Synthesis and Structure–Activity Relationships of Oxamic Acid and Acetic Acid Derivatives Related to L-Thyronine

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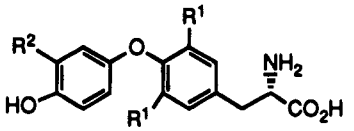
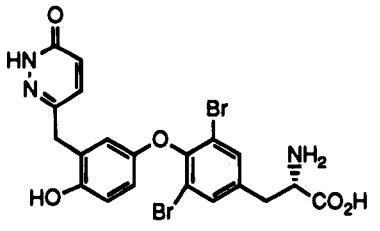
Aryloxamic acids **7** and **23**, (arylamino)acetic acids **29**, arylpropionic acids **33**, arylthioacetic acids **37**, and (aryloxy)acetic acid **41** related to L-triiodothyronine (L-T_3) were prepared and tested *in vitro* for binding to the rat liver nuclear L-T_3 receptor and the rat membrane L-T_3 receptor. The structure–activity relationships for these compounds are described, with **7f**, **23a**, **29c**, **33a**, **37b**, and **41** showing excellent potency (IC_{50}'s of 0.19, 0.16, 1.1, 0.11, 3.5, and 0.10 nM, respectively) to the nuclear receptor and significantly lower binding affinity to the membrane receptor (IC_{50}'s > 5 μM). Some of these compounds, especially in the oxamic acid series **7** and **23**, showed an unprecedented potency for methyl-substituted derivatives such as **7f** and **23a**. Compounds **7f** and **23a** showed good lipid lowering effects in rats with ED_{50}'s of 20 and 5 μg/kg po, respectively, and a lack of cardiac side effects in rats at doses as high as 10 and 25 mg/kg po, respectively.

Administration of triiodothyronine (L-T_3) **1a** or related analogs lowers plasma cholesterol levels in animal models[1] and humans.[2,3] This property results from the action of thyroid hormone on its liver nuclear receptors to stimulate the synthesis of low-density lipoprotein (LDL) receptors[4] as well as the synthesis of several lipolytic enzymes.[5] However, these agents are not used therapeutically to treat hypercholesterolemia due to adverse cardiac side effects, which arise either directly by acting on cardiac receptors or indirectly through an increase in metabolic rate.[3] If the undesired activity of thyromimetics were to be limited by restricting their access to cardiac muscle tissue, then a cardiac sparing agent might be identified. Selective uptake of thyromimetics into the nuclei of liver cells compared to nuclei of cardiac cells was originally demonstrated for the stereoisomers of T_3.[6] It was noted that while L-T_3 administered *in vivo* displayed equivalent occupancy in the liver and heart nuclei, D-T_3 had a 5–6-fold preferential occupancy of the liver versus heart nuclei. SK&F L-94901 (**2**) was the first synthetic thyromimetic designed to take advantage of this concept of selective nuclear access as a means of achieving cardiac sparing hypolipidemic activity.[7] Speculation as to the mechanism responsible for the liver selectivity of D-T_3, D-T_4, and **2** includes tissue differences in (i) cytoplasmic protein binding, (ii) active transport at the cell membrane, and/or (iii) activities of a putative stereospecific cytoplasm to nucleus energy-dependent transport system.[6b,8] In the studies reported herein, novel thyromimetics were initially identified by *in vitro* competitive binding studies using [^{125}I]L-T_3 and intact rat liver nuclei. Compounds of interest were then evaluated *in vitro* for competitive binding with [^{125}I]L-T_3 using a highly purified plasma membrane preparation from rat liver which exhibited stereospecificity for L-T_3.[9] Several biological effects of thyroid hormone have been attributed to direct effects on the plasma membrane, e.g., glucose transport, activation of Ca^{2+}-ATPase, and membrane resistance and hyperpolarization.[10] Some of these effects have been noted to be stereospecific for L-T_3 and correlate with the plasma membrane binding.[10a] To avoid potential exacerbation of these thyromimetic effects, compounds devoid of plasma membrane binding were sought.



1a, $R^1 = R^2 = I$
1b, $R^1 = Me$, $R^2 = I$
1c, $R^1 = Br$, $R^2 = iPr$
1d, $R^1 = Me$, $R^2 = iPr$
1e, $R^1 = H$, $R^2 = I$



2 (L-94901)

Another putative function attributed to thyroid hormone membrane binding is the cellular uptake of thyroid hormone.[11] Numerous investigators using a variety of cell types have demonstrated that cellular transport of thyroid hormone is an energy-dependent process with stereoisomeric and structural specificity[12] which correlates with the stereoisomeric and structural specificity for plasma membrane binding in these cell types.[13] The structural and stereoisomeric plasma membrane binding affinities are independent of the cell type; in fact, the ratios for **2**/L-T_3 binding were identical for liver and cardiac plasma cell membranes.[8a] Compound **2** exhibited the weaker binding in each instance. Compounds exhibiting poor plasma membrane binding (D-T_3, D-T_4, **2**, and triiodothyroacetic acid (TRIAC)) have been reported to exhibit favorable lipid lowering com-

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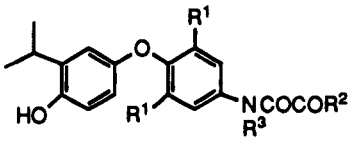
Table 1. 3'-Isopropyloxamic Acid Derivatives



no.	R^1	R^2	R^3	formula[a]	mp (°C)	nuclear IC_{50} (nM)[b]	membrane IC_{50} (μM)[b]
7a	H	OH	H	$C_{17}H_{17}NO_5$	105–110	48 ± 9	>5
7b	I	OH	H	$C_{17}H_{15}I_2O_5$	160–170	0.10 ± 0.01	0.8
7c	Br	OH	H	$C_{17}H_{15}Br_2NO_5$	142–152	6.0 ± 1.3	4
8a	Br	NH_2	H	$C_{17}H_{16}Br_2N_2O_4$	86–90	3.0 ± 1.3	1
8b	Br	NHMe	H	$C_{18}H_{18}Br_2N_2O_4$	140–145	47 ± 12	ND[c]
7d	Cl	OH	H	$C_{17}H_{15}Cl_2NO_5$	111–118	1.1 ± 0.2	>5
7e	F	OH	H	$C_{17}H_{15}F_2NO_5$	160–162	3.6 ± 0.5	ND
7f	Me	OH	H	$C_{19}H_{21}NO_5$	144–150	0.19 ± 0.02	>5
8c	Me	NH_2	H	$C_{19}H_{22}N_2O_4$	74–78	0.95 ± 0.4	>5
7g	Me	OH	Me	$C_{20}H_{23}NO_5$	140–156	120 ± 28	ND
7h	iPr	OH	H	$C_{23}h_{29}NO_5$	72–90	22 ± 11	>5
9a	Me	OEt	H	$C_{21}H_{25}NO_5$	154–161	0.23 ± 0.03	ND
9b	Me	OCH_2Ph	H	$C_{26}H_{27}NO_5$	138–140	0.26 ± 0.01	ND
6	Me			$C_{21}H_{25}NO_5$	138–140	1.0 ± 0.85	ND
10[d]				$C_{20}H_{23}NO_5$	179–183	14 ± 0.7	ND
14[d]				$C_{20}H_{23}NO_4$	105–108	8.0 ± 2.8	ND[c]
1a (L-T_3)						1.8 ± 0.2	0.1 ± 0.03
2[e]				$C_{20}H_{17}Br_2N_3O_5$	279	48 ± 9	1.0
1c[f]				$C_{18}H_{19}Br_2NO_4$	>200	4.5 ± 2	0.2
D-T_3						4.4 ± 0.4	0.5 ± 0.15
D-T_4						35 ± 17	2.5 ± 0.7
TRIAC						0.15 0.04	>5

[a] All compounds had satisfactory C, H, and N elemental analyses unless otherwise indicated and IR and NMR spectra consistent with the structure. [b] The IC_{50} value is the concentration of compound which inhibits 50% of bound [^{125}I]L-T_3 and represents the mean ± the standard error (SE) of two or more assays using six to eight concentrations of compound/assay. Values lacking SE are from single assays using six to eight concentrations of compound. For details see the Experimental Section. [c] ND = not determined. [d] See Scheme 1 for structure. [e] Reference 7. [f] Reference 21b.

pared to cardiovascular effects.[14] The *in vitro* binding data for a number of reference thyromimetics are included at the bottom of Table 1. This same relationship is demonstrated for the compounds identified in the studies to be presented herein. If poor membrane binding is involved in hepatic vs cardiac specificity, one might postulate that membrane binding and active transport into the cell are more important for ultimate nuclear occupancy of thyromimetics in the cardiac cell than in the hepacocyte, so that lack of binding affects cardiac function more than hepatocyte function. An alternative explanation for this correlation is that the lack of plasma membrane binding is simply a predictor of a another process; e.g., binding to a putative protein is suggested to be responsible for cytoplasmic to nuclear translocation.[11,15]

In this report we describe some of our work directed to the discovery of thyromimetic agents which have desirable lipid lowering properties without cardiovascular side effects. Herein we describe the synthesis and biological profile of a series of oxamic acids and related derivatives.

Chemistry

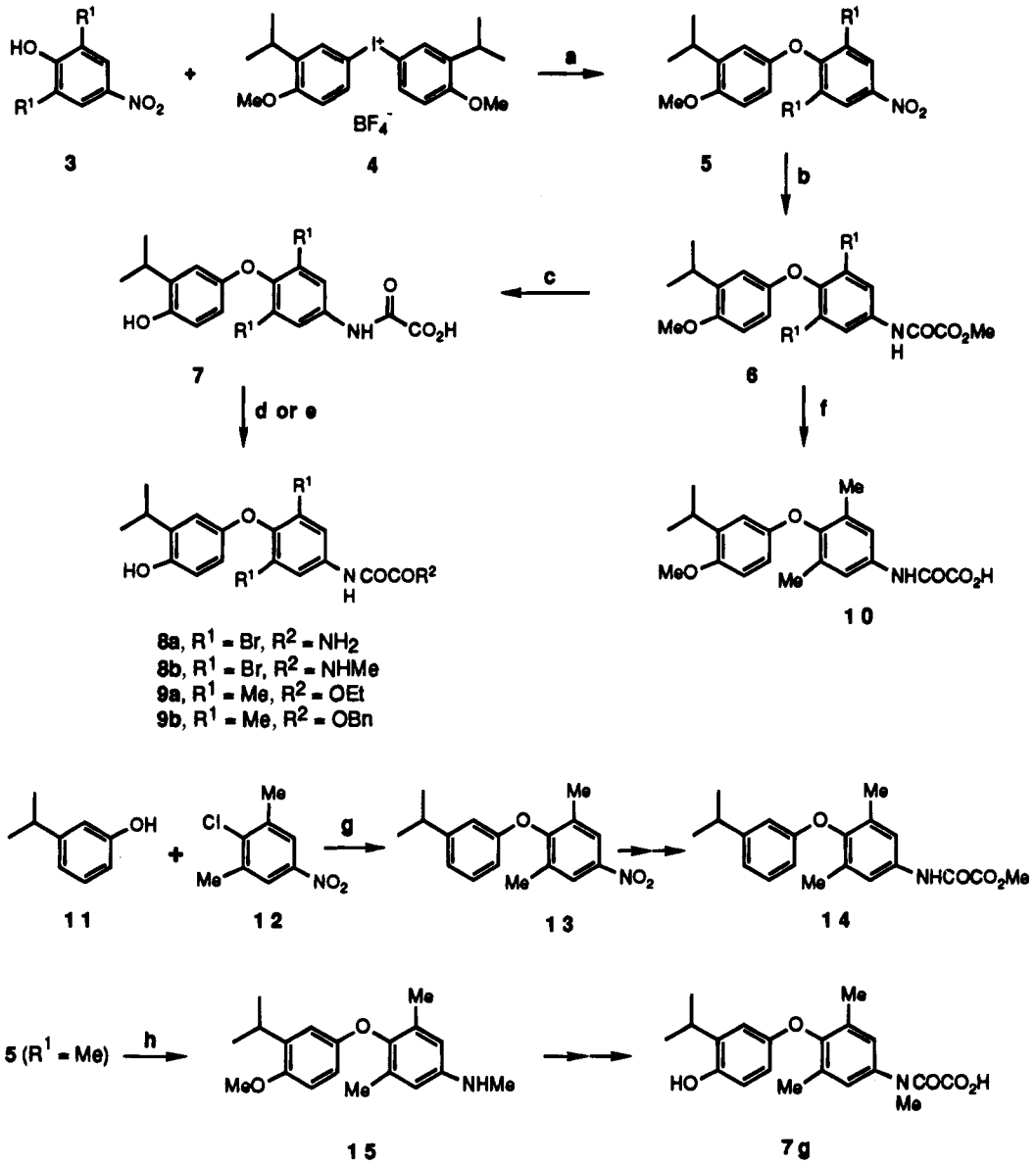
A series of oxamic acid derivatives with an isopropyl substituent at the 3'-position was prepared as outlined in Scheme 1. 2,6-Disubstituted 4-nitrophenols **3** were treated with bis(3-isopropyl-4-methoxyphenyl)iodonium tetrafluoroborate **4** in the presence of copper bronze and triethylamine to give the diphenyl ethers **5**.[21,22] The use of tetrafluoroborate salt in place of nucleophilic counterions such as bromide or iodide avoided competitive attack of the anion on the iodonium cation and led to substantially improved yields in the coupling reaction. Nitro group reduction followed by treatment with an excess of dimethyl oxalate at 120 °C generated the oxamate esters **6**. Addition of boron tribromide deprotected both the methyl ether and methyl ester groups to yield **7**. In many cases, purification of crude **7** was made easier by conversion to the methyl ester with dimethyl sulfate, purification using flash column chromatography, followed by alkaline hydrolysis and crystallization of pure **7**.

The corresponding amides **8a,b** were prepared by coupling of **7c** with 2-ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ)[16] and ammonia or methylamine, respectively. Esters **9a,b** were produced by treatment of acid **7f** with cesium carbonate and dimethyl sulfate or benzyl bromide, respectively. Methoxy analog **10** was prepared by alkaline hydrolysis of ester **6**.

Derivative **14** lacking a phenolic hydroxyl group was prepared by carrying out an aromatic substitution reaction with 3-isopropylphenol **11** and 4-chloro-3,5-dimethylnitrobenzene **12** to give diphenyl ether **13**. Nitro group reduction, condensation with dimethyl oxalate, and alkaline hydrolysis as described above generated the deshydroxy analog **14**. An *N*-methyl analog **7g** was prepared from **5** by reduction and N-acylation with ethyl chloroformate, followed by lithium aluminum hydride reduction to give **15**. Treatment of **15** with dimethyl oxalate followed by reaction with boron tribromide resulted in concomitant methyl ether cleavage and methyl de-esterification to produce the phenolic acid **7g**. Compounds prepared as described in Scheme 1 are listed in Table 1.

The preparation of analogs with the 3'-isopropyl group replaced by substituted benzyl groups is shown in Scheme 2. Reaction of 2,6-disubstituted 4-nitrophenols **3** with (4,4'-dimethoxydiphenyl)iodonium tetrafluorobo-

Scheme 1. 3′-Isopropyloxamic Acid Derivatives[a]



[a] (a) Cu/Et_3N; (b) (1) H_2/Pt–C, (2) MeO_2CCO_2Me; (c) (1) BBr_3, (2) Me_2SO_4/Cs_2CO_3, (3) NaOH; (d) NH_3 or $MeNH_2$, EEDQ; (e) EtOH or BnOH, Cs_2CO_3; (f) NaOH; (g) K_2CO_3; (h) (1) H_2, Pd–C, (2) $ClCO_2Et$, (3) LAH.

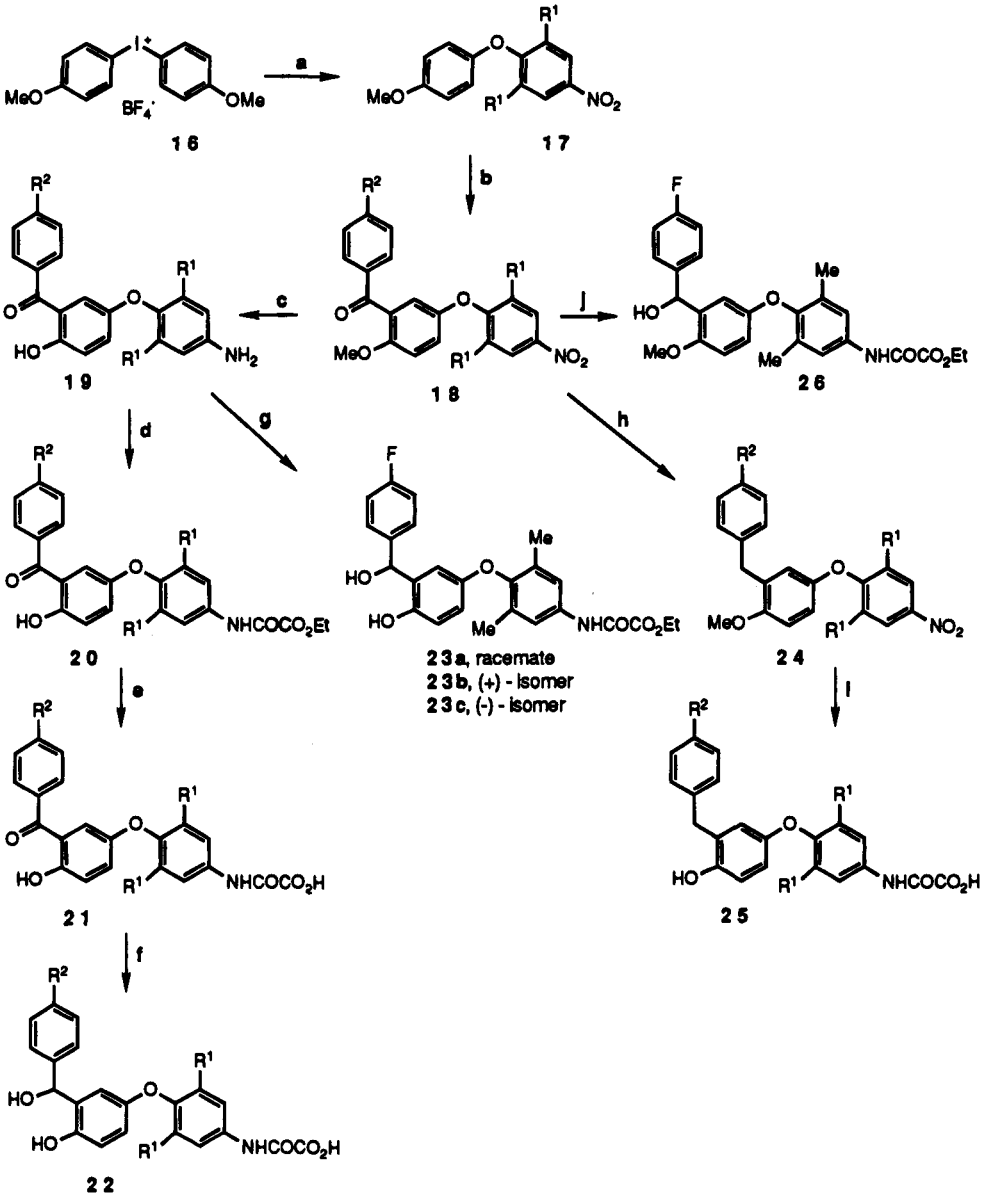
rate (**16**) in the presence of copper powder and triethylamine generated the diphenyl ether **17**. Titanium tetrachloride-catalyzed Friedel–Crafts acylation of **17** with substituted benzoyl chlorides led to **18**. Demethylation with boron trichloride followed by nitro group reduction gave **19**. Treatment of **19** with an excess of diethyl oxalate at 100 °C produced oxamate esters **20**. Alkaline hydrolysis of **20** yielded **21**, which could be reduced with sodium borohydride to **22**. Catalytic reduction of **20** led to the hydroxy ester **23a**. Resolution of racemic **23a** was carried out using HPLC with a Chiralcel OD (Daicel) column. Complete reduction of the ketone carbonyl group contained in **18** to give **24** was achieved by reaction with triethylsilane and trifluoroacetic acid.[17] Elaboration of **24** to **25** was carried out as described above. Analog **26** was prepared from **18** by nitro group reduction, condensation with diethyl oxalate, and ketone reduction with sodium borohydride. Compounds described in Scheme 2 are summarized in Table 2.

Several (*N*-arylamino)acetic acid derivatives were prepared as outlined in Scheme 3. Deprotection of the phenol **5** with boron tribromide followed by reprotection with *tert*-butyldimethylsilyl chloride led to **27**. Nitro group reduction followed by N-alkylation produced intermediates **28**. Deprotection of **28** with tetrabutylammonium fluoride followed by sodium hydroxide led to **29**.

Several arylpropionic acid derivatives were synthesized as shown in Scheme 4. 4-Hydroxyhydrocinnamic acid underwent bromination in acetic acid to give **31** (R^1 = Br).[18] 4-Bromo-2,6-dimethylphenol underwent a Heck reaction with ethyl acrylate to yield a cinnamate derivative,[19] which was hydrogenated to give **31** (R^1 = Me). Treatment of **31** with iodonium salt **4** led to **32**, which was deprotected with boron tribromide to produce **33**.

Several arylthioacetic acid analogs were prepared as outlined in Scheme 5. Aniline derivative **34**, prepared by hydrogenation of nitro compound **5**, was diazotized with sodium nitrite in hydrochloric acid and treated with potassium ethyl xanthate to yield **35**. Alkaline hydrolysis of **35** led to intermediate thiophenol derivatives, which underwent alkylation with ethyl bromoace-

Scheme 2. (3′-Arylmethyl)oxamic Acid Derivatives[a]



[a] (a) 3, Cu/Et_3N; (b) ArCOCl, $TiCl_4$; (c) (1) BCl_3, (2) H_2, Pd–C; (d) EtO_2CCO_2Et; (e) NaOH; (f) $NaBH_4$; (g) H_2, Ni(Ra); (h) Et_3SiH, TFA; (l) (1) BBr_3, (2) H_2, Ni(Ra), (3) EtO_2CCO_2Et, (4) NaOH; (j) (1) H_2, (2) EtO_2CCO_2Et, (3) $NaBH_4$ or H_2, Ni(Ra).

tate to produce **36**. Deprotection of **36** with boron tribromide gave **37**.

Aryloxyacetic acid derivatives were prepared as illustrated in Scheme 6. Coupling of 2,6-dibromo-4-methoxyphenol **38** with iodonium salt **4** gave **39**, which was demethylated with boron tribromide to yield **40**. Regioselective alkylation of **40** with ethyl bromoacetate and cesium carbonate followed by alkaline hydrolysis generated **41**. Compounds described in Schemes 3–6 are listed in Table 3.

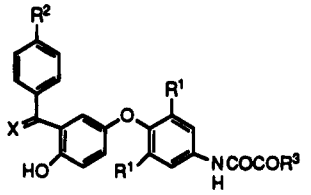
In Vitro Results and Discussion

The oxamic acid and acetic acid derivatives described above were tested *in vitro* for binding to the L-T_3 rat liver nuclear receptor and to the L-T_3 rat liver plasma membrane receptor. In contrast to L-T_3 (**1a**) or classical analogs such as **1c**,[21b] which exhibit comparable potency at each receptor, compounds in the oxamic acid and related acetic acid series showed marked selectivity for binding to the nuclear receptor, as shown in Tables 1–3. All of the tested compounds showed at least 3 orders of magnitude lower potency at the membrane receptor. Furthermore, compounds not containing halogens were inactive at the membrane receptor at the highest test concentration (5 μM).

Extensive structure–activity studies of classical thyroid hormone analogs have led to a well-defined picture of the binding requirements to the nuclear receptor.[20] These findings conclude that the 4′-hydroxyl group participates in a donor hydrogen bond, that the 3′-substituent should be no larger than isopropyl, that the optimal 3,5-substituents are iodo and bromo, with methyl having significantly reduced activity and hydrogen having virtually no activity, and that the alanine side chain participates in an electrostatic interaction between the carboxylate anion and a positively charged amino acid residue on the receptor. In the oxamic acid series, exceptions to this classical model were found at the 4′-position, the 3,5-substituents, and at the alanine position.

In the 3′-isopropyl oxamic series (Table 1), several compounds (e.g., **7b**, **7d**, **7f**) showed potency greater

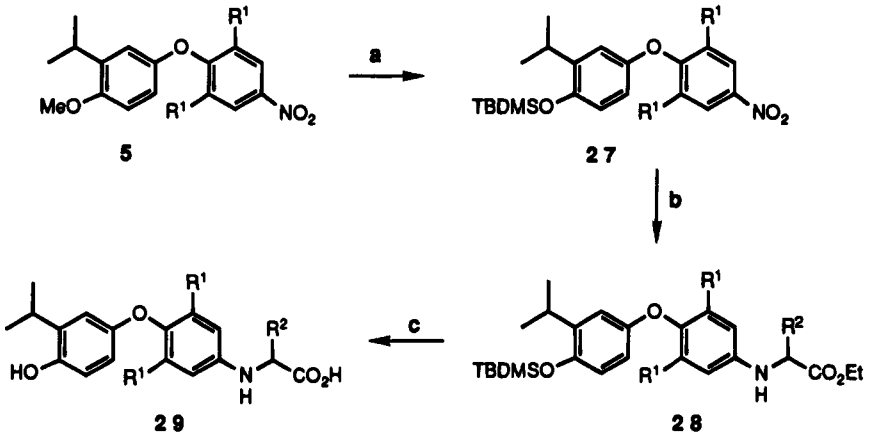
Table 2. 3′-(Arylmethyl)oxamic Acid Derivatives



no.	R^1	R^2	R^3	X	formula[a]	mp (°C)	nuclear IC_{50} (nM)[b]	membrane IC_{50} (μM)[b]
21a	Cl	F	OH	O	$C_{21}H_{12}Cl_2FNO_6$	196 dec	0.37 ± 0.08	>5
25a	Cl	F	OH	H_2	$C_{21}H_{14}Cl_2FNO_5$	180 dec	0.68 ± 0.11	3
21b	Cl	Cl	OH	O	$C_{21}H_{12}Cl_3NO_6$	199 dec	52 ± 7	ND[c]
22a	Cl	Cl	OH	H, OH	$C_{21}H_{14}Cl_3NO_6$[d]	155 dec	1.5 ± 0.8	ND
25b	Cl	Cl	OH	H_2	$C_{21}H_{14}Cl_3NO_5$	185 dec	0.27 ± 0.05	>5
21c	Me	Cl	OH	O	$C_{23}H_{18}ClNO_6$	188 dec	3.3 ± 1.2	ND
25c	Me	Cl	OH	H_2	$C_{23}H_{20}ClNO_5$	155 dec	0.43 ± 0.18	>5
21d	Me	F	OH	O	$C_{23}H_{18}FNO_6$	164 dec	2.5 ± 2.1	ND
22b	Me	F	OH	H, OH	$C_{23}H_{20}FNO_6$[d]	147–149	0.8 ± 0.3	>5
23a	Me	F	OEt	H, OH	$C_{25}H_{24}FNO_6$	115–118	0.16 ± 0.06	>5
23b	Me	F	OEt	H, OH[e]	$C_{25}H_{24}FNO_6$	150–152	0.14 ± 0.02	ND
23c	Me	F	OEt	H, OH[e]	$C_{25}H_{24}FNO_6$	147–150	0.23 ± 0.05	ND
26					$C_{26}H_{26}FNO_6$	155–156	34 ± 8	ND

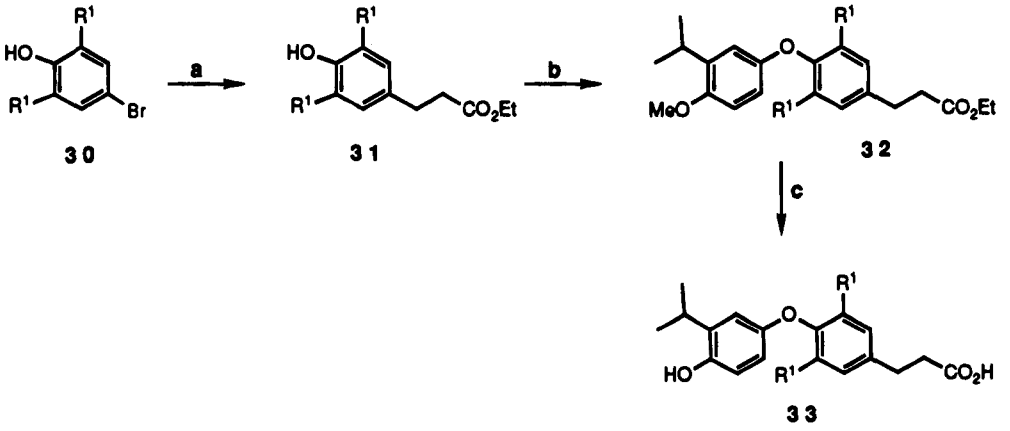
[a] All compounds had satisfactory C, H, and N elemental analyses unless noted otherwise and exhibited IR and NMR spectra consistent with the structure. [b] The IC_{50} value is the concentration of compound which inhibits 50% of bound [^{125}I]L-T_3 and represents the mean ± the standard error (SE) of two or more assays using six to eight concentrations of compound/assay. Values lacking SE are from single assays using six to eight concentrations of compound. For details, see the Experimental Section. [c] ND = not determined. [d] Compound did not pass elemental analysis. See the Experimental Section. [e] Compound **23b** is the (+)-isomer of **23a**; compound **23c** is the (−)-isomer.

Scheme 3. (Arylamino)acetic Acid Derivatives[a]



[a] (a) (1) BBr_3, (2) TBDMSCl; (b) (1) H_2, Pt/C (2) $BrCH(R^2)CO_2Et$; (c) (1) Bu_4NF, (2) NaOH.

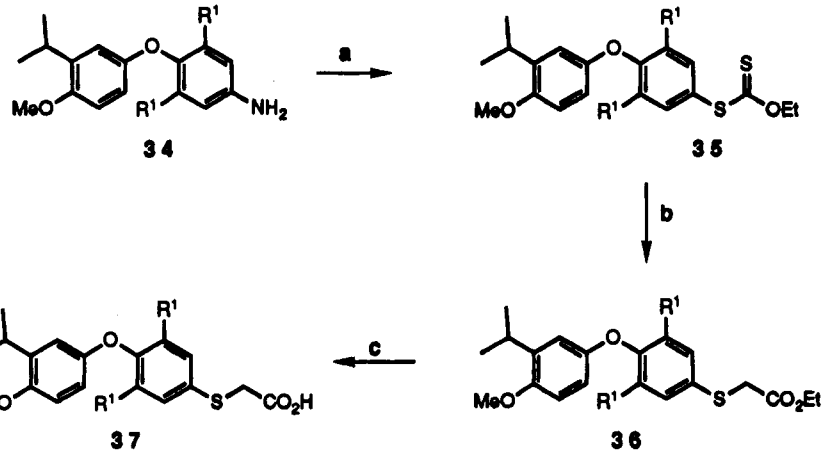
Scheme 4. Arylpropionic Acid Derivatives[a]



[a] (a) (1) Ethyl acrylate, Heck reaction, (2) H_2, Pd–C; (b) **4**, Cu, Et_3N; (c) BBr_3.

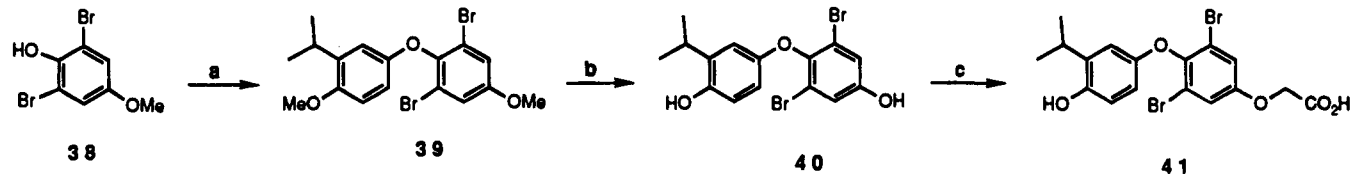
than L-T_3 (**1a**) at the nuclear receptor. Like L-T_3 analogs, replacement of the 3′-iodo or -bromo group with isopropyl (e.g., **1c**) retained good potency. Also, consistent with the classical structure–activity profile, analogs with 3,5-dihalo substituents (**7b**, **7c**, and **7d**) demonstrated excellent binding potency. However, unexpectedly, the analog with a 3,5-dimethyl substituent (**7f**) was also extremely potent and even the 3,5-unsubstituted compound (**7a**) had an IC_{50} of **48** nM. These findings are contrary to those elucidated from

Scheme 5. Arylthioacetic Acid Derivatives[a]



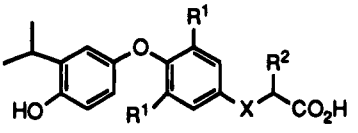
[a] (a) (1) HONO, (2) KS_2COEt; (b) (1) KOH, (2) $BrCH_2CO_2Et$; (c) BBr_3.

Scheme 6. (Aryloxy)acetic Acid Derivatives[a]



[a] (a) 4, Cu, Et_3N; (b) BBr_3, (c) (1) $BrCH_2CO_2Et$, Cs_2CO_3, (2) NaOH.

Table 3. (Arylamino)-, (Arylthio)-, and (Aryloxy)acetic Acid and Arylpropionic Acid Derivatives



no.	X	R^1	R^2	formula[a]	mp (°C)	nuclear IC_{50} (nM)[b]	membrane IC_{50} (μM)[b]
29a	NH	I	H	$C_{17}H_{17}I_2NO_4$	188–190	0.31 ± 0.05	0.7
29b	NH	Me	H	$C_{19}H_{23}NO_4$	140–155	12 ± 3	>5
29c	NH	Cl	H	$C_{17}H_{17}Cl_2NO_4$	181–185	1.1 ± 0.1	>5
29d	NH	Cl	Me	$C_{18}H_{19}Cl_2NO_4$	70–77	48 ± 19	ND[c]
29e	NH	Cl	CH_2Ph	$C_{24}H_{24}BrCl_2NO_4$		58 ± 4	ND
29f	NH	Me	Me	$C_{20}H_{25}NO_4$	144–154	550 ± 350	ND
29g	NH	Me	CH_2Ph	$C_{26}H_{29}NO_4$	125–130	400 ± 140	ND
33a	CH_2	Br	H	$C_{18}H_{18}Br_2O_4$		0.11 ± 0.06	>5
33b	CH_2	Me	H	$C_{20}H_{24}O_4$	187–189	>5000	ND
37a	S	Br	H	$C_{17}H_{16}Br_2O_4S$		1.5 ± 0.3	>5
37b	S	Me	H	$C_{19}H_{22}O_4S$		3.5 ± 3	>5
41	O	Br	H	$C_{17}H_{16}Br_2O_5$		0.10 ± 0.01	>5

[a] All compounds had satisfactory C, N, and H elemental analyses unless noted otherwise and exhibited IR and NMR spectra consistent with the structure. [b] The IC_{50} value is the concentration of compound which inhibits 50% of bound [^{125}I]L-T_3 and represents the mean ± the standard error (SE) of two or more assays using six to eight concentrations of compound/assay. Values lacking SE are from single assays using six to eight concentrations of compound. For details, see the Experimental Section. [c] ND = not determined.

previously prepared classical analogs of L-T_3. For example, the 3,5-dimethyl analog of L-T_3 (**1b**)[21a] and the 3′-isopropyl 3,5-dimethyl analog **1d** were 2 orders of magnitude less active than L-T_3,[22] and the 3,5-unsubstituted analog of L-T_3 (**1e**) was 4 orders of magnitude less active.[20a] Further unprecedented results with this series were uncovered with ester derivatives **9a** and **9b** and primary amide analogs **8a** and **8c**, which maintained low nanomolar potency. The *N*-methyl oxamides **8b** and **7g** showed somewhat diminished potency. Finally, although the classical structure–activity relationships indicate that a free 4′-hydroxyl group is required for binding, the 4′-methoxy analog **10** produced an IC_{50} of 14 nM and the 4′-unsubstituted derivative **14** showed comparable activity with an IC_{50} of 8.0 nM. Overall, these results, although not proven, are consistent with the hypothesis that compounds in the oxamic acid series either bind to the L-T_3 receptor differently from the endogenous hormone and classical L-T_3 analogs or that they have different access to the nuclear receptors.[11,15]

With the discovery that the oxamic acid series had a novel structure–activity profile, further exploration of this template was carried out at the 3′ position. This work was based on a report[7] indicating that L-T_3 analogs such as **2**, with 3′-arylmethyl substituents, had reduced cardiac side effects compared to L-T_3. A number of substituted benzoyl, α-hydroxybenzyl, and benzyl derivatives were prepared and found to have excellent nuclear binding potency (Table 2). As with the 3′-isopropyl series, it was found that replacement of 3,5-dihalo substituents (**21a**, **21b**, **22a**, **25a** **25b**) with

3,5-dimethyl groups (**21c**, **21d**, **22b**, **25c**) as well as conversion of the free carboxylic acid group to ethyl ester (**22b** vs **23a**) maintained excellent *in vitro* potency. Blockade of the 4'-hydroxy group (**26**) produced somewhat reduced activity. Whether the 3'-benzylic group was unsubstituted, hydroxyl or oxo did not seem critical for good activity. In the α-hydroxylbenzyl series, the potency was not enantioselective; both isomers (**23b** and **23c**) of racemic **23a** showed equivalent potency.

On the basis of the discovery that the oxamic acid group could replace the alanine group contained in L-T_3, further investigation at this site led to series of aminoacetic acid, thioacetic acid, and oxyacetic acid derivatives (Table 3). These derivatives again showed good potency. The 3,5-dimethyl analogs showed somewhat lower potency relative to iodo or chloro in the aminoacetic acid series (**29a** and **29c** vs **29b**), but in the thioacetic acid series the dimethyl and dibromo analogs had similar activity (**37a** and **37b**). In the aminoacetic acid series, α-methyl and α-benzyl analogs (**29d**, **39e**, **29f**, **39g**) showed reduced activity. Unlike these heteroatom-substituted acetic acid derivatives, the methylene analogs (**33a** and **33b**), related to the known thyromimetic triprop,[23] displayed a classical SAR, with the 3,5-dimethyl analog (**33b**) being several orders of magnitude less active than the 3,5-dibromo derivative (**33a**). Overall, the *in vitro* data suggest that compounds containing oxamic acids and related side chains have a significantly different structure–activity profile compared to classical L-T_3 analogs. These compounds offer the possibility for future studies to further probe the mechanism of receptor interactions.

In Vivo Results and Discussion

Compounds with the desired *in vitro* potency and selectivity were tested *in vivo* at 2.5 mg/kg po for cardiac side effects and then, if inactive, were tested for lipid lowering effects. Four compounds (**7d**, **7f**, **22b**, and **23a**) were noted to lower cholesterol without exhibiting cardiac effects, and in each instance the compounds failed to bind to the rat liver membrane receptor (Tables 1 and 2). Similarly, the cardiac-sparing, hypocholesterolemic thyromimetics reported in the literature, SK&F L-94901(**2**), TRIAC, D-T_3, and D-T_4, also bind less avidly than L-T_3 to the rat membrane receptor (Table 1). While in our study not all thyromimetic compounds devoid of membrane binding activity lacked cardiovascular effects at cholesterol-lowering doses, all of the cholesterol-lowering thyromimetics devoid of cardiovascular effects lacked membrane binding. The correlation between lack of cardiovacular effects and weak or the absence of membrane receptor binding, coupled with reports of potential biological effects of L-T_3 exerted directly as a consequence of membrane binding,[10] provides an empirical rationale for selecting thyromimetics devoid of membrane binding in order to identify cardiac-sparing, hypocholesterolemic thyromimetics.

The results for three of the more interesting compounds, **7d**, **7f**, and **23a**, are summarized in Table 4. When administered orally to rats, compounds **7d**, **7f**, and **23a** showed no effects on heart weight, atrial rate, or atrial tension at doses as high as 10 000 μg/kg for **7d** and **7b**, and 25 000 μg/kg for **23a**. In contrast, L-T_3 (**1a**) produced significant cardiac effects at doses as low as 25 μg/kg.

When tested orally in hypercholesterolemic rats, the onset of significant reduction in cholesterol with **7d**, **7f**, and **23a** was 12.5, 10, and 1 μg/kg, respectively. A dose–response study indicated ED_{50}'s of 50, 20, and 5 μg/kg, respectively. Thus **7d**, **7f**, and **23a** were considerably more potent in lowering cholesterol compared to L-T_3 (**1a**), which had an ED_{50} of 100 μg/kg. The lipid profile for these compounds indicates that the reduction occurs almost exclusively in the LDL fraction. Thus these compounds show more than 3 orders of magnitude separation of lipid lowering effects from cardiac effects in rats.

Table 4. *In Vivo* Profile of Oxamic Acid **7d**, **7f**, and **23a**

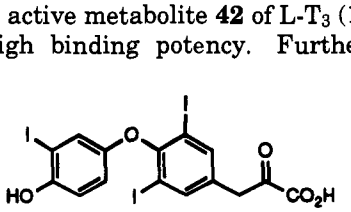
	hypercholesterolemic rats					normal cholesterol rats cardiac effects[d] no effect dose (μg/kg po)
	min eff dose[a]	ED_{50}[b]	% change[c]			
no.	(μg/kg po)	(μg/kg po)	LDL	HDL	dose (μg/kg po)	
7d	12.5	50				10 000
7f	10	20	−67	−5	25	10 000
23a	<1	5	−73	0	10	>25 000
1a	25	100	−65	−8	100	<25

[a] Minimum effective dose (min eff) is defined as the lowest dose which significantly ($p < 0.05$; Student's t distribution) lowered total cholesterol as compared to vehicle treated control rats ($n = 6$ rats/dose). [b] ED_{50} is defined as the dose at which total serum cholesterol is lowered by 50% compared to values from vehicle treated controls and is interpolated graphically from a plot of percent inhibition vs compound dose using a minimum of five different doses ($n = 6$ rats/dose). [c] The percent change in the serum LDL and HDL fractions was calculated by dividing the mean values for each lipid fraction by that obtained from vehicle treated control rats ($n = 6$ rats/group). [d] The no effect dose was the highest dose which did not significantly ($p < 0.10$; Student's t distribution) modify the heart wt/body wt ratio, atrial rate, or atrial tension compared to values of vehicle-treated control rats ($n = 6$ rats/dose).

To date, we cannot account for the mechanism responsible for the cardiac sparing hypocholesterolemic activity of **23a**, but this selectivity is clearly not a consequence of any differences in nuclear receptor affinity for **23a** between rat liver and cardiac myocyte nuclear L-T_3 receptors.[29] However, in cell culture studies, **23a** is orders of magnitude less potent in displacing [^{125}I]L-T_3 from the nuclei of intact cardiac myocytes than from the nuclei of intact human hepatocytes.[29] This suggests that, like D-T_4[6] and **2**,[7] **23a** exhibits a preferential access to nuclei of intact liver cells as compared to nuclei of intact cardiac myocytes.

Conclusion

Among the thyromimetic compounds described above, those containing the oxamic acid chain, which is reminiscent of an active metabolite **42** of L-T_3 (**1**),[24] provide especially high binding potency. Furthermore, the



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unprecedented SAR for this series, which allows the replacement of halogens with methyl groups, offers the possibility for good potency *in vivo*. The excellent selectivity of these oxamic acid derivatives provides the opportunity for these compounds to serve as especially effective lipid lowering agents without producing undesired cardiovascular side effects.

Experimental Section

Proton NMR spectra were determined on a Brucker AM-300 spectrometer with Me_4Si as the internal standard. Infrared spectra were recorded on a Nicolet 5SXFT spectrophotometer. Optical rotations were measured with a JASCO DIP370 polarimeter. Melting points were taken on a Thomas-Hoover Unimelt melting point apparatus and are uncorrected. Mass spectra were recorded on a Hewlett-Packard GCMS 5985 spectrometer. Flash chromatography was performed with silica gel (Bodman 230-400 mesh). All compounds were prepared by methods analogous to those described below. Intermediate products were used directly without further purification.

Bis(3-isopropyl-4-methoxyphenyl)iodonium Tetrafluoroborate (4). Fuming nitric acid (>90%), 12.4 mL, 16.7 g, 265 mmol) was added dropwise to 31.4 mL of acetic acid cooled in a dry ice/CCl_4 bath. Iodine (11.3 g, 44.4 mmol) was added in one portion followed by dropwise addition of trifluoroacetic acid (20.5 mL, 30.3 g, 266 mmol). The reaction mixture was stirred at room temperature until homogeneous and then sparged with N_2 to remove nitrogen oxides. The reaction mixture was evaporated, the residue was dissolved in 126 mL of acetic anhydride, and the reaction mixture was cooled in a dry ice/CCl_4 bath. 2-Isopropylanisole (40 g, 266 mmol) in 150 mL of acetic anhydride and 22.6 mL of trifluoroacetic acid was added dropwise. The reaction mixture was left to stand at 4 °C for 16 h and then evaporated. The residue was taken up in 150 mL of MeOH and treated with 150 mL of 10% aqueous $NaHSO_3$ and 1 L of 2 M $NaBF_4$. After the precipitate had aggregated, the supernatant was decanted. The residue was triturated with hexane, filtered, washed with hexane, and dried at room temperature in vacuo to afford 4 (39.0 g, 76.1 mmol, 85%): mp 146–148 °C; ^{1}H NMR (DMSO-d_6) δ 1.1 (d, 6H, J = 6.8 Hz), 3.2 (heptet, 1H, J = 6.8 Hz), 3.8 (s, 6H), 7.0 (d, 1H, J = 8.7 Hz), 8.0 (dd, 1H, J = 8.7, 1.9 Hz), 8.1 (d, 1H, J = 1.9 Hz).

2',6'-Dimethyl-3-isopropyl-4-methoxy-4'-nitrodiphenyl Ether (5f). To compound 4 (116.5 g, 228 mmol) and copper bronze (19.3 g, 303 mmol) in 300 mL of CH_2Cl_2 at 0 °C was added dropwise a solution of 2,6-dimethyl-4-nitrophenol (**3f**, 25.4 g, 152 mmol) and triethylamine (16.9 g, 167 mmol) in 200 mL of CH_2Cl_2. The reaction mixture was stirred in the dark for 5 d and then filtered through Celite. The filtrate was evaporated, and the residue was purified by column chromatography (silica gel, 97:3 hexane/ethyl acetate) to give **5f** (38.2 g, 121 mmol, 79%): ^{1}H NMR ($CDCl_3$) δ 1.1 (d, 6H, J = 6.9 Hz), 2.2 (s, 6H), 3.3 (heptet, 1H, J = 6.9 Hz), 3.7 (s, 3H), 6.3 (dd, 1H, J = 8.7, 3.1 Hz), 6.6 (d, 1H, J = 8.7 Hz), 6.7 (d, 1H, J = 3.1 Hz), 8.0 (s, 2H).

Methyl *N*-[3,5-Dimethyl-4-(4'-methoxy-3'-isopropylphenoxy)phenyl]oxamate (6f). Compound **5f** (6.0 g, 19.0 mmol) and 10% Pd/C (600 mg) in 200 mL of EtOH were hydrogenated at 3 atm at room temperature. After hydrogen uptake had ceased, the reaction mixture was filtered through Celite, and the filtrate was evaporated to yield **5f** (5.6 g), used directly without purification.

A solution of **5f** (5.6 g, 19.0 mmol) and dimethyl oxalate (37.5 g, 318 mmol) were stirred at 120 °C for 4 h. The reaction mixture was evaporated, and the residue was purified by chromatography (silica gel, gradient: 95:5→90:10 toluene/ethyl acetate) to give **6f** (6.4 g, 17.2 mol, 85%): ^{1}H NMR ($DCCl_3$) δ 1.1 (d, 6H, J = 6.9 Hz), 2.1 (s, 6H), 3.2 (heptet, 1H, J = 6.9 Hz), 3.7 (s, 3H), 4.0 (s, 3H), 6.3 (dd, 1H, J = 8.7, 3.1 Hz), 6.6 (d, 1H, J = 8.7 Hz), 6.7 (d, 1H, J = 3.1 Hz), 7.3 (s, 2H), 8.7 (s, 1H). Anal. ($C_{21}H_{25}NO_5$) C, H, N.

***N*-[3,5-Dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)phenyl]oxamic Acid (7f).** To **6f** (10.0 g, 26.9 mmol) in 150 mL of CH_2Cl_2 cooled in a dry ice/acetone bath was added 54 mL of 1 M boron tribromide dropwise. The reaction mixture was stirred overnight at room temperature and poured onto ice, and the layers were separated. The aqueous portion was extracted with 2 × 50 mL of ethyl acetate. The combined organic portions were dried ($MgSO_4$), filtered, and evaporated to give the crude phenolic carboxylic acid. To the crude acid in 100 mL of DMF at 0 °C was added cesium carbonate (9.15 g, 28.1 mmol) and dimethyl sulfate (3.55 g, 28.1 mmol). The reaction mixture was stirred overnight at room temperature, poured into 500 mL of ethyl acetate, and washed with 6 × 100 mL of brine. The organic portion was dried ($MgSO_4$), filtered, and evaporated to give an oil, which was purified by chromatography (silica gel, gradient: 90:10→75:25 toluene/ethyl acetate) to give the phenolic methyl ester (5.53 g, 15.5 mmol, 57%), mp 190–193 °C, used directly in the next reaction.

To the above ester (8.70 g, 24.3 mmol) in 125 mL of methanol was added 51 mL of 1.0 N NaOH. The reaction was refluxed 30 min and evaporated. The residue in 250 mL of water was extracted with 2 × 150 mL of diethyl ether. The aqueous portion was cooled to 0 °C and acidified to pH 1 with 12 N HCl. The precipitate was collected by filtration, dissolved in 150 mL of ethyl acetate, dried ($mgSO_4$), filtered, and evaporated. The residue was crystallized from toluene to give **7b** (6.78 g, 19.7 mmol, 81%): mp 183–185 °C; ^{1}H NMR (CD_3OD) δ 1.1 (d, 6H, J = 6.9 Hz), 2.1 (s, 6H), 3.2 (heptet, 1H, J = 6.9 Hz), 6.3 (dd, 1H, J = 8.7, 3.1 Hz), 6.6 (m, 2H), 7.4 (s, 2H). Anal. ($C_{19}H_{21}NO_5$) C, H, N.

***N*-[3,5-Dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)phenyl]-*N*-methyloxamic acid (7g).** To 3,5-dimethyl-4-(3'-isopropyl-4'-methoxyphenoxy)aniline (2.75 g, 9.00 mmol) and diisopropylethylamine (1.28 g, 1.73 mL, 9.94 mmol) in 30 mL of THF at 0 °C was added ethyl chloroformate (1.08 g, 0.95 mL, 9.94 mmol) dropwise. After stirring for 18 h at room temperature the reaction mixture was evaporated. The residue was dissolved in 100 mL of ethyl acetate and washed with 50 mL of water. The organic layer was dried (Na_2SO_4), filtered, and evaporated to give an oil, which was purified by flash column chromatography (silica gel, 9:1 hexane/ethyl acetate) to afford ethyl *N*-[3,5-dimethyl-4-(3'-isopropyl-4'-methoxyphenoxy)phenyl]carbamate as an oil (3.06 g, 8.56 mmol, 95%): ^{1}H NMR ($CDCl_3$) δ 1.0 (d, 6H, J = 7 Hz), 1.2 (t, 3H, J = 7 Hz), 2.0 (s, 6H), 3.3 (heptet, 1H, J = 7), 3.7 (s, 3H), 4.2 (q, 2H, J = 7), 6.3 (dd, 1H, J = 8.7, 3.1 Hz), 6.6 (d, 1H, J = 8.7 Hz), 6.7 (d, 1H, J = 3.1 Hz), 7.1 (s, 2H).

To lithium aluminum hydride (650 mg, 17.2 mmol) in 100 mL of THF at 0 °C was added dropwise the above carbamate (3.06 g, 8.56 mmol) in 20 mL of THF. The reaction mixture was refluxed for 3 h, cooled to 0 °C, and treated sequentially with 0.65 mL of water, 0.65 mL of 15% NaOH, and 1.95 mL of water. The precipitate was filtered off and washed with 20 mL of THF. The combined filtrate was concentrated, and the residue was purified by flash column chromatography (silica gel, 95:5 toluene/ethyl acetate) to give *N*-methyl 3,5-dimethyl-4-(3'-isopropyl-4'-methoxyphenoxy)aniline (1.75 g, 5.85 mmol, 68%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.2 (d, 6H, J = 7 Hz) 2.1 (s, 6H), 2.8 (s, 3H), 3.3 (heptet, 1H, J = 7 Hz), 3.8 (s, 3H), 6.4 (m, 3H), 6.7 (d, 1H, J = 8.7 Hz), 6.8 (d, 1H, J = 3.1 Hz).

The above amine (1.75 g, 5.85 mmol) was converted by the procedure described for the synthesis of **7f** to give **7g** (60 mg, 0.17 mmol, 3%): mp 140–156 °C; ^{1}H NMR (DMSO-d_6) δ 1.1 (d, 6H, J = 6.9 Hz), 2.0 (s, 6H), 3.2 (heptet, 1H, J = 6.9 Hz), 3.7 (br s, 3H), 6.2 (m, 1H), 6.6 (d, 1H, J = 8.7 Hz), 6.8 (d, 1H, J = 3.1 Hz), 7.0 (s, 1H), 7.1 (s, 1H), 9.0 (s, 1H). Anal. ($C_{20}H_{23}NO_5$), C, H, N.

***N*-[3,5-Dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)phenyl]oxamide (8a).** *N*-[3,5-Dibromo-4-(4'-hydroxy-3'-isopropylphenoxy)phenyl]oxamic acid (**7c**) (500 mg, 1.06 mmol), prepared analogously as described for **7f**, and 2-ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline (290 mg, 1.17 mmol) in 20 mL of DMF were stirred for 20 min at room temperature. The solution was saturated with ammonia gas, sealed, and stirred for 3 d at room temperature. The reaction mixture was evaporated, and the residue was triturated with diethyl ether to give a solid, which was dissolved in 50 mL of ethyl acetate and washed with 25 mL of 2 N HCl. The organic portion was dried ($MgSO_4$), filtered, and evaporated to give the crude product. Purification using flash column chromatography (silica gel, 1:1 toluene/ethyl acetate) gave **8a** (130 mg, 0.28 mmol, 25%): mp 84–90 °C; ^{1}H NMR (DMSO-d_6) δ 1.1 (d, 6H, J = 6.9 Hz), 3.2 (heptet, 1H, J = 6.9 Hz), 6.3 (dd, 1H, J = 8.7, 3.1 Hz), 6.6 (m, 2H), 8.1 (br s, 1H), 8.3 (s, 2 H), 8.4 (br s, 1H), 9.0 (s, 1H), 10.9 (br s, 1H). Anal. ($C_{17}H_{16}Br_2N_2O_4$) H, N; C: calcd, 43.25; found, 44.48.

Ethyl *N*-[3,5-Dimethyl-4-(4'-hydroxy-3'-isopropylphenoxy)phenyl]oxamate (9a). To a solution of **7f** (200 mg, 0.58

mmol) and cesium carbonate (190 mg, 0.58 mmol) in 5 mL of DMF at 0 °C was added 80 μL (90 mg, 610 μmol) of diethyl sulfate. The reaction mixture was stirred for 18 h at room temperature, diluted with 100 mL of ethyl acetate, and washed with 25 mL of water and 5 × 25 mL of brine. The organic portion was dried ($MgSO_4$), filtered, and evaporated to give the crude product, which was purified by chromatography (silica gel, gradient: 9:1 → 8:2 toluene/ethyl acetate) to yield **9a** (173 mg, 0.47 mmol, 80%): mp 154–161 °C; ^{1}H NMR (CD_3OD) δ 1.1 (d, 6H, J = 6.9 Hz), 1.4 (t, 3H, J = 7.1 Hz), 2.1 (s, 6H), 3.2 (heptet, 1H, J = 6.9 Hz), 4.5 (9, 2H, J = 7.1 Hz), 6.2 (dd, 1H, J = 3.1), 8.7 (Hz), 6.6 (m, 2H), 7.4 (s, 2H). Anal. ($C_{21}H_{25}NO_5$) C, H, N.

***N*-[3,5-Dimethyl-4-(3′-isopropyl-4′-methoxyphenoxy)-phenyl]oxamic Acid (10).** To **6** (R^1 = Me) (2.02 g, 5.44 mmol) in 50 mL of methanol was added 60 mL of 1 N NaOH. The reaction mixture was refluxed for 30 min and evaporated. The residue in 100 mL of water was washed with 50 mL of diethyl ether. The aqueous portion was acidified with 6 N HCl. The resulting precipitate was filtered, washed with water, dissolved in 100 mL of ethyl acetate, dried ($MgSO_4$), filtered, and evaporated to give the crude product. Crystallization from toluene yielded **10** (1.35 g, 3.78 mmol, 69%): mp 179–183 °C; ^{1}H NMR (CD_3OD) δ 1.1. (d, 6 H, J = 6.9 Hz), 2.1 (s, 6H), 3.2 (heptet, 1H, J = 6.9 Hz), 3.7 (s, 3H), 6.4 (dd, 1H, J = 8.7, 3.1 Hz), 6.7 (d, 1H, J = 8.7 Hz), 6.8 (d, 1H, J = 3.1 Hz), 7.5 (s, 2H). Anal. ($C_{20}H_{23}NO_5$) C, H, N.

Methyl *N*-[3,5-Dimethyl-4-(3′-isopropylphenoxy)phenyl]oxamate (14). A mixture of 3-isopropylphenol (**11**) (1.56 g, 11.5 mmol), 4-chloro-3,5-dimethylnitrobenzene (**12**) (2.12 g, 11.4 mmol), and potassium carbonate (1.74 g, 12.6 mmol) in 25 mL of DMSO was heated at 125 °C for 18 h. The reaction mixture was cooled to room temperature, diluted with 250 mL of ethyl acetate, and washed with 150 mL of water and 5 × 100 mL of brine. The organic portion was dried ($MgSO_4$), filtered, and evaporated to give an oil, which was purified by flash column chromatography (silica gel, 98:2 hexane/ethyl acetate) to afford 3,5-dimethyl-4-(3′-isopropylphenoxy)nitrobenzene (**13**) (2.21 g, 7.75 mmol, 67%): ^{1}H NMR ($CDCl_3$) δ 1.2 (d, 6H, J = 7 Hz), 2.2 (s, 3H), 2.8 (heptet, 1H, J = 7 Hz), 6.5 (dd, 1H, J = 8.0, 2.3 Hz), 6.7 (t, 1H, J = 2.3 Hz), 6.8 (dd, 1H, J = 8.0, 2.3 Hz), 7.2 (t, 1H, J = 8.0 Hz), 8.0 (s, 2H).

The above nitro compound (5.21 g, 18.3 mmol) was converted by the procedure described in the synthesis of **7f** to give **14** (881 mg, 2.58 mmol, 14% overall yield): mp 105–108 °C; ^{1}H NMR (CD_3OD) δ 1.1 (d, 6H, J = 6.9 Hz), 2.1 (s, 6H), 3.2 (heptet, 1H, J = 6.9 Hz), 3.7 (s, 3H), 6.4 (dd, 1H, J = 8.0, 2.3 Hz), 6.7 (t, 1H, J = 2.3 Hz), 6.8 (dd, 1H, J = 8.0, 2.3 Hz), 7.2 (t, 1H, J = 8.0 Hz), 7.5 (s, 2H). Anal. ($C_{20}H_{23}NO_4$) C, H, N.

3,5-Dimethyl-4-(4′-methoxyphenoxy)nitrobenzene (17, R^1 = Me). A mixture of bis(4-methoxyphenyl)iodonium tetrafluoroborate (26.0 g, 61.0 mmol), 2,6-dimethyl-4-nitrophenol (10.7 g, 64.0 mmol), copper powder (0.5 g), and triethylamine (10 mL, 72.0 mmol) in methylene chloride (250 mL) was stirred for 6 d at room temperature. The mixture was filtered, and the filtrate was washed with 1 N HCl (100 mL) and then water (100 mL). The organic solution was dried ($CaSO_4$) and the solvent evaporated. The residue was triturated with ethanol and the solid collected by filtration to give **17** (R^1 = Me) (12.6 g, 46 mmol, 76%) as a tan solid, mp 117–120 °C. A 100 mg sample recrystallized from methanol gave white needles: mp 121–122 °C; ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 6H), 3.77 (s, 3H), 6.67 (dd, 2H, J = 2, 7 Hz), 6.81 (dd, 2H, J = 2, 7 Hz), 8.00 (s, 2H).

[5-(2,6-Dimethyl-4-nitrophenoxy)-2-methoxyphenyl](4-fluorophenyl)methanone (18, R^1 = CH_3, R^2 = F). To a solution of **17** (4.5 g, 16.5 mmol) and *p*-fluorobenzoyl chloride (5.0 mL, 6.63 g, 41.8 mmol) in methylene chloride (100 mL) was added titanium tetrachloride (9.0 mL, 15.8 g, 83.0 mmol). The reaction mixture was stirred for 8 d at room temperature, poured into ice water (300 mL), and stirred 2 h. The organic layer was separated, washed with 5% sodium carbonate (100 mL) and then water (100 mL), and dried ($CaSO_4$). The solution was evaporated and the residue triturated with ether–petroleum ether. The solid was collected by filtration to give **18** (R^1 = Me, R^2 = F) (4.2 g, 10.6 mmol, 64%) as a tan solid, mp 160–165 °C. A 100 mg sample recrystallized from methanol gave white crystals, mp 167–169 °C. Anal. ($C_{22}H_{18}FNO_5$) C, H, N.

[5-(4-Amino-2,6-dimethylphenoxy)-2-hydroxyphenyl](4-fluorophenyl)methanone (19, R^1 = Me, R^2 = F). To a solution of **18** (R^1 = Me, R^2 = F) (2.1 g, 5.3 mmol) in methylene chloride (70 mL) was added a 1.0 M solution of boron trichloride in methylene chloride (16 mL, 16.0 mmol). The reaction mixture was stirred for 3 h at room temperature, poured into ice water (200 mL), and stirred 0.5 h. The organic layer was separated, washed with water (100 mL), and dried ($CaSO_4$). The solvent was evaporated to give [5-(4-nitro-2,6-dimethylphenoxy)-2-hydroxyphenyl](4-fluorophenyl)methanone (1.9 g, 5.0 mmol, 94%) as a yellow solid, mp 145–147 °C. A 100 mg sample recrystallized from ethanol gave yellow crystals, mp 148–150 °C. Anal. ($C_{21}H_{16}FNO_5$) C, H, N.

A solution of the above phenol (2.77 g, 7.3 mmol) in ethyl acetate (200 mL) containing 10% palladium on carbon (200 mL) was hydrogenated at 3 atm of pressure on a Parr apparatus. When hydrogen uptake was complete (1.5 h), the catalyst was filtered off and the filtrate was evaporated to give 2.5 g (7.1 mmol, 97.5%) of **19** (R^1 = Me, R^2 = F) as a yellow solid. This material was used in the next step without further purification.

Ethyl *N*-[4-3-(4-Fluorobenzoyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl]oxamate (20, R^1 = Me, R^2 = F). A mixture of **19** (R^1 = Me, R^2 = F) (700 mg, 2.0 mmol) and diethyl oxalate (5 mL) was heated 1.0 h at 100 °C and then at reflux for 5 min. The excess diethyl oxalate was evaporated with a nitrogen stream. The residual oil was triturated with petroleum ether and filtered to give 900 mg (2.0 mmol, 100%) of **20** (R^1 = Me, R^2 = F) as a yellow solid. A 100 mg sample was recrystallized from hexane to give yellow crystals, mp 151-155 °C. Anal. ($C_{24}H_{22}FNO_6$) C, H, N.

***N*-[4-[3-(4-Fluorobenzoyl)-4-hydroxyphenoxy]-3,5-dichlorophenyl]oxamic Acid (21a).** A mixture of **19** (R^1 = Cl, R^2 = F) (130 mg, 0.33 mmol), prepared by methods used to obtain **19** (R^1 = Me, R^2 = F), and diethyl oxalate (3 mL) was heated at 100 °C for 2 h. The excess diethyl oxalate dissolved in ethanol (5 mL) and 1 N sodium hydroxide (3 mL) was added. A solid precipitated. The mixture was refluxed for 2 h. The ethanol was evaporated, and the residue was diluted with H_2O (50 mL), acidified with 1 N HCl, and extracted with ether (50 mL). The ether layer was washed with water (50 mL), dried ($CaSO_4$), and evaporated. The residue was dissolved in methylene chloride. The solvent was evaporated to give 100 mg of a tan solid (0.216 mmol, 65.5%), mp 194–195 °C. The solid was triturated with methylene chloride and filtered to give **21a** (70 mg, 0.15 mmol, 46%) as a tan solid: mp 195–196 °C; ^{1}H NMR (DMSO-d_6) δ 6.73 (d, 1H, J = 3 Hz), 6.94 (s, 2H), 7.33 (t, 2H, J = 9 Hz), 7.76 (dd, 2H, J = 5, 9 Hz), 8.04 (s, 2H), 9.92 (s, 1H), 11.06 (s, 1H). Anal. ($C_{21}H_{12}Cl_2FNO_6 \cdot 0.5H_2O$) C, H, N.

***N*-[4-[3-[(4-Fluorophenyl)hydroxymethyl]-4-hydroxyphenoxy]-3,5-dimethylphenyl]-oxamic Acid (22b).** To a solution of **21d** (300 mg, 0.71 mmol), prepared in a manner analogous to **21**, in methanol (10 mL) was added sodium borohydride (130 mg, 3.5 mmol). The reaction mixture was stirred for 2 h at room temperature. The solution was then diluted with water, acidified with 1 N HCl, and extracted with ether. The ether layer was washed with brine, dried ($CaSO_4$), and evaporated. The residue was dissolved in methylene chloride, filtered, and evaporated. The solid was triturated with boiling petroleum ether (containing some methylene chloride) and filtered. The filtrate was evaporated and the residue recrystallized from methylene chloride–petroleum ether to give **22b** (28 mg, 9.5%): white solid; mp 142–147 °C; ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 6H), 4.59 (s, 1H), 6.30 (d, 1H), J = 3 Hz), 6.52 (dd, 1H, J = 3, 9 Hz), 6.75 (d, 1H, J = 9 Hz), 6.99 (t, 1H, J = 9 Hz), 7.32 (s, 2H), 7.90 (s, 1H), 8.85 (s, 1H). Anal. ($C_{23}H_{20}FNO_6$) N; C: calcd, 64.94; found, 66.41; H: calcd, 4.74; found, 5.24.

Ethyl [[4-[3-(4-Fluoro-α-hydroxybenzyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl]amino]oxoacetate (23a). To a solution of **20** (R_1 = Me, R_2 = F) (1.25 g, **3**.55 mmol) in 4:1 ethanol/ethyl acetate (120 mL) was added nickel catalyst (10 mL, water and ethanol washed). The mixture was hydrogenated at 3 atm on a Parr apparatus. When hydrogen uptake

was complete (1.0 h), the catalyst was filtered off, and the filtrate was evaporated to give **23a** (1.15 g) as a white solid, mp 141–145 °C. The solid was triturated with ether and filtered to give **23a** (570 mg, 1.26 mmol, 35%) as a white solid: mp 147–149 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (t, 3H, J = 7 Hz), 2.08 (s, 6H), 2.90 (bs, 1H), 4.42 (q, 2H, J = 7 Hz), 5.90 (s, 1H), 6.36 (d, 1H, J = 3 Hz), 6.54 (dd, 1H, J = 3, 9 Hz), 6.77 (d, 1H, J = 9 Hz), 7.04 (t, 2H, J = 9 Hz), 7.25 (s, 1H), 7.36 (m, 4H), 8.77 (s, 1H). Anal. ($C_{25}H_{24}FNO_6$) C, H, N.

Resolution of **23a** was accomplished by HPLC on a Chiralcel OD (Daicel) column (cellulose *p*-methylbenzoate coated on silica gel), eluting with 80:20 hexane/ethanol to give **23b** (retention time 115 min), α_D = +23.1° (c = 0.64 in acetonitrile), mp 150–152 °C, and **23c** (retention time 150 min), α_D = −21.7° (c = 0.47 acetonitrile), mp 147–150 °C.

4-[3-(4-Chlorobenzyl)-4-methoxyphenoxy]-3,5-dimethylnitrobenzene (24) (R^1 = Me, R^2 = Cl). To a solution of **18** (R^1 = Me, R^2 = Cl) (1.9 g, 4.6 mmol), prepared as described for **18** (R^1 = Me, R^2 = F), and trifluoroacetic acid (3 mL) in methylene chloride (5 mL) was added triethylsilane (1.83 g, 15.8 mmol). After stirring overnight at room temperature, the reaction mixture was treated with water (100 mL) and extracted with ether (200 mL). The ether layer was washed with 5% sodium carbonate (50 mL) and water (50 mL), dried ($CaSO_4$), and evaporated to give **24**, R^1 = Me, R^2 = Cl (1.8 g, 98%), as a yellow solid, mp 119–125 °C. A 100 mg sample recrystallized from petroleum ether gave white crystals: mp 133–134 °C; ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 6H), 3.75 (s, 3H), 3.87 (s, 2H), 6.44 (dd, 1H, J = 3, 9 Hz), 6.57 (d, 1H, J = 3 Hz), 6.71 (d, 1H, J = 9 Hz), 7.09 (d, 2H, J = 7 Hz), 7.23 (d, 2H, J = 8 Hz), 7.98 (s, 2H). Anal. ($C_{22}H_{20}ClNO_4$) C, H, N.

4-[3-(4-Chlorobenzyl)-4-hydroxyphenoxy]-3,5-dimethylnitrobenzene. To a solution of **24** (R^1 = Me, R^2 = Cl) (1.75 g, 4.4 mmol) in methylene chloride (100 mL) was added 1.0 N boron tribromide/methylene chloride solution (13 mL, 13.0 mmol). The dark red solution was stirred overnight at room temperature, poured into ice water (300 mL), and stirred for 3 h. The organic layer was separated, washed with 5% sodium carbonate (200 mL) and water (200 mL), dried ($CaSO_4$), and evaporated. Chromatography (silica gel, 2:1 hexane/methylene chloride, 1:1 hexane/methylene chloride) gave the intermediate phenol (520 mg, 31%) as a brown solid, mp 136–148 °C. A 50 mg sample recrystallized from hexane gave yellow crystals, mp 143–152 °C. Anal. ($C_{21}H_{18}ClNO_4$) C, H, N.

***N*-[4-[3-(4-Chlorobenzyl)-4-hydroxyphenoxy]-3,5-dimethyl]oxamic Acid (25c) (R^1 = Me, R^2 = Cl).** A slurry of Raney nickel (7 mL) was washed with water (3 × 25 mL) and ethanol (3 × 25 mL) and added to a solution of the above phenol (960 mg, 2.5 mmol) in ethanol (100 mL). The mixture was hydrogenated at 3 atm. The catalyst was filtered off and the solvent evaporated. The residue was dissolved in ether (100 mL), washed with brine (50 mL), dried ($CaSO_4$), and evaporated. The residue was dissolved in methylene chloride, and a tan solid (280 mg, mp 184–187 °C) was collected by filtration. The filtrate was chromatographed (silica gel, 2:1 hexane/ether, 1:1 hexane/ether) to give more solid (222 mg), mp 181–185 °C. The total yield of intermediate amine was 502 mg (57%).

A 50 mg sample was recrystallized from methylene chloride–petroleum ether to give white crystals, mp 188–190 °C. Anal. ($C_{21}H_{20}ClNO_2$) C, H, N.

By a reaction of the above amine analogous to the preparation of **20** (R^1 = Me, R^2 = F), there was obtained the corresponding intermediate oxamate ester (445 mg, 81.5%), mp 176–180 °C. Recrystallization (methylene chloride–petroleum ether) of 50 mg gave white crystals, mp 180–181 °C.

A solution of the above oxamate (395 mg, 0.87 mmol) and 1 N NaOH (1.0 mL, 1.0 mmol) in ethanol (25 mL) was refluxed for 1 h. The solvent was evaporated and the residue dissolved in water and washed with ether. The aqueous layer was acidified with 1 N HCl and extracted with ether. The ether layer was washed with brine, dried ($CaSO_4$), and evaporated to give **25c** (R^1 = Me, R^2 = Cl) (280 mg, 76%): mp 155–158 °C; ^{1}H NMR (DMSO-d_6) δ 1.99 (s, 6H), 3.78 (s, 2H), 6.32 (dd, 1H, J = 3, 9 Hz), 6.53 (d, 1H, J = 3 Hz), 6.68 (d, 1H, J = 9 Hz), 7.18 (d, 1H, J = 9 Hz), 7.29 (d, 2H, J = 9 Hz), 7.59 (s, 2H), 9.08 (s, 1H), 10.57 (s, 1H).

A sample was recrystallized (methylene chloride–petroleum ether) to give ivory crystals, mp 159–161 °C. Anal. ($C_{23}H_{20}ClNO_5$) C, H, N.

Ethyl *N*-[4-[3-[(4-Fluorophenyl)hydroxymethyl]-4-methoxyphenoxy]-3,5-dimethylphenyl]oxamate (26) (R^1 = Me, R^2 = F). A solution of **18** (R^1 = Me, R^2 = F) (1.1 g, 2.8 mmol) in 1:1 ethyl acetate/ethanol (200 mL) was hydrogenated on a Parr apparatus at 3 atm using 10% palladium on carbon (0.4 g) as catalyst. When hydrogen uptake was complete (0.5 h), the catalyst was filtered off and the solvent evaporated. The residue was dissolved in ether (150 mL) and filtered and the solvent evaporated to give the intermediate aniline derivative as a yellow oil (1.0 g, 2.75 mmol, 98%). The material was used without further purification.

A mixture of the above amine (1.05 g, 2.9 mmol) and diethyl oxalate (10 mL) was heated at 100 °C for 2.25 h. The excess diethyl oxalate was evaporated with a stream of nitrogen. The residual oil was chromatographed (silica gel 3:1 hexane/ethyl acetate) to give the intermediate oxamate (1.01 g, 75%) as an orange oil: ^{1}H NMR ($CDCl_3$) δ 1.43 (t, 3H, J = 7 Hz), 2.14 (s, 6H), 3.67 (s, 3H), 4.42 (q, 2H, J = 7 Hz), 6.78 (d, 1H, J = 3 Hz), 6.83 (d, 1H, J = 3 Hz), 6.87 (d, 1H, J = 9 Hz), 7.10 (t, 2H, 9 = Hz), 7.37 (s, 2H), 7.82 (dd, 2H, J = 5, 9 Hz), 8.80 (s, 1H). The material was used in the next step without further purification.

A slurry of Raney nickel (7 mL) was washed with H_2O (2 × 25 mL) and then ethanol (3 × 25 mL) and added to a solution of the above oxamate (930 mg, 2.0 mmol) in ethanol (50 mL). The mixture was hydrogenated at 3 atm at 40 °C. The catalyst was filtered off and the solvent evaporated. The residue was dissolved in ether (100 mL), washed with water (50 mL), dried ($CaSO_4$), and evaporated. Chromatography (silica gel, 3:1 hexane/ethyl acetate) gave **26** (500 mg, 53.5%) as a tan solid: mp 148–151 °C; ^{1}H NMR ($CDCl_3$) 1.42 (t, 3H, J = 7 Hz), 2.08 (s, 6H), 2.99 (d, 1H, J = 5 Hz), 3.71 (s, 3H), 4.40 (q, 2H, J = 7 Hz), 5.90 (d, 1H, J = 5 Hz), 6.50 (dd, 1H, J = 3, 9 Hz), 6.69 (s, 1H), 6.73 (t, 1H, J = 3Hz), 6.97 (t, 3H, J = 9 Hz), 7.31–7.26 (m, 2H), 7.34 (s, 2H), 8.77 (s, 1H).

A 150 mg sample recrystallized from ether–petroleum ether gave 120 mg of white crystals, mp 155–156 °C. Anal. ($C_{26}H_{26}FNO_6$) C, H, N.

***N*-[3,5-Dichloro-4-(4′-hydroxy-3′-isopropylphenoxy)-phenyl]acetic Acid (29c).** To **5** (R^1 = Cl) (10.6 g, 29.8 mmol) in 100 mL of methylene chloride cooled in a dry ice/acetone bath was added 60 mL of 1 M boron tribromide in methylene chloride. The reaction mixture was stirred for 18 h at room temperature, poured onto 50 g of ice, and extracted with ethyl acetate (2 × 150 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated to yield 3,5-dichloro-4-(4′-hydroxy-3′-isopropylphenoxy)nitrobenzene (11.5 g), used without further purification: ^{1}H NMR ($CDCl_3$) δ 1.2 (d, 6H, J = 7 Hz), 3.3 (heptet, 1H, J = 7 Hz), 6.5 (dd, 1H, J = 8.7, 3.1 Hz), 6.7 (d, 1H, J = 8.7 Hz), 6.8 (d, 1H, J = 3.1 Hz), 8.3 (s, 2H).

The above phenol (10.2 g, 29.8 mmol), *tert*-butyldimethylsilyl chloride (6.75 g, 44.8 mmol), imidazole (4.06 g, 59.6 mmol), and 4-(dimethylamino)pyridine (2 mg) in 10 mL of DMF were stirred 18 h at room temperature. The reaction mixture was poured into 150 mL of diethyl ether and washed with 6 × 100 mL of water. The organic layer was dried ($MgSO_4$), filtered, and evaporated to afford the silylated intermediate **27** (R^1 = Cl), used without further purification: ^{1}H NMR ($CDCl_3$) δ 0.2 (s, 6H), 1.1 (s, 9H), 1.2 (d, 6H, J = 7 Hz), 3.3 (heptet 1H, J = 7 Hz), 6.3 (dd, 1H, J = 8.7, 3.1 Hz), 6.7 (d, 1H, J = 8.7 Hz), 6.8 (d, 1H, J = 3.1 Hz), 8.3 (s, 2H).

A mixture of **27** (R^1 = Cl) (11.5 g, 25.3 mmol) and 10% Pd/C (1.15 g) in 200 mL of ethanol were hydrogenated at 3 atm at room temperature. The catalyst was removed by filtration through Celite, and the filtrate was evaporated to yield the corresponding aniline derivative, used directly.

The above aniline, ethyl bromoacetate (4.64 g, 27.8 mmol), and diisopropylethylamine (3.43 g, 26.6 mmol) in 50 mL of DMF were stirred at 140 °C for 18 h. The reaction mixture was evaporated. The residue was taken up in 150 mL of ethyl acetate and washed with 2 × 100 mL of water. The organic

portion was dried ($MgSO_4$), filtered, and evaporated to give the crude anilinoacetate, which was purified by column chromatography (silica gel, gradient: 85:15 → 80:20 hexane/ethyl acetate) to give **28** (R^1 = Cl) (6.69 g, 13.1 mmol, 51%): ^1H NMR ($CDCl_3$) δ 0.2 (s, 6H), 1,0 (s, 9H), 1.2 (d, 6H, J = 7 Hz), 1.3 (t, **3H**, J = 7 Hz), 3.3 (heptet, 1H, J = 7 Hz), 3.9 (d, 2H, J = 6.9 Hz), 4.3 (q, 2H, J = 7 Hz), 4.4 (t, 1H, 7 Hz), 6.4 (dd, 1H, J = 8.7, 3.1 Hz), 6.6 (s, 2H), 6.7 (d, 1H, J = 8.7 Hz), 6.9 (d, 1 H, J = 3.1 Hz).

A solution of **28** (R^1 = Cl) (6.69 g, 13.1 mmol) and 26 mL of 1.0 M tetrabutylammonium fluoride in THF was stirred 18 h at room temperature. The reaction mixture was evaporated, and the residue was taken up in 150 mL of ethyl acetate and washed with 50 mL of saturated aqueous ammonium chloride. The organic portion was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (silica gel, 95:5 toluene/ethyl acetate) to produce the intermediate desilylated phenol (4.00 g, 10.0 mmol, 76%): ^1H NMR ($CDCl_3$) δ 1.2 (d, 6H, J = 7 Hz), 1.3 (t, 3H, J = 7 Hz), 3.2 (heptet, 1H, J = 7 Hz), 3.9 (d, 2H, J = Hz), 4.3 (q, 2H, J = 7 Hz), 4.4 (t, 1H, J = Hz), 4.5 (s, 1H), 6.4 (dd, 1H, J = Hz), 6.6 (s, 2H), 6.6 (d, 1H, J = Hz), 6.8 (d, 1H, J = Hz).

The above ester (4.00 g, 10 mmol) and 30 mL of 1.0 N aqueous NaOH in 100 mL of methanol were refluxed 30 min. The reaction mixture was evaporated. The residue in 150 mL of water was extracted with 2 × 100 mL of diethyl ether. The aqueous phase was acidified with acetic acid and extracted with 3 × 100 mL of ethyl acetate. The combined organic portions were dried ($MgSO_4$), filtered, and evaporated. The residue was crystallized from toluene to yield **29c** (3.02 g, 8.16 mmol, 81%): mp 181−185 °C; ^1H NMR ($CDCl_3$) δ 1.1 (d, 6H, J = 6.9 Hz), 3.2 (heptet, 1H, J = 6.9 Hz), 3.9 (s, 2H), 6.3 (dd, 1H, J = 8.7, 3.1 Hz), 6.6 (d, 1H, J = 8.7 Hz), 6.6 (d, 1H, J = 3.1 Hz), 6.7 (s, 2H). Anal. ($C_{17}H_{17}Cl_2NO_4$) C, H, N.

Ethyl (3,5-Dibromo-4-hydroxyphenyl)propionate (31a). The compound **30a** was brominated following a procedure described for a similar compound.[18] Thus, to (4-hydroxyphenyl)propionic acid (**30a**) (25 g, 150 mmol) in 750 mL of glacial acetic acid at room temperature was added bromine (68.8 g, 430 mmol) in 25 mL of acetic acid dropwise over 25 min. After the mixture was stirred overnight at room temperature, TLC (15:4:1 hexane/ethyl acetate/acetic acid) indicated only a trace of starting acid remained. The reaction mixture was evaporated and dried overnight under vacuum to give crude (3,5-dibromo-4-hydroxyphenyl)propionic acid (47.2 g, 97%), used directly without purification.

The above acid (47.2 g, 146 mmol) and *p*-toluenesulfonic acid monohydrate (2.8 g) in 300 mL of ethanol were refluxed for 5 h, cooled to room temperature, and evaporated. The residue in 600 mL of ethyl acetate was washed with 2 × 300 mL of saturated aqueous $NaHCO_3$. The organic layer was washed with brine (200 mL), dried ($MgSO_4$), and evaporated to give 53 g of crude product, which was purified by flash column chromatography (hexane/ethyl acetate 9:1→4:1 gradient) to give **31a** (50.3 g, 97%): ^1H NMR ($CDCl_3$) δ 1.21 (t, 3H, J = 7 Hz), 2.68 (m, 4H), 4.18 (q, 2H, J = 7 Hz), 6.13 (bs, 1H), 7.34 (s, 2H).

Ethyl [3,5-Dibromo-4-(3-isopropyl-4-methoxyphenoxy)phenyl]propionate (32, R^1 = Br). To a suspension of **4** (17.0 g, 33.2 mmol) and copper bronze (4.33 g, 68.2 mmol) in 30 mL of methylene chloride at room temperature were added dropwise **31a** (10.0 g, 28.4 mmol) and triethylamine (3.02 g, 29.8 mmol) in 25 mL of methylene chloride. After stirring for 8 h at room temperature, the reaction was filtered through Celite. The filtrate in 120 mL of ethyl acetate was washed with 2 N HCl (2 × 200 mL) and brine (200 mL). The organic portion was dried ($MgSO_4$) and evaporated to give an oil (26.1 g). Purification by flash column chromatography (hexane/ethyl acetate 95:5→8:2 gradient) gave **32** (R^1 = Br) (14.4 g, 92%): ^1H NMR ($CDCl_3$) δ 1.17 (d, 6H, J = 6 Hz), 1.21 (t, 3H, J = 7 Hz), 2.62 (t, 2H, J = 6 Hz), 2.90 (t, 2H, J = 6 Hz), 3.27 (heptet, 1H, J = 6 Hz), 3.78 (s, 3H), 4.14 (q, 2H, J = 7 Hz), 6.39 (dd, 1H, J = 1, 9 Hz), 6.68 (d, 1H, J = 9 Hz), 6.81 (d, 1H, J = 1 Hz), 7.45 (s, 2H); IR (KBr) 2962, 1736, 1456, 1176 cm^{-1}.

[3,5-Dibromo-4-(4′-hydroxy-3′-isopropylphenoxy)phenyl]propionic Acid (33a). To **32** (R^1 = Br) (500 mg, 1.00 mmol) in 15 mL of methylene chloride at −78 °C was added 20 mL of boron tribromide (1.0 M in methylene chloride). The reaction mixture was stirred for 15 min at −78 °C and then stirred at room temperature for 3 days. The reaction mixture was cautiously poured into 60 mL of 10% aqueous $NaHCO_3$ and extracted with ethyl acetate (2 × 10 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to give 556 mg of crude product, which was purified by flash column chromatogaphy (800:200;7 hexane/ethyl acetate/acetic acid) to give **33a** (479 mg, 100%): ^1H NMR ($CDCl_3$) δ 1.22 (d, 6H, J = 7 Hz), 2.78 (m, 4H), 3.18 (heptet, 1H, J = 7 Hz), 6.53 (dd, 1H, J = 2, 10 Hz), 6.66 (d, 1H, J = 10 Hz), 7.48 (s, 2H), 8.88 (bs, 2 H); IR (KBr) 3563, 3028, 2968, 2931, 1703, 1453, 1249, 1141 cm^{-1}. Anal. ($C_{18}H_{18}Br_2O_4$) C, H.

[3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylphenoxy)phenyl]thioacetic Acid (37b). To 3,5-dimethyl-4-(3′-isopropyl-4′-methoxyphenoxy)aniline (2.72 g, 9.51 mmol) in 25 mL of ethanol at 0 °C was added 15 mL of 12 N aqueous HCl followed by sodium nitrite (720 mg, 10.4 mmol). The reaction mixture was stirred at 0 °C for 30 min and then added portionwise over 10 min to a solution of potassium ethyl xanthate (3.05 g, 19.0 mmol) in 5 mL of water. The reaction mixture was stirred at 45 °C for 18 h, poured into 100 mL of water, and extracted with 2 × 100 mL of ethyl acetate. The combined organic portions were washed with brine (50 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (silica gel, 97:3 hexane/ethyl acetate) to give the xanthate **35** (R^1 = Me) (1.30 g, 3.33 mmol, 34%): ^1H NMR ($CDCl_3$) δ 1.2 (d, 6H, J = 7 Hz), 1.4 (t, 3H, J = 7 Hz), 2.1 (s, 6H), 3.3 (heptet, 1H, J = 7 Hz), 3.7 (s, 3H), 4.7 (q, 2H, J = 7 Hz), 6.3 (dd, 1H, J = Hz), 6.6 (d, 1H, J = Hz), 6.7 (d, 1H, J = Hz), 7.1 (s, 2H).

A solution of **35** (R^1 = Me) (2.23 g, 5.68 mmol) in 25 mL of ethanol and KOH (455 mg, 8.1 mmol) in 5 mL of water was refluxed for 3 h. The reaction mixture was evaporated, taken up in 100 mL of water, acidified to pH 1 with 12 N HCl, and extracted with 2 × 100 mL of diethyl ether. The combined organic portions were dried ($MgSO_4$), filtered, and evaporated to yield 3,5-dimethyl-4-(3′-isopropyl-4′-methoxyphenoxy)thiophenol (1.25 g, 4.13 mmol, 72%), used immediately without further purification.

A solution of the above thiophenol compound (1.25 g, 4.13 mmol), ethyl bromoacetate (790 mg, 4.73 mmol), and diisopropylethylamine (610 mg, 4.72 mmol) in 20 mL of DMF was stirred at 140 °C for 16 h. The reaction mixture was evaporated. The residue was taken up in 100 mL of ethyl acetate and washed with 2 × 50 mL of water. The organic layer was dried ($MgSO_4$), filtered, and evaporated to give an oil which was purified by column chromatography (silica gel gradient 95:5→90:10 hexane/ethyl acetate) to afford ethyl [3,5-dimethyl-4-(3′-isopropyl-4′-methoxyphenoxy)phenyl]thioacetate (230 mg, 0.59 mmol, 14%), used directly in the following reaction: ^1H NMR ($CDCl_3$) δ 1.1 (d, 6H, J = 7 Hz), 1.2 (t, 3H, J = 7 Hz), 2.1 (s, 6H), 3.3 (heptet, 1H, J = 7 Hz), 3.6 (s, 2H), 2.7 (s, 3H), 4.1 (q, 2H, J = 7 Hz), 6.3 (dd, 1H, J = Hz), 6.6 (d, 1H, J = Hz), 6.7 (d, 1H, J = Hz), 7.1 (s, 2H).

To the above compound (230 mg, 0.59 mmol) in 20 mL of methylene chloride cooled in a dry ice/acetone bath was added dropwise 1.2 mL of 1.0 M boron tribromide in methylene chloride. The reaction mixture was stirred for 16 h at room temperature, poured onto 50 g of ice, and extracted with 2 × 50 mL of ethyl acetate. The combined organic portions were dried ($MgSO_4$), filtered, and evaporated to give the crude phenolic acid as an oil.

In order to simplify purification, this compound was converted to the corresponding methyl ester as follows. The above crude acid, cesium carbonate (193 mg, 0.59 mmol), and dimethyl sulfate (80 mg, 0.63 mmol) in 5 mL of DMF were stirred for 16 h at room temperature. The reaction mixture was diluted with 50 mL of ethyl acetate and washed with 2 × 25 mL of water and 2 × 25 mL of brine. The organic portion was dried ($MgSO_4$), filtered, and evaporated to give an oil which was purified by column chromatography (silica gel, gradient: 80:20→70:30 hexane/ethyl acetate) to produce methyl [3,5-dimethyl-4-(4′-hydroxy-3′-isopropylphenoxy)phenyl]-thioacetate (120 mg, 0.33 mmol) as an oil: ^1H NMR ($CDCl_3$) δ 1.1 (d, 6H, J = 7 Hz), 2.0 (s, 6H), 3.1 (heptet, 1H, J = 7 Hz),

3.6 (s, 2H), 3.7 (s, 3H), 4.9 (s, 1H), 6.2 (dd, 1H, J = 8.7, 3.1 Hz), 6.5 (d, 1H, J = 8.7 Hz), 6.6 (d, 1H, J = 3.1 Hz), 7.1 (s, 2H).

A solution of the above ester (120 mg, 0.33 mmol) in 20 mL of methanol and 7.0 mL of 0.10 N NaOH was refluxed 30 min and evaporated. The residue in 25 mL of water was washed with 25 mL of ether. The aqueous layer was acidified with 12 N HCl and extracted with 2 × 25 mL of ethyl acetate. The combined ethyl acetate portions were dried ($MgSO_4$), filtered, and evaporated to yield **37b** (90 mg, 0.26 mmol, 78%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.1 (d, 6H, J = 7 Hz), 2.0 (s, 6H), 3.2 (heptet, 1H), 3.7 (s, 2H), 6.2 (dd, 1H, J = 8.7, 3.1 Hz), 6.6 (d, 1H, J = 8.7 Hz), 6.7 (d, 1H, J = 3.1 Hz), 7.2 (s, 2H). Anal. ($C_{19}H_{22}O_4S$), C, H.

3,5-Dibromo-4-(3′-isopropyl-4′-methoxyphenoxy)anisole (39). To 2,6-dibromo-4-methoxyphenol (**38**) (1.51 g, 53.7 mmol) and triethylamine (1.57 g, 26.8 mmol) in 25 mL of methylene chloride was added copper bronze (1.7 g, 26.8 mmol) and iodonium salt **4** (8.23 g, 16.1 mmol). The reaction mixture was stirred for 1.5 h at room temperature and filtered through Celite. The filtrate was diluted with 50 mL of ethyl acetate and washed with 2.5 mL of 2 N HCl. The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography (95:5 hexane/ethyl acetate) to give **39** (1.78 g, 77%).

3,5-Dibromo-4-(4′-hydroxy-3′-isopropylphenoxy)phenol (40). To **39** (1.29 g, 2.99 mmol) in 75 mL of methylene chloride at −78 °C was added 60.5 mL of boron tribromide (1.0 M in methylene chloride). The reaction mixture was stirred for 10 min at −78 °C and for 40 h at room temperature. The reaction mixture was washed with water (2 × 100 mL), dried ($MgSO_4$), and evaporated to give crude product (1.4 g). Purification using flash column chromatography (hexane/ethyl acetate 4:1→3:2 gradient) gave **40** (981 mg, 82%): ^{1}H NMR ($CDCl_3$) δ 1.19 (d, 6H, J = 7 Hz), 3.25 (heptet, 1H, J = 7 Hz), 6.51 (m, 1H), 6.68 (m, 2H), 7.11 (s, 2H).

[3,5-Dibromo-4-(4′-hydroxy-3′-isopropylphenoxy)phenoxy]acetic Acid (41). To cesium carbonate (810 mg, 2.49 mmol) and **39** (200 mg, 0.497 mmol) in 10 mL of DMF was added ethyl bromoacetate (83.1 mg, 0.497 mmol). The reaction mixture was stirred for 30 min at room temperature, poured into 40 mL of cold 1 N HCl, and extracted with ethyl acetate (2 × 100 mL). The combined organic portions were dried ($MgSO_4$) and evaporated to yield 3.4 mg of crude product, which was purified using flash column chromatography (4:1 hexane/ethyl acetate) to yield the product (201 mg), used directly in the following reaction: ^{1}H NMR ($CDCl_3$) δ 1.22 (d, 6H, J = 7 Hz), 1.31 (5, 3H, J = 7 Hz), 3.17 (heptet, 1H, J = 7 Hz), 4.28 (q, 2H, J = 7 Hz), 4.63 (s, 2H), 6.34 (dd, 1H, J = 1, 10 Hz), 6.67 (s, 1H, J = 10 Hz), 6.78 (d, 1H, J = 1 Hz), 7.16 (s, 2H).

To the above ester (250 mg, 0.51 mmol) in 4 mL of methanol was added 2.6 mL of 1 N NaOH. The reaction mixture was stirred for 1 h at room temperature, acidified with 3 mL of 2 N HCl, and extracted with ethyl acetate (2 × 25 mL). The combined organic portions were dired ($MgSO_4$) and evaporated to give **41** (220 mg, 93%): ^{1}H NMR (CD_3OD) δ 1.1 (d, 6H, J = 7 Hz), 3.20 (heptet, 1H, J = 7 Hz), 4.63 (s, 2H), 6.29 (dd, 1H, J = 1,9 Hz), 6.61 (m, 2H), 7.24 (s, 2H); IR (KBr) 3508, 2963, 1735, 1457, 1215 cm^{-1}.

***In Vitro* Binding to the Hepatic L-T_3 Nuclear Receptor.** Rat liver nuclei were prepared from male Sprague–Dawley rats [Tac: N(SD)fBR] as described by Emmelot et al.[25] with minor modifications as described below and then further purified according to the method of Spindler et al.[26] To measure total binding, nuclei (300 μg of nuclear protein) were incubated with 0.3 nM [^{125}I]L-T_3 (1080 μCi/μg) for 50 min at 22 °C in a final volume of 1.0 mL of buffer A (20 mM Tris HCl, 1 mM $MgCl\cdot H_2O$, 0.1 mM dithiothreitol, 0.25 M sucrose, 2.0 mM EDTA, 56 mM NaCl, 5% glycerol; pH 7.2). Parallel incubations were conducted with tubes containing, in addition to the nuclear suspensions and radioactive L-T_3, either various concentrations of the test compounds or excess of unlabeled L-T_3 (3 μM). The latter was a measure of nonspecific binding. Following the incubation, the samples were chilled in an ice bath for 5 min and then centrifuged at 800g for 7 min at 4 °C. The pellet was washed by suspending in 2 mL of buffer B (Buffer A with 0.5% Triton X-100; pH 7.2) and mixing for 5 s. The tubes were then centrifuged at 800g for 7 min at 4 °C. The supernatant was aspirated off, and then the pellet was again washed and isolated as described above.

Radioactivity in the pellet was measured in an LKB 1282 γ counter. Specific binding was calculated as the difference between total binding (incubation in the presence of excess unlabeled L-T_3). The concentration of the test compounds corresponding to half-maximal inhibition (IC_{50}) of specific binding of [^{125}I]L-T_3 was determined from the reciprocal plot of specific binding versus concentration of test compounds.

***In Vitro* Binding to the Hepatic L-T_3 Plasma Membrane Receptor.** The plasma membranes were obtained as described by Ray[27] with only minor modifications. The specific binding to rat liver plasma membranes was performed according to the method of Pliam and Goldfine.[9] To measure total binding the reaction mixture containing 90 mg of membrane protein, 0.2 nM [^{125}I]L-T_3 (1080 μCi/μg), and Tris buffer (20 mM Tris HCl, 50 mM NaCl, 1 mM $MgCl_2\cdot H_2O$, 0.1 mM dithiothreitol, 0.25 M sucrose, 2.0 mM EDTA, and 5% glycerol; pH 7.2) were incubated at 23 °C for 30 min. To measure nonspecific binding, parallel incubations were conducted with tubes containing, in addition to the membrane suspension and radioactive L-T_3, either various concentrations of the test compounds or excess of unlabeled L-T_3 (6 μM). Following the incubations, the reaction mixtures were chilled in an ice bath and centrifuged at 1500g for 10 min at 4 °C. The pellet obtained was resuspended in 2 mL of bicarbonate solution (1 mM $NaHCO_3$, 0.5 mM $CaCl_2$; pH 7.5) by mixing with a Vortyex mixer for 5 s. The suspension was centrifuged at 1500g 10 min. The radioactivity within the pellet was determined using an LKB 1282 γ counter. Specific binding and IC_{50}'s were calculated as described above for the nuclear receptor assay.

***In Vivo* Cholesterol Lowering Activity.** Cholesterol lowering was determined as previously described[28] using euthyroid male Sprague–Dawley rats fed a hypercholesterolemic diet containing 1.5% cholesterol and 0.5% cholic acid for 2 weeks prior to and during the 7-day oral treatment with the test compounds.

Cardiovacular Activity. The heart weights and the spontaneous atrial rate and contractile force of the right and left atrium, respectively, were measured *in vitro* using hearts from euthyroid normal chow-fed Sprague Dawley male rats as previously described.[28] The test compounds were given orally for the 7 days preceding the day on which the measurements were made.

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