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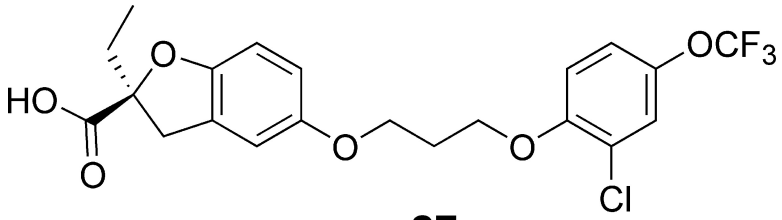

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Novel 2,3-Dihydrobenzofuran-2-carboxylic Acids: Highly Potent and Subtype-Selective PPARα Agonists with Potent Hypolipidemic Activity

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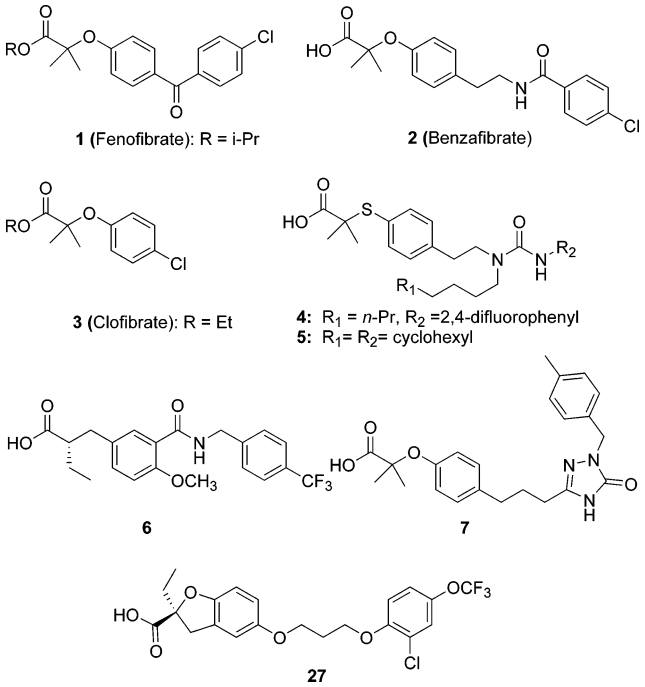
The design and synthesis of a novel class of 2,3-dihydrobenzofuran-2-carboxylic acids as highly potent and subtype-selective PPARα agonists are reported. Systematic study of structure−activity relationships has identified several key structural elements within this class for maintaining the potency and subtype selectivity. Select compounds were evaluated in animal models of dyslipidemia using Syrian hamsters and male Beagle dogs, and all these compounds displayed excellent cholesterol- and triglyceride-lowering activity at dose levels that were much lower than the marketed weak PPARα agonist fenofibrate.

Introduction

Hypertriglyceridemia and hypercholesterolemia are two major risk factors for coronary heart disease (CHD),[1,2] which remains the leading cause of death in the developed world. The fibrate drugs (Chart 1) have been widely used for the clinical treatment of dyslipidemia by lowering serum triglycerides and raising HDL cholesterol (HDLc) and remain the current treatment of choice for patients with severe hypertriglyceridemia.[3,4] Several studies have provided evidence that the hypolipidemic effect of the fibrate drugs is attributed to the activation of PPARα,[5−7] one of the three isoforms (α, γ and δ) of the peroxisome proliferator-activated receptors (PPARs).[8] As a ligand-activated transcription factor, PPARα, first cloned in the early 1990s,[9] plays an important role in lipid metabolism. It acts as a dietary fat sensor by upregulating lipid metabolism (predominantly β-oxidation) in the presence of fatty acids which are presumed to be the natural ligands for PPARα.[9,10] As PPARα agonists, the fibrates, e.g. compounds **1**−**3** (Chart 1), function by increasing the clearance and decreasing the synthesis of very low-density lipoproteins (VLDL), which are rich in triglycerides, and lowering serum level of apolipoprotein CIII (apoCIII) which is a known inhibitor of VLDL clearance.[11,12] The elevation of HDL-cholesterol levels observed with fibrates arises in part from the transcriptional induction of the major HDL apolipoproteins, apoA-I and apoA-II.[12] PPARα is also implicated as an anti-atherosclerosis approach. Agonists have been shown to down-regulate the expression of VCAM-1, to inhibit NF-κB and AP-1, and to mediate the reduction of plasma levels of interleukin-6, fibrinogen, and C-reactive protein.[13−15]

Chart 1. Structures of PPARα Agonists



Although fibrates are ligands for the PPARα receptor, they only show weak agonist activity and moderate subtype selectivity in cell-based assays.[10] More potent and subtype-selective human PPARα agonists are expected to provide a better tool for studying the biology of PPARα and a superior clinical profile for therapeutic intervention in dyslipidemia and other metabolic disorders. In addition, PPARα agonists with improved subtype selectivity could avoid the potential known side effects associated with the activation of the PPARγ, e.g. peripheral edema and weight gain,[16] and thus find broader use among patients with dyslipidemia as their primary indication. Compared to a large number of PPARγ selective agonists, exemplified by the marketed TZD (thiazolidinedione) drugs, and PPARα/γ dual ago-

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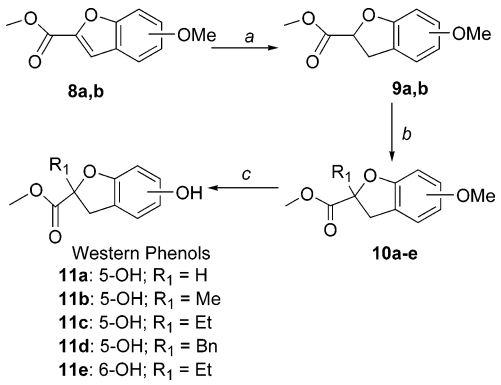
nists that have been published in the literature, only a few selective PPARα ligands with at least 100 fold selectivity over the other isoforms (PPARγ and δ) have been reported. The first reported examples of selective PPARα agonists were ureido-based fibric acids **4** (GW9578) and **5** (GW7647) (Chart 1),[17,18] which showed 20-fold and 200-fold selectivity respectively over PPARγ and PPARδ and possessed potent lipid-lowering activities in a cholesterol/cholic acid-fed rat assay. The Kyorin group has reported a nonfibrate phenylpropanoic acid derivative **6** that is a potent hPPARα agonist in vitro with selectivity for PPARα over PPARγ.[19] More recently researchers at Lilly disclosed their α-phenoxyphenylpropanoic acid, **7** (LY518674), as a potent PPARα agonist (EC_{50} = 42 nM) with 200-fold binding selectivity over PPARγ and PPARδ receptors.[20] Structurally, all these ligands contained an acidic headgroup with a carboxylic acid moiety connected through a conformationally flexible spacer to a phenyl ring.

We have sought to develop our highly potent and selective PPARα agonists based on the use of a 1,3-bis(oxy)propylidene linker to connect an acidic headgroup and a lipophilic tail, a general strategy which has been previously adopted in our laboratories for the construction of several classes of PPARγ selective and PPARα/γ dual agonists.[21−25] Given that the inherent subtype selectivity of most existing PPAR ligands are primarily driven by the acidic headgroups they carry, our attention was focused on the search for new types of PPARα subtype selective acidic headgroups. Gratifyingly, we have discovered that the conformationally constrained 2,3-dihydrobenzofuran-2-carboxylic acids are one type of such subtype selective acidic headgroups and their use has led us to build a novel class of PPARα agonists that displayed very high potentecy (EC_{50} < 10 nM) and subtype-selectivity (>1000-fold) (the best selectivity among the PPARα-selectives reported to date) as well as highly potent and efficacious hypolipidemic activity in animal models. This account describes the synthesis and structure−activity relationships and in vivo studies of a novel series of 2,3-benzodihydrofuran-based PPARα agonists which culminated in the discovery of compound **27**.

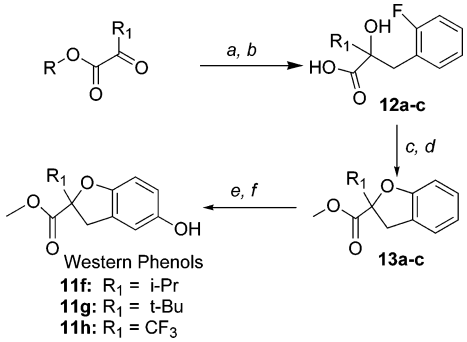
Chemistry. The synthesis of all compounds started with the preparation of various R_1-substituted Western Phenols **11a**−**h** (Schemes 1 and 2). Two different synthetic approaches have been used for their synthesis depending on the nature of R_1 groups. When R_1 is an unbranched alkyl, direct electrophilic alkylation of the enolate generated from the unsubstituted 2,3-benzofuran-2-carboxylates **9a**−**b** with various R_1-X (X = Br, I) was employed to give intermediates **10a**−**b**, whose demethylation provided the desired phenols **11a**−**e**. When R_1 is a branched alkyl or a trifluoromethyl group, a different approach has to be adopted involving the *de novo* construction of the furan ring.[26] This was accomplished first by the addition of a fluorine-containing Grignard reagent to various α-ketocarboxylates to afford intermediates **12a**−**c** and then by an intramolecular cyclization of **12a**−**c** to furnish **13a**−**c**. A hydroxy group was installed to **13a**−**c** by a standard two-step sequence involving the Friedal-Crafts acylation of **13a**−**c** followed by the Bayer-Villiger oxidation of the resulting ketone to give phenols **11f**−**h**. All phenols so obtained were

Scheme 1. First Approach to Western Phenols[a]



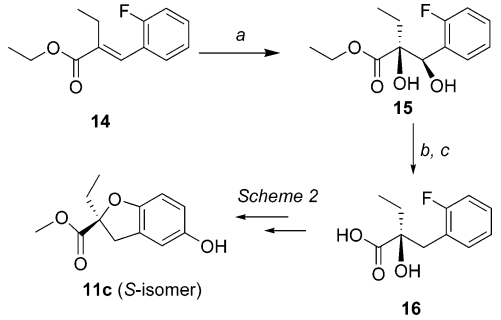
[a] Reagents and conditions: a) H_2, Pd/C, HOAc; b) LiHMDS, R_1−Br (or I), THF, −75 °C; c) BBr_3, CH_2Cl_2.

Scheme 2. Second Approach to Western Phenols[a]



[a] Reagents and conditions: a) *o*-F−$PhCH_2MgBr$, THF; b) NaOH, MeOH; c) NaH, DMF−PhMe; d) $TMSCHN_2$, PhH-MeOH; e) AcCl, $AlCl_3$, CH_3Cl_2; f) m-CPPBA, $NaHCO_3$, CH_2Cl_2.

Scheme 3. Asymmetric Synthesis of Phenol **11c**[a]

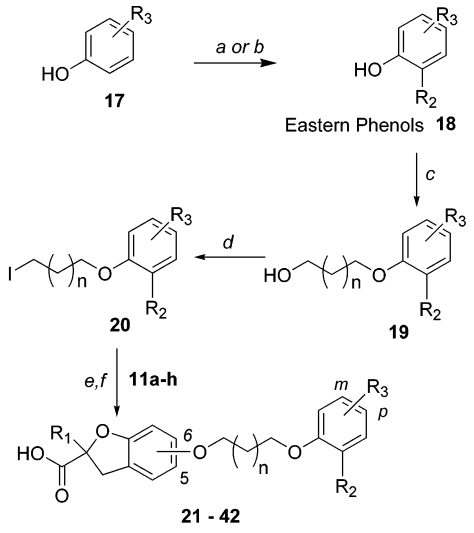


[a] Reagents and conditions: a) AD-mix-β, t-BuOH−H_2O, 0 °C; b) H_2 (45 psi), cat. H_2SO_4, EtOH; c) NaOH, MeOH.

racemic and they were separated by preparative chiral HPLC to give nonracemic phenols in cases where the final compounds need to be synthesized as single enantiomers.

For the large-scale synthesis of one of the enantiomers of phenol **11c**, we have developed a highly efficient route using the Sharpless asymmetric dihydroxylation (AD) reaction as the key step (Scheme 3). Thus, the reaction of the α,β-unsaturated ester **7** with AD-mix-β gave the diol **15** in high yield and 98% ee. Selective removal of the benzylic hydroxyl group by catalytic hydrogenation and subsequent hydrolysis of the ester readily afforded the chiral hydroxy acid **16**, which was converted to the chiral phenol **11c** following the same synthetic sequence as depicted for the racemic compounds **12a**−**c** in Scheme 2. The absolute stereochemistry was assigned based on

Scheme 4. Synthesis of Compounds **21**−**42**[a]



n = 1; phenol position: 5; R_3 position: *p*

21: R_1 = Me;	R_2 = Cl;	R_3 = CF_3CH_2O;	racemic
22: R_1 = H;	R_2 = Cl;	R_3 = CF_3CH_2O;	racemic
23: R_1 = Et;	R_2 = Cl;	R_3 = CF_3CH_2O;	racemic
24: R_1 = t-Bu;	R_2 = Cl;	R_3 = CF_3CH_2	racemic
25: R_1 = CF_3;	R_2 = Cl;	R_3 = CF_3CH_2	racemic
26: R_1 = $PhCH_2$;	R_2 = Cl;	R_3 = CF_3O;racemic	
27: R_1 = Et;	R_2 = Cl;	R_3 = CF_3O;	*S*
28: R_1 = Et;	R_2 = Cl;	R_3 = CF_3O;	*R*
29: R_1 = i-Pr;	R_2 = Cl;	R_3 = CF_3O;	*R*
30: R_1 = i-Pr;	R_2 = Cl;	R_3 = CF_3O ;	*S*
31: R_1 = Et;	R_2 = H;	R_3 = CF_3CH_2O	*S*
32: R_1 = Et;	R_2 = n-Pr;	R_3 = CF_3S;	racemic
33: R_1 = Et;	R_2 = Cl;	R_3 = CF_3	racemic
34: R_1 = Et;	R_2 = Cl;	R_3 = t-Bu	racemic
35: R_1 = Et;	R_2 = Cl;	R_3 = CF_3S	racemic
36: R_1 = Et;	R_2 = Cl;	R_3 = t-$BuCH_2$;	racemic
37: R_1 = Et;	R_2 = Cl;	R_3 = CF_3CH_2;	*S*
38: R_1 = Et;	R_2 = Cl;	R_3 = $CF_3CH_2CH_2$;	*S*

n = 1; phenol position: 5; R_3 position *m*

39: R_1 = i-Pr;	R_2 = Cl;	R_3 = CF_3;	*R*

n = 1; phenol position: 6; R_3 position *p*

40: R_1 = Et;	R_2 = Cl;	R_3 = CF_3O;	racemic

n = 0; phenol position: 5; R_3 position *p*

41: R_1 = i-Pr;	R_2 = Cl;	R_3 = CF_3O;	*R*
42: R_1 = t-Bu;	R_2 = Cl;	R_3 = CF_3O;	*R*

[a] Reagents and conditions: a) SO_2Cl_2, i-$BuNH_2$ (cat.), tolune (for R_2 = Cl); b) allyl bromide, Cs_2CO_3, DMF, then 1,2,4-trichlorobenzene, reflux, then H_2, 10% Pd/C, EtOAc (for R_2 = *n*-Pr); c) 3-bromopropanol (for n = 1) or 2-bromoethanol (for n = 0), Cs_2CO_3, DMF; d) I_2, Ph_3P, CH_2Cl_2; e) phenol **11**, Cs_2CO_3, DMF; f) NaOH, MeOH-THF.

the mechanism of the AD reaction and further confirmed with X-ray crystallographic analysis of a single crystal of an amide derivative of **11c**.

Once the Western Phenols were prepared, they were connected to the Eastern Phenols with a ethylene or a 1,3-propylidene linker (Scheme 4). The Eastern Phenols were relatively simple and their syntheses were usually made possible either by direct ortho-chlorination (R_2 = Cl) or a two-step sequence involving Claisen rearrangement/hydrogenation (R_2 = *n*-propyl) of the allyl ether derived from various R_3-substituted phenols. The attachment of the linker was then accomplished by a two step sequence involving the reaction of the phenol **18** with 3-bromopropanol and subsequent conversion of the resulting alcohol to the corresponding iodide **20**. A simple S_N2 coupling of the iodide **20** with the Western Phenols **11a**−**h** and the hydrolysis of the resulting coupling product provided the target compounds **21**−**42**.

Results and Discussion

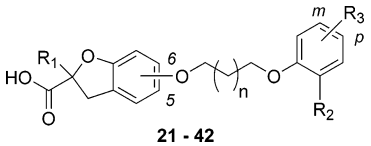
In Vitro SAR Studies. Compounds were evaluated for in vitro potency and subtype selectivity in PPAR scintillation proximity assays (SPA); results are expressed as IC_{50}'s for displacement of a radiolabeled reference compound. Their functional potency and agonist responses were measured in cell-based transactivation (TA) assays using hPPAR-GAL4 chimeric receptors and a reporter gene containing a GAL-4 response element;[27,28] results are expressed as EC_{50}'s, defined as the concentration of test compound to produce 50% of maximal reporter activity. Because of the known differences of the amino acid residues lining the ligand binding domains (LBDs) of PPARα receptors derived from different species,[29,30] most compounds were also assessed in the hamster and dog PPARα-GAL4 transactivation assays to better assist the interpretation of the in vivo efficacy data obtained in the corresponding animal models.

The initial compound **21** (Table 1) was rationally designed based on the use of our traditional 1,3-bis(oxy)-propylidene chain as the linker and 2-methyl-substituted 2,3-dihydrobenzofuran-2-carboxylic acid as the headgroup. The latter was conceptually derived via cyclization of the fibric acid for the conformational control of the carboxylic acid pharmacophore (Chart 2). Compound **21** showed submicromolar binding activity to PPARα with no measurable activity on PPARγ and δ receptor up to 15 μM. In contrast, the corresponding compounds with the fibric acid[31] or the previously reported six-membered chromane-2-carboxylic acid[25] as the headgroups were found to be less subtype selective. Encouraged by this preliminary result, we synthesized a series of analogues of **21** in order to improve its in vitro potency as well as to identify compounds for in vivo lipid lowering studies. The results of our structure−activity studies are summarized in Table 1.

As shown in Table 1, a clear indication of the critical requirement for substitution at the 2-position of the benzofuran ring was provided by the observation of a dramatic increase of potency and subtype selectivity by a lipophilic R_1 group. Thus, from the unsubstituted compound **22** (R_1 = H) to the corresponding ethyl substituted analogue **23** (R_1 = Et), there was more than 20-fold gain of binding potency on PPARα. Further increase of potency was realized in analogues substituted with the more lipophilic *tert*-butyl and trifluoromethyl groups (compound **24** and **25**), although these two groups imparted the compounds some undesirable physical properties. However, the installation of a benzyl group resulted in analogues with diminished potency (compound **26**), suggesting that highly lipophilic alkyl but not aryl groups are preferred for potent PPARα binding activity. Importantly, all the analogues maintained very high subtype selectivity over PPARγ and δ, with the exception of compound **25** in which the presence of an electron-withdrawing trifluoromethyl group triggered some binding activity for PPARδ.

Having established a critical need for a lipophilic alkyl at the R_1 position of the benzofuran ring, we began to

Table 1. In Vitro Binding and Functional PPAR Activity of 2,3-Dihydrobenzofuran-2-carboxylic Acids

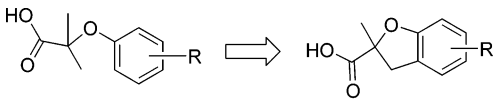


21 - 42

	binding IC_{50} (μM)[a]			transactivation EC_{50} (μM)[b]			
compd	PPARα	PPARδ	PPARγ	hamster PPARα	dogPPARα	hPPARα	hPPARγ
21	0.106	>15	>15	0.860	0.042	0.138	>3.0
22	0.786	>15	>15	>3.0	1.350	ND	ND
23	0.032	>15	>15	0.402	0.008	0.034	>3 (19%)
24	0.007	>50	>15	0.034	0.002	0.002	>3 (6%)
25	0.009	0.399	>15	0.750	0.026	0.037	> 3.0 (2%)
26	0.275	>50	>15	>3.0	>3.0	ND	ND
27	**0.006**	**>15**	**>15**	**0.025**	**0.002**	**0.002**	**>3.0 (30%)**
28	2.227	>50	>15	ND	ND	ND	ND
29	**0.003**	**>15**	**>15**	**0.015**	**<0.001**	**0.002**	**>3 (25%)**
30	1.28	>15	>50	ND	ND	ND	ND
31	0.231	>15	>50	>3.0	0.130	ND	ND
32	0.011	5.230	3.110	0.100	<0.001	0.008	>3.0 (59%)
33	0.042	0.834	>15	ND	ND	ND	ND
34	0.017	>15	4.330	0.280	0.020	0.009	>3.0 (56%)
35	0.003	>15	6.77	0.031	<0.001	0.003	>3.0 (30%)
36	0.004	>50	5.6	0.250	0.002	0.015	>3.0 (12%)
37	**0.004**	**>15**	**>15**	**0.026**	**<0.001**	**0.002**	**>3.0 (28%)**
38	0.021	>15	>15	0.13	0.002	ND	ND
39	0.162	>15	>15	0.420	0.042	0.041	>3.0 (11%)
40	0.022	1.190	3.220	0.037	<0.001	ND	ND
41	0.264	>50	>50	0.370	0.010	0.057	>3.0 (4%)
42	1.390	>50	>50	ND	ND	ND	ND

[a] Mean value of three determinations using scintillation proximity assay (SPA). [b] TA (transactivation assay). Mean value of three determinations. EC_{50} values were not calculated for compounds whose activity did not reach plateau at the maximal concentration of 3 μM; instead their percentage responses at a concentration of 3 μM were listed.

Chart 2



fibric acid constrained "fibric acid"

explore the effects of various R_2 and R_3 groups on the Western Phenol ring. A general consideration in the selection of these two groups was to obtain the best potency and selectivity while minimizing their potential for in vivo oxidative metabolism. For the R_2 group, it was found that the presence of a chlorine atom ortho to the phenolic oxygen was very crucial for potency. Thus, the removal of chlorine from compound **23** (R_2 = Cl) resulted in more than 10-fold loss of activity (compound **31**, R_2 = H). Although replacing the chlorine with an *n*-propyl group (compound **32**) restored much of the binding activity, we preferred to use the chlorine instead of the propyl as our standard R_2 group for all analogues based on the its superior metabolic stability. With regard to R_3 groups, all highly lipophilic groups appeared to be good at maintaining high PPARα binding potency, though a subtle loss of selectivity was noticed for the trifluoromethyl analogue **33** (R_3 = *p*-CF_3) and *tert*-butyl analogue **34** (R_3 = *p*-*t*-Bu). As for the position of R_3, there was clearly a need for the R_3 group to be placed at the *para*-position relative to the phenolic oxygen, as there was more than 50-fold loss of activity for compound **39** (R_3 = *m*-CF_3) in comparison with most of the *p*-substituted analogues (e.g. compound **29**).

The effects of chirality on the activity were investigated by comparing the activity of the two pairs of enanantiomers from the 2-ethyl and 2-isopropyl substituted series, i.e. compounds **27** versus **28** and **29** versus **30**. It was found that the *S*-enantiomers **27** and the *R*-enantiomer **29** (both with the same R_1 group orientation but different stereo designation due to group priority change) were about 400 times more potent than their respective antipodes **28** and **30**. This pronounced difference is consistent with the expectation drawn from the enantio-dependent behavior of the published PPARα ligands containing an α-substituted phenylpropanoic acid moiety.[19,32,33] It is believed that the steric bias of the carboxylic acid in the present series of compounds may have been further reinforced by the additional conformational constraint imposed by the rigid cyclic structure. Because of the significant activity differences between the enantiomers, all compounds selected for in vivo evaluation were made as optically pure isomer either by chiral HPLC separation or asymmetric synthesis.

The importance of chain length and the point of its attachment to the acidic headgroup were next examined. It was known from our earlier work on the PPARγ selective series that a 1,3-propylidene chain (n = 1) generally offered the best PPAR activity.[21,22] This was also found to be true for the present class of compounds. Thus, when the chain length was shortened to that of an ethylene (n = 0), a dramatic loss of activity was observed (compound **41** and **42**), suggesting that optimal chain length is critical for controlling the conformation of the molecule and hence the way it binds to PPARα. Interestingly, the attachment of the chain to position 6 instead of 5 of the benzofuran ring eroded the subtype selectivity significantly (compound **40**) while maintaining the potency on PPARα.

Table 2. Effects of Compounds **27**, **29**, **37** and Fenofibrate on Serum Cholesterol and Triglyceride in Hamster[a]

compd	dose mg/kg/day	TC (%)[b]	TG (%)[b]	drug level (μM·h)[c]
27	0.1	−15%	−11.78	3.6
	0.3	−30%	−31.85	6.9
	1	−42%	−43.65	23
29	0.1	−43	−52	−
	0.3	−54	−52	−
37	0.1	−33	−13	−
	0.3	−37	−26	−
fenofibrate	100	−28.55	−24.08	3000−4100

[a] Male Golden Syrian hamsters fed a normal rodent chow were orally dosed for 9 days with the test compounds. See Experimental Section for details. [b] Mean value ($n = 10$). $p < 0.01$ vs vehicle control. [c] Mean value ($n = 4$). Limit of quantification = 0.02 μM.

As an indication of good cell permeability, all compounds with nanomolar binding potency also exhibited comparable levels of potent cellular activity toward PPARα receptors while remaining devoid of celluar activity at concentrations up to 3 μM on other PPAR receptor subtypes. Further selectivity of the present class of compounds was examined using a panel of other nuclear receptors including PXR, LXR, TRα and TRβ. All tested compounds either failed to bind to these receptors or were unable to produce agonist activity at concentrations up to 10 μM.

The activities obtained from the hamster and dog PPARα transactivation assays have been compared with that from humans. It has been reported that some PPARα agonists show species-dependent transactivation characteristics. The classical PPARα agonist WY-14643 and the recently disclosed ureido-based agonist GW-9578 were found to preferentially activate rodent PPARα over human PPARα.[17] On the other hand, the phenylpropanoic acid based PPARα agonists reported by Kyorin and Lilly showed the reverse preference; *i.e.*, they are 20 to100-fold less potent toward murine receptors than human PPARα.[19,20] As can be seen from Table 1, there was also a notable species-dependent change of transactivation activity observed within the present class of compounds. Thus, while there was a good match in potency between the human and dog PPARα transactivation activities, a result consistent with the high degree of the structural homology between the LBDs of these two receptors,[34] a 10−100 fold diminution of potency with the hamster PPARα receptor was generally observed as a result of the aforementioned species-specific structural differences between the human and rodent receptors. Moreover, most of the compounds exhibited a further decrease in activity (>100 fold) when assessed in a mouse PPARα transactivation assay (data not shown here), suggesting that murine (mouse or rat) may not be a suitable model for assessing the behavior of these agonists and how this behavior might extrapolate to humans.

In Vivo Studies. Based on their superior in vitro potency and consistent cross-species PPARα activity, compounds **27**, **29** and **37** were selected for the in vivo evaluation of their hypolipidemic efficacy. As our primary in vivo model for lipid-lowering studies, Male Syrian hamsters were used to investigate the effects of compounds **27**, **29** and **37** on the serum levels of triglyceride and total cholesterol. As shown in Table 2, when administered orally to hamsters ($N = 6$) daily for 14 days at dose range of 0.1 mpk to 1 mpk, all three compounds lowered the serum total cholesterol and triglyceride up to more than 50% in a dose-dependent manner. In contrast, fenofibrate produced only 28% and 24% reduction in serum cholesterol and triglycerides respectively at a much higher dose of 100 mpk. To further appreciate the differences in these in vivo effects, the 24 h drug exposures of **27** and fenofibrate were measured after giving the final dose of the each compound. It was found that compound **27** required only about 1/500 of the exposure of fenofibrate in order to achieve comparable lipid lowering efficacy, suggesting that the in vivo efficacy of these two compounds is well correlated with their potency as PPARα agonists in vitro.

The match of the in vitro potency and the high degree of the PPARα-LBD homology between humans and dogs[34] suggest that dogs may be a more suitable animal model for evaluating the potential pharmacological benefits and risks of PPARα agonists in humans. Accordingly, compound **27** was selected for further evaluation in a cholesterol-lowering model using male Beagle dogs. Historically, this preclinical animal model had faithfully predicted the clinical lipid modulating efficacy of the statin drugs.[35] In the present study, both the clinically used PPARα agonist fenofibrate and the HMG CoA inhibitor simvastatin were included as comparators to better assess the potential clinical impact of compound **27**. As shown in Table 3, when dosed orally for 15 days at doses of 0.01, 0.1 and 0.3 mpk, compound **27** at all doses achieved a superior cholesterol-lowering efficacy compared to fenofibrate dosed at 50 mpk and simvastatin dosed at 4 mpk. Subsequent analysis of the drug exposures revealed that compound **27** displayed, at all dose levels, much lower exposure than fenofibrate and, at the 0.1 mpk dose, a similar exposure to simvastatin. The apparent lack of dose response with **27** might suggest a saturation of response at all doses. Moreover, when co-dosed with simvastatin, compound **27** exhibited an additive effect

Table 3. Time Course of Cholesterol Lowering by Compound **27**, Fenofibrate, and Simvastain in Male Beagle Dogs[a]

	compound **27**				fenofibrate	simvastatin	compd **27** + simvastatin
days	0.01 mkd TC (%)[b]	0.03 mkd TC (%)[b]	0.1 mkd TC (%)[b]	0.3 mkd TC (%)[b]	50 mkd TC (%)[b]	4 mkd TC (%)[b]	0.3 mkd + 4 mkd TC (%)[b]
0	0	0	0	0	0	0	0
3	−6.7	−6.5	−7.5	−10.1	−2.2	−7.8	−14.2
7	−7.2	−11.2	−18.0	−17.4	−5.5	−13.3	−27.8
10	−11.7	−17.9	−22.1	−20.5	−5.9	−9.9	−36.9
15	−21.0	−24.3	−22.1	−24.2	−12.3	−17.1	−39.7
exposure (μM·h)[c]	0.17 ± 0.03	0.45 ± 0.42	2.2 ± 1.1	7.2 ± 2.7	38 ± 22[d]	1.2 ± 0.52	−

[a] Male beagle dog were orally dosed for 15 days with the test compounds. See Experimental Section for details. [b] Mean value ($n = 5$), $p < 0.05$. [c] Mean ± SD have been given as $n = 5$. [d] Exposure from one dog was excluded due to abnormal high exposure.

on overall cholesterol reduction, a clear manifestation of the efficacy driven by two distinct mechanisms. Since statins do not effectively lower serum triglyceride and fibrates must be used at very high doses (about 300−12000 mg/day), the results from these hamster and dog models suggest that a potent PPARα agonist such as **27** may offer significantly better hypolipidemic efficacy than the currently marketed lipid modulating agents.

Conclusion

In summary, we have identified a novel series of 2,3-dihydrobenzofuran-2-carboxylic acids as highly potent and subtype selective PPARα agonists. It was believed that the inherent selectivity of this class of compounds is primarily contributed by the conformational constraint rendered by the structurally unique 2,3-dihydrobenzofuran ring. Several other key structural elements for maintaining the high potency of binding and cellular activity have also been identified through detailed structure−activity relationship studies. As a result of these studies and extensive in vivo testing, compound **27** and related analogues were selected for further preclinical evaluation. It was found that the dramatically increased potency of these compounds versus the currently marketed fibrates translated into superior efficacy in the hamster and dog lipid models. Overall, these results suggest that development of potent human PPARα selective agonists may lead to improved therapies for hyperlipidemia with potential for the prevention of coronary heart disease.

Experimental Section

In Vitro Assays. 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).[25] Second, potencies of PPAR gene activation were evaluated in cell-based transcription assays using GAL4-PPAR chimeric receptors as previous described.[26] All results were produced in triplicate, and mean values are reported.

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 (10 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. For the determination of the exposure of the testing compounds in the hamster and dog lipid-lowering studies, blood samples from the animals were taken at 0.5, 1, 2, 4, 6 and 24 h following the final oral dose. The plasma was separated, acidified by the addition of 0.5 M formate buffer, pH 3.0 (0.3 mL formate buffer per mL plasma) and stored at −70 °C prior to extraction and analysis. Concentrations of the testing compounds were determined following protein precipitation with acetonitrile. Calibration curves were constructed using control hamster or dog plasma by addition of known quantities of the testing compounds used as an internal standard. Quantitative analysis was carried out by LC-MS/MS using a PE Sciex API 3000 triple quadrupole mass spectrometer. Plasma concentrations and PK parameters were determined using Watson software.

Synthetic Materials and Methods. Reagents and solvents were obtained from commercial suppliers and used without further purification. Flash chromatography was performed using E. Merck silica gel (230−400 mesh). ^{1}H NMR nuclear magnetic resonance (NMR) spectra were recorded in the deuterated solvents specified on a Varian Unity INOVA 500 MHz instrument. Chemical shifts are reported in ppm from the tetramethylsilane resonance in the indicated solvent (TMS: 0.0 ppm). The mass spectrum was measured using HP1100 and Micromass ZQ instruments (LC-MS system) using the positive electrospray ionization technique (+ESI) using a mobile phase of acetonitrile/water with 0.1% trifluoroacetic acid. Elemental analyses were obtained from Robertson Microlit Laboratories (Madison, NJ).

Methyl 6-methoxy-1-benzofuran-2-carboxylate (8b). A mixture of methyl bromoacetate (1.53 g, 10 mmol), 2-hydroxy-4-methoxybenzaldehyde (1.52 g, 10 mmol) and Cs_2CO_3 (6.5 g, 20 mmol) in DMF (100 mL) was stirred vigorously at 50 °C for 3 h and then at 150 °C for 5 min. The reaction was cooled, diluted with ethyl acetate and washed with water. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel to give the title product as a solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (s, 1H), 7.10 (d, J = 2.5 Hz, 1H), 6.91 (dd, J = 8.5, 2.5 Hz, 1H), 6.80 (d, J = 8.5, 1H), 3.91 (s, 3H), 3.83 (s, 3H). MS (ESI, *m/z*) 207.03 (MH^+).

Methyl 5-methoxy-2,3-dihydro-1-benzofurane-2-carboxylate (9a). Methyl 5-methoxy-1-benzofuran-2-carboxylate (**8a**) (2.2 g, 10 mmol) and 10% Pd−C (0.44 g) in ethanol (50 mL) was agitated under hydrogen (45 psi) for 72 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was chromatographed on silica gel eluting with 8:2 hexane:ethyl acetate to give 1.3 g title compound as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (d, J = 8.5 Hz, 1H), 6.77 (d, J = 3.0 Hz, 1H), 6.70 (dd, J = 8.5, 3.0, 1H), 5.18 (dd, J = 10.5, 7.0 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.55 (dd, J = 16.0, 10.5 Hz, 1H), 3.36 (dd, J = 16.0, 7.0 Hz, 1H).

Methyl 5-methoxy-2-methyl-2,3-dihydro-1-benzofuran-2-carboxylate (10b, R_1 = Me)). To a solution of **9a** (0.44 g, 2.0 mmol) and HMPA (0.20 mL) in THF (15 mL) at −78 °C was added lithium bis(trimethylsilyl)amide (1M in THF, 3.0 mL, 3.0 mmol). After 15 min, methyl iodide (0.42 g, 3.0 mmol) was added and the reaction was gradually warmed to 25 °C overnight. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous solution of NH_4Cl. The organic phase was dried and concentrated. The residue was chromatographed on silica gel eluting with 8:2 hexane:ethyl acetate to give 0.32 g title compound as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, J = 8.5 Hz, 1H), 6.62 (d, J = 3.0 Hz, 1H), 6.60 (dd, J = 8.5, 3.0, 1H), 3.80 (s, 3H), 3.75(s, 3H), 3.52 (d, J = 16.0 Hz, 1H), 3.05 (d, J = 16.0 Hz, 1H), 1.60 (s, 3H). MS (ESI, *m/z*) 223.04 (MH^+).

Methyl 5-hydroxy-2-methyl-2,3-dihydro-1-benzofuran-2-carboxylate (11b). Compound **10a** (0.32 g, 1.4 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. A solution of boron tribromide in dichloromethane (1.0 M, 3.5 mL, 3.5 mmol) was added. After 1 h at 0 °C, the reaction was diluted with dichloromethane and washed with brine. The organic phase was dried and concentrated. The residue was dissolved in 7:1 benzene:methanol (10 mL) and treated with $TMSCHN_2$ (1.0 M in hexane) until gas evolution ceased. Removal of the solvent gave a residue which was chromatographed on silica gel eluting with 7:3 hexane:ethyl acetae to give 0.26 g (90% yield) of the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, J = 8.5 Hz, 1H), 6.67 (d, J = 3.0 Hz, 1H), 6.61 (dd, J = 8.5, 3.0, 1H), 5.50 (br.s, 1H), 3.80 (s, 3H), 3.53 (d, J = 16.0 Hz, 1H), 3.10 (d, J = 16.0 Hz, 1H), 1.61 (s, 3H). MS (ESI, *m/z*) 209.20 (MH^+).

Methyl 5-hydroxy-2-ethyl-2,3-dihydro-1-benzofuran-2-carboxylate (11c) The title compound was prepared following the procedure described for **10b** and **11b** employing ethyl iodide instead of methyl iodide in the preparation of **10b**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, J = 8.5 Hz, 1H), 6.67 (d, J = 3 Hz, 1H), 6.61 (dd, J = 8.5, 3.0, 1H), 3.80 (s, 3H), 3.54 (d, J = 14.0 Hz, 1H), 3.16 (d, J = 14.0 Hz, 1H), 2.05 (m, 2H), 1.0 (t, J = 7.5 Hz, 3H). MS (ESI, *m/z*) 223 (MH^+).

Methyl 2-benzyl-5-hydroxy-2,3-dihydro-1-benzofuran-2-carboxylate (11d). The title compound was prepared following the procedure described for **10b** and **11b** employing benzyl bromide instead of methyl iodide in the preparation of **10b**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25−7.50 (m, 5H), 6.77 (d, J = 8.5 Hz, 1H), 6.65 (d, J = 3 Hz, 1H), 6.60 (dd, J = 8.5, 3.0, 1H), 3.85 (s, 3H), 3.55 (d, J = 14.0 Hz, 1H), 3.15 (d, J = 14.0 Hz, 1H), 2.25 (s, 2H). MS (ESI, *m/z*) 285.05 (MH^+).

Methyl 2-ethyl-6-hydroxy-2,3-dihydroxy-1-benzofuran-2-carboxylate (11e). The title compound was prepared following the procedure described for **10a** employing compound **8b** instead of **8a** and then following the procedure for **11b** employing ethyl iodide instead of methyl iodide. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, J = 8.5 Hz, 1H), 6.44 (d, J = 2.5 Hz, 1H), 6.37 (dd, J = 8.5, 2.5 Hz, 1H), 3.81 (s, 3H), 3.49 (d, J = 16.0 Hz, 1H), 3.13 (d, J = 16.0 Hz, 1H), 2.08 (dq, J = 14.5, 7.5 Hz, 1H), 2.01(dq, J = 14.5, 7.5 Hz, 1H), 1.00 (t, J = 7.5 Hz, 3H). MS (ESI, *m/z*): 223.02 (MH^+).

2-(2-Fluorobenzyl)-2-hydroxy-3-methylbutanoic acid (12a, R_1 = i-Pr). A solution of (*o*-fluorobenzyl)magnesium bromide in diethyl ether (100 mL), prepared from the corresponding *o*-fluorobenzyl bromide (9.45 g, 50.0 mmol) and magnesium turnings (1.32 g, 55.0 mmol), was added to a solution of ethyl 3-methyl-2-oxobutanoate (7.2 g, 50 mmol) in diethyl ether (50 mL) cooled at −78 °C. After 30 min at −78 °C, the reaction mixture was warmed to 0 °C and poured into saturated aqueous NH_4Cl. The organic layer was washed with brine, dried and concentrated. The residue was dissolved in methanol (200 mL) and treated with 2 N KOH (75 mL) at 50 °C for 2 h. The reaction mixture was diluted with water and washed with hexane. The aqueous layer was acidified with 2 N HCl, saturated with sodium chloride and extracted with ethyl acetate. Removal of solvents gave the crude title product as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.35 (m, 1H), 7.18−7.23 (m, 1H), 7.06 (t, J = 7.8 Hz, 1H), 7.00 (dd, J = 7.8, 9.0 Hz, 1H), 3.17 (d, J = 14.0 Hz, 1H), 3.05 (d, J = 14.0 Hz, 1H), 2.18 (m, 1H), 1.1 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H).

Methyl 2-isopropyl-2,3-dihydro-1-benzofuran-2-carboxylate (13a, R_1 = *i*-Pr). To a solution of the acid **12a** (4.2 g, 20 mmol) in 1:4 DMF:toluene (100 mL) was added 60% NaH in mineral oil (1.76 g, 44 mmol) in three portions. The reaction mixture was stirred at 110 °C under N_2 for 4 h. The reaction was cooled to room temperature and poured into cold water (100 mL). The aqueous layer was washed with hexane (50 mL), acidified with 2 N aqueous HCl and extracted with ethyl acetate (3 × 50 mL). The extracts were washed with brine (50 mL), dried and concentrated. The residue was dissolved in 7:1 benzene:MeOH (80 mL) and treated with $TMSCHN_2$ (1M in hexane) until gas evolution ceased. The reaction was concentrated and the residue was chromatographed on silica gel eluting with 85:15 hexane:ethyl acetate to give 3.7 g (75% yield) of the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13−7.19 (m, 2H), 6.89−6.92 (m, 2H), 3.80 (s, 3H), 3.63 (d, J = 16.5 Hz, 1H), 3.22 (d, J = 16.5 Hz, 1H), 2.32 (m, 1H), 1.02 (d, J = 6.5 Hz, 3H), 0.97 (d, J = 6.5 Hz, 3H). MS (ESI, *m/z*) 251.02 (MH^+).

Methyl 5-hydroxy-2-isopropyl-2,3-dihydro-1-benzofuran-2-carboxylate (11f). Compound **13a** (3.3 g, 15 mmol) was mixed with acetyl chloride (3.5 g, 45 mmol) and aluminum chloride (6.0 g, 45 mmol) in dichloromethane (100 mL). The reaction mixture was stirred at 25 °C for 1 h and then poured into 1 N aqueous HCl (100 mL). The organic layer was separated and the aqueous phase was extracted with dichloromethane (50 mL). The combined extracts were washed with brine and concentrated. The residue (4.0 g, 15 mmol) was mixed with *m*-chloroperbenzoic acid (70%, 7.7 g, 30 mmol) and $NaHCO_3$ (3.8 g, 45 mmol) in dichloromethane (150 mL) and the mixture was stirred under reflux for 2 h. The reaction mixture was washed successively with saturated aqueous sodium sulfite (100 mL) and aqueous $NaHCO_3$ (2 × 100 mL). After removal of the solvent, the residue was dissolved in methanol (100 mL) and treated with aqueous KOH (5 N, 3 mL) at 0 °C for 30 min. The reaction mixture was neutralized with concentrated hydrochloric acid and concentrated. The crude product was purified by chromatography on silica gel eluting with 8:2 hexane:ethyl acetate to give 3.0 g (85% yield) of the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, J = 8.5 Hz, 1H), 6.67 (d, J = 3.0 Hz, 1H), 6.61 (dd, J = 8.5, 3.0 Hz, 1H), 4.82 (br. s, 1H), 3.81 (s, 3H), 3.53 (d, J = 16.5 Hz, 1H), 3.23 (d, J = 16.5 Hz, 1H), 2.33 (m, 1H), 1.02 (d, J = 6.5 Hz, 3H), 0.97 (d, J = 6.5 Hz, 3H). MS (ESI, *m/z*) 237.20 (MH^+).

Methyl (2*R*)-5-hydroxy-2-isopropyl-2,3-dihydro-1-benzofuran-2-carboxylate (11f, *R*-isomer). A racemic mixture of **11f** was separated by preparative HPLC on a 2.0 × 25 cm Chiracel OD column eluting with 1:9 isopropyl alcohol:heptane with a flow rate of 6.0 mL/min. The fraction corresponding to the second peak was collected and concentrated to give the title compound. The stereochemistry of the title compound at the chiral center was assigned *R* based on the assumption that the elution order of the two enantiomers of **11f** on the chiral OD column was the same as that of the two enantiomers of the corresponding phenol **11c**, whose stereochemistry was assigned by X-ray crystallography (see Supporting Information). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, J = 8.5 Hz, 1H), 6.67 (d, J = 3.0 Hz, 1H), 6.61 (dd, J = 8.5, 3.0 Hz, 1H), 4.82 (br. s, 1H), 3.81 (s, 3H), 3.53 (d, J = 16.5 Hz, 1H), 3.23 (d, J = 16.5 Hz, 1H), 2.33 (m, 1H), 1.02 (d, J = 6.5 Hz, 3H), 0.97 (d, J = 6.5 Hz, 3H).

Methyl 2-*tert*-butyl-5-hydroxy-2,3-dihydro-1-benzofuran-2-carboxylate (11 g). The title compound was prepared following the procedure described for **12a**, **13a** and **11f**, employing methyl 3,3-dimethyl-2-oxobutanoate instead of methyl 3-methyl-2-oxobutanoate in the preparation of **12a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, J = 8.5 Hz, 1H), 6.67 (d, J = 3.0 Hz, 1H), 6.61 (dd, J = 8.5, 3.0 Hz, 1H), 4.90 (br. s, 1H), 3.81 (s, 3H), 3.40 (s, 2H), 1.1 (s, 9H). MS (ESI, *m/z*) 251.03 (MH^+).

Methyl 5-hydroxy-2-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-carboxylate (11h). The title compound was prepared following the procedure described for **12a**, **13a** and **11f**, using methyl 3,3,3-trifluoro-2-oxopropanoate instead of methyl 3-methyl-2-oxobutanoate in the preparation of **12a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, J = 8.5 Hz, 1H), 6.67 (d, J = 3.0 Hz, 1H), 6.61 (dd, J = 8.5, 3.0 Hz, 1H), 5.2 (br. s, 1H), 3.91 (s, 3H), 3.65 (AB system, J = 17 Hz, 2H). MS (ESI, *m/z*) 263.03 (MH^+).

Ethyl (2*S*)-2-[(*R*)-(2-fluorophenyl)(hydroxy)methyl]-2-hydroxybutanoate (15). Ethyl (*E*)-2-ethyl-3-(2-fluorophenyl)-propenoate (4.4 g, 20 mmol), AD-mix-β (28.0 g) and methylsulfonamide (1.9 g, 2.0 mmol) were mixed in 1:1 *t*-BuOH:H_2O (200 mL). The resulting mixture was stirred at 4 °C for 2 days and quenched by addition of an aqueous solution of Na_2SO_3 (2 N, 20 mL). The mixture was diluted with ethyl acetate (200 mL), washed with brine (2 × 100 mL) and dried. Removal of solvent gave 4.9 g (96% yield) of the title compound with 97% ee, as determined by HPLC on a Chiracel OD column using 30% 2-propanol in heptane as the eluent. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (td, J = 8.0, 1.5 Hz, 1H), 7.30 (m, 1H), 7.19 (m, 1H), 7.05 (m, 1H), 5.30 (s, 1H), 4.38 (m, 2H), 1.84 (m, 1H), 1.38 (t, J = 7.0 Hz, 3H), 1.25 (m, 1H), 0.79 (t, J = 7.0 Hz, 3H). MS (ESI, *m/z*) 257.02 (MH^+).

(2*S*)-2-(2-Fluorobenzyl)-2-hydroxybutanoic acid (16). Compound **15** (5.2 g, 20 mmol), 10% palladium on carbon (2.5 g) and concentrated sulfuric acid (0. 53 mL, 10 mmol) were mixed in acetic acid (100 mL). The reaction mixture was hydrogenated at 45 psi for 48 h. Sodium acetate (1.7 g, 20 mmol) was added and the reaction mixture was stirred for 10 min before it was filtered through silica gel. The filtrate was concentrated and the residue was treated with KOH (2 N, 25

mL) in methanol (150 mL) for 2 h. The reaction mixture was acidified with 2 N HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to give the crude title compound. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22−7.30 (m, 2H), 7.08 (t, J = 7.8 Hz, 1H), 7.03 (dd, J = 7.8, 9.0 Hz, 1H), 3.17 (d, J = 14.0 Hz, 1H), 3.08 (d, J = 14 Hz, 1H), 2.03 (dq, J = 13.8, 7.8 Hz, 1H), 1.76 (dq, J = 13.8, 7.8 Hz, 1H), 0.97 (t, J = 7.8 Hz, 3H).

Methyl (2*S*)-2-ethyl-5-hydroxy-2,3-dihydro-1-benzofuran-2-carboxylate (11c, *S*-isomer). The crude acid **16** was converted to title compound following the procedure described for the preparation of the racemic compound **11f**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, J = 8.5 Hz, 1H), 6.67 (d, J = 3 Hz, 1H), 6.61 (dd, J = 8.5, 3.0, 1H), 3.80 (s, 3H), 3.54 (d, J = 14.0 Hz, 1H), 3.16 (d, J = 14.0 Hz, 1H), 2.05 (m, 2H), 1.0 (t, J = 7.5 Hz, 3H). MS (ESI, *m/z*): 223.02 (MH^+).

General Procedure A: Preparation of *ortho*-Chlorinated Phenols 18a−c. To a solution of a *p*-R_3-substituted phenol (5.0 mmol) and diisobutylamine (0.064 g, 0.5 mmol) in toluene (30 mL) was added SO_2Cl_2 (0.40 mL, 5.0 mmol) dropwise. After being stirred at 25 °C for 2 h, the reaction was diluted with ethyl acetate, washed with brine and dried. Removal of the solvent gave a residue which was purified by chromatography on silica gel elutinng with a mixture of ethyl acetate and hexane. Using this general procedure, phenols **18a−c** were prepared.

2-Chloro-4-(trifluoroethoxy)phenol (18a: R_2 = Cl, R_3 = OCH_2CF_3). The title compound was prepared in 90% yield according to general procedure A using 4-(trifluoroethoxy)-phenol as the *p*-R_3-substituted phenol. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (d, J = 2.5 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 6.84 (dd, J = 8.5, 2.5 Hz, 1H), 5.33 (br. s, 1H), 4.30 (q, J = 9.0 Hz, 2H).

2-Chloro-4-(trifluoromethoxy)phenol (18b: R_2 = Cl, R_3 = OCF_3). The title compound was prepared in 93% yield according to general procedure A using 4-trifluoromethoxy-phenol as *p*-R_3-substituted phenol. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 2.5 Hz, 1H), 7.15 (dd, J = 9.0, 2.5 Hz, 1H), 7.10 (d, J = 9.0 Hz, 1H), 4.30 (br. s, 1H).

2-Chloro-4-trifluoromethylthiophenol (18c: R_2 = Cl, R_3 = SCF_3). The title compound was prepared in 95% yield following the general procedure A using 4-(trifluoromethyl-thio)phenol as the *p*-R_3-substituted phenol. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 2.5 Hz, 1H), 7.29 (dd, J = 8.5, 2.5 Hz, 1H), 7.05 (d, J = 8.5 Hz, 1H), 4.50 (br. s, 1H).

2-Chloro-4-(3,3,3-trifluoroethyl)phenol (18d: R_2 = Cl, R_3 = CH_2CF_3). This compound was prepared in the following four steps.

Step 1. To a solution of 4-benzyloxy-3-chlorobenzaldehyde (4.9 g, 20 mmol) and trimethyl(trifluoromethyl)silane (4.4 mL, 30 mmol) in THF (0.10 L) was added a solution tetrabutyl-ammonium fluoride (1.0 M in THF, 2.0 mL). After the reaction was stirred at 25 °C for 3 h, it was acidified with 2 N HCl to pH 2, diluted with ethyl acetate and washed with brine. The organic phase was dried and concentrated and the residue was purified by chramotography on silica gel eluting with 8:2 hexane:ethyl acetate to give 1-(4-benzyloxy-3-chlorophenyl)-2,2,2-trifluoroethanol.

Step 2. The product from Step 1 (5.1 g, 16.1 mmol) and thiocarbonyldiimidazole (4.3 g, 24.2 mmol) were dissolved in THF (50 mL) and the solution was heated under reflux for 2 h. The reaction mixture was diluted with ethyl acetate, washed with brine and dried. Removal of solvent give crude 1-(4-benzyloxy-3-chlorophenyl)-2,2,2-trifluoroethyl N-imidazolyl thio-carbonate.

Step 3. The crude product from Step 2 (7.0 g, ca. 16.1 mmol), tributyltin hydride (6.9 g, 24.2 mmol) and AIBN (0.53 g, 3.2 mmol) were mixed in toluene and the resulting solution was heated at 85 °C under nitrogen for 3 h. The reaction mixture was concentrated and the residue was purified by chromatography on silica gel eluting sequentially with 100% hexane and 10:1 hexane:ethyl acetate to give 1-benzyloxy-2-chloro-4-(2,2,2-trifluoroethyl)benzene.

Step 4. The product from Step 3 (4.0 g, 13.0 mmol) was dissolved in dichloromethane (50 mL) and cooled to −78 °C. A solution of boron tribromide (1.0 M in CH_2Cl_2, 14.3 mL, 14.3 mmol) was added. The reaction mixture was warmed to 0 °C, diluted with dichloromethane and washed with brine. After removal of solvent, the residue was chromatographed on silica gel eluting with 9:1 hexane:ethyl acetate to give the title compound. ^{1}H NMR (500 MHz, CD_3Cl) δ 7.32 (d, J = 2.0 Hz, 1H), 7.22 (dd, J = 8.5, 2.0 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 4.50 (br.s, 1H), 3.48 (q, J = 11.0 Hz, 2H).

2-Propyl-4-(trifluoromethylthio)phenol (18e: R_2 = n-Pr, R_3 = SCF_3). A mixture of 4-(trifluoromethylthio)phenol (1.9 g, 10 mmol), allyl brimide (1.8 g, 15 mmol) and Cs_2CO_3 (6.5 g, 20 mmol) in DMF, 80 mL) was stirred for 2 h at 50 °C. The reaction was diluted with ethyl acetate and washed with water. The organic phase was dried and concentrated to give a residue. The residue (2.3 g, 10 mmol) was dissolved in 1,2,4-trichlorobenzene (10 mL) and the solution was heated at reflux for 4 h. The reaction was cooled and poured on the top of a silica gel column. Sequential elution with 100% hexane and 9:1 hexane:ethyl acetate gave 1.8 g 2-allyl-4-(trifluoromethyl-thio)phenol. This compound was hydrogenated (1 atm) in ethyl acetate (20 mL) in the presence of 10% Pd−C (0.36 g) to give 1.8 g of the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 2.5 Hz, 1H), 7.33 (dd, J = 8.5, 2.5 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 4.60 (br.s., 1H), 2.58 (t, J = 7.5 Hz, 2H), 1.93 (m, 2H) 0.97 (t, J = 7.5 Hz,3H).

2-Chloro-4-(3,3,3-trifluoropropyl)phenol (18f: R = Cl, R_3 = $CH_2CH_2CF_3$). A solution of 4-benzyloxy-3-chlorobenz-aldehyde (0.25 g, 2. 0 mmol), 2,2,2-trifluoroethyltriphenylphos-phonium trifluoromethanesulfonate (0.49 g, 1.0 mmol) and CsF (0.76 g, 5.0 mmol) in DMF (10 mL) was stirred at 25 °C for 16 h. The reaction was then diluted with ethyl acetate, washed with water and dried. Removal of the solvent gave a residue which was purified by preparative TLC to give 1-(3-chloro-4-benzyloxyphenyl)-3,3,3-trifluoropropene. This product (65 mg, 0.2 mmol) was dissolved in ethyl acetate (2 mL) and hydro-genated (1 atm) in the presence of 10% palladium on carbon for 1 h. Removal of the catalyst and the solvent gave the title compound as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J = 2.5 Hz, 1H), 7.13 (dd, J = 8.5, 2.5 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H), 4.50 (br. s, 1H), 2.80−2.77 (m, 2H), 2.47−2.37 (m, 2H).

General Procedure B: Preparation of iodide 20 from phenol 18. Step 1. A mixture of phenol **18** (10 mmol), 3-bromopropanol (4.2 g, 30 mmol) and Cs_2CO_3 (6.5 g, 20 mmol) in DMF (100 mL) was stirred at 60 °C for 5 h. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (2 × 200 mL) and concentrated. The residue was purified by chromatography on silica gel eluting with 1:1 hexane:ethyl acetate to give 3-(2,4-disubstituted phenoxy)-1-propanol (**19**). **Step 2.** Compound **19** (8 mmol) was then dissolved in dichloro-methane (50 mL) followed by addition of triphenylphosphine (2.5 g, 9.6 mmol), imidazole (1.1 g, 16 mmol) and iodine (2.4 g, 0.96 mmol). The reaction mixture was stirred at 25 °C for 60 min and then concentrated. The residue was triturated with 1:1 hexane:diethyl ether and filtered through silica gel to give essentially pure 3-(2,4-disubstituted phenoxy)prop-1-yl iodide (**20a−h**) which was directly used without further furification.

3-[2-Chloro-4-(trifluoroethoxy)phenoxy]propyl iodide (20a: R_2 = Cl, R_3 = *p*-OCH_2CF_3, n = 1). The title compound was prepared according to general procedure B using phenol **18a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, J = 2.5 Hz, 1H), 6.94 (d, J = 8.5 Hz, 1H), 6.84 (dd, J = 8 0.5, 2.5 Hz, 1H), 4.33 (q, J = 9.0 Hz, 2H), 4.08 (t, J = 6.0 Hz, 2H), 3.42 (t, 6.5 Hz, 2H), 2.30 (m, 2H).

3-[(2-Chloro-4-(2,2,2-trifluoroethyl)phenoxy]propyl iodide (20b: R_2 = Cl, R_3 = *p*-CH_2CF_3, n = 1). The title compound was prepared according to general procedure B using the phenol **18d**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 2.0 Hz, 1H), 7.32 (dd, J = 8.5, 2.0 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H), 4.09 (t, J = 6.5 Hz, 2H), 3.48 (q, J = 11.0 Hz, 2H). 3.40 (t, J = 6.5 Hz, 2H), 2.33 (m, 2H).

3-[2-Chloro-4-(trifluoromethoxy)phenoxy]propyl iodide (20c: R_2 = Cl, R_3 = *p*-OCF_3, *n* = 1). The title compound was prepared according to general procedure B using the phenol **18b**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 2.5 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.88 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.09 (t, *J* = 6.0 Hz, 2H), 3.41 (t, *J* = 6.5 Hz, 2H), 2.33 (m, 2H).

3-[2-Chloro-4-(trifluoromethylthio)phenoxy]propyl iodide (20d: R_2 = Cl, R_3 = *p*-SCF_3, n = 1). The title compound was prepared according to general procedure B using phenol **18c**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 2.5 Hz, 1H), 7.39 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 4.15 (t, *J* = 6.0 Hz, 2H), 3.45 (t, *J* = 6.5 Hz, 2H), 2.33 (m, 2H).

3-[2-Propyl-4-(trifluoromethylthio)phenoxy]propyl iodide (20e: R_2 = n-Pr, R_3 = *p*-SCF_3, n = 1). The title compound was prepared according to general procedure B using phenol **18e**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.38 (d, *J* = 2.5 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 4.15 (t, *J* = 6.5 Hz, 2H), 3.40 (t, *J* = 6.5 Hz, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 2.22 (m, 2H) 1.57 (m, 2H), 0.89 (t, *J* = 7.5 Hz, 3H).

3-[2-Chloro-4-(3,3,3-trifluoropropyl)phenoxy]propyl iodide (20f: R_2 = Cl, R_3 = *p*-$CH_2CH_2CF_3$, n = 1). The iodide was prepared according to general procedure B using phenol **18f**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 2.5 Hz, 1H), 7.10 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 4.09 (t, *J* = 6.0 Hz, 2H), 3.46 (t, *J* = 6.5 Hz, 2H), 2.80−2.77 (m, 2H), 2.47−2.37 (m, 2H), 2.12 (m, 2H).

3-[2-Chloro-4-(trifluoromethy)phenoxy]propyl iodide (20 g: R_2 = Cl, R_3 = *p*-CF_3, *n* = 1). The title compound was prepared according to general procedure B using 2-chloro-4-(trifluoromethyl)phenol as phenol **18**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 2.5 Hz, 1H), 7.04 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.44 (t, 6.5 Hz, 2H), 2.32 (m, 2H).

3-[2-Chloro-4-(neopentyl)phenoxy]propyl iodide (20h R_2 = Cl, R_3 = *t*-$BuCH_2$, *n* = 1). The title compound was prepared according to general procedure B using the 2-chloro-4-neopentylphenol as phenol **18**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 2.5 Hz, 1H), 6.97 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 4.15 (t, *J* = 6.0 Hz, 2H), 3.45 (t, 6.5 Hz, 2H), 2.41 (s, 2H), 2.12 (m, 2H), 0.92 (s, 9H).

2-[2-Chloro-4-(trifluoromethoxy)phenoxy]ethyl iodide (20i: R_2 = Cl, R_3 = *p*-OCF_3, *n* = 0). A mixture of 2-chloro-3-(trifluoromethoxy)phenol (2.13 g, 10.0 mmol), methyl bromoacetate (1.8 g, 12 mmol) and Cs_2CO_3 (6.5 g, 20 mmol) in DMF (80 mL) was stirred at 25 °C for 6 h. The reaction mixture was diluted with ethyl acetate and washed with water. Removal of solvent give the alkylated product. The crude alkylated product (2.9 g, 10 mmol) was dissolved in dichloromethane (50 mL) and cooled to −78 °C. A solution of diisobutylaluminum hydride in CH_2Cl_2 (1 M, 20 mL) was added and the reaction was warmed to 25 °C over 30 min. The reaction was quenched with methanol (2.0 mL) and poured into 0.5 N aqueous HCl. The aqueous phased was extracted with ethyl acetate and the combined organic layers were washed with brine and concetrated. The residue was chromatographed on silica gel eluting with 1:1 hexane:ethyl acetate gave 2-[2-chloro-4-(trifluoromethoxy)phenoxy]ethanol, which was converted to the title compound following Step 2 of general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, *J* = 2.5 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.85 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.39 (t, *J* = 6.5 Hz, 2H), 3.51 (t, *J* = 6.5 Hz, 2H).

General Procedure C: Preparation of Compounds 21−42. A mixture of phenol **11** (0.20 mmol), iodide **20** (0.22 mmol) and Cs_2CO_3 (0.13 g, 0.40 mmol) in DMF (2.0 mL) was stirred at 25 °C for 6 h. The reaction mixture was diluted with ethyl acetate, washed with water and concentrated. The residue was purified by preparative TLC or flas chromatography on silica gel eluting with a mixture of hexane and ethyl acetate to give the coupling product. The coupling product (0.17 mmol) was dissolved in methanol (2.0 mL) and 2 N KOH (0.25 mL) was added. After 3 h at 25−60 °C, depending on the hydrolytic stability of the ester group, the reaction mixture was acidified with 2 N HCl and extratracted with ethyl acetate. The organic phase was washed with brine, dried and concentrated. The residue was purified by preparative HPLC on a 100 × 20 mm YMC C-18 column using 10−100% gradient CH_3CN-H_2O containing 0.1% TFA as the eluent to give the final compound.

5-{3-[2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy]propoxy}-2-methyl-2,3-dihydro-1-benzofuran-2-carboxylic acid (21). The title compound was prepared according to general procedure C using phenol **11b** and iodide **20a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 3.0 Hz, 1H), 7.02 (d, *J* = 9.0 Hz, 1 H), 6.90 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.7 (d, *J* = 2.5 Hz, 1H), 6.70 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.66 (d, *J* = 9.0 Hz, 1H), 4.46 (q, *J* = 8.5 Hz, 2H), 4.16 (t, *J* = 6.0 Hz, 2H), 4.12 (t, J-6.0 Hz, 2H), 3.53(d, *J* = 16.5 Hz, 1H), 3.11 (d, *J* = 16.5 Hz, 1H), 2.19 (m, 2H), 1.63 (s, 3H). MS (ESI, *m/z*) 460.1 (M^+). Anal. ($C_{21}H_{20}ClF_3O_6$) C, H.

2-*tert*-Butyl-5-{3-[2-chloro-4-(2,2,2-trifluoroethyl)phenoxy]propoxy}-2,3-dihydro-1-benzofuran-2-carboxylic acid (24). The title compound was prepared according to general procedure C employing phenol **11g** and iodide **20b**. ^{1}H NMR (500 MHz, CD_3OD) δ 7.33 (s, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.79 (s, 1H), 6. 70 (m, 2H), 4.21 (t, *J* = 6.0 Hz, 2H), 4.12 (t, *J* = 6.0 Hz, 2H), 3.40 (q, *J* = 11.0 Hz, 2H), 3.39 (s, 2H), 2.22 (m, 2H), 1.07 (s, 9H). MS (ESI, *m/z*) 487.9 (MH^+). Anal. ($C_{24}H_{26}ClF_3O_5$) C, H.

5-{3-[2-Chloro-4-(2,2,2-trifluoroethyl)phenoxy]propoxy}-2-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-carboxylic acid (25). The title compound was prepared according to general procedure C employing phenol **11h** and iodide **20b**. ^{1}H NMR (500 MHz, CD_3OD) δ 7.33 (d, *J* = 1.0 Hz, 1H), 7.21 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.87 (s, 1H), 6. 78 (s, 2H), 4.22 (t, *J* = 6.0 Hz, 2H), 4.16 (t, *J* = 6.0 Hz, 2H), 3.67 (d, *J* = 17.0 Hz, 1H), 3.63 (d, *J* = 17 Hz, 1H), 3.40 (q, *J* = 11.0 Hz, 2H), 2.24 (m, 2H). MS (ESI, *m/z*) 499 (MH^+). Anal. ($C_{21}H_{17}ClF_6O_5$) C, H.

(2*S*)-2-Ethyl-5-{3-[2-chloro-4-(trifluoromethoxy)phenoxy]propoxy}-2,3-dihydro-1-benzofuran-2-carboxylic acid (27). The title compound was prepared according to general procedure C employing phenol **11c** (*S*-isomer) and iodide **20c**. ^{1}H NMR (500 MHz, CD_3OD) δ 7.31 (d, *J* = 2.5 Hz, 1H), 7.17 (dd, *J* = 8.0, 2.5 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 6.78 (br. s, 1H), 6.69 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 4.22 (t, *J* = 6.0 Hz, 2H), 4.11 (t, *J* = 6.0 Hz, 2H), 3.47 (d, *J* = 16.0 Hz, 1H), 3.14 (d, *J* = 16.0 Hz, 1H), 2.24−2.19 (m, 2H), 2.03 (dq, *J* = 14.0, 7.5 Hz, 1H), 1.93 (dq, *J* = 14.0, 7.5 Hz, 1H), 0.98 (t, *J* = 7.5 Hz, 3H). MS (ESI, *m/z*) 482.3 (MNa^+). Anal. ($C_{21}H_{20}ClF_3O_6$) C, H.

(2*R*)-5-{3-[2-Chloro-4-(trifluoromethoxy)phenoxy]-propoxy}-2-isopropyl-2,3-dihydro-1-benzofuran-2-carboxylic acid (29). The title compound was prepared according to general procedure C employing phenol **11f** (*R*-isomer) and iodide **20c**. ^{1}H NMR (500 MHz, CD_3OD) δ 7.33 (d, *J* = 2.0 Hz, 1H), 7.20 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 6.73 (s, 1H), 6. 62−6.66 (m, 2H), 4.24 (t, *J* = 6.0 Hz, 2H), 4.11 (t, *J* = 6.0 Hz, 2H), 3.44 (d, *J* = 16.5 Hz, 1H), 3.18 (d, *J* = 16.5 Hz, 1H), 2.22 (m, 2H), 1.02(d, *J* = 7.5 Hz, 3H), 0.89 (d, *J* = 7.5 Hz, 3H). MS (ESI, *m/z*) 497.1 (MNa^+). Anal. ($C_{22}H_{22}ClF_3O_6$) C, H.

2-Ethyl-5-(3-{2-propyl-4-[(trifluoromethyl)thio]-phenoxy}propoxy)-2,3-dihydro-1-benzofuran-2-carboxylic acid (32). The title compound was prepared according to general procedure C using phenol **11c** and iodo intermediate **20e**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.5, 2.5, 1H), 7.38 (d, 2.5 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 1H), 6.78 (m, 1H), 6.66−6.71 (m, 2H), 4.21 (t, *J* = 6.0 Hz, 2H), 4.11 (t, *J* = 6.0 Hz, 2H), 3.48 (d, *J* = 16.5 Hz, 1H), 3.15 (d, *J* = 16.5 Hz, 1H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.22 (m, 2H), 2.03 (dq, *J* = 14.5, 7.5 Hz, 1H), 1.93 (dq, *J* = 14.5, 7.5 Hz, 1H), 1.56 (m, 2H), 0.97 (t, *J* = 7.5 Hz,3H), 0.89 (t, *J* = 7.5 Hz, 3H). MS (ESI, *m/z*) 507.2 (MNa^+). Anal. ($C_{24}H_{27}F_3O_5S$) C, H.

5-{3-[2-Chloro-4-(trifluoromethyl)phenoxy]propoxy}-2-ethyl-2,3-dihydro-1-benzofuran-2-carboxylic acid (33). The title compound was prepared according to general procedure C employing phenol **11c** and iodide **20g**. ^{1}H NMR (500 MHz, CD_3OD) δ 7.66 (d, J = 2.0 Hz, 1H), 7.56 (dd, J = 9.0, 2.0 Hz, 1H), 7.23 (d, J = 9.0 Hz, 1H), 6.80 (d, J = 2.5 Hz, 1H), 6.71 (dd, J = 8.5, 2.5 Hz, 1H), 6.68 (d, J = 8.5 Hz, 1H), 4.31 (t, J = 6.0 Hz, 2H), 4.14 (t, J = 6.0 Hz, 2H), 3.48 (d, J = 16.5 Hz, 1H), 3.16 (d, J = 16.5 Hz, 1H), 2.29−2.24 (m, 2H), 2.08−2.00 (m, 1H), 1.97−1.90 (m, 1H), 0.99 (t, J = 7.5 Hz, 3H). MS (ESI, *m/z*) 445.8 (MH^+). Anal. ($C_{21}H_{20}ClF_3O_5$) C, H.

5-(3-{2-Chloro-4-[(trifluoromethyl)thio]phenoxy}-propoxy)-2-ethyl-2,3-dihydro-1-benzofuran-2-carboxylic acid (35). The title compound was prepared according to general procedure C employing phenol **11c** and iodide **20d**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 2.0 Hz, 1H), 7.58 (dd, J = 8.0, 2.0 Hz, 1H), 7.18 (d, 8.0 Hz, 1H), 6.79 (d, J = 1.5 Hz, 1H), 6.70 (dd, J = 9.0, 1.5 Hz, 1H), 6.67 (d, J = 9.0 Hz, 1H), 4.29 (t, J = 6.0 Hz, 2H), 4.13 (t, J = 6.0 Hz, 2H), 3.47 (d, J = 16.5 Hz, 1H), 3.15 (d, J = 16.5 Hz, 1H), 2.54 (m, 2H), 2.03 (dq, J = 14.5, 7.5 Hz, 1H), 1.93 (dq, J = 14.5, 7.5 Hz, 1H), 0.99 (t, J = 7.5 Hz, 3H). MS (ESI, *m/z*) 499.1 (MNa^+). Anal. ($C_{21}H_{20}ClF_3O_5S$) C, H.

5-{3-[2-Chloro-4-(2,2-dimethylpropyl)phenoxy]propoxy}-2-ethyl-2,3-dihydro-1-benzofuran-2-carboxylic acid (36). The title compound was prepared according to general procedure C employing phenol **11c** (*S*-isomer) and iodide **20h**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, J = 1.5 Hz, 1H), 6.98 (dd, J = 8.0, 1.5 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 2.0 Hz, 1H), 6.70 (dd, J = 8.5, 2.0 Hz, 1H), 6.67 (d, J = 8.5 Hz, 1H), 4.17 (t, J = 6.0 Hz, 2H), 4.12 (t, J = 6.0 Hz, 2H), 3.48 (d, J = 16.5 Hz, 1H), 3.15 (d, J = 16.5 Hz, 1H), 2.20 (m, 2H), 2.02 (dq, J = 14.5, 7.5 Hz, 1H), 1.93(dq, J = 14.5, 7.5 Hz, 1H), 0.99 (t, J = 7.5 Hz, 3H), 0.88 (s, 9H). MS (ESI, *m/z*) 447.2 (MH^+). Anal. ($C_{25}H_{31}ClO_5$) C, H.

(2*S*)-5-{3-[2-Chloro-4-(2,2,2-trifluoroethyl)phenoxy]propoxy}-2-ethyl-2,3-dihydro-1-benzofuran-2-carboxylic acid (37). The title compound was prepared according to general procedure C employing phenol **11c** (*S*-isomer) and iodide **20b**. ^{1}H NMR (500 MHz, CD_3OD) δ 7.35 (d, J = 2.0 Hz, 1H), 7.21 (dd, J = 8.5, 2.0 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 2.0 Hz, 1H), 6.70 (dd, J = 8.5, 2.0 Hz, 1H), 6.68 (d, J = 8.5 Hz, 1H), 4.22 (t, J = 6.5 Hz, 2H), 4.14 (t, J = 6.5 Hz, 2H), 3.48 (d, J = 16.0 Hz, 1H), 3.48 (q, J = 11.0 Hz, 2H), 3.16 (d, J = 16.0 Hz, 1H), 2.23 (m, 2H), 2.03 (dq, J = 14.0, 7.5 Hz, 1H), 1.93 (dq, J = 14.0, 7.5 Hz, 1H), 0.99 (t, J = 7.5 Hz, 3H). MS (ESI, *m/z*): 481.0 (MNa^+). Anal. ($C_{22}H_{22}ClF_3O_5$) C, H.

(2*S*)-5-{3-[2-Chloro-4-(3,3,3-trifluoropropyl)phenoxy]-propoxy}-2-ethyl-2,3-dihydro-1-benzofuran-2-carboxylic acid (38). The title compound was prepared according to general procedure C employing phenol **11c** (*S*-isomer) and iodide **20f**. ^{1}H NMR (500 MHz, CD_3OD) δ 7.26 (d, J = 2.5 Hz, 1H), 7.11 (dd, J = 8.5, 2.5 Hz, 1H), 6.70 (d, J = 8.5 Hz, 1H), 6.79 (m, 1H), 6.71−6.66 (m, 2H), 4.18 (t, J = 6.0 Hz, 2H), 4.12 (t, J = 6.0 Hz, 2H), 3.47 (d, J = 16.0 Hz, 1H), 3.15 (d, J = 16.0 Hz, 1H), 2.80−2.77 (m, 2H), 2.47−2.37 (m, 2H), 2.24−2.18 (m, 2H), 2.04 (dq, J = 14.0, 7.5 Hz, 1H), 1.93 (dq, J = 14.0, 7.5 Hz, 1H), 0.99 (t, J = 7.5 Hz, 3H). MS (ESI, *m/z*): 495.1 (MNa^+). Anal. ($C_{23}H_{24}ClF_3O_5$) C, H.

6-{3-[2-Chloro-4-(trifluoromethoxy)phenoxy]propoxy}-2-ethyl-2,3-dihydro-1-benzofuran-2-carboxylic acid (40). The title compound was prepared according to general procedure C employing phenol **11e** and iodide **20c**. ^{1}H NMR (500 MHz, CD_3OD) δ 7.32 (d, J = 2.0 Hz, 1H), 7.19 (dd, J = 8.5, 2.0 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 6.99 (d, J = 9.0 Hz, 1H), 6.41−6.46 (m, 2H), 4.23 (t, J = 6.0 Hz, 2H), 4.15 (t, J = 6.0 Hz, 2H), 3.42 (d, J = 16.5 Hz, 1H), 3.11 (d, J = 16.5 Hz, 1H), 2.23 (m, 2H), 2.03 (dq, J = 14.5, 7.5 Hz, 1H), 1.94 (dq, J = 14.5, 7.5 Hz, 1H), 0.99 (t, J = 7.5 Hz, 3H). MS (ESI, *m/z*) 461.2 (MH^+). Anal. ($C_{21}H_{20}ClF_3O_6$) C, H.

5-{2-[2-Chloro-4-(trifluoromethoxy)phenoxy]ethoxy}-2-isopropyl-2,3-dihydro-1-benzofuran-2-carboxylic acid (41). The title compound was prepared according to general procedure C employing phenol **11f** (*R*-isomer) and iodide **20i**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 2.5 Hz, 1H), 7.12 (dd, J = 9.0, 2.5 Hz, 1H), 7.00 (d, J = 9.0 Hz, 1H), 6.83 (d, J = 2.5 Hz, 1H), 6.81 (d, J = 9.0 Hz, 1H), 6.78 (dd,, J = 9.0, 2.5 Hz, 1H), 4.36 (t, J = 6.5 Hz, 2H), 4.14 (t, J = 6.5 Hz, 2H), 3.56 (d, J = 16.5 Hz, 1H), 3.33 (d, J = 16.5 Hz, 1H), 2.32 (m, 1H), 1.09 (d, J = 7.0 Hz, 3H), 1.02 (d, J = 7.0 Hz, 3H). MS (ESI, *m/z*) 460.1 (M^+). Anal. ($C_{21}H_{20}ClF_3O_6$) C, H.

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Supporting Information Available: Preparation of an oxazolinone amide derivation of the *R*-enantiomer of phenol **11c** and its X-ray crystallographic data. This material is available free of charge via Internet at http://pubs.acs.org.

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