan reverse transcription reagents (Applied BioSystems). The RT reaction was 20 μL and contained 1× RT buffer, 5.5 mM $MgCl_2$, 0.5 mM dNTP, 2.5 μM of random hexamer, 1 unit of RNase Inhibitor, 1 unit of MultisScribe RT enzyme, and 0.5 μg of total RNA. The reaction was carried out at 48 °C for 30 min, and then 95 °C for 5 min, and finally 4 °C. The reaction volume was extended into 62.5 μL, and 5 μL of the RT (equivalent to 40 ng of total RNA) was used for PCR amplification. Each reaction was carried out a total volume of 25 μL containing 5 μL of RT, 1× Master Mix (reaction buffer, dNTP, polymerase, Applied Biosystems), 0.2 μM of forward, reverse primers, and TaqMan probe. The reaction was performed in a DNA sequence detector (Model 7900, Applied BioSystems) with the conditions of 50 °C for 2 min and 94 °C for 10 min, followed by 40 cycles of 94 °C for 15 s and 59 °C for 1 min. For real time PCR quatitation, the measurement of human 18S ribosomal RNA was used as an internal control for normalization of measuring and loading errors. PCR data were collected by Ct value (the cycle number at which logarithmic PCR plots cross a calculated threshold line) according to the manufacturer's guidelines and the value was used to determine the Δ^{Ct} (Ct of the target gene minus the Ct of 18S ribosomal RNA controls). Relative mRNA level was calculated using the equation $2^{-\Delta\Delta^{Ct}}$.

In Vivo Rat Model. Male Sprague−Dawley rats weighing between 275 and 325 g at the start of treatment were used (ACE Animals, Inc, Boyertown, PA). All but six rats were fed an atherogenic (high cholesterol) diet (C13002, Research Diets, New Brunswick, NJ) for 6 days before starting treatment. The remaining six rats received normal chow (Purina 5001) and were also orally dosed with vehicle during the treatment period. The diets continued during the treatment period. The compound was formulated in 0.5% Methocel, which was also the vehicle for the control animals, and the animals were orally dosed at a volume of 10 mL/kg once daily for 8 days. On day 9, the animals were anesthetized with 70%CO_2/30%O_2 and blood was obtained from the retro-orbital sinus. Serum was prepared and the lipid parameters were measured using a COBAS analyzer (Roche Diagnostics). The animals were then sacrificed, and the livers were removed (from six animals per group) and weighed.

In Vivo hApoA1 and ob/ob Mouse Models. Male hAPOA1 transgenic mice and Female ob/ob mice (C57BL/6J-Lepob) were purchased from Jackson Labs (Bar Harbor, ME). Compound **24** in 0.5% methylcellulose suspension was dosed orally for 7 or 11 days, respectively. Serum levels of HDL-C, triglyceride, free fatty acids, and/or glucose were collected under fed conditions and measured using a COBAS Mira Plus blood chemistry analyzer (Roche Diagnostic Systems, Indianapolis, IN). Statistical analysis was performed using the program Prism (Graphpad, Monrovia, CA) and with one-way analysis of variance and Dunnett's multiple comparison test.

Pharmacokinetic Assay. Rats were dosed intravenously (iv) at levels of 1−3 mg/kg and by oral gavage at a level of 3−10 mg/kg with drug candidates. Drug compound was formulated for iv dosing as a solution in 10% w/v Solutol in 5% dextrose in sterile water vehicle (D5W). Drug compound was formulated for oral dosing as a uniform suspension in 0.5% methylcellulose vehicle. Blood samples (0.5 mL) were collected into heparinized tubes post dose via orbital sinus puncture. Blood samples were centrifuged for cell removal, and precisely 200 μL of plasma supernatant was then transferred to a clean vial, placed on dry ice, and subsequently stored in a −70 °C freezer prior to analysis. Plasma samples were prepared as follows. Four hundred microliters of acetonitrile containing internal standard was added to 200 μL of plasma to precipitate proteins. Samples were centrifuged at 5000*g* for 3 min, and supernatant was removed for analysis by LC-MS−MS. Calibration standards were prepared by adding appropriate volumes of stock solution directly into plasma and treated identically to collected plasma samples. Calibration standards were prepared in the range from 0.1 to 10 mM for quantitation. LC-MS−MS analysis was performed using either multiple reaction or selected ion monitoring for detection of characteristic ions for each drug candidate, and the internal standard used was Propranolol.

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Supporting Information Available: Elemental analysis data for target molecules, PPARα agonist (compound **2.1**), and PPARδ agonist (compound **f**) are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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