Naphthalenic Lignan Lactones as Selective, Nonredox 5-Lipoxygenase Inhibitors. Synthesis and Biological Activity of (Methoxyalkyl)thiazole and Methoxytetrahydropyran Hybrids

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Combinations of structural elements found in (methoxyalkyl)thiazole **1a** and methoxytetrahydropyran **2a** with a naphthalenic lignan lactone produce the potent 5-lipoxygenase (5-LO) inhibitors **3** and **4**. While the nature of link Y–Z has a major effect on the *in vitro* activity of compounds **1** and **2**, inhibitors **3** and **4** retain their potencies with either an oxymethylene (Y = O, Z = CH_2) or a methyleneoxy (Y = CH_2, Z = O) link. Compound **4b** inhibits the oxidation of arachidonic acid to 5-hydroperoxyeicosatetraenoic acid by 5-LO (IC_{50} = 14 nM) and the formation of leukotriene B_4 in human polymorphonuclear leukocytes (IC_{50} = 1.5 nM) as well as in human whole blood (IC_{50} = 50 nM). Compound **4b** is a selective 5-LO inhibitor showing no significant inhibition of human 15-lipoxygenase or porcine 12-lipoxygenase or binding to human 5-lipoxygenase-activating protein up to 10 μM and inhibits leukotriene biosynthesis by a direct, nonredox interaction with 5-LO. Compound **15**, the open form of lactone **4b**, is well absorbed in the rat and is transformed into the active species **4b**. In addition, **15** is orally active in the rat pleurisy model (ED_{50} = 0.6 mg/kg) and in the functional model of antigen-induced bronchoconstriction in allergic squirrel monkeys (95% inhibition at 0.3 mg/kg).

Introduction

Leukotrienes are important biological mediators derived from arachidonic acid through the action of 5-lipoxygenase (5-LO).[1] Leukotriene B_4 (LTB_4) is a potent chemotactic agent and is considered to be a mediator of inflammation.[2] The peptidoleukotrienes LTC_4, LTD_4, and LTE_4 are powerful spasmogenic agents and have been shown to be implicated in the pathology of several diseases.[3] Thus, selective inhibitors of 5-LO could form a new class of therapeutic agents for the treatment of disease states such as asthma,[4] inflammatory bowel disease, and rheumatoid arthritis.

Our continuing quest for a potent, specific, and nonredox inhibitor of 5-LO[5] led us to explore a new series of naphthalenic lignan lactones[6] exemplified by structure **A** (Chart 1). Members of this class, identified from a wide screening effort, are moderately potent, nonredox inhibitors of 5-LO. While we were pursuing these investigations, Bird *et al.*[7] reported the discovery of the new (methoxyalkyl)thiazole class of inhibitors exemplified by ICI211965 (**1a**, Chart 1). The same group later reported on the discovery of a related series of inhibitors, the methoxytetrahydropyrans, exemplified by 2-[[3-(4-methoxytetrahydro-2*H*-pyran-4-yl)phenoxy]methyl]naphthalene (**2a**).[8] Since these three compounds are potent, selective, and nonredox inhibitors of 5-LO and potentially bind to a same site on the enzyme, we became intrigued by the possibility that substitution of the naphthalene in structures **1** and **2** by lignan lactone derivatives (to generate compounds such as **3** and **4**) might produce potent inhibitors of 5-LO. Such inhibitors would have the advantage that they could be dosed either as the lactone or as the corresponding hydroxy acid. We now report that linkage of the 3-[1-methoxy-1-(thiazol-2-yl)propyl]phenyl and 3-(4-methoxytetrahydro-2*H*-pyran-4-yl)phenyl moieties to the 4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-on-7-yl group by a suitably chosen unit, Y–Z, yields highly potent, specific, and nonredox 5-LO inhibitors.

Chemistry

In order to assess the influence of link Y–Z on inhibitor potency, access to compounds **1–4** with an oxymethylene link (Chart 1; **a**: Y = O, Z = CH_2) and with a methyleneoxy link (**b**: Y = CH_2, Z = O) was desirable. Compounds **1–4** were prepared by alkylation of phenols **5a–8a** (Chart 2) with the appropriate (chloro- or bromomethyl)arene **5–8** (**b** or **c**) in the presence of potassium carbonate in dimethylformamide.

The required phenols **5a**,[7] **7a**,[8] and **8a**[6] were prepared according to literature procedures, while 2-naphthol (**6a**) is commercially available.

The corresponding (halogenomethyl)arenes **5–8** (**b** or **c**) were prepared in the following ways.

Triflation of phenol **5a** (Scheme 1) followed by palladium-catalyzed methoxycarbonylation[9] afforded ester **10**. Reduction and chlorination gave the desired benzyl chloride **5b**. A similar approach was used to accomplish a one-carbon homologation of phenolic lignan lactone **8a** to methyl ester **11** (Scheme 2). In this case, immediate reduction of the ester was precluded by the presence of the lactone. Consequently, ester **11** was hydrolized, and the resulting acid was derivatized into an isopropylacyl carbonate. The mixed carbonate was selectively reduced with sodium borohydride to the hydroxymethyl derivative **12**. Bromination then gave the bromomethylated lignan lactone **8c**. Preparation of benzyl bromide **7c** involved *in situ* preparation of 3-lithiotoluene (Scheme 3) by lithium–bromine exchange followed by addition of tetrahydro-4*H*-pyran-4-one to afford tertiary alcohol **13**. Methylation

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Chart 1

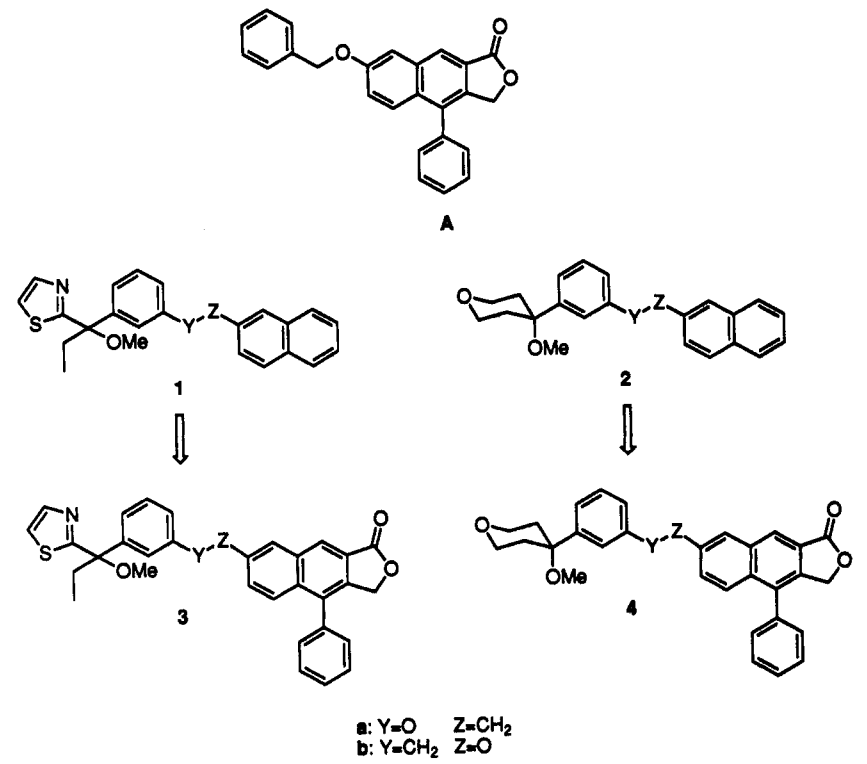
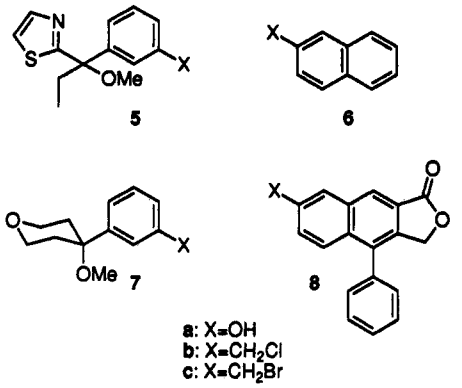
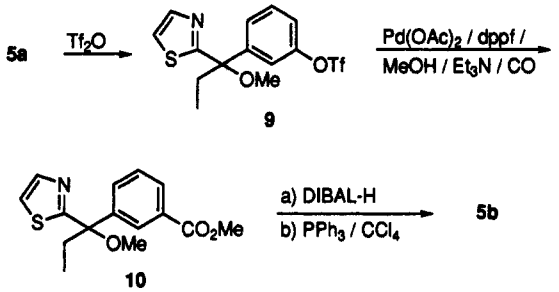


Chart 2



Scheme 1

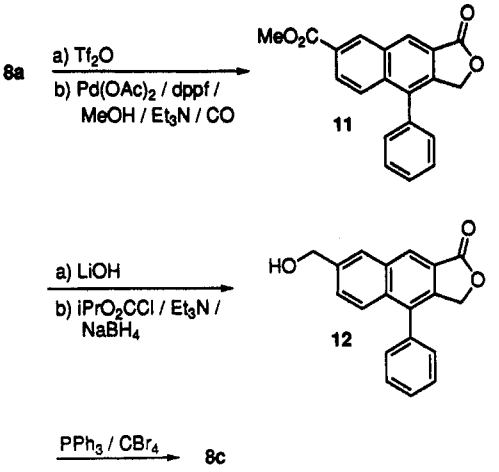


and radical bromination completed the synthetic sequence. 2-(Bromomethyl)naphthalene (**6c**) is commercially available.

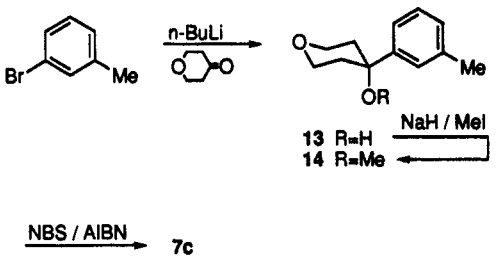
Structure–Activity Relationship *in Vitro*

Compounds 1–4 were evaluated for their potency to inhibit (a) oxidation of arachidonic acid by recombinant human 5-LO (H5-LO), (b) production of LTB_4 in human peripheral blood polymorphonuclear leukocytes (HPMN), and (c) production of LTB_4 in human whole blood (HWB).

Scheme 2

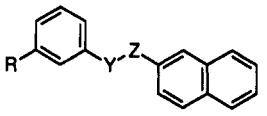


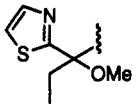
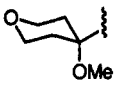
Scheme 3



The nature of link Y–Z, oxymethylene in series **a** and methyleneoxy in series **b**, has a major effect on the potency of naphthalene derivatives **1** and **2** (Table 1). In this group, methyleneoxy thiazole **1b** (IC_{50} = 1.3 μM in H5-LO) is 10-fold less potent than its oxymethylene counterpart **1a** (IC_{50} = 150 nM). Even more striking is the difference between the two tetrahydropyran analogs. In the H5-LO assay, methyleneoxy **2b** (IC_{50} = 1 μM) is 100-fold less potent than oxymethylene **2a** (IC_{50} = 10 nM). In the cell assays, this discrepancy is also observed but to a lesser extent

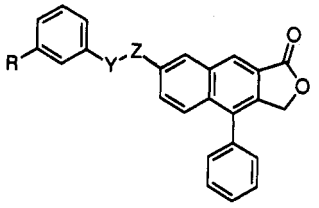
Table 1. *In Vitro* Potency of Naphthalene Derivatives

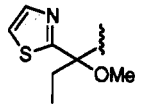
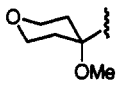


	R	Y	Z	IC_{50} (nM)[a] H5-LO	HPMN	HWB
1a		O	CH_2	150	4.4	700
1b		CH_2	O	1300	11	>3000
2a		O	CH_2	10	1.2	60
2b		CH_2	O	1000	55	1500

[a] Each IC_{50} value is an average of at least two independent determinations.

Table 2. *In Vitro* Potency of Lignan Lactone Derivatives



	R	Y	Z	IC_{50} (nM)[a] H5-LO	HPMN	HWB
3a		O	CH_2	50	2.2	700
3b		CH_2	O	160	4.8	1400
4a		O	CH_2	20	0.9	50
4b		CH_2	O	14	1.5	50

[a] Each IC_{50} value is an average of at least two independent determinations.

with 3-fold differences in the thiazole series and (25–50)-fold differences in the tetrahydropyran series.

Replacement of the naphthalene moiety by the lignan lactone substructure provides compounds **3** and **4** and leads to a markedly different situation (Table 2). Substitution of the oxymethylene link by methyleneoxy in thiazole **3a** brings only a (2–3)-fold loss of *in vitro* potency. Furthermore, the two tetrahydropyran analogs **4a** and **4b** are equipotent. With either link, the last two compounds have an excellent overall *in vitro* profile with IC_{50} values in the order of 20 nM for the H5-LO assay, 1 nM for the HPMN assay, and 50 nM for inhibition of LTB_4 formation in human whole blood. Thus, substitution of naphthalene by the 4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-on-7-yl group allows the utilization of both links without any loss of potency.

The inhibitory properties of compound **4b** were evaluated in more detail using the HPMN and H5-LO assays. The inhibitory potency of compound **4b** was found to be dependent on cell concentration in the HPMN leukocyte assay, with an average 6-fold shift in IC_{50} values over a 10-fold range of cell concentrations (IC_{50} values from 0.56 ± 0.07 nM to 3.1 ± 1.1 nM, n = 3, ±SE for cell concentrations ranging from (1.6 to 16) × 10^5 cells/mL).

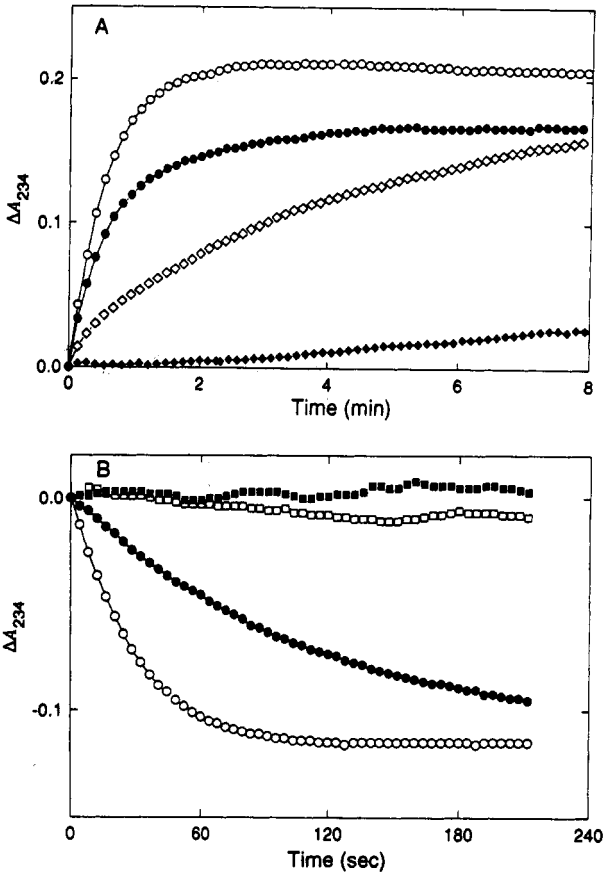


Figure 1. Effect of compound **4b** on the oxygenase and pseudoperoxidase activities of purified human 5-LO. (A) Time course of the production of 5-HPETE by 5-LO (0.3 μg/mL) using a spectrophotometric assay in the absence (○) or presence of 25 nM (●), 77 nM (◇), and 230 nM (◆) **4b**. (B) Consumption of 13-HPOD catalyzed by 5-LO measured spectrophotometrically. Assay mixtures contained 10 μM 13-HPOD, 3 μg/mL 5-LO, and (□) 10 μM **4b**, (○) 10 μM CPHU, (●) 10 μM CPHU + 3.3 μM **4b**, or (■) 10 μM CPHU + 10 μM **4b**.

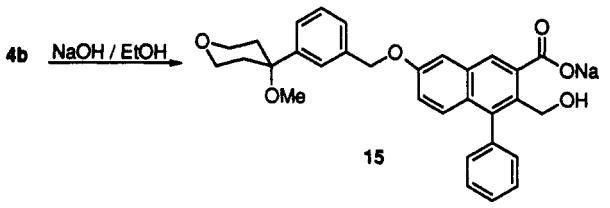
Compound **4b** inhibited the activity of recombinant human 5-LO in soluble cell-free extracts with an IC_{50} value of 14 ± 3 nM and was more potent than the recently described nonredox inhibitors L-689,065[5,10] (IC_{50} = 300 nM) and L-691,816[10] (IC_{50} = 60 nM) as well as Zileuton[10,11] (IC_{50} = 3.7 μM). The lower apparent potency of compound **4b** on the purified enzyme might be due to higher concentrations of the arachidonate substrate and activating hydroperoxides as compared to those achieved in leukocytes. The effects of compound **4b** on 5-LO are similar to those described for (methoxyalkyl)thiazole and thiopyranoindole inhibitors and are consistent with a nonredox mechanism of enzyme inhibition.[12] Figure 1A shows the time course of 5-hydroperoxyeicosatetraenoic acid (5-HPETE) production by 5-LO and the protection against enzyme inactivation which occurred during the inhibition by **4b**. At the concentration of 77 nM, the apparent first-order rate constant of inactivation of 5-LO was reduced by a factor of 5. Compound **4b** was somewhat less potent as an inhibitor of the purified enzyme than an inhibitor of 5-LO activity in soluble cell extracts, which presumably reflects differences in the levels of activating hydroperoxides of the two systems. 5-LO is known to catalyze the decomposition of lipid hydroperoxides in the presence of reducing substrates.[13] An example of this pseudoperoxidase activity is shown in Figure 1B, where the consumption of 13-hydroperoxyoctadecadienoic acid (13-HPOD) by

Table 3. Comparison of *in Vitro* Potency of Zileuton, MK-0591, D-2138, and **4b**

	IC_{50} (nM)[a]		
	H5-LO	HPMN	HWB
Zileuton	3700	1100	2000
MK-0591	5000	3	500
D-2138	330	10	80
4b	14	1.5	50

[a] Each IC_{50} value is an average of at least two independent determinations.

Scheme 4



5-LO was followed as a function of time after incubation with *N*-(4-chlorophenyl)-*N*-hydroxy-*N'*-(3-chlorophenyl)-urea (CPHU), a reducing hydroxyurea inhibitor of the enzyme.[14] Incubation of 13-HPOD and the enzyme with compound **4b** instead of with CPHU did not result in any hydroperoxide consumption, indicating that inhibitor **4b** does not function as a reducing substrate for the enzyme. However, compound **4b** can interact with the enzyme at the concentration used (10 μM) since it could completely block the pseudoperoxidase reaction observed with CPHU under the same conditions (Figure 1B).

Compound **4b** is a selective inhibitor of 5-LO that causes little or no inhibition (<15% at a concentration of 10 μM) of human 15-lipoxygenase or porcine 12-lipoxygenase activities. Furthermore, the inhibitor was found to be inactive (IC_{50} > 10 μM) in a binding assay to the 5-lipoxygenase-activating protein (FLAP).[15]

Compound **4b** was found to be more potent *in vitro* than Zileuton,[11] MK-0591,[16] and ICI D2138[8] in the H5-LO, HPMN and HWB assays (Table 3).

In Vivo Studies

In spite of its excellent *in vitro* potency, **4b** showed disappointingly weak activity in inhibiting LTB_4 biosynthesis *in vivo* in a rat pleurisy model[16] (33% inhibition using a 3-h oral pretreatment with a dose of 3 mg/kg). This result correlates with the absence of any detectable amount of drug in rat plasma samples after oral administration (20 mg/kg as a suspension in 0.5% methocel). We expected that **4b** would have better chances to be absorbed if it was administered as its open hydroxy acid form. Consequently, **4b** was saponified with sodium hydroxide to the water soluble sodium carboxylate **15** (Scheme 4) which shows only weak inhibitory properties on 5-LO (IC_{50} = 6 μM). After oral dosing of **15** (50 mg/kg as a solution in 0.5% methocel), the potent lactone **4b** was detected in rat plasma samples (C_{max} = 4 μM at 1 h). This significant plasma level can be explained by one or both of the following hypotheses. Firstly, carboxylate **15** cyclizes to a readily absorbed solid form of lactone **4b** in the acidic environment of the stomach. The second possibility is that carboxylate **15** is the absorbed entity and cyclizes *in vivo* to lactone **4b**. The improved pharmacokinetic behavior of **15** was reflected in the rat pleurisy model. After 3 h of oral pretreatment, dose-dependent inhibition of LTB_4 was observed (ED_{50} = 0.6 mg/kg). This is comparable to the activity of FLAP inhibitor MK-0591 (ED_{50} = 0.5 mg/kg after 2 h of oral pretreatment).[16]

The effect of **15** on antigen-induced bronchoconstriction in allergic squirrel monkeys[16] was also measured. A 4-h pretreatment at 0.3 mg/kg oral dose followed by a challenge with an aerosol of *Ascaris* antigen produced a 95% inhibition of the increase in airway resistance (R_L) and a 95% inhibition of decrease in dynamic compliance (C_{dyn}). For MK-0591, the values obtained at this dose were R_L = 44% and C_{dyn} = 46%.[16] Thus, **15** is more potent than MK-0591 in this functional model.

Conclusion

Linkage of the 3-[1-methoxy-1-(thiazol-2-yl)propyl]-phenyl and 3-(4-methoxytetrahydro-2*H*-pyran-4-yl)phenyl substructures to a naphthalene lignan lactone moiety by oxymethylene or methyleneoxy units produces the highly potent 5-LO inhibitors **3** and **4**. Compound **4b** inhibits leukotriene biosynthesis by a selective and direct interaction with 5-LO and not by nonspecific antioxidant mechanisms or binding to FLAP. Sodium carboxylate **15** is orally active in the rat pleurisy model and in the functional model of antigen-induced bronchoconstriction in allergic squirrel monkeys. Thus, the development of this new series of selective and nonredox inhibitors may result in the identification of novel antiasthma and antiinflammation agents.

Experimental Section

Biology. Generation of LTB_4 in HPMN and in HWB. The generation of LTB_4 in human peripheral blood polymorphonuclear leukocytes and in human whole blood was measured as previously described by Brideau *et al.*[16]

Assay of 5-LO Activity (H5-LO). The activity of 5-LO was measured using the soluble cell-free fraction from Sf9 insect cells infected with recombinant baculovirus carrying the coding region of human 5-LO.[17] The activity of the oxygenase reaction was measured using a spectrophotometric assay by monitoring the formation of conjugated diene (A_{234}) after incubation of the enzyme preparation (10 μg of protein/mL, 1 μmol of 5-HPETE/mg of protein) with arachidonic acid (20 μM), ATP (0.2 mM), $CaCl_2$ (0.4 mM), and phosphatidylcholine (12 μg/mL) in 0.05 M sodium phosphate, pH 7.4. Enzyme activity was determined from the optimal change in A_{234}, and the apparent rate constant of enzyme inactivation was established assuming a first-order decay of enzyme activity. Inhibitors were added from 500-fold concentrated stock solutions in dimethyl sulfoxide. Inhibitor concentrations causing a 50% decrease of the initial velocity were determined by nonlinear regression analysis.

Assay of the Pseudoperoxidase Activity of 5-LO. The pseudoperoxidase activity was determined from the reducing-agent-dependent consumption of 13-HPOD catalyzed by the purified 5-LO using the variation in A_{234} as previously described.[14] The assay mixture contained 10 μM 13-HPOD, 0.4 mM $CaCl_2$, 12 μg/mL phosphatidylcholine, purified 5-LO (3 μg/mL), 0.05 M sodium phosphate, pH 7.4, and either the diarylhydroxyurea CPHU as reducing substrate or the inhibitor to be evaluated.

Recombinant human 5-LO was purified by ATP–agarose affinity chromatography as previously described.[17]

Leukotriene Biosynthesis in the Rat Pleural Cavity. LTB_4 levels in rat pleural exudates following interpleural injection of carrageenan followed 16–20 h later by ionophore A23187 were determined as previously described.[16]

***Ascaris*-Induced Bronchoconstriction in Squirrel Monkeys.** Naturally sensitized, male squirrel monkeys were challenged with an aerosol of *Ascaris* antigen. Changes in pulmonary mechanics (airway resistance (R_L) and dynamic compliance (C_{dyn})) were monitored in conscious animals using airflow measurements from a face mask and measurements of pleural pressure as previously described.[16]

Measurement of Plasma Level and Bioavailability. Male Sprague–Dawley rats (2) were starved overnight and dosed orally with the compound at 50 mg/kg as a solution in 0.5% methocel (1 mL/100 g). Blood was taken from the jugular vein at 0, 0.5, 1, 2, 4, 6, and 8 h after dosing. In the intravenous studies, compounds were dissolved in 5% dextrose and injected intravenously in the jugular vein at a dose of 10 mg/kg (dose volume = 0.1 mL/100 g). Blood was taken from the jugular vein at 0, 5, 15, and 30 min and 1, 2, 4, and 6 h after dosing. Blood was centrifuged and plasma collected. To 100 μL of each plasma sample was added an equal volume of acetonitrile to precipitate proteins. An aliquot (30 μL) of the supernatant after centrifugation was subjected to reversed-phase HPLC. The parent compound was quantitated from the area of the corresponding peak, relative to the standard (plasma sample at time 0 min, spiked with varying concentration of the compound).

Chemistry. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker AM 250 and AMX 300 spectrometers, and proton chemical shifts are relative to tetramethylsilane as internal standard. The infrared spectra were measured on a Perkin-Elmer 681 spectrophotometer. Melting points were measured on a Buchi 510 or an Electrothermal 9100 apparatus in open capillary tubes and are uncorrected. Low-resolution mass spectral and elemental analyses were performed by Oneida Research Services, Whitesboro, NY. Where elemental analyses are reported only by symbols of the elements, results were within 0.4% of the theoretical values. All reactions as well as column chromatography were monitored routinely by thin-layered chromatography using precoated silica gel 60F-254 plates (E. Merck).

Preparation of Phenols (5a–8a). The required phenols, 3-[1-methoxy-1-(thiazol-2-yl)propyl]phenol (**5a**),[7] 3-(4-methoxy-tetrahydro-2*H*-pyran-4-yl)phenol (**7a**),[8] and 7-hydroxy-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (**8a**)[6] were prepared according to literature procedures, while 2-naphthol (**6a**) is commercially available.

Preparation of (Halogenomethyl)arenes [5–8 (b or c)]. 3-[1-Methoxy-1-(thiazol-2-yl)propyl]benzyl Chloride (5b). Step 1: 1-[1-methoxy-1-(thiazol-2-yl)propyl]-3-[[(trifluoromethyl)sulfonyl]oxy]benzene (**9**). Trifluoromethanesulfonic anhydride (1.5 mL, 8.9 mmol) was added to a 0 °C solution of phenol **5a**[7] (1.83 g, 7.34 mmol) and 2,6-di-*tert*-butylpyridine (2.3 mL, 10.2 mmol) in dichloromethane (30 mL). The reaction mixture was stirred at room temperature for 40 min, and the solvent was evaporated. The residue was diluted with ether and filtered. The filtrate was washed successively with 5% aqueous HCl, water, and brine and then dried ($MgSO_4$) and evaporated. Purification by flash chromatography using hexane–EtOAc (75:25) as eluant gave triflate **9** (2.76 g, 98%) as an amber oil: ^{1}H NMR ($CDCl_3$) δ 7.7 (d, 1 H), 7.5–7.1 (m, 5 H), 3.25 (s, 3 H), 2.65 (m, 1 H), 2.4 (m, 1 H), 0.75 (t, 3 H).

Step 2: methyl 3-[1-methoxy-1-(thiazol-2-yl)propyl]benzoate (**10**). To a solution of triflate **9** (2.75 g, 7.21 mmol) in DMF (15 mL) was added methanol (6 mL), triethylamine (2.0 mL, 14.3 mmol), 1,1-bis(diphenylphosphino)ferrocene (0.90 g, 1.6 mmol), and palladium(II) acetate (0.14 g, 0.6 mmol). The reaction mixture was saturated with carbon monoxide (bubbling for 5 min) and then heated at 70 °C for 18 h under a CO atmosphere. The reaction mixture was cooled, and brine (100 mL) was added. The aqueous phase was extracted with ether (2 × 100 mL). The combined organic phases were washed successively with 5% aqueous HCl, water, and brine and then dried ($MgSO_4$) and evaporated. Purification by flash chromatography using hexane–EtOAc (80:20) as eluant gave methyl ester **10** (1.09 g, 52%): ^{1}H NMR ($CDCl_3$) δ 8.2 (s, 1 H), 7.95 (d, 1 H), 7.7 (d, 1 H), 7.65 (d, 1 H), 7.4 (t, 1 H), 7.3 (d, 1 H), 3.9 (s, 3 H), 3.2 (s, 3 H), 2.7 (m, 1 H), 2.45 (m, 1 H), 0.8 (t, 3 H).

Step 3: 3-[1-methoxy-1-(thiazol-2-yl)propyl]benzyl chloride (**5b**). (a) Diisobutylaluminum hydride (1.5 M in toluene, 2.6 mL, 3.9 mmol) was added to a 0 °C solution of ester **10** (433 mg, 1.49 mmol) in toluene (15 mL). After 1.5 h at 0 °C, water was added and the mixture was brought to pH 1 with 10% aqueous HCl before being extracted with ether. The organic phase was dried ($MgSO_4$) and evaporated to afford 3-[1-methoxy-1-(thiazol-2-yl)propyl]benzyl alcohol (388 mg, 99%) as a colorless gum: ^{1}H NMR ($CDCl_3$) δ 7.7 (d, 1 H), 7.5 (s, 1 H), 7.4–7.2 (m, 4 H), 4.7 (d, 2 H), 3.2 (s, 3 H), 2.7 (m, 1 H), 2.45 (m, 1 H), 1.7 (t, 1 H), 0.8 (t, 3 H). (b) To a solution of the alcohol from step 3a (388 mg, 1.47 mmol) in acetonitrile (10 mL) were added carbon tetrachloride (1 mL) and triphenylphosphine (422 mg, 1.61 mmol). The reaction mixture was stirred at room temperature for 18 h before the volatiles were evaporated. Purification of the residue by flash chromatography using hexane–EtOAc (80:20) as eluant gave benzyl chloride **5b** (300 mg, 72%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 1 H), 7.51 (s, 1 H), 7.43–7.26 (m, 4 H), 4.58 (s, 2 H), 3.23 (s, 3 H), 2.69 (m, 1 H), 2.44 (m, 1 H), 0.78 (t, 3 H).

7-(Bromomethyl)-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (8c). Step 1: 7-(methoxycarbonyl)-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (**11**). The procedure used to prepare ester **10** applied to phenolic lignan lactone **8a** gave ester **11** (71%) as a pale yellow solid: ^{1}H NMR ($CDCl_3$) δ 8.83 (d, 1 H), 8.6 (s, 1 H), 8.16 (dd, 1 H), 7.86 (d, 1 H), 7.6–7.5 (m, 3 H), 7.41–7.37 (m, 2 H), 5.3 (s, 2 H), 4.0 (s, 3 H).

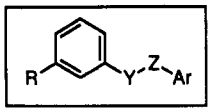
Step 2: 7-(hydroxymethyl)-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (**12**). (a) To a solution of ester **11** (110 mg, 0.35 mmol) in tetrahydrofuran (THF)–water (4:1, 10 mL) was added lithium hydroxide monohydrate (50 mg, 1.2 mmol). After 30 min, the reaction mixture was acidified to pH 2–3 and the aqueous phase was saturated with NaCl. The organic phase was separated, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography using chloroform–methanol (85:15) as eluant to afford 7-(hydroxycarbonyl)-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (94 mg, 90%) as a pale yellow solid: ^{1}H NMR (MeOH-d_4) δ 8.82 (d, 1 H), 8.6 (s, 1 H), 8.15 (dd, 1 H), 7.82 (d, 1 H), 7.65–7.52 (m, 3 H), 7.50–7.45 (m, 2 H), 5.35 (s, 2 H). (b) To a solution of the acid described above (94 mg, 0.31 mmol) in THF (10 mL) at −70 °C were added Et_3N (65 μL, 0.47 mmol) and isopropyl chloroformate (48 μL, 0.37 mmol). After 20 min, sodium borohydride (25 mg, 0.66 mmol) in water (2 mL) was added and the reaction mixture was stirred at room temperature for 30 min. The reaction was then diluted with EtOAc and saturated aqueous NH_4Cl solution. The organic phase was washed with water and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography using chloroform–methanol (99:1–97:3) as eluant to give primary alcohol **12** (76 mg, 85%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.48 (s, 1 H), 8.06 (s, 1 H), 7.82 (d, 1 H), 7.63–7.50 (m, 4 H), 7.40–7.35 (m, 2 H), 5.28 (s, 2 H), 4.92 (d, 2 H), 2.15 (t, 1 H).

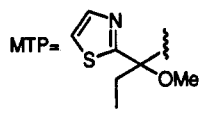
Step 3: 7-(bromomethyl)-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (**8c**). To a solution of alcohol **12** (76 mg, 0.26 mmol) in dichloromethane (10 mL) at 0 °C were added carbon tetrabromide (90 mg, 0.27 mmol), triphenylphosphine (76 mg, 0.29 mmol), and imidazole (20 mg, 0.29 mmol). The reaction mixture was stirred at 0 °C for 30 min. It was then washed with water and brine, dried ($MgSO_4$), and evaporated. Purification of the residue by flash chromatography using hexane–EtOAc (85:15) as eluant gave bromide **8c** (70 mg, 76%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.47 (s, 1 H), 8.15 (d, 1 H), 7.8 (d, 1 H), 7.60–7.48 (m, 4 H), 7.38–7.32 (m, 2 H), 5.25 (s, 2 H), 4.65 (s, 2 H).

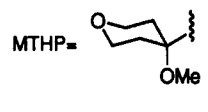
3-(4-Methoxytetrahydro-2*H*-pyran-4-yl)benzyl Bromide (7c). Step 1: 3-(4-hydroxytetrahydro-2*H*-pyran-4-yl)toluene (**13**). To a solution of 3-bromotoluene (24.3 mL, 200 mmol) in THF (250 mL) stirred at −78 °C was added a solution of *n*-butyllithium in hexane (1.75 M, 114 mL, 200 mmol). After 45 min, the resulting white suspension was treated with a solution of tetrahydro-4*H*-pyran-4-one (18.5 mL, 200 mmol) in THF (125 mL). After 45 min at −78 °C, the mixture was stirred for 1.5 h at room temperature. Saturated aqueous ammonium chloride was then added and the organic phase separated. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine and then dried ($MgSO_4$) and evaporated. Purification by flash chromatography using hexane–EtOAc (50:50) as eluant followed by crystallization in hexane–EtOAc gave tertiary alcohol **13** (22.2 g, 58%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.31–7.26 (m, 3 H), 7.11 (m, 1 H), 4.0–3.8 (m, 4 H), 2.38 (s, 3 H), 2.24–2.11 (m, 2 H), 1.68 (d, 2 H), 1.60 (s, 1 H).

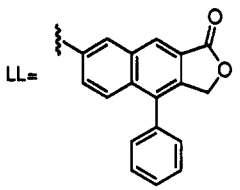
Step 2: 3-(4-methoxytetrahydro-2*H*-pyran-4-yl)toluene (**14**). To a solution of alcohol **13** (38 g, 198 mmol) in DMF (300 mL) were added sodium hydride (60% dispersion in mineral oil, 16 g, 400 mmol) and methyl iodide (31 mL, 500 mmol). The mixture was stirred for 15 h at room temperature before water (1 L) was

Table 4. Physical and Synthetic Data for Compounds 1-4









	R	Y	Z	Ar	formula	anal.[a]	mp (°C)	yield (%)[b]
1a	MTP	O	CH_2	2-naphthyl	$C_{24}H_{23}NO_2S$	C,H,N	89–91[d]	93
1b	MTP	CH_2	O	2-naphthyl	$C_{24}H_{23}NO_2S$	*c*	oil	77
2a	MTHP	O	CH_2	2-naphthyl	$C_{23}H_{24}O_3$	C,H	71.5–73.5[e]	95
2b	MTHP	CH_2	O	2-naphthyl	$C_{23}H_{24}O_3$	C,H	78–9	55
3a	MTP	O	CH_2	LL	$C_{32}H_{27}NO_4S$	C,H,N	159–61	86
3b	MTP	CH_2	O	LL	$C_{32}H_{27}NO_4S$	C,H,N,S	197–8	61
4a	MTHP	O	CH_2	LL	$C_{31}H_{28}O_5$	*c*	165–8	70
4b	MTHP	CH_2	O	LL	$C_{31}H_{28}O_5 \cdot 0.2EtOAc$	C,H	191–2	71

[a] Elemental analyses were within ±0.4% of the calculated value. [b] Isolated yield of the final step. [c] High-resolution mass spectrum was obtained for this compound. [d] Lit.[7] mp = 93.5 °C. [e] Lit.[8] mp = 73 °C.

added. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated. Purification by flash chromatography using hexane–EtOAc (80:20) as eluant gave methyl ether **14** (16.0 g, 53%) as a colorless liquid: ^1H NMR ($CDCl_3$) δ 7.30–7.01 (m, 4 H), 3.91–3.80 (m, 4 H), 2.98 (s, 3 H), 2.38 (s, 3 H), 2.10–1.93 (m, 4 H).

Step 3: 3-(4-methoxytetrahydro-2*H*-pyran-4-yl)benzyl bromide (**7c**). A mixture of ether **14** (16 g, 77.6 mmol), *N*-bromosuccinimide (14.6 g, 82 mmol), and azoisobutyronitrile (127 mg, 0.8 mmol) in carbon tetrachloride (250 mL) was refluxed for 1.5 h. When the reaction mixture was cooled, it was filtered, and evaporation of the filtrate gave the crude benzyl bromide **7c** which was used without further purification: ^1H NMR ($CDCl_3$) δ 7.45–7.2 (m, 4 H), 4.5 (s, 2 H), 3.95–3.8 (m, 4 H), 3.0 (s, 3 H), 2.1–1.9 (m, 4 H).

Preparation of Final Products (1–4). 7-[[3-(4-Methoxytetrahydro-2*H*-pyran-4-yl)phenyl]methoxy]-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (4b). A mixture of 7-hydroxy-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (**8a**)[6] (0.60 g, 2.17 mmol), benzyl bromide **7c** (1.04 g, 3.65 mmol), and potassium carbonate (0.78 g, 5.64 mmol) in DMF (15 mL) was stirred at room temperature for 17 h. Water was then added, and the organic phase was extracted with EtOAc. The combined organic phases were washed with 1 N aqueous NaOH, water, and brine before being dried ($MgSO_4$) and evaporated. Recrystallization of the resulting solid in EtOAc afforded **4b** as a pale yellow solid (0.67 g, 64%): ^1H NMR ($CDCl_3$) δ 8.38 (s, 1 H), 7.74 (d, 1 H, J = 9.3 Hz), 7.60–7.50 (m, 4 H), 7.48–7.30 (m, 7 H), 5.25 (s, 4 H), 3.92–3.84 (m, 4 H), 2.99 (s, 3 H), 2.15–1.95 (m, 4 H).

The following compounds were prepared according to an analogous alkylation procedure. Physical data for final compounds 1–4 are shown in Table 4.

2-[[3-[1-Methoxy-1-(thiazol-2-yl)propyl]phenoxy]methyl]naphthalene (1a):[7] white solid; ^1H NMR ($CDCl_3$) δ 7.87–7.82 (m, 4 H), 7.67 (d, 1 H, J = 3.3 Hz), 7.54–7.47 (m, 3 H), 7.26–7.21 (m, 2 H), 7.16 (m, 1 H), 7.06 (m, 1 H), 6.90 (m, 1 H), 5.20 (s, 2 H), 3.20 (s, 3 H), 2.67 (sext, 1 H), 2.42 (sext, 1 H), 0.77 (t, 3 H).

2-[[3-[1-Methoxy-1-(thiazol-2-yl)propyl]phenyl]methoxy]naphthalene (1b): colorless oil; ^1H NMR ($CDCl_3$) δ 7.80–7.65 (m, 4 H), 7.58 (s, 1 H), 7.45–7.30 (m, 5 H), 7.25–7.15 (m, 3 H), 5.15 (s, 2 H), 3.22 (s, 3 H), 2.72 (sext, 1 H), 2.45 (sext, 1 H), 0.80 (t, 3 H); exact mass $C_{24}H_{23}NO_2S + H^+$ calcd 390.1528, found 390.1529.

2-[[3-(4-Methoxytetrahydro-2*H*-pyran-4-yl)phenoxy]methyl]naphthalene (2a):[8] white solid; ^1H NMR ($CDCl_3$) δ 7.89–7.82 (m, 4 H), 7.55 (dd, 1 H, J_1 = 8.4 Hz, J_2 = 1.7 Hz), 7.49–7.46 (m, 2 H), 7.31–7.24 (m, 1 H), 7.08 (m, 1 H), 7.00–6.93 (m, 2 H), 5.23 (s, 2 H), 3.90–3.70 (m, 4 H), 2.95 (s, 3 H), 2.1–1.9 (m, 4 H).

2-[[3-(4-Methoxytetrahydro-2*H*-pyran-4-yl)phenyl]methoxy]naphthalene (2b): white solid; ^1H NMR ($CDCl_3$) δ 7.77–7.70 (m, 3 H), 7.52 (s, 1 H), 7.43–7.33 (m, 5 H), 7.26–7.22 (m, 2 H), 5.20 (s, 2 H), 3.90–3.80 (m, 4 H), 2.98 (s, 3 H), 2.1–1.9 (m, 4 H).

7-[[3-[1-Methoxy-1-(thiazol-2-yl)propyl]phenoxy]methyl]-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (3a): white solid; ^1H NMR ($CDCl_3$) δ 8.50 (s, 1 H), 8.11 (s, 1 H), 7.82 (d, 1 H, J = 8.8 Hz), 7.68 (d, 1 H, J = 3.3 Hz), 7.64–7.50 (m, 4 H), 7.38 (m, 2 H), 7.28–7.22 (m, 2 H), 7.17 (s, 1 H), 7.08 (d, 1 H, J = 8.0 Hz), 6.88 (m, 1 H), 5.27 (s, 2 H), 5.23 (s, 2 H), 3.21 (s, 3 H), 2.67 (sext, 1 H), 2.43 (sext, 1 H), 0.77 (t, 3 H).

7-[[3-[1-Methoxy-1-(thiazol-2-yl)propyl]phenyl]methoxy]-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (3b): white solid; ^1H NMR ($CDCl_3$) δ 8.35 (s, 1 H), 7.80–7.25 (m, 14 H), 5.25 (s, 2 H), 5.20 (s, 2 H), 3.25 (s, 3 H), 2.65 (sext, 1 H), 2.45 (sext, 1 H), 0.80 (t, 3 H).

7-[[3-(4-Methoxytetrahydro-2*H*-pyran-4-yl)phenoxy]methyl]-4-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (4a): white solid; ^1H NMR ($CDCl_3$) δ 8.50 (s, 1 H), 8.15 (s, 1 H), 7.85 (d, 1 H), 7.65 (dd, 1 H), 7.60–7.50 (m, 3 H), 7.39 (m, 2 H), 7.30 (t, 1 H), 7.08 (dd, 1 H), 7.00 (d, 1 H), 6.80 (dd, 1 H), 5.28 (s, 4 H), 3.89–3.82 (m, 4 H), 2.97 (s, 3 H), 2.06–1.92 (m, 4 H); exact mass $C_{31}H_{28}O_5 + H^+$ calcd 481.2015, found 481.2015.

Preparation of Sodium Carboxylate 15. A mixture of lactone **4b** (498 mg, 1.04 mmol) and sodium hydroxide (43.4 mg, 1.08 mmol) was refluxed in water (1 mL) and ethanol (15 mL) for 21 h. Evaporation of the resulting solution afforded a residue which was dissolved in water (3 mL). Lyophilization yielded the desired carboxylate **15** as a yellow solid (530 mg, 98%): ^1H NMR (DMSO-d_6) δ 8.07 (s, 1 H), 7.82 (t, 1 H, J = 6.6 Hz), 7.55–7.35 (m, 8 H), 7.24 (m, 2 H), 7.14–7.05 (m, 2 H), 5.23 (s, 2 H), 4.18 (d, 2 H, J = 6.5 Hz), 3.71–3.67 (m, 4 H), 2.86 (s, 3 H), 1.94–1.89 (m, 4 H); exact mass $C_{31}H_{29}O_6Na_2$ ($M + Na^+$) calcd 543.1760, found 543.1758.

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