Design of 5-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-1,3,4-thiadiazoles, -1,3,4-oxadiazoles, and -1,2,4-triazoles as Orally-Active, Nonulcerogenic Antiinflammatory Agents

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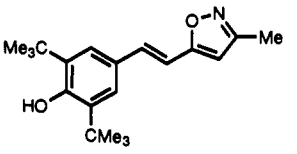
To discover dual inhibitors of 5-lipoxygenase (LO) and cyclooxygenase (CO) with improved pharmacokinetic properties, we have designed and synthesized series of 1,2,4-triazole, 1,3,4-oxadiazole, and 1,3,4-thiadiazole di-*tert*-butylphenol derivatives which exhibit a wide range of log *P* (2.3 to >4) and pK_a (5.5–12) values. From this work 5-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-thiadiazole-2(3*H*)-thione, choline salt (**12a**, CI-986) was found to be a potent inhibitor of 5-LO (IC_{50} = 2.8 μM) and CO (IC_{50} = 0.8 μM), orally active in rat models of inflammation and nonulcerogenic.

Cyclooxygenase (CO) and 5-lipoxygenase (5-LO) are enzymes which catalyze the rate-limiting steps in the biosynthesis of prostaglandins and leukotrienes, respectively, from arachidonic acid.[2] Nonsteroidal antiinflammatory drugs (NSAIDs), widely used for the treatment of inflammatory diseases, exert their antiinflammatory effect primarily by inhibiting cyclooxygenase, thereby blocking the biosynthesis of prostaglandins.[3] Leukotrienes, the products of 5-lipoxygenase, also have been implicated in inflammatory processes.[4] As a result, many laboratories are pursuing the discovery and development of selective 5-LO inhibitors and CO/5-LO dual inhibitors as antiinflammatory agents which may have improved efficacy over NSAIDs.

Major side effects of NSAIDs include dyspepsia, gastric ulceration, and nephrotoxicity.[3] It has been hypothesized that prostaglandins are cytoprotective, and therefore the undesirable gastrointestinal side effects of NSAIDs are due to their ability to block prostaglandin synthesis.[5] In addition, there is evidence that suggests leukotrienes promote gastric ulceration.[6] On the basis of this information, we reasoned that a dual inhibitor of cyclooxygenase and 5-lipoxygenase would provide an antiinflammatory agent with not only improved efficacy, but with fewer side effects.

Toward this end, we recently have reported the discovery of a series of styrylpyrazoles, -isoxazoles, and -isothiazoles which were dual inhibitors of cyclooxygenase and 5-lipoxygenase in rat basophilic leukemia cells. From this series, isoxazole **1** was found to be nonulcerogenic and showed modest, oral activity in various animal models of inflammation.[7a] It was shown that the 3,5-di-*tert*-butyl-4-hydroxy substitution pattern on the benzene ring was optimal to obtain the desired biological profile. KME-4 (**2**)[8] and E-5110 (**3**)[9] are examples of di-*tert*-butylphenols which have been evaluated in the clinic as antiinflammatory agents.

Further evaluation of **1** revealed two major problems: (1) low oral bioavailability due to its poor systemic absorption and (2) long plasma half-life.[10] We hypothesized that these problems were due to the lipophilicity of the molecule (log *P* > 4.5). Our strategy for overcoming these problems was to modulate the physical properties of **1** by modifying the styryl heterocyclic portion of the molecule while leaving the critical di-*tert*-butylphenol portion intact (Figure 1). For this purpose, we designed compounds in which the double bond linker was removed and the methyl group and a ring carbon of the isoxazole ring were replaced with a nitrogen, oxygen, or sulfur. This strategy was designed to: (1) reduce lipophilicity and (2) introduce an ionizable functionality to aid in absorption and elimination of the compounds. These modifications led to series of 5-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-oxadiazoles, -1,2,4-triazoles, and -1,3,4-thiadiazoles as target compounds. Unangst and co-workers have recently reported on a series of 1,2,4-oxadiazoles and 1,2,4-thiadiazoles based on this strategy.[7b] In addition, we prepared several styryl analogs for comparative purposes. The syntheses, physical properties, biological activities, and structure–activity relationships of these compounds will be described in this paper.



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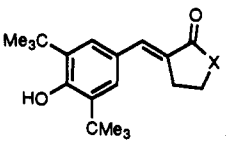

2 X = O
3 X = NOMe

Chemistry

The synthesis of 1,3,4-oxadiazoles, 1,2,4-triazoles, and 1,3,4-thiadiazoles are outlined in Schemes I–IV. The log *P* and pK_a values for these compounds are recorded in Table I.

Oxadiazoles. Hydrazides **15a** and **15b**, prepared from benzoic acid **13a** and cinnamic acid **13b**, were used as key intermediates for the preparation of 1,3,4-oxadiazoles **4–6** (Scheme I). Treatment of **15** with cyanogen bromide under aqueous basic conditions gave aminooxadiazole **4** in 50–60% yield. Oxadiazolone **5** was prepared by treating **15** with 1,1-carbonyldiimidazole in the presence of triethylamine. Hydrazide **15** was converted to oxadiazolethione **6** using carbon disulfide under basic conditions, followed by acid workup.

Triazoles. To prepare the 3-aminotriazole **7a**, it was first necessary to protect the phenolic group of **16** with a

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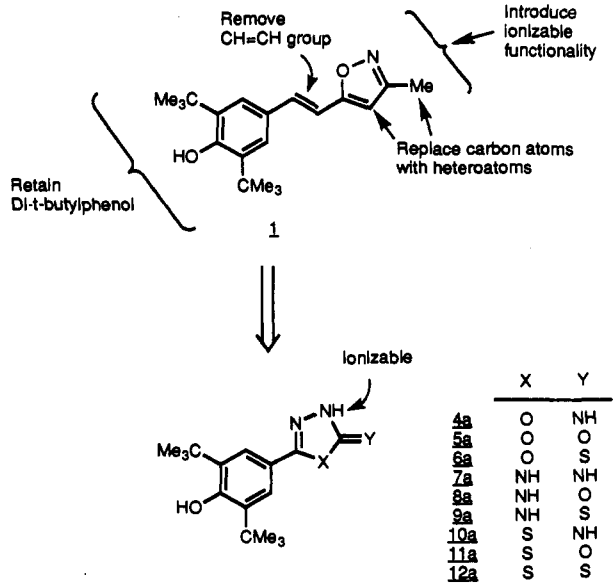
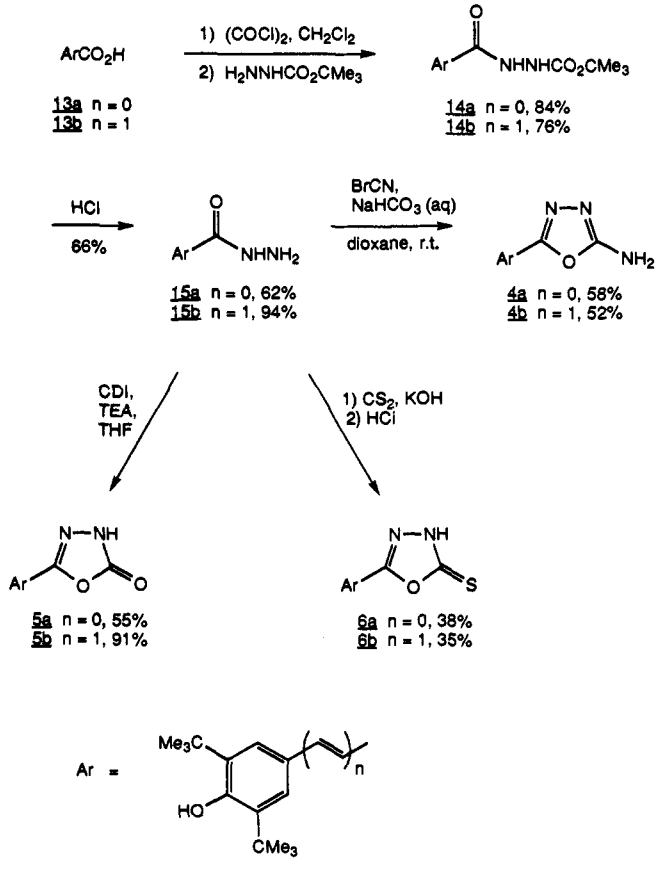


	X	Y
4a	O	NH
5a	O	O
6a	O	S
7a	NH	NH
8a	NH	O
9a	NH	S
10a	S	NH
11a	S	O
12a	S	S

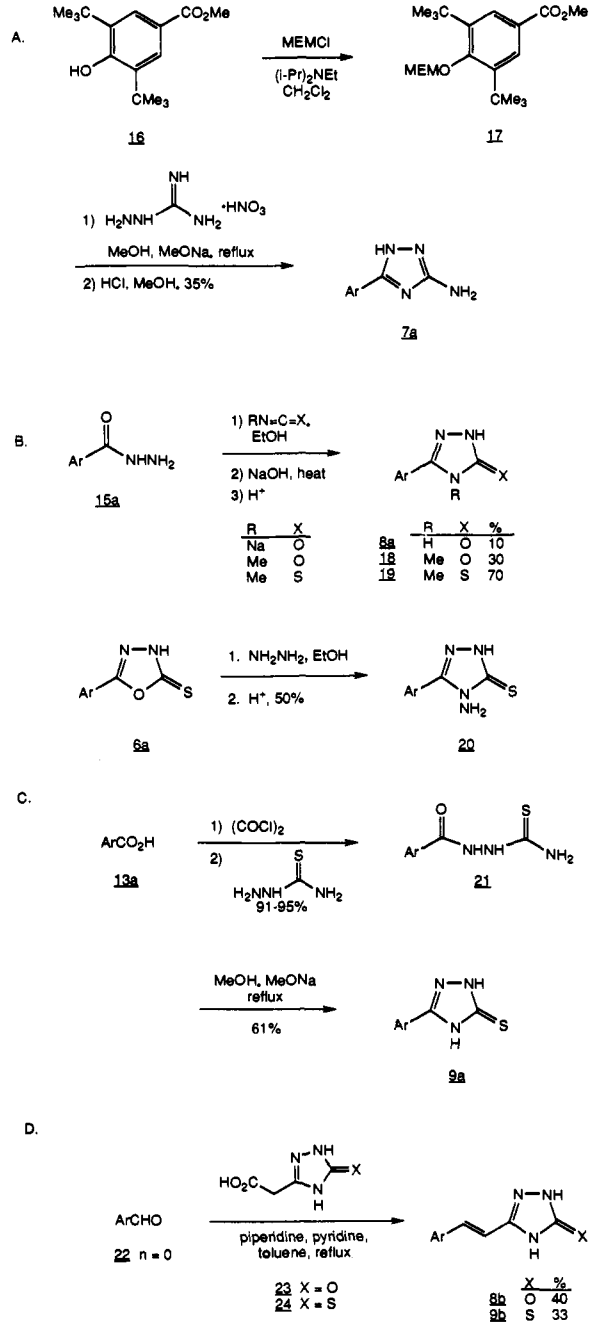
Figure 1. Strategy to improve pharmacokinetic properties.

Scheme I. Synthesis of 1,3,4-Oxadiazoles



MEM group.[12,13] The reaction of the MEM-protected compound **17** with aminoguanidine,[14] followed by removal of the MEM group with methanolic HCl, gave **7a** in 48% yield (Scheme IIA).[13] All attempts to directly prepare the 3-aminotriazole **7a** from carboxylic acid **13a**, the carbonyl chloride of **13a**, or ester **16** were unsuccessful. In Scheme IIB, hydrazide **15a** also was used to prepare triazolone **8a**, 4-methyltriazolone **18**, and 4-methyltriazolethione **19**[15] from the appropriate isocyanate. 4-Aminotriazolethione **20** was prepared from oxadiazolethione **6a** and hydrazine.[16] To complete the synthesis of the directly attached triazoles, benzoic acid **13a** was converted to **21** which was cyclized with sodium methoxide to give triazolethione **9a**[17] (Scheme

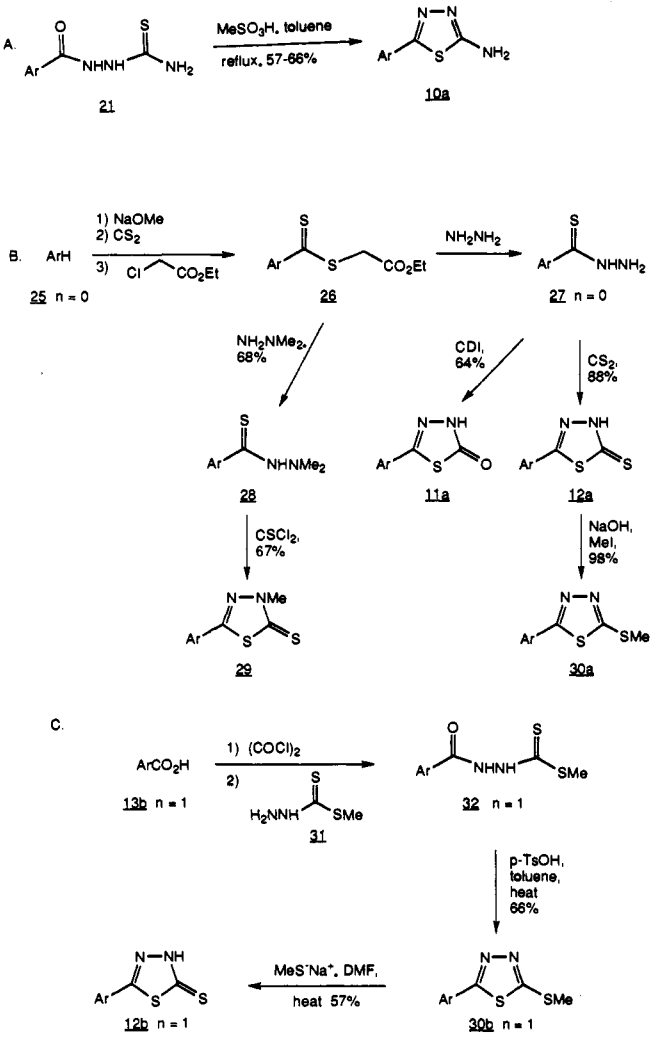
Scheme II. Synthesis of 1,2,4-Triazoles



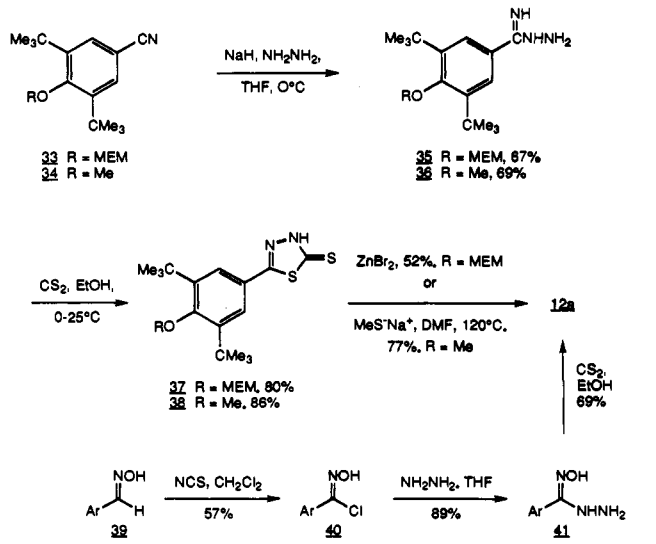
IIC). The styryl triazoles **8b** and **9b** were prepared from benzaldehyde **22**[12] and triazoleacetic acids **23** and **24**[18] in a Knoevenagel reaction (Scheme IID).

Thiadiazoles. 2-Aminothiadiazole **10a** was prepared by an acid-promoted cyclization of intermediate **21**[19] (Scheme IIIA). The known thiohydrazide **27**[20] was converted to thiadiazolone **11a** and thiadiazolethione **12a** with 1,1-carbonyldiimidazole and carbon disulfide,[21] respectively (Scheme IIIB). The 3-NMe analog of **12a**, **29** was prepared from **26** by the reaction of 1,1-dimethylhydrazine to give **28** followed by treatment with thiophosgene. The *S*-methyl compound **30a** was prepared from **12a** with NaOH and MeI. The styryl thiadiazolethione **12b** was prepared from cinnamic acid **13b**. The acid chloride of **13b** was treated with **31**[22] to give intermediate **32** which was cyclized with *p*-TsOH to give 2-(methylthio)thiadiazole **30b** in 73% yield. Deprotection of the 2-thio substituent with sodium thiomethoxide gave **12b** (Scheme IIIC). Alternate syntheses of **12a** are outlined in Scheme

Scheme III. Synthesis of 1,3,4-Thiadiazoles



Scheme IV. Alternate Syntheses of 12a



IV. Nitriles[12] **33** and **34** were reacted with sodium hydrazide[23] to give iminohydrazines **35** and **36**, respectively. Treatment of the iminohydrazines with carbon disulfide provided the O-protected thiadiazolethiones **37** and **38**.[21] Removal of the protecting groups with $ZnBr_2$,[13] for **37** (R = MEM) or sodium thiomethoxide for **38** (R = Me) gave **12a**. **12a** was also efficiently prepared from oxime **39**[12] in three steps.[24] The oxime **39** was converted to the chlorooxime **40** with *N*-chlorosuccinimide (NCS) which was then converted to (hydroxyimino)hydrazine **41** with hydrazine. Treatment of **41** with carbon disulfide afforded **12a** in good yield.

Physical Properties. The log *P* and pK_a values of these compounds are recorded in Table I. Following the strategy in Figure 1, we were able to successfully reduce the lipophilicity as compared to **1** and introduce an ionizable functionality into the target molecules. The log *P* of the target compounds ranged from 2.3 to >4.0, and the pK_a values ranged from 5.5 to 12.

Biological Results and Discussion

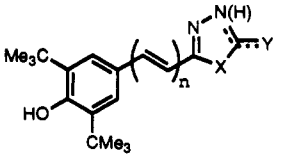
The ability of these target compounds to inhibit 5-LO and CO was determined by measuring the reduction of LTB_4 and $PGF_{2\alpha}$ production, respectively, in intact basophilic rat leukemia cells (Table I).[7] The permutations in Figure 1, where X and Y are NH, O, or S, result in a set of nine compounds **4a–12a.** Of these nine compounds, seven were potent dual inhibitors. The two remaining compounds, 3-aminotriazole **7a** and thiadiazolone **11a**, were selective inhibitors of 5-LO. The three triazoles **18**, **19**, and **20**, bearing a substituent of the ring nitrogen in the 4-position were inactive in both assays. Interestingly, the three methylated forms of **12a**, **29** (3-NMe), **30a** (SMe), and **38** (OMe), were potent dual inhibitors. Four of the six styryl analogs, **6b**, **8b**, **9b**, and **12b**, were more potent 5-LO inhibitors, and six of the styryl compounds, **4b**, **5b**, **6b**, **8b**, **9b**, and **12b**, were less potent CO inhibitors than the corresponding compounds without the double bond linker. This may be due to the fact that these styryl compounds were generally more lipophilic. Styryl compound **30**, in which the exocyclic sulfur is methylated, is inactive in both assays. Our active compounds exhibited similar potency to the standards KME-4 (**2**) and E-5110 (**3**) in the 5-LO assay and were less potent in the CO assay; thus, they were more "balanced" inhibitors of 5-LO and CO than the standards.

The in vivo (PO) efficacy of the potent dual inhibitors was evaluated in the carrageenan footpad edema (CFE) model,[25] an acute model of inflammation. Only the oxadiazoles **4a** and **6a** and the thiadiazoles **10a** and **12a** were orally active (Table II). These compounds did not contain the double bond linker, and the exocyclic heteroatom, Y, was either NH or S. The di-*tert*-butylphenols **2** and **3** were less active in this assay. Further evaluation in the *Mycobacterium* footpad edema (MFE) model,[7] a subacute (3-day) inflammation model, found that only the thiadiazoles **10a** and **12a** were active (Table II). In contrast to **2** and **3**, compound **10a** showed only one incidence of ulcers ($N = 10$) when administered orally to fasted rats[7] at a 200 mg/kg dose, and **12a**, as the sodium or the choline salt, showed no ulcers at this dosage. **12a** was chosen for evaluation in the adjuvant induced polyarthritis assay,[26] a chronic model of inflammation. The choline salt **12a**, as (CI-986),[27] was found to inhibit inflammation in this assay when dosed orally with ID_{40}s of 7.2 when give prophylactically and 4.9 with therapeutic administration. Compound **12a** formed a water-soluble (1.7 mg/mL), nonhygroscopic salt with choline, whereas aminothiadiazole **10a** would not form a salt with either organic or inorganic acids and bases.

Conclusions

Using a divergent synthetic strategy we have synthesized a series of 3,5-di-*tert*-butylphenols which are potent dual

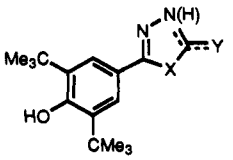
Table I. 5-LO and CO Activity in Rat Basophilic Leukemia Cells



no.	n	X	Y	log P[a]	pK$_a$[b]	IC$_{50}$ (μM)[c,d] 5-LO	IC$_{50}$ (μM)[c,d] CO
1				>4.0	>10.0	2.4	1.5
2	KME-4			>4.0	*i*	2.5	0.15
3	E-5110			>4.0	*i*	4.3[g]	0.04
	meclomen			*i*	*i*	24	0.10
4a	0	O	NH_2	3.7	11.3	0.70	2.4
4b	1	O	NH_2	*i*	11.7	1.1	8.0
5a	0	O	=O	3.4	8.7	1.4	2.5
5b[e]	1	O	=O	3.4	8.5	0.21	>32
6a	0	O	=S	2.3	5.5	4.8[f]	3.7[f]
6b	1	O	=S	3.0	5.4	0.58	9.4
7a	0	NH	NH_2	3.1	12.0	5.1	>30
8a	0	NH	=O	3.1	10.2	4.5	5.5
8b	1	NH	=O	3.8	10.3	1.6	>32
9a	0	NH	=S	2.4	8.5	11	0.78
9b	1	NH	=S	3.1	8.4	2.4	6.7
10a	0	S	NH_2	3.7	*i*	1.4[g]	0.13
11a	0	S	=O	4.0	9.0	5.9	>16
12a[f]	0	S	=S	2.7	6.5	2.8	0.80
12b	1	S	=S	>4.0	6.5	1.8	5.2
18	0	NMe	=O	3.2	*i*	*d*	*d*
19	0	NMe	=S	3.7	insol	>32	>32
20	0	NNH_2	=S	3.3	9.2	>32	>32
29[m]	0	S	=S	*i*	*i*	5.0	0.65
30a	0	S	SMe	>4.0	10.7	1.2	0.41
30b	1	S	SMe	*i*	*i*	>10	>10
38[h]	0	S	=S	*i*	*i*	0.92	0.35

[a] log *P*-values determined using HPLC correlation method at pH 7.4; see Experimental Section for conditions. The precision is estimated to be ±0.2 log *p* units. [b] pK_a values determined in 67% DMF/H_2O. [c] Concentration of test compounds causing 50% inhibition of LTB_4 (5-LO) or $PGF_{2\alpha}$ (CO) production. Standard errors average 16% of the values shown for 5-LO and 11% for CO. [d] Solubility of compound limited its assay concentration to 2.5 μM. [e] Sodium salt. [f] Choline salt. [g] Average of two determinations. [h] 3-NMe analog of **12a**. [i] Not determined. [j] OMe analog of **12a**.

Table II. In Vivo Antiinflammatory Activity



no.	X	Y	ID$_{40}$ (mg/kg) CFE[a]	ID$_{40}$ (mg/kg) MFE[b]	UD$_{50}$ (mg/kg) ulcers[c]
1			*d*	33	0% at 200[e]
2	KME-4		>10[h]	3.7 (2.0–7.2)	93.1
3	E-5110		24.1[h]	1.9 (1.1–2.9)	10% at 10[e]
	meclomen		5.6 (2.8–50.5)	0.35 (0–1.1)	36.2
4a	O	$-NH_2$	8.2 (5.2–21.4)	*d*	*d*
6a[f]	O	=S	3.9 (2.5–7.0)	59.9 (22.7–1729.7)	*d*
10a	S	$-NH_2$	1.9 (0.9–8.0)	2.3 (0.5–4.5)	10% at 200[e]
12a[f]	S	=S	1.1 (0.8–1.4)	7.8 (6.4–10.5)	0% at 200[e,g]

[a] Carrageenan footpad edema (po). [b] Mycobacterium footpad edema (po). [c] Acute gastric ulcerogenicity (n = 10 rats per experimental group). [d] Not determined. [e] Gastric ulcerogenicity data are presented as percent rats with ulcers at indicated dose (mg/kg), po (n = 10 rats per experimental group). [f] Sodium salt. [g] Choline salt. [h] 95% confidence limits could not be estimated from the data.

inhibitors of 5-lipoxygenase and cyclooxygenase. By design these compounds exhibited a wide range of log *P* (2.3 to >4.0) and pK_a (5.5–12) values and allowed us to explore the effects of these physical properties on oral activity in in vivo models of inflammation. As a result, we have discovered that the choline salt of **12a** is nonulcerogenic, orally-active antiinflammatory agent.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The ^{1}H NMR spectra were determined at 200 MHz on a Varian XL-200 or at 250 MHz on a Brukër AM-250 spectrometer with tetramethylsilane as an internal standard. The infrared spectra were recorded on a Digilab FTS-14 or a Nicolet FT-IRMS-1 spectrophotometer. Elemental analysis were provided by the Analytical Chemistry staff of this department. All new compounds yielded spectral data consistent with the proposed structure and microanalysis within ±0.4% of the theoretical values unless indicated otherwise.

4-(5-Amino-1,3,4-oxadiazol-2-yl)-2,6-bis(1,1-dimethylethyl)phenol (4a). To a solution of 2.2 g (8.3 mmol) of hydrazide **15a** in 10 mL of dioxane was added 0.9 g (8.3 mmol) of CNBr followed by a solution of 0.7 g (8.3 mmol) of sodium bicarbonate

in 10 mL of water. The resulting mixture was stirred 2 h at room temperature. The solution was concentrated to $^1/_2$ volume in vacuo. The mixture was diluted with 10 mL of water and the resulting solid isolated by filtration. The solid was recrystallized from EtOAc/hexane to provide 1.4 g (58%) of **4a**: mp 244–245 °C; IR (KBr) 3616, 3300 (br), 1683, 1245 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (s, 18 H, *tert*-butyl), 5.6 (s, 1 H, OH), 5.7 (s, 2 H, NH_2), 7.7 (s, 2 H, ArH). Anal. ($C_{16}H_{23}N_3O_2$) C, H, N.

(*E*)-4-[2-(5-Amino-1,3,4-oxadiazol-2-yl)ethenyl]-2,6-bis(1,1-dimethylethyl)phenol (4b). To a solution of 1.9 g (6.5 mmol) of hydrazide **15b** in 10 mL of dioxane was added 0.7 g (6.7 mmol) of CNBr followed by a solution of 0.56 g (6.7 mmol) of $NaHCO_3$ in 10 mL of water. The resulting mixture was stirred 2 h at room temperature. The mixture was concentrated in vacuo and the residue suspended in water and filtered. The solid was recrystallized from EtOAc/hexane to provide 1.5 g (52%) of **4b**: mp 221 °C; IR (KBr) 3620, 3300 (br), 2970, 1650, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (s, 18 H, *tert*-butyl), 5.3 (br s, 2 H, NH_2), 5.5 (br s, 1 H, OH), 6.7 (d, J = 16.3 Hz, 1 H, olefinic), 7.2 (d, J = 16.3 Hz, 1 H, olefinic), 7.3 (s, 2 H, ArH). Anal. ($C_{18}H_{25}N_3O_2$) C, H, N.

5-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-oxadiazol-2(3*H*)-one (5a). To a 0 °C solution of 1.0 g (4.0 mmol) of hydrazide **15a** in 12 mL of THF was added 0.4 g (4.0 mmol) of triethylamine (TEA) followed by 0.8 g (5 mmol) of 1,1'-carbonyldiimidazole (CDI) in one portion. The resulting mixture was stirred 18 h at room temperature. The mixture was then concentrated in vacuo and the residue dissolved in ether. The organic layer was washed with aqueous 2 M HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl and dried over $MgSO_4$. Chromatography (flash, SiO_2, 230–400 mesh, 10% EtOAc/hexane eluant) followed by recrystallization from ethyl acetate/hexane provided 0.6 g (55%) of **5a**: mp 246 °C; IR (KBr) 3628, 3400 (br), 2961, 1774, 1620, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (s, 18 H, *tert*-butyl), 5.7 (s, 1 H, OH), 7.7 (s, 2 H, ArH), 9.3 (br s, 1 H, NH). Anal. ($C_{16}H_{22}N_2O_3$) C, H, N.

5-[2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethenyl]-1,3,4-oxadiazol-2(3*H*)-one (5b). To a stirred 0 °C solution of 1.0 g (3.0 mmol) of hydrazide **15b** and 0.4 g (4 mmol) of TEA in 12 mL of THF was added 0.7 g (4.0 mmol) of CDI in one portion. The mixture was stirred at 0 °C for 0.25 h and then allowed to warm to room temperature and stir for 0.75 h. The solution was concentrated and residue dissolved in 50 mL ether and washed with aqueous 2 M HCl. The product was extracted from the organic layer with 20 mL of aqueous 1 M NaOH. The aqueous extract was neutralized with cold aqueous 2 M HCl and the product extracted with ether. The organic layer is washed with saturated aqueous NaCl and dried over $MgSO_4$. Filtration and concentration provided a solid which was recrystallized from EtOAc/hexane to yield 1.0 g (91%) of **5b**: mp >260 °C; IR (KBr) 3631, 3200 (br), 2961, 1774, 1643, 1211 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (s, 18 H, *tert*-butyl), 5.5 (s, 1 H, OH), 6.5 (d, J = 16.4 Hz, 1 H, olefinic), 7.3 (dd, J = 16.4 Hz, 3.5 Hz, 1 H, olefinic), 7.4 (s, 2 H, ArH), 9.1 (br s, 1 H, NH). Anal. ($C_{18}H_{24}N_2O_3$) C, H, N.

5-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-oxadiazole-2(3*H*)-thione (6a). To a 0 °C solution of 5.0 g (19 mmol) of hydrazide **15a** and 3.4 g (44.0 mmol) of CS_2 in 60 mL of absolute ethanol was added 1.1 g (19 mmol) of KOH in one portion. The resulting mixture was stirred 0.5 h at 0 °C before being warmed to room temperature and stirred for 1 h. The solution was then heated to reflux for 2.5 h. The solvent was removed in vacuo and the residue dissolved in 100 mL of water and washed with ether (2×). The aqueous layer was made acidic with aqueous 2 M HCl and the product extracted with a 1:1 mixture of EtOAc/ether (2×). The combined organic layers were washed with saturated aqueous NaCl and dried over $MgSO_4$. Filtration and concentration in vacuo gave a solid which was recrystallized from EtOAc/isopropyl ether to give 2.2 g (38%) of **6a**: mp 253.5 °C; IR (KBr) 3625, 2900 (br), 1616, 1516, 1347, 952 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (s, 18 H, *tert*-butyl), 6.0 (s, 1 H, OH), 7.7 (s, 2 H, ArH), 14.01 (br s, 1 H, NH). Anal. ($C_{16}H_{22}N_2O_2S$) C, H, N.

5-[2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethenyl]-1,3,4-oxadiazole-2(3*H*)-thione (6b). To a 0 °C solution of 3.0 g (10.3 mmol) of hydrazide **15b** in 15 mL of dry ethanol was added 0.58 g (10.3 mmol) of KOH followed by 1.8 g (23.7 mmol) of CS_2. The resulting mixture was stirred 1.5 h at 0 °C. The resulting suspension was then diluted with ethanol and heated to reflux for 4 h. The homogeneous mixture was cooled and concentrated in vacuo. The residue was partitioned between ether and water. The layers were separated, and the aqueous layer was neutralized with aqueous 2 M HCl. The product was extracted out with a 1:1 mixture of EtOAc/ether (3×). The combined organic layers were washed with saturated aqueous NaCl and dried over $MgSO_4$. Filtration and concentration gave a solid which was recrystallized from EtOAc/hexane to give 1.2 g (35%) of **6b**: mp 209.5 °C; IR (KBr) 3622, 3100 (br), 2959, 1640, 1503, 974 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (s, 18 H, *tert*-butyl), 5.6 (s, 1 H, OH), 6.6 (d, J = 16.4 Hz, 1 H, olefinic), 7.4 (s, 2 H, ArH), 7.5 (d, J = 16.4 Hz, 1 H, olefinic), 11.0 (br s, 1 H, NH). Anal. ($C_{18}H_{24}N_2O_2S$) C, H, N.

4-(3-Amino-1*H*-1,2,4-triazol-5-yl)-2,6-bis(1,1-dimethylethyl)phenol (7a). Step 1. A 0 °C solution of 3.62 g (67.01 mmol) of anhydrous $NaOCH_3$ in 40 mL of anhydrous methanol was treated with 9.20 g (67.10 mmol) of aminoguanidine·HNO_3 followed by 10 mL of methanol. The resulting mixture was treated dropwise with 5.92 g (16.8 mmol) of **17** in 21 mL of methanol over 15 min. The reaction was heated at reflux for 26 h, poured onto 450 mL of ice water, brought to pH 7 with aqueous 3 N HCl, filtered, and dried at 50 °C under vacuum overnight to give 5.30 g of the desired triazole: ^1H NMR (DMSO-d_6) δ 1.42 (s, 18 H, *tert*-butyl), 3.28 (s, 3 H, OCH_3), 3.55 (m, 2 H, $OCH_2CH_2OCH_3$), 3.87 (m, 2 H, $OCH_2CH_2OCH_3$), 4.94 (s, 2 H, OCH_2O), 6.06 (br s, 2 H, NH_2), 7.82 (s, 2 H, ArH), 11.95 (br s, 1 H, NH).

Step 2. HCl(g) was bubbled through a 0 °C solution of 5.30 g of the above solid in 200 mL of methanol for 45 min, and the sealed reaction mixture was stirred at 0 °C for 15 min and at room temperature for 2 h. The reaction mixture was concentrated in vacuo, dissolved in 300 mL of aqueous 1 N NaOH, and extracted *tert*-butyl methyl ether (3 × 100 mL). The cold basic solution was neutralized to pH 7 with concentrated aqueous HCl. The resulting precipitate was collected by filtration recrystallized from ethanol/water and triturated with hot CH_3CN to give 1.70 g (35%) of **7a**: mp >250 °C; IR (KBr) 2960, 1636, 1400 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40 (s, 18 H, *tert*-butyl), 6.95 (br s, 2 H, NH_2), 7.10 (br s, 1 H, OH), 7.69 (s, 2 H, ArH), 11.85 (br s, 1 H, NH). Anal. ($C_{16}H_{24}N_4O$) C, H, N.

5-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (8a). To a solution of 3,5-bis(1,1-dimethylethyl)-4-hydroxybenzoic acid hydrazide (**15a**, 2.8 g, 10.6 mmol) in ethanol (140 mL) and water (50 mL) was added aqueous 1 N HCl (16 mL) and NaNCO (1.03 g, 16 mmol). The reaction mixture was stirred at room temperature for 30 min and then at 35 °C for 5 min. The reaction mixture was cooled, evaporated, and partitioned between water (100 mL) and EtOAc (100 mL). The organic layer was dried ($MgSO_4$) and evaporated. The crude intermediate was dissolved in aqueous 1 N NaOH (3 equiv) and heated at reflux for 2 h to effect cyclization. The solution was cooled, neutralized with aqueous 1 N HCl, and extracted with EtOAc. The organic layer was evaporated and the residue purified by flash chromatography (silica, EtOAc) to give 5-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**8a**, 0.32 g, 10%): mp 276–280 °C; ^1H NMR (DMSO-d_6) δ 1.40 (s, 18 H), 7.36 (s, 1 H), 7.55 (s, 2 H), 11.44 (s, 1 H), 11.93 (s, 1 H); MS (EI) m/e 289. Anal. ($C_{16}H_{23}N_3O_2$) C, H, N.

5-[2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (8b). A solution of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde,[13] **22** (3.5 g, 15.0 mmol), 2-(5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)acetic acid[18] (2.15 g, 15.0 mmol), and piperidine (1.3 g, 15.0 mmol) in pyridine (15 mL) and toluene (45 mL) was heated at reflux with removal of water for 40 h. The reaction mixture was cooled, filtered, and evaporated. The residue was taken up in EtOAc (100 mL) and washed with aqueous 1 N HCl (3 × 400 mL), dried over $MgSO_4$, and evaporated. The residue was recrystallized first from CH_2Cl_2 and then from isopropyl ether/EtOAc to give pure 5-[2-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**8b**, 2.49 g, 40%): mp 280–284 °C; ^1H NMR (DMSO-d_6) δ 1.38 (s, 18 H), 6.53 (d, 1 H), 7.10 (d, 1 H), 7.21 (s, 2 H), 11.46 (s, 1 H), 11.54 (s, 1 H); MS (EI) m/e 315. Anal. ($C_{18}H_{25}N_3O_2$) C, H, N.

5-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-3*H*-1,2,4-triazole-3-thione (9a). To a stirred 0 °C solution of 4.0 g (12.4 mmol) of **21** in 50 mL of methanol was added 2.2 g (41.0 mmol) of $NaOCH_3$ in one portion. The resulting mixture was heated at reflux for 24 h before being cooled and concentrated in vacuo. The residue was dissolved in water and washed with ether (2×). The aqueous layer was acidified with aqueous 2 M HCl and the product extracted with a 1:1 mixture of EtOAc/ether (2×). The combined organic extracts were washed with saturated aqueous NaCl and dried over $MgSO_4$. Filtration and concentration gave a residue which was purified by chromatography (flash, SiO_2, 230–400 mesh, 30% EtOAc/hexane eluant). Recrystallization from EtOAc/hexane gave 2.3 g (61%) of **9a**: mp 271 °C; IR (KBr) 3630, 3300 (br), 2961, 1566, 1424, 1216 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (s, 18 H, *tert*-butyl), 6.1 (br s, 1 H, OH), 7.8 (s, 2 H, ArH). Anal. ($C_{16}H_{23}N_3OS$) C, H, N.

(*E*)-2,4-Dihydro-5-[2-[4-hydroxy-3,5-bis(1,1-dimethylethyl)phenyl]ethenyl]-3*H*-1,2,4-triazole-3-thione (9b). To a solution of 4.9 g (20.7 mmol) of aldehyde **22**[13] and 3.3 g (20.7 mmol) of 2-(5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)acetic acid[18] in a 2:1 mixture of 300 mL of toluene/pyridine was added 1.8 g (20.7 mmol) of piperidine. The resulting mixture was heated to reflux for 48 h. The mixture was cooled and concentrated in vacuo. The residue was dissolved in ether, and the product was extracted from the organic phase with aqueous 1 M NaOH (2×). The combined aqueous layers were neutralized with aqueous 2 M HCl, and the product was extracted with a 1:1 mixture of EtOAc/ether. The organic layer was washed with saturated aqueous NaCl and dried over $MgSO_4$. Filtration and concentration in vacuo gave a solid which was triturated in hot isopropyl ether to provide 2.3 g (33%) of **9b**: mp 243 °C; IR (KBr) 3630, 3200 (br), 2960, 1645, 1560, 1213 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (s, 18 H, *tert*-butyl), 5.4 (s, 1 H, OH), 6.5 (d, J = 16.6 Hz, 1 H, olefinic), 7.1 (s, 2 H, ArH), 7.2 (d, J = 16.6 Hz, 1 H, olefinic), 12.7 (br s, 1 H, NH), 13.1 (br s, 1 H, NH). Anal. ($C_{18}H_{25}N_3OS$) C, H, N.

4-(5-Amino-1,3,4-thiadiazol-2-yl)-2,6-bis(1,1-dimethylethyl)phenol (10a). To a 0 °C suspension of 10.9 g (33.7 mmol) of **21** in 100 mL of toluene was added 4.9 g (50.8 mmol) of CH_3SO_3H, dropwise. After the addition was complete, the suspension was heated to reflux for 4 h. The mixture was cooled to 10 °C and filtered. The filtrate was washed with cold toluene. The solid is suspended in 20 mL of water and treated with concentrated NH_4OH. The mixture was filtered, washed with 30 mL of cold water, and dried in vacuo at 70 °C for 18 h to give 5.9 g (57%) of solid **10a**: mp 261 °C; IR (KBr) 3200 (br), 1654, 1598, 1206, 1040 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.4 (s, 18 H, *tert*-butyl), 4.5 (br, 1 H, OH), 7.4 (s, 2 H, ArH), 7.8 (br, 2 H, NH_2). Anal. ($C_{16}H_{23}N_3OS$) C, H, N.

5-[2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethenyl]-1,3,4-thiadiazol-2(3*H*)-one (11a). To a 0 °C solution of 2.0 (7.2 mmol) of 3,5-bis(1,1-dimethylethyl)-4-hydroxybenzenecarbothioic acid, hydrazide[20] **27** and 0.78 g (7.8 mmol) of TEA in 20 mL of THF was added 1.6 g (9.6 mmol) of CDI in one portion. The resulting mixture was stirred at 0 °C for 1 h. The mixture was diluted with 20 mL of ether and the product extracted with aqueous 1 M NaOH (2 × 10 mL). The aqueous extracts were combined and acidified with aqueous 6 M HCl. The product was extracted with a 1:1 mixture of EtOAc/ether (3 × 20 mL). The combined organic extracts were washed with saturated aqueous NaCl and dried over $MgSO_4$. Filtration and concentration in vacuo provided a solid which was recrystallized from EtOAc/hexane to give 1.4 g (64%) of **11a**: mp 229 °C; IR (KBr) 3500 (br), 3100 (br), 3010, 1651, 1239 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (s, 18 H, *tert*-butyl), 5.6 (s, 1 H, OH), 7.5 (s, 2 H, ArH), 9.4 (br s, 1 H, NH). Anal. ($C_{16}H_{22}N_2O_2S$) C, H, N.

5-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-thiadiazole-2(3*H*)-thione (12a). Method A. The thiohydrazide **27**[20] (17.2 g, 61.3 mmol) was placed in absolute ethanol (40 mL). CS_2 (9.33 g, 122 mmol) was added. The mixture was heated, in a 60–65 °C oil bath, under reflux. After 30 min, the mixture became a solution. After an additional 15 min, a large portion of solid precipitated from solution. After a total of 1 h under reflux, an additional 9.33 g of CS_2 was added. The mixture was heated under reflux for an additional 1 h. The reaction mixture was allowed to cool to room temperature and then cooled in an ice bath to 0 °C. The mixture was filtered, and the solid was washed with cold 95% ethanol. The product was dried under reduced pressure at 50 °C for 14 h to give 15.1 g (76%) of product as a white crystalline solid (mp 261–265 °C). A second crop of crystals was obtained by concentrating the mother liquors, filtering, and washing the solid with toluene. The solid was dried under reduced pressure (50 °C) to give an additional 2.4 g (12%) of product as a white solid: mp 261–265 °C.

Method B. To a solution of 2.7 g (6.5 mmol) of **37** in 10 mL of CH_2Cl_2 was added 7.3 g (33.0 mmol) of anhydrous ZnBr in one portion. The mixture was stirred 18 h at room temperature before diluting with 50 mL of CH_2Cl_2, washing the organic layer with water (1×), saturated aqueous $NaHCO_3$ (1×), and saturated aqueous NaCl, and drying over $MgSO_4$. Filtration and concentration gave a solid which was recrystallized from ethyl acetate/hexane to give 1.1 g (52%) of **12a**: mp 259.5–260 °C; IR (KBr) 3629, 3500 (br), 2960, 2881, 1309, 1237, 1069 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (s, 18 H, *tert*-butyl), 6.2 (s, 1 H, OH), 7.5 (s, 2 H, ArH), 14.8 (br s, 1 H, NH). Anal. ($C_{16}H_{22}N_2OS_2$) C, H, N.

Method C. A mixture of 0.5 g (1.49 mmol) of **38** and 2.52 g (7.42 mmol) of $NaSCH_3$ in 3 mL of DMF was heated at 120 °C for 3 h. The reaction was poured onto ice water (100 mL) and acidified with aqueous 3 N HCl to give a white solid. Recrystallization from toluene gave 0.37 g (77%) of **12a** as white crystalline needles: mp 242–243 °C. Anal. ($C_{16}H_{22}N_2OS_2$) C, H, N.

Method D. To a solution of 414 g (1.48 mol) of **41** in 5 L of THF cooled to 5 °C was added dropwise a solution of 354 g (4.45 mol) of carbon disulfide in 1 L THF. After the addition was complete, the mixture was warmed to 20 °C and stirred for 3 h. The solution was concentration in vacuo. The residue was treated with 2 L of cold aqueous 2 N NaOH, and the product was extracted with ether (2×). The layers were separated, and the aqueous layer was neutralized with 2.1 L of aqueous 2 M HCl. The mixture was slurred with 400 mL of EtOAc, and the solid product was filtered and washed with 3:1 heptane/EtOAc (3 × 250 mL). The product was recrystallized from 3.5 L ethanol and 500 mL of water to yield 329 g (69%) of **12a** after drying: mp 263–265 °C. Anal. ($C_{16}H_{22}N_2OS_2$) C, H, N.

5-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-thiadiazole-2(3*H*)-thione, Choline Salt. Choline bicarbonate (46.6% aqueous solution, 0.0763 mol) was added to a warm solution of 5-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-thiadiazole-2(3*H*)-thione (**12a**, 25.0 g, 0.0775 mol) in methanol (100 mL). After the addition was complete, the mixture was heated to reflux for 1 h, cooled, and concentrated in vacuo. The residue was crystallized from hot *tert*-butyl methyl ether, filtered, and dried in vacuo to give 23.9 g (32.9 g, theor, 73%) 5-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl[-1,3,4-thiadiazole-2(3*H*)-thione, ion(1−), 2-hydroxy-*N*,*N*,*N*-trimethylethanamium (1:1) salt: mp 190–191 °C; IR (KBr) 3400 (br), 2963, 1321, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (s, 18 H, *tert*-butyl), 3.4 (s, 9 H, $N(CH_3)_3$), 3.9 (m, 2 H, CH_2), 4.3 (m, 2 H, CH_2), 7.5 (s, 2 H, ArH). Anal. ($C_{21}H_{35}N_3O_2S_2$) C, H, N.

(*E*)-5-[2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethenyl]-1,3,4-thiadiazole-2(3*H*)-thione (12b). To a solution of 1.0 g (2.8 mmol) of **30b** in 16 mL of DMF was added 0.5 g (7.0 mmol) of $NaSCH_3$ in one portion. The resulting mixture was heated to 80 °C for 1 h and then allowed to stir overnight at room temperature. The mixture was diluted with water and treated with 5 mL of aqueous 1 M NaOH. The aqueous layer was washed with ether (2×) and then neutralized with aqueous 2 M HCl. The product was extracted out with a 1:1 mixture of EtOAc/ether (2×). The combined organic layers were washed with saturated aqueous NaCl and dried over $MgSO_4$. Filtration and concentration gave a solid which was recrystallized from methanol/water to give 0.55 g (57%) of **12b**: mp 248–249 °C; IR (KBr) 3629, 3000 (br), 1625, 1421, 1207 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (s, 18 H, *tert*-butyl), 5.5 (s, 1 H, OH), 6.9 (s, 2 H, $CH{=}CH$), 7.3 (s, 2 H, ArH). Anal. ($C_{18}H_{24}N_2OS_2$) C, H, N.

1,1-Dimethylethyl 2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxybenzoyl]hydrazinecarboxylate (14a). Step 1. To a 0 °C solution of 14.9 g (59.9 mmol) of acid **13a** in 250 mL of THF and 0.5 mL of DMF was added 11.6 g (91.7 mmol) of oxalyl chloride dropwise. After the addition was complete, the mixture was stirred for 1 h at room temperature before being concentrated

in vacuo. The yellow solid was dissolved in CH_2Cl_2 and concentrated again to give 17.1 g (99%) of 3,5-bis(1,1-dimethylethyl)-4-hydroxybenzoic acid, acid chloride. The material was used in the next step without purification.

Step 2. To a stirred 0 °C suspension of 15.6 g (118.0 mmol) of (1,1-dimethylethyl)hydrazinecarboxylic acid in 200 mL of THF was added dropwise a solution of 17.1 g (59.9 mmol) of 3,5-bis-(1,1-dimethylethyl)-4-hydroxybenzoic acid chloride in 120 mL of THF. After the addition was complete, the mixture was allowed to stir at room temperature for 18 h. The solvent was removed in vacuo, and the residue was passed through a pad of silica gel (SiO_2, 230–400 mesh, petroleum ether eluant). Trituration with 1:1 isopropyl ether/hexane provided 12.2 g (84%) of **14a**: mp 196.5 °C; IR (KBr) 3634, 3400 (br), 1720, 1665, 1241, 1162 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (s, 18 H, CO_2t-Bu), 1.6 (s, 9 H, CO_2t-Bu), 5.6 (s, 1 H, OH), 6.7 (br s, 1 H, NH), 7.7 (s, 2 H, ArH), 8.4 (br s, 1 H, NH). Anal. ($C_{20}H_{32}N_2O_4$) C, H, N.

1,1-Dimethylethyl 2-[3-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1-oxo-2-propenyl]hydrazinecarboxylate (14b). A solution of 4.9 g (16.0 mmol) of 3,5-bis(1,1-dimethylethyl)-4-hydroxycinnamic acid, acid chloride (prepared in a similar manner as described in **14a**) was added to a 0 °C solution of 4.5 g (34.0 mmol) of (1,1-dimethylethyl)hydrazinecarboxylic acid in 30 mL of CH_2Cl_2. After the addition was complete, the mixture was allowed to stir overnight at room temperature. The mixture was concentrated in vacuo, and the residue was dissolved in 50 mL of CH_2Cl_2 and washed with cold aqueous 2 M HCl and saturated aqueous NaCl, and dried over $MgSO_4$. Filtration and concentration gave a solid which was recrystallized from EtOAc/isopropyl ether to give 4.6 g (76%) of **14b**: mp 198–200 °C; IR (KBr) 3573, 3383, 3268, 1752, 1618, 1442, 1228 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (s, 18 H, t-Bu), 1.5 (s, 9 H, CO_2 t-Bu), 5.5 (s, 1 H, OH), 6.3 (d, J = 16.1 Hz, 1 H, olefinic), 7.3 (s, 2 H, ArH), 7.7 (d, J = 16.1 Hz, 1 H, olefinic). Anal. ($C_{22}H_{34}N_2O_4$) C, H, N.

3,5-Bis(1,1-dimethylethyl)-4-hydroxybenzoic Acid Hydrazide (15a). A solution of 4.0 g (11.0 mmol) of **14a** in 100 mL of THF was treated with a mixture of 12 mL of water and 30 mL of concentrated aqueous HCl. The resulting mixture was heated on a steam bath for 0.5 h. The mixture was concentrated in vacuo, and the residue was diluted with 100 mL of water and treated with aqueous 1 M NaOH until the solution was slightly basic. The product was extracted into ether (3 × 200 mL), and the combined organic extracts were washed with saturated aqueous NaCl and dried over $MgSO_4$. Filtration and concentration provided a solid which was recrystallized from isopropyl ether/hexane to yield 1.9 g (62%) of **15a**: mp 187–188 °C; IR (KBr) 3632, 3500 (br), 2958, 1649, 1434, 1239 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (s, 18 H, t-Bu), 3.2 (br s, 2 H, NHNH_2), 5.6 (s, 1 H, OH), 7.6 (s, 2 H, ArH). Anal. ($C_{15}H_{24}N_2O_2$) C, H, N.

(*E*)-3-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2-propenoic Acid Hydrazide (15b). To a solution of 4.3 g (11.0 mmol) of **14b** in 20 mL of absolute ethanol was added 11.0 mL (22 mmol) of aqueous 2 M HCl. The resulting mixture was heated on a steam bath for 1 h. The mixture was concentrated in vacuo and the residue partitioned between ether and water. The layers were separated, and the aqueous phase was made basic with saturated aqueous $NaHCO_3$. The product was extracted out with a 1:1 mixture of EtOAc/ether. The organic extract was washed with saturated aqueous NaCl and dried over $MgSO_4$. Filtration and concentration provided a solid which was triturated in hexane and filtered to yield 3.0 g (94%) of **15b**: mp 166.5–167 °C; IR (KBr) 3300 (br), 2918, 1654, 1596, 1427, 1208, 1155 cm^{-1}; ^1H NMR (DMSO) δ 1.4 (s, 18 H, *tert*-butyl), 4.4 (s, 1 H, OH), 6.4 (d, J = 15.8 Hz, 1 H, olefinic), 7.3 (s, 2 H, ArH), 7.4 (d, J = 15.8 Hz, 1 H, olefinic), 9.1 (s, 1 H, CON*H*NH_2). Anal. ($C_{17}H_{26}N_2O_2$) C, H, N.

Methyl 3,5-Bis(1,1-dimethylethyl)-4-[(2-methoxyethoxy)methoxy]benzoate (17). (2-Methoxyethoxy)methyl chloride (24.0 g, 192.7 mmol) was added dropwise to a 0 °C mixture of 25.0 g (94.6 mmol) of **16**[12] and 27.5 g (212.4 mmol) of diisopropylethylamine in 50 mL of CH_2Cl_2 under a nitrogen atmosphere. The reaction was stirred at 25 °C for 24 h and poured onto saturated aqueous NH_4Cl, and the layers were separated. The aqueous layer is extracted with *tert*-butyl methyl ether (2 × 150 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl, water, and saturated aqueous NaCl (2×), dried over Na_2SO_4, and concentrated in vacuo to give 33.2 g of the desired product as an orange oil. The product was used as is in subsequent reactions. A sample was purified by chromatography (flash, SiO_2, 230–400 mesh, 29 × 6.5 cm, 15% *tert*-butyl methyl ether–hexane) followed by Kugelrohr distillation to give an oil: IR (film) 2912, 1719, 1304, 1217, 1136, 1107, 949 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40 (s, 18 H, *tert*-butyl), 3.27 (s, 3 H, CH_2OCH_3), 3.52 (t, 2 H, J = 4.7 Hz, $OCH_2CH_2OCH_3$), 3.82 (s, 3 H, CO_2CH_3), 3.88 (t, 2 H, J = 4.7 Hz, $OCH_2CH_2OCH_3$), 4.96 (s, 2 H, OCH_2O), 7.87 (s, 1 H, ArH). Anal. ($C_{20}H_{32}O_5$) C, H, N.

5-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2,4-dihydro-4-methyl-3*H*-1,2,4-triazol-3-one (18). Methyl isocyanate (1.02 g, 18.0 mmol) was added dropwise to a solution of 2.35 g (8.9 mmol) of **15a** in 100 mL of absolute ethanol. The reaction was stirred at room temperature for 1 h, concentrated in vacuo, and poured onto ice water. The precipitate was collected by filtration, dissolved in 20 mL of aqueous 1 N NaOH, heated at reflux for 3 h, cooled, and neutralized with aqueous 3 N HCl. The aqueous mixture was extracted with EtOAc (3 × 50 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated in vacuo to give a solid. Recrystallization twice from methanol gave 0.8 g (30%) of **18**: mp 308–312 °C; IR (KBr) 3505, 3184, 2960, 1700 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.4 (s, 18 H, *tert*-butyl), 3.4 (s, 3 H, Me), 7.4 (s, 2 H, ArH), 7.5 (s, 1 H), 11.7 (s, 1 H). Anal. ($C_{17}H_{25}N_3O_2$) C, H, N.

5-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2,4-dihydro-4-methyl-3*H*-1,2,4-triazole-3-thione (19). To a solution of 7.6 g (28.6 mmol) of **15a** in 300 mL of absolute ethanol was added 4.2 g (57.1 mmol) of methyl isothiocyanate dropwise. The reaction mixture was stirred at room temperature for 12 h, concentrated in vacuo, and treated with ice water. The resulting precipitate was collected by filtration, dissolved in 60 mL of aqueous 1 N NaOH, and heated to reflux for 3 h. The cooled reaction was acidified with aqueous 3 N HCl and extracted with EtOAc (3×). The combined extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated in vacuo to give a white solid. Recrystallization from 2-methoxyethanol gave 6.34 g (70%) of **19** as a white solid: mp >300 °C; IR (KBr) 3490, 3135, 2967, 1612, 1558, 1484, 1425, 1384, 1330, 1197, 1079, 973 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.41 (s, 18 H, *tert*-butyl), 7.41 (s, 2 H, ArH), 7.59 (br s, 1 H, OH), 13.75 (br s, 1 H, NH). Anal. ($C_{17}H_{25}N_3OS$) C, H, N.

4-Amino-3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2,4-dihydro-5*H*-1,2,4-triazole-5-thione (20). To a solution of 4.0 g (0.13 mol) of **6a** in 100 mL of ethanol was added 20.64 g (0.41 mol) of hydrazine hydrate dropwise. The reaction was heated at reflux for 4 h, cooled, diluted with water, and acidified with cold aqueous 3 N HCl. The resulting precipitate was collected by filtration and recrystallized from DMF–water to give 2.10 g (50%) of **20** as a white solid: mp 267–270 °C; IR (KBr) 3512, 3152, 2963, 1616, 1554, 1484, 1422, 1102, 954, 886 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.42 (s, 18 H, *tert*-butyl), 5.78 (s, 2 H, NH_2), 7.50 (s, 1 H, OH), 7.82 (s, 2 H, ArH), 13.75 (s, 1 H, NH). Anal. ($C_{16}H_{24}N_4OS$).

2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxybenzoyl]hydrazinecarbothioamide (21). To a stirred 0 °C suspension of 10.9 g (120 mmol) of thiosemicarbazide in 300 mL of tetrahydrofuran was added dropwise a solution of 17.1 g (59.0 mmol) of 3,5-bis-(1,1-dimethylethyl)-4-hydroxybenzoic acid chloride (preparation described in experimental of **14a**) in 70 mL of tetrahydrofuran. After the addition was complete, the mixture was allowed to stir at room temperature for 18 h. The solvent was removed in vacuo and the residue passed through a pad of silica gel (SiO_2, 230–400 mesh, 1:1 EtOAc/hexane eluant). Trituration with 1:1 isopropyl ether/hexane yielded 17.6 g (91%) of pure **21**: mp 210–211 °C; IR (KBr) 3626, 3300 (br), 2959, 1670, 1602, 1432, 1238 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5 (s, 18 H, *tert*-butyl), 2.8 (s, 2 H, NH_2), 6.1 (s, 1 H, OH), 6.9 (br s, 2 H, NH_2), 7.7 (s, 2 H, ArH). Anal. ($C_{16}H_{25}N_3O_2S$) C, H, N.

3,5-Bis(1,1-dimethylethyl)-4-hydroxybenzenecarbothioic Acid 2,2-Dimethylhydrazide (28). Via the procedure for **27**,[20] 5.00 g (13.57 mmol) of **26** and 4.0 g (65.9 mmol) of 1,1-dimethylhydrazine gave 2.85 g (68%) of **28** as a white solid: mp 175.5–176.5 °C (*tert*-butyl methyl ether); IR (KBr) δ 2924, 1457, 1432, 1298, 1205 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 18 H, *tert*-

butyl), 3.05 (s, 6 H, $(CH_3)_2$), 5.40 (s, 1 H, OH), 7.91 (s, 2 H, ArH), 12.09 (br s, 1 H, NH). Anal. ($C_{17}H_{28}N_2OS$) C, H, N.

5-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-3-methyl-1,3,4-thiadiazole-2(3*H*)-thione (29). A solution of 1.15 g (9.96 mmol) of thiophosgene in 5 mL of $CHCl_3$ was added dropwise (10 min) to a $CHCl_3$ (10 mL) solution of 2.05 g (6.65 mmol) of thiohydrazide **28**. The reaction was stirred at room temperature for 2 h and concentrated in vacuo to give a foam. The foam was suspended in 25 mL of *tert*-butyl methyl ether–hexane (1:1) and concentrated in vacuo to give an off-white solid. Recrystallization from absolute ethanol gave 1.50 g (67%) of **29** as a beige solid: mp 158–159 °C; ^{1}H NMR (DMSO-d_6) δ 1.40 (s, 18 H, *tert*-butyl), 3.86 (s, 3 H, CH_3), 7.43 (s, 2 H, ArH), 7.83 (s, 1 H, OH). Anal. ($C_{17}H_{24}N_2OS_2$) C, H, N.

2,6-Bis(1,1-dimethylethyl)-4-[5-(methylthio)-1,3,4-thiadiazol-2-yl]phenol (30a). To a 0 °C solution of 30 g (93. mmol) of thiadiazolethione **12a** in 150 mL of THF was added 93.0 mL (93.0 mmol) of aqueous 1 M NaOH dropwise. After the addition was complete, the mixture was stirred 0.5 h at 0 °C before 14.5 g (102.3 mmol) of CH_3I was added dropwise over 0.17 h. The mixture was stirred 0.33 h and then concentrated in vacuo. The resulting solid was recrystallized from methanol/water to give 30.6 g (98%) of desired product (**30a**) after drying in vacuo at 70 °C overnight: mp 124.5 °C; IR (KBr) 3573, 2955, 1411, 1228 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.5 (s, 18 H, *tert*-butyl), 2.8 (s, 3 H, SCH_3), 5.6 (s, 1 H, OH), 7.7 (s, 2 H, ArH). Anal. ($C_{17}H_{24}N_2OS_2$) C, H, N.

(*E*)-2,6-Bis(1,1-dimethylethyl)-4-[2-[5-(methylthio)-1,3,4-thiadiazol-2-yl]ethenyl]phenol (30b). To a solution of 3.3 g (8.7 mmol) of hydrazide **32** in 40 mL toluene was added 1.6 g (8.7 mmol) of *p*-toluenesulfonic acid. The resulting mixture was heated to reflux for 1 h. The solution was then cooled and concentrated. The solid residue was recrystallized from EtOAc/*tert*-butyl methyl ether to provide 2.1 g (66%) of (**30b**): mp 194–195 °C; IR (KBr) 3450 (br), 2980, 1630, 1601, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.5 (s, 18 H, *tert*-butyl), 2.8 (s, 3 H, SMe), 5.5 (s, 1 H, OH), 7.1 (d, J = 16.2 Hz, 1 H, olefinic), 7.2 (d, J = 16.2 Hz, 1 H, olefinic), 7.4 (s, 2 H, ArH). Anal. ($C_{19}H_{26}N_2OS_2$) C, H, N.

(*E*)-3-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2-propenoic Acid 2-[(Methylthio)thioxomethyl]hydrazide (32). A 0 °C solution of 50 mL of THF and 11.3 g (36.2 mmol) of 3,5-bis(1,1-dimethylethyl)-4-hydroxycinnamic acid, acid chloride was prepared following the procedure described for the synthesis of **14a**, step 1. This solution was added dropwise to a 0 °C mixture of 4.5 g (37.0 mmol) of methyl hydrazinecarbodithioate (**31**)[22] and 3.7 g (37.0 mmol) of TEA in 20 mL of THF. After the addition was complete, the mixture was allowed to warm to room temperature and stir overnight. The mixture was concentrated in vacuo, and the residue was dissolved in ether, washed with aqueous 0.5 M HCl and saturated aqueous NaCl, and dried over $MgSO_4$. Filtration and concentration in vacuo gave a residue which was purified by chromatography (flash, SiO_2, 230–400 mesh, 20% EtOAc/hexane eluant) followed by recrystallization from EtOAc/hexane to provide 4.5 g (33%) of **32**: mp 200.5 °C; IR (KBr) 3300 (br), 2960, 1640, 1440, 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.3 (s, 18 H, *tert*-butyl), 2.6 (s, 3 H, SCH_3), 5.6 (s, 1 H, OH), 6.5 (d, J = 15.6 Hz, 1 H, olefinic), 7.4 (s, 2 H, ArH), 7.7 (d, J = 15.6 Hz, olefinic), 10.1 (br s, 2 H, N*H*N*H*). Anal. ($C_{19}H_{28}N_2O_2S_2$) C, H, N.

3,5-Bis(1,1-dimethylethyl)-4-[(2-methoxyethoxy)methoxy]benzonitrile (33). To a stirred solution of 5.0 g (22.0 mmol) of 3,5-bis(1,1-dimethylethyl)-4-hydroxybenzonitrile[12] and 4.2 g (32.0 mmol) of diisopropylaminomethane in 50 mL of CH_2Cl_2 was added 4.1 g (32.0 mmol) of (2-methoxyethoxy)methyl chloride dropwise. After the addition was complete, the mixture was allowed to warm to room temperature and stir 18 h. The mixture was diluted with 25 mL of CH_2Cl_2, washed with water (1×) cold aqueous 2 M HCl (1×) and saturated aqueous NaCl, and dried over $MgSO_4$. Filtration and concentration in vacuo afforded 6.7 g (97%) of **33** as a yellow oil: IR (film) 2966, 2231, 1393, 1166, 1109 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.4 (s, 18 H, *tert*-butyl), 3.4 (s, 3 H, OCH_3), 3.6 (m, 2 H, OCH_2CH_2O), 3.9 (m, 2 H, OCH_2CH_2O), 5.0 (s, 2 H, OCH_2O), 7.6 (s, 2 H, ArH).

3,5-Bis(1,1-dimethylethyl)-4-[(2-methoxyethoxy)methoxy]benzenecarboximidic Acid Hydrazide (35). To a 0 °C suspension of 2.8 g (71.0 mmol) of NaH (60% in oil dispersion; washed with hexane) in tetrahydrofuran under nitrogen was added 4.8 g (151 mmol) of 97% anhydrous hydrazine dropwise.[23] After the addition was complete, the mixture was stirred 1.5 h at 0 °C before adding 6.7 g (21 mmol) of **33** in 15 mL of THF dropwise. After stirring 2 h at 0 °C, 2.4 mL of water was added dropwise. The mixture was then poured into 20 mL of cold, saturated aqueous $NaHCO_3$. The product was extracted with 60 mL of 1:1 EtOAc/ether. The organic layer was washed with saturated aqueous NaCl and dried over $MgSO_4$. Filtration and concentration in vacuo provided a solid which was recrystallized from EtOAc/hexane to give 4.9 g (67%) of **35**: mp 133 °C; IR (KBr) 3364, 3000 (br), 1640, 1381, 1106, 969 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.5 (s, 18 H, *tert*-butyl), 3.4 (s, 3 H, OCH_3), 3.6 (m, 2 H, OCH_2CH_2O), 3.9 (m, 2 H, OCH_2O), 4.9 (s, 2 H, OCH_2O), 7.5 (s, 2 H, ArH).

3,5-Bis(1,1-dimethylethyl)-4-methoxybenzenecarboximidic Acid Hydrazide (36). Via the procedure[23] described for **35**, 5.0 g (20.78 mmol) of nitrile **34** was converted to 3.96 g (69%) of the iminohydrazine **36**: mp 154–155 °C; IR (KBr) 3345, 3187, 2953, 1649, 1384 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.39 (s, 18 H, *tert*-butyl), 3.62 (s, 3 H, OCH_3), 5.06 and 5.75 (2 br s, 2 H each, imidohydrazine), 7.54 (s, 2 H, ArH). Anal. ($C_{16}H_{27}N_3O$) C, H, N.

5-[3,5-Bis(1,1-dimethylethyl)-4-[(2-methoxyethoxy)methoxy]phenyl]-1,3,4-thiadiazole-2(3*H*)-thione (37). To a 0 °C solution of 3.0 g (8.5 mmol) of iminohydrazine **35** in 36 mL of absolute ethanol was added 1.6 g (21 mmol) of CS_2 dropwise. The mixture was allowed to warm to room temperature and stir 3 h. The solution was concentrated in vacuo and the product crystallized from isopropyl ether to give 2.8 g (80%) of **37**: mp 134–135 °C; IR (KBr) 3000 (br), 1457, 1252, 1100, 975 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.5 (s, 18 H, *tert*-butyl), 3.4 (s, 3 H, OCH_3), 3.6 (m, 2 H, OCH_2CH_2O), 3.9 (m, 2 H, OCH_2CH_2O), 5.0 (s, 2 H, OCH_2O), 7.6 (br s, 2 H, ArH). Anal. ($C_{20}H_{30}N_2O_3S_2$) C, H, N.

5-[3,5-Bis(1,1-dimethylethyl)-4-methoxyphenyl]-1,3,4-thiadiazole-2(3*H*)-thione (38). Via the procedure for **37**, 3.45 g (12.44 mmol) of **37** was converted to 3.62 g (86%) of thiadiazole **38**: mp 216–219 °C; IR (KBr) 2969, 1471, 1261, 1227 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.41 (s, 18 H, *tert*-butyl), 3.68 (s, 3 H, OCH_3), 7.55 (s, 2 H, ArH). Anal. ($C_{17}H_{24}N_2OS_2$) C, H, N.

3,5-Bis(1,1-dimethylethyl)-*N*,4-dihydroxybenzenecarboximidoyl Chloride (40). To a 25 °C solution of 950.0 g (3.81 mol) of oxime[12] **39** in 2 L of CH_2Cl_2 was added a solution of 633.0 g (4.76 mol) of *N*-chlorosuccinimide in 15 L of CH_2Cl_2 dropwise over 4 h. The solution was then washed with 5 L of ice-cold water (2×) and dried over $MgSO_4$. Filtration and concentration in vacuo to 4.5-L volume yielded a solid which was filtered and dried in vacuo to yield 540.0 g (55%) of pure **40**: mp 168–170 °C; IR (KBr) 3619, 3300 (br), 2950, 1222, 976, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.5 (s, 18 H, *tert*-butyl), 5.5 (s, 1 H, OH), 7.7 (s, 2 H, ArH), 7.8 (br, 1 H, NO*H*). Anal. ($C_{15}H_{22}ClNO_2$) C, H, N.

3,5-Bis(1,1-dimethylethyl)-*N*,4-dihydroxybenzenecarboximidic Acid Hydrazide (41). A 4-necked 12-L flask equipped with a mechanical stirrer, 3-L dropping funnel, and an argon inlet adapter was charged with 6 L of THF, 260 g (8.12 mol) of 97% anhydrous hydrazine, 500 mL of TEA, and 500 mL of anhydrous ethanol. The resulting mixture was cooled to 0 °C, and a solution of 573.0 g (2.02 mol) of **40** in 2 L of THF was added dropwise over a 1-h period. The mixture was then warmed to 15 °C over 1 h. The mixture was concentrated in vacuo while maintaining the temperature at 25 °C. The resulting viscous oil was treated with 2 L of EtOAc and saturated aqueous $NaHCO_3$. The product was isolated by filtration. The resulting damp cake was dissolved in 8 L of THF and the solution dried with $MgSO_4$. Filtration provided a solution of the product **41** which could be used directly in the next step. A small aliquot was concentrated to dryness and the resulting residue recrystallized from EtOAc/hexane to provide 89% of desired **41**: mp 120 °C (**Caution: violent decomposition observed**); IR (KBr) 3610, 3300 (br), 3000, 1633, 1439, 1365, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 18 H, *tert*-butyl), 3.5 (br, 2 H, NH_2), 5.4 (br, 2 H), 7.3 (s, 2 H, ArH). Anal. ($C_{15}H_{25}N_3O_2$) C, H, N.

Pharmacology. A. Whole Cell 5-Lipoxygenase (5-LO) and Cyclooxygenase (CO) Assays. Materials. The rat basophilic leukemia cell line (RBL-1) was obtained from the

American Type Culture Collection (Rockville, MD). Radioimmunoassay (RIA) kits for LTB_4 and $PGF_{2\alpha}$ were obtained from Amersham (Arlington Heights, IL) and Seragen (Boston, MA), respectively. All tissue culture media were obtained from GIBCO (Grand Island, NY).

Method. RBL-1 cells were grown at 37 °C in suspension culture in Eagle's minimum essential medium supplemented with 12% fetal bovine serum under 5% CO_2 in air. Cells were harvested by centrifugation, washed with cold phosphate buffered saline, pH 7.4 (PBS; NaCl, 7.1 g; Na_2HPO, 1.15 g; KH_2PO_4, 0.2 g; and KCl, 0.2 g/L), and suspended in PBS containing 1.0 mM calcium at a density of 2×10^6 cell/mL. Cells were incubated with and without test agent in 1% DMSO for 10 min at room temperature. Calcium ionophore A23187 (5 μm) was added and incubations continued for 7 min at 37 °C. The reaction was stopped by chilling the tubes on ice for 10 min. Cells were removed by centrifugation, and the supernatant was stored at −20 °C. Aliquots (100 μL) were analyzed for LTB_4 and $PGF_{2\alpha}$ by RIA according to the manufacturer's instructions. Product formation in the compound and vehicle treated incubations were compared to obtain percent inhibition. The IC_{50} values were determined by linear regression analysis of the percent inhibition vs log inhibitor concentration data.

B. Carrageenan Footpad Edema. Carrageenan solution (1% w/v) was prepared by dissolving 100 mg of carrageenan (Marine Colloidal Div., Springfield, NJ) in 10 mL of sterile saline (0.9%) solution (Travenol). Male Wistar rats were orally dosed with compound (in 10 mL/kg of 0.5% (hydroxypropyl)methylcellulose/0.2% Tween 80 or Labrafils) 1 h before carrageenan challenge. Foot paw edema was induced by injecting 0.10 mL of the carrageenan solution subcutaneously into the planter portion of the right hind paw of each rat under light anesthesia. Initial foot paw volume was measured immediately by mercury plethysmography (Buxco Electronics) following carrageenan challenge. Edema was measured 5 h after carrageenan administration. The swelling in each test group of animals was used to calculate the percent inhibition ± SEM of edema achieved by the compound at the test dose compared with the vehicle control group. Compounds were tested at doses of 1.0, 3.0, 10.0, and 30.0 mg/kg po, with 7–14 animals at each dose.

C. Mycobacterium Footpad Edema. *Mycobacterium butyricum* (5 mg/mL) was suspended in paraffin oil by sonication for 10 min in an ice batch. Footpad edema was induced on day 0 by injecting 0.1 mL of the *Mycobacterium* mixture into the left hindpaw of lightly anesthetized rats. Swelling in the injected hindpaw was determined by mercury plethamography 72 h after injection. Groups of rats were orally dosed with test compounds (suspended in 0.5% (hydroxypropyl)methylcellulose with 0.2% Tween-80) or vehicle 1 h before *Mycobacterium* injection and on day 1 or 2. Inhibition of swelling was determined by comparing the change in hindpaw volume in compound- and vehicle-treated rats.

log *P* Measurements.[28] The method is based on the linear relationship which has been established between the log K' values of most compounds and their log *P* values. The method used an unmodified, commercially available, 10-μm octadecylsilane (C-18) column. The mobile phase consists of 55 parts methanol and 45 parts 0.05 M ammonium phosphate buffer. The *apparent* pH of the mobile phase was adjusted to 7.4. Detector output was monitored at 214 nm.

A four-component calibration mixture consisting of the following was used:

compound	log *P*
benzyl alcohol	1.16
acetophenone	1.66
toluene	2.74
naphthalene	3.37

A plot of log K' v log *P* generated from the calibration mixture usually exhibited a correlation coefficient of 0.99 or greater. The plot was used for calculation of log *P* values for unknowns from the logarithms of their chromatographic capacity factors.

Method requirements and limitations: (1) log *P* range: 1.0–3.5. (2) pH range: 2.5–8.0. (3) Precision estimated at ±0.2 log *P* units.

pK_a Measurements. Dissociation constants (pK_a) were determined by direct titration of the compound in a 2:1 DMF/H_2O solution. Dissociation constants determined in this solvent system may be higher or lower by one or two p*K* units than would be expected in pure water; however, the values are useful for comparison within a series of analogs.

In practice, a small sample of the compound (3–10 mg) was dissolved in a small volume of solvent (3 mL), to which was added 0.1 mL of 0.2 N HCl, to fully protonate the compound. The solution was titrated with 0.2 N NaOH (correcting for solvent blank if necessary) using a glass/calomel electrode pair with an automatic titration apparatus (Radiometer or Metrohm) equipped with a program for determining the dissociation constant from the titration curve. The pK_a was automatically determined from the inflection points on the titration curve, but only values between 3 and 12 were usable.

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