Structure-Based Design of Potent Retinoid X Receptor α Agonists

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A series of tetrahydrobenzofuranyl and tetrahydrobenzothienyl propenoic acids that showed potent agonist activity against RXRα were synthesized via a structure-based design approach. Among the compounds studied, **46a**,**b** showed not only very good potency against RXRα (K_i = 6 nM) but was also found to be greater than 167-fold selective vs RARα (K_i > 1000 nM). This compound profiled out as a full agonist in a cell-based transient transfection assay (EC_{50} = 3 nM). The two antipodes were separated via chiral chromatography, and **46b** was found to be 40-fold more potent than **46a**. Interestingly, cocrystallization of **46a**,**b** with the RXRα protein generated a liganded structure whereby the (*S*)-antipode was found in the binding pocket. Given orally in *db*/*db* mice or ZDF rats, **46a**,**b** showed a significant glucose-lowering effect and an increase in liver mass. Triglycerides decreased significantly in *db*/*db* mice but increased in the ZDF rats. A dose-dependent decrease of nonesterified free fatty acids was seen in ZDF rats but not in *db*/*db* mice. These differences indicate a species specific effect of RXR agonists on lipid metabolism.

Introduction

Retinoids, both natural and synthetic, are derivatives of vitamin A. Retinoids have been recognized to induce a broad spectrum of biological effects. They regulate a wide variety of physiological processes including carbohydrate and lipid metabolism and cell differentiation, proliferation, and morphogenesis.[1] Retinoids interact with members of the following protein families: retinoid X receptors (RXRα, RXR*β*, and RXR*γ*), retinoic acid receptors (RARα, RAR*β*, and RAR*γ*), cytoplasmic retinoic acid binding protein, retinol-binding protein, cytochrome P450, and P-glycoprotein. RXR and RAR act as ligand-activated transcription factors.

The natural ligands for RAR and RXR have been identified as all-*trans*-retinoic acid (ATRA)[2] and 9-*cis*-retinoic acid (9-*cis*-RA),[3] respectively. Interestingly, both ATRA and 9-*cis*-RA activate RAR; however, only 9-*cis*-RA activates RXR.[4] The identification of the natural ligands and the physiological significance of both receptors have elicited the design of numerous synthetic analogues against both receptors.[5]

The RXR receptors can either form homo- or hetereodimers that bind to direct repeats called retinoid X response elements (RXRE).[6] Selective RXR agonists and modulators have been identified.[7] It has been suggested that selective activation of either the homo- or the heterodimers may elicit quite different physiological responses.[8] For example, hetero- and homodimer activation stimulates liver triglyceride synthesis, whereas heterodimer activation, homodimer inactivation does not stimulate liver triglyceride synthesis.[9] Recently, it has been shown that compounds that activate the RXR:PPAR*γ* heterodimer can act as insulin sensitizers.[10] The RXR agonist LG100268 has been shown to cause less weight gain than a PPAR*γ* agonist, and combination treatment of both agonists was more efficacious at lowering serum glucose than either agonist alone in *db*/*db* mice.[11b] Therefore, identification of selective RXR agonists may offer an alternative approach for the treatment of type II diabetes and obesity while improving the efficacy or attenuating the adverse events when combined with PPAR*γ* agonists.[11]

We report herein the discovery of a new class of RXRα agonists that are selective vs other nuclear receptors including RARα. These compounds were discovered via the initial identification of weak screening hits, **1** and **2** (Figure 1). Utilization of the published RXRα *apo* structure to create an "active" conformation[12] in combination with modeling, along with a limited number of synthetic iterations from **1** and **2**, provided the active tetrahydrobenzofuranyl and tetrahydrobenzothienyl propenoic acids. The X-ray crystallographic structure of the RXRα:PPAR*γ* heterodimer[13] was solved and later used to assist in the understanding of the structure−activity relationships that were observed. We have found that these compounds not only have potent agonist activity in vitro but also show antidiabetic activity in rodent models of diabetes.

Chemistry

The chemistry to access the acyclic tetrahydrobenzofuranyl propenoic acids **6**, **19**, and **20** is outlined in Schemes 1 and 2. Synthesis of the 2,5-substituted furan was accomplished by first coupling the known boronic acid **3**[14a] with 5-bromo-2-furaldehyde generating aldehyde **4**. Wittig reaction and hydrolysis then produced the desired propenoic acid **6** (Scheme 1). The synthesis into the 2,4- or 2,4,5-substituted furans was carried out by initially treating the known bromide **7**[15] under metal

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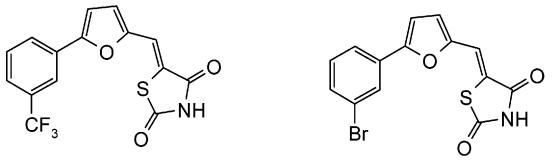


1, Ki = 7.4 μM **2, Ki = 1.5 μM**

Figure 1. Screening hits.

halogen exchange conditions followed by reaction with 3-furaldehyde producing the benzylic alcohol **8**. Deprotonation with *t*-BuLi and quenching with dimethylformamide (DMF) afforded aldehyde **13**. A small amount of the regioisomeric aldehyde was also seen. The alcohol was removed via trifluoroacetic acid (TFA) and triethylsilane yielding furaldehyde **15**. Wittig reaction and hydrolysis afforded the desired furanyl propenoic acid **19**. Propenoic acid **20** was obtained by starting with 2-methyl-3-furancarboxylic acid. The Weinreb amide was generated under *O*-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HATU) coupling conditions giving **10**. Reaction of **10** with the anion formed via metal halogen exchange of **7** as above produced ketone **11**. Reduction of **11** with $NaBH_4$ gave alcohol **12** that could be converted to the desired acid **20** utilizing the same conditions as described for acid **19** (Scheme 2).

The synthetic route to generate both the cyclic tetrahydrobenzofuranyl and the tetrahydrobenzothienyl propenoic acids started with the commercially available furanyl and thienyl ketones **21** and **22**. Reaction of these ketones with the known bromide **7** under metal halogen conditions afforded alcohols **26** and **27**. The alcohols were then dehydroxylated utilizing $NaBH_4$ and $BF_3 \cdot Et_2O$ in tetrahydrofuran (THF) or TFA and triethylsilane, respectively, generating compounds **31** and **32**. Deprotonation with butyllithium followed by quenching with DMF yielded aldehydes **36** and **37**. The aldehydes were then subjected to Horner−Emmons conditions with triethylphosphonoacetate to generate unsaturated esters **41a**,**b** and **42**. Hydrolysis afforded the desired products **46a**,**b** and **47** as racemic mixtures. This synthetic sequence was also used to make the substituted tetramethyltetrahydronaphthalenes **48**−**50** starting from the known bromotetramethyltetrahydronaphthalenes **23**−**25**.[14] The saturated acid **51** was generated via the reduction of **47** under hydrogenation conditions (Scheme 3).

The *cis*-methyl-substituted propenoic acid **54** was synthesized from tetrahydrobenzofuran **31**. Deprotonation and quenching with N-methoxy-N-methylacetamide gave methyl ketone **52** that could be converted to the requisite acid by utilizing similar conditions as described previously yielding **54**. Replacement of the acid moiety with the acidic thiazolidinedione residue was accomplished by treating aldehyde **36** with thiazolidinedione under basic conditions affording the desired compound **56**. The truncated acid **55** was generated by treating aldehyde **36** with Ag_2O in methanol (MeOH) (Scheme 4).

The corresponding benzofuranyl propenoic acid could be made starting with alcohol **26**. Treatment of this alcohol under oxidative conditions [2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), 100 °C] yielded the benzofuran **57**. Utilization of the conditions described above produced the unsaturated acid **60** (Scheme 5).

A tetrahydrobenzoxazole ring system was also synthesized as a replacement for the benzofuranyl and benzothiophienyl ring systems (Scheme 6). The synthesis started from the known ketooxazole **61**.[16] Metal halogen exchange of bromide **7** followed by reaction with oxazole **61** gave the corresponding alcohol **62**. Dehydroxylation as before and benzylic bromination [N-bromosuccinimide (NBS), 2,2′-azobisisobutyronitrile (AIBN), 90 °C] afforded bromide **64**. Attempted direct oxidation of this bromide to the aldehyde gave very poor yields or the benzoxazole. Therefore, the bromide was reacted with potassium acetate, hydrolyzed, and oxidized to give the desired aldehyde **67**. Wittig reaction followed by hydrolysis as before gave the desired unsaturated acid **69**.

A tetrahydropyridinyl propenoic acid was also synthesized in an attempt to identify potent agonists that may possess better solubility properties. The synthesis started with the known ketone **70**[17] that was reacted under the same conditions as described in Scheme 3 to afford alcohol **71**. The alcohol was reduced as before followed by $LiAlH_4$ reduction to produce N-methyl furan **73**. Formylation (*t*-BuLi, DMF, −78 °C), Wittig reaction, and hydrolysis yielded the desired propenoic acid **76** (Scheme 7).

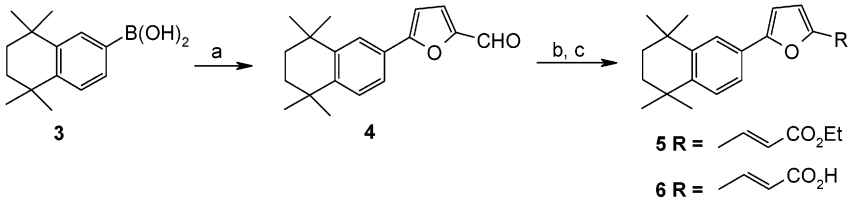
Biological Evaluation

Three in vitro assays were utilized to evaluate RXRα and RARα binding affinity and functional activity. Details of the expression and purification of the RXRα and RARα protein are reported in the Experimental Section. Details of the assay development and data analysis are similar to previously reported SPA assays from our group.[18] The functional profiles of selected compounds were evaluated in a transient transfection assay utilizing a monkey kidney cell line (CV-1) transfected with expression vectors containing full length hRXRα or GAL4 hRARα and a RXRα or a RARα responsive reporter gene construct. C3H10T1/2 clone 8 fibroblasts were used to measure triglyceride accumulation, a surrogate marker for lipogenesis and RXR activity. Alkaline phosphatase (ALP) activity was measured in the same fibroblasts and was a surrogate marker for altered RAR activity.[19] Details of the functional assays reported in the Experimental Section are modified from those that we reported previously.[19] Male diabetic (*db*/*db*) mice and Zucker diabetic fatty (ZDF) rats were examined via oral administration of vehicle or **46a**,**b** in vehicle to evaluate its efficacy. After 2 weeks of oral dosing measurements of nonfasting glucose, glycohemoglobin, triglyceride, nonesterified free fatty acid, and aspartate aminotransferase levels were determined. Details of these studies can be found in the Experimental Section.

Results and Discussion

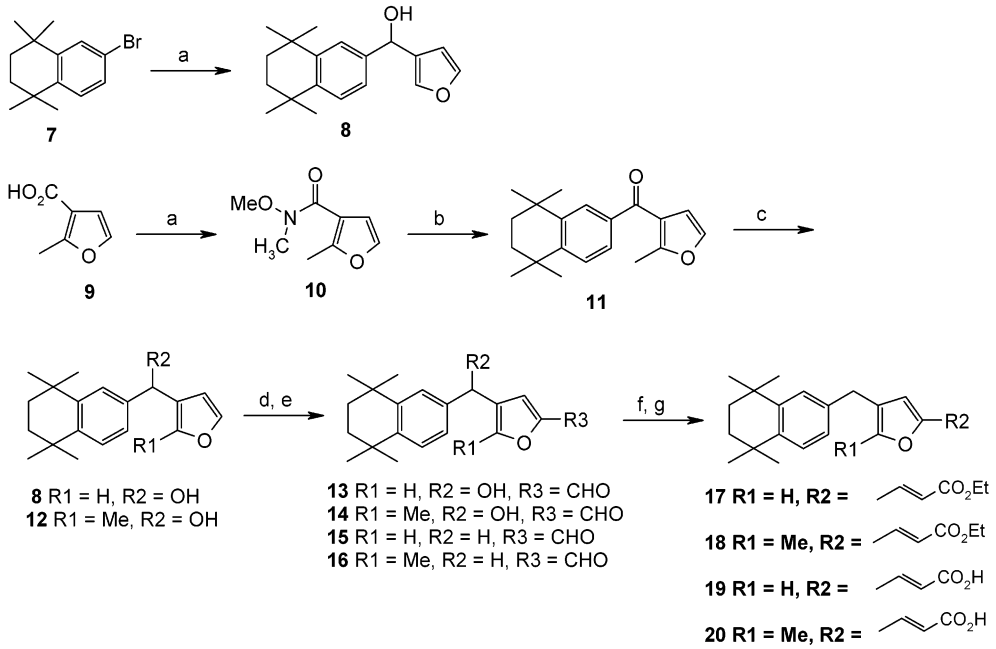
The chemistry effort that led to the discovery of the novel tetrahydrobenzofuranyl and tetrahydrobenzothienyl propenoic acids began with the two high throughput screening hits **1** and **2** (Figure 1). A homology model of an "active" conformation of the RXRα LBD (Figure 3) was generated since the available RXRα *apo* struc-

Scheme 1[a]



[a] Reagents: (a) 5-Bromo-2-furaldehyde, dppf·$PdCl_2$·CH_2Cl_2, toluene, EtOH, 80 °C, 2.0 M Na_2CO_3. (b) NaH, DME, $(EtO)_2POCH_2CO_2Et$. (c) LiOH·H_2O, dioxane, H_2O.

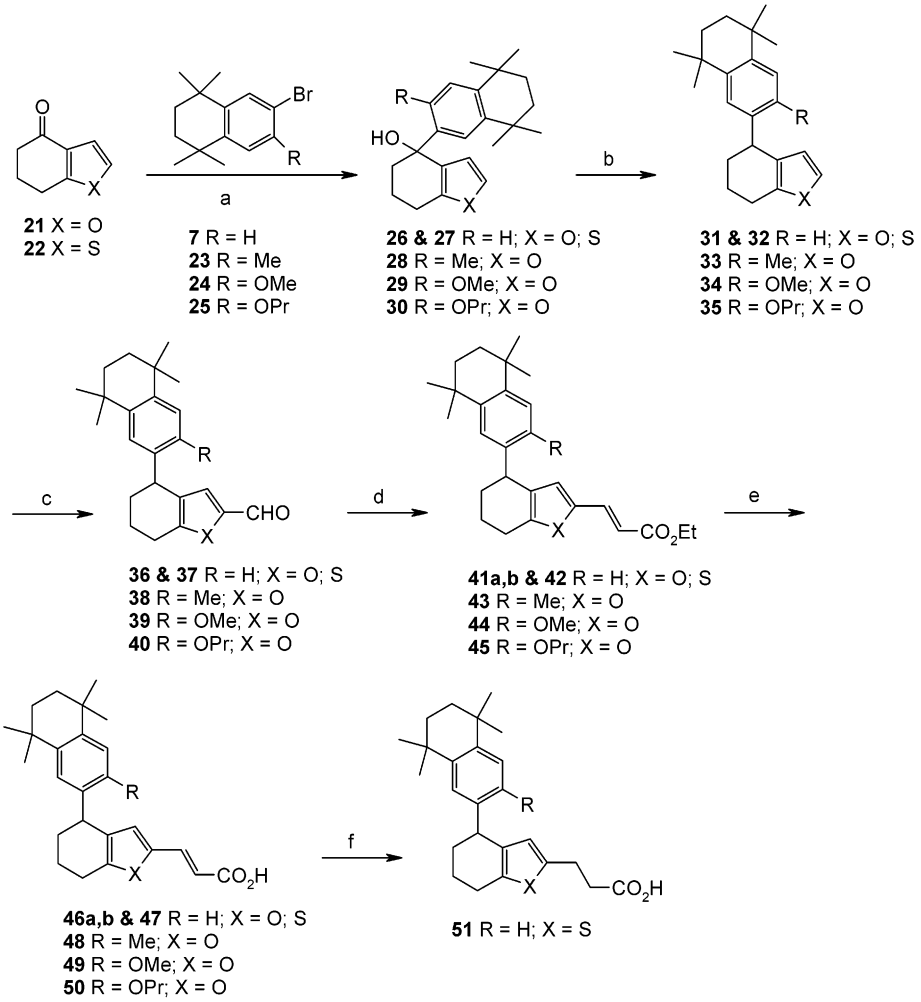
Scheme 2[a]



[a] Reagents: (a) 3-Furaldehyde, BuLi, THF, −78 °C. Reagents: (a) DMF, HATU, $^{i}Pr_2NEt$, (MeO)(Me)NH·HCl. (b) BuLi, **7**, THF, −78 °C. (c) $NaBH_4$, MeOH. (d) ^{t}BuLi, DMF, −78 °C, Et_2O. (e) CH_2Cl_2, TFA, Et_3SiH. (f) NaH, THF, $(EtO)_2POCH_2CO_2Et$. (g) ^{i}PrOH, H_2O, NaOH.

ture[12] (1LBD) had adopted a previously unseen conformation (see Experimental Section). Compound **6** was prepared following up on screening hits **1** and **2**. Subsequent docking in the "active" model suggested that the position of the acidic moiety and substituted aryl residue needed to be in a 2,4-relationship rather than the 2,5-position about the furan ring. Modeling also indicated that the substituted aryl residue had not been optimized in terms of its spatial position within the binding pocket. Therefore, a methylene group was added at the 4-position to allow for the correct conformation along with the known tetramethyldihydronaphthalene moiety[15] to fill the putative hydrophobic pocket. These chemical modifications led to **19**, a compound with a RXRα affinity of 138 nM, a 54- and 11-fold increase over the original screening hits **1** and **2**, respectively. However, when this compound was tested in the functional ALP assay, which is a surrogate marker for RAR signaling,[19] it had an EC_{50} of 57 nM. Interestingly, compound **19** had a $K_i > 1\ \mu M$ in the RAR binding assay. The reason for this is unclear, although one possibility is that **19** was metabolized by the cells to generate an active RARα metabolite. It was hypothesized that the conformational flexibility of compound **19** did not allow the desired selectivity to be achieved. It was felt that if constraints or biases could be built in such that the compound was "L-shaped" rather than linear, like **19**, the desired selectivity could be achieved. Possible solutions to test this hypothesis were to put substituents at the 3-position on the tetramethyltetrahydronaphthalene ring with or without a substituent at the 5-position on the furan ring. Another solution was to tie back the methylene spacer into a ring that was attached at the 5-position on the furan ring (Figure 2). The first compound that was made to test this hypothesis was acid **20**. Synthesis of this compound produced one that was now more selective than **19** (Table 1); however, some RARα activity still remained in the functional assay (EC_{50}ALP = 1000 nM). The synthesis of bicyclic compound **46a**,**b** (Scheme 3) provided a very potent compound (K_i = 6 nM) with greater than 167-fold selectivity vs RARα (Table 1). It was also found to be inactive against PPARα,*δ*,*γ* in both the binding and the transient transfection assays (data not shown). However, because of the newly generated stereogenic center, **46a**,**b** was produced as a racemic mixture. The two antipodes were separated at the ethyl ester intermediate **41a**,**b** via chiral chromatography (see the Experimental Section for the details) and tested in the RXRα binding assay. There was a 40-fold potency difference between the two antipodes (Table 1). Interestingly, the predicted (*S*)-antipode was exclusively seen in the binding pocket of the RXRα receptor when cocrystallized utilizing the racemic **46a**,**b** (see below for more details

Scheme 3[a]



[a] Reagents: (a) BuLi, THF, −78 °C. (b) $NaBH_4$, BF_3·Et_2O, THF, 0 °C or TFA, Et_3SiH, CH_2Cl_2. (c) BuLi, THF, DMF, 0 °C or ^{t}BuLi, −40 °C, Et_2O, DMF. (d) NaH, DME, $(EtO)_2POCHCO_2Et$. (e) LiOH·H_2O, dioxane, H_2O. (f) $Pd(OH)_2$, H_2, EtOAc.

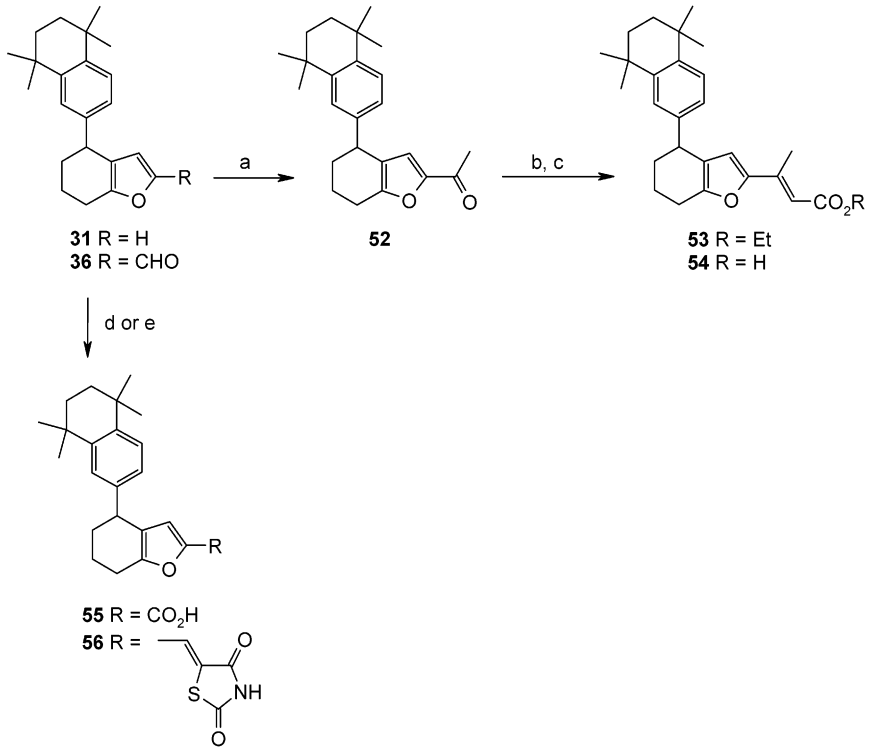
pertaining to the X-ray structure). Docking studies using the program MVP (see Experimental Section) reveal that the (*S*)-antipode was much lower in energy (better fit) than the (*R*)-antipode. The geometric strain energy for the (*S*)-antipode was only 0.3 kcal in energy above its global minimum whereas the (*R*)-antipode was 3.3 kcal higher in energy.

Alterations about the acid moiety yielded compounds that were less potent than **46a**,**b** (see compounds **55** and **56**). The loss of activity of the truncated acid **55** was especially dramatic. The methyl-substituted propenoic acid **54** also lost some potency. Two alternate heterocycles that were examined in place of the furan were also synthesized. The thiophene **47** did retain potency, albeit less than **46a**,**b**. This reduction in potency could be due to steric occlusions near the heteroatom with the larger atom (sulfur) not fitting as well as oxygen. Reduction of the olefin in **47** afforded saturated propanoic acid **51**. This compound was approximately 5-fold less potent than **47**, which presumably results from the entropic cost of a more flexible compound.

An effort was undertaken to identify analogues of **46a**,**b** that may profile out differently. It had already been demonstrated in the literature that substitutions at the 3-position on the tetramethyltetrahydronaphthalene ring could modulate the RXR activity.[7d,j,8a] Therefore, compounds **48**−**50** were synthesized (Scheme 3). The 3-methyl compound profiled out as a full agonist in the lipogenesis assay, whereas compounds **49** and **50** profiled as partial agonists (Table 1). Although the crystal structure of **46a**,**b** has the 3-position pointed away from the direction of helix 12 (AF-2), our prediction would be that the tetramethyltetrahydronaphthalene ring would flip so that the 3-position would now be directed toward helix 12 for compounds **48**−**50**. Steric interaction with helix 12 is a well-known mechanism of partial agonism and antagonism in nuclear receptor modulators.[7]

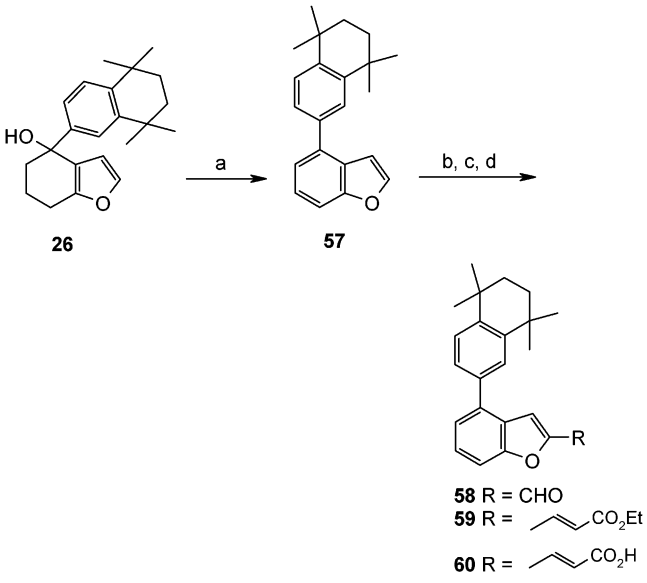
Modifications were made to explore other parameters in the series. In one example, benzofuran **60** was synthesized as shown in Scheme 5. Removal of the stereogenic center had a deleterious effect on binding, functional activity, and selectivity as can be seen in Table 1. Without the stereogenic center, **60** cannot adopt to the shape of the receptor in a low energy conformation. The calculated energy for a docked conformation of **60** using MVP is 3.3 kcal higher than the calculated global minimum, whereas that of **46b** is only 0.3 kcal. This geometric strain difference, 3.0 kcal, is similar to the difference between the stereoisomers of **46a**,**b**, and the affinities of **46a** and **60** are also similar. The oxazole **69** (Scheme 6) lost potency vs **46a**,**b**. This result was

Scheme 4[a]



[a] Reagents: (a) BuLi, THF, −78 °C, $CH_3CON(OMe)(CH_3)$. (b) NaH, DME, 80 °C, $(EtO)_2POCH_2CO_2Et$. (c) $LiOH·H_2O$, dioxane, H_2O. (d) MeOH, Ag_2O, $NaOH_{(aq)}$. (e) 2,5-Thiazolidinedione, toluene, morpholine, reflux, sieves.

Scheme 5[a]



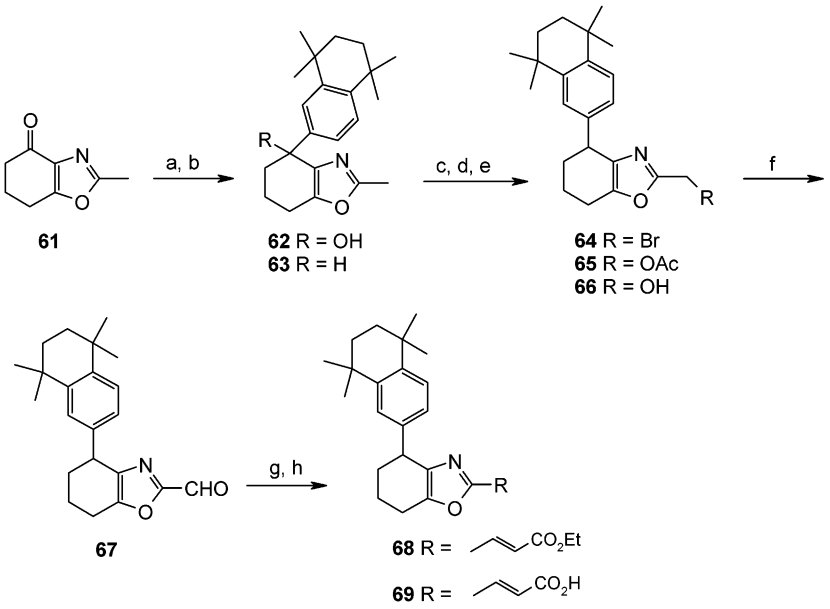
[a] Reagents: (a) DDQ, toluene, 100 °C. (b) ^{t}BuLi, Et_2O, DMF, −40 °C. (c) NaH, DME, $(EtO)_2POCH_2CO_2Et$. (d) $LiOH·H_2O$, dioxane, H_2O.

unexpected due to the small perturbation in the structure (nitrogen replacement for CH). Another modification was to insert a basic nitrogen into the core. It was felt that the nitrogen could serve two purposes: first, reducing the lipophilicity of the compound; and second, adding a point of attachment that could be used to explore another region of the binding site. Ultimately, compound **76** was synthesized (Scheme 7), and although retaining reasonable potency (K_i = 79 nM) against RXRα and selectivity vs RARα (K_i > 1000 nM), it was less potent than **46a**,**b**. Subsequent analysis of the RXRα crystal structure (see below) revealed a possible explanation of why both **69** and **76** were less potent than expected. The crystal structure was used to identify all polar atoms of the binding site not involved in hydrogen bonding. The result of the analysis is seen in Figure 5 where the surface of "free" polar atoms is colored in yellow. Other than the acid binding residues, only C432 and H435 have a single polar atom that is available for hydrogen bonding. Both **69** and **76** place polar atoms in areas where the receptor is hydrophobic and thus incur a desolvation penalty when binding.

In parallel with the synthetic work utilizing the published RXRα *apo* structure, the X-ray crystallographic structure of the RXRα:PPARγ heterodimer was solved containing both receptor ligand binding domains (LBDs) and their respective ligands [the (*S*)-antipode of **46a**,**b** {(*S*)-**46a**,**b**} and farglitazar[20]] as well as peptide coactivators bond to each protein (Figure 4A).[21] Both activated LBDs adopt the familiar three layer α-helical sandwich fold previously reported for many other ligand-bound nuclear receptors.[13,22] The structure displays an extensive helix−10 dimer interface, hydrophobic ligand binding pockets, and coactivated AF2 regions that are mostly consistent with our previously reported structure of the RXRα:PPARγ heterodimer bound with 9-*cis*-RA, farglitazar, and SRC-1 peptides.[13] Absent or poor electron density prevented complete structure building for residues 245−262, 444−448, and 457−462 in RXRα and residues 250−279 and 461−464 for PPARγ and regions within each coactivator peptide.

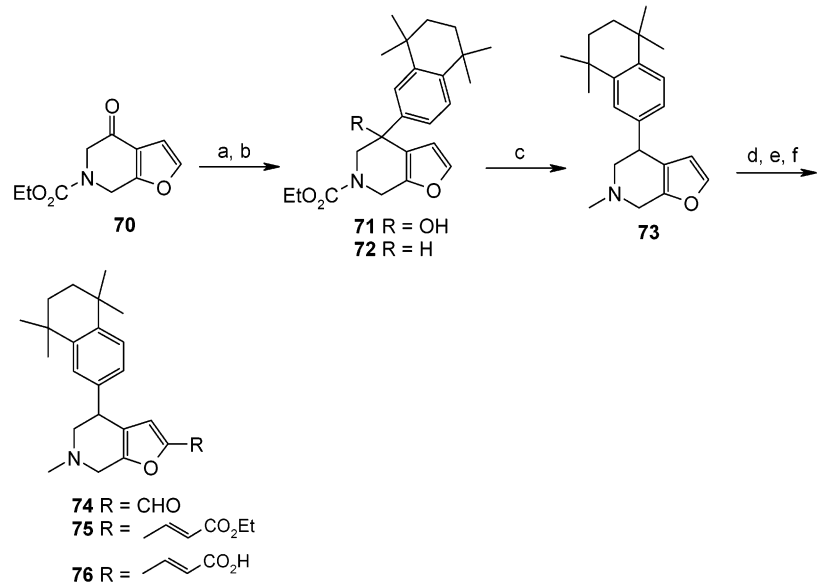
The potent and selective rexinoid, (*S*)-**46a**,**b**, sits in the distinctive L-shaped hydrophobic ligand binding cavity and occupies a large portion of the available space. Shaped by residues from H3, H4, H5, H7, H10,

Scheme 6[a]



[a] Reagents: (a) BuLi, THF, −78 °C, **7**. (b) $NaBH_4$, $BF_3{\cdot}Et_2O$, THF, 0 °C. (c) NBS, AlBN, CCl_4, 90 °C. (d) KOAc, CH_3CN. (e) K_2CO_3, MeOH, H_2O. (f) TPAP, CH_2Cl_2, molecular sieves. (g) NaH, DME, $(EtO)_2POCH_2CO_2Et$. (h) $LiOH{\cdot}H_2O$, dioxane, H_2O.

Scheme 7[a]



[a] Reagents: (a) BuLi, THF, −78 °C, **7**. (b) $NaBH_4$, $BF_3{\cdot}Et_2O$, THF, 0 °C. (c) $LiAlH_4$, THF, reflux. (d) ^{t}BuLi, Et_2O, −40 °C, DMF. (e) NaH, DME, $(EtO)_2POCH_2CO_2Et$. (f) $LiOH{\cdot}H_2O$, dioxane, H_2O.

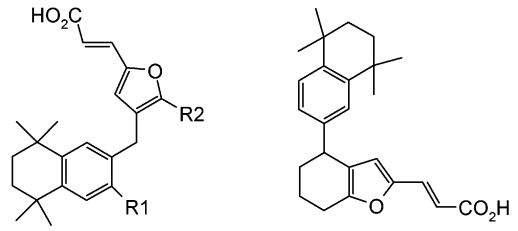


Figure 2. Conformationally biased or constrained propenoic acids.

and the *β*-turn, the cavity presents a sharp turn near residue L436 (Figure 4B). Although a racemic mixture of compound **46a**,**b** was used during crystallization, the (*S*)-antipode best fit the initial electron density. This potent and selective rexinoid displays similar electrostatic and hydrophobic interactions as reported for the potent and selective natural rexinoid, 9-*cis*-RA.[13,23] The carboxylate of (*S*)-**46a**,**b** hydrogen bonds with the side chain of R316 and the backbone amide of A327 (Figure 4B−D). The new rexinoid makes a series of van der Waals interactions as it traverses the hydrophobic lined pocket. Similar to the triene group of 9-*cis*-RA, the tetrahydrobenzofuran linkage between the carboxylate and the tetramethyltetrahydronaphthalene of (*S*)-**46a**,**b** lies proximal to Q275, A271, L309, L326, F313, I268, A272, L309, I310, W305, L436, and M432 but is larger and makes more interactions than the triene linkage of 9-*cis*-RA. Much like the *β*-ionone of 9-*cis*-RA, the bulky tetramethyltetrahydronaphthalene of (*S*)-**46a**,**b** fits in a pocket that is formed by V265 and C269 in H3 and V342, I345, F346, V349 in H7, C432, H435, and

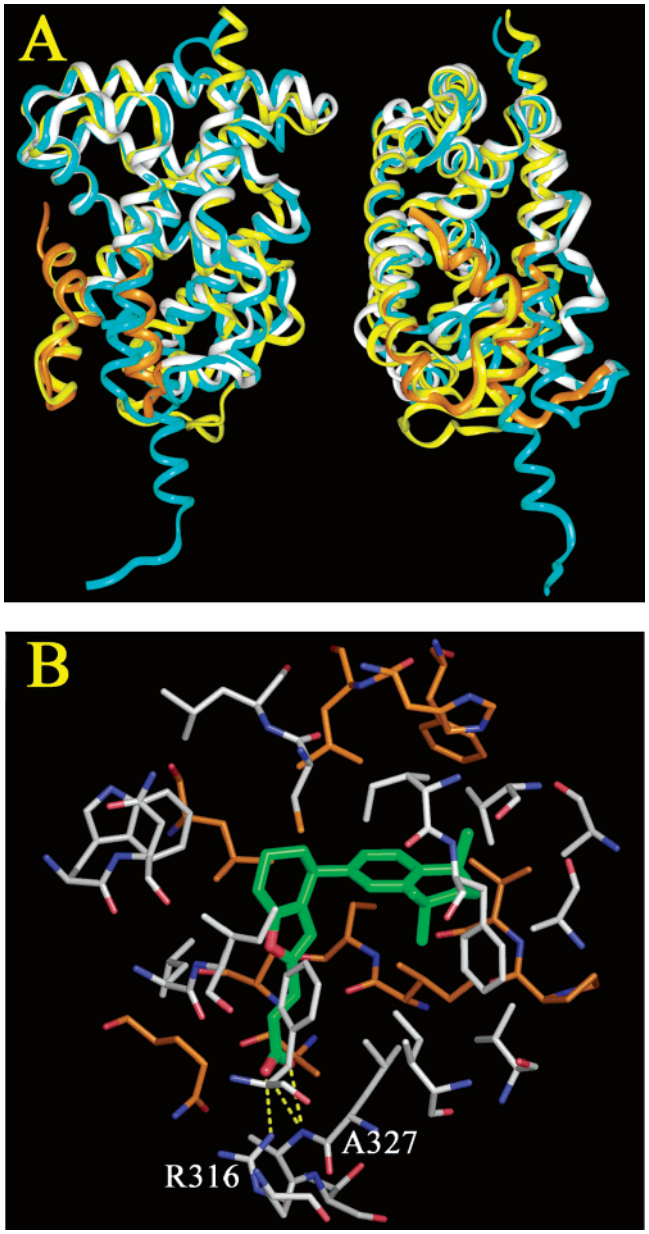


Figure 3. (A) Ribbon structures of *apo* RXRα (1LBD) in cyan, RARγ (2LBD) in yellow, and the resulting "active" RXRα LBD model in white and orange. The orange color indicates the sections of the RXRα that were remodeled using the RARγ structure as a template. Two angles are shown with the second view rotated by 90°. (B) Binding site of RXRα "active" model with (*S*)-**46a**,**b** docked using the same color scheme as in panel A.

L436 in H10 (Figure 4B,C). The rigid geometry afforded by the tetrahydrobenzofuran ring along with the added bulk from the tetramethyltetrahydronaphthalene certainly contribute to the greater than 167-fold selectivity of (*S*)-**46a**,**b** toward RXRα over RARα. Moreover, the fixed geometry of (*S*)-**46a**,**b** prevents interconversion to a less selective isomer.

We were also interested in evaluating the propenoic acids in rodent models of type 2 diabetes mellitus. The *db*/*db* mouse and ZDF rat are characterized by hyperglycemia, hyperlipidemia, and insulin resistance. Compound **46a**,**b** or vehicle (control) was given for 2 weeks to *db*/*db* mice (10−100 mg/kg compound **46a**,**b**) or ZDF rats (3−30 mg/kg compound **46a**,**b**). Values in Table 2

Table 1. In Vitro Potency, Selectivity, and Functional Activities

	RXRα			RARα		
	K_i[a] (nM)	EC_{50} TT[b] (nM)	EC_{50} lipo[c] (nM)	K_i (nM)	EC_{50} TT (nM)	EC_{50} ALP (nM)
6	>1000	ND[d]	ND[e]	93	ND	ND
19	138	ND	ND	>1000	ND	57
20	158	106	1000	>1000	>10 000	1000
46a,**b**	6	3	<10	>1000	>10 000	>10 000
46a	200	40	329	>1000	>10 000	>10 000
46b	5	5	4	>1000	>10 000	>10 000
47	40	20	72	>1000	>10 000	>10 000
48	40	29	3000	>1000	>10 000	>10 000
49	20	48 (p)[f]	123 (p)[g]	>1000	>10 000	>10 000
50	100	137 (p)	40 (p)	>1000	>10 000	≥1000[h]
51	200	97	ND	>1000	>10 000	ND
54	63	60	10	>1000	>10 000	>10 000
55	>3000	>10000	ND	>1000	ND	ND
56	20	4	5	>1000	>10 000	>10 000
60	90	97	660	>1000	790	2000
69	158	42	749	>1000	ND	>10 000
76	79	70	22	>1000	ND	>10 000

[a] K_i values were determined for all compounds by competition of 2.5 nM 9-*cis*-RA for both RXRα and RARα at a maximum concentration of 10 μM. The calculation used to determine the K_i can be found in the Experimental Section. [b] TT = transient transfection. The maximum concentration tested was 10 μM, and the calculation used to determine the EC_{50} can be found in the Experimental Section. [c] lipo = lipogenesis. [d] ND = not determined. [e] Could not be determined due to RAR activity. [f] (p) = partial agonist, which is defined for compounds that irrespective of how high the concentration are unable to produce maximal activation. [g] (p) = partial agonist, which is defined for compounds stimulating lipogenesis by <50% relative to 9-*cis*-RA. [h] This compound was found to be an antagonist in this assay, and the reported value is an IC_{50}.

represent glucose and glycohemoglobin levels, surrogate markers for overall glycemic control. Glucose and glycohemoglobin levels decreased significantly ($P < 0.05$) with an increasing dose of compound **46a**,**b** in both rodent species. Insulin levels also decreased significantly ($P < 0.05$) in ZDF rats treated with 30 mg/kg test compound (data not shown). This provides further evidence that in vitro activity at RXR is a predictor of in vivo antihyperglycemic activity.

An indication of lipid effects was determined by measuring triglyceride and nonesterified free fatty acid levels in *db*/*db* mice and ZDF rats (Table 3). Compound **46a**,**b** increased nonesterified free fatty acid levels at 3 mg/kg and decreased nonesterified free fatty acid levels at 10 and 30 mg/kg in ZDF rats but not *db*/*db* mice. However, triglyceride levels decreased significantly in *db*/*db* mice and increased in ZDF rats. These differences indicate that there are species specific effects of compound **46a**,**b** on triglyceride and nonesterfied free fatty acid levels. Likewise, other RXR agonists have been shown to decrease triglyceride levels in mice[11b] and increase triglyceride levels in rats.[24] One possibility is that genetic factors may influence the efficacy and safety of RXR ligands.

It has also been noted in the literature that one of the possible adverse events associated with some RXR agonists is hypothyroidism,[25] although there have been recent reports that antidiabetic efficacy can been achieved in rodents without lowering T4 levels.[7p,q] We also looked at T4 levels in ZDF rats and found with **46a**,**b** that the T4 levels had been lowered in a dose-dependent manner.

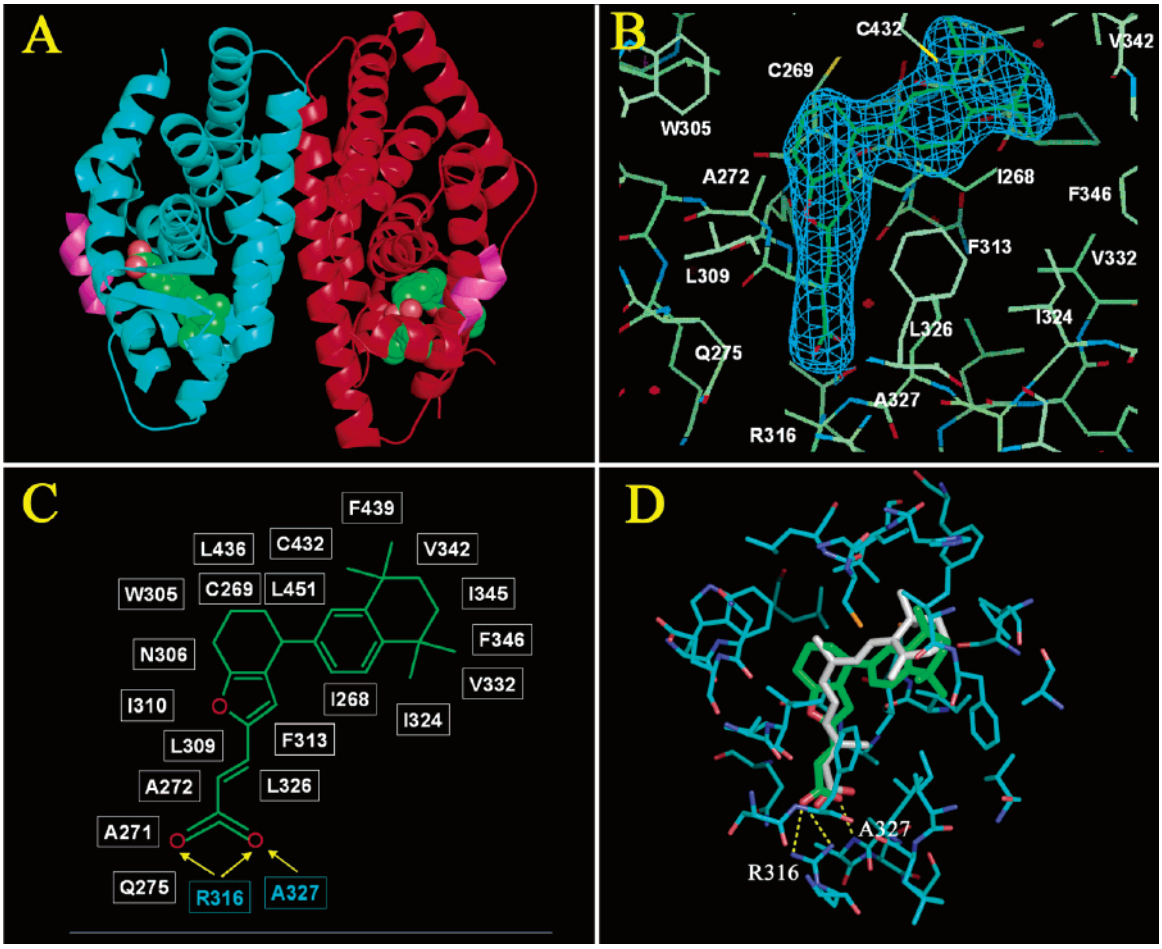


Figure 4. (A) Ribbon rendered illustration of the RXRα (cyan):PPARγ (red) LBDs bound with coactivator peptides (magenta), (*S*)-**46a**,**b**, and farglitazar (both ligands with space-filling atoms where green is carbon, red is oxygen, and blue is nitrogen), respectively. (B) The 2Fo-Fc electron density map (blue) contoured at 1.0 σ for (*S*)-**46a**,**b** bound to RXRα (carbons are shown in green). (C) 2D representation of interactions between (*S*)-**46a**,**b** and RXRα. Some key residues involved in hydrogen bonds and hydrophobic interactions are indicated in blue and white text, respectively. (D) Superimposition of (*S*)-**46a**,**b** (green carbon atoms) and 9-*cis*-RA bound to the RXRα ligand binding pocket from the RXRα:PPARγ heterodimer structure. The new rexinoid, (*S*)-**46a**,**b**, occupies a volume similar to and superimposes very well with RXRα bound 9-*cis*-RA.

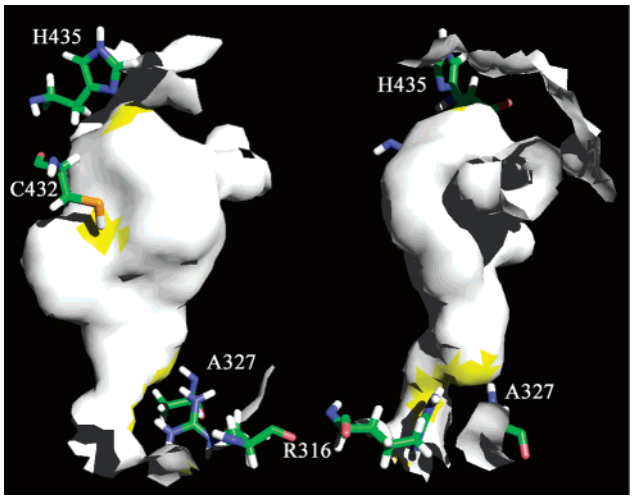


Figure 5. Surface of the RXRα binding site colored by polarity. The surface from unoccupied polar atoms is colored in yellow, and all other surface colored in white represent hydrophobic area. Two different angles are shown with the second rotated by 90° from the first.

However, this lowering of T4 levels was not seen in *db*/*db* mice (data not shown).

Table 2. In Vivo Antihyperglycemic Activity of **46a**,**b** in *db*/*db* Mice and ZDF Rats

	glucose (mg/dL)		% glycosylated hemoglobin	
	db/*db*	ZDF	*db*/*db*	ZDF
vehicle	583 ± 32	425 ± 25	11.17 ± 2.3	10.32 ± 0.51
3 mg/kg	ND	147 ± 17[a]	ND	7.75 ± 0.55[a]
10 mg/kg	346 ± 33[a]	129 ± 13[a]	9.41 ± 1.77	7.44 ± 0.24[a]
30 mg/kg	309 ± 29[a]	118 ± 5[a]	8.84 ± 0.88[a]	7.04 ± 0.69[a]
100 mg/kg	233 ± 19[a]	ND	8.51 ± 1.16[a]	ND

[a] $P < 0.05$, comparing control (vehicle) and treated groups.

Table 3. In Vivo Lipid Effects of **46a**,**b** in *db*/*db* Mice and ZDF Rats

	triglyceride (mg/dL)		nonesterified free fatty acid (mequiv/L)	
	db/*db*	ZDF	*db*/*db*	ZDF
vehicle	160 ± 18	1020 ± 135	0.47 ± 0.04	0.63 ± 0.04
3 mg/kg	ND	2462 ± 196[a]	ND	0.8 ± 0.08[a]
10 mg/kg	91 ± 8[a]	2199 ± 118[a]	0.45 ± 0.03	0.49 ± 0.05[a]
30 mg/kg	83 ± 5.2[a]	1353 ± 167	0.56 ± 0.04	0.38 ± 0.05[a]
100 mg/kg	62 ± 6[a]	ND	0.4 ± 0.02	ND

[a] $P < 0.05$, comparing control (vehicle) and treated groups.

Values in Table 4 represent the effect of treatment on liver weight and aspartate aminotransferase, a surrogate marker for liver toxicity. A significant dose-

Table 4. In Vivo Liver Effect of **46a**,**b** in *db*/*db* Mice and ZDF Rats

	aspartate aminotransferase (U/L)		liver % of body weight	
	db/*db*	ZDF	*db*/*db*	ZDF
vehicle	210 ± 71	101 ± 19	5.24 ± 0.069	5.09 ± 0.14
3 mg/kg	ND	98 ± 10	ND	5.74 ± 0.27[a]
10 mg/kg	137 ± 37	108 ± 9	8.23 ± 0.378*	6.56 ± 0.16[a]
30 mg/kg	116 ± 23	136 ± 7[a]	8.58 ± 0.295*	7.06 ± 0.18[a]
100 mg/kg	158 ± 31	ND	9.33 ± 0.333*	ND

[a] $P < 0.05$, comparing control (vehicle) and treated groups.

dependent increase in liver weight was observed in both species whereas aspartate aminotransferase increased (35%) only in ZDF rats treated with 30 mg/kg compound **46a**,**b**. These observations suggest that RXR agonists may affect metabolism by altering hepatocyte growth and gene expression. This is consistent with results showing that RXR agonists increase expression of lauric acid hydroxylase[11b] and fatty acid synthase[9] in hepatocytes in vivo and in vitro, respectively. RXR agonists have also been shown to stimulate triglyceride synthesis in human hepatoma cells[9] by increasing apo C-III expression.[26]

Conclusion

In conclusion, we have described a structure-based design approach into novel RXRα agonists. The utilization of the published RXRα *apo* structure along with modeling created an "active" structure that led to our intial lead **19**. Further modifications via refined docking quickly led to **46a**,**b**. A liganded crystal structure with **46a**,**b** was solved whereby only the (*S*)-antipode was found in the binding pocket. The strain energy for the (*S*)-antipode was calculated to be 3.0 kcal lower than the (*R*)-antipode. Binding of the separated antipodes showed a 40-fold difference in potency as well. Additional analogues within this bicyclic series did show in vitro activity including compounds that profiled as partial agonists. Oral administration of compound **46a**,**b** significantly decreased glucose and glycohemoglobin in both *db*/*db* mice and ZDF rats. Although disparate effects were observed on lipid metabolism in *db*/*db* mice and ZDF rats, stimulation of hepatomegaly revealed that liver was a target organ for **46a**,**b** in both species. A combination of an "active" model along with liganded crystal structures (additional liganded structures were solved, but the data were not shown) led to novel tetrahydrobenzofuranyl and tetrahydrobenzothienyl propenoic acids as RXRα activators that show potential as novel antidiabetic agents.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. All commercial chemicals and solvents were reagent grade and were used without further purification unless otherwise specified. The following solvents and reagents have been abbreviated: THF, diethyl ether (Et_2O), dimethyl sulfoxide (DMSO), ethyl acetate (EtOAc), dichloromethane (CH_2Cl_2), TFA, DMF, MeOH, dimethoxyethane (DME), HATU, DDQ, AIBN, N-methylmorpholine-N-oxide (NMO), ethylenediaminetetraacetic acid (EDTA), 4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid (HEPES), dithiothreitol (DTT), isopropyl β-D-1-thiogalactopyranoside (IPTG). All reactions except those in aqueous media were carried out with the use of standard techniques for the exclusion of moisture. Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel plates (60F-254, E. Merck) and visualized with UV light, cerium molybdate, or 5% phosphomolybdic acid in 95% ethanol.

Final compounds were typically purified either by flash chromatography on silica gel (E. Merck 40−63 mm), radial chromatography on a Chromatotron using prepared silica gel plates, or on Biotage Horizon pump and fraction collection system utilizing prepacked silica gel columns. Analytical purity was assessed by reversed phase high-performance liquid chromatography (RP-HPLC) using an Agilent 1100 system equipped with a diode array spectrometer (λ range 190−400 nm). The stationary phase was a Keystone Scientific BDS Hypersil C-18 column (5 μm, 4.6 mm × 200 mm). The mobile phase employed 0.1% aqueous TFA with acetonitrile as the organic modifier and a flow rate of 1.0 mL/min. Analytical data are reported as retention time (t_R) in minutes and % purity.

^{1}H NMR spectra were recorded on either a Varian VXR-300, a Varian Unity-400, or a Varian Unity-300 instrument. Chemical shifts are reported in parts per million (ppm, δ units). Coupling constants are reported in units of hertz (Hz). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; or br, broad. Low-resolution mass spectra (MS) were recorded on JEOL JMS-AX505HA, JEOL SX-102, or SCIEX-APIiii spectrometers. High-resolution MS were recorded on a Waters (Micromass) LCT time-of-flight mass spectrometer. Mass spectra were obtained under electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or fast atom bombardment (FAB) methods. Combustion analyses were performed by Atlantic Microlabs, Inc. (Norcross, GA).

5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-2-furaldehyde (4). A toluene solution (20 mL) containing **3**[14a] (690 mg, 2.98 mmol), dppf·$PdCl_2$·CH_2Cl_2 (16 mg), and 5-bromo-2-furaldehyde (520 mg, 2.98 mmol) had 5 mL of EtOH and 3 mL of 2.0 M Na_2CO_3 added to it. The solution was then immersed in an oil bath that had been preheated to 80 °C. After 6.5 h, the dark solution was dissolved in EtOAc and washed with saturated $NaHCO_3$ (2×). After it was dried over $MgSO_4$, the solvent was removed in vacuo and the residual oil was purified on the Biotage (10−30% EtOAc/hexanes) producing 681 mg (2.42 mmol, 81% yield) of **4** as a white solid. ^{1}H NMR ($CDCl_3$): 400 MHz δ 9.63 (s, 1H), 7.74 (d, 1H, J = 1.6 Hz), 7.55 (dd, 1H, J = 8.2 and 1.7 Hz), 7.37 (d, 1H, J = 8.2 Hz), 7.30 (d, 1H, J = 3.6 Hz), 6.78 (d, 1H, J = 3.7 Hz), 1.70 (s, 4H), 1.33 (s, 6H), 1.29 (s, 6H). Low-resolution MS (AP^+) *m*/*e* 283 (MH^+).

Ethyl (2*E*)-3-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-2-furyl]prop-2-enoate (5). To a DME solution (10 mL) containing sodium hydride (144 mg, 3.59 mmol, 60% dispersion in mineral oil) was added triethylphosphonoacetate (805 mg, 3.59 mmol) at room temperature. After 5 min, **4** (675 mg, 2.40 mmol) in 10 mL of DME was added. After the mixture was stirred for 15 min, the reaction was quenched with H_2O and poured into additional H_2O, and the organics were extracted with EtOAc. After it was dried over $MgSO_4$, the solvent was removed in vacuo and the residual oil was purified on the Biotage (5−20% EtOAc/hexanes) yielding 755 mg (2.14 mmol, 89% yield) of **5**. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.64 (d, 1H, J = 1.7 Hz), 7.47−7.41 (m, 2H), 7.33 (d, 1H, J = 8.2 Hz), 6.66−6.65 (m, 2H), 6.37 (d, 1H, J = 15.7 Hz), 4.26 (q, 2H, J = 7.1 Hz), 1.70 (s, 4H), 1.35−0.88 (m, 15H). Low-resolution MS (ES^+) *m*/*e* 353 (MH^+).

(2*E*)-3-[5-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-2-furyl]pro-2-enoic Acid (6). A dioxane (10 mL)/H_2O (3 mL) solution containing **5** (813 mg, 2.31 mmol) and lithium hydroxide hydrate (970 mg, 23.1 mmol) was stirred at room temperature overnight at which time it was acidified with saturated $NaHSO_4$. The organics were extracted with EtOAc and dried ($MgSO_4$), and the solvent was removed in vacuo. The residual solid was purified on the Biotage (50−80% EtOAc/hexanes) affording 53 mg (1.67 mmol, 72% yield) of **6** as a yellow solid. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.66 (d, 1H, J = 1.6 Hz), 7.53 (d, 1H, J = 15.4 Hz), 7.47 (dd, 1H, J = 8.3 and 1.8 Hz), 7.34 (d, 1H, J = 8.3 Hz), 6.74 (d, 1H, J = 3.7

Hz), 6.69 (d, 1H, J = 3.6 Hz), 6.38 (d, 1H, J = 15.3 Hz), 1.70 (s, 4H), 1.34 (s, 6H), 1.29 (s, 6H). HRMS: $C_{21}H_{24}O_3$ requires M + H at m/z 325.1804; found, 325.1813. RP-HPLC, t_R = 3.14 min, 98.6% purity.

3-Furyl(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)methanol (8). A flame-dried round bottom flask was mixed with anhydrous THF (100 mL) and 6-bromo-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene **7**[15] (5.0 g, 18.7 mmol). The resulting solution was cooled to −70 °C and was mixed with 2.5 M *n*-butyllithium in hexanes (9.0 mL, 22.4 mmol). The resulting solution was mixed with 3-furaldehyde (2.1 g, 22.4 mmol) and allowed to stir at −70 °C to 0 °C over a period of 1.0 h followed by quenching with 1.0 N HCl (50 mL). The reaction mixture was extracted with ether, dried over $MgSO_4$, and concentrated to dryness. The crude oil was purified using silica gel chromatography (90% hexanes/10% EtOAc) to afford 3.5 g (12.3 mmol, 66% yield) of **8**. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.37−7.27 (m, 4H), 7.13 (dd, 1H, J = 8.0 and 1.4 Hz), 6.36 (s, 1H), 5.72 (d, 1H, J = 3.6 Hz), 2.08 (d, 1H, J = 4.0 Hz), 1.68 (s, 4H), 1.27 (s, 12H). Low-resolution MS (ES^+) m/e 285 (MH^+).

4-[Hydroxy-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)methyl]-2-furaldehyde (13). A flame-dried round bottom flask was filled with anhydrous ether (125 mL) and **8** (3.5 g, 12.3 mmol). The resulting solution was cooled to −70 °C and was mixed with 1.7 M *tert*-butyl lithium in pentane (18.1 mL, 30.8 mmol). The reaction was quenched by addition of DMF (1.0 mL). The resulting solution was allowed to stir at −70 to −20 °C over a period of 2.0 h followed by quenching with 0.5 N HCl (25 mL). The reaction mixture was extracted with ether, dried over $MgSO_4$, and concentrated to dryness. The crude oil was purified using silica gel chromatography (75% hexanes/25% EtOAc) to afford 1.4 g (4.48 mmol, 36% yield) of **13**. Note that the regioisomer 3-[hydroxy(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)methyl]-2-furaldehyde was also obtained (1.0 g, 26% yield). ^{1}H NMR ($CDCl_3$): 400 MHz δ 9.84 (s, 1H), 7.56 (d, 1H, J = 2.4 Hz), 7.35 (d, 1H, J = 2.0 Hz), 7.28−7.26 (m, 1H), 7.10 (dd, 1H, J = 8.0 and 2.0 Hz), 6.47 (d, 1H, J = 1.2 Hz), 6.01 (d, 1H, J = 5.6 Hz), 1.67 (s, 4H), 1.26 (s, 12H). Low-resolution MS (ES^+) m/e 313 (MH^+).

4-[(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)methyl]-2-furaldehyde (15). A round bottom flask containing **13** (700 mg, 2.24 mmol) and triethylsilane (521 mg, 4.48 mmol) in 25 mL of anhydrous CH_2Cl_2 was cooled to 0 °C, and then, TFA (511 mg, 4.48 mmol) was added via syringe. The solution was stirred at room temperature for a period of 2.0 h and quenched with saturated $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated to dryness. The residual oil was purified on silica gel (90% hexanes/10% EtOAc) to yield 365 mg (1.23 mmol, 55% yield) of **15**. ^{1}H NMR ($CDCl_3$): 400 MHz δ 9.77 (s, 1H), 7.54 (d, 1H, J = 1.2 Hz), 7.22 (d, 1H, J = 8.4 Hz), 7.14 (d, 1H, J = 1.6 Hz), 6.94 (dd, 1H, J = 8.0 and 1.4 Hz), 6.39 (d, 1H, J = 1.2 Hz), 4.10 (s, 2H), 1.66 (s, 4H), 1.24 (s, 12H). Low-resolution MS (ES^+) m/e 297 (MH^+).

Ethyl (2*E*)-3-{4-[(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)methyl]-2-furyl}prop-2-enoate (17). A flame-dried round bottom flask was charged with anhydrous THF (20 mL) and sodium hydride (148 mg, 6.15 mmol). The solution was cooled to 0−5 °C and mixed with triethylphosphonoacetate (552 mg, 2.46 mmol). The reaction was stirred for 30 min at 0−5 °C. To this mixture was added **15** (365 mg, 1.23 mmol), and the reaction was stirred at room temperature for 16 h. The reaction mixture was slowly poured into cold 1.0 N HCl (25 mL) while maintaining a temperature less than 15 °C. The reaction mixture was extracted with ether, and the organics were dried over $MgSO_4$. The organics were concentrated, and the resulting oil was chromatographed on silica gel (95% hexanes/5% EtOAc) to yield a total of 352 mg (0.96 mmol, 78% yield) of **17**. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.52 (d, 1H, J = 15.2 Hz), 7.40 (s, 1H), 7.21(d, 1H, J = 8.0 Hz), 7.11 (s, 1H), 6.89 (d, 1H, J = 8.0 Hz), 6.32−6.28 (m, 2H), 4.24 (q, 2H, J = 7.2 Hz), 3.83 (s, 2H), 1.66 (s, 4H), 1.32 (t, 3H, J = 7.2 Hz), 1.25 (s, 12H). Low-resolution MS (ES^+) m/e 367 (MH^+).

(2*E*)-3-{4-[(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)methyl]-2-furyl}prop-2-enoic Acid (19). A mixture containing **17** (352 mg, 0.960 mmol), 2-propanol (5.0 mL), and 5.0 N NaOH (2.5 mL) was allowed to stir at room temperature for a period of 16.0 h (heating with a heat gun was needed to achieve homogeneity). The reaction mixture was cooled to 0−5 °C and made acidic using concentrated HCl (pH 3.5). The reaction mixture was mixed with water and then was extracted with EtOAc, dried over $MgSO_4$, and concentrated to dryness to afford a crude solid. The resulting solid was chromatographed on silica gel (75% hexanes/25% EtOAc) to give 263 mg (1.26 mmol, 81% yield) of **19** as a solid. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.56 (d, 1H, J = 15.6 Hz), 7.42 (d, 1H, J = 1.2 Hz), 7.21 (d, 1H, J = 8.0 Hz), 7.10 (d, 1H, J = 1.2 Hz), 6.88 (dd, 1H, J = 8.0, 1.6 Hz), 6.31−6.27 (m, 2H), 3.84 (s, 2H), 1.66 (s, 4H), 1.24 (m, 12H). HRMS: $C_{25}H_{34}O_3Si$ requires M + H at m/z 410.2277; found, 410.2273 (product silylated with TMSCl). RP-HPLC, t_R = 7.77 min, 96.0% purity.

N-Methoxy-N,2-dimethyl-3-furamide (10). To a flask containing 2-methylfuran-3-carboxylic acid (7.0 g, 55.5 mmol) in DMF (150 mL) was added N,N-diisopropylethylamine (7.53 g, 58.3 mmol) followed by HATU (22.2 g, 58.3 mmol) at room temperature After 30 min, a DMF solution (50 mL) containing N-methoxy-N-methylamine hydrochloride (5.96 g, 61.0 mmol) and N,N-diisopropylethylamine (8.68 g, 67.2 mmol) was added to the dark solution. After it was stirred overnight, the solution was poured into EtOAc and the organics were washed with H_2O (2×), saturated $NaHCO_3$, and saturated $NaHSO_4$. Drying over $MgSO_4$ and removal of the solvent in vacuo provided a dark orange oil that was purified on the Biotage (30−40% EtOAc/hexanes) affording 3.52 g (20.8 mmol, 38% yield) of **10**. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.22 (d, 1H, J = 2.0 Hz), 6.66 (d, 1H, J = 1.8 Hz), 3.62 (s, 3H), 3.30 (s, 3H), 2.53 (s, 3H). Low-resolution MS (AP^+) m/e 170 (MH^+).

(2-Methyl-3-furyl)(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)methanone (11). To a THF solution (80 mL) containing **7** (6.08 g, 22.8 mmol) cooled to −78 °C was added 9.6 mL of a 2.5 M hexanes solution of *n*-BuLi. After 30 min at −78 °C, a THF solution (20 mL) containing **10** (3.50 g, 20.7 mmol) was added. The resulting orange solution was stirred for 2.5 h at which time it was quenched with saturated $NaHSO_4$. The solution was then poured into additional saturated $NaHSO_4$, and the organics were extracted with EtOAc. After it was washed with saturated NaCl and dried over $MgSO_4$, the solvent was removed in vacuo. The residual oil was purified on the Biotage (0−20% EtOAc/hexanes) yielding 3.18 g (10.7 mmol, 52% yield) of **11**. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.76 (d, 1H, J = 1.6 Hz), 7.56 (dd, 1H, J = 8.2 and 1.8 Hz), 7.38 (d, 1H, J = 8.2 Hz), 7.28 (d, 1H, J = 1.9 Hz), 6.58 (d, 1H, J = 1.8 Hz), 2.54 (s, 3H), 1.71 (s, 4H), 1.30 (s, 12H). Low-resolution MS (ES^+) m/e 297 (MH^+). HRMS: $C_{20}H_{24}O_2$ requires M + H at m/z 296.1776; found, 296.1787.

(2-Methyl-3-furyl)(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)methanol (12). A mixture of sodium borohydride (842 mg, 22.2 mmol) and anhydrous THF (50 mL) was cooled to a temperature of 0−5 °C. To this mixture was added **11** (3.3 g, 11.1 mmol) dissolved in dry MeOH (25 mL). The reaction was allowed to stir at room temperature for a period of 17 h. The reaction mixture was slowly poured into a solution of saturated $NaHCO_3$ and extracted with ether. The organics were dried over $MgSO_4$ and concentrated to dryness to afford a crude oil. The oil was purified using silica gel chromatography (90% hexanes/10% EtOAc) to give 3.1 g (10.4 mmol, 93% yield) of **12** as a white solid. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.34 (d, 1H, J = 1.6 Hz), 7.27−7.25 (m, 1H), 7.22 (d, 1H, J = 1.6 Hz), 7.10 (dd, 1H, J = 8.4 and 2.0 Hz), 6.28 (d, 1H, J = 1.6 Hz), 5.71 (d, 1H, J = 3.6 Hz), 2.28 (s, 3H), 1.96 (d, 1H, J = 3.6 Hz), 1.66 (s, 4H), 1.26 (s, 12H). Low-resolution MS (ES^+) m/e 299 (MH^+).

4-[Hydroxy-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)methyl]-5-methyl-2-furaldehyde (14). Following the procedure to synthesize compound **13**, but where

alcohol **12** was used in place of alcohol **8**, the title compound **14** was obtained in 15% yield (488 mg, 1.50 mmol). ^{1}H NMR ($CDCl_3$): 400 MHz δ 9.45 (s, 1H), 7.30−7.25 (m, 2H), 7.14 (s, 1H), 7.08 (dd, 1H, J = 8.4 and 2.0 Hz), 5.72 (s(br), 1H), 2.37 (s, 3H), 2.13 (d, 1H, J = 2.4 Hz), 1.66 (s, 4H), 1.26 (s, 12H). Low-resolution MS (ES^+) *m/e* 327 (MH^+).

5-Methyl-4-[(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)methyl]-2-furaldehyde (16). Following the procedure to synthesize compound **15**, but where aldehyde **14** was used in place of aldehyde **13**, the title compound **16** was obtained in 66% yield (488 mg, 1.50 mmol). ^{1}H NMR ($CDCl_3$): 400 MHz δ 9.45 (s, 1H), 7.23 (d, 1H, J = 8.0 Hz), 7.08 (d, 1H, J = 1.2 Hz), 7.02 (s, 1H), 6.88 (dd, 1H, J = 8.0 and 1.8 Hz), 3.69 (s, 2H), 2.37 (s, 3H), 1.67 (s, 4H), 1.26 (s, 12H). Low-resolution MS (ES^+) *m/e* 311 (MH^+).

(2*E*)-3-{5-Methyl-4-[(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)methyl]-2-furyl}prop-2-enoic Acid (20). A round bottom flask was filled with dry THF (20 mL) and cooled to 0−5 °C. The solution was then mixed with 95% NaH (124 mg, 5.16 mmol) and stirred at 0−5 °C for 5 min. This solution was mixed with triethylphosphonoacetate (442 mg, 2.0 mmol) and stirred at 0−5 °C for 30 min. The reaction mixture was then mixed with **16** (306 mg, 0.99 mmol), and the mixture was stirred at room temperature for a period of 17 h. The reaction mixture was cooled to 5 °C and mixed with 1.0 N NaOH (20 mL) and 2-propanol (5.0 mL). The reaction was stirred for an additional 2.0 h and was made acidic using concentrated HCl (pH 3.0). The organics were extracted with ether, dried over $MgSO_4$, and concentrated to give a crude oil. The oil was chromatographed on silica gel (75% hexanes/25% EtOAc) to afford 67 mg (0.19 mmol, 20% yield for 2 steps) of **20**. ^{1}H NMR (d_6-acetone): 400 MHz δ 7.32 (d, 1H, J = 15.6 Hz), 7.24−7.18 (m, 3H), 6.94 (dd, 1H, J = 8.4 and 2.0 Hz), 6.63 (s, 1H), 6.09 (d, 1H, J = 15.6 Hz), 3.66 (s, 2H), 2.36 (s, 3H), 1.60 (s, 4H), 1.23 (s, 12H). HRMS: $C_{28}H_{23}O_3$ requires M + H at *m/z* 352.2029; found, 352.2038. RP-HPLC, t_R = 8.23 min, 94.0% purity.

Representative Procedure for the Synthesis of Both the Furanyl and Thienyl Propenoic Acids. 4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran-4-ol (26). To a THF solution (200 mL) containing 6-bromo-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene **7** (43.2 g, 161.8 mmol) cooled to −78 °C was added 68.0 mL of a 2.5 M hexanes solution of *n*-BuLi (170.0 mmol). The resulting reddish-orange solution was stirred for 30 min when 6,7-dihydro-4(5H)benzofuranone **21** (20.0 g, 147.0 mmol) in 100 mL of THF was added. After the mixture was stirred for 45 min, the reaction was quenched with H_2O. When it was warmed, the solution was poured into additional H_2O and the organics were extracted with Et_2O. After it was dried over $MgSO_4$, the solvent was removed in vacuo and the residual oil was purified via column chromatography [hexanes/EtOAc (7:1)] yielding 40.9 g (126.2 mmol, 86% yield) of **26** as a white solid; mp 55−57 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.29 (d, 1H, J = 2.0 Hz), 7.25 (d, 1H, J = 1.6 Hz), 7.19 (d, 1H, J = 8.2 Hz), 7.07 (dd, 1H, J = 8.3 and 2.1 Hz), 6.15 (d, 1H, J = 1.8 Hz), 2.71−2.62 (m, 2H), 2.05−2.00 (m, 3H), 1.92−1.78 (m, 2H), 1.63 (s, 4H), 1.26 (s, 6H), 1.23 (s, 3H), 1.20 (s, 3H). Anal. ($C_{22}H_{28}O_2$) C, H.

4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran (31). To a THF solution (100 mL) containing sodium borohydride (12.2 g, 324 mmol) cooled to 0 °C was added $BF_3{\cdot}Et_2O$ (69.0 g, 486 mmol). The resulting white slurry was stirred for 10 min when **26** (10.5 g, 32.4 mmol) in 200 mL of THF was added. After 10 min, the reaction mixture was very carefully poured into saturated $NaHCO_3$. The solution was then poured into additional saturated $NaHCO_3$, and the organics were extracted with Et_2O. After it was dried over $MgSO_4$, the solvent was removed in vacuo and the residual oil was purified via column chromatography [hexanes/EtOAc (19:1)] yielding 8.18 g (26.6 mmol, 82% yield) of **31**. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.26 (s, 1H), 7.19 (d, 1H, J = 8.3 Hz), 7.07 (d, 1H, J = 1.9 Hz), 6.89 (dd, 1H, J = 8.1 and 1.8 Hz), 6.06 (d, 1H, J = 1.6 Hz), 3.81 (m, 1H), 2.69−2.66 (m, 2H), 2.08 (m, 1H), 1.96−1.91 (m, 1H), 1.80−1.76 (m, 1H), 1.69−1.64 (m, 5H), 1.30 (s, 6H), 1.27 (s, 3H), 1.23 (s, 3H). Low-resolution MS (ES^+) *m/e* 309 (MH^+).

[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran]-2-carboxaldehyde (36). To a THF solution (380 mL) containing **31** (30.4 g, 98.7 mmol) cooled to 0 °C was added 41.4 mL of a 2.5 M hexanes solution of *n*-BuLi (103.6 mmol). The yellow-orange solution was stirred for 15 min at which time DMF (10.8 g, 148.0 mmol) was added at which point the solution turned nearly colorless. After 10 min, the reaction was quenched with saturated $NaHSO_4$ and poured into additional saturated $NaHSO_4$ and the organics were extracted with Et_2O. After it was dried over $MgSO_4$, the solvent was removed in vacuo and the residual yellow oil was purified via column chromatography [hexanes/EtOAc (9:1)] affording 29.3 g (87.2 mmol, 88% yield) of **36** as a white solid; mp 91−94 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 9.45 (s, 1H), 7.22 (d, 1H, J = 8.1 Hz), 7.05 (d, 1H, J = 1.8 Hz), 6.91 (s, 1H), 6.85 (dd, 1H, J = 8.2 and 2.0 Hz), 3.84 (m, 1H), 2.80−2.78 (m, 2H), 2.17−2.11 (m, 1H), 2.10−2.01 (m, 1H), 1.88−1.82 (m, 1H), 1.75−1.66 (m, 5H), 1.31 (s, 6H), 1.26 (s, 3H), 1.23 (s, 3H). Low-resolution MS (ES^+) *m/e* 337 (MH^+). Anal. ($C_{23}H_{28}O_2$) C, H.

Ethyl (2*E*)-3-[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran-2-yl]-2-propenoate (41a,b). To a DME solution (300 mL) containing sodium hydride (5.23 g, 130.8 mmol, 60% dispersion in mineral oil) was added tiethylphosphonoacetate (29.3 g, 130.8 mmol) at room temperature. To the resulting solution was added **36** (29.3 g, 87.2 mmol) in 100 mL of DME. The reaction was stirred for 20 min at which time it was quenched with H_2O. The solution was diluted with Et_2O, and the organic layer was separated. The aqueous layer was extracted with Et_2O, and then, the combined organic layers were dried over $MgSO_4$. Removal of the solvent in vacuo and purification via column chromatography [hexanes/EtOAc (9:1)] yielded 32.3 g (80.7 mmol, 92% yield) of **41a**,**b** as a light yellow foam; mp 47−49 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.32 (d, 1H, J = 15.6 Hz), 7.20 (d, 1H, J = 8.3 Hz), 7.05 (d, 1H, J = 1.7 Hz), 6.86 (dd, 1H, J = 8.0 and 1.9 Hz), 6.28 (s, 1H), 6.22 (d, 1H, J = 15.6 Hz), 4.22 (q, 2H, J = 7.2 Hz), 3.81−3.78 (m, 1H), 2.73−2.71 (m, 2H), 2.11−2.00 (m, 1H), 1.99−1.95 (m, 1H), 1.83−1.79 (m, 1H), 1.70−1.64 (m, 5H), 1.30 (t, 3H, J = 7.1 Hz), 1.26 (s, 6H), 1.22 (s, 3H), 1.19 (s, 3H). Low-resolution MS (ES^+) *m/e* 407 (MH^+). Anal. ($C_{27}H_{34}O_3$) C, H. The enantiomers **41a**,**b** were separated utilizing supercritical fluid chromatography with a chiralpak-AS column eluting with CO_2/10%MeOH (containing 0.2% isopropylamine). The separated antipodes were taken directly into the ester hydrolysis step outlined below.

(2*E*)-3[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)tetrahydro-1-benzofuran-2-yl]-2-propenoic Acid (46a,b). To a dioxane solution (200 mL) containing **41a**,**b** (30.5 g, 75.0 mmol) was added lithium hydroxide hydrate (31.5 g, 750 mmol) followed by 60 mL of H_2O. After the solution was stirred overnight, TLC showed some starting material left so the solution was heated at 60 °C for 3 h. The solution was acidified with saturated $NaHSO_4$, extracted with EtOAc, and dried ($MgSO_4$). The organics were then heated with Darco, and the solution was filtered through a bed of Celite with the Celite being rinsed thoroughly with EtOAc. The solvent was removed in vacuo, and the residual light yellow solid was triturated with hexanes and collected via vacuum filtration yielding 24.5 g (64.8 mmol, 86% yield) of **46a**,**b** as a light yellow solid; mp 210−213 °C decomp. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.39 (d, 1H, J = 15.4 Hz), 7.21 (d, 1H, J = 8.0 Hz), 7.05 (d, 1H, J = 1.6 Hz), 6.86 (dd, 1H, J = 8.2 and 1.8 Hz), 6.35 (s, 1H), 6.21 (d, 1H, J = 15.4 Hz), 3.82−3.79 (m, 1H), 2.74−2.72 (m, 2H), 2.12−2.07 (m, 1H, 2.00−1.98 (m, 1H), 1.81−1.70 (m, 1H), 1.67 (s(br), 5H), 1.26 (s, 6H), 1.22 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 156.0, 148.8, 144.8, 142.9, 141.4, 133.4, 126.4, 125.8, 124.9, 123.6, 117.7, 112.2, 39.7, 35.2, 35.1, 34.2, 34.0, 33.3, 31.9, 31.9, 23.5, 21.3. Low-resolution MS (ES^+) *m/e* 379 (MH^+). Anal. ($C_{25}H_{30}O_3$) C, H.

The separated ethyl ester enantiomers (see above) were hydrolyzed using the aforementioned conditions yielding both enantiomers **46a** and **46b** identical in all respects to racemic material. There was not enough material to get a reproducible optical rotation; however, both enantiomers were checked for final purity on a chiralpak-AS column eluting with CO_2/10% MeOH (containing 0.2% isopropylamine), flow = 2 mL/min at 2000 psi. Enantiomer **46a**: t_R = 7.46 min, 97.6% purity; enantiomer **46b**: t_R = 8.14 min, 97.8% purity.

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran-4-ol (28). Following the procedure to synthesize compound **26**, but where bromide **23** was used in place of bromide **7**, the title compound **28** was obtained in 53% yield (1.32 g, 3.91 mmol) as a white solid; mp 122−124 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.42 (s, 1H), 7.27 (d, 1H, J = 1.7 Hz), 7.00 (s, 1H), 6.15 (d, 1H, J = 1.9 Hz), 2.73 (m, 1H), 2.63 (m, 1H), 2.11−1.96 (m, 4H), 1.85 (m, 1H), 1.66 (s, 4H), 1.25 (s, 6H), 1.22 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6, 143.4, 141.7, 141.2, 141.1, 132.1, 130.3, 125.4, 123.8, 108.9, 73.6, 38.0, 35.4, 35.4, 34.2, 33.9, 32.0, 32.0, 31.9, 31.9, 23.2, 21.1, 20.2. Low-resolution MS (CI^+) *m/e* 321 [MH^+ ($-H_2O$)]. Anal. ($C_{23}H_{30}O_2$) C, H.

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran (33). Following the procedure to synthesize compound **31**, but where alcohol **28** was used in place of alcohol **26**, the title compound **33** was obtained in 60% yield (383 mg, 1.19 mmol) as a white solid; mp 68−71 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.26 (d, 1H, J = 1.5 Hz), 7.06 (s, 1H), 6.85 (s, 1H), 6.03 (d, 1H, J = 1.9 Hz), 4.02 (m, 1H), 2.33 (s, 3H), 2.71−2.66 (m, 2H), 1.92 (m, 1H), 1.79 (m, 1H), 1.66−1.54 (m, 6H), 1.27 (s, 6H), 1.15 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0, 142.4, 142.3, 140.4, 140.3, 132.6, 128.1, 126.3, 119.9, 110.6, 36.2, 35.4, 35.4, 34.1, 34.0, 32.1, 32.0, 32.0, 32.0, 31.8, 23.4, 21.7, 19.2. Low-resolution MS (ES^+) *m/e* 323 (MH^+). Anal. ($C_{23}H_{30}O$) C, H.

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran-2-carbaldehyde (38). Following the procedure to synthesize compound **36**, but where furan **33** was used in place of **31**, the title compound **38** was obtained in 87% yield based on unreacted starting material (508 mg, 1.45 mmol) as a white solid; mp 126−128 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 9.46 (s, 1H), 7.08 (s, 1H), 6.89 (s, 1H), 6.78 (s, 1H), 4.06 (m, 1H), 2.83−2.79 (m, 2H), 2.33 (s, 3H), 2.12 (m, 1H), 2.06 (m, 1H), 1.86 (m, 1H), 1.67−1.61 (m, 5H), 1.28 (s(br), 6H), 1.15 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 160.0, 151.5, 143.1, 142.7, 139.0, 132.6, 128.5, 125.8, 124.4, 36.1, 35.3, 35.2, 34.1, 34.0, 32.0, 31.9, 31.3, 23.8, 21.2, 19.2. Low-resolution MS (ES^+) *m/e* 351 (MH^+). Anal. ($C_{24}H_{30}O_2$) C, H.

Ethyl (2*E*)-3-[4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran-2-yl]-2-propenoate (43). Following the procedure to synthesize compound **41a,b**, but where aldehyde **38** was used in place of **36**, the title compound **43** was obtained in 89% yield (541 mg, 1.29 mmol) as a clear oil that solidified on standing; mp 59−61 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.32 (d, 1H, J = 15.6 Hz), 7.06 (s, 1H), 7.00 (s, 1H), 6.82 (s, 1H), 6.24 (d, 1H, J = 15.6 Hz), 4.22 (q, 2H, J = 7.2 Hz), 4.02 (m, 1H), 2.77−2.71 (m, 2H), 2.32 (s, 3H), 2.08 (m, 1H), 1.98 (m, 1H), 1.81 (m, 1H), 1.66−1.55 (m, 5H), 1.31 (t, 3H, J = 7.1 Hz), 1.27 (s, 6H), 1.15 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 155.6, 149.2, 142.7, 142.5, 139.6, 132.6, 131.6, 128.3, 126.0, 123.5, 116.6, 113.7, 60.4, 36.2, 35.4, 35.3, 34.1, 34.0, 32.1, 32.0, 31.9, 31.6, 23.6, 21.5, 19.2, 14.5. Anal. ($C_{28}H_{36}O\cdot 1/4H_2O$) C, H.

(2*E*)-3-[4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran-2-yl]-2-propenoic Acid (48). Following the procedure to synthesize compound **46a**,**b**, but where ester **43** was used in place of **41a**,**b**, the title compound **48** was obtained in 80% yield (398 mg, 1.02 mmol) as a light yellow solid after triteration with hexanes; mp 220−225 °C decomp. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.40 (d, 1H, J = 15.5 Hz), 7.07 (s, 1H), 6.82 (s, 1H), 6.31 (s, 1H), 6.23 (d, 1H, J = 15.6 Hz), 4.00 (m, 1H), 2.77−2.74 (m, 2H), 2.32 (s, 3H), 2.08 (m, 1H), 1.98 (m, 1H), 1.81 (m, 1H), 1.66−1.56 (m, 5H), 1.27 (s, 6H), 1.15 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 156.2, 148.8, 142.6, 142.4, 139.3, 133.4, 132.4, 128.2, 125.7, 123.7, 117.7, 112.4, 36.0, 35.2, 35.1, 33.9, 33.8, 31.9, 31.8, 31.7, 31.4, 23.5, 21.3, 19.0. Low-resolution MS (ES^+) *m/e* 393 (MH^+). Anal. ($C_{26}H_{32}O\cdot 1/2H_2O$) C, H.

4-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran-4-ol (29). Following the procedure to synthesize compound **26**, but where bromide **24** was used in place of bromide **7**, the title compound **29** was obtained in 48% yield (5.41 g, 15.3 mmol) as a white solid; mp 124−127 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.31 (d, 1H, J = 1.8 Hz), 6.79 (s, 1H), 6.77 (s, 1H), 6.32 (d, 1H, J = 1.9 Hz), 4.74 (s, 1H), 3.89 (s, 3H), 2.68−2.56 (m, 2H), 2.14−2.11 (m, 2H), 1.96 (m, 1H), 1.64−1.56 (m, 5H), 1.27 (s, 3H), 1.24 (s, 3H), 1.09 (s, 3H), 1.05 (s, 3H). Anal. ($C_{23}H_{30}O_3$) C, H.

4-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran (34). Following the procedure to synthesize compound **31**, but where alcohol **29** was used in place of alcohol **26**, the title compound **34** was obtained in 84% yield (2.65 g, 7.84 mmol) as a white solid; mp 94−96 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.24 (d, 1H, J = 1.5 Hz), 6.81 (s, 1H), 6.73 (s, 1H), 6.04 (d, 1H, J = 1.5 Hz), 4.21 (m, 1H), 3.82 (s, 3H), 2.66−2.61 (m, 2H), 2.05 (m, 1H), 1.84−1.73 (m, 2H), 1.66−1.56 (m, 5H), 1.27 (s, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 1.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.7, 152.0, 143.2, 140.1, 136.3, 130.7, 126.9, 119.3, 110.5, 107.4, 55.3, 35.3, 35.2, 34.3, 33.6, 32.6, 31.9, 31.8, 31.1, 23.3, 21.3.

4-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran-2-carbaldehyde (39). Following the procedure to synthesize compound **36**, but where furan **34** was used in place of **31**, the title compound **39** was obtained in 55% yield (1.64 g, 4.48 mmol) as a viscous oil, which solidified on standing; mp 58−60 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 9.45 (s, 1H), 6.92 (s, 1H), 6.78 (s, 2H), 4.27 (m, 1H), 3.83 (s, 3H), 2.80−2.76 (m, 2H), 2.08 (m, 1H), 1.96 (m, 1H), 1.85 (m, 1H), 1.74−1.61 (m, 5H), 1.26 (s, 6H), 1.14 (s, 3H), 1.12 (s, 3H). Low-resolution MS (ES^+) *m/e* 365 (MH^+).

Ethyl (2*E*)-3-[4-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran-2-yl]-2-propenoate (44). Following the procedure to synthesize compound **41a**,**b**, but where aldehyde **39** was used in place of **36**, the title compound **44** was obtained in 71% yield (1.40 g, 3.20 mmol) as an oil, which solidified on standing; mp 67−69 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.32 (d, 1H, J = 15.5 Hz), 6.78 (s, 1H), 6.74 (s, 1H), 6.27 (s, 1H), 6.21 (d, 1H, J = 15.6 Hz), 4.23−4.18 (m, 3H), 3.81 (s, 3H), 2.71−2.66 (m, 2H), 2.05 (m, 1H), 1.86 (m, 1H), 1.79−1.58 (m, 6H), 1.31−1.27 (m, 9H), 1.11 (s, 3H), 1.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 155.6, 154.7, 148.9, 143.6, 136.5, 131.5, 130.0, 126.5, 123.0, 116.6, 113.3, 107.6, 60.2, 55.3, 35.2, 35.1, 34.4, 33.6, 32.6, 31.9, 31.8, 31.8, 31.8, 30.8, 23.5, 21.2, 14.4. Low-resolution MS (ES^+) *m/e* 437 (MH^+). Anal. ($C_{28}H_{36}O_4$) C, H.

(2*E*)-3-[4-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran-2-yl]-2-propenoic Acid (49). Following the procedure to synthesize compound **46a**,**b**, but where ester **44** was used in place of **41a**,**b**, the title compound **49** was obtained in 74% yield (922 mg, 2.26 mmol) after recrystallization from hexanes as a white solid; mp 231−233 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.42 (d, 1H, J = 15.3 Hz), 6.80 (s, 1H), 6.76 (s, 1H), 6.36 (s, 1H), 6.23 (d, 1H, J = 15.6 Hz), 4.22 (m, 1H), 3.38 (s, 3H), 2.74−2.70 (m, 2H), 2.08 (m, 1H), 1.19 (m, 1H), 1.81 (m,1H), 1.68−1.61 (m, 6H), 1.29 (s, 6H), 1.14 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 156.6, 154.9, 148.9, 143.9, 136.8, 133.6, 130.0, 126.7, 123.6, 118.0, 112.3, 107.8, 55.5, 35.4, 35.3, 34.6, 33.8, 32.8, 32.1, 32.0, 32.0, 31.9, 31.0, 23.8, 21.4. Low-resolution MS (ES^-) *m/e* 437 (M − 1). Anal. ($C_{26}H_{32}O_4$) C, H.

4-(5,5,8,8-Tetramethyl-3-propoxy-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran-4-ol (30). Following the procedure to synthesize compound **26**, but where

bromide **25** was used in place of bromide **7**, the title compound **30** was obtained in 46% yield (2.1 g, 5.50 mmol) as a white solid; mp 139−142 °C. ^{1}H NMR ($CDCl_3$): δ 7.30 (d, 1H, J = 1.7 Hz), 6.79 (s, 1H), 6.77 (s, 1H), 6.31 (d, 1H, J = 1.9 Hz), 4.81 (s, 1H), 4.06−3.95 (m, 2H), 2.70−2.54 (m, 2H), 2.21−2.09 (m, 2H), 1.98 (m, 1H), 1.88−1.80 (m, 2H), 1.65−1.58 (m, 5H), 1.26 (s, 3H), 1.23 (s, 3H), 1.09 (s, 3H), 1.07−1.04 (m, 6H). Anal. ($C_{25}H_{34}O_3$) C, H.

4-(5,5,8,8-Tetramethyl-3-propoxy-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran (35). Following the procedure to synthesize compound **31**, but where alcohol **30** was used in place of alcohol **26**, the title compound **35** was obtained in 91% yield (1.56 g, 4.26 mmol) as a clear oil. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.23 (d, 1H, J = 1.5 Hz), 6.81 (s, 1H), 6.71 (s, 1H), 6.05 (d, 1H, J = 1.7 Hz), 4.23 (m, 1H), 3.93−3.88 (m, 2H), 2.66−2.60 (m, 2H), 2.05 (m, 1H), 1.84−1.73 (m, 4H), 1.66−1.57 (m, 5H), 1.26 (s, 3H), 1.25 (s, 3H), 1.11 (s, 3H), 1.10 (s, 3H), 1.02 (t, 3H, J = 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.4, 152.1, 143.4, 140.2, 136.3, 131.0, 127.1, 119.6, 110.8, 108.4, 69.5, 35.5, 35.4, 34.5, 33.8, 33.1, 32.1, 32.0, 31.3, 23.5, 23.1, 21.5, 11.1. Low-resolution MS (ES^+) *m/e* 367 (MH^+).

4-(5,5,8,8-Tetramethyl-3-propoxy-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran-2-carbaldehyde (40). Following the procedure to synthesize compound **36**, but where furan **35** was used in place of **31**, the title compound **40** was obtained in 74% yield (1.13 g, 2.86 mmol) as a clear oil. ^{1}H NMR ($CDCl_3$): 400 MHz δ 9.43 (s, 1H), 6.90 (s, 1H), 6.76 (s, 1H), 6.72 (s, 1H), 4.23 (m, 1H), 3.95−3.84 (m, 2H), 2.77−2.73 (m, 2H), 2.06 (m, 1H), 1.94 (m, 1H), 1.84−1.71 (m, 4H), 1.65−1.58 (m, 4H), 1.26 (s, 3H), 1.25 (s, 3H), 1.12 (s, 3H), 1.10 (s, 3H), 0.99 (t, 3H, J = 7.4 Hz). Low-resolution MS (ES^+) *m/e* 395 (MH^+).

Ethyl (2*E*)-3-[4-(5,5,8,8-Tetramethyl-3-propoxy-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran-2-yl]-2-propenoate (45). Following the procedure to synthesize compound **41a**,**b**, but where aldehyde **40** was used in place of **36**, the title compound **45** was obtained in 62% yield (748 mg, 1.61 mmol) as an oil, which solidified on standing; mp 52−54 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.31 (d, 1H, J = 15.7 Hz), 6.78 (s, 1H), 6.71 (s, 1H), 6.28 (s, 1H), 6.20 (d, 1H, J = 15.7 Hz), 4.23−4.17 (m, 3H), 3.93−3.85 (m, 2H), 2.70−2.66 (m, 2H), 2.03 (m, 1H), 1.88 (m, 1H), 1.79−1.69 (m, 2H), 1.68−1.57 (m, 6H), 1.28 (t, 3H, J = 7.2 Hz), 1.26 (s, 3H), 1.25 (s, 3H), 1.11 (s, 3H), 1.10 (s, 3H), 1.01 (t, 3H, J = 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 155.6, 154.2, 148.9, 143.6, 136.2, 131.5, 130.0, 126.5, 123.2, 116.7, 113.3, 108.4, 69.3, 60.2, 35.2, 35.1, 34.3, 33.6, 33.0, 31.9, 31.8, 31.8, 31.8, 30.7, 23.6, 22.8, 21.2, 14.4, 10.8. Low-resolution MS (ES^+) *m/e* 465 (MH^+).

(2*E*)-3-[4-(5,5,8,8-Tetramethyl-3-propoxy-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran-2-yl]-2-propenoic Acid (50). Following the procedure to synthesize compound **46a**,**b**, but where ester **45** was used in place of **41a**,**b**, the title compound **50** was obtained in 96% yield (921 mg, 2.11 mmol) after recrystallization from hexanes as a white solid; mp 195−196 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.42 (d, 1H, J = 15.5 Hz), 6.81 (s, 1H), 6.74 (s, 1H), 6.37 (s, 1H), 6.22 (d, 1H, J = 15.5 Hz), 4.23 (m, 1H), 3.95−3.89 (m, 2H), 2.74−2.70 (m, 2H), 2.08 (m, 1H), 1.92 (m, 1H), 1.83−1.69 (m, 2H), 1.67−1.60 (m, 6H), 1.28 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H), 1.03 (t, 3H, J = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 156.6, 154.4, 148.8, 143.8, 136.5, 133.7, 130.1, 126.7, 123.8, 118.1, 112.2, 108.6, 69.5, 35.4, 35.4, 34.5, 33.8, 33.2, 32.1, 32.0, 32.0, 32.0, 30.9, 23.8, 23.0, 21.4, 11.0. Low-resolution MS (ES^+) *m/e* 437 (MH^+). Anal. ($C_{28}H_{36}O_4$) C, H.

4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzothiophen-4-ol (27). Following the procedure to synthesize compound **26**, but where ketone **22** was used in place of ketone **21**, the title compound **27** was obtained in 45% (564 mg, 1.66 mmol) as an oil, which solidified on standing; mp 42−44 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.27 (d, 1H, J = 1.9 Hz), 7.18 (d, 1H, J = 8.2 Hz), 7.02 (d, 1H, J = 5.2 Hz), 6.97 (dd, 1H, J = 8.2 and 2.0 Hz), 6.67 (d, 1H, J = 5.2 Hz), 2.89−2.83 (m, 2H), 2.11−1.99 (m, 4H), 1.81 (m, 1H), 1.64 (s, 4H), 1.29−1.19 M, 9H), 0.86 (s, 3H). Low-resolution MS (ES^+) *m/e* 341 (MH^+).

4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzothiophene (32). To a CH_2Cl_2 solution (10 mL) containing **27** (654 mg, 1.92 mmol) and triethylsilane (671 mg, 5.77 mmol) was added TFA (680 mg, 5.96 mmol) at −40 °C. After 30 min, the reaction was quenched with dilute $NaHCO_3$. The two phase solution was poured into additional saturated $NaHCO_3$, and the organics were extracted with CH_2Cl_2. After it was dried over $MgSO_4$, the solvent was removed in vacuo and the residual oil was purified via column chromatography [hexanes/EtOAc (19:1)] yielding 557 mg (1.72 mmol, 90% yield) of **32** as a white solid; mp 79−81 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.17 (d, 1H, J = 8.0 Hz), 7.03 (d, 1H, J = 1.8 Hz), 6.98 (d, 1H, J = 5.2 Hz), 6.81 (dd, 1H, J = 8.0 and 1.8 Hz), 6.53 (d, 1H, J = 5.3 Hz), 3.93 (m, 1H), 2.88−2.84 (m, 2H), 2.12 (m, 1H), 1.96 (m, 1H), 1.82−1.76 (m, 2H), 1.66 (s, 4H), 1.26−1.25 (m, 9H), 1.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4, 143.0, 142.4, 138.0, 136.6, 128.2, 126.2, 126.1, 125.2, 121.2, 42.8, 35.2, 35.1, 34.2, 34.0, 33.1, 31.9, 31.8, 25.2, 22.0. Low-resolution MS (ES^+) *m/e* 325 (MH^+). Anal. ($C_{22}H_{28}S$) C, H, S.

4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzothiophene-2-carbaldehyde (37). To a Et_2O solution (50 mL) containing **32** (6.40 g, 19.8 mmol) cooled to −20 °C was added 34.9 mL of a 1.7 M pentane solution of *t*-BuLi (59.4 mmol). The resulting yellow solution was stirred at −20 °C for 30 min at which time DMF (2.17 g, 29.7 mmol) was added. After 30 min, the reaction had warmed to −10 °C at which time it was quenched with H_2O. The solution was then poured into saturated $NaHSO_4$, and the organics were extracted with Et_2O. After it was dried over $MgSO_4$, the solvent was removed in vacuo. The residual yellow solid was dissolved in MeOH, and a small amount of Et_2O was added. After it was stored in the freezer overnight, the precipitated solid was collected via vacuum filtration yielding 6.73 g (19.1 mmol, 96% yield) of **37** as a light orange solid; mp 142−145 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 9.71 (s, 1H), 7.23 (s, 1H), 7.21 (d, 1H, J = 8.0 Hz), 7.04 (d, 1H, J = 1.9 Hz), 6.81 (dd, 1H, J = 8.0 and 2.0 Hz), 3.93 (m, 1H), 2.95−2.92 (m, 2H), 2.15 (m, 1H), 2.01 (m, 1H), 1.86−1.77 (m, 2H), 1.68 (s, 4H), 1.27 (s, 6H), 1.26 (s, 3H), 1.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.9, 148.7, 144.9, 143.0, 141.9, 140.4, 140.0, 138.5, 126.6, 126.1, 125.0, 42.8, 35.1, 35.0, 34.2, 34.0, 32.7, 31.9, 31.8, 26.1, 21.8. Low-resolution MS (ES^+) *m/e* 353 (MH^+). Anal. ($C_{23}H_{28}OS$) C, H, S.

Ethyl (2*E*)-3-[4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzothien-2-yl]-2-propenoate (42). Following the procedure to synthesize compound **41a**,**b**, but where aldehyde **37** was used in place of **36**, the title compound **42** was obtained in 95% yield (3.51 g, 8.32 mmol) as an oil, which solidified on standing; mp 52−55 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.59 (d, 1H, J = 15.6 Hz), 7.17 (d, 1H, J = 8.1 Hz), 7.01 (s(br), 1H), 6.79 (d, 1H, J = 8.0 Hz), 6.67 (s, 1H), 6.04 (d, 1H, J = 15.6 Hz), 4.18 (q, 2H, J = 7.1 Hz), 3.86 (m, 1H), 2.84−2.82 (m, 2H), 2.11 (m, 1H), 1.94 (m, 1H), 1.79−1.73 (m, 2H), 1.65 (s, 4H), 1.29−1.25 (m, 12H), 1.20 (s, 3H). Low-resolution MS (AP^+) *m/e* 423 (MH^+). Anal. ($C_{27}H_{34}O_2S$) C, H, S.

(2*E*)-3-[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzothien-2-yl]-2-propenoic Acid (47). Following the procedure to synthesize compound **46a**,**b**, but where ester **42** was used in place of **341**,**b**, the title compound **47** was obtained in 75% yield (202 mg, 0.51 mmol) as a white solid; mp 225−229 °C decomp. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.68 (d, 1H, J = 15.6 Hz), 7.19 (d, 1H, J = 8.0 Hz), 7.03 (d, 1H, J = 1.6 Hz), 6.80 (dd, 1H, J = 8.0 and 1.7 Hz), 6.73 (s, 1H), 6.04 (d, 1H, J = 15.5 Hz), 3.88 (m, 1H), 2.87−2.85 (m, 2H), 2.12 (m, 1H), 1.97 (m, 1H), 1.81−1.76 (m, 2H), 1.67 (s, 4H), 1.27 (s, 6H), 1.22 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 144.9, 143.0, 142.4, 142.3, 140.2, 140.1, 135.5, 134.0, 126.6, 126.3, 125.2, 114.3, 42.9, 35.4, 35.3, 34.4, 34.2, 32.9, 32.1, 32.1, 25.9, 22.1. Anal. ($C_{25}H_{30}O_2S$) C, H, S.

4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran]-2-acetophenone (52). A flame-dried round bottom flask was charged with **31** (500 mg, 1.6 mmol) and anhydrous ether (25 mL). This solution was cooled to −78 °C while stirring under a nitrogen blanket. To this solution was added 1.0 mL of a 2.5 M pentane solution of *tert*-butyl lithium (2.5 mmol). The reaction mixture was allowed to stir for 30 min at which time it was quenched via the addition of N-methoxy-N-methylacetamide (330 mg, 3.2 mmol). The reaction was allowed to warm to room temperature where it was stirred for 4.0 h followed by quenching via the addition of 1.0 N HCl (20 mL). The reaction mixture was extracted using ether. The organics were separated and dried over $MgSO_4$ followed by concentration to dryness. The resulting oil was chromatographed on silica gel (90% hexanes/10% EtOAc) to afford **52** (487 mg, 1.39 mmol, 87% yield) as an oil. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.20 (d, 1H, J = 8.1 Hz), 7.24 (s, 1H), 7.05 (d, 1H, J = 1.7 Hz), 6.86−6.83 (m, 2H), 3.82 (m, 1H), 2.77−2.74 (m, 2H), 2.37 (s, 3H), 2.04 (m, 1H), 1.82 (m, 1H), 1.72−1.67 (m, 5H), 1.26−1.22 (m, 12H). Low-resolution MS (ES^+) *m/e* 351 (MH^+).

Ethyl (2*E*)-3-[4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-4,5,6,7-tetrahydro-1-benzofuran-2-yl]-but-2-enoate (53). To a DME solution (10 mL) containing sodium hydride (149 mg, 3.74 mmol, 60% dispersion in mineral oil) was added triethylphosphonoacetate (837 mg, 3.74 mmol) at room temperature. After 5 min, **52** (873 mg, 2.49 mmol) in 10 mL of DME was added. After it was stirred for 30 min at room temperature, the reaction was heated to 80 °C. After the reaction was heated overnight and cooled to ambient temperature, the reaction was quenched with H_2O. The solution was poured into additional H_2O, and the organics were extracted with EtOAc. After it was dried over $MgSO_4$, the solvent was removed in vacuo and the residual oil was purified on the Biotage (5−20% EtOAc/hexanes) affording 768 mg (1.83 mmol, 73% yield) of **53** as a 4:1 mixture of diastereomers. The mixture was taken on. ^{1}H NMR ($CDCl_3$): 400 MHz (major diastereomer) δ 7.20 (d, 1H, J = 8.2 Hz), 7.06 (d, 1H, J = 1.6 Hz), 6.86 (dd, 1H, J = 8.0 and 1.7 Hz), 6.34 (s, 1H), 6.31 (s, 1H), 4.17 (q, 2H, J = 7.2 Hz), 3.79 (m, 1H), 2.71−2.66 (m, 2H), 2.35 (s, 3H), 2.08 (m, 1H), 1.95 (m, 1H), 1.79 (m, 1H), 1.66−1.62 (m, 5H), 1.31−1.22 (m, 15H). Low-resolution MS (ES^+) *m/e* 421 (MH^+).

4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran]-2-(2,3(*cis*)propenoic Acid (54). To a dioxane solution containing **53** (565 mg, 1.34 mmol) was added lithium hydroxide hydrate (565 mg, 13.4 mmol) followed by 3 mL of H_2O. The solution was stirred at room temperature for 3 h and then at 75 °C overnight. After it was cooled, the solution was dissolved in EtOAc and acidified with saturated $NaHSO_4$. After it was dried over $MgSO_4$, the solvent was removed in vacuo and the residual solid was purified on the Biotage (30−60% EtOAc/hexanes) affording 290 mg (0.74 mmol, 55% yield) of **54** as a white solid. By NMR, a ∼6:1 ratio of diasteromers was found. Recrystallization in EtOAc and a minimal amount of CH_2Cl_2 yielded pure **54**. ^{1}H NMR ($CDCl_3$): 400 MHz (major diastereomer) δ 7.21 (d, 1H, J = 8.1 Hz), 7.07 (d, 1H, J = 1.8 Hz), 6.87 (dd, 1H, J = 8.0 and 1.8 Hz), 6.41 (s, 1H), 6.34 (s, 1H), 3.80 (m, 1H), 2.73−2.71 (m, 2H), 2.37 (s, 3H), 2.09 (s, 1H), 1.97 (m, 1H), 1.80 (m, 1H), 1.67−1.63 (m, 5H), 1.27−1.23 (m, 12H). HRMS: $C_{26}H_{32}O_3$ requires M + H at *m/z* 393.2430; found, 393.2438. RP-HPLC, t_R = 4.00 min, 96.0% purity.

4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran-2-carboxylic Acid (55). A MeOH solution (20 mL) was mixed with **36** (100 mg, 0.30 mmol), 5.0 N NaOH (10 mL), and Ag_2O (138 mg, 0.59 mmol. The resulting black heterogeneous reaction mixture was allowed to stir at room temperature for a period of 17 h. The reaction mixture was diluted with water and washed with ethyl ether. The ether washes were discarded, and the aqueous mixture was made acidic (pH 3.0) using concentrated HCl. The resulting mixture was extracted with ether and dried over $MgSO_4$. The solvent was evaporated in vacuo to yield **55** (73 mg, 0.21 mmol, 69% yield). ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.20 (d, 1H, J = 8.1 Hz), 7.04 (s, 1H), 6.98 (s, 1H), 6.83 (d, 1H, J = 7.9 Hz), 3.81 (m, 1H), 2.76−2.75 (m, 2H), 2.12 (m, 1H), 2.02 (m, 1H), 1.82 (m, 1H), 1.70−1.66 (m, 5H), 1.29−1.22 (m, 12H). HRMS: $C_{23}H_{28}O_3$ requires M + H at *m/z* 353.2117; found, 353.2106. RP-HPLC, t_R = 8.78 min, 89.6% purity.

[4-(5,5,8,8,-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzofuran]-2-(2,4-thiazolidinedione) (56). A toluene solution (10 mL) was mixed with **36** (100 mg, 0.30 mmol), 2,5-thiazolidinedione (62 mg, 0.53 mmol), morpholine (200 mg, 2.3 mmol), molecular sieves, and 10 mL of anhydrous toluene. The reaction mixture was stirred at reflux for 4.0 h at which time it was cooled to 0−5 °C. The resulting yellow solid was filtered in vacuo and washed with 10 mL of cold toluene. The resulting solid was dried in vacuo for 17 h to afford **56** (34 mg, 0.08 mmol, 26% yield). ^{1}H NMR ($CDCl_3$): 400 MHz δ 8.83 (s(br), 1H), 7.49 (s, 1H), 7.21 (d, 1H, J = 8.0 Hz), 7.05 (d, 1H, J = 1.7 Hz), 6.85 (dd, 1H, J = 8.0, 1.8 Hz), 6.51 (s, 1H), 3.83 (m, 1H), 2.80−2.76 (m, 2H), 2.14−2.00 (m, 2H), 1.82 (m, 1H), 1.69−1.66 (m, 5H), 1.28−1.18 (m, 12H). HRMS: $C_{26}H_{29}NO_3S$ requires M + H at *m/z* 436.1946; found, 436.1935. RP-HPLC, t_R = 10.0 min, 88% purity.

4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-1-benzofuran (57). To a dioxane solution (25 mL) containing **26** (985 mg, 3.04 mmol) was added DDQ (1.73 g, 7.60 mmol). The solution was then heated to 100 °C for 4 h at which time the dark solution was filtered through a bed of Celite. The Celite was rinsed thoroughly with Et_2O followed by washing the filtrate with H_2O (2×) and then drying over $MgSO_4$. The solvent was then removed in vacuo, and the residual dark oil was purified via column chromatography (hexanes/2% EtOAc) yielding 430 mg (1.42 mmol, 47% yield) of **57** as a white solid after trituration with hot MeOH and filtration; mp 153−154 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.69 (d, 1H, J = 2.2 Hz), 7.61 (d, 1H, J = 1.1 Hz), 7.52−7.35 (m, 5H), 6.99 (d, 1H, J = 2.1 Hz), 1.78 (s, 4H), 1.39 (s, 6H), 1.38 (s, 6H). Low-resolution MS (ES^+) *m/e* 305 (MH^+). Anal. ($C_{22}H_{24}O$) C, H.

4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-1-benzofuran-2-carbaldehyde (58). A Et_2O solution (20 mL) containing **57** (2.43 g, 7.99 mmol) cooled to −40 °C had 7.0 mL of a 1.7 M pentane solution of *t*-BuLi (11.9 mmol) added to it. The orange solution was stirred for 30 min at which time DMF (876 mg, 12.0 mmol) was added. The reaction slowly was warmed to 0 °C over 1 h and was then quenched with H_2O. The solution was poured into H_2O, and the organics were extracted with Et_2O. After it was dried over $MgSO_4$, the solvent was removed in vacuo and the residual yellow solid was purified via column chromatography (3% hexanes/EtOAc) yielding 1.98 g (5.97 mmol, 75% yield) of **58** as a white solid; mp 122−124 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 9.84 (s, 1H), 7.70 (s, 1H), 7.56−7.34 (m, 6H), 1.73 (s, 4H), 1.34 (s, 6H), 1.33 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.8, 157.0, 153.0, 145.8, 145.3, 138.7, 136.2, 129.6, 127.4, 126.9, 125.9, 125.6, 123.5, 118.3, 111.3, 35.2, 35.1, 34.6, 34.5, 32.2, 32.0. Low-resolution MS (ES^+) *m/e* 333 (MH^+). Anal. ($C_{23}H_{24}O_2$) C, H.

Ethyl (2*E*)-3-[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-1-benzofuran-2-yl]-2-propenoate (59). To a DME solution (10 mL) containing sodium hydride (358 mg, 8.96 mmol, 60% dispersion in mineral oil) was added triethylphosphonoacetate (2.01 g, 8.96 mmol) at room temperature. After 5 min, **58** (1.98 g, 5.97 mmol) in 20 mL of DME was added. The resulting orange solution was stirred for 30 min at which time it was quenched with H_2O. The solution was poured into additional H_2O, and the organics were extracted with Et_2O. After the solution was dried over $MgSO_4$, the solvent was removed in vacuo and the residual oil was purified via column chromatography (3% EtOAc/hexanes) yielding 2.12 g (5.28 mmol, 88% yield) of **59** as a white solid; mp 119−121 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.54−7.51 (m, 2H), 7.41−7.33 (m, 4H), 7.29 (dd, 1H, J = 6.6 and 1.8 Hz), 7.08 (s, 1H), 6.56 (d, 1H, J = 15.7 Hz), 4.25 (q, 2H, J = 7.1 Hz), 1.72 (s, 4H), 1.34−1.30 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 156.2, 152.7, 145.5, 144.7, 136.8, 136.6, 131.4, 127.3, 127.0, 126.9, 126.8, 125.8, 122.8, 119.0, 111.2, 110.1, 60.9, 35.3, 35.2,

34.6, 34.4, 32.2, 32.0, 14.5. Low-resolution MS (ES^+) *m/e* 403 (MH^+). Anal. ($C_{27}H_{30}O_3$) C, H.

(2*E*)-3-[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-1-benzofuran-2-yl]-2-propenoic Acid (60). To a dioxane solution (2 mL) containing **59** (88 mg, 0.22 mmol) was added lithium hydroxide hydrate (46 mg, 1.09 mmol) and 0.5 mL of H_2O at room temperature. After 2 days, the solution was acidified with saturated $NaHSO_4$, and the organics were extracted with EtOAc. After it was dried over $MgSO_4$, the solvent was removed in vacuo and the residual liquid was purified via column chromatography [CH_2Cl_2/MeOH (15:1)] yielding 63 mg (0.17 mmol, 76% yield) of **60** as a white solid; mp 216−219 °C decomp. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.63 (d, 1H, J = 15.5 Hz), 7.53 (d, 1H, J = 1.5 Hz), 7.44−7.32 (m, 5H), 7.16 (s, 1H), 6.60 (d, 1H, J = 15.6 Hz), 1.75 (s, 4H), 1.36 (s, 6H), 1.35 (s, 6H). Anal. ($C_{25}H_{26}O_3$) C, H.

2-Methyl-4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1,3-benzoxazol-4-ol (62). Following the procedure to synthesize compound **26**, but where ketone **61** was used in place of ketone **21**, the title compound **62** was obtained in 67% yield (4.0 g, 11.8 mmol) as an oil. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.37 (d, 1H, J = 2.0 Hz), 7.17 (d, 1H, J = 8.3 Hz), 6.91 (dd, 1H, J = 8.2 and 2.0 Hz), 2.68−2.64 (m, 2H), 2.53 (s, 1H, −OH), 2.40 (s, 3H), 2.11−1.95 (m, 3H), 1.78 (m, 1H), 1.63 (s, 4H), 1.25−1.21 (m, 12H).

2-Methyl-4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1,3-benzoxazole (63). Following the procedure to synthesize compound **31**, but where alcohol **62** was used in place of alcohol **26**, the title compound **63** was obtained in 38% yield (1.44 g, 4.47 mmol). ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.13 (d, 1H, J = 8.0 Hz), 7.03 (d, 1H, J = 2.0 Hz), 6.77 (dd, 1H, J = 8.1 and 2.0 Hz), 3.83 (m, 1H), 2.65−2.60 (m, 2H), 2.36 (s, 3H), 2.07 (m, 1H), 1.91 (m, 1H), 1.77−1.68 (m, 2H), 1.61 (s, 4H), 1.20 (s, 9H), 1.19 (s, 3H).

2-(Bromomethyl)-4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1,3-benzoxazole (64). To a CCl_4 solution (60 mL) containing **63** (4.79 g, 14.8 mmol) were added AIBN (24 mg, 0.15 mmol, 1 mol %) and NBS (3.16 g, 17.8 mmol). The solution was then immersed in an oil bath, which had been preheated to 90 °C. After 30 min, the solution was allowed to cool to room temperature and the precipitated succinimide was removed via filtration. Removal of the solvent in vacuo and purification via column chromatography [hexanes/EtOAc (15:1)] yielded 2.23 g (5.55 mmol, 37% yield) of **64** as a white foam. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.16 (d, 1H, J = 8.1 Hz), 7.02 (d, 1H, J = 1.9 Hz), 6.78 (dd, 1H, J = 8.1 and 1.9 Hz), 4.41 (s, 2H), 2.73−2.67 (m, 2H), 2.12 (m, 1H), 1.94 (m, 1H), 1.82−1.69 (m, 2H), 1.62 (s, 4H), 1.21 (s, 12H).

[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1,3benzoxazol-2-yl]methyl Acetate (65). To a CH_3CN solution (50 mL) containing **64** (2.0 g, 4.98 mmol) was added potassium acetate (978 mg, 9.96 mmol) at room temperature. The resulting slurry was stirred for 24 h at which time it was diluted with H_2O, and the organics were extracted with EtOAc (2×). After it was dried over $MgSO_4$, the solvent was removed in vacuo and the residual oil was purified via column chromatography [hexanes/EtOAc (4:1)] yielding 1.54 g (4.04 mmol, 81% yield) of **65**. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.15 (d, 1H, J = 8.1 Hz), 7.03 (d, 1H, J = 1.9 Hz), 6.78 (dd, 1H, J = 8.1 and 1.9 Hz), 5.08 (s, 2H), 3.90 (m, 1H), 2.72−2.66 (m, 2H), 2.13−2.08 (m, 4H), 1.94 (m, 1H), 1.79−1.73 (m, 2H), 1.62 (s, 4H), 1.21 (s, 6H), 1.20 (s, 6H).

[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1,3-benzoxazol-2-yl]methanol (66). To a MeOH solution (50 mL) containing **65** (1.62 g, 4.24 mmol) was added 75 μL of H_2O and potassium carbonate (1.17 g, 8.48 mmol) at room temperature. After 15 min, the solution was diluted with H_2O and the organics were extracted with EtOAc. After the solution was dried over $MgSO_4$, the solvent was removed in vacuo yielding 1.33 g (3.92 mmol, 92% yield) of **66** as a white solid, which was pure enough to take on. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.15 (d, 1H, J = 8.1 Hz), 7.04 (d, 1H, J = 1.4 Hz), 6.77 (dd, 1H, J = 8.1 and 1.6 Hz), 4.62−4.51 (m, 2H), 3.89 (m, 1H), 2.69−2.64 (m, 2H), 2.48 (t, 1H, J = 6.4 Hz), 2.10 (m, 1H), 1.92 (m, 1H), 1.78−1.72 (m, 2H), 1.62 (s, 4H), 1.22 (s, 6H), 1.21 (s, 3H), 1.20 (s, 3H).

4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1,3-benzoxazole-2-carbaldehyde (67). To a CH_2Cl_2 solution (30 mL) containing **66** (1.43 g, 4.23 mmol), NMO (743 mg, 6.34 mmol), and 2.1 g of 4 Å powdered molecular sieves was added TPAP (74 mg, 0.21 mmol, 5 mol %). After the solution was stirred for 30 min at room temperature, the dark slurry was filtered through a bed of Celite. The Celite was rinsed thoroughly with CH_2Cl_2, and then, the solvent was removed in vacuo. The residual dark oil was purified via column chromatography [hexanes/EtOAc (4:1)] yielding 671 mg (1.99 mmol, 47% yield) of **67**. ^{1}H NMR ($CDCl_3$): 400 MHz δ 9.62 (s, 1H), 7.19 (d, 1H, J = 8.1 Hz), 7.04 (d, 1H, J = 1.8 Hz), 6.77 (dd, 1H, J = 8.1 and 1.9 Hz), 4.00 (m, 1H), 2.84−2.79 (m, 2H), 2.18 (m, 1H), 1.86−1.80 (m, 2H), 1.63 (s, 4H), 1.23 (s, 6H), 1.22 (s, 3H), 1.21 (s, 3H).

Ethyl (2*E*)-3-[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1,3-benzoxazol-2-yl]-2-propenoate (68). To a DME solution (10 mL) containing sodium hydride (121 mg, 3.03 mmol, 60% dispersion in mineral oil) was added triethylphosphonoacetate (679 mg, 3.03 mmol) at room temperature. To this solution was added **67** (682 mg, 2.02 mmol) in 10 mL of DME. After 15 min, the reaction was quenched with H_2O and the organics were extracted with Et_2O. After it was dried over $MgSO_4$, the solvent was removed in vacuo and the residual oil was purified via column chromatography [hexanes/EtOAc (9:1)] yielding 648 mg (1.59 mmol, 79% yield) of **68**. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.36 (d, 1H, J = 16.0 Hz), 7.15 (d, 1H, J = 8.1 Hz), 7.04 (d, 1H, J = 1.9 Hz), 6.77 (dd, 1H, J = 8.1 and 1.9 Hz), 6.61 (d, 1H, J = 16.1 Hz), 4.21 (q, 2H, J = 7.2 Hz), 3.93 (m, 1H), 2.75−2.69 (m, 2H), 2.12 (m, 1H), 1.95 (m, 1H), 1.82−1.75 (m, 2H), 1.61 (s, 4H), 1.27 (t, 3H, J = 7.1 Hz), 1.21 (s, 6H), 1.20 (s, 6H).

(2*E*)-3-[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1,3-benzoxazol-2-yl]-2-propenoic Acid (69). To a dioxane solution (12 mL) containing **68** (645 mg, 1.58 mmol) was added 3 mL of H_2O followed by lithium hydroxide hydrate (664 mg, 15.8 mmol). After it was stirred overnight at room temperature, the reaction was acidified with saturated $NaHSO_4$ and the organics were extracted with EtOAc. After the organics were dried over $MgSO_4$ and the solvent was removed in vacuo, the residual material was purified via column chromatography [CH_2Cl_2/MeOH (9:1)] affording 599 mg (1.58 mmol, 100% yield) of **69** as an off-white solid; mp 176−178 °C. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.44 (d, 1H, J = 15.9 Hz), 7.16 (d, 1H, J = 8.1 Hz), 7.05 (d, 1H, J = 1.9 Hz), 6.78 (dd, 1H, J = 8.1 and 1.9 Hz), 6.62 (d, 1H, J = 16.1 Hz), 3.95 (m, 1H), 2.78−2.72 (m, 2H), 2.15 (m, 1H), 1.96 (m, 1H), 1.82−1.77 (m, 2H), 1.62 (s, 4H), 1.22 (s, 6H), 1.21 (s, 6H). HRMS: $C_{24}H_{29}NO_3$ requires M + H at *m/z* 380.2226; found, 380.2218. RP-HPLC, t_R = 8.88 min, 90.6% purity. Anal. ($C_{24}H_{29}NO_3$): H, N; C required 75.96; found, 74.78%.

[4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro-1-benzothiaphene]-2-propionic Acid (51). A solution was made containing EtOAc (20 mL), **47** (200 mg, 0.51 mmol), and Pearlman's catalyst (50 mg). The reaction mixture was degassed in vacuo and stirred under a hydrogen atmosphere (1 atm) for a period of 2.0 h. The reaction mixture was degassed and filtered over Celite in vacuo. The resulting solution was concentrated to dryness in vacuo. The resulting oil was dissolved into Et_2O and washed with saturated NaCl. The organics were dried ($MgSO_4$) and concentrated to afford **51** (176 mg, 0.44 mmol, 87% yield). ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.20 (d, 1H), 7.00 (s, 1H), 6.80 (d, 1H), 6.13 (s, 1H), 3.82 (m, 1H), 3.00 (t, 2H), 2.80 (m, 2H), 2.61 (t, 2H), 2.17−2.03 (m, 1H), 1.97−1.80 (m, 1H), 1.78−1.62 (m, 6H), 1.30−1.17 (m, 12H). HRMS: $C_{25}H_{32}O_2S$ requires M + 1 at *m/z* 397.2201; found, 397.2202. RP-HPLC, t_R = 6.18 min, 100% purity.

Ethyl 4-Hydroxy-4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,7-dihydrofuro[2,3-c]pyridine-6(5H)-

carboxylate (71). Following the procedure to synthesize compound **26**, but where ketone **70** was used in place of ketone **21**, the title compound **71** was obtained in 50% yield (2.56 g, 6.45 mmol) as a waxy solid; mp 56−57 °C. ^{1}H NMR signals were very broad due to rotamers; however, GC-MS showed 1 peak.

Ethyl 4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,7-dihydrofuro[2,3-c]pyridine-6(5H)carboxylate (72). Following the procedure to synthesize compound **31**, but where alcohol **71** was used in place of alcohol **26**, the title compound **72** was obtained in 48% yield (149 mg, 0.38 mmol) as a white solid; mp 92−94 °C. ^{1}H NMR signals were very broad due to rotamers. Low-resolution MS (ES^+) *m/e* 382 (MH^+); 100% by GC.

6-Methyl-4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydrofuro[2,3-c]pyridine (73). To a THF solution (10 mL) containing **72** (528 mg, 1.39 mmol) was added 3.5 mL of a 1.0 M Et_2O solution of $LiAlH_4$ (3.5 mmol) at room temperature. The resulting solution was then heated to reflux for 30 min. After it was cooled to room temperature, the reaction was carefully quenched with 1 mL of 2.0 M NaOH. The heterogeneous solution then had $MgSO_4$ added to it and was diluted with Et_2O. The slurry was filtered through a bed of Celite and rinsed thoroughly with Et_2O. The filtrate was washed with 2.0 M NaOH and dried ($MgSO_4$), and the solvent was removed in vacuo. The residual oil was purified via column chromatography [hexanes/EtOAc (1:1)] yielding 353 mg (1.10 mmol, 79% yield) of **73** as a colorless oil. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.25 (d, 1H, J = 1.4 Hz), 7.18 (d, 1H, J = 8.1 Hz), 7.09 (d, 1H, J = 1.9 Hz), 6.90 (dd, 1H, J = 8.1 and 1.9 Hz), 6.10 (d, 1H, J = 1.8 Hz), 3.97 (m, 1H), 3.69 (d, 1H, J = 14.4 Hz), 3.38 (dd, 1H, J = 14.3 and 2.4 Hz), 2.99 (dd, 1H, J = 11.6 and 5.1 Hz), 2.45 (2, 3H), 2.34 (dd, 1H, J = 11.6 and 9.2 Hz), 1.65 (s, 4H), 1.24−1.22 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0, 144.7, 143.0, 140.8, 139.2, 126.4, 126.1, 125.2, 118.2, 109.8, 62.2, 52.3, 45.3, 40.1, 35.2, 35.1, 34.2, 34.0, 31.9, 31.8, 31.8, 31.8. Low-resolution MS (ES^+) *m/e* 324 (MH^+).

6-Methyl-4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7tetrahydrofuro[2,3-c]pyridin-2-carbaldehyde (74). To a Et_2O solution (8 mL) containing **73** (350 mg, 1.08 mmol) cooled to −40 °C was added 1.9 mL of a 1.7 M pentane solution of *t*-BuLi (3.25 mmol). The yellow solution was allowed to warm to −30 °C where it was held. After 30 min, DMF (237 mg, 3.24 mmol) was added. The reaction slowly warmed and was quenched with H_2O after 15 min. The orange solution was poured into additional H_2O, and the organics were extracted with Et_2O. After the organics were dried over $MgSO_4$, the solvent was removed in vacuo and the residual oil was purified via column chromatography [EtOAc/hexanes (3:2)] yielding 194 mg (0.55 mmol, 51% yield) of **74** as an oil. ^{1}H NMR ($CDCl_3$): 400 MHz δ 9.47 (s, 1H), 7.20 (d, 1H, J = 8.1 Hz), 7.07 (d, 1H, J = 1.9 Hz), 6.94 (s, 1H), 6.86 (dd, 1H, J = 8.0 and 1.9 Hz), 4.0 (m, 1H), 3.78 (d, 1H, J = 16.1 Hz), 3.45 (dd, 1H, J = 16.0 and 2.1 Hz), 3.03 (dd, 1H, J = 12.0 and 5.3 Hz), 2.48 (s, 3H), 2.41 (dd, 1H, J = 12.0 and 9.1 Hz), 1.67 (s, 3H), 1.26−1.18 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 152.4, 149.7, 144.9, 143.3, 138.5, 131.2, 126.6, 126.0, 125.1, 121.7, 115.4, 114.2, 61.9, 60.3, 52.2, 45.3, 40.0, 35.1, 35.0, 34.2, 34.0, 31.9, 31.8, 31.8, 14.3. Low-resolution MS (ES^+) *m/e* 352 (MH^+).

Ethyl (2*E*)-3-[6-Methyl-4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydrofuro[2,3-c]-pyridin-2-yl]-2-propenoate (75). To a DME solution (2 mL) containing sodium hydride (33 mg, 0.83 mmol, 60% dispersion in mineral oil) was added triethylphosphonoacetate (186 mg, 0.83 mmol) at room temperature. After 5 min, **74** (194 mg, 0.55 mmol) in 2 mL of DME was added. The reaction was stirred for 20 min at which time it was quenched with H_2O. The solution was poured into additional H_2O, and the organics were extracted with Et_2O. After the organics were dried over $MgSO_4$, the solvent was removed in vacuo and the residual oil was purified via column chromatography [hexanes/EtOAc (3:2)] yielding 169 mg (0.30 mmol, 71% yield) of **75** as an oil. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.31 (d, 1H, J = 15.5 Hz), 7.19 (d, 1H, J = 8.1 Hz), 7.06 (d, 1H, J = 1.7 Hz), 6.88 (dd, 1H, J = 8.2 and 1.7 Hz), 6.32 (s, 1H), 6.20 (d, 1H, J = 15.7 Hz), 4.19 (q, 2H, J = 7.1 Hz), 3.95 (m, 1H), 3.72 (d, 1H, J = 15.6 Hz), 3.42 (dd, 1H, J = 15.4 and 2.2 Hz), 2.99 (dd, 1H, J = 11.8 and 5.3 Hz), 2.46 (s, 3H), 2.36 (dd, 1H, J = 11.8 and 9.4 Hz), 1.64 (s, 4H), 1.28 (t, 3H, J = 7.1 Hz), 1.24−1.21 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 152.4, 149.7, 144.9, 143.3, 138.5, 131.2, 126.6, 126.0, 125.1, 121.7, 115.4, 114.2, 61.9, 60.3, 52.2, 45.3, 40.0, 35.1, 35.0, 34.2, 34.0, 31.9, 31.8, 31.8, 14.3. Low-resolution MS (ES^+) *m/e* 422 (MH^+).

(2*E*)-3-[6-Methyl-4-(5,5,8,8,-tetramethyl-5,6,7,8-tetrahydro-2-naphthalenyl)-4,5,6,7-tetrahydro[2,3-c]pyridin-2-yl]-2-propenoic Acid (76). To a dioxane solution (2 mL) containing **75** (169 mg, 0.39 mmol) was added lithium hydroxide hydrate (164 mg, 3.92 mmol) followed by 0.7 mL of H_2O. The reaction went for 24 h at room temperature at which time 702 mg of $NaHSO_4$ was added along with H_2O and EtOAc. After it was stirred for 10 min, the solution was poured into additional H_2O and the organics were extracted with EtOAc. After the organics were dried over $MgSO_4$, the solvent was removed in vacuo and the residual material was purified via column chromatography [CH_2Cl_2/MeOH (9:1)] affording 101 mg (0.26 mmol, 66% yield) of **76** as an off-white solid; mp 128−130 °C decomp. ^{1}H NMR ($CDCl_3$): 400 MHz δ 7.32 (d, 1H, J = 15.7 Hz), 7.28 (d, 1H, J = 8.1 Hz), 7.23 (d, 1H, J = 1.5 Hz), 6.96 (dd, 1H, J = 8.2 and 1.6 Hz), 6.22 (d, 1H, J = 15.7 Hz), 4.46 (d, 1H, J = 15.6 Hz), 4.36 (m, 1H), 4.30 (d, 1H, J = 15.6 Hz), 3.63 (dd, 1H, J = 12.2 and 5.4 Hz), 3.13 (t, 1H, J = 11.7 Hz), 2.98 (s, 3H), 1.68 (s, 4H), 1.26−1.22 (m, 12H). Low-resolution MS (ES^-) *m/e* 392 (M − 1). Anal. ($C_{25}H_{31}NO_3 \cdot 1/2H_2O$) C, H, N

Biological Assays. Expression of RXRα LBD. The RXRα LBD construct (amino acids 225−462) was expressed in *Escherichia coli* strain BL21(DE3) as an amino-terminal polyHistidine-tagged fusion protein. Expression was under the control of an IPTG inducible T7 promoter. DNA encoding this recombinant protein and a modified histidine tag were subcloned into the expression vector pRSETa (Invitrogen). The sequence of the modified polyHistidine tag (MKKGHHHHHHG) was fused in frame to residues 225−462 of RXRα. (The sequence used in our construction of RXRα LBD was derived from Genbank accession number X52773). The resulting complete encoded sequence is as follows: MKKGHHHHHHG SANEDMPVER ILEAELAVEP KTETYVEANM GLNPSSP-NDP VTNICQAADK QLFTLVEWAK RIPHFSELPL DDQ-VILLRAG WNELLIASFS HRSIAVKDGI LLATGLHVHR NSAHSAGVGA IFDRVLTELV SKMRDMQMDK TELGCL-RAIV LFNPDSKGLS NPAEVEALRE KVYASLEAYC KH-KYPEQPGR FAKLLLRLPA LRSIGLKCLE HLFFFKLIGD TPIDTFLMEMLEAPHQMT.

Ten liter fermentation batches were grown in Rich PO4 media with 0.1 mg/mL Ampicillin at 25 °C for 12 h, cooled to 9 °C, and held at that temperature for 36 h to a density of OD_{600} = 14. At this cell density, 0.25 mM IPTG was added and induction proceeded for 24 h at 9 °C, to a final OD_{600} = 16. Cells were harvested by centrifugation (20 min, 3500*g*, 4 °C), and concentrated cell slurries were stored in PBS at −80 °C.

Purification of RXRα LBD. Routinely, 40−50 g of frozen cell paste (equivalent to 2−3 L of the fermentation batch) was thawed and resuspended in 300 mL of tris-buffered saline (TBS), pH 7.2 (25 mM Tris,150 mM NaCl). Cells were lysed by three passages through a homogenizer (Rannie), and cell debris was removed by centrifugation (30 min, 20 000*g*, 4 °C). The cleared supernatant was filtered through coarse prefilters and TBS, pH 7.2, containing 500 mM imidazole was added to obtain a final imidazole concentration of 50 mM. This lysate was loaded onto a column (3 cm × 8 cm) packed with Sepharose (Ni^{++} charged) Chelation resin (Pharmacia) and preequilibrated with TBS, pH 7.2, containing 50 mM imidazole. After it was washed to baseline absorbance, the column was developed with a linear gradient of 50−500 mM imidazole in TBS, pH 7.2. Column fractions were pooled and dialyzed against TBS, pH 7.2, containing 5 mM DTT and 0.5 mM

EDTA. After dialysis, the sample was concentrated using Centri-prep 10K (Amicon) and subjected to size exclusion with a column (3 cm × 90 cm) packed with Sepharose S-75 resin (Pharmacia) preequilibrated with the same buffer.

Biotinylation of Human RXR LBD. Purified RXRα LBD was desalted/buffer exchanged using PD-10 gel filtration columns into phosphate-buffered saline (PBS) (100 mM Na-Phosphate, pH 7.2, 150 mM NaCl). RXRα LBD was diluted to approximately 25 μM in PBS, and a 5-fold molar excess of N-hydroxysuccinimide long chain biotin (Pierce) was added in a minimal volume of PBS. This solution was incubated with gentle mixing for 60 min at ambient room temperature. The biotinylation modification reaction was stopped by the addition of 2000× molar excess of Tris-HCl, pH 8. The modified RXRα LBD was dialyzed against four buffer changes, each of at least 50 volumes, TBS containing 5 mM DTT, 2 mM EDTA, and 2% sucrose. The biotinylated RXRα LBD was subjected to mass spectrometric analysis to reveal the extent of modification by the biotinylation reagent. Approximately 85% of the protein had at least a single site of biotinylation, the mean extent of biotinylation was 1.8 mol of biotin per mole of LBD, and the overall extent of biotinylation followed a normal distribution of multiple sites, ranging from one to four.

Expression of RARα LBD. Human RARα LBD was expressed in *E. coli* strain BL21(DE3) as an amino-terminal polyhistidine-tagged fusion protein. Expression was under the control of an IPTG inducible T7 promoter. DNA encoding the recombinant protein was subcloned into the pRSETa expression vector (Invitrogen). Sequence encoding a modified polyhistidine tag (MKKGHHHHHHG) was fused in frame to sequence encoding residues 146−432 of RARα (X06538). The resulting complete encoded sequence is as follows: MKKGHHHHHH GESYTLPEV GELIEKVRKA HQETFPALCQ LGKYTTNNSS EQRVSLDIDL WDKFSELSTK CIIKTVEFAK QLPGFTTLTI ADQITLLKAA CLDILILRIC TRYTPEQDTM TFSDGLTLNR TQMHNAGFGP LTDLVFAFAN QLLPLEMDDA ETGLLSAICL ICGDRQDLEQ PDRVDMLQEP LLEALKVYVR KRRPSRPHMF PKMLMKITDL RSISAKGAER VITLKMEIPG SMPPLIQEML ENSEGLDTLS GQPGGGGRDG GGLAPPPGSC SPSLSPSSNR SSPATHSP.

Cells were grown in 12 1 L flasks at ∼25 °C in Luria−Bertani (LB) medium with 0.1 mg/mL carbenicillin for approximately 20 h. Cells were harvested by centrifugation, and concentrated cell slurries were stored in TBS, pH 8.0, at −80 °C.

Purification of RARα LBD. Approximately 66 g of wet cell paste was resuspended in ∼400 mL of TBS, pH 8.0 (25 mM Tris, 150 mM NaCl). Cells were lysed by passing three times through an APV Rannie MINI-lab homogenizer, and cell debris was removed by centrifugation (30 min, 20 000*g*, 4 °C). The cleared supernatant was filtered through coarse prefilters, and TBS, pH 8.0, containing 500 mM imidazole was added to obtain a final imidazole concentration of 50 mM. This lysate was loaded onto a column (XK-26, 10 cm) packed with Sepharose (Ni++ charged) Chelation resin (Pharmacia) and preequilibrated with TBS (pH 8.0)/50 mM imidazole. After it was washed to baseline absorbance with equilibration buffer, the column was washed with approximately one column volume of TBS, pH 8.0, containing 95 mM imidazole. RARα LBD (146−432) was eluted with a gradient from 50 to 500 mM imidazole. Column peak fractions were pooled immediately and diluted 5-fold with 25 mM Tris, pH 8.0, containing 5% 1,2-propanediol, 0.5 mM EDTA, and 5 mM DTT. The diluted protein sample was then loaded onto a column (XK-16, 10 cm) packed with Poros HQ resin (anion exchange). After it was washed to baseline absorbance with the dilution buffer, the protein was eluted with a gradient from 50 to 500 mM NaCl. Peak fractions were pooled and concentrated using Centri-prep 10K (Amicon) and subjected to size exclusion, using a column (XK-26, 90 cm) packed with Superdex-75 resin (Pharmacia) preequilibrated with TBS, pH 8.0, containing 5% 1,2-propanediol, 0.5 mM EDTA, and 5 mM DTT.

Biotinylation of Human RAR LBD. Biotinylation of the purified RARα LBD was carried out analogously to RXRα LBD.

Radioligand Binding Assays. Ligand binding to either purified human RXRα or RARα LBD was measured using scintillation proximity assay similar to that described for PPARγ.[18] Each well contained (100 μL total volume) receptor-coated beads, 2.5 nM 9-*cis*-[^{3}H]retinoic acid, and the desired concentration of test compound(s) or controls. To each well to be assayed was added the desired concentration of the previously prepared solution of 9-*cis*-[^{3}H]retinoic acid previously incubated with receptor-coated SPA bead slurry (80 μL). In general, the total volume was held constant by varying the concentration and volume of radioligand to compensate for any changes in the volume of a particular set of samples, whereas the concentration and volume of receptor-coated bead stock were held constant. The plates were incubated for at least 1 h at room temperature and bound radioactivity for each well was determined in a Wallac 1450 Microbeta counter. During this incubation, the plates were protected from direct laboratory light. K_i calculations are made using the IC_{50} and the Cheng−Prusoff equation: $K_i = IC_{50}/1 + ([L]/K_d)$ where [L] = ligand concentration of free radioligand used in the assay and IC_{50} = molar concentration that produces 50% of maximal possible inhibition.

Cell-Based Functional Assay. RARα and RXRα Transcriptional Assays. CV-1 cells were maintained and transiently transfected essentially as previously described.[27] RARα was transfected as a galactose4-LBD (GAL4-LBD) chimera construct in combination with an upstream activation sequence−thymidine kinase−luciferase (UAS-tk-luciferase) reporter construct and β-actin secreted placental alkaline phosphatase (SPAP) as internal control. The RAR GAL4 expression construct was prepared as previously described.[28] RXRα was tested as a full-length receptor expression construct cotransfected with a cellular retinol binding protein-tk-SPAP (pCRBPII-tk-SPAP) reporter construct[29] and β-galactosidase expression vector pCH110 (Amersham Pharmacia Biotech, Piscataway, NJ) as internal control. Drug stocks were prepared in DMSO and were diluted in phenol red-free Dulbecco's modified Eagle medium with 15 mM HEPES supplemented with 10% charcoal-stripped, delipidated calf serum (Sigma). Cells were incubated for 24 h in the presence of drugs after which the medium was sampled and assayed for ALP activity. Cell extracts from cells transfected with RAR were assayed for β-galactosidase activity. Luciferase reporter activity was measured using the LucLite assay system (Packard Instrument Co., Meridian, CT). The equation used to calculate EC_{50} values is as follows: response = $(B \times Kn + M \times Xn)/(Kn + Xn)$, where B = the response at 0 dose, M = the response for infinite dose, K = the dose fitting response of 50% between M and B, and n = the Hill coefficient.

Cell-Based Functional Assays: Lipogenesis and ALP. C3H10T1/2 clone 8 fibroblasts (American Type Culture Collection) were grown in DMEM high glucose containing 10% fetal calf serum. Adipogenesis was induced by adding 1 μM BRL49653 and 200 nM insulin to near confluent cells in 96 well microtiter plates as previously described.[19] Various concentrations of RXR ligands were added to the cells upon induction of adipogenesis. After 7 days in culture, triglyceride accumulation, a surrogate marker for lipogenesis, was measured using the Sigma Diagnostic Glycerol-Triglyceride assay (Trinder reagent 337; Sigma, St. Louis, MO). ALP activity was measured using Sigma-Fast pNPP substrate (N-2770) according to the manufacturer's specification (Sigma).

Experimental Animal Protocol. Age- and weight-matched male diabetic (*db*/*db*) mice (Jackson Labs, Bar Harbor, ME) and ZDF rats (Genetic Models, Indianapolis, IN) were housed at 72 °F and 50% relative humidity with a 12 h light and dark cycle. Animals (12 mice/group and six rats/group) at 8 weeks of age were orally gavaged once daily (8:00−9:00 AM) with vehicle (0.5% hydroxypropylmethylcellulase/0.1% Tween 80) or compound **46a**,**b** in vehicle. After 2 weeks of dosing, the animals were anesthetized with isofluorane, blood was drawn

by cardiac puncture, and serum was collected for measurements of nonfasting glucose, glycohemoglobin, triglyceride, nonesterified free fatty acid, and aspartate aminotransferase levels. All serum chemistry tests, with the exception of glycohemoglobin, were determined using an automated chemistry analyzer (Technicon Axon). Glycohemoglobin measurements were performed using a Columnmate Analyzer (Helena Instrument). Body and liver weights were recorded at the end of the study. Data were calculated as the mean and standard error from experiments performed on six rats and 12 mice per treatment group. Two-tailed tests were performed to calculate *P* values. This research complied with the principles of laboratory animal care (NIH publication No. 86-23, revised 1985) and company policy on the care and use of animals and related codes of practice.

Homology Modeling. The available RXRα *apo* structure (1LBD) was used as the starting point for the model of the "active" model of the LBD of RXRα. There were two areas that were remodeled. Residue Ser 259 to Leu 276 of RXRα was remodeled using the RARγ crystal structure (2LBD) available from the protein databank. Also, the C-terminal half of helix 10/11 to the end of helix 12 (Glu 434 to Pro 458) was remodeled using the same RARγ structure. There were no gaps in the alignment. The nonidentical residues were manually rotated to relieve any bad contacts using the residue libraries within the HOMOLOGY module of the program InsightII. Minimization was done using the Discover cvff force field.[30]

Docking. Docking was done using the growth procedure within the MVP program.[31] The carboxylate positions from the cocrystallized ligand 9-*cis*-retinoic in the RAR crystal structure were used as the anchor positions for the docking procedure. A 1.25 Å maximum displacement was allowed for the carboxylate oxygens positions, and no other restraints were used during the growth procedure.

Protein Preparation and Crystallization of the RXRα: PPARγ Heterodimer. The heterodimer protein reagent was expressed, purified, and crystallized as previously described.[13] In this work, pooled aliquots with equimolar amounts of RXRα and PPARγ were complexed with approximately 5 mol equiv of a racemic mixture of **46a**,**b**, farglitazar, and 2 mol equiv each of LxxLL motif peptides derived from the SRC-1 (Ac-CPSSHSSLTERHKILHRLLQEGSPS-NH_2) or CBP (Ac-NLVP-DAASKHKQLSELLRGGSGS-NH_2) coactivator proteins. Prior to crystallization, the sample was filtered and concentrated to about 10 mg/mL. Room temperature hanging drops containing 1 μL each of protein complex and well buffer composed of 17% PEG 4K, 200 mM NaSCN, 8% ethylene glycol, and 8% glycerol produced crystals within a couple of weeks. The crystals were taken directly from the drops and flash-frozen in liquid nitrogen.

X-ray Data Collection and Structure Determination. X-ray diffraction data were collected with a MAR 165 CCD detector at sector 17ID of the IMCA beam line facility within the Argonne National Labs. The observed reflections were reduced, merged, and scaled with Denzo and Scalepack[32] in the HKL2000 package. Crystals of (*S*)-**46a**,**b** and farglitazar complex diffracted to 2.4 Å and occupied the *P*212121 space group (a = 46.7 Å, b = 54.6 Å, and c = 211.7 Å) with one heterodimer complex in the asymmetric unit. The structure was determined by molecular replacement methods with the CCP4 AmoRe program (Collaborative Computational Project),[33] using our published 2.1 Å RXRα:PPARγ structure.[13] Phases from the molecular replacement solutions were used to calculate the initial electron density maps that displayed the six component complex. Subsequent structure building was performed with Quanta 2000 and refined with CNX 2000.[34] The final structure for the (*S*)-**46a**,**b**:farglitazar structure with one heterodimer complex and 196 water molecules has an *R* factor of 22.8% and free *R* of 25.0%. The structure coordinates are deposited under access code 1RDT at the Protein Data Bank (www.rcsb.org).

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References

(1) For reviews, see (a) Orfanos, C. E.; Ehlert, R.; Gollnick, H. The Retinoids. A Review of Their Clinical Pharmacology and Therapeutic Use. *Drugs* **1987**, *34*, 459−503. (b) Linney, E. Retinoic Acid Receptors: Transcription Factors Modulating Gene Regulation, Development, and Differentiation. *Current Topics in Developmental Biology*; Academic Press: Orlando, FL, 1992; pp 309−350. (c) *The Retinoids: Biology, Chemistry, and Medicine*, 2nd ed.; Sporn, M. B., Roberts, A. B., Goodman, D. S., Eds.; Raven Press Ltd.: New York, 1994. (d) Giguere, V. Retinoic Acid Receptors and Cellular Retinoid Binding Proteins: Complex Interplay in Retinoid Signaling. *Endocr. Rev.* **1994**, *15*, 61−79. (e) Redfern, C. P. F. Molecular Mechanism of Retinoid Function. *Adv. Organ Biol.* **1997**, *3*, 35−77. (f) Harvat, B.; Jetten, A. M. Growth Control by Retinoids: Regulation of Cell Cycle Progression and Apoptosis. *Handbook Exp. Pharmacol.* **1999**, *139* (Retinoids), 239−276.

(2) (a) Giguere, V.; Ong, E. S.; Segui, P.; Evans, R. M. Identification of a Receptor for the Morphogen Retinoic Acid. *Nature* **1987**, *330*, 624−629. (b) Petrovich, M.; Brand, N. J.; Krust, A.; Chambon, P. A Human Retinoic Acid Receptor Which Belongs to the Family of Nuclear Receptors. *Nature* **1987**, *330*, 444−450. (c) Allenby, G.; Bocquel, M.-T.; Saunders, M.; Kazmer, S.; Speck, J.; Rosenberger, M.; Lovey, A.; Kastner, P.; Grippo, J. F.; Chambon, P.; Levin, A. A. Retinoic Acid Receptors and Retinoid X Receptors: Interactions with Endogeneous Reetinoic Acids. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 30−34.

(3) (a) Heyman, R. A.; Mangelsdorf, D. J.; Dyck, J. A.; Stein, R. B.; Eichele, G.; Evans, R. M.; Thaller, C. 9-cis-Retinoic Acid is a High Affinity Ligand for the Retinoid X Receptor. *Cell* **1992**, *68*, 397−406. (b) Levin, A. A.; Sturzenbecker, L. J.; Kazmer, S.; Bosakowski, T.; Huselton, C.; Allenby, G.; Speck, J.; Kratzeisen, C.; Rosenberger, M.; Lovey, A.; Grippo, J. F. 9-*cis*-Retinoic Acid Stereoisomer Binds and Activates the Nuclear Receptor RXRα. *Nature* **1992**, *355*, 359−361. (c) Boehm, M. F.; McClurg, M. R.; Pathirana, C.; Mangelsdorf, D. J.; White, S. W.; Hebert, J. J.; Winn, D.; Goldman, M. E.; Heyman, R. A. Synthesis of High Specific Activity [^{3}H]-9-*cis*-Retinoic Acid and Its Application for Identifying Retinoids with Unusual Binding Properties. *J. Med. Chem.* **1994**, *37*, 408−414.

(4) (a) Mangelsdorf, D. J.; Ong, E. S.; Dyck, J. A.; Evans, R. M. Nuclear Receptor That Identifies a Novel Retinoic Acid Response Pathway. *Nature* **1990**, *345*, 224−229. (b) Mangelsdorf, D. J.; Borgmeyer, U.; Heyman, R. A.; Zhou, J. Y.; Ong, E. S.; Oro, A. E.; Kakizuka, A.; Evans, R. M. Characterization of Three RXR Genes That Mediate the Action of 9-*cis*-Retnoic Acid. *Genes Dev.* **1992**, *6*, 329−344.

(5) For recent reviews, see (a) Dawson, M. I.; Zhang, X. Discovery and Design of Retinoic Acid Receptor and Retinoid X Receptor Class- and Subtype-Selective Synthetic Analogues of All-*trans*-Retinoic Acid and 9-*cis*-Retinoic Acid. *Curr. Med. Chem.* **2002**, *9*, 623−637. (b) Kagechika, H. Novel Synthetic Retinoids and Separation of the Pleiotropic Retinoidal Activities. *Curr. Med. Chem.* **2002**, *9*, 591−608.

(6) (a) Mangelsdorf, D. J.; Evans, R. M. The RXR Heterodimers and Orphan Receptors. *Cell* **1995**, *83*, 841−850. (b) Rastinejad, F. Retinoid X Receptor and Its Partners in the Nuclear Receptor Family. *Curr. Opin. Struct. Biol.* **2001**, *11*, 33−38.

(7) (a) Boehm, M. F.; Zhang, L.; Badea, B. A.; White, S. K.; Mais, D. E.; Berger, E.; Suto, C. M.; Glodman, M. E.; Heyman, R. A. Synthesis and Structure−Activity of Novel Retinoid X Receptor Selective Retinoids. *J. Med. Chem.* **1994**, *37*, 2930−2941. (b) Boehm, M. F.; Zhang, L.; Zhi, L.; McClurg, M. R.; Berger, E.; Wagoner, M.; Mais, D. E.; Suto, C. M.; Davies, P. J. A.; Heyman, R. A.; Nadzan, A. M. Design and Synthesis of Potent Retinoid X Receptor Selective Ligands That Induce Apoptosis in Leukemia Cells. *J. Med. Chem.* **1995**, *38*, 3146−3155. (c) Beard, R. L.; Colon, D. F.; Song, T. K.; Davies, P. J. A.; Kochhar, D. M.; Chandraratna, A. S. Synthesis and Structure−Activity Relationships of Retinoid X Receptor Selective Daryl Sulfide Analogues of Retinoic Acid. *J. Med. Chem.* **1996**, *39*, 3556−3563. (d) Canan Koch, S. S.; Dardashti, L. J.; Hebert, J. J.; White, S. K.; Croston,

G. E.; Flatten, K. S.; Heyman, R. A.; Nadzan, A. M. Identification of the First Retinoid X Receptor Homodimer Antagonist. *J. Med. Chem.* **1996**, *39*, 3229−3234. (e) Vuligonda, V.; Lin, Y.; Chandraratna, A. S. Synthesis of Highly Potent RXR Specific Retinoids: The Use of a Cyclopropyl Group as a Double Bond Isostere. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 213−218. (f) Hibi, S.; Kikuchi, K.; Yoshimura, H.; Nagai, M.; Tai, K.; Hida, T. Syntheses and Structure−Activity Relationships of Novel Retinoid X Receptor Agonists. *J. Med. Chem.* **1998**, *41*, 3245−3252. (f) Vuligonda, V.; Garst, M. E.; Chandraratna, A. S. Stereoselective Synthesis and Receptor Activity of Conformationally Defined Retinoid X Receptor Selective Ligands. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 589−594. (g) Canan Koch, S. S.; Dardashti, L. J.; Cesario, R. M.; Croston, G. E.; Boehm, M. F.; Heyman, R. A.; Nadzan, A. M. Synthesis of Retinoid X Receptor-Specific Ligands That Are Potent Inducers of Adipogenesis in 3T3-L1 Cells. *J. Med. Chem.* **1999**, *42*, 742−750. (h) Ebisawa, M.; Umemiya, H.; Ohta, K.; Fukasawa, H.; Kawachi, E.; Christoffel, G.; Gronemeyer, H.; Tsuji, M.; Hashimoto, Y.; Shudo, K.; Kagechika, H. *Chem. Pharm. Bull.* **1999**, *47*, 1778−1786. (i) Dawson, M. I.; Hobbs, P. D.; Jong, L.; Xiao, D.; Chao, W.; Pan, C.; Zhang, X. sp2-Bridged Diaryl Retinoids: Effects of Bridge-Region Substitution on Retinoid X Receptor (RXR) Selectivity. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1307−1310. (j) Takahashi, B.; Ohta, K.; Kawachi, E.; Fukasawa, H.; Hashimoto, Y.; Kagechika, H. Novel Retinoid X Receptor Antagonists: Specific Inhibition of Retinoid Synergism in RXR−RAR Heterodimer Actions. *J. Med. Chem.* **2002**, *45*, 3327−3330. (k) Faul, M. M.; Grese, T. A. Selective RXR Modulators for the Treatment of Type II Diabetes. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 974−985. (l) Farmer, L. J.; Zhi, L.; Jeong, S.; Lamph, W. W.; Osburn, D. L.; Croston, G.; Flatten, K. S.; Heyman, R. A.; Nadzan, A. M. Retinoic Acid Receptor Ligands Based on the 6-Cyclopropyl-2,4-hexadienoic Acid. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 261−264. (m) Bell, M. G.; Grese, T. A.; Gernert, D. L.; Yumbie, N. P.; Boehm, M. F.; Michellys, P.-Y.; Ardecky, R. J.; Mapes, C. M.; Chen, J.-H. Fluorinated Trienes and Their Use as RXR Modulators. WO 02/072528, 2002. (n) Gardinier, K. M.; Gernert, D. L.; Grese, T. A.; Neel, D. A.; Mapes, C. M.; Michellys, P.-Y.; Boehm, M. F. Retinoid X Receptor Modulators. WO 02/071827, 2002. (o) Grese, T. A.; Gardinier, K. M.; Boehm, M. F. (Pyridinyl and Pyrimidyl)Trienoic Acid Derivatives as Retinoid X Receptor Modulators. WO 03/007950, 2003. (p) Michellys, P. Y.; Ardecky, R. J.; Chen, J. H.; Crombie, D. L.; Etgen, G. J.; Faul, M. M.; Faulkner, A. L.; Grese, T. A.; Heyman, R. A.; Karanewsky, D. S.; Klausing, K.; Leibowitz, M. D.; Liu, S.; Mais, D. A.; Mapes, C. M.; Marschke, K. B.; Reifel-Miller, A.; Ogilive, K. M.; Rungta, D.; Thompson, A. W. Novel (2*E*,4*E*,6*Z*)-7-(2-Alkoxy-3,5-dialkylbenzene)-3-methylocta-2,4,6-tienoic Acid Retinoid X Receptor Modulators Are Active in Models of Type 2 Diabetes. *J. Med. Chem.* **2003**, *46*, 2683−2696. (q) Michellys, P.-Y.; Ardecky, R. J.; Chen, J.-H.; D'Arrigo, J.; Grese, T. A.; Karanewsky, D. S.; Leibowitz, M. D.; Liu, S.; Mais, D. A.; Mapes, C. M.; Montrose-Rafizadeh, C.; Oglive, K. M.; Reifel-Miller, A.; Rungta, D.; Thompson, A. W.; Tyhonas, J. S.; Boehm, M. F. Design, Synthesis, and Structure−Activity Relationship Studies of Novel 6,7-Locked-[7-(2-alkoxy-3,5-dialkylbenzene)-3-methylocta]-2,4,6-trienoic Acids. *J. Med. Chem.* **2003**, *46*, 4087−4103.

(8) (a) Schulman, D.; Crombie, R. P.; Bissonnette, R. P.; Cesario, R.; Roegner, K.; Shao, G.; Heyman, R. A. RXR Specific Agonists and Modulators: A New Retinoid Pharmacolgy. *Handbook Exp. Pharmacol.* **1999**, *139* (Retinoids), 215−235. (b) Cesario, R. M.; Klausing, K.; Razzaghi, H.; Crombie, D.; Rungta, D.; Heyman, R. A.; Lala, D. S. The Rexinoid LG100754 is a Novel RXR:PPARγ Agonist and Decreases Glucose Levels In Vivo. *Mol. Endocrinol.* **2001**, *15*, 1360−1369.

(9) Lenhard, J. M.; Croom, D. K.; Weiel, J. E.; Winegar, D. A. HIV Protease Inhibitors Stimulate Hepatic Triglyceride Syntheis. *Arterioscler., Thromb., Vasc. Biol.* **2000**, *20*, 2625−2629.

(10) Lenhard, J. M. PPARγ/RXR as a Therapeutic Target for Diabetes. *Receptors Channels* **2001**, *7*, 249−258.

(11) (a) Mukherjee, R.; Davies, P. J. A.; Crombie, D. L.; Bischoff, E. D.; Cesario, R. M.; Jow, L.; Hamann, L. G.; Boehm, M. F.; Mondon, C. E.; Nadzan, A. M.; Paterniti, J. R., Jr.; Heyman, R. A. Sensitization of Diabetic and Obese Mice to Insulin by Retinoid X Receptor Agonists. *Nature* **1997**, *386*, 407−410. (b) Lenhard, J. M.; Lancaster, M. E.; Paulik, M. A.; Weiel, J. E.; Binz, J. G.; Sundseth, S. S.; Gaskill, B. A.; Lightfoot, R. M.; Brown, H. R. The RXR Agonist LG100268 Causes Hepatomegaly, Improves Glycaemic Control and Decreases Cardivascular Risk and Cachexia in Diabetic Mice Suffering From Pancreatic Beta-Cell Dysfunction. *Diabetologia* **1999**, *42*, 545−554. (c) Paterniti, J. R., Jr.; Mukherjee, R. The PPAR/RXR Heterodimer: Therapeutic Target for Insulin Resistance and Obesity. In *Nutrition, Genetics and Obesity: Pennington Center Nutrition Series*; Louisiana State University Press: LA, 1999; Vol. 9, pp 477−492. (d) Liu, Y. L.; Sennit, M. V.; Hislop, D. C.; Crombie, D. L.; Heyman, R. A.; Cawthorne, M. A. Retinoid X Receptor Agonists Have Anti-obesity Effects and Improve Insulin Sensitivity in Zucker *fa/fa* Rats. *Int. J. Obes. Relat. Metab. Disord.* **2000**, *24*, 997−1004. (e) Cha, B. S.; Ciaraldi, T. P.; Carter, L.; Nikoulina, S. E.; Mudaliar, S.; Mukherjee, R.; Paterniti, J. R., Jr.; Henry, R. R. Peroxisome Proliferator-Activated (PPAR)γ and retinoid X Receptor (RXR) Agonists Have Complementary Effects on Glucose and Lipid Metabolism in Human Skeletal Muscle. *Diabetologia* **2001**, *44*, 444−452. (f) Cesario, R. M.; Klausing, K.; Razzaghi, H.; Crombie, D.; Rungta, D.; Heyman, R. A.; Lala, D. S. The Rexinoid LG100754 Is a Novel RXR:PPARγ Agonist and Decreases Glucose Levels in Vivo. *Mol. Endocrinol.* **2001**, *15*, 1360−1369.

(12) Bourguet, W. R. M.; Chambon, P.; Gronemeyer, H.; Moras, D. Crystal Structure of the Ligand Binding Domain of the Human Nuclear Receptor RXRα. *Nature* **1995**, *375*, 377−382.

(13) Gampe, R. T., Jr.; Montana, V. G.; Lambert, M. H.; Miller, A. B.; Bledsoe, R. K.; Milburn, M. V.; Kliewer, S. A.; Willson, T. M.; Xu, H. E. Asymmetry in the PPARγ/RXRα Crystal Structure Reveals the Molecular Basis of Heterodimerization Amoung Nuclear Receptors. *Mol. Cell* **2000**, *5*, 545−555.

(14) (a) Compound **23**: Dawson, M. I.; Jong, L.; Hobbs, P. D.; Cameron, J. F.; Chao, W.; Pfahl, M.; Lee, M.-O.; Shroot, B.; Pfahl, M. Conformational Effects on Retinoid Receptor Selectivity. 2. Effects of Retinoid Bridging Group on Retinoid X Receptor Activity and Selectivity. *J. Med. Chem.* **1995**, *38*, 3368−3383. (b) Compound **24**: Qing, F.-L.; Fan, J.; Sun, H.-B.; Yue, X.-J. First Synthesis of ortho-Trifluoromethylated Aryl Triflates. *J. Chem. Soc., Perkin Trans. 1* **1997**, *20*, 3053−3057. (c) Compound **25**: Canan-Koch, S.; Hwang, C. K.; Boehm, M. F.; Badea, B. A.; Dardashti, L. J.; Zhang, L.; Nadzan, A. M.; Heyman, R. A.; Mukherjee, R.; Lala, D. S.; Farmer, L. J. Dimer-Selective RXR Modulators and Methods For Their Use. WO 9712853, 1997.

(15) Wood, T. F.; Evans, W. F. Method and Composition for Controlling Weeds With Acylated Tetrahydronaphthalene. U.S. Patent 3499751, 1970.

(16) Lee, Y. R.; Suk, Y. Rhodium(II)-Catalyzed Cycloaddition of Cyclic Diazodicarbonyl Compounds With Nitriles. Synthesis of Tetrahydrobenzoxazoles, Tetrahydrobenzofurans, and Tetrahydrobenzodioxoles. *Heterocycles* **1998**, *48*, 875−883.

(17) Schneider, C. S.; Pook, K. H. Acid-Catalyzed Cyclization of 1-Aryl-2-thienylmethyl and 1-Aryl-2-furfurylaminoethanols via Spiro Intermediates. *J. Chem. Soc., Perkin Trans. 1* **1986**, 877−883.

(18) Nichols, J. S.; Parks, D. J.; Consler, T. G.; Blanchard, S. G. Development of a Scintillation Proximity Assay for Peroxisome Proliferator-Activated Receptor γ Ligand Binding Domain. *Anal. Biochem.* **1998**, *257*, 112−119.

(19) Paulik, M. A.; Lenhard, J. M. Thiazolidinediones Inhibit Alkaline Phosphatase While Increasing Expression of Uncoupling Protein and Deiodinase and Increasing Mitochondrial Mass in C3H10T1/2 Cells. *Cell Tissue Res.* **1997**, *290*, 79−87.

(20) Henke, B. R.; Blanchard, S. G.; Brackeen, M. F.; Brown, K. K.; Cobb, J. E.; Collins, J. L.; Harrington, W. W., Jr.; Hashim, M. A.; Hull-Ryde, E. A.; Kaldor, I.; Kliewer, S. A.; Lake, D. H.; Leesnitzer, L. M.; Lehmann, J. M.; Lenhard, J. M.; Orband-Miller, L. A.; Miller, J. F.; Mook, R. A.; Noble, S. A.; Oliver, W.; Parks, D. J.; Plunket, K. D.; Szewczyk, J. R.; Willson, T. M. N-(2-Benzoylphenyl)-L-tyrosine PPARγ. 1. Discovery of a Novel Series of Potent Antihyperglycemic and Antihyperlipidemic Agents. *J. Med. Chem.* **1998**, *41*, 5020−5036.

(21) Freedman, L. P. Increasing the Complexity of Coactivation in Nuclear Receptor Signaling. *Cell* **1999**, *97*, 5−8.

(22) (a) Bourguet, W.; Ruff, M.; Chambon, P.; Gronmeyer, H.; Moras, D. Crystal Structure of the Ligand-Binding Domain of the Human Nuclear Receptor RXRα. *Nature* **1995**, *375*, 377−382. (b) Renaud, J.-P.; Rochel, N.; Ruff, M.; Vivat, V.; Chambon, P.; Moras, D. Crystal Structure of the PPARγ Ligand Binding Domain Bound to All-Trans Retinoic Acid. *Nature* **1995**, *378*, 681−689. (c) Nolte, R. T.; Wisely, G. B.; Westin, S.; Cobb, J. E.; Lambert, M. H.; Kurokawa, R.; Rosenfeld, M. G.; Willson, T. M.; Glass, C. K.; Milburn, M. V. Ligand Binding and Co-activator Assembly of the Peroxisome Proliferator-Activated Receptor-γ. *Nature* **1998**, *395*, 137−143. (d) Xu, H. E.; Lambert, M. H.; Montana, V. G.; Parks, D. J.; Blanchard, S. G.; Brown, P. J.; Sternbach, D. D.; Lehmann, J. M.; Wisely, G. B.; Willson, T. M.; Kliewer, S. A.; Milburn, M. V. Molecular Recognition of Fatty Acids by Peroxisome Proliferator-Activated Receptors. *Mol. Cell* **1999**, *3*, 397−403.

(23) (a) Heyman, R. A.; Mangelsdorf, D. J.; Dyck, J. A.; Stein, R.; Eichele, G.; Evans, R. M.; Thaller, C. 9-Cis Retinoic Acid is a High Affinity Ligand for the Retinoid X Receptor. *Cell* **1992**, *68*, 397−406. (b) Levin, A. A.; Sturzenbecker, L. J.; Kazmer, S.; Bosakowski, T.; Huselton, C.; Allenby, G.; Speck, J.; Kratzeisen, C.; Rosenberger, M.; Lovey, A. 9-Cis Retinoic Acid Stereoisomer Binds and Activates the Nuclear Receptor RXRα. *Nature* **1992**, *355*, 359−361.

(24) Standeven, A. M.; Escobar, M.; Beard, R. L.; Yuan, Y.-D.; Chandraratna, R. A. S. Mitogenic Effect of Retinoid X Receptor Agonists in Rat Liver. *Biochem. Pharm.* **1997**, *54*, 517−524.
(25) (a) Sherman, S. I.; Gopal, J.; Haugen, B. R.; Chiu, A. C.; Whaley, K.; Nowlakha, P.; Duvic, M. Central Hypothyroidism Associated With Retinoid X Receptor-Selective Ligands. *N. Engl. J. Med.* **1999**, *340*, 1075−1079. (b) Liu, S.; Ogilive, K. M.; Klausing, K.; Lawson, M. A.; Jolley, D.; Li, D.; Bilakovics, J.; Pascul, B.; Hein, N.; Urcan, M.; Leibowitz, M. D. Mechanism of Selective Retinoid X Receptor Agonist-Induced Hypothyroidism in the Rat. *Endocrinology* **2002**, *143*, 2880−2885.
(26) Vu-Dac, N.; Gervois, P.; Torra, I. P.; Fruchart, J. C.; Kosykh, V.; Kooistra, T.; Princen, H. M.; Dallongeville, J.; Staels, B. Retinoids Increase Human Apo C-III Expression at the Transcriptional Level Via the Retinoid X Receptor. Contribution to the Hypertriglyceridemic Action of Retinoids. *J. Clin. Invest.* **1998**, *102*, 625−632.
(27) Willson, T. M.; Cobb, J. E.; Cowan, D. J.; Wiethe, R. W.; Correa, I. D.; Prakash, S. R.; Beck, K. D.; Moore, L. B.; Kliewer, S. A.; Lehmann, J. M. The Structure−Activity Relationship Between Peroxisome Proliferator-Activated Receptor γ Agonsim and the Antihyperglycemic Activity of Thiazolidinediones. *J. Med. Chem.* **1996**, *39*, 665−668.
(28) Lehmann, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkinson, W. O.; Willson, T. M.; Kliewer, S. A. An Antidiabetic Thiazolidinedione is a High Affinity Ligand for Peroxisome Proliferator-Activated Receptor γ (PPARγ). *J. Biol. Chem.* **1995**, *270*, 12953−12956.
(29) Mangelsdorf, D. J.; Umesono, K.; Kliewer, S. A.; Borgmeyer, U.; Ong, E. S.; Evans, R. M. A Direct Repeat in the Cellular Retinol-Binding protein Type II Gene Confers Differential Regulation by RXR and RAR. *Cell* **1991**, *66*, 555−561.
(30) InsightII, Discover, CNX, and Quanta are available from Accelrys Inc., 9685.
(31) Lambert, M. H. Docking Conformationally Flexible Molexules into Protein Binding Sites. In *Practical Aplication of Computer-Aided Drug Design*; Charifson, P. S., Ed.; Marcel-Dekker: New York, 1997; pp 243−303.
(32) Otwinowski, Z.; Minor, W. Processing of X-ray Diffraction Data Collected in Oscillation Mode. *Methods Enzymol.* **1997**, *276*, 307−326.
(33) (a) Navaza, J. AmoRe: An Automated Package for Molecular Replacement. *Acta Crystallogr.* **1994**, *A50*, 157−163. (b) Collaborative Computational Project Number 4. *Acta Crystallogr.* **1994**, *D50*, 760−776.
(34) Brunger, A. T.; Adams, P. D.; Clore, G. M.; DeLano, W. L.; Gros, P.; Grosse-Kunstleve, R. W.; Jiang, J. S.; Kuszewski, J.; Nilges, M.; Pannu, N. S.; Read, R. J.; Rice, L. M.; Simonson, T.; Warren, G. L. Crystallography and NMR System: A New Software Suite for Macromolecular Structure Determination. *Acta Crystallogr. D* **1998**, *54*, 905−921.
(35) Figures 3B, 4A,D, and 5 were made using PYMOL (www.pymol.org). Figure 3A was made using Insight and Figure 4B was made using Quanta.

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