The network gave minor errors such as classifying **34**, **35**, and **38** into, respectively, rank 3, 2, and 4 instead of the observed ranks 2, 3, and 3. It may be generally said that output patterns with one of the elements being close to 1 and other elements being close to 0 steadily give reliable results. The rate of correct grading was 26/29 (= 0.90), which is far better than those of ALS method (0.62–0.76).

We again tried the prediction ability of the network: eight arbitrary data points were removed from the original data to make the weight matrix, then the removed data were fed to the network to get the results. Good convergence was not obtained: the maximum squared difference was 0.723 at the 1381st iteration. The results are shown in Table V. The rate of correct classification was 19/21 (=0.90) and that of correct prediction was 6/8 (=0.75).

Thus we found that the neural network makes best use of the information included in the given data, resulting in an excellent grading compared to other conventional methods. Moreover, the prediction ability in addition to the easy operation indicated that the neural network will be a valuable tool in developing new drugs.

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Articles

Antioxidant-Based Inhibitors of Leukotriene Biosynthesis. The Discovery of 6-[1-[2-(Hydroxymethyl)phenyl]-1-propen-3-yl]-2,3-dihydro-5-benzofuranol, a Potent Topical Antiinflammatory Agent

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The leukotrienes, metabolites of arachidonic acid produced through the action of the enzyme 5-lipoxygenase, are important mediators of immediate hypersensitivity and inflammation. Among the variety of diseases in which the leukotrienes may play a symptomatic or causative role is the dermatological condition psoriasis, a chronic proliferative disease of the skin. This study reports the synthesis and comparative biological activities of various ortho-substituted phenols including 4-methoxyphenols, 6-hydroxy-1,2,3,4-tetrahydrobenzopyrans, 2,3-dihydro-5-benzofuranols, and 5-benzofuranols. The phenols prepared in this study were evaluated for their ability to inhibit the production of leukotriene B_4(LTB_4) in isolated human polymorphonuclear leukocytes (PMNs) and to inhibit a topical inflammatory response in the topical mouse ear (TME) model. In the former case, when the log IC_{50} was plotted versus the log of the octanol/water partition coefficient (log P), to eliminate the effect of lipophilicity, the 2,3-dihydro-5-benzofuranol ring system was shown to be more potent than the other ring systems examined throughout the range of partition coefficients studied. The ability to inhibit leukotriene production in vitro in human PMNs can be rationalized on the basis of a model that suggests that the observed inhibition is dependent on the kinetic ability of the inhibitor to reduce a radical species and on the fraction of inhibitor that is partitioned into the cell membrane. While the in vivo antiinflammatory activity as measured by the TME did not correlate with the in vitro data, it was felt that the TME represented a valuable measure of the ability of a compound to penetrate the skin to the site of an ongoing inflammatory response. Of the compounds synthesized in this study, 6-[1-[2-(hydroxymethyl)phenyl]-1-propen-3-yl]-2,3-dihydro-5-benzofuranol (1, L-651896) was chosen for further development.

The leukotrienes, metabolites of arachidonic acid produced through the action of the enzyme 5-lipoxygenase, are important mediators of immediate hypersensitivity and inflammation.[1] In particular leukotriene C_4 (LTC_4) and LTD_4 cause a prolonged constriction of bronchial smooth muscle and have been identified as the slow-reacting substances of anaphylaxis (SRSAs).[2] Leukotriene B_4 is a potent chemotactic agent for polymorphonuclear leukocytes (PMNs), which are also a rich source of LTB_4.[3]

Among the variety of diseases in which the leukotrienes may play a symptomatic or causative role is the dermatological condition psoriasis. Psoriasis is a chronic proliferative disease of the skin whose lesions are characterized by the accumulation of PMNs.[4] Leukotriene B_4, along with other metabolites of arachidonic acid, has been found in elevated concentration in the involved skin of psoriatic patients.[5] It therefore seemed reasonable to hypothesize that a potent topical inhibitor of leukotriene biosynthesis

(1) For recent reviews on the leukotrienes, see: (a) Taylor, G. W.; Clarke, S. R. *Trends Pharmacol. Sci.* **1986**, *7*, 100. (b) Sirois, P. *Adv. Lipid Res.* **1985**, *21*, 79.
(2) Dahlen, S.; Hedqvist, P.; Hammarstrom, S.; Samuelsson, B. *Nature (London)* **1980**, *288*, 484.
(3) Ford-Hutchinson, A. W. *J. R. Soc. Med.* **1981**, *74*, 831.
(4) Anderson, T. F. *Med. Clin. North Am.* **1982**, *66*, 769. For a discussion of current approaches in the development of therapeutic agents for the treatment of psoriasis, see: Venuti, M. C. *Annu. Rev. Med. Chem.* **1987**, *22*, 201.
(5) Camp, R. D. R.; Mallet, A. I.; Woolard, P. M.; Brain, S. D.; Kobza-Black, A.; Greaves, M. W. *Prostaglandins* **1983**, *26*, 432.

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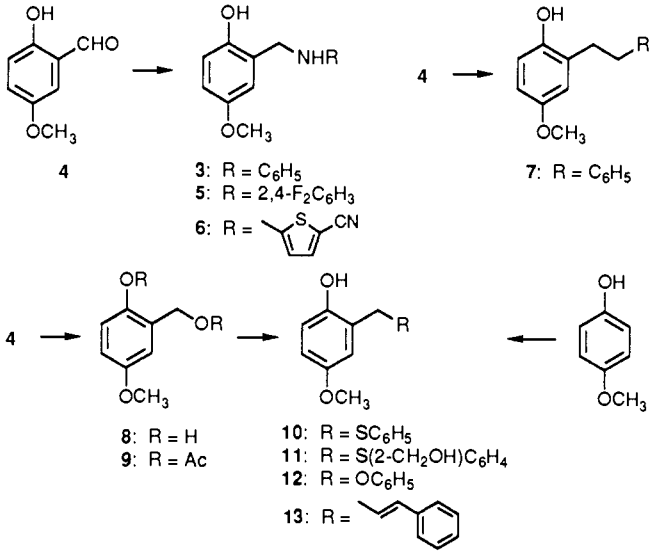
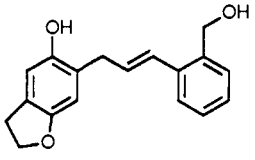
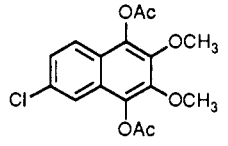
Scheme I



would be therapeutically useful in the treatment of psoriasis. Certain clinical observations support this view. It has been reported that the use of the cyclooxygenase inhibitor indomethacin in psoriatic patients leads to an exacerbation of the disease.[6] While the reason for this is unclear, one potential explanation is the shunting of the available arachidonic acid through the 5-lipoxygenase pathway to the leukotrienes. More direct clinical evidence comes from the demonstrated clinical efficacy of benzoxaprofen in psoriasis.[7] While benoxaprofen undoubtedly has effects on prostaglandin biosynthesis, it has been reported to be an inhibitor of leukotriene biosynthesis as well.[8] Finally, the acylated hydroquinone lonapalene (**2**) has been reported to inhibit leukotriene biosynthesis and has been demonstrated to be as effective as steroid therapy in the clinical treatment of psoriasis.[9]



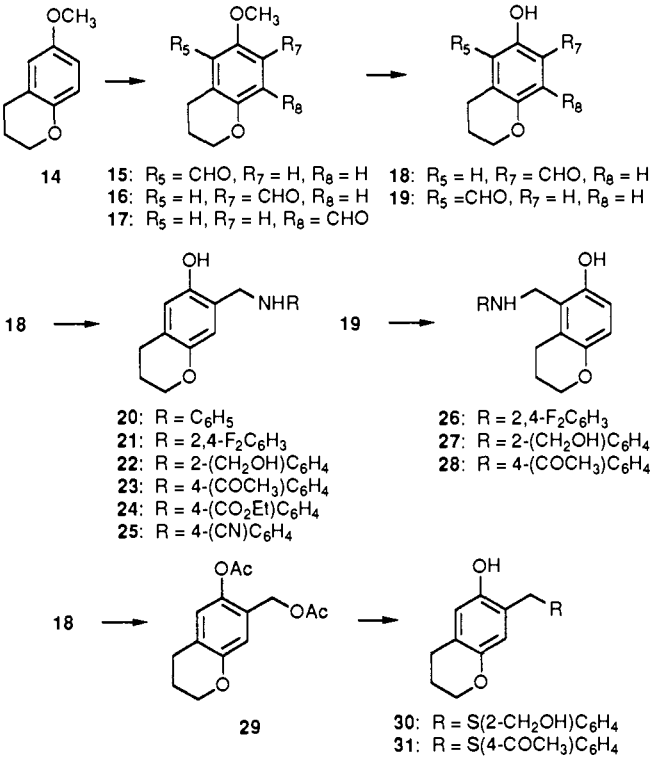
1



2

We have recently reported a series of 2,3-dihydro-5-benzofuranols that are potent antioxidant-based inhibitors of leukotriene biosynthesis in human PMNs.[10] In particular we pointed out that within this series the ability to inhibit leukotriene biosynthesis is directly correlated with the overall lipophilicity of the molecule. We now report our earlier studies in this area in which several closely related ring systems were compared and the 2,3-dihydro-5-benzofuranol ring system selected for further examination. These studies resulted in the discovery of a potent topical antiinflammatory agent, 6-[1-[2-(hydroxymethyl)phenyl]-1-propen-3-yl]-2,3-dihydro-5-benzofuranol (**1**, L-651896), as a potential candidate for the treatment of psoriasis.

Scheme II



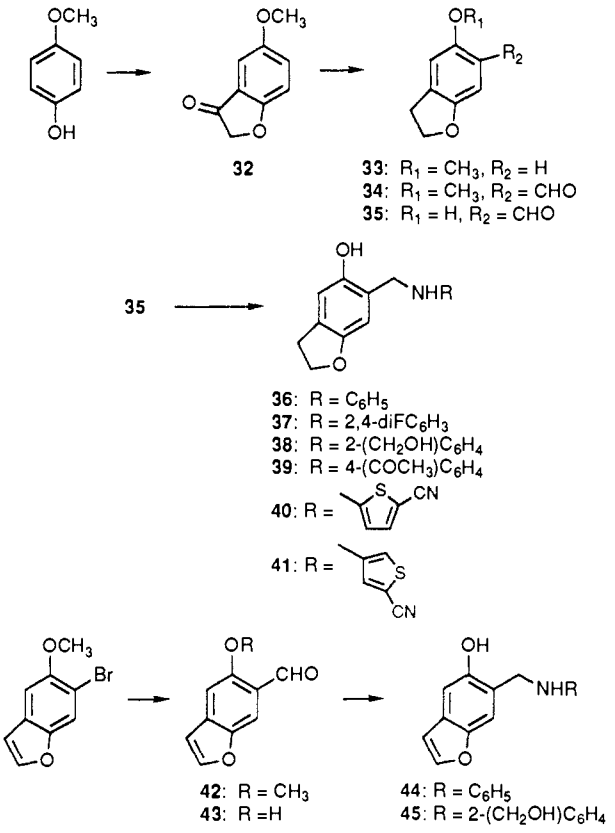
Chemistry

As part of an ongoing effort to discover novel antiinflammatory agents we identified **3** as a lead structure on the basis of its ability to inhibit the metabolism of arachidonic acid in vitro. As shown in Scheme I, **3** is easily prepared by condensing the commercially available aldehyde **4** with aniline and reducing the resultant Schiff's base by catalytic hydrogenation or reduction with sodium borohydride. In a similar fashion **5** and **6** were prepared from the corresponding amines. Direct Wittig reaction of **4** with benzyltriphenylphosphonium chloride afforded after catalytic reduction the phenethyl compound **7** in good yield. Replacement of the amine linkage present in **3** with a thioether or ether linkage was readily accomplished by reduction of **4** with sodium borohydride followed by acylation to give the diacetate **9**. Displacement of the benzylic acetate of **9** with thiophenoxides gave the thioethers **10** and **11** in fair to excellent yields. However, the more basic and less nucleophilic potassium phenoxide gave only a low yield of **12**. Replacement of the amine in **3** with an ethenyl linkage was accomplished by direct C-alkylation of the sodium salt of 4-methoxyphenol with cinnamyl bromide in refluxing benzene.[11] Although the yield of this reaction was disappointing, it allowed the direct preparation of **13** in a single step.

The synthesis of a short series of 6-hydroxytetrahydrobenzopyrans is detailed in Scheme II. Formylation of the known methoxy compound **14**[12] ($TiCl_4$, dichloromethyl methyl ether) gave approximately equal amounts of the three possible aldehydes **15**, **16**, and **17**. These isomers

(6) Voorhees, J. J. *Arch. Dermatol.* **1982**, *118*, 869.
(7) Kragballe, K.; Herlin, T. *Arch. Dermatol.* **1983**, *119*, 548.
(8) Dawson, W.; Boot, J. R.; Harvey, J. *Eur. J. Rheumatol. Inflammation* **1982**, *5*, 206.
(9) Lassus, A.; Forsstrom, S. *Br. J. Dermatol.* **1985**, *113*, 103. For references to **2** and derivatives, see: (a) Jones, G. H.; Venuti, M. C.; Young, J. M.; Krishna Murthy, D. V.; Loe, B. E.; Simpson, R. A.; Berks, A. H.; Spires, D. A.; Maloney, P. J.; Kruseman, M.; Rouhafza, S.; Kappas, K. C.; Beard, C. C.; Unger, S. H.; Cheung, P. S. *J. Med. Chem.* **1986**, *29*, 1504. (b) Venuti, M. C.; Loe, B. E.; Jones, G. H.; Young, J. M. *J. Med. Chem.* **1988**, *31*, 2132.
(10) Hammond, M. L.; Kopka, I. E.; Zambias, R. A.; Caldwell, C. G.; Boger, J.; Baker, F.; Bach, T.; Luell, S.; MacIntyre, D. E. *J. Med. Chem.* **1989**, *32*, 1006.
(11) Tarbell, D. S. *Org. React. (N.Y)* **1944**, *2*, 2.
(12) Bradsher, K.; Reames, D. C. *J. Org. Chem.* **1981**, *46*, 1384.

Scheme III

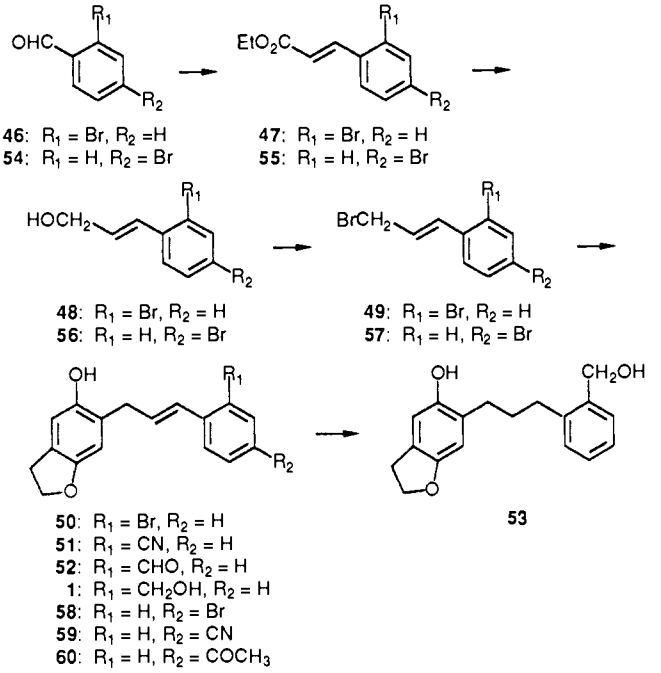


were readily separable chromatographically. Deprotection of the 7- and 5-carboxaldehydes **16** and **15** with boron tribromide in methylene chloride gave the hydroxy aldehydes **18** and **19**, respectively. The regiochemistry of the ether cleavage is apparently directed by complexation of the Lewis acid to the aldehyde since attempted deprotection of **17** under identical conditions led only to ring cleavage. With the required hydroxy aldehydes in hand it was a simple matter to condense these materials with a variety of aromatic amines and reduce the resulting Schiff's bases with sodium borohydride to afford the (N-arylamino)methyl derivatives **20–28**. In addition **18** was reduced and acylated to give the diacetate **29**, which could be reacted with the appropriate thiophenoxides to give the thioethers **30** and **31**.

As shown in Scheme III a similar strategy to that employed with the tetrahydrobenzopyrans was used to prepare the corresponding dihydrobenzofurans. Acylation of 4-methoxyphenol with chloroacetonitrile using the modified Houben–Hoesch conditions of Toyoda[13] (BCl_3 and $AlCl_3$ in CH_2Cl_2) followed by direct cyclization (NaOAc in MeOH, reflux, 90 min) gave the benzofuranone **32** in 31% yield after recrystallization. Catalytic hydrogenation then gave the required methoxy compound **33**. Formylation as described above for **14** gave primarily the 6-carboxaldehyde **34**, which, after chromatographic purification, was directly deprotected to the required hydroxy aldehyde **35**. Treatment with the appropriate arylamines followed by reduction in the usual way gave the (*N*-arylamino)methyl derivatives **36–41**.

Since direct electrophilic formylation of 2-carbomethoxy-5-methoxybenzofuran proceeds exclusively at the 4-position,[14] the desired 6-carboxaldehyde **42** was prepared

Scheme IV



via transmetalation of the known 6-bromo-5-methoxybenzofuran[15] with *n*-butyllithium and quenching the resulting anion with dimethylformamide. Deprotection as described above gave the hydroxy aldehyde **43**, which was then converted to the aminomethyl derivatives **44** and **45**.

The preparation of further dihydrobenzofuranol derivatives including **1** is described in Scheme IV. The aldehyde **46** was converted to the trans propenoate **47** by using well-established Wittig methodology. Reduction of **47** with diisobutylaluminum hydride is uneventful; however, on larger scales care must be exercised to dissipate the heat generated when quenching this reaction. In this way the carbinol **48** can be isolated in nearly quantitative yields and directly converted to the bromide **49** with phosphorus tribromide. Direct C-alkylation of 2,3-dihydro-5-benzofuranol[16] under heterogeneous conditions with **49** gave **50**, which could be isolated from the crude product by trituration. The bromide **50** was then treated with cuprous cyanide to give the nitrile **51**, which could be reduced to the aldehyde **52** with diisobutylaluminum hydride. A final reduction with sodium borohydride gave **1** in 17% overall yield from the aldehyde **46**. Careful hydrogenation of **1** over platinum oxide gave the dihydro compound **53**. In a manner entirely analogous to that described above, 4-bromobenzaldehyde (**54**) was converted to the nitrile **59**. After protection as the methoxy methyl ether, **59** was converted to the methyl ketone by treatment with methylmagnesium bromide followed by hydrolysis to **60**.

Results

The phenols prepared in this study was evaluated for their ability to inhibit the production of LTB_4 in isolated

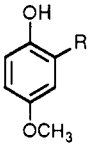
(13) Toyoda, T.; Sasakura, S.; Sugasawa, T. *J. Org. Chem.* **1981**, *46*, 189.

(14) Rene, L.; Buisson, J.; Royer, R. *Bull. Soc. Chim. Fr.* **1975**, 2763.

(15) Clavel, J. M.; Guillaumel, J.; Demerseman, P.; Royer, R. *J. Heterocycl. Chem.* **1977**, *14*, 219.

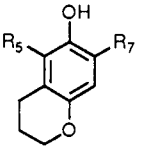
(16) (a) Selander, H.; Nilsson, J. L. G. *Acta Chem. Scand.* **1972**, *26*, 2433. (b) Pearlman, W. M. *Tetrahedron Lett.* **1967**, *17*, 1663. (c) Alabaster, R. J.; Cottrell, I. F.; Marley, H.; Wright, S. H. B. *Synthesis* **1988**, 950. (d) Alternatively 2,3-dihydro-5-benzofuranol can be prepared by catalytic hydrogenation of 5-hydroxybenzofuran. For the preparation of 5-hydroxybenzofuran, see: Rene, L.; Royer, R. *Bull. Soc. Chim. Fr.* **1973**, 2355.

Table I. Inhibition of LTB_4 Biosynthesis in Human PMNs by 2-Substituted 4-Methoxyphenols



compd	R	IC_{50}, nM	log *P* calcd	formula	mp, °C	anal.
3	$CH_2NHC_6H_5$	4700	2.8	$C_{14}H_{15}NO_2$	82–83	C, H, N
5	$CH_2NH(2,4\text{-diF}C_6H_3)$	1300	3.5	$C_{14}H_{13}NF_2NO_2\cdot HCl$	200	C, H, N
6	$CH_2NH(2\text{-CN-5-thienyl})$	2600	2.7	$C_{13}H_{12}N_2O_2S\cdot 0.33H_2O$	86–89	C, H, N, S
7	$CH_2CH_2C_6H_5$	120	4.3	$C_{15}H_{16}O_2\cdot 0.125H_2O$	oil	C, H
10	$CH_2SC_6H_5$	590	3.9	$C_{14}H_{14}O_2S$	oil	C, H
11	$CH_2S(2\text{-}CH_2OHC_6H_4)$	8700	2.9	$C_{15}H_{16}O_3S$	83–85	C, H, S
12	$CH_2OC_6H_5$	1400	3.3	$C_{14}H_{14}O_3\cdot 0.25H_2O$	oil	C, H
13	$CH_2CHCHC_6H_5$	250	4.4	$C_{16}H_{16}O_2$	84–86	C, H

Table II. Inhibition of LTB_4 Biosynthesis in Human PMNs by 5- or 7-Substituted 1,2,3,4-Tetrahydro-6-hydroxybenzopyrans



compd	R_5	R_7	IC_{50}, nM	log *P* calcd	formula	mp, °C	anal.
20	H	$CH_2NHC_6H_5$	1700	3.5	$C_{16}H_{17}NO_2$	135–137	C, H, N
21	H	$CH_2NH(2,4\text{-}F_2C_6H_3)$	1300	4.2	$C_{16}H_{15}F_2NO_2$	103–105	C, H, N
22	H	$CH_2NH(2\text{-}CH_2OHC_6H_4)$	21000	2.4	$C_{17}H_{19}NO_3\cdot 0.125H_2O$	141–142	C, H, N
23	H	$CH_2NH(4\text{-}COCH_3C_6H_4)$	4100	3.5	$C_{18}H_{19}NO_3$	177–179	C, H, N
24	H	$CH_2NH(4\text{-}CO_2EtC_6H_4)$	600	4.6	$C_{19}H_{21}NO_4$	150–151	C, H, N
25	H	$CH_2NH(4\text{-}CNC_6H_4)$	1600	3.6	$C_{17}H_{16}N_2O_2\cdot 0.125H_2O$	163–165	C, H, N
26	$CH_2NH(2,4\text{-}F_2C_6H_3)$	H	1400	4.2	$C_{16}H_{15}F_2NO_2$	120–121	C, H, N
27	$CH_2NH(2\text{-}CH_2OHC_6H_4)$	H	17000	2.4	$C_{17}H_{19}NO_3$	151–153	C, H, N
28	$CH_2NH(4\text{-}COCH_3C_6H_4)$	H	11000	3.5	$C_{18}H_{19}NO_3\cdot 0.25H_2O$	213–215	C, H, N
30	H	$CH_2S(2\text{-}CH_2OHC_6H_4)$	1400	3.6	$C_{17}H_{18}O_3S\cdot 0.25H_2O$	140–141	C, H, S
31	H	$CH_2S(4\text{-}COCH_3C_6H_4)$	440	4.2	$C_{18}H_{18}O_3S$	192–193	C, H, S

human polymorphonuclear leukocytes as previously described.[10] Leukotriene biosynthesis was initiated with calcium ionophore A23187 and the amount of LTB_4 produced was measured by radioimmunoassay. The logarithm of the octanol/water partition coefficients (log *P*) were estimated by calculation using commercially available software.[17] As shown in Table I we initially examined simple analogues of **3** in which the aniline nitrogen was replaced by carbon (**7**), sulfur (**10**), oxygen (**12**), and ethenyl (**13**) linkages. From inspection it became clear that increases in activity were obtained by increasing the overall lipophilicity of the molecule. A more potent compound was also obtained when lipophilic substitutions were made on the aniline ring as in the 2,4-difluoro analogue **5**. When the log IC_{50} was plotted versus log *P*,[18] as shown in Figure 1, a linear relationship consistent with what we have earlier reported for an extensive series of 2,3-dihydro-5-benzofuranols was obtained.[10]

With a rudimentary understanding of the side chain structure–activity relationships, we turned our attention to modifications of the phenolic ring in an effort to find increases in in vitro potency unrelated to lipophilicity. Among our first thoughts was to incorporate the methoxy group into a fused ring system, and therefore we prepared a series of 5- or 7-substituted tetrahydro-6-hydroxybenzopyrans. The ability of these compounds to inhibit leukotriene synthesis in vitro is shown in Table II. A comparison of the unsubstituted compound **20** with the initial lead compound **3** results in the conclusion that a 2–3-fold increase in in vitro potency is obtained by incorporating the fused 6-membered ring into the molecule. However comparison of the 2,4-difluoro analogues **5** and

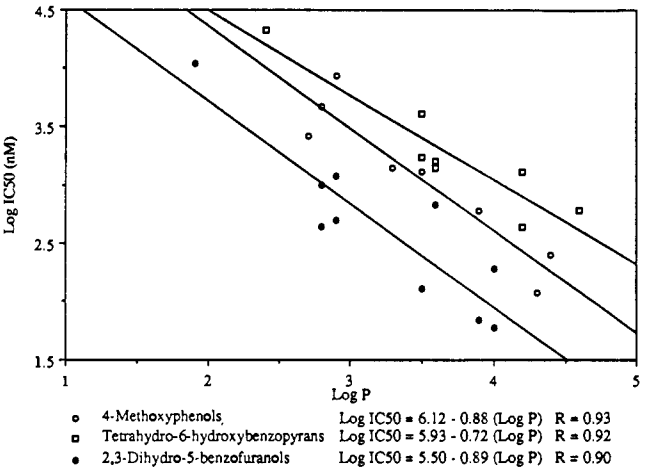
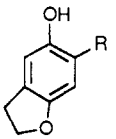


Figure 1. The linear dependence of the log of the IC_{50} (nM) for leukotriene biosynthesis inhibition on the calculated log of the octanol/water partition coefficient (log *P*). The data shown is contained in Tables I–III. For comparison purposes only the 7-substituted tetrahydro-6-hydroxybenzopyrans have been plotted.

(17) Hansch, C.; Leo, A. CLOGP3 Release 3.33. Medicinal Chemistry Project, Claremont, CA, 1985.
(18) (a) Hansch, C.; Dunn, W. J. *J. Pharm. Sci.* **1972**, *61*, 1. (b) Hansch, C.; Clayton, J. M. *J. Pharm. Sci.* **1973**, *62*, 1.

Table III. Inhibition of LTB_4 Biosynthesis in Human PMNs by 6-Substituted 2,3-Dihydro-5-benzofuranols



compd	R	IC_{50}, nM	log P calcd	formula	mp, °C	anal.
		2,3-Dihydro-5-benzofuranols				
1	(E)-$CH_2CHCH(2\text{-}CH_2OHC_6H_4)$	130	3.5	$C_{18}H_{18}O_3$	118–119	C, H
36	$CH_2NHC_6H_5$	490	2.9	$C_{15}H_{15}NO_2 \cdot 0.125H_2O$	130–131	C, H, N
37	$CH_2NH(2,4\text{-}F_2C_6H_3)$	660	3.6	$C_{15}H_{13}F_2NO_2$	119–121	C, H, N
38	$CH_2NH(2\text{-}CH_2OHC_6H_4)$	11000	1.9	$C_{16}H_{17}NO_3$	149–150	C, H, N
39	$CH_2NH(4\text{-}COCH_3C_6H_4)$	1200	2.9	$C_{17}H_{17}NO_3$	180–181	C, H, N
40	CH_2NH(5-CN-2-thienyl)	990	2.8	$C_{14}H_{12}N_2O_2S$	138–139	C, H, N
41	CH_2NH(5-CN-3-thienyl)	440	2.8	$C_{14}H_{12}N_2O_2S$	158–160	C, H, N[a]
52	(E)-$CH_2CHCH(2\text{-}CHOC_6H_4)$	70	3.9	$C_{18}H_{16}O_3 \cdot 0.125H_2O$	117–118	C, H
53	$CH_2CH_2CH_2(2\text{-}CH_2OHC_6H_4)$	190[b]	4.0	$C_{18}H_{20}O_3$	110–111	C, H
60	(E)-$CH_2CHCH(4\text{-}COCH_3C_6H_4)$	60[c]	4.0	$C_{19}H_{18}O_3$	152–153	C, H
		5-Benzofuranols				
44	$CH_2NHC_6H_5$	11000	3.3	$C_{15}H_{13}NO_2 \cdot 0.25H_2O$	116–117	C, H, N
45	$CH_2NH(2\text{-}CH_2OHC_6H_3)$	42000	2.2	$C_{16}H_{15}NO_3$	118–120	C, H, N

[a] N: calcd, 10.29; found, 11.08. [b] SE = 143 nM for two titrations. [c] IC_{50} based on a single titration.

21 suggests little change in activity. When the in vitro activities of the tetrahydro-6-hydroxybenzopyrans are compared graphically with the 4-methoxyphenols as shown in Figure 1, little difference is seen between the two series. This analysis points out that any differences in activity are best attributed to a systematic difference in lipophilicity between 4-methoxyphenol and the tetrahydro-6-hydroxybenzopyran ring system.

As shown in Table III the 2,3-dihydro-5-benzofuranols were more potent than either the corresponding 4-methoxyphenols or the tetrahydro-6-hydroxybenzopyrans. For example, the 2,3-dihydrobenzofuranol **36** is nearly 7-fold more potent than the initial lead **3** and 3 times as potent as the more lipophilic 6-membered ring analogue **20**. The relatively isosteric and somewhat more lipophilic 5-benzofuranol **44** is over 1 order of magnitude less potent than **36**. Although less striking, a similar effect is seen by comparing the 2,4-difluorophenyl analogues **5**, **21**, and **37**. When plotted to eliminate the effect of lipophilicity, Figure 1 shows that the 2,3-dihydro-5-benzofuranols have increased potency throughout the range of partition coefficients examined. For this reason we focussed our attention on preparing more potent analogues containing the 2,3-dihydrobenzofuranol ring system. The 2-propenyl analogues **1** and **60** resulted in, as expected, a 15–20-fold increase in activity over the corresponding (aminomethyl)-2,3-dihydro-5-benzofuranols **38** and **39**, respectively. Reduction of **1** to the propyl analogue **53** resulted in no further increase in activity.

As a measure of in vivo topical antiinflammatory activity the compounds prepared in this study were evaluated in the topical mouse ear (TME) model.[19] In this assay test compounds were coadministered with the irritant phorbol myristate acetate (PMA) and the ability of the test compounds to inhibit the resulting edema was determined. In general compounds were routinely tested at a single dose of 300 μg/site, and those showing promising inhibition were titrated to obtain the ED_{50} values shown in Table IV. Many of the compounds prepared in this study were potent topical antiinflammatory agents as compared with indomethacin, a known inhibitor of PMA induced edema.[19]

(19) Carlson, R. P.; O'Neill-Davis, L.; Chang, J.; Lewis, A. J. *Agents Actions* **1985**, *17*, 197.

Table IV. Topical Antiinflammatory Activity of Ortho-Substituted Phenols in the Topical Mouse Ear Assay (TME)

compd	ED_{50} (μmol/site) + SE
1	0.74 + 0.11 (n = 3)
3	0.61[a]
11	0.87 + 0.50 (n = 4)
13	1.08[a]
20	0.67[a]
22	0.49 + 0.12 (n = 4)
23	0.35 + 0.06 (n = 2)
25	1.61 + 1.21 (n = 2)
27	0.60 + 0.42 (n = 4)
39	0.35 + 0.17 (n = 3)
44	0.97[a]
45	0.44 + 0.30 (n = 2)
60	0.54[a]
indomethacin	0.64 + 0.24 (n = 3)

[a] ED_{50} based on a single four-point titration.

However the antiinflammatory activity did not correlate with the ability of these compounds to inhibit leukotriene biosynthesis. For example, the 5-benzofuranol **45**, while practically inactive as a leukotriene biosynthesis inhibitor, was a potent antiinflammatory agent. Nevertheless we felt the TME represented a valuable measure of the ability of a compound to penetrate the skin to the site of an ongoing inflammatory response. We therefore chose to pursue compounds that demonstrated potent inhibition of leukotriene biosynthesis in vitro and topical antiinflammatory activity. On this basis **1** and **60** seemed to be viable candidates, and of these two **1** was selected for further development.

Discussion

In our previous paper we pointed out that the ability of a series of 2,3-dihydro-5-benzofuranols to inhibit leukotriene biosynthesis in vitro is directly related to the overall lipophilicity of the molecule.[10] We suggested that this effect might arise from a partitioning of the inhibitor between free solution and the cell membrane. In this study we show that two other closely related ring systems, the 4-methoxyphenols and the tetrahydro-6-hydroxybenzopyrans also show a linear relationship between log IC_{50} and the calculated log P. While this is hardly surprising, it is interesting to note that the 2,3-dihydro-5-benzofuranol ring

system routinely results in more potent inhibition than either of the other two ring systems or for that matter the 5-benzofuranols. We have previously suggested that such an effect might be due to intrinsic differences in the ability of various antioxidants to intercept an oxidized species along the 5-lipoxygenase reaction pathway.[10] Subsequent to the completion of this work, Ingold et al. have described the preparation of an extensive series of antioxidants and noted that the 2,3-dihydro-5-benzofuranol ring system maximizes the stereoelectronic effects necessary for efficient hydrogen atom abstraction by peroxyl radicals.[20] Thus it would seem that in addition to lipophilicity, the kinetic ability to intercept a free radical may be important in maximizing the in vitro potencies of antioxidant-based inhibitors of leukotriene biosynthesis.

In summary, we have described our initial efforts at maximizing the in vitro and in vivo activities of a series of ortho-substituted phenols. The ability to inhibit leukotriene production in vitro in human PMNs can be rationalized on the basis of a model that suggests that the observed inhibition is dependent on the intrinsic ability of the antioxidant to reduce an activated enzyme species and on the fraction of inhibitor that is partitioned into the cell membrane. Antiinflammatory activity in vivo was assessed by using the TME and we were successful in identifying 1 as a compound that was equipotent with indomethacin, a potent cyclooxygenase inhibitor, as an antiinflammatory agent while maintaining the ability to be a potent inhibitor of leukotriene biosynthesis. It should be noted that 1 is only a weakly active cyclooxygenase inhibitor.[21] Subsequent to this work it was shown that 1 is an effective inhibitor of leukotriene biosynthesis in vivo and a detailed account of its biochemical and pharmacological properties has appeared.[21]

Experimental Section

General. All reagents and solvents were analytical reagent grade and were used without further purification unless otherwise noted. Routine ^{1}H nuclear magnetic resonance (NMR) spectra were obtained on a Varian T 60, EM 390, or XL 200 instruments as solutions in deuteriochloroform with tetramethylsilane (TMS, δ 0.00) as internal standard. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed at the Merck analytical laboratory. Flash chromatography was performed essentially as described in the literature[22] using Kieselgel 60 (EM Science, 230–400 mesh) as stationary phase. Preparative HPLC refers to separations performed on a Waters PrepLC 500A instrument using Waters PrepPAK-500/SILICA cartridges as stationary phase. Analytical thin-layer chromatography (TLC) was performed using silica gel GHLF plates of 0.25-mm thickness obtained from Analtech Inc.

***N*-Phenyl-2-(aminomethyl)-4-methoxyphenol (3).** A solution of 4 (50.00 g, 328 mmol) and aniline (40.00 g, 430 mmol) in methanol (600 mL) was allowed to stir at room temperature for 2 h. To the resulting bright red solution was added 10% palladium on carbon (3.00 g) and the mixture hydrogenated at 3 atm pressure for 15 min. The catalyst was removed by filtration through a pad of Celite and the filtrate concentrated. Two recrystallizations from ether/hexane afforded 3 (67.00 g, 89%): ^{1}H NMR δ 7.30–6.60 (m, 8 H), 4.27 (s, 2 H), 3.70 (s, 3 H).

***N*-(2,4-Difluorophenyl)-2-(aminomethyl)-4-methoxyphenol (5).** As described above for 3, 4 (1.53 g, 10.0 mmol) was treated with 2,4-difluoroaniline (1.33 g, 10.0 mmol) and then hydrogenated and finally converted to the hydrochloride salt by treatment with a slow stream of HCl gas to afford 5 (1.41 g, 47%) as a white crystalline solid: ^{1}H NMR δ 6.94–6.70 (m, 6 H), 4.38 (s, 2 H), 3.76 (s, 3 H).

2-Cyano-4(5)-nitrothiophene. To a 10 °C solution of fuming nitric acid (90%, 30 mL) in glacial acetic acid (150 mL) was added dropwise over 45 min a solution of 2-cyanothiophene (11.20 g, 103 mmol) in acetic anhydride (25 mL). During the exothermic addition the reaction temperature was maintained below 25 °C and then allowed to stir at ambient temperature for 16 h. The reaction was worked up by pouring into ice water (300 mL) and extracting with ether (700 mL). The organic layer was dried ($MgSO_4$) and concentrated. Recrystallization from ether/hexane afforded a yellow solid which was a 3:1 mixture of 2-cyano-4-nitrothiophene and 2-cyano-5-nitrothiophene.

***N*-(5-Cyanothien-2-yl)-2-(aminomethyl)-4-methoxyphenol (6).** A stock solution of a mixture of 2-cyano-4-aminothiophene and 2-cyano-5-aminothiophene was prepared by catalytic hydrogenation at 3 atm of the mixture of 2-cyano-4-nitrothiophene and 2-cyano-5-nitrothiophene (4.95 g, 32.0 mmol) described above in ethyl acetate (100 mL) using 10% palladium on carbon (5.0 g) as catalyst. After the theoretical amount of hydrogen had been consumed (2 h) the mixture was filtered through Celite and 4 (4.05 g, 26.0 mmol) was added along with *p*-toluenesulfonic acid (0.20 g) as catalyst. The Schiff's base, a bright orange solid which crystallized, was collected and taken up in absolute ethanol (200 mL) and reduced with sodium borohydride (1.50 g, 39.7 mmol) at room temperature. The ethanol was removed by concentration and the residue partitioned between ethyl acetate and water. The organic extracts were dried (Na_2SO_4) and concentrated. Column chromatography over silica gel using 30% ethyl acetate in hexane as eluant afforded an off-white solid, and this material was crystallized from chloroform to afford 6 (3.75 g, 55%): ^{1}H NMR δ 7.29 (d, 1 H, J = 3 Hz), 6.78 (m, 3 H), 6.08 (d, 1 H, J = 3 Hz), 5.54 (br s, 1 H), 4.92 (br s, 1 H), 4.26 (s, 2 H), 3.76 (s, 3 H).

2-(2-Phenylethyl)-4-methoxyphenol (7). To a suspension of benzyltriphenylphosphonium chloride (2.00 g, 5.14 mmol), prepared from benzyl chloride and triphenylphosphine, in benzene (160 mL) was added *n*-butyllithium (1.6 M in hexane, 3.21 mL, 5.14 mmol) and the bright red solution allowed to stir at room temperature for 1 h. To the resulting solution was added 4 (0.780 g, 5.14 mmol) and stirring continued for 2 h. The reaction was then worked up by adding ethyl acetate (200 mL) and water (200 mL). The layers were separated, and the aqueous layer was washed with an additional portion of ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated to a yellow solid (1.10 g). This material was then purified by chromatography through a short column of silica gel and the residue taken up in ethanol (10 mL). This material was then hydrogenated over 10% palladium on carbon (0.10 g) to afford 7 as an oil (0.900 g, 77%): ^{1}H NMR δ 7.38–7.16 (m, 5 H), 6.74–6.60 (m, 3 H), 4.22 (s, 1 H), 3.72 (s, 3 H), 2.90 (s, 4 H).

2-(Hydroxymethyl)-4-methoxyphenol (8). To a cooled suspension (5 °C) of sodium borohydride (2.50 g, 65.80 mmol) in absolute ethanol (100 mL) was added dropwise over 1 h a solution of 4 (10.00 g, 65.8 mmol) in absolute ethanol (35 mL). Upon completion of the addition the reaction was allowed to stir an additional 10 min and then quenched with the dropwise addition of 10% acetic acid (75 mL). The resulting mixture was concentrated in vacuo (final volume 100 mL) and poured into water (250 mL). The aqueous mixture was extracted with ethyl acetate (3 × 100 mL), and the combined extracts were washed sequentially with 5% $NaHCO_3$ (50 mL) and 20% NaCl (3 × 100 mL), dried (Na_2SO_4), and concentrated. Trituration from hexane (15 mL) and ether (10 mL) afforded 8 (7.00 g, 70%) as a solid: ^{1}H NMR (DMSO-d_6) δ 6.90–6.50 (m, 3 H), 4.93 (br s, 1 H), 4.43 (s, 2 H), 3.66 (s, 3 H).

2-(Hydroxymethyl)-4-methoxyphenol Diacetate (9). To a solution of 8 (41.30 g, 213 mmol) in pyridine (400 mL) was added acetic anhydride (43.50 g, 426 mmol) dropwise over a few minutes. Upon completion of the addition, the reaction mixture, which had warmed to 45 °C, was heated to 80 °C for 40 min. The mixture was allowed to cool and then poured into water (1200 mL). The oil which separated was removed and the remaining aqueous layer extracted with ethyl acetate (3 × 300 mL). The combined extracts were washed sequentially with 2 N HCl (3 × 100 mL), water (100 mL), and 20% NaCl (2 × 100 mL) and then dried (Na_2SO_4) and

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(21) Bonney, R. J.; Davies, P.; Dougherty, H.; Egan, R.; Gale, P.; Chang, M.; Hammond, M. L.; Jensen, N.; MacDonald, J.; Thompson, K.; Zambias, R.; Opas, E.; Meurer, R.; Pacholok, S.; Humes, J. *J. Biochem. Pharmacol.* **1987**, *36*, 3885.
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concentrated to afford **9** (43.0 g, 82%) as an oil: ^{1}H NMR δ 7.16–6.70 (m, 3 H), 5.03 (s, 2 H), 3.80 (s, 3 H), 2.30 (s, 3 H), 2.10 (s, 3 H).

2-[(Phenylthio)methyl]-4-methoxyphenol (10). To a solution of **9** (1.70 g, 6.91 mmol) in dry dimethylformamide (4 mL) was added a solution of potassium thiophenoxide (1.02 g, 6.89 mmol) in dimethylformamide (10 mL) and the mixture heated to 60 °C for 30 min. During this time a gelatinous precipitate was deposited and an additional 5 mL of dimethylformamide added to facilitate stirring. The reaction mixture was cooled, poured into water (100 mL), and extracted with ethyl acetate (2 × 50 mL). The combined extracts were washed with 20% NaCl (2 × 50 mL), dried (Na_2SO_4), and concentrated to afford an oil (1.98 g). This material was directly saponified in absolute ethanol (15 mL) containing 2.5 N sodium hydroxide (3 mL). After 30 min at room temperature the reaction mixture was diluted with water (100 mL) and neutralized with acetic acid (0.5 mL). The mixture was extracted with ethyl acetate (2 × 50 mL) and washed sequentially with 5% $NaHCO_3$ (50 mL) and 20% NaCl (50 mL), dried (Na_2SO_4), and concentrated. This material was purified by preparative HPLC using 20% ethyl acetate in hexane as eluant to afford **10** (1.10 g, 65%) as an oil: bp 150 °C (0.05 mmHg); ^{1}H NMR δ 7.41–7.19 (m, 5 H), 6.81 (d, 1 H, J = 7 Hz), 6.71 (dd, 1 H, J = 2, 7 Hz), 6.60 (d, 1 H, J = 2 Hz), 5.43 (s, 1 H), 4.13 (s, 2 H), 3.68 (s, 3 H).

2-[[[2-(Hydroxymethyl)phenyl]thio]methyl]-4-methoxyphenol (11). To a solution of *o*-mercaptobenzyl alcohol (28.30 g, 199 mmol) in dry dimethylformamide (225 mL) under nitrogen was added sodium hydride (60% dispersion in mineral oil, 8.10 g, 202 mmol) in portions. The reaction mixture was allowed to stir until hydrogen evolution had ceased and then for an additional 30 min. The resulting solution was then added dropwise to a mechanically stirred solution of **9** (50.00 g, 203 mmol) in dry dimethylformamide (600 mL). A precipitate was deposited almost immediately and the resulting reaction mixture allowed to stir for 3 h at room temperature and then at 50 °C for 30 min. The reaction mixture was cooled to room temperature and 2.5 N sodium hydroxide (280 mL) was added to saponify the acetates. After 1 h the reaction mixture was diluted with water (1500 mL) and acidified to pH 6.0 with 2.5 N hydrochloric acid. The mixture was then extracted with ether (3 × 350 mL), and the combined extracts were washed with 20% NaCl (1000 mL), dried (Na_2SO_4), and concentrated to an oil (45.0 g). This material was purified by preparative HPLC using 33% ethyl acetate in hexane as eluant to afford **11** (29.0 g, 52%) as a pale yellow solid. Recrystallization from hexane/methylene chloride afforded an analytically pure sample (24.7 g) as a white solid: ^{1}H NMR δ 7.13–6.76 (m, 4 H), 6.66–6.46 (m, 2 H), 6.06 (d, 1 H, J = 2 Hz), 4.67 (d, 2 H, J = 4 Hz), 4.00 (s, 2 H), 3.63 (s, 3 H).

2-(Phenoxymethyl)-4-methoxyphenol (12). To a solution of **9** (12.70 g, 53.4 mmol) in acetone (200 mL) was added phenol (7.00 g, 74.5 mmol) and potassium carbonate (289.4 mmol), and the resulting mixture was heated to reflux with mechanical stirring overnight. The reaction mixture was allowed to cool, and the solids were removed by filtration. The filtrate was concentrated and chromatographed with 20% ethyl acetate in hexane as eluant to afford **12** (1.12 g, 9%) as an oil: ^{1}H NMR δ 7.39–7.24 (m, 2 H), 7.06–6.96 (m, 3 H), 6.90–6.76 (m, 3 H), 6.01 (s, 1 H), 5.18 (s, 2 H), 3.76 (s, 3 H).

2-(1-Phenyl-1-propen-3-yl)-4-methoxyphenol (13). A mixture of the sodium salt of 4-methoxyphenol (prepared by deprotonation of the phenol with sodium hydroxide in absolute ethanol, 2.92 g, 20.0 mmol) and cinnamyl bromide (3.94 g, 20.0 mmol) in benzene (100 mL) was heated to reflux for 4 h. After cooling, the solvents were removed and the residue taken up in water and acidified with concentrated HCl. The aqueous mixture was extracted with methylene chloride (2×), and the combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by preparative HPLC to afford **13** (0.900 g, 19%). Recrystallization from hexane afforded an analytical sample: ^{1}H NMR δ 7.40–7.16 (m, 5 H), 6.80–6.64 (m, 3 H), 6.51 (d, 1 H, J = 15 Hz), 6.36 (dt, 1 H, J = 6, 15 Hz), 4.58 (s, 1 H), 3.75 (s, 3 H), 3.53 (d, 2 H, J = 6 Hz).

6-Methoxy-1,2,3,4-tetrahydrobenzopyran-5-, -7-, and -8-carboxaldehydes (15–17). A solution of **14**[12] (133.0 g, 811 mmol) in dry methylene chloride (1850 mL) was cooled to 5 °C with an ice bath, and titanium tetrachloride (250 g, 145 mL, 1320 mmol) was added dropwise to the mechanically stirred solution over about 15 min. After the reaction was cooled to 5 °C dichloromethyl methyl ether (76.3 g, 60 mL, 664 mmol) was added dropwise over 45 min. During the addition the reaction temperature rose to 16 °C and the reaction was allowed to stir and come to room temperature over 3 h. The reaction was quenched by the dropwise addition of water (300 mL) and then poured into water (1000 mL). The layers were separated, and the organic layer was washed with 20% NaCl (2 × 1000 mL), dried (Na_2SO_4), and concentrated to a dark oil (152 g). Preparative HPLC (several runs) using 10% ethyl acetate in hexane as eluant afforded in order of polarity **15** (32.52 g, 20.9%), **17** (31.83 g, 20.4%), and **16** (31.49 g, 20.2%). **15**: ^{1}H NMR δ 10.58 (s, 1 H), 6.96 (d, 1 H, J = 7 Hz), 6.75 (d, 1 H, J = 7 Hz), 4.07 (t, 2 H, J = 6 Hz), 3.80 (s, 3 H), 3.06 (t, 2 H, J = 6 Hz), 1.89 (tt, 2 H, J = 6, 6 Hz). **16**: ^{1}H NMR δ 10.36 (s, 1 H), 7.23 (s, 1 H), 6.67 (s, 1 H), 4.13 (t, 2 H, J = 6 Hz), 3.86 (s, 3 H), 2.83 (t, 2 H, J = 6 Hz), 2.00 (tt, 2 H, J = 6, 6 Hz). **17**: ^{1}H NMR δ 10.36 (s, 1 H), 7.14 (d, 1 H, J = 2 Hz), 6.83 (d, 1 H, J = 2 Hz), 4.20 (t, 2 H, J = 6 Hz), 3.73 (s, 3 H), 2.77 (t, 2 H, J = 6 Hz), 2.00 (tt, 2 H, J = 6, 6 Hz).

6-Hydroxy-1,2,3,4-tetrahydrobenzopyran-7-carboxaldehyde (18). A solution of **16** (30.00 g, 156.3 mmol) in dry methylene chloride (625 mL) was cooled to an internal temperature of −67 °C and then a solution of boron tribromide (1 M in methylene chloride, 67.5 mL, 67.5 mmol) was added dropwise. The cooling bath was removed and the mixture allowed to stir for 3 h and then quenched by the dropwise addition of methanol (75 mL). The reaction mixture was then poured into saturated NaCl (1200 mL), the layers were separated, and the organic layer was washed with saturated NaCl (600 mL), dried (Na_2SO_4), and concentrated. The crude dark oil (31.0 g) was purified by preparative HPLC using 10% ethyl acetate in hexane as eluant to afford **18** (18.80 g, 68%): mp 97–100 °C; ^{1}H NMR δ 10.32 (s, 1 H), 9.64 (s, 1 H), 6.83 (s, 1 H), 6.55 (s, 1 H), 4.08 (t, 2 H, J = 7 Hz), 2.75 (t, 2 H, J = 7 Hz), 1.96 (tt, 2 H, J = 7, 7 Hz).

6-Hydroxy-1,2,3,4-tetrahydrobenzopyran-5-carboxaldehyde (19). In a manner exactly as described above for its isomer **15** (30.00 g, 156.3 mmol) was converted to **19** (22.46 g, 81%): ^{1}H NMR δ 11.86 (s, 1 H), 10.50 (s, 1 H), 7.03 (d, 1 H, J = 8 Hz), 6.70 (d, 1 H, J = 8 Hz), 4.13 (t, 2 H, J = 6 Hz), 3.10 (t, 2 H, J = 6 Hz), 2.06 (tt, 2 H, J = 6, 6 Hz).

General Procedure for the Preparation and Reduction of Schiff's Bases. To a 10% solution of the aldehyde in methanol was added the aromatic amine (1 equiv) and the mixture heated to reflux for 30–60 min. Upon cooling, the desired Schiff's base generally crystallized and was collected by filtration. In most cases the Schiff's bases were directly reduced without further purification.

To a suspension of the Schiff's base in 10 portions of methanol was added sodium borohydride (1 equiv) as a solid in portions. The mixture was allowed to stir for 10–30 min or until all of the color was quenched. The mixture was then poured into water, acidified with 2 N HCl, filtered to remove any insolubles, and basified with 5% $NaHCO_3$. In most cases the product that precipitated was collected by filtration and vacuum dried. In those cases where the product does not precipitate the product was isolated by extraction with ethyl acetate.

***N*-Phenyl-7-(aminomethyl)-6-hydroxy-1,2,3,4-tetrahydrobenzopyran (20).** As described above, **18** (0.429 g, 2.41 mmol) was treated with aniline (0.224 g, 2.41 mmol) and the resulting Schiff's base reduced with sodium borohydride (0.090 g, 2.41 mmol) to afford **20** (0.277 g, 43%): ^{1}H NMR δ 7.32–7.17 (m, 2 H), 6.94–6.80 (m, 3 H), 6.61 (s, 1 H), 6.56 (s, 1 H), 4.31 (s, 2 H), 4.12 (t, 2 H, J = 6 Hz), 2.72 (t, 2 H, J = 6 Hz), 1.96 (tt, 2 H, J = 6, 6 Hz).

***N*-(2,4-Difluorophenyl)-7-(aminomethyl)-6-hydroxy-1,2,3,4-tetrahydrobenzopyran (21).** As described above, **18** (0.414 g, 2.33 mmol) was treated with 2,4-difluoroaniline (0.303 g, 2.33 mmol) and the resulting Schiff's base reduced with sodium borohydride (0.060 g, 1.60 mmol) to afford **21** (0.350 g, 52%): ^{1}H NMR δ 7.38 (s, 1 H), 6.89–6.65 (m, 3 H), 6.59 (s, 1 H), 6.56 (s, 1 H), 4.28 (d, 2 H, J = 4 Hz), 4.11 (t, 2 H, J = 6 Hz), 4.03 (br s, 1 H), 2.71 (t, 2 H, J = 8 Hz), 1.93 (tt, 2 H, J = 6, 6 Hz).

***N*-[2-(Hydroxymethyl)phenyl]-7-(aminomethyl)-6-hydroxy-1,2,3,4-tetrahydrobenzopyran (22).** As described

above, 18 (0.400 g, 2.24 mmol) was treated with 2-aminobenzyl alcohol (0.282 g, 2.24 mmol) and the resulting Schiff's base reduced with sodium borohydride (0.060 g, 1.6 mmol) to afford **22** (0.300 g, 46%): ^{1}H NMR δ 7.76 (br s, 1 H), 7.30–7.06 (m, 2 H), 6.96–6.76 (m, 2 H), 6.62 (s, 1 H), 6.52 (s, 1 H), 5.18 (br s), 4.68 (s, 2 H), 4.34 (s, 2 H), 4.10 (t, 2 H, J = 6 Hz), 2.70 (t, 2 H, J = 6 Hz), 1.94 (tt, 2 H, J = 6, 6 Hz).

***N*-(4-Acetylphenyl)-7-(aminomethyl)-6-hydroxy-1,2,3,4-tetrahydrobenzopyran (23).** As described above, 18 (0.400, 2.25 mmol) was treated with 4-aminoacetophenone (0.304 g, 2.25 mmol) and the resulting Schiff's base (0.525 g) was reduced with sodium borohydride (0.066 g, 1.76 mmol) to afford **23**: (0.460 g, 69%): ^{1}H NMR δ 7.81 d, 2 H, J = 8 Hz), 6.69 (d, 2 H, J = 8 Hz), 6.63 (s, 1 H), 6.51 (s, 1 H), 5.93 (s, 1 H), 4.37 (br s, 1 H), 4.32 (s, 2 H, 4.09 (t, 2 H, J = 6 Hz), 2.68 (t, 2 H, J = 6 Hz), 2.46 (s, 3 H), 1.92 (tt, 2 H, J = 6, 6 Hz).

***N*-(4-Carbethoxyphenyl)-7-(aminomethyl)-6-hydroxy-1,2,3,4-tetrahydrobenzopyran (24).** As described above 18 (0.550 g, 3.09 mmol) was treated with ethyl 4-aminobenzoate (0.51 g, 3.09 mmol) and the resulting Schiff's base (0.620 g) was reduced with sodium borohydride (0.080 g, 2.13 mmol) to afford **24** (0.560 g, 55%): ^{1}H NMR δ 7.94 (d, 2 H, J = 8 Hz), 6.77 (d, 2 H, J = 8 Hz), 6.68 (s, 1 H), 6.58 (s, 1 H), 4.36 (s, 2 H), 4.35 (q, 2 H, J = 6 Hz), 4.15 (t, 2 H, J = 6 Hz), 2.75 (t, 2 H, J = 6 Hz), 1.98 (tt, 2 H, J = 6, 6 Hz), 1.38 (t, 3 H, J = 6 Hz).

***N*-(4-Cyanophenyl)-7-(aminomethyl)-6-hydroxy-1,2,3,4-tetrahydrobenzopyran (25).** As described above, 18 (0.480 g, 2.70 mmol) was treated with 4-aminobenzonitrile (0.320 g, 2.70 mmol) and the resulting Schiff's base (0.300 g) reduced with sodium borohydride (0.045 g, 1.2 mmol) to afford **25** (0.100 g, 13%): ^{1}H NMR δ 7.49 (d, 2 H, J = 7 Hz), 6.74 (d, 2 H, J = 7 Hz), 6.68 (s, 1 H), 6.57 (s, 1 H), 5.56 (s, 1 H), 4.50 (br, 1 H), 4.34 (d, 2 H, J = 5 Hz), 4.16 (t, 2 H, J = 6 Hz), 2.76 (t, 2 H, J = 6 Hz), 2.00 (tt, 2 H, J = 6, 6 Hz).

***N*-(2,4-Difluorophenyl)-5-(aminomethyl)-6-hydroxy-1,2,3,4-tetrahydrobenzopyran (26).** As described above, **19** (0.299 g, 1.68 mmol) was treated with 2,4-difluoroaniline and the resulting Schiff's base reduced with sodium borohydride (0.025 g, 0.67 mmol) to afford **26** (0.17 g, 35%): ^{1}H NMR δ 7.58 (s, 1 H), 6.90–6.58 (m, 5 H), 4.30 (s, 2 H), 4.06 (t, 2 H, J = 6 Hz), 3.89 (br, 1 H), 2.72 (t, 2 H, J = 6 Hz), 1.98 (tt, 2 H, J = 6, 6 Hz).

***N*-[2-(Hydroxymethyl)phenyl]-5-(aminomethyl)-6-hydroxy-1,2,3,4-tetrahydrobenzopyran (27).** As described above **19** (0.400 g, 2.24 mmol) was treated with 2-aminobenzyl alcohol (0.282 g, 2.24 mmol) and the resulting Schiff's base reduced with sodium borohydride (0.063 g, 1.68 mmol) to afford **27** (0.375 g, 58%): ^{1}H NMR δ 8.10 (br s, 1 H), 7.30–7.08 (m, 2 H), 6.90–6.80 (m, 2 H), 6.70 (d, 1 H, J = 7 Hz), 6.64 (d, 1 H, J = 7 Hz), 5.04 (br s, 1 H), 4.69 (s, 2 H), 4.36 (s, 2 H), 4.08 (t, 2 H, J = 6 Hz), 2.76 (t, 2 H, J = 6 Hz), 1.99 (tt, 2 H, J = 6, 6 Hz).

***N*-(4-Acetylphenyl)-5-(aminomethyl)-6-hydroxy-1,2,3,4-tetrahydrobenzopyran (28).** As described above **19** (0.308 g, 1.73 mmol) was treated with 4-aminoacetophenone (0.236 g, 1.73 mmol) and the resulting Schiff's base reduced with sodium borohydride (0.028 g, 0.74 mmol) to afford **28** (0.170 g, 33%): ^{1}H NMR δ 7.71 (d, 2 H, J = 7 Hz), 6.76 (d, 2 H, J = 7 Hz), 6.75 (d, 1 H, J = 8 Hz), 6.70 (d, 1 H, J = 8 Hz), 5.90 (s, 1 H), 4.38 (s, 2 H), 4.18 (br, 1 H), 4.14 (t, 2 H, J = 6 Hz), 2.80 (t, 2 H, J = 6 Hz), 2.54 (s, 3 H), 2.02 (tt, 2 H, J = 6, 6 Hz).

6-Hydroxy-7-(hydroxymethyl)-1,2,3,4-tetrahydrobenzopyran Diacetate (29). To a solution of 18 (5.00 g, 28.1 mmol) in pyridine (15 mL) was added acetic anhydride (3.5 mL, 31.1 mmol), and the mixture was allowed to stir at room temperature for 4 h. The reaction mixture was poured into ice water (75 mL) and the product that crystallized out was collected by filtration and air-dried to afford 6-acetoxy-1,2,3,4-tetrahydrobenzopyran-7-carboxaldehyde (5.86 g, 95%): mp 76–77 °C.

To a suspension of sodium borohydride (0.985 g, 25 mmol) in ethyl acetate (55 mL) at 5 °C was added dropwise a solution of 6-acetoxy-1,2,3,4-tetrahydrobenzopyran-7-carboxaldehyde (5.68 g, 25.8 mmol) in ethyl acetate (55 mL) followed by ethanol (4 mL), and the mixture was allowed to warm to room temperature and stir for 1 h. The reaction mixture was quenched with the dropwise addition of 10% acetic acid (50 mL) and the layers separated. The organic layer was washed with 5% $NaHCO_3$ (3 × 100 mL), dried (Na_2SO_4), and concentrated to afford crude 6-acetoxy-7-(hydroxymethyl)-1,2,3,4-tetrahydrobenzopyran (5.35 g, 93%) as a thick yellow oil, which was directly acetylated with acetic anhydride (3.5 mL) in pyridine (15 mL) at reflux for 10 min. After cooling the reaction mixture was poured into ice water (100 mL) and extracted with ethyl acetate (100 mL). The organic extract was washed sequentially with 2.5 N HCl (100 mL), 5% $NaHCO_3$ (2 × 100 mL), and 20% NaCl (100 mL), dried, and concentrated to an oil (6.19 g). This material was purified by preparative HPLC using 10% ethyl acetate in hexane as eluant to afford **29** as a pale yellow oil (3.89 g, 58%): ^{1}H NMR δ 6.73 (s, 1 H), 6.67 (s, 1 H), 4.94 (s, 2 H), 4.14 (t, 2 H, 8 Hz), 2.70 (t, 2 H, J = 6 Hz), 2.23 (s, 3 H, 2.02 (s, 3 H), 1.92 (m, 2 H).

7-[[[2-(Hydroxymethyl)phenyl]thio]methyl]-6-hydroxy-1,2,3,4-tetrahydrobenzopyran (30). In a manner identical with that described above for 11, 2-mercaptobenzyl alcohol (0.288 g, 2.06 mmol) was converted to the sodium salt with sodium hydride (60% dispersion in mineral oil, 0.083 g, 2.07 mmol) in dimethylformamide (3 mL) and added to a solution of **29** (0.543 g, 1.93 mmol) in dimethylformamide (5 mL). After workup and chromatographic purification **30** (0.285 g, 46%) was obtained as a pale yellow solid: ^{1}H NMR δ 7.60–7.24 (m, 4 H), 6.56 (s, 1 H), 6.52 (s, 1 H), 5.92 (s, 1 H), 4.80 (d, 2 H), J = 4 Hz), 4.10 (t, 2 H, J = 7 Hz), 4.06 (s, 2 H), 2.70 (t, 2 H, J = 7 Hz), 2.51 (t, 1 H, J = 4 Hz), 1.94 (tt, 2 H, J = 7, 7 Hz).

7-[[(4-Acetylphenyl)thio]methyl]-6-hydroxy-1,2,3,4-tetrahydrobenzopyran (31). In a manner analogous to that described above for **10**, **29** (1.00 g, 3.78 mmol) was treated with potassium 4-acetylthiophenoxide (0.720, 3.80 mmol) to afford, after workup and saponification, **31** (0.172 g, 15%) as a white solid: ^{1}H NMR δ 9.01 (br s, 1 H), 7.76 (d, 2 H, J = 7 Hz), 7.31 (d, 2 H, J = 7 Hz), 6.56 (s, 1 H), 6.42 (s, 1 H), 4.13 (s, 2 H), 3.93 (t, 2 H, J = 8 Hz), 2.56 (t, 2 H, J = 6 Hz), 2.50 (s, 3 H), 1.80 (m, 2 H).

5-Methoxy-2,3-dihydrobenzofuran-3-one (32). To an ice-cooled solution of boron trichloride (1 M in methylene chloride, 1210 mL) was added a solution of 4-methoxyphenol (125.0 g, 1008 mmol) in 1,2-dichloroethane (500 mL) dropwise over 1 h. To the resulting mixture was added sequentially chloroacetonitrile (76.5 mL, 91.3 g, 1209 mmol) dropwise over 10 min and solid aluminum chloride (67.25 g, 504 mmol) in portions such that the reaction temperature did not exceed 35 °C. The reaction mixture was allowed to stir for 2.5 h and then poured into a mixture of ice and 2 N HCl (1000 mL, total volume 2200 mL). The layers were separated, the aqueous layer was reextracted with methylene chloride (2 × 250 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated to afford a crude α-chloro-2-hydroxy-5-methoxyacetophenone. This material was directly taken up in methanol (1000 mL). Sodium acetate (275 g, 3048 mmol) was added and the mixture was refluxed for 1.5 h, allowed to cool, and filtered, and the filtrate was poured into 5% NaCl (2500 mL). The red solid (84 g) that precipitated was collected by filtration, dried, and recrystallized from ether to afford **32** (51.04 g, 31%): mp 90–92 °C; ^{1}H NMR δ 7.15 (dd, 1 H, J = 2, 8 Hz), 6.98 (d, 1 H, J = 2 Hz), 6.97 (d, 1 H, J = 8 Hz), 4.55 (s, 2 H), 3.42 (s, 3 H).

5-Methoxy-2,3-dihydrobenzofuran (33). A solution of **32** (50.30 g, 307 mmol) in absolute ethanol (1000 mL) was hydrogenated over 20% palladium hydroxide (10.0 g) at 3 atm pressure. After the requisite amount of hydrogen had been taken up, the catalyst was removed by filtration through a pad of Celite and the filtrate concentrated to afford **33** (45.5 g, 99%) as an oil sufficiently pure for further chemistry: ^{1}H NMR δ 6.76–6.53 (m, 3 H), 4.43 (t, 2 H, J = 8 Hz), 3.37 (s, 3 H), 3.10 (t, 2 H, J = 8 Hz).

5-Methoxy-2,3-dihydrobenzofuran-6-carboxaldehyde (34). To an ice-cooled solution of **33** (7.30 g, 48.7 mmol) in dry methylene chloride (75 mL) was added titanium tetrachloride (8.72 mL, 15.1 g, 79.5 mmol) dropwise followed by dichloromethyl methyl ether (4.32 g, 40.2 mmol). The reaction mixture was allowed to stir at ambient temperature for 1.5 h and then quenched with the careful addition of water. The resulting mixture was poured into water (200 mL), and the layers were separated. The aqueous layer was reextracted with two portions of methylene chloride, and the combined organic extracts were washed with 5% NaCl and dried (Na_2SO_4). The resulting solution was concentrated to a dark oil. Analysis of this crude mixture by NMR showed the prescence of two aldehyde protons in a ratio of approximately 4:1. Purification of the crude product by

preparative HPLC using 15% ethyl acetate in hexane as eluant afforded the major product **34** (3.54 g, 41%): mp 82–84 °C; ^{1}H NMR δ 10.28 (s, 1 H), 7.07 (s, 1 H), 6.81 (s, 1 H), 4.48 (t, 2 H, J = 8 Hz), 3.85 (s, 3 H), 3.18 (t, 2 H, J = 8 Hz).

5-Hydroxy-2,3-dihydrobenzofuran-6-carboxaldehyde (35). A solution of **34** (24.00 g, 134.8 mmol) in dry methylene chloride (800 mL) was cooled to −78 °C and then a solution of boron tribromide (1 M in methylene chloride, 63 mL) was added dropwise over 20 min. The resulting mixture was stirred at −78 °C for 15 min and then the cooling bath was removed and the reaction allowed to warm to ambient temperature over 2.5 h. The reaction was quenched by the dropwise addition of methanol (25 mL) and the reaction mixture poured into 10% NaCl (1000 mL). The layers were separated and the aqueous layers backwashed with two portions of methylene chloride. The combined organic extracts were washed with 10% NaCl (2 × 500 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by preparative HPLC using 10% ethyl acetate in hexane as eluant to afford **35** (16.82 g, 76%): mp 102–104 °C; ^{1}H NMR δ 10.89 (s, 1 H), 9.73 (s, 1 H), 6.84 (s, 2 H), 4.55 (t, 2 H, J = 8 Hz), 3.22 (t, 2 H, J = 8 Hz).

***N*-Phenyl-6-(aminomethyl)-5-hydroxy-2,3-dihydrobenzofuran (36).** As described above **35** (0.300 g, 1.83 mmol) was condensed with aniline (0.171 g, 1.83 mmol) to afford *N*-phenyl-6-(iminomethyl)-5-hydroxy-2,3-dihydrobenzofuran (0.400 g, 91%) as orange needles.

Reduction *N*-phenyl-6-(iminomethyl)-5-hydroxy-2,3-dihydrobenzofuran (0.350 g, 1.46 mmol) with sodium borohydride (0.056 g, 1.48 mmol) provided **36** (0.305 g, 86%): ^{1}H NMR δ 7.94 (br, 1 H), 7.30–7.16 (m, 2 H), 6.94–6.78 (m, 3 H), 6.74 (s, 1 H), 6.58 (s, 1 H), 4.52 (t, 2 H, J = 8 Hz), 4.11 (s, 2 H), 3.14 (t, 2 H, J = 8 Hz).

***N*-(2,4-Difluorophenyl)-6-(aminomethyl)-5-hydroxy-2,3-dihydrobenzofuran (37).** As described above **35** (0.305 g, 1.85 mmol) was treated with 2,4-difluoroaniline and then directly reduced with sodium borohydride (0.055 g, 1.47 mmol) to provide **37** (0.335 g, 65%): ^{1}H NMR δ 7.62 (s, 1 H), 6.98–6.68 (m, 4 H), 6.62 (s, 1 H), 4.56 (t, 2 H, J = 8 Hz), 4.36 (d, 2 H, J = 4 Hz), 4.07 (br, 1 H), 3.19 (t, 2 H, J = 8 Hz).

***N*-[2-(Hydroxymethyl)phenyl]-6-(aminomethyl)-5-hydroxy-2,3-dihydrobenzofuran (38).** As described above **35** (0.300 g, 1.83 mmol) was condensed with 2-aminobenzyl alcohol (0.230 g, 1.83 mmol) to afford 6-[[[2-(hydroxymethyl)phenyl]imino]methyl]-5-hydroxy-2,3-dihydrobenzofuran (0.290 g, 59%) as a yellow-orange solid.

Reduction of 6-[[[2-(hydroxymethyl)phenyl]imino]methyl]-5-hydroxy-2,3-dihydrobenzofuran (0.250 g, 0.93 mmol) with sodium borohydride (0.035 g, 0.93 mmol) provided **38** (0.226 g, 90%): ^{1}H NMR δ 7.91 (br s, 1 H), 7.31–7.09 (m, 2 H), 6.91–6.77 (m, 2 H), 6.72 (s, 2 H), 6.62 (s, 1 H), 5.17 (br s, 1 H), 4.71 (s, 2 H), 4.51 (t, 2 H, J = 8 Hz), 4.36 (s, 2 H), 3.14 (t, 2 H, J = 8 Hz), 1.57 (br s, 1 H).

***N*-(4-Acetylphenyl)-6-(aminomethyl)-5-hydroxy-2,3-dihydrobenzofuran (39).** As described above **35** (13.70 g, 83.5 mmol) was treated with 4-aminoacetophenone (11.3 g, 83.7 mmol) to afford 6-[[(4-acetylphenyl)imino]methyl]-5-hydroxy-2,3-dihydrobenzofuran (20.7 g, 88%): mp 185–187 °C.

Reduction of 6-[[(4-acetylphenyl)imino]methyl]-5-hydroxy-2,3-dihydrobenzofuran by hydrogenation at 3 atm over 10% palladium on carbon (2.34 g) provided **39** (11.50 g, 55%), which was recrystallized from methylene chloride in hexane to afford analytically pure material: ^{1}H NMR (DMSO-d_6) δ 9.06 (br s, 1 H), 7.72 (d, 2 H, J = 8 Hz), 7.01 (br t, 1 H, J = 5 Hz), 6.75 (s, 1 H), 6.60 (d, 2 H, J = 8 Hz), 6.55 (s, 1 H), 4.41 (t, 2 H, J = 8 Hz), 4.23 (d, 2 H, J = 5 Hz), 3.08 (t, 2 H, J = 8 Hz), 2.41 (s, 3 H).

6-[[(2-Cyanothien-5-yl)amino]methyl]-2,3-dihydro-5-benzofuranol (40) and 6-[[(2-Cyanothien-4-yl)amino]-methyl]-2,3-dihydro-5-benzofuranol (41). A stock solution of a mixture of 2-cyano-4-aminothiophene and 2-cyano-5-aminothiophene was prepared by catalytic hydrogenation at 3 atm of the mixture of 2-cyano-4-nitrothiophene and 2-cyano-5-nitrothiophene (4.62 g, 30.0 mmol) described above in ethyl acetate (100 mL) using 10% palladium on carbon (5.0 g) as catalyst. After the theoretical amount of hydrogen had been consumed (2 h), the mixture was filtered through Celite and the filtrate used directly. A 5-mL aliquot was added to a mixture of 2,3-dihydro-5-hydroxybenzofuran-6-carboxaldehyde (0.200 g, 1.22 mmol) and *p*-toluenesulfonic acid (0.001 g), and the mixture was allowed to stir at ambient temperature for 40 min. The orange solid that precipitated was collected by filtration and air-dried to afford a mixture of 6-[[(2-cyanothien-4-yl)imino]methyl]-2,3-dihydro-5-benzofuranol and 6-[[(2-cyanothien-5-yl)imino]methyl]-2,3-dihydro-5-benzofuranol (0.250 g). The crude mixture of Schiff's bases was taken up in ethanol (5 mL) and reduced with sodium borohydride (0.050 g, 1.32 mmol) at room temperature for 1 h. The ethanol was removed in vacuo and the residue partitioned between ethyl acetate (2 × 10 mL) and water (10 mL). The combined organic extracts were dried and concentrated. The products were purified by flash chromatography using 25% ethyl acetate in hexane as eluant to give in order of elution **41** (0.130 g, 39%) and **40** (0.055 g, 17%). **40**: ^{1}H NMR δ 7.26 (d, 1 H, J = 2 Hz), 6.78 (s, 1 H), 6.70 (d, 1 H, J = 2 Hz), 6.58 (s, 1 H), 4.55 (t, 2 H, J = 8 Hz), 4.31 (s, 2 H), 3.17 (t, 2 H, J = 8 Hz). **41**: ^{1}H NMR δ 7.19 (d, 1 H, J = 2 Hz), 6.76 (s, 1 H, 6.59 (s, 1 H), 6.52 (d, 1 H, J = 2 Hz), 4.54 (t, 2 H, J = 8 Hz), 4.29 (s, 2 H), 3.17 (t, 2 H, J = 8 Hz).

5-Methoxybenzofuran-6-carboxaldehyde (42). To a solution of 6-bromo-5-methoxybenzofuran (1.00 g, 4.41 mmol) in dry ether (17 mL) was added a solution of *n*-butyllithium (2.93 M in hexane, 1.50 mL, 4.40 mmol) all at once. Immediately following the addition the reaction mixture was added via syringe over 5 min to a solution of dimethylformamide (1.25 mL) in dry ether. The resulting mixture was allowed to stir at room temperature for 20 min and then poured into water (50 mL), and the layers were separated. The aqueous layer was reextracted with ether, and the combined organic extracts were washed with 2 N HCl, dried (Na_2SO_4), and concentrated to afford crude **42** (0.710 g, 91%) sufficiently pure for further chemistry: mp 94–95 °C (lit.[23] mp 99 °C); ^{1}H NMR δ 10.36 (s, 1 H), 7.83 (s, 1 H), 7.61 (d, 1 H, J = 2 Hz), 6.98 (s, 1 H), 6.65 (m, 1 H), 3.90 (s, 3 H).

5-Hydroxybenzofuran-6-carboxaldehyde (43). A solution of **42** (1.50 g, 8.52 mmol) in dry methylene chloride was cooled to −78 °C under a nitrogen atmosphere and then a solution of boron tribromide (1 M in methylene chloride, 3.7 mL, 3.7 mmol) was added dropwise via syringe over about 5 min. The resulting mixture was allowed to stir for 15 min and then allowed to warm to room temperature and stir for an additional 2.5 h. The reaction was then quenched with methanol (5 mL) and poured into water (200 mL). The aqueous layer was reextracted with methylene chloride (100 mL), and the combined organic layers were washed with 20% NaCl, dried (Na_2SO_4), and concentrated. The resulting crude product was purified by preparative HPLC using 7% ethyl acetate in hexane as eluant to afford **43** (0.890 g, 64%): mp 114–115 °C (lit.[23] mp 106 °C); ^{1}H NMR δ 10.80 (s, 1 H), 9.86 (s, 1 H), 7.75 (d, 1 H, J = 2 Hz), 7.60 (s, 1 H), 6.93 (s, 1 H), 6.70 (d, 2 H, J = 2 Hz).

***N*-Phenyl-6-(aminomethyl)-5-hydroxybenzofuran (44).** As described above **43** (0.300 g, 1.85 mmol) was treated with aniline (0.182 g, 1.95 mmol) and the resulting Schiff's base was reduced with sodium borohydride (0.105 g 2.8 mmol) to afford **44** (0.318 g, 72%): ^{1}H NMR δ 8.19 (s, 1 H), 7.60 (d, 1 H, J = 2 Hz), 7.36 (s, 1 H), 7.33–7.24 (m, 2 H), 7.11 (s, 1 H), 7.01–6.85 (m, 3 H), 6.71 (d, 1 H, J = 2 Hz), 4.51 (s, 2 H), 4.01 (br s, 1 H).

***N*-[2-(Hydroxymethyl)phenyl]-6-(aminomethyl)-5-hydroxybenzofuran (45).** As described above **43** (0.300 g, 1.85 mmol) was treated with 2-aminobenzyl alcohol (0.230 g, 1.87 mmol) and the resulting Schiff's base was reduced with sodium borohydride (0.105 g 2.8 mmol) to afford **45** (0.275 g, 55%): ^{1}H NMR δ 7.54 (d, 1 H, J = 2 Hz), 7.34 (s, 1 H), 7.30–6.76 (m, 4 H), 7.04 (s, 1 H), 6.64 (d, 1 H, J = 2 Hz), 4.70 (s, 2 H), 4.50 (s, 2 H).

Ethyl 3-(2-Bromophenyl)propenoate (47). To a solution of (carboxymethylene)triphenylphosphorane (2295 g, 6600 mmol) in methylene chloride (3500 mL) at 10 °C was added **46** (1210 g, 6540 mmol), dropwise over 45 min. Upon completion of the addition the mixture was stirred for an additional 45 min and then the methylene chloride was removed by concentration. The resulting pasty oil was diluted with hexane (4000 mL) and the

(23) Bastian, G.; Rene, L.; Buisson, J. P.; Royer, R.; Averbeck, D.; Averbeck, S. *Eur. J. Med. Chem.-Chim. Ther.* **1981**, *16*, 563.

triphenylphosphine oxide that precipitated was removed by filtration and the filter cake washed with an additional portion of hexane (4000 mL). The filtrate and washings were concentrated to a yellow oil, which was distilled to give 47 (1387 g, 87%) sufficiently pure for further chemistry: bp 90–93 °C (0.05 mmHg); ^{1}H NMR δ 7.96 (d, 1 H, J = 15 Hz), 7.63–7.03 (m, 4 H), 6.30 (d, 1 H, J = 15 Hz), 4.23 (q, 2 H, J = 7 Hz), 1.31 (t, 3 H, J = 7 Hz).

1-(2-Bromophenyl)-1-propen-3-ol (48). To a solution of 47 (148.0 g, 570 mmol) in dry toluene (750 mL) at −78 °C under nitrogen was added dropwise a solution of diisobutylaluminum hydride (1.53 M in toluene, 820 mL, 1254 mmol). Upon completion of the addition the reaction mixture was allowed to warm to ambient temperature over 1 h and then carefully added in a dropwise fashion to a stirred mixture of 2 N HCl (1500 mL) and ice. After stirring for 30 min, the layers were separated and the aqueous layer was extracted with methylene chloride (2 × 1000 mL). The combined extracts were dried ($MgSO_4$) and concentrated to afford 48 (118.0 g, 98%) as a colorless oil. Substantial decomposition of this material was observed during attempted distillation, and therefore this material was used without further purification in the next step. 48: ^{1}H NMR δ 7.71–7.01 (m, 4 H), 6.95 (d, 1 H, J = 16 Hz), 6.25 (dt, 1 H, J = 5, 16 Hz), 4.38 (br, 3 H; +D_2O d, 2 H, J = 5 Hz).

1-(2-Bromophenyl)-1-propen-3-yl Bromide (49). A 5000-mL three-neck flask fitted with an internal thermometer, mechanical stirring, a 125-mL pressure-equilibrated dropping funnel, and a drying tube was charged with 48 (500 g, 2350 mmol) and carbon tetrachloride (500 mL). The stirred mixture was cooled to −20 °C and then phosphorus tribromide (85 mL, 245 g, 905 mmol) was added dropwise over 30 min while the reaction temperature was maintained at −20 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture allowed to warm to 10 °C over 75 min. The reaction mixture was then worked up in two batches as follows. Approximately one-half of the reaction mixture was poured with stirring into ice water (1500 mL), and the layers were separated. The aqueous layer was washed with methylene chloride (500 mL), and the combined organic layers were washed sequentially with 5% $NaHCO_3$ (500 mL) and 10% NaCl (500 mL), dried (Na_2SO_4), and concentrated. Distillation of the resulting oil gave 49 (517 g, 80%) as a yellow oil: bp 100–102 °C (0.2 mmHg); ^{1}H NMR δ 7.73–7.03 (m, 4 H), 7.03 (d, 1 H, J = 16 Hz), 6.30 (dt, 1 H, J = 7, 16 Hz), 4.16 (d, 2 H, J = 7 Hz).

6-[1-(2-Bromophenyl)-1-propen-3-yl]-2,3-dihydro-5-benzofuranol (50). To a mechanically stirred suspension of 97% sodium hydride (3.00 g, 125 mmol) in dry benzene (500 mL) under nitrogen was added solid 2,3-dihydro-5-benzofuranol[16] (13.6 g, 100 mmol) in portions, and the mixture was stirred vigorously for 90 min. To the resulting mixture was added 49 (34.50 g, 120 mmol) dropwise, and the resulting mixture was heated to 75 °C for 6 h. The reaction mixture was allowed to cool to room temperature and then poured into cold 2.5 N HCl (600 mL) with vigorous stirring. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 400 mL). The combined extracts were dried and concentrated to an oil, which was triturated with 4:1 ethyl acetate/hexane (200 mL) and allowed to stand in the refrigerator overnight. The product (15.1 g) was isolated by filtration and the filtrate concentrated. The residue was purified by preparative HPLC using 20% ethyl acetate in hexane as eluant to give an additional portion (7.5 g) of 50 (total yield 22.6 g, 66%): mp 110–112 °C; ^{1}H NMR δ 7.50–7.30 (m, 2 H), 7.23–6.93 (m, 2 H), 6.77 (d, 1 H, J = 15 Hz), 6.60 (s, 1 H), 6.53 (s, 1 H), 6.13 (dt, 1 H, J = 6, 15 Hz), 4.63 (s, 1 H), 4.37 (t, 2 H, J = 8 Hz), 3.47 (d, 2 H, J = 6 Hz), 3.06 (t, 2 H, J = 8 Hz).

6-[1-(2-Cyanophenyl)-1-propen-3-yl]-2,3-dihydro-5-benzofuranol (51). To a solution of 50 (15.0 g, 45 mmol) in dry N-methylpyrrolidinone (120 mL) was added cuprous cyanide (8.10 g, 90 mmol). The mixture was heated to 175 °C for 4.5 h, cooled, and poured into 6 N ammonium hydroxide (400 mL). The mixture was extracted with ethyl acetate (2 × 300 mL), and the combined extracts were washed with ice water (3 × 200 mL). The organic layer was dried ($MgSO_4$) and concentrated to a dark red oil, which was triturated with 20% ethyl acetate in hexane. The product was collected by filtration as an off-white solid (5.50 g) and the filtrate concentrated. The residue was purified by preparative HPLC using 30% ethyl acetate in hexane as eluant to afford 51 (3.10 g, total yield 8.60 g, 68%): mp 137–139 °C; ^{1}H NMR δ 7.60–7.10 (m, 4 H), 6.77 (d, 1 H, J = 15 Hz), 6.60 (s, 1 H), 6.53 (s, 1 H), 6.43 (dt, 1 H, J = 6, 15 Hz), 4.61 (s, 1 H), 4.45 (t, 2 H, J = 8 Hz), 3.50 (d, 2 H, J = 6 Hz), 3.08 (t, 2 H, J = 8 Hz).

2-[3-(2,3-Dihydro-5-hydroxy-6-benzofuranyl)-1-propenyl]benzaldehyde (52). A solution of 51 (59.6 g, 215 mmol) in toluene (450 mL) in a flame-dried 3000-mL three-neck flask equipped with mechanical stirring under nitrogen was cooled to −5 °C and then a solution of diisobutylaluminum hydride (1.53 M in toluene, 309 mL, 472 mmol) was added dropwise over 45 min with vigorous stirring. Upon completion of the addition the reaction mixture was allowed to warm to 5 °C and stir for 1 h. At this point all of the solids had dissolved. The reaction mixture was then added carefully in small portions to a vigorously stirred solution of 20% ammonium chloride (75 mL), 2 N HCl (110 mL), and water (1050 mL). This mixture was allowed to stir for 3 h to ensure complete quenching of the aluminum salts. The layers were separated, and the aqueous layer was washed with chloroform (2 × 300 mL). The combined organic layers were washed with 20% NaCl, dried (Na_2SO_4), and concentrated. The residue was applied to an 8-cm pad of silica gel in a 600-mL fritted glass funnel. The short column was eluted with 5% ether in methylene chloride, and the fractions were collected. The fractions containing the desired aldehyde were combined and concentrated to afford 52 (37.0 g, 61%): ^{1}H NMR δ 10.22 (s, 1 H), 7.80 (d, 1 H, J = 7 Hz), 7.56–7.36 (m, 3 H), 7.27 (d, 1 H, J = 15 Hz), 6.75 (s, 1 H), 6.62 (s, 1 H), 6.23 (dt, 1 H, J = 6, 15 Hz), 4.81 (s, 1 H), 4.52 (t, 2 H, J = 8 Hz), 3.54 (d, 2 H, J = 6 Hz), 3.15 (t, 2 H, J = 8 Hz).

6-[1-[2-(Hydroxymethyl)phenyl]-1-propen-3-yl]-2,3-dihydro-5-benzofuranol (1). To a solution of 52 (101 g, 361 mmol) in absolute ethanol (750 mL) at 0 °C was added in portions sodium borohydride (5.10 g, 136 mmol). When all the starting material had been consumed by TLC (15% ethyl acetate in methylene chloride as eluant), the reaction mixture was worked up by diluting with water (400 mL) and neutralizing the excess sodium borohydride with 2 N HCl. The resulting mixture was extracted with ethyl acetate (3 × 300 mL) and methylene chloride (2 × 200 mL), and the combined organic layers were washed with 20% NaCl, dried (Na_2SO_4), and concentrated. The residue was filtered through a short column of silica gel (10 cm in a 3000-mL fritted glass funnel) and eluted with 40% ethyl acetate in methylene chloride to afford 1 (94.0 g, 93%). An analytically pure sample was obtained by taking the product up in 20% ethyl acetate in methylene chloride and precipitating the product out with hexane: ^{1}H NMR δ 7.44 (d, 1 H, J = 7 Hz), 7.34–7.20 (m, 3 H), 6.82 (d, 1 H, J = 15 Hz), 6.72 (s, 1 H), 6.62 (s, 1 H), 6.23 (dt, 1 H, J = 6, 15 Hz), 4.74 (s, 2 H), 4.54 (t, 2 H, J = 8 Hz), 3.51 (d, 2 H, J = 6 Hz), 3.14 (t, 2 H, J = 8 Hz).

6-[3-[2-(Hydroxymethyl)phenyl]propyl]-2,3-dihydro-5-benzofuranol (53). To a solution of 1 (2.82 g, 10.0 mmol) in acetic acid (35 mL) and ethanol (10 mL) was added platinum oxide (0.30 g). The mixture was hydrogenated at 3 atm pressure for 3 min. The catalyst was removed by filtration through Celite and the filter cake washed with ethanol. The combined filtrate and washings were concentrated and then taken up in ether (50 mL). The ether solution was washed sequentially with 5% $NaHCO_3$ (2 × 50 mL) and 20% NaCl (2 × 50 mL), dried ($MgSO_4$), and concentrated to a crude solid. Recrystallization from ethyl acetate/hexane afforded 53 as white needles (1.40 g, 49%): ^{1}H NMR δ 7.39 (m, 1 H), 7.24 (m, 3 H), 6.66 (s, 1 H), 6.58 (s, 1 H), 4.70 (s, 2 H), 4.52 (t, 2 H, J = 8 Hz), 3.13 (t, 2 H, J = 8 Hz), 2.76 (t, 2 H, J = 8 Hz), 2.42 (t, 2 H, J = 7 Hz), 1.93 (tt, 2 H, J = 7, 8 Hz).

1-(4-Bromophenyl)-1-propen-3-ol (56). In a manner analogous to that described above for 48, 4-bromobenzaldehyde (54; 25.00 g, 136 mmol) was treated with (carboxymethylene)triphenylphosphorane (47.32 g, 136 mmol) to afford 55 (26.50 g, 77%) as a colorless oil and a portion of this material (22.00 g, 86.00 mmol) was reduced with diisobutylaluminum hydride (255 in toluene, 200 mL) to afford 56 as a white solid (18.30 g, quantitative): mp 56–59 °C; ^{1}H NMR δ 7.25 (d, 2 H, J = 7 Hz), 7.05 (d, 2 H, J = 7 Hz), 6.41 (d, 1 H, J = 15 Hz), 6.13 (dt, 1 H, J = 6, 15 Hz), 4.18 (d, 2 H, J = 6 Hz), 2.60 (br s, 1 H).

1-(4-Bromophenyl)-1-propen-3-yl Bromide (57). In a manner analogous to that described above for 49, 56 (2.71 g, 13.0 mmol) was treated with phosphorus tribromide (1.25 g, 4.6 mmol) to afford 57 (3.07 g, 86%) as a white solid: mp 72–76 °C; ^{1}H NMR

δ 7.26 (d, 2 H, J = 7 Hz), 7.07 (d, 2 H, J = 7 Hz), 6.43 (d, 1 H, J = 15 Hz), 6.15 (dt, 1 H, J = 6, 15 Hz), 4.02 (d, 2 H, J = 6 Hz).

6-[1-(4-Bromophenyl)-1-propen-3-yl]-2,3-dihydro-5-benzofuranol (58). In a manner analogous to that described above for **50**, 2,3-dihydro-5-benzofuranol[16] (1.50 g, 11.0 mmol) was C-alkylated with **57** (3.05 g, 11.0 mmol) to afford **58** (1.85 g, 51%) as a white solid: mp 184–186 °C. Anal. ($C_{17}H_{15}BrO_2$) C, H, Br.

6-[1-(4-Cyanophenyl)-1-propen-3-yl]-2,3-dihydro-5-benzofuranol (59). In a manner analogous to that described above for **51**, **58** (1.50 g, 4.8 mmol) was treated with cuprous cyanide (1.70 g, 15.0 mmol) to afford **59** (1.10 g, 87%) as an off-white solid: mp 164–165 °C. Anal. ($C_{18}H_{15}O_2N \cdot 0.25H_2O$).

6-[1-(4-Cyanophenyl)-1-propen-3-yl]-2,3-dihydro-5-benzofuranol Methoxymethyl Ether. To a solution of **59** (18.10 g, 65.3 mmol) in dry tetrahydrofuran (350 mL) at −10 °C was added in portions sodium hydride (97%, 1.78 g, 77.4 mmol) and the resulting mixture allowed to stir at −10 °C for 1 h. To the resulting mixture was added chloromethyl methyl ether (15 mL, 15.90 g, 197.5 mmol) dropwise. The dark solution faded to a pale yellow quickly and after 30 min at 0 °C a pale yellow cloudy solution was obtained. The reaction was worked up by adding water (125 mL) and ether (500 mL), and the layers were separated. The organic layer was washed with water (2 × 100 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography using 25% ethyl acetate in hexane as eluant to afford 6-[1-(4-cyanophenyl)-1-propen-3-yl]-2,3-dihydro-5-benzofuranol methoxymethyl ether (20.10 g, 96%) as an off-white solid: ^{1}H NMR δ 7.56 (d, 2 H, J = 8 Hz), 7.40 (d, 2 H, J = 8.5 Hz), 7.02 (s, 1 H), 6.63 (s, 1 H), 6.52 (dt, 1 H, J = 6, 16 Hz), 6.41 (d, 1 H, J = 16 Hz), 5.13 (s, 2 H), 4.55 (t, 2 H, J = 8 Hz), 3.52 (d, J = 6 Hz), 3.48 (s, 3 H), 3.19 (t, 2 H, J = 8 Hz).

6-[1-(4-Acetylphenyl)-1-propen-3-yl]-2,3-dihydro-5-benzofuranol (60). To a solution of 6-[1-(4-cyanophenyl)-1-propen-3-yl]-2,3-dihydro-5-benzofuranol methoxymethyl ether (20.50 g, 63.9 mmol) in dry tetrahydrofuran (300 mL) under nitrogen was added methylmagnesium bromide (2.8 M in ether, 25 mL, 70.0 mmol), and the resulting mixture was heated to reflux overnight. After cooling the reaction mixture was poured into 2 N HCl (250 mL) and then diluted with methanol (400 mL). The resulting pale yellow solution was concentrated on a steam bath for 1 h at which point all of the organic solvents had been removed and the crude product had precipitated. The product was collected by filtration and then taken up in ethyl acetate and flushed through a short column of silica gel to remove a small amount of base-line material. The ethyl acetate solution was concentrated to 250 mL and then diluted with hexane (250 mL) and cooled to 0 °C. The product that crystallized was filtered to afford a white solid (5.30 g). The mother liquors were concentrated and purified by flash chromatography using 25% ethyl acetate as eluant to afford an additional amount of **60** (8.60 g, total yield 13.90 g, 71%): ^{1}H NMR δ 7.79 (d, 2 H, J = 8 Hz), 7.42 (d, 2 H, J = 8 Hz), 6.73 (s, 1 H), 6.63 (s, 1 H), 6.51 (d, 1 H, J = 5 Hz), 6.51 (s, 1 H), 4.55 (t, 2 H, J = 9 Hz), 4.51 (s, 1 H), 3.53 (d, J = 5 Hz), 3.16 (t, 2 H, J = 9 Hz), 2.58 (s, 3 H).

Human PMN LTB_4 Assay. The human PMN LTB_4 assay was performed as previously described.[10] Inhibitory concentration–response curves were constructed from five-point titrations using a four-parameter algorithm, and from these the IC_{50} values were determined. In general, compounds were tested at least in duplicate, and the reported IC_{50} values reflect the mean value of all the IC_{50} values obtained. Unless otherwise noted the standard error of the mean (SEM) was less than 50% of the mean value.

Topical Mouse Ear Assay. A solution of vehicle (acetone/pyridine/water 97:2:1) or test solution (25 μL) was applied to the inner surface of one ear of each mouse. Five mice were used in each test group. Control mice were treated with either vehicle alone or vehicle containing 200 μg/mL of phorbol myristate acetate (PMA; Sigma, St. Louis, MO). Test solutions were prepared by dissolving test compounds at the appropriate concentration in vehicle with PMA. Solvent was removed from each ear by evaporation at room temperature with a hair dryer. After 4 h mice were sacrificed by cervical dislocation, and a 6-mm disk of tissue was punched from each treated ear. Edema was measured as the change in wet weight. Inhibitory dose–response curves were constructed from four-point titrations, and from these the ED_{50} values were determined.

Registry No. 1, 120694-96-4; **3**, 84819-29-4; 4, 672-13-9; **5**, 124855-03-4; **5**·HCl, 124854-90-6; **6**, 94631-65-9; **7**, 54888-83-4; **8**, 41951-76-2; **9**, 91497-79-9; **10**, 60530-20-3; 11, 104774-97-2; **12**, 124854-91-7; **13**, 34591-41-8; 14, 3722-76-7; **15**, 99385-73-6; **16**, 99385-75-8; **17**, 99385-74-7; **18**, 99385-77-0; **19**, 99385-76-9; **20**, 99385-63-4; **21**, 99385-59-8; **22**, 99385-64-5; **23**, 99385-60-1; **24**, 99385-62-3; **25**, 99385-61-2; **26**, 124854-92-8; **27**, 99385-58-7; **28**, 99385-55-4; **29**, 103447-30-9; **30**, 103447-31-0; **31**, 103447-32-1; **32**, 39581-55-0; **33**, 13391-30-5; **34**, 99355-75-6; **35**, 99385-88-3; **36**, 99385-65-6; **37**, 99385-67-8; **38**, 99385-66-7; **39**, 99385-68-9; **40**, 99385-70-3; 41, 99385-69-0; **42**, 59254-34-1; **43**, 63376-65-8; **44**, 124854-93-9; **45**, 124942-32-1; **46**, 6630-33-7; **47**, 91047-77-7; **48**, 124854-94-0; **49**, 124854-95-1; **50**, 124854-96-2; **51**, 124854-97-3; **52**, 124854-98-4; **53**, 120694-92-0; **54**, 1122-91-4; **55**, 24393-53-1; **56**, 105515-33-1; **57**, 124854-99-5; **58**, 124855-00-1; **59**, 124855-01-2; **60**, 124855-02-3; LTB_4, 71160-24-2; 2,4-difluoroaniline, 367-25-9; 2-cyanothiophene, 1003-31-2; 2-cyano-4-nitrothiophene, 42137-24-6; 2-cyano-5-nitrothiophene, 16689-02-4; benzyltriphenylphosphonium chloride, 1100-88-5; o-mercaptobenzyl alcohol, 4521-31-7; 4-methoxyphenol sodium salt, 1122-95-8; (*E*)-cinnamyl bromide, 26146-77-0; 2-cyano-4-aminothiophene, 73781-74-5; 2-cyano-5-aminothiophene, 52532-63-5; 6-acetoxy-1,2,3,4-tetrahydrobenzopyran-7-carboxaldehyde, 103460-66-8; 6-acetoxy-7-(hydroxymethyl)-1,2,3,4-tetrahydrobenzopyran, 103447-36-5; α-chloro-2-hydroxy-5-methoxyacetophenone, 75717-53-2; *N*-phenyl-5-hydroxy-2,3-dihydrobenzofuran-6-carboximine, 99385-89-4; 6-[[[2-(hydroxymethyl)phenyl]imino]methyl]-5-hydroxy-2,3-dihydrobenzofuran, 99385-90-7; 6-[[(4-acetylphenyl)imino]-methyl]-5-hydroxy-2,3-dihydrobenzofuran, 99385-92-9; 6-[[(2-cyanothien-4-yl)imino]methyl]-2,3-dihydro-5-benzofuranol, 99385-93-0; 6-[[(2-cyanothien-5-yl)imino]methyl]-2,3-dihydro-5-benzofuranol, 99385-94-1; 6-bromo-5-methoxybenzofuran, 63272-68-4; 2,3-dihydro-5-benzofuranol, 40492-52-2; (*E*)-6-[1-(4-cyanophenyl)-1-propen-3-yl]-2,3-dihydro-5-benzofuranol methoxymethyl ether, 124855-04-5.