(2*R*)-2-Ethylchromane-2-carboxylic Acids: Discovery of Novel PPARα/γ Dual Agonists as Antihyperglycemic and Hypolipidemic Agents

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A series of chromane-2-carboxylic acid derivatives was synthesized and evaluated for PPAR agonist activities. A structure−activity relationship was developed toward PPARα/γ dual agonism. As a result, (2*R*)-7-{3-[2-chloro-4-(4-fluorophenoxy)phenoxy]propoxy}-2-ethylchromane-2-carboxylic acid (**48**) was identified as a potent, structurally novel, selective PPARα/γ dual agonist. Compound **48** exhibited substantial antihyperglycemic and hypolipidemic activities when orally administered in three different animal models: the *db*/*db* mouse type 2 diabetes model, a Syrian hamster lipid model, and a dog lipid model.

Introduction

Type 2 diabetes is a chronic disease characterized by insulin resistance in the liver and peripheral tissues accompanied by a defect in pancreatic β-cells.[1−3] Insulin resistance is a state in which the body fails to sufficiently respond to normal circulating levels of insulin. In the United States, diabetes is the fifth leading cause of death and approximately 12 million people were diagnosed with diabetes, over 90% with type 2. The cost for lost productivity and medical treatment in 2002 was estimated at $132 billion.[4] In the late 1990s, a new class of drugs called "glitazones" (or "thiazolidinediones")[5] was approved by the FDA for the treatment of type 2 diabetes (Chart 1). These agents share a common partial chemical structure: thiazolidine-2,4-dione (TZD). Glitazones correct hyperglycemia by enhancing insulin sensitivity of adipose, hepatic, and skeletal muscle tissues.[6] Because of this mode of action, glitazone treatment is not associated with dangerous hypoglycemic incidents that have been observed with conventional sulfonylurea agents and insulin therapy. In the mid 1990s, the molecular target of glitazones was discovered to be the peroxisome proliferator-activated receptor-γ (PPARγ).[7−9] The PPARs[10−17] are a group of nuclear receptors that act as transcriptional factors, which play a major role in the regulation of lipid metabolism and storage. To date, three isoforms (γ, δ(β), and α) have been identified. PPARγ is predominantly expressed in adipose tissue; its activation enhances adipocyte differentiation and lipid uptake and storage by adipocytes.

Obesity, insulin resistance, and dyslipidemia are generally found as a part of a complex mixture of metabolic abnormalities collectively known as the metabolic syndrome.[18−20] The majority (∼80%) of type 2 diabetes patients are obese,[21] and atherogenic lipid abnormalities such as elevated triglyceride levels and low high-density lipoprotein (HDL)-cholesterol (HDLc) levels are frequently observed among patients with type 2 diabetes (diabetic dyslipidemia).[21−25] Epidemiological studies have shown that type 2 diabetes is associated with a 2−4-fold increased risk of coronary heart disease (CHD) and a 2−3-fold increased risk of ischemic stroke.[22,23] Approximately 75−80% of adult diabetic patients die from CHD or cerebrovascular disease.[23] These findings clearly indicate the unmet clinical needs of lipid profile management among diabetics.

Fibric acid derivatives (fibrates) have been used clinically to treat dyslipidemia for the past two decades (Chart 2). Fibrates effectively lower the plasma triglyceride level and modestly increase the HDLc concentration while lowering the low-density lipoprotein-cholesterol level to a variable extent.[22,26] While fibrates were first identified as weak agonists of PPARα in the early

Chart 1. Glitazone Class of Antidiabetic Drugs

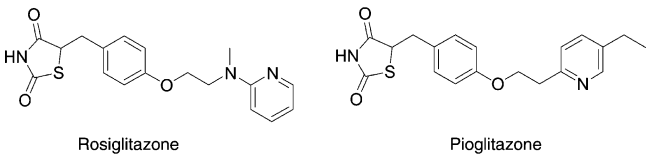
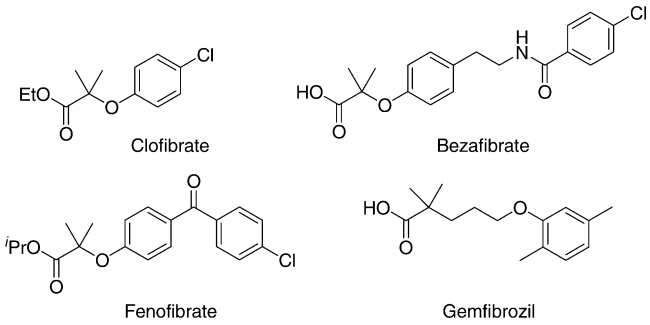


Chart 2. Fibrate Class of Hypolipidemic Drugs



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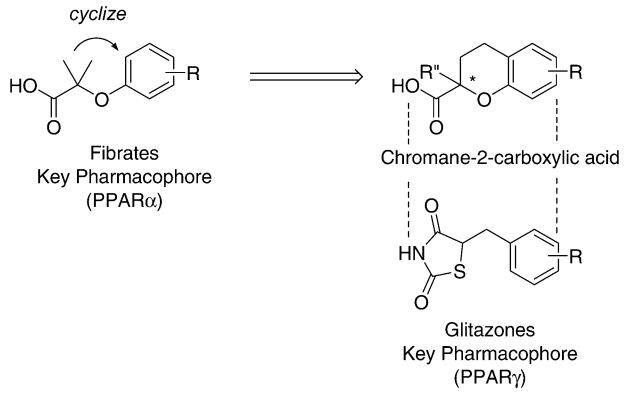


Figure 1. Cyclized fibrate concept.

1990s,[15] a recent study revealed that fibrates are rather nonselective PPAR agonists.[10] Their beneficial effect on lipids is considered to be mainly driven by the activation of PPARα. PPARα is predominantly expressed in the liver, where its activation results in enhanced lipid uptake and catabolic metabolism. In a recent large clinical trial, gemfibrozil treatment resulted in a 22% decrease in CHD death and nonfatal myocardial infarction incidents among patients with coronary disease and low HDLc levels (VA-HIT study).[27,28] Also, fenofibrate has been shown to reduce the progression of atherosclerosis and coronary events among patients with diabetes.[29]

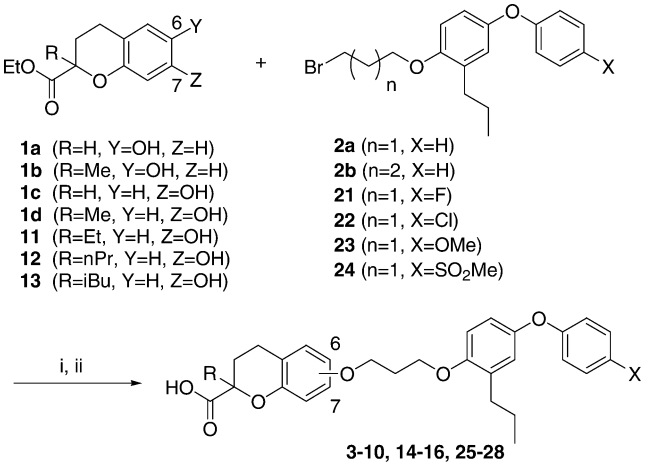
Considering the significantly increased risk of CHD among patients with type 2 diabetes and the demonstrated clinical beneficial effects of fibrates on lipid profiles, we and others have postulated that a PPARα/γ dual agonist might present a superior agent for the treatment of type 2 diabetes and dyslipidemia.[30−40] A number of new chemical entities with PPARα/γ dual activity are currently in preclinical and clinical studies. A successful launch of the first agent of this class would ultimately validate the concept of PPARα/γ dual activation for the treatment of hyperglycemia and dyslipidemia in type 2 diabetes.

Design Concept for the PPARα/γ Dual Agonists

As a class, glitazones have a chiral center at the 5-positon of the TZD ring. In the case of rosiglitazone, it has been recently reported that only the (*S*)-enantiomer carries the PPAR activity and that the enantiomers quickly racemize under physiological conditions.[41,42] To date, all glitazones have been developed as racemates. Glitazones are generally PPARγ selective agonists. Fibric acid (2-phenoxyisobutyric acid) is a common substructure of fibrates. Gemfibrozil has a tris-homo fibric acid moiety instead of fibric acid. Currently, marketed fibrates are all achiral entities.

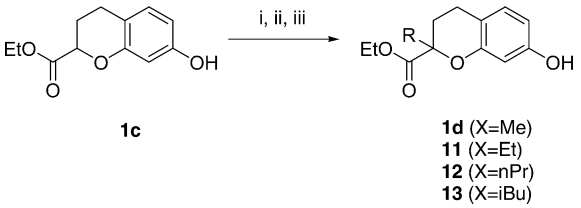
With this background, we set out to discover a potent PPARα/γ dual agonist, which is chiral and structurally distinct from glitazones. For the structural design, we started from fibric acid. Thus, by forming a ring between the phenyl group and the alkyl substituent α to the carboxylate moiety, we conceived chromane-2-carboxylic acid with a chiral center at the 2-position of the chromane ring (Figure 1). We hoped that the PPARα activities from the fibric acid moiety would be preserved even after forming an extra ring. Given that TZD can be viewed as a replacement of the carboxylic acid moiety, it is interesting to note that the key functional groups, namely, the acidic functional groups and the phenyl group, are laid out in a very similar fashion in both chromane-2-carboxylic acids and glitazones. On the basis of this structural similarity, we assumed that it would be possible to build PPARγ activity into the chromane-2-carboxylic acid series. This "cyclized fibrate" concept for generating chiral fibrates is not entirely new. A few attempts have been reported since the 1970s, but almost no improvement in the hypolipidemic activity was observed.[43,44] The scope of our structure−activity relationship (SAR) studies is summarized in the structure in Table 1.

Scheme 1[a]



[a] Reagents: (i) Cs_2CO_3, DMF, 65 °C. (ii) 2N NaOH, ^{i}PrOH, 70 °C.

Scheme 2[a]



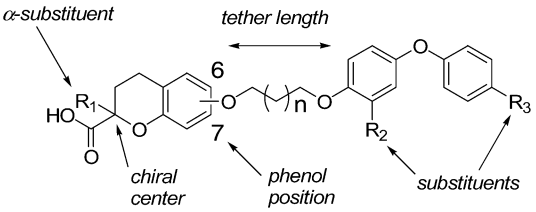
[a] Reagents: (i) Bzl−Br, K_2CO_3, acetone refluxed. (ii) Na−HMDS, R−I, THF−HMPA, −78 °C. (iii) Pd/C, H_2, EtOH.

Chemistry

Compounds **3**−**10** were synthesized as described in Scheme 1. An ether bond was formed between the 6- or the 7-hydroxy-chromane-2-carboxylates (**1a**−**d**) shown in Scheme 1 and the bromides (**2a**,**b**) using cesium carbonate in dimethyl formamide (DMF) at 65 °C. The resulting ester products were hydrolyzed to give the desired carboxylic acids (**3**−**10**). Ethyl 6-hydroxychromane-2-carboxylate (**1a**),[45] ethyl 6-hydroxy-2-methylchromane-2-carboxylate (**1b**),[46] and ethyl 7-hydroxychromane-2-carboxylate (**1c**)[47] were prepared according to the procedures reported in the literature. Compounds **1d** and **11**−**13** were prepared from **1c** through a sequence of reactions: (i) protection of the phenol by a benzyl group; (ii) standard ester enolate alkylation using alkyl iodide and HMPA as a cosolvent; and (iii) deprotection of the benzyl group (Scheme 2).

Compounds **14**−**16** were prepared as described in general Scheme 1 employing phenols **11**−**13**. Compounds **25**−**28** in Scheme 1 were synthesized from

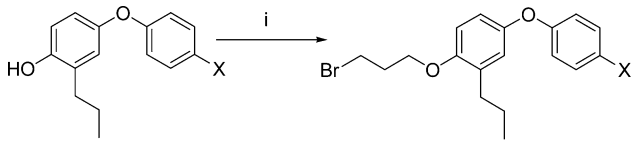
Table 1. In Vitro Human PPAR Activities of Chromane-2-carboxylic Acids



compd	phenol position	*n*	R_1	R_2	R_3	(*R*/*S*)[b]	SPA IC_{50} (μM)[a] α	SPA IC_{50} (μM)[a] δ	SPA IC_{50} (μM)[a] γ	TA EC_{50} (μM)[a] α	TA EC_{50} (μM)[a] γ
3	6	1	H	$^{n-}$Pr	H	racemic[c]	>15	>15	2.9	NA[d]	2.8
4	6	1	Me	$^{n-}$Pr	H	racemic	3.3	>50	1.7	NA	6.8
5	6	2	H	$^{n-}$Pr	H	racemic	5.8	>50	3.0	NA	2.5
6	6	2	Me	$^{n-}$Pr	H	racemic	2.0	>50	2.3	NA	1.2
7	7	1	H	$^{n-}$Pr	H	racemic	1.5	0.17	0.98	3.0	7.3
8	7	1	Me	$^{n-}$Pr	H	racemic	1.9	>50	0.75	0.1	1.0
9	7	2	H	$^{n-}$Pr	H	racemic	>15	>15	1.8	6.3	1.6
10	7	2	Me	$^{n-}$Pr	H	racemic	>15	>50	5.1	5.2	3.6
14	7	1	Et	$^{n-}$Pr	H	racemic	0.36	>50	0.44	0.03	1.0
15	7	1	$^{n-}$Pr	$^{n-}$Pr	H	racemic	2.1	>50	0.37	0.12	0.83
16	7	1	$^{i-}$Bu	$^{n-}$Pr	H	racemic	3.0	5.0	1.2	NT[e]	NT
25	7	1	Et	$^{n-}$Pr	F	racemic	0.97	>50	1.2	0.01	0.75
26	7	1	Et	$^{n-}$Pr	Cl	racemic	4.0	>50	1.4	0.21	0.67
27	7	1	Et	$^{n-}$Pr	OMe	racemic	>15	>50	0.63	4.6	0.89
28	7	1	Et	$^{n-}$Pr	SO_2Me	racemic	>15	>50	0.37	NA	2.8
37	7	1	Et	H	H	racemic	1.7	>50	>15	0.22	10
38	7	1	Et	F	H	racemic	0.37	>50	4.7	0.05	1.0
39	7	1	Et	Cl	H	racemic	0.12	>15	0.69	0.03	0.16
40	7	1	Me	Cl	H	racemic	0.12	>15	1.4	0.08	0.36
46	7	1	Et	Cl	H	(*R*)	0.06	>15	0.25	0.01	0.08
47	7	1	Et	Cl	H	(*S*)	>15	>50	1.4	4.2	7.6
48	7	1	Et	Cl	F	(*R*)	0.06	>15	0.26	0.04	0.17
49	7	1	Et	Cl	F	(*S*)	>15	>50	4.4	6.1	5.0
rosiglitazone							>15	>50	0.2	NA	0.02

[a] Mean values are shown ($n = 3$); SD ± 15%; SPA (scintillation proximity assay);[51] TA (chimeric GAL4-*h*PPAR transactivation assay).[52] [b] Absolute stereochemistry of the chiral center at the 2-position of the chromane ring. [c] Racemic mixture. [d] Not active: <20% activation at 10 μM. [e] Not tested.

Scheme 3[a]



17 (X=F)
18 (X=Cl)
19 (X=OMe)
20 (X=SO_2Me)

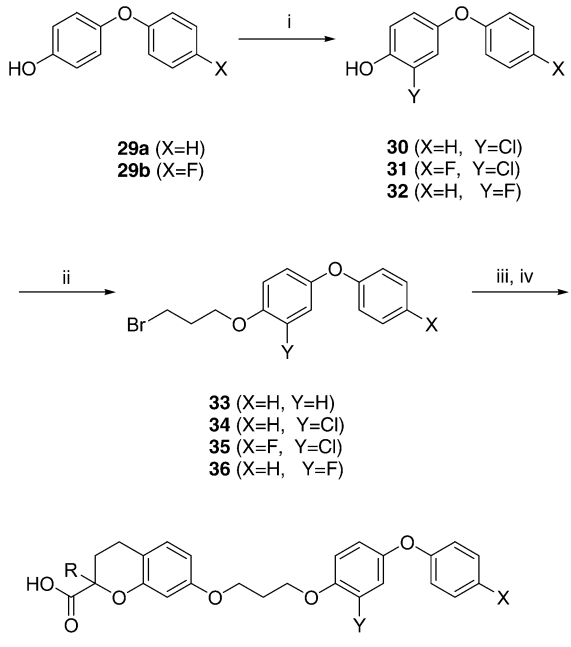
21 (X=F)
22 (X=Cl)
23 (X=OMe)
24 (X=SO_2Me)

[a] Reagents: (i) $Br(CH)_3Br$, Cs_2CO_3, DMF, 65 °C.

chromane carboxylate **11** and the bromides **21**−**24** (Scheme 3). Bromides **21**−**24** were prepared from known phenols **17**−**20** by forming an ether bond with 1,3-dibromopropane employing cesium carbonate (Scheme 3).[48−50]

Compounds **37**−**40** were synthesized from appropriately substituted chromanes **1d** and **11** and the bromides **33**−**36** (Scheme 4), followed by ester hydrolysis. Introduction of a halogen atom at the ortho position of the phenols **29a**,**b** was performed by electrophilic aromatic substitution reactions (Scheme 4). Upon treatment with sulfuryl chloride in toluene at 70 °C, phenoxyphenol derivatives **29a**,**b** gave the chloro-substituted phenols **30** and **31**. Introduction of a fluoro group to phenol **29a** was performed using 3,5-dichloro-1-fluoropyridinium triflate, giving **32**. These ortho halogen-substituted phenols were reacted with 1,3-dibromopropane, giving bromides **34**−**36**. Bromide **33** was synthesized from **29a** reacting with 1,3-dibromopropane.

Scheme 4[a]



29a (X=H)
29b (X=F)

30 (X=H, Y=Cl)
31 (X=F, Y=Cl)
32 (X=H, Y=F)

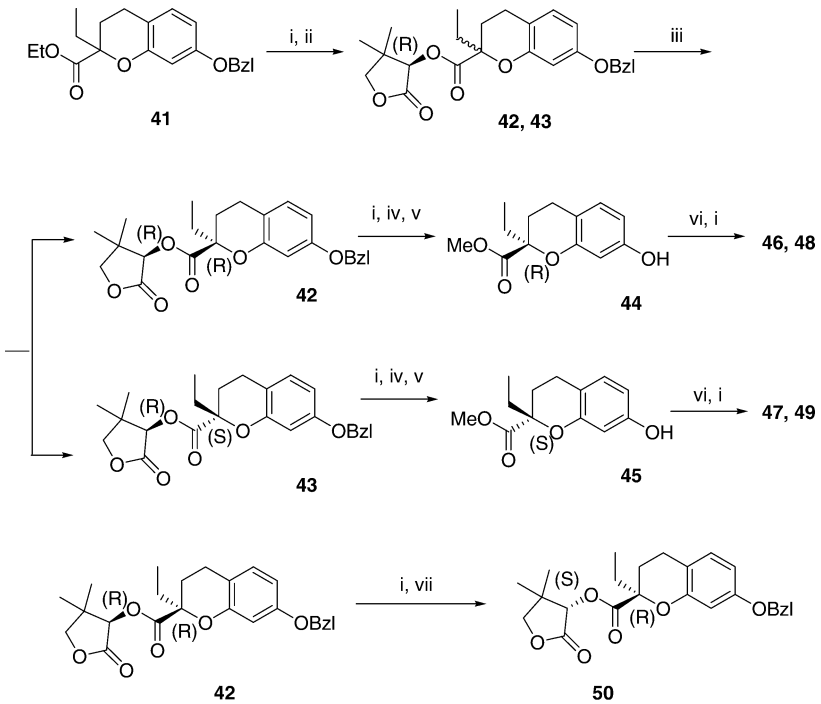
33 (X=H, Y=H)
34 (X=H, Y=Cl)
35 (X=F, Y=Cl)
36 (X=H, Y=F)

37-40

[a] Reagents: (i) SO_2Cl_2, diisobutylamine, toluene, 70 °C, or 3,5-dichloro-1-fluoropyridinium triflate, CH_2Cl_2−CH_3CN (9:1), 0 °C to room temperature. (ii) $Br(CH_2)_3Br$, Cs_2CO_3, DMF, 65 °C. (iii) Compounds **1d** or **11**, Cs_2CO_3, DMF, 65 °C. (iv) 2N NaOH, ^{i}PrOH, 70 °C.

Chiral resolution of the intermediate **41** was accomplished by forming a covalent bond with the chiral

Scheme 5[a]



[a] Reagents: (i) 2N NaOH, ^{i}PrOH, 70 °C. (ii) (*R*)-Pantolactone, EDCI, CH_2Cl_2. (iii) Chromatographic separation. (iv) CH_2N_2. (v) 10% Pd/C, H_2, EtOH. (vi) Bromide **34** or **35**, Cs_2CO_3, DMF, 65 °C. (vii) (*S*)-Pantolactone, EDCI, CH_2Cl_2.

auxiliary (*R*)-pantolactone, which generated a pair of chromatographically separable diastereomers (Scheme 5). The ethyl ester group of **41** was hydrolyzed to give the corresponding carboxylic acid, which was esterified with (*R*)-pantolactone using EDCI in dichloromethane to give a mixture of the (*R*,*R*)-isomer **42** and the (*R*,*S*)-isomer **43**. These diastereomers were easily separated by flash chromatography. We decided to determine the absolute stereochemistry of the pantolactone-ester that gave the more active final compounds. While this isomer (which turned out to be **42** afterward) tended to remain as an oil, replacement of its pantolactone moiety (*R*-isomer) with the other enantiomer (*S*-pantolactone) gave **50** that was found to be highly crystalline (Scheme 5). By using X-ray crystal analysis, the absolute stereochemistry of the 2-position of the chromane ring of **50** was determined to be (*R*) relative to the known chiral center of (*S*)-pantolactone. On the basis of this finding, the absolute stereochemistries of **42**−**49** were assigned as shown in Scheme 5. After the chiral resolution, isomers **42** and **43** were individually hydrolyzed, esterified with diazomethane, and debenzylated to give compounds **44** and **45**, respectively. Chiral intermediates **44** and **45** were separately recrystallized from dichloromethane/hexanes to yield prisms, which have the same rotation value in opposite directions. Chiral compounds **46**−**49** were synthesized starting from the chiral intermediates **44** and **45** as described in Scheme 5.

Biology

In Vitro. Activities of compounds were evaluated for both binding affinity and functional activity. First, binding affinities for the PPARs were measured in a scintillation proximity assay (SPA).[51] Second, potencies of PPAR gene activation were evaluated in cell-based transcription assays using GAL4-PPAR chimeric receptors.[52] All results were produced in triplicate, and mean values are reported. Generally, the SAR was directed based on the results of these two in vitro assays. Because the high binding affinity for the receptor did not necessarily translate into significant functional activity, the binding assay was mainly used as a primary screen to exclude inactive compounds.

In Vivo. *db/db* Mouse Studies. *db*/*db* (lepr^{db-3J}/lepr^{db-3J}) mice were used as a type 2 diabetic animal model. Male *db*/*db* mice at 12−13 weeks of age and nondiabetic *db*/+ (lean) mice from Jackson Laboratories were housed seven mice per cage and fed a rodent chow (Purina no. 5001) ad libitum with free access to water. Mice (seven per group) received a once daily oral dosing of test compounds with vehicle (0.25% methylcellulose) by oral gavage for 11 days. The blood was collected from the tail immediately prior to the next dosing at days 0, 4, 7, and 11 for measurement of the plasma glucose levels.

Hamster Lipid Studies. Golden Syrian hamsters weighing between 120 and 150 g were purchased from Charles River Laboratories and used for the experiments. Hamsters were housed in boxes (five per box) and fed a normal rodent chow ad libitum with free access to water. Hamsters (ten for each group) were orally dosed with compounds (suspended in 0.5% methylcellulose) for 9 days. On the morning of the 10th day, hamsters were euthanized with carbon dioxide, and blood samples were obtained via heart puncture. Serum cholesterol and triglyceride levels were determined from the samples.

Dog Lipid Studies. Mature male Beagle dogs weighing between 12 and 18 kg were purchased from Marshall Farm, PA. They were housed individually and fed a cholesterol-free chow diet ad libitum with free access to water. Prior to starting experiments, the dogs (five for each group) were bled weekly from the jugular vein

and their serum cholesterol levels were determined. Test compounds were suspended in 0.5% methylcellulose and gavaged daily to the dogs for 2 weeks. Blood samples were taken during and after the dosing periods, and serum cholesterol levels were determined.

Pharmacokinetic Studies. Male Sprague−Dawley rats ($n = 3$), male adult Beagle dogs ($n = 4$), and male adult Rhesus monkeys ($n = 3$) that had been fasted overnight received an oral gavage dose of 2 mg/kg, or an intravenous dose of 0.5 mg/kg by bolus injection. Blood samples were obtained from the femoral arterial cannula for rat, the jugular vein for dog, and the saphenous vein for monkey at designated time points into heparin-containing tubes. The plasma was prepared immediately by centrifugation, acidified by the addition of 0.5 M formate buffer, pH 3.0, and stored at −70 °C. Quantitative analysis was carried out with LC-MS/MS using the PE Sciex API 3000 triplex quadruple mass spectrometer.

Results and Discussion

Activities of compounds with human PPARs are summarized in Table 1. Compounds **3**−**10** belong to the initial set of compounds synthesized. The effects of phenol linkage position, tether length, and α-substituent were investigated. As for the effect of the phenol linkage position, compounds with a 6-phenol linkage (**3**−**6**) clearly lack in PPARα functional activity as seen in the transactivation assay results. On the contrary, compounds with a 7-phenol linkage (**7**−**10**) have both PPARγ and PPARα activities, albeit not really potent. For the tether length, the three-methylene tether ($n = 1$) seemed to give superior results as compared with the four-methylene tether ($n = 2$) on both PPARγ and PPARα binding affinities (comparing compounds **7** and **9**, **8** and **10**). The effect of the α-substituent was not clear from these data. It was quite encouraging that we were able to see PPARα/γ dual activity from the very first set of the compounds prepared. On the basis of these findings, we decided to take compound **8** as a lead and continue SAR studies with the 7-phenol linkage and the three-methylene tether.

We then decided to investigate the effect of the α-substituent more carefully. From the results of compounds **7**, **8**, and **14**−**16**, it became clear from the binding affinity results that there is a desirable range of size for the α-substituent. While methyl and ethyl groups showed comparable levels of PPARγ activation, the ethyl group gave superior PPARα activation. Therefore, we decided to continue SAR studies primarily with the ethyl group as the α-substituent.

Having optimized structural features for the left side of the molecule, we then turned our attention to the right side of the molecule and synthesized compounds (**25**−**28**). We anticipated that the R_3 position, para to the oxygen substituent, might be metabolically vulnerable. We assumed that it was prudent to block this position with a substituent that is resistant to metabolic oxidation. When compounds **14** and **25**−**28** were compared, it appeared that the spacial requirement for this position was rather critical; only hydrogen and fluoro substituents seemed to be tolerated in order to maintain potent PPARα activity. With respect to the PPARγ activity, the effect of the R_3 substituent did not seem to be significant. In our previous series of PPAR agonists, the propyl substituent at the R_2 position has been essential for the PPARγ activity.[38,50−52] The effect of the R_2 group can be seen when compounds **14** and **37**−**39** and compounds **8** and **40** are compared. As the size of the substituent increased, the PPARγ binding affinity seemed to improve. However, as for the functional activities, there seemed to be a desirable range of size for the R_2 group. The chlorine substituent at the R_2 position gave consistently superior functional activity for PPARγ as compared with the ones with the propyl group at the R_2 position (**14** and **39** and **8** and **40**). From this study, it became clear that the chloro substituent at the R_2 position is optimal for both PPARγ and PPARα functional activities.

Finally, we decided to examine the effect of chirality. Chiral resolution was performed on our most potent compound **39**. Compounds **46** and **47** are the (*R*)- and (*S*)-enantiomers of compound **39**, respectively. Clearly, the (*R*)-enantiomer carries far superior activity. Compounds **48** and **49** were prepared as fluoro-substituted analogues of **46** and **47** because of the potential metabolism concern that was described earlier. Again, the more active enantiomer has the (*R*)-stereochemistry. Compound **48** showed no appreciable level of activity in the human PPARδ transactivation assay (25% activation at 10 μM). Table 2 summarizes the pharmacokinetic profiles of **46** and **48**. In rat, compound **48** has a significantly higher exposure (nAUC = dose-normalized AUC), lower clearance (Clp), and longer half-life ($t_{1/2}$) than compound **46**. Although compound **46** has slightly better in vitro activities than **48**, we opted for **48** because of its superior pharmacokinetic profile. Pharmacokinetic profiles and in vitro PPAR activities of compound **48** in other experimental animal species are listed in Tables 2 and 3. We were pleased to find that compound **48** has desirable pharmacokinetic profiles and in vitro activities also in dogs and rhesus monkeys.

Having optimized the in vitro activities, we then decided to test our most potent compound in the *db*/*db* mouse type 2 diabetes model. The *db*/*db* mouse is an obese animal model of type 2 diabetes and is characterized by severe insulin resistance and marked hyper-

Table 2. Pharmacokinetic Profiles of **46** and **48**

compd	species	route	dose (mpk)	nAUC[a,b] (μM h)	Clp[a] (mL/min/kg)	$t_{1/2}$[a] (h)	F (%)
46	rat	iv	0.5	5.6 ± 0.2	5.8 ± 0.2	1.2 ± 0.3	
		po	2.0	2.6 ± 1.4			43
48	rat	iv	0.5	10 ± 1.9	3.4 ± 0.6	4.6 ± 0.8	
		po	2.0	4.8 ± 0.6		3.7 ± 0.7	48
	dog	iv	0.5		3.5 ± 1.2	10 ± 2.0	
		po	2.0	9.2 ± 4.3			92
	monkey	iv	0.5		8.6 ± 1.2	3.5 ± 1.7	
		po	2.0	1.7 ± 0.6			43

[a] Mean ± SD ($n = 3$ for rat and monkey; $n = 4$ for dog). [b] Dose-normalized AUC.

Table 3. In Vitro Activity of **48** on PPARα and PPARγ of Human and Preclinical Species

	TA EC_{50} (μM)[a]	
species	α	γ
mouse	>3	0.15
hamster	0.02	0.2
dog	0.11	0.14
human	0.04	0.17

[a] Mean values ($n = 3$) are shown; SD ± 15%.

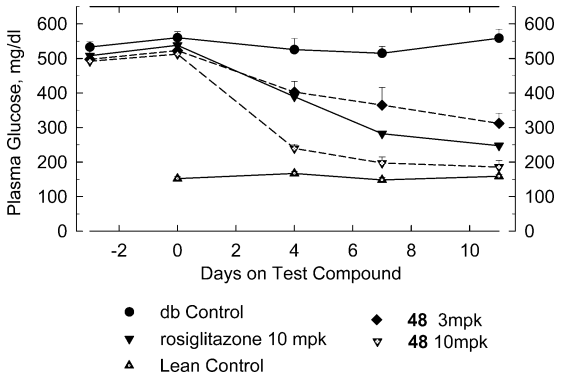


Figure 2. In vivo activity of PPARα/γ dual agonist **48** in *db*/*db* mice. Time course of antihyperglycemic activity. Lean mice ($n = 7$) and *db*/*db* mice ($n = 7$) received a once daily dosing of **48** or rosiglitazone by oral gavage with vehicle. Blood glucose levels were measured 24 h after dosing on the preceding day. The figure plots the mean value ± SD.

Table 4. Effects of **48** on Serum Cholesterol and Triglyceride in Hamster

treatment	dose (mpk)	cholesterol[a] (mg/dL)	change (%)	triglyceride[a] (mg/dL)	change (%)
vehicle		108 ± 5		305 ± 17	
fenofibrate	100	67 ± 3	−38[b]	161 ± 4	−44[b]
48	3	85 ± 3	−21[b]	222 ± 18	−27[b]
48	10	65 ± 2	−40[b]	159 ± 9	−48[b]

[a] Mean ± SD ($n = 10$). [b] $p < 0.01$ vs vehicle control.

Table 5. Effect of **48** on Serum Cholesterol in Dog[a]

treatment	dose (mpk)	change (%)
fenofibrate	50	−16.3[b]
48	1	−23.3[b]
48	3	−31.6[b]

[a] Mean values are shown ($n = 5$). [b] $p < 0.05$ vs vehicle control.

triglyceridemia. The in vivo antihyperglycemic activity of **48** is depicted in Figure 2. Compound **48** exhibited robust serum glucose level lowering in a dose-dependent manner that was comparable to rosiglitazone. Antihyperglycemic activity of **48** in the *db*/*db* mouse is mainly driven by its PPARγ activity because **48** does not have significant activity on mouse PPARα. In addition, the lipid-lowering activity of **48** was assessed in two animal models: a Syrian hamster model and a dog model. The results are summarized in Tables 4 and 5. In the hamster model, compound **48** at 10 mpk caused comparable levels of cholesterol and triglyceride lowering with fenofibrate treatment at 100 mpk. In the dog studies, compound **48** achieved superior cholesterol lowering to fenofibrate even at significantly lower doses. Importantly, compound **48** was tested against other nuclear receptors and was found to be inactive in GAL4 assays for the following receptors: no activation of hLXRα, hLXRβ, RXR, or PXR at concentrations up to 10 μM. In addition, no binding to hERα, hERβ, FXR, hTRβ, and hGR at concentrations up to 10 μM was observed.

Conclusion

We have identified a series of structurally novel antidiabetic (2*R*)-chromane-2-carboxylic acids as potent PPARα/γ dual agonists. By combining the cyclized fibrate concept and the side chains from our previous studies, we were able to successfully incorporate both PPARα and PPARγ activities into one structure. Systematic SAR studies directed toward selective PPARα/γ dual agonism culminated in the discovery of compound **48**, which exhibited comparable antihyperglycemic activities to rosiglitazone in the *db*/*db* mouse type 2 diabetes animal model studies. In addition, the lipid-lowering activities of compound **48** were amply demonstrated in a Syrian hamster model and a dog model. Unlike the currently marketed glitazone class of antidiabetic drugs, compound **48** is a single enantiomer that is not vulnerable to racemization. To date, the clinical utility of PPARγ and PPARα agonists has been proven separately by the glitazones and the fibrates, respectively. However, the general strategy of treating type 2 diabetes and dyslipidemia through the use of PPARα/γ dual agonists and the ideal balance of PPARα and PPARγ activities have yet to be validated in the clinic. Compound **48** is one such PPARα/γ dual agonist that could demonstrate the viability of this approach. It is hoped that the PPARα/γ dual activation strategy will provide a comprehensive treatment for type 2 diabetes and dyslipidemia.

Experimental Section

General. All commercial chemicals and solvents are reagent grade and were used without further purification unless otherwise specified. All reactions except those in aqueous media were carried out under nitrogen atmosphere. Chromatographic purification was performed using flash chromatography techniques and silica gel (E. Merck 230−400 mesh). The following solvents were abbreviated: tetrahydrofuran (THF), ethyl acetate (AcOEt), and methyl-*tert*-butyl-ether (MTBE). ^{1}H NMR spectra were measured using Varian Unity INOVA 500 MHz instrument. Chemical shifts were reported in parts per million (ppm, δ units) using tetramethylsilane as an internal standard. The mass spectrum was measured in the positive ion mode using HP1100 and micromass ZMD instruments (LC-MS system). Elemental analyses were obtained from Robertson Microlit Laboratories (Madison, NJ).

General Procedure for the Synthesis of 3−10, 14−16, 25−28, and 37−40. To a DMF solution of ethyl-6 (or -7)-hydroxy-chromane-carboxylate (**1a**−**d** or **11**−**13**) (1.0 equiv) and the bromide (**2a**,**b**, **21**−**24**, or **33**−**36**) (1.1 equiv) was added cesium carbonate (1.2 equiv). The resulting suspension was heated to 65 °C for 5 h. The reaction mixture was diluted with MTBE and water. The organic layer was separated. The aqueous layer was extracted twice with MTBE. The combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure, and chromatographed on silica gel eluting with a gradient mixture of AcOEt/hexanes to give the corresponding ether product. This product was dissolved in 2-propanol−2 N NaOH(aq) (3:1 v/v) and heated to 70 °C overnight. After most of the solvent was removed under reduced pressure, the residue was diluted with AcOEt and 2 N HCl(aq). The organic layer was separated. The aqueous layer was extracted twice with AcOEt. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to give the title compound (70−95% yield).

6-{3-[2-Propyl-4-phenoxyphenoxy]propoxy}chromane-2-carboxylic Acid (3). ^{1}H NMR (500 MHz, CD_3OD): δ 7.27 (m, 2H), 7.01 (t, 1H, $J = 7.4$ Hz), 6.89 (m, 3H), 6.77 (m, 3H), 6.69 (dd, 1H, $J = 2.8$, $J = 8.8$ Hz), 6.63 (d, 1H, $J = 2.8$ Hz), 4.62 (m, 1H), 4.13 (m, 4H), 2.82 (m, 1H), 2.72 (m, 1H), 2.55 (m, 2H), 2.25 (m, 1H), 2.22 (p, 2H, $J = 6$ Hz), 2.01 (m, 1H), 1.55 (sext, 2H, $J = 7.5$), 0.89 (t, 3H, $J = 7.3$). MS: $m/e = 463$ (M + 1). Anal. ($C_{28}H_{30}O_6$) C, H.

General Procedure of the Ester-Enolate Alkylation for the Synthesis of (1d and 11−13). The synthesis of **11** is described below. Compounds **1d**, **12**, and **13** were synthesized

following a similar procedure that employs the appropriate alkyliodide instead of iodoethane in step B.

Ethyl 2-Ethyl-7-hydroxychromane-2-carboxylate (11). Step A: Ethyl 7-Benzyloxychromane-2-carboxylate. To a 5 L acetone solution of ethyl 7-hydroxy-chromane-2-carboxylate (630.1 g, 2.84 mol) were added potassium carbonate powder (785 g, 5.68 mol) and benzyl bromide (405 mL, 3.41 mol). The resulting suspension was heated to reflux for 16 h. The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated to give solid material, which was redissolved in AcOEt, washed with water to remove residual salt, dried over anhydrous magnesium sulfate, filtered, and concentrated to a small volume. The addition of hexanes caused precipitation of the title compound, which was collected by suction−filtration. The filtrate was triturated from dichloromethane/hexanes to give more precipitates. Finally, the filtrate was concentrated and then chromatographed on silica gel, eluting with a gradient mixture of 20−80% dichloromethane/hexanes. The combination of all of the crops yielded the title compound 760.2 g as an off-white solid (86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.46 (m, 5H), 6.96 (d, 1H), 6.621 (d, 1H), 6.58 (dd, 1H), 5.05 (s, 2H), 4.72 (q, 1H), 4.29 (q, 2H), 2.69−2.84 (m, 2H), 2.29 (m, 1H), 2.21 (m, 1H), 1.33 (t, 3H).

Step B: Ethyl 7-Benzyloxy-2-ethylchromane-2-carboxylate. To a 320 mL anhydrous THF solution of ethyl 7-benzyloxychromane-2-carboxyate (14.6 g, 46.6 mmol) was added hexamethylphosphoramide (distitilled from CaH_2) (10.5 mL, 60.4 mmol). After the mixture was cooled in a dry ice−acetone bath, sodium bis(trimethylsilyl)amide (1.0 M/THF) (60.5 mL, 60.5 mmol) was added via syringe over a 15 min period. The resulting orange solution was stirred at that temperature for 30 min before iodoethane (18.6 mL, 233 mmol) was added via syringe. The reaction was slowly warmed to room temperature and stirred overnight. The solvent was removed under reduced pressure, and the residue was diluted with AcOEt and aqueous ammonium chloride (NH_4Cl 7.2 g/200 mL water). The organic layer was separated, and the aqueous layer was extracted with AcOEt twice. The combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated, and chromatographed on silica gel eluting with 7.5% AcOEt/hexanes to give the title compound 15.2 g (96%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (m, 4H), 7.30 (m, 1H), 6.89 (d, 1H, J = 8.3 Hz), 6.53 (d, 1H, J = 2.6 Hz), 6.45 (dd, 1H, J = 2.5 Hz, 8.2 Hz), 4.54 (s, 2H), 4.19 (m, 2H), 4.07 (m, 2H), 3.67 (t, 2H, J = 6.3 Hz), 2.66−2.61 (m, 2H), 2.33 (m, 1H), 2.09 (p, 2H, J = 6.2 Hz), 2.00 (m, 1H), 1.91 (m, 2H), 1.23 (t, 3H J = 7.1 Hz), 1.04 (t, 3H, J = 7.4 Hz). MS m/e = 341 (M + 1).

Step C: Ethyl 7-Hydroxy-2-ethylchromane-2-carboxylate (11). To a 5 mL ethanol solution of ethyl 7-benzyloxy-2-ethylchromane-2-carboxylate (228 mg, 0.67 mmol) were added 0.25 mL of water and 10 mg of 10% Pd/C. The resulting suspension was placed in a Parr shaker and hydrogenated under hydrogen atmosphere at 50 psi overnight. The reaction suspension was then filtered through a pad of Celite, concentrated, and chromatographed on silica gel. Elution with a gradient mixture of 20−30% AcOEt/hexanes gave the title compound (166 mg, quant.) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.87 (d, 1H, J = 8 Hz), 6.47 (d, 1H, J = 2.8 Hz), 6.38 (dd, 1H, J = 2.8 Hz, 8 Hz), 4.99 (brs, 1H), 4.20 (m, 2H), 2.65 (m, 2H), 2.32 (m, 1H), 2.05−1.85 (m, 4H), 1.24 (t, 3H, J = 7 Hz), 1.04 (t, 3H, J = 7 Hz). MS m/e = 251 (M + 1). Anal. ($C_{14}H_{18}O_4$) C, H.

General Procedure for the Synthesis of 21−24 and 33−36. To a DMF solution (0.2 M based on the phenol) of the phenol (**17**−**20** and **30**−**32**) (1.0 equiv) and 1,3-dibromopropane (5.0 equiv) was added cesium carbonate (1.3 equiv). The resulting suspension was heated to 65 °C overnight. The reaction mixture was diluted with AcOEt and water. The organic layer was separated. The aqueous layer was extracted twice with AcOEt. The combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated, and chromatographed on silica gel. Elution with a gradient mixture of AcOEt/hexanes or MTBE/hexanes yielded the title compounds (yield 70−90%). Generally, the product contained a small amount (5%) of an elimination product (3-[2-propyl-4-phenoxyphenoxy]-1-propene).

3-[2-Propyl-4-(4-fluorophenoxy)phenoxy]-1-bromopropane (21). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.03−6.99 (m, 2H), 6.95−6.92 (m, 2H), 6.86−6.79 (m, 3H), 4.11 (t, 2H, J = 5.8 Hz), 3.66 (t, 2H, J = 5.8 Hz), 2.58 (t, 2H, J = 7.8 Hz), 2.37 (q, 2H, J = 5.8 Hz), 1.60 (m, 2H), 0.96 (t, 3H, J = 7.3 Hz).

2-Chloro-4-phenoxyphenol (30). A 54 mL toluene solution of 4-phenoxyphenol (2.0 g, 107 mmol) and diisobutylamine (0.15 mL, 0.86 mmol) was heated to 70 °C. To it was added sulfuryl chloride (0.69 mL, 8.6 mmol) over 2 h. The reaction mixture was stirred for 1 h after the addition was complete. Then, the reaction mixture was concentrated and diluted in AcOEt and saturated aqueous sodium bicarbonate solution. The organic layer was separated. The aqueous layer was extracted twice with AcOEt. The combined organic layer was dried over anhydrous sodium sulfate, filtered, concentrated, and chromatographed on silica gel. Elution with 15% AcOEt/hexanes gave the title compound as a pale yellow syrup (2.3 g, 97%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (m, 2H), 7.12 (m, 1H), 7.06 (d, 1H), 7.02 (d, 1H), 6.99 (d, 2H), 6.92 (dd, 1H), 5.69 (s, 1H). Anal. ($C_{12}H_9O_2Cl_1$) C, H, Cl.

2-Chloro-4-(4-fluorophenoxy)phenol (31). This compound was prepared from 4-(4-fluorophenoxy)phenol according to a procedure similar to the one used for the synthesis of compound **30**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.06−7.00 (m, 4H), 6.98−6.94 (m, 2H), 6.88 (app. q. 1H), 5.40 (s, 1H).

2-Fluoro-4-phenoxyphenol (32). To a 250 mL dichloromethane solution of 4-phenoxyphenol (2.0 g, 10.7 mmol) was added 3,5-dichloro-1-fluoro-pyridinium triflate (4.14 g, 13.1 mmol). After the mixture was heated to reflux for 1 h, the solvent was removed. The residue was diluted with AcOEt and saturated aqueous sodium bicarbonate solution. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, concentrated, and chromatographed on silica gel. Elution with 10% MTBE/hexanes gave 312 mg of the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (m, 2H), 7.11 (m, 1H), 6.98 (m, 3H), 6.82 (dd, 1H), 6.76 (m, 1H), 5.00 (s, 1H).

Optical Resolution of Ethyl 7-Benzyloxy-2-ethylchromane-2-carboxylate (41). (2*R*)-Methyl 2-Ethyl-7-hydroxychromane-2-carboxylate (44). Step A: 7-Benzyloxy-2-ethylchromane-2-carboxylic Acid. To a 2 L 2-propanol solution of ethyl 7-benzyloxy-2-ethylchromane-2-carboxylate (**41**) (155 g, 0.455 mol) was added 1 L of aqueous 5 N sodium hydroxide. This solution was heated to 70 °C overnight. 2-Propanol was removed under reduced pressure. The residue was acidified with 300 mL of concentrated hydrochloric acid and 2 N hydrochloric acid to pH 1. The acidic solution was extracted three times with AcOEt. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to give a yellow oil, which crystallized upon standing (130 g, 91%).

Step B: Resolution of the Racemate. (1) Ester Formation with (*R*)-Pantolactone. To a 1.1 L dichloromethane solution of 7-benzyloxy-2-ethylchromane-2-carboxylic acid (75 g, 0.24 mol) and (*R*)-pantolactone (100 g, 0.768 mol) were added EDCI (55.5 g, 0.289 mol) and 4-(dimethylamino)pyridine (6.4 g, 0.054 mol). This solution was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue was diluted with AcOEt, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to give a yellow oil (137 g, crude).

(2) Chromatographic Separation of the Diastereomers. The crude ester obtained as described above was dissolved in hexanes and a small amount of dichloromethane and then charged on a silica gel column. Elution with 10% THF/hexanes (48 Ls), 12.5% THF/hexanes (64 Ls), and 25% AcOEt/hexanes (4 Ls) gave the faster eluting **42** (*R*,*R*)-isomer (30.4 g, 30%) as a thick colorless oil, the more slowly eluting **43** (*R*,*S*)-isomer (34.5 g, 34%) as a white solid, and a mixture of the diastereomers (7 g, 7%) as a yellow oil.

Compound 42. (*R*,*R*)-Isomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (m, 2H), 7.44 (m, 2H), 7.33 (m, 1H), 6.93 (d,

1H, J = 8.5 Hz), 6.61 (d, 1H, J = 2.5 Hz), 6.55 (dd, 1H, J = 2.6, 8.4 Hz), 5.35 (s, 1H), 5.05 (s, 2H), 4.00 (s, 2H), 2.75 (m, 2H), 2.45 (m, 1H), 2.10 (m, 1H), 1.95 (m, 2H), 1.31 (t, 3H, J = 7.5 Hz), 1.03 (s, 3H), 0.87 (s, 3H).

Compound 43. (*R*,*S*)-Isomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (m, 2H), 7.39 (m, 2H), 7.33 (m, 1H), 6.93 (d, 1H, J = 8.5 Hz), 6.59 (1H, J = 2.5 Hz), 6.54 (dd, 1H, J = 2.6, 8.4 Hz), 5.35 (s, 1H), 5.05 (s, 2H), 4.0 (s, 2H), 2.75 (m, 2H), 2.35 (m, 1H), 2.10 (m, 1H), 2.00 (m, 2H), 1.20 (s, 3H), 1.12 (t, 3H, J = 7.5 Hz), 1.03 (s, 3H).

Step C: (2*R*)-Methyl 2-Ethyl-7-hydroxychromane-2-carboxylate (44). To a 250 mL round-bottomed flask were added the **42** (*R*,*R*) ester (5.07 g, 11.9 mmol) obtained as described in step B, 50 mL of 2-propanol, and 50 mL of aqueous 2.5 N sodium hydroxide. This solution was heated to 65 °C overnight. 2-Propanol was removed under reduced pressure. The residue was acidified to pH 1 with 2 N hydrochloric acid and then extracted with AcOEt three times. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to give a thick oil. This crude product was dissolved in dichloromethane and treated with diazomethane ethereal solution. After the gas evolution ceased, the solution was concentrated and the resulting oil was chromatographed on silica gel. Elution with a gradient mixture of 10−12.5% AcOEt/hexanes gave the corresponding methyl ester. Then, the methyl ester was dissolved in 200 mL of ethanol and 6 mL of water, combined with 200 mg of 10% Pd/C, placed in a Parr shaker, and hydrogenated (H_2, 50 psi) overnight. The catalyst was removed by suction−filtration through a pad of Celite. The filtrate was concentrated and chromatographed on silica gel using gradient elution 20−30% AcOEt/hexanes to give 2.75 g of the title compound (97%). Recrystallization from dichloromethane/hexanes gave prisms; mp 98.0−98.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.8 (d, 1H, J = 8.2 Hz), 6.45 (d, 1H, J = 2.6), 6.38 (dd, 1H, J = 2.5, J = 8.0 Hz), 3.73 (s, 3H), 2.59−2.66 (m, 2H), 2.33 (m, 1H), 1.99 (sext, 1H), 1.91 (m, 2H), 1.04 (t, 3H). MS: m/e = 237 (M + 1). $[\alpha]_D^{20}$ +106.6 (c = 1, MeOH). Anal. ($C_{13}H_{16}O_4$) C, H.

(2*S*)-Methyl 2-Ethyl-7-hydroxychromane-2-carboxylate (45). Following the same procedure as compound **44**, the title compound was synthesized from the **43** (*R*,*S*)-isomer. Recrystallization from dichloromethane/hexanes gave prisms; mp 98.0−98.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.8 (d, 1H, J = 8.2 Hz), 6.45 (d, 1H, J = 2.6), 6.38 (dd, 1H, J = 2.5, J = 8.0 Hz), 3.73 (s, 3H), 2.59−2.66 (m, 2H), 2.33 (m, 1H), 1.99 (sext, 1H), 1.91 (m, 2H), 1.04 (t, 3H). MS: m/e = 237 (M + 1). $[\alpha]_D^{20}$ −108.6 (c = 1, MeOH). Anal. ($C_{13}H_{16}O_4$) C, H.

Determination of Absolute Stereochemistry. Compound 50. (*S*,*R*)-Isomer. Compound 42. The (*R*,*R*)-isomer was treated as described in steps A and C in the procedure as described above and yielded **50** (*S*,*R*)-isomer. Compound **50** was recrystalized from 2-propanol−water to give crystals suitable from single X-ray crystallographic analysis. The absolute stereochemistry of **50** was determined to be (*R*) relative to the known chiral center of (*S*)-pantolactone. An ORTEP structure drawing and coordinates are included in the Supporting Information.

(2*R*)-7-[3-(2-Chloro-4-phenoxyphenoxy)propoxy]-2-ethylchromane-2-carboxylic Acid (46). To an 80 mL DMF solution of (2*R*)-methyl 2-ethyl-7-hydroxychromane-2-carboxylate (**44**) (2.71 g, 11.5 mmol) and 3-(2-chloro-4-phenoxyphenoxy)-1-bromopropane (**34**) (4.4 g, 13.0 mmol) was added cesium carbonate (4.1 g, 12.6 mmol). The resulting suspension was stirred at 65 °C for 5 h. The reaction mixture was diluted in MTBE and water. The organic layer was separated. The aqueous layer was extracted twice with MTBE. The combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated, and chromatographed on silica gel. Elution with 15% AcOEt/hexanes yielded the methyl ester of the title compound as a pale yellow oil (5.1 g). This material was dissolved in 175 mL of 2-propanol and 94 mL of 1 N NaOH(aq). The resulting solution was heated to 70 °C for overnight. Then, the solvent was removed under reduced pressure. The residue was dissolved in AcOEt and 2 N HCl(aq). The organic layer was separated. The aqueous layer was extracted twice with AcOEt. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to give the title compound as a pale yellow oil (4.48 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (m, 2H), 7.09 (m, 2H), 6.99−6.89 (m, 5H), 6.54 (d, 1H, J = 2 Hz), 6.51 (dd, 1H, J = 1.6, 8.2 Hz), 4.20 (t, 2H, J = 6 Hz), 4.19 (t, 2H, J = 5.9 Hz), 2.71 (m, 2H), 2.30 (m, 1H), 2.30 (p, 2H, J = 6 Hz), 2.05−1.90 (m, 3H), 1.06 (t, 3H, J = 7.4 Hz). MS: m/e = 483 (M + 1). Anal. ($C_{27}H_{27}O_6Cl_1$) C, H, Cl.

(2*S*)-7-[3-(2-Chloro-4-phenoxyphenoxy)propoxy]-2-ethylchromane-2-carboxylic Acid (47). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (m, 2H), 7.09 (m, 2H), 6.99−6.89 (m, 5H), 6.54 (d, 1H, J = 2 Hz), 6.51 (dd, 1H, J = 1.6, 8.2 Hz), 4.20 (t, 2H, J = 6 Hz), 4.19 (t, 2H, J = 5.9 Hz), 2.71 (m, 2H), 2.3 (m, 1H), 2.30 (p, 2H, J = 6 Hz), 2.05−1.90 (m, 3H), 1.06 (t, 3H, J = 7.4 Hz). MS: m/e = 483 (M + 1). Anal. ($C_{27}H_{27}O_6Cl_1$) C, H, Cl.

(2*R*)-7-{3-(2-Chloro-4-(4-fluorophenoxy)phenoxy]propoxy}-2-ethylchromane-2-carboxylic Acid (48). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05−7.01 (m, 2H), 6.97−6.9 (m, 5H), 6.86 (dd, 1H J = 3, J = 8.9 Hz), 6.55−6.51 (m, 2H), 4.20 (m, 4H), 2.70 (m, 2H), 2.32 (m, 1H), 2.30 (p, 2H, J = 6 Hz), 2.00 (m, 2H), 1.93 (m, 1H), 1.06 (t, 3H, J = 7.3 Hz). MS: m/e = 501 (M + 1). $[\alpha]_D^{20}$ +59.3 (c = 1, MeOH) Anal. ($C_{27}H_{26}O_6F_1Cl_1$) C, H, F, Cl.

(2*S*)-7-{3-(2-Chloro-4-(4-fluorophenoxy)phenoxy]propoxy}-2-ethylchromane-2-carboxylic Acid (49). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05−7.01 (m, 2H), 6.97−6.90 (m, 5H), 6.86 (dd, 1H J = 3, J = 8.9 Hz), 6.55−6.51 (m, 2H), 4.20 (m, 4H), 2.70 (m, 2H), 2.32 (m, 1H), 2.30 (p, 2H, J = 6 Hz), 2.00 (m, 2H), 1.93 (m, 1H), 1.06 (t, 3H, J = 7.3 Hz). MS: m/e = 501 (M + 1). Anal. ($C_{27}H_{26}O_6F_1Cl_1$) C, H, F, Cl.

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Supporting Information Available: NMR spectral data and results of elemental analysis for all final compounds not included in the Experimental Section and the X-ray crystallographic data of compound **50**. This material is available free of charge via the Internet at http://pubs.acs.org.

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