Articles

Second-Generation Leukotriene B_4 Receptor Antagonists Related to SC-41930: Heterocyclic Replacement of the Methyl Ketone Pharmacophore

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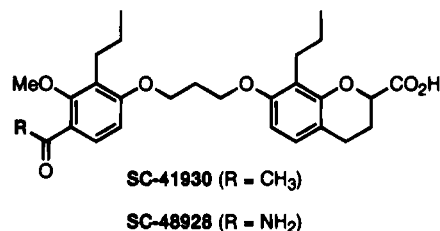
Received October 21, 1994®

Our previous reports have highlighted the first-generation leukotriene B_4 (LTB_4) receptor antagonist SC-41930 (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylic acid) which has potent oral, topical, and intracolonic activity in various animal models of inflammation. Extensive structure–activity relationship studies, in which a series of heterocyclic replacements for the methyl ketone functional group of SC-41930 was explored, identified SC-50605 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylic acid) as an optimized analog within a series of thiazoles. SC-50605 was found to be significantly more potent than SC-41930 in LTB_4 receptor binding, chemotaxis, and degranulation assays. It also displayed very good activity in animal models of colitis and epidermal inflammation by oral, topical, intravenous, and intracolonic routes of administration. The resolved enantiomers of SC-50605 were obtained by chiral chromatography and both demonstrated good *in vitro* and *in vivo* activity. The (+)-isomer (SC-52798) is currently being evaluated as a potential clinical candidate for psoriasis and ulcerative colitis therapy.

Leukotriene B_4 (LTB_4), a 5-lipoxygenase-derived metabolite of arachidonic acid, has been shown to possess potent chemotactic and degranulatory properties for human neutrophils. Elevated levels of LTB_4 have been reported in a number of inflammatory disease states characterized by PMN accumulation, including psoriasis[1] and ulcerative colitis (UC).[2] In addition, clinical remission appears to correlate well with diminished LTB_4 levels in this population.[3] Substantial efforts have been underway in the pharmaceutical industry to modulate LTB_4 function, particularly in the area of LTB_4 receptor antagonist research.[4] As part of our program directed toward the identification of novel therapeutic agents for inflammatory diseases, we discovered the orally active, pharmacologically selective LTB_4 receptor antagonist SC-41930.[5,6] In this report we describe our efforts to identify a second-generation back-up compound for SC-41930 with improved potency and selectivity.

During our early efforts to identify a successor to SC-41930, we found through extensive structure–activity relationship (SAR) studies that the primary amide, SC-48928, demonstrated enhanced potency relative to SC-41930 in a number of our *in vitro* biological assays. Exploitation of this lead led to the discovery of the very potent and selective LTB_4 receptor antagonist SC-53228, a monomethyl amide that has recently been disclosed[7,8] and is currently in preclinical development. Concurrently, the work described herein has sought to exploit this lead by introduction of various nitrogen-containing 5-membered ring heterocycles as surrogates of the amide functionality.[9] It has been found that the thiazole moiety is a particularly effective replacement for the amide group, leading to the discovery of SC-50605 as a relatively optimized analog within the thiazole series.



Chemistry

Because of the ready availability of SC-41930 and other acetophenone analogs from our analog program, the heterocyclic analogs described were constructed from these compounds rather than a *de novo* synthesis of each. The method of preparation of acetophenones **1a–f** has been previously described.[10] The initial SAR work in this series was carried out with **1a** (the methyl ester of SC-41930).

Scheme 1 illustrates the synthesis of isoxazole **4** and pyrazole **5**. The methyl ketone **1a** was condensed with DMF–dimethyl acetal or tris(dimethylamino)methane in DMF at 120 °C to provide enamino ketone **2**.[11] Reaction with either hydroxylamine or hydrazine gave **4** and **5**, respectively.[12]

The synthesis of imidazole analogs is shown in Scheme 2. Acetophenone **1a** was converted to the silyl enol ether, which was chlorinated to provide α-chloro ketone **6**. Reaction with 2-benzyl-2-thiopseudourea hydrochloride[13] in the presence of NaI and Na_2CO_3 furnished imidazole **7**, which was saponified with LiOH

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® Abstract published in *Advance ACS Abstracts*, February 15, 1995.

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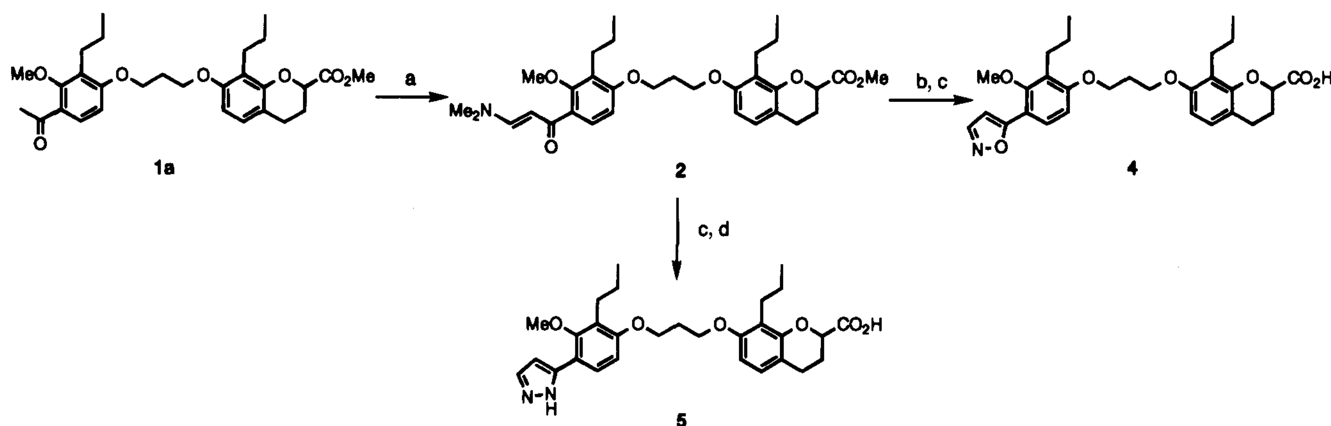
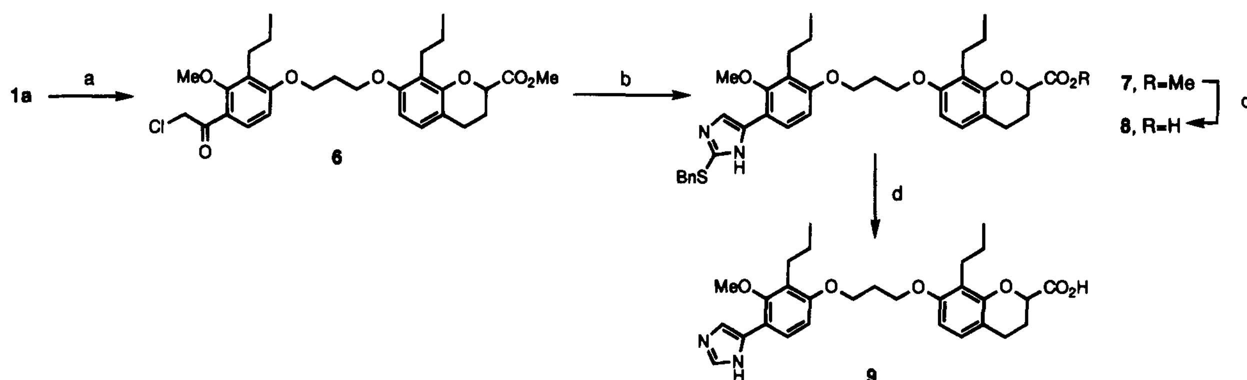
Scheme 1[a]



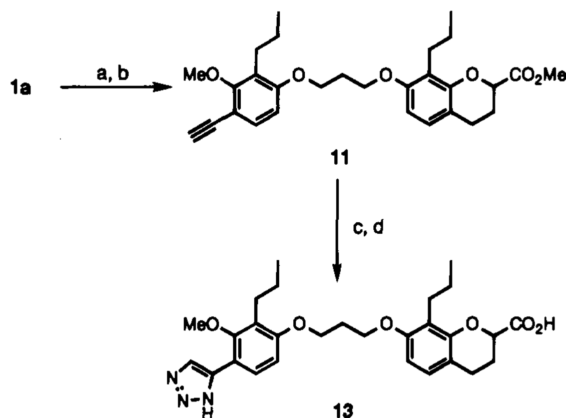
[a] (a) $(MeO)_2CHNMe_2$, DMF, 120 °C; (b) $NH_2OH{\cdot}HCl$, MeOH, H_2O; (c) LiOH; (d) NH_2NH_2, MeOH, H_2O.

Scheme 2[a]



[a] (a) 1. LiHMDS, 2. TMSCl, 3. NCS, 4. TBAF; (b) $NH{=}C(NH_2)SBn{\cdot}HCl$, NaI, K_2CO_3, DMF, 80 °C; (c) LiOH; (d) Ra Ni, NaOH, EtOH.

Scheme 3[a]



[a] (a) Oxalyl chloride, benzene; (b) LDA, THF; (c) $TMSN_3$, toluene 120–160 °C; (d) LiOH.

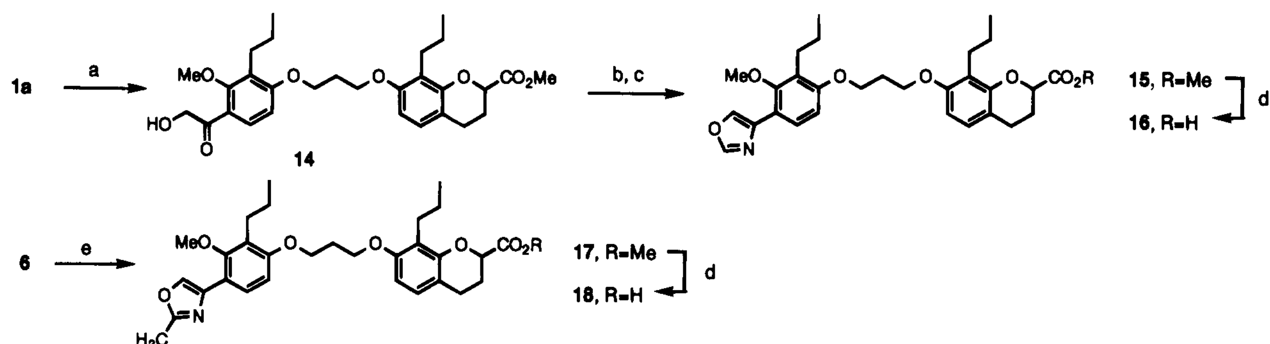
to give the carboxylic acid **8**. Desulfurization of **7** using Raney nickel proceeded with concomitant hydrolysis of the methyl ester to provide the monosubstituted imidazole carboxylic acid **9**.

A triazole analog was constructed as described in Scheme 3. Again, starting with ketone **1a** and reaction with oxalyl chloride gave the vinyl chloride. Dehydrohalogenation with LDA provided acetylene **11**. Triazole **13** was obtained by reaction with trimethylsilyl azide[14] followed by saponification with LiOH.

As shown in Scheme 4, acetophenone **1a** was converted to the silyl enol ether, which was oxidized with *m*-CPBA to give hydroxy ketone **14**.[15] Oxazole **15** was obtained by conversion of alcohol **14** to the triflate with triflic anhydride followed by reaction with formamide in DMF at 170 °C.[16a] Saponification with LiOH provided the carboxylic acid **16**. It was necessary to use the triflate in this sequence since reaction of the corresponding chloride with formamide failed to provide any substantial amounts of the desired oxazole. In an attempt to synthesize the 2-aminooxazole, α-chloro ketone **6** was heated in AcOH at 120 °C with urea. Instead of the 2-aminooxazole, 2-methyloxazole **17** was obtained, apparently via generation of acetamide from acetic acid and urea at this temperature.[16b] Treatment with LiOH furnished acid **18**.

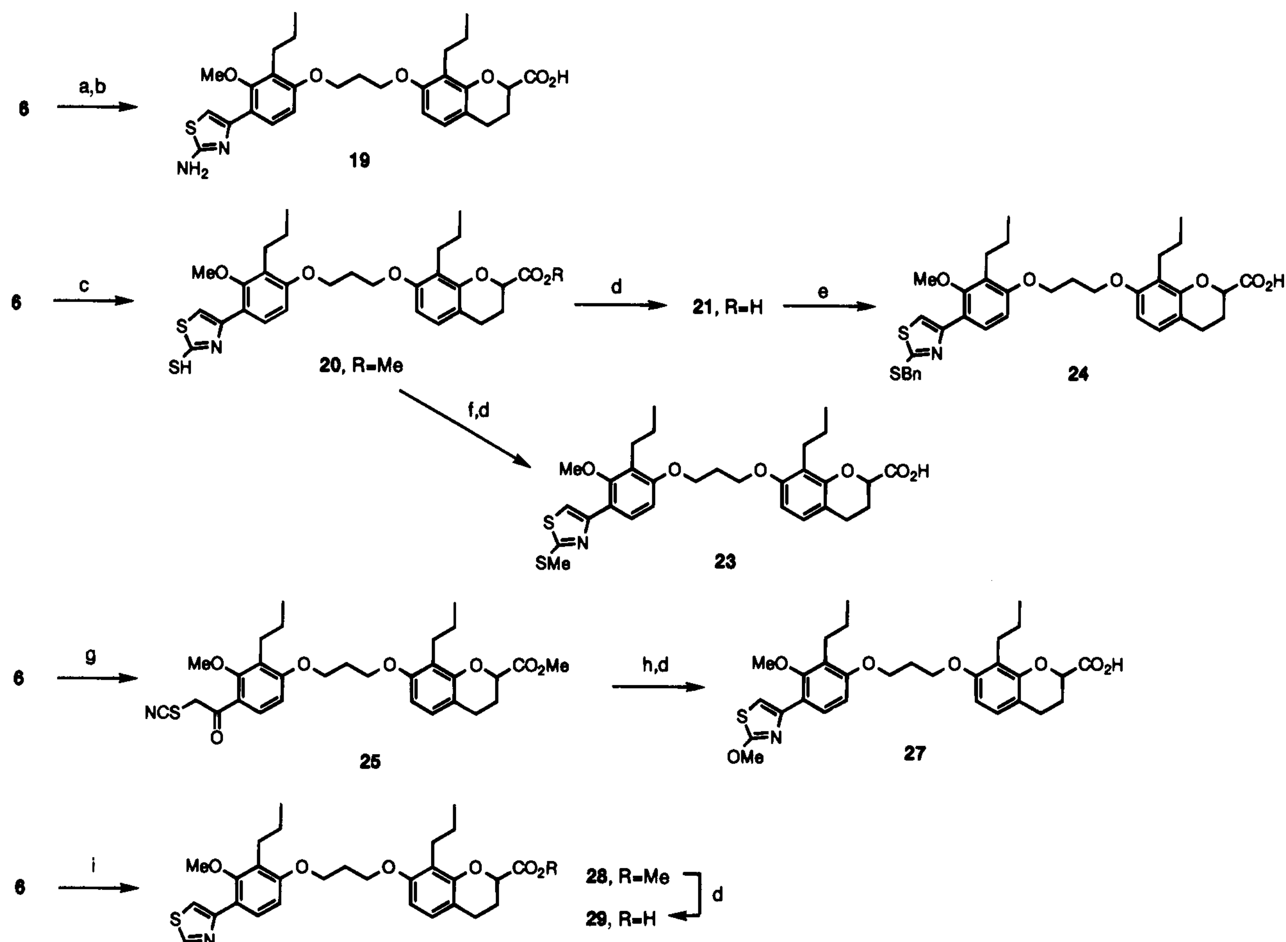
The synthesis of thiazole analogs is shown in Scheme 5. Reaction of the previously described α-chloro ketone **6** with thiourea in ethanol/water[17] yielded, after NaOH workup, the 2-aminothiazole **19**. Likewise, the 2-mercaptothiazole **21** was obtained by reaction of **6** with ammonium dithiocarbamate[18] in ethanol/water followed by LiOH treatment. S-Methylation of methyl ester **20** with methyl iodide, followed by treatment with LiOH, provided the 2-(methylthio)thiazole **23**. The 2-(benzylthio)thiazole analog **24** was obtained by benzylation of acid **21** with benzyl bromide. A 2-methoxy analog was produced via a thiocyanate.[19] Treatment of **6** with potassium thiocyanate in refluxing ethanol gave α-thiocyanato ketone **25**. Reaction of the thiocyanate with NaOMe provided, after saponification, thiazole **27**. The simple monosubstituted thiazole **28** was synthesized by treatment of α-chloro ketone **6** with a freshly prepared solution of thioformamide (formamide/P_2S_5) and mag-

Scheme 4[a]



[a] (a) 1. LiHMDS, 2. TMSCl, 3. MCPBA, 4. TsOH; (b) Tf_2O, 2,6-lutidine, CH_2Cl_2; (c) $HCONH_2$, DMF, 170 °C; (d) LiOH; (e) urea, AcOH, 120 °C.

Scheme 5[a]



[a] (a) Thiourea, EtOH, H_2O, reflux; (b) NaOH; (c) $NH_2C(S)S^-NH_4^+$, EtOH, H_2O, reflux; (d) LiOH; (e) BnBr, CH_3NO_2; (f) MeI, CH_3NO_2; (g) KSCN, EtOH, reflux; (h) NaOMe; (i) $HCONH_2$, P_2S_5, $MgCO_3$, dioxane, 100 °C.

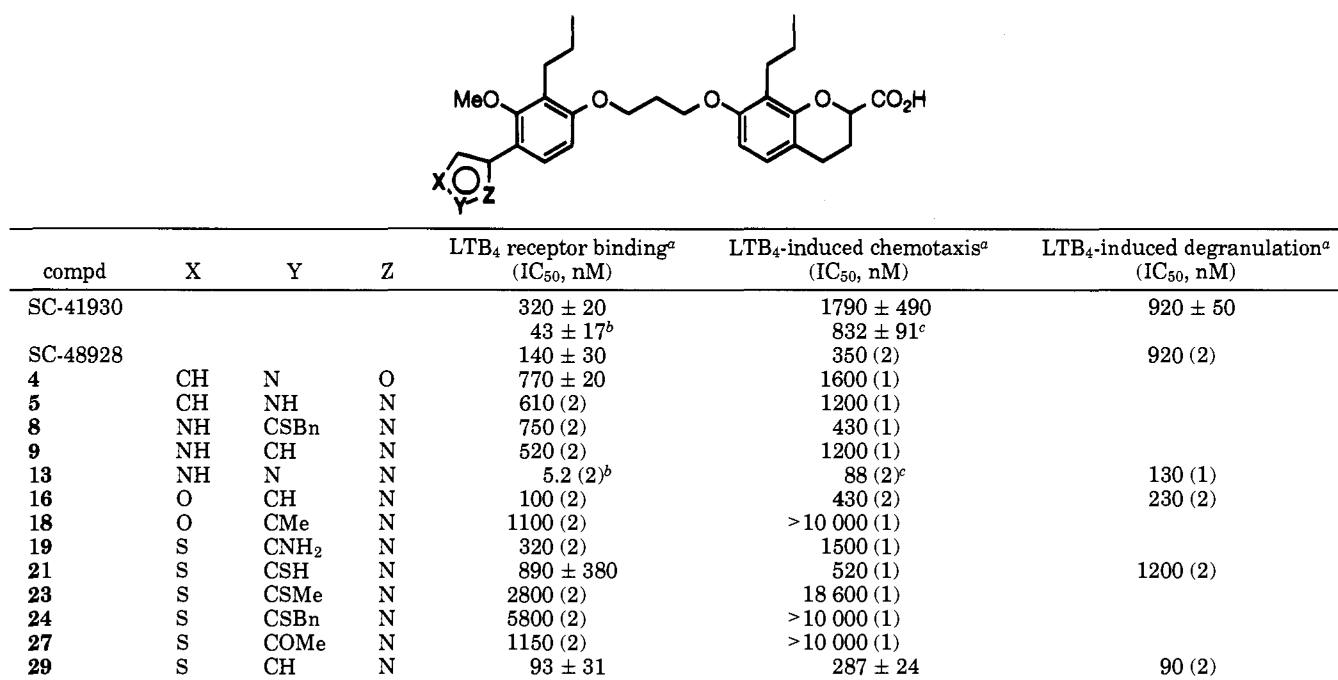
nesium carbonate in dioxane at 100 °C.[20] Saponification with LiOH furnished acid **29**.

On the basis of promising *in vitro* biological results obtained with **29**, a series of monosubstituted thiazoles was synthesized in an attempt to optimize the *in vitro* pharmacology. The previously described[10] acetophenones **1b–f** were each treated with cuprous bromide[21] to provide the corresponding α-bromo ketone. The α-bromo ketones were preferred because they were more convenient to generate and utilize than the analogous α-chloro ketones. The bromides were each treated with freshly prepared thioformamide as described above and saponified in the usual manner to give the corresponding thiazoles **32**, **35**, **38**, **41** and **44**.

Results and Discussion

Early SAR studies based on our lead LTB_4 receptor antagonist, SC-41930, led to the identification of the primary amide, SC-48928, a compound that demonstrated a 2–5-fold enhancement in potency *in vitro* relative to SC-41930. As a continuation of these studies, we sought to exploit this lead via the introduction of various nitrogen-containing 5-membered ring heterocycles in place of the critical acetyl or carboxamido functional group in SC-41930 and SC-48928. It was presumed that the carbonyl oxygen acted as a hydrogen-bond acceptor and that the nitrogen of an appropriate heterocycle would function in a similar manner. A

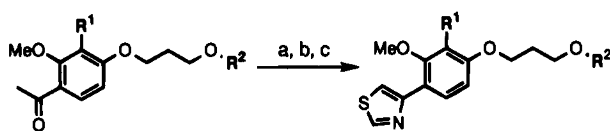
Table 1. Comparison of *in Vitro* Data for SC-41930 Analogs



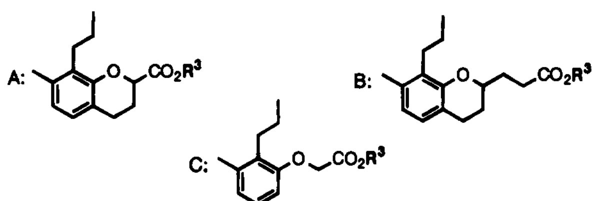
compd	X	Y	Z	LTB_4 receptor binding[a] (IC_{50}, nM)	LTB_4-induced chemotaxis[a] (IC_{50}, nM)	LTB_4-induced degranulation[a] (IC_{50}, nM)
SC-41930				320 ± 20	1790 ± 490	920 ± 50
				43 ± 17[b]	832 ± 91[c]	
SC-48928				140 ± 30	350 (2)	920 (2)
4	CH	N	O	770 ± 20	1600 (1)	
5	CH	NH	N	610 (2)	1200 (1)	
8	NH	CSBn	N	750 (2)	430 (1)	
9	NH	CH	N	520 (2)	1200 (1)	
13	NH	N	N	5.2 (2)[b]	88 (2)[c]	130 (1)
16	O	CH	N	100 (2)	430 (2)	230 (2)
18	O	CMe	N	1100 (2)	>10 000 (1)	
19	S	CNH_2	N	320 (2)	1500 (1)	
21	S	CSH	N	890 ± 380	520 (1)	1200 (2)
23	S	CSMe	N	2800 (2)	18 600 (1)	
24	S	CSBn	N	5800 (2)	>10 000 (1)	
27	S	COMe	N	1150 (2)	>10 000 (1)	
29	S	CH	N	93 ± 31	287 ± 24	90 (2)

[a] Numbers in parentheses are number of determinations. [b] Experiment conducted in the absence of NDGA. [c] Test compound added to upper and lower wells.

Scheme 6[a]



1b, R¹=allyl, R²= A (R³ = Me) — **32** (R³ = H)
1c, R¹=CpMe, R²= A — **35**
1d, R¹=n-Pr, R²= B — **38**
1e, R¹=CpMe, R²= B — **41**
1f, R¹=CpMe, R²= C — **44**



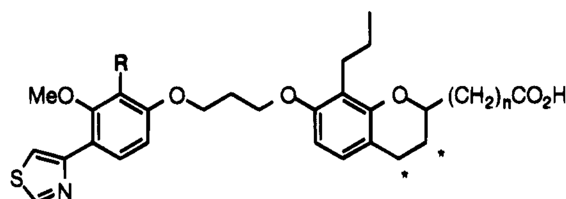
[a] CpMe = cyclopropylmethyl. (a) $CuBr_2$, EtOAc, $CHCl_3$, reflux; (b) $HCONH_2$, P_2S_5, $MgCO_3$, dioxane, reflux; (c) LiOH.

series of heterocycles based on the SC-41930/48928 structure was evaluated in the LTB_4 receptor binding and LTB_4-induced chemotaxis and degranulation assays. Table 1 delineates the *in vitro* biological results for these compounds and compares them to that of SC-41930. It should be noted that nordihydroguaiaretic acid (NDGA) was initially added in the binding assay to inhibit endogenous LTB_4 production but was omitted in later assays, resulting in an increased potency for these test compounds.[22] For the sake of comparison, binding affinity for SC-41930 is shown in the presence and absence of NDGA. Test compounds run in the absence of NDGA are noted in Tables 1 and 2. Also, in the chemotaxis assay (modified Boyden chamber), test compound was initially added only to the lower well but was later added to both upper and lower wells to eliminate the necessity of compound diffusion into the upper well. These conditions resulted in a small increase in compound potency in the assay. Again, for comparison, values for SC-41930 are given under both assay conditions. Test compounds added to both wells are noted in the tables.

As shown in Table 1, the isoxazole, pyrazole, and imidazole analogs **4**, **5**, **8**, and **9** exhibited no substantial increase in potency in the binding and chemotaxis assays relative to SC-41930. This is in contrast to some pyrazole analogs in a 2,4,5-substituted acetophenone series of LTB_4 antagonists recently reported by Lilly[23] which showed significantly enhanced potency relative to the parent acetophenones. Likewise, the substituted oxazoles and thiazoles **18**, **23**, **24**, and **27** were, in general, considerably less potent than SC-41930 in these assays. The only exceptions were aminothiazole **19**, which was equipotent in the binding and chemotaxis assays, and **21**, which was more potent than SC-41930 only in the chemotaxis assay. However, triazole **13** and unsubstituted oxazole and thiazole **16** and **29** were substantially more potent in all three *in vitro* assays, with potencies from 3 to 10 times that of SC-41930. It is likely that a combination of conformational and electronic effects plays a role in the enhanced potency of these particular analogs; however, this has not been examined further at this time.

Because of its overall biological profile, we performed further SAR studies on thiazole analog **29**, based on what we had learned from modifications carried out in our previous studies in this area.[7,24] From this previous work we found that modifications such as replacement of the *n*-propyl group on the acetophenone portion of the molecule with allyl or cyclopropylmethyl or insertion of two methylene units between the chroman ring and the carboxylic acid generally resulted in compounds with increased potency. The application of these modifications to **29** is summarized in Table 2. This study led to the identification of SC-50605 (**35**) and **41** as

Table 2. Comparison of *in Vitro* Data for Thiazole Analogs



compd	R	*n*	LTB_4 receptor binding[a] (IC_{50}, nM)	LTB_4-induced chemotaxis[a] (IC_{50}, nM)	LTB_4-induced degranulation[a] (IC_{50}, nM)
SC-41930			320 ± 20	1790 ± 490	920 ± 050
			43 ± 17[b]	832 ± 91[c]	
29	propyl	0	93 ± 31	287 ± 24	90 (2)
32	allyl	0	25 (2)	110 (1)	23 (2)
SC-50605 (**35**)	CpMe[d]	0	42 ± 5	89 ± 6[c]	57 ± 7
			11.4 ± 2[b]		
SC-52798 ((+)-**35**)	CpMe	0	3.2 ± 0.6[b]	67 ± 10[c]	48 ± 16
SC-52799 ((−)-**35**)	CpMe	0	4.5 ± 0.9[b]	188 ± 16[c]	79 ± 25
38	propyl	2	26 (2)	1540 ± 582	70 ± 31
41	CpMe	2	12.3 (2)[b]	49 (2)[c]	7 ± 2
44	CpMe	0[e]	15.5 (2)[b]	360 (2)[c]	220 (2)

[a] Numbers in parentheses are number of determinations. [b] Experiment conducted in the absence of NDGA. [c] Test compound added to upper and lower wells. [d] CpMe = cyclopropylmethyl. [e] Carbons marked with an asterisk are deleted in this molecule.

Table 3. Comparison of *in Vivo* Data

compd	LTB_4-induced cavine intradermal chemotaxis (ED_{50})			murine epidermal inflammation	SCOA-induced colitis (ED_{50}, mg/kg)	
	topical (ng)	iv (mg/kg)	oral (mg/kg)	(topical ED_{50}, mg)	murine (intracolonic)	cavine (oral)
SC-41930	340 ± 42	0.5 ± 0.01	1.7 ± 0.2	1.4 ± 0.18	28 ± 3.1	20 ± 2.7
SC-50605 (**35**)	70 ± 6.7	0.02 ± 0.009	0.74 ± 0.04	0.8 ± 0.07	12 ± 1.3	3.4 ± 0.5
SC-52798 ((+)-**35**)	18 ± 2		0.20 ± 0.02	0.29± 0.04	7.1 ± 0.9	2.3 ± 0.3
SC-52799 ((−)-**35**)	98 ± 8		1.21 ± 0.13	0.98 ± 0.10	11.7 ± 1.4	5.9 ± 0.7

optimized analogs within this series. Whereas **41** was more potent than SC-50605 *in vitro*, SC-50605 was chosen for further investigation on the basis of its overall pharmacological profile. SC-50605 was significantly more potent than SC-41930 in the binding, chemotaxis, and degranulation assays. Resolution of SC-50605 by chiral HPLC provided the individual antipodes, both of which were very potent antagonists in all *in vitro* assays. However, the (+)-isomer (SC-52798) was approximately twice as potent as the (−)-isomer (SC-52799) in these assays. This is consistent with previous reports that the (+)-isomer of SC-41930 and the (+)-isomer of SC-51146 (SC-53228) are slightly more potent than the corresponding (−)-isomers.[7,8,25]

SC-52798 and SC-50605 also demonstrated significant selectivity toward LTB_4- over fMLP (f-Met-Leu-Phe)-mediated degranulation and chemotaxis. In the PMN degranulation assay, SC-52798 inhibited fMLP-induced degranulation with an IC_{50} of 5900 ± 700 nM compared to 48 nM for LTB_4-induced degranulation, a 123-fold selectivity. In the chemotaxis assay, the IC_{50} ratio was 21, with IC_{50}s of 1410 ± 336 nM for fMLP and 67 nM for LTB_4. (For SC-50605, these ratios were 54 and 12 for the degranulation and chemotaxis assays, respectively.) In addition, SC-50605 and SC-52798 inhibited 12(*R*)-HETE (12(*R*)-hydroxyeicosatetraenoic acid)-induced chemotaxis with IC_{50}s of 106 and 52 nM, respectively. This could prove to be a beneficial property in the treatment of psoriasis due to recent evidence that 12(*R*)-HETE may be an important mediator in that disease state.[26] SC-50605 also demonstrated excellent potency against LTB_4 binding to its receptors on eosinophils (IC_{50} = 2.6 ± 6 nM) as well as LTB_4-induced eosinophil chemotaxis (IC_{50} = 9 nM (*n* = 2)). At concentrations up to 10 μM, SC-50605 displayed no agonist properties in the PMN chemotaxis assay, nor did it inhibit LTD_4-stimulated contractions of guinea pig ileal longitudinal muscle at concentrations up to 1 μM.

SC-50605 also inhibited eicosanoid production in A23187-stimulated human PMN and HL-60 cells. It inhibited LTB_4 production with an IC_{50} of 520 ± 25 nM in PMNs and 660 nM in HL-60s and inhibited PGE_2 production in HL-60s with an IC_{50} of 928 ± 221 nM. The mechanisms for these inhibitions have not yet been defined.

SC-50605 and its individual enantiomers were compared to SC-41930 in several animal models of inflammation, and all were substantially more potent than SC-41930, regardless of the route of administration (Table 3). In the cavine intradermal chemotaxis assay, SC-50605 was 2−25 times more potent than SC-41930, and it was 2−6 times more potent in the short-chain organic acid (SCOA)-induced colitis models. Consistent with the *in vitro* assay data, the (+)-isomer (SC-52798) was more potent than both the (−)-isomer and the racemate (SC-50605) in all of the animal models. In addition, in the LTB_4-induced intradermal chemotaxis assay, when administered orally at a dose of 3 mg/kg, SC-52798 demonstrated a substantial increased duration of action relative to SC-41930, 27 h vs 5.5 h. Furthermore, SC-50605 demonstrated oral activity at a dose of 30 mg/kg in a 12(*R*)-HETE-induced cavine intradermal chemotaxis assay (data not shown).

Conclusion

We have succeeded in identifying a potent and selective back-up compound to SC-41930. SC-50605 and its antipodes, SC-52798 and SC-52799, have demonstrated

a greater potency and overall efficacy in our panel of *in vitro* and *in vivo* pharmacological assays than SC-41930. In our paradigms of dermal inflammation and colitis, these compounds have shown significant efficacy via oral, topical, intravenous, and intracolonic routes of administration. These compounds may well have an application in disease states where LTB_4 is thought to play a role, such as inflammatory bowel disease and psoriasis, and, potentially, in asthma, rheumatoid arthritis, cystic fibrosis, and contact and atopic dermatitis. Whether compounds such as these, which target a specific inflammatory mediator such as LTB_4, will be effective in the medical management of complex human inflammatory disease states remains to be determined in clinical trials.

Experimental Section

Biological Methods. Human Neutrophil Preparation. As described previously,[6] human neutrophils were isolated from citrated peripheral blood sedimented in 5% dextran, followed by centrifugation on Ficoll-paque and hypotonic erythrocyte lysis. BSA (0.25%) was present during lysis for degranulation and chemotaxis studies but absent for receptor binding studies. After lysis, neutrophils were washed with HEPES-buffered Hank's balanced salt solution (HBSS) and resuspended in HBSS to a final concentration of $(3-5) \times 10^6$ cells/mL.

LTB_4 Receptor Binding.[6,8] Neutrophils (4×10^6 cells) and 0.6 nM [^{3}H]LTB_4 were incubated in the presence or absence of test compound at 0 °C for 45 min in 1 mL of HBSS (30 μM NDGA (nordihydroguaiaretic acid) was also present in some assays). Following incubation, 5 mL of ice-cold HBSS was added to the incubation mixture followed by vacuum filtration through glass fiber filters (Whatman GF/C) to separate free from bound [^{3}H]LTB_4. The filters were washed with 2×5 mL HBSS. Specific binding was calculated as the difference between total binding and binding not displaced by 0.1 μM unlabeled LTB_4 (nonspecific binding).

LTB_4-Induced Chemotaxis. The chemotaxis assay was performed in modified Boyden chambers as previously described.[6] A neutrophil suspension (3.2×10^6 cells/0.8 mL) in HBSS was added to the upper well of a modified Boyden chamber. The lower well (0.2 mL), separated by a PVC-coated poly(carbonate) membrane (3 μM), contained HBSS or 3×10^{-8} M LTB_4 in the presence or absence of test compound (in some assays, test compound was added to the upper as well as the lower well). Following a 90-min incubation at 37 °C, the number of cells from the lower well was quantitated with a Coulter counter. Percent inhibition was calculated from cell counts corrected for random migration by subtracting the mean of the HBSS control.

LTB_4-Induced Degranulation.[6] A neutrophil suspension (3×10^6 cells) in 1 mL of HBSS was preincubated with cytochalasin B (5 μg) at 37 °C for 5 min followed by preincubation with the test compound for 7 min. Neutrophils were then incubated for 2 min with LTB_4 (5×10^{-8} M) to induce degranulation. Myeloperoxidase (MPO) activity in the cell pellet and supernatant was determined spectophotometrically via decomposition of peroxide using *o*-dianisidine hydrochloride. After subtracting the basal MPO activity in the supernatant, data were expressed as the percentage of total MPO activity released into the supernatant induced by LTB_4.

Cavine LTB_4-Induced Dermal Chemotaxis.[27] A solution of LTB_4 (35 ng) in 0.1 mL of 0.9% NaCl was injected intradermally into the shaved backs of lightly anesthetized guinea pigs. Appropriate vehicle controls were used throughout. After 4 h, the animals were killed and the skins removed and frozen (−70 °C). Skin punches (12 mm diameter) of injection sites were mechanically homogenized, and the MPO was extracted with detergent−buffer using sonication and freeze−thaw procedures. After centrifugation, MPO activity in the supernatant was assayed spectrophotometrically. Test compounds were either coinjected with LTB_4 or administered iv 5 min before or orally 1 h prior to injection of LTB_4.

Mouse Epidermal Inflammation.[28] Phorbol-12-myristate-13-acetate (PMA, 25 μg) in acetone was applied to the dorsal ear surface of one mouse ear and control vehicle to the contralateral ear. After 18 h, the animals were killed and the ears extirpated, weighed, and frozen. Edema was assessed by ear weight gain relative to the contralateral ear. MPO activity was also assayed as described above for the dermal chemotaxis assay. Test compounds were applied with the PMA topically as a solution in acetone.

SCOA-Induced Colitis. The short-chain organic acid (SCOA)-induced colitis model was reported previously.[29] Colitis was induced by a single intrarectal (ir) enema of 3% acetic acid in water for mice and 4% for guinea pigs, under light anesthesia. After 24 h the animals were killed and the colonic tissues assessed for MPO activity. Test compounds were given ir in the mouse 1 h before and 1 h after acid instillation and orally 30 min prior to colitis induction in the guinea pig.

Chemistry. Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer PE 241 polarimeter using a 1-dm cell. High-field ^{1}H NMR spectra were recorded on a GE QE-300 spectrometer. Chemical shifts are reported in parts per million relative to internal tetramethylsilane. Microanalyses were performed by the Searle Physical Methodology Department. Mass spectra were recorded on a Finnigan MAT-8430 instrument operating in either the electron impact (EI) or chemical ionization (CI) mode as indicated.

Methyl 7-[3-[4-[3-(Dimethylamino)-1-oxo-2-propenyl]-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylate (2). Acetophenone **1a** (0.95 g, 1.90 mmol) was stirred in 1 mL of *N,N*-dimethylformamide (DMF) and 0.3 mL of DMF−dimethyl acetal at 110−120 °C for 23.5 h. The mixture was cooled and poured into EtOAc and 1 M HCl and the organic layer separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using a gradient of 1:2 hexane/EtOAc to 100% EtOAc provided **2** (0.88 g, 84%) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.92 (3H, t), 0.97 (3H, t), 1.55 (4H, m), 2.18 (2H, m), 2.29 (2H, m), 2.63 (4H, m), 2.71 (2H, m), 2.91 (3H, br), 3.07 (3H, br), 3.74 (3H, s), 3.78 (3H, s), 4.14 (2H, t), 4.20 (2H, t), 4.77 (1H, dd), 5.74 (1H, br d), 6.47 (1H, d), 6.67 (1H, d), 6.79 (1H, d), 7.42 (1H, d), 7.68 (1H, br d). Anal. ($C_{32}H_{43}NO_7$·$0.3H_2O$) C, H, N.

Methyl 3,4-Dihydro-7-[3-[4-(5-isoxazolyl)-3-methoxy-2-propylphenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylate (3). Enamino ketone **2** (0.155 g, 0.277 mmol) was stirred in 5 mL of MeOH and 1.25 mL of H_2O with NH_2OH·HCl (48 mg, 0.7 mmol) at reflux for 1 h. The mixture was cooled and poured into ether and water. The ether layer was separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using a gradient of 10:1−5:1 hexane/EtOAc furnished **3** (0.13 g, 90%) as a colorless gum: ^{1}H NMR ($CDCl_3$) δ 0.92 (3H, t), 0.98 (3H, t), 1.57 (4H, m), 2.19 (2H, m), 2.31 (2H, m), 2.64 (6H, m), 3.68 (3H, s), 3.74 (3H, s), 4.14 (2H, t), 4.22 (2H, t), 4.75 (1H, dd), 6.47 (1H, d), 6.68 (1H, d, J = 2 Hz), 6.78 (1H, d), 6.80 (1H, d), 7.75 (1H, d), 8.29 (1H, d, J = 2 Hz). Anal. ($C_{30}H_{37}NO_7$) C, H, N.

A. General Procedure for the Saponification of Esters. To a 0.05 M solution of the ester in 4:1 MeOH/tetrahydrofuran (THF) at 0 °C was added 3−4 equiv of 1 N LiOH, and the solution was stirred at 25 °C until TLC analysis indicated all the starting ester was consumed (generally 1−3 h). The mixture was poured into EtOAc and 0.5 M HCl and the organic layer separated, washed with brine, dried over Na_2SO_4, and concentrated to give the desired carboxylic acid.

3,4-Dihydro-7-[3-[4-(5-isoxazolyl)-3-methoxy-2-propylphenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylic Acid (4). Ester **3** (60 mg, 0.114 mmol) was saponified as described in general procedure A to afford the crude acid which was flash chromatographed on silica gel using a gradient of 100:20:1−75:25:1 hexane/EtOAc/AcOH to furnish **4** (42 mg, 72%) as a colorless gum: ^{1}H NMR ($CDCl_3$) δ 0.91 (3H, t), 0.96

(3H, t), 1.56 (4H, m), 2.20 (1H, m), 2.29 (3H, m), 2.65 (4H, m), 2.76 (2H, m), 3.67 (3H, s), 4.13 (2H, t), 4.21 (2H, t), 4.76 (1H, dd, J = 6.9, 3.8 Hz), 6.49 (1H, d), 6.67 (1H, d, J = 1.5 Hz), 6.76 (1H, d), 6.82 (1H, d), 7.74 (1H, d), 8.30 (1H, d, J = 1.5 Hz); HRMS (EI) m/z 509.2423 (calcd for $C_{29}H_{35}NO_7$ 509.2413).

3,4-Dihydro-7-[3-[3-methoxy-2-propyl-4-(pyrazol-3-yl)-phenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylic Acid (5). Enamino ketone **2** (0.11 g, 0.20 mmol) was saponified as described in general procedure A. The crude acid was stirred in 4 mL of MeOH and 1 mL of water with 0.1 mL of hydrazine hydrate at reflux for 2 h. The mixture was cooled and poured into EtOAc and 1 N HCl. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using a gradient of 100:20:1−66:33:1 hexane/EtOAc/AcOH provided **5** (82 mg, 81%) as a white solid: mp 156−158 °C; ^1H NMR ($CDCl_3$) δ 0.93 (3H, t), 0.98 (3H, t), 1.58 (4H, m), 2.28 (4H, m), 2.67 (4H, m), 2.78 (2H, m), 3.61 (3H, s), 4.16 (2H, t), 4.21 (2H, t), 4.80 (1H, dd), 6.47 (1H, d), 6.59 (1H, br s), 6.72 (1H, d), 6.82 (1H, d), 7.41 (1H, d), 7.58 (1H, br s). Anal. ($C_{29}H_{36}N_2O_6$) C, H, N.

Methyl 7-[3-[4-(2-Chloro-1-oxoethyl)-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylate (6). To acetophenone **1a** (2.48 g, 4.97 mmol) in 50 mL of dry THF at −78 °C was added 5.5 mL of 1 M lithium bis(trimethylsilyl)amide (LiHMDS) in THF. The mixture was stirred at −78 °C for 15 min, and chlorotrimethylsilane (TMSCl; 1.27 mL, 10 mmol) was added. The mixture was warmed to 0 °C and stirred for 15 min. The solution was concentrated and the residue dissolved in hexane, filtered, and concentrated. To the crude enol ether in 50 mL of THF at 0 °C was added *N*-chlorosuccinimide (0.73 g, 5.5 mmol). The mixture was warmed to 25 °C, stirred for 15 min, and then refluxed for 1.5 h. The mixture was cooled, and 4 mL of water and 6 mL of 1 N Bu_4NF in THF were added. After 5 min the mixture was poured into ether and water and the ether layer separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using a gradient of 20:1−10:1 hexane/EtOAc furnished minor amounts of di- and trichloroacetophenones along with the desired monochloroacetophenone **6** (1.53 g, 58%) as a white solid: mp 47−49 °C; ^1H NMR ($CDCl_3$) δ 0.90 (3H, t), 0.95 (3H, t), 1.56 (4H, m), 2.19 (2H, m), 2.31 (2H, m), 2.61 (4H, m), 2.73 (2H, m), 3.77 (6H, s), 4.13 (2H, t), 4.24 (2H, t), 4.76 (2H, s, CH_2Cl), 4.78 (1H, m), 6.45 (1H, d), 6.74 (1H, d), 6.80 (1H, d), 7.62 (1H, d); HRMS (EI) m/z 532.2249 (calcd for $C_{29}H_{37}O_7{}^{35}Cl$ 532.2228).

Methyl 3,4-Dihydro-7-[3-[3-methoxy-4-[2-[(phenylmethyl)thio]-1*H*-imidazol-4-yl]-2-propylphenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylate (7). Chloromethyl ketone **6** (19 mg, 35.6 μmol) was stirred in 0.5 mL of DMF with 2-benzyl-2-thiopseudourea hydrochloride (9.0 mg, 44.4 μmol) in the presence of NaI (2.0 mg, 13.3 μmol) and K_2CO_3 (20 mg, 0.19 μmol) at 80 °C for 5 min. The mixture was cooled and poured into ether and water. The ether layer was separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using 3:1 hexane/EtOAc furnished imidazole **7** (18 mg, 78%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.92 (3H, t), 0.97 (3H, t), 1.54 (4H, m), 2.19 (2H, m), 2.27 (2H, m), 2.63 (4H, m), 2.72 (2H, m), 3.40 (3H, br s), 3.76 (3H, s), 4.24 (2H, t), 4.28 (2H, t), 4.30 (2H, s, CH_2Ph), 4.76 (1H, dd), 6.45 (1H, d), 6.71 (1H, d), 6.80 (1H, d), 7.23 (6H, m), 7.37 (1H, s); HRMS (EI) m/z 644.2918 (calcd for $C_{37}H_{44}N_2O_6S$ 644.2920).

3,4-Dihydro-7-[3-[3-methoxy-4-[2-[(phenylmethyl)thio]-1*H*-imidazol-4-yl]-2-propylphenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylic Acid (8). Ester **7** (12 mg, 18.6 μmol) was saponified as described in general procedure A to afford the crude acid which was flash chromatographed on silica gel using a gradient of 3:1−1:1 hexane/EtOAc to furnish **8** (12 mg, 100%) as a white solid: mp 90−93 °C; ^1H NMR ($CDCl_3$) δ 0.91 (3H, t), 0.96 (3H, t), 1.52 (4H, m), 2.27 (4H, m), 2.53−2.85 (6H, m), 3.35 (3H, s), 4.12 (2H, t), 4.19 (4H, m), 4.76 (1H, br), 6.44 (1H, d), 6.66 (1H, d), 6.79 (1H, d), 7.21 (5H, m), 7.37 (1H, d), 7.48 (1H, s); HRMS (CI) m/z 631.2830 (calcd for $C_{36}H_{43}N_2O_6S$ (M + 1) 631.2842).

3,4-Dihydro-7-[3-[4-(1*H*-imidazol-4-yl)-3-methoxy-2-propylphenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylic Acid (9). Imidazole **7** (35 mg, 54 μmol) was stirred in 1 mL of EtOH and 1.25 mL of 20% aqueous NaOH with 0.5 g of 50% RaNi in water and the mixture heated at reflux for 2.5 h. The mixture was cooled and filtered and the filtrate concentrated. The product was dissolved in EtOAc and the solution washed with 0.5 M HCl and brine, dried over Na_2SO_4, and concentrated to provide **9** as a colorless oil: ^1H NMR (CD_3CO_2D) δ 0.87 (3H, t), 0.98 (3H, t), 1.57 (4H, m), 2.21 (2H, m), 2.32 (2H, m), 2.69 (6H, m), 3.68 (3H, s), 4.21 (2H, t), 4.31 (2H, t), 4.83 (1H, dd), 6.52 (1H, d), 6.81 (1H, d), 6.92 (1H, d), 7.60 (1H, d), 7.78 (1H, s), 9.03 (1H, s). Anal. ($C_{29}H_{36}N_2O_6$·AcOH·H_2O) C, H, N.

Methyl 7-[3-[4-(1-Chloroethenyl)-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylate (10). To acetophenone **1a** (1.1 g, 2.2 mmol) in 15 mL of benzene containing 1 drop of DMF was added oxalyl chloride (0.35 mL, 4.0 mmol), and the mixture was stirred at 25 °C for 2.5 days. The mixture was poured into ether and water and the ether layer separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using 20:1 hexane/EtOAc furnished vinyl chloride **10** (0.91 g, 80%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.92 (3H, t), 0.97 (3H, t), 1.53 (4H, m), 2.18 (2H, m), 2.27 (2H, m), 2.64 (4H, m), 2.72 (2H, m), 3.75 (3H, s), 3.76 (3H, s), 4.13 (2H, t), 4.18 (2H, t), 4.75 (1H, dd), 5.61 (1H, s, C=CH), 5.71 (1H, s, C=CH), 6.45 (1H, d), 6.64 (1H, d), 6.80 (1H, d), 7.27 (1H, d). Anal. ($C_{29}H_{37}O_6Cl$) C, H, Cl.

Methyl 3,4-Dihydro-7-[3-(4-ethynyl-3-methoxy-2-propylphenoxy)propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylate (11). To vinyl chloride **10** (0.108 g, 0.208 mmol) in 10 mL of dry THF at 0 °C was added 1.5 M lithium diisopropylamide (LDA) in cyclohexane (0.4 mL, 0.6 mmol). After the mixture was stirred at 0 °C for 30 min and at 25 °C for 1 h, the reaction was quenched with aqueous NH_4Cl. The mixture was poured into ether and water and the ether layer separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using a gradient of 20:1−15:1 hexane/EtOAc gave acetylene 11 (46 mg, 46%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.92 (3H, t), 0.94 (3H, t), 1.52 (4H, m), 2.19 (2H, m), 2.28 (2H, m), 2.61 (4H, m), 2.72 (2H, m), 3.22 (1H, s, C≡CH), 3.77 (3H, s), 3.92 (3H, s), 4.13 (2H, t), 4.17 (2H, t), 4.78 (1H, dd), 6.46 (1H, d), 6.59 (1H, d), 6.80 (1H, d), 7.28 (1H, d). Anal. ($C_{29}H_{36}O_6$·0.9H_2O) C, H.

Methyl 3,4-Dihydro-7-[3-[3-methoxy-2-propyl-4-(1,2,3-triazol-4-yl)phenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylate (12). A solution of 11 (0.20 g, 0.416 mmol) and excess azidotrimethylsilane ($TMSN_3$) in 7 mL of toluene was heated in a sealed tube at 120 °C for 18 h and at 150−160 °C for 24 h. The mixture was cooled and poured into EtOAc and water. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using a gradient of 5:1−2:1 hexane/EtOAc provided the starting acetylene 11 (160 mg, 80%) along with the desired triazole **12** (30 mg, 14%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.92 (3H, t), 0.99 (3H, t), 1.58 (4H, m), 2.19 (2H, m), 2.31 (2H, m), 2.69 (6H, m), 3.63 (3H, s), 3.78 (3H, s), 4.15 (2H, t), 4.22 (2H, t), 4.77 (1H, t), 6.47 (1H, d), 6.78 (1H, d), 6.81 (1H, d), 7.62 (1H, d), 8.06 (1H, s); HRMS (EI) m/z 523.2682 (calcd for $C_{29}H_{37}N_3O_6$ 523.2682).

3,4-Dihydro-7-[3-[3-methoxy-2-propyl-4-(1,2,3-triazol-4-yl)phenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylic Acid (13). Ester **12** (30 mg, 57.2 μmol) was saponified as described in general procedure A to afford the crude acid which was flash chromatographed on silica gel using a gradient of 100:20:1−66:33:1 hexane/EtOAc/AcOH to furnish **13** (18 mg, 62%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.91 (3H, t), 0.98 (3H, t), 1.56 (4H, m), 2.22 (1H, m), 2.30 (3H, m), 2.66 (4H, m), 2.77 (2H, m), 3.61 (3H, s), 4.15 (2H, t), 4.22 (2H, t), 4.80 (1H, t), 6.47 (1H, d), 6.75 (1H, d), 6.82 (1H, d), 7.58 (1H, d), 8.09 (1H, s); HRMS (EI) m/z 465.2629 (calcd for $C_{27}H_{35}N_3O_4$ (M − CO_2) 465.2627).

Methyl 7-[3-[4-(2-Hydroxy-1-oxoethyl)-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylate (14). To acetophenone **1a** (3.17 g, 6.36 mmol) in 60 mL of dry THF at −78 °C was added 7.0 mL of 1 M LiHMDS. The mixture was stirred at −78 °C for 10

min, and TMSCl (1.8 mL, 14.2 mmol) was added. The mixture was warmed to 0 °C and stirred for 15 min. The solution was concentrated and the residue dissolved in hexane, filtered, and concentrated. The crude enol ether was stirred in 60 mL of CH_2Cl_2 at 0 °C with 2 g of $NaHCO_3$, and 1.4 g of 80–85% *m*-chloroperoxybenzoic acid (*m*-CPBA) was added in portions. After stirring at 0 °C for 1 h, the mixture was diluted with hexane, filtered, and concentrated. The residue was dissolved in 50 mL of diethyl ether and stirred with catalytic *p*-toluenesulfonic acid (TsOH) at 25 °C for 1.5 h. The mixture was poured into water and the ether layer separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using a gradient of 10:1–3:1 hexane/ethyl acetate provided recovered **1a** (0.87 g, 27%) along with of **14** (2.06 g, 63%) as a white solid: mp 87–88 °C; ^1H NMR ($CDCl_3$) δ 0.89 (3H, t), 0.96 (3H, t), 1.56 (4H, m), 2.19 (2H, m), 2.30 (2H, m), 2.63 (4H, m), 2.71 (2H, m), 3.73 (1H, t, OH), 3.76 (3H, s), 3.79 (3H, s), 4.14 (2H, t, J = 5.9 Hz), 4.25 (2H, t, J = 6 Hz), 4.76 (1H, m), 4.77 (2H, d, J = 4.7 Hz, CH_2-OH), 6.45 (1H, d, J = 8.4 Hz), 6.76 (1H, d, J = 8.9 Hz), 6.80 (1H, d, J = 8.4 Hz), 7.77 (1H, d, J = 8.8 Hz). Anal. ($C_{29}H_{38}O_8$) C, H.

Methyl 3,4-Dihydro-7-[3-[3-methoxy-4-(4-oxazolyl)-2-propylphenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylate (15). To α-hydroxy ketone **14** (0.41 g, 0.80 mmol) in 6 mL of CH_2Cl_2 at −78 °C was added trifluoromethanesulfonic anhydride (0.2 mL, 1.17 mmol) followed by 2,6-lutidine (0.14 g, 1.17 mmol). The mixture was stirred at −78 °C for 45 min and poured into ether and water. The ether layer was separated, washed with brine, dried over Na_2SO_4, and concentrated to give 0.50 g of a light orange solid. The crude triflate (0.13 g, 0.20 mmol) in 2 mL of formamide and 1 mL of DMF was heated in a sealed tube at 170–180 °C for 3 h. The mixture was cooled and poured into EtOAc and water. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using 5:1 hexane/EtOAc provided **15** (0.03 g, 29%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.92 (3H, t), 0.98 (3H, t), 1.58 (4H, m), 2.19 (2H, m), 2.29 (2H, m), 2.65 (6H, m), 3.68 (3H, s), 3.75 (3H, s), 4.15 (2H, t), 4.20 (2H, t), 4.76 (1H, dd), 6.46 (1H, d), 6.79 (2H, 2d), 7.84 (1H, d), 7.92 (1H, s), 8.13 (1H, s). Anal. ($C_{30}H_{37}NO_7$) C, H, N.

3,4-Dihydro-7-[3-[3-methoxy-4-(4-oxazolyl)-2-propylphenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylic Acid (16). Ester **15** was saponified as described in general procedure A to afford acid **16** as a white solid: mp 136–137 °C; ^1H NMR ($CDCl_3$) δ 0.92 (3H, t), 0.97 (3H, t), 1.58 (4H, m), 2.21 (1H, m), 2.29 (3H, m), 2.65 (4H, m), 2.77 (2H, m), 3.69 (3H, s), 4.15 (2H, t, J = 6 Hz), 4.22 (2H, t, J = 6.1 Hz), 4.77 (1H, dd, J = 7, 3.8 Hz), 6.49 (1H, d, J = 8.4 Hz), 6.75 (1H, d, J = 8.7 Hz), 6.83 (1H, d, J = 8.4 Hz), 7.78 (1H, d, J = 8.6 Hz), 8.00 (1H, s), 8.14 (1H, s). Anal. ($C_{29}H_{35}NO_7$) C, H, N.

Methyl 3,4-Dihydro-7-[3-[3-methoxy-4-(2-methyl-4-oxazolyl)-2-propylphenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylate (17). Chloromethyl ketone **6** (0.105 g, 0.2 mmol) was stirred in 3 mL of AcOH with urea (50 mg, 0.8 mmol) at 120 °C for 47 h. The mixture was cooled and poured into EtOAc and water and the organic layer separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using 5:1 hexane/EtOAc provided **17** (37 mg, 32%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.92 (3H, t), 0.98 (3H, t), 1.57 (6H, m), 2.19 (2H, m), 2.28 (2H, m), 2.51 (3H, s), 2.67 (4H, m), 3.68 (3H, s), 3.77 (3H, s), 4.15 (2H, t), 4.20 (2H, t), 4.76 (1H, dd), 6.46 (1H, d), 6.74 (1H, d), 6.80 (1H, d), 7.79 (1H, d), 7.97 (1H, s); HRMS (EI) *m/z* 537.2728 (calcd for $C_{31}H_{39}NO_7$ 537.2726).

3,4-Dihydro-7-[3-[3-methoxy-4-(2-methyl-4-oxazolyl)-2-propylphenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylic Acid (18). Ester **17** (45 mg, 77 μmol) was saponified as described in general procedure A to afford acid **18** as a white solid: mp 112–114 °C; ^1H NMR ($CDCl_3$) δ 0.92 (3H, t), 0.97 (3H, t), 1.57 (4H, m), 2.26 (4H, m), 2.54 (3H, s), 2.64 (4H, m), 2.78 (2H, m), 3.66 (3H, s), 4.15 (2H, t), 4.23 (2H, m), 4.80 (1H, dd), 6.46 (1H, d), 6.67 (1H, d), 6.80 (1H, d), 7.67 (1H, d), 7.98 (1H, s). Anal. ($C_{30}H_{37}NO_7$) C, H, N.

7-[3-[4-(2-Amino-4-thiazolyl)-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylic Acid (19). Chloromethyl ketone **6** (0.13 g, 0.244 mmol) and thiourea (22 mg, 0.29 mmol) in 5 mL of EtOH and 1 mL of water were stirred at reflux for 4 h. The mixture was cooled and 1 mL of 5 M NaOH added. After stirring at 25 °C for 10 min, the mixture was poured into CH_2Cl_2 and 0.5 M HCl. The CH_2Cl_2 layer was separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using a gradient of 66:33:1–33:66:1 hexane/EtOAc/AcOH afforded acid **19** (0.125 g, 95%) as a tan foam: ^1H NMR ($CDCl_3$) δ 0.94 (3H, t), 0.97 (3H, t), 1.55 (4H, m), 2.12 (1H, m), 2.28 (3H, m), 2.58 (2H, m), 2.71 (4H, m), 3.58 (3H, s), 4.17 (2H, m), 4.27 (1H, m), 4.40 (1H, m), 4.85 (1H, t), 6.39 (1H, d), 6.46 (1H, d), 6.77 (1H, d), 6.88 (1H, s), 7.40 (1H, d); HRMS (CI) *m/z* 541.2379 (calcd for $C_{29}H_{37}N_2O_6S$ (M + 1) 541.2372).

Methyl 3,4-Dihydro-7-[3-[4-(2,3-dihydro-2-thioxo-4-thiazolyl)-3-methoxy-2-propylphenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylate (20). Chloro ketone **6** (0.115 g, 0.216 mmol) and ammonium dithiocarbamate (30 mg, 0.27 mmol) were stirred in 7 mL of EtOH and 0.7 mL of H_2O at 40–50 °C for 2 h. The mixture was poured into ether and water and the ether layer separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using a gradient of 10:1–5:1 hexane/EtOAc gave thiazole **20** (74 mg, 60%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.91 (3H, t), 0.95 (3H, t), 1.53 (4H, m), 2.17 (2H, m), 2.38 (2H, m), 2.61 (4H, m), 2.72 (2H, m), 3.65 (3H, s), 3.77 (3H, s), 4.14 (2H, t), 4.21 (2H, t), 4.75 (1H, dd), 6.47 (1H, d), 6.65 (1H, s), 6.73 (1H, d), 6.80 (1H, d), 7.26 (1H, d), 10.93 (1H, br); HRMS (EI) *m/z* 571.2082 (calcd for $C_{30}H_{37}NO_6S_2$ 571.2062).

3,4-Dihydro-7-[3-[4-(2,3-dihydro-2-thioxo-4-thiazolyl)-3-methoxy-2-propylphenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylic Acid (21). Ester **20** (47 mg, 82.2 μmol) was saponified as described in general procedure A to afford the crude acid which was flash chromatographed on silica gel using a gradient of 87:12:1–83:16:1 hexane/EtOAc/AcOH to furnish **21** (44 mg, 96%) as a white solid: mp 149–151 °C; ^1H NMR ($CDCl_3$) δ 0.95 (6H, t), 1.55 (4H, m), 2.13 (1H, m), 2.31 (3H, m), 2.60 (2H, m), 2.76 (4H, m), 3.61 (3H, s), 4.18 (2H, t), 4.29 (1H, m), 4.42 (1H, m), 4.99 (1H, t), 6.41 (1H, d), 6.44 (1H, d), 6.78 (1H, d), 6.99 (1H, s), 7.20 (1H, d), 12.00 (1H, br); HRMS (EI) *m/z* 557.1895 (calcd for $C_{29}H_{35}NO_6S_2$ 557.1906).

Methyl 3,4-Dihydro-7-[3-[3-methoxy-4-[2-(methylthio)-4-thiazolyl]-2-propylphenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylate (22). Thiazole **20** (51 mg, 89.1 μmol) was stirred in 2.5 mL of nitromethane with 0.7 mL of MeI at 25 °C for 1 h. The mixture was poured into ether and water and the ether layer separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using a gradient of 20:1–10:1 hexane/EtOAc gave thiazole **22** (51 mg, 97.6%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.93 (3H, t), 0.99 (3H, t), 1.58 (4H, m), 2.21 (2H, m), 2.30 (2H, m), 2.67 (6H, m), 2.77 (3H, s), 3.64 (3H, s), 3.78 (3H, s), 4.15 (2H, t), 4.22 (2H, t), 4.77 (1H, dd), 6.49 (1H, d), 6.74 (1H, d), 6.83 (1H, d), 7.66 (1H, s), 7.91 (1H, d); HRMS (EI) *m/z* 585.2223 (calcd for $C_{31}H_{39}NO_6S_2$ 585.2219).

3,4-Dihydro-7-[3-[3-methoxy-4-[2-(methylthio)-4-thiazolyl]-2-propylphenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylic Acid (23). Ester **22** (48 mg, 81.9 μmol) was saponified as described in general procedure A to afford acid **23** (44 mg, 94%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.92 (3H, t), 1.00 (3H, t), 1.58 (4H, m), 2.20 (1H, m), 2.30 (3H, m), 2.67 (4H, m), 2.75 (3H, s), 2.76 (2H, m), 3.63 (3H, s), 4.16 (2H, t), 4.21 (2H, t), 4.78 (1H, dd), 6.51 (1H, d), 6.73 (1H, d), 6.82 (1H, d), 7.65 (1H, s), 7.89 (1H, d). Anal. ($C_{30}H_{37}NO_6S_2$) C, H, N.

3,4-Dihydro-7-[3-[3-methoxy-4-[2-[(phenylmethyl)thio]-4-thiazolyl]-2-propylphenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylic Acid (24). Thiazole **21** (30 mg, 53.7 μmol) was stirred in 1.5 mL of nitromethane and 0.5 mL of THF with BnBr (30 μL, 0.25 mmol) at 25 °C for 1 h. The mixture was poured into ether and water and the ether layer separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using a gradient of 10:1–7:1 hexane/EtOAc gave thiazole **24** (25 mg, 72%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.93 (3H, t), 0.99 (3H, t),

1.56 (4H, m), 2.16 (1H, m), 2.29 (3H, m), 2.65 (4H, m), 2.77 (2H, m), 3.61 (3H, s), 4.15 (2H, t), 4.21 (2H, t), 4.50 (2H, s), 4.72 (1H, dd), 6.50 (1H, d), 6.73 (1H, d), 6.82 (1H, d), 7.29 (3H, m), 7.41 (2H, d), 7.64 (1H, s), 7.91 (1H, d). Anal. ($C_{36}H_{41}NO_6S_2$) C, H, N.

Methyl 3,4-Dihydro-7-[3-[3-methoxy-4-(1-oxo-2-thiocyanatoethyl)-2-propylphenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylate (25). Chloro ketone **6** (0.11 g, 0.206 mmol) and potassium thiocyanate (21 mg, 0.216 mmol) were stirred in 2 mL of EtOH at reflux for 4.5 h. The mixture was cooled and poured into ether and water. The ether layer was separated, washed with brine, dried over Na_2SO_4, and concentrated to provide thiocyanate **25** (0.111 g, 97%) as a white solid: ^1H NMR ($CDCl_3$) δ 0.90 (3H, t), 0.96 (3H, t), 1.53 (4H, m), 2.19 (2H, m), 2.31 (2H, m), 2.61 (4H, m), 2.72 (2H, m), 3.75 (3H, s), 3.79 (3H, s), 4.12 (2H, t), 4.26 (2H, t), 4.71 (2H, s, CH_2SCN), 4.77 (1H, dd), 6.45 (1H, d), 6.78 (1H, d), 6.81 (1H, d), 7.72 (1H, d).

Methyl 3,4-Dihydro-7-[3-[3-methoxy-4-(2-methoxy-4-thiazolyl)-2-propylphenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylate (26). Thiocyanate **25** (40 mg, 71.8 μmol) was stirred in 2 mL of MeOH with 10 mg of NaOMe at 25 °C for 30 min. The mixture was poured into ether and water and the ether layer separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using a gradient of 20:1−10:1 hexane/EtOAc gave thiazole **26** (24 mg, 39%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.92 (3H, t), 0.98 (3H, t), 1.57 (4H, m), 2.19 (2H, m), 2.30 (2H, m), 2.69 (6H, m), 3.66 (3H, s), 3.77 (3H, s), 4.13 (3H, s), 4.15 (2H, t), 4.21 (2H, t), 4.78 (1H, t), 6.48 (1H, d), 6.72 (1H, d), 6.81 (1H, d), 7.17 (1H, s), 7.82 (1H, d); HRMS (EI) *m/z* 569.2438 (calcd for $C_{31}H_{39}NO_7S$ 569.2443).

3,4-Dihydro-7-[3-[3-methoxy-4-(2-methoxy-4-thiazolyl)-2-propylphenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylic Acid (27). Ester **26** (20 mg, 35.1 μmol) was saponified as described in general procedure A to afford acid **27** (19 mg, 97%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.78 (3H, t), 0.95 (3H, t), 1.42 (2H, m), 1.55 (2H, m), 1.96 (2H, m), 2.18 (2H, m), 2.59 (6H, m), 3.63 (3H, s), 4.03 (2H, t), 4.10 (3H, s), 4.11 (2H, t), 4.30 (1H, m), 6.34 (1H, d), 6.67 (2H, 2d), 7.14 (1H, s), 7.78 (1H, d).

B. General Procedure for the Bromination of Acetophenones. A 0.5 M solution of the acetophenone in $CHCl_3$ was added to a hot 1.0 M solution of $CuBr_2$ (2 equiv) in EtOAc. The mixture was refluxed for 3 h, cooled, stirred with decolorizing carbon for 30 min, filtered, and concentrated. Flash chromatography on silica gel using 15:1 hexane/EtOAc gave the desired bromomethyl ketone.

C. General Procedure for the Synthesis of 2-Unsubstituted Thiazoles. A 0.4 M solution of thioformamide in dioxane was generated by stirring P_2S_5 with 5−6 equiv of formamide in refluxing dioxane for 2 h. The solution was decanted away from the solids and used without any purification. To a 0.1 M solution of the chloromethyl or bromomethyl ketone in dioxane was added 10 equiv of $MgCO_3$ followed by 10 equiv of the thioformamide solution. The mixture was refluxed for 2 h, cooled, and poured into ether and 0.5 M NaOH. The ether layer was separated, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel using 8:1 hexane/EtOAc gave the desired thiazole.

Methyl 3,4-Dihydro-7-[3-[3-methoxy-2-propyl-4-(thiazol-4-yl)phenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylate (28). Reaction of chloromethyl ketone **6** (30 mg, 56 μmol) with thioformamide as described in general procedure C furnished thiazole **28** (30 mg, 99%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.92 (3H, t), 0.99 (3H, t), 1.58 (4H, m), 2.20 (2H, m), 2.30 (2H, m), 2.69 (6H, m), 3.61 (3H, s), 3.76 (3H, s), 4.17 (2H, t), 4.22 (2H, t), 4.77 (1H, t), 6.49 (1H, d), 6.78 (1H, d), 6.81 (1H, d), 7.82 (1H, d, J = 1.7 Hz), 7.91 (1H, d), 8.84 (1H, d, J = 1.7 Hz); HRMS (EI) *m/z* 539.2335 (calcd for $C_{30}H_{37}NO_6S$ 539.2341).

3,4-Dihydro-7-[3-[3-methoxy-2-propyl-4-(thiazol-4-yl)-phenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylic Acid (29). Ester **28** (27 mg, 50 μmol) was saponified as described in general procedure A to afford acid **29** as a white solid: mp 101−103 °C; ^1H NMR ($CDCl_3$) δ 0.92 (3H, t), 0.98 (3H, t), 1.55 (4H, m), 2.20 (1H, m), 2.29 (3H, m), 2.65 (4H, m), 2.75 (2H, m), 3.56 (3H, s), 3.76 (3H, s), 4.14 (2H, t), 4.21 (2H, t), 4.77 (1H, t), 6.48 (1H, d), 6.72 (1H, d), 6.81 (1H, d), 7.80 (1H, d), 7.82 (1H, d, J = 1.7 Hz), 8.91 (1H, d, J = 1.7 Hz). Anal. ($C_{29}H_{35}NO_6S$) C, H, N, S.

Methyl 7-[3-[4-(2-Bromo-1-oxoethyl)-3-methoxy-2-(2-propenyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylate (30). The title compound was prepared by general procedure B from acetophenone **1b** (0.156 g, 0.314 mmol) to provide **30** (59 mg, 33%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.92 (3H, t), 1.52 (2H, m), 2.20 (2H, m), 2.29 (2H, m), 2.67 (4H, m), 3.43 (2H, d), 3.77 (3H, s), 3.78 (3H, s), 4.11 (2H, t), 4.23 (2H, t), 4.58 (2H, s, CH_2Br), 4.77 (1H, dd), 4.97 (2H, m), 5.95 (1H, m), 6.43 (1H, d), 6.77 (1H, d), 6.80 (1H, d), 7.65 (1H, d).

Methyl 3,4-Dihydro-7-[3-[3-methoxy-2-(2-propenyl)-4-(thiazol-4-yl)phenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylate (31). The title compound was prepared by general procedure C from bromomethyl ketone **30** (59 mg, 0.103 mmol) to afford thiazole **31** (38 mg, 68%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.93 (3H, t), 1.55 (2H, m), 2.18 (2H, m), 2.28 (2H, m), 2.69 (4H, m), 3.51 (2H, d), 3.61 (3H, s), 3.77 (3H, s), 4.14 (2H, t), 4.22 (2H, t), 4.77 (1H, dd), 4.98 (2H, m), 6.00 (1H, m), 6.46 (1H, d), 6.80 (2H, 2d), 7.84 (1H, d, J = 1.9 Hz), 7.95 (1H, d), 8.84 (1H, d, J = 1.9 Hz); HRMS (EI) *m/z* 537.2195 (calcd for $C_{30}H_{35}NO_6S$ 537.2185).

3,4-Dihydro-7-[3-[3-methoxy-2-(2-propenyl)-4-(thiazol-4-yl)phenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-carboxylic Acid (32). Ester **31** (22 mg, 40.9 μmol) was saponified as described in general procedure A to afford the crude acid which was flash chromatographed on silica gel using 83:16:1 hexane/EtOAc/AcOH to furnish **32** (20 mg, 93%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.92 (3H, t), 1.52 (2H, m), 2.20 (1H, m), 2.29 (3H, m), 2.65 (2H, m), 2.77 (2H, m), 3.48 (2H, d), 3.59 (3H, s), 4.13 (2H, t), 4.23 (2H, t), 4.76 (1H, dd), 4.97 (2H, m), 6.00 (1H, m), 6.49 (1H, d), 6.75 (1H, d), 6.82 (1H, d), 7.84 (1H, d), 7.87 (1H, d), 8.89 (1H, d); HRMS (EI) *m/z* 479.2114 (calcd for $C_{28}H_{33}NO_4S$ (M − CO_2) 479.2130).

Methyl 7-[3-[4-(2-Bromo-1-oxoethyl)-2-(cyclopropylmethyl)-3-methoxyphenoxy]propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylate (33). The title compound was prepared by general procedure B from acetophenone **1c** (0.147 g, 0.288 mmol) to provide **33** (107 mg, 63%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.22 (2H, m), 0.37 (2H, m), 0.90 (3H, t), 0.99 (1H, m), 1.52 (2H, m), 2.19 (2H, m), 2.31 (2H, m), 2.59 (4H, m), 2.60 (2H, m), 3.73 (3H, s), 3.77 (3H, s), 4.14 (2H, t), 4.25 (2H, t), 4.58 (2H, s, CH_2Br), 4.75 (1H, dd), 6.44 (1H, d), 6.76 (1H, d), 6.80 (1H, d), 7.61 (1H, d).

Methyl 7-[3-[2-(Cyclopropylmethyl)-3-methoxy-4-(thiazol-4-yl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylate (34). The title compound was prepared by general procedure C from bromomethyl ketone **33** (107 mg, 0.18 mmol) to afford thiazole **34** (76 mg, 76%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.26 (2H, m), 0.38 (2H, m), 0.94 (3H, t), 1.06 (1H, m), 1.56 (2H, m), 2.20 (2H, m), 2.31 (2H, m), 2.67 (6H, m), 3.58 (3H, s), 3.77 (3H, s), 4.18 (2H, t), 4.24 (2H, t), 4.77 (1H, dd), 6.47 (1H, d), 6.79 (1H, d), 6.80 (1H, d), 7.83 (1H, d, J = 1.9 Hz), 7.91 (1H, d), 8.84 (1H, d, J = 1.9 Hz); HRMS (EI) *m/z* 551.2346 (calcd for $C_{31}H_{37}NO_6S$ 551.2341).

7-[3-[2-(Cyclopropylmethyl)-3-methoxy-4-(thiazol-4-yl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylic Acid (35). Ester **34** (43 mg, 77.9 μmol) was saponified as described in general procedure A to afford the crude acid which was flash chromatographed on silica gel using 83:16:1 hexane/EtOAc/AcOH to furnish **35** (41 mg, 98%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.24 (2H, m), 0.39 (2H, m), 0.93 (3H, t), 1.04 (1H, m), 1.55 (2H, m), 2.20 (1H, m), 2.30 (3H, m), 2.62 (4H, m), 2.77 (2H, m), 3.57 (3H, s), 4.18 (2H, t), 4.23 (2H, t), 4.78 (1H, dd), 6.50 (1H, d), 6.76 (1H, d), 6.82 (1H, d), 7.81 (1H, d), 7.83 (1H, d), 8.92 (1H, d). Anal. ($C_{30}H_{35}NO_6S$) C, H, N, S.

Separation of Enantiomers of 35. Racemic **35** (180 mg, 0.335 mmol) was resolved by chiral HPLC using a Chiracel O.D. column and eluting with 10:90:0.1 2-propanol/hexane/trifluoroacetic acid (3 mL/min flow rate) to provide (−)-**35** (31.7 mg, 17.6%), mp 111−112 °C, $[\alpha]^{25}_D$ −17.7° (c 1.585, $CHCl_3$),

and (+)-**35** (25.8 mg, 14.3%), mp 109–110 °C, $[\alpha]^{25}_D$ +17.8° (c 1.29, $CHCl_3$). Anal. ($C_{30}H_{35}NO_6S \cdot 0.5H_2O$) C, H, N.

Methyl 7-[3-[4-(2-Bromo-1-oxoethyl)-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-propionate (36). The title compound was prepared by general procedure B from acetophenone **1d** (0.55 g, 1.04 mmol) to provide **36** (0.34 g, 54%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.89 (3H, t), 0.96 (3H, t), 1.40–1.77 (5H, m), 1.98 (3H, m), 2.30 (2H, m), 2.46-2.87 (8H, m), 3.68 (3H, s), 3.75 (3H, s), 3.97 (1H, dt), 4.12 (2H, t), 4.23 (2H, t), 4.57 (2H, s, CH_2Br), 6.44 (1H, d), 6.73 (1H, d), 6.82 (1H, d), 7.60 (1H, d).

Methyl 3,4-Dihydro-7-[3-[3-methoxy-2-propyl-4-(thiazol-4-yl)phenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-propionate (37). The title compound was prepared by general procedure C from bromomethyl ketone **36** (0.22 g, 0.36 mmol) to afford thiazole **37** (0.16 g, 78%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.91 (3H, t), 0.98 (3H, t), 1.41–1.78 (5H, m), 1.98 (3H, m), 2.29 (2H, m), 2.48–2.89 (8H, m), 3.60 (3H, s), 3.69 (3H, s), 3.96 (1H, dt), 4.15 (2H, t), 4.21 (2H, t), 6.44 (1H, d), 6.77 (1H, d), 6.82 (1H, d), 7.83 (1H, d), 7.92 (1H, d), 8.83 (1H, d).

3,4-Dihydro-7-[3-[3-methoxy-2-propyl-4-(thiazol-4-yl)-phenoxy]propoxy]-8-propyl-2*H*-1-benzopyran-2-propionic Acid (38). Ester **37** (0.15 g, 0.264 mmol) was saponified as described in general procedure A to afford the crude acid which was chromatographed by reverse phase on a C18 column using 25:75:1 $H_2O/CH_3CN/AcOH$ to furnish **38** (113 mg, 77%) as a white solid: mp 110–113 °C; ^1H NMR ($CDCl_3$) δ 0.90 (3H, t), 0.99 (3H, t), 1.41–1.79 (5H, m), 1.99 (3H, m), 2.30 (2H, m), 2.53-2.89 (8H, m), 3.59 (3H, s), 3.98 (1H, m), 4.14 (2H, t), 4.21 (2H, t), 6.45 (1H, d), 6.77 (1H, d), 6.82 (1H, d), 7.83 (1H, d), 7.87 (1H, d), 8.90 (1H, d). Anal. ($C_{31}H_{39}NO_6S \cdot H_2O$) C, H, N.

Methyl 7-[3-[4-(2-Bromo-1-oxoethyl)-2-(cyclopropylmethyl)-3-methoxyphenoxy]propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-propionate (39). The title compound was prepared by general procedure B from acetophenone **1e** (0.56 g, 1.04 mmol) to provide **39** (0.50 g, 77%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.21 (2H, m), 0.38 (2H, m), 0.91 (3H, t), 1.00 (1H, m), 1.46 (2H, m), 1.70 (1H, m), 1.97 (3H, m), 2.29 (2H, m), 2.46–2.88 (8H, m), 3.70 (3H, s), 3.76 (3H, s), 3.98 (1H, m), 4.12 (2H, t), 4.26 (2H, t), 4.58 (2H, s, CH_2Br), 6.43 (1H, d), 6.77 (1H, d), 6.83 (1H, d), 7.63 (1H, d).

Methyl 7-[3-[2-(Cyclopropylmethyl)-3-methoxy-4-(thiazol-4-yl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-propionate (40). The title compound was prepared by general procedure C from bromomethyl ketone **39** (0.45 g, 0.73 mmol) to afford thiazole **40** (0.34 g, 80%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.26 (2H, m), 0.39 (2H, m), 0.92 (3H, t), 1.07 (1H, m), 1.48 (2H, m), 1.68 (1H, m), 1.98 (3H, m), 2.32 (2H, m), 2.31–2.90 (8H, m), 3.58 (3H, s), 3.70 (3H, s), 3.97 (1H, m), 4.15 (2H, t), 4.23 (2H, t), 6.46 (1H, d), 6.79 (1H, d), 6.82 (1H, d), 7.83 (1H, d), 7.91 (1H, d), 8.84 (1H, d).

7-[3-[2-(Cyclopropylmethyl)-3-methoxy-4-(thiazol-4-yl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-propionic Acid (41). Ester **40** (0.22 g, 0.379 mmol) was saponified as described in general procedure A to afford the crude acid which was purified by reverse phase chromatography on a C18 column using 25:75:1 $H_2O/CH_3CN/AcOH$ to furnish **41** (90 mg, 42%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.26 (2H, m), 0.38 (2H, m), 0.91 (3H, t), 1.06 (1H, m), 1.51 (2H, m), 1.70 (1H, m), 1.99 (3H, m), 2.29 (2H, m), 2.47–2.89 (8H, m), 3.57 (3H, s), 3.97 (1H, m), 4.15 (2H, t), 4.22 (2H, t), 6.44 (1H, d), 6.78 (1H, d), 6.82 (1H, d), 7.83 (1H, s), 7.87 (1H, d), 8.89 (1H, s). Anal. ($C_{32}H_{39}NO_6S \cdot 0.75H_2O$) C, H, N.

Methyl 2-[3-[3-[4-(2-Bromo-1-oxoethyl)-2-(cyclopropylmethyl)-3-methoxyphenoxy]propoxy]-2-propylphenoxy]-acetate (42). The title compound was prepared by general procedure B from acetophenone **1f** (0.32 g, 0.66 mmol) to provide **42** (0.19 g, 51%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.15–0.25 (2H, m), 0.25–0.42 (2H, m), 0.92 (3H, t), 0.94–1.08 (1H, m), 1.42–1.58 (2H, m), 2.25–2.40 (2H, m), 2.59 (2H, d), 2.68 (2H, t), 3.75 (3H, s), 3.79 (3H, s), 4.16 (2H, t), 4.26 (2H, t), 4.58 (2H, s), 4.64 (2H, s), 6.38 (1H, d), 6.56 (1H, d), 6.75 (1H, d), 7.06 (1H, t), 7.62 (1H, d).

Methyl 2-[3-[3-[2-(Cyclopropylmethyl)-3-methoxy-4-(thiazol-4-yl)phenoxy]propoxy]-2-propylphenoxy]acetate (43). The title compound was prepared by general procedure C from bromomethyl ketone **42** (0.14 g, 0.25 mmol) to afford thiazole **43** (12 mg, 9%) as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.16–0.42 (4H, m), 0.94 (3H, t), 0.96–1.12 (1H, m), 1.42–1.60 (2H, m), 2.25–2.48 (2H, m), 2.64 (2H, d), 2.69 (2H, t), 3.48 (3H, s), 3.78 (3H, s), 4.19 (2H, t), 4.24 (2H, t), 4.64 (2H, s), 6.38 (1H, d), 6.58 (1H, d), 6.78 (1H, d), 7.06 (1H, t), 7.85 (1H, d, J = 2 Hz), 7.90 (1H, d), 8.85 (1H, d, J = 2 Hz).

2-[3-[3-[2-(Cyclopropylmethyl)-3-methoxy-4-(thiazol-4-yl)phenoxy]propoxy]-2-propylphenoxy]acetic Acid (44). Ester **43** (12 mg, 0.091 mmol) was saponified as described in general procedure A to furnish the acid **44** as a colorless gum: ^1H NMR ($CDCl_3$) δ 0.14–0.26 (2H, m), 0.26–0.44 (2H, m), 0.92 (3H, t), 0.96–1.10 (1H, m), 1.44–1.62 (2H, m), 2.20–2.38 (2H, m), 2.64 (2H, d), 2.70 (2H, t), 3.54 (3H, s), 4.19 (2H, t, J = 5.5 Hz), 4.26 (2H, t, J = 5.5 Hz), 4.66 (2H, s), 6.42 (1H, d, J = 8.5 Hz), 6.59 (1H, d, J = 8.5 Hz), 6.72 (1H, d, J = 8.5 Hz), 7.06 (1H, t, J = 8.6 Hz), 7.76 (1H, d, J = 8.6 Hz), 7.84 (1H, d, J = 2 Hz), 8.89 (1H, d, J = 2 Hz). Anal. ($C_{28}H_{33}NO_6S \cdot H_2O$) C, H, N.

Acknowledgment. The authors would like to thank the Searle Physical Methodology Department for mass spectral and microanalytical data and Ms. Patricia Finnegan for NMR interpretive assistance. We would also like to acknowledge Ms. Dorothy Honda for the chromatographic resolution of SC-50605 and Dr. Paul Collins for his helpful advice.

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JM940702X