Synthetic and Structure/Activity Studies on Acid-Substituted 2-Arylphenols: Discovery of 2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]phenoxy]benzoic Acid, a High-Affinity Leukotriene B_4 Receptor Antagonist[1]

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Structural derivatives of LY255283 have been studied as receptor antagonists of leukotriene B_4. Substitution of the 2-hydroxyacetophenone subunit of **1** (LY255283) with a 2-arylphenol group provided entry into several new series that feature various mono- and diacidic core functionality. These new analogues, the subject of a broad structure–activity investigation, displayed significantly increased in vitro and in vivo activity as receptor antagonists of LTB_4. A series of diaryl ether carboxylic acids demonstrated especially interesting activity and led to the discovery of compound **43b**, 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]phenoxy]benzoic acid (LY293111), a 2-arylphenol-substituted diaryl ether carboxylic acid which displayed potent binding to human neutrophils (IC_{50} = 17 ± 4.6 nM) and guinea pig lung membranes (IC_{50} = 6.6 ± 0.71 nM), inhibition of LTB_4-induced expression of the CD11b/CD18 receptor on human neutrophils (IC_{50} = 3.3 ± 0.81 nM), and inhibition of LTB_4-induced contraction of guinea pig lung parenchyma (pK_B = 8.7 ± 0.16). In vivo, **43b** demonstrated potent activity in inhibiting LTB_4-induced airway obstruction in the guinea pig when dosed by the oral (ED_{50} = 0.40 mg/kg) or intravenous (ED_{50} = 0.014 mg/kg) routes. A specific LTB_4 receptor antagonist, **43b** had little effect on inhibiting contractions of guinea pig lung parenchyma induced by leukotriene D_4 (LTD_4), histamine, carbachol, or U46619. Compound **43b** has been chosen as a clinical candidate and is currently in phase I studies for a variety of inflammatory diseases.

The pharmacologic activity of leukotriene B_4 (LTB_4), a product derived from the action of 5-lipoxygenase on arachidonic acid, continues to generate intense research interest. LTB_4 is known to stimulate degranulation, aggregation, chemotaxis, and chemokinesis of polymorphonuclear leukocytes, as well as promote superoxide generation.[2] Such effects are known to be mediated through specific surface receptors associated with a number of inflammatory cells such as neutrophils[3,4] and lymphocytes.[5] Enhanced concentrations of LTB_4 have been observed in tissues of patients with several important diseases, including psoriasis,[6] inflammatory bowel disease,[7] rheumatoid arthritis,[8] bronchial asthma,[9] and adult respiratory distress syndrome (ARDS).[10] Hence, it seems likely that a potent antagonist of this eicosanoid would be a promising antiinflammatory agent.

A number of potent LTB_4 receptor antagonists (Chart 1)[11] have appeared since the disclosure of first-generation compounds LY255283 (**1**),[12] LY223982 (**2**),[13] LY210073 (**3**),[14] and SC-41930 (**4**).[15] Compound **4** has evolved into SC-53228 (**5**),[16] featuring *N*-methylamide as a replacement for the acetyl group, while entirely new classes of antagonists have emerged such as naphthalene-based RG 14893 (**6**)[17] and biphenylyl-substituted CP-105,696 (**7**).[18] Compound CGS 25019C (**8**) remains an exception to the general trend of lipophilic acids through the utilization of an aromatic amidine group.[19]

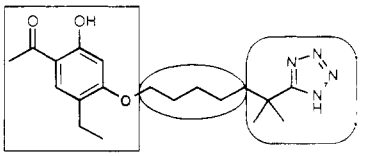

Figure 1. SAR domains for compound 1.

The most recent installment of our program involved the further modification of compound **1** with the goal of fashioning a potent, orally active LTB_4 receptor antagonist with clinical potential for the treatment of inflammation. An in vitro testing protocol was established to first evaluate both binding and functional activity of new compounds. Selected compounds exhibiting strong in vitro activity were then evaluated in vivo with a particular emphasis on oral dosing.

Compound **1** was divided into three regions (Figure 1). The western (lipophilic) region had already proven interesting due to the dissimilarity between the acetophenone substitution pattern of **1** compared to that of antagonist **4** and the more profound structural differences noted between **1** and **2**/**3**. The central (linker) region was believed to be essentially optimized based on the SAR previously conducted on compounds **1**[12] and **4**.[20]

Finally, we viewed the eastern (acid) region as a critical focal point due in part to the known presence of

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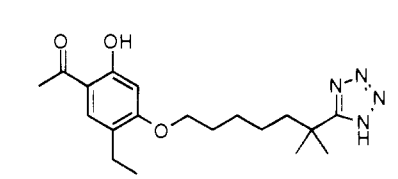
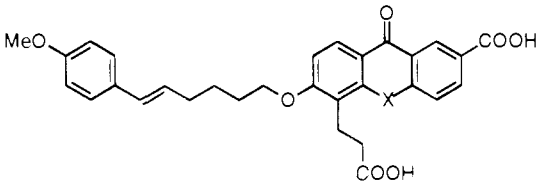
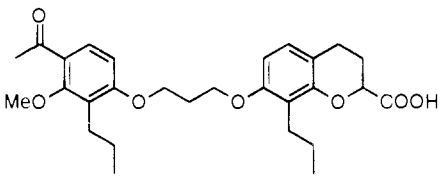
Chart 1



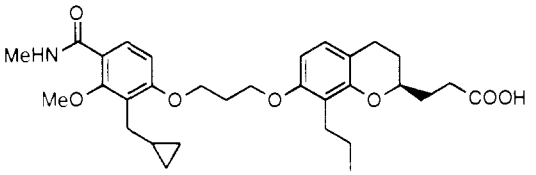
1



2 X = H,H
3 X = O



4



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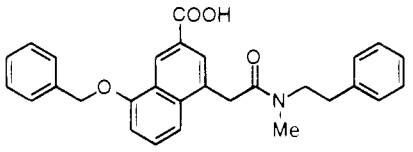

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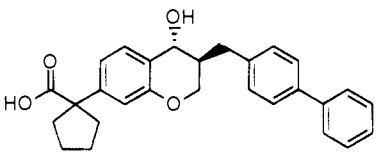

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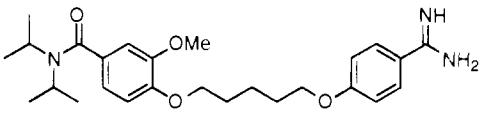


8

a secondary acid binding site first delineated by benzophenone antagonist **2**.

Chemistry

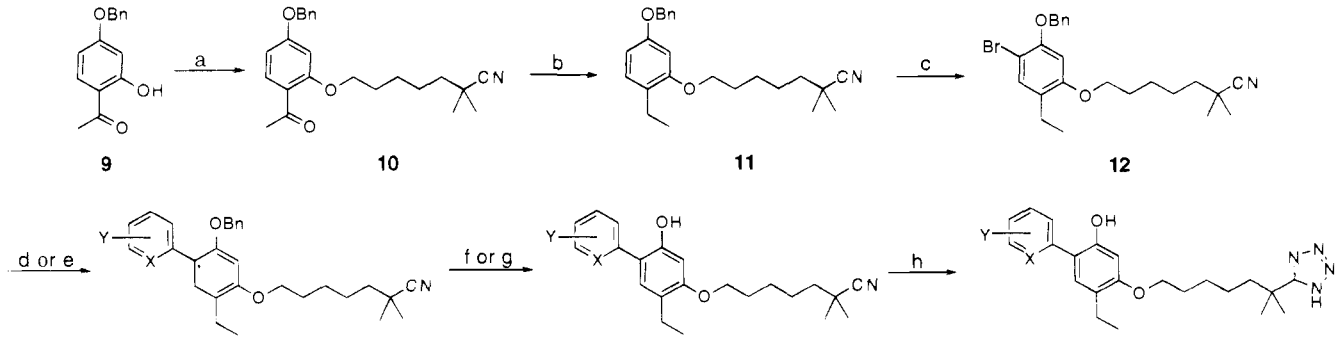
We thought it desirable to develop a synthetic plan that would allow sufficient flexibility with regard to substitutions in all three of the critical domains outlined by our SAR strategy. Toward this end, 4-(benzyloxy)-2-hydroxyacetophenone (**9**) was chosen as a suitable synthon with potential for selective elaboration within each domain. Many of the final products were prepared as sodium salts, which greatly enhanced their solubility in dilute sodium bicarbonate solution, the vehicle of choice for the assays used.

Preparation of the 2-arylphenol-substituted *gem*-dimethyltetrazole series **15a**–**k** began with appendage of the *gem*-dimethylnitrile side chain to **9** to provide compound **10** (Scheme 1). Full reduction of the keto group of **11** was accomplished using an acidic solution of triethylsilane in carbon tetrachloride.[21] Selective bromination of **11** with *N*-bromosuccinimide proceeded rapidly to give compound **12**. While aryl-substituted intermediates **13a**–**g**, **13i**, and **13k**,**l** were synthesized using the appropriate boronic acids under Suzuki coupling conditions,[22] compounds **13h** and **13j** were prepared via a palladium-catalyzed, zinc-mediated coupling using either 1-bromo-3-(trifluoromethyl)benzene or 2-bromopyridine.[23] Removal of the benzyl protecting group was accomplished by hydrogenolysis or, in the case of pyridine intermediate **13j**, boron tribromide-assisted ether cleavage. Utilization of tetrazole-forming conditions on nitriles **14a**–**k** provided final products **15a**–**k**. The order of deprotection and tetrazole formation may be reversed, as is demonstrated for the synthesis of 3-fluorophenyl analogue **17** (Scheme 2).

The general preparation of biphenylyl-substituted haloalkoxy intermediates **21a**–**d** and **22a**,**b**, which were stockpiled and conjoined to various acid units, is illustrated in Scheme 3. Appendage of chloroalkyl side chains to **9** provided compounds **18a**–**c**, which were then subjected to triethylsilane/trifluoroacetic acid-mediated reduction to produce **19a**–**c**, as described above. As with the *gem*-dimethyltetrazole series, bromination proved to be rapid and highly regiospecific. Bromides **20a**–**c**, which were submitted to the Suzuki palladium-catalyzed cross-coupling reaction with either phenylboronic acid or (4-fluorophenyl)boronic acid, gave intermediates **21a**–**d** with yields ranging from 77 to 87%. With the exception of small amounts of terminal olefin formation upon side chain alkylation, the haloalkoxy group remained intact through all of the transformations in Scheme 3. Compounds **21b**,**c** were further converted to iodides **22a**,**b**, which served as the key alkylation intermediates for a select group of acid units.

Preparation of the chromancarboxylic acid analogues **27b** and **28b** began with alkylation of known phenol **23**[15,20] with either aryl bromide **20a** or the 4-fluorophenyl-substituted intermediate **22a** (Scheme 4). Suzuki coupling of **24** with either phenylboronic acid or (4-fluorophenyl)boronic acid was then performed to provide compounds **25** and **26**, respectively. Hydrogenolysis and ester hydrolysis of **25** and **26** provided the final chroman acids **27b** and **28b**.

Scheme 1[a]



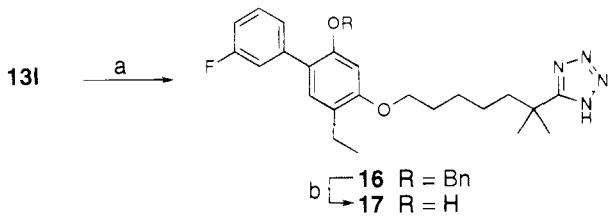
13a X = CH, Y = H
13b X = CH, Y = 4-Me
13c X = CH, Y = 3-Me
13d X = CH, Y = 2-Me
13e X = CH, Y = 4-MeO
13f X = CH, Y = 3-MeO
13g X = CH, Y = 4-NMe_2
13h X = CH, Y = 3-CF_3
13i X = CH, Y = 4-Cl
13j X = N, Y = H
13k X = CH, Y = 4-F
13l X = CH, Y = 3-F

14a X = CH, Y = H
14b X = CH, Y = 4-Me
14c X = CH, Y = 3-Me
14d X = CH, Y = 2-Me
14e X = CH, Y = 4-MeO
14f X = CH, Y = 3-MeO
14g X = CH, Y = 4-NMe_2
14h X = CH, Y = 3-CF_3
14i X = CH, Y = 4-Cl
14j X = N, Y = H
14k X = CH, Y = 4-F

15a X = CH, Y = H
15b X = CH, Y = 4-Me
15c X = CH, Y = 3-Me
15d X = CH, Y = 2-Me
15e X = CH, Y = 4-MeO
15f X = CH, Y = 3-MeO
15g X = CH, Y = 4-NMe_2
15h X = CH, Y = 3-CF_3
15i X = CH, Y = 4-Cl
15j X = N, Y = H
15k X = CH, Y = 4-F

[a] (a) 6-Cyano-1-chloro-6-methylheptane, K_2CO_3, KI, DMF; (b) Et_3SiH, trifluoroacetic acid, CCl_4; (c) NBS, CCl_4; (d) arylboronic acid, EtOH, benzene, aqueous Na_2CO_3, catalytic $Pd(PPh_3)_4$; (e) (1) *t*-BuLi, THF −78 °C, (2) $ZnCl_2$, (3) aryl halide; (f) H_2, Pd/C, EtOAc; (g) BBr_3, CH_2Cl_2; (h) NaN_3, diglyme, $Me_2N(CH_2)_2OH$·HCl, 135 °C.

Scheme 2[a]

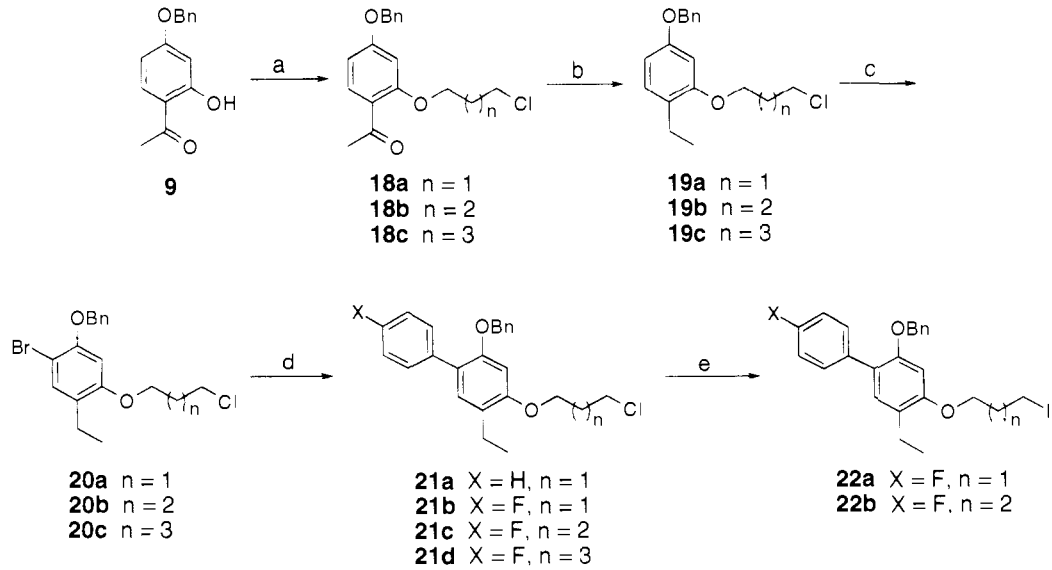


[a] (a) NaN_3, Et_3N–HCl, DMF; (b) H_2, 10% Pd/C, EtOH.

Construction of the xanthone analogues involved a concise strategy that we have previously reported.[14,24] Differential alkylation of diester **29**[14] with either **21a** or **22a**, followed by protecting group removal as described above, readily provided xanthone diacids **30b** and **31b** (Scheme 5). The xanthone monoester intermediate **34** was easily synthesized from commercially available 3-hydroxy-9-oxo-9*H*-xanthene (**32**) by treatment with triethyl orthoacrylate and pivalic acid in refluxing toluene to give lactal **33**, followed by acid-catalyzed ring opening (Scheme 6).[25] Alkylation with fragment **21a** or **21b**, followed by exhaustive protecting group removal, provided final products **35b** and **36b** in good yields.

The synthesis of the key diaryl ether acid antagonists is illustrated in Scheme 7. Generally, the sequence involved alkylation of 1,3-dimethoxybenzene (**37**) at the 2-position (compounds **38a–d**), pyridium hydrochloride-promoted demethylation (compounds **39a–d**), and reaction of the resulting diols with the appropriate aryl

Scheme 3[a]



18a n = 1
18b n = 2
18c n = 3

19a n = 1
19b n = 2
19c n = 3

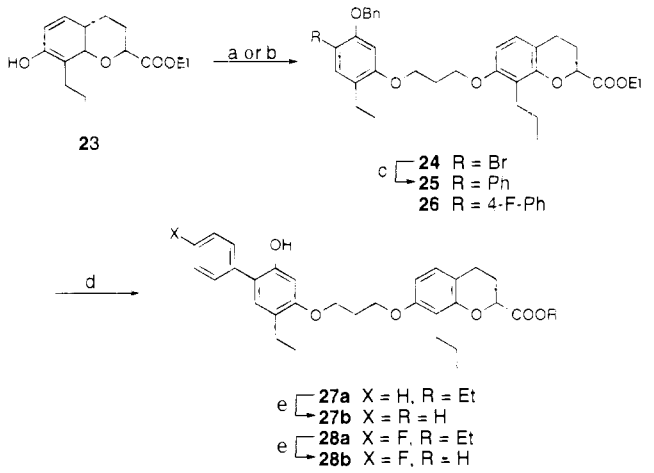
20a n = 1
20b n = 2
20c n = 3

21a X = H, n = 1
21b X = F, n = 1
21c X = F, n = 2
21d X = F, n = 3

22a X = F, n = 1
22b X = F, n = 2

[a] (a) $BrCH_2(CH_2)_nCH_2Cl$, K_2CO_3, 2-butanone, DMSO; (b) Et_3SiH, trifluoroacetic acid, CCl_4; (c) NBS, CCl_4; (d) phenylboronic acid or 4-fluorophenylboronic acid, EtOH, benzene, aqueous Na_2CO_3, $Pd(PPh_3)_4$(cat.); (e) NaI, 2-butanone.

Scheme 4[a]



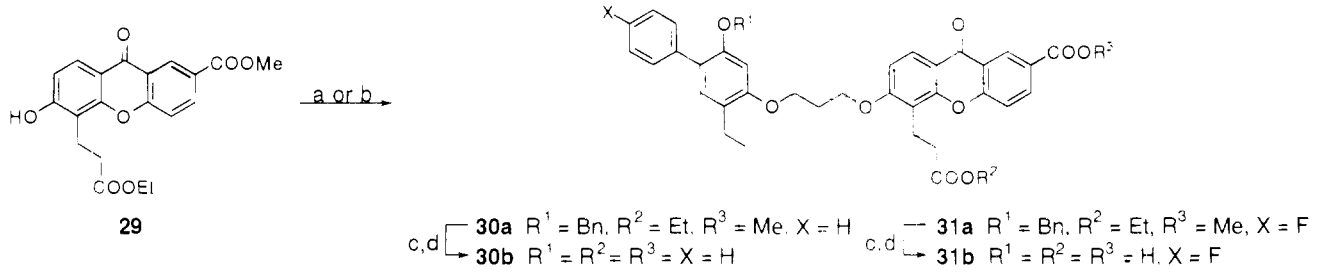
[a] (a) (1) **20a**, NaI, 2-butanone; (2) **23**, NaH, 18-crown-6, DMF; (b) **22a**, K_2CO_3, DMF; (c) phenylboronic acid, EtOH, benzene, aqueous Na_2CO_3, $Pd(PPh_3)_4$(cat.); (d) H_2, 10% Pd/C, EtOAc; (e) aqueous NaOH, dioxane.

halide **40** using the Ullmann ether synthesis (compounds **41a–h**).[14,26] Alkylation of the diaryl ether units with the appropriate 2-arylphenol-substituted haloalkoxy fragments provided advanced intermediates **42a–l**, which were then exhaustively deprotected to give the final carboxylic acid products **43a–l**. For compound **43e**, alkylation of diaryl ether **41c** with bromophenoxy-substituted propyl chloride **20a** produced **42e**, which was subjected to Suzuki cross-coupling conditions with (4-fluorophenyl)boronic acid, followed by ester hydrolysis, to provide the final acid. Tetrazole **43l** was secured by treatment of the nitrile intermediate **42l** with lithium azide and triethylammonium chloride in 2-methoxyethanol.[27]

Because of our particular interest in compound **43b** (LY293111), we pursued an alternate route to diaryl ether ester **41a** devoid of the low-yielding Ullmann ether procedure. Toward this end, we turned to recently published methodology expressly designed to allow smooth access to diaryl ethers similar to **41a**.[28] In the event, alumina-supported potassium fluoride-mediated coupling of phenol **44** (obtained in high yield by monodemethylation of **38a** by sodium ethyl mercaptide) with 2-fluorobenzonitrile gave diaryl ether **45** in 99% yield (Scheme 8). A further demethylation with boron tribromide, nitrile hydrolysis, and esterification provided intermediate **41a** in good overall yield. The formation of intermediate **41h**, previously used in the synthesis of final tetrazole product **43l**, proved to be an added bonus with this sequence.

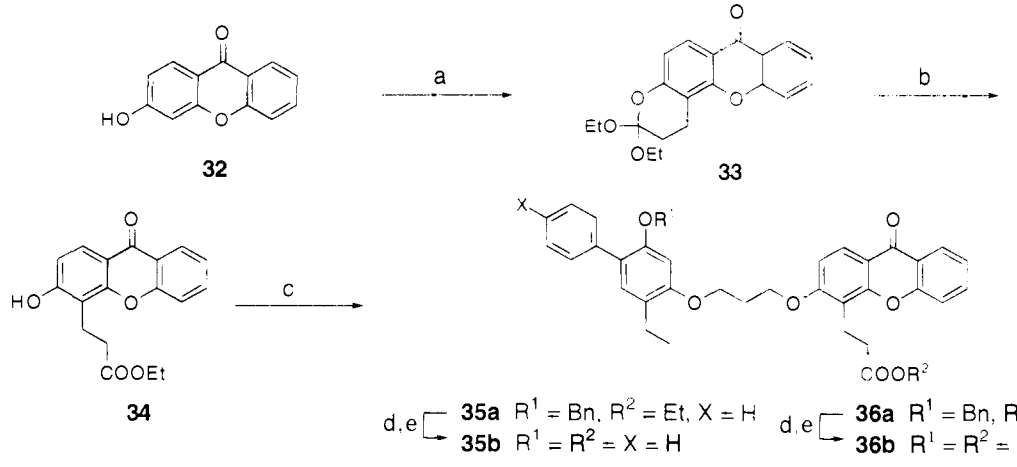
Modification of the diaryl ether oxygen of compound **43b** was confined to analogues featuring carbonyl, methylene, sulfide, sulfoxide, and sulfone substitutions. Halogen–metal exchange and acylation of compound **46** with phthalic anhydride produced carboxylic acid **47a**, which was then refluxed in acidic methanol to provide **47b** (Scheme 9). Thermal Claisen rearrangement of **47b** gave both regioisomers **48** and **49** in a 1:2.5 ratio, which were separated by flash chromatography. Alkylation of phenol **49** with iodide **22a**, followed by hydrogenolysis and hydrolysis, provided the carbonyl analogue **50b**. Alternatively, catalytic hydrogenation of **49** in the presence of strong acid provided intermediate **51**, which was then alkylated with chloride **21b** to produce **52a**. Exhaustive protecting group removal gave methylene analogue **52b**.

Scheme 5[a]



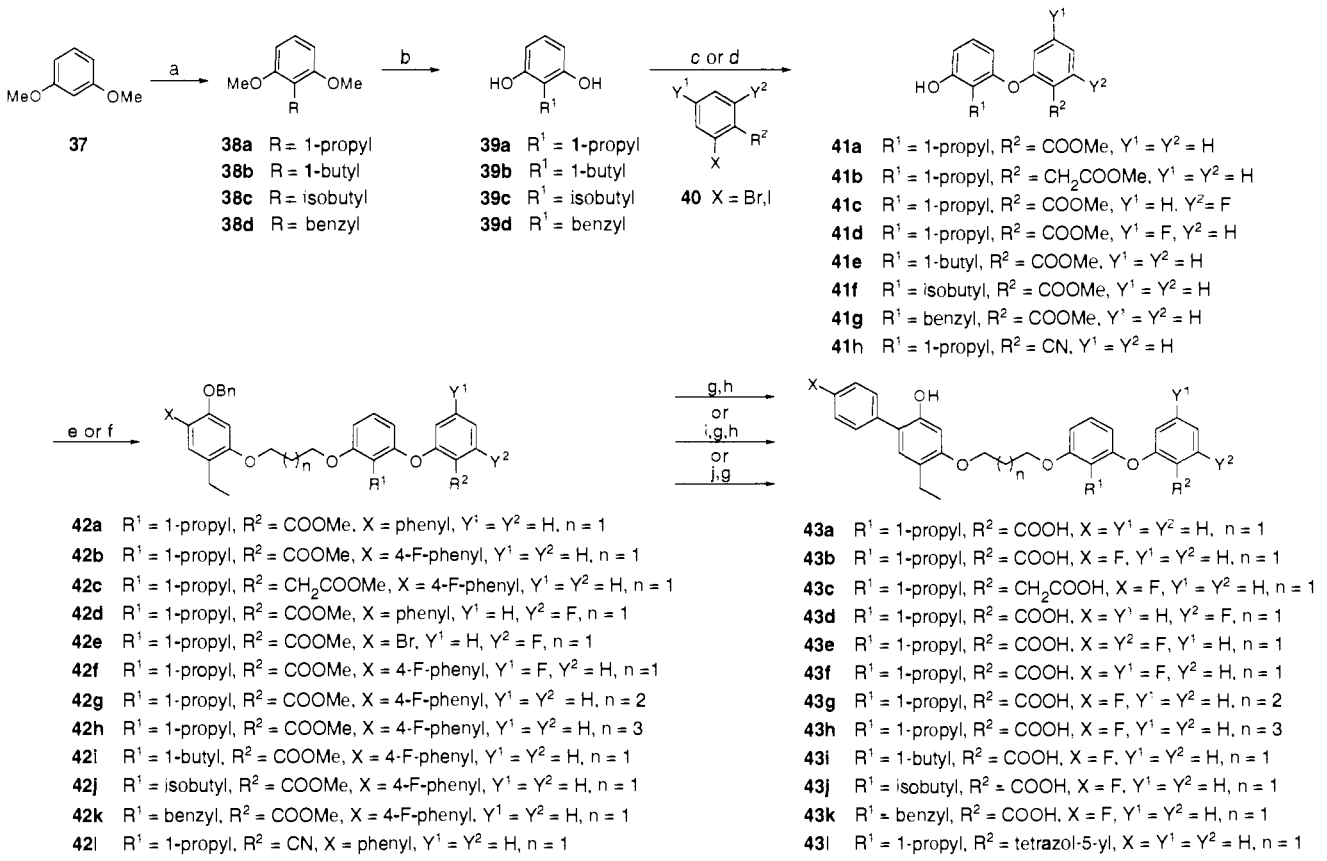
[a] (a) **21a**, K_2CO_3, KI, 2-butanone; (b) **22a**, K_2CO_3, DMF; (c) H_2, 10% Pd/C, EtOAc; (d) aqueous NaOH, MeOH, THF.

Scheme 6[a]



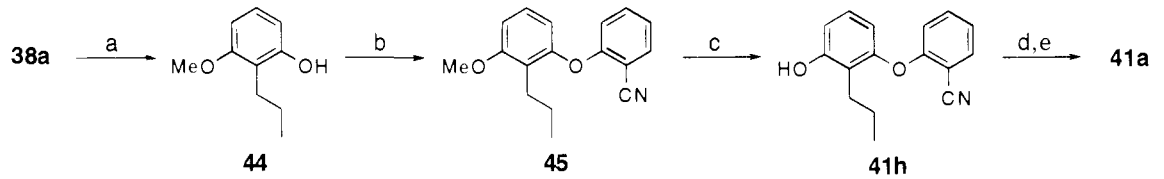
[a] (a) CH_2=CHC(OEt)$_3$, pivalic acid, toluene; (b) dilute HCl, THF; (c) **21a** or **21b**, K_2CO_3, KI, 2-butanone; (d) H_2, 10% Pd/C, EtOAc; (e) aqueous NaOH, MeOH, THF.

Scheme 7[a]



[a] (a) *n*-BuLi, THF, then RI; (b) py-HCl, 180 °C; (c) Cu°, K_2CO_3, py; (d) CuI, *t*-BuOK, py; (e) RX, K_2CO_3, DMF; (f) RX, K_2CO_3, KI, 2-butanone; (g) H_2, catalytic 10% Pd(C), EtOAc; (h) aqueous NaOH, MeOH, THF; (i) (4-fluorophenyl)boronic acid, EtOH, benzene, aqueous Na_2CO_3, catalytic $Pd(PPh_3)_4$; (j) LiN_3, Et_3N–HCl, 2-methoxyethanol, then aqueous HCl.

Scheme 8[a]



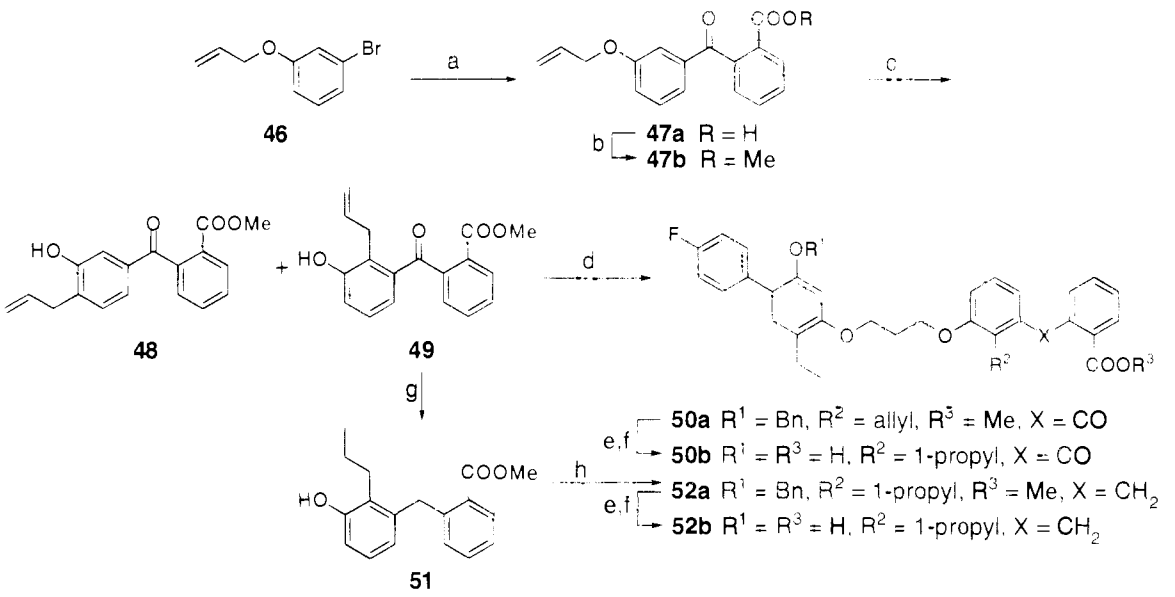
[a] (a) NaSEt, DMF; (b) 2-fluorobenzonitrile, KF–Al_2O_3, 18-crown-6(cat.), CH_3CN; (c) BBr_3, CH_2Cl_2; (d) 5 N NaOH, reflux; (e) concentrated HCl, MeOH, reflux.

Returning to bromide **46**, two halogen-exchange/electrophilic addition sequences followed by esterfication provided methyl ester **53b** (Scheme 10). Claisen rearrangement of **53b** also produced a mixture of regioisomers **54** and **55** (1:1.5 ratio), separable by flash chromatography. Alkylation of major isomer **55** with chloride **21b** smoothly gave ester **56a**. Not unexpectedly, hydrogenation of sulfur-substituted **56a** failed to remove the benzyl group, although the propenyl side chain was effectively reduced. Conversion of **56a** to **56b** was eventually accomplished by hydrogenation followed by treatment of the resulting propyl-substituted intermediate at low temperature with boron tribromide. Ester hydrolysis provided analogue **56c**, which was sequentially oxidized to sulfone **56e** through sulfoxide **56d** with *m*-chloroperoxybenzoic acid.

Synthesis of the 3-phenylpropanoic acid-substituted structures utilized phenols **58**–**60** as a starting point (Scheme 11). Alkylation of esters **58** (prepared as described above for the synthesis of xanthone intermediate **34**) and **59** with chloride **21b** led to compounds **61a** and **62a**, respectively, which were then subjected to base hydrolysis and hydrogenolysis to give final products **61c** and **62c**. Alkylation of nitrile **60** with **21b** gave **63a**, which was converted to the corresponding tetrazole **63b** with sodium azide/triethylammonium chloride in DMF. Hydrogenolysis provided final product **63c**.

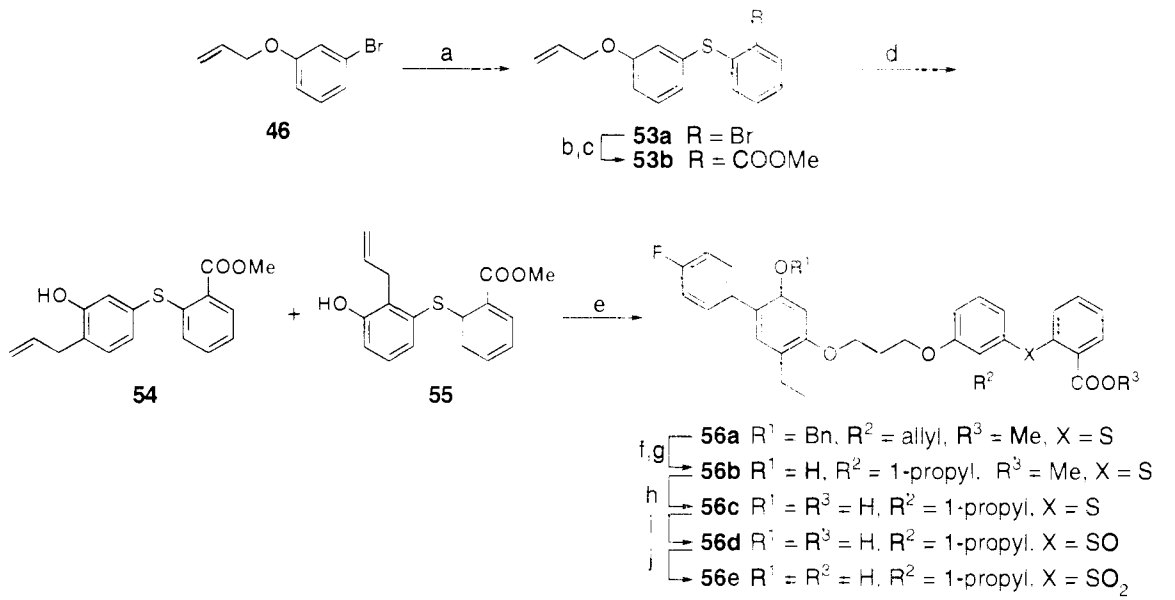
Non-xanthanoid compounds containing two acidic chains, or one acidic and one nonacidic polar chain, were obtained in a similar manner (Scheme 12). Monoalkylation of resorcinol provided nitrile **65** and ester **66a**, which was further transformed to amide **66b**. These were converted under standard conditions to propanoic esters **67**–**69**. Alkylation with chloride **21b** led to esters **70a**, **71a**, and **72a**. Installation of the tetrazole group onto compound **70a** with the sodium azide method produced **70b**, which was subsequently hydrolyzed to

Scheme 9[a]



[a] (a) *n*-BuLi, −78 °C, then phthalic anhydride; (b) HCl gas, MeOH; (c) neat, 175 °C; (d) **22a**, K_2CO_3, DMF; (e) H_2, Pd(C), EtOAc; (f) aqueous NaOH, MeOH, THF; (g) H_2, catalytic 10% Pd(C), concentrated H_2SO_4, MeOH; (h) **21b**, K_2CO_3, KI, 2-butanone.

Scheme 10[a]



[a] (a) *n*-BuLi, −78 °C, then bis(2-bromophenyl) disulfide; (b) *n*-BuLi, −78 °C, then CO_2 gas; (c) HCl gas, MeOH; (d) neat, 175 °C; (e) **21b**, K_2CO_3, KI, 2-butanone; (f) H_2, catalytic 10% Pd(C), EtOAc; (g) BBr_3, CH_2Cl_2, −78 °C; (h) aqueous NaOH, MeOH, THF; (i) 85% MCPBA, CH_2Cl_2, −78 °C; (j) 85% MCPBA, CH_2Cl_2, 0 °C.

provide tetrazole/carboxylic acid **70c**. Base hydrolysis was also used to convert **71a** to **71b**, and **72a** to **72b**. Compounds **70c**, **71b**, and **72b** were then progressed to the free phenols (**73**–**75**) by hydrogenolysis.

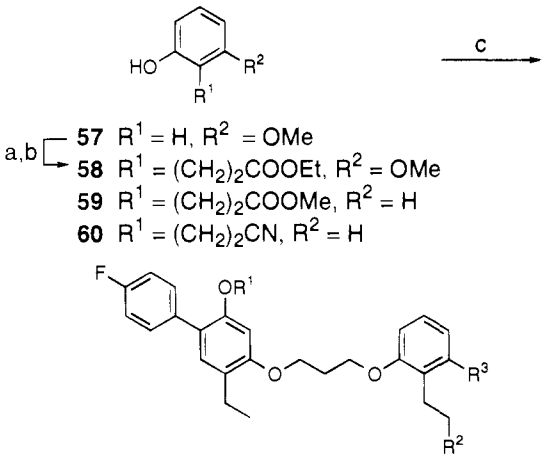
Biological Evaluation

Several assays were used to evaluate in vitro and in vivo activity of compounds. The ability of the compounds to bind at the LTB_4 receptor was assessed by measuring inhibition of binding of [^{3}H]LTB_4 to isolated human neutrophils[29] and guinea pig lung membranes.[30] Two functional assays were used to evaluate the antagonist activity: inhibition of LTB_4-induced expression of human neutrophil integrin CD11b/CD18[31] and inhibition of LTB_4-induced contraction of guinea pig lung parenchyma.[30] Since LTB_4 is known to induce bronchoconstriction in the guinea pig via a receptor-mediated mechanism,[32] select compounds were evaluated for their ability to inhibit LTB_4-induced airway responses when administered by the intravenous, oral, or aerosol routes, using excised-lung gas volume (ELGV) as a measure of the degree of airway obstruction.[33]

Structure–Activity Relationships

***gem*-Dimethyltetrazoles and Chromancarboxylic Acids.** In our refinement of compound 1 we initially examined the western region with emphasis on replacements for the acetyl group. In the original series, the acetyl group of an analogue of **1** was substituted with other ketones such as propionyl and benzoyl.[12] Although a loss of activity was observed with ketones other than acetyl, the initial analogues examined did

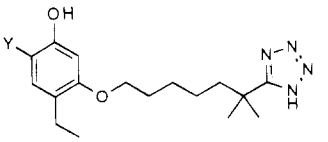
Scheme 11[a]



[a] (a) CH_2=$CHC(OEt)_3$, pivalic acid, toluene; (b) dilute HCl, THF; (c) **21b**, K_2CO_3, KI, DMF; (d) aqueous NaOH, MeOH, THF; (e) H_2, 10% Pd(C), EtOAc; (f) Bu_3SnN_3, 95 °C.

not contain an acidic group in the eastern region, now known to be critical for maximum receptor affinity. Compounds in which the acetyl group of **1** was directly replaced with alkoxy (particularly ethyloxy-substituted example **1a**)[34] or alkyl (particularly propyl-substituted example **1b**)[35] were later shown to be much more potent antagonists, as was the 1*H*-pyrazol-3-yl derivative **1c**[36] (Table 1). Unfortunately, compounds **1a–c** exhibited disappointing oral activity similar to our findings with compound **1**.

Table 1. Western Variations

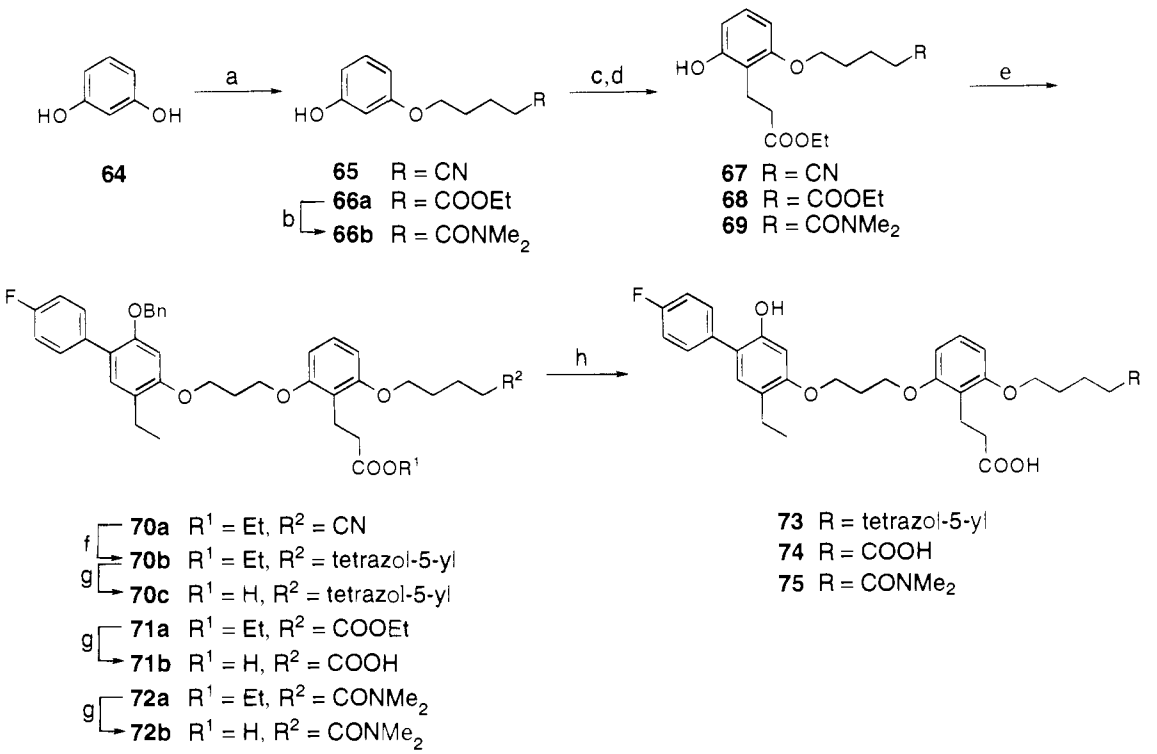


compd	Y	K_i, nM: human neutrophil	K_i, nM: guinea pig lung membranes	human neutrophil CD11b/CD18 up-regulation, IC_{50}, nM
1	CH_3CO	85 ± 7.9	78 ± 10	2900 ± 470
1a	CH_3CH_2O	8.4	14 ± 2.9	210
1b	$CH_3(CH_2)_2$	9.3	14 ± 6.3	160
1c	3-pyrazole	4.2 ± 0.30	42 ± 8.8	ND[a]
15a	Ph	3.0	4.4 ± 1.0	32 ± 3.4

[a] ND = not determined.

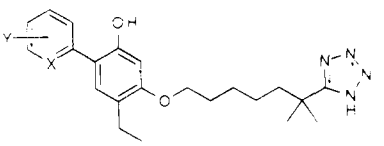
While the 2-position on the phenol ring appeared to be intolerant of long hydrocarbon chains, we believed it was possible that a shorter lipophilic group such as phenyl could effectively fill the acetyl binding cleft. Compound **15a** proved that this was indeed the case and led to a new western variation that was subsequently shown to have much greater in vitro and in vivo activity.[37] We were especially encouraged by the increase in capacity to inhibit LTB_4-induced up-regulation of CD11b/CD18 receptor expression displayed by **15a**, a 90-fold improvement over compound **1**. Overall, this result suggests the existence of a lipophilic binding cleft within the LTB_4 receptor that exhibits a preference for relatively planar groups.

Scheme 12[a]



[a] (a) R(CH2)4Br, K_2CO_3, DMF; (b) Me_2NH, H_2O; (c) CH_2=$CHC(OEt)_3$, pivalic acid, toluene; (d) dilute HCl, THF; (e) **21b**, K_2CO_3, KI, DMF; (f) NaN_3, Et_3N–HCl, DMF; (g) aqueous NaOH, MeOH, THF; (h) H_2, catalytic 10% Pd(C), EtOAc.

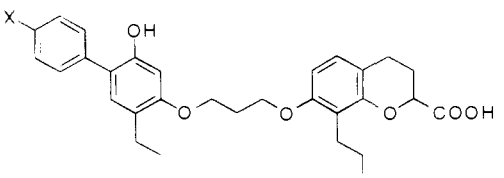
Table 2. *gem*-Dimethyltetrazoles[a]



compd	X	Y	K_i, nM: human neutrophil	K_i, nM: guinea pig lung membranes	human neutrophil CD11b/CD18 up-regulation, IC_{50}, nM
15a	CH	H	3.0	4.5 ± 1.0	32 ± 3.4
15b	CH	4-Me	4.0	37 ± 6.6	ND
15c	CH	3-Me	8.0	72 ± 17	ND
15d	CH	2-Me	11	70 ± 14	ND
15e	CH	4-MeO	2.9	55 ± 12	ND
15f	CH	3-MeO	4.0	21 ± 5.6	ND
15g	CH	4-NMe_2	16	86 ± 28	ND
15h	CH	3-CF_3	33	77 ± 2.0	ND
15i	CH	4-Cl	5.0	25 ± 8.8	12
15j	N	H	453	200 ± 39	ND
15k	CH	4-F	2.8	3.7 ± 1.0	13 ± 0.39
17	CH	3-F	3.0	6.2 ± 1.9	17

[a] ND = not determined.

Table 3. Eastern Variations: Chromancarboxylic Acids



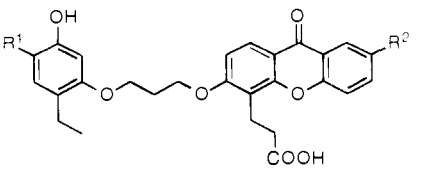
compd	X	K_i, nM: human neutrophil	K_i, nM: guinea pig lung membranes	human neutrophil CD11b/CD18 up-regulation, IC_{50}, nM
27b	H	3.3	2.8 ± 0.82	110 ± 10
28b	F	3.8	4.4 ± 2.1	17 ± 1.3

Substitution of the phenyl ring of **15a** with a series of electron-donating and -withdrawing functional groups (Table 2) revealed that the binding cleft possesses a certain tolerance to a variety of electronic pertubations (an exception is pyridine analogue **15j**, where our attempt to access an additional binding point through the introduction of a heteroatom was unsuccessful). The first indication of LTB_4 receptor heterogeneity came in the course of comparing binding constants for the human neutrophil against that of guinea pig lung membranes. With the exception of the 3- and 4-fluoro-substituted analogues, binding to the guinea pig receptor averaged 16-fold less potent than the unsubstituted phenyl compound **15a**. The heterogeneity of the LTB_4 receptor has been speculated upon previously.[38] Evaluation of **15a**, **15k**, and **17** (each known to possess high affinity for the guinea pig receptor) in the parenchyma contraction assay demonstrated a significant increase in inhibitory activity relative to compound **1** (Table 8).

We have previously demonstrated that replacement of the *gem*-dimethyltetrazole group of compound 1 with the propyloxy-substituted chromancarboxylic acid unit found in compound **4** results in a hybrid with no loss of in vitro activity, and an increase in oral activity.[39] This chroman acid group has also been successfully incorporated into alkoxy analogues of compound 1 with similar results.[40] Our results with the 2-arylphenol series were consistent with these observations, as compounds **27b** and **28b** (Table 3) displayed an in vitro activity profile very similar to their *gem*-dimethyltetrazole counterparts (i.e., **15a** and **15k**). Compound **27b** also possessed excellent oral activity (vide infra).

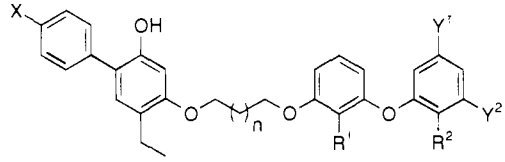
Xanthonecarboxylic Acids. As our remaining focus centered largely on modification of the eastern region of compound 1, we contemplated a merger of the 2-arylphenol unit with the xanthonedicarboxylic acid moiety first revealed in 3.[14] Our earlier work readily illustrates the structural hybridization possible between the series of antagonists represented by **1** and **3** to produce the new antagonist LY282210 (**1d**, Table 4).[41] Beyond the general conclusion that two important series of structurally distinct LTB_4 antagonists could be merged, we also demonstrated that deletion of the propanoic acid side chain led to a significant loss of binding affinity. Substitution of the acetyl group of **1d** with phenyl provided a new, highly potent variation on the xanthone class of antagonists (Table 4).[24] Compound **30b**, where phenyl is directly substituted for the acetyl moiety, exhibited a 7-fold increase in binding affinity for human neutrophils relative to **1d**, while an 11-fold increase was observed for guinea pig lung membranes. These results parallel the increase in activity displayed by *gem*-dimethyltetrazole **15a** over 1 and clearly highlight the superior nature of the phenyl group in interaction with a critical pharmacophore of the LTB_4 receptor. This is especially apparent when comparing **1d** with the aryl-substituted xanthones in their ability to inhibit LTB_4-induced integrin up-regulation.

Table 4. Eastern Variations: Xanthones



compd	R^1	R^2	K_i, nM: human neutrophil	K_i, nM: guinea pig lung membranes	human neutrophil CD11b/CD18 up-regulation, IC_{50}, nM
1d	acetyl	COOH	4.0[41]	1.2 ± 0.11[41]	47[24]
30b	Ph	COOH	0.57	0.11 ± 0.047	3.4 ± 0.29
31b	4-F-Ph	COOH	0.47	0.040 ± 0.016	1.2 ± 0.10
35b	Ph	H	22	12 ± 2.4	5.4 ± 0.10
36b	4-F-Ph	H	36	4.0 ± 1.2	1.8 ± 0.040
LTB_4			1.9 ± 0.050	0.12 ± 0.015	

Table 5. Eastern Variations: Diaryl Ether Acids



compd	R^1	R^2	X	Y^1	Y^2	n	K_i, nM: human neutrophil	K_i, nM: guinea pig lung membranes	human neutrophil CD11b/CD18 up-regulation, IC_{50}, nM
43a	1-propyl	COOH	H	H	H	1	19	16 ± 5.1	11
43b	1-propyl	COOH	F	H	H	1	17 ± 4.6	6.6 ± 0.71	3.3 ± 0.81
43c	1-propyl	CH_2COOH	F	H	H	1	210	8.4 ± 1.3	7.8
43d	1-propyl	COOH	H	H	F	1	10	14 ± 2.4	3.2
43e	1-propyl	COOH	F	H	F	1	4.4	9.5 ± 3.0	2.5
43f	1-propyl	COOH	F	F	H	1	48	19 ± 6.1	2.7
43g	1-propyl	COOH	F	H	H	2	39	19 ± 4.5	5.1
43h	1-propyl	COOH	F	H	H	3	150	6.8 ± 1.5	9.5
43i	1-butyl	COOH	F	H	H	1	34	16 ± 2.3	14
43j	isobutyl	COOH	F	H	H	1	36	14 ± 2.4	8.5
43k	benzyl	COOH	F	H	H	1	390	55 ± 9.0	220
43l	1-propyl	tet[a]	H	H	H	1	45	13 ± 2.5	ND[b]
4							12	15 ± 3.0	2300 ± 220

[a] tet = 1*H*-tetrazol-5-yl. [b] ND = not determined.

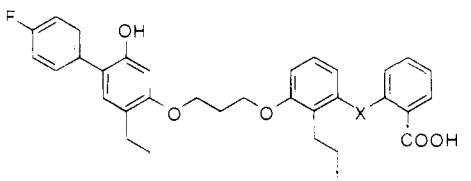
As previously disclosed, the propanoic acid group of the earlier xanthone series is critical for potent receptor binding to both human and guinea pig receptors, as deletion of this side chain in **1d** resulted in weak binding.[41] To ascertain the importance of the aromatic carboxyl group, monoacid **35b** was synthesized. Interestingly, while 40–100-fold less potent at binding to human neutrophils and guinea pig lung membranes than its diacid analogue **30b**, **35b** still retained potent antagonism against LTB_4-induced CD11b/CD18 up-regulation and was particularly effective in the guinea pig lung parenchyma contraction assay (Table 8). Binding to human neutrophils correlated well with the structure–activity relationship observed for the benzophenone (**2**) class[42] of LTB_4 receptor antagonists.

Compound **31b**, the 4-fluoro analogue of **30b**, displayed somewhat higher activity in vitro, with the most significant gain observed in blocking up-regulation of the CD11b/CD18 receptor. Compound **31b** appears overall to be the most potent in vitro LTB_4 receptor antagonist yet described. It was especially tenacious in binding to both human neutrophils (K_i = 0.47 nM) and guinea pig lung membranes (K_i = 0.040 nM), a 2–4-fold increase over that of the natural agonist. Additionally, removal of the aromatic carboxylic acid (compound **36b**) led to an 80–100-fold loss of human neutrophil and guinea pig lung membrane binding affinity relative to **31b**. However, as found with the nonfluoro analogues **30b** and **35b**, functional activity toward the CD11b/CD18 receptor was not significantly affected. We have commented extensively on the relationship between the secondary acid group and the known heterogeneity of the human neutrophil LTB_4 receptor.[41] In the present series, the secondary aromatic carboxylic acid of compounds **30b** and **31b** appears to be necessary only for tight receptor binding to the human neutrophil. The nature of the secondary acid binding site of the LTB_4 receptor, which has proven to be especially accommodating to the xanthone nucleus, has been further elucidated by the study of three spatial analogues of compound **31b**.[43]

Diaryl Ether Acids. In our search for novel modifications of the eastern portion of **1**, we decided to further examine the acid fragment of **4**, which is comprised of a constrained scaffolding in which the carboxyl group is directed out-of-plane relative to a chroman aromatic ring substituted with a secondary lipophilic group. We reasoned that an acid-substituted moiety similar to the chroman unit of **4**, preferably devoid of chiral centers, might allow sufficient flexibility to enhance receptor binding. Implementation of this plan led to the development of a derivative of **1** containing the novel 2-propylphenoxybenzoic acid unit in place of the *gem*-dimethyltetrazole group.[26] Molecular modeling suggested that such a diaryl ether manifold would place the critical carboxylic acid in a spatial position similar to that observed for **4**. Development of the 2-aryl-substituted series began with the preparation of **43a** (Table 5). Contrary to many of the *gem*-dimethyltetrazole analogues listed in Table 2, compound **43a** possessed potent binding activity with little discrimination between human and guinea pig receptors, similar to **15a**, **15k**, and **17**. Compound **43b**, the 4-fluoro derivative, also exhibited excellent binding activity and in addition was similar to the xanthone antagonists (Table 4) in strongly inhibiting expression of the CD11b/CD18 receptor.[31b] The structural novelty and potent activity of compound **43b**, which contains additional lipophilicity about the acid functionality relative to the *gem*-dimethyltetrazoles or the primary xanthone acid binding chain, encouraged us to further investigate this unique series.

Variation of the diaryl ether acid series involved modification at four key positions: the acid group, the lipophilic appendage, the central spacer region, and the diaryl linker atom. Insertion of a methylene group between the carboxylic acid and the phenyl ring (compound **43c**) resulted in a substantial decrease in binding for the human neutrophil receptor, but did not affect CD11b/CD18 up-regulation. Interestingly, **4** was found to be far more potent at binding to the human and guinea pig LTB_4 receptor than at inhibiting the LTB_4-induced expression of CD11b/CD18 (Table 5). Boosting acidity of the benzoic acid group by introduction of fluorine atoms failed to improve receptor activity (compounds **43d–f**), while a three-carbon central linker

Table 6. Diaryl Linker Variations



compd	X	K_i, nM: human neutrophil	K_i, nM: guinea pig lung membranes	K_i, nM: guinea pig spleen cells	human neutrophil CD11b/CD18 up-regulation, IC_{50}, nM
43b	O	17 ± 4.6	6.6 ± 0.71	17	3.3 ± 0.81
50b	CO	35	11 ± 3.1	33	13
52b	CH_2	99	11 ± 2.1	25	2.8
56c	S	350	11 ± 0.87	42	7.4
56d	SO	14	1.4	5.9	95
56e	SO_2	15	11	36	160

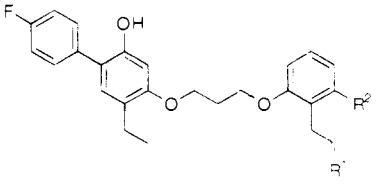
group was preferred over longer spacings (compare **43b** to **43g** and **43h**) for neutrophil binding. In addition, replacement of the carboxylic acid with a tetrazole group (compound **43l**) also failed to increase receptor binding. Our original work in the acetophenone series demonstrated the importance of accessing the lipophilic binding pocket adjacent to the benzoic acid.[26] This pocket was shown to accommodate smaller groups such as 1-butyl and isobutyl (compounds **43i** and **43j**), but was less receptive to benzyl (compound **43k**). Several of these diaryl ether antagonists had good inhibitory activity on guinea pig lung parenchyma (Table 8), in particular compounds **43a** and **43b**. The selectivity of compound **43b** was also assessed on guinea pig lung parenchyma. For example, the compound had no effect on contractions of guinea pig lung parenchyma induced by leukotriene D_4 (LTD_4), histamine, carbachol, or the thromboxane mimetic U46619.

Diaryl Linker Variations. Some of the most interesting results with this series were obtained by varying the connecting functionality between the two rings of the eastern region. The tendency to favor inhibition of expression of human neutrophil CD11b/CD18 over simple receptor binding, displayed by compounds such as **43c** and **43h**, was again apparent in the carbonyl derivative **50b** and to a greater extent with methylene analogue **52b** and sulfur analogue **56c** (Table 6). Alternatively, oxidation to the sulfoxide (**56d**) or sulfone (**56e**) inverted the relative activities in favor of receptor binding. Any speculation as to the reason for the activity profile displayed by these diaryl linker analogues would be inadequate without consideration of the possible existence of two or more receptor subtypes (or different states of the same receptor) on the human neutrophil. This reinforces the concept that specific LTB_4 receptor subtypes or substates exist for the different cell functions activated by LTB_4, such as chemotaxis and degranulation.[38,42]

Phenylpropanoic Acids. A further examination of the xanthone nucleus found in compounds **30b** and **31b** prompted us to consider eastern acid variations built around the phenylpropanoic acid group. Monoacids with a completely excised xanthone ring such as **61c** and **62c** retained tight binding to both human neutrophil and guinea pig lung membrane receptors, with some loss of activity at inhibiting up-regulation of the CD11b/CD18 receptor (Table 7). Replacement of the methoxy group of **61c** with an oxyvaleric acid side chain regained much of the activity lost by elimination of the xanthone. The secondary carboxylic acid of **74**, while not as rigidly positioned as in xanthone **31b**, nonetheless provides a highly potent antagonist. This valeric acid-substituted phenylpropanoic acid fragment has been reported previously in connection with the development of ONO-4057, an antagonist related to **2**.[44] Tetrazole substituents at either the primary site (compound **63c**) or secondary site (compound **73**) resulted in similar activity relative to the corresponding carboxylic acids. Amide **75** displayed excellent binding activity on both human neutrophils and guinea pig lung membranes consistent with the known propensity for the secondary site to accept nonacidic polar groups. The activity of **75** on up-regulation of the CD11b/CD18 receptor was similar to that observed for the xanthone series.

In Vivo Activity. Selected antagonists were evaluated in vivo by way of either intravenous, oral, or aerosol administration. Our primary model consisted of evaluation of the compounds as inhibitors of LTB_4-induced airway obstruction in the guinea pig. Several compounds (Table 9) were active in vivo with ED_{50} values of less than 1 mg/kg (oral) and 0.1 mg/kg (intravenous). In particular, compound **43b** proved to be superior to **4** when dosed by both oral (13-fold more potent) and intravenous (25-fold more potent) routes with ED_{50}'s of 0.40 and 0.014 mg/kg, respectively. Furthermore, a

Table 7. Eastern Variations: Phenylpropanoic Acids



compd	R^1	R^2	K_i, nM: human neutrophil	K_i, nM: guinea pig lung membranes	human neutrophil CD11b/CD18 up-regulation, IC_{50}, nM
61c	COOH	OMe	8.3	6.4 ± 0.53	64
62c	COOH	H	8.0	3.8 ± 0.93	31
63c	tet[a]	H	15	15 ± 2.0	ND[b]
73	COOH	$(CH_2)_4$tet[a]	2.3	1.1 ± 0.18	ND[b]
74	COOH	$(CH_2)_3COOH$	2.3	0.72 ± 0.17	13
75	COOH	$(CH_2)_4CONMe_2$	3.1	8.6 ± 1.4	7.8

[a] tet = 1*H*-tetrazol-5-yl. [b] ND = not determined.

Table 8. Inhibition of LTB_4-Induced Contraction of Guinea Pig Lung Parenchyma

compd	guinea pig lung parenchyma contraction, pK_B (n)	compd	guinea pig lung parenchyma contraction, pK_B (n)
1	6.6 ± 0.11 (5)	**35b**	9.3 ± 0.23 (4)
4	7.6 ± 0.60 (4)	**43a**	9.1 ± 0.10 (6)
15a	7.9 ± 0.10 (5)	**43b**	8.7 ± 0.16 (9)
15k	8.4 ± 0.16 (5)	**43d**	8.2 ± 0.12 (3)
17	8.6 ± 0.13 (5)	**43f**	8.3 ± 0.30 (6)
30b	8.3 ± 0.050 (5)	**43l**	8.4 ± 0.17 (4)

Table 9. Inhibition of LTB_4-Induced Airway Obstruction in the Guinea Pig

compd	inhibition of increase in ELGV, ED_{50} (mg/kg) iv	po
4	0.36	5.2
15a	0.05	0.7
15k	0.05	0.3
17	0.03	0.6
27b	0.01	0.5
43a	0.008	0.4
43b	0.01	0.4

duration of action study in the guinea pig indicated that compound **43b** at a dose of 1.0 mg/kg orally caused a prolonged inhibition of LTB_4-induced airway obstruction with a pharmacologic $t_{1/2}$ of greater than 8 h.

Dosing of diacid antagonists via either intravenous or oral routes invariably resulted in poor inhibition of LTB_4-induced responses. Diacids such as xanthone **31b** appear to be cleared from the blood rapidly, a phenomenon that has been noted with other moderately high molecular weight diacid leukotriene antagonists.[45] However, when compounds **30b** and **31b** were administered by the aerosol route at an estimated inhaled dose of 10.0 μg/kg, followed by LTB_4 inhalation challenge, ELGV values were reduced by 69 ± 20% and 81 ± 8%, respectively. The 10.0 μg/kg dose is well within the delivery range of current metered dose or dry powder inhalers. This suggests the potential for topical application of these highly potent diacid agents in inflammatory lung diseases such as asthma.

Conclusions

Since our earlier observation that the binding functionality of antagonists represented by **1** may be merged with that of **3** or **4** accompanied by an overall gain in activity, it has become increasingly apparent that the LTB_4 receptor is a very complex entity. While it has been previously established that the hydroxyl and ethyl groups of **1** are critical for potent activity,[12] development of compounds containing the 2-arylphenol substituent has further refined our model of the LTB_4 receptor to reflect the preference of the primary lipophilic cleft for planar groups. On the basis of the examination of many diverse series of antagonist structures, this pocket clearly possesses a high degree of discrimination beyond that of a simple large hole into which any lipophilic group will bind. More importantly, the 2-arylphenol modification has contributed significantly in the realm of oral bioavailability.

A clearer picture is beginning to emerge with respect to the acid binding sites of the receptor. While a typical LTB_4 antagonist normally requires only one acid group for interaction at the primary acid-binding domain, compounds which can also access the secondary site, such as **31b** and **74**, tend to display overall the most potent in vitro activity. However, when oral activity is the defining criteria for selection of a clinical candidate, monoacids still remain the best choice. Interestingly, the above observations concerning the lipophilic binding cleft and mono- versus diacid functionality are also applicable to the LTD_4/LTE_4 receptor. As with LTB_4 receptor antagonists, the incorporation of lipophilic bulk in close proximity to a single acid group (e.g. the methyl groups of **1** or the n-propyl group of **43b**) has also been exploited in the design of potent LTD_4/LTE_4 receptor antagonists.[46] In contrast, while our understanding of the molecular shape criteria required to design a potent LTD_4/LTE_4 receptor antagonist is fairly well established, it is apparent that our knowledge concerning the spatial demands of the LTB_4 receptor is still in its infancy. Other obvious inconsistencies in the comparison of these two receptors, such as the potent LTB_4 receptor antagonist activity of arylamidine-substituted compound **8**, will have to be accounted for in any comprehensive leukotriene receptor model.

Of the several 2-arylphenol-substituted series discussed above, the diaryl ether acids have proven especially interesting in vivo, with potent oral activity observed in the guinea pig at doses of less than 1.0 mg/kg. While the ability of these compounds to inhibit human neutrophil binding was somewhat variable for most of this series, their capacity to inhibit an LTB_4-induced function on human cells such as up-regulation of the CD11b/CD18 adhesion protein was consistently high. The exceptions to this trend (e.g. compound **43k**) imply the existence of receptor subtypes or substates in human neutrophils. The diaryl ether class also provides an excellent foundation for further structural modification, including the addition of a secondary acid chain. Compound **43b**, which has been chosen as a clinical candidate, has demonstrated pharmacologic activity in humans[47] and is currently in phase I studies for a variety of inflammatory diseases.[11a]

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. NMR spectra were determined on a GE QE-300 spectrometer. All chemical shifts are reported in parts per million (δ) relative to tetramethylsilane. The following abbreviations are used to denote signal patterns: s = singlet, d = doublet, t = triplet, q = quartet, b = broad, m = multiplet. Infrared spectra were determined on a Nicolet DX10 FT-IR spectrometer. Mass spectral data were determined on a MAT-731 spectrometer using free desorption (FD) conditions or a VG ZAB-3F spectrometer using fast atom bombardment (FAB) conditions. With the exception of NMR spectra, all spectroscopic and analytical data were determined by the Physical Chemistry Department (MC525) of the Lilly Research Laboratories. Silica gel flash chromatography was performed using a Waters Prep-500 HPLC, or E. Merck silica gel 60 with ethyl acetate/hexane gradients, unless otherwise indicated. Reversed-phase chromatography was performed on MCI CHP-20P gel using acetonitrile/water or methanol/water gradients. In general, salts were isolated via lyophilization. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use. All reactions were conducted under argon atmosphere with stirring unless otherwise noted.

Method A. 4-(Benzyloxy)-2-[(6-methyl-6-cyanoheptyl)oxy]acetophenone (10). To a solution of 4-(benzyloxy)-2-hydroxyacetophenone (**9**, 9.65 g, 39.9 mmol) in dimethylformamide (150 mL) were added 6-cyano-1-chloro-6-methylheptane (6.86 g, 39.5 mmol), potassium carbonate (10.6 g, 76.8 mmol),

and potassium iodide (1.6 g, 9.6 mmol). The mixture was stirred and heated at 90 °C for 24 h. After cooling to room temperature, the mixture was filtered and the resulting solution was concentrated in vacuo. Silica gel chromatography provided a clear oil (12.1 g, 80%): ^{1}H NMR ($CDCl_3$) 7.85 (d, J = 7.4 Hz, 1H), 7.3–7.5 (m, 5H), 6.60 (dd, J = 7.4, 1.8 Hz, 1H), 6.53 (d, J = 1.8 Hz, 1H), 5.12 (s, 2H), 4.04 (t, J = 5.3 Hz, 2H), 2.61 (s, 3H), 1.85–1.95 (m, 2H), 1.5–1.6 (m, 6H), 1.37 (s, 6H).

Method B. 4-(Benzyloxy)-2-[(6-methyl-6-cyanoheptyl)oxy]ethylbenzene (11). To a solution of compound **10** (12.1 g, 31.6 mmol) in carbon tetrachloride (30 mL) were added trifluoroacetic acid (44.4 g, 390 mmol) and triethylsilane (21.8 g, 188 mmol). The mixture was stirred at room temperature for 1.5 h, then diluted with ethyl acetate, and washed with aqueous sodium carbonate. The organic layers were collected, dried (magnesium sulfate), filtered, and concentrated in vacuo. Silica gel chromatography provided the desired product (10.6 g, 92%) as a clear oil: ^{1}H NMR ($CDCl_3$) 7.35–7.5 (m, 5H), 7.06 (d, J = 6.5 Hz, 1H), 6.53 (s, 1H), 6.52 (dd, J = 6.5, 2 Hz, 1H), 5.06 (s, 2H), 3.96 (t, J = 5.3 Hz, 2H), 2.60 (q, J = 6.3 Hz, 2H), 1.8–1.85 (m, 2H), 1.5–1.6 (m, 6H), 1.37 (s, 6H), 1.20 (t, J = 6.3 Hz, 3H).

Method C. 1-Bromo-2-(benzyloxy)-5-ethyl-4-[(6-methyl-6-cyanoheptyl)oxy]benzene (12). To a stirred solution of compound **11** (10.6 g, 28.9 mmol) in carbon tetrachloride (125 mL) was added *N*-bromosuccinimide (6.0 g, 33 mmol). Stirring was continued for 6 h at room temperature. The mixture was then diluted with methylene chloride and washed once with water. The organic layer was dried (magnesium sulfate), filtered, and concentrated in vacuo. The residue was recrystallized from hexane/ethyl acetate to provide the title compound (12.6 g, 98%) as a pale yellow solid: ^{1}H NMR ($CDCl_3$) 7.4–7.5 (m, 5H), 7.22 (s, 1H), 6.50 (s, 1H), 5.17 (s, 2H), 3.90 (t, J = 5.3 Hz, 2H), 2.58 (q, J = 6.3 Hz, 2H), 1.75–1.85 (m, 2H), 1.50–1.65 (m, 6H), 1.37 (s, 6H), 1.18 (t, J = 6.3 Hz, 3H).

Method D. Representative Procedures for Suzuki Biaryl Couplings. In a round-bottom flask was placed a solution of the appropriate aryl bromide (1 equiv) in benzene (5 mL/mmol aryl bromide). To this solution were added $Pd(PPh_3)_4$ (10 mol %) and 2.0 M aqueous sodium carbonate solution (1.5 mL/mmol aryl bromide). In a separate flask, the aryl boronic acid[18] (2 equiv) was dissolved in ethanol (1.5 mL/mmol aryl bromide). To the aryl boronic acid solution was added the aryl bromide solution, and the resulting mixture was heated to reflux with stirring for 16 h. The mixture was diluted with ethyl acetate and washed once with saturated aqueous ammonium chloride solution. The organic layers were dried (magnesium sulfate), filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography to provide the desired biaryl product.

Method E. A solution of the appropriate aryl bromide in THF was cooled to −78 °C. To this solution was added *tert*-butyllithium (2 equiv). After stirring at −78 °C for 30 min, a solution of zinc chloride (1 equiv) dissolved in a minimum of THF was added. The mixture was warmed to room temperature and stirred for 15 min. In a separate flask, a solution was prepared containing the appropriate aryl halide (1 equiv) and $Pd(PPh_3)_4$ (10 mol %) in tetrahydrofuran. This solution was added to the arylzinc solution, and the mixture was stirred at room temperature for 2–18 h. The reaction mixture was diluted with ethyl acetate and washed once with aqueous ammonium chloride solution. The organic layer was dried (magnesium sulfate), filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography to provide the desired biaryl product.

1-(Benzyloxy)-4-ethyl-5-[(6-methyl-6-cyanoheptyl)oxy]-2-phenylbenzene (13a). Compound **12** was converted to the desired product in 75% yield by method D: ^{1}H NMR ($CDCl_3$) 7.60 (d, J = 6.5 Hz, 2H), 7.3–7.5 (m, 8H), 7.18 (s, 1H), 6.59 (s, 1H), 5.04 (s, 2H), 3.95 (t, J = 5.3 Hz, 2H), 2.63 (q, J = 6.3 Hz, 2H), 1.8–1.9 (m, 2H), 1.5–1.6 (m, 6H), 1.38 (s, 6H), 1.25 (t, J = 6.3 Hz, 3H); MS-FD *m/e* 439 (p); IR ($CHCl_3$, cm^{-1}) 3013, 2977, 2943, 2238, 1611, 1488. Anal. ($C_{30}H_{35}NO_2$) C, H, N.

1-(Benzyloxy)-4-ethyl-5-[(6-methyl-6-cyanoheptyl)oxy]-2-(4-methylphenyl)benzene (13b). Compound **12** was converted to the desired product in 58% yield by method D. Anal. ($C_{31}H_{37}NO_2$) C, H, N.

1-(Benzyloxy)-4-ethyl-5-[(6-methyl-6-cyanoheptyl)oxy]-2-(3-methylphenyl)benzene (13c). Compound **12** was converted to the desired product in 75% yield by method D. Anal. ($C_{31}H_{37}NO_2$) C, H, N.

1-(Benzyloxy)-4-ethyl-5-[(6-methyl-6-cyanoheptyl)oxy]-2-(2-methylphenyl)benzene (13d). Compound **12** was converted to the desired product in 40% yield by method D. Anal. ($C_{31}H_{37}NO_2$) C, H, N.

1-(Benzyloxy)-4-ethyl-2-(4-methoxyphenyl)-5-[(6-methyl-6-cyanoheptyl)oxy]benzene (13e). Compound **12** was converted to the desired product in 82% yield by method D. Anal. ($C_{31}H_{37}NO_3$) C, H, N.

1-(Benzyloxy)-4-ethyl-2-(3-methoxyphenyl)-5-[(6-methyl-6-cyanoheptyl)oxy]benzene (13f). Compound **12** was converted to the desired product in 53% yield by method D. Anal. ($C_{31}H_{37}NO_3$) H, N; C: calcd, 78.95; found, 77.12.

1-(Benzyloxy)-2-[4-(dimethylamino)phenyl]-4-ethyl-5-[(6-methyl-6-cyanoheptyl)oxy]benzene (13g). Compound **12** was converted to the desired product in 94% yield by method D. Anal. ($C_{32}H_{40}N_2O_2$) H, N; C: calcd, 79.30; found, 77.04.

1-(Benzyloxy)-4-ethyl-5-[(6-methyl-6-cyanoheptyl)oxy]-2-[3-(trifluoromethyl)phenyl]benzene (13h). Compound **12** was converted to the desired product in 55% yield by method E: ^{1}H NMR ($CDCl_3$) 7.88 (s, 1H), 7.71 (d, J = 5 Hz, 1H), 7.3–7.5 (m, 7H), 7.14 (s, 1H), 6.60 (s, 1H), 5.06 (s, 2H), 4.01 (t, J = 5.3 Hz, 2H), 2.64 (q, J = 6.3 Hz, 2H), 1.8–1.9 (m, 2H), 1.5–1.7 (m, 6H), 1.38 (s, 6H), 1.22 (t, J = 6.3 Hz, 3H).

1-(Benzyloxy)-2-(4-chlorophenyl)-4-ethyl-5-[(6-methyl-6-cyanoheptyl)oxy]benzene (13i). Compound **12** was converted to the desired product in 67% yield by method D. Anal. ($C_{30}H_{32}NO_2Cl$) C, H, N.

1-(Benzyloxy)-4-ethyl-5-[(6-methyl-6-cyanoheptyl)oxy]-2-(2-pyridinyl)benzene (13j). Compound **12** was converted to the desired product in 60% yield by method E. Anal. Calcd for $C_{29}H_{32}N_2O_2$: C, H; N: calcd, 6.33; found, 5.74.

1-(Benzyloxy)-4-ethyl-2-(4-fluorophenyl)-5-[(6-methyl-6-cyanoheptyl)oxy]benzene (13k). Compound **12** was converted to the desired product in 80% yield by method D: mp 77–79 °C. Anal. ($C_{30}H_{33}NO_2F$) C, H, N, F.

1-(Benzyloxy)-4-ethyl-2-(3-fluorophenyl)-5-[(6-methyl-6-cyanoheptyl)oxy]benzene (13l). Compound **12** was converted to the desired product in 80% yield by method D.

Method F. Representative Procedure for Debenzylation. To a solution of the aryl benzyl ether in ethyl acetate or ethanol was added 10% Pd–carbon (10% wt/wt). The atmosphere of the reaction was exchanged for hydrogen gas (1 atm) and the reaction mixture stirred at room temperature for 2–48 h. The dispersion was filtered over Celite and washed with ethyl acetate several times. The resulting solution was concentrated in vacuo and purified by silica gel chromatography to provide the desired phenol.

4-Ethyl-5-[(6-methyl-6-cyanoheptyl)oxy]-2-phenylphenol (14a). Compound **13a** was converted to the desired product in 79% yield by method F. Anal. ($C_{23}H_{29}NO_2$) C, H, N.

4-Ethyl-5-[(6-methyl-6-cyanoheptyl)oxy]-2-(4-methylphenyl)phenol (14b). Compound **13b** was converted to the desired product in 44% yield by method F. Anal. ($C_{24}H_{31}NO_2$) H, N; C: calcd, 78.86; found, 76.84.

4-Ethyl-5-[(6-methyl-6-cyanoheptyl)oxy]-2-(3-methylphenyl)phenol (14c). Compound **13c** was converted to the desired product in 80% yield by method F. Anal. ($C_{24}H_{31}NO_2$) C, H, N.

4-Ethyl-5-[(6-methyl-6-cyanoheptyl)oxy]-2-(2-methylphenyl)phenol (14d). Compound **13d** was converted to the desired product in 47% yield by method F. Anal. ($C_{24}H_{31}NO_2$) H, N; C: calcd, 78.86; found, 78.11.

4-Ethyl-5-[(6-methyl-6-cyanoheptyl)oxy]-2-(4-methoxyphenyl)phenol (14e). Compound **13e** was converted to the desired product in quantitative yield by method F. Anal. ($C_{24}H_{31}NO_3$) C, H, N.

4-Ethyl-5-[(6-methyl-6-cyanoheptyl)oxy]-2-(3-methoxyphenyl)phenol (14f). Compound **13f** was converted to the

desired product in 72% yield by method F. Anal. ($C_{24}H_{31}NO_3$) H; C: calcd, 75.56; found, 73.95; N: calcd, 3.67; found, 2.59.

2-[4-(Dimethylamino)phenyl]-4-ethyl-5-[(6-methyl-6-cyanoheptyl)oxy]phenol (14g). Compound **13g** was converted to the desired product in 39% yield by method F: ^{1}H NMR ($CDCl_3$) 7.32 (d, J = 7.3 Hz, 2H), 6.99 (s, 1H), 6.85 (d, J = 7.3 Hz, 2H), 6.52 (s, 1H), 3.99 (t, J = 5.3 Hz, 2H), 3.01 (s, 6H), 1.8–1.9 (m, 2H), 1.5–1.6 (m, 6H), 1.37 (s, 6H), 1.20 (t, J = 6.3 Hz, 3H).

4-Ethyl-5-[(6-methyl-6-cyanoheptyl)oxy]-2-[3-(trifluoromethyl)phenyl]phenol (14h). Compound **13h** was converted to the desired product in 56% yield by method F. Anal. ($C_{24}H_{28}F_3NO_2$) C, H, N.

2-(4-Chlorophenyl)-4-ethyl-5-[(6-methyl-6-cyanoheptyl)oxy]phenol (14i). Compound **13i** was converted to the desired product in 97% yield by method F. Anal. ($C_{23}H_{28}NO_2Cl$) C, H, N.

4-Ethyl-5-[(6-methyl-6-cyanoheptyl)oxy]-2-(2-pyridinyl)-phenol (14j). To a solution of compound **13j** (1.0 g, 2.2 mmol) in methylene chloride (25 mL) at −78 °C was added a 1 M solution of BBr_3 in methylene chloride (2.0 mL). The reaction mixture was stirred at −78 °C for 10 min, then warmed to room temperature, and stirred for 1 h. The mixture was quenched with aqueous $NaHCO_3$ and diluted with methylene chloride. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography to provide the phenol (400 mg, 50% yield). Anal. ($C_{22}H_{28}N_2O_2$) C, H, N.

4-Ethyl-2-(4-fluorophenyl)-5-[(6-methyl-6-cyanoheptyl)oxy]phenol (14k). Compound **13k** was converted to the desired product in 75% yield by method F. Anal. ($C_{23}H_{28}NO_2F$) C, H, N.

Method G. Representative Procedure for the Formation of *gem*-Dimethyltetrazoles. To a solution of the *gem*-dimethylnitrile (1 equiv) in diglyme was added (*N*,*N*-dimethylamino)ethanol hydrochloride (2 equiv) and sodium azide (4 equiv). The suspension was heated and maintained at 130 °C with stirring for 8–72 h. The mixture was diluted with methylene chloride and acidified with dilute hydrochloric acid. The organic layer was dried (magnesium sulfate), filtered, and concentrated in vacuo. The residue was dissolved in ethanol, stirred with aqueous sodium hydroxide (4 equiv) at room temperature for 30 min, and then concentrated in vacuo. Except where noted, the product was purified on HP-20P reverse phase resin eluting with water followed by a methanol/water gradient. The desired fractions were combined and concentrated in vacuo. The residue was then lyophilized to produce the tetrazole as its sodium salt.

2-Phenyl-4-ethyl-5-[[6-(2*H*-tetrazol-5-yl)-6-methylheptyl]oxy]phenol Sodium Salt Dihydrate (15a). Compound **14a** was converted to the desired product in 34% yield by method G: ^{1}H NMR (DMSO-d_6) 7.55 (d, J = 6.5 Hz, 2H), 7.35 (t, J = 6.5 Hz, 2H), 7.20 (t, J = 6.5 Hz, 1H), 6.98 (s, 1H), 6.60 (s, 1H), 3.82 (t, J = 5.3 Hz, 2H), 2.65 (q, J = 6.3 Hz, 2H), 1.55–1.70 (m, 6H), 1.25–1.35 (m, 8H), 1.10 (t, J = 6.3 Hz, 3H); MS-FAB *m/e* 439 (p); IR (KBr, cm^{-1}) 3192, 2970, 2937, 1617, 1488, 1453, 1214. Anal. ($C_{23}H_{29}N_4O_2Na_2 \cdot 2H_2O$) C, H, N.

4-Ethyl-2-(4-methylphenyl)-5-[[6-methyl-6-(2*H*-tetrazol-5-yl)heptyl]oxy]phenol Disodium Salt Sesquihydrate (15b). Compound **14b** was converted to the desired product in 29% yield by method G. Anal. ($C_{24}H_{30}N_4O_2Na_2 \cdot 1.5\ H_2O$) C, H, N.

4-Ethyl-2-(3-methylphenyl)-5-[[6-methyl-6-(2*H*-tetrazol-5-yl)heptyl]oxy]phenol Sodium Salt (15c). Compound **14c** was converted to the desired product in 27% yield by method G: ^{1}H NMR (DMSO-d_6) 7.40 (d, J = 6.0 Hz, 2H), 7.15 (d, J = 6.0 Hz, 2H), 6.95 (s, 1H), 6.60 (s, 1H), 3.82 (t, J = 5.3 Hz, 2H), 2.45 (q, J = 6.3 Hz, 2H), 2.32 (s, 3H), 1.5–1.7 (m, 6H), 1.2–1.4 (m, 8H), 1.07 (t, J = 6.3 Hz, 3H); MS-FAB *m/e* 453 (p).

4-Ethyl-2-(2-methylphenyl)-5-[[6-methyl-6-(2*H*-tetrazol-5-yl)heptyl]oxy]phenol Disodium Salt 1.7 Hydrate (15d). Compound **14d** was converted to the desired product in 35% yield by method G. Anal. ($C_{24}H_{30}N_4O_2Na_2 \cdot 1.7\ H_2O$) C, N; H: calcd, 6.99; found, 7.41.

4-Ethyl-5-[[6-methyl-6-(2*H*-tetrazol-5-yl)heptyl]oxy]-2-(4-methoxyphenyl)phenol Sodium Salt (15e). Compound **14e** was converted to the desired product in 29% yield by method G: ^{1}H NMR (DMSO-d_6) 7.43 (d, J = 7.3 Hz, 2H), 6.91 (s, 1H), 6.89 (d, J = 7.3 Hz, 2H), 6.57 (s, 1H), 3.81 (t, J = 5.3 Hz, 2H), 3.74 (s, 3H), 2.43 (q, J = 6.3 Hz, 2H), 1.7–1.9 (m, 6H), 1.2–1.4 (m, 8H), 1.06 (t, J = 6.3 Hz, 3H); MS-FAB *m/e* 425 (p).

4-Ethyl-5-[[6-methyl-6-(2*H*-tetrazol-5-yl)heptyl]oxy]-2-(3-methoxyphenyl)phenol Disodium Salt (15f). Compound **14f** was converted to the desired product in 16% yield by method G: ^{1}H NMR (DMSO-d_6) 7.26 (t, J = 6 Hz, 1H), 7.05–7.10 (m, 2H), 6.98 (s, 1H), 6.80 (dd, J = 2,6 Hz, 1H), 6.60 (s, 1H), 3.84 (t, J = 5.3 Hz, 2H), 3.76 (s, 3H), 2.46 (q, J = 6.3 Hz, 3H), 1.5–1.7 (m, 6H), 1.2–1.4 (m, 8H) 1.08 (t, J = 6.3 Hz, 3H); IR (KBr) 3416, 2961, 2936, 2869, 1608, 1487, 1140 cm^{-1}; MS-FAB *m/e* 469 (p).

2-[4-(Dimethylamino)phenyl]-4-ethyl-5-[[6-methyl-6-(2*H*-tetrazol-5-yl)heptyl]oxy]phenol Disodium Salt (15g). Compound **14g** was converted to the desired product in 29% yield by method G: ^{1}H NMR (DMSO-d_6) 7.36 (d, J = 7.3 Hz, 2H), 6.89 (s, 1H), 6.71 (d, J = 7.3 Hz, 2H), 6.53 (s, 1H), 3.81 (t, J = 5.3 Hz, 2H), 2.45 (q, J = 6.3 Hz, 2H), 1.5–1.7 (m, 6H), 1.2–1.4 (m, 8H), 1.06 (t, J = 6.3 Hz, 3H).

4-Ethyl-5-[[6-methyl-6-(2*H*-tetrazol-5-yl)heptyl]oxy]-2-[4-(trifluoromethyl)phenyl]phenol Disodium Salt (15h). Compound **14h** was converted to the desired product in 29% yield by method G: ^{1}H NMR (DMSO-d_6) 7.80–7.90 (m, 2H), 7.55–7.60 (m, 1H), 7.55 (s, 1H), 7.04 (s, 1H), 6.65 (s, 1H), 3.84 (t, J = 5.3 Hz, 2H), 2.48 (q, J = 6.3 Hz, 2H), 1.7–1.9 (m, 6H), 1.2–1.4 (m, 8H), 1.05 (t, J = 6.3 Hz, 3H); MS-FAB *m/e* 507 (p).

2-(4-Chlorophenyl)-4-ethyl-5-[[6-methyl-6-(2*H*-tetrazol-5-yl)heptyl]oxy]phenol Sodium Salt (15i). Compound **14i** was converted to the desired product in 38% yield by method G. Anal. ($C_{23}H_{28}N_4O_2ClNa \cdot 0.75\ H_2O$) C, H, N.

4-Ethyl-5-[[6-methyl-6-(2*H*-tetrazol-5-yl)heptyl]oxy]-2-(2-pyridinyl)phenol Disodium Salt (15j). Compound **14j** was converted to the desired product in 28% yield by method G. Anal. ($C_{22}H_{27}N_5O_2Na_2 \cdot 2H_2O$) C, N; H: calcd, 6.53; found, 7.04.

4-Ethyl-2-(4-fluorophenyl)-5-[[6-methyl-6-(2*H*-tetrazol-5-yl)heptyl]oxy]phenol Sodium Salt (15k). Compound **14k** was converted to the desired product in 56% yield by method G. Anal. ($C_{23}H_{28}N_4O_2FNa$) C, H, N.

Method H. 7-[2-Ethyl-4-(3-fluorophenyl)-5-(benzyloxy)phenoxy]-2-methyl-2-(1*H*-tetrazol-5-yl)heptane (16). A mixture of compound **13l** (1.44 g, 3.22 mmol), triethylamine hydrochloride (4.10 g, 29.8 mmol), and sodium azide (1.95 g, 30.0 mmol) in dimethylformamide (40 mL) was heated in an oil bath at 125 °C for 17 h. Further triethylamine hydrochloride (4.0 g) and sodium azide (2.0 g) were added after 5 h. The mixture was cooled, diluted with water, acidified with 1.0 N hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed once with water and once with saturated sodium chloride solution, dried (sodium sulfate), and concentrated in vacuo. Silica gel chromatography with dichloromethane/methanol provided 1.12 g (72%) of the desired product: ^{1}H NMR ($CDCl_3$) 7.56 (m, 1H), 8.0 (m, 7H), 7.16 (s, 1H), 7.00 (m, 1H), 6.60 (s, 1H), 5.08 (s, 2H), 3.90 (m, 2H), 2.66 (m, 2H), 1.93 (m, 2H), 1.80 (m, 2H), 1.60 (s, 9H), 1.50 (m, 2H), 1.60 (m, 2H), 1.20 (t, 3H).

7-[2-Ethyl-4-(3-fluorophenyl)-5-(benzyloxy)phenoxy]-2-methyl-2-(1*H*-tetrazol-5-yl)heptane (17). A mixture compound **16** (1.0 g) and 10% Pd–carbon (1.0 g) in ethanol (200 mL) was hydrogenated on a Parr apparatus at 35–40 psi for 2 h. The mixture was filtered and the filtrate evaporated in vacuo. Silica gel chromatography of the residue eluting with dichloromethane/methanol provided the desired product (620 mg, 75%) as a white crystalline solid: mp 107–110 °C. Anal. ($C_{23}H_{29}N_4O_2F$) C, H, N.

Method I. 4-(Benzyloxy)-2-(3-chloropropoxy)acetophenone (18a). A mixture of 4-(benzyloxy)-2-hydroxyacetophenone (**9**, 150 g, 0.618 mol), 1-bromo-3-chloropropane (245 mL, 2.46 mol), potassium carbonate (166 g, 1.20 mol), and methyl sulfoxide (400 mL) in 2-butanone (1 L) was refluxed for 24 h. The reaction mixture was cooled and filtered. The mixture was concentrated in vacuo, diluted with ethyl acetate, and

washed twice with water and twice with saturated sodium chloride solution. The organic layer was dried (magnesium sulfate), filtered, and concentrated in vacuo. Silica gel chromatography (ethyl acetate, methylene chloride) of the resulting oil provided 162 g (82%) of the desired product as a white crystalline solid: mp 69–70 °C. Anal. ($C_{18}H_{19}O_3Cl$) C, H.

4-(Benzyloxy)-2-(4-chlorobutoxy)acetophenone (18b). Alkylation of compound **9** (37.9 mmol) with 1-bromo-4-chlorobutane (152 mmol) using method I provided 7.70 g (61%) of product as a white solid: mp 58–60 °C. Anal. ($C_{19}H_{21}O_3Cl$) C, H.

4-(Benzyloxy)-2-(5-chloropentoxy)acetophenone (18c). Alkylation of compound **9** (64.0 mmol) with 1-bromo-5-chloropentane (64.0 mmol) using method I provided 16.1 g (73%) of product as a white solid: mp 76–77 °C.

4-(Benzyloxy)-2-(3-chloropropoxy)ethylbenzene (19a). Reduction of compound **18a** (232 mmol) using method B provided 48.9 g (69%) of the desired product as a colorless oil.

4-(Benzyloxy)-2-(4-chlorobutoxy)ethylbenzene (19b). Reduction of compound **18b** (10.5 mmol) using method B provided 2.60 g (79%) of product as a colorless oil. Anal. ($C_{19}H_{23}O_2Cl$) C, H.

4-(Benzyloxy)-2-(5-chloropentoxy)ethylbenzene (19c). Reduction of compound **18c** (43.2 mmol) using method B provided 10.4 g (73%) of product as a faint yellow oil. Anal. ($C_{20}H_{25}O_2Cl$) H; C: calcd, 72.17; found, 71.24.

4-(Benzyloxy)-5-bromo-2-(3-chloropropoxy)ethylbenzene (20a). Bromination of compound **19a** (164 mmol) using method C provided 4.60 g (73%) of pure product as a crystalline solid: mp 45–46 °C. Anal. ($C_{18}H_{20}O_2BrCl$) C, H.

4-(Benzyloxy)-5-bromo-2-(4-chlorobutoxy)ethylbenzene (20b). Bromination of compound **19b** (7.84 mmol) using method C provided 2.52 g (81%) of product as a crystalline solid from hexane: mp 65–66 °C. Anal. ($C_{19}H_{22}O_2BrCl$) C, H.

4-(Benzyloxy)-5-bromo-2-(5-chloropentoxy)ethylbenzene (20c). Bromination of compound **19c** (31.0 mmol) using method C provided 10.0 g (81%) of product as a white crystalline solid from hexane. Anal. ($C_{20}H_{24}O_2BrCl$) C, H.

4-(Benzyloxy)-2-(3-chloropropoxy)-5-phenylethylbenzene (21a). Reaction of compound **20a** (13.1 mmol) with phenylboronic acid (40.2 mmol) using method D provided 4.00 g (80%) of the desired product as a colorless oil: ^{1}H NMR ($CDCl_3$) 7.63 (d, J = 9 Hz, 2H), 7.28–7.53 (m, 9H), 7.21 (s, 1H), 6.63 (s, 1H), 5.09 (s, 2H), 4.15 (t, J = 6 Hz, 2H), 3.81 (t, J = 6 Hz, 2H), 2.67 (q, J = 7 Hz, 2H), 2.28 (quintet, J = 6 Hz, 2H), 1.28 (t, J = 7 Hz, 3H).

4-(Benzyloxy)-2-(3-chloropropoxy)-5-(4-fluorophenyl)-ethylbenzene (21b). Reaction of compound **20a** (2.60 mmol) with (4-fluorophenyl)boronic acid (3.89 mmol) using method D provided 870 mg (84%) of the desired product as a crystalline solid: mp 60–63 °C. Anal. ($C_{24}H_{24}O_2FCl$) C, H.

4-(Benzyloxy)-2-(4-chlorobutoxy)-5-(4-fluorophenyl)-ethylbenzene (21c). Reaction of compound **20b** (26.4 mmol) with (4-fluorophenyl)boronic acid (79.2 mmol) using method D provided 2.07 g (87%) of product as a white solid: mp 48–49 °C. Anal. ($C_{25}H_{26}O_2ClF$) C, H.

4-(Benzyloxy)-2-(5-chloropentoxy)-5-(4-fluorophenyl)-ethylbenzene (21d). Reaction of compound **20c** (21.4 mmol) with (4-fluorophenyl)boronic acid (32.0 mmol) using method D provided 7.04 g (77%) of product as a white solid from hexane: mp 54–56 °C. Anal. ($C_{26}H_{28}O_2ClF$) C, H.

Method J. 4-(Benzyloxy)-5-(4-fluorophenyl)-2-(3-iodopropoxy)ethylbenzene (22a). A mixture of compound **21b** (20.0 g, 50.2 mmol) and sodium iodide (75.3 g, 502 mmol) in 2-butanone (200 mL) was refluxed for 6 h. The reaction mixture was cooled to room temperature, diluted with an equal volume of ether, and washed once with water. The organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo to provide 24.6 g (100%) of product as a colorless oil. Anal. ($C_{24}H_{24}O_2FI$) H; C: calcd, 58.79; found, 60.00.

4-(Benzyloxy)-5-(4-fluorophenyl)-2-(4-iodobutoxy)ethylbenzene (22b). Reaction of compound **21c** (4.84 mmol) using method J provided the desired product in quantitative yield as a colorless oil. This material was not characterized further but used directly.

7-[3-[5-(Benzyloxy)-4-bromo-2-ethylphenoxy]propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylic Acid Ethyl Ester (24). To a solution of compound **23** (2.1 g, 8.1 mmol)[15,20] in dimethylformamide (5 mL) was carefully added a suspension of sodium hydride (190 mg, 8.1 mmol, 60% oil dispersion) in dimethylformamide (10 mL) at room temperature and the resulting mixture stirred for 30 min. Compound **20a** (5.09 g, 13.3 mmol) was converted to the iodide by use of method J. A mixture of the crude iodide and 18-crown-6 (110 mg, 0.40 mmol) was added, and the resulting mixture was stirred at room temperature for 1.5 h. The reaction was quenched with water, and the reaction mixture was extracted twice with ethyl acetate. The organic layer was dried (magnesium sulfate), filtered, and concentrated in vacuo. The resulting product was purified by silica gel chromatography to give 2.5 g (86%) of desired product. Anal. ($C_{33}H_{39}O_6Br$) C, H.

7-[3-[[2-(Benzyloxy)-5-ethyl[1,1'-biphenyl]-4-yl]oxy]propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylic Acid Ethyl Ester (25). Reaction of compound **24** (2.24 mmol) with phenylboronic acid (10.7 mmol) using method D provided 880 mg (64%) of product as an oil. Anal. ($C_{39}H_{44}O_6$) H; C: calcd, 76.94; found, 75.70.

7-[3-[(5-Ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylic Acid Ethyl Ester (27a). Compound **25** (1.4 mmol) was debenzylated using method F. Purification via silica gel chromatography provided 354 mg (49%) of pure product as a colorless oil. Anal. ($C_{32}H_{38}O_6$) C, H.

Method K. 7-[3-[(5-Ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylic Acid (27b). A solution of compound **27a** (0.37 g, 0.71 mmol) in THF (5 mL) and methanol (5 mL) was treated with 5 N sodium hydroxide solution (1 mL) with stirring at room temperature for 1 h. The reaction mixture was concentrated in vacuo, diluted with water, and acidified to pH 1 with 5 N hydrochloric acid. The resulting suspension was extracted with ethyl acetate. The organic layer was dried (magnesium sulfate), filtered, and concentrated in vacuo. Recrystallization from toluene/hexane provided 245 mg (71%) of product as a white solid: ^{1}H NMR ($CDCl_3$) 7.45 (m, 6H), 7.02 (s, 1H), 6.86 (d, J = 8.57 Hz, 1H), 6.56 (s, 1H), 6.53 (d, J = 8.3 Hz, 1H), 5.30 (br s, 1H), 4.78 (dd, J = 3.7, 7.5 Hz, 1H), 4.20 (t, J = 6.0 Hz, 2H), 4.18 (t, J = 6.0 Hz, 2H), 2.69 (m, 8H), 2.26 (m, 6H), 1.55 (m, 2H), 1.19 (t, J = 7.5 Hz, 3H), 0.96 (t, J = 7.3 Hz, 3H); MS-FAB *m/e* 491 (p − 1), 490 (p), 277; IR (KBr, cm^{-1}) 3426, 2959, 2870, 1718, 1615. Anal. ($C_{30}H_{34}O_6$) C, H.

Method L. 8-Propyl-7-[3-[5-(benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]-3,4-dihydro-2*H*-1-benzopyran-2-carboxylic Acid Ethyl Ester (26). A mixture of compound **22a** (700 mg, 1.50 mmol), compound **23** (374 mg, 1.42 mmol), and potassium carbonate (490 mg, 3.55 mmol) in dimethylformamide (10 mL) was stirred at room temperature for 24 h. The reaction mixture was diluted with water and extracted once with ethyl acetate. The organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo. Purification via silica gel flash chromatography provided 0.46 g (52%) of product as a clear oil. Anal. ($C_{39}H_{43}O_6$) C, H, F.

8-Propyl-7-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-3,4-dihydro-2*H*-1-benzopyran-2-carboxylic Acid Ethyl Ester (28a). Compound **26** (2.57 mmol) was debenzylated using method F. Purification via silica gel chromatography provided 1.02 g (74%) of pure product. Anal. ($C_{32}H_{37}O_6$) C, H.

8-Propyl-7-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-3,4-dihydro-2*H*-1-benzopyran-2-carboxylic Acid (28b). Compound **28a** (1.8 mmol) was hydrolyzed using method K. Recrystallization of the resulting solid from ethyl acetate/hexane provided 568 mg (62%) of product as a white solid. Anal. ($C_{30}H_{33}O_6$) C, H.

Ethyl 3-[4-[7-Carbomethoxy-9-oxo-3-[3-[5-(benzyloxy)-2-ethyl-4-phenylphenoxy]propoxy]-9*H*-xanthene]]propanoate (30a). Compound **29**[15] (1.97 mmol) was reacted with compound **21a** (1.97 mmol) using method O to provide crude product as an oil. This material was not purified further but converted directly to compound **30b**.

3-[4-[7-Carboxy-9-oxo-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)propoxy]-9*H*-xanthene]]propanoic Acid Disodium Trihydrate (30b). Compound **30a** was debenzylated using method F and hydrolyzed using method K. The residue was dissolved in a minimum of 1 N sodium hydroxide solution and purified on CHP-20 resin to provide 390 mg (56%) of product as the disodium salt trihydrate. Anal. ($C_{34}H_{28}O_9Na_2 \cdot H_2O$) C, H.

Ethyl 3-[4-[7-Carbomethoxy-9-oxo-3-[3-[2-ethyl-5-(benzyloxy)-4-(4-fluorophenyl)phenoxy]propoxy]-9*H*-xanthene]]propanoate (31a). Compound **29** (1.49 mmol) was reacted with compound **22a** using method L to provide crude product. Recrystallization (hexane/ethyl acetate) provided 755 mg (69%) of pure product as an off-white crystalline material: mp 100 °C. Anal. ($C_{14}H_{41}O_9F$) C, H.

3-[4-[7-Carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-9*H*-xanthene]]propanoic Acid Disodium Trihydrate (31b). Compound **31a** (1.89 mmol) was debenzylated using method F and hydrolyzed using method K. The residue was dissolved in a minimum of 1 N sodium hydroxide solution and purified on CHP-20 resin to provide 242 mg (46%) of product as the disodium salt trihydrate: ^{1}H-NMR (DMSO-d_6) 8.65 (d, J = 1.8 Hz, 1H), 8.29 (dd, J = 8.6, 1.8 Hz, 1H), 8.00 (d, J = 8.9 Hz, 1H), 7.52 (m, 3H), 7.11 (m, 3H), 6.92 (s, 1H), 6.89 (s, 1H), 4.26 (m, 4H), 3.10 (m, 2H), 2.48 (q, J = 7.2 Hz, 2H), 2.21 (m, 4H), 1.09 (t, J = 7.5 Hz, 3H); MS-FAB *m/e* 645 (18, p), 624 (30), 623 (61), 601 (74), 309 (100), 307 (54); IR (KBr, cm^{-1}) 3414 (b), 2926, 1609, 1391, 1276, 1101, 785. Anal. ($C_{34}H_{27}O_9FNa_2 \cdot 3H_2O$) C, H.

Method M. 3,3-Diethoxy-2,3-dihydro-1*H*,7*H*-pyrano[2,3-*c*]xanthen-7-one (33). A mixture of 3-hydroxy-9-oxo-9*H*-xanthene (**32**, 3.00 g, 14.2 mmol), triethyl orthoacrylate (5.26 g, 28.4 mmol), and pivalic acid (0.720 g, 7.06 mmol) in toluene (75 mL) was refluxed for 16 h.[1,25] The mixture was cooled to room temperature and diluted with ether. The resulting mixture was washed once with water and once with dilute sodium hydroxide solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Recrystallization (hexane/ethyl acetate) of the residue provided 4.31 g (90%) of product as a white crystalline solid: mp 156 °C. Anal. ($C_{20}H_{20}O_5$) C, H.

Method N. 3-[4-(3-Hydroxy-9-oxo-9*H*-xanthene)]propanoic Acid Ethyl Ester (34). Compound **33** (3.40 g, 10.0 mmol) was dissolved in tetrahydrofuran (30 mL) and treated at room temperature with 1 N hydrochloric acid solution (0.20 mL) for 1 h. The reaction was diluted with ethyl acetate and washed twice with water. The organic phase was dried (sodium sulfate), filtered, and concentrated in vacuo. The resulting solid was recrystallized (hexane/ethyl acetate) to provide 3.09 g (99%) of product as a white microcrystalline solid: mp 181 °C; ^{1}H-NMR ($CDCl_3$) 9.10 (s, 1H, O*H*), 8.34 (dd, J = 7.9, 2.0 Hz, 1H), 8.17 (d, J = 8.8 Hz, 1H), 7.71 (t, J = 8 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.22 (t, J = 5.7 Hz, 2H), 2.90 (t, J = 6.6 Hz, 2H), 1.25 (t, J = 7.3 Hz, 3H); MS-FD *m/e* 312 (p); IR ($CHCl_3$, cm^{-1}) 3260 (b), 3025, 1648, 1620, 1607, 1467, 1328, 1242. Anal. ($C_{18}H_{16}O_5$) C, H.

Method O. 3-[4-[3-[3-[5-(Benzyloxy)-2-ethyl-4-phenylphenoxy]propoxy]-9-oxo-9*H*-xanthene]]propanoic Acid Ethyl Ester (35a). A mixture of compound **34** (0.821 g, 2.63 mmol), compound **21a** (1.00 g, 2.63 mmol), potassium carbonate (1.82g, 13.2 mmol), potassium iodide (44 mg, 0.26 mmol), and methyl sulfoxide (2 mL) in 2-butanone (15 mL) was refluxed for 18 h. The reaction mixture was cooled to room temperature, diluted with ether, and washed once with water and once with dilute aqueous sodium hydroxide. The organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo to provide an orange oil. Silica gel chromatography provided 1.48 g (86%) of pure product as a white solid: mp 99–102 °C. Anal. ($C_{12}H_{35}O_7$) C, H.

3-[4-[3-[3-(2-Ethyl-5-hydroxy-4-phenylphenoxy)propoxy]-9-oxo-9*H*-xanthene]]propanoic Acid Disodium Hemihydrate (35b). Compound **35a** (1.89 mmol) was debenzylated using method F and hydrolyzed using method K. The residue was dissolved in a minimum of 1 N sodium hydroxide solution and purified on CHP-20 resin to provide 817 mg (73%) of product as the disodium salt hemihydrate. Anal. ($C_{33}H_{28}O_7Na_2 \cdot 0.5H_2O$) C, H.

Ethyl 3-[4-[9-oxo-3-[3-[5-(benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]-9*H*-xanthene]]propanoate (36a). Compound **34** (2.63 mmol) was reacted with compound **21b** using method O to provide crude product, which was recrystallized (hexane/ethyl acetate) to provide 610 mg (61%) of pure product as an off-white crystalline solid: mp 115 °C. Anal. ($C_{42}H_{39}O_7F$) C, H, F.

3-[4-[9-Oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-9*H*-xanthene]]propanoic Acid (36b). Compound **36a** (0.742 mmol) was debenzylated using method F and hydrolyzed using method K to provide crude product. Recrystallization (toluene/ethyl acetate) provided 278 mg (67%) of product as a white crystalline solid. Anal. ($C_{33}H_{29}O_7F$) C, H.

Method P. 1,3-Dimethoxy-2-propylbenzene (38a). To a solution of 1,3-dimethoxybenzene (**37**, 160 g, 1.10 mol) in THF (1.6 L) cooled to −70 °C was added *n*-butyllithium in hexane (1.28 mol) at a rate which maintained the temperature of the reaction mixture at less than −45 °C. When addition was complete, the mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was cooled to −10 °C and 1-iodopropane (197 g, 1.16 mol) added dropwise. The mixture was allowed to warm to room temperature and stirred for 18 h. The mixture was then refluxed for 5 h, cooled to −10 °C, and carefully treated with methanol and ice water. The resulting mixture was extracted twice with 1 L portions of ether. The combined organic layers were dried (magnesium sulfate), filtered, and concentrated in vacuo. The crude product was passed through a short pad of silica eluting with 80% hexane/20% ethyl acetate. Concentration of the combined washings in vacuo provided 194 g (93%) of pure product.

2-Butyl-1,3-dimethoxybenzene (38b). 1,3-Dimethoxybenzene (109 mmol) was reacted with 1-iodobutane (115 mmol) using method P except that the final reaction mixture was not refluxed. Purification via silica gel chromatography provided 15.0 g (71%) of product as a yellow oil.

1,3-Dimethoxy-2-[1-(2-methylpropyl)]benzene (38c). 1,3-Dimethoxybenzene (272 mmol) was reacted with 1-iodo-2-methylpropane (272 mmol) using method P to provide crude product. Purification via silica chromatography provided 13.8 g (26%) of product as a colorless oil.

2-Benzyl-1,3-dimethoxybenzene (38d). 1,3-Dimethoxybenzene (391 mmol) was reacted with benzyl bromide (411 mmol) using method P except that the final reaction mixture was not refluxed. Purification via silica gel chromatography (ether/hexane) provided 18.8 g (8%) of product as a white solid: 53–55 °C. Anal. ($C_{15}H_{16}O_2$) C, H.

Method Q. 2-Propylresorcinol (39a). Compound **38a** (1.00 mol) was melted with pyridinium hydrochloride (925 g, 8.00 mol) at 180 °C for 8 h. The mixture was cooled to 110 °C, diluted with water (800 mL), cooled to room temperature, and stirred for 18 h. The mixture was diluted with additional water (1 L) and extracted four times with ethyl acetate (1 L portions). The organic layers were combined and washed four times with 1 N HCl (1 L portions). The organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo. The resulting material was dissolved in 90% hexane/10% ethyl acetate, passed down a short plug of silica gel, and concentrated in vacuo to provide 145 g (95%) of product as a crystalline solid.

2-Butylresorcinol (39b). Compound **38b** (77.6 mmol) was demethylated using method Q to provide 19 g of the desired product as a light brown oil. This material was not purified further but used directly in the preparation of compound **41e**.

2-[1-(2-Methylpropyl)]resorcinol (39c). Compound **38c** (92.8 mmol) was demethylated using method Q to provide crude product. Purification via silica gel chromatography (ether/hexane) provided 15.0 g (98%) of product as a light yellow oil. Anal. ($C_{10}H_{14}O_2$) C, H.

2-Benzylresorcinol (39d). Compound **38d** (65.8 mmol) was demethylated using method Q to provide crude product. Purification via silica gel chromatography provided 7.76 g (60%) of product as an off-white crystalline material: mp 81–83 °C. Anal. ($C_{13}H_{12}O_2$) C, H.

Method R. 2-[3-Hydroxy-2-propylphenoxy]benzoic Acid Methyl Ester (41a). A mixture of compound **39a** (75.0 g, 0.490 mol), methyl 2-iodobenzoate (129 g, 0.490 mol), copper bronze (47.0 g, 0.740 mol), and potassium carbonate (81.7 g, 0.592 mol) in dry pyridine (1 L) was thoroughly degassed with nitrogen and then refluxed for 6 h. The mixture was cooled to room temperature, filtered, and concentrated in vacuo to reveal a dark sludge. This material was dissolved in ethyl acetate and passed down a short (~500 cm^3) Florisil column. The resulting solution was washed twice with saturated copper sulfate solution and concentrated in vacuo. The residue was dissolved in methylene chloride and washed twice with 0.5 N sodium hydroxide solution. The organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo to provide a clear brown oil. Silica gel chromatography provided 45.4 g (32%) of product as a white solid: mp 80 °C; ^1H NMR ($CDCl_3$) 7.92 (dd, J = 7.8, 1.6 Hz, 1H), 7.42 (t, J = 8.4 Hz, 1H), 7.13 (t, J = 7.2 Hz, 1H), 6.97 (t, J = 8.1 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.62 (d, J = 8.0 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 5.65 (bs, 1H, OH), 3.88 (s, 3H), 2.66 (t, J = 7.6 Hz, 2H), 1.62 (hextet, J = 7.6 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H); MS-FD *m/e* 286 (p); IR ($CHCl_3$, cm^{-1}) 3350 (b), 2950, 1718, 1602, 1480, 1306, 1255, 1086, 981. Anal. ($C_{17}H_{18}O_4$) C, H.

2-(3-Hydroxy-2-propylphenoxy)phenylacetic Acid Methyl Ester (41b). Compound **39a** (39.9 mmol) was reacted with methyl 2-iodophenylacetate (39.9 mmol) using method R to provide 1.27 g (11%) of product as a yellow oil.

2-Fluoro-6-(3-hydroxy-2-propylphenoxy)benzoic Acid Methyl Ester (41c). Compound **39a** (46.8 mmol) was reacted with 2-fluoro-6-iodobenzoic acid methyl ester (46.8 mmol) using method R to provide 3.10 g (22%) of product as an oil.

Method S. 4-Fluoro-6-(3-hydroxy-2-propylphenoxy)-benzoic Acid Methyl Ester (41d). To a solution of compound **39a** (10.0 g, 65.7 mmol) in pyridine (120 mL) was added potassium *tert*-butoxide (7.00 g, 62.5 mmol) at room temperature with stirring. To this was added a mixture of methyl 2-bromo-4-fluorobenzoate (7.60 g, 34.4 mmol) and copper(I) iodide (12.5 g, 65.7 mmol) in pyridine (120 mL). The resulting mixture was gently refluxed for 4 h. The reaction mixture was cooled to room temperature and stirred for 18 h. The mixture was concentrated in vacuo and the resulting material dissolved in ethyl ether. The solution was washed once with 5 N aqueous hydrochloric acid. The aqueous layer was extracted once with a fresh portion of ether, and the combined organic layers were washed twice with 5 N aqueous ammonium hydroxide. The organic layer was washed once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Silica gel chromatography of the resulting residue provided 1.45 g (15%) of product as a light tan solid: mp 92–94 °C. Anal. ($C_{17}H_{17}O_3F$) C, H.

2-(2-Butyl-3-hydroxyphenoxy)benzoic Acid Methyl Ester (41e). Compound **39b** (90.4 mmol) was reacted with methyl 2-iodobenzoate (180 mmol) using method S to provide 3.02 g (11%) of product as an orange oil. Anal. ($C_{18}H_{20}O_4$) H; C: calcd, 71.98; found, 70.82.

2-[3-Hydroxy-2-[1-(2-methylpropyl)]phenoxy]benzoic Acid Methyl Ester (41f). Compound **39c** (87.3 mmol) was reacted with methyl 2-iodobenzoate (87.3 mmol) using method R to provide 3.11 g (12%) of product as a light yellow oil. Anal. ($C_{18}H_{20}O_4$) C, H.

2-(2-Benzyl-3-hydroxyphenoxy)benzoic Acid Methyl Ester (41g). Compound **39d** (87.3 mmol) was reacted with methyl 2-iodobenzoate (87.3 mmol) using method R to provide 900 mg (7%) of product as a white crystalline material: mp 79–81 °C. Anal. ($C_{21}H_{18}O_4$) C, H.

3-(2-Cyanophenoxy)-2-propylphenol (41h). Compound **39a** (49.3 mmol) was reacted with 2-bromobenzonitrile using method R to provide 1.79 g (14%) of product as a white crystalline material: mp 103–107 °C. Anal. ($C_{16}H_{15}NO_2$) H, N; C: calcd, 75.87; found, 75.09.

2-[2-Propyl-3-[3-[5-(benzyloxy)-2-ethyl-4-phenylphenoxy]propoxy]phenoxy]benzoic Acid Methyl Ester (42a). Compound **41a** (1.57 mmol) was reacted with compound **21a** using method O to provide crude product, which was not purified but immediately converted to compound **43a**.

2-[2-Propyl-3-[3-[5-(benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic Acid Methyl Ester (42b). Compound **41a** (50.2 mmol) was reacted with compound **22a** (50.2 mmol) using method L to provide crude product as a yellow oil. Silica gel chromatography provided 25.4 g (78%) of pure product as a pale golden oil: ^1H NMR ($CDCl_3$) 7.91 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 8.6 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.25–7.43 (m, 6H), 7.03–7.38 (m, 5H), 6.84 (d, J = 8.3 Hz, 1H), 6.71 (d, J = 8.1 Hz, 1H), 6.63 (s, 1H), 6.47 (d, J = 8.1 Hz, 1H), 5.03 (s, 2H), 4.24 (t, J = 5.7 Hz, 2H), 4.21 (t, J = 5.8 Hz, 2H), 3.86 (s, 3H), 2.69 (t, J = 7.8 Hz, 2H), 2.64 (t, J = 7.7 Hz, 2H), 2.34 (quintet, J = 6.0 Hz, 2H), 1.60 (hextet, J = 5.0 Hz, 2H), 1.22 (t, J = 7.5 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H); MS-FD *m/e* 648 (p); IR ($CHCl_3$, cm^{-1}) 2960, 1740, 1604, 1497, 1461, 1112. Anal. ($C_{41}H_{41}O_6F$) C, H.

2-[2-Propyl-3-[3-[5-benzyl-2-ethyl-4-(4-fluorophenyl)-phenoxy]propoxy]phenoxy]phenylacetic Acid Methyl Ester (42c). Compound **41b** (2.51 mmol) was reacted with compound **22a** (2.51 mmol) using method L to provide crude product. Purification via silica gel chromatography provided 750 mg (45%) of pure product as a colorless oil. Anal. ($C_{42}H_{43}O_6F$) C, H.

2-Fluoro-6-[2-propyl-3-[3-[5-(benzyloxy)-2-ethyl-4-phenylphenoxy]propoxy]phenoxy]benzoic Acid Methyl Ester (42d). Compound **41c** (2.17 mmol) was reacted with compound **21a** (2.17 mmol) using method O to provide the expected product, which was not purified but immediately converted to compound **43d**.

2-Fluoro-6-[2-propyl-3-[3-(5-[benzyloxy)-4-bromo-2-ethylphenoxy]propoxy]phenoxy]benzoic Acid Methyl Ester (42e). Compound **41c** (4.80 mmol) was reacted with compound **20a** (4.80 mmol) using method O to provide a light brown oil. Silica gel chromatography provided 2.05 g (66%) of pure product as a colorless oil: ^1H NMR ($CDCl_3$) 7.49 (d, J = 7.1 Hz, 2H), 7.20–7.45 (m, 5H), 7.14 (t, J = 8.2 Hz, 1H), 6.82 (t, J = 8.5 Hz, 1H), 6.73 (d, J = 8.3 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 6.53 (s, 1H), 6.52 (d, J = 8.5 Hz, 1H), 5.13 (s, 2H), 4.20 (t, J = 6.0 Hz, 2H), 4.13 (t, J = 6.0 Hz, 2H), 3.92 (s, 3H), 2.58 (m, 4H), 2.30 (quintet, J = 6.0 Hz, 2H), 1.51 (hextet, J = 7.6 Hz, 2H), 1.16 (t, J = 7.9 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H).

4-Fluoro-6-[2-propyl-3-[3-[5-(benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic Acid Methyl Ester (42f). Compound **41d** (1.75 mmol) was alkylated with compound **21b** (1.75 mmol) using method O to provide crude product as an oil. Purification via silica gel chromatography provided 640 mg (55%) of product as a white crystalline solid: mp 77–78 °C. Anal. ($C_{41}H_{40}O_6F_2$) C, H.

2-[2-Propyl-3-[4-[5-(benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]butoxy]phenoxy]benzoic Acid Methyl Ester (42g). Compound **41a** (4.84 mmol) was reacted with compound **21c** (4.84 mmol) using method O to provide crude product as an oil. Purification via silica gel chromatography provided 2.40 g (75%) of product as a colorless oil. Anal. ($C_{42}H_{43}O_6F$) C, H.

2-[2-Propyl-3-[5-[5-(benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]pentoxy]phenoxy]benzoic Acid Methyl Ester (42h). Compound **41a** (6.99 mmol) was reacted with compound **21d** (6.99 mmol) using method O to provide crude product as an oil. Purification via silica gel chromatography provided 3.90 g (83%) of product as a colorless oil. Anal. ($C_{42}H_{43}O_6F$) C, H.

2-[2-Butyl-3-[3-[5-(benzyloxy)-2-ethyl-4-(4-fluorophenyl)-phenoxy]propoxy]phenoxy]benzoic Acid Methyl Ester (42i). Compound **41e** (1.76 mmol) was reacted with compound **21b** (1.76 mmol) using method O to provide crude product as an oil. Purification via silica gel chromatography provided 700 mg (60%) of product as a yellow oil. Anal. ($C_{42}H_{43}O_6F$) C, H.

2-[2-[1-(2-Methylpropyl)]-3-[3-[5-(benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic Acid Methyl Ester (42j). Compound **41f** (2.51 mmol) was reacted with compound **21b** (2.51 mmol) using method O to provide crude product as an oil. Purification via silica gel chromatography (ether/hexane) provided 620 mg (35%) of product as an off-white solid: mp 82–84 °C. Anal. ($C_{42}H_{43}O_6F$) C, H.

2-[2-Benzyl-3-[3-[5-(benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic Acid Methyl Ester (42k). Compound **41g** (2.51 mmol) was reacted with compound **21b** (2.51 mmol) using method O to provide crude product as an oil. Purification via silica gel chromatography provided 680 mg (40%) of pure product as a glass. Anal. ($C_{45}H_{41}O_6F$) C, H.

5-Ethyl-4-[3-[2-propyl-3-(2-cyanophenoxy)phenoxy]propoxy][1,1'-biphenyl]-2-ol (42l). Compound **41h** (6.56 mmol) was reacted with compound **21a** (6.56 mmol) using method O to provide crude product as an oil. The crude product was dissolved in hexane/ethyl acetate and passed through a short silica gel column. This material was not purified further but directly converted to compound **43l**.

2-[2-Propyl-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)-propoxy]phenoxy]benzoic Acid Sodium Salt Hemihydrate (43a). Compound **42a** was debenzylated using method F and hydrolyzed using method K to provide crude product. The residue was dissolved in a minimum of 1 N sodium hydroxide solution and purified on CHP-20 resin to provide 200 mg (21%) of product as a fluffy white solid. Anal. ($C_{33}H_{32}O_6 \cdot 0.5H_2O$) C, H.

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic Acid Sodium Salt (43b). Compound **42b** (50.9 mmol) was debenzylated using method F and hydrolyzed using method K to provide crude product. The crude acid was dissolved in a minimum of 1 N sodium hydroxide solution and purified on CHP-20 resin to provide 21.2 g (74%) of product as a white amorphous solid: ^{1}H NMR (DMSO-d_6) 10.50 (bs, 1H, O*H*), 7.51 (m, 3H), 7.20 (t, J = 7.4 Hz, 1H), 7.13 (m, 2H), 7.00 (m, 2H), 6.95 (s, 1H), 6.67 (dd, J = 8.2, 3.3 Hz, 2H), 6.62 (s, 1H), 6.26 (d, J = 8.2 Hz, 1H), 4.14 (t, J = 5.8 Hz, 2H), 4.02 (t, J = 5.7 Hz, 2H), 2.60 (t, J = 6.8 Hz, 2H), 2.47 (q, J = 7.3 Hz, 2H), 2.16 (t, J = 5.9 Hz, 2H), 1.45 (hextet, J = 7.5 Hz, 2H), 1.07 (t, J = 7.5 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H); MS-FAB *m/e* 568 (38, p + 1), 567 (100, p), 544 (86), 527 (77), 295 (65), 253 (45); IR (KBr, cm^{-1}) 3407 (b), 2962, 1603, 1502, 1446, 1395, 1239, 1112. Anal. ($C_{33}H_{32}O_6FNa$) C, H, F.

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]phenylacetic Acid (43c). Compound **42c** (1.10 mmol) was debenzylated using method F and hydrolyzed using method K to provide crude product. Purification via silica gel chromatography provided 320 mg (60%) of product as a glass. Anal. ($C_{34}H_{35}O_6F$) C, H.

2-Fluoro-6-[2-propyl-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)propoxy]phenoxy]benzoic Acid Disodium Salt (43d). Compound **42d** was debenzylated using method F and hydrolyzed using method K to provide crude product. The residue was dissolved in a minimum of 1 N sodium hydroxide solution and purified on CHP-20 resin to provide 468 mg (37%) of product as a fluffy white solid. Anal. ($C_{33}H_{31}O_6FNa_2$) C, H, F.

2-Fluoro-6-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic Acid Sodium Salt Hydrate (43e). Compound **42e** (2.72 mmol) was reacted with (4-fluorophenyl)boronic acid (8.16 mmol) using method D. The resulting crude product was debenzylated using method F and hydrolyzed using method K. The residue was dissolved in a minimum of 1 N sodium hydroxide solution and purified on CHP-20 resin to provide 403 mg (25%) of product as a fluffy white solid. Anal. ($C_{33}H_{31}O_6F_2Na \cdot H_2O$) C, H.

4-Fluoro-6-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic Acid (43f). Compound **42f** (1.02 mmol) was debenzylated using method F and hydrolyzed using method K to provide 354 mg (72%) of product as a white solid: mp 62–64 °C. Anal. ($C_{33}H_{32}O_6F_2$) C, H.

2-[2-Propyl-3-[4-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]butoxy]phenoxy]benzoic Acid Sesquihydrate (43g). Compound **42g** (3.32 mmol) was debenzylated using method F and hydrolyzed using method K to provide 1.00 g (85%) of product as a white solid: mp 65–68 °C. Anal. ($C_{34}H_{35}O_6F \cdot 1.5H_2O$) C, H.

2-[2-Propyl-3-[5-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]pentoxy]phenoxy]benzoic Acid (43h). Compound **42h** (5.32 mmol) was debenzylated using method F and hydrolyzed using method K to provide 2.64 g (91%) of product as a white crystalline solid. Anal. ($C_{35}H_{37}O_6F$) C, H.

2-[2-Butyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic Acid Hydrate (43i). Compound **42i** (1.04 mmol) was debenzylated using method F and hydrolyzed using method K to provide 114 mg (30%) of product as an off-white solid: mp 62–64 °C. Anal. ($C_{34}H_{35}O_6F \cdot H_2O$) C, H.

2-[2-[1-(2-Methylpropyl)]-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic Acid (43j). Compound **42j** (0.906 mmol) was debenzylated using method F and hydrolyzed using method K to provide 250 mg (57%) of product as an off-white solid: mp 48–49 °C. Anal. ($C_{34}H_{35}O_6F$) C, H.

2-[2-Benzyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic Acid (43k). Compound **42k** (0.947 mmol) was debenzylated using method F and hydrolyzed using method K to provide crude product. Purification via silica gel chromatography provided 450 mg (80%) of product as a glass. Anal. ($C_{37}H_{33}O_6F$) C, H.

5-Ethyl-4-[3-[2-propyl-3-[2-(2*H*-tetrazol-5-yl)phenoxy]-phenoxy]propoxy][1,1'-biphenyl]-2-ol Disodium Salt Sesquihydrate (43l). Compound **42l** (6.56 mmol) was dissolved in 2-methoxyethanol (50 mL). To this solution were added lithium azide (1.38 g, 24.2 mmol) and triethylammonium bromide (1.30 g, 7.14 mmol). The resulting mixture was refluxed for 48 h, cooled to room temperature, and passed down a short silica gel column. The column was washed with excess ethyl acetate, and the combined washings were concentrated in vacuo. The resulting material was debenzylated using method F. The crude tetrazole was dissolved in a minimum of 1 N sodium hydroxide solution and purified on CHP-20 resin to provide 320 mg (8%) of product as a fluffy white solid: ^{1}H NMR (DMSO-d_6) 7.81 (dd, J = 7.7, 1.5 Hz, 1H), 7.49 (d, J = 7.5 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.21 (m, 2H), 7.11 (t, J = 7.3 Hz, 1H), 6.99 (m, 2H), 6.76 (d, J = 8.1 Hz, 1H), 6.68 (d, J = 8.2 Hz, 1H), 6.56 (s, 1H), 6.22 (d, J = 8.2 Hz, 1H), 4.16 (t, J = 5.8 Hz, 2H), 4.10 (t, J = 5.9 Hz, 2H), 2.61 (t, J = 6.5 H, 2H), 2.48 (m, 2H), 2.22 (m, 2H), 1.45 (hextet, J = 7.4 Hz, 2H), 1.08 (t, J = 7.4 Hz, 3H), 0.79 (t, J = 7.3 Hz, 3H); MS-FAB *m/e* 595 (35, p − 1), 574 (39), 573 (100), 551(99); IR (KBr, cm^{-1}) 3418 (b), 2962, 1577, 1458, 1243, 1229, 1147, 1117. Anal. ($C_{33}H_{32}N_4O_4Na_2 \cdot 1.5H_2O$) C, H, N.

3-Methoxy-2-propylphenol (44). To a suspension of 97% sodium hydride (1.21 g, 50.0 mmol) in dry DMF (40 mL) at room temperature was carefully added a solution of ethanethiol (2.65 g, 40.5 mmol) dissolved in a minimum of DMF. After stirring for 5 min, compound **38a** (2.51 g, 13.9 mmol) was added and the resulting mixture stirred for 48 h. The reaction mixture was cooled to 0 °C and treated with 10% aqueous hydrochloric acid (70 mL). The mixture was diluted with ethyl acetate and washed three times with water. The combined aqueous layers were extracted once with ether. The combined organic layers were dried (sodium sulfate), filtered, and concentrated in vacuo to provide 2.20 g (90%) of product as an oil.

2-(3-Methoxy-2-propylphenoxy)benzonitrile (45). A mixture of compound **44** (1.00 g, 6.02 mmol), 2-fluorobenzonitrile (0.728 g, 6.02 mmol), 37% potassium fluoride–alumina (1.00 g), and 18-crown-6 (0.160 g, 0.606 mmol) in acetonitrile (25 mL) was refluxed for 48 h. The mixture was cooled to room temperature, filtered, and diluted with ethyl acetate. The organic layer was washed once with saturated potassium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo to provide 1.58 g (99%) of pure product as an oil. Anal. ($C_{17}H_{17}NO_2$) C, H, N.

Alternate Synthesis of 3-(2-Cyanophenoxy)-2-propylphenol (41h). To a solution of compound **45** (8.0 g, 30 mmol) in methylene chloride (50 mL) at −78 °C was added boron tribromide (8.5 mL, 90 mmol) dropwise via syringe. The resulting mixture was allowed to warm to −15 °C, and the reaction was followed to completion via TLC. The mixture was filtered and concentrated in vacuo at room temperature. The

residue was dissolved in ethyl acetate and washed once with water. The organic phase was dried (sodium sulfate), filtered, and concentrated in vacuo. Silica chromatography (hexane/ethyl acetate) provided 4.0 g (52%) of product identical to the material described above.

Alternate Synthesis of 2-(3-Hydroxy-2-propylphenoxy)benzoic Acid Methyl Ester (41a). Compound **41h** (520 mg, 2.05 mmol) was dissolved in methanol (5 mL) and treated with 5 N aqueous sodium hydroxide solution at reflux for 48 h. The mixture was cooled to room temperature and carefully neutralized with 5 N aqueous hydrochloric acid. Addition of a slight excess of acid resulted in precipitation of a crystalline material which was collected via vacuum filtration. This material was dissolved in methanol (10 mL) and treated with concentrated sulfuric acid (0.20 mL) at reflux for 18 h. The mixture was cooled to room temperature and diluted with ether and water. The organic phase was separated and washed once with saturated sodium bicarbonate solution, dried (sodium sulfate), filtered, and concentrated in vacuo to provide 480 mg (82%) of product as a white solid identical to the material described above.

2-[3-(Allyloxy)benzoyl]benzoic Acid (47a). To a solution of 3-(allyloxy)bromobenzene (**46**, 15.0 g, 70.5 mmol) in tetrahydrofuran (750 mL) at −70 °C was added 1.6 M *n*-butyllithium (44.1 mL, 70.5 mmol). After stirring for 1 h, a solution of phthalic anhydride (11.4 g, 77.0 mmol) in tetrahydrofuran (100 mL, previously cooled to −70 °C) was added over 1 h. The mixture was allowed to warm to room temperature and stirred for 3 h. The mixture was diluted with saturated ammonium chloride solution and extracted with ether. The organic layer was washed three times with 1 N sodium hydroxide solution, and the combined aqueous layers were back-extracted with a fresh portion of ether. The aqueous layer was adjusted to pH ~3 with aqueous hydrochloric acid and extracted three times with fresh portions of ether. The combined organic layers were washed once with water and once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo to reveal an off-white solid. Recrystallization from ether/hexane provided 10.3 g (52%) of product as a white crystalline solid: mp 109 °C. Anal. ($C_{17}H_{14}O_4$) C, H.

Method T. 2-[3-(Allyloxy)benzoyl]benzoic Acid Methyl Ester (47b). A solution of compound **47a** (9.00 g, 31.9 mmol) in methanol (100 mL) was saturated with hydrogen chloride gas. The resulting solution was stirred at room temperature for 18 h. The reaction mixture was concentrated in vacuo and diluted with ether. The resulting solution was washed once with saturated sodium bicarbonate solution, water, and saturated sodium chloride solution. The organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo. The resulting pale yellow oil solidified upon standing to provide 9.45 g (100%) of product as a white solid: mp 50−52 °C. Anal. ($C_{18}H_{16}O_4$) C, H.

Method U. 2-[3-Hydroxy-4-[3-(1-propenyl)]benzoyl]benzoic Acid Methyl Ester (48) and 2-[3-Hydroxy-2-[3-(1-propenyl)]benzoyl]benzoic Acid Methyl Ester (49). Compound **47b** (6.70 g) was heated neat at 175 °C for 30 h. The product mixture was cooled to room temperature and purified via silica gel chromatography (95:5 methylene chloride/ethyl acetate) to provide 1.44 g (21%) of **48** and 3.62 g (54%) of **49** as white solids.

48: mp 139−140 °C; ^{1}H NMR ($CDCl_3$) 8.08 (dd, J = 7.9, 3.1 Hz, 1H), 7.63 (t, J = 8 Hz, 1H), 7.55 (t, J = 8 Hz, 1H), 7.40 (d, J = 8 Hz, 1H), 7.35 (s, 1H), 7.16 (s, 2H), 6.00 (m, 1H), 5.62 (bs, 1H, *OH*), 5.15 (m, 2H), 3.65 (s, 3H), 3.47 (d, J = 5 Hz, 2H). Anal. ($C_{18}H_{16}O_4$) C, H.

49: mp 107−109 °C; ^{1}H NMR ($CDCl_3$) 7.91 (dd, J = 7.8, 2.2 Hz, 1H), 7.43−7.63 (m, 3H), 7.08 (m, 1H), 7.02 (d, J = 8 Hz, 1H), 6.80 (dd, J = 8, 2 Hz, 1H), 6.15 (m, 1H), 5.42 (bs, 1H, *OH*), 5.23 (d, J = 16 Hz, 1H), 5.16 (d, J = 11 Hz, 1H), 3.81 (d, J = 6 Hz, 2H), 3.68 (s, 3H). Anal. ($C_{18}H_{16}O_4$) C, H.

2-[2-[3-(1-Propenyl)]-3-[3-[5-(benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]benzoyl]benzoic Acid Methyl Ester (50a). Compound **49** (1.75 mmol) was reacted with compound **22a** using method L to provide crude product. Recrystallization from ether/hexane provided 750 mg (65%) of product as a white solid: mp 90−91 °C. Anal. ($C_{42}H_{39}O_5F$) C, H.

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]benzoyl]benzoic Acid (50b). Compound **50a** (0.483 mmol) was hydrogenated using method F and hydrolyzed using method K. Purification of the crude product via silica gel chromatography provided 150 mg (56%) of product as a glass. Anal. ($C_{33}H_{33}O_5F$) H; C: calcd, 73.36; found, 69.71.

2-[(3-Hydroxy-2-propylphenyl)methyl]benzoic Acid Methyl Ester (51). Compound **49** (10.1 mmol) was hydrogenated using method F (with methanol as the solvent) in the presence of concentrated sulfuric acid (1 mL). The mixture was concentrated in vacuo to a volume of approximately 30 mL, filtered, and saturated with hydrogen chloride gas. The resulting mixture was stirred for 18 h and then concentrated in vacuo. The residue was dissolved in ether and washed once with saturated sodium bicarbonate solution. The aqueous layer was back-extracted with a fresh portion of ether. The combined organic layers were washed once with saturated sodium chloride solution, dried, filtered, and concentrated in vacuo to provide 2.60 g (90%) of product as an orange oil, which was converted directly to compound **52a**.

2-[[2-Propyl-3-[3-[5-(benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]phenyl]methyl]benzoic Acid Methyl Ester (52a). Compound **51** (4.68 mmol) was reacted with compound **21b** using method O to provide crude product. Recrystallization from hexane provided 1.72 g (38%) of product as a white solid: mp 83−84 °C. Anal. ($C_{42}H_{43}O_5F$) C, H.

2-[[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenyl]methyl]benzoic Acid (52b). Compound **52a** (2.32 mmol) was debenzylated using method F and hydrolyzed using method K to provide a crude product. Recrystallization from ether/hexane provided 860 mg (68%) of product as a white solid: mp 150−151 °C. Anal. ($C_{35}H_{35}O_5F$) C, H.

2-[3-(Allyloxy)thiophenoxy]bromobenzene (53a). To a solution of 3-(allyloxy)bromobenzene (**46**, 8.20 g, 38.7 mmol) in tetrahydrofuran (600 mL) at −74 °C was added 1.6 M *n*-butyllithium (24.2 mL, 38.7 mmol). After stirring for 30 min this solution was cannulated into a solution of bis(2-bromophenyl) disulfide (16.0 g, 42.5 mmol) in tetrahydrofuran (160 mL) at −74 °C. The resulting mixture was allowed to warm to room temperature, then diluted with saturated ammonium chloride solution, and filtered. The aqueous layer was extraced three times with ether, and the combined organic layers were washed once with water and once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo to provide a yellow oil. Purification via silica gel chromatography provided 9.40 g (76%) of product as a light yellow oil. Anal. ($C_{15}H_{13}OBrS$) C, H.

2-(3-Allyloxythiophenoxy)benzoic Acid Methyl Ester (53b). To a solution of compound **53a** (9.00 g, 28.0 mmol) in tetrahydrofuran (175 mL) at −78 °C was added 1.6 M *n*-butyllithium (19.2 mL, 30.8 mmol) dropwise. After stirring for 15 min, the solution was saturated with carbon dioxide gas, resulting in a thick gel. Tetrahydrofuran (50 mL) was added and the resulting mixture allowed to warm to room temperature. The mixture was diluted with saturated ammonium chloride solution. The aqueous layer was extracted once with ether, and the combined organic layers were concentrated in vacuo. The residue was dissolved in a fresh portion of ether and extracted with 1 N aqueous sodium hydroxide. The aqueous layer was washed once with a fresh portion of ether and acidified with aqueous hydrochloric acid. The resulting aqueous layer was extracted with a fresh portion of ether. This last organic layer was washed once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. The crude acid was converted to the methyl ester using method T to provide crude product. Purification via silica gel chromatography provided 4.80 g (68%) of product as a faint yellow oil. Anal. ($C_{17}H_{16}O_3S$) C, H.

2-[3-Hydroxy-4-[3-(1-propenyl)]thiophenoxy]benzoic Acid Methyl Ester (54) and 2-[3-Hydroxy-2-[3-(1-propenyl)]thiophenoxy]benzoic Acid Methyl Ester (55). Com-

pound **53b** (15.0 mmol) was rearranged using method U to provide crude product. Purification via silica gel chromatography (methylene chloride) provided 1.46 g (27%) of **54** and 2.22 g (41%) of **55** as white solids. **54**: mp 96–97 °C. Anal. ($C_{17}H_{16}O_3S$) C, H. **55**: mp 72–74 °C. Anal. ($C_{17}H_{16}O_3S$) C, H.

2-[2-[3-(1-Propenyl)]-3-[3-[5-(benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]thiophenoxy]benzoic Acid Methyl Ester (56a). Compound **55** (6.66 mmol) was reacted with compound **21b** using method O to provide crude product. Purification via silica gel chromatography (hexane/diethyl ether) provided 2.90 g (66%) of pure product as a white solid: mp 76–77 °C. Anal. ($C_{41}H_{39}O_5FS$) C, H.

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]thiophenoxy]benzoic Acid Methyl Ester (56b). Compound **56a** (4.07 mmol) was hydrogenated using method F to provide an oil (~2 g). A solution of this material (1.39 g) in methylene chloride (25 mL) at −78 °C was treated with 1 M boron tribromide (3.61 mL, 3.61 mmol) and allowed to stir for 1 h. The reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was washed once with water, dried (sodium sulfate), filtered, and concentrated in vacuo to provide a yellow oil. Purification via silica gel chromatography provided 770 mg (47%) of product as a white solid. Anal. ($C_{34}H_{35}O_5FS$) C, H.

2-[2-(1-Propyl)-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]thiophenoxy]benzoic Acid (56c). Compound **56b** (1.22 mmol) was hydrolyzed using method K to provide 689 mg (100%) of product as a white solid: mp 153–155 °C. Anal. ($C_{33}H_{33}O_5FS$) C, H.

2-[[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenyl]sulfinyl]benzoic Acid (56d). To a solution of compound **56c** (450 mg, 0.803 mmol) in methylene chloride (10 mL) at −78 °C was added a solution of 85% *m*-chloroperoxybenzoic acid (138 mg) in methylene chloride (2 mL). After 40 min the mixture was concentrated in vacuo. Purification of the residue via silica gel chromatography (95% chloroform/4.5% methanol/0.5% acetic acid) provided 380 mg (80%) of product as an off-white solid: mp >100 °C dec. Anal. ($C_{33}H_{33}O_6FS$) H; C: calcd, 68.73; found, 67.54.

2-[[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenyl]sulfonyl]benzoic Acid Hydrate (56e). To a solution of compound **56d** (150 mg, 0.260 mmol) in methylene chloride (3.0 mL) at 0 °C was added a solution of 85% *m*-chloroperoxybenzoic acid (53 mg) in methylene chloride (1 mL). After 1 h the mixture was warmed to 4 °C and stirred for 18 h. The mixture was concentrated in vacuo and purified via silica gel chromatography (90% chloroform/9.5% methanol/0.5% acetic acid) to provide 90 mg (58%) of product as a white solid: mp 80–90 °C. Anal. ($C_{33}H_{33}O_7FS \cdot H_2O$) C, H.

Ethyl 3-(2-Hydroxy-6-methoxyphenyl)propionate (58). 3-Methoxyphenol (**57**, 9.1 mmol) was reacted with triethyl orthoacrylate using method M and hydrolyzed using method N to provide crude product. Silica gel chromatography provided 540 mg (**31**%) of product as a crystalline solid: mp 77–79 °C. Anal. ($C_{12}H_{16}O_4$) C, H.

3-[2-[3-[5-(Benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]-6-methoxyphenyl]propanoic Acid Ethyl Ester (61a). Compound **58** (2.9 mmol) was reacted with compound **21b** using method O to provide crude product. Purification via silica gel chromatography (hexane/diethyl ether) provided 750 mg (44%) of pure product as a white solid: mp 76–78 °C. Anal. ($C_{36}H_{39}O_6F$) C, H.

3-[2-[3-[5-(Benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]-6-methoxyphenyl]propanoic Acid (61b). Compound **61a** (1.18 mmol) was hydrolyzed using method K to provide 485 mg (74%) of product as an amorphous solid. Anal. ($C_{34}H_{35}O_6F$) C, H.

3-[2-[3-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-6-methoxyphenyl]propanoic Acid (61c). Compound **61b** (0.81 mmol) was hydrogenated using method F to provide 295 mg (78%) of the desired product as a solid which was recrystallized from ethanol/diethyl ether: mp 142–144 °C. Anal. ($C_{27}H_{29}O_6F$) C: calcd, 69.22; found, 66.08; H: calcd, 6.24; found, 5.74.

3-[2-[3-[5-(Benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]phenyl]propanoic Acid Ethyl Ester (62a). A solution of compound **59** (1.1 g, 6.1 mmol) in methyl sulfoxide (75 mL) and tetrahydrofuran (20 mL) was treated with 60% sodium hydride in mineral oil (6.5 mmol) at room temperature for 15 min. Compound **21b** (3.4 g, 7.0 mmol) was added and the resulting solution stirred for 1.5 h. The mixure was diluted with water and extracted with ethyl acetate. The organic layer was washed once with water and once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo to provide crude product. Purification via silica gel chromatography (hexane/diethyl ether) provided 1.8 g (52%) of pure product as a colorless oil. Anal. ($C_{34}H_{35}O_5F$) C, H.

3-[2-[3-[5-(Benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]phenyl]propanoic Acid (62b). Compound **62a** (2.03 mmol) was hydrolyzed using method K to provide 750 mg (70%) of product as a crystalline solid: mp 78–79 °C. Anal. ($C_{33}H_{33}O_5F$) C, H.

3-[2-[3-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenyl]propanoic Acid (62c). Compound **62b** (5.7 mmol) was hydrogenated using method F to provide 1.9 g (75%) of the desired product as a solid which was recrystallized from toluene/hexane: mp 77–78 °C. Anal. ($C_{26}H_{27}O_5F$) C, H.

3-[2-[3-[5-(Benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]phenyl]propionitrile (63a). Compound **60** (5.7 mmol) was reacted with compound **21b** using method A to provide crude product. Purification via silica gel chromatography (hexane/diethyl ether) provided 1.7 g (56%) of pure product as an oil. Anal. ($C_{33}H_{32}NO_3$) C, H, N.

2-[2-[3-[5-(Benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]phenyl]-1-(1*H*-tetrazol-5-yl)ethane (63b). A solution of compound **63a** (1.7 g, 3.5 mmol) in tri-*n*-butyltin azide (15 mL) was heated at 95 °C for 23 h, cooled to room temperature, and diluted with a mixture of acetic acid (30 mL), THF (15 mL), and acetonitrile (75 mL). The mixture was stirred for 3 h, washed several times with hexane, and concentrated in vacuo. Purification of the resulting residue via silica gel chromatography (diethyl ether hexane) provided 1.8 g (98%) of pure product as a solid: mp 153–155 °C. Anal. ($C_{33}H_{33}N_4O_3F$) C, H, N.

2-[2-[3-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenyl]-1-(1*H*-tetrazol-5-yl)ethane (63c). Compound **63b** (3.3 mmol) was hydrogenated using method F to provide 280 mg (19%) of the desired product as an amorphous solid. Anal. ($C_{26}H_{27}N_4O_3F$) H, N; C: calcd, 67.52; found, 66.69.

3-[(4-Cyanobutyl)oxy]phenol (65). Resorcinol (5.5 g, 50 mmol) was alkylated with 5-bromovaleronitrile (2.5 mmol) using method L to provide crude product. Purification via silica gel chromatography (methanol/dichloromethane) and recrystalization from hexane provided 3.1 g (64%) of pure product: mp 58–60 °C. Anal. ($C_{11}H_{13}NO_2$) C, H, N.

3-[[4-(Ethoxycarbonyl)butyl]oxy]phenol (66a). Resorcinol (5.5 g, 50 mmol) was alkylated with ethyl 5-bromovalerate (2.5 mmol) using method L to provide crude product. Purification via silica gel chromatography (diethyl ether/hexane) and recrystallization from hexane provided 3.4 g (58%) of pure product: mp 37–39 °C. Anal. ($C_{11}H_{18}O_4$) C, H.

3-[[4-[(Dimethylamino)carbonyl]butyl]oxy]phenol (66b). Compound **66a** (3.7 g, 17 mmol) was dissolved in 40% aqueous diethylamine and stirred at room temperature for 24 h. The mixture was extracted with dichloromethane and the organic layer washed once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo. Purification via silica gel chromatography (methanol/diethyl ether) and recrystallization from ether provided 1.6 g (44%) of product: mp 111–113 °C. Anal. ($C_{13}H_{19}NO_3$) C, H, N.

3-[6-[(4-Cyanobutyl)oxy]-2-hydroxyphenyl]propanoic Acid Ethyl Ester (67). Compound **65** (11 mmol) was reacted with triethyl orthoacrylate using method M and hydrolyzed using method N to provide crude product. Silica gel chromatography (diethyl ether/hexane) provided 500 mg (17%) of product as an oil. Anal. ($C_{16}H_{21}NO_4$) C, H, N.

3-[6-[[4-(Ethoxycarbonyl)butyl]oxy]-2-hydroxyphenyl]propanoic Acid Ethyl Ester (68). Compound **66a** (26 mmol) was reacted with triethyl orthoacrylate using method M and

hydrolyzed using method N to provide crude product. Silica gel chromatography (diethyl ether/hexane) provided 2.2 g (25%) of product as an oil. Anal. ($C_{18}H_{26}O_6$) H; C: calcd, 78.40; found, 64.38.

3-[6-[[4-[(Dimethylamino)carbonyl]butyl]oxy]-2-hydroxyphenyl]propanoic Acid Ethyl Ester (69). Compound **66b** (15.6 mmol) was reacted with triethyl orthoacrylate using method M and hydrolyzed using method N to provide crude product. Silica gel chromatography (methanol/dichloromethane) provided 970 mg (21%) of product as an oil. Anal. ($C_{18}H_{27}NO_5$) C, H, N.

3-[2-[3-[5-(Benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]-6-[(4-cyanobutyl)oxy]phenyl]propanoic Acid Ethyl Ester (70a). Compound **67** (1.72 mmol) was reacted with compound **21b** using method A to provide crude product. Purification via silica gel chromatography (hexane/diethyl ether) provided 500 mg (52%) of pure product as an oil. Anal. ($C_{40}H_{44}NO_5F$) C, H.

3-[2-[3-[5-(Benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]-6-[[4-(1*H*-tetrazol-5-yl)butyl]oxy]phenyl]propanoic Acid Ethyl Ester (70b). Compound **70a** (10 mmol) was reacted with sodium azide using method H to provide crude product. Purification via silica gel chromatography (methanol/dichloromethane) provided 420 mg (71%) of pure product as a crystalline solid which was recrystallized from hexane: mp 90–91 °C. Anal. ($C_{40}H_{45}N_4O_6F$) C, H, N.

3-[2-[3-[5-(Benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]-6-[[4-(1*H*-tetrazol-5-yl)butyl]oxy]phenyl]propanoic Acid (70c). Compound **70b** (0.60 mmol) was hydrolyzed using method K to provide 400 mg (100%) of product as a crystalline solid which was recrystallized from hexane/diethyl ether: mp 131–133 °C. Anal. ($C_{38}H_{41}N_4O_6F$) C, H, N.

3-[2-[3-[5-(Benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]-6-[[4-(ethoxycarbonyl)butyl]oxy]phenyl]propanoic Acid Ethyl Ester (71a). Compound **68** (2.4 mmol) was reacted with compound **21b** using method O to provide crude product. Purification via silica gel chromatography (hexane/diethyl ether) provided 790 mg (56%) of pure product as an oil. Anal. ($C_{42}H_{49}O_8F$) C, H.

3-[2-[3-[5-(Benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]-6-[(4-carboxybutyl)oxy]phenyl]propanoic Acid (71b). Compound **71a** (1.64 mmol) was hydrolyzed using method K to provide 585 mg (58%) of product as a crystalline solid which was recrystallized from hexane/diethyl ether: mp 117–118 °C. Anal. ($C_{38}H_{41}O_8F$) H; C: calcd, 70.79; found, 69.90.

3-[2-[3-[5-(Benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]-6-[[4-[(dimethylamino)carbonyl]butyl]oxy]phenyl]propanoic Acid Ethyl Ester (72a). Compound **69** (1.78 mmol) was reacted with compound **21b** using method O to provide crude product. Purification via silica gel chromatography (hexane/diethyl ether) followed by recrystallization from hexane provided 495 mg (40%) of pure product: mp 58–60 °C. Anal. ($C_{42}H_{50}NO_7F$) C, H, N.

3-[2-[3-[5-(Benzyloxy)-2-ethyl-4-(4-fluorophenyl)phenoxy]propoxy]-6-[[4-[(dimethylamino)carbonyl]butyl]oxy]phenyl]propanoic Acid (72b). Compound **72a** (0.707 mmol) was hydrolyzed using method K to provide 495 mg (56%) of product as a glass. Anal. ($C_{40}H_{46}NO_7F$) C, H, N.

3-[2-[3-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-6-[[4-(1*H*-tetrazol-5-yl)butyl]oxy]phenyl]propanoic Acid (73). Compound **70c** (0.18 mmol) was hydrogenated using method F to provide 45 mg (44%) of the desired product as an amorphous solid. Anal. ($C_{31}H_{35}N_4O_6F$) C: calcd, 64.35; found, 58.65; H: calcd, 6.10; found, 5.69; N: calcd, 9.69; found, 8.55.

3-[2-[3-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-6-[(4-carboxybutyl)oxy]phenyl]propanoic Acid (74). Compound **71b** (0.25 mmol) was hydrogenated using method F to provide 140 mg (92%) of the desired product as crystalline solid: mp 95–98 °C. Anal. ($C_{31}H_{35}O_8F$).

3-[2-[3-[2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-6-[[4-[(dimethylamino)carbonyl]butyl]oxy]phenyl]propanoic Acid (75). Compound **72b** (0.595 mmol) was hydrogenated using method F to provide 145 mg (42%) of the desired product as a glass. Anal. ($C_{33}H_{40}NO_7F$).

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(48) Boronic acids which were not commercially available were prepared by one of two methods. **Method 1.** A solution of the appropriate aryl bromide in THF at −78 °C under a nitrogen atmosphere was metalated with *t*-BuLi (2 equiv). This was added to a solution of triisopropyl borate in THF previously cooled to −78 °C. After stirring for 15 min the reaction mixture was warmed to room temperature, stirred for an additional 15 min, diluted with ethyl acetate, and shaken with a portion of 10% aqueous hydrochloric acid. The organic layer was separated, dried (sodium sulfate), filtered and concentrated in vacuo. The resulting crude boronic acid was recrystallized from hexane/ethyl acetate mixtures. **Method 2.** The appropriate aryl iodide or bromide was metalated as described above and treated at −78 °C with trimethylsilyl chloride (1.8 equiv). The reaction mixture was allowed to warm to room temperature, diluted with saturated aqueous ammonium chloride solution, and extracted with ethyl acetate. The organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo. The crude arylsilane was dissolved in methylene chloride, cooled to −78 °C, and treated with boron tribromide (1 equiv). The reaction mixture was warmed to roomed temperature, stirred for 15 h, cooled to −78 °C, and treated with excess methanol. The reaction mixture was warmed to room temperature, stirred for 30 min, diluted with methylene chloride, and washed with aqueous 5 N hydrochloric acid. The crude boronic acid was recrystallized from hexane/ethyl acetate mixtures. See: Sharp, M. J.; Cheng, W.; Snieckus, V. Synthetic Connections to the Aromatic Directed Metalation Reaction. Functionalized Aryl Boronic Acids by IPSO and *m*-Terphenyls. *Tetrahedron Lett.* **1987**, *28*, 5093−5096.

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