Synthesis and Biological Evaluation of 5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]oxazoles, -thiazoles, and -imidazoles: Novel Dual 5-Lipoxygenase and Cyclooxygenase Inhibitors with Antiinflammatory Activity[1]

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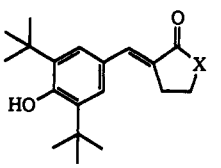
A variety of benzylideneoxazoles, -thiazoles, and -imidazoles derived from 2,6-di-*tert*-butylphenol were prepared and evaluated as dual inhibitors of 5-lipoxygenase and cyclooxygenase in rat basophilic leukemia (RBL-1) cells. The target compounds exhibit varying degrees of selectivity toward the two enzymes. Several compounds are orally active in the rat carageenan footpad edema (CFE) and mycobacterium footpad edema (MFE) antiinflammatory models. Structure–activity relationships are discussed. From this work, (*Z*)-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-methylene]-2-imino-4-thiazolidinone methanesulfonate salt (CI-1004) was identified as a potent dual inhibitor of 5-lipoxygenase (IC_{50} = 0.77 μM) and cyclooxygenase (IC_{50} = 0.39 μM), with oral activity (ID_{40} = 0.6 mg/kg) in the rat MFE model of inflammation.

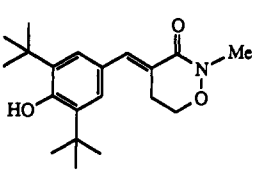
Nonsteroidal antiinflammatory drugs (NSAIDS) are widely used in the treatment of rheumatoid arthritis and other inflammatory diseases.[2] However, long-term NSAID use has been associated with gastrointestinal ulceration, bleeding, and nephrotoxicity.[3] The beneficial effects of NSAIDS have been historically attributed to inhibition of the enzyme cyclooxygenase, thereby preventing production of proinflammatory prostaglandins.[4a] Recently, two related isoenzymes of cyclooxygenase have been identified in mammalian cells.[4b,c] One isoenzyme is thought to be involved in the conversion of arachidonic acid to regulatory prostaglandins that control normal kidney and gastric function, while the other isoenzyme produces prostaglandins involved in inflammation. The identification of selective isoenzyme inhibitors may eventually lead to safer drugs for inflammation therapy.

In addition to cyclooxygenase (CO), the 5-lipoxygenase (5-LO) enzyme is also associated with the metabolism of cellular arachidonic acid.[5] Leukotrienes, produced through the 5-lipoxygenase enzyme pathway, may also contribute to both inflammation and NSAID-induced side effects.[6] For these reasons, compounds that are dual inhibitors of both cyclooxygenase and 5-lipoxygenase are being studied as potential antiinflammatory agents with an improved safety profile in comparison to NSAIDS.

Derivatives of 2,6-di-*tert*-butylphenol have been extensively studied as dual CO/5-LO inhibitors. Earlier reports from our laboratories described a variety of chemical series in which the di-*tert*-butylphenol ring is either directly bonded[7a,b] or linked by a two-carbon chain[7c] to various heterocyclic systems. Others[8] have reported related compounds in which the phenol portion of the molecule is part of a benzylidene moiety attached to a heterocyclic ring. Examples of the latter type include **1a** (KME-4),[9] **1b** (E-5110),[10] and **2** (BF-389).[11]



1a X = O
1b X = NOMe



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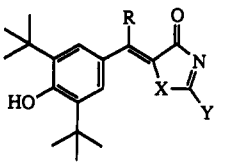

3 X = O, S, NMe

Many di-*tert*-butylphenol bicyclic derivatives are highly lipophilic compounds, resulting in generally poor aqueous solubility and associated bioavailability. Results from our earlier chemical series[7a,b] demonstrated that the addition of ionizable functionality to the heterocyclic ring linked to the phenol ring would reduce the lipophilicity and aid in adsorption and elimination of these compounds.

This paper describes the synthesis and biological activity of a series of benzylideneoxazoles, -thiazoles, and -imidazoles, generically represented in **3**. Many of these compounds are dual inhibitors of cyclooxygenase and 5-lipoxygenase activity as measured in rat basophilic leukemia (RBL-1) cells. A number of compounds also show oral activity in animal models of inflammation.

Chemistry

A series of benzylidene derivatives **6** (Scheme 1) were prepared by Knoevenagel condensation (methods A, D) of the di-*tert*-butyl aldehyde **4** with heterocycles **5a–c**, **5d**,[12] **5e**, **5f**,[13] and **5g**[14] (Table 1). Alkylation of benzylidene thiones **6c**,[15] **6g**, and **6j** with iodomethane (method E) provided the methyl thioether intermediates **7a–c**. Reaction of **7a–c** with various amines (methods F, I, J, K)

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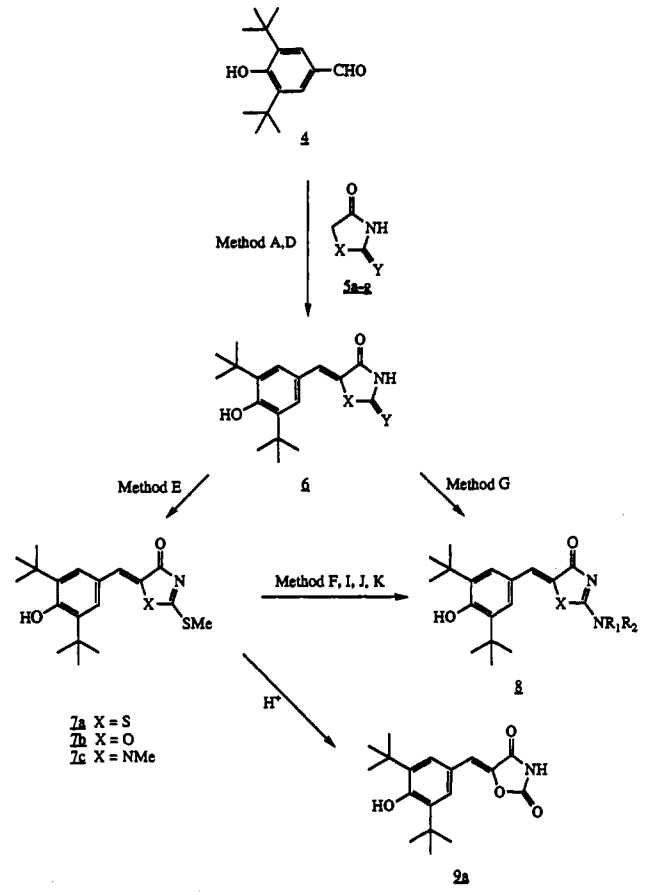
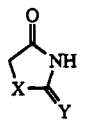
Scheme 1[a]



[a] Method A: NaOAc, HOAc. Method D: β-alanine, HOAc. Method E: MeI, $(i\text{-}Pr)_2NEt$. Method F: R_1R_2NH. Method G: R_1R_2NH, $BaCO_3$. Method I: R_1R_2NH, t-BuOK. Method J: guanidine, t-BuOK. Method K: cyanamide, t-BuOK. Variations **5a–g** are listed in Table 1, while variations of **6** and **8** are listed in Table 3.

Table 1. Intermediate Heterocycles for Knoevenagel Condensation

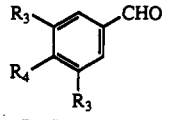


no.	X	Y
5a	S	O
5b	S	S
5c	S	NH_2
5d	O	S
5e	NMe	O
5f	NMe	S
5g	CH_2	S

gave the amino derivatives **8**. Additional examples of **8** were obtained by reaction of amines with thione **6c** (method G). A benzylideneoxazoledione **9a** was obtained by acidic hydrolysis of thioether **7b**. Benzylidene derivatives **6–9** are listed in Table 3.

A sequence of reactions similar to that described in Scheme 1 was used to prepare analogs containing a methyl substituent on the benzylidene double bond. Knoevenagel condensation (method L) of the di-*tert*-butyl ketone **10**[16] (Scheme 2) with heterocycles **5a** and **5b** gave thiazoles **11a** and **11c**, respectively. Alkylation of **11c** (method E) provided the thioether intermediate **12**, and reaction of **12** with cyanamide (method K) or guanidine (method J) gave derivatives **13a** and **13b**, respectively.

Table 2. Intermediate Aldehydes for Knoevenagel Condensation



no.	R_3	R_4
14a	Ph	OH
14b	i-Pr	OH
14c	I	OH
14d	H	OH
14e	t-Bu	H

Benzylidenethiazoles **15** (Scheme 3) without the di-*tert*-butylphenol substituent pattern were obtained by Knoevenagel condensation (method D) of heterocycle **5a** with aldehydes **14a**, **14b**,[17] **14c**,[18] **14d**, and **14e**.[19] The aldehydes used are listed in Table 2, while the thiazole products **11**, **13**, and **15** are listed in Table 4.

Choline (methods B, C), methanesulfonate, and hydrochloride (method H) salts of selected target compounds were prepared as described in the Experimental Section.

In all cases of the Knoevenagel condensation, only a single stereoisomer was obtained for the olefinic product.[20]

Table 5 summarizes the physicochemical data for the benzylideneoxazoles, -thiazoles, and -imidazoles prepared.

Results and Discussion

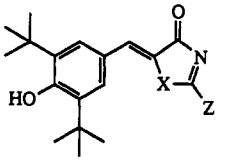
Our overall goal was the discovery of a balanced dual inhibitor of cyclooxygenase and 5-lipoxygenase with substantial antiinflammatory activity and a low potential for ulcerogenicity. Test compounds were evaluated for inhibition of $PGF_{2\alpha}$ (a product of CO) formation and LTB_4 (a product of 5-LO) formation in intact rat basophilic leukemia (RBL-1) cells stimulated with the calcium ionophore A23187. Those compounds with IC_{50} values ≤ 10 μM for both enzymes were then tested in an acute animal model of inflammation, the carrageenan footpad edema (CFE) test. Compounds active in CFE (defined as showing ≥40% inhibition at a dose of 30 mg/kg po) were next tested in the mycobacterium footpad edema (MFE) test, a 3-day subacute model more demanding of antiinflammatory efficacy than CFE. Selected compounds with oral activity in both the CFE and MFE tests received additional pharmacological evaluation.

Results from the enzyme assays and in vivo antiinflammatory models for compounds **6–9** are shown in Table 3. Thiazole and oxazole di-*tert*-butylphenols with a 2-hydroxy (**6a** and **9b**), 2-mercapto (**6c** and **6g**), or 2-amino (**6f**) substituent were found to be potent dual inhibitors and orally active in the animal models. The corresponding imidazoles **6i** and **6j**, although dual inhibitors, were inactive in vivo, while the pyrrolidine derivative **6k** and the thiazole thioether **7a** were active in CFE but not in MFE.

In view of the potent activity of thiazoles **6a**, **6c**, and **6f**, a further series (**8a–o**) of 2-substituted thiazoles was synthesized. Several additional dual inhibitors were identified, including compounds with a methoxymethylamino (**8h**), cyanoimino (a bioisosteric thione replacement;[21] **8i**), and guanidino (**8l**) substituent. However, these compounds did not exhibit a satisfactory overall profile after secondary pharmacological evaluation.

The cyanoimino and guanidino substituent patterns were also investigated in the oxazole (**8q** and **8s**) and imidazole (**8t** and **8v**) series. Once again, potent dual inhibitors were obtained in both series.

Table 3. Biochemical and in Vivo Antiinflammatory Activity of Benzylidene Derivatives 6–9



no.	X	Z	IC_{50}, μM[a] 5-LO	IC_{50}, μM[a] CO	CFE:[b] inhibn ± SEM at dose in mg/kg po 30	CFE:[b] inhibn ± SEM at dose in mg/kg po 10	MFE:[c] ID_{40}, mg/kg po
6a	S	OH	1.4	0.35	59 ± 4.6[d]	54 ± 4.3	2.0 (1.0–3.2)[d]
6c	S	SH	0.38	0.012	36 ± 5.0[e]	32 ± 4.4	
6f	S	NH_2·$MeSO_3H$	0.77	0.39	61 ± 4.5	52 ± 3.6	0.6 (0.3–0.9)
6g	O	SH	0.84	1.7	40 ± 2.9	32 ± 6.5	12.4 (8.0–20.2)
6i	NMe	OH	0.78	4.6	N[f]		
6j	NMe	SH	0.17	0.79	N		
6k	CH_2	SH	1.7	2.4	39 ± 3.9	19 ± 4.7	N[g]
7a	S	SMe	0.65	0.60	47 ± 7.1	36 ± 6.2	N
8a	S	NHMe	N[h]	N			
8b	S	NMe_2	65[i]	N			
8c	S	NHOH	3.7	0.80	N[j]		
8e	S	NMeOH	7.3	10.0	N		
8f	S	NHOMe	N	61[i]			
8h	S	NMeOMe·HCl	1.7	0.33	36 ± 2.7	41 ± 3.8	6.2 (2.4–11.8)
8i	S	NHCN	0.63	0.16	49 ± 5.9[k]	29 ± 4.4	N[k]
8l	S	$NHCNHNH_2$·HCl	0.91	0.083	40 ± 3.1	34 ± 5.4	2.2 (0.8–3.9)
8m	S	$NHCNHNMe_2$	100[i]	N			
8n	S	$NH(CH_2)_2NMe_2$	79[i]	N			
8o	S	$NH(CH_2)_3CO_2H$	53[i]	N			
8q	O	NHCN·choline	2.6	1.1	N		
8s	O	$NHCNHNH_2$·$MeSO_3H$	1.2	0.34	48 ± 3.3	33 ± 4.0	5.7 (4.1–7.5)
8t	NMe	NHCN	0.70	3.5	N[l]		
8v	NMe	$NHCNHNH_2$	1.3	2.1	N		
9b	O	OH·choline	2.8	0.65	51 ± 2.7	35 ± 3.6	3.7 (2.4–5.0)
1a			2.5	0.15	28 ± 5.1	17 ± 9.5	3.7 (2.0–7.2)
1b			0.56	0.040	26 ± 4.7	29 ± 3.1	1.9 (1.1–2.9)
sodium meclofenamate			24.0	0.10	41 ± 5.3	34 ± 5.5	0.40 (0.02–1.0)

[a] The concentration (μM) of test compound causing 50% inhibition of LTB_4 (5-LO) or $PGF_{2\alpha}$ (CO) formation. The standard errors average 11% of the values shown for 5-LO and 8% for CO. [b] Percent inhibition ±SEM of edema in the carageenan footpad edema test. [c] The dose (mg/kg) of test compound causing 40% inhibition of induced edema in the mycobacterium footpad edema test; 95% confidence limits are in parentheses. [d] Data from the choline salt 6b. [e] Data from the choline salt 6d. [f] Inactive (N) is defined as <25% inhibition at a dose of 30 mg/kg po. [g] Inactive (N) is defined as <30% inhibition at a dose of 10 mg/kg po. [h] Inactive (N) is defined as <50% inhibition at a screening concentration of 10 μM. [i] Percent inhibition at 10 μM screening concentration. [j] Data from the choline salt 8d. [k] Data from the choline salt 8j. [l] Data from the choline salt 8u.

Biological test results for compounds 11–15 are shown in Table 4. Analogs of the thiazole dual inhibitors **6a**, **6c**, **8i**, and **8l** were prepared in which the benzylidene proton was replaced by a methyl group (**11b**, **11c**, **13a**, and **13b**). In all cases, the methyl derivatives were inactive in the animal models and were generally of lower potency as dual inhibitors when compared to the corresponding non-methyl analogs.

Thiazole **6a** was also used as a model to explore a limited substituent variation in the phenol ring of the molecule. Replacement of both *tert*-butyl groups of **6a** with phenyl (**15a**), isopropyl (**15c**), iodo (**15d**), or hydrogen (**15e**) resulted in compounds with overall activity inferior to that of **6a**. Replacement of the phenolic hydroxyl group of **6a** with hydrogen (**15f**) produced a dual inhibitor without activity in the animal models. These results agree with earlier work[7c,22,23] in a number of diverse chemical series demonstrating the preference for the di-*tert*-butylphenol substructure.

The 2-hydroxythiazole **6a** and the 2-aminothiazole **6f** were selected for additional evaluation. These two compounds exhibited an improved balance in the enzyme inhibitory assays and a similar potency in the in vivo models when compared to the standards **1a**, **1b**, and sodium meclofenamate.

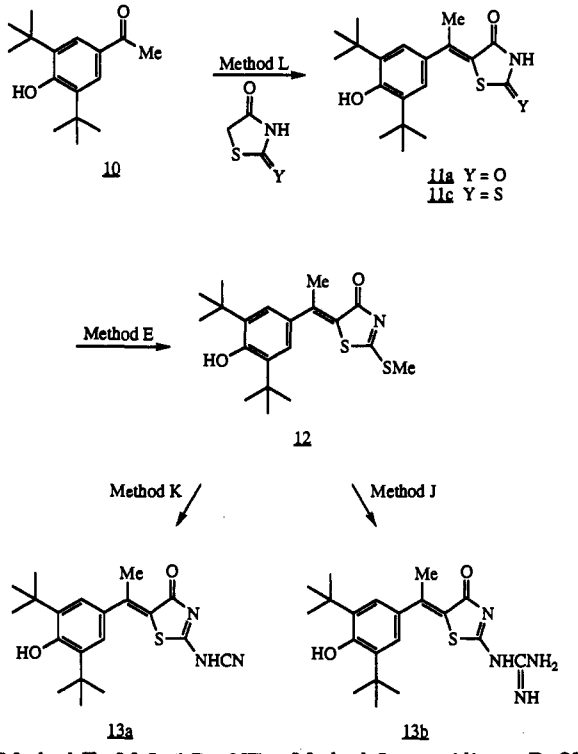
Thiazoles **6a** and **6f** were evaluated for gastric ulcerogenic potential in a rat stress model.[7a] When administered orally to fasted rats ($N = 10$ animals), neither compound caused ulcers at a 200 mg/kg dose in contrast to **1a** (30% incidence of ulcers at 30 mg/kg dose) and sodium meclofenamate (50% incidence of ulcers at 36 mg/kg dose). When tested orally in an adjuvant induced polyarthritis assay[24] (a chronic model of inflammation in which sodium meclofenamate has ID_{40} = 1.3 mg/kg for prophylactic administration), **6a** and **6f** had ID_{40} values of 2.2 and 1.7 mg/kg, respectively.

We have described the synthesis of novel thiazole, oxazole, and imidazole derivatives of 3,5-di-*tert*-butylphenol. Several of these compounds are relatively balanced dual inhibitors of the 5-lipoxygenase and cyclooxgenase enzyme pathways. Thiazoles **6a** (designated as CI-987) and **6f** (designated as CI-1004) were identified as nonulcerogenic, orally active antiinflammatory agents.

Experimental Section

Melting points were determined on a Thomas-Hoover or Electrothermal capillary apparatus and are uncorrected. Elemental analyses were performed by the Analytical Chemistry staff of Parke-Davis (Ann Arbor, MI) and were within ±0.4% of the theoretical values, unless indicated otherwise. Infrared spectra were recorded as KBr disks on a Nicolet MX-1 FTIR spectrometer. Proton NMR spectra were recorded on a Brüker AM 250 spectrometer, with chemical shifts reported in δ units relative to internal TMS. Reactions were generally run under a nitrogen atmosphere. Organic solutions were concentrated at

Scheme 2[a]



[a] Method E: MeI, $(i\text{-Pr})_2$NEt. Method J: guanidine, t-BuOK. Method K: cyanamide, t-BuOK. Method L: NH_4OAc, toluene.

aspirator vacuum on a rotary evaporator. Flash chromatography was performed with E. Merck silica gel 60, 230–400-mesh ASTM, according to the method of Still.[25]

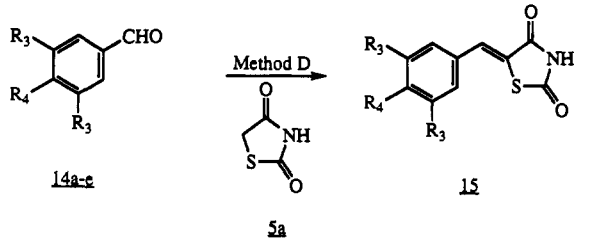
Method A. (*Z*)-5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione (6a). A suspension of **4** (6.5 g, 28 mmol), **5a** (3.0 g, 26 mmol), and NaOAc (7.6 g, 93 mmol) in HOAc (40 mL) was stirred at reflux for 48 h. The cooled reaction mixture was added to H_2O (200 mL), and the precipitated product was filtered and washed with H_2O. Recrystallization from EtOH gave 2.3 g (27%) of **6a**: mp 238–240 °C; IR 3619, 1741, 1583, 1214 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.41 (s, 18H, t-Bu), 7.38 (s, 2H, ArH), 7.77 (s, 1H, olefin), 7.79 (s, 1H, OH), 12.48 (br s, 1H, NH). Anal. ($C_{18}H_{23}NO_3S$) C, H, N.

Method B. (*Z*)-5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione Choline Salt (6b). A stirred suspension of **6a** (10.0 g, 30 mmol) in EtOH (100 mL) was treated dropwise with a 47% aqueous choline bicarbonate solution (10.6 g, 30 mmol). The mixture was heated at reflux for 1 h, cooled, and evaporated. Fresh EtOH (50 mL) was added and the mixture again evaporated two additional times. The final residue was triturated with Et_2O to yield 12.8 g (86%) of **6b**: mp 215 °C dec; IR 1675, 1617, 1571, 1206 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40 (s, 18H, t-Bu), 3.11 (s, 9H, NMe), 3.40 (m, 2H, CH_2), 3.85 (m, 2H, CH_2), 5.40 (br s, 1H, choline OH), 7.23 (s, 1H olefin), 7.30 (s, 2H, ArH). Anal. ($C_{18}H_{22}NO_3S{\cdot}C_5H_{14}NO$) C, H, N.

(*Z*)-5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2-imino-4-thiazolidinone Methanesulfonate Salt (6f). A solution of methanesulfonic acid (0.50 mL, 0.74 g, 7.7 mmol) in THF (4.0 mL) was added at room temperature to a stirred solution of **6e** (2.3 g, 7.0 mmol) in THF (190 mL). The mixture was stirred for 30 min, and the solvent was evaporated. Trituration of the residue with Et_2O gave a solid which was recrystallized from MeOH/Et_2O to yield 2.7 g (90%) of **6f**: mp 252 °C dec; IR 3600, 1734, 1608, 1192 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.42 (s, 18H, t-Bu), 2.43 (s, 3H, Me), 6.67 (br s, 2H, NH_2), 7.39 (s, 2H, ArH), 7.65 (s, 1H, olefin), 7.69 (br s <1H, OH), 9.58 (br s, 1H, NH). Anal. ($C_{18}H_{24}N_2O_2S{\cdot}CH_3SO_3H$) C, H, N.

(*Z*)-5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2-thioxo-4-oxazolidinone (6g). A mixture of **4** (18.8 g, 80 mmol), **5d**[12] (10.0 g, 85 mmol), and β-alanine (1.6 g, 18 mmol) in HOAc (28 mL) and toluene (80 mL) was stirred at reflux through a Dean–Stark trap for 4 h. The solid that precipitated from the cooled reaction mixture was filtered and washed with hexane. Recrystallization from MeCN/H_2O gave 11.1 g (41%) of **6g**: mp 240 °C dec; IR 3612, 1728, 1653, 1432 cm^{-1}, ^1H NMR (DMSO-d_6) δ 1.41 (s, 18H, t-Bu), 6.77 (s, 1H, olefin), 7.72 (s, 2H, ArH), 7.74 (s, 1H, OH), 13.75 (br s, 1H, NH). Anal. ($C_{18}H_{23}NO_3S$) C, H, N.

Scheme 3[a]



[a] Method D: β-alanine, HOAc. Variations **14a–e** are listed in Table 2. The condensation products **15** are listed in Table 4.

Method C. (*Z*)-5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2-thioxo-4-oxazolidinone Choline Salt (6h). A solution of 47% aqueous choline bicarbonate (2.5 g, 7.1 mmol) in MeOH (50 mL) was treated over 5 min with **6g** (2.3 g, 6.9 mmol). The mixture was warmed to reflux for 5 min on the steam bath and filtered hot. The cooled filtrate was evaporated, and the residue was redissolved in methanol and reevaporated three times. Recrystallization of the final residue from acetone/t-BuOMe gave 2.1 g (70%) of salt **6h**: mp 167 °C dec; IR 1634, 1653, 1366, 1199 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40 (s, 18H, t-Bu), 3.11 (s, 9H, NMe), 3.39 (m, 2H, CH_2), 3.84 (m, 2H, CH_2), 5.32 (br s, 1H, choline OH), 6.03 (s, 1H, olefin), 7.26 (br s, 1H, phenol OH), 7.57 (s, 2H, ArH). Anal. ($C_{18}H_{22}NO_3S{\cdot}C_5H_{14}NO$) C, H, N.

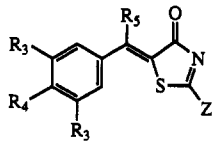
Method D. (*Z*)-5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-1-methyl-2-thioxo-4-imidazolidinone (6j). A mixture of **4** (19.0 g, 81 mmol), **5f**[13] (10.6 g, 81 mmol), and β-alanine (4.7 g, 53 mmol) in HOAc (150 mL) was stirred at reflux for 24 h. The cooled reaction mixture was added to H_2O (1.5 L) and stirred for 1 h. The precipitated product was filtered and washed with H_2O and then recrystallized from MeCN to yield 17.5 g (62%) of **6j**: mp 242–244 °C; IR 3630, 1734, 1497, 1240 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40 (s, 18H, t-Bu), 3.48 (s, 3H, NMe), 6.74 (s, 1H, olefin), 7.50 (s, 1H, OH), 8.07 (s, 2H, ArH), 12.29 (br s, 1H, NH). Anal. ($C_{19}H_{26}N_2O_2S$) H, N; C: calcd, 61.17; found, 60.60.

(*Z*)-5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2-(methylthio)-4(5*H*)-oxazolone (7b). A solution of **6g** (5.0 g, 15 mmol) in THF (75 mL) was cooled in ice and treated with Et_3N (2.4 mL, 1.7 g, 17 mmol). The mixture was stirred for 30 min, and MeI (4.5 mL, 10.3 g, 72 mmol) was added. The ice bath was removed, and the mixture was stirred for 24 h. The insoluble material was filtered, and the filter cake was washed several times with fresh THF. The filtrates were evaporated, and the residue was purified by flash chromatography (2.5–5% EtOAc in CH_2Cl_2) to yield 4.3 g (83%) of **7b**. Sample recrystallized from EtOAc/hexane: mp 164–166 °C; IR 3568, 1719, 1656, 1505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 18H, t-Bu), 2.74 (s, 3H, SMe), 5.68 (s, 1H, OH), 6.82 (s, 1H, olefin), 7.60 (1s, 2H, ArH). Anal. ($C_{19}H_{25}NO_3S$) C, H, N.

Method E. (*Z*)-5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-1,5-dihydro-1-methyl-2-(methylthio)-4*H*-imidazol-4-one (7c). A suspension of **6j** (4.0 g, 12 mmol) and *N*,*N*-diisopropylethylamine (2.4 mL, 1.8 g, 14 mmol) in EtOH (50 mL) was treated with MeI (1.2 mL, 2.7 g, 19 mmol). The mixture was stirred at room temperature for 18 h and then added to H_2O (300 mL). After 1 h the product was filtered, washed with H_2O, and recrystallized from EtOAc to yield 3.0 g (70%) of **7c**: mp 177–179 °C; IR 3572, 1677, 1588, 1430 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.42 (s, 18H, t-Bu), 2.63 (s, 3H, SMe), 3.32 (s, 3H, NMe), 6.78 (s, 1H, olefin), 7.47 (br s, 1H, OH), 8.20 (s, 2H, ArH). Anal. ($C_{20}H_{26}N_2O_2S{\cdot}0.25CH_3CN$) C, H, N.

Method F. (*Z*)-5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2-(methylamino)-4(5*H*)-thiazolone (8a). A mixture of **7a** (3.6 g, 9.9 mmol) and 40% aqueous methylamine (5.3 g, 68 mmol) in EtOH (300 mL) was stirred at reflux for 22

Table 4. Biochemical and in Vivo Antiinflammatory Activity of Benzylidene Derivatives 11, 13, 15



no.	Z	R_3	R_4	R_5	IC_{50}, μM[a] 5-LO	CO	CFE:[b] % inhibn ± SEM at dose in mg/kg po 30	10	MFE:[c] ID_{40}, mg/kg po
11b	OH·choline	t-Bu	OH	Me	0.48	52[d]			
11c	SH	t-Bu	OH	Me	2.3	4.5	N[e,f]		
13a	NHCN	t-Bu	OH	Me	1.2	5.1	N		
13b	$NHCNHNH_2$	t-Bu	OH	Me	1.6	1.9	N		
15a	OH	Ph	OH	H	0.16	9.6	41 ± 5.1[g]	11 ± 7.6	N[g,h]
15c	OH	i-Pr	OH	H	0.22	0.82			N
15d	OH	I	OH	H	N[i]	60[d]			
15e	OH	H	OH	H	N	N			
15f	OH	t-Bu	H	H	3.3	4.6	N[j]		

[a] The concentration (μM) of test compound causing 50% inhibition of LTB_4 (5-LO) or $PGF_{2\alpha}$ (CO) formation. The standard errors average 11% of the values shown for 5-LO and 8% for CO. [b] Percent inhibition ±SEM of edema in the carageenan footpad edema test. [c] The dose (mg/kg) of test compound causing 40% inhibition of induced edema in the mycobacterium footpad edema test; 95% confidence limits are in parentheses. [d] Percent inhibition at 10 μM screening concentration. [e] Data from the choline salt **11d**. [f] Inactive (N) is defined as <25% inhibition at a dose of 30 mg/kg po. [g] Data from choline salt **15b**. [h] Inactive (N) is defined as <30% inhibition at a dose of 10 mg/kg po. [i] Inactive (N) is defined as <50% inhibition at a screening concentration of 10 μM. [j] Data from the choline salt **15g**.

h. After cooling to room temperature, the precipitated product was filtered and washed with EtOH. Recrystallization from DMF/EtOAc gave 2.4 g (69%) of **8a**: mp 308–310 °C; IR 3541, 1679, 1591, 1260 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.44 (s, 18H, t-Bu), 3.14 (s, 3H, Me), 7.41 (s, 2H, ArH), 7.71 (s, 1H, olefin). Anal. ($C_{19}H_{28}N_2O_2S$) C, H, N.

Method G. (*Z*)-5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2-(hydroxymethylamino)-4(5*H*)-thiazolone (8e). A mixture of *N*-methylhydroxylamine hydrochloride (12.5 g, 150 mmol), $BaCO_3$ (14.8 g, 75 mmol), EtOH (50 mL), and H_2O (50 mL) was stirred at room temperature for 10 min. Additional EtOH (600 mL) and **6c** (17.5 g, 50 mmol) were added, and the new mixture was stirred at reflux for 8 h. The cooled reaction mixture was filtered and the filtrate evaporated. The residue was stirred in ice H_2O, and the resulting solid was filtered, washed with H_2O, and dissolved in CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to give 19 g of residue. Purification by flash chromatography (CH_2Cl_2, followed by 9:1 CH_2Cl_2/MeOH), followed by recrystallization from MeOH/EtOAc gave 8.6 g (48%) of **8e**: mp 199–200 °C; IR 3627, 1613, 1438, 1210 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.42 (s, 18H, t-Bu), 3.54 (s, 3H, Me), 7.38 (s, 2H, ArH), 7.58 (s, 1H, olefin), 7.63 (br s, <1H, phenol OH), 11.80 (br s, <1H, NOH). Anal. ($C_{19}H_{26}N_2O_3S$) C, H, N.

Method H. (*Z*)-5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2-(methoxymethylamino)-4(5*H*)-thiazolone Hydrochloride (8h). A solution of **8g** (8.3 g, 22 mmol) in CH_2Cl_2 (50 mL) was treated with excess ethereal HCl. The precipitated salt was filtered and recrystallized from CH_2Cl_2/MeOH/Et_2O to yield 6.0 g (66%) of salt **8h**: mp 177–179 °C; IR 3417, 1734, 1588, 1422 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.42 (s, 18H, t-Bu), 3.56 (s, 3H, NMe), 3.92 (s, 3H, OMe), 7.40 (s, 2H, ArH), 7.67 (s, 1H, olefin). Anal. ($C_{20}H_{28}N_2O_3S$·HCl) H, N; C: calcd, 58.17; found, 58.60.

Method I. (*Z*)-*N*-[5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-4,5-dihydro-4-oxo-2-thiazolyl]-*N*′,*N*′-dimethylguanidine (8m). A mixture of 1,1-dimethylguanidine sulfate (6.7 g, 25 mmol) and t-BuOK (4.8 g, 43 mmol) in EtOH (500 mL) was stirred at room temperature for 15 min. After the addition of **7a** (7.3 g, 20 mmol), the new mixture was stirred at reflux for 6 h. The cooled mixture was evaporated, and the residue was partitioned between Et_2O and ice H_2O made slightly acidic with 1.0 N HCl. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. Purification of the residue by flash chromatography (CH_2Cl_2, then 9:1 CH_2Cl_2/MeOH elution) followed by recrystallization from EtOH/DMF gave 5.1 g (63%) of **8m**: mp 293–295 °C; IR 3620, 1660, 1513, 1261 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.43 (s, 18H, t-Bu), 3.07 (s, 3H, NMe), 3.14 (s, 3H, NMe), 7.41 (s, 2H, ArH), 7.85 (s, 1H, olefin). Anal. ($C_{21}H_{30}N_4O_2S$) C, H, N.

(*Z*)-5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2-[[2-(dimethylamino)ethyl]amino-4(5*H*)-thiazolone (8n). A mixture of **6c**[15] (7.0 g, 20 mmol) and (*N*,*N*-dimethylamino)ethylamine (5.3 g, 60 mmol) in EtOH (250 mL) was stirred at reflux for 8 h. The solvent was evaporated and the residue recrystallized first from toluene and then from MeOH/EtOAc/toluene to give 3.4 g (42%) of **8n**: mp 209–211 °C; IR 1684, 1628, 1440, 1315 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.42 (s, 18H, t-Bu), 2.19 (s, 6H, NMe), 2.46 (t, J = 6 Hz, 2H, CH_2), 3.59 (t, J = 6 Hz, 2H, CH_2), 7.36 (s, 2H, ArH), 7.53 (s, 1H, olefin). Anal. ($C_{22}H_{33}N_3O_2S$) C, H, N.

(*Z*)-4-[[[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-4,5-dihydro-4-oxo-2-thiazolyl]amino]butanoic Acid (8o). A mixture of 4-aminobutyric acid (1.9 g, 18 mmol) and t-BuOK (1.4 g, 12 mmol) in EtOH (250 mL) was stirred at room temperature for 30 min and then treated with **7a** (3.6 g, 9.9 mmol). The new mixture was stirred at reflux for 22 h, cooled, and evaporated. The residue was treated with cold H_2O made slightly acidic with 2.0 N HCl. The insoluble solid was filtered and washed with H_2O. The crude product was dissolved in CH_2Cl_2/THF, and the solution was dried (Na_2SO_4) and evaporated. The residue was digested in warm Et_2O and filtered. Recrystallization of the final solid from THF/EtOAc gave 2.7 g (65%) of **8o**: mp 239–240 °C; IR 3621, 1717, 1570, 1423 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.42 (s, 18H, t-Bu), 1.84 (m, 2H, $CH_2CH_2CH_2$), 2.33 (t, J = 7 Hz, 2H, CH_2CO_2H), 3.52 (m, 2H, $NHCH_2$), 7.36 (s, 2H, ArH), 7.56 (s, 1H, olefin), 9.54 (m, 1H, NH), 12.00 (br s, <1, CO_2H). Anal. ($C_{22}H_{30}N_2O_4S$) C, N, H.

(*Z*)-[5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-4,5-dihydro-4-oxo-2-oxazolyl]cyanamide (8p). A suspension of cyanamide (0.38 g, 9.0 mmol) in EtOH (50 mL) was cooled in ice and treated in small portions with t-BuOK (0.93 g, 8.3 mmol). After the mixture was stirred for 15 min, **7b** (2.6 g, 7.5 mmol) was added, followed by additional EtOH (25 mL). The mixture was stirred at reflux for 3 h and then cooled, and the precipitated potassium salt of the product was filtered and washed with Et_2O. The salt was suspended in H_2O (100 mL) and acidified with 1.0 mL of HOAc. The mixture was stirred for 30 min and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated to yield 1.0 g (38%) of **8p**. Sample recrystallized from EtOAc/hexane: mp 220 °C dec; IR 3545, 2219, 1755, 1431 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.41 (s, 18H, t-Bu), 6.88 (s, 1H, olefin), 7.71 (s, 2H, ArH), 7.72 (s, 1H, OH). Anal. ($C_{19}H_{23}N_3O_3$) C, H, N.

Method J. (*Z*)-[5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-4,5-dihydro-4-oxo-2-oxazolyl]guanidine (8r). A solution of guanidine hydrochloride (2.0 g, 21 mmol) in EtOH (75 mL) was cooled in ice and treated in portions with t-BuOK (2.2 g, 20 mmol). The mixture was stirred for 15 min

Table 5. Physicochemical Data for Benzylidene Derivatives

no.	method	yield, %	mp, °C	recryst solvent	formula	anal.
6a	A	26	238–240	EtOH	$C_{18}H_{23}NO_3S$	C,H,N
6b[a]	B	98	215 dec	*b*	$C_{18}H_{22}NO_3S \cdot C_5H_{14}NO$	C,H,N
6c	A	30	248–249	EtOAc	$C_{18}H_{23}NO_2S_2$	C,H,N
6d[a]	B	93	196 dec	*b*	$C_{18}H_{22}NO_2S_2 \cdot C_5H_{14}NO$	C,N; H[c]
6e	A	38	277–279	EtOAc/MeOH	$C_{18}H_{24}N_2O_2S$	C,H,N
6f[d]	*e*	90	252 dec	MeOH/Et_2O	$C_{18}H_{24}N_2O_2 \cdot CH_3SO_3H$	C,H,N
6g	*e*	41	240 dec	MeCN/H_2O	$C_{18}H_{23}NO_3S$	C,H,N
6h[a]	C	70	167 dec	acetone/t-BuOMe	$C_{18}H_{22}NO_3S \cdot C_5H_{14}NO$	C,H,N
6i	D	10	211–212	EtOH	$C_{19}H_{26}N_2O_3$	C,H,N
6j	D	62	242–244	MeCN	$C_{18}H_{26}N_2O_2S$	H,N; C[f]
6k	A	7	237–239	EtOH	$C_{19}H_{25}NO_2S$	C,H,N
7a	E	55	159–160	MeOH	$C_{18}H_{25}NO_2S_2$	C,H,N
7b	*e*	83	164–166	EtOAc/hexane	$C_{18}H_{25}NO_3S$	C,H,N
7c	E	70	177–179	EtOAc	$C_{20}H_{28}N_2O_2S \cdot 0.25CH_3CN$	C,H,N
8a	F	69	308–310	DMF/EtOAc	$C_{18}H_{26}N_2O_2S$	C,H,N
8b	F	77	247–249	MeOH	$C_{20}H_{28}N_2O_2S$	C,H,N
8c	G	30	241 dec	Et_2O/toluene	$C_{18}H_{24}N_2O_3S \cdot CH_3OH$	C,H,N
8d[a]	C	27	178–180	MeOH/EtOAc	$C_{18}H_{23}N_2O_3S \cdot C_5H_{14}NO$	H,N; C[g]
8e	G	48	199–200	MeOH/EtOAc	$C_{18}H_{26}N_2O_3S$	C,H,N
8f	I	77	245–246	MeOH	$C_{19}H_{26}N_2O_3S$	C,H,N
8g	G	27	187–189	CH_2Cl_2/EtOAc	$C_{20}H_{28}N_2O_3S$	C,H,N
8h[h]	H	66	177–179	CH_2Cl_2/MeOH/Et_2O	$C_{20}H_{23}N_2O_3S \cdot HCl$	H,N; C[i]
8i	K	70	240–242	MeOH	$C_{18}H_{23}N_3O_2S \cdot 0.25CH_3OH$	C,H,N
8j[a]	C	89	189–190	MeOH/EtOAc	$C_{19}H_{22}N_3O_2S \cdot C_5H_{14}NO$	C,H,N
8k	I	31	267–268	MeOH/EtOAc	$C_{18}H_{26}O_2S \cdot 0.5H_2O$	C,H; N[j]
8l[h]	H	24	217–220	MeOH/EtOAc	$C_{19}H_{26}N_4O_2S \cdot HCl$	C,H,N
8m	I	63	293–295	DMF/EtOH	$C_{21}H_{30}N_4O_2S$	C,H,N
8n	*e*	42	209–211	MeOH/EtOAc/toluene	$C_{22}H_{33}N_3O_2S$	C,H,N
8o	*e*	65	239–240	THF/EtOAc	$C_{22}H_{30}N_2O_4S$	C,H,N
8p	*e*	38	220 dec	EtOAc/hexane	$C_{18}H_{23}N_3O_3$	C,H,N
8q[a]	C	53	85 dec	*b*	$C_{18}H_{22}N_3O_3 \cdot C_5H_{14}NO \cdot 0.5H_2O$	C,H,N
8r	J	55	258 dec	MeCN/H_2O	$C_{18}H_{26}N_4O_3$	C,H,N
8s[d]	e	83	278 dec	*b*	$C_{18}H_{26}N_4O_3 \cdot CH_3SO_3H$	C,H,N
8t	K	51	257–259	MeCN	$C_{20}H_{26}N_4O_2$	C,H,N
8u[a]	B	94	185–186	*b*	$C_{20}H_{25}N_4O_2 \cdot C_5H_{14}NO$	C,H,N
8v	J[k]	47	288–290	EtOH/DMF	$C_{20}H_{26}N_5O_2$	C; H,N[l]
9a	*e*	53	239 dec	EtOAc/hexane	$C_{18}H_{23}NO_4$	C,H,N
9b[a]	C	60	165 dec	acetone/t-BuOMe	$C_{18}H_{22}NO_4 \cdot C_5H_{14}NO$	C,H,N
11a	L	67	253–254	*b*	$C_{19}H_{25}NO_3S$	C,H,N
11b[a]	B	96	191 dec	*b*	$C_{19}H_{24}NO_3S \cdot C_5H_{14}NO$	C,H,N
11c	L	76	244–246	MeCN	$C_{19}H_{25}NO_2S_2$	C,H,N
11d[a]	B	77	213 dec	*b*	$C_{18}H_{24}NO_2S_2 \cdot C_5H_{14}NO$	C,H,N
12	E	93	224–226	MeCN	$C_{20}H_{27}NO_2S_2$	C,H,N
13a	K	88	229–230	MeCN	$C_{20}H_{25}N_3O_2S$	C,H,N
13b	J	92	277 dec	MeCN/EtOH	$C_{20}H_{23}N_4O_2S$	C,H,N
15a	D	54	228–229	MeOH	$C_{22}H_{15}NO_3S$	C; H,N[m]
15b[a]	B	91	113–125	*b*	$C_{22}H_{14}NO_3S \cdot C_5H_{14}NO \cdot 0.5H_2O$	C,H,N
15c	D	98	201–203	*b*	$C_{18}H_{19}NO_3S$	C,H,N
15d	D	85	>285	*b*	$C_{10}H_5I_2NO_3S$	C,H,N
15e	D	89	>290	*b*	$C_{10}H_7NO_3S$	C,H,N
15f	D	56	193–197	MeOH	$C_{18}H_{23}NO_2S$	C,H,N
15g[a]	B	88	216 dec	*b*	$C_{18}H_{22}NO_2S \cdot C_5H_{14}NO$	C,H,N

[a] This compound is the choline salt of the preceding compound in the table. [b] Compound not recrystallized. [c] H: calcd, 8.02; found, 7.59. [d] This compound is the methanesulfonate salt of the preceding compound in the table. [e] See the Experimental Section. [f] C: calcd, 65.86; found 66.27. [g] C: calcd, 61.17; found, 60.60. [h] This compound is the hydrochloride salt of the preceding compound in the table. [i] C: calcd, 58.17; found, 58.60. [j] N: calcd, 14.61; found, 14.12. [k] Heating time increased to 21 h. [l] C: calcd, 64.67; found, 65.08. [m] C: calcd, 70.76; found, 70.31.

and then rapidly filtered into a suspension of **7b** (4.6 g, 13 mmol) in EtOH (75 mL). The new reaction mixture was stirred at reflux for 3 h, cooled, and filtered. The filtrate was condensed 50% and added to ice and H_2O (500 g). The precipitated solid was filtered, washed with H_2O, and dissolved in EtOAc (200 mL). The solution was washed with brine, dried (Na_2SO_4), and evaporated. Purification of the residue by flash chromatography (10% MeCN in EtOAc elution) gave 2.6 g (55%) of **8r**. Sample recrystallized from MeCN/H_2O: mp 258 °C dec; IR 1708, 1653, 1560, 1301 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40 (s, 18H, t-Bu), 6.43 (s, 1H, olefin), 7.33 (br s, 2H, NH), 7.40 (s, 1H, OH), 7.56 (s, 2H, ArH), 8.18 (br s, 2H, NH). Anal. ($C_{19}H_{26}N_4O_3$) C, H, N.

(*Z*)-*N*-[5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-4,5-dihydro-4-oxo-2-oxazolyl]guanidinium Methanesulfonate Salt (8s). A solution of **8r** (1.9 g, 5.3 mmol) in i-PrOH (100 mL) was filtered warm and treated immediately with a solution of methanesulfonic acid (0.40 mL, 0.59 g, 6.2 mmol) in a few mL of i-PrOH. Upon cooling, the precipitated salt was filtered and washed with Et_2O to yield 2.0 g (83%) of **8s**: mp 278 °C dec; IR 1773, 1669, 1432, 1172 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40 (s, 18H, t-Bu), 2.34 (s, 3H, Me), 6.83 (s, 1H, olefin), 7.63 (s, 2H, ArH), 7.67 (s, 1H, OH), 8.29 (br s, 2H, NH), 8.55 (br s, 2H, NH). Anal. ($C_{19}H_{26}N_4O_3 \cdot CH_3SO_3H$) C, H, N.

Method K. (*Z*)-[5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-4,5-dihydro-1-methyl-4-oxo-1*H*-imidazol-2-yl]cyanamide (8t). Cyanamide (0.20 g, 4.8 mmol) was added to a mixture of **7c** (1.5 g, 4.2 mmol) and t-BuOK (0.50 g, 4.5 mmol) in EtOH (25 mL). The mixture was stirred at reflux for 2.5 h, cooled, and added to H_2O (200 mL). The mixture was acidified with H_3PO_4, and the precipitated product was filtered and washed with H_2O. Recrystallization from MeCN gave 0.70 g (51%) of **8t**: mp 257–259 °C; IR 3622, 2198, 1745, 1388 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.41 (s, 18H, t-Bu), 3.21 (s, 3H, NMe), 6.69 (s, 1H, olefin), 7.48 (s, 1H, OH), 7.99 (s, 2H, ArH). Anal. ($C_{20}H_{26}N_4O_2$) C, H, N.

(*Z*)-5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-oxazolidinedione (9a). A solution of **7b** (3.0 g, 8.6 mmol) in warm EtOH (25 mL) was diluted with warm H_2O

(8 mL). The solution was treated over 10 min with 5.0 mL of concentrated HCl. After the mixture was stirred for 4 h, the precipitated product was filtered and washed with hexane to yield 1.4 g (51%) of **9a**. Sample recrystallized from EtOAc/hexane: mp 239 °C dec; IR 3613, 1827, 1664, 1332 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40 (s, 18H, t-Bu), 6.69 (s, 1H, olefin), 7.58 (s, 1H, OH), 7.61 (s, 2H, ArH), 12.30 (br s, 1H, NH). Anal. ($C_{18}H_{23}NO_4$) C, H, N.

Method L. (*Z*)-5-[1-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethylene]-2,4-thiazolidinedione (11a). A mixture of **10**[16] (4.0 g, 16 mmol), **5a** (3.0 g, 26 mmol), and NH_4OAc (1.9 g, 25 mmol) in toluene (12 mL) was stirred at reflux for 48 h. The reaction mixture was cooled and evaporated. The residue was digested briefly in warm MeOH (20 mL), cooled, and filtered to provide 3.7 g (67%) of **11a**: mp 253–254 °C; IR 3613, 1734, 1575, 1434 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.39 (s, 18H, t-Bu), 2.66 (s, 3H, olefin Me), 7.21 (s, 2H, ArH), 7.46 (br s, 1H, OH), 12.17 (br s, 1H, NH). Anal. ($C_{19}H_{25}NO_3S$) C, H, N.

3,5-Diphenyl-4-hydroxybenzaldehyde (14a). A stirred mixture of 2,6-diphenylphenol (5.0 g, 20 mmol) and hexamethylenetetramine (5.5 g, 39 mmol) was treated dropwise with HOAc (45 mL). After 20 min, H_2O (10 mL) was added, and the mixture heated to reflux. Distillate was removed until the reaction pot temperature was 114 °C; reflux was then maintained for 6 h. The cooled mixture was treated with H_2O (20 mL), and the precipitated product was filtered and washed with H_2O. Recrystallization from EtOH gave 3.5 g (64%) of **14a**: mp 168–170 °C; IR 1673, 1583, 1429, 1325 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.37–7.61 (m, 10H, ArH), 7.76 (s, 2H, ArH), 9.53 (br s, 1H, OH), 9.93 (s, 1H, CHO). Anal. ($C_{19}H_{14}O_2$) C, H.

Pharmacology. The whole cell 5-lipoxygenase and cyclooxygenase, carrageenan footpad edema, microbacterium footpad edema, and gastric ulcerogenicity assays were performed as previously described.[7a]

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